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# Exploration of Hetarynes as Versatile Synthetic Intermediates

A dissertation submitted in partial satisfaction of the

requirements for the degree Doctor of Philosophy

in Chemistry

by

Adam Edward Goetz

2014

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ABSTRACT OF THE DISSERTATION

Exploration of Hetarynes as Versatile Synthetic Intermediates

by

Adam Edward Goetz

Doctor of Philosophy in Chemistry

University of California, Los Angeles, 2014

Professor Neil K. Garg, Chair

This dissertation describes the study of heterocyclic arynes and their applications to synthetic organic chemistry. Heterocyclic arynes are highly reactive intermediates that undergo a variety of unique reactions. The ability to employ these intermediates in organic synthesis allows for the synthesis of substituted heterocyclic compounds.

Chapter one reviews previous efforts in the area of hetaryne chemistry. Emphasis is placed on the chemistry of indolynes and pyridynes and applications to the synthesis of natural products.

Chapters two and three discuss experimental studies involving indolyne intermediates. Chapter two pertains to the development of various indolyne precursors and studies of their reactivity using both experimental and computational methods. This culminates in an explanation for the observed regioselectivity of the indolyne intermediates. Chapter three covers the design

of a substituted indolyne that reacts with an opposite sense of regioselectivity from the parent system and the use of this species in the synthesis of the natural product indolactam V.

Chapter four describes a simple computational model for predicting the accessibility and preferred site of attack for a hetaryne intermediate that utilizes Density Functional Theory calculations. Also included is a comparison of predicted regioselectivities to experimental data from published examples.

Chapter five discusses the development of a method for controlling the regioselectivity in reactions of 3,4-pyridynes. The use of substituted pyridyne derivatives allows for either product isomer to be obtained selectively. The directing group is used for subsequent functionalization.

Chapter six pertains to the synthesis of the natural product tubingensin A. Our studies focus on the use of a carbazolyne intermediate for the introduction of the key vicinal quaternary centers of the natural product.

The dissertation of Adam Edward Goetz is approved.

Kendall N. Houk

David B. Teplow

Neil K. Garg, Committee Chair

University of California, Los Angeles

2014

*For my parents, sisters, and wife: Mary, Gary, Stephanie, Laura, and Maraia*

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LIST OF ABBREVIATIONS

| | |
|---|---|
| ‡ | transition state |
| ° | degrees |
| $[\alpha]_D$ | specific rotation at wavelength of sodium D line |
| Å | Ångström |
| Ac | acetyl, acetate |
| app. | apparent |
| aq. | aqueous |
| atm | atmosphere |
| B3LYP | Becke, 3-parameter, Lee–Yang (functional) |
| 9-BBN | 9-Borabicyclo(3.3.1)nonane |
| Bn | benzyl |
| Boc | *tert*-butyloxycarbonyl |
| br | broad |
| Bu | butyl |
| *n*-Bu | butyl |
| *sec*-Bu | *sec*-butyl |
| *t*-Bu | *tert*-butyl |
| *c* | concentration for specific rotation measurements |
| C | Celsius |
| calcd | calculated |
| cod | 1,5-cyclooctadiene |
| CPCM | conductor-like polarizable continuum model |
| d | doublet |
| DBU | 1,8-diazabicycloundec-7-ene |
| DDQ | 2,3-dichloro-5,6-dicyano-1,4-benzoquinone |
| Δ | mathematical difference |
| DFT | density functional theorem |
| DMAP | 4-dimethylaminopyridine |
| DME | dimethoxyethane |
| DMF | *N*,*N*-dimethylformamide |
| DMIPS | dimethylisopropylsilyl |
| DMSO | dimethyl sulfoxide |

| | |
|---|---|
| dvds | 1,3-divinyl-1,1,3,3-tetramethyldisiloxane |
| e | electrons |
| $E_d$ | distortion energy |
| equiv | equivalent |
| ESI | electrospray ionization |
| Et | ethyl |
| g | gram(s) |
| G | Gibbs free energy |
| h | hour(s) |
| H | enthalpy |
| *n*-Hex | Hexyl |
| Hex | hexanes |
| HMDS | hexamethyldisilazane |
| HMPA | hexamethylphosphoramide |
| HRMS | high resolution mass spectroscopy |
| hν | light |
| Hz | hertz |
| IBX | 2-Iodoxybenzoic acid |
| IPA | Isopropyl alcohol |
| IR | infrared (spectroscopy) |
| *J* | coupling constant |
| kcal/mol | kilocalories to mole ratio |
| KHMDS | potassium bis(trimethylsilyl)amide |
| λ | wavelength |
| L | liter |
| LANL2DZ | Los Alamos National Laboratory 2 double ζ (basis set) |
| LDA | lithium diisopropylamide |
| LG | Leaving group |
| Li(Hg) | Lithium amalgam |
| LiHMDS | lithium bis(trimethylsilyl)amide |
| LUMO | lowest unoccupied molecular orbital |
| m | multiplet or milli |
| *m* | meta |
| *m*CPBA | *meta*-chloroperoxybenzoic acid |
| min | minute |

| | |
|---|---|
| *m/z* | mass to charge ratio |
| μ | micro |
| Me | methyl |
| MHz | megahertz |
| min | minute(s) |
| mol | mole(s) |
| MOM | methoxymethyl |
| mp | melting point |
| MP2 | Møller Plesset 2 (theorem) |
| MS | molecular sieves |
| N | normality |
| NBS | *N*-bromosuccinimide |
| NiClCpIMes | ($\eta^5$-$C_5H_5$)NiCl(1,3-dimesitylimidazol- 2-ylidene) |
| NMO | *N*-methylmorpholine-*N*-oxide |
| NMR | nuclear magnetic resonance |
| NOE | Nuclear Overhauser Effect |
| NOESY | Nuclear Overhauser Enhancement Spectroscopy |
| Nuc | nucleophile |
| p | pentet |
| *p* | para |
| Pd/C | palladium on carbon |
| Ph | phenyl |
| pH | hydrogen ion concentration in aqueous solution |
| PhH | benzene |
| ppm | parts per million |
| Pr | propyl |
| *i*-Pr | isopropyl |
| q | quartet |
| *rac* | racemic or racemate |
| rt | room temperature |
| $R_f$ | retention factor |
| s | singlet |
| SF-CCSD | spin-flip coupled-cluster with single and double excitations (method) |
| SIPr•HCl | 1,3-Bis-(2,6-diisopropylphenyl)imidazolidinium chloride |

| | |
|---|---|
| t | triplet |
| TBAT | tetrabutylammonium difluorotriphenylsilicate |
| TBAF | tetrabutylammonium fluoride |
| TBS | *tert*-butyldimethylsilyl |
| TBTU | *O*-(benzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium tetrafluoroborate |
| TES | triethylsilyl |
| Tf | trifluoromethanesulfonyl (trifyl) |
| TFA | trifluoroacetic acid |
| θ | angle |
| THF | tetrahydrofuran |
| TIPS | triisopropylsilyl |
| TLC | thin layer chromatography |
| TMDSO | 1,1,3,3-tetramethyldisiloxane |
| TMEDA | tetramethylethylenediamine |
| TMS | trimethylsilyl |
| TS | transition state |
| $\mu$wave | microwave |
| UV | ultraviolet |

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**7.** **Concise Enantiospecific Total Synthesis of Tubingensin A.** Adam E. Goetz, Amanda L. Silberstein, Michael A. Corsello, and Neil K. Garg. *J. Am. Chem. Soc.* **2014**, *136*, 3036–3039.

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**5.** **Regioselective Reactions of 3,4-Pyridynes Enabled by the Aryne Distortion Model.** Adam E. Goetz and Neil K. Garg. *Nat. Chem.* **2013**, *5*, 54–60.

**4.** **An Efficient Computational Model to Predict the Synthetic Utility of Heterocyclic Arynes.** Adam E. Goetz, Sarah M. Bronner, Jordan D. Cisneros, Joshua M. Melamed, Robert S. Paton, K. N. Houk, and Neil K. Garg. *Angew. Chem. Int. Ed.* **2012**, *51*, 2758–2762.

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**Patents:**

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1. **Ketal Amide Compounds, Methods of Making, and Applications.** Sergey Selifonov, Adam E. Goetz, Marc Scholten, and Ning Zhou. CA 2676892, June 21, 2011.

**Presentations:**

7. **Heterocyclic Arynes: From Computational Design to Synthetic Applications.** Adam E. Goetz, Neil K. Garg. 246th National Meeting of the American Chemical Society, Indianapolis, IN, September 10, 2013. (Oral presentation)

6. **Heterocyclic Arynes: From Computational Design to Synthetic Applications.** Adam E. Goetz, Sarah M. Bronner, Jordan D. Cisneros, Joshua M. Melamed, Robert S. Paton, K. N. Houk, and Neil K. Garg. 43rd National Organic Symposium, Seattle, WA, June 23, 2013. (Poster Presentation)

5. **Heterocyclic Arynes: From Computational Design to Synthetic Applications.** Adam E. Goetz, Sarah M. Bronner, Jordan D. Cisneros, Joshua M. Melamed, Robert S. Paton, K. N. Houk, and Neil K. Garg. Heterocyclic Compounds Gordon Research Conference, Newport, RI, June 17–18, 2013. (Poster Presentation)

4. **Understanding, Predicting, and Modulating Aryne Regioselectivities.** Adam E. Goetz, Sarah M. Bronner, and Neil K. Garg. 243rd National Meeting of the American Chemical Society, San Diego, CA, March 28, 2012. (Poster presentation)

3. **Understanding and Modulating Indolyne Regioselectivities.** Sarah M. Bronner, Adam E. Goetz, Tejas K. Shah, Suzanne V. Nguyen, and Neil K. Garg 43rd Western Regional Meeting of the American Chemical Society, Pasadena, CA, November 11, 2011. (Poster presentation)

2. **Modulating Indolyne Selectivity: Applications of Indolynes to Total Synthesis.** Adam E. Goetz, Sarah M. Bronner, and Neil K. Garg. UCLA Research Showcase, 241st National Meeting of the American Chemical Society, Anaheim, CA, March 28, 2011. (Poster presentation)

1. **Internal Redox via [1,5]-Hydride Shifts: An Alternative to C–H Bond Functionalization.** Adam E. Goetz. UCLA Second Year Talk, April 4, 2011. (Oral presentation)

# CHAPTER ONE

## A Brief Review of Indolynes, Pyridynes, and Synthetic Applications

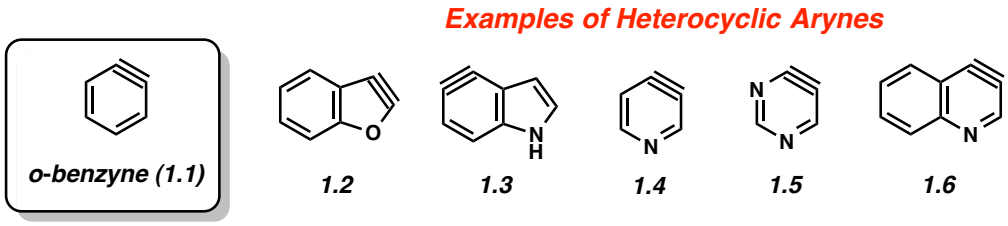
### 1.1 Abstract

Heterocyclic arynes, or hetarynes, have been proposed as intermediates for over 100 years. However, challenges associated with observing these reactive species, as well as developing synthetically useful methods for their generation and trapping, have limited their use. This review focuses on the development of two classes of hetarynes: pyridynes and indolynes. Methods for hetaryne generation, the scope of their reactivity, and their utility in the synthesis of natural products is presented.

### 1.2 Introduction

The importance of heterocyclic compounds in modern chemistry cannot be overstated. Methods for the synthesis of functionalized heterocyclic compounds are highly prized because of their applications in pharmaceutical chemistry, materials chemistry, natural products synthesis, organometallic chemistry, and many other fields. Among the various methods for functionalizing heterocycles, the use of highly reactive heterocyclic arynes, or hetarynes,[1] offers a strategically different approach compared to many conventional methods. Arynes have a rich history, and despite being studied experimentally for over 60 years, many of these species are still treated as scientific curiosities rather than as useful synthetic intermediates. The majority of studies related to arynes focus on all-carbon arynes, such as *ortho*-benzyne (**1.1**),[2] rather than heterocyclic arynes (e.g., **1.2–1.6**, Figure 1.1).

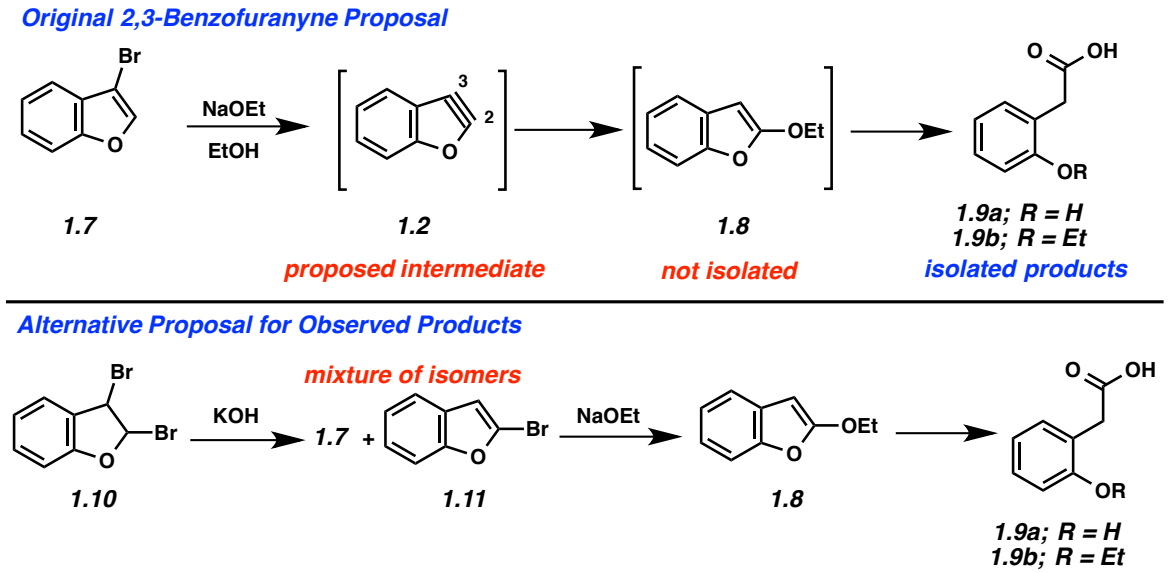
*Figure 1.1. Examples of Arynes*




## 1.3 Early Aryne Reports

The first appearance of any type of aryne in the literature comes from Stoermer and Kahlert's 1902 report invoking the hetaryne 2,3-benzofuranyne (**1.2**) as an intermediate (Figure 1.2).[3] The authors proposed that treatment of 3-bromobenzofuran (**1.7**) with sodium ethoxide led to aryne **1.2**, which was trapped by excess ethoxide to give **1.8**. This proposal, despite its influence on the field of aryne chemistry, has been called into question.[1b] In the original report, compound **1.8** was not isolated, but rather was inferred based on the formation of **1.9a** and **1.9b**, which were thought to arise from ring opening of **1.8**. Alternative proposals suggest that contamination of precursor **1.7** with the isomeric 2-bromobenzofuran (**1.11**) would readily give the proposed intermediate **1.8** through an $S_NAr$ pathway.[1b] Given that bromide **1.7** was prepared through elimination of dibromide **1.10**, the alternate mechanism is certainly plausible.

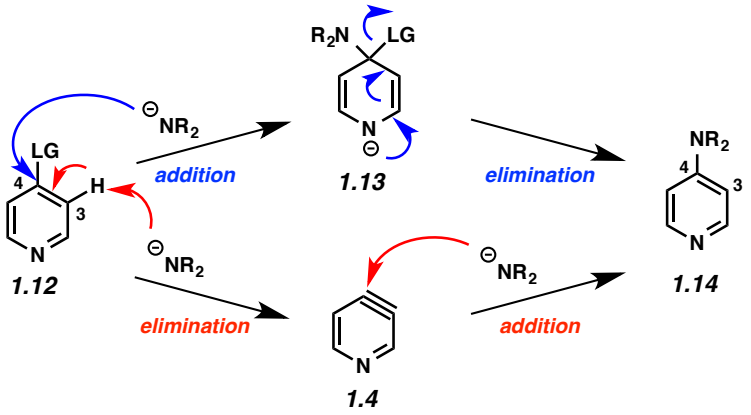
*Figure 1.2. Initial 2,3-Benzofuranyne Proposal*




This example highlights one of the inherent challenges with the study of arynes and hetarynes, specifically, the fact that they cannot be readily observed. Typically, the strongest evidence for the presence of an aryne is the identity of the products obtained, however, even this can lead to incorrect assumptions. As shown in Figure 1.3, it is possible to arrive at so-called "aryne products" through pathways that do not involve aryne formation. This possibility is especially relevant when strong bases, which are also nucleophilic, are employed to generate arynes through dehydrohalogenation, as is demonstrated using pyridine **1.12**. In what is termed the addition/elimination pathway ($A_E$) pathway, nucleophilic attack by the amide on the electrophilic C4 position generates stabilized adduct **1.13**, which then undergoes ejection of the leaving group to give product **1.14**. This is in contrast to the desired elimination/addition pathway ($E_A$). In this route, pyridine **1.12** can undergo deprotonation at C3 followed by elimination of the leaving group to generate 3,4-pyridyne (**1.4**). Attack on this species by a nucleophile at C4 then provides product **1.14**. Additionally, it is also possible that both aryne and non-aryne mechanisms are operating simultaneously in a given reaction. Since many of the early

aryne studies relied on this method of aryne generation, not all claims of aryne generation are likely accurate, and care must be taken in interpretation of results. Previous reviews have sought to identify certain aryne precursors that are prone to favor one mechanism over the other.[1]

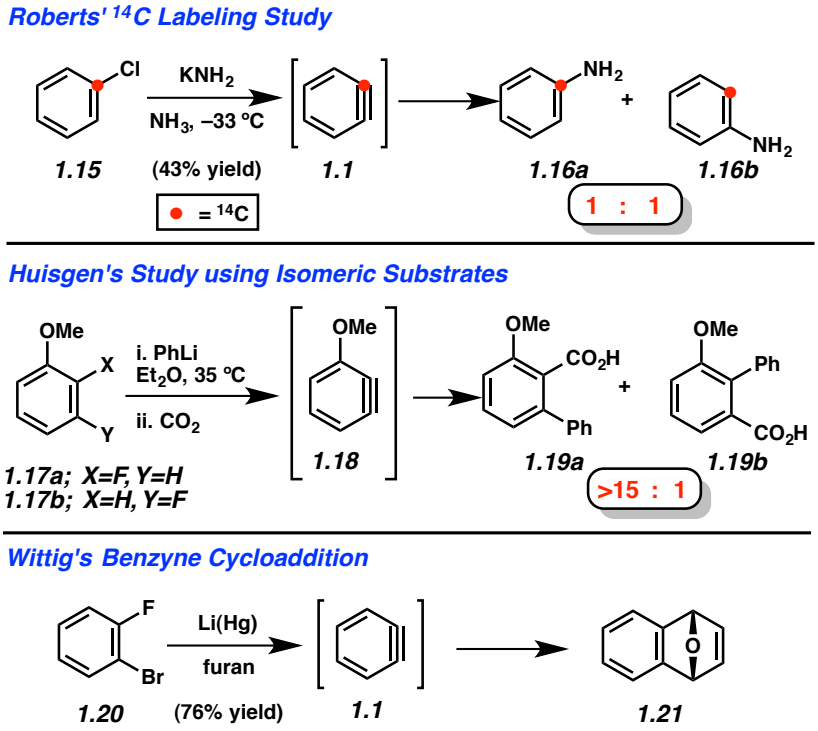
*Figure 1.3. Competing Aryne and Non-Aryne Mechanisms*




Given the early uncertainty over the generation of arynes such as **1.2**, solid evidence for the intermediacy of these highly reactive species was not obtained until over 50 years after the initial claim. Following several reports of unexplained "rearrangements" in reactions of halobenzenes with amide bases,[4] Roberts demonstrated that treatment of $^{14}$C-labeled chlorobenzene (**1.15**) with potassium amide gave an equimolar mixture of products **1.16a** and **1.16b** (Figure 1.4).[5] This was rationalized by the presence of the symmetrical "benzyne" (**1.1**) intermediate. Shortly thereafter, Huisgen demonstrated that treating either 2- or 3-fluoroanisole (**1.17a** or **1.17b**) with phenyllithium, followed by $CO_2$ led to the isolation of compounds **1.19a** and **1.19b** with a strong preference for **1.19a** (Figure 1.4).[6] Similar to Roberts' reasoning, Huisgen noted that since the two isomeric starting materials gave the same major product with similar ratios, a common intermediate, **1.18**, was likely involved. He also noted that the π-system of the proposed intermediate **1.18** would be orthogonal to the aromatic system. Finally, Wittig demonstrated that treatment of dihalobenzene **1.20** with lithium amalgam in furan led to the

isolation of cycloadduct **1.21**, which further suggested the intermediacy of benzyne (**1.1**).[7] These three studies represent the first solid evidence for the intermediacy of any aryne and inspired the development of much of the hetaryne chemistry reported since.

*Figure 1.4. Early ortho-Benzyne Studies*




## 1.4 Hetaryne Experimental Results

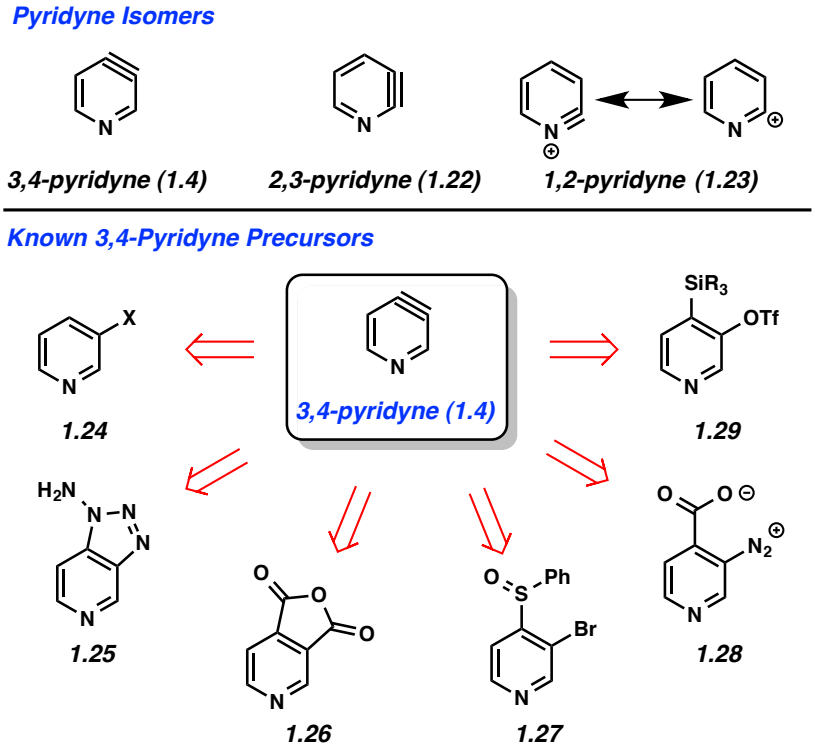
Throughout the years, many heterocyclic arynes have been proposed as intermediates. As discussed above, it is likely that some of the reported reactions do not actually involve the reported aryne as an intermediate.[1] Additionally, aryne reactions frequently give low yields of products, likely due to a combination of the high instability of these intermediates, as well as the harsh conditions that have been traditionally used to generate these species. As a result, the following sections will focus on the aryne derivatives of pyridines and indoles, two of the most well-studied classes of hetarynes. Both of these families of hetarynes have undergone an

evolution from their initial discovery to their current uses as versatile intermediates for organic synthesis. Emphasis will be placed on developments that have sought to address key challenges related to the utility of these species, as well as their applications to the total synthesis of natural products.

### 1.4.1 Pyridynes

Considering all classes of heterocyclic arynes, pyridynes have been the most intensely studied over the past 60 years. Of the three pyridyne isomers shown in Figure 1.5, 3,4-pyridyne (**1.4**) is suggested computationally[8] to be the most stable, followed by 2,3-pyridyne (**1.22**). Attempts to study 1,2-pyridyne (**1.23**, alternatively represented as the 2-pyridyl cation) in solution have been unsuccessful,[9] however, studies in the gas phase have shown evidence of this species.[10] All of these isomers have long been recognized as promising intermediates for the preparation of substituted pyridines, and collectively have been the target of much synthetic effort.

*Figure 1.5. Pyridyne Isomers and Methods of Generation*

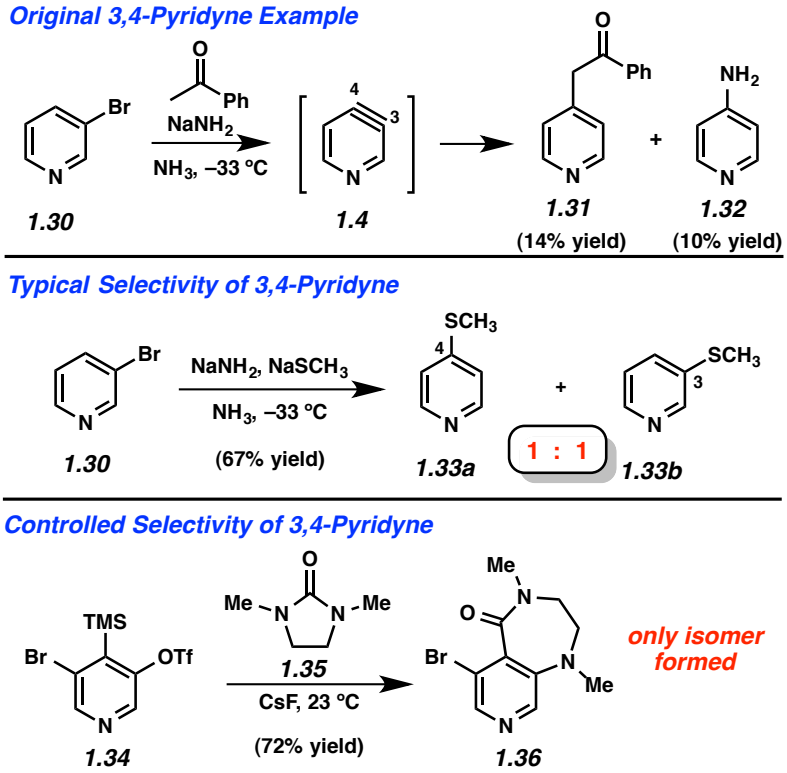



The 3,4-pyridyne can be used to illustrate the wide range of methods typically used to generate arynes (Figure 1.5). Most of the methods are derived from analogous precursors to *o*-benzyne, illustrating that the same strategies could be applicable for the generation of other hetarynes. For example, 3,4-pyridyne (**1.4**) is accessible from 3-halopyridines upon treatment with strong base (**1.24→1.4**),[11] oxidation of aminotriazoles with $Pb(OAc)_4$ (**1.25→1.4**),[12] photolysis of anhydrides (**1.26→1.4**),[13] magnesium-sulfur exchange followed by elimination (**1.27→1.4**),[14] thermolysis of diazonium carboxylates (**1.28→1.4**),[15] or fluoride-induced elimination of *ortho*-trialkylsilyl pyridyl triflates (**1.29→1.4**).[16] Of note, this latter method, which was first pioneered by Kobayashi for *o*-benzyne generation,[17] has demonstrated the most functional group tolerance in terms of both the trapping agents that can be utilized and the substituents present on the precursors themselves. Although there is always the possibility that some precursors may react through non-aryne mechanisms, the isolation of pyridyne **1.4** in an $N_2$

matrix and subsequent characterization by IR spectroscopy[18] demonstrated that pyridyne **1.4** is a valid intermediate.

The 3,4-pyridyne has been demonstrated to be useful for the preparation of 3- and 4-substituted pyridines as well as 3,4-disubstituted derivatives. Leake and Levine reported the first generation of 3,4-pyridyne utilizing 3-bromopyridine (**1.30**), which upon treatment with acetophenone and sodium amide in liquid ammonia gave low yields of 4-aminopyridine (**1.32**) and adduct **1.31**, which arises from attack by the enolate of acetophenone (Figure 1.6). Many early studies that relied on dehydrohalogenation for pyridyne generation were limited in the scope of the trapping agent employed. In order to minimize the byproducts resulting from attack by the base used for pyridyne generation, strongly nucleophilic groups such as alkoxides, amide salts, and thiolates were often employed. In an example of the latter reported by Zoltewicz, treatment of bromopyridine **1.30** with sodium methanethiolate and sodium amide led to an equimolar mixture of adducts **1.33a** and **1.33b** (Figure 1.6).[19] This lack of regioselectivity is characteristic of pyridyne **1.4** and, as will be discussed in Section 1.5, has limited the synthetic utility of this intermediate. Recent studies have focused on methods for controlling this selectivity,[16,20] and include a report by our laboratory in 2013,[21] which systematically explored the use of substituents to control selectivity. For example, treating 5-bromo-3,4-pyridyne precursor **1.34** with cesium fluoride (CsF) in the presence of cyclic urea **1.35** delivered compound **1.36** as a single regioisomer (Figure 1.6). Related studies by Saito and coworkers also demonstrated the ability to achieve high regioselectivities in a variety of C–N bond-insertion reactions.[22] Further efforts towards controlling the selectivity of reactions of 3,4-pyridyne derivatives are reported in Chapter 5 of this dissertation, in addition to a discussion of the aryne distortion model in the context of pyridynes.

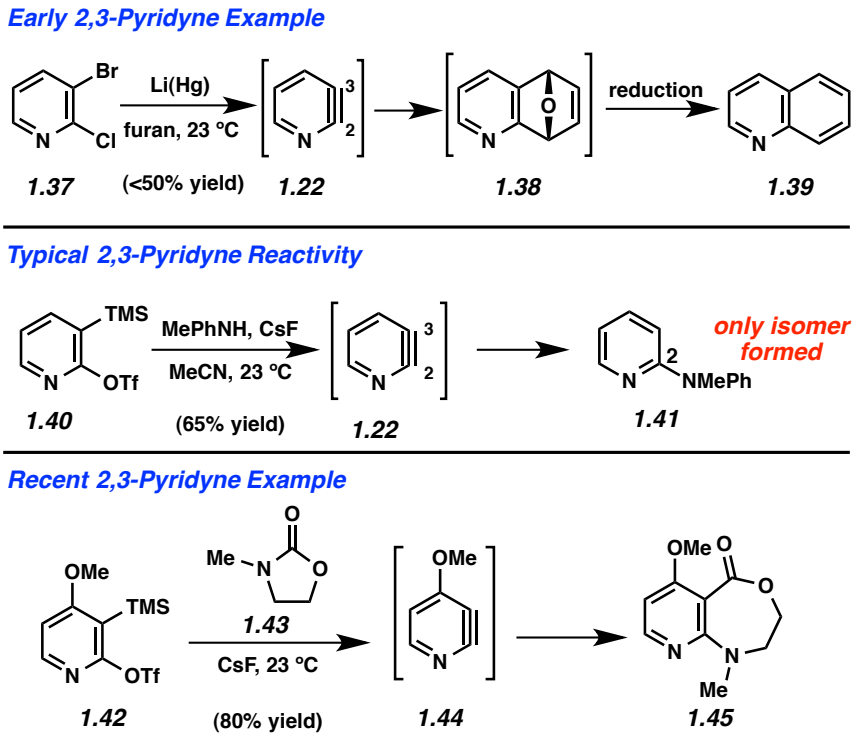
*Figure 1.6. Examples of 3,4-Pyridyne Studies*




Early attempts to generate the 2,3-pyridyne (**1.22**) were more ambiguous than those targeting the 3,4-pyridyne. Dehydrohalogenation cannot be easily utilized, as 3-halopyridine precursors (i.e. **1.30**, Figure 1.6) have been shown to lead to formation of the 3,4-pyridyne (**1.4**) selectively,[11] and the use of 2-halopyridines makes it difficult to determine whether products arise through an aryne pathway or through an $S_NAr$ pathway. However, in 1962, Martens and den Hertog demonstrated that treatment of dihalide **1.37** with lithium amalgam in the presence of furan led to the isolation of quinoline (**1.39**) in moderate yield (Figure 1.7).[23] The formation of this product was rationalized by a pathway involving 2,3-pyridyne (**1.22**) formation, cycloaddition to give **1.38**, followed by reduction. The development of silyltriflate precursor **1.40** has allowed for a reliable means of generating the 2,3-pyridyne under mild conditions[24] and can be used to demonstrate the high regioselectivity that is typically observed in these reactions

(Figure 1.7). Treatment of precursor **1.40** with CsF leads to aryne **1.22**, which undergoes attack by *N*-Me-aniline to exclusively give the 2-amino product **1.41**.[25] The high selectivity typically obviates the need to separate isomeric products, and can be used to form 2,3-disubstituted pyridines. For example, **1.45** is obtained through a formal C–N bond-insertion reaction between pyridyne **1.44** into carbamate **1.43** (Figure 1.7).[22] A further discussion of the contrasting selectivity of the 2,3- and 3,4-pyridyne isomers, as well as related polyazine systems is reported in Chapter 4 of this dissertation.

*Figure 1.7. Examples of 2,3-Pyridyne Studies*

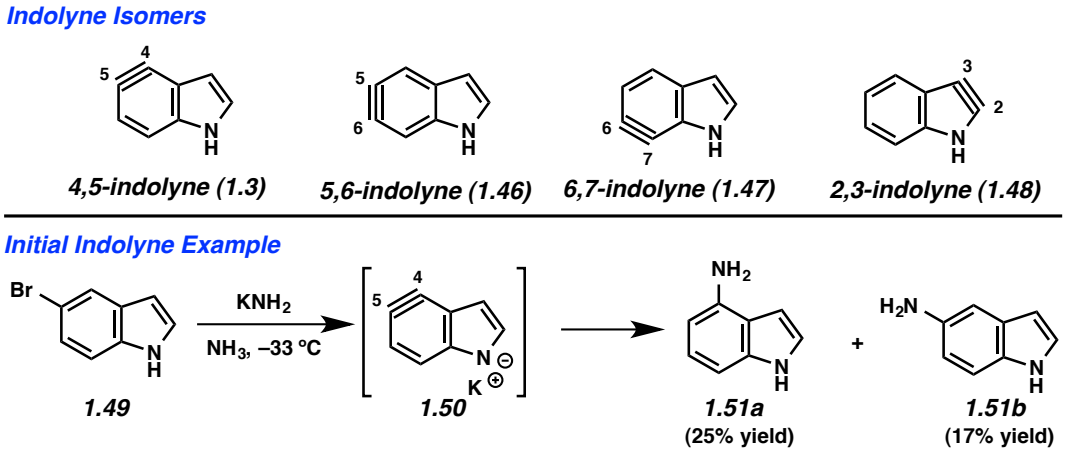



Although the focus of this section has been limited to the chemistry of pyridynes, the corresponding 2,3- and 3,4-pyridyne-*N*-oxides have also been reported.[26] Additionally, related quinolynes (i.e. **1.6**, Figure 1.1) have been studied and display similar reactivity and selectivity as pyridynes.[22,25,27]

### 1.4.2 Indolynes

Given the importance of the indole heterocycle, attempts to utilize the corresponding indolyne to prepare substituted indole derivatives has received significant attention. Of the four possible indolyne isomers, three contain the reactive triple bond within the benzenoid ring (**1.3**, **1.46**, and **1.47**, Figure 1.8), whereas the 2,3-indolyne (**1.48**) contains the triple bond in the pyrrole ring. The first report concerning indolynes came from Julia and coworkers, who in 1967 showed that treatment of 5-bromoindole (**1.49**) with potassium amide led to a mixture of 4- and 5-aminoindole products (**1.51a** and **1.51b**), likely arising through indolyne intermediate **1.50**.[28] Despite the promise demonstrated by this early work,[29] indolynes saw little attention over the subsequent 40 years, with one exception being the work of Iwao and coworkers in the synthesis of a variety of Makaluvamine natural products (see Section 1.5).[30]

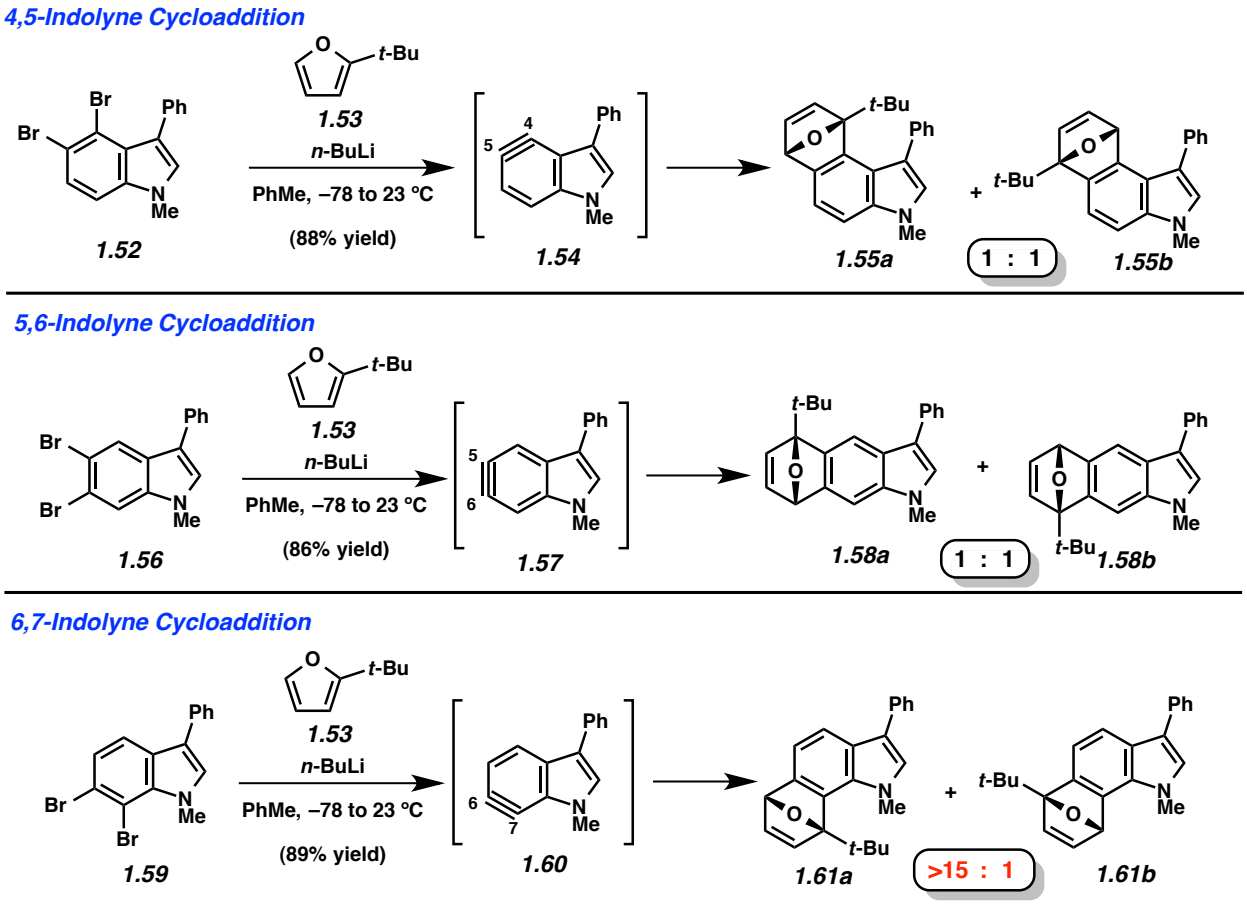
*Figure 1.8. Indolyne Isomers and Original Example*




In 2007, Buszek and coworkers reported the generation of C3-substituted 4,5-, 5,6-, and 6,7-indolynes (**1.54**, **1.57**, and **1.60**, respectively) from the corresponding dibromide compounds **1.52**, **1.56**, and **1.59**, respectively (Figure 1.9).[31] The authors focused on Diels–Alder reactions of the indolynes and observed an interesting trend in terms of regioselectivity when unsymmetrical dienes were used. In the case of 2-*tert*-butylfuran (**1.53**), the authors reported that 4,5-indolyne

**1.54** and 5,6-indolyne **1.57** gave equimolar mixtures of products **1.55a–b** and **1.58a–b**, respectively. Conversely, 6,7-indolyne **1.60** showed high selectivity for the formation of product **1.61a**, which would seemingly be the disfavored product based on steric arguments.[31b,g] Subsequent computational studies by Cramer suggested that the high electrophilicity at C6 of indolyne **1.60** led to initial attack at that position despite steric interactions.[31d]

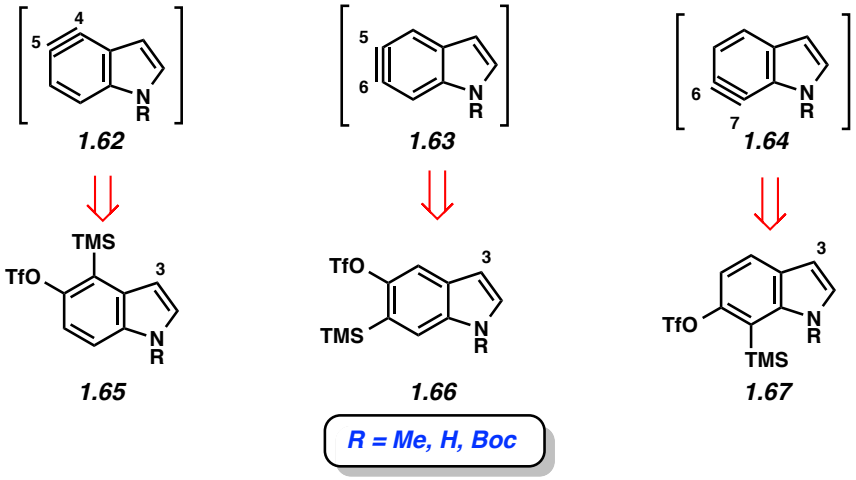
*Figure 1.9. Buszek's Indolyne Cycloaddition Studies*




Alternatively, 4,5-, 5,6-, and 6,7-indolynes **1.62**–**1.64** were shown by our laboratory to be accessible from silyltriflate precursors **1.65–1.67**, respectively (Figure 1.10).[32] These precursors were accessible as *N*-Me, *N*-Boc, or *N*-H variants for each indolyne isomer and also left C3 available for later functionalization.[32c] Indolyne formation could be achieved upon treatment of the indolyne precursors with fluoride sources such as TBAF or CsF. Of note, Buszek has also

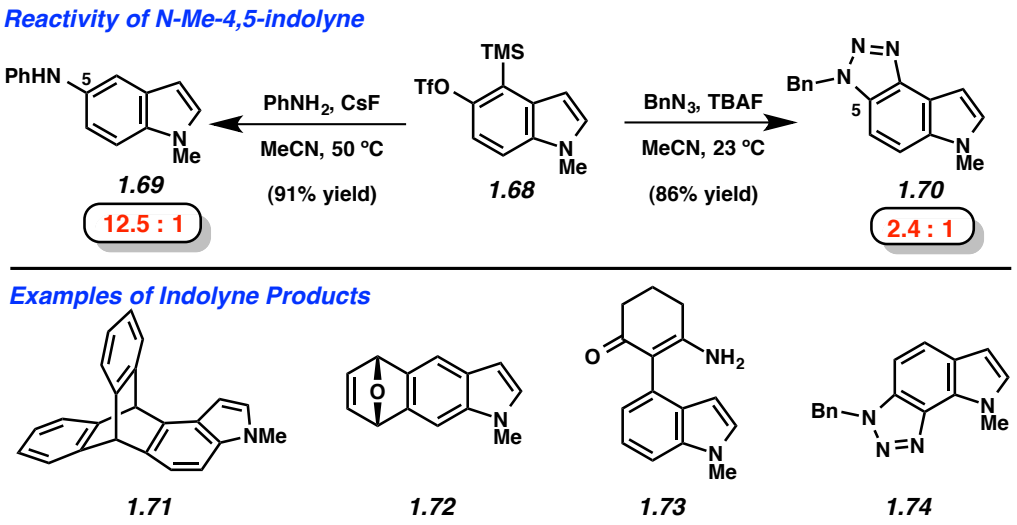
reported an alternative strategy for the preparation of similar silyltriflate precursors that contain a phenyl substituent at C3.[31b]

*Figure 1.10. Silyltriflates as Indolyne Precursors*




The mild fluoride-based conditions for indolyne generation allowed for the scope of trapping agents to be significantly expanded compared to prior indolyne studies. As seen in Figure 1.11, treatment of 4,5-indolyne precursor **1.68** with CsF in the presence of aniline led to the formation of C5 adduct **1.69** preferentially over the corresponding formation of the C4-substituted product in a ratio of 12.5:1. Trapping of the same indolyne with benzyl azide demonstrated the compatibility of cycloaddition reactions and provided triazole product **1.70** and its regioisomer in a 2.4:1 ratio. Further demonstrations of the scope of indolyne reactions can be seen in products **1.71–1.74**. The regioselectivity observed in the formation of products **1.69**, **1.70**, **1.73**, and **1.74** was explained using the Aryne Distortion Model.[32b,c] Generally speaking, both the 4,5- and 5,6-indolynes tend to preferentially give products resulting from initial attack at C5, while the 6,7-indolyne typically gives products resulting from attack at C6. A further examination of the Aryne Distortion Model and methods to influence indolyne regioselectivities is presented in Chapters 2 and 3 of this dissertation.

*Figure 1.11. Sample Reactivity of Indolyne Intermediates*

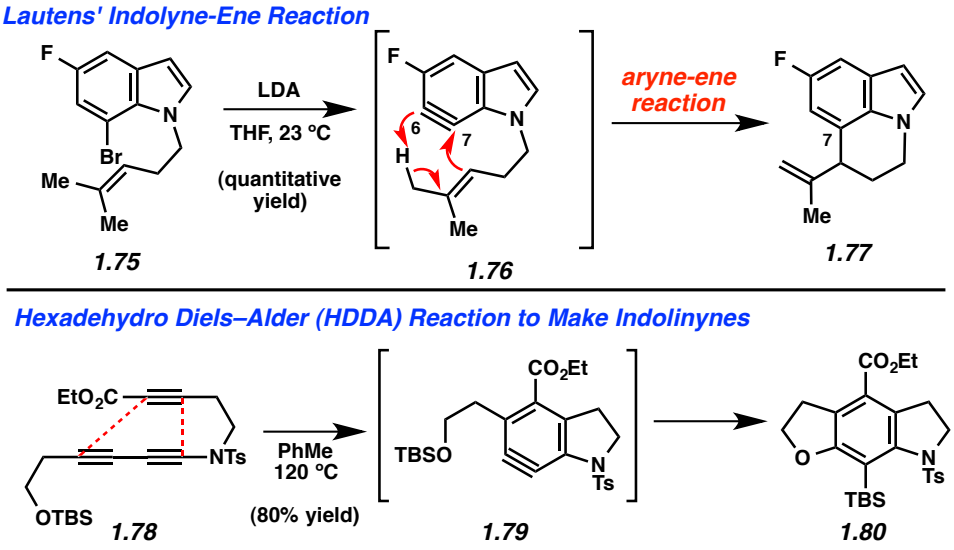



Recent reports of indolynes and related species have further demonstrated the utility of these hetarynes for the assembly of complex indole derivatives. Lautens and coworkers reported that treatment of bromoindole **1.75** with LDA led to the generation of 6,7-indolyne **1.76** (Figure 1.12). This species was found to undergo an intramolecular ene reaction involving the homoprenyl group on the indole nitrogen to afford tricyclic product **1.77**.[33] Interestingly, the observed regioselectivity is due to the fact that the homoprenyl group is tethered to the indole nitrogen. This represents a rare example of a 6,7-indolyne reaction that is selective for giving products resulting from attack at C7.

The Hoye group has recently reported a novel method for generation of benzynes in which a molecule containing three alkynes undergoes a "Hexadehydro Diels–Alder (HDDA) Reaction" to provide the benzyne intermediate.[34] The authors demonstrated that molecules such as tri-yne **1.78** could be used to form indolinyne **1.79**, which further reacted to furnish product **1.80** (Figure 1.12).[34a] Of note, this reaction can be used to prepare indoline systems in which the benzenoid ring is fully substituted. Almost simultaneously, Lee and coworkers have reported a

nearly identical strategy for the generation of indolinynes and explored a variety of reactions of these species.[35]

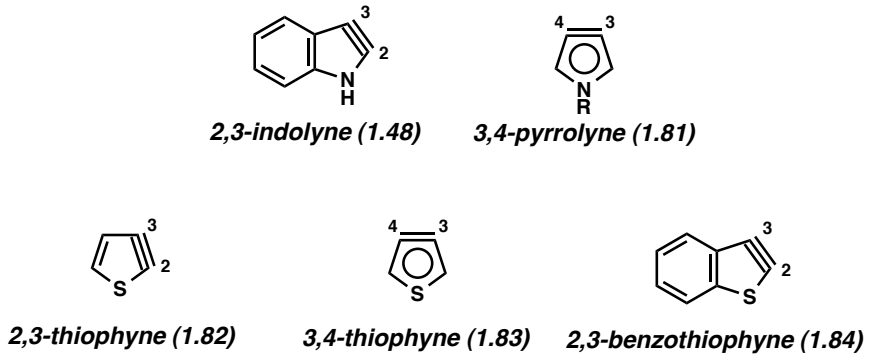
*Figure 1.12. Recent Examples of Indolyne Reactivity*




In contrast to the benzenoid indolyne isomers discussed above, the 2,3-indolyne (**1.48**, Figure 1.13) likely experiences extreme strain due to the presence of the triple bond within the five-membered ring. As a result, **1.48** has not yet been unambiguously generated. Gribble and Conway have reported an extensive study of unsuccessful attempts to generate **1.48**[36] and, while there are claims of this intermediate being involved in reactions,[37] unambiguous proof has yet to be offered. In fact, there have been many attempts over the years to generate various 5-membered hetarynes, however, most claims are lacking in conclusive proof.[1b] In addition to the 2,3-indolyne (**1.48**), attempts to generate the 3,4-pyrrolyne (**1.81**) have been made, resulting only in < 5% yields of any products suggestive of an aryne mechanism.[38] The strongest case for formation of any of the 5-membered hetarynes can be made for thiophynes **1.82**–**1.84**, especially the 3,4-thiophyne (**1.83**).[39] It was suggested that the longer C–S bond would help relieve some of the strain present in these molecules compared to other 5-membered hetarynes. Unfortunately,

isolated yields of cycloadducts suggestive of **1.83** are ≤ 30%. Thus, although these species may be accessible, their synthetic utility is currently limited.

*Figure 1.13. 2,3-Indolyne and other 5-Membered Hetarynes*



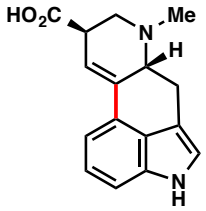

***2,3-indolyne (1.48)*** ***3,4-pyrrolyne (1.81)***

***2,3-thiophyne (1.82)*** ***3,4-thiophyne (1.83)*** ***2,3-benzothiophyne (1.84)***

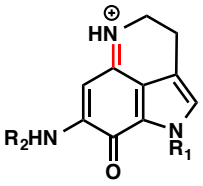
**1.5 Use of Hetarynes in Total Synthesis**

Despite early limitations, hetarynes have been demonstrated to be useful for total synthesis as seen from the examples highlighted in Figure 1.14. Indolynes (or related species) have found use for the synthesis of C4-substituted indole derivatives[40] including lysergic acid (**1.85**),[29c] various makaluvamines (**1.86**),[30] and members of the welwitindolinone (**1.87**)[41] and indolactam (**1.88**)[42] families. All of these syntheses utilize the electrophilic nature of the indolyne to functionalize C4 of the indole ring, a position that is often difficult to access. Additionally, the natural product tubingensin A (**1.89**) was prepared by our laboratory using a related carbazolyne intermediate.[43] A complete discussion of the synthesis of **1.89** is reported in Chapter 6 of this dissertation. Finally, indolynes have been utilized as cycloaddition partners for the synthesis of *cis*-trikentrin A (**1.90**) and herbindole B (**1.91**).[31c,e] Pyridynes have found use mainly as cycloaddition partners for the synthesis of molecules such as ellipticine (**1.92**)[20b,d,44] and macrostomine (**1.93**),[45] but also for intramolecular arylation reactions to build perlolidine (**1.94**)[46] and eupolauramine (**1.95**).[47]

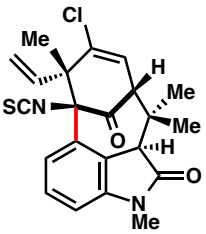
*Figure 1.14. Natural Products Synthesized using Indolynes and Pyridynes*



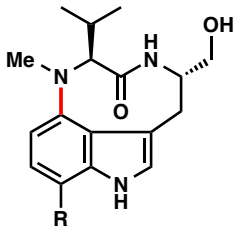

***lysergic acid (1.85)***
***(Julia, 1969)***



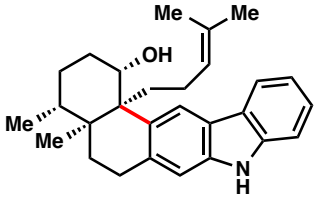

***makaluvamines (1.86)***
***(Iwao, 1998)***



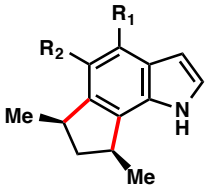

***N-methylwelwitindolinone C isothiocyanate (1.87)***
***(Garg, 2011)***



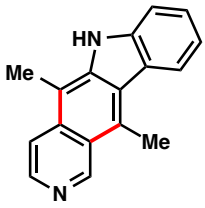

***indolactam alkaloids (1.88)***
***(Garg, 2011)***
***(Garg, 2014)***



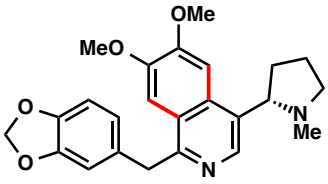

***tubingensin A (1.89)***
***(Garg, 2014)***



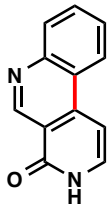

***(±)-cis-trikentrin A (1.90)***
***(±)-herbindole B (1.91)***
***(Buszek, 2009)***



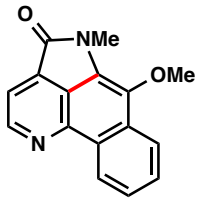

***ellipticine (1.92)***
***(Moody, 1984; Gribble, 1984; Sha, 1992; Guitian, 1998)***




***(S)-macrostomine (1.93)***
***(Comins, 2010)***




***perlolidine (1.94)***
***(Singh, 1976)***

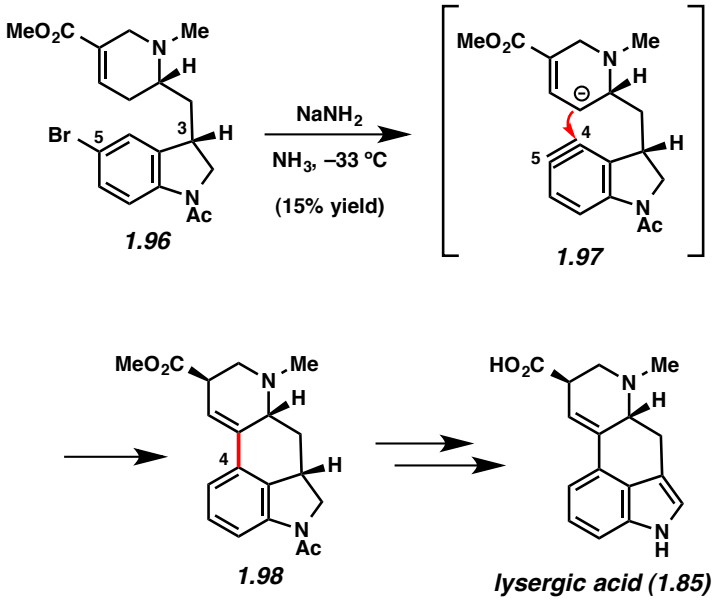



***eupolauramine (1.95)***
***(Couture, 2001)***

Of these examples, the first use of a hetaryne in total synthesis was reported by Julia and coworkers in their formal synthesis of lysergic acid (**1.85**) in 1969 (Scheme 1.1).[29c] The authors found that treatment of 5-bromoindoline **1.96** with $NaNH_2$ led to cyclized product **1.98** in a modest 15% yield. Compound **1.98** presumably arises from attack of vinylogous enolate **1.97** onto the C4 position of the indolinyne, where the regiochemistry is controlled by geometrical constraints. Of note, the authors reported that the use of C3-*epi*-**1.96** did not provide any of the corresponding product when reacted under the same conditions. Tetracycle **1.98** could be

elaborated to the natural product following the procedure reported by Woodward and coworkers.[48] Despite the low yield in the key aryne step, this synthesis served as inspiration for utilizing hetarynes to build complex heterocyclic substrates.

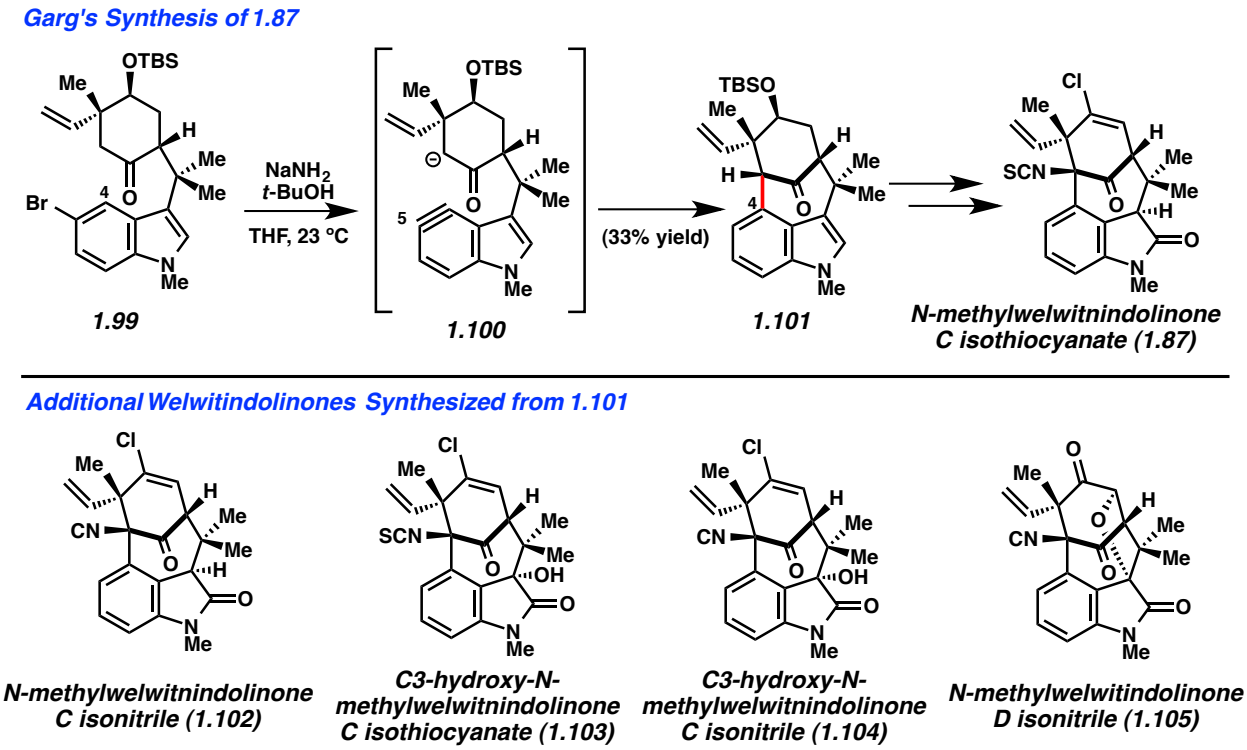
*Scheme 1.1. Julia's Formal Synthesis of Lysergic Acid*




In a more recent example, our laboratory reported what is arguably the most complex aryne cyclization to date as part of the synthesis of *N*-methylwelwitindolinone C isothiocyanate (**1.87**), which also utilizes an enolate/aryne cyclization to forge a key C–C bond (Figure 1.15).[41a] Exposure of 5-bromoindole **1.99** to the complex base conditions first developed by Caubere[49] led to generation of intermediate **1.100**, which contains both the enolate and 4,5-indolyne. Cyclization led to *C*-arylated product **1.101** in 33% percent yield as well as the corresponding *O*-arylated product in 13% yield. Product **1.101** possesses the necessary tetracyclic core, including the congested linkage at C4 of the indole ring. This intermediate was successfully converted to the natural product.[41a] The indolyne cyclization was subsequently utilized for the synthesis of a number of related family members including isonitrile derivative **1.102** and the C3-hydroxy derivatives **1.103** and **1.104**.[41b] Additionally, indolyne product **1.101** has been converted to

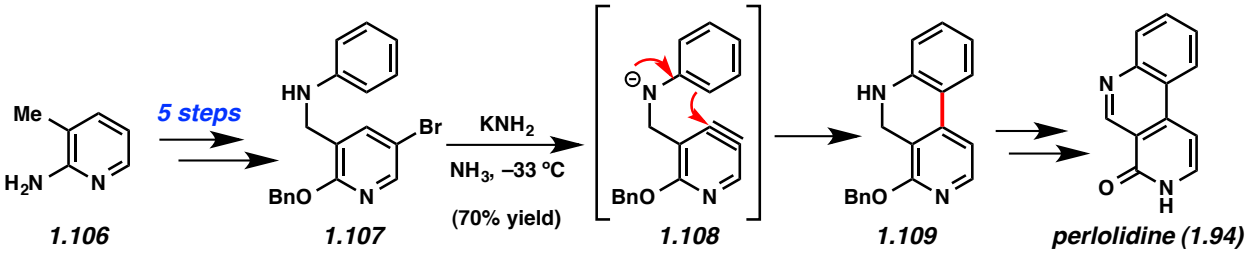
another family member, *N*-methylwelwitindolinone D isonitrile (**1.105**), which contains an additional ethereal bridge.[41c]

*Figure 1.15. Synthesis of Welwitindolinones*




Pyridynes also have a rich history in total synthesis dating back to the seminal report by Singh and coworkers in 1976 on the synthesis of the grass alkaloid perlolidine (**1.94**, Scheme 1.2).[46] Starting from readily available 2-amino-3-methylpyridine (**1.106**), the authors were able to quickly access compound **1.107**. Exposure of this compound to standard aryne-forming conditions resulted in formation of the biaryl linkage to provide **1.109** in good yield. It is proposed that the aniline ring in compound **1.108** undergoes a Friedel–Crafts type intramolecular arylation reaction with the highly reactive tethered pyridyne. Compound **1.109** was successfully elaborated to perlolidine (**1.94**) by oxidation, followed by benzyl ether cleavage.

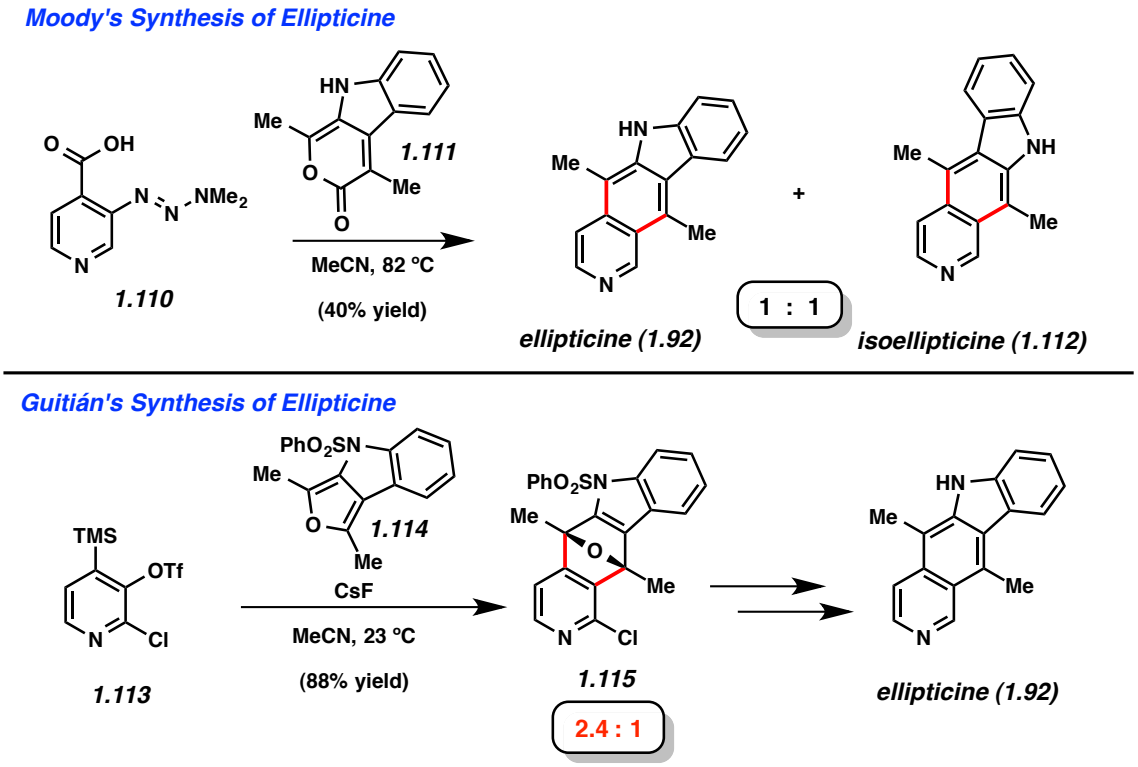
*Scheme 1.2. Singh's Synthesis of Perlolidine*




The natural product ellipticine (**1.92**, Figure 1.14) has been targeted by multiple groups using pyridyne-based approaches, however, this compound has not been without its challenges. Moody reported the synthesis of ellipticine using the strategy shown in Figure 1.16.[44a,c] 3,4-pyridyne precursor **1.110** (which decomposes to diazonium carboxylate **1.28**, Figure 1.5) was reacted with pyrone **1.111**, which in turn was readily prepared from indole in only two steps. This gave ellipticine (**1.92**) and isoellipticine (**1.112**) each in 20% yield. Despite the conciseness of this synthesis, the formation of the two isomeric products in equimolar amounts was undesirable. This result was not entirely surprising given the poor regioselectivity often seen in 3,4-pyridyne reactions as discussed in Section 1.4.1. Further efforts by Gribble[44b] and Sha[44d] utilizing alternative dienes or pyridyne precursors showed essentially no improvement in the selectivity of the key cycloaddition step.

Alternatively, Guitián examined the effect of employing substituted 3,4-pyridynes as the dienophile with a variety of different dienes (Figure 1.16).[20b,d] Although other substituted pyridynes showed variable levels of selectivity depending on the diene present, when 2-chloro-3,4-pyridyne precursor **1.113** was reacted with CsF and furan **1.114** a 2.4:1 mixture of cycloadducts was obtained favoring the desired regioisomer **1.115**. Compound **1.115** could then be elaborated to ellipticine (**1.92**). Further efforts to influence the regioselectivity of reactions of 3,4-pyridynes are discussed in Chapter 5 of this dissertation.

*Figure 1.16. Syntheses of Ellipticine*




## 1.6 Conclusion

Over the last 60 years, the chemistry of heterocyclic arynes has lagged behind that of their all-carbon counterparts such as *o*-benzyne. Although many of the early claims were questionable regarding the generation of these reactive intermediates, more recent studies have demonstrated that these species are accessible and offer a unique alternative for the synthesis of substituted heterocycles. The increasing popularity of easy-to-use precursors, such as *o*-trimethylsilyl triflates, allow for the generation of hetarynes under mild conditions that allow for a significantly expanded scope of trapping agents to be employed. In fact, some heterocyclic aryne silyltriflate precursors are now commercially available. The ability to incorporate hetarynes into the synthesis of complex molecules demonstrates that their high reactivity can be exploited for the construction of motifs that would otherwise be difficult to

access. It is envisioned that the development of even more exotic heterocyclic arynes and trapping agents will be seen in the future, along with more challenging applications in the synthesis of drugs and natural products.

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# CHAPTER TWO

## Indolyne Experimental and Computational Studies: Synthetic Applications and Origins of Selectivities of Nucleophilic Additions

Im, G-Y. J.; Bronner, S. M.; Goetz, A. E.; Paton, R. S.; Cheong, P. H.-Y.; Houk, K. N.; Garg, N. K. *J. Am. Chem. Soc.* **2010**, *132*, 17933–17944.

### 2.1 Abstract

Efficient syntheses of 4,5-, 5,6-, and 6,7-indolyne precursors beginning from commercially available hydroxyindole derivatives are reported. The synthetic routes are versatile and allow access to indolyne precursors that remain unsubstituted on the pyrrole ring. Indolynes can be generated under mild fluoride-mediated conditions, trapped by a variety of nucleophilic reagents, and used to access a number of novel substituted indoles. Nucleophilic addition reactions to indolynes proceed with varying degrees of regioselectivity; distortion energies control regioselectivity and provide a simple model to predict the regioselectivity in the nucleophilic additions to indolynes and other unsymmetrical arynes. This model has led to the design of a substituted 4,5-indolyne that exhibits enhanced nucleophilic regioselectivity.

### 2.2 Introduction

The indole heterocycle (**2.1**, Figure 2.1) is observed in an astonishing number of natural products and medicinal agents.[1,2] More than 10,000 biologically active indole derivatives have been discovered to date, of which over two hundred are currently marketed as pharmaceuticals or are undergoing clinical trials.[3] These include the common chemotherapeutics vincristine, vinorelbine, and vinblastine.[4] Despite the development of an impressive array of strategies to

synthesize C2- and C3-functionalized indoles,[5] methods to access benzenoid-substituted indoles remain limited.[1]

Our approach to benzenoid-substituted indoles contrasts with the usual paradigm of indole reactivity. The indole heterocycle is typically exploited for its nucleophilic character (**2.1→2.2**, Figure 2.1);[6] however, methods for rendering indoles susceptible to attack by nucleophiles are rare (**2.1→2.3**).[7] We envisioned that aryne derivatives of indoles, or "indolynes" (e.g., **2.4**–**2.6**), could serve as electrophilic indole surrogates. This umpolung of the indole reactivity would not only be conceptually interesting, but would also provide unconventional strategies to access polysubstituted indoles. Such motifs are often considered medicinally 'privileged' and are also observed in countless natural products, such as the complex bioactive alkaloids **2.7**–**2.18** (Figure 2.2).

*Figure 2.1. Typical Indole Reactivity and Indolyne Isomers*

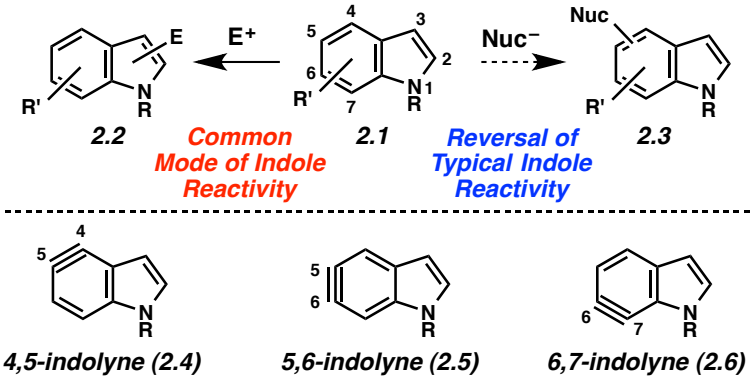
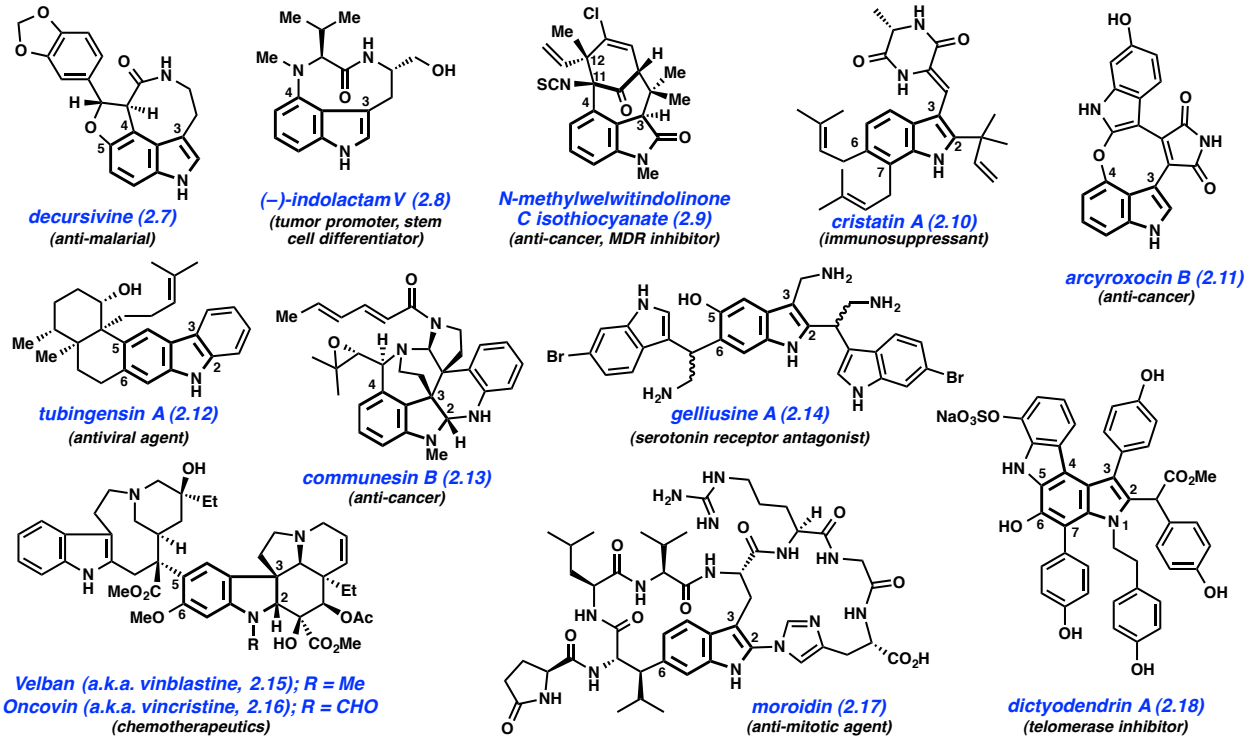


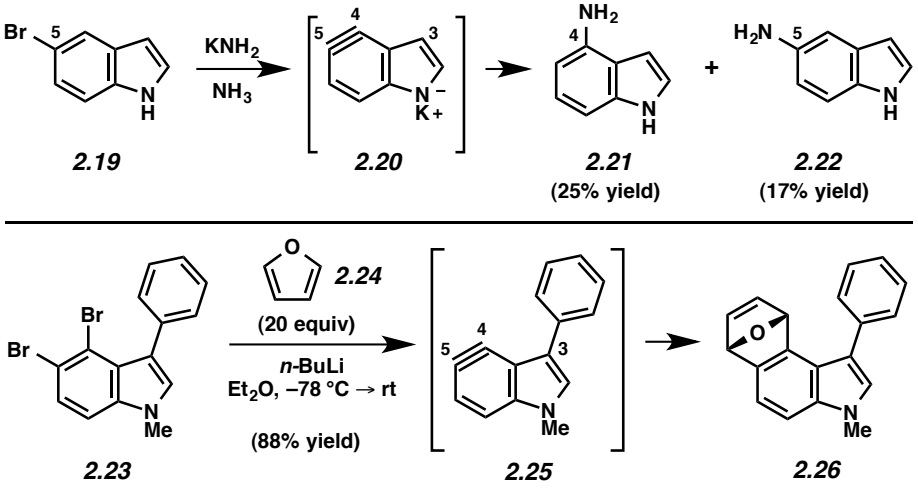
*Figure 2.2. Indole-Containing Natural Products*




Whereas arynes have been studied extensively over the past century,[8,9] indole derivatives of arynes have received less attention. Indolynes were first reported in the 1960's by Julia and co-workers.[10] In a key experiment, it was found that C3-unsubstituted 4,5-indolyne **2.20** could be generated from 5-bromoindole (**2.19**) and $KNH_2$ in ammonia to afford a complex mixture of products, which upon purification, furnished 4- and 5-aminoindole products **2.21** and **2.22** (Figure 2.3). The field of indolyne chemistry lay dormant for over four decades,[11] until our groups and Buszek's laboratory entered the area. In 2007, Buszek's laboratory demonstrated that C3-substituted indolynes could be generated from dihaloindoles in the presence of butyllithium reagents.[12a] The presumed indolyne intermediates were trapped with furan to afford Diels–Alder products (e.g., **2.23**+**2.24**→**2.26**). Further studies have been reported by Buszek,[12] which include indolyne Diels–Alder reactions of substituted furans and cyclopentadiene, the total synthesis of

trikentrin A and herbindole A using an indolyne Diels–Alder reaction, and access to *N*- and C3-substituted indolynes from silyltriflate precursors for use in the furan Diels–Alder reaction.

*Figure 2.3. Previous Indolyne Studies*



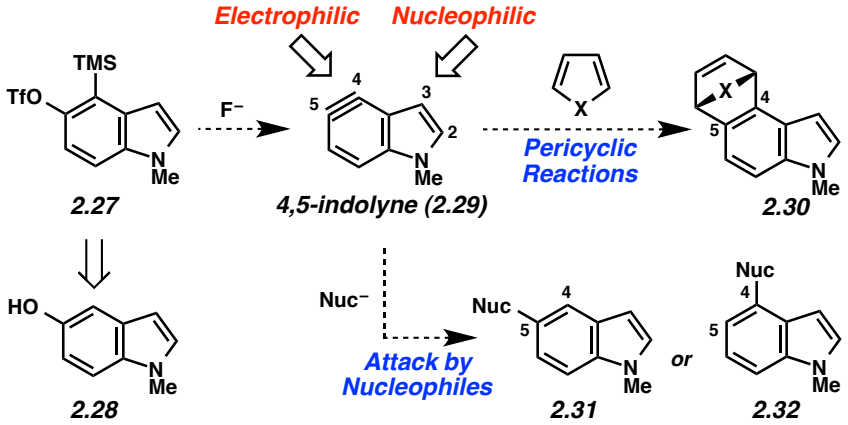

In this chapter,[13] we report efficient syntheses of 4,5-, 5,6-, and 6,7-indolyne precursors beginning from commercially available hydroxyindole derivatives. The synthetic routes are versatile, and for the first time, allow access to indolynes that remain unsubstituted at N1, C2, and C3 of the pyrrole ring. Indolynes can be generated under mild fluoride-mediated conditions, trapped by a variety of reagents, and used to access a number of novel substituted indoles. Nucleophilic addition reactions to indolynes proceed with varying degrees of regioselectivity. A computational and experimental study reveals that distortion energies control regioselectivity and provides a simple model for predicting the regioselectivity in the nucleophilic addition to indolynes and unsymmetrical arynes. This model has led to the design of a substituted 4,5-indolyne that exhibits enhanced nucleophilic regioselectivity.

## 2.3 Synthesis of a 4,5-Indolyne Precursor and Synthetic Applications

To initiate studies, 4,5-indolyne **2.29** was selected as our primary target (Scheme 2.1). If accessible under mild reaction conditions, indolyne **2.29** could undergo nucleophilic additions

and pericyclic reactions to provide a range of synthetic applications. We elected to utilize Kobayashi's approach to aryne generation[14] and hypothesized that indolyne **2.29** could be obtained from indolylsilyltriflate precursor **2.27**. At the time of our studies, routes to indolylsilyltriflates were not known,[15] but could plausibly begin from commercially available hydroxyindole derivatives (e.g., **2.28**).

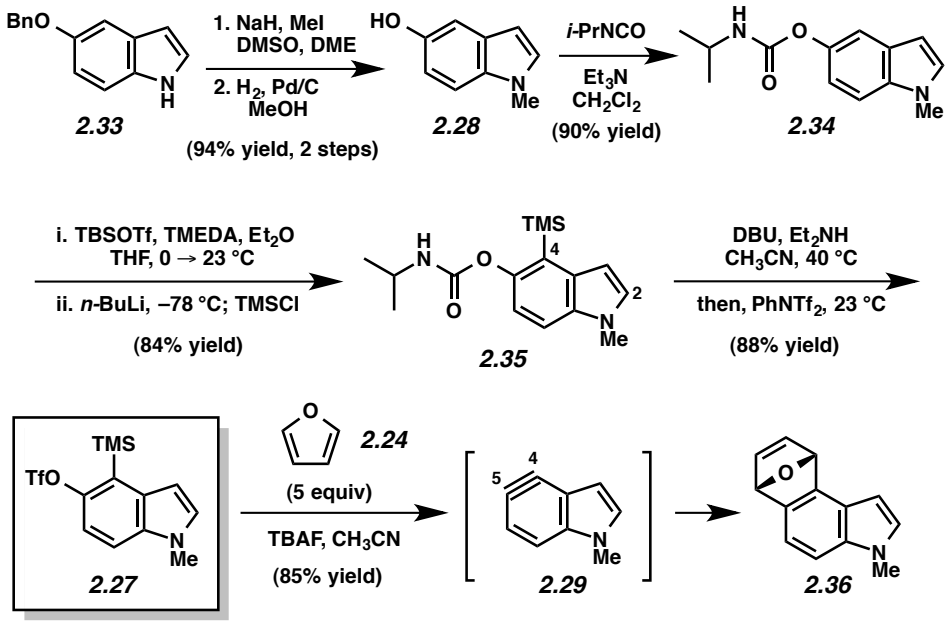
*Scheme 2.1. Modes of Indolyne Reactivity*




The synthesis of an appropriate indolyl silyltriflate proved challenging, primarily because of the acidity of the C2 hydrogen and the electron-rich nature of the indole ring.[16] Nonetheless, extensive experimentation led to the development of an efficient route to silyltriflate **2.27** (Scheme 2.2). Commercially available 5-benzyloxyindole (**2.33**) was converted to hydroxyindole **2.28** following a known two-step sequence.[17,18] Reaction of hydroxyindole **2.28** with isopropyl isocyanate, in the presence of catalytic $Et_3N$, afforded carbamate **2.34**. Of note, the conversion of **2.33** to carbamate **2.34** proceeds in 85% yield, and requires only one final chromatographic purification. Following the protocol disclosed by Snieckus and Hoppe,[19] carbamate **2.34** underwent *o*-lithiation / silylation to provide silyl carbamate **2.35**.[20] Testament to the outstanding *ortho*-directing ability of carbamates,[21] the relatively acidic C2 proton of the *N*-methylindole is not disturbed in this process. Although initial attempts to elaborate silyl carbamate **2.35** to

silyltriflate **2.27** in a stepwise fashion were met with difficulty,[22] an efficient one-pot deprotection / triflation sequence proved successful. Our optimized route to silyltriflate **2.27** can be carried out on multigram scale, and proceeds in 63% overall yield. To confirm that silyltriflate **2.27** would function as a suitable precursor to the targeted 4,5-indolyne **2.29**, silyltriflate **2.27** was reacted with TBAF in the presence of furan (**2.24**) to afford Diels–Alder product **2.36** in 85% yield.

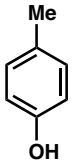
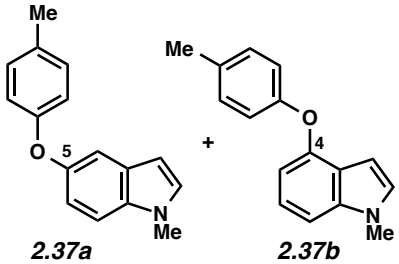
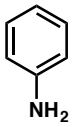
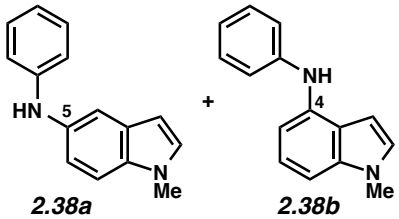
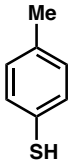
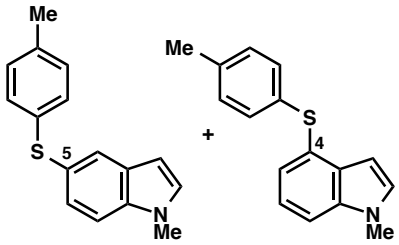
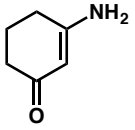
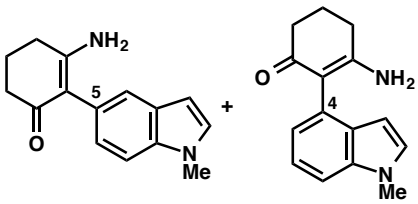
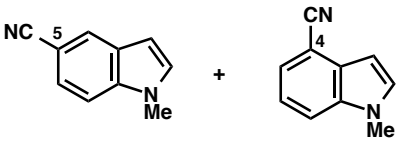
*Scheme 2.2. Synthesis of Indolyne Precursor **2.27**.*




A number of heteroatom- and carbon-based nucleophiles undergo smooth reaction with indolyne **2.29**, which indeed functions as an electrophilic indole surrogate (Table 2.1). Treatment of silyltriflate **2.27** with *p*-cresol in the presence of CsF led to the formation of products **37a** and **2.37b** (entry 1). Similarly, the use of aniline as the nucleophilic trapping agent provided adducts **2.38a** and **2.38b** (entry 2),[23] whereas trapping with *p*-methylthiophenol afforded sulfur-containing products **2.39a** and **2.39b** (entry 3). With respect to carbon-based nucleophiles, the use of a cyclic β-enaminoketone generated indole products **2.40a** and **2.40b** (entry 4).[24]

Furthermore, trapping with potassium cyanide afforded cyanoindoles **2.41a** and **2.41b** (entry 5). The latter result is notable because cyanide has rarely been used in nucleophilic addition reactions to arynes.[25]

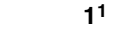
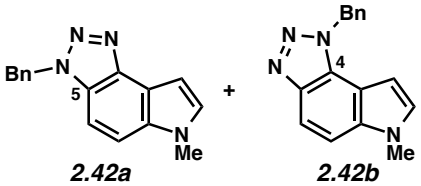
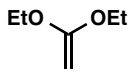
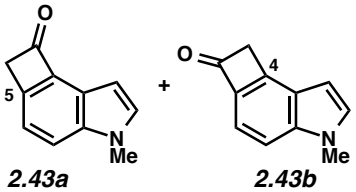
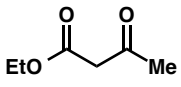
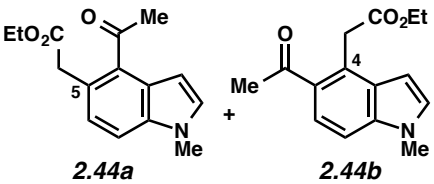
*Table 2.1. Nucleophilic Additions to Indolyne **2.29***

| entry | trapping agent | products | yield (ratio) |
|---|---|---|---|
| 1[a] |  |  **2.37a** + **2.37b** | ***80% yield*** **(3:1)** |
| 2[a] |  |  **2.38a** + **2.38b** | ***91% yield*** **(12.5:1)** |
| 3[a] |  |  **2.39a** + **2.39b** | ***88% yield*** **(2:1)** |
| 4[b] |  |  **2.40a** + **2.40b** | ***58% yield*** **(10:1)** |
| 5[a] | KCN |  **2.41a** + **2.41b** | ***85% yield*** **(3.3:1)** |

[a] Conditions: **2.27**, CsF, $CH_3CN$, 50 °C. [b] Conditions: **2.27**, CsF, $CH_3CN$, 40 °C.

A variety of formal cycloaddition processes involving indolyne **2.29** were used to access several unique 4,5-disubstituted indole derivatives (Table 2.2). For instance, reaction of benzylazide and silyltriflate **2.27**, in the presence of TBAF, provided access to indolyltriazoles **2.42a** and **2.42b** in 86% yield, via a formal aryne cycloaddition (entry 1).[26] Moreover, a formal [2+2] cycloaddition provided indolylcyclobutanones **2.43a** and **2.43b** (entry 2), whereas a variant involving cycloaddition followed by fragmentation provided ketoesters **2.44a** and **2.44b** (entry 3).[27] Of note, each of the examples shown in Tables 2.1 and 2.2 reflect an interesting general preference for initial nucleophilic attack at C5 of the presumed 4,5-indolyne intermediate **2.29** with selectivity as high as 12.5:1 (Table 2.1, entry 2). An explanation for this observation is presented in the latter part of this chapter (see Section 2.7).

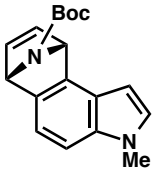
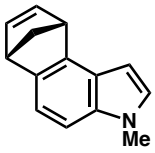
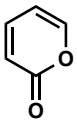
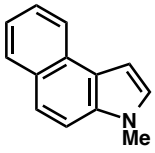
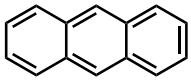
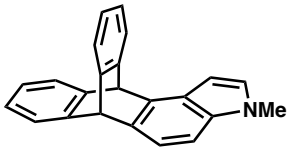
*Table 2.2. Formal Cycloadditions of Indolyne **2.29***

| entry | trapping agent | products | yield (ratio) |
|---|---|---|---|
| 1[1] |  |  ***2.42a*** + ***2.42b*** | ***86% yield*** **(2.4:1)** |
| 2[b] |  |  ***2.43a*** + ***2.43b*** | ***86% yield*** **(5.5:1)** |
| 3[c] |  |  ***2.44a*** + ***2.44b*** | ***68% yield*** **(2:1)** |

[a] Conditions: **2.27**, TBAF, $CH_3CN$, 23 °C. [b] Conditions: **2.27**, CsF, $CH_3CN$, 23 °C. [c] Conditions: **2.27**, CsF, $CH_3CN$, 80 °C.

Diels–Alder reactions of indolyne **2.29** were also investigated as a means to access additional 4,5-disubstituted indole products from silyltriflate **2.27** (Table 2.3). In addition to furan (see Scheme 2.2), *N*-Boc-pyrrole and cyclopentadiene could also be used to trap indolyne **2.29**, thus affording adducts **2.45** and **2.46**, respectively (entries 1 and 2). Furthermore, reaction in the presence of α-pyrone produced benzoindole **2.47** (entry 3), presumably via a Diels–Alder / retro Diels–Alder process with concomitant loss of $CO_2$. Finally, trapping of indolyne **2.29** with anthracene furnished indolyltriptycene **2.48** in 72% yield (entry 4).

*Table 2.3. Diels–Alder Reactions of Indolyne **2.29***

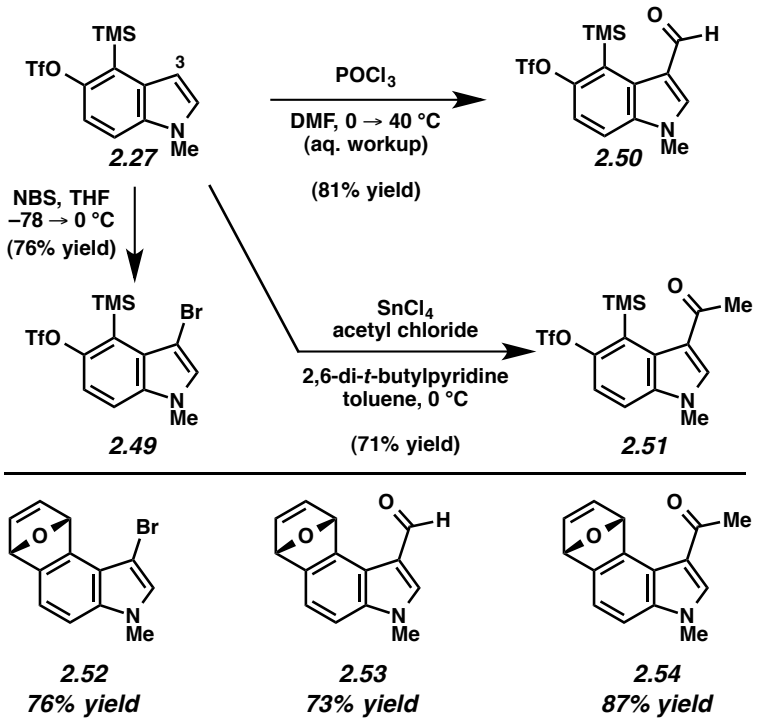
| entry | trapping agent | product | yield |
|---|---|---|---|
| 1[a] |  |  **2.45** | ***83% yield*** |
| 2[a] |  |  **2.46** | ***65% yield*** |
| 3[b] |  |  **2.47** | ***85% yield*** |
| 4[c] |  |  **2.48** | ***72% yield*** |

[a] Conditions: **2.27**, TBAF, $CH_3CN$, 23 °C. [b] Conditions: **2.27**, CsF, $CH_3CN$, 100 °C. [c] Conditions: **2.27**, CsF, $CH_3CN$, 80 °C.

## 2.4 Stability and Functionalization of Indolyne Precursors

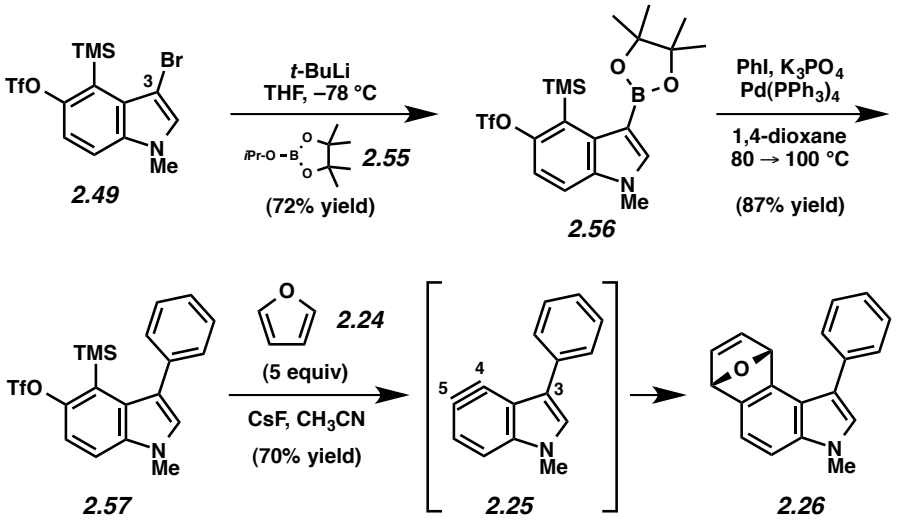
Our studies (vide supra) show that indolyne methodology can be used to access a range of unique indole derivatives. It should be noted that C3 in all indolyne adducts remains unfunctionalized, and could be easily substituted if so desired. Alternatively, we hypothesized that silyltriflate **2.27** could be further substituted before indolyne generation and trapping. As shown in Scheme 2.3, silyltriflate **2.27** is stable to a range of reaction conditions and can be readily functionalized at C3 through bromination (**2.27→2.49**),[28] formylation (**2.27→2.50**),[29] or Lewis acid-mediated acetylation (**2.27→2.51**).[7d] Furthermore, in each case, the silyltriflate remains intact, allowing for subsequent indolyne generation and trapping. By employing furan (**2.24**) as a trapping agent, indolyne cycloadducts **2.52**, **2.53**, and **2.54** could be obtained in good yield.

*Scheme 2.3. C3 Functionalization of Indolyne Precursor **2.27***



The reaction sequence highlighted in Scheme 2.4 demonstrates the viability of carrying indolyl silyltriflates through multistep synthesis. 3-Bromo silyltriflate **2.49** was treated with *t*-BuLi at –78 °C to facilitate halogen-metal exchange. Subsequent quenching with borolane **2.55** delivered boronic ester **2.56** in 72% yield.[28] Next, boronic ester **2.56** underwent Pd-catalyzed Suzuki–Miyaura coupling with iodobenzene at 100 °C to furnish 3-phenyl silyltriflate **2.57**. It is noteworthy that the silyltriflate functionality withstands both harsh base (i.e., *t*-BuLi) and Pd(0). Treatment of silyltriflate **2.57** with CsF in the presence of furan (**2.24**) provided adduct **2.26** in 70% yield, thus demonstrating that silyltriflate **2.57** serves as an efficient precursor to indolyne **2.25**.

*Scheme 2.4. Further Derivatization of Indolyne Precursor **2.49***

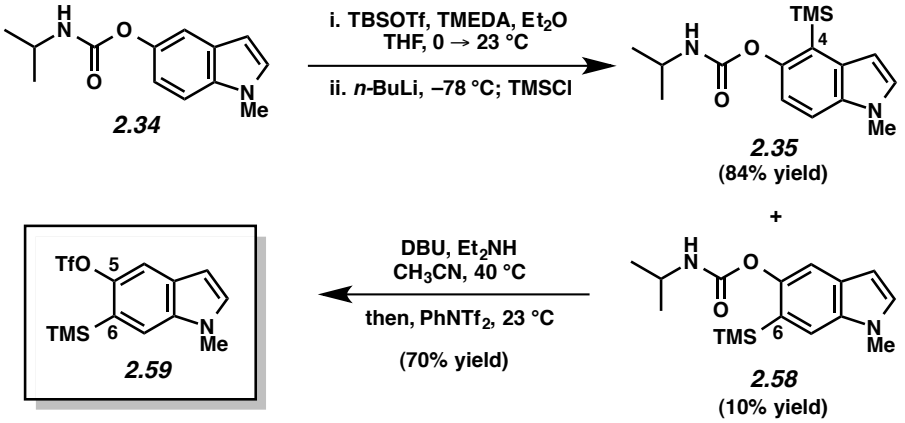



## 2.5 Generation and Trapping of 5,6- and 6,7-Indolynes

Our strategy for preparing indolyl silyltriflates from hydroxyindole precursors proved amenable to the synthesis of 5,6- and 6,7-indolyne precursors. The synthesis of 5,6-indolyne precursor **2.59** is depicted in Scheme 2.5. As described earlier, *o*-lithiation / silylation of carbamate **2.34** afforded C4-silylated indole **2.35** in 84% yield, which could be elaborated to 4,5-

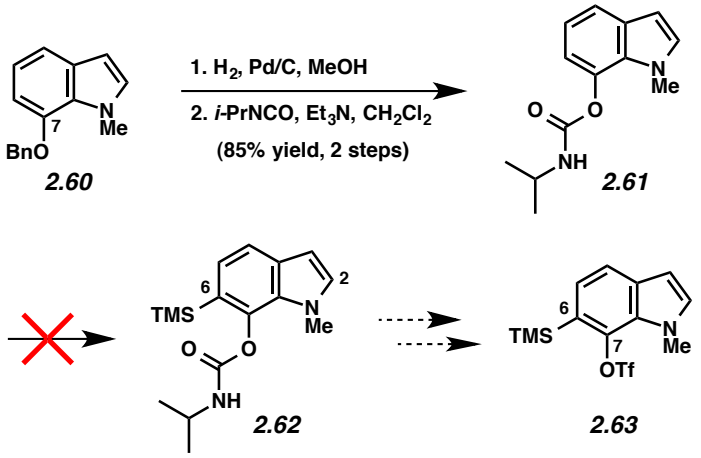
indolyne precursor **2.27** (see Scheme 2.2). However, the C6-silylated indole **2.58** also formed in this process in 10% yield. Carbamate cleavage, followed by stirring with $PhNTf_2$, provided silyltriflate **2.59** in 70% yield. The overall route to **2.59**, although low-yielding, enabled our early studies of 5,6-indolynes. Higher yielding routes to 5,6-indolyne precursors were later developed (vide infra).

*Scheme 2.5. Initial Route to 5,6-Indolyne Precursor **2.59***

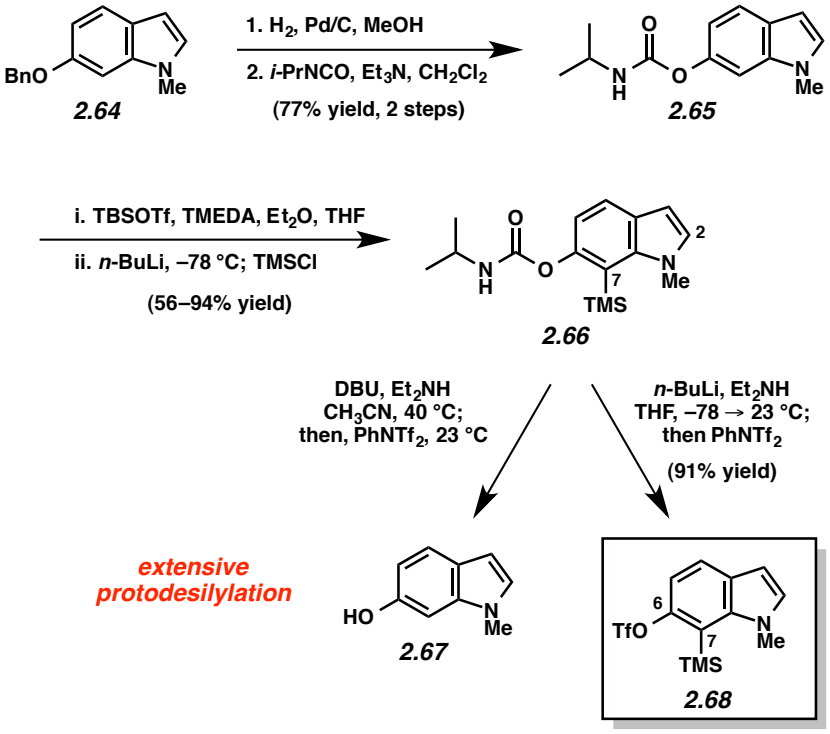



A suitable silyltriflate precursor to a 6,7-indolyne proved most difficult to access. Exploratory efforts beginning from 7-hydroxyindole derivatives failed. For example, 7-benzyloxyindole **2.60** was elaborated to carbamate **2.61** using our standard two-step sequence (Scheme 2.6). Attempts to effect the *o*-lithiation / silylation of carbamate **2.61** led to competitive C2 lithiation and decomposition products, rather than to the desired silylcarbamate **2.62**. Thus, silyltriflate **2.63** was inaccessible.

*Scheme 2.6. Unsuccessful Attempts to Prepare 6,7-Indolyne Precursor* ***2.63***




*Scheme 2.7. Preparation of 6,7-Indolyne Precursor* ***2.68***

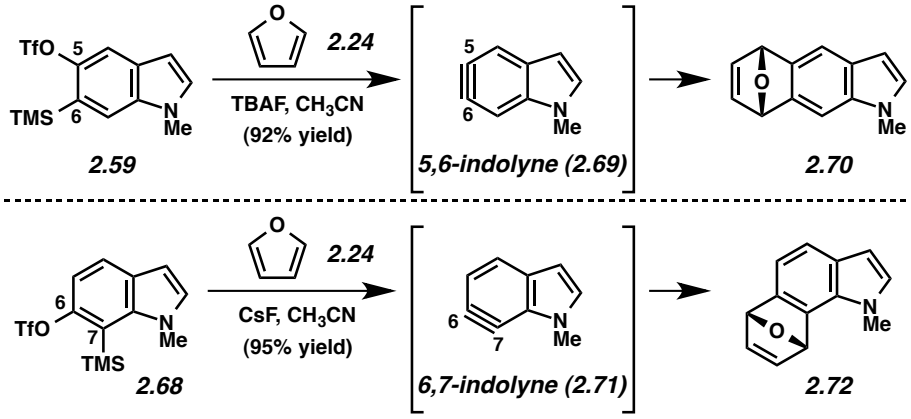



Unsuccessful efforts to synthesize silyltriflate **2.63** (see Scheme 2.6) led us to pursue the synthesis of regioisomeric silyltriflate **2.68** (Scheme 2.7). Readily available 6-benzyloxyindole **2.64** was smoothly converted to carbamate **2.65** in 77% yield. Subsequent treatment of carbamate **2.65** with TBSOTf and TMEDA, followed by *n*-BuLi, led primarily to C7 lithiation.[30]

Quenching with TMSCl delivered silylcarbamate **2.66**. Although our previously described protocol for elaborating aryl carbamates to aryl triflates led primarily to hydroxyindole **2.67**,[31] a modified procedure using *n*-BuLi in place of DBU furnished silyltriflate **2.68** in 91% yield.

To confirm that silyltriflates **2.59** and **2.68** serve as efficient indolyne precursors, each compound was independently subjected to furan (**2.24**) in the presence of fluoride sources (Figure 2.4). Trapping of 5,6-indolyne **2.69** delivered adduct **70** in 92% yield. Similarly, 6,7-indolyne **2.71** underwent [4+2] cycloaddition to provide adduct **2.72** in 95% yield. Nucleophilic additions and formal cycloadditions of indolynes **2.69** and **2.71** were also carried out and, as will be described below, found to proceed efficiently and with interesting regioselectivities.

*Figure 2.4. Trapping of 5,6- and 6,7-Indolynes with Furan*

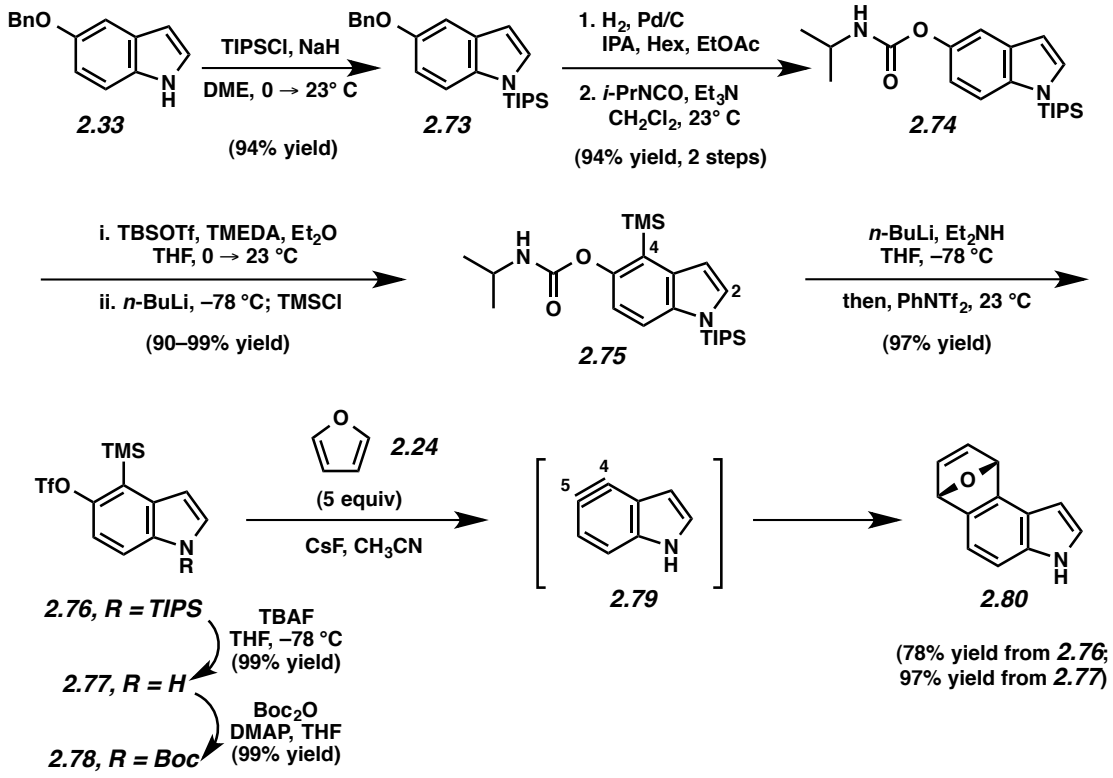



## 2.6 Indolyne Precursors with Alternative *N*-Substituents

Having discovered that indolynes can be generated under mild fluoride-mediated conditions and serve as building blocks for the synthesis of polysubstituted indoles, we synthesized indolyne precursors with alternative *N*-substituents. Indolyl silyltriflates with removable groups, such as Boc and TIPS, were pursued, in addition to *N*-unsubstituted silyltriflates. Syntheses of the targeted indolyne precursors in the 4,5-indolyne series are shown

in Scheme 2.8, and parallel our synthesis of 4,5-indolyne precursor **2.27** (see Scheme 2.2). Beginning with TIPS-protection of 5-benzyloxyindole (**2.33**), *N*-TIPS-silyltriflate **2.76** was prepared in 85% yield over five steps. *N*-TIPS-silyltriflate **2.76** served as the precursor to the corresponding *N*-H and *N*-Boc compounds **2.77** and **2.78**, respectively. Of note, when treated with CsF in the presence of furan (**2.24**), both substrates **2.76** and **2.77** are converted to the identical unprotected bicycle **2.80**, likely via *N*-H indolyne intermediate **2.79**.[32] Free *N*-H indolynes of the type **2.79** have never been synthesized previously, but provide a valuable synthetic tool for the synthesis of unprotected, benzenoid-substituted indoles.

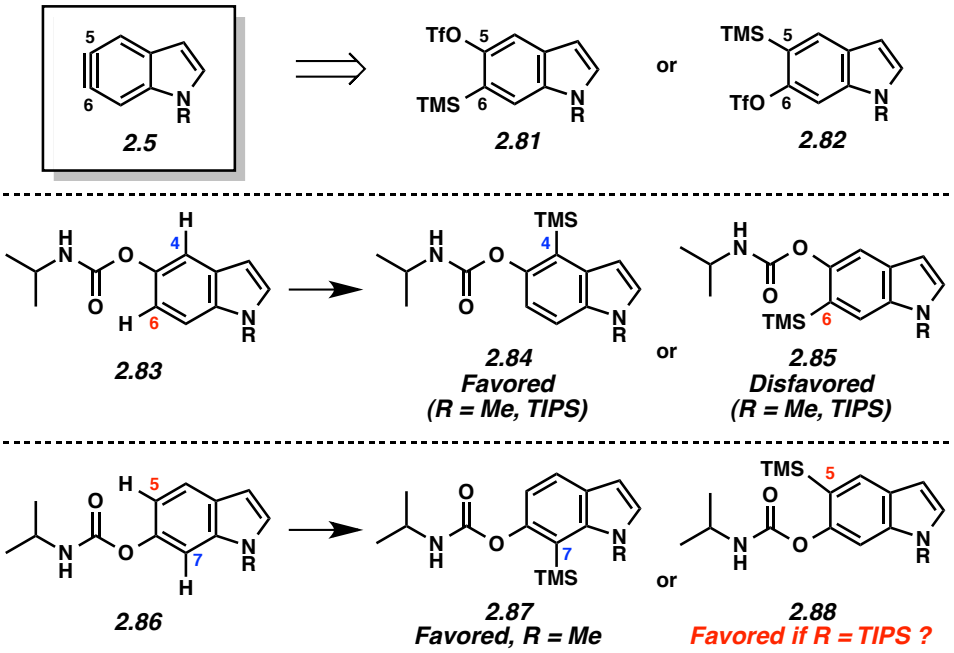
*Scheme 2.8. Synthesis of NH- and N-Boc-4,5-Indolyne Precursors*




As described earlier, our synthesis of an *N*-methyl-5,6-indolyne precursor proceeded in low yield (see Scheme 2.5). To address this limitation and access 5,6-indolyne precursors with alternative *N*-substitutents, we considered the strategies depicted in Scheme 2.9. Indolyne **2.5**

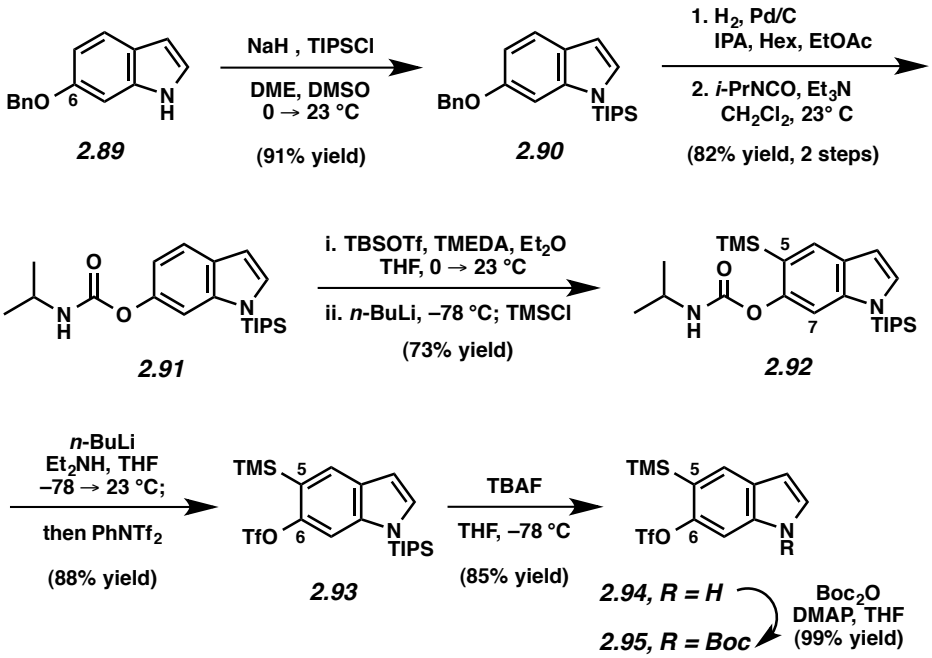
could be derived from either regioisomeric silyltriflates **2.81** or **2.82**, which in turn, would be derived from 5- or 6-substituted precursors **2.83** or **2.86**, respectively. Since the 5-substituted carbamate was observed to favor formation of the 4,5-substituted species **2.84** over the desired 5,6-substituted product **2.85**, we explored the use of 6-carbamoylated substrates. Although C7 lithiation of **2.86** was favored when R=Me, it was hypothesized that a bulky TIPS protective group would disfavor C7 lithiation, ultimately allowing access to 5-silylated product **2.88**.

*Scheme 2.9. Designing an Approach to 5,6-Indolyne Precursor **2.82***



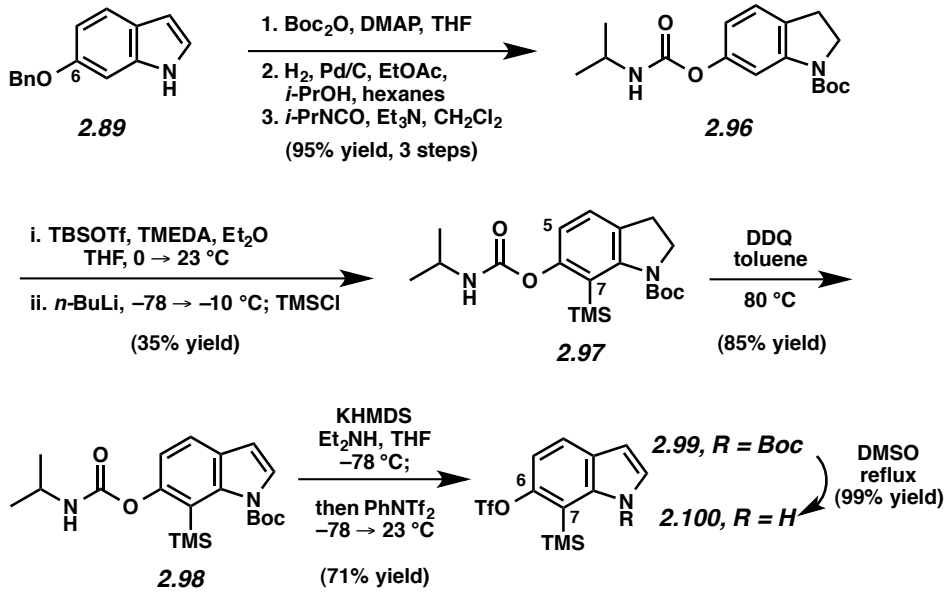

The execution of this approach to 5,6-indolynes is shown in Scheme 2.10. Commercially available 6-benzyloxyindole (**2.89**) was TIPS-protected under standard conditions. Conversion of **2.90** to carbamate **2.91** proceeded in 82% yield using our robust two-step sequence. In the key *o*-lithiation / silylation experiment, functionalization of **2.91** occurred exclusively at C5 to deliver silylcarbamate **2.92**. Analogous to previous studies, carbamate **2.92** was elaborated to *N*-TIPS silyltriflate **2.93**, which in turn, was readily converted to *N*-H and *N*-Boc silyltriflates **2.94** and **2.95**, respectively.

*Scheme 2.10. Synthesis of NH- and N-Boc-5,6-Indolyne Precursors*



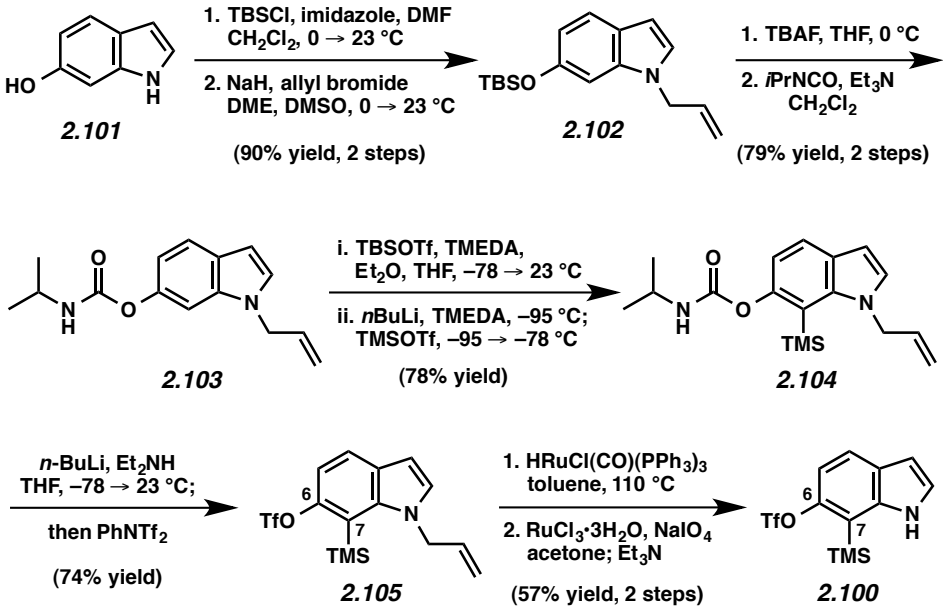

The synthesis of 6,7-indolyne precursors with variable *N*-substituents proved challenging. Nevertheless, two routes were developed beginning from 6-hydroxyindole derivatives. The first generation approach is shown in Scheme 2.11. Boc-protection of benzyloxyindole **2.89**, followed by treatment with $H_2$ and Pd/C furnished a hydroxyindoline intermediate. Subsequent reaction with *i*-PrNCO in the presence of $Et_3N$ furnished carbamate **2.96**. *o*-Lithiation / silylation of carbamate **2.96** delivered 6,7-disubstituted indoline **2.97**, albeit with competitive functionalization at C5.[33] Nonetheless, DDQ oxidation furnished indole **2.98**, which was readily converted to silyltriflate **2.99**. The *N*-Boc group of **2.99** was removed by thermolysis to provide *N*-H indolyne precursor **2.100**.

*Scheme 2.11. Initial Preparation of NH- and N-Boc-6,7-Indolyne Precursors*




A higher yielding route to *N*-H indolyne **2.100** is depicted in Scheme 2.12. *O*-silylation and *N*-allylation of 6-hydroxyindole (**2.101**) afforded protected indole **2.102**. Subsequent elaboration of TBS ether **2.102** to carbamate **2.103** proceeded without event. Lithiation of carbamate **2.103**, followed by quenching with TMSOTf, furnished silylcarbamate **2.104** in 78% yield. After installing the silyltriflate (**2.104→2.105**), the *N*-allyl group was removed[34] to deliver *N*-H silyltriflate **2.100**.

*Scheme 2.12. Alternative Preparation of NH-6,7-Indolyne Precursor* ***2.100***



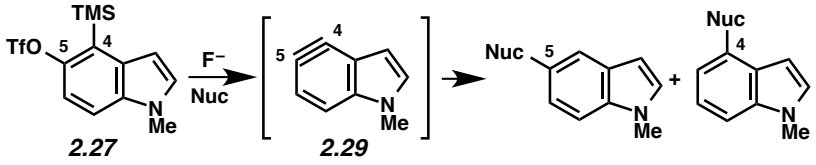

## 2.7 Regioselectivity in Nucleophilic Additions to Indolynes

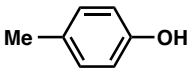
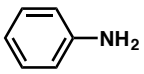
Our studies demonstrate that nucleophilic additions to 4,5-indolynes can occur with significant regioselectivities. A combination of experimental and computational studies was undertaken to determine the origin of these observations. Quantum chemical calculations were performed using Gaussian.[35] The arynes and their transition structures for nucleophilic addition were optimized with B3LYP[36] and M06-2X[37] hybrid density functionals employing 6-31G(d) or 6-311+G(d,p) basis sets. In addition, optimizations were performed with the B2PLYP double hybrid functional[38] and with MP2 pertubation theory[39] using a 6-31G(d) basis set. All density functional calculations used a fine grid for numerical integration. Solvation effects were evaluated through single point calculations using an implicit CPCM model of acetonitrile,[40] defining the solute surface by UAKS radii.[41] In the manuscript we discuss the results of the B3LYP/6-31G(d) calculations, although optimizations at B3LYP/6-311+G(d,p) and M06-2X/6-

311+G(d,p) levels of theory give very similar aryne geometries and also predict the same sense of regioselectivity in each case studied.

The results of several nucleophilic additions to 4,5-indolyne **2.29** are shown in Table 2.4, in addition to the results of density functional computations performed at the B3LYP/6-31G(d) level of theory. The experimental preference for attack at C5 was matched well by the activation free energies of the competing transition structures for each of the nucleophiles we studied, while the magnitudes are usually exaggerated. Activation barriers are very low, in some cases zero, so that variational effects and dynamics may cause selectivities to be less than predicted by $\Delta\Delta G^{\ddagger}$. Cyanide addition has no energetic barrier, but approach of the nucleophile at C5 is favored over C4 for all distances.[42] The major indolotriazole adduct formed from azide cycloaddition involves attack at C5 by the nucleophilic internal nitrogen. Ion pairing and entropic effects should cause these reactions to have positive barriers.

*Table 2.4. Computed Product Ratios of Reactions of 4,5-Indolyne* ***2.29***[a]



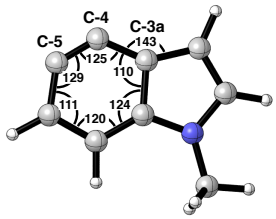

| trapping agent (Nuc) | yield (ratio) | *(computed)* |
|---|---|---|
|  | *80%* (3 : 1) | $\Delta\Delta G^{\ddagger}$ = 2.8 *(115 : 1)* |
|  | *91%* (12.5 : 1) | $\Delta\Delta G^{\ddagger}$ = 3.0 *(160 : 1)* |
| $N_3$—Bn | *86%* (2.4 : 1) | $\Delta\Delta G^{\ddagger}$ = 0.6 *(2.5 : 1)* |
| KCN | *85%* (3.3 : 1) | C-5 preferred[b] |

[a] Conditions: see Section 2.12. Computed ratios obtained from Boltzmann factors using B3LYP/6-31G(d) free energies including CPCM solvation by MeCN. [b] Attack at C5 is favored.

Figures 2.5 and 2.6, respectively, show the calculated structures of 4,5-indolyne **2.29** and transition state (TS) geometries for nucleophilic addition of aniline, *p*-cresol and methylazide (as a model for benzylazide used in experiment). For each of the nucleophiles, the bond angle of the terminus of the aryne that undergoes attack is flattened in the transition structure, whereas the angle at the other terminus is compressed. This picture can be understood in terms of the polarization of the C≡C bond, with developing positive charge at the site of attack and negative charge at the adjacent carbon. We have also found that the computed distortion energies, $\Delta E_d^{\ddagger}$, are useful in quantifying the transition state stabilities. These distortion energies (also termed deformation energy[43] or activation strain[44]) are defined as the energies required to distort the indolyne and nucleophile into their TS geometries without interaction between them. These are shown in Figure 2.6. Computed distortion energies have been shown to correlate well with activation barriers in a number of bimolecular reactions: 1,3-dipolar cycloadditions,[45] 1,4-dihydrogenations, Diels–Alder cycloadditions[46] and cycloadditions involving fullerenes and nanotubes.[47] While this is the first time that distortion energies have been used to understand regioselectivities of additions to arynes,[13b] one of us previously explored the LUMO-lowering effect of bending distortions on alkynes and benzynes that leads to their greater reactivity towards nucleophiles over electrophiles.[48]

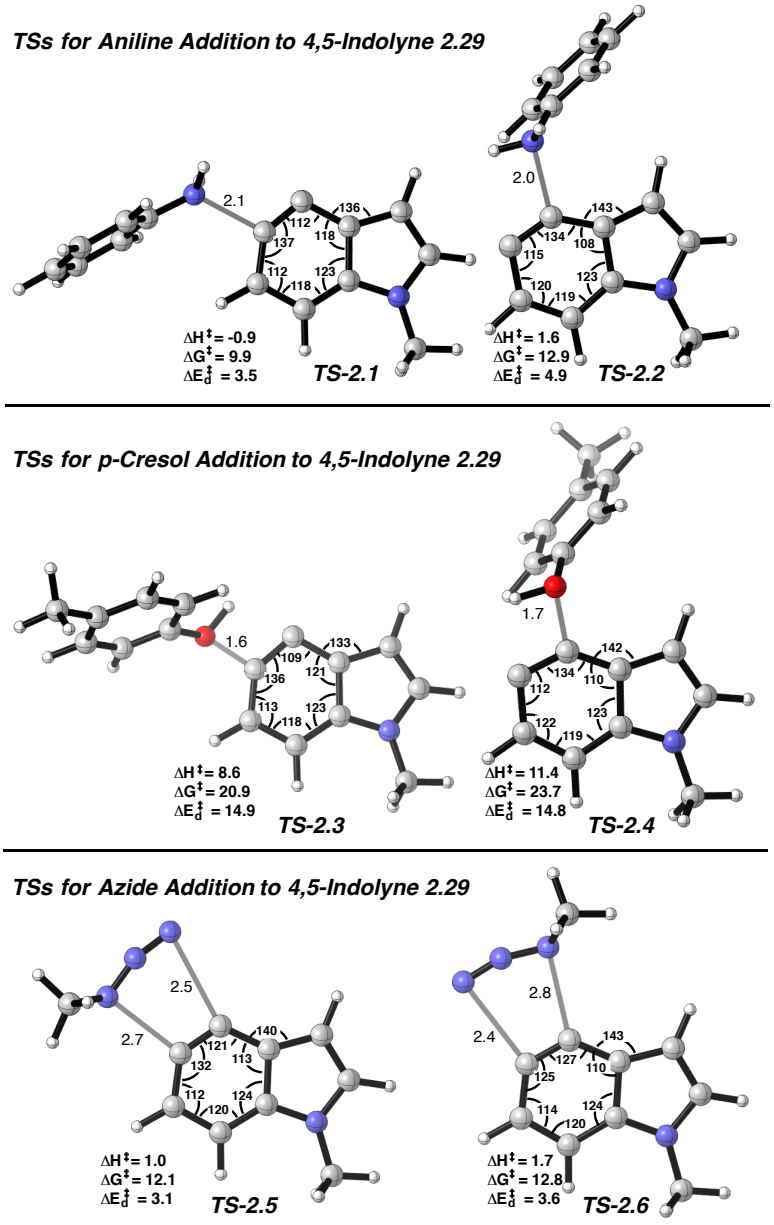
Internal angles of 4,5-indolyne **2.29** show that the aryne is distorted, particularly at C3a ($\theta_{CCC}$ = 110° *vs*. $\theta_{HCC}$ = 126° in pyrrole). Nucleophilic attack at C5 relieves some of the strain at C3a (e.g., opening from 110 to 118° in **TS-2.1**), but attack at C4 adds to the unfavorable distortion at C3a (e.g., closing from 110 to 108° in **TS-2.2**). Attack at C4 has 1.4 kcal/mol greater distortion energy than at C5 due to compression at C3a, leading to a lower activation barrier.

*Figure 2.5. Geometry of 4,5-Indolyne **2.29** from DFT B3LYP/6-31G(d) Calculations*




***4,5-indolyne (2.29)***

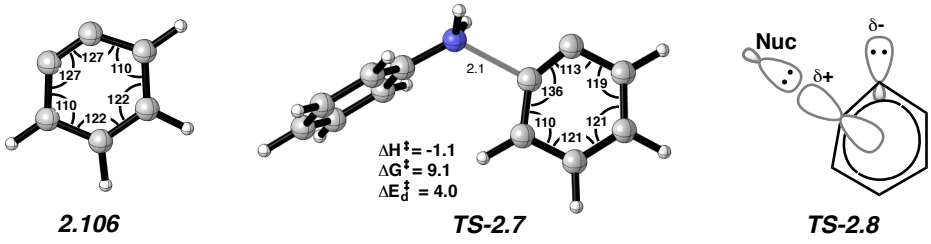
*Figure 2.6. Competing Transition States for Reactions of 4,5-Indolyne **2.29**[a,b]*




[a] B3LYP/6-31G(d) optimized. [b] Energies in kcal/mol.

The types of distortions present in the indolyne TSs shown in Figure 2.6 can be understood from the geometry for nucleophilic attack on benzyne (**2.106**). As shown in Figure 2.7, benzyne is flattened at the point of attack of aniline in **TS-2.7** ($\theta_{CCC}$ = 136°), giving the orbital at the site of attack significant p-character and a slight positive charge, while the adjacent angle is compressed ($\theta_{CCC}$ = 113°) increasing s-character to stabilize the developing carbanion (see **TS-2.8**). We reasoned that nucleophilic addition to unsymmetrical arynes (e.g., indolynes) is favored for attack at the carbon that requires minimal geometrical and energetic change from aryne to TS structure. This is the carbon at which the internal angle is larger, as it is in the nucleophilic addition transition state. In the structure of 4,5-indolyne (see Figure 2.5), C5 is flatter than C4 (129° vs. 124°) and accordingly, nucleophilic addition is preferred at C5.

*Figure 2.7. Geometrical Changes Resulting from Nucleophilic Attack on ortho-Benzyne*




***2.106*** ***TS-2.7*** ***TS-2.8***

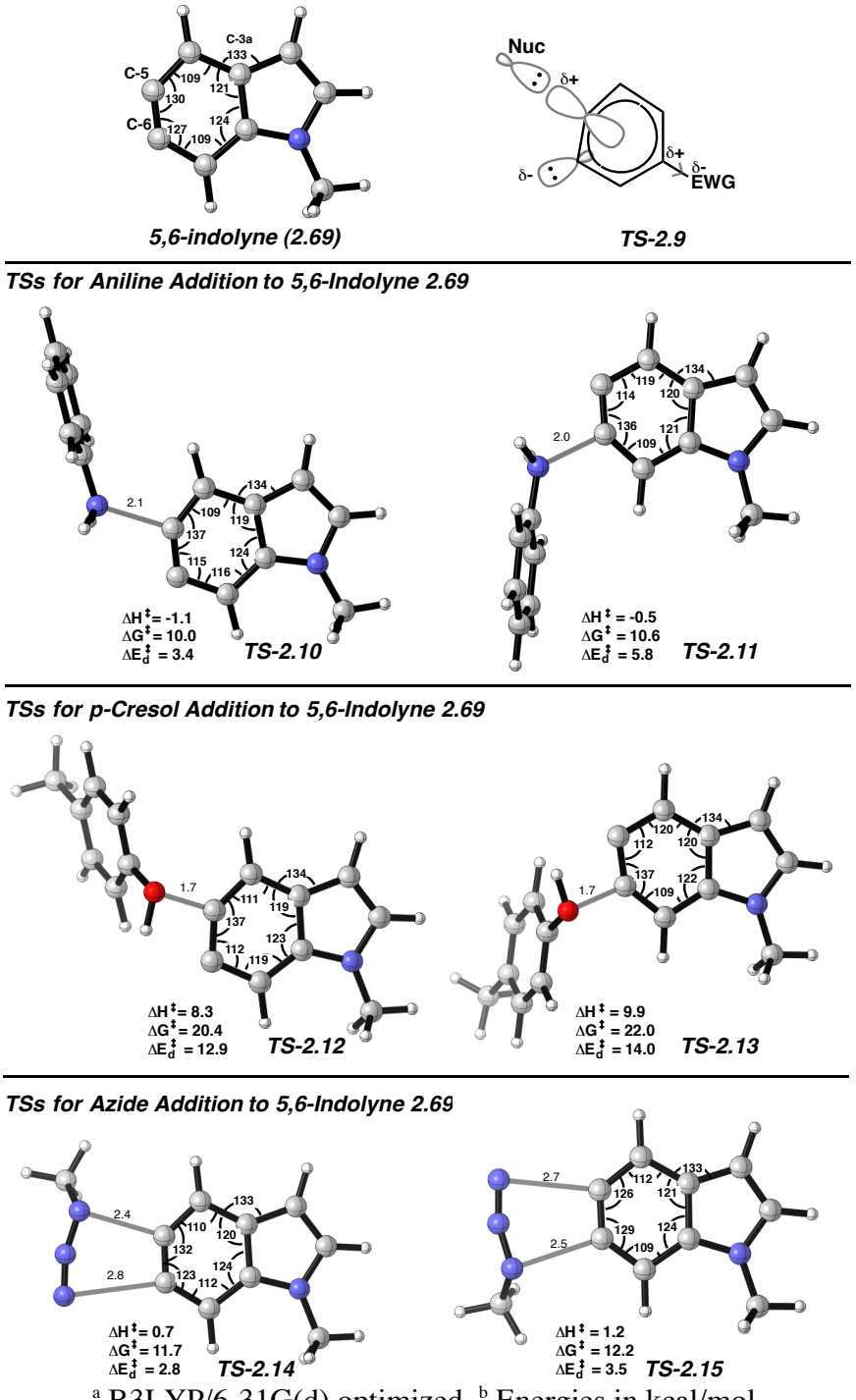
***B3LYP/6-31G(d) Optimized Benzyne***

***TS for Aniline Additions to Benzyne***

Regioselectivities of nucleophilic attack on 5,6- and 6,7-indolynes were studied computationally prior to experiment. There is uniformly lower unsymmetrical distortion and lower addition selectivity in nucleophilic attack on 5,6-indolyne seen in the results of our calculations and also in experiment (Table 2.5). Figure 2.8 shows the computed structures of 5,6-indolyne **2.69** and the TSs for nucleophilic addition. The slightly greater flattening of **2.69** at C5 than at C6 (internal angles are 130° and 127° respectively) can be attributed to electron withdrawal by the indole nitrogen (the charges at C5 and C6 are −0.01 and −0.03e, respectively).

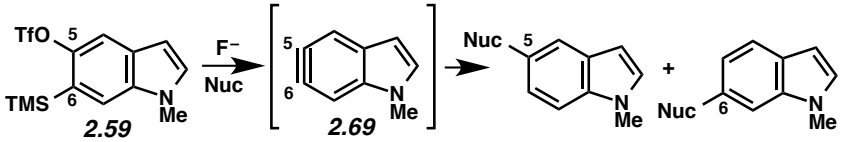
This facilitates attack at C5 in **TS-2.10**, **TS-2.12**, and **TS-2.14**, albeit to only a small extent, paralleling the reactivity depicted in **TS-2.9**.

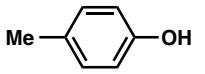
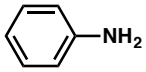
*Figure 2.8. Competing Transition States for Reactions of 5,6-Indolyne* ***2.69***[a,b]




[a] B3LYP/6-31G(d) optimized. [b] Energies in kcal/mol.

*Table 2.5. Calculated and Observed Selectivities in Reactions of 5,6-Indolyne **2.69***[a]



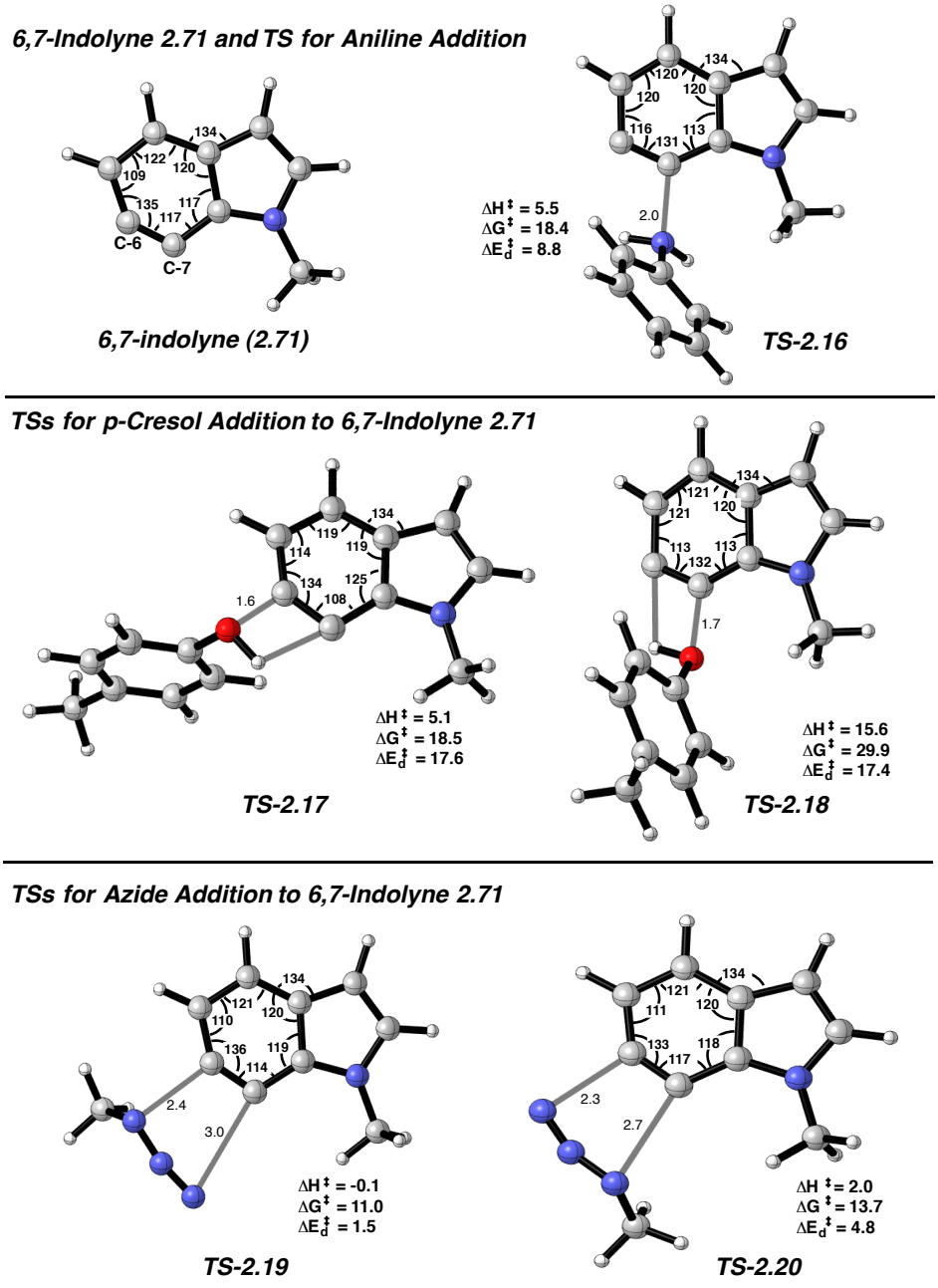

| trapping agent (Nuc) | yield (ratio) | *(computed)* |
|---|---|---|
|  | *64%* (2 : 1) | ΔΔG‡ = 1.7 *(18 : 1)* |
|  | *73%* (3 : 1) | ΔΔG‡ = 0.7 *(3.3 : 1)* |
|  | *94%* (1.6 : 1) | ΔΔG‡ = 0.4 *(1.8 : 1)* |
| KCN | *84%* (1.7 : 1) | C-5 preferred[b] |

[a] Conditions: see section 2.12. [b] Attack at C5 is favored.

In contrast to the 5,6-indolyne, the computed internal angles at the C≡C termini of 6,7-indolyne **2.71** are very different from each other with $\theta_{CCC}$ = 135 and 117° (Figure 2.9). Since the flatter of the two termini is more susceptible to nucleophilic attack, we expected that the 6,7-indolyne would display a high regiochemical preference for addition to C6. Nucleophilic attack on 6,7-indolyne at C6 is highly favored because of the smaller distortion energy, as the indolyne is already distorted into the TS geometry.[49] In fact, the structure of 6,7-indolyne is practically identical to that of the TS for aniline addition to benzyne (see Figure 2.7, **TS-2.7**). There is no calculated energetic barrier for the attack at C6 by aniline, while C7 attack (**TS-2.12**) has a $\Delta E_d$ of 8.8 kcal/mol, which is higher than that for any other of the TSs computed for the indolyne isomers. These results are in accord with the greater selectivity for C6 attack shown here. Extremely high levels of regioselectivity are observed experimentally (Table 2.6), and even azide cycloaddition gives very high selectivity. The 6,7-indolynes also display remarkably high regioselectivity in cycloadditions with 2-substituted furans, unlike 4,5- and 5,6-indolynes.[12e] Complementary to our rationalization based on the distortion energies required to achieve the transition state geometry, Buszek and Cramer have also shown that regioselectivity of additions

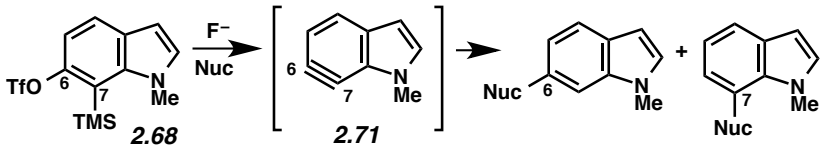
of electron-rich furans to indolynes are influenced by the computed polarization of the C≡C bond.[12e] This polarization is related to the unsymmetrical bending distortions of the indolyne.

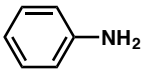
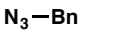
*Figure 2.9. Competing Transition States for Reactions of 6,7-Indolyne* ***2.71****[a,b]*




[a] B3LYP/6-31G(d) optimized. [b] Energies in kcal/mol.

*Table 2.6. Calculated and Observed Selectivities in Reactions of Indolyne **2.71***[a]



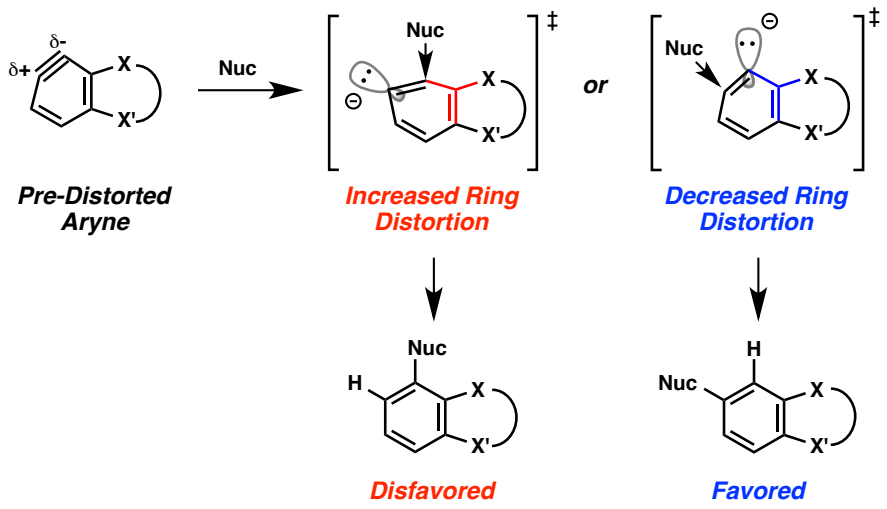

| trapping agent (Nuc) | yield (ratio) | *(computed)* |
|---|---|---|
|  | *53%* (C7 not observed) | $\Delta\Delta G^{\ddagger} = 11.4$ *(solely C6)* |
|  | *91%* (C7 not observed) | $\Delta\Delta G^{\ddagger} > 5.5$[b] *(solely C6)* |
|  | *77%* (C7 not observed) | $\Delta\Delta G^{\ddagger} = 2.7$ *(63 : 1)* |
| KCN | *70%* (C7 not observed) | C6 preferred[c] |

[a] Conditions: see section 2.12. [b] C6 attack has no energetic barrier; C7 attack has $\Delta\Delta H^{\ddagger} = 5.5$. [c] Attack at C6 is preferred

## 2.8 A Model for Predicting Regioselectivity in the Nucleophilic Addition to Indolynes and Unsymmetrical Arynes

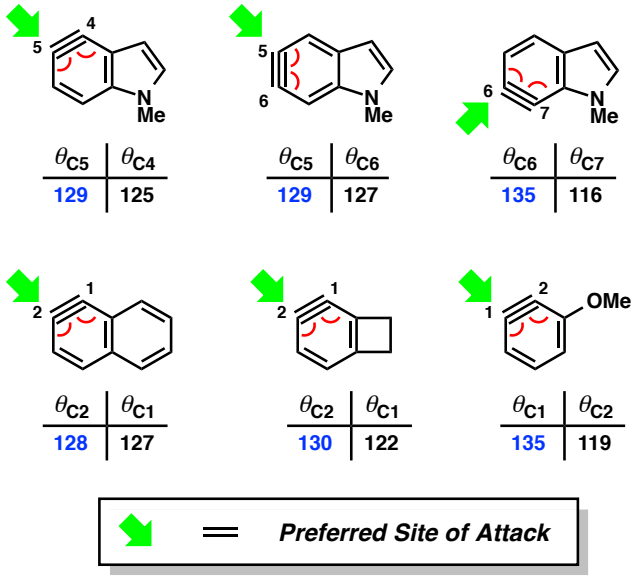
These studies show that computed atomic charges at the triple bond termini are related to the asymmetric distortion of indolynes. Based on this, a distortion model for regioselective nucleophilic addition to fused arynes is depicted in Figure 2.10. Regioselectivity is controlled by the relative ease of distorting the aryne into the two possible transition structures shown. Unsymmetrical distortion is already present in ring-fused arynes and electron-withdrawing groups (X) can further enhance this distortion by polarizing the aryne. The unsymmetrical distortion biases nucleophilic attack to the flatter, more electropositive end of the aryne, leading to an energetically favorable decrease in ring distortion.

*Figure 2.10. Effect of Aryne Distortion on Regioselectivity*




Furthermore, we advocate a comparison of computed internal angles in indolynes as a rapid and reliable method to predict nucleophilic regioselectivity. As exemplified in Figure 2.11, this predictive tool holds for other unsymmetrical arynes with fused rings,[50,51] in addition to arynes with adjacent polar substituents.[52] In all cases, the terminus of the aryne that is flatter, or more distorted, correlates to the experimentally favored site of nucleophilic attack. The difference in internal angles also relates to the degree of regioselectivity, with higher selectivity observed in the addition to arynes that possess large differences between internal angles. If angle differences are small (4° or less), regioselectivity may be modest or somewhat variable. This predictive model functions at various different levels of theory, where the angles are essentially the same as in these cases.

*Figure 2.11. Calculated Internal Angles for Various Indolynes and Benzynes*[a]

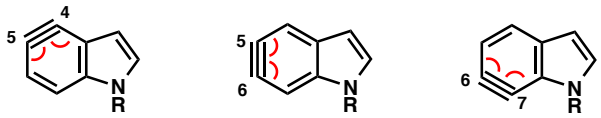



[a] Internal angles for unsymmetrical arynes obtained from B3LYP/6-31G(d) optimized geometries.

## 2.9 Influence of *N*-Substituents on the Regioselectivity of Indolyne Reactions

With a predictive model for determining the regioselectivity in nucleophilic additions to indolynes, we examined the role of substituents on the presumed indolyne intermediates. Figure 2.12 shows the results of B3LYP/6-31G(d) geometry optimization on 4,5-, 5,6-, and 6,7-indolynes as a function of the nitrogen substituent. Computed geometries for the *N*-H indolynes and *N*-Me indolynes are very similar, indicating that their regioselectivities would also be very similar. Effects of Boc protection on the indolyne geometry were more noticeable: *N*-Boc-4,5-indolyne is slightly more distorted than the *N*-H and *N*-Me structures, while 5,6- and 6,7-indolynes were slightly less distorted. Although some minor perturbations are observed, these computational results suggest that regioselectivity in nucleophilic additions to each indolyne would not vary significantly by changing the *N*-substituent from methyl to H or Boc.

*Figure 2.12. Influence of Nitrogen Substituent on Indolyne Distortion*[a]



| R | $\theta_{C5}$ | $\theta_{C4}$ |
|---|---|---|
| Me | 129.2 | 125.2 |
| H | 129.2 | 125.1 |
| Boc | 130.5 | 123.2 |

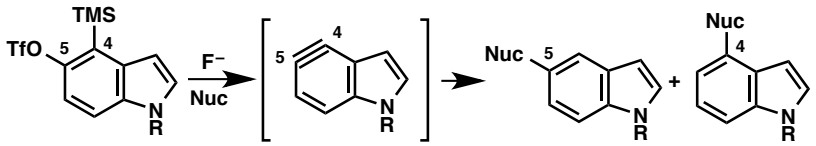
| R | $\theta_{C5}$ | $\theta_{C6}$ |
|---|---|---|
| Me | 129.7 | 127.1 |
| H | 129.9 | 126.9 |
| Boc | 128.2 | 128.7 |

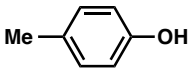
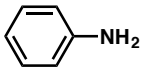
| R | $\theta_{C6}$ | $\theta_{C7}$ |
|---|---|---|
| Me | 135.2 | 116.8 |
| H | 135.0 | 117.1 |
| Boc | 132.4 | 120.0 |

[a] Internal angles calculated from B3LYP/6-31G(d) optimized geometries.

As described earlier, our robust route to indolyl silyltriflates provided access to a variety of indolyne precursors with differing *N*-substituents. By employing these indolyne precursors in nucleophilic additions and formal cycloaddition reactions, we verified our computational predictions. Experimental results for the 4,5-, 5,6-, and 6,7-indolynes are shown in Tables 2.7, 2.8, and 2.9, respectively. As expected, only minor variations in regioselectivity were observed in all cases. It should be noted that in all reactions involving the *N*-H-6,7-indolyne (Table 2.9), products indicative of initial attack at C7 were also observed. Although it is not possible to significantly improve regioselectivities based on the *N*-substituent, these studies validate our predictive regioselectivity model and demonstrate that an array of indolyl silyltriflates can be used as building blocks for the synthesis of substituted indoles.

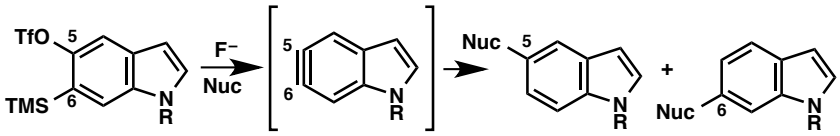
*Table 2.7. Effect of N-Substituent on 4,5-Indolyne Regioselectivities*[a]

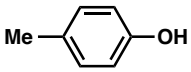
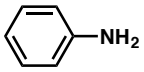



| trapping agent (Nuc) | *N*-substituent (R) | yield | ratio (C5:C4) |
|---|---|---|---|
|  | Me | *80%* | 3 : 1 |
| | H | *67%* | 5 : 1 |
| | Boc | *68%* | 8.2 : 1 |
|  | Me | *91%* | 12.5 : 1 |
| | H | *93%* | 6.4 : 1 |
| | Boc | *84%* | 8.3 : 1 |
| **Bn—N$_3$** | Me | *86%* | 2.4 : 1 |
| | H | *75%* | 1.7 : 1 |
| | Boc | *78%* | 5 : 1 |
| **KCN** | Me | *85%* | 3.3 : 1 |
| | H | *67%*[b] | 3.4 : 1 |
| | Boc | *78%* | 3.5 : 1 |

[a] Conditions: see Section 2.12. [b] Yield reported after Boc-protection

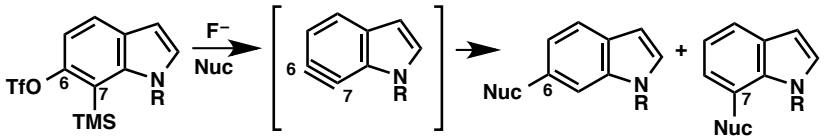
*Table 2.8. Effect of N-Substituent on 5,6-Indolyne Regioselectivities*[a]

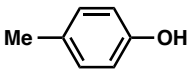
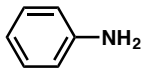



| trapping agent (Nuc) | *N*-substituent (R) | yield | ratio (C5:C6) |
|---|---|---|---|
|  | Me | *64%* | 2 : 1 |
| | H | *72%* | 2 : 1 |
| | Boc | *72%* | 1.1 : 1 |
|  | Me | *73%* | 3 : 1 |
| | H | *91%* | 2.9 : 1 |
| | Boc | *83%* | 1.5 : 1 |
| **Bn—N$_3$** | Me | *94%* | 1.6 : 1 |
| | H | *90%* | 1.8 : 1 |
| | Boc | *82%* | 1.3 : 1 |
| **KCN** | Me | *84%* | 1.7 : 1 |
| | H | *40%*[b] | 1.8 : 1 |
| | Boc | *67%* | 1.6 : 1 |

[a] Conditions: see Section 2.12. [b] Yield reported after Boc-protection

*Table 2.9. Effect of N-Substituent on 6,7-Indolyne Regioselectivities*[a]



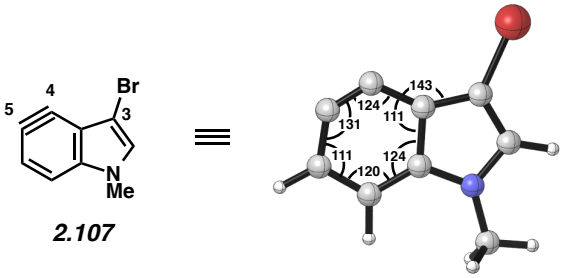

| trapping agent (Nuc) | *N*-substituent (R) | yield | ratio (C6:C7) |
|---|---|---|---|
|  | Me | *53%* | C6 only |
| | H | *52%* | 10.7 : 1 |
| | Boc | *59%* | C6 only |
|  | Me | *91%* | C6 only |
| | H | *79%* | 13.8 : 1 |
| | Boc | *66%* | C6 only |
|  | Me | *77%* | C6 only |
| | H | *60%* | 6.9 : 1 |
| | Boc | *63%* | C6 only |
|  | Me | *70%* | C6 only |
| | H | *44%* | 7.6 : 1 |
| | Boc | *80%* | C6 only |

[a] Conditions: see Section 2.12.

## 2.10 Influence of a C3 Halide Substituent on the Regioselectivity of 4,5-Indolyne Reactions

As a means to further probe our predictive regioselectivity model and ultimately improve regioselectivities, the influence of C3 halide substituents on 4,5-indolynes was evaluated. The results of geometry optimization (B3LYP/6-31G(d) for all atoms except Br, for which the Hay–Wadt LANL2DZ effective core potential[53] was used) for 3-bromo-4,5-indolyne **2.107** are shown in Figure 2.13. The internal angles at C5 and C4 were found to be 131° and 124°, respectively. This finding suggests that bromoindolyne **2.107** should display a greater preference for nucleophilic attack at C5 compared to its C3-unsubstituted derivative (for comparison, the desbromo derivative of **2.107** possesses internal angles of 129° and 125°; see Figure 2.5).

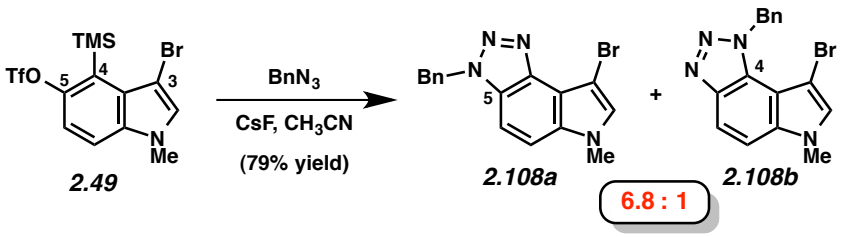
*Figure 2.13. Computed Geometry of 3-Bromo-4,5-Indolyne* ***2.107***[a]




[a] Internal angles obtained using B3LYP/6-31G(d) optimized geometry.

Our computational prediction was tested experimentally by the reaction of 3-bromosilyltriflate **2.49** (see Scheme 2.3 for preparation) with benzylazide in the presence of CsF (Scheme 2.13). Adduct **2.108a** was the major product obtained, showing that initial attack of the presumed indolyne intermediate **2.107** is favored at C5. Of note, the degree of regioselectivity was higher compared to that seen for the corresponding desbromo species (6.8:1 versus 2.4:1), consistent with our calculations. Analogous results were obtained in the nucleophilic addition of cyanide.[54] The fact that a bromo-substituent could lead to improvements in regioselectivity is significant since the C3 bromide is easy to introduce. Moreover, after the necessary indolyne reaction, the bromide substituent could either be removed reductively or used as a handle for the installation of other functional groups.

*Scheme 2.13. Effect of a C3-Bromide on 4,5-Indolyne Regioselectivity*



## 2.11 Conclusion

In summary, we have developed an efficient method for accessing a variety of indole derivatives that bear functional groups on the benzenoid ring. Our strategy relies on the generation of indolynes, which act as electrophilic indole surrogates, thus opposing the typical mode of indole reactivity. A series of 4,5-, 5,6-, and 6,7-indolynes are accessible from indolylsilyltriflate precursors and can be readily employed in both nucleophilic additions and formal cycloaddition processes. Varying degrees of regioselectivity are observed, and we have shown that these regioselectivities are controlled by distortion energies. These studies have led to the discovery of a simple model to predict the regioselectivity in the nucleophilic additions to indolynes and other unsymmetrical arynes. Applications of indolyne methodology in the synthesis of complex molecules are currently being explored in our laboratories.

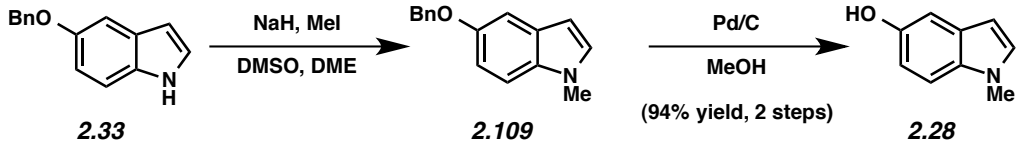
## 2.12 Experimental Section

### 2.12.1 Materials and Methods

Unless stated otherwise, reactions were conducted in flame-dried glassware under an atmosphere of nitrogen using anhydrous solvents (either freshly distilled or passed through activated alumina columns). All commercially obtained reagents were used as received unless otherwise specified. Cesium fluoride (CsF) was obtained from Strem Chemicals. All benzyloxyindoles were obtained from Combi-Blocks, Inc. The following reagents were distilled prior to use: chlorotrimethylsilane (TMSCl), trimethylsilyl trifluoromethanesulfonate (TMSOTf), *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf), and tetramethylethylenediamine (TMEDA); 1,4-dioxane was degassed (two freeze-pump-thaw cycles), and then distilled over sodium metal. 2-Isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane was dried over 3 Å molecular sieves. Diethylamine ($Et_2NH$) was stirred over KOH for 1 h and then passed over basic Brockman Grade I 58 Å activated alumina prior to use. Aniline was passed over neutral Brockman Grade I 58 Å activated alumina prior to use. DMSO, *n*-pentane, and furan were dried over $MgSO_4$. Reaction temperatures were controlled using an IKAmag temperature modulator, and unless stated otherwise, reactions were performed at room temperature (rt, approximately 23 °C). Thin-layer chromatography (TLC) was conducted with EMD gel 60 F254 pre-coated plates (0.25 mm) and visualized using a combination of UV, anisaldehyde, iodine, vanillin, and potassium permanganate staining. Silicycle Siliaflash P60 (particle size 0.040–0.063 mm) or EMD silica gel 60 (particle size 0.040–0.063 mm) was used for flash column chromatography. $^1$H NMR and 2D-NOESY spectra were recorded on Bruker spectrometers (at 300 MHz or 500 MHz) and are reported relative to deuterated solvent signals. Data for $^1$H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz) and integration.

$^{13}C$ NMR spectra were recorded on Bruker Spectrometers (at 75 or 125 MHz). Data for $^{13}C$ NMR spectra are reported in terms of chemical shift, and when necessary, multiplicity, coupling constant (Hz) and carbon type. IR spectra were recorded on a Perkin-Elmer 100 spectrometer and are reported in terms of frequency of absorption ($cm^{-1}$). High resolution mass spectra were obtained from the UC Irvine Mass Spectrometry Facility.

### 2.12.2 Preparative Procedures

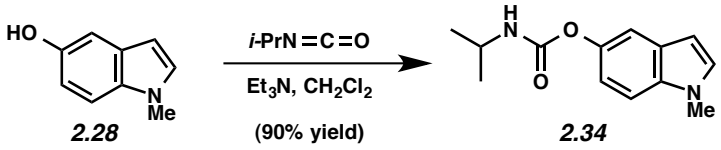



*2.33* *2.109* *2.28*

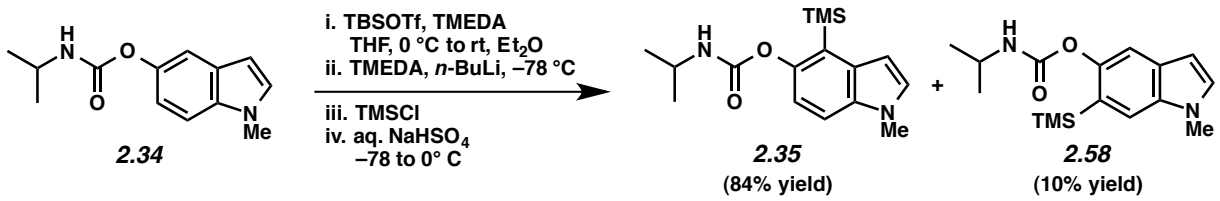
**Hydroxyindole 2.28**. Hydroxyindole **2.28** was prepared following a known procedure,[17a,b] with minor modifications. 95% NaH (0.60 g, 25.0 mmol, 2.8 equiv) was added to a solution of 5-benzyloxyindole **2.33** (1.99 g, 8.92 mmol) in dimethoxyethane (24.8 mL) and DMSO (2.8 mL). The resulting solution was stirred at 23 °C for 40 min, then MeI (0.83 mL, 13.4 mmol, 1.5 equiv) was added dropwise over 1 min. The resulting mixture was stirred for 70 min, then quenched with $H_2O$ (8 mL), then brine (8 mL). The biphasic mixture was further diluted with brine (40 mL) and EtOAc (40 mL). The layers were separated, and then the aqueous layer was extracted with EtOAc (2 × 40 mL). The combined organic layers were washed with $H_2O$ (40 mL), washed brine (40 mL), then dried over $MgSO_4$. Evaporation of the solvent under reduced pressure afforded crude **2.109** as a white solid, which was used in the subsequent step without further purification. $R_f$ 0.64 (3:1 Hexanes:EtOAc); $^1$H NMR (500 MHz, $CDCl_3$): δ 7.50 (d, $J$ = 7.5, 2H), 7.41 (app. t, $J$ = 8.0, 2H), 7.35–7.32 (m, 1H), 7.24 (d, $J$ = 9.0, 1H), 7.19 (d, $J$ = 2.5, 1H), 7.04 (d, $J$ = 3.0, 1H), 6.99 (dd, $J$ = 9.0, 2.5, 1H), 6.41 (dd, $J$ = 3.0, 0.5, 1H), 5.13 (s, 2H), 3.78 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 153.4, 138.0, 132.5, 129.6, 128.9, 128.7, 127.9, 127.7, 112.8, 110.1, 104.4, 100.7, 71.2, 33.2; IR (film): 3035, 1491, 1234 cm$^{-1}$; HRMS-ESI ($m/z$) [M + Na]$^+$ calcd for $C_{16}H_{15}NONa$, 260.1051; found, 260.1059.

Crude **2.109** was dissolved in MeOH (18.6 mL) and 10% Pd/C (0.89 g, 0.84 mmol, 10 mol% Pd) was added. The mixture was placed under an atmosphere of hydrogen (double-balloon), stirred for 23 h at 23 °C, and then filtered over celite (MeOH eluent, 500 mL). Evaporation of the solvent under reduced pressure afforded hydroxyindole **2.28** (1.23 g, 94%

yield over 2 steps) as a grey solid. $R_f$ 0.30 (3:1 Hexanes:EtOAc); $^1$H NMR (500 MHz, $CDCl_3$): δ 7.19 (d, $J$ = 8.5, 1H), 7.03 (app. s, $J$ = 7.03, 2H), 6.81 (d, $J$ = 8.5, 1H), 6.36 (s, 1H), 4.48 (s, 1H), 3.77 (s, 3 H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 149.5, 132.5, 129.9, 129.3, 111.5, 110.0, 105.4, 100.2, 33.2; IR (film): 3170, 1489 cm$^{-1}$. HRMS-ESI (*m/z*) [M + H]$^+$ calcd for $C_9H_{10}NO$, 148.0762; found, 148.0766.

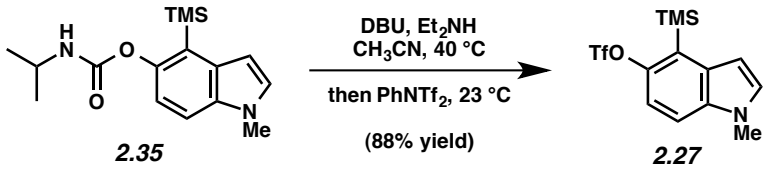



**Carbamate 2.34.** Carbamate **2.34** was prepared following the general procedure described by Igarashi et al.[55] To a stirred solution of hydroxyindole **2.28** (1.75 g, 11.89 mmol) in $CH_2Cl_2$ (60 mL) was added *i*-PrNCO (1.75 mL, 17.84 mmol, 1.5 equiv), followed by $Et_3N$ (0.50 mL, 3.57 mmol, 0.3 equiv). The solution was stirred at 23 °C for 8 h, then concentrated to dryness *in vacuo*. Purification by flash chromatography (1:2 EtOAc:Hexanes) provided carbamate **2.34** (2.48 g, 90% yield) as a light pink powder. $R_f$ 0.50 (1:1 Hexanes:EtOAc); $^1$H NMR (500 MHz, $CDCl_3$): δ 7.37 (d, $J$ = 2.4, 1H), 7.27 (d, $J$ = 8.8, 1H), 7.07 (d, $J$ = 3.0, 1H), 7.02 (dd, $J$ = 8.8, 2.4, 1H), 6.46 (d, $J$ = 3.0, 1H), 4.92 (app. d, $J$ = 4.9, 1H), 3.97–3.89 (m, 1H), 3.77 (s, 3H), 1.24 (d, $J$ = 6.4, 6H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 154.9, 144.7, 134.6, 130.0, 128.7, 116.2, 113.2, 109.6, 101.2, 43.5, 33.2, 23.1; IR (film): 3387, 2972, 1739 cm$^{-1}$; HRMS-ESI (*m/z*) [M + Na]$^+$ calcd for $C_{13}H_{16}N_2O_2Na$, 255.1109; found, 255.1114.

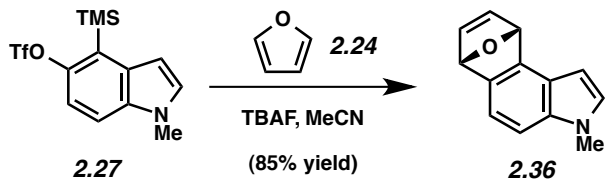



**Silyl carbamates 2.35 and 2.58.** Silyl carbamates **2.35** and **2.59** were prepared following the general procedure of Hoppe and Snieckus for *o*-lithiation of isopropyl carbamates, with minor modifications.[19] To a solution of carbamate **2.34** (1.93 g, 8.31 mmol) and TMEDA (1.74 mL, 11.63 mmol, 1.4 equiv) in 80 mL of 3:1 $Et_2O$:THF at 0 °C was added a solution of TBSOTf in *n*-pentane (1.30 M, 7.56 mL, 9.97 mmol, 1.2 equiv). After stirring for 5 min, the white suspension was allowed to warm to rt over 30 min, by which time TMEDA·TfOH had formed as an colorless oil on the bottom of the flask, and the pale supernatant had become clear and homogeneous. TMEDA (3.74 mL, 24.93 mmol, 3.0 equiv) was added, and the mixture was cooled to –78 °C.[56] A solution of *n*-BuLi in hexanes (2.43 M, 10.26 mL, 24.93 mmol, 3.0 equiv) was added dropwise over 10 min.[57] The mixture was stirred at –78 °C for 3 h, then neat TMSCl (7.38 mL, 58.16 mmol, 7.0 equiv) was added dropwise over 15 min.[57] The resulting mixture was stirred at –78 °C for 1 h, quenched with 1 M aqueous $NaHSO_4$ (75 mL), and allowed to warm to 23 °C over 45 min with vigorous stirring. The organic layer was separated, washed successively with 1 M aqueous $NaHSO_4$ (50 mL) and brine (50 mL), then dried over $Na_2SO_4$. Evaporation under reduced pressure afforded the crude products, which were purified by flash chromatography (19:1 Hexanes: EtOAc) to afford silylcarbamates **2.35** (2.13 g, 84% yield) and **2.58** (0.25 g, 10% yield) as white powders. Silylcarbamate **2.35**: $R_f$ 0.27 (2:1 Hexanes:EtOAc); $^1$H NMR (500 MHz, $CDCl_3$): δ 7.31 (d, *J* = 8.7, 1H), 7.09 (d, *J* = 3.0, 1H), 6.96 (d, *J* = 8.7, 1H), 6.64 (d, *J* = 3.0, 1H), 4.77 (app. d, *J* = 7.4, 1H), 3.98–3.91 (m, 1H), 3.78 (s, 3H), 1.25 (d, *J* = 6.5, 6H), 0.44 (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 155.0, 149.7, 133.9, 132.7, 129.5, 122.3,

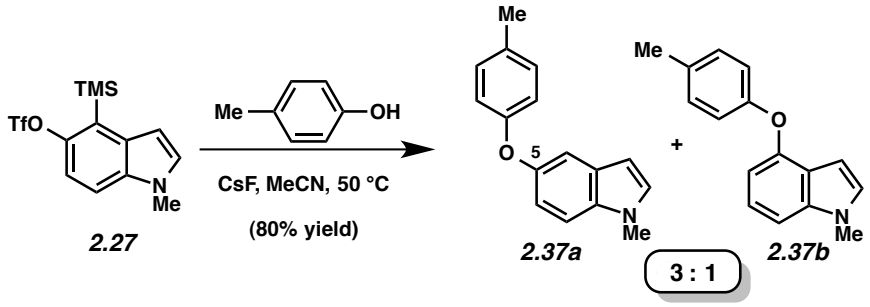
117.0, 111.1, 102.7, 43.5, 33.2, 23.3, 1.2; IR (film): 3357, 2963, 1723 $cm^{-1}$; HRMS-ESI (*m/z*) [M + Na]$^+$ calcd for $C_{16}H_{24}N_2O_2SiNa$, 327.1505; found, 327.1506. Silylcarbamate **2.58**: $R_f$ 0.38 (2:1 Hexanes:EtOAc); $^1H$ NMR (500 MHz, $CDCl_3$): δ 7.35 (s, 1H), 7.34 (s, 1H), 7.06 (d, *J* = 3.0, 1H), 6.43 (d, *J* = 3.0, 1H), 4.79 (app. d, *J* = 7.5, 1H), 3.99–3.92 (m, 1H), 3.80 (s, 3H), 1.26 (d, *J* = 6.5, 6H), 0.35 (s, 9H); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 155.0, 149.2, 135.0, 130.6, 130.3, 125.0, 115.1, 114.0, 101.2, 43.7, 33.3, 23.4, –0.2; IR (film): 3330, 2970, 1707, 1207 $cm^{-1}$; HRMS-ESI (*m/z*) [M + Na]$^+$ calcd for $C_{16}H_{24}N_2O_2SiNa$, 327.1505; found, 327.1510.




**Silyltriflate 2.27.** To a solution of silyl carbamate **2.35** (1.04 g, 3.43 mmol) in MeCN (31 mL) was added DBU (1.28 mL, 8.58 mmol, 2.5 equiv) and $Et_2NH$ (0.53 mL, 5.15 mmol, 1.5 equiv). The resulting mixture was placed in a heating bath maintained at 40 °C for 50 min, then allowed to cool to 23 °C. Next, a solution of $PhNTf_2$ (1.84 g, 5.15 mmol, 1.5 equiv) in MeCN (10 mL) was added. After stirring for 80 min, the reaction mixture was passed over a plug of silica gel (EtOAc eluent). Evaporation under reduced pressure afforded the crude product, which was further purified by flash chromatography (99:1 Hexanes:EtOAc) to provide silyltriflate **2.27** (1.06 g, 88% yield) as a colorless oil. $R_f$ 0.55 (2:1 Hexanes:EtOAc); $^1H$ NMR (500 MHz, $CDCl_3$): δ 7.35 (d, *J* = 9.0, 1H), 7.20 (d, *J* = 9.0, 1H), 7.19 (d, *J* = 3.0, 1H), 6.71 (d, *J* = 3.0, 1H), 3.82 (s, 3H), 0.52 (s, 9H); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 148.8, 134.6, 133.1, 130.8, 124.2, 119.0 (q, *J* = 324, $CF_3$), 114.3, 111.5, 103.7, 33.3, 1.2; IR (film): 2956, 1401 $cm^{-1}$; HRMS-ESI (*m/z*) [M + Na]$^+$ calcd for $C_{13}H_{16}F_3NO_3SSiNa$, 374.0470; found, 374.0477.

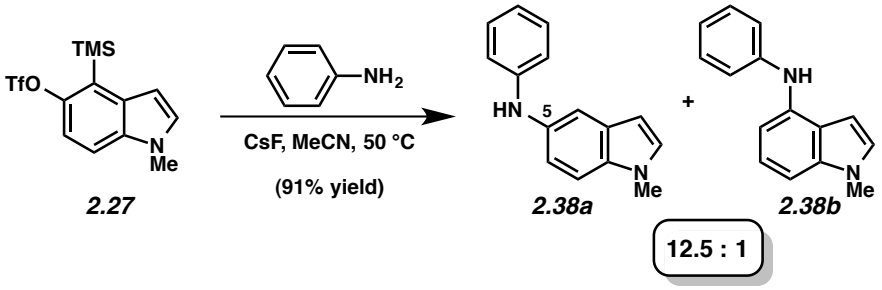



**Furan Diels-Alder adduct 2.36.** To a solution of silyltriflate **2.27** (43.5 mg, 0.124 mmol) and furan (**2.24**) (45 μL, 0.620 mmol, 5 equiv, dried over $Na_2SO_4$) in MeCN (1.2 mL) at 23 °C was added a solution of TBAF in THF (1.0 M, 248 μL, 0.248 mmol, 2.0 equiv). The solution was stirred for 15 min, then filtered over silica gel (EtOAc eluent). Evaporation under reduced pressure afforded the crude product, which was further purified by flash chromatography (5:1 Hexanes:EtOAc) to provide adduct **2.36** (20.8 mg, 85% yield) as a pale oil. $R_f$ 0.47 (2:1 Hexanes:EtOAc); $^1$H NMR (500 MHz, $CDCl_3$): δ 7.24 (d, $J$ = 7.9, 1H), 7.16 (dd, $J$ = 5.5, 1.6, 1H), 7.14 (dd, $J$ = 5.5, 1.6, 1H), 7.07 (d, $J$ = 3.0, 1H), 6.93 (d, $J$ = 7.9, 1H), 6.42 (d, $J$ = 3.0, 1H), 6.03 (s, 1H), 5.86 (s, 1H), 3.76 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 145.2, 143.0, 142.2, 140.5, 136.6, 131.0, 123.7, 114.6, 104.5, 97.8, 83.2, 82.0, 33.4; IR (film): 3003, 2922, 1513, 1283 cm$^{-1}$; HRMS-ESI ($m/z$) [M + Na]$^+$ calcd for $C_{13}H_{11}NONa$, 220.0738; found, 220.0745.



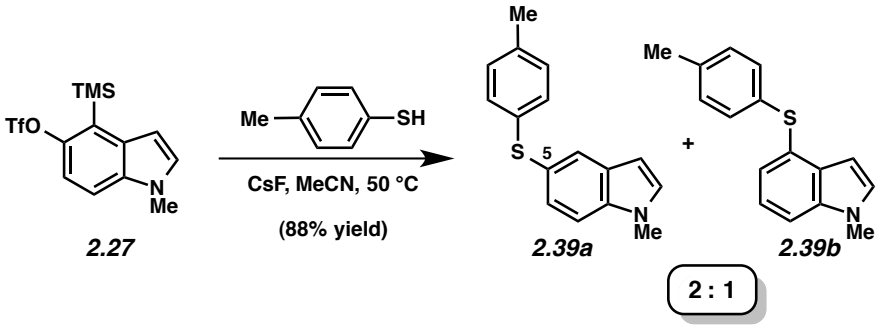

**Ethers 2.37a and 2.37b.** To a stirred solution of silyltriflate **2.27** (28 mg, 0.080 mmol) and *p*-cresol (13 mg, 0.12 mmol, 1.5 equiv) in MeCN (0.8 mL) was added CsF (36 mg, 0.24 mmol, 3 equiv). The resulting mixture was stirred at 50 °C for 14 h, then filtered over silica gel (EtOAc eluent). Evaporation under reduced pressure afforded the crude products, which were further purified by flash chromatography (4:1 Hexanes:Benzene) to provide a mixture of ethers **2.37a**

and **2.37b** (3:1 ratio of **2.37a**:**2.37b**, 15 mg, 80% yield). Analytical samples of **2.37a** and **2.37b** were obtained by preparative TLC (1:1 Hexanes:Benzene) and flash chromatography (4:1 Hexanes:Benzene), respectively. **2.37a**: $R_f$ 0.45 (1:1 Hexanes:Benzene); $^1$H NMR (500 MHz, $CDCl_3$): δ 7.30–7.26 (m, 2H), 7.10–7.07 (m, 3H), 6.98 (dd, *J* = 8.5, 2.5, 1H), 6.89–6.86 (m, 2H), 6.42 (dd, *J* = 3.0, 0.5, 1H), 3.81 (s, 3H), 2.32 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 157.3, 150.6, 133.9, 131.6, 130.2, 130.0, 129.2, 117.7, 115.3, 111.1, 110.2, 101.0, 33.3, 20.8; IR (film): 2921, 1506, 1485, 1232 cm$^{-1}$; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{16}H_{16}NO$, 238.1232; found, 238.1236. **2.37b**: $R_f$ 0.48 (1:1 Hexanes:benzene); $^1$H NMR (500 MHz, $CDCl_3$): δ 7.16–7.09 (m, 4H), 6.98 (d, *J* = 3.0, 1H), 6.96 (d, *J* = 8.5, 2H), 6.64 (d, *J* = 7.5, 1H), 6.40 (d, *J* = 3.0, 1H), 3.81 (s, 3H), 2.33 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 155.8, 150.6, 139.1, 132.4, 130.2, 128.4, 122.4, 121.0, 118.6, 108.1, 105.0, 98.7, 33.3, 20.9; IR (film): 2921, 1506, 1491 cm$^{-1}$; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{16}H_{16}NO$, 238.1232; found, 238.1227.



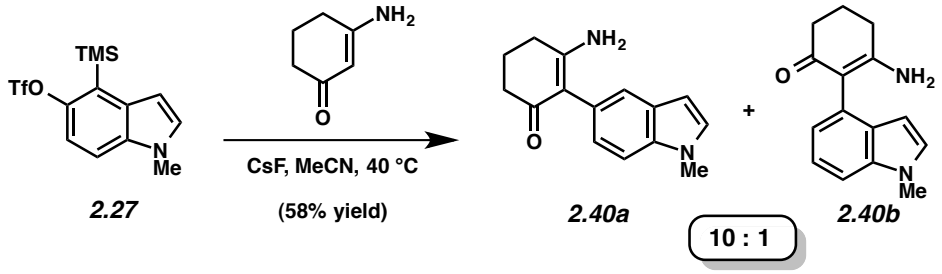

**Amines 2.38a and 2.38b.** To a stirred solution of silyltriflate **2.27** (40.5 mg, 0.115 mmol) and aniline (31.5 μL, 0.346 mmol, 3 equiv) in MeCN (1.2 mL) was added CsF (52.5 mg, 0.346 mmol, 3 equiv). The reaction vessel was placed in an aluminum heating block maintained at 50 °C for 20 h. After cooling to 23 °C, the reaction mixture was filtered over silica gel (EtOAc eluent). Evaporation under reduced pressure afforded the crude products, which were further purified by flash chromatography (1:1 Hexanes:Benzene) to provide a mixture of amines **2.38a**

and **2.38b** (12.5:1 ratio of **2.38a**:**2.38b**, 23.3 mg, 91% yield). An analytical sample of **2.38a** was obtained by flash chromatography ($CH_2Cl_2$:$Et_2O$:Hexanes 1:1:30). **2.38a**: $R_f$ 0.22 (1:1 Hexanes:Benzene); $^1$H NMR (500 MHz, $CDCl_3$): δ 7.43 (d, *J* = 2.0, 1H), 7.29 (d, *J* = 9.0, 1 H), 7.22 (dt, *J* = 7.0, 1.5, 2H), 7.09 (dd, *J* = 9.0, 2.0, 1H), 7.06 (d, *J* = 3.0, 1H), 6.95 (d, *J* = 8.0, 2H), 6.82 (t, *J* = 7.0, 1H), 6.43, (d, *J* = 2.5, 1H), 5.62 (s, 1H), 3.81 (s, 1H). Spectral data for **2.38a** match those previously reported.[58] **2.38b**: $R_f$ 0.30 (1:1 Hexanes:Benzene).



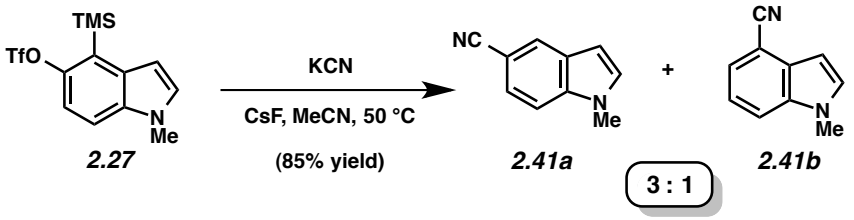

**Thioethers 2.39a and 2.39b.** To a stirred solution of silyltriflate **2.27** (35 mg, 0.10 mmol) and 4-methylbenzenethiol (19 μL, 0.15 mmol, 1.5 equiv) in MeCN (1 mL) was added CsF (46 mg, 0.30 mmol, 3 equiv). The reaction vessel was placed in an aluminum heating block maintained at 50 °C for 14 h. After cooling to 23 °C, the reaction mixture was filtered over silica gel (EtOAc eluent). Evaporation under reduced pressure afforded the crude products, which were further purified by flash chromatography (1:4 $CH_2Cl_2$:Hexanes → 3:7 $CH_2Cl_2$:Hexanes) to provide a mixture of thioethers **2.39a** and **2.39b** (2:1 ratio of **2.39a**:**2.39b**, 22 mg, 88% yield). These products were characterized as the mixture. $R_f$ 0.30 (1:1 $CH_2Cl_2$:Hexanes); **2.39a**: $^1$H NMR (500 MHz, $d_8$-Toluene): δ 7.90 (d, *J* = 1.5, 1H), 7.42 (dd, *J* = 8.5, 2.0, 1H), 7.21 (d, *J* = 8.0, 2H), 6.84 (d, *J* = 8.5, 1H), 6.80 (d, *J* = 8.0, 2H), 6.45 (d, *J* = 3.0, 1H), 6.29 (d, *J* = 3.0, 1H), 2.88 (s, 3H), 2.02 (s, 3H); $^{13}$C NMR (125 MHz, $d_8$-Toluene): δ 137.0, 136.8, 135.1, 130.4, 129.91, 129.85, 129.2, 128.9, 127.7, 127.4, 122.1, 110.3, 101.5, 31.9; **2.39b**: $^1$H NMR (500 MHz, $d_8$-Toluene): δ

7.32 (dd, $J$ = 7.0, 1.0, 1H), 7.25 (d, $J$ = 8.0, 2H), 7.04 (d, $J$ = 8.0, 1H), 6.87 (d, $J$ = 8.5, 1H), 6.76 (d, $J$ = 8.0, 2H), 6.67 (dd, $J$ = 3.0, 0.5, 1H), 6.43 (d, $J$ = 3.5, 1H), 2.90 (s, 3H), 1.99 (s, 3H); $^{13}$C NMR (125 MHz, $d_8$-Toluene): δ 137.2, 135.8, 133.9, 130.6, 130.1, 129.9, 129.4, 129.2, 128.2, 127.1, 122.1, 109.2, 101.2, 32.0; IR (film): 3097, 2917, 1420 cm$^{-1}$; HRMS-ESI ($m/z$) [M + H]$^+$ calcd for $C_{16}H_{16}NS$, 254.1003; found, 254.1005.

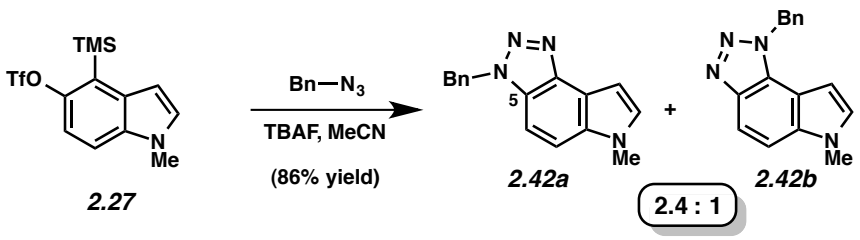



**β-Enaminoketones 2.40a and 2.40b.** To a stirred solution of silyltriflate **2.27** (16.8 mg, 0.048 mmol) and 3-amino-2-cyclohexen-1-one (15.9 μL, 0.143 mmol, 3 equiv) in MeCN (0.5 mL) was added CsF (21.9 mg, 0.143 mmol, 3 equiv). The reaction vessel was placed in an aluminum heating block maintained at 40 °C for 15 h. After cooling to 23 °C, the reaction mixture was filtered over silica gel (EtOAc eluent). Evaporation under reduced pressure afforded the crude products, which were purified by flash chromatography (1:19 MeOH:EtOAc). The resulting mixture of products was dissolved in $CH_2Cl_2$ (4 mL) and washed with water (1 × 1 mL). Evaporation under reduced pressure provided an inseparable mixture of β-enaminoketones **2.40a** and **2.40b** (10:1 ratio of **2.40a**:**2.40b**, 7.2 mg, 58% yield). Characterization data for the major isomer, **2.40a**, is as follows: $R_f$ 0.30 (2:1 $CH_2Cl_2$:Acetone); $^1$H NMR (500 MHz, $CDCl_3$): δ 7.44 (s, 1H), 7.37 (d, $J$ = 8.4, 1H), 7.05–7.03 (m, 2H), 6.45 (d, $J$ = 3.0, 1H), 4.42 (s, 2H), 3.80 (s, 3H), 2.55–2.50 (m, 4H), 2.10 (quintet, $J$ = 6.3, 2H). $^{13}$C NMR (125 MHz, $CDCl_3$): δ 195.1, 159.9, 136.0, 129.0, 128.8, 125.0, 124.5, 122.8, 114.4, 109.8, 100.9, 37.0, 32.9, 29.4, 21.5; IR (film):

3449, 3307, 3171, 2941, 1633 $cm^{-1}$. HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{15}H_{16}N_2ONa$, 263.1160; found, 263.1165.

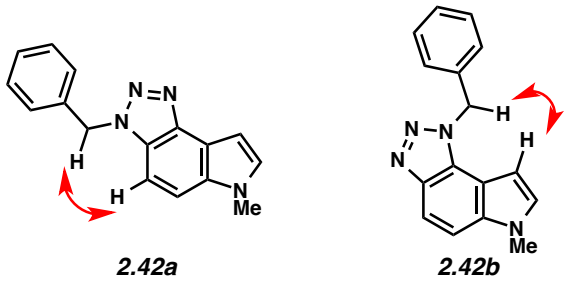



**Cyanoindoles 2.41a and 2.41b.** To a stirred solution of silyltriflate **2.27** (29 mg, 0.083 mmol) and potassium cyanide (8.0 mg, 0.12 mmol, 1.5 equiv) in MeCN (0.83 mL) was added CsF (38 mg, 0.25 mmol, 3 equiv). The reaction vessel was placed in an aluminum heating block maintained at 50 °C for 16 h. After cooling to 23 °C, the reaction mixture was filtered over silica gel (EtOAc eluent). Evaporation under reduced pressure afforded the crude products, which were further purified by flash chromatography (1:1 $Et_2O$:Hexanes) to provide a mixture of cyanoindoles **2.41a** and **2.41b** (3:1 ratio of **2.41a**:**2.41b**, 11 mg, 85% yield). **2.41a**: $R_f$ 0.48 (1:1 Toluene:$CH_2Cl_2$); $^1$H NMR (500 MHz, $CDCl_3$): δ 7.98 (t, *J* = 0.6, 1H), 7.46 (dd, *J* = 8.5, 1.4, 1H), 7.38 (d, *J* = 8.5, 1H), 7.19 (d, *J* = 3.2, 1H), 6.58 (d, *J* = 3.1, 1H), 3.85 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 138.1, 131.1, 128.1, 126.5, 124.4, 120.9, 110.0, 102.3, 102.1, 33.1. Spectral data for **2.41a** match those previously reported.[59] **2.41b**: $R_f$ 0.52 (1:1 Toluene:$CH_2Cl_2$).

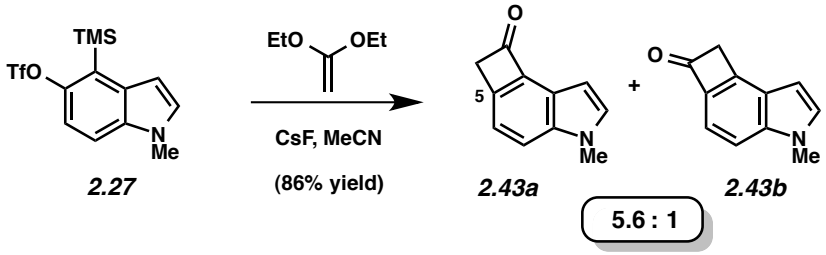



**Triazoles 2.42a and 2.42b.** To a stirred solution of silyltriflate **2.27** (43.5 mg, 0.124 mmol) and benzyl azide[60] (82.3 mL, 0.619 mmol, 5 equiv) in MeCN (1.24 mL) was added a solution of TBAF in THF (1.0 M, 248 μL, 0.248 mmol, 2 equiv). The solution was stirred for 10 min, then filtered over silica gel (EtOAc eluent). Evaporation under reduced pressure afforded the crude products, which were further purified by flash chromatography (7:1 Benzene:EtOAc) to provide triazoles **2.42a** and **2.42b** (2.4:1 ratio of **2.42a**:**2.42b**, 28.0 mg, 86% yield). Analytical samples of **2.42a** and **2.42b** were obtained by flash chromatography (9:1 Benzene:EtOAc). **2.42a**: $R_f$ 0.10 (20:1 Benzene:EtOAc); $^1$H NMR (300 MHz, $CDCl_3$): δ 7.40 (d, *J* = 9.0, 1H), 7.33–7.24 (m, 5H), 7.19 (d, *J* = 3.0, 1H), 7.12 (s, 1H), 7.10 (d, *J* = 4.8, 1H), 5.89 (s, 2H), 3.89 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 140.9, 135.5, 133.4, 129.1, 129.0, 128.4, 127.6, 118.1, 112.0, 103.2, 100.0, 52.6, 33.8; IR (film): 2936, 1218 cm$^{-1}$; HRMS-ESI (*m/z*) [M + Na]$^+$ calcd for $C_{16}H_{14}N_4Na$, 285.1116; found, 285.1113. **2.42b**: $R_f$ 0.14 (20:1 Benzene:EtOAc); $^1$H NMR (500 MHz, $CDCl_3$): δ 7.84 (d, *J* = 9.0, 1H), 7.36 (d, *J* = 9.0, 1H), 7.32–7.25 (m, 5H), 7.07 (d, *J* = 3.0, 1H), 6.55 (d, *J* = 3.0, 1H), 6.05 (s, 2H), 3.89 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 142.3, 135.9, 135.2, 129.1, 128.3, 128.2, 127.2, 113.3, 110.6, 109.0, 99.5, 52.9, 33.9; IR (film): 3109, 2932, 1107 cm$^{-1}$; HRMS-ESI (*m/z*) [M + Na]$^+$ calcd for $C_{16}H_{14}N_4Na$, 285.1116; found, 285.1110.

The structures of **2.42a** and **2.42b** were confirmed by 2D-NOESY experiments, as the following interactions were observed:




*2.42a* *2.42b*

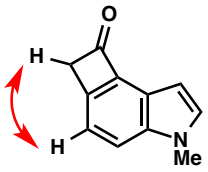



*2.27* *2.43a* *2.43b*

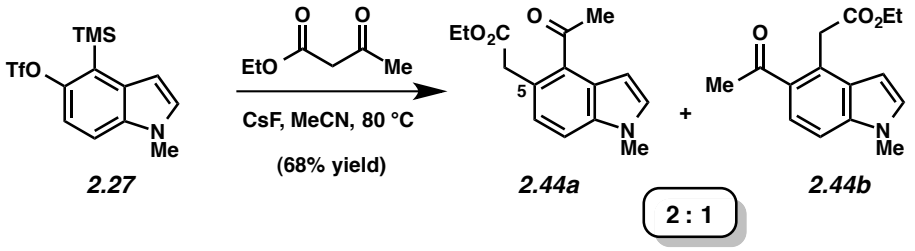
**Cyclobutanones 2.43a and 2.43b.** To a stirred solution of silyltriflate **2.27** (29.6 mg, 0.124 mmol) and ketene diethyl acetal (55.4 mL, 0.420 mmol, 5 equiv) in MeCN (1.24 mL) was added CsF (38.3 mg, 0.252 mmol, 3 equiv). The solution was stirred at 23 °C for 2 d, then filtered over silica gel (EtOAc eluent). Evaporation under reduced pressure afforded a mixture of intermediate cyclobutyl ketals, which, in turn, were dissolved in $CH_2Cl_2$ (3 mL) and stirred with silica gel (2 mL) for 16 h. Filtration over silica gel (EtOAc eluent) and evaporation of solvent under reduced pressure afforded the crude cyclobutanones, which were further purified by flash chromatography (2:1 Hexanes:$CH_2Cl_2$) to provide cyclobutanones **2.43a** and **2.43b** (5.6:1 ratio of **2.43a**:**2.43b**, 12.4 mg, 86% yield). An analytical sample of **2.43a** was prepared by flash chromatography (1:99:120 MeOH:$CH_2Cl_2$:Hexanes). $R_f$ 0.16 (2:1 Hexanes:$CH_2Cl_2$); $^1$H NMR (500 MHz, $CDCl_3$): δ 7.54 (dd, $J$ = 8.1, 0.6, 1H), 7.32 (d, $J$ = 8.4, 1H), 7.22 (d, $J$ = 3.3, 1H), 6.61 (d, $J$ = 3.0, 1H), 4.01 (s, 2H), 3.87 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 188.0, 146.0, 138.6,

137.5, 132.6, 121.0, 117.3, 115.4, 100.3, 51.2, 33.5; IR (film): 3107, 2906, 1726, 1504 $cm^{-1}$; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{11}H_9NONa$, 194.0582; found, 194.0583.

The structure of **2.43a** was confirmed by 2D-NOESY experiments, as the following interactions were observed:




***2.43a***

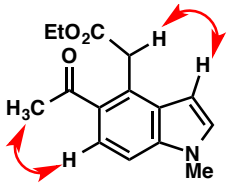



***2.27*** ***2.44a*** ***2.44b***

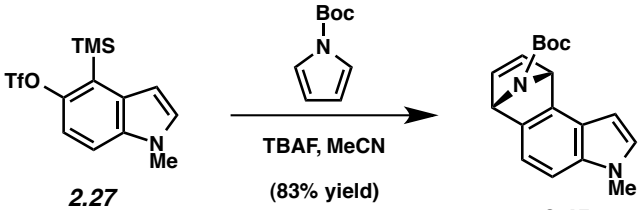
**Ketoesters 2.44a and 2.44b.** To a stirred solution of silyltriflate **2.27** (45.0 mg, 0.128 mmol) and ethyl acetoacetate (25 μL, 0.192 mmol, 1.5 equiv) in MeCN (1.3 mL) was added CsF (58.3 mg, 0.384 mmol, 3 equiv). The reaction vessel was placed in an aluminum heating block maintained at 80 °C for 1 h. After cooling to 23 °C, the reaction mixture was filtered over silica gel (EtOAc eluent). Evaporation under reduced pressure afforded the crude products, which were further purified by flash chromatography (20:1 Benzene:EtOAc → 6:1 Benzene:EtOAc) to provide ketoesters **2.44a** (15.1 mg, 45% yield) and **2.44b** (7.5 mg, 23% yield). **2.44a**: $R_f$ 0.44 (6:1 Benzene:EtOAc); $^1H$ NMR (300 MHz, $CDCl_3$): δ 7.37 (d, *J* = 8.1, 1H), 7.11–7.16 (m, 2H), 6.53 (d, *J* = 3.3, 1H), 4.15 (q, *J* = 7.2, 2H), 3.90 (s, 2H), 3.82 (s, 3H), 2.74 (s, 3H), 1.26 (t, *J* = 6.9, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 204.7, 172.5, 136.8, 132.8, 130.5, 126.4, 125.3, 123.8, 111.8, 100.8, 60.9, 39.2, 33.2, 32.0, 14.5; IR (film): 2982, 1732, 1683 $cm^{-1}$; HRMS-ESI (*m/z*) [M

+ Na]$^+$ calcd for $C_{15}H_{17}NO_3Na$, 282.1106; found, 282.1103. **2.44b:** $R_f$ 0.33 (6:1 Benzene:EtOAc); $^1$H NMR (300 MHz, $CDCl_3$): δ 7.73 (d, *J* = 8.7, 1H), 7.24 (s, 1H), 7.10 (d, *J* = 3.0, 1H), 6.60 (dd, *J* = 3.3, 0.9, 1H), 4.25 (s, 2H), 4.15 (q, *J* = 7.2, 2H), 3.79 (s, 3H), 2.63 (s, 3H), 1.25 (t, *J* = 7.2, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 201.2, 171.8, 138.3, 130.55, 130.45, 129.1, 128.5, 124.5, 107.9, 101.4, 60.8, 36.9, 33.3, 29.6, 14.5; IR (film): 2982, 1733, 1667 cm$^{-1}$; HRMS-ESI (*m/z*) [M + Na]$^+$ calcd for $C_{15}H_{17}NO_3Na$, 282.1106; found, 282.1108.

The structure of **2.44b** was confirmed by 2D-NOESY experiments, as the following interactions were observed:



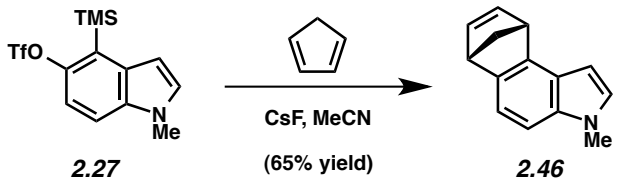

*2.44b*




*2.27* *2.45*

**Pyrrole Diels-Alder adduct 2.45.** To a solution of silyltriflate **2.27** (43.5 mg, 0.124 mmol) and *N*-Boc-pyrrole[61] (104 mg, 0.619 mmol, 5 equiv) in MeCN (1.2 mL) at 23 °C was added a solution of TBAF in THF (1.0 M, 248 μL, 0.248 mmol, 2.0 equiv). The solution was stirred for 15 min, then filtered over silica gel (EtOAc eluent). Evaporation under reduced pressure afforded the crude product, which was further purified by flash chromatography (20:1 Benzene:EtOAc) to provide adduct **2.45** (30.4 mg, 83% yield) as a pale oil. $R_f$ 0.36 (20:1 Benzene:EtOAc); $^1$H NMR (500 MHz, 47 °C, $CDCl_3$): δ 7.23 (d, *J* = 8.0, 1H), 7.08 (d, *J* = 8.5, 2H), 7.04 (d, *J* = 3.0, 1H), 6.90 (d, *J* = 8.0, 1H), 6.45 (d, *J* = 3.0, 1H), 5.79 (s, 1H), 5.61 (s, 1H), 3.73 (s, 3H), 1.40 (s, 9H);

$^{13}$C NMR (125 MHz, 47 °C, $CDCl_3$): δ 155.3, 145.1, 143.1, 141.5, 140.0, 136.7, 130.8, 124.4, 115.3, 104.5, 98.0, 80.4, 67.4, 66.1, 33.2, 28.5; IR (film): 2975, 1699, 1161 cm$^{-1}$; HRMS-ESI (*m*/*z*) $[M + Na]^+$ calcd for $C_{18}H_{20}N_2O_2Na$, 319.1422; found, 319.1414.

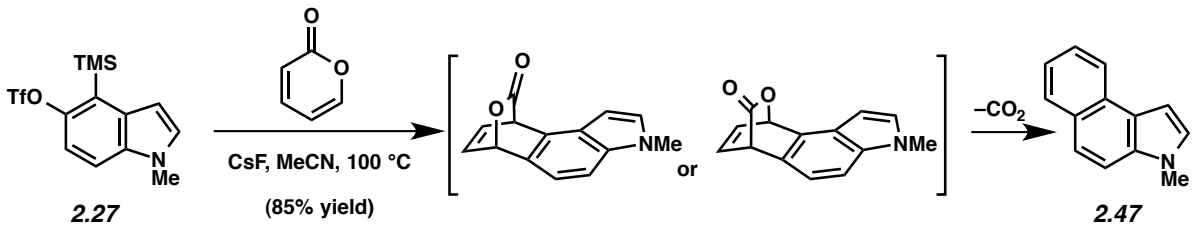


*2.27* *2.46*

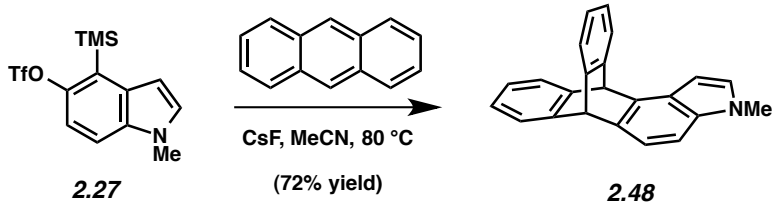
**Cyclopentadiene Diels-Alder adduct 2.46.** Cyclopentadiene was purified as follows: a 250 mL round bottom flask containing a stir bar was attached to a Vigreux column. The Vigreux column was fitted with a short-path distillation head, which in turn, was connected to a Schlenk tube. The apparatus was flame-dried, then the 250 mL round bottom flask was charged with dicyclopentadiene (100 mL). The apparatus was purged with $N_2$, and the 250 mL round bottom flask was heated to 220 °C. After several hours, approximately 50 mL of cyclopentadiene was collected in the Schlenk tube, which was submerged in a –78 °C bath (acetone/dry ice). The distillate was stored at –80 °C.

To a stirred solution of silyltriflate **2.27** (54.8 mg, 0.156 mmol) and cyclopentadiene (63.6 μL, 0.780 mmol, 5 equiv) in MeCN (1.6 mL) at 23 °C was added a solution of TBAF in THF (1.0 M, 312 μL, 0.312 mmol, 2 equiv). The solution was stirred for 5 min, then concentrated under reduced pressure. Purification of the residue by flash chromatography (20:1 Hexanes:$CH_2Cl_2$) provided cycloadduct **2.46** (19.9 mg, 65% yield) as a light yellow solid. $R_f$ 0.68 (2:1 Hexanes:$Et_2O$); $^1$H NMR (500 MHz, $CDCl_3$): δ 7.21 (d, *J* = 7.5, 1H), 7.03 (d, *J* = 3.0, 1H), 6.93–6.88 (m, 3H), 6.43 (dd, *J* = 3.5, 0.5, 1H), 4.22 (s, 1H), 4.01 (s, 1H), 3.73 (s, 3H), 2.42 (td, *J* = 6.5, 1.5, 1H), 2.35–2.34 (m, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 144.9, 144.4, 142.8, 142.6,

136.0, 129.9, 124.9, 116.2, 103.8, 97.9, 72.1, 50.8, 49.3, 33.3; IR (film): 2937, 1513, 1417, 1286 $cm^{-1}$; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{14}H_{14}N$, 196.1126; found, 196.1123.

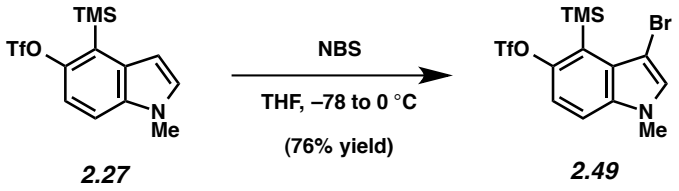



**Benzoindole 2.47.** To a stirred solution of silyltriflate **2.27** (48.3 mg, 0.137 mmol) and 2H-pyran-2-one (33.1 μL, 0.412 mmol, 3 equiv) in MeCN (1.4 mL) was added CsF (62.6 mg, 0.412 mmol, 3 equiv). The reaction vessel was placed in an aluminum heating block maintained at 100 °C for 5 h. After cooling to 23 °C, the reaction mixture was filtered over silica gel (EtOAc eluent). Evaporation under reduced pressure afforded the crude product, which was further purified by flash chromatography (10:1 Hexanes:$CH_2Cl_2$) to provide benzoindole **2.47** (21.0 mg, 85% yield) as a white solid. $R_f$ 0.45 (2:1 Hexanes:$CH_2Cl_2$); $^1$H NMR (500 MHz, $CDCl_3$): δ 8.26 (d, *J* = 8.0, 1H), 7.96 (d, *J* = 8.5, 1H), 7.64 (d, *J* = 9.0, 1H), 7.57 (td, *J* = 6.5, 1.0, 1H), 7.52 (d, *J* = 9, 1H), 7.43 (td, *J* = 7.0, 1.5, 1H), 7.15 (d, *J* = 3.0, 1H), 7.04 (dd, *J* = 2.5, 1.0, 1H), 3.94 (s, 3H). Spectral data for **2.26** match those previously reported.[62]




**Indolyl triptycene 2.48.** To a stirred solution of silyltriflate **2.27** (46.0 mg, 0.131 mmol) and anthracene (46.7 mg, 0.262 mmol, 2 equiv) in MeCN (1.3 mL) was added CsF (59.7 mg, 0.393 mmol, 3 equiv). The reaction vessel was placed in an aluminum heating block maintained at 80

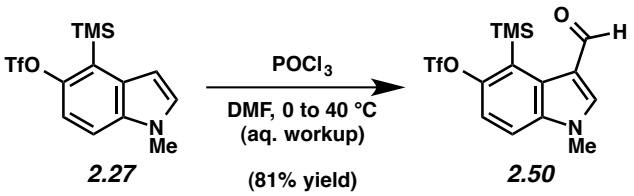
°C for 47 h. After cooling to 23 °C, the reaction mixture was filtered over silica gel (EtOAc eluent). Evaporation under reduced pressure afforded the crude product, which was further purified by flash chromatography (8:1 Hexanes:$CH_2Cl_2$→1:1 Hexanes:Benzene) to provide triptycene **2.48** (28.9 mg, 72% yield) as a white solid. $R_f$ 0.40 (2:1 Hexanes:$CH_2Cl_2$); $^1$H NMR (300 MHz, $CDCl_3$): δ 7.45–7.38 (m, 4H), 7.35 (d, *J* = 8.1, 1H), 7.05 (d, *J* = 3.3, 1H), 6.99–6.93 (m, 5H), 6.72 (dd, *J* = 3.0, 0.6, 1H), 5.80 (s, 1H), 5.53 (s, 1H), 3.70 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 147.1, 145.9, 137.9, 137.1, 135.7, 129.7, 125.1, 125.0, 124.8, 123.7, 123.4, 118.0, 105.2, 97.9, 54.4, 51.5, 33.2; IR (film): 3064, 2914, 1455 cm$^{-1}$; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{23}H_{18}N$, 308.1439; found, 308.1440.



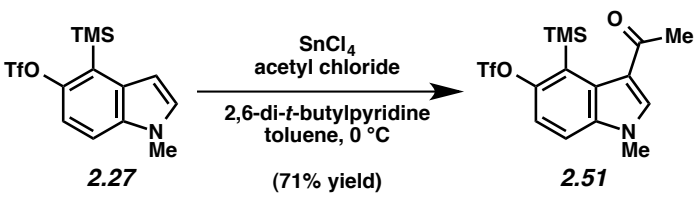
*2.27* *2.49*

**3-Bromo silyltriflate 2.49.** To a solution of silyltriflate **2.27** (69.1 mg, 0.20 mmol) in THF (2 mL) at –78 °C was added NBS (39.2 mg, 0.22 mmol, 1.1 equiv). After stirring for 5 min, the reaction was allowed to warm to 0 °C over 5 min. The reaction mixture was quenched with aqueous $Na_2S_2O_5$ (5 mL), further diluted with $Et_2O$ (5 mL), and allowed to warm to 23 °C. The layers were separated and the aqueous layer was extracted with $Et_2O$ (2 × 5 mL). The combined organic layers were dried over $Na_2SO_4$. Evaporation under reduced pressure afforded the crude product, which was further purified by flash chromatography (8:1 Hexanes:EtOAc) to give 3-bromo silyltriflate **2.49** (64.2 mg, 76% yield) as a white crystalline solid. $R_f$ 0.43 (4:1 Hexanes:EtOAc); $^1$H NMR (500 MHz, $C_6D_6$): δ 7.04 (d, *J* = 9.0, 1H), 6.53 (d, *J* = 9.0, 1H), 6.39 (s, 1H), 2.56 (s, 3H), 0.77 (s, 9H); $^{13}$C NMR (125 MHz, $C_6D_6$): δ 149.0, 134.6, 131.8, 130.7,

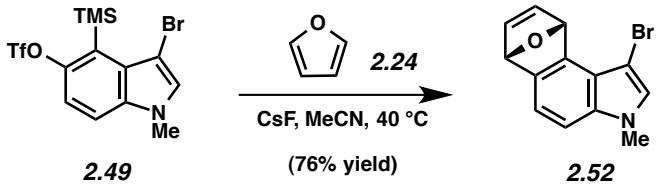
125.0, 118.9 (q, $J$ = 319, $CF_3$), 115.4, 111.9, 89.2, 31.6, 3.4; IR (film): 1415, 1397, 1212, 1131 $cm^{-1}$; HRMS-ESI ($m/z$) $[M + H]^+$ calculated for $C_{13}H_{16}BrF_3NO_3SSi$, 429.9756; found, 429.9738.




**3-Formyl silyltriflate 2.50:** To a vial containing DMF (1.5 mL) at 0 °C was added $POCl_3$ (150 μL, 1.61 mmol, 2.5 equiv). After stirring for 5 min, silyltriflate **2.27** (223.4 mg, 0.64 mmol) was added as a solution in DMF (1.25 mL), and the reaction was allowed to warm to 23 °C. After stirring for 45 min, the reaction vessel was placed in an aluminum heating block maintained at 40 °C. After stirring for an additional 45 min, the reaction was cooled to 23 °C and saturated aqueous $NaHCO_3$ (7 mL) was added. The reaction mixture was stirred at 23 °C for 3.3 h, then diluted with $Et_2O$ (15 mL). The layers were separated, and then the aqueous layer was extracted with $Et_2O$ (2 × 15 mL). The combined organic layers were washed with brine (5 mL), then dried over $Na_2SO_4$. Evaporation under reduced pressure afforded 3-formyl silyltriflate **2.50** (194.6 mg, 81% yield), which was used in the subsequent step without further purification. $R_f$ 0.42 (1:1 Hexanes:EtOAc); $^1H$ NMR (500 MHz, $CDCl_3$): δ 10.11 (s, 1H), 7.95 (s, 1H), 7.41 (d, $J$ = 9.0, 1H), 7.23 (d, $J$ = 9.0, 1H), 3.89 (s, 3H), 0.51 (s, 9H); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 184.9, 150.9, 139.3, 136.3, 130.6, 127.0, 120.4, 118.8 (q, $J$ = 318, $CF_3$), 116.9, 112.9, 34.2, 2.0; IR (film): 3063, 2952, 1663, 1527, 1414, 1202, 1132 $cm^{-1}$; HRMS-ESI ($m/z$) $[M + Na]^+$ calculated for $C_{14}H_{16}F_3NO_4SSiNa$, 402.0419; found, 402.0424.

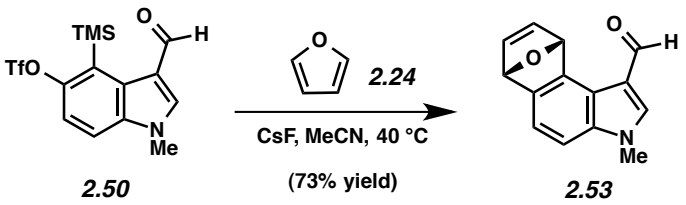



**3-Acetyl silyltriflate 2.51.** To a solution of silyltriflate **2.27** (1.00 g, 2.85 mmol) and 2,6-di-*t*-butylpyridine (700 μL, 3.24 mmol, 1.1 equiv) in toluene (26 mL) at 0 °C was added sequentially acetyl chloride (370 μL, 5.20 mmol, 1.8 equiv) and a solution of $SnCl_4$ in $CH_2Cl_2$ (1 M, 5.25 mL, 5.25 mmol, 1.8 equiv). The resulting mixture was stirred for 30 min, poured into a 23 °C solution of saturated aqueous $NaHCO_3$ (25 mL), and further diluted with brine (25 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 25 mL). The combined organic layers were dried over $Na_2SO_4$. Evaporation under reduced pressure afforded the crude product, which was further purified by flash chromatography (2:1:1 Hexanes:$CH_2Cl_2$:$Et_2O$) to afford 3-acetyl silyltriflate **2.51** (800 mg, 71% yield) as a white solid. $R_f$ 0.44 (1:1 Hexanes:EtOAc); $^1$H NMR (500 MHz, $CDCl_3$): δ 7.49 (s, 1H), 7.21 (d, $J$ = 9.0, 1H), 7.13 (d, $J$ = 8.5, 1H), 3.70 (s, 3H), 2.43 (s, 3H), 0.43 (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 192.2, 151.1, 137.6, 135.8, 130.3, 128.8, 120.2, 118.5 (q, $J$ = 318, $CF_3$), 116.3, 111.9, 33.6, 27.4, 2.0; IR (film): 2956, 1647, 1525, 1406, 1212, 1198 cm$^{-1}$; HRMS-ESI (*m/z*) [M + Na]$^+$ calculated for $C_{15}H_{18}F_3NO_4SSiNa$, 416.0576; found, 416.0577.



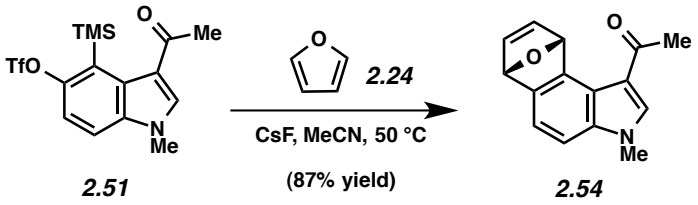

**3-Bromo Diels–Alder adduct 2.52.** To a solution of 3-bromo silyltriflate **2.49** (30.7 mg, 0.071 mmol) and furan (**2.24**) (26 μL, 0.359 mmol, 5 equiv) in MeCN (0.8 mL) was added CsF (33.9

mg, 0.223 mmol, 3 equiv). The reaction vessel was placed in an aluminum heating block maintained at 40 °C for 90 min. After cooling to 23 °C, the reaction was filtered over silica gel (99:1 EtOAc:$Et_3N$ eluent). Evaporation under reduced pressure afforded the crude product, which was further purified by flash chromatography (60:20:20:1 Hexanes:$CH_2Cl_2$:$Et_2O$:$Et_3N$) to give Diels–Alder adduct **2.52** (15.0 mg, 76% yield) as a white crystalline solid. $R_f$ 0.38 (4:1 Hexanes:EtOAc); $^1$H NMR (500 MHz, $C_6D_6$): δ 7.03 (d, $J$ = 8.0, 1H), 6.92 (dd, $J$ = 5.5, 1.5, 1H), 6.77 (dd, $J$ = 5.5, 1.5, 1H), 6.69 (s, 1H), 6.44 (d, $J$ = 8.0, 1H), 6.28 (s, 1H), 5.62 (s, 1H), 2.65 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 144.5, 143.4, 142.0, 141.9, 135.8, 129.6, 122.8, 115.3, 104.7, 86.5, 82.4, 80.6, 33.2; IR (film): 3116, 3017, 2919, 1523, 1290, 1279, 1042 cm$^{-1}$; HRMS-ESI (*m/z*) [M + Na]$^+$ calculated for $C_{13}H_{10}BrNONa$, 297.9843; found 297.9853.

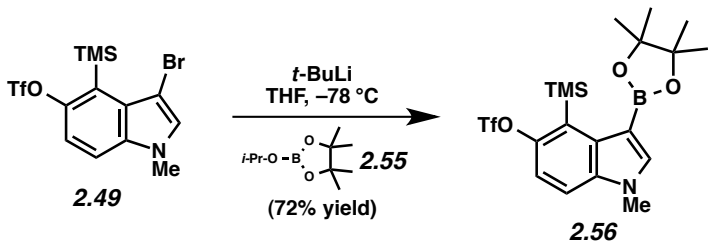



**3-Formyl Diels–Alder adduct 2.53.** To a solution of aldehyde **2.50** (32.2 mg, 0.085 mmol) and furan (**2.24**) (31 μL, 0.428 mmol, 5 equiv) in MeCN (0.9 mL) was added CsF (42.0 mg, 0.276 mmol, 3 equiv). The reaction vessel was placed in an aluminum heating block maintained at 40 °C for 2 h. After cooling to 23 °C, the reaction mixture was filtered over silica gel (EtOAc eluent). Evaporation under reduced pressure afforded the crude product, which was further purified by flash chromatography (1:1 Hexanes:EtOAc) to give adduct **2.53** (13.9 mg, 73% yield) as a white solid. $R_f$ 0.22 (1:1 Hexanes:EtOAc); $^1$H NMR (500 MHz, $CDCl_3$): δ 9.86 (s, 1H), 7.66 (s, 1H), 7.32 (d, $J$ = 7.5, 1H), 7.22 (dd, $J$ = 5.4, 1.7, 1H), 7.09 (dd, $J$ = 5.4, 1.6, 1H), 6.94 (d, $J$ = 7.9, 1H), 6.69 (s, 1H), 5.84 (s, 1H), 3.81 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$):

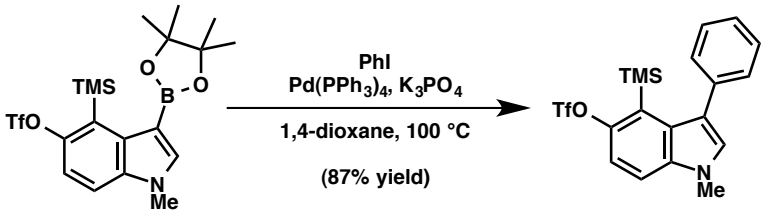
(13/14 C), δ 183.1, 145.2, 144.3, 143.7, 141.7, 137.2, 119.3, 117.4, 116.3, 105.2, 84.0, 82.7, 33.9; IR (film): 3101, 2800, 1655, 1533 $cm^{-1}$; HRMS-ESI (*m/z*) $[M + Na]^+$ calculated for $C_{14}H_{11}NO_2Na$, 248.0687; found, 248.0685.




**3-Acetyl Diels–Alder adduct 2.54.** To a solution of ketone **2.51** (31.1 mg, 0.079 mmol) and furan (**2.24**) (30 μL, 0.414 mmol, 5 equiv) in MeCN (0.8 mL) was added CsF (36.2 mg, 0.238 mmol, 3 equiv). The reaction vessel was placed in an aluminum heating block maintained at 50 °C for 130 min. After cooling to 23 °C, the reaction mixture was filtered over silica gel (EtOAC eluent). Evaporation under reduced pressure afforded the crude product, which was further purified by flash chromatography (1:1 Hexanes:EtOAc) to give adduct **2.54** (16.4 mg, 87% yield) as a white solid. $R_f$ 0.20 (1:1 Hexanes:EtOAc); $^1$H NMR (500 MHz, $CDCl_3$): δ 7.65 (s, 1H), 7.28 (d, *J* = 7.8, 1H), 7.24 (dd, *J* = 5.5, 1.9, 1H), 7.08 (dd, *J* = 5.5, 1.8, 1H), 6.89 (d, *J* = 7.9, 1H), 6.81 (s, 1H), 5.81 (s, 1H), 3.76 (s, 3H), 2.47 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 191.5, 144.9, 144.6, 144.5, 143.6, 137.9, 136.9, 120.6, 116.0, 115.9, 104.9, 84.4, 82.6, 33.7, 26.9; IR (film): 3013, 1635, 1533, 1454, 1374 $cm^{-1}$; HRMS-ESI (*m/z*) $[M + Na]^+$ calculated for $C_{15}H_{13}NO_2Na$, 262.0844; found, 262.0844.

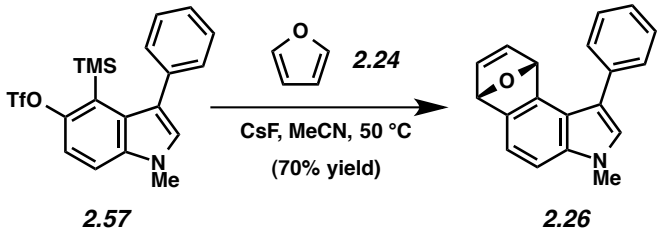



**3-Boronic ester silyltriflate 2.56.** To a solution of 3-bromo silyltriflate **2.49** (72.9 mg, 0.169 mmol) in THF (2 mL) at –78 °C was added *t*-BuLi (550 μL, 0.484 mmol, 2.9 equiv) dropwise over 3 min. After stirring for 20 min, borolane **2.55** (175 μL, 0.856 mmol, 5.1 equiv) was added dropwise over 2 min. The reaction was stirred for 5.5 h, quenched with aqueous $NH_4Cl$ (1 mL), and allowed to warm to 23 °C. The solution was further diluted with $H_2O$ (5 mL) and $Et_2O$ (10 mL). The layers were separated, and the aqueous layer was extracted with $Et_2O$ (2 × 10 mL). The combined organic layers were dried over $Na_2SO_4$ and concentrated under reduced pressure. The crude residue was purified by flash chromatography (12:1 Hexanes:EtOAc) to afford boronic ester **2.56** (58.2 mg, 72% yield) as a white solid. $R_f$ 0.34 (4:1 Hexanes:EtOAc); $^1$H NMR (500 MHz, $CDCl_3$): δ 7.68 (s, 1H), 7.32 (d, $J$ = 8.9, 1H), 7.13 (d, $J$ = 8.9, 1H), 3.77 (s, 3H), 1.35 (s, 12H), 0.53 (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$, 12/13 C): δ 150.0, 142.3, 137.0, 136.2, 127.8, 118.8 (q, $J$ = 318, $CF_3$), 115.0, 111.6, 83.3, 33.4, 25.1, 2.1; IR (film): 2987, 1516, 1415, 1217, 1132 cm$^{-1}$; HRMS-ESI [M + Na]$^+$ calculated for $C_{19}H_{27}BF_3NO_5SSiNa$, 500.1326; found, 500.1331.



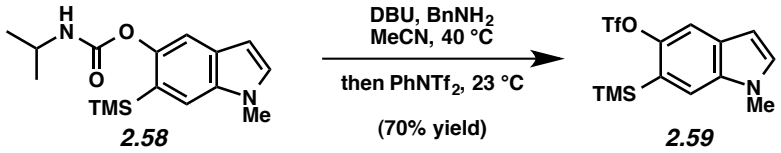

*2.56* *2.57*

**3-Phenyl silyltriflate 2.57. 2.57** was prepared following the general procedure described by Fürstner for cross-coupling of indolyl 3-boronic esters.[63] A Schlenk tube was charged with boronic ester **2.56** (61.1 mg, 0.128 mmol) and $K_3PO_4$ (81.6 mg, 0.384 mmol, 3 equiv), and then brought into a glovebox. To this mixture was added $Pd(PPh_3)_4$ (8.4 mg, 7.3 μmol, 0.057 equiv), iodobenzene (22 μL, 0.197 mmol, 1.5 equiv), and 1,4-dioxane (1 mL). The vessel was sealed under inert atmosphere, removed from the glovebox, and heated to 80 °C. After 19.5 h the temperature was raised to 100 °C and maintained for 8 h. The reaction was then cooled to 23 °C, diluted with EtOAc (5 mL), and filtered over silica gel (EtOAc eluent). Evaporation under reduced pressure afforded the crude product, which was further purified by flash chromatography (8:1:1 Hexanes:Benzene:$Et_2O$) to afford cross-coupled product **2.57** (47.7 mg, 87% yield) as an off-white solid. $R_f$ 0.51 (4:1 Hexanes:EtOAc); $^1$H NMR (500 MHz, $CDCl_3$): δ 7.47–7.43 (m, 2H), 7.41 (app. t, $J$ = 7.6, 2H), 7.39 (d, $J$ = 9.0, 1H), 7.33–7.29 (m, 1H), 7.17 (d, $J$ = 9.0, 1H), 7.16 (s, 1H), 3.83 (s, 3H), 0.12 (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 150.4, 137.4, 135.6, 131.3, 130.9, 129.0, 128.5, 126.4, 125.9, 120.5, 118.6 (q, $J$ = 318, $CF_3$), 114.7, 111.8, 33.1, 1.8; IR (film): 2948, 1604, 1417, 1405, 1207 cm$^{-1}$; HRMS-ESI ($m/z$) $[M + H]^+$ calculated for $C_{19}H_{21}O_3NF_3SSi$, 428.0963; found, 428.0969.




*2.57* *2.26*

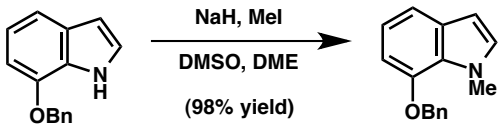
**3-Phenyl Diels–Alder adduct 2.26.** To a solution of silyltriflate **2.57** (35.9 mg, 0.084 mmol) and furan (**2.14**) (30 μL, 0.414 mmol, 5 equiv) in MeCN (0.85 mL) at 23 °C was added CsF (38.2 mg, 0.251 mmol, 3 equiv). The reaction vessel was placed in an aluminum heating block maintained at 50 °C for 6.25 h. After cooling to 23 °C, the reaction mixture was filtered over silica gel (EtOAc eluent). Evaporation under reduced pressure afforded the crude product, which was further purified by flash chromatography (6:1 Hexanes:EtOAc) to give adduct **2.26** (16.1 mg, 70% yield) as a white solid. $R_f$ 0.37 (6:1 Hexanes:EtOAc); $^1$H NMR (500 MHz, $CDCl_3$): δ 7.52–7.50 (m, 2H), 7.49–7.45 (m, 2H), 7.36–7.32 (m, 1H), 7.29 (d, $J$ = 8.0, 1H), 7.20 (app. t, $J$ = 1.0, 2H), 7.12 (s, 1H), 6.96 (d, $J$ = 8.0, 1H), 6.02 (s, 1H), 6.84 (d, $J$ = 1.0, 1H), 3.78 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 145.2, 142.4, 142.0, 141.2, 136.7, 135.7, 128.52, 128.48, 128.4, 126.1, 122.2, 115.6, 114.7, 104.5, 82.6, 81.9, 33.1; IR (film): 3021, 2922, 1601, 1549, 1456, 1416, 1214 cm$^{-1}$; HRMS-ESI $[M + Na]^+$ calculated for $C_{19}H_{15}NONa$, 296.1051; found, 296.1056.




*2.58* *2.59*

**Silyltriflate 2.59.** To a solution of silyl carbamate **2.58** (0.596 g, 1.96 mmol) in MeCN (10 mL) was added DBU (0.732 mL, 4.90 mmol, 2.5 equiv) and $BnNH_2$ (0.321 mL, 2.94 mmol, 1.5 equiv). The resulting mixture was placed in a heating bath maintained at 40 °C for 3 h, then

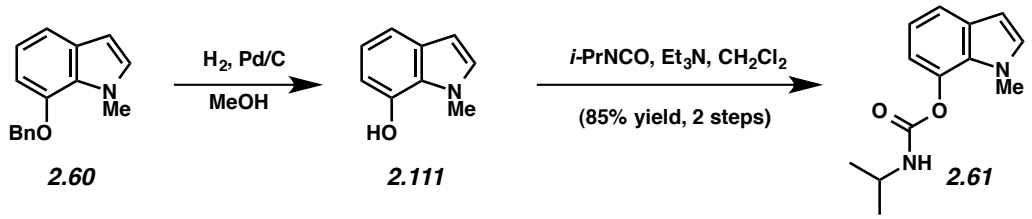
allowed to cool to 23 °C. Next, a solution of $PhNTf_2$ (1.05 g, 2.94 mmol, 1.5 equiv) in MeCN (4 mL) was added. After stirring for 1 h, the reaction mixture was passed over a plug of silica gel (EtOAc eluent). Evaporation under reduced pressure afforded the crude product, which was further purified by flash chromatography (99:1 Hexanes:EtOAc) to provide silyltriflate **2.59** (0.480 g, 70% yield) as a white solid. $R_f$ 0.52 (2:1 Hexanes:$Et_2O$); $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.60 (s, 1H), 7.41 (s, 1H), 7.15 (d, $J$ = 3.0, 1H), 6.51 (d, $J$ = 3.0, 1H), 3.83 (s, 3H), 0.44 (s, 9H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 149.5, 135.6, 131.8, 130.1, 124.8, 119.0 (q, $J$ = 320.1, $CF_3$), 116.3, 111.8, 101.9, 33.4, –0.1; IR (film): 2958, 1610, 1410 $cm^{-1}$; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{13}H_{16}F_3NO_3SSiNa$, 374.0470; found, 374.0470.



***2.110*** ***2.60***

***N*-Methyl-benzyloxyindole 2.60.** Benzyloxyindole **2.60** was prepared following a known procedure, with minor modifications.[17a,b] 95% NaH (0.23 g, 9.0 mmol, 2 equiv) was added to a solution of 7-benzyloxyindole (**2.110**) (1.0 g, 4.5 mmol) in 1,2-dimethoxyethane (12.4 mL) and DMSO (1.4 mL). The resulting solution was stirred at 23 °C for 40 min, then MeI (0.42 mL, 6.7 mmol, 1.5 equiv) was added dropwise over 1 min. The resulting mixture was stirred for 1.5 h, then quenched with $H_2O$ (4 mL), then brine (4 mL). The biphasic mixture was further diluted with $H_2O$ (20 mL) and EtOAc (20 mL). The layers were separated, and then the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with brine (20 mL), then dried over $MgSO_4$. Evaporation under reduced pressure afforded crude **2.60** (1.04 g, 98% yield) as a red oil, which was used in the subsequent step without further purification. $R_f$ 0.67 (3:1 Hexanes:EtOAc); $^1H$ NMR (500 MHz, $CDCl_3$) δ: 7.51 (d, $J$ = 7.3, 2H), 7.44–7.41 (m,

2H), 7.38–7.35 (m, 1H), 7.25 (d, $J$ = 7.9, 1H), 6.99 (app. t, $J$ = 8.2, 1H), 6.94 (d, $J$ = 3.0, 1H), 6.71 (d, $J$ = 7.7, 1H), 6.44 (d, $J$ = 2.9, 1H), 5.20 (s, 2H), 4.06 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 146.9, 137.2, 131.0, 129.8, 128.5, 127.8, 127.4, 126.4, 119.7, 114.0, 103.4, 100.9, 70.3, 36.6; IR (film): 3064, 3030, 2953, 2923, 1575, 1258 cm$^{-1}$; HRMS-ESI ($m/z$) $[M + H]^+$ calcd for $C_{16}H_{16}NO$, 238.1232; found, 238.1236.

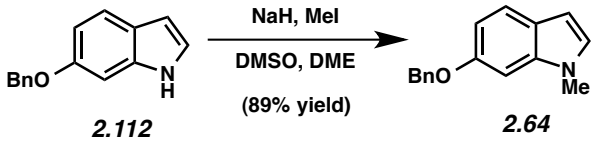


*2.60* *2.111* *2.61*

**Carbamate 2.61.** *N*-Methyl-benzyloxyindole **2.60** (0.50 g, 2.1 mmol) was dissolved in MeOH (4.9 mL) and 10% Pd/C (0.11 g, 0.11 mmol, 5.0 mol% Pd) was added.[17b] The mixture was placed under an atmosphere of hydrogen (double-balloon), stirred for 11 h at 23 °C, and then filtered over celite (MeOH eluent, 200 mL). Evaporation of the solvent under reduced pressure afforded hydroxyindole **2.111** (0.30 g, crude) as a grey solid, which was used in the subsequent step without further purification. $R_f$ 0.41 (3:1 Hexanes:EtOAc).

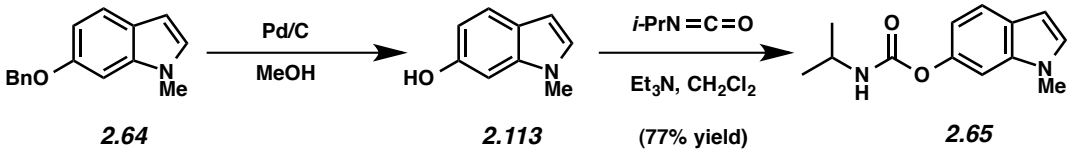
To a solution of crude **2.111** in $CH_2Cl_2$ (5 mL) were added sequentially *i*-PrNCO (0.59 mL, 6.0 mmol, 3 equiv) and $Et_3N$ (0.084 mL, 0.6 mmol, 0.3 equiv). The solution was stirred at 23 °C for 9 h, then concentrated to dryness under reduced pressure. Purification by flash chromatography (3:1 Hexanes:EtOAc) provided carbamate **2.61** (0.41 g, 85% yield, 2 steps). $R_f$ 0.21 (3:1 Hexanes:EtOAc); $^1$H NMR (500 MHz, $CDCl_3$): δ 7.44 (d, $J$ = 7.9, 1H), 7.02 (app. t, $J$ = 7.7, 1H), 6.93 (d, $J$ = 2.9, 1H), 6.90 (d, $J$ = 7.6, 1H), 6.45 (d, $J$ = 3.0, 1H), 4.96 (s, 1H), 3.98–3.87 (m, 4H), 1.26 (d, $J$ = 6.5, 6H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 154.1, 136.8, 131.9, 130.3,

128.8, 119.4, 118.4, 115.2, 101.3, 43.5, 35.4, 22.9; IR (film): 3333, 2978, 1696, 1517 $cm^{-1}$; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{13}H_{16}N_2O_2Na$, 255.1109; found, 255.1116.




***2.112*** ***2.64***

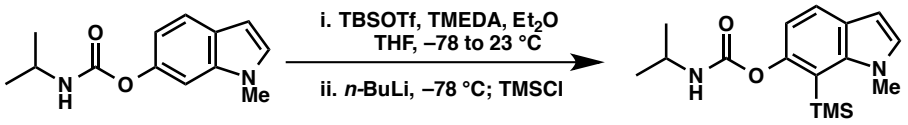
***N*-Methyl-benzyloxyindole 2.64**. **2.64** was prepared following a known procedure,[17a,b] with minor modifications. 95% NaH (0.45 g, 17.9 mmol, 2 equiv) was added to a solution of 6-benzyloxyindole **2.112** (2.0 g, 8.96 mmol) in dimethoxyethane (24.8 mL) and DMSO (2.8 mL). The resulting solution was stirred at 23 °C for 40 min, then MeI (0.84 mL, 13.4 mmol, 1.5 equiv) was added dropwise over 1 min. The resulting mixture was stirred for 2 h, then quenched with $H_2O$ (10 mL). The biphasic mixture was further diluted with water (40 mL) and EtOAc (40 mL). The layers were separated, and then the aqueous layer was extracted with EtOAc (2 × 40 mL). The combined organic layers were dried over $MgSO_4$. Evaporation of the solvent under reduced pressure afforded the crude product, which was further purified by flash chromatography (9:1 Hexanes:EtOAc) to provide *N*-methyl-benzyloxyindole **2.64** (1.89 g, 89% yield). $R_f$ 0.50 (3:1 Hexanes:EtOAc); $^1H$ NMR (500 MHz, $CDCl_3$): δ 7.52–7.49 (m, 3H), 7.41 (t, *J* = 7.5, 2H), 7.35–7.33 (m, 1H), 6.96 (d, *J* = 3.0, 1H), 6.89–6.87 (m, 2H), 6.42 (d, *J* = 3.0, 1H), 5.15 (s, 2H), 3.74 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 155.6, 137.7, 137.5, 128.7, 128.1, 128.0, 127.8, 123.2, 121.6, 110.0, 101.0, 70.9, 33.0; IR (film): 2935, 1617, 1462 $cm^{-1}$; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{16}H_{15}NONa$, 260.1051; found, 260.1051.




*2.64* *2.113* *2.65*

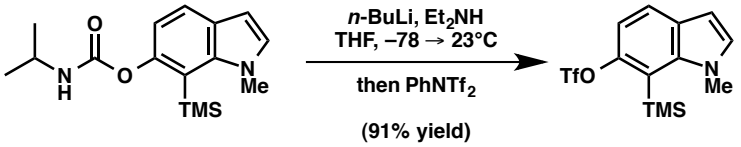
**Carbamate 2.65.** *N*-methyl-benzyloxyindole **2.64** (1.9 g, 8.0 mmol) was dissolved in MeOH (18.6 mL) and 10% Pd/C (0.21 g, 0.20 mmol, 2.5 mol% Pd) was added. The mixture was placed under an atmosphere of hydrogen (double-balloon), stirred for 4.5 h at 23 °C, and then filtered over celite (MeOH eluent, 500 mL). Evaporation of the solvent under reduced pressure afforded hydroxyindole **2.113** as a grey solid, which was used in the subsequent step without further purification. $R_f$ 0.22 (3:1 Hexanes:EtOAc).

Carbamate **2.65** was prepared following the general procedure described by Igarashi et al.[55] Crude **2.113** was dissolved in $CH_2Cl_2$ (20 mL) and *i*-PrNCO (1.19 mL, 12.1 mmol, 1.5 equiv) was added, followed by $Et_3N$ (0.22 mL, 1.6 mmol, 0.2 equiv). The solution was stirred at 23 °C for 16 h, then concentrated to dryness *in vacuo*. Purification by flash chromatography (6:1 Hexanes:EtOAc→4.5:1 Hexanes:EtOAc) provided carbamate **2.65** (1.45 g, 77% yield). $R_f$ 0.78 (1:1 Hexanes:EtOAc:$CH_2Cl_2$); $^1$H NMR (500 MHz, $CDCl_3$): δ 7.56 (d, $J$ = 8.5, 1H), 7.14 (s, 1H), 7.04 (d, $J$ = 3.0, 1H), 6.87 (d, $J$ = 7.5, 1H), 6.46 (d, $J$ = 2.5, 1H), 4.86 (d, $J$ = 4.0, 1H), 3.95–3.90 (m, 1H), 3.76 (s, 3H), 1.26 (d, $J$ = 6.0, 6H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 154.7, 146.7, 136.8, 129.5, 126.2, 121.2, 114.1, 102.6, 101.1, 43.6, 33.1, 23.2; IR (film): 3331, 2969, 1700, 1530 $cm^{-1}$; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{13}H_{16}N_2O_2Na$, 255.1109, found, 255.1105.



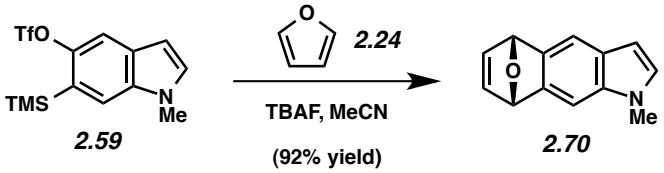

*2.65* *2.66*

**Silyl carbamate 2.66.** To a solution of carbamate **2.65** (146.4 mg, 0.630 mmol) in 3:1 $Et_2O$:THF (6.05 mL) at –78 °C was added TMEDA (0.132 mL, 0.882 mmol, 1.40 equiv), followed by a solution of TBSOTf in *n*-pentane (1.30 M, 0.573 mL, 0.756 mmol, 1.2 equiv).[19] After stirring for 30 min, the white suspension was allowed to warm to 23 °C over 80 min, by which time TMEDA·TfOH had formed as an oil on the bottom of the flask. TMEDA (0.329 mL, 2.21 mmol, 3.5 equiv) was added, and the mixture was cooled to –78 °C.[56] A solution of *n*-BuLi in hexanes (1.85 M, 1.19 mL, 2.21 mmol, 3.5 equiv) was added dropwise over 5 min.[57] The mixture was stirred at –78 °C for 3 h, then neat TMSCl (0.560 mL, 4.41 mmol, 7.0 equiv) was added dropwise over 5 min. The resulting mixture was stirred at –78 °C for 2 h, quenched with 0.5 M aqueous $NaHSO_4$ (5 mL), and allowed to warm to 23 °C over 1 h with vigorous stirring. The organic layer was separated, and then the aqueous layer was extracted with $Et_2O$ (5 mL). The combined organic layers were washed successively with 0.5 M aqueous $NaHSO_4$ (5 mL) and brine (5 mL), then dried over $Na_2SO_4$. Evaporation under reduced pressure afforded the crude product, which was purified by flash chromatography (6:1 Hexanes:EtOAc) to afford silylcarbamate **2.66** (0.180 g, 94% yield). $R_f$ 0.26 (6:1 Hexanes:EtOAc); $^1$H NMR (500 MHz, $CDCl_3$): δ 7.58 (d, $J$ = 8.5, 1H), 6.99 (d, $J$ = 3.0, 1H), 6.82 (d, $J$ = 8.5, 1H), 6.51 (d, $J$ = 3.0, 1H), 4.82 (d, $J$ = 7.5, 1H), 3.99–3.92 (m, 1H), 3.89 (s, 3H), 1.24 (d, $J$ = 6.5, 6H), 0.49 (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 154.7, 152.5, 142.3, 131.8, 126.9, 123.0, 115.1, 113.4, 102.7, 43.3, 37.7, 22.8, 3.2; IR (film): 3333, 2972, 1709, 1515 cm$^{-1}$; HRMS-ESI (*m*/*z*) [M + Na]$^+$ calcd for $C_{16}H_{24}N_2O_2SiNa$, 327.1505, found, 327.1501.




*2.66* *2.68*

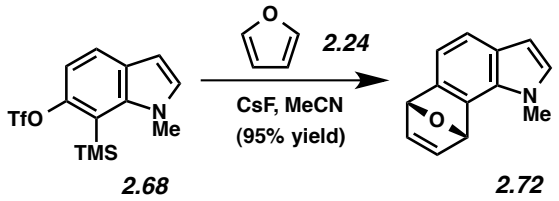
**Silyltriflate 2.68.** To a solution of silyl carbamate **2.66** (0.621 g, 2.04 mmol) in THF (6.3 mL) at –78 °C was added dropwise *n*-BuLi in hexanes (1.67 M, 1.47 mL, 2.45 mmol, 1.2 equiv) and $Et_2NH$ (0.25 mL, 2.45 mmol, 1.2 equiv). The resulting mixture was stirred at –78 °C for 20 min, then allowed to warm to 23 °C over an additional 25 min. Next, $PhNTf_2$ (0.87 g, 2.45 mmol, 1.2 equiv) was added as a solid in a single portion. After stirring for 15 min, the reaction mixture was passed over a plug of silica gel (EtOAc eluent). Evaporation under reduced pressure afforded the crude product, which was further purified by flash chromatography (98:2 Hexanes:EtOAc) to provide silyltriflate **2.68** (0.65 g, 91% yield) as a colorless oil. $R_f$ 0.74 (3:1:1 Hexanes:$Et_2O$:$CH_2Cl_2$); $^1$H NMR (500 MHz, $CDCl_3$): δ 7.63 (d, *J* = 9.0, 1H), 7.11 (d, *J* = 3.5, 1H), 7.00 (d, *J* = 9.0, 1H), 6.57 (d, *J* = 3.5, 1H), 3.88 (s, 3H), 0.55 (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 151.3, 142.9, 133.8, 128.8, 123.7, 118.9 (q, *J* = 321, $CF_3$), 115.8, 113.6, 103.2, 38.0, 2.9; IR (film): 2962, 1391, 1204 cm$^{-1}$; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{13}H_{16}F_3NO_3SSiNa$, 374.0470; found, 374.0461.



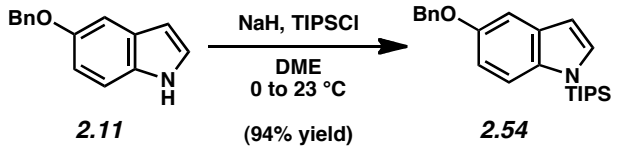

*2.59* *2.70*

**Furan Diels-Alder adduct 2.70.** To a solution of silyltriflate **2.59** (44 mg, 0.125 mmol) and furan (**2.24**) (46 μL, 0.626 mmol, 5 equiv, dried over $Na_2SO_4$) in MeCN (2.0 mL) at 23 °C was added a solution of TBAF in THF (1.0 M, 250 μL, 0.25 mmol, 2.0 equiv). The solution was

stirred for 30 min, then filtered over silica gel ($Et_2O$ eluent). Evaporation under reduced pressure afforded the crude product, which was further purified by flash chromatography (19:1 Hexanes:EtOAc) to provide adduct **2.70** (23.0 mg, 92% yield) as a pale oil. $R_f$ 0.35 (2:1 hexanes:EtOAc); $^1$H NMR (500 MHz, $CDCl_3$): δ 7.44 (s, 1H), 7.24 (s, 1H), 7.03 (dd, $J$ = 5.6, 1.6, 1H), 7.00 (dd, $J$ = 5.6, 1.6, 1H), 6.98 (d, $J$ = 3.0, 1H), 6.37 (d, $J$ = 3.0, 1H), 5.76 (s, 2H), 3.75 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 143.4, 142.6, 142.5, 139.4, 134.3, 128.4, 125.5, 113.3, 103.4, 101.9, 82.8, 82.7, 33.3; IR (film): 3091, 3004, 2921, 1506, 1285 cm$^{-1}$; HRMS-ESI (*m*/*z*) [M + Na]$^+$ calcd for $C_{13}H_{11}NONa$, 220.0738; found, 220.0731.

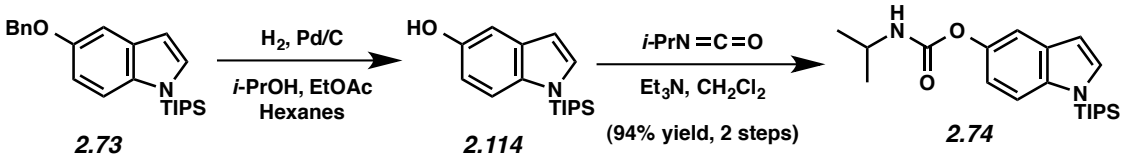



**Furan Diels–Alder adduct 2.72.** To a stirred solution of silyltriflate **2.68** (39.4 mg, 0.1121 mmol) and furan (**2.24**) (40.8 μL, 0.561 mmol, 5 equiv) in MeCN (1.1 mL) was added CsF (34.1 mg, 0.561 mmol, 2.0 equiv). The solution was stirred at 23 °C for 3 h, then filtered over silica gel (EtOAc eluent). Evaporation under reduced pressure afforded the crude product, which was further purified by flash chromatography (3:1:1 Hexanes:$CH_2Cl_2$:$Et_2O$) to provide adduct **2.72** (21.1 mg, 95% yield). $R_f$ 0.33 (3:1:1 Hexanes:$CH_2Cl_2$:$Et_2O$); $^1$H NMR (500 MHz, $CDCl_3$): δ 7.37 (d, $J$ = 7.5, 1H), 7.29–7.21 (m, 2H), 7.22 (dd, $J$ = 5.5, 1.5, 1H), 7.07 (d, $J$ = 3.0, 1H), 6.54 (d, $J$ = 3.0, 1H), 6.403–6.400 (m, 1H), 5.97 (d, $J$ = 1.0, 1H), 4.03 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 144.8, 144.2, 143.4, 132.1, 131.2, 130.4, 128.9, 117.2, 113.2, 101.6, 83.0, 81.2, 34.9; IR (film): 3089, 3033, 2908, 1304, 1276 cm$^{-1}$; HRMS-ESI (*m*/*z*) [M + Na]$^+$ calcd for $C_{13}H_{11}NONa$, 220.0738; found, 220.0737.



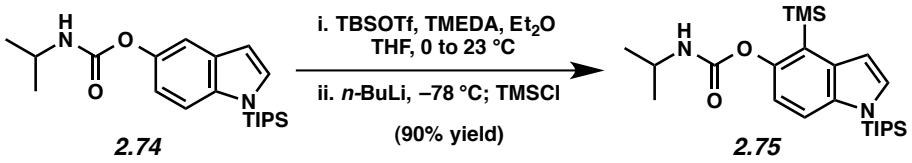

*2.11* *2.54*

***N*-TIPS benzyloxyindole 2.54.** To a solution of 5-benzyloxyindole (**2.11**) (3.00 g, 13.4 mmol) in 1,2-dimethoxyethane (42.0 mL) at 0 °C was added 60% NaH (1.07 g, 26.9 mmol, 2 equiv). The resulting solution was stirred at 0 °C for 20 min, then TIPSCl (4.31 mL, 20.2 mmol, 1.5 equiv) was added dropwise over 5 min. The resulting mixture was removed from the bath and allowed to warm to 23 °C. After stirring for an additional 90 min, the reaction was quenched with brine (60 mL). The biphasic mixture was further diluted with EtOAc (60 mL). The layers were separated, and then the aqueous layer was extracted with EtOAc (2 × 60 mL). The combined organic layers were washed with brine (20 mL), $H_2O$ (20 mL), then dried over $MgSO_4$. Evaporation of the solvent under reduced pressure afforded crude **2.54**, which was further purified by flash chromatography (3:1 Hexanes:$CH_2Cl_2$) to afford **2.54** (4.79 g, 94% yield) as a white solid. $R_f$ 0.73 (3:1 Hexanes:EtOAc); $^1$H NMR (300 MHz, $CDCl_3$): δ 7.60–7.30 (m, 8H), 7.02 (dd, $J$ = 8.7, 2.4, 1H), 6.67 (d, $J$ = 3.0, 1H), 5.18 (s, 2H), 1.75 (septet, $J$ = 7.8, 3H), 1.25 (d, $J$ = 7.5, 18H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 153.5, 138.0, 136.1, 132.1, 132.0, 128.6, 127.8, 127.7, 114.6, 112.1, 104.7, 103.7, 70.7, 18.2, 12.9; IR (film): 2943, 2864, 1463, 1450, 1158 cm$^{-1}$; HRMS-ESI ($m/z$) [M + Na]$^+$ calcd for $C_{24}H_{33}NOSiNa$, 402.2229; found, 402.2217.



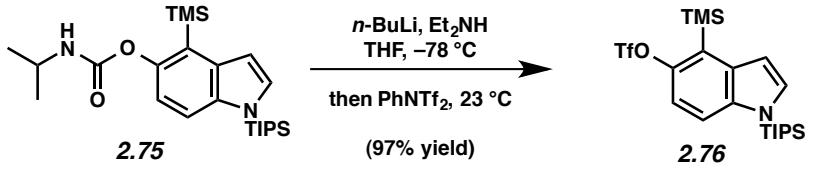

***N*-TIPS carbamate 2.74.** Carbamate **2.74** was prepared following the general procedure described by Igarashi.[55] To a solution of *N*-TIPS benzyloxyindole (**2.73**) (4.79 g, 12.6 mmol) in 1:1:1 *i*-PrOH:Hexanes:EtOAc (108 mL) was added 5% Pd/C (0.67 g, 0.32 mmol, 2.5 mol% Pd). The mixture was placed under an atmosphere of hydrogen (double-balloon), stirred for 2.5 h at 23 °C, and then filtered over celite (EtOAc eluent). Evaporation of the solvent under reduced pressure afforded crude **2.114** as a pink solid, which was used in the subsequent step without further purification. $R_f$ 0.07 (2:1 Hexanes:$CH_2Cl_2$).

Crude **2.114** was dissolved in $CH_2Cl_2$ (63.1 mL), and $Et_3N$ (0.53 mL, 3.79 mmol, 0.3 equiv), followed by *i*-PrNCO (2.66 mL, 27.1 mmol, 2.1 equiv), was added. The solution was stirred at 23 °C for 24 h, then concentrated to dryness under reduced pressure. Purification by flash chromatography (7:3 Hexanes:$Et_2O$) provided *N*-TIPS carbamate **2.74** (4.42 g, 94% yield, 2 steps). $R_f$ 0.58 (3:1 Hexanes:EtOAc); $^1$H NMR (500 MHz, $CDCl_3$): δ 7.45 (d, *J* = 2.0, 1H), 7.43 (d, *J* = 9.0, 1H), 7.25 (s, 1H), 6.91 (dd, *J* = 9.0, 2.0, 1H), 6.58 (d, *J* = 3.5, 1H), 4.87 (d, *J* = 7.0, 1H), 3.91 (m, 1H), 1.68 (septet, *J* = 7.5, 3H), 1.23 (d, *J* = 6.5, 6H), 1.13 (d, *J* = 7.5, 18H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 155.0, 145.0, 138.7, 132.6, 132.2, 116.0, 114.2, 112.9, 105.3, 43.7, 23.3, 18.4, 13.1; IR (film): 3281, 2955, 2868, 1712 cm$^{-1}$; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{21}H_{34}N_2O_2SiNa$, 397.2287; found, 397.2282.

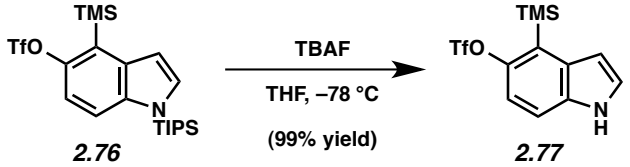


*2.74* *2.75*

***N*-TIPS silylcarbamates 2.75.** Silyl carbamate **2.75** was prepared following the general procedure described by Hoppe and Snieckus for *o*-lithiation of isopropyl carbamates, with minor modifications.[19] To a solution of *N*-TIPS carbamate **2.74** (1.02 g, 2.72 mmol) and TMEDA (0.61 mL, 3.82 mmol, 1.4 equiv) in 3:1 $Et_2O$:THF (27 mL) at 0 °C was added a solution of TBSOTf in *n*-pentane (1.30 M, 3.21 mL, 3.3 mmol, 1.2 equiv). After stirring for 5 min, the white suspension was allowed to warm to 23 °C over 30 min. TMEDA (1.53 mL, 9.56 mmol, 3.5 equiv) was added, and the mixture was cooled to –78 °C. A solution of *n*-BuLi in hexanes (2.21 M, 4.35 mL, 9.56 mmol, 3.5 equiv) was added dropwise over 8 min. The mixture was stirred at –78 °C for 3 h, then neat TMSCl (2.43 mL, 19.1 mmol, 7 equiv) was added dropwise over 15 min. The resulting mixture was stirred at –78 °C for 1 h, quenched with 1 M $NaHSO_4$ (25 mL), and allowed to warm to 23 °C over 45 min with vigorous stirring. The organic layer was separated, washed successively with 1 M $NaHSO_4$ (25 mL) and brine (25 mL), then dried over $Na_2SO_4$. Evaporation under reduced pressure afforded the crude product, which was purified by flash chromatography (15:1:1 Hexanes:$Et_2O$:$CH_2Cl_2$) to afford *N*-TIPS silylcarbamate **2.75** (1.10 g, 90% yield). $R_f$ 0.27 (3:1 Hexanes:EtOAc); $^1$H NMR (500 MHz, $CDCl_3$): δ 7.49 (d, $J$ = 9.0, 1H), 7.29 (d, $J$ = 3.0, 1H), 6.88 (d, $J$ = 9.0, 1H), 6.79 (d, $J$ = 3.5, 1H), 4.82 (d, $J$ = 8, 1H), 3.98–3.92 (m, 1H), 1.69 (septet, $J$ = 7.5, 3H), 1.24 (d, $J$ = 6.5, 6H), 1.15 (d, $J$ = 7.5, 18H), 0.44 (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 155.1, 150.0, 138.0, 136.1, 132.1, 121.7, 116.6, 115.6, 106.6, 43.6, 23.3, 18.5, 13.1, 1.5; IR (film): 3400, 2945, 2869, 1742 cm$^{-1}$; HRMS-ESI (*m*/*z*) [M + Na]$^+$ calcd for $C_{24}H_{42}N_2O_2Si_2Na$, 469.2682; found, 469.2666.

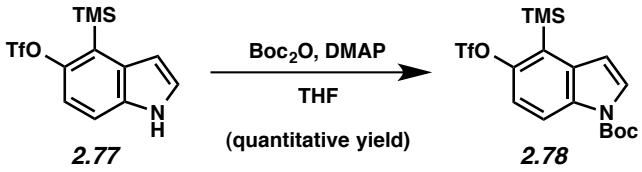



***N*-TIPS silyltriflate 2.76.** To a solution of silyl carbamate **2.75** (6.29 g, 14.1 mmol) in THF (142 mL) at –78 °C was added a solution of *n*-BuLi (1.43 M, 12.5 mL, 17.9 mmol, 1.3 equiv) dropwise over 30 min. $Et_2NH$ (1.90 mL, 18.4 mmol, 1.3 equiv) was added and the resulting mixture was stirred at –78 °C for 15 min, then allowed to warm to 23 °C over 15 min. Next, $PhNTf_2$ (7.58 g, 21.2 mmol, 1.5 equiv) was added as a solid. The mixture was allowed to stir for 2 h and then passed over a plug of silica gel (EtOAc eluent). Evaporation under reduced pressure afforded the crude product, which was further purified by flash chromatography (95:5 Hexanes:Benzene) to provide *N*-TIPS silyltriflate **2.76** (6.74 g, 97% yield). $R_f$ 0.74 (2:1 Hexanes:$Et_2O$); $^1$H NMR (500 MHz, $CDCl_3$): δ 7.53 (d, $J$ = 9.0, 1H), 7.38 (d, $J$ = 3.0, 1H), 7.12 (d, $J$ = 9.0, 1H), 6.84 (d, $J$ = 3.0, 1H), 1.71 (septet, $J$ = 7.5, 3H), 1.17 (d, $J$ = 7.5, 18H), 0.53 (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 149.2, 138.8, 136.5, 133.3, 123.1, 118.8 (q, $J$ = 318, $CF_3$), 115.8, 113.6, 107.2, 18.2, 13.0, 1.3; IR (film): 2955, 2872, 1411, 1391, 1401 cm$^{-1}$; HRMS-ESI (*m*/*z*) $[M + Na]^+$ calcd for $C_{21}H_{34}F_3NO_3SSi_2Na$, 516.1648; found, 516.1649.



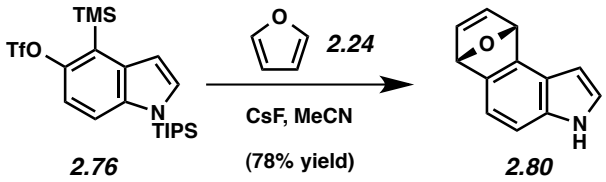

***N*-H silyltriflate 2.77.** To a solution of *N*-TIPS silyltriflate **2.76** (0.427 g, 0.865 mmol) in THF (8.9 mL) at –78 °C was added a solution of TBAF in THF (1.0 M, 0.865 mL, 0.865 mmol, 1 equiv) dropwise over 2 min. The solution was stirred for 15 min, then quenched with $H_2O$ (10 mL). After warming to 23 °C, the biphasic mixture was further diluted with $Et_2O$ (10 mL). The

layers were separated, and then the aqueous layer was extracted with $Et_2O$ (3 × 10 mL). The combined organic layers were dried over $MgSO_4$. Evaporation under reduced pressure afforded the crude product, which was further purified by flash chromatography (3:1 Hexanes:EtOAc) to provide *N*-H silyltriflate **2.77** (289 mg, 99% yield). $R_f$ 0.37 (3:1:1 Hexanes:$Et_2O$:$CH_2Cl_2$); $^1$H NMR (500 MHz, $CDCl_3$): δ 8.33 (br s, 1H), 7.35 (dd, *J* = 8.9, 0.8, 1H), 7.30 (app. t, *J* = 2.9, 1H), 7.16 (d, *J* = 8.9, 1H) 6.78–6.77 (m, 1H), 0.56 (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 148.8, 133.5, 132.5, 126.1, 123.7, 118.7 (q, *J* = 319, $CF_3$), 114.9, 113.2, 105.0, 1.0; IR (film): 3446, 1396, 1211 cm$^{-1}$; HRMS-ESI (*m*/*z*) [M + H]$^+$ calcd for $C_{12}H_{15}F_3NO_3SSi$, 338.0494; found, 338.0490.

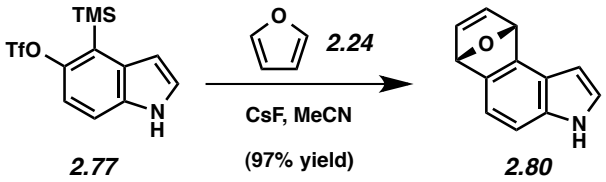



***N*-Boc silyltriflate 2.78.** *N*-Boc silyltriflate **2.78** was prepared following the general procedure described by Gribble for Boc-protection of indoles.[64] DMAP (5.4 mg, 0.044 mmol, 0.1 equiv) was added to a solution of *N*-H silyltriflate **2.77** (0.150 g, 0.44 mmol) in THF (5 mL). The resulting solution was stirred at 23 °C for 5 min, then $Boc_2O$ (97 mg, 0.44 mmol, 1 equiv) was added. The resulting mixture was stirred for 15 h, then filtered over silica gel ($Et_2O$ eluent). Evaporation under reduced pressure afforded *N*-Boc silyltriflate **2.78** (0.195 g, quantitative yield). $R_f$ 0.74 (3:2 Hexanes:$Et_2O$); $^1$H NMR (500 MHz, $CDCl_3$): δ 8.26 (d, *J* = 9.0, 1H), 7.73 (d, *J* = 3.8, 1H), 7.27 (d, *J* = 9.1, 1H), 6.78 (d, *J* = 3.8, 1H), 1.68 (s, 9H), 0.51 (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 150.3, 149.2, 135.9, 133.3, 127.5, 124.7, 118.7 (q, *J* = 319, $CF_3$), 117.4, 116.3,

108.5, 84.4, 28.1, 1.1; IR (film): 2982, 1742, 1399, 1210 $cm^{-1}$; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{17}H_{22}F_3NO_5SSiNa$, 460.0838; found, 460.0835.

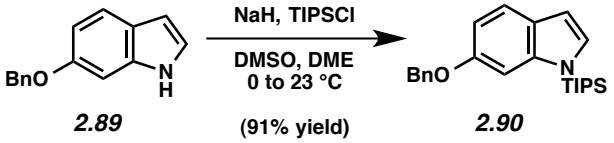



**Furan Diels–Alder adduct 2.80.** To a stirred solution of silyltriflate **2.76** (35.0 mg, 0.0708 mmol) and furan (**2.24**) (25.7 μL, 0.354 mmol, 5 equiv) in MeCN (1.4 mL) was added CsF (32.3 mg, 0.212 mmol, 3.0 equiv). The solution was stirred at 23 °C for 3.5 h, then filtered over silica gel (EtOAc eluent). Evaporation under reduced pressure afforded the crude product, which was further purified by flash chromatography (3:1:1 Hexanes:$CH_2Cl_2$:$Et_2O$) to provide adduct **2.80** (10.1 mg, 78% yield) as a white solid. $R_f$ 0.27 (3:1:1 Hexanes:$CH_2Cl_2$:$Et_2O$); $^1H$ NMR (500 MHz, $CDCl_3$): δ 8.11 (br s, 1H), 7.24 (dd, *J* = 3.0, 2.5, 1H), 7.21 (d, *J* = 8.0, 1H), 7.16 (app. qd, *J* = 5.5, 2.0, 2H), 7.02 (dd, *J* = 7.5, 0.5, 1H), 6.50–6.49 (m, 1H), 6.04–6.03 (m, 1H), 5.86–5.85 (m, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 145.1, 143.0, 142.0, 141.0, 135.0, 126.2, 123.1, 115.1, 106.2, 99.6, 83.2, 82.0; IR (film): 3293, 3011, 1430 $cm^{-1}$; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{12}H_9NONa$, 206.0582; found, 206.0583.



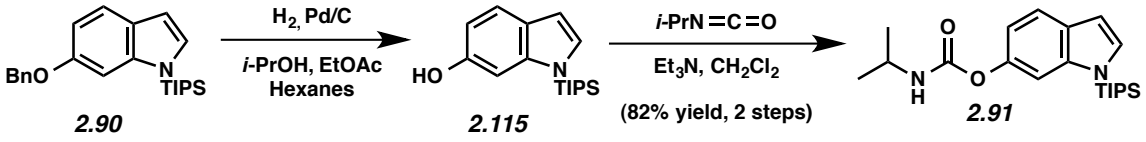

**Furan Diels–Alder adduct 2.80.** To a stirred solution of silyltriflate **2.77** (32.2 mg, 0.0954 mmol) and furan (**2.24**) (34.7 μL, 0.477 mmol, 5 equiv) in MeCN (1.9 mL) was added CsF (29.0

mg, 0.1908 mmol, 2.0 equiv). The solution was stirred at 23 °C for 2 h, then filtered over silica gel (EtOAc eluent). Evaporation under reduced pressure afforded the crude product, which was further purified by flash chromatography (3:1:1 Hexanes:$CH_2Cl_2$:$Et_2O$) to provide adduct **2.80** (16.9 mg, 97% yield) as a white solid. Spectral data match those reported on page 99 of this dissertation.




***N*-TIPS benzyloxyindole 2.90.** To a solution of 6-benzyloxyindole **2.89** (3.00 g, 13.4 mmol) in 1,2-dimethoxyethane (37.0 mL) and DMSO (4.1 mL) at 0 °C was added 95% NaH (0.97 g, 40.3 mmol, 3 equiv). The resulting solution was stirred at 0 °C for 30 min, then TIPSCl (5.73 mL, 26.8 mmol, 2 equiv) was added dropwise over 5 min. The resulting mixture was stirred at 0 °C for 10 min, and then the reaction was allowed to warm to 23 °C. After 24 h, the mixture was placed in a 0 °C bath and additional NaH (0.50 g, 20.8 mmol, 1.56 equiv), followed by TIPSCl (5.70 mL, 26.6 mmol, 1.99 equiv) were added. The reaction was allowed to warm to 23 °C and stirred for 18.5 h. The reaction was cooled to 0 °C and additional NaH (0.5 g, 20.8 mmol, 1.56 equiv) and TIPSCl (5.7 mL, 26.6 mmol, 1.99 equiv) were added. The reaction was allowed to warm to 23 °C. Following 23 h of stirring at 23 °C, the mixture was cooled to 0 °C and quenched with brine (60 mL). The biphasic mixture was further diluted with EtOAc (60 mL) and $H_2O$ (60 mL). The layers were separated, and then the aqueous layer was extracted with EtOAc (2 × 60 mL). The combined organic layers were washed with washed brine (60 mL), $H_2O$ (60 mL), then dried over $MgSO_4$. Evaporation of the solvent under reduced pressure afforded crude **2.90**, which was further purified by flash chromatography (100% Hexanes → 3:1 Hexanes:$CH_2Cl_2$) to afford

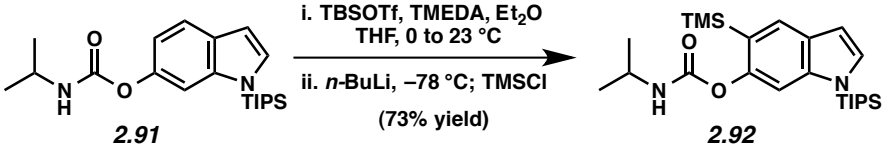
**2.90** (4.65 g, 91% yield). $R_f$ 0.74 (3:1 Hexanes:EtOAc); $^1$H NMR (500 MHz, $CDCl_3$): δ 7.50 (d, $J$ = 8.5, 1H), 7.46 (d, $J$ = 7.0, 2H), 7.38 (app. t, $J$ = 8.0, 2H), 7.33–7.30 (m, 1H), 7.13 (d, $J$ = 3.5, 1H), 7.00 (d, $J$ = 2.0, 1H), 6.89 (dd, $J$ = 8.5, 2.0, 1H), 6.54 (d, $J$ = 3.5, 1H), 5.13 (s, 2H), 1.58 (septet, $J$ = 7.5, 3H), 1.09 (d, $J$ = 7.0, 18H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 155.1, 141.6, 138.0, 130.3, 128.7, 127.8, 127.3, 126.0, 120.8, 110.4, 104.5, 100.0, 71.1, 18.2, 12.9; IR (film): 2948, 2868, 1416, 1207 cm$^{-1}$; HRMS-ESI ($m/z$) [M + Na]$^+$ calcd for $C_{24}H_{33}NOSiNa$, 402.2229; found, 402.2233.




***N*-TIPS carbamate 2.91.** To a solution of *N*-TIPS benzyloxyindole **2.90** (4.65 g, 12.2 mmol) in 1:1:1 *i*-PrOH:Hexanes:EtOAc (45 mL) was added 10% Pd/C (1.29 g, 1.22 mmol, 10 mol% Pd). The mixture was placed under an atmosphere of hydrogen (double-balloon), stirred for 25.5 h at 23 °C, at which point was added additional 10% Pd/C (2.07 g, 1.95 mmol, 15 mol% Pd). After stirring for another 48 h at 23 °C was added additional 10% Pd/C (1.16 g, 1.09 mmol, 9 mol% Pd). The reaction was stirred for 5 h at 23 °C, and then filtered over celite (EtOAc eluent). Evaporation of the solvent under reduced pressure afforded crude **2.115** as a light brown oil, which was used in the subsequent step without further purification. $R_f$ 0.63 (3:1 Hexanes:EtOAc).

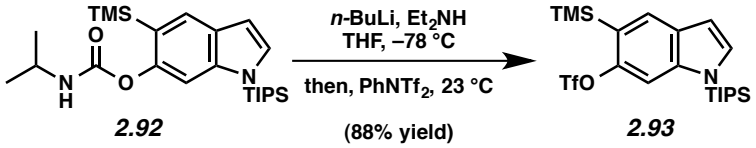
Carbamate **2.91** was prepared following the general procedure described by Igarashi.[55] Crude **2.115** was dissolved in $CH_2Cl_2$ (61.0 mL), and $Et_3N$ (0.85 mL, 6.1 mmol, 0.5 equiv), followed by *i*-PrNCO (1.41 mL, 14.4 mmol, 2.0 equiv), was added. The solution was stirred at

23 °C for 4 h, and then additional *i*-PrNCO (1.41 mL, 14.4 mmol, 2.0 equiv) was added. The solution continued to be stirred for 11 h, and then additional *i*-PrNCO (0.70 mL, 7.1 mmol, 0.58 equiv) was added. After stirring at 23 °C for 3 h, the mixture was concentrated to dryness under reduced pressure. Purification by flash chromatography (9:1 Hexanes:EtOAc) provided *N*-TIPS carbamate **2.91** (3.74 g, 82% yield, 2 steps). $R_f$ 0.63 (2:1 Hexanes:$Et_2O$); $^1$H NMR (500 MHz, $CDCl_3$): δ 7.56 (d, *J* = 8.5, 1H), 7.24 (d, *J* = 3.5, 1H), 6.91 (dd, *J* = 8.5, 2.5, 1H), 6.60 (dd, *J* = 3.0, 0.5, 1H), 4.82 (d, *J* = 6.0, 1H), 3.95–3.91 (m, 1H), 1.68 (septet, *J* = 7.5, 3H), 1.24 (d, *J* = 6.0, 6H), 1.15 (d, *J* = 7.5, 18H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 154.4, 146.6, 140.8, 131.8, 129.2, 120.6, 114.5, 107.0, 104.8, 43.5, 23.2, 18.4, 13.0; IR (film): 3324, 2950, 2867, 1735, 1470 $cm^{-1}$; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{21}H_{34}N_2O_2SiNa$, 397.2287; found, 397.2286.



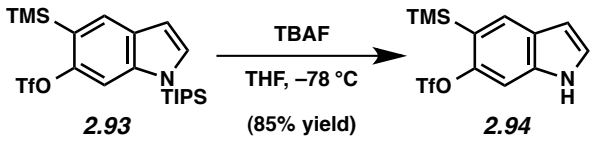

***N*-TIPS silylcarbamate 2.92.** *N*-TIPS silyl carbamate **2.92** was prepared following the general procedure described by Hoppe and Snieckus for *o*-lithiation of isopropyl carbamates, with minor modifications.[19] To a solution of *N*-TIPS carbamate **2.91** (0.659 g, 1.76 mmol) and TMEDA (0.394 mL, 2.47 mmol, 1.4 equiv) in 3:1 $Et_2O$:THF (16.9 mL) at –78 °C was added a solution of TBSOTf in *n*-pentane (1.30 M, 1.61 mL, 2.11 mmol, 1.2 equiv). After stirring for 5 min, the white suspension was allowed to warm to 23 °C over 35 min. TMEDA (0.987 mL, 6.16 mmol, 3.5 equiv) was added, and the mixture was cooled to –78 °C. A solution of *n*-BuLi in hexanes (1.54 M, 4.00 mL, 6.16 mmol, 3.5 equiv) was added dropwise over 20 min. The mixture was stirred at –78 °C for 3 h, then neat TMSCl (1.56 mL, 12.3 mmol, 7 equiv) was added dropwise over 16 min. The resulting mixture was stirred at –78 °C for 1 h, quenched with 1 M $NaHSO_4$

(10 mL), and allowed to warm to 23 °C over 45 min with vigorous stirring. The organic layer was separated, washed successively with 1 M $NaHSO_4$ (10 mL) and brine (10 mL), then dried over $MgSO_4$. Evaporation under reduced pressure afforded the crude product, which was purified by flash chromatography (10:1 Hexanes:Acetone) to afford *N*-TIPS silylcarbamate **2.92** (0.570 g, 73% yield). $R_f$ 0.67 (3:1 Hexanes:EtOAc); $^1$H NMR (500 MHz, $CDCl_3$): δ 7.69 (s, 1H), 7.25 (s, 1H), 7.23 (d, *J* = 3.5, 1H), 6.61 (dd, *J* = 3.0, 0.5, 1H), 4.70 (d, *J* = 8.0, 1H), 3.99–3.93 (m, 1H), 1.69 (septet, *J* = 7.5, 3H), 1.24 (d, *J* = 6.5, 6H), 1.15 (d, *J* = 8.0, 18H), 0.32 (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 154.3, 151.1, 142.0, 131.8, 129.4, 126.7, 122.9, 107.9, 104.8, 43.5, 23.3, 18.3, 12.9, –0.3; IR (film): 3331, 2945, 2868, 1704 cm$^{-1}$; HRMS-ESI (*m/z*) [M + Na]$^+$ calcd for $C_{24}H_{42}N_2O_2Si_2Na$, 469.2682; found, 469.2677.

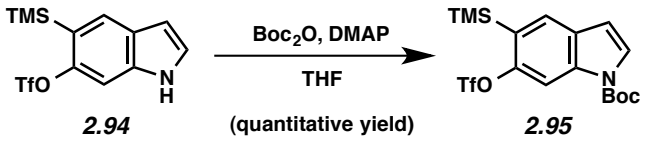



***N*-TIPS silyltriflate 2.93.** To a solution of *N*-TIPS silylcarbamate **2.92** (0.468 g, 1.05 mmol) in THF (10.5 mL) at –78 °C was added *n*-BuLi in hexanes (2.91 M, 0.432 mL, 1.26 mmol, 1.2 equiv) and $Et_2NH$ (0.130 mL, 1.26 mmol, 1.2 equiv). The resulting mixture was stirred at –78 °C for 15 min, then allowed to warm to 23 °C over an additional 30 min. Next, $PhNTf_2$ (0.449 g, 1.26 mmol, 1.2 equiv) was added as a solid in a single portion. After stirring for 1 h, the reaction mixture was passed over a plug of silica gel (EtOAc eluent). Evaporation under reduced pressure afforded the crude product, which was further purified by flash chromatography (98:2 Hexanes:Benzene) to provide silyltriflate **2.93** (0.456 g, 88% yield) as a white solid. $R_f$ 0.79 (9:1 Hexanes:$Et_2O$); $^1$H NMR (500 MHz, $CDCl_3$): δ 7.74 (s, 1H), 7.57 (s, 1H), 7.31 (d, *J* = 3.0, 1H), 6.65 (d, *J* = 3.0, 1H), 1.67 (septet, *J* = 2.5, 3H), 1.15 (d, *J* = 7.5, 18H), 0.40 (s, 9H); $^{13}$C NMR

(125 MHz, $CDCl_3$): δ 151.2, 141.5, 133.4, 130.8, 127.7, 122.5, 118.8 (q, $J$ = 318, $CF_3$), 105.4, 105.0, 18.1, 12.8, –0.3; IR (film): 2955, 2866, 1417, 1138 $cm^{-1}$; HRMS-ESI ($m/z$) $[M + Na]^+$ calcd for $C_{21}H_{34}F_3NO_3SSi_2Na$, 516.1648; found, 516.1634.

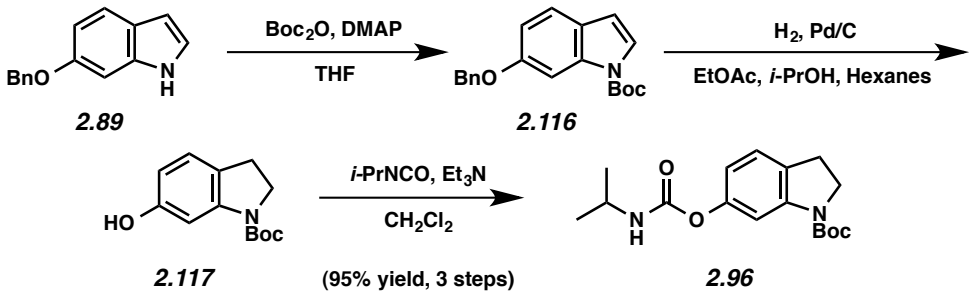



***N*-H silyltriflate 2.94.** To a solution of *N*-TIPS silyltriflate **2.93** (0.440 g, 0.891 mmol) in THF (10 mL) at –78 °C was added a solution of TBAF in THF (1.0 M, 0.891 mL, 0.891 mmol, 1 equiv) dropwise. The solution was stirred for 10 min, diluted with $Et_2O$ (5 mL), then quenched with $H_2O$ (5 mL). The biphasic mixture was allowed to warm to 23 °C over 30 min. The layers were separated, and then the aqueous layer was extracted with $Et_2O$ (3 × 10 mL). The combined organic layers were washed with brine (10 mL), then dried over $MgSO_4$. Evaporation under reduced pressure afforded the crude product, which was further purified by flash chromatography (3:1 Hexanes:$Et_2O$) to provide *N*-H silyltriflate **2.94** (285 mg, 85% yield). $R_f$ 0.21 (4:1 Hexanes:$Et_2O$); $^1H$ NMR (500 MHz, $CDCl_3$): δ 8.28 (br s, 1H), 7.80 (s, 1H), 7.44 (s, 1H), 7.24 (dd, $J$ = 3.1, 2.5, 1H), 6.59–6.58 (m, 1H), 0.44 (s, 9H); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 151.0, 136.0, 128.0, 127.2, 126.2, 122.5, 118.5 (q, $J$ = 318, $CF_3$), 102.7, 102.4, –0.5; IR (film): 3447, 2958, 1208 $cm^{-1}$; HRMS-ESI ($m/z$) $[M + H]^+$ calcd for $C_{12}H_{15}F_3NO_3SSi$, 338.0494; found, 338.0490.




*2.94* *2.95*

***N*-Boc silyltriflate 2.95.** *N*-Boc silyltriflate **2.95** was prepared following the general procedure described by Gribble for Boc-protection of indoles.[64] To a stirred solution of *N*-H silyltriflate **2.94** (0.200 g, 0.59 mmol) in THF (6 mL) were added $Boc_2O$ (0.142 g, 0.65 mmol, 1 equiv) and then DMAP (7.2 mg, 0.059 mmol, 0.1 equiv). The resulting mixture was stirred at 23 °C for 14 h, then additional $Boc_2O$ (70 mg, 0.32 mmol, 0.54 equiv) was added. After stirring at 23 °C for an additional 2 h, the reaction mixture was filtered over silica gel (EtOAc eluent). Evaporation under reduced pressure afforded *N*-Boc silyltriflate **2.95** (0.261 g, quantitative yield). $R_f$ 0.57 (9:1 Hexanes:$Et_2O$); $^1$H NMR (500 MHz, 40 °C, $CDCl_3$): δ 8.20 (s, 1H), 7.692–7.687 (m, 2H), 6.58 (d, $J$ = 3.7, 1H), 1.69 (s, 9H), 0.41 (s, 9H); $^{13}$C NMR (125 MHz, 40 °C, $CDCl_3$): δ 152.2, 149.1, 135.5, 129.6, 127.9, 127.7, 125.9, 118.5 (q, $J$ = 318, $CF_3$), 106.9, 106.7, 84.7, 28.0, –0.8; IR (film): 2983, 1740, 1140 cm$^{-1}$; HRMS-ESI (*m/z*) [M + Na]$^+$ calcd for $C_{17}H_{22}F_3NO_5SSiNa$, 460.0838; found, 460.0842.




*2.89* *2.116* *2.117* (95% yield, 3 steps) *2.96*

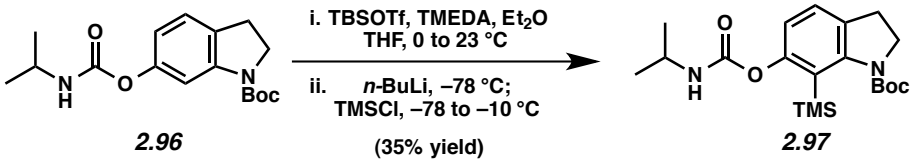
***N*-Boc carbamate 2.96.** *N*-Boc benzyloxyindole **2.96** was prepared following the general procedure described by Gribble for Boc-protection of indoles.[64] To a stirred solution of benzyloxyindole **2.89** (5.00 g, 22.4 mmol) in THF (223 mL) was added $Boc_2O$ (5.38 g, 24.6

mmol, 1.1 equiv) and DMAP (0.274 g, 2.24 mmol, 0.1 equiv). The resulting mixture was stirred at 23 °C for 2 h, then filtered over silica gel (EtOAc eluent). Evaporation under reduced pressure afforded crude **2.116**, which was used in the subsequent step without further purification. $R_f$ 0.49 (9:1 Hexanes:$Et_2O$); $^1$H NMR (500 MHz, 40 °C, $CDCl_3$): δ 7.86 (s, 1H), 7.48–7.46 (m, 3H), 7.42 (d, *J* = 8.5, 1H), 7.39 (app. t, *J* = 7.7, 2H), 7.32 (app. t, *J* = 7.4, 1H), 6.95 (dd, *J* = 8.5, 2.3, 1H), 6.49 (d, *J* = 3.7, 1H), 5.15 (s, 2H), 1.67 (s, 9H); $^{13}$C NMR (125 MHz, 40 °C, $CDCl_3$): δ 156.9, 149.7, 137.2, 136.1, 128.3, 127.7, 127.4, 124.6, 124.5, 121.1, 112.7, 106.9, 100.8, 83.3, 70.5, 28.1; IR (film): 2979, 2917, 1729, 1343, 1151 cm$^{-1}$; HRMS-ESI (*m*/*z*) [M + Na]$^+$ calcd for $C_{20}H_{21}NO_3Na$, 346.1419; found, 346.1422.

Crude **2.116** was dissolved in 1:1:1 *i*-PrOH:Hexanes:EtOAc (120 mL), then 10% Pd/C (2.38 g, 2.24 mmol, 10 mol% Pd) was added. The mixture was placed under an atmosphere of hydrogen (double-balloon), stirred for 14 h at 23 °C, and then filtered over celite (EtOAc eluent, 250 mL). Evaporation of the solvent under reduced pressure afforded crude **2.117** as a light brown oil, which was used in the subsequent step without further purification. $R_f$ 0.35 (4:1 Hexanes:EtOAc); $^1$H NMR (500 MHz, 40 °C, $CDCl_3$): δ 7.36 (br s, 1H), 6.95 (d, *J* = 8.0, 1H), 6.43 (d, *J* = 8.0, 1H), 5.47 (br s, 1H), 3.97 (dd, *J* = 8.5, 8.3, 2H), 2.99 (dd, *J* = 8.7, 8.4, 2H), 1.56 (s, 9H); $^{13}$C NMR (125 MHz, 40 °C, $CDCl_3$): δ 155.5, 152.6, 143.6, 124.9, 122.8, 108.9, 102.9, 80.9, 48.4, 28.2, 26.4; IR (film): 3329, 2989, 1657 cm$^{-1}$; HRMS-ESI (*m*/*z*) [M + Na]$^+$ calcd for $C_{13}H_{17}NO_3Na$, 258.1106; found, 258.1110.

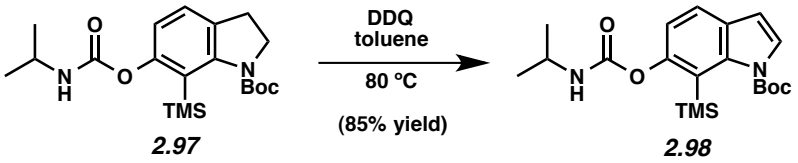
Carbamate **2.96** was prepared following the general procedure described by Igarashi et al.[55] To a solution of crude **2.117** in $CH_2Cl_2$ (224 mL) was added subsequently *i*-PrNCO (3.30 mL, 33.6 mmol, 1.5 equiv) and $Et_3N$ (0.936 mL, 6.72 mmol, 0.3 equiv). The solution was stirred at 23 °C for 18 h, then concentrated to dryness under reduced pressure. Purification by flash

chromatography (7:3 Hexanes:EtOAc) provided *N*-Boc carbamate **2.96** (6.83 g, 95% yield over 3 steps). $R_f$ 0.25 (3:2 Hexanes:$Et_2O$); $^1$H NMR (500 MHz, 40 °C, $CDCl_3$): δ 7.54 (br s, 1H), 7.05 (d, *J* = 7.9, 1H), 6.68 (d, *J* = 7.8, 1H), 4.79 (br s, 1H), 3.98 (app. t, *J* = 8.3, 2H), 3.88 (d, *J* = 5.9, 1H), 3.03 (app. t, *J* = 8.6, 2H), 1.55 (s, 9H), 1.22 (d, *J* = 5.4, 6H); $^{13}$C NMR (125 MHz, 40 °C, $CDCl_3$): δ 153.8, 152.2, 150.6, 143.4, 127.8, 124.4, 115.1, 108.9, 80.8, 48.2, 43.3, 28.3, 26.7, 22.8; IR (film): 3348, 2977, 1732, 1681 $cm^{-1}$; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{17}H_{24}N_2O_4Na$, 343.1634; found, 343.1632.

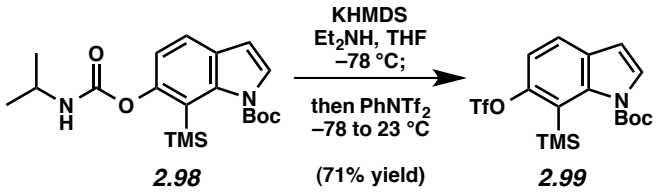



***N*-Boc silylcarbamate indoline 2.97.** *N*-Boc silylcarbamate **2.97** was prepared following the general procedure described by Hoppe and Snieckus for *o*-lithiation of isopropyl carbamates, with modifications.[19] To a solution of *N*-Boc carbamate **2.96** (3.70 g, 11.5 mmol) and TMEDA (1.32 mL, 16.2 mmol, 1.4 equiv) in 3:1 $Et_2O$:THF (116 mL) at 0 °C was added a solution of TBSOTf in *n*-pentane (1.30 M, 10.7 mL, 13.9 mmol, 1.2 equiv). After stirring for 5 min, the mixture was allowed to warm to 23 °C over 30 min. TMEDA (3.12 mL, 38.1 mmol, 3.3 equiv) was added, and the mixture was cooled to –78 °C. A solution of *n*-BuLi in hexanes (1.60 M, 23.8 mL, 38.1 mmol, 3.3 equiv) was added dropwise over 45 min. The mixture was stirred at –78 °C for 4 h, then neat TMSCl (10.3 mL, 80.8 mmol, 7 equiv) was added. The resulting mixture was stirred at –78 °C for 1 h, then stirred at –10 °C for 14 h. The reaction mixture was cooled to –78 °C, then quenched with 1 M $NaHSO_4$ (90 mL) and allowed to warm to 23 °C over 1 h with vigorous stirring. The organic layer was separated, washed successively with 1 M $NaHSO_4$ (50 mL) and brine (50 mL), then dried over $MgSO_4$. Evaporation under reduced pressure afforded

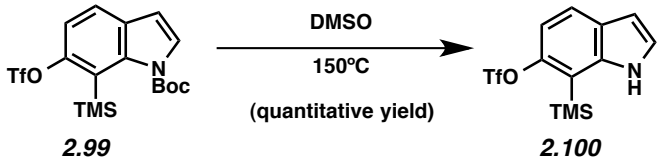
the crude product, which was purified by flash chromatography (85:15 Hexanes:Acetone) to afford *N*-Boc silylcarbamate **2.97** (1.58 g, 35% yield). $R_f$ 0.29 (4:1 Hexanes:EtOAc); $^1$H NMR (500 MHz, 40 °C, $CDCl_3$): δ 7.13 (d, *J* = 7.9, 1H), 6.83 (d, *J* = 7.9, 1H), 4.72 (br s, 1H), 4.05 (t, *J* = 7.7, 2H), 3.93 (br s, 1H), 2.91 (t, *J* = 7.7, 2H), 1.52 (s, 9H), 1.24 (d, *J* = 6.5, 6H), 0.30 (s, 9H); $^{13}$C NMR (125 MHz, 40 °C, $CDCl_3$): δ 155.1, 155.0, 153.7, 148.8, 129.8, 124.8, 122.5, 118.0, 80.4, 50.1, 43.2, 28.7, 28.3, 22.8, 0.3; IR (film): 3343, 2976, 2245, 1722, 1683 cm$^{-1}$; HRMS-ESI (*m/z*) [M + Na]$^+$ calcd for $C_{20}H_{32}N_2O_4SiNa$, 415.2029; found, 415.2028.




***N*-Boc silyltriflate indole 2.98.** To a stirred solution of *N*-Boc silyltriflate indoline **2.97** (1.11 g, 2.83 mmol) in toluene (28 mL) was added DDQ (0.770 g, 3.39 mmol, 1.2 equiv). The reaction vessel was placed in an oil bath maintained at 80 °C for 2.5 h. After cooling to 23 °C, the reaction mixture was filtered over neutral Brockman Grade I 58 Å activated alumina (packed with Hexanes; EtOAc eluent). Evaporation under reduced pressure afforded the crude product, which was further purified by flash chromatography (7:3 Hexanes:$Et_2O$) to provide **2.98** (0.933 g, 85% yield) as a white solid. $R_f$ 0.56 (7:3 Hexanes:$Et_2O$); $^1$H NMR (500 MHz, $CDCl_3$): δ 7.49 (d, *J* = 8.3, 1H), 7.43 (d, *J* = 3.8, 1H), 7.05 (d, *J* = 8.4, 1H), 6.51 (d, *J* = 3.7, 1H), 4.83 (d, *J* = 7.9, 1H), 3.98–3.91 (m, 1H), 1.60 (s, 9H), 1.25 (d, *J* = 6.5, 6H), 0.36 (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 154.1, 154.0, 150.5, 140.8, 128.11, 128.08, 121.9, 119.7, 118.2, 107.8, 83.1, 43.2, 28.1, 22.9, 1.4; IR (film): 2978, 2250, 1737, 1153 cm$^{-1}$; HRMS-ESI (*m/z*) [M + Na]$^+$ calcd for $C_{20}H_{30}N_2O_4SiNa$, 413.1873; found, 413.1873.

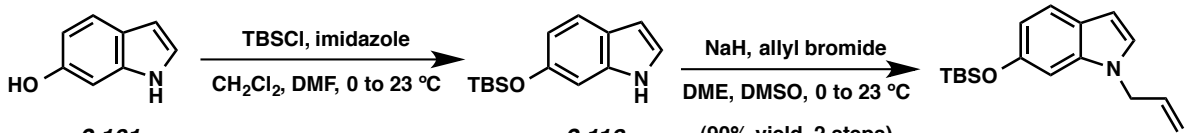



***N*-Boc silyltriflate 2.99.** To a solution of *N*-Boc silylcarbamate **2.98** (1.05 g, 2.69 mmol) in THF (27 mL) at –78 °C was added $Et_2NH$ (0.334 mL, 3.23 mmol, 1.2 equiv), followed by a solution of KHMDS in toluene (0.5 M, 6.45 mL, 3.23 mmol, 1.2 equiv) dropwise over 10 min. The reaction was stirred at –78 °C for 20 min, then additional KHMDS in toluene (0.5 M, 1.61 mL, 0.805 mmol, 0.30 equiv), followed by $Et_2NH$ (83 μL, 0.805 mmol, 0.30 equiv), was added. After stirring for 20 min at –78 °C, a solution of $PhNTf_2$ (1.44 g, 4.03 mmol, 1.5 equiv) in THF (8 mL) was added. After stirring for 1 h, the reaction mixture was allowed to warm to 23 °C. The reaction stirred for an additional 14 h at 23 °C, then was passed over a plug of silica gel (EtOAc eluent). Evaporation under reduced pressure afforded the crude product, which was further purified by flash chromatography (85:15 Hexanes:$CH_2Cl_2$) to provide *N*-Boc silyltriflate **2.99** (0.830 g, 71% yield). $R_f$ 0.46 (9:1 Hexanes:EtOAc); $^1$H NMR (500 MHz, $CDCl_3$): δ 7.57–7.54 (m, 2H), 7.17 (d, $J$ = 8.5, 1H), 6.56 (d, $J$ = 3.8, 1H), 1.62 (s, 9H), 0.43 (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 152.5, 149.9, 140.7, 130.0, 129.6, 122.7, 122.4, 118.5 (q, $J$ = 318, $CF_3$), 116.3, 107.4, 84.0, 28.0, 1.5; IR (film): 2985, 1737, 1199 cm$^{-1}$; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{17}H_{22}F_3NO_5SSiNa$, 460.0838; found, 460.0838.




*2.99* *2.100*

***N*-H silyltriflate 2.100.** A solution of *N*-Boc silyltriflate **2.99** (0.234 g, 0.53 mmol) in DMSO (5.3 mL) was stirred at 150 °C for 1 h. After cooling to 23 °C, the reaction mixture was poured into a 1:1 solution of $Et_2O$:$H_2O$ (15 mL). The layers were separated and the aqueous layer was further diluted with $H_2O$ (10 mL). The aqueous layer was extracted with $Et_2O$, followed by EtOAc (2 × 20 mL). The combined organic layers were washed successively with $H_2O$ (20 mL) and brine (20 mL), then dried over $MgSO_4$. Evaporation under reduced pressure afforded the crude product, which was purified by flash chromatography (9:1 Hexanes:$Et_2O$) to afford *N*-H silyltriflate **2.100** (0.180 g, quantitative yield). $R_f$ 0.29 (6:1 Hexanes:EtOAc); $^1$H NMR (500 MHz, $CDCl_3$): δ 8.52 (br s, 1H), 7.70 (d, *J* = 8.7, 1H), 7.31 (app. t, *J* = 2.9, 1H), 7.17 (d, *J* = 8.7, 1H), 6.61 (dd, *J* = 3.2, 2.0, 1H), 0.59 (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 151.1, 139.5, 126.3, 126.0, 123.0, 118.6 (q, *J* = 318, $CF_3$), 113.1, 112.4, 102.5, 0.7; IR (film): 3489, 2957, 1410, 1208 cm$^{-1}$; HRMS-ESI (*m/z*) [M + Na]$^+$ calcd for $C_{12}H_{14}F_3NO_3SSiNa$, 360.0313; found, 360.0312.



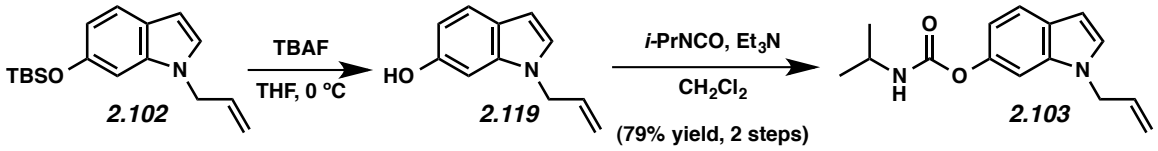

*2.101* *2.118* *2.102*

***N*-Allyl silylether 2.102.** To a solution of hydroxyindole **2.101** (1.60 g, 12.0 mmol) in $CH_2Cl_2$ (120 mL) and DMF (12 mL) at 0 °C was added imidazole (2.05 g, 30.1 mmol, 2.5 equiv) and TBSCl (2.18 g, 14.4 mmol, 1.2 equiv). After stirring for 10 min at 0 °C, the mixture was warmed to 23 °C and allowed to stir for an additional 80 min. The reaction mixture was quenched with

$H_2O$ (80 min), and stirred for 1 min. The layers were separated and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 30 mL). The combined organic layers were washed with brine (20 mL), then dried over $Na_2SO_4$. Evaporation under reduced pressure afforded the crude product, which was purified by flash chromatography (9:1 Hexanes:EtOAc) to afford *N*-H silylether **2.118** as a white solid, which was used directly in the subsequent step. $R_f$ 0.29 (6:1 Hexanes:EtOAc); **2.118:** $^1$H NMR (500 MHz, $CDCl_3$): δ 7.93 (br s, 1H), 7.53 (d, *J* = 8.5, 1H), 7.06 (dd, *J* = 3.1, 2.4, 1H), 6.873–6.870 (m, 1H), 6.79 (dd, *J* = 8.5, 2.1, 1H), 6.53–6.52 (m, 1H), 1.10 (s, 9H), 0.29 (s, 6H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 151.6, 136.5, 123.3, 122.7, 120.8, 114.4, 102.3, 101.7, 25.8, 18.2, –4.4; IR (film): 3400, 2955, 2929, 2887, 2858, 1621, 1252 cm$^{-1}$; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{14}H_{22}NOSi$, 248.1471; found, 248.1474.

To a solution of *N*-H silyl ether **2.118** in 1,2-dimethoxyethane (120 mL) and DMSO (12 mL) at 0 ºC was added 60% NaH (1.36 g, 34.0 mmol, 2.8 equiv). The resulting solution was stirred at 0 °C for 20 min, then allyl bromide (1.5 mL, 17.0 mmol, 1.4 equiv) was added dropwise over 5 min. The mixture was stirred at 0 °C for 10 min, warmed to 23 °C over 90 min, then quenched with $H_2O$ (30 mL). The biphasic mixture was stirred for an additional 10 min. The layers were separated, and then the aqueous layer was extracted with $Et_2O$ (3 × 50 mL). The combined organic layers were washed with $H_2O$ (30 mL), washed with brine (30 mL), then dried over $Na_2SO_4$. Evaporation of the solvent under reduced pressure afforded the crude product, which was purified by flash chromatography (97:3 Hexanes:$Et_2O$) to provide *N*-allyl silyl ether **2.102** (3.10 g, 90% yield over 2 steps) as a colorless oil. $R_f$ 0.64 (3:1 Hexanes:EtOAc); $^1$H NMR (500 MHz, $CDCl_3$): δ 7.48 (d, *J* = 8.5, 1H), 7.01 (d, *J* = 3.1, 1H), 6.79 (d, *J* = 1.8, 1H), 6.72 (dd, *J* = 8.5, 2.1, 1H), 6.46 (d, *J* = 3.1, 1H), 6.04–5.97 (m, 1H), 5.22 (dd, *J* = 10.2, 1.3, 1H), 5.11 (dd, 17.06, 1.4, 1H), 4.66 (dd, *J* = 3.8, 1.2, 2H), 1.05 (s, 9H), 0.24 (s, 6H); $^{13}$C NMR (125 MHz,

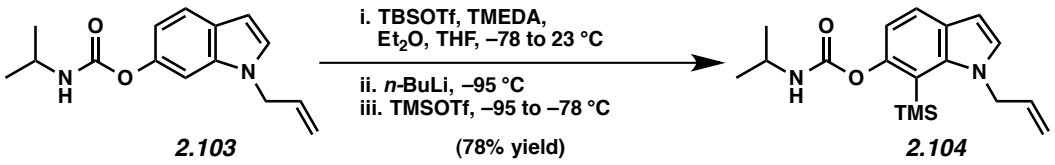
$CDCl_3$): δ 151.4, 136.8, 133.3, 126.9, 123.4, 121.0, 117.1, 113.9, 101.1, 100.4, 48.8, 25.8, 18.2, –4.4; IR (film): 2955, 2930, 2858, 1620, 1486, 1263 $cm^{-1}$; HRMS-ESI (*m*/*z*) $[M + H]^+$ calcd for $C_{17}H_{26}NOSi$, 288.1784; found, 288.1776.




***N*-Allyl carbamate 2.103.** To a solution of *N*-allyl silyl ether **2.102** (4.06 g, 14.12 mmol) in THF (150 mL) at 0 °C was added a solution of TBAF in THF (1.0 M, 15.5 mL, 15.5 mmol, 1.1 equiv). The solution was stirred for 1 h, then quenched with $H_2O$ (100 mL) and diluted with $Et_2O$ (50 mL) allowed to warm to 23 °C over 60 min. The layers were separated, and then the aqueous layer was extracted with $Et_2O$ (3 × 100 mL). The combined organic layers were washed with brine (50 mL), then dried over $MgSO_4$. Evaporation under reduced pressure afforded crude product **2.119**, which was further purified by flash chromatography (4:1 Hexanes:EtOAc) and then used in the subsequent reaction. $R_f$ 0.10 (9:1 Hexanes:$Et_2O$); $^1H$ NMR (500 MHz, $CDCl_3$): δ 7.46 (d, *J* = 8.4, 1H), 6.98 (d, *J* = 3.2, 1H), 6.76 (d, *J* = 2.2, 1H), 6.67 (dd, *J* = 8.4, 2.2, 1H), 6.44 (dd, *J* = 3.2, 0.7, 1H), 6.01–5.93 (m, 1H), 5.21 (dq, *J* = 10, 1.5, 1H), 5.08 (dq, *J* = 17.5, 1.5, 1H), 4.64–4.63 (m, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 151.4, 136.9, 133.2, 126.9, 123.1, 121.4, 117.1, 109.3, 101.3, 95.4, 48.7; IR (film): 3338, 2919, 1624, 1180 $cm^{-1}$; HRMS-ESI (*m*/*z*) $[M + H]^+$ calcd for $C_{11}H_{12}NO$, 174.0919; found, 174.0916.

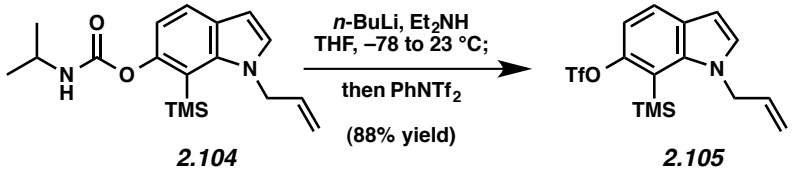
Crude **2.119** was dissolved in $CH_2Cl_2$ (150 mL) and *i*-PrNCO (2.08 mL, 21.18 mmol, 1.5 equiv), followed by $Et_3N$ (0.590 mL, 4.24 mmol, 0.3 equiv), was added. The solution was stirred at 23 °C for 16 h, then concentrated to dryness under reduced pressure. Purification by flash

chromatography (99:1 $CH_2Cl_2$:$Et_2O$) provided *N*-allyl carbamate **2.103** (2.89 g, 79% yield over 2 steps) as a white solid. $R_f$ 0.29 (4:1 Hexanes:EtOAc); $^1$H NMR (500 MHz, $CDCl_3$): δ 7.56 (d, *J* = 8.5, 1H), 7.12 (d, *J* = 1.3, 1H), 7.08 (d, *J* = 3.1, 1H), 6.88 (dd, *J* = 8.5, 1.8, 1H), 6.49 (d, *J* = 3.0, 1H), 6.02–5.94 (m, 1H), 5.21 (d, *J* = 10.2, 1H), 5.10 (d, *J* = 17.1, 1H), 4.87 (br s, 1H), 4.68 (d, *J* = 4.5, 2H), 3.95–3.90 (m, 1H), 1.24 (d, *J* = 6.3, 6H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 154.3, 146.5, 136.0, 133.1, 128.2, 126.1, 121.0, 117.3, 114.0, 102.7, 101.4, 48.8, 43.3, 22.9; IR (film): 3302, 2975, 1736, 1702, 1239 cm$^{-1}$; HRMS-ESI (*m/z*) [M + Na]$^+$ calcd for $C_{15}H_{18}N_2O_2Na$, 281.1266; found, 281.1260.




***N*-Allyl silylcarbamate 2.104.** *N*-allyl silylcarbamate **2.104** was prepared following the general procedure described by Hoppe and Snieckus for *o*-lithiation of isopropyl carbamates, with modifications.[19] To a solution of *N*-allyl carbamate **2.103** (1.45 g, 5.61 mmol) in 3:1 $Et_2O$:THF (60 mL) at –78 °C was added TMEDA (1.15 mL, 14.0 mmol, 2.5 equiv), followed by a solution of TBSOTf in *n*-pentane (1.30 M, 8.64 mL, 11.22 mmol, 2.0 equiv) dropwise over 10 min. The resulting mixture was stirred at –78 ºC for 5 min and allowed to warm to 23 °C over 30 min, by which time TMEDA·TfOH had formed as an oil on the bottom of the flask. TMEDA (1.89 mL, 22.45 mmol, 4 equiv) was added, and the mixture was cooled to –95 °C. A solution of *n*-BuLi in hexanes (1.43 M, 15.7 mL, 22.45 mmol, 4 equiv) was added dropwise over 60 min. The mixture was stirred at –95 °C for 4 h, then neat TMSOTf (7.11 mL, 39.29 mmol, 7.0 equiv) was added dropwise over 30 min. The resulting mixture was stirred at –95 °C for 5 min, stirred at –78 °C

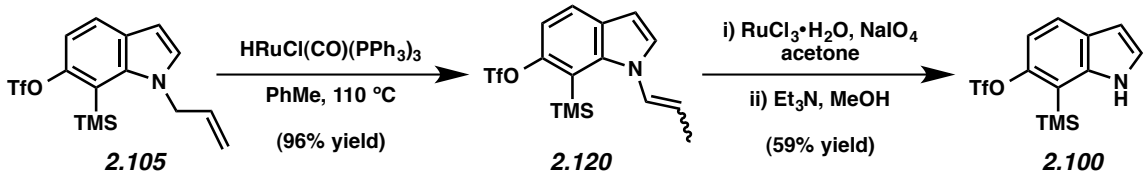
for 2 h, then quenched with 1 M aqueous $NaHSO_4$ (50 mL), and allowed to warm to 23 °C over 1 hour with vigorous stirring. The biphasic mixture was further diluted with $Et_2O$ (50 mL). The organic layer was separated, washed successively with 1 M aqueous $NaHSO_4$ (50 mL) and brine (40 mL), then dried over $MgSO_4$. Evaporation under reduced pressure afforded the crude product, which was purified by flash chromatography (9:1 Hexanes:EtOAc) to afford *N*-allyl silylcarbamate **2.104** (1.45 g, 78% yield). $R_f$ 0.53 (4:1 Hexanes:EtOAc); $^1$H NMR (500 MHz, $CDCl_3$): δ 7.58 (d, *J* = 8.4, 1H), 7.07 (d, *J* = 3.2, 1H), 6.83 (d, *J* = 8.4, 1H), 6.55 (d, *J* = 3.3, 1H), 5.88–5.81 (m, 1H), 5.14 (d, *J* = 10.2, 1H), 4.96 (d, *J* = 17.1, 1H), 4.79 (d, *J* = 5.2, 3H), 3.97–3.91 (m, 1H), 1.24 (d, *J* = 6.5, 6H), 0.46 (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 154.5, 152.5, 141.9, 134.2, 130.1, 127.0, 123.0, 117.3, 115.2, 113.3. 103.6, 52.1, 43.3, 22.9, 2.4; IR (film): 3325, 2972, 1706, 1513, 1200, 1168 $cm^{-1}$; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{18}H_{26}N_2O_2SiNa$, 353.1661; found, 353.1659.



*2.104* *2.105*

***N*-Allyl silyltriflate 2.105.** To a solution of *N*-allyl silylcarbamate **2.104** (1.08 g, 3.26 mmol) in THF (40 mL) at –78 °C were added dropwise over 10 min *n*-BuLi in hexanes (1.59 M, 2.4 mL, 3.84 mmol, 1.2 equiv), and then $Et_2NH$ (405 μL, 3.91 mmol, 1.2 equiv). The resulting mixture was stirred at –78 °C for 25 min, then allowed to warm to 23 °C over an additional 30 min. Next, $PhNTf_2$ (1.42 g, 3.90 mmol, 1.2 equiv) was added as a solid in a single portion. After stirring for 1 h, the reaction mixture was passed over a plug of silica gel (EtOAc eluent). Evaporation under reduced pressure afforded the crude product, which was further purified by flash

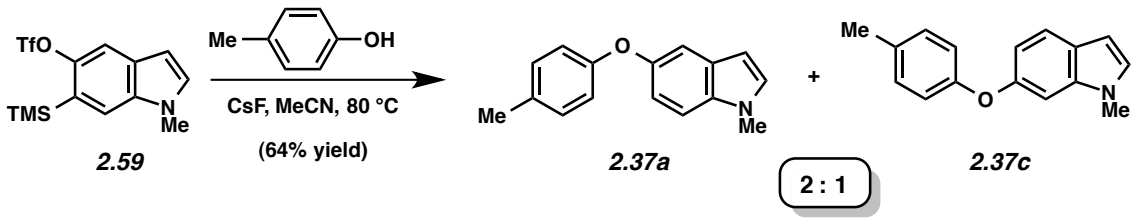
chromatography (9:1 Hexanes: $Et_2O$) to provide *N*-allyl silyltriflate **2.105** (1.00 g, 88% yield). $R_f$ 0.65 (4:1 Hexanes:EtOAc); $^1H$ NMR (500 MHz, $CDCl_3$): δ 7.63 (d, *J* = 8.5, 1H), 7.18 (d, *J* = 3.2, 1H), 7.02 (d, *J* = 8.5, 1H), 6.60 (d, *J* = 3.2, 1H), 5.86–5.78 (m, 1H), 5.14 (dd, *J* = 10.8, 0.5, 1H), 4.93 (dd, *J* = 17.1, 0.5, 1H), 4.82 (d, *J* = 5.4, 2H), 0.54 (s, 9H); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 151.0, 142.0, 133.3, 131.9, 128.7, 123.5, 118.6 (q, *J* = 319, $CF_3$), 117.8, 115.5, 113.6, 103.7, 52.3, 2.0; IR (film): 2959, 1408, 1210 $cm^{-1}$; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{16}H_{18}F_3NO_3SSi$, 378.0807; found, 378.0800.



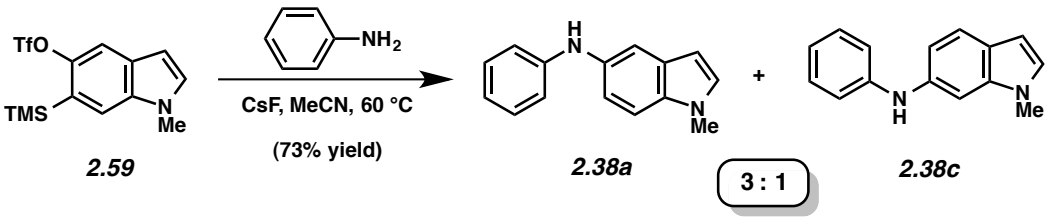

***N*-H silyltriflate 2.100.** To a solution of *N*-allyl silyltriflate **2.105** (0.210 g, 0.56 mmol) in toluene (5.5 mL) was added $HRuCl(CO)(PPh_3)_3$ (26.6 mg, 27.9 μmol, 0.05 equiv). The flask was topped with a reflux condenser and left open to the air. The flask was placed in a preheated oil bath maintained at 110 ºC. After 55 min, the flask was removed from the oil bath. After cooling to 23 °C, the reaction mixture was filtered over silica gel (EtOAc eluent). Evaporation under reduced pressure afforded the crude product, which was further purified by flash chromatography (9:1 Hexane:Benzene) to provide the isomerized product **2.120** (202.2 mg, 96% yield) as a mixture of isomers (E:Z = 3:1), which was used in the next step without further purification. $R_f$ = 0.59 (9:1 Hexane:EtOAc).

To a solution of **2.120** (31.3 mg, 0.083 mmol) in acetone (1.6 mL, filtered over activated, neutral alumina prior to use) were added a 0.035 M aqueous solution of $RuCl_3•H_2O$ (85 μL, 2.9 μmol, 0.035 equiv) and $NaIO_4$ (73.6 mg, 0.344 mmol, 4.1 equiv, added as 4 equal portions over

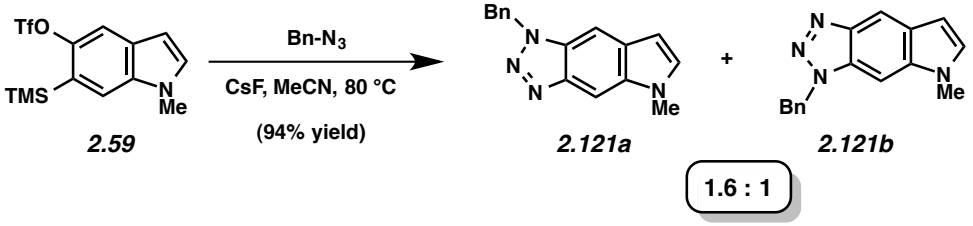
5 min). The reaction was stirred for 4 h and then $Et_2O$ (1 mL) was added. After stirring for 1 min, the reaction was further diluted with a solution of saturated aqueous $Na_2S_2O_3$ (1 mL) and stirred for 10 min. The layers were separated, and the aqueous layer was extracted with $Et_2O$ (3 x 2 mL). The combined organic layers were washed with $H_2O$ (2 mL), and then concentrated under reduced pressure. The crude reaction mixture was redissolved in MeOH (1.5 mL), and $Et_3N$ (2.5 μL, 18 μmol, 0.2 equiv) was added. After stirring for 30 min, the reaction was concentrated under reduced pressure to afford crude **2.100**, which was further purified by flash chromatography (9:1 Hexane:EtOAc) to provide *N*-H silyltriflate **2.100** (16.4 mg, 59% yield from **2.100**, 68% based on recovered **2.120**). Spectral data of **2.100** match those reported on page 110 of this dissertation.




**Ethers 2.37a and 2.37c.** To a stirred solution of silyltriflate **2.59** (20 mg, 0.057 mmol) and *p*-cresol (31 mg, 0.28 mmol, 5 equiv) in MeCN (1 mL) was added CsF (26 mg, 0.17 mmol, 3 equiv). The reaction vessel was placed in an aluminum heating block maintained at 80 °C for 24 h. After cooling to 23 °C, the reaction mixture was filtered over silica gel (EtOAc eluent). Evaporation under reduced pressure afforded the crude products, which were further purified by flash chromatography (4:1 Hexanes:$CH_2Cl_2$) to provide a mixture of ethers **2.37a** and **2.37c** (2:1 ratio of **2.37a**:**2.37c**, 8.6 mg, 64% yield). Spectral data for **2.37a** and **2.37c** match those reported on pages 69 and 120 of this dissertation, respectively.



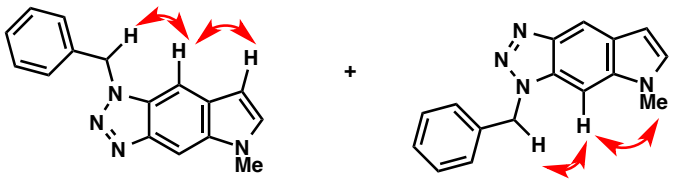

**Amines 2.38a and 2.38c.** To a stirred solution of silyltriflate **2.59** (31.8 mg, 0.095 mmol) and aniline (24.7 μL, 0.285 mmol, 3 equiv) in MeCN (0.9 mL) was added CsF (41.0 mg, 0.285 mmol, 3 equiv). The reaction vessel was placed in an aluminum heating block maintained at 60 °C for 21 h. After cooling to 23 °C, the reaction mixture was filtered over silica gel (EtOAc eluent). Evaporation under reduced pressure afforded the crude products, which were further purified by flash chromatography (1.5:1.5:30 $CH_2Cl_2$:$Et_2O$:Hexanes) to provide a mixture of amines **2.38a** and **2.38c** (3:1 ratio of **2.38a**:**2.38c**, 14.7 mg, 73% yield). Spectral data for **2.38a** and **2.38c** match those reported on pages 70 and 120 of this dissertation, respectively. Spectral data for **2.38a** and **2.38c** also match those previously reported.[58] **2.38c**: $R_f$ 0.55 (2:1 Hexanes:$CH_2Cl_2$).



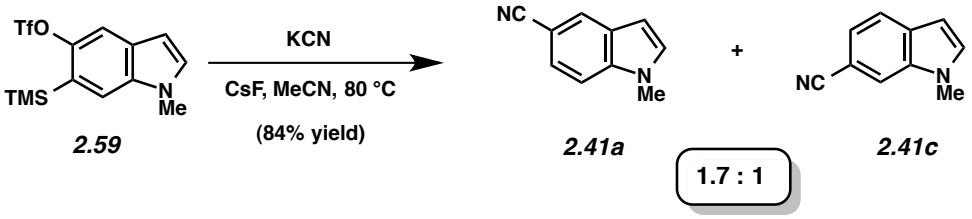

**Triazoles 2.121a and 2.121b.** To a stirred solution of silyltriflate **2.59** (60 mg, 0.17 mmol) and benzyl azide[60] (114 mg, 0.85 mmol, 5 equiv) in MeCN (1.7 mL) was added CsF (78 mg, 0.51 mmol, 3 equiv). The reaction vessel was placed in an aluminum heating block maintained at 80 °C for 24 h. After cooling to 23 °C, the reaction mixture was filtered over silica gel (EtOAc eluent). Evaporation under reduced pressure afforded the crude products, which were further

purified by flash chromatography (3:2 Hexanes:EtOAc) to provide triazoles **2.121a** and **2.121b** (1.6:1 ratio of **2.121a**:**2.121b**, 42.3 mg, 94% yield). Analytical samples of **2.121a** and **2.121b** were obtained by flash chromatography (4:1 Benzene:$Et_2O$) followed by preparative TLC (1:1 Benzene:$Et_2O$). **2.121a**: $R_f$ 0.26 (3:2 Hexanes:EtOAc); $^1$H NMR (500 MHz, $CDCl_3$): δ 7.87 (s, 1H), 7.44 (s, 1H), 7.32–7.26 (m, 5H), 7.23 (d, *J* = 3.2, 1H), 6.47 (d, *J* = 3.2, 1H), 5.87 (s, 2H), 3.81 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 144.0, 136.6, 135.3, 134.0, 131.4, 129.0, 128.8, 128.0, 127.3, 99.7, 97.8, 96.7, 52.0, 33.1; IR (film): 2919, 1524, 1456, 1253, 1194, 1115 cm$^{-1}$; HRMS-ESI (*m*/*z*) $[M + Na]^+$ calcd for $C_{16}H_{14}N_4Na$, 285.1116; found, 285.1112. **2.121b**: $R_f$ 0.14 (3:2 Hexanes:EtOAc); $^1$H NMR (500 MHz, $CDCl_3$): δ 8.25 (s, 1H), 7.36–7.25 (m, 5H), 7.14 (d, *J* = 3.3, 1H), 6.60 (d, *J* = 3.3, 1H), 5.88 (s, 2H), 3.72 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 142.7, 138.7, 135.3, 132.4, 130.6, 128.9, 128.8, 128.1, 127.3, 109.8, 101.1, 85.9, 51.9, 33.1; IR (film): 2917, 2849, 1633, 1526, 1455, 1352, 1257, 1061 cm$^{-1}$; HRMS-ESI (*m*/*z*) $[M + H]^+$ calcd for $C_{16}H_{15}N_4$, 263.1297; found, 263.1296.

The structures of **2.121a** and **2.121b** were confirmed by 2D-NOESY experiments, as the following correlations were observed:

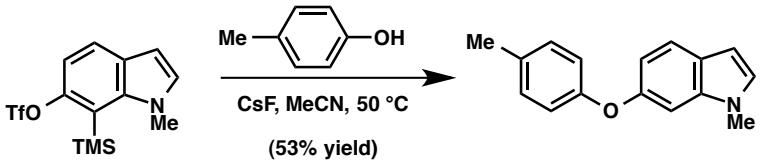



***2.121a*** ***2.121b***




*2.59* *2.41a* *2.41c*

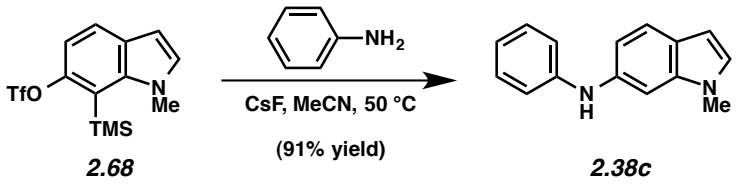
**Cyanoindoles 2.41a and 2.41c.** To a stirred solution of silyltriflate **2.59** (20 mg, 0.057 mmol, 1 equiv) and potassium cyanide (47 mg, 0.28 mmol, 5 equiv) in MeCN (1 mL) was added CsF (26 mg, 0.17 mmol, 3 equiv). The reaction vessel was sealed and placed in an aluminum heating block maintained at 80 °C for 24 h. After cooling to 23 °C, the reaction mixture was filtered over silica gel (EtOAc eluent). Evaporation under reduced pressure afforded the crude products, which were further purified by flash chromatography (7:3 Hexanes:$Et_2O$) to provide a mixture of cyanoindoles **2.41a** and **2.41c** (1.7:1 ratio of **2.41a**:**2.41c**, 7.5 mg, 84% yield). Spectral data for **2.41a** and **2.41c** match those reported on pages 72 and 122 of this dissertation. **2.41a** and **2.41c**: $R_f$ 0.20 (3:2 Hexane: $Et_2O$).




*2.68* *2.37c*

**Ether 2.37c:** To a stirred solution of silyltriflate **2.68** (20 mg, 0.057 mmol) in MeCN (1 mL) was added *p*-cresol (31 mg, 0.28 mmol, 5 equiv) as a solution in MeCN (207 μl). The reaction was further treated with CsF (26 mg, 0.17 mmol, 3 equiv). The reaction vessel was sealed and placed in an aluminum heating block maintained at 50 °C for 3 h. After cooling to 23 °C, the reaction mixture was filtered over silica gel (EtOAc eluent). Evaporation under reduced pressure afforded the crude product, which was further purified by flash chromatography (4:1 Hexanes:$CH_2Cl_2$) to

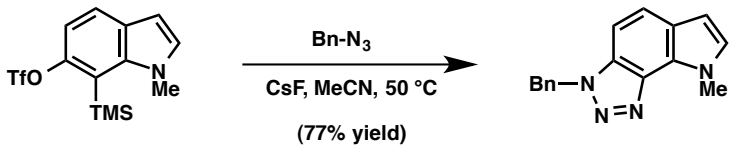
provide exclusively **2.37c** (7.1 mg, 53% yield) as a yellow solid. **2.37c**: $R_f$ 0.20 (4:1 Hexanes:$CH_2Cl_2$); $^1$H NMR (500 MHz, $CDCl_3$): δ 7.55 (d, *J* = 8.5, 1H), 7.11 (d, *J* = 8.4, 2H), 7.02 (d, *J* = 3.2, 1H), 6.96 (d, *J* = 1.9, 1H), 6.91 (d, *J* = 8.5, 2H), 6.86 (dd, *J* = 8.5, 2.1, 1H), 6.47 (dd, *J* = 3.1, 0.5, 1H), 3.71 (s, 3H), 2.33 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 156.4, 152.7, 137.1, 131.7, 129.9, 128.7, 124.7, 121.5, 117.7, 112.7, 100.9, 99.9, 32.8, 20.5; IR (film): 2912, 1622, 1607, 1506, 1484, 1470, 1244, 1223 $cm^{-1}$; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{16}H_{15}NONa$, 260.1051; found, 260.1053.



*2.68* *2.38c*

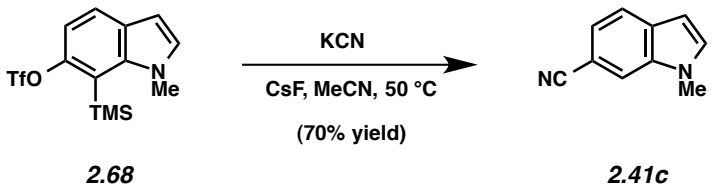
**Amine 2.38c:** To a stirred solution of silyltriflate **2.68** (20 mg, 0.057 mmol) and aniline (26 μL, 0.28 mmol, 5 equiv) in MeCN (1 mL) was added CsF (26 mg, 0.17 mmol, 3 equiv). The reaction vessel was sealed and placed in an aluminum heating block maintained at 50 °C for 14 h. After cooling to 23 °C, the reaction mixture was filtered over silica gel (EtOAc eluent). Evaporation under reduced pressure afforded the crude product, which was further purified by flash chromatography (9:1 Hexanes:EtOAc) to provide exclusively amine **2.38c** (11.5 mg, 91% yield) as a yellow solid. **2.38c**: $R_f$ 0.46 (4:1 Hexanes:EtOAc); $^1$H NMR (500 MHz, $CDCl_3$): δ 7.54 (d, *J* = 8.5, 1H), 7.24 (d, *J* = 7.5, 2H), 7.12 (s, 1H), 7.04 (d, *J* = 7.5, 2H), 6.98 (d, *J* = 3.0, 1H), 6.91 (dd, *J* = 8.5, 2.0, 1H), 6.87 (t, *J* = 7.0), 6.44 (d, *J* = 3.0), 5.74 (br s, 1H), 3.73 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 145.4, 137.67, 137.65, 129.5, 128.4, 124.5, 121.7, 119.9, 116.3, 114.7,

101.1, 100.5, 33.0; IR (film): 3389, 3051, 3024, 1599, 1496 $cm^{-1}$; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{15}H_{15}N_2$, 223.1235; found, 223.1234.



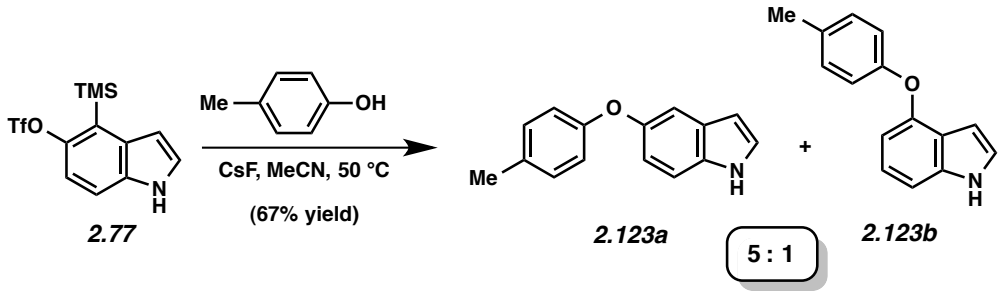

*2.68* *2.122*

**Triazole 2.103.** To a stirred solution of silyltriflate **2.68** (20 mg, 0.057 mmol) and benzyl azide[60] (38 mg, 0.28 mmol, 5 equiv) in MeCN (1 mL) was added CsF (26 mg, 0.17 mmol, 3 equiv). The reaction vessel was placed in an aluminum heating block maintained at 50 °C for 14 h. After cooling to 23 °C, the reaction mixture was filtered over silica gel (EtOAc eluent). Evaporation under reduced pressure afforded the crude product, which was further purified by flash chromatography (1:1 Hexanes:$Et_2O$) to provide exclusively triazole **2.122** as a white solid (18.5 mg, 77% yield). **2.122**: $R_f$ 0.09 (9:1 Hexanes:$Et_2O$); $^1H$ NMR (500 MHz, $CDCl_3$): δ 7.61 (d, *J* = 8.7, 1H), 7.33–7.25 (m, 5H), 7.08 (d, *J* = 3.0, 1H), 7.01 (d, *J* = 8.7, 1H), 6.62 (d, *J* = 3.0, 1H), 5.88 (s, 2H), 4.39 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 135.5, 135.1, 131.0, 128.8, 128.1, 127.3, 126.8, 125.8, 123.6, 122.3, 103.2, 101.3, 52.2, 35.8; IR (film): 3032, 2942, 1634, 1581, 1496, 1455, 1360, 1315, 1221, 1100 $cm^{-1}$; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{16}H_{14}N_4Na$, 285.1116; found, 285.1120.




*2.68* *2.41c*

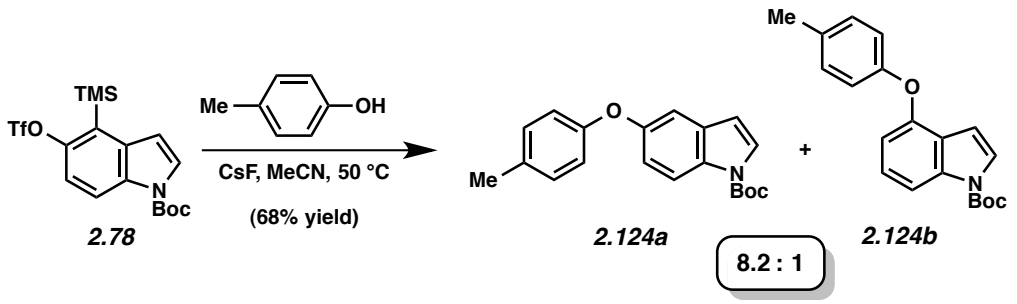
**Cyanoindole 2.41c.** To a stirred solution of silyltriflate **2.68** (20 mg, 0.057 mmol) and potassium cyanide (14 mg, 0.085 mmol, 1.5 equiv) in MeCN (1 mL) was added CsF (26 mg, 0.17 mmol, 3 equiv). The reaction vessel was placed in an aluminum heating block maintained at 50 °C for 14 h. After cooling to 23 °C, the reaction mixture was filtered over silica gel (EtOAc eluent). Evaporation under reduced pressure afforded the crude product, which was further purified by flash chromatography (7:3 Hexanes:$Et_2O$) to provide exclusively cyanoindole **2.41c** (6.2 mg, 70% yield) as a yellow solid. **2.41c**: $R_f$ 0.17 (3:1 Hexanes: $Et_2O$); $^1$H NMR (500 MHz, $CDCl_3$): δ 7.67–7.66 (m, 2H), 7.33 (dd, *J* = 8.3, 1.2, 1H), 7.25 (d, *J* = 3.1, 1H), 6.56 (dd, *J* = 3.1, 0.8, 1H), 3.84 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 135.4, 132.5, 131.5, 122.1, 121.5, 120.7, 114.1, 103.8, 101.9, 33.0. IR (film): 3101, 2939, 2922, 2219, 1612, 1508, 1472, 1344, 1327, 1246 $cm^{-1}$; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{10}H_8N_2Na$, 179.0585; found, 179.0581.




*2.77* *2.123a* *2.123b*

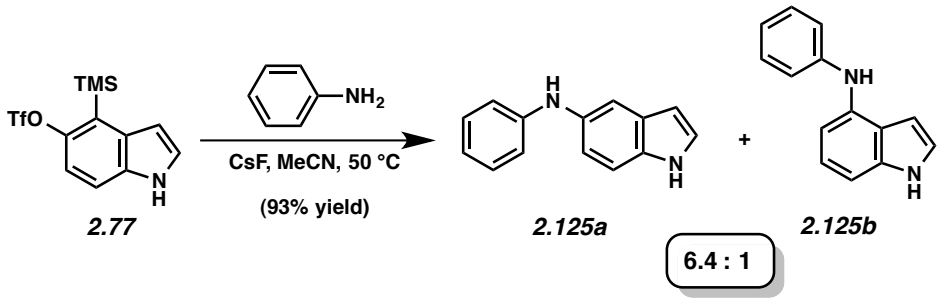
***N*-H Ethers 2.123a and 2.123b.** To a stirred solution of *N*-H silyltriflate **2.77** (40 mg, 0.12 mmol) and *p*-cresol (64 mg, 0.59 mmol, 5 equiv) in MeCN (1.6 mL) was added CsF (54 mg, 0.360 mmol, 3 equiv). The reaction vessel was placed in an aluminum heating block maintained at 50 °C for 14 h. After cooling to 23 °C, the reaction mixture was filtered over silica gel (EtOAc

eluent). Evaporation under reduced pressure afforded the crude products, which were further purified by flash chromatography (65:35 Hexanes:$CH_2Cl_2$) to provide a mixture of *N*-H ethers **2.123a** and **2.123b** (5:1 ratio of **2.123a**:**2.123b**, 17.6 mg, 67% yield). An analytical sample of **2.123a** was obtained by preparative TLC (1:1 Hexanes:$CH_2Cl_2$). **2.123a**: $R_f$ 0.31 (1:1 Hexanes:$CH_2Cl_2$); $^1$H NMR (500 MHz, $CDCl_3$): δ 8.15 (br s, 1H), 7.36 (d, *J* = 8.7, 1H), 7.27–7.26 (m, 1H), 7.24 (app. t, *J* = 2.8, 1H), 7.09 (d, *J* = 8.3, 2H), 6.95 (dd, *J* = 8.7, 2.3, 1H), 6.90–6.87 (m, 2H), 6.50–6.49 (m, 1H), 2.31 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 156.8, 150.6, 132.5, 131.4, 129.9, 128.4, 125.2, 117.5, 115.4, 111.7, 110.6, 102.6, 20.5; IR (film): 3420, 3030, 2921, 1504 $cm^{-1}$; HRMS-ESI (*m/z*) [M + Na]$^+$ calcd for $C_{15}H_{13}NONa$, 246.0895; found, 246.0892. **2.123b**: $R_f$ 0.34 (1:1 Hexanes:$CH_2Cl_2$).



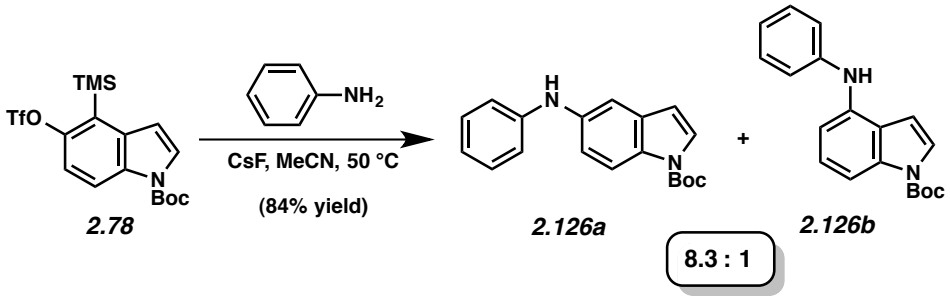

***N*-Boc Ethers 2.124a and 2.124b.** To a stirred solution of *N*-H silyltriflate **2.78** (20 mg, 0.046 mmol) and *p*-cresol (7.4 mg, 0.068 mmol, 1.5 equiv) in MeCN (1 mL) was added CsF (21 mg, 0.14 mmol, 3 equiv). The reaction vessel was placed in an aluminum heating block maintained at 50 °C for 14 h. After cooling to 23 °C, the reaction mixture was filtered over silica gel (EtOAc eluent). Evaporation under reduced pressure afforded the crude products, which were further purified by preparative TLC (1:1 Hexanes:$CH_2Cl_2$) to provide a mixture of *N*-Boc ethers **2.124a** and **2.124b** (8.2:1 ratio of **2.124a**:**2.124b**, 9.6 mg, 68% yield). An analytical sample of **2.124a** was obtained by flash chromatography (85:15 Hexanes:$CH_2Cl_2$ → 4:1 Hexanes:$CH_2Cl_2$). **2.124a**:

$R_f$ 0.57 (9:1 Hexanes:$Et_2O$); $^1$H NMR (500 MHz, 40 °C, $CDCl_3$): δ 8.09 (d, $J$ = 8.9, 1H), 7.59 (d, $J$ = 3.7, 1H), 7.15 (d, $J$ = 2.4, 1H), 7.11 (d, $J$ = 8.3, 2H), 7.02 (dd, $J$ = 8.9, 2.4, 1H), 6.92–6.89 (m, 2H), 6.48 (d, $J$ = 3.6, 1H), 2.33 (s, 3H), 1.68 (s, 9H); $^{13}$C NMR (125 MHz, 40 °C, $CDCl_3$, 15/16 C): δ 156.0, 153.1, 149.5, 132.0, 131.4, 129.9, 126.7, 118.1, 116.3, 115.9, 110.4, 106.9, 83.5, 28.1, 20.4; IR (film): 2979, 1734, 1464 cm$^{-1}$; HRMS-ESI ($m/z$) [M + Na]$^+$ calcd for $C_{20}H_{21}NO_3Na$, 346.1419; found, 346.1417. **2.124b**: $R_f$ 0.57 (9:1 Hexanes:$Et_2O$).

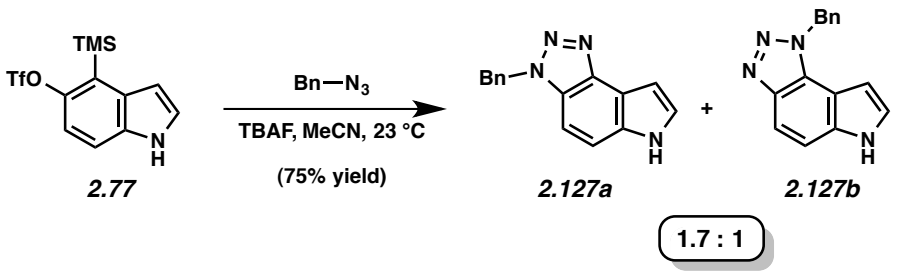



***N*-H Amines 2.125a and 2.125b.** To a stirred solution of *N*-H silyltriflate **2.77** (20 mg, 0.059 mmol) and aniline (27 μL, 0.30 mmol, 5 equiv) in MeCN (1 mL) was added CsF (27 mg, 0.18 mmol, 3 equiv). The reaction vessel was placed in an aluminum heating block maintained at 50 °C for 14 h. After cooling to 23 °C, the reaction mixture was filtered over silica gel (EtOAc eluent). Evaporation under reduced pressure afforded the crude products, which were further purified by flash chromatography (3:7 Hexanes:$CH_2Cl_2$) to provide a mixture of *N*-H amines **2.125a** and **2.125b** (6.4:1 ratio of **2.125a**:**2.125b**, 11.4 mg, 93% yield). An analytical sample of **2.125a** was obtained by preparative TLC (100% $CH_2Cl_2$). **2.125a**: $R_f$ 0.40 (100% $CH_2Cl_2$); $^1$H NMR (500 MHz, $CDCl_3$): δ 8.09 (br s, 1H), 7.44 (d, $J$ = 1.9, 1H), 7.34 (d, $J$ = 8.6, 1H), 7.23–7.20 (m, 3H), 7.04 (dd, $J$ = 8.6, 2.1, 1H), 6.95 (d, $J$ = 7.7, 2H), 6.82 (app. t, $J$ = 7.3, 1H), 6.50–6.49 (m, 1H), 5.64 (br s, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 146.1, 135.1, 132.6, 129.1, 128.5, 124.8, 118.9, 118.2, 115.2, 113.0, 111.5, 102.3; IR (film): 3403, 3043, 2918, 2850, 1712, 1598,

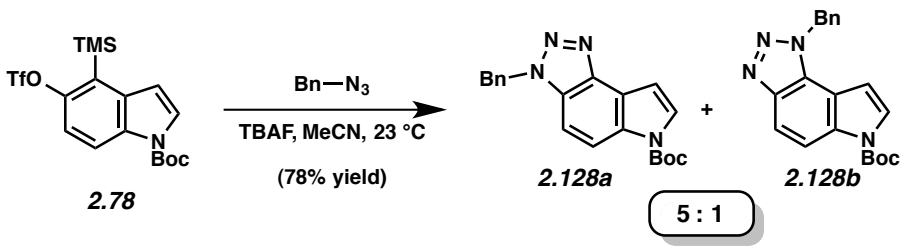
1496, 1307 $cm^{-1}$; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{14}H_{13}N_2$, 209.1079; found, 209.1080. **2.125b**: $R_f$ 0.49 (100% $CH_2Cl_2$).



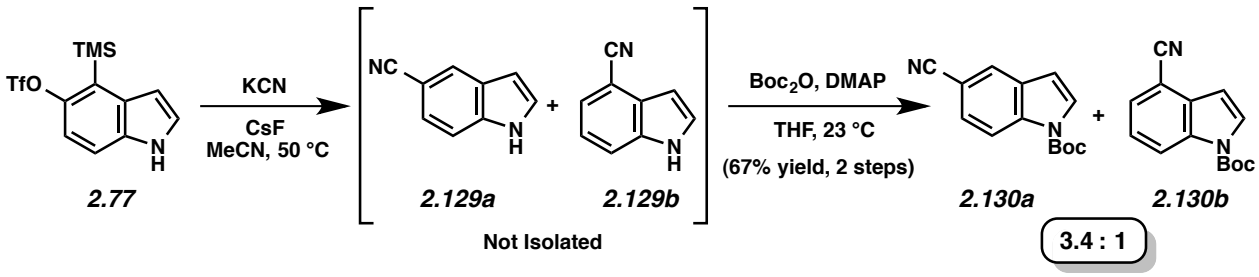

***N*-Boc Amines 2.126a and 2.126b.** To a stirred solution of *N*-Boc silyltriflate **2.78** (25 mg, 0.057 mmol) and aniline (26 μL, 0.29 mmol, 5 equiv) in MeCN (1 mL) was added CsF (26 mg, 0.17 mmol, 3 equiv). The reaction vessel was placed in an aluminum heating block maintained at 50 °C for 14 h. After cooling to 23 °C, the reaction mixture was filtered over silica gel (EtOAc eluent). Evaporation under reduced pressure afforded the crude products, which were further purified by flash chromatography (9:1 Hexanes:$Et_2O$) to provide a mixture of *N*-Boc amines **2.126a** and **2.126b** (8.3:1 ratio of **2.126a**:**2.126b**, 14.7 mg, 84% yield). An analytical sample of **2.126a** was obtained by preparative TLC (7:3 Hexanes:$Et_2O$). **2.126a**: $R_f$ 0.58 (3:1 Hexanes:$Et_2O$); $^1H$ NMR (500 MHz, $CDCl_3$): δ 8.05 (br s, 1H), 7.58 (s, 1H), 7.31 (d, *J* = 2.0, 1H), 7.26–7.23 (m, 2H), 7.08 (dd, *J* = 9.0, 2.0, 1H), 7.02–7.01 (m, 2H), 6.88 (app. t, *J* = 7.5, 1H), 6.48 (d, *J* = 3.5, 1H), 5.68 (br s, 1H), 1.68 (s, 9H); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 149.6, 144.7, 137.9, 131.4, 130.9, 129.2, 126.4, 119.9, 117.9, 116.2, 115.7, 111.2, 106.9, 83.4, 28.1; IR (film): 3393, 2979, 2936, 1730, 1371, 1126 $cm^{-1}$; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{19}H_{21}N_2O_2$, 309.1603; found, 309.1596. **2.126b**: $R_f$ 0.58 (3:1 Hexanes:$Et_2O$).



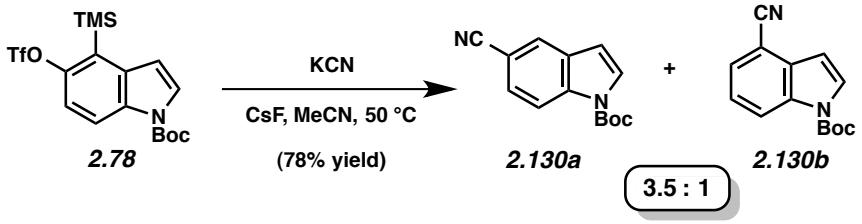

***N*-H triazoles 2.127a and 2.127b.** To a stirred solution of *N*-H silyltriflate **2.77** (20 mg, 0.059 mmol) and benzyl azide[60] (39 mg, 0.30 mmol, 5 equiv) in MeCN (1 mL) at 23 °C was added a solution of TBAF in THF (1.0 M, 120 μL, 0.120 mmol, 2 equiv). The solution was stirred for 10 min, then filtered over silica gel (EtOAc eluent). Evaporation under reduced pressure afforded the crude products, which were further purified by flash chromatography (3:2 Hexanes:EtOAc → 1:1 Hexanes:EtOAc) to provide a mixture of *N*-H triazoles **2.127a** and **2.127b** (1.7:1 ratio of **2.127a**:**2.127b**, 11 mg, 75% yield). These compounds were characterized as a mixture. $R_f$ 0.34 (1:1 Hexanes:EtOAc); **2.127a**: $^1$H NMR (500 MHz, $d_6$-DMSO): δ 11.65 (s, 1H), 7.56 (d, $J$ = 8.5, 1H), 7.453–7.445 (m, 1H), 7.39–7.37 (m, 1H), 7.31–7.20 (m, 5H), 6.85 (s, 1H), 5.93 (s, 2H); **2.127b**: $^1$H NMR (500 MHz, $d_6$-DMSO): δ 11.76 (s, 1H), 7.61 (d, $J$ = 9.0, 1H), 7.453–7.445 (m, 1H), 7.39–7.37 (m, 1H), 7.31–7.20 (m, 5H), 6.81 (s, 1H), 6.07 (s, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 142.1, 140.4, 135.5, 135.1, 134.2, 132.1, 129.0, 128.82, 128.79, 128.1, 128.0, 127.8, 127.3, 126.9, 124.1, 123.2, 117.3, 113.5, 113.4, 110.5, 109.9, 103.4, 101.4, 100.8, 52.6, 52.3; IR (film): 3194, 3079, 2920, 1221 cm$^{-1}$; HRMS-ESI (*m/z*) [M + Na]$^+$ calcd for $C_{15}H_{12}N_4Na$, 271.0960; found, 271.0965.



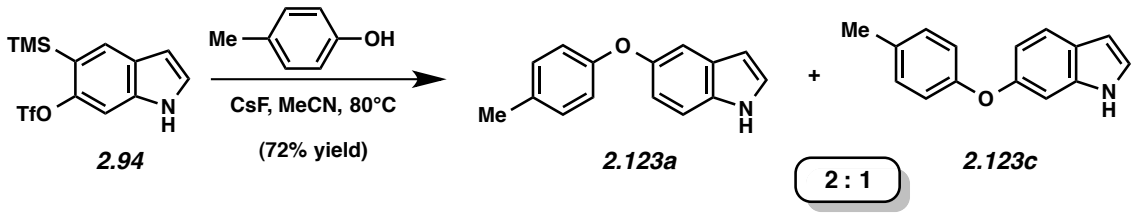

***N*-Boc triazoles 2.128a and 2.128b.** To a stirred solution of *N*-Boc silyltriflate **2.78** (20 mg, 0.046 mmol) and benzyl azide[60] (30 mg, 0.23 mmol, 5 equiv) in MeCN (1 mL) at 23 °C was added a solution of TBAF in THF (1.0 M, 90 μL, 0.090 mmol, 2 equiv). The solution was stirred for 10 min, then filtered over silica gel (EtOAc eluent). Evaporation under reduced pressure afforded the crude products, which were further purified by flash chromatography (7:3 Hexanes:$Et_2O$) to provide a mixture of *N*-Boc triazoles **2.128a** and **2.128b** (5:1 ratio of **2.128a**:**2.128b**, 12.4 mg, 78% yield). These compounds were characterized as a mixture. $R_f$ 0.17 (3:2 Hexanes:$Et_2O$); **2.128a**: $^1$H NMR (500 MHz, 40 °C, $CDCl_3$): δ 8.36 (d, *J* = 9.0, 1H), 7.74 (d, *J* = 3.5, 1H), 7.33–7.26 (m, 5H), 7.21–7.20 (m, 2H), 5.89 (s, 2H), 1.68 (s, 9H); **2.128b:** $^1$H NMR (500 MHz, 40 °C, $CDCl_3$): δ 8.29 (d, *J* = 9.5, 1H), 7.94 (d, *J* = 9.5, 1H), 7.62 (d, *J* = 3.5, 1H), 7.33–7.26 (m, 5H), 6.58 (d, *J* = 3.5, 1H), 6.04 (s, 2H), 1.68 (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 149.7, 149.5, 143.5, 140.2, 135.5, 135.1, 134.1, 132.0, 130.2, 129.2, 129.1, 128.5, 128.4, 127.6, 127.2, 126.9, 126.7, 126.0, 120.8, 116.6, 115.6, 113.6, 113.1, 105.4, 105.1, 104.1, 84.9, 84.5, 53.0, 52.6, 28.28, 28.25; IR (film): 2981, 1734, 1126 $cm^{-1}$; HRMS-ESI (*m*/*z*) $[M + H]^+$ calcd for $C_{20}H_{21}N_4O_2$, 349.1664; found, 349.1666.



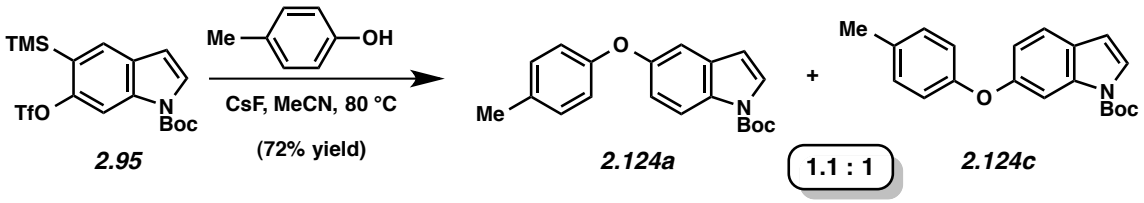

***N*-Boc cyanoindoles 2.130a and 2.130b.** To a stirred solution of *N*-H silyltriflate **2.77** (20 mg, 0.059 mmol) and potassium cyanide (5.8 mg, 0.089 mmol, 1.5 equiv) in MeCN (1 mL) was added CsF (27 mg, 0.18 mmol, 3 equiv). The reaction vessel was placed in an aluminum heating block maintained at 50 °C for 14 h. After cooling to 23 °C, the reaction mixture was filtered over silica gel (EtOAc eluent). Evaporation under reduced pressure afforded a mixture of crude *N*-H cyanoindoles **2.129a** and **2.129b**. This crude mixture was dissolved in THF (1 mL) and treated with DMAP (1 mg, 0.0082 mmol, 0.14 equiv). The mixture was allowed to stir at 23 °C for 5 min, then $Boc_2O$ (13 mg, 0.059 mmol, 1 equiv) was added. The resulting mixture was stirred at 23 °C for an additional 14 h, then filtered over silica gel (EtOAc eluent). Evaporation under reduced pressure afforded the crude products, which were further purified by flash chromatography (95:5 Hexanes:$Et_2O$) and then preparative TLC (4:1 Hexanes:$Et_2O$) to provide *N*-Boc cyanoindoles **2.130a and 2.130b** (5.7 mg and 1.7 mg, respectively; 3.4:1 ratio of **2.130a:2.130b**, 67% combined yield). Spectral data for **2.130a** and **2.130b** match those reported on page 129 of this dissertation.



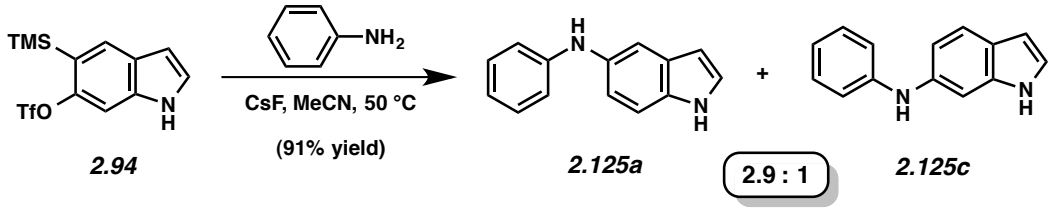

***N*-Boc cyanoindoles 2.130a and 2.130b.** To a stirred solution of *N*-Boc silyltriflate **2.78** (20 mg, 0.046 mmol) and potassium cyanide (4.5 mg, 0.069 mmol, 1.5 equiv) in MeCN (1 mL) was added CsF (21 mg, 0.14 mmol, 3 equiv). The reaction vessel was placed in an aluminum heating block maintained at 50 °C for 14 h. After cooling to 23 °C, the reaction mixture was filtered over silica gel (EtOAc eluent). Evaporation under reduced pressure afforded the crude products, which were further purified by preparative TLC (4:1 Hexanes:$Et_2O$) to provide *N*-Boc cyanoindoles **2.130a** and **2.130b** (6.7 mg and 1.9 mg, respectively; 3.5:1 ratio of **2.130a**:**2.130b**, 78% combined yield). **2.130a:** $R_f$ 0.30 (9:1 Hexanes:$Et_2O$); $^1$H NMR (500 MHz, $CDCl_3$): δ 8.25 (d, *J* = 8.3, 1H), 7.90 (d, *J* = 1.0, 1H), 7.70 (d, *J* = 3.6, 1H), 7.56 (dd, *J* = 8.6, 1.5, 1H), 6.63 (d, *J* = 3.7, 1H), 1.68 (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 148.9, 137.0, 130.4, 128.0, 127.2, 125.7, 119.7, 115.9, 106.8, 106.0, 84.8, 28.0; IR (film): 2930, 2226, 1741, 1365 cm$^{-1}$; HRMS-ESI (*m/z*) [M + Na]$^+$ calcd for $C_{14}H_{14}N_2O_2Na$, 265.0953; found, 265.0956. **2.130b:** $R_f$ 0.34 (9:1 Hexanes:$Et_2O$); $^1$H NMR (500 MHz, 40 °C, $CDCl_3$): δ 8.40 (d, *J* = 8.4, 1H), 7.74 (d, *J* = 3.7, 1H), 7.54 (d, *J* = 7.5, 1H), 7.35 (app. t, *J* = 8.1, 1H), 6.78 (d, *J* = 3.7, 1H), 1.69 (s, 9H); $^{13}$C NMR (125 MHz, 40 °C, $CDCl_3$): δ 148.9, 135.1, 132.2, 128.3, 127.0, 123.9, 119.6, 117.5, 105.3, 103.8, 84.7, 28.0; IR (film): 2980, 2225, 1726, 1120 cm$^{-1}$; HRMS-ESI (*m/z*) [M + Na]$^+$ calcd for $C_{14}H_{14}N_2O_2Na$, 265.0953; found, 265.0948.



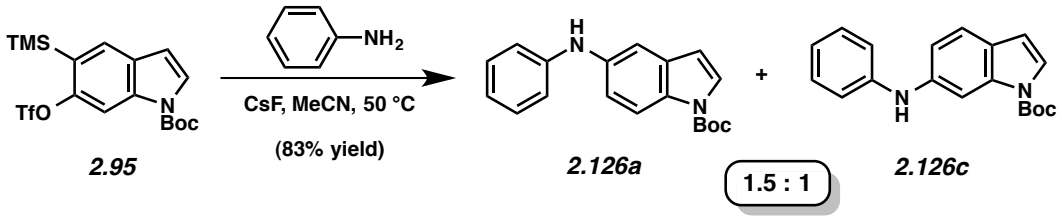

***N*-H ethers 2.123a and 2.123c.** To a stirred solution of *N*-H silyltriflate **2.94** (20 mg, 0.059 mmol) and *p*-cresol (32 mg, 0.30 mmol, 5 equiv) in MeCN (1 mL) was added CsF (27 mg, 0.18 mmol, 3 equiv). The reaction vessel was placed in an aluminum heating block maintained at 80 °C for 14 h. After cooling to 23 °C, the reaction mixture was filtered over silica gel (EtOAc eluent). Evaporation under reduced pressure afforded the crude products, which were further purified by flash chromatography (7:3 Hexanes:$CH_2Cl_2$) to provide a mixture of *N*-H ethers **2.123a** and **2.123c** (2:1 ratio of **2.123a**:**2.123c**, 8.9 mg, 72% yield). Spectral data for **2.123a** and **2.123c** match those reported on pages 123 and 135 of this dissertation, respectively.




***N*-Boc ethers 2.124a and 2.124c.** To a stirred solution of *N*-Boc silyltriflate **2.95** (20 mg, 0.046 mmol) and *p*-cresol (7.4 mg, 0.069 mmol, 1.5 equiv) in MeCN (1 mL) was added CsF (21 mg, 0.14 mmol, 3 equiv). The reaction vessel was placed in an aluminum heating block maintained 80 °C for 14 h. After cooling to 23 °C, the reaction mixture was filtered over silica gel (EtOAc eluent). Evaporation under reduced pressure afforded the crude products, which were further purified by flash chromatography (3:1 Hexanes:$CH_2Cl_2$) to provide a mixture of *N*-Boc ethers **2.124a** and **2.124c** (1.1:1 ratio of **2.124a**:**2.124c**, 10.7 mg, 72% yield). Spectral data for **2.124a** and **2.124c** match those reported on pages 124 and 136 of this dissertation, respectively.

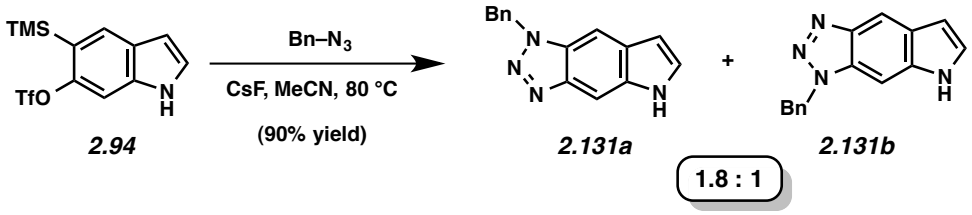



***N*-H amines 2.125a and 2.125c.** To a stirred solution of *N*-H silyltriflate **2.94** (21.4 mg, 0.0634 mmol) and aniline (24.9 μL, 0.317 mmol, 5 equiv) in MeCN (1.26 mL) was added CsF (28.9 mg, 0.190 mmol, 3 equiv). The reaction vessel was placed in an aluminum heating block maintained at 80 °C for 14 h. After cooling to 23 °C, the reaction mixture was filtered over silica gel (EtOAc eluent). Evaporation under reduced pressure afforded the crude products, which were further purified by flash chromatography (100% Benzene) to provide a mixture of *N*-H amines **2.125a** and **2.125c** (2.9:1 ratio of **2.125a**:**2.125c**, 12.0 mg, 91% yield). Spectral data for **2.125a** and **2.125c** match those reported on pages 124 and 137 of this dissertation, respectively.



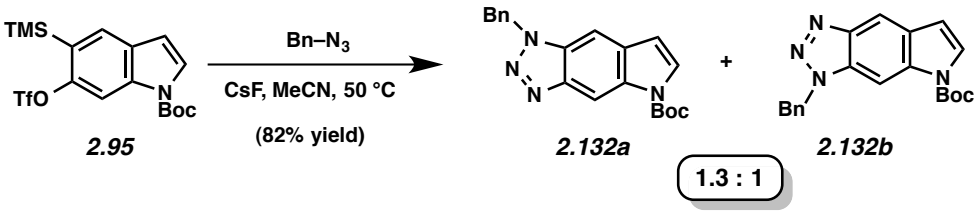

***N*-Boc amines 2.126a and 2.126c.** To a stirred solution of *N*-Boc silyltriflate **2.95** (25.7 mg, 0.0587 mmol) and aniline (26.8 μL, 0.294 mmol, 5 equiv) in MeCN (1.17 mL) was added CsF (17.8 mg, 0.117 mmol, 2 equiv). The reaction vessel was placed in an aluminum heating block maintained at 50 °C for 15.5 h. After cooling to 23 °C, the reaction mixture was filtered over silica gel (EtOAc eluent). Evaporation under reduced pressure afforded the crude products, which were further purified by flash chromatography (1.5:1 Benzene:Hexanes) to provide a

mixture of *N*-Boc amines **2.126a** and **2.126c** (1.5:1 ratio of **2.126a**:**2.126c**, 15.1 mg, 83% yield). Spectral data for **2.126a** and **2.126c** match those reported on pages 125 and 138 of this dissertation, respectively.

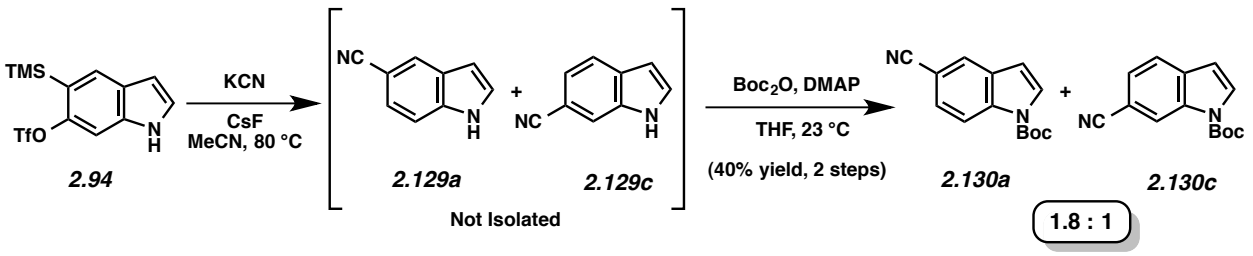



***N*-H triazoles 2.131a and 2.131b.** To a stirred solution of *N*-H silyltriflate **2.94** (20 mg, 0.059 mmol) and benzyl azide[60] (39 mg, 0.30 mmol, 5 equiv) in MeCN (1 mL) was added CsF (27 mg, 0.18 mmol, 3 equiv). The reaction vessel was placed in an aluminum heating block maintained at 80 °C for 14 h. After cooling to 23 °C, the reaction mixture was filtered over silica gel (EtOAc eluent). Evaporation under reduced pressure afforded the crude products, which were further purified by flash chromatography (7:3 Hexanes:EtOAc → 1:1 Hexanes:EtOAc) to provide a mixture of *N*-H triazoles **2.131a** and **2.131b** (1.8:1 ratio of **2.131a**:**2.131b**, 13.2 mg, 90% yield). Analytical samples of **2.131a** and **2.131b** were obtained by preparative TLC (4:1 Hexanes:Acetone). **2.131a:** $R_f$ 0.25 (1:1 Hexanes:EtOAc); $^1$H NMR (500 MHz, $CDCl_3$): δ 8.65 (br s, 1H), 8.01 (s, 1H), 7.47 (s, 1H), 7.42 (app. t, $J$ = 2.9, 1H), 7.33–7.25 (m, 5H), 6.55 (s, 1H), 5.89 (s, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 144.1, 135.6, 135.2, 131.0, 129.7, 129.3, 128.8, 128.1, 127.4, 101.5, 98.6, 97.6, 52.1; IR (film): 3182, 2919, 1447, 1242 cm$^{-1}$; HRMS-ESI (*m*/*z*) [M + H]$^+$ calcd for $C_{15}H_{13}N_4$, 249.1140; found, 249.1141. **2.131b:** $R_f$ 0.33 (1:1 Hexanes:EtOAc); $^1$H NMR (500 MHz, $CDCl_3$): δ 8.27 (s, 1H), 8.10 (br s, 1H), 7.32–7.25 (m, 6H), 7.15 (s, 1H), 6.67 (s, 1H), 5.86 (s, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 143.1, 137.6, 135.1, 130.6, 128.8,

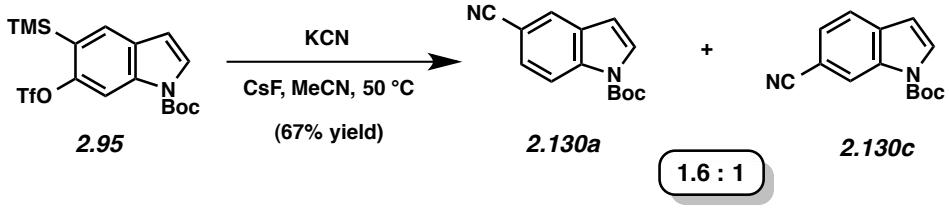
128.3, 128.1, 127.6, 127.3, 109.6, 102.8, 88.0, 52.0; IR (film): 3204, 2918, 1250 $cm^{-1}$; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{15}H_{12}N_4Na$, 271.0960; found, 271.0956.




***N*-Boc triazoles 2.132a and 2.132b.** To a stirred solution of *N*-Boc silyltriflate **2.95** (20 mg, 0.046 mmol) and benzyl azide[60] (30 mg, 0.23 mmol, 5 equiv) in MeCN (1 mL) was added CsF (21 mg, 0.14 mmol, 3 equiv). The reaction vessel was placed in an aluminum heating block maintained at 50 °C for 14 h. After cooling to 23 °C, the reaction mixture was filtered over silica gel (EtOAc eluent). Evaporation under reduced pressure afforded the crude products, which were further purified by flash chromatography (3:2 Hexanes:$Et_2O$) to provide a mixture of *N*-Boc triazoles **2.132a** and **2.132b** (1.3:1 ratio of **2.132a**:**2.132b**, 13 mg, 82% yield). These compounds were characterized as a mixture. $R_f$ 0.29 (7:3 Hexanes:EtOAc); **2.132a:** $^1$H NMR (500 MHz, $CDCl_3$): δ 8.76 (br s, 1H), 7.75 (br s, 1H), 7.35 (s, 1H), 7.34–7.25 (m, 5H), 6.56 (d, *J* = 3.8, 1H), 5.86 (s, 2H), 1.70 (s, 9H); **2.132b:** $^1$H NMR (500 MHz, $CDCl_3$): δ 8.19 (br s, 1H), 8.15 (s, 1H), 7.64 (br s, 1H), 7.34–7.25 (m, 5H), 6.66 (d, *J* = 3.8, 1H), 5.87 (s, 2H), 1.64 (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 149.5, 149.4, 145.1, 143.6, 136.0, 135.0, 134.9, 133.5, 132.8, 131.5, 130.2, 130.1, 129.9, 128.84, 128.81, 128.4, 128.2, 128.1, 127.31, 127.30, 110.2, 107.4, 106.7, 104.8, 98.9, 94.4, 84.1, 83.8, 52.1, 51.8, 28.14, 28.08; IR (film): 2979, 2933, 1727, 1143 $cm^{-1}$; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{20}H_{20}N_4O_2Na$, 371.1484; found, 371.1473.

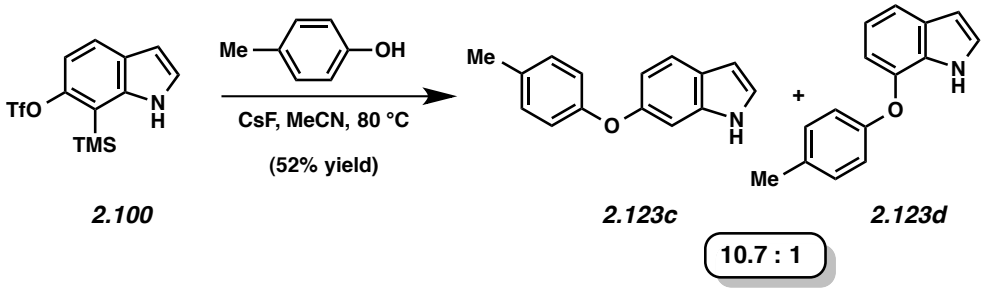



***N*-H cyanoindoles 2.129a and 2.129c.** To a stirred solution of *N*-H silyltriflate **2.94** (20 mg, 0.059 mmol) and potassium cyanide (14.7 mg, 0.226 mmol, 3.8 equiv) in MeCN (1 mL) was added CsF (27 mg, 0.18 mmol, 3 equiv). The reaction vessel was placed in an aluminum heating block maintained at 80 °C for 14 h. After cooling to 23 °C, the reaction mixture was filtered over silica gel (EtOAc eluent). Evaporation under reduced pressure afforded crude *N*-H cyanoindoles **2.129a** and **2.129c**. This crude mixture was dissolved in THF (1 mL) and treated with DMAP (1 mg, 0.0081 mmol, 0.14 equiv) and $Boc_2O$ (14.2 mg, 0.065 mmol, 1.1 equiv). The resulting mixture was stirred at 23 °C for an additional 14 h, then filtered over silica gel (EtOAc eluent). Evaporation under reduced pressure afforded the crude products, which were further purified by flash chromatography (95:5 Hexanes:$Et_2O$ → 9:1 Hexanes:$Et_2O$) to provide a mixture of *N*-Boc cyanoindoles **2.130a** and **2.130c** (1.8:1 ratio of **2.130a:2.130c**, 4.4 mg, 40% yield). Spectral data for **2.130a** and **2.130c** match those reported on pages 129 and 141 of this dissertation, respectively.



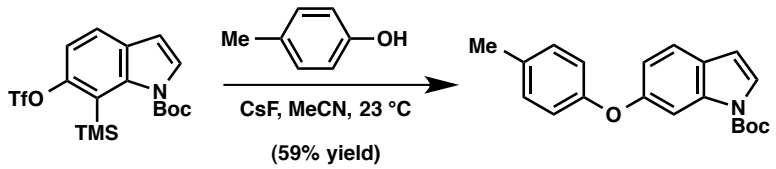

***N*-Boc cyanoindoles 2.130a and 2.130c.** To a stirred solution of *N*-Boc silyltriflate **2.95** (20 mg, 0.046 mmol) and potassium cyanide (38 mg, 0.584 mmol, 12.7 equiv) in MeCN (1 mL) was

added CsF (21 mg, 0.14 mmol, 3 equiv). The reaction vessel was placed in an aluminum heating block maintained at 50 °C for 24 h. After cooling to 23 °C, the reaction mixture was filtered over silica gel (EtOAc eluent). Evaporation under reduced pressure afforded the crude products, which were further purified by flash chromatography (95:5 Hexanes:$Et_2O$) to provide a mixture of *N*-Boc cyanoindoles **2.130a** and **2.130c** (1.6:1 ratio of **2.130a:2.130c**, 7.4 mg, 67% yield) as a white solid. Spectral data for **2.130a** and **2.130c** match those reported on pages 129 and 141 of this dissertation, respectively.




***N*-H ethers 2.123c and 2.123d.** To a stirred solution of *N*-H silyltriflate **2.100** (37.5 mg, 0.11 mmol) and *p*-cresol (60 mg, 0.56 mmol, 5 equiv) in MeCN (1.2 mL) was added CsF (51 mg, 0.33 mmol, 3 equiv). The reaction vessel was placed in an aluminum heating block maintained at 80 °C for 14 h. After cooling to 23 °C, the reaction mixture was filtered over silica gel (EtOAc eluent). Evaporation under reduced pressure afforded the crude products, which were purified by flash chromatography (3:1 Hexanes:$CH_2Cl_2$) to provide *N*-H ether **2.123c** (11.8 mg) and crude **2.123d**. Further purification by preparative TLC (3:2 Hexanes:$CH_2Cl_2$) afforded **2.123d** (1.1 mg; 10.7:1 ratio of **2.123c**:**2.123d**, 52% combined yield). **2.123c**: $R_f$ 0.12 (85:15 Hexanes:$CH_2Cl_2$); $^1$H NMR (500 MHz, $CDCl_3$): δ 8.05 (br s, 1H), 7.58 (d, $J$ = 8.5, 1H), 7.16 (app. t, $J$ = 2.9, 1H), 7.12 (d, $J$ = 8.3, 2H), 7.01 (d, $J$ = 1.8, 1H), 6.93–6.91 (m, 2H), 6.88 (dd, $J$ = 6.4, 2.1, 1H), 6.54–6.53 (m, 1H), 2.33 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 156.1, 153.3, 136.1, 131.9, 130.0, 124.02,

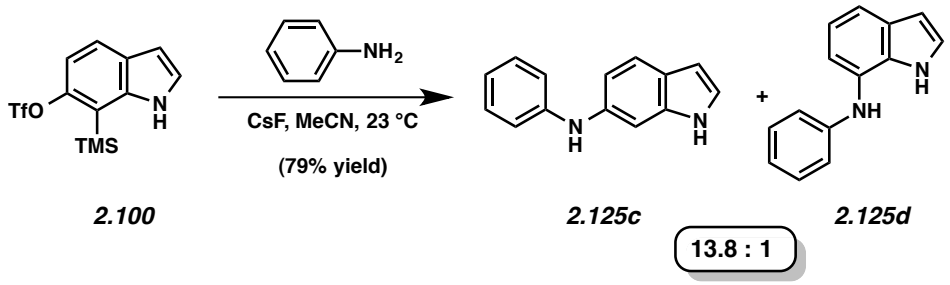
123.97, 121.3, 118.1, 113.1, 102.5, 101.3, 20.5; IR (film): 3418, 2921, 1506, 1491, 1243, 1219 $cm^{-1}$; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{15}H_{14}NO$, 224.1075; found, 224.1075. **2.123d**: $R_f$ 0.25 (85:15 Hexanes:$CH_2Cl_2$); $^1H$ NMR (500 MHz, $CDCl_3$): δ 8.24 (br s, 1H), 7.40 (d, *J* = 7.9, 1H), 7.18 (app. t, *J* = 2.7, 1H), 7.13 (d, *J* = 8.3, 2H), 7.02 (app. t, *J* = 7.8, 1H), 6.96 (d, *J* = 8.5, 2H), 6.73 (d, *J* = 7.7, 1H), 6.58 (app. t, *J* = 2.8, 1H), 2.34 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 154.6, 142.6, 132.6, 130.3, 130.1, 127.7, 124.1, 120.1, 118.0, 115.8, 110.1, 102.9, 20.6; IR (film): 3426, 2924, 2852, 1713, 1505, 1241 $cm^{-1}$; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{15}H_{14}NO$, 224.1075; found, 224.1079.



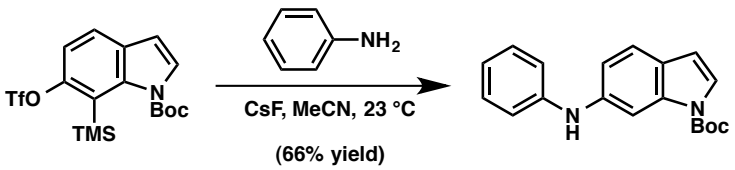

***2.99*** ***2.124c***

***N*-Boc ether 2.124c.** To a stirred solution of *N*-Boc silyltriflate **2.99** (20 mg, 0.046 mmol) and *p*-cresol (24.7 mg, 0.23 mmol, 5 equiv) in MeCN (1 mL) at 23 °C was added CsF (21 mg, 0.14 mmol, 3 equiv). The solution was stirred for 18 h, then filtered over silica gel (EtOAc eluent). Evaporation under reduced pressure afforded the crude product, which was further purified by flash chromatography (85:15 Hexanes:$CH_2Cl_2$ → 3:1 Hexanes:$CH_2Cl_2$) to provide *N*-Boc ether **2.124c** (8.7 mg, 59% yield) as a light pink solid. $R_f$ 0.31 (4:1 Hexanes:$CH_2Cl_2$); $^1H$ NMR (500 MHz, $CDCl_3$): δ 7.73 (br s, 1H), 7.55 (d, *J* = 3.5, 1H), 7.47 (d, *J* = 8.5, 1H), 7.13 (d, *J* = 8.3, 2H), 6.97–6.93 (m, 3H), 6.53 (dd, *J* = 3.7, 0.5, 1H), 2.33 (s, 3H), 1.58 (s, 9H); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 155.4, 155.3, 149.6, 135.6, 132.4, 130.1, 126.1, 125.5, 121.3, 118.8, 114.7, 107.0,

105.5, 83.7, 27.9, 20.6; IR (film): 2979, 1735 $cm^{-1}$; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{20}H_{21}NO_3Na$, 346.1419; found, 346.1412.

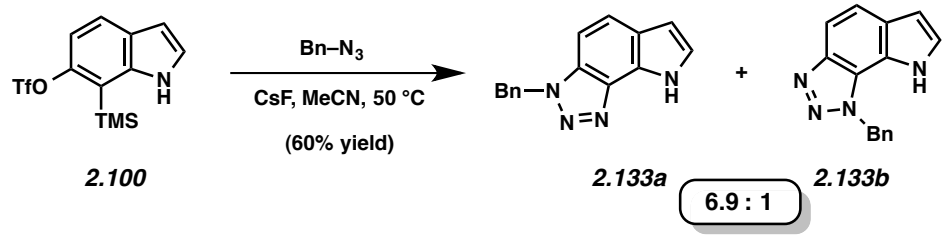



***N*-H amines 2.125c and 2.125d.** To a stirred solution of *N*-H silyltriflate **2.100** (40 mg, 0.12 mmol) and aniline (54 μL, 0.59 mmol, 5 equiv) in MeCN (1.2 mL) at 23 °C was added CsF (54 mg, 0.36 mmol, 3 equiv). The solution was stirred for 14 h, then filtered over silica gel (EtOAc eluent). Evaporation under reduced pressure afforded the crude products, which were further purified by flash chromatography (2:3 Hexanes:$CH_2Cl_2$) to provide a mixture of *N*-H amines **2.125c** and **2.125d** (13.8:1 ratio of **2.125c**:**2.125d**, 19.6 mg, 79% yield). An analytical sample of **2.125c** was obtained by preparative TLC (3:7 Hexanes:$CH_2Cl_2$). **2.125c:** $R_f$ 0.46 (3:7 Hexanes:$CH_2Cl_2$); $^1$H NMR (500 MHz, $CDCl_3$): δ 7.98 (br s, 1H), 7.55 (d, *J* = 9.0, 1H), 7.26–7.22 (m, 2H), 7.178–7.176 (m, 1H), 7.12 (app. t, *J* = 3.0, 1H), 7.04–7.03 (m, 2H), 9.19 (dd, *J* = 8.5, 2.0, 1H), 6.87 (app. t, *J* = 7.5, 1H), 6.51–6.50 (m, 1H), 5.70 (br s, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 144.9, 137.9, 136.5, 129.2, 123.5, 123.4, 121.2, 119.7, 116.3, 114.8, 102.5, 101.6; IR (film): 3399, 3048, 1627, 1597, 1494 $cm^{-1}$; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{14}H_{13}N_2$, 209.1079; found, 209.1078. **2.125d:** $R_f$ 0.46.




*2.99* *2.126c*

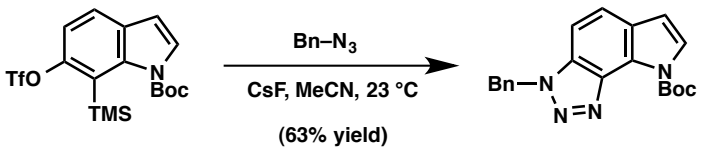
***N*-Boc amine 2.126c.** To a stirred solution of *N*-H silyltriflate **2.99** (40 mg, 0.091 mmol) and aniline (43 μL, 0.46 mmol, 5 equiv) in MeCN (1 mL) at 23 °C was added CsF (42 mg, 0.27 mmol, 3 equiv). The solution was stirred for 14 h, then filtered over silica gel (EtOAc eluent). Evaporation under reduced pressure afforded the crude product, which was further purified by flash chromatography (97:3 Hexanes:$Et_2O$) to provide *N*-Boc amine **2.126c** (18.6 mg, 66% yield). $R_f$ 0.17 (95:5 Hexanes:$CH_2Cl_2$); $^1$H NMR (500 MHz, 40 °C, $CDCl_3$): δ 7.94 (br s, 1H), 7.50 (d, *J* = 3.7, 1H), 7.43 (d, *J* = 8.4, 1H), 7.26 (app. t, *J* = 7.8, 2H), 7.09 (d, *J* = 7.6, 2H), 7.00 (dd, *J* = 8.3, 2.0, 1H), 6.91 (app. t, *J* = 7.3, 1H), 6.50 (d, *J* = 3.7, 1H), 5.75 (br s, 1H), 1.64 (s, 9H); $^{13}$C NMR (125 MHz, 40 °C, $CDCl_3$): δ 149.7, 144.0, 140.3, 136.2, 129.2, 125.2, 124.7, 121.2, 120.4, 117.2, 115.3, 107.1, 105.2, 83.4, 28.1; IR (film): 3391, 2979, 2931, 1727, 1337, 1149 cm$^{-1}$; HRMS-ESI (*m/z*) [M + Na]$^+$ calcd for $C_{19}H_{20}N_2O_2Na$, 331.1422; found, 331.1423.




*2.100* *2.133a* *2.133b*

***N*-H triazoles 2.133a and 2.133b.** To a stirred solution of *N*-H silyltriflate **2.100** (20 mg, 0.059 mmol) and benzyl azide[60] (39 mg, 0.30 mmol, 5 equiv) in MeCN (1 mL) was added CsF (27 mg, 0.18 mmol, 3 equiv). The reaction vessel was placed in an aluminum heating block maintained at 50 °C for 14 h. After cooling to 23 °C, the reaction mixture was filtered over silica gel (EtOAc

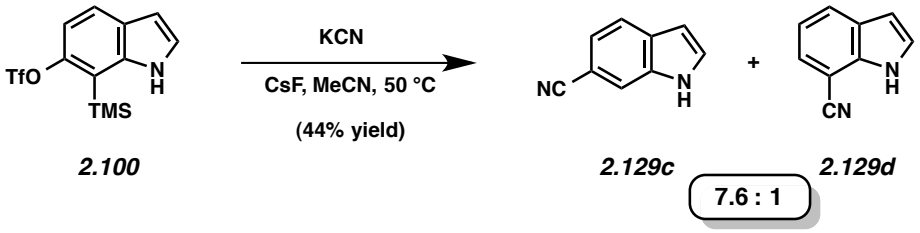
eluent). Evaporation under reduced pressure afforded the crude products, which were further purified by flash chromatography (85:15 Hexanes:EtOAc) to provide a mixture of *N*-H triazoles **2.133a** and **2.133b** (6.9:1 ratio of **2.133a**:**2.133b**, 8.8 mg, 60% yield). An analytical sample of **2.133a** was obtained by preparative TLC (4:1 Hexanes:Acetone). **2.133a:** $R_f$ 0.46 (3:1 Hexanes:EtOAc); $^1$H NMR (500 MHz, $CDCl_3$): δ 10.3 (br s, 1H), 7.68 (d, *J* = 8.7, 1H), 7.36–7.28 (m, 6H), 7.07 (d, *J* = 8.7, 1H), 6.72 (app. t, *J* = 2.3, 1H), 5.91 (s, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 134.9, 134.8, 130.9, 128.8, 128.2, 127.3, 124.4, 123.7, 122.6, 122.3, 104.0, 101.7, 52.4; IR (film): 3181, 3113, 2921, 2851, 1225 cm$^{-1}$; HRMS-ESI (*m/z*) [M + Na]$^+$ calcd for $C_{15}H_{12}N_4Na$, 271.0960; found, 271.0963. **2.114b:** $R_f$ 0.46 (3:1 Hexanes:EtOAc); $^1$H NMR (500 MHz, $CDCl_3$): δ 7.75 (d, *J* = 8.8, 1H), 7.68 (br s, 1H), 7.58 (d, *J* = 8.9, 1H), 7.46 (m, 3H), 7.35–7.34 (m, 2H), 7.01 (app. t, *J* = 2.5, 1H), 6.63 (app. t, *J* = 2.3, 1H), 6.05 (s, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 144.7, 134.9, 129.8, 129.1, 127.0, 126.5, 123.7, 121.9, 118.7, 118.2, 111.8, 104.6, 53.5; IR (film): 3256, 2918, 1235 cm$^{-1}$; HRMS-ESI (*m/z*) [M + Na]$^+$ calcd for $C_{15}H_{12}N_4Na$, 271.0960; found, 271.0963.



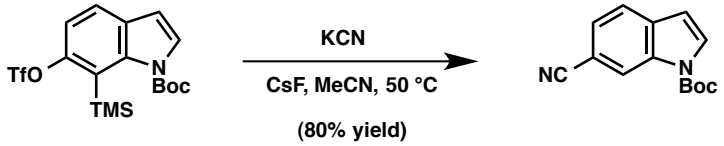

*2.99* *2.134*

***N*-Boc triazole 2.134.** To a stirred solution of *N*-Boc silyltriflate **2.99** (20 mg, 0.046 mmol) and benzyl azide[60] (30.4 mg, 0.23 mmol, 5 equiv) in MeCN (1 mL) at 23 °C was added CsF (21 mg, 0.14 mmol, 3 equiv). The solution was stirred for 18 h, then filtered over silica gel (EtOAc eluent). Evaporation under reduced pressure afforded the crude product, which was further purified by flash chromatography (95:5 Benzene:$Et_2O$) to provide *N*-Boc triazole **2.134** (10 mg,

63% yield). $R_f$ 0.31 (3:2 Hexanes:$Et_2O$); $^1$H NMR (500 MHz, $CDCl_3$): δ 7.68 (d, $J$ = 3.6, 1H), 7.58 (d, $J$ = 8.6, 1H), 7.31–7.24 (m, 5H), 7.21 (d, $J$ = 8.6, 1H), 6.70 (d, $J$ = 3.6, 1H), 5.90 (s, 2H), 1.78 (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 149.0, 135.9, 134.9, 132.4, 128.8, 128.2, 127.3, 126.4, 125.1, 123.7, 121.7, 107.8, 105.0, 84.8, 52.2, 28.1; IR (film): 2979, 2933, 1760, 1732, 1327, 1150 cm$^{-1}$; HRMS-ESI (*m/z*) [M + Na]$^+$ calcd for $C_{20}H_{20}N_4O_2Na$, 371.1484; found, 371.1478.

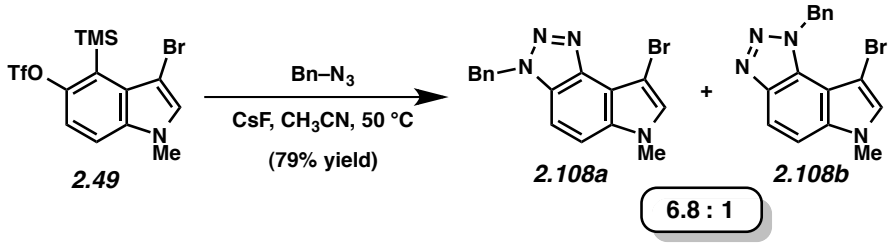



***N*-H cyanoindoles 2.129c and 2.129d.** To a stirred solution of *N*-H silyltriflate **2.100** (20 mg, 0.060 mmol) and potassium cyanide (49.0 mg, 0.30 mmol, 5 equiv) in MeCN (1 mL) was added CsF (27 mg, 0.18 mmol, 3 equiv). The reaction vessel was placed in an aluminum heating block maintained at 50 °C for 14 h. After cooling to 23 °C, the reaction mixture was filtered over silica gel (EtOAc eluent). Evaporation under reduced pressure afforded the crude products, which were further purified by flash chromatography (4:1 Hexanes:EtOAc) to provide a mixture of *N*-H cyanoindoles **2.129c** and **2.129d** (7.6:1 ratio of **2.129c**:**2.129d**, 5.4 mg, 44% yield). An analytical sample of **2.129c** was obtained by preparative TLC (1:1 Hexanes:$Et_2O$). **2.129c:** $R_f$ 0.29 (3:1 Hexanes:EtOAc); $^1$H NMR (500 MHz, $CDCl_3$): δ 8.51 (br s, 1H), 7.76 (s, 1H), 7.70 (d, $J$ = 8.2, 1H), 7.43 (app. t, $J$ = 2.8, 1H), 7.36 (dd, $J$ = 8.2, 1.1, 1H), 6.65–6.64 (m, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 134.5, 131.0, 127.8, 122.7, 121.4, 120.5, 115.8, 104.4, 103.4; IR (film): 3414, 2220, 1348 cm$^{-1}$; HRMS-ESI (*m/z*) [M + Na]$^+$ calcd for $C_9H_6N_2Na$, 165.0429; found, 165.0430. **2.129d:** $R_f$ 0.29 (3:1 Hexanes:EtOAc).




*2.99* *2.130c*

***N*-Boc cyanoindole 2.130c.** To a stirred solution of *N*-Boc silyltriflate **2.99** (22.0 mg, 0.050 mmol) and potassium cyanide (41.5 mg, 0.25 mmol, 5 equiv) in MeCN (1.0 mL) was added CsF (23.0 mg, 0.15 mmol, 3 equiv). The reaction vessel was placed in an aluminum heating block maintained at 50 °C for 14 h. After cooling to 23 °C, the reaction mixture was filtered over silica gel (EtOAc eluent). Evaporation under reduced pressure afforded the crude product, which was further purified by flash chromatography (9:1 Hexanes:$Et_2O$) to provide cyanoindole **2.130c** (9.8 mg, 80% yield) as a white solid. $R_f$ 0.26 (9:1 Hexanes:$Et_2O$); $^1$H NMR (500 MHz, 40 °C, $CDCl_3$): δ 8.50 (s, 1H), 7.76 (d, *J* = 3.7, 1H), 7.62 (d, *J* = 8.1, 1H), 7.47 (dd, *J* = 8.1, 1.2, 1H), 6.62 (d, *J* = 3.6, 1H), 1.70 (s, 9H); $^{13}$C NMR (125 MHz, 40 °C, $CDCl_3$): δ 148.8, 134.2, 133.7, 129.1, 125.6, 121.5, 119.7, 119.6, 107.2, 107.1, 84.9, 28.0; IR (film): 2981, 2224, 1736, 1342 $cm^{-1}$; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{14}H_{14}N_2O_2Na$, 265.0953; found, 265.0948.




*2.49* *2.108a* *2.108b*

**3-Bromo triazoles 2.108a and 2.108b.** To a solution of 3-bromo silyltriflate **2.49** (41.6 mg, 0.097 mmol), and benzyl azide[60] (55.8 mg, 0.420 mmol, 4.3 equiv) in MeCN (1 mL) was added CsF (45.2 mg, 0.300 mmol, 3.1 equiv). The reaction vessel was placed in an aluminum heating block maintained at 50 °C for 7.75 h. After cooling to 23 °C, the reaction mixture was filtered

over silica gel (EtOAc eluent). Evaporation under reduced pressure afforded the crude product, which was further purified by flash chromatography (2:1 Hexanes:EtOAc) to give a mixture of 3-bromo triazoles **2.108a** and **2.108b** (6.8:1 ratio of **2.108a**:**2.108b**, 26.0 mg, 79% yield) as a white solid. These compounds were characterized as a mixture. $R_f$ 0.21 (2:1 Hexanes:EtOAc); **2.108a:** $^1$H NMR (500 MHz, $CDCl_3$): δ 7.16 (d, $J$ = 9.0, 1H), 7.35–7.23 (m, 5H), 7.22 (s, 1H), 7.18 (d, $J$ = 9.0, 1H), 5.89 (s, 2H), 3.85 (s, 3H); **2.108b:** $^1$H NMR (500 MHz, $CDCl_3$): δ 7.85 (d, $J$ = 9.1, 1H), 7.35–7.23 (m, 4H), 7.18 (s, 1H), 7.10–7.06 (m, 2H), 6.55 (s, 2H), 3.87 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 143.0, 139.9, 137.0, 135.8, 135.2, 132.8, 129.4, 129.0, 128.6, 128.4, 128.3, 128.0, 127.8, 127.6, 127.4, 126.7, 117.0, 114.6, 111.6, 110.2, 109.1, 104.3, 87.9, 86.5, 54.8, 52.4, 34.1, 33.9; IR (film): 3028, 2945, 1447, 1307, 1102 cm$^{-1}$; HRMS-ESI (*m*/*z*) [M + Na]$^+$ calculated for $C_{16}H_{13}N_4BrNa$, 363.0221; found, 363.0227. The major isomer was identified by dissolving the mixture of isomers in EtOAc and exposing the mixture to a balloon of $H_2$ in the presence of Pd/C (10 mol%) and $Et_3N$ (1 equiv) to afford the corresponding debrominated compounds. Spectral data for **2.42a** and **2.42b** match those reported on page 73 of this dissertation.

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# APPENDIX ONE

## Spectra Relevant to Chapter Two:

**Indolyne Experimental and Computational Studies: Synthetic Applications and Origins of Selectivities of Nucleophilic Additions**

G-Yoon J. Im, Sarah M. Bronner, Adam E. Goetz, Robert S. Paton,

Paul H.-Y. Cheong, K. N. Houk, Neil K. Garg

*J. Am. Chem. Soc.* **2010**, *132*, 17933–17944.

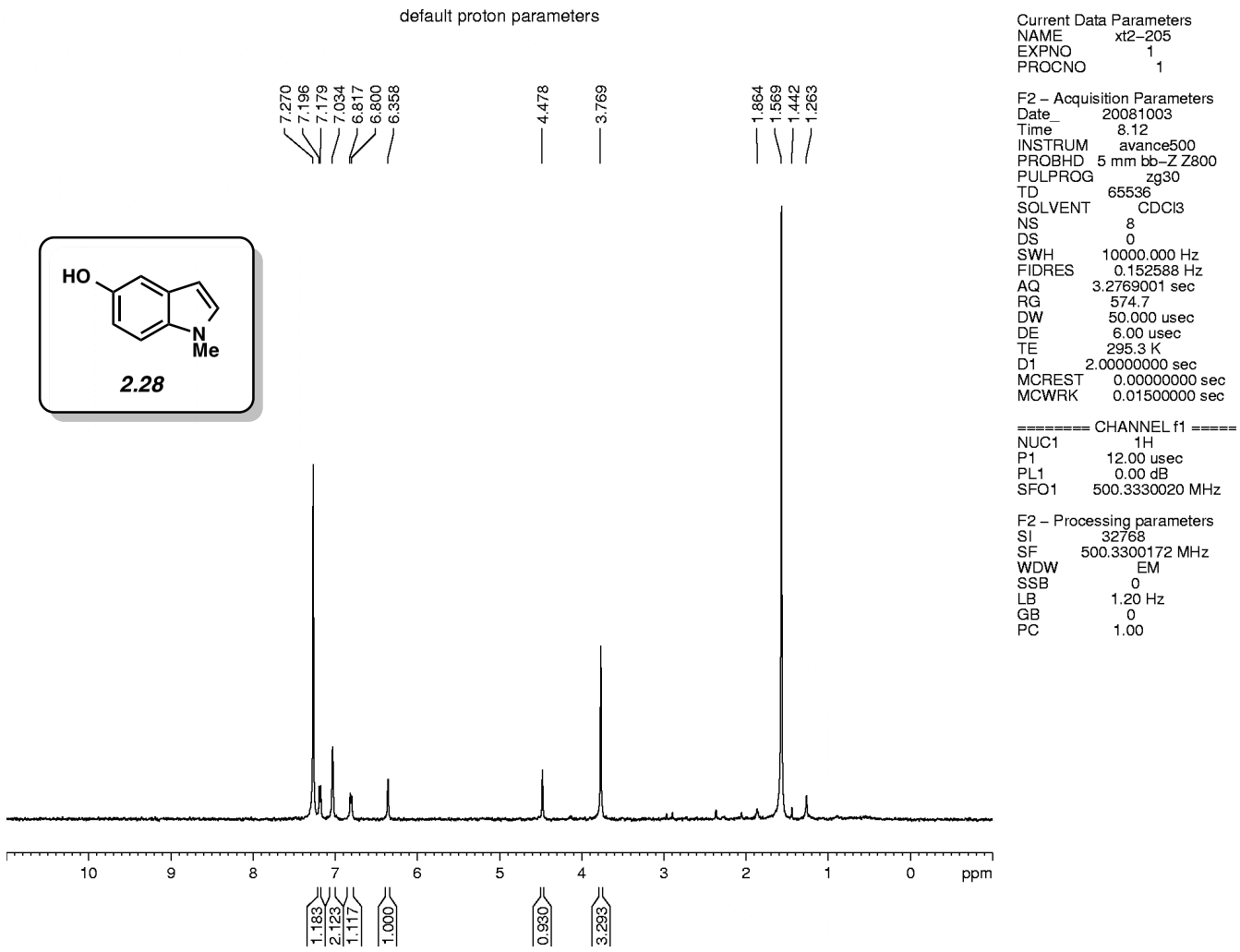



*Figure A1.1* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **2.28**.

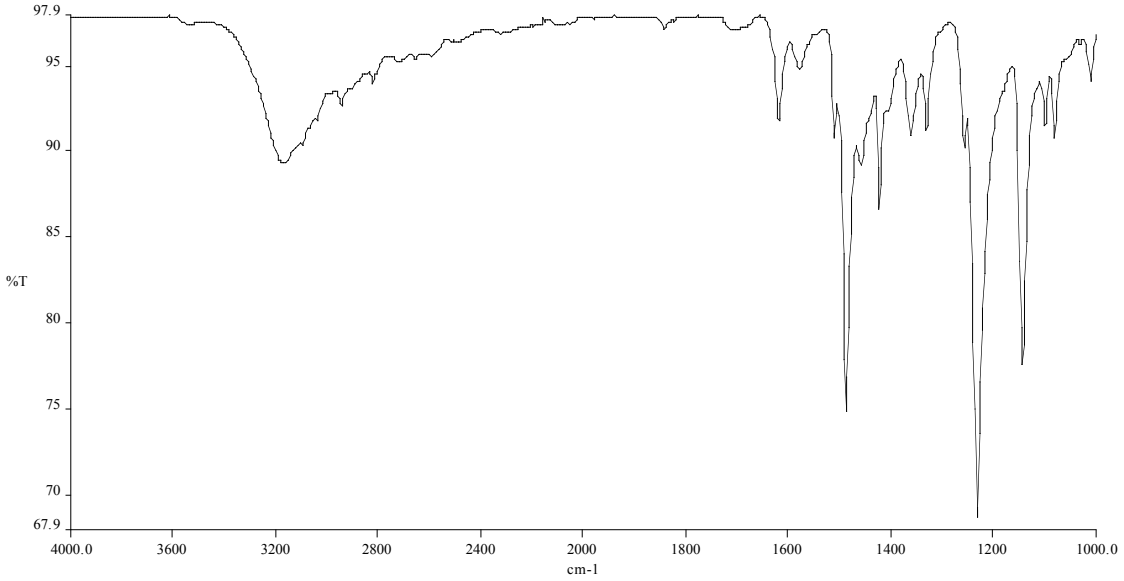



*Figure A1.2* Infrared spectrum of compound **2.28**.

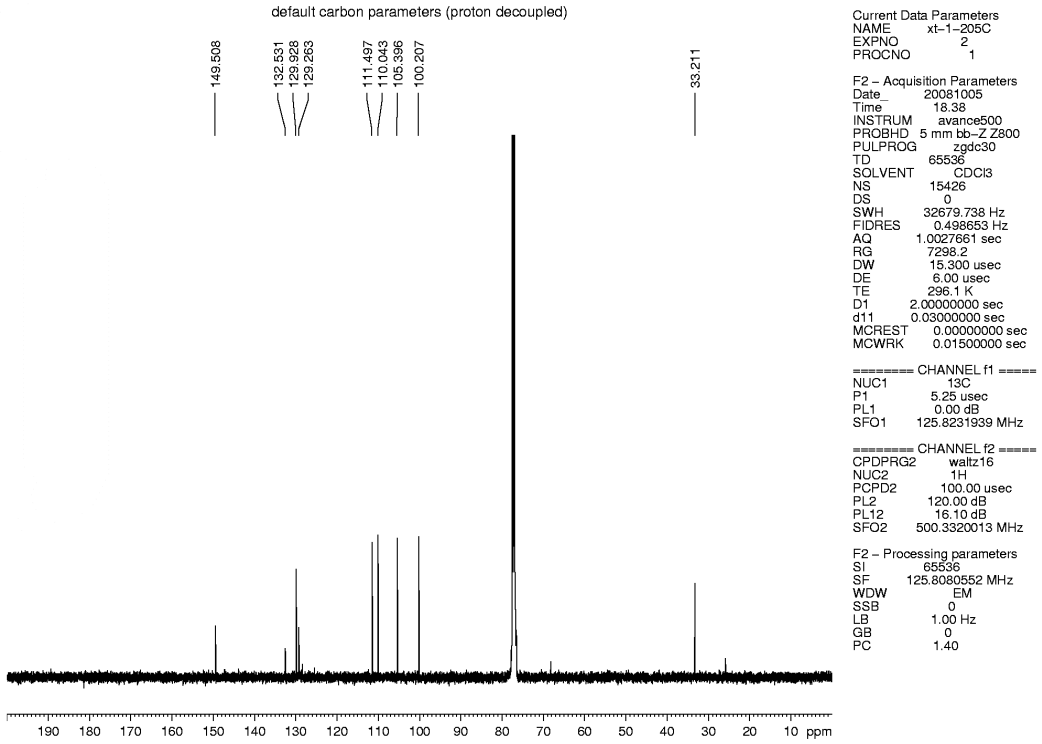



*Figure A1.3* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compound **2.28**.

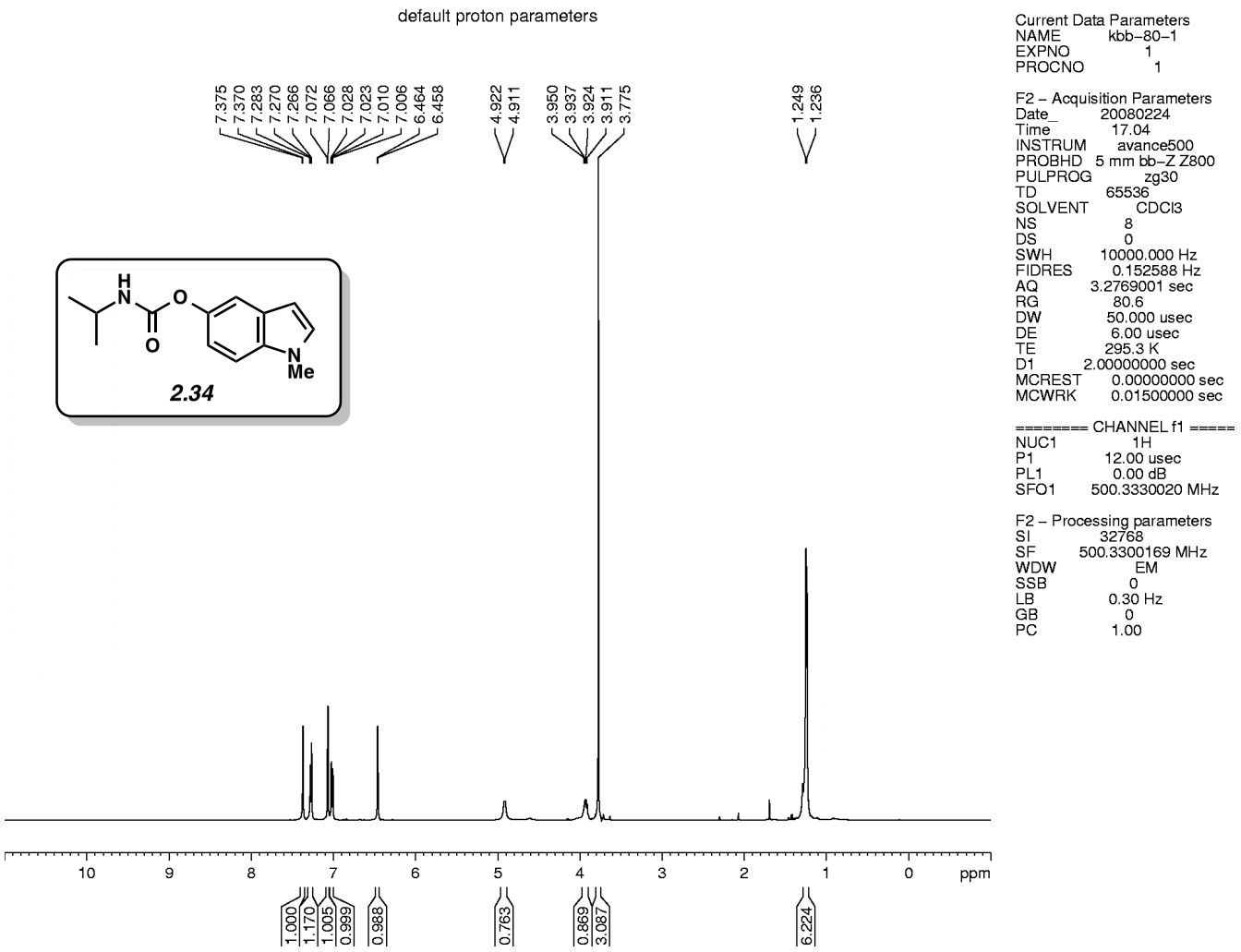



*Figure A1.4* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **2.34**.

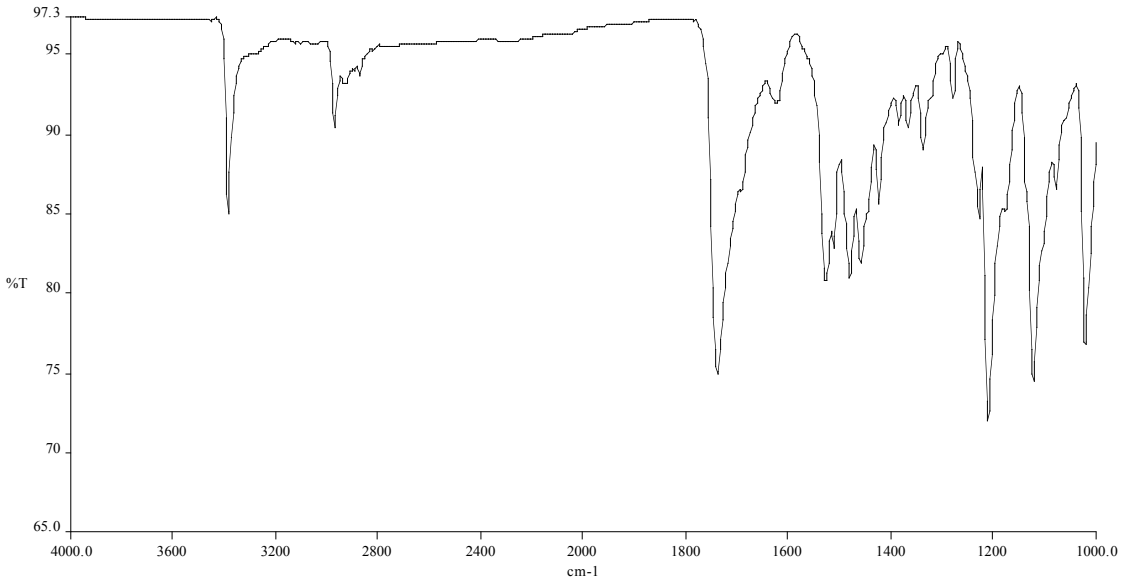



*Figure A1.5* Infrared spectrum of compound **2.34**.

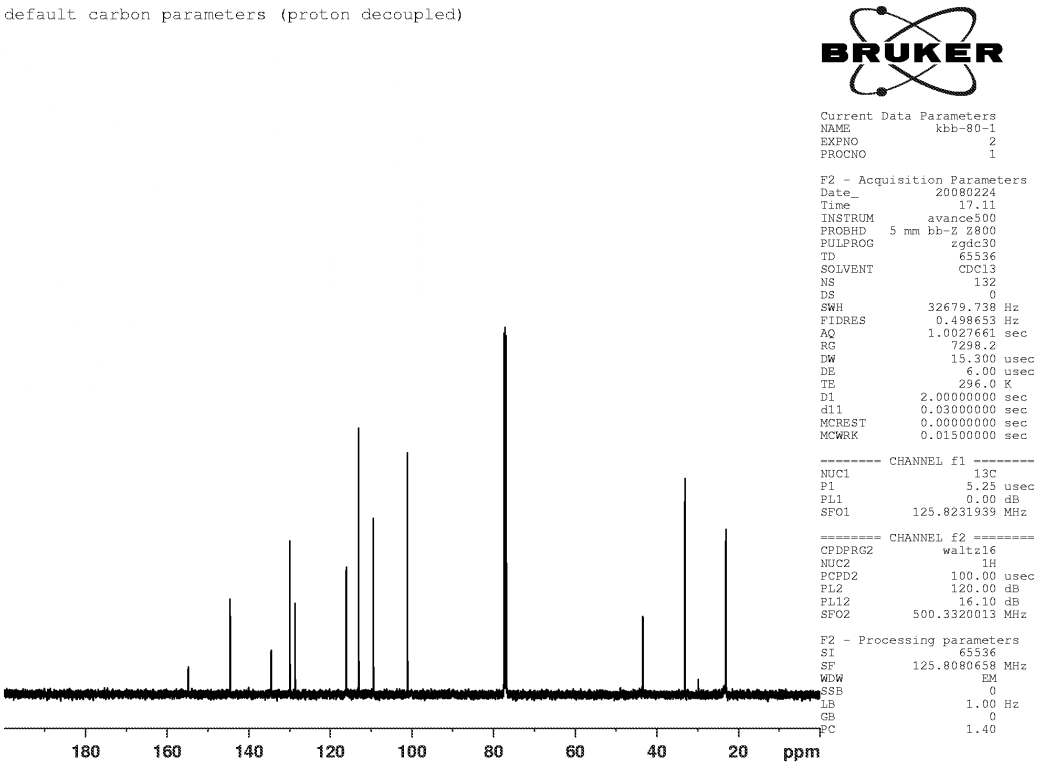



*Figure A1.6* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compound **2.34**.

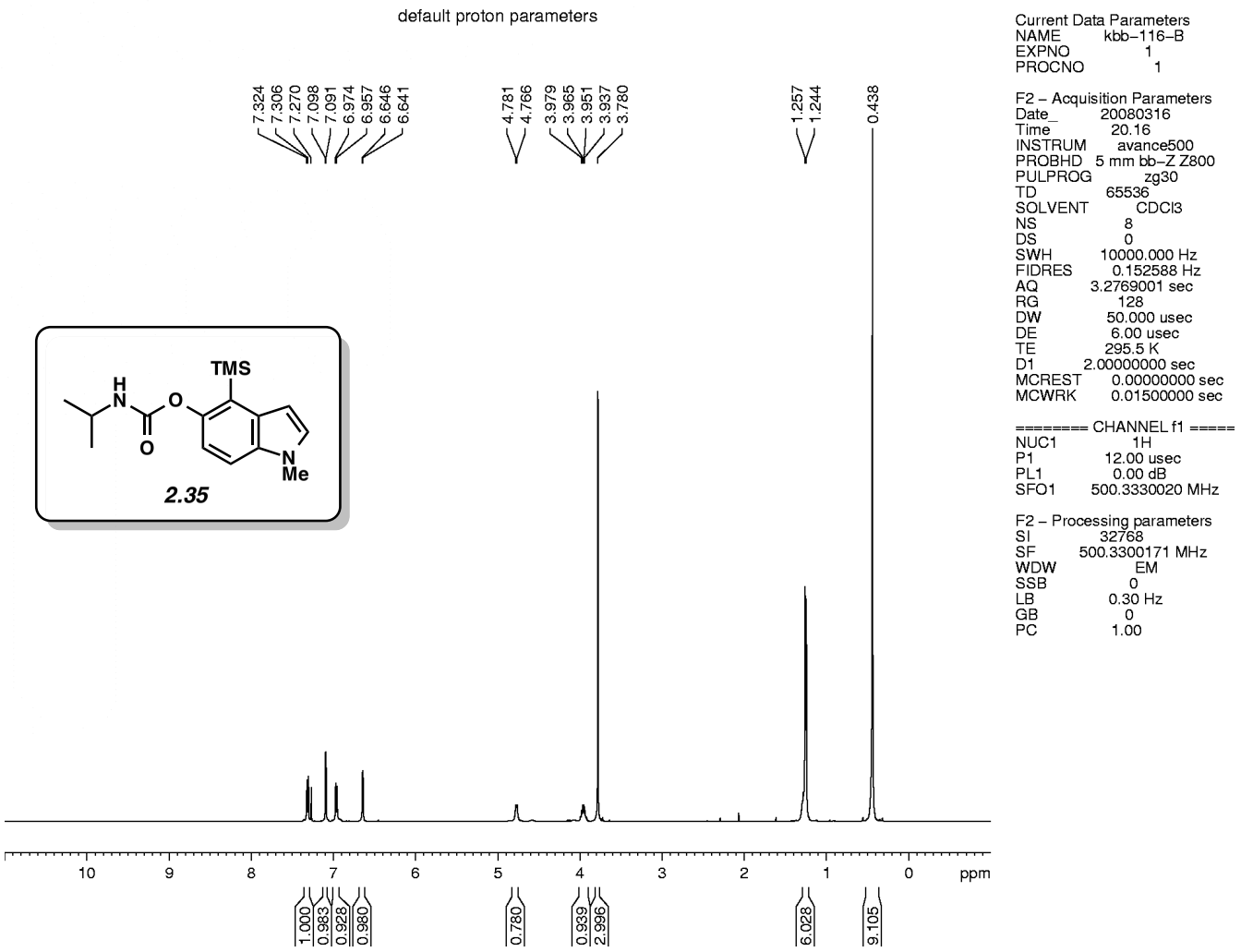



*Figure A1.7* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **2.35**.

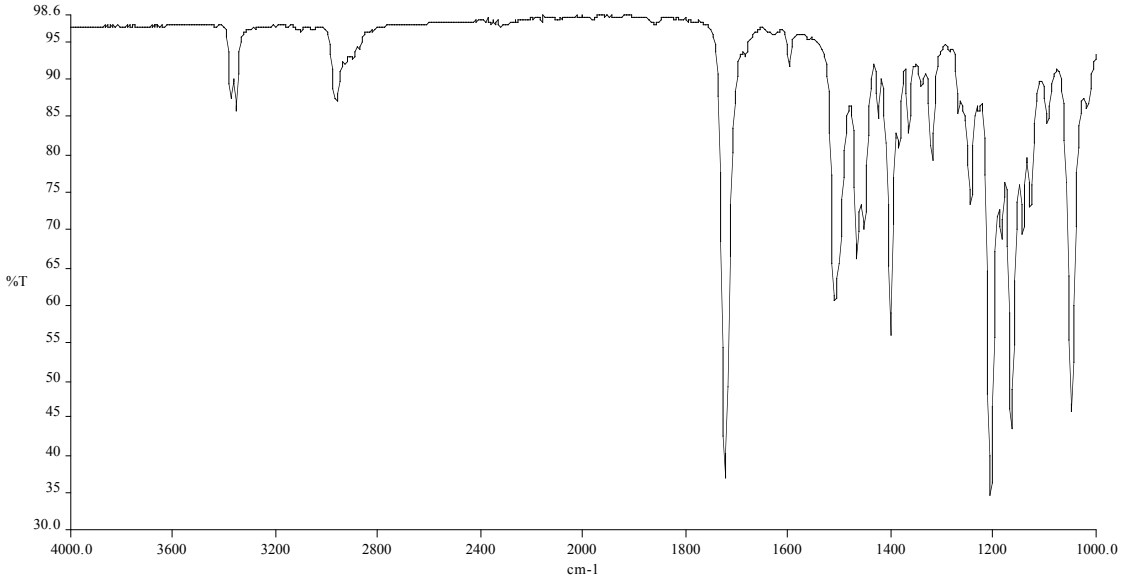



*Figure A1.8* Infrared spectrum of compound **2.35**.

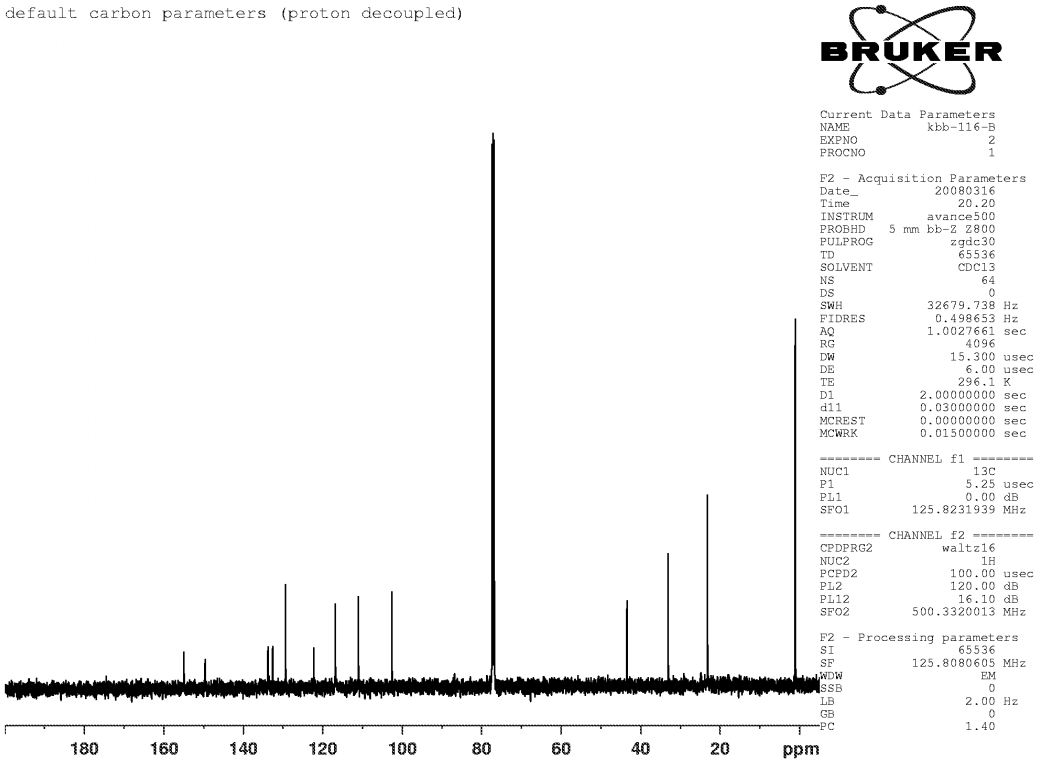



*Figure A1.9* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compound **2.35**.

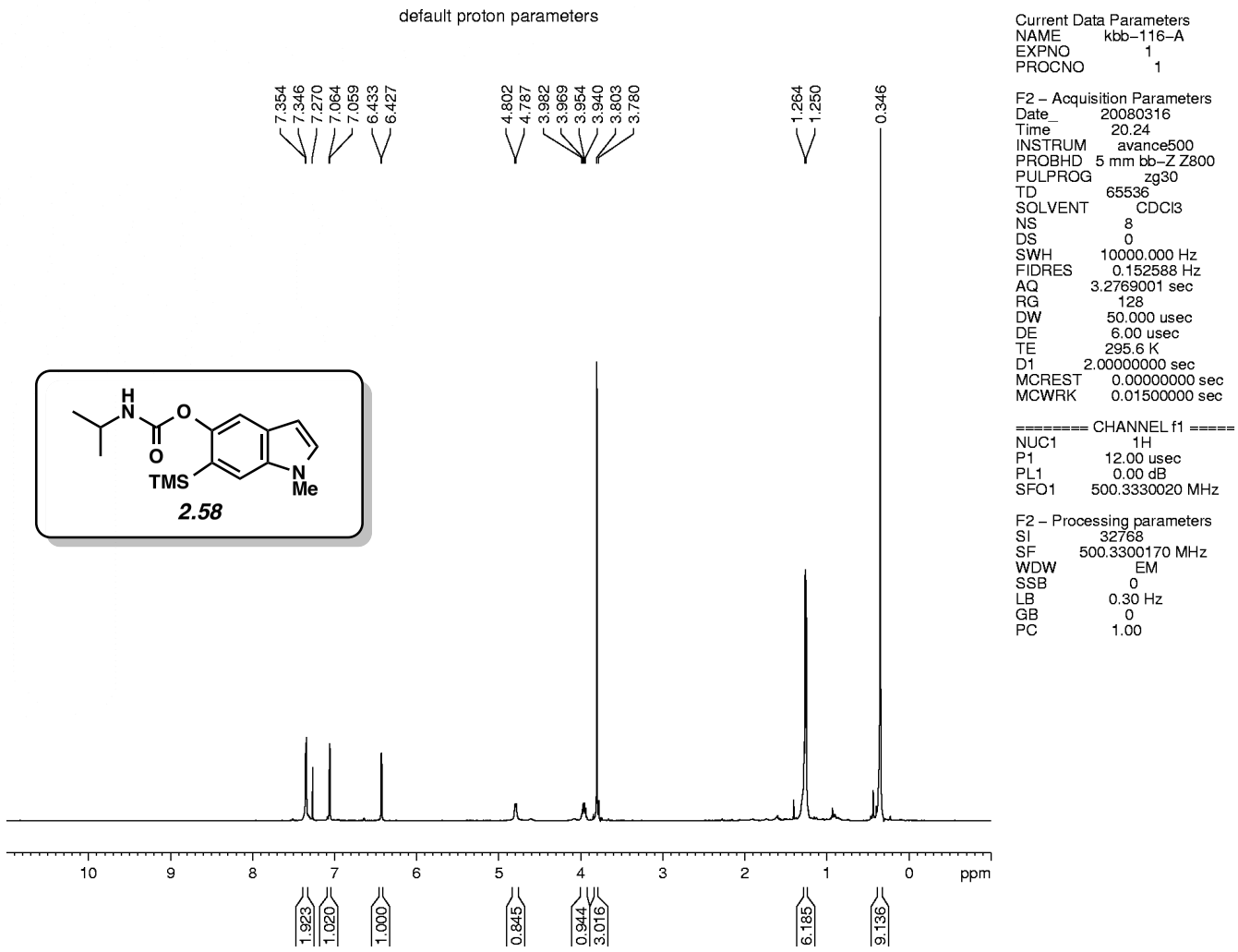



*Figure A1.10* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **2.58**.

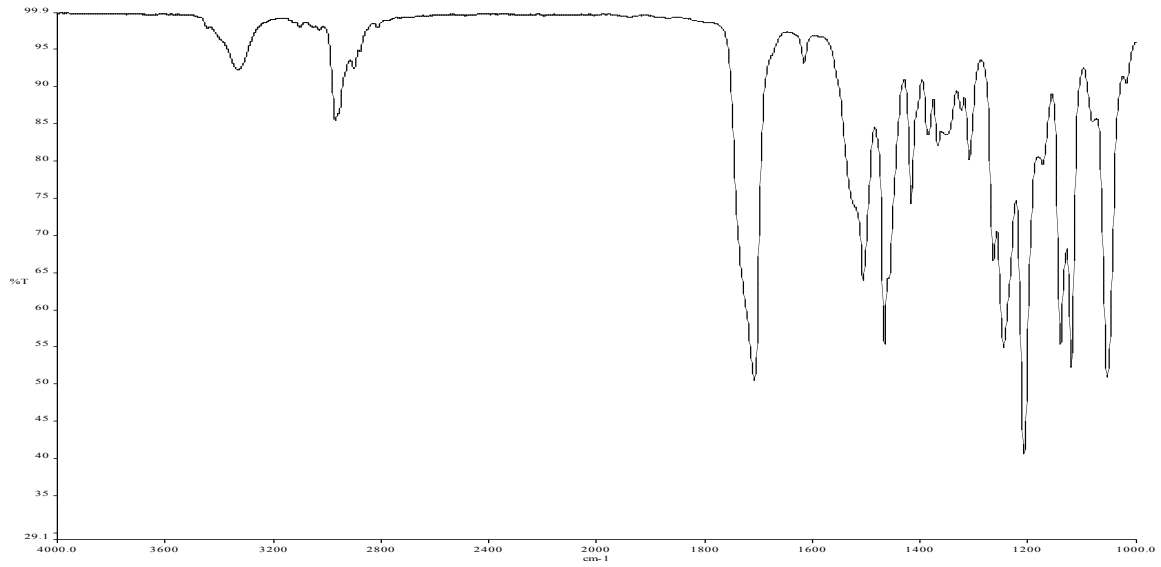



*Figure A1.11* Infrared spectrum of compound **2.58**.

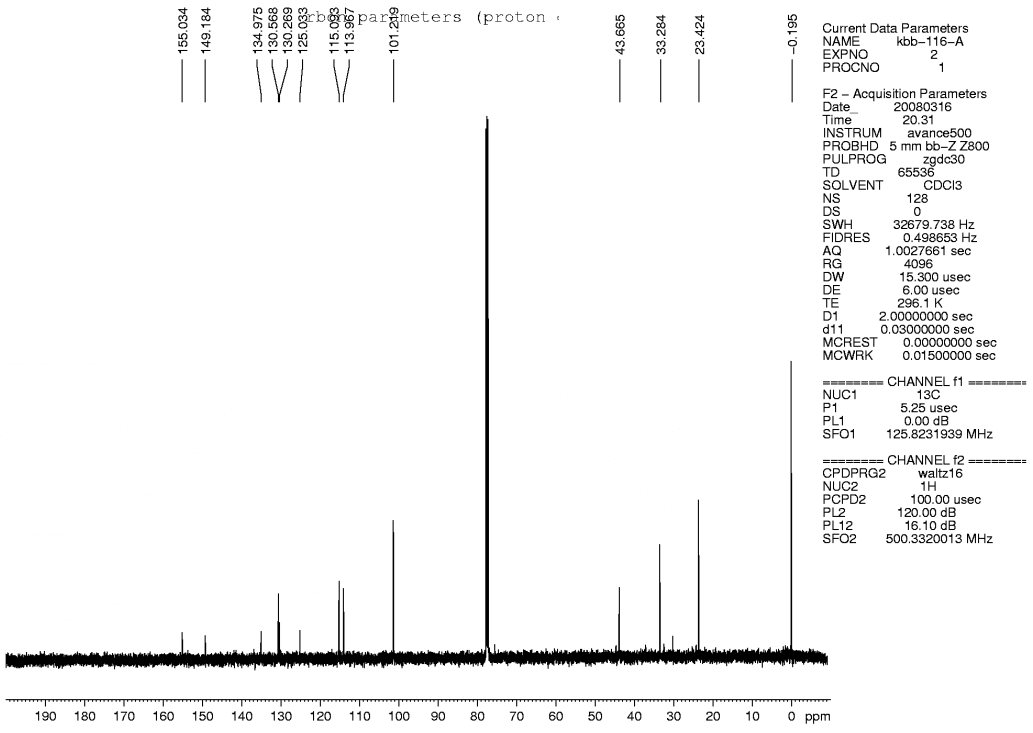



*Figure A1.12* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compound **2.58**.

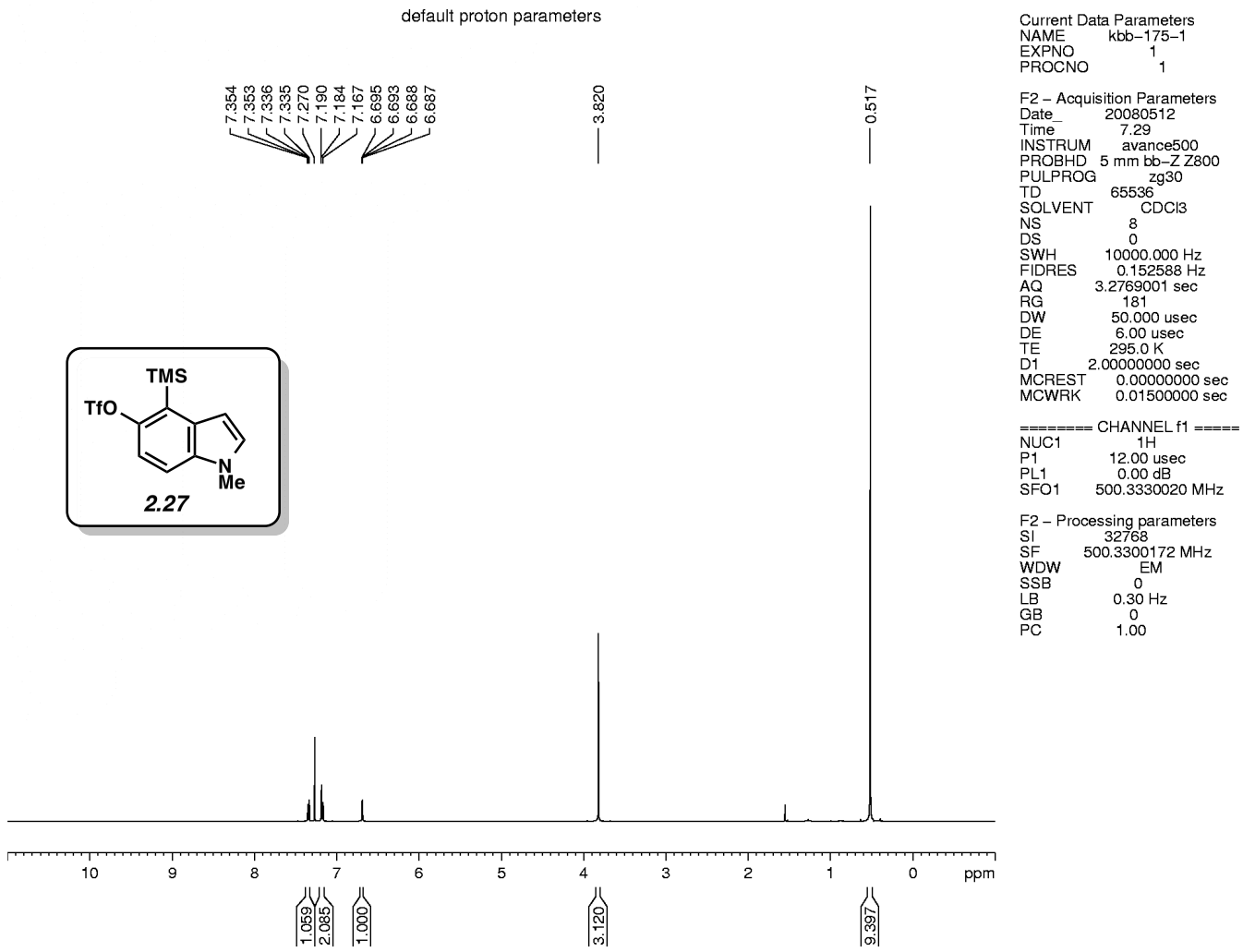



*Figure A1.13* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **2.27**.

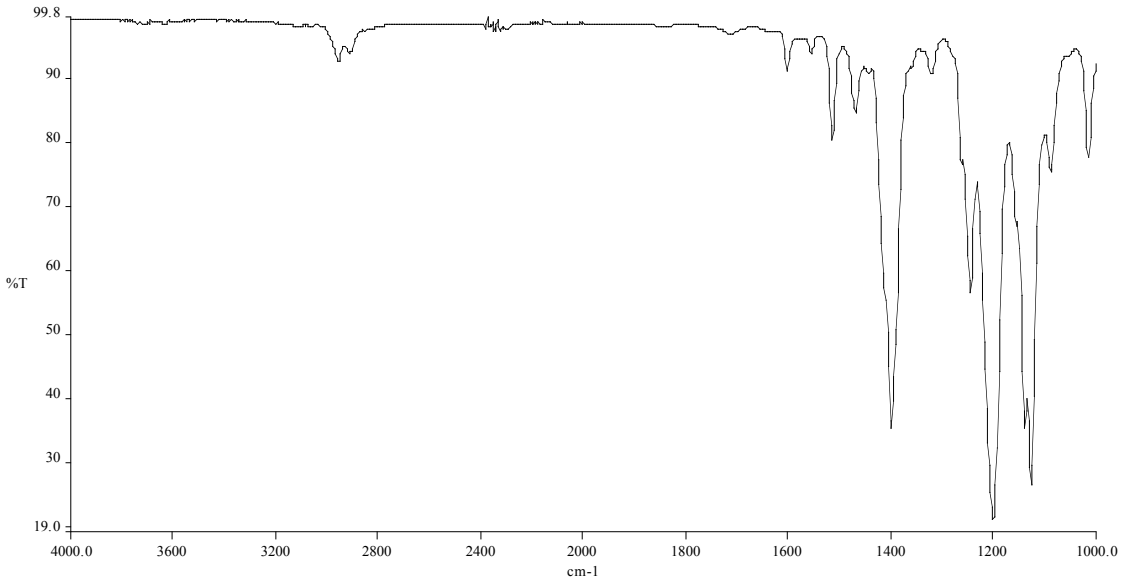



*Figure A1.14* Infrared spectrum of compound **2.27**.

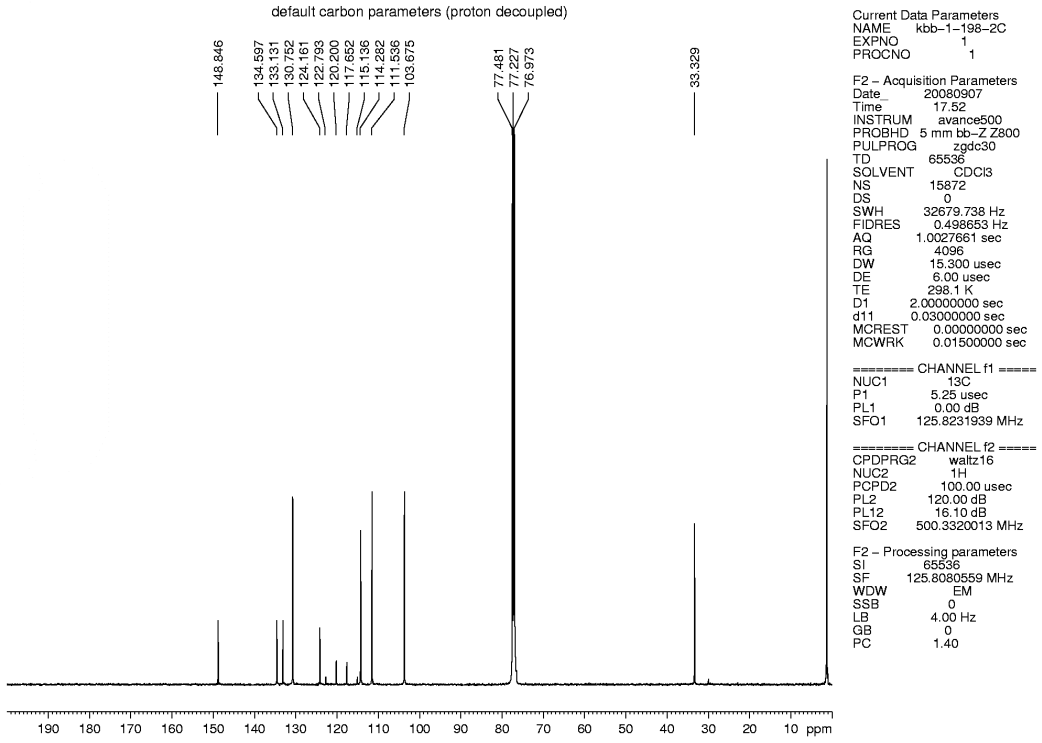



*Figure A1.15* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compound **2.27**.

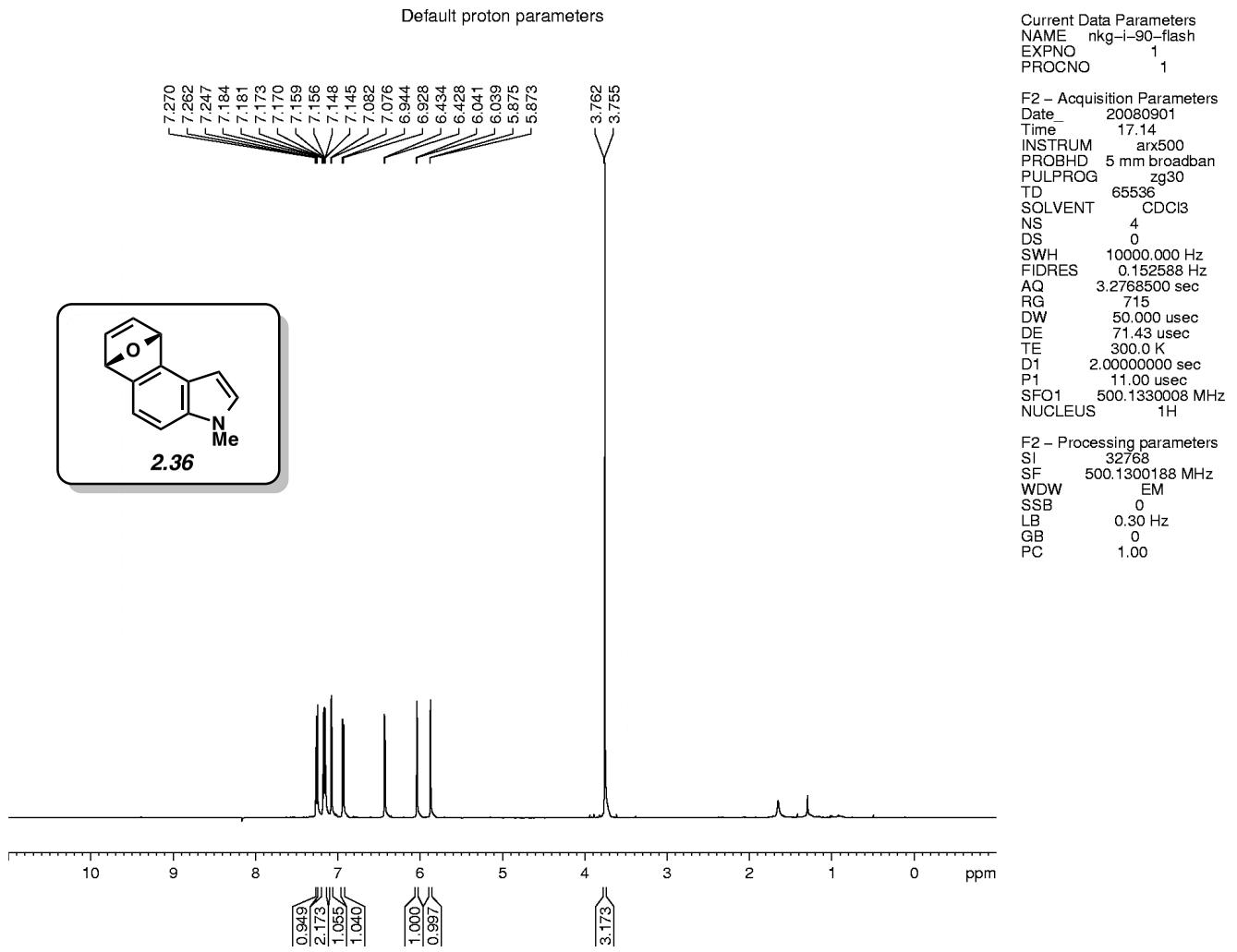



*Figure A1.16* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **2.36**.

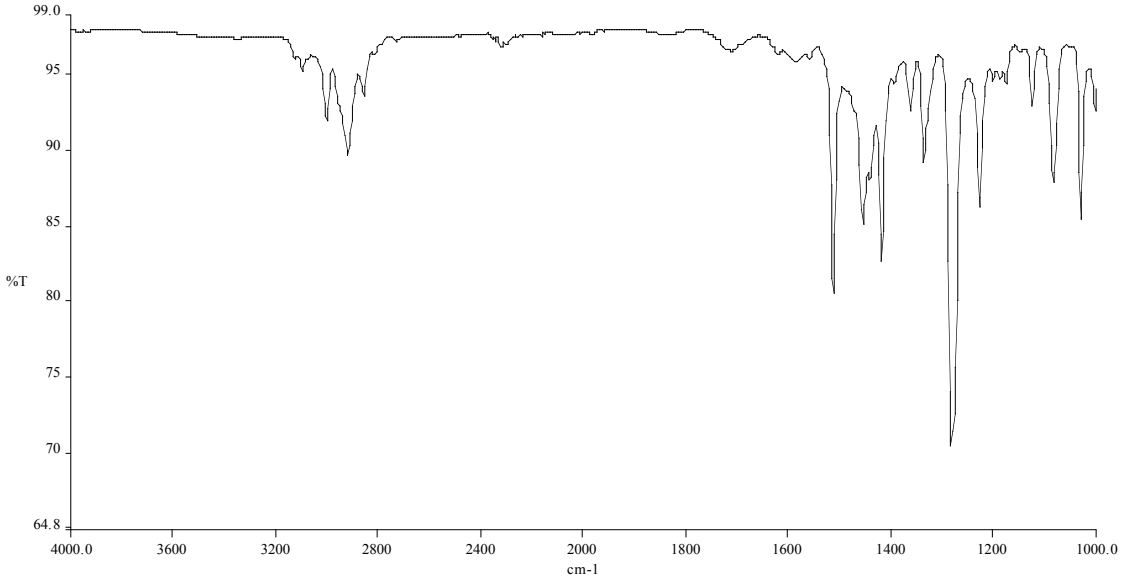



*Figure A1.17* Infrared spectrum of compound **2.36**.

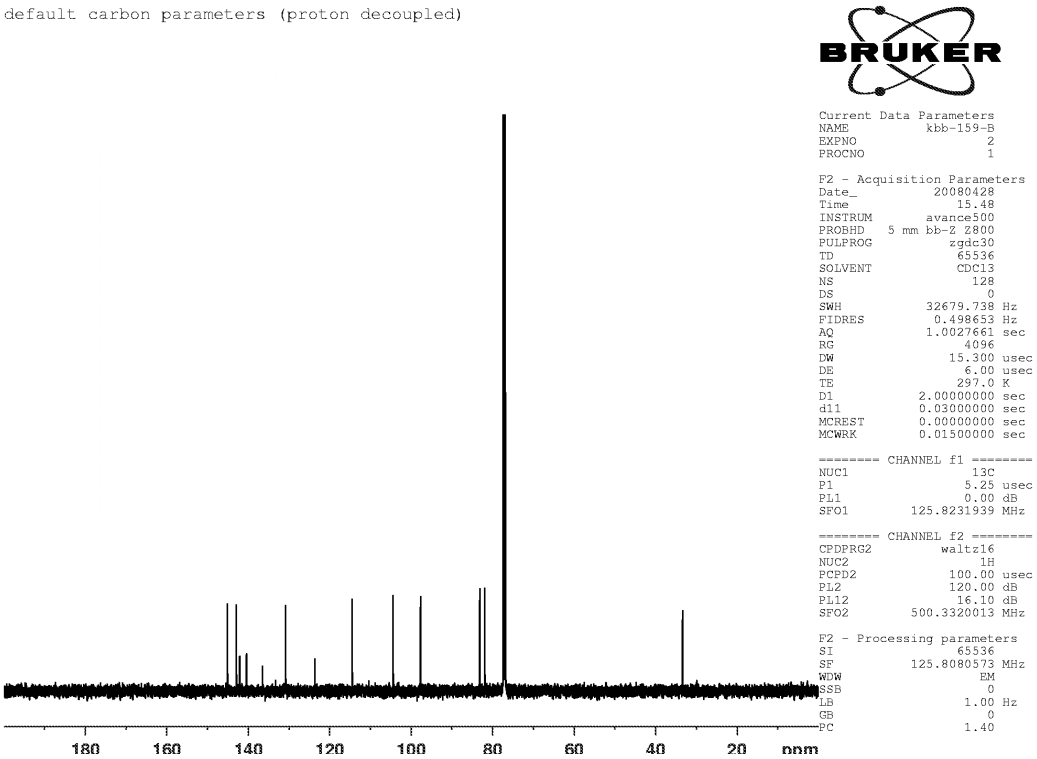



*Figure A1.18* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compound **2.36**.

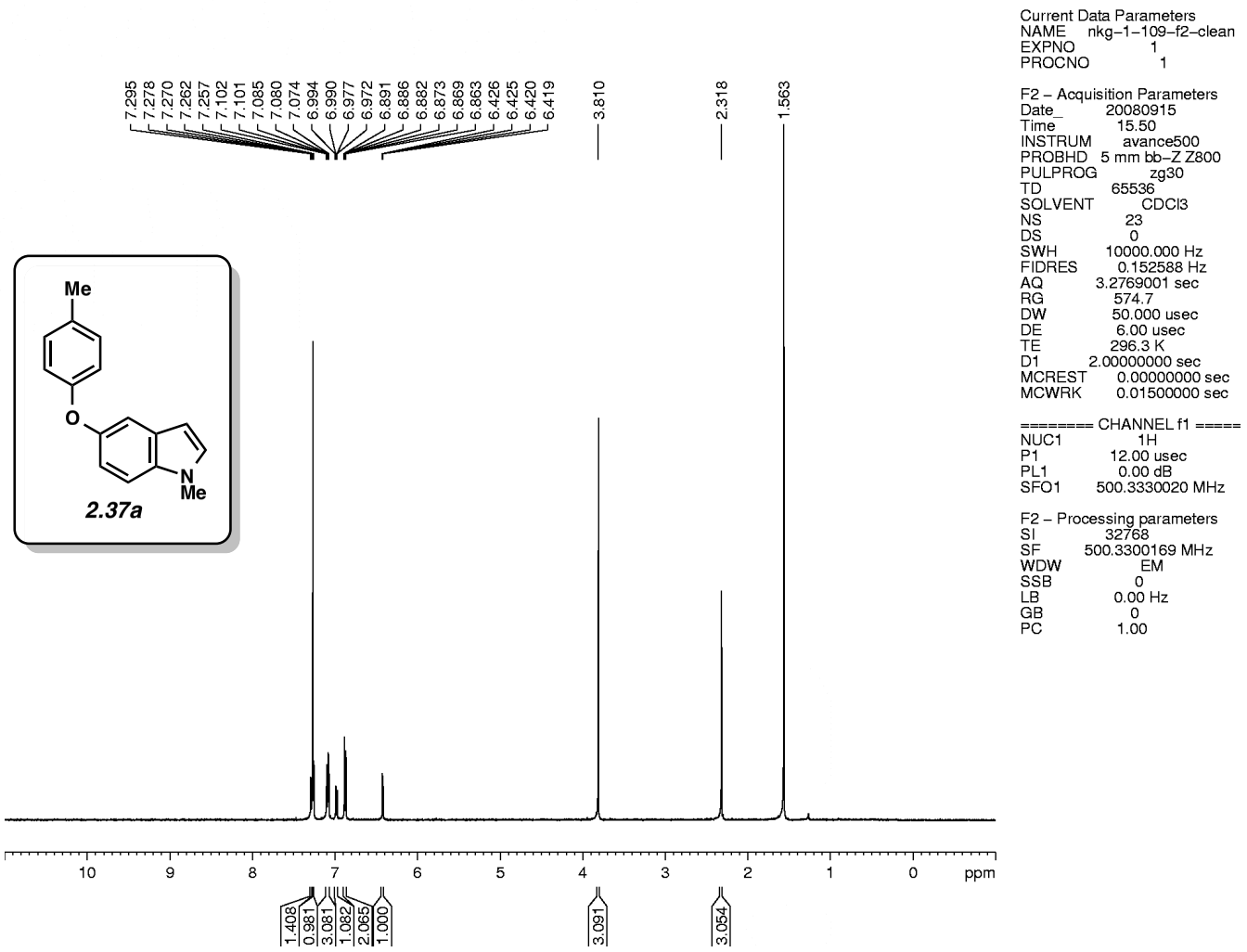



*Figure A1.19* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **2.37a**.

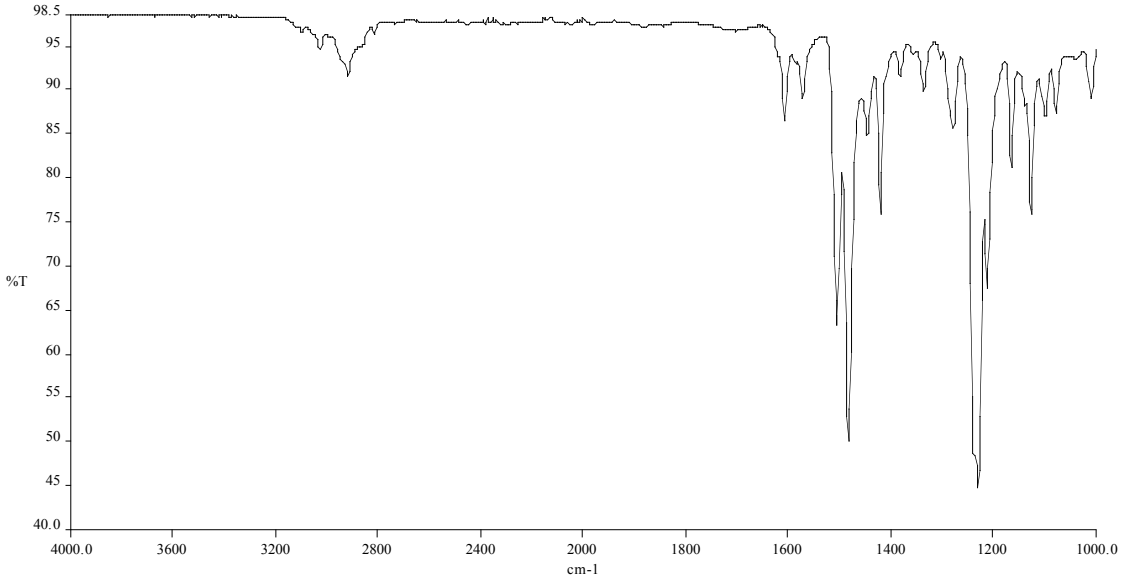



*Figure A1.20* Infrared spectrum of compound **2.37a**.

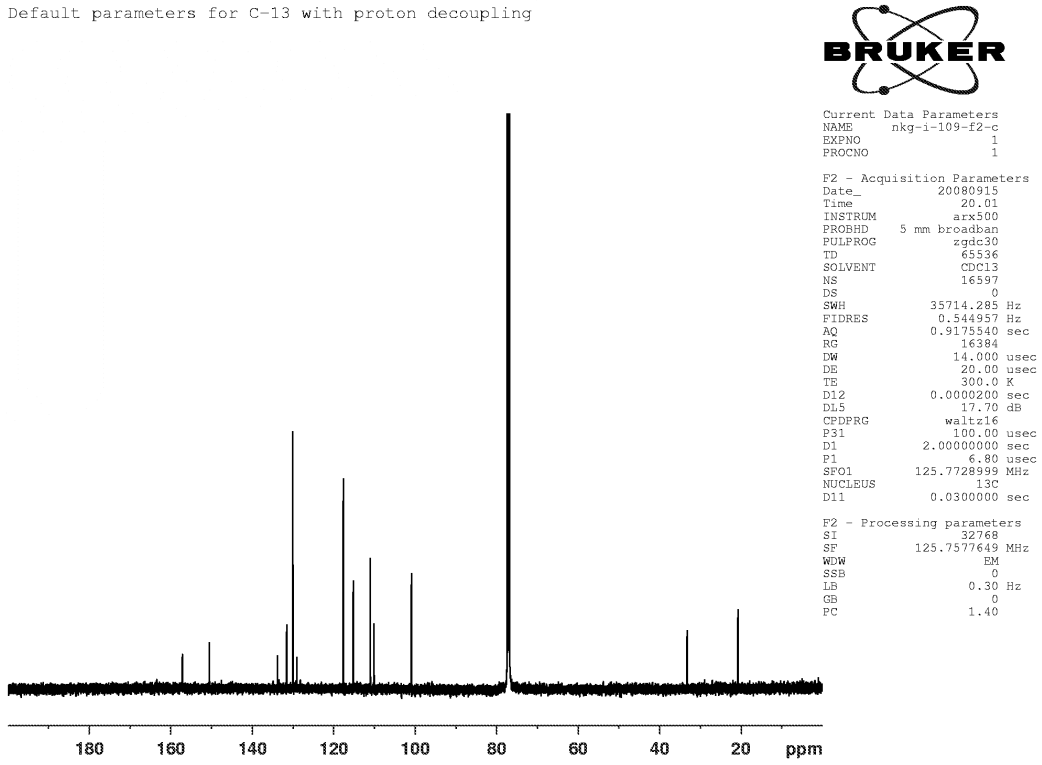



*Figure A1.21* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compound **2.37a**.

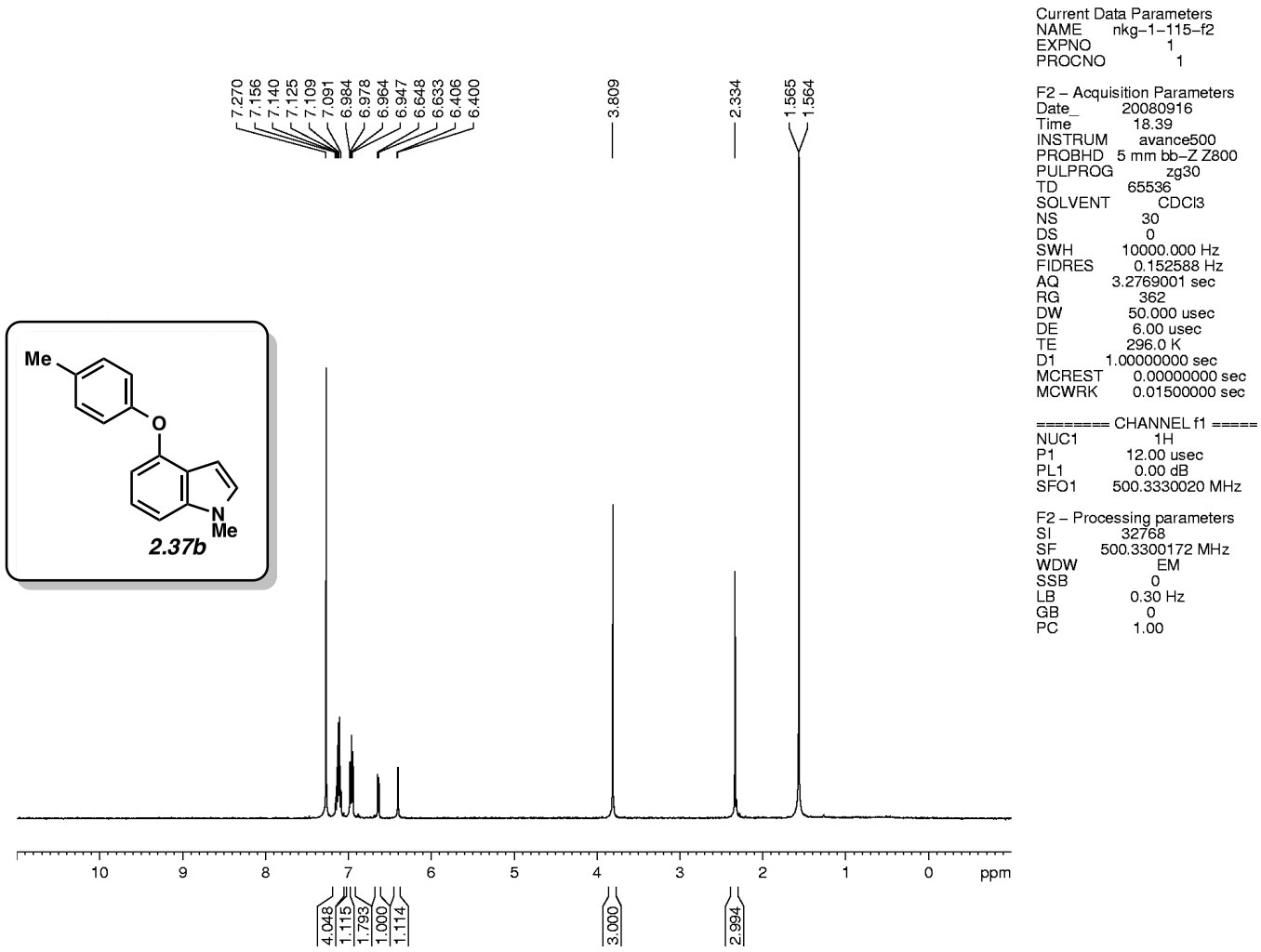



*Figure A1.22* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **2.37b**.

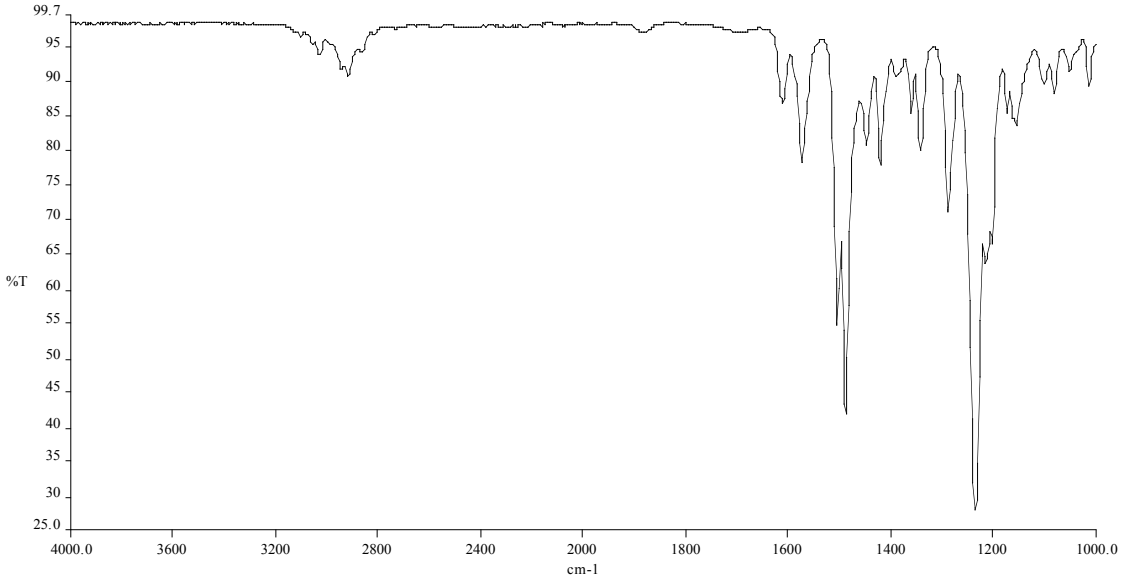



*Figure A1.23* Infrared spectrum of compound **2.37b**.

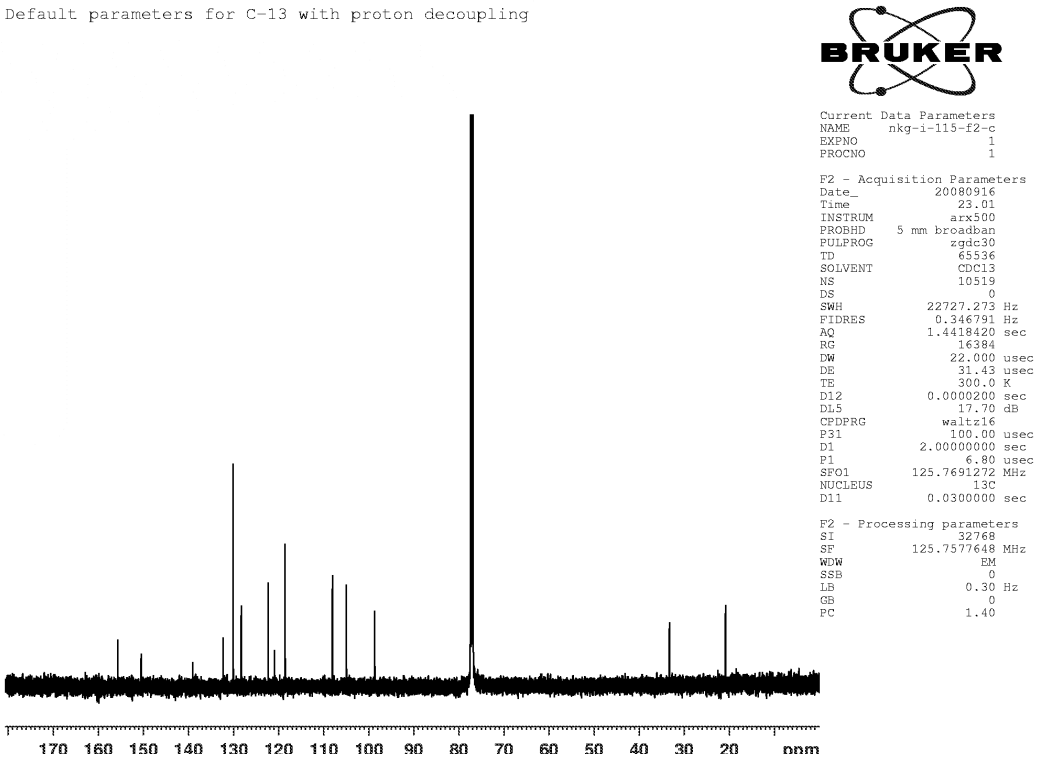



*Figure A1.24* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compound **2.37b**.

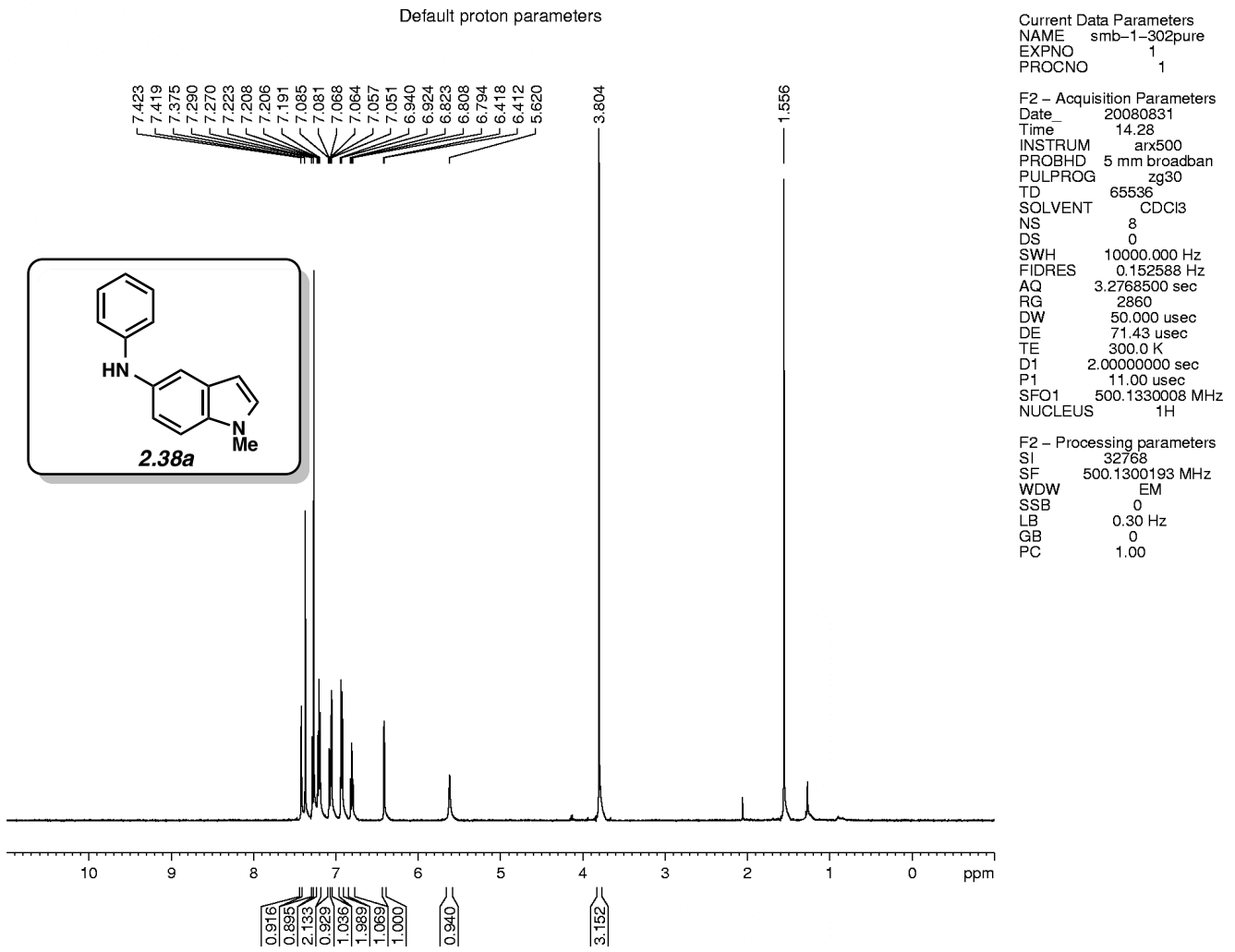



*Figure A1.25* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **2.38a**.

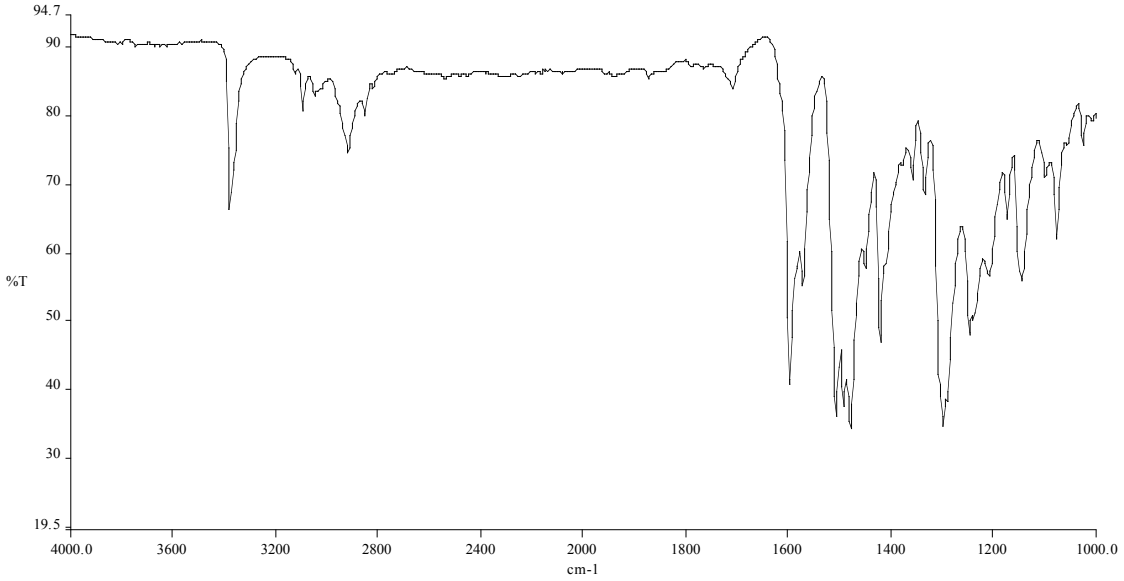



*Figure A1.26* Infrared spectrum of compound **2.38a**.

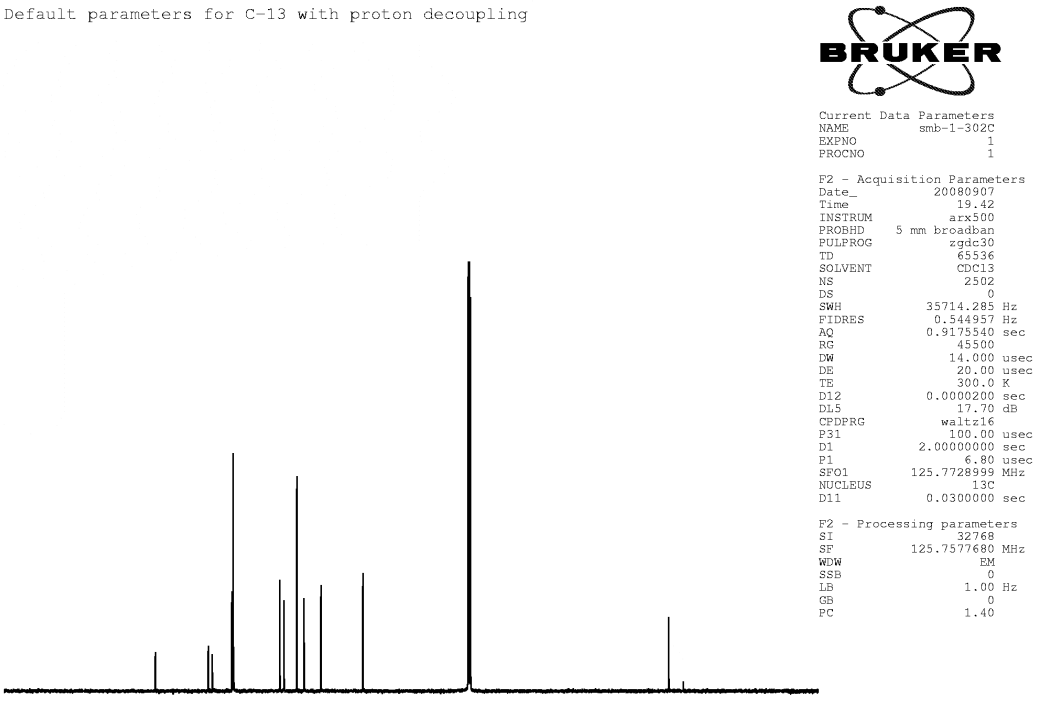



*Figure A1.27* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compound **2.38a**.

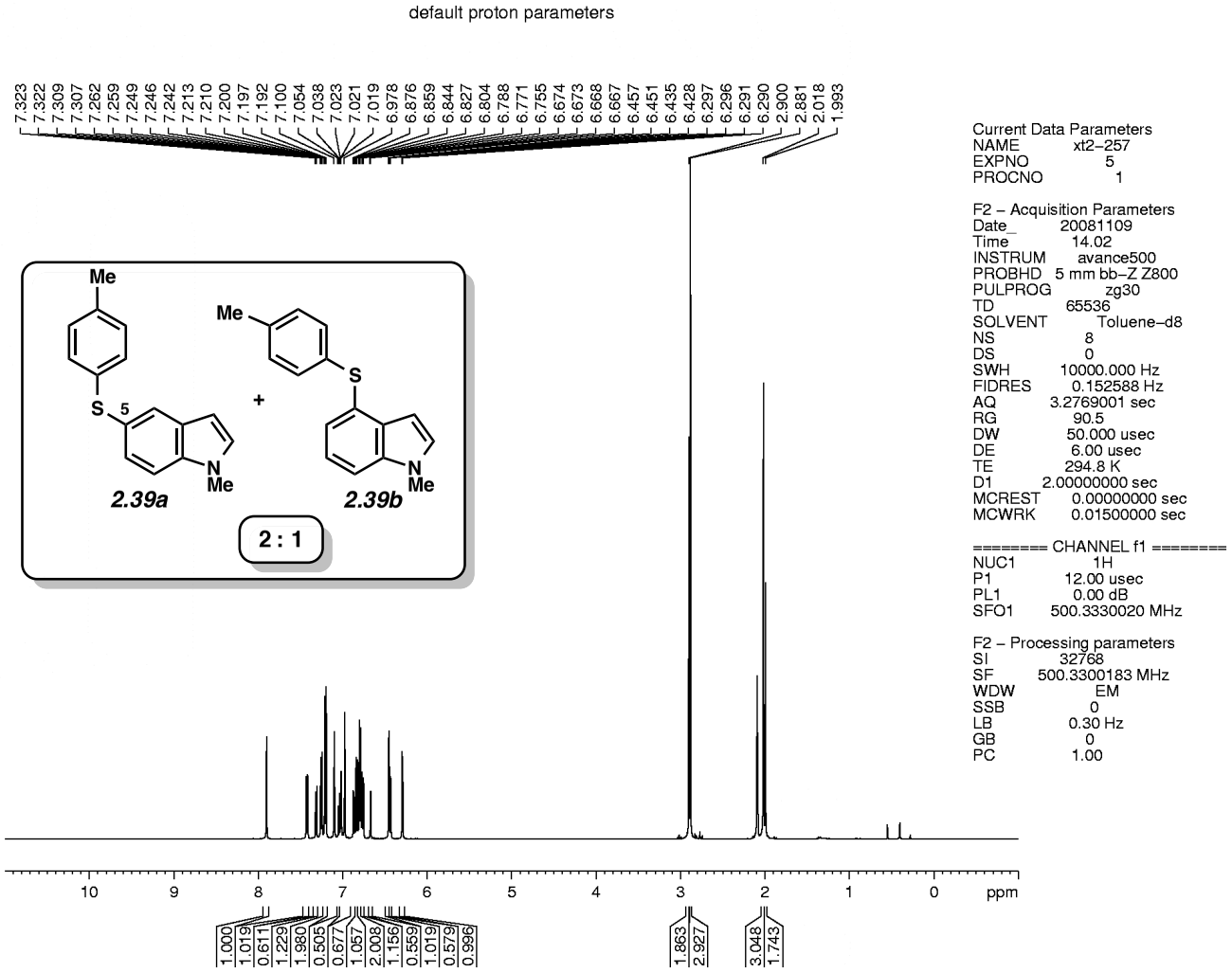



*Figure A1.28* $^{1}$H NMR (500 MHz, Toluene- $d_8$) of compounds **2.39a** and **2.39b**.

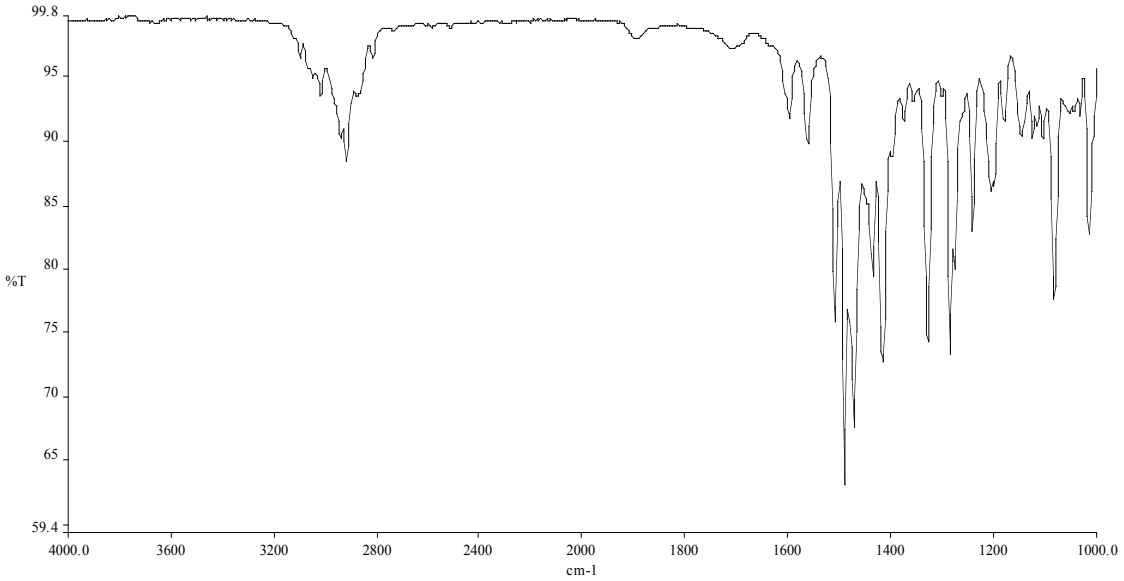



*Figure A1.29* Infrared spectrum of compounds **2.39a** and **2.39b**.

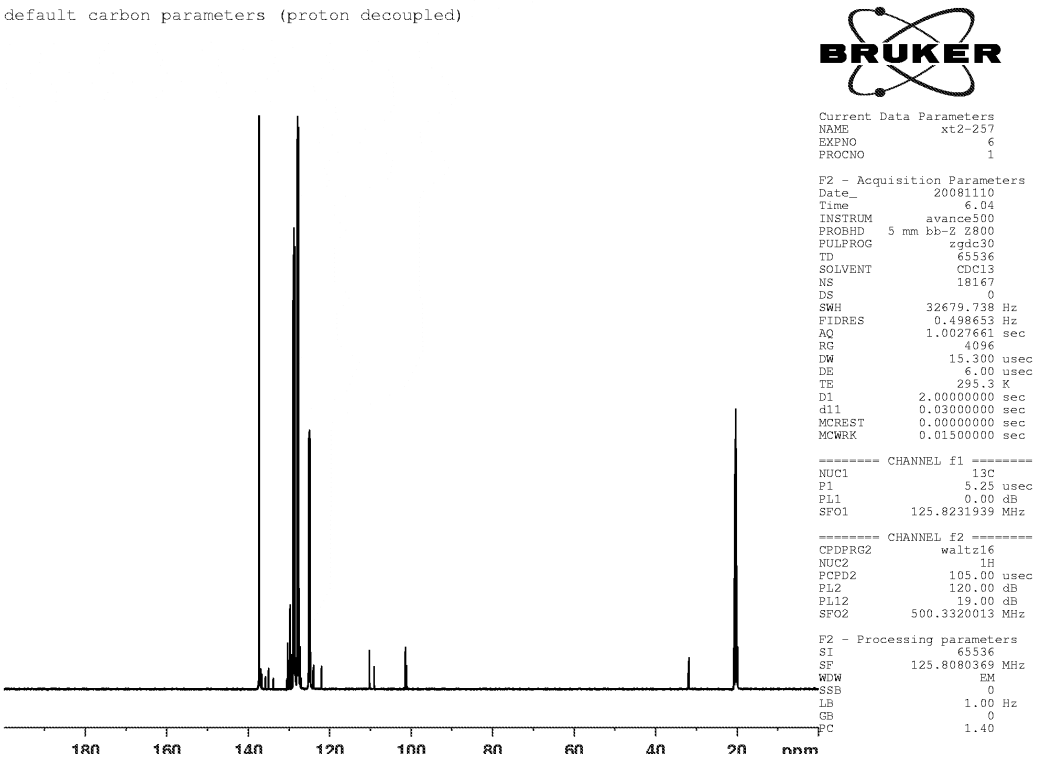



*Figure A1.30* $^{13}$C NMR (125 MHz, Toluene-$d_8$) of compounds **2.39a** and **2.39b**.

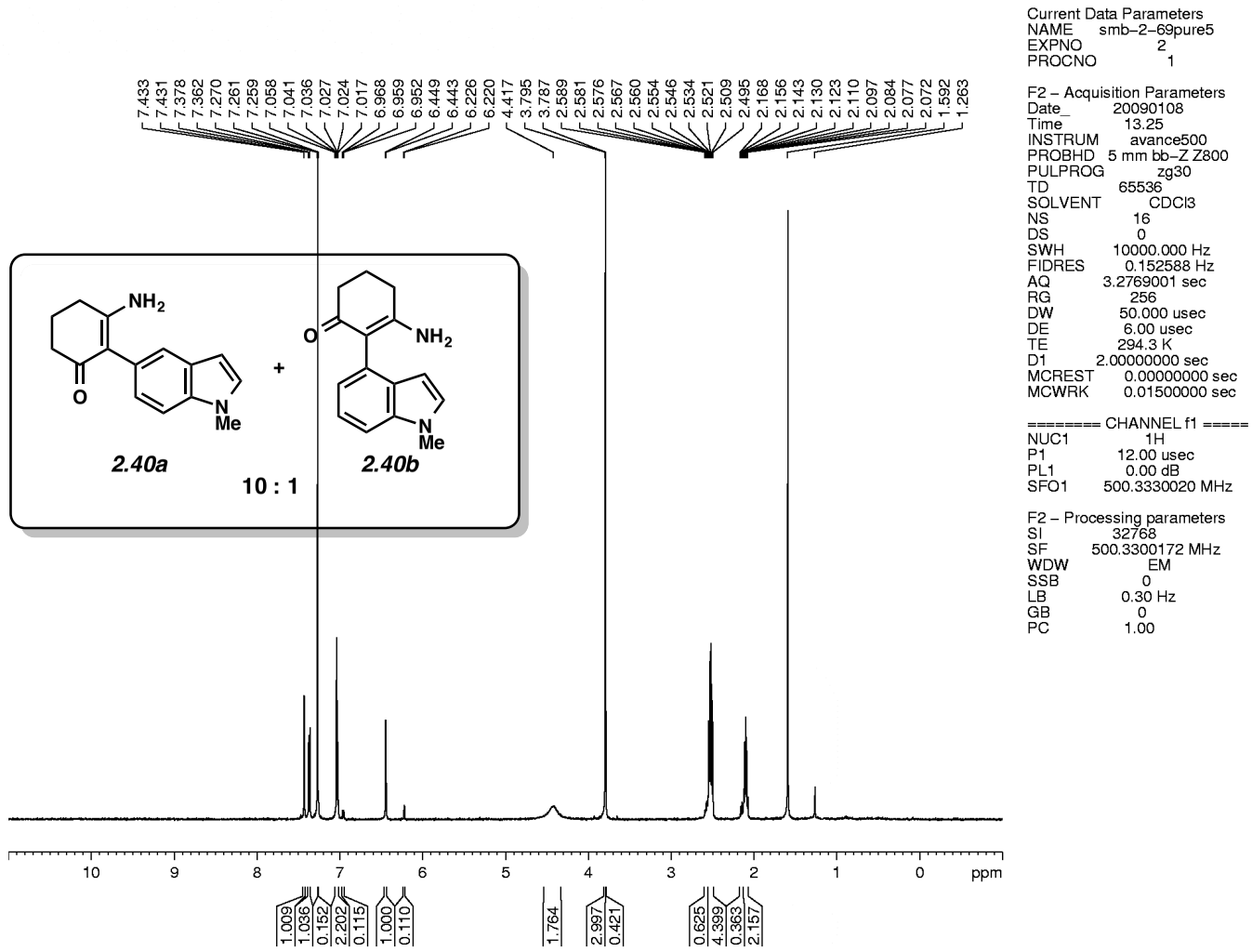



*Figure A1.31* $^{1}$H NMR (500 MHz, $CDCl_3$) of compounds **2.40a** and **2.40b**.

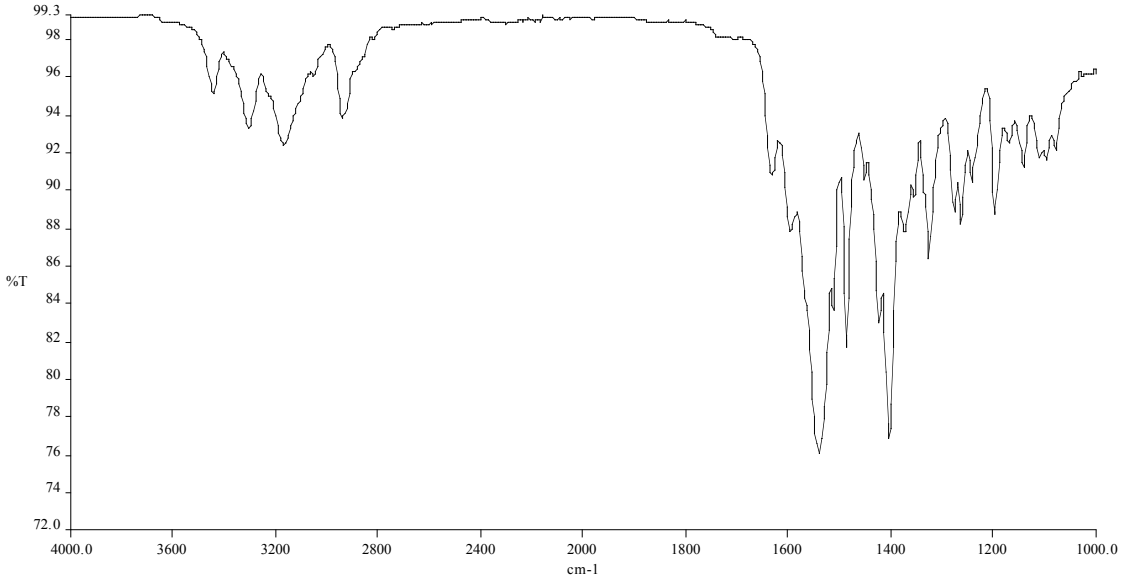



*Figure A1.32* Infrared spectrum of compounds **2.40a** and **2.40b**.

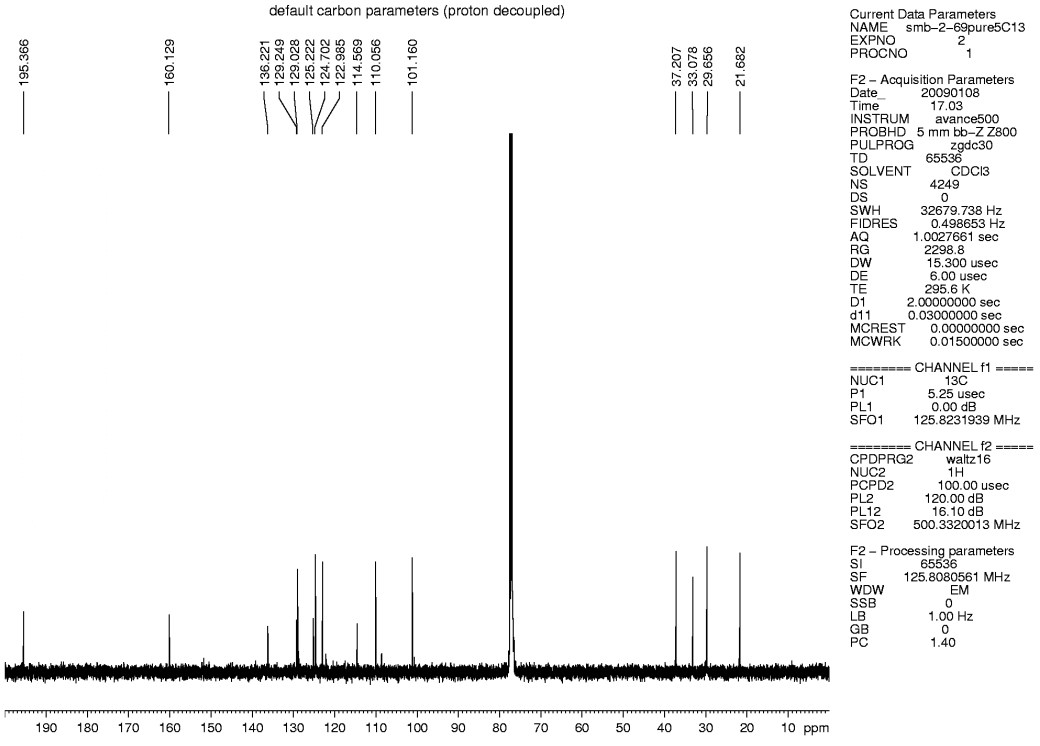



*Figure A1.33* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compound **2.40a** and **2.40b**.

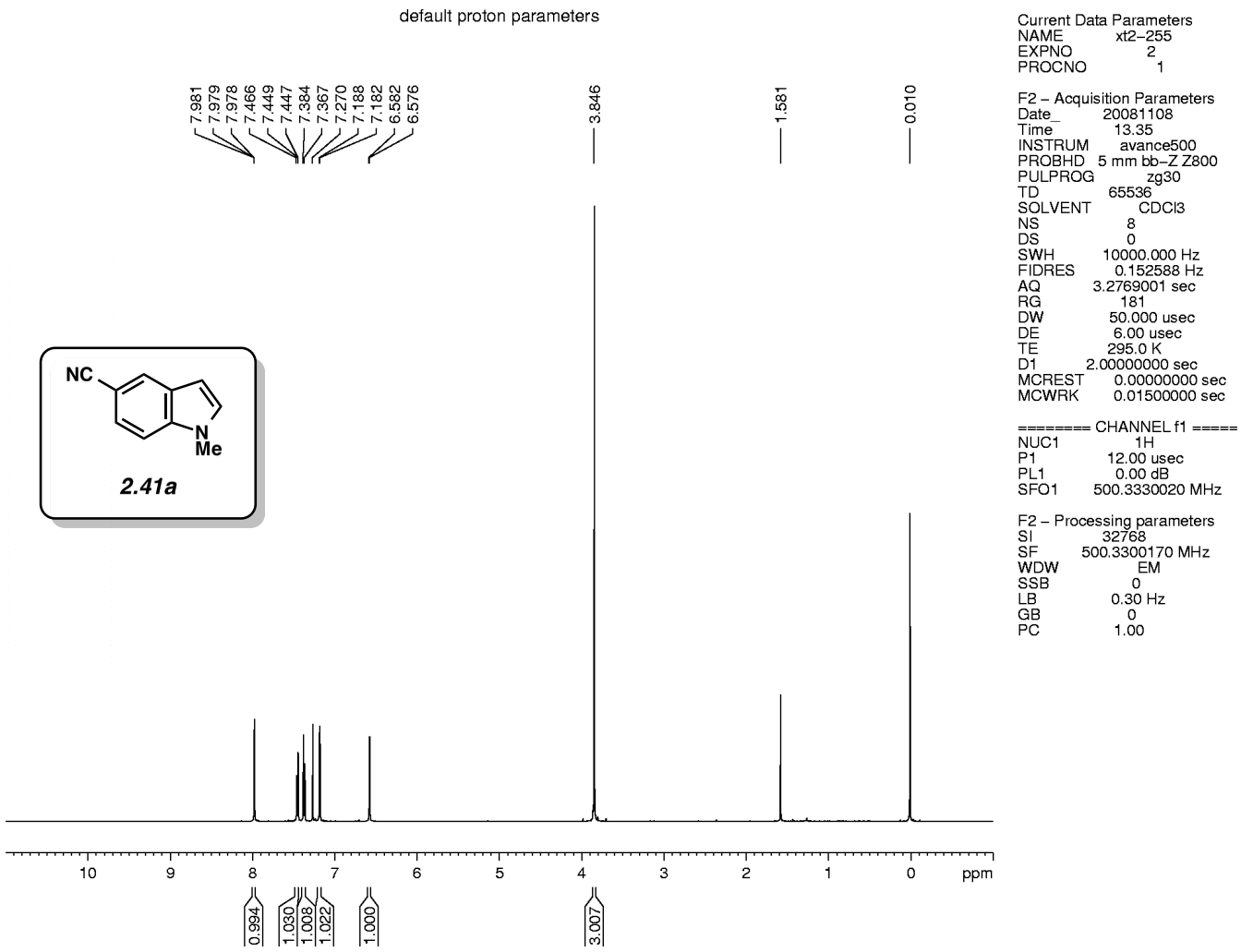



*Figure A1.34* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **2.41a**.

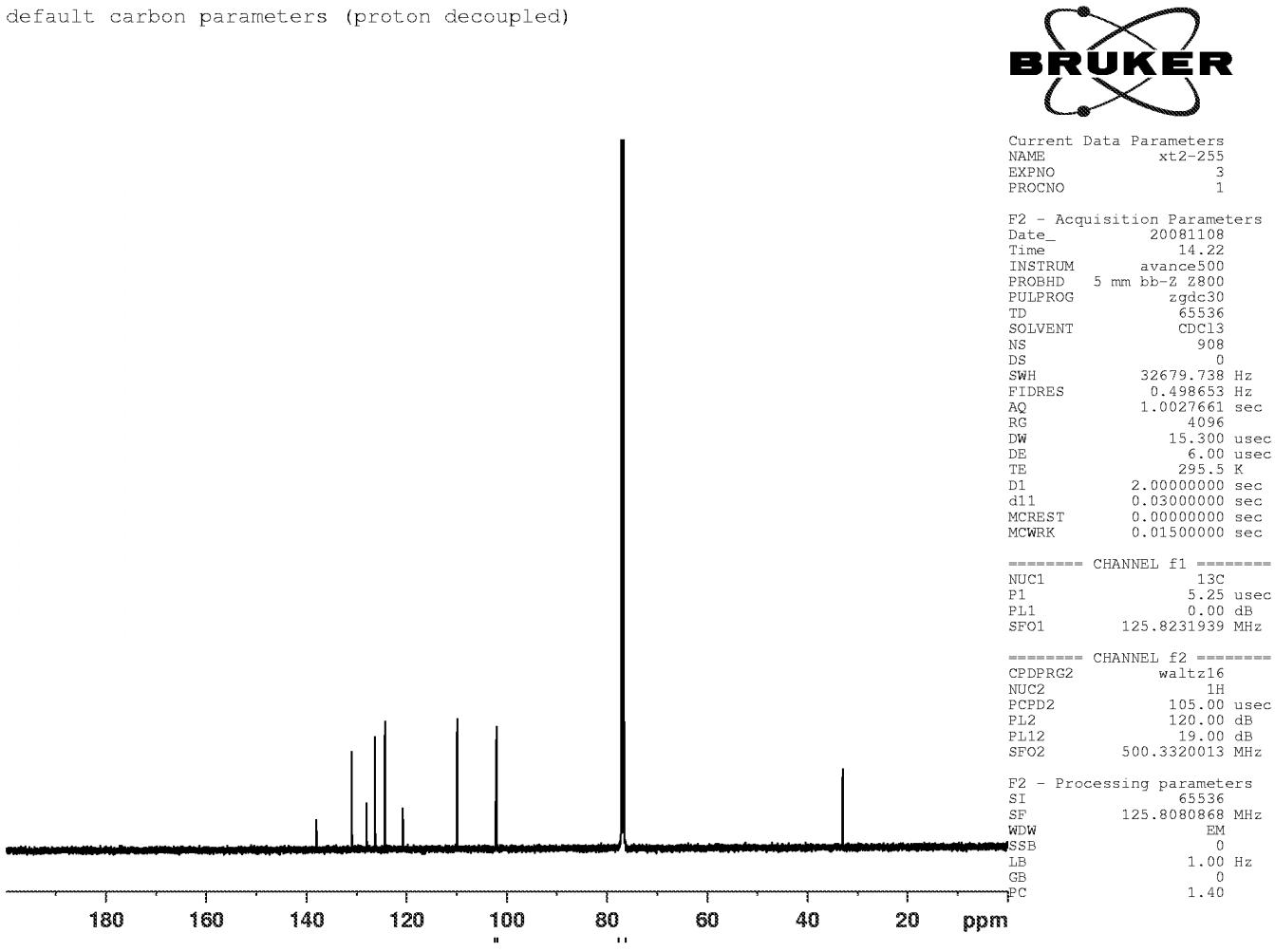



*Figure A1.35* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compound **241a**.

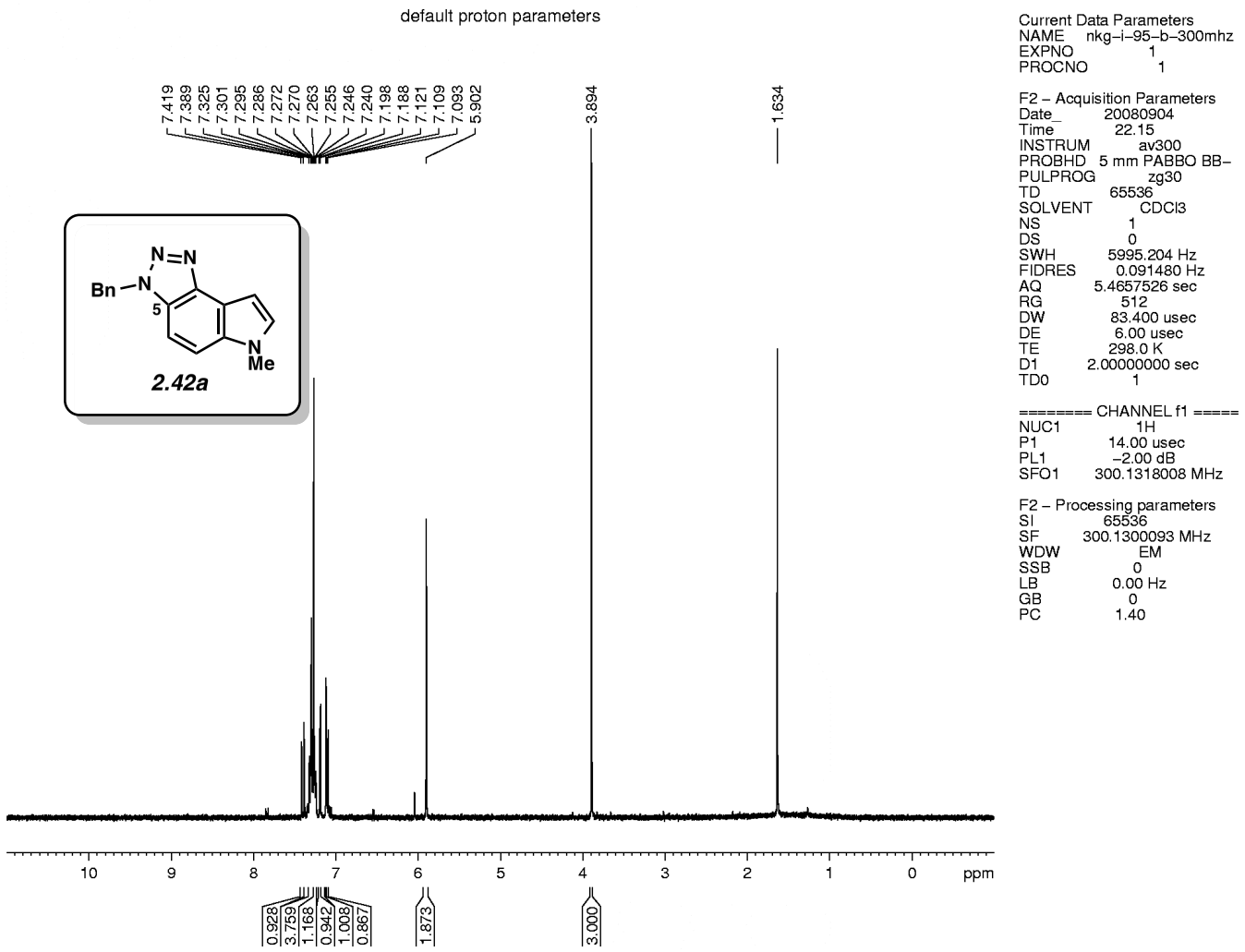



*Figure A1.36* $^{1}$H NMR (300 MHz, $CDCl_3$) of compound **2.42a**.

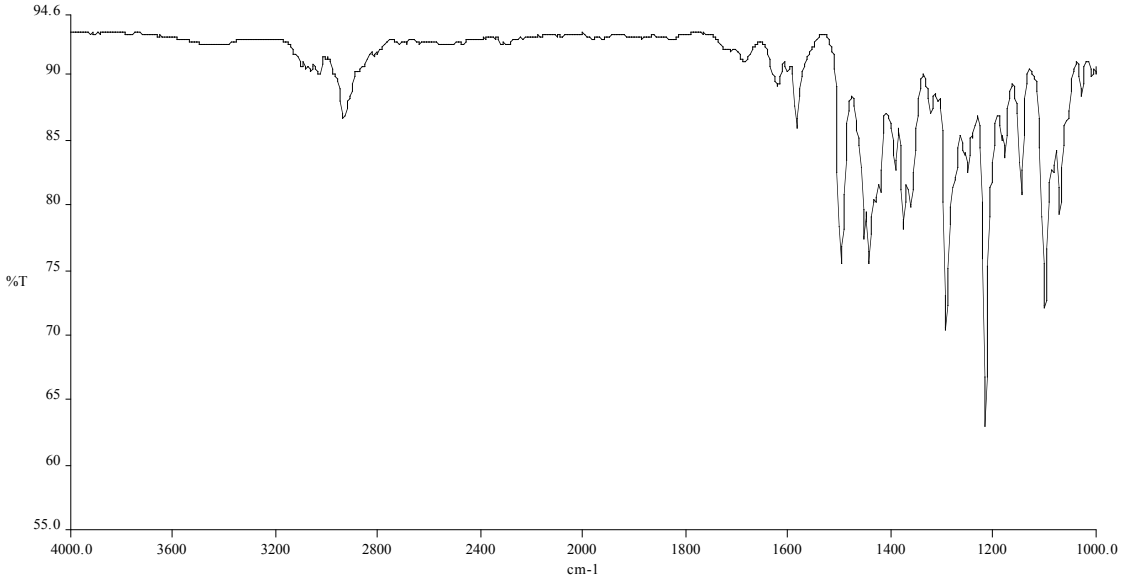



*Figure A1.37* Infrared spectrum of compound **2.42a**.

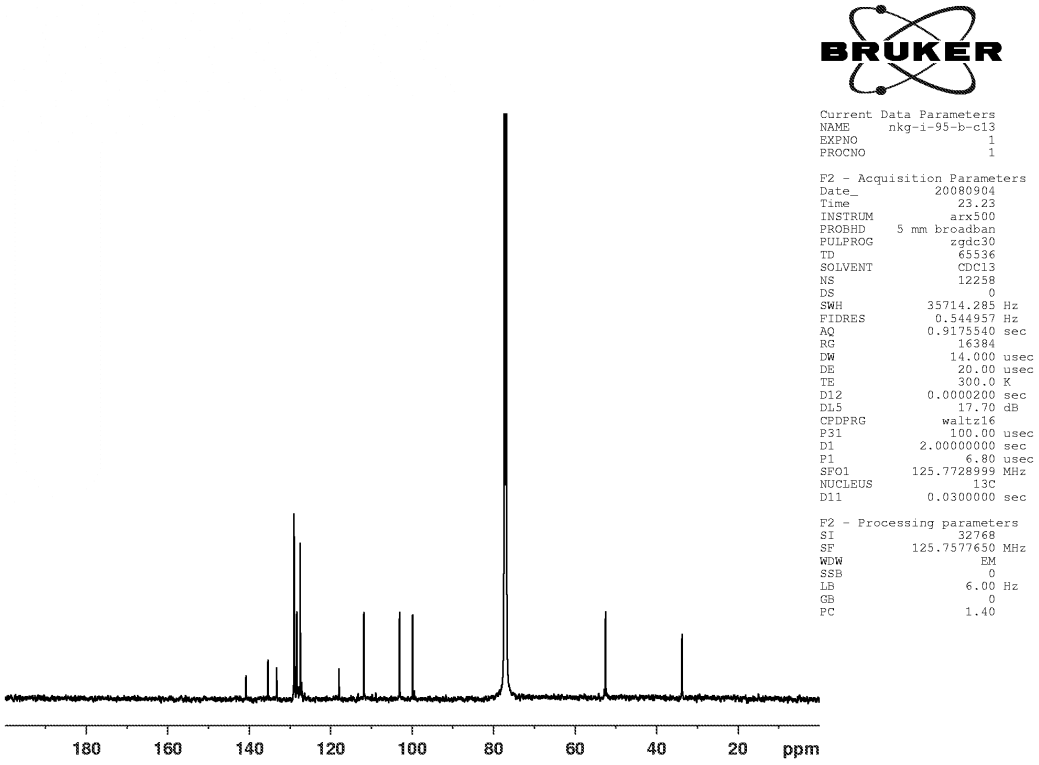



*Figure A1.38* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compound **2.42a**.

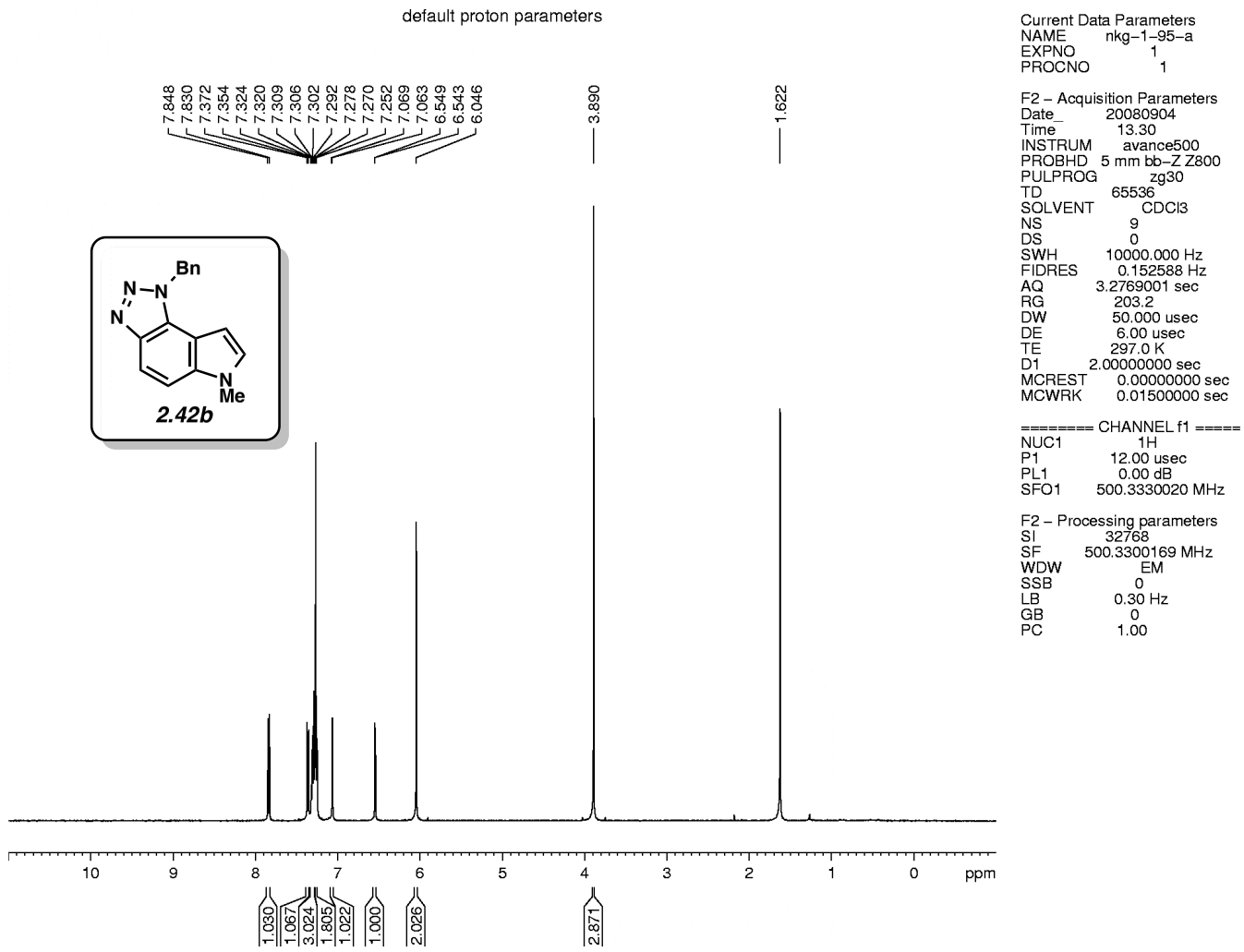



*Figure A1.39* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **2.42b**.

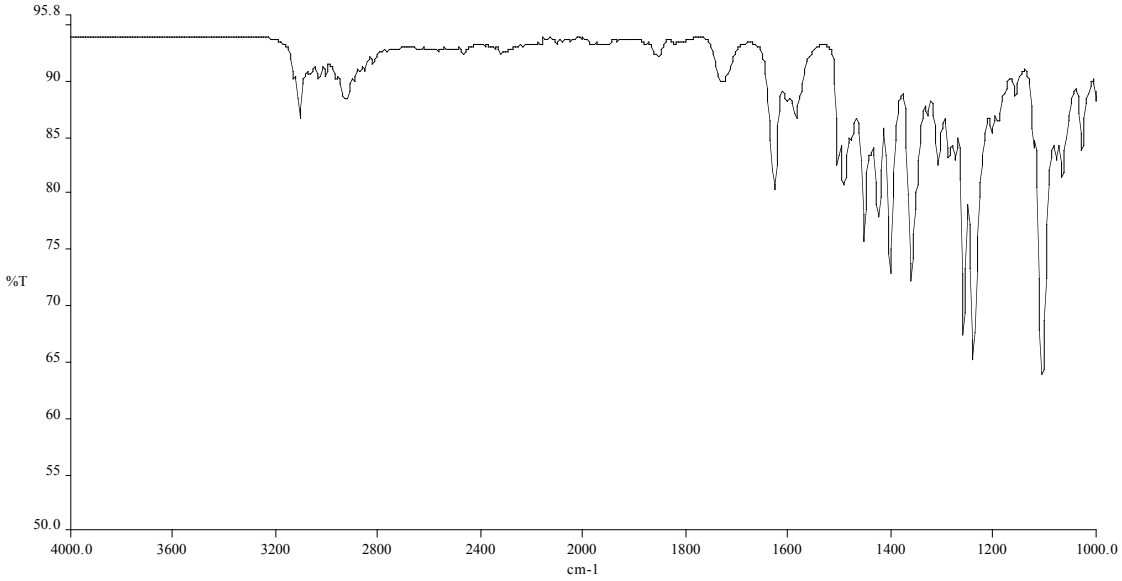



*Figure A1.40* Infrared spectrum of compound **2.42b**.

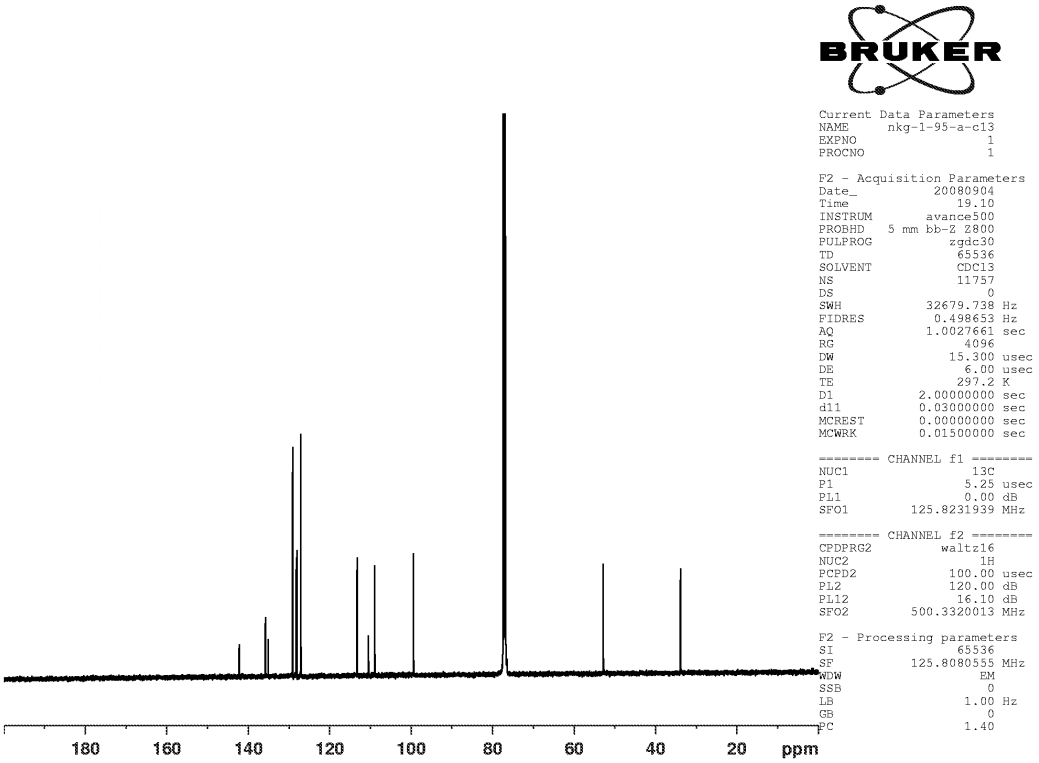



*Figure A1.41* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compound **2.42b**.

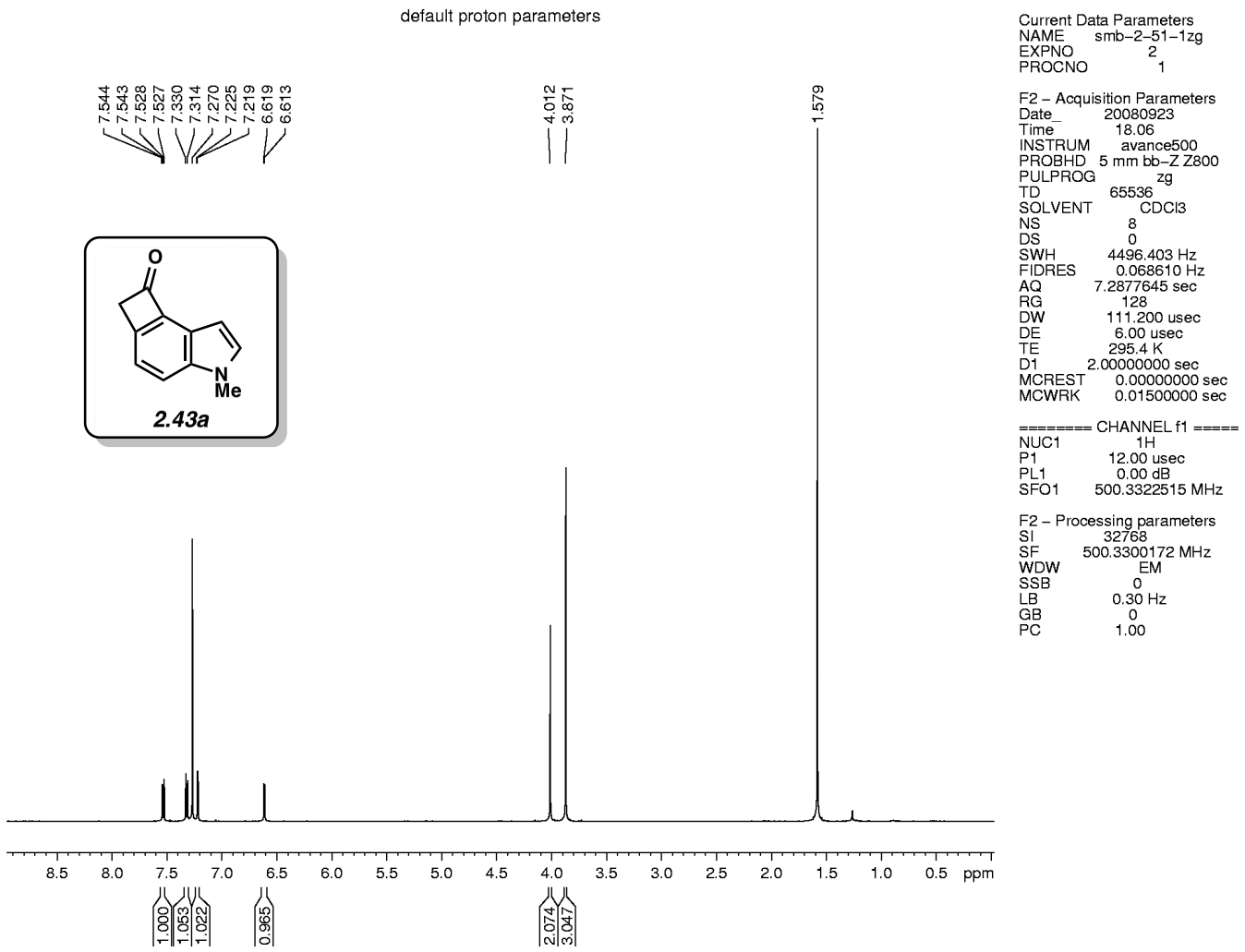



*Figure A1.42* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **2.43a**.

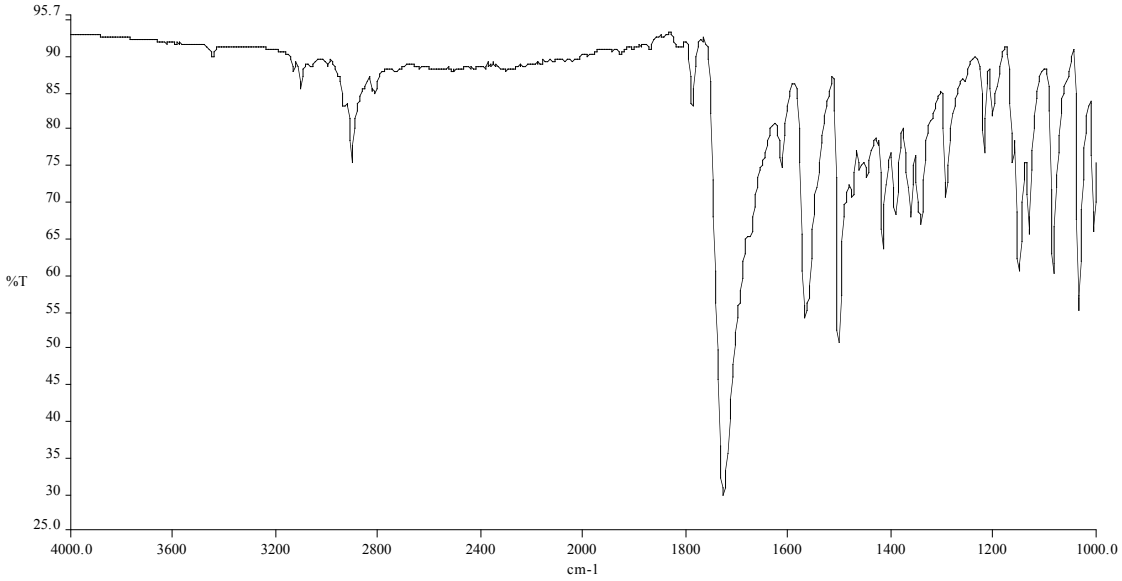



*Figure A1.43* Infrared spectrum of compound **2.43a**.

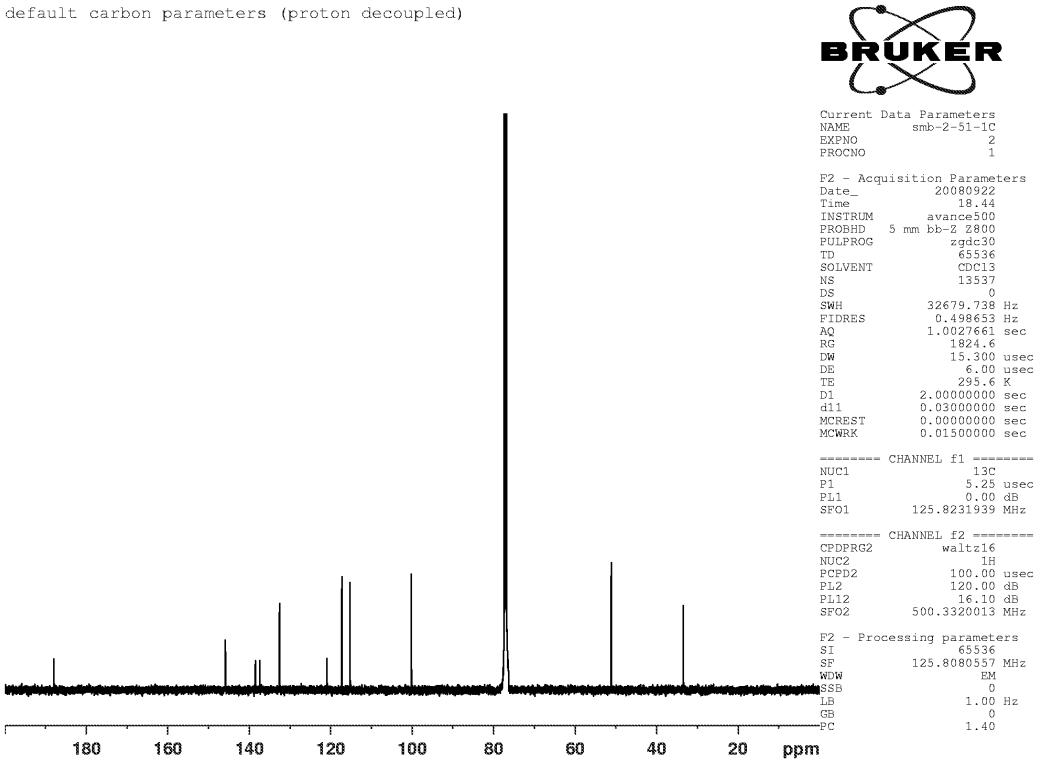



*Figure A1.44* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compound **2.43a**.

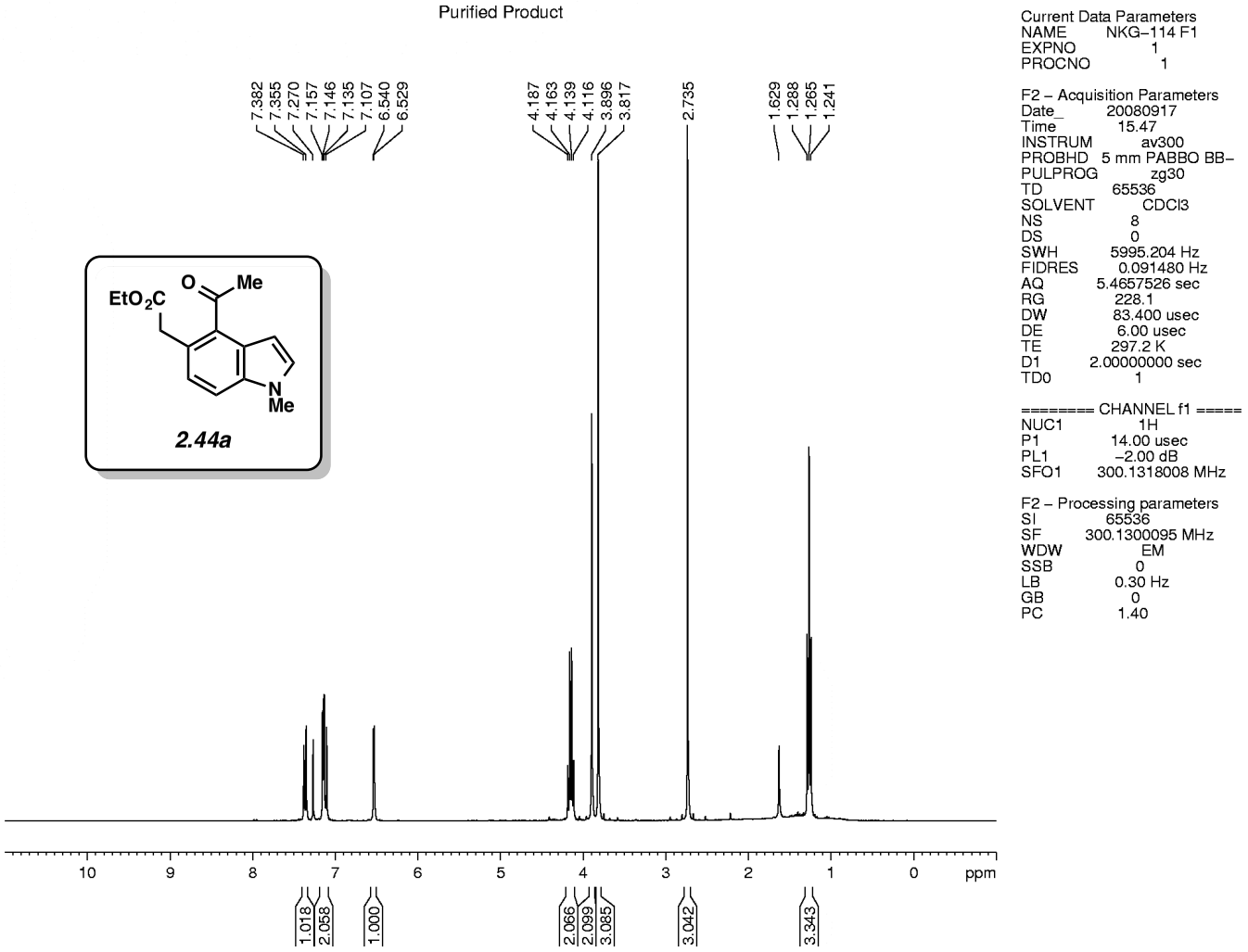



*Figure A1.45* $^{1}$H NMR (300 MHz, $CDCl_3$) of compound **2.44a**.

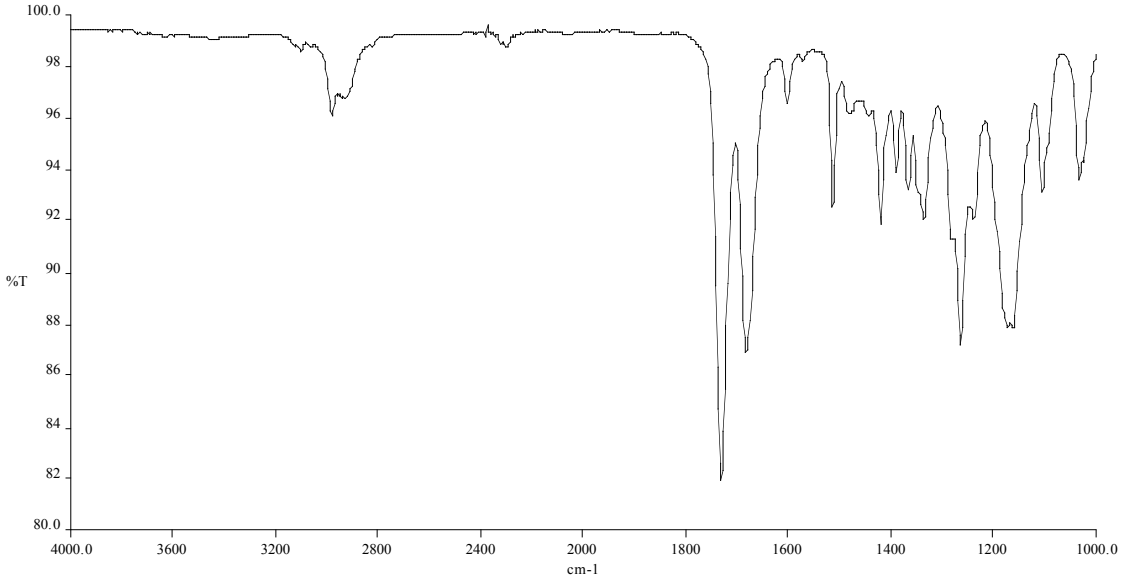



*Figure A1.46* Infrared spectrum of compound **2.44a**.

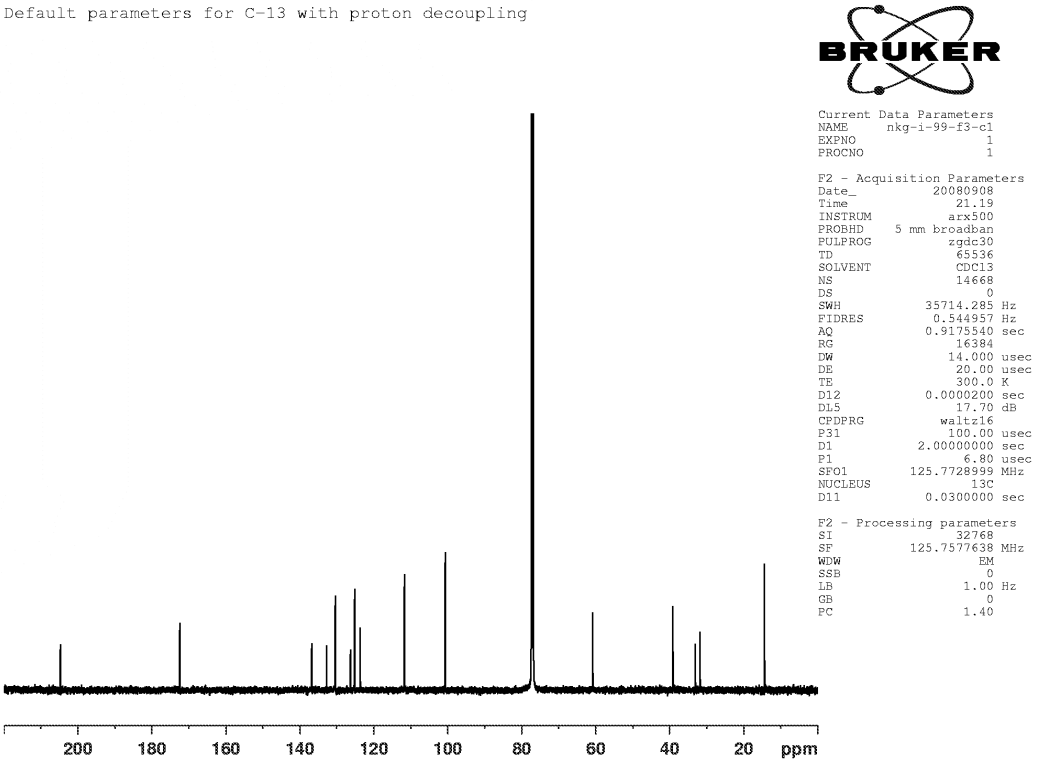



*Figure A1.47* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compound **2.44a**.

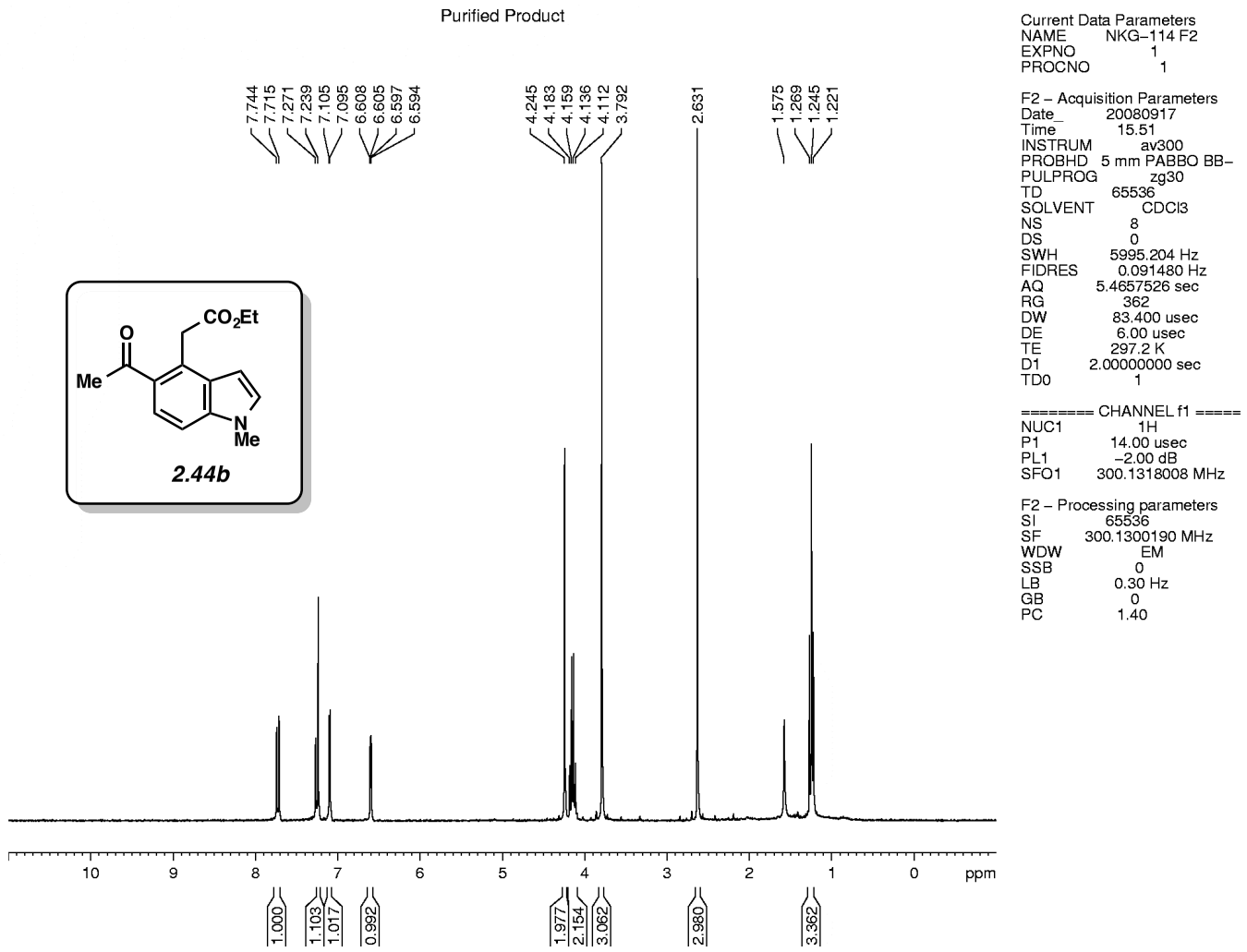



*Figure A1.48* $^{1}$H NMR (300 MHz, $CDCl_3$) of compound **2.44b**.

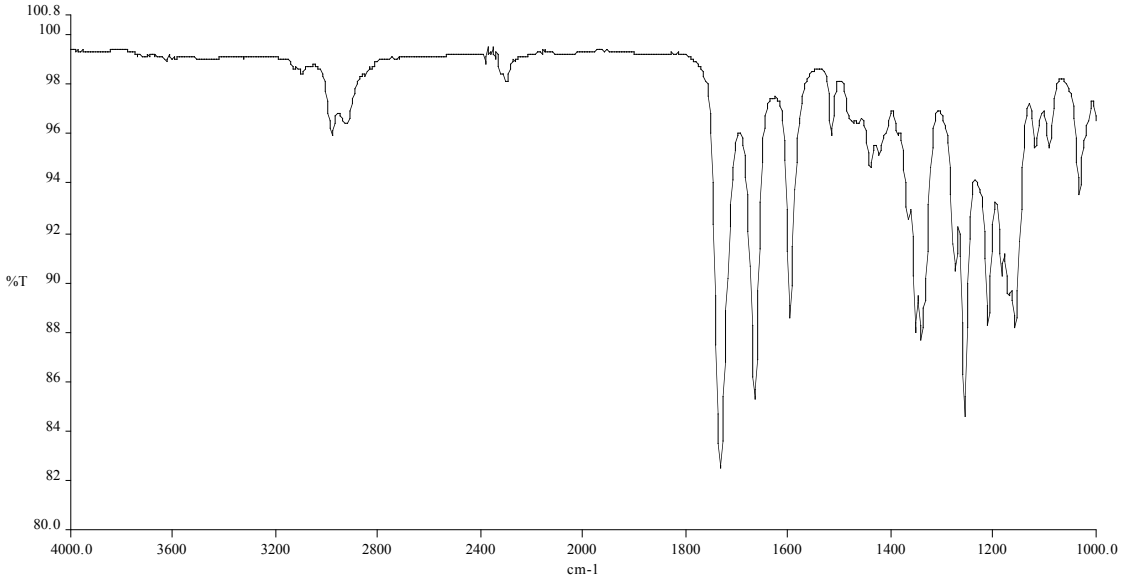



*Figure A1.49* Infrared spectrum of compound **2.44b**.

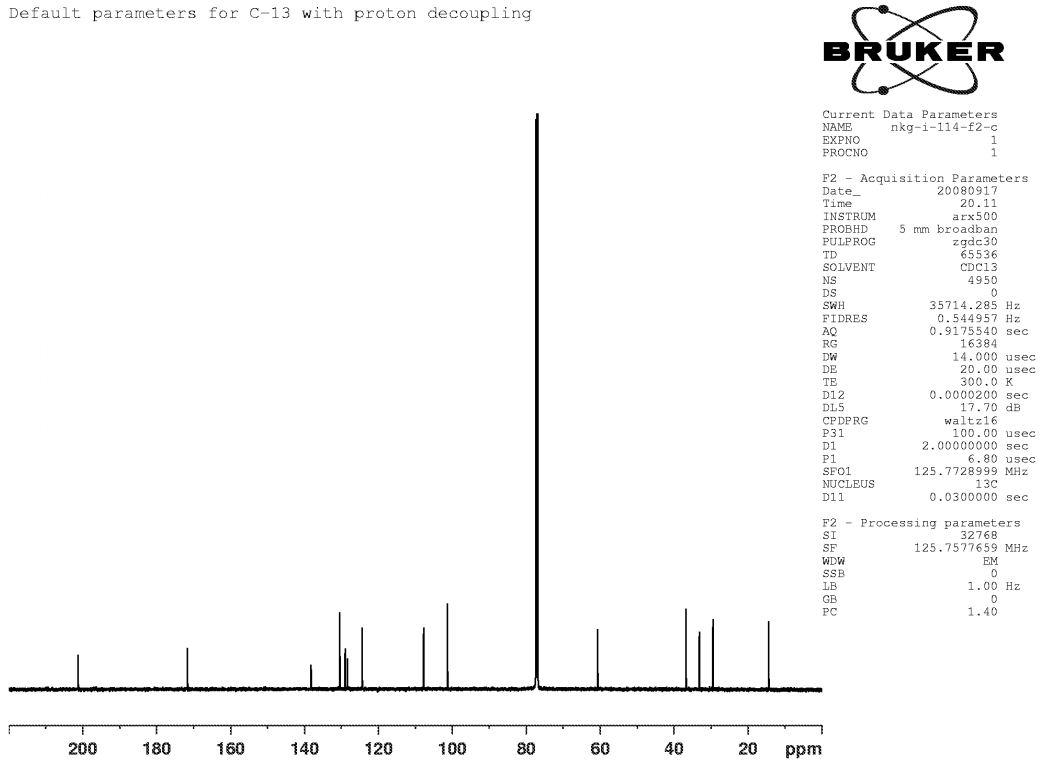



*Figure A1.50* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compound **2.44b**.

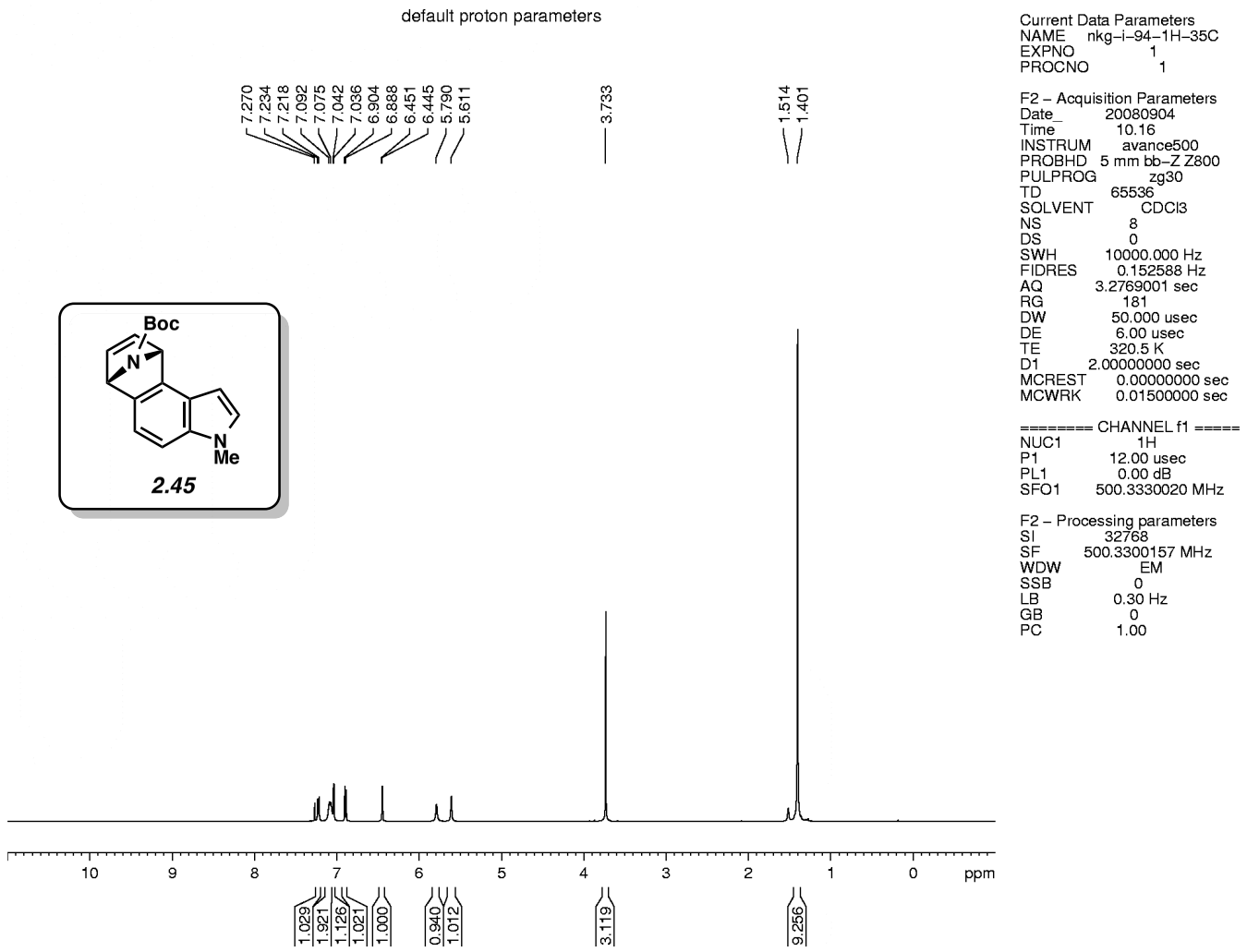



*Figure A1.51* $^{1}$H NMR (500 MHz, 47 °C, $CDCl_3$) of compound **2.45**.

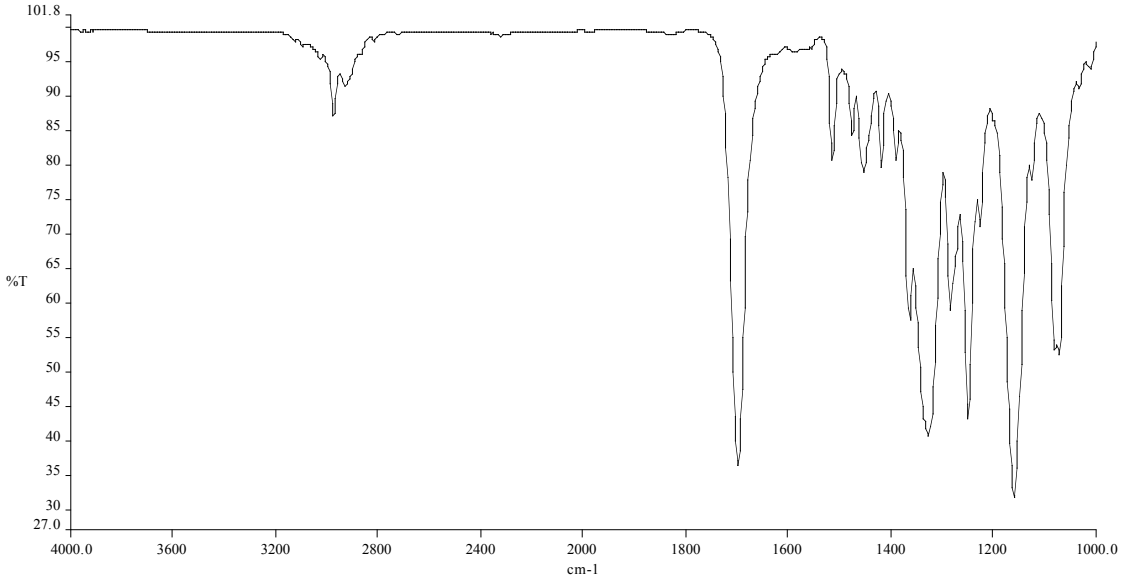



*Figure A1.52* Infrared spectrum of compound **2.45**.

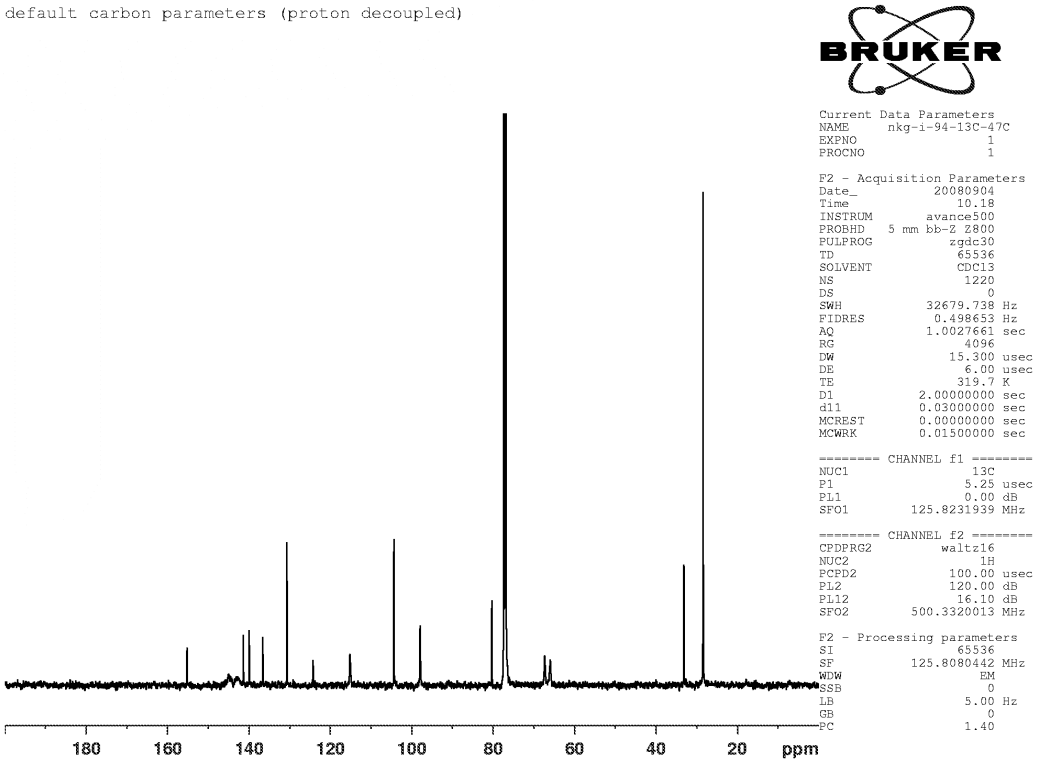



*Figure A1.53* $^{13}C$ NMR (125 MHz, 47 °C, $CDCl_3$) of compound **2.45**.

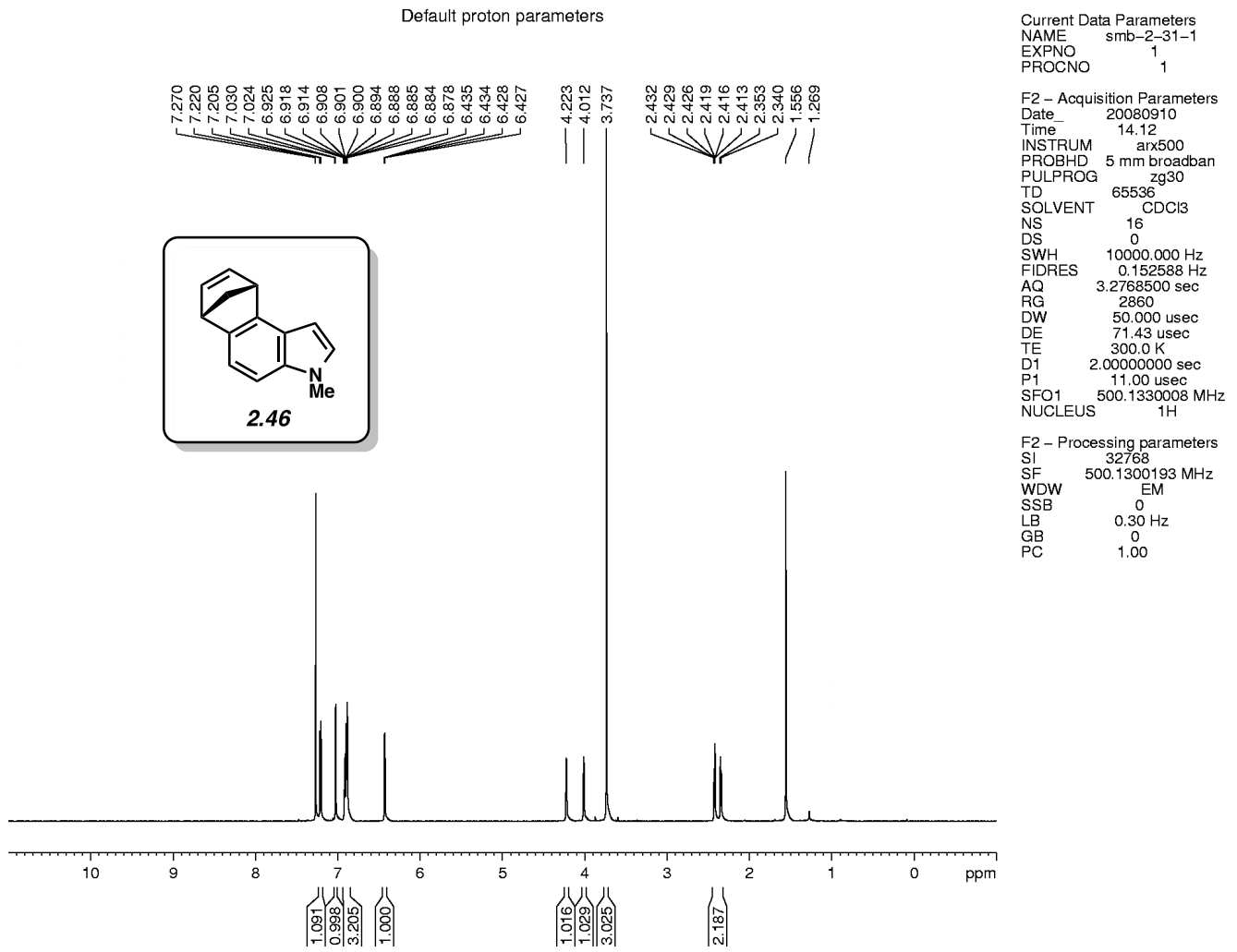



*Figure A1.54* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **2.46**.

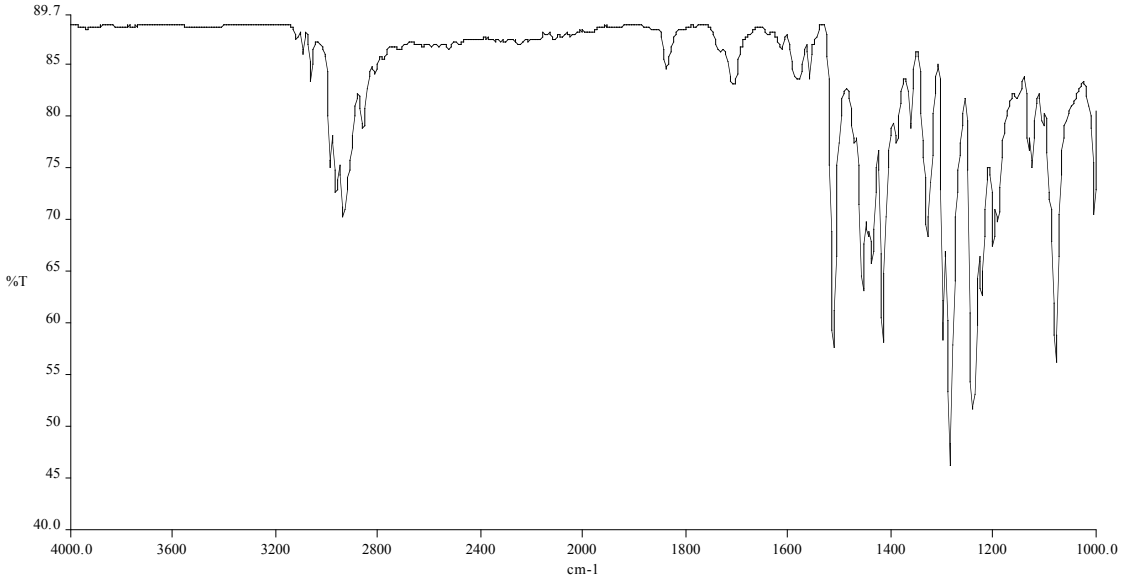



*Figure A1.55* Infrared spectrum of compound **2.46**.

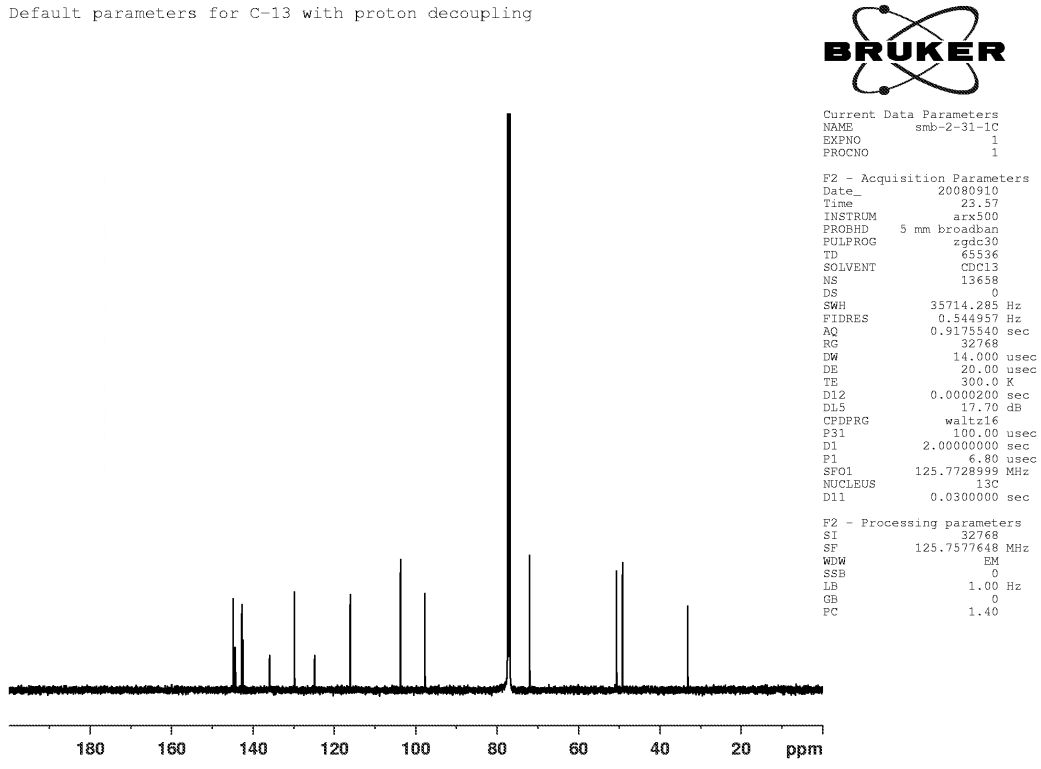



*Figure A1.56* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compound **2.46**.

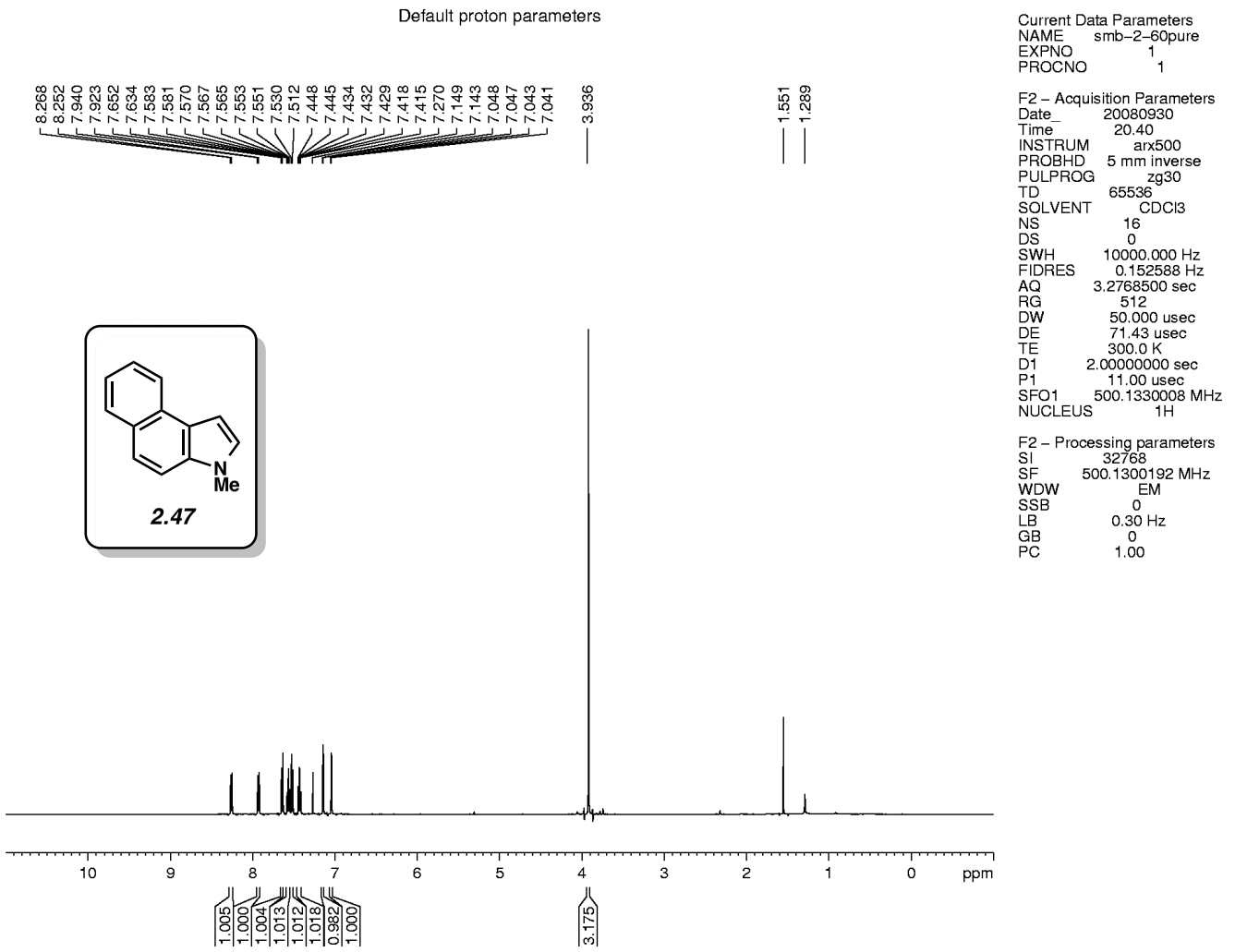



*Figure A1.57* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **2.47**.

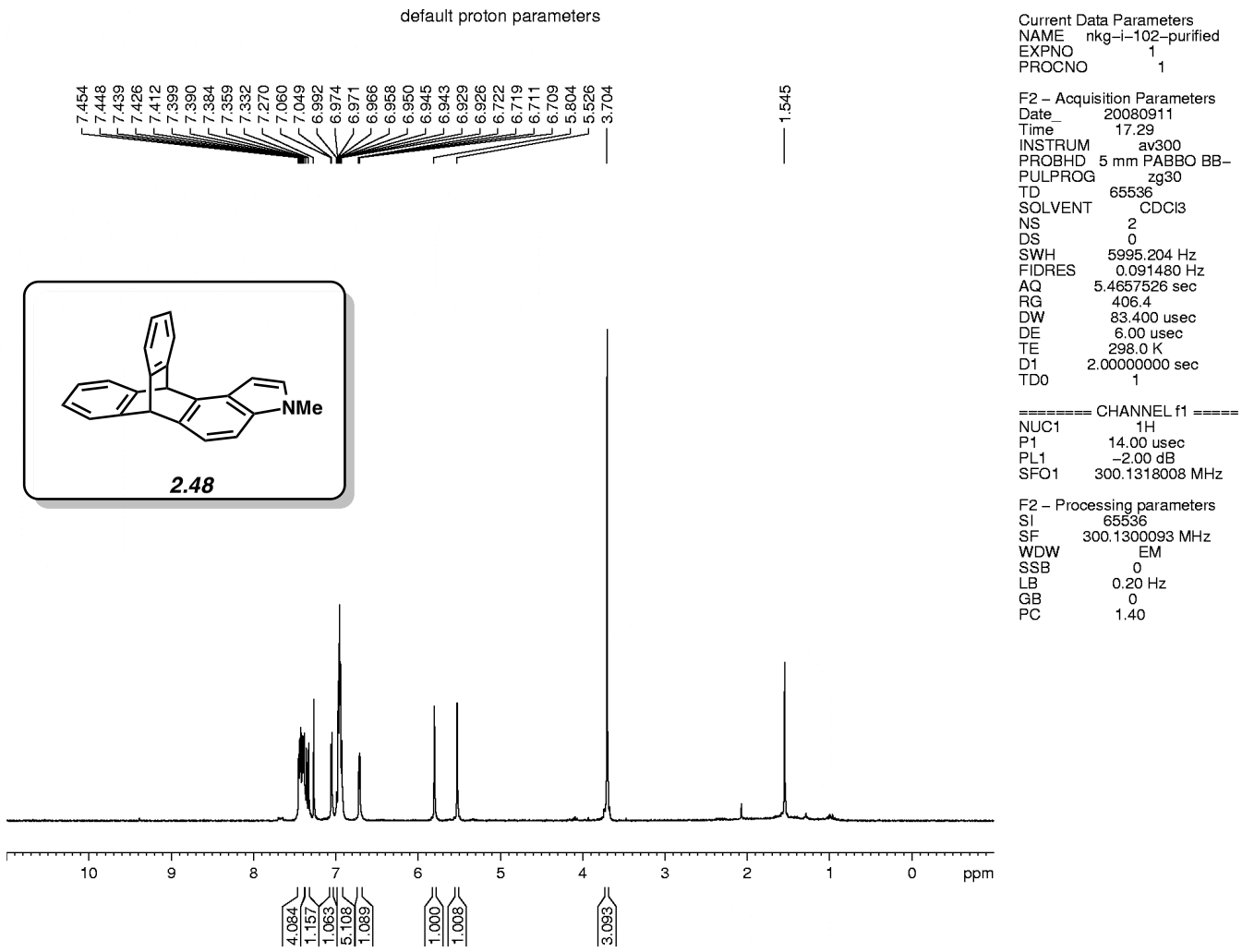



*Figure A1.58* $^{1}$H NMR (300 MHz, $CDCl_3$) of compound **2.48**.

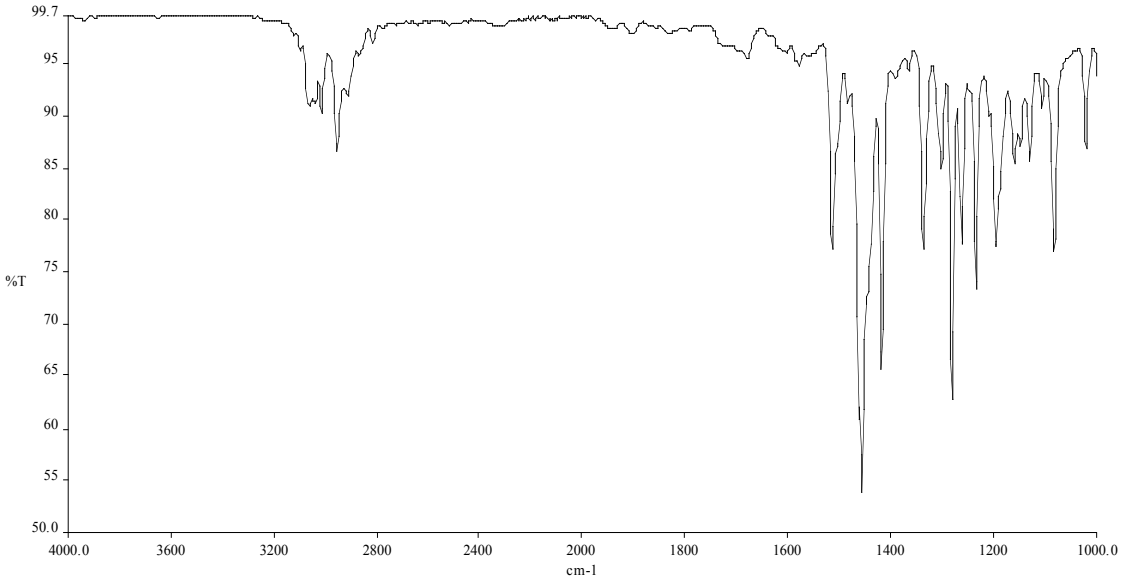



*Figure A1.59* Infrared spectrum of compound **2.48**.

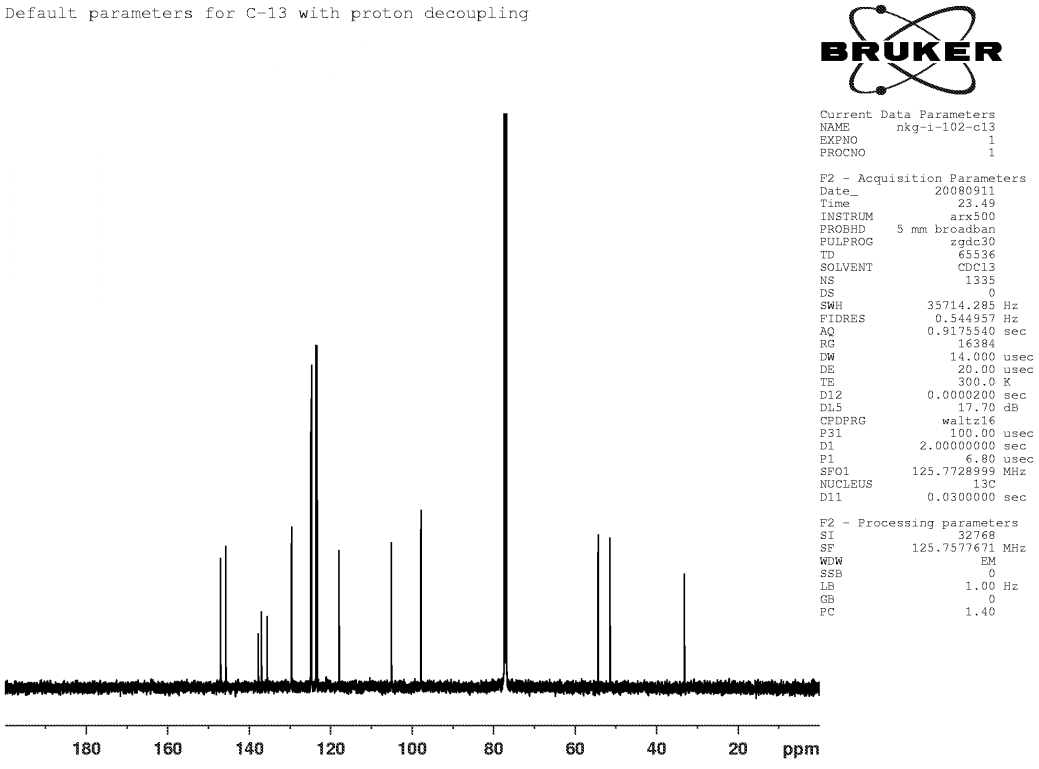



*Figure A1.60* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compound **2.48**.

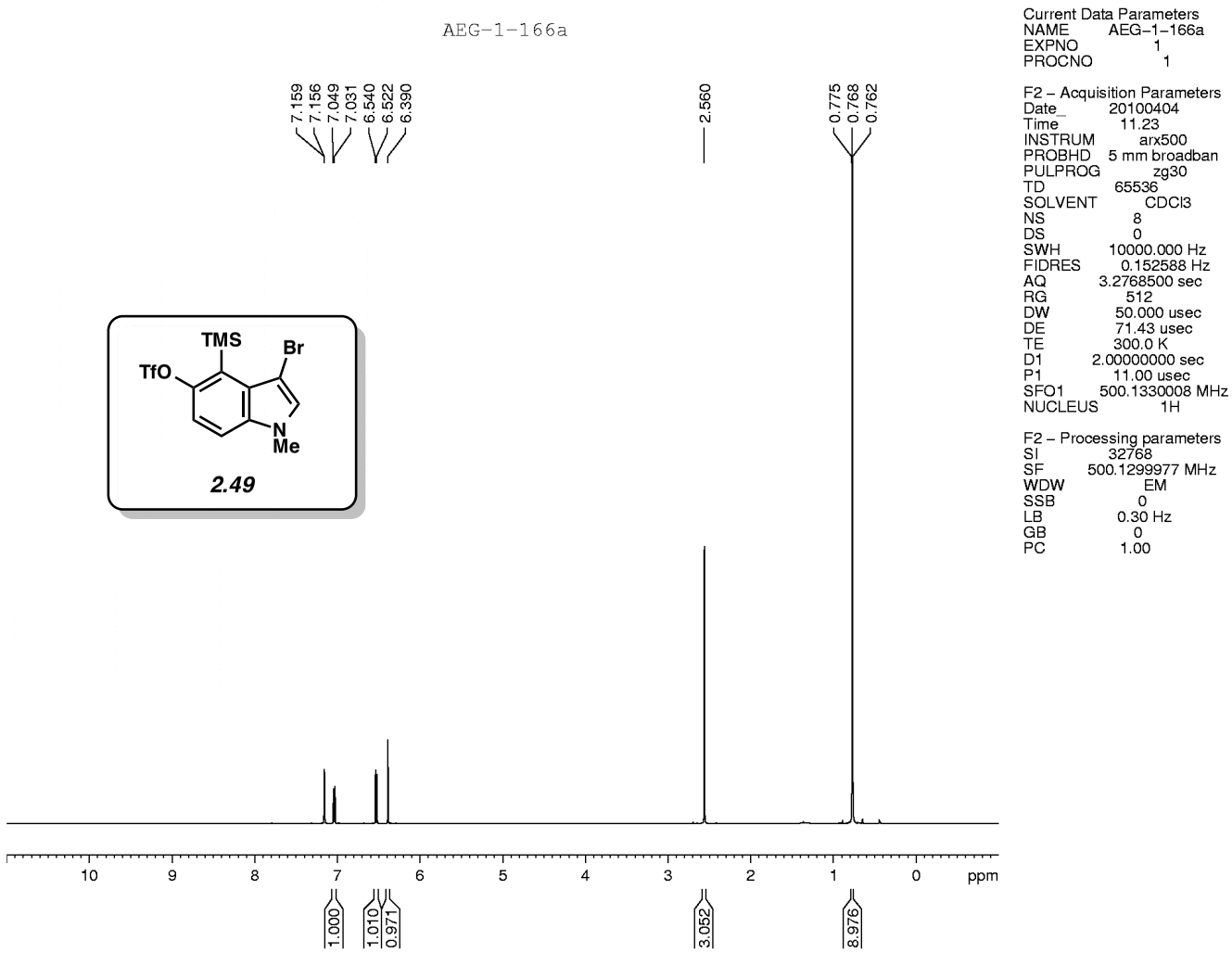



*Figure A1.61* $^{1}$H NMR (500 MHz, $C_6D_6$) of compound **2.49**.

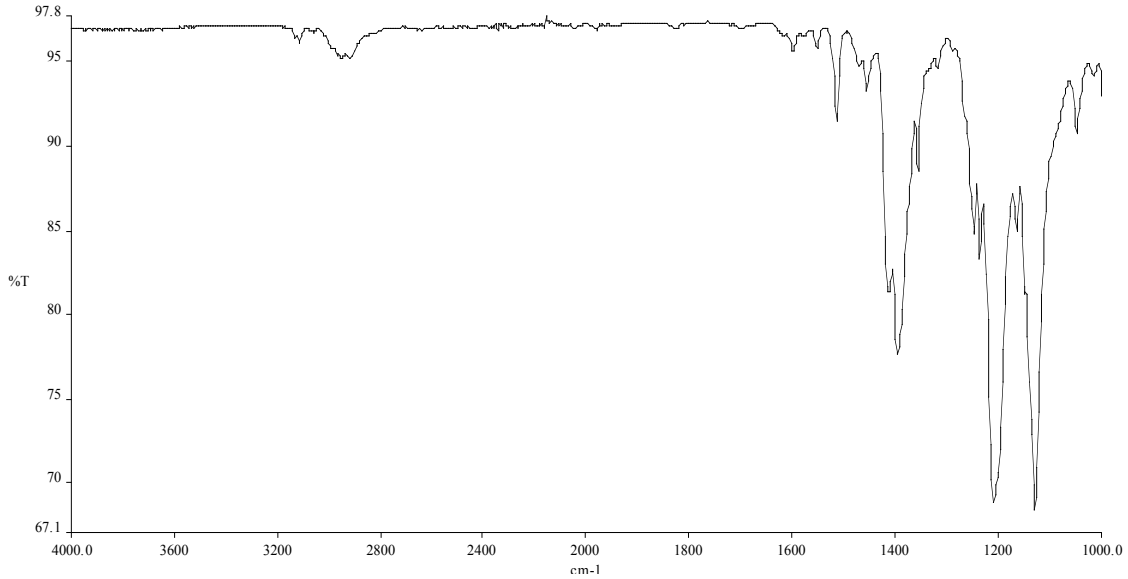



*Figure A1.62* Infrared spectrum of compound **2.49**.

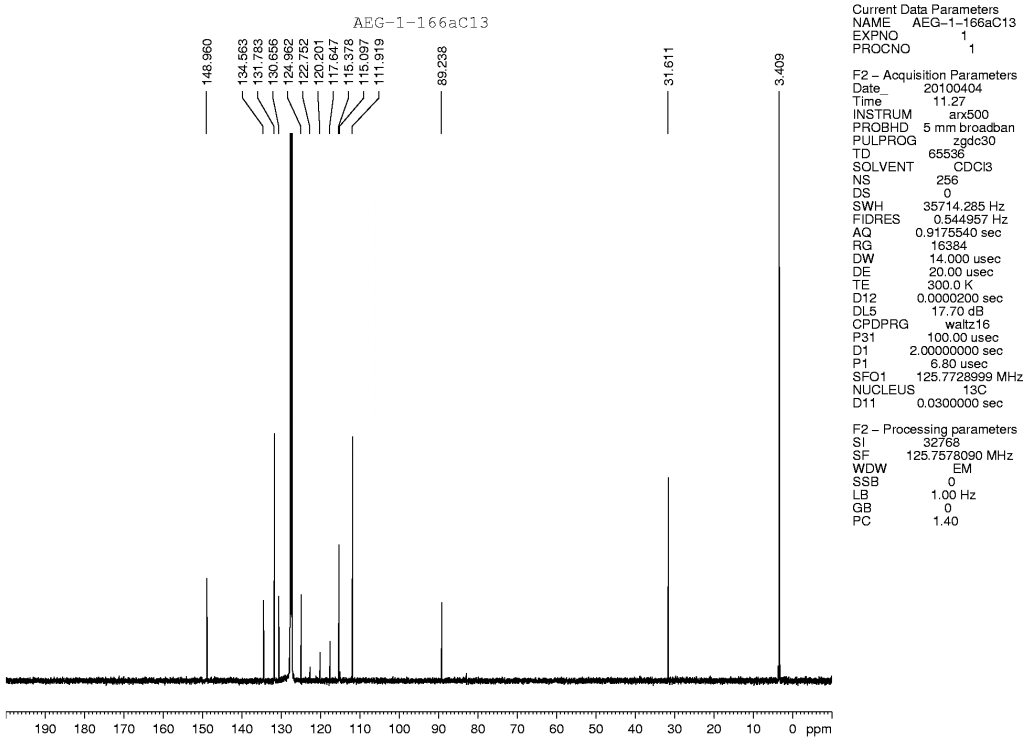



*Figure A1.63* $^{13}$C NMR (125 MHz, $C_6D_6$) of compound **2.49**.

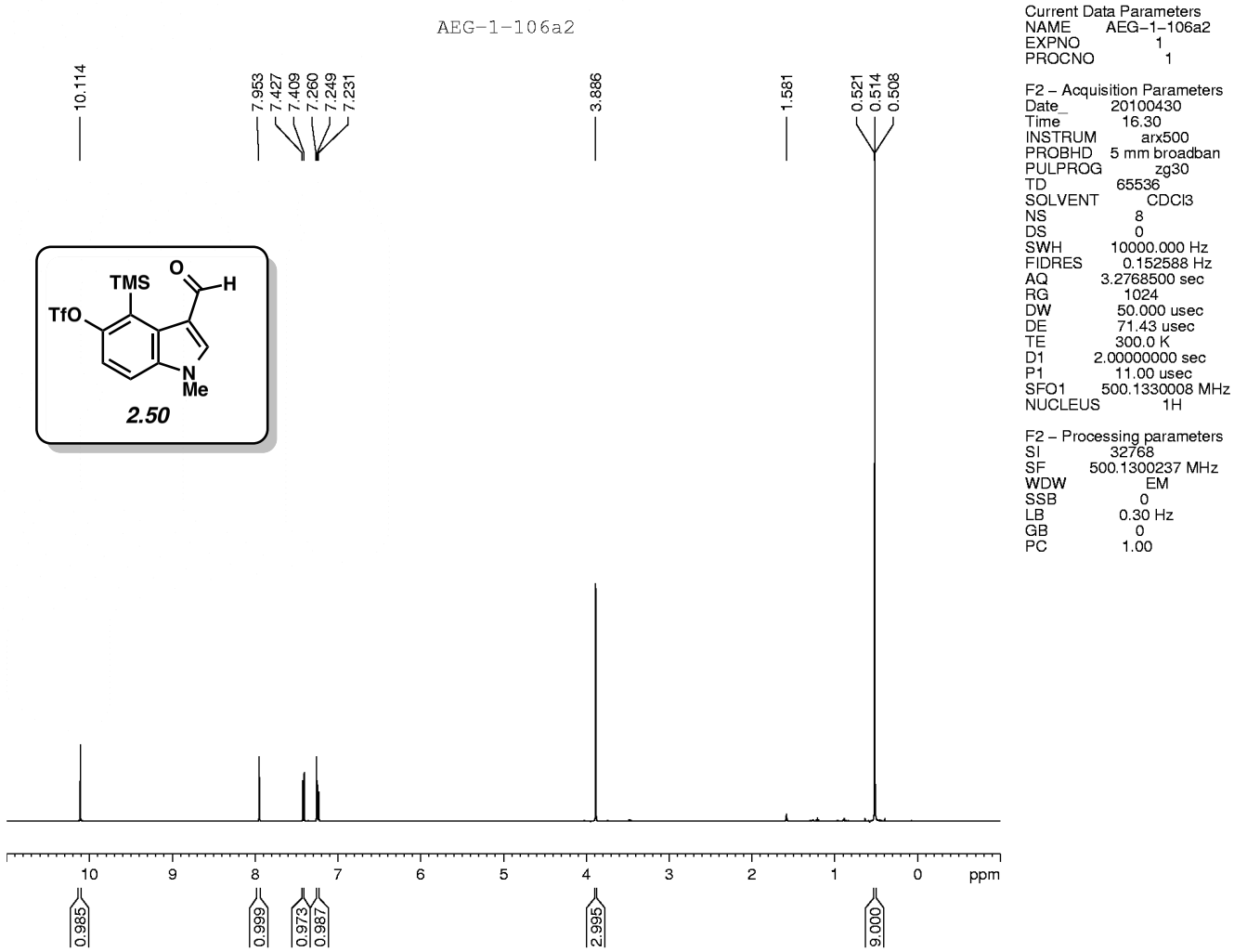



*Figure A1.64* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **2.50**.

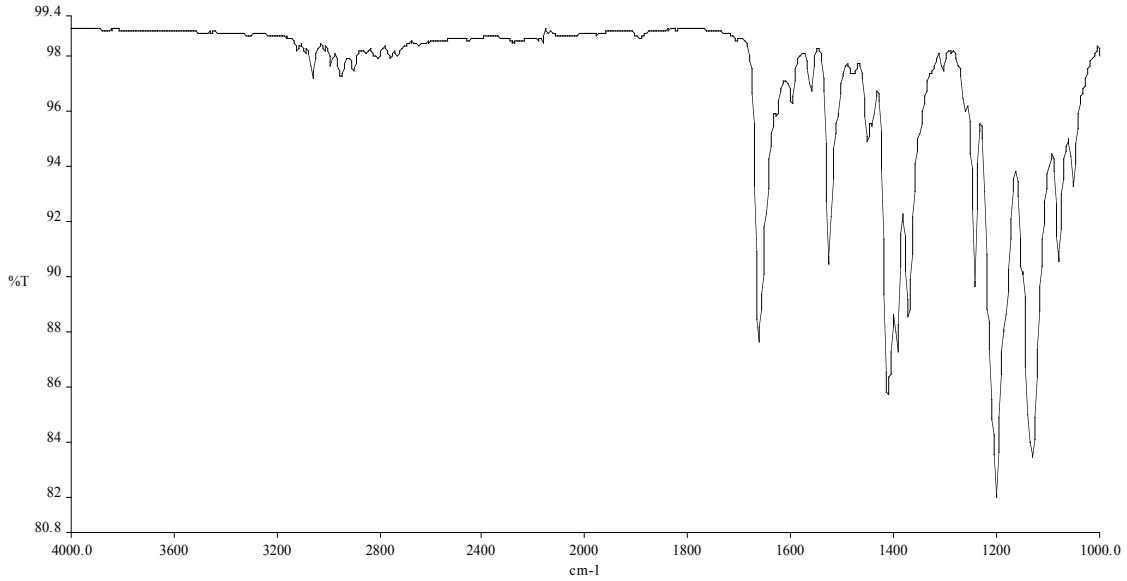



*Figure A1.65* Infrared spectrum of compound **2.50**.

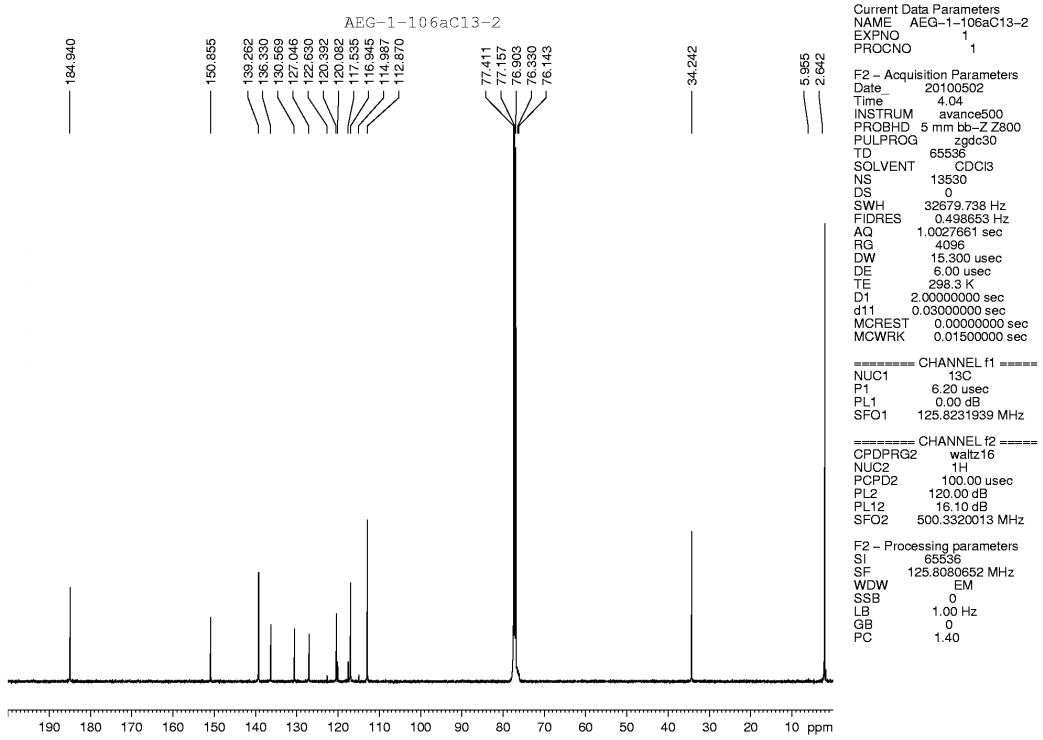



*Figure A1.66* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compound **2.50**.

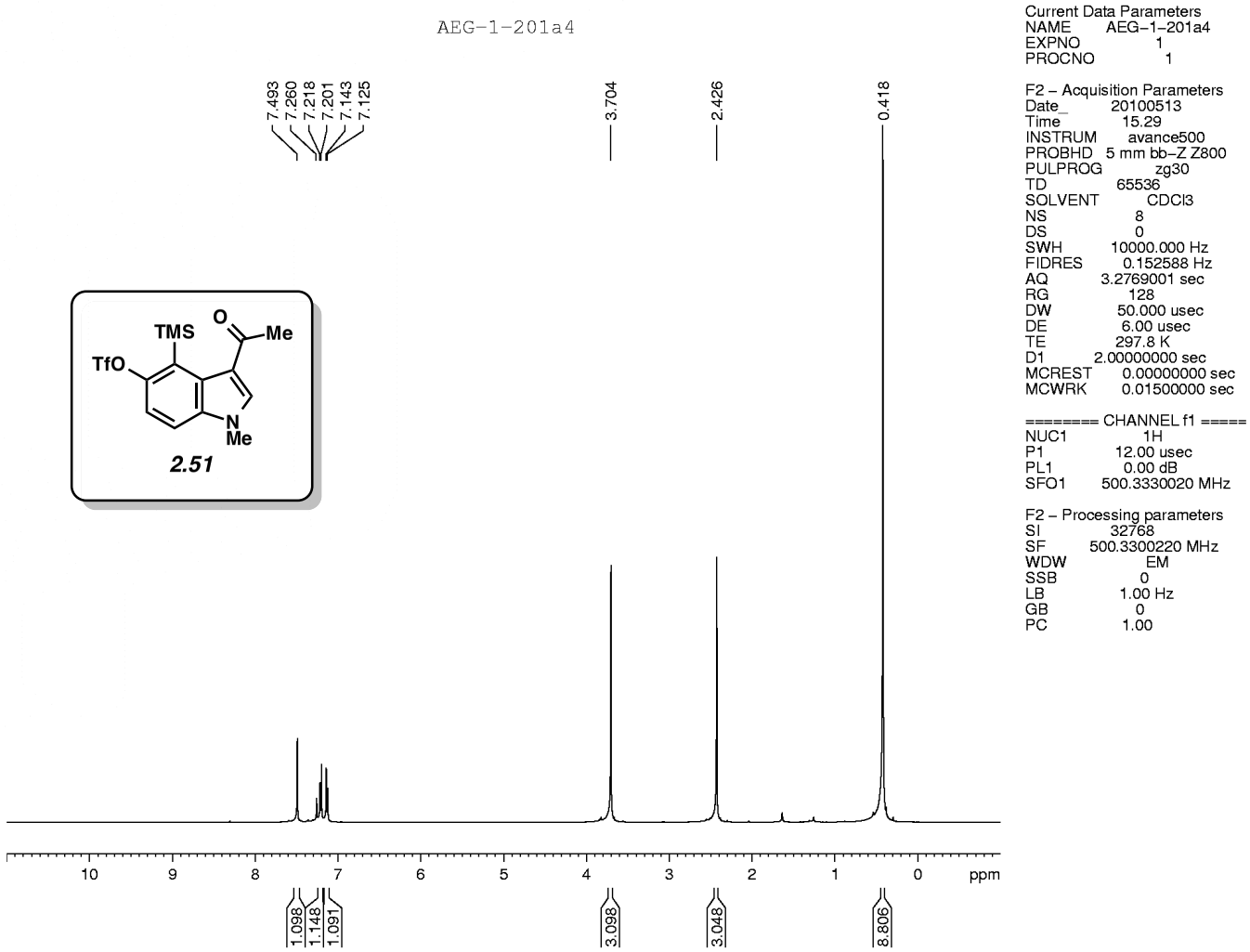



*Figure A1.67* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **2.51**.

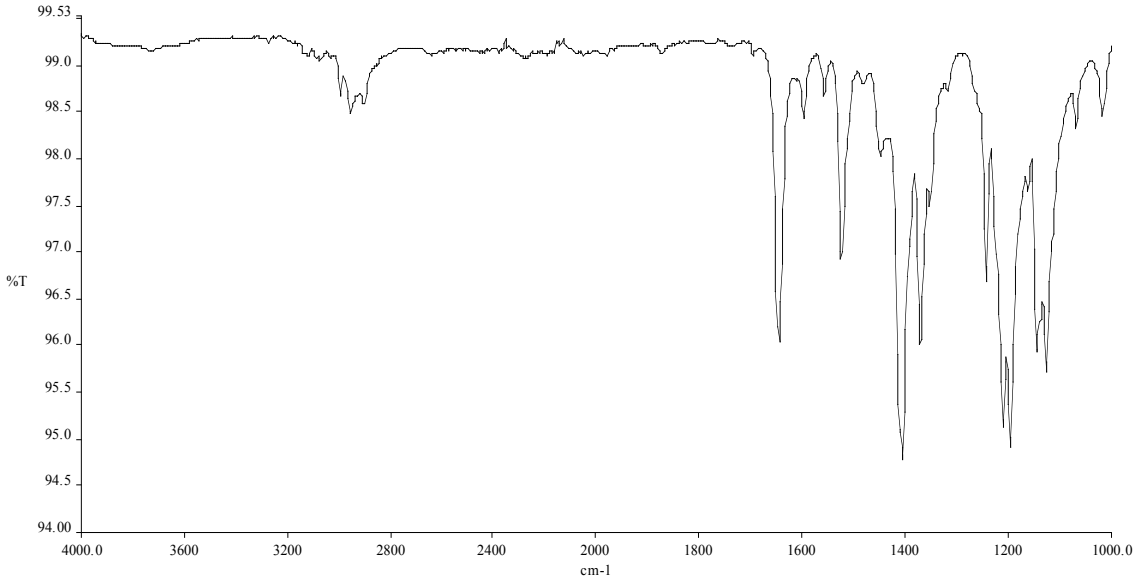



*Figure A1.68* Infrared spectrum of compound **2.51**.

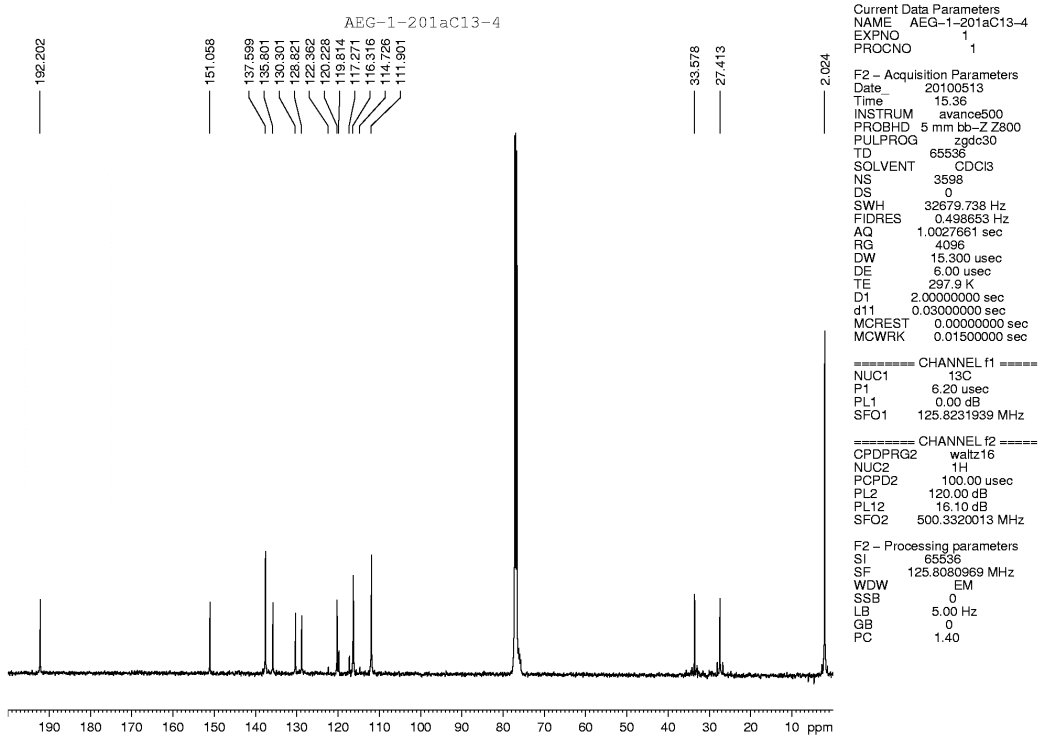



*Figure A1.69* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compound **2.51**.

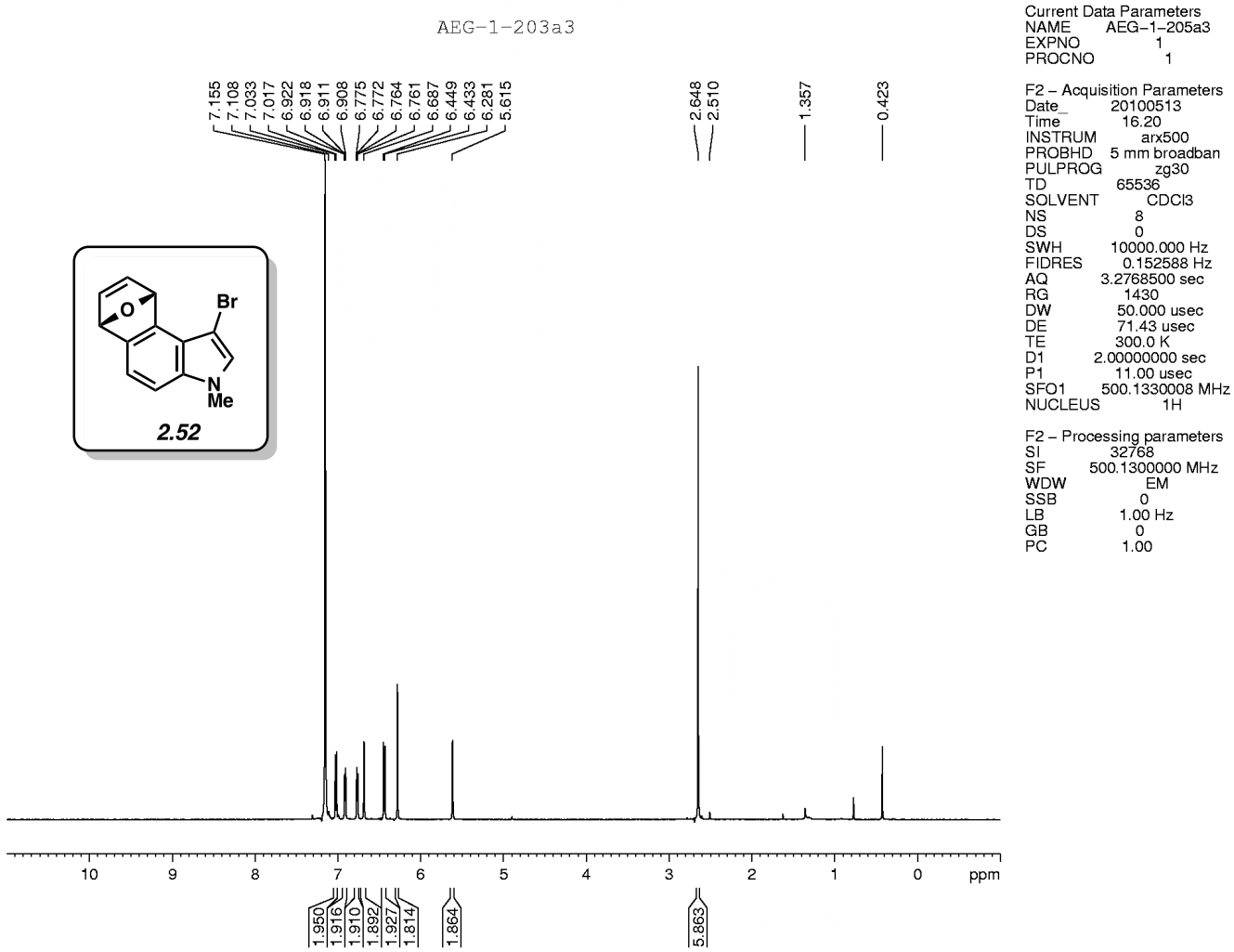



*Figure A1.70* $^{1}$H NMR (500 MHz, $C_6D_6$) of compound **2.52**.

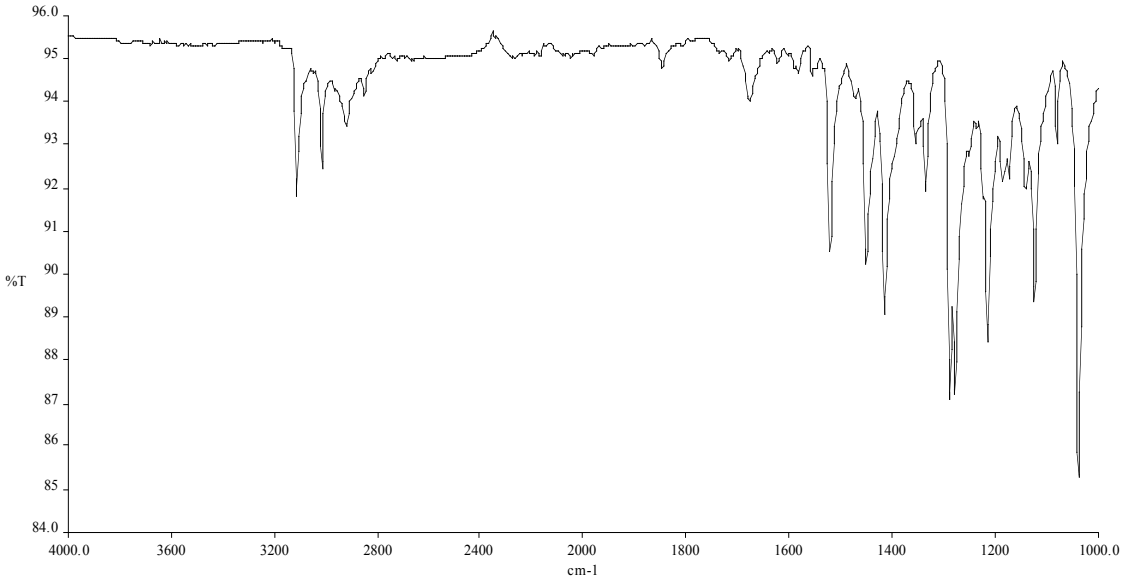



*Figure A1.71* Infrared spectrum of compound **2.52**.

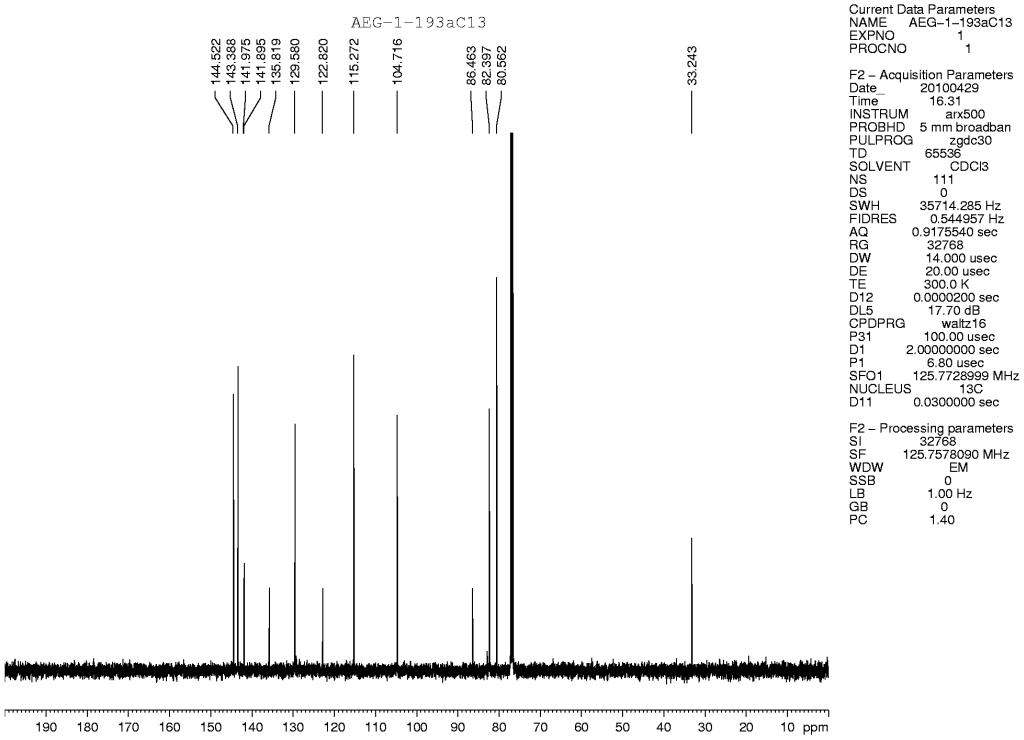



*Figure A1.72* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compound **2.52**.

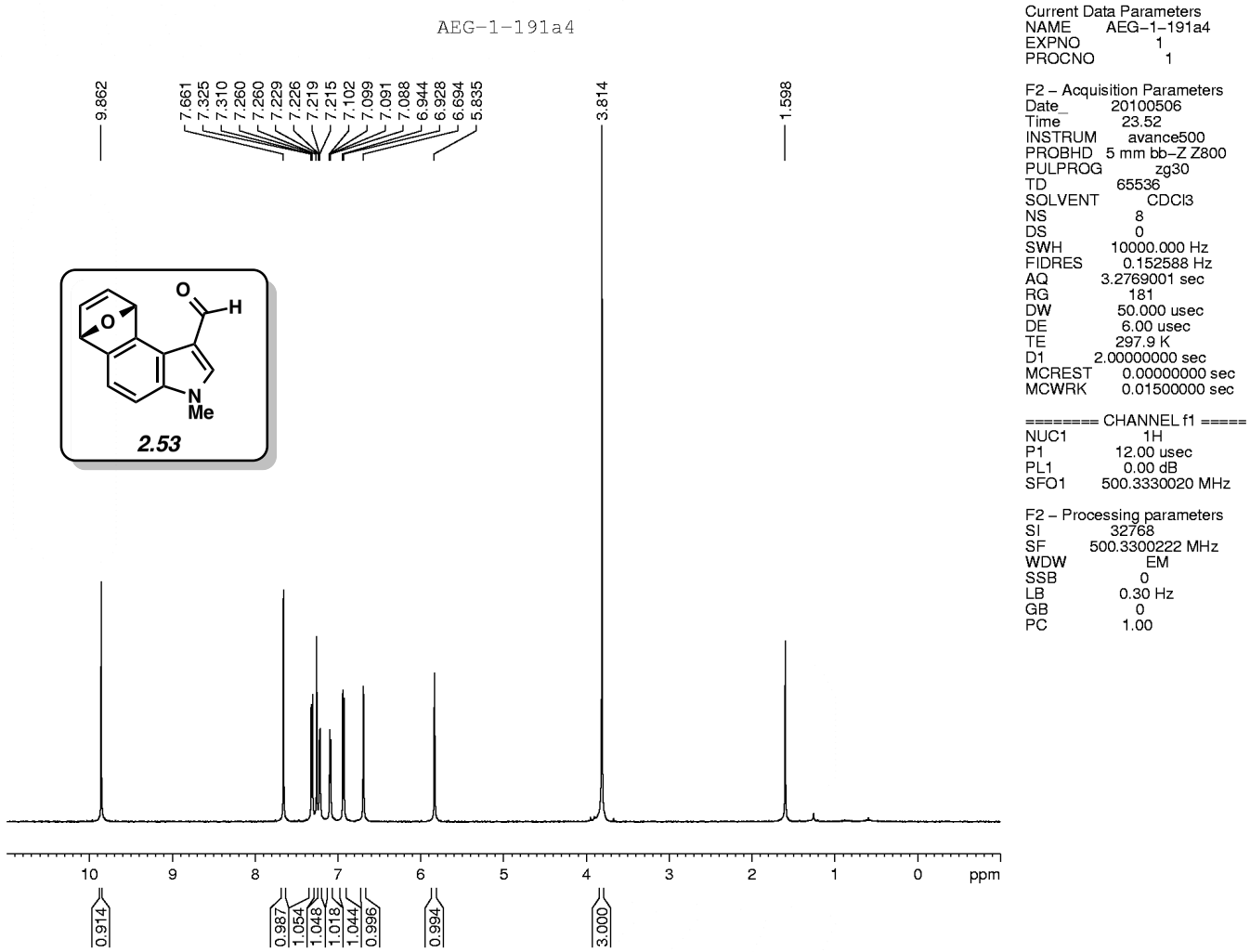



*Figure A1.73* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **2.53**.

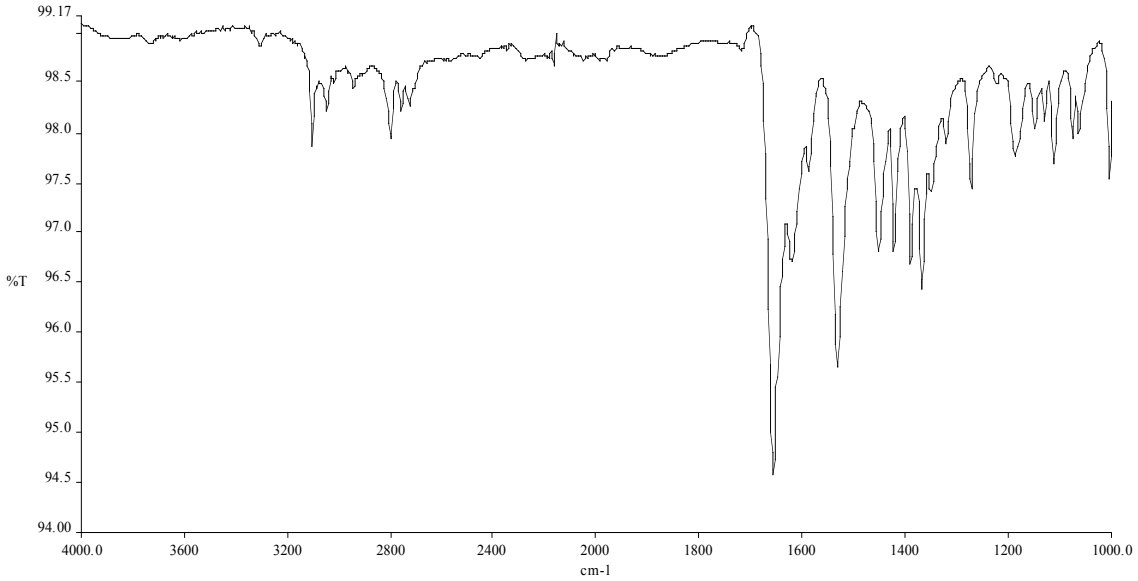



*Figure A1.74* Infrared spectrum of compound **2.53**.

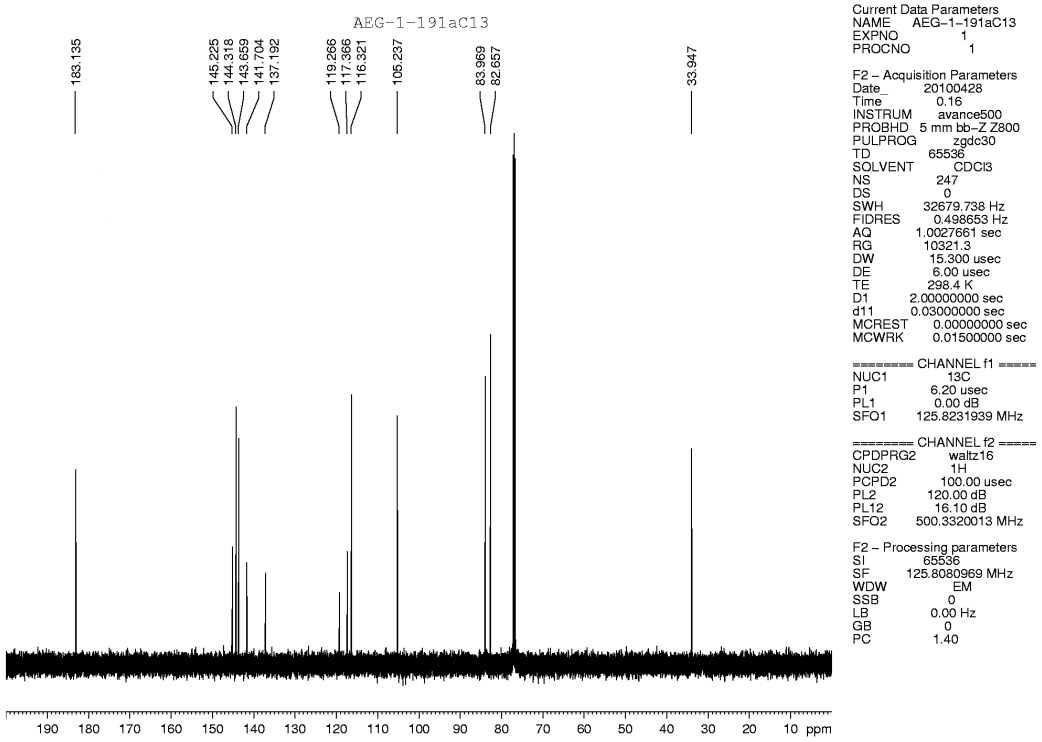



*Figure A1.75* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compound **2.53**.

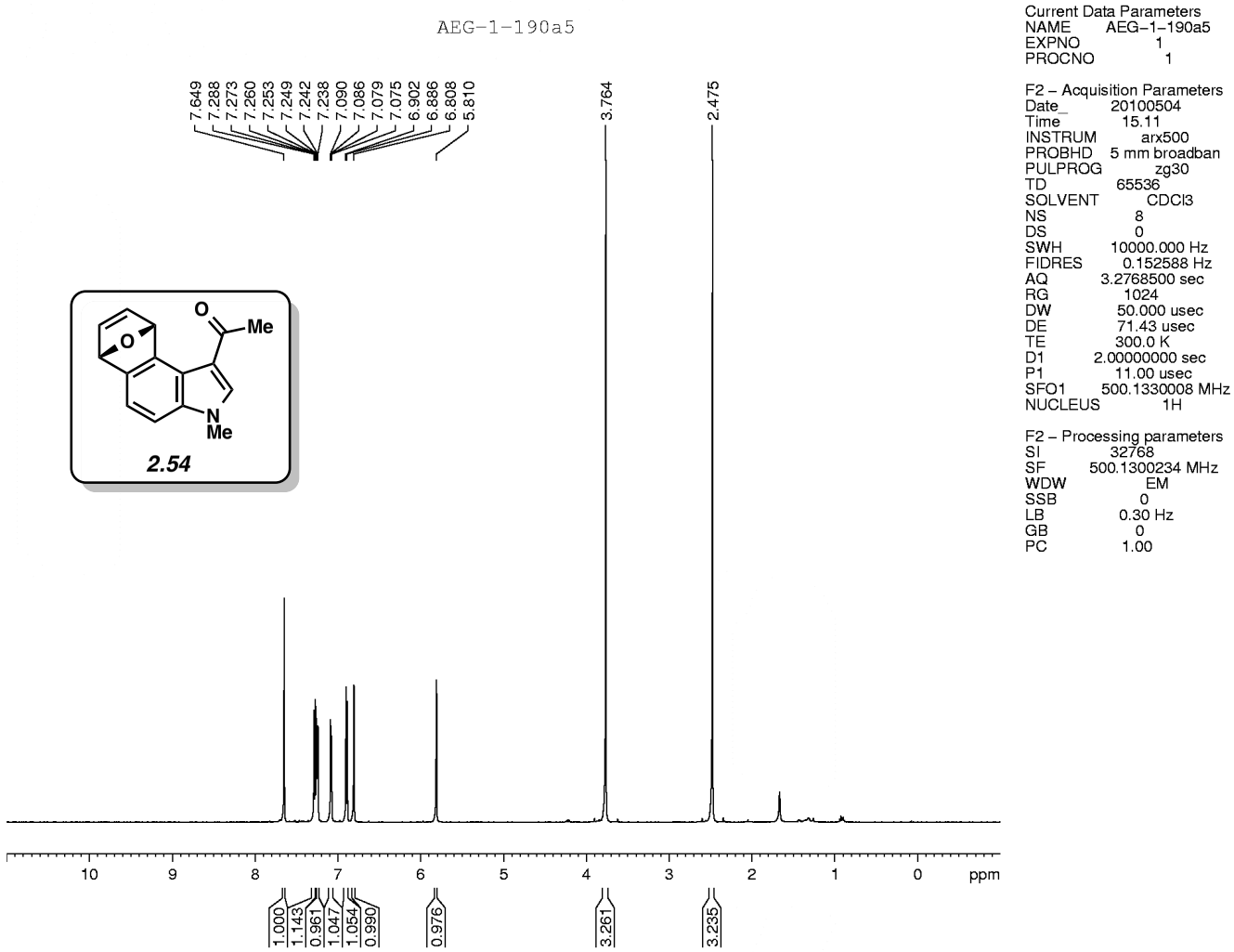



*Figure A1.76* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **2.54**.

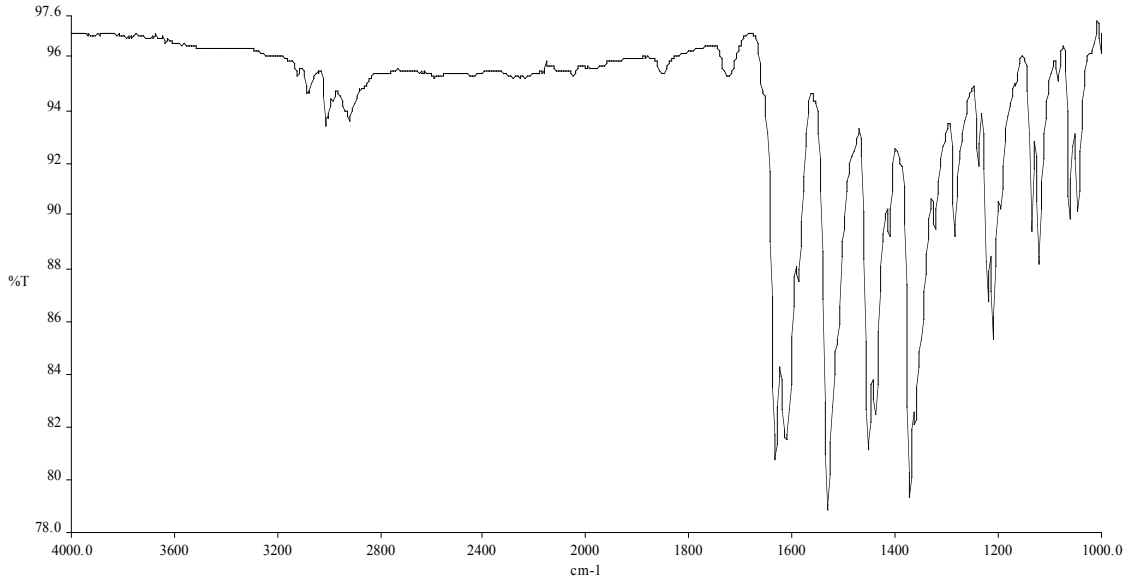



*Figure A1.77* Infrared spectrum of compound **2.54**.

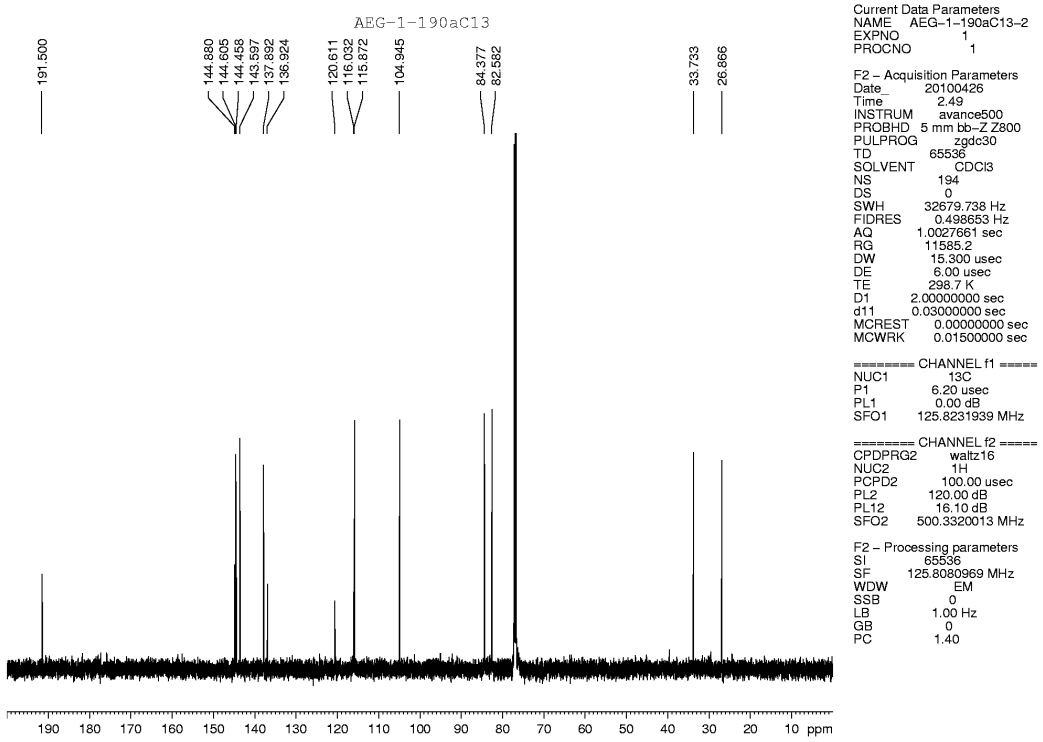



*Figure A1.78* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compound **2.54**.

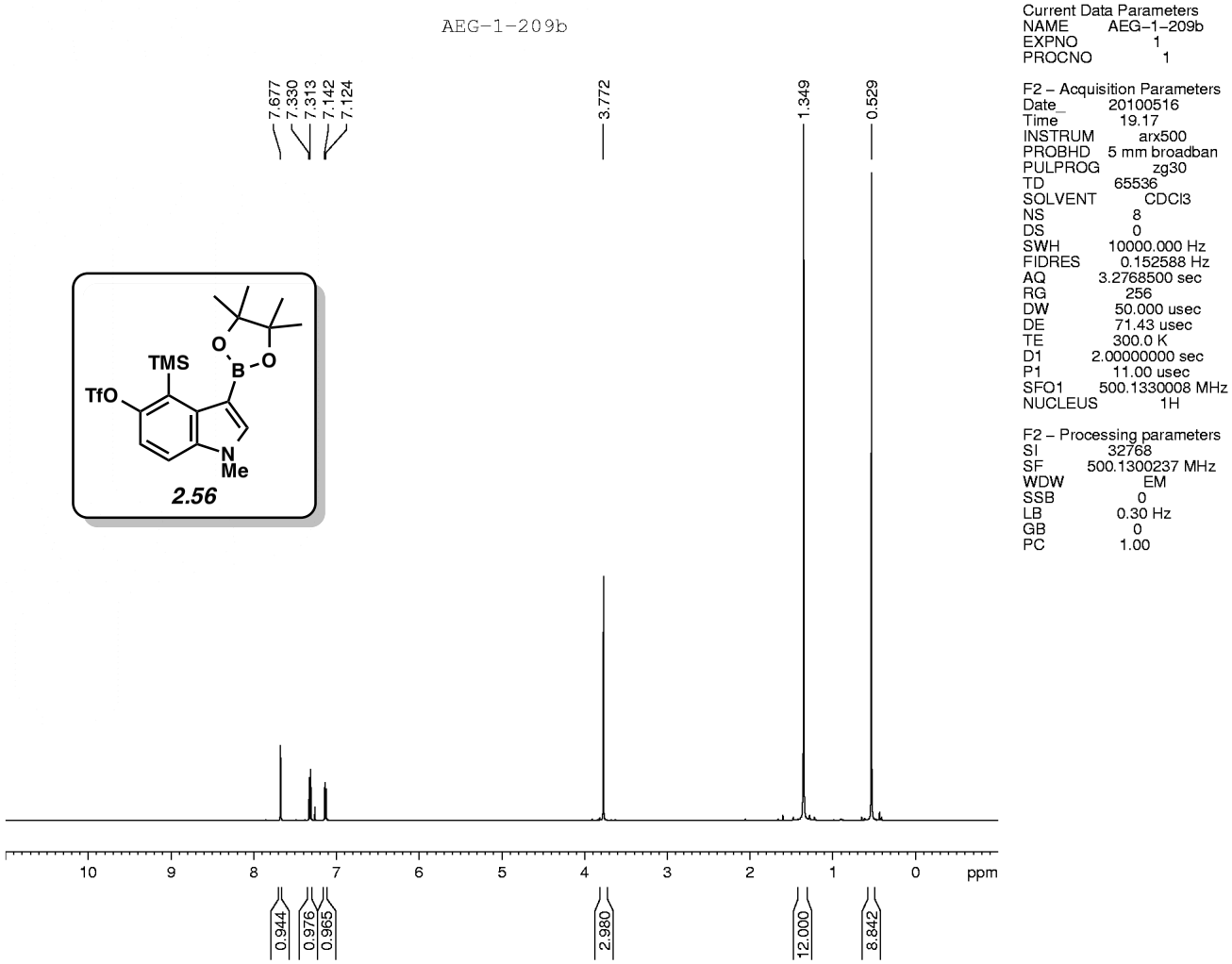



*Figure A1.79* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **2.56**.

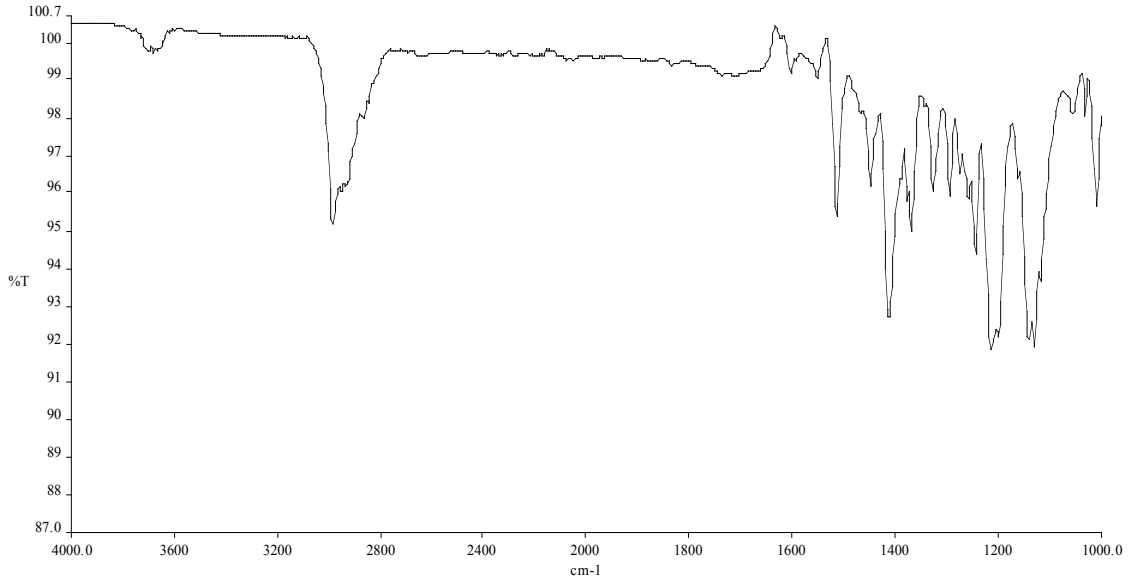



*Figure A1.80* Infrared spectrum of compound **2.56**.

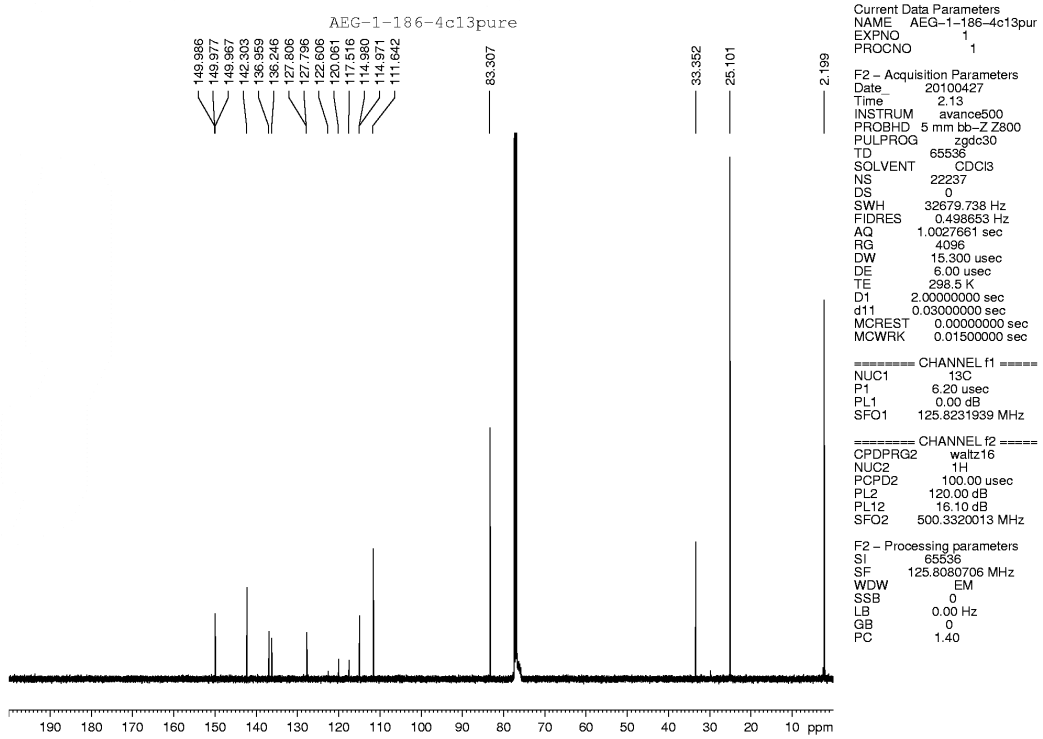



*Figure A1.81* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compound **2.56**.

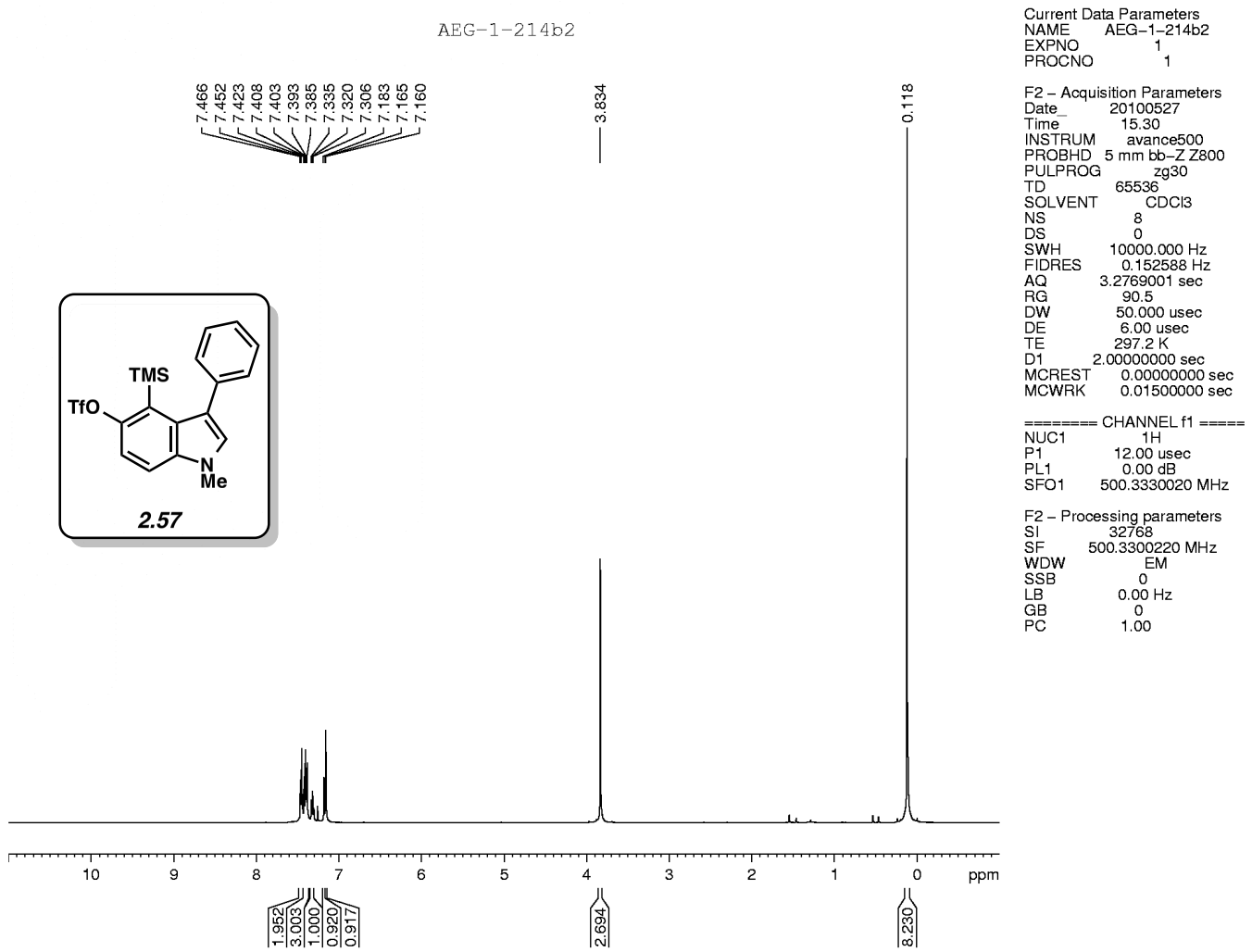



*Figure A1.82* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **2.57**.

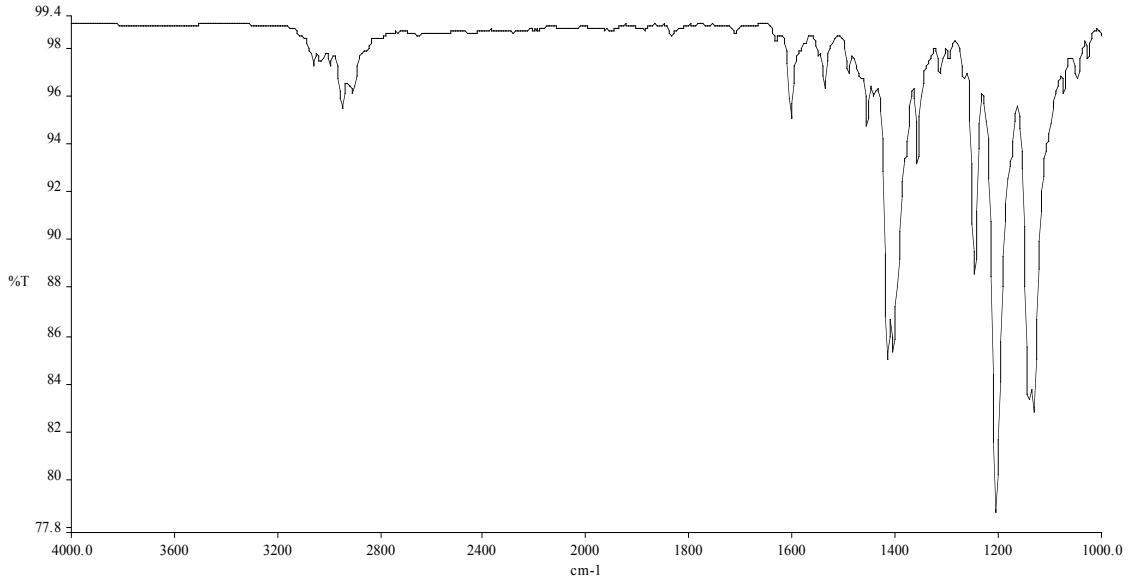



*Figure A1.83* Infrared spectrum of compound **2.57**.

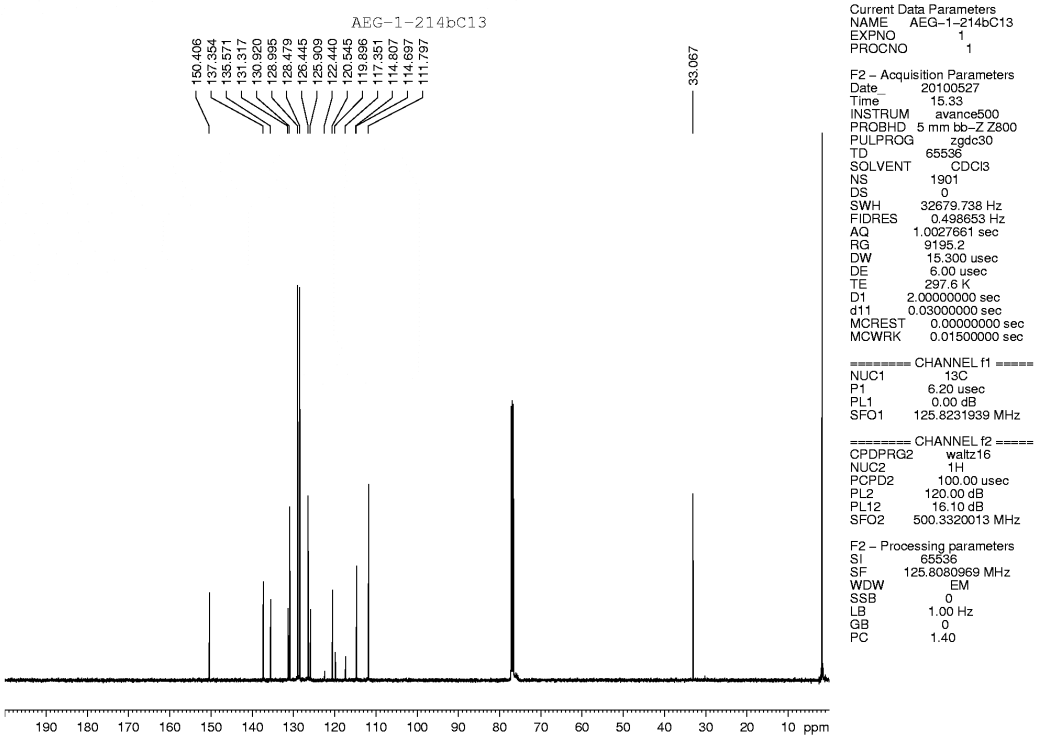



*Figure A1.84* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compound **2.57**.

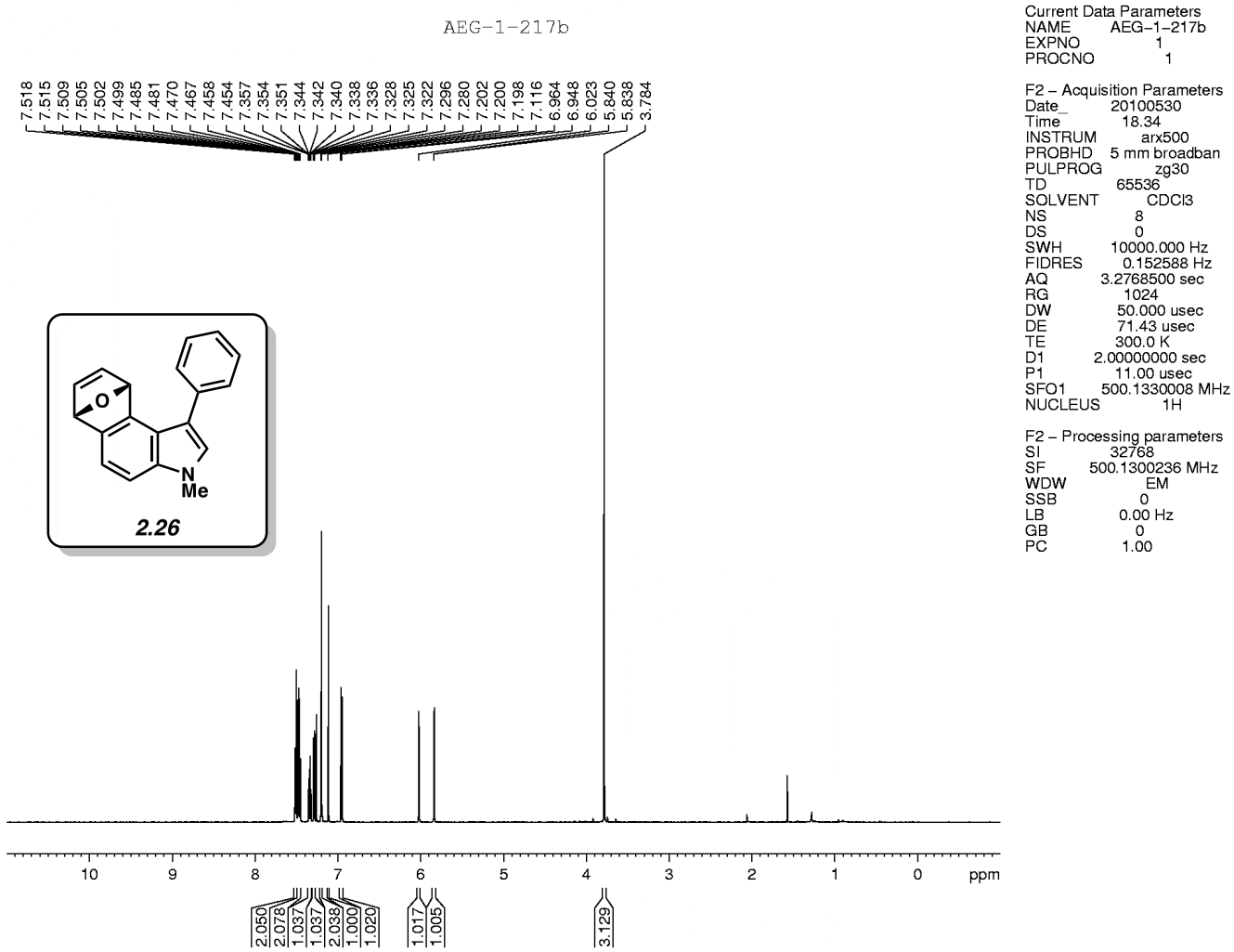



*Figure A1.85* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **2.26**.

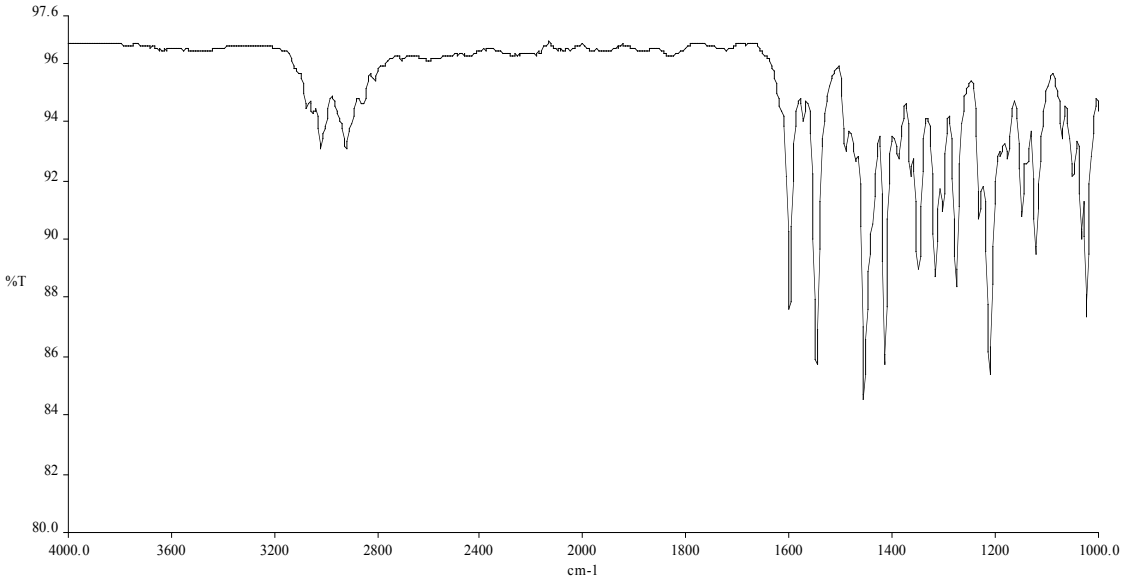



*Figure A1.86* Infrared spectrum of compound **2.26**.

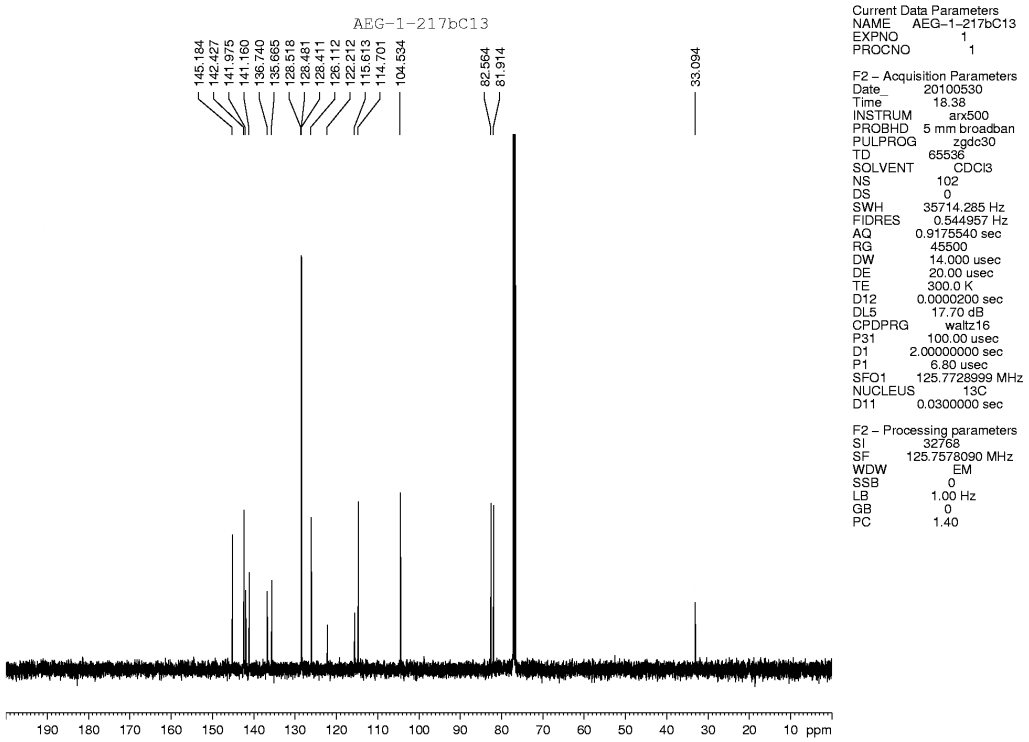



*Figure A1.87* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compound **2.26**.

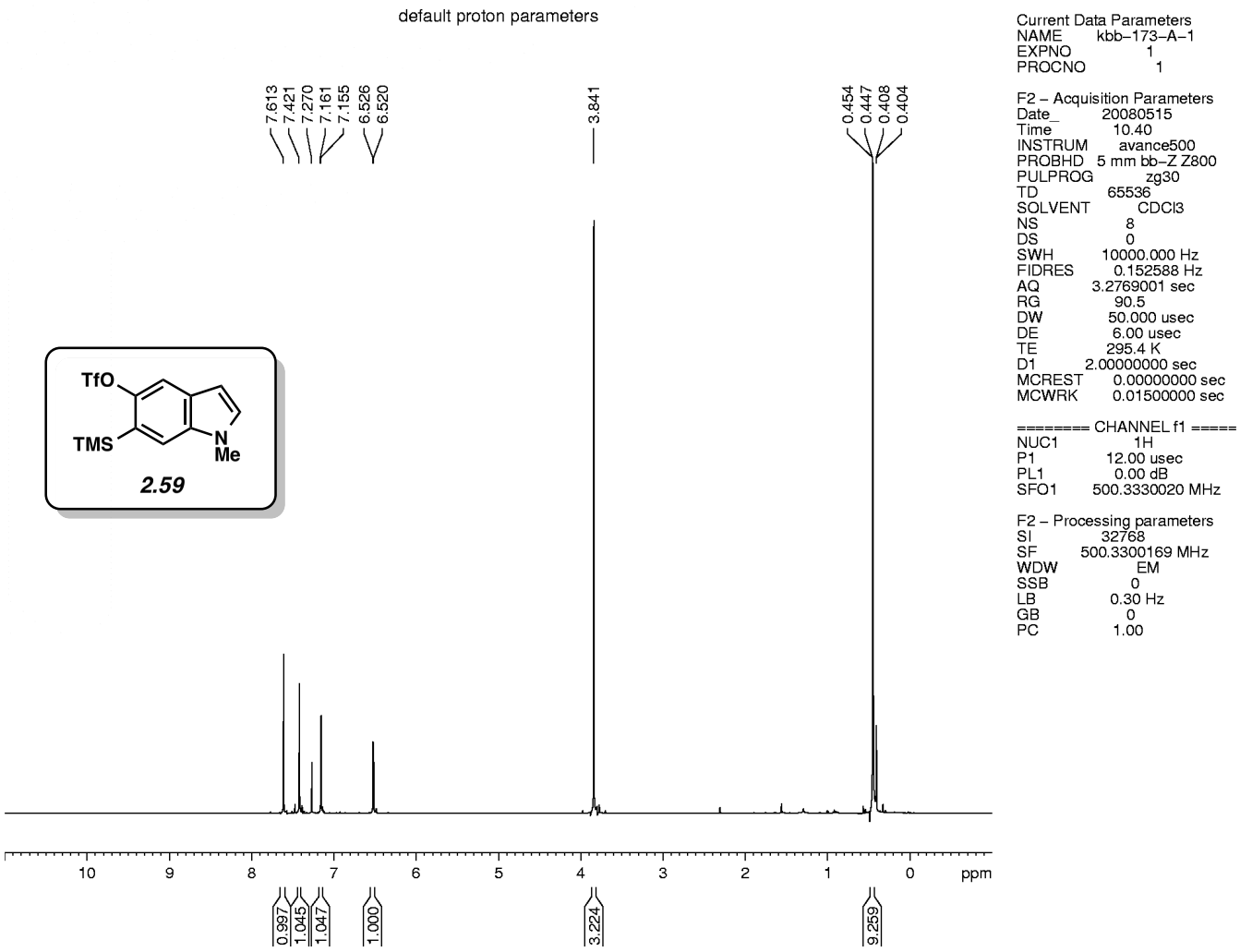



*Figure A1.88* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **2.59**.

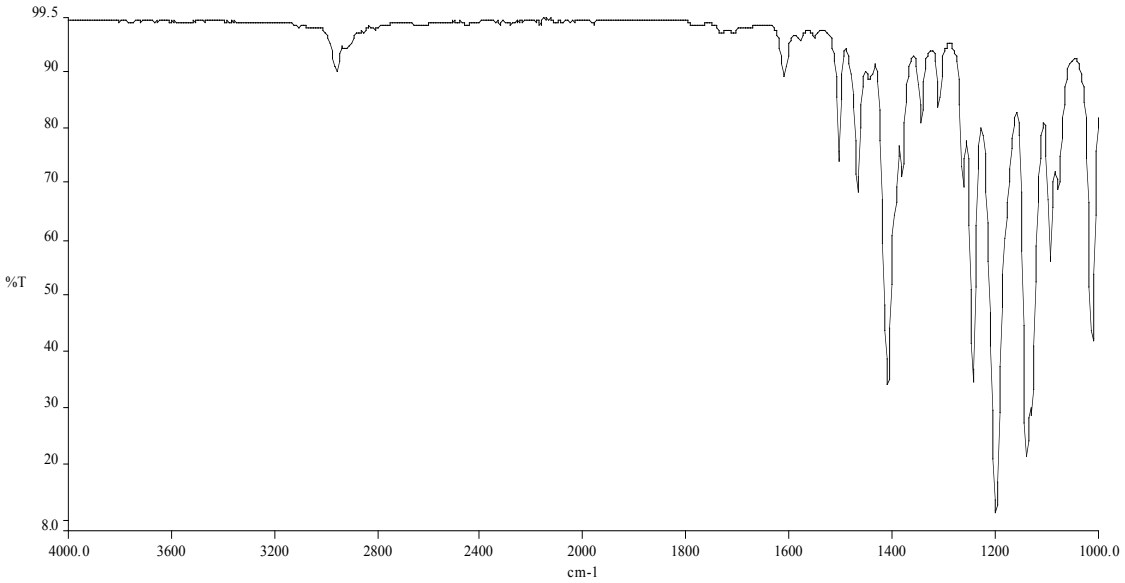



*Figure A1.89* Infrared spectrum of compound **2.59**.

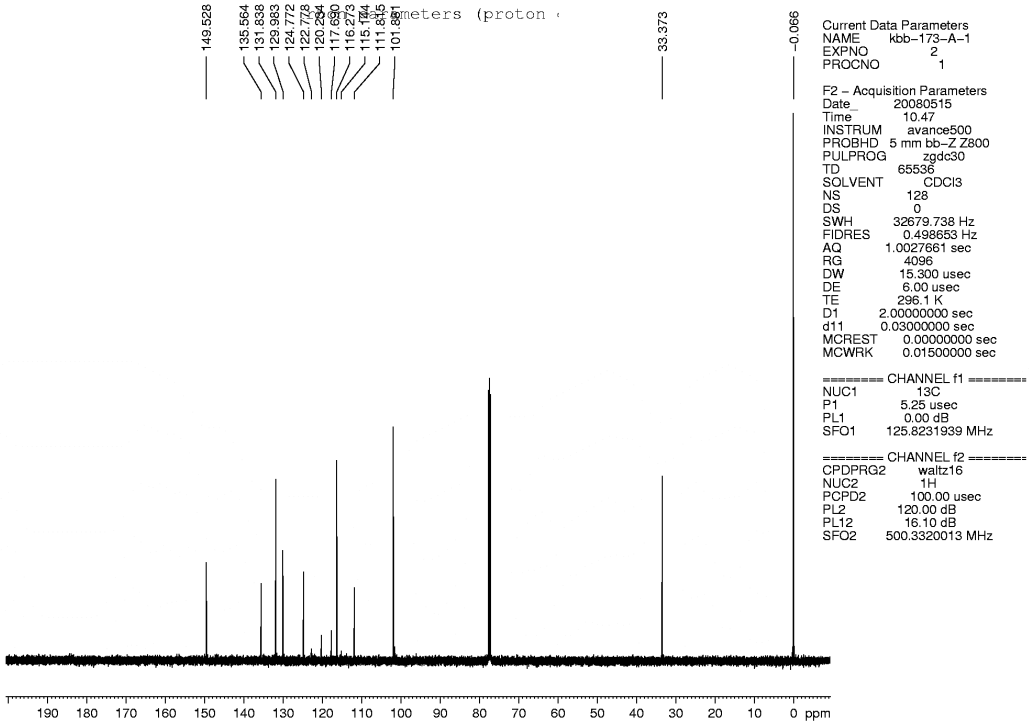



*Figure A1.90* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compound **2.59**.

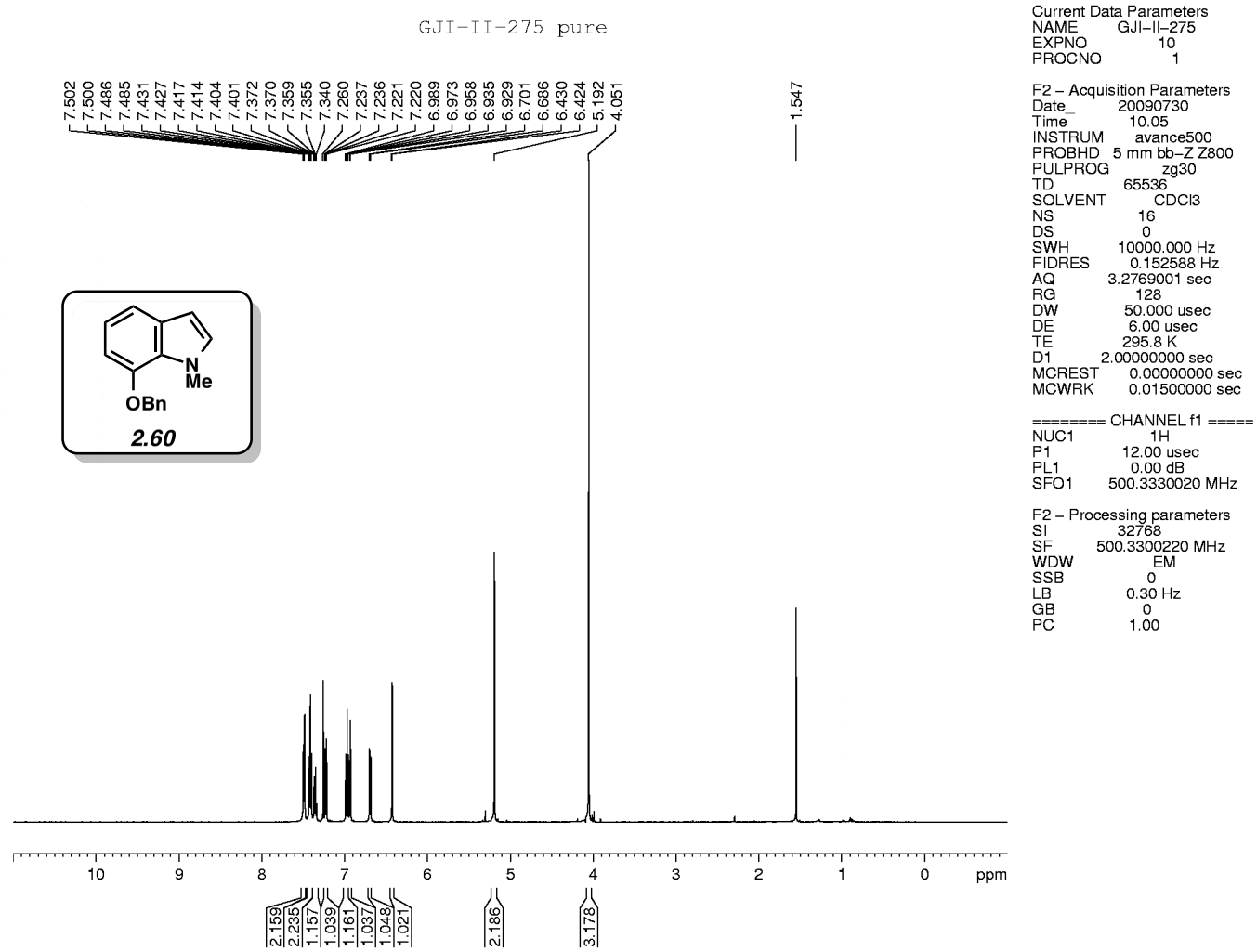



*Figure A1.91* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **2.60**.

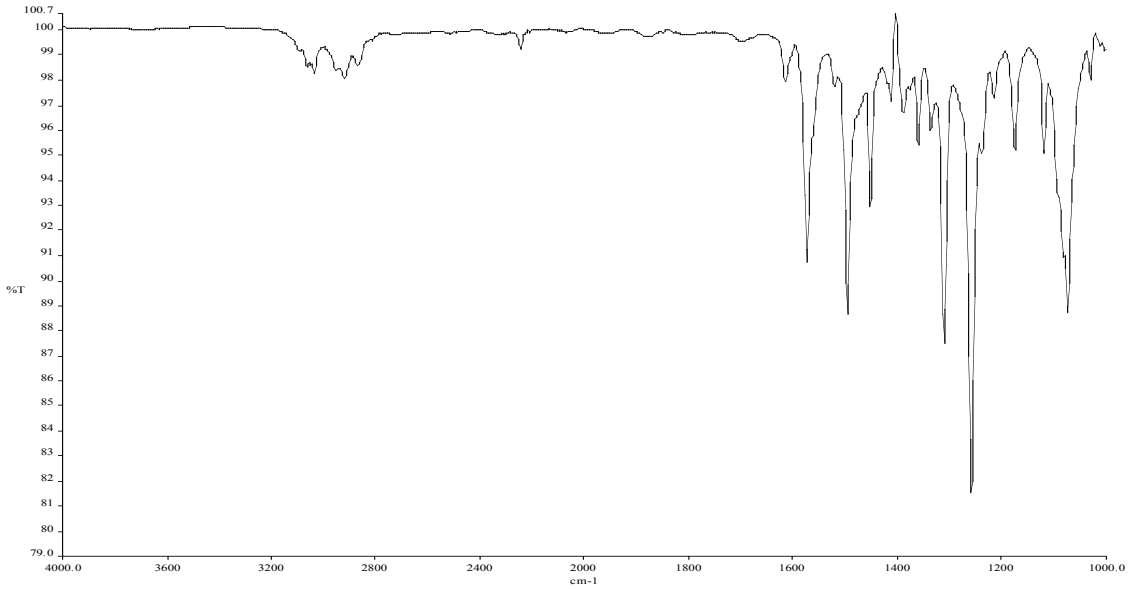



*Figure A1.92* Infrared spectrum of compound **2.60**.

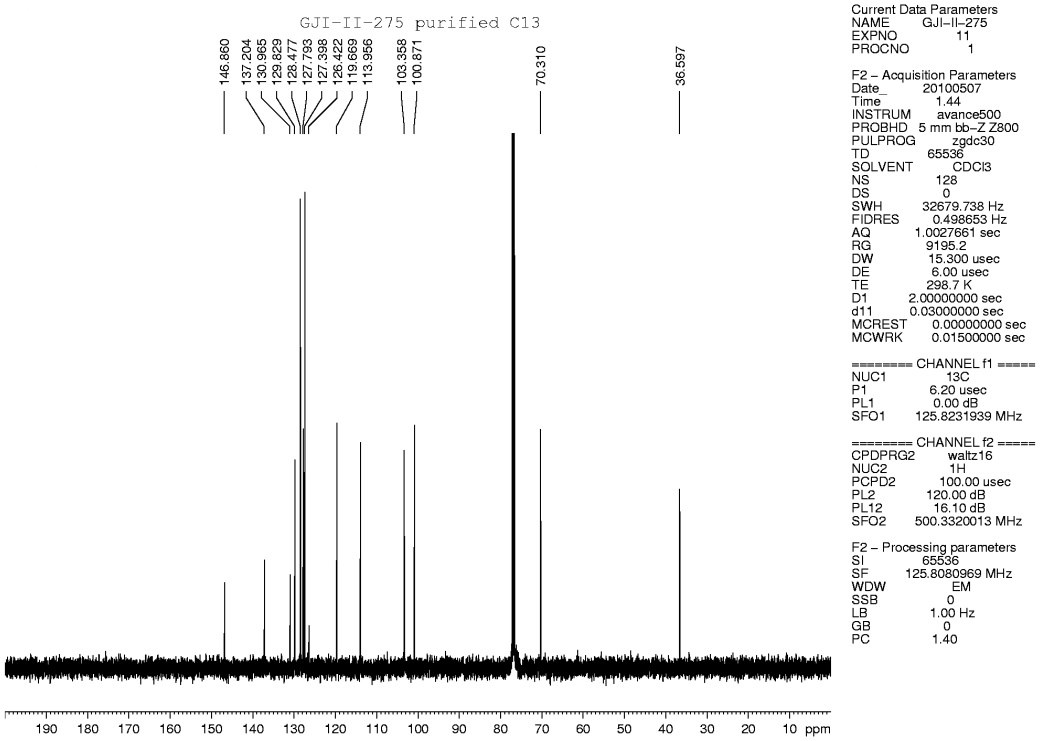



*Figure A1.93* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compound **2.60**.

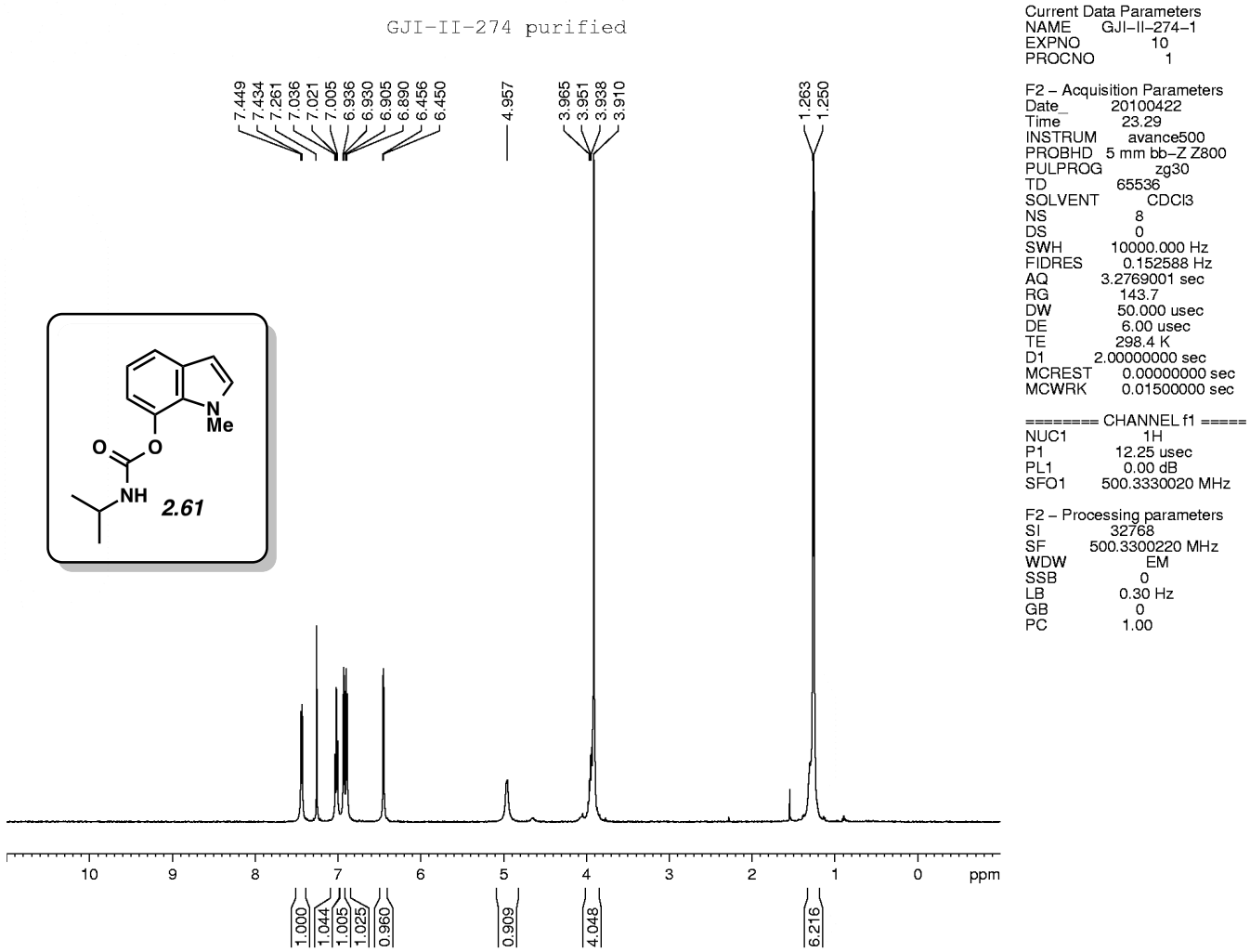



*Figure A1.94* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **2.61**.

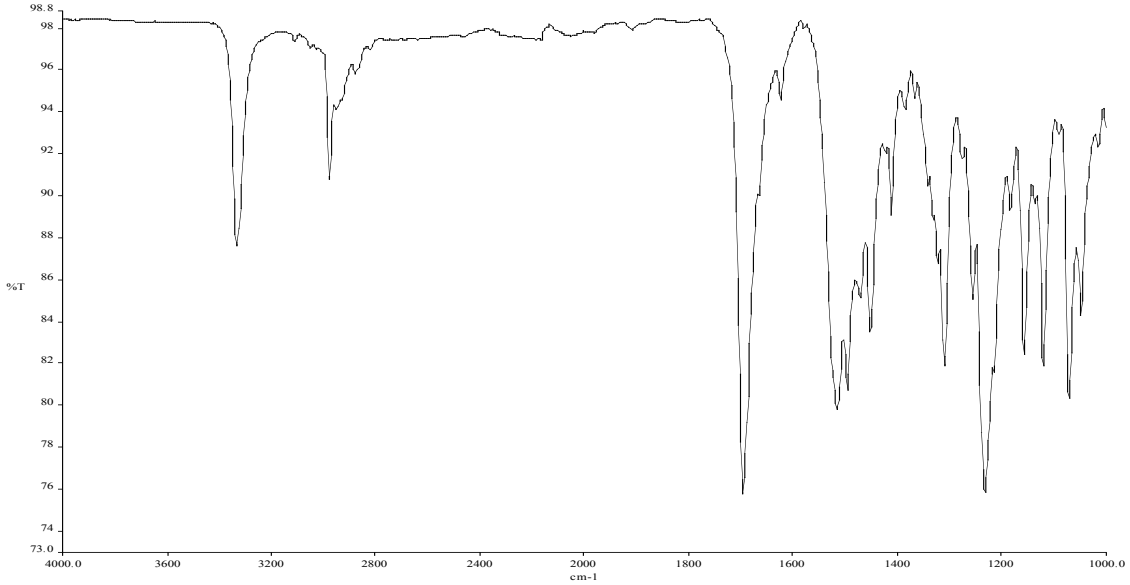



*Figure A1.95* Infrared spectrum of compound **2.61**.

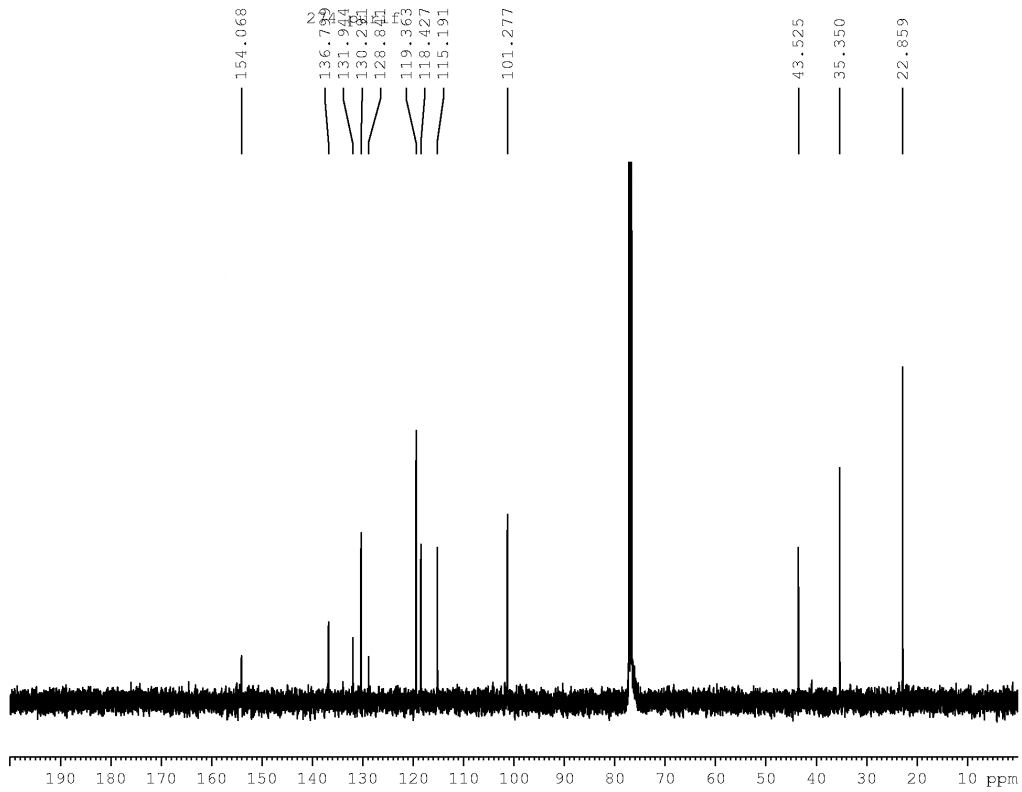



*Figure A1.96* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compound **2.61**.

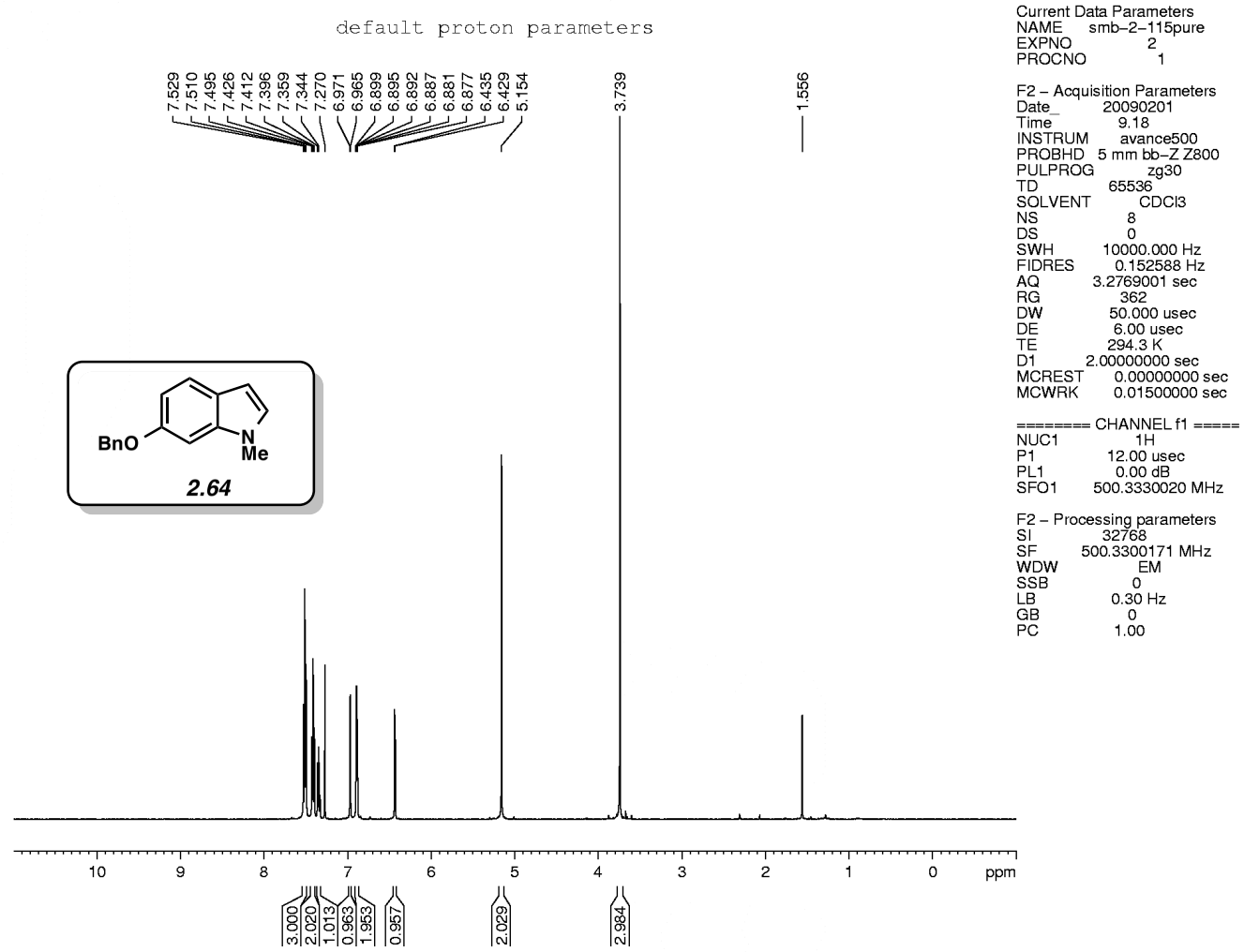



*Figure A1.97* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **2.64**.

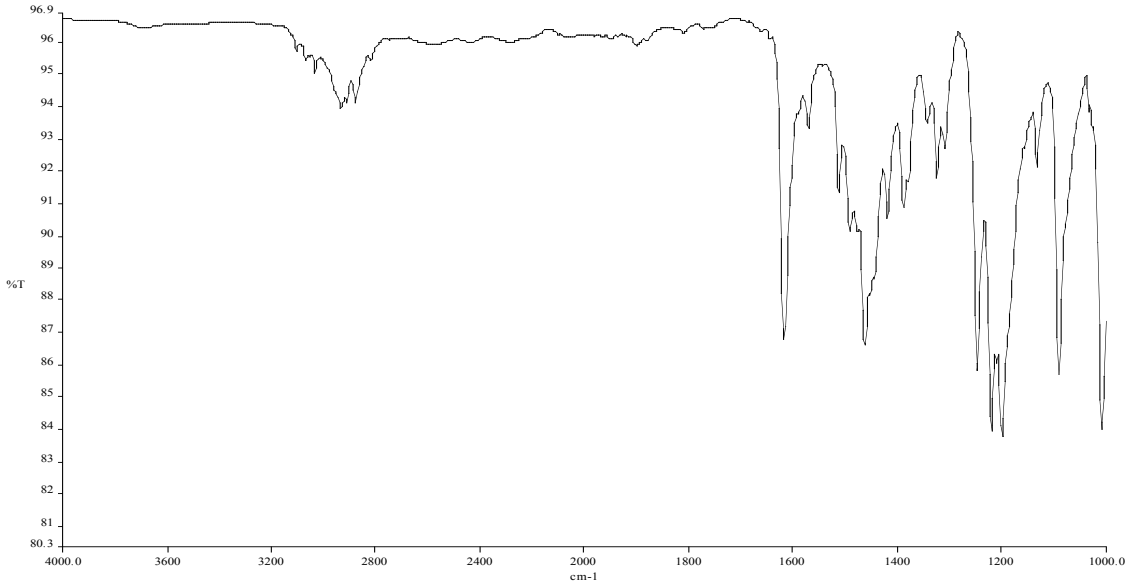



*Figure A1.98* Infrared spectrum of compound **2.64**.

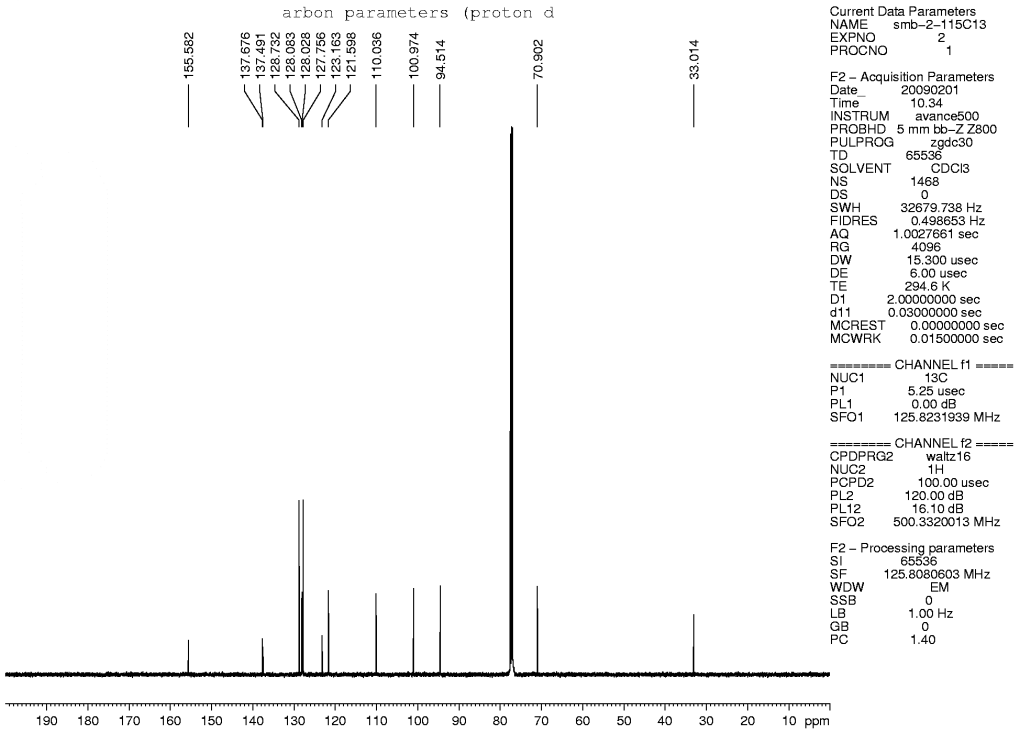



*Figure A1.99* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compound **2.64**.

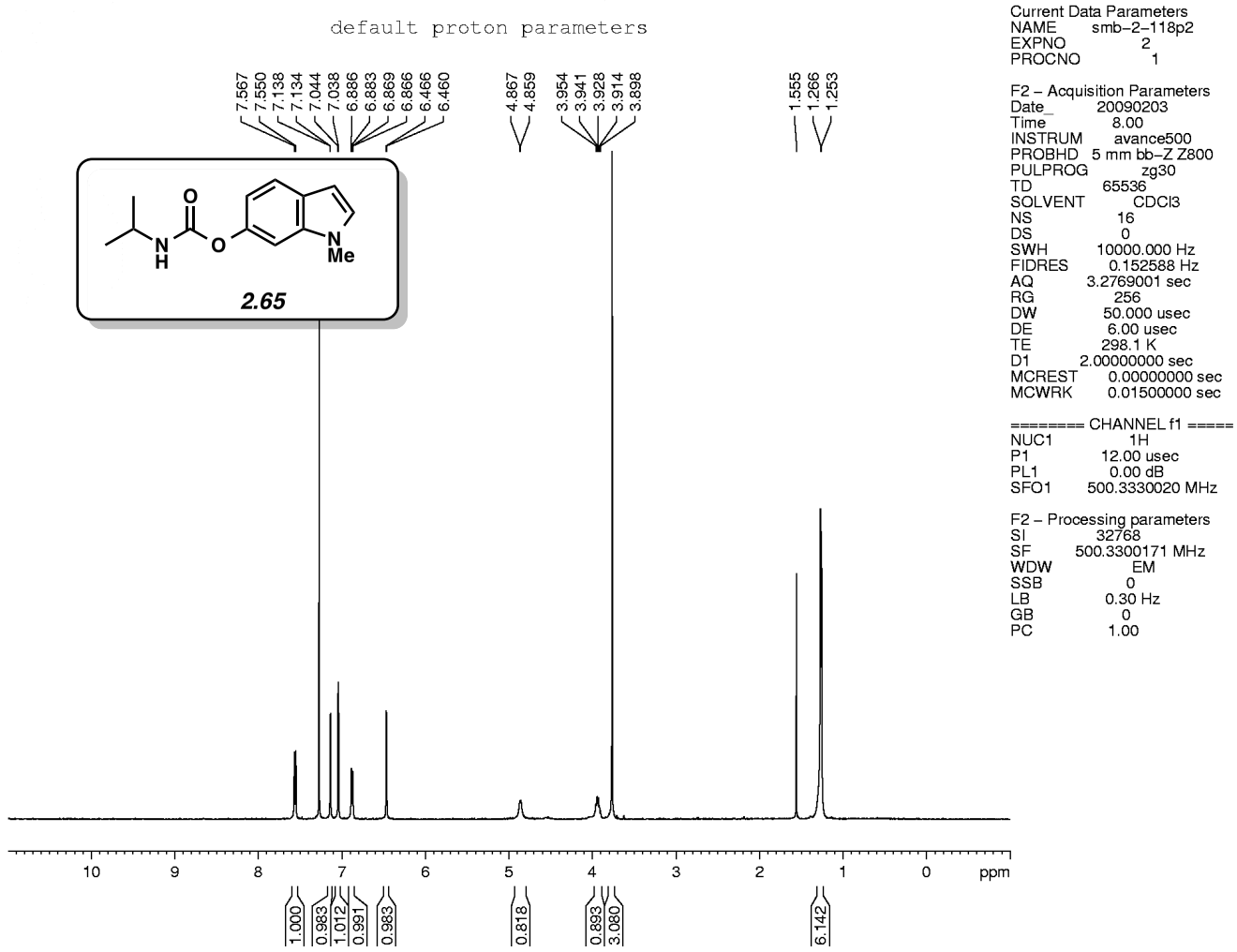



*Figure A1.100* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **2.65**.

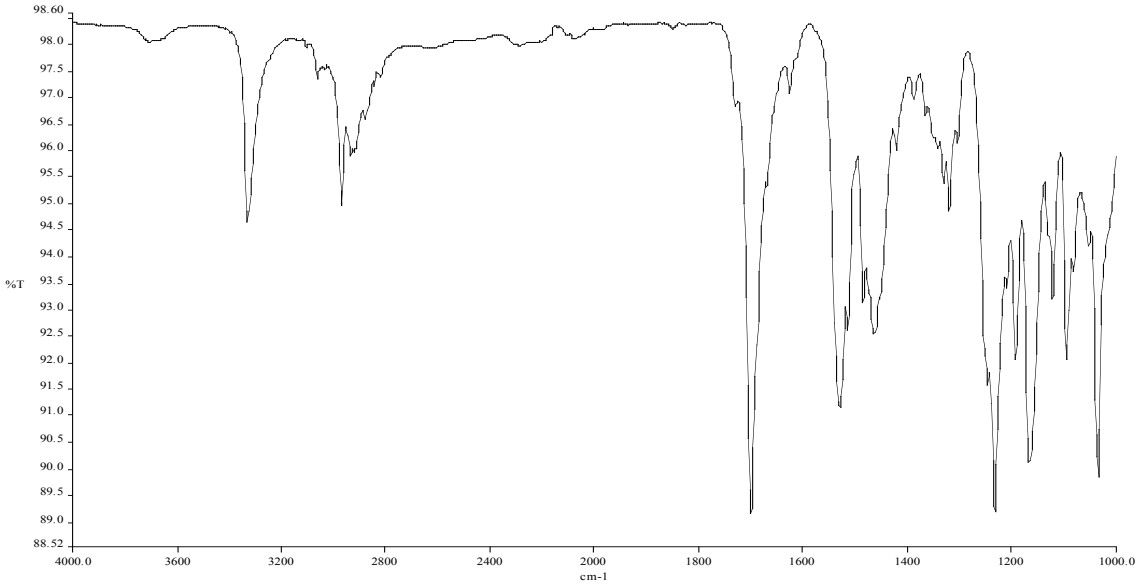



*Figure A1.101* Infrared spectrum of compound **2.65**.

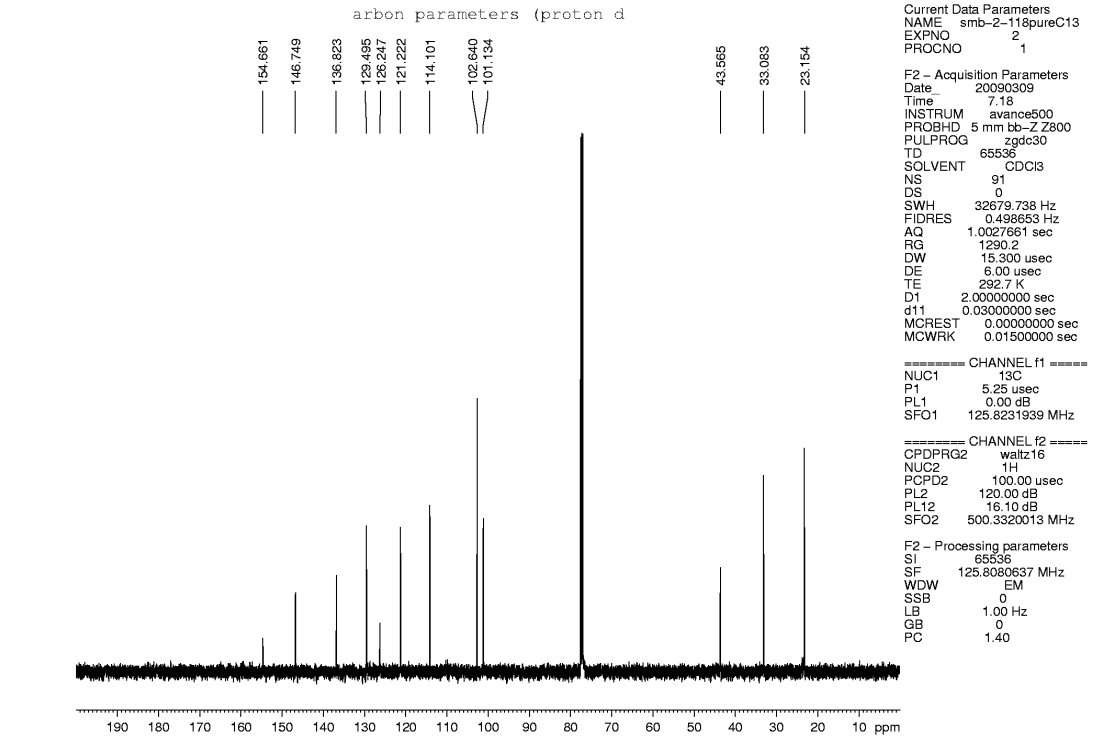



*Figure A1.102* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compound **2.65**.

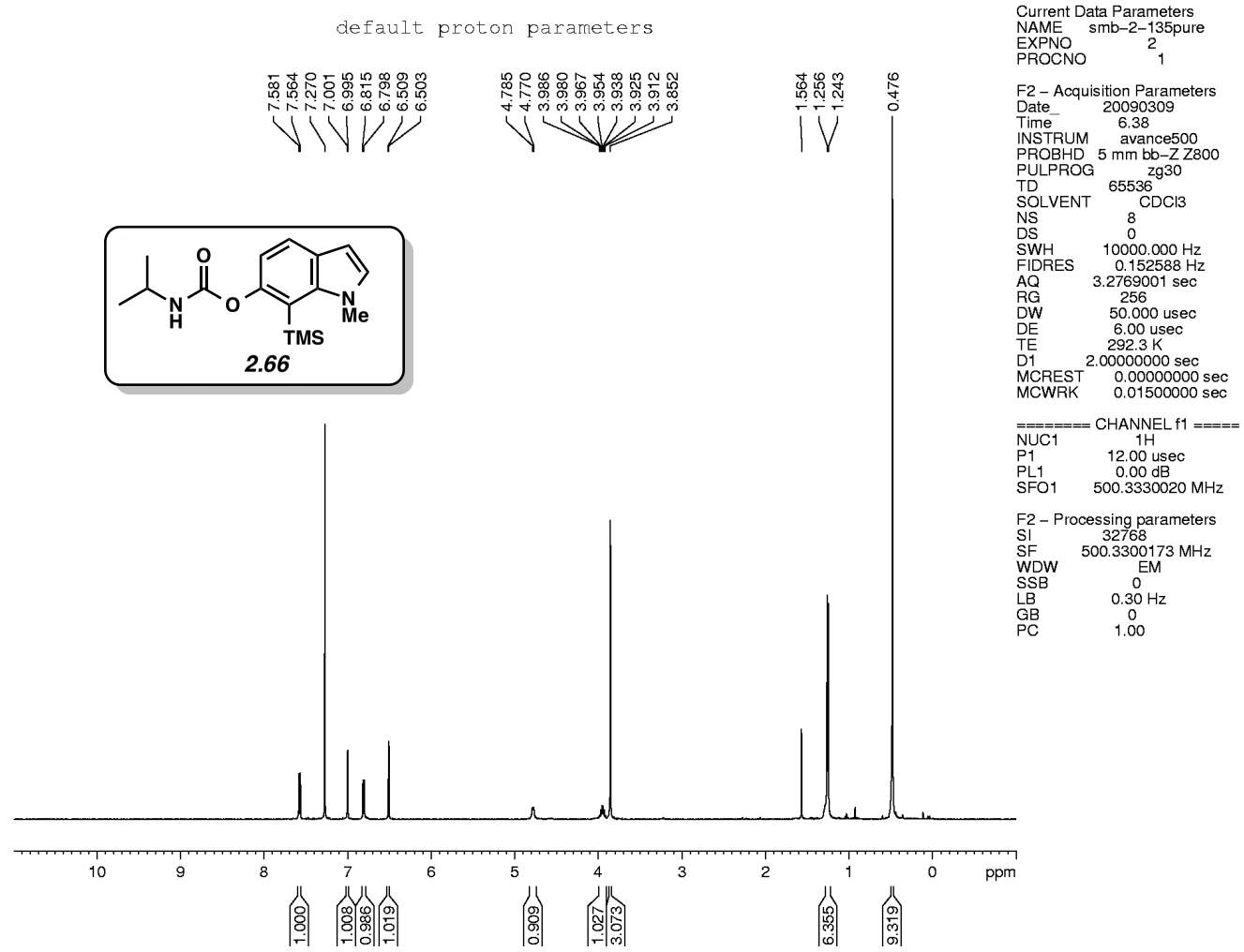



*Figure A1.103* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **2.66**.

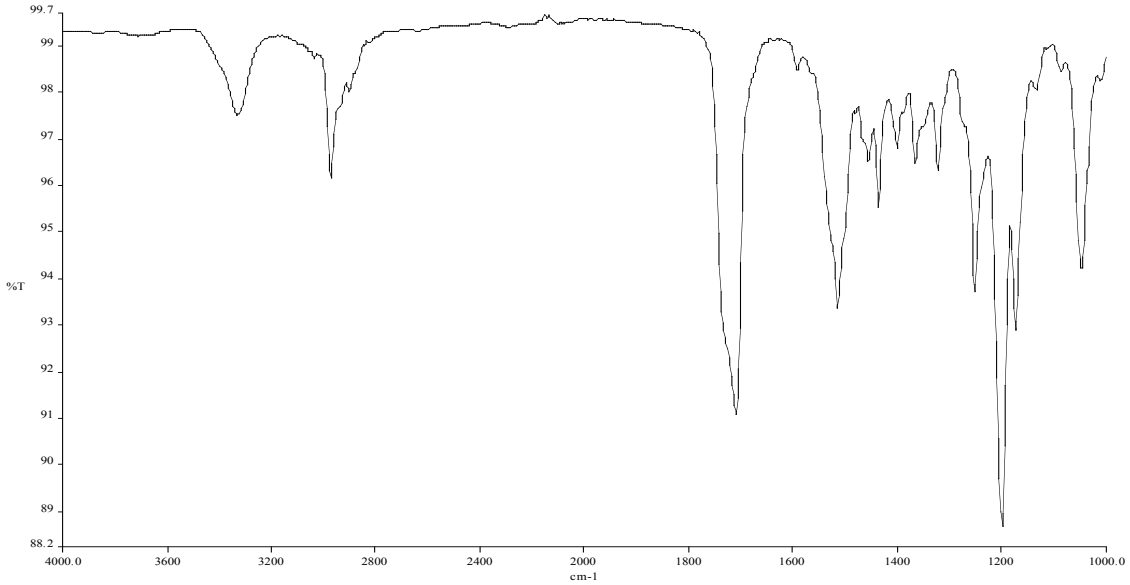



*Figure A1.104* Infrared spectrum of compound **2.66**.

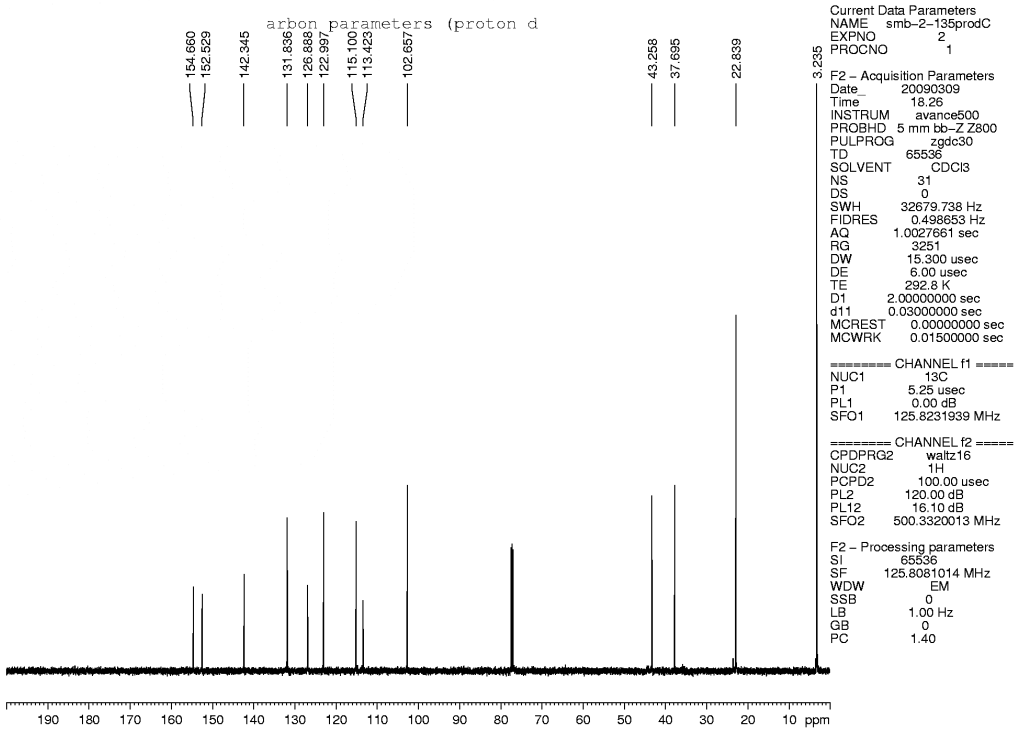



*Figure A1.105* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compound **2.66**.

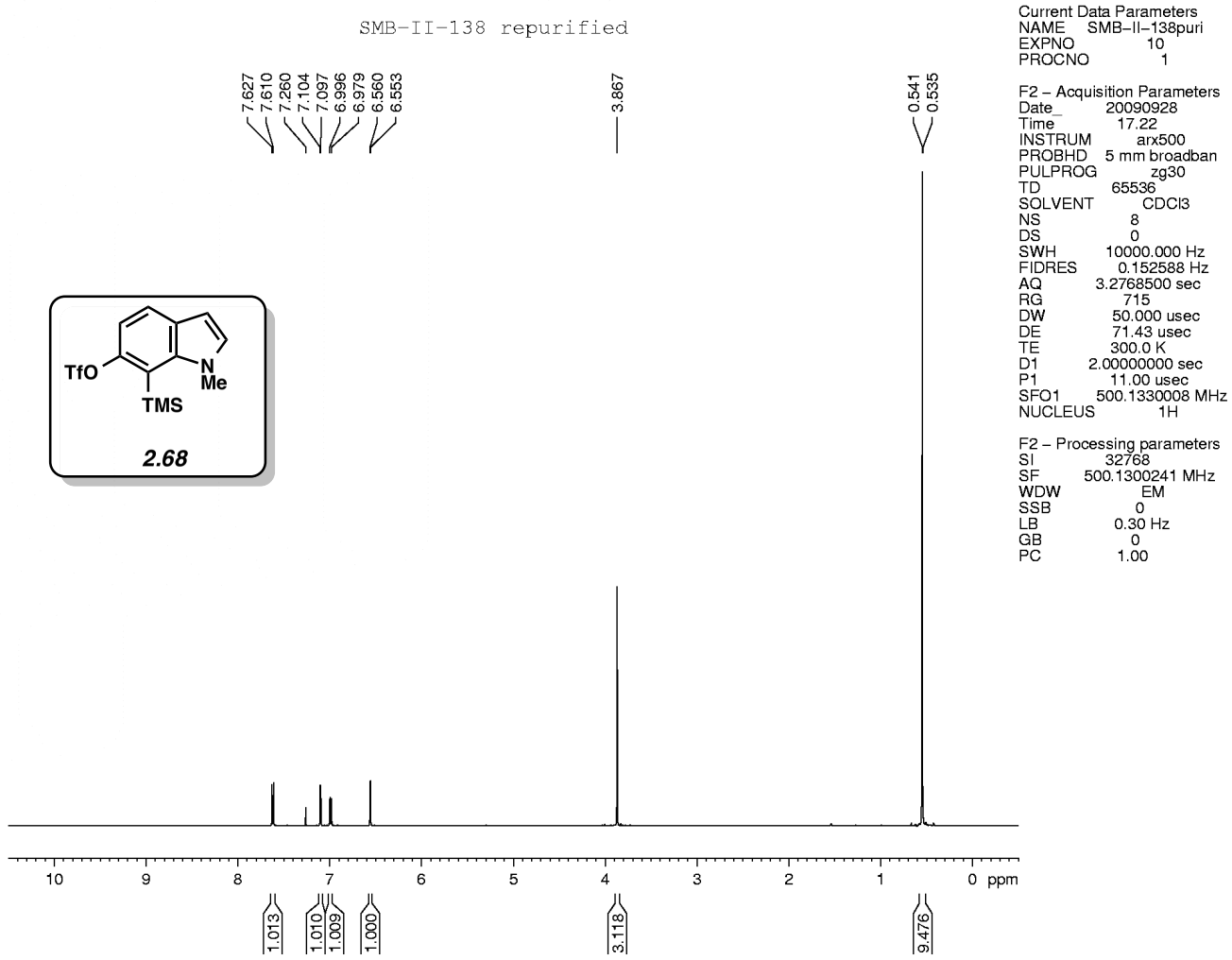



*Figure A1.106* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **2.68**.

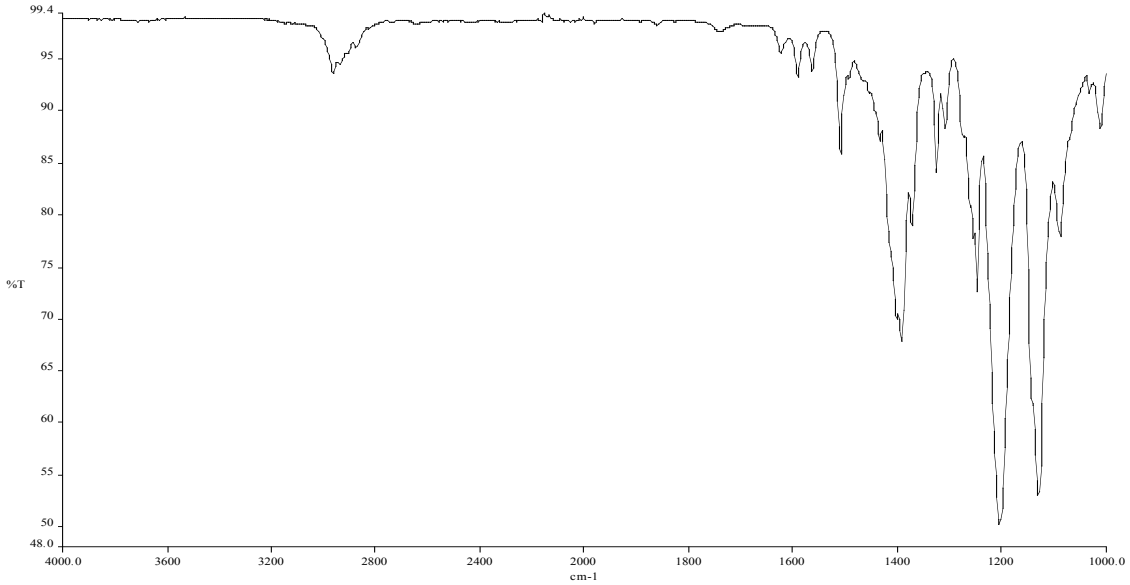



*Figure A1.107* Infrared spectrum of compound **2.68**.

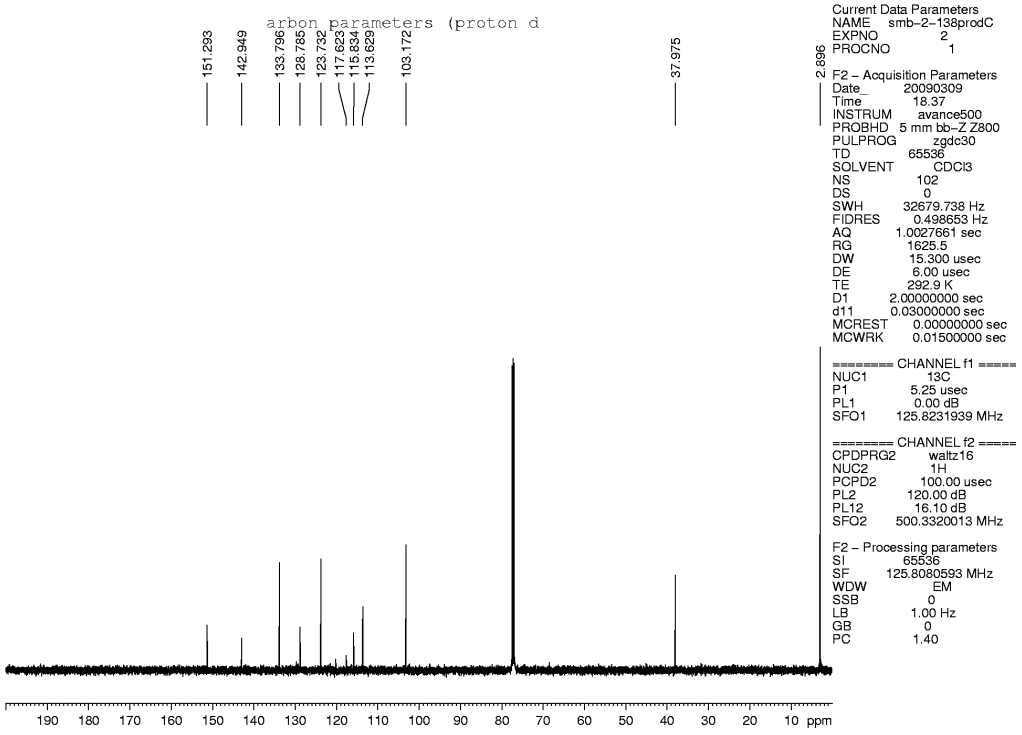



*Figure A1.108* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compound **2.68**.

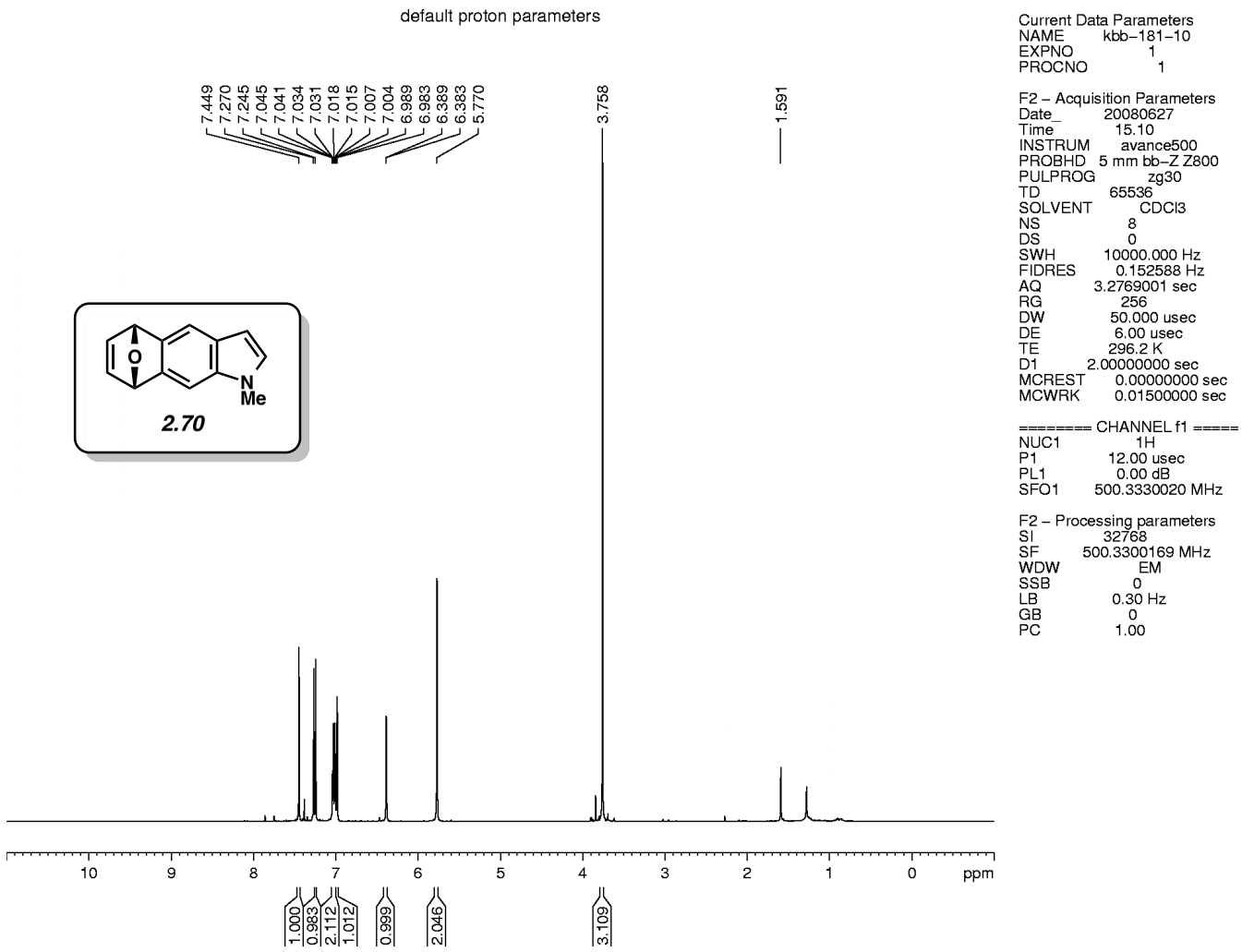



*Figure A1.109* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **2.70**.

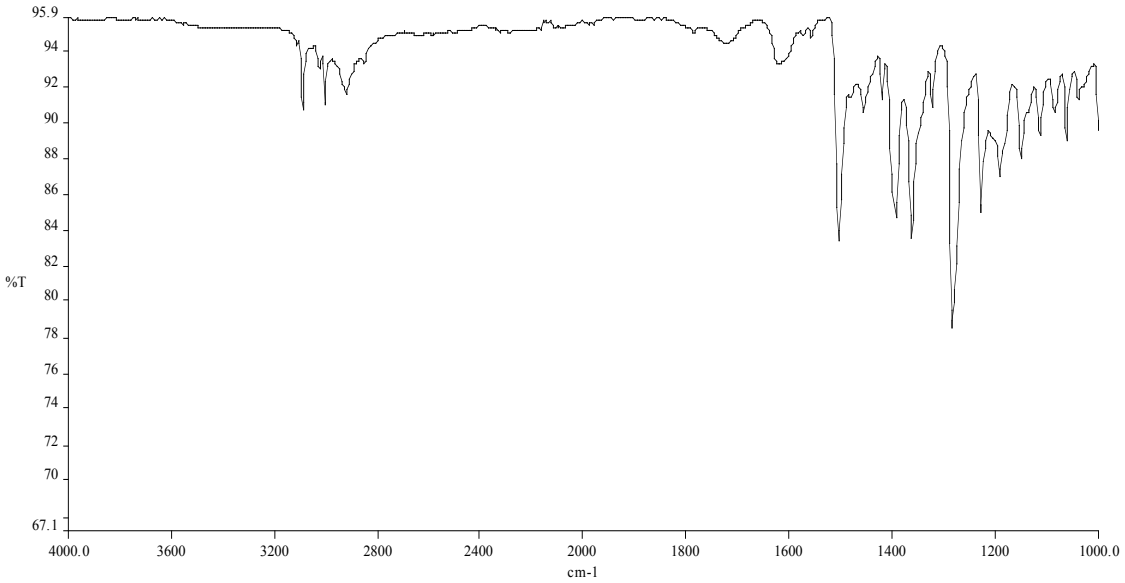



*Figure A1.110* Infrared spectrum of compound **2.70**.

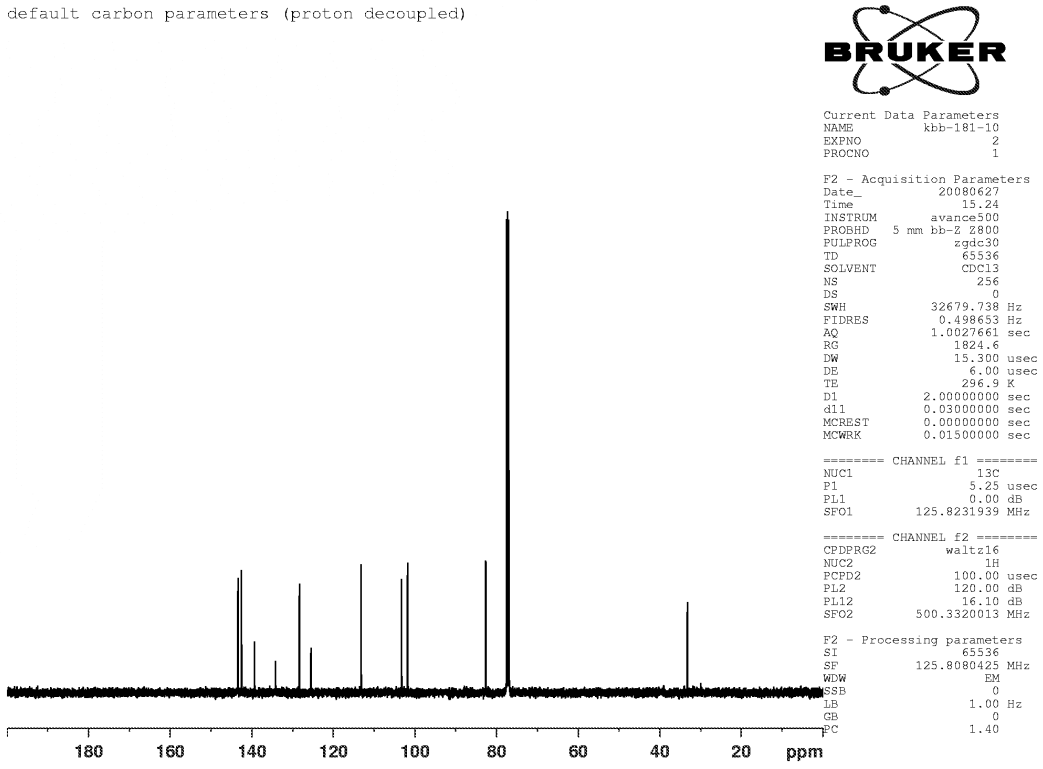



*Figure A1.111* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compound **2.70**.

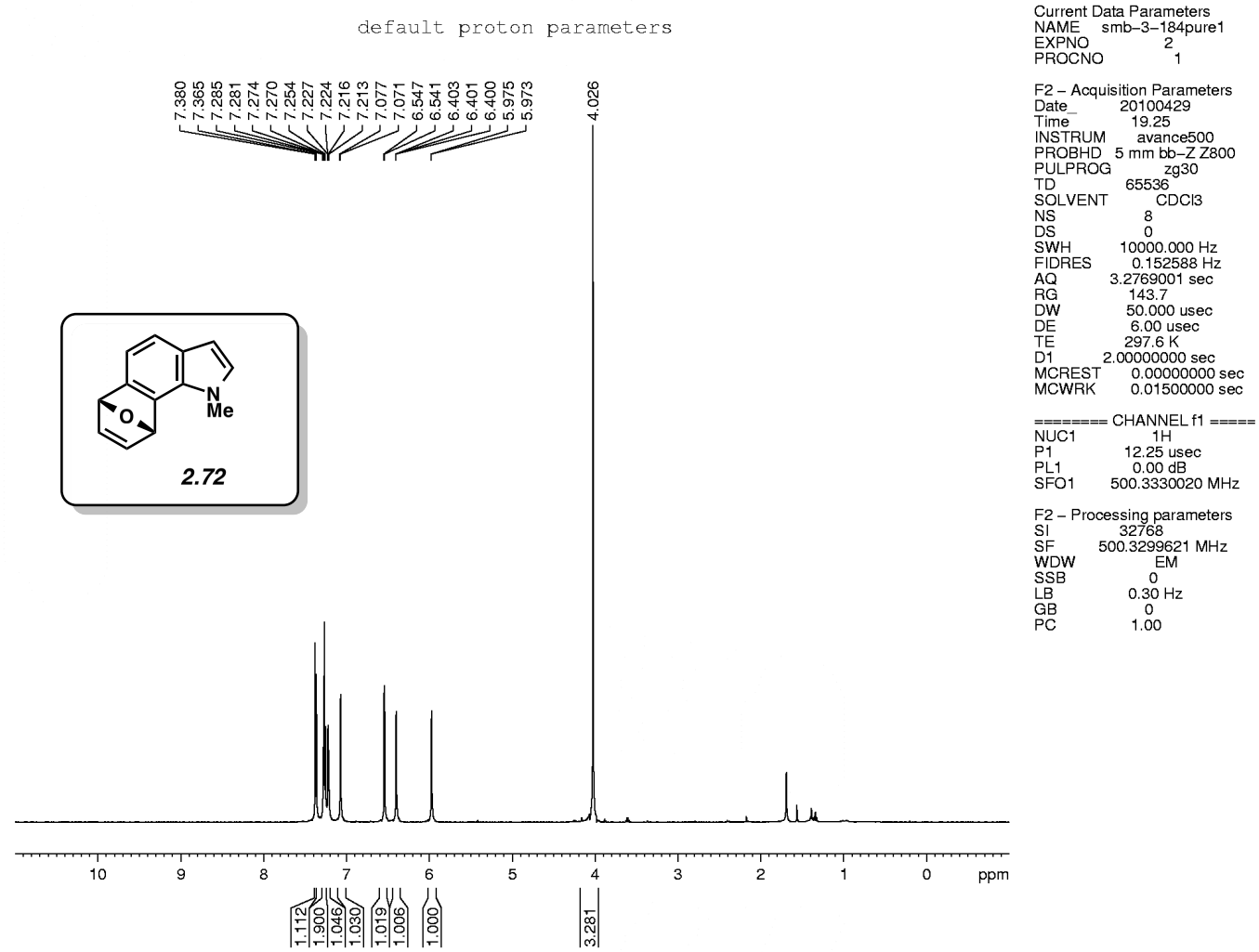



*Figure A1.112* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **2.72**.

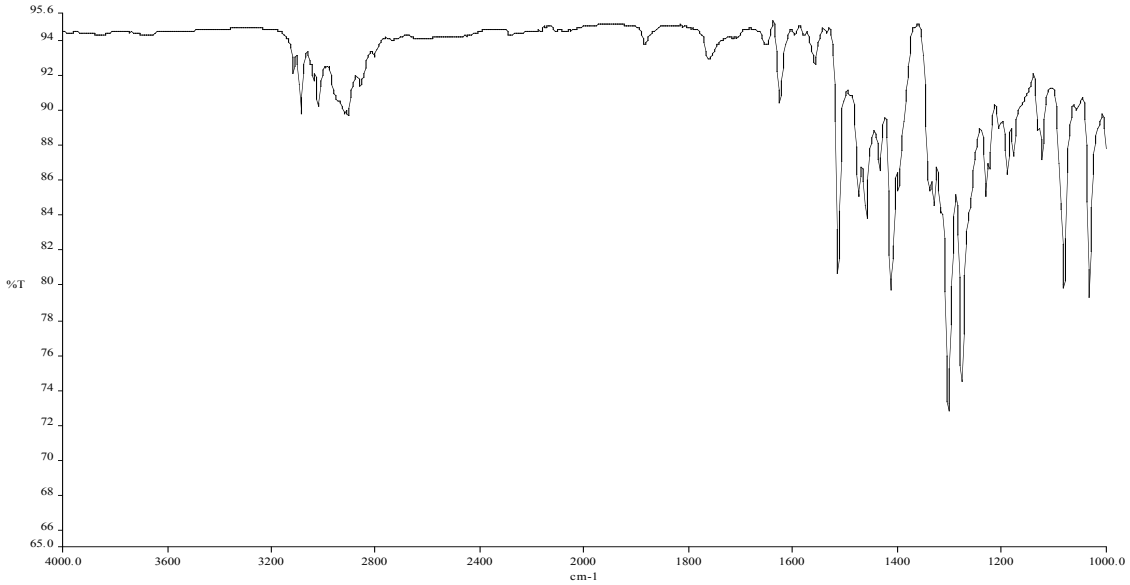



*Figure A1.113* Infrared spectrum of compound **2.72**.

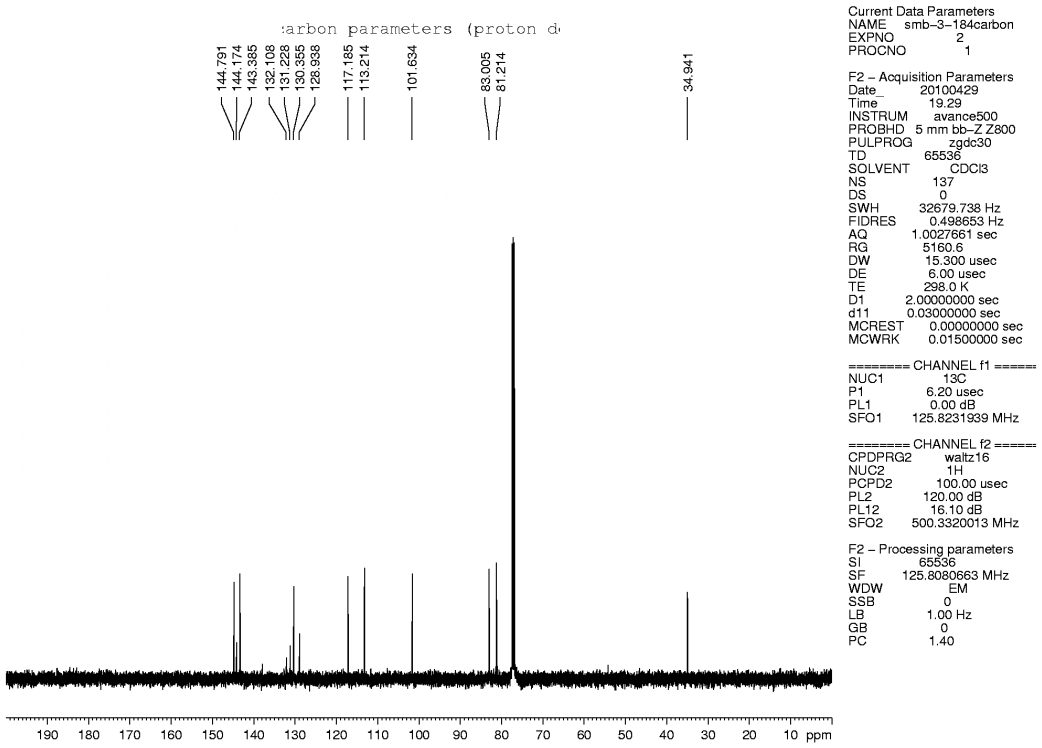



*Figure A1.114* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compound **2.72**.

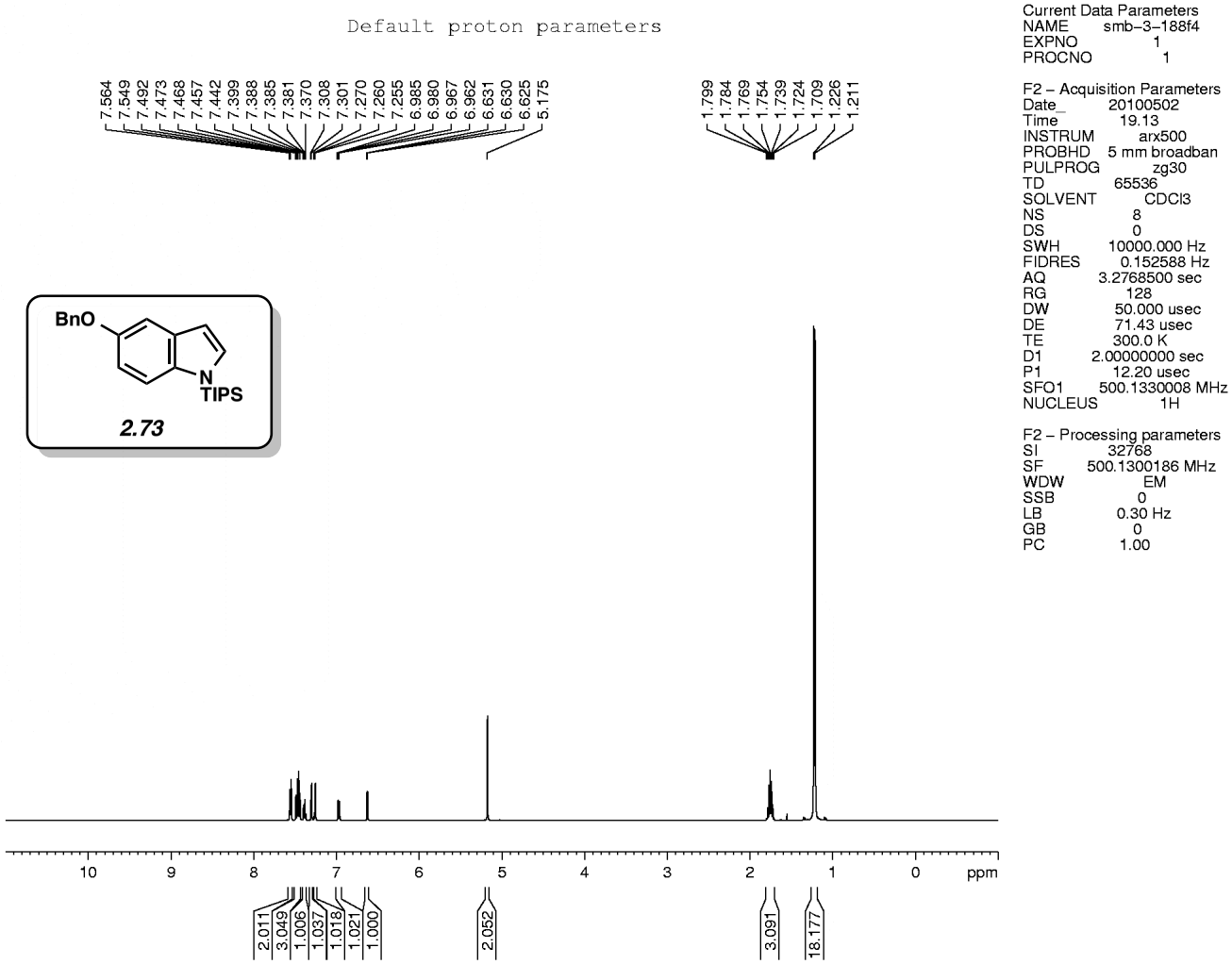



*Figure A1.115* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **2.73**.

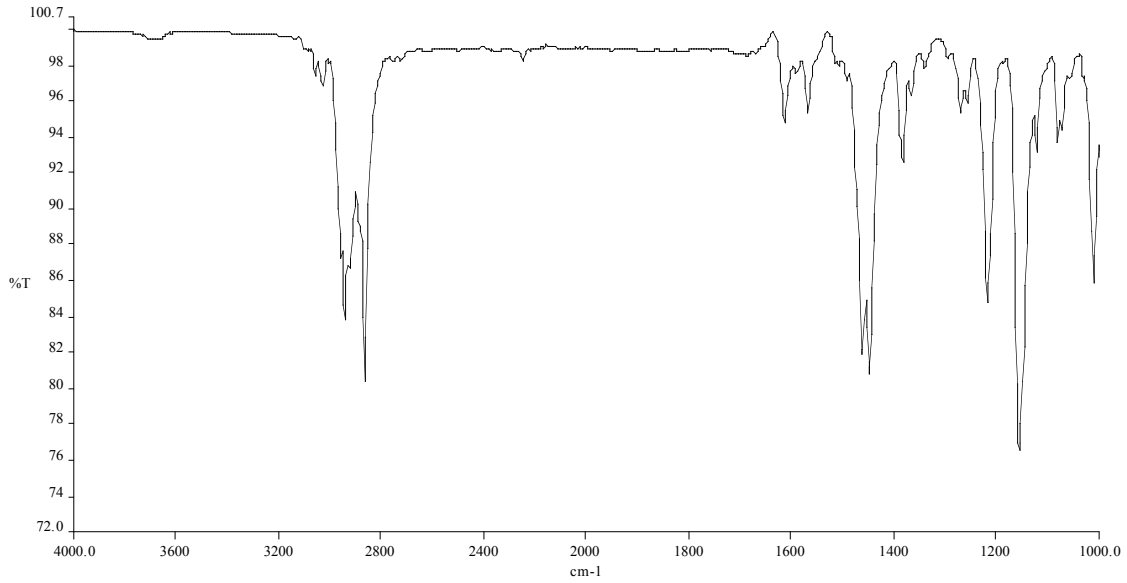



*Figure A1.116* Infrared spectrum of compound **2.73**.

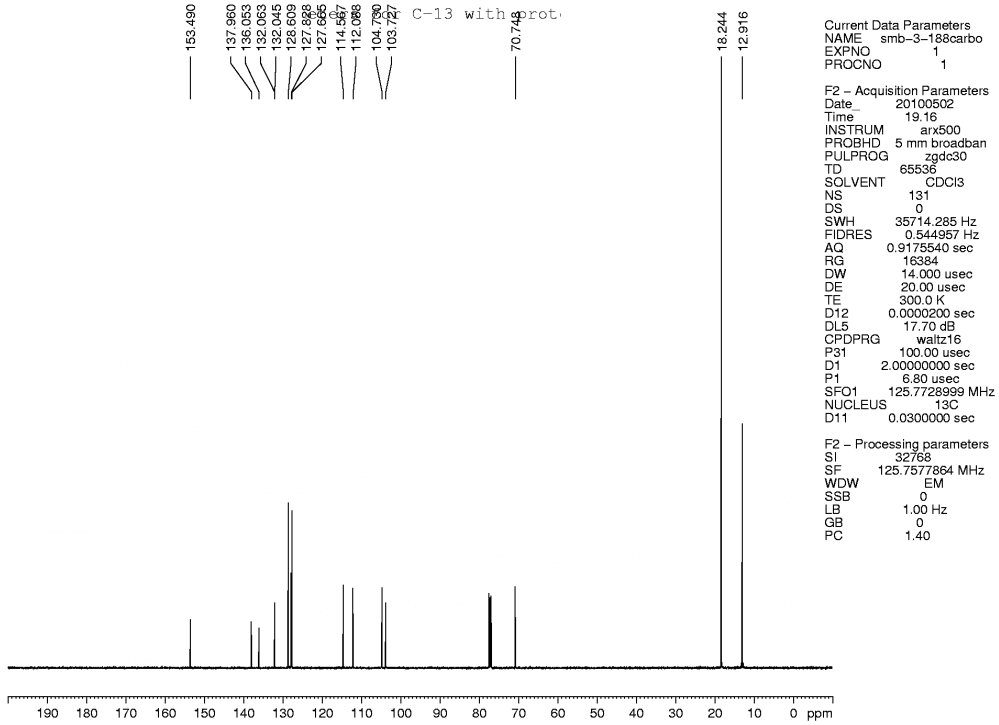



*Figure A1.117* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compound **2.73**.

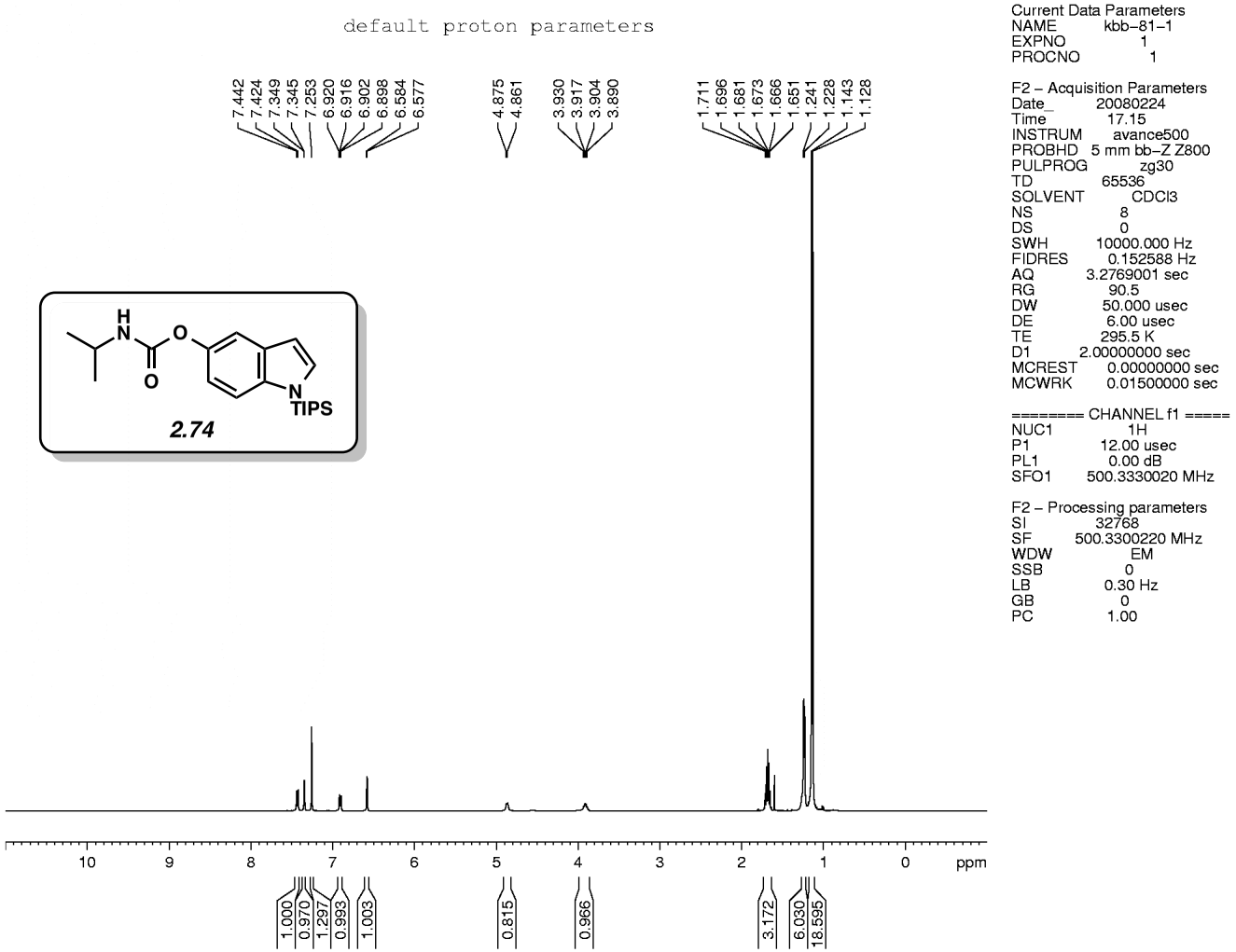



*Figure A1.118* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **2.74**.

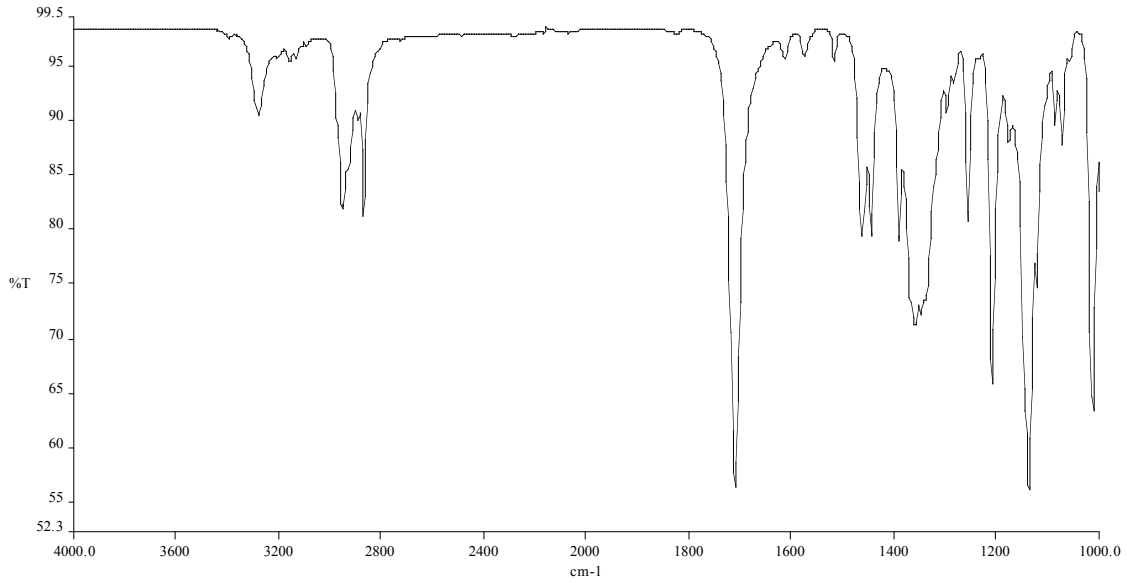



*Figure A1.119* Infrared spectrum of compound **2.74**.

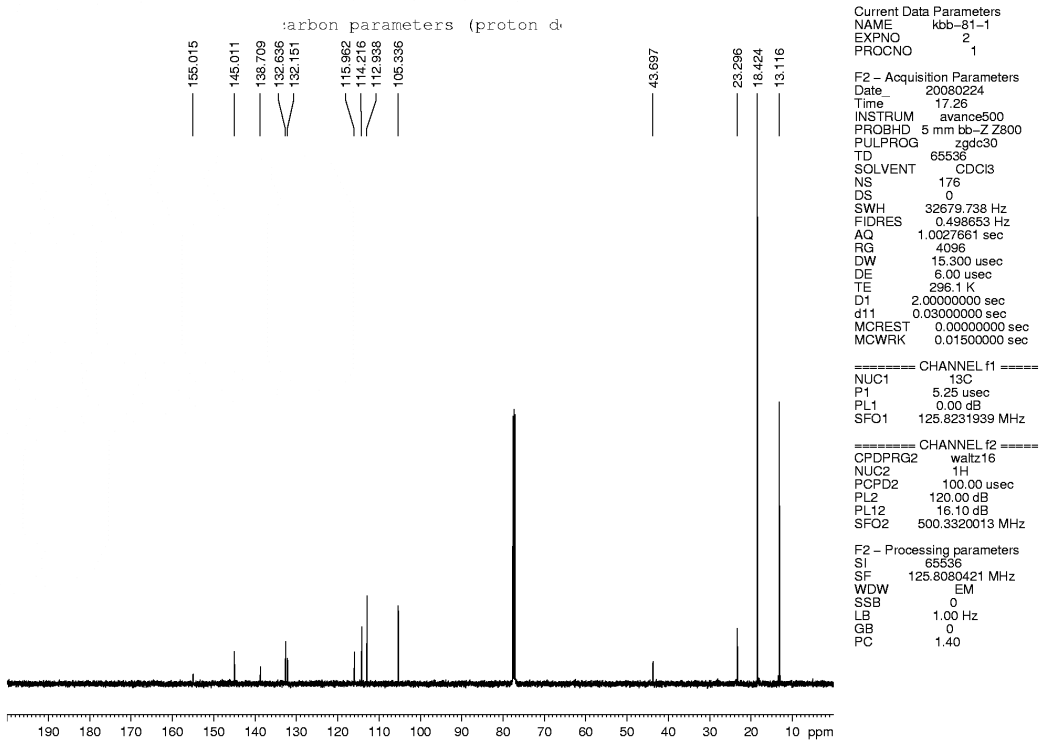



*Figure A1.120* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compound **2.74**.

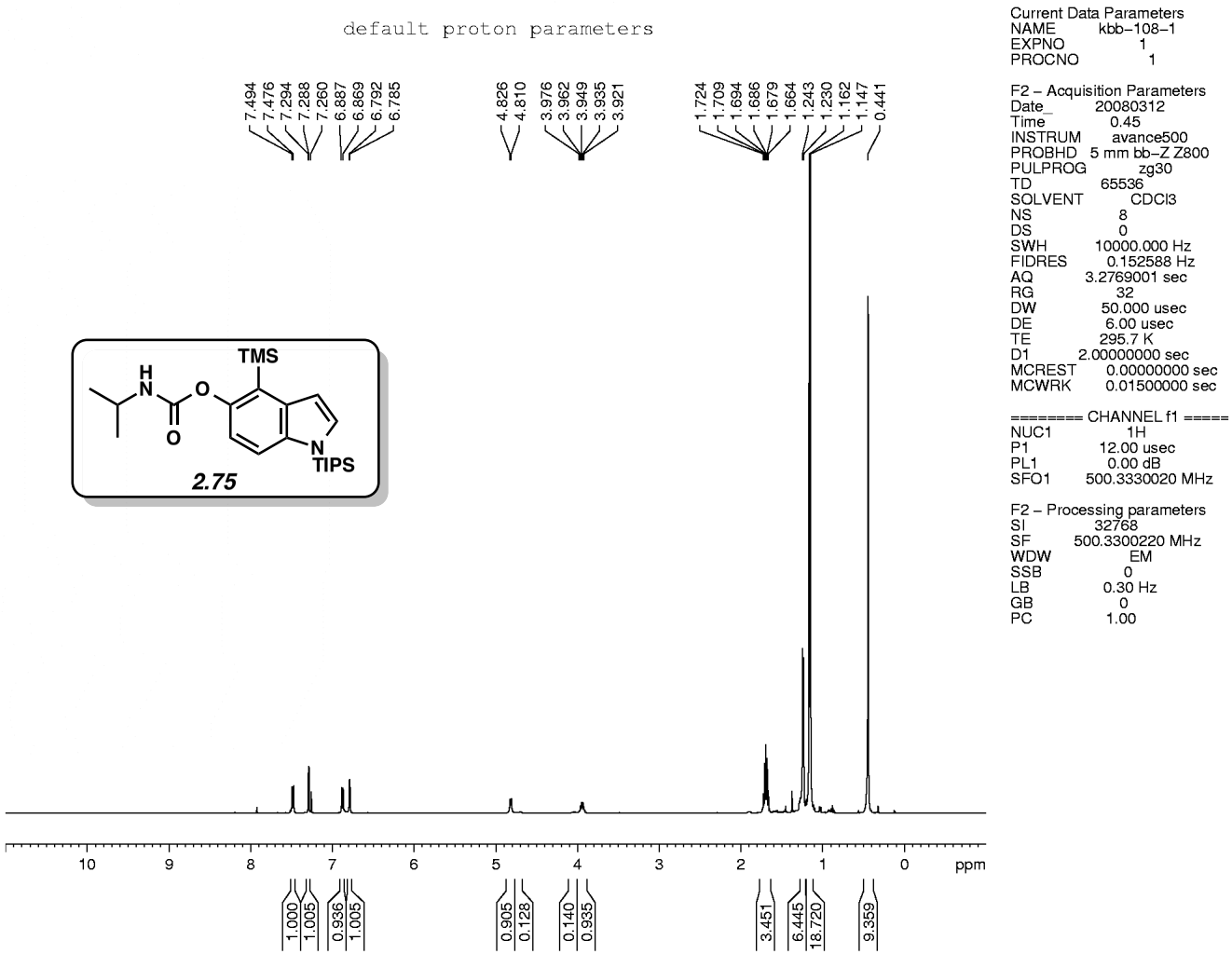



*Figure A1.121* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **2.75**.

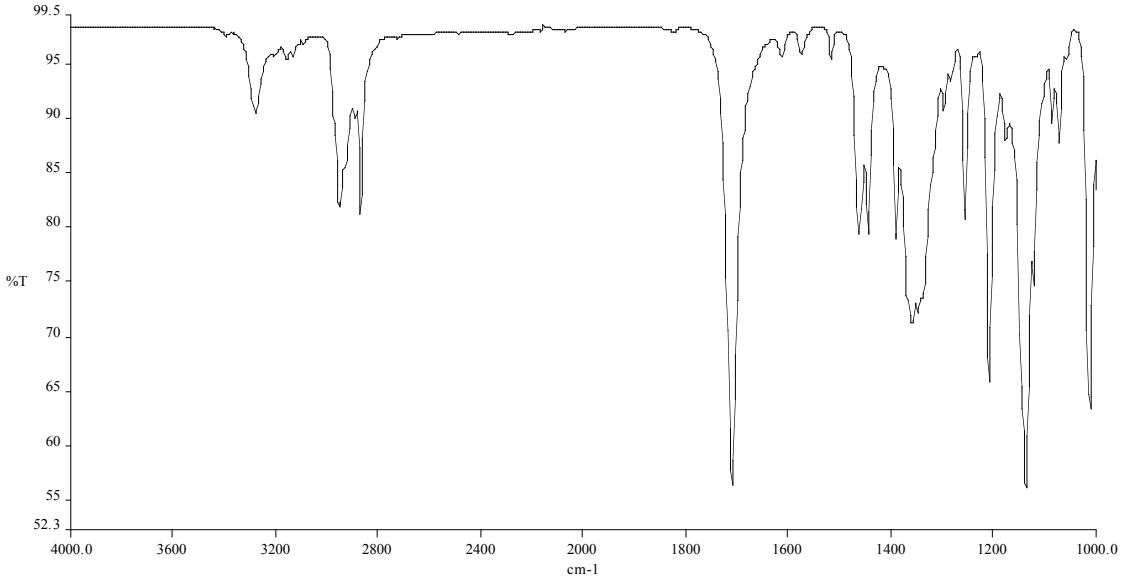



*Figure A1.122* Infrared spectrum of compound **2.75**.

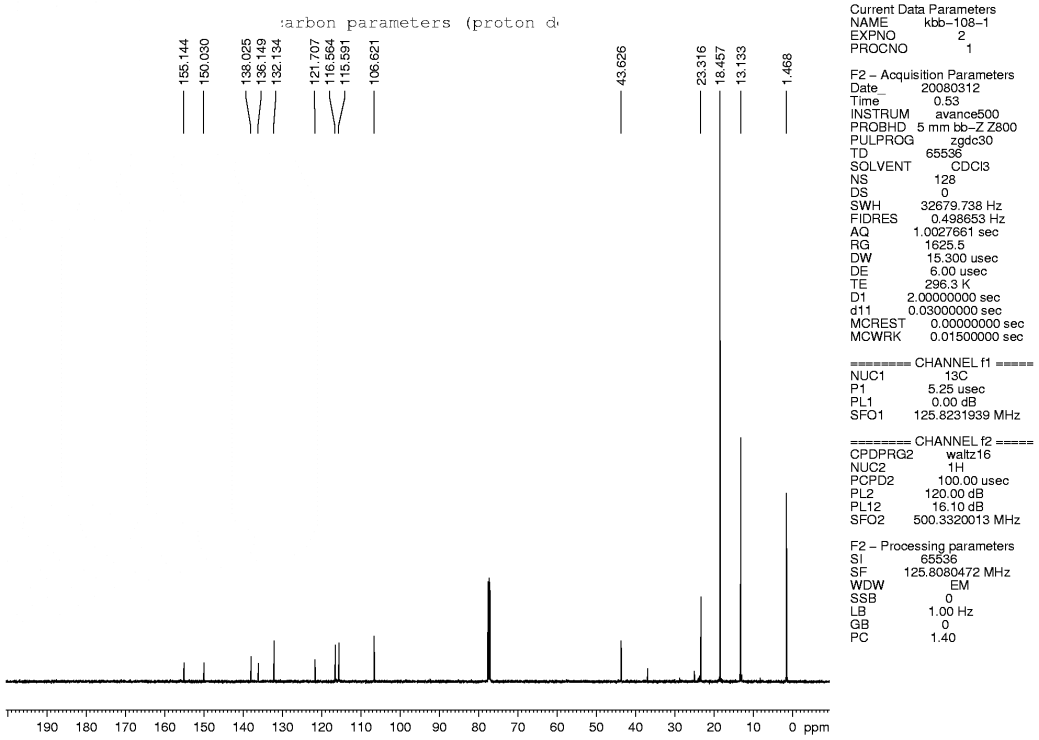



*Figure A1.123* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compound **2.75**.

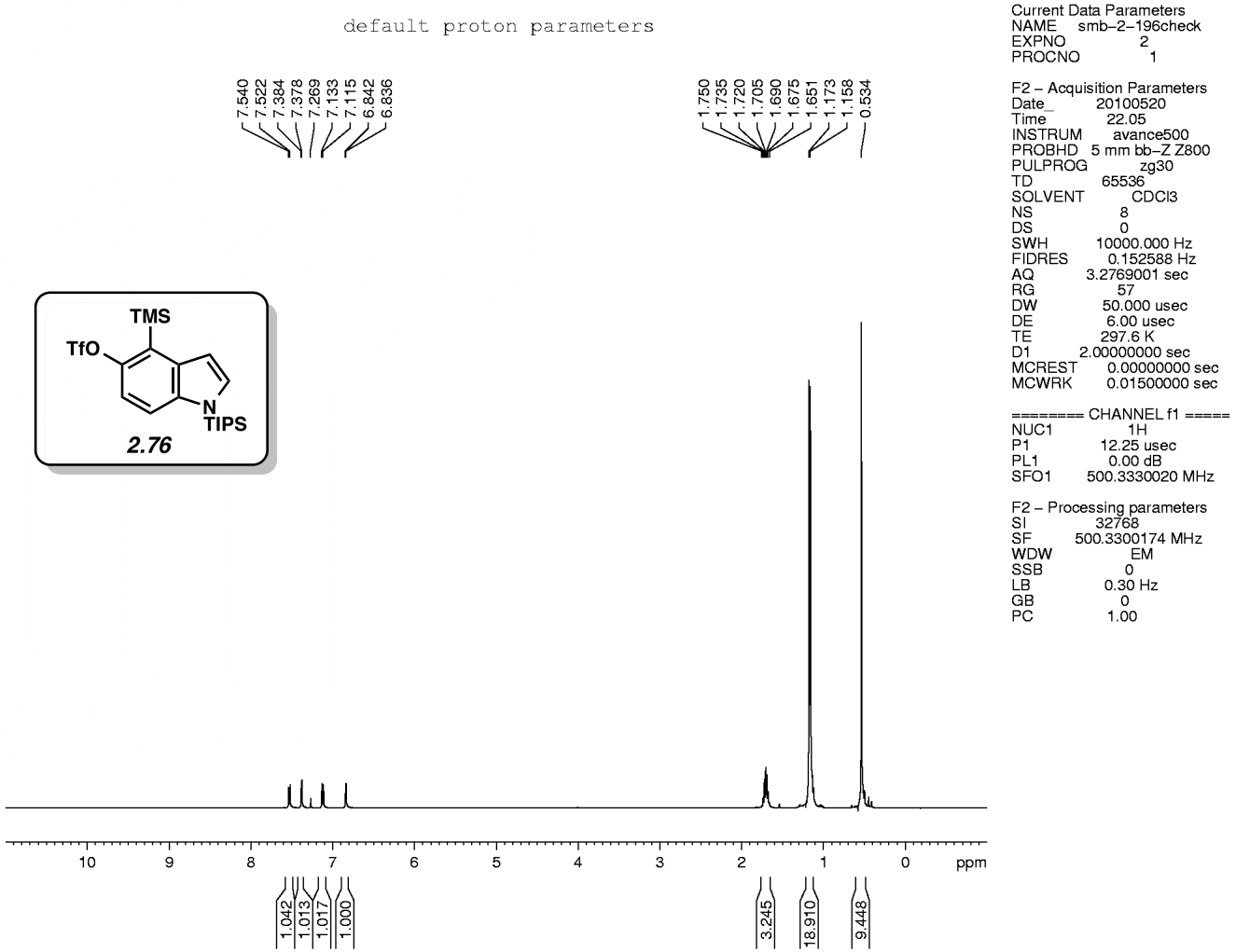



*Figure A1.124* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **2.76**.

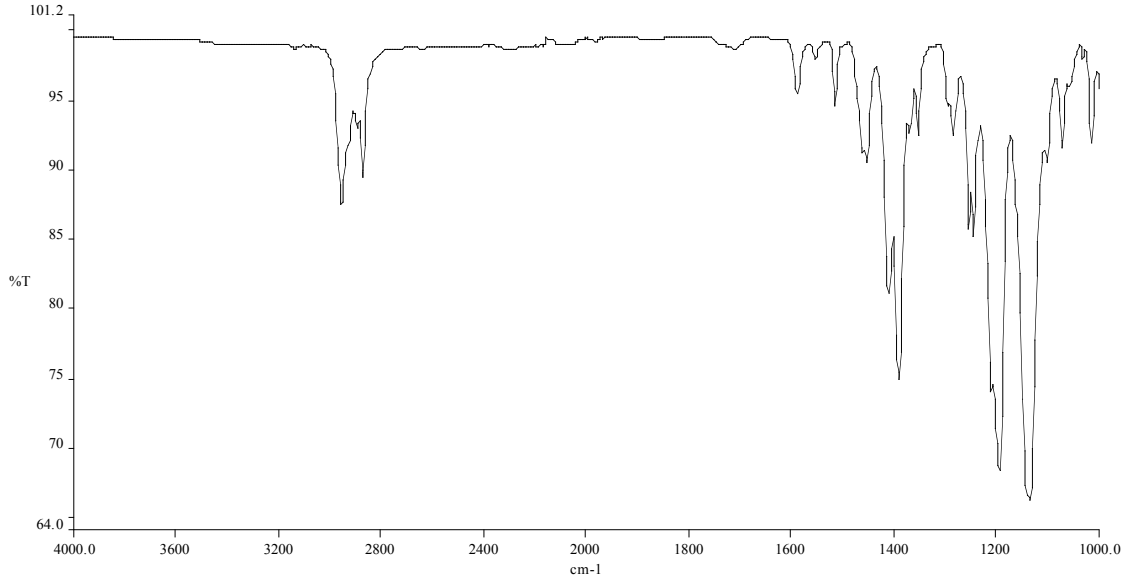



*Figure A1.125* Infrared spectrum of compound **2.76**.

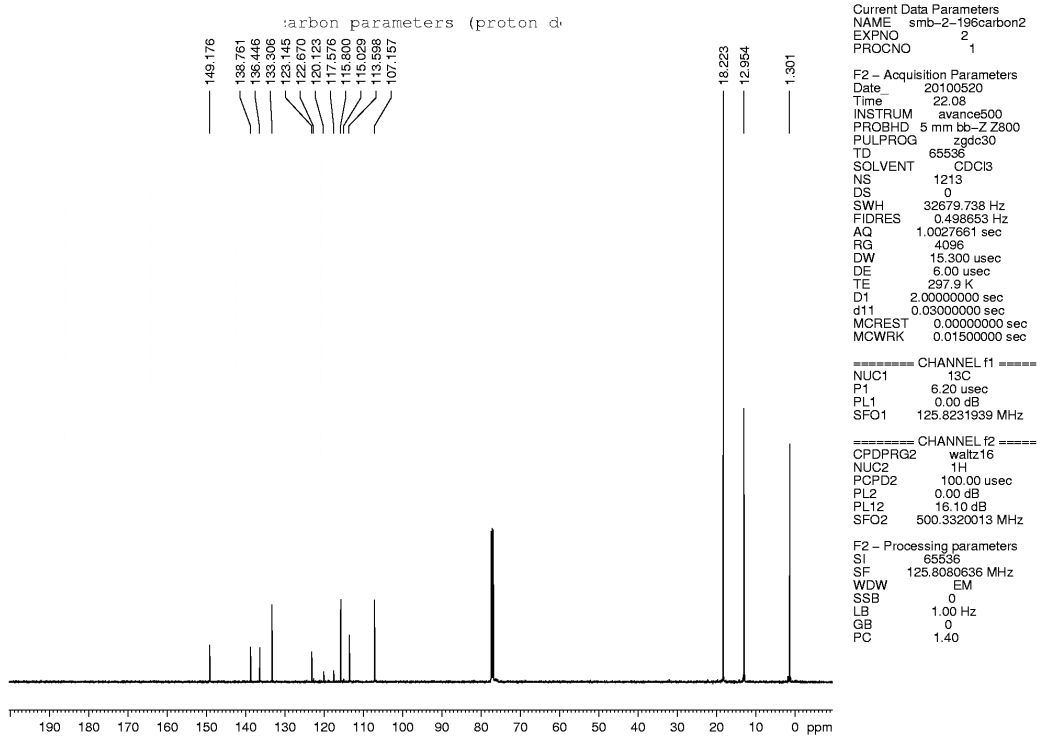



*Figure A1.126* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compound **2.76**.

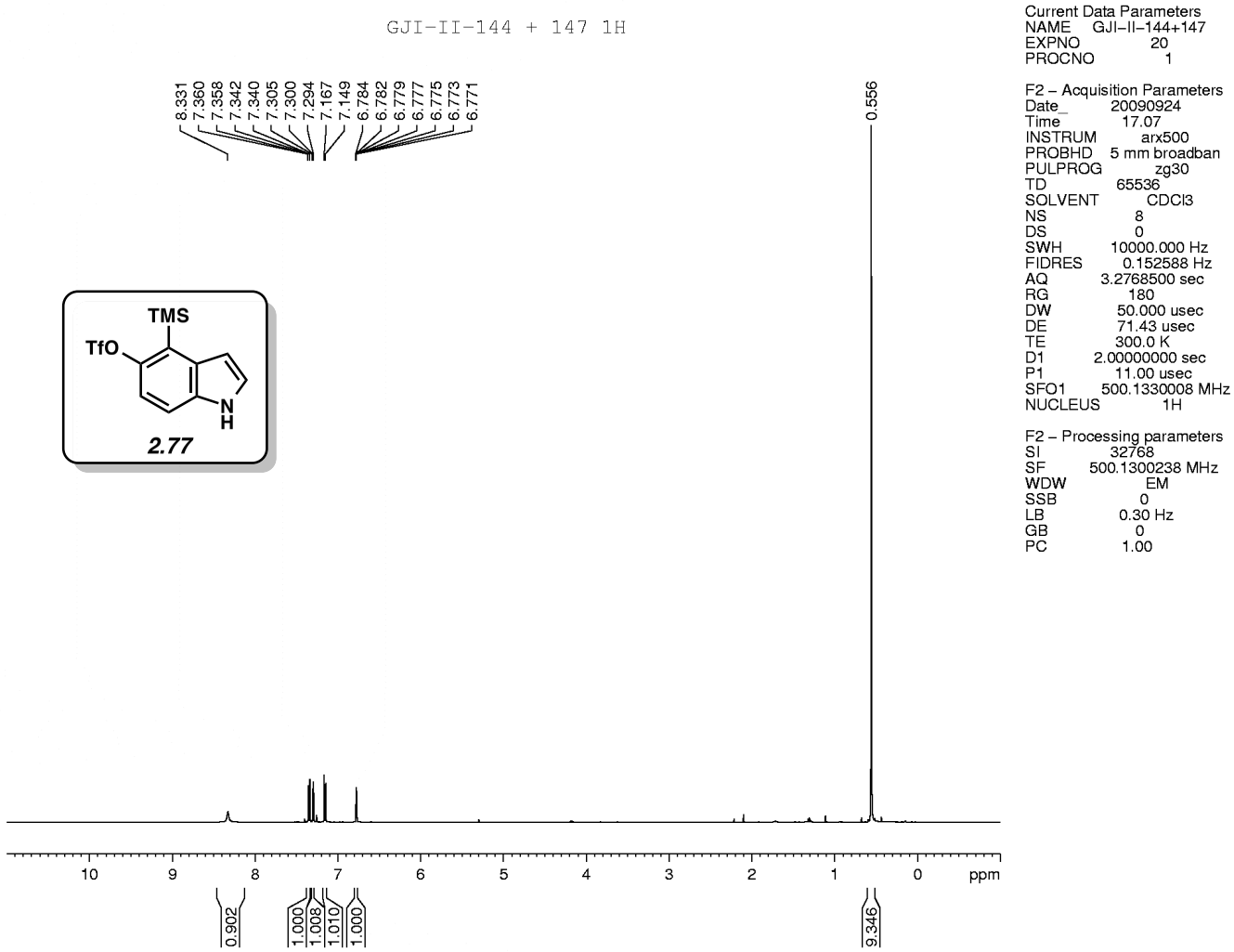



*Figure A1.127* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **2.77**.

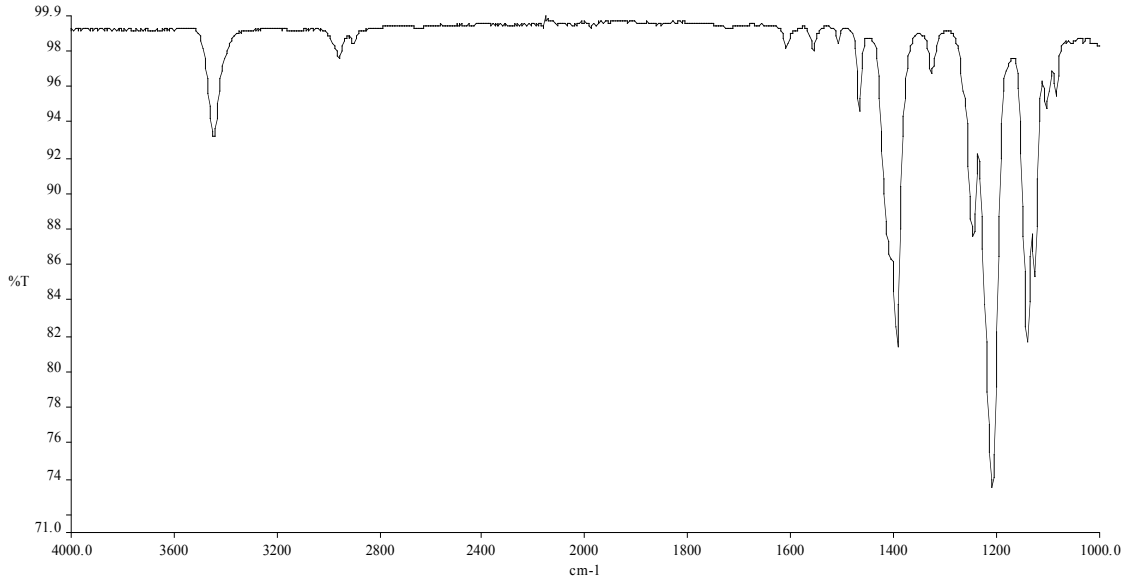



*Figure A1.128* Infrared spectrum of compound **2.77**.

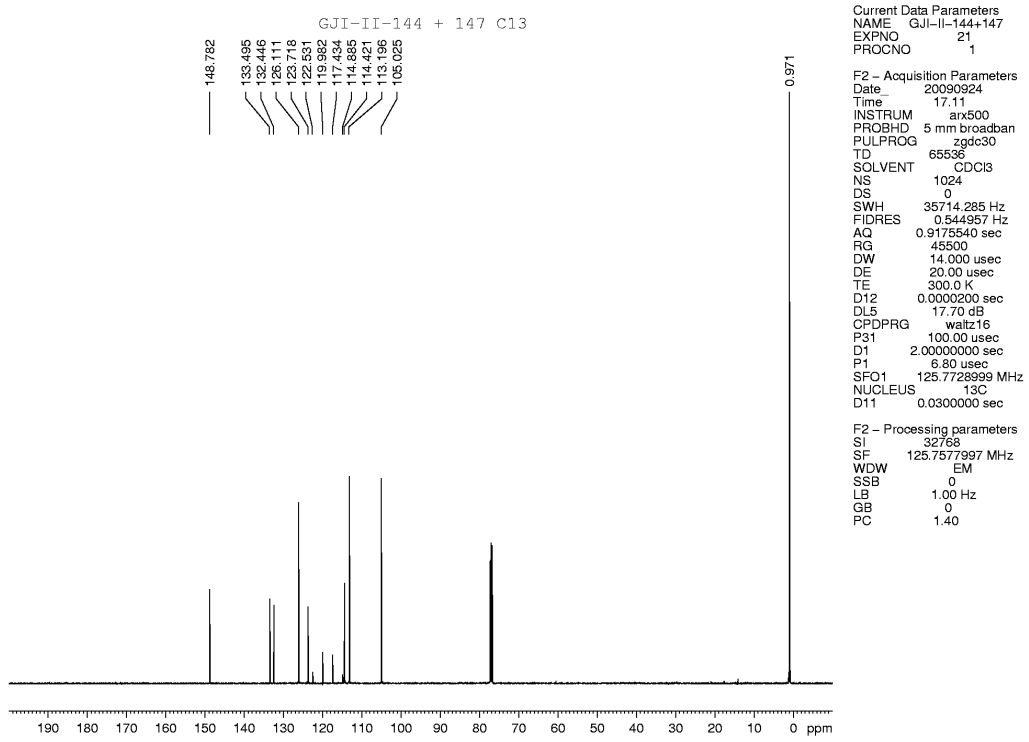



*Figure A1.129* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compound **2.77**.

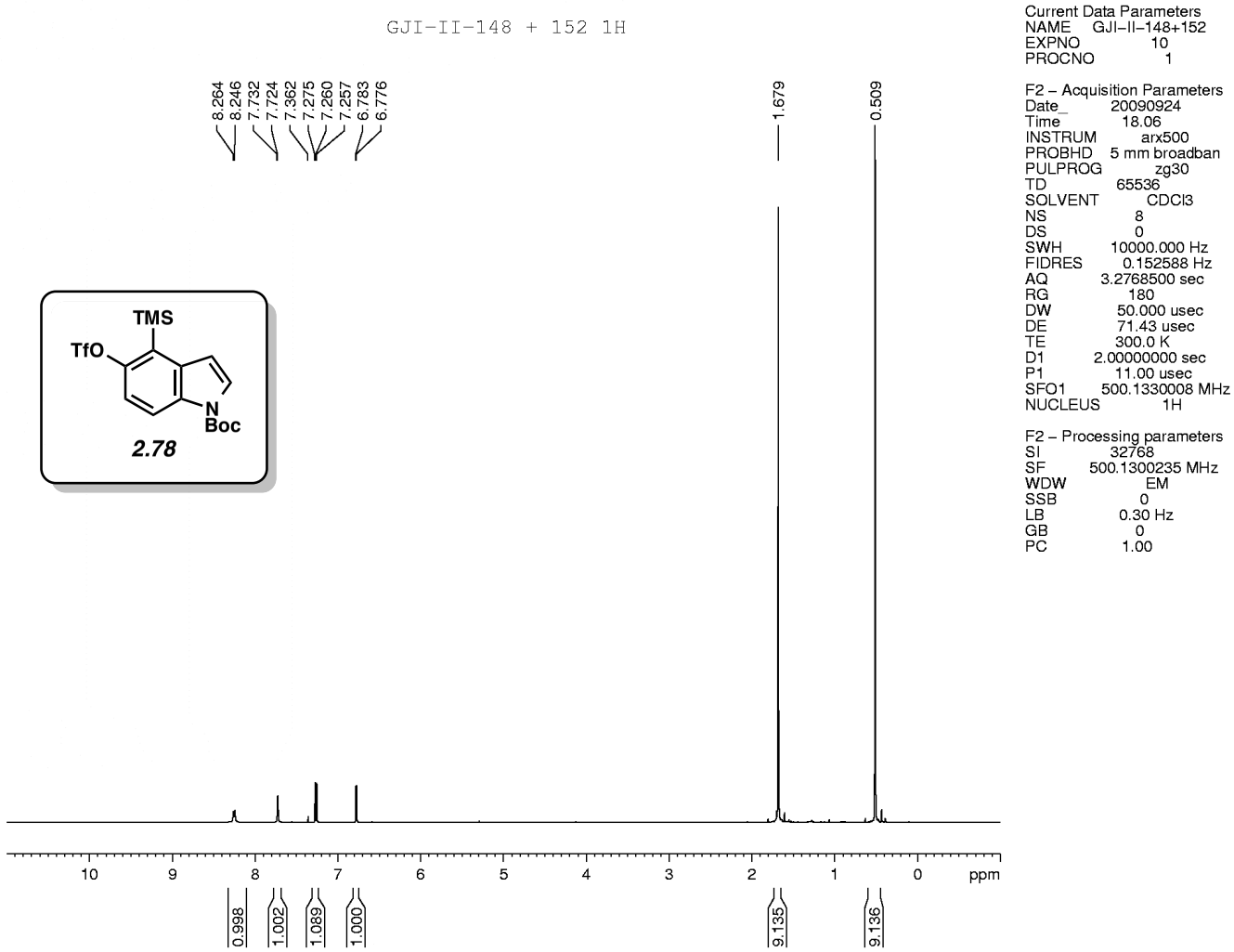



*Figure A1.130* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **2.78**.

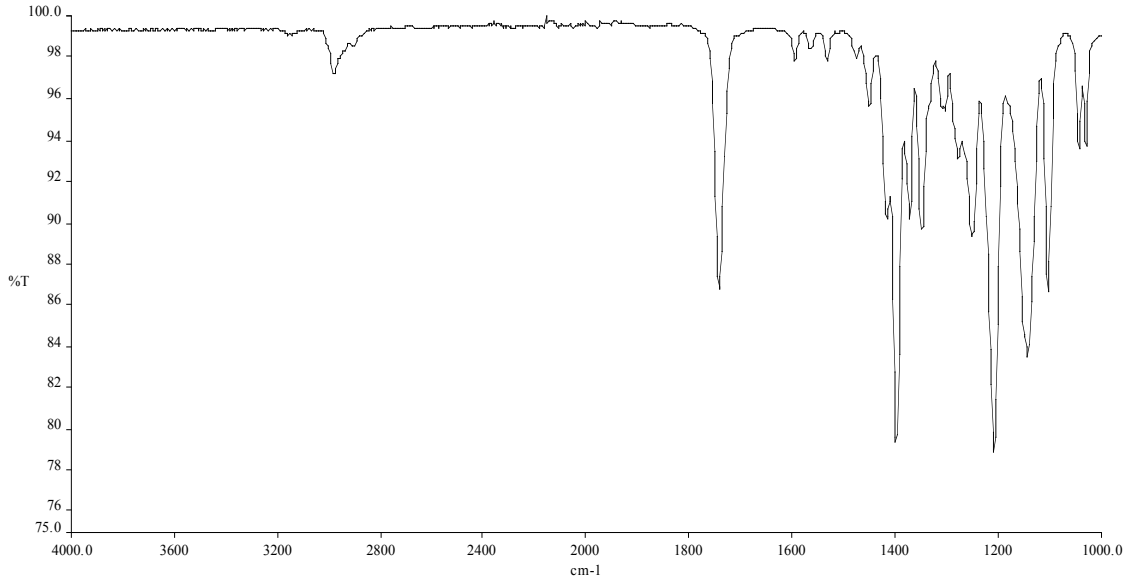



*Figure A1.131* Infrared spectrum of compound **2.78**.

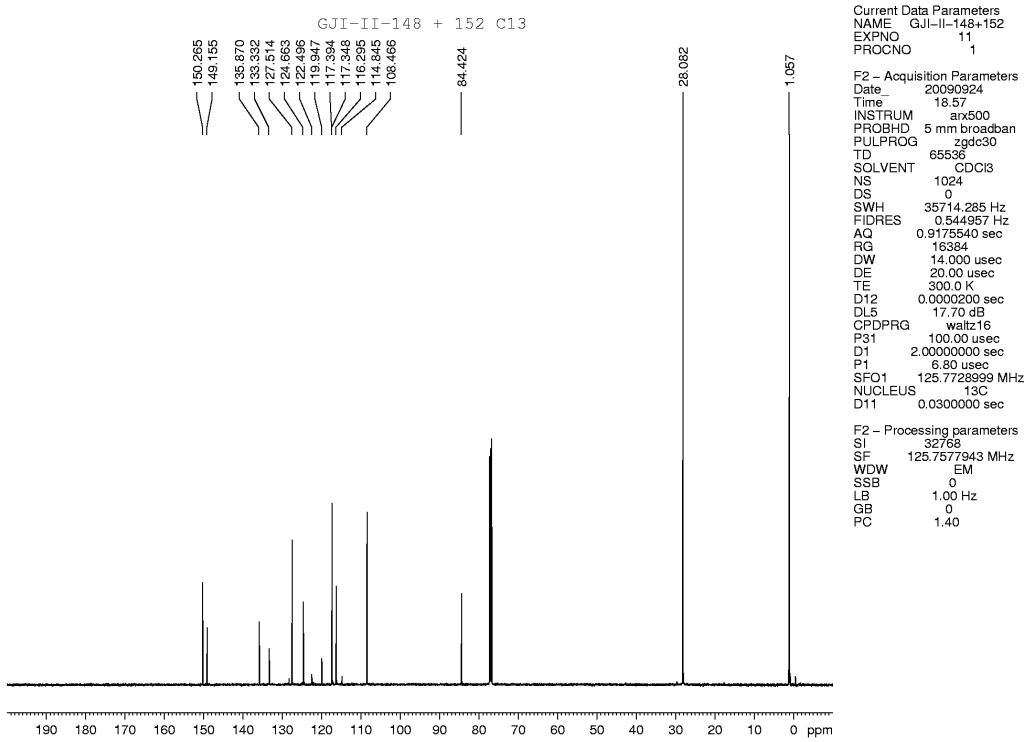



*Figure A1.132* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compound **2.78**.

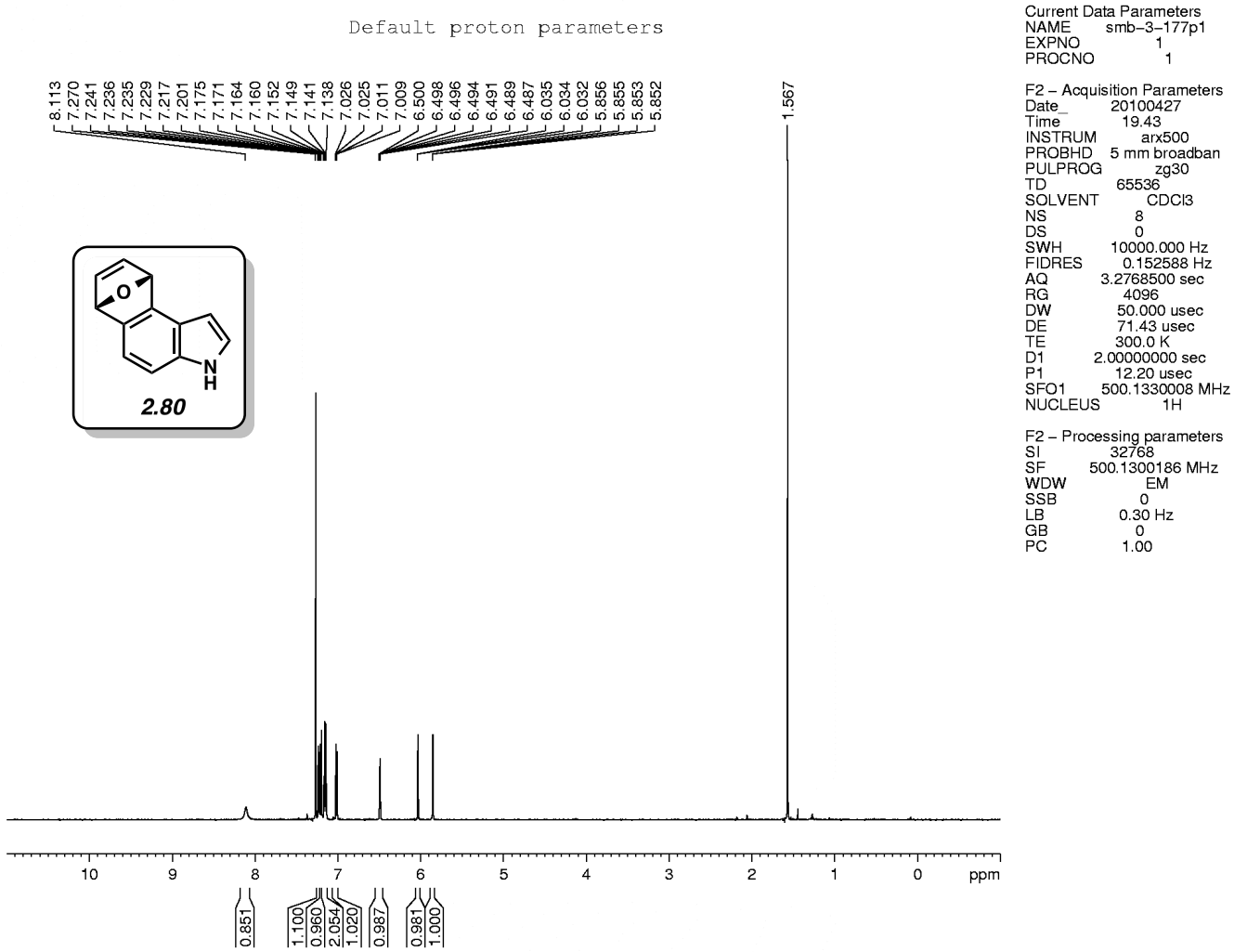



*Figure A1.133* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **2.80**.

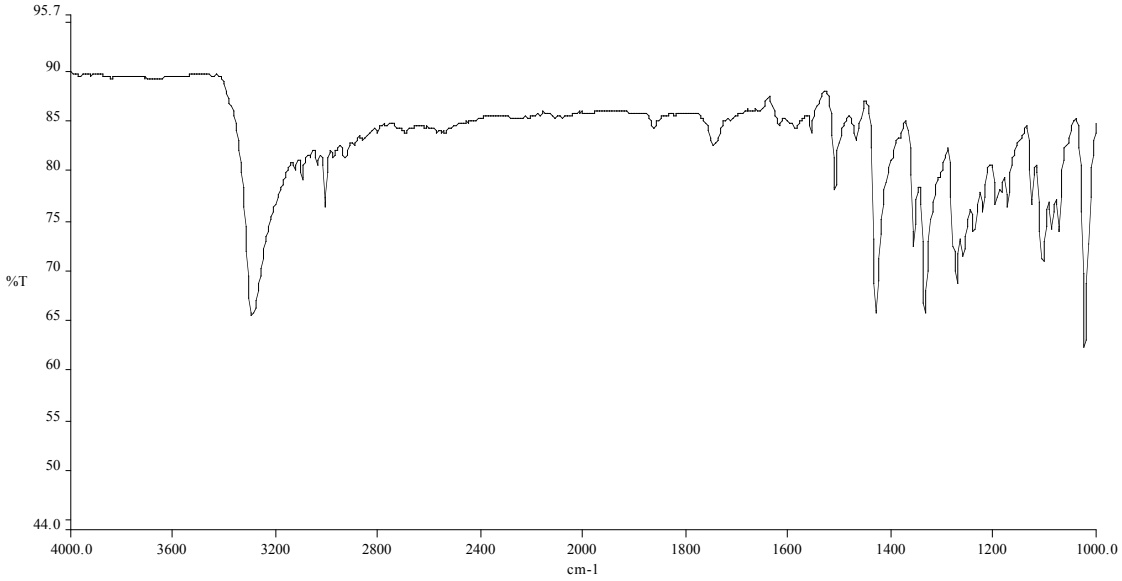



*Figure A1.134* Infrared spectrum of compound **2.80**.

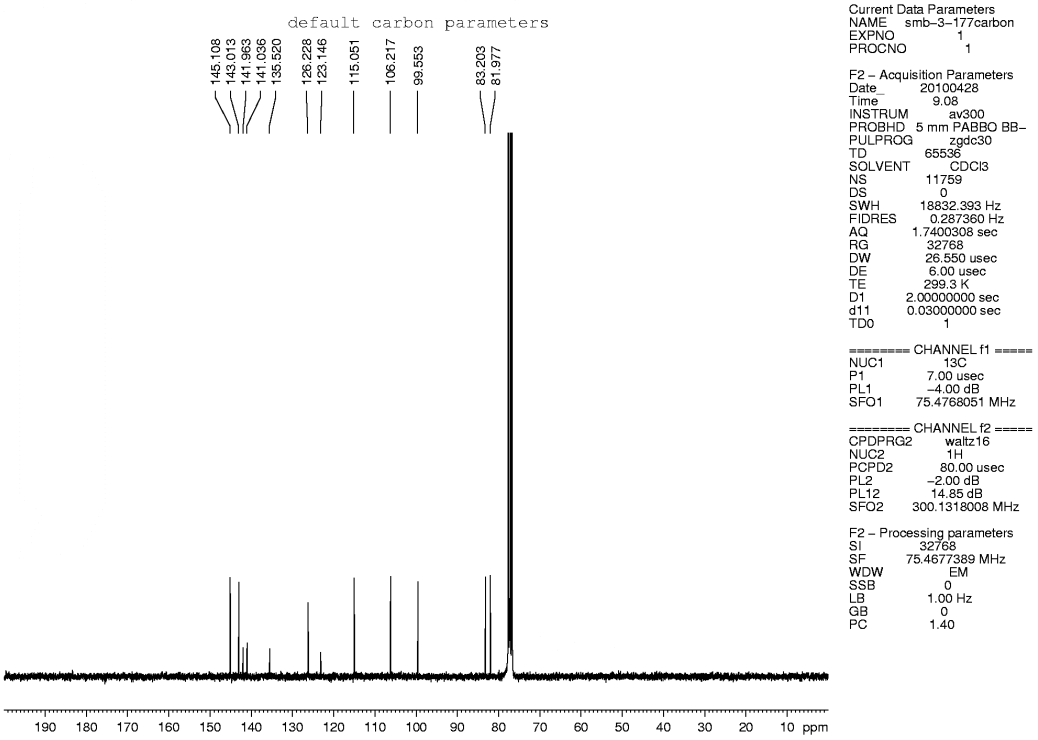



*Figure A1.135* $^{13}$C NMR (75 MHz, $CDCl_3$) of compound **2.80**.

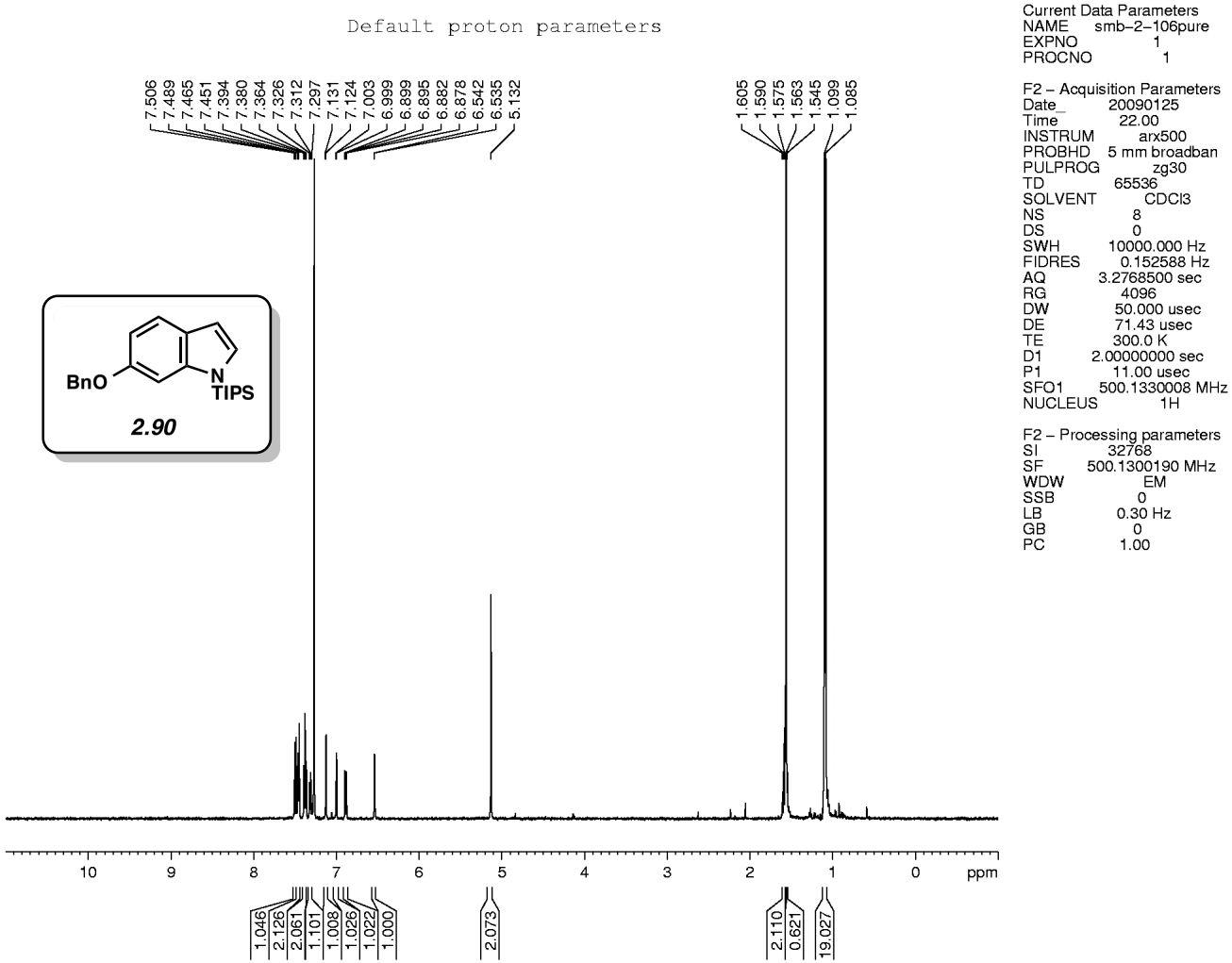



*Figure A1.136* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **2.90**.

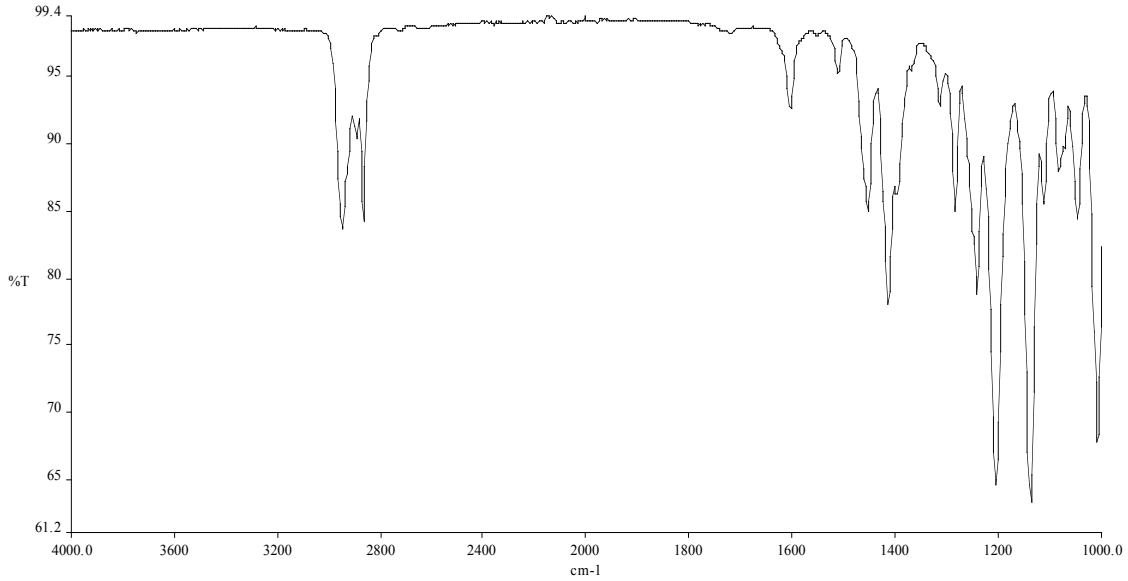



*Figure A1.137* Infrared spectrum of compound **2.90**.

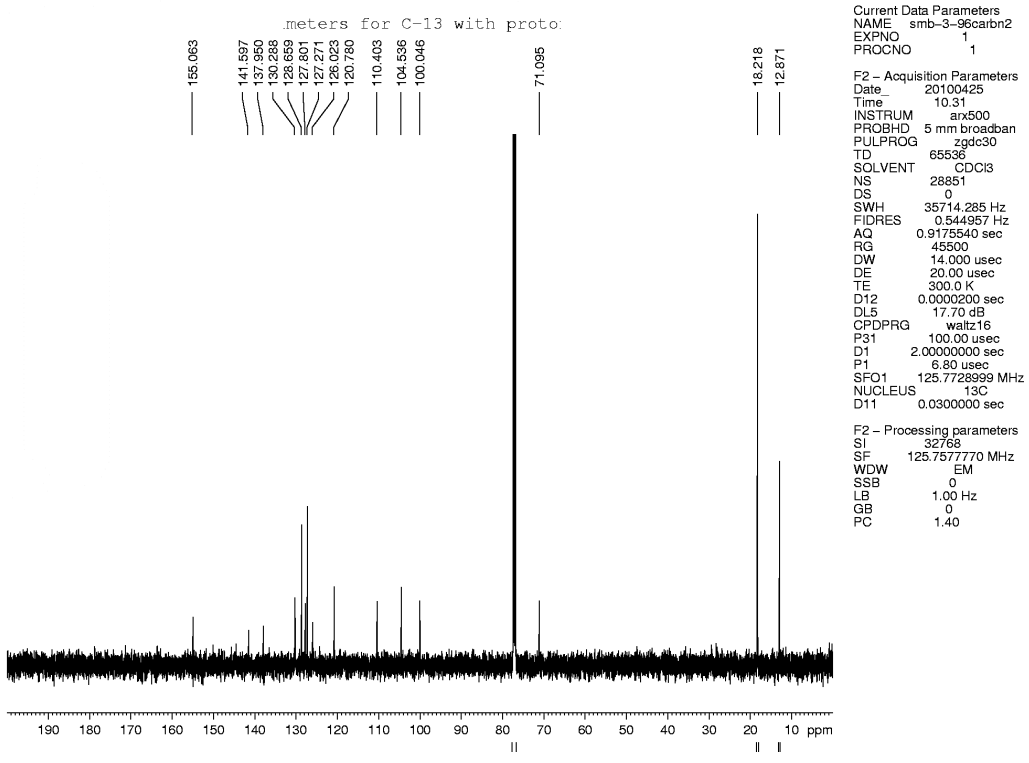



*Figure A1.138* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compound **2.90**.

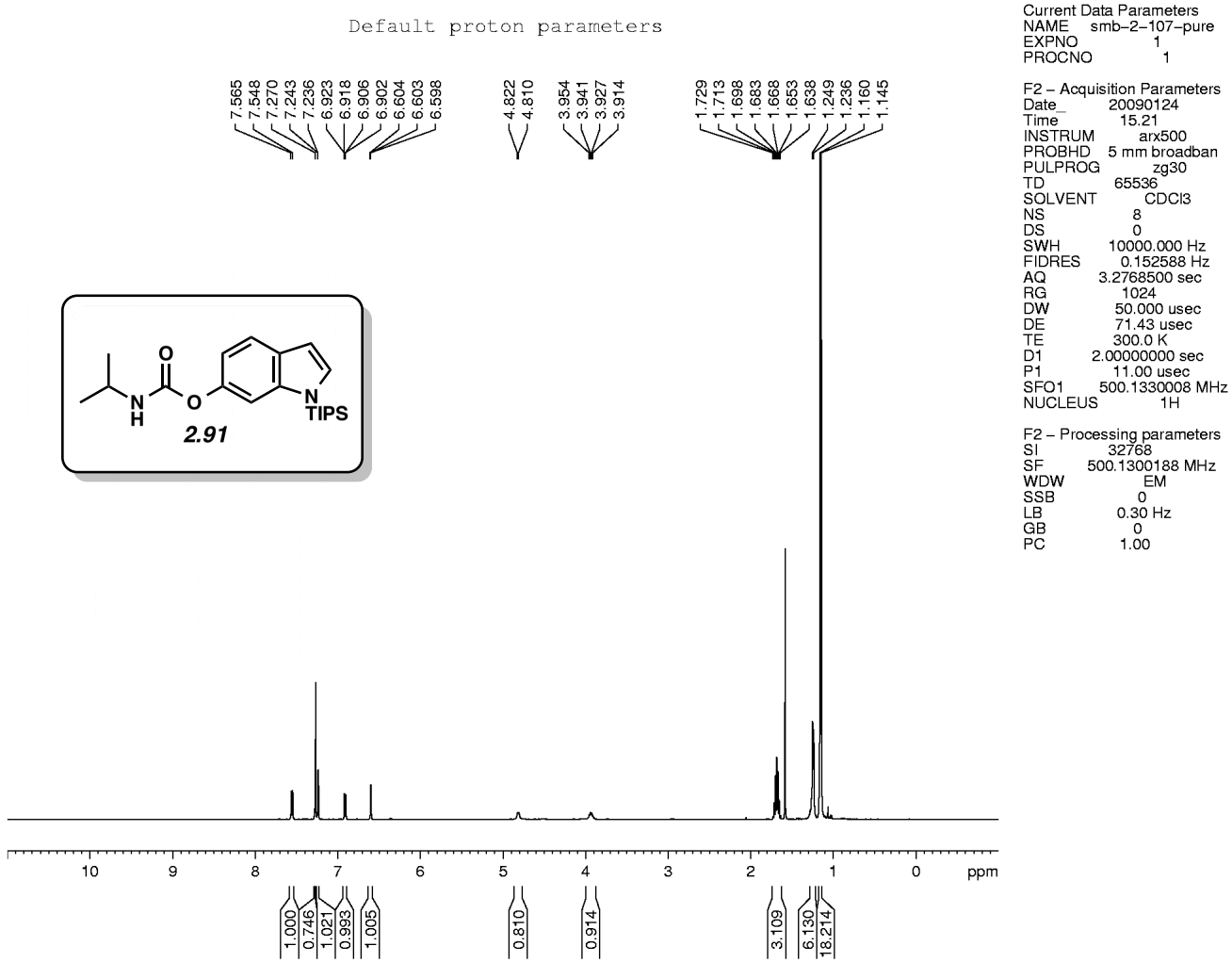



*Figure A1.139* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **2.91**.

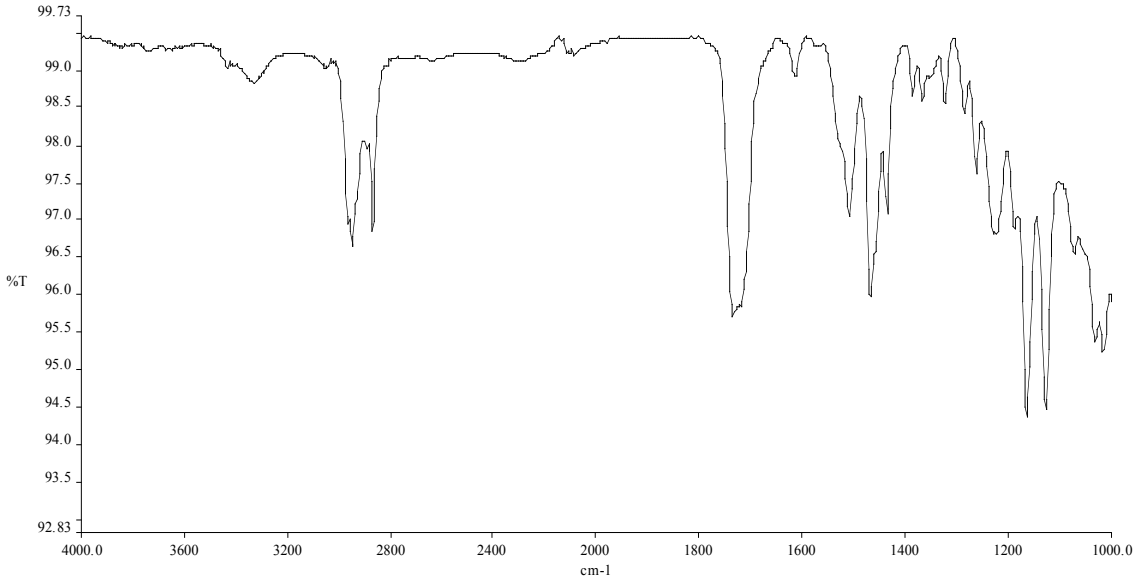



*Figure A1.140* Infrared spectrum of compound **2.91**.

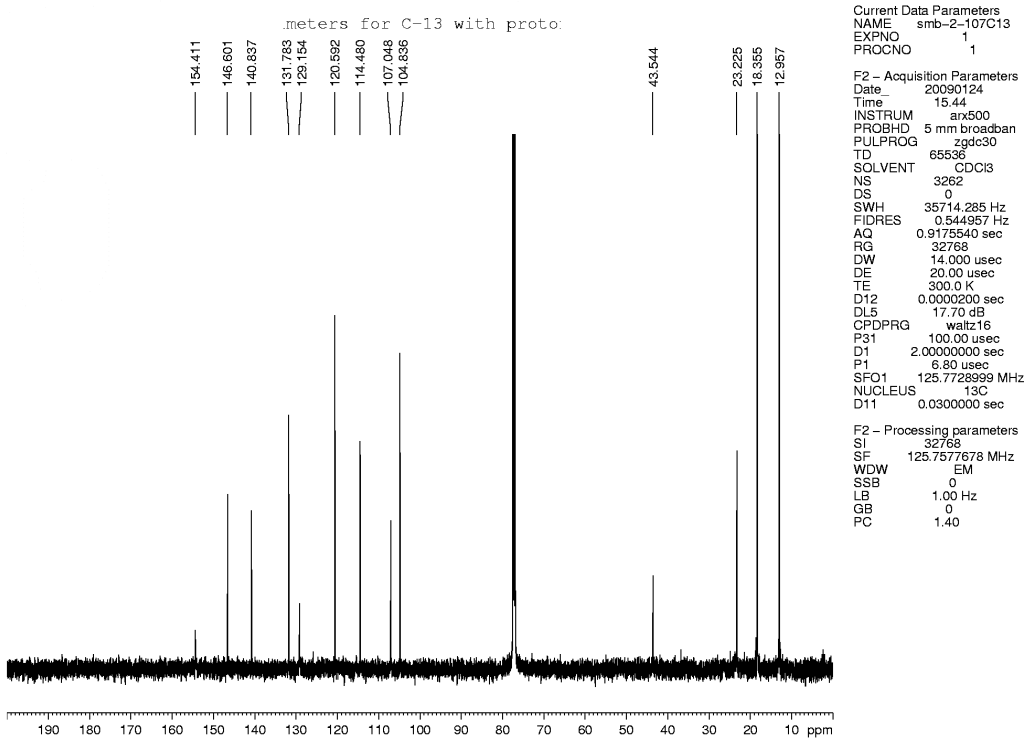



*Figure A1.141* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compound **2.91**.

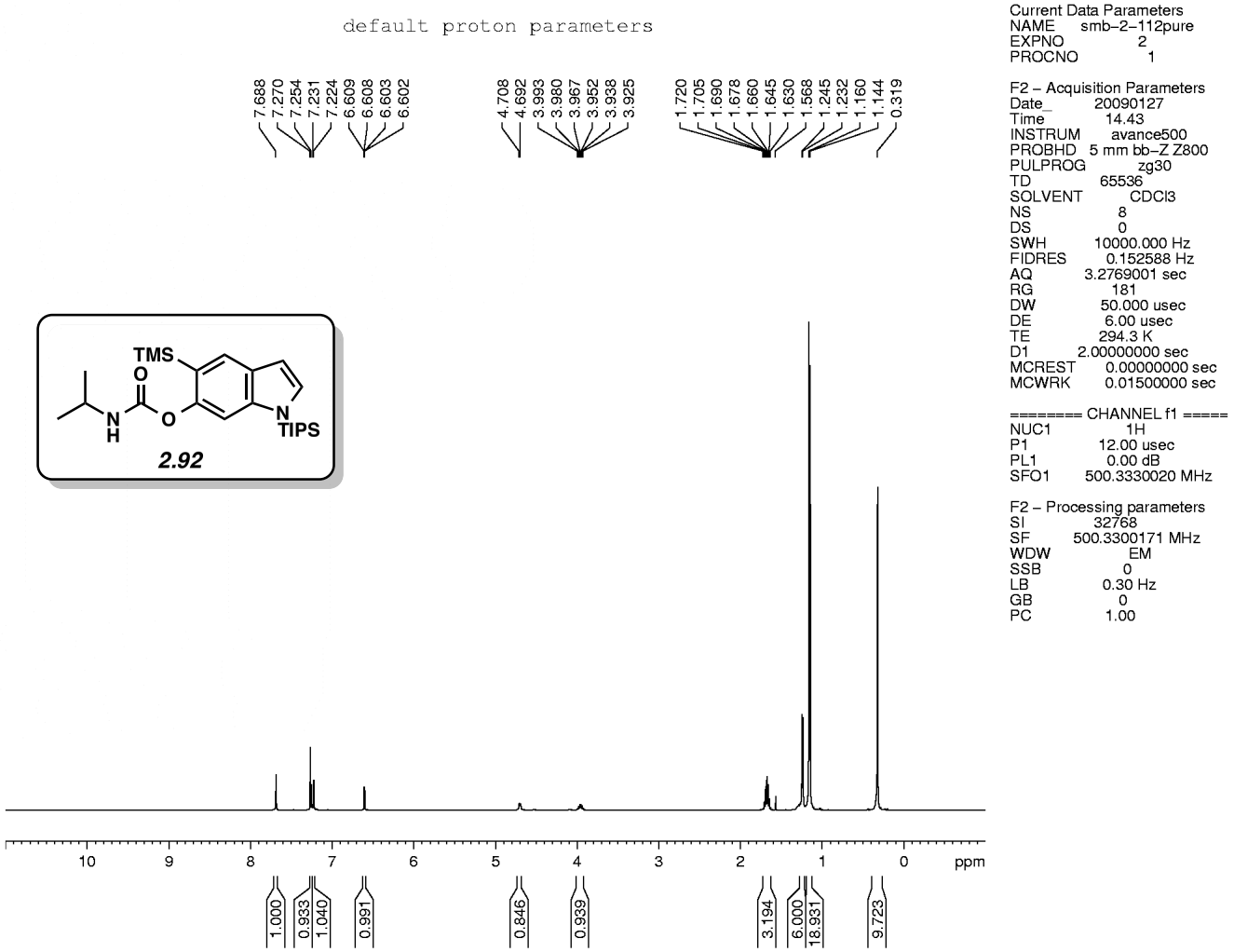



*Figure A1.142* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **2.92**.

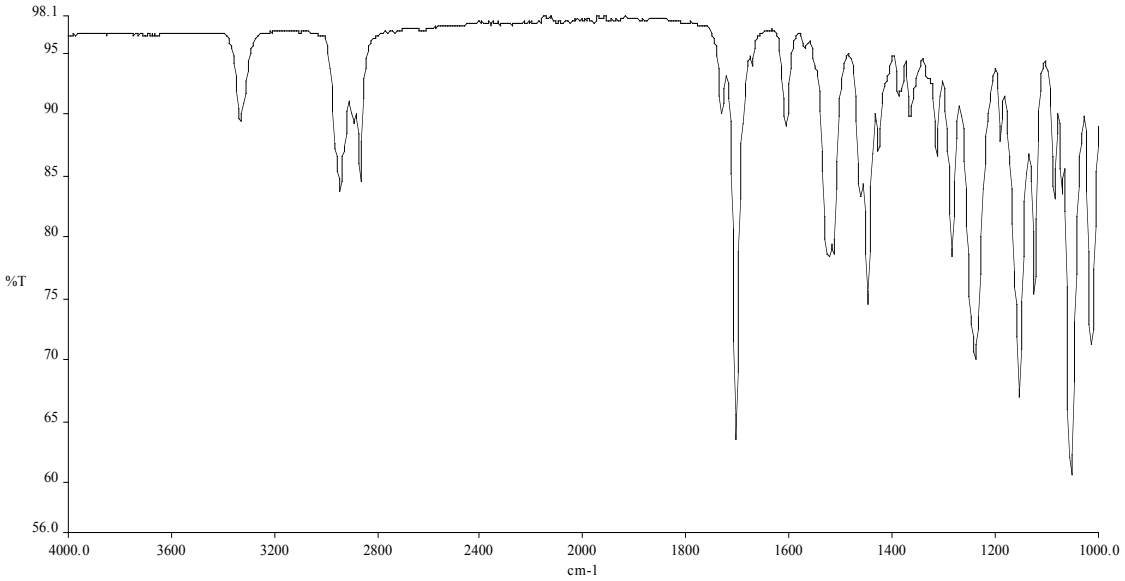



*Figure A1.143* Infrared spectrum of compound **2.92**.

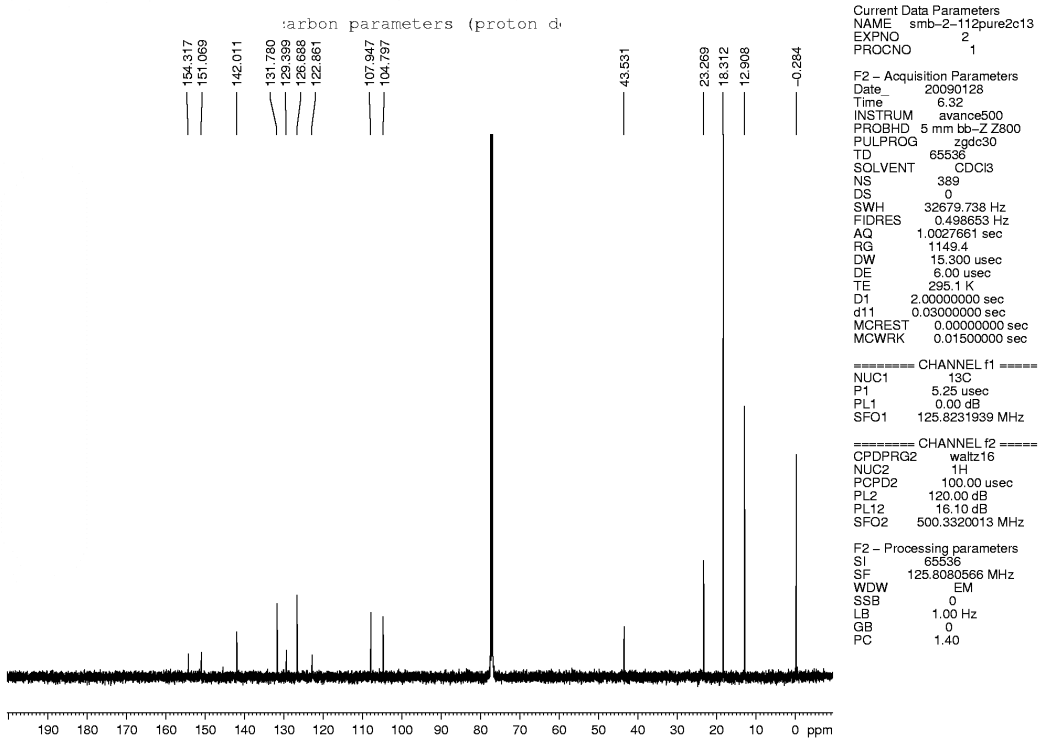



*Figure A1.144* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compound **2.92**.

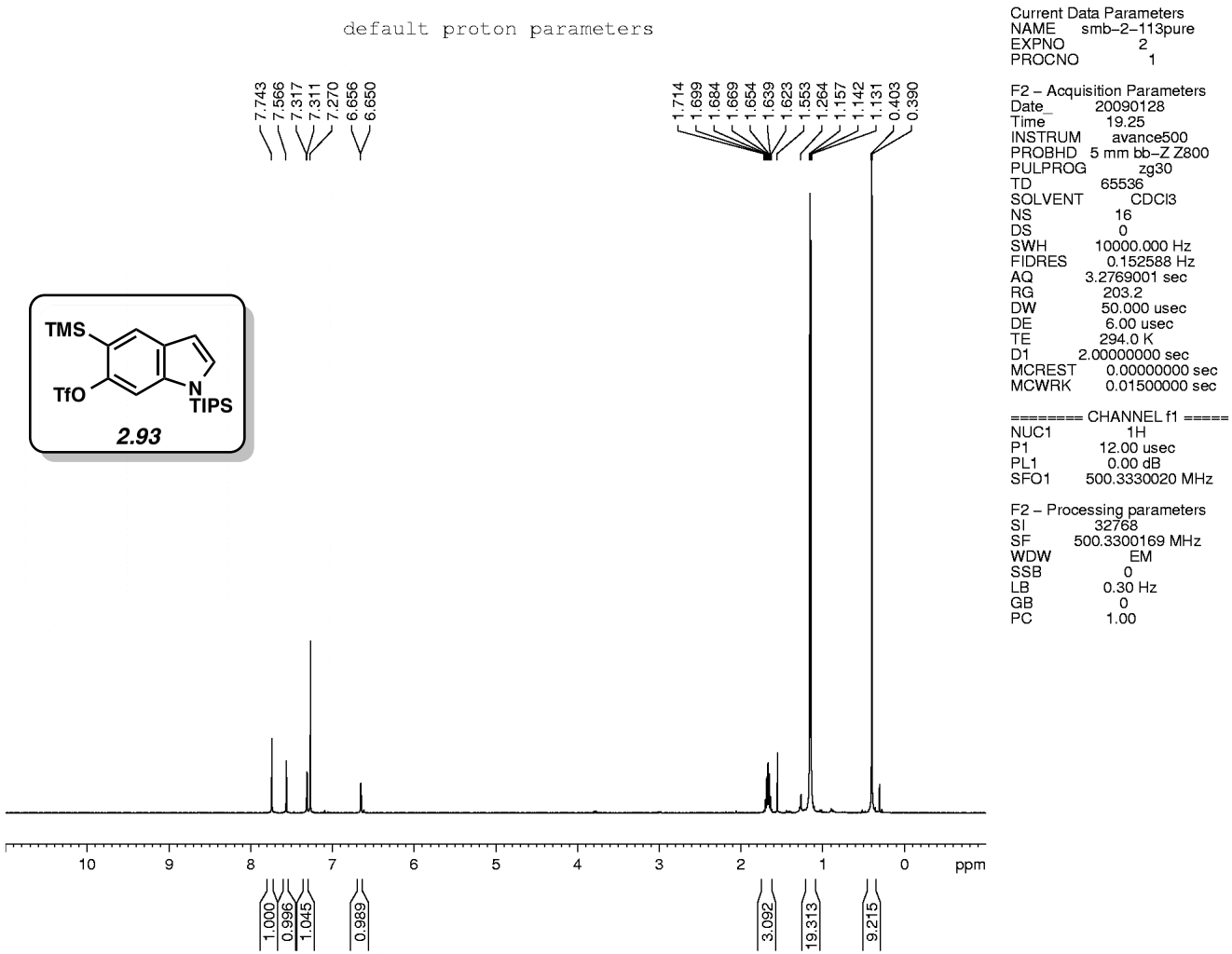



*Figure A1.145* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **2.93**.

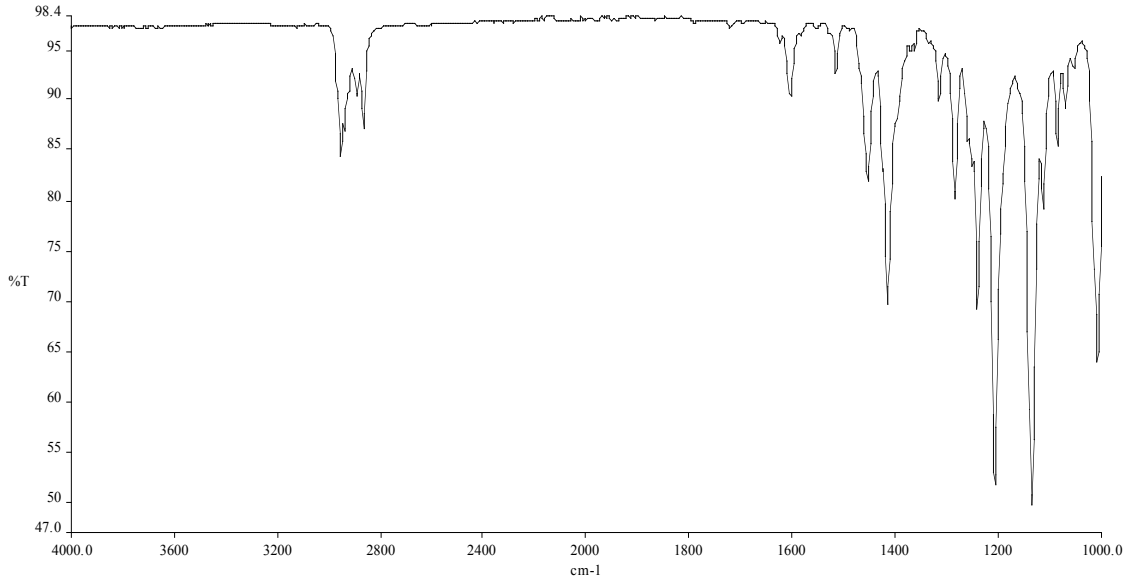



*Figure A1.146* Infrared spectrum of compound **2.93**.

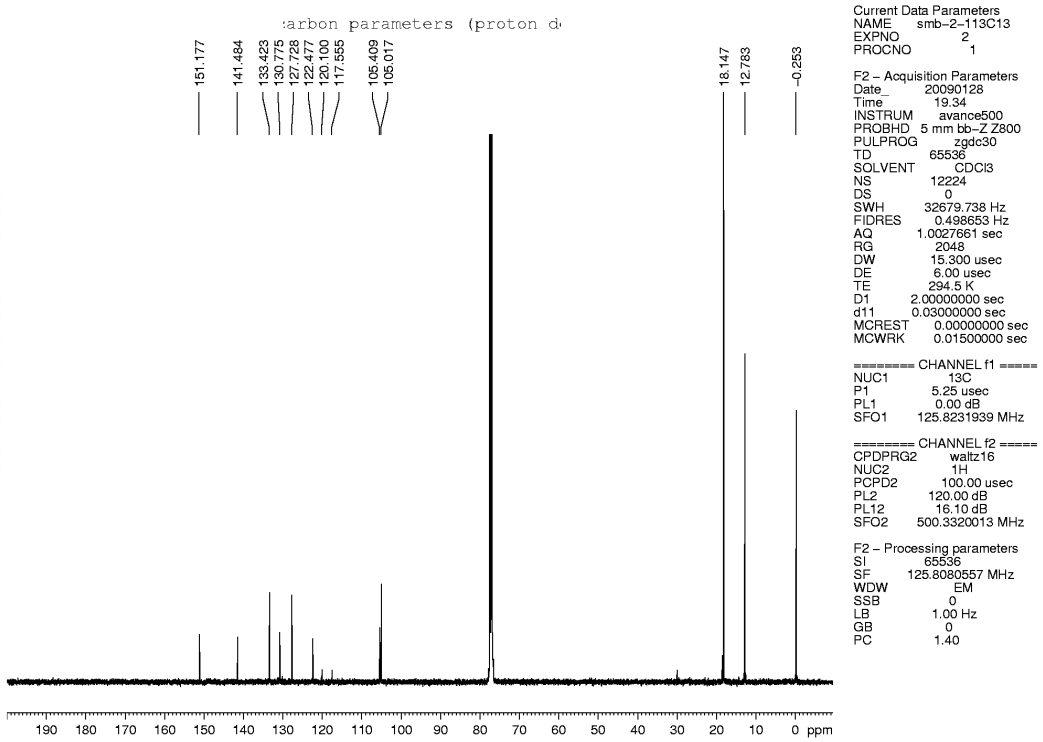



*Figure A1.147* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compound **2.93**.

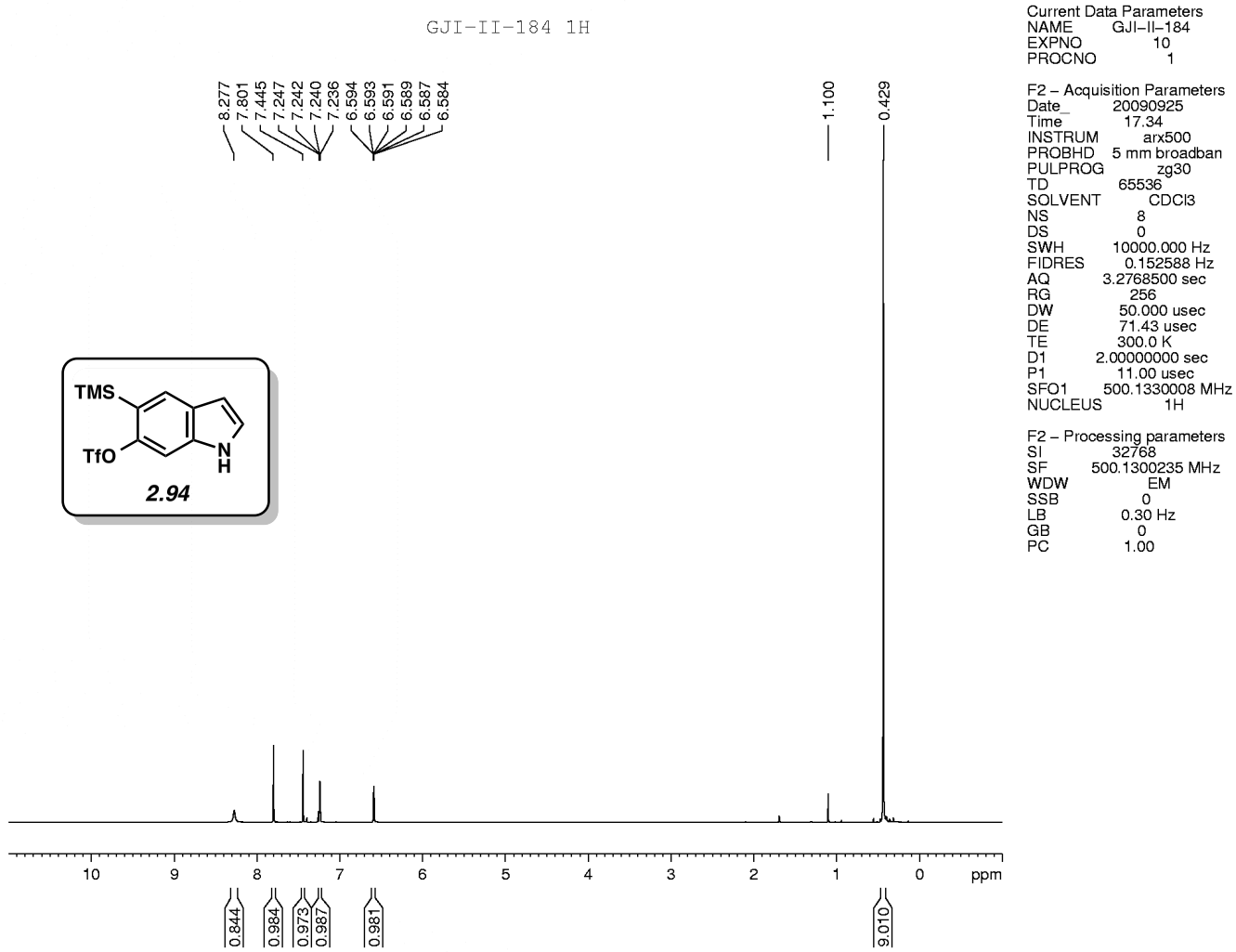



*Figure A1.148* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **2.94**.

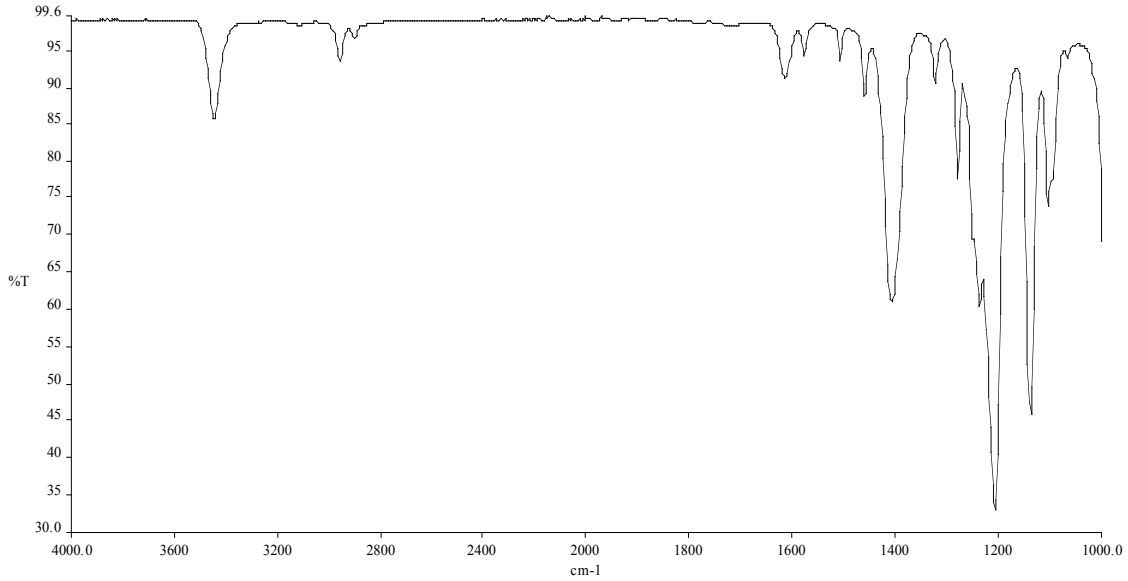



*Figure A1.149* Infrared spectrum of compound **2.94**.

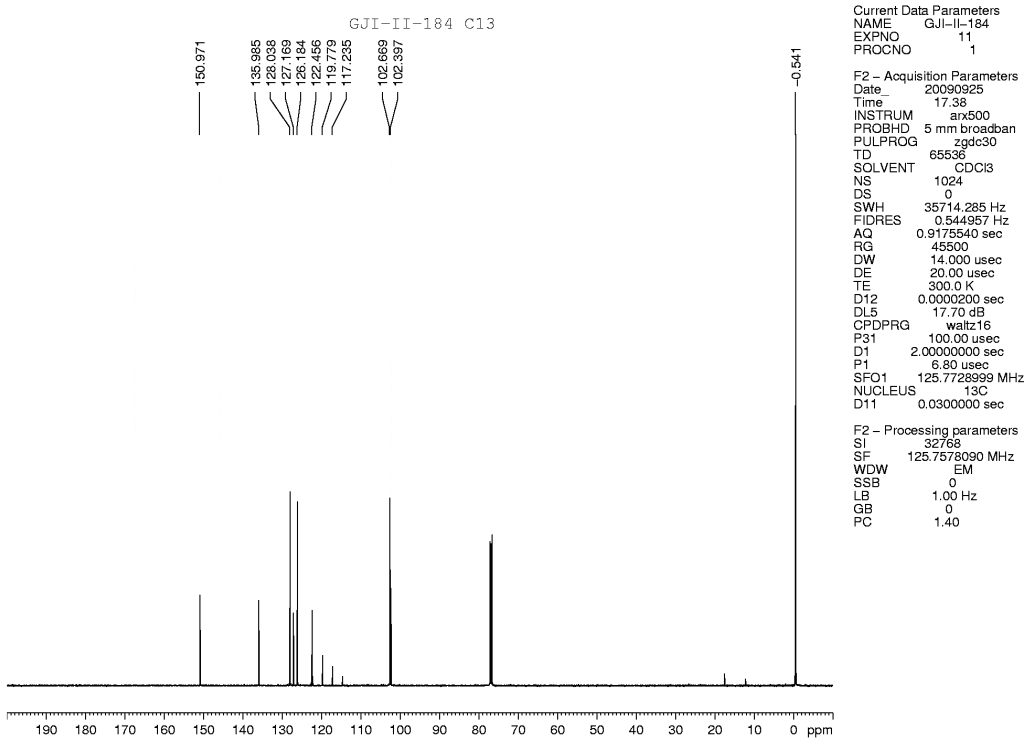



*Figure A1.150* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compound **2.94**.

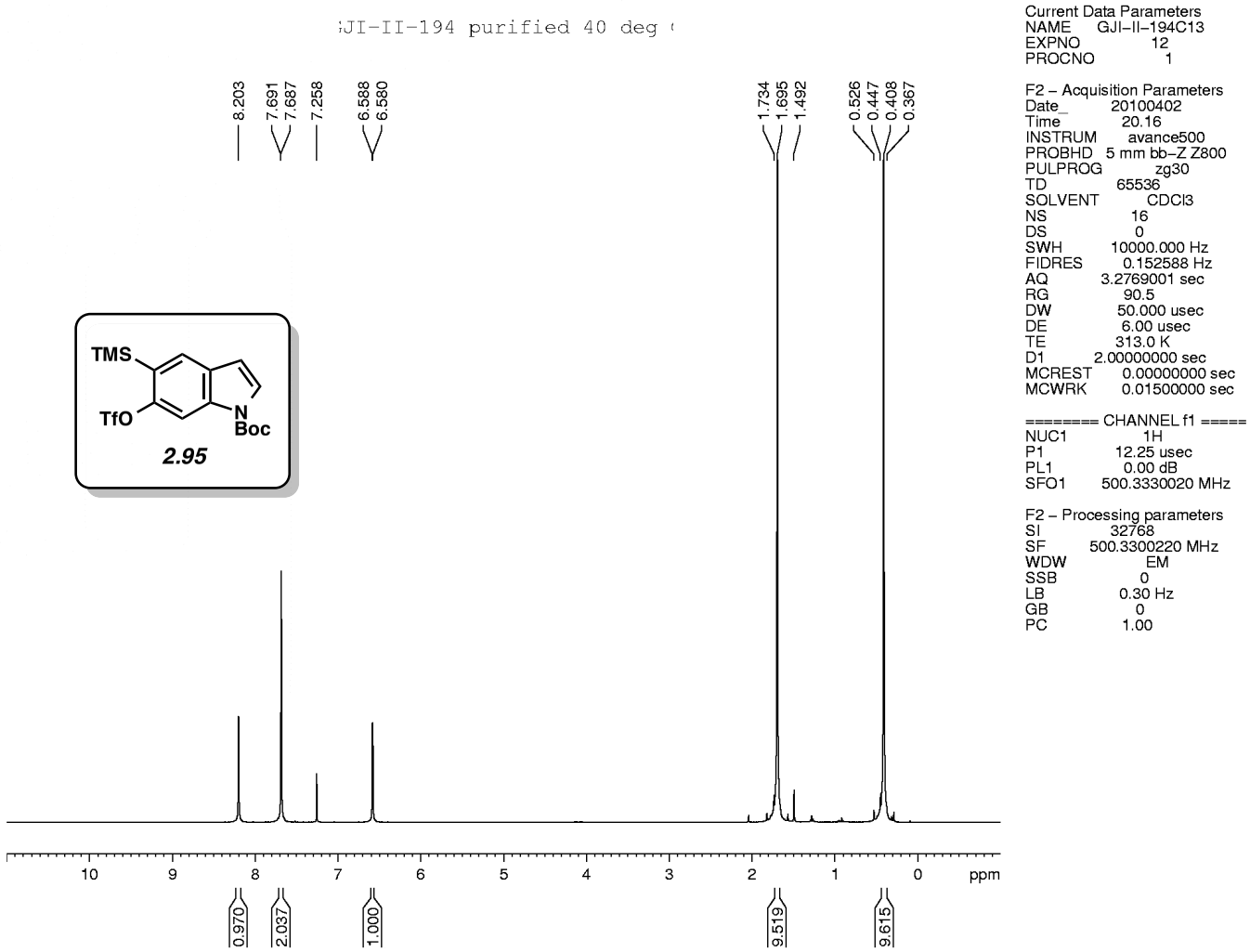



*Figure A1.151* $^{1}$H NMR (500 MHz, 40 °C, $CDCl_3$) of compound **2.95**.

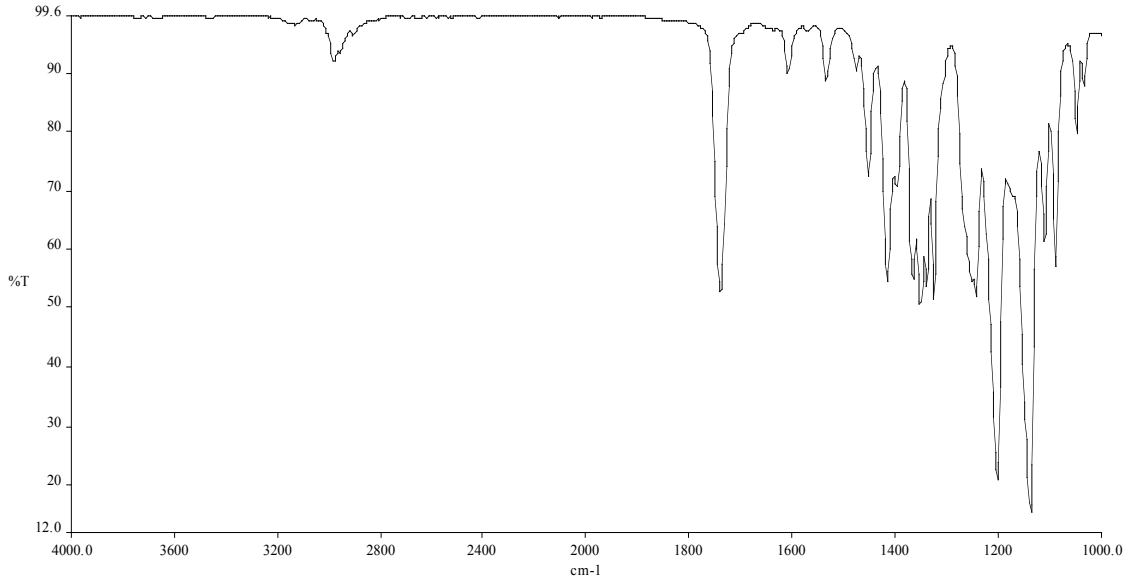



*Figure A1.152* Infrared spectrum of compound **2.95**.

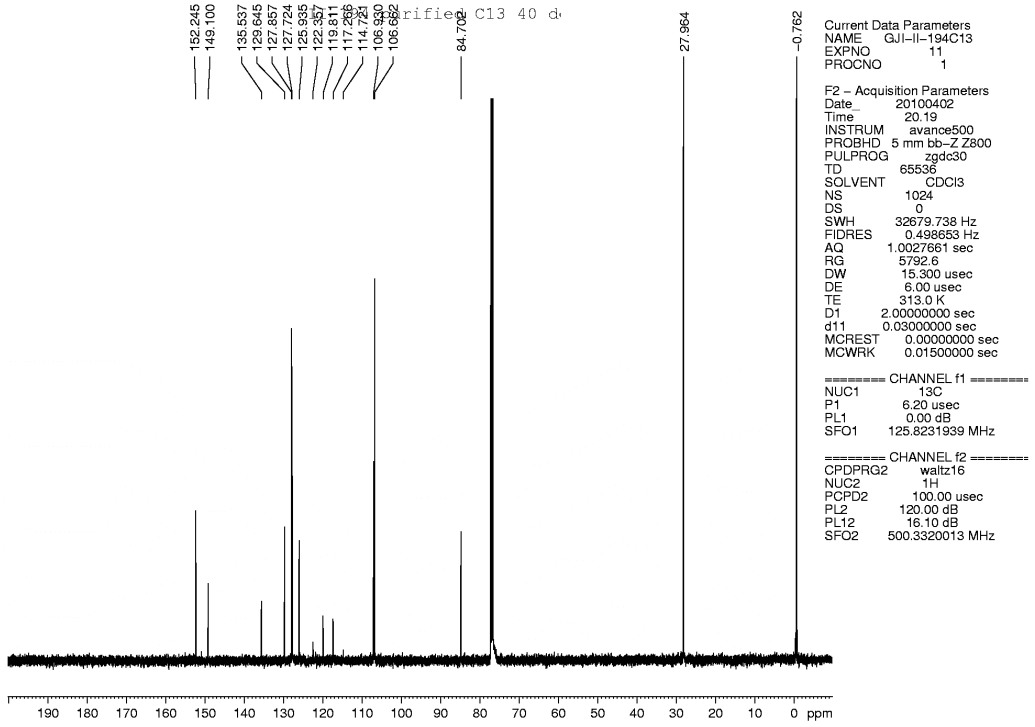



*Figure A1.153* $^{13}C$ NMR (125 MHz, 40 °C, $CDCl_3$) of compound **2.95**.

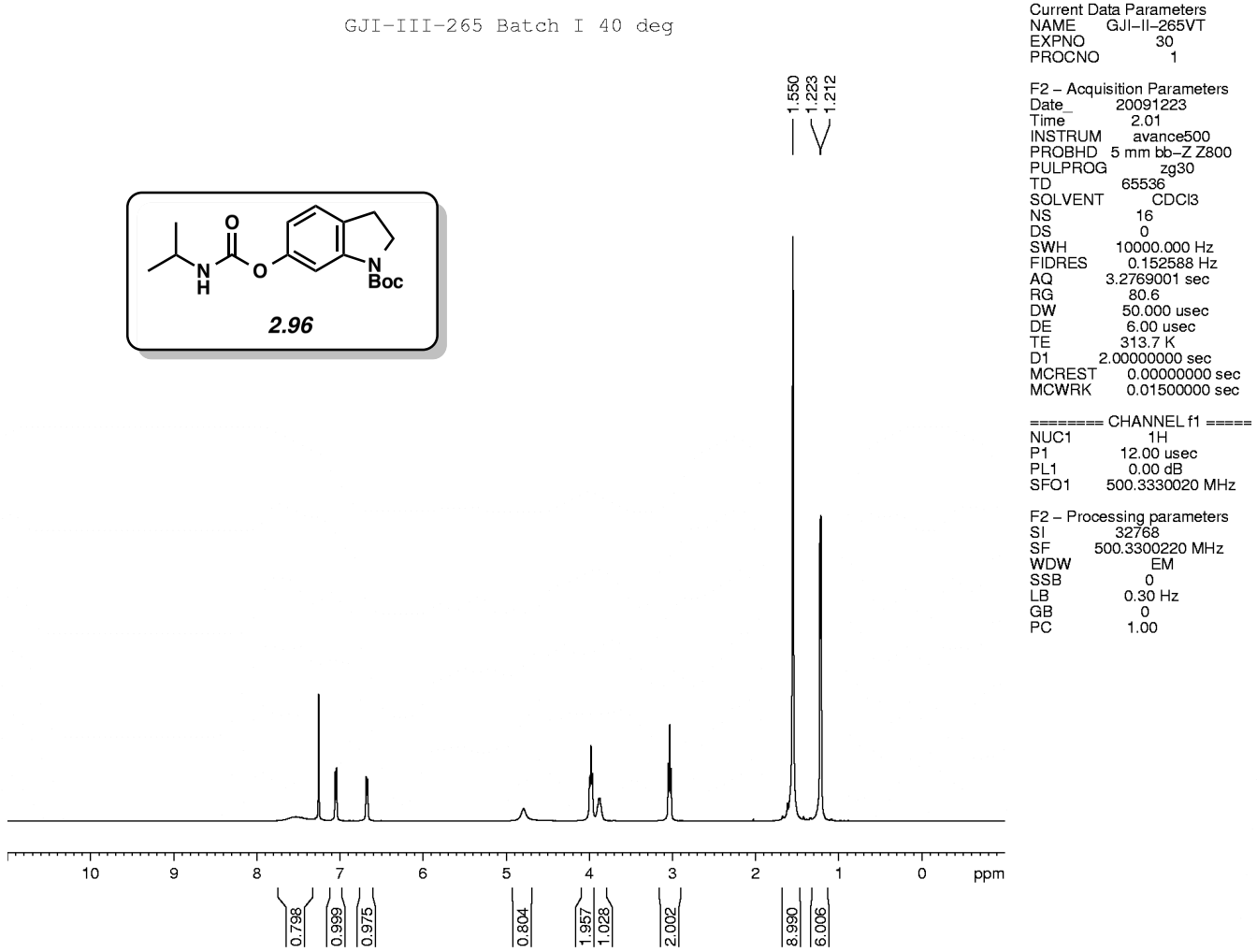



*Figure A1.154* $^{1}$H NMR (500 MHz, 40 °C, $CDCl_3$) of compound **2.96**.

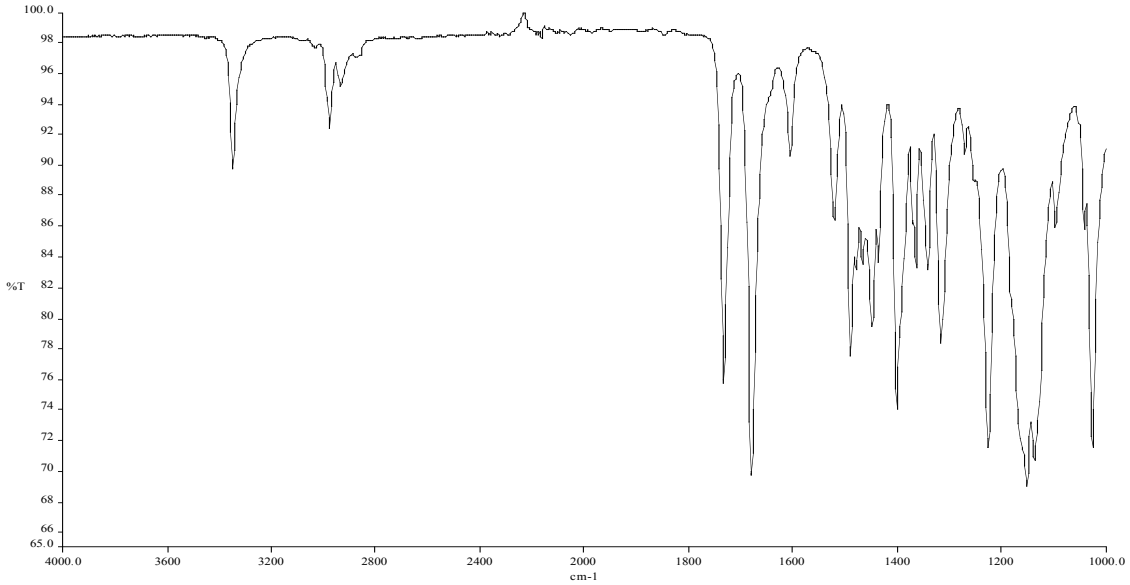



*Figure A1.155* Infrared spectrum of compound **2.96**.

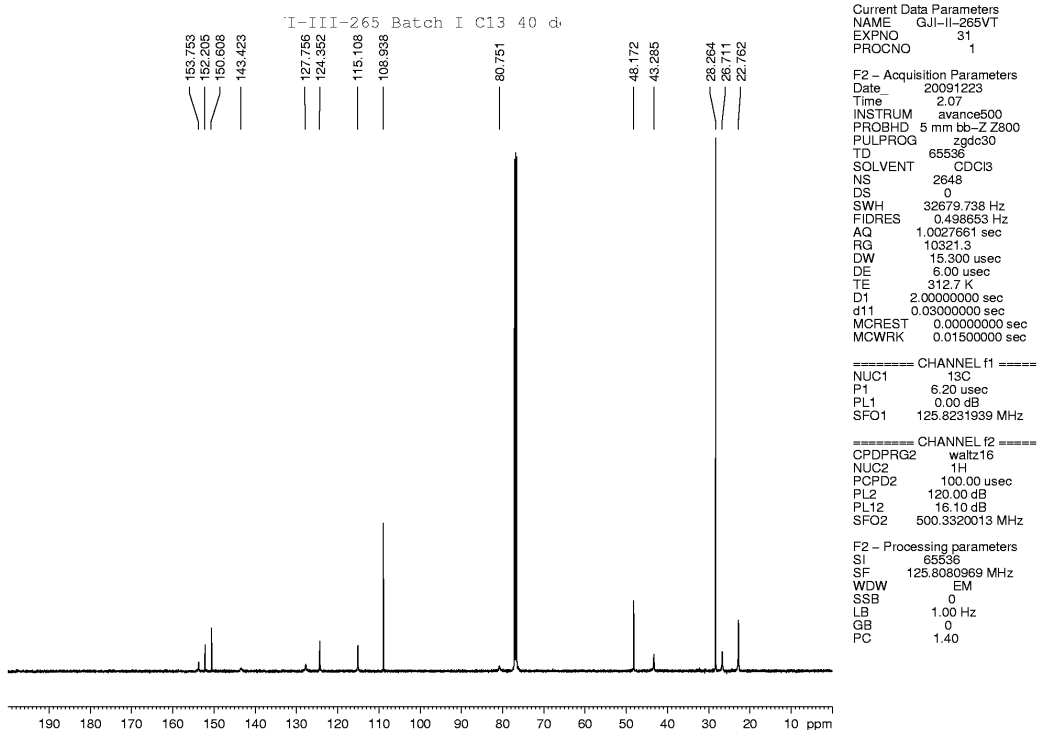



*Figure A1.156* $^{13}$C NMR (125 MHz, 40 °C, $CDCl_3$) of compound **2.96**.

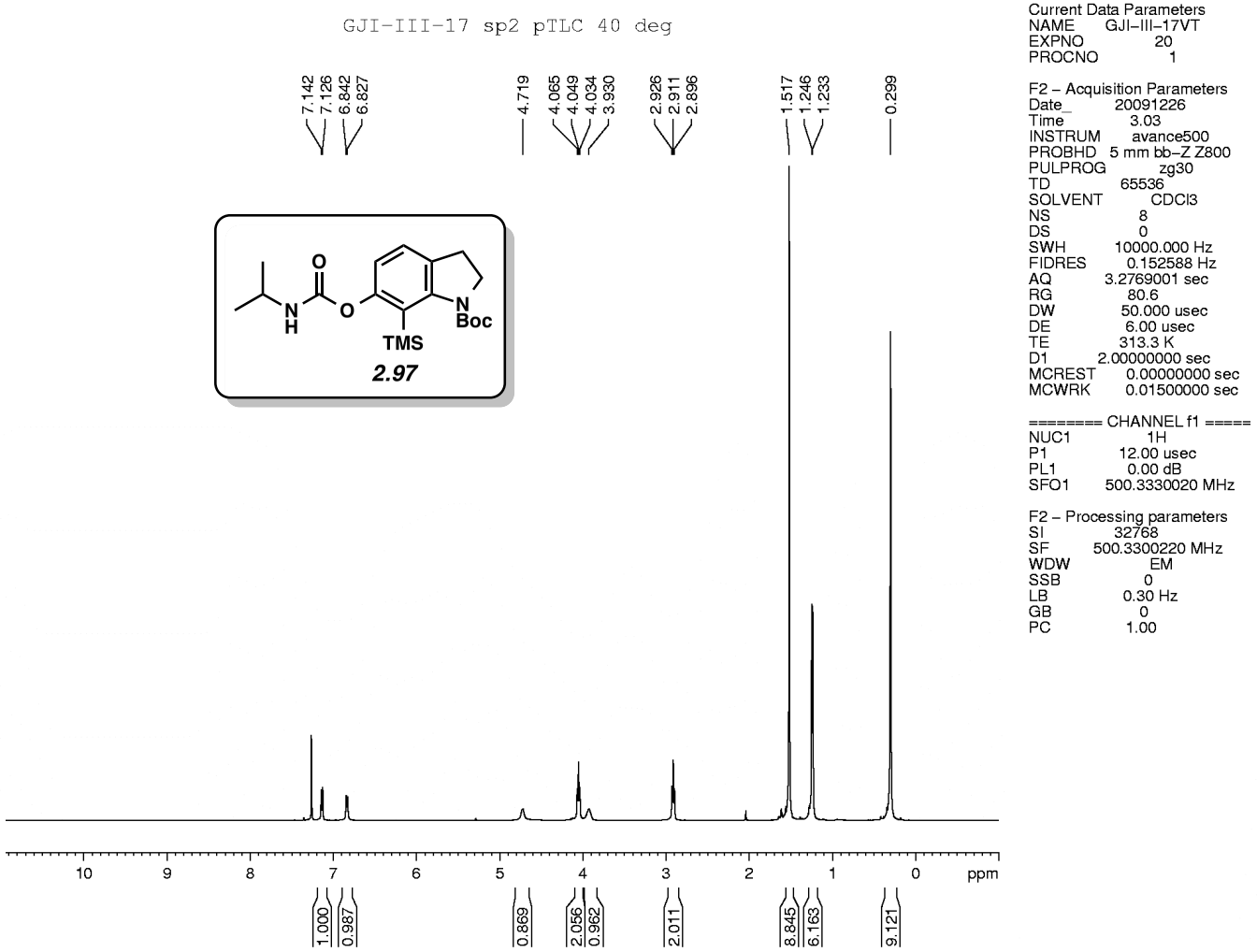



*Figure A1.157* $^{1}$H NMR (500 MHz, 40 °C, $CDCl_3$) of compound **2.97**.

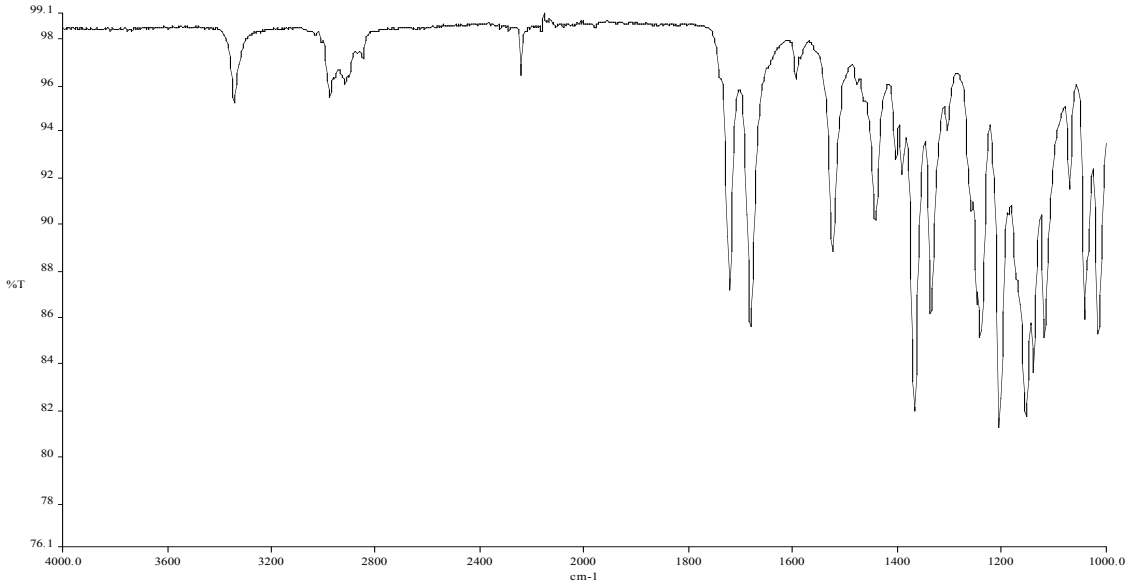



*Figure A1.158* Infrared spectrum of compound **2.97**.

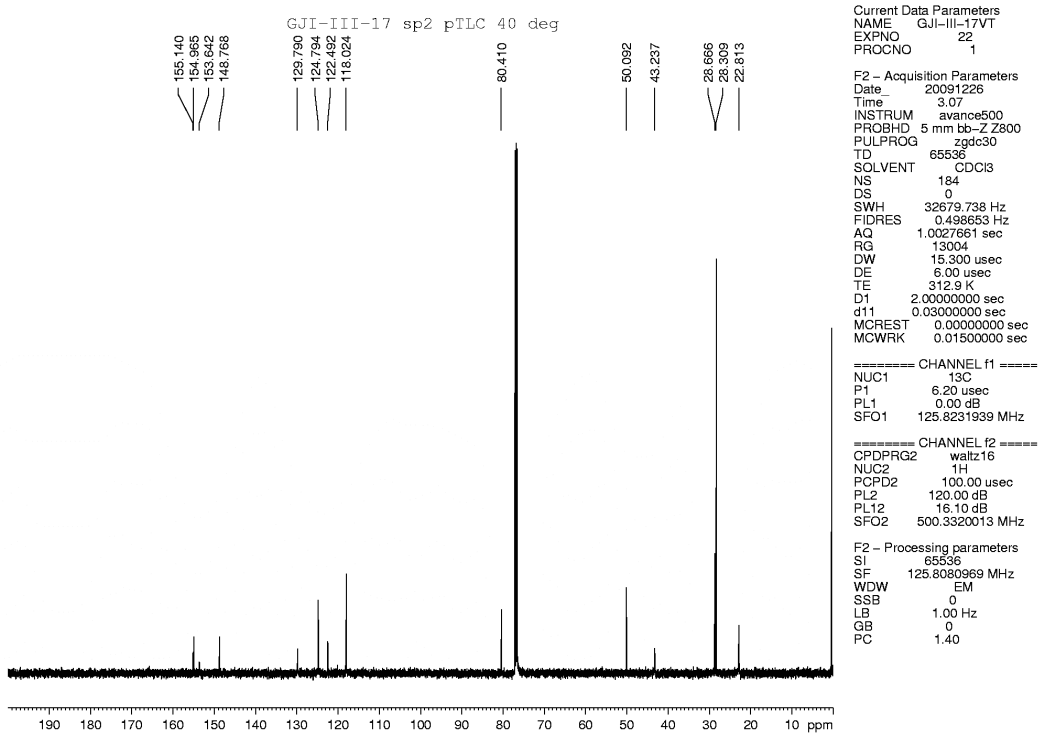



*Figure A1.159* $^{13}$C NMR (125 MHz, 40 °C, $CDCl_3$) of compound **2.97**.

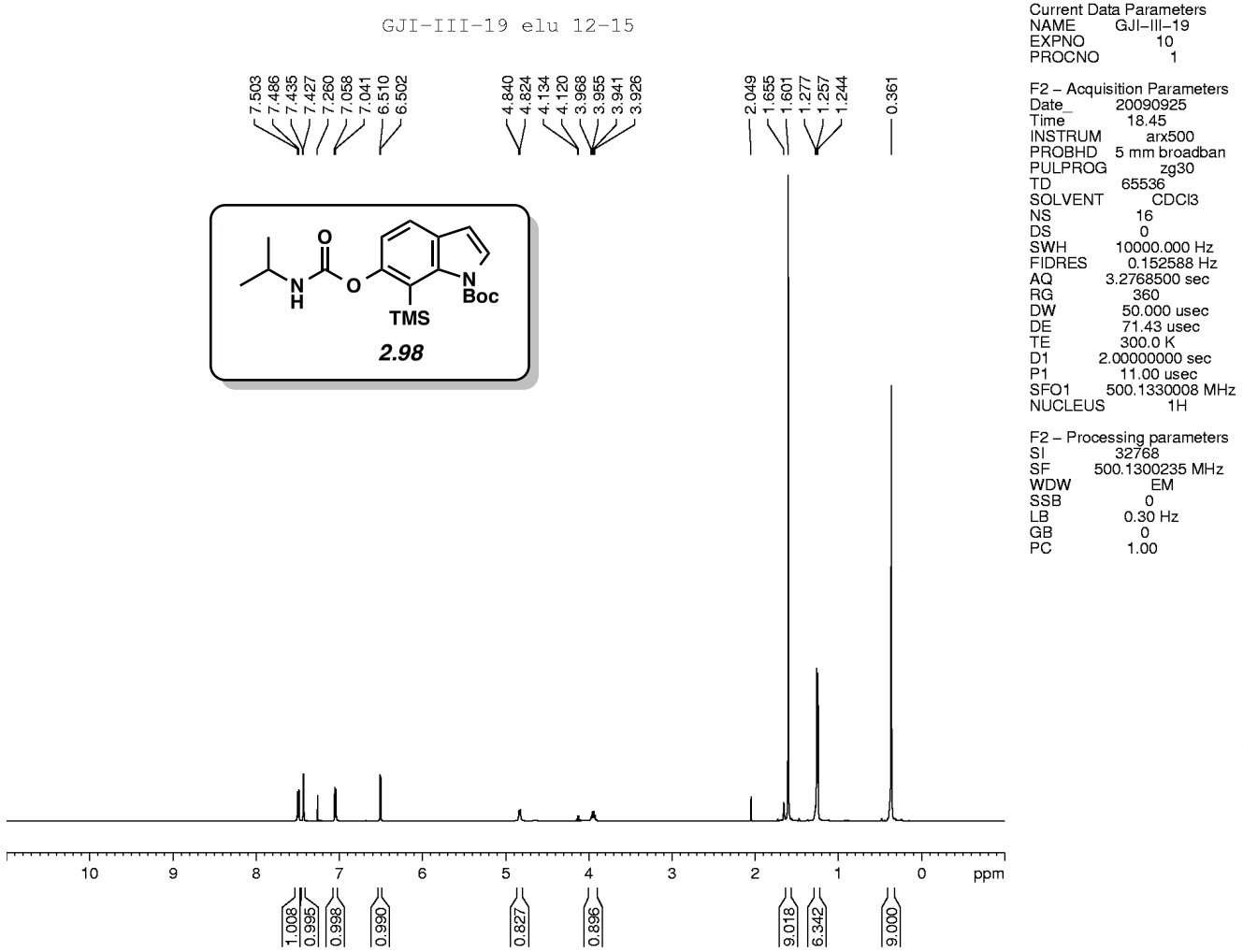



*Figure A1.160* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **2.98**.

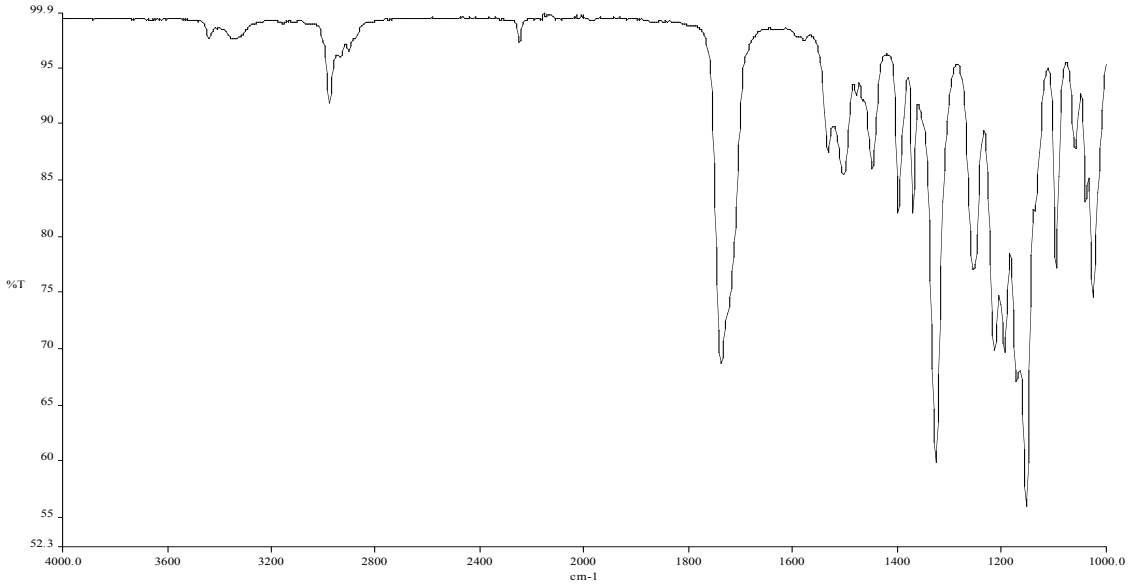



*Figure A1.161* Infrared spectrum of compound **2.98**.

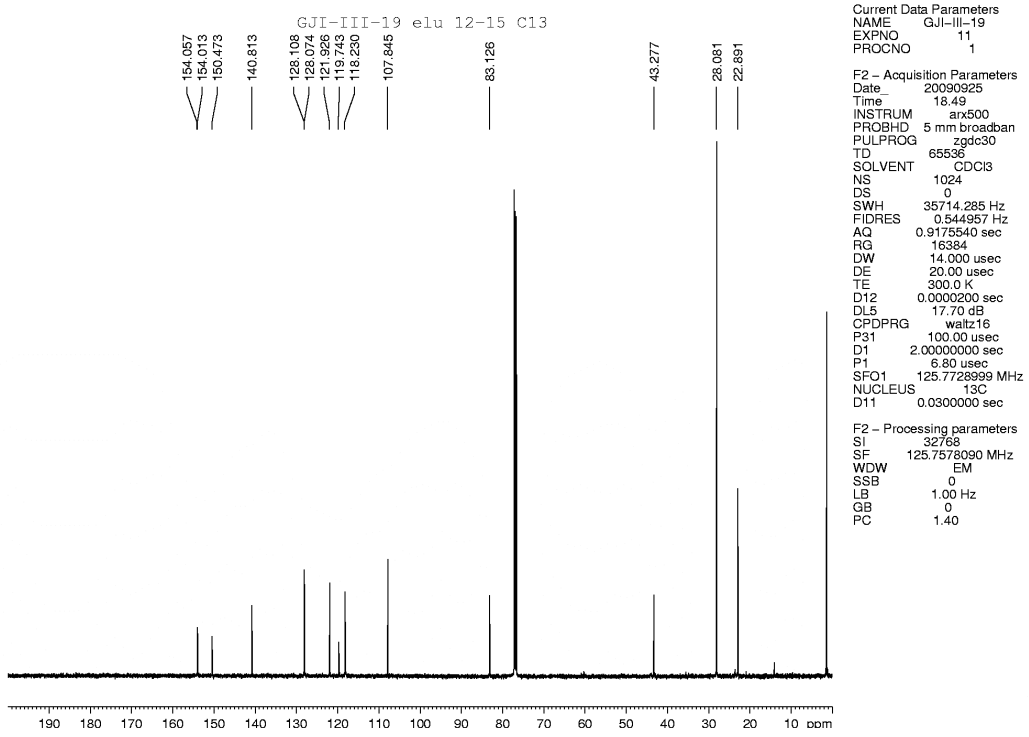



*Figure A1.162* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compound **2.98**.

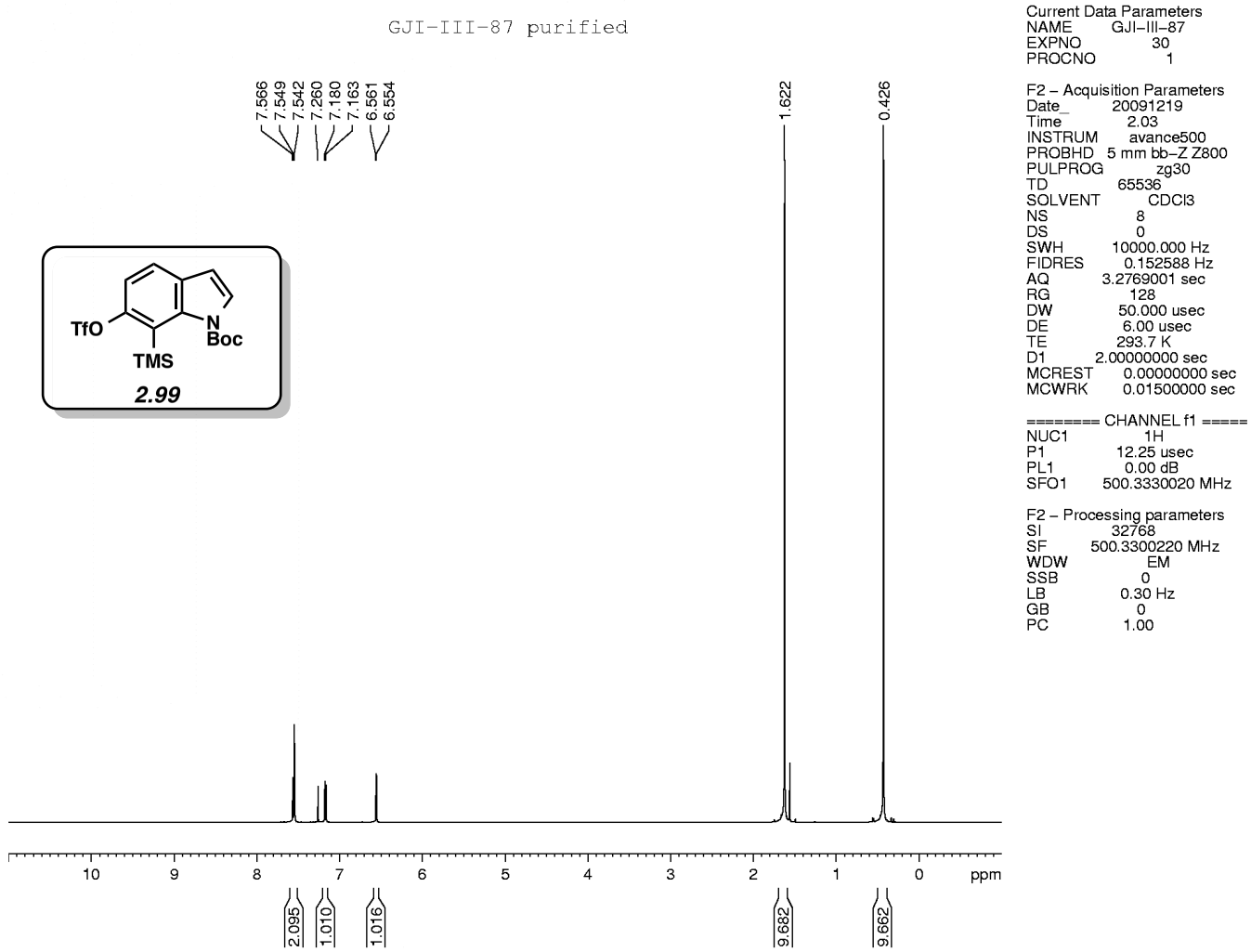



*Figure A1.163* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **2.99**.

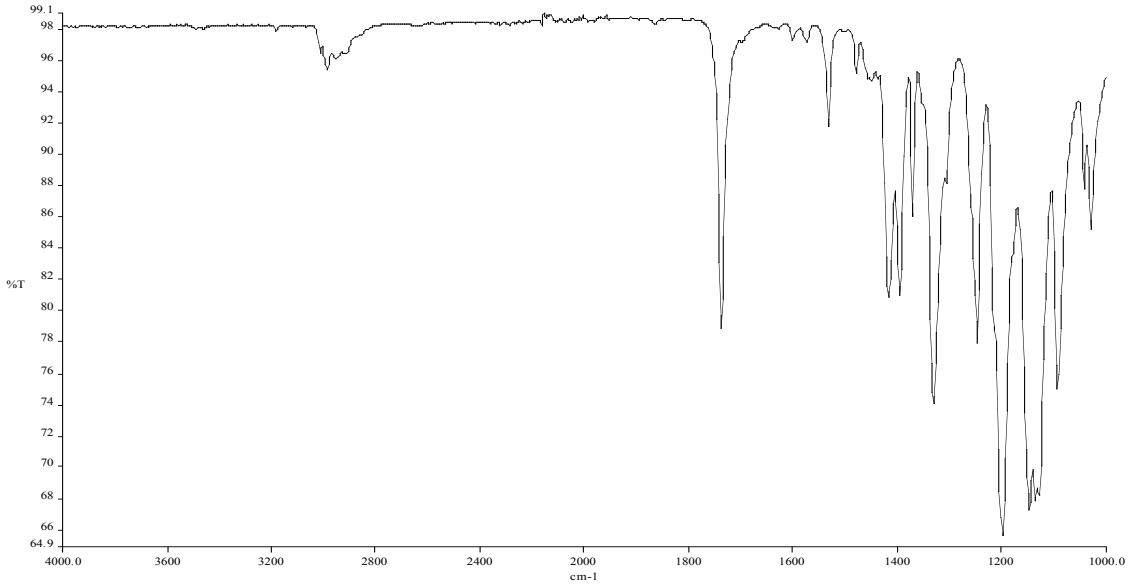



*Figure A1.164* Infrared spectrum of compound **2.99**.

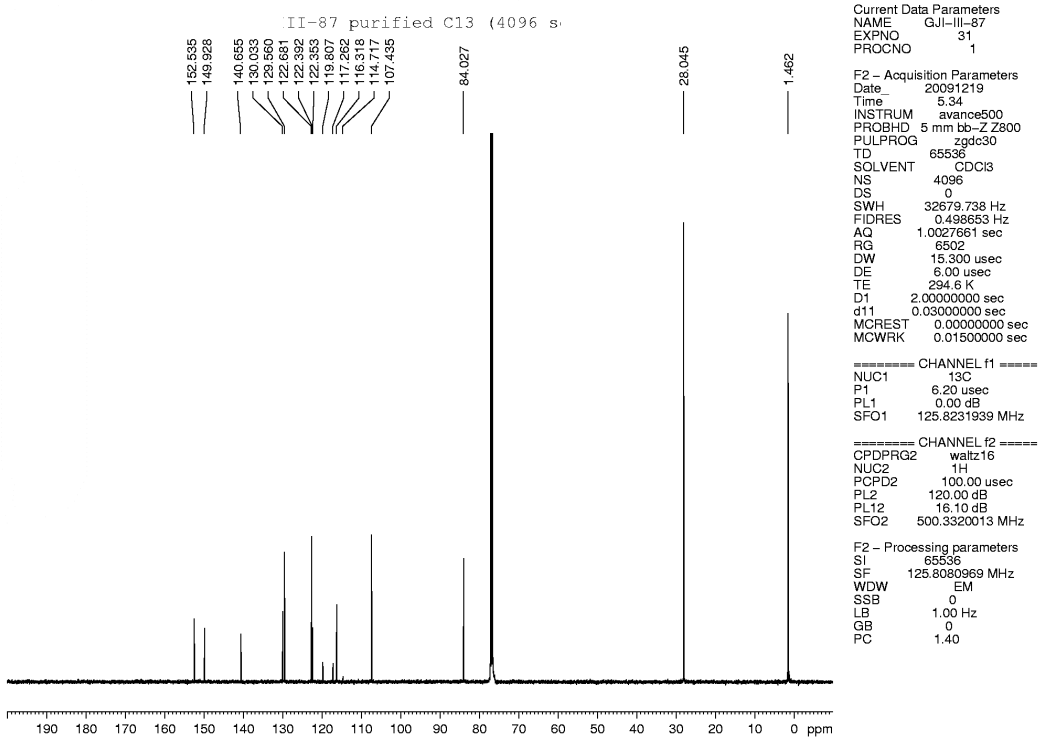



*Figure A1.165* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compound **2.99**.

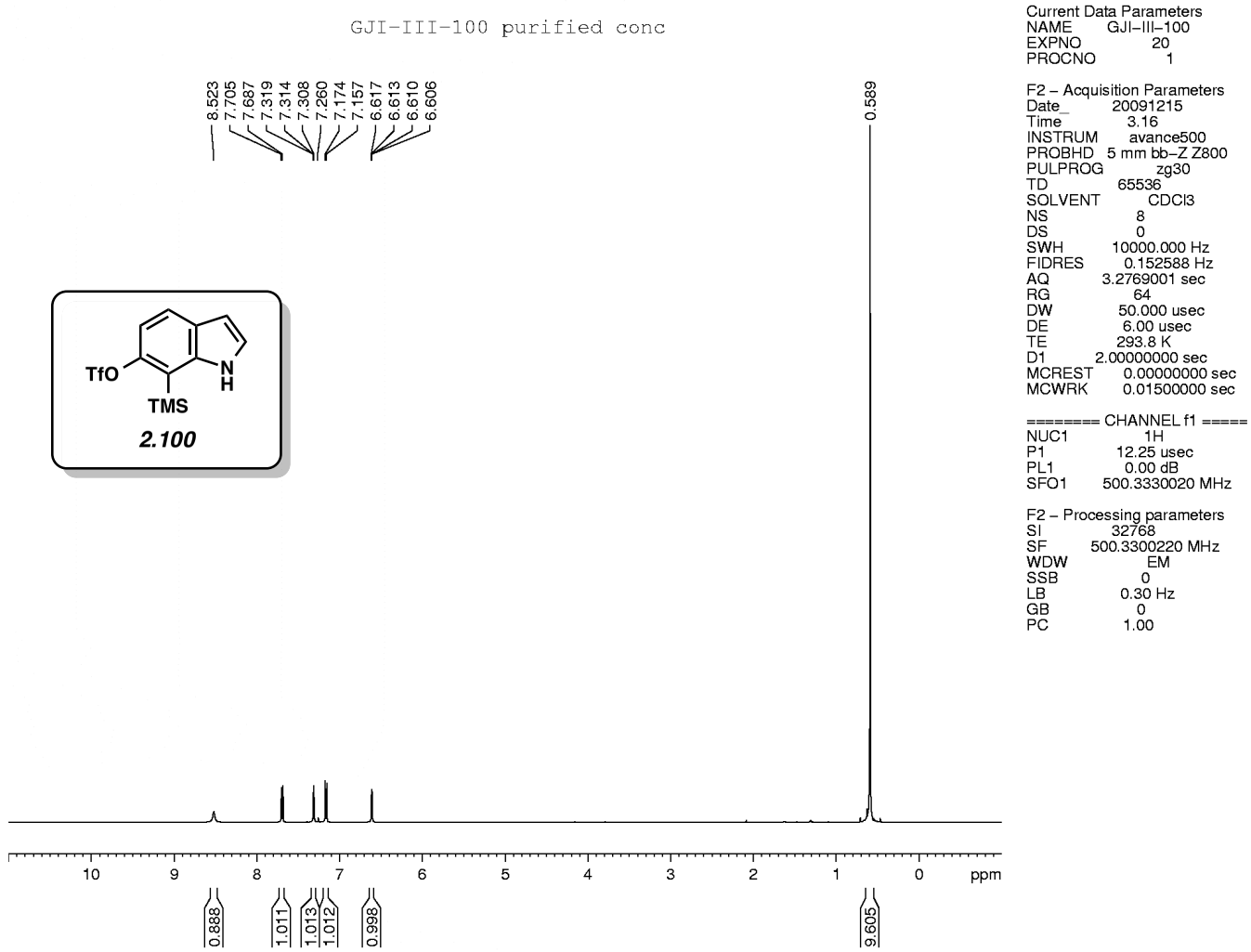



*Figure A1.166* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **2.100**.

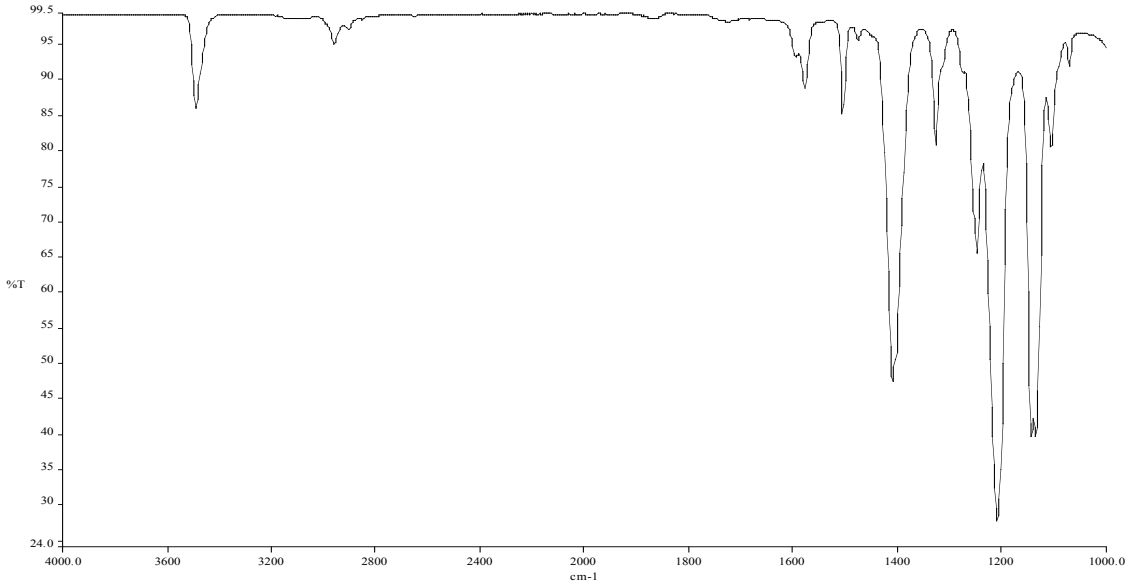



*Figure A1.167* Infrared spectrum of compound **2.100**.

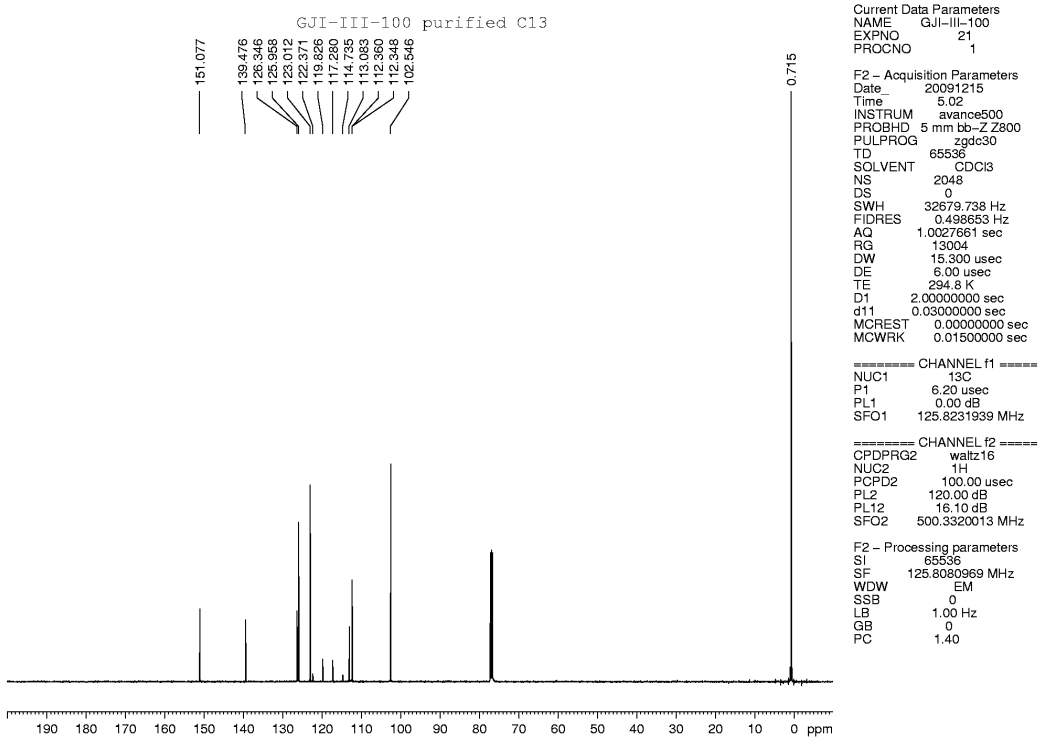



*Figure A1.168* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compound **2.100**.

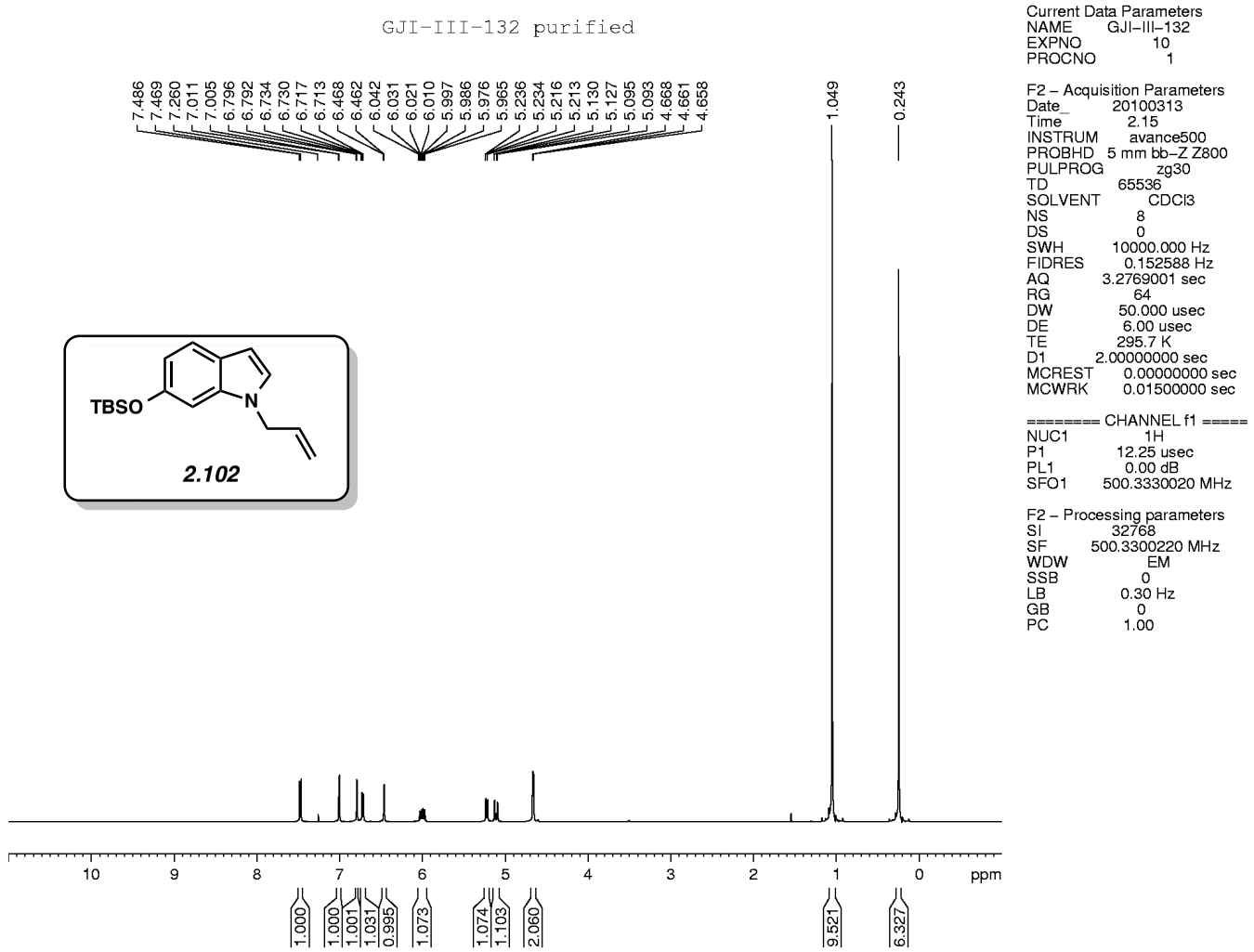



*Figure A1.169* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **2.102**.

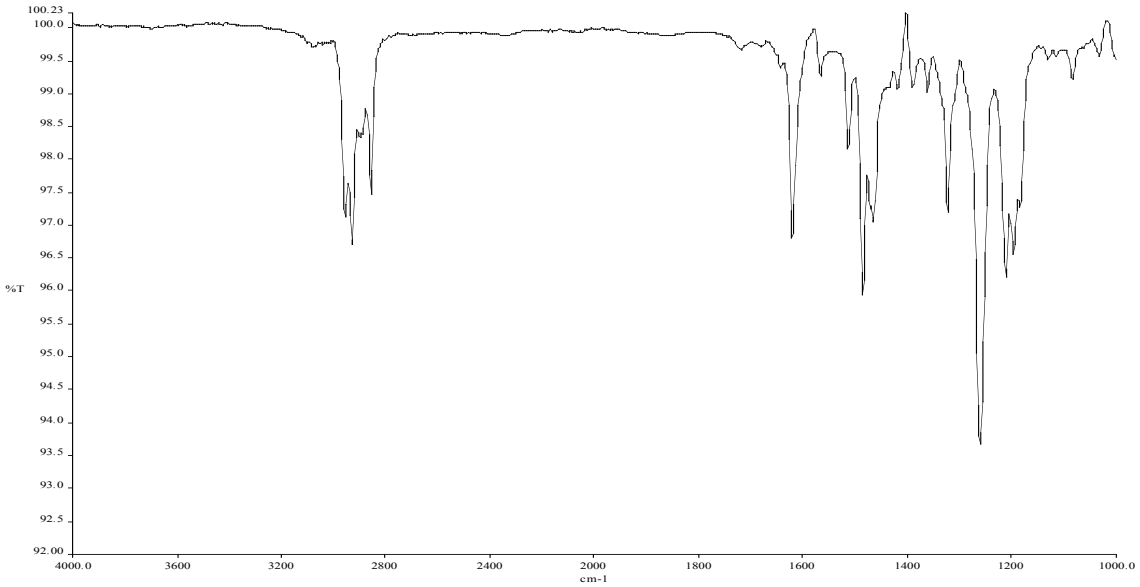



*Figure A1.170* Infrared spectrum of compound **2.102**.

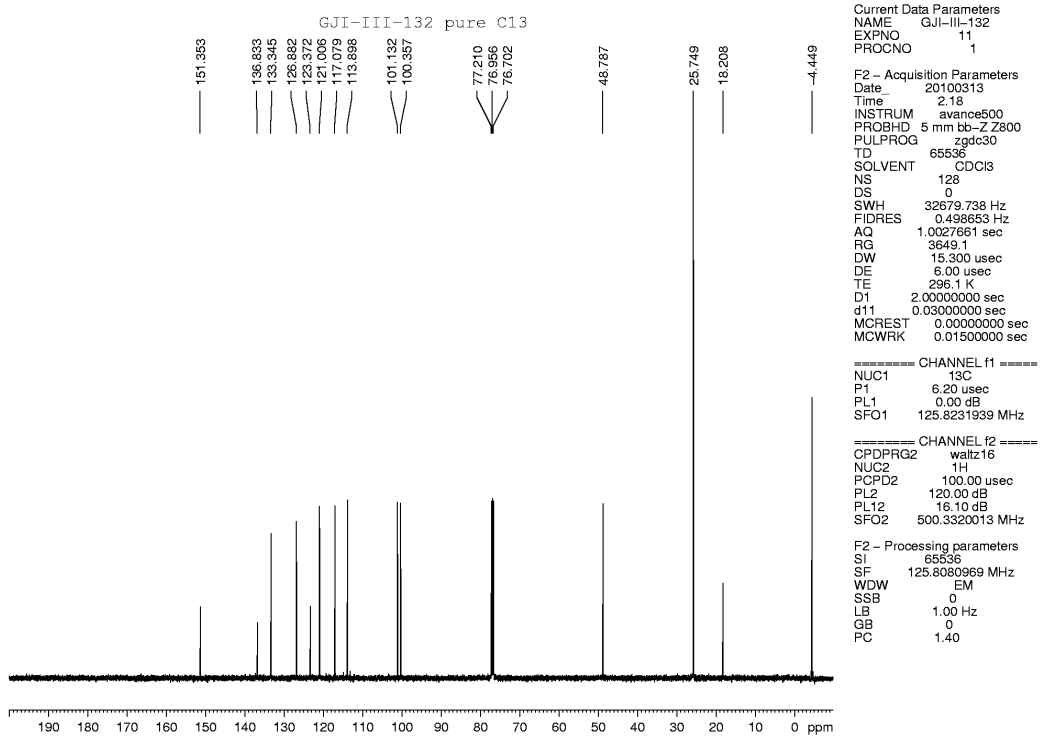



*Figure A1.171* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compound **2.102**.

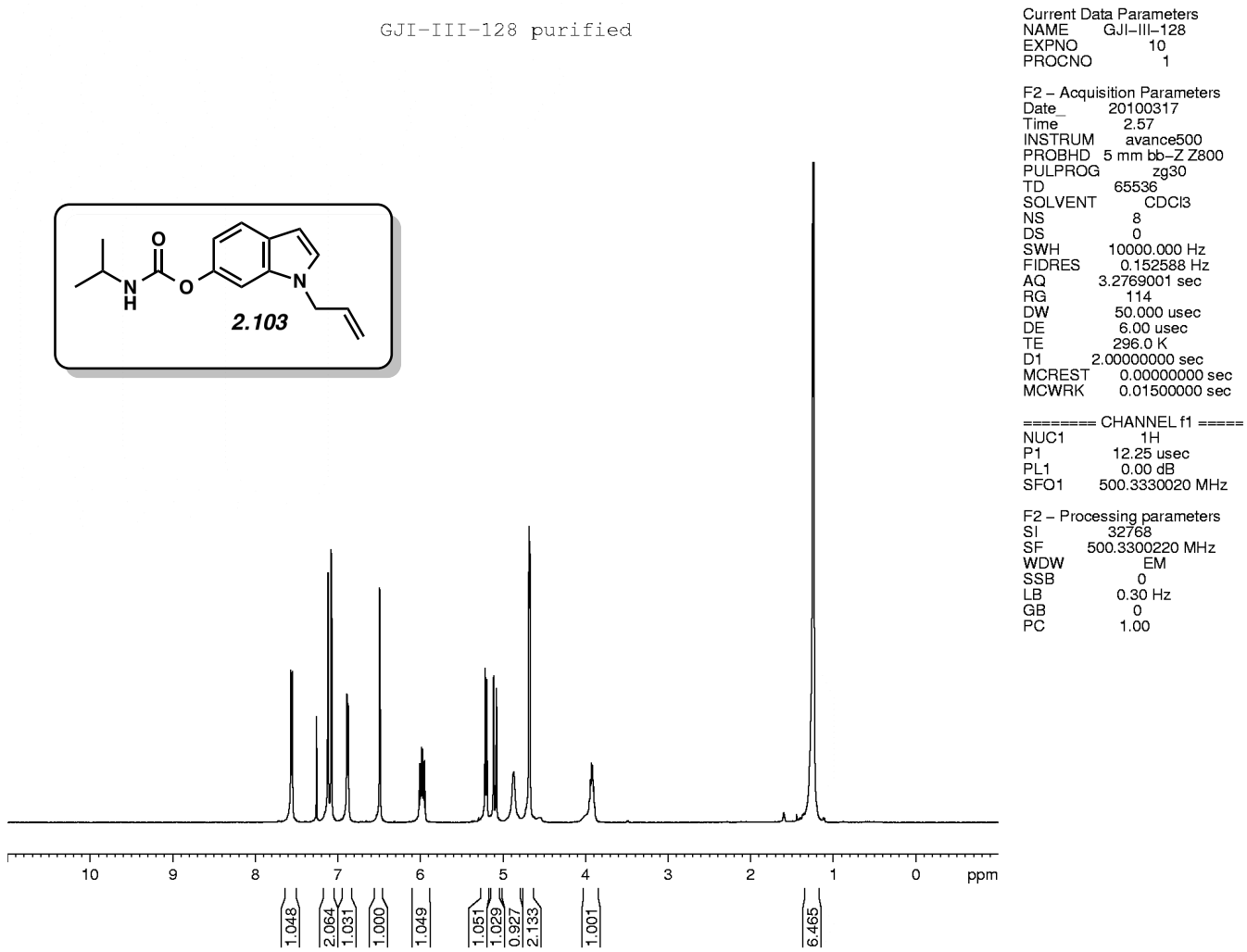



*Figure A1.172* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **2.103**.

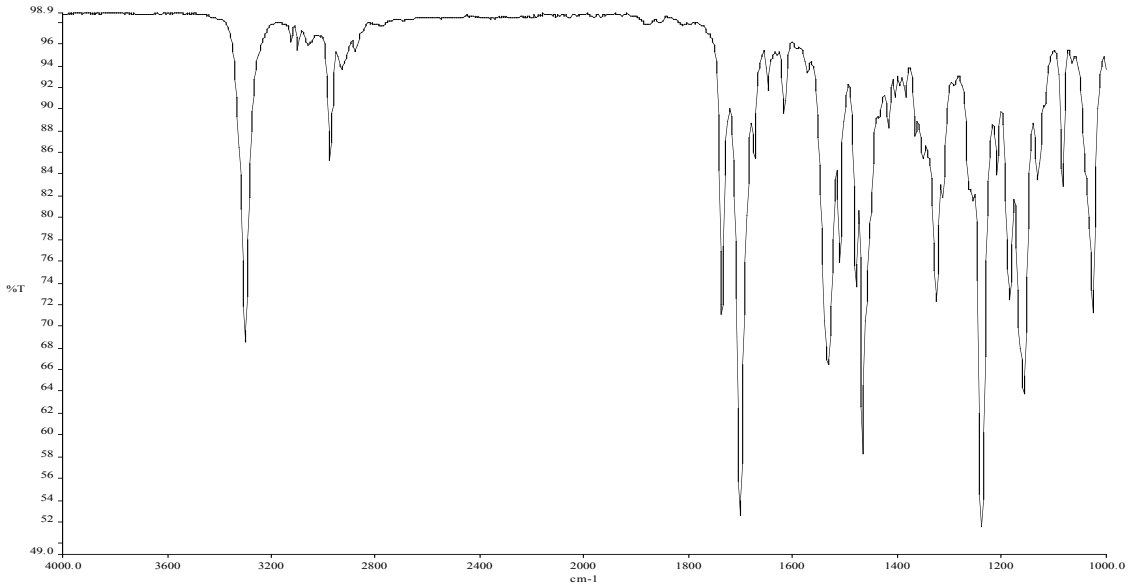



*Figure A1.173* Infrared spectrum of compound **2.103**.

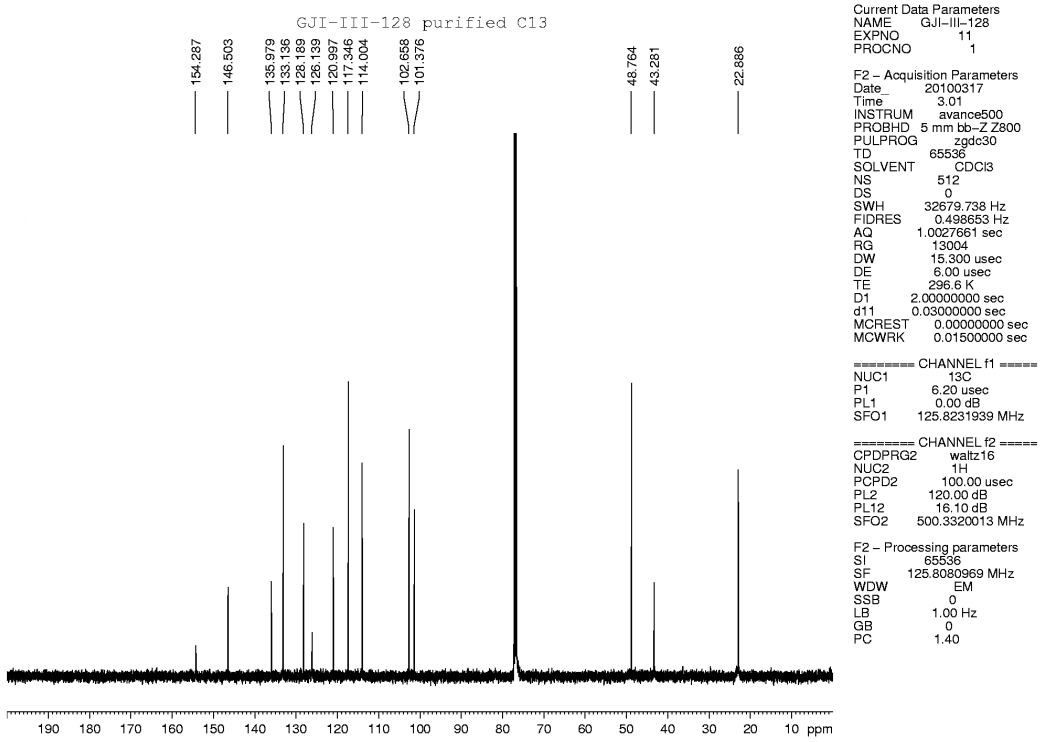



*Figure A1.174* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compound **2.103**.

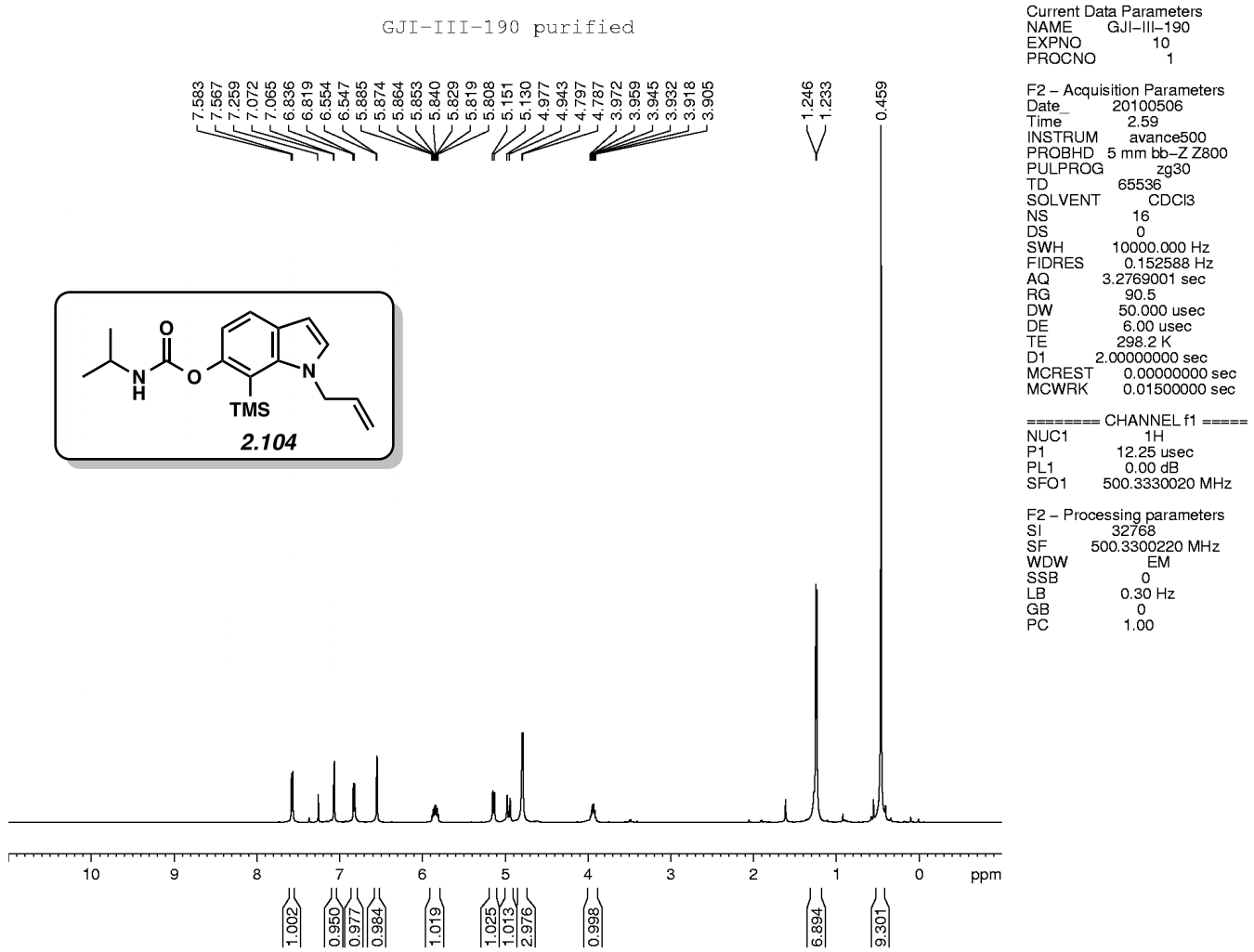



*Figure A1.175* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **2.104**.

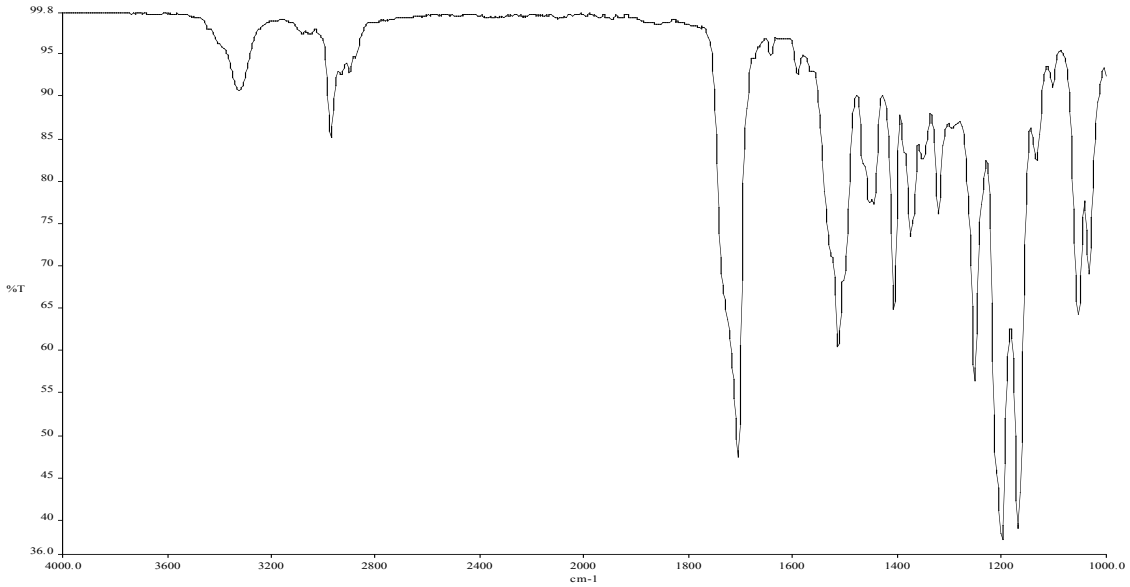



*Figure A1.176* Infrared spectrum of compound **2.104**.

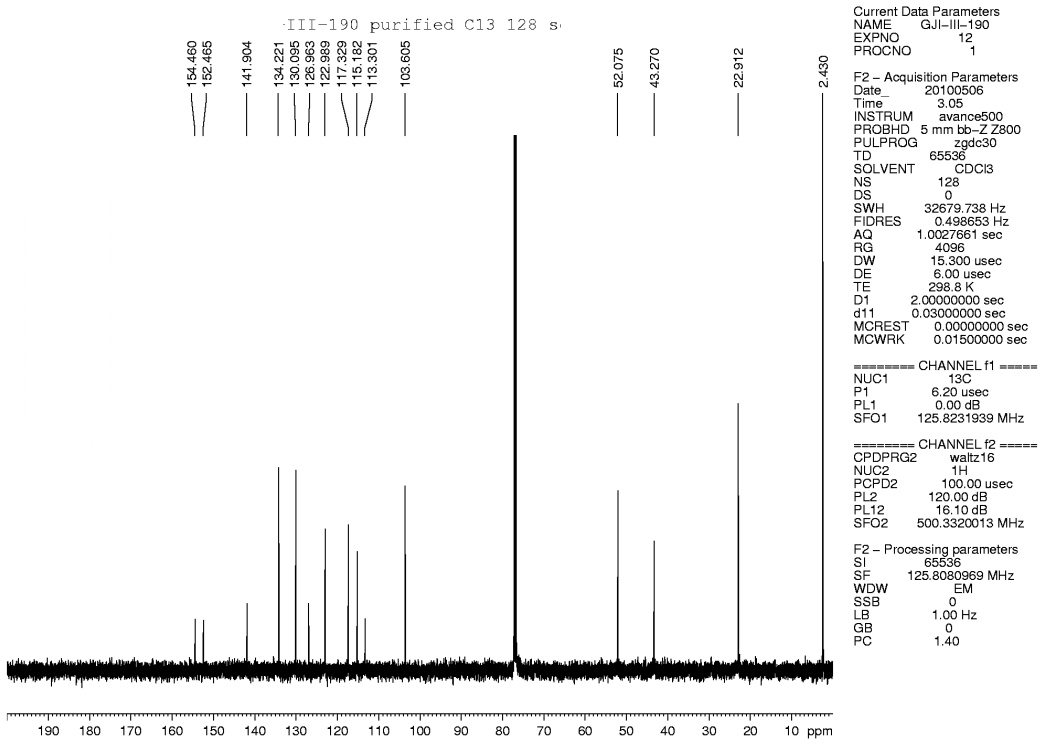



*Figure A1.177* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compound **2.104**.

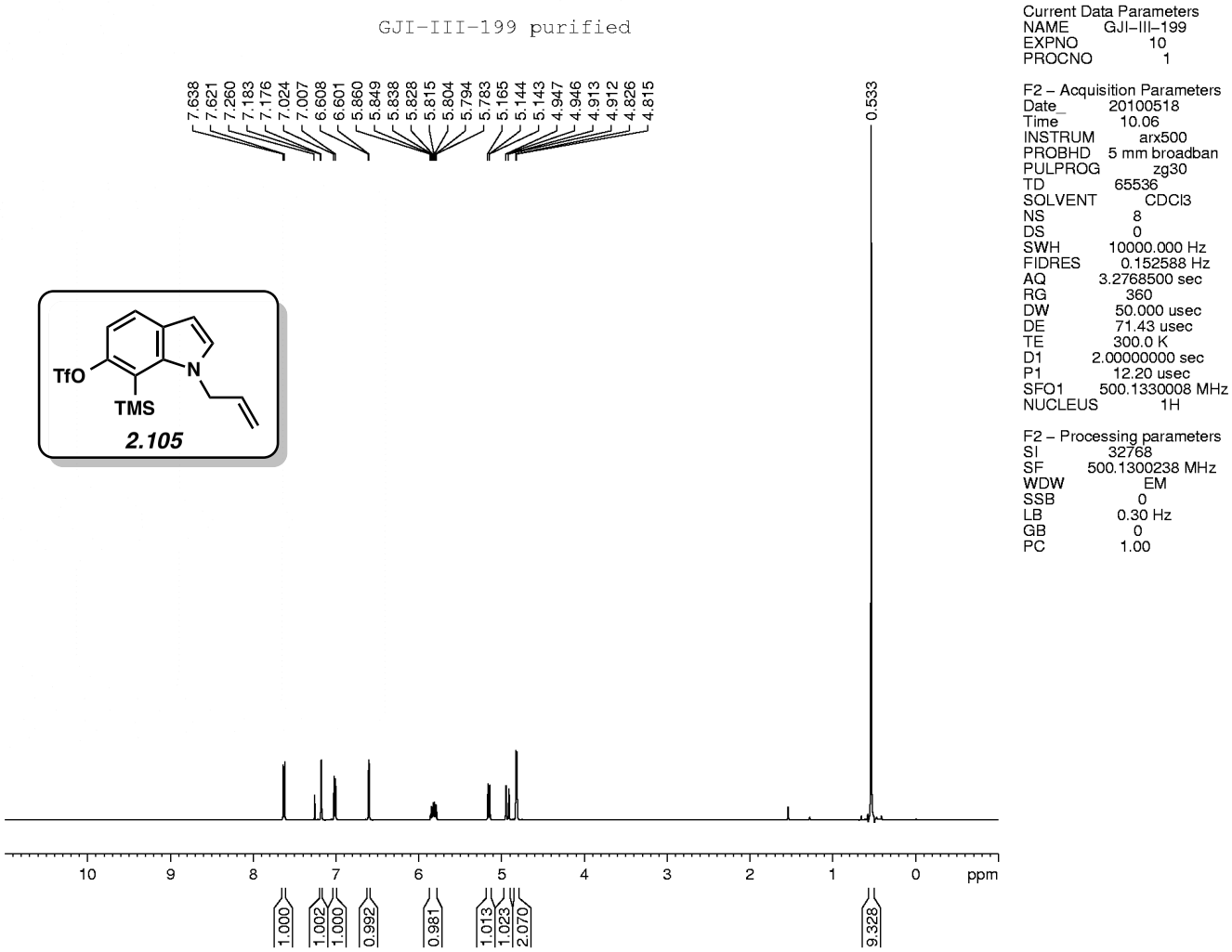



*Figure A1.178* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **2.105**.

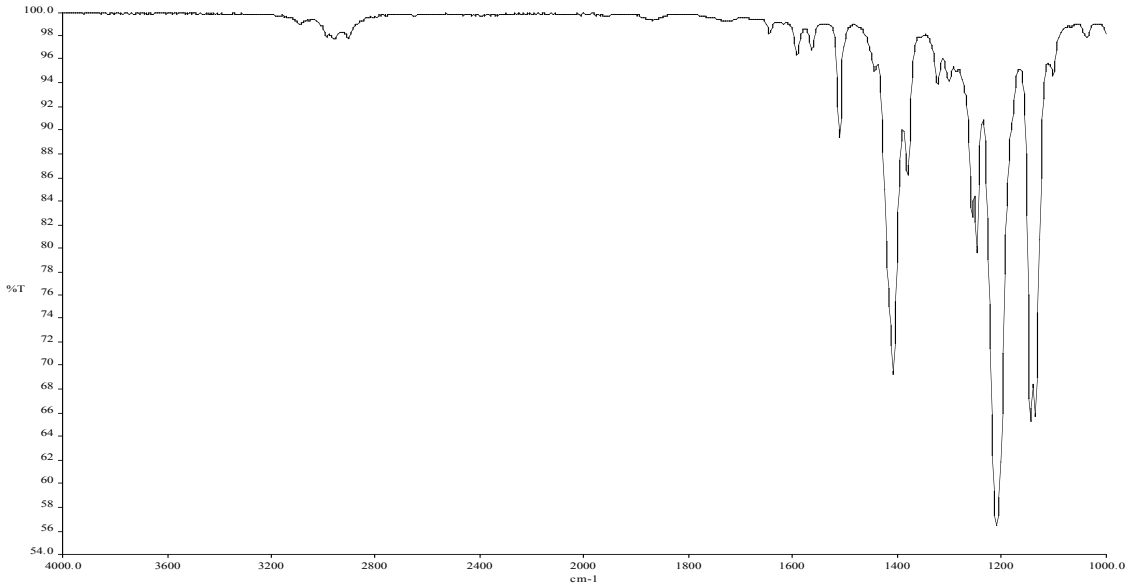



*Figure A1.179* Infrared spectrum of compound **2.105**.

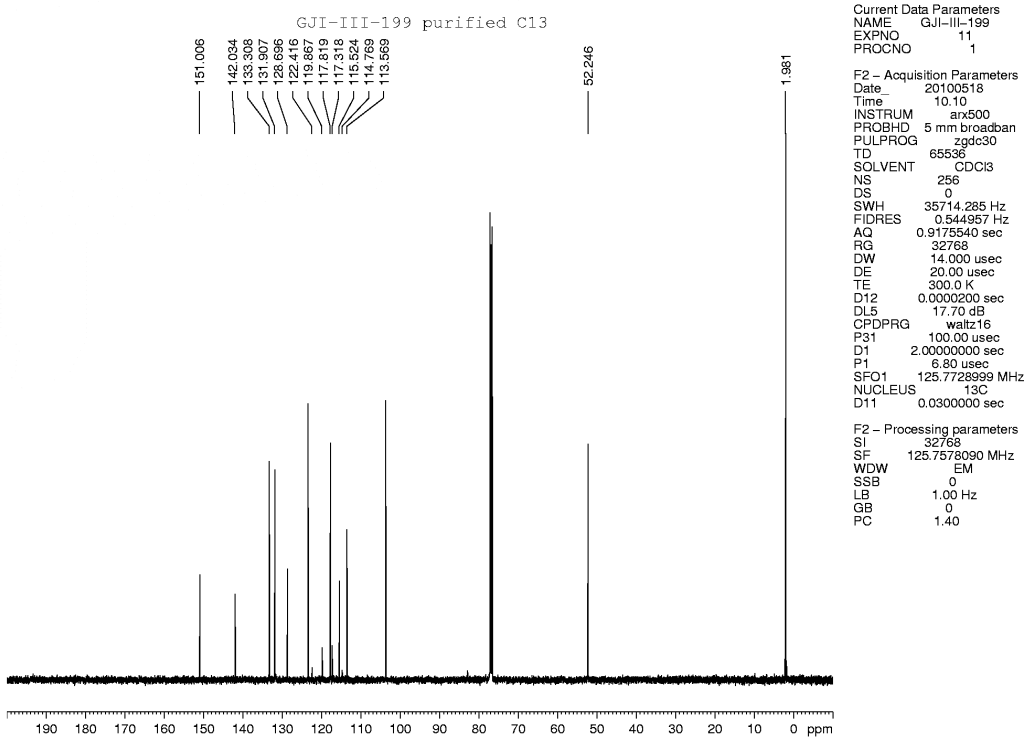



*Figure A1.180* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compound **2.105**.

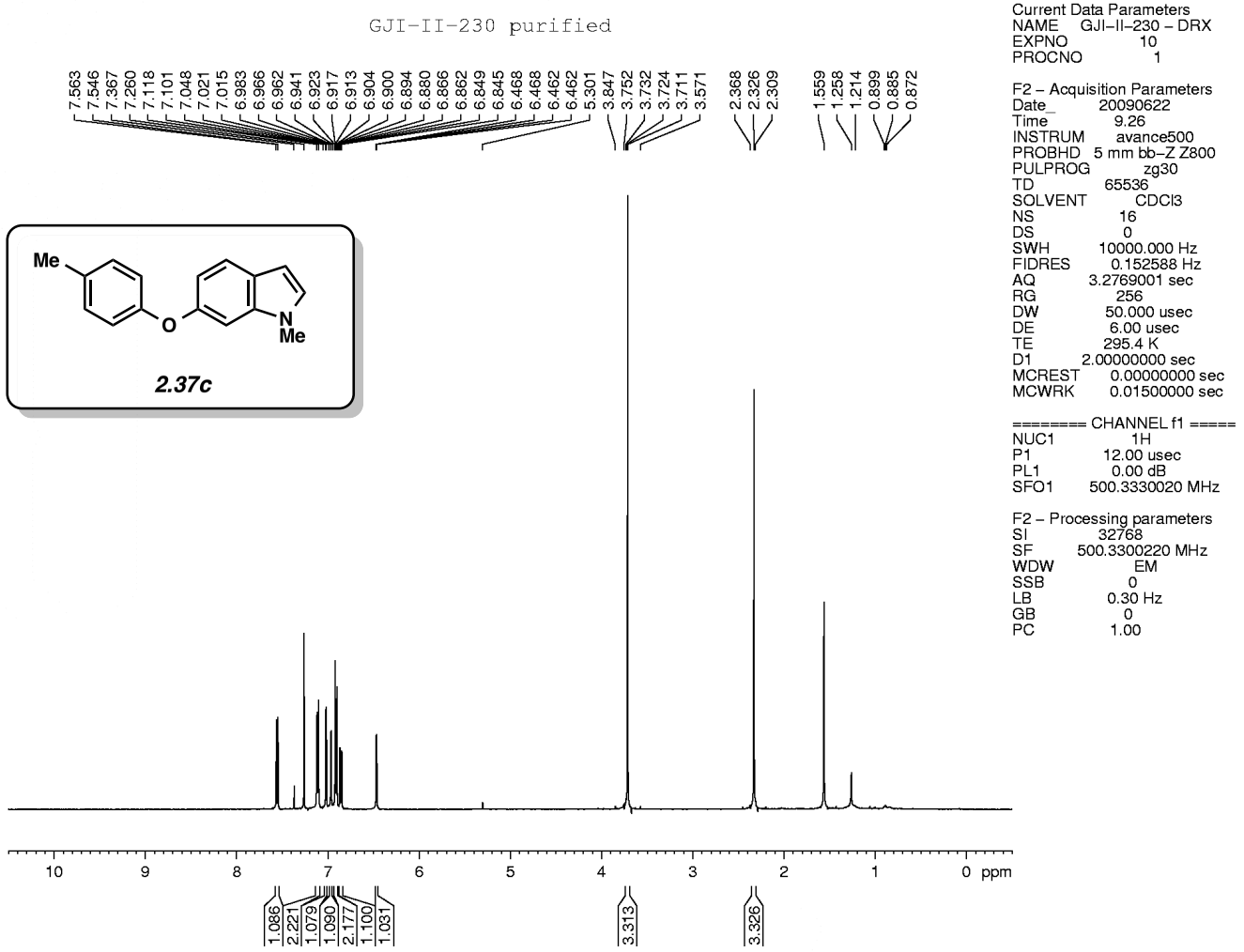



*Figure A1.181* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **2.37c**.

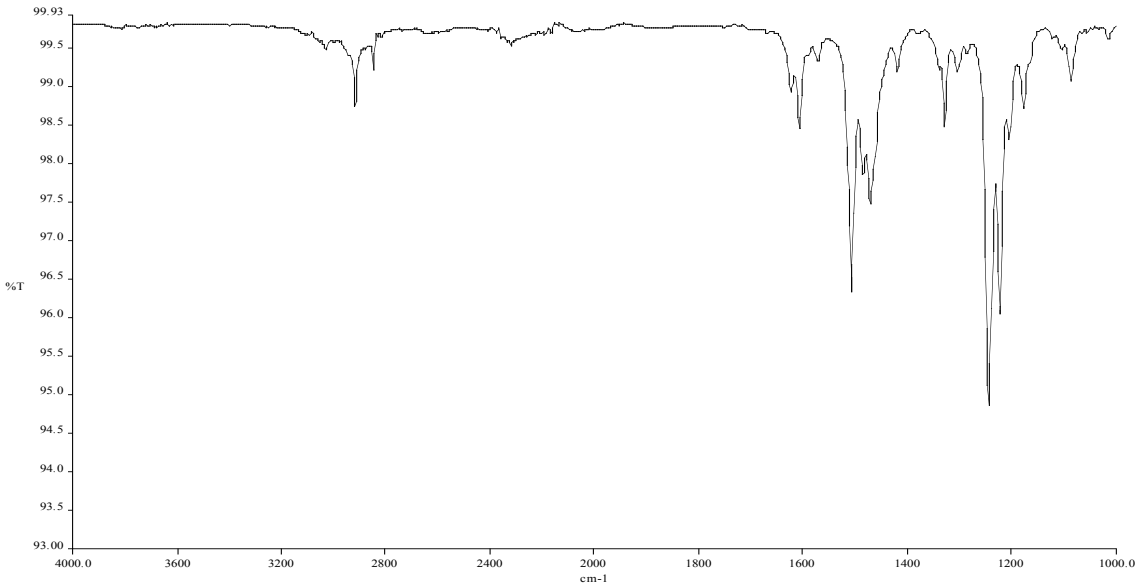



*Figure A1.182* Infrared spectrum of compound **2.37c**.

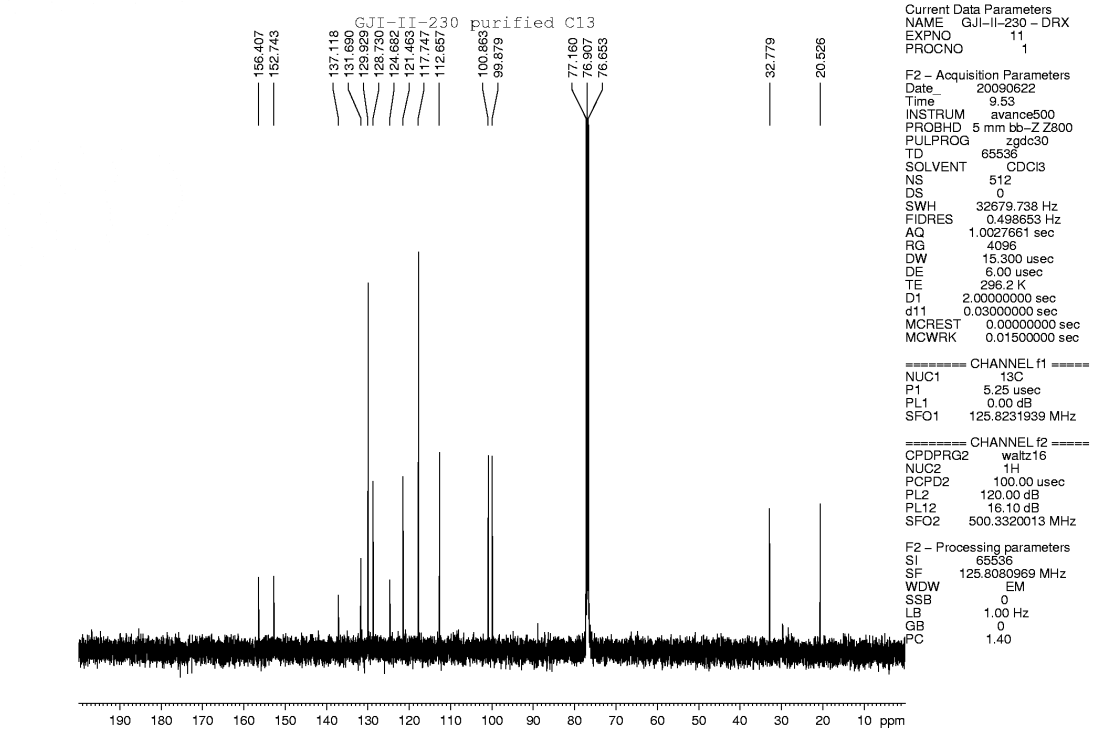



*Figure A1.183* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compound **2.37c**.

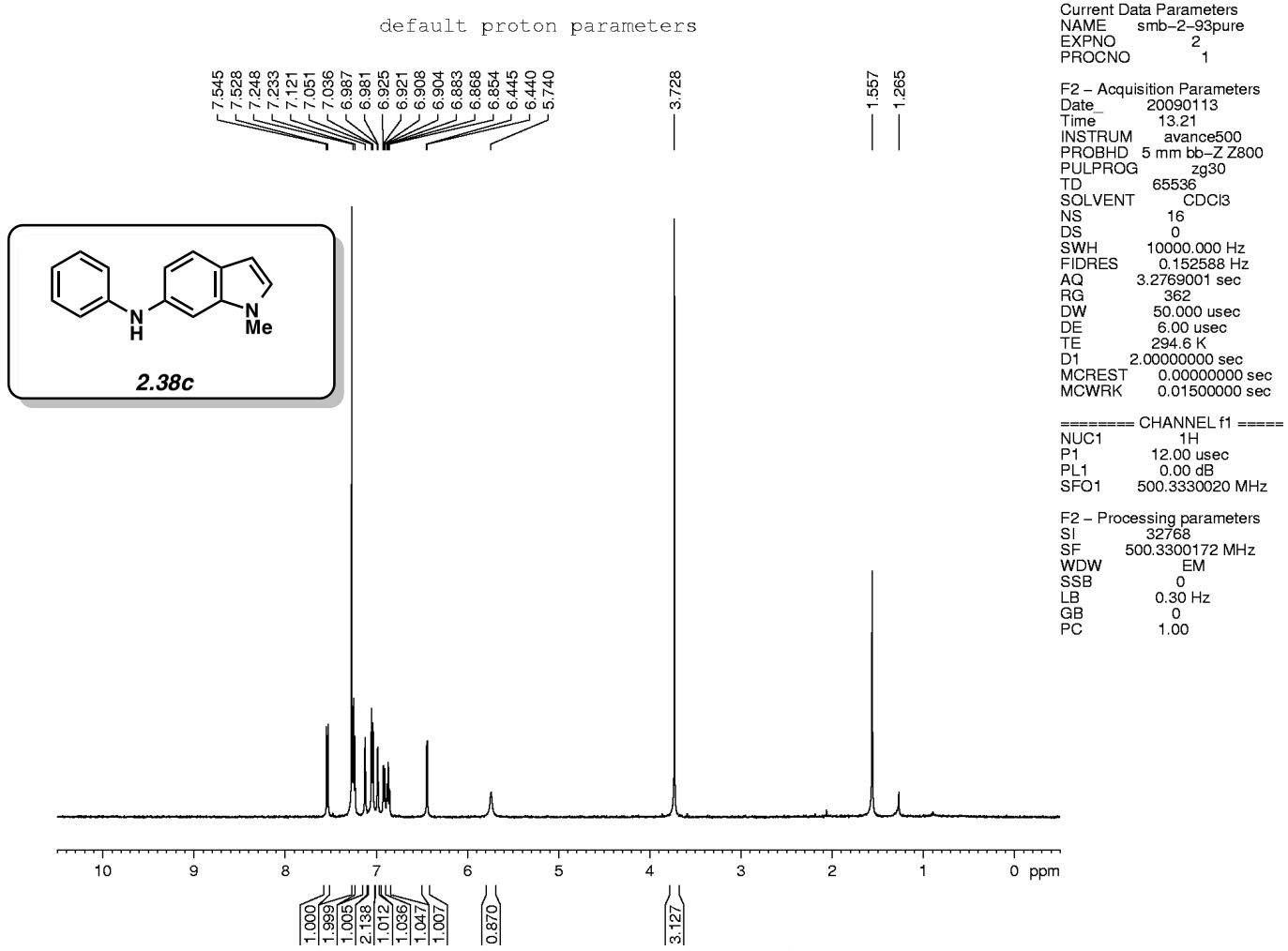



*Figure A1.184* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **2.38c**.

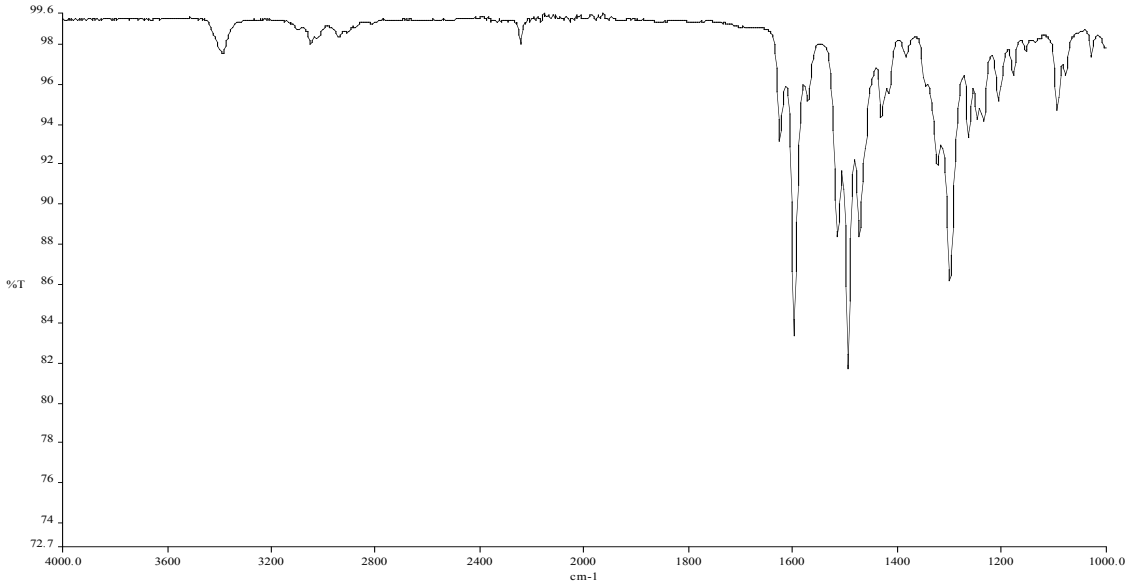



*Figure A1.185* Infrared spectrum of compound **2.38c**.

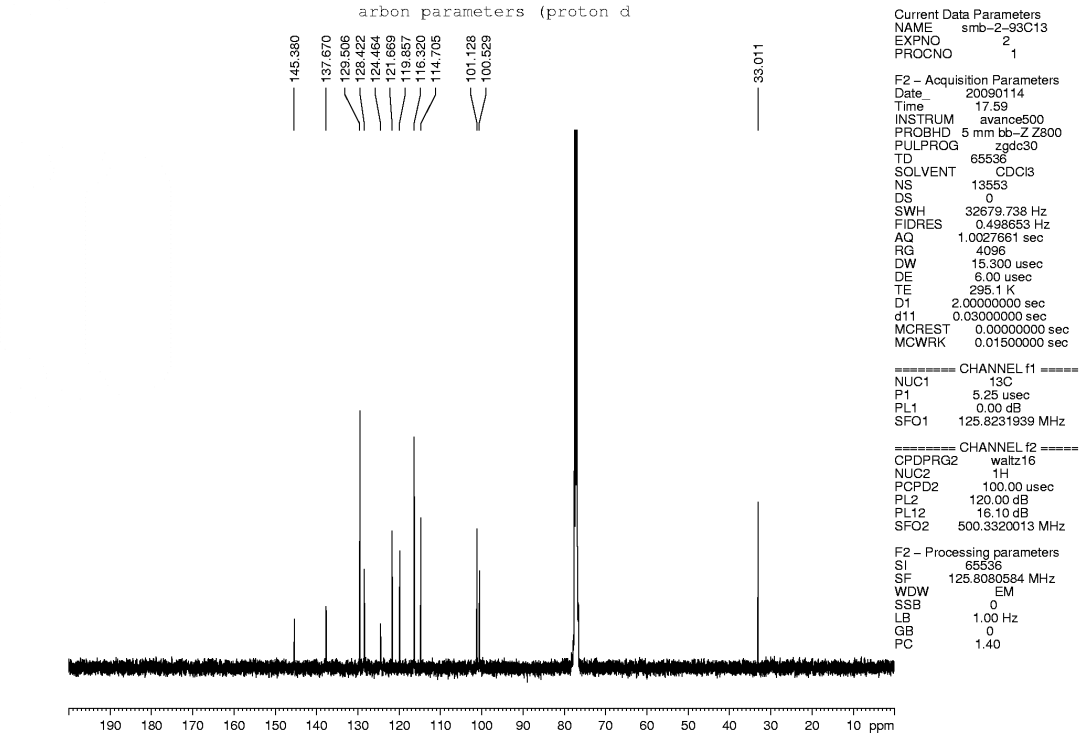



*Figure A1.186* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compound **2.38c**.

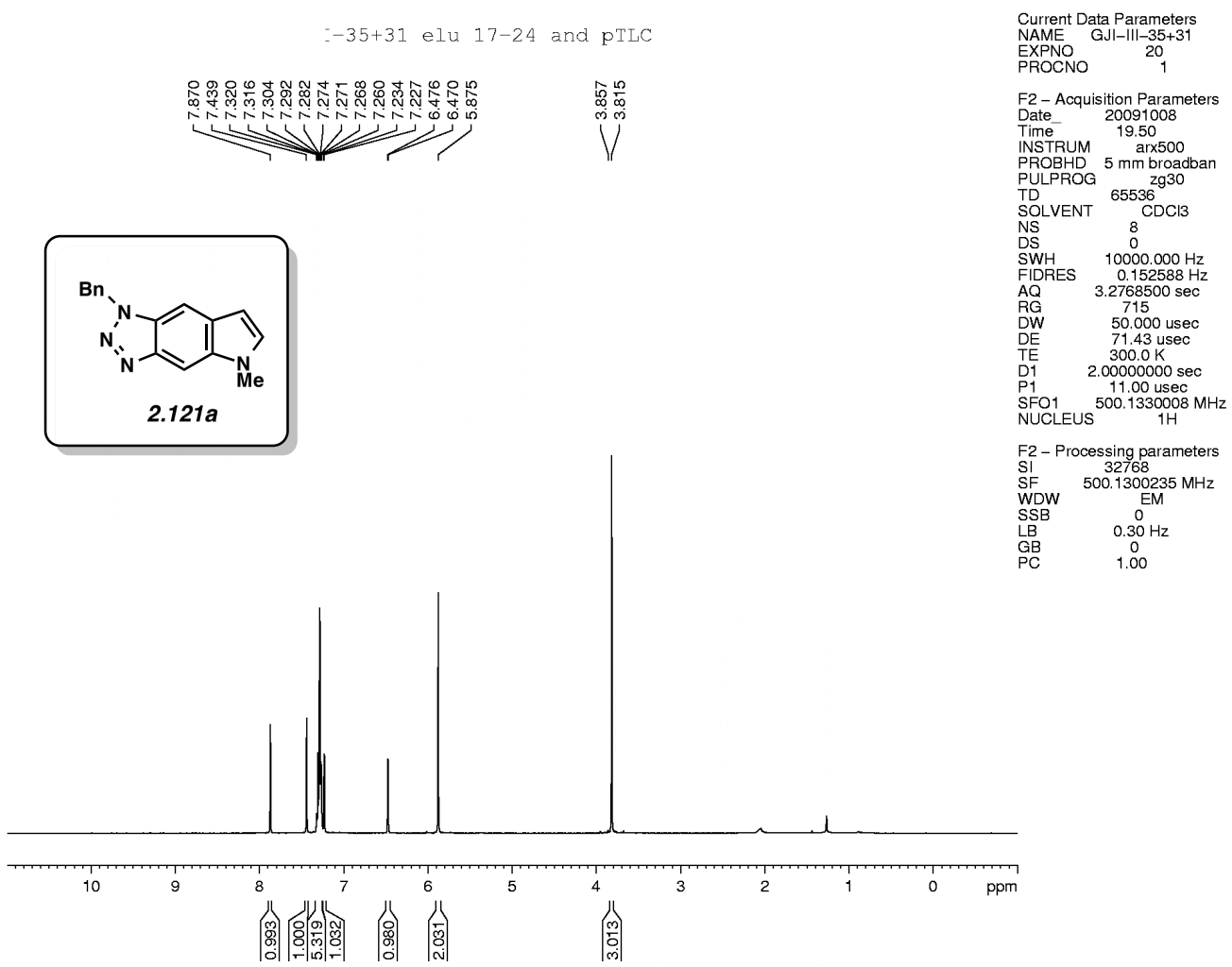



*Figure A1.187* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **2.121a**.

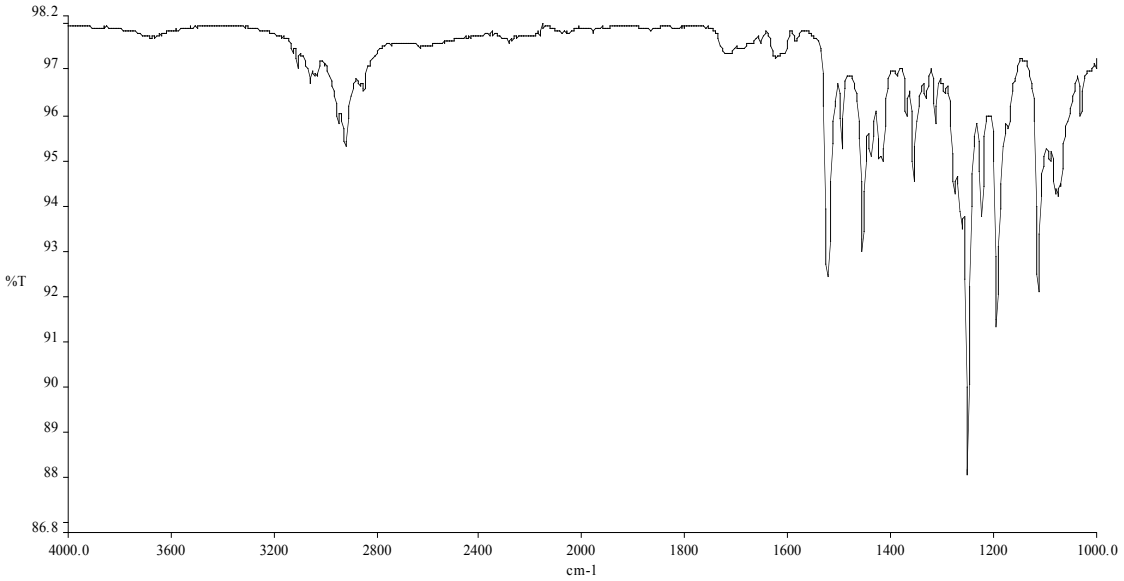



*Figure A1.188* Infrared spectrum of compound **2.121a**.

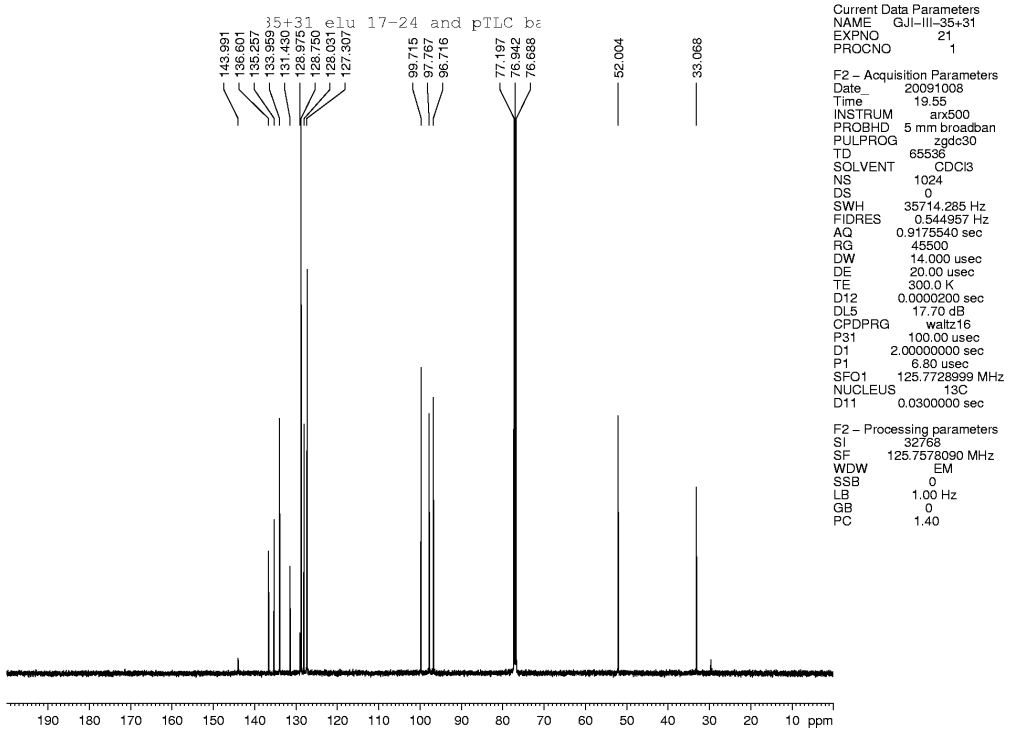



*Figure A1.189* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compound **2.121a**.

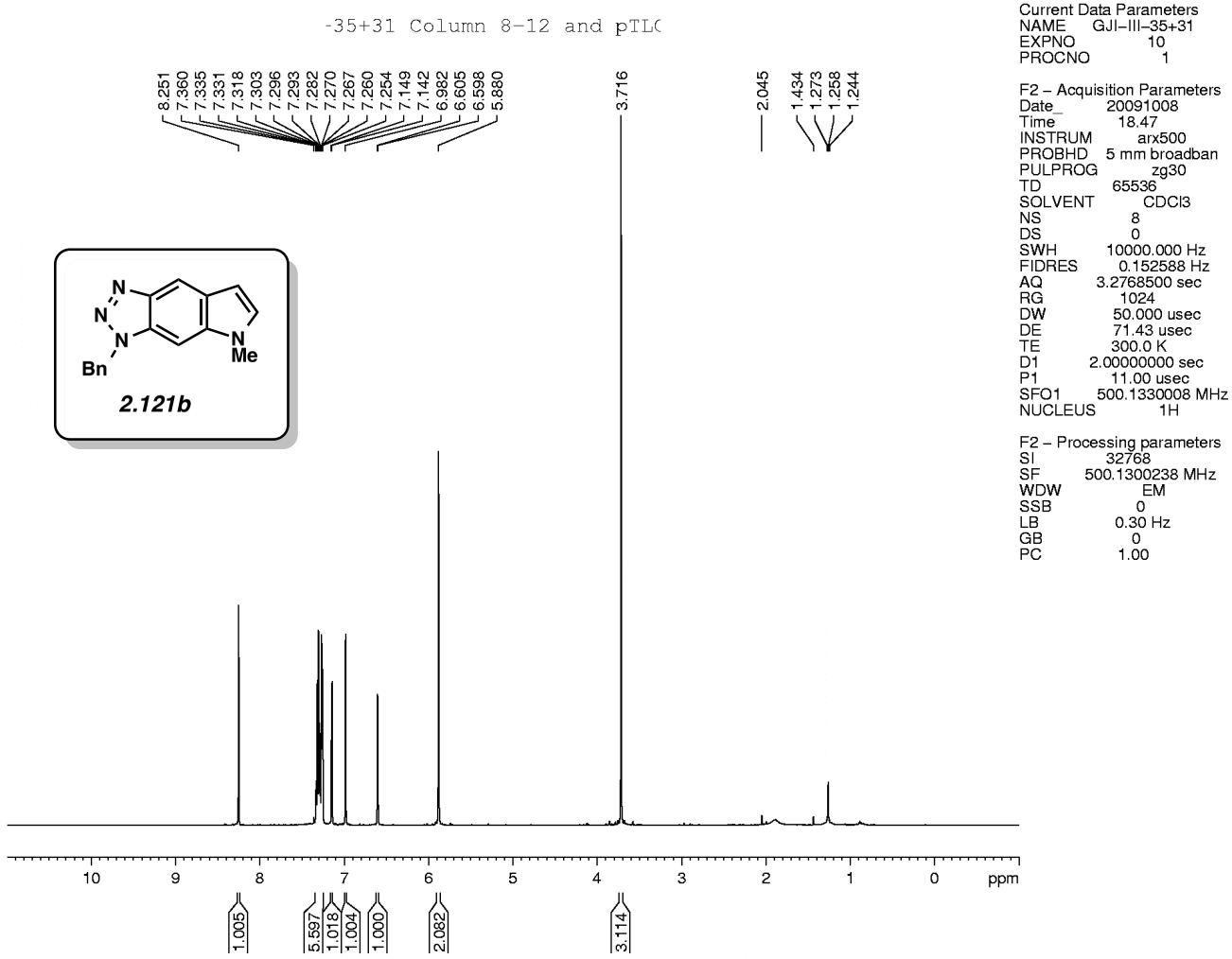



*Figure A1.190* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **2.121b**.

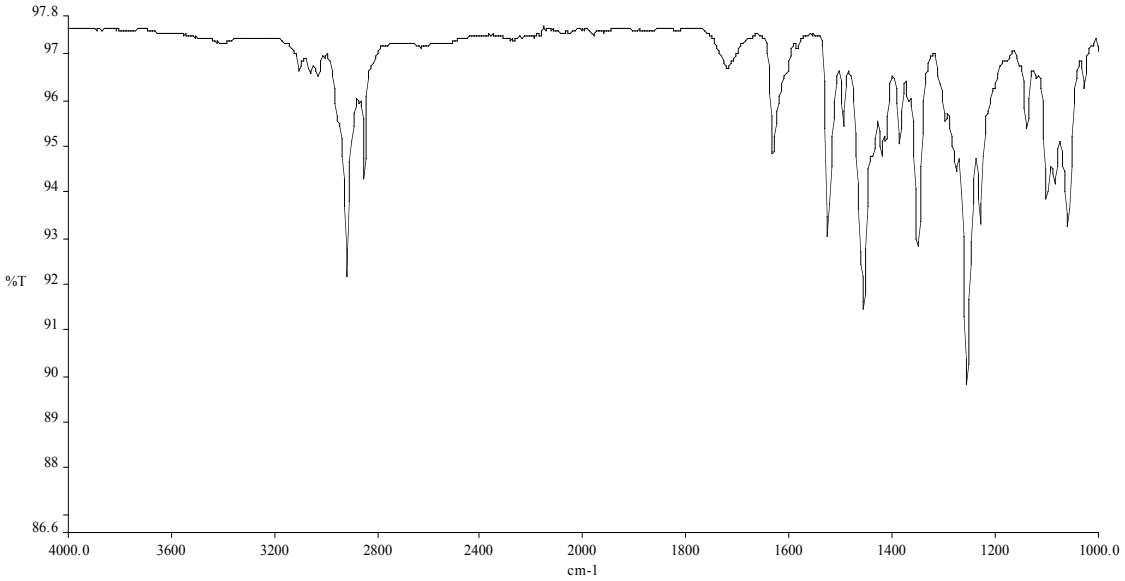



*Figure A1.191* Infrared spectrum of compound **2.121b**.

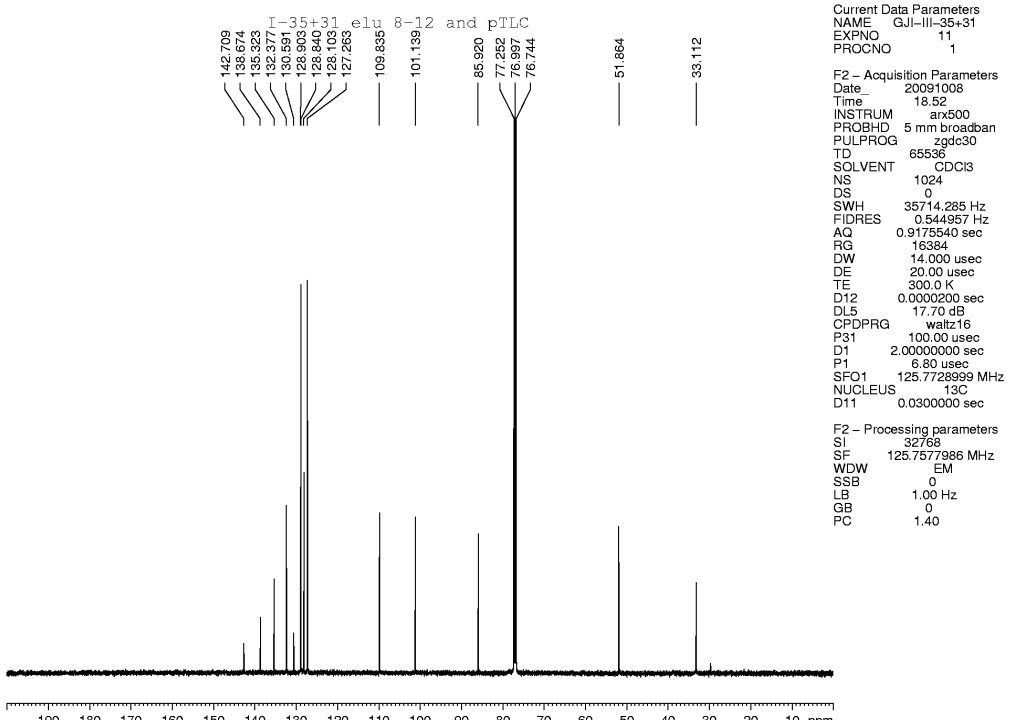



*Figure A1.192* $^{13}$C NMR (125 MHz, $CDCl_3$) of compound **2.121b**.

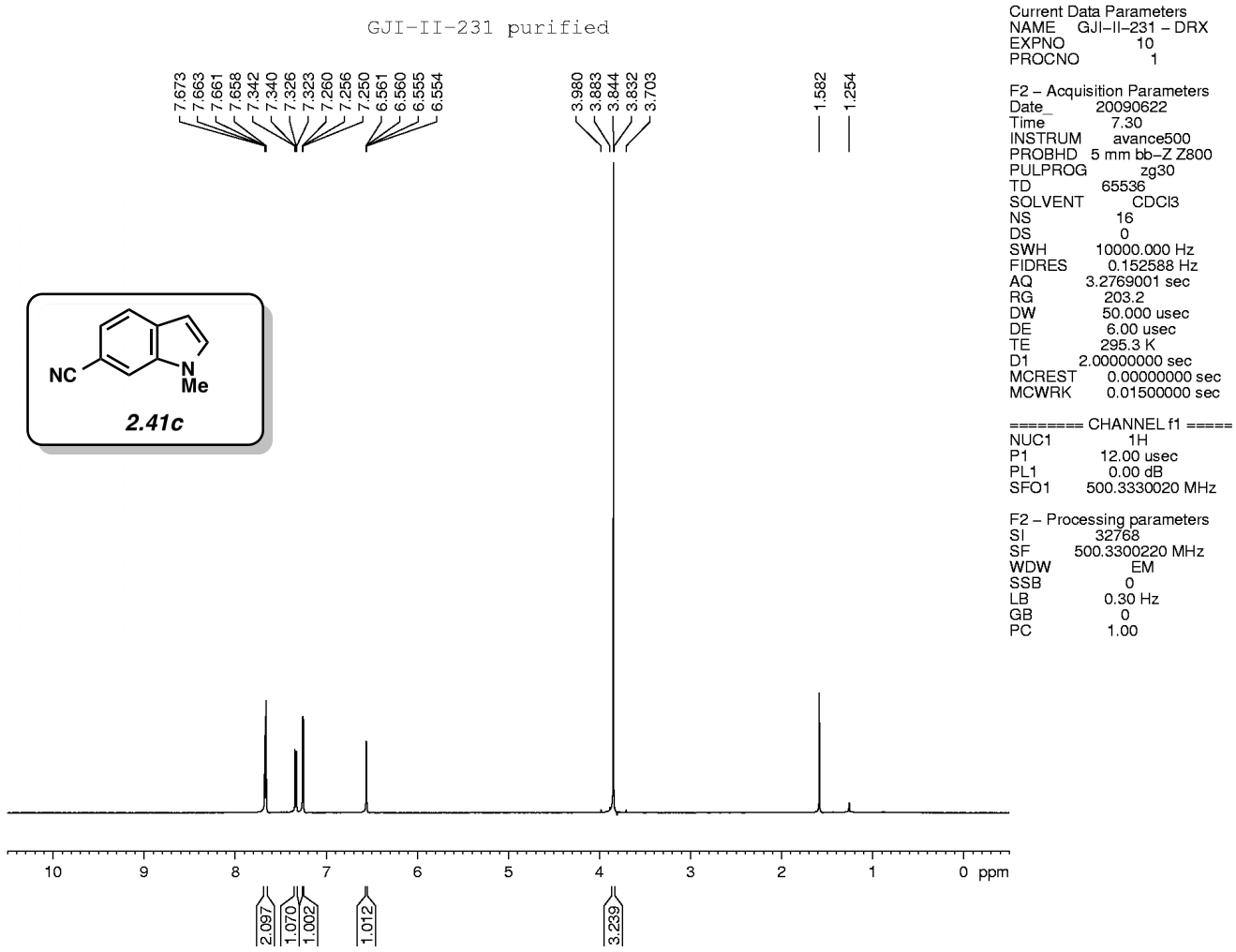



*Figure A1.193* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **2.41c**.

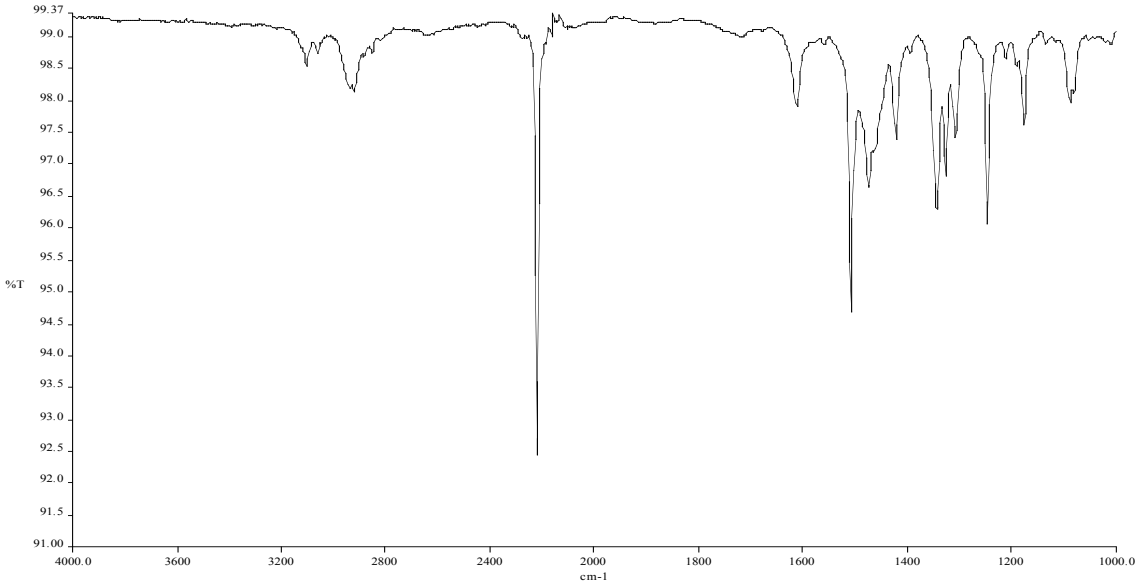



*Figure A1.194* Infrared spectrum of compound **2.41c**.

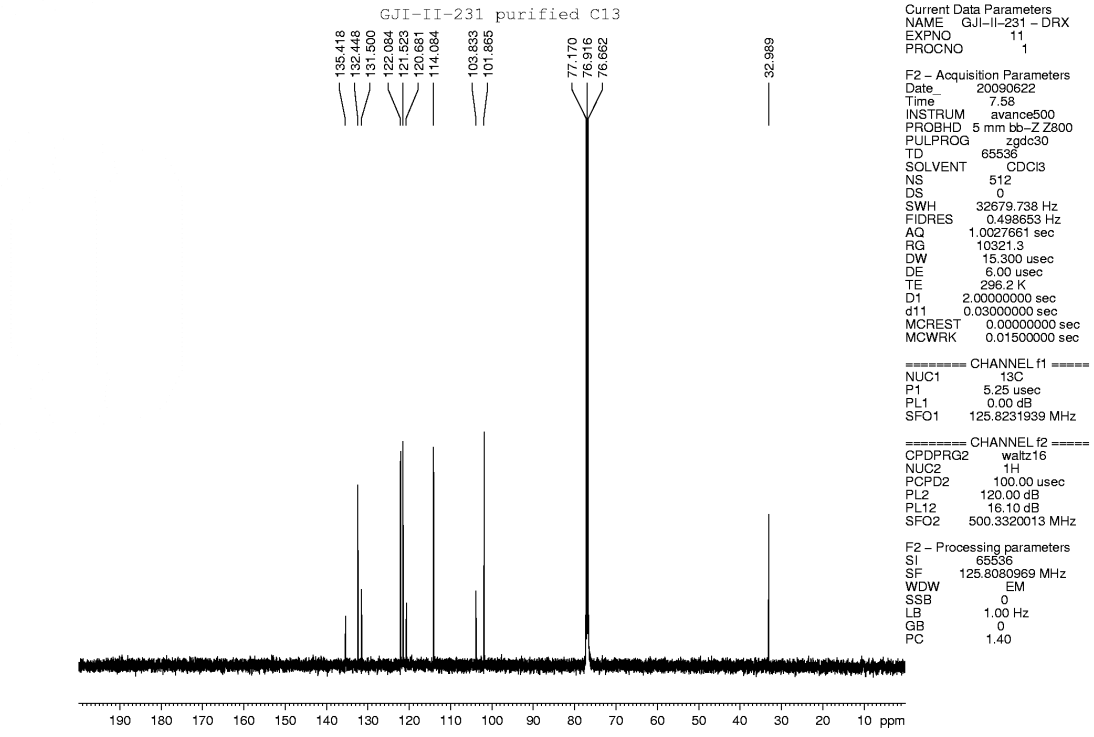



*Figure A1.195* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compound **2.41c**.

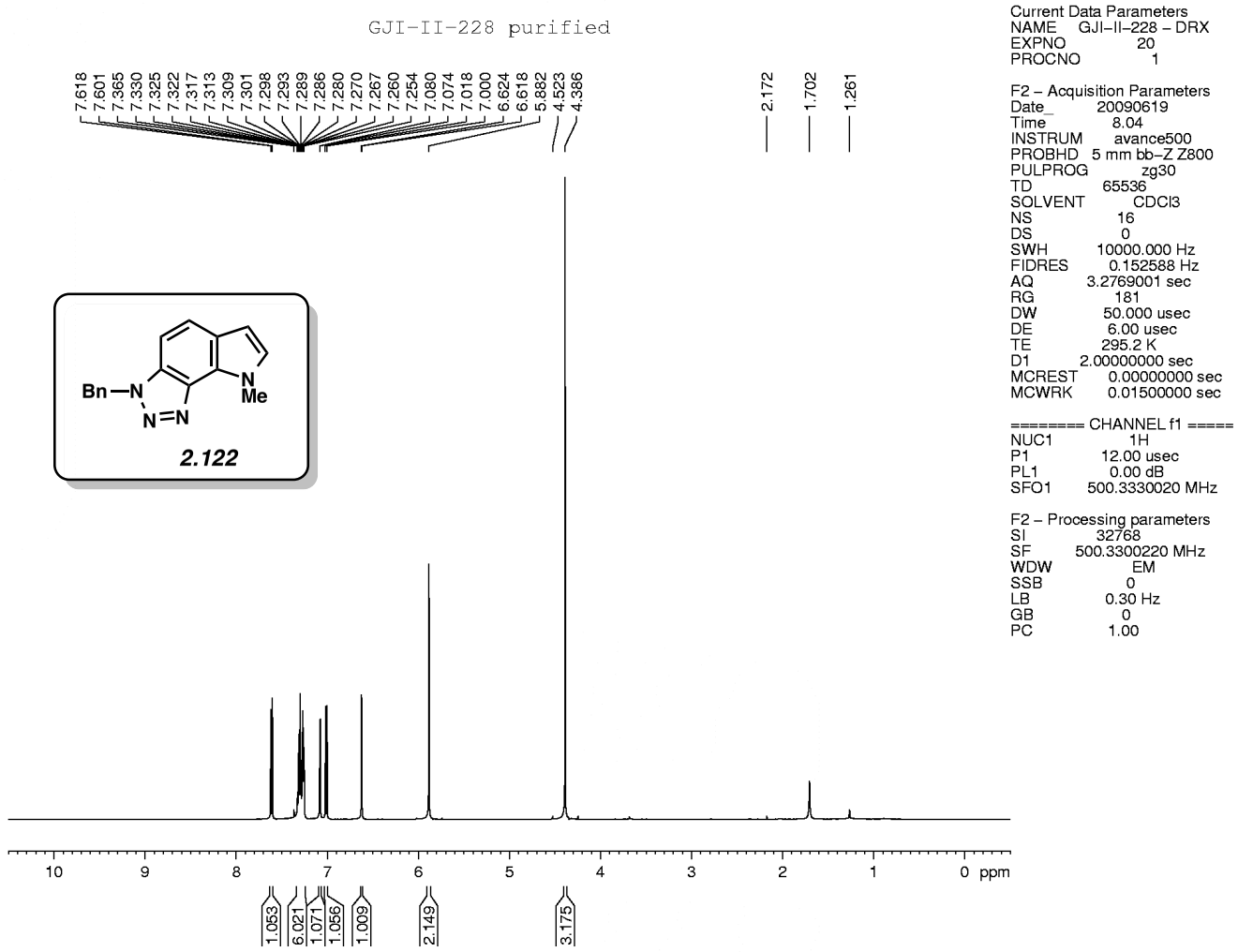



*Figure A1.196* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **2.122**.

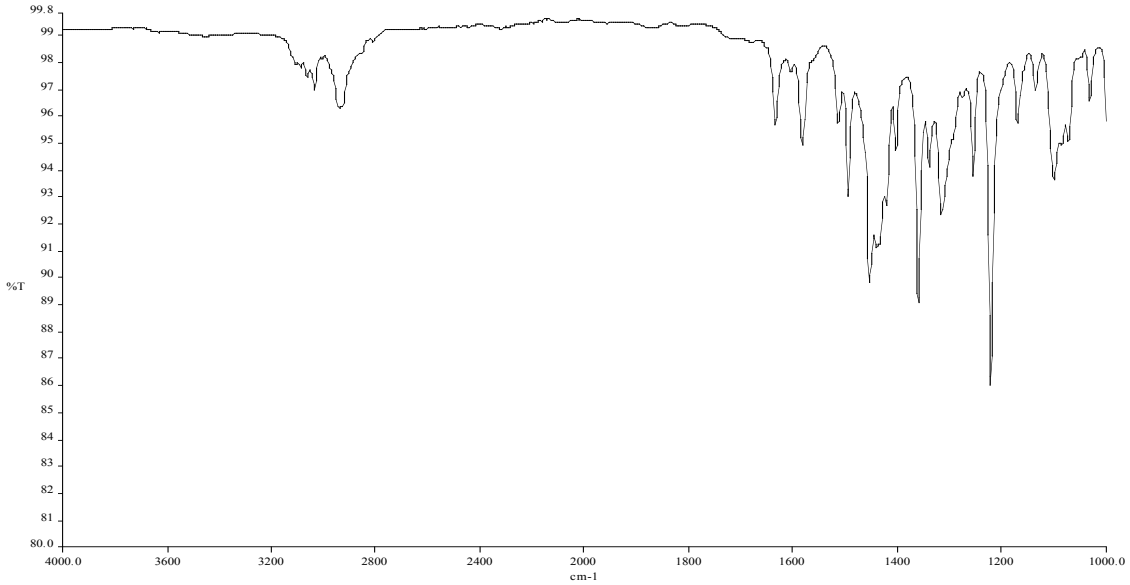



*Figure A1.197* Infrared spectrum of compound **2.122**.

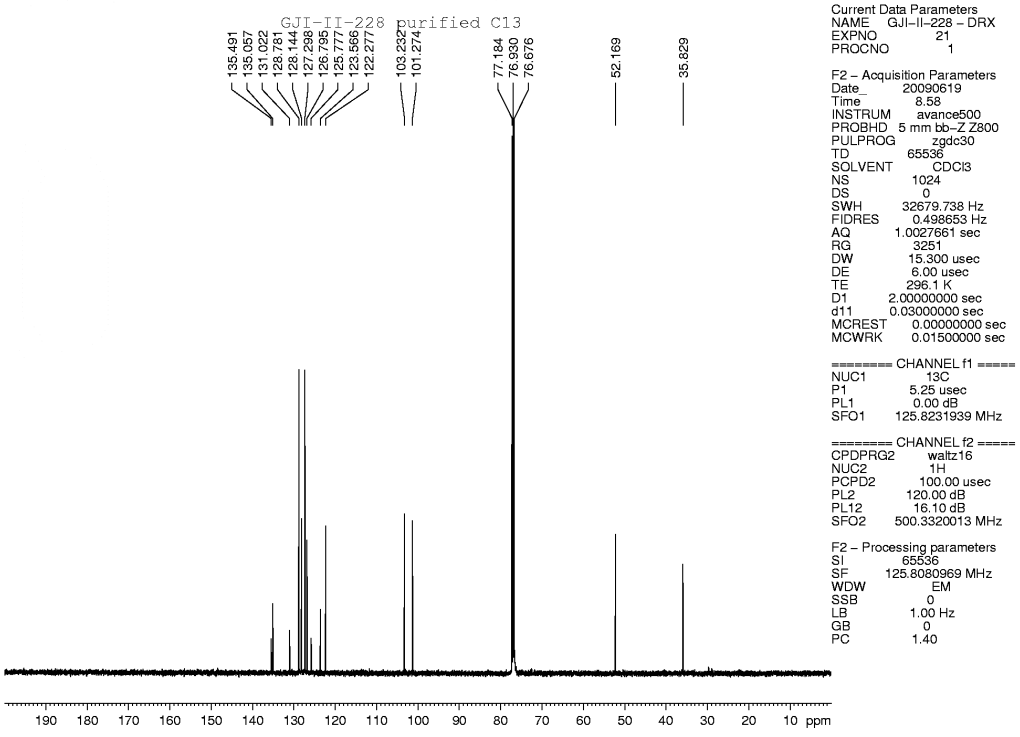



*Figure A1.198* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compound **2.122**.

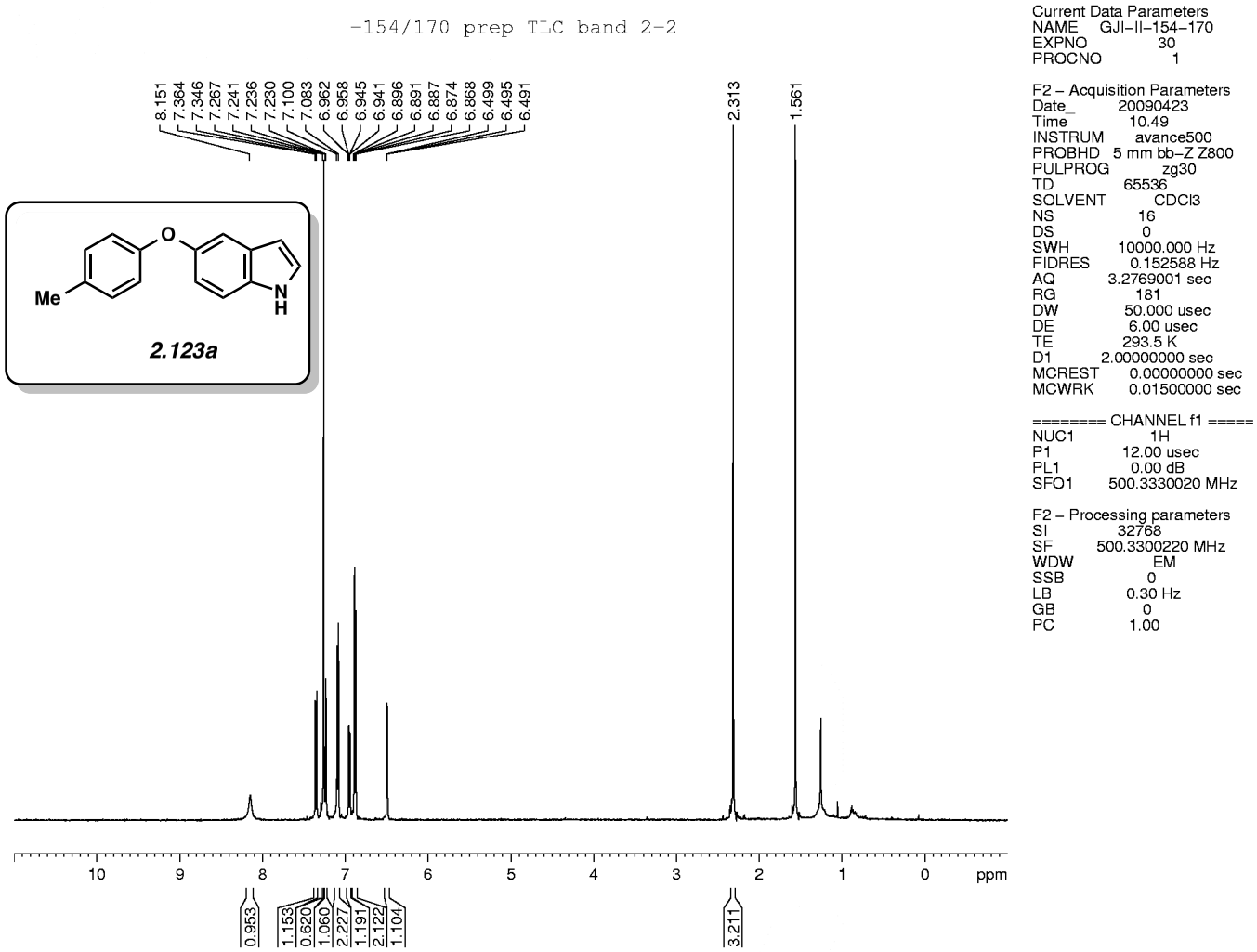



*Figure A1.199* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **2.123a**.

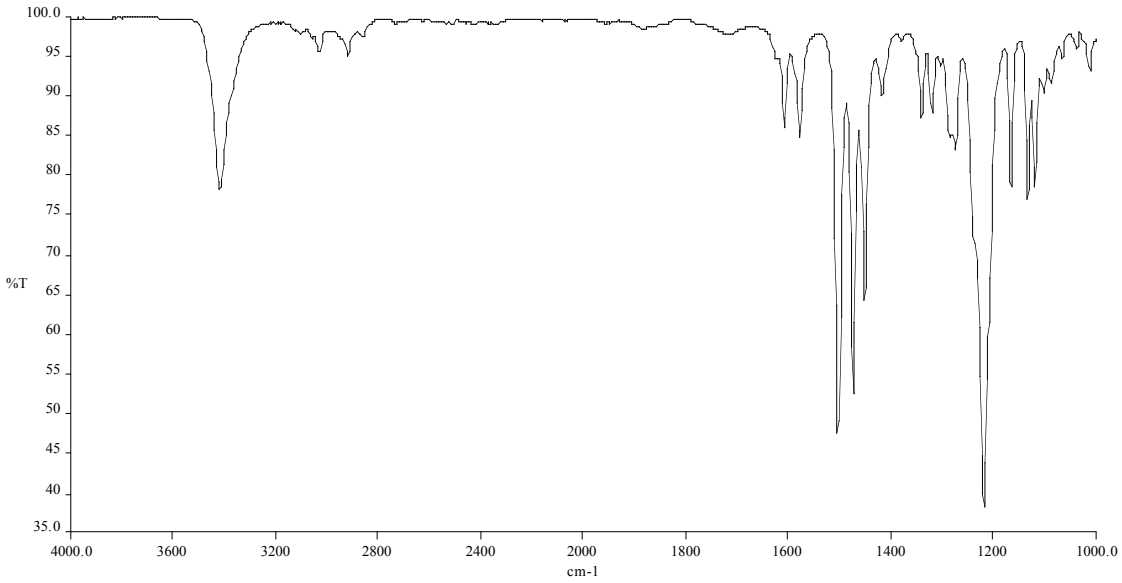



*Figure A1.200* Infrared spectrum of compound **2.123a**.

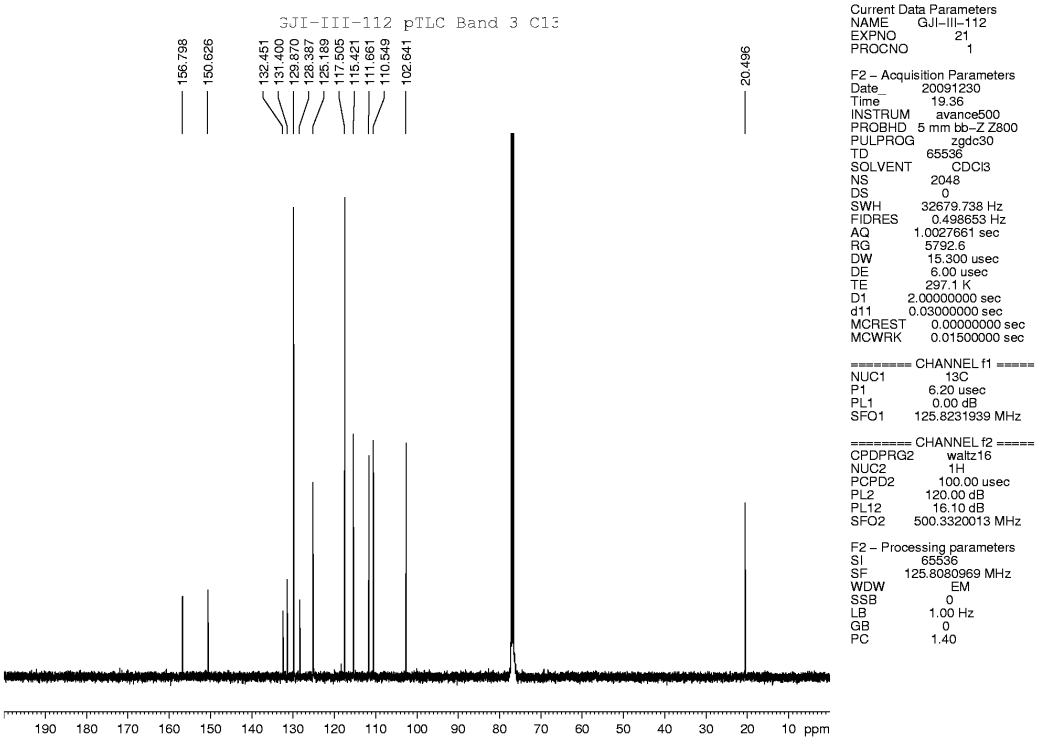



*Figure A1.201* $^{13}$C NMR (125 MHz, $CDCl_3$) of compound **2.123a**.

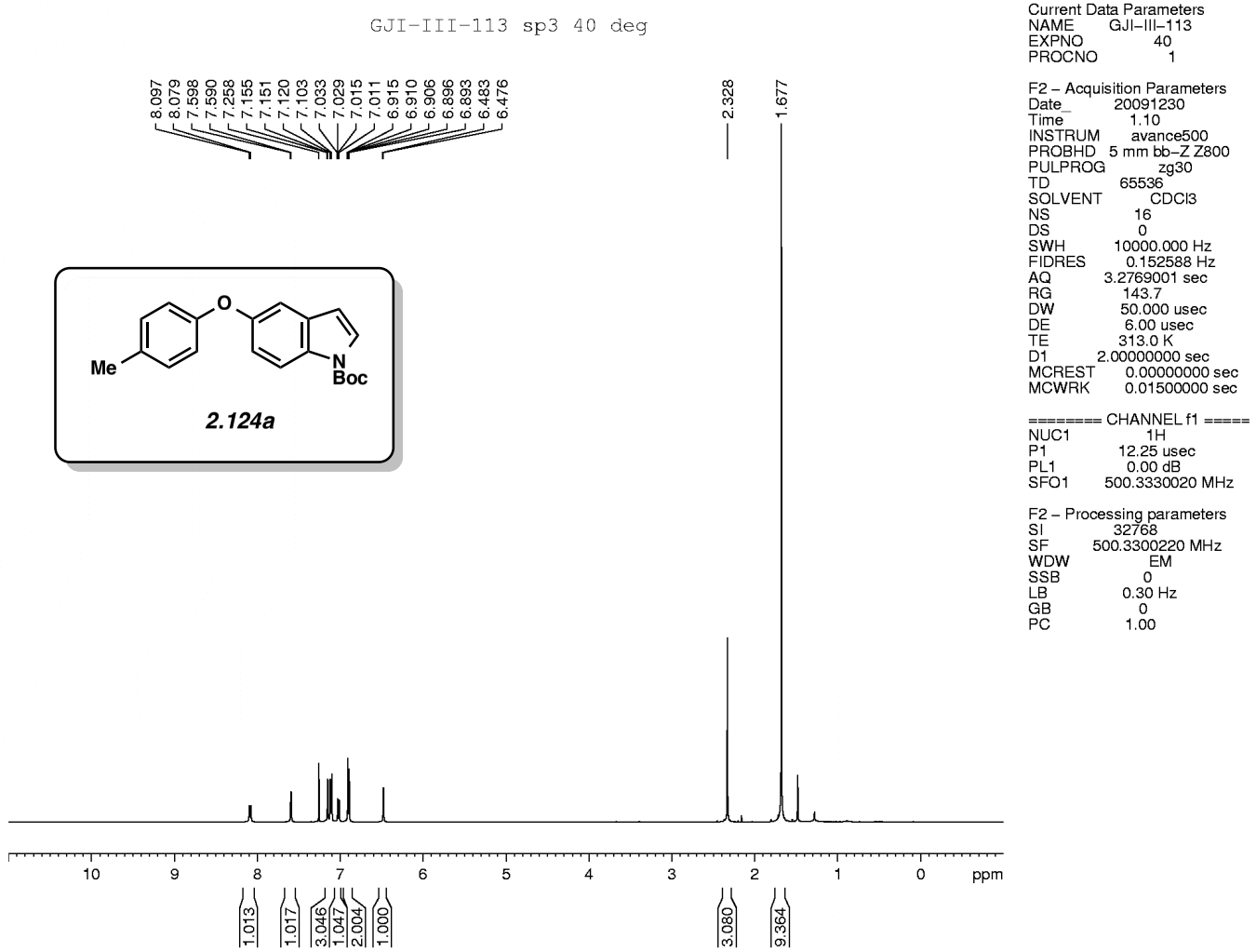



*Figure A1.202* $^{1}$H NMR (500 MHz, 40 °C, $CDCl_3$) of compound **2.124a**.

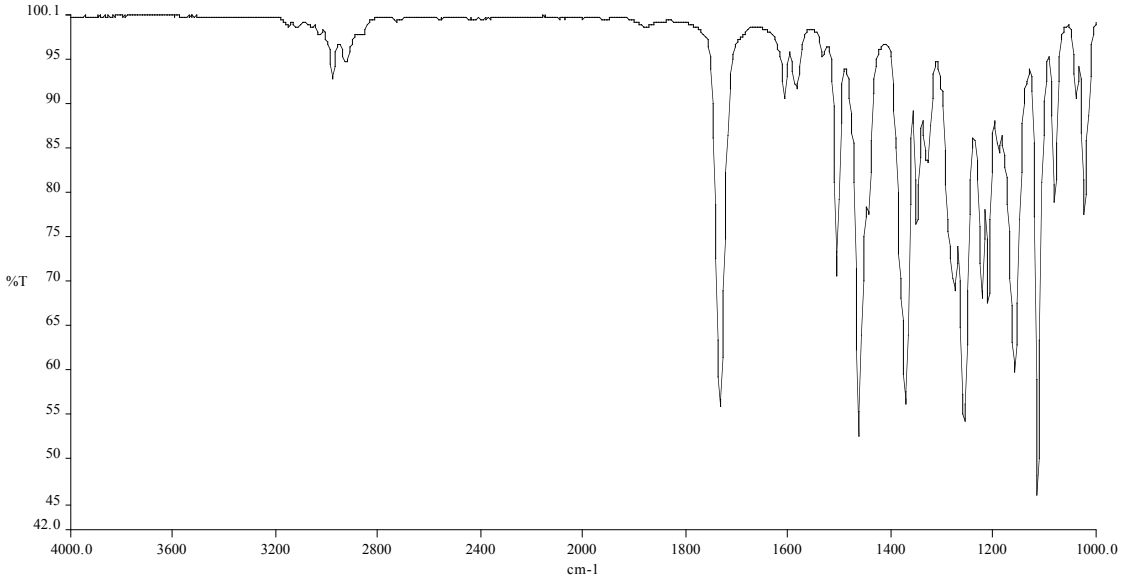



*Figure A1.203* Infrared spectrum of compound **2.124a**.

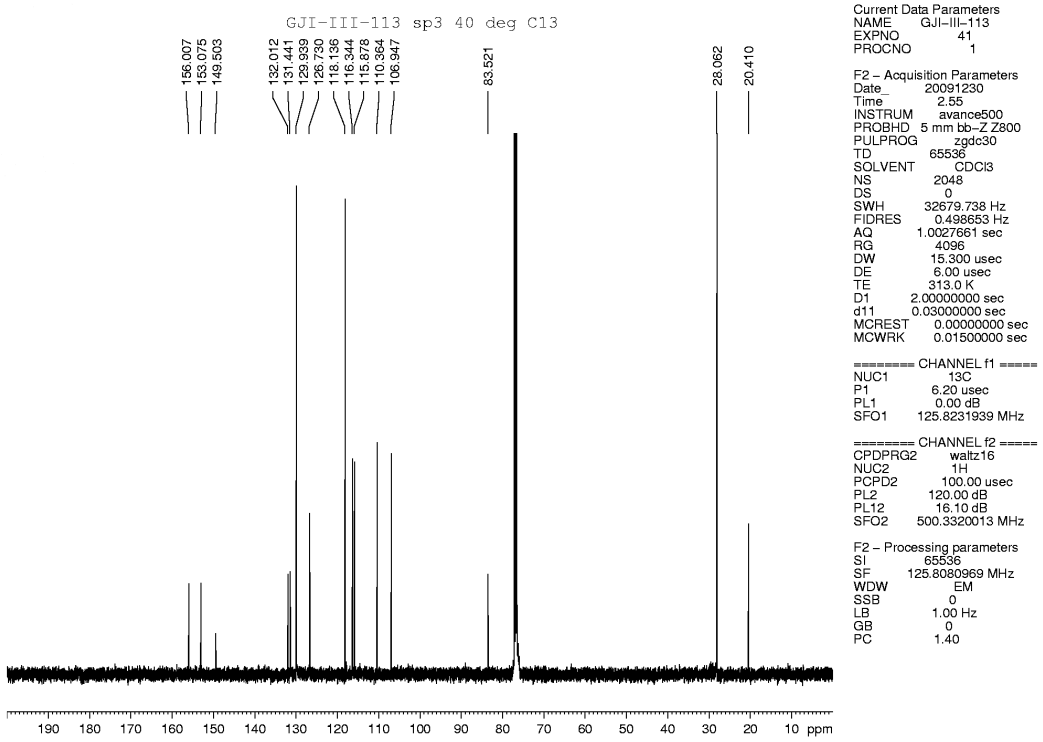



*Figure A1.204* $^{13}$C NMR (125 MHz, 40 °C, $CDCl_3$) of compound **2.124a**.

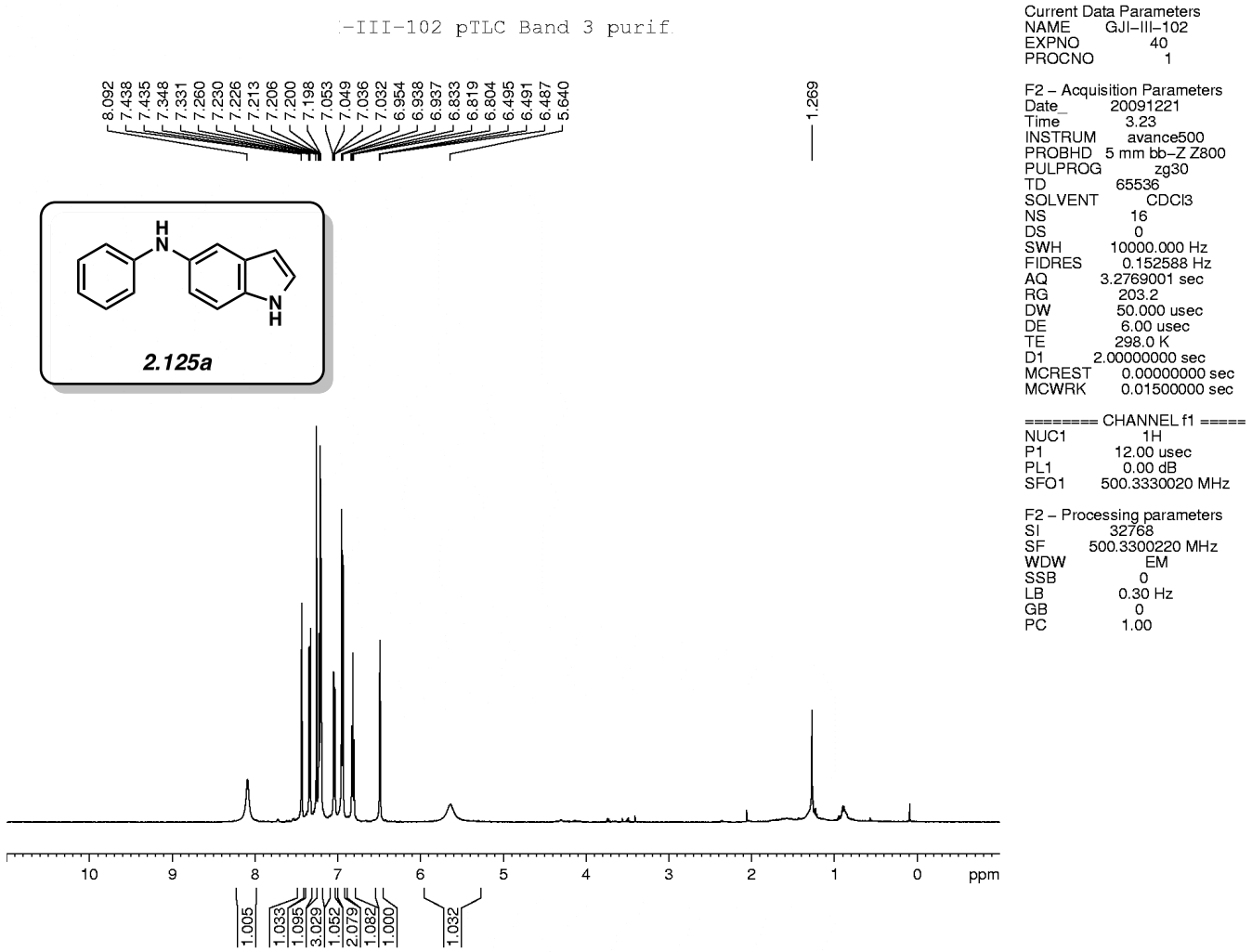



*Figure A1.205* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **2.125a**.

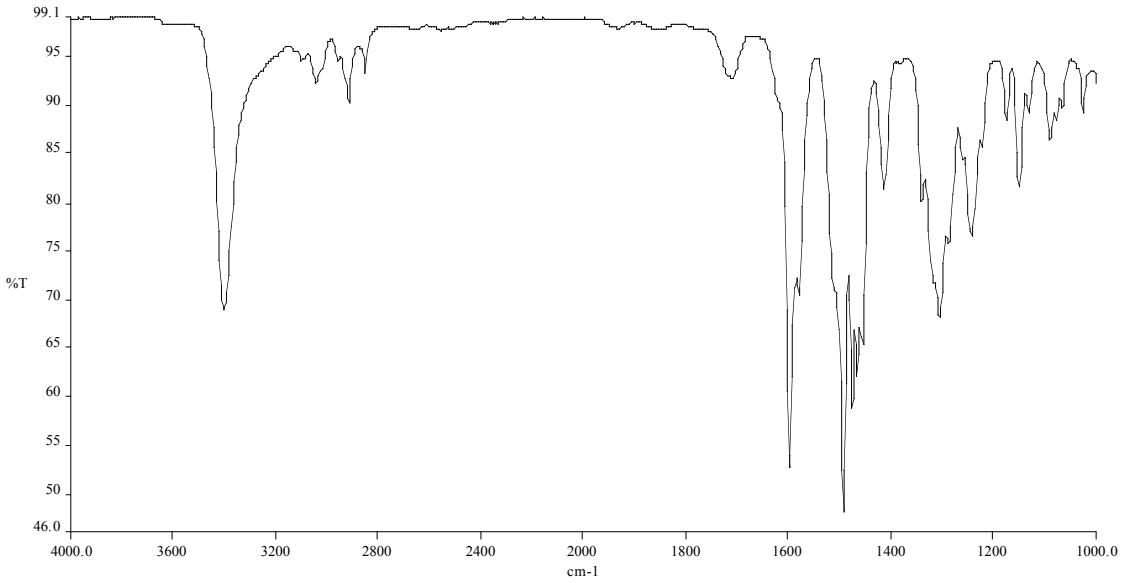



*Figure A1.206* Infrared spectrum of compound **2.125a**.

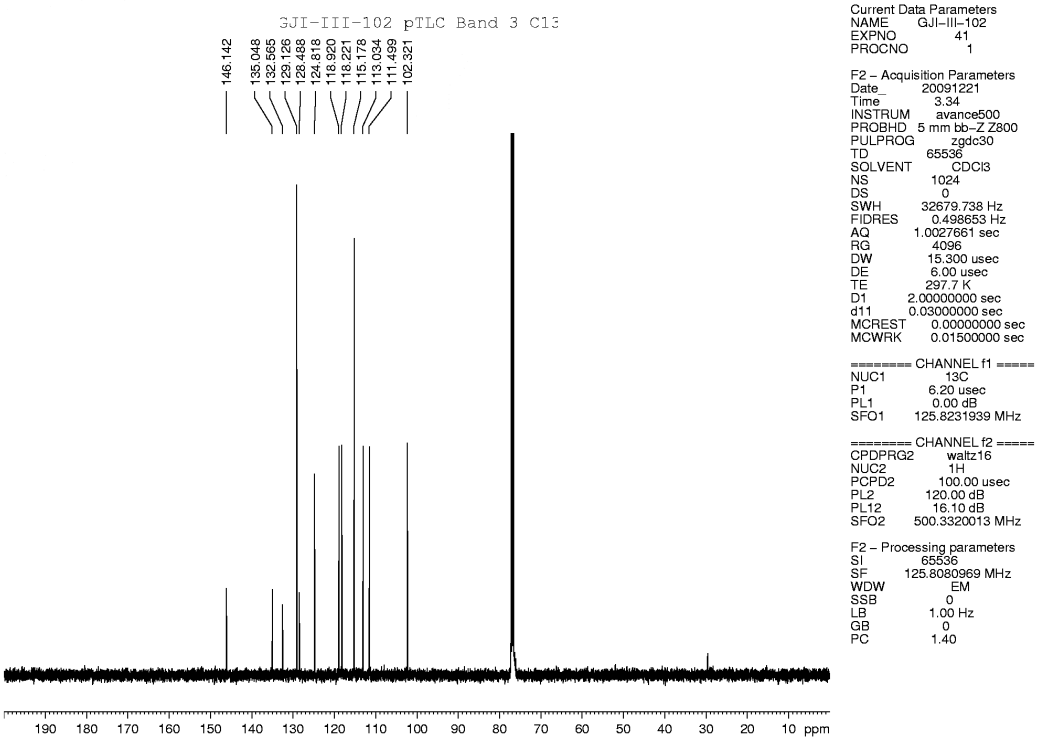



*Figure A1.207* $^{13}$C NMR (125 MHz, $CDCl_3$) of compound **2.125a**.

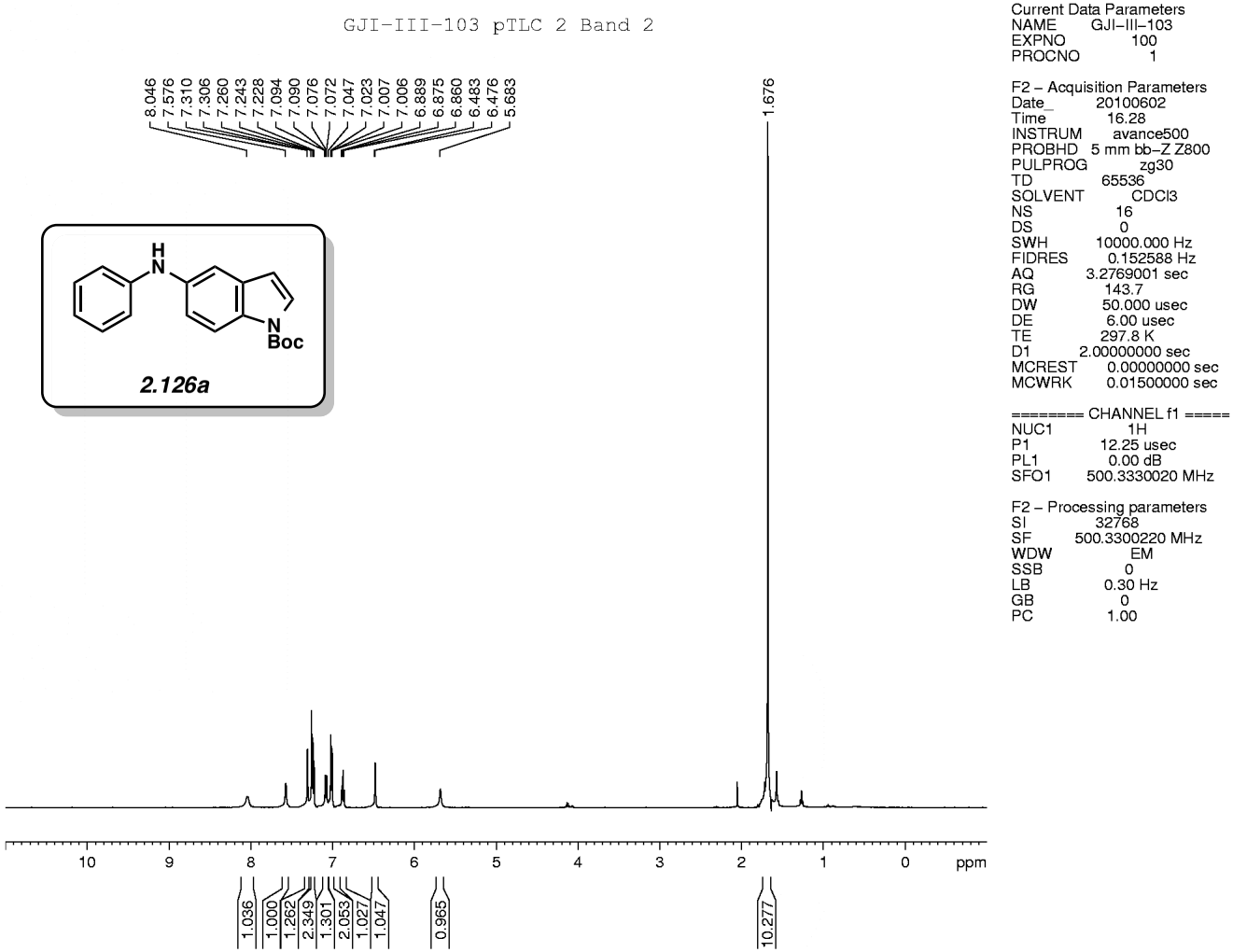



*Figure A1.208* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **2.126a**.

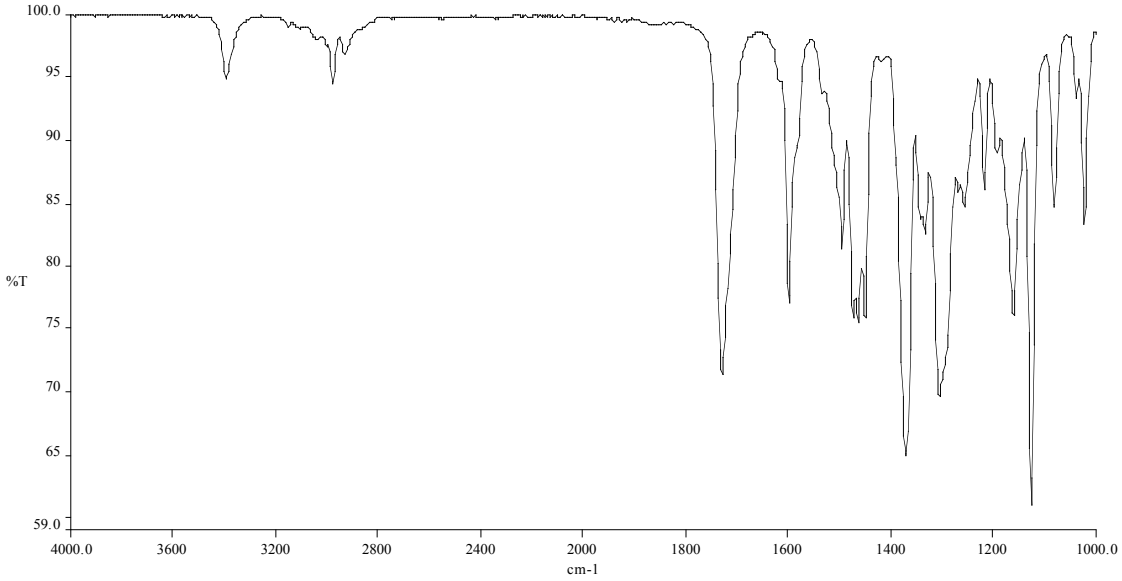



*Figure A1.209* Infrared spectrum of compound **2.126a**.

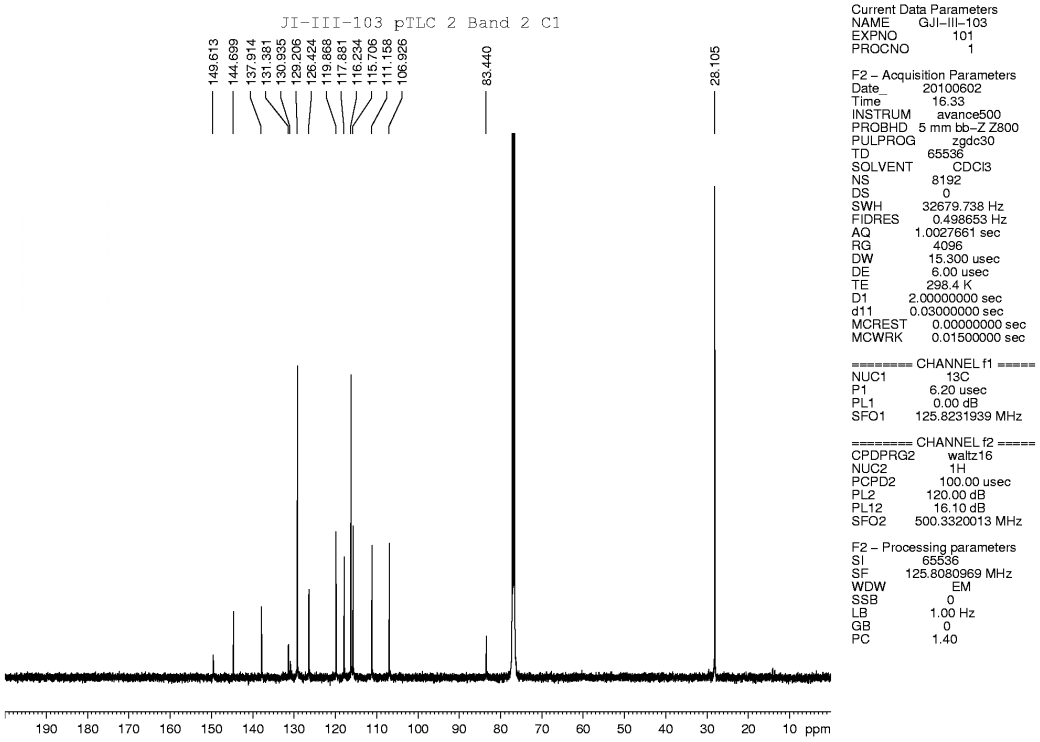



*Figure A1.210* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compound **2.126a**.

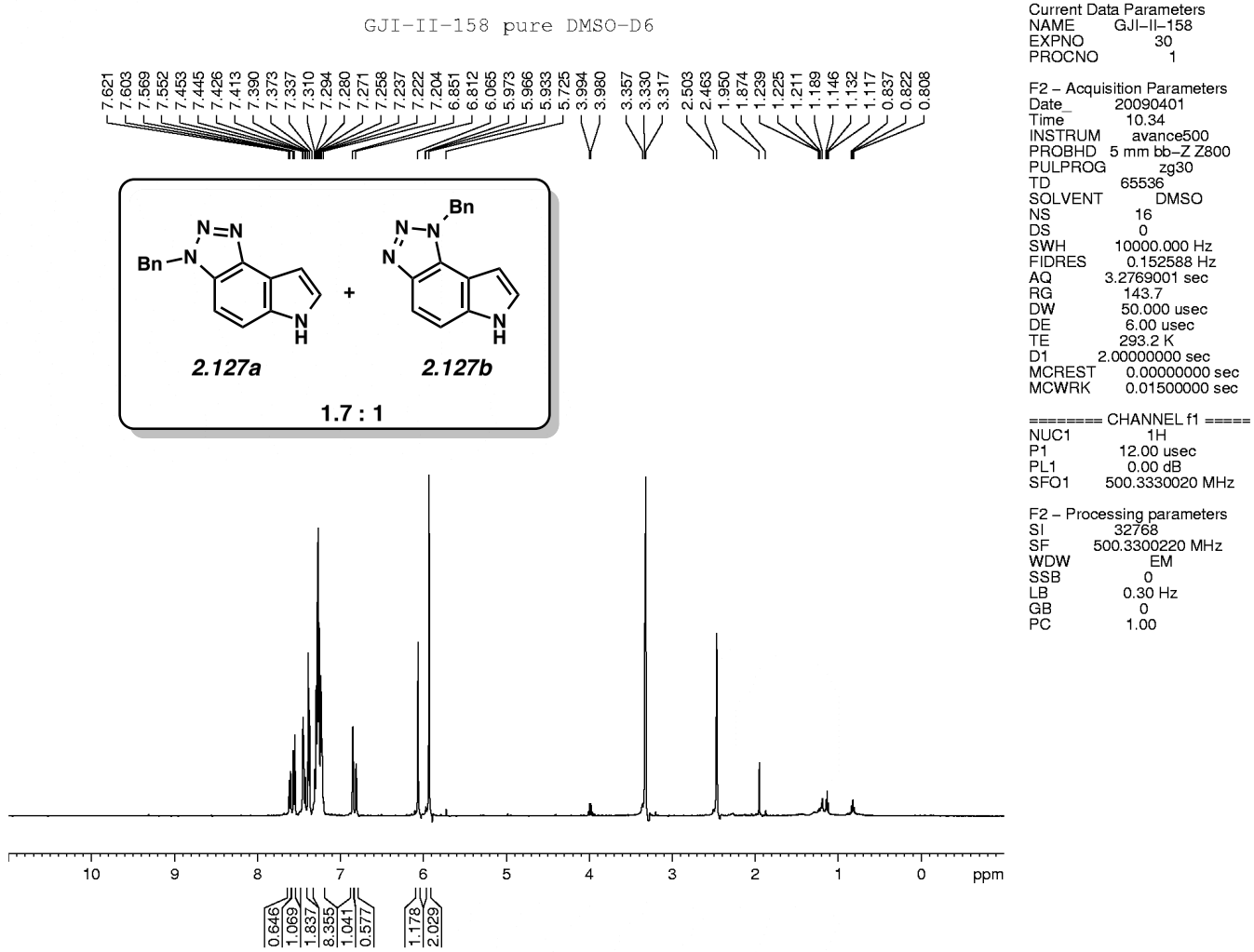



*Figure A1.211* $^{1}$H NMR (500 MHz, DMSO- $d_6$) of compounds **2.127a** and **2.127b**.

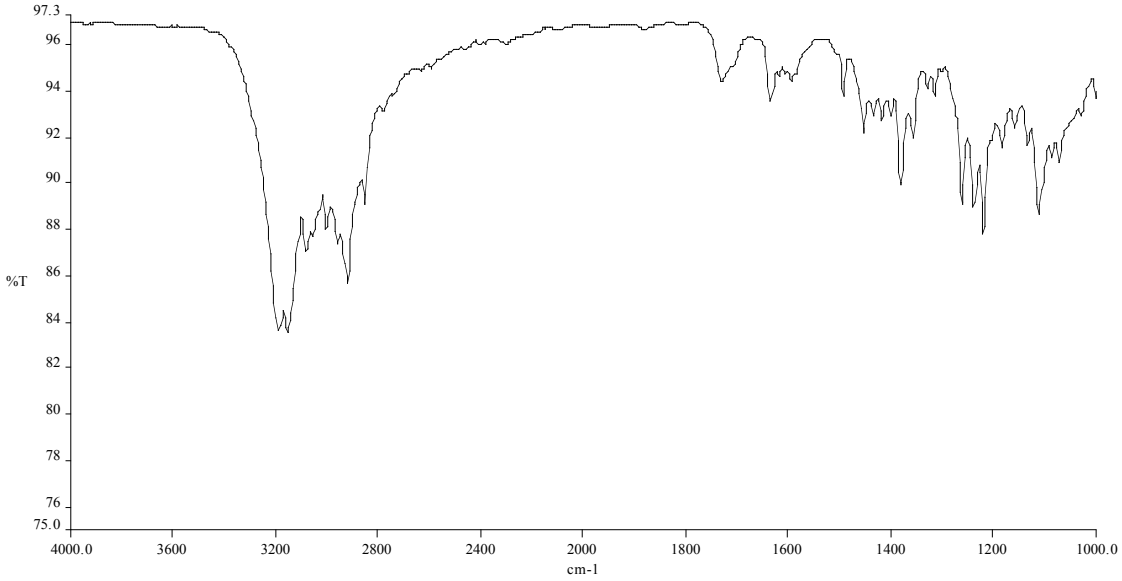



*Figure A1.212* Infrared spectrum of compounds **2.127a** and **2.127b**.

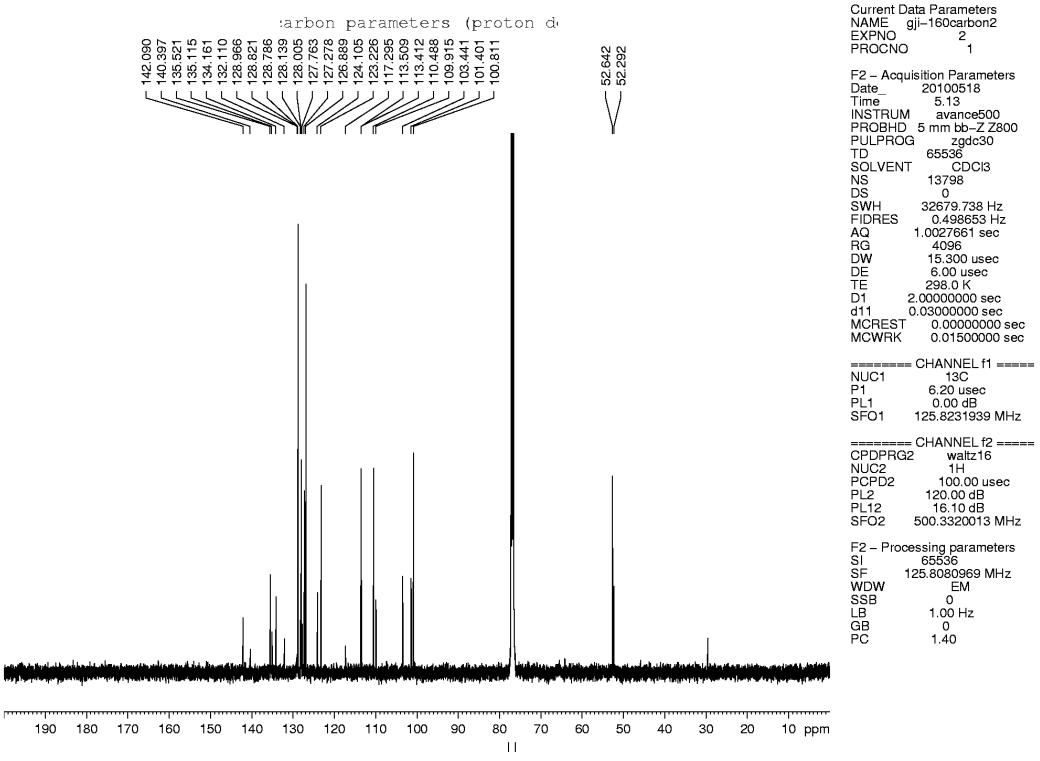



*Figure A1.213* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compounds **2.127a** and **2.127b**.

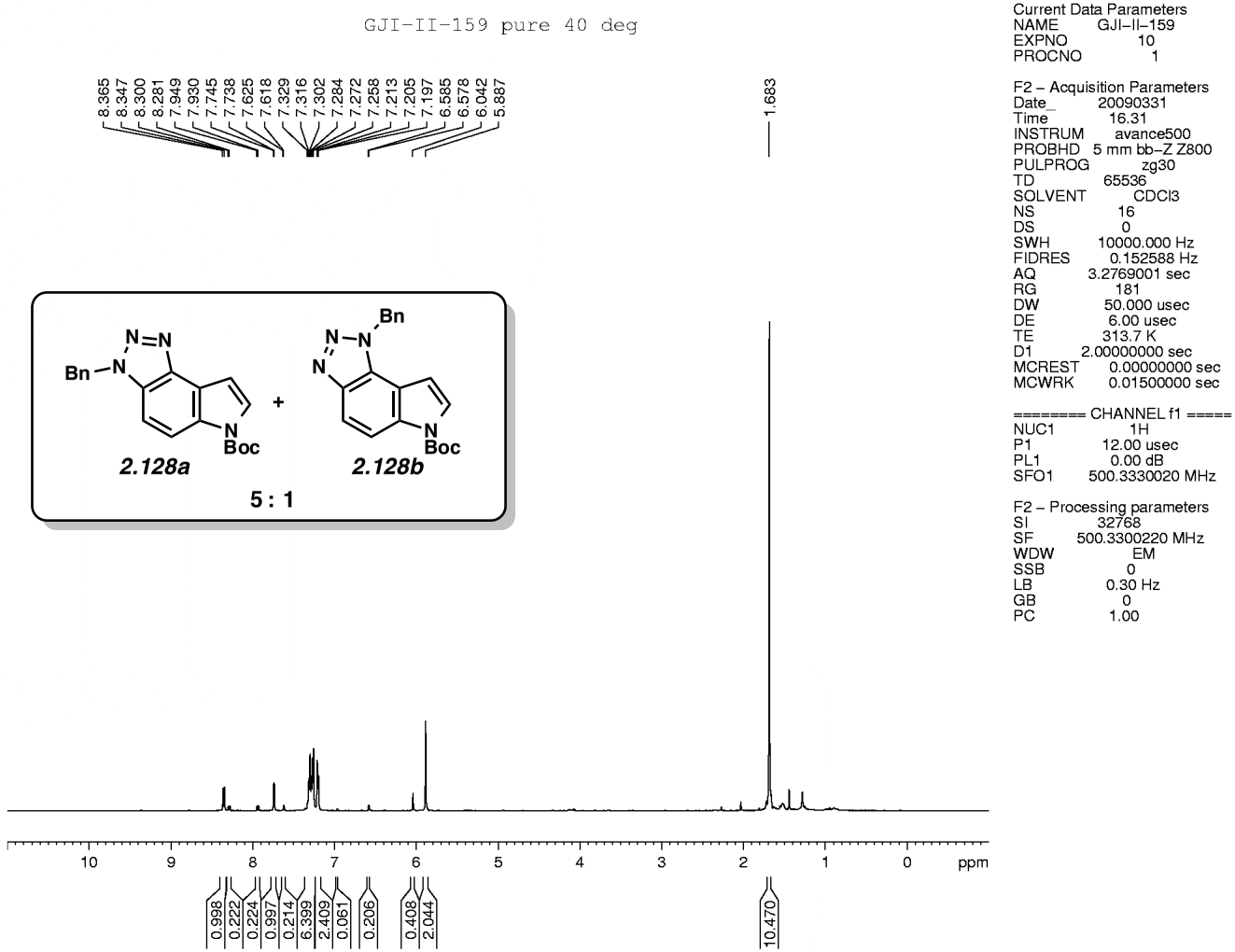



*Figure A1.214* $^{1}$H NMR (500 MHz, 40 °C, $CDCl_3$) of compounds **2.128a** and **2.128b**.

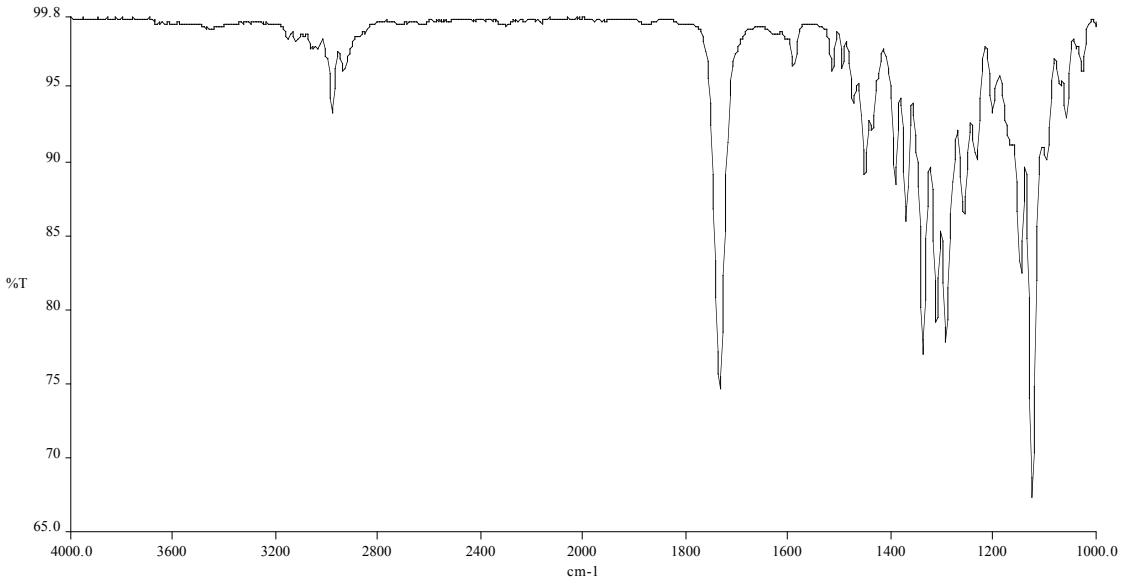



*Figure A1.215* Infrared spectrum of compounds **2.128a** and **2.128b**.

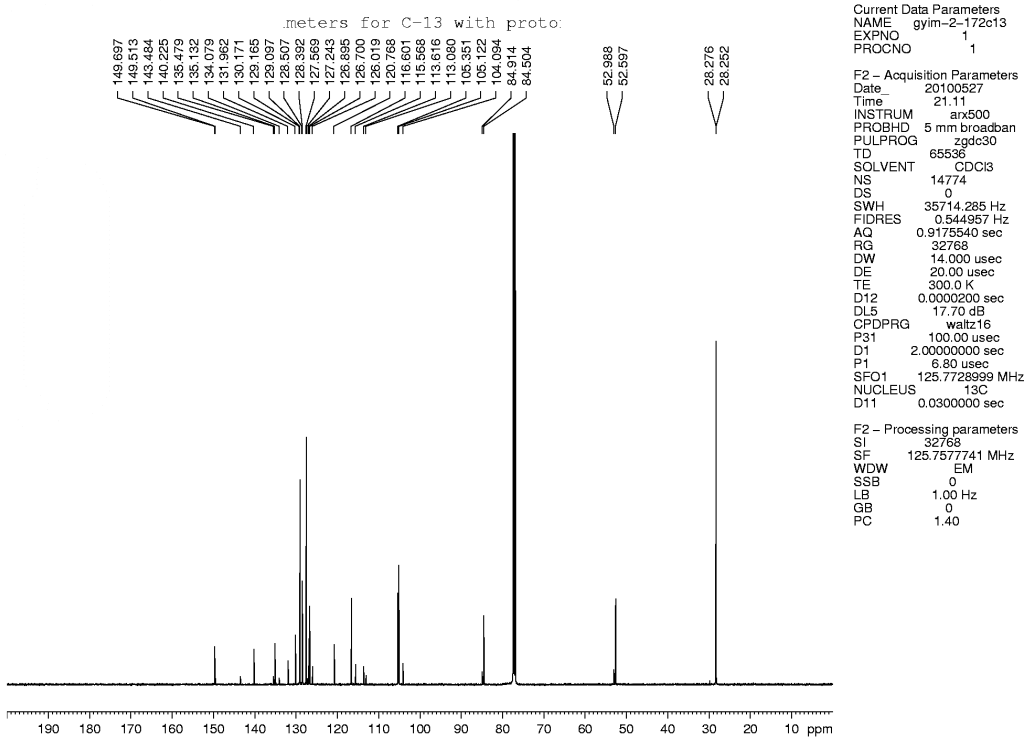



*Figure A1.216* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compounds **2.128a** and **2.128b**.

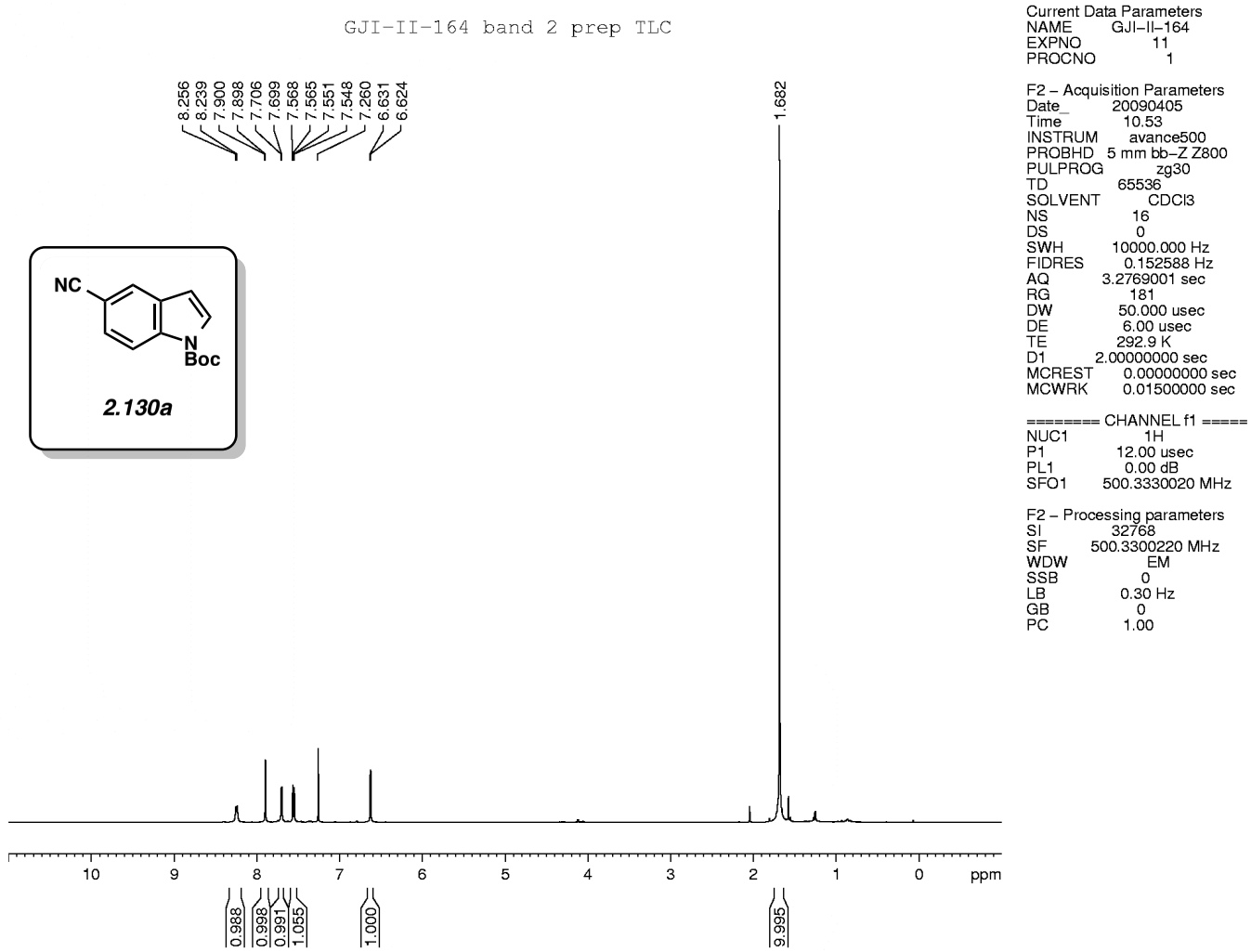



*Figure A1.217* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **2.130a**.

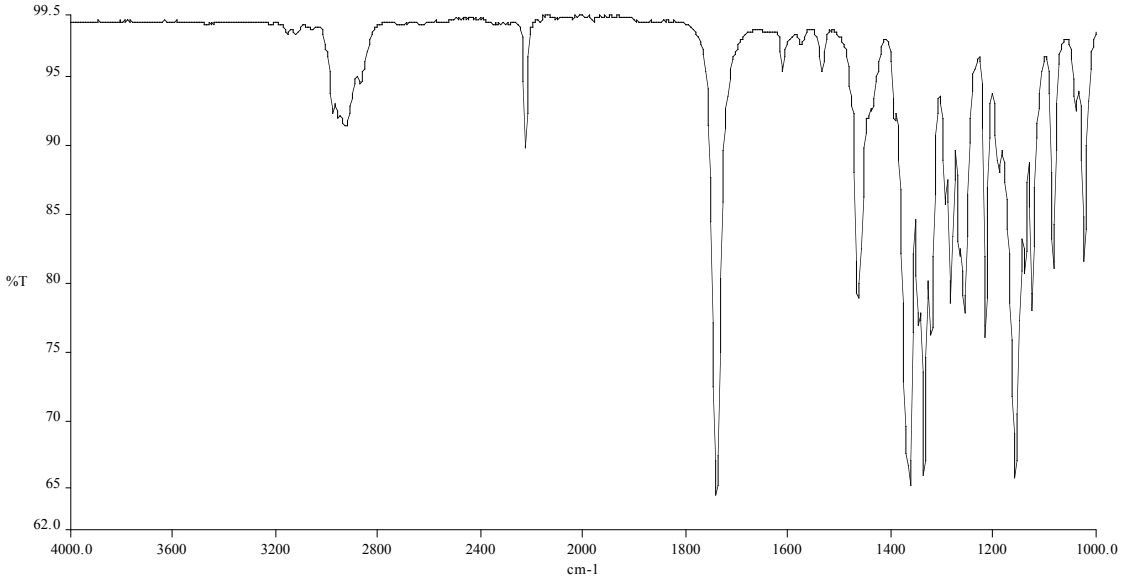



*Figure A1.218* Infrared spectrum of compound **2.130a**.

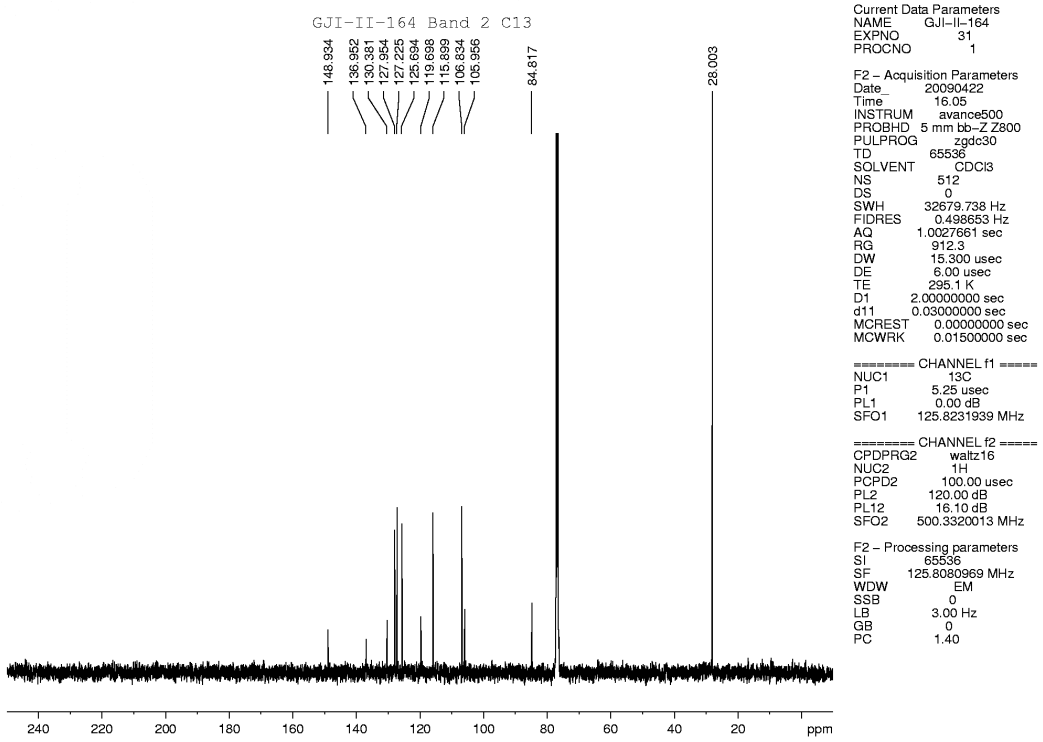



*Figure A1.219* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compound **2.130a**.

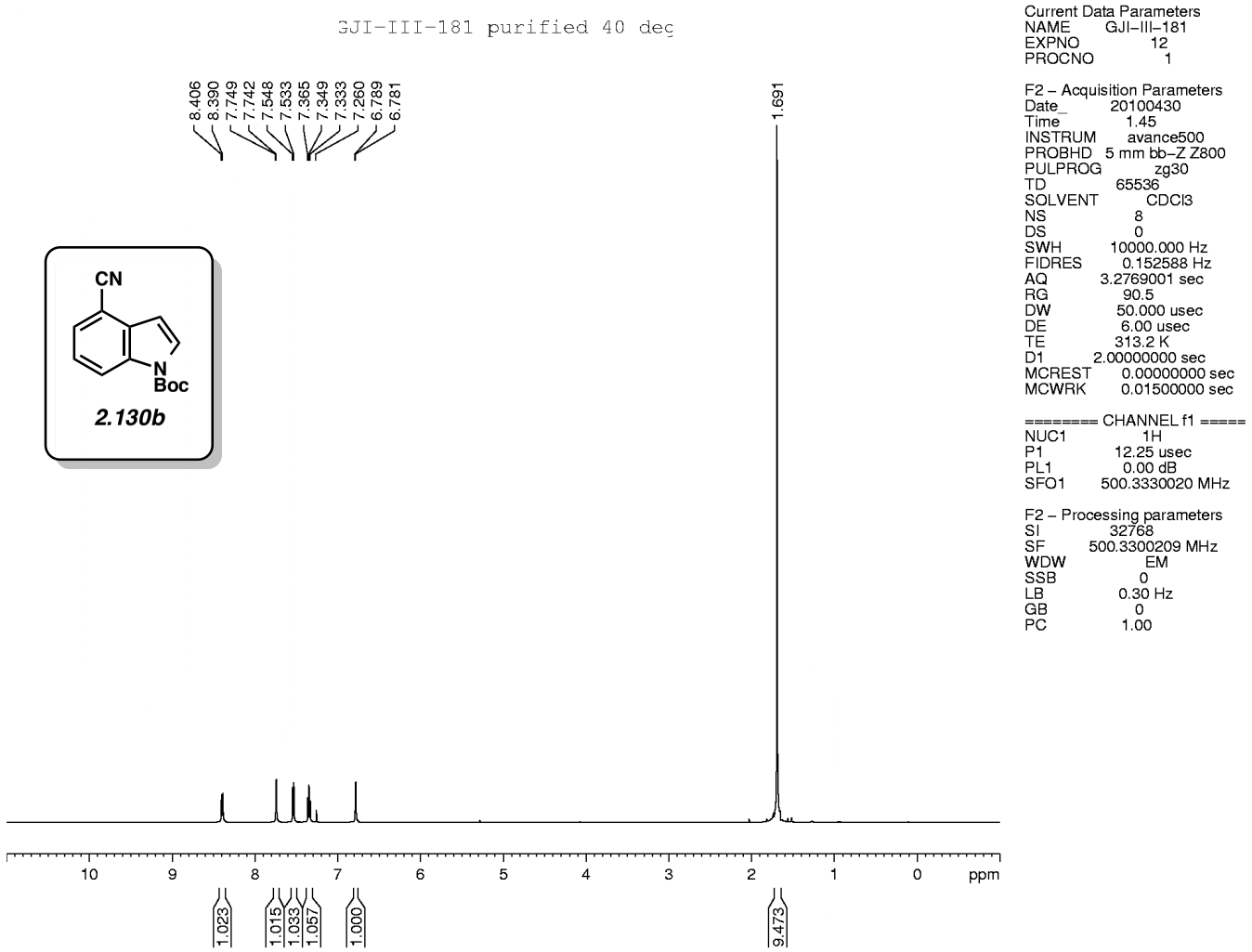



*Figure A1.220* $^{1}$H NMR (500 MHz, 40 °C, $CDCl_3$) of compound **2.130b**.

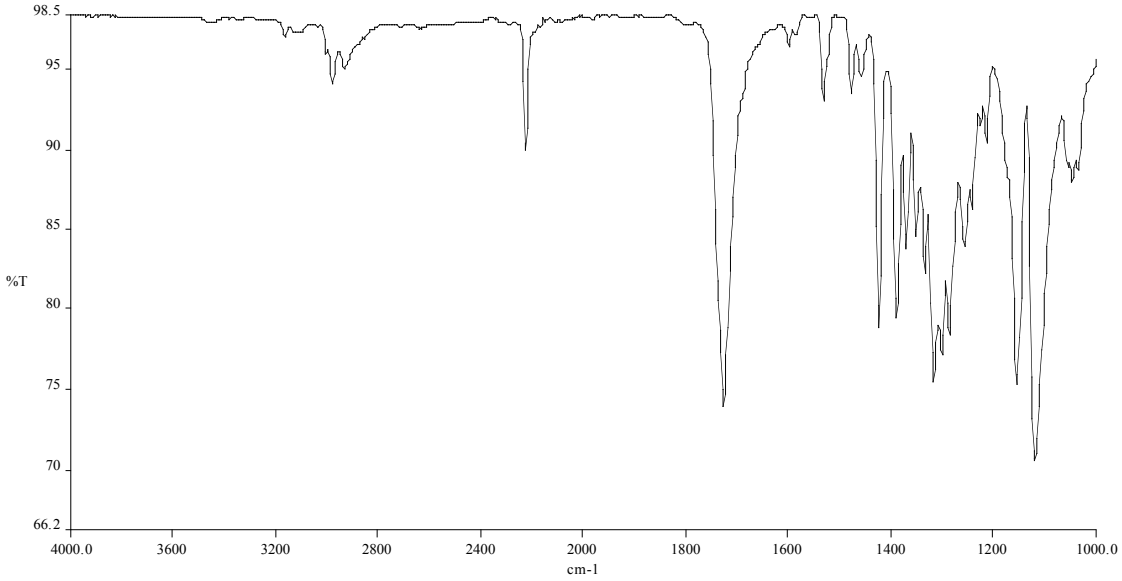



*Figure A1.221* Infrared spectrum of compound **2.130b**.

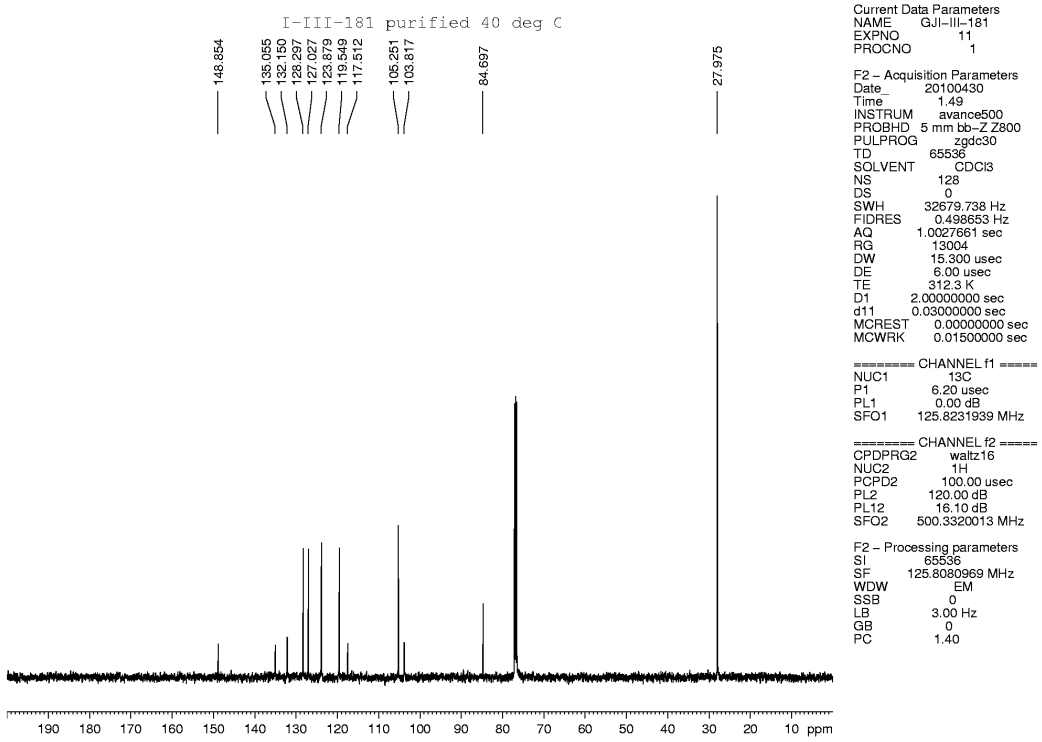



*Figure A1.222* $^{13}$C NMR (125 MHz, $CDCl_3$) of compound **2.130b**.

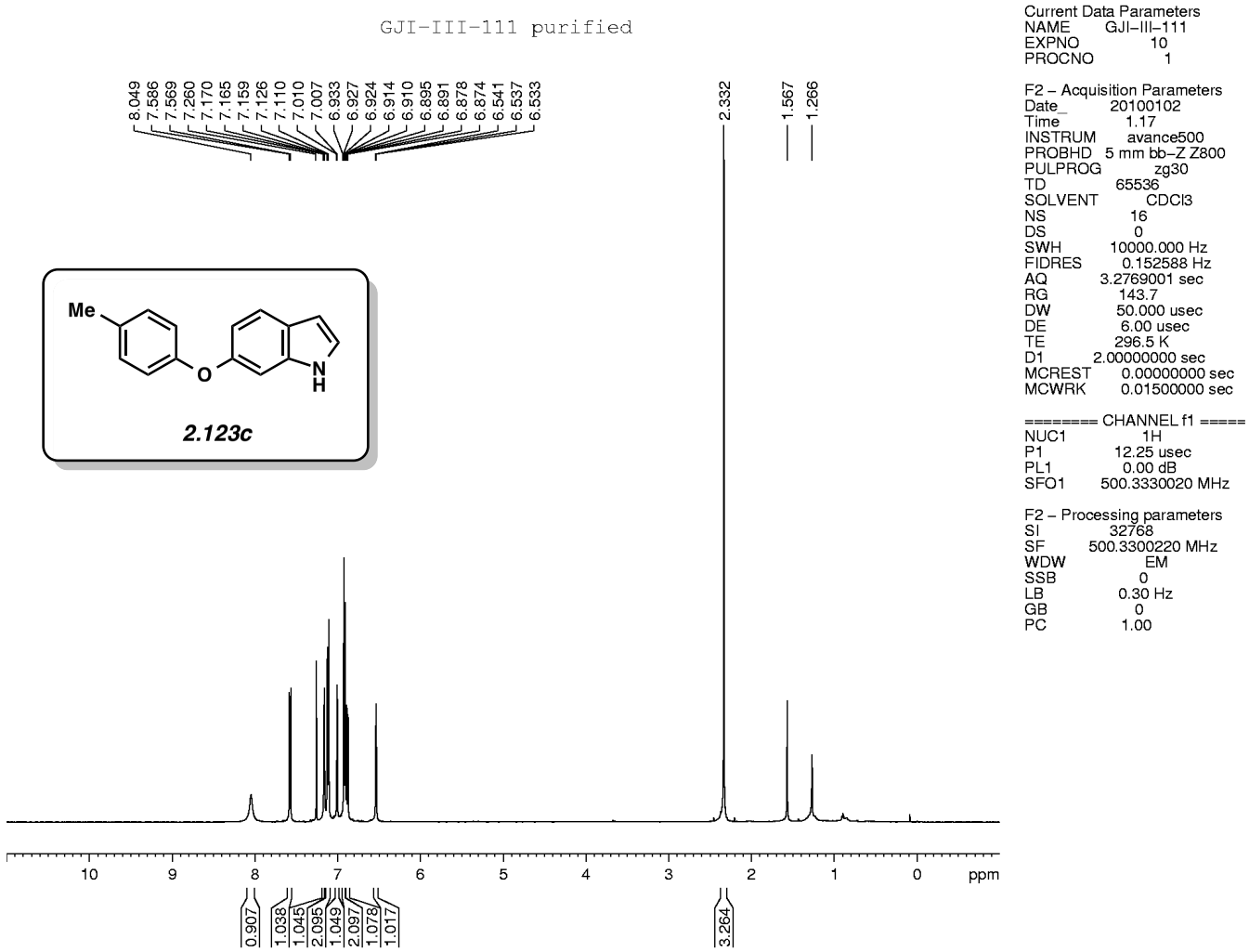



*Figure A1.223* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **2.123c**.

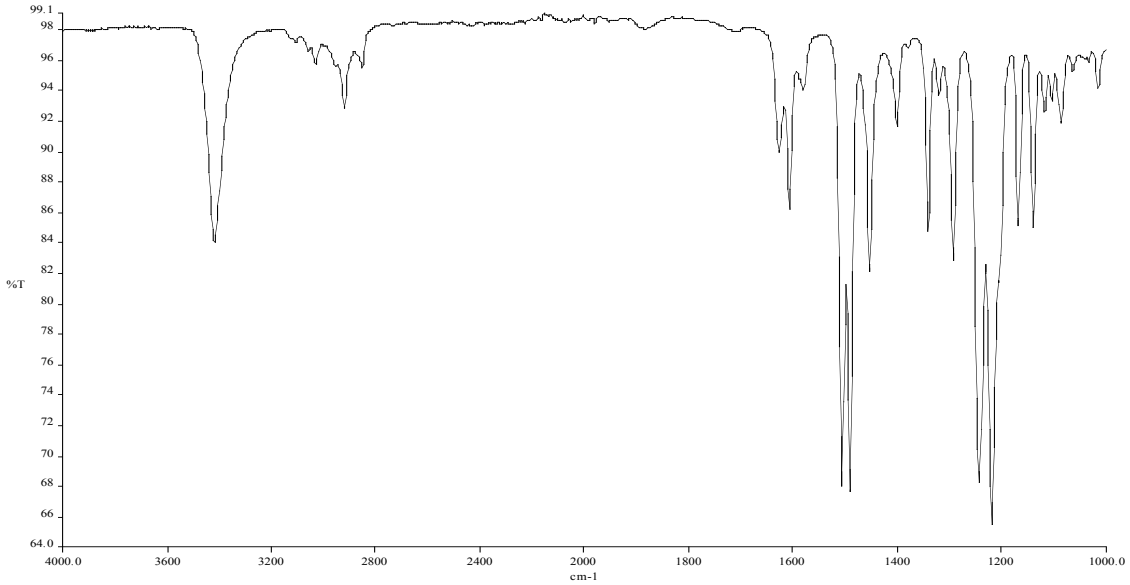



*Figure A1.224* Infrared spectrum of compound **2.123c**.

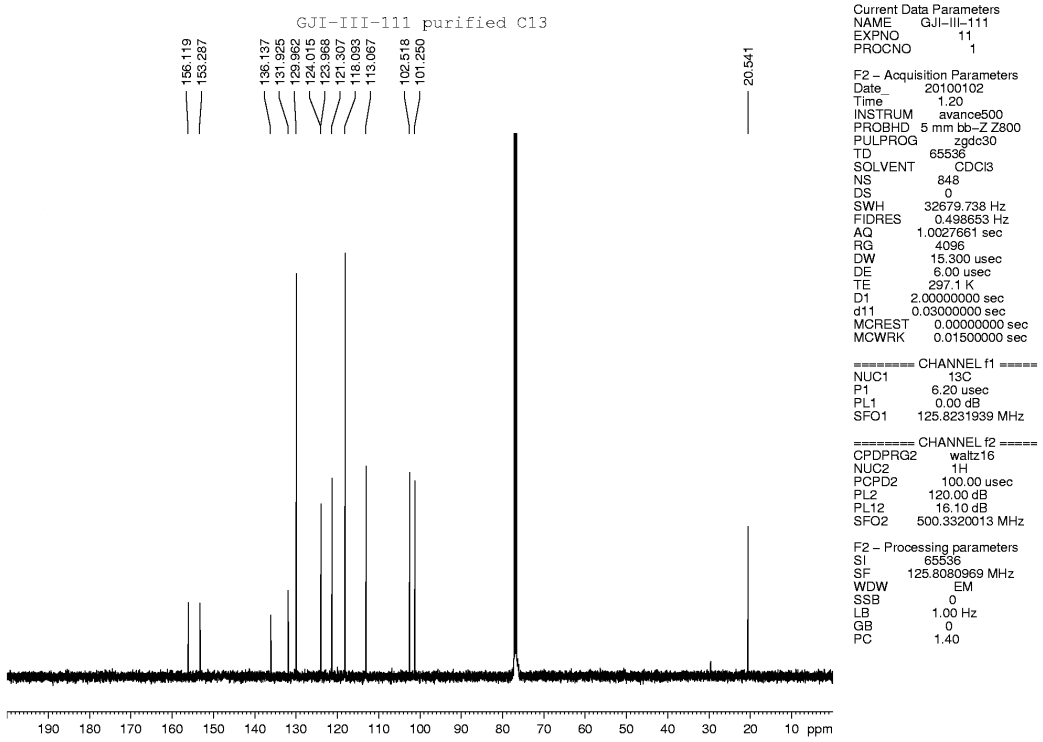



*Figure A1.225* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compound **2.123c**.

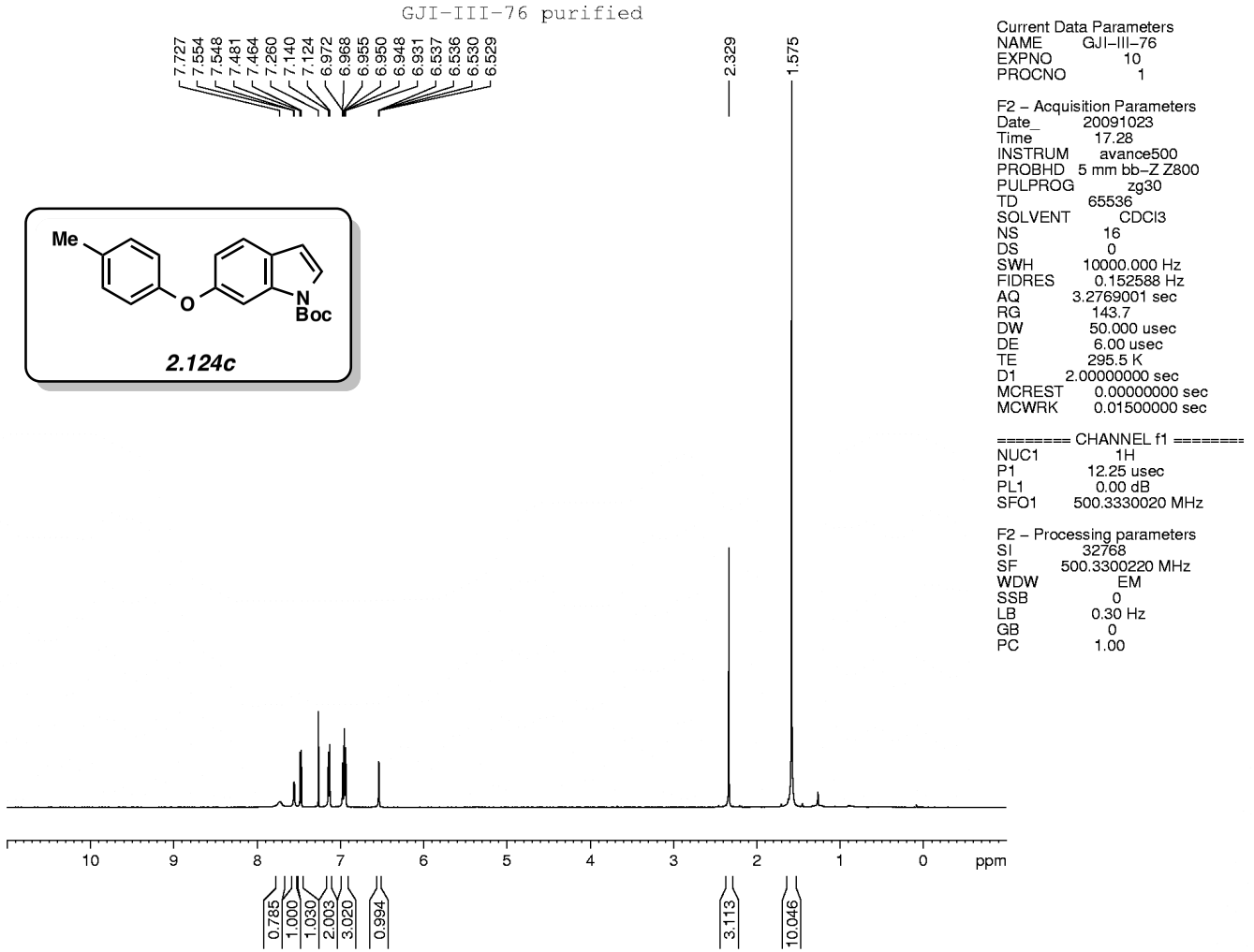



*Figure A1.226* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **2.124c**.

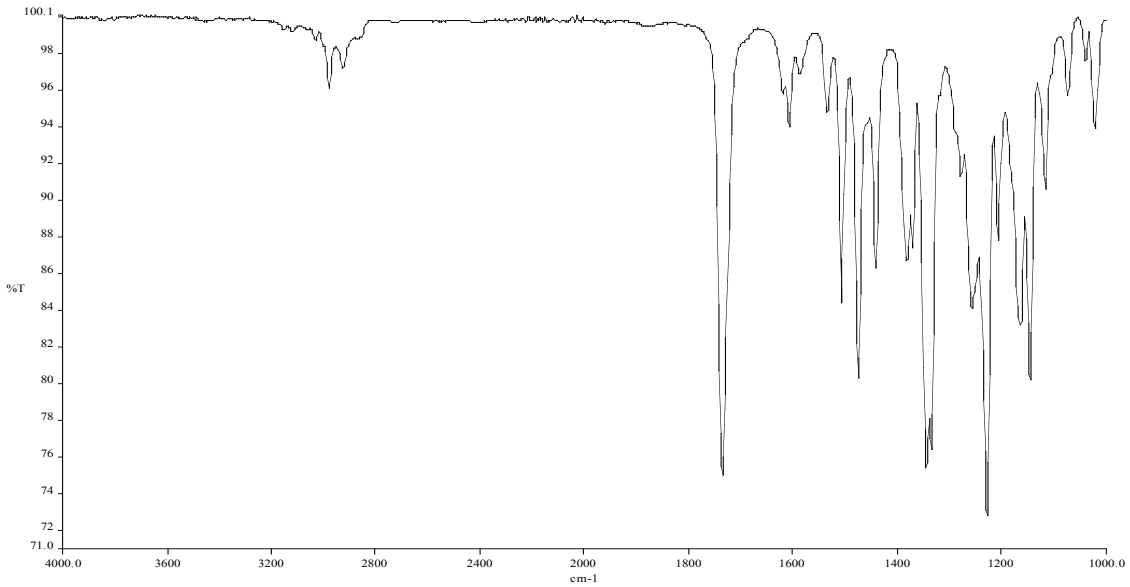



*Figure A1.227* Infrared spectrum of compound **2.124c**.

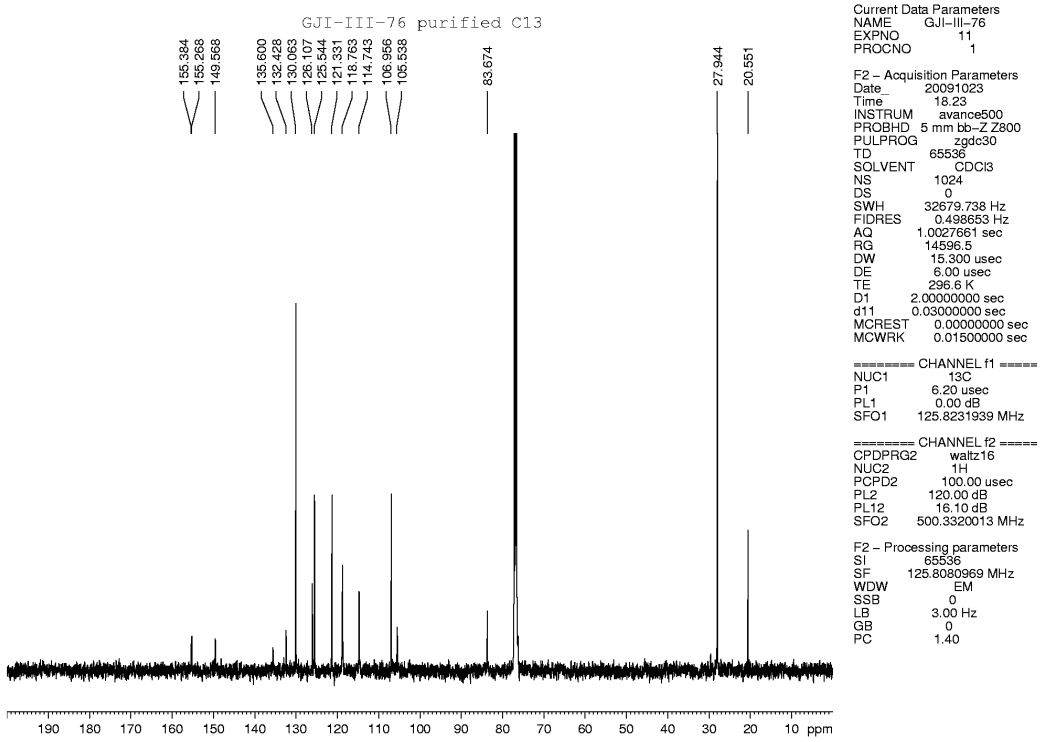



*Figure A1.228* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compound **2.124c**.

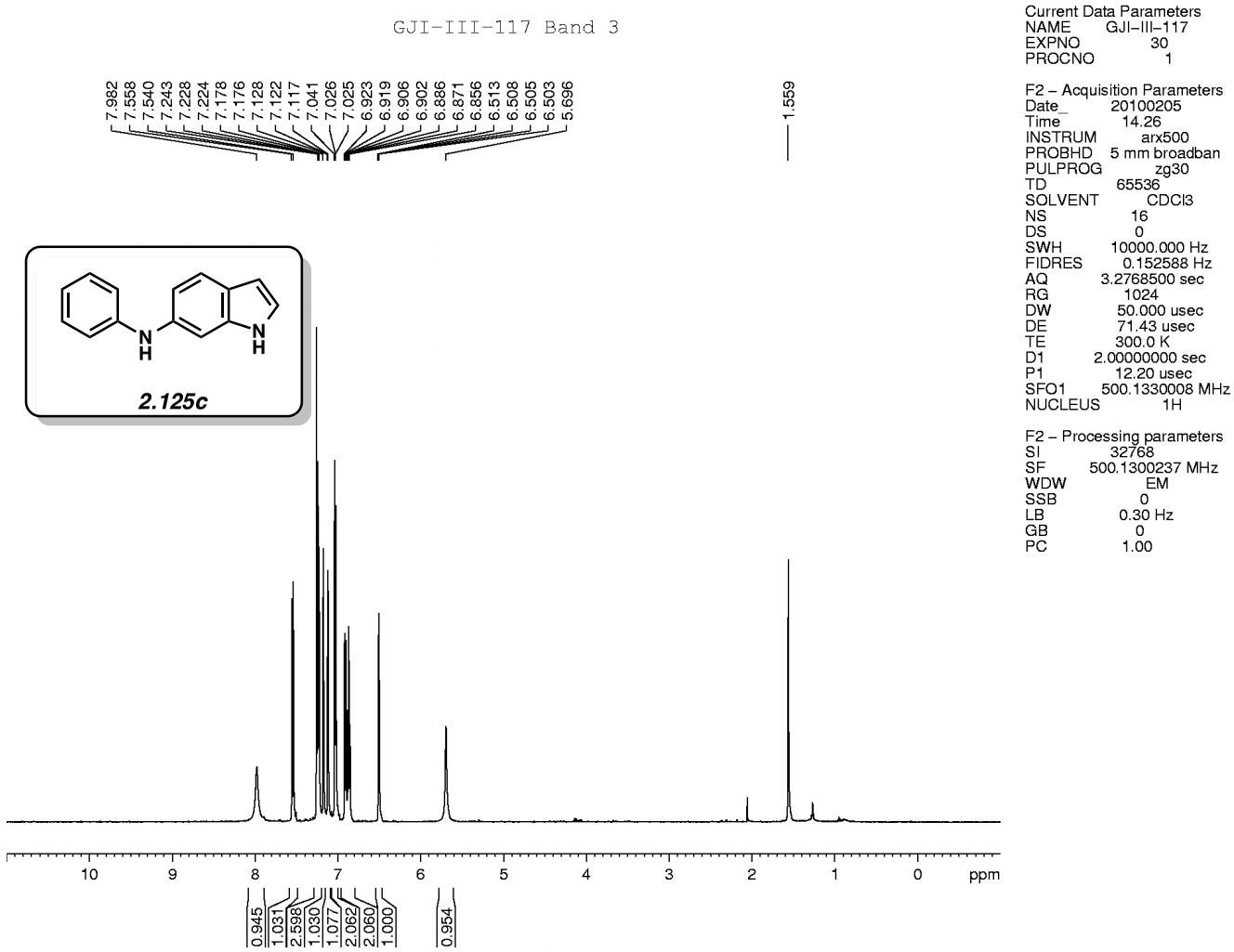



*Figure A1.229* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **2.125c**.

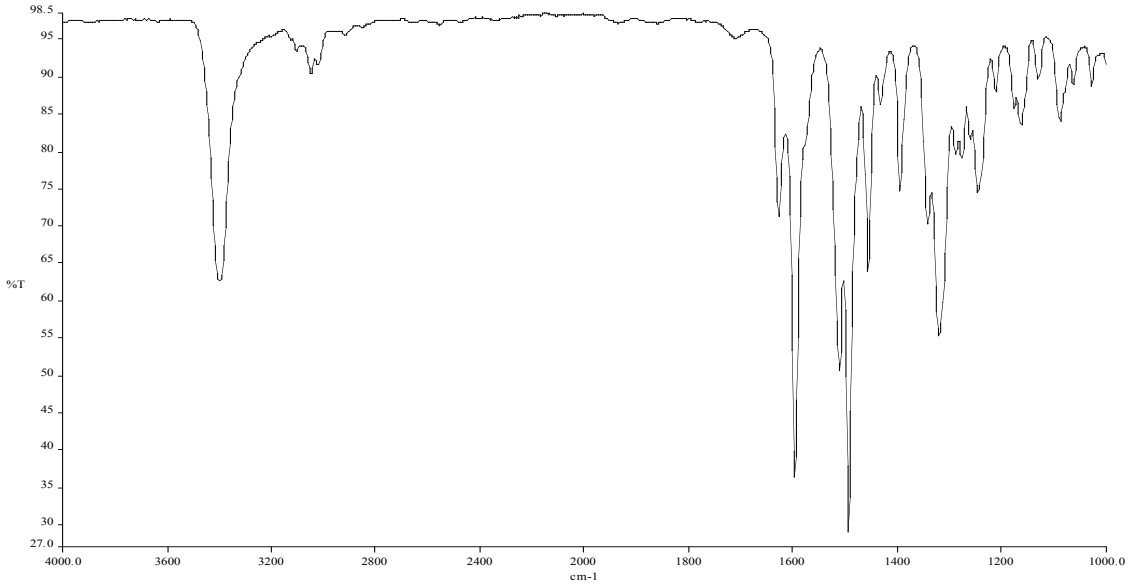



*Figure A1.230* Infrared spectrum of compound **2.125c**.

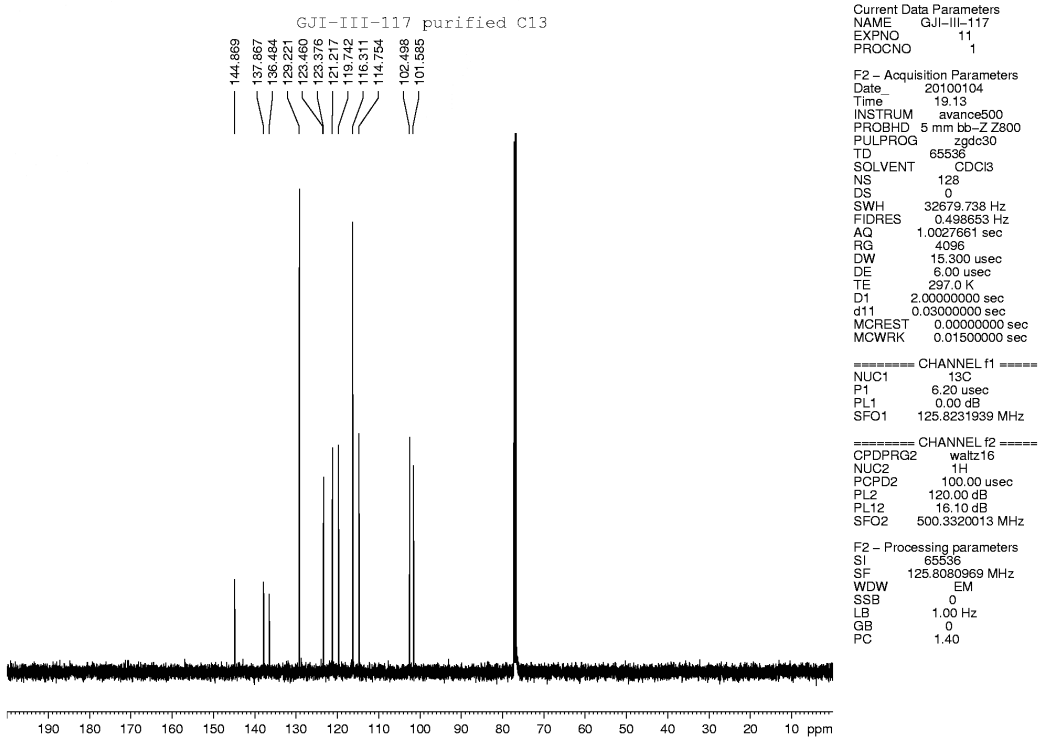



*Figure A1.231* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compound **2.125c**.

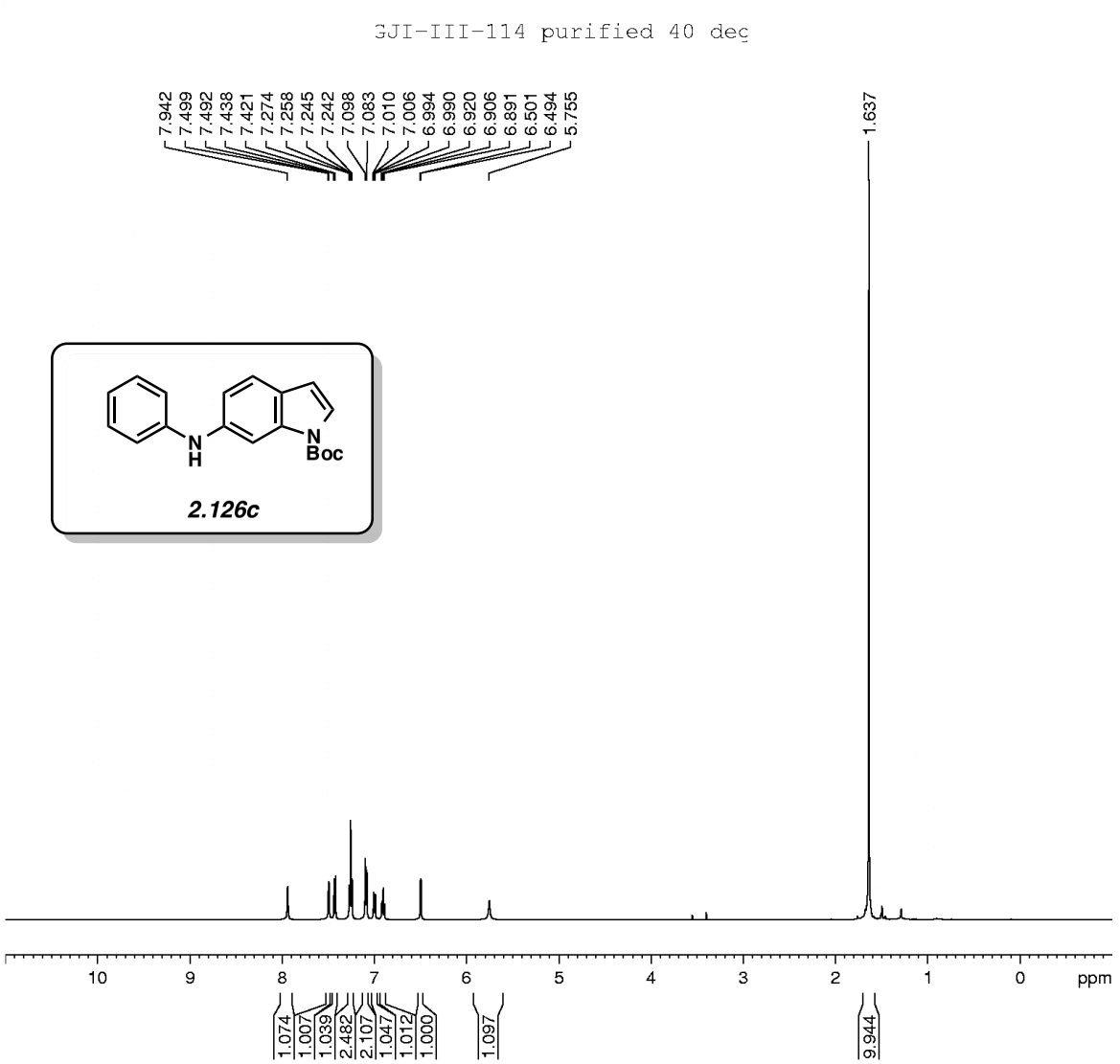



*Figure A1.232* $^{1}$H NMR (500 MHz, 40 °C, $CDCl_3$) of compound **2.126c**.

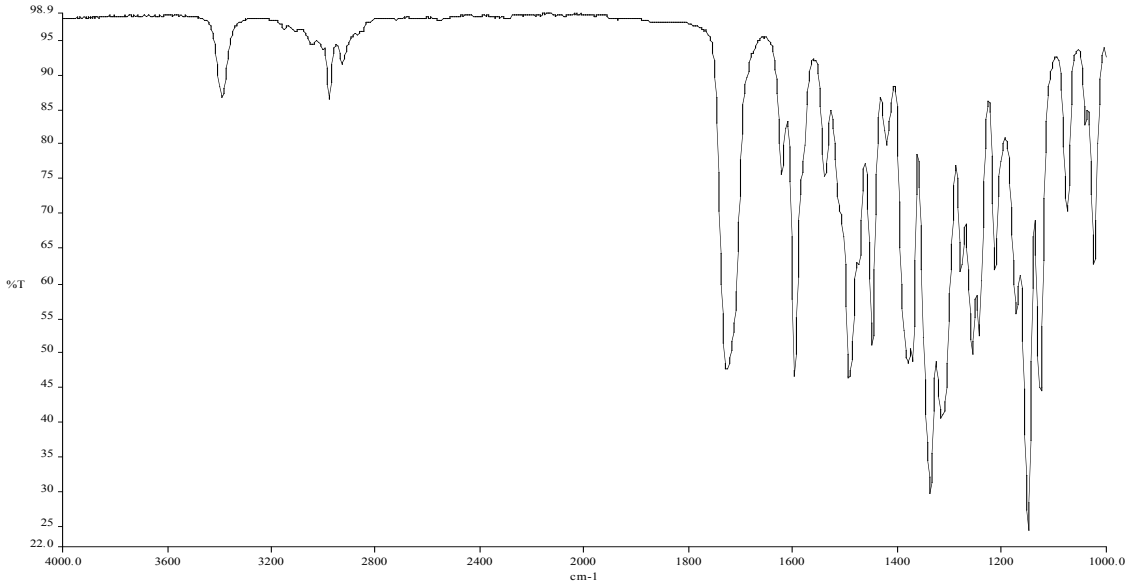



*Figure A1.233* Infrared spectrum of compound **2.126c**.

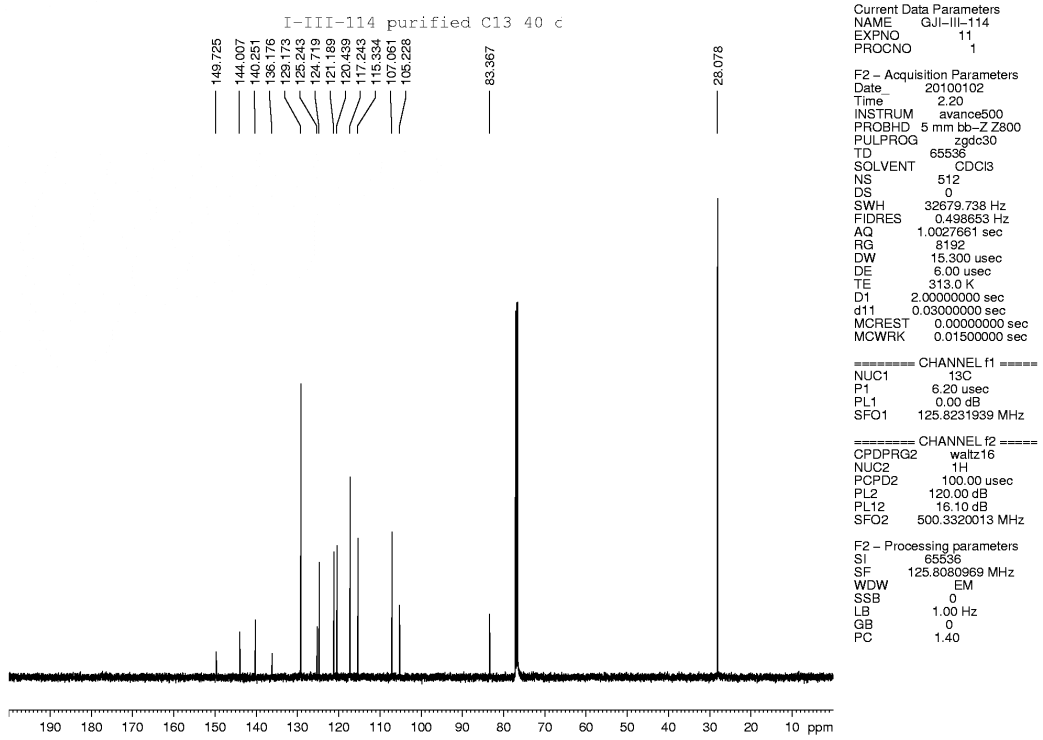



*Figure A1.234* $^{13}C$ NMR (125 MHz, 40 °C, $CDCl_3$) of compound **2.126c**.

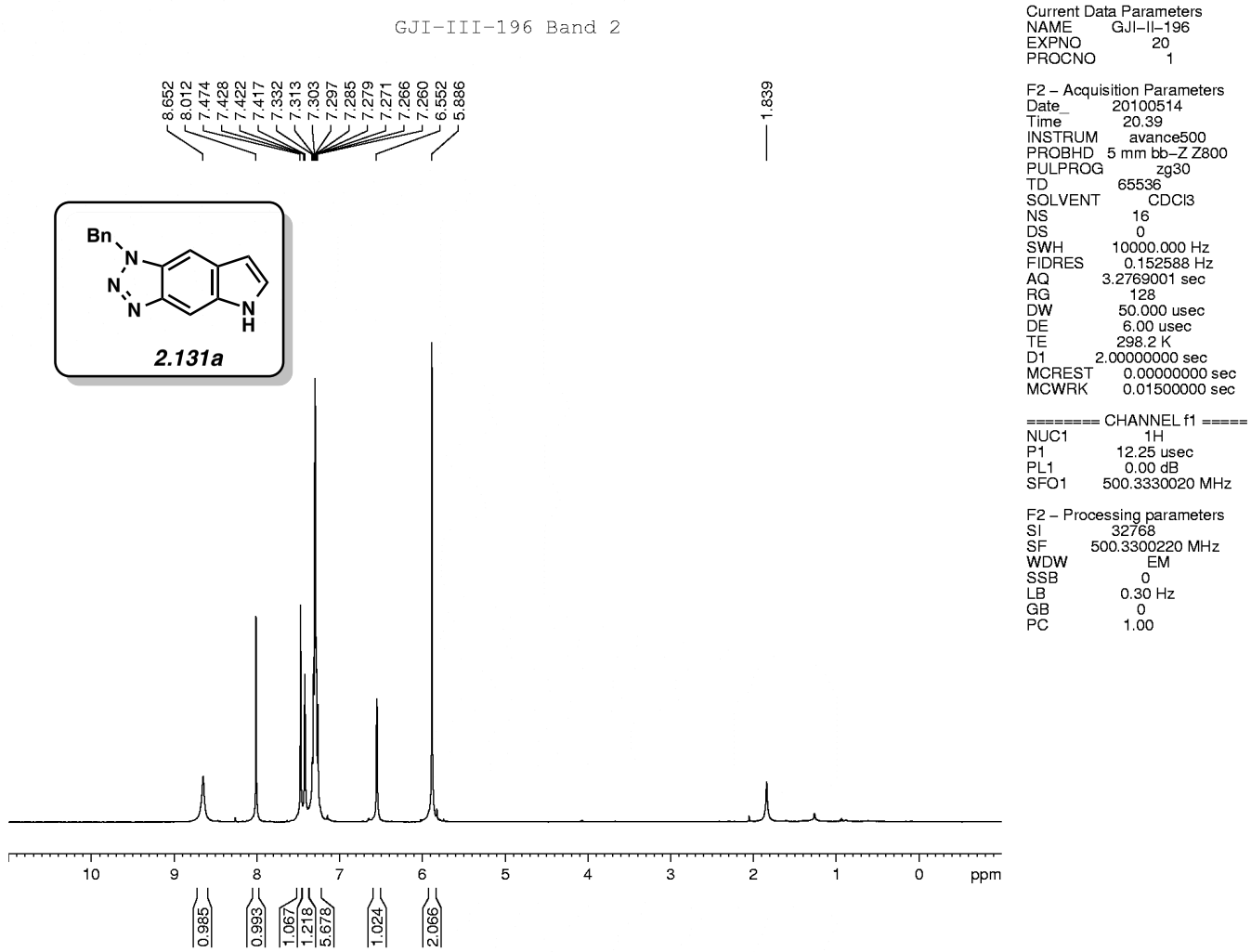



*Figure A1.235* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **2.131a**.

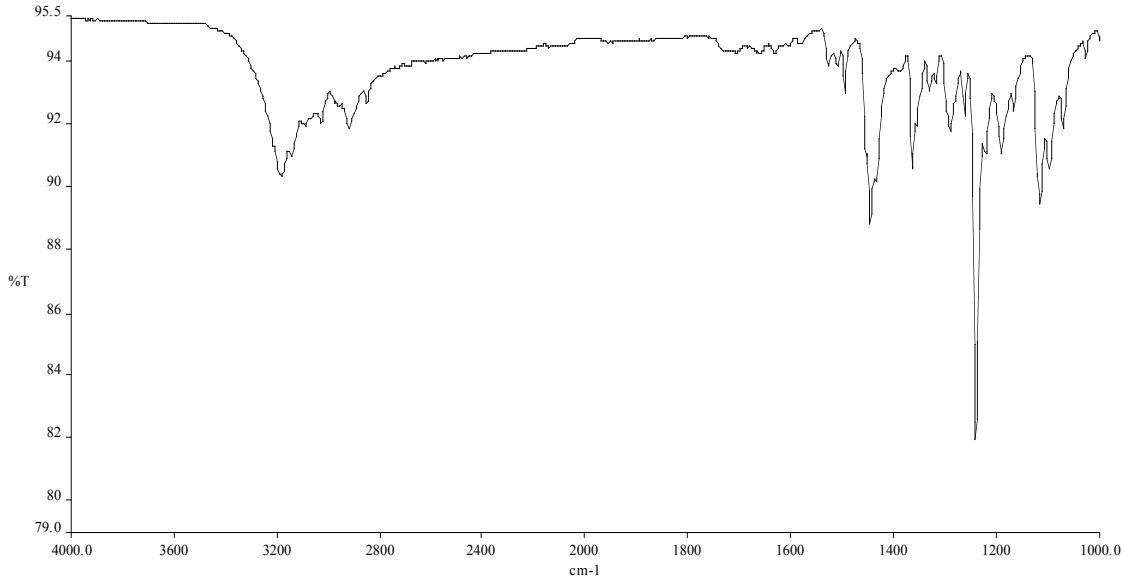



*Figure A1.236* Infrared spectrum of compound **2.131a**.

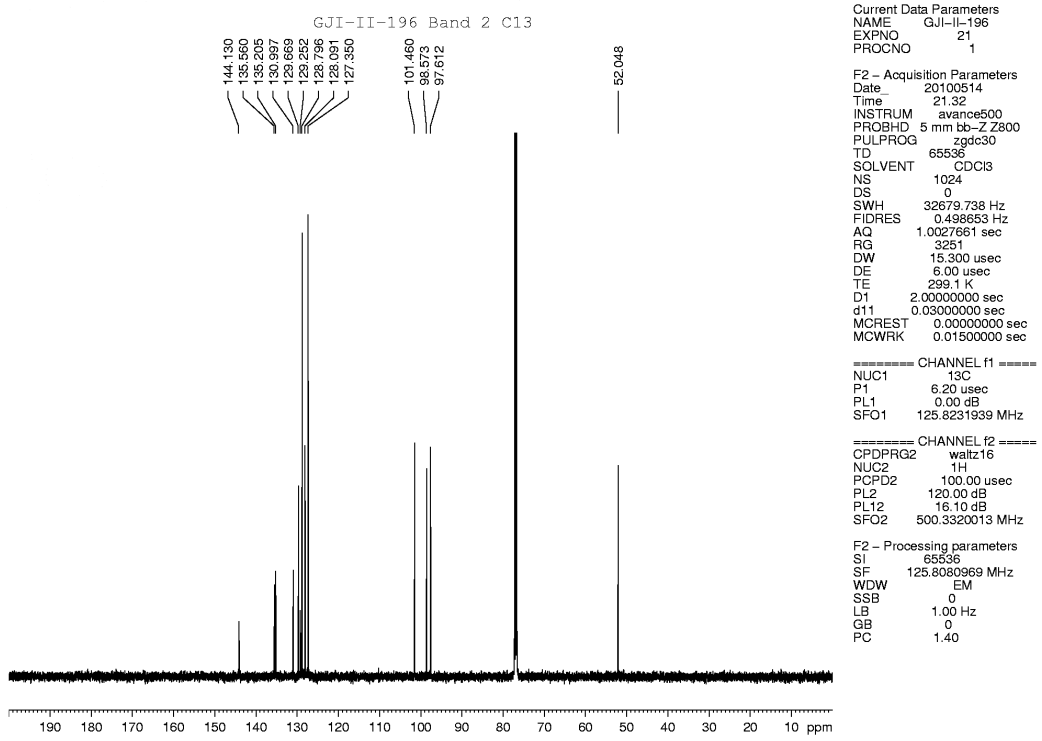



*Figure A1.237* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compound **2.131a**.

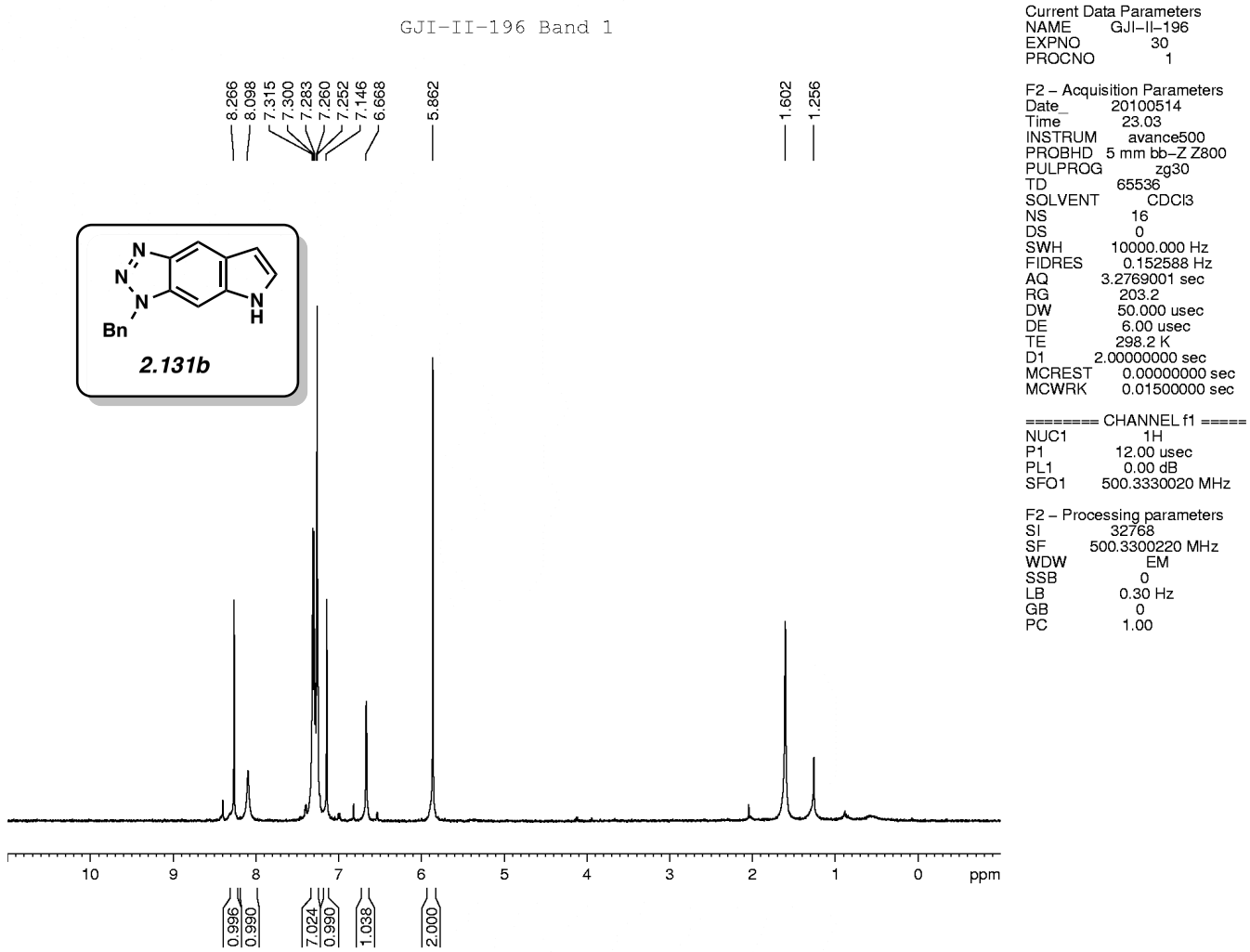



*Figure A1.238* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **2.131b**.

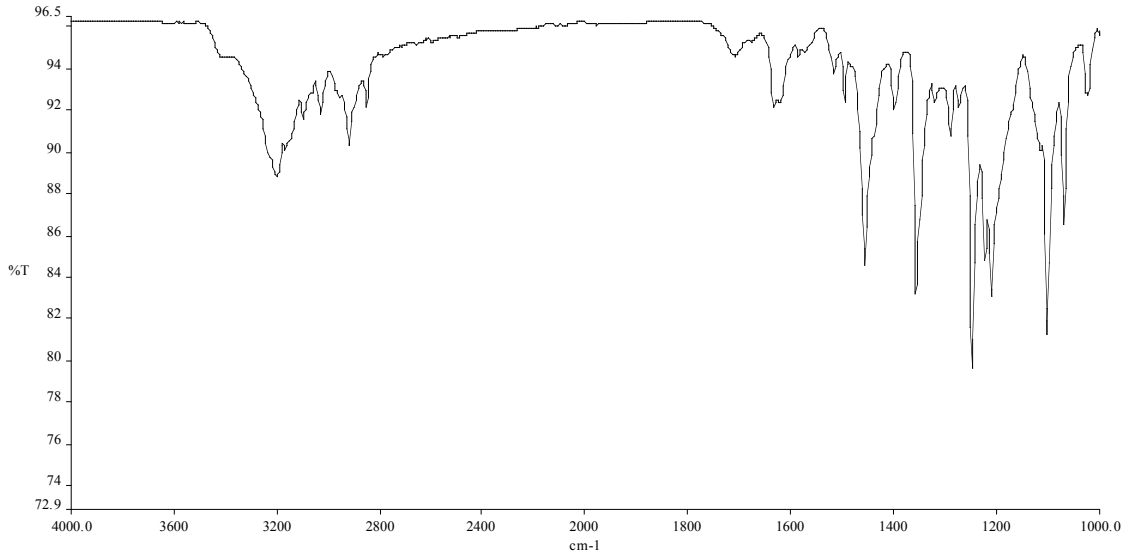



*Figure A1.239* Infrared spectrum of compound **2.131b**.

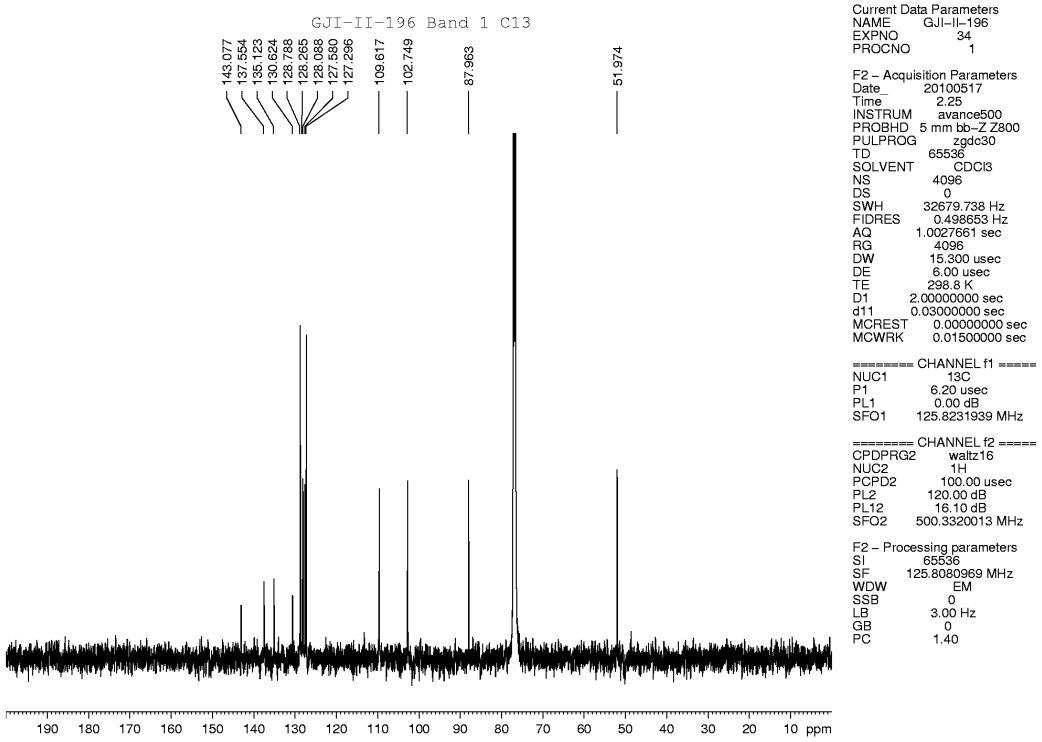



*Figure A1.240* $^{13}$C NMR (125 MHz, $CDCl_3$) of compound **2.131b**.

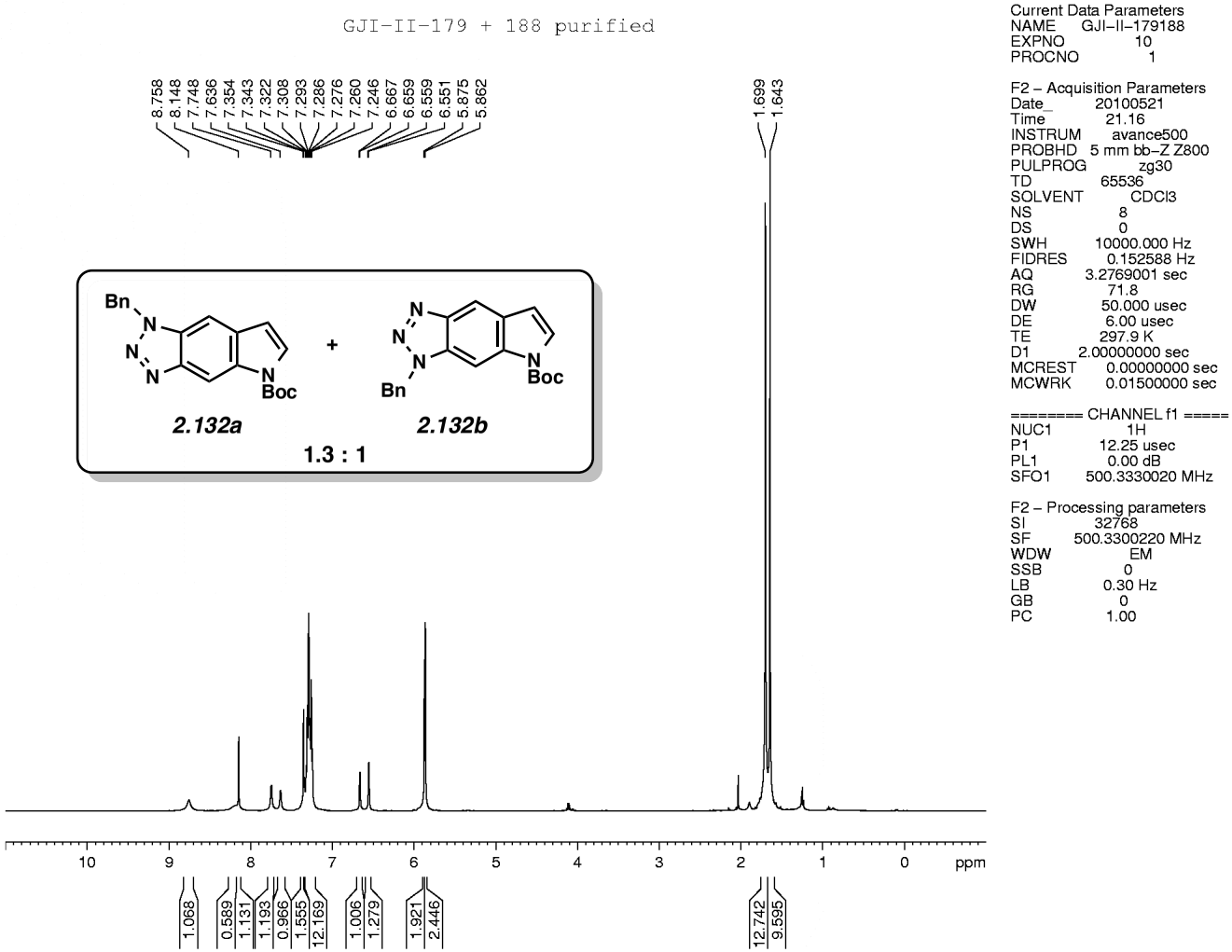



*Figure A1.241* $^{1}$H NMR (500 MHz, $CDCl_3$) of compounds **2.132a** and **2.132b**.

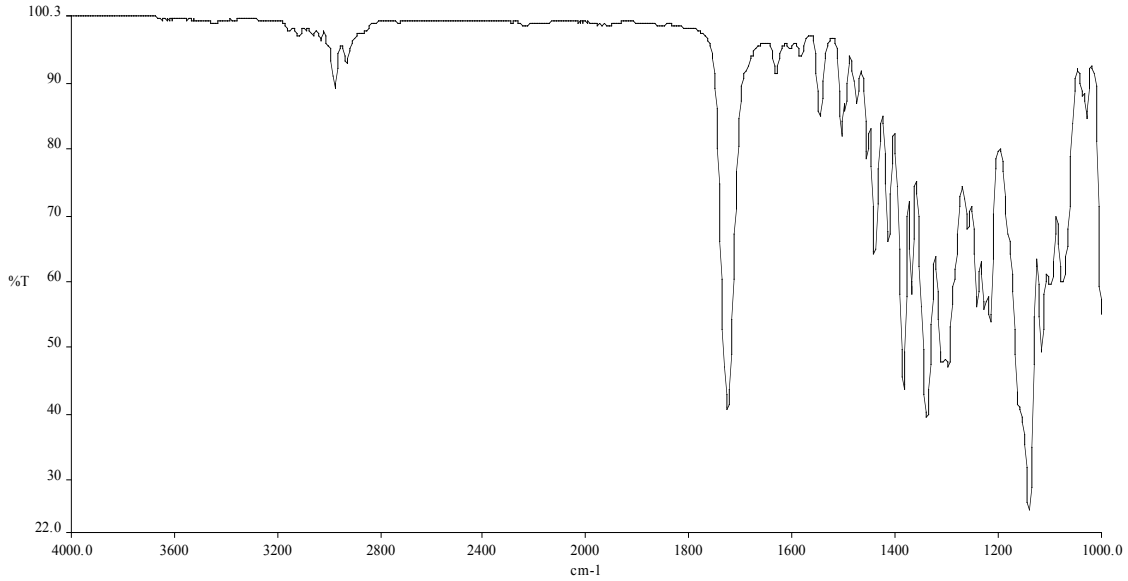



*Figure A1.242* Infrared spectrum of compounds **2.132a** and **2.132b**.

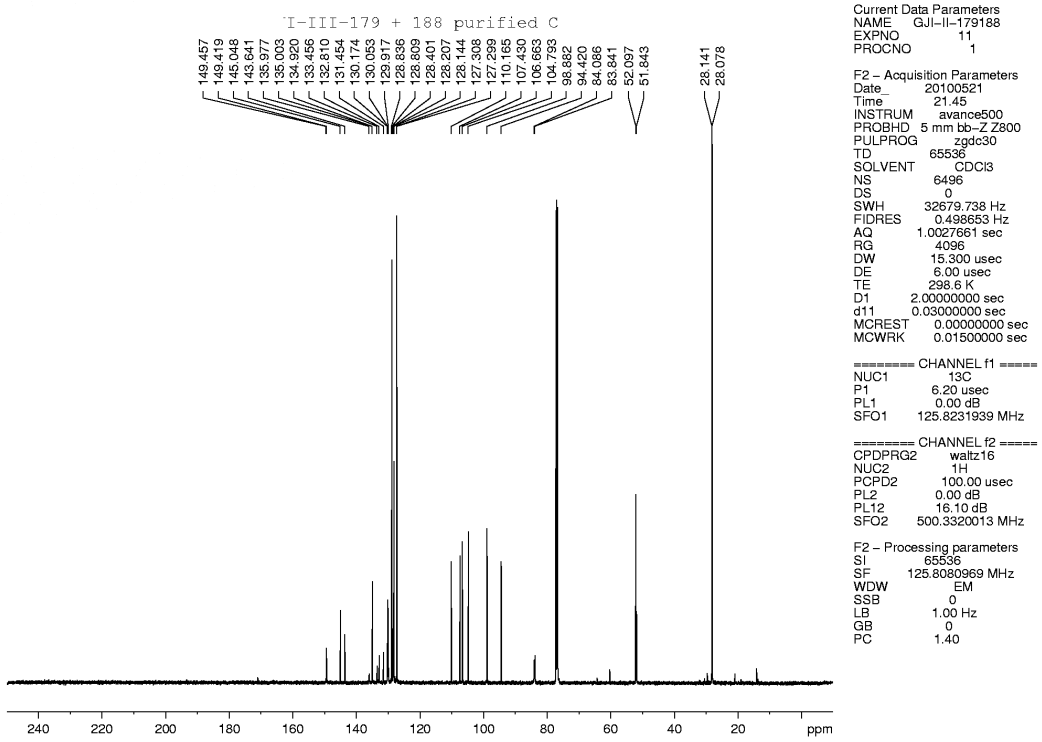



*Figure A1.243* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compounds **2.132a** and **2.132b**.

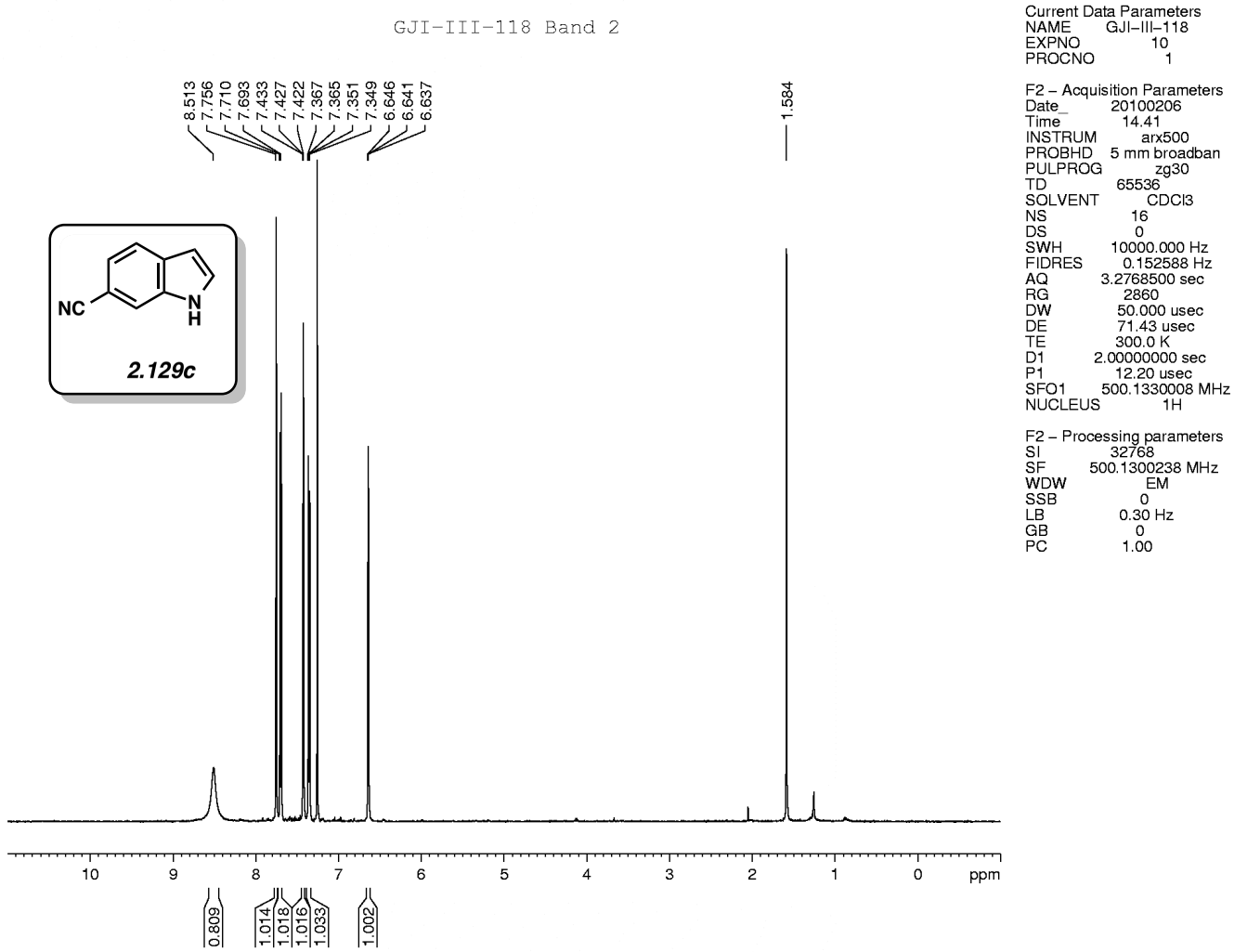



*Figure A1.244* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **2.129c**.

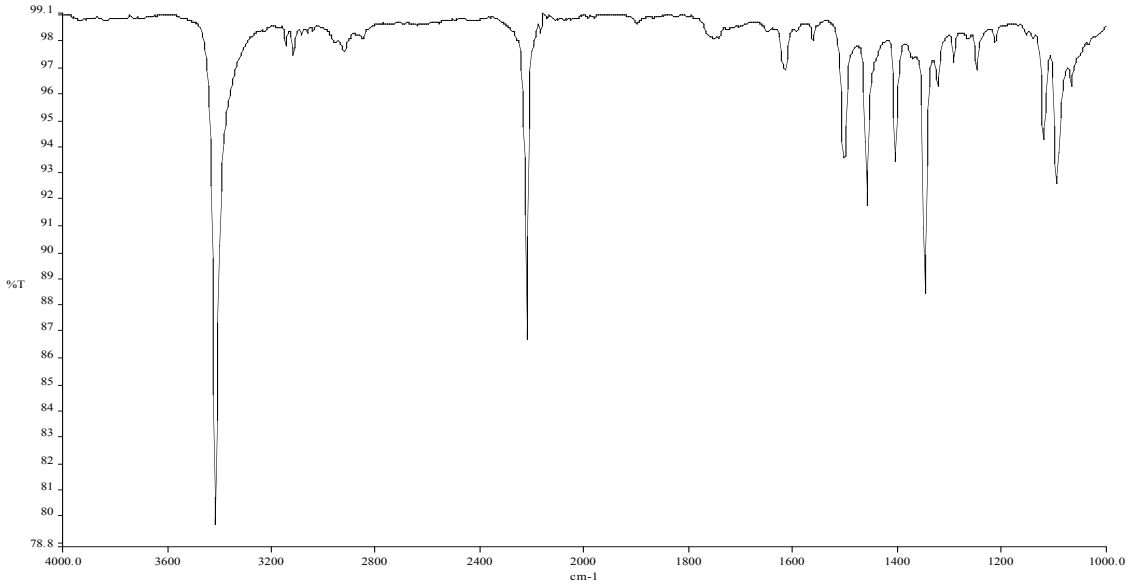



*Figure A1.245* Infrared spectrum of compound **2.129c**.

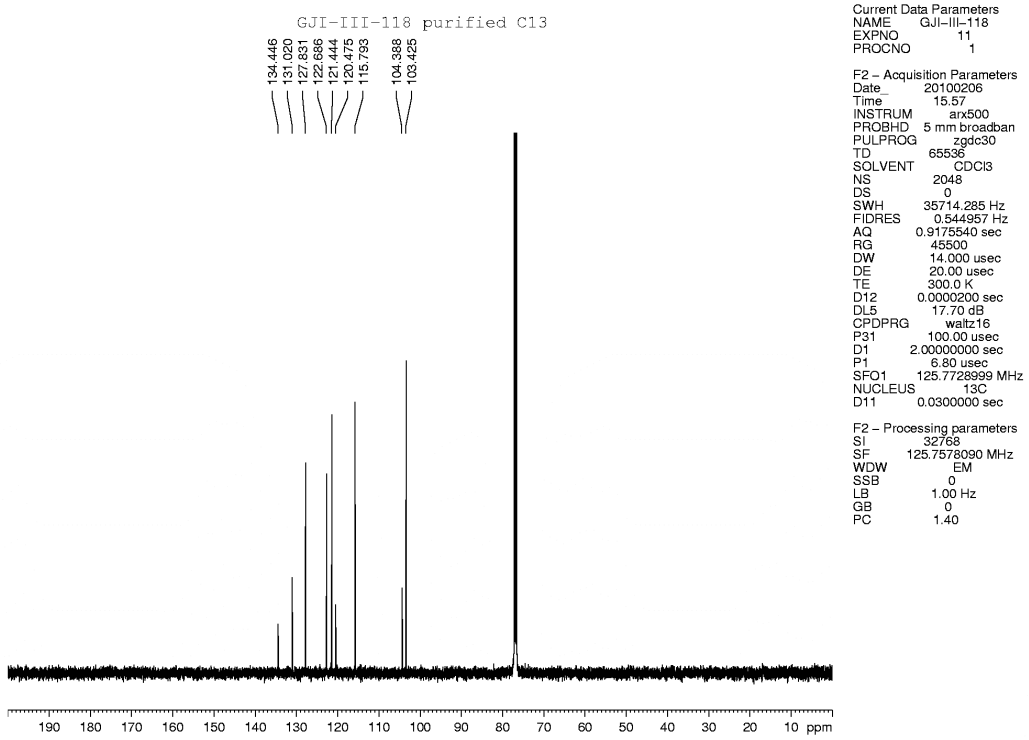



*Figure A1.246* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compound **2.129c**.

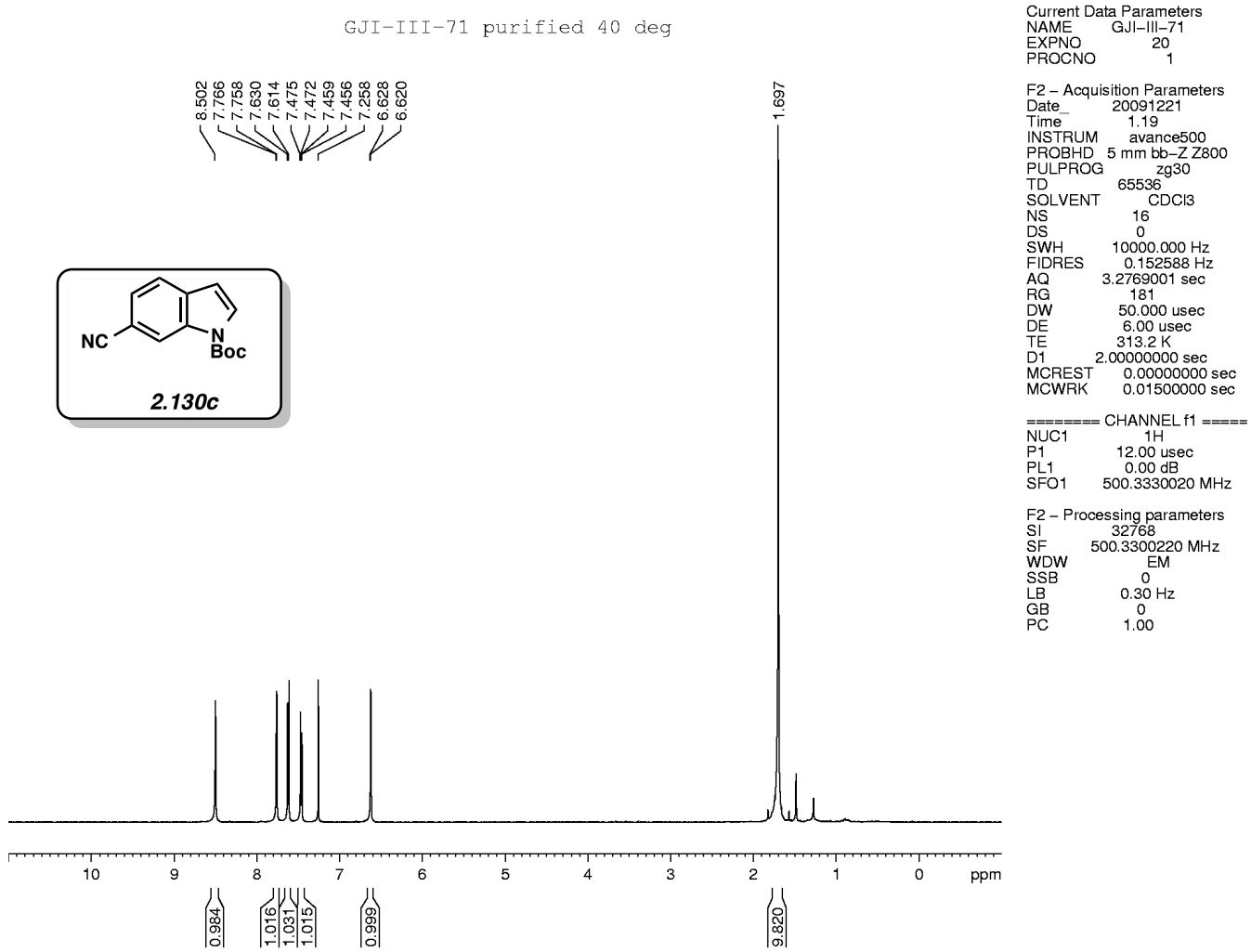



*Figure A1.247* $^{1}$H NMR (500 MHz, 40 °C, $CDCl_3$) of compound **2.130c**.

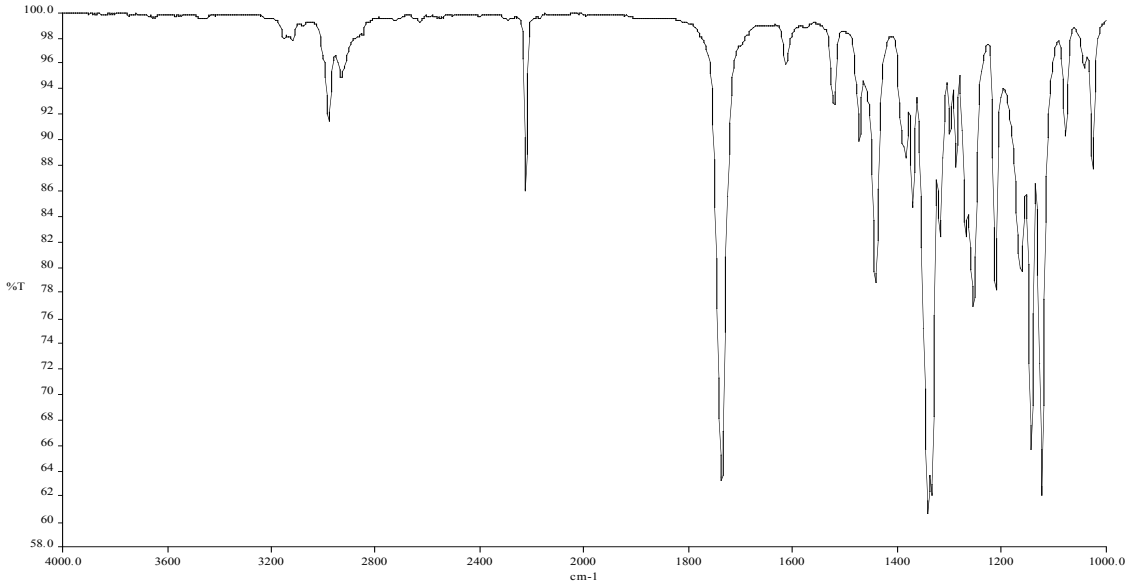



*Figure A1.248* Infrared spectrum of compound **2.130c**.

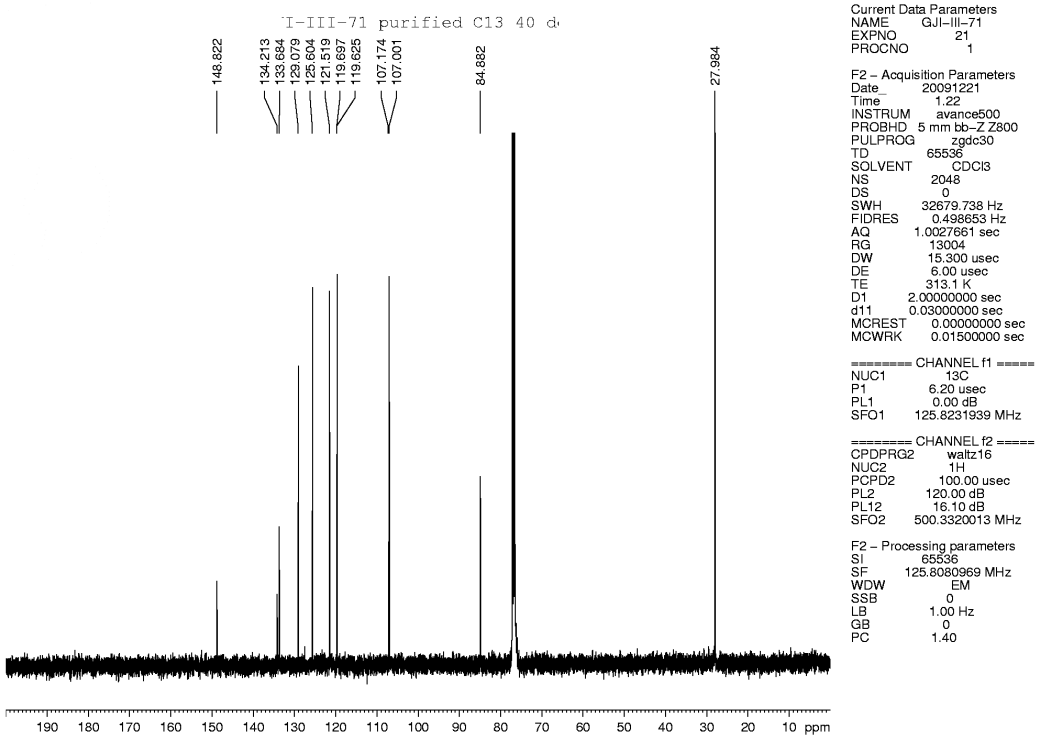



*Figure A1.249* $^{13}C$ NMR (125 MHz, 40 °C, $CDCl_3$) of compound **2.130c**.

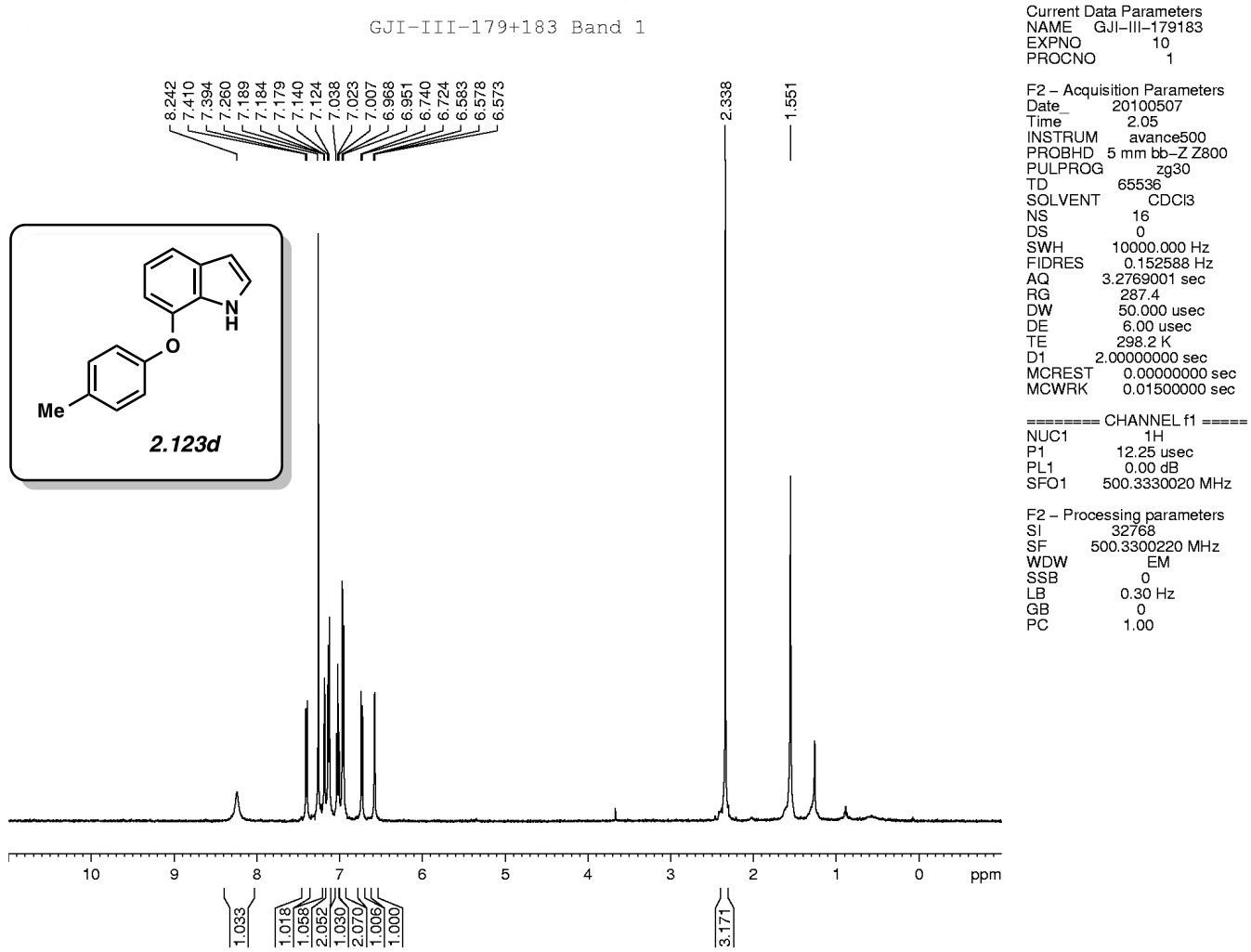



*Figure A1.250* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **2.123d**.

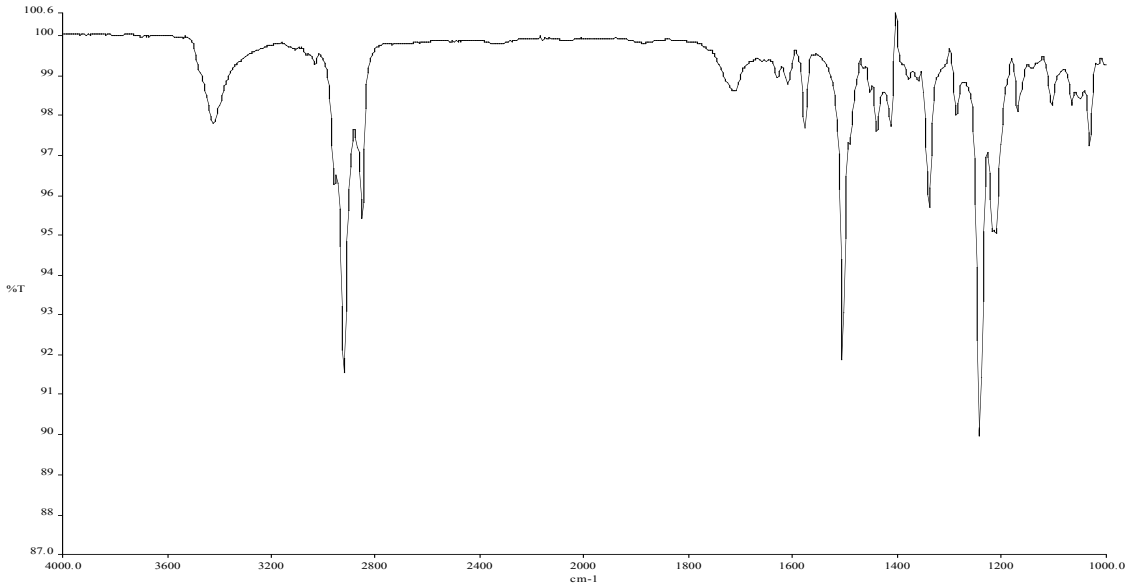



*Figure A1.251* Infrared spectrum of compound **2.123d**.

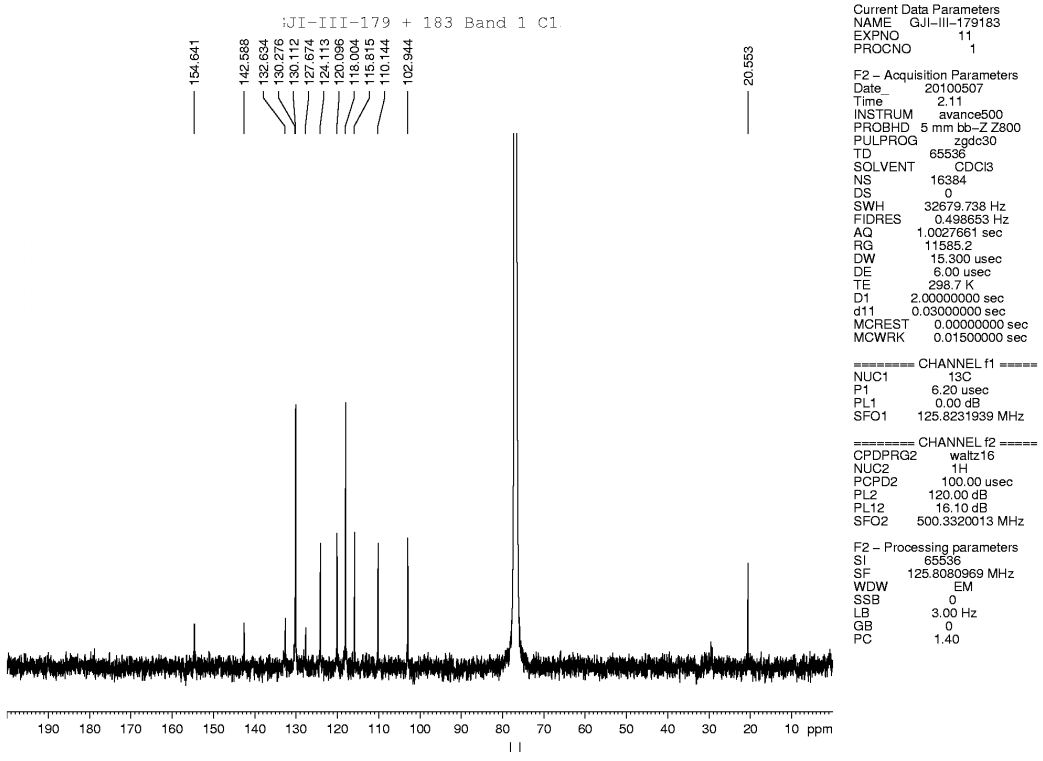



*Figure A1.252* $^{13}$C NMR (125 MHz, $CDCl_3$) of compound **2.123d**.

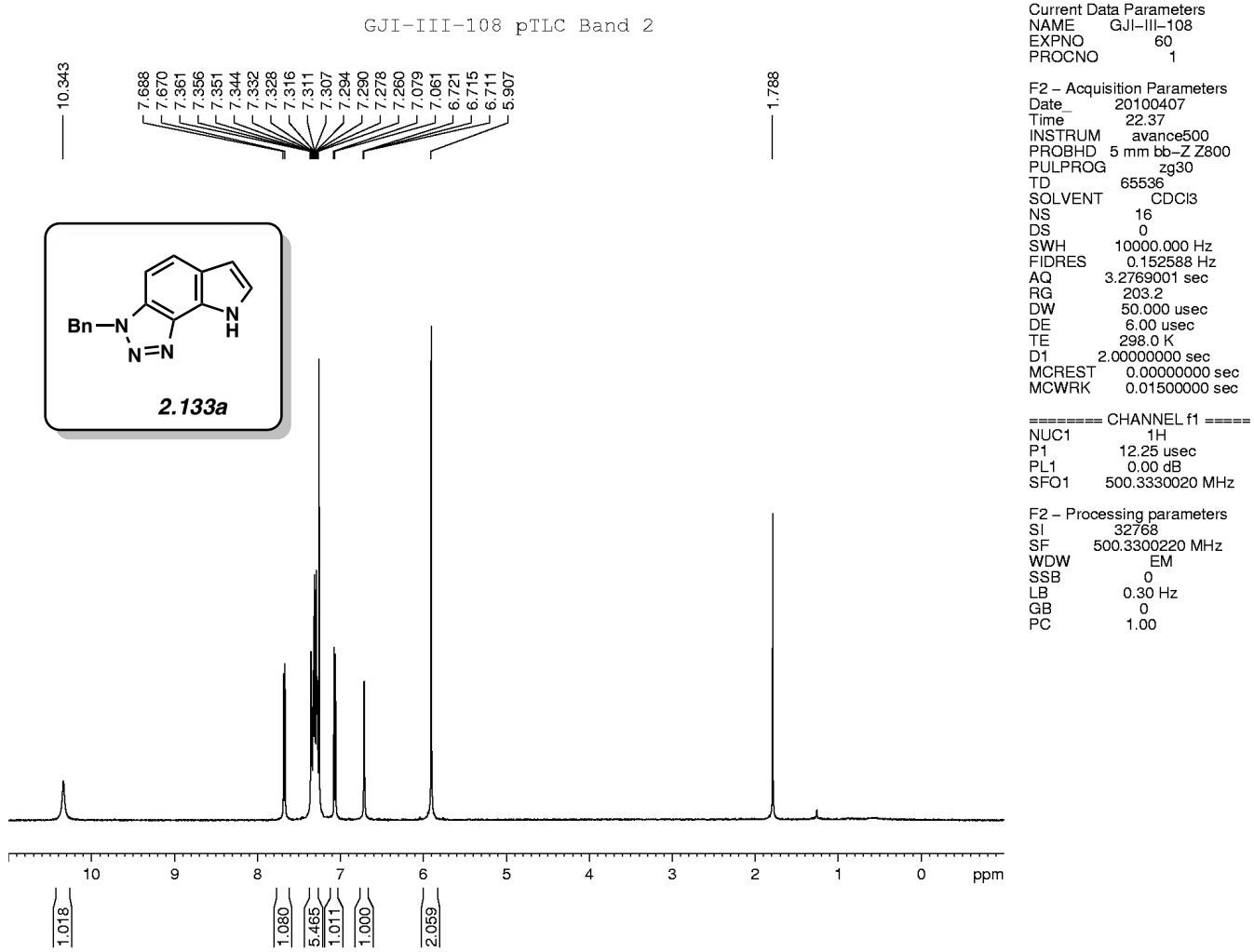



*Figure A1.253* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **2.133a**.

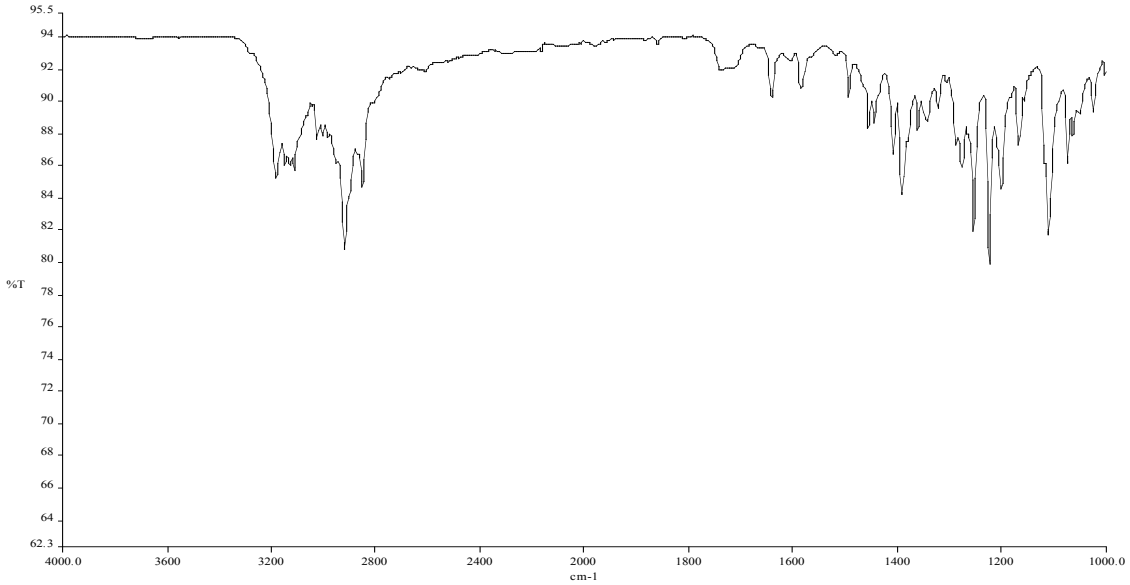



*Figure A1.254* Infrared spectrum of compound **2.133a**.

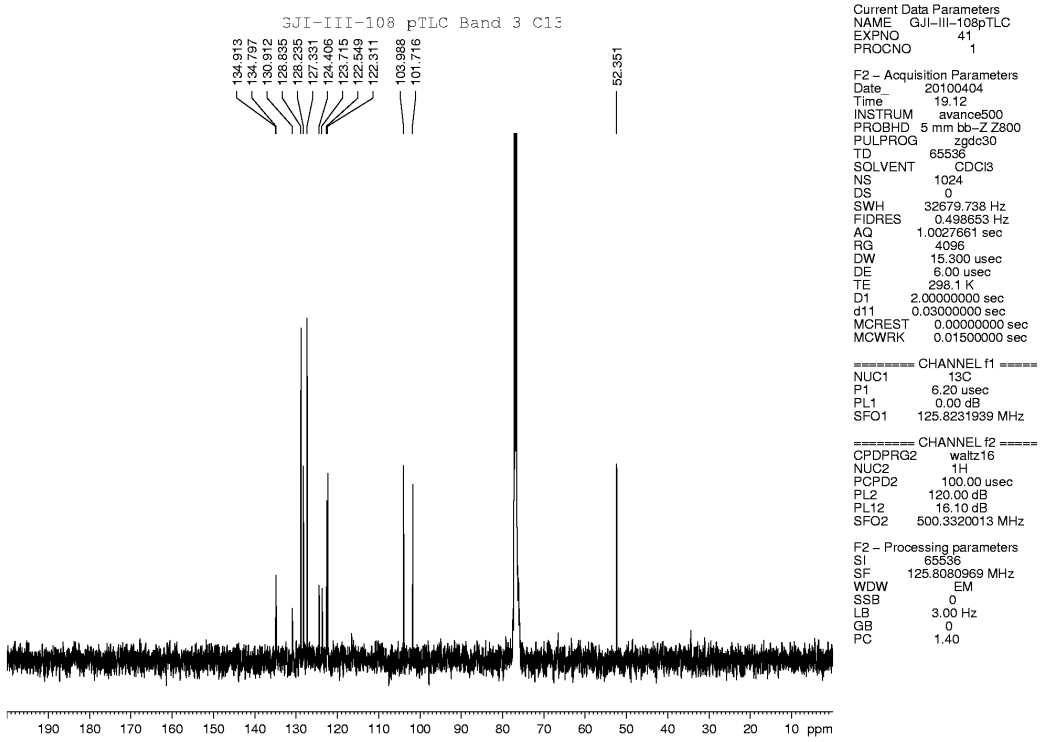



*Figure A1.255* $^{13}$C NMR (125 MHz, $CDCl_3$) of compound **2.133a**.

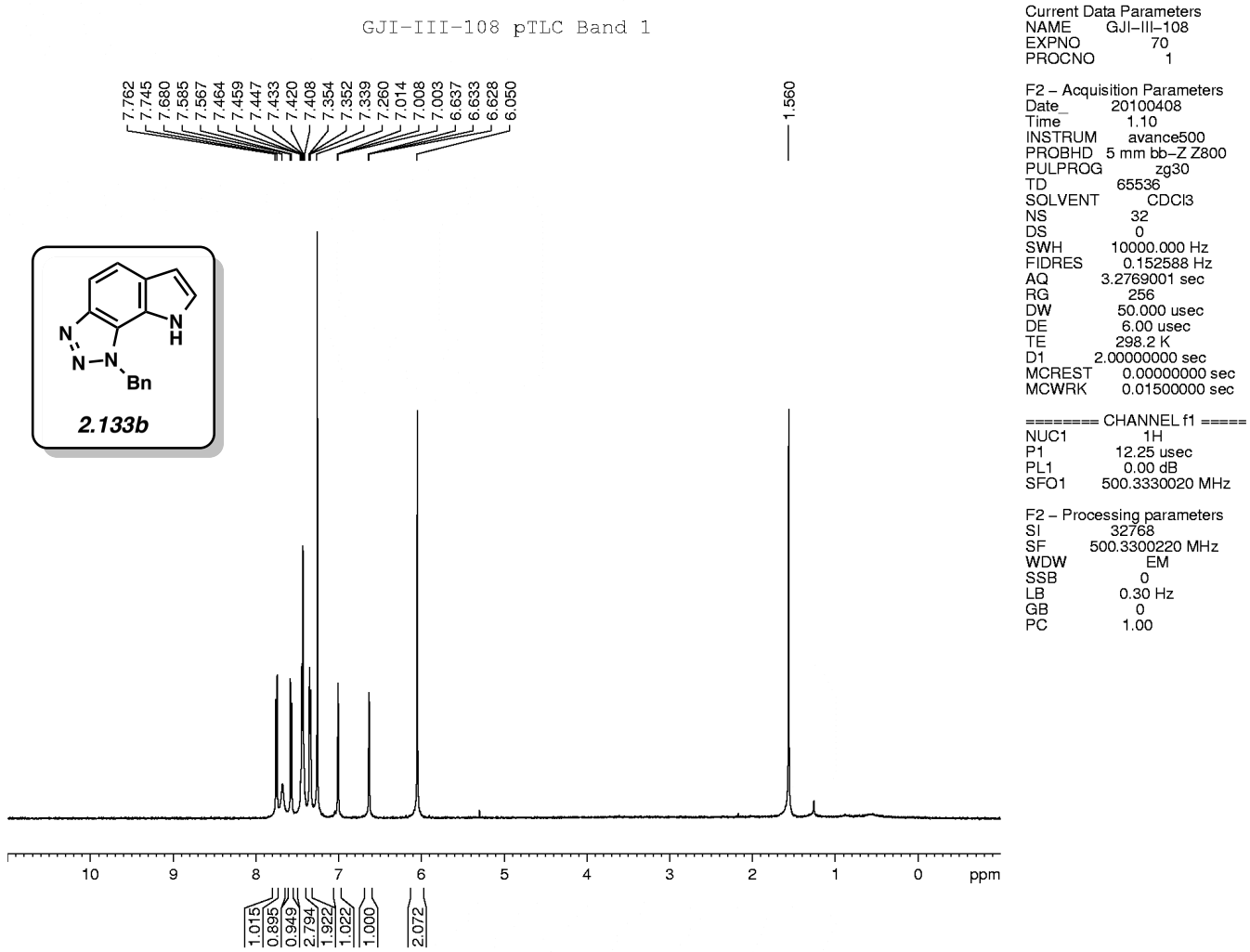



*Figure A1.256* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **2.133b**.

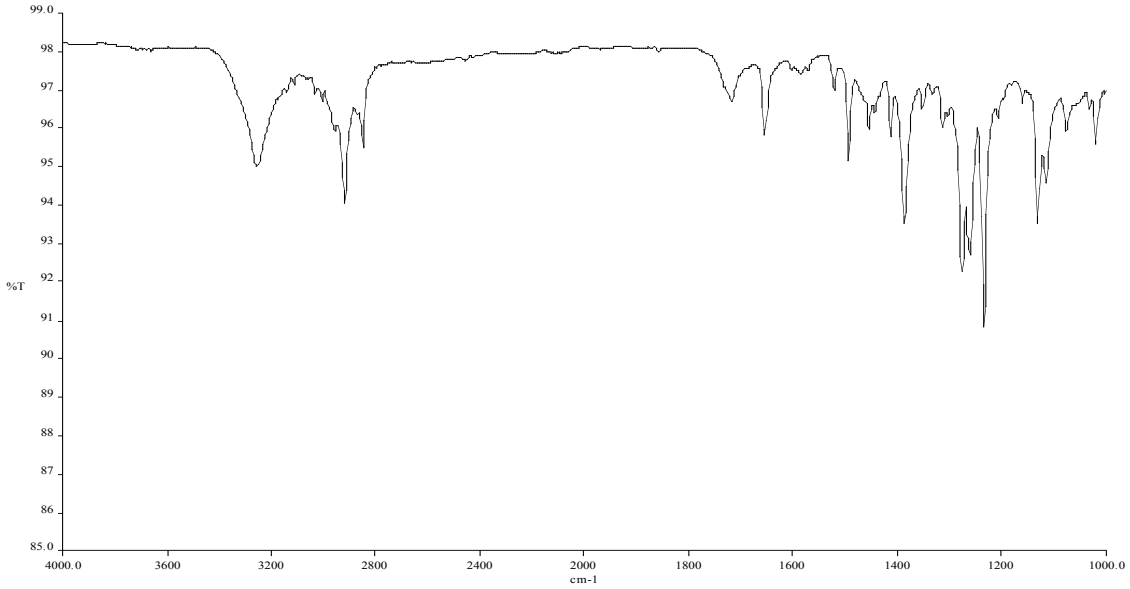



*Figure A1.257* Infrared spectrum of compound **2.133b**.

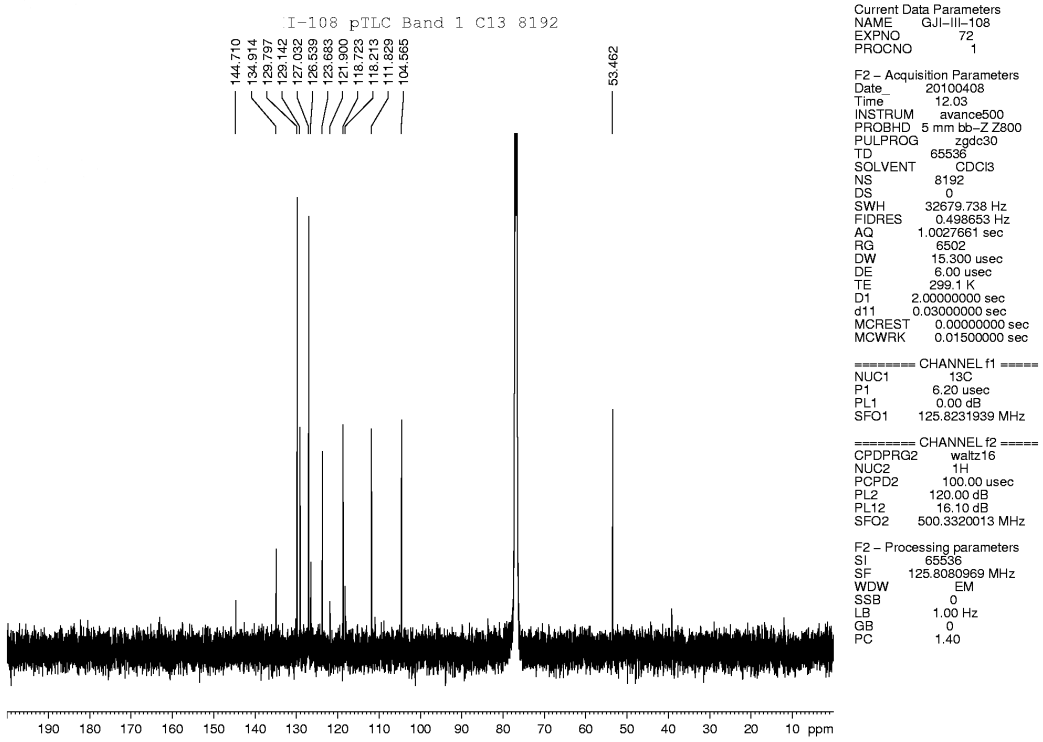



*Figure A1.258* $^{13}$C NMR (125 MHz, $CDCl_3$) of compound **2.133b**.

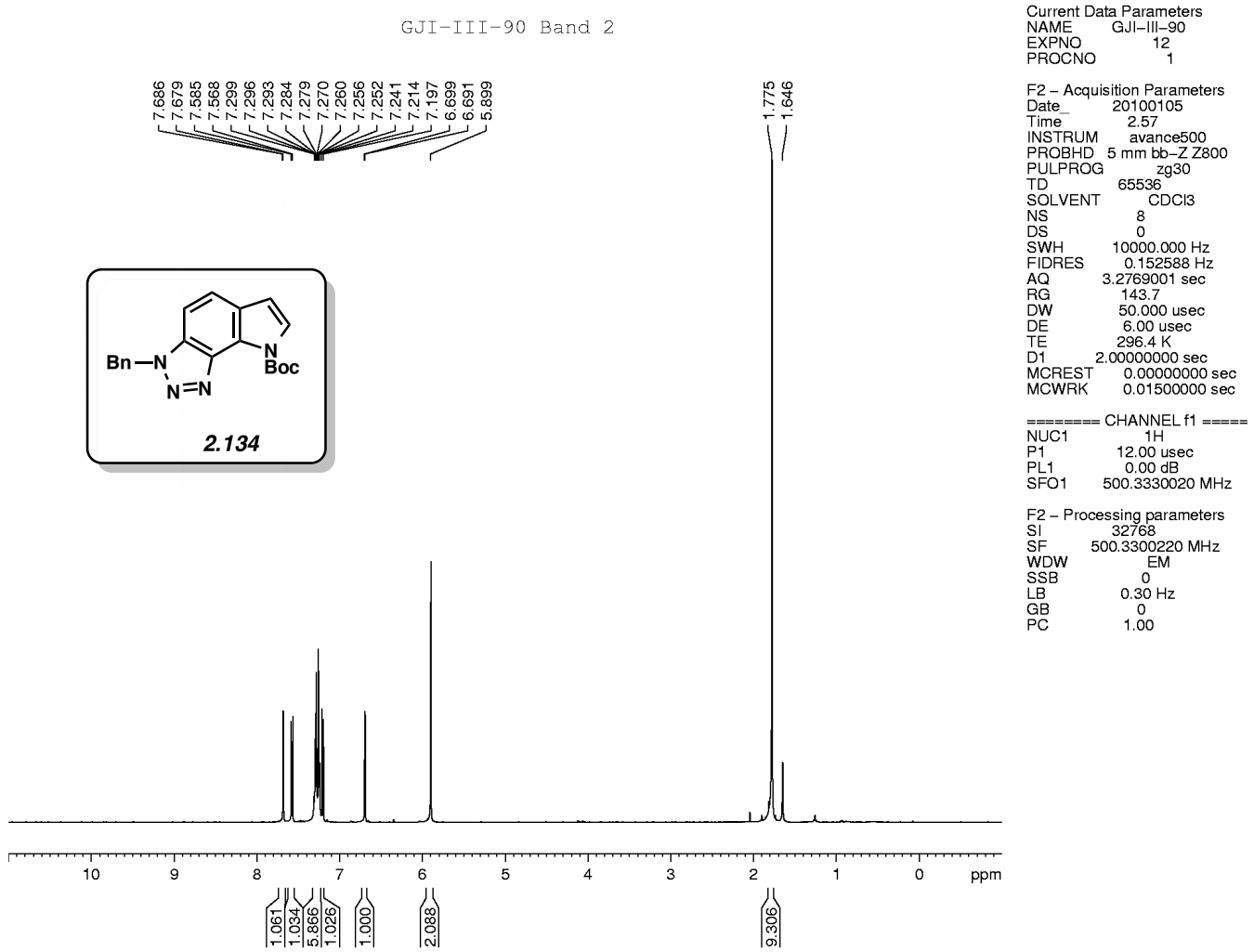



*Figure A1.259* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **2.134**.

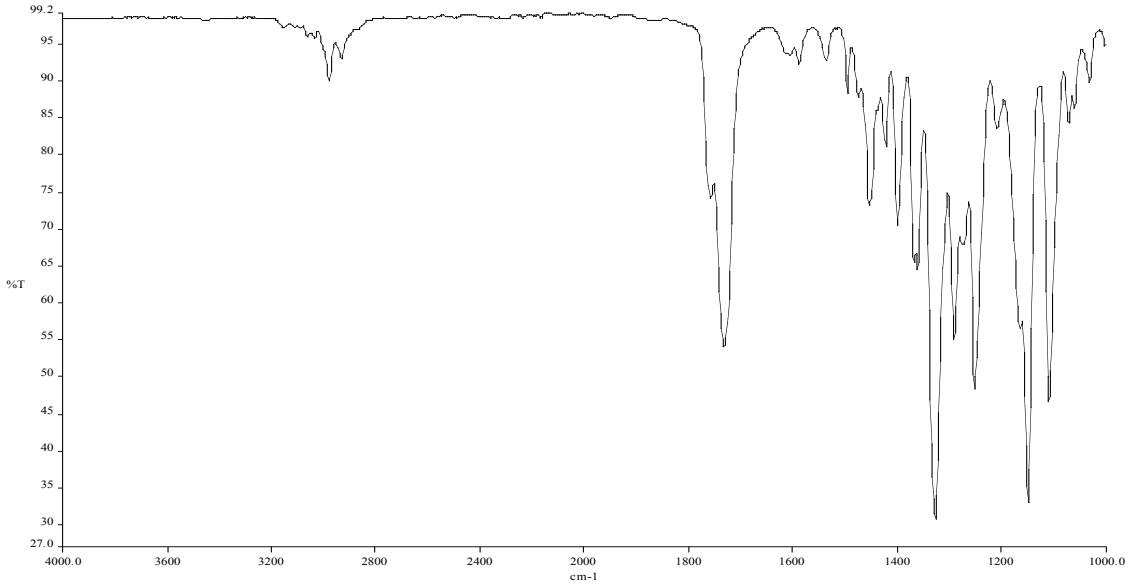



*Figure A1.260* Infrared spectrum of compound **2.134**.

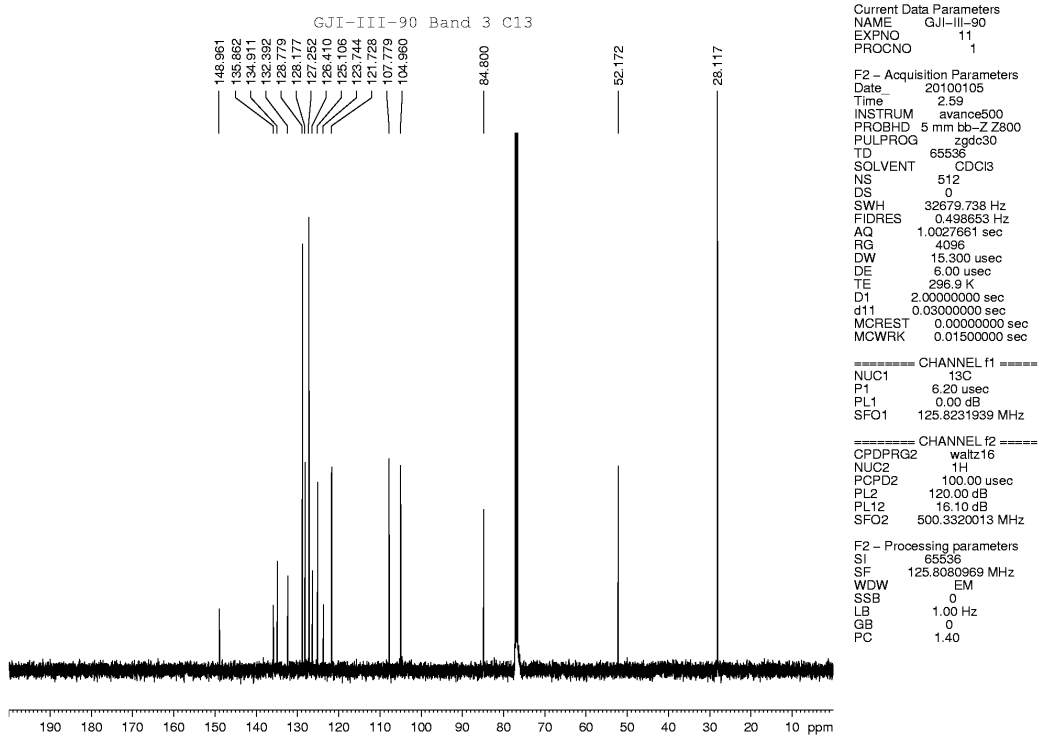



*Figure A1.261* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compound **2.134**.

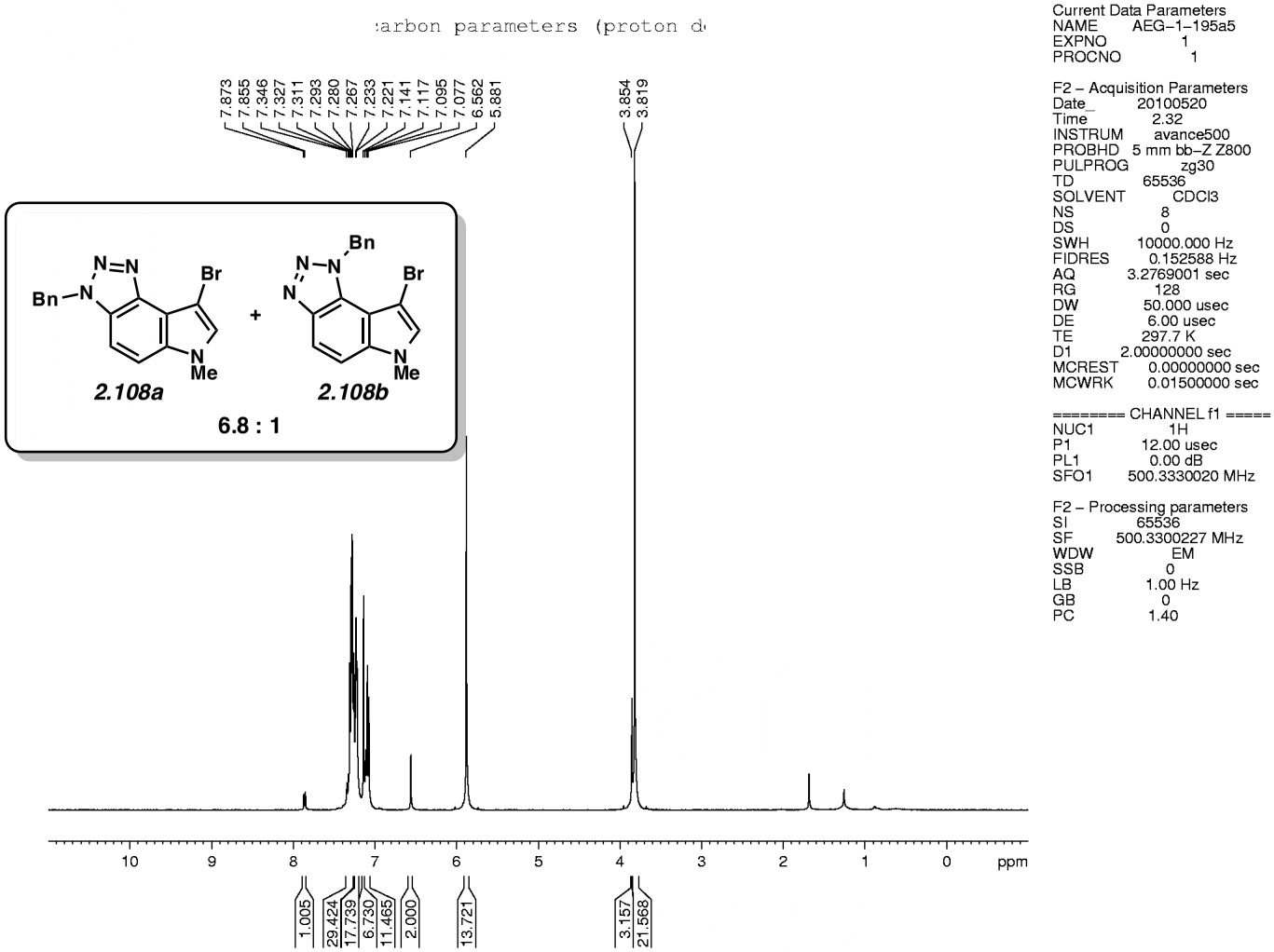



*Figure A1.262* $^{1}$H NMR (500 MHz, $CDCl_3$) of compounds **2.108a** and **2.108b**.

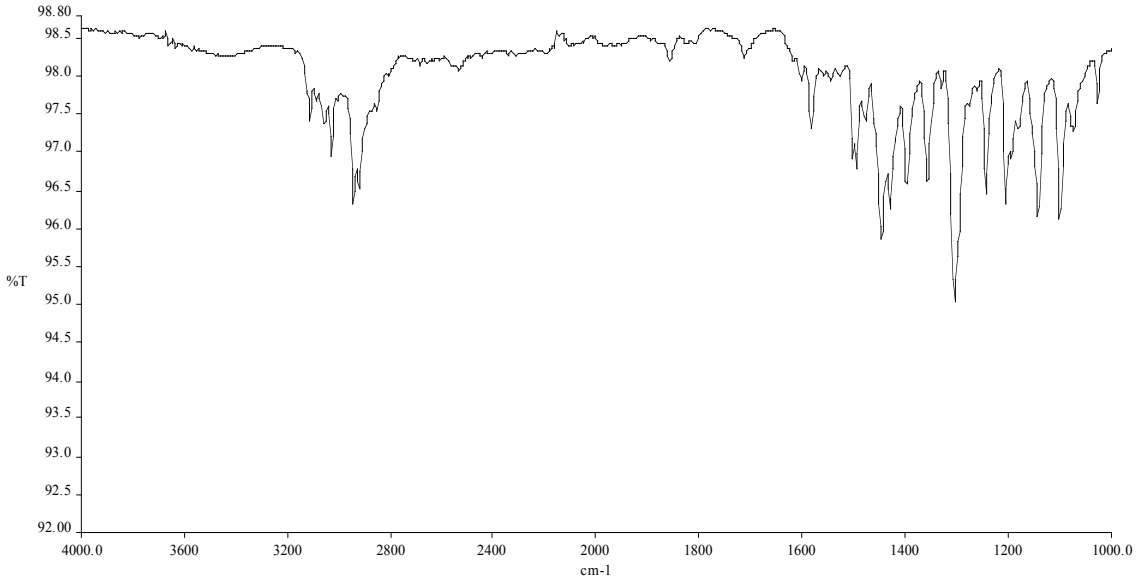



*Figure A1.263* Infrared spectrum of compounds **2.108a** and **2.108b**.

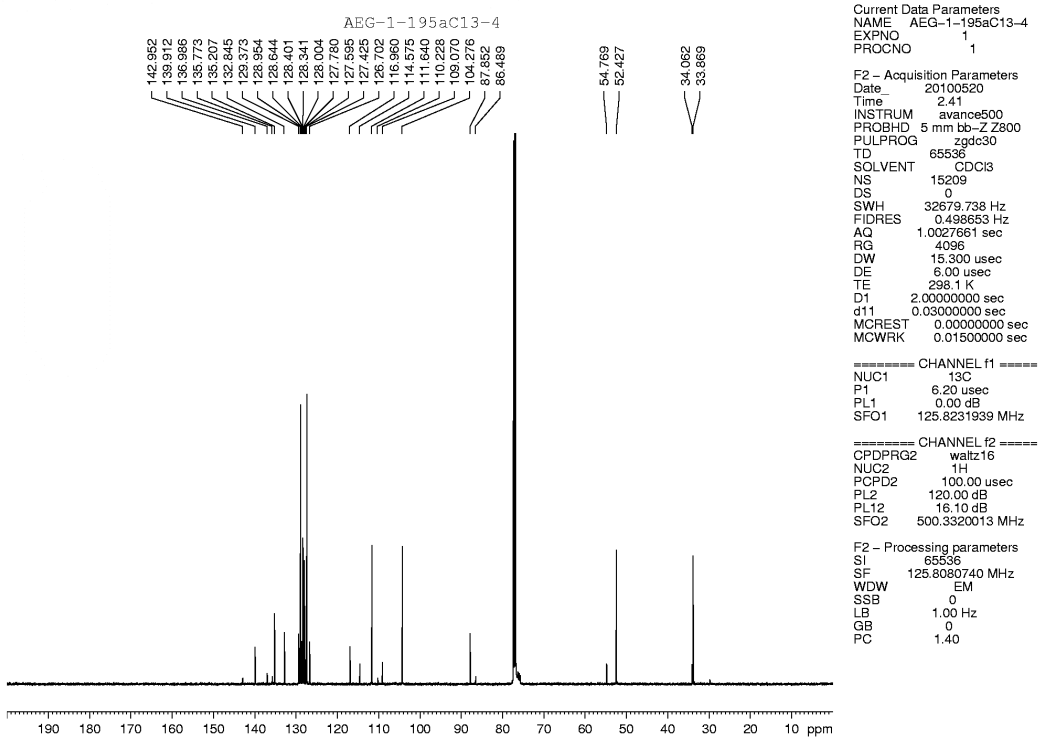



*Figure A1.264* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compounds **2.108a** and **2.108b**.

# CHAPTER THREE

## Overturning Indolyne Regioselectivities and Synthesis of Indolactam V

Bronner, S. M.; Goetz, A. E.; Garg, N. K. *J. Am. Chem. Soc.* **2011**, *133*, 3832–3835.

### 3.1 Abstract

We report the design and synthesis of an indolyne that displays a reversal in regioselectivity, in both nucleophilic addition and cycloaddition reactions, compared to typical 4,5-indolynes. Our approach utilizes simple computations to predict regioselectivity in reactions of unsymmetrical arynes. With this methodology, novel benzenoid-substituted indoles can be accessed with significant regiocontrol. Furthermore, the technology provides an unconventional tactic for the synthesis of C4-substituted indole alkaloids, as demonstrated by a synthesis of indolactam V.

### 3.2 Introduction

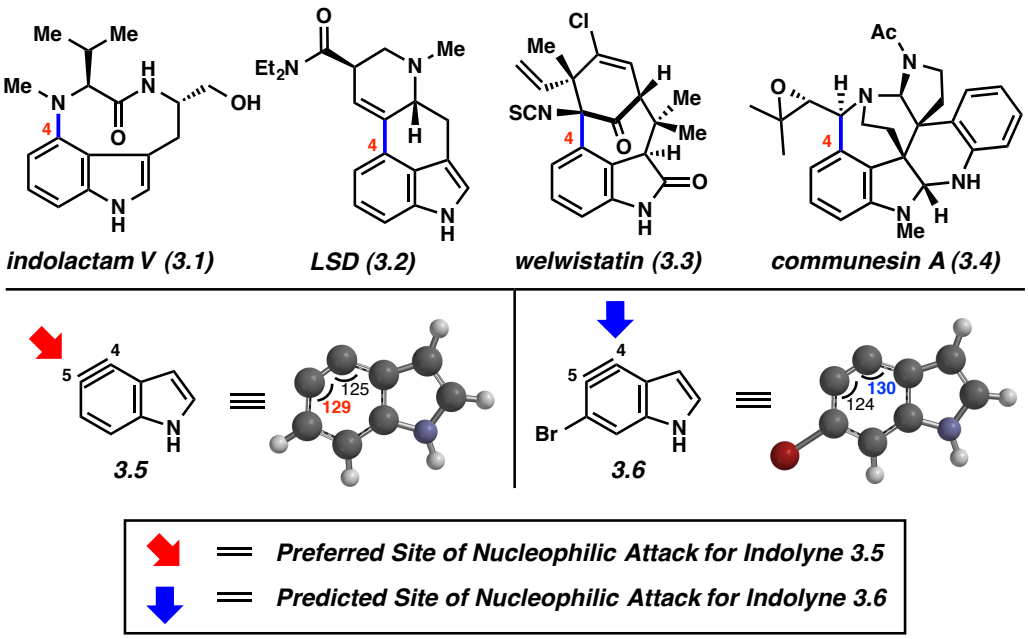
The past decades have witnessed a resurgence in the chemistry of arynes. Whereas classical methods for aryne generation are typically plagued by low yields, modern methodologies have overcome these limitations; arynes can now be employed efficiently in a variety of synthetic applications.[1] These advances have been accompanied by an interest in exploiting unsymmetrical arynes as synthetic intermediates, although such studies have been largely constrained by a lack of regiocontrol.[2]

In collaboration with Houk and coworkers, we recently proposed that distortion in unsymmetrical arynes controls regioselectivity, and simple computations may be used to make

selectivity predictions.[3] To test this distortion model and its predictive powers, we sought to control regioselectivity in nucleophilic addition to indolynes,[3,4,5] which are unsymmetrical arynes that our laboratory has examined for their synthetic versatility. A method for overturning indolyne regioselectivity has not been previously established, but would provide an invaluable tool for synthesizing both natural and unnatural derivatives of the medicinally privileged indole scaffold.[6,7]

In this communication, we demonstrate that regioselectivity in the nucleophilic addition to indolynes can be readily manipulated using the predictive capabilities of the distortion model. The studies provide access to unique benzenoid-substituted indoles and offer a strategically distinct approach to C4-substituted indole alkaloids.[8] The latter notion is exemplified by a concise synthesis of indolactam V (**3.1**, Figure 3.1).[9]

*Figure 3.1. C4-Substituted Indole Alkaloids and 4,5-Indolyne Geometries*

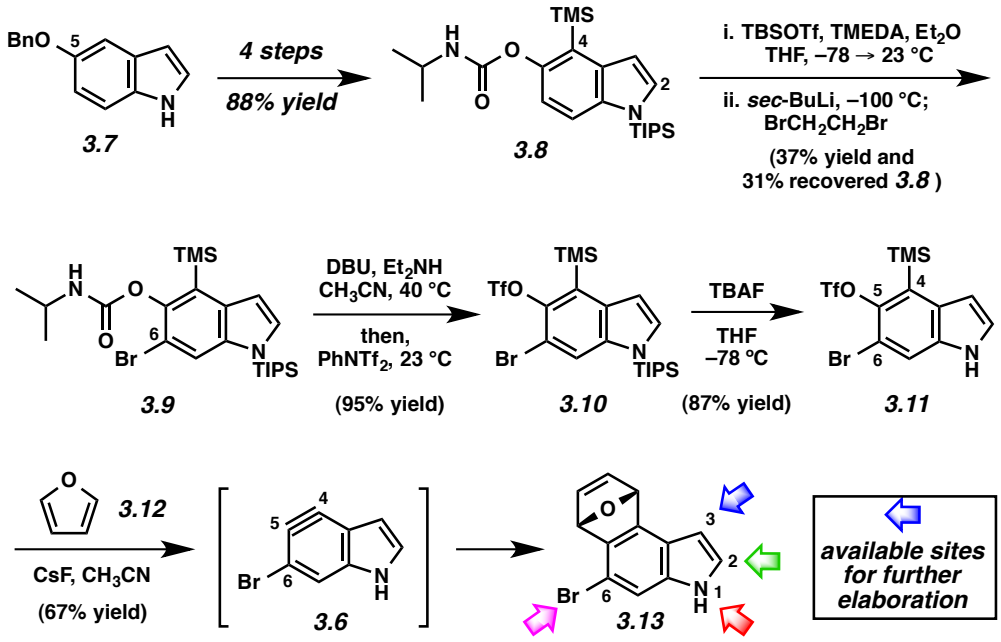


### 3.3 Design and Synthesis of a C6-Bromo-4,5-Indolyne Precursor

As highlighted in Figure 3.1, we focused our efforts on 4,5-indolynes, which could potentially be used to access 4-substituted indole derivatives, such as **3.1**–**3.4**.[8] Whereas 4,5-indolyne **3.5** exhibits a preference for nucleophilic attack at C5,[3b] we hypothesized that brominated derivative **3.6** may be prone to undergo attack at C4.[10,11] Although the relative influence of the bromide substituent and ring fusion on aryne distortion were not obvious,[12] simple calculations were used to validate our hypothesis. Specifically, geometry optimization of bromoindolyne **3.6** showed that C4 possesses a larger internal angle compared to C5 (i.e., $\theta_4$ = 130° and $\theta_5$ = 124°).[13] Following our distortion model,[3] the flatter, more electropositive carbon (C4) was predicted to be the preferred site of attack by nucleophiles.[14]

We envisioned accessing bromoindolyne **3.6** from a silyltriflate precursor. Although halobenzynes have not previously been generated by the Kobayashi method,[15] we were able to synthesize the targeted silyltriflate **3.11** using the route shown in Scheme 3.1. Commercially available 5-benzyloxyindole (**3.7**) was elaborated to silylcarbamate **3.8** using our previously reported, high-yielding sequence.[3b] Subsequent C6 bromination was achieved using the general lithiation/quenching protocol developed by Snieckus and Hoppe to afford intermediate **3.9**.[16,17] Installation of the triflate (**3.9→3.10**), followed by removal of the *N*-TIPS group, furnished the desired indolyne precursor **3.11**. The sequence is robust and can be used to prepare gram quantities of **3.11**. To validate that indolyne **3.6** would be accessible, silyltriflate **3.11** was treated with CsF in the presence of furan to generate oxabicycle **3.13**. Of note, compound **3.13** possesses sites for further functionalization on both the pyrrolo[7,18] and benzenoid ring.[19]

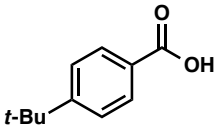
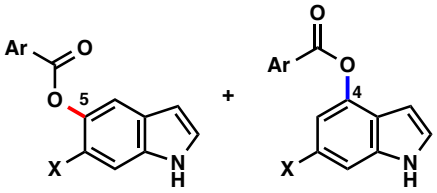
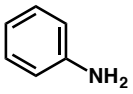
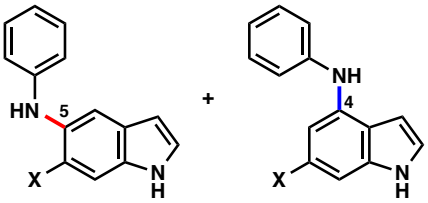
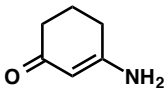
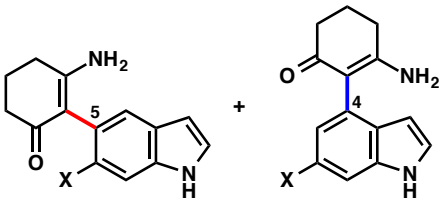
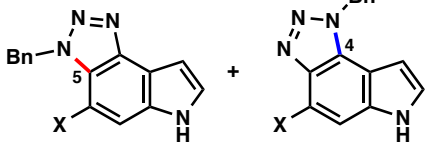
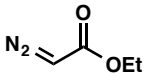
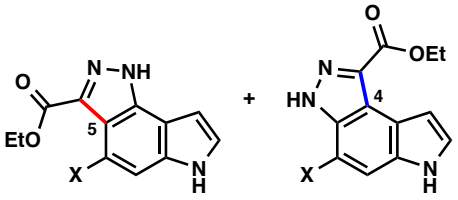
*Scheme 3.1. Synthesis of 6-Bromo-4,5-Indolyne* ***3.6***




### 3.4 Regioselectivity Studies of the 3-Bromo-4,5-Indolyne

With access to bromoindolyne **3.6** and parent indolyne **3.5**,[3b] each from a silyltriflate precursor, a comparative regioselectivity study was carried out with a range of trapping agents (Table 3.1). In each case, the indolyne precursors were treated with CsF in the presence of the appropriate trapping agent. When 4-*t*-Bu-benzoic acid was used to trap indolyne **3.5**,[20] the reaction occurred with significant regioselectivity favoring attack at C5 (entry 1). In contrast, the corresponding reaction of bromoindolyne **3.6** displayed a preference for attack at C4 (regioselectivity = 1:13 for attack at C5:C4). Similar trends were observed in reactions involving aniline[20] (entries 3 and 4) and an enamine derivative[21] (entries 5 and 6). In the latter case, selectivity was 1:20 favoring attack at C4 on indolyne **3.6**. Cycloadditions were also examined and similar reversals in regioselectivity were observed. For example, cycloaddition of indolyne **3.5** with benzyl azide[22] gave a mixture of products, favoring attack at C5 over C4 in a 2:1 ratio

*Table 3.1. Influence of a C6-Bromide on 4,5-Indolyne Regioselectivity*[a]

| entry | trapping agent | products | ratio (yield[b]) |
|---|---|---|---|
| 1 |  |  | ***X = H*** ***6:1*** **(73% yield)** |
| 2 | | | ***X = Br*** ***1:13*** **(58% yield)** |
| 3 |  |  | ***X = H*** ***6:1*** **(93% yield)** |
| 4 | | | ***X = Br*** ***1:14*** **(70% yield)** |
| 5 |  |  | ***X = H*** ***8:1*** **(64% yield)** |
| 6 | | | ***X = Br*** ***1:20*** **(68% yield)** |
| 7 |  |  | ***X = H*** ***2:1*** **(75% yield)** |
| 8 | | | ***X = Br*** ***1:4*** **(72% yield)** |
| 9 |  |  | ***X = H*** ***2:1*** **(78% yield)** |
| 10 | | | ***X = Br*** ***1:4*** **(65% yield)** |

[a] See section 3.7 for details. [b] Isolated yields.

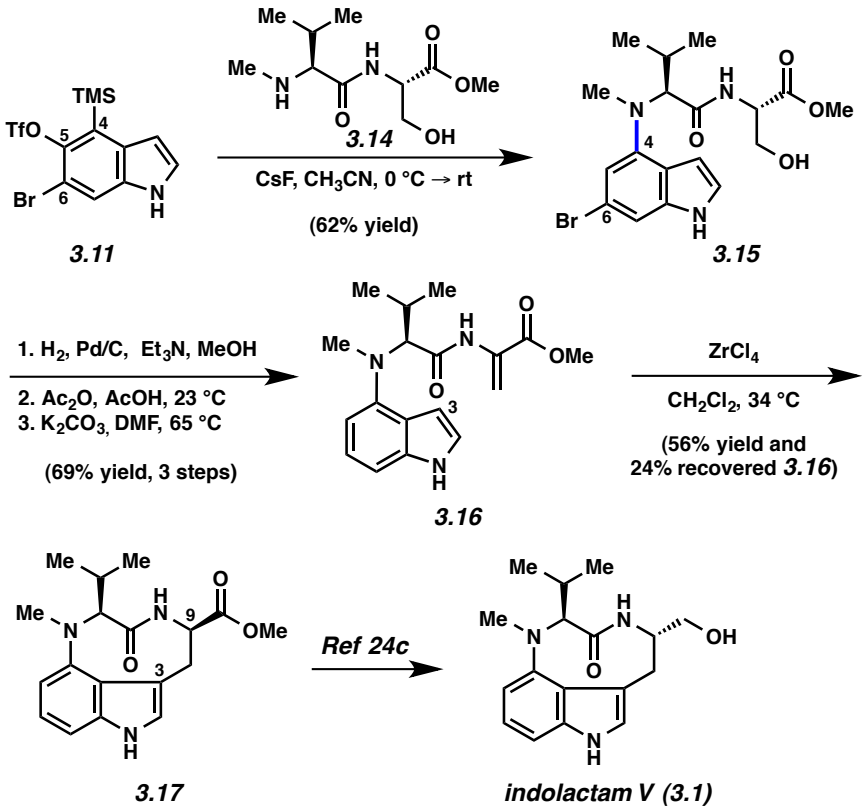
(entry 7). However, the corresponding reaction with indolyne **3.6** led to a 1:4 mixture of products favoring attack at C4 (entry 8). Analogous results were obtained in reactions with diazoesters[2a,23] to furnish unique indolylpyrazoles (entries 9 and 10). These results clearly indicate that bromoindolyne **3.6** displays a reversal in regioselectivity compared to its non-brominated

counterpart **3.5** and validate the distortion model for predicting regioselectivities in additions to unsymmetrical arynes.

### 3.5 Synthesis of Indolactam V

To probe the utility of our findings in a complex setting, we undertook a total synthesis of indolactam V (**3.1**), one of many biologically active C4-substituted indoles.[8,9] In nearly all previous syntheses of **3.1**,[24] the nine-membered ring is fashioned by late-stage amide bond formation. We envisioned a strategically distinct approach to **3.1**, which involved initial C4 functionalization using bromoindolyne **3.6**, followed by ring closure at C3.[25] As shown in Scheme 3.2, treatment of silyltriflate **3.11** with peptide **3.14** in the presence of CsF furnished C4-aminated product **3.15** in 62% yield, even though **3.14** possesses multiple nucleophilic sites. As expected based on our distortion model and experimental studies (see Table 3.1), the transformation proceeded with high regioselectivity.[26] Subsequent debromination, followed by dehydration,[27] provided unsaturated ester **3.16** without event. We next examined the critical cyclization at C3. After extensive experimentation, it was found that exposure of **3.16** to $ZrCl_4$ in $CH_2Cl_2$ facilitated the desired annulation to give tricycle **3.17**,[28] thus completing a formal synthesis of **3.1**.[24c,29] Interestingly, the stereochemical configuration at C9 of **3.17** was set with complete diastereoselectivity, albeit in the undesired sense. Nonetheless, C9 epimerization and reduction using Nakatsuka's protocol[24c] furnished indolactam V (**3.1**). This is the first total synthesis in which an indolyne has been exploited for its electrophilic character.[30] We expect that our approach to **3.1**, using an umpolung of typical indole reactivity, will be suitable for the synthesis of other indole alkaloids.

*Scheme 3.2. Completion of Indolactam V*




## 3.6 Conclusion

In summary, we have designed and synthesized an indolyne (i.e., **3.6**) that displays a reversal in regioselectivity, in both nucleophilic addition and cycloaddition reactions, compared to the parent 4,5-indolyne **3.5**. Our approach validates the aryne distortion model,[3] which in turn, utilizes simple computations[13] to predict regioselectivity in reactions of unsymmetrical arynes. With this methodology, novel benzenoid-substituted indoles can be accessed with significant regiocontrol. Moreover, the technology provides an unconventional tactic for the synthesis of C4-substituted indole alkaloids, as demonstrated by our synthesis of indolactam V (**3.1**). Further studies aimed at probing the aryne distortion model in complex molecule synthesis are currently underway in our laboratory.

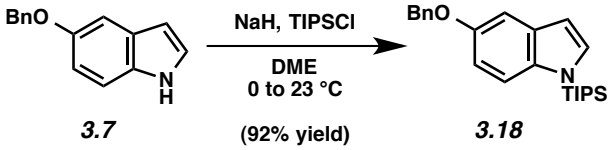
## 3.7 Experimental Section

### 3.7.1 Materials and Methods

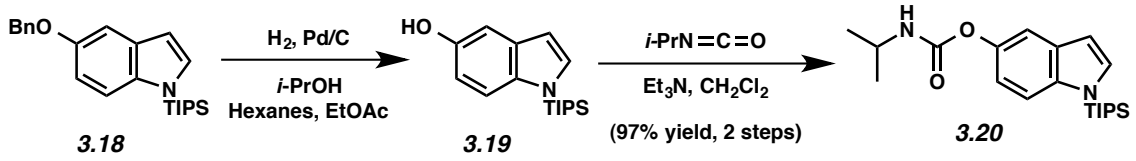
Unless stated otherwise, reactions were conducted in flame-dried glassware under an atmosphere of nitrogen using anhydrous solvents (either freshly distilled or passed through activated alumina columns). All commercially obtained reagents were used as received unless otherwise specified. Cesium fluoride (CsF) was obtained from Strem Chemicals. 5-Benzyloxyindole was obtained from Combi-Blocks, Inc. Evonik E4 50% wetted, 10% palladium on carbon (Pd/C) was purchased from Strem Chemicals. The following reagents were distilled prior to use: chlorotrimethylsilane (TMSCl), *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf), and tetramethylethylenediamine (TMEDA); 1,2-dibromoethane was passed over basic Brockman Grade I 58 Å activated alumina and then stirred over 4 Å molecular sieves for 7 h before distillation. Diethylamine ($Et_2NH$) was stirred over KOH for 1 h and then passed over basic Brockman Grade I 58 Å activated alumina prior to use. DBU was stirred over 4 Å molecular sieves for 3 h and then passed over basic Brockman Grade I 58 Å activated alumina. Aniline was passed over neutral Brockman Grade I 58 Å activated alumina prior to use. DMSO, *n*-pentane, and furan were dried over $MgSO_4$. Reaction temperatures were controlled using an IKAmag temperature modulator, and unless stated otherwise, reactions were performed at room temperature (rt, approximately 23 °C). Thin-layer chromatography (TLC) was conducted with EMD gel 60 F254 pre-coated plates (0.25 mm) and visualized using a combination of UV, anisaldehyde, iodine, vanillin, ninhydrin, and potassium permanganate staining. Silicycle Siliaflash P60 (particle size 0.040–0.063 mm) was used for flash column chromatography. $^1$H NMR and 2D-NOESY spectra were recorded on Bruker spectrometers (at 300 MHz or 500 MHz) and are reported relative to deuterated solvent signals. Data for $^1$H NMR spectra are

reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz) and integration. $^{13}C$ NMR spectra were recorded on Bruker Spectrometers (at 75 or 125 MHz). Data for $^{13}C$ NMR spectra are reported in terms of chemical shift, and when necessary, multiplicity, coupling constant (Hz) and carbon type. IR spectra were recorded on a Perkin-Elmer 100 spectrometer and are reported in terms of frequency of absorption ($cm^{-1}$). Optical rotations were measured with a Rudolf Autopol IV Automatic Polarimeter. High resolution mass spectra were obtained from the UC Irvine Mass Spectrometry Facility.

### 3.7.2 Preparative Procedures

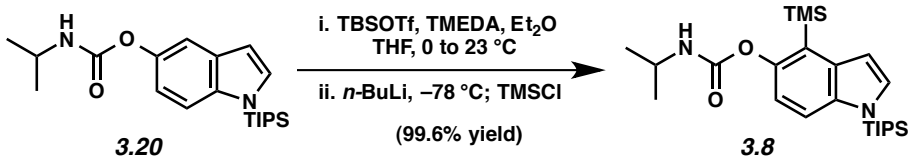



***N*-TIPS benzyloxyindole 3.18.** To a flask containing 60% NaH (0.700 g, 17.5 mmol, 1.3 equiv) at 0 °C was added a solution of 5-benzyloxyindole (**3.7**) (3.00 g, 13.5 mmol) in 1,2-dimethoxyethane (40 mL). The resulting solution was stirred at 0 °C for 20 min, then TIPSCl (4.34 mL, 20.3 mmol, 1.5 equiv) was added dropwise over 5 min. The resulting mixture was removed from the bath and allowed to warm to 23 °C. After stirring for an additional 90 min, the reaction was quenched with $H_2O$ (2 mL). The biphasic mixture was concentrated under reduced pressure, then further diluted with $Et_2O$ (50 mL) and $H_2O$ (10 mL). The layers were separated, and then the aqueous layer was extracted with $Et_2O$ (2 × 50 mL). The combined organic layers were dried over $MgSO_4$. Evaporation of the solvent under reduced pressure afforded the crude product, which was further purified by flash chromatography (3:1 Hexanes:$CH_2Cl_2$) to afford **3.18** (4.72 g, 92% yield) as a white solid. Spectral data match those reported in a previous publication and in Chapter 2 of this dissertation.[3a]



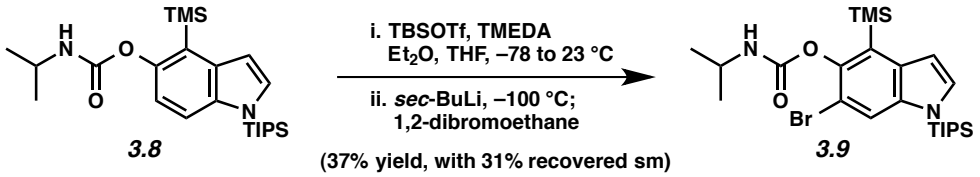

***N*-TIPS carbamate 3.20.** Carbamate **3.20** was prepared following the general procedure described by Igarashi.[31] To a solution of *N*-TIPS benzyloxyindole **3.18** (4.72 g, 12.4 mmol) in 1:1:1 *i*-PrOH:Hexanes:EtOAc (108 mL) was added 5% Pd/C (0.67 g, 0.32 mmol, 2.6 mol% Pd). The mixture was placed under an atmosphere of hydrogen (double-balloon), stirred for 2.5 h at 23 °C, and then filtered over celite (EtOAc eluent). Evaporation of the solvent under reduced pressure afforded crude **3.19** as a pink solid, which was used in the subsequent step without further purification.

Crude **3.19** was dissolved in $CH_2Cl_2$ (60.0 mL), and $Et_3N$ (0.518 mL, 3.72 mmol, 0.3 equiv), followed by *i*-PrNCO (3.64 mL, 37.2 mmol, 3 equiv), was added. The solution was stirred at 23 °C for 24 h, then concentrated to dryness under reduced pressure. Purification by flash chromatography (2:1 Hexanes:$Et_2O$) provided *N*-TIPS carbamate **3.20** (4.48 g, 97% yield, 2 steps). Spectral data match those reported in a previous publication and in Chapter 2 of this dissertation.[3a]



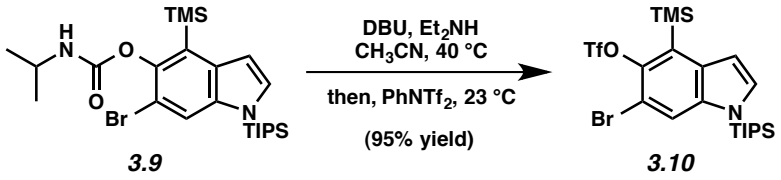

***N*-TIPS silylcarbamate 3.8.** Silyl carbamate **3.8** was prepared following the general procedure described by Hoppe and Snieckus for *o*-lithiation of isopropyl carbamates, with minor modifications.[32,16a] To a solution of *N*-TIPS carbamate **3.20** (4.48 g, 11.98 mmol) and TMEDA (2.51 mL, 16.8 mmol, 1.4 equiv) in 3:1 $Et_2O$:THF (120 mL) at 0 °C was added a solution of

TBSOTf in *n*-pentane (1.30 M, 17.3 mL, 14.4 mmol, 1.2 equiv). After stirring for 5 min, the white suspension was allowed to warm to 23 °C over 30 min. TMEDA (6.28 mL, 41.9 mmol, 3.5 equiv) was added, and the mixture was cooled to –78 °C. A solution of *n*-BuLi in hexanes (1.43 M, 29.3 mL, 41.9 mmol, 3.5 equiv) was added dropwise over 55 min. The mixture was stirred at –78 °C for 3 h, then neat TMSCl (10.6 mL, 83.9 mmol, 7 equiv) was added dropwise over 1 h. The resulting mixture was stirred at –78 °C for 1 h, quenched with 1 M $NaHSO_4$ (50 mL), and allowed to warm to 23 °C over 45 min with vigorous stirring. The biphasic mixture was further diluted with $Et_2O$ (50 mL), the layers were separated, and then the aqueous layer was extracted with $Et_2O$ (2 × 50 mL). The combined organic layers were dried over $MgSO_4$. Evaporation of the solvent under reduced pressure afforded the crude product, which was further purified by flash chromatography (2:1 Hexanes:$Et_2O$) to afford **3.8** (5.33 g, 99.6% yield) as a white solid. Spectral data match those reported in a previous publication and in Chapter 2 of this dissertation.[3a]




**6-Bromo silylcarbamate 3.9.** 6-Bromo silylcarbamate **3.9** was prepared following the general procedure described by Snieckus for *o*-lithiation, with modifications.[33] To a solution of silylcarbamate **3.8** (2.19 g, 4.90 mmol) in 3:1 $Et_2O$:THF (69.6 mL) at –78 °C was added TMEDA (1.02 mL, 6.86 mmol, 1.4 equiv), followed by a solution of TBSOTf in *n*-pentane (1.30 M, 3.91 mL, 5.90 mmol, 1.2 equiv). After stirring for 5 min, the white suspension was allowed to warm to 23 °C over 28 min, by which time TMEDA·TfOH had formed as an oil on the bottom of the flask. The mixture was placed in a hexanes and liquid nitrogen bath at –100 °C and TMEDA

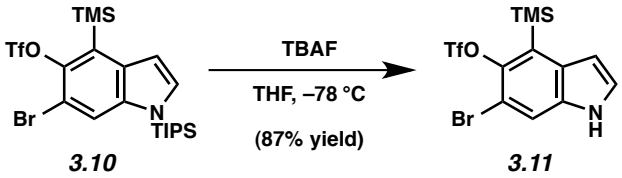
(2.56 mL, 17.2 mmol, 3.5 equiv) was added. A solution of *sec*-BuLi in cyclohexane [(1.18 M, 30.0 mL) + (1.04 M, 8.40 mL); 44.1 mmol, 9 equiv] was added dropwise over 1.2 h. The mixture was stirred at –100 °C for 4.5 h, then neat 1,2-dibromoethane[34] (5.09 mL, 58.8 mmol, 12.0 equiv) was added dropwise over 10 min. The resulting mixture was stirred at –100 °C for 3 h, quenched with 0.5 M aqueous $NaHSO_4$ (50 mL), and allowed to warm to 23 °C over 40 min with vigorous stirring. The organic layer was separated, and then the organic layer was washed successively with 1 M aqueous $NaHSO_4$ (50 mL) and brine (50 mL), then dried over $MgSO_4$. Evaporation under reduced pressure afforded the crude product, which was purified by flash chromatography (3:3:1 Hexanes:Benzene:DCE→99:1 Benzene:EtOAc) to afford silylcarbamate **3.8** (0.688 g, 31% yield) and 6-bromo silylcarbamate **3.9** (0.958 g, 37% yield). Silylcarbamate **3.9**: $R_f$ 0.45 (3:1:1 Hexanes:$CH_2Cl_2$:$Et_2O$); $^1$H NMR (500 MHz, $CDCl_3$): δ 7.71 (s, 1H), 7.26 (d, $J$ = 3.5, 1H), 6.75 (d, $J$ = 3.0, 1H), 4.91 (d, $J$ = 8.5, 1H), 3.97–3.93 (m, 1H), 1.66 (septet, $J$ = 7.5, 3H), 1.27 (d, $J$ = 7.0, 6H), 1.15 (d, $J$ = 8.0, 18H), 0.43 (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 154.0, 145.8, 138.9, 135.7, 132.7, 124.9, 119.1, 111.4, 106.8, 43.8, 23.4, 18.5, 13.1, 1.4; IR (film): 3327, 2951, 2870, 1718 cm$^{-1}$; HRMS-ESI (*m/z*) [M + Na]$^+$ calcd for $C_{24}H_{41}BrN_2O_2Si_2Na$, 547.1788; found, 547.1791.



*3.9* *3.10*

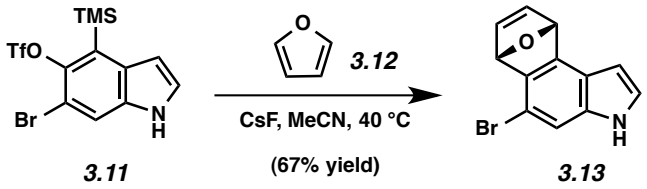
***N*-TIPS 6-bromo silyltriflate 3.10.** To a solution of 6-bromo silylcarbamate **3.9** (0.636 g, 1.21 mmol) in MeCN (24 mL) was added DBU (0.427 mL, 3.03 mmol, 2.5 equiv) and $Et_2NH$ (187 μL, 1.82 mmol, 1.5 equiv). The resulting mixture was placed in a heating bath maintained at 40

°C for 15 min, then allowed to cool to 23 °C. Next, a solution of $PhNTf_2$ (0.650 g, 1.82 mmol, 1.5 equiv) in MeCN (2.1 mL) was added. After stirring for 25 min, the reaction mixture was passed over a plug of silica gel (EtOAc eluent). Evaporation under reduced pressure afforded the crude product, which was further purified by flash chromatography (30:1 Hexanes:$Et_2O$) to provide *N*-TIPS 6-bromo silyltriflate **3.10** (0.654 g, 95% yield). $R_f$ 0.78 (2:1 Hexanes:$Et_2O$); $^1H$ NMR (500 MHz, $CDCl_3$): δ 7.76 (d, *J* = 0.5, 1H), 7.34 (d, *J* = 3.5, 1H), 6.77 (dd, *J* = 3.5, 0.5, 1H), 1.67 (septet, *J* = 7.5, 3H), 1.16 (d, *J* = 7.5, 18H), 0.51 (S, 9H); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 141.5, 139.6, 136.0, 133.6, 127.9, 120.2, 119.0 (q, *J* = 321, $CF_3$), 108.9, 107.8, 18.4, 13.1, 1.5; IR (film): 2952, 2871, 1210 $cm^{-1}$; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{21}H_{33}BrF_3NO_3SSi_2Na$, 594.0753; found, 594.0743.

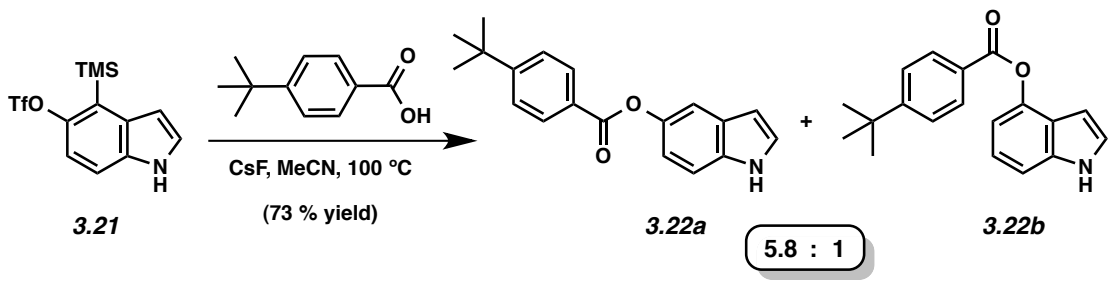



***N*-H 6-bromo silyltriflate 3.11.** To a solution of *N*-TIPS 6-bromo silyltriflate **3.10** (0.143 g, 0.250 mmol) in THF (9.4 mL) at –78 °C was added a solution of TBAF in THF (1.0 M, 250 μL, 0.250 mmol, 1 equiv) dropwise over 3 min. The solution was stirred for 15 min, then quenched with $H_2O$ (12 mL). The biphasic mixture was further diluted with EtOAc (12 mL). The layers were separated, and then the aqueous layer was extracted with EtOAc (2 × 12 mL). The combined organic layers were dried over $MgSO_4$. Evaporation under reduced pressure afforded the crude product, which was further purified by flash chromatography (2.5:1 Hexanes:$CH_2Cl_2$) to provide **3.11** (90.9 mg, 87% yield). $R_f$ 0.38 (2:1 Hexanes:$CH_2Cl_2$); $^1H$ NMR (500 MHz, $CDCl_3$): δ 8.29 (br s, 1H), 7.65 (s, 1H), 7.29–7.27 (m, 1H), 6.70–6.69 (m, 1H), 0.52 (s, 9H); $^{13}C$

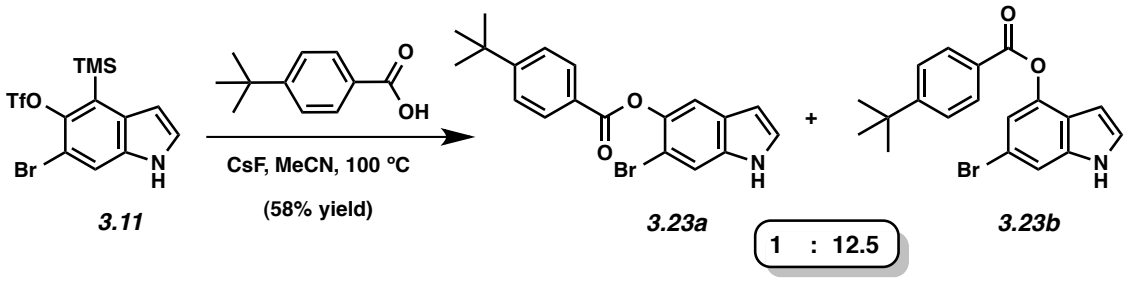
NMR (125 MHz, $CDCl_3$): δ 141.1, 134.2, 132.0, 128.4, 126.3, 118.8 (q, $J$ = 319, $CF_3$), 117.7, 109.5, 105.7, 1.6; IR (film): 3443, 2958, 1386, 1210 $cm^{-1}$; HRMS-ESI ($m/z$) $[M + H]^+$ calcd for $C_{12}H_{14}BrF_3NO_3SSi$, 415.9599; found, 415.9597.



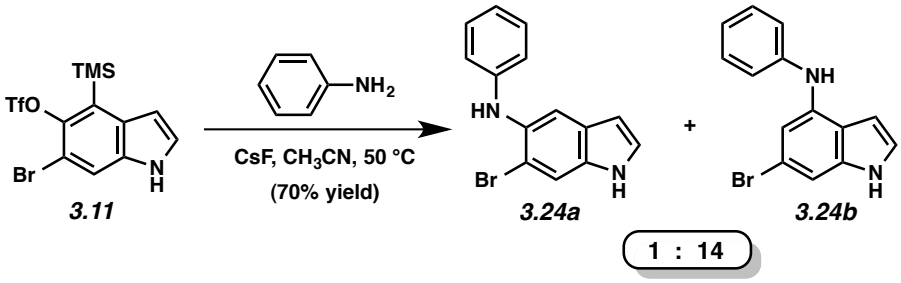

**Diels–Alder adduct 3.13.** To a solution of 6-bromosilyltriflate **3.11** (29.2 mg, 0.0704 mmol) and furan (**3.12**) (25 μL, 0.345 mmol, 5 equiv) in MeCN (0.90 mL) was added CsF (33.4 mg, 0.220 mmol, 3.1 equiv). The reaction vessel was placed in an aluminum heating block maintained at 40 °C for 2.5 h. After cooling to 23 °C, the reaction mixture was filtered over silica gel (EtOAc eluent). Evaporation under reduced pressure afforded the crude product, which was further purified by flash chromatography (Benzene eluent) to give adduct **3.13** (12.3 mg, 67% yield). $R_f$ 0.50 (2:1 Hexanes:EtOAc); $^1$H NMR (500 MHz, $C_6D_6$): δ 6.82 (dd, $J$ = 5.5, 2.0, 1H), 6.78 (d, $J$ = 1.0, 1H), 6.65 (dd, $J$ = 5.5, 2.0, 1H), 6.53 (br s, 1H), 6.42 (dd, $J$ = 3.0, 2.5, 1H), 6.18–6.17 (m, 1H), 6.00 (dd, $J$ = 1.5, 1.0, 1H), 5.81 (dd, $J$ = 1.5, 1.0, 1H); $^{13}$C NMR (125 MHz, $C_6D_6$): δ 144.35, 144.30, 142.9, 141.7, 136.4, 125.9, 122.1, 108.6, 108.4, 98.8, 83.4, 82.5; IR (film): 3412, 3298, 3010, 1035 $cm^{-1}$; HRMS-ESI ($m/z$) $[M + Na]^+$ calculated for $C_{12}H_8BrNONa$, 283.9687; found, 283.9685.




***N*-H Esters 3.22a and 3.22b.** To a stirred solution of NH-silyltriflate[3b] **3.21** (38.9 mg, 0.115 mmol) and *p-tert*-butylbenzoic acid (62.2 mg, 0.349 mmol, 3 equiv) in MeCN (5.75 mL) was added CsF (86.7 mg, 0.571 mmol, 5 equiv). The reaction vessel was placed in an aluminum heating block maintained at 100 °C for 140 min. After cooling to 23 °C, the reaction mixture was filtered over silica gel (EtOAc eluent). Evaporation under reduced pressure afforded the crude products, which were further purified by flash chromatography (6:1 Hexanes:EtOAc) to provide a mixture of *N*-H esters **3.22a** and **3.22b** (5.8:1 ratio of **3.22a**:**3.22b**, 24.6 mg, 73% yield). These compounds were characterized as a mixture. $R_f$ 0.30 (4:1 Hexanes:EtOAc); **3.22a:** $^1$H NMR (500 MHz, $CDCl_3$): δ 8.25 (br s, 1H), 8.19 (d, *J* = 8.4, 2H), 7.55 (d, *J* = 8.5, 2H), 7.46–7.44 (m, 1H), 7.36 (d, *J* = 8.9, 1H), 7.23–7.21 (m, 1H), 7.02 (dd, *J* = 8.7, 2.1, 1H), 6.56–6.54 (m, 1H), 1.39 (s, 9H); **3.22b:** $^1$H NMR (500 MHz, $CDCl_3$): δ 8.31 (br s, 1H), 8.24 (d, *J* = 8.4, 2H), 7.58–7.56 (m, 2H), 7.29 (dd, *J* = 8.2, 0.6, 1H), 7.20 (d, *J* = 7.9, 1H), 7.15–7.13 (m, 1H), 7.00–6.98 (m, 1H), 6.47–6.45 (m, 1H), 1.40 (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$, 29/30 C): δ 166.2, 165.1, 157.4, 157.2, 144.9, 144.2, 137.9, 133.8, 130.3, 130.2, 128.4, 127.4, 127.2, 125.7, 125.64, 125.56, 124.5, 122.4, 121.6, 116.5, 113.0, 112.2, 111.5, 109.2, 103.2, 99.8, 35.4, 35.3, 31.3; IR (film): 3370, 2961, 1713, 1269, 1140 $cm^{-1}$; HRMS-ESI (*m/z*) $[M + Na]^+$ calculated for $C_{19}H_{19}NO_2Na$, 316.1313; found, 316.1305.

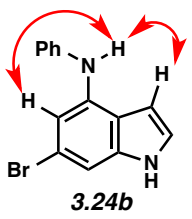


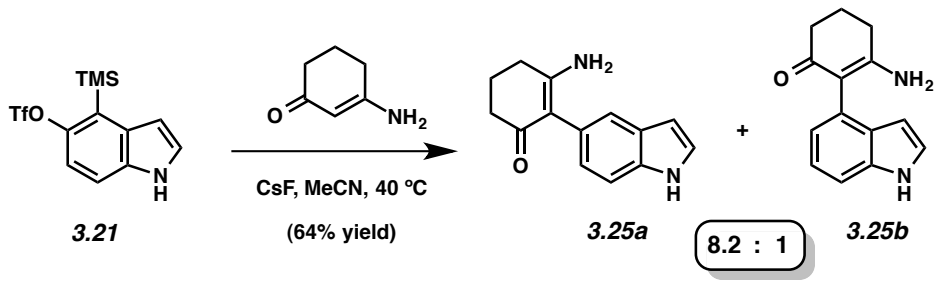

**6-Bromo esters 3.23a and 3.23b.** To a stirred solution of silyltriflate **3.11** (25.3 mg, 0.061 mmol) and *p-tert*-butylbenzoic acid (33.4 mg, 0.187 mmol, 3 equiv) in MeCN (3.1 mL) was added CsF (46.0 mg, 0.303 mmol, 5 equiv). The reaction vessel was placed in an aluminum heating block maintained at 100 °C for 25 min. After cooling to 23 °C, the reaction mixture was filtered over silica gel ($Et_2O$ eluent). Evaporation under reduced pressure afforded the crude products, which were further purified by flash chromatography (Benzene eluent) to provide a mixture of *N*-H esters **3.23a** and **3.23b** (1:12.5 ratio of **3.23a**:**3.23b**, 13.2 mg, 58% yield). An analytical sample of **3.23b** was obtained by preparative TLC (Benzene eluent). **3.23b:** $R_f$ 0.28 (Benzene); $^1$H NMR (500 MHz, $CD_3CN$): δ 9.58 (br s, 1H), 8.17–8.14 (m, 2H), 7.66–7.63 (m, 2H), 7.59 (app. t, *J* = 1.2, 1H), 7.27 (dd, *J* = 3.2, 2.5, 1H), 7.12 (d, *J* = 1.6, 1H), 6.42–6.40 (m, 1H), 1.38 (s, 9H); $^{13}$C NMR (125 MHz, $CD_3CN$): δ 165.6, 158.7, 145.1, 139.3, 130.9, 127.6, 127.3, 126.9, 122.0, 116.2, 114.2, 113.3, 99.7, 35.9, 31.3; IR (film): 3360, 2965, 1717, 1265, 1086 $cm^{-1}$; HRMS-ESI (*m/z*) $[M + Na]^+$ calculated for $C_{19}H_{18}BrNO_2Na$, 394.0419; found, 394.0421.



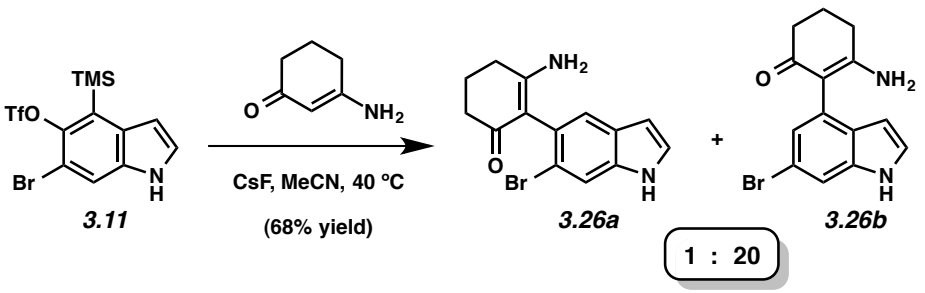

**6-Bromo aniline adducts 3.24a and 3.24b.** To a stirred solution of *N*-H 6-bromo silyltriflate **3.11** (24.5 mg, 0.0588 mmol) and aniline (26.8 μL, 0.294 mmol, 5 equiv) in MeCN (1.18 mL) was added CsF (17.9 mg, 0.118 mmol, 2 equiv). The reaction vessel was placed in an aluminum heating block maintained at 50 °C for 2 h. After cooling to 23 °C, the reaction mixture was filtered over silica gel (EtOAc eluent). Evaporation under reduced pressure afforded the crude products, including trace amounts of **3.24a**, which were further purified by flash chromatography (2:1 Hexanes:Benzene) to provide aniline adduct **3.24b** (11.9 mg, 70% yield). **3.24b:** $R_f$ 0.52 (3:1:1 Hexanes:$CH_2Cl_2$:$Et_2O$); $^1$H NMR (500 MHz, $CDCl_3$): δ 8.17 (br s, 1H), 7.35–7.31 (m, 2H), 7.18–7.16 (m, 3H), 7.13 (dd, *J* = 3.0, 2.5, 1H), 7.06 (d, *J* = 1.5, 1H), 7.01 (app. tt, *J* = 7.5, 1.0, 1H), 6.47–6.46 (m, 1H), 5.93 (br s, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 142.5, 137.5, 137.2, 129.5, 123.3, 121.9, 119.2, 118.5, 116.4, 109.2, 107.4, 99.9; IR (film): 3336, 3247, 2920, 1491 $cm^{-1}$; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{14}H_{12}BrN_2$, 287.0184; found, 287.0179.

The structure of **3.24b** was confirmed by a 2D-NOESY experiment, as the following interactions were observed:

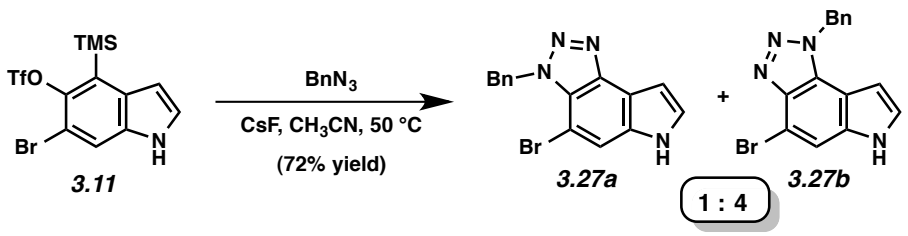





**β-Enaminoketones 3.25a and 3.25b.** To a stirred solution of NH-silyltriflate[3b] **3.21** (45.1 mg, 0.134 mmol) and 3-amino-2-cyclohexen-1-one (49.1 mg, 0.442 mmol, 3.3 equiv) in MeCN (1.45 mL) was added CsF (61.4 mg, 0.404 mmol, 3 equiv). The reaction vessel was placed in an aluminum heating block maintained at 40 °C for 24 h. After cooling to 23 °C, the reaction mixture was filtered over silica gel (19:1 $CH_2Cl_2$:MeOH eluent). Evaporation under reduced pressure afforded the crude products, which were further purified by flash chromatography (19:1 EtOAc:MeOH) to provide a mixture of β-enaminoketones **3.25a** and **3.25b** (8.2:1 ratio of **3.25a**:**3.25b**, 19.3 mg, 64% yield). An analytical sample of **3.25a** was obtained by preparative TLC (10:10:1 Benzene:EtOAc:MeOH). **3.25a:** $R_f$ 0.20 (19:1 $CH_2Cl_2$:MeOH); $^1$H NMR (500 MHz, $CD_3OD$, 11/14 H): δ 7.41 (d, *J* = 8.5, 1H), 7.32 (d, *J* = 1.0, 1H), 7.21 (d, *J* = 3.0, 1H), 6.85 (dd, *J* = 8.0, 1.5, 1H), 6.42 (dd, *J* = 3.0, 1.0, 1H), 2.61 (t, *J* = 6.5, 2H), 2.43 (t, *J* = 6.5, 2H), 2.05 (app. quintet, *J* = 6.5, 2H); $^{13}$C NMR (125 MHz, $CD_3OD$): δ 195.5, 166.2, 135.3, 128.5, 124.4, 124.2, 123.9, 122.1, 112.4, 111.1, 100.8, 35.9, 28.3, 21.1; IR (film): 3304, 3172, 2943, 1528, 1402 $cm^{-1}$; HRMS-ESI (*m*/*z*) $[M + H]^+$ calculated for $C_{14}H_{15}N_2O$, 227.1184; found, 227.1175.

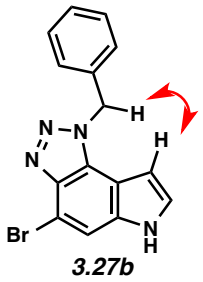



**6-Bromo β-enaminoketones 3.26a and 3.26b.** To a stirred solution of silyltriflate **3.11** (22.0 mg, 0.053 mmol) and 3-amino-2-cyclohexen-1-one (17.8 mg, 0.160 mmol, 3 equiv) in MeCN (1.0 mL) was added CsF (25.2 mg, 0.166 mmol, 3 equiv). The reaction vessel was placed in an aluminum heating block maintained at 40 °C for 5 h. After cooling to 23 °C, the reaction mixture was diluted with 1 mL brine followed by 2 mL $Et_2O$. The layers were separated, and the aqueous layer was extracted with $Et_2O$ (3 x 2 mL) and the combined organic layers were dried over $Na_2SO_4$. Evaporation of the solvent under reduced pressure afforded the crude product, which was purified by flash chromatography (50:1 EtOAc:MeOH) to provide a mixture of β-enaminoketones **3.26a** and **3.26b** (1:20 ratio of **3.26a**:**3.26b**, 10.9 mg, 68% yield). An analytical sample of **3.25b** was obtained by flash chromatography (95:5 $CH_2Cl_2$:MeOH). **3.26b:** $R_f$ 0.14 (95:5 $CH_2Cl_2$:MeOH): $^1$H NMR (500 MHz, $CD_3OD$, 10/13 H): δ 7.50 (dd, *J* = 1.5, 0.9, 2H), 7.19 (d, *J* = 3.2, 1H), 6.93, (d, *J* = 1.7, 1H), 6.17 (dd, *J* = 3.2, 0.9, 1H), 2.67 (app. q *J* = 6.5, 2H), 2.48 (dt, *J* = 6.4, 3.5, 2H), 2.10 (app. p, *J* = 6.5, 2H); $^{13}$C NMR (125 MHz, $CD_3OD$): δ 196.6, 167.5, 138.8, 129.3, 128.4, 126.2, 125.9, 115.7, 114.1, 110.0, 102.3, 37.4, 30.0, 22.7; IR (film): 3314, 3164, 2941, 1532, 1409 cm$^{-1}$; HRMS-ESI (*m/z*) $[M + H]^+$ calculated for $C_{14}H_{14}BrN_2O$, 305.0290; found, 305.0285.

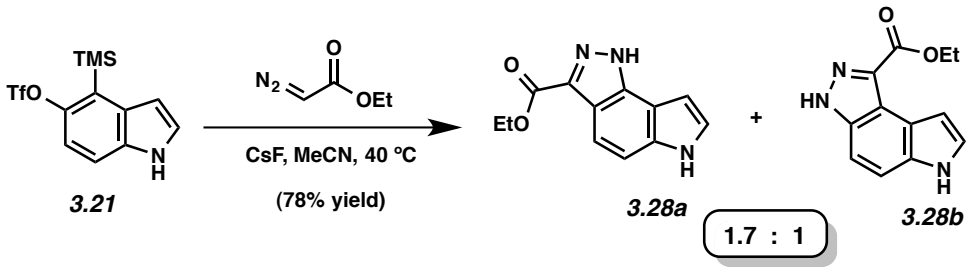



**6-Bromo triazoles 3.27a and 3.27b.** To a stirred solution of *N*-H 6-bromo silyltriflate **3.11** (17.7 mg, 0.0425 mmol) and benzyl azide[35] (37.7 μL, 0.287 mmol, 6.8 equiv) in MeCN (0.85 mL) was added CsF (12.9 mg, 0.0850 mmol, 2 equiv). The reaction vessel was placed in an aluminum heating block maintained at 50 °C for 90 min. After cooling to 23 °C, the reaction mixture was filtered over silica gel (EtOAc eluent). Evaporation under reduced pressure afforded the crude products, which were further purified by flash chromatography (19:1 Benzene:EtOAc) to provide triazoles **3.27a** and **3.27b** (1:4 ratio of **3.27a**:**3.27b**, 10.0 mg, 72% yield) as a white solid. These compounds were characterized as a mixture. $R_f$ 0.17 (19:1 Benzene:EtOAc); **3.27a**: $^1$H NMR (500 MHz, $d_6$-DMSO): δ 11.76 (br s, 1H), 7.85 (s, 1H), 7.55 (app. t, $J$ = 3.0, 1H), 7.33–7.25 (s, 3H), 7.09 (d, $J$ = 7.0, 2H), 6.94–6.93 (m, 1H), 6.23 (s, 2H); **3.27b**: $^1$H NMR (500 MHz, $d_6$-DMSO): 11.87 (br s, 1H), 7.72 (s, 1H), 7.45 (app. t, $J$ = 3.0, 1H), 7.33–7.25 (m, 5H), 6.87–6.86 (m, 1H), 6.11 (s, 2H); $^{13}$C NMR (75 MHz, $d_6$-DMSO): δ 140.5, 139.8. 137.7, 136.6, 134.9, 133.6, 129.3, 129.1, 128.4, 128.3, 128.1, 127.6, 127.0, 126.9, 126.6, 125.9, 118.6, 116.6, 114.4, 109.5, 103.9, 100.8, 100.1, 94.4, 52.43, 52.37; IR (film): 3127, 2920 cm$^{-1}$; HRMS-ESI (*m*/*z*) [M + Na]$^+$ calcd for $C_{15}H_{11}N_4Na$, 349.0065; found, 349.0055.

The structure of **3.27b** was confirmed by 2D-NOESY experiments, as the following interaction was observed:



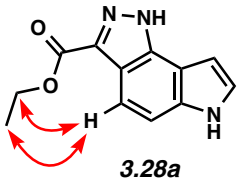

*3.27b*



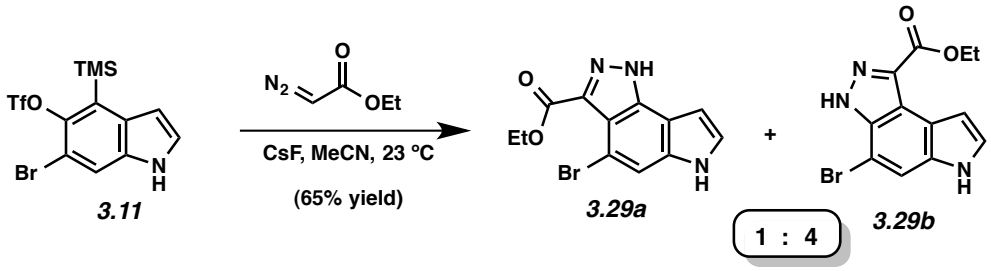

**Indolylpyrazoles 3.28a and 3.28b.** To a stirred solution of NH-silyltriflate[3b] (48.8 mg, 0.145 mmol) and ethyl diazoacetate (62 μL, 0.590 mmol, 4 equiv) in MeCN (1.8 mL) was added CsF (63.4 mg, 0.417 mmol, 3 equiv). The reaction vessel was placed in an aluminum heating block maintained at 40 ºC for 15 h. After cooling to 23 ºC, the reaction mixture was filtered over silica gel (EtOAc eluent). Evaporation of the solvent under reduced pressure afforded the crude product, which was purified by flash chromatography (3:1 $CH_2Cl_2$:$Et_2O$) to provide indolylpyrazoles **3.28a** and **3.28b** (1.7:1 ratio of **3.28a**:**3.28b**, 25.8 mg, 78% yield) as an off-white solid. An analytical sample of **3.28a** was obtained by preparative TLC (5:1 $CH_2Cl_2$:$Et_2O$). **3.28a:** $R_f$ 0.42 (3:1 $CH_2Cl_2$:$Et_2O$); $^1$H NMR (500 MHz, $CD_3CN$): δ 11.90 (br s, 1H), 9.78 (br s, 1H), 7.86 (d, *J* = 8.9, 1H), 7.45 (dd, *J* = 9.0, 0.7, 1H), 7.32 (app. t, *J* = 7.8, 1H), 6.83–6.81 (m, 1H), 4.43 (q, *J* = 7.1, 2H), 1.43 (t, *J* = 7.1, 3H); $^{13}$C NMR (125 MHz, $d_6$-DMSO, 11/12 C): δ 162.6, 135.6, 134.0, 123.7, 116.3, 113.5, 110.7, 110.2, 99.2, 60.0, 14.3; IR (film): 3302, 3104,

2980, 2913, 1705, 1377, 1279, 1246 $cm^{-1}$; HRMS-ESI (*m/z*) $[M + Na]^+$ calculated for $C_{12}H_{11}N_3O_2Na$, 252.0749; found, 252.0744.

The structure of **3.28a** was confirmed by a 2D-NOESY experiment, as the following interactions were observed:



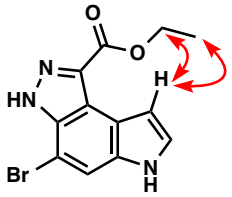

***3.28a***



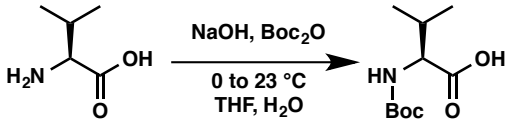

**6-Bromo indolylpyrazoles 3.29a and 3.29b.** To a stirred solution of silyltriflate **3.11** (28.5 mg, 0.068 mmol) and ethyl diazoacetate (29 μL, 0.276 mmol, 4 equiv) in MeCN (1.0 mL) was added CsF (31.1 mg, 0.205 mmol, 3 equiv). The reaction was stirred at 23 ºC for 7.75 h, and then filtered over silica gel (EtOAc eluent). Evaporation under reduced pressure afforded the crude products, which were further purified by flash chromatography (4:1 $CH_2Cl_2$:$Et_2O$) to provide a mixture of bromoindolylpyrazoles **3.29a** and **3.29b** (1:4 ratio of **3.29a**:**3.29b**, 13.7 mg, 65% yield). An analytical sample of **3.29b** was obtained by preparative TLC (4:1 $CH_2Cl_2$:$Et_2O$). **3.29b:** $R_f$ 0.21 (19:1 $CH_2Cl_2$:MeOH); $^1$H NMR (500 MHz, $d_6$-DMSO): δ 14.05 (s, 1H), 11.57 (s, 1H), 7.78 (s, 1H), 7.44 (s, 1H), 7.21 (s, 1H), 4.45 (q, *J* = 7.0, 2H), 1.41 (t, *J* = 7.0, 3H); $^{13}$C NMR (125 MHz, $CD_3OD$): δ 163.0, 136.5, 136.0, 132.3, 123.5, 117.4, 116.2, 115.9, 103.6, 95.7, 60.5,

13.3; IR (film): 3232, 2972, 2896, 1717, 1442, 1241, 1150 $cm^{-1}$; HRMS-ESI (*m/z*) $[M + Na]^+$ calculated for $C_{12}H_{10}BrN_3O_2Na$, 329.9854; found, 329.9853.

The structure of **3.29b** was confirmed by 2D-NOESY a experiment, as the following interactions were observed:

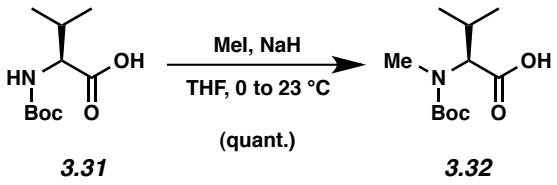



***3.29b***

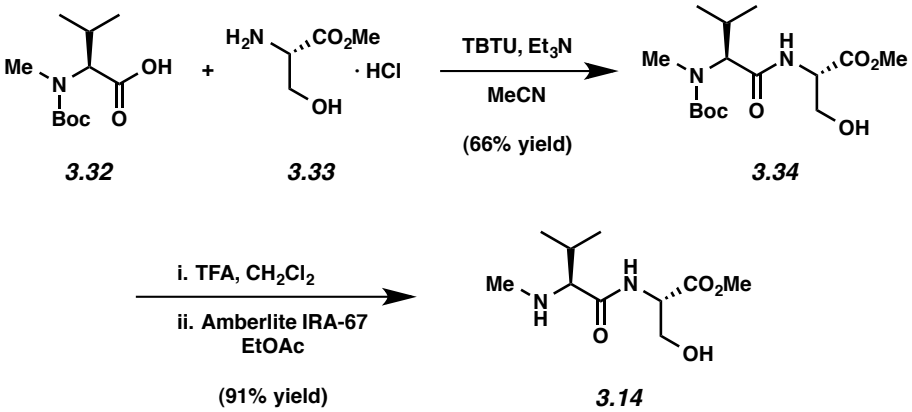



***3.30*** ***3.31***

***N*-Boc-L-valine (3.31).** *N*-Boc-L-valine (**3.31**) was prepared following a known procedure.[36] To a solution of L-valine (**3.30**, 2.20 g, 18.8 mmol) in 1:1 THF:$H_2O$ (88 mL) at 0 °C was added NaOH (1.65 g, 41.3 mmol, 2.2 equiv), followed by $Boc_2O$ (4.70 g, 22.6 mmol, 1.2 equiv). The resulting mixture was removed from the bath and allowed to warm to 23 °C. After stirring for an additional 24 h, the volatiles were removed under reduced pressure. The aqueous layer was washed with $CH_2Cl_2$ (40 mL), then acidified to pH 4 with 1 M HCl. The aqueous layer was extracted with $CH_2Cl_2$ (4 × 40 mL). The combined organic extractions were dried over $Na_2SO_4$ and concentrated under reduced pressure to give **3.31** (3.50 g, 86% yield). Spectral data match those previously reported.[37,38]



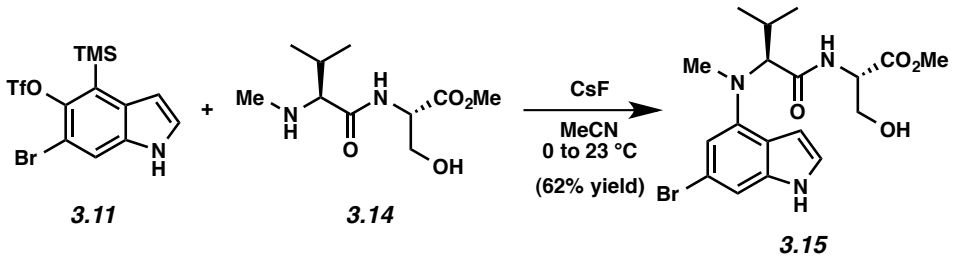

**Boc-*N*-Me-L-valine (3.32).** Boc-*N*-Me-L-valine (**3.32**) was prepared following a known procedure.[39] To a solution of *N*-Boc-L-valine (**3.31**, 6.31 g, 29.0 mmol) and MeI (18.1 mL, 290 mmol, 10 equiv) in THF (126 mL) at 0 °C was added 60% NaH (11.6 g, 290 mmol, 10 equiv) slowly over 5 min. After stirring for 1.5 h, the resulting mixture was removed from the bath and allowed to warm to 23 °C. The reaction was stirred for an additional 28 h, then quenched with $H_2O$ (20 mL) and diluted with EtOAc (15 mL). The volatiles were removed under reduced pressure. The aqueous layer was diluted with $H_2O$ (400 mL) and washed with EtOAc (200 mL), then acidified to pH 3.5 with 5% aqueous citric acid. The aqueous layer was extracted with EtOAc (3 × 128 mL), the combined organic extractions were dried over $MgSO_4$, and then concentrated under reduced pressure to give **3.32** (6.84 g, quantitative yield). Spectral data match those previously reported.[40,41]



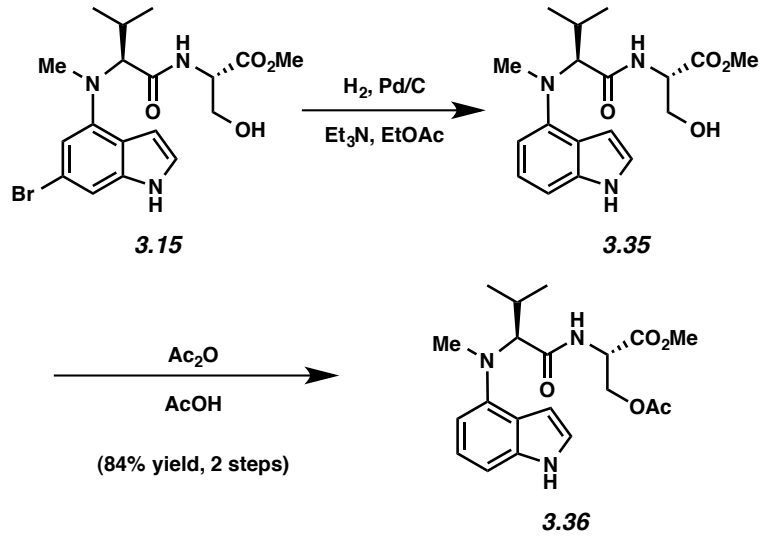

**Peptide 3.14.** To a stirred solution of Boc-*N*-Me-L-valine **3.32** (2.00 g, 8.66 mmol) and L-serine methyl ester hydrochloride (**3.33**, 1.35 g, 8.66 mmol, 1 equiv) in MeCN (86.6 mL) was added

$Et_3N$ (3.62 mL, 26.0 mmol, 3 equiv), followed by TBTU (3.06 g, 9.53 mmol, 1.1 equiv). The resulting solution was stirred at 23 °C for 4.3 h, then diluted with EtOAc (200 mL). The organic layer was washed with saturated aqueous $NH_4Cl$ (200 mL), dried with $Na_2SO_4$, then placed into a –78 °C bath to allow salts to precipitate. After filtering (EtOAc eluent), evaporation under reduced pressure afforded the crude product. Further purification by flash chromatography (1:1 Hexanes:EtOAc) provided **3.34** (1.91 g, 66% yield). $R_f$ 0.23 (1:1 Hexanes:EtOAc)

**3.34** was dissolved in $CH_2Cl_2$ (120 mL) and the solution was cooled to 0 °C. TFA (60 mL) was added dropwise over 15 min. After stirring for 45 min, the solution was concentrated under reduced pressure. The resulting oil was dissolved in EtOAc (96 mL) and stirred at 23 °C over Amberlite IRA-67 ion exchange resin (21.7 g) for 3 d, while the disappearance of the TFA-salt was monitored by $^{19}F$ NMR. The mixture was filtered (EtOAc eluent), and then concentrated under reduced pressure to provide **3.14** (1.22 g, 91% yield) as a white solid. $R_f$ 0.14 (1:4 MeOH:EtOAc); $^1H$ NMR (500 MHz, $CD_3CN$, 18/20 H): δ 7.70 (br s, 1H), 4.50–4.46 (m, 1H), 3.88 (dd, $J$ = 11.0, 4.0, 1H), 3.72–3.69 (m, 4H), 2.70 (d, $J$ = 5.0, 1H), 2.35 (s, 3H), 1.92–1.89 (m, 1H), 0.96 (d, $J$ = 7, 3H), 0.90 (d, $J$ = 7.0, 3H); $^{13}C$ NMR (125 MHz, $CD_3CN$): δ 174.5, 172.2, 71.7, 63.2, 55.0, 52.7, 36.0, 32.3, 19.7, 18.5; IR (film): 3309, 2961, 1750, 1645 $cm^{-1}$; HRMS-ESI ($m/z$) $[M + H]^+$ calcd for $C_{10}H_{21}N_2O_4$, 233.1501, found, 233.1504; $[\alpha]^{22}_D$ –15.00º (c 0.10 $CH_2Cl_2$).



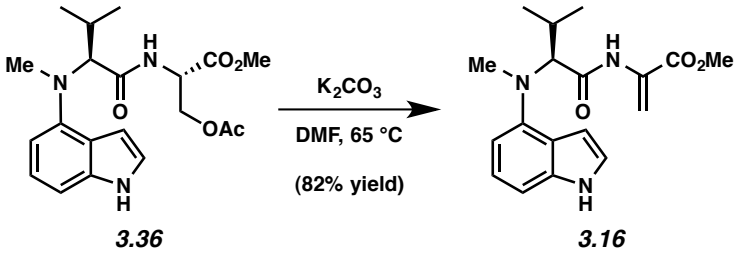

**Indolyne adduct 3.15.** To a stirred solution of *N*-H 6-bromo silyltriflate **3.11** (52.1 mg, 0.125 mmol) and **3.14** (87.1 mg, 0.375 mmol, 3 equiv) in MeCN (1.25 mL) was added CsF (38.0 mg, 0.250 mmol, 2 equiv). The reaction vessel was placed in a 0 °C bath for 6 h, then allowed to warm to 23 °C. After stirring for an additional 25 h, the reaction mixture was filtered over silica gel (EtOAc eluent). Evaporation under reduced pressure afforded the crude product, which was further purified by flash chromatography (1:0.7:0.7 Hexanes:$CH_2Cl_2$:$Et_2O$) to provide adduct **3.15** (33.2 mg, 62% yield). $R_f$ 0.15 (1:1 Hexanes:EtOAc); $^1$H NMR (500 MHz, $CD_3CN$): δ 9.36 (br s, 1H), 7.19–7.17 (m, 2H), 6.65 (d, *J* = 1.5, 1H), 6.58–6.54 (m, 2H), 4.41–4.37 (m, 1H), 3.99 (d, *J* = 10.0, 1H), 3.74–3.70 (m, 1H), 3.63 (s, 3H), 3.55–3.51 (m, 1H), 2.90 (s, 3H), 2.86 (t, *J* = 6.0, 1H), 2.38–2.31 (m, 1H), 1.05 (d, *J* = 7.0, 3H), 0.98 (d, *J* = 7.0, 3H); $^{13}$C NMR (75 MHz, $CD_3CN$): δ 171.8, 171.4, 147.4, 139.0, 124.6, 120.1, 116.0, 111.7, 108.6, 102.2, 71.6, 62.8, 55.2, 52.7, 35.3, 28.7, 20.2, 20.0; IR (film): 3313, 2959, 1739, 1655, 1211 cm$^{-1}$; HRMS-ESI (*m/z*) [M + Na]$^+$ calcd for $C_{18}H_{24}BrN_3O_4Na$, 448.0848, found, 448.0863; $[\alpha]^{22}_D$ –66.00° (c 0.10 $CH_2Cl_2$).




**Acetate 3.36.** To a solution of **3.15** (41.4 mg, 0.0973 mmol) in EtOAc (4.9 mL) was added 5% Pd/C (22.8 mg, 0.0107 mmol, 11 mol% Pd). The mixture was placed under an atmosphere of hydrogen, $Et_3N$ (40.7 μL, 0.292 mmol, 3 equiv) was added, and the solution stirred for 2 h at 23 °C. Additional $Et_3N$ (20.0 μL, 0.143 mmol, 1.5 equiv) was added, and after 35 min of stirring, the mixture was filtered over celite (EtOAc eluent). Evaporation of the solvent under reduced pressure afforded crude **3.35**, which was used in the subsequent step without further purification. $R_f$ 0.74 (100% EtOAc).

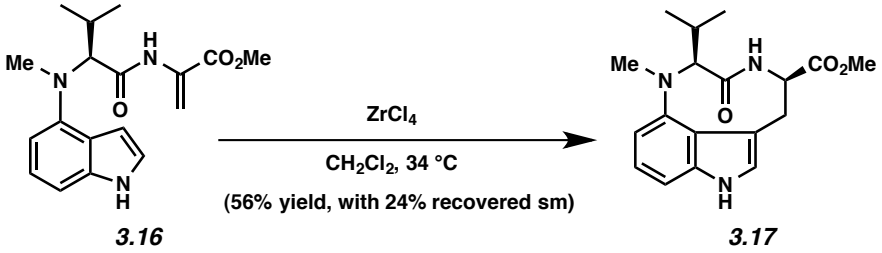
Crude **3.35** was dissolved in AcOH (3 mL) and $Ac_2O$ (76.9 μL, 0.808 mmol, 8.3 equiv) was added. The solution was stirred for 3 d at 23 °C, then added dropwise to 0 °C saturated aqueous $NaHCO_3$ (20 mL). Once bubbling stopped, the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over $Na_2SO_4$. Evaporation under reduced pressure afforded the crude product, which was further purified by flash chromatography (1.5:1 Hexanes:EtOAc) to provide **3.36** (31.8 mg, 84% over 2 steps). $R_f$ 0.43 (1:1 Hexanes:EtOAc); $^1H$ NMR (500 MHz, $CDCl_3$): δ 8.28 (br s, 1H), 7.19 (app. t, $J$ = 3.0, 1H), 7.09–7.03 (m, 2H), 6.65–6.61 (m, 2H), 6.09 (d, $J$ = 8.0, 1H), 4.86–4.83 (m, 1H), 4.28 (dd, $J$ = 11.0, 4.0, 1H), 4.06 (d, $J$ =

9.5, 1H), 4.01 (dd, *J* = 11.0, 3.5, 1H), 3.68 (s, 3H), 2.87 (s, 3H), 2.50–2.43 (m, 1H), 1.88 (s, 3H), 1.20 (d, *J* = 6.5, 3H), 1.03 (d, *J* = 6.5, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$ 19/20 C): δ 170.4, 170.1, 170.0, 145.2, 137.5, 122.9, 120.6, 109.2, 105.6, 101.6, 71.6, 64.5, 52.8, 50.8, 34.9, 27.3, 20.7, 20.3, 19.7; IR (film): 3394, 2960, 1745, 1662, 1508, 1223 cm$^{-1}$; HRMS-ESI (*m/z*) [M + Na]$^+$ calcd for $C_{20}H_{27}N_3O_5Na$, 412.1848, found, 412.1853; $[\alpha]^{21}_D$ –104.00° (c 0.10 $CH_2Cl_2$).




*3.36* *3.16*

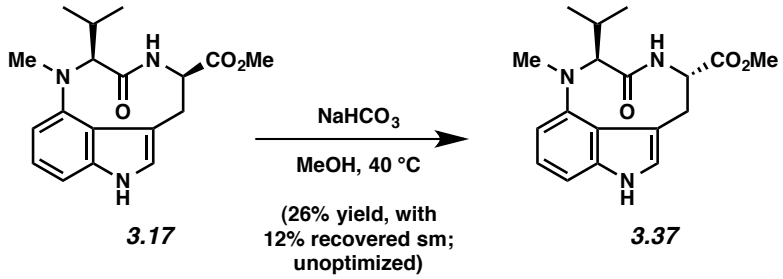
**Unsaturated ester 3.16.** To a solution of **3.36** (98.2 mg, 0.252 mmol) in DMF (2.5 mL) was added $K_2CO_3$ (69.7 mg, 0.504 mmol, 2 equiv). The resulting mixture was placed in a heating bath maintained at 65 °C for 10 h, then allowed to cool to 23 °C. The reaction mixture was passed over a plug of cotton (EtOAc eluent). Evaporation at 60 °C under reduced pressure afforded the crude product, which was further purified by flash chromatography (5:1 Hexanes:EtOAc) to provide adduct **3.16** (68.1 mg, 82% yield). $R_f$ 0.60 (1:1 Hexanes:EtOAc); $^1$H NMR (500 MHz, $CDCl_3$): δ 8.23 (br s, 1H), 8.10 (br s, 1H), 7.19 (app. t, 1H), 7.12–7.08 (m, 2H), 6.67 (d, *J* = 6.5, 1H), 6.64 (app. t, 1H), 6.59 (s, 1H), 5.84 (d, *J* = 1.5, 1H), 4.12 (d, *J* = 8.5, 1H), 3.7 (s, 3H), 2.90 (s, 3H), 2.48–2.44 (m, 1H), 1.16 (d, *J* = 7.0, 3H), 1.04 (d, *J* = 6.5, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 170.0, 163.9, 144.5, 137.3, 130.7, 122.74, 122.69, 120.6, 109.3, 108.4, 105.7, 101.2, 72.2, 52.5, 35.9, 27.5, 19.81, 19.75; IR (film): 3357, 2960, 1723, 1678, 1510 cm$^{-1}$; HRMS-ESI (*m/z*) [M + Na]$^+$ calcd for $C_{18}H_{23}N_3O_3Na$, 352.1637, found, 352.1631; $[\alpha]^{23}_D$ –206.00° (c 0.10 $CH_2Cl_2$).




*3.16* *3.17*

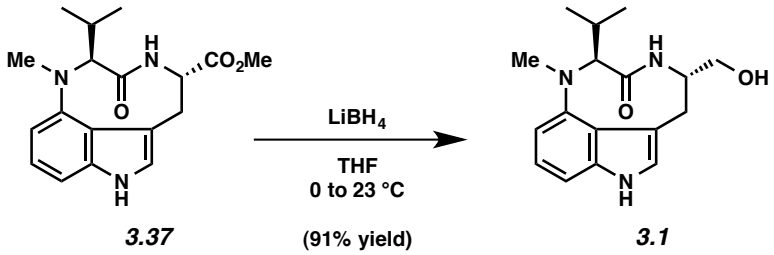
**Tricycle 3.17.** A modification of Piersanti's procedure for alkylation of indoles was employed to construct the desired 9-membered ring.[28] Inside a glove box, $ZrCl_4$ (109 mg, 0.468 mol, 15 equiv) and then $CH_2Cl_2$ (0.31 mL) were added to a vial containing **3.16** (10.3 mg, 0.312 mmol). The reaction vessel was placed into an aluminum block maintained at 34 °C. After stirring for 41 h, the vial was transferred out of the glove box and the reaction mixture was added dropwise to saturated aqueous $NaHCO_3$ (10 mL) at 0 °C. The resulting solids were removed by filtration over celite (EtOAc eluent). The layers were separated and the aqueous layer was extracted with EtOAc (15 mL). The combined organic layers were dried over $Na_2SO_4$. Evaporation under reduced pressure afforded the crude product, which was further purified by flash chromatography (5:1 → 2:1 Hexanes:EtOAc) to afford unsaturated ester **3.16** (2.5 mg, 24% yield) and tricycle **3.17** (5.8 mg, 56% yield). Tricycle **3.17**: $R_f$ 0.22 (3:2 Hexanes:EtOAc); $^1$H NMR (500 MHz, $CDCl_3$): δ 8.06 (br s, 1H), 7.06 (app. t, *J* = 8.0, 1H), 7.02 (d, *J* = 2.0, 1H), 6.98 (d, *J* = 8.0, 1H), 6.79 (d, *J* = 7.5, 1H), 6.67 (br d, *J* = 6.0, 1H), 4.51–4.48 (m, 1H), 3.93 (s, 3H), 3.81 (d, *J* = 10.0, 1H), 3.47 (dd, *J* = 15.5, 3.0, 1H), 3.32 (dd, *J* = 15.5, 3.5, 1H), 3.13 (s, 3H), 2.69–2.64 (m, 1H), 0.76 (d, *J* = 7.0, 3H), 0.71 (d, *J* = 6.5, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$): δ 172.6, 172.5, 148.0, 138.5, 122.9, 122.7, 120.5, 113.4, 109.8, 105.5, 69.9, 57.4, 53.2, 35.3, 32.6, 28.6, 20.6, 20.2; IR (film): 3242, 2956, 1746, 1654, 1212 $cm^{-1}$; HRMS-ESI (*m/z*) $[M + Na]^+$

calculated for $C_{18}H_{23}N_3O_3Na$, 352.1637; found, 352.1630; $[\alpha]^{20}_D$ –216.00° (c 0.10 $CH_2Cl_2$). Characterization data for **3.17** matched the data reported by Nakatsuka.[24c]




**Tricycle 3.37.** Nakatsuka's procedure was employed to epimerize **3.17** to **3.37**.[24c] To a solution of **3.17** (24.4 mg, 0.074 mmol) in MeOH (4.9 mL) was added $NaHCO_3$ (170 mg, 2.03 mmol, 27.4 equiv). The resulting mixture was placed in a heating bath maintained at 40 °C for 51.5 h. After cooling to 23 °C, the reaction mixture was diluted with 20 mL brine followed by 30 mL $Et_2O$. The layers were separated, and the aqueous layer was extracted with $Et_2O$ (2 x 30 mL) and the combined organic layers were dried over $Na_2SO_4$. Evaporation of the solvent under reduced pressure afforded the crude product, which was purified by preparative TLC (1:1:2 $CH_2Cl_2$:$Et_2O$:Hexanes; plate ran up multiple times) to provide **3.17** (2.9 mg, 12% yield) and **3.37** (6.3 mg, 26% yield). **3.37**: $R_f$ 0.19 (1:1:2 $CH_2Cl_2$:$Et_2O$:Hexanes); $^1$H NMR (500 MHz, $CDCl_3$; 1:1 mixture of conformers): δ 8.25 (br s, 1H), 8.09 (br s, 1H), 7.28–7.26 (m, 2H), 7.16 (app. t, *J* = 7.5, 1H), 7.08 (app. t, *J* = 7.5, 1H), 7.05 (dd, *J* = 7.0, 0.5, 1H), 6.98 (s, 1H), 6.95 (d, *J* = 8.0, 1H), 6.92 (d, *J* = 2.5, 1H), 6.77 (s, 1H), 6.55 (d, *J* = 7.5, 1H), 5.15 (ddd, *J* = 10.5, 4.5, 2.0, 1H), 5.10 (app. quintet, *J* = 2.5, 1H), 4.28 (d, *J* = 10.0, 1H), 3.76 (s, 3H), 3.70 (s, 3H), 3.63 (dd, *J* = 17.5, 5.0, 1H), 3.30 (br d, *J* = 17.0, 1H), 3.25 (dd, *J* = 14.5, 4.5, 1H), 3.17 (dd, *J* = 14.5, 2.5, 1H) 3.05 (d, *J* = 11.0, 1H), 2.91 (s, 3H), 2.74 (s, 3H), 2.66–2.59 (m, 1H), 2.43 (m, 1H), 1.26 (d, *J* = 6.5, 3H), 0.95 (app. d, *J* = 6.5, 6H), 0.65, (d, *J* = 6.5, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$, 1:1

mixture of conformers): δ 172.9, 171.7, 171.6, 170.5, 147.8, 145.2, 139.5, 139.2, 128.0, 124.4, 123.2, 123.0, 121.6, 118.3, 114.6, 110.4, 108.8, 107.2, 104.6, 76.5, 71.7, 58.3, 55.7, 53.0, 52.2, 36.4, 35.8, 33.2, 30.4, 28.7, 24.6, 21.9, 19.72, 19.71, 19.5; IR (film): 3305, 2959, 1739, 1655, 1088, 1028 $cm^{-1}$; HRMS-ESI (*m/z*) $[M + Na]^+$ calculated for $C_{18}H_{23}N_3O_3Na$, 352.1637; found, 352.1634; $[\alpha]^{22}_D$ –76.00º (c 0.10 $CH_2Cl_2$). Characterization data for **3.36** matched the data reported by Nakatsuka.[24c]




*3.37* (91% yield) *3.1*

**Indolactam V (3.1).** Nakatsuka's procedure was employed to reduce **3.37** to indolactam V (**3.1**).[24c] To a stirred solution of **3.37** (5.5 mg, 0.0167 mmol) in THF (1.25 mL) at 0 °C was added a solution of $LiBH_4$ (0.69 mg, 0.032 mmol, 2 equiv) in THF (159 μL). After stirring at 0 °C for 40 min, the reacting was allowed to warm to 23 °C. After stirring at 23 °C for 75 min, additional $LiBH_4$ (0.87 mg, 0.040 mmol, 2.3 equiv) was added as a solution in THF (200 μL). After stirring for an additional 2 h, $LiBH_4$ (0.44 mg, 0.020 mmol, 1.2 equiv) was added as a solution in THF (100 μL). The solution was allowed to stir at 23 °C for 3 h, and then quenched with brine (1.5 mL). The reaction mixture was diluted with EtOAc (2 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 2 mL) and the combined organic layers were filtered over $SiO_2$ (EtOAc eluent). Evaporation of the solvent under reduced pressure afforded the crude product, which was purified by flash chromatography (4:1 Hexanes:EtOAc) to afford indolactam V (4.6 mg, 91% yield). Indolactam V (**3.1**): $R_f$ 0.10 (1:1.5 Benzene:$Et_2O$); $^1H$ NMR

(500 MHz, $CDCl_3$, 3.3:1 mixture of conformers, major conformer reported): 8.01 (br s, 1H), 7.19 (br s, 1H), 7.07 (app. t, *J* = 8.0, 1H), 6.91 (app. dd, *J* = 7.5, 0.5, 2H), 6.51 (d, *J* = 8.0, 1H), 4.40 (d, *J* = 10.5, 1H), 4.34–4.31 (m, 1H), 3.77–3.74 (m, 1H), 3.60–3.55 (m, 1H), 3.19 (br d, *J* = 17.5, 1H), 3.05 (dd, *J* = 17.0, 3.5, 1H), 2.93 (s, 3H), 2.71 (br s, 1H), 2.64–2.57 (m, 1H), 0.94 (d, *J* = 6.0, 3H), 0.64 (d, *J* = 6.5, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$, 3.3:1 mixture of conformers): δ 174.0, 172.6, 147.8, 145.5, 139.4, 139.2, 128.0, 124.7, 123.12, 123.08, 122.9, 121.3, 117.9, 114.6, 110.1, 109.2, 106.4, 104.0, 71.1, 65.1, 63.1, 55.8, 54.9, 35.8, 34.0, 33.1, 29.7, 28.8, 28.5, 24.6, 21.6, 19.7, 19.55, 19.49; IR (film): 3302, 2927, 1648 $cm^{-1}$; HRMS-ESI (*m/z*) $[M + Na]^+$ calculated for $C_{17}H_{23}N_3O_2Na$, 324.1688; found, 324.1689; $[\alpha]^{23}_D$ –124.00º (c 0.10 MeOH). For comparison, Endo reported $[\alpha]_D$ –134.50º (c 0.70 MeOH).[24a] Characterization data matched the data reported by Irie.[42]

### 3.8 Notes and References


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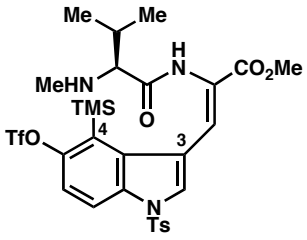
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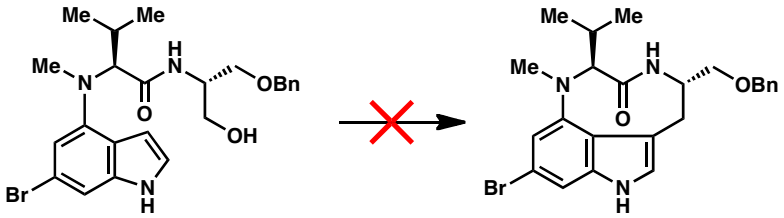
(25) Prior to the development of our distortion model, we attempted to construct the C4–N bond of indolactam V by indolyne cyclization of substrate ***i*** (and derivatives thereof). These efforts led to substantial decomposition, without trace of cyclized products.




*i*

(26) Less than 5% of the corresponding C5-substituted product was detected.

(27) All attempts to activate the alcohol of **3.15** (or the corresponding des-bromo derivative) for indole displacement were accompanied by dehydration. Efforts to convert related indolyne adduct *ii* to cyclized product *iii* were also unsuccessful.




*ii* *iii*

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# APPENDIX TWO

## Spectra Relevant to Chapter Three:

### Overturning Indolyne Regioselectivities and Synthesis of Indolactam V

Sarah M. Bronner, Adam E. Goetz, Neil K. Garg

*J. Am. Chem. Soc.* **2011**, *133*, 3832–3835.

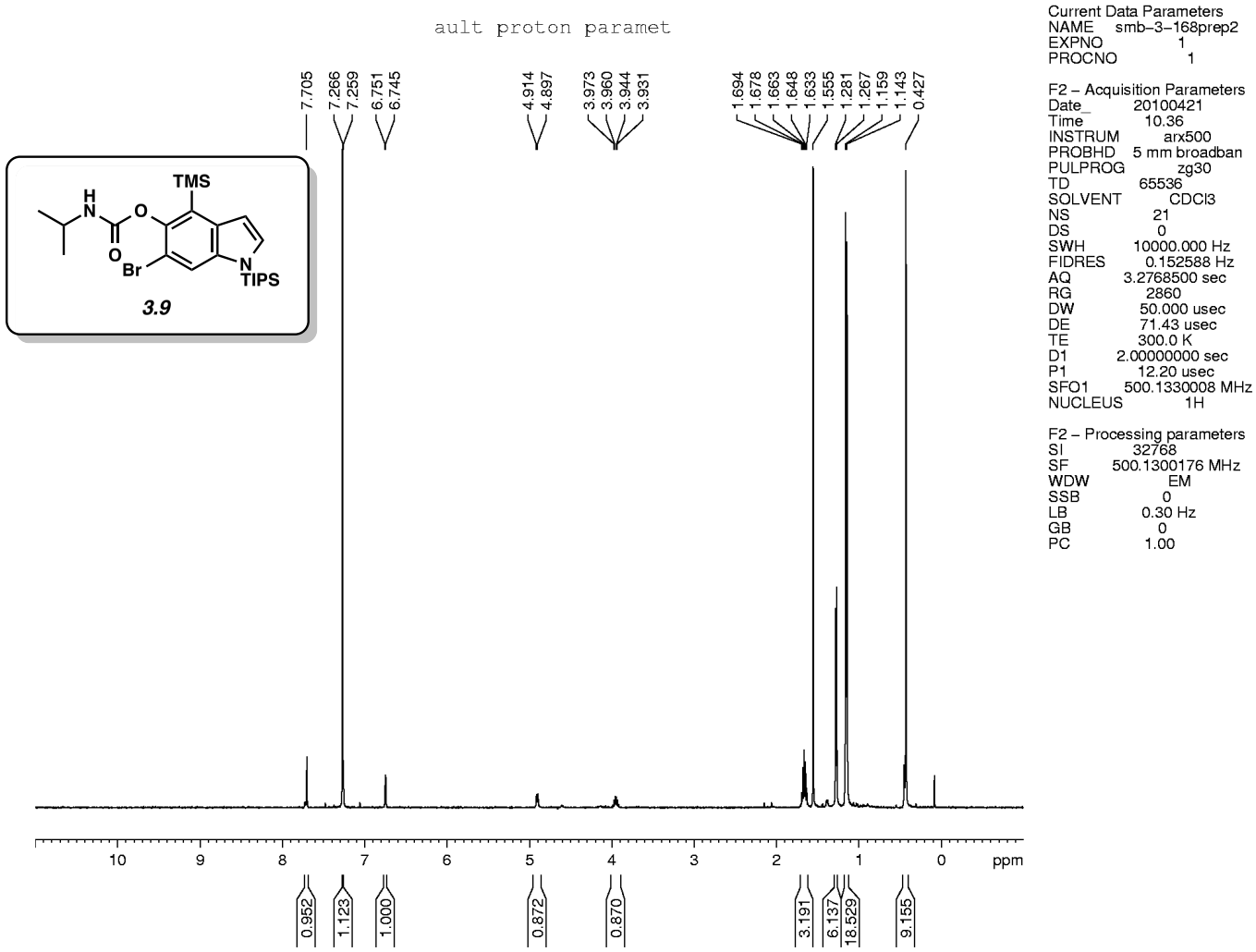



*Figure A2.1* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **3.9**.

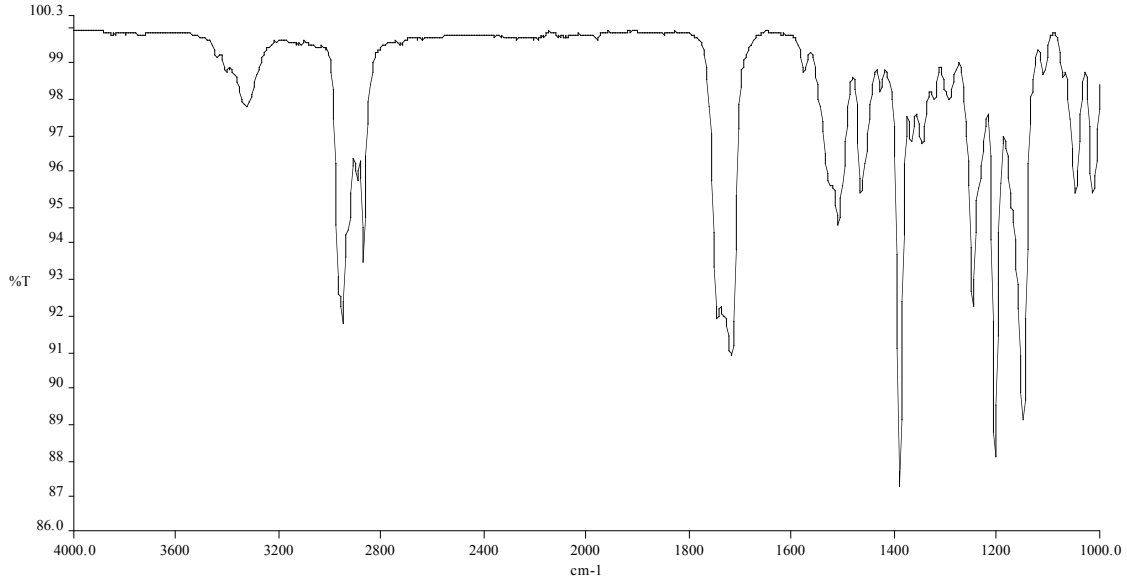



*Figure A2.2* Infrared spectrum of compound **3.9**.

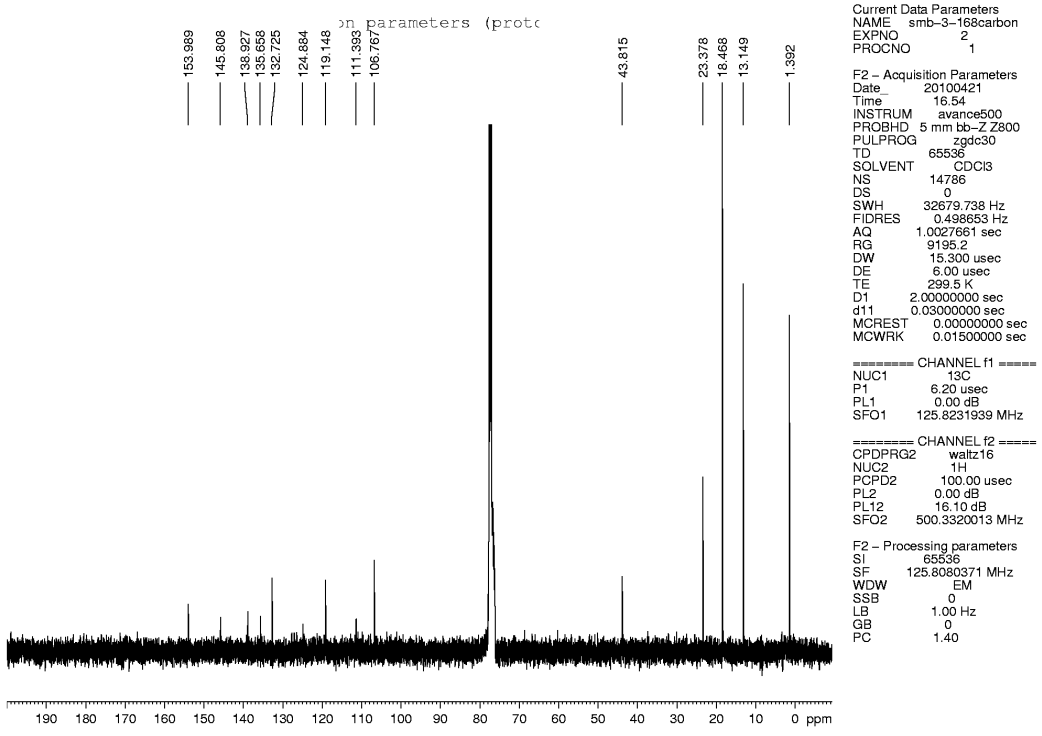



*Figure A2.3* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compound **3.9**.

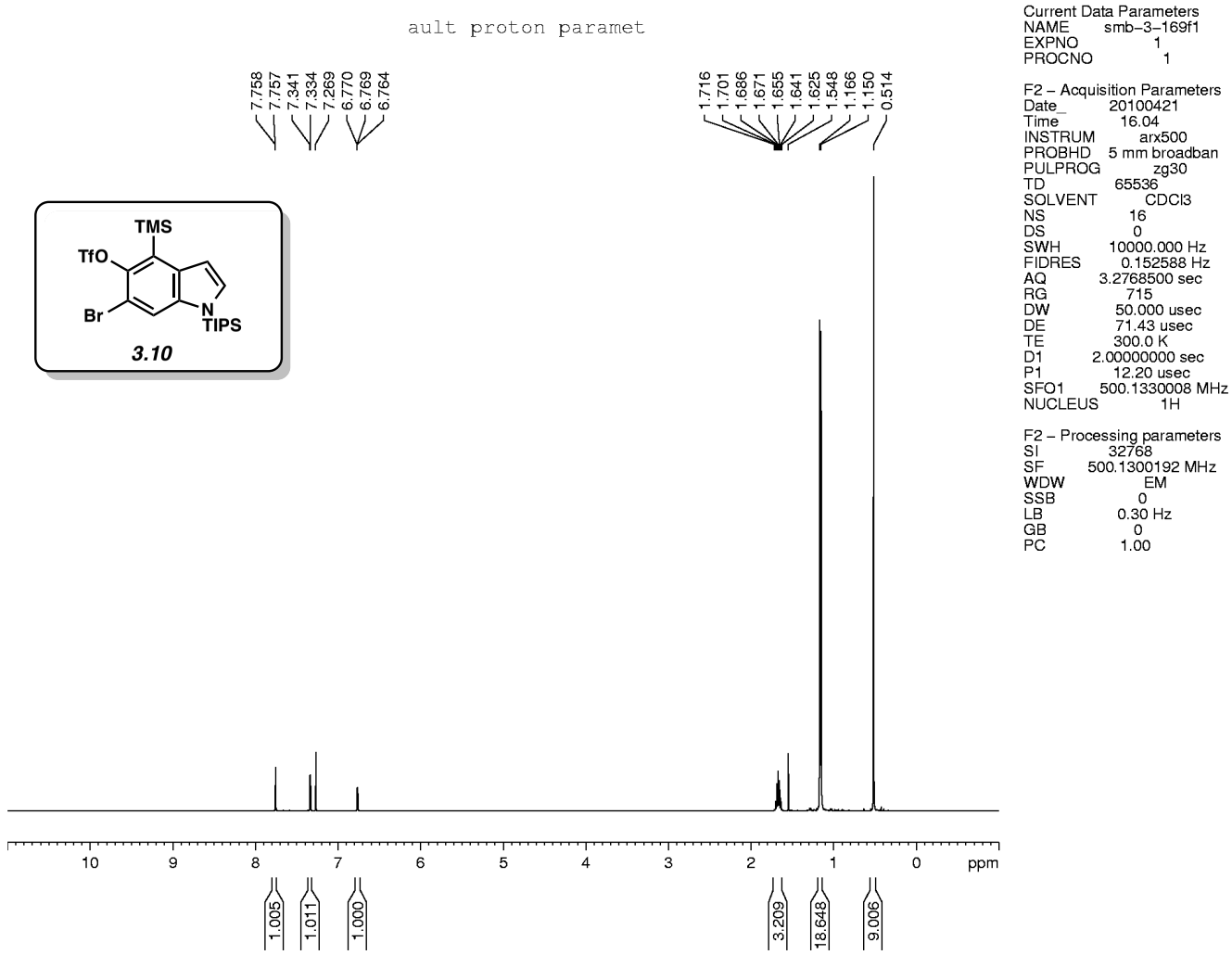



*Figure A2.4* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **3.10**.

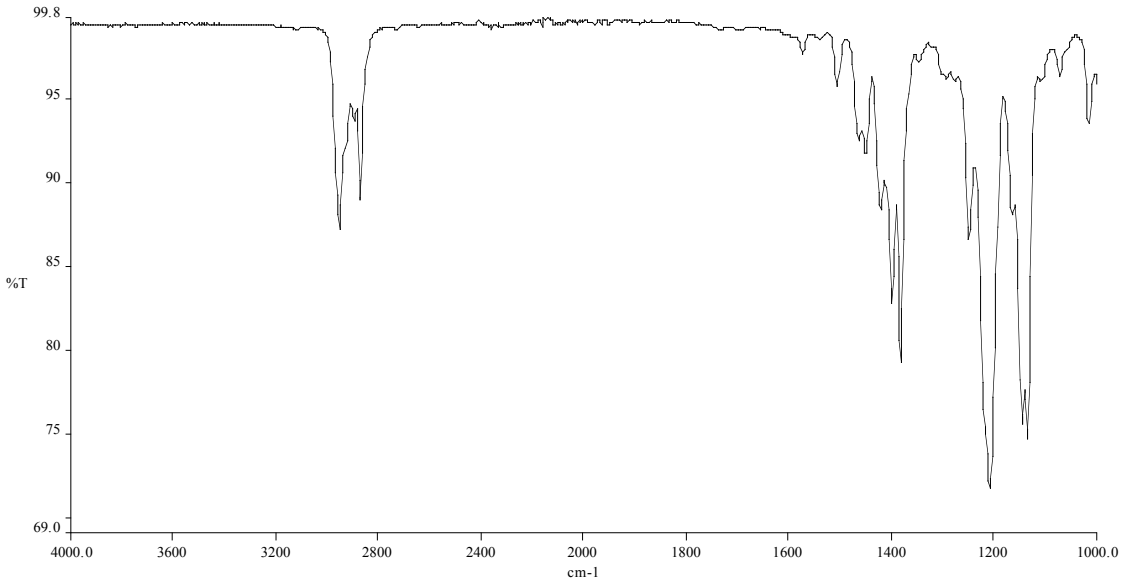



*Figure A2.5* Infrared spectrum of compound **3.10**.

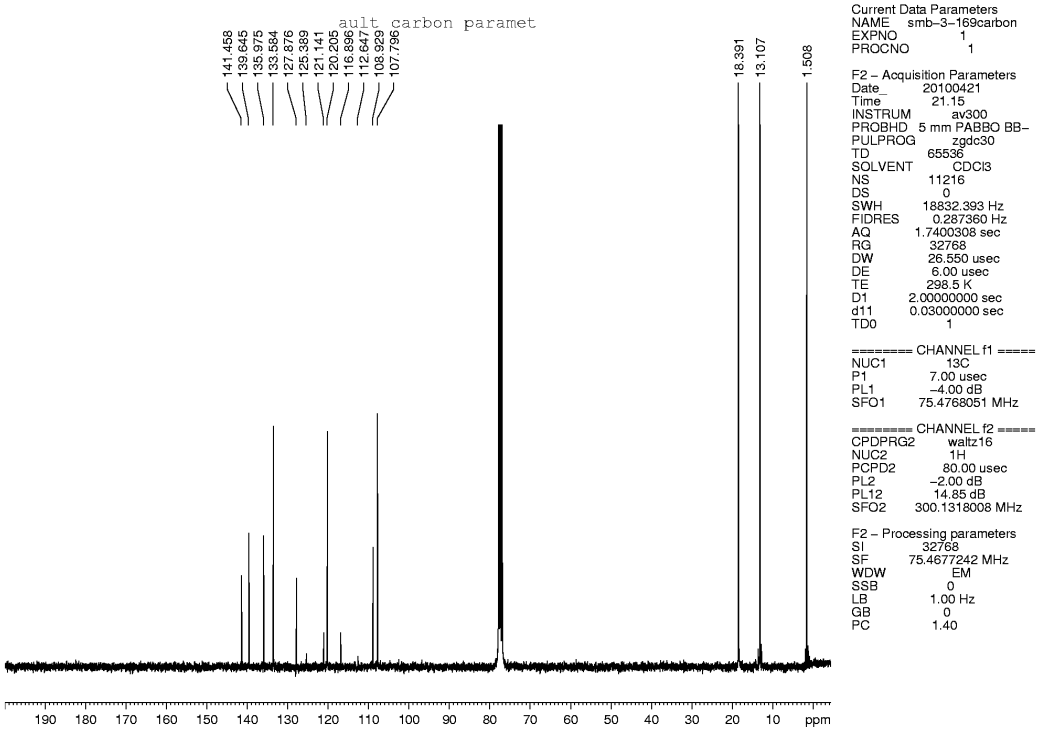



*Figure A2.6* $^{13}C$ NMR (75 MHz, $CDCl_3$) of compound **3.10**.

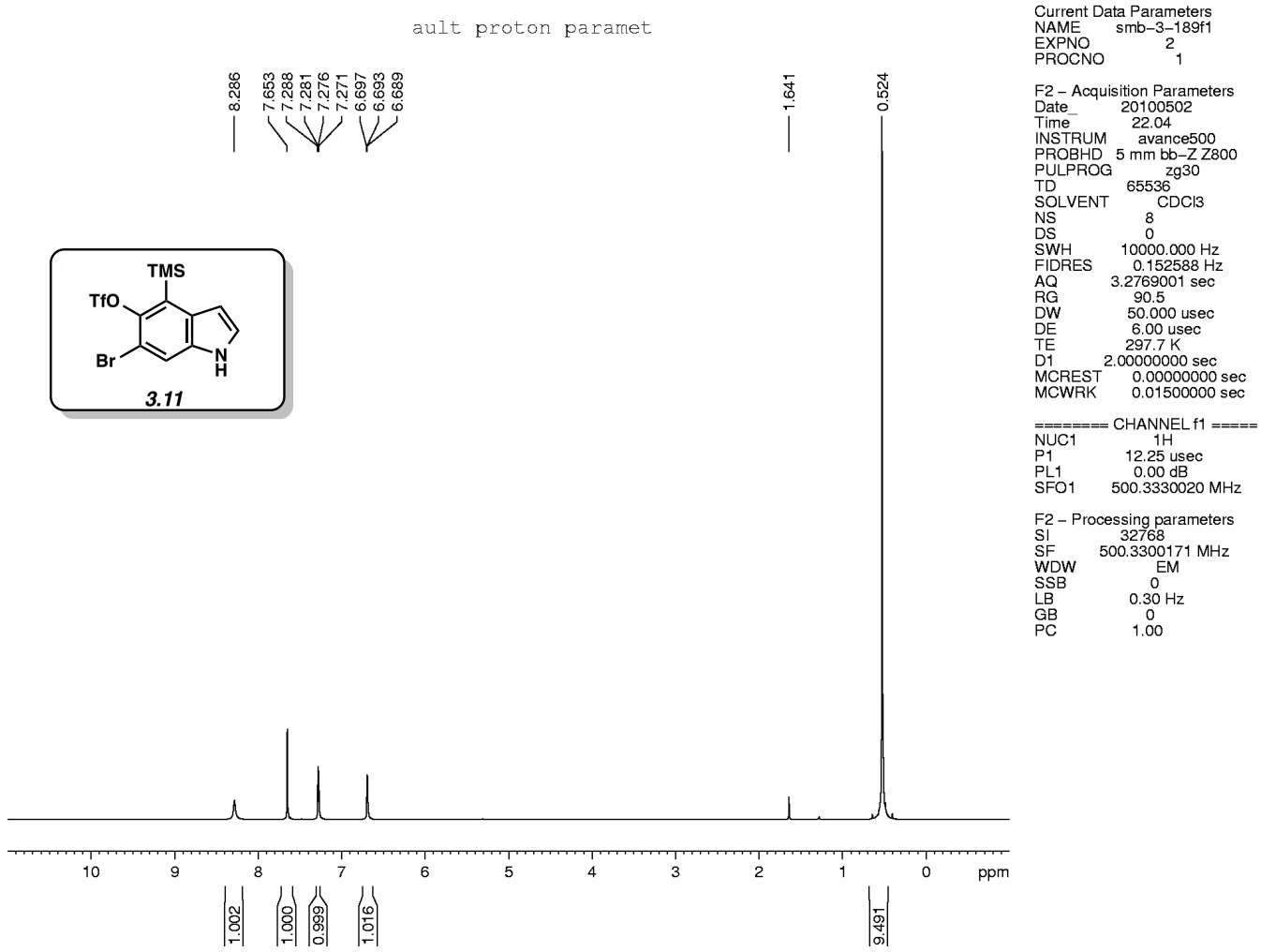



*Figure A2.7* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **3.11**.

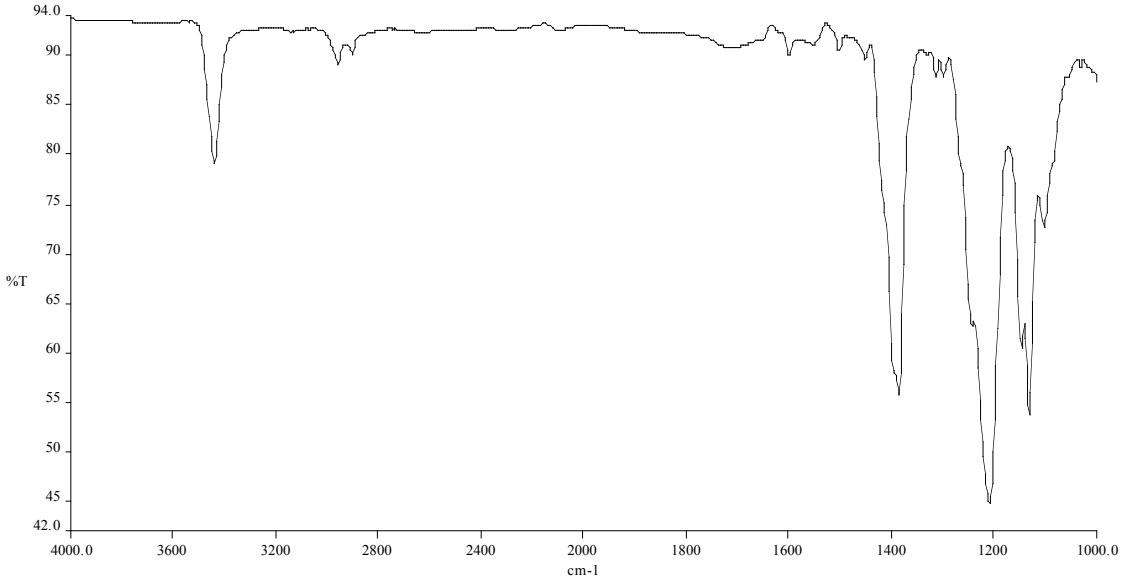



*Figure A2.8* Infrared spectrum of compound **3.11**.

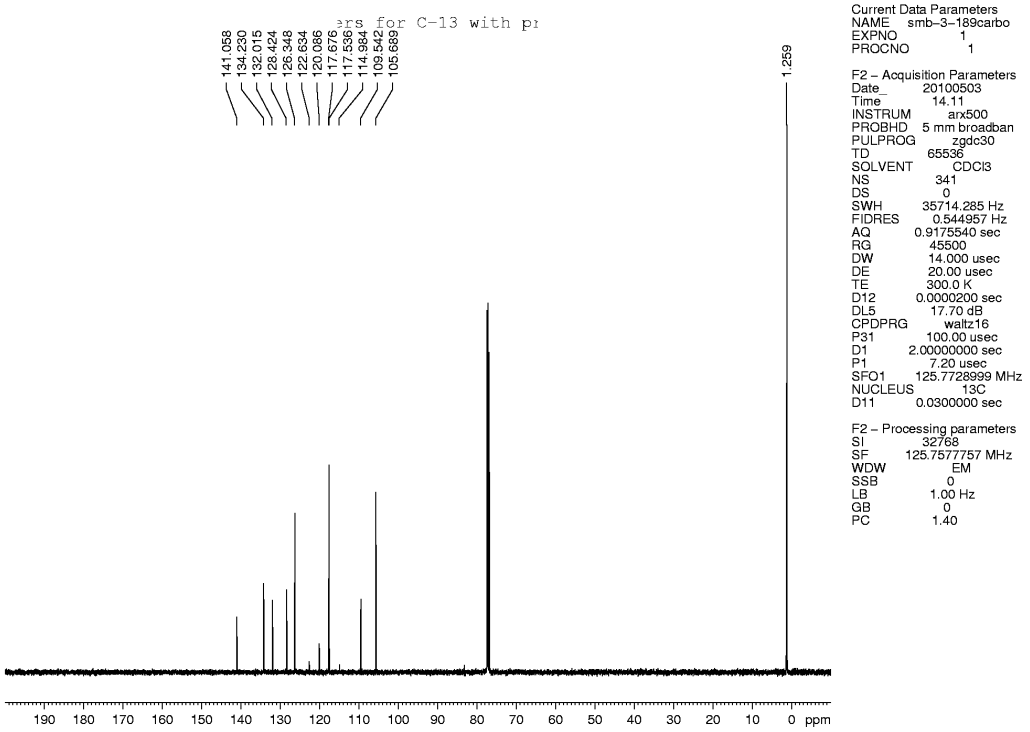



*Figure A2.9* $^{13}$C NMR (125 MHz, $CDCl_3$) of compound **3.11**.

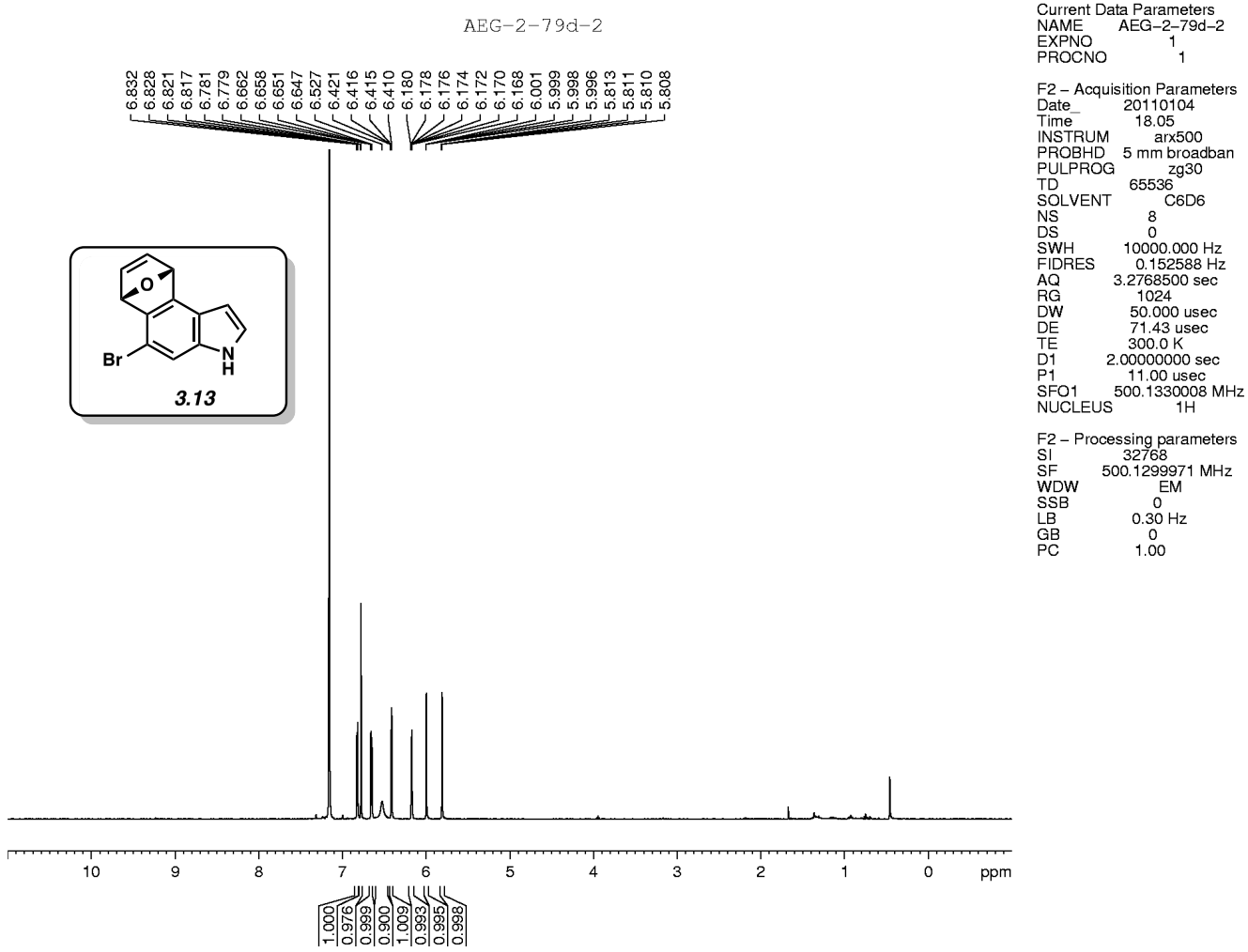



*Figure A2.10* $^{1}$H NMR (500 MHz, $C_6D_6$) of compound **3.13**.

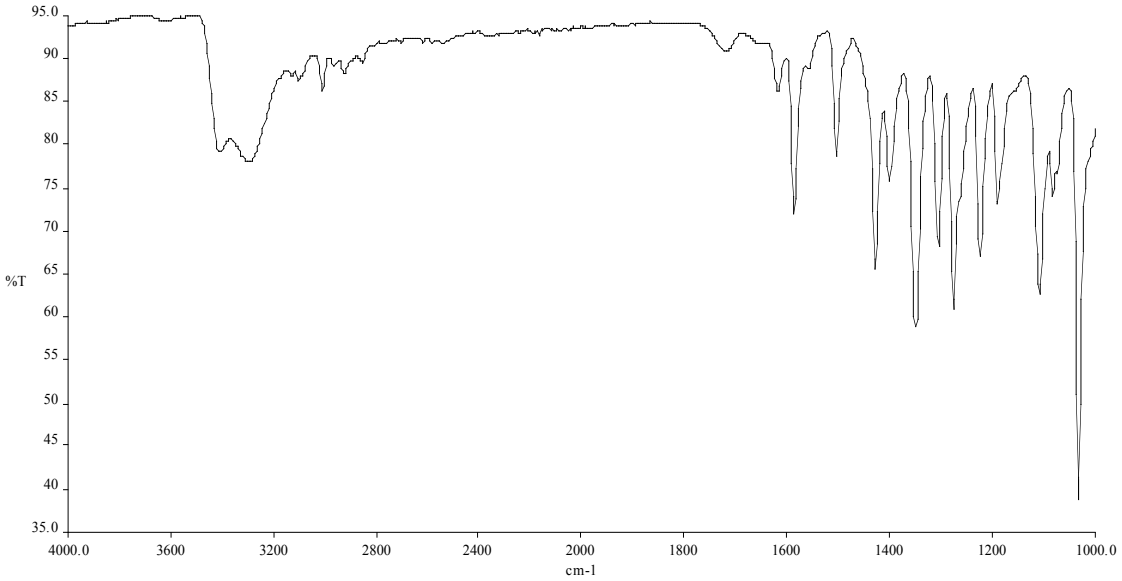



*Figure A2.11* Infrared spectrum of compound **3.13**.

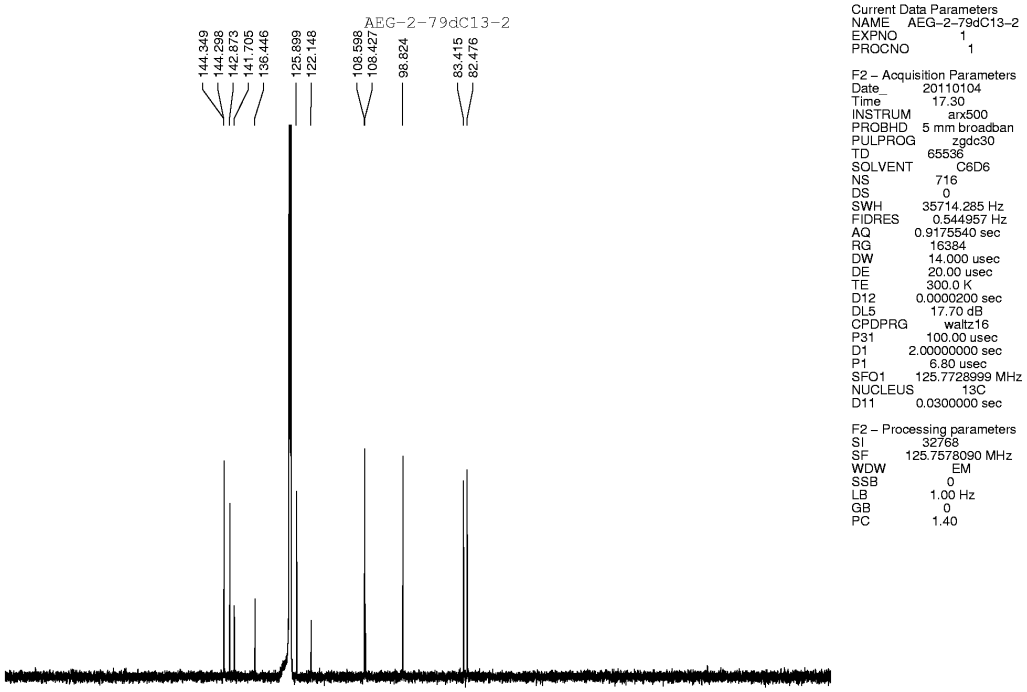



*Figure A2.12* $^{13}$C NMR (125 MHz, $C_6D_6$) of compound **3.13**.

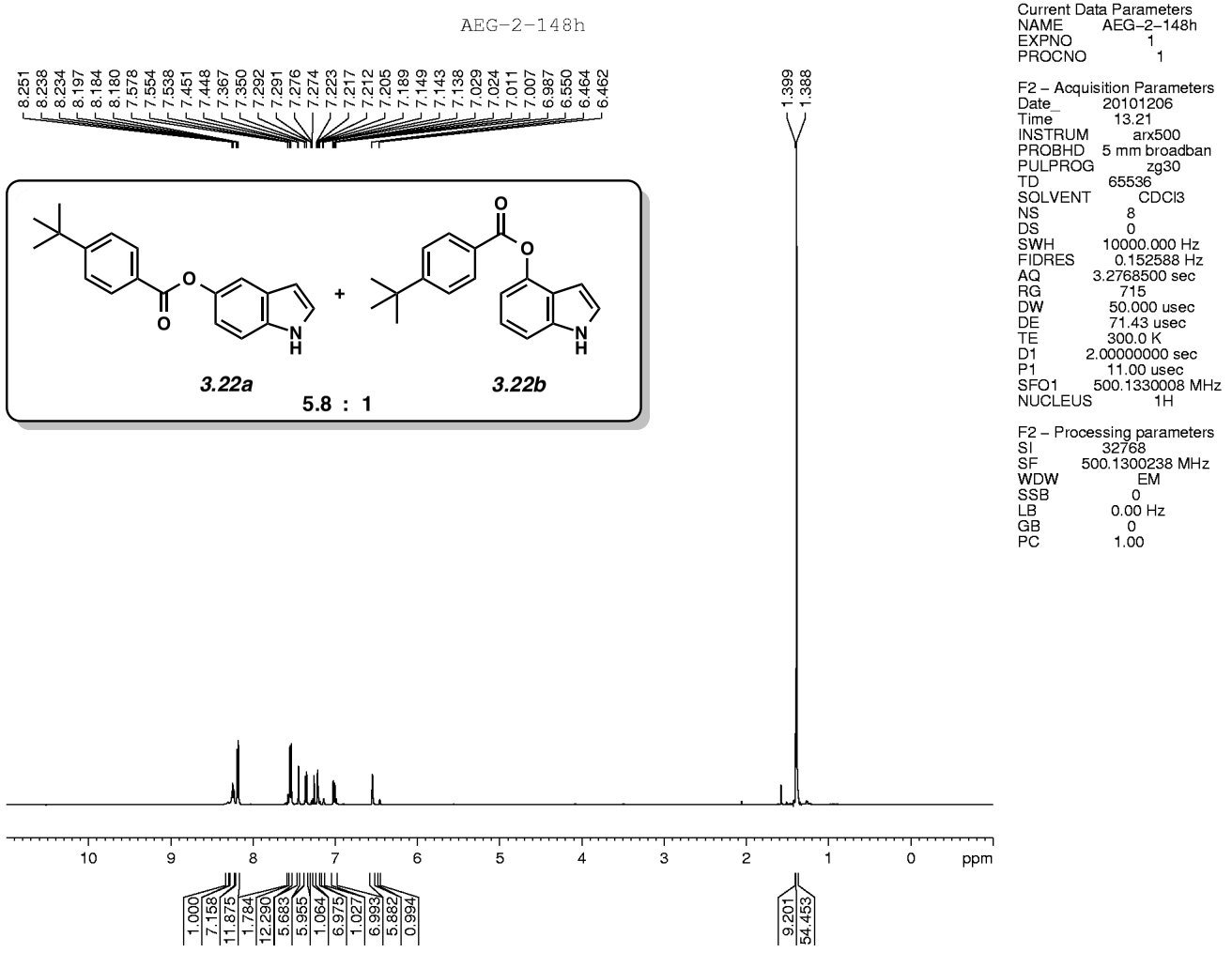



*Figure A2.13* $^{1}$H NMR (500 MHz, $CDCl_3$) of compounds **3.22.a** and **3.22b**.

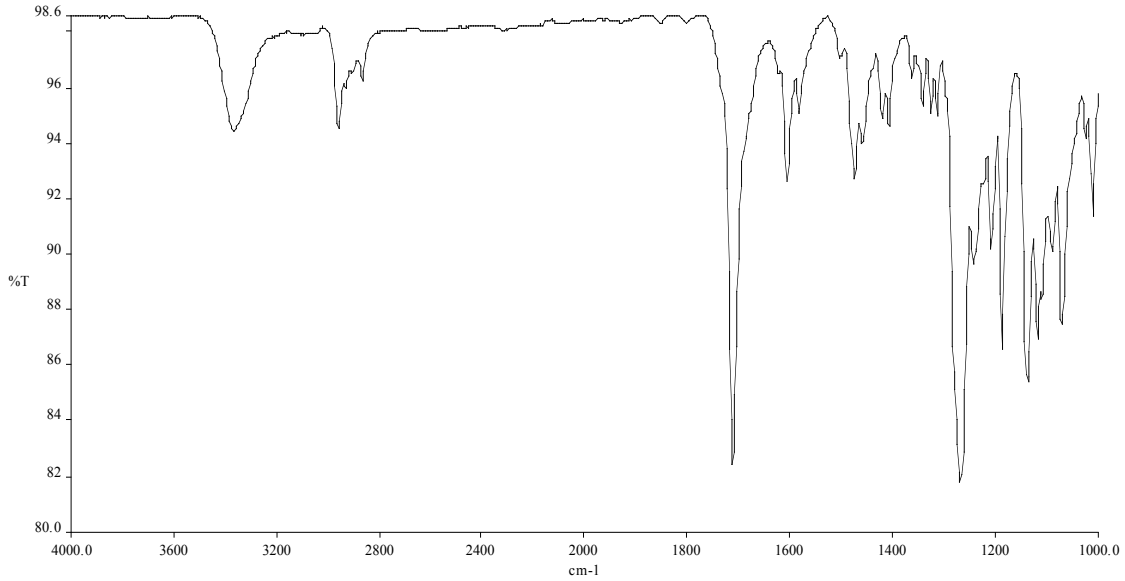



*Figure A2.14* Infrared spectrum of compounds **3.22a** and **3.22b**.

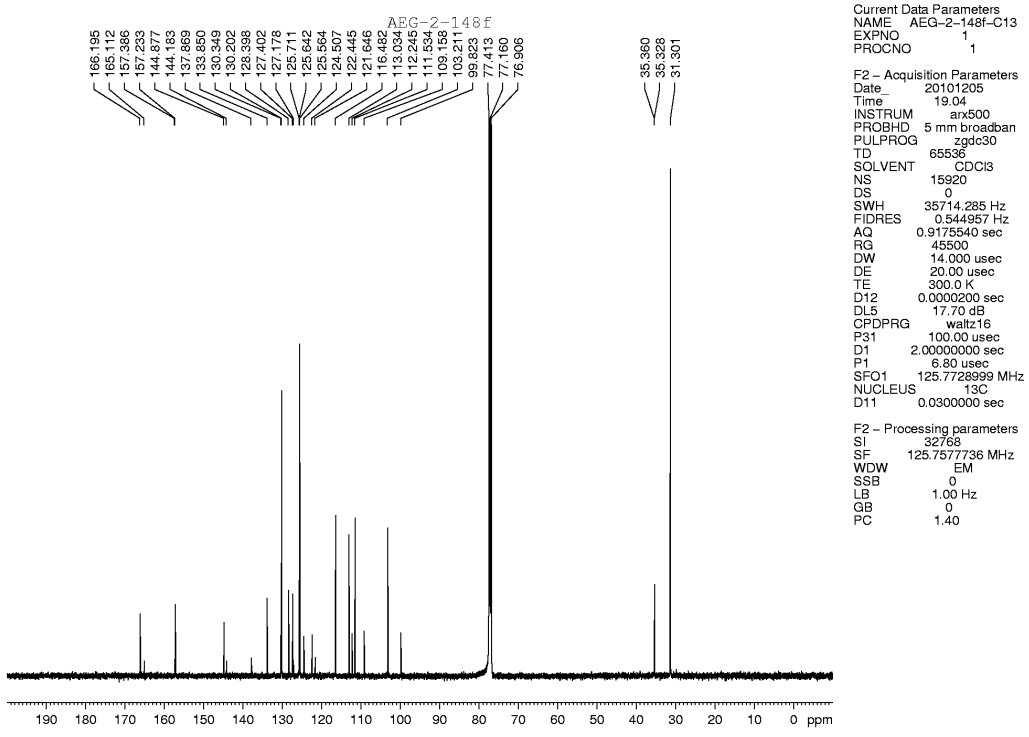



*Figure A2.15* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compounds **3.22a** and **3.22b**.

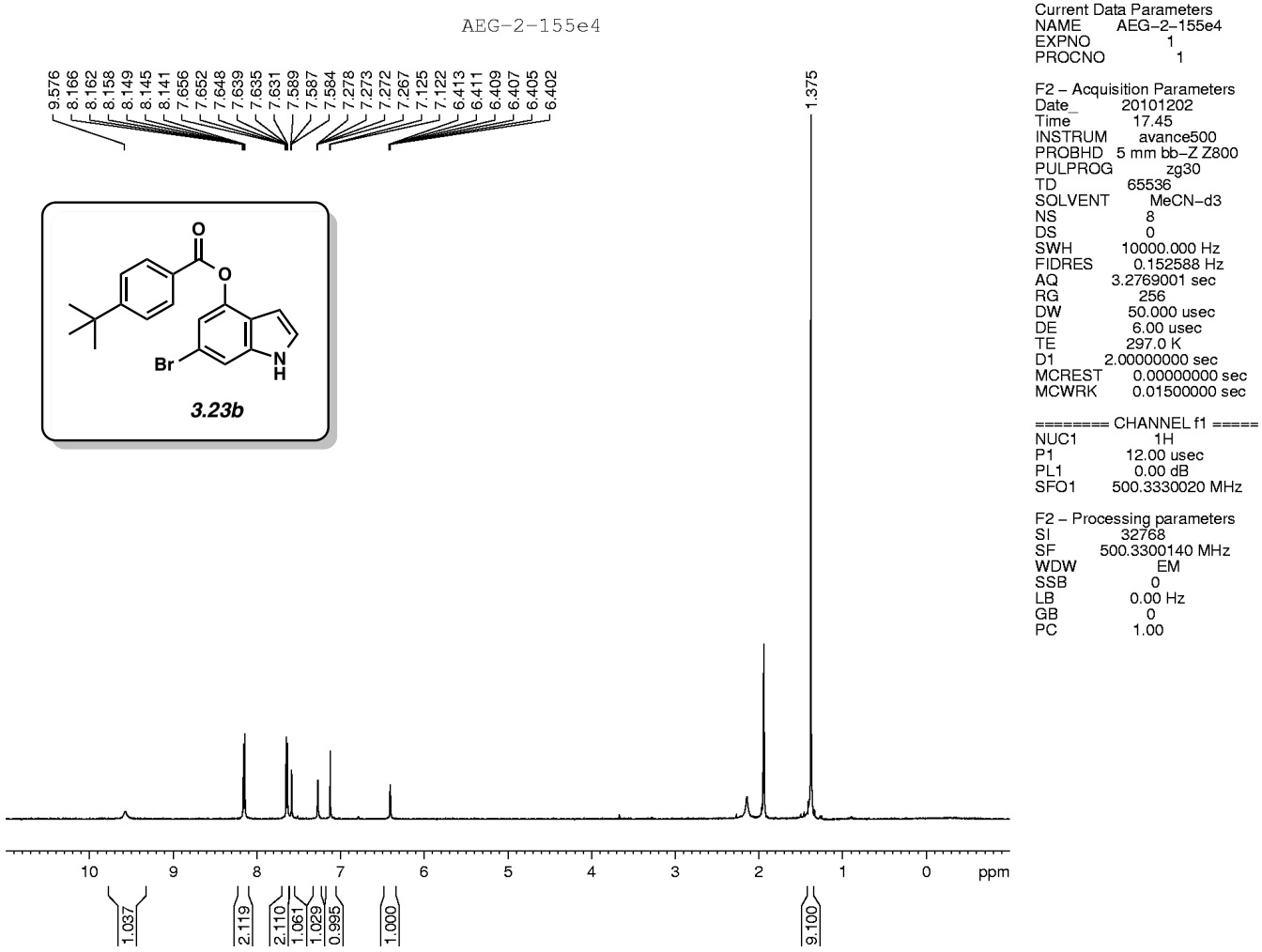



*Figure A2.16* $^{1}$H NMR (500 MHz, $CD_3CN$) of compound **3.23b**.

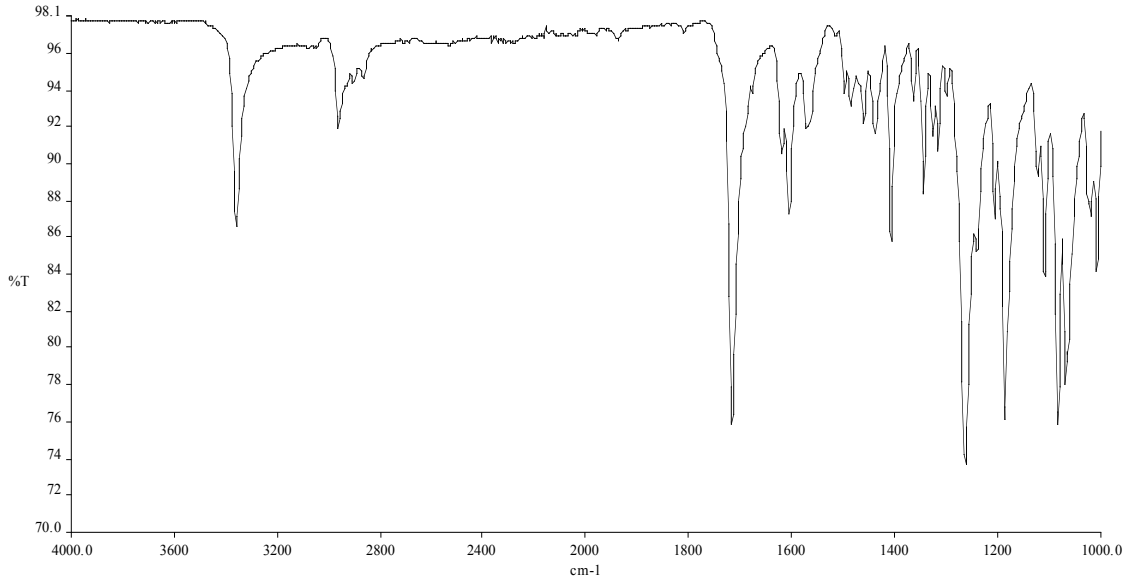



*Figure A2.17* Infrared spectrum of compound **3.23b**.

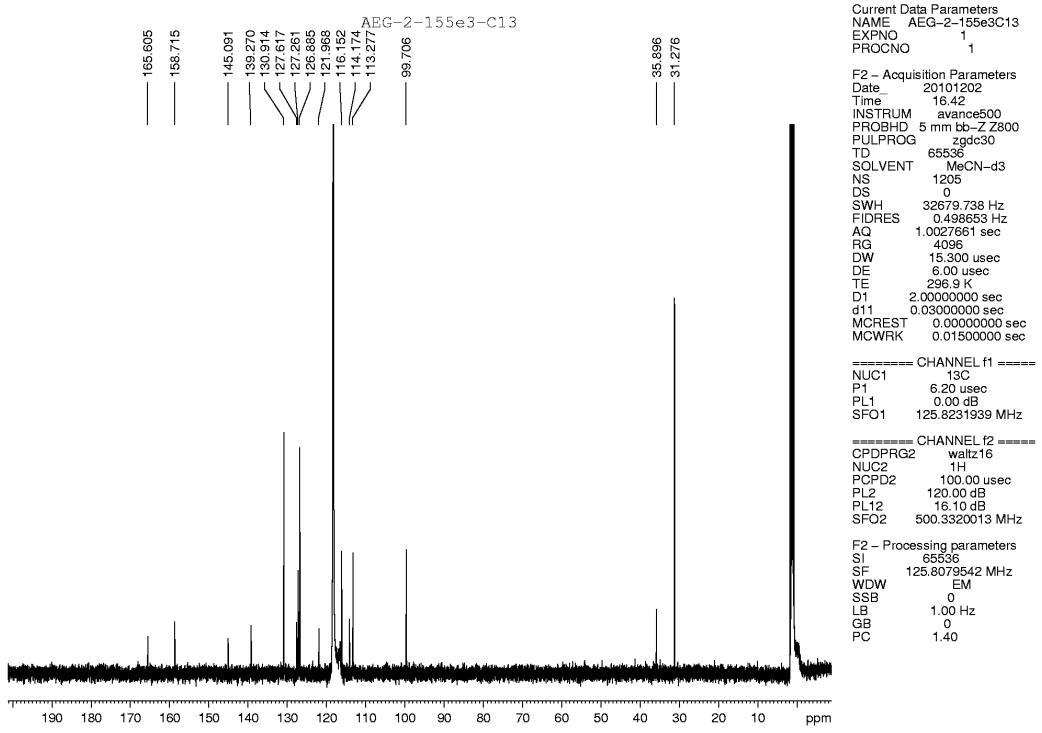



*Figure A2.18* $^{13}$C NMR (125 MHz, $CD_3CN$) of compound **3.23b**.

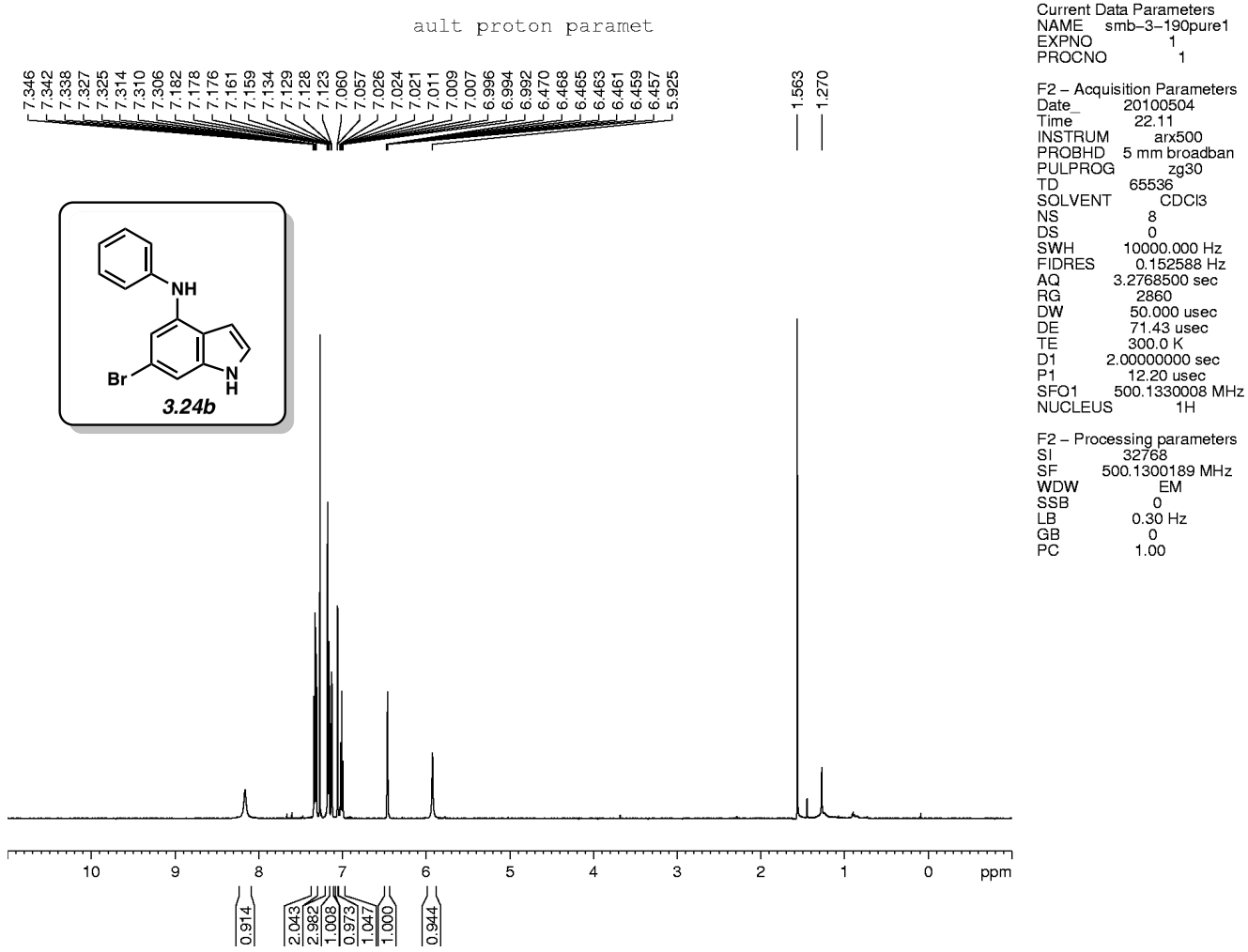



*Figure A2.19* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **3.24b**.

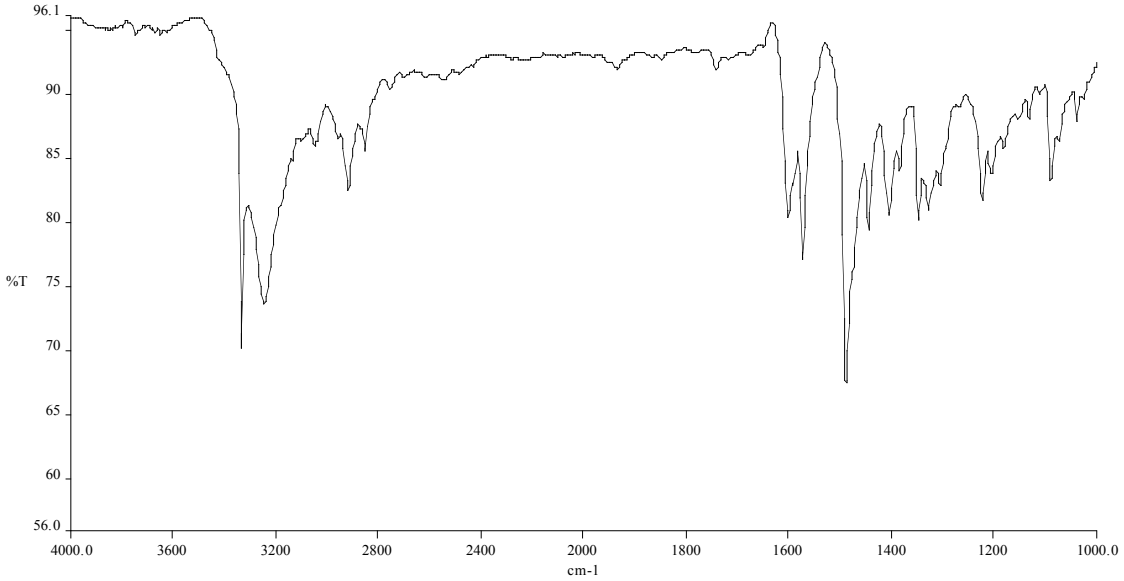



*Figure A2.20* Infrared spectrum of compound **3.24b**.

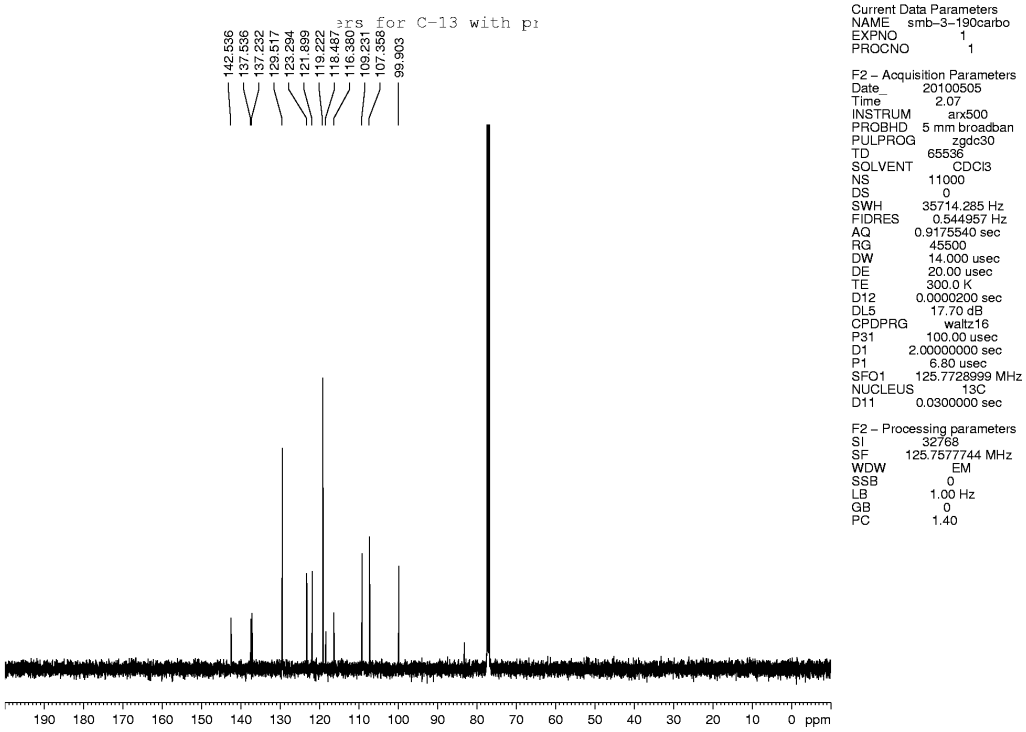



*Figure A2.21* $^{13}$C NMR (125 MHz, $CDCl_3$) of compound **3.24b**.

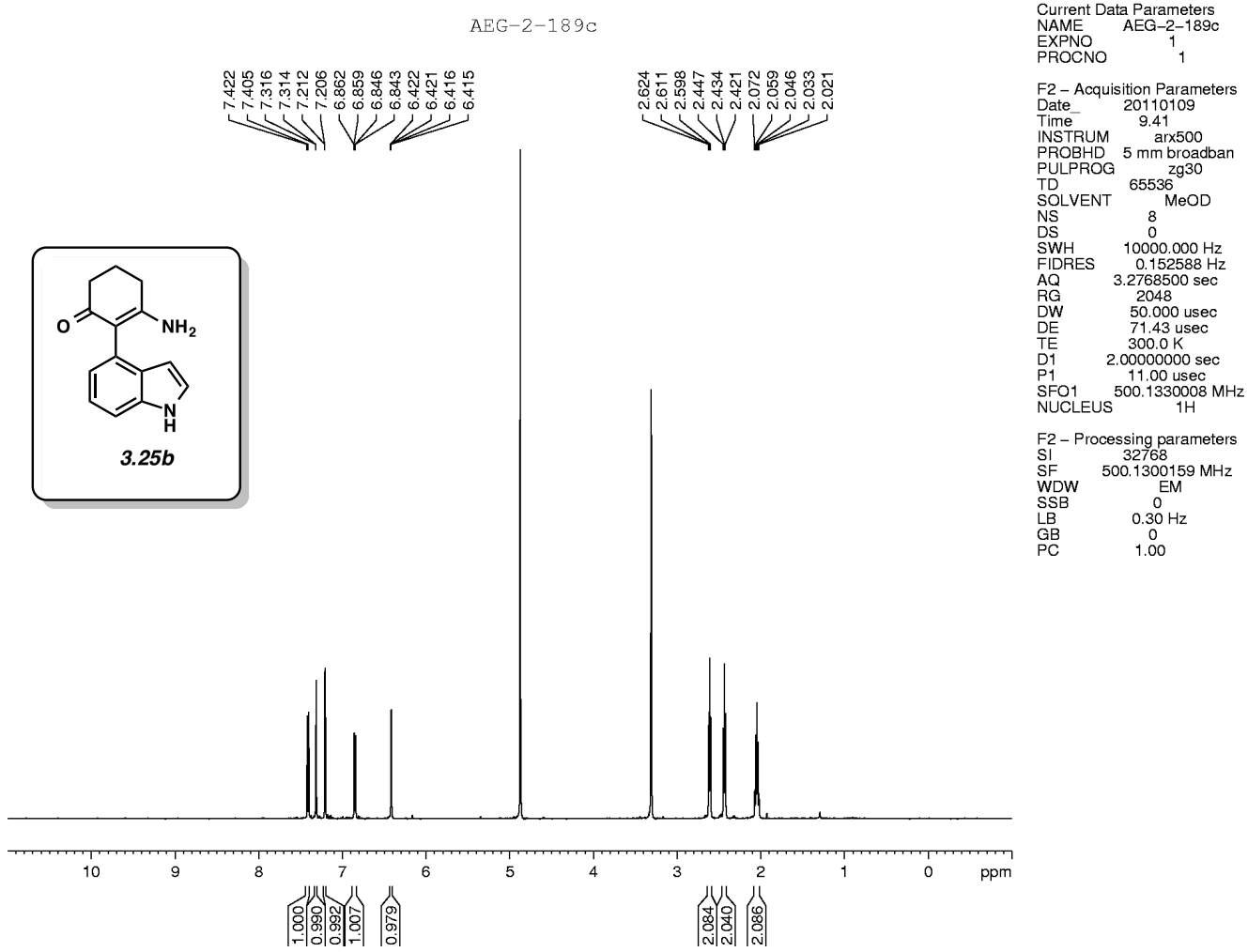



*Figure A2.22* $^{1}$H NMR (500 MHz, $CD_3OD$) of compound **3.25b**.

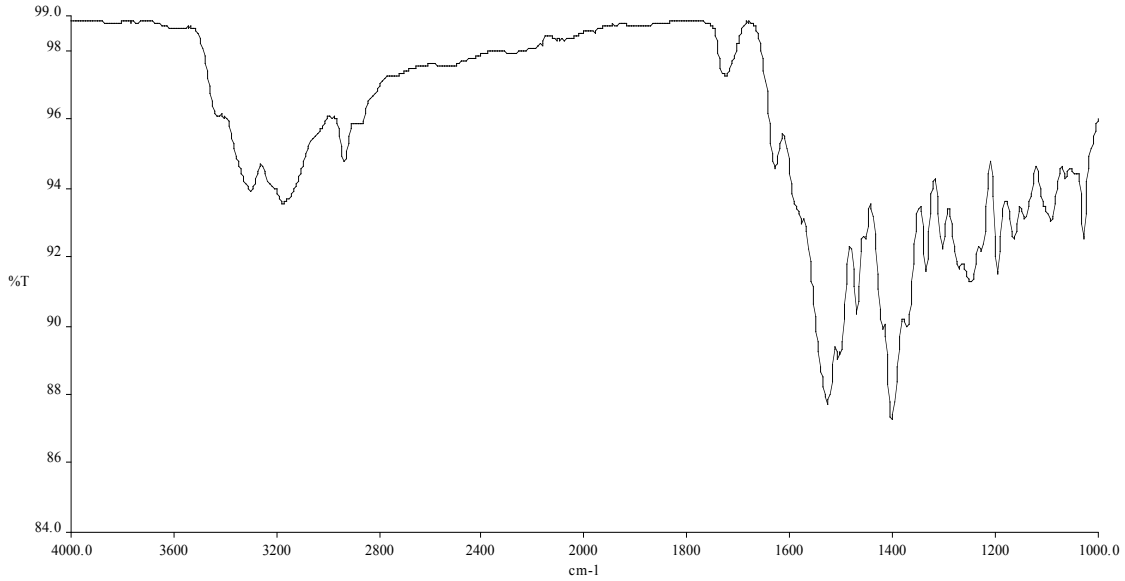



*Figure A2.23* Infrared spectrum of compound **3.25b**.

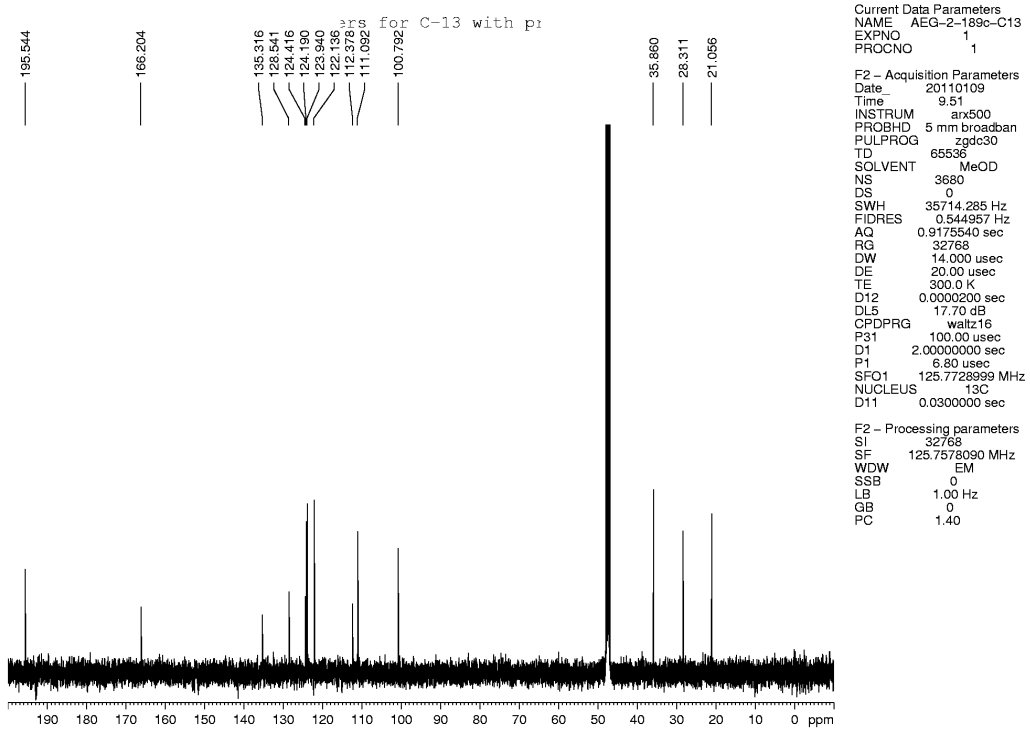



*Figure A2.24* $^{13}$C NMR (125 MHz, $CD_3OD$) of compound **3.25b**.

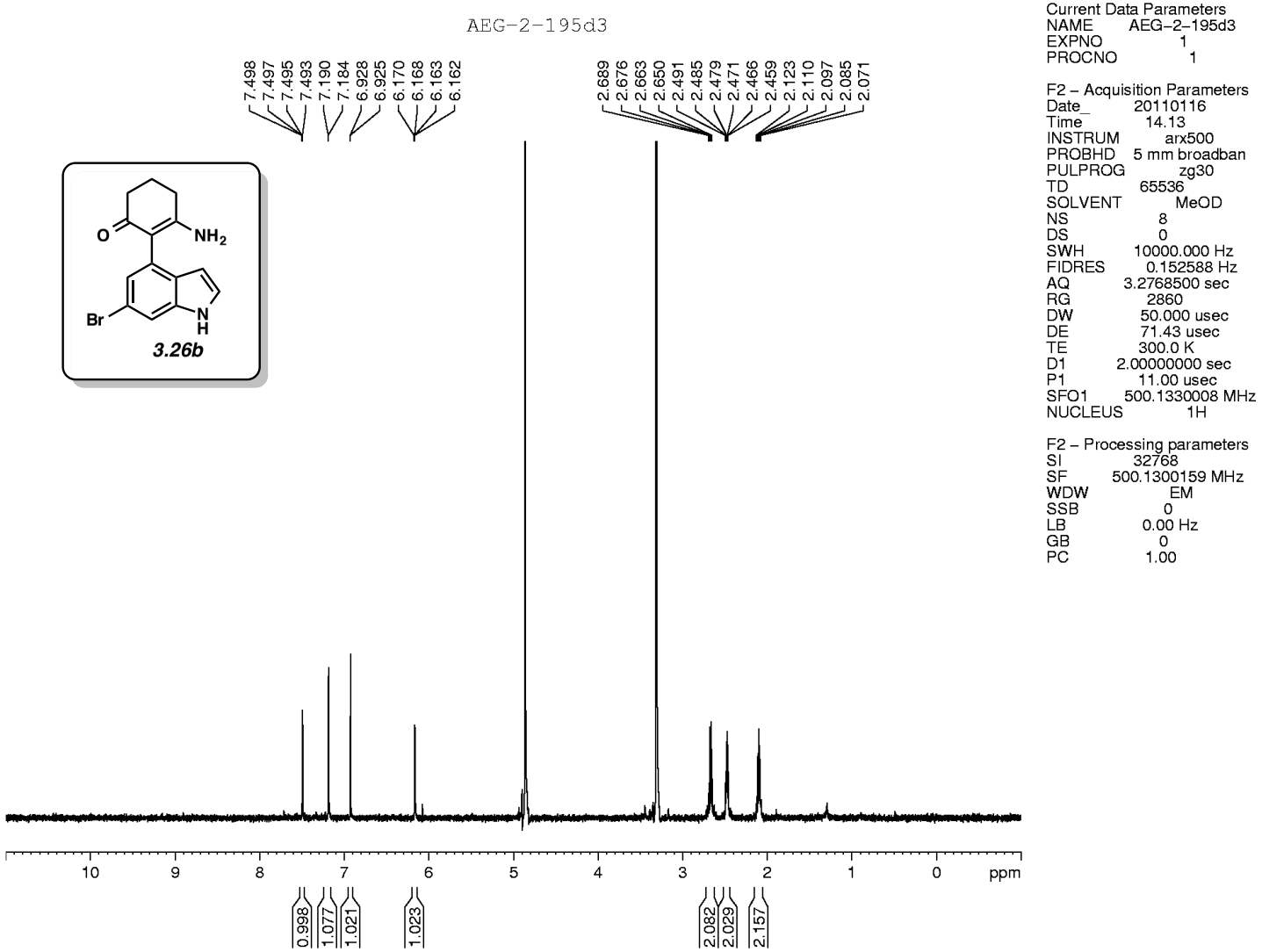



*Figure A2.25* $^{1}$H NMR (500 MHz, $CD_3OD$) of compound **3.26b**.

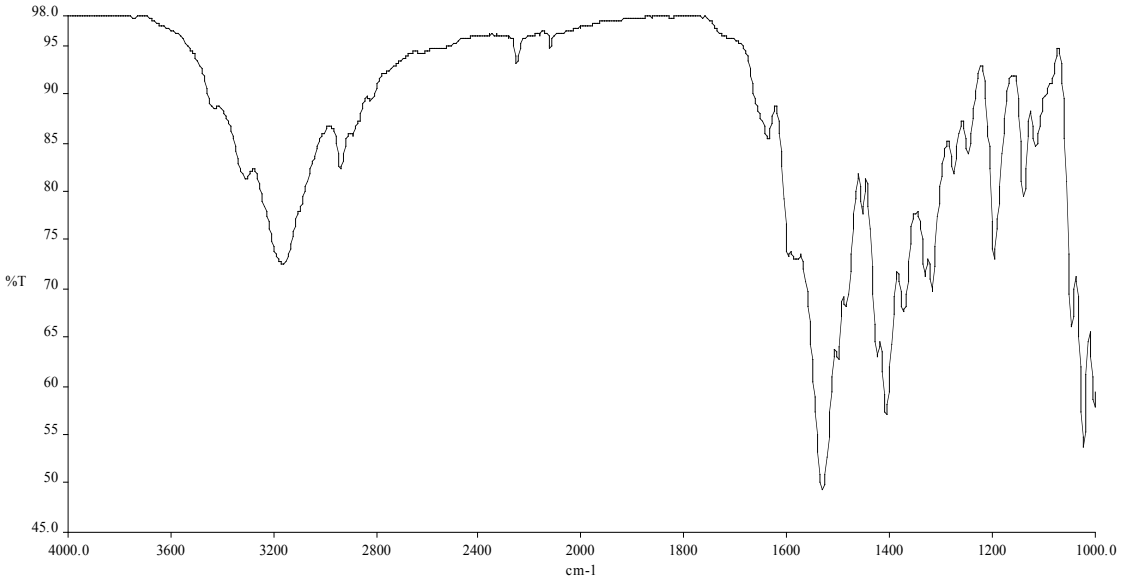



*Figure A2.26* Infrared spectrum of compound **3.26b**.

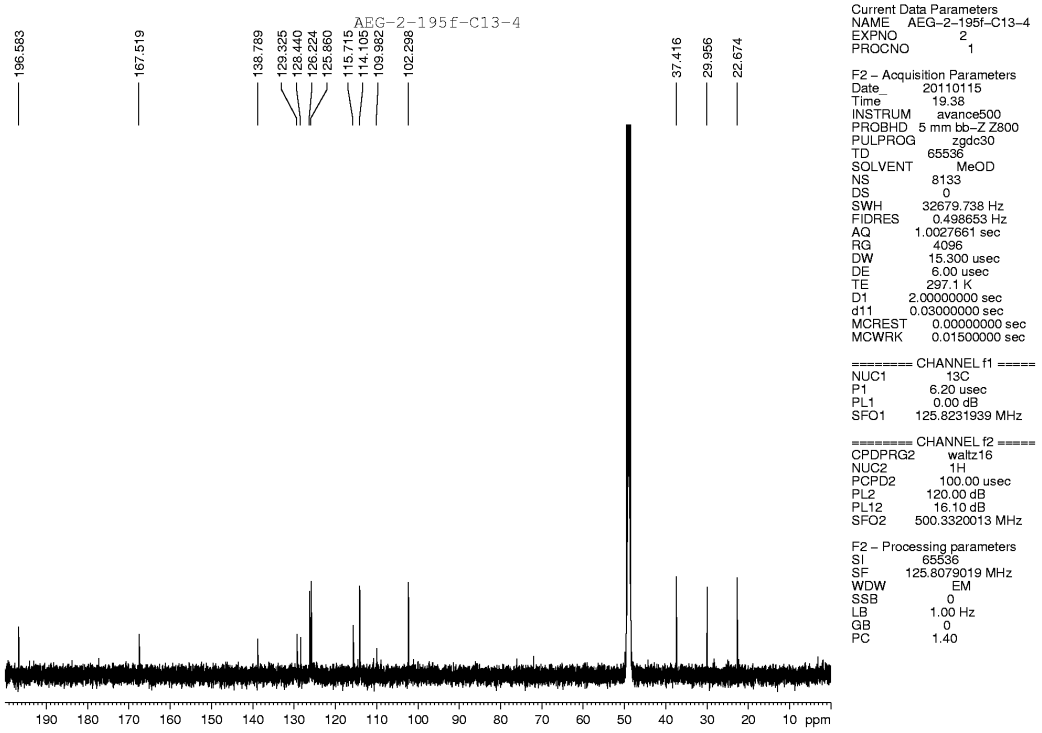



*Figure A2.27* $^{13}$C NMR (125 MHz, $CD_3OD$) of compound **3.26b**.

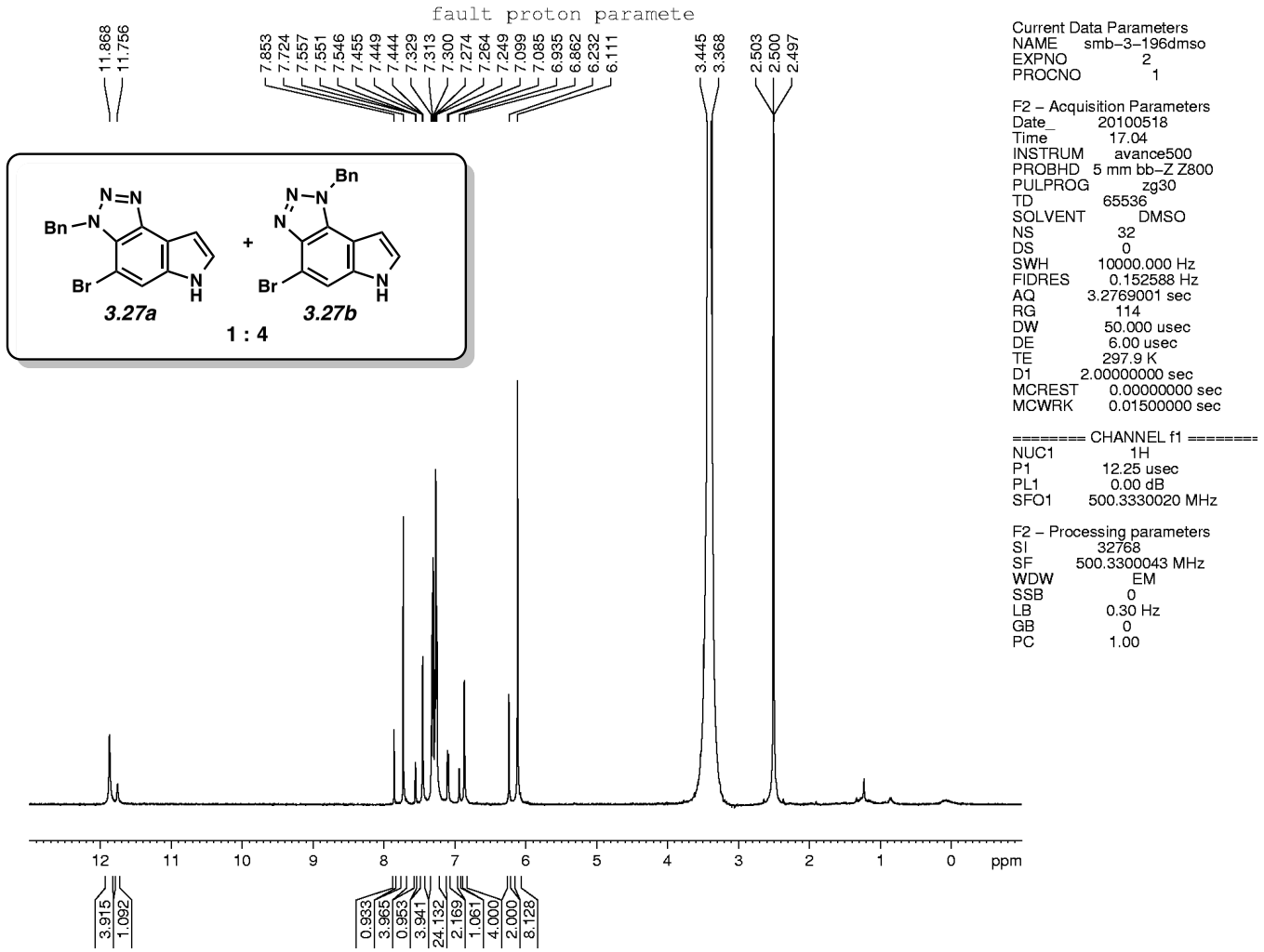



*Figure A2.28* $^{1}$H NMR (500 MHz, DMSO- $d_6$) of compounds **3.27a** and **3.27b**.

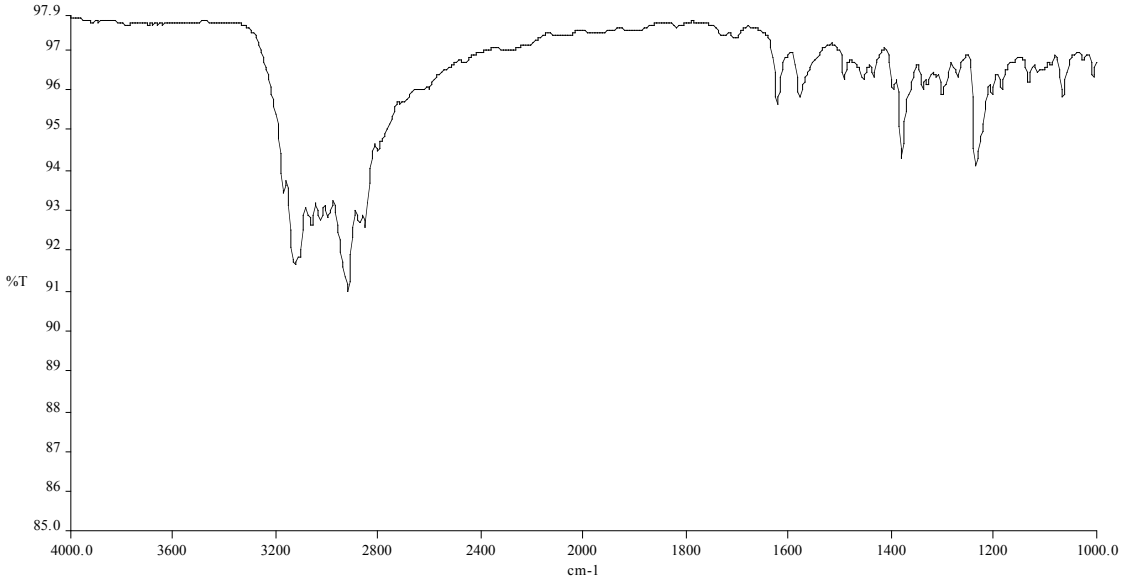



*Figure A2.29* Infrared spectrum of compounds **3.27a** and **3.27b**.

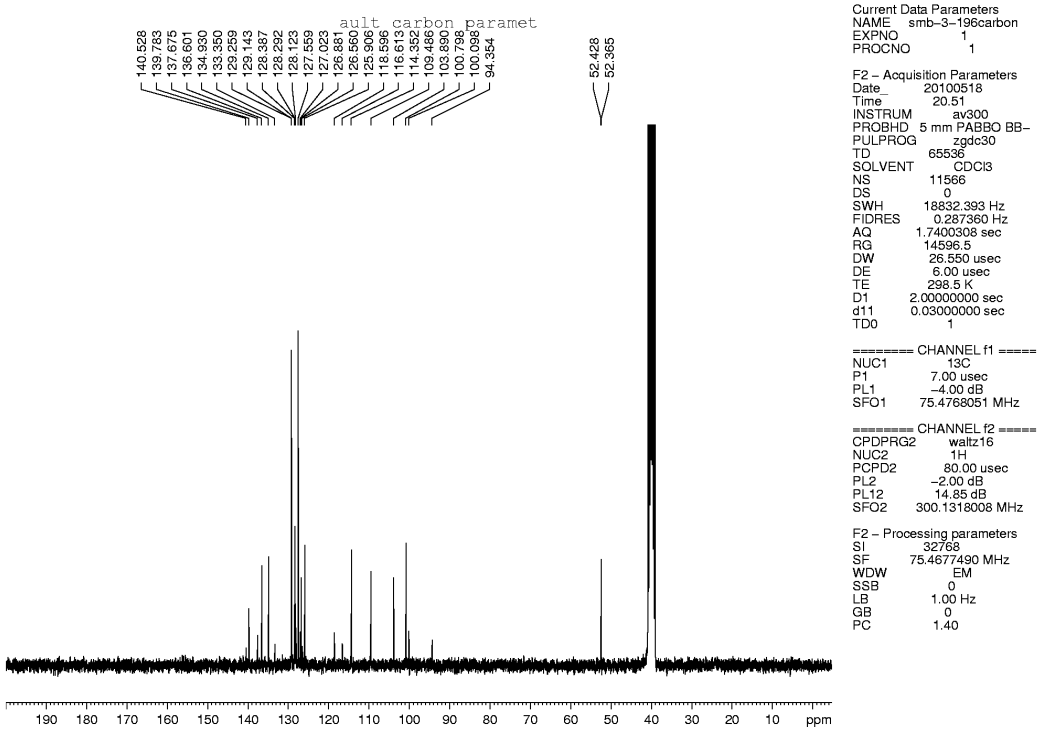



*Figure A2.30* $^{13}$C NMR (75 MHz, $d_6$-DMSO) of compounds **3.27a** and **3.27b**.

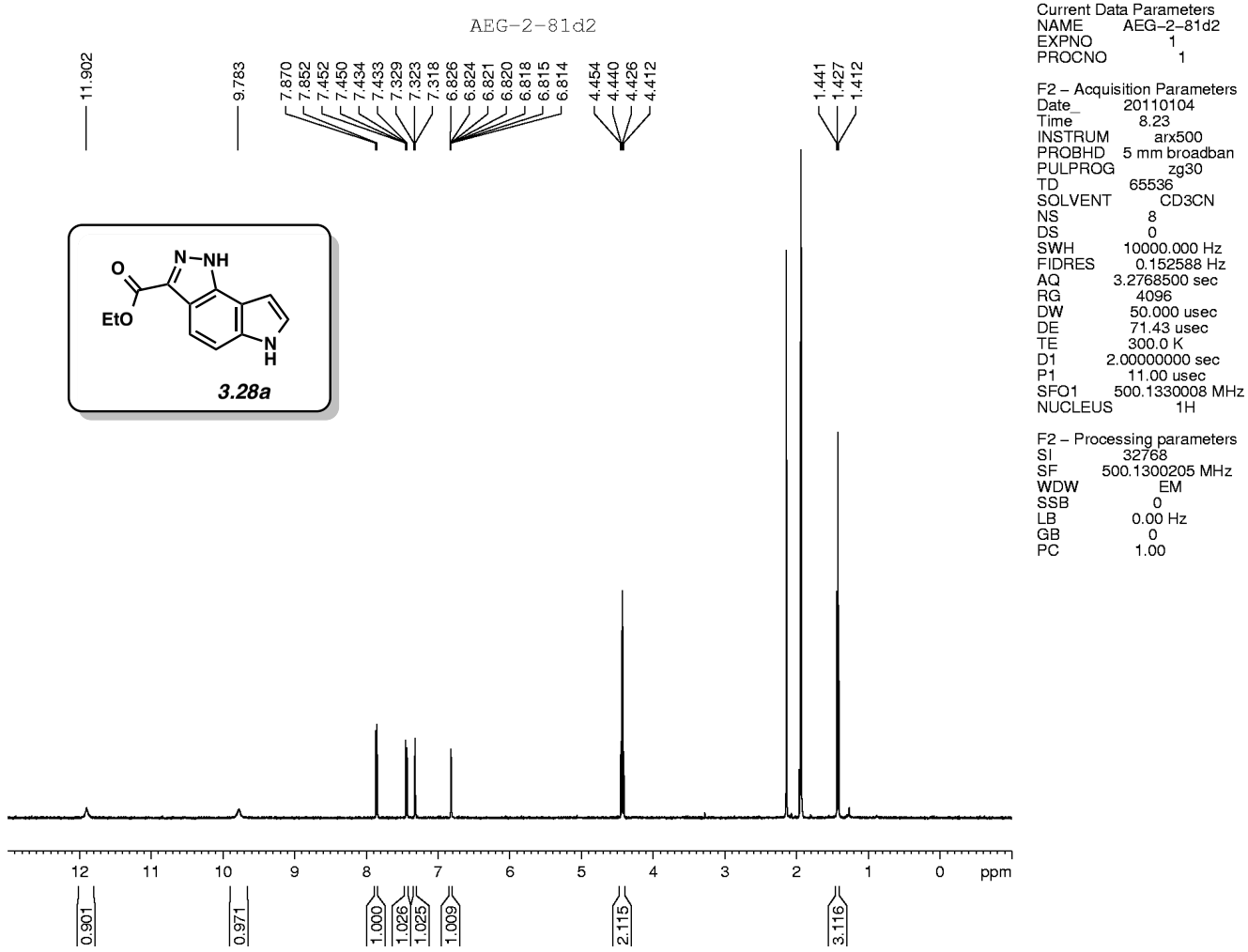



*Figure A2.31* $^{1}$H NMR (500 MHz, $CD_3CN$) of compound **3.28a**.

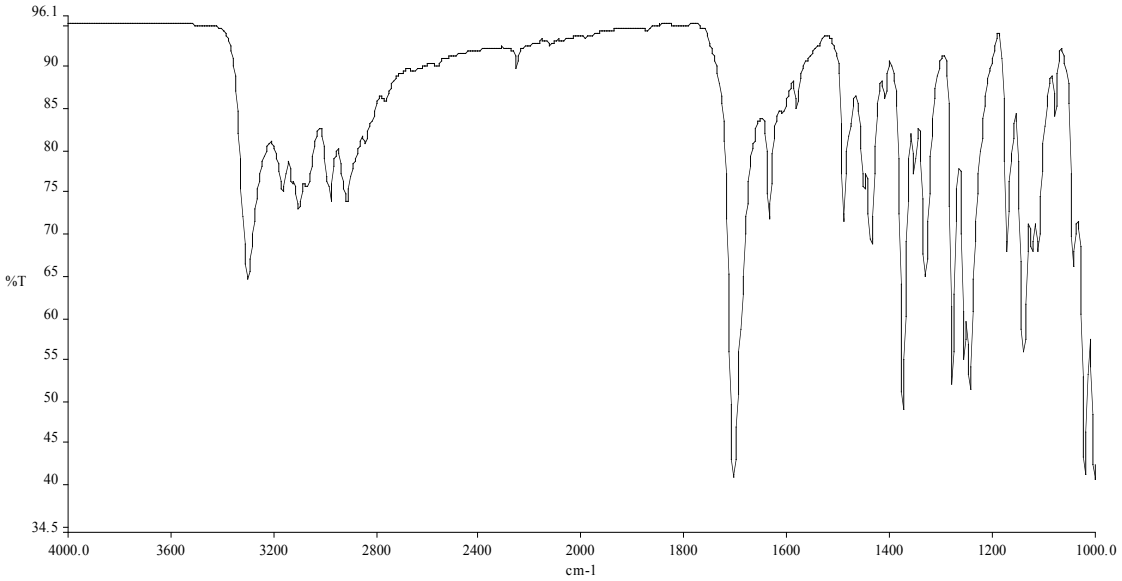



*Figure A2.32* Infrared spectrum of compound **3.28a**.

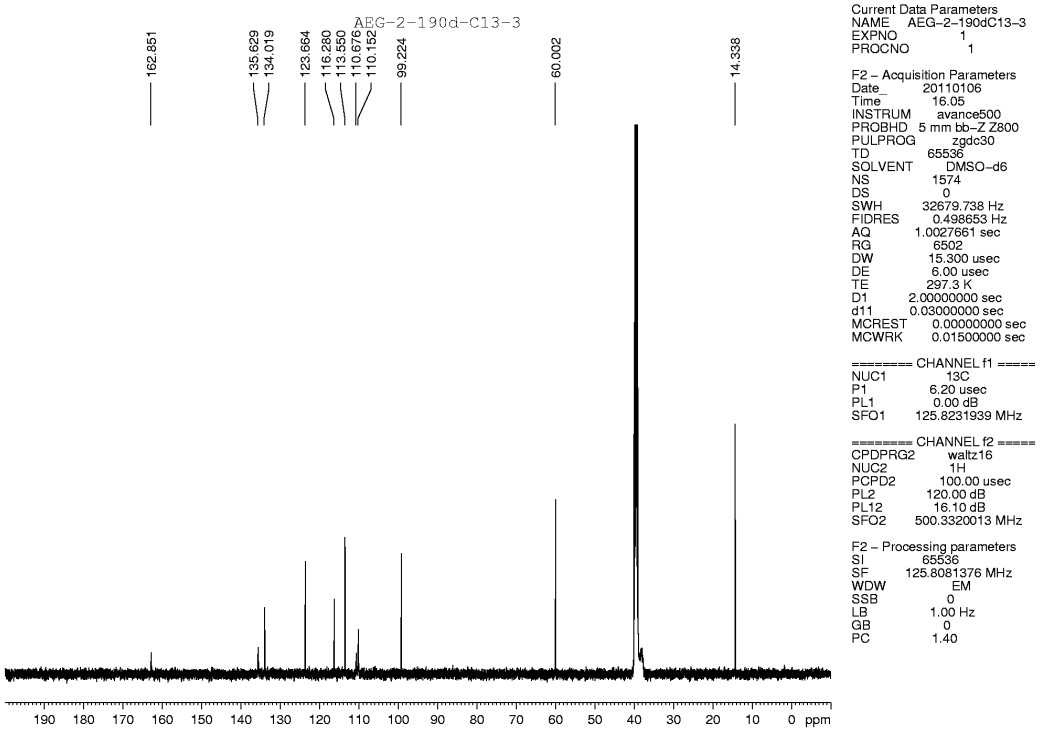



*Figure A2.33* $^{13}$C NMR (125 MHz, DMSO-$d_6$) of compound **3.28a**.

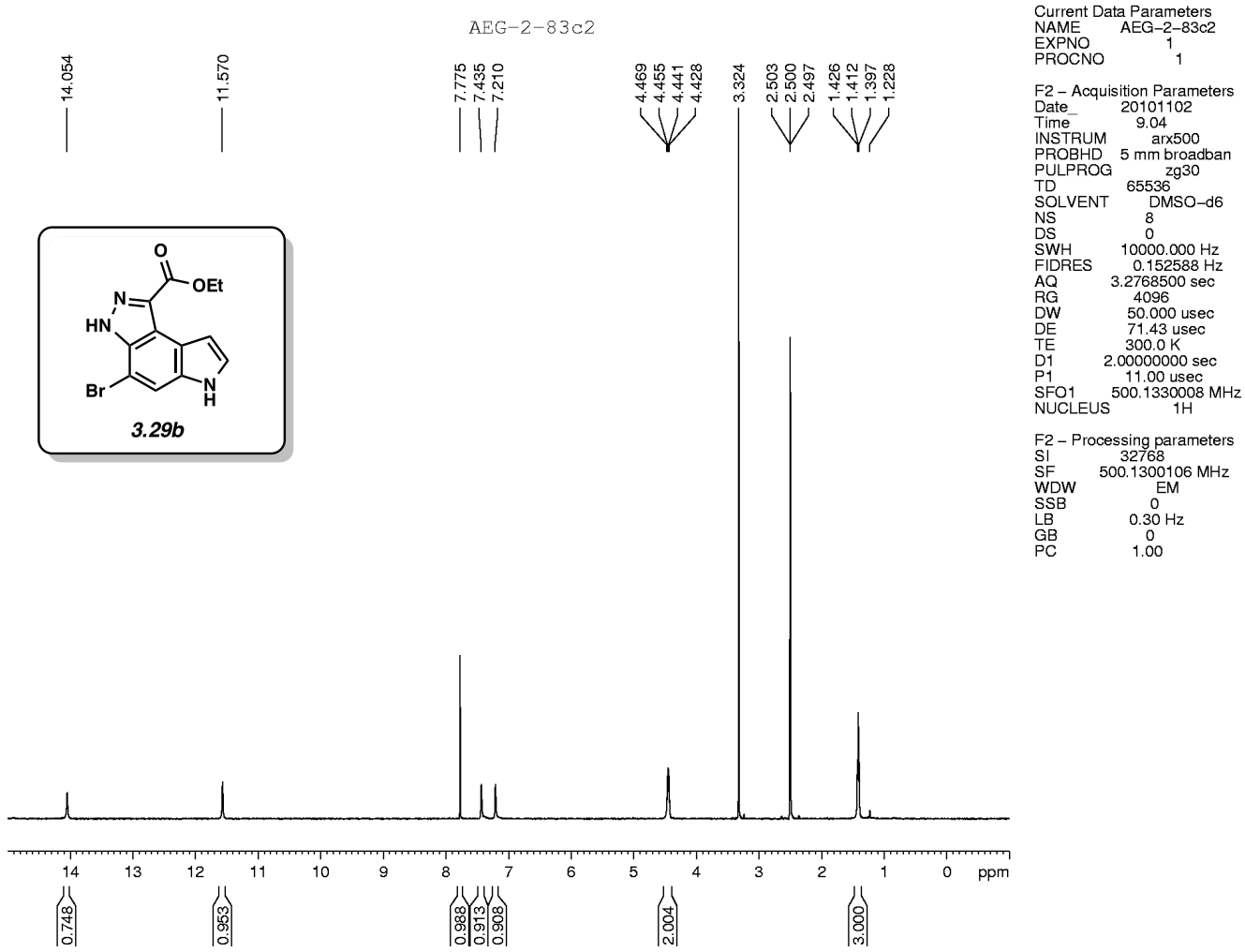



*Figure A2.34* $^{1}$H NMR (500 MHz, DMSO- $d_6$) of compound **3.29b**.

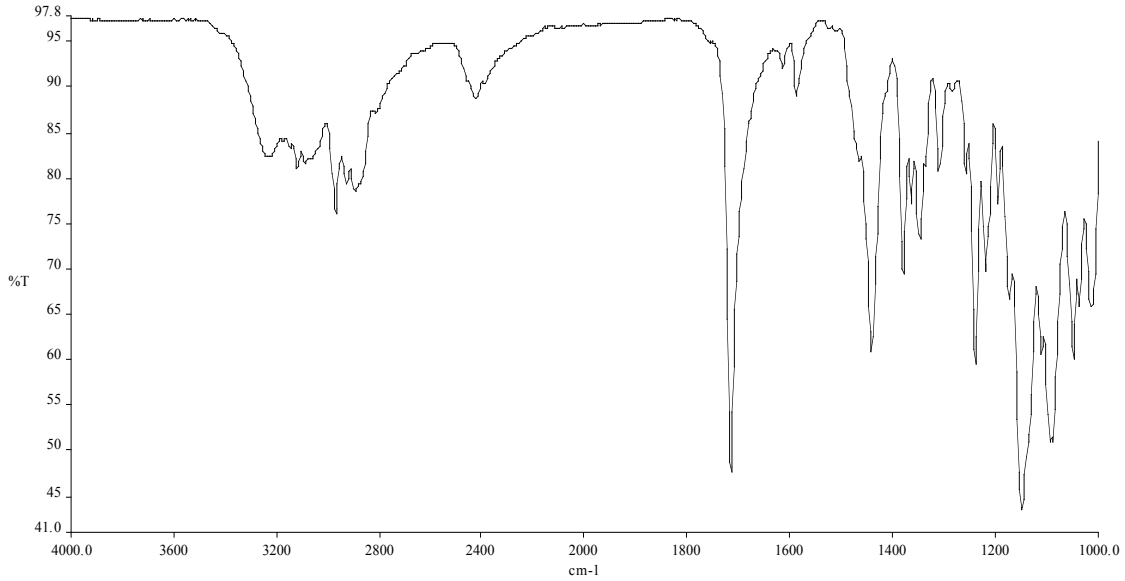



*Figure A2.35* Infrared spectrum of compound **3.29b**.

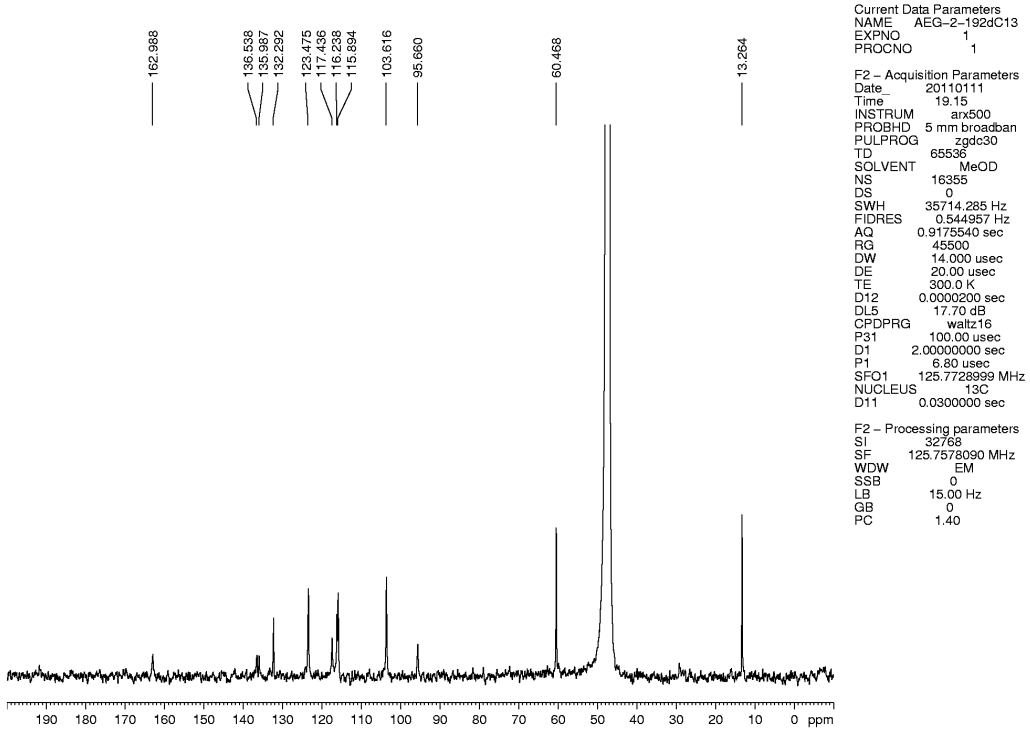



*Figure A2.36* $^{13}$C NMR (125 MHz, $CD_3OD$) of compound **3.29b**.

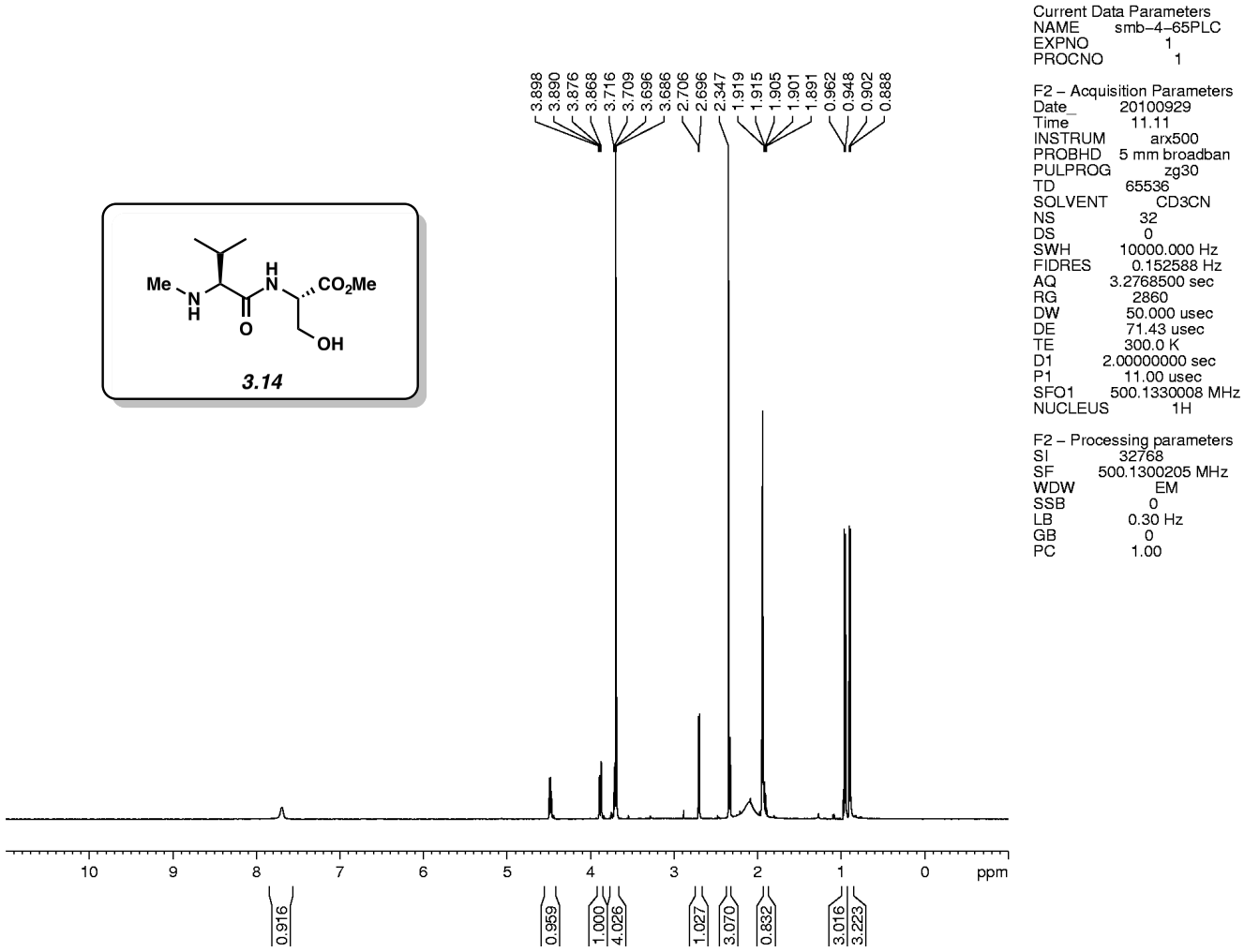



*Figure A2.37* $^{1}$H NMR (500 MHz, $CD_3CN$) of compound **3.14**.

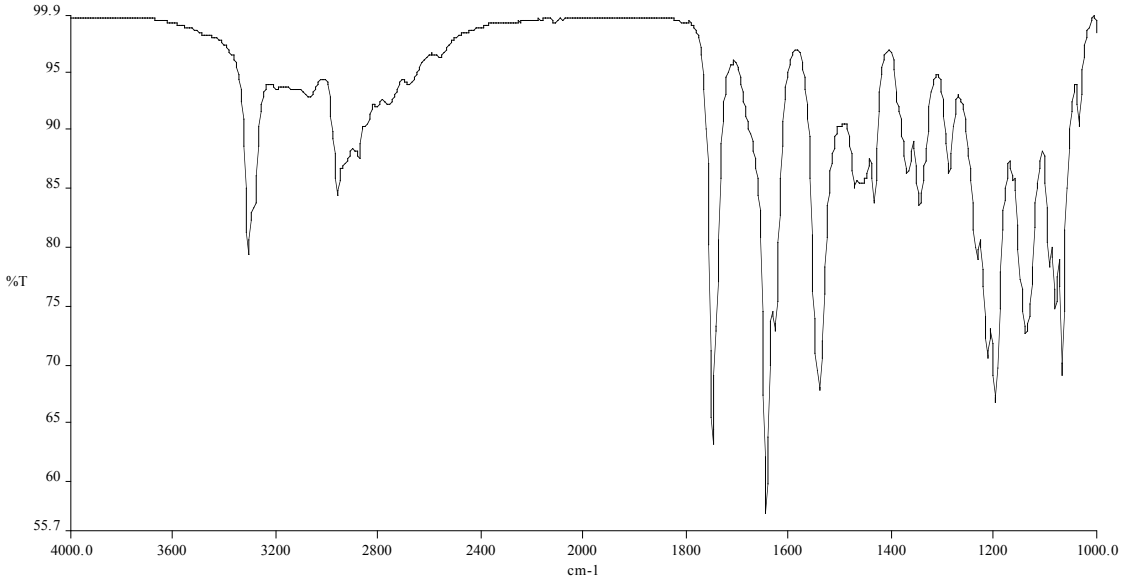



*Figure A2.38* Infrared spectrum of compound **3.14**.

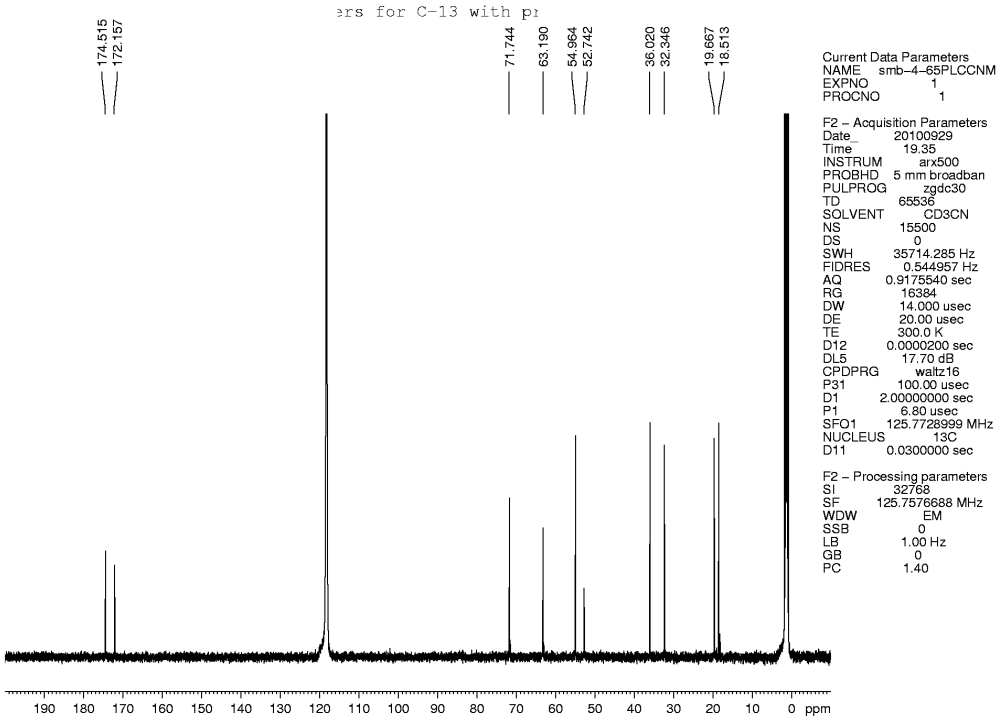



*Figure A2.39* $^{13}$C NMR (125 MHz, $CD_3CN$) of compound **3.14**.

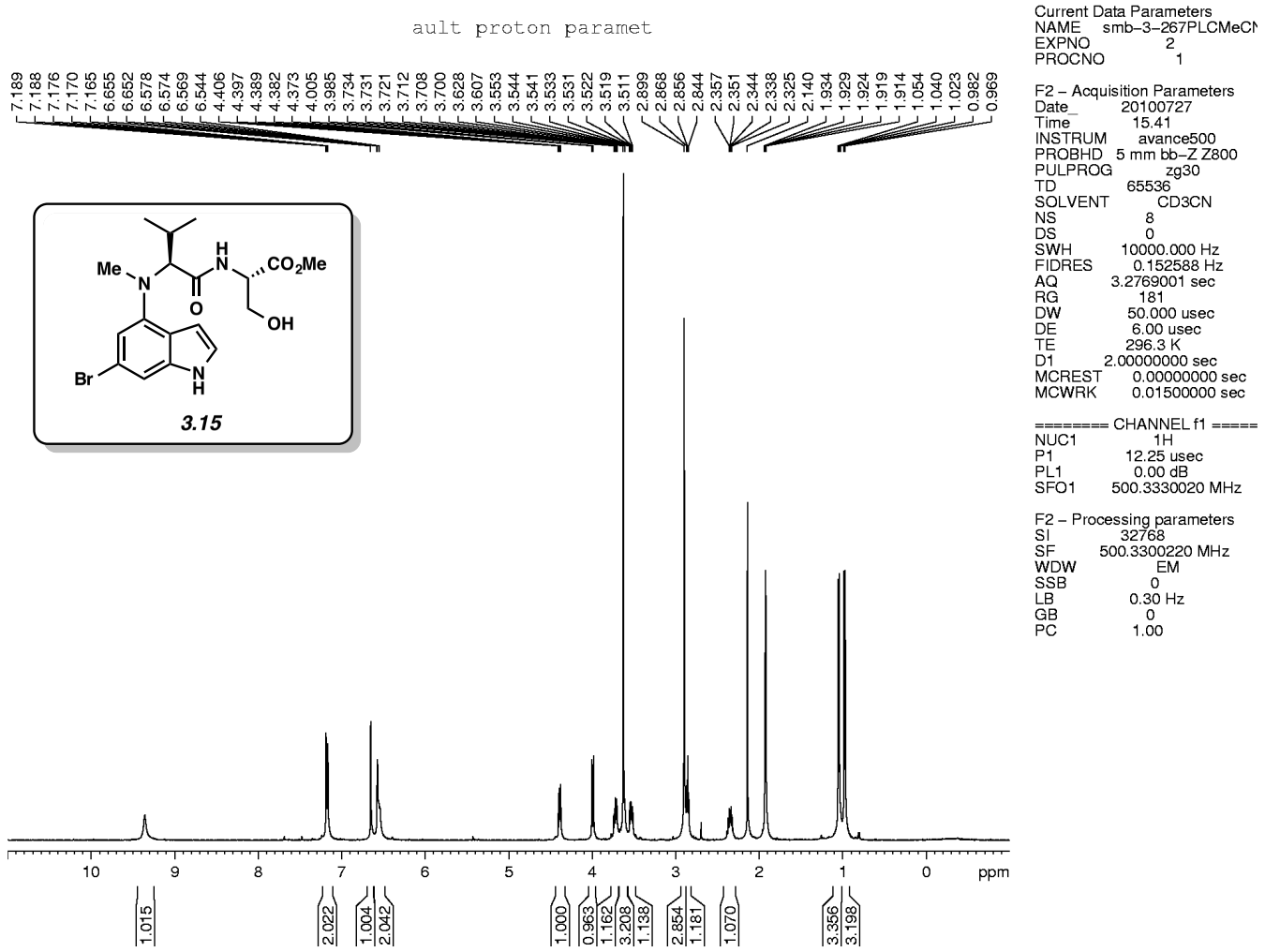



*Figure A2.40* $^{1}$H NMR (500 MHz, $CD_3CN$) of compound **3.15**.

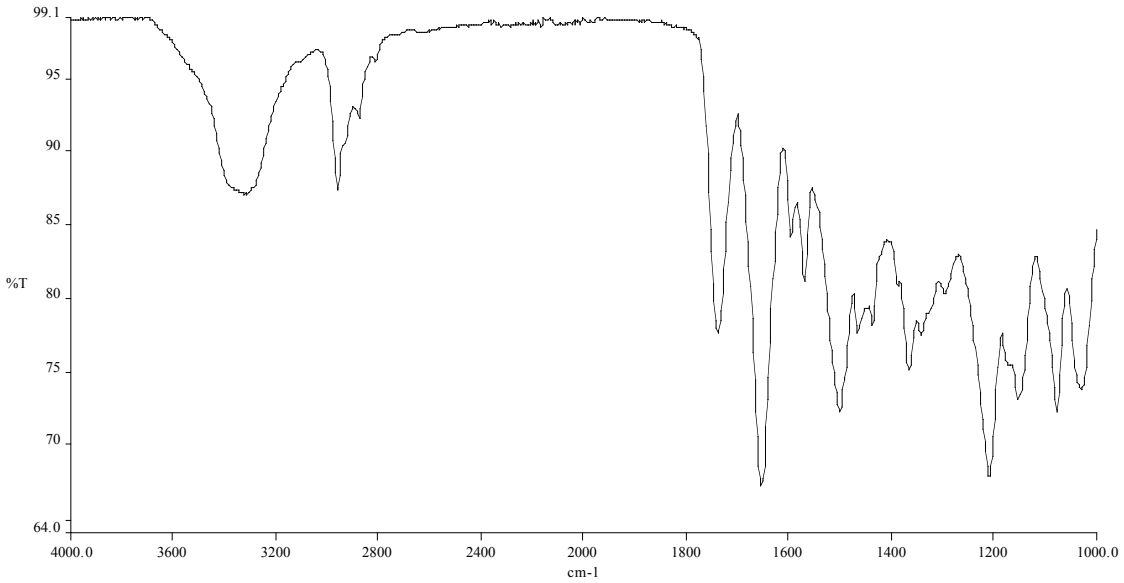



*Figure A2.41* Infrared spectrum of compound **3.15**.

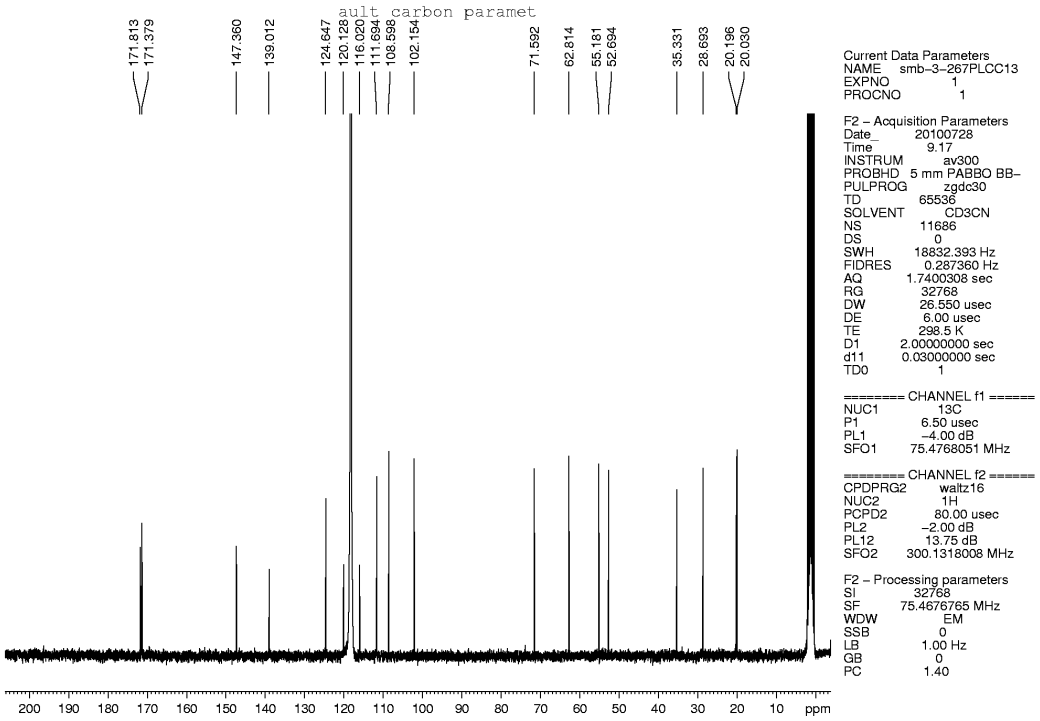



*Figure A2.42* $^{13}$C NMR (75 MHz, $CD_3CN$) of compound **3.15**.

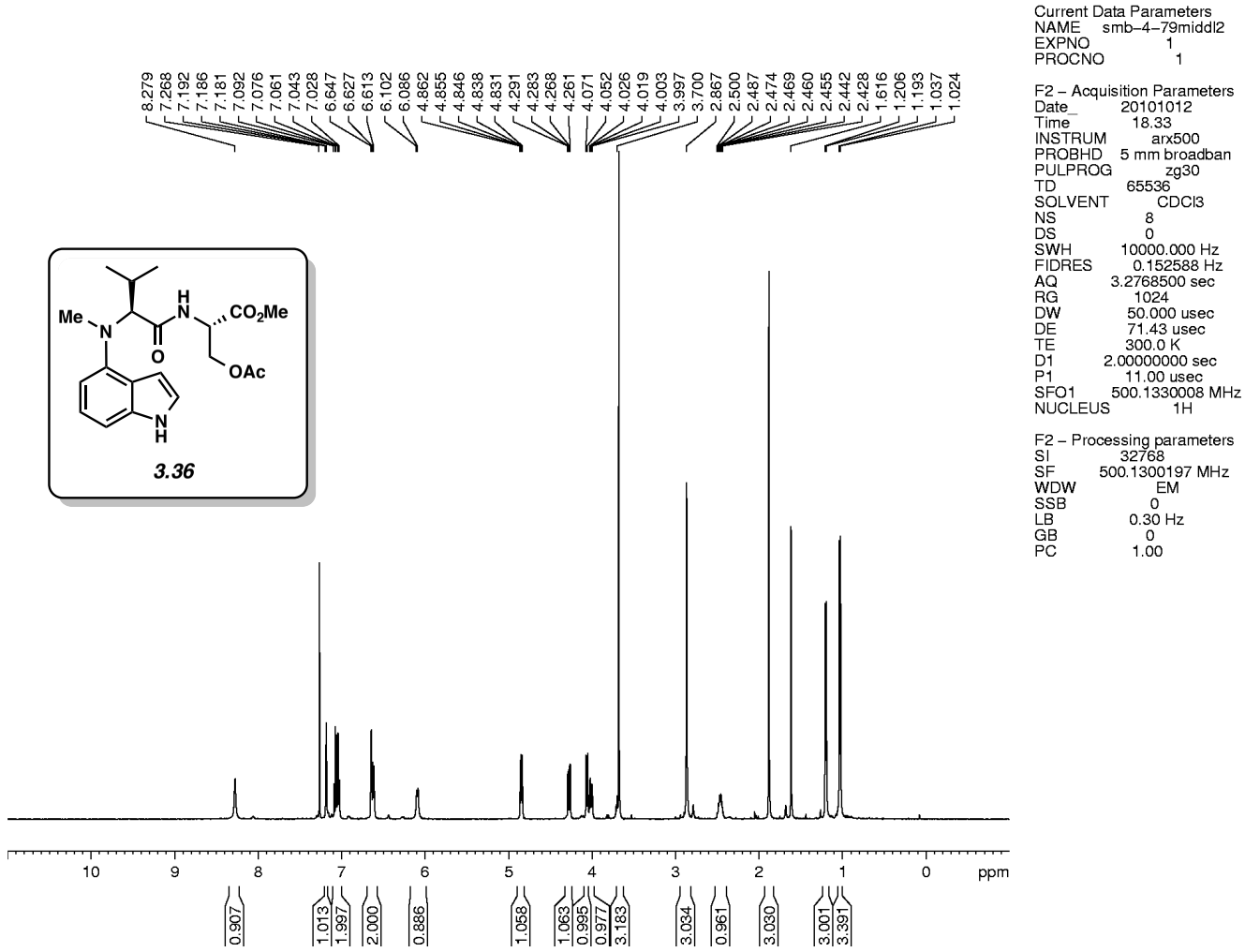



*Figure A2.43* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **3.36**.

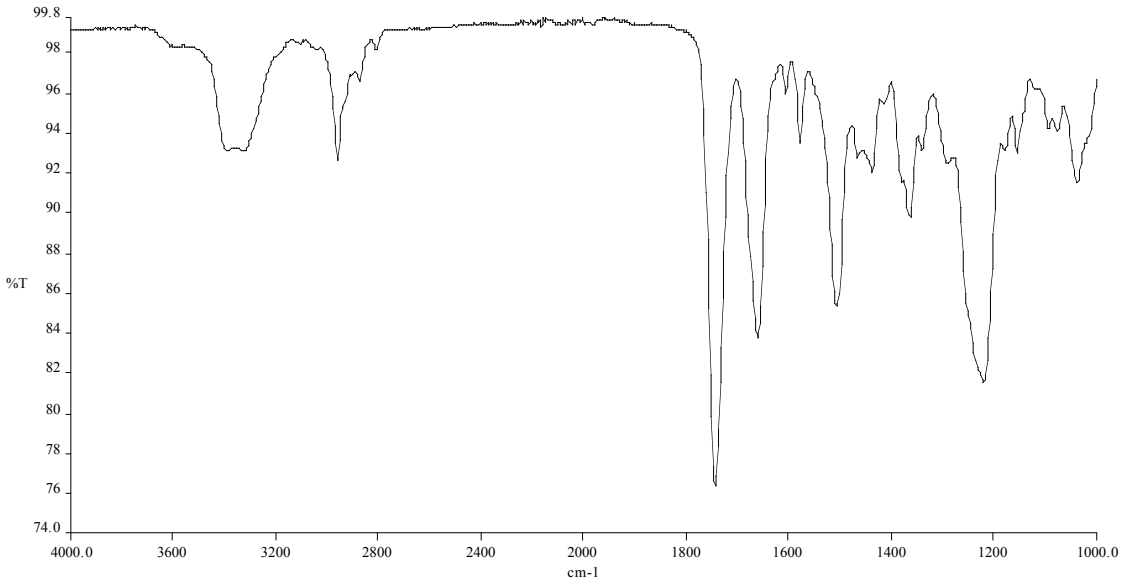



*Figure A2.44* Infrared spectrum of compound **3.36**.

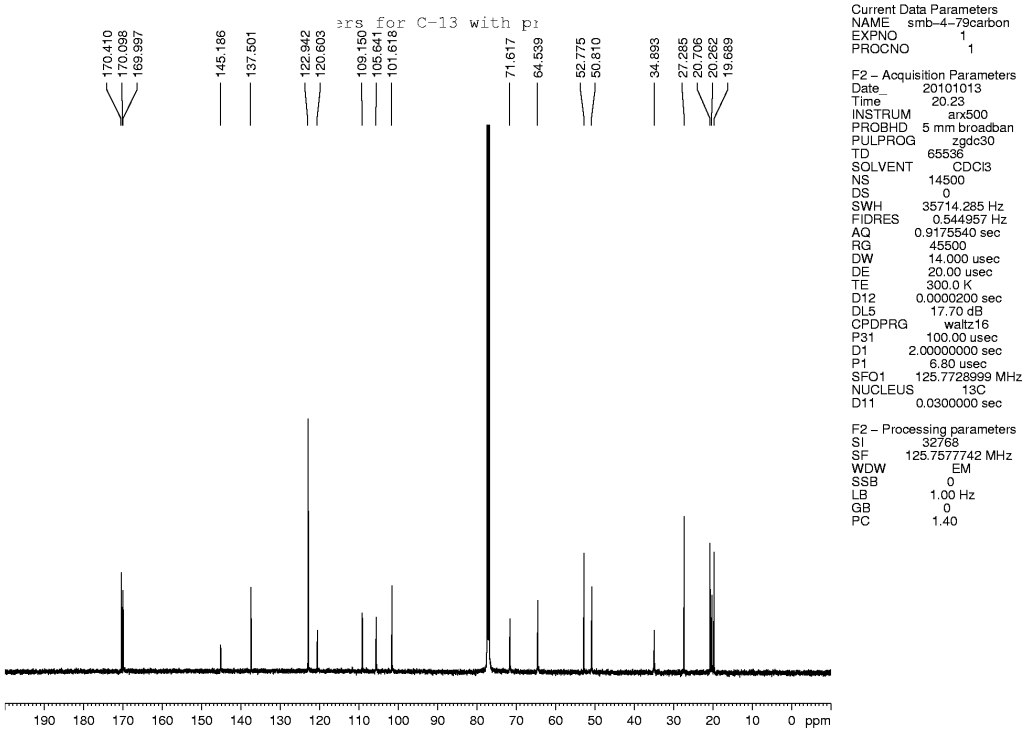



*Figure A2.45* $^{13}$C NMR (125 MHz, $CDCl_3$) of compound **3.36**.

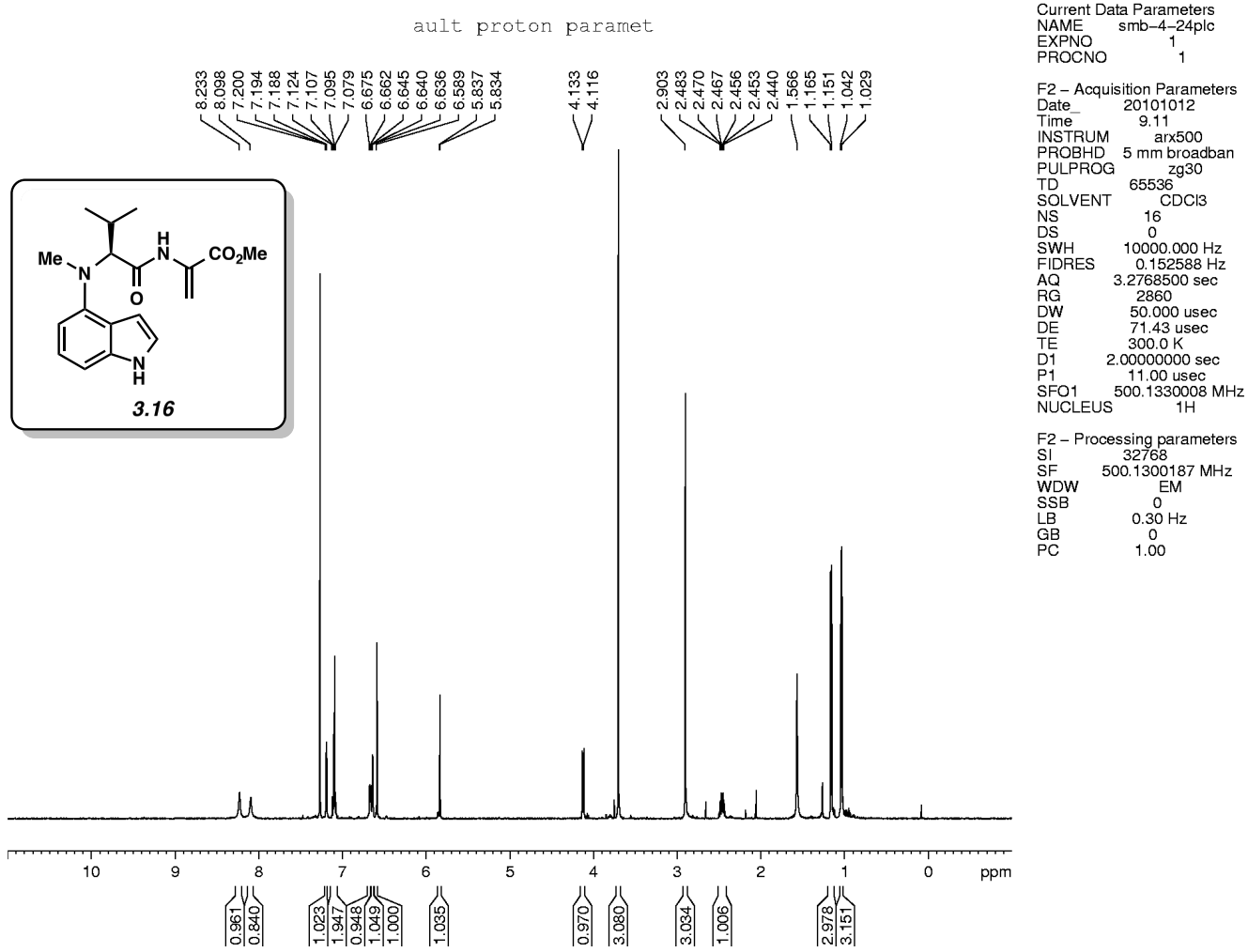



*Figure A2.46* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **3.16**.

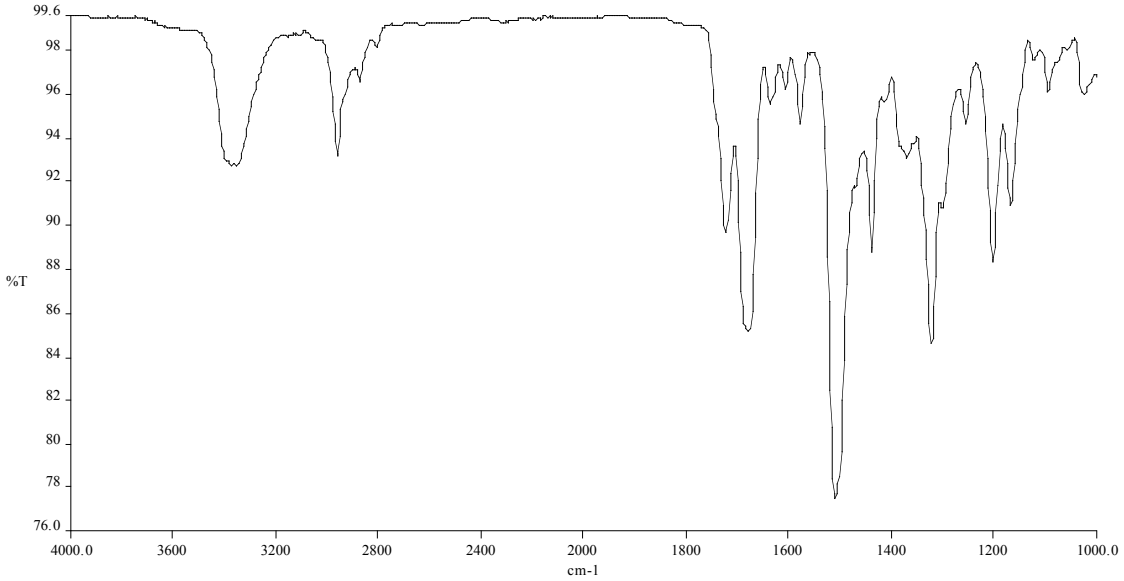



*Figure A2.47* Infrared spectrum of compound **3.16**.

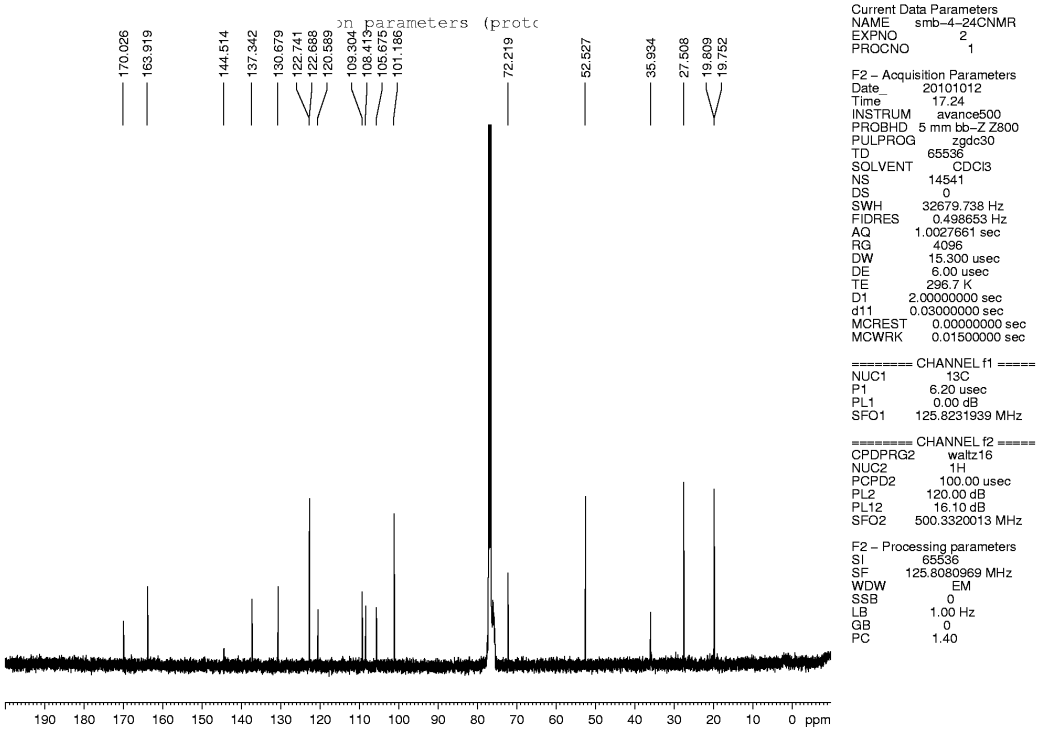



*Figure A2.48* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compound **3.16**.

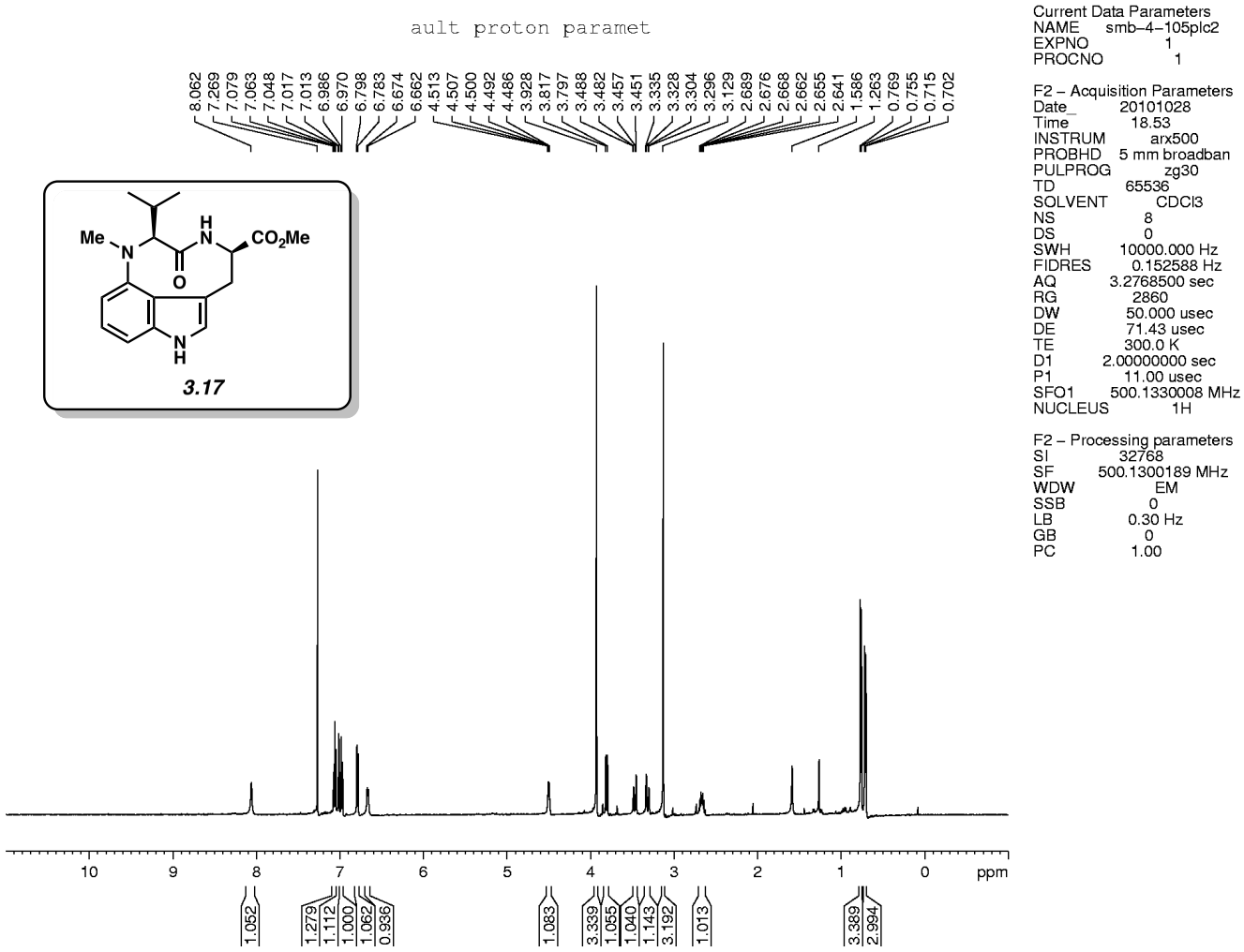



*Figure A2.49* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **3.17**.

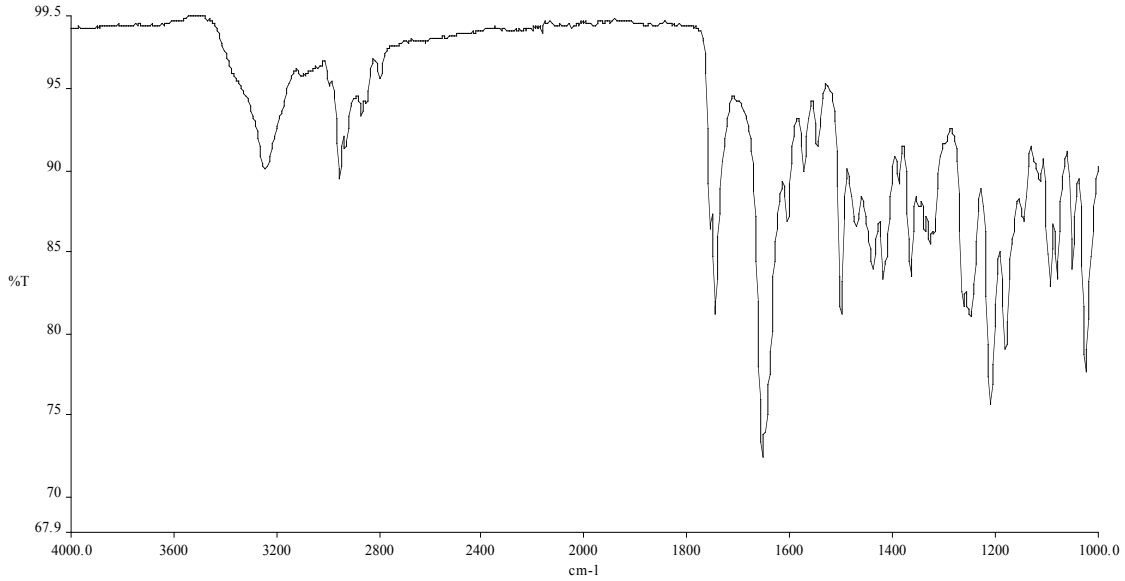



*Figure A2.50* Infrared spectrum of compound **3.17**.

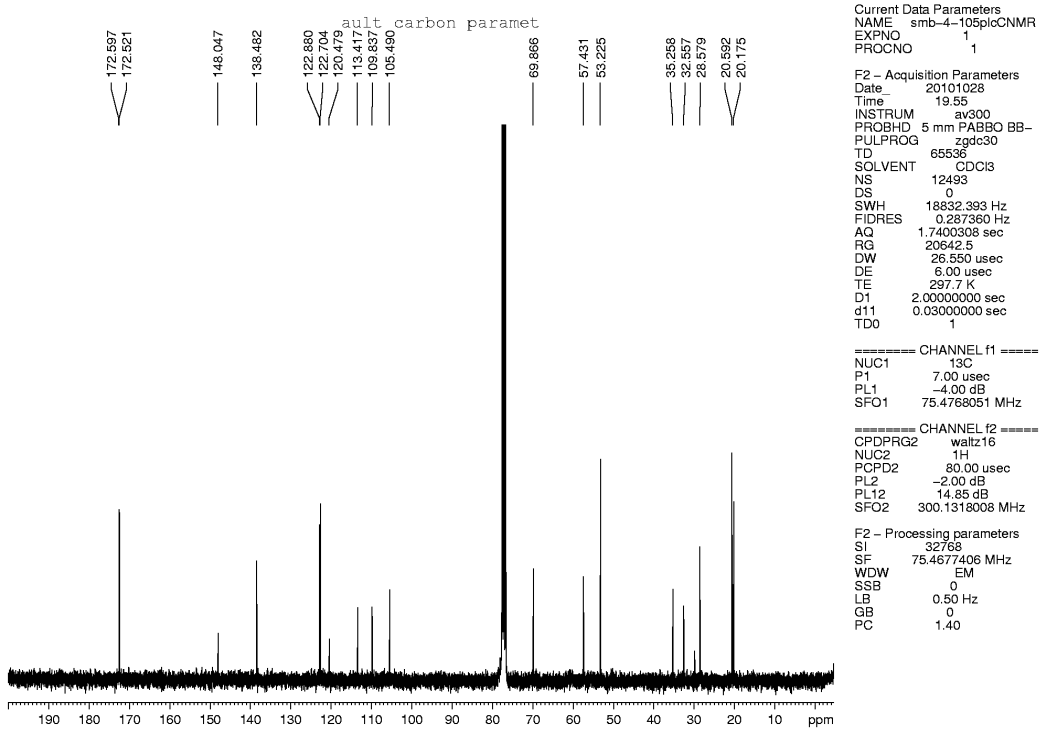



*Figure A2.51* $^{13}C$ NMR (75 MHz, $CDCl_3$) of compound **3.17**.

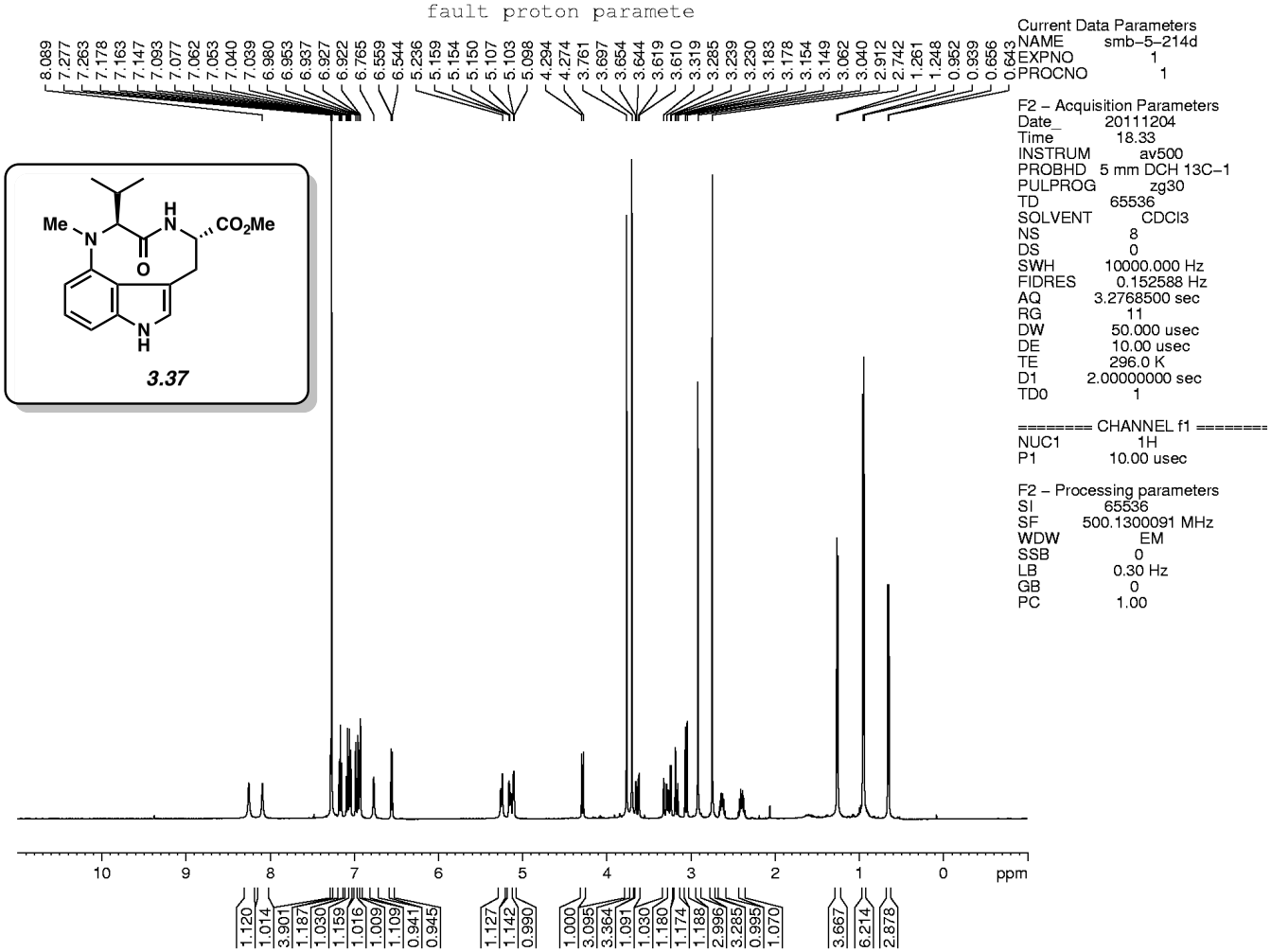



*Figure A2.52* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **3.37**.

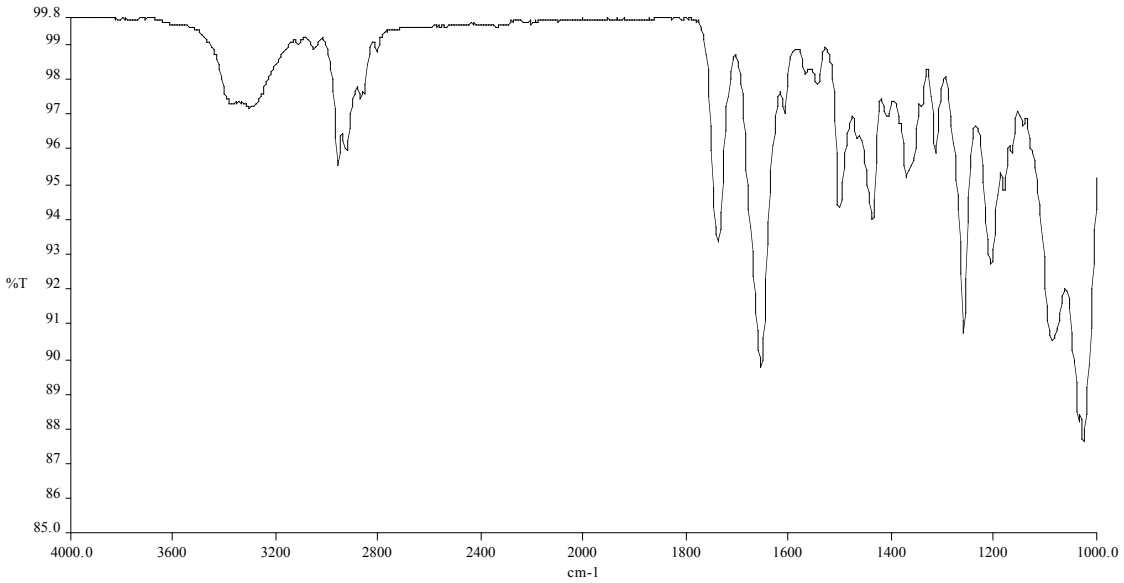



*Figure A2.53* Infrared spectrum of compound **3.37**.

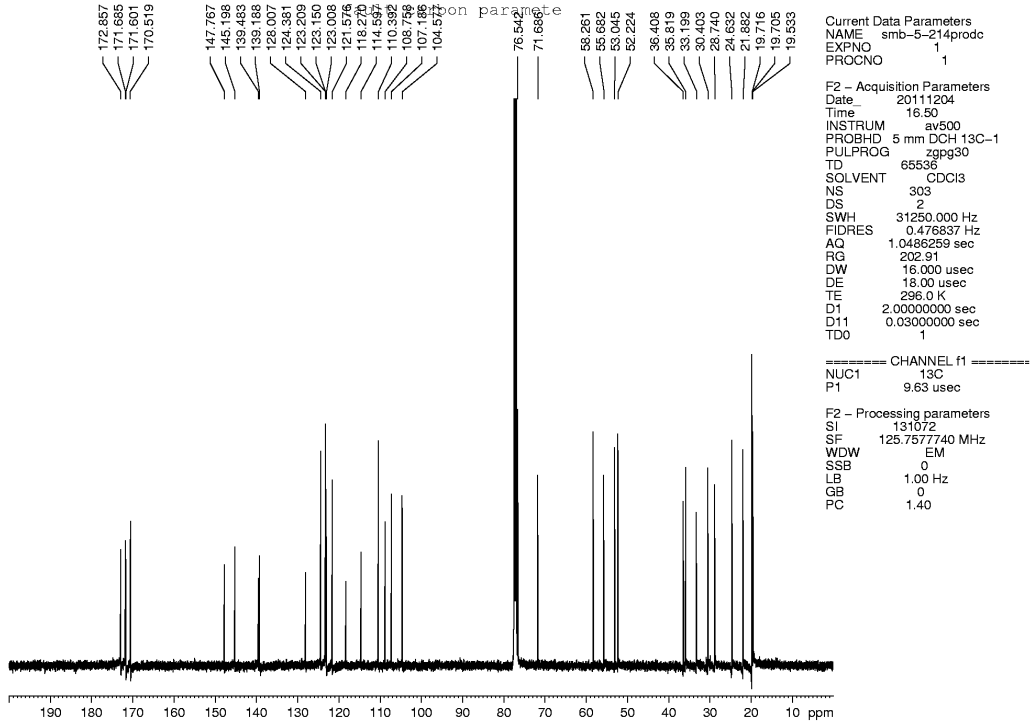



*Figure A2.54* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compound **3.37**.

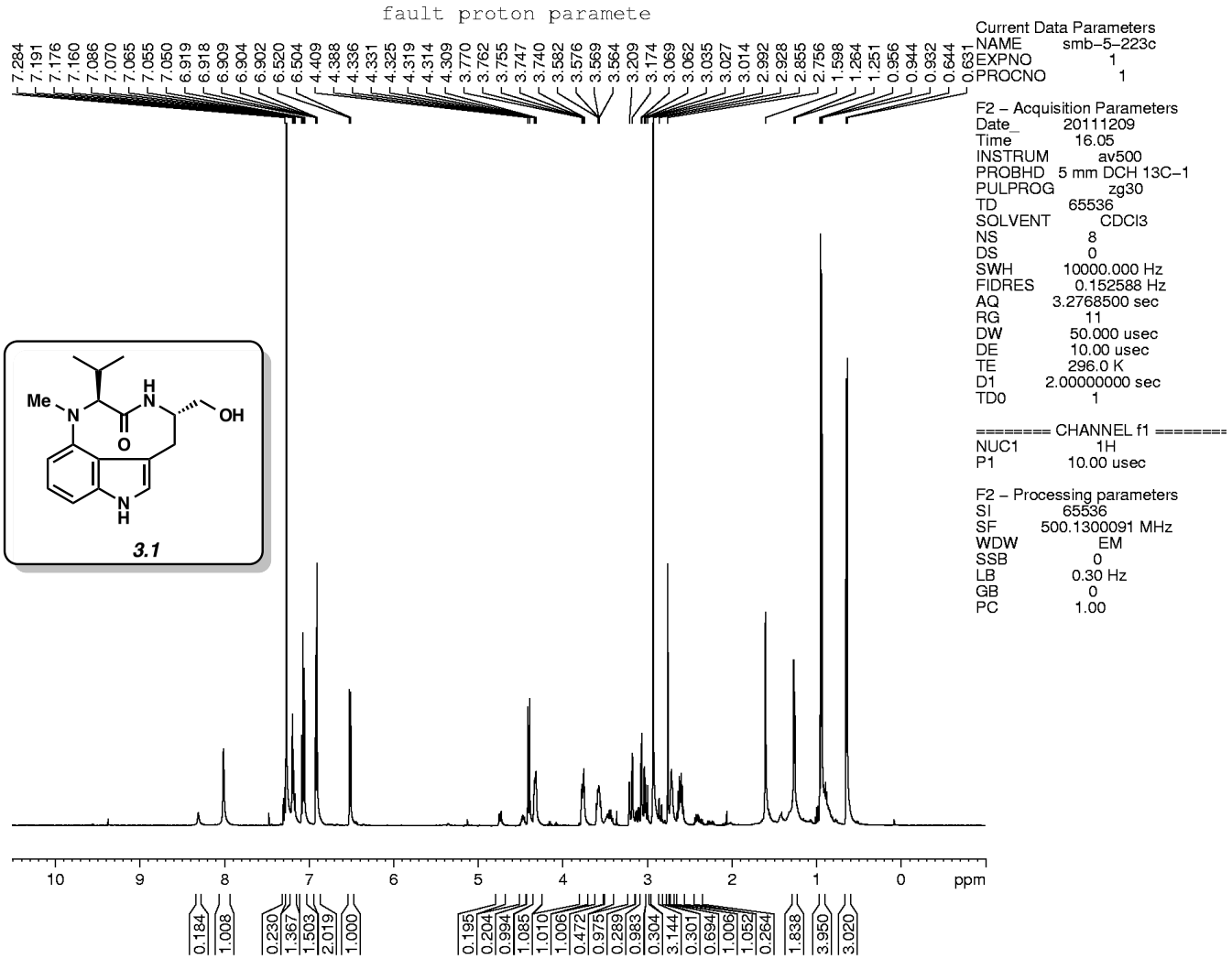



*Figure A2.55* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **3.1**.

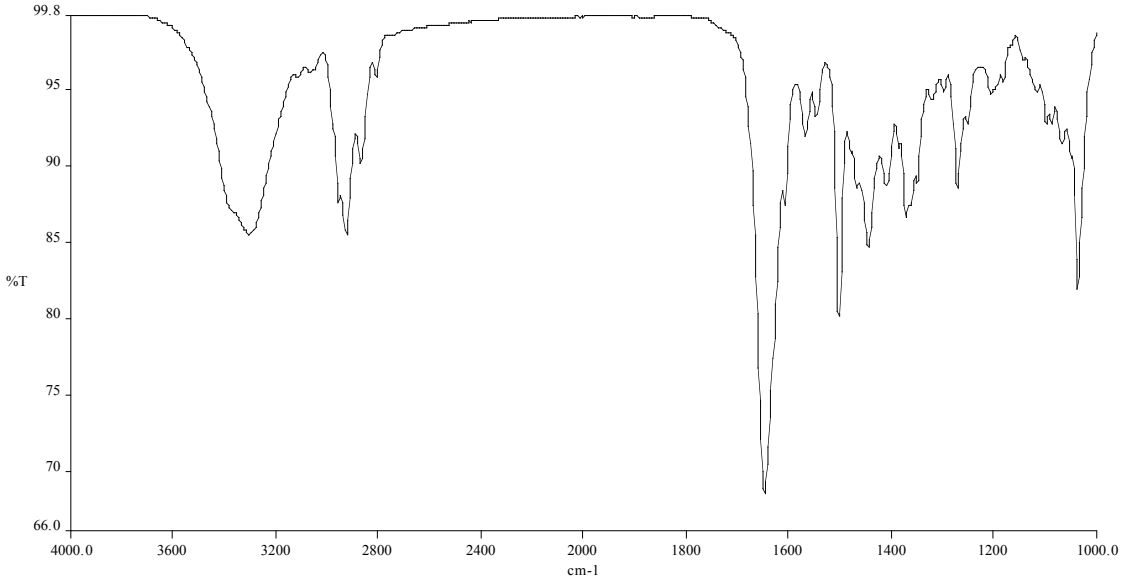



*Figure A2.56* Infrared spectrum of compound **3.1**.

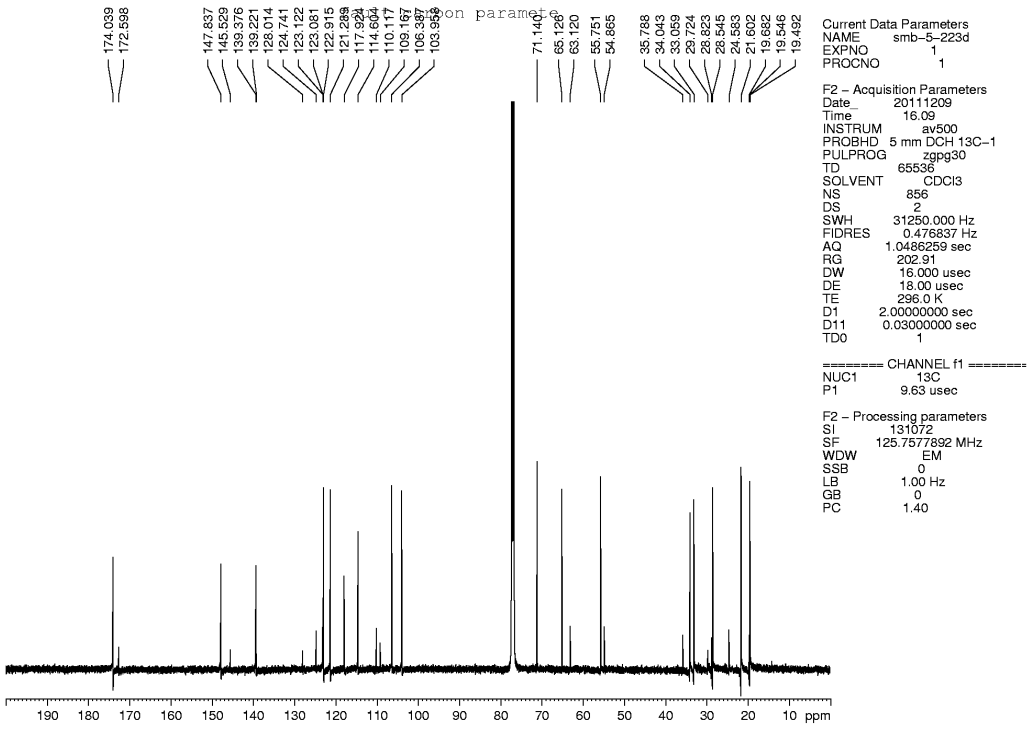



*Figure A2.57* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compound **3.1**.

# CHAPTER FOUR

## An Efficient Computational Model to Predict the Synthetic Utility of Heterocyclic Arynes

Goetz, A. E.; Bronner, S. M.; Cisneros, J. D.; Melamed, J. M.; Paton, R. S.; Houk, K. N.; Garg, N. K. *Angew. Chem. Int. Ed.* **2012**, *52*, 2758–2762.

### 4.1 Abstract

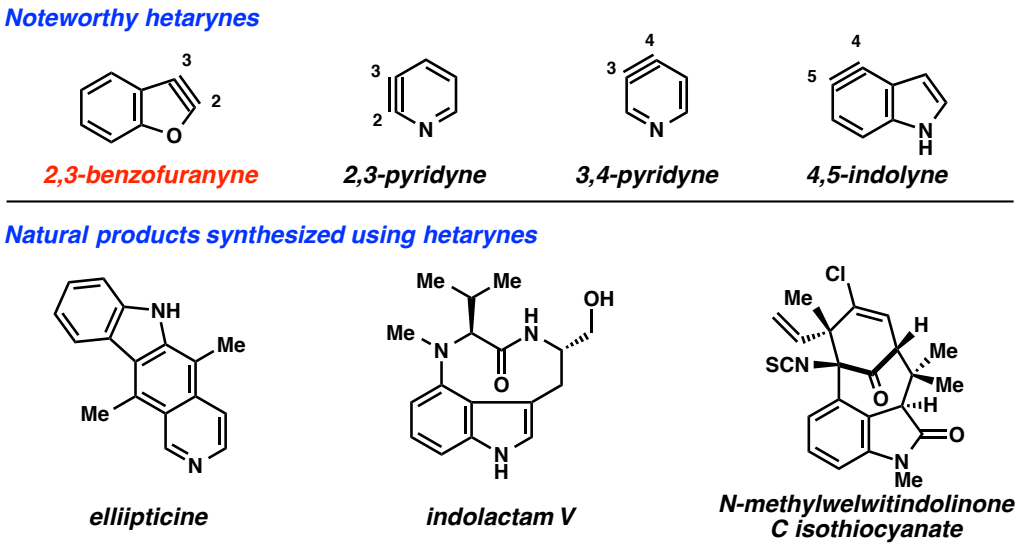
We report an efficient computational approach for evaluating the synthetic potential of heterocyclic arynes. Routine and rapid calculations of arene dehydrogenation energies and aryne angle distortion predict the likelihood that a given hetaryne can be generated, as well as the degree of regioselectivity expected in a reaction between a given hetaryne and a nucleophilic trapping agent. Comparisons between calculations and experimental data validate the utility of this predictive tool.

### 4.2 Introduction

Over the past decade, there has been a rapidly expanding interest in the field of aryne chemistry.[1] The reactivity of benzyne and its derivatives has been well explored, with numerous trapping methodologies now available for the efficient assembly of functionalized arenes. In contrast, relatively fewer achievements have been made with respect to heterocyclic arynes, or hetarynes.[2] Hetarynes have been a subject of interest and controversy since 1902, when Stoermer and coworkers proposed the intermediacy of a 2,3-benzofuranyne (Figure 4.1),[3] which was later

called into question.[2a,4] Several reports of hetarynes have appeared over the past fifty years, but only recently have a few hetarynes been deemed useful in synthesis. Pyridynes and indolynes have been the most thoroughly studied from a methodological standpoint, and have also been tested in complex settings.[5,6] For example, 3,4-pyridynes have been employed as key building blocks in syntheses of ellipticine,[5b–g] whereas 4,5-indolynes were recently used to construct key bonds in indolactam V[6g] and *N*-methylwelwitindolinone C isothiocyanate.[6h]

*Figure 4.1. Key Hetarynes and Examples in Synthesis*




Given the numerous synthetic advantages that arynes possess, along with their recent resurgence in the chemical literature,[7] we sought to evaluate the potential synthetic utility of a variety of heterocyclic arynes. We report a computational approach to predict: a) the likelihood that a given hetaryne can be generated, and b) the degree of regioselectivity one may expect in a nucleophilic addition reaction involving the hetaryne intermediate. This approach makes the distortion[8] model developed by Cheong et al.[6e,f] generally accessible through routine and rapid calculations. Moreover, we expect these studies will enable synthetic chemists to exploit heterocyclic arynes for the synthesis of natural products, compounds of medicinal value, and other functionalized heterocycles of practical importance.

### 4.3. Hetaryne Generation

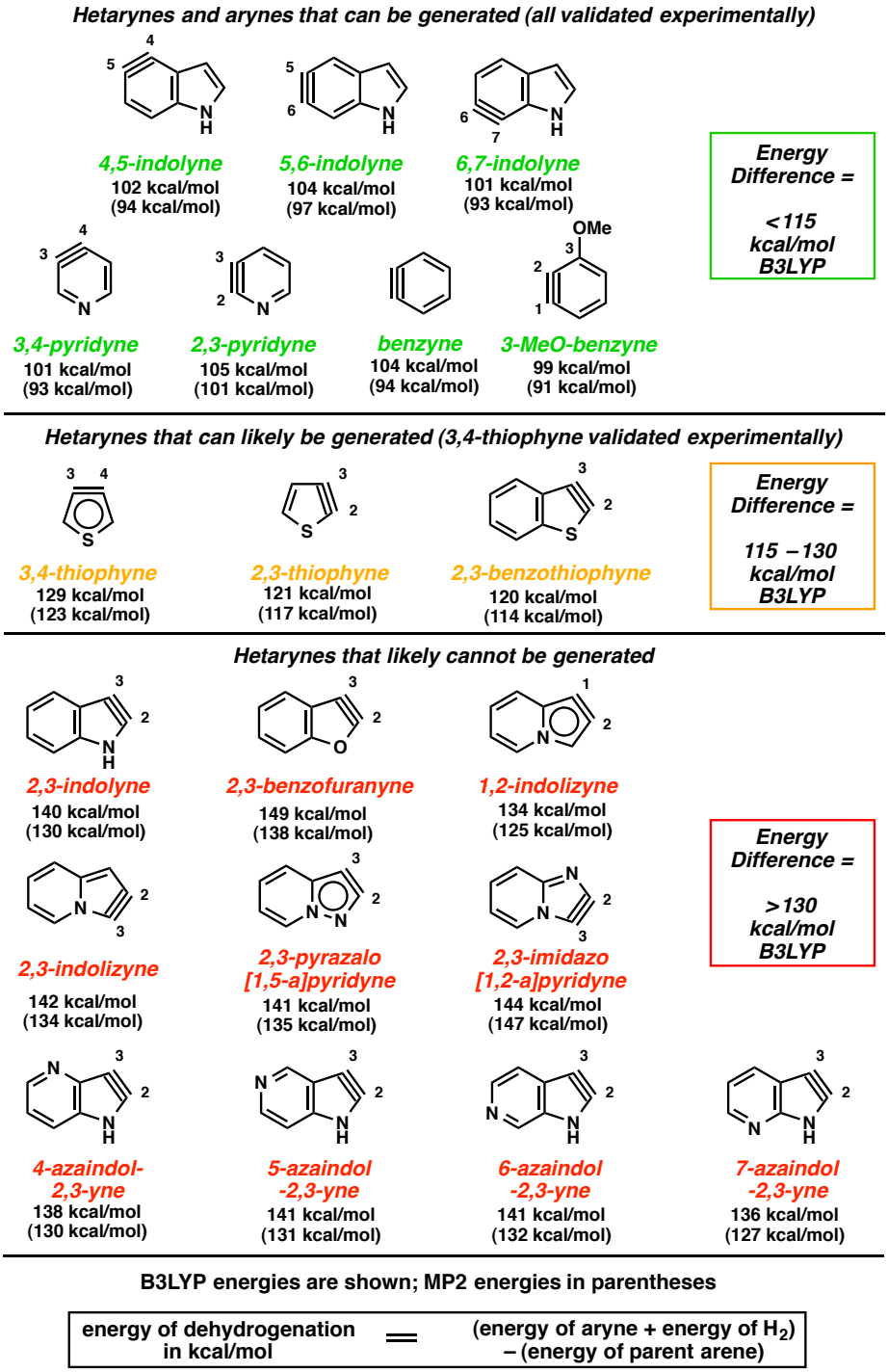
We first established a computational means to assess if a given hetaryne species should be accessible.[9] Several computational studies of hetaryne energetics have been reported,[10] including energy comparisons for pyridyne isomers.[11] However, to our knowledge, no method has been put forth to predict the accessibility of a hetaryne intermediate. The heat of hydrogenation is a well-established means to explore the strains and relative stabilities of alkynes,[12] and we examined a simple method to estimate hetaryne stability involving the difference between electronic energies of arene and aryne.

Geometry optimization of several known hetarynes[5,6] and the corresponding parent heterocycles was conducted using DFT (B3LYP/6-31G*) and ab initio methods (MP2/6-311+G**).[13] These results were also checked versus other functionals, as well as literature data. Using these optimized structures, and accounting for the energy of $H_2$ in the hypothetical dehydrogenation reaction, the energy of dehydrogenation of arene to aryne can be calculated. This straightforward calculation provides a measure of relative stability for the hetarynes that were examined.[14] We found that both B3LYP and MP2 methods gave comparable results for energy of dehydrogenation (Figure 4.2). While the MP2 results were typically 4–10 kcal/mol lower than B3LYP, both methods predicted essentially the same relative stabilities.[9] Given that B3LYP calculations require less computing time, this method provides a rapid means to assess stabilities. Using B3LYP, the energy of dehydrogenation between an aryne and its parent heterocycle is on the order of 100 kcal/mol.[9] Benzyne and the frequently studied 3-methoxybenzyne were subjected to the same analysis and gave comparable energy differences. Numerous studies that validate the existence of indolynes,[6] pyridynes,[5] benzyne,[1] and 3-methoxybenzyne[15] are available.

Several 5-membered hetarynes were also evaluated. Interestingly, thiophynes, which have been suggested based on experimental evidence[16] are approximately 120–130 kcal/mol higher in energy compared to thiophene. The 2,3-indolyne and 2,3-benzofuranyne, neither of which has been conclusively accessed,[2,17] are >140 kcal/mol higher in energy compared to their parent heterocycle.

Based on these results, an energy difference of approximately 115 kcal/mol or less suggests that the aryne can be readily generated.[18] An energy difference of roughly 115 to 130 kcal/mol suggests that an aryne may be accessible, although its preparation is likely to be challenging. Finally, an energy difference greater than approximately 130 kcal/mol reflects a hetaryne that is predicted to not be accessible experimentally. Several 5-membered hetarynes that fall into the latter two categories are depicted in Figure 4.2. In the system studied, 6-membered arynes are accessible, thiophynes are borderline, and most other 5-membered arynes are inaccessible.[19] Importantly, the predictive capabilities of this model are independent of the method used for aryne generation,[20] allowing experimentalists to pursue their method of choice based on precursor availability.[1]

*Figure 4.2. Calculated Energies of Dehydrogenation of Selected Hetarynes*



### 4.4 Regioselectivity in Reactions of Heterocyclic Arynes

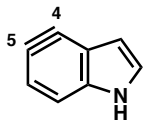
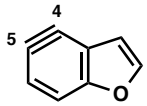
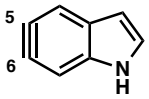
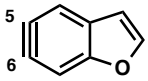
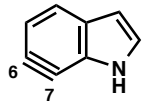
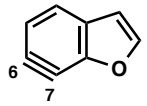
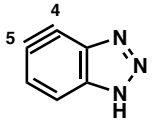
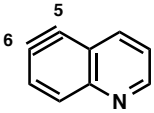
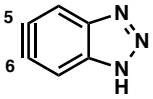
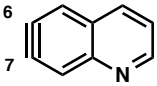
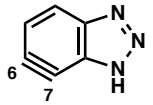
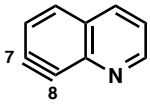
With a general means available to assess the feasibility of hetaryne generation, we evaluated the prospects for a variety of hetarynes to react regioselectively in nucleophilic addition reactions using the aryne distortion model. This predictive model uses routine DFT calculations, but has also been shown to operate comparably well using other functionals or higher level calculations.[6f] A comparison of internal angles of the geometry-optimized hetaryne reveals the preferred site of attack. Specifically, the more linear terminus of the aryne is most electrophilic and is the preferred site of attack by nucleophiles. As shown by Cheong et al.,[6e,f] and as described above, this is due to less distortion being required to achieve the transition state when the nucleophile attacks the carbon with the larger internal angle. The degree of regioselectivity can be correlated to the difference in angles, with angle differences ≥ 4° generally suggesting synthetically useful regioselectivities and lower values giving low and variable levels of selectivity. For arynes with angle differences between the termini being < 4°, adjacent substituents, such as halides, may be used to modulate regioselectivities.[6g]

The structures of approximately 150 plausible hetarynes were optimized using rapid DFT (B3LYP/6-31G*) calculations. Selected results are depicted in Tables 4.1 and 4.2 with MP2 results for comparison, while the remaining data are available in section 4.7. Table 4.1 features a sampling of hetarynes where the triple bond is in the non-heterocyclic ring. For both indolynes and benzofuranynes, significant regioselectivities are predicted for most isomers, with the exception of the 5,6-arynes (entries 1 and 2). Replacing C2, C3, or both with N or O causes minimal perturbation of these trends, except additions to 4,5-hetarynes are expected to occur with improved regioselectivities. This is likely because of an inductive effect caused by the proximal heteroatoms. An example of this trend is shown in entry 3 for benzotriazolynes,

although similar results were found for benzimidazolynes, benzoxazolynes, indazolynes, and other derivatives.[9] Finally, for 6,6-bicyclic hetarynes, regioselectivities are generally predicted to be less controlled, likely because of decreased ring strain present in the 6-membered ring, compared to the 5-membered ring.[21] For example, the aryne termini internal angles for each of the quinolyne isomers are nearly identical, suggesting modest regioselectivity in all cases (entry 4). Analogous trends were seen for an array of related hetarynes, including isoquinolynes, phthalazynes, and quinazolynes.[9]

The 2,3-pyridyne and related compounds in Table 4.2 show enormous angular distortions, which have been noted previously.[22] In 2,3-pyridyne, resonance involving the in-plane lone pair on N causes even greater distortions than the inductive effects and angle restrictions from ring fusion that were noted earlier.[6e–g] However, the B3LYP calculations (and calculations with other density functionals, such as M06-2X) exaggerate the difference in angles for 2,3-pyridyne and 3,4-pyridizyne. Computational studies of 2,3-pyridine with SF-CCSD predict angles at C2 and C3 of 143° and 114°, respectively, while B3LYP predicts 151° and 104°, respectively, leading to an angle difference of 29° with SF-CCSD and 47° with B3LYP. Table 4.2 also contains results for geometry optimizations with MP2/6-311+G**; this method gives angles closer to the accurate SF-CCSD values in addition to energies of dehydrogenation ($\Delta E_D$) that are 3–8 kcal/mol lower. While B3LYP exaggerates the angular distortions, the qualitative model proposed here gives rapid and important predictions about the magnitudes of regioselectivities of nucleophilic additions.

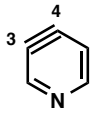
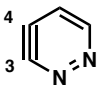
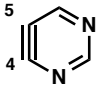
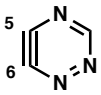
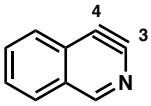
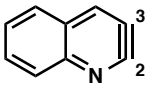
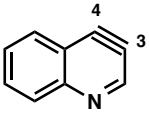
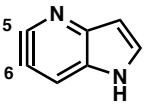
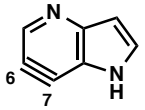
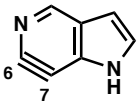
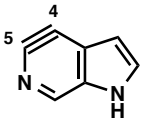
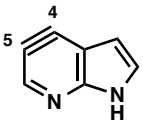
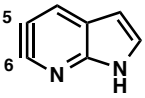
*Table 4.1. Predicted Sites of Attack of Benzenoid Hetarynes*

| entry | site of attack[a] (angle difference) | hetaryne | entry | site of attack[a] (angle difference) | hetaryne |
|---|---|---|---|---|---|
| 1 | C5 (4°) / B3LYP<br>C5 (1°) / MP2 |  | 2 | C5 (7°) / B3LYP<br>C5 (3°) / MP2 |  |
| | C5 (3°) / B3LYP<br>C5 (<1°) / MP2 |  | | C5 (2°) / B3LYP<br>N/A (0°) / MP2 |  |
| | C6 (17°) / B3LYP<br>C6 (7°) / MP2 |  | | C6 (20°) / B3LYP<br>C6 (9°) / MP2 |  |
| | | ***indolynes*** | | | ***benzofuranynes*** |
| 3 | C5 (11°) / B3LYP<br>C5 (4°) / MP2 |  | 4 | C6 (2°) / B3LYP<br>C6 (<1°) / MP2 |  |
| | C5 (2°) / B3LYP<br>C5 (1°) / MP2 |  | | C7 (1°) / B3LYP<br>C7 (1°) / MP2 |  |
| | C6 (20°) / B3LYP<br>C6 (9°) / MP2 |  | | C7 (2°) / B3LYP<br>C7 (3°) / MP2 |  |
| | | ***benzotriazolynes*** | | | ***quinolynes*** |

[a] Predicted site of attack based on the aryne distortion model.

Aza and diaza analogues of the 2,3-pyridyne all possess similar properties and presumably would undergo attack by nucleophiles with excellent regioselectivity (entries 2 and 3). Quinolyne and isoquinolynes were also examined. Although the 3,4-quinolyne is predicted to display modest regioselectivity, the other isomers appear more promising (entries 4 and 5). Finally, a series of azaindolynes were surveyed (entries 6–8). With the exception of the 7-aza-4,5-indolyne, these species are likely to undergo attack by nucleophiles with excellent regioselectivity. Promising data regarding more exotic hetarynes is presented in Section 4.7.

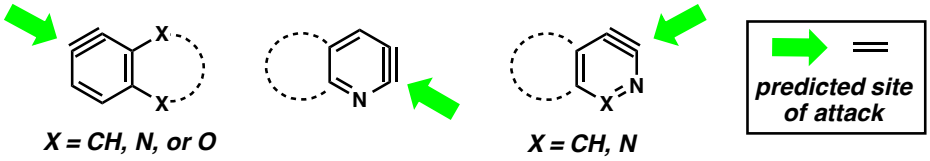
*Table 4.2. Predicted Sites of Attack of Non-Benzenoid Hetarynes*

| entry | site of attack[a] (angle difference) | hetaryne |
|---|---|---|
| 1 | C4 (1°) /B3LYP<br>C4 (3°) /MP2 |  |
| | C2 (47°) /B3LYP<br>C2 (34°) /MP2 |  |
| | | ***pyridynes*** |
| 2 | C3 (42°) /B3LYP<br>C3 (23°) /MP2 |  |
| | C4 (44°) /B3LYP<br>C4 (31°) /MP2 |  |
| | | ***pyridizyne and pyrimidyne*** |
| 3 | C5 (51°) /B3LYP<br>C5 (9°) /MP2 |  |
| | | ***triazyne*** |
| 4 | C3 (45°) /B3LYP<br>C3 (25°) /MP2 |  |
| | | ***isoquinolyne*** |
| 5 | C2 (49°) /B3LYP<br>C2 (43°) /MP2 |  |
| | C4 (3°) /B3LYP<br>C4 (3°) /MP2 |  |
| | | ***quinolynes*** |
| 6 | C5 (45°) /B3LYP<br>C5 (36°) /MP2 |  |
| | C6 (13°) /B3LYP<br>C6 (2°) /MP2 |  |
| | | ***4-azaindolynes*** |
| 7 | C6 (53°) /B3LYP<br>C6 (49°) /MP2 |  |
| | C5 (48°) /B3LYP<br>C5 (47°) /MP2 |  |
| | | ***5- and 6-azaindolynes*** |
| 8 | N/A (0°) /B3LYP<br>C4 (2°) /MP2 |  |
| | C6 (41°) /B3LYP<br>C6 (25°) /MP2 |  |
| | | ***7-azaindolynes*** |

[a] Predicted site of attack based on the aryne distortion model.

Even though the model for predicting regioselectivities in nucleophilic additions to hetarynes is exceptionally efficient using routine computations, in some cases, computations are not necessary. Three general classes of hetarynes and their preferred site of attack by nucleophiles are shown in Figure 4.3. While not encompassing every hetaryne discussed in this manuscript, we expect these general guidelines will enable synthetic applications of hetaryne intermediates.

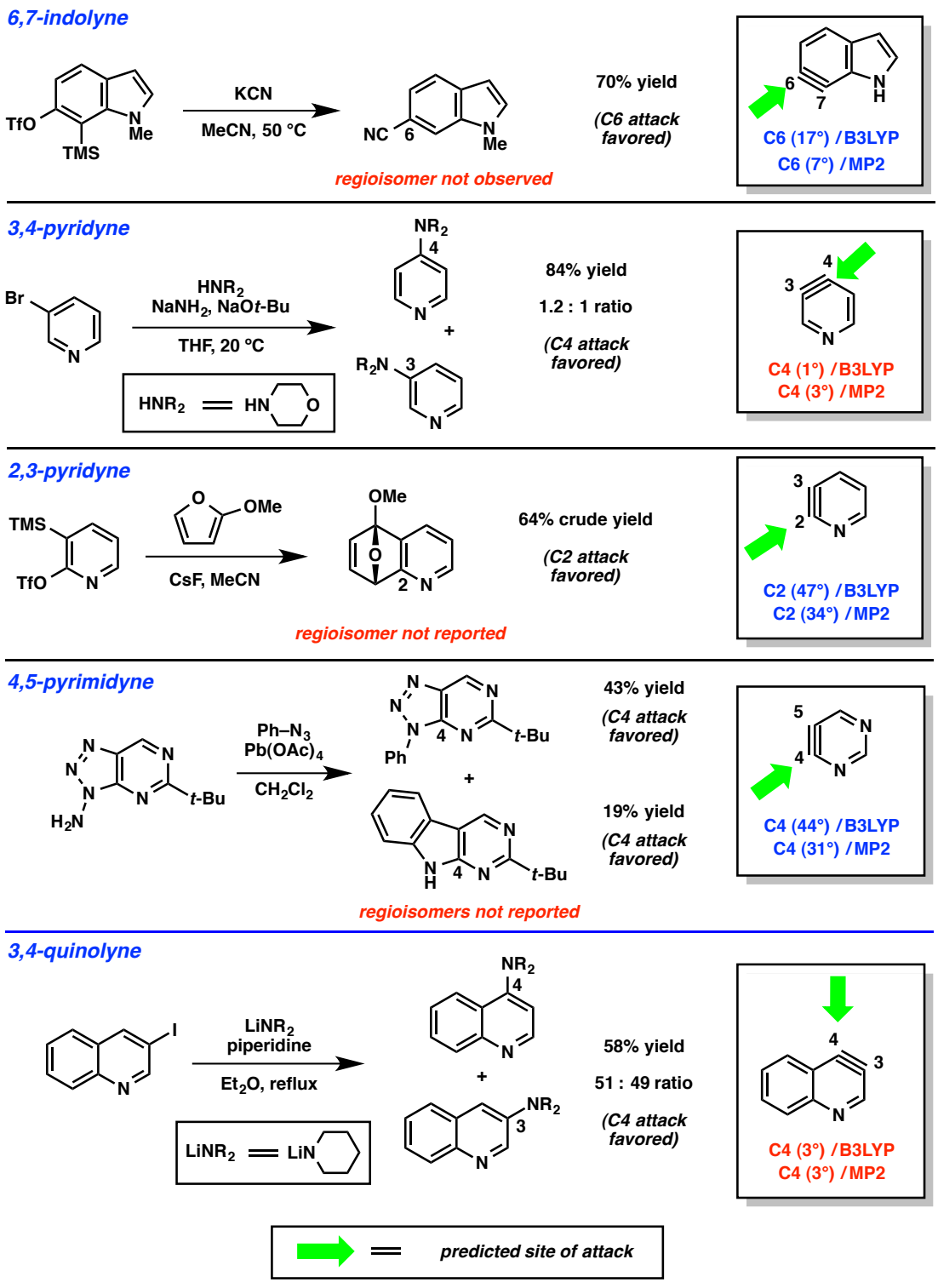
*Figure 4.3. General Model for Predicting Site of Attack*




## 4.5 A Comparison of Computational and Experimental Data

Although relatively few unsymmetrical hetarynes have been prepared, regioselectivity data is available for comparison to the computational predictions. In all cases where significant yields of product are obtained,[23] the predictions and experimental results are in agreement (Figure 4.4). Indolynes have recently been studied by our laboratories, and each of the >20 examples that have been reported are in accord with the aryne distortion model.[6e–g] An example pertaining to a 6,7-indolyne is depicted. The remaining literature examples predominantly involve pyridynes and their derivatives. As shown, our findings for the 3,4-pyridyne[5h,i] and 2,3-pyridyne[5j] are also consistent with experimental data regarding the preferred site of attack and the degree of regioselectivity in each case.[5b–g] Comparisons of computational and experimental data for a 4,5-pyrimidyne[10b] and a 3,4-quinolyne[24] were also found to be in good accord. Several additional examples are depicted in the Section 4.7 pertaining to 2,3-pyridyne-*N*-oxide, 4,5-benzofurazanyne, and 1,2-dibenzofuranyne.

*Figure 4.4. Literature Examples of Hetaryne Regioselectivity*



## 4.6 Conclusion

In summary, we have developed an efficient computational approach for evaluating the synthetic potential of heterocyclic arynes. DFT or ab initio calculations can be used to predict the likelihood that a given hetaryne can be generated, in addition to the degree of regioselectivity one may expect in a reaction between a given hetaryne and a nucleophilic trapping agent. Although both methods give comparable predictions, DFT requires less computing time. Our predictive tool requires only routine and rapid calculations, and further validates the aryne distortion model as a means to gauge nucleophilic regioselectivities. We expect that these findings will enable synthetic chemists to judiciously design syntheses of functionalized heterocycles using hetarynes as versatile intermediates.

## 4.7 Computational Section

### 4.7.1 Materials and Methods

All computations were carried out using Spartan '06 for Mac[13a] unless otherwise noted. All structures were minimized using Molecular Mechanics, and then further minimized using Density Functional Theory B3LYP/6–31G*.

Literature references for various computational methods are as follows:

B3LYP: ref 25

MP2: ref 26

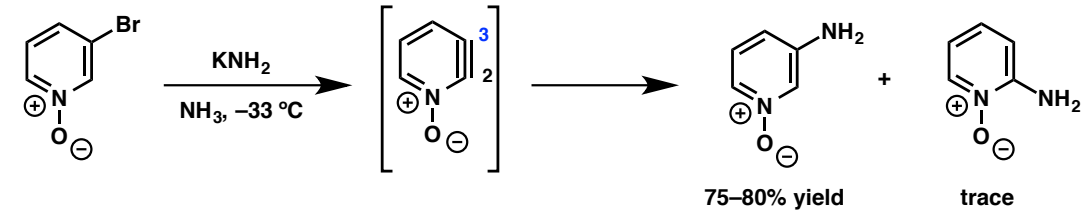
M06-2X: ref 27

SF-CCSD: ref 28

*Note:* Although the use of hybrid-GGA density functionals such as B3LYP is commonplace throughout organic chemistry, reaction energies are often predicted with errors of the order of 6-8 kcal/mol.[29] Grimme and others have shown that the incorporation of dispersion corrections can partially mitigate these errors and are essential for greater quantitative accuracy with DFT calculations. In the current work, while we would expect the absolute reaction energies to alter upon the inclusion of a dispersion correction, the relative aryne stabilities would likely remain unchanged leaving our conclusions unaltered.

## 4.7.2 Additional Published Hetaryne Examples

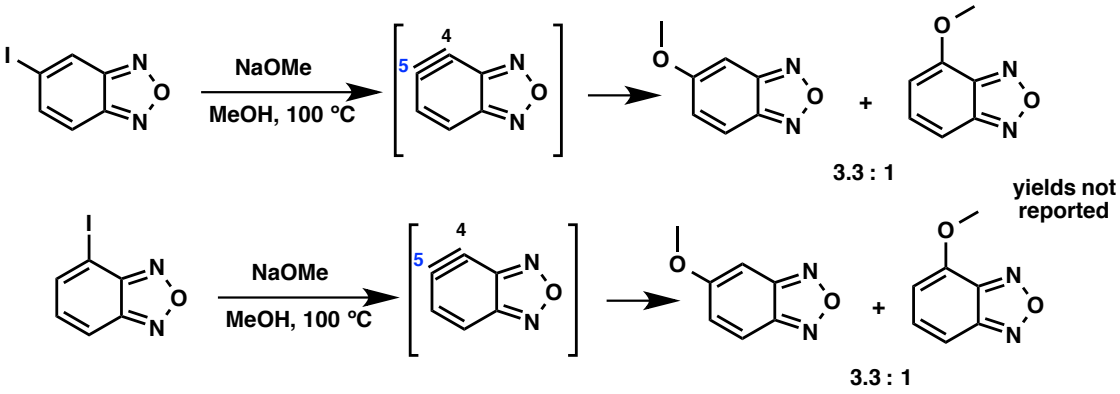
### *2,3-pyridyne-N-oxide*




Martens, R. J.; den Hertog, H. J. *Rec. Trav. Chim. Pays–Bas* **1967**, *86*, 655–669.

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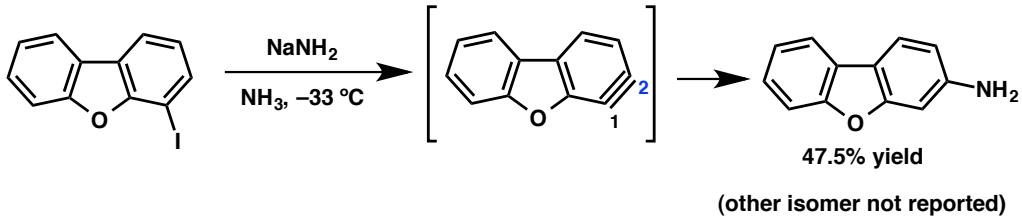
### *4,5-benzofurazanyne*




Di Nunno, L.; Florio, S.; Todesco, P. E. *J. Chem. Soc., Perkin Trans. II* **1974**, 1171–1175.

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### *1,2-dibenzofuranyne*



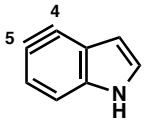

Gilman, H.; Avakian, S. *J. Am. Chem. Soc.* **1945**, *67*, 349–351.

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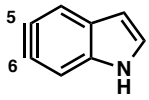
## 4.7.3 Selected Energy Calculations using DFT (M06/6-311+G**)

*computed using DFT M06/6-311+G***

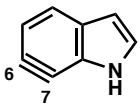
*Hetarynes and arynes that can be generated (all validated experimentally)*



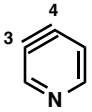
*4,5-indolyne*
100 kcal/mol



*5,6-indolyne*
102 kcal/mol



*6,7-indolyne*
99 kcal/mol



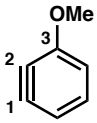
*3,4-pyridyne*
99 kcal/mol



*2,3-pyridyne*
100 kcal/mol



*benzyne*
101 kcal/mol



*3-MeO-benzyne*
97 kcal/mol

***Energy Difference = 95 – 115 kcal/mol***

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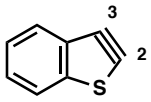
*Hetarynes that can likely be generated (3,4-thiophyne validated experimentally)*



*3,4-thiophyne*
127 kcal/mol



*2,3-thiophyne*
118 kcal/mol

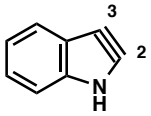


*2,3-benzothiophyne*
116 kcal/mol

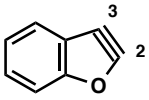
***Energy Difference = 115 – 130 kcal/mol***

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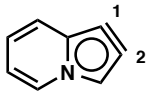
*Hetarynes that likely cannot be generated*



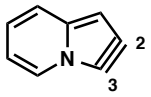
*2,3-indolyne*
138 kcal/mol



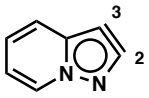
*2,3-benzofuranyne*
146 kcal/mol



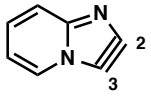
*1,2-indolizyne*
132 kcal/mol



*2,3-indolizyne*
140 kcal/mol

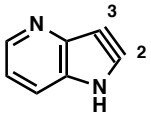


*2,3-pyrazalo [1,5-a]pyridyne*
137 kcal/mol

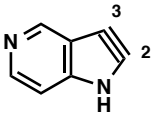


*2,3-imidazo [1,2-a]pyridyne*
139 kcal/mol

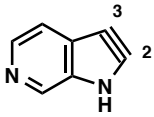
***Energy Difference = >130 kcal/mol***



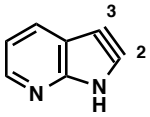
*4-azaindol-2,3-yne*
136 kcal/mol



*5-azaindol -2,3-yne*
139 kcal/mol



*6-azaindol -2,3-yne*
139 kcal/mol



*7-azaindol -2,3-yne*
134 kcal/mol

| energy difference or energy of dehydrogenation in kcal/mol | = | (energy of aryne + energy of $H_2$) – (energy of parent arene) |
|---|---|---|

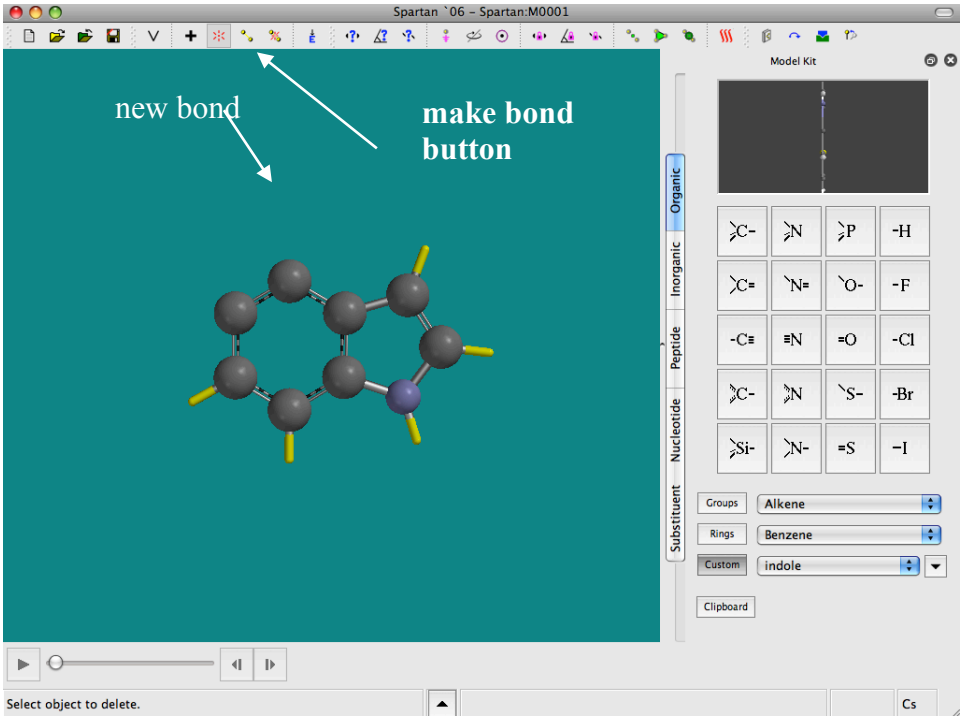
The energies of hetarynes from Figure 4.2 were computed in Spartan '10[30] using Density Functional Theory (M06/6-311+G**) from the previously minimized structures used throughout the manuscript. While there are small differences (typically ~ 2 kcal/mol) in the absolute energies, in all cases the hetarynes still fall into the same categories as outlined in Figure 4.2 in section 4.2.

### 4.7.4 Sample Calculation Setup

*Note to user: The following section provides a simple guide for setting up hetaryne calculations. However, users should have some basic understanding of computational chemistry in order to conduct and interpret such computations.*

**Predicting the Preferred Site of Attack on an Aryne**

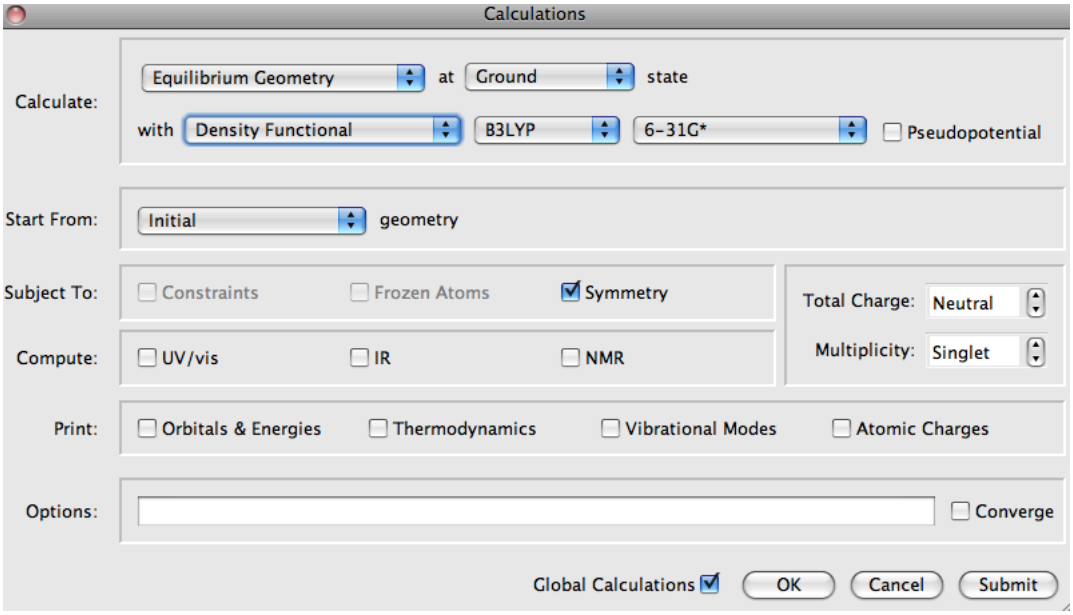
1) Construct the parent arene in Spartan. Connect the two adjacent carbons using the "**make bond**" button by clicking the adjacent yellow connection points.



2) Perform an energy minimization by clicking the "**minimize**" button. 

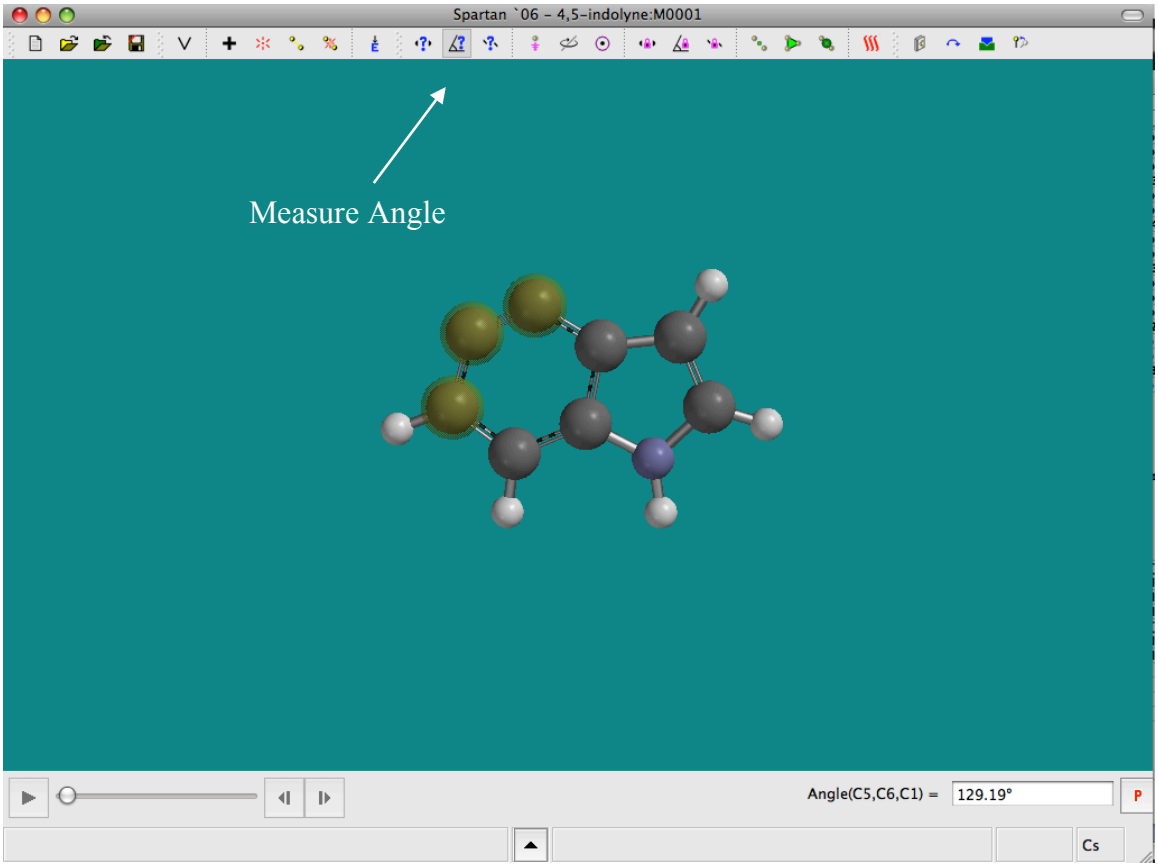
3) Start the calculation by choosing "Setup" followed by "Calculations"

4) Calculate "**Equilibrium Geometry**" at "**Ground**" state with "**Density Functional/B3LYP/6-31G***". Everything else should already be setup properly.




5) Click "**submit**" and create a file name for the molecule.

6) After the computation has finished, measure the angles, using the "**Measure Angle**" button. Click 3 adjacent atoms in order to measure the angle of the central atom.



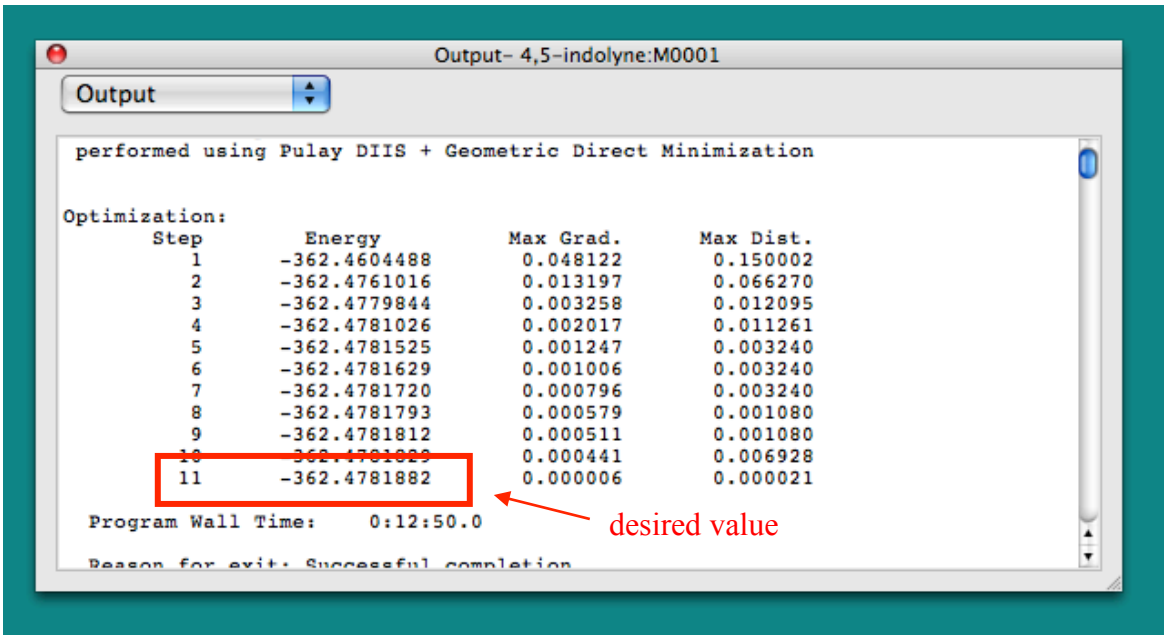

7) Compare the two termini of the aryne to find the larger angle.

**Calculating the Dehydrogenation Energy of the Aryne**

1) To calculate the dehydrogenation energy, you must first model the aryne in question, the parent arene (i.e. indole to correspond to 4,5-indolyne) and hydrogen ($H_2$).

2) After these calculations are all complete, obtain the energy of each species by choosing "**Output**" under the "**Display**" menu

3) Scroll through the output until you see a section with the heading "**Optimization**". This contains a series of "steps" as well as energies for each step. The energy that corresponds to the bottom "step" is the desired energy.



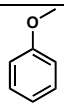
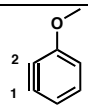

4) After obtaining the value from each calculation (aryne, arene, and $H_2$), they must be converted from their given units (Hartrees) to kcal/mol. The conversion for this is 1 Hartree = 627.51 kcal/mol.

5) The dehydrogenation energy is calculated as (Energy of aryne + Energy of $H_2$) – (Energy of arene). This should give a positive value. Higher values correspond to less stable arynes.

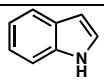
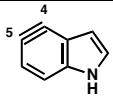
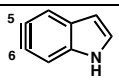
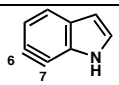
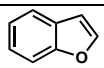
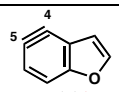
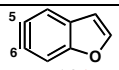
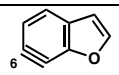
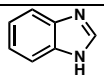
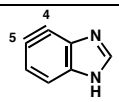
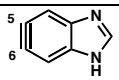
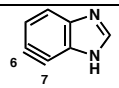
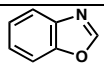
### 4.7.5 Energies and Key Angles of Calculated Structures.

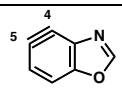
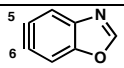
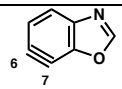
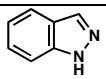
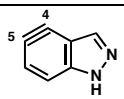
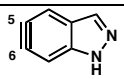
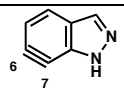
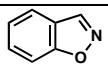
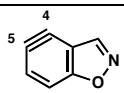
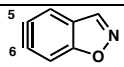
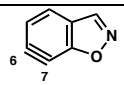
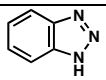
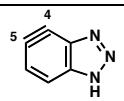
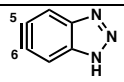
The dehydrogenation energy (kcal/mol) was obtained by calculating (energy of aryne + energy of $H_2$) – (energy of parent arene). The energy differences relative to that of *o*-benzyne are also shown as the Standardized Energy. Positive standardized energies correspond to arynes that are higher in energy compared to *o*-benzyne. Standardized energies that are negative are predicted to be lower in energy than *o*-benzyne. Structures marked with a (*) are included in the accompanying communication.

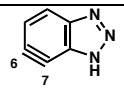
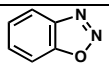
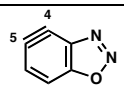
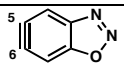
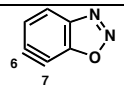
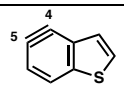
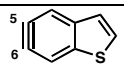
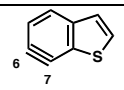
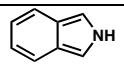
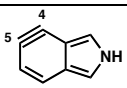
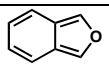
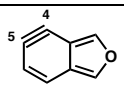
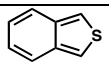
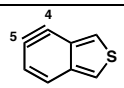
#### 4.7.5.1 Benzyne Derived Arynes

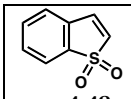
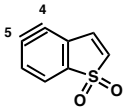
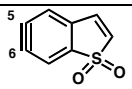
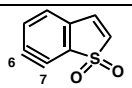
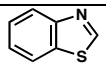
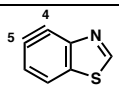
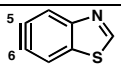
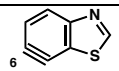
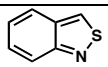
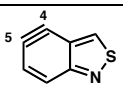
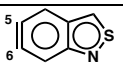
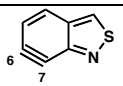
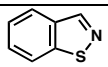
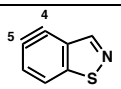
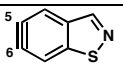
| Structure | Energy (hartrees) | Energy (kcal/mol) | Dehydro-genation Energy (kcal/mol) | Standard-ized Energy (kcal/mol) | Larger Terminus | Smaller Terminus | Angle Difference |
|---|---|---|---|---|---|---|---|
| H—H **4.1** | -1.17548 | -737.6 | | | | | |
|  **4.2** | -232.2507 | -145739.6 | | | | | |
|  **4.3*** | -230.90996 | -144898.3 | 103.7 | 0.0 | 127.1 (N/A) | 127.1 (N/A) | 0.0 |
|  **4.4** | -346.7714 | -217602.5 | | | | | |
|  **4.5*** | -345.4388 | -216766.3 | 98.6 | -5.1 | 134.90 (C1) | 119.2 (C2) | 15.7 |

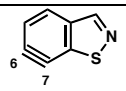
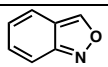
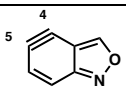
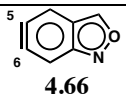
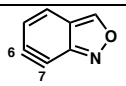
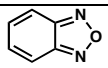
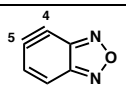
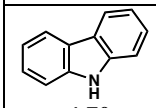
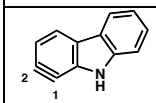
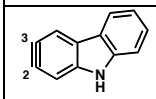
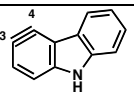
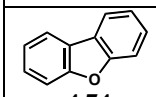
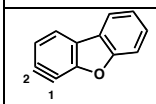
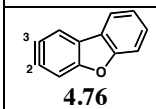
### 4.7.5.2 6,5-Bicyclic Hetarynes (Aryne Outside of Heterocycle)

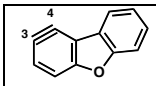
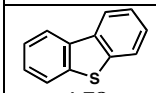
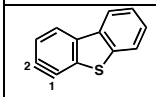
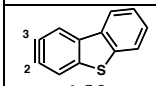
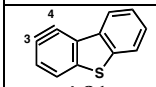
| Structure | Energy (hartrees) | Energy (kcal/mol) | Dehydro-genation Energy (kcal/mol) | Standard-ized Energy (kcal/mol) | Larger Terminus | Smaller Terminus | Angle Difference |
|---|---|---|---|---|---|---|---|
|  **4.6** | -363.8167 | -228298.6 | | | | | |
|  **4.7*** | -362.4782 | -227458.7 | 102.3 | -1.4 | 129.2 (C5) | 125.1 (C4) | 4.1 |
|  **4.8*** | -362.4754 | -227456.9 | 104.1 | 0.4 | 130.0 (C5) | 126.8 (C6) | 3.2 |
|  **4.9*** | -362.4797 | -227459.6 | 101.4 | -2.3 | 134.7 (C6) | 117.4 (C7) | 17.3 |
|  **4.10** | -383.6734 | -240758.9 | | | | | |
|  **4.11*** | -382.3329 | -239917.7 | 103.6 | -0.1 | 130.6 (C5) | 123.3 (C4) | 7.3 |
|  **4.12*** | -382.3317 | -239917.0 | 104.3 | 0.6 | 129.7 (C5) | 127.4 (C6) | 2.3 |
|  **4.13*** | -382.3341 | -239918.5 | 102.8 | -0.9 | 135.5 (C6) | 115.8 (C7) | 19.7 |
|  **4.14** | -379.8661 | -238369.8 | | | | | |
|  **4.15** | -378.5264 | -237529.1 | 103.0 | -0.6 | 131.4 (C5) | 122.1 (C4) | 9.3 |
|  **4.16** | -378.525 | -237528.2 | 103.9 | 0.2 | 130.4 (C5) | 127.1 (C6) | 3.3 |
|  **4.17** | -378.5278 | -237530.0 | 102.2 | -1.5 | 135.5 (C6) | 116.2 (C7) | 19.3 |
|  **4.18** | -399.7232 | -250830.3 | | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
|  **4.19** | -398.3816 | -249988.4 | 104.2 | 0.5 | 132.5 (C5) | 120.4 (C4) | 12.1 |
|  **4.20** | -398.3817 | -249988.5 | 104.2 | 0.5 | 129.9 (C5) | 127.8 (C6) | 2.10 |
|  **4.21** | -398.3827 | -249989.1 | 103.6 | -0.1 | 136.4 (C6) | 114.4 (C7) | 22.0 |
|  **4.22** | -379.8436 | -238355.7 | | | | | |
|  **4.23** | -378.5034 | -237514.7 | 103.4 | -0.3 | 129.8 (C5) | 123.7 (C4) | 6.1 |
|  **4.24** | -378.5009 | -237513.1 | 104.9 | 1.2 | 129.5 (C5) | 128.0 (C6) | 1.5 |
|  **4.25** | -378.5057 | -237516.1 | 101.9 | -1.8 | 135.2 (C6) | 116.8 (C7) | 18.4 |
|  **4.26** | -399.6831 | -250805.1 | | | | | |
|  **4.27** | -398.3405 | -249962.6 | 104.9 | 1.2 | 131.3 (C5) | 121.4 (C4) | 9.9 |
|  **4.28** | -398.3398 | -249962.2 | 105.3 | 1.6 | 128.9 (C6) | 128.7 (C5) | 0.20 |
|  **4.29** | -398.3425 | -249963.9 | 103.6 | -0.1 | 135.8 (C6) | 115.7 (C7) | 20.1 |
|  **4.30** | -395.8672 | -248410.6 | | | | | |
|  **4.31*** | -394.5256 | -247568.8 | 104.2 | 0.5 | 131.8 (C5) | 120.9 (C4) | 10.9 |
|  **4.32*** | -394.5243 | -247567.9 | 105.1 | 1.4 | 129.9 (C5) | 128.3 (C6) | 1.6 |
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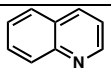
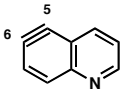
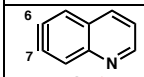
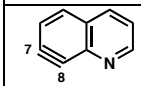
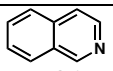
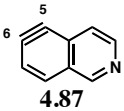
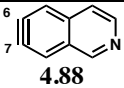
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|---|---|---|---|---|---|---|---|
|  **4.33*** | -394.5272 | -247569.8 | 103.2 | -0.5 | 135.7 (C6) | 115.9 (C7) | 19.8 |
|  **4.34** | -415.7125 | -260863.8 | | | | | |
|  **4.35** | -414.3691 | -260020.8 | 105.4 | 1.7 | 133.9 (C5) | 117.6 (C4) | 16.3 |
|  **4.36** | -414.3689 | -260020.6 | 105.5 | 1.8 | 129.9 (C6) | 128.4 (C5) | 1.5 |
|  **4.37** | -414.3701 | -260021.4 | 104.7 | 1.0 | 135.9 (C6) | 116.3 (C7) | 19.6 |
|  **4.38** | -706.6536 | -443432.2 | | | | | |
|  **4.39** | -705.3153 | -442592.4 | 102.2 | -1.5 | 129.0 (C5) | 125.6 (C4) | 3.4 |
|  **4.40** | -705.3118 | -442590.2 | 104.4 | 0.7 | 130.0 (C5) | 126.8 (C6) | 3.2 |
|  **4.41** | -705.3146 | -442592.0 | 102.6 | -1.1 | 131.7 (C6) | 121.4 (C7) | 10.3 |
|  **4.42** | -363.8019 | -228289.3 | | | | | |
|  **4.43** | -362.4668 | -227451.5 | 100.2 | -3.5 | 129.9 (C5) | 124.3 (C4) | 5.6 |
|  **4.44** | -383.6504 | -240744.5 | | | | | |
|  **4.45** | -382.3143 | -239906.0 | 100.8 | -2.9 | 130.7 (C5) | 123.3 (C4) | 7.4 |
|  **4.46** | -706.6357 | -443421.0 | | | | | |
|  **4.47** | -705.3003 | -442583.0 | 100.4 | -3.3 | 130.1 (C5) | 124.6 (C4) | 5.5 |
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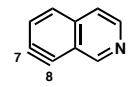
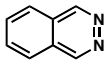
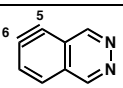
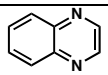
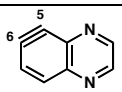
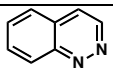
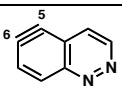
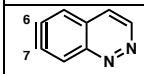
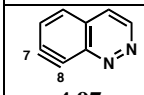
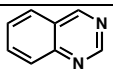
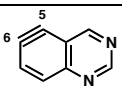
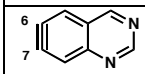
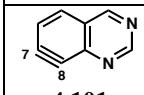
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|  **4.48** | -857.0075 | -537780.8 | | | | | |
|  **4.49** | -855.6661 | -536939.0 | 104.1 | 0.4 | 129.9 (C5) | 124.3 (C4) | 5.6 |
|  **4.50** | -855.665 | -536938.3 | 104.8 | 1.1 | 128.0 (C6) | 127.6 (C5) | 0.4 |
|  **4.51** | -855.6624 | -536936.7 | 106.4 | 2.7 | 131.1 (C6) | 121.3 (C7) | 9.8 |
|  **4.52** | -722.6996 | -453501.2 | | | | | |
|  **4.53** | -721.3600 | -452660.6 | 103.0 | -0.7 | 131.1 (C5) | 123.1 (C4) | 8.0 |
|  **4.54** | -721.3576 | -452659.1 | 104.5 | 0.8 | 128.7 (C5) | 128.0 (C6) | 0.7 |
|  **4.55** | -721.36 | -452660.6 | 103.0 | -0.7 | 132.6 (C6) | 120.5 (C7) | 12.1 |
|  **4.56** | -722.6759 | -453486.4 | | | | | |
|  **4.57** | -721.3389 | -452647.4 | 101.4 | -2.3 | 130.4 (C5) | 123.8 (C4) | 6.6 |
|  **4.58** | -721.3336 | -452644.0 | 104.7 | 1.0 | 130.4 (C6) | 128.6 (C5) | 1.8 |
|  **4.59** | -721.3395 | -452647.7 | 101.0 | -2.7 | 131.9 (C6) | 122.7 (C7) | 9.2 |
|  **4.60** | -722.6891 | -453494.6 | | | | | |
|  **4.61** | -721.3491 | -452653.8 | 103.2 | -0.5 | 130.1 (C5) | 123.6 (C4) | 6.5 |
|  **4.62** | -721.346 | -452651.8 | 105.2 | 1.5 | 128.3 (N/A) | 128.3 (N/A) | 0.0 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
|  **4.63** | -721.3492 | -452653.8 | 103.2 | -0.5 | 132.1 (C6) | 121.1 (C7) | 11.0 |
|  **4.64** | -399.6653 | -250794.0 | | | | | |
|  **4.65** | -398.3266 | -249953.9 | 102.4 | -1.3 | 131.2 (C5) | 121.9 (C4) | 9.3 |
|  **4.66** | -398.3221 | -249951.1 | 105.2 | 1.6 | 130.9 (C6) | 128.8 (C5) | 2.1 |
|  **4.67** | -398.3274 | -249954.4 | 101.9 | -1.8 | 132.8 (C6) | 120.7 (C7) | 12.1 |
|  **4.68** | -415.678 | -260842.1 | | | | | |
|  **4.69** | -414.3375 | -260000.9 | 103.6 | -0.1 | 133.9 (C5) | 119.5 (C4) | 14.4 |
|  **4.70** | -517.4707 | -324718.0 | | | | | |
|  **4.71** | -516.1333 | -323878.8 | 101.6 | -2.1 | 134.5 (C2) | 118.0 (C1) | 16.5 |
|  **4.72** | -516.1291 | -323876.2 | 104.2 | 0.5 | 128.9 (C3) | 127.4 (C2) | 1.5 |
|  **4.73** | -516.131 | -323877.4 | 103.0 | -0.6 | 129.5 (C3) | 124.4 (C4) | 5.1 |
|  **4.74** | -537.3291 | -337179.4 | | | | | |
|  **4.75** | -535.9896 | -336338.8 | 102.9 | -0.8 | 135.3 (C2) | 116.4 (C1) | 18.9 |
|  **4.76** | -535.9873 | -336337.4 | 104.4 | 0.7 | 129.1 (C3) | 127.7 (C2) | 1.40 |

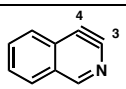
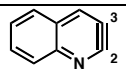
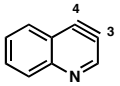
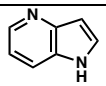
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|  **4.77** | -535.9881 | -336337.9 | 103.9 | 0.2 | 130.6 (C3) | 123.1 (C4) | 7.5 |
|  **4.78** | -860.3069 | -539851.2 | | | | | |
|  **4.79** | -858.9674 | -539010.6 | 102.9 | -0.8 | 131.6 (C2) | 121.5 (C1) | 10.1 |
|  **4.80** | -858.9648 | -539009.0 | 104.6 | 0.9 | 129.1 (C3) | 127.7 (C2) | 1.4 |
|  **4.81** | -858.9687 | -539011.4 | 102.1 | -1.6 | 130.6 | 123.1 | 7.5 |

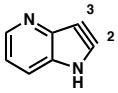
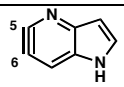
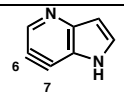
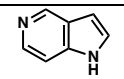
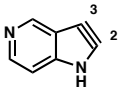
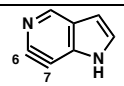
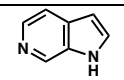
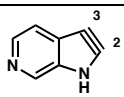
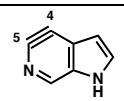
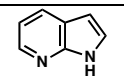
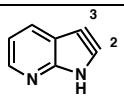
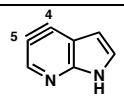
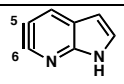
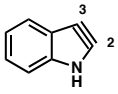
### 4.7.5.3 6,6-Bicyclic Hetarynes (Aryne Outside of Heterocycle)

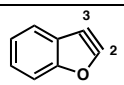
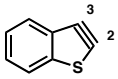
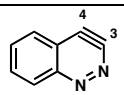
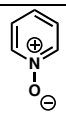
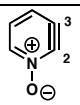
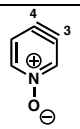
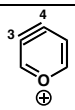
| Structure | Energy (hartrees) | Energy (kcal/mol) | Dehydro-genation Energy (kcal/mol) | Standard-ized Energy (kcal/mol) | Larger Terminus | Smaller Terminus | Angle Difference |
|---|---|---|---|---|---|---|---|
|  **4.82** | -401.9308 | -252215.6 | | | | | |
|  **4.83*** | -400.5933 | -251376.3 | 101.7 | -2.0 | 128.4 (C6) | 126.4 (C5) | 2.0 |
|  **4.84*** | -400.5898 | -251374.1 | 103.9 | 0.2 | 128.7 (C7) | 127.5 (C6) | 1.2 |
|  **4.85*** | -400.5932 | -251376.2 | 101.7 | -2.0 | 128.4 (C7) | 126.8 (C8) | 1.6 |
|  **4.86** | -401.9291 | -252214.5 | | | | | |
|  **4.87** | -400.5917 | -251375.3 | 101.6 | -2.1 | 128.6 (C6) | 126.4 (C5) | 2.2 |
|  **4.88** | -400.5885 | -251373.3 | 103.6 | -0.1 | 128.1 (N/A) | 128.1 (N/A) | 0.00 |

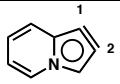
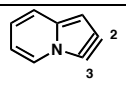
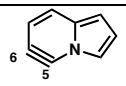
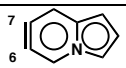
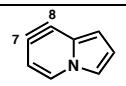
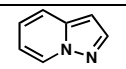
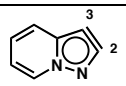
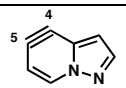
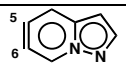
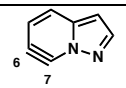
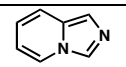
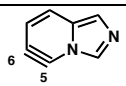
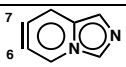
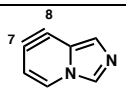
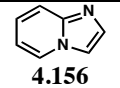
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|---|---|---|---|---|---|---|---|
|  **4.89** | -400.5906 | -251374.6 | 102.3 | -1.4 | 128.5 (C7) | 125.8 (C8) | 2.7 |
|  **4.90** | -417.9343 | -262258.0 | | | | | |
|  **4.91** | -416.5944 | -261417.2 | 103.2 | -0.5 | 129.2 (C6) | 124.9 (C5) | 4.3 |
|  **4.92** | -417.9650 | -262277.2 | | | | | |
|  **4.93** | -416.6269 | -261437.5 | 102.0 | -1.6 | 129.2 (C6) | 125.7 (C5) | 3.5 |
|  **4.94** | -417.9321 | -262256.6 | | | | | |
|  **4.95** | -416.5941 | -261417.0 | 102.0 | -1.7 | 128.3 (C6) | 126.0 (C5) | 2.3 |
|  **4.96** | -416.591 | -261415.0 | 103.9 | 0.2 | 129.0 (C7) | 127.8 (C6) | 1.2 |
|  **4.97** | -416.5922 | -261415.8 | 103.2 | -0.5 | 128.7 (C7) | 125.9 (C8) | 2.8 |
|  **4.98** | -417.9701 | -262280.4 | | | | | |
|  **4.99** | -416.6308 | -261440.0 | 102.8 | -0.9 | 129.2 (C6) | 124.9 (C5) | 4.3 |
|  **4.100** | -416.6295 | -261439.2 | 103.6 | -0.1 | 128.9 (C7) | 127.8 (C6) | 1.1 |
|  **4.101** | -416.6319 | -261440.7 | 102.1 | -1.6 | 129.2 (C7) | 125.8 (C8) | 3.4 |

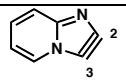
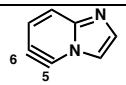
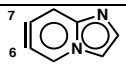
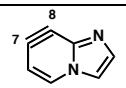
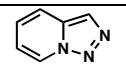
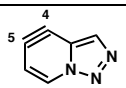
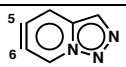
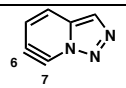
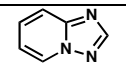
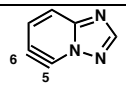
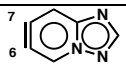
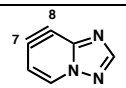
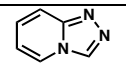
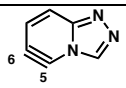
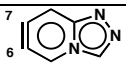
### 4.7.5.4 Other Hetarynes (Aryne Within Heterocycle)

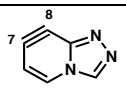
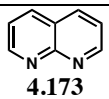
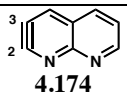
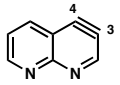
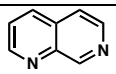
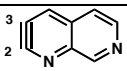
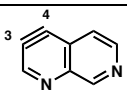
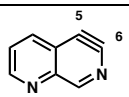
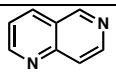
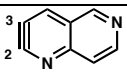
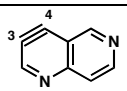
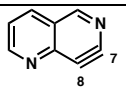
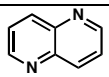
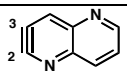
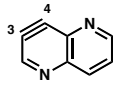
| Structure | Energy (hartrees) | Energy (kcal/mol) | Dehydro-genation Energy (kcal/mol) | Standard-ized Energy (kcal/mol) | Larger Terminus | Smaller Terminus | Angle Difference |
|---|---|---|---|---|---|---|---|
|  **4.102** | -248.285 | -155801.3 | | | | | |
|  **4.103*** | -246.9493 | -154963.2 | 100.5 | -3.2 | 125.3 (C4) | 124.7 (C3) | 0.6 |
|  **4.104*** | -246.9413 | -154958.1 | 105.6 | 1.9 | 151.2 (C2) | 104.0 (C3) | 47.2 |
|  **4.105** | -264.2876 | -165843.1 | | | | | |
|  **4.106*** | -262.946 | -165001.2 | 104.2 | 0.5 | 148.7 (C3) | 107.0 (C4) | 41.7 |
|  **4.107** | -264.3237 | -165865.8 | | | | | |
|  **4.108*** | -262.9847 | -165025.5 | 102.6 | -1.1 | 147.2 (C4) | 103.4 (C5) | 43.8 |
|  **4.109** | -280.3221 | -175904.9 | | | | | |
|  **4.110*** | -278.9624 | -175051.7 | 115.6 | 11.9 | 147.7 (C5) | 96.6 (C6) | 51.1 |
|  **4.111*** | -400.5880 | -251373.0 | 103.9 | 0.2 | 150.8 (C3) | 105.4 (C4) | 45.4 |
|  **4.112*** | -400.5905 | -251374.5 | 103.4 | 0.7 | 153.0 (C2) | 104.0 (C3) | 49.0 |
|  **4.113*** | -400.5968 | -251378.5 | 99.5 | -4.2 | 126.6 (C4) | 124.1 (C3) | 2.5 |
|  **4.114** | -379.8538 | -238362.1 | | | | | |

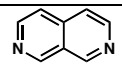
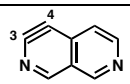
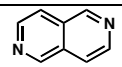
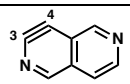
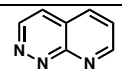
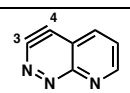
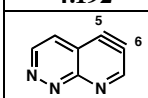
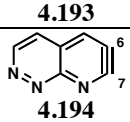
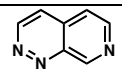
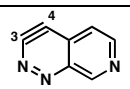
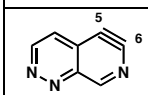
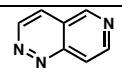
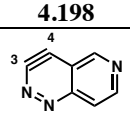
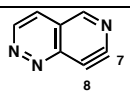
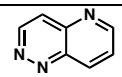
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|---|---|---|---|---|---|---|---|
|  **4.115*** | -378.4577 | -237486.0 | 138.4 | 34.7 | 114.1 (C3) | 110.5 (C2) | 3.6 |
|  **4.116*** | -378.5116 | -237519.8 | 104.6 | 0.9 | 151.8 (C5) | 106.7 (C6) | 45.1 |
|  **4.117*** | -378.5207 | -237525.5 | 98.9 | -4.8 | 130.6 (C6) | 117.9 (C7) | 12.7 |
|  **4.118** | -379.8545 | -238362.5 | | | | | |
|  **4.119*** | -378.4537 | -237483.5 | 141.4 | 37.7 | 113.7 (C3) | 110.5 (C2) | 3.2 |
|  **4.120*** | -378.5208 | -237525.6 | 99.3 | -4.4 | 152.9 (C6) | 100.0 (C7) | 52.9 |
|  **4.121** | -379.8535 | -238361.9 | | | | | |
|  **4.122*** | -378.4529 | -237483.0 | 141.3 | 37.6 | 114.0 (C3) | 110.7 (C2) | 3.3 |
|  **4.123*** | -378.5125 | -237520.4 | 103.9 | 0.2 | 151.8 (C5) | 103.5 (C4) | 48.3 |
|  **4.124** | -379.8608 | -238366.5 | | | | | |
|  **4.125*** | -378.4683 | -237492.6 | 136.2 | 32.5 | 114.9 (C3) | 110.0 (C2) | 4.9 |
|  **4.126*** | -378.513 | -237520.7 | 101.3 | -2.4 | 125.5 (C5) | 125.3 (C4) | 0.2 |
|  **4.127*** | -378.5239 | -237527.5 | 108.1 | 4.4 | 149.3 (C6) | 108.8 (C5) | 40.5 |
|  **4.128*** | -362.4177 | -227420.7 | 140.3 | 36.6 | 114.5 (C3) | 110.1 (C2) | 4.4 |

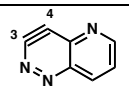
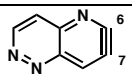
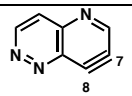
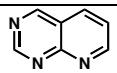
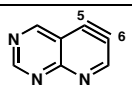
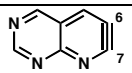
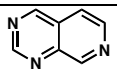
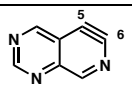
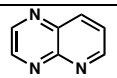
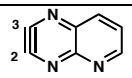
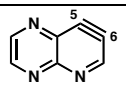
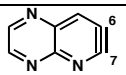
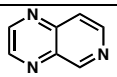
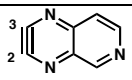
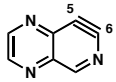
| | | | | | | | |
|---|---|---|---|---|---|---|---|
|  **4.129*** | -382.26 | -239872.0 | 149.3 | 45.6 | 126.9 (C2) | 100.3 (C3) | 26.6 |
|  **4.130*** | -705.2874 | -442574.9 | 119.7 | 16.0 | 132.6 (C3) | 102.3 (C2) | 30.3 |
|  **4.131** | -553.0026 | -347014.7 | | | | | |
|  **4.132*** | -551.621 | -346147.7 | 129.3 | 25.6 | 118.2 (N/A) | 118.2 (N/A) | 0.0 |
|  **4.133*** | -551.6334 | -346155.5 | 121.6 | 17.9 | 135.6 (C3) | 97.0 (C2) | 38.6 |
|  **4.134** | -416.5896 | -261414.1 | 104.8 | 1.1 | 147.5 (C3) | 108.3 (C4) | 39.2 |
|  **4.135** | -323.4472 | -202966.4 | | | | | |
|  **4.136** | -322.0926 | -202116.3 | 112.4 | 8.7 | 132.1 (C3) | 124.6 (C2) | 7.5 |
|  **4.137** | -322.1004 | -202121.2 | 107.5 | 3.8 | 127.1 (C4) | 125.4 (C3) | 1.7 |
|  **4.138** | -268.4764 | -168471.6 | | | | | |
|  **4.139** | -267.0862 | -167599.3 | 134.7 | 31.0 | 132.2 (C2) | 123.1 (C3) | 9.1 |
|  **4.140** | -267.1193 | -167620.0 | 114.0 | 10.3 | 132.7 (C4) | 119.5 (C3) | 13.2 |
|  **4.141** | -363.7988 | -228287.4 | | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
|  **4.142*** | -362.4096 | -227415.6 | 134.1 | 30.4 | 114.2 (C2) | 110.1 (C1) | 4.1 |
|  **4.143*** | -362.3962 | -227407.2 | 142.5 | 38.8 | 118.5 (C2) | 106.1 (C3) | 12.4 |
|  **4.144** | -362.4455 | -227438.2 | 111.6 | 7.9 | 130.1 (C6) | 124.4 (C5) | 5.7 |
|  **4.145** | -362.4507 | -227441.4 | 108.3 | 4.6 | 134.2 (C7) | 120.9 (C6) | 13.3 |
|  **4.146** | -362.4601 | -227447.3 | 102.4 | -1.3 | 130.1 (C7) | 124.1 (C8) | 6.0 |
|  **4.147** | -379.8340 | -238349.6 | | | | | |
|  **4.148*** | -378.4337 | -237470.9 | 141.1 | 37.4 | 133.2 (C2) | 94.6 (C3) | 38.6 |
|  **4.149** | -378.4942 | -237508.9 | 103.1 | -0.6 | 130.9 (C5) | 122.9 (C4) | 8.0 |
|  **4.150** | -378.4857 | -237503.6 | 108.4 | 4.7 | 134.4 (C5) | 121.1 (C6) | 13.3 |
|  **4.151** | -378.4766 | -237497.9 | 114.2 | 10.5 | 130.2 (C6) | 123.4 (C7) | 6.8 |
|  **4.152** | -379.8431 | -238355.3 | | | | | |
|  **4.153** | -378.4888 | -237505.5 | 112.2 | 8.5 | 131.1 (C6) | 122.9 (C5) | 8.2 |
|  **4.154** | -378.4937 | -237508.6 | 109.1 | 5.4 | 134.5 (C7) | 121.3 (C6) | 13.2 |
|  **4.155** | -378.5035 | -237514.7 | 103.0 | -0.7 | 130.7 (C7) | 123.1 (C8) | 7.6 |
|  **4.156** | -379.8496 | -238359.4 | | | | | |

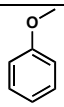
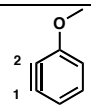
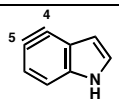
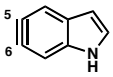
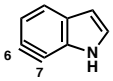
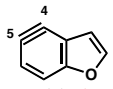
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|  **4.157*** | -378.4444 | -237477.6 | 144.2 | 40.5 | 136.4 | 89.9 | 46.5 |
|  **4.158** | -378.495 | -237509.4 | 112.4 | 8.7 | 129.7 (C6) | 124.1 (C5) | 5.6 |
|  **4.159** | -378.502 | -237513.8 | 108.0 | 4.3 | 134.7 (C7) | 120.9 (C6) | 13.8 |
|  **4.160** | -378.5095 | -237518.5 | 103.3 | -0.4 | 131.4 (C7) | 122.7 (C8) | 8.7 |
|  **4.161** | -395.8547 | -248402.8 | | | | | |
|  **4.162** | -394.5125 | -247560.5 | 104.6 | 0.9 | 131.0 (C5) | 122.1 (C4) | 8.9 |
|  **4.163** | -394.5044 | -247555.5 | 109.7 | 6.0 | 134.1 (C5) | 121.7 (C6) | 12.4 |
|  **4.164** | -394.4956 | -247549.9 | 115.2 | 11.5 | 131.2 (C6) | 121.9 (C7) | 9.3 |
|  **4.165** | -395.8872 | -248423.2 | | | | | |
|  **4.166** | -394.5285 | -247570.6 | 115.0 | 11.3 | 130.4 (C6) | 122.3 (C5) | 8.1 |
|  **4.167** | -394.5392 | -247577.3 | 108.3 | 4.6 | 134.8 (C7) | 121.2 (C6) | 13.6 |
|  **4.168** | -394.5457 | -247581.4 | 104.2 | 0.5 | 132.1 (C7) | 121.4 (C8) | 10.7 |
|  **4.169** | -395.8681 | -248411.2 | | | | | |
|  **4.170** | -394.5115 | -247559.9 | 113.7 | 10.0 | 130.4 (C6) | 122.7 (C5) | 7.7 |
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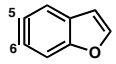
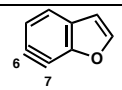
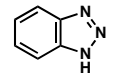
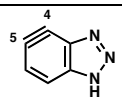
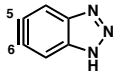
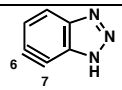
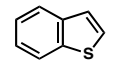
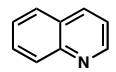
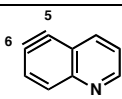
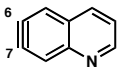
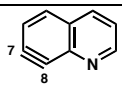
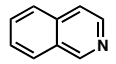
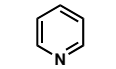
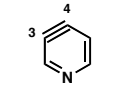
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|  **4.173** | -417.966 | -262277.8 | | | | | |
|  **4.174** | -416.6274 | -261437.9 | 102.4 | -1.3 | 153.5 (C2) | 103.2 (C3) | 50.3 |
|  **4.175** | -416.6305 | -261439.8 | 100.4 | -3.3 | 125.6 (C4) | 124.3 (C3) | 1.3 |
|  **4.176** | -417.9652 | -262277.3 | | | | | |
|  **4.177** | -416.6239 | -261435.7 | 104.1 | 0.4 | 152.5 (C2) | 105.2 (C3) | 47.3 |
|  **4.178** | -416.6306 | -261439.9 | 99.8 | -3.9 | 125.5 (C4) | 125.1 (C3) | 0.3 |
|  **4.179** | -416.6236 | -261435.5 | 104.2 | 0.5 | 151.5 (C6) | 104.4 (C5) | 47.1 |
|  **4.180** | -417.9661 | -262277.9 | | | | | |
|  **4.181** | -416.6250 | -261436.4 | 103.9 | 0.2 | 152.6 (C2) | 104.9 (C3) | 47.7 |
|  **4.182** | -416.6303 | -261439.7 | 100.6 | -3.1 | 125.1 (C4) | 125.0 (C3) | 0.1 |
|  **4.183** | -416.6229 | -261435.0 | 105.2 | 1.5 | 149.8 (C7) | 107.5 (C8) | 42.3 |
|  **4.184** | -417.9685 | -262279.4 | | | | | |
|  **4.185** | -416.6255 | -261436.7 | 105.1 | 1.4 | 152.9 (C2) | 105.1 (C3) | 47.8 |
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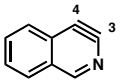
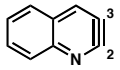
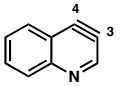
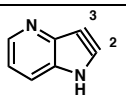
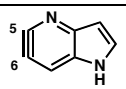
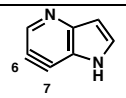
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|  **4.187** | -417.964 | -262276.6 | | | | | |
|  **4.188** | -416.6224 | -261434.7 | 104.2 | 0.5 | 151.0 (C3) | 105.0 (C4) | 46.0 |
|  **4.189** | -417.9629 | -262275.9 | | | | | |
|  **4.190** | -416.6208 | -261433.7 | 104.6 | 0.9 | 151.2 (C3) | 103.8 (C4) | 47.4 |
|  **4.191** | -433.9645 | -272317.1 | | | | | |
|  **4.192** | -432.6200 | -271473.4 | 106.1 | 2.4 | 148.7 (C3) | 106.4 (C4) | 42.3 |
|  **4.193** | -432.6286 | -271478.8 | 100.7 | -3.0 | 125.4 (C5) | 124.3 (C6) | 1.0 |
|  **4.194** | -432.6245 | -271476.2 | 103.2 | -0.5 | 153.3 (C7) | 104.3 (C6) | 49.0 |
|  **4.195** | -433.9648 | -272317.3 | | | | | |
|  **4.196** | -432.6216 | -271474.4 | 105.2 | 1.5 | 147.4 (C3) | 108.1 (C4) | 39.3 |
|  **4.197** | -432.6225 | -271474.9 | 104.7 | 1.0 | 151.5 (C6) | 104.2 (C5) | 47.1 |
|  **4.198** | -433.9645 | -272317.1 | | | | | |
|  **4.199** | -432.6206 | -271473.8 | 105.7 | 2.0 | 148.4 (C3) | 106.3 (C4) | 42.1 |
|  **4.200** | -432.6192 | -271472.9 | 106.6 | 2.9 | 149.9 (C7) | 106.2 (C8) | 43.7 |
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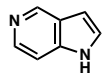
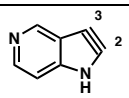
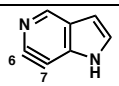
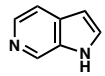
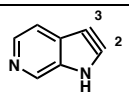
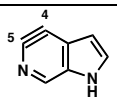
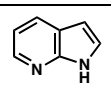
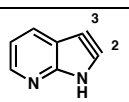
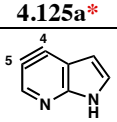
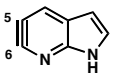
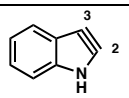
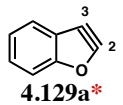
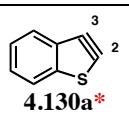
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|  **4.202** | -432.6252 | -271476.6 | 105.4 | 1.7 | 146.2 (C3) | 109.9 (C4) | 36.3 |
|  **4.203** | -432.6248 | -271476.4 | 105.7 | 2.0 | 152.5 (C6) | 106.1 (C7) | 46.4 |
|  **4.204** | -432.6314 | -271480.5 | 101.5 | -2.2 | 125.6 (C7) | 124.6 (C8) | 1.0 |
|  **4.205** | -434.0045 | -272342.2 | | | | | |
|  **4.206** | -432.6671 | -271502.9 | 101.6 | -2.1 | 124.9 (C6) | 124.5 (C5) | 0.4 |
|  **4.207** | -432.6647 | -271501.4 | 103.1 | -0.6 | 153.0 (C7) | 104.3 (C6) | 48.7 |
|  **4.208** | -434.0037 | -272341.7 | | | | | |
|  **4.209** | -432.6592 | -271498.0 | 106.1 | 2.4 | 151.9 (C6) | 102.6 (C5) | 49.3 |
|  **4.210** | -434.0001 | -272339.4 | | | | | |
|  **4.211** | -432.6304 | -271479.9 | 121.9 | 18.2 | 154.1 (C2) | 91.8 (C3) | 62.3 |
|  **4.212** | -432.6637 | -271500.8 | 101.0 | -2.7 | 125.5 (C6) | 124.4 (C5) | 1.1 |
|  **4.213** | -432.6583 | -271497.4 | 104.4 | 0.7 | 153.5 (C7) | 104.4 (C6) | 49.1 |
|  **4.214** | -433.9981 | -272338.1 | | | | | |
|  **4.215** | -432.6244 | -271476.1 | 124.4 | 20.7 | 131.9 (C3) | 131.5 (C2) | 0.4 |
|  **4.216** | -432.6546 | -271495.1 | 105.4 | 1.7 | 150.4 (C6) | 106.4 (C5) | 44.0 |

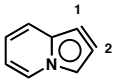
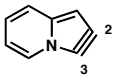
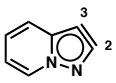
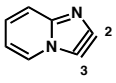
### 4.7.5.5 Selected Energies using MP2/6-311+G**

| Structure | Energy (hartrees) | Energy (kcal/mol) | Dehydrogenation Energy (kcal/mol) | Standardized Energy (kcal/mol) | Larger Terminus | Smaller Terminus | Angle Difference |
|---|---|---|---|---|---|---|---|
| H—H<br>**4.1a** | -1.1602722 | -728.1 | | | | | |
|  <br>**4.2a** | -231.5838779 | -145321.2 | | | | | |
|  <br>**4.3a*** | -230.2732476 | -144498.8 | 94.4 | 0.0 | 126.8 (N/A) | 126.8 (N/A) | 0.0 |
|  <br>**4.4a** | -345.8429028 | -217019.9 | | | | | |
|  <br>**4.5a*** | -344.5380523 | -216201.1 | 90.7 | -3.6 | 130.6 (C1) | 122.8 (C2) | 7.8 |
|  <br>**4.6a** | -362.8267529 | -227677.4 | | | | | |
|  <br>**4.7a*** | -361.5173825 | -226855.8 | 93.6 | -0.8 | 127.4 (C5) | 126.1 (C4) | 1.3 |
|  <br>**4.8a*** | -361.5120066 | -226852.4 | 96.9 | 2.6 | 128.3 (C6) | 128.0 (C5) | 0.3 |
|  <br>**4.9a*** | -361.5181322 | -226856.2 | 93.1 | -1.3 | 129.2 (C6) | 122.3 (C7) | 6.9 |
|  <br>**4.10a** | -382.6636787 | -240125.3 | | | | | |
|  <br>**4.11a*** | -381.3515379 | -239301.9 | 95.3 | 0.9 | 127.8 (C5) | 125.2 (C4) | 2.6 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
|  **4.12a*** | -381.3488424 | -239300.2 | 97.0 | 2.6 | 128.3 (N/A) | 128.3 (N/A) | 0.0 |
|  **4.13a*** | -381.3520756 | -239302.2 | 95.0 | 0.6 | 129.9 (C6) | 120.8 (C7) | 9.1 |
|  **4.30a** | -394.8552468 | -247775.6 | | | | | |
|  **4.31a*** | -393.5423481 | -246951.8 | 95.8 | 1.4 | 128.1 (C5) | 124.0 (C4) | 4.1 |
|  **4.32a*** | -393.5378788 | -246949.0 | 98.6 | 4.2 | 129.5 (C6) | 128.3 (C5) | 1.2 |
|  **4.33a*** | -393.5433232 | -246952.4 | 95.2 | 0.8 | 129.7 (C6) | 121.1 (C7) | 8.6 |
|  **4.38a** | -705.2721885 | -442565.4 | | | | | |
|  **4.82a** | -400.8327162 | -251526.5 | | | | | |
|  **4.83a*** | -399.5239462 | -250705.3 | 93.2 | -1.2 | 127.3 (C5) | 126.8 (C6) | 0.5 |
|  **4.84a*** | -399.5173046 | -250701.1 | 97.4 | 3.0 | 128.2 (C7) | 127.2 (C6) | 1.0 |
|  **4.85a*** | -399.5236281 | -250705.1 | 93.4 | -1.0 | 128.7 (C7) | 125.5 (C8) | 3.2 |
|  **4.86a** | -400.8304960 | -251525.1 | | | | | |
|  **4.102a** | -247.6089605 | -155377.1 | | | | | |
|  **4.103a*** | -246.3010004 | -154556.3 | 92.7 | -1.7 | 126.2 (C4) | 123.0 (C3) | 3.2 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
|  **4.104a*** | -246.2879319 | -154548.1 | 100.9 | 6.5 | 145.9 (C2) | 111.6 (C3) | 34.3 |
|  **4.105a** | -263.6000902 | -165411.7 | | | | | |
|  **4.106a*** | -262.2797103 | -164583.1 | 100.5 | 6.1 | 140.0 (C3) | 116.6 (C4) | 23.4 |
|  **4.107a** | -263.63605 | -165434.3 | | | | | |
|  **4.108a*** | -262.3192632 | -164608.0 | 98.2 | 3.9 | 141.9 (C4) | 110.5 (C5) | 31.4 |
|  **4.109a** | -279.6239417 | -175466.8 | | | | | |
|  **4.110a*** | -278.2851891 | -174626.7 | 112.0 | 17.6 | 132.8 (C5) | 123.9 (C6) | 8.9 |
|  **4.111a*** | -399.5109697 | -250697.1 | 99.9 | 5.6 | 141.5 (C3) | 117.0 (C4) | 24.5 |
|  **4.112a*** | -399.5123645 | -250698.0 | 100.5 | 6.1 | 151.0 (C2) | 107.7 (C3) | 43.3 |
|  **4.113a*** | -399.5278657 | -250707.7 | 90.7 | -3.6 | 126.8 (C4) | 123.3 (C3) | 3.5 |
|  **4.114a** | -378.8526836 | -237733.8 | | | | | |
|  **4.115a*** | -377.4848399 | -236875.5 | 130.3 | 35.9 | 118.0 (C2) | 105.2 (C3) | 12.8 |
|  **4.116a*** | -377.5302974 | -236904.0 | 101.7 | 7.4 | 148.5 (C5) | 112.2 (C6) | 36.3 |
|  **4.117a*** | -377.5473884 | -236914.8 | 91.0 | -3.3 | 125.1 (C6) | 122.8 (C7) | 2.3 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
|  **4.118a** | -378.8527666 | -237733.9 | | | | | |
|  **4.119a*** | -377.4832556 | -236874.5 | 131.3 | 36.9 | 116.6 (C2) | 106.0 (C3) | 10.6 |
|  **4.120a*** | -377.5387573 | -236909.3 | 96.5 | 2.1 | 151.7 (C6) | 103.0 (C7) | 48.7 |
|  **4.121** | -378.8521074 | -237733.5 | | | | | |
|  **4.122a*** | -377.4820657 | -236873.8 | 131.6 | 37.3 | 117.5 (C2) | 105.4 (C3) | 12.1 |
|  **4.123a*** | -377.5313632 | -236904.7 | 100.7 | 6.3 | 144.3 (C5) | 113.4 (C4) | 30.9 |
|  **4.124a** | -378.8594773 | -237738.1 | | | | | |
|  **4.125a*** | -377.4963563 | -236882.7 | 127.3 | 32.9 | 116.9 (C2) | 106.5 (C3) | 10.4 |
|  **4.126a*** | -377.5512763 | -236917.2 | 92.8 | -1.5 | 126.2 (C4) | 123.9 (C5) | 2.3 |
|  **4.127a*** | -377.5343047 | -236906.6 | 103.5 | 9.1 | 142.4 (C6) | 117.2 (C5) | 25.2 |
|  **4.128a*** | -361.4587617 | -226819.0 | 130.3 | 36.0 | 116.9 (C2) | 106.1 (C3) | 10.8 |
|  **4.129a*** | -381.2835416 | -239259.2 | 138.0 | 43.6 | 118.8 (C2) | 106.4 (C3) | 12.4 |
|  **4.130a*** | -703.9307758 | -441723.6 | 113.7 | 19.3 | 118.1 (C2) | 114.5 (C3) | 3.6 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
|  **4.131a** | -552.0441704 | -346413.2 | | | | | |
|  **4.132a*** | -550.6874736 | -345561.9 | 123.3 | 28.9 | 116.7 (N/A) | 116.7 (N/A) | 0.0 |
|  **4.133a*** | -550.6969653 | -345567.9 | 117.3 | 23.0 | 115.9 (C2) | 114.7 (C3) | 1.2 |
|  **4.141a** | -362.8059171 | -227664.3 | | | | | |
|  **4.142a*** | -361.4470206 | -226811.6 | 124.6 | 30.3 | 113.1 (C2) | 110.0 (C1) | 3.1 |
|  **4.143a*** | -361.4325605 | -226802.5 | 133.7 | 39.4 | 114.2 (C3) | 109.2 (C2) | 5.0 |
|  **4.147a** | -378.8302728 | -237719.8 | | | | | |
|  **4.148a*** | -377.4548064 | -236856.7 | 135.0 | 40.7 | 119.4 (C2) | 106.4 (C3) | 13.0 |
|  **4.156a** | -378.8460432 | -237729.7 | | | | | |
|  **4.157a*** | -377.4509762 | -236854.3 | 147.3 | 53.0 | 113.0 (C3) | 112.2 (C2) | 0.8 |

## 4.7.6 Coordinates of Computed Structures

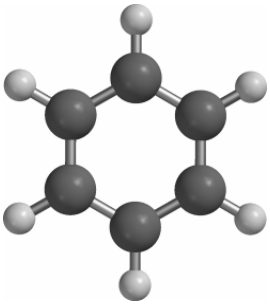
### 4.7.6.1 Structures Using B3LYP/6-31G*

**4.1**



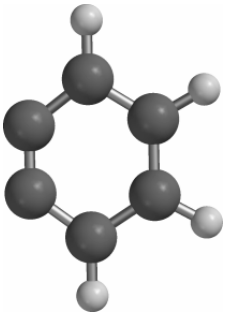
| | | | |
|---|---|---|---|
| H | 0.000000 | 0.000000 | 0.371578 |
| H | 0.000000 | 0.000000 | -0.371578 |

**4.2**



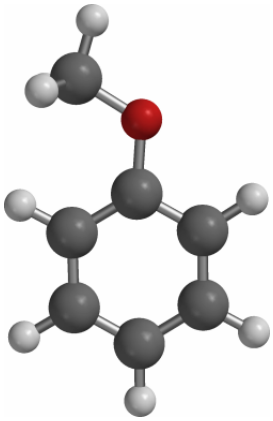
| | | | |
|---|---|---|---|
| H | 2.484269 | 0.000000 | -0.000000 |
| C | 1.397048 | 0.000000 | -0.000000 |
| C | -1.397048 | -0.000000 | 0.000000 |
| C | 0.698524 | 1.209879 | 0.000000 |
| C | 0.698524 | -1.209879 | -0.000000 |
| C | -0.698524 | -1.209879 | -0.000000 |
| C | -0.698524 | 1.209879 | 0.000000 |
| H | 1.242135 | 2.151440 | 0.000000 |
| H | 1.242135 | -2.151440 | -0.000000 |
| H | -1.242135 | -2.151440 | -0.000000 |
| H | -1.242135 | 2.151440 | 0.000000 |
| H | -2.484269 | -0.000000 | 0.000000 |

**4.3***



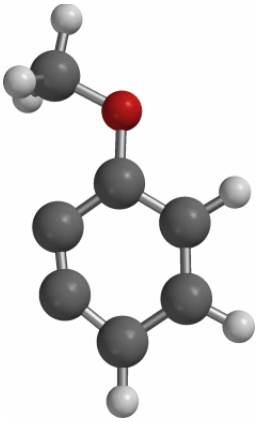
| | | | |
|---|---|---|---|
| C | 0.625554 | 0.000000 | 1.237609 |
| C | -0.703547 | -0.000000 | -1.058538 |
| C | -0.625554 | -0.000000 | 1.237609 |
| C | 1.461350 | 0.000000 | 0.133663 |
| C | 0.703547 | 0.000000 | -1.058538 |
| C | -1.461350 | -0.000000 | 0.133663 |
| H | 2.546616 | 0.000000 | 0.134515 |
| H | 1.229529 | 0.000000 | -2.010917 |
| H | -2.546616 | -0.000000 | 0.134515 |
| H | -1.229529 | -0.000000 | -2.010917 |

**4.4**



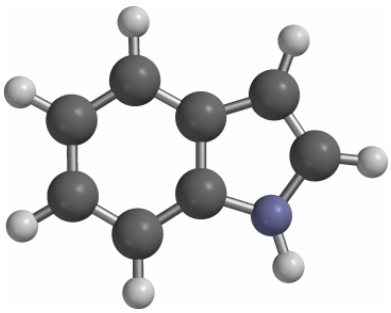
| | | | |
|---|---|---|---|
| H | -0.135193 | -2.330225 | 0.000000 |
| C | -0.492177 | -1.304778 | 0.000000 |
| C | -1.343988 | 1.346699 | 0.000000 |
| C | 0.453709 | -0.268524 | 0.000000 |
| C | -1.849965 | -1.007648 | 0.000000 |
| C | -2.286811 | 0.321871 | 0.000000 |
| C | 0.025817 | 1.063988 | 0.000000 |
| H | -2.573123 | -1.819173 | 0.000000 |
| H | -3.348440 | 0.551637 | 0.000000 |
| H | 0.739070 | 1.880156 | 0.000000 |
| H | -1.667645 | 2.384512 | 0.000000 |
| O | 1.762023 | -0.664345 | 0.000000 |
| C | 2.765670 | 0.336671 | 0.000000 |
| H | 2.705220 | 0.971054 | -0.894707 |
| H | 3.719247 | -0.194937 | 0.000000 |
| H | 2.705220 | 0.971054 | 0.894707 |

## 4.5*



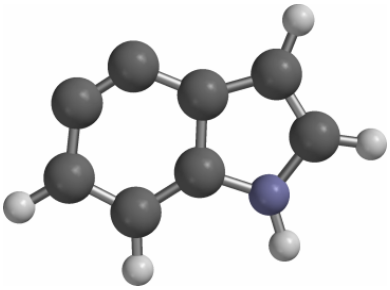
| | | | |
|---|---|---|---|
| H | -0.279144 | -2.243871 | 0.000000 |
| C | -0.560704 | -1.194627 | 0.000000 |
| C | -1.220427 | 1.310456 | 0.000000 |
| C | 0.473728 | -0.226055 | 0.000000 |
| C | -1.912589 | -0.830830 | 0.000000 |
| C | -2.343404 | 0.520072 | 0.000000 |
| C | 0.014839 | 1.093266 | 0.000000 |
| H | -2.667498 | -1.614583 | 0.000000 |
| H | -3.383608 | 0.820240 | 0.000000 |
| O | 1.759860 | -0.642419 | 0.000000 |
| C | 2.744737 | 0.386160 | 0.000000 |
| H | 2.651629 | 1.016573 | -0.892610 |
| H | 3.711716 | -0.119566 | 0.000000 |
| H | 2.651629 | 1.016573 | 0.892610 |

## 4.6



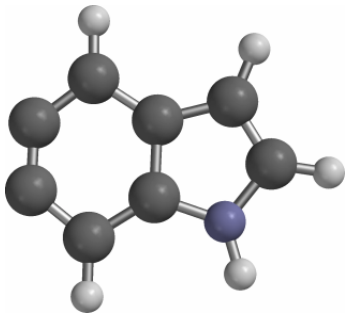
| | | | |
|---|---|---|---|
| H | -1.016054 | -2.513274 | 0.000000 |
| C | -0.985787 | -1.426483 | 0.000000 |
| C | -0.934480 | 1.420966 | 0.000000 |
| C | 0.247658 | -0.751135 | 0.000000 |
| C | -2.161696 | -0.687735 | 0.000000 |
| C | -2.136209 | 0.722456 | 0.000000 |
| C | 0.247797 | 0.672737 | 0.000000 |
| H | -3.119466 | -1.201144 | 0.000000 |
| H | -3.072698 | 1.273637 | 0.000000 |
| H | -0.916247 | 2.508033 | 0.000000 |
| C | 1.622707 | -1.168675 | 0.000000 |
| H | 1.993539 | -2.184640 | 0.000000 |
| C | 2.388865 | -0.033424 | 0.000000 |
| H | 3.463985 | 0.082184 | 0.000000 |
| N | 1.567169 | 1.079268 | 0.000000 |
| H | 1.883789 | 2.036046 | 0.000000 |

## 4.7*



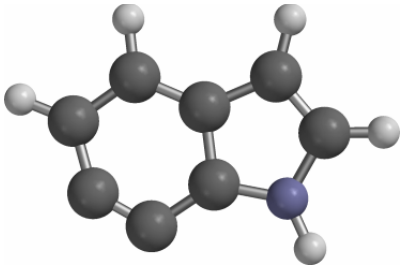
| | | | |
|---|---|---|---|
| C | -0.999055 | -1.465025 | 0.000000 |
| C | -1.119874 | 1.247945 | 0.000000 |
| C | 0.260615 | -0.864366 | 0.000000 |
| C | -2.084933 | -0.852996 | 0.000000 |
| C | -2.322232 | 0.523128 | 0.000000 |
| C | 0.119028 | 0.572630 | 0.000000 |
| H | -3.288928 | 1.014761 | 0.000000 |
| H | -1.149899 | 2.335151 | 0.000000 |
| C | 1.656839 | -1.161591 | 0.000000 |
| H | 2.117196 | -2.139101 | 0.000000 |
| C | 2.315393 | 0.043591 | 0.000000 |
| H | 3.376305 | 0.251677 | 0.000000 |
| N | 1.403907 | 1.080172 | 0.000000 |
| H | 1.645458 | 2.058821 | 0.000000 |

## 4.8*



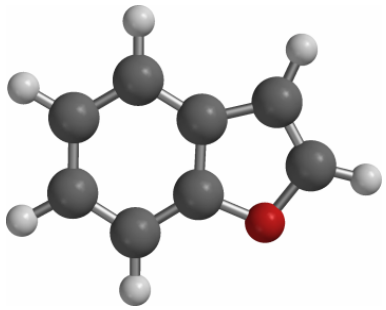
| | | | |
|---|---|---|---|
| H | -1.137958 | -2.575893 | 0.000000 |
| C | -1.099803 | -1.491332 | 0.000000 |
| C | -1.059455 | 1.475166 | -0.000000 |
| C | 0.121887 | -0.760476 | 0.000000 |
| C | -2.156485 | -0.611040 | -0.000000 |
| C | -2.161208 | 0.644711 | -0.000000 |
| C | 0.116248 | 0.682985 | -0.000000 |
| H | -1.046542 | 2.561466 | -0.000000 |
| C | 1.501365 | -1.165227 | 0.000000 |
| H | 1.876684 | -2.179267 | 0.000000 |
| C | 2.262569 | -0.027547 | 0.000000 |
| H | 3.337696 | 0.090979 | 0.000000 |
| N | 1.437982 | 1.082782 | 0.000000 |
| H | 1.753550 | 2.039798 | -0.000000 |

## 4.9*



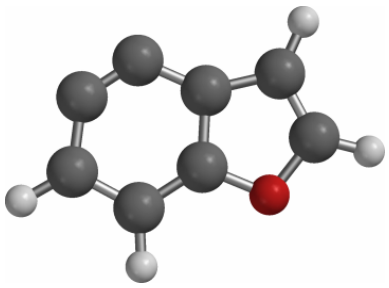
| | | | |
|---|---|---|---|
| H | -1.257405 | -2.341034 | 0.000000 |
| C | -1.166698 | -1.257261 | 0.000000 |
| C | -0.934782 | 1.505611 | 0.000000 |
| C | 0.116526 | -0.660828 | 0.000000 |
| C | -2.340641 | -0.483505 | 0.000000 |
| C | -2.008758 | 0.864042 | 0.000000 |
| C | 0.250204 | 0.773065 | 0.000000 |
| H | -3.332302 | -0.919301 | 0.000000 |
| C | 1.456396 | -1.181163 | 0.000000 |
| H | 1.749941 | -2.222165 | 0.000000 |
| C | 2.314449 | -0.112211 | 0.000000 |
| H | 3.395239 | -0.089322 | 0.000000 |
| N | 1.591861 | 1.068688 | 0.000000 |
| H | 1.981978 | 1.998035 | 0.000000 |

## 4.10



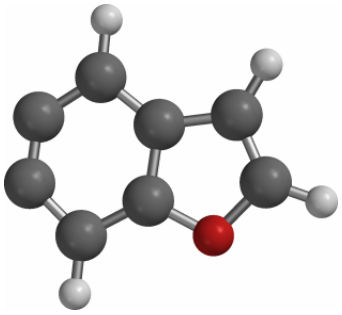
| | | | |
|---|---|---|---|
| H | -0.876074 | -2.499235 | 0.000000 |
| C | -0.911963 | -1.414616 | 0.000000 |
| C | -0.964783 | 1.440415 | 0.000000 |
| C | 0.249954 | -0.651998 | 0.000000 |
| C | -2.115688 | -0.711741 | 0.000000 |
| C | -2.140674 | 0.695892 | 0.000000 |
| C | 0.260367 | 0.755890 | 0.000000 |
| H | -3.052220 | -1.262374 | 0.000000 |
| H | -3.098727 | 1.208605 | 0.000000 |
| H | -0.995211 | 2.526662 | 0.000000 |
| C | 1.655982 | 1.127045 | 0.000000 |
| H | 2.074639 | 2.124094 | 0.000000 |
| C | 2.352486 | -0.035617 | 0.000000 |
| H | 3.410051 | -0.254982 | 0.000000 |
| O | 1.531489 | -1.137232 | 0.000000 |

## 4.11*



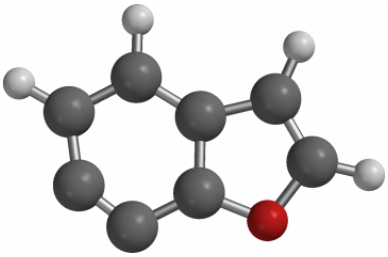
| | | | |
|---|---|---|---|
| C | -0.984044 | -1.484390 | 0.000000 |
| C | -1.101388 | 1.244675 | 0.000000 |
| C | 0.265578 | -0.865982 | 0.000000 |
| C | -2.060443 | -0.852761 | 0.000000 |
| C | -2.306077 | 0.518698 | 0.000000 |
| C | 0.119361 | 0.551482 | 0.000000 |
| H | -3.274453 | 1.006061 | 0.000000 |
| H | -1.109049 | 2.330292 | 0.000000 |
| C | 1.679376 | -1.120323 | 0.000000 |
| H | 2.182058 | -2.076646 | 0.000000 |
| C | 2.268934 | 0.103456 | 0.000000 |
| H | 3.303505 | 0.413185 | 0.000000 |
| O | 1.360126 | 1.130814 | 0.000000 |

## 4.12*



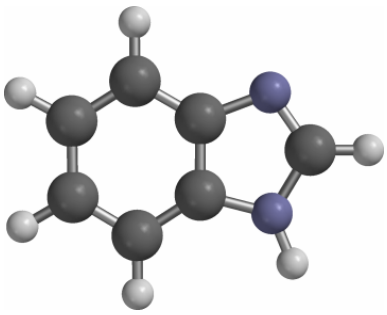
| | | | |
|---|---|---|---|
| H | -1.144718 | -2.576332 | 0.000000 |
| C | -1.095012 | -1.492582 | 0.000000 |
| C | -1.024714 | 1.481654 | 0.000000 |
| C | 0.122798 | -0.765101 | 0.000000 |
| C | -2.147046 | -0.599424 | 0.000000 |
| C | -2.132468 | 0.654411 | 0.000000 |
| C | 0.121751 | 0.663860 | 0.000000 |
| H | -0.984070 | 2.565320 | 0.000000 |
| C | 1.518551 | -1.135662 | 0.000000 |
| H | 1.932272 | -2.134492 | 0.000000 |
| C | 2.222251 | 0.022271 | 0.000000 |
| H | 3.281470 | 0.234667 | 0.000000 |
| O | 1.409150 | 1.128841 | 0.000000 |

## 4.13*



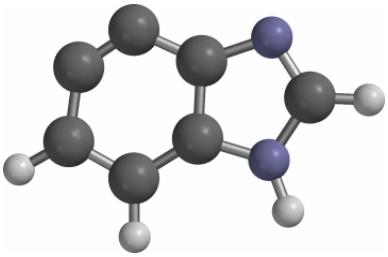
| | | | |
|---|---|---|---|
| H | -1.244032 | -2.349703 | 0.000000 |
| C | -1.146057 | -1.267136 | 0.000000 |
| C | -0.897150 | 1.507194 | 0.000000 |
| C | 0.132354 | -0.667956 | 0.000000 |
| C | -2.314896 | -0.479834 | 0.000000 |
| C | -1.970403 | 0.859538 | 0.000000 |
| C | 0.261696 | 0.750725 | 0.000000 |
| H | -3.310305 | -0.906649 | 0.000000 |
| C | 1.491013 | -1.156215 | 0.000000 |
| H | 1.824751 | -2.184811 | 0.000000 |
| C | 2.289830 | -0.059774 | 0.000000 |
| H | 3.362682 | 0.062330 | 0.000000 |
| O | 1.574915 | 1.114169 | 0.000000 |

## 4.14



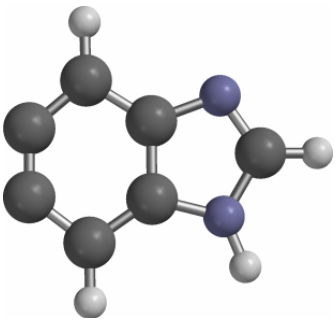
| | | | |
|---|---|---|---|
| C | -0.274193 | -0.720132 | 0.000000 |
| C | -0.256889 | 0.696219 | 0.000000 |
| N | -1.582746 | -1.191123 | 0.000000 |
| C | -2.321586 | -0.112562 | 0.000000 |
| H | -3.404715 | -0.098727 | 0.000000 |
| N | -1.593957 | 1.056711 | 0.000000 |
| H | -1.968205 | 1.993733 | 0.000000 |
| C | 0.934003 | -1.429087 | 0.000000 |
| H | 0.928841 | -2.514731 | 0.000000 |
| C | 2.119952 | -0.702661 | 0.000000 |
| H | 3.070597 | -1.228630 | 0.000000 |
| C | 2.117529 | 0.707435 | 0.000000 |
| H | 3.064321 | 1.240380 | 0.000000 |
| C | 0.929427 | 1.433446 | 0.000000 |
| H | 0.931990 | 2.520063 | 0.000000 |

## 4.15



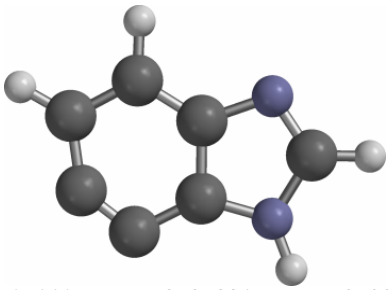
| | | | |
|---|---|---|---|
| C | -0.935530 | -1.485329 | 0.000000 |
| C | -1.103408 | 1.257746 | 0.000000 |
| C | 0.297977 | -0.833243 | 0.000000 |
| C | -2.016687 | -0.860778 | 0.000000 |
| C | -2.290806 | 0.503571 | 0.000000 |
| C | 0.137687 | 0.594206 | 0.000000 |
| H | -3.268660 | 0.971694 | 0.000000 |
| H | -1.155775 | 2.343429 | 0.000000 |
| N | 1.441586 | 1.062248 | 0.000000 |
| H | 1.739439 | 2.026739 | 0.000000 |
| C | 2.267467 | -0.036986 | 0.000000 |
| H | 3.344690 | 0.071969 | 0.000000 |
| N | 1.629130 | -1.182087 | 0.000000 |

## 4.16



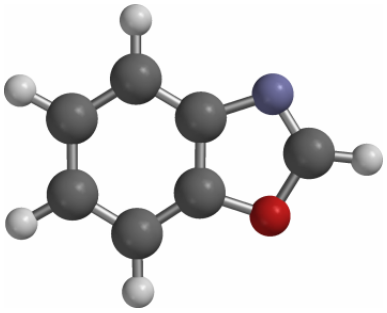
| | | | |
|---|---|---|---|
| H | -1.063894 | -2.574431 | 0.000000 |
| C | -1.053603 | -1.490434 | 0.000000 |
| C | -1.040279 | 1.491372 | 0.000000 |
| C | 0.148314 | -0.735075 | 0.000000 |
| C | -2.113798 | -0.612857 | 0.000000 |
| C | -2.131938 | 0.641939 | 0.000000 |
| C | 0.132259 | 0.703385 | 0.000000 |
| H | -1.044562 | 2.577203 | 0.000000 |
| N | 1.474061 | 1.046579 | 0.000000 |
| H | 1.854476 | 1.981178 | 0.000000 |
| C | 2.196808 | -0.125230 | 0.000000 |
| H | 3.280265 | -0.115310 | 0.000000 |
| N | 1.454527 | -1.200682 | 0.000000 |

## 4.17



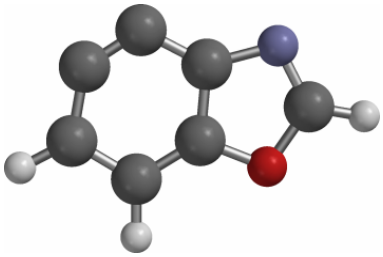
| | | | |
|---|---|---|---|
| H | -1.174415 | -2.358845 | 0.000000 |
| C | -1.117038 | -1.274398 | 0.000000 |
| C | -0.921662 | 1.507547 | 0.000000 |
| C | 0.148779 | -0.646299 | 0.000000 |
| C | -2.297755 | -0.511987 | 0.000000 |
| C | -1.980782 | 0.839198 | 0.000000 |
| C | 0.262937 | 0.778951 | 0.000000 |
| H | -3.286090 | -0.955088 | 0.000000 |
| N | 1.620518 | 1.027903 | 0.000000 |
| H | 2.066661 | 1.933131 | 0.000000 |
| C | 2.242880 | -0.201132 | 0.000000 |
| H | 3.322728 | -0.282104 | 0.000000 |
| N | 1.415004 | -1.215215 | 0.000000 |

## 4.18



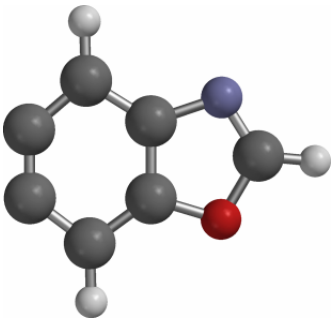
| | | | |
|---|---|---|---|
| H | -0.933123 | -2.522706 | 0.000000 |
| C | -0.926882 | -1.437477 | 0.000000 |
| C | -0.896639 | 1.434753 | 0.000000 |
| C | 0.276878 | -0.728234 | 0.000000 |
| C | -2.106531 | -0.694794 | 0.000000 |
| C | -2.092383 | 0.712815 | 0.000000 |
| C | 0.262349 | 0.672766 | 0.000000 |
| H | -3.061802 | -1.211816 | 0.000000 |
| H | -3.035041 | 1.252624 | 0.000000 |
| H | -0.873782 | 2.519250 | 0.000000 |
| O | 1.570134 | 1.099402 | 0.000000 |
| C | 2.287097 | -0.068213 | 0.000000 |
| H | 3.362444 | 0.044815 | 0.000000 |
| N | 1.607511 | -1.164251 | 0.000000 |

## 4.19



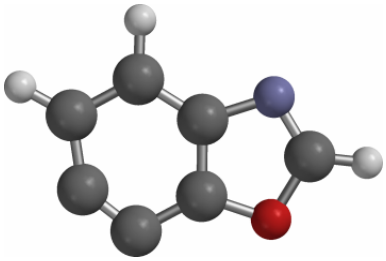
| | | | |
|---|---|---|---|
| C | -0.921033 | -1.489046 | 0.000000 |
| C | -1.074132 | 1.270420 | 0.000000 |
| C | 0.302150 | -0.824390 | 0.000000 |
| C | -1.991360 | -0.842926 | 0.000000 |
| C | -2.266385 | 0.518823 | 0.000000 |
| C | 0.146513 | 0.584426 | 0.000000 |
| H | -3.243735 | 0.987153 | 0.000000 |
| H | -1.103065 | 2.355277 | 0.000000 |
| O | 1.413011 | 1.117992 | 0.000000 |
| C | 2.231781 | 0.019942 | 0.000000 |
| H | 3.292264 | 0.229395 | 0.000000 |
| N | 1.655589 | -1.136273 | 0.000000 |

## 4.20



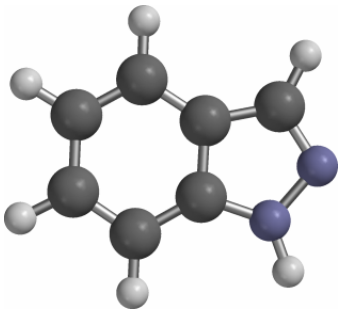
| | | | |
|---|---|---|---|
| H | -1.070857 | -2.579363 | 0.000000 |
| C | -1.050854 | -1.495750 | 0.000000 |
| C | -1.015329 | 1.495396 | 0.000000 |
| C | 0.143676 | -0.739305 | 0.000000 |
| C | -2.109478 | -0.608703 | 0.000000 |
| C | -2.109099 | 0.644716 | 0.000000 |
| C | 0.130611 | 0.684533 | 0.000000 |
| H | -0.997595 | 2.579320 | 0.000000 |
| O | 1.441851 | 1.094893 | 0.000000 |
| C | 2.155840 | -0.074475 | 0.000000 |
| H | 3.231796 | 0.034897 | 0.000000 |
| N | 1.472395 | -1.167275 | 0.000000 |

## 4.21



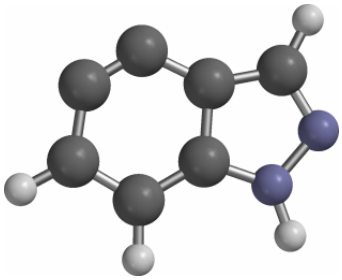
| | | | |
|---|---|---|---|
| H | -1.162187 | -2.364978 | 0.000000 |
| C | -1.099292 | -1.281145 | 0.000000 |
| C | -0.891077 | 1.514507 | 0.000000 |
| C | 0.158555 | -0.647048 | 0.000000 |
| C | -2.276309 | -0.506224 | 0.000000 |
| C | -1.947769 | 0.837536 | 0.000000 |
| C | 0.268175 | 0.763451 | 0.000000 |
| H | -3.268173 | -0.940982 | 0.000000 |
| O | 1.602343 | 1.079580 | 0.000000 |
| C | 2.216961 | -0.145380 | 0.000000 |
| H | 3.297846 | -0.124398 | 0.000000 |
| N | 1.448873 | -1.183301 | 0.000000 |

## 4.22



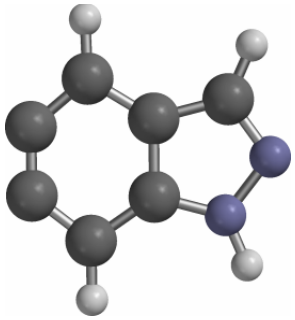
| | | | |
|---|---|---|---|
| H | -0.999303 | -2.519540 | 0.000000 |
| C | -0.973118 | -1.433152 | 0.000000 |
| C | -0.926134 | 1.426835 | 0.000000 |
| C | 0.254464 | -0.744808 | 0.000000 |
| C | -2.145529 | -0.695014 | 0.000000 |
| C | -2.118729 | 0.720014 | 0.000000 |
| C | 0.259450 | 0.674257 | 0.000000 |
| H | -3.104670 | -1.204949 | 0.000000 |
| H | -3.058300 | 1.265971 | 0.000000 |
| H | -0.912681 | 2.513073 | 0.000000 |
| C | 1.638698 | -1.101084 | 0.000000 |
| H | 2.081609 | -2.088683 | 0.000000 |
| N | 2.418863 | -0.034746 | 0.000000 |
| N | 1.578649 | 1.035284 | 0.000000 |
| H | 1.976291 | 1.961543 | 0.000000 |

## 4.23



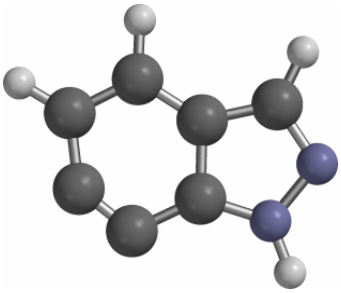
| | | | |
|---|---|---|---|
| C | -0.975395 | -1.478955 | 0.000000 |
| C | -1.116485 | 1.252269 | 0.000000 |
| C | 0.273281 | -0.851378 | 0.000000 |
| C | -2.057795 | -0.863846 | 0.000000 |
| C | -2.305383 | 0.512689 | 0.000000 |
| C | 0.130562 | 0.580745 | 0.000000 |
| H | -3.277569 | 0.993179 | 0.000000 |
| H | -1.158872 | 2.338154 | 0.000000 |
| C | 1.675822 | -1.078329 | 0.000000 |
| H | 2.212297 | -2.017242 | 0.000000 |
| N | 2.346275 | 0.064014 | 0.000000 |
| N | 1.413935 | 1.051045 | 0.000000 |
| H | 1.732450 | 2.007862 | 0.000000 |

## 4.24



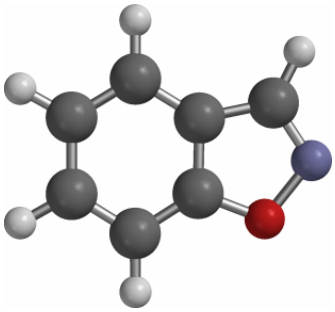
| | | | |
|---|---|---|---|
| H | -1.139314 | -2.572536 | 0.000000 |
| C | -1.098367 | -1.488268 | 0.000000 |
| C | -1.044230 | 1.488055 | 0.000000 |
| C | 0.123362 | -0.753535 | 0.000000 |
| C | -2.148628 | -0.604734 | 0.000000 |
| C | -2.136389 | 0.652820 | 0.000000 |
| C | 0.131592 | 0.684109 | 0.000000 |
| H | -1.031198 | 2.573350 | 0.000000 |
| N | 1.454723 | 1.030731 | 0.000000 |
| H | 1.856791 | 1.955007 | 0.000000 |
| N | 2.291588 | -0.041948 | 0.000000 |
| C | 1.508766 | -1.105906 | 0.000000 |
| H | 1.949766 | -2.094210 | 0.000000 |

## 4.25



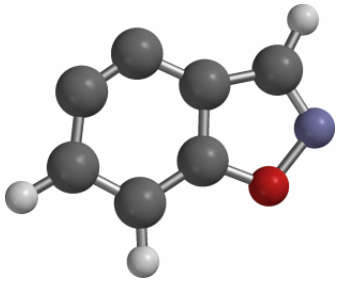
| | | | |
|---|---|---|---|
| H | -1.249819 | -2.345974 | 0.000000 |
| C | -1.158061 | -1.262722 | 0.000000 |
| C | -0.917883 | 1.510424 | 0.000000 |
| C | 0.124125 | -0.660191 | 0.000000 |
| C | -2.324651 | -0.485174 | 0.000000 |
| C | -1.986991 | 0.865228 | 0.000000 |
| C | 0.266774 | 0.768369 | 0.000000 |
| H | -3.318843 | -0.914363 | 0.000000 |
| N | 1.605219 | 1.014635 | 0.000000 |
| H | 2.078659 | 1.904912 | 0.000000 |
| N | 2.344156 | -0.128272 | 0.000000 |
| C | 1.473983 | -1.125317 | 0.000000 |
| H | 1.838605 | -2.144678 | 0.000000 |

## 4.26



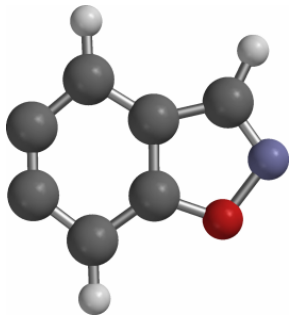
| | | | |
|---|---|---|---|
| H | -0.999503 | -2.531250 | 0.000000 |
| C | -0.968355 | -1.445592 | 0.000000 |
| C | -0.897814 | 1.419067 | 0.000000 |
| C | 0.253405 | -0.753862 | 0.000000 |
| C | -2.136708 | -0.695311 | 0.000000 |
| C | -2.098263 | 0.716209 | 0.000000 |
| C | 0.265213 | 0.647388 | 0.000000 |
| H | -3.099479 | -1.197638 | 0.000000 |
| H | -3.033458 | 1.269149 | 0.000000 |
| H | -0.860841 | 2.502956 | 0.000000 |
| O | 1.542655 | 1.098898 | 0.000000 |
| N | 2.408238 | -0.017411 | 0.000000 |
| C | 1.649712 | -1.080069 | 0.000000 |
| H | 2.121958 | -2.055212 | 0.000000 |

## 4.27



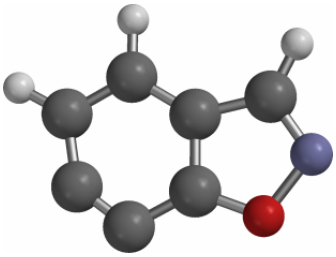
| | | | |
|---|---|---|---|
| H | 3.254364 | -0.988418 | 0.000000 |
| C | 2.280028 | -0.513092 | 0.000000 |
| C | -0.283332 | 0.838389 | 0.000000 |
| C | 1.089275 | -1.256422 | 0.000000 |
| C | 2.022273 | 0.856927 | 0.000000 |
| C | 0.949352 | 1.492414 | 0.000000 |
| C | -0.143235 | -0.572259 | 0.000000 |
| H | 1.113686 | -2.341185 | 0.000000 |
| O | -1.372350 | -1.136815 | 0.000000 |
| N | -2.342934 | -0.109623 | 0.000000 |
| C | -1.698993 | 1.028093 | 0.000000 |
| H | -2.267028 | 1.949588 | 0.000000 |

## 4.28



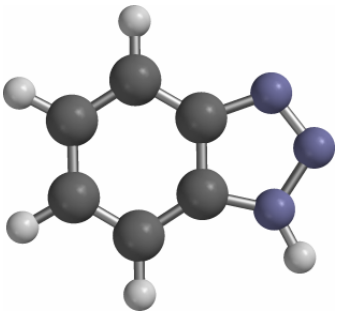
| | | | |
|---|---|---|---|
| C | 2.112681 | -0.626035 | 0.000000 |
| C | 2.124611 | 0.629725 | 0.000000 |
| C | 1.063475 | 1.506844 | 0.000000 |
| H | 1.095336 | 2.591010 | 0.000000 |
| C | -0.140308 | 0.753110 | 0.000000 |
| C | -0.136262 | -0.667031 | 0.000000 |
| C | 1.026059 | -1.474220 | 0.000000 |
| H | 1.002588 | -2.557618 | 0.000000 |
| O | -1.411693 | -1.123029 | 0.000000 |
| N | -2.289029 | -0.016441 | 0.000000 |
| C | -1.541890 | 1.054319 | 0.000000 |
| H | -2.027341 | 2.022707 | 0.000000 |

## 4.29



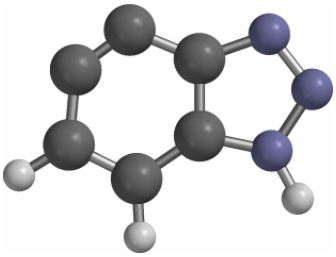
| | | | |
|---|---|---|---|
| C | 1.961199 | -0.833422 | 0.000000 |
| C | -0.145042 | 0.664513 | 0.000000 |
| C | 0.898309 | -1.493065 | 0.000000 |
| C | 2.295087 | 0.513029 | 0.000000 |
| C | 1.122788 | 1.288073 | 0.000000 |
| C | -0.273957 | -0.747286 | 0.000000 |
| H | 3.287296 | 0.946399 | 0.000000 |
| H | 1.205457 | 2.371546 | 0.000000 |
| O | -1.573944 | -1.101292 | 0.000000 |
| N | -2.349513 | 0.081139 | 0.000000 |
| C | -1.513360 | 1.086355 | 0.000000 |
| H | -1.920033 | 2.090693 | 0.000000 |

## 4.30



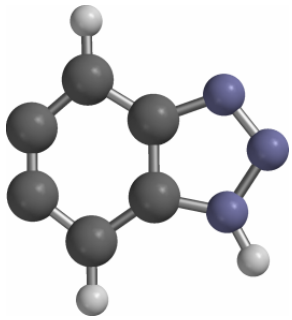
| | | | |
|---|---|---|---|
| H | -0.936129 | -2.514189 | 0.000000 |
| C | -0.936883 | -1.428955 | 0.000000 |
| C | -0.911917 | 1.445163 | 0.000000 |
| C | 0.272326 | -0.715167 | 0.000000 |
| C | -2.111653 | -0.694094 | 0.000000 |
| C | -2.096085 | 0.722163 | 0.000000 |
| C | 0.273445 | 0.695456 | 0.000000 |
| H | -3.068211 | -1.208399 | 0.000000 |
| H | -3.041316 | 1.257887 | 0.000000 |
| H | -0.909411 | 2.530831 | 0.000000 |
| N | 1.580122 | -1.160660 | 0.000000 |
| N | 2.365426 | -0.135220 | 0.000000 |
| N | 1.604321 | 0.998129 | 0.000000 |
| H | 2.067931 | 1.894848 | 0.000000 |

## 4.31*



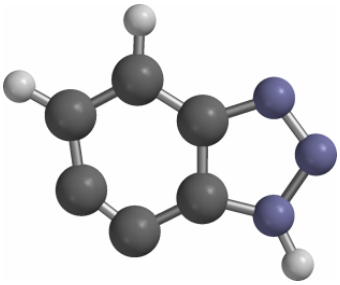
| | | | |
|---|---|---|---|
| H | 3.246004 | -0.990687 | 0.000000 |
| C | 2.267555 | -0.524056 | 0.000000 |
| C | -0.303016 | 0.812434 | 0.000000 |
| C | 1.087424 | -1.280382 | 0.000000 |
| C | 1.997465 | 0.845170 | 0.000000 |
| C | 0.924923 | 1.479359 | 0.000000 |
| C | -0.157550 | -0.610908 | 0.000000 |
| H | 1.142002 | -2.365071 | 0.000000 |
| N | -1.455634 | -1.026632 | 0.000000 |
| H | -1.841442 | -1.960010 | 0.000000 |
| N | -2.318159 | 0.030173 | 0.000000 |
| N | -1.635252 | 1.130937 | 0.000000 |

## 4.32*



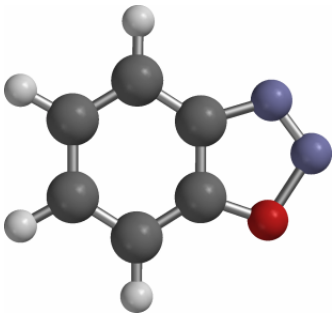
| | | | |
|---|---|---|---|
| C | 2.111054 | -0.657535 | 0.000000 |
| C | -0.140580 | 0.726025 | 0.000000 |
| C | 1.027571 | -1.507014 | 0.000000 |
| C | 2.115777 | 0.600063 | 0.000000 |
| C | 1.065897 | 1.483101 | 0.000000 |
| C | -0.145104 | -0.705099 | 0.000000 |
| H | 1.026985 | -2.591785 | 0.000000 |
| H | 1.081753 | 2.566853 | 0.000000 |
| N | -1.479626 | -0.990074 | 0.000000 |
| H | -1.949564 | -1.883508 | 0.000000 |
| N | -2.235856 | 0.147012 | 0.000000 |
| N | -1.444734 | 1.168288 | 0.000000 |

## 4.33*



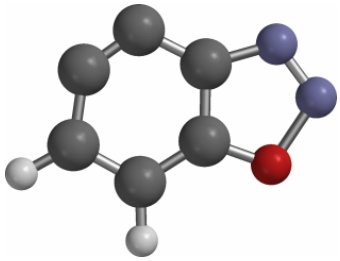
| | | | |
|---|---|---|---|
| C | 1.960354 | -0.853015 | 0.000000 |
| C | -0.152171 | 0.637795 | 0.000000 |
| C | 0.903190 | -1.518541 | 0.000000 |
| C | 2.285749 | 0.501842 | 0.000000 |
| C | 1.115547 | 1.270513 | 0.000000 |
| C | -0.281550 | -0.780817 | 0.000000 |
| H | 3.277641 | 0.936236 | 0.000000 |
| H | 1.176123 | 2.354495 | 0.000000 |
| N | -1.627314 | -0.974688 | 0.000000 |
| H | -2.161204 | -1.831811 | 0.000000 |
| N | -2.287774 | 0.220885 | 0.000000 |
| N | -1.418394 | 1.180748 | 0.000000 |

## 4.34



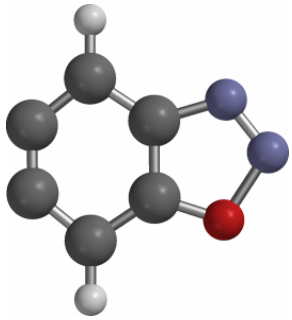
| | | | |
|---|---|---|---|
| H | -0.905502 | -2.525113 | 0.000000 |
| C | -0.914277 | -1.440423 | 0.000000 |
| C | -0.893226 | 1.437103 | 0.000000 |
| C | 0.277618 | -0.708839 | 0.000000 |
| C | -2.093870 | -0.707271 | 0.000000 |
| C | -2.077047 | 0.705796 | 0.000000 |
| C | 0.288306 | 0.691327 | 0.000000 |
| H | -3.048659 | -1.223899 | 0.000000 |
| H | -3.022850 | 1.240363 | 0.000000 |
| H | -0.882883 | 2.521104 | 0.000000 |
| N | 1.605206 | -1.114851 | 0.000000 |
| N | 2.373414 | -0.134781 | 0.000000 |
| O | 1.559592 | 1.109484 | 0.000000 |

## 4.35



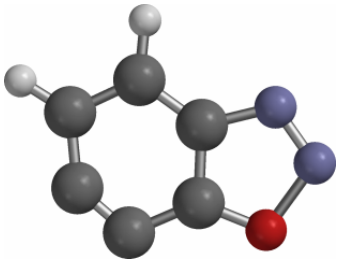
| | | | |
|---|---|---|---|
| C | -0.886904 | -1.518760 | 0.000000 |
| C | -1.086328 | 1.264110 | 0.000000 |
| C | 0.304950 | -0.800420 | 0.000000 |
| C | -1.954175 | -0.869713 | 0.000000 |
| C | -2.256351 | 0.486295 | 0.000000 |
| C | 0.164735 | 0.612466 | 0.000000 |
| H | -3.244213 | 0.932016 | 0.000000 |
| H | -1.143562 | 2.347220 | 0.000000 |
| N | 1.660910 | -1.069062 | 0.000000 |
| N | 2.329630 | -0.023048 | 0.000000 |
| O | 1.380376 | 1.153982 | 0.000000 |

## 4.36



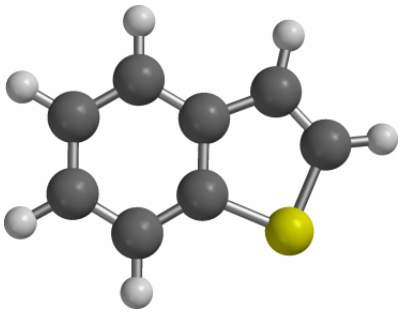
| | | | |
|---|---|---|---|
| C | 2.080315 | -0.624393 | 0.000000 |
| C | 2.096422 | 0.631131 | 0.000000 |
| C | 1.028931 | 1.500466 | 0.000000 |
| H | 1.031549 | 2.584350 | 0.000000 |
| C | -0.154132 | 0.720348 | 0.000000 |
| C | -0.161472 | -0.702672 | 0.000000 |
| C | 1.010689 | -1.494637 | 0.000000 |
| H | 1.009987 | -2.577787 | 0.000000 |
| N | -1.478640 | 1.113308 | 0.000000 |
| N | -2.250173 | 0.136266 | 0.000000 |
| O | -1.433910 | -1.111030 | 0.000000 |

## 4.37



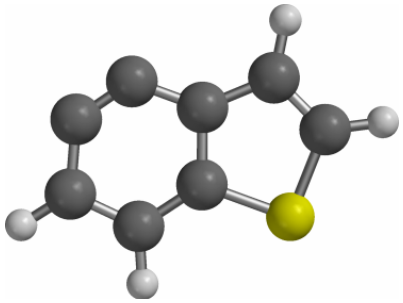
| | | | |
|---|---|---|---|
| H | -1.156787 | -2.354485 | 0.000000 |
| C | -1.100883 | -1.270490 | 0.000000 |
| C | -0.876032 | 1.513961 | 0.000000 |
| C | 0.154521 | -0.625707 | 0.000000 |
| C | -2.271272 | -0.497698 | 0.000000 |
| C | -1.936153 | 0.851632 | 0.000000 |
| C | 0.307259 | 0.783458 | 0.000000 |
| H | -3.264527 | -0.928323 | 0.000000 |
| N | 1.436030 | -1.146131 | 0.000000 |
| N | 2.296597 | -0.247045 | 0.000000 |
| O | 1.600420 | 1.086861 | 0.000000 |

## 4.38



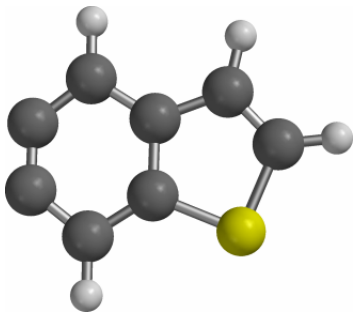
| | | | |
|---|---|---|---|
| H | -0.899493 | -2.505831 | 0.000000 |
| C | -1.037730 | -1.428432 | 0.000000 |
| C | -1.403072 | 1.376939 | 0.000000 |
| C | 0.061047 | -0.563518 | 0.000000 |
| C | -2.313621 | -0.875370 | 0.000000 |
| C | -2.494585 | 0.519883 | 0.000000 |
| C | -0.100360 | 0.844853 | 0.000000 |
| H | -3.180588 | -1.530295 | 0.000000 |
| H | -3.501230 | 0.928780 | 0.000000 |
| H | -1.546493 | 2.454484 | 0.000000 |
| C | 1.166869 | 1.531402 | 0.000000 |
| H | 1.262214 | 2.612224 | 0.000000 |
| C | 2.228432 | 0.685436 | 0.000000 |
| H | 3.279705 | 0.942647 | 0.000000 |
| S | 1.763672 | -1.003957 | 0.000000 |

## 4.39



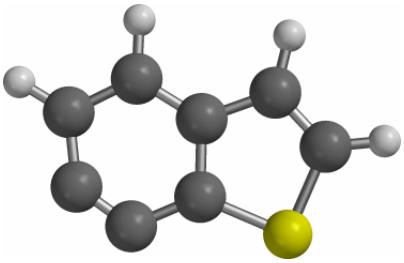
| | | | |
|---|---|---|---|
| C | -1.442077 | -1.403698 | 0.000000 |
| C | -1.211176 | 1.284790 | 0.000000 |
| C | -0.115006 | -0.975945 | 0.000000 |
| C | -2.443392 | -0.661077 | 0.000000 |
| C | -2.502992 | 0.730041 | 0.000000 |
| C | -0.066122 | 0.461571 | 0.000000 |
| H | -3.395649 | 1.345546 | 0.000000 |
| H | -1.098656 | 2.366030 | 0.000000 |
| S | 1.608343 | 0.996988 | 0.000000 |
| C | 2.182454 | -0.655847 | 0.000000 |
| H | 3.249219 | -0.838378 | 0.000000 |
| C | 1.184831 | -1.579812 | 0.000000 |
| H | 1.350836 | -2.650620 | 0.000000 |

## 4.40



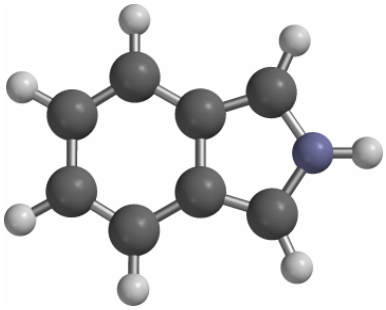
| | | | |
|---|---|---|---|
| H | -1.753502 | -2.450830 | 0.000000 |
| C | -1.569734 | -1.381101 | 0.000000 |
| C | -1.097197 | 1.533036 | 0.000000 |
| C | -0.253135 | -0.835598 | 0.000000 |
| C | -2.499716 | -0.368148 | 0.000000 |
| C | -2.305943 | 0.871319 | 0.000000 |
| C | -0.045535 | 0.584193 | 0.000000 |
| H | -0.927170 | 2.604849 | 0.000000 |
| S | 1.675566 | 0.960362 | 0.000000 |
| C | 2.085329 | -0.743813 | 0.000000 |
| H | 3.128078 | -1.034963 | 0.000000 |
| C | 0.997540 | -1.554113 | 0.000000 |
| H | 1.058263 | -2.637263 | 0.000000 |

## 4.41



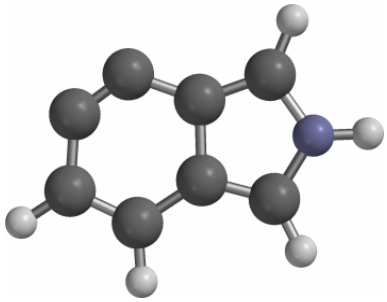
| | | | |
|---|---|---|---|
| H | -1.792994 | -2.254537 | 0.000000 |
| C | -1.581148 | -1.187757 | 0.000000 |
| C | -1.023267 | 1.480767 | 0.000000 |
| C | -0.231910 | -0.753280 | 0.000000 |
| C | -2.657970 | -0.285806 | 0.000000 |
| C | -2.183487 | 1.018397 | 0.000000 |
| C | 0.084472 | 0.648413 | 0.000000 |
| H | -3.692584 | -0.608409 | 0.000000 |
| S | 1.813658 | 0.926812 | 0.000000 |
| C | 2.107328 | -0.800997 | 0.000000 |
| H | 3.128753 | -1.158956 | 0.000000 |
| C | 0.971373 | -1.546444 | 0.000000 |
| H | 0.973932 | -2.631337 | 0.000000 |

## 4.42



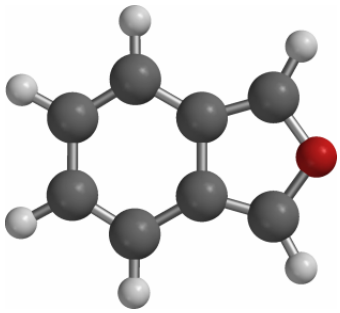
| | | | |
|---|---|---|---|
| C | 0.714999 | 0.000000 | 2.153016 |
| H | 1.238782 | 0.000000 | 3.105450 |
| C | 1.430766 | 0.000000 | 0.980872 |
| H | 2.518142 | 0.000000 | 0.992527 |
| C | -0.714999 | 0.000000 | 2.153016 |
| H | -1.238782 | 0.000000 | 3.105450 |
| C | -1.430766 | 0.000000 | 0.980872 |
| H | -2.518142 | 0.000000 | 0.992527 |
| C | 0.726058 | 0.000000 | -0.255083 |
| C | -0.726058 | 0.000000 | -0.255083 |
| C | 1.134924 | 0.000000 | -1.587443 |
| H | 2.117187 | 0.000000 | -2.036008 |
| C | -1.134924 | 0.000000 | -1.587443 |
| H | -2.117187 | 0.000000 | -2.036008 |
| N | 0.000000 | 0.000000 | -2.354387 |
| H | 0.000000 | 0.000000 | -3.363930 |

## 4.43



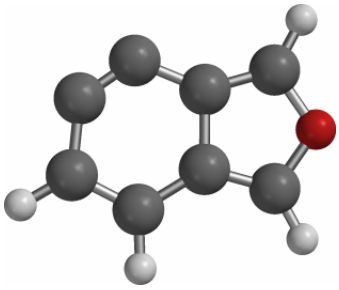
| | | | |
|---|---|---|---|
| C | -0.987781 | -1.455736 | 0.000000 |
| C | -2.070407 | -0.851822 | 0.000000 |
| C | -2.333624 | 0.535957 | 0.000000 |
| H | -3.312355 | 1.002831 | 0.000000 |
| C | -1.158667 | 1.274216 | 0.000000 |
| H | -1.217946 | 2.360398 | 0.000000 |
| C | 0.127893 | 0.644704 | 0.000000 |
| C | 0.271838 | -0.825035 | 0.000000 |
| C | 1.626709 | -1.116069 | 0.000000 |
| H | 2.160843 | -2.053482 | 0.000000 |
| C | 1.425233 | 1.152611 | 0.000000 |
| H | 1.795303 | 2.167469 | 0.000000 |
| N | 2.285838 | 0.088489 | 0.000000 |
| H | 3.291301 | 0.178124 | 0.000000 |

## 4.44



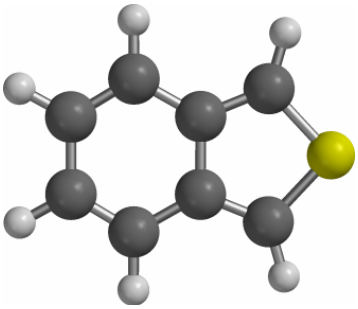
| | | | |
|---|---|---|---|
| C | -1.437862 | 0.000000 | 0.981922 |
| H | -2.524388 | 0.000000 | 0.993307 |
| C | -0.719051 | 0.000000 | 2.146076 |
| H | -1.238232 | 0.000000 | 3.100707 |
| C | 0.719051 | 0.000000 | 2.146076 |
| H | 1.238232 | 0.000000 | 3.100707 |
| C | 1.437862 | 0.000000 | 0.981922 |
| H | 2.524388 | 0.000000 | 0.993307 |
| C | 0.727608 | 0.000000 | -0.258078 |
| C | -0.727608 | 0.000000 | -0.258078 |
| C | -1.103412 | 0.000000 | -1.581820 |
| H | -2.052316 | 0.000000 | -2.094975 |
| C | 1.103412 | 0.000000 | -1.581820 |
| H | 2.052316 | 0.000000 | -2.094975 |
| O | 0.000000 | 0.000000 | -2.373275 |

## 4.45



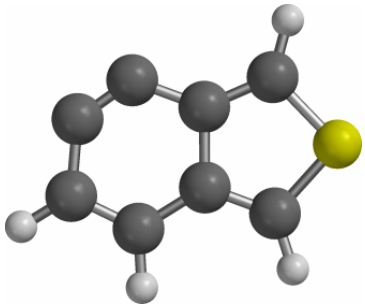
| | | | |
|---|---|---|---|
| C | 1.148545 | -1.278632 | 0.000000 |
| H | 1.211275 | -2.363931 | 0.000000 |
| C | 2.313730 | -0.534985 | 0.000000 |
| H | 3.295453 | -0.994617 | 0.000000 |
| C | 2.043174 | 0.856214 | 0.000000 |
| C | 0.968509 | 1.469001 | 0.000000 |
| C | -0.290919 | 0.826503 | 0.000000 |
| C | -0.144496 | -0.647293 | 0.000000 |
| C | -1.635862 | 1.083434 | 0.000000 |
| H | -2.234415 | 1.979996 | 0.000000 |
| C | -1.433876 | -1.124356 | 0.000000 |
| H | -1.869391 | -2.111880 | 0.000000 |
| O | -2.317760 | -0.094660 | 0.000000 |

## 4.46



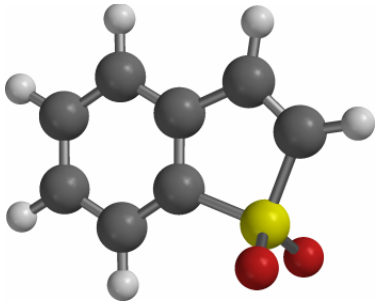
| | | | |
|---|---|---|---|
| C | -1.426903 | 0.000000 | 1.306048 |
| H | -2.513713 | 0.000000 | 1.311467 |
| C | -0.716954 | 0.000000 | 2.475314 |
| H | -1.241222 | 0.000000 | 3.427216 |
| C | 0.716954 | 0.000000 | 2.475314 |
| H | 1.241222 | 0.000000 | 3.427216 |
| C | 1.426903 | 0.000000 | 1.306048 |
| H | 2.513713 | 0.000000 | 1.311467 |
| C | -0.727176 | 0.000000 | 0.056999 |
| C | 0.727176 | 0.000000 | 0.056999 |
| C | 1.248444 | 0.000000 | -1.226762 |
| H | 2.287221 | 0.000000 | -1.527599 |
| C | -1.248444 | 0.000000 | -1.226762 |
| H | -2.287221 | 0.000000 | -1.527599 |
| S | 0.000000 | 0.000000 | -2.407968 |

## 4.47



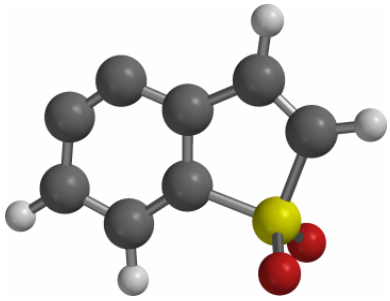
| | | | |
|---|---|---|---|
| C | 1.467868 | 1.278860 | 0.000000 |
| H | 1.502876 | 2.365699 | 0.000000 |
| C | 2.650536 | 0.565431 | 0.000000 |
| H | 3.622468 | 1.045699 | 0.000000 |
| C | 2.406260 | -0.828826 | 0.000000 |
| C | 1.336829 | -1.449816 | 0.000000 |
| C | 0.056152 | -0.844600 | 0.000000 |
| C | 0.177322 | 0.632288 | 0.000000 |
| C | -1.251931 | -1.276419 | 0.000000 |
| H | -1.624650 | -2.290627 | 0.000000 |
| C | -1.072572 | 1.225912 | 0.000000 |
| H | -1.312627 | 2.280577 | 0.000000 |
| S | -2.338359 | 0.060563 | 0.000000 |

## 4.48



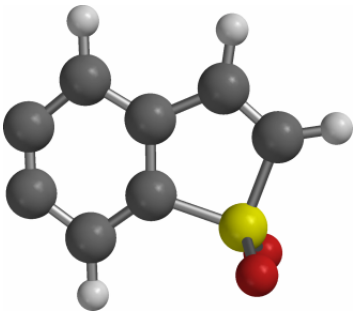
| | | | |
|---|---|---|---|
| H | 2.572660 | -2.153310 | 0.000000 |
| C | 2.159369 | -1.148150 | 0.000000 |
| C | 1.095469 | 1.472599 | 0.000000 |
| C | 0.779400 | -0.951912 | 0.000000 |
| C | 3.004363 | -0.031581 | 0.000000 |
| C | 2.482444 | 1.263916 | 0.000000 |
| C | 0.278474 | 0.356931 | 0.000000 |
| H | 4.080921 | -0.176051 | 0.000000 |
| H | 3.153379 | 2.117899 | 0.000000 |
| H | 0.678631 | 2.475128 | 0.000000 |
| C | -0.284734 | -1.973525 | 0.000000 |
| H | -0.050258 | -3.034000 | 0.000000 |
| C | -1.531543 | -1.487306 | 0.000000 |
| H | -2.476553 | -2.014479 | 0.000000 |
| S | -1.524537 | 0.310849 | 0.000000 |
| O | -2.059964 | 0.825665 | -1.268547 |
| O | -2.059964 | 0.825665 | 1.268547 |

## 4.49



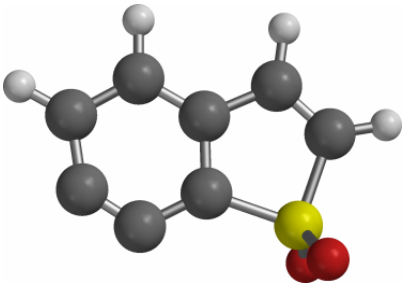
| | | | |
|---|---|---|---|
| C | 2.181325 | -1.165656 | 0.000000 |
| C | 1.265635 | 1.375674 | 0.000000 |
| C | 0.801104 | -1.071327 | 0.000000 |
| C | 2.956528 | -0.180711 | 0.000000 |
| C | 2.671926 | 1.169276 | 0.000000 |
| C | 0.395623 | 0.288676 | 0.000000 |
| H | 3.375642 | 1.993608 | 0.000000 |
| H | 0.876561 | 2.390250 | 0.000000 |
| S | -1.412121 | 0.336804 | 0.000000 |
| O | -1.918560 | 0.875503 | 1.269398 |
| O | -1.918560 | 0.875503 | -1.269398 |
| C | -1.523451 | -1.459105 | 0.000000 |
| H | -2.501051 | -1.923758 | 0.000000 |
| C | -0.312448 | -2.030016 | 0.000000 |
| H | -0.142551 | -3.101493 | 0.000000 |

## 4.50



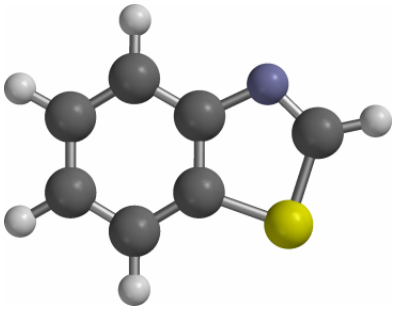
| | | | |
|---|---|---|---|
| S | -1.433466 | 0.277308 | 0.000000 |
| O | -1.985238 | 0.770032 | -1.269179 |
| O | -1.985238 | 0.770032 | 1.269179 |
| C | -1.359252 | -1.516677 | 0.000000 |
| H | -2.277888 | -2.089407 | 0.000000 |
| C | -0.090427 | -1.944448 | 0.000000 |
| H | 0.188155 | -2.994170 | 0.000000 |
| C | 0.935574 | -0.884484 | 0.000000 |
| C | 2.456916 | 1.288218 | 0.000000 |
| C | 0.372510 | 0.413964 | 0.000000 |
| C | 2.335372 | -1.074424 | 0.000000 |
| C | 2.979924 | 0.152857 | 0.000000 |
| C | 1.105046 | 1.605938 | 0.000000 |
| H | 2.791932 | -2.059096 | 0.000000 |
| H | 0.649663 | 2.590115 | 0.000000 |

## 4.51



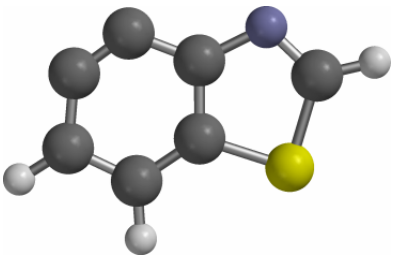
| | | | |
|---|---|---|---|
| H | 2.719526 | -1.947495 | 0.000000 |
| C | 2.276825 | -0.954543 | 0.000000 |
| C | 1.151898 | 1.519672 | 0.000000 |
| C | 0.879419 | -0.815840 | 0.000000 |
| C | 3.134414 | 0.174593 | 0.000000 |
| C | 2.392648 | 1.334900 | 0.000000 |
| C | 0.274620 | 0.466220 | 0.000000 |
| H | 4.214449 | 0.083342 | 0.000000 |
| S | -1.526524 | 0.306888 | 0.000000 |
| O | -2.090788 | 0.779816 | 1.270506 |
| O | -2.090788 | 0.779816 | -1.270506 |
| C | -1.401645 | -1.487939 | 0.000000 |
| H | -2.308001 | -2.079622 | 0.000000 |
| C | -0.126768 | -1.897031 | 0.000000 |
| H | 0.166429 | -2.942831 | 0.000000 |

## 4.52



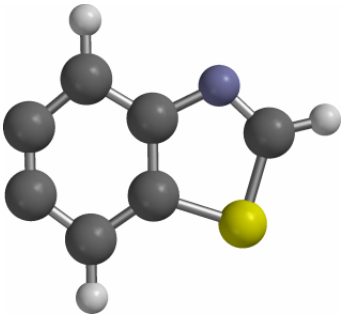
| | | | |
|---|---|---|---|
| H | -1.489381 | -2.454492 | 0.000000 |
| C | -1.373124 | -1.375369 | 0.000000 |
| C | -1.023525 | 1.441413 | 0.000000 |
| C | -0.082921 | -0.825308 | 0.000000 |
| C | -2.468176 | -0.521130 | 0.000000 |
| C | -2.294780 | 0.874581 | 0.000000 |
| C | 0.078276 | 0.581963 | 0.000000 |
| H | -3.472903 | -0.934073 | 0.000000 |
| H | -3.166380 | 1.523227 | 0.000000 |
| H | -0.895658 | 2.519553 | 0.000000 |
| S | 1.789875 | 0.965111 | 0.000000 |
| C | 2.118829 | -0.772856 | 0.000000 |
| H | 3.146868 | -1.119380 | 0.000000 |
| N | 1.096359 | -1.560254 | 0.000000 |

## 4.53



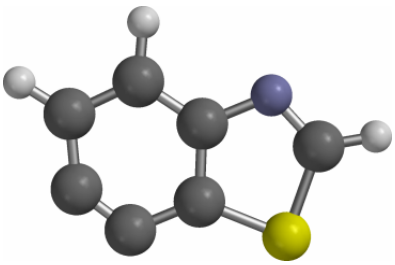
| | | | |
|---|---|---|---|
| C | -1.373162 | -1.430147 | 0.000000 |
| C | -1.203575 | 1.290227 | 0.000000 |
| C | -0.066255 | -0.947902 | 0.000000 |
| C | -2.374265 | -0.684821 | 0.000000 |
| C | -2.480613 | 0.699153 | 0.000000 |
| C | -0.044380 | 0.490272 | 0.000000 |
| H | -3.390888 | 1.287663 | 0.000000 |
| H | -1.119535 | 2.373588 | 0.000000 |
| S | 1.631356 | 1.006437 | 0.000000 |
| C | 2.108835 | -0.693714 | 0.000000 |
| H | 3.163239 | -0.947552 | 0.000000 |
| N | 1.161034 | -1.573230 | 0.000000 |

## 4.54



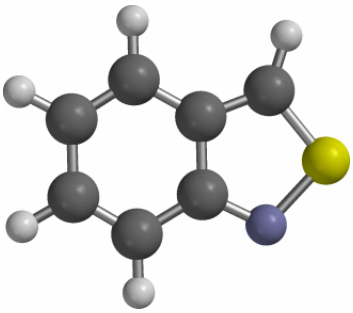
| | | | |
|---|---|---|---|
| H | -1.652665 | -2.480422 | 0.000000 |
| C | -1.512542 | -1.405482 | 0.000000 |
| C | -1.101969 | 1.529547 | 0.000000 |
| C | -0.216749 | -0.821647 | 0.000000 |
| C | -2.461639 | -0.409606 | 0.000000 |
| C | -2.293591 | 0.832776 | 0.000000 |
| C | -0.034195 | 0.604210 | 0.000000 |
| H | -0.963925 | 2.605446 | 0.000000 |
| S | 1.687474 | 0.949683 | 0.000000 |
| C | 1.989392 | -0.793223 | 0.000000 |
| H | 3.012237 | -1.155654 | 0.000000 |
| N | 0.954847 | -1.563219 | 0.000000 |

## 4.55



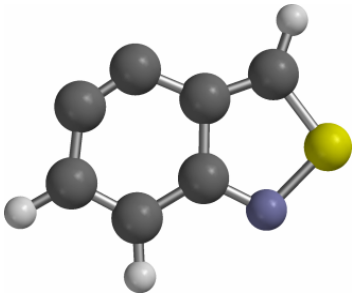
| | | | |
|---|---|---|---|
| H | -1.709902 | -2.247667 | 0.000000 |
| C | -1.534154 | -1.176145 | 0.000000 |
| C | -1.002752 | 1.511027 | 0.000000 |
| C | -0.195345 | -0.714750 | 0.000000 |
| C | -2.618245 | -0.285176 | 0.000000 |
| C | -2.152966 | 1.022423 | 0.000000 |
| C | 0.109509 | 0.687463 | 0.000000 |
| H | -3.650766 | -0.613799 | 0.000000 |
| S | 1.845531 | 0.918008 | 0.000000 |
| C | 2.007318 | -0.843667 | 0.000000 |
| H | 2.998817 | -1.283732 | 0.000000 |
| N | 0.918546 | -1.539326 | 0.000000 |

## 4.56



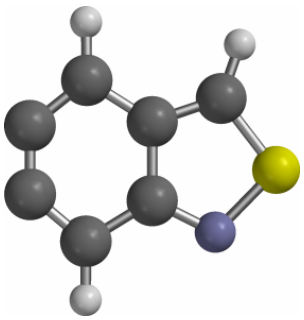
| | | | |
|---|---|---|---|
| C | 1.266471 | -1.417250 | 0.000000 |
| H | 1.246032 | -2.502213 | 0.000000 |
| C | 2.439502 | -0.710333 | 0.000000 |
| H | 3.387446 | -1.241723 | 0.000000 |
| C | 2.455180 | 0.722932 | 0.000000 |
| H | 3.412705 | 1.236309 | 0.000000 |
| C | 1.292829 | 1.447019 | 0.000000 |
| H | 1.307355 | 2.533396 | 0.000000 |
| C | 0.045558 | 0.750798 | 0.000000 |
| C | 0.030125 | -0.699819 | 0.000000 |
| N | -1.172303 | -1.287324 | 0.000000 |
| S | -2.331232 | -0.097969 | 0.000000 |
| C | -1.257338 | 1.229012 | 0.000000 |
| H | -1.598580 | 2.256457 | 0.000000 |

## 4.57



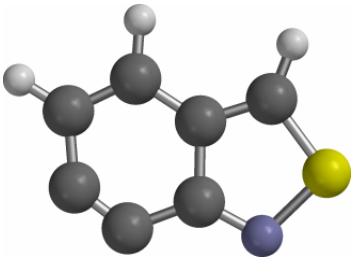
| | | | |
|---|---|---|---|
| C | 2.630099 | 0.514878 | 0.000000 |
| H | 3.608812 | 0.981611 | 0.000000 |
| C | 1.457615 | 1.242615 | 0.000000 |
| H | 1.480929 | 2.327943 | 0.000000 |
| C | 2.374224 | -0.878063 | 0.000000 |
| C | 1.302687 | -1.496916 | 0.000000 |
| C | 0.163402 | 0.599029 | 0.000000 |
| C | 0.035171 | -0.873165 | 0.000000 |
| N | -0.987898 | 1.271898 | 0.000000 |
| C | -1.296228 | -1.237919 | 0.000000 |
| H | -1.724773 | -2.231109 | 0.000000 |
| S | -2.246535 | 0.184546 | 0.000000 |

## 4.58



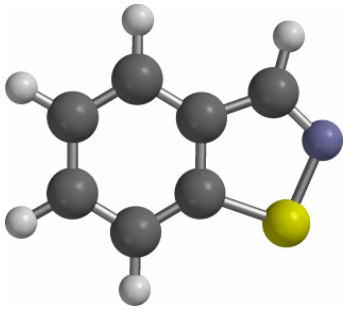
| | | | |
|---|---|---|---|
| C | 1.136110 | -1.227667 | 0.000000 |
| H | 1.479949 | -2.254170 | 0.000000 |
| S | 2.211691 | 0.097381 | 0.000000 |
| N | 1.058049 | 1.286591 | 0.000000 |
| C | -0.170256 | -0.759794 | 0.000000 |
| C | -0.148462 | 0.714249 | 0.000000 |
| C | -1.413163 | -1.503676 | 0.000000 |
| H | -1.444739 | -2.588514 | 0.000000 |
| C | -2.456852 | -0.633652 | 0.000000 |
| C | -2.430362 | 0.632052 | 0.000000 |
| C | -1.380314 | 1.487800 | 0.000000 |
| H | -1.367778 | 2.571568 | 0.000000 |

## 4.59



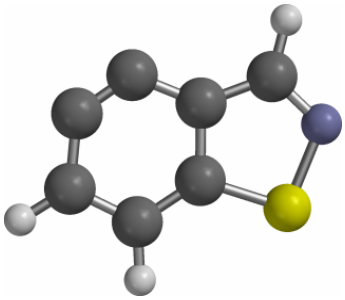
| | | | |
|---|---|---|---|
| C | 2.634978 | 0.481423 | 0.000000 |
| H | 3.629668 | 0.911814 | 0.000000 |
| C | 1.486191 | 1.251144 | 0.000000 |
| H | 1.568129 | 2.335081 | 0.000000 |
| C | 2.316357 | -0.893997 | 0.000000 |
| C | 1.231870 | -1.491090 | 0.000000 |
| C | 0.176377 | 0.653719 | 0.000000 |
| C | -0.014456 | -0.814506 | 0.000000 |
| C | -1.071343 | 1.254720 | 0.000000 |
| H | -1.311717 | 2.310470 | 0.000000 |
| N | -1.260727 | -1.265828 | 0.000000 |
| S | -2.283195 | 0.047886 | 0.000000 |

## 4.60



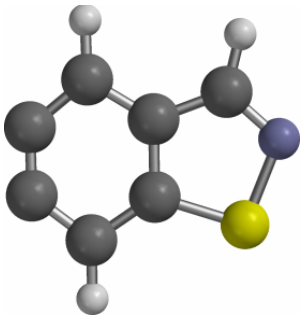
| | | | |
|---|---|---|---|
| H | -1.569175 | -2.440009 | 0.000000 |
| C | -1.418433 | -1.363724 | 0.000000 |
| C | -1.018942 | 1.447614 | 0.000000 |
| C | -0.115571 | -0.832955 | 0.000000 |
| C | -2.497496 | -0.493818 | 0.000000 |
| C | -2.296047 | 0.901930 | 0.000000 |
| C | 0.072821 | 0.569082 | 0.000000 |
| H | -3.510290 | -0.886299 | 0.000000 |
| H | -3.157464 | 1.564251 | 0.000000 |
| H | -0.875590 | 2.524005 | 0.000000 |
| S | 1.790481 | 0.896219 | 0.000000 |
| N | 2.233064 | -0.747947 | 0.000000 |
| C | 1.162915 | -1.495627 | 0.000000 |
| H | 1.289931 | -2.576277 | 0.000000 |

## 4.61



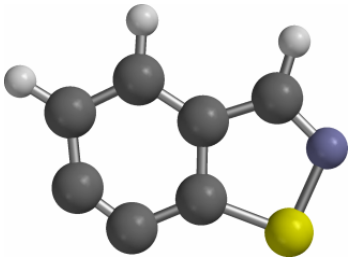
| | | | |
|---|---|---|---|
| C | 2.510649 | 0.684893 | 0.000000 |
| H | 3.422828 | 1.270993 | 0.000000 |
| C | 1.239078 | 1.282643 | 0.000000 |
| H | 1.163627 | 2.366733 | 0.000000 |
| C | 2.408366 | -0.703029 | 0.000000 |
| C | 1.398399 | -1.433581 | 0.000000 |
| C | 0.090617 | -0.944298 | 0.000000 |
| C | 0.069378 | 0.491304 | 0.000000 |
| S | -1.605350 | 0.984083 | 0.000000 |
| N | -2.220065 | -0.599943 | 0.000000 |
| C | -1.243273 | -1.469040 | 0.000000 |
| H | -1.487797 | -2.527748 | 0.000000 |

## 4.62



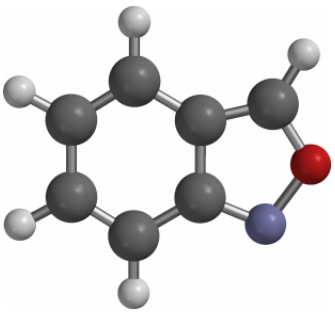
| | | | |
|---|---|---|---|
| C | 2.316456 | -0.816487 | 0.000000 |
| C | 2.482104 | 0.428287 | 0.000000 |
| C | 1.525411 | 1.413436 | 0.000000 |
| H | 1.676199 | 2.488200 | 0.000000 |
| C | 0.228605 | 0.819782 | 0.000000 |
| C | 0.052314 | -0.599791 | 0.000000 |
| C | 1.133438 | -1.519931 | 0.000000 |
| H | 0.999975 | -2.596442 | 0.000000 |
| S | -1.667818 | -0.933254 | 0.000000 |
| N | -2.124588 | 0.708342 | 0.000000 |
| C | -1.060289 | 1.463266 | 0.000000 |
| H | -1.197296 | 2.542663 | 0.000000 |

## 4.63



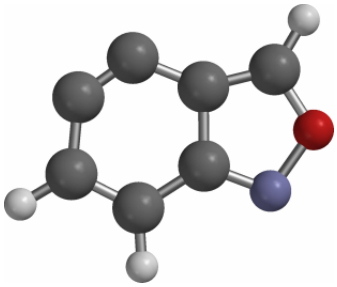
| | | | |
|---|---|---|---|
| C | 2.167467 | 1.008952 | 0.000000 |
| C | 1.018021 | 1.494558 | 0.000000 |
| C | 2.624966 | -0.303850 | 0.000000 |
| H | 3.655184 | -0.639263 | 0.000000 |
| C | 1.536715 | -1.189551 | 0.000000 |
| H | 1.728220 | -2.259920 | 0.000000 |
| C | 0.198203 | -0.723497 | 0.000000 |
| C | -0.105434 | 0.678266 | 0.000000 |
| S | -1.833447 | 0.890537 | 0.000000 |
| N | -2.154203 | -0.780843 | 0.000000 |
| C | -1.037379 | -1.460180 | 0.000000 |
| H | -1.102615 | -2.546220 | 0.000000 |

## 4.64



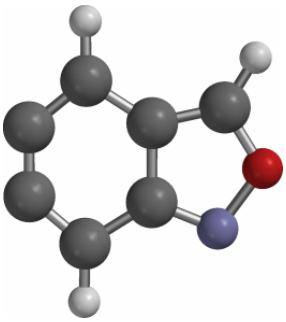
| | | | |
|---|---|---|---|
| C | 0.915939 | -1.448130 | 0.000000 |
| H | 0.881874 | -2.532527 | 0.000000 |
| C | 2.095275 | -0.753723 | 0.000000 |
| H | 3.035763 | -1.298092 | 0.000000 |
| C | 2.139907 | 0.683412 | 0.000000 |
| H | 3.109857 | 1.172239 | 0.000000 |
| C | 0.996852 | 1.436749 | 0.000000 |
| H | 1.035174 | 2.522073 | 0.000000 |
| C | -0.252387 | 0.749948 | 0.000000 |
| C | -0.295848 | -0.691578 | 0.000000 |
| N | -1.540988 | -1.156530 | 0.000000 |
| O | -2.337756 | -0.009778 | 0.000000 |
| C | -1.583038 | 1.095198 | 0.000000 |
| H | -2.118116 | 2.033995 | 0.000000 |

## 4.65



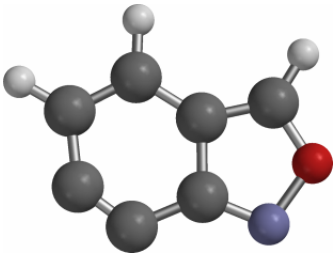
| | | | |
|---|---|---|---|
| C | 2.016840 | 0.897412 | 0.000000 |
| C | 0.942278 | 1.511429 | 0.000000 |
| C | 2.299192 | -0.491126 | 0.000000 |
| H | 3.287065 | -0.937731 | 0.000000 |
| C | 1.145825 | -1.250662 | 0.000000 |
| H | 1.199508 | -2.334726 | 0.000000 |
| C | -0.299614 | 0.841301 | 0.000000 |
| C | -0.148905 | -0.615767 | 0.000000 |
| C | -1.657358 | 1.019280 | 0.000000 |
| H | -2.308206 | 1.880876 | 0.000000 |
| N | -1.330066 | -1.218184 | 0.000000 |
| O | -2.261259 | -0.178463 | 0.000000 |

## 4.66



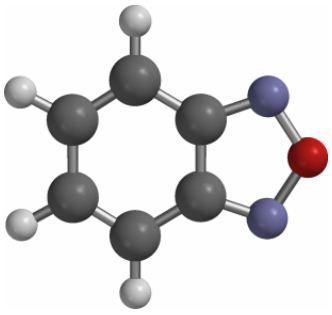
| | | | |
|---|---|---|---|
| N | 1.395181 | -1.208174 | 0.000000 |
| O | 2.226340 | -0.089651 | 0.000000 |
| C | 1.509660 | 1.040791 | 0.000000 |
| H | 2.078011 | 1.959680 | 0.000000 |
| C | 0.165816 | 0.749804 | 0.000000 |
| C | 0.163034 | -0.711759 | 0.000000 |
| C | -1.056417 | 1.526396 | 0.000000 |
| H | -1.071552 | 2.611163 | 0.000000 |
| C | -2.109296 | 0.668933 | 0.000000 |
| C | -2.102103 | -0.598928 | 0.000000 |
| C | -1.072826 | -1.479096 | 0.000000 |
| H | -1.086124 | -2.562632 | 0.000000 |

## 4.67



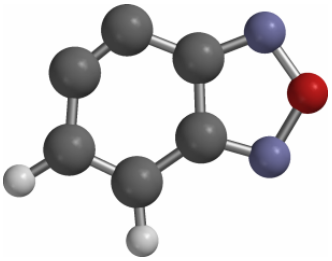
| | | | |
|---|---|---|---|
| C | 1.970199 | 0.892785 | 0.000000 |
| C | 0.890472 | 1.498075 | 0.000000 |
| C | 2.301380 | -0.481945 | 0.000000 |
| H | 3.300005 | -0.902086 | 0.000000 |
| C | 1.161444 | -1.265809 | 0.000000 |
| H | 1.255600 | -2.348317 | 0.000000 |
| C | -0.335755 | 0.790221 | 0.000000 |
| C | -0.141532 | -0.663817 | 0.000000 |
| N | -1.610604 | 1.136626 | 0.000000 |
| C | -1.436710 | -1.118801 | 0.000000 |
| H | -1.891662 | -2.099446 | 0.000000 |
| O | -2.290193 | -0.086468 | 0.000000 |

## 4.68



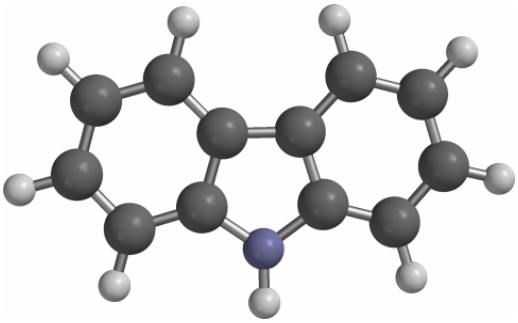
| | | | |
|---|---|---|---|
| C | 0.720345 | 0.000000 | 2.078185 |
| H | 1.232909 | 0.000000 | 3.035809 |
| C | 1.451187 | 0.000000 | 0.921510 |
| H | 2.535637 | 0.000000 | 0.916825 |
| C | 0.718347 | 0.000000 | -0.302124 |
| C | -0.718347 | 0.000000 | -0.302124 |
| C | -1.451187 | 0.000000 | 0.921510 |
| H | -2.535637 | 0.000000 | 0.916825 |
| C | -0.720345 | 0.000000 | 2.078185 |
| H | -1.232909 | 0.000000 | 3.035809 |
| N | 1.143822 | 0.000000 | -1.554690 |
| N | -1.143822 | 0.000000 | -1.554690 |
| O | 0.000000 | 0.000000 | -2.306189 |

## 4.69



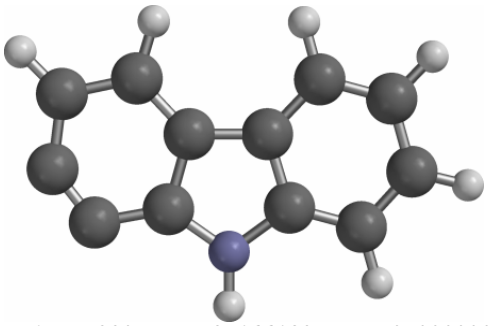
| | | | |
|---|---|---|---|
| C | 1.103863 | -1.284942 | 0.000000 |
| H | 1.156735 | -2.368694 | 0.000000 |
| C | 2.254403 | -0.521853 | 0.000000 |
| H | 3.245348 | -0.960128 | 0.000000 |
| C | 1.956689 | 0.862895 | 0.000000 |
| C | 0.898782 | 1.505208 | 0.000000 |
| C | -0.333981 | 0.813808 | 0.000000 |
| C | -0.182373 | -0.638409 | 0.000000 |
| N | -1.388548 | -1.171286 | 0.000000 |
| N | -1.614953 | 1.115742 | 0.000000 |
| O | -2.247140 | -0.101280 | 0.000000 |

## 4.70



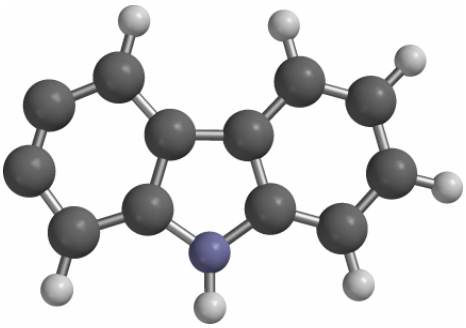
| | | | |
|---|---|---|---|
| H | -1.406069 | 0.000000 | 2.558366 |
| C | -1.698575 | 0.000000 | 1.511352 |
| C | -2.481856 | 0.000000 | -1.219974 |
| C | -0.725217 | 0.000000 | 0.505213 |
| C | -3.044395 | 0.000000 | 1.154675 |
| C | -3.428441 | 0.000000 | -0.197894 |
| C | -1.133657 | 0.000000 | -0.855344 |
| H | -3.807626 | 0.000000 | 1.927725 |
| H | -4.484561 | 0.000000 | -0.454109 |
| H | -2.785201 | 0.000000 | -2.263745 |
| C | 0.725217 | 0.000000 | 0.505213 |
| C | 3.428441 | 0.000000 | -0.197894 |
| C | 1.698575 | 0.000000 | 1.511352 |
| C | 1.133657 | 0.000000 | -0.855344 |
| C | 2.481856 | 0.000000 | -1.219974 |
| C | 3.044395 | 0.000000 | 1.154675 |
| H | 1.406069 | 0.000000 | 2.558366 |
| H | 2.785201 | 0.000000 | -2.263745 |
| H | 3.807626 | 0.000000 | 1.927725 |
| H | 4.484561 | 0.000000 | -0.454109 |
| N | 0.000000 | 0.000000 | -1.653872 |
| H | 0.000000 | 0.000000 | -2.661728 |

## 4.71



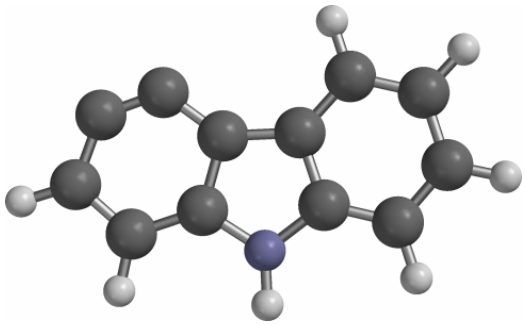
| | | | |
|---|---|---|---|
| H | -1.557930 | -2.466489 | 0.000000 |
| C | -1.840311 | -1.416133 | 0.000000 |
| C | -2.549936 | 1.252796 | 0.000000 |
| C | -0.840250 | -0.423874 | 0.000000 |
| C | -3.211389 | -1.087978 | 0.000000 |
| C | -3.350201 | 0.289971 | 0.000000 |
| C | -1.188817 | 0.969856 | 0.000000 |
| H | -3.996332 | -1.834035 | 0.000000 |
| C | 0.609876 | -0.466759 | 0.000000 |
| C | 1.066677 | 0.880031 | 0.000000 |
| N | -0.035089 | 1.725298 | 0.000000 |
| H | -0.003485 | 2.732813 | 0.000000 |
| H | 1.226659 | -2.540637 | 0.000000 |
| C | 1.552342 | -1.503540 | 0.000000 |
| H | 3.645132 | -1.989347 | 0.000000 |
| C | 2.908410 | -1.191000 | 0.000000 |
| H | 4.402679 | 0.367905 | 0.000000 |
| C | 3.338644 | 0.147665 | 0.000000 |
| H | 2.762297 | 2.233050 | 0.000000 |
| C | 2.426241 | 1.199464 | 0.000000 |

**4.72**



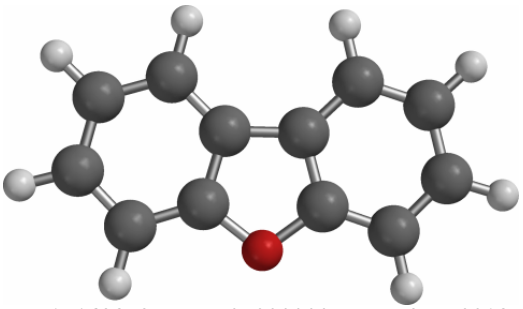
| | | | |
|---|---|---|---|
| H | -1.457794 | -2.662883 | 0.000000 |
| C | -1.757343 | -1.619762 | 0.000000 |
| C | -2.626627 | 1.210583 | 0.000000 |
| C | -0.827344 | -0.551794 | 0.000000 |
| C | -3.041901 | -1.116348 | 0.000000 |
| C | -3.419739 | 0.078847 | 0.000000 |
| C | -1.266667 | 0.819828 | 0.000000 |
| H | -2.949454 | 2.247467 | 0.000000 |
| C | 0.623510 | -0.518045 | 0.000000 |
| C | 1.007362 | 0.848663 | 0.000000 |
| N | -0.139931 | 1.628330 | 0.000000 |
| H | -0.154330 | 2.636086 | 0.000000 |
| C | 1.615109 | -1.506720 | 0.000000 |
| H | 1.342567 | -2.559004 | 0.000000 |
| H | 3.730666 | -1.885330 | 0.000000 |
| C | 2.954005 | -1.125948 | 0.000000 |
| H | 4.364799 | 0.508604 | 0.000000 |
| C | 3.313592 | 0.233273 | 0.000000 |
| H | 2.632149 | 2.287180 | 0.000000 |
| C | 2.348555 | 1.237935 | 0.000000 |

**4.73**



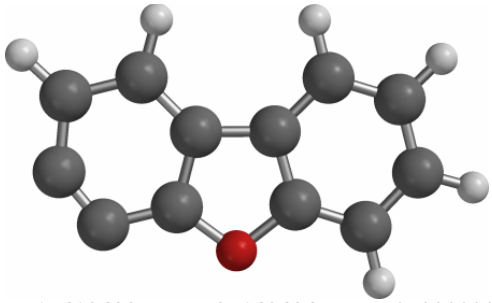
| | | | |
|---|---|---|---|
| C | 1.782008 | -1.558426 | 0.000000 |
| C | 2.607360 | 1.030209 | 0.000000 |
| C | 0.734863 | -0.643399 | 0.000000 |
| C | 2.991240 | -1.247724 | 0.000000 |
| C | 3.580111 | 0.012456 | 0.000000 |
| C | 1.236320 | 0.706718 | 0.000000 |
| H | 4.641684 | 0.234671 | 0.000000 |
| H | 2.924430 | 2.070341 | 0.000000 |
| C | -0.702986 | -0.571544 | 0.000000 |
| C | -1.033081 | 0.811650 | 0.000000 |
| N | 0.137644 | 1.553828 | 0.000000 |
| H | 0.179547 | 2.561023 | 0.000000 |
| H | -1.485911 | -2.585480 | 0.000000 |
| C | -1.728541 | -1.526373 | 0.000000 |
| H | -3.855444 | -1.825314 | 0.000000 |
| C | -3.050347 | -1.096146 | 0.000000 |
| H | -4.400699 | 0.589831 | 0.000000 |
| C | -3.359917 | 0.277364 | 0.000000 |
| H | -2.607924 | 2.305496 | 0.000000 |
| C | -2.361348 | 1.246959 | 0.000000 |

**4.74**



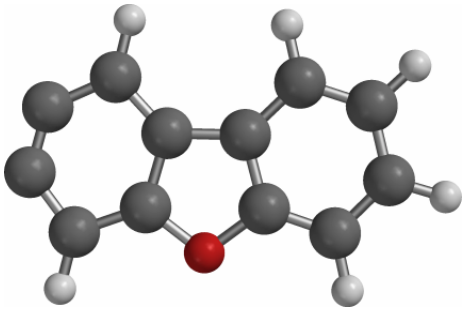
| | | | |
|---|---|---|---|
| H | -1.469879 | 0.000000 | 2.570018 |
| C | -1.726383 | 0.000000 | 1.514170 |
| C | -2.419614 | 0.000000 | -1.249272 |
| C | -0.726178 | 0.000000 | 0.535458 |
| C | -3.059550 | 0.000000 | 1.107228 |
| C | -3.400461 | 0.000000 | -0.255695 |
| C | -1.099272 | 0.000000 | -0.822026 |
| H | -3.848369 | 0.000000 | 1.854115 |
| H | -4.447596 | 0.000000 | -0.545218 |
| H | -2.668604 | 0.000000 | -2.305273 |
| C | 0.726178 | 0.000000 | 0.535458 |
| C | 3.400461 | 0.000000 | -0.255695 |
| C | 1.726383 | 0.000000 | 1.514170 |
| C | 1.099272 | 0.000000 | -0.822026 |
| C | 2.419614 | 0.000000 | -1.249272 |
| C | 3.059550 | 0.000000 | 1.107228 |
| H | 1.469879 | 0.000000 | 2.570018 |
| H | 2.668604 | 0.000000 | -2.305273 |
| H | 3.848369 | 0.000000 | 1.854115 |
| H | 4.447596 | 0.000000 | -0.545218 |
| O | 0.000000 | 0.000000 | -1.651381 |

**4.75**



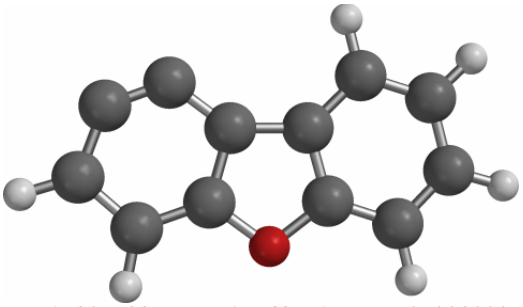
| | | | |
|---|---|---|---|
| H | -1.619628 | -2.468636 | 0.000000 |
| C | -1.863522 | -1.409227 | 0.000000 |
| C | -2.482899 | 1.296251 | 0.000000 |
| C | -0.836766 | -0.446060 | 0.000000 |
| C | -3.222280 | -1.026745 | 0.000000 |
| C | -3.307626 | 0.351527 | 0.000000 |
| C | -1.147035 | 0.944254 | 0.000000 |
| H | -4.035031 | -1.742367 | 0.000000 |
| C | 0.614850 | -0.497341 | 0.000000 |
| C | 3.319637 | 0.193470 | 0.000000 |
| C | 1.579545 | -1.512130 | 0.000000 |
| C | 1.041528 | 0.845664 | 0.000000 |
| C | 2.377046 | 1.222514 | 0.000000 |
| C | 2.926563 | -1.155391 | 0.000000 |
| H | 1.284173 | -2.557742 | 0.000000 |
| H | 2.664282 | 2.268696 | 0.000000 |
| H | 3.686304 | -1.931795 | 0.000000 |
| H | 4.376916 | 0.442846 | 0.000000 |
| O | -0.021946 | 1.723688 | 0.000000 |

**4.76**



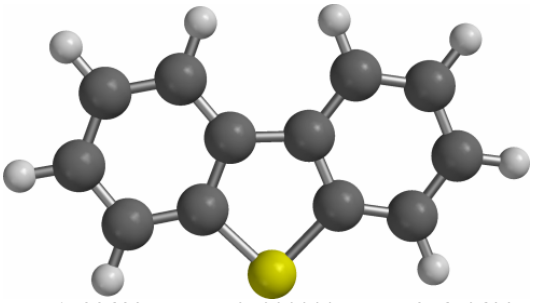
| | | | |
|---|---|---|---|
| H | -1.528968 | -2.672800 | 0.000000 |
| C | -1.789690 | -1.619693 | 0.000000 |
| C | -2.561397 | 1.247240 | 0.000000 |
| C | -0.831310 | -0.580222 | 0.000000 |
| C | -3.056896 | -1.067424 | 0.000000 |
| C | -3.391590 | 0.139586 | 0.000000 |
| C | -1.231263 | 0.791624 | 0.000000 |
| H | -2.829515 | 2.297744 | 0.000000 |
| C | 0.621216 | -0.547971 | 0.000000 |
| C | 3.282950 | 0.287152 | 0.000000 |
| C | 1.637923 | -1.510088 | 0.000000 |
| C | 0.973045 | 0.814677 | 0.000000 |
| C | 2.285863 | 1.264148 | 0.000000 |
| C | 2.963803 | -1.081163 | 0.000000 |
| H | 1.399929 | -2.570159 | 0.000000 |
| H | 2.516115 | 2.324346 | 0.000000 |
| H | 3.764358 | -1.815339 | 0.000000 |
| H | 4.325156 | 0.593586 | 0.000000 |
| O | -0.139349 | 1.627492 | 0.000000 |

## 4.77



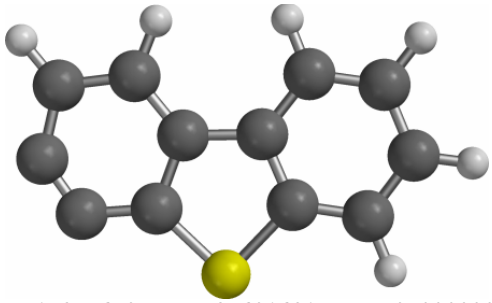
| | | | |
|---|---|---|---|
| C | 1.807598 | -1.568551 | 0.000000 |
| C | 2.551130 | 1.057251 | 0.000000 |
| C | 0.740040 | -0.676906 | 0.000000 |
| C | 3.002185 | -1.202952 | 0.000000 |
| C | 3.557645 | 0.070945 | 0.000000 |
| C | 1.203597 | 0.670472 | 0.000000 |
| H | 4.612269 | 0.322350 | 0.000000 |
| H | 2.811419 | 2.111137 | 0.000000 |
| C | -0.701973 | -0.605442 | 0.000000 |
| C | -3.325323 | 0.331541 | 0.000000 |
| C | -1.753220 | -1.530208 | 0.000000 |
| C | -0.997063 | 0.772779 | 0.000000 |
| C | -2.293134 | 1.270524 | 0.000000 |
| C | -3.059936 | -1.049408 | 0.000000 |
| H | -1.548767 | -2.596828 | 0.000000 |
| H | -2.483794 | 2.338548 | 0.000000 |
| H | -3.889415 | -1.750694 | 0.000000 |
| H | -4.355235 | 0.677063 | 0.000000 |
| O | 0.142717 | 1.546761 | 0.000000 |

## 4.78



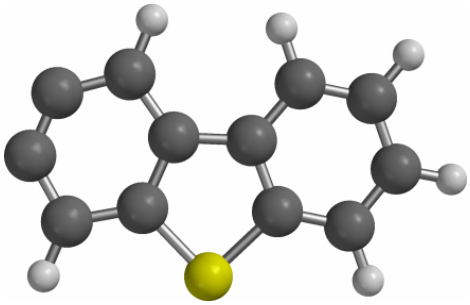
| | | | |
|---|---|---|---|
| H | -1.226895 | 0.000000 | 2.670699 |
| C | -1.613205 | 0.000000 | 1.654878 |
| C | -2.637744 | 0.000000 | -0.973243 |
| C | -0.727675 | 0.000000 | 0.566358 |
| C | -2.985508 | 0.000000 | 1.430923 |
| C | -3.495678 | 0.000000 | 0.123581 |
| C | -1.260639 | 0.000000 | -0.742513 |
| H | -3.668824 | 0.000000 | 2.275472 |
| H | -4.570227 | 0.000000 | -0.037067 |
| H | -3.031679 | 0.000000 | -1.985564 |
| C | 0.727675 | 0.000000 | 0.566358 |
| C | 3.495678 | 0.000000 | 0.123581 |
| C | 1.613205 | 0.000000 | 1.654878 |
| C | 1.260639 | 0.000000 | -0.742513 |
| C | 2.637744 | 0.000000 | -0.973243 |
| C | 2.985508 | 0.000000 | 1.430923 |
| H | 1.226895 | 0.000000 | 2.670699 |
| H | 3.031679 | 0.000000 | -1.985564 |
| H | 3.668824 | 0.000000 | 2.275472 |
| H | 4.570227 | 0.000000 | -0.037067 |
| S | 0.000000 | 0.000000 | -1.982579 |

## 4.79



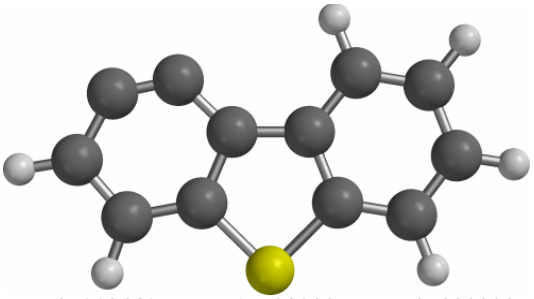
| | | | |
|---|---|---|---|
| H | -1.357650 | -2.601631 | 0.000000 |
| C | -1.741409 | -1.584285 | 0.000000 |
| C | -2.687375 | 0.963880 | 0.000000 |
| C | -0.832974 | -0.501741 | 0.000000 |
| C | -3.136691 | -1.397331 | 0.000000 |
| C | -3.427129 | -0.043380 | 0.000000 |
| C | -1.308636 | 0.849324 | 0.000000 |
| H | -3.838443 | -2.223007 | 0.000000 |
| C | 0.622496 | -0.539796 | 0.000000 |
| C | 3.405453 | -0.179173 | 0.000000 |
| C | 1.478083 | -1.653516 | 0.000000 |
| C | 1.196317 | 0.753335 | 0.000000 |
| C | 2.580348 | 0.941713 | 0.000000 |
| C | 2.855798 | -1.470575 | 0.000000 |
| H | 1.063072 | -2.657769 | 0.000000 |
| H | 3.003397 | 1.942184 | 0.000000 |
| H | 3.513070 | -2.335495 | 0.000000 |
| H | 4.484189 | -0.050655 | 0.000000 |
| S | -0.015171 | 2.043391 | 0.000000 |

## 4.80



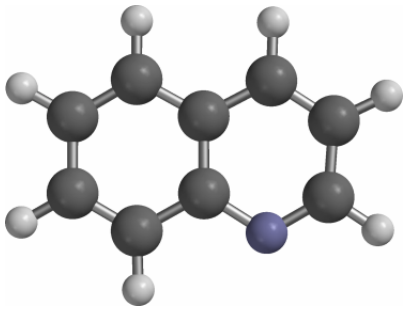
| | | | |
|---|---|---|---|
| H | -1.214968 | -2.797946 | 0.000000 |
| C | -1.627211 | -1.794139 | 0.000000 |
| C | -2.782503 | 0.914266 | 0.000000 |
| C | -0.807902 | -0.633179 | 0.000000 |
| C | -2.959218 | -1.442144 | 0.000000 |
| C | -3.454001 | -0.291011 | 0.000000 |
| C | -1.389083 | 0.673838 | 0.000000 |
| H | -3.209600 | 1.911812 | 0.000000 |
| C | 0.648425 | -0.577914 | 0.000000 |
| C | 3.401613 | -0.046923 | 0.000000 |
| C | 1.569032 | -1.637680 | 0.000000 |
| C | 1.140315 | 0.745623 | 0.000000 |
| C | 2.508825 | 1.021479 | 0.000000 |
| C | 2.933307 | -1.369814 | 0.000000 |
| H | 1.217051 | -2.665795 | 0.000000 |
| H | 2.869199 | 2.046274 | 0.000000 |
| H | 3.642969 | -2.192214 | 0.000000 |
| H | 4.470353 | 0.148223 | 0.000000 |
| S | -0.157962 | 1.947166 | 0.000000 |

## 4.81



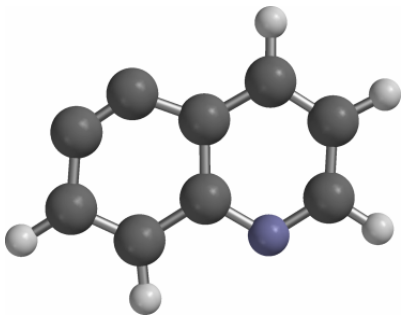
| | | | |
|---|---|---|---|
| H | 3.148661 | -1.792929 | 0.000000 |
| C | 2.737324 | -0.786708 | 0.000000 |
| C | 1.670496 | 1.694962 | 0.000000 |
| C | 1.341626 | -0.602029 | 0.000000 |
| C | 3.617089 | 0.313670 | 0.000000 |
| C | 2.904453 | 1.504900 | 0.000000 |
| C | 0.712814 | 0.684565 | 0.000000 |
| H | 4.694582 | 0.193006 | 0.000000 |
| C | -0.729483 | 0.615627 | 0.000000 |
| C | -3.461715 | 0.035609 | 0.000000 |
| C | -1.187752 | -0.720822 | 0.000000 |
| C | -1.662719 | 1.663470 | 0.000000 |
| C | -3.020456 | 1.369466 | 0.000000 |
| C | -2.552387 | -1.018854 | 0.000000 |
| H | -1.312584 | 2.692203 | 0.000000 |
| H | -3.747817 | 2.176234 | 0.000000 |
| H | -2.897880 | -2.048700 | 0.000000 |
| H | -4.526801 | -0.179026 | 0.000000 |
| S | 0.135115 | -1.896938 | 0.000000 |

## 4.82



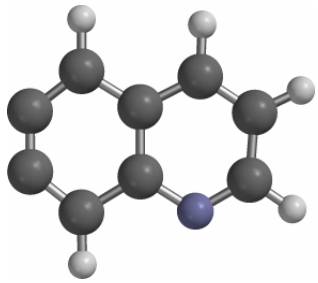
| | | | |
|---|---|---|---|
| H | 3.397968 | -1.132760 | 0.000000 |
| C | 2.421728 | -0.657021 | 0.000000 |
| H | 1.289647 | -2.484344 | 0.000000 |
| C | 1.263204 | -1.396797 | 0.000000 |
| N | 1.189343 | 1.425076 | 0.000000 |
| C | 0.012125 | -0.729011 | 0.000000 |
| C | 2.325518 | 0.757952 | 0.000000 |
| C | 0.029192 | 0.703234 | 0.000000 |
| C | -1.235014 | -1.407397 | 0.000000 |
| H | 3.236056 | 1.357068 | 0.000000 |
| H | -1.167263 | 2.490006 | 0.000000 |
| C | -2.415297 | -0.698458 | 0.000000 |
| H | -1.242434 | -2.495141 | 0.000000 |
| H | -3.366133 | -1.224392 | 0.000000 |
| C | -2.399171 | 0.718935 | 0.000000 |
| H | -3.339302 | 1.263974 | 0.000000 |
| C | -1.205510 | 1.405089 | 0.000000 |

## 4.83*



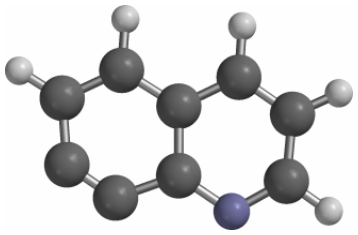
| | | | |
|---|---|---|---|
| H | 3.417249 | -0.961824 | 0.000000 |
| C | 2.403627 | -0.572153 | 0.000000 |
| H | 1.430072 | -2.496043 | 0.000000 |
| C | 1.314497 | -1.416405 | 0.000000 |
| N | 0.998660 | 1.399473 | 0.000000 |
| C | 0.022956 | -0.850361 | 0.000000 |
| C | 2.188102 | 0.826205 | 0.000000 |
| C | -0.103528 | 0.601221 | 0.000000 |
| C | -1.248049 | -1.449976 | 0.000000 |
| H | 3.043932 | 1.500474 | 0.000000 |
| H | -1.400907 | 2.319381 | 0.000000 |
| C | -2.340455 | -0.860831 | 0.000000 |
| C | -2.586128 | 0.523333 | 0.000000 |
| H | -3.558922 | 1.003239 | 0.000000 |
| C | -1.394818 | 1.233572 | 0.000000 |

## 4.84*



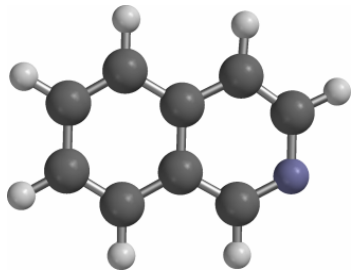
| | | | |
|---|---|---|---|
| H | 3.273607 | -1.130427 | 0.000000 |
| C | 2.298311 | -0.653102 | 0.000000 |
| H | 1.172187 | -2.481141 | 0.000000 |
| C | 1.140894 | -1.394033 | 0.000000 |
| N | 1.064605 | 1.424177 | 0.000000 |
| C | -0.118224 | -0.738278 | 0.000000 |
| C | 2.202828 | 0.760261 | 0.000000 |
| C | -0.097861 | 0.712555 | 0.000000 |
| C | -1.353649 | -1.472098 | 0.000000 |
| H | 3.111151 | 1.362296 | 0.000000 |
| H | -1.292357 | 2.555496 | 0.000000 |
| C | -2.423259 | -0.622197 | 0.000000 |
| H | -1.370354 | -2.558288 | 0.000000 |
| C | -2.402059 | 0.637523 | 0.000000 |
| C | -1.324895 | 1.472043 | 0.000000 |

## 4.85*



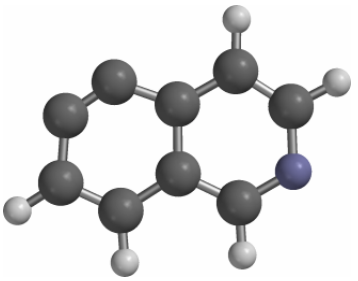
| | | | |
|---|---|---|---|
| C | 0.055910 | -0.829680 | 0.000000 |
| C | -0.112972 | 0.620670 | 0.000000 |
| C | -1.410008 | 1.228747 | 0.000000 |
| H | -1.463581 | 2.315583 | 0.000000 |
| C | -2.588578 | 0.492763 | 0.000000 |
| H | -3.569143 | 0.956477 | 0.000000 |
| C | -2.314304 | -0.883432 | 0.000000 |
| C | -1.209675 | -1.449707 | 0.000000 |
| N | 1.257633 | -1.441671 | 0.000000 |
| C | 2.333307 | -0.672745 | 0.000000 |
| H | 3.291819 | -1.190380 | 0.000000 |
| C | 2.301847 | 0.740025 | 0.000000 |
| H | 3.231527 | 1.300861 | 0.000000 |
| C | 1.082229 | 1.381434 | 0.000000 |
| H | 1.026118 | 2.467479 | 0.000000 |

## 4.86



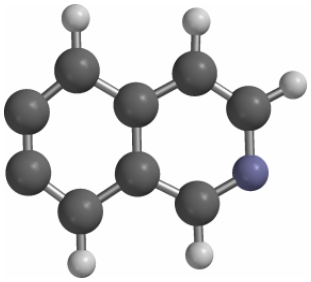
| | | | |
|---|---|---|---|
| H | 3.401837 | -1.081834 | 0.000000 |
| C | 2.421846 | -0.609449 | 0.000000 |
| H | 1.335556 | -2.457244 | 0.000000 |
| C | 1.276440 | -1.371833 | 0.000000 |
| C | 1.263171 | 1.362652 | 0.000000 |
| C | 0.011285 | -0.729664 | 0.000000 |
| N | 2.430161 | 0.752978 | 0.000000 |
| C | 0.004925 | 0.698560 | 0.000000 |
| C | -1.229482 | -1.421080 | 0.000000 |
| H | -1.226258 | 2.481035 | 0.000000 |
| H | 1.281951 | 2.453830 | 0.000000 |
| C | -2.415324 | -0.721022 | 0.000000 |
| H | -1.228436 | -2.508320 | 0.000000 |
| H | -3.360750 | -1.256924 | 0.000000 |
| C | -2.419481 | 0.696898 | 0.000000 |
| H | -3.366202 | 1.229866 | 0.000000 |
| C | -1.231929 | 1.393511 | 0.000000 |

## 4.87



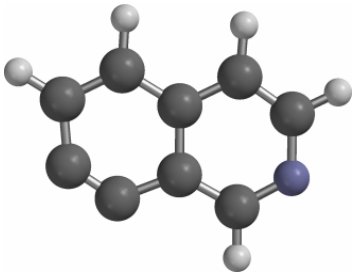
| | | | |
|---|---|---|---|
| H | 3.418129 | -0.899305 | 0.000000 |
| C | 2.400143 | -0.515560 | 0.000000 |
| H | 1.479029 | -2.459477 | 0.000000 |
| C | 1.328803 | -1.384884 | 0.000000 |
| C | 1.073706 | 1.354517 | 0.000000 |
| C | 0.026003 | -0.847164 | 0.000000 |
| N | 2.287943 | 0.838184 | 0.000000 |
| C | -0.129129 | 0.596922 | 0.000000 |
| C | -1.238554 | -1.463739 | 0.000000 |
| H | -1.465314 | 2.303191 | 0.000000 |
| H | 1.011767 | 2.443502 | 0.000000 |
| C | -2.337942 | -0.887740 | 0.000000 |
| C | -2.605061 | 0.490114 | 0.000000 |
| H | -3.582128 | 0.960483 | 0.000000 |
| C | -1.419465 | 1.216205 | 0.000000 |

## 4.88



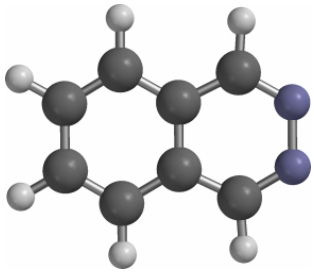
| | | | |
|---|---|---|---|
| H | 3.277555 | -1.078799 | 0.000000 |
| C | 2.298317 | -0.605472 | 0.000000 |
| H | 1.217425 | -2.453808 | 0.000000 |
| C | 1.154243 | -1.369028 | 0.000000 |
| C | 1.139407 | 1.366411 | 0.000000 |
| C | -0.116526 | -0.735179 | 0.000000 |
| N | 2.304568 | 0.755110 | 0.000000 |
| C | -0.123853 | 0.706896 | 0.000000 |
| C | -1.348095 | -1.485332 | 0.000000 |
| H | -1.355378 | 2.542461 | 0.000000 |
| H | 1.158811 | 2.456980 | 0.000000 |
| C | -2.423556 | -0.646194 | 0.000000 |
| H | -1.348932 | -2.570917 | 0.000000 |
| C | -2.425388 | 0.614874 | 0.000000 |
| C | -1.353123 | 1.456569 | 0.000000 |

## 4.89



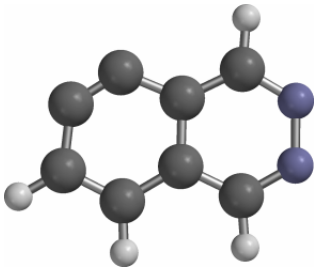
| | | | |
|---|---|---|---|
| H | 3.234784 | -1.254043 | 0.000000 |
| C | 2.300314 | -0.697139 | 0.000000 |
| H | 1.072528 | -2.452058 | 0.000000 |
| C | 1.094174 | -1.365462 | 0.000000 |
| C | 1.322047 | 1.375600 | 0.000000 |
| C | -0.116936 | -0.628660 | 0.000000 |
| N | 2.428309 | 0.655064 | 0.000000 |
| C | 0.023887 | 0.815896 | 0.000000 |
| C | -1.410314 | -1.246693 | 0.000000 |
| H | 1.434090 | 2.458868 | 0.000000 |
| C | -2.594889 | -0.518075 | 0.000000 |
| H | -1.459113 | -2.333282 | 0.000000 |
| H | -3.571257 | -0.990818 | 0.000000 |
| C | -2.334830 | 0.860290 | 0.000000 |
| C | -1.237819 | 1.439887 | 0.000000 |

## 4.90



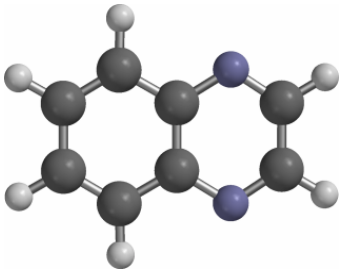
| | | | |
|---|---|---|---|
| N | 0.684733 | 0.000000 | 2.437193 |
| H | 2.415792 | 0.000000 | 1.368043 |
| C | 1.328591 | 0.000000 | 1.292434 |
| C | -1.328591 | 0.000000 | 1.292434 |
| C | 0.708706 | 0.000000 | 0.010185 |
| N | -0.684733 | 0.000000 | 2.437193 |
| C | -0.708706 | 0.000000 | 0.010185 |
| C | 1.411033 | 0.000000 | -1.218437 |
| H | -2.498073 | 0.000000 | -1.213840 |
| H | -2.415792 | 0.000000 | 1.368043 |
| C | 0.708236 | 0.000000 | -2.405560 |
| H | 2.498073 | 0.000000 | -1.213840 |
| H | 1.241026 | 0.000000 | -3.352364 |
| C | -0.708236 | 0.000000 | -2.405560 |
| H | -1.241026 | 0.000000 | -3.352364 |
| C | -1.411033 | 0.000000 | -1.218437 |

## 4.91



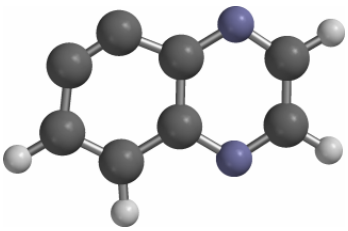
| | | | |
|---|---|---|---|
| N | 2.428991 | 0.572514 | 0.000000 |
| H | 1.524818 | 2.403585 | 0.000000 |
| C | 1.351013 | 1.329811 | 0.000000 |
| C | 1.104919 | -1.331009 | 0.000000 |
| C | 0.029588 | 0.821632 | 0.000000 |
| N | 2.302373 | -0.784230 | 0.000000 |
| C | -0.121971 | -0.608910 | 0.000000 |
| C | -1.221220 | 1.461669 | 0.000000 |
| H | -1.457889 | -2.317812 | 0.000000 |
| H | 1.094269 | -2.420321 | 0.000000 |
| C | -2.317972 | 0.878146 | 0.000000 |
| C | -2.589973 | -0.495059 | 0.000000 |
| H | -3.569039 | -0.961497 | 0.000000 |
| C | -1.406420 | -1.231502 | 0.000000 |

## 4.92



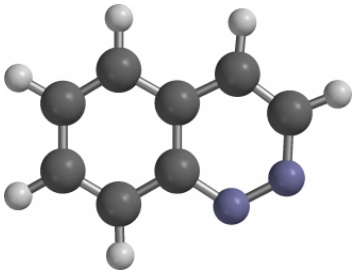
| | | | |
|---|---|---|---|
| H | -1.255283 | 0.000000 | 3.262032 |
| C | -0.710773 | 0.000000 | 2.318524 |
| N | -1.421038 | 0.000000 | 1.210595 |
| N | 1.421038 | 0.000000 | 1.210595 |
| C | -0.715519 | 0.000000 | 0.041912 |
| C | 0.710773 | 0.000000 | 2.318524 |
| C | 0.715519 | 0.000000 | 0.041912 |
| C | -1.411356 | 0.000000 | -1.194109 |
| H | 1.255283 | 0.000000 | 3.262032 |
| H | 2.496704 | 0.000000 | -1.166927 |
| C | -0.709419 | 0.000000 | -2.378726 |
| H | -2.496704 | 0.000000 | -1.166927 |
| H | -1.242586 | 0.000000 | -3.325439 |
| C | 0.709419 | 0.000000 | -2.378726 |
| H | 1.242586 | 0.000000 | -3.325439 |
| C | 1.411356 | 0.000000 | -1.194109 |

## 4.93



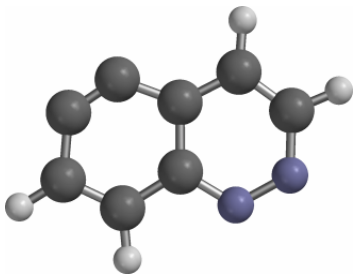
| | | | |
|---|---|---|---|
| H | 3.307889 | -1.083631 | 0.000000 |
| C | 2.320531 | -0.624601 | 0.000000 |
| N | 1.278136 | -1.435032 | 0.000000 |
| N | 1.021570 | 1.395554 | 0.000000 |
| C | 0.066086 | -0.843944 | 0.000000 |
| C | 2.191603 | 0.786220 | 0.000000 |
| C | -0.085749 | 0.607475 | 0.000000 |
| C | -1.197806 | -1.462999 | 0.000000 |
| H | 3.080149 | 1.415510 | 0.000000 |
| H | -1.394995 | 2.318250 | 0.000000 |
| C | -2.291653 | -0.875246 | 0.000000 |
| C | -2.557850 | 0.504885 | 0.000000 |
| H | -3.537787 | 0.969700 | 0.000000 |
| C | -1.378059 | 1.232518 | 0.000000 |

## 4.94



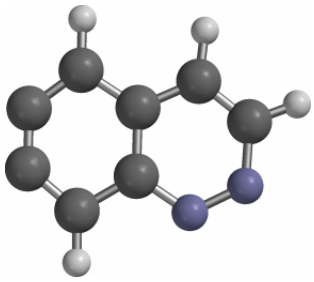
| | | | |
|---|---|---|---|
| H | 3.408599 | -0.952523 | 0.000000 |
| C | 2.400512 | -0.548089 | 0.000000 |
| H | 1.388440 | -2.446626 | 0.000000 |
| C | 1.292219 | -1.363623 | 0.000000 |
| N | 1.183361 | 1.415075 | 0.000000 |
| C | 0.024125 | -0.748159 | 0.000000 |
| N | 2.342322 | 0.814153 | 0.000000 |
| C | 0.030287 | 0.679226 | 0.000000 |
| C | -1.218420 | -1.436745 | 0.000000 |
| H | -1.162482 | 2.471520 | 0.000000 |
| C | -2.396461 | -0.726522 | 0.000000 |
| H | -1.222203 | -2.524015 | 0.000000 |
| H | -3.346523 | -1.253795 | 0.000000 |
| C | -2.389590 | 0.694691 | 0.000000 |
| H | -3.334133 | 1.231295 | 0.000000 |
| C | -1.202109 | 1.386830 | 0.000000 |

## 4.95



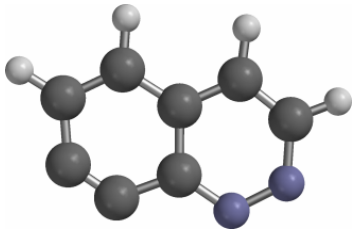
| | | | |
|---|---|---|---|
| H | 3.416761 | -0.805337 | 0.000000 |
| C | 2.381642 | -0.476186 | 0.000000 |
| H | 1.514636 | -2.451921 | 0.000000 |
| C | 1.338912 | -1.380938 | 0.000000 |
| N | 1.022967 | 1.392172 | 0.000000 |
| C | 0.039957 | -0.855469 | 0.000000 |
| N | 2.223219 | 0.873609 | 0.000000 |
| C | -0.080222 | 0.591533 | 0.000000 |
| C | -1.233589 | -1.450314 | 0.000000 |
| H | -1.357451 | 2.327811 | 0.000000 |
| C | -2.318817 | -0.848537 | 0.000000 |
| C | -2.556167 | 0.539704 | 0.000000 |
| H | -3.525908 | 1.024959 | 0.000000 |
| C | -1.362401 | 1.242210 | 0.000000 |

## 4.96



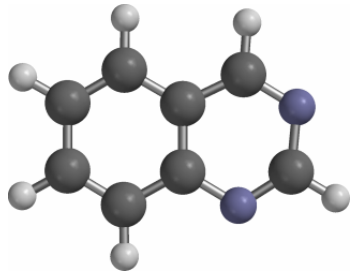
| | | | |
|---|---|---|---|
| H | 3.285121 | -0.943776 | 0.000000 |
| C | 2.277642 | -0.538150 | 0.000000 |
| H | 1.274360 | -2.438638 | 0.000000 |
| C | 1.170842 | -1.356664 | 0.000000 |
| N | 1.058515 | 1.420212 | 0.000000 |
| C | -0.104557 | -0.754936 | 0.000000 |
| N | 2.218649 | 0.821097 | 0.000000 |
| C | -0.096810 | 0.689897 | 0.000000 |
| C | -1.335268 | -1.502452 | 0.000000 |
| H | -1.295127 | 2.535149 | 0.000000 |
| C | -2.403834 | -0.654389 | 0.000000 |
| H | -1.344068 | -2.588241 | 0.000000 |
| C | -2.389711 | 0.607394 | 0.000000 |
| C | -1.324087 | 1.451646 | 0.000000 |

## 4.97



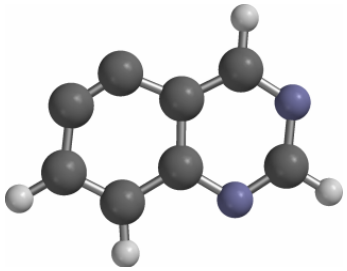
| | | | |
|---|---|---|---|
| H | 3.258220 | -1.146578 | 0.000000 |
| C | 2.294345 | -0.645952 | 0.000000 |
| H | 1.120221 | -2.447307 | 0.000000 |
| C | 1.112918 | -1.360253 | 0.000000 |
| N | 1.268252 | 1.424279 | 0.000000 |
| C | -0.097158 | -0.642064 | 0.000000 |
| N | 2.368116 | 0.709396 | 0.000000 |
| C | 0.067644 | 0.803406 | 0.000000 |
| C | -1.393745 | -1.254167 | 0.000000 |
| C | -2.567033 | -0.512434 | 0.000000 |
| H | -1.448770 | -2.340464 | 0.000000 |
| H | -3.549118 | -0.973019 | 0.000000 |
| C | -2.292350 | 0.865855 | 0.000000 |
| C | -1.191948 | 1.436991 | 0.000000 |

## 4.98



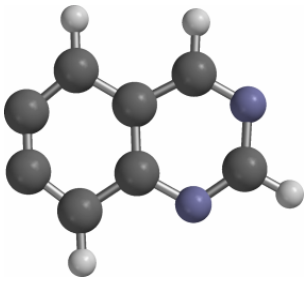
| | | | |
|---|---|---|---|
| N | 2.419423 | 0.703643 | 0.000000 |
| H | 1.329072 | 2.448766 | 0.000000 |
| C | 1.276642 | 1.358493 | 0.000000 |
| N | 1.232388 | -1.388762 | 0.000000 |
| C | 0.013134 | 0.714328 | 0.000000 |
| C | 2.324563 | -0.656766 | 0.000000 |
| C | 0.046140 | -0.711585 | 0.000000 |
| C | -1.230616 | 1.394610 | 0.000000 |
| H | 3.273771 | -1.189211 | 0.000000 |
| H | -1.134442 | -2.513585 | 0.000000 |
| C | -2.403720 | 0.674163 | 0.000000 |
| H | -1.242368 | 2.482108 | 0.000000 |
| H | -3.360644 | 1.188236 | 0.000000 |
| C | -2.372885 | -0.744430 | 0.000000 |
| H | -3.310067 | -1.294576 | 0.000000 |
| C | -1.177286 | -1.429091 | 0.000000 |

## 4.99



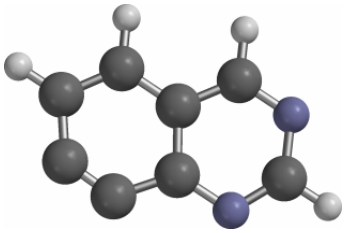
| | | | |
|---|---|---|---|
| N | 2.417448 | 0.598340 | 0.000000 |
| H | 1.490093 | 2.442506 | 0.000000 |
| C | 1.341055 | 1.363459 | 0.000000 |
| N | 1.047481 | -1.380239 | 0.000000 |
| C | 0.035619 | 0.827823 | 0.000000 |
| C | 2.201692 | -0.743338 | 0.000000 |
| C | -0.079018 | -0.616926 | 0.000000 |
| C | -1.229502 | 1.440536 | 0.000000 |
| H | 3.098095 | -1.360100 | 0.000000 |
| H | -1.366851 | -2.346654 | 0.000000 |
| C | -2.312265 | 0.833686 | 0.000000 |
| C | -2.554131 | -0.549768 | 0.000000 |
| H | -3.526063 | -1.031408 | 0.000000 |
| C | -1.362174 | -1.261047 | 0.000000 |

## 4.100



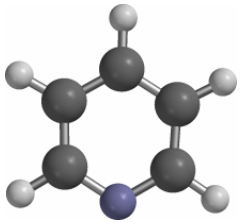
| | | | |
|---|---|---|---|
| N | 2.292893 | 0.702878 | 0.000000 |
| H | 1.206827 | 2.449212 | 0.000000 |
| C | 1.151719 | 1.359659 | 0.000000 |
| N | 1.108530 | -1.385410 | 0.000000 |
| C | -0.118077 | 0.723609 | 0.000000 |
| C | 2.202615 | -0.654685 | 0.000000 |
| C | -0.079925 | -0.720401 | 0.000000 |
| C | -1.352096 | 1.455721 | 0.000000 |
| H | 3.150651 | -1.188561 | 0.000000 |
| H | -1.254360 | -2.580608 | 0.000000 |
| C | -2.409589 | 0.591516 | 0.000000 |
| H | -1.377981 | 2.541560 | 0.000000 |
| C | -2.377907 | -0.668944 | 0.000000 |
| C | -1.295247 | -1.497587 | 0.000000 |

## 4.101



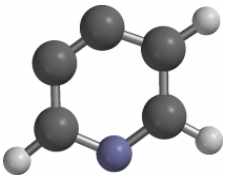
| | | | |
|---|---|---|---|
| N | 2.290669 | 0.794314 | 0.000000 |
| H | 1.058326 | 2.440526 | 0.000000 |
| C | 1.093079 | 1.350215 | 0.000000 |
| N | 1.299844 | -1.396501 | 0.000000 |
| C | -0.112958 | 0.606348 | 0.000000 |
| C | 2.323221 | -0.562729 | 0.000000 |
| C | 0.074261 | -0.834698 | 0.000000 |
| C | -1.408460 | 1.210654 | 0.000000 |
| H | 3.315732 | -1.008292 | 0.000000 |
| C | -2.578685 | 0.460378 | 0.000000 |
| H | -1.470895 | 2.296829 | 0.000000 |
| H | -3.565127 | 0.910657 | 0.000000 |
| C | -2.284570 | -0.911392 | 0.000000 |
| C | -1.178931 | -1.477238 | 0.000000 |

## 4.102



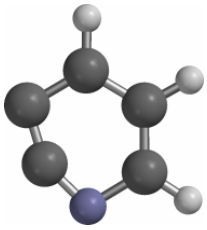
| | | | |
|---|---|---|---|
| H | 2.157893 | 0.000000 | -1.180546 |
| C | 1.198748 | 0.000000 | -0.670841 |
| C | -1.142285 | 0.000000 | 0.724114 |
| C | 1.142285 | 0.000000 | 0.724114 |
| C | 0.000000 | 0.000000 | -1.383231 |
| C | -1.198748 | 0.000000 | -0.670841 |
| N | 0.000000 | 0.000000 | 1.422944 |
| H | 2.059750 | 0.000000 | 1.311063 |
| H | 0.000000 | 0.000000 | -2.470159 |
| H | -2.157893 | 0.000000 | -1.180546 |
| H | -2.059750 | 0.000000 | 1.311063 |

## 4.103*



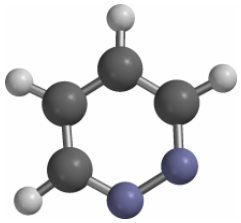
| | | | |
|---|---|---|---|
| C | 0.676457 | -1.197022 | 0.000000 |
| C | -0.662355 | 1.034551 | -0.000000 |
| C | 1.414698 | -0.020590 | 0.000000 |
| C | -0.580771 | -1.253776 | 0.000000 |
| C | -1.426420 | -0.165545 | -0.000000 |
| N | 0.667732 | 1.100300 | 0.000000 |
| H | 2.494944 | 0.077167 | 0.000000 |
| H | -2.511276 | -0.152871 | -0.000000 |
| H | -1.187450 | 1.987886 | -0.000000 |

## 4.104*



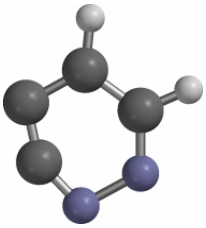
| | | | |
|---|---|---|---|
| C | 0.135156 | -1.533551 | 0.000000 |
| C | -0.345784 | 1.244114 | 0.000000 |
| C | -0.890673 | -0.774999 | 0.000000 |
| C | 1.233202 | -0.626745 | 0.000000 |
| C | 0.966903 | 0.763711 | 0.000000 |
| N | -1.419451 | 0.373928 | 0.000000 |
| H | 2.265024 | -0.978229 | 0.000000 |
| H | 1.785211 | 1.477501 | 0.000000 |
| H | -0.591922 | 2.300797 | 0.000000 |

## 4.105



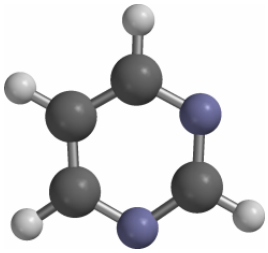
| | | | |
|---|---|---|---|
| H | 1.272030 | 0.000000 | 2.095067 |
| C | 0.692022 | 0.000000 | 1.176795 |
| N | -0.668236 | 0.000000 | -1.236408 |
| C | 1.323035 | 0.000000 | -0.071790 |
| C | -0.692022 | 0.000000 | 1.176795 |
| C | -1.323035 | 0.000000 | -0.071790 |
| N | 0.668236 | 0.000000 | -1.236408 |
| H | 2.407245 | 0.000000 | -0.156040 |
| H | -1.272030 | 0.000000 | 2.095067 |
| H | -2.407245 | 0.000000 | -0.156040 |

## 4.106*



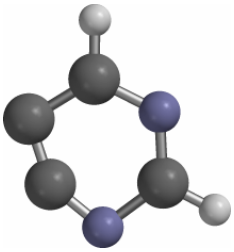
| | | | |
|---|---|---|---|
| C | 0.117577 | -1.478973 | 0.000000 |
| N | -0.299202 | 1.296307 | 0.000000 |
| C | -0.922600 | -0.732774 | 0.000000 |
| C | 1.229094 | -0.631346 | 0.000000 |
| C | 0.915223 | 0.763998 | 0.000000 |
| N | -1.418118 | 0.433400 | 0.000000 |
| H | 2.265535 | -0.965902 | 0.000000 |
| H | 1.709610 | 1.506570 | 0.000000 |

## 4.107



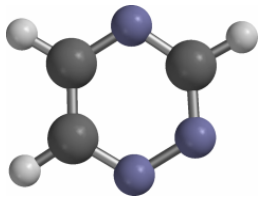
| | | | |
|---|---|---|---|
| N | -1.199190 | 0.000000 | -0.717565 |
| C | 1.184475 | 0.000000 | 0.621298 |
| C | 0.000000 | 0.000000 | -1.310466 |
| C | -1.184475 | 0.000000 | 0.621298 |
| C | 0.000000 | 0.000000 | 1.355217 |
| N | 1.199190 | 0.000000 | -0.717565 |
| H | 0.000000 | 0.000000 | -2.398906 |
| H | -2.154491 | 0.000000 | 1.116389 |
| H | 0.000000 | 0.000000 | 2.440526 |
| H | 2.154491 | 0.000000 | 1.116389 |

## 4.108*



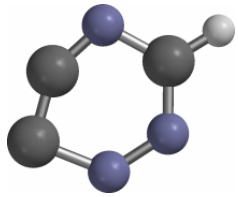
| | | | |
|---|---|---|---|
| N | 1.435253 | -0.140692 | 0.000000 |
| C | -1.284055 | 0.349476 | 0.000000 |
| C | 0.471585 | -1.148780 | 0.000000 |
| C | 0.760700 | 0.927724 | 0.000000 |
| C | -0.399142 | 1.467007 | 0.000000 |
| N | -0.827504 | -0.924569 | 0.000000 |
| H | 0.849694 | -2.164927 | 0.000000 |
| H | -2.365797 | 0.467080 | 0.000000 |

## 4.109



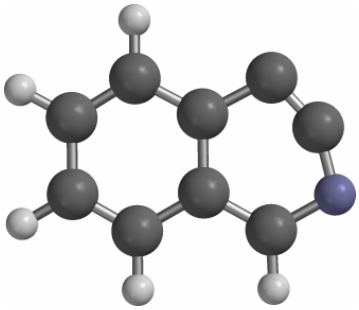
| | | | |
|---|---|---|---|
| N | 0.309867 | -1.351235 | 0.000000 |
| N | -0.972326 | -0.974817 | 0.000000 |
| C | -1.242058 | 0.333445 | 0.000000 |
| H | -2.297332 | 0.594740 | 0.000000 |
| N | -0.359476 | 1.344298 | 0.000000 |
| C | 0.912431 | 0.958465 | 0.000000 |
| H | 1.676803 | 1.733967 | 0.000000 |
| C | 1.245564 | -0.400409 | 0.000000 |
| H | 2.276995 | -0.743015 | 0.000000 |

## 4.110*



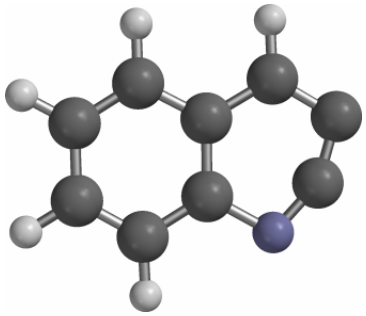
| | | | |
|---|---|---|---|
| N | -0.445087 | -1.139143 | 0.000000 |
| N | -1.308825 | -0.183672 | 0.000000 |
| C | -0.986513 | 1.268868 | 0.000000 |
| C | 0.335869 | 1.132744 | 0.000000 |
| C | 0.866903 | -0.934152 | 0.000000 |
| H | 1.571995 | -1.755687 | 0.000000 |
| N | 1.314896 | 0.362946 | 0.000000 |

## 4.111*



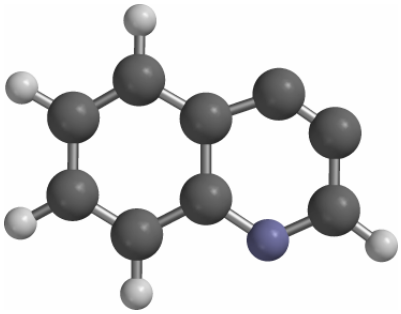
| | | | |
|---|---|---|---|
| C | 2.219409 | 0.648498 | 0.000000 |
| C | 1.327756 | 1.540945 | 0.000000 |
| C | 1.406472 | -1.279447 | 0.000000 |
| C | 0.068078 | 0.825752 | 0.000000 |
| N | 2.568554 | -0.588586 | 0.000000 |
| C | 0.136103 | -0.628110 | 0.000000 |
| C | -1.205972 | 1.446606 | 0.000000 |
| H | -1.024487 | -2.461973 | 0.000000 |
| H | 1.484683 | -2.363538 | 0.000000 |
| C | -2.353972 | 0.682779 | 0.000000 |
| H | -1.249468 | 2.530929 | 0.000000 |
| H | -3.325587 | 1.169880 | 0.000000 |
| C | -2.289680 | -0.732553 | 0.000000 |
| H | -3.209651 | -1.310242 | 0.000000 |
| C | -1.072901 | -1.375653 | 0.000000 |

## 4.112*



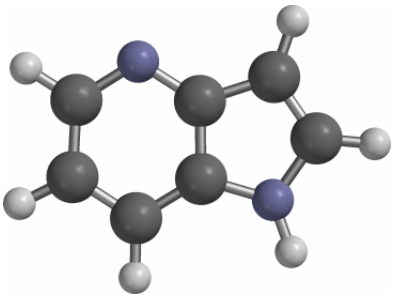
| | | | |
|---|---|---|---|
| C | 2.590094 | 0.696050 | 0.000000 |
| H | 1.357111 | 2.504052 | 0.000000 |
| C | 1.385378 | 1.412744 | 0.000000 |
| N | 1.355722 | -1.439809 | 0.000000 |
| C | 0.131146 | 0.699234 | 0.000000 |
| C | 2.219051 | -0.537614 | 0.000000 |
| C | 0.125626 | -0.741212 | 0.000000 |
| C | -1.123746 | 1.360860 | 0.000000 |
| H | -1.046941 | -2.543485 | 0.000000 |
| C | -2.302089 | 0.644159 | 0.000000 |
| H | -1.140714 | 2.447959 | 0.000000 |
| H | -3.254470 | 1.166586 | 0.000000 |
| C | -2.282441 | -0.769222 | 0.000000 |
| H | -3.219672 | -1.318718 | 0.000000 |
| C | -1.085864 | -1.459104 | 0.000000 |

## 4.113*



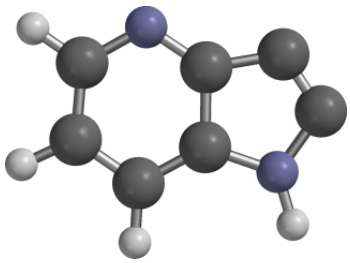
| | | | |
|---|---|---|---|
| C | 2.368529 | 0.844729 | 0.000000 |
| C | 1.272111 | 1.439458 | 0.000000 |
| N | 1.369827 | -1.237788 | 0.000000 |
| C | 0.002986 | 0.850930 | 0.000000 |
| C | 2.506137 | -0.561910 | 0.000000 |
| C | 0.163534 | -0.610496 | 0.000000 |
| C | -1.287564 | 1.420407 | 0.000000 |
| H | 3.442036 | -1.111603 | 0.000000 |
| H | -0.908012 | -2.475342 | 0.000000 |
| C | -2.400429 | 0.604602 | 0.000000 |
| H | -1.385406 | 2.501318 | 0.000000 |
| H | -3.393269 | 1.045552 | 0.000000 |
| C | -2.263332 | -0.802357 | 0.000000 |
| H | -3.154208 | -1.424233 | 0.000000 |
| C | -1.018731 | -1.396068 | 0.000000 |

## 4.114



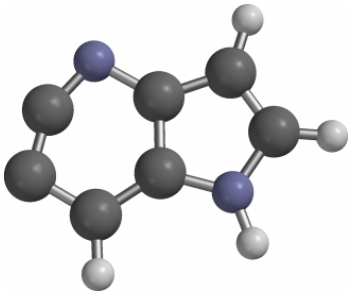
| | | | |
|---|---|---|---|
| C | 0.230276 | -0.696663 | 0.000000 |
| C | -2.054906 | 0.754076 | 0.000000 |
| C | 0.213823 | 0.730457 | 0.000000 |
| C | -0.965082 | -1.413316 | 0.000000 |
| C | -2.130521 | -0.653822 | 0.000000 |
| N | -0.921272 | 1.453814 | 0.000000 |
| H | -0.991476 | -2.500268 | 0.000000 |
| H | -3.102720 | -1.137368 | 0.000000 |
| H | -2.974998 | 1.336866 | 0.000000 |
| C | 1.580445 | 1.168476 | 0.000000 |
| H | 1.927976 | 2.191541 | 0.000000 |
| C | 2.355903 | 0.039413 | 0.000000 |
| H | 3.432095 | -0.065055 | 0.000000 |
| N | 1.550578 | -1.087682 | 0.000000 |
| H | 1.883932 | -2.039099 | 0.000000 |

## 4.115*



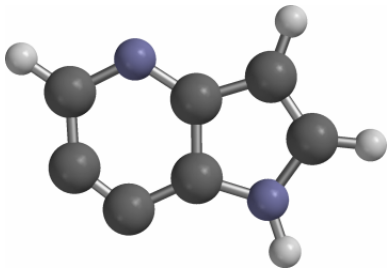
| | | | |
|---|---|---|---|
| C | 0.334735 | -0.637410 | 0.000000 |
| C | -1.994956 | 0.769108 | 0.000000 |
| C | 0.271660 | 0.817973 | 0.000000 |
| C | -0.844965 | -1.366450 | 0.000000 |
| C | -2.034777 | -0.633197 | 0.000000 |
| N | -0.867403 | 1.488266 | 0.000000 |
| H | -0.849428 | -2.453892 | 0.000000 |
| H | -2.992862 | -1.143499 | 0.000000 |
| H | -2.922370 | 1.337676 | 0.000000 |
| N | 1.691303 | -1.019594 | 0.000000 |
| H | 2.032637 | -1.970029 | 0.000000 |
| C | 2.426746 | 0.137697 | 0.000000 |
| C | 1.670483 | 1.139575 | 0.000000 |

## 4.116*



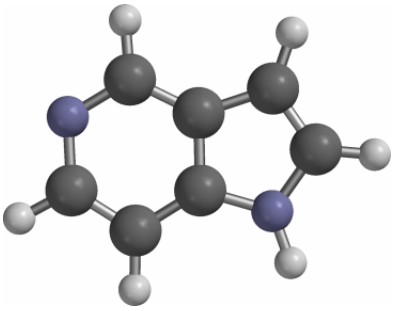
| | | | |
|---|---|---|---|
| N | 1.095429 | -1.475247 | 0.000000 |
| C | -0.105352 | -0.780094 | 0.000000 |
| C | -0.111323 | 0.659624 | 0.000000 |
| H | 1.047538 | 2.514768 | 0.000000 |
| C | 1.079406 | 1.424314 | 0.000000 |
| C | 2.283914 | 0.686258 | 0.000000 |
| C | 1.957563 | -0.550586 | 0.000000 |
| N | -1.440287 | 1.028483 | 0.000000 |
| H | -1.781095 | 1.977379 | 0.000000 |
| C | -2.236263 | -0.097876 | 0.000000 |
| H | -3.313584 | -0.004158 | 0.000000 |
| C | -1.455742 | -1.230076 | 0.000000 |
| H | -1.801501 | -2.253219 | 0.000000 |

## 4.117*



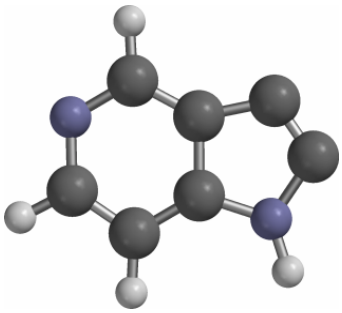
| | | | |
|---|---|---|---|
| N | 1.108932 | -1.263614 | 0.000000 |
| C | -0.081719 | -0.649267 | 0.000000 |
| C | -0.235139 | 0.795272 | 0.000000 |
| C | 0.958404 | 1.492901 | 0.000000 |
| C | 2.028711 | 0.828673 | 0.000000 |
| H | 3.193633 | -1.069493 | 0.000000 |
| C | 2.242311 | -0.550828 | 0.000000 |
| N | -1.579309 | 1.066272 | 0.000000 |
| H | -1.989117 | 1.987282 | 0.000000 |
| C | -2.279855 | -0.128648 | 0.000000 |
| H | -3.360710 | -0.121433 | 0.000000 |
| C | -1.411282 | -1.189111 | 0.000000 |
| H | -1.678195 | -2.235929 | 0.000000 |

## 4.118



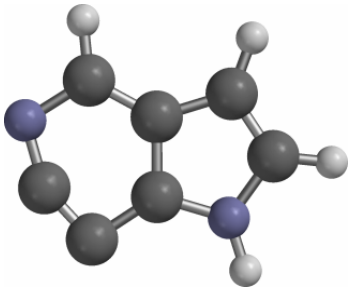
| | | | |
|---|---|---|---|
| C | 0.237122 | -0.739323 | 0.000000 |
| C | -2.126241 | 0.631638 | 0.000000 |
| C | -1.010976 | -1.382750 | 0.000000 |
| C | 0.237607 | 0.681812 | 0.000000 |
| C | -0.964924 | 1.394690 | 0.000000 |
| N | -2.164926 | -0.719978 | 0.000000 |
| H | -1.075091 | -2.470782 | 0.000000 |
| H | -1.003803 | 2.480355 | 0.000000 |
| H | -3.095074 | 1.127398 | 0.000000 |
| C | 1.610533 | -1.163031 | 0.000000 |
| H | 1.980328 | -2.179039 | 0.000000 |
| C | 2.374305 | -0.028196 | 0.000000 |
| H | 3.448993 | 0.089807 | 0.000000 |
| N | 1.550398 | 1.088577 | 0.000000 |
| H | 1.868315 | 2.045407 | 0.000000 |

## 4.119*



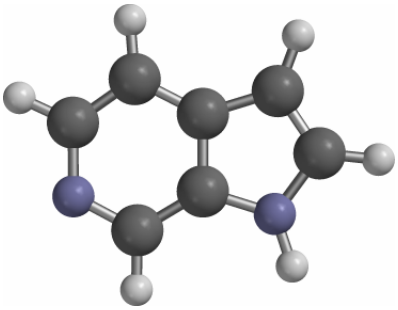
| | | | |
|---|---|---|---|
| C | 0.307605 | -0.811172 | 0.000000 |
| C | -2.021863 | 0.601077 | 0.000000 |
| C | -0.939620 | -1.437209 | 0.000000 |
| C | 0.342758 | 0.636521 | 0.000000 |
| C | -0.848836 | 1.355799 | 0.000000 |
| N | -2.080493 | -0.745097 | 0.000000 |
| H | -1.020428 | -2.522678 | 0.000000 |
| H | -0.879578 | 2.441952 | 0.000000 |
| H | -2.983037 | 1.111210 | 0.000000 |
| N | 1.689597 | 1.037565 | 0.000000 |
| H | 2.019648 | 1.991226 | 0.000000 |
| C | 2.444439 | -0.113987 | 0.000000 |
| C | 1.706425 | -1.121603 | 0.000000 |

## 4.120*



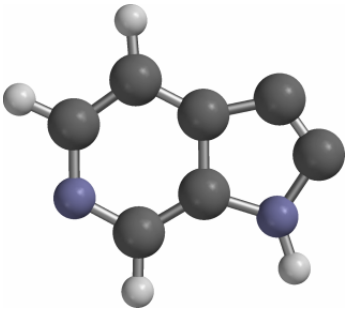
| | | | |
|---|---|---|---|
| N | 2.292795 | 0.527054 | 0.000000 |
| H | 1.309106 | 2.376001 | 0.000000 |
| C | 1.159935 | 1.301315 | 0.000000 |
| C | -0.103849 | 0.687956 | 0.000000 |
| C | -0.168611 | -0.761129 | 0.000000 |
| C | 0.990732 | -1.579676 | 0.000000 |
| C | 1.897331 | -0.679947 | 0.000000 |
| N | -1.499383 | -1.094062 | 0.000000 |
| H | -1.846775 | -2.041348 | 0.000000 |
| C | -2.269545 | 0.058273 | 0.000000 |
| H | -3.348754 | -0.008510 | 0.000000 |
| C | -1.460438 | 1.161770 | 0.000000 |
| H | -1.794613 | 2.190058 | 0.000000 |

## 4.121



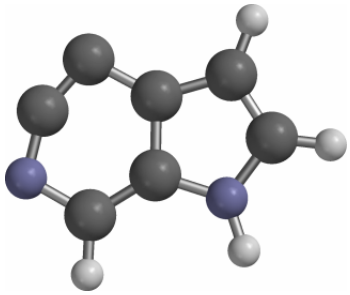
| | | | |
|---|---|---|---|
| C | 0.239074 | -0.660636 | 0.000000 |
| C | -2.151077 | 0.590284 | 0.000000 |
| C | -0.958599 | -1.381362 | 0.000000 |
| C | 0.233750 | 0.760409 | 0.000000 |
| C | -1.019978 | 1.394896 | 0.000000 |
| N | -2.136319 | -0.762910 | 0.000000 |
| H | -0.969844 | -2.471685 | 0.000000 |
| H | -1.110560 | 2.477540 | 0.000000 |
| H | -3.140356 | 1.043559 | 0.000000 |
| C | 1.603630 | 1.184029 | 0.000000 |
| H | 1.974029 | 2.199795 | 0.000000 |
| C | 2.371201 | 0.046624 | 0.000000 |
| H | 3.447066 | -0.063353 | 0.000000 |
| N | 1.558234 | -1.068121 | 0.000000 |
| H | 1.879042 | -2.023816 | 0.000000 |

## 4.122*



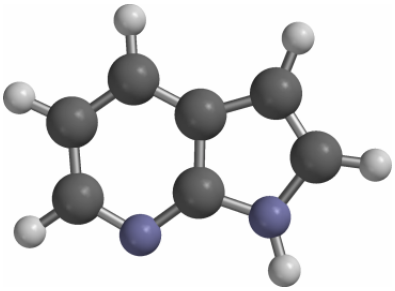
| | | | |
|---|---|---|---|
| C | 0.353290 | -0.616104 | 0.000000 |
| C | -2.059942 | 0.611563 | 0.000000 |
| C | -0.831773 | -1.345538 | 0.000000 |
| C | 0.308370 | 0.832495 | 0.000000 |
| C | -0.945058 | 1.446416 | 0.000000 |
| N | -2.020290 | -0.735924 | 0.000000 |
| H | -0.833203 | -2.435972 | 0.000000 |
| H | -1.053480 | 2.526318 | 0.000000 |
| H | -3.056917 | 1.047224 | 0.000000 |
| N | 1.710503 | -1.011424 | 0.000000 |
| H | 2.048455 | -1.962186 | 0.000000 |
| C | 2.448622 | 0.142584 | 0.000000 |
| C | 1.700598 | 1.146030 | 0.000000 |

## 4.123*



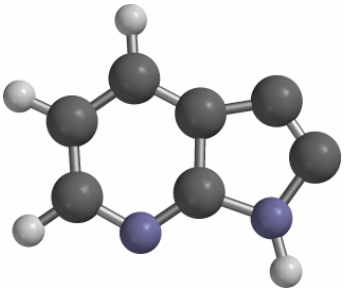
| | | | |
|---|---|---|---|
| C | -1.038406 | -1.566237 | 0.000000 |
| C | -1.109882 | 1.296712 | 0.000000 |
| C | 0.192756 | -0.836651 | 0.000000 |
| C | -1.922542 | -0.654279 | 0.000000 |
| N | -2.272224 | 0.574340 | 0.000000 |
| C | 0.113448 | 0.612593 | 0.000000 |
| C | 1.583013 | -1.170680 | 0.000000 |
| H | 2.008465 | -2.163826 | 0.000000 |
| C | 2.280653 | 0.012360 | 0.000000 |
| H | 3.348595 | 0.184304 | 0.000000 |
| N | 1.410176 | 1.082257 | 0.000000 |
| H | 1.687213 | 2.051610 | 0.000000 |
| H | -1.202753 | 2.378347 | 0.000000 |

## 4.124



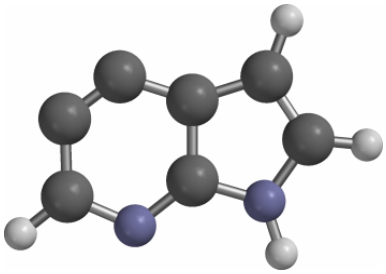
| | | | |
|---|---|---|---|
| C | 0.230554 | -0.778267 | 0.000000 |
| C | -2.026743 | 0.788279 | 0.000000 |
| C | 0.210803 | 0.647319 | 0.000000 |
| C | -1.016858 | -1.416536 | 0.000000 |
| C | -2.153682 | -0.613794 | 0.000000 |
| N | -0.859326 | 1.440051 | 0.000000 |
| H | -1.096418 | -2.500813 | 0.000000 |
| H | -3.144799 | -1.057330 | 0.000000 |
| H | -2.918579 | 1.412297 | 0.000000 |
| C | 1.609221 | -1.175558 | 0.000000 |
| H | 2.000646 | -2.183693 | 0.000000 |
| C | 2.354638 | -0.024150 | 0.000000 |
| H | 3.427922 | 0.105746 | 0.000000 |
| N | 1.518354 | 1.076530 | 0.000000 |

## 4.125*



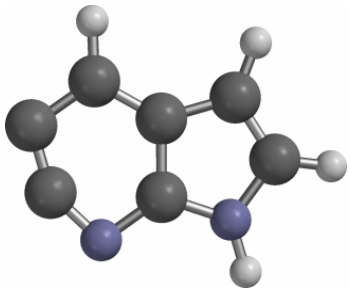
| | | | |
|---|---|---|---|
| C | 0.312378 | -0.862952 | 0.000000 |
| C | -1.920405 | 0.750632 | 0.000000 |
| C | 0.328864 | 0.599645 | 0.000000 |
| C | -0.938451 | -1.472290 | 0.000000 |
| C | -2.064735 | -0.643167 | 0.000000 |
| N | -0.729000 | 1.369626 | 0.000000 |
| H | -1.038237 | -2.553506 | 0.000000 |
| H | -3.060738 | -1.074774 | 0.000000 |
| H | -2.795597 | 1.395573 | 0.000000 |
| N | 1.674593 | 1.022945 | 0.000000 |
| H | 1.967430 | 1.989524 | 0.000000 |
| C | 2.444261 | -0.115915 | 0.000000 |
| C | 1.707645 | -1.133365 | 0.000000 |

## 4.126*



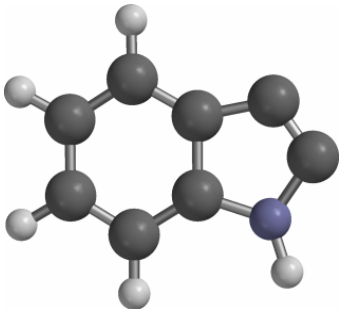
| | | | |
|---|---|---|---|
| C | -1.019176 | -1.452085 | 0.000000 |
| N | -1.050878 | 1.256190 | 0.000000 |
| C | 0.244872 | -0.887963 | 0.000000 |
| C | -2.097846 | -0.811925 | 0.000000 |
| C | -2.214404 | 0.583929 | 0.000000 |
| C | 0.082766 | 0.560812 | 0.000000 |
| H | -3.134990 | 1.156764 | 0.000000 |
| C | 1.644940 | -1.156716 | 0.000000 |
| H | 2.125966 | -2.124038 | 0.000000 |
| C | 2.280057 | 0.062048 | 0.000000 |
| H | 3.337531 | 0.285476 | 0.000000 |
| N | 1.354262 | 1.085585 | 0.000000 |
| H | 1.558631 | 2.073267 | 0.000000 |

## 4.127*



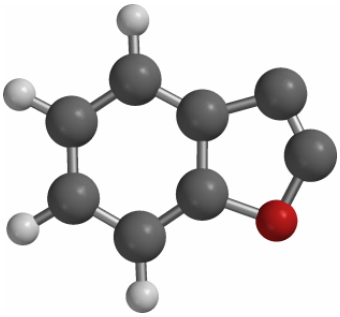
| | | | |
|---|---|---|---|
| H | -1.169342 | -2.513799 | 0.000000 |
| C | -1.136286 | -1.424670 | 0.000000 |
| N | -1.017741 | 1.479876 | 0.000000 |
| C | 0.106311 | -0.738579 | 0.000000 |
| C | -2.296932 | -0.617256 | 0.000000 |
| C | -1.947303 | 0.603517 | 0.000000 |
| C | 0.106942 | 0.699308 | 0.000000 |
| C | 1.492099 | -1.124699 | 0.000000 |
| H | 1.883025 | -2.132787 | 0.000000 |
| C | 2.240546 | 0.021295 | 0.000000 |
| H | 3.313407 | 0.153575 | 0.000000 |
| N | 1.402852 | 1.129968 | 0.000000 |
| H | 1.687295 | 2.097619 | 0.000000 |

## 4.128*



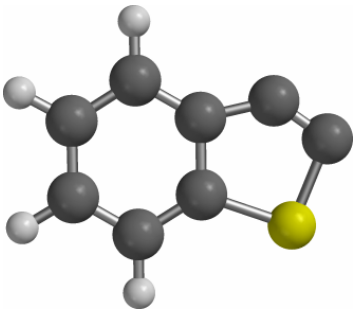
| | | | |
|---|---|---|---|
| H | -0.955078 | -2.566511 | 0.000000 |
| C | -0.909617 | -1.481663 | 0.000000 |
| C | -0.815439 | 1.378124 | 0.000000 |
| C | 0.322385 | -0.824155 | 0.000000 |
| C | -2.073912 | -0.716482 | 0.000000 |
| C | -2.028162 | 0.688590 | 0.000000 |
| C | 0.357380 | 0.627621 | 0.000000 |
| H | -3.038443 | -1.216179 | 0.000000 |
| H | -2.956693 | 1.252455 | 0.000000 |
| H | -0.789165 | 2.465238 | 0.000000 |
| C | 1.722783 | -1.122336 | 0.000000 |
| C | 2.467265 | -0.117525 | 0.000000 |
| N | 1.711292 | 1.029816 | 0.000000 |
| H | 2.039132 | 1.983915 | 0.000000 |

## 4.129*



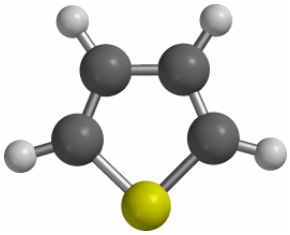
| | | | |
|---|---|---|---|
| H | -0.724179 | -2.503237 | 0.000000 |
| C | -0.779898 | -1.419684 | 0.000000 |
| C | -0.891210 | 1.451392 | 0.000000 |
| C | 0.350708 | -0.631449 | 0.000000 |
| C | -2.000793 | -0.731184 | 0.000000 |
| C | -2.051223 | 0.670032 | 0.000000 |
| C | 0.342923 | 0.802267 | 0.000000 |
| H | -2.925831 | -1.300189 | 0.000000 |
| H | -3.019246 | 1.163074 | 0.000000 |
| H | -0.945538 | 2.535235 | 0.000000 |
| C | 1.761283 | 1.204392 | 0.000000 |
| C | 2.308303 | 0.091222 | 0.000000 |
| O | 1.704096 | -1.098421 | 0.000000 |

## 4.130*



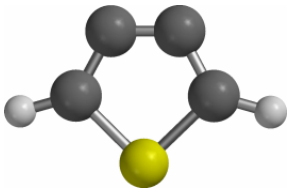
| | | | |
|---|---|---|---|
| H | -0.781308 | -2.472060 | 0.000000 |
| C | -0.946336 | -1.397504 | 0.000000 |
| C | -1.392755 | 1.415172 | 0.000000 |
| C | 0.127610 | -0.513042 | 0.000000 |
| C | -2.238145 | -0.870921 | 0.000000 |
| C | -2.455617 | 0.516903 | 0.000000 |
| C | -0.091589 | 0.902841 | 0.000000 |
| H | -3.089165 | -1.545876 | 0.000000 |
| H | -3.472987 | 0.897167 | 0.000000 |
| H | -1.563706 | 2.486914 | 0.000000 |
| C | 1.235789 | 1.399299 | 0.000000 |
| C | 2.349911 | 0.833143 | 0.000000 |
| S | 1.907628 | -0.862472 | 0.000000 |

## 4.131



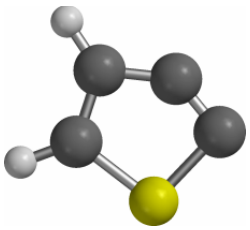
| | | | |
|---|---|---|---|
| C | 0.714739 | 0.000000 | 1.267680 |
| H | 1.319482 | 0.000000 | 2.168299 |
| C | 1.243534 | 0.000000 | 0.006768 |
| H | 2.284636 | 0.000000 | -0.286596 |
| C | -0.714739 | 0.000000 | 1.267680 |
| H | -1.319482 | 0.000000 | 2.168299 |
| C | -1.243534 | 0.000000 | 0.006768 |
| H | -2.284636 | 0.000000 | -0.286596 |
| S | 0.000000 | 0.000000 | -1.204293 |

## 4.132*



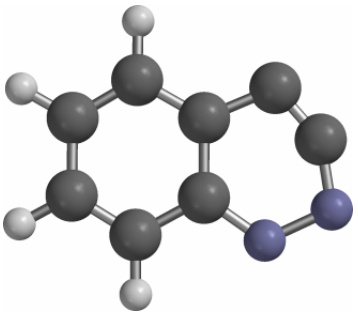
| | | | |
|---|---|---|---|
| C | 0.637374 | 0.000000 | 1.363027 |
| C | 1.278310 | 0.000000 | 0.167900 |
| H | 2.319786 | 0.000000 | -0.124165 |
| C | -0.637374 | 0.000000 | 1.363027 |
| C | -1.278310 | 0.000000 | 0.167900 |
| H | -2.319786 | 0.000000 | -0.124165 |
| S | 0.000000 | 0.000000 | -1.069113 |

## 4.133*



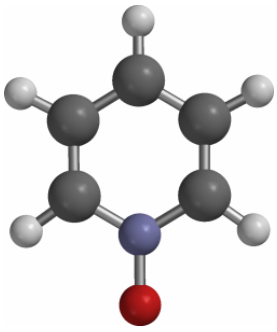
| | | | |
|---|---|---|---|
| C | 1.000778 | 0.834889 | 0.000000 |
| C | -0.104263 | 1.438999 | 0.000000 |
| C | 1.410095 | -0.512513 | 0.000000 |
| H | 2.404679 | -0.933919 | 0.000000 |
| C | 0.204330 | -1.171916 | 0.000000 |
| H | 0.021088 | -2.241119 | 0.000000 |
| S | -1.125938 | 0.017570 | 0.000000 |

## 4.134



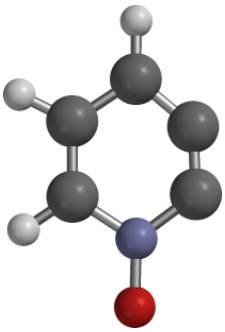
| | | | |
|---|---|---|---|
| C | 2.233494 | 0.594894 | 0.000000 |
| C | 1.338159 | 1.485057 | 0.000000 |
| N | 1.325421 | -1.322381 | 0.000000 |
| C | 0.067390 | 0.840391 | 0.000000 |
| N | 2.517138 | -0.669201 | 0.000000 |
| C | 0.160747 | -0.618827 | 0.000000 |
| C | -1.210548 | 1.453755 | 0.000000 |
| H | -0.962415 | -2.465514 | 0.000000 |
| C | -2.343633 | 0.672738 | 0.000000 |
| H | -1.267741 | 2.537312 | 0.000000 |
| H | -3.322985 | 1.143312 | 0.000000 |
| C | -2.259078 | -0.746249 | 0.000000 |
| H | -3.174344 | -1.331248 | 0.000000 |
| C | -1.043028 | -1.383753 | 0.000000 |

## 4.135



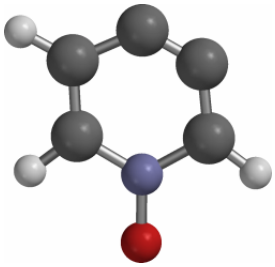
| | | | |
|---|---|---|---|
| C | -0.280947 | -1.172238 | 0.000000 |
| H | -0.918779 | -2.045875 | 0.000000 |
| C | 1.101829 | -1.197442 | 0.000000 |
| H | 1.597909 | -2.163153 | 0.000000 |
| C | 1.833941 | -0.008525 | 0.000000 |
| H | 2.918331 | -0.017146 | 0.000000 |
| C | 1.120860 | 1.191907 | 0.000000 |
| H | 1.632488 | 2.149465 | 0.000000 |
| C | -0.262173 | 1.188768 | 0.000000 |
| H | -0.885962 | 2.072490 | 0.000000 |
| N | -0.975369 | 0.013894 | 0.000000 |
| O | -2.249704 | 0.024046 | 0.000000 |

## 4.136



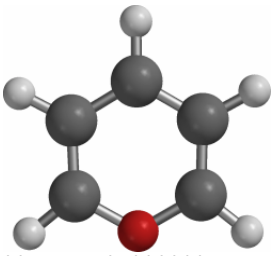
| | | | |
|---|---|---|---|
| C | -0.911132 | -1.257399 | 0.000000 |
| C | 0.174736 | 1.076263 | 0.000000 |
| C | 0.334200 | -1.189921 | 0.000000 |
| C | -1.888359 | -0.285181 | 0.000000 |
| C | -1.210852 | 0.957630 | 0.000000 |
| H | -2.964558 | -0.394400 | 0.000000 |
| H | -1.786513 | 1.880521 | 0.000000 |
| H | 0.697482 | 2.023682 | 0.000000 |
| N | 1.048993 | -0.021130 | 0.000000 |
| O | 2.294319 | 0.125613 | 0.000000 |

## 4.137



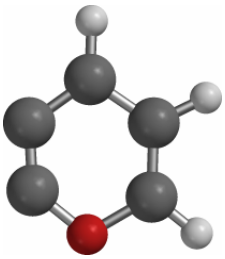
| | | | |
|---|---|---|---|
| C | -1.050925 | -1.271657 | 0.000000 |
| C | 0.032534 | 1.138350 | 0.000000 |
| C | 0.317248 | -1.270615 | 0.000000 |
| C | -1.775688 | -0.251787 | 0.000000 |
| C | -1.357905 | 1.068814 | 0.000000 |
| H | 1.048606 | -2.066394 | 0.000000 |
| H | -1.974435 | 1.960777 | 0.000000 |
| H | 0.589658 | 2.065333 | 0.000000 |
| N | 0.861999 | 0.019677 | 0.000000 |
| O | 2.126003 | 0.161617 | 0.000000 |

## 4.138



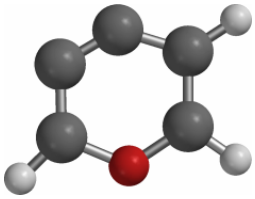
| | | | |
|---|---|---|---|
| H | 0.000000 | 0.000000 | 2.498849 |
| C | 0.000000 | 0.000000 | 1.412619 |
| C | 1.211328 | 0.000000 | 0.707751 |
| C | -1.211328 | 0.000000 | 0.707751 |
| C | -1.164638 | 0.000000 | -0.667049 |
| C | 1.164638 | 0.000000 | -0.667049 |
| H | 2.171940 | 0.000000 | 1.210711 |
| H | -2.171940 | 0.000000 | 1.210711 |
| H | -2.011743 | 0.000000 | -1.343003 |
| H | 2.011743 | 0.000000 | -1.343003 |
| O | 0.000000 | 0.000000 | -1.314931 |

## 4.139



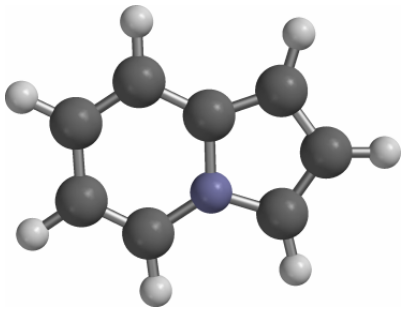
| | | | |
|---|---|---|---|
| C | 0.454895 | -1.225561 | 0.000000 |
| C | -0.785266 | -1.155000 | 0.000000 |
| H | -2.550219 | 0.192683 | 0.000000 |
| C | -1.474050 | 0.044524 | 0.000000 |
| H | -0.913948 | 2.157912 | 0.000000 |
| C | -0.545853 | 1.134908 | 0.000000 |
| H | 1.585512 | 1.710206 | 0.000000 |
| C | 0.818547 | 0.944676 | 0.000000 |
| O | 1.377587 | -0.317977 | 0.000000 |

## 4.140



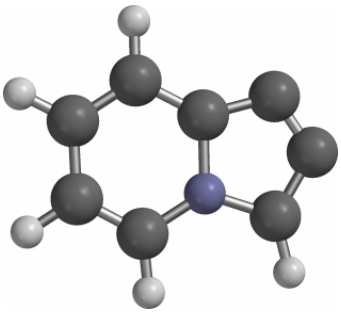
| | | | |
|---|---|---|---|
| C | -0.937371 | -0.973150 | 0.000000 |
| C | -1.443687 | 0.302463 | 0.000000 |
| C | 0.234856 | -1.423301 | 0.000000 |
| C | 1.282754 | -0.558963 | 0.000000 |
| C | -0.344502 | 1.171646 | 0.000000 |
| H | -2.470079 | 0.651281 | 0.000000 |
| H | 2.358036 | -0.691729 | 0.000000 |
| H | -0.414822 | 2.255154 | 0.000000 |
| O | 0.917601 | 0.752772 | 0.000000 |

## 4.141



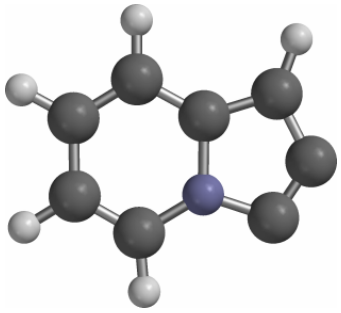
| | | | |
|---|---|---|---|
| C | 0.985853 | -1.410868 | 0.000000 |
| H | 1.002258 | -2.496667 | 0.000000 |
| C | 2.147258 | -0.681094 | 0.000000 |
| H | 3.111246 | -1.179893 | 0.000000 |
| C | 2.089245 | 0.745491 | 0.000000 |
| H | 2.998524 | 1.336832 | 0.000000 |
| C | 0.885130 | 1.384807 | 0.000000 |
| H | 0.771230 | 2.462965 | 0.000000 |
| N | -0.284342 | 0.656645 | 0.000000 |
| C | -0.273123 | -0.760583 | 0.000000 |
| C | -1.602787 | -1.179063 | 0.000000 |
| H | -1.934435 | -2.208247 | 0.000000 |
| C | -2.410275 | -0.022979 | 0.000000 |
| H | -3.492191 | 0.005952 | 0.000000 |
| C | -1.588084 | 1.092018 | 0.000000 |
| H | -1.818780 | 2.147461 | 0.000000 |

## 4.142*



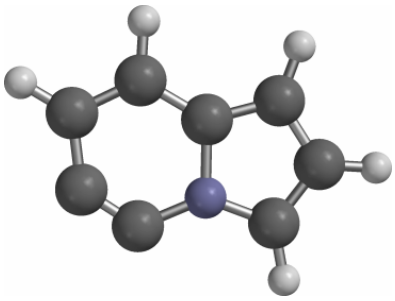
| | | | |
|---|---|---|---|
| N | -0.362636 | -0.642801 | 0.000000 |
| C | -1.683130 | -1.103781 | 0.000000 |
| H | -1.914526 | -2.157179 | 0.000000 |
| C | -2.427388 | 0.063740 | 0.000000 |
| C | -1.733090 | 1.121371 | 0.000000 |
| C | -0.375337 | 0.803022 | 0.000000 |
| C | 0.865621 | 1.471486 | 0.000000 |
| H | 0.862039 | 2.556695 | 0.000000 |
| C | 2.040592 | 0.755744 | 0.000000 |
| H | 2.995118 | 1.272019 | 0.000000 |
| C | 2.009946 | -0.667397 | 0.000000 |
| H | 2.932884 | -1.237467 | 0.000000 |
| C | 0.821487 | -1.342826 | 0.000000 |
| H | 0.739942 | -2.424111 | 0.000000 |

## 4.143*



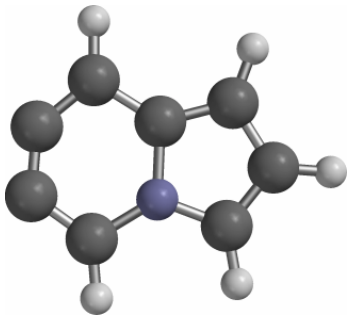
| | | | |
|---|---|---|---|
| N | -0.360769 | -0.733120 | 0.000000 |
| C | -1.662703 | -1.173881 | 0.000000 |
| C | -2.381975 | -0.140655 | 0.000000 |
| C | -1.752135 | 1.114722 | 0.000000 |
| H | -2.133908 | 2.123515 | 0.000000 |
| C | -0.392903 | 0.712875 | 0.000000 |
| C | 0.845674 | 1.398380 | 0.000000 |
| H | 0.841256 | 2.484384 | 0.000000 |
| C | 2.021405 | 0.689426 | 0.000000 |
| H | 2.971623 | 1.214385 | 0.000000 |
| C | 2.010094 | -0.738760 | 0.000000 |
| H | 2.940124 | -1.296622 | 0.000000 |
| C | 0.830500 | -1.423327 | 0.000000 |
| H | 0.746478 | -2.503086 | 0.000000 |

## 4.144



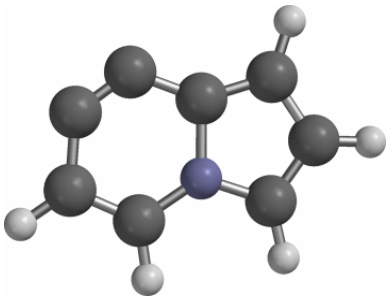
| | | | |
|---|---|---|---|
| C | 1.975691 | -0.932453 | 0.000000 |
| C | -0.131848 | 0.667063 | 0.000000 |
| C | 0.855118 | -1.456005 | 0.000000 |
| N | -0.311203 | -0.767719 | 0.000000 |
| C | -1.417847 | 1.205674 | 0.000000 |
| H | -1.652384 | 2.261424 | 0.000000 |
| C | -2.340495 | 0.138699 | 0.000000 |
| H | -3.418844 | 0.227953 | 0.000000 |
| C | -1.646621 | -1.062995 | 0.000000 |
| H | -1.988984 | -2.086676 | 0.000000 |
| C | 2.342787 | 0.429443 | 0.000000 |
| H | 3.342333 | 0.844607 | 0.000000 |
| C | 1.189693 | 1.204036 | 0.000000 |
| H | 1.282330 | 2.287218 | 0.000000 |

## 4.145



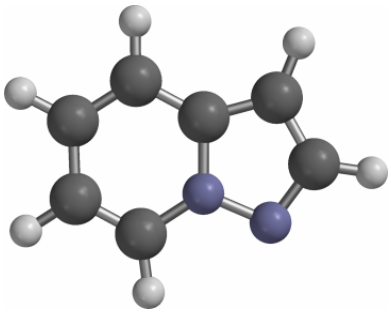
| | | | |
|---|---|---|---|
| C | 1.052936 | -1.424746 | 0.000000 |
| H | 0.935602 | -2.502423 | 0.000000 |
| C | 2.176328 | -0.667379 | 0.000000 |
| C | 2.108449 | 0.598520 | 0.000000 |
| C | 1.091997 | 1.486800 | 0.000000 |
| H | 1.119618 | 2.569923 | 0.000000 |
| C | -0.153563 | 0.762776 | 0.000000 |
| N | -0.131351 | -0.671248 | 0.000000 |
| C | -1.492151 | 1.148650 | 0.000000 |
| H | -1.844650 | 2.170732 | 0.000000 |
| C | -2.274436 | -0.024387 | 0.000000 |
| H | -3.355872 | -0.074834 | 0.000000 |
| C | -1.429028 | -1.122196 | 0.000000 |
| H | -1.642203 | -2.181203 | 0.000000 |

## 4.146



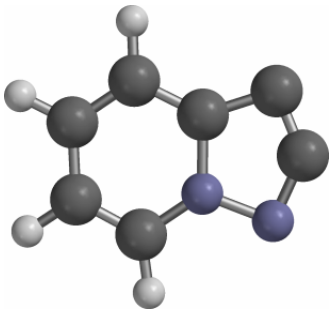
| | | | |
|---|---|---|---|
| C | 2.293305 | 0.475883 | 0.000000 |
| H | 3.258616 | 0.965470 | 0.000000 |
| C | 2.019226 | -0.904714 | 0.000000 |
| C | 0.935122 | -1.503578 | 0.000000 |
| C | -0.314180 | -0.867349 | 0.000000 |
| C | 1.111611 | 1.186789 | 0.000000 |
| H | 1.090726 | 2.271151 | 0.000000 |
| N | -0.127107 | 0.575632 | 0.000000 |
| C | -1.676278 | -1.102138 | 0.000000 |
| H | -2.140749 | -2.077683 | 0.000000 |
| C | -2.326428 | 0.156399 | 0.000000 |
| H | -3.396127 | 0.319972 | 0.000000 |
| C | -1.376427 | 1.158451 | 0.000000 |
| H | -1.486269 | 2.233229 | 0.000000 |

## 4.147



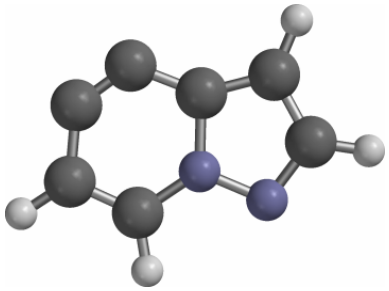
| | | | |
|---|---|---|---|
| C | 0.955270 | -1.439384 | 0.000000 |
| H | 0.964631 | -2.524650 | 0.000000 |
| C | 0.881046 | 1.364490 | 0.000000 |
| H | 0.747977 | 2.438904 | 0.000000 |
| C | -0.292218 | -0.765912 | 0.000000 |
| C | -1.644662 | -1.115156 | 0.000000 |
| H | -2.057072 | -2.113273 | 0.000000 |
| C | -2.328768 | 0.107273 | 0.000000 |
| H | -3.399015 | 0.271347 | 0.000000 |
| N | -0.275309 | 0.634145 | 0.000000 |
| N | -1.515576 | 1.174320 | 0.000000 |
| C | 2.081704 | 0.711765 | 0.000000 |
| H | 2.998026 | 1.291301 | 0.000000 |
| C | 2.120550 | -0.712575 | 0.000000 |
| H | 3.079990 | -1.220602 | 0.000000 |

## 4.148*



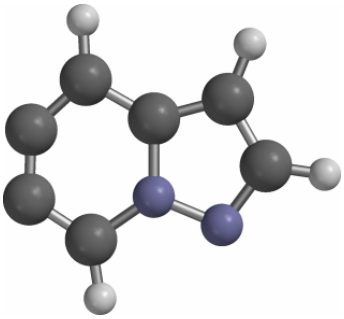
| | | | |
|---|---|---|---|
| N | -0.367279 | -0.644900 | 0.000000 |
| N | -1.657701 | -1.163738 | 0.000000 |
| C | -2.225445 | 0.019824 | 0.000000 |
| C | -1.765628 | 1.205971 | 0.000000 |
| C | -0.405132 | 0.800988 | 0.000000 |
| C | 0.778545 | -1.380589 | 0.000000 |
| H | 0.655044 | -2.456258 | 0.000000 |
| C | 1.976566 | -0.713141 | 0.000000 |
| H | 2.895760 | -1.288301 | 0.000000 |
| C | 2.011241 | 0.706205 | 0.000000 |
| H | 2.971809 | 1.212306 | 0.000000 |
| C | 0.849465 | 1.448559 | 0.000000 |
| H | 0.866135 | 2.532780 | 0.000000 |

## 4.149



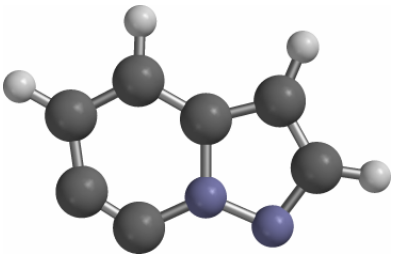
| | | | |
|---|---|---|---|
| C | 2.275585 | 0.475868 | 0.000000 |
| H | 3.239677 | 0.967358 | 0.000000 |
| C | 2.005155 | -0.903983 | 0.000000 |
| C | 0.929434 | -1.519544 | 0.000000 |
| C | -0.316264 | -0.876635 | 0.000000 |
| C | 1.087939 | 1.179469 | 0.000000 |
| H | 1.027863 | 2.260720 | 0.000000 |
| N | -0.132066 | 0.544089 | 0.000000 |
| N | -1.316505 | 1.199983 | 0.000000 |
| C | -1.689103 | -1.069572 | 0.000000 |
| H | -2.210862 | -2.014291 | 0.000000 |
| C | -2.233930 | 0.226800 | 0.000000 |
| H | -3.280910 | 0.502594 | 0.000000 |

## 4.150



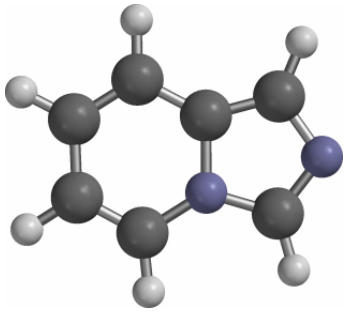
| | | | |
|---|---|---|---|
| H | -1.157990 | -2.568816 | 0.000000 |
| C | -1.099548 | -1.487303 | 0.000000 |
| C | -2.094437 | -0.569447 | 0.000000 |
| C | -2.128015 | 0.695302 | 0.000000 |
| C | 0.154797 | -0.782953 | 0.000000 |
| H | 1.902468 | -2.147346 | 0.000000 |
| C | 1.503354 | -1.143932 | 0.000000 |
| C | -0.986664 | 1.430641 | 0.000000 |
| H | -0.816807 | 2.499762 | 0.000000 |
| N | 0.157881 | 0.636670 | 0.000000 |
| N | 1.406336 | 1.146356 | 0.000000 |
| H | 3.277695 | 0.215117 | 0.000000 |
| C | 2.204704 | 0.068149 | 0.000000 |

## 4.151



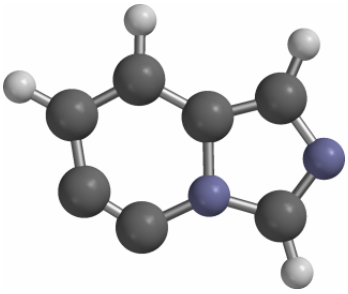
| | | | |
|---|---|---|---|
| C | 1.934720 | -0.938155 | 0.000000 |
| C | 2.314615 | 0.414566 | 0.000000 |
| H | 3.320214 | 0.815954 | 0.000000 |
| C | 1.175967 | 1.213007 | 0.000000 |
| H | 1.284665 | 2.294112 | 0.000000 |
| C | -0.147201 | 0.681005 | 0.000000 |
| C | 0.807867 | -1.452730 | 0.000000 |
| N | -0.333607 | -0.737198 | 0.000000 |
| N | -1.623579 | -1.103545 | 0.000000 |
| C | -1.447399 | 1.188949 | 0.000000 |
| H | -1.737709 | 2.229426 | 0.000000 |
| C | -2.285928 | 0.065376 | 0.000000 |
| H | -3.368099 | 0.047320 | 0.000000 |

## 4.152



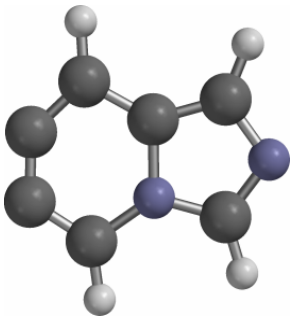
| | | | |
|---|---|---|---|
| N | 0.281407 | -0.661682 | 0.000000 |
| C | -0.896857 | -1.382125 | 0.000000 |
| H | -0.797350 | -2.461452 | 0.000000 |
| C | -2.085499 | -0.719742 | 0.000000 |
| H | -3.006823 | -1.292105 | 0.000000 |
| C | -2.120971 | 0.712492 | 0.000000 |
| H | -3.079138 | 1.222143 | 0.000000 |
| C | -0.953930 | 1.429067 | 0.000000 |
| H | -0.956213 | 2.514605 | 0.000000 |
| C | 0.293047 | 0.751933 | 0.000000 |
| C | 1.641704 | 1.088772 | 0.000000 |
| H | 2.072389 | 2.081001 | 0.000000 |
| N | 2.418821 | -0.030433 | 0.000000 |
| C | 1.592483 | -1.061899 | 0.000000 |
| H | 1.875013 | -2.105766 | 0.000000 |

## 4.153



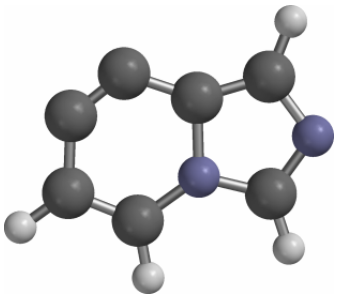
| | | | |
|---|---|---|---|
| C | 1.944611 | 0.942233 | 0.000000 |
| C | 0.827925 | 1.472035 | 0.000000 |
| C | -0.138051 | -0.672631 | 0.000000 |
| C | -1.436359 | -1.166020 | 0.000000 |
| H | -1.746479 | -2.202665 | 0.000000 |
| N | -2.350837 | -0.155463 | 0.000000 |
| C | -1.673980 | 0.981945 | 0.000000 |
| H | -2.093674 | 1.977671 | 0.000000 |
| N | -0.329393 | 0.756956 | 0.000000 |
| C | 2.328441 | -0.417530 | 0.000000 |
| H | 3.333391 | -0.818837 | 0.000000 |
| C | 1.187801 | -1.205048 | 0.000000 |
| H | 1.291218 | -2.286973 | 0.000000 |

## 4.154



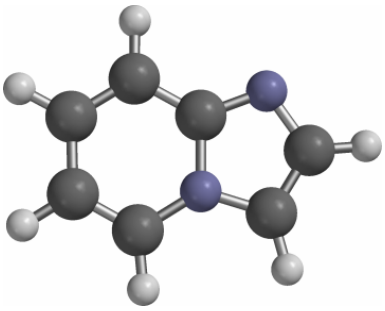
| | | | |
|---|---|---|---|
| C | 2.093747 | 0.590816 | 0.000000 |
| C | 1.088443 | 1.488209 | 0.000000 |
| H | 1.123106 | 2.570950 | 0.000000 |
| C | 2.155528 | -0.677672 | 0.000000 |
| C | 1.035868 | -1.435382 | 0.000000 |
| H | 0.913654 | -2.512127 | 0.000000 |
| N | -0.144879 | -0.666672 | 0.000000 |
| C | -0.159761 | 0.763085 | 0.000000 |
| C | -1.509063 | 1.094349 | 0.000000 |
| H | -1.938430 | 2.087085 | 0.000000 |
| N | -2.285795 | -0.024155 | 0.000000 |
| C | -1.457653 | -1.055790 | 0.000000 |
| H | -1.744624 | -2.098361 | 0.000000 |

## 4.155



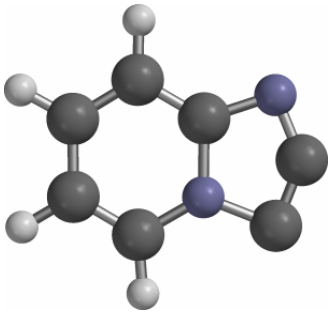
| | | | |
|---|---|---|---|
| C | 2.281077 | 0.472816 | 0.000000 |
| H | 3.250501 | 0.954086 | 0.000000 |
| C | 1.108408 | 1.192372 | 0.000000 |
| H | 1.090572 | 2.276538 | 0.000000 |
| C | 2.000547 | -0.909577 | 0.000000 |
| C | 0.920951 | -1.514269 | 0.000000 |
| C | -0.323521 | -0.862460 | 0.000000 |
| C | -1.692028 | -1.030864 | 0.000000 |
| H | -2.239805 | -1.962602 | 0.000000 |
| N | -2.330125 | 0.179391 | 0.000000 |
| C | -1.396873 | 1.109504 | 0.000000 |
| H | -1.570575 | 2.177254 | 0.000000 |
| N | -0.131950 | 0.575992 | 0.000000 |

## 4.156



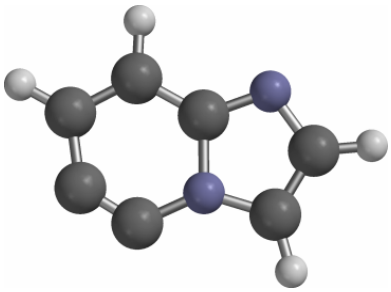
| | | | |
|---|---|---|---|
| N | 0.301270 | -0.670655 | 0.000000 |
| C | -0.859527 | -1.405762 | 0.000000 |
| H | -0.748805 | -2.483977 | 0.000000 |
| C | -2.062688 | -0.758186 | 0.000000 |
| H | -2.974841 | -1.344854 | 0.000000 |
| C | -2.115384 | 0.665395 | 0.000000 |
| H | -3.079570 | 1.163992 | 0.000000 |
| C | -0.955621 | 1.401522 | 0.000000 |
| H | -0.954598 | 2.485917 | 0.000000 |
| C | 0.294799 | 0.740774 | 0.000000 |
| C | 1.626549 | -1.051249 | 0.000000 |
| H | 1.924399 | -2.088805 | 0.000000 |
| N | 1.534692 | 1.225608 | 0.000000 |
| C | 2.343221 | 0.128580 | 0.000000 |
| H | 3.421413 | 0.229373 | 0.000000 |

## 4.157*



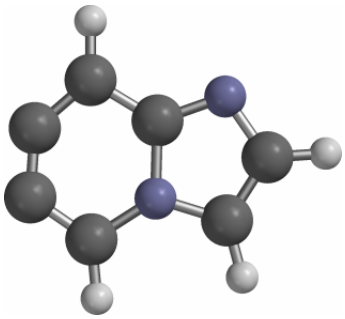
| | | | |
|---|---|---|---|
| N | -0.387277 | -0.718795 | 0.000000 |
| C | -1.713263 | -1.249666 | 0.000000 |
| C | -2.192037 | -0.045979 | 0.000000 |
| N | -1.711198 | 1.148708 | 0.000000 |
| C | -0.406472 | 0.723768 | 0.000000 |
| C | 0.802570 | -1.400705 | 0.000000 |
| H | 0.720900 | -2.479883 | 0.000000 |
| C | 1.979120 | -0.698476 | 0.000000 |
| H | 2.913910 | -1.248406 | 0.000000 |
| C | 1.982898 | 0.721730 | 0.000000 |
| H | 2.930281 | 1.251498 | 0.000000 |
| C | 0.802716 | 1.435800 | 0.000000 |
| H | 0.774939 | 2.519556 | 0.000000 |

## 4.158



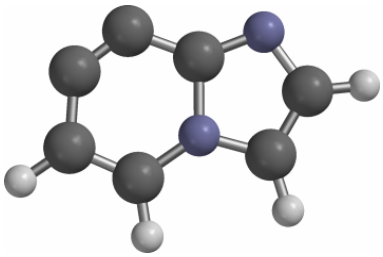
| | | | |
|---|---|---|---|
| C | 1.956281 | 0.945218 | 0.000000 |
| C | 0.833957 | 1.469360 | 0.000000 |
| C | -0.153631 | -0.652219 | 0.000000 |
| C | -1.676252 | 1.018977 | 0.000000 |
| H | -2.079497 | 2.019369 | 0.000000 |
| N | -0.324416 | 0.776473 | 0.000000 |
| N | -1.342834 | -1.240959 | 0.000000 |
| C | -2.261706 | -0.233081 | 0.000000 |
| H | -3.322210 | -0.449552 | 0.000000 |
| C | 2.313169 | -0.418311 | 0.000000 |
| H | 3.314028 | -0.831601 | 0.000000 |
| C | 1.165603 | -1.198824 | 0.000000 |
| H | 1.240345 | -2.281542 | 0.000000 |

## 4.159



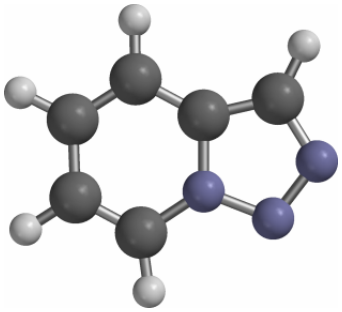
| | | | |
|---|---|---|---|
| C | 2.078096 | 0.587768 | 0.000000 |
| C | 1.061667 | 1.479712 | 0.000000 |
| H | 1.068533 | 2.562072 | 0.000000 |
| C | 2.153808 | -0.675355 | 0.000000 |
| C | 1.030715 | -1.442329 | 0.000000 |
| H | 0.923821 | -2.520975 | 0.000000 |
| N | -0.142533 | -0.688086 | 0.000000 |
| C | -0.173426 | 0.744543 | 0.000000 |
| C | -1.461962 | -1.084555 | 0.000000 |
| H | -1.743680 | -2.126598 | 0.000000 |
| C | -2.205195 | 0.078945 | 0.000000 |
| H | -3.285565 | 0.155531 | 0.000000 |
| N | -1.421582 | 1.194032 | 0.000000 |

## 4.160



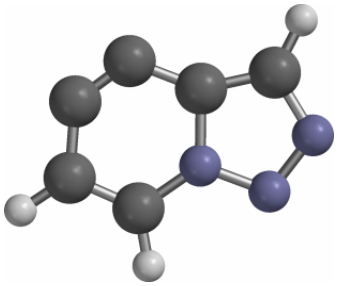
| | | | |
|---|---|---|---|
| C | 2.265243 | 0.473680 | 0.000000 |
| H | 3.237113 | 0.949901 | 0.000000 |
| C | 1.090481 | 1.201514 | 0.000000 |
| H | 1.079827 | 2.285858 | 0.000000 |
| C | 1.970949 | -0.897483 | 0.000000 |
| C | 0.889313 | -1.504015 | 0.000000 |
| C | -0.348238 | -0.845880 | 0.000000 |
| C | -1.414793 | 1.133340 | 0.000000 |
| H | -1.583078 | 2.199636 | 0.000000 |
| N | -0.143814 | 0.590685 | 0.000000 |
| N | -1.629629 | -1.141037 | 0.000000 |
| C | -2.280658 | 0.063444 | 0.000000 |
| H | -3.362126 | 0.107719 | 0.000000 |

## 4.161



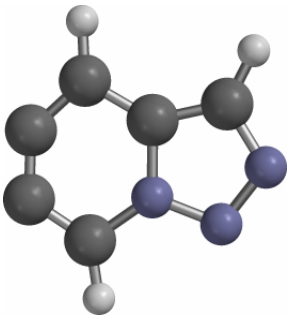
| | | | |
|---|---|---|---|
| C | 0.884290 | -1.364703 | 0.000000 |
| H | 0.759331 | -2.440149 | 0.000000 |
| C | 0.933747 | 1.449014 | 0.000000 |
| H | 0.932503 | 2.533992 | 0.000000 |
| N | -0.274629 | -0.633293 | 0.000000 |
| C | -0.301904 | 0.755171 | 0.000000 |
| C | -1.668009 | 1.034773 | 0.000000 |
| H | -2.167270 | 1.992533 | 0.000000 |
| N | -2.355528 | -0.126783 | 0.000000 |
| N | -1.533143 | -1.151436 | 0.000000 |
| C | 2.102661 | 0.730107 | 0.000000 |
| H | 3.059057 | 1.243348 | 0.000000 |
| C | 2.075240 | -0.697735 | 0.000000 |
| H | 2.998968 | -1.265589 | 0.000000 |

## 4.162



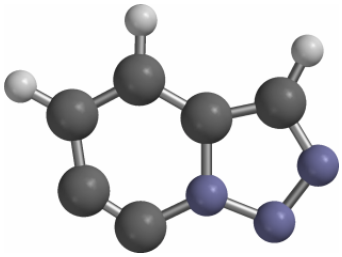
| | | | |
|---|---|---|---|
| C | 2.269703 | 0.453028 | 0.000000 |
| H | 3.241310 | 0.929689 | 0.000000 |
| C | 1.982415 | -0.924738 | 0.000000 |
| C | 0.901625 | -1.530288 | 0.000000 |
| C | -0.328865 | -0.858663 | 0.000000 |
| C | 1.095716 | 1.176782 | 0.000000 |
| H | 1.050098 | 2.258833 | 0.000000 |
| N | -0.130171 | 0.547081 | 0.000000 |
| C | -1.708347 | -0.976019 | 0.000000 |
| H | -2.316551 | -1.867714 | 0.000000 |
| N | -2.257364 | 0.263051 | 0.000000 |
| N | -1.330590 | 1.188938 | 0.000000 |

## 4.163



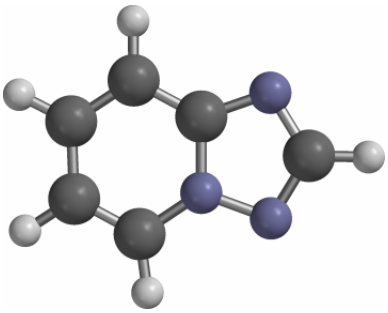
| | | | |
|---|---|---|---|
| C | 1.026232 | -1.414449 | 0.000000 |
| H | 0.884907 | -2.487577 | 0.000000 |
| C | 2.142561 | -0.645165 | 0.000000 |
| C | 2.079622 | 0.619607 | 0.000000 |
| C | 1.062555 | 1.511251 | 0.000000 |
| H | 1.090486 | 2.593881 | 0.000000 |
| N | -0.136135 | -0.640064 | 0.000000 |
| C | -0.168352 | 0.766107 | 0.000000 |
| C | -1.536126 | 1.033418 | 0.000000 |
| H | -2.038230 | 1.989639 | 0.000000 |
| N | -2.220628 | -0.129386 | 0.000000 |
| N | -1.391536 | -1.150999 | 0.000000 |

## 4.164



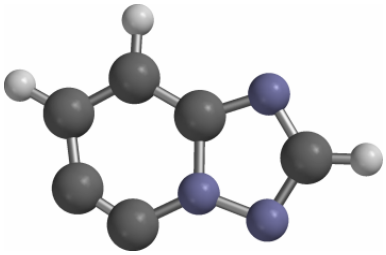
| | | | |
|---|---|---|---|
| C | 1.913232 | -0.928176 | 0.000000 |
| C | -0.157344 | 0.682186 | 0.000000 |
| C | 0.793614 | -1.456871 | 0.000000 |
| N | -0.342082 | -0.724266 | 0.000000 |
| C | -1.473339 | 1.134446 | 0.000000 |
| H | -1.846520 | 2.148372 | 0.000000 |
| N | -2.316625 | 0.077573 | 0.000000 |
| N | -1.649217 | -1.057234 | 0.000000 |
| C | 2.298290 | 0.424049 | 0.000000 |
| H | 3.304807 | 0.822239 | 0.000000 |
| C | 1.161859 | 1.223900 | 0.000000 |
| H | 1.269925 | 2.304823 | 0.000000 |

## 4.165



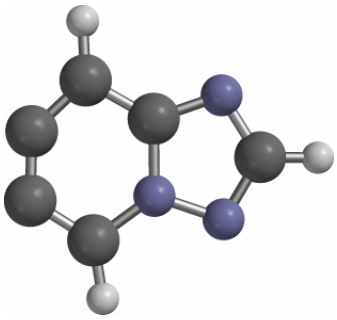
| | | | |
|---|---|---|---|
| N | -0.310224 | -0.636561 | 0.000000 |
| N | -1.590937 | -1.088647 | 0.000000 |
| C | -2.275659 | 0.058107 | 0.000000 |
| H | -3.358178 | 0.046425 | 0.000000 |
| N | -1.558798 | 1.202375 | 0.000000 |
| C | -0.297361 | 0.756648 | 0.000000 |
| C | 0.954012 | 1.411926 | 0.000000 |
| H | 0.973509 | 2.495787 | 0.000000 |
| C | 2.100509 | 0.650426 | 0.000000 |
| H | 3.072191 | 1.134560 | 0.000000 |
| C | 2.032534 | -0.770617 | 0.000000 |
| H | 2.937977 | -1.366898 | 0.000000 |
| C | 0.817748 | -1.403457 | 0.000000 |
| H | 0.663277 | -2.474905 | 0.000000 |

## 4.166



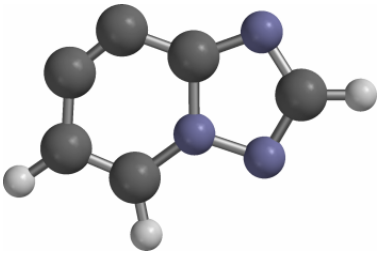
| | | | |
|---|---|---|---|
| C | 1.909945 | -0.945109 | 0.000000 |
| C | -0.169918 | 0.665755 | 0.000000 |
| C | 0.785252 | -1.469555 | 0.000000 |
| N | -0.345829 | -0.744625 | 0.000000 |
| N | -1.380563 | 1.222595 | 0.000000 |
| C | -2.215867 | 0.158621 | 0.000000 |
| H | -3.292524 | 0.265799 | 0.000000 |
| N | -1.658494 | -1.056289 | 0.000000 |
| C | 2.282746 | 0.407950 | 0.000000 |
| H | 3.289116 | 0.808164 | 0.000000 |
| C | 1.146872 | 1.210712 | 0.000000 |
| H | 1.238209 | 2.291854 | 0.000000 |

## 4.167



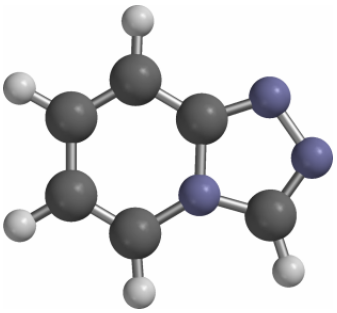
| | | | |
|---|---|---|---|
| C | 0.996719 | -1.436848 | 0.000000 |
| H | 0.857413 | -2.510473 | 0.000000 |
| C | 2.124548 | -0.671518 | 0.000000 |
| C | 2.059041 | 0.589892 | 0.000000 |
| C | 1.048568 | 1.494896 | 0.000000 |
| H | 1.069729 | 2.576914 | 0.000000 |
| C | -0.179894 | 0.756439 | 0.000000 |
| N | -1.451978 | 1.155312 | 0.000000 |
| C | -2.136042 | -0.009071 | 0.000000 |
| H | -3.217871 | -0.050972 | 0.000000 |
| N | -1.417132 | -1.134627 | 0.000000 |
| N | -0.149538 | -0.660102 | 0.000000 |

## 4.168



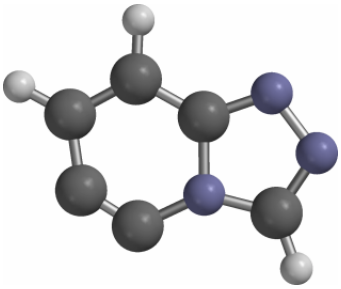
| | | | |
|---|---|---|---|
| C | 2.245510 | 0.471106 | 0.000000 |
| H | 3.217060 | 0.947429 | 0.000000 |
| C | -0.351616 | -0.851251 | 0.000000 |
| C | 1.066621 | 1.195283 | 0.000000 |
| H | 1.021002 | 2.277273 | 0.000000 |
| N | -0.149238 | 0.561372 | 0.000000 |
| N | -1.651043 | -1.100422 | 0.000000 |
| C | -2.197159 | 0.140810 | 0.000000 |
| H | -3.267113 | 0.302915 | 0.000000 |
| N | -1.360342 | 1.177018 | 0.000000 |
| C | 1.952491 | -0.899236 | 0.000000 |
| C | 0.877698 | -1.520328 | 0.000000 |

## 4.169



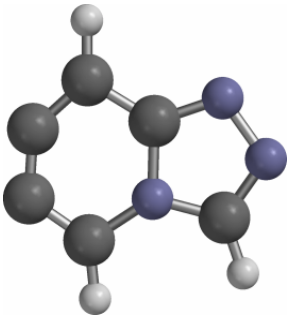
| | | | |
|---|---|---|---|
| N | -0.312396 | -0.663455 | 0.000000 |
| N | -1.528803 | 1.209701 | 0.000000 |
| C | -0.287842 | 0.737217 | 0.000000 |
| C | 0.971174 | 1.392243 | 0.000000 |
| H | 0.985892 | 2.476231 | 0.000000 |
| C | 2.113174 | 0.636345 | 0.000000 |
| H | 3.086378 | 1.116966 | 0.000000 |
| C | 2.041803 | -0.793156 | 0.000000 |
| H | 2.948787 | -1.387469 | 0.000000 |
| C | 0.835344 | -1.426172 | 0.000000 |
| H | 0.705507 | -2.501926 | 0.000000 |
| N | -2.369981 | 0.132227 | 0.000000 |
| C | -1.650290 | -0.969331 | 0.000000 |
| H | -2.031127 | -1.980297 | 0.000000 |

## 4.170



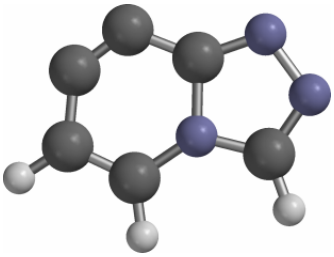
| | | | |
|---|---|---|---|
| C | -0.799113 | -1.488208 | 0.000000 |
| C | -1.922355 | -0.969747 | 0.000000 |
| C | -2.303681 | 0.390987 | 0.000000 |
| H | -3.312265 | 0.784635 | 0.000000 |
| C | -1.175378 | 1.191886 | 0.000000 |
| H | -1.267854 | 2.273016 | 0.000000 |
| C | 0.153101 | 0.654300 | 0.000000 |
| N | 1.340737 | 1.237853 | 0.000000 |
| N | 2.293618 | 0.254317 | 0.000000 |
| C | 1.700893 | -0.922440 | 0.000000 |
| H | 2.189326 | -1.885126 | 0.000000 |
| N | 0.343772 | -0.759734 | 0.000000 |

## 4.171



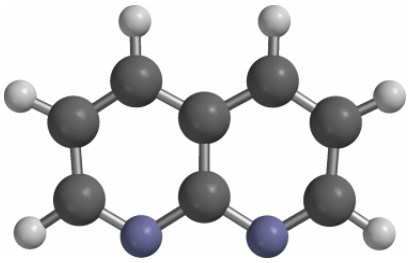
| | | | |
|---|---|---|---|
| C | 1.004028 | -1.458906 | 0.000000 |
| H | 0.878496 | -2.535217 | 0.000000 |
| C | 2.130731 | -0.705787 | 0.000000 |
| C | 2.067297 | 0.561331 | 0.000000 |
| C | 1.074016 | 1.471575 | 0.000000 |
| H | 1.097377 | 2.553605 | 0.000000 |
| C | -0.172013 | 0.741767 | 0.000000 |
| N | -1.421628 | 1.179615 | 0.000000 |
| N | -2.238466 | 0.083525 | 0.000000 |
| C | -1.491847 | -1.001379 | 0.000000 |
| H | -1.855810 | -2.018561 | 0.000000 |
| N | -0.159721 | -0.677464 | 0.000000 |

## 4.172



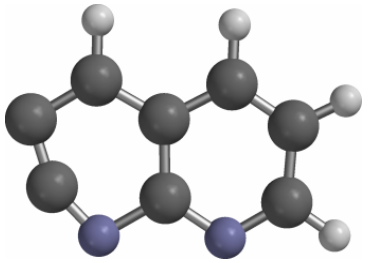
| | | | |
|---|---|---|---|
| C | 1.073968 | -1.217013 | 0.000000 |
| H | 1.056947 | -2.301013 | 0.000000 |
| C | 2.244588 | -0.490724 | 0.000000 |
| H | 3.217280 | -0.964810 | 0.000000 |
| C | 1.951331 | 0.885237 | 0.000000 |
| C | 0.879681 | 1.504838 | 0.000000 |
| C | -0.356122 | 0.833775 | 0.000000 |
| N | -1.641132 | 1.106344 | 0.000000 |
| N | -2.313454 | -0.091849 | 0.000000 |
| C | -1.443138 | -1.075273 | 0.000000 |
| H | -1.686337 | -2.128178 | 0.000000 |
| N | -0.157998 | -0.591533 | 0.000000 |

## 4.173



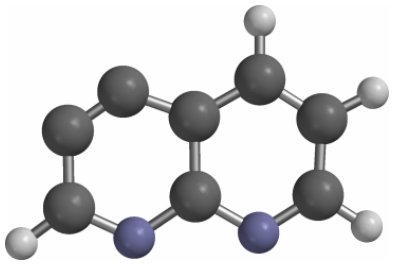
| | | | |
|---|---|---|---|
| N | -1.154884 | 0.000000 | 1.426752 |
| C | -2.292941 | 0.000000 | 0.763537 |
| H | -3.199960 | 0.000000 | 1.368311 |
| C | -2.403481 | 0.000000 | -0.651109 |
| H | -3.383432 | 0.000000 | -1.118662 |
| C | -1.250124 | 0.000000 | -1.397122 |
| H | -1.277887 | 0.000000 | -2.484697 |
| C | 0.000000 | 0.000000 | -0.729176 |
| C | 0.000000 | 0.000000 | 0.704072 |
| N | 1.154884 | 0.000000 | 1.426752 |
| C | 2.292941 | 0.000000 | 0.763537 |
| H | 3.199960 | 0.000000 | 1.368311 |
| C | 2.403481 | 0.000000 | -0.651109 |
| H | 3.383432 | 0.000000 | -1.118662 |
| C | 1.250124 | 0.000000 | -1.397122 |
| H | 1.277887 | 0.000000 | -2.484697 |

## 4.174



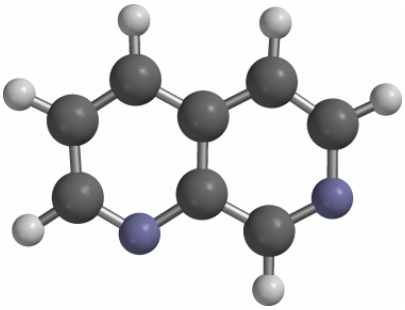
| | | | |
|---|---|---|---|
| C | 2.179473 | -0.551313 | 0.000000 |
| C | 2.575007 | 0.678067 | 0.000000 |
| C | 1.372017 | 1.400887 | 0.000000 |
| H | 1.353123 | 2.492578 | 0.000000 |
| C | 0.114542 | 0.698772 | 0.000000 |
| C | 0.082499 | -0.745265 | 0.000000 |
| N | 1.309613 | -1.442627 | 0.000000 |
| C | -1.142812 | 1.347742 | 0.000000 |
| H | -1.182862 | 2.434363 | 0.000000 |
| C | -2.295842 | 0.592862 | 0.000000 |
| H | -3.275712 | 1.059831 | 0.000000 |
| C | -2.188685 | -0.815690 | 0.000000 |
| H | -3.089837 | -1.426983 | 0.000000 |
| N | -1.040565 | -1.476687 | 0.000000 |

## 4.175



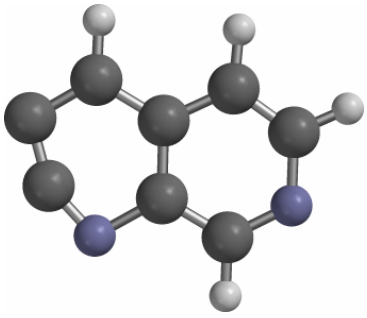
| | | | |
|---|---|---|---|
| C | -0.135225 | -0.614459 | 0.000000 |
| C | 0.005487 | 0.849724 | 0.000000 |
| C | -1.258679 | 1.446855 | 0.000000 |
| C | -2.348442 | 0.839843 | 0.000000 |
| C | -2.477043 | -0.570158 | 0.000000 |
| H | -3.413194 | -1.120024 | 0.000000 |
| N | -1.343943 | -1.243171 | 0.000000 |
| C | 1.300047 | 1.407052 | 0.000000 |
| H | 1.418896 | 2.485980 | 0.000000 |
| C | 2.383926 | 0.557776 | 0.000000 |
| H | 3.400047 | 0.940117 | 0.000000 |
| C | 2.155276 | -0.838152 | 0.000000 |
| H | 3.006206 | -1.518665 | 0.000000 |
| N | 0.965380 | -1.408175 | 0.000000 |

## 4.176



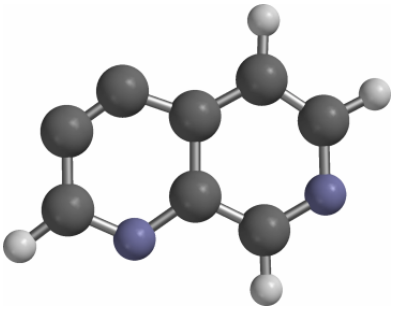
| | | | |
|---|---|---|---|
| N | -1.175124 | -1.412317 | 0.000000 |
| C | -2.310244 | -0.744550 | 0.000000 |
| H | -3.222503 | -1.340168 | 0.000000 |
| C | -2.402088 | 0.673410 | 0.000000 |
| H | -3.379014 | 1.147830 | 0.000000 |
| C | -1.247427 | 1.418035 | 0.000000 |
| H | -1.274463 | 2.505071 | 0.000000 |
| C | 0.000989 | 0.742794 | 0.000000 |
| C | -0.023480 | -0.682445 | 0.000000 |
| C | 1.268634 | 1.376671 | 0.000000 |
| H | 1.338537 | 2.461550 | 0.000000 |
| C | 1.225360 | -1.366736 | 0.000000 |
| H | 1.210763 | -2.455733 | 0.000000 |
| N | 2.395796 | -0.763815 | 0.000000 |
| C | 2.404044 | 0.598474 | 0.000000 |
| H | 3.389750 | 1.058630 | 0.000000 |

## 4.177



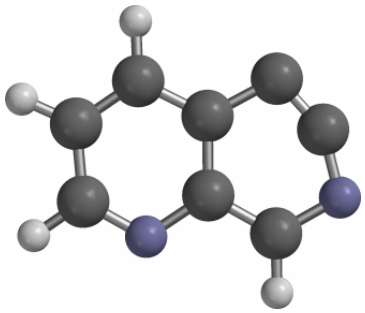
| | | | |
|---|---|---|---|
| N | 1.339261 | 1.434591 | 0.000000 |
| C | 0.117448 | 0.722607 | 0.000000 |
| C | 0.114503 | -0.711029 | 0.000000 |
| C | 1.365686 | -1.434724 | 0.000000 |
| H | 1.338453 | -2.525315 | 0.000000 |
| C | 2.201736 | 0.531017 | 0.000000 |
| C | 2.559712 | -0.707287 | 0.000000 |
| C | -1.109823 | 1.421606 | 0.000000 |
| H | -1.095363 | 2.509936 | 0.000000 |
| N | -2.280748 | 0.812127 | 0.000000 |
| C | -2.293911 | -0.544911 | 0.000000 |
| H | -3.280189 | -1.002868 | 0.000000 |
| C | -1.159155 | -1.329640 | 0.000000 |
| | -1.237216 | -2.413502 | 0.000000 |

## 4.178



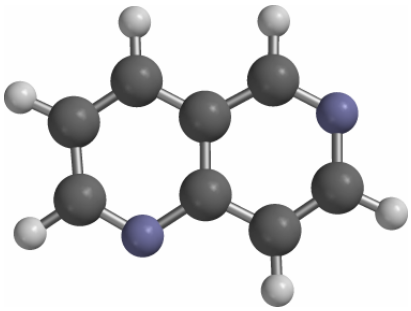
| | | | |
|---|---|---|---|
| N | 1.359917 | -1.221453 | 0.000000 |
| C | 2.495572 | -0.544438 | 0.000000 |
| H | 3.433860 | -1.089257 | 0.000000 |
| C | 2.345574 | 0.861235 | 0.000000 |
| C | 1.255019 | 1.466392 | 0.000000 |
| C | -0.009583 | 0.862474 | 0.000000 |
| C | 0.159898 | -0.589244 | 0.000000 |
| C | -1.318187 | 1.382769 | 0.000000 |
| H | -1.481875 | 2.455198 | 0.000000 |
| C | -2.378802 | 0.500092 | 0.000000 |
| H | -3.400673 | 0.872531 | 0.000000 |
| N | -2.250990 | -0.851694 | 0.000000 |
| C | -1.035981 | -1.362409 | 0.000000 |
| H | -0.943483 | -2.446675 | 0.000000 |

## 4.179



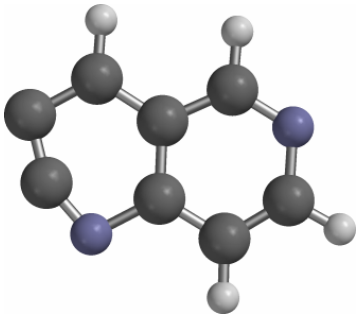
| | | | |
|---|---|---|---|
| N | -1.008693 | -1.391635 | 0.000000 |
| C | -2.173070 | -0.776085 | 0.000000 |
| H | -3.055505 | -1.414734 | 0.000000 |
| C | -2.333533 | 0.634640 | 0.000000 |
| H | -3.334112 | 1.057552 | 0.000000 |
| C | -1.220098 | 1.442620 | 0.000000 |
| H | -1.293081 | 2.525718 | 0.000000 |
| C | 0.062907 | 0.838485 | 0.000000 |
| C | 0.110568 | -0.611355 | 0.000000 |
| C | 1.322258 | 1.551503 | 0.000000 |
| C | 2.197871 | 0.640632 | 0.000000 |
| N | 2.538707 | -0.597680 | 0.000000 |
| C | 1.375810 | -1.282466 | 0.000000 |
| H | 1.419286 | -2.366741 | 0.000000 |

## 4.180



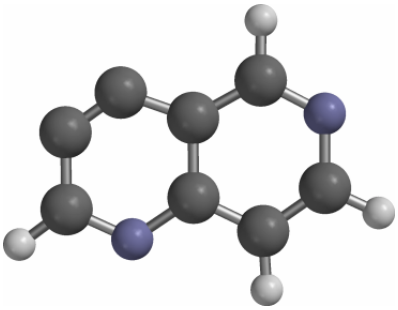
| | | | |
|---|---|---|---|
| N | -1.171314 | -1.446884 | 0.000000 |
| C | -2.306763 | -0.776897 | 0.000000 |
| H | -3.216767 | -1.376704 | 0.000000 |
| C | -2.410319 | 0.639398 | 0.000000 |
| H | -3.389701 | 1.107932 | 0.000000 |
| C | -1.255658 | 1.384987 | 0.000000 |
| H | -1.281894 | 2.472367 | 0.000000 |
| C | -0.010139 | 0.710558 | 0.000000 |
| C | -0.017733 | -0.716075 | 0.000000 |
| C | 1.237192 | -1.374213 | 0.000000 |
| H | 1.263061 | -2.458998 | 0.000000 |
| C | 2.387727 | -0.618649 | 0.000000 |
| H | 3.363965 | -1.098290 | 0.000000 |
| N | 2.409610 | 0.744349 | 0.000000 |
| C | 1.250170 | 1.368037 | 0.000000 |
| H | 1.278605 | 2.458976 | 0.000000 |

## 4.181



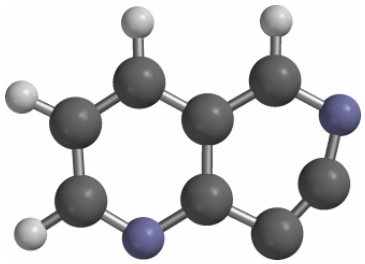
| | | | |
|---|---|---|---|
| N | 1.336936 | -1.463848 | 0.000000 |
| C | 0.117373 | -0.750891 | 0.000000 |
| C | 0.132589 | 0.684685 | 0.000000 |
| C | 1.382621 | 1.400501 | 0.000000 |
| H | 1.361667 | 2.491415 | 0.000000 |
| C | 2.576400 | 0.667756 | 0.000000 |
| C | 2.206974 | -0.564489 | 0.000000 |
| C | -1.134321 | 1.327858 | 0.000000 |
| H | -1.172095 | 2.417467 | 0.000000 |
| N | -2.292382 | 0.696347 | 0.000000 |
| C | -2.270049 | -0.660929 | 0.000000 |
| H | -3.243992 | -1.144963 | 0.000000 |
| C | -1.117544 | -1.422550 | 0.000000 |
| H | -1.144709 | -2.506749 | 0.000000 |

## 4.182



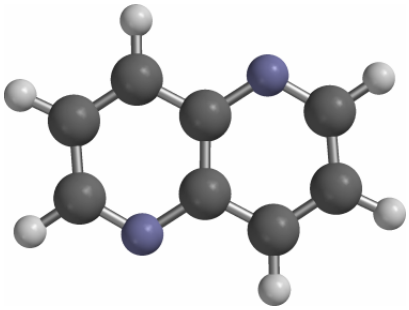
| | | | |
|---|---|---|---|
| N | 1.352727 | -1.257358 | 0.000000 |
| C | 2.488181 | -0.577518 | 0.000000 |
| H | 3.425158 | -1.125372 | 0.000000 |
| C | 2.346559 | 0.826625 | 0.000000 |
| C | 1.258359 | 1.436726 | 0.000000 |
| C | -0.003500 | 0.830403 | 0.000000 |
| C | 0.150323 | -0.623935 | 0.000000 |
| C | -1.308058 | 1.374364 | 0.000000 |
| H | -1.432670 | 2.455927 | 0.000000 |
| N | -2.404292 | 0.639628 | 0.000000 |
| C | -2.261969 | -0.711315 | 0.000000 |
| H | -3.191493 | -1.276147 | 0.000000 |
| C | -1.052036 | -1.372940 | 0.000000 |
| H | -0.999305 | -2.456316 | 0.000000 |

## 4.183



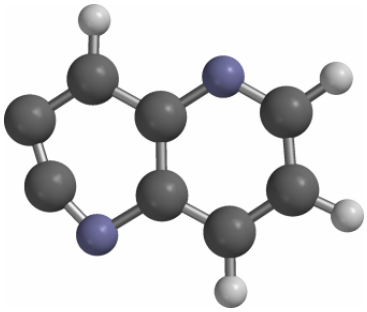
| | | | |
|---|---|---|---|
| N | 1.170209 | -1.473559 | 0.000000 |
| C | -0.023223 | -0.830701 | 0.000000 |
| C | -0.117177 | 0.625558 | 0.000000 |
| C | 1.094334 | 1.362419 | 0.000000 |
| H | 1.067720 | 2.449708 | 0.000000 |
| C | 2.288064 | 0.681068 | 0.000000 |
| H | 3.238671 | 1.205215 | 0.000000 |
| C | 2.265419 | -0.736256 | 0.000000 |
| H | 3.208275 | -1.282916 | 0.000000 |
| C | -1.390478 | 1.269830 | 0.000000 |
| H | -1.469945 | 2.354191 | 0.000000 |
| N | -2.551379 | 0.579136 | 0.000000 |
| C | -2.194239 | -0.661915 | 0.000000 |
| C | -1.282596 | -1.527698 | 0.000000 |

## 4.184



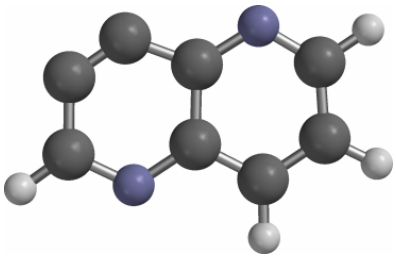
| | | | |
|---|---|---|---|
| N | -1.183714 | -1.425847 | 0.000000 |
| C | -2.309995 | -0.740590 | 0.000000 |
| H | -3.229130 | -1.325859 | 0.000000 |
| C | -2.385144 | 0.676573 | 0.000000 |
| H | -3.355940 | 1.163540 | 0.000000 |
| C | -1.219162 | 1.404807 | 0.000000 |
| H | -1.206125 | 2.490659 | 0.000000 |
| C | 0.019659 | 0.714465 | 0.000000 |
| C | -0.019659 | -0.714465 | 0.000000 |
| N | 1.183714 | 1.425847 | 0.000000 |
| C | 2.309995 | 0.740590 | 0.000000 |
| H | 3.229130 | 1.325859 | 0.000000 |
| C | 2.385144 | -0.676573 | 0.000000 |
| H | 3.355940 | -1.163540 | 0.000000 |
| C | 1.219162 | -1.404807 | 0.000000 |
| H | 1.206125 | -2.490659 | 0.000000 |

## 4.185



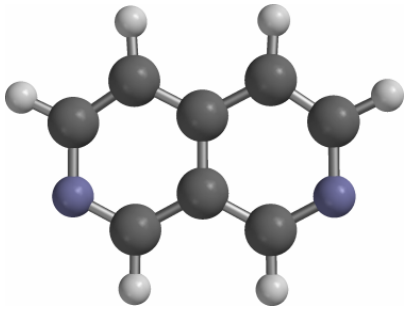
| | | | |
|---|---|---|---|
| C | 2.201548 | -0.532924 | 0.000000 |
| C | 2.549619 | 0.704375 | 0.000000 |
| C | 1.347602 | 1.421882 | 0.000000 |
| H | 1.286634 | 2.509498 | 0.000000 |
| C | 0.104962 | 0.685789 | 0.000000 |
| C | 0.123538 | -0.755558 | 0.000000 |
| N | 1.349078 | -1.451484 | 0.000000 |
| N | -1.065300 | 1.379854 | 0.000000 |
| C | -2.192264 | 0.691896 | 0.000000 |
| H | -3.111326 | 1.276359 | 0.000000 |
| C | -2.265344 | -0.721836 | 0.000000 |
| H | -3.234067 | -1.212154 | 0.000000 |
| C | -1.098150 | -1.455020 | 0.000000 |
| H | -1.087522 | -2.540478 | 0.000000 |

## 4.186



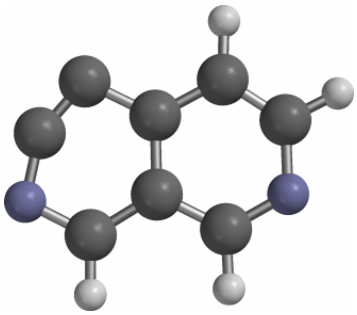
| | | | |
|---|---|---|---|
| C | 2.315177 | 0.648367 | 0.000000 |
| H | 3.280815 | 1.151720 | 0.000000 |
| C | 2.261448 | -0.764080 | 0.000000 |
| H | 3.183604 | -1.337287 | 0.000000 |
| C | 1.035665 | -1.391907 | 0.000000 |
| H | 0.941848 | -2.473065 | 0.000000 |
| C | -0.147979 | -0.612430 | 0.000000 |
| C | 0.041168 | 0.846229 | 0.000000 |
| N | 1.250912 | 1.432921 | 0.000000 |
| N | -1.355781 | -1.233148 | 0.000000 |
| C | -2.482086 | -0.539625 | 0.000000 |
| H | -3.426552 | -1.073884 | 0.000000 |
| C | -2.315998 | 0.861270 | 0.000000 |
| C | -1.222946 | 1.463237 | 0.000000 |

## 4.187



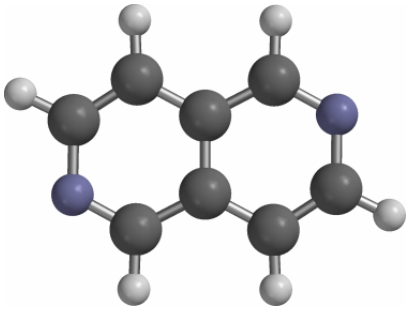
| | | | |
|---|---|---|---|
| C | 1.251535 | 0.000000 | 1.354816 |
| H | 1.270763 | 0.000000 | 2.445554 |
| N | 2.416952 | 0.000000 | 0.741446 |
| C | 2.404200 | 0.000000 | -0.621829 |
| H | 3.384291 | 0.000000 | -1.093889 |
| C | 1.260950 | 0.000000 | -1.388819 |
| H | 1.320878 | 0.000000 | -2.473699 |
| C | 0.000000 | 0.000000 | -0.740290 |
| C | 0.000000 | 0.000000 | 0.683241 |
| C | -1.251535 | 0.000000 | 1.354816 |
| H | -1.270763 | 0.000000 | 2.445554 |
| N | -2.416952 | 0.000000 | 0.741446 |
| C | -2.404200 | 0.000000 | -0.621829 |
| H | -3.384291 | 0.000000 | -1.093889 |
| C | -1.260950 | 0.000000 | -1.388819 |
| H | -1.320878 | 0.000000 | -2.473699 |

## 4.188



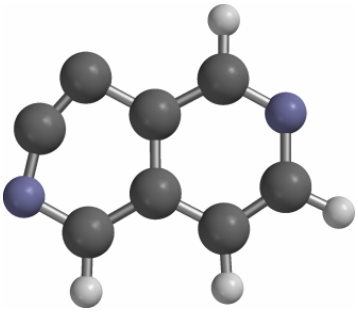
| | | | |
|---|---|---|---|
| C | 1.086644 | -1.342577 | 0.000000 |
| H | 1.058379 | -2.432924 | 0.000000 |
| N | 2.278091 | -0.784126 | 0.000000 |
| C | 2.335033 | 0.576785 | 0.000000 |
| H | 3.338580 | 0.996847 | 0.000000 |
| C | 1.234938 | 1.408044 | 0.000000 |
| H | 1.343827 | 2.487248 | 0.000000 |
| C | -0.057792 | 0.834470 | 0.000000 |
| C | -0.135287 | -0.613439 | 0.000000 |
| C | -1.401921 | -1.266921 | 0.000000 |
| H | -1.485033 | -2.350510 | 0.000000 |
| N | -2.558700 | -0.567760 | 0.000000 |
| C | -2.203973 | 0.668314 | 0.000000 |
| C | -1.311068 | 1.559767 | 0.000000 |

## 4.189



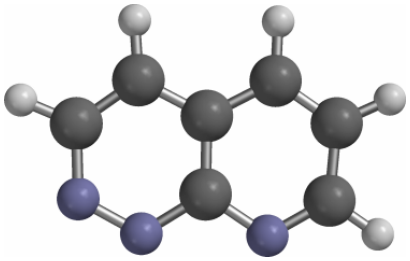
| | | | |
|---|---|---|---|
| C | 1.248628 | -1.381357 | 0.000000 |
| H | 1.270291 | -2.471874 | 0.000000 |
| N | 2.411206 | -0.764291 | 0.000000 |
| C | 2.408706 | 0.598805 | 0.000000 |
| H | 3.390597 | 1.066165 | 0.000000 |
| C | 1.264399 | 1.363379 | 0.000000 |
| H | 1.319952 | 2.448765 | 0.000000 |
| C | 0.007366 | 0.711146 | 0.000000 |
| C | -0.007366 | -0.711146 | 0.000000 |
| C | -1.248628 | 1.381357 | 0.000000 |
| H | -1.270291 | 2.471874 | 0.000000 |
| N | -2.411206 | 0.764291 | 0.000000 |
| C | -2.408706 | -0.598805 | 0.000000 |
| H | -3.390597 | -1.066165 | 0.000000 |
| C | -1.264399 | -1.363379 | 0.000000 |
| H | -1.319952 | -2.448765 | 0.000000 |

## 4.190



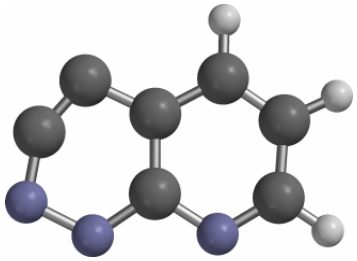
| | | | |
|---|---|---|---|
| C | 1.392920 | 1.298124 | 0.000000 |
| H | 1.480944 | 2.380967 | 0.000000 |
| N | 2.543613 | 0.590181 | 0.000000 |
| C | 2.195263 | -0.643414 | 0.000000 |
| C | 1.306722 | -1.544297 | 0.000000 |
| C | 0.062526 | -0.801974 | 0.000000 |
| C | 0.122766 | 0.644159 | 0.000000 |
| C | -1.106919 | 1.351918 | 0.000000 |
| H | -1.117712 | 2.438714 | 0.000000 |
| C | -2.284563 | 0.640064 | 0.000000 |
| H | -3.241768 | 1.156121 | 0.000000 |
| N | -2.354375 | -0.719542 | 0.000000 |
| C | -1.228248 | -1.402142 | 0.000000 |
| H | -1.294360 | -2.488845 | 0.000000 |

## 4.191



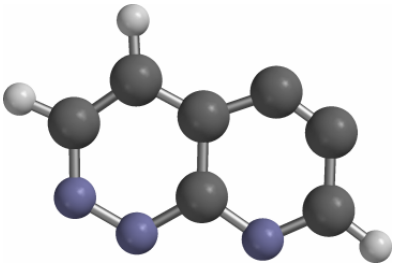
| | | | |
|---|---|---|---|
| C | -0.024519 | -0.672748 | 0.000000 |
| N | -1.203003 | -1.367333 | 0.000000 |
| N | -2.336803 | -0.721664 | 0.000000 |
| C | -2.354504 | 0.641549 | 0.000000 |
| H | -3.349288 | 1.076989 | 0.000000 |
| C | -1.219570 | 1.418875 | 0.000000 |
| H | -1.273495 | 2.505011 | 0.000000 |
| C | 0.021184 | 0.752292 | 0.000000 |
| C | 1.293780 | 1.382753 | 0.000000 |
| H | 1.359099 | 2.468239 | 0.000000 |
| C | 2.414053 | 0.592276 | 0.000000 |
| H | 3.411374 | 1.021606 | 0.000000 |
| C | 2.255856 | -0.823313 | 0.000000 |
| H | 3.142954 | -1.456141 | 0.000000 |
| N | 1.098506 | -1.445395 | 0.000000 |

## 4.192



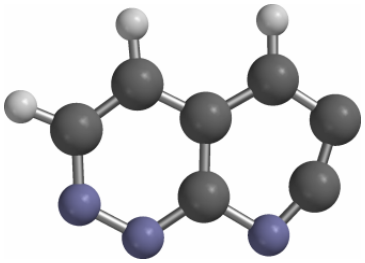
| | | | |
|---|---|---|---|
| N | 2.486148 | 0.674446 | 0.000000 |
| N | 1.301175 | 1.331486 | 0.000000 |
| C | 2.204103 | -0.586833 | 0.000000 |
| C | 1.326699 | -1.497657 | 0.000000 |
| C | 0.063375 | -0.838125 | 0.000000 |
| C | -1.220330 | -1.443621 | 0.000000 |
| H | -1.295138 | -2.526422 | 0.000000 |
| C | 0.133740 | 0.619276 | 0.000000 |
| C | -2.324820 | -0.630018 | 0.000000 |
| H | -3.329657 | -1.041909 | 0.000000 |
| N | -0.987812 | 1.398836 | 0.000000 |
| C | -2.147974 | 0.784063 | 0.000000 |
| H | -3.028003 | 1.426459 | 0.000000 |

## 4.193



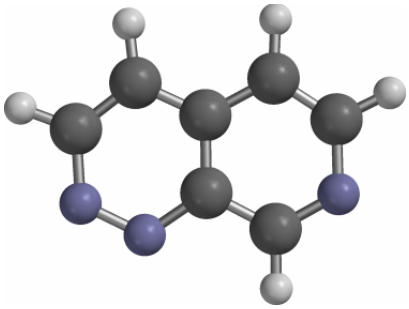
| | | | |
|---|---|---|---|
| N | 2.161543 | 0.902226 | 0.000000 |
| N | 0.956668 | 1.403049 | 0.000000 |
| C | 2.353641 | -0.442378 | 0.000000 |
| H | 3.395681 | -0.747926 | 0.000000 |
| C | 1.329566 | -1.366535 | 0.000000 |
| H | 1.523809 | -2.434012 | 0.000000 |
| C | 0.020899 | -0.868750 | 0.000000 |
| C | -0.136641 | 0.585932 | 0.000000 |
| N | -1.344828 | 1.211913 | 0.000000 |
| C | -2.470654 | 0.531983 | 0.000000 |
| H | -3.411266 | 1.073583 | 0.000000 |
| C | -1.238198 | -1.481241 | 0.000000 |
| C | -2.331890 | -0.882233 | 0.000000 |

## 4.194



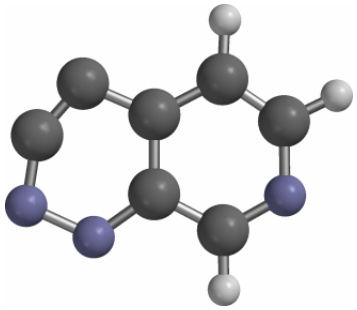
| | | | |
|---|---|---|---|
| N | 2.212354 | 0.873751 | 0.000000 |
| N | 1.043145 | 1.473533 | 0.000000 |
| C | 2.283430 | -0.479614 | 0.000000 |
| H | 3.294781 | -0.875015 | 0.000000 |
| C | 1.180703 | -1.311977 | 0.000000 |
| H | 1.290689 | -2.393319 | 0.000000 |
| C | -0.091876 | -0.715908 | 0.000000 |
| C | -1.345008 | -1.435957 | 0.000000 |
| H | -1.318827 | -2.526832 | 0.000000 |
| C | -0.074364 | 0.722690 | 0.000000 |
| C | -2.539065 | -0.709523 | 0.000000 |
| N | -1.300775 | 1.426121 | 0.000000 |
| C | -2.160509 | 0.527176 | 0.000000 |

## 4.195



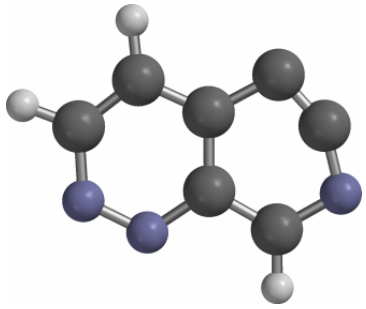
| | | | |
|---|---|---|---|
| C | -0.034555 | -0.660050 | 0.000000 |
| N | -1.188349 | -1.387747 | 0.000000 |
| N | -2.339388 | -0.772589 | 0.000000 |
| C | -2.376351 | 0.592813 | 0.000000 |
| H | -3.379661 | 1.008653 | 0.000000 |
| C | -1.260783 | 1.398736 | 0.000000 |
| H | -1.344642 | 2.482359 | 0.000000 |
| C | -0.002809 | 0.760317 | 0.000000 |
| C | 1.268111 | 1.388631 | 0.000000 |
| H | 1.347766 | 2.472291 | 0.000000 |
| C | 2.392472 | 0.597107 | 0.000000 |
| H | 3.382734 | 1.046798 | 0.000000 |
| N | 2.376083 | -0.769228 | 0.000000 |
| C | 1.204485 | -1.364399 | 0.000000 |
| H | 1.177825 | -2.452758 | 0.000000 |

## 4.196



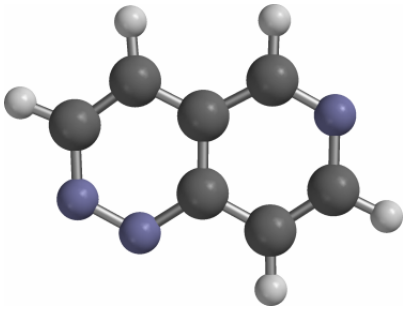
| | | | |
|---|---|---|---|
| N | 2.506239 | 0.651682 | 0.000000 |
| N | 1.317201 | 1.306824 | 0.000000 |
| C | 2.221128 | -0.614443 | 0.000000 |
| C | 1.323966 | -1.501649 | 0.000000 |
| C | 0.055520 | -0.849445 | 0.000000 |
| C | 0.158798 | 0.600700 | 0.000000 |
| C | -1.240482 | -1.415520 | 0.000000 |
| H | -1.363717 | -2.493101 | 0.000000 |
| C | -2.325775 | -0.568471 | 0.000000 |
| H | -3.335526 | -0.972062 | 0.000000 |
| C | -1.061241 | 1.351000 | 0.000000 |
| H | -1.002451 | 2.437447 | 0.000000 |
| N | -2.249381 | 0.795366 | 0.000000 |

## 4.197



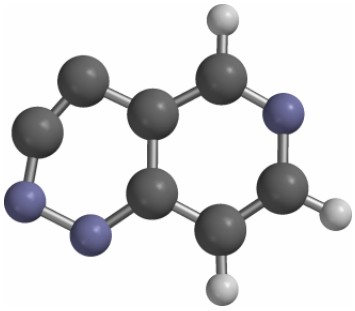
| | | | |
|---|---|---|---|
| N | -0.996713 | -1.384415 | 0.000000 |
| N | -2.180779 | -0.838646 | 0.000000 |
| C | -2.303449 | 0.520511 | 0.000000 |
| H | -3.331609 | 0.871119 | 0.000000 |
| C | -1.244149 | 1.402677 | 0.000000 |
| H | -1.391256 | 2.477864 | 0.000000 |
| C | 0.053305 | 0.855062 | 0.000000 |
| C | 0.113426 | -0.589149 | 0.000000 |
| C | 1.380322 | -1.261232 | 0.000000 |
| H | 1.428495 | -2.345298 | 0.000000 |
| C | 1.307959 | 1.577803 | 0.000000 |
| C | 2.187194 | 0.672322 | 0.000000 |
| N | 2.533650 | -0.567812 | 0.000000 |

## 4.198



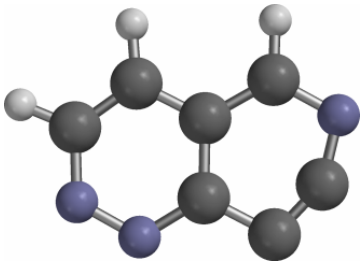
| | | | |
|---|---|---|---|
| C | -0.019789 | -0.691909 | 0.000000 |
| N | -1.169496 | -1.435825 | 0.000000 |
| N | -2.325329 | -0.830735 | 0.000000 |
| C | -2.390879 | 0.532264 | 0.000000 |
| H | -3.401335 | 0.929825 | 0.000000 |
| C | -1.284902 | 1.352673 | 0.000000 |
| H | -1.379808 | 2.435683 | 0.000000 |
| C | -0.023381 | 0.729108 | 0.000000 |
| C | 1.235296 | 1.396790 | 0.000000 |
| H | 1.261159 | 2.487232 | 0.000000 |
| C | 1.232854 | -1.355812 | 0.000000 |
| H | 1.257027 | -2.440506 | 0.000000 |
| N | 2.390484 | 0.770842 | 0.000000 |
| C | 2.378261 | -0.595825 | 0.000000 |
| H | 3.358080 | -1.066666 | 0.000000 |

## 4.199



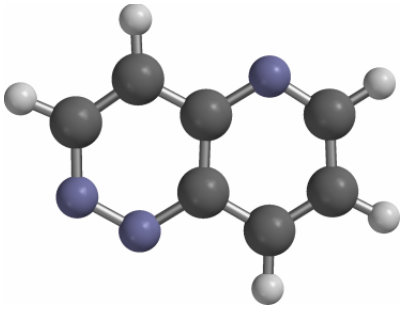
| | | | |
|---|---|---|---|
| N | 2.495582 | 0.672495 | 0.000000 |
| N | 1.312485 | 1.344372 | 0.000000 |
| C | 2.210597 | -0.584601 | 0.000000 |
| C | 1.323921 | -1.489449 | 0.000000 |
| C | 0.066455 | -0.816034 | 0.000000 |
| C | 0.149985 | 0.634237 | 0.000000 |
| C | -1.228790 | -1.409484 | 0.000000 |
| H | -1.308559 | -2.495291 | 0.000000 |
| C | -1.074512 | 1.358703 | 0.000000 |
| H | -1.054277 | 2.443098 | 0.000000 |
| C | -2.252936 | 0.653192 | 0.000000 |
| H | -3.205689 | 1.176647 | 0.000000 |
| N | -2.340997 | -0.710355 | 0.000000 |

## 4.200



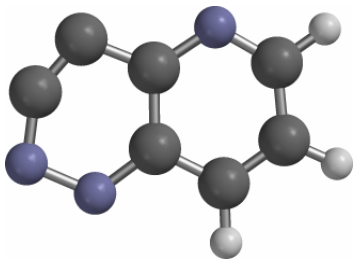
| | | | |
|---|---|---|---|
| N | 2.295003 | 0.776205 | 0.000000 |
| N | 1.180611 | 1.460557 | 0.000000 |
| C | 2.276251 | -0.585658 | 0.000000 |
| H | 3.259957 | -1.045381 | 0.000000 |
| C | 1.124240 | -1.339602 | 0.000000 |
| H | 1.160652 | -2.426287 | 0.000000 |
| C | -0.101228 | -0.645307 | 0.000000 |
| C | -0.014860 | 0.803190 | 0.000000 |
| C | -1.264120 | 1.520707 | 0.000000 |
| C | -2.170585 | 0.647943 | 0.000000 |
| C | -1.376379 | -1.295069 | 0.000000 |
| H | -1.460378 | -2.378810 | 0.000000 |
| N | -2.525818 | -0.592623 | 0.000000 |

## 4.201



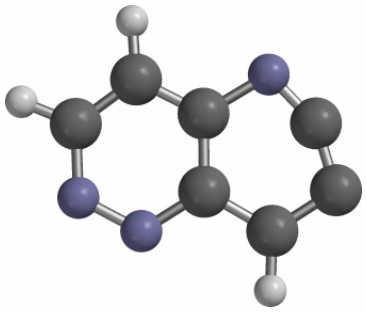
| | | | |
|---|---|---|---|
| C | -0.016404 | -0.694773 | 0.000000 |
| N | -1.170384 | -1.425694 | 0.000000 |
| N | -2.323251 | -0.812390 | 0.000000 |
| C | -2.368361 | 0.550722 | 0.000000 |
| H | -3.373494 | 0.962339 | 0.000000 |
| C | -1.254682 | 1.361211 | 0.000000 |
| H | -1.319054 | 2.444843 | 0.000000 |
| C | 0.003722 | 0.729107 | 0.000000 |
| C | 1.224844 | -1.383640 | 0.000000 |
| H | 1.217023 | -2.469431 | 0.000000 |
| C | 2.379690 | -0.642447 | 0.000000 |
| H | 3.357436 | -1.114483 | 0.000000 |
| N | 1.158724 | 1.457894 | 0.000000 |
| C | 2.287147 | 0.778301 | 0.000000 |
| H | 3.202210 | 1.369767 | 0.000000 |

## 4.202



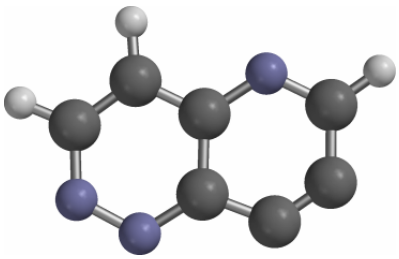
| | | | |
|---|---|---|---|
| N | 2.496477 | 0.645761 | 0.000000 |
| N | 1.312844 | 1.305287 | 0.000000 |
| C | 2.204561 | -0.623668 | 0.000000 |
| C | 1.286648 | -1.486662 | 0.000000 |
| C | 0.019176 | -0.844602 | 0.000000 |
| C | 0.143446 | 0.615023 | 0.000000 |
| N | -1.177959 | -1.473343 | 0.000000 |
| C | -2.259126 | -0.719221 | 0.000000 |
| H | -3.211418 | -1.248319 | 0.000000 |
| C | -2.257261 | 0.703297 | 0.000000 |
| H | -3.201931 | 1.238126 | 0.000000 |
| C | -1.061522 | 1.374147 | 0.000000 |
| H | -0.998090 | 2.457477 | 0.000000 |

## 4.203



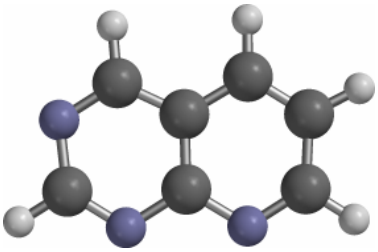
| | | | |
|---|---|---|---|
| N | 2.204295 | 0.751924 | 0.000000 |
| N | 1.053457 | 1.375117 | 0.000000 |
| C | 2.241861 | -0.606172 | 0.000000 |
| H | 3.243158 | -1.026795 | 0.000000 |
| C | 1.123405 | -1.417985 | 0.000000 |
| H | 1.186753 | -2.501141 | 0.000000 |
| C | -0.115902 | -0.771743 | 0.000000 |
| C | -0.109707 | 0.665174 | 0.000000 |
| N | -1.333151 | -1.485203 | 0.000000 |
| C | -2.192130 | -0.571120 | 0.000000 |
| C | -2.539909 | 0.666021 | 0.000000 |
| C | -1.353926 | 1.402302 | 0.000000 |
| H | -1.300528 | 2.489860 | 0.000000 |

## 4.204



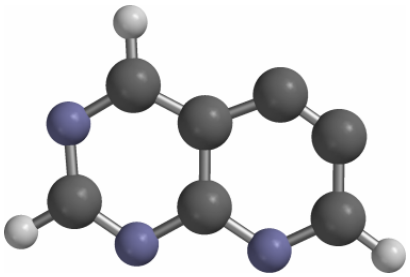
| | | | |
|---|---|---|---|
| N | 2.347546 | 0.683387 | 0.000000 |
| N | 1.258874 | 1.414255 | 0.000000 |
| C | 0.049692 | 0.818158 | 0.000000 |
| C | -0.135170 | -0.634536 | 0.000000 |
| C | 1.062930 | -1.371591 | 0.000000 |
| H | 1.033438 | -2.456247 | 0.000000 |
| C | 2.252516 | -0.670878 | 0.000000 |
| H | 3.209187 | -1.184939 | 0.000000 |
| N | -1.342320 | -1.259506 | 0.000000 |
| C | -2.464461 | -0.561298 | 0.000000 |
| H | -3.410383 | -1.093270 | 0.000000 |
| C | -2.300187 | 0.842812 | 0.000000 |
| C | -1.209316 | 1.445610 | 0.000000 |

## 4.205



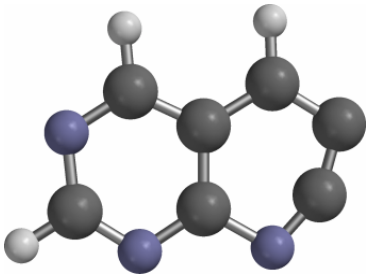
| | | | |
|---|---|---|---|
| C | -0.017092 | -0.712585 | 0.000000 |
| N | -1.197838 | -1.389985 | 0.000000 |
| C | 0.001694 | 0.713949 | 0.000000 |
| C | -2.292773 | -0.661773 | 0.000000 |
| H | -3.239022 | -1.199455 | 0.000000 |
| C | 1.250465 | 1.380447 | 0.000000 |
| H | 1.286304 | 2.467615 | 0.000000 |
| C | -1.260598 | 1.358996 | 0.000000 |
| H | -1.314421 | 2.449164 | 0.000000 |
| N | -2.399020 | 0.698800 | 0.000000 |
| N | 1.124088 | -1.453751 | 0.000000 |
| C | 2.266644 | -0.795785 | 0.000000 |
| H | 3.168738 | -1.407566 | 0.000000 |
| C | 2.394103 | 0.619371 | 0.000000 |
| H | 3.380586 | 1.072362 | 0.000000 |

## 4.206



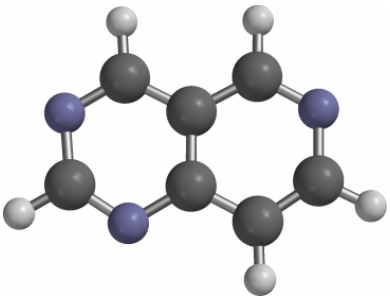
| | | | |
|---|---|---|---|
| C | 2.163743 | 0.745703 | 0.000000 |
| H | 3.056926 | 1.367009 | 0.000000 |
| N | 2.388204 | -0.594655 | 0.000000 |
| C | 1.315249 | -1.362554 | 0.000000 |
| H | 1.464841 | -2.441079 | 0.000000 |
| C | 0.008053 | -0.831614 | 0.000000 |
| C | -1.253530 | -1.433475 | 0.000000 |
| C | -2.333631 | -0.808817 | 0.000000 |
| C | -0.116528 | 0.625140 | 0.000000 |
| N | 1.009416 | 1.381276 | 0.000000 |
| N | -1.314606 | 1.269587 | 0.000000 |
| C | -2.452457 | 0.600975 | 0.000000 |
| H | -3.384863 | 1.157110 | 0.000000 |

## 4.207



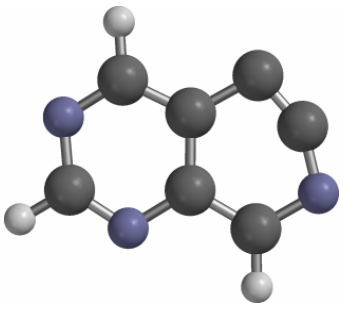
| | | | |
|---|---|---|---|
| C | 2.161203 | -0.593089 | 0.000000 |
| C | 2.562147 | 0.632208 | 0.000000 |
| C | 1.378074 | 1.383165 | 0.000000 |
| H | 1.376121 | 2.474401 | 0.000000 |
| C | 0.119734 | 0.687278 | 0.000000 |
| N | 1.276290 | -1.474161 | 0.000000 |
| C | 0.067562 | -0.750289 | 0.000000 |
| N | -1.084672 | -1.434743 | 0.000000 |
| C | -2.188186 | -0.704516 | 0.000000 |
| H | -3.130292 | -1.247803 | 0.000000 |
| N | -2.287055 | 0.647624 | 0.000000 |
| C | -1.148460 | 1.316868 | 0.000000 |
| H | -1.213797 | 2.405227 | 0.000000 |

## 4.208



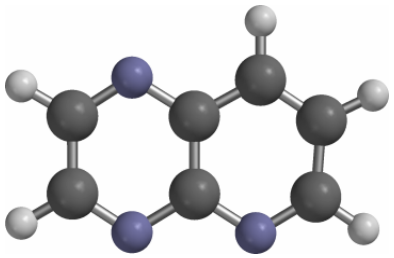
| | | | |
|---|---|---|---|
| C | -0.045606 | -0.719113 | 0.000000 |
| N | -1.237024 | -1.385815 | 0.000000 |
| C | 0.001391 | 0.701461 | 0.000000 |
| C | 1.187586 | -1.413930 | 0.000000 |
| H | 1.190055 | -2.498795 | 0.000000 |
| C | 2.353816 | -0.680583 | 0.000000 |
| H | 3.318626 | -1.182664 | 0.000000 |
| C | -2.317269 | -0.634608 | 0.000000 |
| H | -3.274228 | -1.152861 | 0.000000 |
| C | 1.269786 | 1.337826 | 0.000000 |
| H | 1.324738 | 2.427297 | 0.000000 |
| N | 2.412001 | 0.682437 | 0.000000 |
| C | -1.246590 | 1.371134 | 0.000000 |
| H | -1.284640 | 2.461585 | 0.000000 |
| N | -2.396275 | 0.728194 | 0.000000 |

## 4.209



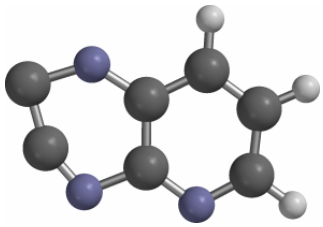
| | | | |
|---|---|---|---|
| N | 2.334215 | -0.670705 | 0.000000 |
| C | 2.177901 | 0.684366 | 0.000000 |
| H | 3.101096 | 1.259516 | 0.000000 |
| N | 1.053457 | 1.365555 | 0.000000 |
| C | 1.236291 | -1.396571 | 0.000000 |
| H | 1.336557 | -2.481122 | 0.000000 |
| C | -0.092334 | 0.626133 | 0.000000 |
| C | -0.062322 | -0.815897 | 0.000000 |
| C | -1.309599 | -1.550298 | 0.000000 |
| C | -2.175289 | -0.624176 | 0.000000 |
| N | -2.506667 | 0.612562 | 0.000000 |
| C | -1.350822 | 1.308740 | 0.000000 |
| H | -1.400269 | 2.392482 | 0.000000 |

## 4.210



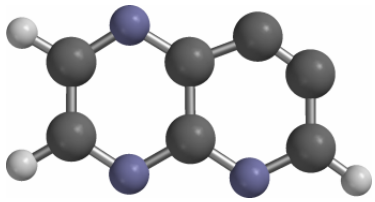
| | | | |
|---|---|---|---|
| C | -0.021495 | -0.716949 | 0.000000 |
| N | -1.184641 | -1.428949 | 0.000000 |
| C | -0.012986 | 0.713333 | 0.000000 |
| C | 1.222100 | -1.396537 | 0.000000 |
| H | 1.221279 | -2.482548 | 0.000000 |
| C | 2.375607 | -0.650280 | 0.000000 |
| H | 3.355078 | -1.119017 | 0.000000 |
| N | 1.137843 | 1.437390 | 0.000000 |
| C | 2.272602 | 0.766666 | 0.000000 |
| H | 3.182701 | 1.366021 | 0.000000 |
| N | -1.180922 | 1.415887 | 0.000000 |
| C | -2.286760 | 0.703834 | 0.000000 |
| H | -3.230504 | 1.248488 | 0.000000 |
| C | -2.292256 | -0.718971 | 0.000000 |
| H | -3.236263 | -1.261872 | 0.000000 |

## 4.211



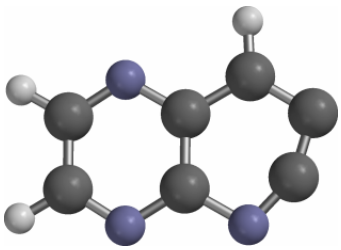
| | | | |
|---|---|---|---|
| C | 2.170855 | -0.527587 | 0.000000 |
| C | 2.645453 | 0.785236 | 0.000000 |
| N | 1.292574 | -1.382832 | 0.000000 |
| N | 1.343933 | 1.302188 | 0.000000 |
| C | 0.140835 | 0.659850 | 0.000000 |
| C | -1.080953 | 1.373006 | 0.000000 |
| H | -1.062521 | 2.457804 | 0.000000 |
| C | 0.034427 | -0.774946 | 0.000000 |
| N | -1.094518 | -1.475546 | 0.000000 |
| C | -2.215485 | -0.763258 | 0.000000 |
| H | -3.142843 | -1.332115 | 0.000000 |
| C | -2.257207 | 0.650291 | 0.000000 |
| H | -3.218827 | 1.153721 | 0.000000 |

## 4.212



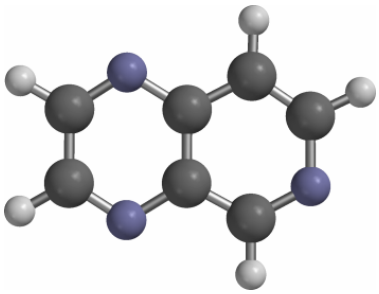
| | | | |
|---|---|---|---|
| C | 2.155625 | 0.806089 | 0.000000 |
| H | 3.037029 | 1.445615 | 0.000000 |
| C | 2.303102 | -0.602695 | 0.000000 |
| H | 3.294173 | -1.052523 | 0.000000 |
| N | 0.982187 | 1.406139 | 0.000000 |
| N | 1.266957 | -1.419361 | 0.000000 |
| C | 0.050567 | -0.845925 | 0.000000 |
| C | -1.207974 | -1.469397 | 0.000000 |
| C | -0.120453 | 0.616594 | 0.000000 |
| N | -1.330190 | 1.237726 | 0.000000 |
| C | -2.452284 | 0.546114 | 0.000000 |
| H | -3.397186 | 1.080163 | 0.000000 |
| C | -2.296995 | -0.860194 | 0.000000 |

## 4.213



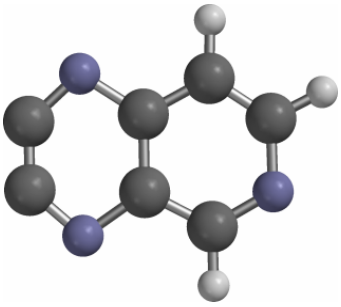
| | | | |
|---|---|---|---|
| C | 2.175521 | 0.773334 | 0.000000 |
| H | 3.109445 | 1.332475 | 0.000000 |
| C | 2.191217 | -0.643674 | 0.000000 |
| H | 3.138890 | -1.178978 | 0.000000 |
| N | 1.088175 | -1.367296 | 0.000000 |
| N | 1.055269 | 1.475130 | 0.000000 |
| C | -0.080220 | 0.759395 | 0.000000 |
| C | -0.087692 | -0.686024 | 0.000000 |
| N | -1.300791 | 1.456093 | 0.000000 |
| C | -1.332839 | -1.411603 | 0.000000 |
| H | -1.282850 | -2.499959 | 0.000000 |
| C | -2.531789 | -0.685885 | 0.000000 |
| C | -2.159074 | 0.547342 | 0.000000 |

## 4.214



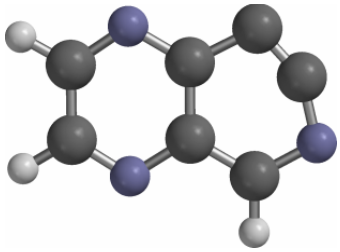
| | | | |
|---|---|---|---|
| C | -0.029290 | -0.729889 | 0.000000 |
| N | -1.193756 | -1.445635 | 0.000000 |
| C | -0.039366 | 0.693574 | 0.000000 |
| C | 1.227256 | -1.380587 | 0.000000 |
| H | 1.265455 | -2.465184 | 0.000000 |
| C | 2.367931 | -0.608480 | 0.000000 |
| H | 3.350030 | -1.075685 | 0.000000 |
| N | -1.201696 | 1.404907 | 0.000000 |
| C | -2.306751 | 0.691454 | 0.000000 |
| H | -3.253072 | 1.230127 | 0.000000 |
| C | -2.299778 | -0.733673 | 0.000000 |
| H | -3.243125 | -1.278434 | 0.000000 |
| C | 1.210692 | 1.372382 | 0.000000 |
| H | 1.206927 | 2.461555 | 0.000000 |
| N | 2.373376 | 0.754944 | 0.000000 |

## 4.215



| | | | |
|---|---|---|---|
| N | 1.329486 | 1.479770 | 0.000000 |
| C | 0.157648 | 0.705792 | 0.000000 |
| C | 0.146264 | -0.735339 | 0.000000 |
| N | 1.320199 | -1.516343 | 0.000000 |
| C | 2.293298 | -0.651336 | 0.000000 |
| C | 2.300133 | 0.610349 | 0.000000 |
| C | -1.093356 | 1.376907 | 0.000000 |
| H | -1.090188 | 2.465317 | 0.000000 |
| N | -2.255566 | 0.755830 | 0.000000 |
| C | -2.252367 | -0.601886 | 0.000000 |
| H | -3.232648 | -1.072344 | 0.000000 |
| C | -1.110371 | -1.376065 | 0.000000 |
| H | -1.151529 | -2.460194 | 0.000000 |

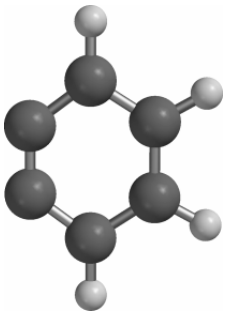
## 4.216



| | | | |
|---|---|---|---|
| C | 2.146228 | 0.818774 | 0.000000 |
| H | 3.036724 | 1.445220 | 0.000000 |
| C | 2.274599 | -0.599302 | 0.000000 |
| H | 3.266628 | -1.049871 | 0.000000 |
| N | 1.243354 | -1.417859 | 0.000000 |
| N | 0.979278 | 1.425126 | 0.000000 |
| C | 0.014640 | -0.835883 | 0.000000 |
| C | -0.114569 | 0.612094 | 0.000000 |
| C | -1.214866 | -1.579020 | 0.000000 |
| C | -2.144229 | -0.729829 | 0.000000 |
| N | -2.541638 | 0.498242 | 0.000000 |
| C | -1.407306 | 1.227228 | 0.000000 |
| H | -1.494904 | 2.309140 | 0.000000 |

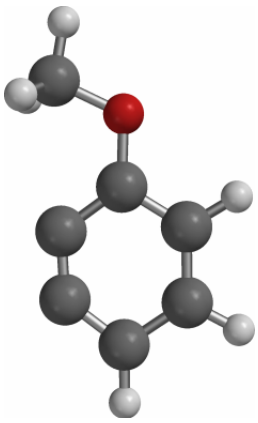
### 4.7.6.2 Structures Using MP2/6-311+G**

#### 4.3a*



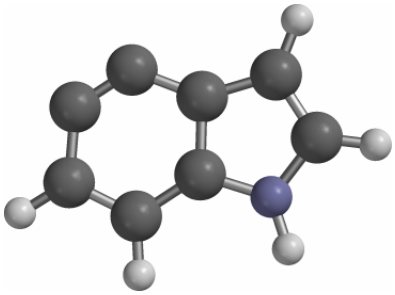
| | | | |
|---|---|---|---|
| C | 0.634257 | 0.000000 | 1.247993 |
| C | -0.706963 | 0.000000 | -1.056667 |
| C | -0.634257 | 0.000000 | 1.247993 |
| C | 1.468416 | 0.000000 | 0.131772 |
| C | 0.706963 | 0.000000 | -1.056667 |
| C | -1.468416 | 0.000000 | 0.131772 |
| H | 2.553435 | 0.000000 | 0.128042 |
| H | 1.231954 | 0.000000 | -2.009581 |
| H | -2.553435 | 0.000000 | 0.128042 |
| H | -1.231954 | 0.000000 | -2.009581 |

#### 4.5a*



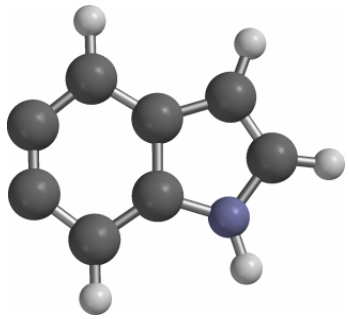
| | | | |
|---|---|---|---|
| H | -0.284472 | -2.258071 | 0.000000 |
| C | -0.553949 | -1.204844 | 0.000000 |
| C | -1.210450 | 1.350307 | 0.000000 |
| C | 0.496125 | -0.256918 | 0.000000 |
| C | -1.908005 | -0.821473 | 0.000000 |
| C | -2.329068 | 0.530242 | 0.000000 |
| C | 0.025548 | 1.060671 | 0.000000 |
| H | -2.668274 | -1.600470 | 0.000000 |
| H | -3.371352 | 0.825689 | 0.000000 |
| O | 1.779337 | -0.670397 | 0.000000 |
| C | 2.731075 | 0.392597 | 0.000000 |
| H | 2.611454 | 1.013247 | -0.893920 |
| H | 3.711280 | -0.082381 | 0.000000 |
| H | 2.611454 | 1.013247 | 0.893920 |

#### 4.7a*



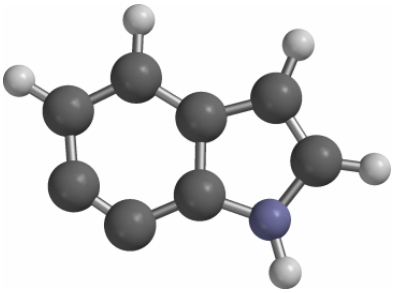
| | | | |
|---|---|---|---|
| C | -0.998970 | -1.468926 | 0.000000 |
| C | -1.120255 | 1.248397 | 0.000000 |
| C | 0.268216 | -0.870681 | 0.000000 |
| C | -2.109773 | -0.863235 | 0.000000 |
| C | -2.324986 | 0.529152 | 0.000000 |
| C | 0.122092 | 0.566976 | 0.000000 |
| H | -3.287581 | 1.029231 | 0.000000 |
| H | -1.147794 | 2.336334 | 0.000000 |
| C | 1.660019 | -1.167335 | 0.000000 |
| H | 2.126117 | -2.142306 | 0.000000 |
| C | 2.320116 | 0.049947 | 0.000000 |
| H | 3.380665 | 0.262865 | 0.000000 |
| N | 1.402640 | 1.076605 | 0.000000 |
| H | 1.639316 | 2.057774 | 0.000000 |

#### 4.8a*



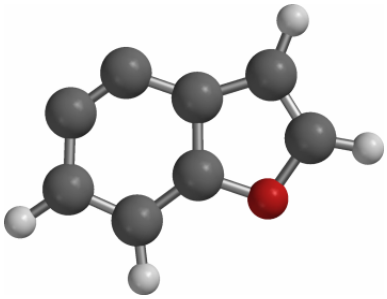
| | | | |
|---|---|---|---|
| H | -1.145698 | -2.575522 | 0.000000 |
| C | -1.109618 | -1.490287 | 0.000000 |
| C | -1.044877 | 1.494882 | 0.000000 |
| C | 0.113510 | -0.761398 | 0.000000 |
| C | -2.181159 | -0.610622 | 0.000000 |
| C | -2.150910 | 0.662040 | 0.000000 |
| C | 0.120641 | 0.686439 | 0.000000 |
| H | -1.023866 | 2.580917 | 0.000000 |
| C | 1.488321 | -1.177700 | 0.000000 |
| H | 1.861004 | -2.192830 | 0.000000 |
| C | 2.261782 | -0.037237 | 0.000000 |
| H | 3.338493 | 0.072829 | 0.000000 |
| N | 1.444741 | 1.075153 | 0.000000 |
| H | 1.767260 | 2.030818 | 0.000000 |

## 4.9a*



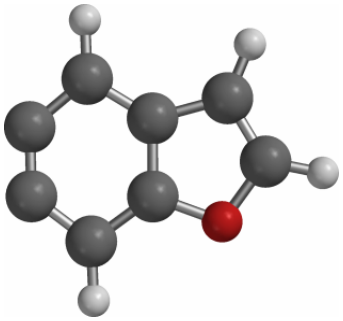
| | | | |
|---|---|---|---|
| H | -1.259010 | -2.337770 | 0.000000 |
| C | -1.170874 | -1.252946 | 0.000000 |
| C | -0.936654 | 1.478071 | 0.000000 |
| C | 0.119703 | -0.657609 | 0.000000 |
| C | -2.345025 | -0.482839 | 0.000000 |
| C | -2.060416 | 0.893559 | 0.000000 |
| C | 0.266972 | 0.776461 | 0.000000 |
| H | -3.330174 | -0.935510 | 0.000000 |
| C | 1.455039 | -1.182887 | 0.000000 |
| H | 1.747955 | -2.224326 | 0.000000 |
| C | 2.324805 | -0.110451 | 0.000000 |
| H | 3.405970 | -0.090142 | 0.000000 |
| N | 1.602751 | 1.069597 | 0.000000 |
| H | 1.994970 | 1.999443 | 0.000000 |

## 4.11a*



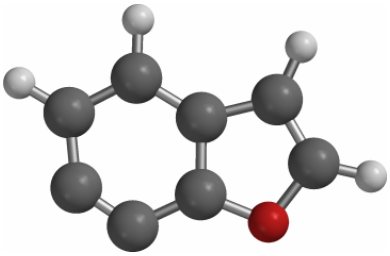
| | | | |
|---|---|---|---|
| H | -1.105081 | -2.329196 | 0.000000 |
| C | -1.102180 | -1.242791 | 0.000000 |
| C | -0.986213 | 1.481815 | 0.000000 |
| C | 0.124020 | -0.543814 | 0.000000 |
| C | -2.307284 | -0.523902 | 0.000000 |
| C | -2.093011 | 0.867931 | 0.000000 |
| C | 0.273740 | 0.873708 | 0.000000 |
| H | -3.270694 | -1.021870 | 0.000000 |
| C | 1.683219 | 1.126181 | 0.000000 |
| H | 2.196313 | 2.076868 | 0.000000 |
| C | 2.269651 | -0.111249 | 0.000000 |
| H | 3.303779 | -0.423737 | 0.000000 |
| O | 1.357223 | -1.128504 | 0.000000 |

## 4.12a*



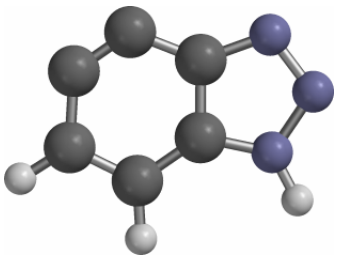
| | | | |
|---|---|---|---|
| H | -0.973159 | -2.574842 | 0.000000 |
| C | -1.018788 | -1.491162 | 0.000000 |
| C | -1.095411 | 1.500382 | 0.000000 |
| C | 0.123672 | -0.665019 | 0.000000 |
| C | -2.129972 | -0.660314 | 0.000000 |
| C | -2.163302 | 0.611447 | 0.000000 |
| C | 0.119769 | 0.768247 | 0.000000 |
| H | -1.138312 | 2.584851 | 0.000000 |
| C | 1.513766 | 1.140019 | 0.000000 |
| H | 1.936440 | 2.134983 | 0.000000 |
| C | 2.218679 | -0.027614 | 0.000000 |
| H | 3.278937 | -0.237315 | 0.000000 |
| O | 1.407893 | -1.131095 | 0.000000 |

## 4.13a*



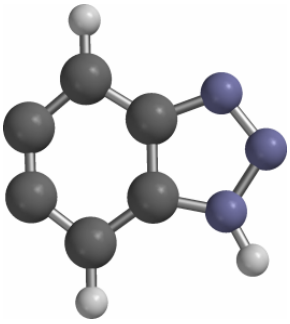
| | | | |
|---|---|---|---|
| C | -0.896820 | -1.478191 | 0.000000 |
| C | -1.151104 | 1.261912 | 0.000000 |
| C | 0.284049 | -0.751600 | 0.000000 |
| C | -2.020276 | -0.891836 | 0.000000 |
| C | -2.318711 | 0.478284 | 0.000000 |
| C | 0.136039 | 0.665227 | 0.000000 |
| H | -3.308171 | 0.921059 | 0.000000 |
| H | -1.245882 | 2.345631 | 0.000000 |
| C | 1.490409 | 1.159138 | 0.000000 |
| H | 1.826877 | 2.186818 | 0.000000 |
| C | 2.299501 | 0.058377 | 0.000000 |
| H | 3.372754 | -0.060738 | 0.000000 |
| O | 1.585734 | -1.115961 | 0.000000 |

## 4.31a*



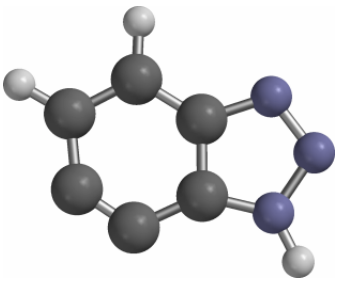
| | | | |
|---|---|---|---|
| C | -0.913376 | -1.477150 | 0.000000 |
| C | -1.093507 | 1.268670 | 0.000000 |
| C | 0.324504 | -0.823447 | 0.000000 |
| C | -2.027782 | -0.880182 | 0.000000 |
| C | -2.270439 | 0.510391 | 0.000000 |
| C | 0.158275 | 0.601221 | 0.000000 |
| H | -3.246350 | 0.983750 | 0.000000 |
| H | -1.150680 | 2.354092 | 0.000000 |
| N | 1.451273 | 1.027528 | 0.000000 |
| H | 1.823373 | 1.968253 | 0.000000 |
| N | 2.328951 | -0.003880 | 0.000000 |
| N | 1.648499 | -1.137545 | 0.000000 |

## 4.32a*



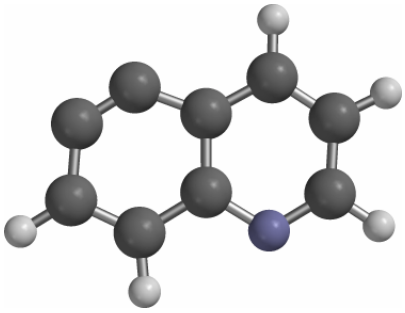
| | | | |
|---|---|---|---|
| H | -1.073464 | -2.576054 | 0.000000 |
| C | -1.064525 | -1.491452 | 0.000000 |
| C | -1.021734 | 1.518893 | 0.000000 |
| C | 0.137880 | -0.729426 | 0.000000 |
| C | -2.132250 | -0.612026 | 0.000000 |
| C | -2.106075 | 0.661376 | 0.000000 |
| C | 0.143244 | 0.707793 | 0.000000 |
| H | -1.019213 | 2.603821 | 0.000000 |
| N | 1.479171 | 0.989407 | 0.000000 |
| H | 1.949035 | 1.884334 | 0.000000 |
| N | 2.237014 | -0.135338 | 0.000000 |
| N | 1.437344 | -1.177655 | 0.000000 |

## 4.33a*



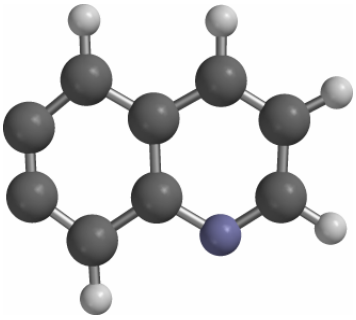
| | | | |
|---|---|---|---|
| H | -1.201197 | -2.336667 | 0.000000 |
| C | -1.135608 | -1.252019 | 0.000000 |
| C | -0.901296 | 1.502667 | 0.000000 |
| C | 0.144137 | -0.630327 | 0.000000 |
| C | -2.299537 | -0.477030 | 0.000000 |
| C | -2.016859 | 0.905361 | 0.000000 |
| C | 0.296359 | 0.791082 | 0.000000 |
| H | -3.287641 | -0.922675 | 0.000000 |
| N | 1.638947 | 0.968889 | 0.000000 |
| H | 2.181486 | 1.822447 | 0.000000 |
| N | 2.291255 | -0.225323 | 0.000000 |
| N | 1.395507 | -1.191910 | 0.000000 |

## 4.83a*



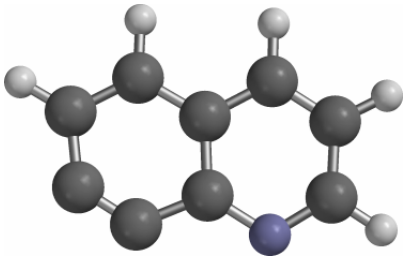
| | | | |
|---|---|---|---|
| H | 3.421433 | -0.957880 | 0.000000 |
| C | 2.406995 | -0.569440 | 0.000000 |
| H | 1.436229 | -2.503503 | 0.000000 |
| C | 1.317640 | -1.423601 | 0.000000 |
| N | 0.994543 | 1.407233 | 0.000000 |
| C | 0.027077 | -0.855059 | 0.000000 |
| C | 2.191393 | 0.828622 | 0.000000 |
| C | -0.103163 | 0.595836 | 0.000000 |
| C | -1.245972 | -1.453111 | 0.000000 |
| H | 3.044536 | 1.505292 | 0.000000 |
| H | -1.395189 | 2.319465 | 0.000000 |
| C | -2.365266 | -0.868662 | 0.000000 |
| C | -2.591561 | 0.526041 | 0.000000 |
| H | -3.559658 | 1.015866 | 0.000000 |
| C | -1.392749 | 1.232205 | 0.000000 |

## 4.84a*



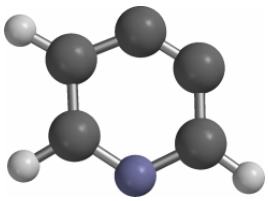
| | | | |
|---|---|---|---|
| H | 3.271940 | -1.131364 | 0.000000 |
| C | 2.296301 | -0.653846 | 0.000000 |
| H | 1.171091 | -2.487769 | 0.000000 |
| C | 1.138790 | -1.400146 | 0.000000 |
| N | 1.063535 | 1.436021 | 0.000000 |
| C | -0.122730 | -0.739851 | 0.000000 |
| C | 2.203460 | 0.763489 | 0.000000 |
| C | -0.102404 | 0.714074 | 0.000000 |
| C | -1.348082 | -1.480392 | 0.000000 |
| H | 3.111857 | 1.364588 | 0.000000 |
| H | -1.280325 | 2.562548 | 0.000000 |
| C | -2.433026 | -0.628221 | 0.000000 |
| H | -1.358860 | -2.566998 | 0.000000 |
| C | -2.412234 | 0.644608 | 0.000000 |
| C | -1.318389 | 1.478045 | 0.000000 |

## 4.85a*



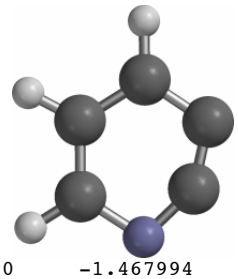
| | | | |
|---|---|---|---|
| H | 3.231628 | -1.302361 | 0.000000 |
| C | 2.302512 | -0.739726 | 0.000000 |
| H | 1.022397 | -2.472204 | 0.000000 |
| C | 1.078975 | -1.385641 | 0.000000 |
| N | 1.259351 | 1.451574 | 0.000000 |
| C | -0.112960 | -0.618255 | 0.000000 |
| C | 2.338649 | 0.673235 | 0.000000 |
| C | 0.057759 | 0.829482 | 0.000000 |
| C | -1.410175 | -1.233477 | 0.000000 |
| H | 3.296602 | 1.190828 | 0.000000 |
| C | -2.592907 | -0.496279 | 0.000000 |
| H | -1.462199 | -2.321059 | 0.000000 |
| H | -3.571682 | -0.964076 | 0.000000 |
| C | -2.322568 | 0.883278 | 0.000000 |
| C | -1.203254 | 1.468255 | 0.000000 |

## 4.103a*



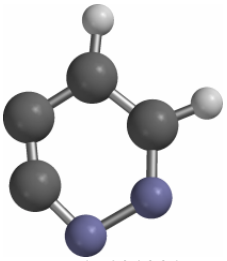
| | | | |
|---|---|---|---|
| C | 0.720372 | -1.205981 | 0.000000 |
| C | -0.692436 | 1.009838 | 0.000000 |
| C | 1.419443 | 0.009475 | 0.000000 |
| C | -0.553363 | -1.275485 | 0.000000 |
| C | -1.430351 | -0.204442 | 0.000000 |
| N | 0.646363 | 1.112700 | 0.000000 |
| H | 2.496415 | 0.135423 | 0.000000 |
| H | -2.514834 | -0.214756 | 0.000000 |
| H | -1.241121 | 1.949351 | 0.000000 |

## 4.104a*



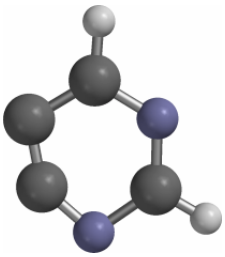
| | | | |
|---|---|---|---|
| C | 0.135020 | -1.467994 | 0.000000 |
| C | -0.350629 | 1.225328 | 0.000000 |
| C | -0.936113 | -0.793948 | 0.000000 |
| C | 1.272209 | -0.633738 | 0.000000 |
| C | 0.972203 | 0.753169 | 0.000000 |
| N | -1.454912 | 0.385054 | 0.000000 |
| H | 2.299871 | -0.990614 | 0.000000 |
| H | 1.778153 | 1.481743 | 0.000000 |
| H | -0.578136 | 2.287527 | 0.000000 |

## 4.106a*



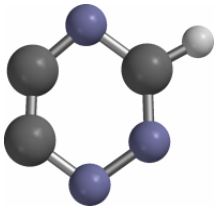
| | | | |
|---|---|---|---|
| C | 0.116289 | -1.404991 | 0.000000 |
| N | -0.306056 | 1.273672 | 0.000000 |
| C | -0.985167 | -0.774865 | 0.000000 |
| C | 1.271576 | -0.636403 | 0.000000 |
| C | 0.925752 | 0.751779 | 0.000000 |
| N | -1.438324 | 0.454903 | 0.000000 |
| H | 2.303124 | -0.977847 | 0.000000 |
| H | 1.709926 | 1.505030 | 0.000000 |

## 4.108a*



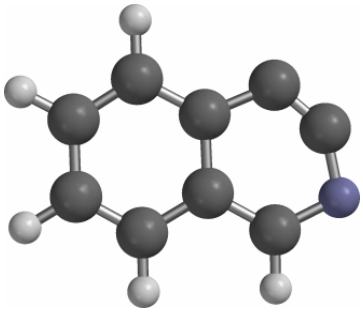
| | | | |
|---|---|---|---|
| N | 1.465652 | -0.143376 | 0.000000 |
| C | -1.319474 | 0.349505 | 0.000000 |
| C | 0.472197 | -1.133533 | 0.000000 |
| C | 0.803134 | 0.955331 | 0.000000 |
| C | -0.388384 | 1.408787 | 0.000000 |
| N | -0.834596 | -0.919175 | 0.000000 |
| H | 0.841244 | -2.153556 | 0.000000 |
| H | -2.399040 | 0.468337 | 0.000000 |

## 4.110a*



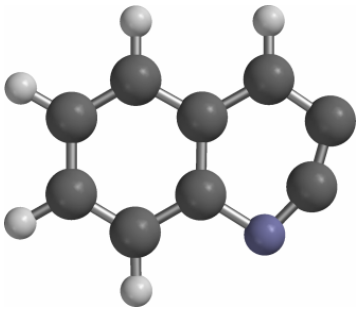
| | | | |
|---|---|---|---|
| N | -0.553603 | -1.111942 | 0.000000 |
| N | -1.464305 | -0.101897 | 0.000000 |
| C | -0.791759 | 1.091335 | 0.000000 |
| C | 0.483504 | 1.190622 | 0.000000 |
| N | 1.440891 | 0.305620 | 0.000000 |
| C | 0.763208 | -0.916136 | 0.000000 |
| H | 1.387129 | -1.804126 | 0.000000 |

## 4.111a*



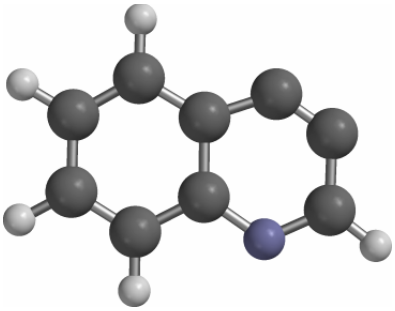
| | | | |
|---|---|---|---|
| C | 2.313636 | 0.660771 | 0.000000 |
| C | 1.330865 | 1.440043 | 0.000000 |
| C | 1.413085 | -1.260175 | 0.000000 |
| C | 0.039197 | 0.848811 | 0.000000 |
| N | 2.612585 | -0.626030 | 0.000000 |
| C | 0.137727 | -0.605264 | 0.000000 |
| C | -1.232564 | 1.467718 | 0.000000 |
| H | -1.007371 | -2.452983 | 0.000000 |
| H | 1.454495 | -2.348756 | 0.000000 |
| C | -2.375583 | 0.684366 | 0.000000 |
| H | -1.292316 | 2.552363 | 0.000000 |
| H | -3.352529 | 1.161111 | 0.000000 |
| C | -2.292690 | -0.730434 | 0.000000 |
| H | -3.205492 | -1.319810 | 0.000000 |
| C | -1.063709 | -1.366442 | 0.000000 |

## 4.112a*



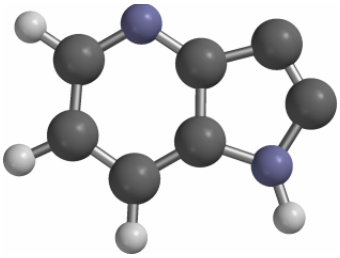
| | | | |
|---|---|---|---|
| C | 2.559472 | 0.680603 | 0.000000 |
| H | 1.355381 | 2.526840 | 0.000000 |
| C | 1.378479 | 1.435928 | 0.000000 |
| N | 1.353781 | -1.468484 | 0.000000 |
| C | 0.135125 | 0.703528 | 0.000000 |
| C | 2.230093 | -0.557601 | 0.000000 |
| C | 0.135237 | -0.740320 | 0.000000 |
| C | -1.122501 | 1.367243 | 0.000000 |
| H | -1.038336 | -2.544504 | 0.000000 |
| C | -2.303566 | 0.646255 | 0.000000 |
| H | -1.139870 | 2.455055 | 0.000000 |
| H | -3.255904 | 1.169344 | 0.000000 |
| C | -2.281831 | -0.769603 | 0.000000 |
| H | -3.217376 | -1.322625 | 0.000000 |
| C | -1.079991 | -1.459180 | 0.000000 |

## 4.113a*



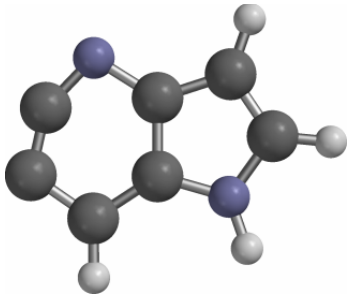
| | | | |
|---|---|---|---|
| C | 2.387743 | 0.846186 | 0.000000 |
| C | 1.269259 | 1.447167 | 0.000000 |
| N | 1.369392 | -1.246593 | 0.000000 |
| C | -0.001107 | 0.855399 | 0.000000 |
| C | 2.512557 | -0.566988 | 0.000000 |
| C | 0.163566 | -0.605221 | 0.000000 |
| C | -1.291629 | 1.427268 | 0.000000 |
| H | 3.445267 | -1.121979 | 0.000000 |
| H | -0.901839 | -2.475411 | 0.000000 |
| C | -2.407064 | 0.603023 | 0.000000 |
| H | -1.390727 | 2.508678 | 0.000000 |
| H | -3.399898 | 1.045094 | 0.000000 |
| C | -2.268782 | -0.803997 | 0.000000 |
| H | -3.156789 | -1.430226 | 0.000000 |
| C | -1.015740 | -1.395200 | 0.000000 |

## 4.115a*



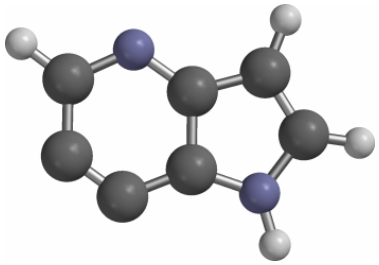
| | | | |
|---|---|---|---|
| C | 0.339501 | -0.645280 | 0.000000 |
| C | -1.975627 | 0.767295 | 0.000000 |
| C | 0.293755 | 0.803030 | 0.000000 |
| C | -0.841026 | -1.390373 | 0.000000 |
| C | -2.019945 | -0.643443 | 0.000000 |
| N | -0.850809 | 1.495921 | 0.000000 |
| H | -0.848762 | -2.477507 | 0.000000 |
| H | -2.983790 | -1.144200 | 0.000000 |
| H | -2.905685 | 1.331565 | 0.000000 |
| C | 1.685243 | 1.230281 | 0.000000 |
| C | 2.367229 | 0.149794 | 0.000000 |
| N | 1.688761 | -1.035476 | 0.000000 |
| H | 2.048323 | -1.978288 | 0.000000 |

## 4.116a*



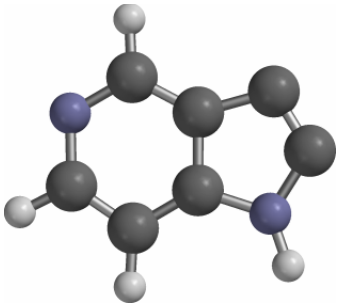
| | | | |
|---|---|---|---|
| C | 1.964899 | 0.583518 | 0.000000 |
| N | 1.080439 | 1.510583 | 0.000000 |
| C | 2.233267 | -0.660412 | 0.000000 |
| C | 1.073369 | -1.452255 | 0.000000 |
| H | 1.053328 | -2.541814 | 0.000000 |
| C | -0.113156 | -0.669789 | 0.000000 |
| C | -0.107234 | 0.776461 | 0.000000 |
| N | -1.438175 | -1.041106 | 0.000000 |
| H | -1.774655 | -1.992626 | 0.000000 |
| C | -2.241381 | 0.079094 | 0.000000 |
| H | -3.318948 | -0.019585 | 0.000000 |
| C | -1.458501 | 1.219590 | 0.000000 |
| H | -1.809382 | 2.241414 | 0.000000 |

## 4.117a*



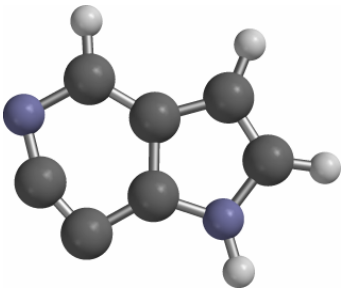
| | | | |
|---|---|---|---|
| C | 2.227114 | 0.608530 | 0.000000 |
| H | 3.161511 | 1.158031 | 0.000000 |
| N | 1.079066 | 1.297159 | 0.000000 |
| C | 2.096149 | -0.803775 | 0.000000 |
| C | 0.990197 | -1.437886 | 0.000000 |
| C | -0.238209 | -0.800630 | 0.000000 |
| C | -0.101773 | 0.650291 | 0.000000 |
| N | -1.566641 | -1.096900 | 0.000000 |
| H | -1.956691 | -2.028009 | 0.000000 |
| C | -2.295909 | 0.082665 | 0.000000 |
| H | -3.376584 | 0.051842 | 0.000000 |
| C | -1.438624 | 1.162726 | 0.000000 |
| H | -1.726304 | 2.204595 | 0.000000 |

## 4.119a*



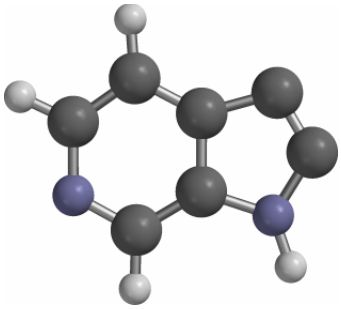
| | | | |
|---|---|---|---|
| H | -0.875642 | -2.457044 | 0.000000 |
| C | -0.842816 | -1.371005 | 0.000000 |
| C | -0.929439 | 1.430638 | 0.000000 |
| C | -2.014587 | -0.614071 | 0.000000 |
| C | 0.349019 | -0.641983 | 0.000000 |
| C | 0.324532 | 0.799123 | 0.000000 |
| N | -2.074865 | 0.741562 | 0.000000 |
| H | -2.976684 | -1.121289 | 0.000000 |
| H | -1.004885 | 2.516171 | 0.000000 |
| N | 1.694695 | -1.045108 | 0.000000 |
| H | 2.043104 | -1.991876 | 0.000000 |
| C | 1.713309 | 1.207976 | 0.000000 |
| C | 2.398679 | 0.126631 | 0.000000 |

## 4.120a*



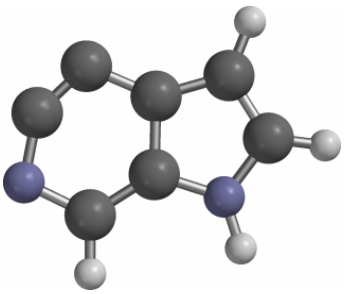
| | | | |
|---|---|---|---|
| C | 1.923626 | 0.652281 | 0.000000 |
| C | 1.012432 | 1.538231 | 0.000000 |
| C | -0.175711 | 0.771799 | 0.000000 |
| C | -0.114805 | -0.679367 | 0.000000 |
| N | -1.500685 | 1.116324 | 0.000000 |
| H | -1.843766 | 2.066538 | 0.000000 |
| C | -2.278940 | -0.028079 | 0.000000 |
| H | -3.358300 | 0.045164 | 0.000000 |
| C | -1.471902 | -1.145869 | 0.000000 |
| H | -1.817990 | -2.170319 | 0.000000 |
| N | 2.309546 | -0.568439 | 0.000000 |
| C | 1.143764 | -1.311100 | 0.000000 |
| H | 1.269194 | -2.389815 | 0.000000 |

## 4.122a*



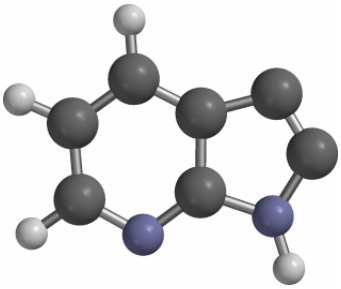
| | | | |
|---|---|---|---|
| C | 0.358726 | -0.619923 | 0.000000 |
| C | -2.050679 | 0.608652 | 0.000000 |
| C | -0.829110 | -1.361651 | 0.000000 |
| C | 0.329000 | 0.821428 | 0.000000 |
| C | -0.930480 | 1.438626 | 0.000000 |
| N | -2.017738 | -0.749083 | 0.000000 |
| H | -0.830145 | -2.451092 | 0.000000 |
| H | -1.035486 | 2.519462 | 0.000000 |
| H | -3.046449 | 1.044968 | 0.000000 |
| N | 1.706076 | -1.023635 | 0.000000 |
| H | 2.058136 | -1.968995 | 0.000000 |
| C | 2.397229 | 0.153588 | 0.000000 |
| C | 1.717989 | 1.236988 | 0.000000 |

## 4.123a*



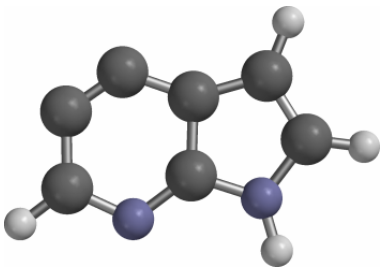
| | | | |
|---|---|---|---|
| C | 1.096523 | -1.295296 | 0.000000 |
| H | 1.127091 | -2.382711 | 0.000000 |
| C | -0.116729 | -0.577537 | 0.000000 |
| C | -0.192119 | 0.873926 | 0.000000 |
| N | -1.416476 | -1.032021 | 0.000000 |
| H | -1.701775 | -2.000517 | 0.000000 |
| C | -2.279985 | 0.039551 | 0.000000 |
| H | -3.349743 | -0.123899 | 0.000000 |
| C | -1.569467 | 1.228271 | 0.000000 |
| H | -1.995981 | 2.221253 | 0.000000 |
| N | 2.309556 | -0.657472 | 0.000000 |
| C | 2.028537 | 0.623251 | 0.000000 |
| C | 1.093835 | 1.463752 | 0.000000 |

## 4.125a*



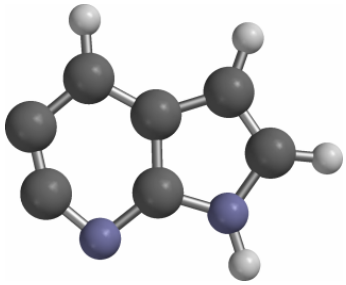
| | | | |
|---|---|---|---|
| C | 0.326964 | -0.849598 | 0.000000 |
| C | -1.907761 | 0.765937 | 0.000000 |
| C | 0.330703 | 0.601813 | 0.000000 |
| C | -0.929403 | -1.468649 | 0.000000 |
| C | -2.051332 | -0.635459 | 0.000000 |
| N | -0.720867 | 1.400043 | 0.000000 |
| H | -1.025282 | -2.550686 | 0.000000 |
| H | -3.050213 | -1.061537 | 0.000000 |
| H | -2.787586 | 1.404781 | 0.000000 |
| N | 1.676493 | 1.029401 | 0.000000 |
| H | 1.987162 | 1.990044 | 0.000000 |
| C | 1.718735 | -1.224950 | 0.000000 |
| C | 2.389949 | -0.132106 | 0.000000 |

## 4.126a*



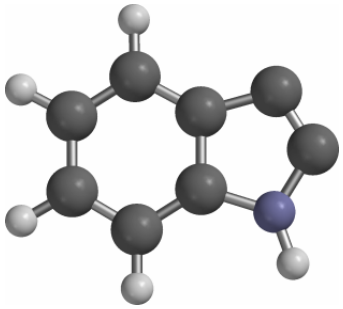
| | | | |
|---|---|---|---|
| C | -0.101158 | -0.556541 | 0.000000 |
| C | -0.236517 | 0.893445 | 0.000000 |
| N | -1.381237 | -1.056939 | 0.000000 |
| H | -1.601647 | -2.042830 | 0.000000 |
| C | -2.287217 | -0.024904 | 0.000000 |
| H | -3.349536 | -0.227992 | 0.000000 |
| C | -1.624114 | 1.193525 | 0.000000 |
| H | -2.089121 | 2.168722 | 0.000000 |
| N | 1.018753 | -1.289380 | 0.000000 |
| C | 2.198855 | -0.647804 | 0.000000 |
| H | 3.103411 | -1.245595 | 0.000000 |
| C | 2.135617 | 0.766700 | 0.000000 |
| C | 1.048834 | 1.427351 | 0.000000 |

## 4.127a*



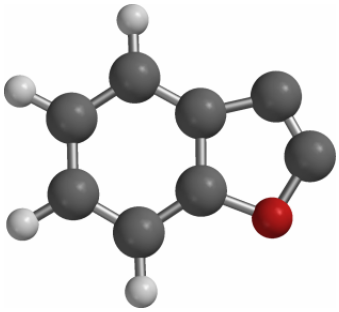
| | | | |
|---|---|---|---|
| C | 2.227482 | 0.595052 | 0.000000 |
| C | 1.128109 | 1.462288 | 0.000000 |
| H | 1.170424 | 2.549295 | 0.000000 |
| C | -0.104181 | 0.749269 | 0.000000 |
| C | -0.095467 | -0.696466 | 0.000000 |
| N | 1.008040 | -1.511833 | 0.000000 |
| C | 1.984373 | -0.651225 | 0.000000 |
| N | -1.394091 | -1.123111 | 0.000000 |
| H | -1.672748 | -2.093866 | 0.000000 |
| C | -1.487448 | 1.133359 | 0.000000 |
| H | -1.884714 | 2.139000 | 0.000000 |
| C | -2.235586 | -0.025560 | 0.000000 |
| H | -3.309066 | -0.159572 | 0.000000 |

## 4.128a*



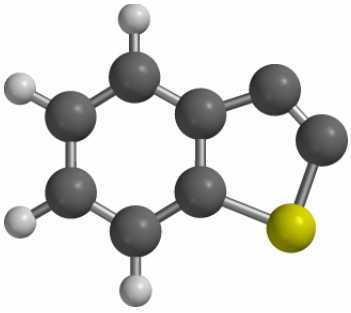
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| C | -0.897625 | -1.478386 | 0.000000 |
| C | -0.819670 | 1.394956 | 0.000000 |
| C | 0.338848 | -0.810885 | 0.000000 |
| C | -2.066322 | -0.717527 | 0.000000 |
| C | -2.027640 | 0.694917 | 0.000000 |
| C | 0.355385 | 0.635061 | 0.000000 |
| H | -3.030038 | -1.219395 | 0.000000 |
| H | -2.960614 | 1.252197 | 0.000000 |
| H | -0.798664 | 2.482052 | 0.000000 |
| C | 1.734484 | -1.207420 | 0.000000 |
| C | 2.410577 | -0.121711 | 0.000000 |
| N | 1.703584 | 1.046185 | 0.000000 |
| H | 2.045310 | 1.994945 | 0.000000 |

## 4.129a*



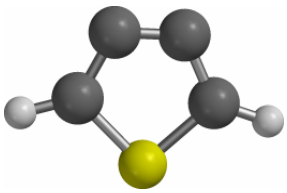
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|---|---|---|---|
| H | -0.744388 | -2.485643 | 0.000000 |
| C | -0.792873 | -1.400958 | 0.000000 |
| C | -0.887028 | 1.477231 | 0.000000 |
| C | 0.357652 | -0.623360 | 0.000000 |
| C | -2.007278 | -0.705190 | 0.000000 |
| C | -2.051374 | 0.704244 | 0.000000 |
| C | 0.346577 | 0.812714 | 0.000000 |
| H | -2.937243 | -1.266587 | 0.000000 |
| H | -3.017417 | 1.201214 | 0.000000 |
| H | -0.930789 | 2.562182 | 0.000000 |
| C | 1.756524 | 1.142899 | 0.000000 |
| C | 2.385669 | 0.032249 | 0.000000 |
| O | 1.676489 | -1.116267 | 0.000000 |

## 4.130a*



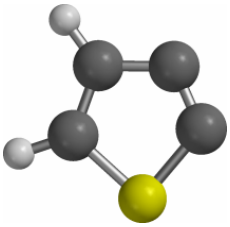
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|---|---|---|---|
| H | -0.701994 | -2.495391 | 0.000000 |
| C | -0.898957 | -1.425824 | 0.000000 |
| C | -1.429957 | 1.376086 | 0.000000 |
| C | 0.149530 | -0.498081 | 0.000000 |
| C | -2.206906 | -0.938955 | 0.000000 |
| C | -2.468500 | 0.446534 | 0.000000 |
| C | -0.100437 | 0.917449 | 0.000000 |
| H | -3.036096 | -1.641210 | 0.000000 |
| H | -3.497980 | 0.793908 | 0.000000 |
| H | -1.633123 | 2.443190 | 0.000000 |
| C | 1.170505 | 1.598036 | 0.000000 |
| C | 2.178771 | 0.830331 | 0.000000 |
| S | 1.905277 | -0.856389 | 0.000000 |

## 4.132a*



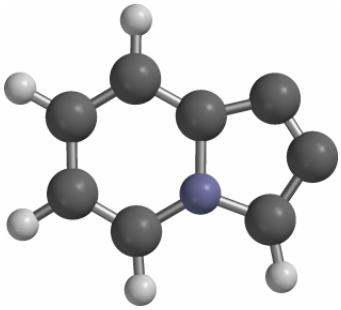
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|---|---|---|---|
| C | 0.643328 | 0.000000 | 1.410770 |
| C | 1.264269 | 0.000000 | 0.177883 |
| H | 2.302155 | 0.000000 | -0.127276 |
| C | -0.643328 | 0.000000 | 1.410770 |
| C | -1.264269 | 0.000000 | 0.177883 |
| H | -2.302155 | 0.000000 | -0.127276 |
| S | 0.000000 | 0.000000 | -1.014694 |

## 4.133a*



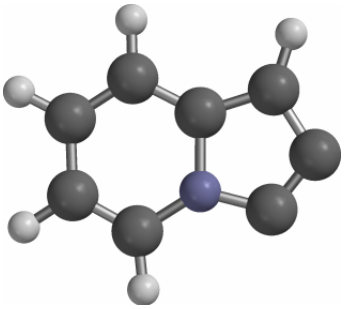
| | | | |
|---|---|---|---|
| C | 1.126355 | 0.979625 | 0.000000 |
| C | -0.113978 | 1.256184 | 0.000000 |
| C | 1.426462 | -0.419338 | 0.000000 |
| H | 2.405041 | -0.884052 | 0.000000 |
| C | 0.234712 | -1.133671 | 0.000000 |
| H | 0.101862 | -2.211987 | 0.000000 |
| S | -1.170022 | -0.072095 | 0.000000 |

## 4.142a*



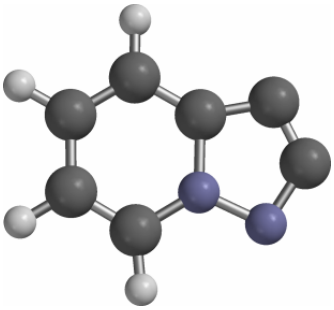
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|---|---|---|---|
| C | 2.040303 | 0.767700 | 0.000000 |
| H | 2.991109 | 1.290797 | 0.000000 |
| C | 0.851901 | 1.481949 | 0.000000 |
| H | 0.843259 | 2.567895 | 0.000000 |
| C | 2.008893 | -0.651487 | 0.000000 |
| H | 2.929785 | -1.225743 | 0.000000 |
| C | 0.817353 | -1.337752 | 0.000000 |
| H | 0.737662 | -2.419914 | 0.000000 |
| N | -0.369870 | -0.637245 | 0.000000 |
| C | -0.378858 | 0.807369 | 0.000000 |
| C | -1.751894 | 1.130502 | 0.000000 |
| C | -2.456193 | 0.054424 | 0.000000 |
| C | -1.677040 | -1.112596 | 0.000000 |
| H | -1.892243 | -2.170393 | 0.000000 |

## 4.143a*



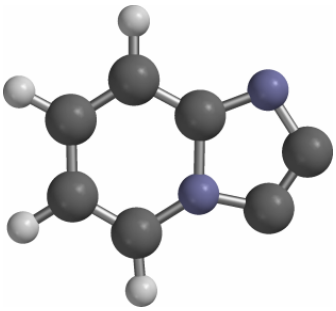
| | | | |
|---|---|---|---|
| C | 2.018661 | 0.718914 | 0.000000 |
| H | 2.955915 | 1.266879 | 0.000000 |
| C | 0.820342 | 1.405727 | 0.000000 |
| H | 0.794138 | 2.492365 | 0.000000 |
| C | 2.035441 | -0.706668 | 0.000000 |
| H | 2.973185 | -1.251668 | 0.000000 |
| C | 0.865630 | -1.422738 | 0.000000 |
| H | 0.805843 | -2.505168 | 0.000000 |
| N | -0.333289 | -0.746396 | 0.000000 |
| C | -0.405677 | 0.700345 | 0.000000 |
| C | -1.782661 | 1.059324 | 0.000000 |
| H | -2.161172 | 2.072665 | 0.000000 |
| C | -2.482012 | -0.178761 | 0.000000 |
| C | -1.631025 | -1.145795 | 0.000000 |

## 4.148a*



| | | | |
|---|---|---|---|
| C | 2.016063 | 0.767368 | 0.000000 |
| H | 2.966859 | 1.291021 | 0.000000 |
| C | 0.832657 | 1.487707 | 0.000000 |
| H | 0.828809 | 2.573203 | 0.000000 |
| C | 1.993239 | -0.651057 | 0.000000 |
| H | 2.918422 | -1.217605 | 0.000000 |
| C | 0.804238 | -1.344729 | 0.000000 |
| H | 0.698460 | -2.423613 | 0.000000 |
| N | -0.366232 | -0.634173 | 0.000000 |
| C | -0.398933 | 0.808236 | 0.000000 |
| N | -1.616241 | -1.205113 | 0.000000 |
| C | -1.778426 | 1.071257 | 0.000000 |
| C | -2.364607 | -0.070192 | 0.000000 |

## 4.157a*



| | | | |
|---|---|---|---|
| C | 1.986440 | 0.728046 | 0.000000 |
| H | 2.920064 | 1.282038 | 0.000000 |
| C | 0.784469 | 1.415969 | 0.000000 |
| H | 0.740797 | 2.500934 | 0.000000 |
| C | 2.016862 | -0.691191 | 0.000000 |
| H | 2.961397 | -1.224299 | 0.000000 |
| C | 0.854569 | -1.427706 | 0.000000 |
| H | 0.809038 | -2.510546 | 0.000000 |
| N | -0.340564 | -0.756495 | 0.000000 |
| C | -0.429480 | 0.704732 | 0.000000 |
| N | -1.722113 | 1.124117 | 0.000000 |
| C | -2.427041 | -0.062759 | 0.000000 |
| C | -1.653591 | -1.085462 | 0.000000 |

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# CHAPTER FIVE

## Regioselective Reactions of 3,4-Pyridynes Enabled by the Aryne Distortion Model

Goetz, A. E.; Garg, N. K. *Nat. Chem.* **2013**, *5,* 54–60.

### 5.1 Abstract

The pyridine heterocycle continues to play a vital role in the development of human medicines. More than 100 currently-marketed drugs contain this privileged unit, which remains highly sought after synthetically. We report an efficient means to access di- and trisubstituted pyridines in an efficient and highly controlled manner using transient 3,4-pyridyne intermediates. Previous efforts to employ 3,4-pyridynes for the construction of substituted pyridines have been hampered by a lack of regiocontrol or the inability to later manipulate an adjacent directing group. The strategy relies on the use of proximal halide or sulfamate substituents to perturb pyridyne distortion, which in turn governs regioselectivities in nucleophilic addition and cycloaddition reactions. After trapping of the pyridynes generated in situ, the neighboring directing groups may be removed or exploited using versatile metal-catalyzed cross-coupling reactions. This methodology now renders 3,4-pyridynes useful synthetic building blocks for the creation of highly decorated derivatives of the medicinally privileged pyridine heterocycle.

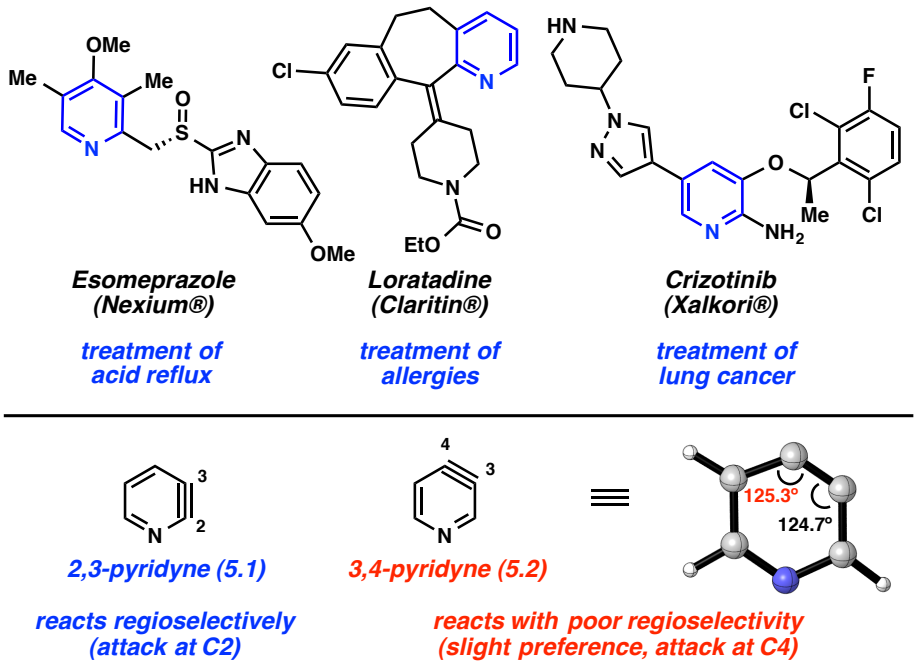
### 5.2 Introduction

The pyridine ring is one of the most important heterocycles in drug discovery.[1,2] It is present in more than 100 currently marketed drugs, including the blockbuster drugs esomeprazole (Nexium®) and loratidine (Claritin®), in addition to the recently approved cancer

therapeutic crizotinib (Xalkori®) (Figure 5.1). Other drugs that contain the pyridine ring, or some derivative thereof, include the life-changing medicines Singulair® (asthma/allergies), Actos® (diabetes), Lunesta® (insomnia), Gleevec® (various cancers), Prevacid® (acid reflux/ulcers), and Mirtazapine (depression). As a result of the immense value of pyridines, for decades methods to access functionalized derivatives of this privileged heterocycle have been highly sought.[1] Several elegant methods were recently reported for the assembly of substituted pyridines.[3–6]

A promising approach toward polyfunctionalized pyridines involves the use of highly reactive pyridyne intermediates,[7–23] such as isomeric hetarynes **5.1** and **5.2** (Figure 5.1), which are valued for their electrophilicity and high reactivity toward nucleophiles and cycloaddition partners.[24,25] The first pyridyne studies were reported in 1955, with Levine and Leake's seminal discovery of 3,4-pyridyne (**5.2**).[7] Despite the many studies that followed over the next fifty years, pyridynes have yet to mature into a widely used tool for the assembly of functionalized pyridine scaffolds. The 2,3-pyridyne (**5.1**) reacts with excellent degrees of regioselectivity to give 2-substituted pyridines or related cycloadducts;[20,21] however, other methods for C2 functionalization of pyridines are available and are often preferred.[1] In the case of 3,4-pyridynes (e.g., **5.2**), nucleophilic additions are known to occur without significant selectivity for attack at either C3 or C4.[9–19] If the regioselectivity in reactions of 3,4-pyridynes could be controlled, these intermediates could serve as valuable building blocks for the synthesis of substituted pyridines that are otherwise difficult to access.

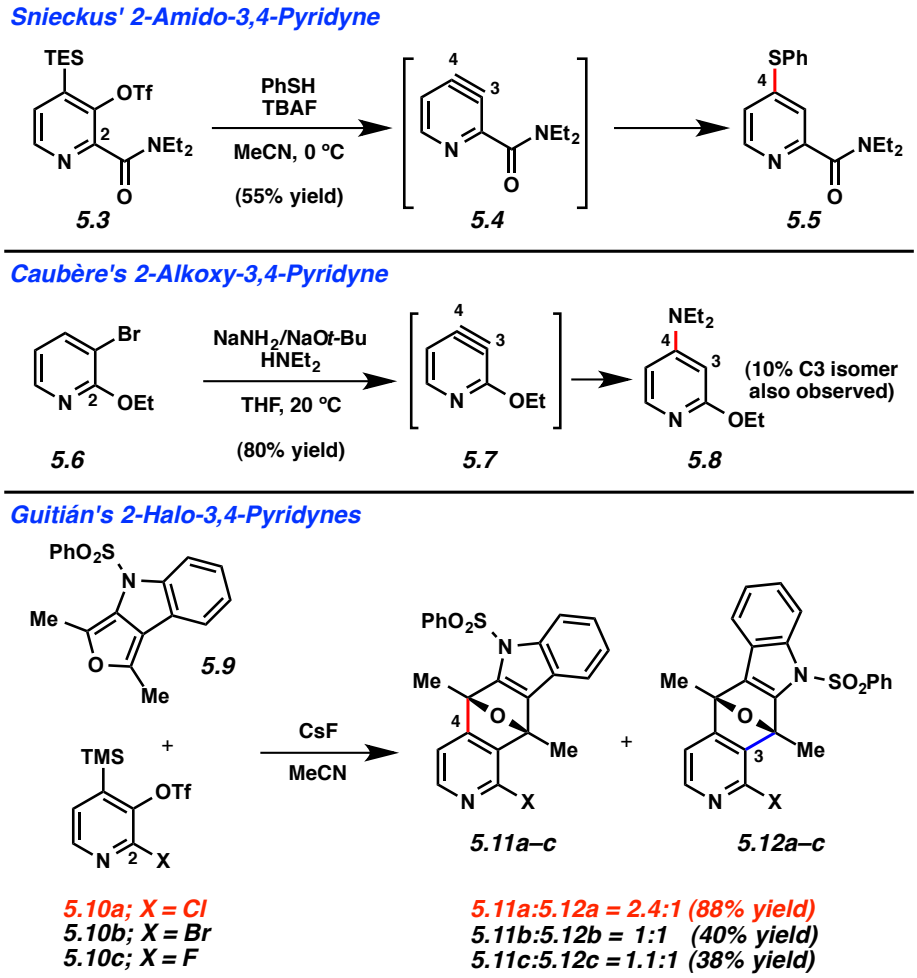
*Figure 5.1. Pyridine-Containing Drugs and Known Reactivity of Pyridynes.*




Prior efforts to modulate regioselectivities of 3,4-pyridynes using substituent effects have been met with promising results and can be summarized as follows (Figure 5.2): (a) Snieckus and co-workers reported a single example using a C2 amido group to enhance nucleophilic addition to C4 of a 3,4-pyridyne intermediate (**5.3**→**5.4**→**5.5**).[18] (b) Caubère and co-workers found that oxygen and nitrogen substituents positioned in close proximity to the 3,4-pyridyne could also lead to enhanced selectivity for the addition of amines.[19] For example, treatment of halopyridine **5.6** with diethylamine under $NaNH_2$/NaO*t*-Bu conditions gave **5.8** in 80% yield, along with 10% of the C3 isomer, both presumably arising via pyridyne **5.7**. (c) Guitián and co-workers examined the influence of C2 halide substituents, which could later be removed later, on the 3,4-pyridyne for applications in a cycloaddition with substituted furans with applications in the synthesis of the natural product ellipticine.[12,13] Although bromide or fluoride groups did not significantly influence regioselectivity, some success was seen using a C2 chloro substituent

(**5.9**+**5.10**→**5.11**+**5.12**). Interestingly, the authors reported that the presence of a chloride at C5 of the 3,4-pyridyne gave an equimolar mixture of cycloadducts using furan **5.9**.

*Figure 5.2. Previous Controlled 3,4-Pyridyne Examples*




The studies highlighted in Figure 5.2 demonstrate that substituent effects can modulate pyridyne regioselectivities, particularly for the favored addition at C4. However, subsequently the ability to manipulate or remove the C2 amide, oxygen, or nitrogen directing groups of Snieckus' and Caubère's work is limited. Guitián's use of neighboring halides to modulate 3,4-pyridyne regioselectivity gave mixed results, with a C2 chloride being the most promising directing group for the specific cycloaddition examined. Moreover, the most well-studied

examples of regioselective 3,4-pyridyne reactions are restricted to the use of amine- or alcohol-based nucleophiles, and various other trapping agents have yet to be explored.

Herein, we report the design and synthesis of substituted 3,4-pyridynes that react with significant regioselectivities. Our strategy renders 3,4-pyridynes synthetically useful for the assembly of highly functionalized pyridine scaffolds and features several key design elements: (a) The pyridynes are accessed from pyridylsilyltriflate precursors using mild fluoride-based reaction conditions. This allows for a broad range of trapping agents (nucleophiles and cycloaddition partners) to be employed, which in turn delivers a more diverse collection of polysubstituted pyridine derivatives. (b) A C5-bromide substituent is used to induce aryne distortion and direct nucleophilic additions to C3 of 3,4-pyridynes. Subsequently, the bromide may be manipulated using conventional Pd-catalyzed reactions. (c) By positioning a sulfamoyl group at C2 of the 3,4-pyridyne, aryne distortion is perturbed to favor attack at C4 of 3,4-pyridynes. Sulfamoyl groups have not been used previously to govern pyridyne or aryne regioselectivities, but when used in conjunction with modern Ni-catalyzed cross-couplings, offer an effective new means to access functionalized pyridines. The methodologies reported herein now render 3,4-pyridynes broadly useful as a tool for the construction of polysubstituted pyridines. We expect our findings will promote the use of 3,4-pyridynes and other heterocyclic arynes in the synthesis of medicinally privileged molecular scaffolds.

### 5.3 Design and Synthesis of Pyridyne Precursors

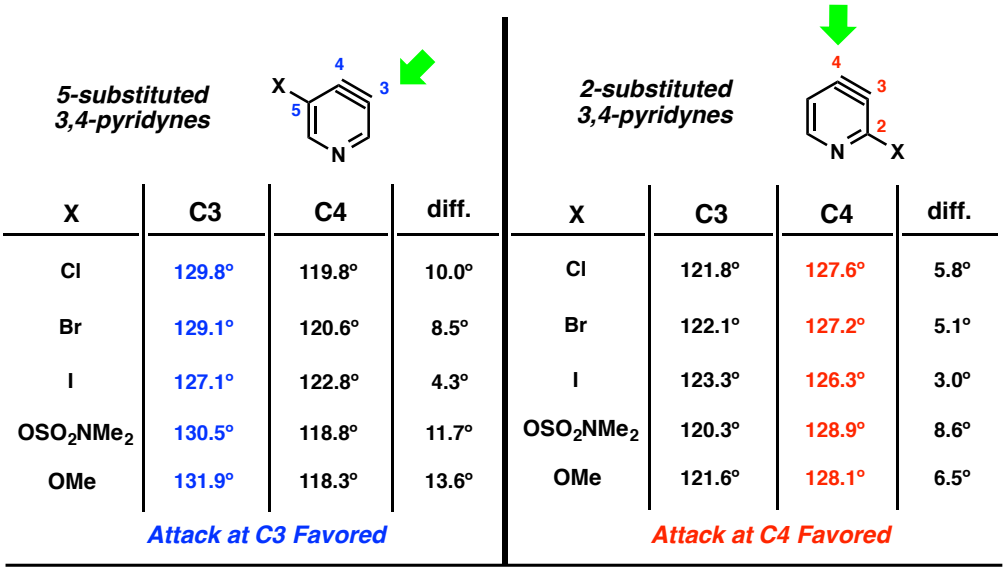
The observation that 3,4-pyridyne **5.2** reacts with poor regioselectivity can be explained by consideration of the aryne distortion model.[26,27,28] The geometry-optimized structure of **5.2** obtained from density functional theory (DFT) calculations (B3LYP/6-31G*)[29] is shown in

Figure 5.1. Pyridyne **5.2** possesses only minor aryne distortion, as evidenced by the nearly identical internal angles at C3 and C4. We hypothesized that neighboring electron-withdrawing substituents at C5 or C2 could increase aryne distortion, thus providing greater degrees of regioselectivity.

Bearing in mind the seminal findings of Guitián,[12,13] and that aryne distortion and subsequent regioselectivities may be perturbed by inductively electron-withdrawing substituents,[24,30] we evaluated a series of 2- and 5-substituted 3,4-pyridynes using computational methods (Figure 5.3, also see Figure 5.8). Parent pyridynes have been studied computationally,[31] but no calculations involving C2- or C5-substituted derivatives are available in the literature. We considered chloride, bromide, iodide, and sulfamate substituents to be particularly attractive pyridyne substituents as each could plausibly serve as a handle for further elaboration after being used to modulate pyridyne regioselectivity. Although less useful synthetically, the methoxy substituent was also evaluated as a point of comparison, since methoxy is well-known to govern regioselectivity in reactions of benzyne due to significant aryne distortion.[24]

As summarized in Figure 5.3, computations predict that a variety of electron-withdrawing substituents could be used to induce 3,4-pyridyne distortion. In the case of 5-substituted pyridynes, the inductively-withdrawing substituents cause a flattening at C3, which, according to the aryne distortion model, suggests this would be the preferred site of attack by nucleophiles.[26,27] Specifically, the orbital located at the more linear terminus of the aryne possesses greater p character and is therefore more electropositive. A similar effect was seen in our studies of 2-substituted 3,4-pyridynes. In all cases, the electron-withdrawing substituents lead to a flattening at C4, which is in turn predicted to be the preferred site of attack by nucleophiles.

*Figure 5.3. Computational Evaluation of Substituted 3,4-Pyridynes*



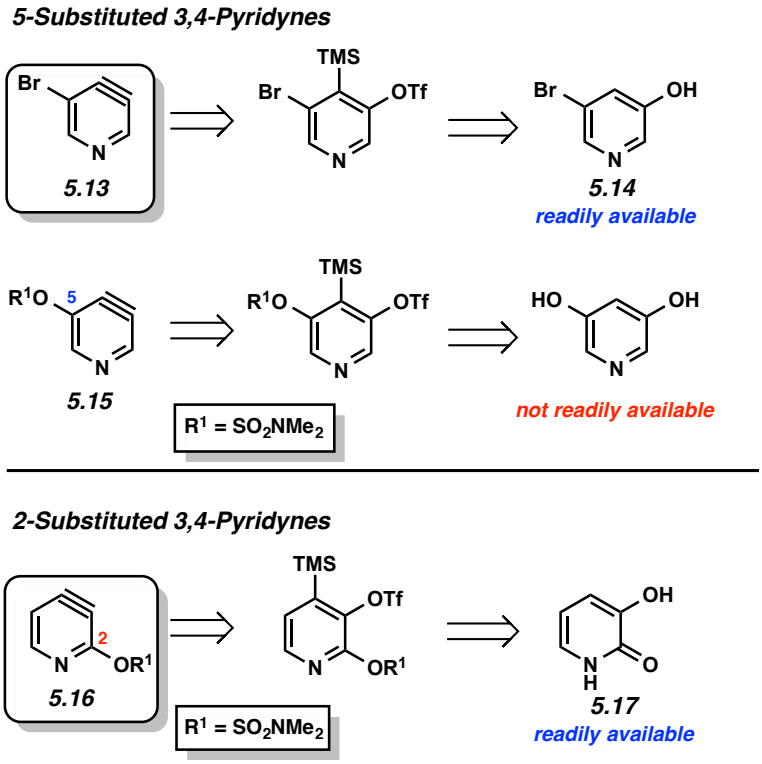

| X | C3 | C4 | diff. |
|---|---|---|---|
| Cl | 129.8° | 119.8° | 10.0° |
| Br | 129.1° | 120.6° | 8.5° |
| I | 127.1° | 122.8° | 4.3° |
| $OSO_2NMe_2$ | 130.5° | 118.8° | 11.7° |
| OMe | 131.9° | 118.3° | 13.6° |

| X | C3 | C4 | diff. |
|---|---|---|---|
| Cl | 121.8° | 127.6° | 5.8° |
| Br | 122.1° | 127.2° | 5.1° |
| I | 123.3° | 126.3° | 3.0° |
| $OSO_2NMe_2$ | 120.3° | 128.9° | 8.6° |
| OMe | 121.6° | 128.1° | 6.5° |

The aryne distortion model suggests that arynes with internal angle differences ≥ 4° should react with significant regioselectivities in nucleophilic addition and cycloaddition reactions.[26,27] As the substituted 3,4-pyridynes shown in Figure 5.3 all meet this criterion and their distortions are generally on par with that of methoxy-substituted pyridynes, we hypothesized that any of the halo- or sulfamoyl-pyridynes would prove useful. We envisioned accessing pyridynes from silyltriflate precursors, as aryne formation would be readily achieved using mild fluoride-based conditions. In addition, this general method (i.e., the Kobayashi approach to aryne generation)[32] was expected to be highly tolerant of an array of functional groups and trapping agents, and therefore could be used in a range of aryne trapping processes.[24]

Figure 5.4 summarizes several key aspects of pyridyne design that were considered prior to the synthesis of substituted pyridynes. With respect to the 5-substituted 3,4-pyridyne, bromopyridyne **5.13** was considered attractive since the bromide induced considerable pyridyne distortion and offered the most versatility for functionalization after pyridyne trapping.

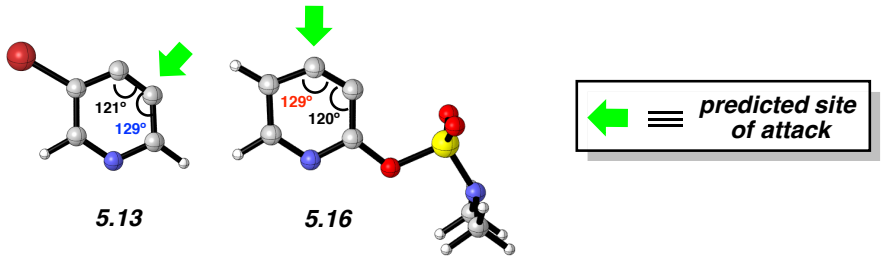
*Figure 5.4. Retrosynthesis of Substituted Pyridynes **5.13**, **5.15**, and **5.16***




Furthermore, the presumed silyltriflate precursor to **5.13** would likely be accessible from commercially available bromohydroxypyridine **5.14**. 5-sulfamoyl-3,4-pyridyne (**5.15**) was also attractive because computations suggested this species would be highly distorted. However, the presumed silyltriflate precursor to **5.15** did not appear readily accessible since its likely predecessor, 3,5-dihydroxypyridine, is not obtained easily. Regarding 2-substituted 3,4-pyridynes, the sulfamate was predicted to induce the greatest degree of distortion. Coupled with the notion that it was plausible for an appropriate silyltriflate to be accessed from commercially available dihydroxypyridine **5.17**, 2-sulfamoyl-pyridyne **5.16** was deemed a suitable target. Previously, sulfamates have not been used to direct aryne regioselectivities, but if successful, would offer a valuable means to functionalize the pyridine ring after an aryne reaction by exploiting modern Ni-catalyzed coupling methodologies.[33] Similarly, as demonstrated herein, the

bromide of pyridyne adducts may be strategically manipulated using conventional Pd-mediated transformations. Geometry-optimized structures of pyridyne targets **5.13** and **5.16**, obtained using DFT methods, are shown in Figure 5.5.

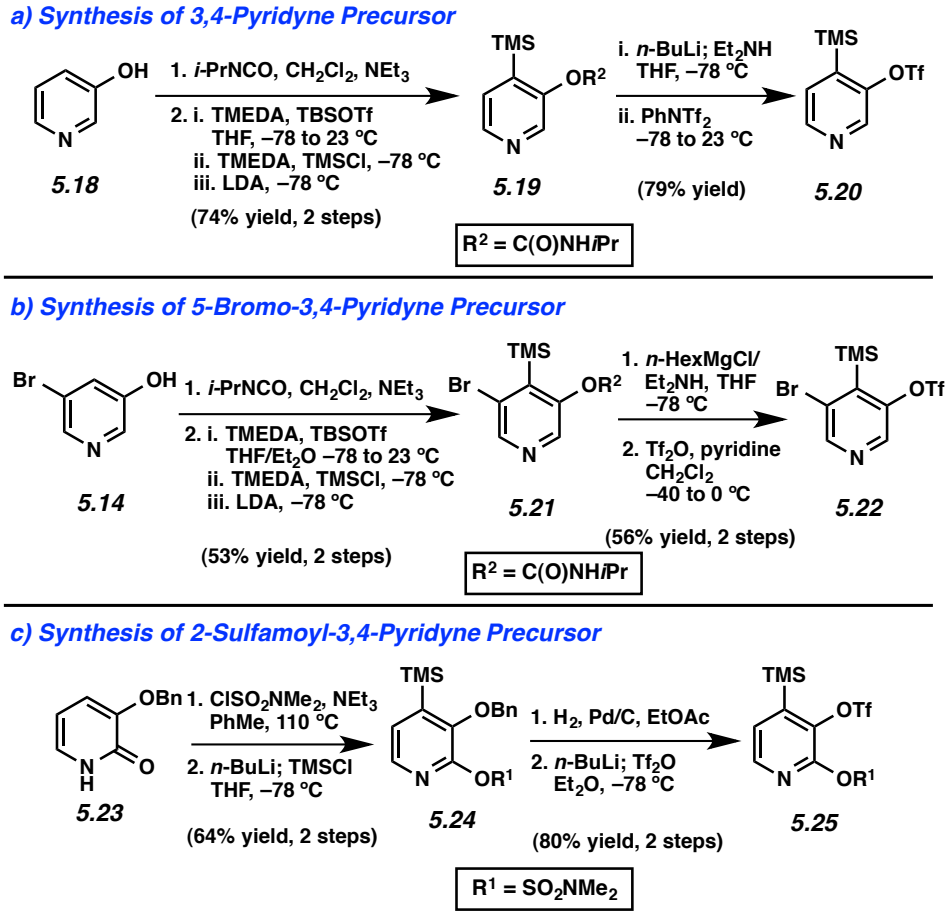
*Figure 5.5. Optimized Geometries of Pyridynes **5.13** and **5.16***




Robust syntheses of pyridylsilyltriflates **5.20**, **5.22**, and **5.25** were developed, as these compounds were expected to function as appropriate precursors to pyridynes **5.2**, **5.13**, and **5.16**, respectively (Scheme 5.1). Starting from commercially available 3-hydroxypyridine (**5.18**), carbamoylation followed by a C4-selective *o*-lithiation gave silylcarbamate **5.19** in 74% yield over 2 steps. A subsequent one-pot deprotection/triflation protocol[27] afforded silyltriflate **5.20** (Scheme 5.1a). This straightforward sequence provided the desired precursor to 3,4-pyridyne (**2**) in three steps and in >50% overall yield. Although regioselectivities in reactions of unsymmetrical arynes are not thought to be dependent upon the isomer of silyltriflate employed,[27,34–38] extensive efforts were made to synthesize the regioisomer of precursor **5.20**, where the positions of the triflate and trimethylsilyl groups are reversed. However, in accord with a previous report, we were unable to prepare this compound, presumably because of its instability[39] and the lability of C4-OR derivatives needed in our routes (e.g., R = TMS, C(O)NH*i*Pr).[40,41] Bromosilyltriflate **5.22** was synthesized using an analogous route starting from the commercially available bromohydroxypyridine **5.20**, although the conversion of **5.21** to **5.22** requires the use of a highly optimized two-step procedure (Scheme 5.1b). Finally, silyltriflate

**5.25** was synthesized from known benzylether **5.23** (see Section 5.8) using an efficient four-step sequence that involved sulfamoylation and C4 silylation (**5.23**→**5.24**), followed by deprotection and triflation (**5.24**→**5.25**) (Scheme 5.1c). Using these practical routes, gram quantities of silyltriflates **5.20**, **5.22**, and **5.25** are readily accessible.

*Scheme 5.1. Synthesis of 3,4-Pyridyne Precursors*



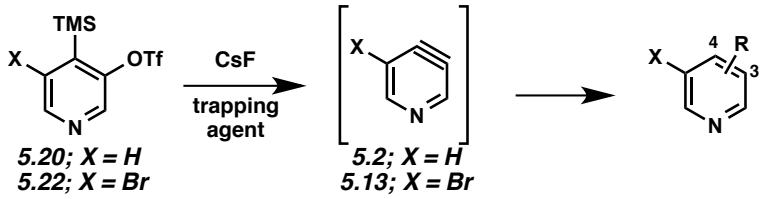

## 5.4 Nucleophilic Additions and Cycloaddition Reactions of 3,4-Pyridynes

To assess the influence of the C5 bromide substituent on 3,4-pyridyne regioselectivities, a comparative study involving pyridynes **5.2** and **5.13** was undertaken (Table 5.1). Consistent with computations and previous studies of 3,4-pyridynes, reactions involving **5.2** proceeded with

modest regioselectivity across a range of nucleophilic trapping agents[42] and cycloaddition partners (entries 1, 3, 5, 7, and 9). Nucleophilic addition at C4 was slightly favored in all cases. In comparison, reactions of the 5-bromo-3,4-pyridyne (**5.13**) uniformly gave improved degrees of regioselectivity with a reversal in selectivity favoring addition at C3. Use of *N*-methylaniline gave a mixture of C3 and C4 adducts in a 5.8:1 ratio (entry 2). Similarly, a 2.9:1 ratio of adducts, which again favored C3, was obtained when morpholine was employed as the trapping reagent (entry 4). Several formal cycloadditions were also tested. Whereas unsubstituted pyridyne **5.2** reacted with 1,3-dimethyl-2-imidazolidinone (DMI)[36] to give a 2.1:1 mixture of isomeric products favoring C4 addition (entry 5), the use of bromopyridyne **5.13** exclusively yielded the isomer indicative of initial C3 addition (entry 6). When *N-tert*-butyl-α-phenylnitrone (entry 8)[43,44] and 2-methoxyfuran (entry 10) were used to trap **5.13**, 3.3:1 and 1.7:1 ratios of product were obtained, respectively, with C3 being favored in both cases. It should be noted that in the latter two cycloaddition reactions, the major products presumably arise from transition states that possess significant steric encumbrances. Consequently, the bromine's influence on aryne distortion and regioselectivity likely arises from electronic considerations, rather than from steric factors.

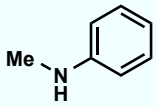
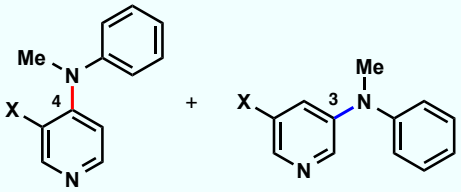
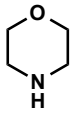
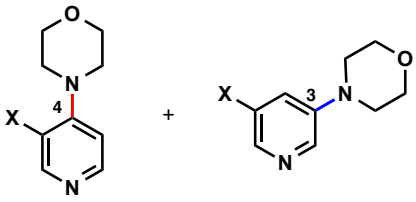
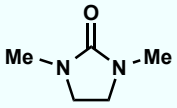
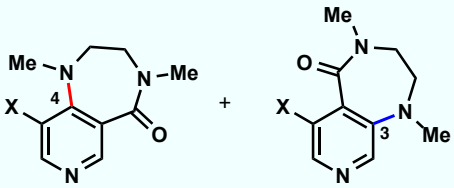
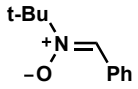
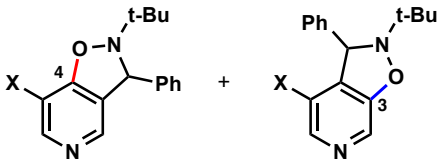
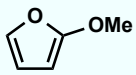
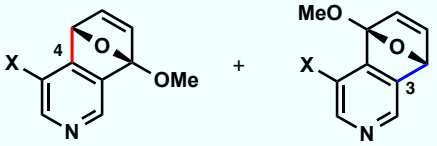
To further probe this notion, we compared bromopyridyne **5.13** with its 5-chloro analogue. Despite a previous example where a 5-Cl substituent minimally perturbed regioselectivity in a 3,4-pyridyne cycloaddition,[13] we found that the chloride governed regioselectivities in reactions with morpholine and *N-tert*-butyl-α-phenylnitrone (see Figure 5.7 in section 5.8). Selectivities were found to be more pronounced compared to those seen in reactions with bromopyridyne **5.13**, which is in agreement with the predictions shown in Figure 5.3 based on the aryne distortion model.

*Table 5.1.*[a] *Reactions of 5-Bromo-3,4-Pyridyne* ***5.13***




*5.20; X = H*
*5.22; X = Br*

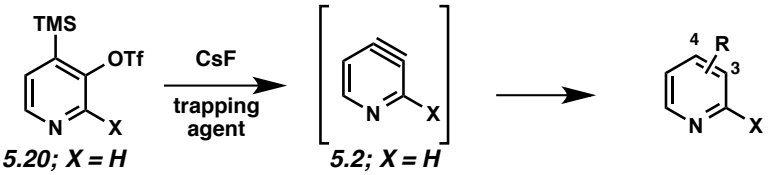
*5.2; X = H*
*5.13; X = Br*

| entry | trapping agent | products | ratio (yield)[b] |
|---|---|---|---|
| 1<br>2 |  |  | *X = H*<br>*1.9 : 1*<br>*(77% yield)*<br><br>*X = Br*<br>*1 : 5.8*<br>*(64% yield)* |
| 3<br>4 |  |  | *X = H*<br>*1.3 : 1*<br>*(73% yield)*<br><br>*X = Br*<br>*1 : 2.9*<br>*(64% yield)* |
| 5<br>6 |  |  | *X = H*<br>*2.1 : 1*<br>*(68% yield)*[c]<br><br>*X = Br*<br>*C3 only*<br>*(72% yield)* |
| 7<br>8 |  |  | *X = H*<br>*1.9 : 1*<br>*(76% yield)*<br><br>*X = Br*<br>*1 : 3.3*<br>*(60% yield)* |
| 9<br>10 |  |  | *X = H*<br>*1.3 : 1*<br>*(64% yield)*[d]<br><br>*X = Br*<br>*1 : 1.7*<br>*(68% yield)*[c] |

[a] See Section 5.8 for details; [b] Yields are isolated yields unless otherwise noted. Ratios refer to amount of C4:C3 products; [c] Yield by $^1$H NMR using external standard; [d] This Diels–Alder cycloadduct readily underwent isomerization to the corresponding isoquinoline; yield refers to the isolated yield of the isoquinoline (see Section 5.8 for details).

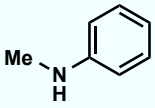
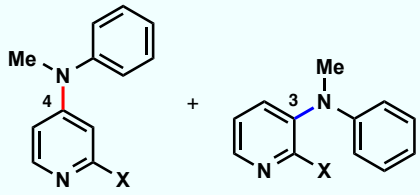
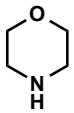
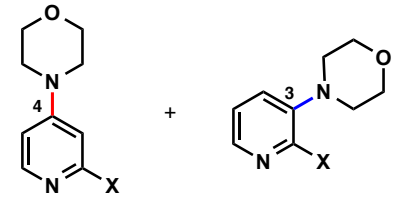
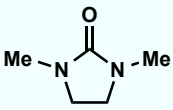
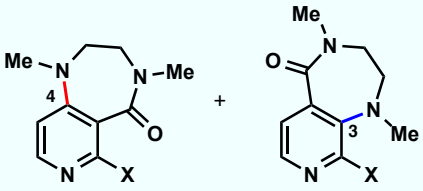
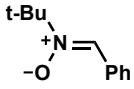
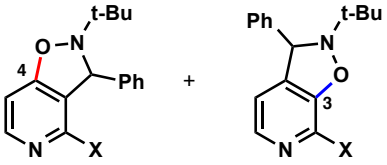
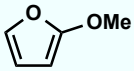
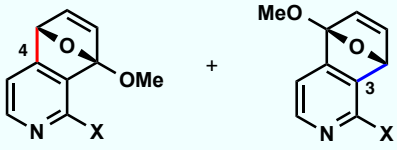
Sulfamoylpyridyne **5.16** was next tested in nucleophilic additions and cycloaddition reactions (Table 5.2). In comparison with unsubstituted pyridyne **5.2**, sulfamate **5.16** was found to react with enhanced regioselectivity for addition to C4. For example, in the absence of the C2 sulfamate, addition of *N*-methylaniline gave a 1.9:1 mixture of C4:C3 adducts (entry 1), whereas the presence of the sulfamate led to an overwhelming preference for attack at C4 (entry 2). Similar results were seen in the addition of morpholine (entries 3 and 4). When DMI was employed to trap sulfamate **5.16**, we obtained a single isomer in 79% yield suggestive of an initial attack at C4 (entry 6). For comparison, only a 2.1:1 ratio of products was observed using pyridyne **5.2** (entry 5). *N-tert*-Butyl-α-phenylnitrone also displayed excellent selectivity for initial attack at C4 (entry 8), despite the steric burden encountered in the assumed transition state. Finally, the use of 2-methoxyfuran to trap sulfamoylpyridyne **5.16** led to a modest improvement in the preference for initial attack at C4 (entry 10), compared to the parent pyridyne **5.2** (entry 9).

*Table 5.2.*[a] *Reactions of 2-Sulfamoyl-3,4-Pyridyne* ***5.16***




*5.20; X = H*
*5.25; X = $OSO_2NMe_2$*

*5.2; X = H*
*5.16; X = $OSO_2NMe_2$*

| entry | trapping agent | products | ratio (yield)[b] |
|---|---|---|---|
| 1 |  |  | *X = H*<br>*1.9 : 1*<br>*(77% yield)* |
| 2 | | | *X = $OSO_2NMe_2$*<br>*>15 : 1*<br>*(64% yield)* |
| 3 |  |  | *X = H*<br>*1.3 : 1*<br>*(73% yield)* |
| 4 | | | *X = $OSO_2NMe_2$*<br>*12 : 1*<br>*(64% yield)* |
| 5 |  |  | *X = H*<br>*2.1 : 1*<br>*(68% yield)*[c] |
| 6 | | | *X = $OSO_2NMe_2$*<br>*C4 only*<br>*(79% yield)* |
| 7 |  |  | *X = H*<br>*1.9 : 1*<br>*(76% yield)* |
| 8 | | | *X = $OSO_2NMe_2$*<br>*10.7:1*<br>*(61% yield)* |
| 9 |  |  | *X = H*<br>*1.3 : 1*<br>*(64% yield)*[d] |
| 10 | | | *X = $OSO_2NMe_2$*<br>*1.8 : 1*<br>*(60% yield)*[c] |

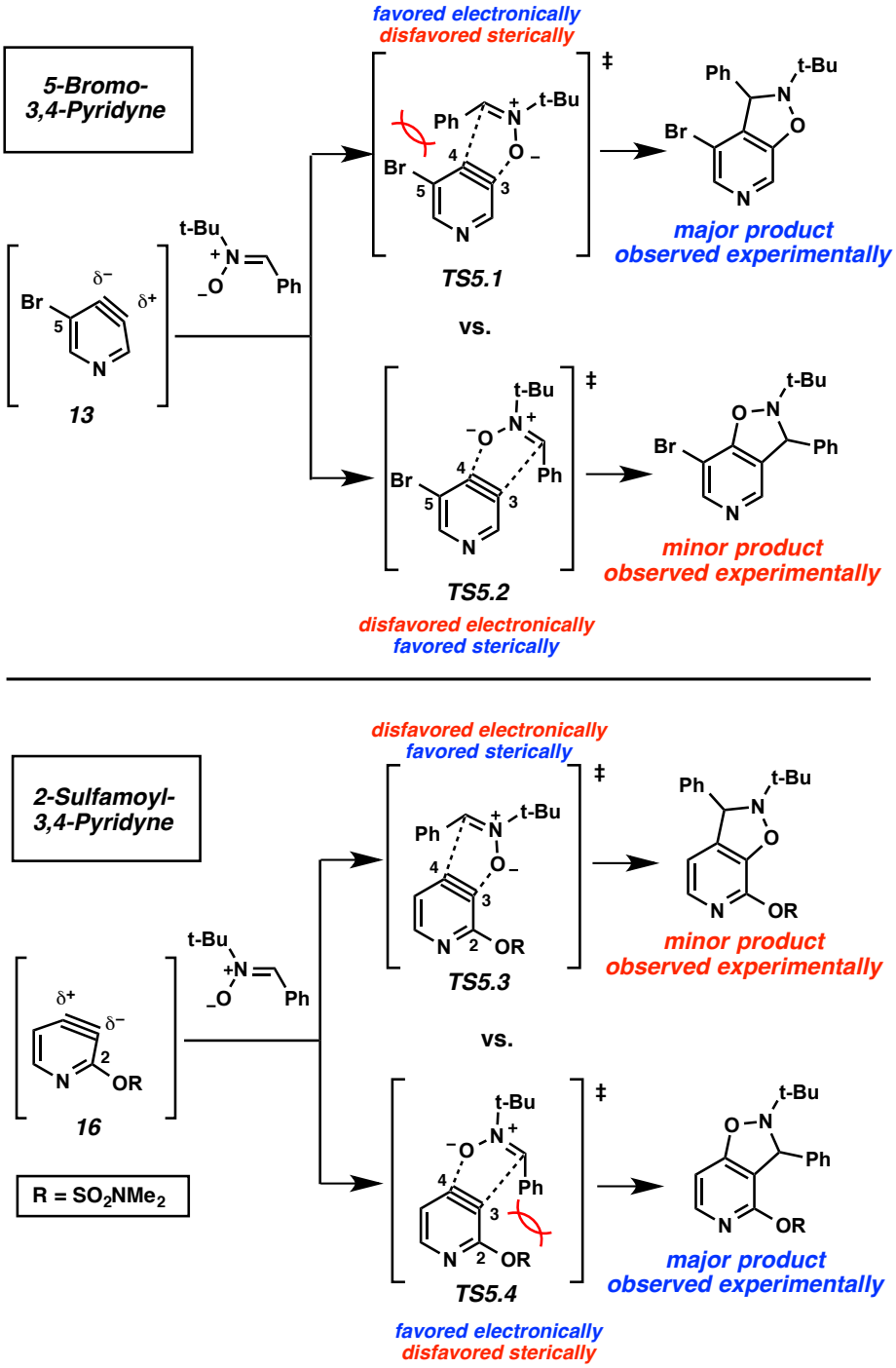
[a] See Section 5.8 for details; [b] Yields are isolated yields unless otherwise noted. Ratios refer to amount of C4:C3 products; [c] Yield by $^1$H NMR using external standard; [d] This Diels–Alder cycloadduct readily underwent isomerization to the corresponding isoquinoline; yield refers to the isolated yield of the isoquinoline (see Section 5.8 for details).

## 5.5 Explanation for the Observed Regioselectivities in Reactions of Substituted Pyridynes

Previously, it was suggested that aryne distortion governs regioselectivity in reactions of unsymmetrical arynes.[26] We surmise that this notion also holds for substituted 3,4-pyridynes, and that 5-bromo and 2-sulfamoyl substituents induce aryne distortion to favor attack by nucleophiles at C3 and C4, respectively. The origin of distortion and regioselectivity is believed to stem from an inductive effect imparted by electron-withdrawing substituents that can polarize the aryne triple bond in the manner suggested in Figure 5.6.

Although steric factors may contribute to the regioselectivities observed in nucleophilic additions to substituted 3,4-pyridynes, experimental results emphasize the importance of electronic considerations. Figure 5.6 shows the probable transition structures for the reactions between *N-tert*-butyl-α-phenylnitrone and pyridynes **5.13** and **5.16**, respectively. In each case, the major product arises from the electronically matched transition structures (i.e., **TS5.1** and **TS5.4**), despite these being more sterically encumbered than **TS5.2** and **TS5.3**, respectively. Thus, although steric considerations should be considered and may impact ratios of products, the electronic nature of these substituents appears to be the guiding factor in reactions of substituted 3,4- pyridynes.

*Figure 5.6. Comparison of Steric and Electronic Effects in Pyridyne Transition States*



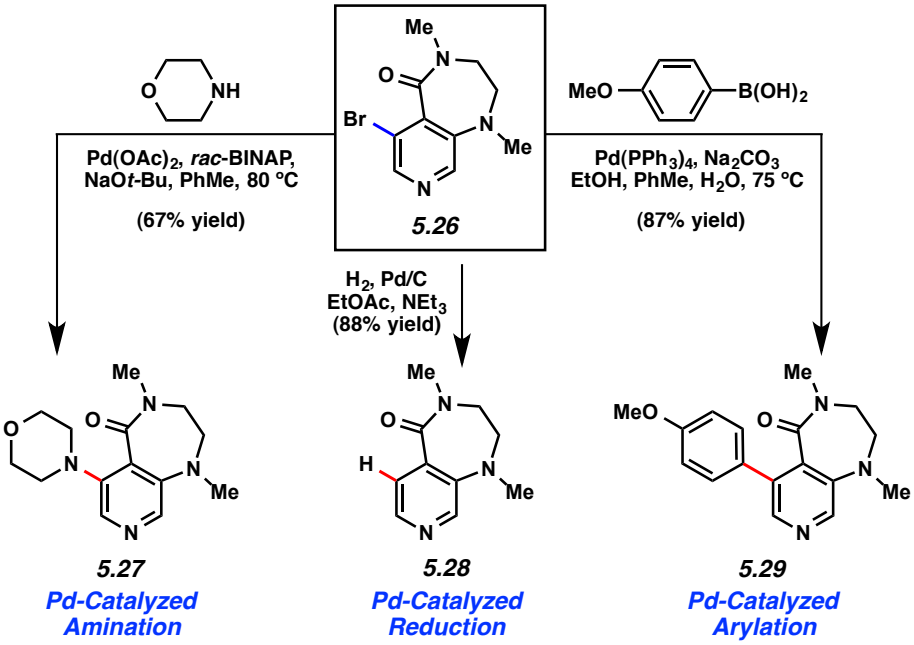
## 5.6 Derivatization of Pyridyne Adducts Using Pd- or Ni-Catalysis

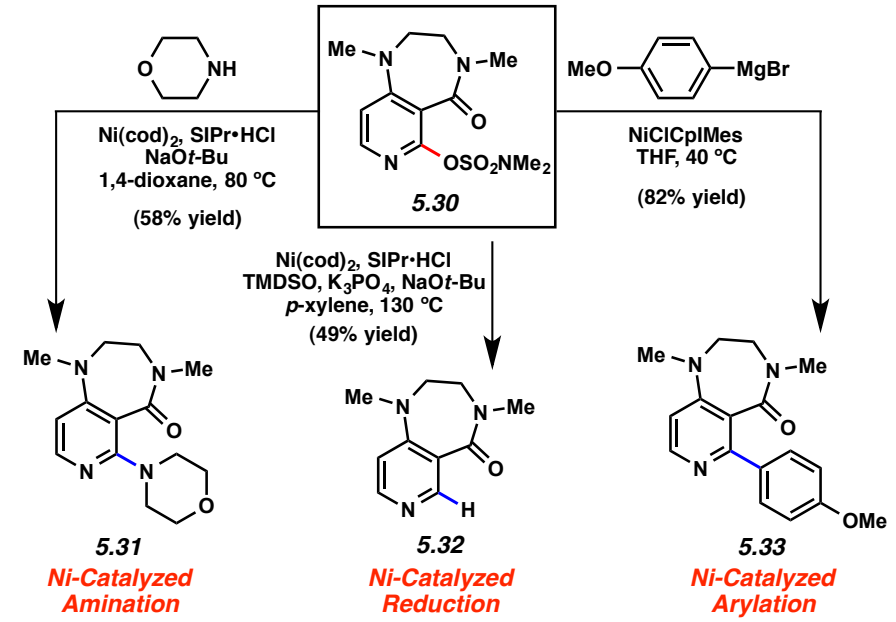
As shown in Scheme 5.2, the halide and sulfamoyl substituents can be removed or used as functional group handles for further elaboration. Bromide **5.26** and sulfamate **5.30**, each of which was accessed as a single regioisomer from its corresponding pyridyne precursor (see Table 5.1, entry 6 and Table 5.2, entry 6, respectively), were selected as the substrates for these studies. Structures **5.26** and **5.30** are reminiscent of the medicinally important benzodiazepines[45] and, therefore, serve as an ideal testing ground for bromide and sulfamate-based derivatization of pyridyne adducts.

Bromide **5.26** underwent smooth reaction using Pd catalysis to afford various analogues (Scheme 5.2). Buchwald–Hartwig amination gave the amine derivative **5.27** in 67% yield, whereas Suzuki–Miyaura coupling furnished the arylated product **5.29** in 87% yield. Additionally, it was found that the bromide could be removed under Pd-catalyzed hydrogenolysis conditions to deliver **5.28** in high yield.

We were also delighted to find that sulfamate **5.30** could be functionalized readily using Ni catalysis (Scheme 5.2). Sulfamate amination provided aminopyridine **5.31** in 58% yield.[46] Furthermore, a Ni-catalyzed Kumada–Corriu coupling[47] proceeded smoothly using the readily prepared, and bench-stable ($\eta^5$-$C_5H_5$)NiCl(1,3-dimesitylimidazol-2-ylidene) complex to give biaryl **5.33** in 82% yield. Finally, we found that the sulfamate could be removed under reductive conditions[48,49] to afford **5.32**, which marks the first example of reductive sulfamate cleavage. The straightforward manipulations of **5.26** and **5.30** demonstrate that: (a) using this methodology diverse arrays of highly substituted pyridine derivatives are accessible in a highly controlled fashion, and (b) the aryl sulfamate group may be readily manipulated through modern Ni-catalyzed coupling reactions, even when adorned with a complex heterocyclic system.

*Scheme 5.2. Derivatization of Adducts **5.26** and **5.30***



## 5.7 Conclusion

In summary, we have developed the first general method to govern 3,4-pyridyne regioselectivities. Our approach relies on the strategic use of bromide and sulfamate directing groups that can be removed or exploited as synthetic handles for further elaboration using transition metal catalysis. Using this methodology, unique di- and trisubstituted pyridine derivatives can be accessed with significant control of regiochemistry. These studies further validate the aryne distortion model and its predictive capabilities in gauging aryne regioselectivities. We expect our findings will promote the use of 3,4-pyridynes and other heterocyclic arynes in the synthesis of medicinally privileged molecular scaffolds.

## 5.8 Experimental Section

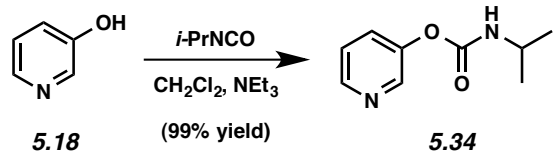
### 5.8.1 Materials and Methods

Unless stated otherwise, reactions were conducted in flame-dried glassware under an atmosphere of nitrogen using anhydrous solvents (either freshly distilled or passed through activated alumina columns). All commercially obtained reagents were used as received unless otherwise specified. Cesium fluoride (CsF), $NiCl_2(PCy_3)_2$, and $Ni(cod)_2$ were obtained from Strem Chemicals. sIPr·HCl was obtained from Aldrich. 3-Hydroxypyridine and 3-bromo-5-hydroxypyridine were obtained from Combi-Blocks, Inc. 2,3-Dihydroxypyridine was obtained from TCI America. Lithium diisopropylamide was obtained as a solid from Aldrich and stored and weighed inside a glovebox. 4-Methoxyphenylmagnesium bromide (4-OMePhMgBr) was purchased from Aldrich as a 0.5 M solution in THF. The following reagents were distilled over $CaH_2$ prior to use: chlorotrimethylsilane (TMSCl), tetramethylethylenediamine (TMEDA), pyridine, *N*-methylaniline, and 1,3-dimethyl-2-imidazolidinone (DMI); *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) was distilled neat prior to use. Diethylamine ($Et_2NH$) and was stirred over KOH for 1 h and then passed over basic Brockman Grade I 58 Å activated alumina prior to use. For aryne reactions, morpholine was stirred over KOH for 1 h, and then passed over neutral Brockman Grade I 58 Å activated alumina prior to use. For the Ni- and Pd-catalyzed amination reactions, morpholine was filtered over basic Brockman Grade I 58 Å activated alumina, distilled over $CaH_2$, and then degassed using freeze-pump-thaw methods before being stored in the glovebox. 1,4-Dioxane was distilled over Na/ketyl radical, and then degassed using freeze-pump-thaw methods before being stored in the glovebox. Toluene was passed through an activated alumina column and then degassed using freeze-pump-thaw methods before being stored in the glovebox. *n*-Pentane was dried over $MgSO_4$ prior to use. Reaction

temperatures were controlled using an IKAmag temperature modulator, and unless stated otherwise, reactions were performed at room temperature (rt, approximately 23 °C). Thin-layer chromatography (TLC) was conducted with EMD gel 60 F254 pre-coated plates (0.25 mm) and visualized using a combination of UV, anisaldehyde, iodine, vanillin, ninhydrin, and potassium permanganate staining. SiliCycle Siliaflash P60 (particle size 0.040–0.063 mm), J. T. Baker Florisil (60–100 mesh, particle size 0.149–0.20 mm), and ICN Biomedicals neutral alumina (Brockmann grade II–III, particle size 0.063–0.200 mm) were used for flash column chromatography. $^{1}$H NMR and 2D-NOESY spectra were recorded on Bruker spectrometers (at 300 MHz or 500 MHz) and are reported relative to deuterated solvent signals. Data for $^{1}$H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz) and integration. $^{13}$C NMR spectra were recorded on Bruker Spectrometers (at 75 or 125 MHz). Data for $^{13}$C NMR spectra are reported in terms of chemical shift, and when necessary, multiplicity, coupling constant (Hz) and carbon type. IR spectra were recorded on a Perkin-Elmer 100 spectrometer and are reported in terms of frequency of absorption ($cm^{-1}$). High resolution mass spectra were obtained from the UC Irvine Mass Spectrometry Facility and the UCLA Molecular Instrumentation Center. Melting points were determined using a MEL–TEMP II melting point apparatus. Images in Figures 5.1 and 5.5 and in Section 5.8.4 were created using CYLview.[50]

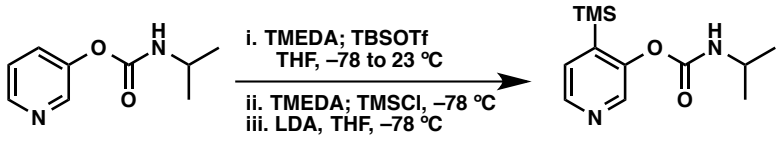
### 5.8.2 Preparative Procedures

#### 5.8.2.1 Synthesis of Pyridylsilyltriflates




*5.18* *5.34*

**Carbamate 5.34.** To a flask containing 3-hydroxypyridine (**5.18**, 0.996 g, 10.5 mmol) in $CH_2Cl_2$ (37 mL) was added triethylamine (300 μL, 2.16 mmol, 0.2 equiv) followed by isopropyl isocyanate (2.1 mL, 21.4 mmol, 2 equiv). The resulting solution was stirred for 2 h, then concentrated under reduced pressure to afford the crude product. Purification by flash chromatography (1.5:1 EtOAc:Hexanes) gave **5.34** (1.88 g, 99% yield) as a white solid. Mp: 67–69 ºC; $R_f$ 0.31 (1.5:1 EtOAc:Hexanes); $^1$H NMR (500 MHz, 45 ºC, $CDCl_3$): δ 8.44 (d, *J* = 2.0, 1H), 8.41 (d, *J* = 4.4, 1H), 7.54–7.38 (m, 1H), 7.26 (dd, *J* = 8.3, 4.4, 1H), 5.08 (br s, 1H) 3.96–3.80 (m, 1H), 1.23 (d, *J* = 6.6, 6H); $^{13}$C NMR (125 MHz, 45 ºC, $CDCl_3$): δ 152.7, 147.8, 145.9, 143.2, 128.9, 123.5, 43.5, 22.6; IR (film): 3244, 2972, 1729, 1530, 1220 cm$^{-1}$; HRMS-ESI (*m/z*) [M + Na]$^+$ calcd for $C_9H_{12}N_2O_2Na$, 203.0797; found, 203.0797.

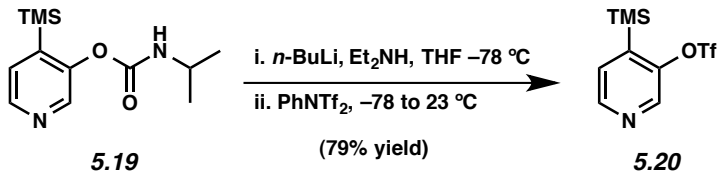



*5.34* *5.19*

(75% yield)

**Silyl carbamate 5.19.** Silyl carbamate **5.19** was prepared following the general procedure described by Hoppe and Snieckus for *o*-lithiation of isopropyl carbamates, with minor modifications.[51,52] To a solution of carbamate **5.34** (626.1 mg, 3.47 mmol) in THF (42 mL) at –

78 ºC was added TMEDA (770 μL, 5.17 mmol, 1.5 equiv), followed by TBSOTf (960 μL, 4.18 mmol, 1.2 equiv) as a 1.4 M solution in *n*-pentanes (3 mL). After 5 min, the reaction was allowed to warm to room temperature over 25 min. The reaction was then recooled to –78 ºC and TMEDA (1.7 mL, 11.41 mmol, 3.3 equiv) was added, followed by TMSCl (530 μL, 4.18 mmol, 1.2 equiv). After 5 min, LDA (928.9 mg, 8.67 mmol, 2.5 equiv) was added as a 1.2 M solution in THF (7.5 mL) dropwise over 25 min. The reaction was stirred at –78 ºC for 2.5 h and then quenched with 1 M aqueous $NaHSO_4$ and allowed to warm to room temperature. The reaction was diluted with $H_2O$ (50 mL) and EtOAc (40 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 x 50 mL). The combined organic layers were dried over $Na_2SO_4$ and evaporated under reduced pressure to give the crude product. This was further purified by flash chromatography (1.5:1 Hexanes:EtOAc) to give silylcarbamate **5.19** (653.5 mg, 75% yield) as a white solid. Mp: 106–108 ºC; $R_f$ 0.23 (1.5:1 Hexanes:EtOAc); $^1$H NMR (500 MHz, $CDCl_3$): δ 8.40 (d, *J* = 4.7, 1H), 8.39 (s, 1H), 7.33 (d, *J* = 4.6, 1H), 4.84 (d, *J* = 6.2, 1H), 3.92 (app. octet, *J* = 6.8, 1H), 1.25 (d, *J* = 6.5, 6H), 0.30 (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 153.3, 152.1, 145.3, 143.8, 141.9, 128.9, 43.8, 23.0, –1.3; IR (film): 3211, 2970, 1740, 1196 $cm^{-1}$; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{12}H_{21}N_2O_2Si$, 253.1372; found, 253.1380; $[M + Na]^+$ calcd for $C_{12}H_{20}N_2O_2SiNa$, 275.1192; found, 275.1199.



*5.19* *5.20*

**Pyridylsilyltriflate 5.20.** To a solution of silyl carbamate **5.19** (456.0 mg, 1.807 mmol) in THF (24 mL) at –78 °C was added a solution of *n*-BuLi in hexanes over 5 min (2.59 M, 830 μL, 2.15

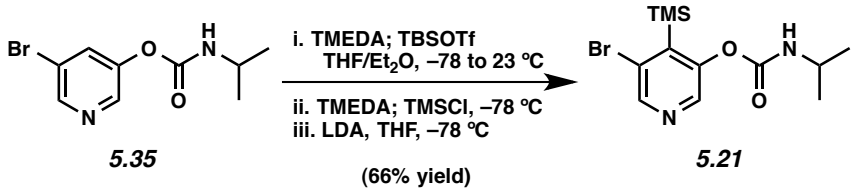
mmol, 1.2 equiv). After stirring for 2 min, diethylamine (225 μL, 2.17 mmol, 1.2 equiv) was added. After stirring for 10 min, $PhNTf_2$ (1.03 g, 2.88 mmol, 1.6 equiv) was added in a single portion, and the reaction stirred an additional 25 min at –78 °C. The reaction was then allowed to warm to room temperature over 25 min. Once warm, the reaction was diluted with saturated aqueous $NaHCO_3$ (15 mL) followed by $H_2O$ (5 mL) and EtOAc (20 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 x 25 mL). The combined organic layers were dried over $Na_2SO_4$. Evaporation of the solvent under reduced pressure afforded the crude product, which was further purified by flash chromatography (800:100:9 Hexanes:$Et_2O$:$NEt_3$) to afford **5.20** (426.0 mg, 79% yield) as a light tan oil. $R_f$ 0.19 (90:10:1 Hexanes:$Et_2O$:$NEt_3$); $^1H$ NMR (500 MHz, $CDCl_3$): δ 8.59 (s, 1H), 8.56 (d, $J$ = 4.7, 1H), 7.44 (dd, $J$ = 4.6, 0.6, 1H), 0.40 (s, 9H); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 152.1, 148.1, 143.3, 141.2, 130.3, 118.6 (q, $J$ = 318, $CF_3$), –1.2; IR (film): 2961, 1401, 1207, 1136 $cm^{-1}$; HRMS-ESI (*m/z*) [M + H]$^+$ calcd for $C_9H_{13}NO_3F_3SSi$, 300.0338; found, 300.0334.



*5.14* *5.35*

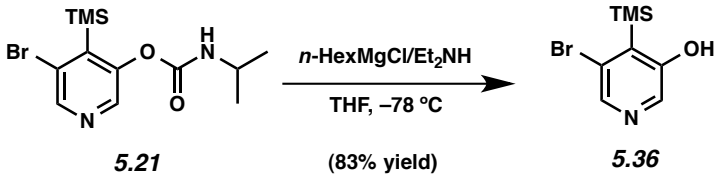
**Bromocarbamate 5.35.** To a flask containing 3-bromo-5-hydroxypyridine (**5.14**, 3.0 g, 17.2 mmol) in $CH_2Cl_2$ (58 mL) was added triethylamine (500 μL, 3.60 mmol, 0.2 equiv) followed by isopropyl isocyanate (2.5 mL, 25.5 mmol, 1.5 equiv). The resulting solution was stirred for 17.5 h, then concentrated under reduced pressure to afford the crude product. Purification by flash chromatography (3:1 Hexanes:EtOAc) gave **5.35** (3.61 g, 81% yield) as a white solid. Mp: 94–97 ºC; $R_f$ 0.23 (3:1 Hexanes:EtOAc); $^1H$ NMR (500 MHz, $CDCl_3$): δ 8.50 (d, $J$ = 1.8, 1H), 8.38 (d, $J$

= 2.2, 1H), 7.76 (app. t, $J$ = 2.1, 1H), 4.93 (br s, 1H), 3.89 (m, 1H), 1.25 (d, $J$ = 6.6, 6H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 152.4, 147.9, 147.2, 141.6, 132.3, 119.9, 43.9, 22.9; IR (film): 3334, 2975, 1711, 1526, 1226 cm$^{-1}$; HRMS-ESI ($m/z$) [M + H]$^+$ calcd for $C_9H_{12}N_2O_2Br$, 259.0082; found, 259.0076.



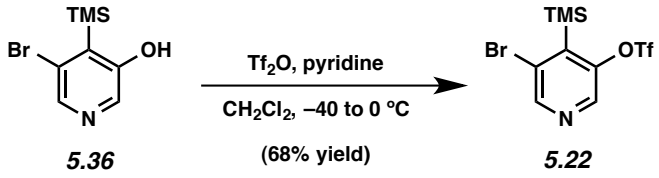

**Bromosilylcarbamate 5.21.** Silyl carbamate **5.21** was prepared following the general procedure described by Hoppe and Snieckus for *o*-lithiation of isopropyl carbamates, with minor modifications.[51,52] To a solution of bromocarbamate **5.35** (499.6 mg, 1.93 mmol) in a mixture of THF (17.5 mL) and $Et_2O$ (8.5 mL) at –78 ºC were added TMEDA (400 μL, 2.68 mmol, 1.4 equiv) followed by TBSOTf (530 μL, 2.31 mmol, 1.2 equiv) as a 1.4 M solution in *n*-pentane (1.6 mL). After 5 min, the reaction was allowed to warm to room temperature over 30 min. During this time, to a separate vial containing *i*-$Pr_2NH$ (980 μL, 6.94 mmol, 3.6 equiv) in THF (5.8 mL) at –78 ºC was added *n*-BuLi (2.52 M in Hexanes, 2.6 mL, 6.55 mmol, 3.4 equiv) dropwise over 5 min. The LDA was stirred for 5 min and then allowed to warm to room temperature. The flask containing carbamate **5.35** was recooled to –78 ºC and TMEDA (1.0 mL, 6.71 mmol, 3.5 equiv) was added. The LDA solution was then added dropwise to the flask containing the carbamate at –78 ºC over 40 min. After allowing the solution of carbamate **5.35** stir at –78 ºC for 4 h, TMSCl (295 μL, 2.32 mmol, 1.2 equiv) was added dropwise over 7 min. The mixture was stirred at –78 ºC for an additional 1.5 h, and then quenched with 1M aqueous $NaHSO_4$ (20 mL) and allowed to warm to room temperature. Once warm, the reaction was

diluted with $H_2O$ (20 mL) and EtOAc (25 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 x 40 mL). The combined organic layers were dried over $Na_2SO_4$. Evaporation under reduced pressure afforded the crude product, which was further purified using flash chromatography (6:1 Hexanes:EtOAc) to give **5.21** (423.8 mg, 66% yield) as a white solid. Mp: 78–81 ºC; $R_f$ 0.16 (6:1 Hexanes:EtOAc); $^1$H NMR (500 MHz, $CDCl_3$): δ 8.50 (s, 1H), 8.25 (s, 1H), 4.85 (d, *J* = 7.5, 1H), 3.89 (m, 1H), 1.25 (d, *J* = 6.6, 6H), 0.44 (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 153.2, 151.9, 148.7, 143.0, 142.6, 127.4, 43.9, 23.0, 1.1; IR (film): 3310, 2978, 1706, 1541, 1227 cm$^{-1}$; HRMS-ESI (*m/z*) [M + Na]$^+$ calcd for $C_{12}H_{19}N_2O_2BrSiNa$, 353.0297; found, 353.0299.

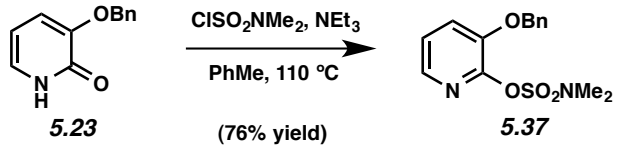



**Bromohydroxypyridine 5.36.** A flask containing a solution of carbamate **5.21** (1.86 g, 5.61 mmol) in THF (56 mL) was cooled to –78 ºC. In a separate vial, to a solution of diethylamine (1.56 mL, 15.08 mmol, 2.7 equiv) in THF (15.1 mL) at –78 ºC was added *n*-HexMgCl (1.5 M in THF, 9.75 mL, 14.63 mmol, 2.6 equiv) dropwise over 10 min. The vial containing the diethylamine/Grignard mixture was allowed to warm to room temperature over 12 min, and then added dropwise to the flask containing carbamate **5.21** over 8 min. The reaction was allowed to stir at –78 ºC for 100 min and then quenched with brine (17 mL) and warmed to room temperature. The reaction was diluted with $H_2O$ (20 mL), and EtOAc (20 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 25 mL). The combined organic layers were dried over $Na_2SO_4$. Evaportation under reduced pressure afforded the crude product

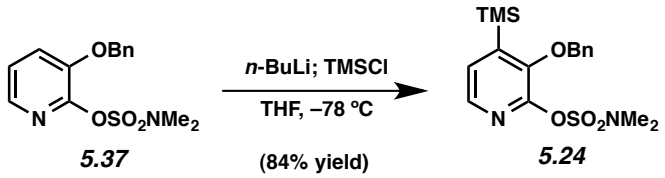
which was further purified by flash chromatography (2.5 :1 Hexanes:EtOAc) to give **5.36** (1.14 g, 83% yield). $R_f$ 0.21 (2.5:1 Hexanes:EtOAc); $^1$H NMR (500 MHz, $CDCl_3$): δ 9.85 (br s, 1H), 8.16 (s, 1H), 8.07 (s, 1H), 0.48 (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 160.5, 141.6, 138.3, 133.5, 128.8, 1.6; IR (film): 2958, 2627, 1571, 1402, 1248 cm$^{-1}$; HRMS-ESI (*m/z*) [M + H]$^+$ calcd for $C_8H_{13}BrNOSi$, 245.9950; found, 245.9955.




**Bromosilyltriflate 5.22.** To a solution of hydroxypyridine **5.36** (274.5 mg, 1.12 mmol) in $CH_2Cl_2$ (10 mL) at –40 ºC was added $Tf_2O$ (230 μL, 1.37 mmol, 1.2 equiv) followed by pyridine (360 μL, 4.46 mmol, 4 equiv). The reaction was stirred for 5 min and then placed in a 0 ºC bath. After stirring at 0 ºC for 5 min, a 5% aqueous solution of $NaHCO_3$ (5 mL) was added and the reaction was allowed to warm to room temperature. The reaction was further diluted with $H_2O$ (5 mL) and $CH_2Cl_2$ (5 mL). The layers were separated, and the aqueous layer was extracted with $CH_2Cl_2$ (3 x 10 mL). The combined organic layers were dried over $Na_2SO_4$. Evaporation of the solvent under reduced pressure afforded the crude product, which was further purified by flash chromatography (25:1 Hexanes:$Et_2O$) to afford **5.22** (290.1 mg, 68% yield) as a colorless oil. $R_f$ 0.75 (3:1 Hexanes:EtOAc); $^1$H NMR (500 MHz, $CDCl_3$): δ 8.67 (s, 1H), 8.50 (s, 1H), 0.54 (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 151.6, 150.6, 143.9, 140.6, 128.4, 118.7 (q, $J$ = 319, $CF_3$), 1.0; IR (film): 2963, 1428, 1392, 1207, 1193 cm$^{-1}$; HRMS-ESI (*m/z*) [M + H]$^+$ calcd for $C_9H_{12}BrNO_3F_3SSi$, 377.9443; found, 377.9436.

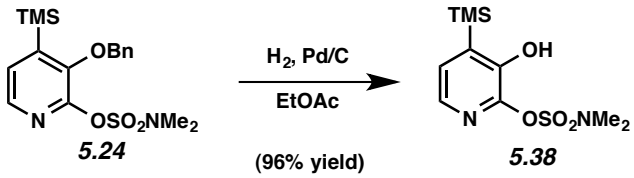



**Pyridyl sulfamate 5.37**. To a solution of benzylether **5.23** (5.04 g, 25.1 mmol), which was prepared following the procedure of Meunier et al[53], in toluene (50 mL) was added triethylamine (4.5 mL, 32.4 mmol, 1.3 equiv) followed by *N*,*N*-dimethylsulfamoyl chloride (3.5 mL, 32.9 mmol, 1.3 equiv). The flask was topped with a water condenser and the system placed under $N_2$. The reaction was heated to reflux and stirred for 15 h. After cooling, the reaction mixture was concentrated under reduced pressure, and then diluted with EtOAc (200 mL), brine (75 mL), and $H_2O$ (100 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 x 150 mL). The combined organic layers were then dried over $Na_2SO_4$. Evaporation under reduced pressure afforded the crude product, which was further purified by flash chromatography (2:1 Hexanes:EtOAc) to give **5.37** (5.88 g, 76% yield) as a white solid. Mp: 47–49 ºC; $R_f$ 0.22 (2.5:1 Hexanes:EtOAc); $^1$H NMR (500 MHz, $CDCl_3$): δ 7.91 (dd, *J* = 4.8, 1.4, 1H), 7.45 (d, *J* = 7.3, 2H), 7.38 (app. t, *J* = 7.4, 2H), 7.33 (app. t, *J* = 7.3, 1H), 7.30 (dd, *J* = 8.0, 1.3, 1H), 7.15 (dd, *J* = 8.0, 4.8, 1H), 5.17 (s, 2H), 3.03 (s, 6H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 147.6, 146.2, 138.7, 135.8, 128.8, 128.4, 127.5, 123.3, 122.9, 71.1, 38.9; IR (film): 2937, 1439, 1375, 1157 cm$^{-1}$; HRMS-ESI (*m*/*z*) $[M + H]^+$ calcd for $C_{14}H_{17}N_2O_4S$, 309.0909; found, 309.0908.



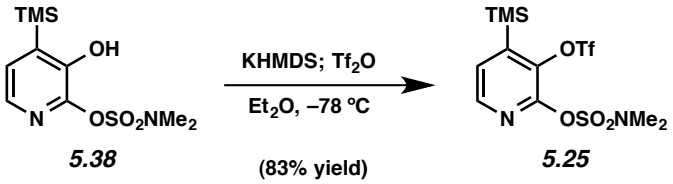

**Trimethylsilyl pyridine 5.24**. Trimethylsilyl pyridine **5.24** was prepared using a modification of the procedure reported by Quéguiner et al. for the lithiation of 2,3-dialkoxypyridines.[54] To a

solution of **5.37** (1.44 g, 4.67 mmol) in THF (52 mL) at –78 ºC was added a solution of *n*-BuLi in hexanes (2.46 M, 4.0 mL, 9.84 mmol, 2.1 equiv) dropwise over 10 min. After 10 min, TMSCl (1.2 mL, 9.46 mmol, 2 equiv) was added dropwise over 10 min. The reaction was stirred at –78 ºC for 90 min and then quenched with aqueous 1 M $NaHSO_4$ (12 mL) and allowed to warm to room temperature with continuous stirring. Once warm, the reaction was further diluted with $H_2O$ (40 mL) and EtOAc (60 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 x 70 mL). The combined organic layers were dried over $Na_2SO_4$. Evaporation under reduced pressure afforded the crude product, which was further purified by flash chromatography (4:1 Hexanes:EtOAc) to give **5.24** (1.49 g, 84% yield) as a white solid. Mp: 72–75 ºC; $R_f$ 0.35 (4:1 Hexanes:EtOAc); $^1$H NMR (500 MHz, $CDCl_3$): δ 8.03 (d, *J* = 4.6, 1H), 7.49 (app. d, *J* = 7.3, 2H), 7.42–7.37 (m, 2H), 7.36–7.31 (m, 1H), 7.22 (d, *J* = 4.6, 1H), 5.17 (s, 2H), 3.01 (s, 6H), 0.25 (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 149.9, 149.2, 146.6, 141.1, 136.9, 128.6, 128.2, 128.1, 128.0, 75.2, 38.8, –0.9; IR (film): 2923, 1402, 1370, 1160 cm$^{-1}$; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{17}H_{24}N_2O_4SSi$, 381.1304; found, 381.1304.



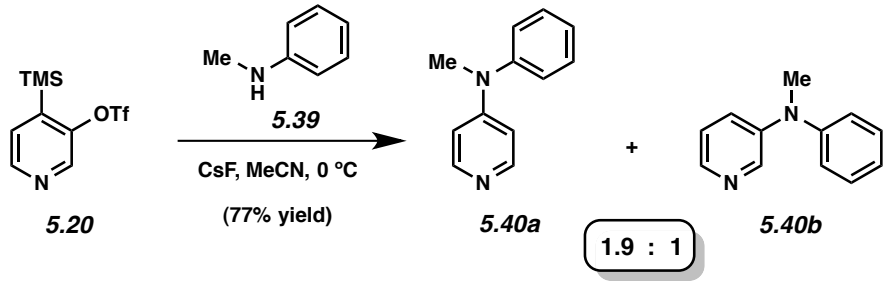

**Hydroxypyridine 5.38.** To a solution of benzylether **5.24** (2.34 g, 6.15 mmol) in EtOAc (61 mL), was added 10% Pd/C (50% wetted powder) (663.4 mg, 0.312 mmol, 5 mol%). The reaction was placed under an atmosphere of $H_2$, and the system evacuated/backfilled with $H_2$ a total of 5 times. After stirring under $H_2$ for 75 min, the reaction was evacuated and backfilled with $N_2$, and filtered over Celite (EtOAc eluent). Evaporation under reduced pressure gave the desired

product, which was further purified by flash chromatography (4:1 Hexanes:EtOAc) to give **5.38** (1.72 g, 96% yield) as a white solid. Mp: 58–60 ºC; $R_f$ 0.34 (4:1 Hexanes:EtOAc); $^1$H NMR (500 MHz, $CDCl_3$): δ 7.84 (d, *J* = 4.6, 1H), 7.20 (d, *J* = 4.6, 1H), 6.36 (br s, 1H), 3.05 (s, 6H), 0.32 (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 147.6, 144.8, 140.1, 138.4, 129.1, 38.9, –1.5; IR (film): 3432, 2953, 1406, 1377, 1158 $cm^{-1}$; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{10}H_{19}N_2O_4SSi$, 291.0835; found, 291.0833.

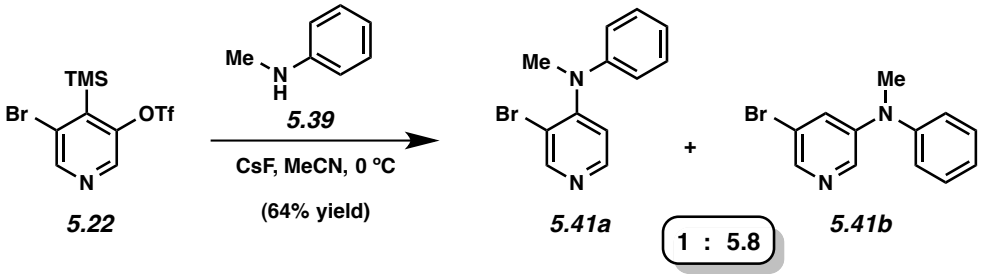



**Sulfamoylsilyltriflate 5.25.** To a solution of hydroxypyridine **5.38** (1.27 g, 4.37 mmol) in $Et_2O$ (60 mL) at –78 ºC was added a solution of KHMDS (1.2 g, 6.02 mmol, 1.4 equiv) in $Et_2O$ (6 mL) dropwise over 8 min. After 5 min, $Tf_2O$ (1.1 mL, 6.55 mmol, 1.5 equiv) was added dropwise over 4 min. After 20 min, the reaction was quenched with 5% aqueous $NaHCO_3$ (10 mL) and warmed to room temperature. The mixture was diluted with $H_2O$ (20 mL) and $Et_2O$ (50 mL). The layers were separated, and the aqueous layer was extracted with $Et_2O$ (2 x 50 mL). The combined organic layers were dried over $Na_2SO_4$. Evaporation under reduced pressure afforded the crude product, which was further purified by flash chromatography (4 :1 Hexanes:EtOAc) to give **5.25** as a white solid (1.54 g, 83% yield). Mp: 56–59 ºC; $R_f$ 0.36 (4:1 Hexanes:EtOAc); $^1$H NMR (500 MHz, $CDCl_3$): δ 8.26 (d, *J* = 4.5, 1H), 7.31 (d, *J* = 4.5, 1H), 3.08 (s, 6H), 0.42 (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 149.8, 149.1, 145.7, 133.1, 128.0, 118.6 (q, *J* = 319, $CF_3$), 38.7, –0.7; IR: (film) 2957, 1419, 1385, 1177, 1128 $cm^{-1}$; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{11}H_{18}F_3N_2O_6S_2Si$, 423.0328; found, 423.0330.

### 5.8.2.2 Reactions of 3,4-Pyridynes

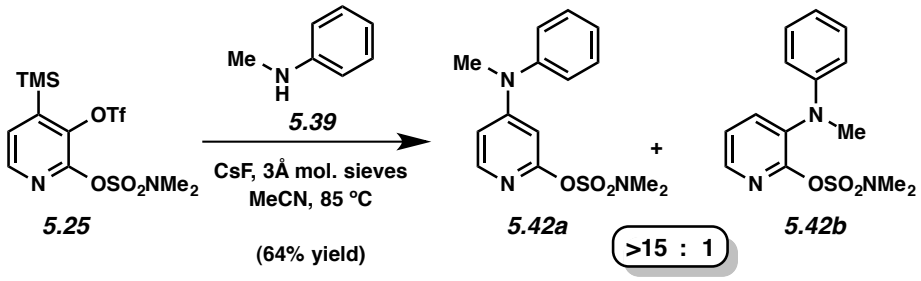



**Diaryl amines 5.40a and 5.40b.** To a stirred solution of silyltriflate **5.20** (29.2 mg, 0.097 mmol) and *N*-methyl aniline (**5.39**, 42 μL, 0.388 mmol, 4 equiv) in MeCN (1.1 mL) at 0 °C was added CsF (49.0 mg, 0.323 mmol, 3.3 equiv). The reaction was stirred for 165 min and then filtered over silica gel (25:1 EtOAc:$NEt_3$ eluent). Evaporation under reduced pressure afforded the crude products in a ratio of 1.9 : 1 favoring **5.40a**. The crude products were further purified by flash chromatography (200:100:3 Hexanes:EtOAc:$NEt_3$→50:50:1 Hexanes:EtOAc:$NEt_3$) to provide amines **5.40a** (9.2 mg, 51% yield) and **5.40b** (4.7 mg, 26% yield). **5.40a:** $R_f$ 0.11 (50:50:1 Hexanes:EtOAc:$NEt_3$); **5.40b:** $R_f$ 0.26 (200:100:3 Hexanes:EtOAc:$NEt_3$). Spectral data for both isomers matched previously reported literature data.[55,56]



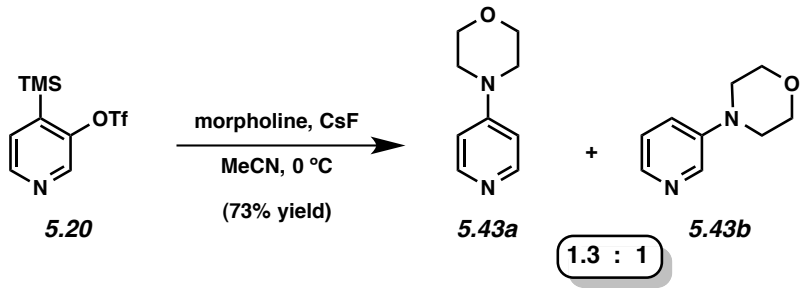

**Bromodiaryl amines 5.41a and 5.41b.** To a stirred solution of silyltriflate **5.22** (28.7 mg, 0.076 mmol) and *N*-methyl aniline (**5.39**, 33 μL, 0.305 mmol, 4 equiv) in MeCN (1.1 mL) at 0 °C was added CsF (36.9 mg, 0.243 mmol, 3.2 equiv). The reaction was stirred for 110 min and then

filtered over silica gel (25:1 EtOAc:$NEt_3$ eluent). Evaporation under reduced pressure afforded the crude products in a ratio of 5.8 : 1 favoring **5.41b**. The crude products were further purified by preparative TLC (4:1 Benzene:EtOAc) to provide amines **5.41b** (10.9 mg, 55% yield) and **5.41a** (1.8 mg, 9% yield). **5.41b:** Mp: 47–50 ºC; $R_f$ 0.50 (4:1 Benzene:EtOAc); $^1$H NMR (500 MHz, $CDCl_3$): δ 8.12 (d, *J* = 2.5, 1H), 8.09 (d, *J* = 1.8, 1H), 7.41–7.36 (m, 2H), 7.24 (app. t, *J* = 2.2, 1H), 7.21–7.14 (m, 3H), 3.32 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 147.1, 146.2, 140.5, 136.7, 130.1, 125.3, 124.7, 124.6, 120.7, 40.2; IR (film): 1744, 1567, 1493, 1446 $cm^{-1}$; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{12}H_{13}BrN_2$, 263.0184; found, 263.0186. **5.41a:** $R_f$ 0.33 (4:1 Benzene:EtOAc).

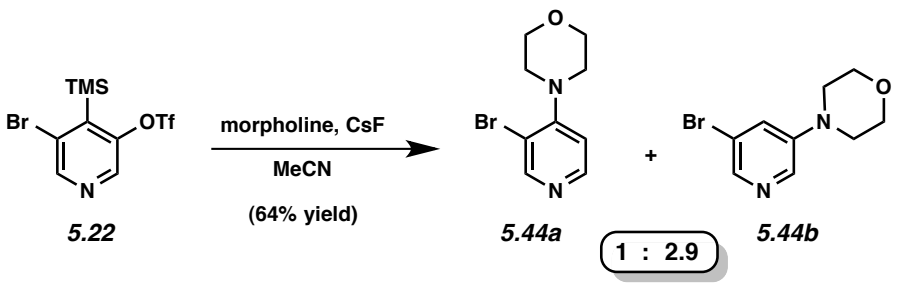



**Sulfamoyldiaryl amines 5.42a and 5.42b**. To a solution of silyltriflate **5.25** (23.4 mg, 0.055 mmol) and *N*-Me-aniline (**5.39**, 42 μL, 0.388 mmol, 7 equiv) in MeCN (0.5 ml) were added 3Å mol. sieves (~20 mg), followed by CsF (24.5 mg, 0.161 mmol, 2.9 equiv). The reaction was placed in a heating block maintained in 85 ºC. After 7 min, the reaction was cooled to room temperature and then filtered through a plug of celite ($Et_2O$ eluent). Evaporation under reduced pressure afforded the crude products in a ratio of >15 : 1 favoring **5.42a**. The crude products were further purified by flash chromatography (4:1 Hexanes:EtOAc, neutral alumina used as stationary phase) to give a >15 :1 mixture of amines **5.429a** and **5.42b** (10.8 mg, 64% yield). An analytical sample of **5.42a** was obtained by preparative TLC (3:1 Benzene:$Et_2O$). **5.42a:** $R_f$ 0.38

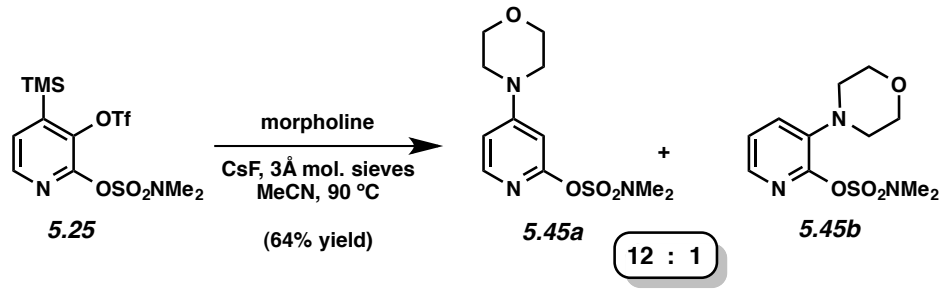
(3:1 Benzene:$Et_2O$); $^1H$ NMR (500 MHz, $C_6D_6$): δ 7.72 (d, *J* = 6.0, 1H), 6.98–6.93 (m, 2H), 6.89–6.85 (m, 1H), 6.63 (d, *J* = 7.6, 2H), 6.44 (d, *J* = 2.2, 1H), 6.02 (dd, *J* = 6.0, 2.2, 1H), 2.70 (s, 6H), 2.45 (s, 3H); $^{13}C$ NMR (125 MHz, $C_6D_6$): δ 159.9, 157.0, 147.7, 146.0, 130.1, 126.74, 126.68, 108.2, 99.3, 39.1, 38.5; IR (film): 1609, 1588, 1495, 1371, 1160 $cm^{-1}$; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{14}H_{18}N_3O_3S$, 308.1069; found, 308.1070. **5.42b:** $R_f$ 0.70 (3:1 Benzene:$Et_2O$).




**Morpholine adducts 5.43a and 5.43b.** To a stirred solution of silyltriflate **5.20** (31.4 mg, 0.105 mmol) and morpholine (36.5 μL, 0.419 mmol, 4 equiv) in MeCN (1.1 mL) at 0 ºC was added CsF (49.8 mg, 0.328 mmol, 3 equiv). The reaction was stirred at room temperature for 4.5 h and then diluted with $Et_2O$ (5 mL). The contents were extracted using 10% aqueous HCl (3 x 5 mL). The combined aqueous layers were then basicified to pH > 12 using 3 M NaOH. The product was extracted using $Et_2O$ (4 x 15 mL) and the combined organic layers dried over $Na_2SO_4$. Evaporation under reduced pressure afforded a 1.3 : 1 mixture of products **5.43a** and **5.43b** (C4 adduct major) (10.2 mg, 73% yield). Spectral data for **5.43a** and **5.43b** match those previously reported.[55]

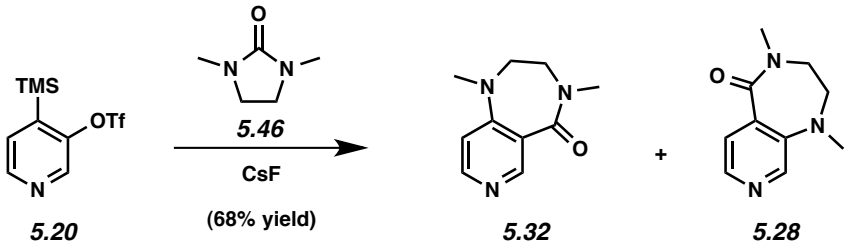



**Morpholine adducts 5.44a and 5.44b.** To a solution of bromosilyltriflate **5.22** (29.6 mg, 0.078 mmol) in MeCN (0.9 mL) was added morpholine (27.5 μL, 0.315 mmol, 4 equiv) followed by CsF (37.8 mg, 0.249 mmol, 3.2 equiv). The reaction was stirred for 90 min and then filtered through a silica plug (25:1 EtOAc:$NEt_3$ eluent). Evaporation under reduced pressure afforded the crude product (1:2.9 ratio of **5.44a:5.44b**), which was further purified by flash chromatography (75:25:1 Hexanes:EtOAc:$NEt_3$) to give a mixture of **5.44a** and **5.44b** (12.2 mg, 64% yield). An analytical sample of **5.44b** was obtained by prep TLC (200:100:3 Hexanes:EtOAc:$NEt_3$), and spectral data matched those previously reported.[57] **5.44a** $R_f$ 0.19 (200:100:3 Hexanes:EtOAc:$NEt_3$).




**Morpholine adducts 5.45a and 5.45b.** To a solution of sulfamoylsilyltriflate **5.25** (21.9 mg, 0.052 mmol) in MeCN (0.5 mL) were added 3Å mol. sieves (~20 mg) followed by morpholine (32 μL, 0.367 mmol, 7 equiv), and CsF (22.4 mg, 0.147 mmol, 2.8 equiv). The reaction was placed in a heating block at 90 ºC and stirred for 8 min. The reaction was allowed to cool to

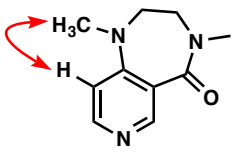
room temperature and filtered through a celite plug ($Et_2O$ eluent). Evaporation under reduced pressure afforded a mixture of the crude products. Purification by flash chromatography (2:1 Hexanes:EtOAc, neutral alumina used as the stationary phase) gave a 12 : 1 mixture of aminopyridines **5.45a** and **5.45b** (9.6 mg, 64% yield). An analytical sample of **5.45a** was obtained by preparative TLC (2:1 EtOAc:Hexanes). **5.45a**: $R_f$ 0.09 (2:1 Hexanes:EtOAc); $^1H$ NMR (500 MHz, $CDCl_3$): δ 8.03 (d, *J* = 6.1, 1H), 6.60 (dd, *J* = 6.1, 2.3, 1H), 6.48 (d, *J* = 2.2, 1H), 3.83 (app. t, *J* = 4.9, 4H), 3.31 (app. t, *J* = 4.9, 4H), 3.02 (s, 6H); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 159.3, 158.5, 148.4, 107.5, 98.6, 66.4, 46.3, 38.9; IR (film): 2854, 1603, 1372, 1155 $cm^{-1}$; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{11}H_{18}N_3O_4S$, 288.1018; found, 288.1017. **5.45b:** $R_f$ 0.20 (2:1 Hexanes:EtOAc).



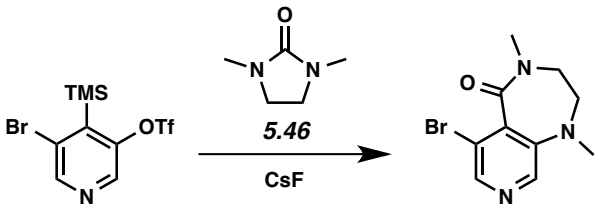

**Pyridyl amides 5.32 and 5.28.** To a solution of silyltriflate **5.20** (27.2 mg, 0.091 mmol) in 1,3-dimethyl-2-imidazolidinone (DMI, **5.46**, 200 μL, 1.86 mmol, 20 equiv) was added CsF (37.5 mg, 0.247 mmol, 2.7 equiv). After stirring for 130 min, the reaction was filtered through a plug of silica gel (9:1 $CHCl_3$:MeOH eluent). Evaporation under reduced pressure afforded the crude products. The yield was determined by $^1H$ NMR analysis of the crude reaction mixture using toluene (9.75 μL, 1 equiv based on **5.20**) as an external standard (68% yield, 2.1:1 ratio of **5.32**:**5.28**). The crude reaction mixture was placed under high vacuum until most of the DMI had been removed, and then purified by preparative TLC (200:1 EtOAc:MeOH) to give analytical

samples of **5.32** and **5.28**. **5.32:** Mp: 159–162 ºC; $R_f$ 0.27 (9:1 $CH_2Cl_2$:MeOH); $^1$H NMR (500 MHz, $CDCl_3$): δ 8.72 (s, 1H), 8.24 (d, *J* = 6.1, 1H), 6.65, (d, *J* = 6.2, 1H), 3.67–3.63 (m, 2H), 3.59–3.55 (m, 2H), 3.16 (s, 3H), 3.02 (s, 3H); $^{13}$C NMR (125MHz, $CDCl_3$): δ 167.8, 152.0, 151.3, 149.0, 119.1, 110.4, 57.2, 47.7, 40.3, 35.8; IR (film): 2919, 1630, 1586, 1516, 1212 cm$^{-1}$; HRMS-ESI (*m/z*) [M + H]$^+$ calcd for $C_{10}H_{14}N_3O$, 192.1137; found, 192.1130. **5.28:** Mp: 89–93 ºC; $R_f$ 0.19 (95:5 $CH_2Cl_2$:MeOH); $^1$H NMR (500 MHz, $CDCl_3$): δ 8.28 (s, 1H), 8.27 (d, *J* = 4.9, 1H), 7.54, (d, *J* = 4.9, 1H), 3.53–3.46 (m, 4H), 3.25 (s, 3H), 3.00 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 168.4, 141.8, 141.3, 139.7, 133.9, 123.2, 57.5, 47.9, 39.5, 34.8; IR (film): 2923, 1637, 1490, 1408, 1054 cm$^{-1}$; HRMS-ESI (*m/z*) [M + Na]$^+$ calcd for $C_{10}H_{13}N_3ONa$, 214.0956; found, 214.0955.

The structure of **5.32** was verified by NOESY, as the following interaction was observed:




***5.32***

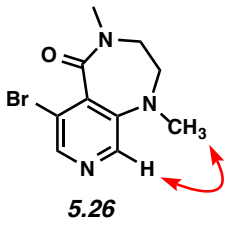



***5.22*** ***5.26***

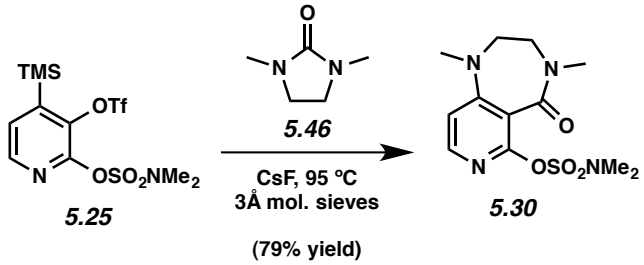
**Bromopyridyl amide 5.26.** To a solution of bromosilyltriflate **5.22** (28.5 mg, 0.075 mmol) in 1,3-dimethyl-2-imidazolidinone (DMI, **5.46**, 200 μL, 1.86 mmol, 25 equiv) was added CsF (28.4 mg, 0.187 mmol, 2.5 equiv). The reaction was stirred for 2.5 h and then filtered through a silica

plug (25:1 EtOAc:$NEt_3$). The crude reaction mixture was placed under high vacuum in order to remove the DMI. Once there was an approximately equimolar ratio of DMI:product (monitored by $^1H$ NMR), the crude material was purified by flash chromatography (2:1 $CH_2Cl_2$:EtOAc, Florisil used as the stationary phase) to give **5.26** as a white solid (14.6 mg, 72% yield). Mp: 201–205 ºC; $R_f$ 0.28 (2:1 $CH_2Cl_2$:EtOAc); $^1H$ NMR (500 MHz, $CDCl_3$): δ 8.39 (s, 1H), 8.15 (s, 1H), 3.46–3.40 (m, 2H), 3.28 (br s, 2H), 3.21 (s ,3H), 2.88 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 165.7, 146.0, 142.8, 138.6, 136.3, 118.6, 56.9, 47.7, 39.8, 33.8; IR (film): 2923, 1736, 1653, 1397 $cm^{-1}$; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{10}H_{12}N_3OBrNa$, 292.0061; found, 292.0060.

The structure of **5.26** was verified by NOESY, as the following interaction was observed:



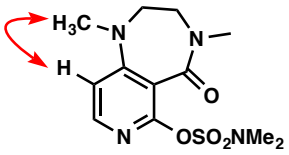

*5.26*



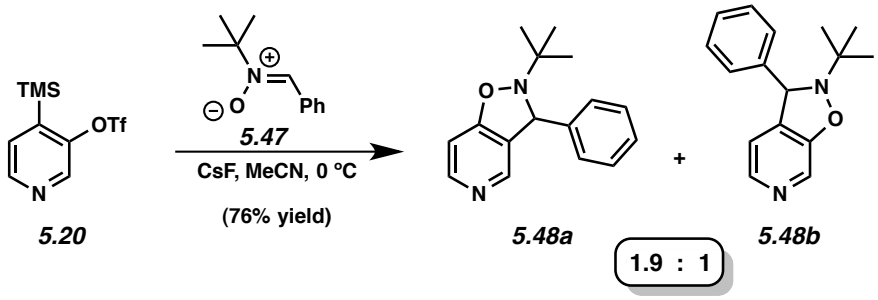

**Sulfamoylpyridyl amide 5.30.** To a solution of sulfamoyl silyltriflate **5.25** (384.5 mg, 0.910 mmol) in 1,3-dimethyl-2-imidazolidinone (DMI, **5.46**, 4 mL, 37.14 mmol, 41 equiv) were added 3Å mol. sieves (~380 mg) and CsF (345.4 mg, 2.27 mmol, 2.5 equiv). The reaction was placed in a heating block at 95 ºC and stirred for 5 min. The reaction was allowed to cool and then filtered

through a plug of celite (EtOAc eluent). The crude reaction mixture was placed under high vacuum to remove the DMI. Once most of the DMI had been removed, the crude material was purified by flash chromatography (200:100:3 EtOAc:Benzene:$NEt_3$ → 50:50:1 $CH_2Cl_2$:EtOAc:$NEt_3$) to give **5.30** as a white solid (224.9 mg, 79% yield). Mp: 124–128 ºC; $R_f$ 0.16 (50:50:1 $CH_2Cl_2$:EtOAc:$NEt_3$); $^1$H NMR (500 MHz, $CDCl_3$): δ 8.10 (d, *J* = 5.8, 1H), 6.63 (d, *J* = 5.9, 1H), 3.55 (app. t, *J* = 5.2, 2H), 3.44 (app. t, *J* = 5.2, 2H), 3.15 (s, 3H), 3.01 (s, 6H), 2.88 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 165.1, 156.1, 155.1, 148.9, 113.3, 111.0, 56.6, 47.0, 39.9, 38.9, 34.1; IR (film): 2924, 1652, 1596, 1374, 1168 cm$^{-1}$; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{12}H_{19}N_4O_4S$, 315.1127; found, 315.1125.

The structure of **5.30** was verified by NOESY, as the following interaction was observed:



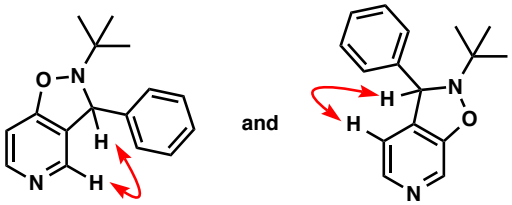

***5.30***



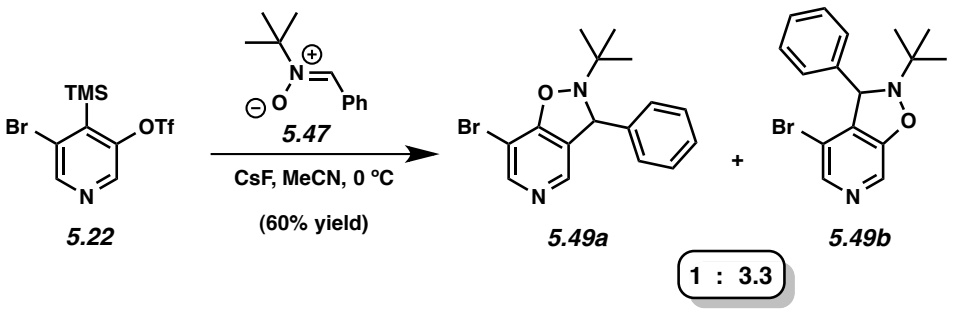

**Isoxazolines 5.48a and 5.48b.** To a solution of silyltriflate **5.20** (37.4 mg, 0.125 mmol) and *N*-*tert*-butyl-α-phenylnitrone (**5.47**, 88.1 mg, 0.497 mmol, 4 equiv) in MeCN (1.7 mL) at 0 ºC was added CsF (59.3 mg, 0.390 mmol, 3.1 equiv). The reaction was stirred at 0 ºC for 5 h and then

filtered through a silica plug (25:1 EtOAc:$NEt_3$). Evaporation of the solvent under reduced pressure gave a mixture of isomers **5.48a** and **5.48b** (1.9:1 ratio). The crude material was further purified by preparative TLC (80:20:1 Benzene:EtOAc:$NEt_3$) to give **5.48b** (8.4 mg, 26% yield), as well as a mixture of **5.48a** and nitrone **5.47**. This mixture was purified by flash chromatography (80:20:1 Hexanes:EtOAc:$NEt_3$) to give **5.48a** (15.7 mg, 49% yield). **5.48:** Mp: 125–128 ºC; $R_f$ 0.13 (80:20:1 Hexanes:EtOAc:$NEt_3$); $^1$H NMR (500 MHz, $CDCl_3$): δ 8.32 (d, *J* = 5.6, 1H), 8.09 (s, 1H), 7.40–7.32 (m, 4H), 7.30–7.26 (m, 1H), 6.76 (d, *J* = 5.5, 1H), 5.65 (s, 1H), 1.18 (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 162.4, 150.1, 145.3, 142.8, 128.9, 127.9, 127.5, 127.2, 103.0, 64.9, 61.6, 25.5; IR (film): 2976, 1589, 1480, 1201 $cm^{-1}$; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{16}H_{19}N_2O$, 255.1497; found, 255.1501. **5.48b:** Mp: 97–99 ºC; $R_f$ 0.51 (2:1 Benzene:EtOAc); $^1$H NMR (500 MHz, $CDCl_3$): δ 8.22 (s, 1H), 8.10 (d, *J* = 4.8, 1H), 7.41–7.32 (m, 4H), 7.31–7.26 (m, 1H), 6.88 (d, *J* = 4.8, 1H), 5.60 (s, 1H), 1.18 (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 153.3, 142.5, 142.4, 138.9, 129.5, 129.0, 128.1, 127.4, 118.7, 66.6, 61.5, 25.6; IR (film): 2975, 1598, 1481, 1415, 1272 $cm^{-1}$; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{16}H_{19}N_2O$, 255.1497; found, 255.1489.

The structures of **5.48a** and **5.48b** were verified by NOESY, as the following interactions were observed:

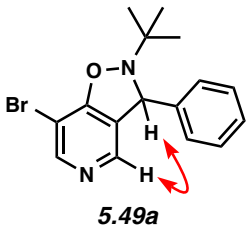



***5.48a*** ***5.48b***

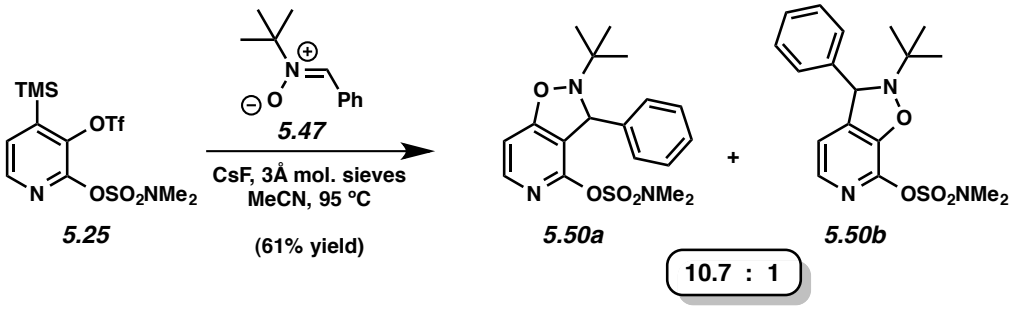



**Bromo isoxazolines 5.49a and 5.49b.** To a solution of bromosilyltriflate **5.22** (45.4 mg, 0.120 mmol) and *N-tert*-butyl-α-phenylnitrone (**5.47**, 86.7 mg, 0.489 mmol, 4 equiv) in MeCN (1.6 mL) at 0 ºC was added CsF (41.2 mg, 0.271 mmol, 2.3 equiv). The reaction was stirred at 0 ºC for 4.5 h and then filtered through a silica plug (25:1 EtOAc:$NEt_3$ eluent). Evaporation of the solvent under reduced pressure gave crude **5.49a** and **5.49b**, which were further purified by flash chromatography (4:1 Hexanes:EtOAc) to give **5.49b** (18.5 mg, 46% yield) and **5.49a** (5.5 mg, 14% yield). **5.49b:** Mp: 98–99 ºC; $R_f$ 0.57 (4:1 Hexanes:EtOAc); $^1$H NMR (500 MHz, $CDCl_3$): δ 8.20 (s, 1H), 8.10 (s, 1H), 7.36–7.27 (m, 5H), 5.56 (s, 1H), 1.18 (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 154.7, 144.1, 140.2, 138.2, 128.8, 128.4, 128.3, 128.1, 116.0, 67.5, 62.1, 25.4; IR (film): 2961, 1576, 1400, 1201 $cm^{-1}$; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{16}H_{18}BrN_2O$, 333.0602; found, 333.0601. **5.49a:** Mp: 98–102 ºC; $R_f$ 0.29 (4:1 Hexanes:EtOAc); $^1$H NMR (500 MHz, $CDCl_3$): δ 8.39 (s, 1H), 7.98 (s, 1H), 7.42–7.39 (m, 2H), 7.38–7.34 (m, 2H), 7.32–7.28 (m, 1H), 5.73 (s, 1H), 1.20 (s, 9H); $^{13}$C NMR ($CDCl_3$ 125 MHz, 10/12 C): δ 160.0, 151.3, 143.7, 142.3, 129.1, 128.2, 127.2, 65.9, 62.1, 25.5; IR (film): 2923, 1577, 1455, 1202 $cm^{-1}$; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{16}H_{18}BrN_2O$, 333.0602; found, 333.0605.

The structure of **5.49a** was verified by NOESY, as the following interaction was observed:



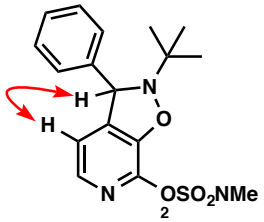

***5.49a***



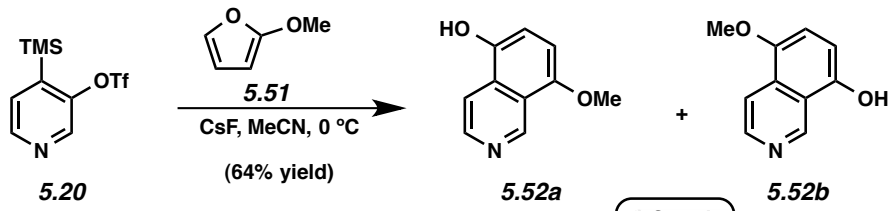

**Sulfamoyl isoxazolines 5.50a and 5.50b.** To a solution of sulfamoylsilyltriflate **5.25** (87.6 mg, 0.207 mmol) and *N-tert*-butyl-α-phenylnitrone (**5.47**, 266.1 mg, 1.50 mmol, 7.3 equiv) in MeCN (2.1 mL) were added 3Å mol. sieves (~80 mg) followed by CsF (80.0 mg, 0.527 mmol, 2.5 equiv). The reaction was placed in a heating block held at 95 ºC for 5 min and then cooled to room temperature. Filtration through a plug of celite ($Et_2O$ eluent) afforded the crude products as a 10.7 : 1 mixture of **5.50a** and **5.50b**. Purification by flash chromatography (5:1 Benzene:EtOAc) afforded a mixture of **5.50a** and **5.50b** (47.9 mg, 61% yield), which was a clear oil. Analytical samples of **5.50a** and **5.50b** were obtained by preparative TLC (8:1 Hexanes:Acetone). **5.50a:** $R_f$ 0.62 (5:1 Benzene:EtOAc); $^1$H NMR (500 MHz, $CDCl_3$) δ 8.10 (d, *J* = 5.6, 1H), 7.40–7.36 (m, 2H), 7.35–7.31 (m, 2H), 7.29–7.24 (m, 1H), 6.75 (d, *J* = 5.6, 1H), 5.78 (s, 1H), 2.85 (s, 6H), 1.19 (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 166.7, 153.3, 148.9, 141.3, 128.8, 128.1, 127.8, 116.7, 103.0, 64.3, 62.3, 38.7, 25.4; IR (film) 2975, 1592, 1380, 1169 $cm^{-1}$; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{18}H_{24}N_3O_4S$, 378.1487; found, 378.1487. **5.50b:** $R_f$

0.58 (8:1:1 Benzene:$Et_2O$:$CH_2Cl_2$); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, *J* = 4.9, 1H), 7.41–7.27 (m, 5H), 6.84 (d, *J* = 4.9, 1H), 5.65 (s, 1H), 3.08 (s, 6H), 1.20 (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 143.8, 143.2, 141.9, 139.9, 139.7, 129.1, 128.3, 127.3, 118.4, 67.2, 62.0, 39.0, 25.4; IR (film) 2976, 1601, 1432, 1383, 1171 cm$^{-1}$; HRMS-ESI (*m/z*) [M + H]$^+$ calcd for $C_{18}H_{24}N_3O_4S$, 378.1487; found, 378.1489.

The structure of **5.50b** was confirmed by NOESY, as the following interaction was observed:



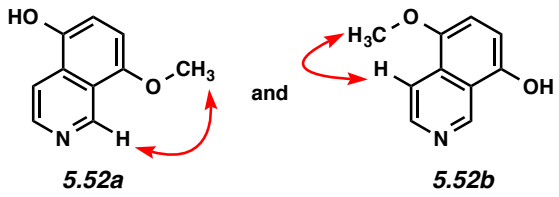

***5.50b***

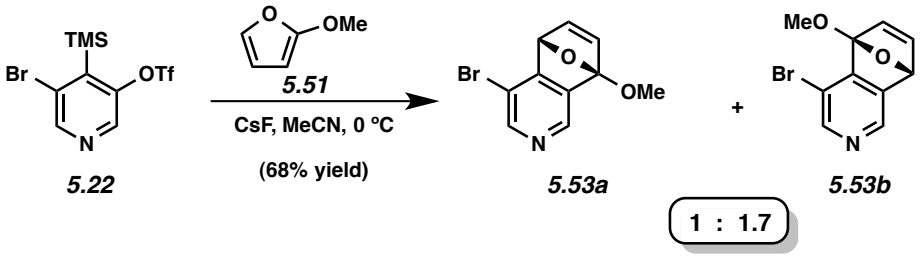



**Isoquinolines 5.52a and 5.52b.** To a solution of silyltriflate **5.20** (32.2 mg, 0.108 mmol) in MeCN (2.2 mL) at 0 ºC was added 2-methoxyfuran (**5.51**, 70 µL, 0.760 mmol, 7 equiv), followed by CsF (47.2 mg, 0.311 mmol, 2.9 equiv). The reaction was stirred at 0 ºC for 135 min and then filtered through a Florisil plug (9:1 $CHCl_3$:MeOH eluent). Evaporation under reduced pressure afforded a mixture of **5.52a** and **5.52b**, as well as their non-aromatized tricyclic isomers, which were further purified by flash chromatography (95:5 $CH_2Cl_2$:MeOH) to give a mixture of only the aromatized products **5.52a** and **5.52b** in a ratio of 1.3 : 1 respectively (12.1 mg, 64%

yield). Compounds **5.52a** and **5.52b** were characterized as a mixture of isomers. $R_f$ 0.12 (3:1 Hexane:EtOAc); **5.52a:** $^1$H NMR ($CDCl_3$, 500 MHz, 8/9 H): δ 9.60 (s, 1H), 8.55 (d, *J* = 6.0, 1H), 8.10 (d, *J* = 6.0, 1H), 7.06 (s, *J* = 8.3, 1H), 6.73 (d, *J* = 8.3, 1H), 3.95 (s, 3H); **5.52b:** $^1$H NMR ($CDCl_3$, 500 MHz, 8/9 H): δ 9.72 (s, 1H), 8.53 (d, *J* = 6.0, 1H), 8.02 (d, *J* -5.9, 1H), 6.93 (d, *J* = 8.3, 1H), 6.88 (d, *J* = 8.3, 1H), 3.94 (2, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 149.9, 148.1, 147.7, 147.3, 146.9, 145.7, 141.7, 141.6, 129.4, 129.1, 121.4, 121.1, 115.9, 115.6, 113.3, 109.9, 109.5, 105.6, 56.1, 55.9; IR (film): 3081, 1578, 1381, 1282, 1109 $cm^{-1}$; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{10}H_{10}NO_2$, 176.0712; found, 176.0712.

The structures of **5.52a** and **5.52b** were verified by NOESY (500 MHz; Acetone-$d_6$), as the following interactions were observed:

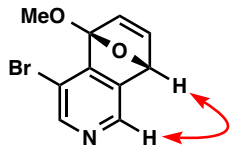


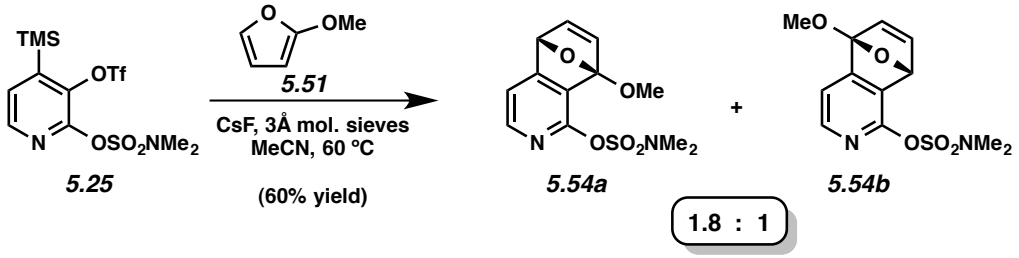

**Methoxyfuran adducts 5.53a and 5.53b.** To a solution of bromosilyltriflate **5.22** (29.3 mg, 0.077 mmol) in MeCN (1.55 mL) at 0 ºC were added 2-methoxyfuran (**5.51**, 50 μL, 0.543 mmol, 7 equiv), and CsF (39.4 mg, 0.259 mmol, 3.4 equiv). The reaction was stirred at 0 ºC for 160 min and then filtered through a Florisil plug (9:1 $CHCl_3$:MeOH). Evaporation under reduced pressure

afforded the crude products. The yield was determined by $^{1}$H NMR analysis of the crude reaction mixture using toluene (8.25 μL, 1 equiv based on **5.22**) as an external standard (68% yield, 1.7:1 ratio of **5.53b** : **5.53a**). Analytical samples of **5.53a** and **5.53b** were obtained by flash chromatography (2:1 Hexanes:$Et_2O$, neutral alumina used as stationary phase). **5.53b:** $R_f$ 0.28 (3:1 Hexanes:EtOAc); $^{1}$H NMR (500 MHz, $CD_3CN$): δ 8.33 (s, 1H), 8.31 (s, 1H), 7.19 (dd, *J* = 5.5, 2.2, 1H), 6.89 (d, *J* = 5.5, 1H), 5.76 (d, *J* = 2.1, 1H), 3.64 (s, 3H); $^{13}$C NMR (125 MHz, $CD_3CN$): δ 155.5, 150.9, 149.6, 148.7, 140.4, 139.4, 117.3, 113.1, 77.1, 55.3; IR (film): 2944, 1449, 1392, 1317 $cm^{-1}$; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{10}H_9BrNO_2$, 253.9817; found, 253.9819. **5.53a:** $R_f$ 0.17 (3:1 Hexanes:EtOAc); $^{1}$H NMR (500 MHz, $CD_3CN$) : δ 8.34 (s, 2H), 7.20 (dd, *J* = 5.6, 2.2, 1H), 6.99 (d, *J* = 5.6, 1H), 5.71 (d, *J* =2.2, 1H), 3.67 (s, 3H); $^{13}$C NMR (125 MHz, $CD_3CN$): δ 160.6, 148.9, 145.2, 144.0, 141.4, 137.8, 116.0, 112.5, 77.3, 54.4; IR (film): 2946, 1723, 1450, 1318 $cm^{-1}$; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{10}H_9BrNO_2$, 253.9817; found, 253.9815.

The structure of **5.53b** was verified by NOESY, as the following interaction was observed:

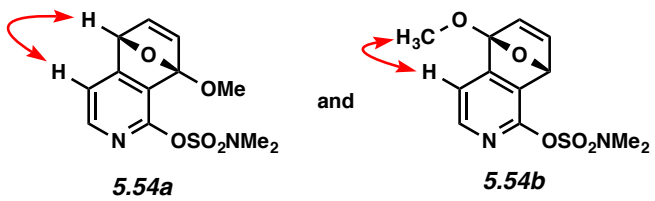



***5.53b***

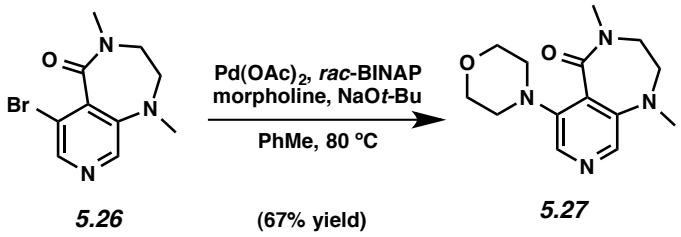



**Methoxyfuran adducts 5.54a and 5.54b.** To a solution of sulfamoylsilyltriflate **5.25** (84.5 mg, 0.200 mmol) and 3Å mol. sieves in MeCN (2.2 mL) were added 2-methoxyfuran (**5.51**, 185 μL, 2.01 mmol, 10 equiv), and CsF (91.7 mg, 0.604 mmol, 3 equiv). The vial was capped and placed in a heating block at 60 ºC. After 6 min, the reaction was cooled to room temperature and filtered through a plug of celite ($Et_2O$ eluent). The yield was determined by $^1H$ NMR analysis of the crude reaction mixture using toluene (21.25 μL, 1 equiv based on **25**) as an external standard (60% yield, 1.8:1 ratio of **5.54a** to **5.54b**). Compounds **5.54a** and **5.54b** were found to be unstable to chromatography, so $^1H$-NMR data are reported from the crude product mixture. **5.54a:** $R_f$ 0.21 (1:1 Hexanes:EtOAc, silica plate); $^1H$ NMR (500 MHz, $C_6D_6$): δ 7.76 (d, $J$ = 4.6, 1H), 6.87 (d, $J$ = 5.5, 1H), 6.46 (d, $J$ = 4.6, 1H), 6.39 (dd, $J$ = 5.5, 2.2, 1H), 5.03 (d, $J$ = 2.1, 1H), 2.70 (s, 3H), 2.65 (s, 6H). **5.54b:** $R_f$ 0.51 (1:1 Hexanes:EtOAc, silica plate); $^1H$ NMR (500 MHz, $C_6D_6$): δ 7.76 (d, $J$ = 4.6, 1H), 6.90 (dd, $J$ = 5.5, 2.2, 1H), 6.87 (d, $J$ = 4.6, 1H), 6.33 (d, $J$ = 5.5, 1H), 5.78 (d, $J$ = 2.1, 1H), 3.36 (s, 3H), 2.54 (s, 6H). HRMS-ESI ($m/z$) $[M + H]^+$ calcd for $C_{12}H_{15}N_2O_5S$, 299.0702; found, 299.0700.

The structures of **5.54a** and **5.54b** were confirmed by NOESY (using the crude reaction mixture), as the following interactions were observed:

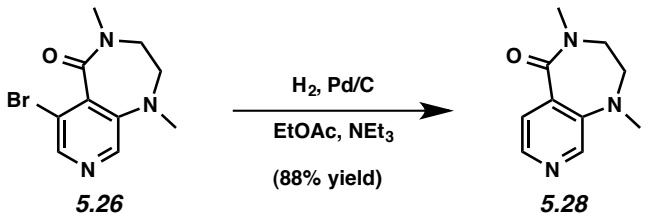


### 5.8.2.3 Derivatizations of Pyridyne Adducts

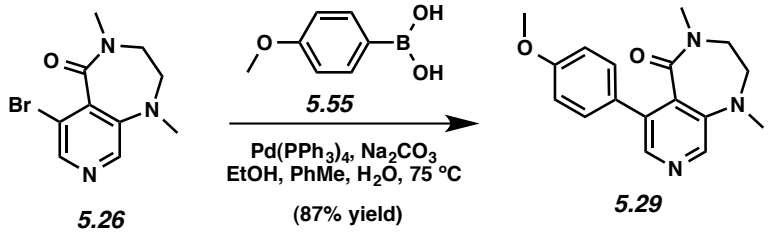



*5.26* (67% yield) *5.27*

**Diamino pyridine 5.27.** To a flame-dried vial containing a stir bar were added bromopyridine **5.26** (27.0 mg, 0.100 mmol) and $Pd(OAc)_2$ (2.5 mg, 0.011 mmol, 11 mol %). The vial was taken into a glovebox and *rac*-BINAP (7.5 mg, 0.012 mmol, 12 mol%), NaO*t*-Bu (13.5 mg, 0.140 mmol, 1.4 equiv), morpholine (10.5 μL, 0.120 mmol, 1.2 equiv), and toluene (0.4 mL) were added. The vial was capped and removed from the glovebox and placed in a heating block at 80 ºC. After 16 h, the reaction was cooled to room temperature, diluted with $Et_2O$ (2 mL) and filtered through a celite plug ($Et_2O$ eluent). Evaporation under reduced pressure gave the crude product, which was further purified by flash chromatography (9:1 EtOAc:MeOH) to give **5.27** as a white solid (18.5 mg, 67% yield). Mp: 182–185 ºC; $R_f$ 0.10 (9:1 EtOAc:MeOH); $^1$H NMR (500 MHz, $CD_3CN$): δ 7.94 (s, 1H), 7.83 (s, 1H), 3.67 (t, $J$ = 4.6, 4H), 3.41 (br s, 4H), 3.07 (s, 3H), 3.05 (br s, 4H), 2.82 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 168.0, 144.8, 141.7, 135.0, 133.1, 126.2, 66.9, 56.3, 50.9, 47.8, 40.1, 33.6; IR (film): 2848, 1642, 1546, 1433, 1110 cm$^{-1}$; HRMS-ESI (*m*/*z*) $[M + H]^+$ calcd for $C_{14}H_{21}N_4O_2$, 277.1664; found, 277.1665.

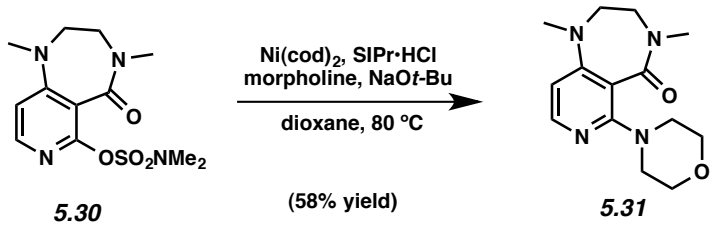



**Pyridyl amide 5.28.** To a solution of bromopyridine **5.26** (20.6 mg, 0.076 mmol) in EtOAc (3 mL) was added triethylamine (16 μL, 0.115 mmol, 1.5 equiv) and 10% Pd/C (50% wetted powder) (10.1 mg, 3.8 μmol, 5 mol%). The reaction vessel was equipped with a balloon of hydrogen and the flask was evacuated and then backfilled with hydrogen 5 times. After stirring under hydrogen for 2 h, the reaction was filtered through a plug of celite (EtOAc eluent). Evaporation under reduced pressure gave the crude product, which was further purified by flash chromatography (95:5 $CH_2Cl_2$:MeOH) to give **5.28** (12.8 mg, 88% yield). Spectral data match those reported above on page 554 of this dissertation.



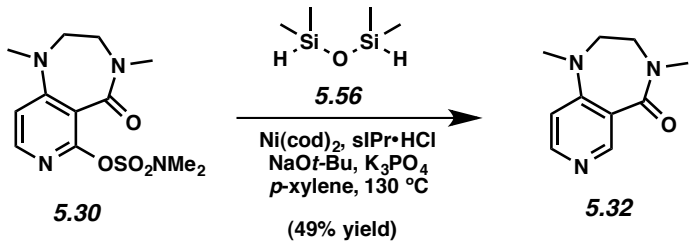

**Biaryl 5.29.** To a solution of bromopyridine **5.26** (21.6 mg, 0.080 mmol) and boronic acid **5.55** (14.6 mg, 0.096 mmol, 1.2 equiv) in toluene (0.55 mL) and ethanol (0.55 mL) was added a 2.0 M aqueous solution of $Na_2CO_3$ (0.83 mL). The mixture was sparged with $N_2$ for ~5 min. A separate vial containing a stirbar was charged with $Pd(PPh_3)_4$ (3.4 mg, 2.9 μmol, 3.5 mol%). The PhMe/$H_2O$/EtOH solution was added to the vial containing the Pd cat. and the reaction heated to 75 ºC. After 4 h, the reaction was cooled to room temperature. The reaction was diluted with EtOAc (5 mL) and $H_2O$ (3 mL), and then the layers were separated. The aqueous layer was

extracted with EtOAc (2 x 5 mL) and the combined organic layers were filtered through a plug of silica gel (EtOAc eluent). Evaporation of the solvent under reduced pressure afforded the crude product, which was further purified by flash chromatography (20:1 $CHCl_3$:MeOH) to give **5.29** as a white solid (20.8 mg, 87% yield). Mp: 229–231 ºC; $R_f$ 0.19 (20:1 $CHCl_3$:MeOH); $^1H$ NMR (500 MHz, $CDCl_3$): δ 8.30 (s, 1H), 8.19 (s, 1H), 7.29–7.25 (m, 2H), 6.95–6.91 (m, 2H), 3.82 (s, 3H), 3.61 (br s, 2H), 3.30 (br s, 2H), 3.16 (s, 3H), 3.03 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 168.1. 159.6, 144.6, 141.2, 138.4, 135.4, 135.0, 129.9, 129.6, 114.3, 56.7, 55.3, 48.0, 39.9, 33.6; IR (film): 2929, 1649, 1512, 1252, 1176 $cm^{-1}$; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{17}H_{20}N_3O_2$, 298.1555; found, 298.1554.



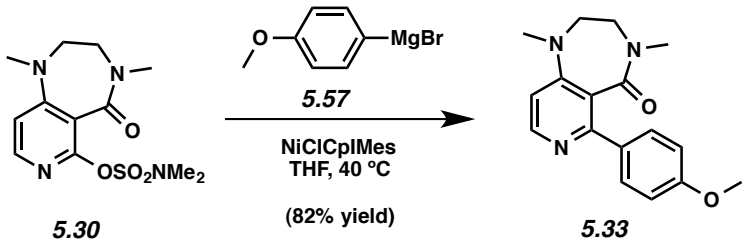

**Diamino pyridine 5.31.** To a 4 mL vial inside a glovebox were added $Ni(cod)_2$ (2.6 mg, 9.5 μmol, 10 mol%), SIPr·HCl (8.2 mg, 19.2 μmol, 20 mol%), and NaO*t*-Bu (13.8 mg, 0.144 mmol, 1.5 equiv). To a separate vial containing sulfamate **5.30** (30.0 mg, 0.095 mmol, 1 equiv), also inside a glove box, was added 1,4-dioxane (0.5 mL). Once the solids had dissolved, morpholine (10 μL, 0.116 mmol, 1.2 equiv) was added. The resulting solution was then transferred to the vial containing the Ni catalyst. The vial was capped, removed from the glovebox, and placed in a heating block at 80 ºC. After 3 h, the reaction was cooled to room temperature, and filtered through a plug of celite (EtOAc eluent). Evaporation under reduced pressure afforded the crude product, which was further purified by flash chromatography (4:1 Acetone:Toluene) to give **5.31**

as a white solid (15.1 mg, 58% yield). Mp: 193–196 ºC; $R_f$ 0.19 (4:1 Acetone:Toluene); $^1$H NMR (300 MHz, $CDCl_3$): δ 8.00 (d, *J* = 5.7, 1H), 6.19 (d, *J* = 5.7, 1H), 3.76 (app. t, *J* = 4.7, 4H), 3.58 (br s, 2H), 3.40 (app. t, *J* = 4.7, 4H), 3.33 (app. t, *J* = 5.2, 2H), 3.18 (s, 3H), 2.81 (s, 3H); $^{13}$C NMR ($CDCl_3$ 125 MHz): δ 169.4, 159.4, 153.9, 149.8, 107.7, 104.3, 67.0, 55.7, 48.5, 47.4, 40.0, 33.7; IR (film): 2942, 1743, 1638, 1426, 1113 $cm^{-1}$; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{14}H_{21}N_4O_2$, 277.1664; found, 277.1663.

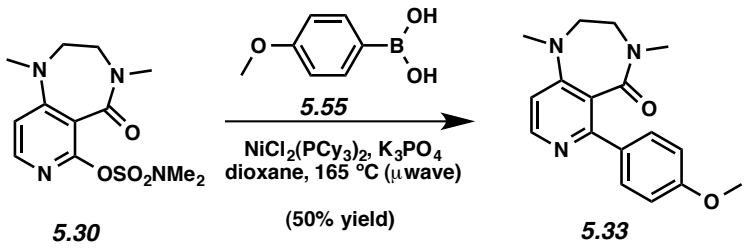



**Pyridyl amide 5.32.** A 4 mL vial containing $K_3PO_4$ (75.2 mg, 0.335 mmol, 4.4 equiv) was flame-dried and allowed to cool under $N_2$. To the vial was added sulfamate **5.30** (25.0 mg, 0.080 mmol, 1 equiv) and the vial was taken into a glovebox. To a separate vial inside the glovebox were added $Ni(cod)_2$ (4.4 mg, 0.016 mmol, 0.2 equiv), sIPr·HCl (13.7 mg, 0.032 mmol, 0.4 equiv), NaO*t*-Bu (3.1 mg, 0.032 mmol, 0.4 equiv), and *p*-xylene (0.4 mL). This mixture was allowed to stir for ~2 min. and then transferred to the vial containing sulfamate **5.30**. Tetramethyldisiloxane (**5.56**, 70 μL, 0.396 mmol, 5 equiv) was added and the vial capped under argon *inside the glovebox*. The vial was then removed from the glovebox and placed in a heating block at 130 ºC. After 15 h, the reaction was cooled to room temperature. The reaction mixture was diluted with EtOAc and filtered through a celite plug (EtOAc eluent). Evaporation under reduced pressure gave the crude product **5.32**, which was further purified by flash

chromatography (1:1 Benzene:Acetone → 9:1 $CHCl_3$:MeOH) to give **5.32** (7.5 mg, 49% yield), as a white solid. Spectral data match those reported on page 554 of this dissertation.



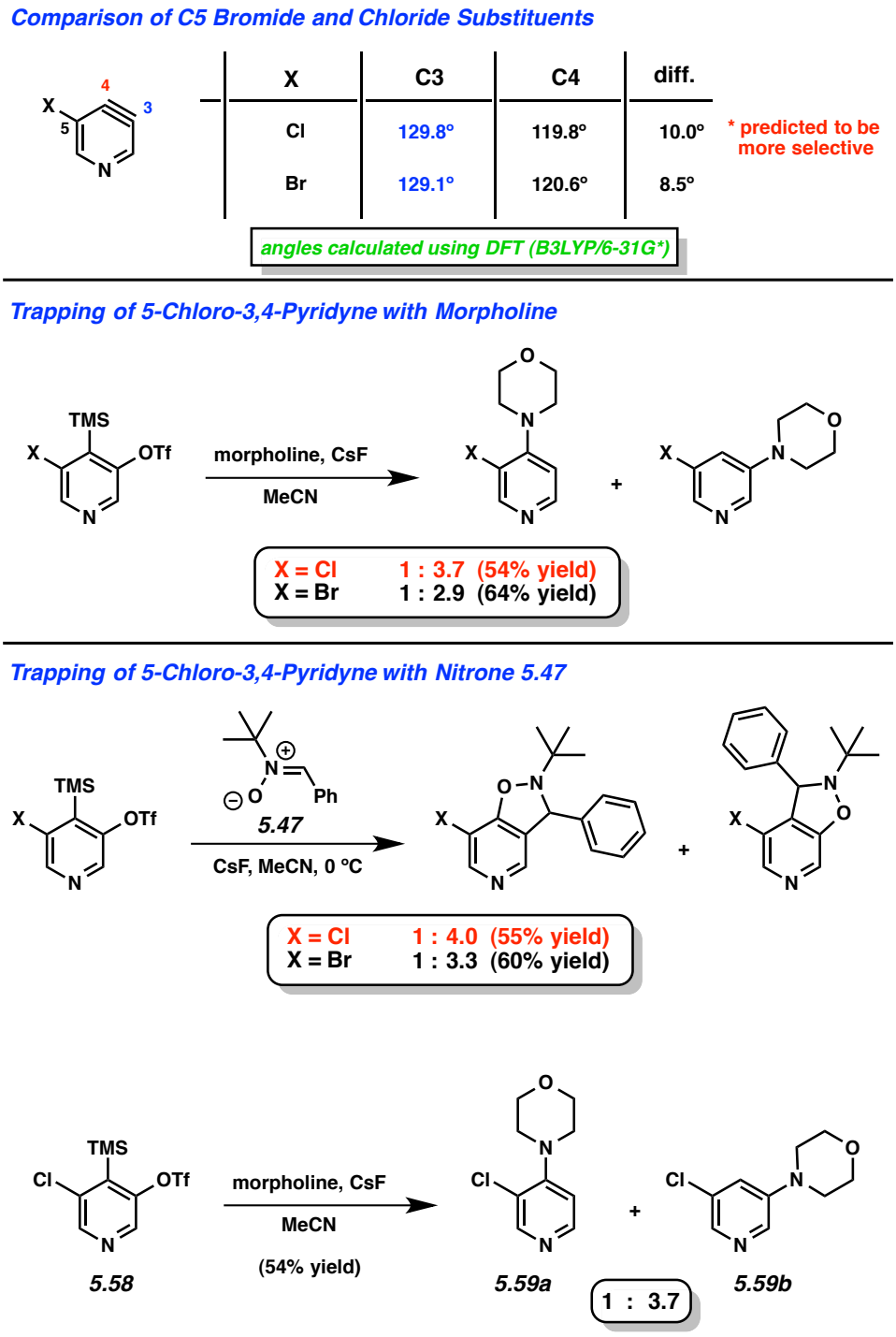

**Biaryl 5.33.** Biaryl **5.33** was synthesized using a modification of the procedure reported by Macklin et al. for the Ni-catalyzed Kumada coupling of aryl sulfamates.[47] To a flame-dried vial were added sulfamate **5.30** (35.2 mg, 0.112 mmol) and NiClCpIMes[58] (2.7 mg, 5.8 μmol, 5 mol%), followed by 4-OMePhMgBr (**5.57**, 0.5 M in THF, 670 μL, 0.335 mmol, 3 equiv). The vial was capped and heated to 40 ºC for 13 h. After cooling, sat. aqueous $NH_4Cl$ (1 mL) was added. The reaction was further diluted with $H_2O$ (2 mL) and EtOAc (6 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 x 6 mL). The combined organic layers were dried over $Na_2SO_4$ and then evaporated under reduced pressure to afford the crude product. Purification by flash chromatography (3:1 Acetone:Benzene) afforded biaryl **5.33** (27.3 mg, 82% yield) as a white solid. Mp: 196–199 ºC; $R_f$ 0.33 (3:1 Acetone:Benzene); $^1$H NMR (500 MHz, $CDCl_3$): δ 8.41 (d, *J* = 5.7, 1H), 7.53 (d, *J* = 8.8, 2H), 6.90 (d, *J* = 8.8, 2H), 6.63 (d, *J* = 5.7, 1H), 3.82 (s, 3H), 3.73 (br s, 2H), 3.42 (br s, 2H), 3.16 (s, 3H), 2.87 (s, 3H); $^{13}$C NMR ($CDCl_3$ 125 MHz): δ 169.6, 160.1, 158.8, 152.8, 150.9, 133.3, 129.9, 121.7, 113.9, 110.1, 56.1, 55.3, 47.6, 39.7, 33.8; IR (film): 2926, 2645, 1567, 1247, 1174 cm$^{-1}$; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{17}H_{20}N_3O_2$, 298.1555; found, 298.1554.




**Biaryl 5.33.** A microwave vial containing $K_3PO_4$ (201.4 mg, 0.95 mmol, 10 equiv) was flame dried and allowed to cool under $N_2$. To this vial were then added sulfamate **5.30** (30.4 mg, 0.097 mmol, 1 equiv), boronic acid **5.55** (81.6 mg, 0.537 mmol, 5.5 equiv), $NiCl_2(PCy_3)_2$ (20.8 mg, 0.030 mmol, 30 mol%), and 1,4-dioxane (750 μL). The vial was capped, placed in the microwave reactor, and heated to 165 ºC (300 W) for 25 min. Once cooled, the reaction was filtered through a plug of celite ($CH_2Cl_2$ eluent). To the resulting mixture was added silica gel (2 mL) and the solvent was evaporated under reduced pressure to give a free-flowing powder. This powder was then dry-loaded onto a silica gel column and purified by flash chromatography (3:1 Acetone:Benzene) to give **5.33** (14.3 mg, 50% yield) as a white solid.

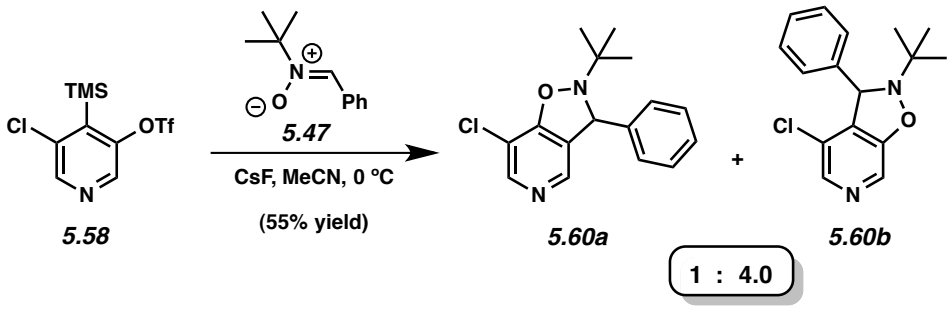
### 5.8.2.4 Comparison Between a C5 Bromide and Chloride

*Figure 5.7. Effect of a C5 Chloride Substituent on Pyridyne Regioselectivity*




**Morpholine Adducts 5.59a and 5.59b.** To a solution of chlorosilyltriflate **5.58**[13] (24.2 mg, 0.073 mmol) in MeCN (0.8 mL) was added morpholine (25.0 μL, 0.287 mmol, 4 equiv) followed

by CsF (36.0 mg, 0.237 mmol, 3.2 equiv). The reaction was stirred for 90 min and then filtered through a silica plug (25:1 EtOAc:$NEt_3$ eluent). Evaporation under reduced pressure afforded the crude product. The yield was determined by $^1$H NMR analysis of the crude reaction mixture using toluene (7.75 μL, 1 equiv based on **5.58**) as an external standard (54% yield, 1:3.7 ratio of **5.59a:5.59b**). Analytical samples of **5.59a** and **5.59b** were obtained by preparative TLC (50:50:1 Benzene:$Et_2O$:$NEt_3$). **5.59b**: Rf 0.41 (50:50:1 Benzene:$Et_2O$:$NEt_3$); $^1$H NMR (500 MHz, $CDCl_3$): δ 8.16 (d, *J* = 2.5, 1H), 8.06 (d, *J* = 1.9, 1H), 7.13 (app. t, *J* = 2.2, 1H), 3.86 (app. t, *J* = 4.9, 4H), 3.20 (app. t, *J* = 4.9, 4H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 147.5, 139.2, 135.8, 132.1, 121.4, 66.5, 48.1; IR (film): 2871, 1578, 1467, 1243, 1119 cm$^{-1}$; HRMS-ESI (*m/z*) [M + H]$^+$ calcd for $C_9H_{12}ClN_2O$,199.0638; found, 199.0635; **5.59a**: Rf 0.30 (50:50:1 Benzene:$Et_2O$:$NEt_3$); $^1$H NMR (500 MHz, $CDCl_3$): δ 8.42 (s, 1H), 8.33 (d, *J* = 5.5, 1H), 6.83 (d, *J* = 5.4, 1H), 3.88 (app. t, *J* = 4.6, 4H), 3.21 (app. t, *J* = 4.6, 4H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 154.9, 150.8, 149.0, 124.3, 114.1, 66.7, 50.1; IR (film) 2855, 1579, 1242, 1117 cm$^{-1}$; HRMS-ESI (*m/z*) ) [M + H]$^+$ calcd for $C_9H_{12}ClN_2O$, 199.0638; found, 199.0634.



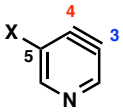

**Chloro isoxazolines 5.60a and 5.60b.** To a solution of chlorosilyltriflate **5.58** (27.7 mg, 0.083 mmol) and *N-tert*-butyl-α-phenylnitrone (**5.47**, 58.9 mg, 0.332 mmol, 4 equiv) in MeCN (1.1 mL) at 0 °C was added CsF (29.1 mg, 0.192 mmol, 2.3 equiv). The reaction was stirred at 0 °C

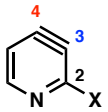
for 2 h and then filtered through a silica plug (25:1 EtOAc:$NEt_3$ eluent). Evaporation of the solvent under reduced pressure gave crude **5.60a** and **5.60b**, The yield was determined by $^1$H NMR analysis of the crude reaction mixture using toluene (9.00 μL, 1 equiv based on **5.58**) as an external standard (55% yield, 1:4.0 ratio of **5.60a** : **5.60b**). An analytical sample of **5.60b** was obtained by preparative TLC (8:1 Hexanes:EtOAc). $R_f$ 0.33 (8:1 Hexanes:EtOAc); $^1$H NMR (500 MHz, $CDCl_3$): δ 8.15 (s, 1H), 8.08 (s, 1H), 7.36–7.27 (m, 5H), 5.63 (s, 1H), 1.18 (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 154.8, 141.8, 140.3, 136.2, 128.8, 128.3, 128.1, 127.7, 127.2, 66.3, 62.1, 25.4; IR (film) 2975, 1579, 1403, 1366, 1205 $cm^{-1}$; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{16}H_{18}ClN_2O$, 289.1108; found, 289.1089.

### 5.8.3 DFT Modeling of Substituted 3,4-Pyridynes

All computations were carried out using Spartan '06 for Mac[29] unless otherwise noted. All structures were minimized using Molecular Mechanics, and then further minimized using Density Functional Theory B3LYP/6–31G*. In the case of compounds, **5.63** and **5.69** a LACVP basis set was used which consists of a 6-31G* basis set for C, N, and H atoms, while a LANL2DZ effective core basis set was used for the iodine atoms.[29]

*Figure 5.8. Computational Evaluation of 2- and 5-Substituted 3,4-Pyridynes*



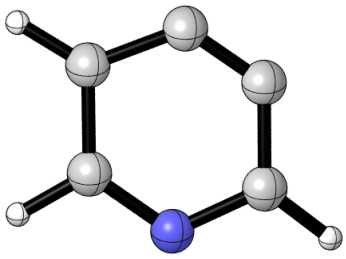




| cmpd. | X | C3 | C4 | diff. |
|---|---|---|---|---|
| *5.61* | F | 132.4° | 116.6° | 15.8° |
| *5.62* | Cl | 129.8° | 119.8° | 10.0° |
| *5.13* | Br | 129.1° | 120.6° | 8.5° |
| *5.63* | I | 127.1° | 122.8° | 4.3° |
| *5.64* | OH | 132.7° | 117.4° | 15.3° |
| *5.65* | OMe | 131.9° | 118.3° | 13.6° |
| *5.15* | $OSO_2NMe_2$ | 130.5° | 118.8° | 11.7° |

| cmpd. | X | C3 | C4 | diff. |
|---|---|---|---|---|
| *5.66* | F | 118.9° | 129.7° | 10.8° |
| *5.67* | Cl | 121.8° | 127.6° | 5.8° |
| *5.68* | Br | 122.1° | 127.2° | 5.1° |
| *5.69* | I | 123.3° | 126.3° | 3.0° |
| *5.70* | OH | 120.9° | 128.8° | 7.9° |
| *5.71* | OMe | 121.6° | 128.1° | 6.5° |
| *5.16* | $OSO_2NMe_2$ | 120.3° | 128.9° | 8.6° |

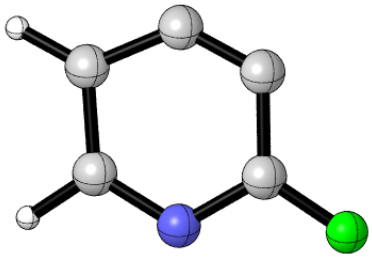
Evaluated experimentally

## 5.8.4 Coordinates of Computed Structures



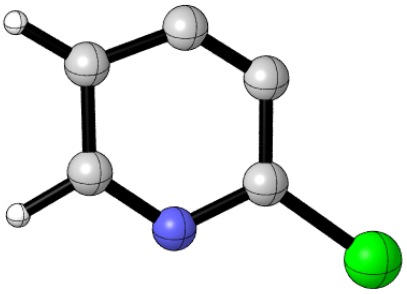
**5.2**

| | | | |
|---|---|---|---|
| C | 0.676457 | -1.197022 | 0.000000 |
| C | -0.662355 | 1.034551 | -0.000000 |
| C | 1.414698 | -0.020590 | 0.000000 |
| C | -0.580771 | -1.253776 | 0.000000 |
| C | -1.426420 | -0.165545 | -0.000000 |
| N | 0.667732 | 1.100300 | 0.000000 |
| H | 2.494944 | 0.077167 | 0.000000 |
| H | -2.511276 | -0.152871 | -0.000000 |
| H | -1.187450 | 1.987886 | -0.000000 |



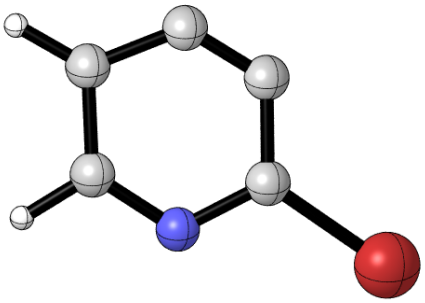
**5.66**

| | | | |
|---|---|---|---|
| C | 0.235527 | -1.247566 | 0.000000 |
| C | -1.113740 | 1.031464 | 0.000000 |
| C | 0.921676 | -0.043502 | 0.000000 |
| C | -1.020500 | -1.231192 | 0.000000 |
| C | -1.885304 | -0.161544 | 0.000000 |
| N | 0.219765 | 1.083272 | 0.000000 |
| H | -2.967944 | -0.152350 | 0.000000 |
| H | -1.630806 | 1.988717 | 0.000000 |
| F | 2.246573 | 0.056415 | 0.000000 |



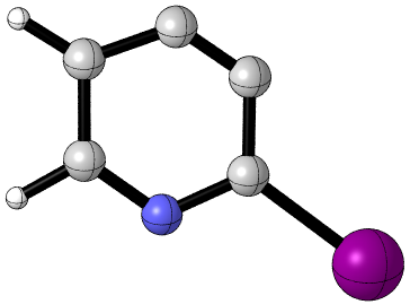
**5.67**

| | | | |
|---|---|---|---|
| C | -0.239210 | -1.238452 | 0.000000 |
| C | -1.531721 | 1.045618 | 0.000000 |
| C | 0.496460 | -0.066572 | 0.000000 |
| C | -1.495598 | -1.230248 | 0.000000 |
| C | -2.327274 | -0.133761 | 0.000000 |
| N | -0.199151 | 1.072294 | 0.000000 |
| H | -3.410142 | -0.098084 | 0.000000 |
| H | -2.028036 | 2.013748 | 0.000000 |
| Cl | 2.237855 | 0.024869 | 0.000000 |



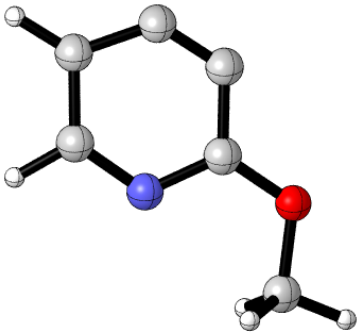
**5.68**

| | | | |
|---|---|---|---|
| C | -0.842764 | -1.234571 | 0.000000 |
| C | -2.169366 | 1.027198 | 0.000000 |
| C | -0.123944 | -0.053715 | 0.000000 |
| C | -2.099392 | -1.250406 | 0.000000 |
| C | -2.945879 | -0.165002 | 0.000000 |
| N | -0.837021 | 1.073355 | 0.000000 |
| H | -4.029325 | -0.145854 | 0.000000 |
| H | -2.680214 | 1.987673 | 0.000000 |
| Br | 1.777610 | 0.074335 | 0.000000 |



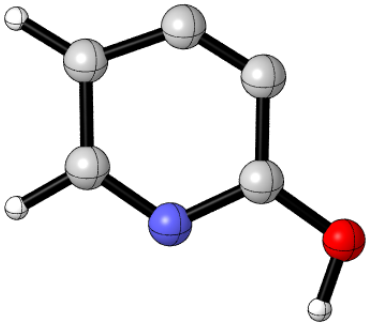
**5.69**

| | | | |
|---|---|---|---|
| C | 1.298654 | -1.228520 | 0.000000 |
| C | 2.617794 | 1.025799 | 0.000000 |
| C | 0.566379 | -0.056180 | 0.000000 |
| C | 2.555445 | -1.257400 | 0.000000 |
| C | 3.395489 | -0.165610 | 0.000000 |
| N | 1.285326 | 1.071350 | 0.000000 |
| H | 4.479314 | -0.143573 | 0.000000 |
| H | 3.127155 | 1.987179 | 0.000000 |
| I | -1.540764 | 0.078270 | 0.000000 |



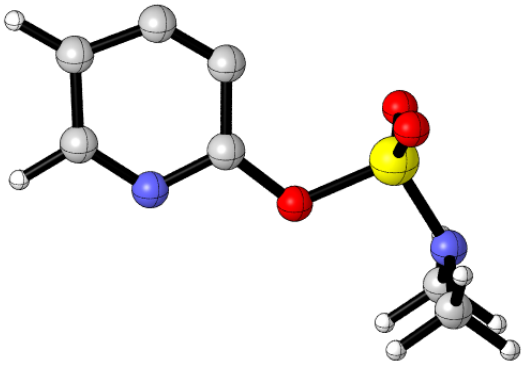
**5.71**

| | | | |
|---|---|---|---|
| C | -0.569538 | -1.351066 | 0.000000 |
| C | -1.312695 | 1.170244 | 0.000000 |
| C | 0.426447 | -0.372959 | 0.000000 |
| C | -1.785183 | -1.050248 | 0.000000 |
| C | -2.352860 | 0.211294 | 0.000000 |
| N | -0.003295 | 0.896941 | 0.000000 |
| H | -3.399453 | 0.489772 | 0.000000 |
| H | -1.574925 | 2.226726 | 0.000000 |
| O | 1.731975 | -0.666328 | 0.000000 |
| C | 2.646605 | 0.437794 | 0.000000 |
| H | 3.639492 | -0.013786 | 0.000000 |
| H | 2.507648 | 1.058083 | 0.890164 |
| H | 2.507648 | 1.058083 | -0.890164 |



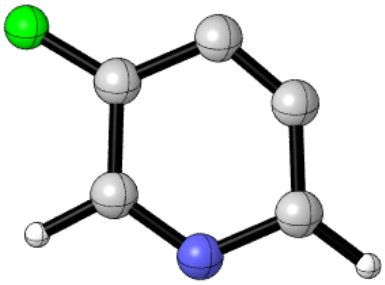
**5.70**

| | | | |
|---|---|---|---|
| C | 0.146080 | -1.261774 | 0.000000 |
| C | -1.080441 | 1.071206 | 0.000000 |
| C | 0.922127 | -0.107505 | 0.000000 |
| C | -1.105181 | -1.196576 | 0.000000 |
| C | -1.912449 | -0.075874 | 0.000000 |
| N | 0.255994 | 1.057946 | 0.000000 |
| H | -2.993200 | -0.009905 | 0.000000 |
| H | -1.544181 | 2.055731 | 0.000000 |
| O | 2.264994 | -0.097267 | 0.000000 |
| H | 2.531588 | 0.839812 | 0.000000 |



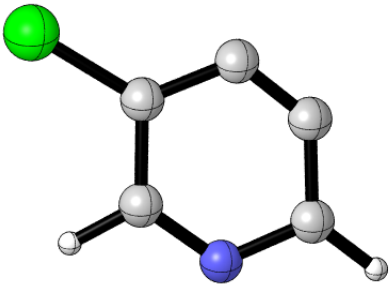
**5.16**

| | | | |
|---|---|---|---|
| C | 1.850068 | -0.959453 | 0.000000 |
| C | 3.403656 | 1.170420 | 0.000000 |
| C | 1.265218 | 0.298981 | 0.000000 |
| C | 3.099587 | -1.076021 | 0.000000 |
| C | 4.059565 | -0.089566 | 0.000000 |
| N | 2.082739 | 1.353554 | 0.000000 |
| H | 5.138475 | -0.181969 | 0.000000 |
| H | 4.008982 | 2.074639 | 0.000000 |
| O | -0.071153 | 0.600145 | 0.000000 |
| S | -1.195945 | -0.674397 | 0.000000 |
| O | -1.068919 | -1.360606 | -1.272938 |
| O | -1.068919 | -1.360606 | 1.272938 |
| N | -2.577857 | 0.225665 | 0.000000 |
| C | -2.900446 | 0.942046 | 1.242292 |
| H | -3.974226 | 1.149885 | 1.233217 |
| H | -2.348761 | 1.888050 | 1.324293 |
| H | -2.671780 | 0.306968 | 2.097681 |
| C | -2.900446 | 0.942046 | -1.242292 |
| H | -3.974226 | 1.149885 | -1.233217 |
| H | -2.671780 | 0.306968 | -2.097681 |
| H | -2.348761 | 1.888050 | -1.324293 |



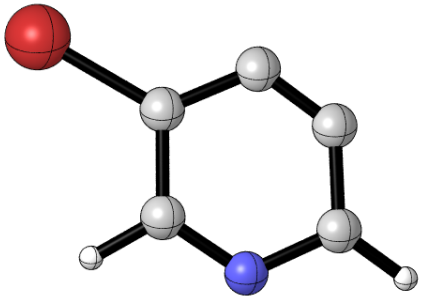
**5.61**

| | | | |
|---|---|---|---|
| C | -1.036424 | -1.177009 | 0.000000 |
| C | 0.146503 | 1.073414 | 0.000000 |
| C | -1.879483 | -0.086383 | 0.000000 |
| C | 0.221782 | -1.281259 | 0.000000 |
| C | 0.939219 | -0.102578 | 0.000000 |
| N | -1.183442 | 1.068138 | 0.000000 |
| H | -2.961629 | -0.061678 | 0.000000 |
| H | 0.642825 | 2.040367 | 0.000000 |
| F | 2.270712 | 0.006765 | 0.000000 |



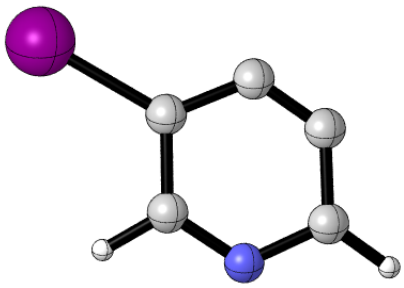
**5.62**

| | | | |
|---|---|---|---|
| C | 1.485699 | -1.202308 | 0.000000 |
| C | 0.304415 | 1.073063 | 0.000000 |
| C | 2.321351 | -0.103094 | 0.000000 |
| C | 0.226784 | -1.257977 | 0.000000 |
| C | -0.511156 | -0.095369 | 0.000000 |
| N | 1.633130 | 1.056396 | 0.000000 |
| H | 3.404104 | -0.078806 | 0.000000 |
| H | -0.174848 | 2.048770 | 0.000000 |
| Cl | -2.252611 | 0.045395 | 0.000000 |



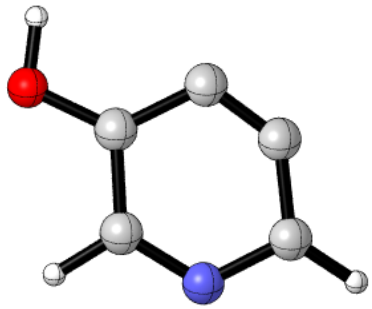
**5.13**

| | | | |
|---|---|---|---|
| C | 2.102561 | -1.208338 | 0.000000 |
| C | 0.919889 | 1.074101 | 0.000000 |
| C | 2.935345 | -0.105663 | 0.000000 |
| C | 0.843322 | -1.252377 | 0.000000 |
| C | 0.103239 | -0.094185 | 0.000000 |
| N | 2.248863 | 1.054601 | 0.000000 |
| H | 4.018240 | -0.081504 | 0.000000 |
| H | 0.444491 | 2.051676 | 0.000000 |
| Br | -1.798488 | 0.054710 | 0.000000 |



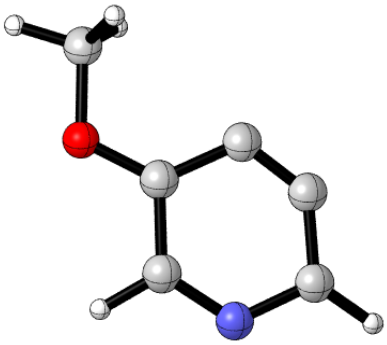
**5.63**

| | | | |
|---|---|---|---|
| C | 2.553065 | -1.227728 | 0.000000 |
| C | 1.373807 | 1.075264 | 0.000000 |
| C | 3.381005 | -0.117641 | 0.000000 |
| C | 1.293752 | -1.236098 | 0.000000 |
| C | 0.542989 | -0.087484 | 0.000000 |
| N | 2.702363 | 1.046360 | 0.000000 |
| H | 4.464354 | -0.095742 | 0.000000 |
| H | 0.908603 | 2.057996 | 0.000000 |
| I | -1.561029 | 0.073737 | 0.000000 |



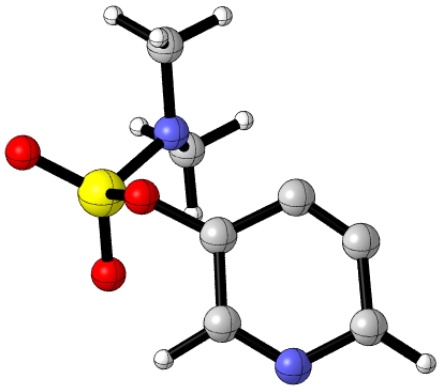
**5.64**

| | | | |
|---|---|---|---|
| C | -1.033948 | -1.197812 | 0.000000 |
| C | 0.092503 | 1.076451 | 0.000000 |
| C | -1.909250 | -0.133550 | 0.000000 |
| C | 0.226727 | -1.269724 | 0.000000 |
| C | 0.936511 | -0.073891 | 0.000000 |
| N | -1.233649 | 1.034627 | 0.000000 |
| H | -2.991348 | -0.133856 | 0.000000 |
| H | 0.558579 | 2.058758 | 0.000000 |
| O | 2.279168 | 0.105489 | 0.000000 |
| H | 2.702218 | -0.767118 | 0.000000 |



**5.65**

| | | | |
|---|---|---|---|
| C | -1.268683 | -1.298741 | 0.000000 |
| C | -0.596966 | 1.156902 | 0.000000 |
| C | -2.327202 | -0.415651 | 0.000000 |
| C | -0.019551 | -1.117576 | 0.000000 |
| C | 0.456675 | 0.189399 | 0.000000 |
| N | -1.889620 | 0.862123 | 0.000000 |
| H | -3.389836 | -0.620943 | 0.000000 |
| H | -0.327193 | 2.210206 | 0.000000 |
| O | 1.730503 | 0.624010 | 0.000000 |
| C | 2.735162 | -0.389874 | 0.000000 |
| H | 2.650361 | -1.019619 | 0.893114 |
| H | 3.692097 | 0.133788 | 0.000000 |
| H | 2.650361 | -1.019619 | -0.893114 |



**5.15**

| | | | |
|---|---|---|---|
| C | -2.800465 | 1.062658 | 0.807637 |
| C | -1.969316 | -0.426234 | -1.101131 |
| C | -3.616756 | 1.020710 | -0.304320 |
| C | -1.703669 | 0.484296 | 1.040677 |
| C | -1.169091 | -0.348218 | 0.072673 |
| N | -3.118122 | 0.220116 | -1.267866 |
| H | -4.555826 | 1.533641 | -0.472225 |
| H | -1.626358 | -1.051542 | -1.920880 |
| O | -0.026008 | -1.113819 | 0.183378 |
| S | 1.409086 | -0.484937 | -0.411164 |
| O | 1.169571 | 0.059632 | -1.738885 |
| O | 2.344390 | -1.571849 | -0.175491 |
| N | 1.620250 | 0.796153 | 0.641399 |
| C | 2.056997 | 0.414107 | 1.991175 |
| H | 1.458705 | -0.426787 | 2.345750 |
| H | 1.877143 | 1.268617 | 2.649539 |
| H | 3.119881 | 0.141684 | 2.025186 |
| C | 2.265919 | 1.993312 | 0.082630 |
| H | 1.838178 | 2.215098 | -0.894177 |
| H | 3.355139 | 1.878049 | -0.010219 |
| H | 2.054099 | 2.824251 | 0.761610 |

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# APPENDIX THREE

## Spectra Relevant to Chapter Five:

**Regioselective Reactions of 3,4-Pyridynes Enabled by the Aryne Distortion Model**

Adam E. Goetz, Neil K. Garg

*Nat. Chem.* **2013**, *5,* 54–60.

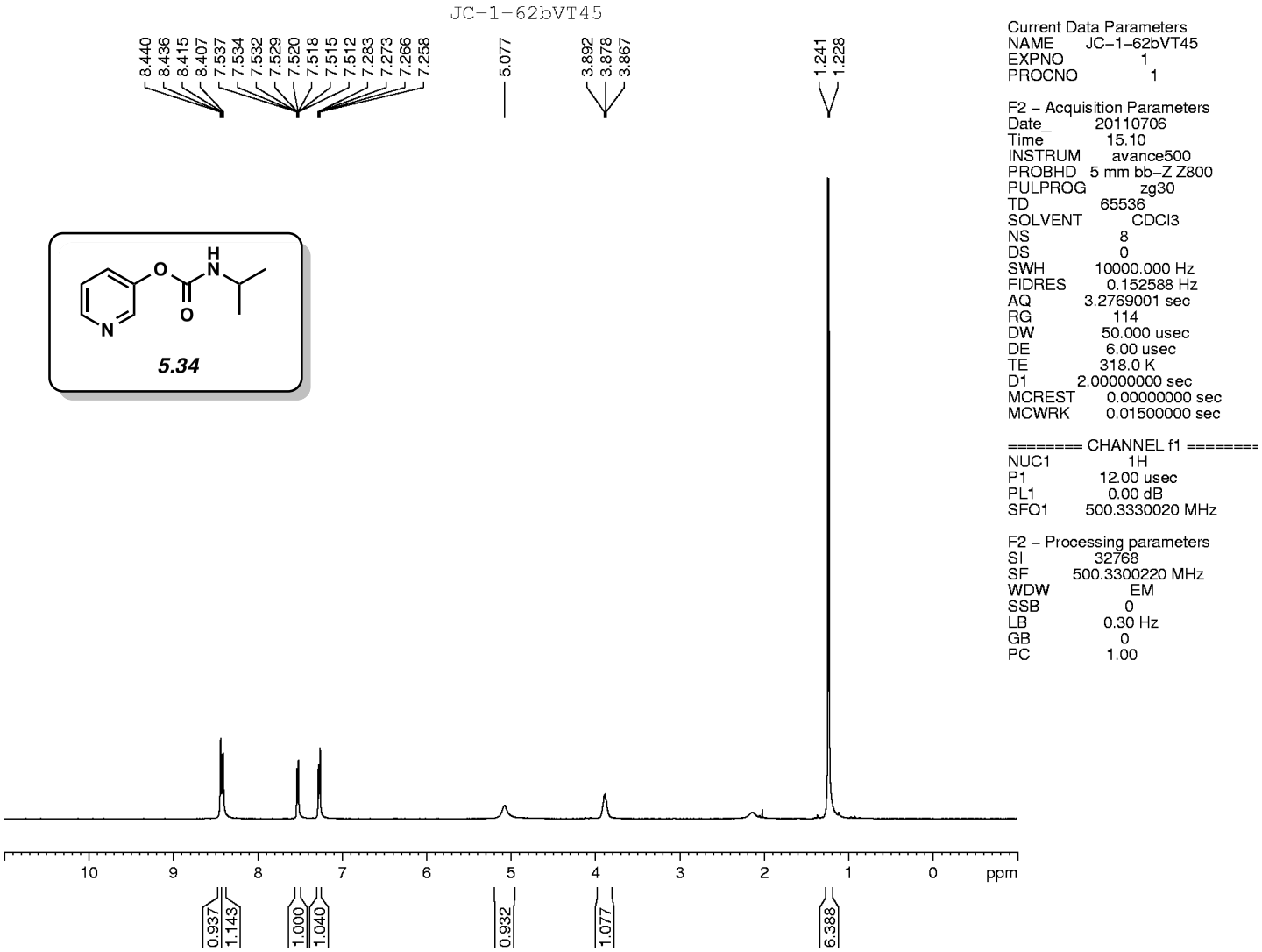



*Figure A3.1* $^{1}$H NMR (500 MHz, 45 ºC, $CDCl_3$) of compound **5.34**.

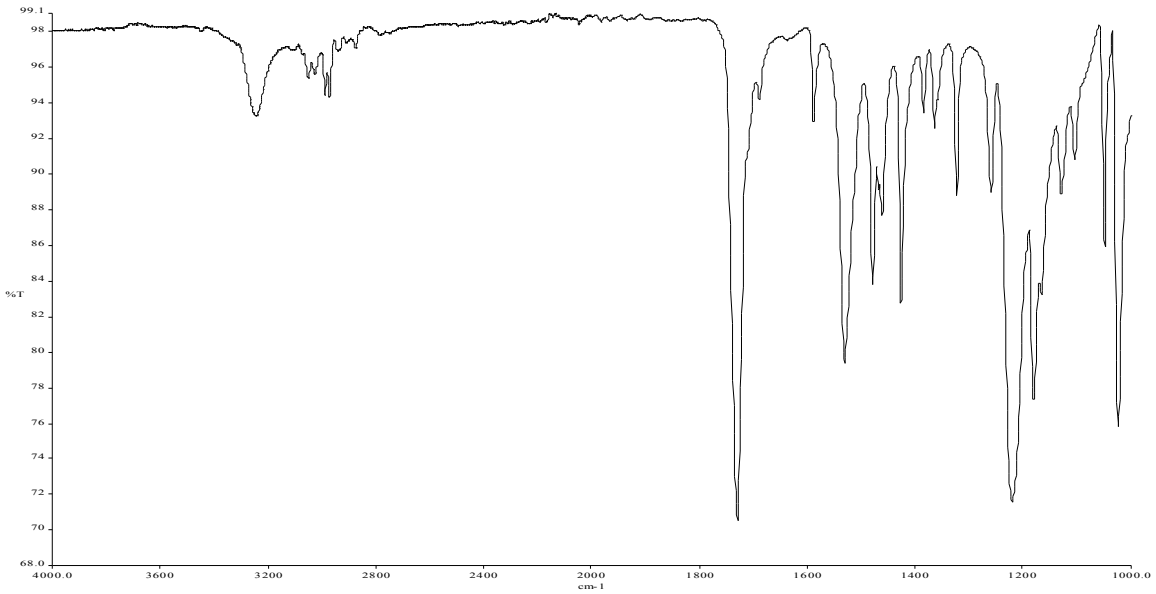



*Figure A3.2* Infrared spectrum of compound **5.34**.

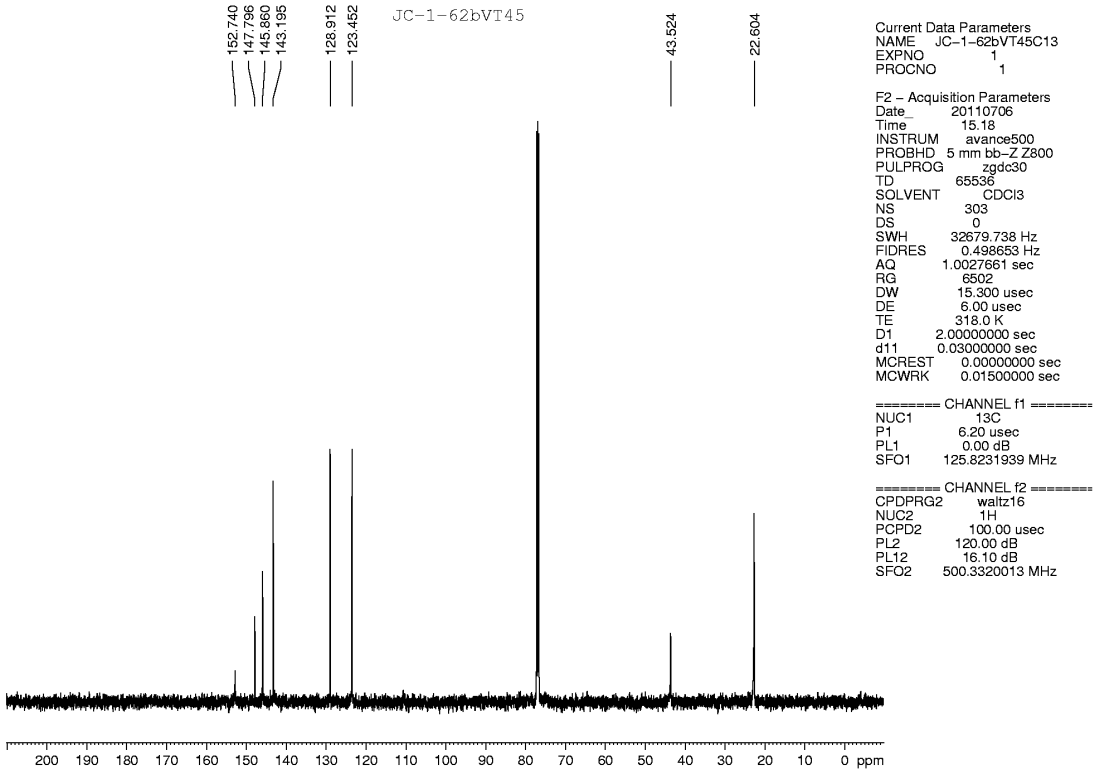



*Figure A3.3* $^{13}C$ NMR (125 MHz, 45 ºC, $CDCl_3$) of compound **5.34**.

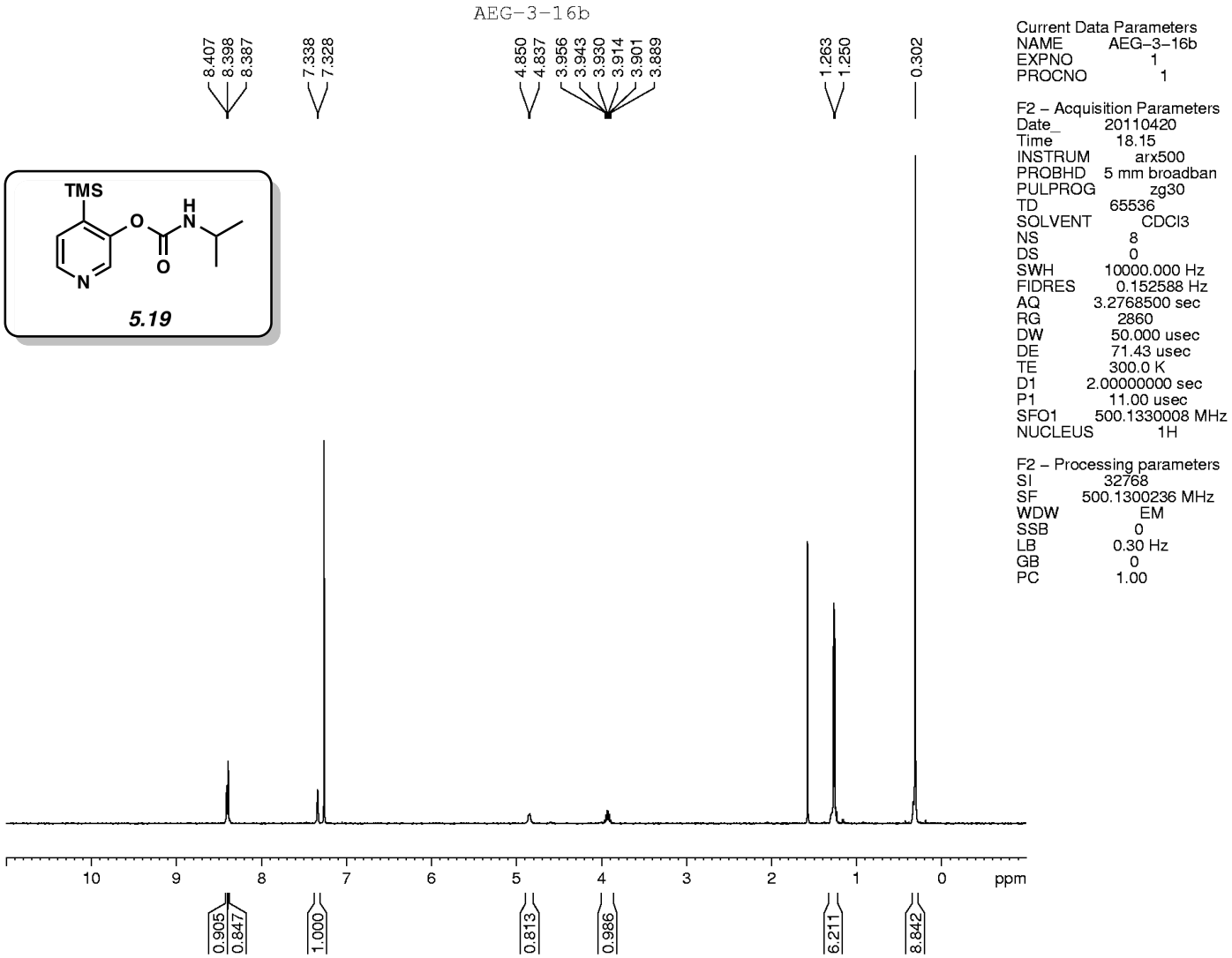



*Figure A3.4* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **5.19**.

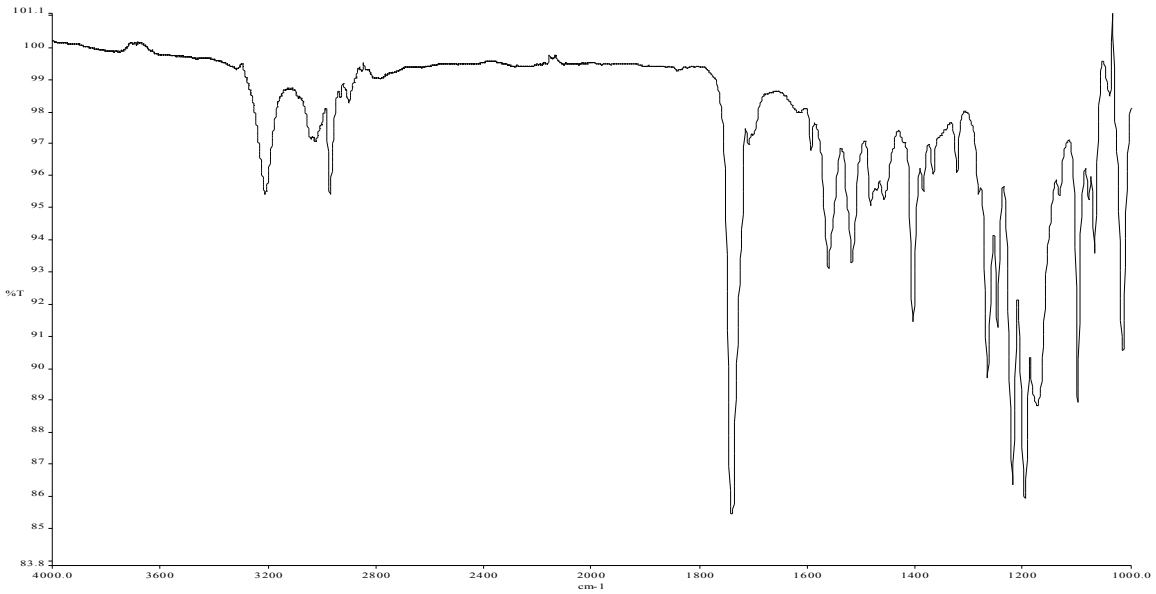



*Figure A3.5* Infrared spectrum of compound **5.19**.

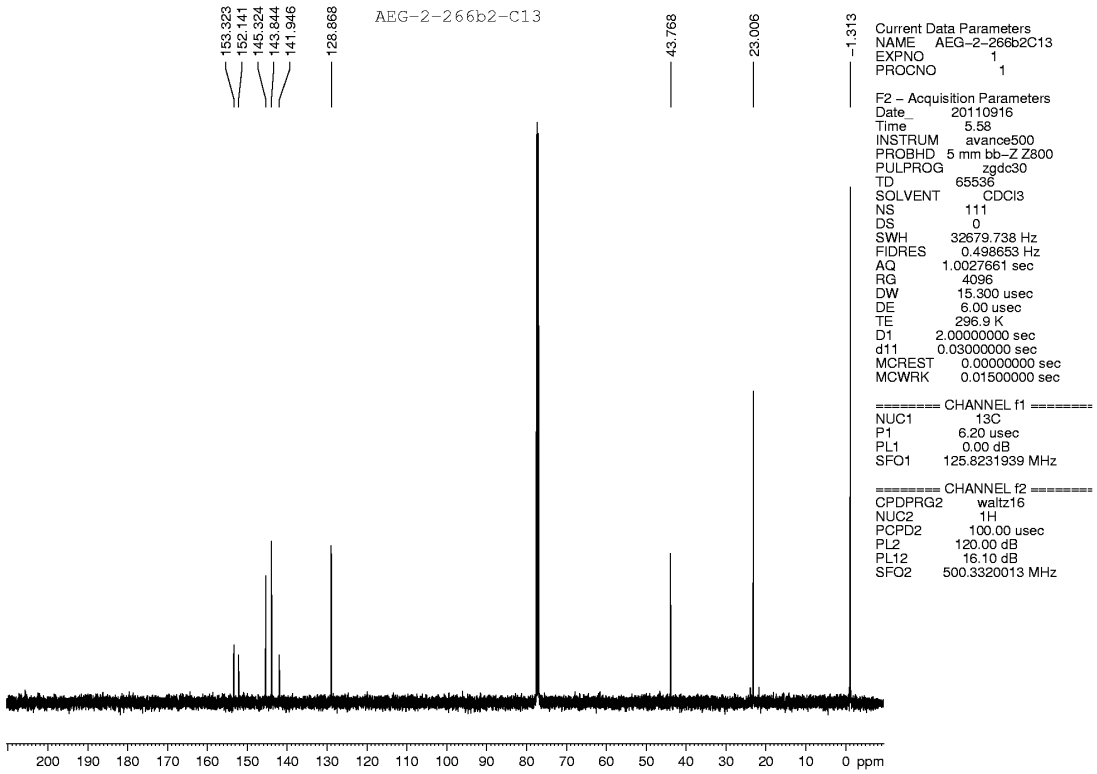



*Figure A3.6* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compound **5.19**.

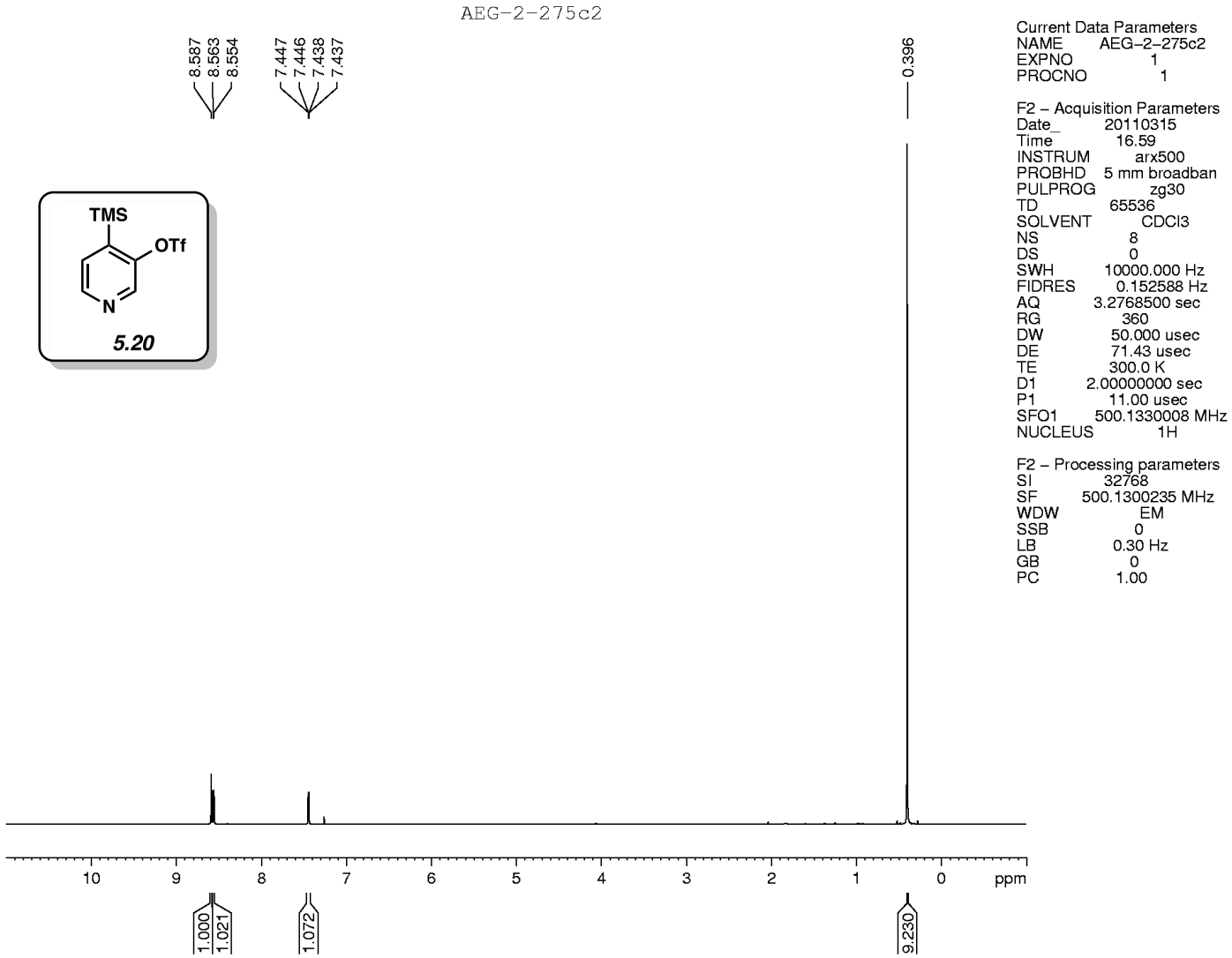



*Figure A3.7* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **5.20**.

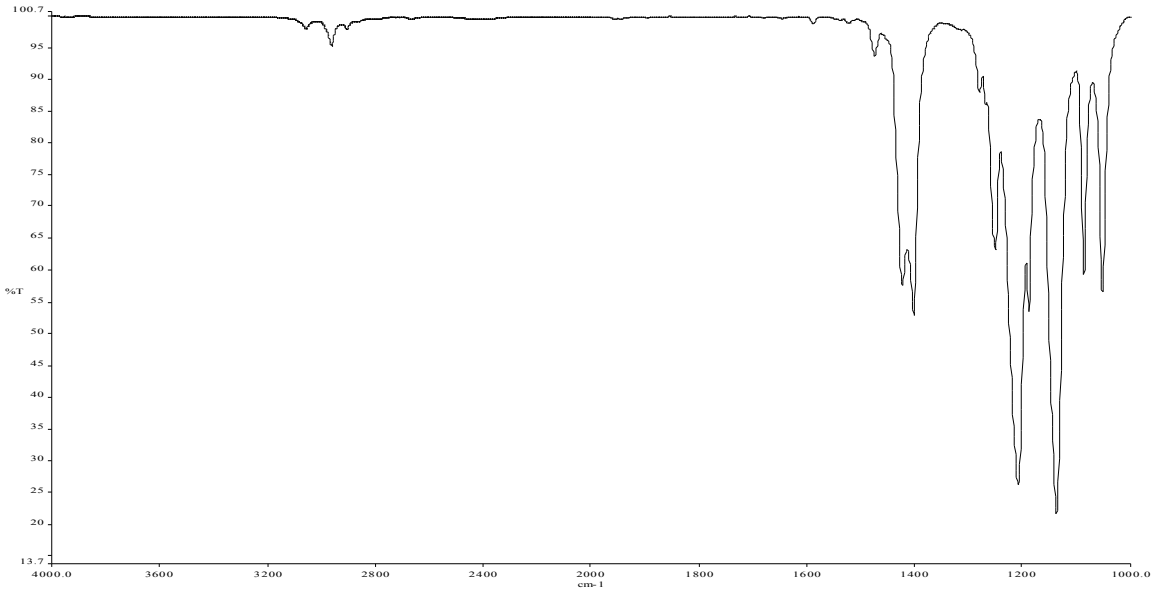



*Figure A3.8* Infrared spectrum of compound **5.20**.

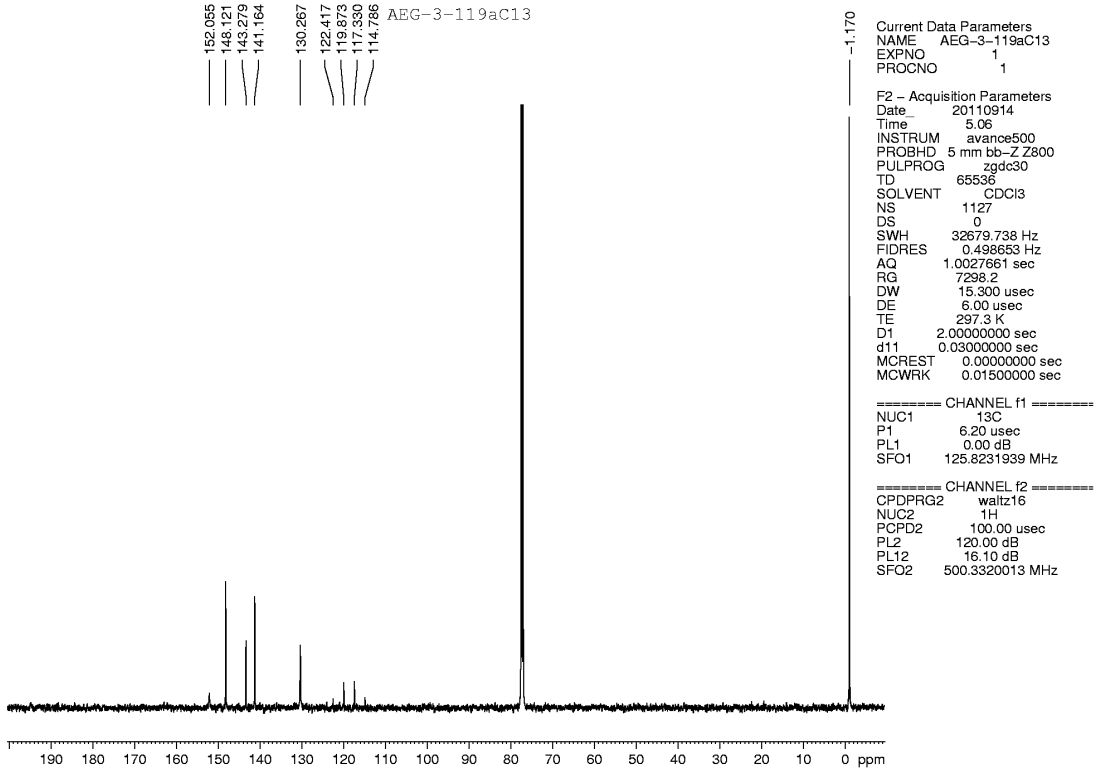



*Figure A3.9* $^{13}$C NMR (125 MHz, $CDCl_3$) of compound **5.20**.

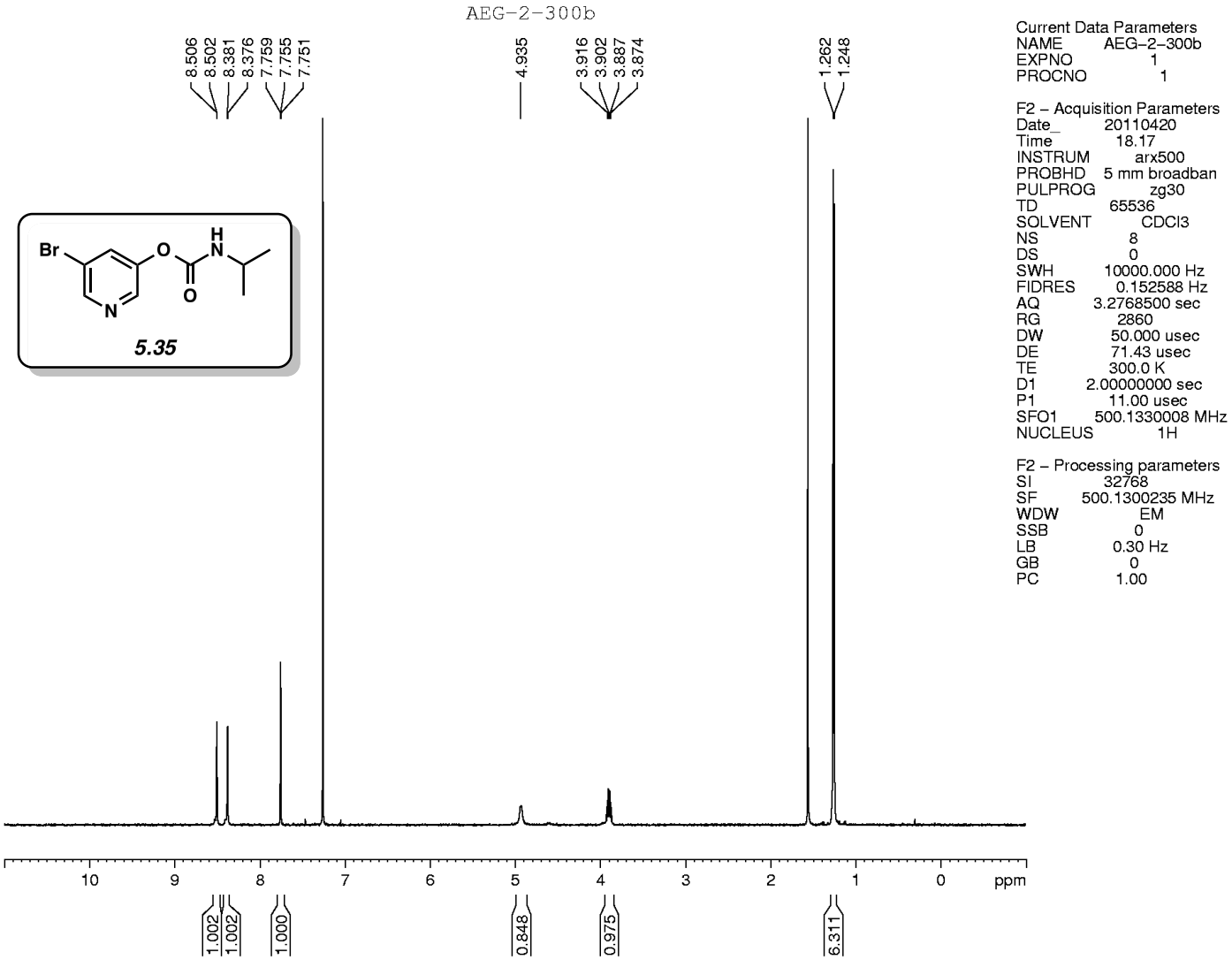



*Figure A3.10* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **5.35**.

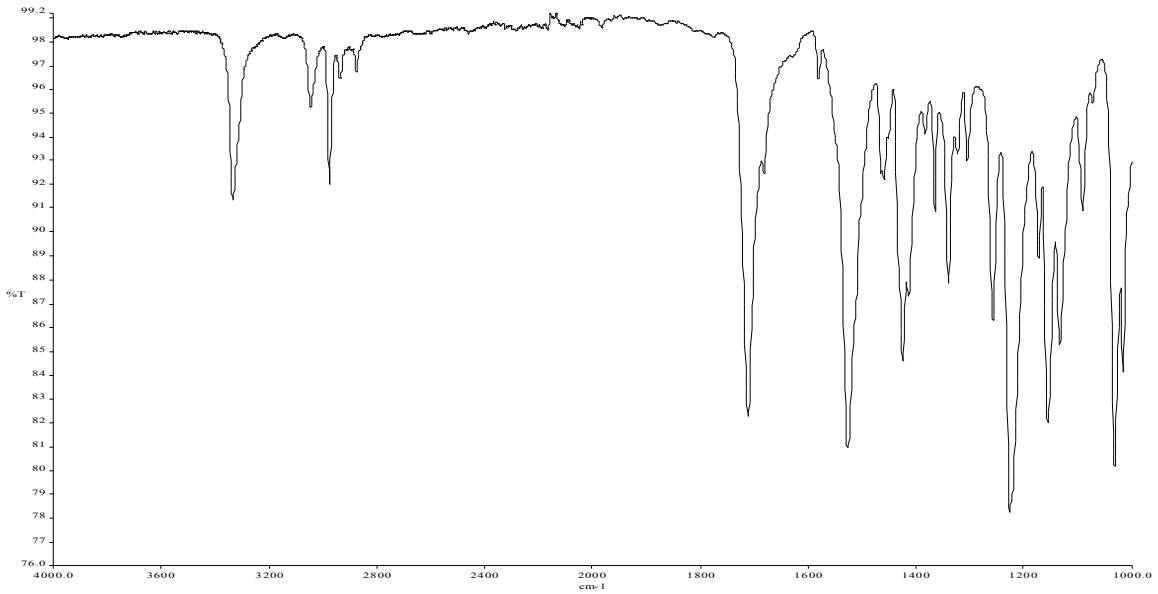



*Figure A3.11* Infrared spectrum of compound **5.35**.

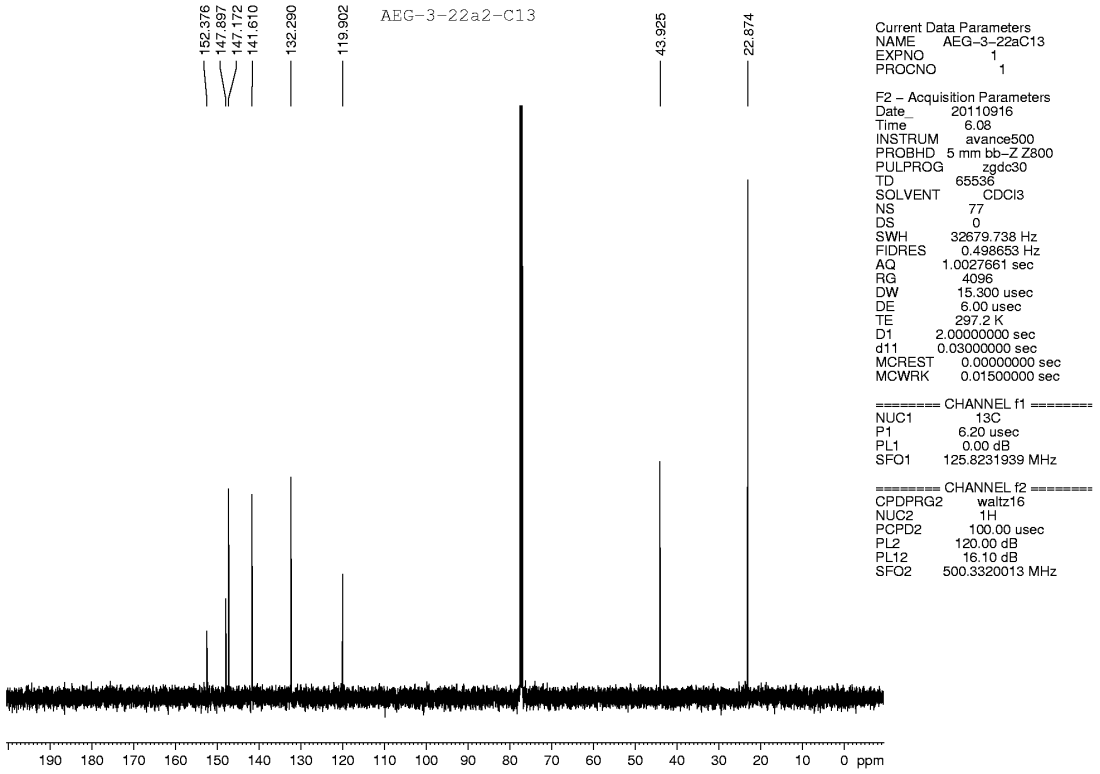



*Figure A3.12* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compound **5.35**.

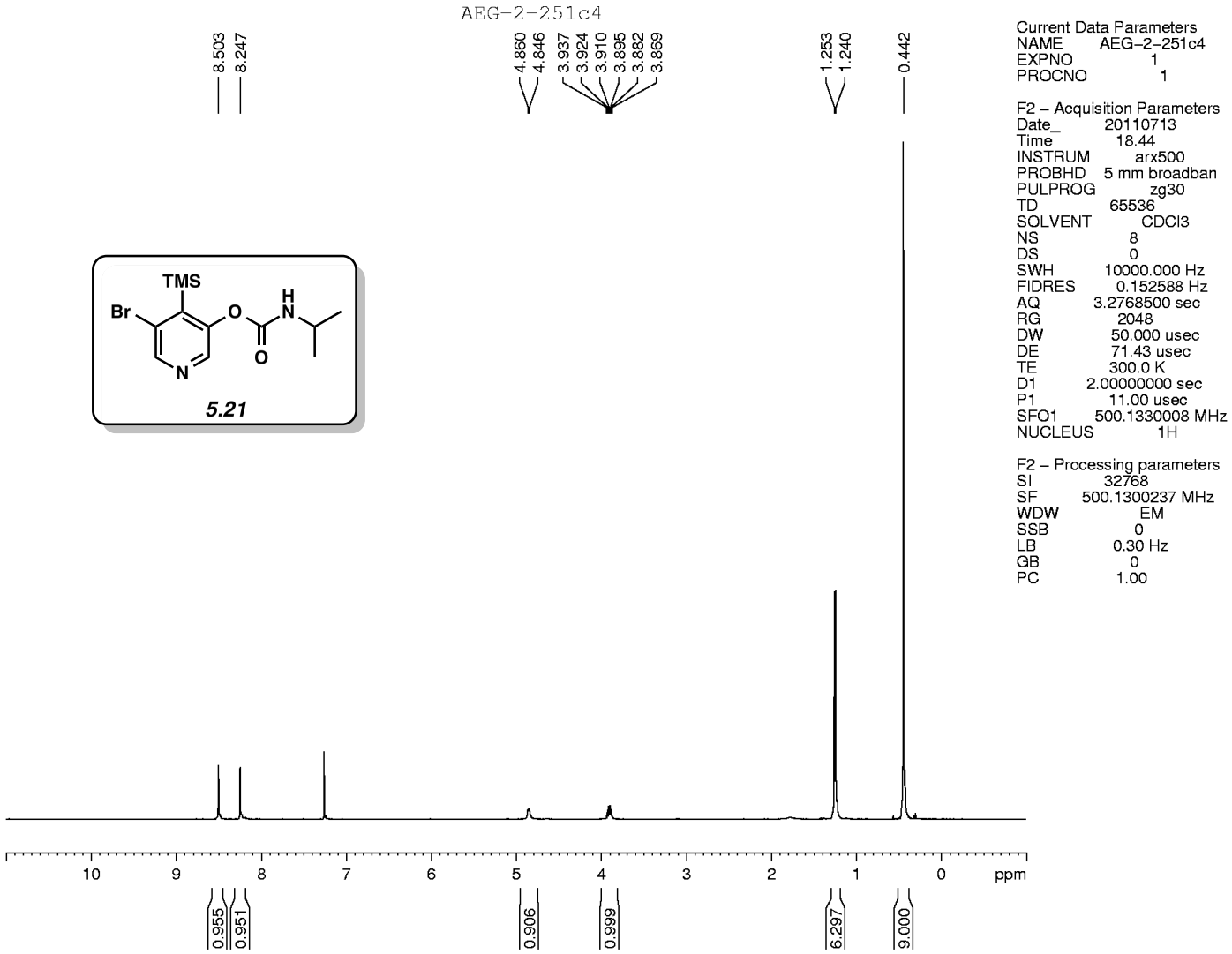



*Figure A3.13* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **5.21**.

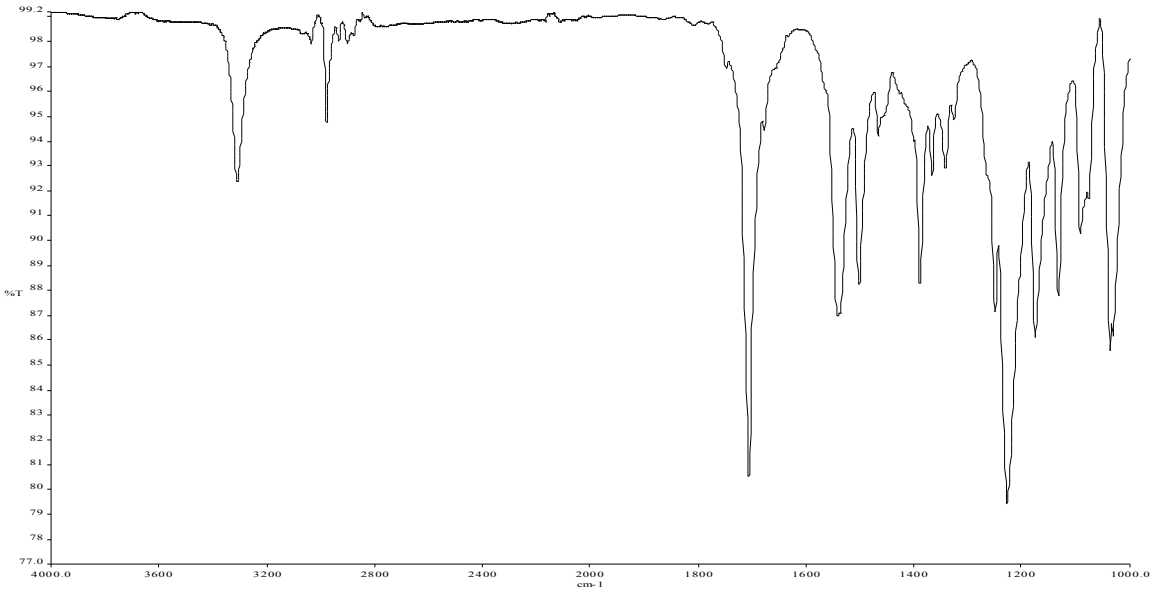



*Figure A3.14* Infrared spectrum of compound **5.21**.

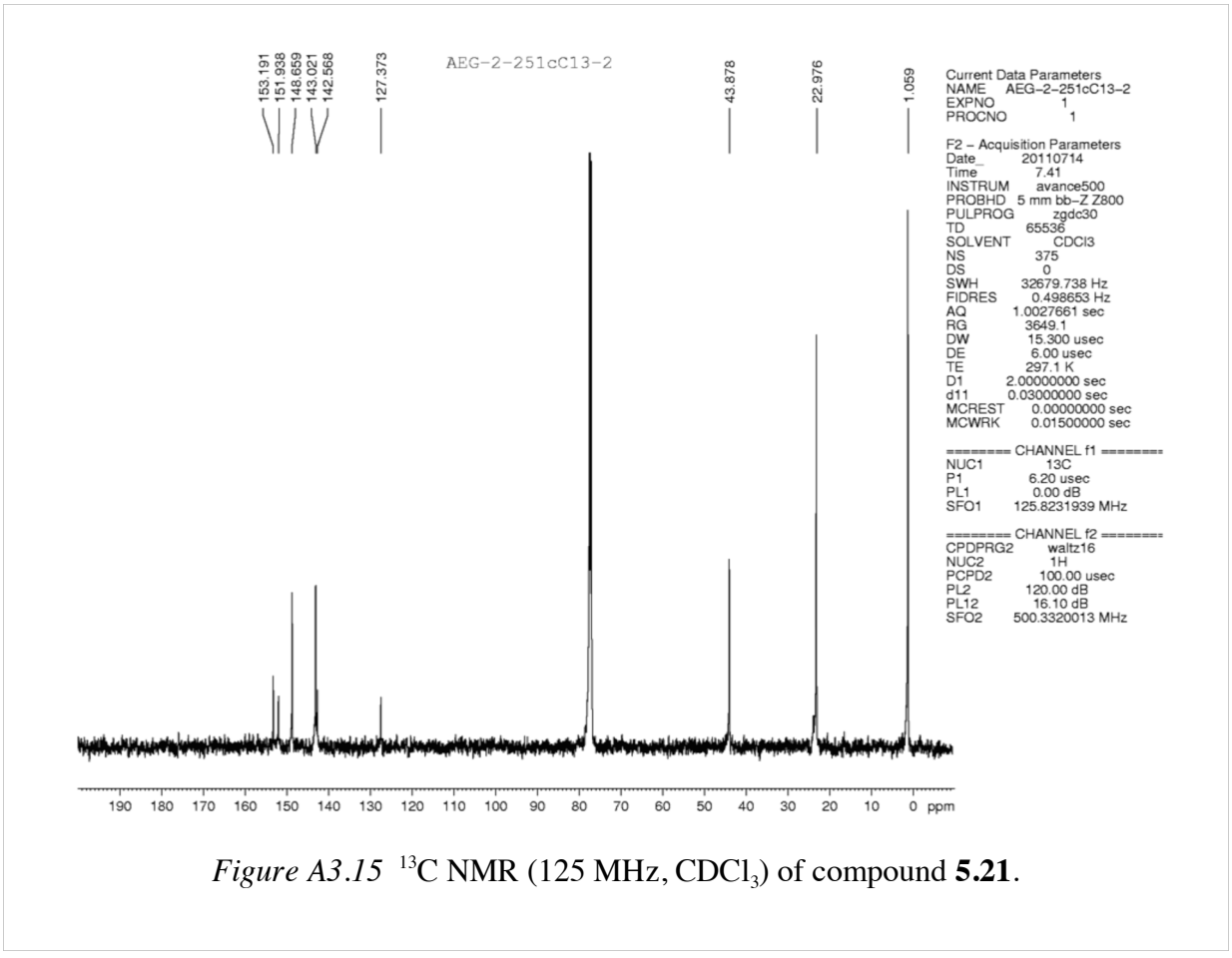



*Figure A3.15* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compound **5.21**.

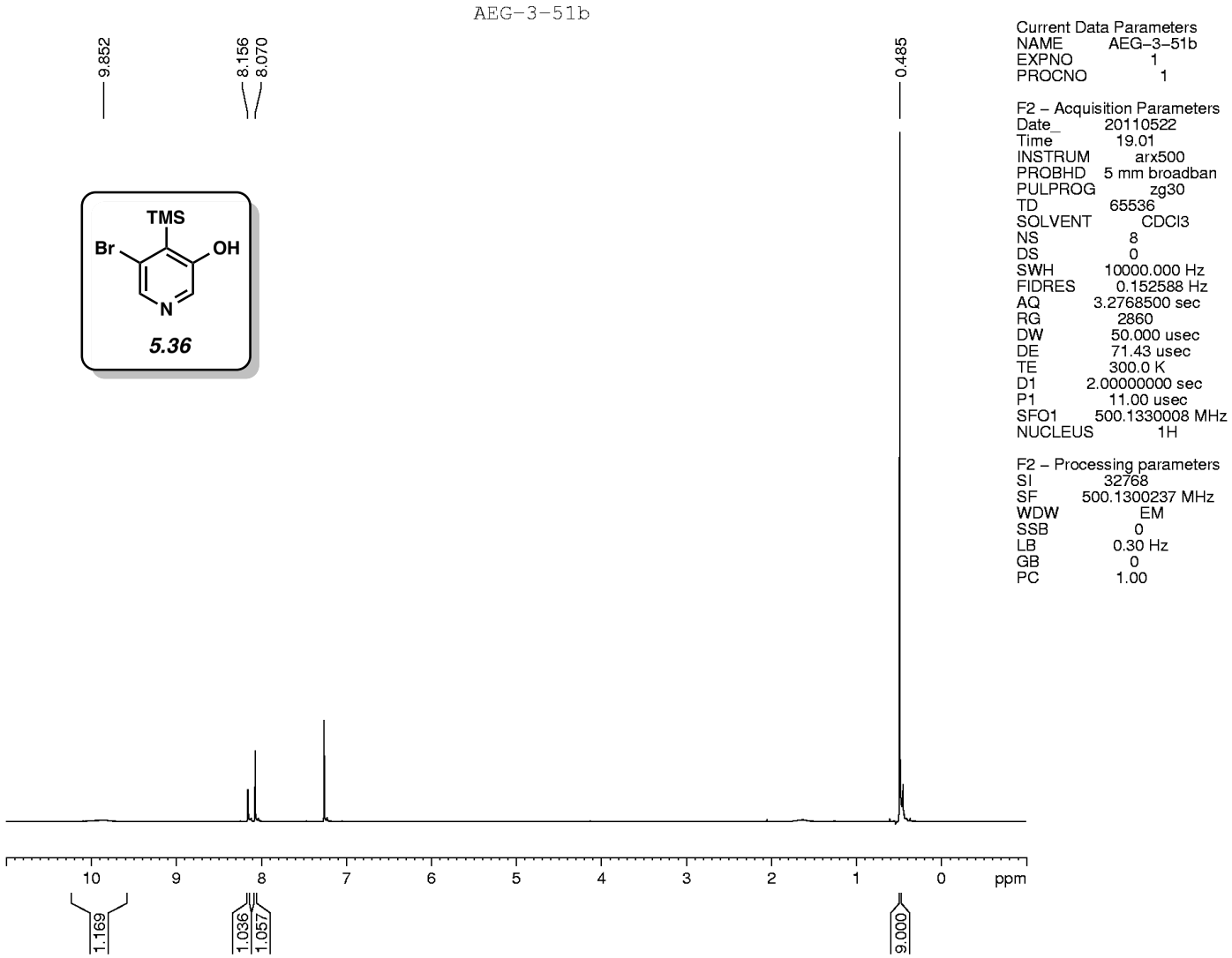



*Figure A3.16* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **5.36**.

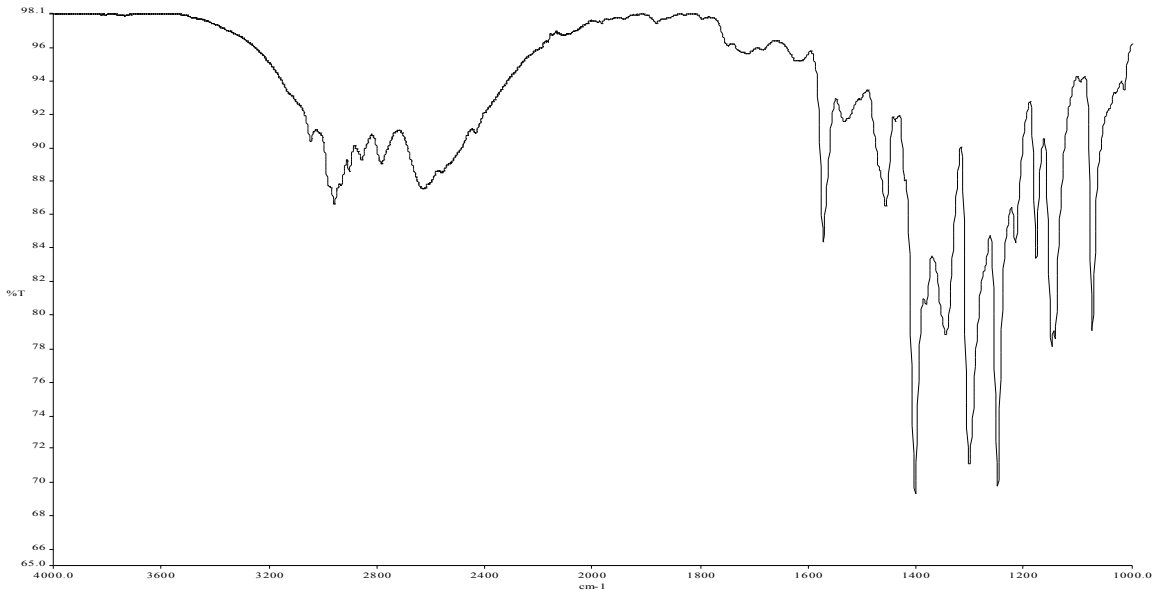



*Figure A3.17* Infrared spectrum of compound **5.36**.

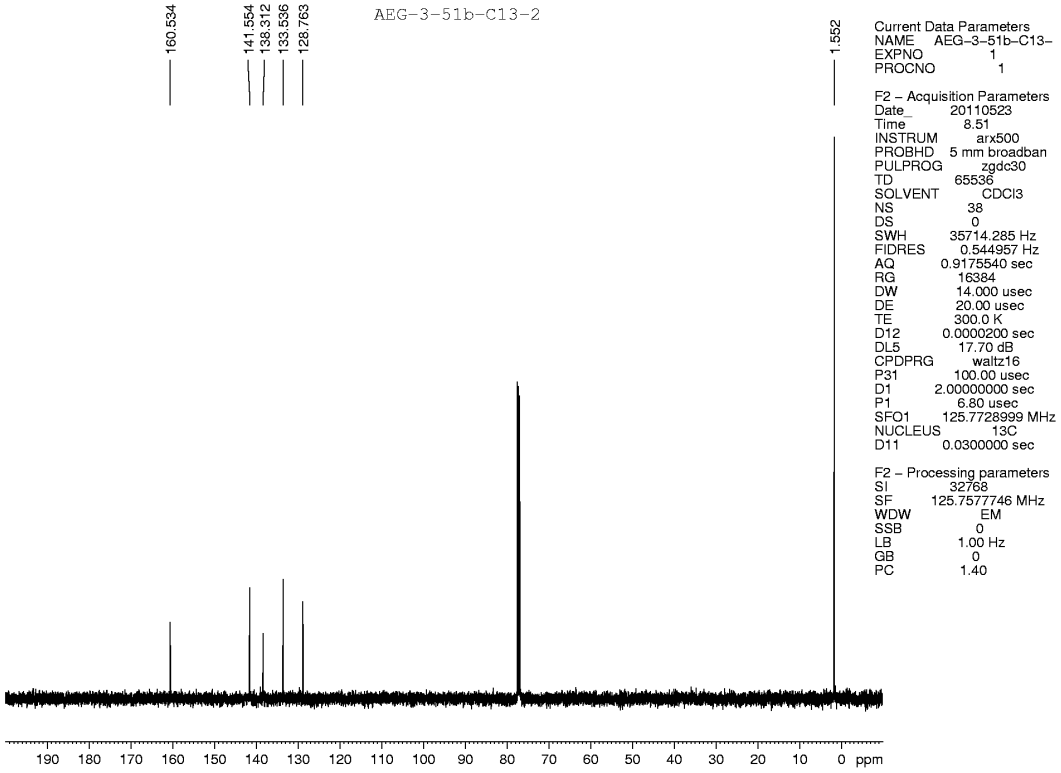



*Figure A3.18* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compound **5.36**.

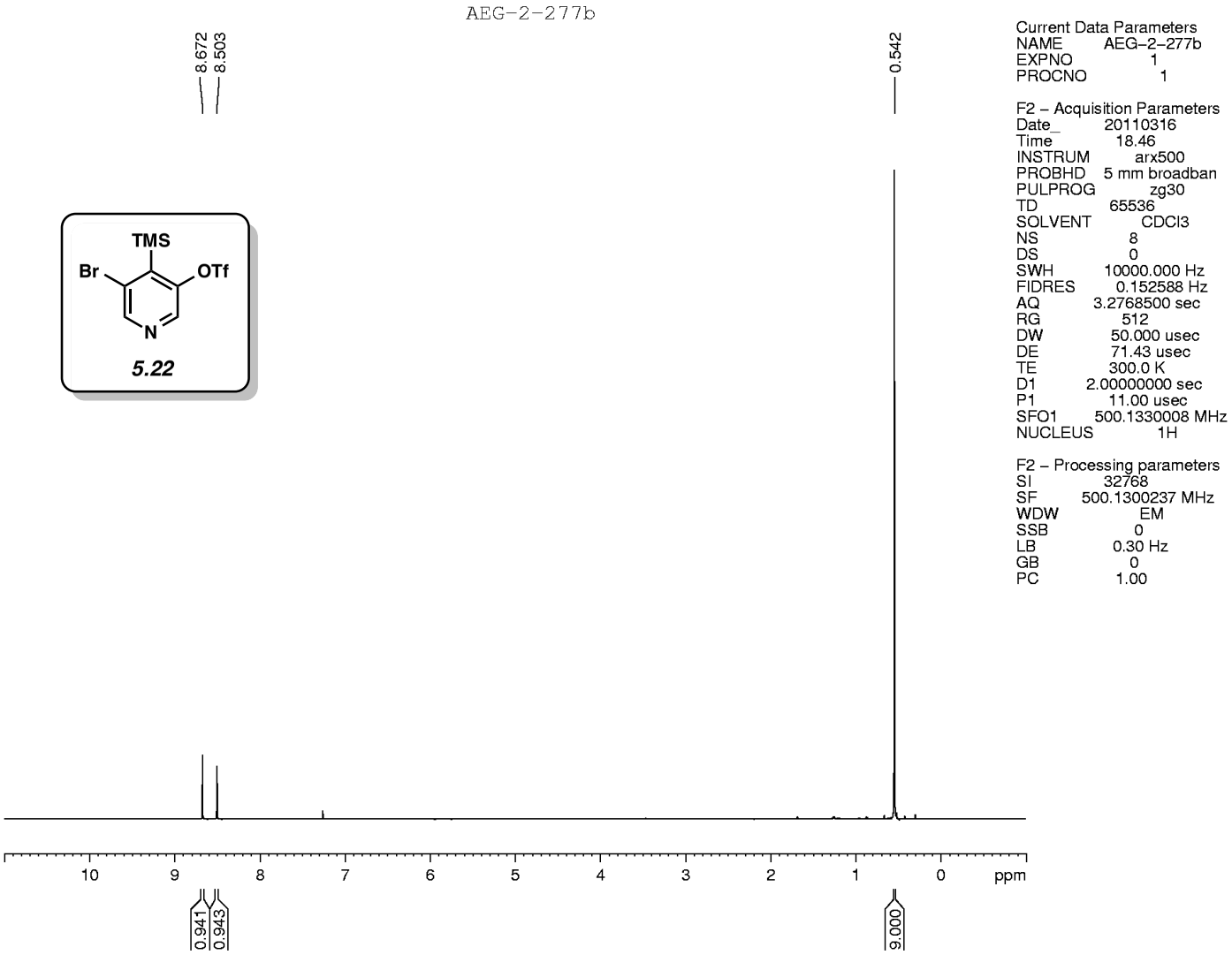



*Figure A3.19* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **5.22**.

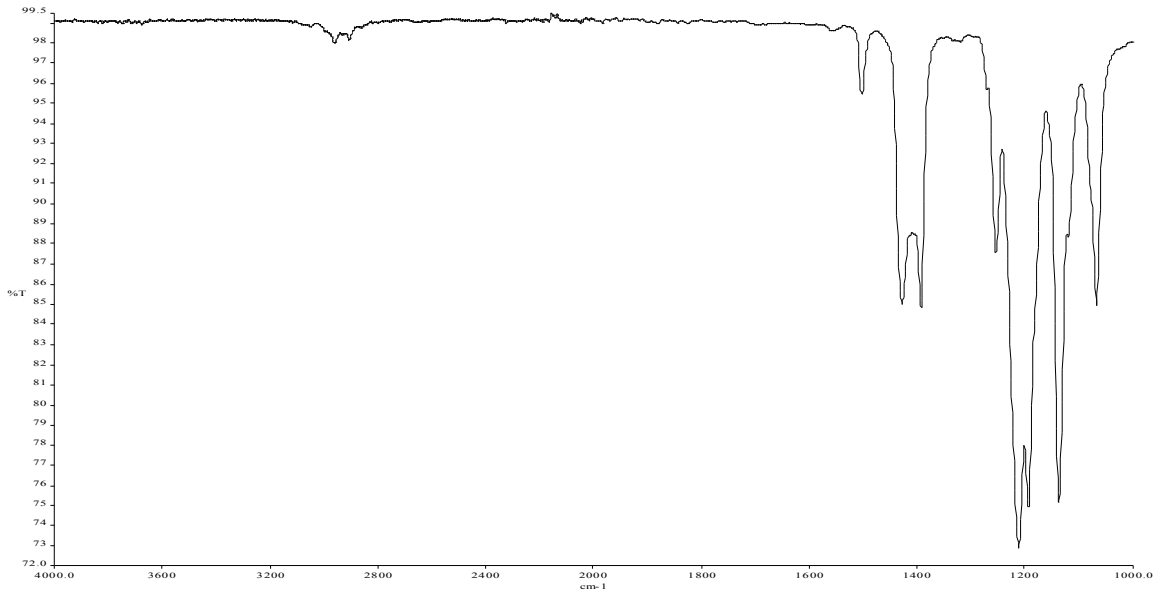



*Figure A3.20* Infrared spectrum of compound **5.22**.

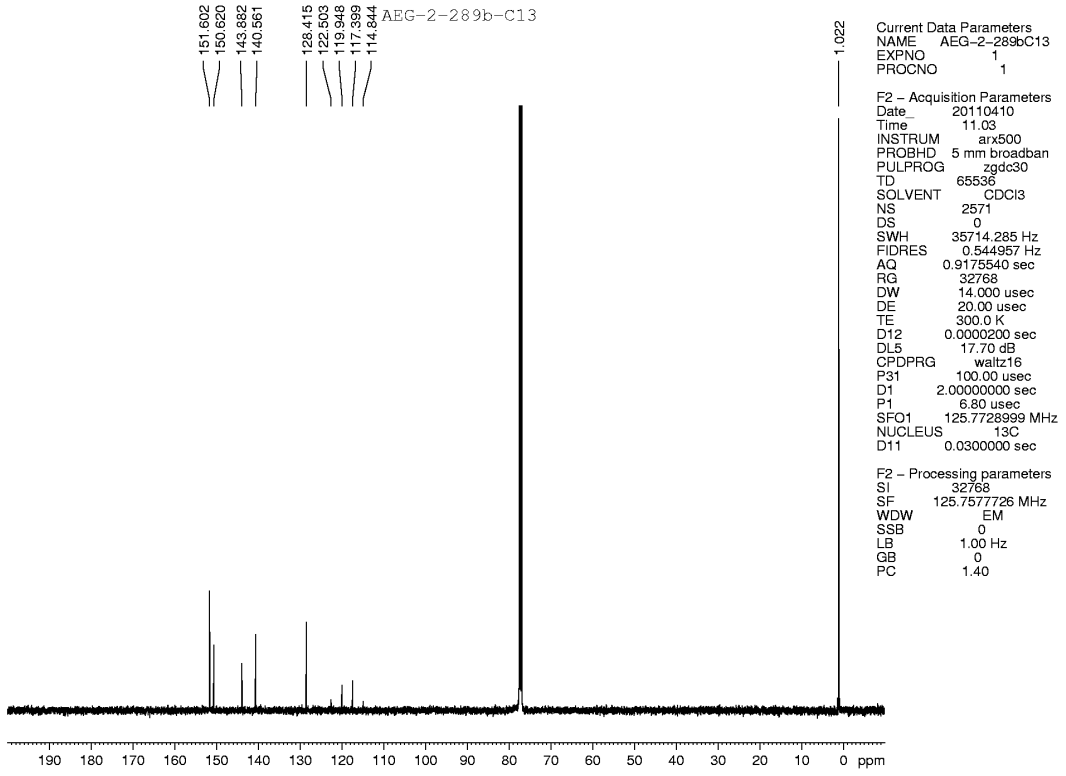



*Figure A3.21* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compound **5.22**.

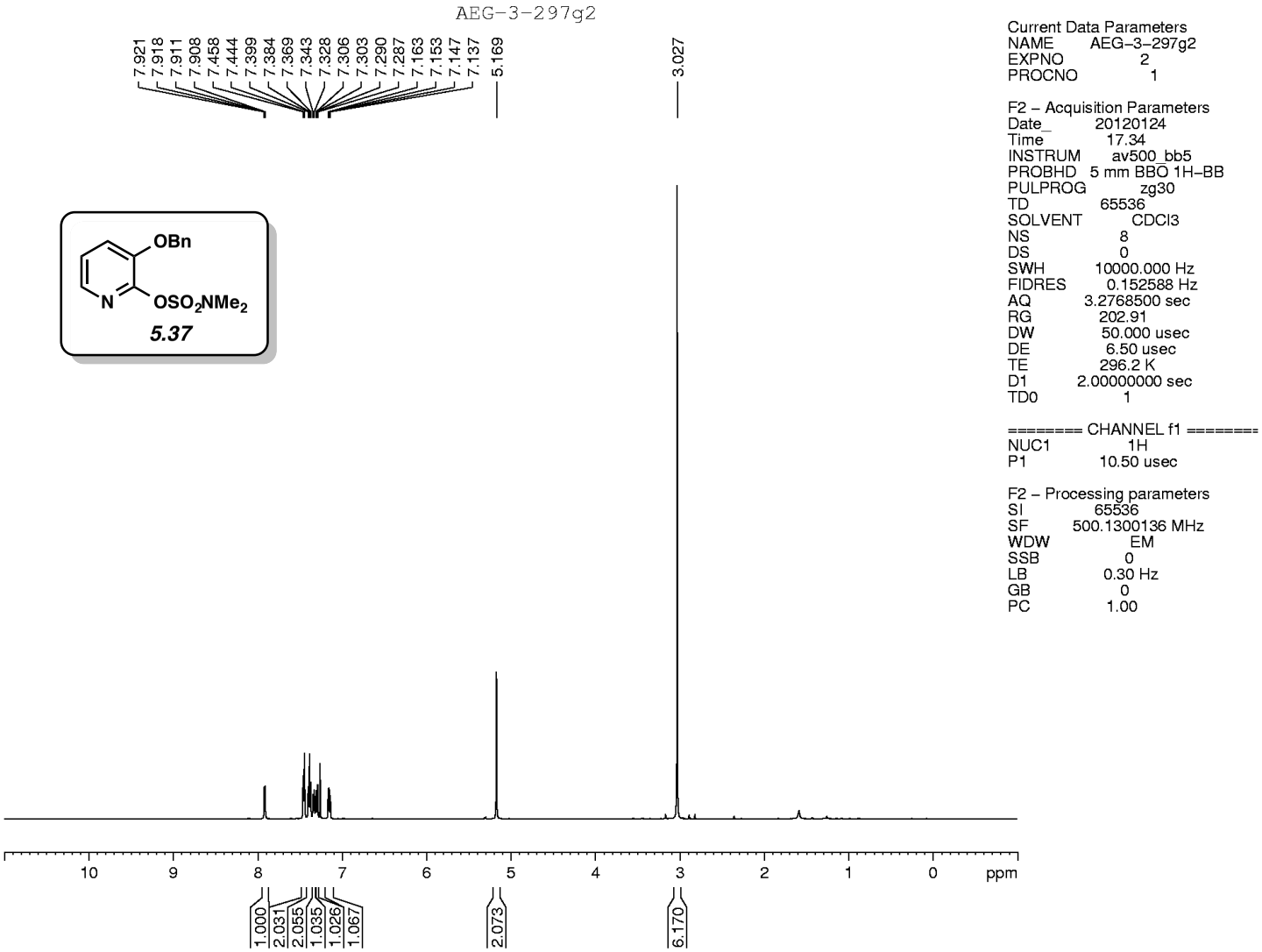



*Figure A3.22* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **5.37**.

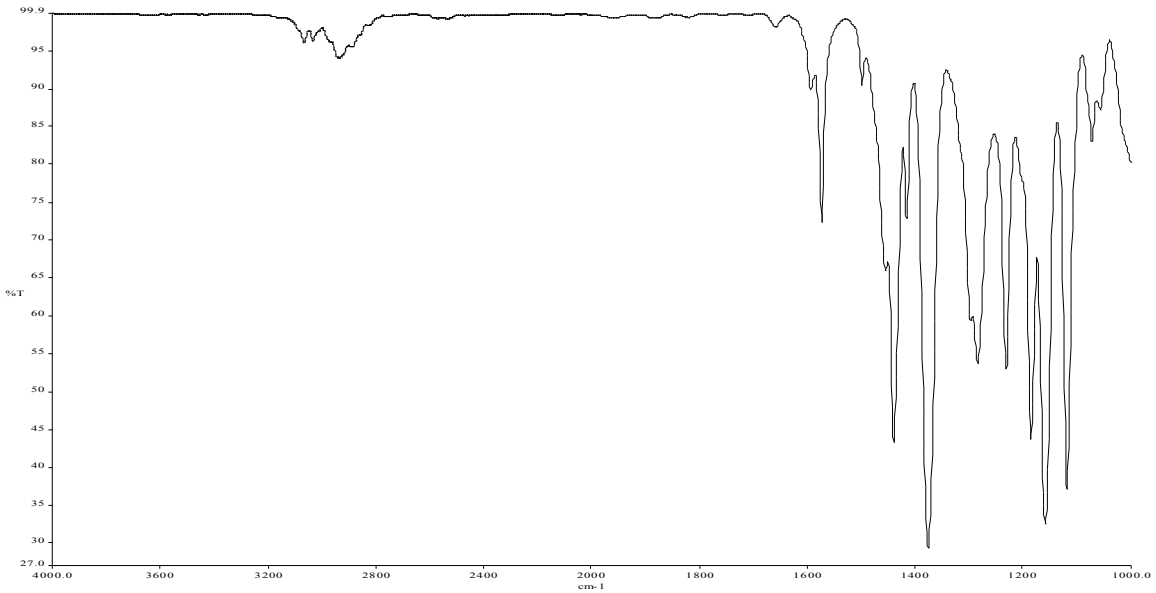



*Figure A3.23* Infrared spectrum of compound **5.37**.

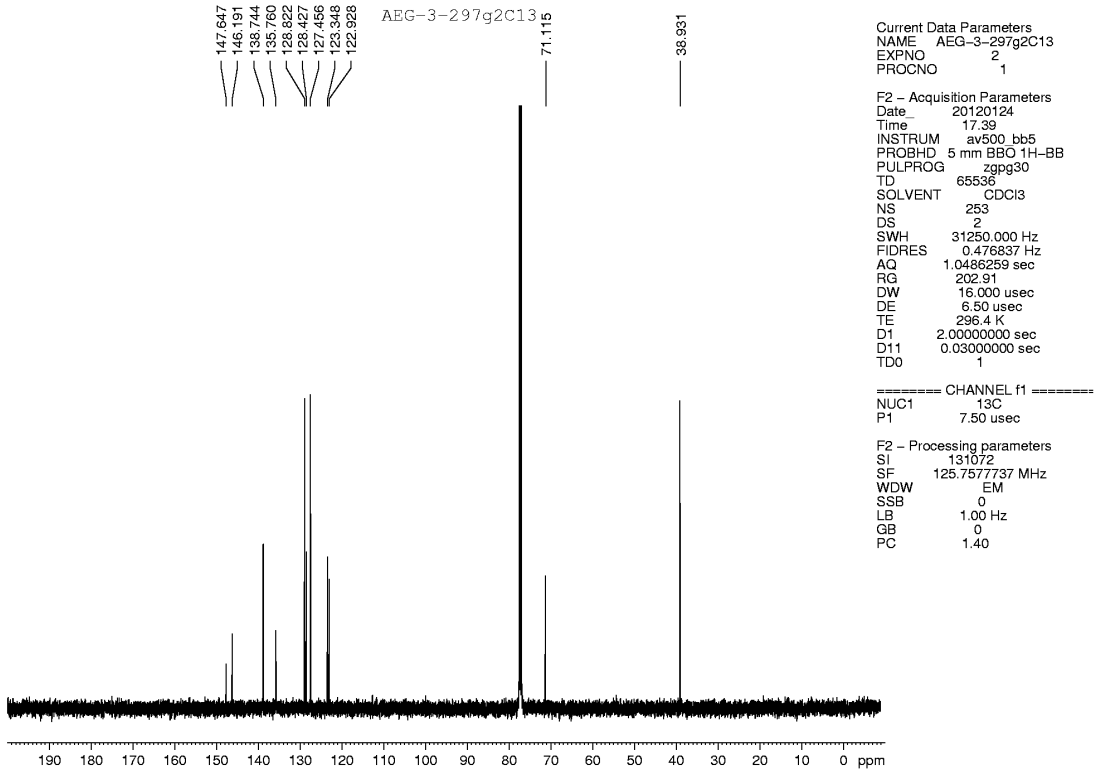



*Figure A3.24* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compound **5.37**.

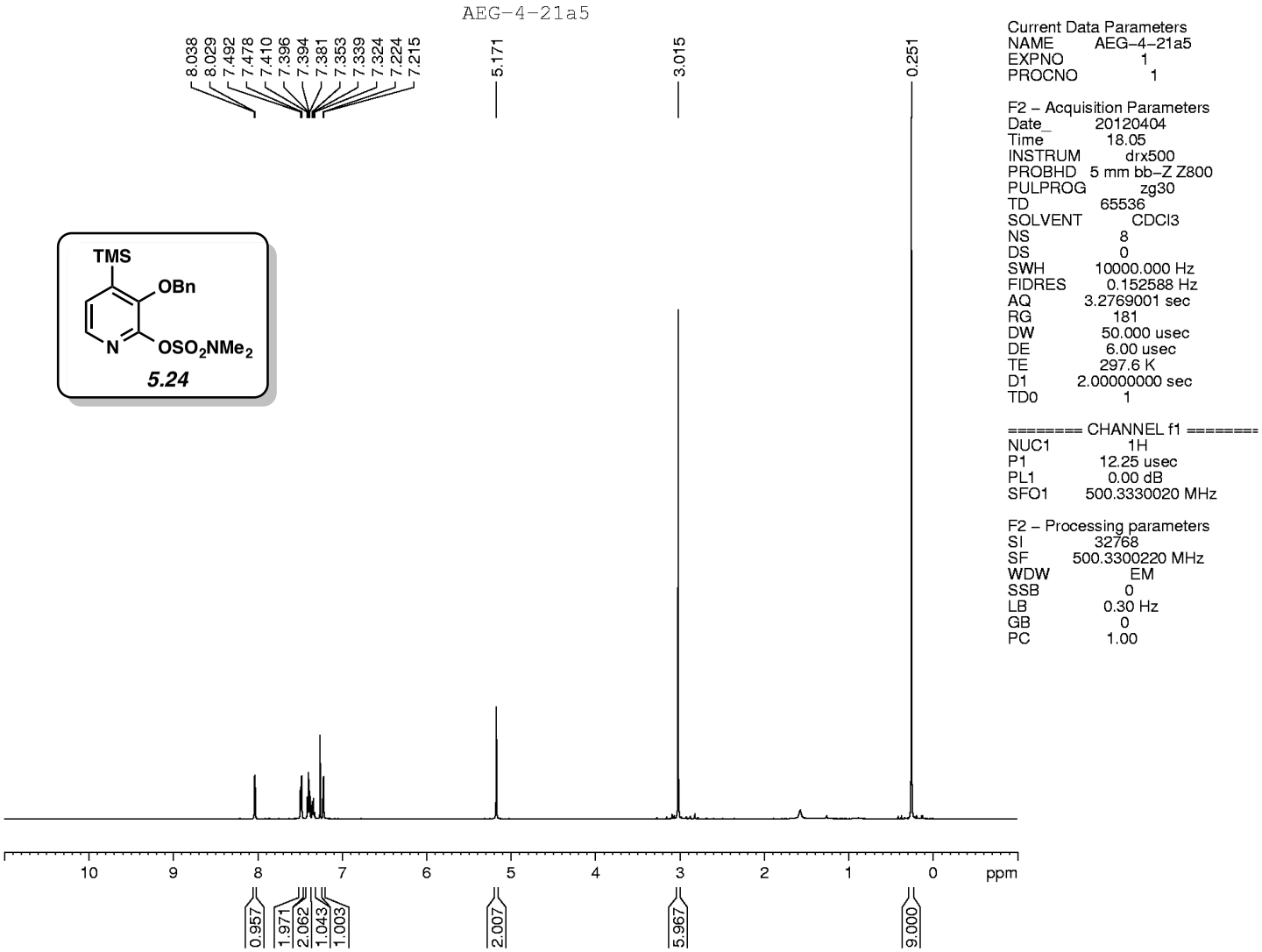



*Figure A3.25* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **5.24**.

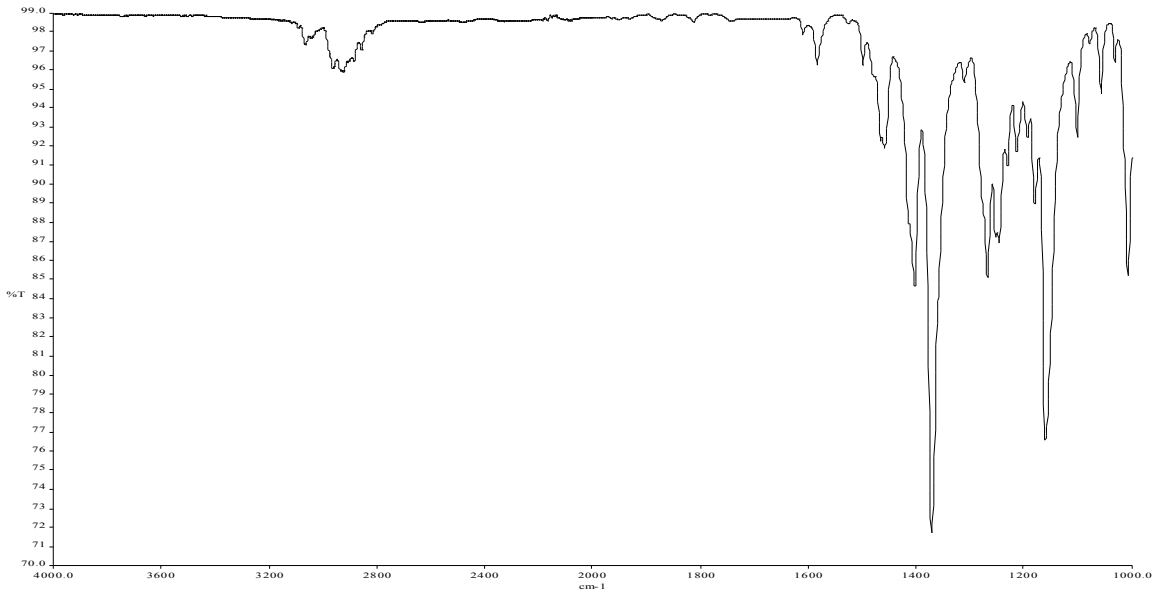



*Figure A3.26* Infrared spectrum of compound **5.24**.

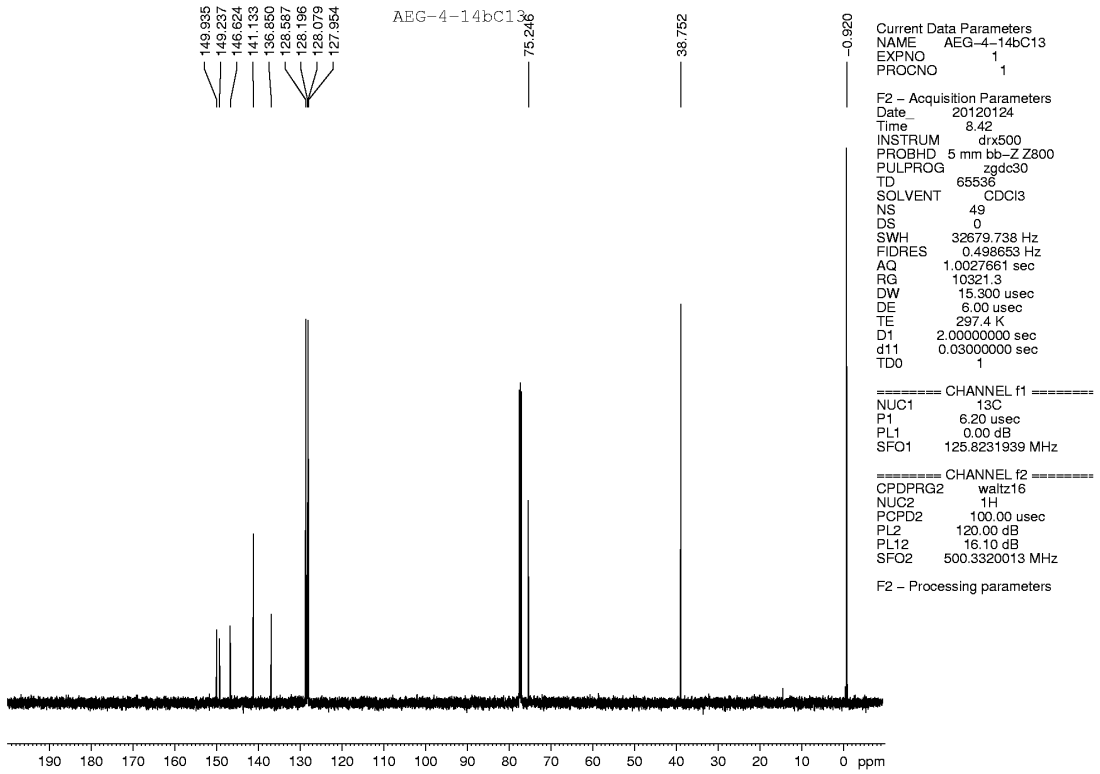



*Figure A3.27* $^{13}$C NMR (125 MHz, $CDCl_3$) of compound **5.24**.

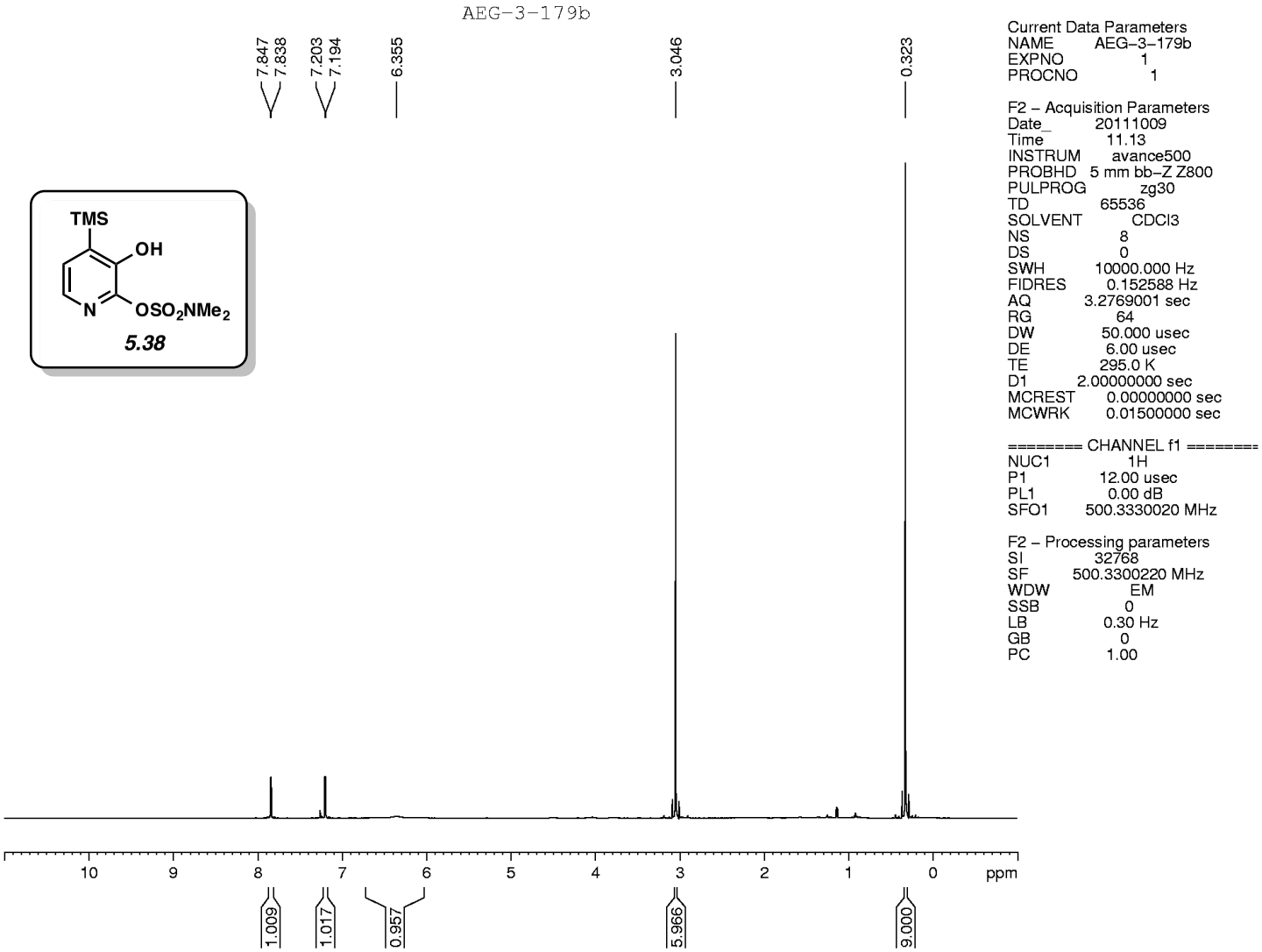



*Figure A3.28* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **5.38**.

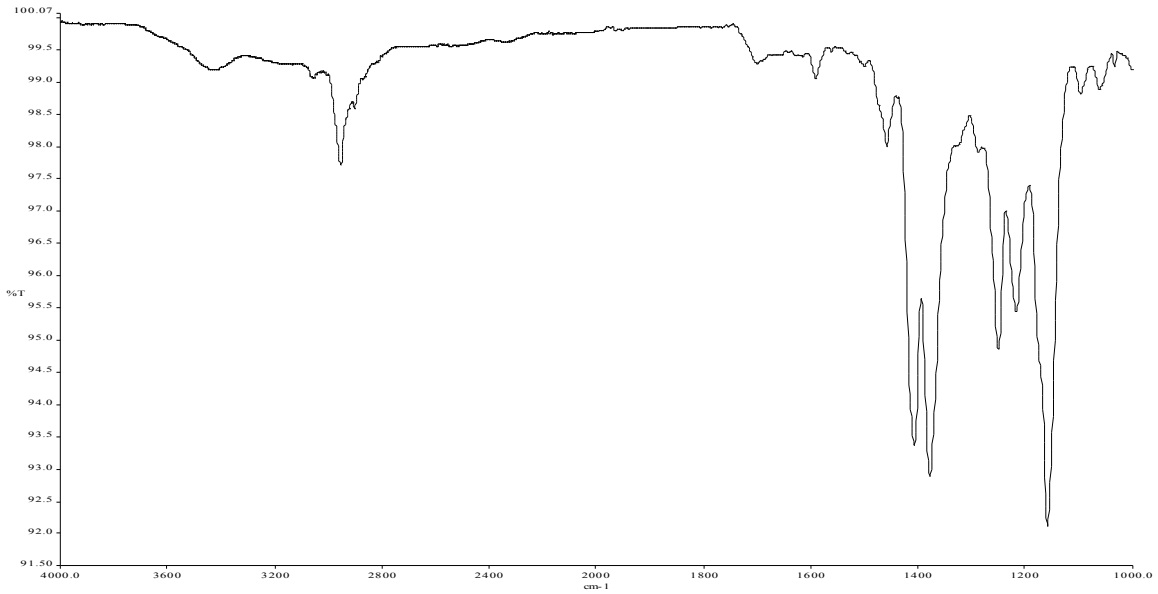



*Figure A3.29* Infrared spectrum of compound **5.38**.

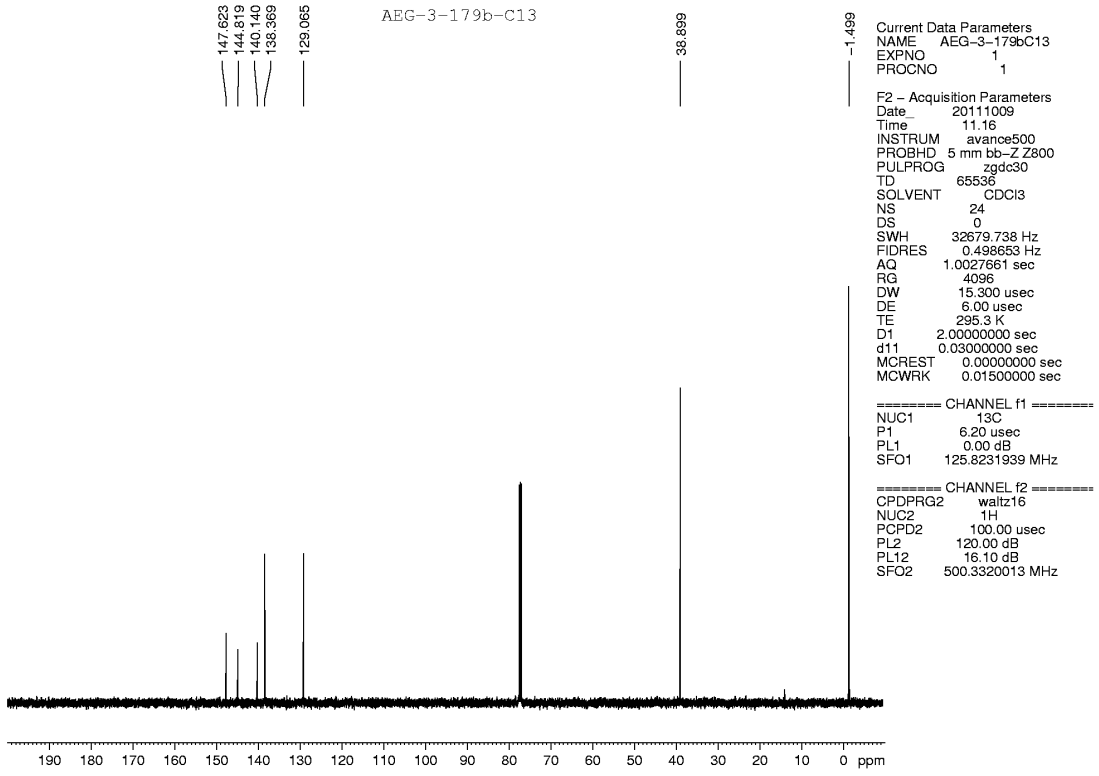



*Figure A3.30* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compound **5.38**.

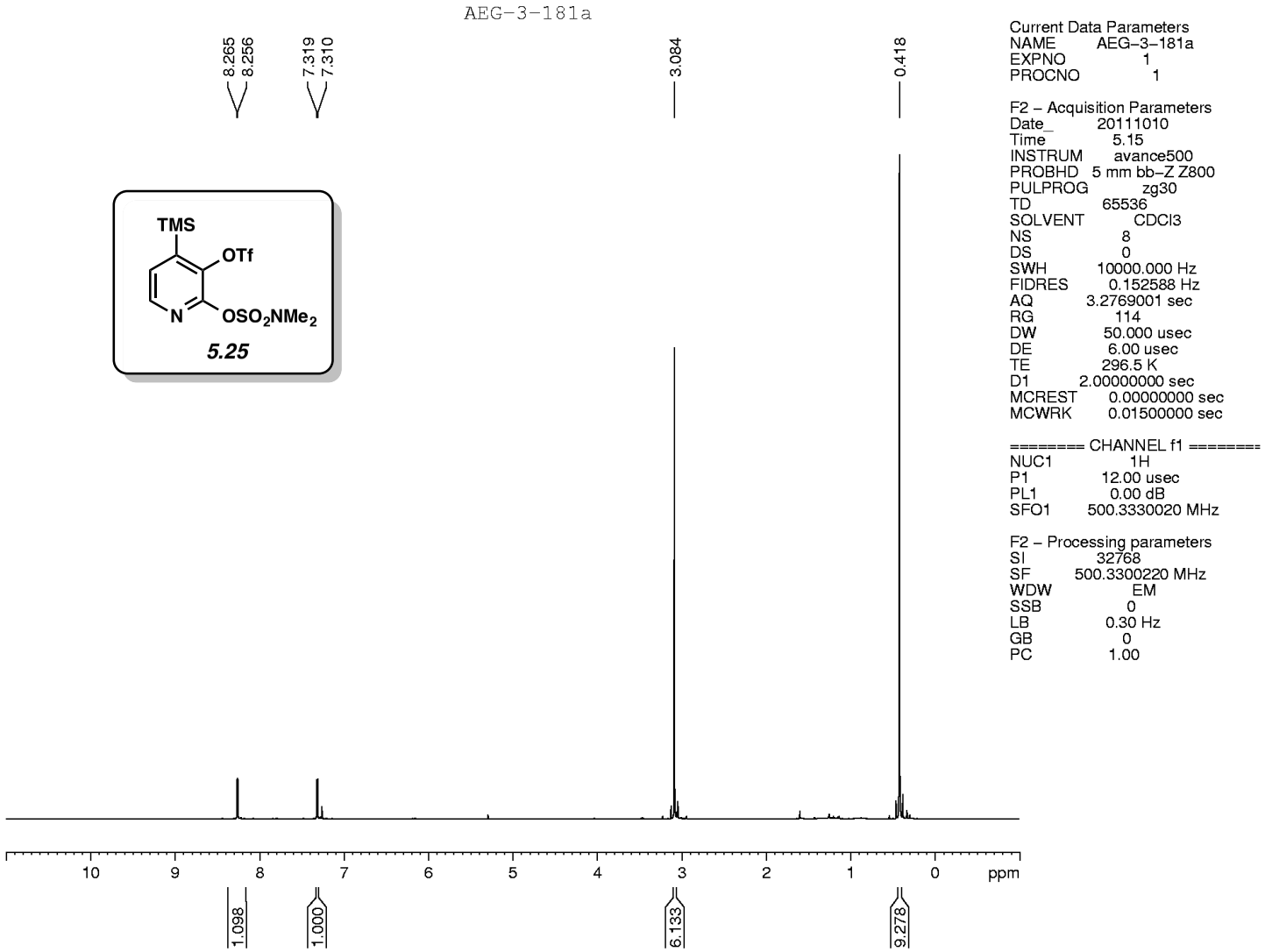



*Figure A3.31* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **5.25**.

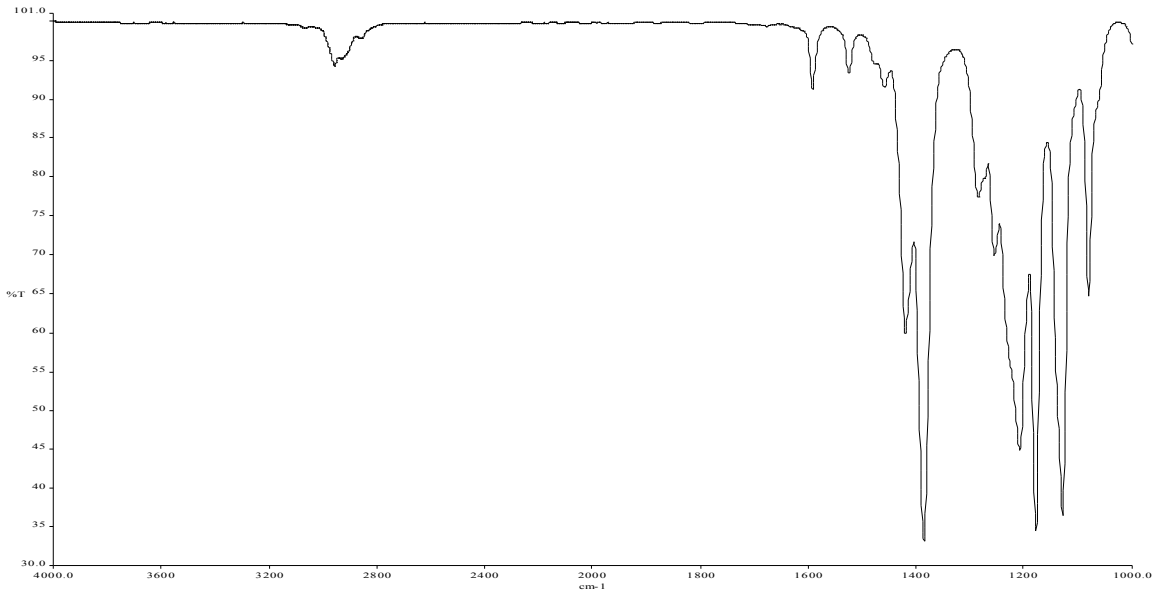



*Figure A3.32* Infrared spectrum of compound **5.25**.

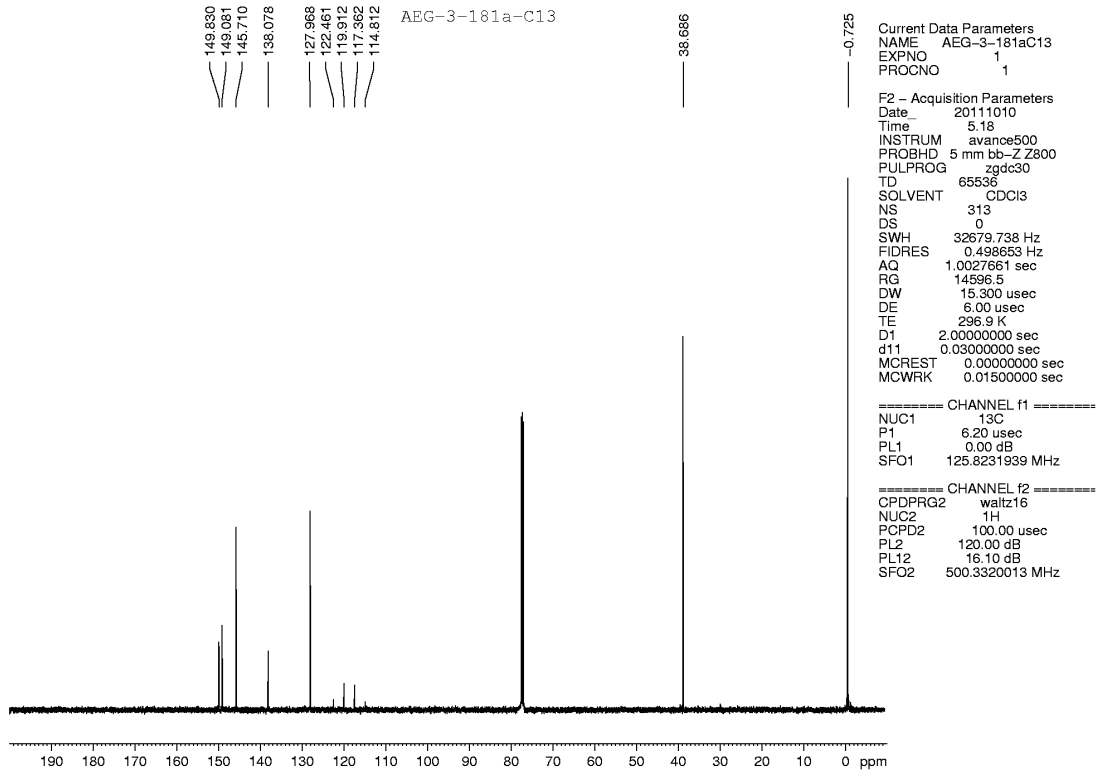



*Figure A3.33* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compound **5.25**.

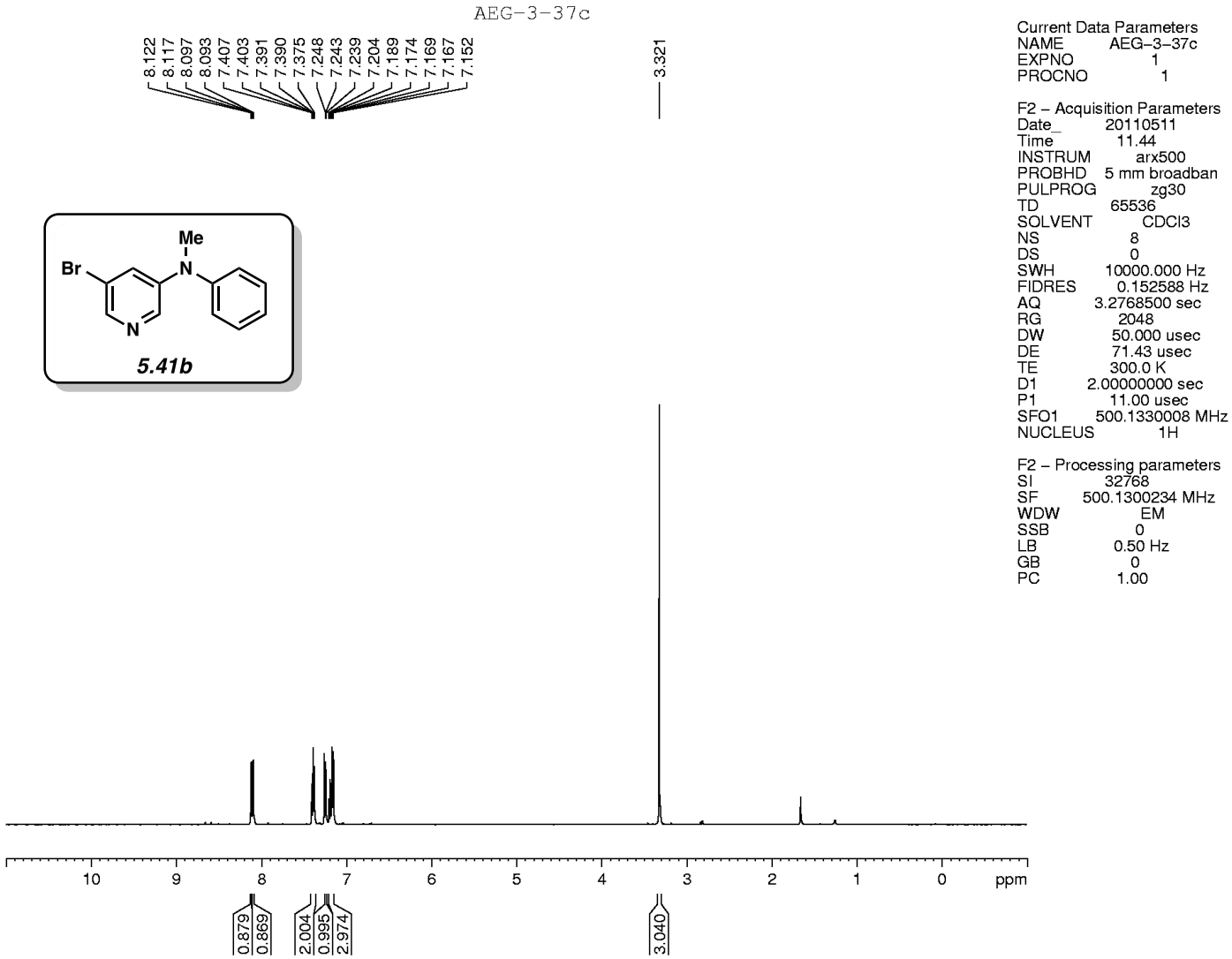



*Figure A3.34* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **5.41b**.

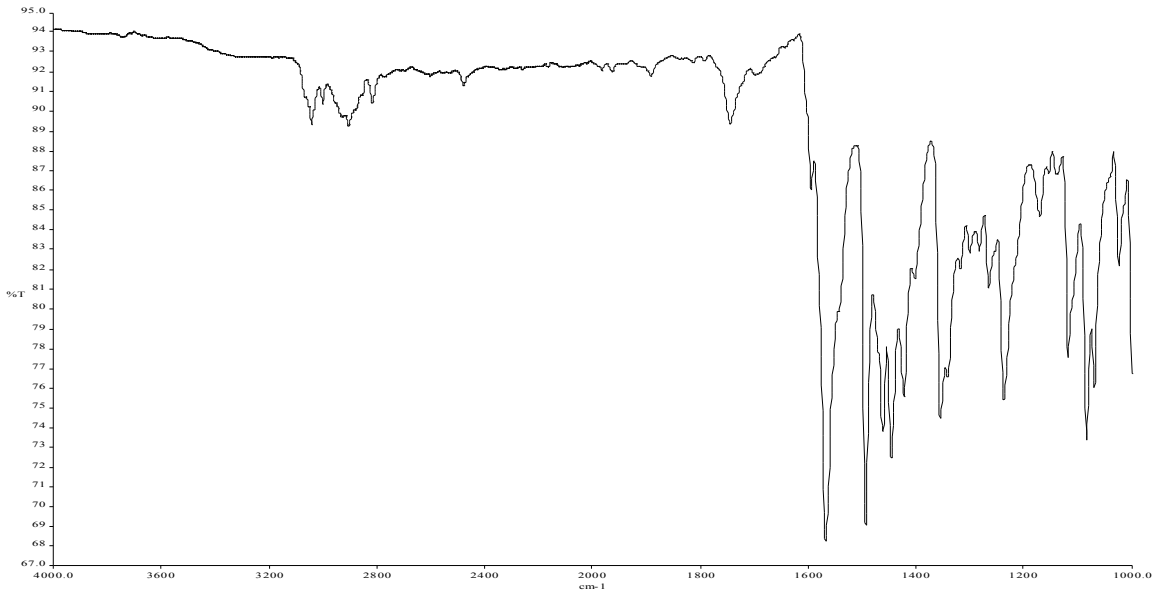



*Figure A3.35* Infrared spectrum of compound **5.41b**.

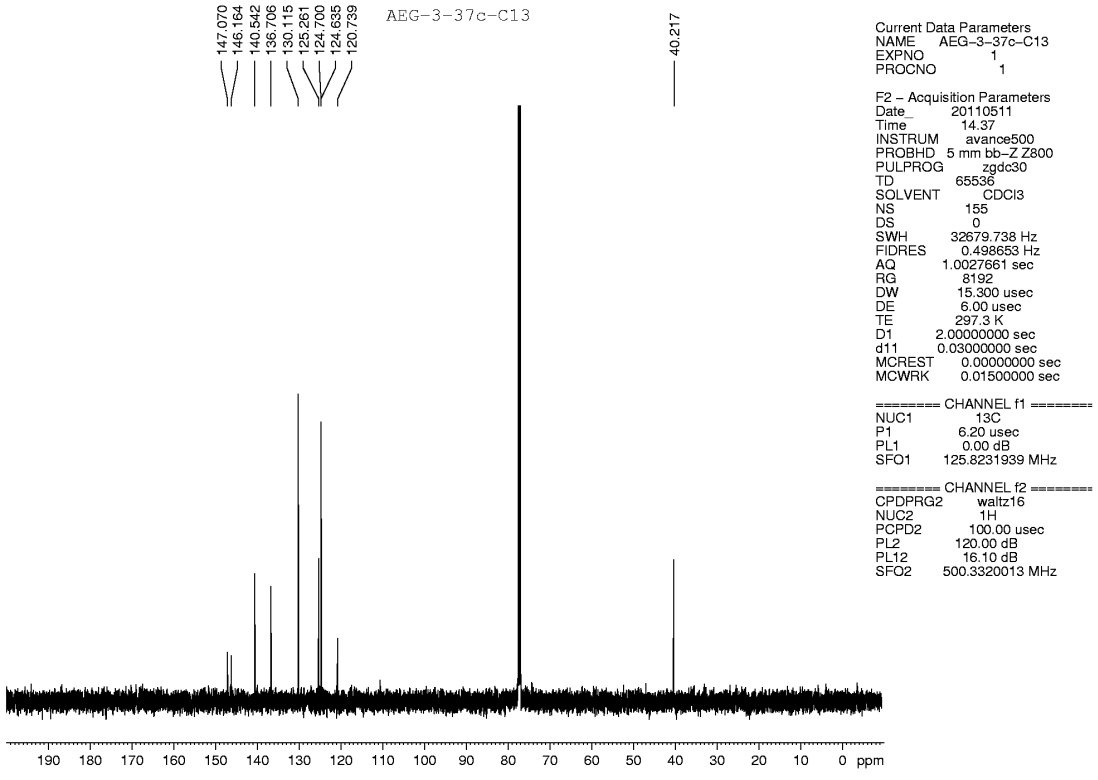



*Figure A3.36* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compound **5.41b**.

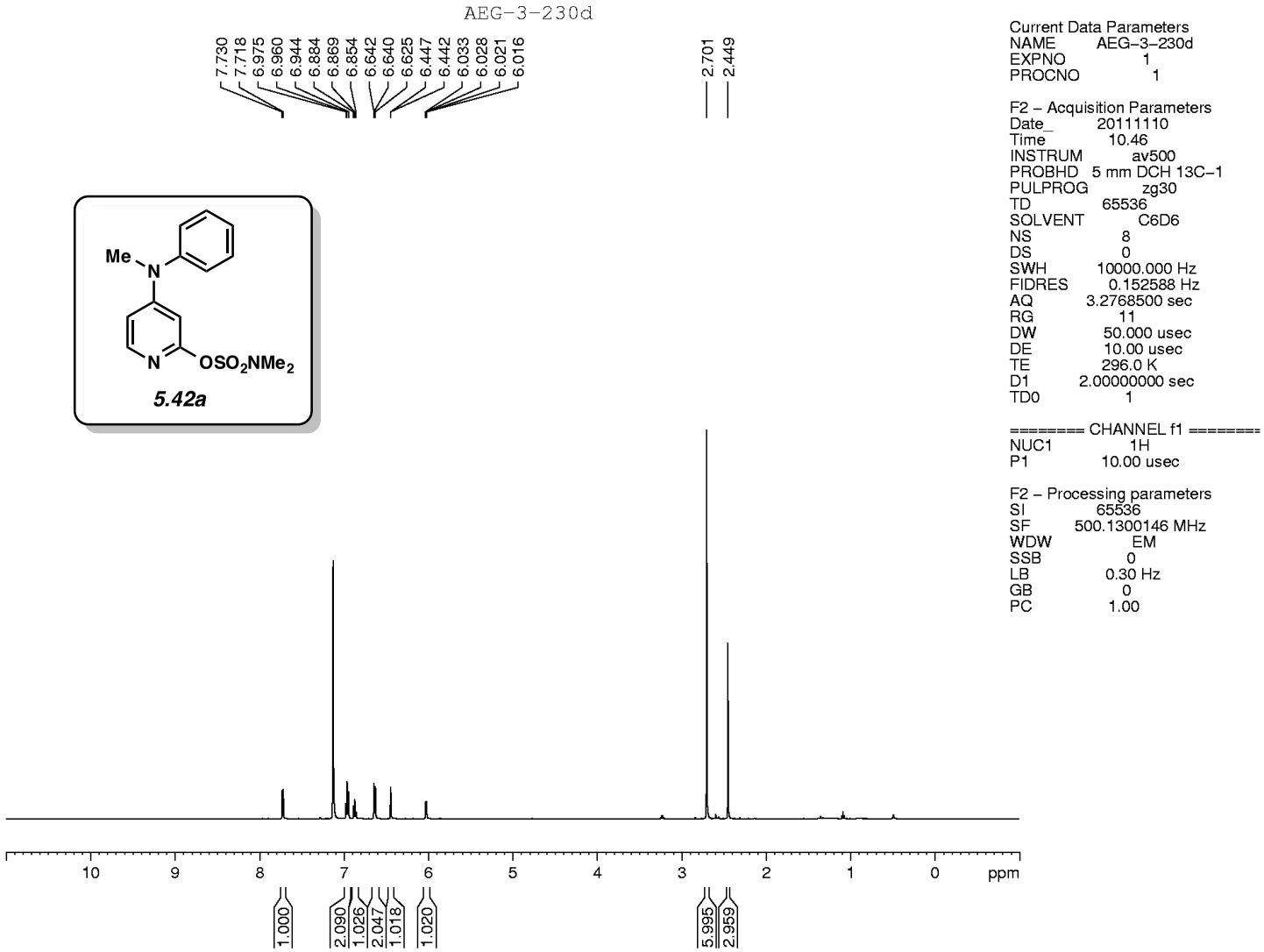



*Figure A3.37* $^{1}$H NMR (500 MHz, $C_6D_6$) of compound **5.42a**.

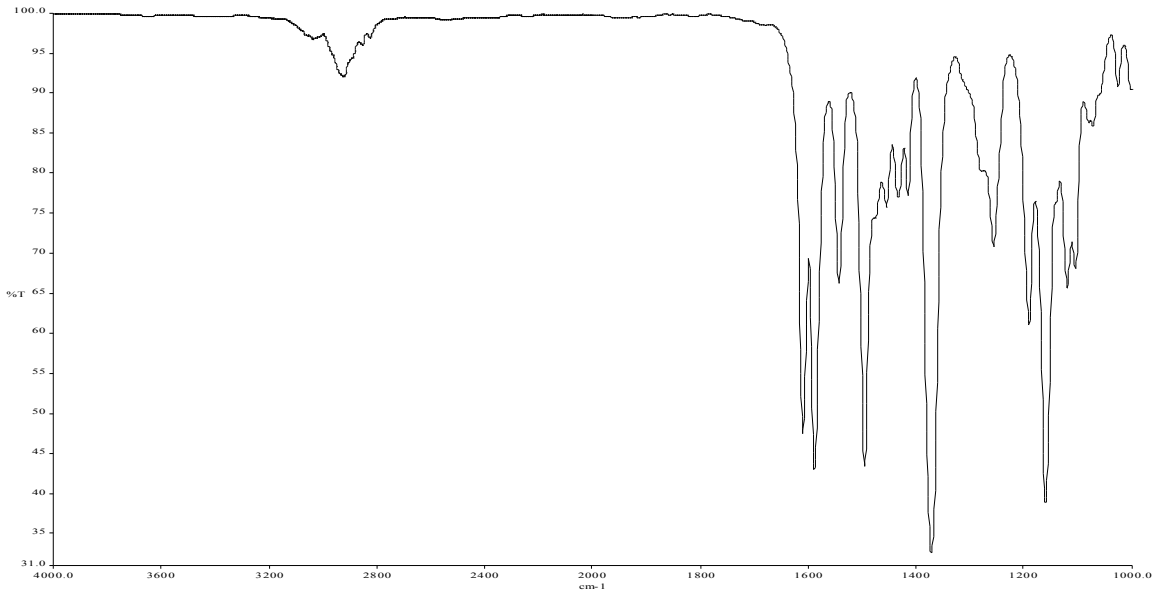



*Figure A3.38* Infrared spectrum of compound **5.42a**.

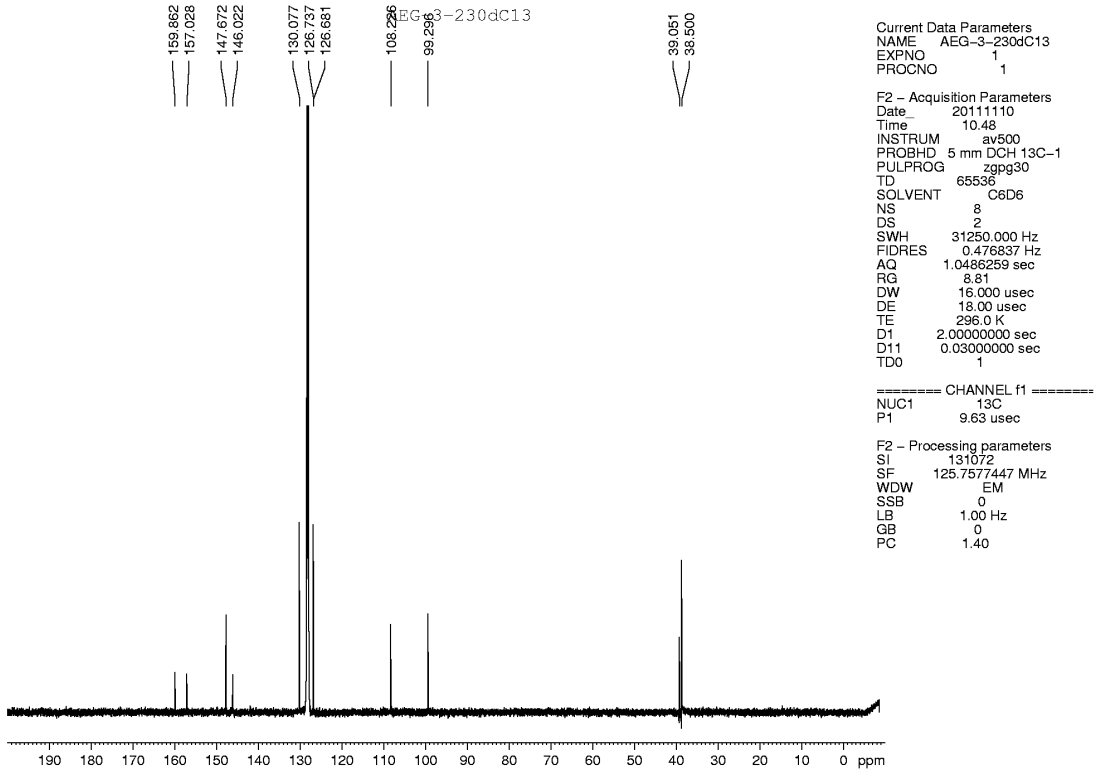



*Figure A3.39* $^{13}C$ NMR (125 MHz, $C_6D_6$) of compound **5.42a**.

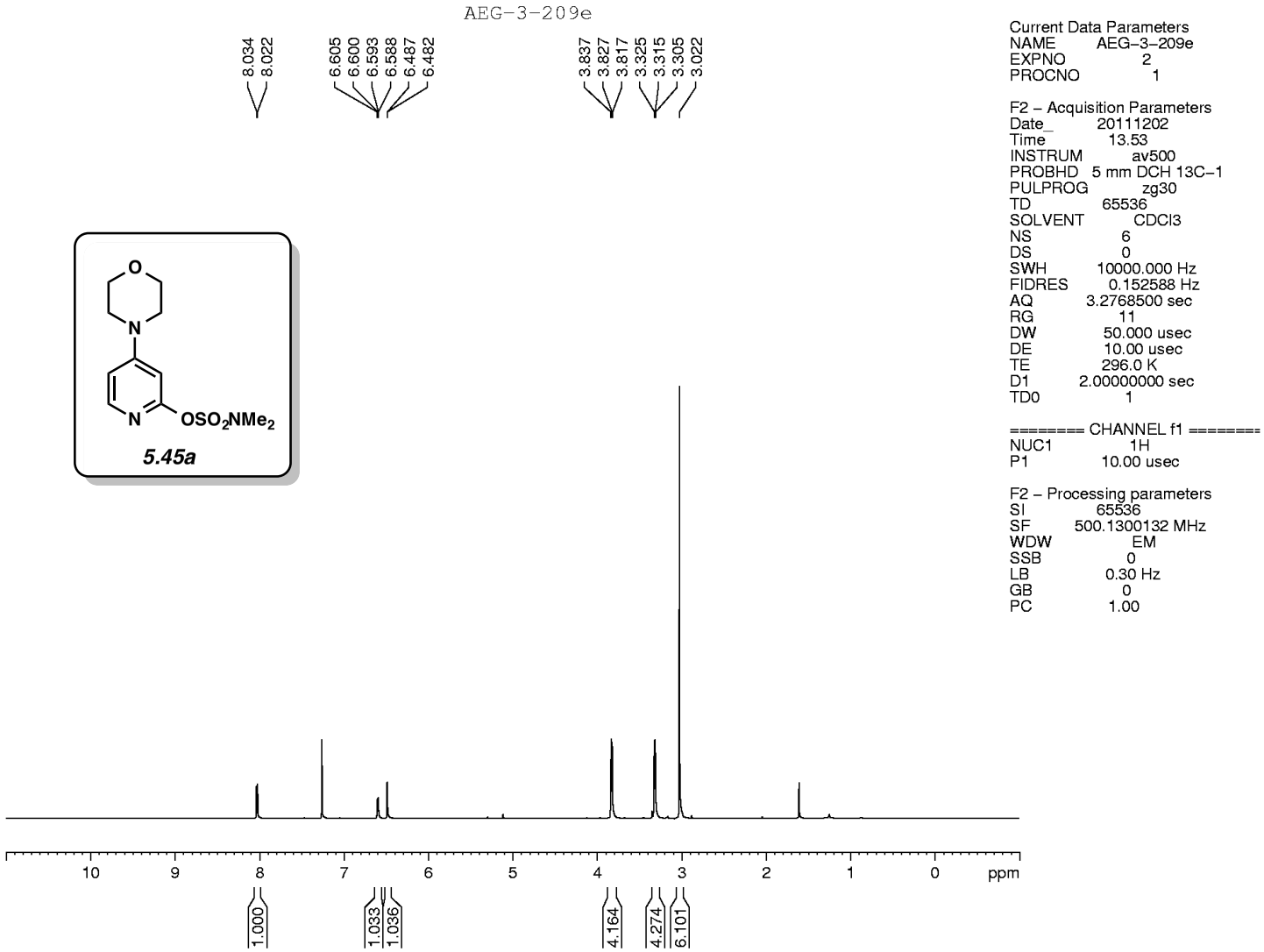



*Figure A3.40* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **5.45a**.

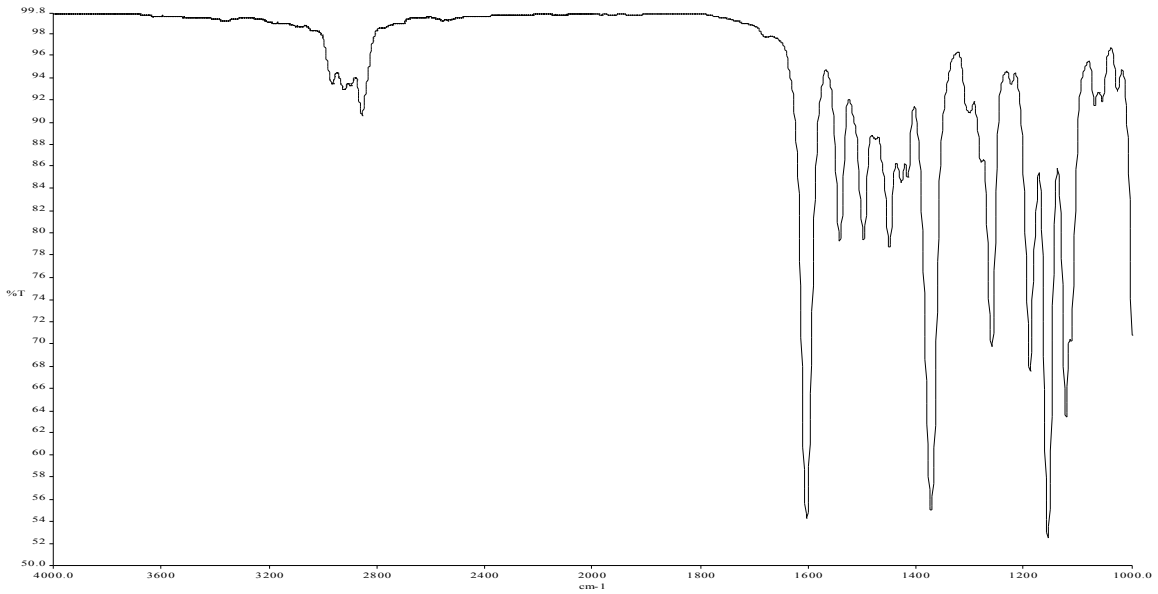



*Figure A3.41* Infrared spectrum of compound **5.45a**.

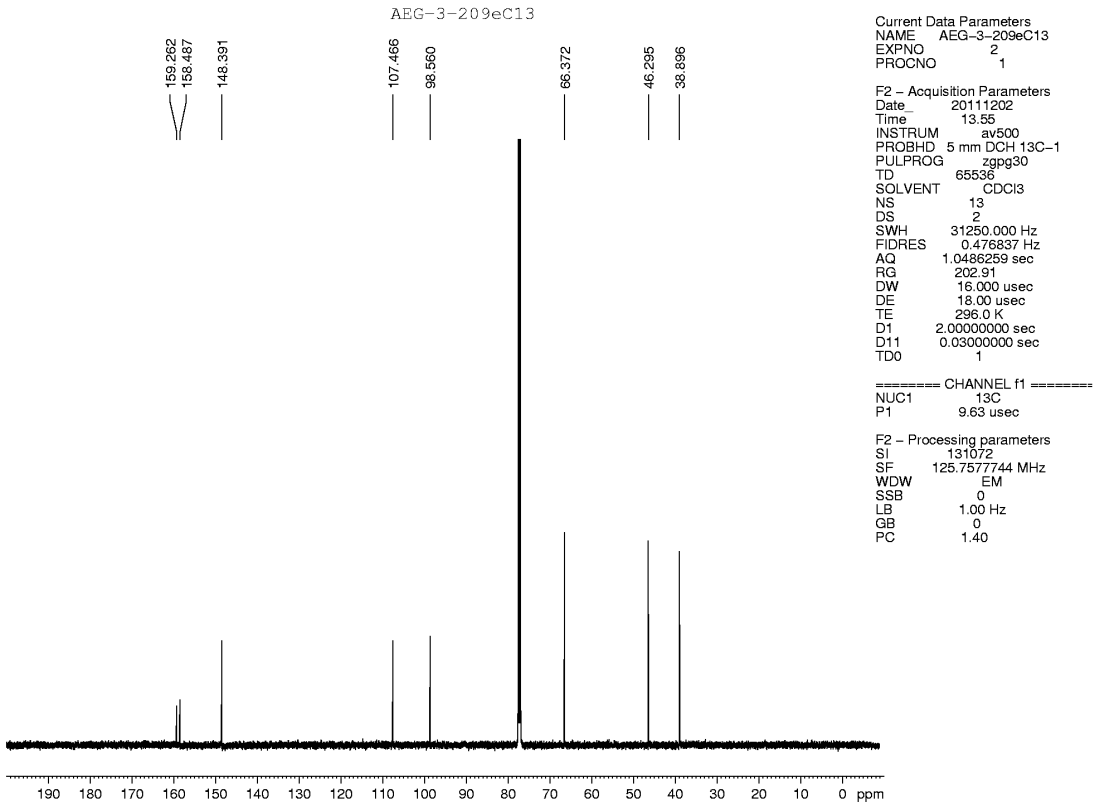



*Figure A3.42* $^{13}$C NMR (125 MHz, $CDCl_3$) of compound **5.45a**.

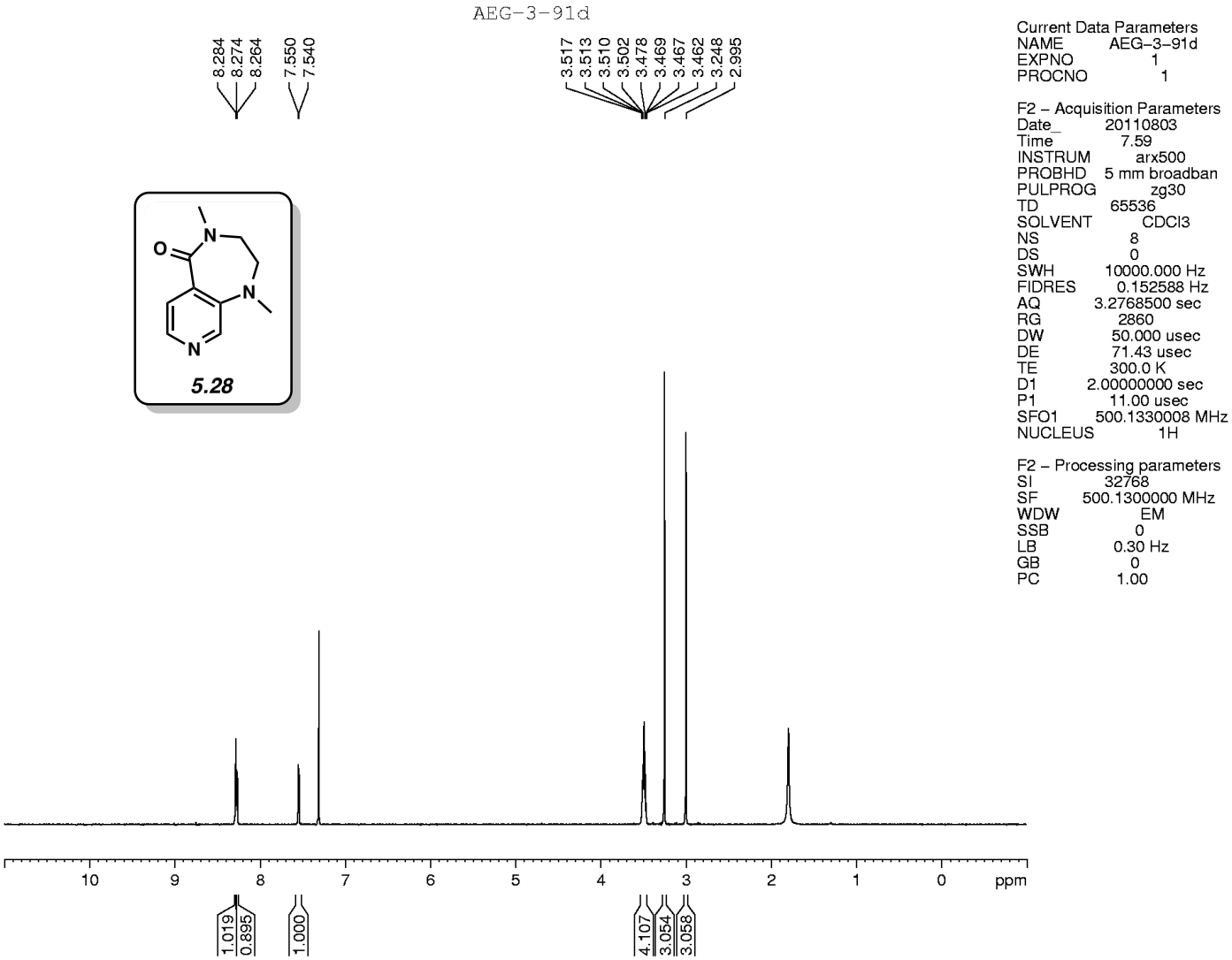



*Figure A3.43* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **5.28**.

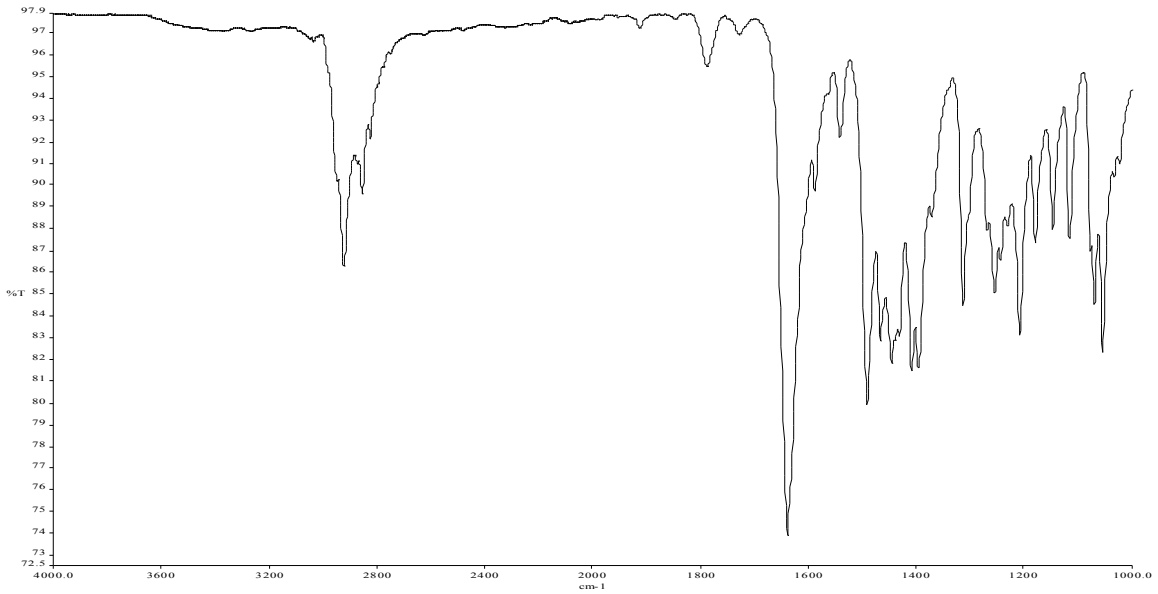



*Figure A3.44* Infrared spectrum of compound **5.28**.

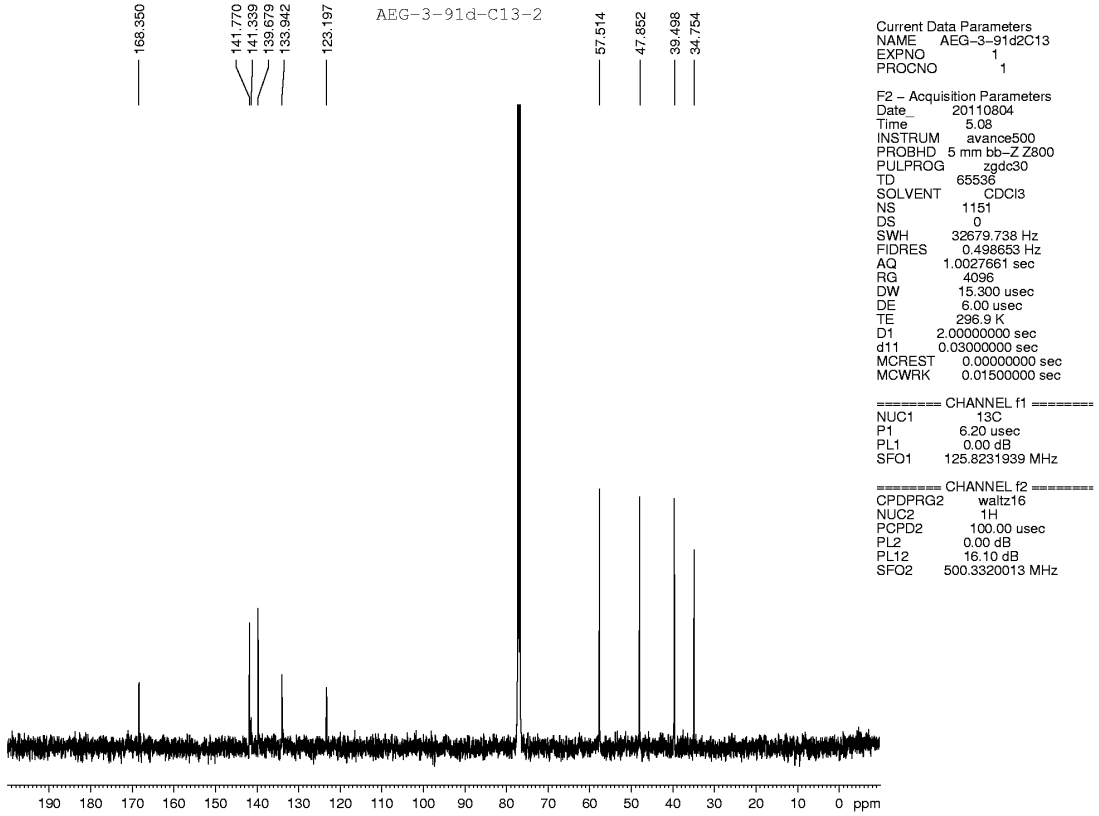



*Figure A3.45* $^{13}$C NMR (125 MHz, $CDCl_3$) of compound **5.28**.

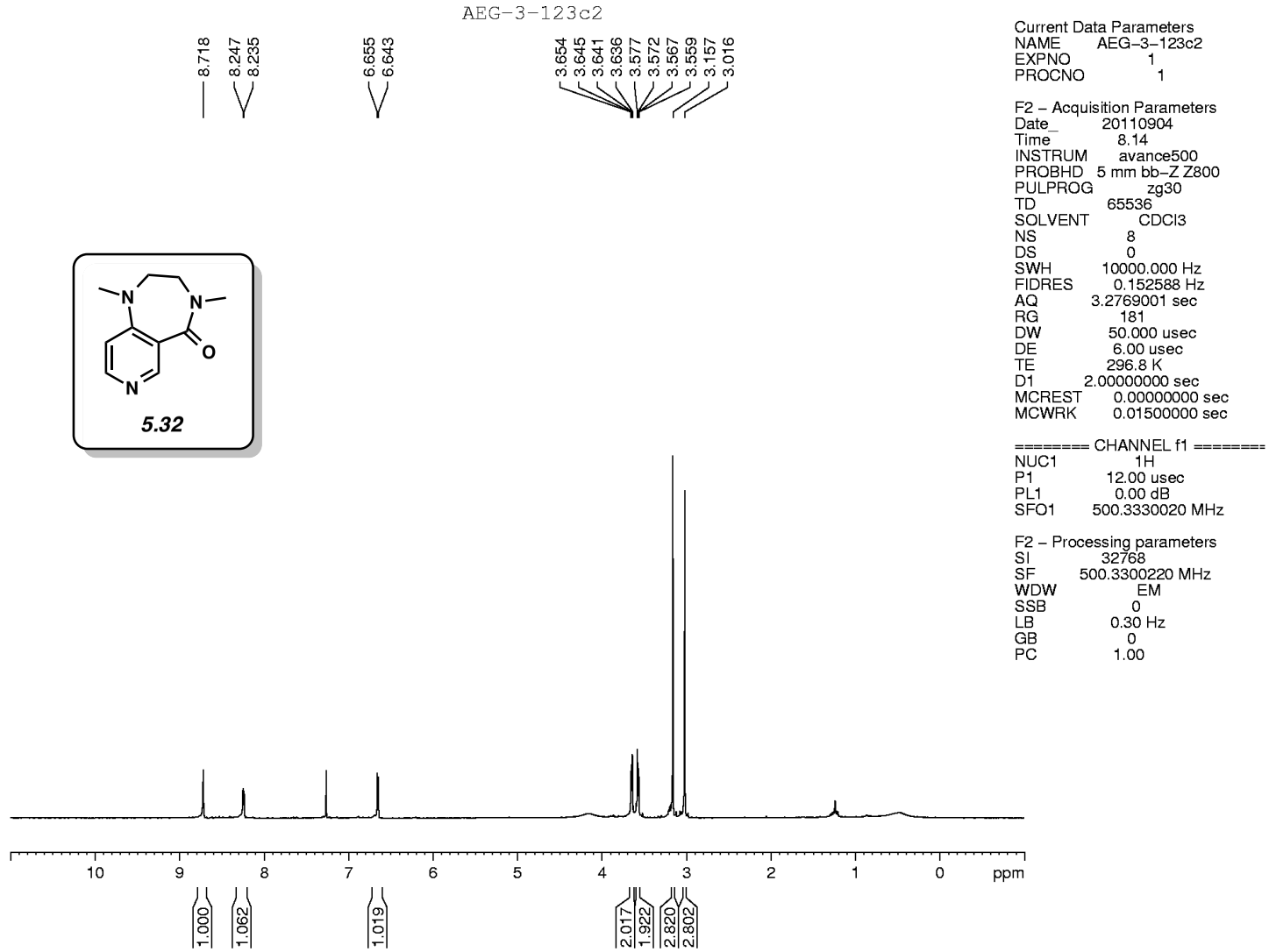



*Figure A3.46* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **5.32**.

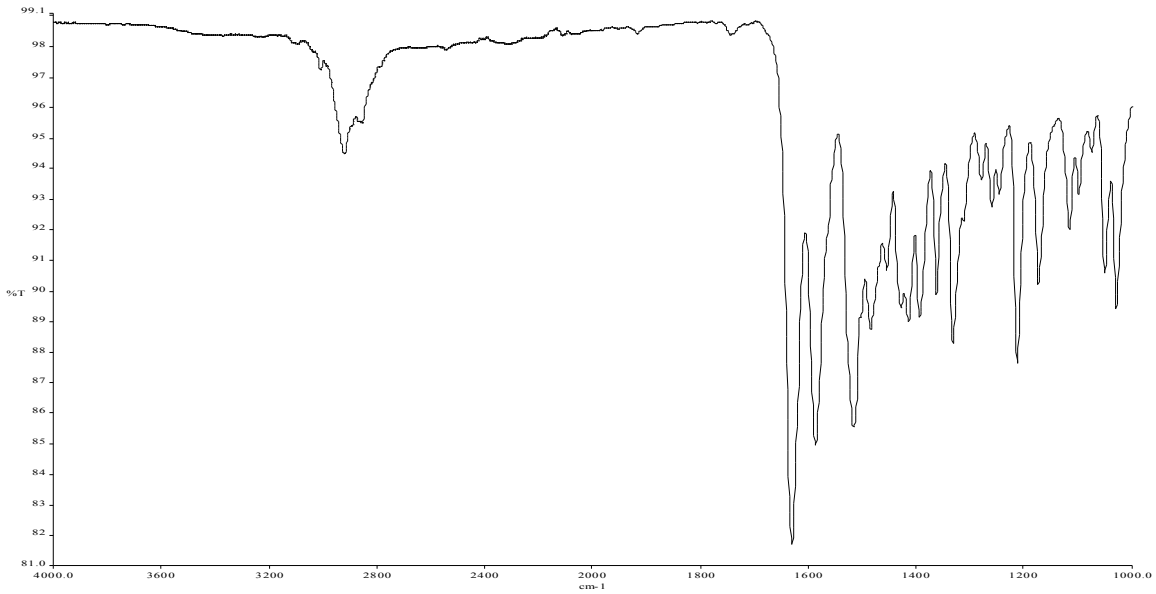



*Figure A3.47* Infrared spectrum of compound **5.32**.

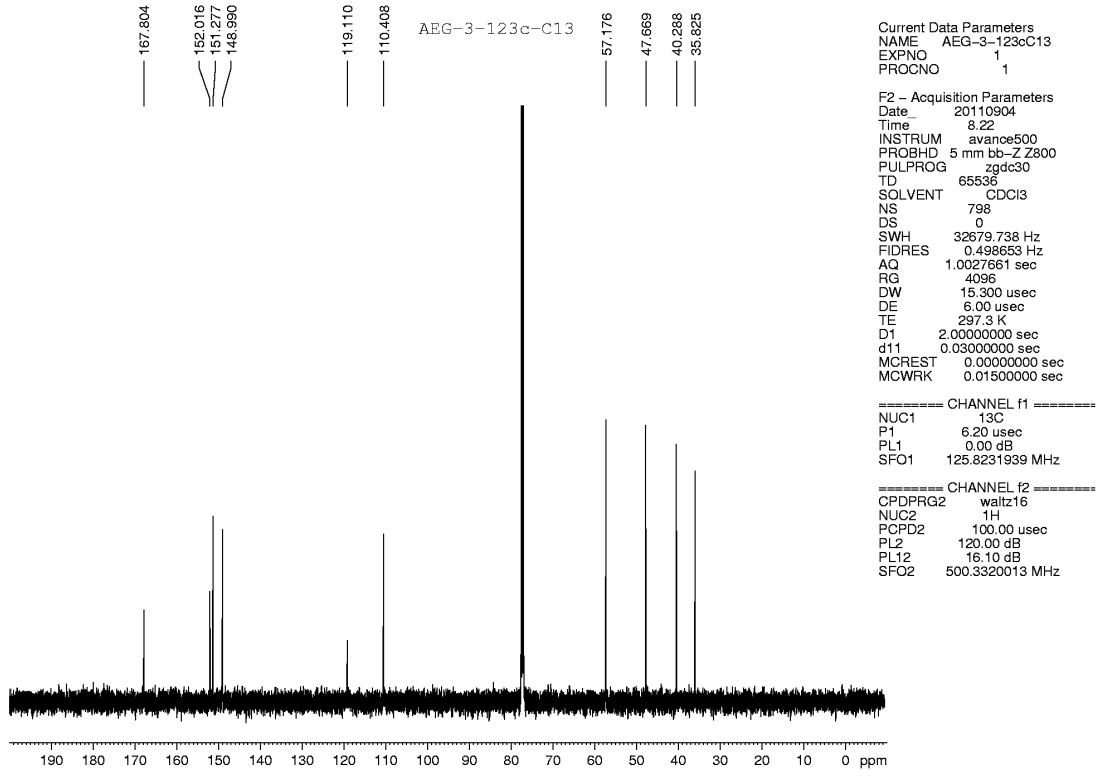



*Figure A3.48* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compound **5.32**.

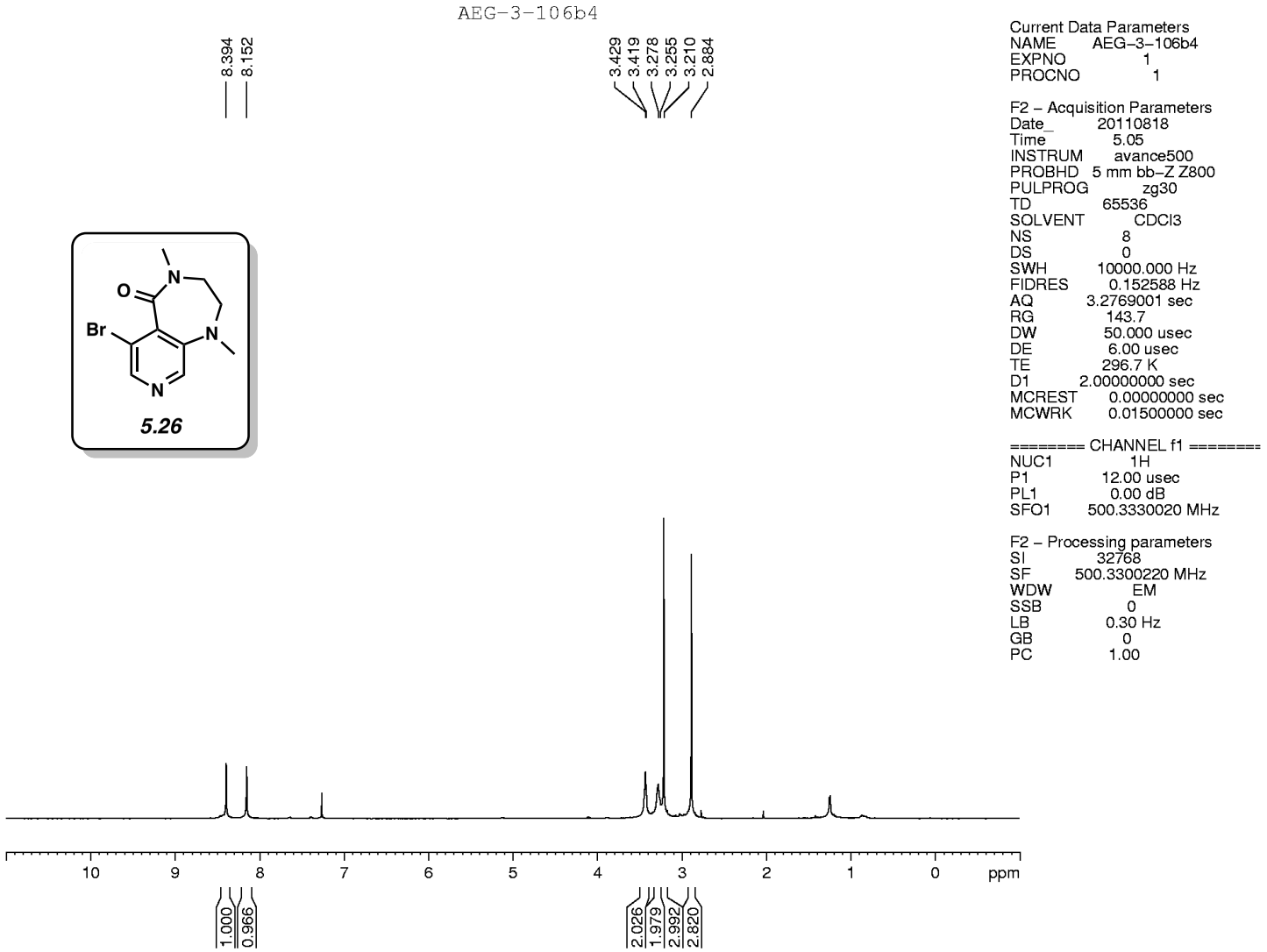



*Figure A3.49* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **5.26**.

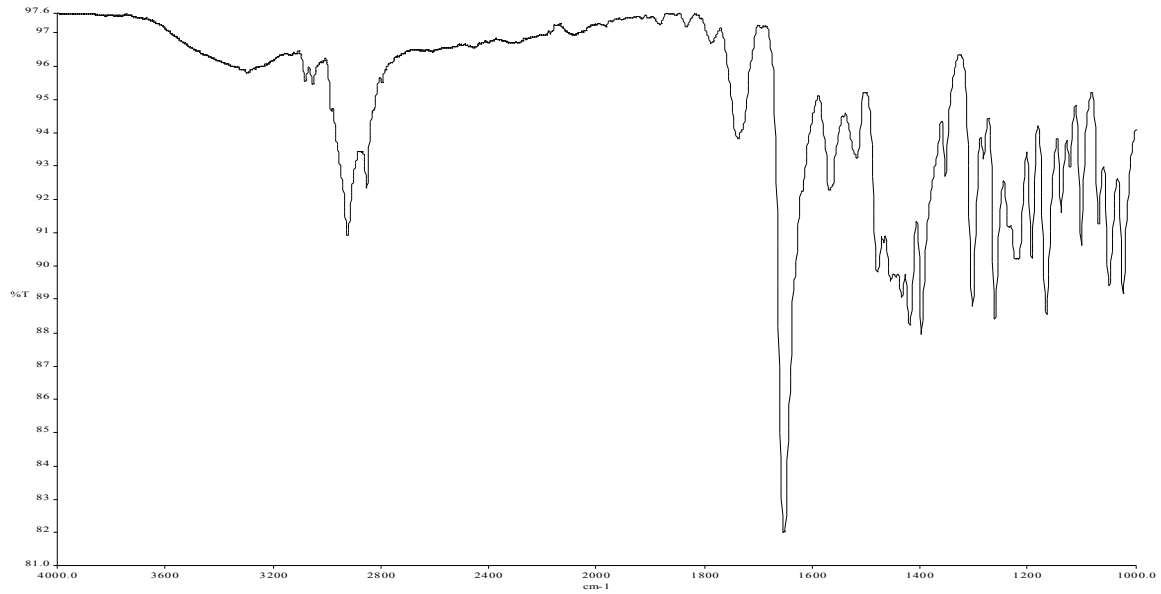



*Figure A3.50* Infrared spectrum of compound **5.26**.

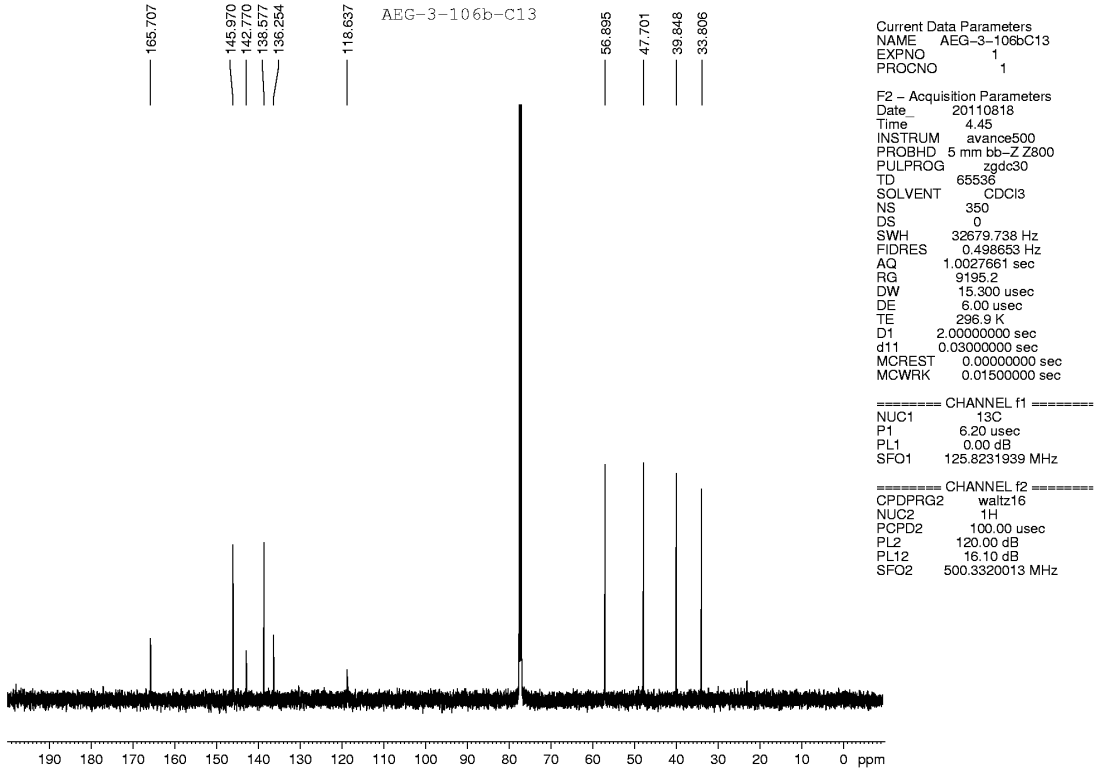



*Figure A3.51* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compound **5.26**.

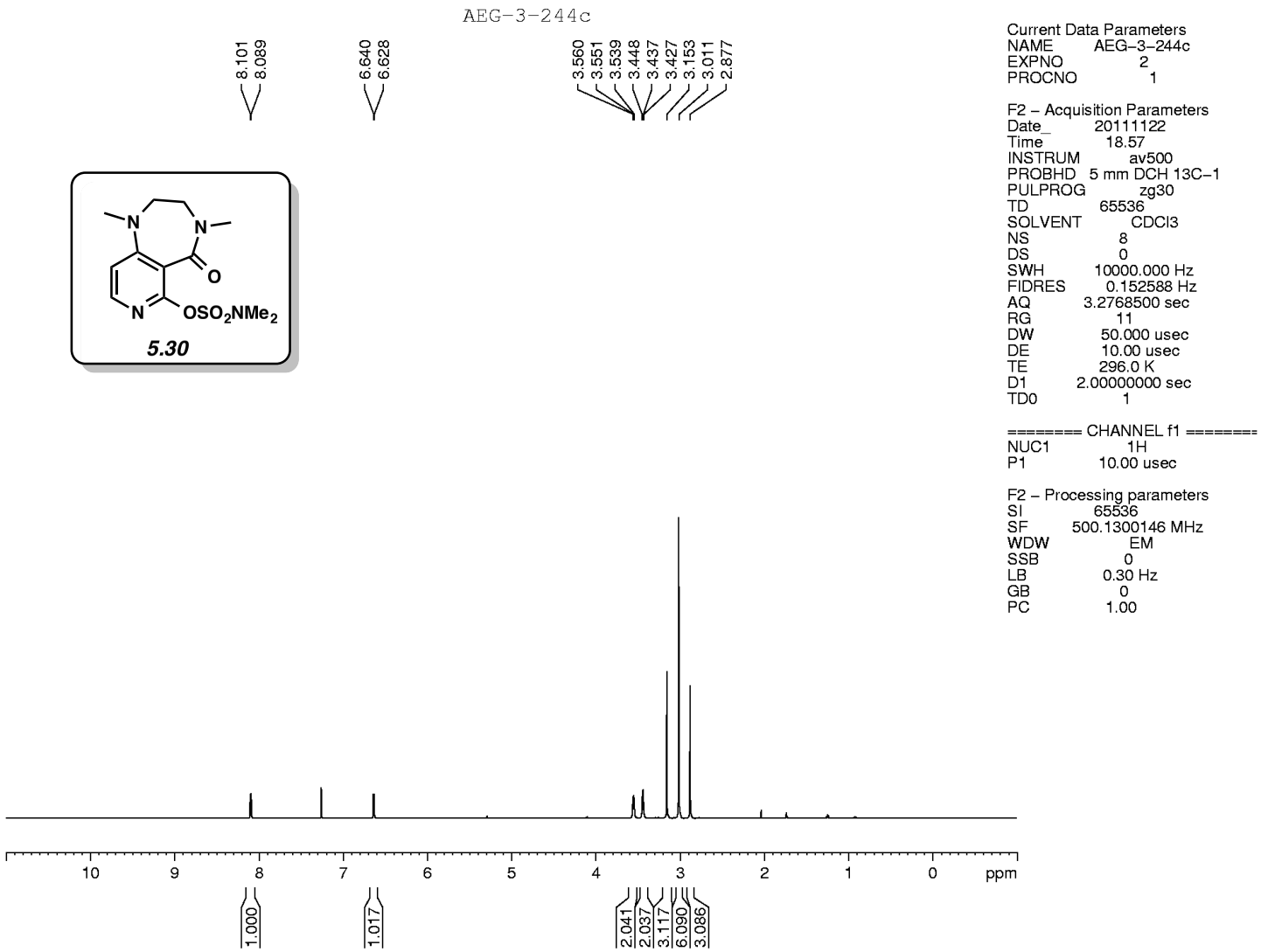



*Figure A3.52* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **5.30**.

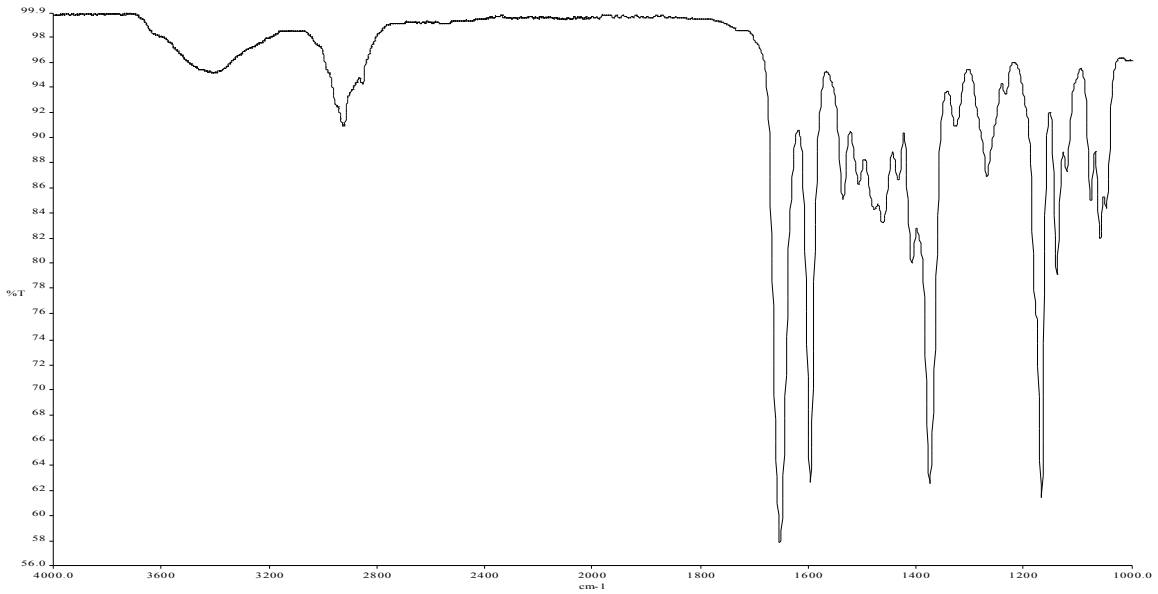



*Figure A3.53* Infrared spectrum of compound **5.30**.

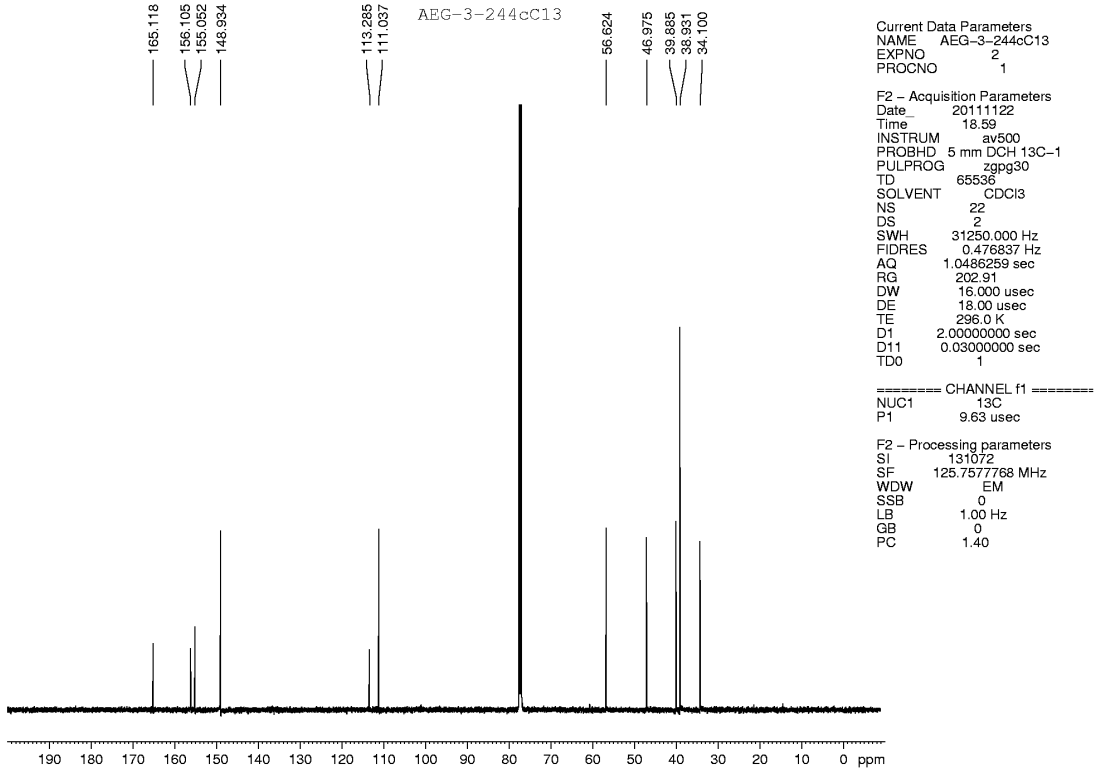



*Figure A3.54* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compound **5.30**.

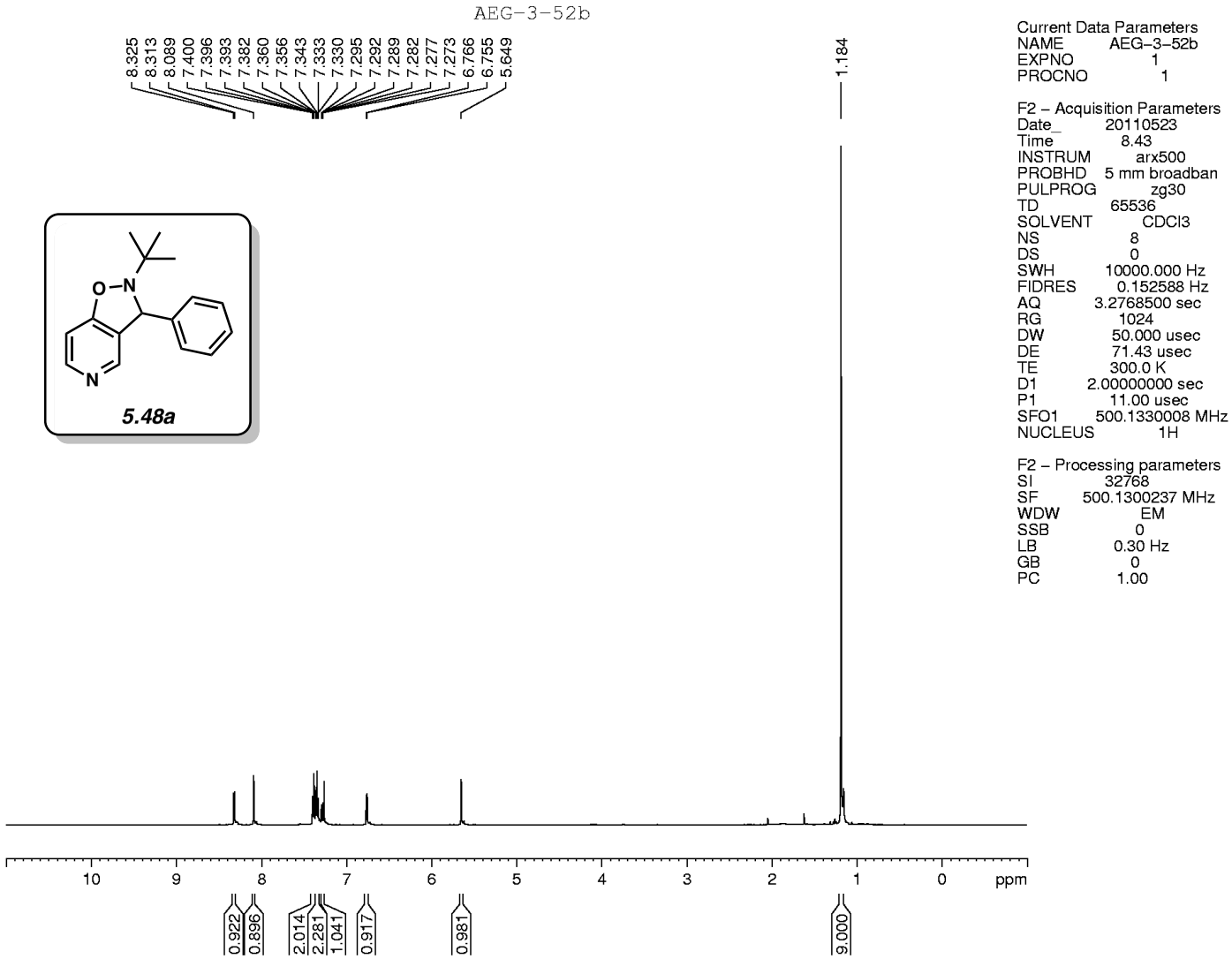



*Figure A3.55* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **5.48a**.

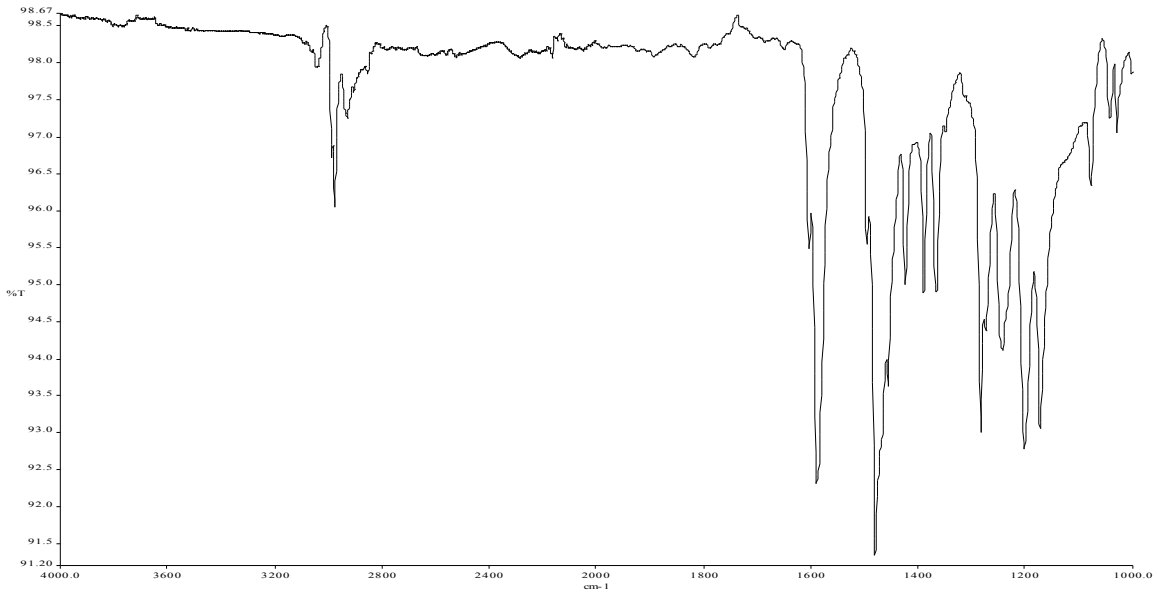



*Figure A3.56* Infrared spectrum of compound **5.48a**.

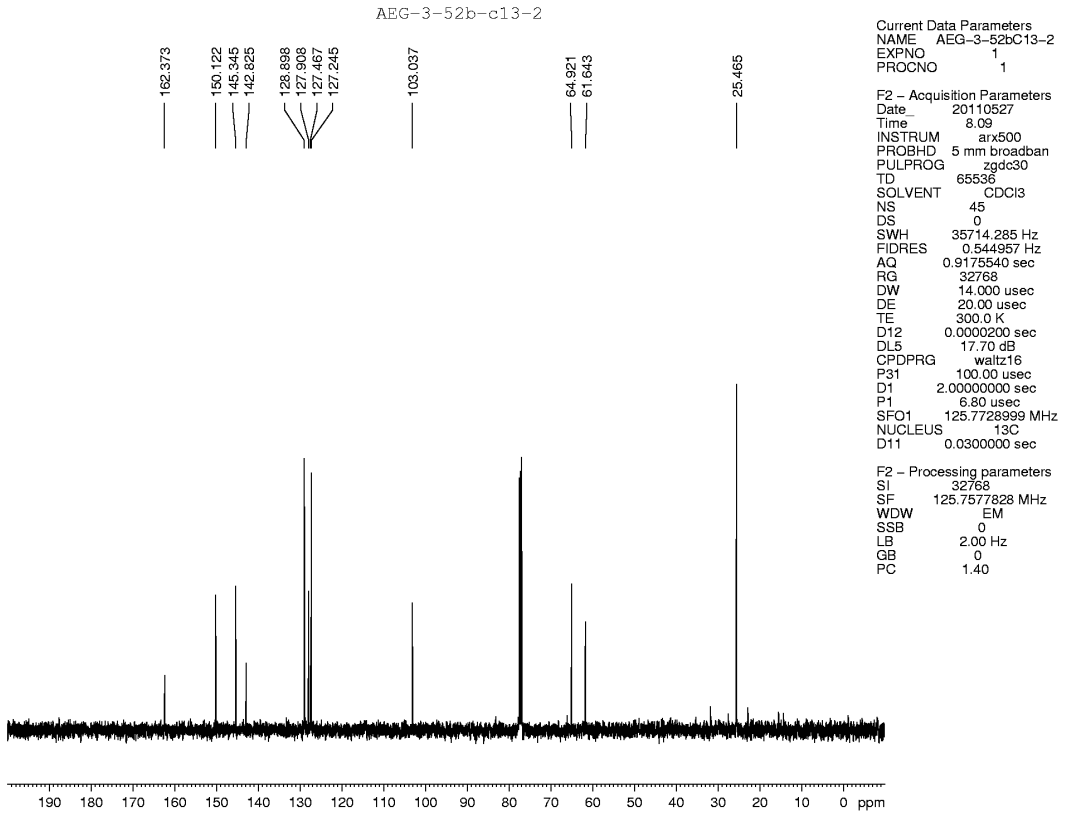



*Figure A3.57* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compound **5.48a**.

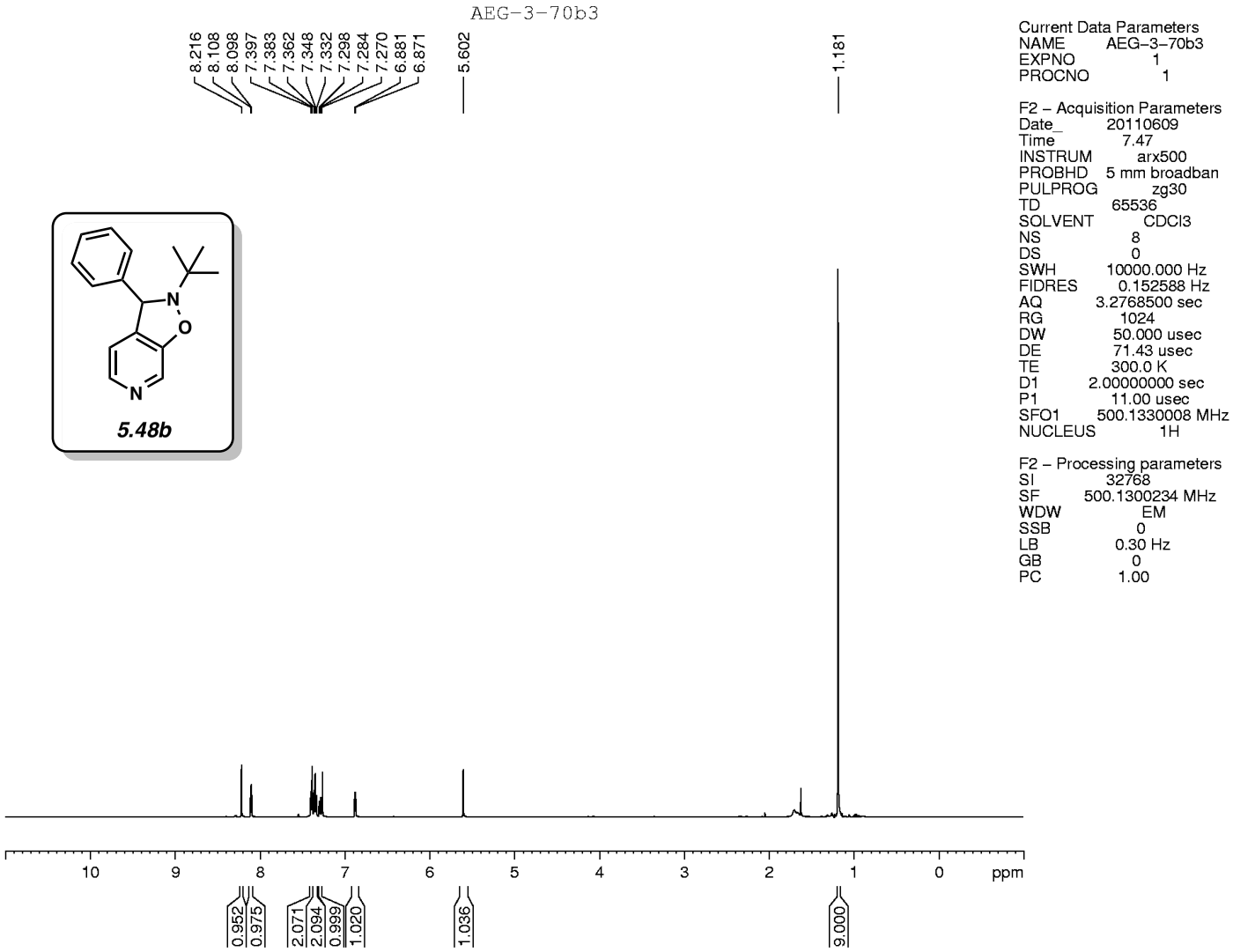



*Figure A3.58* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **5.48b**.

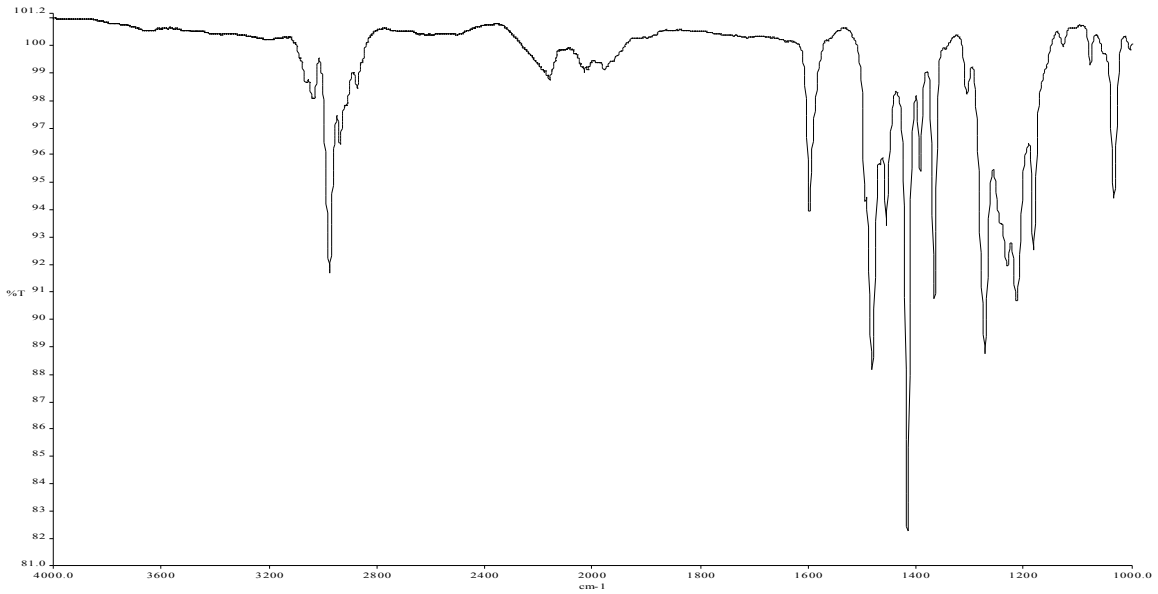



*Figure A3.59* Infrared spectrum of compound **5.48b**.

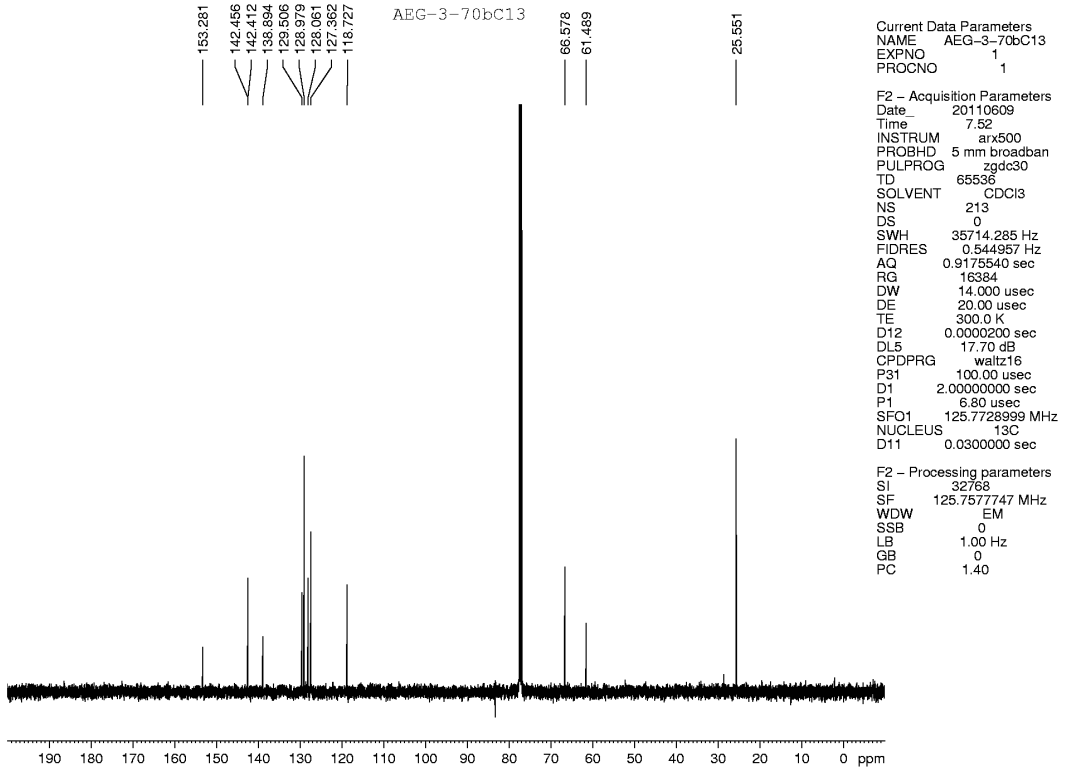



*Figure A3.60* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compound **5.48b**.

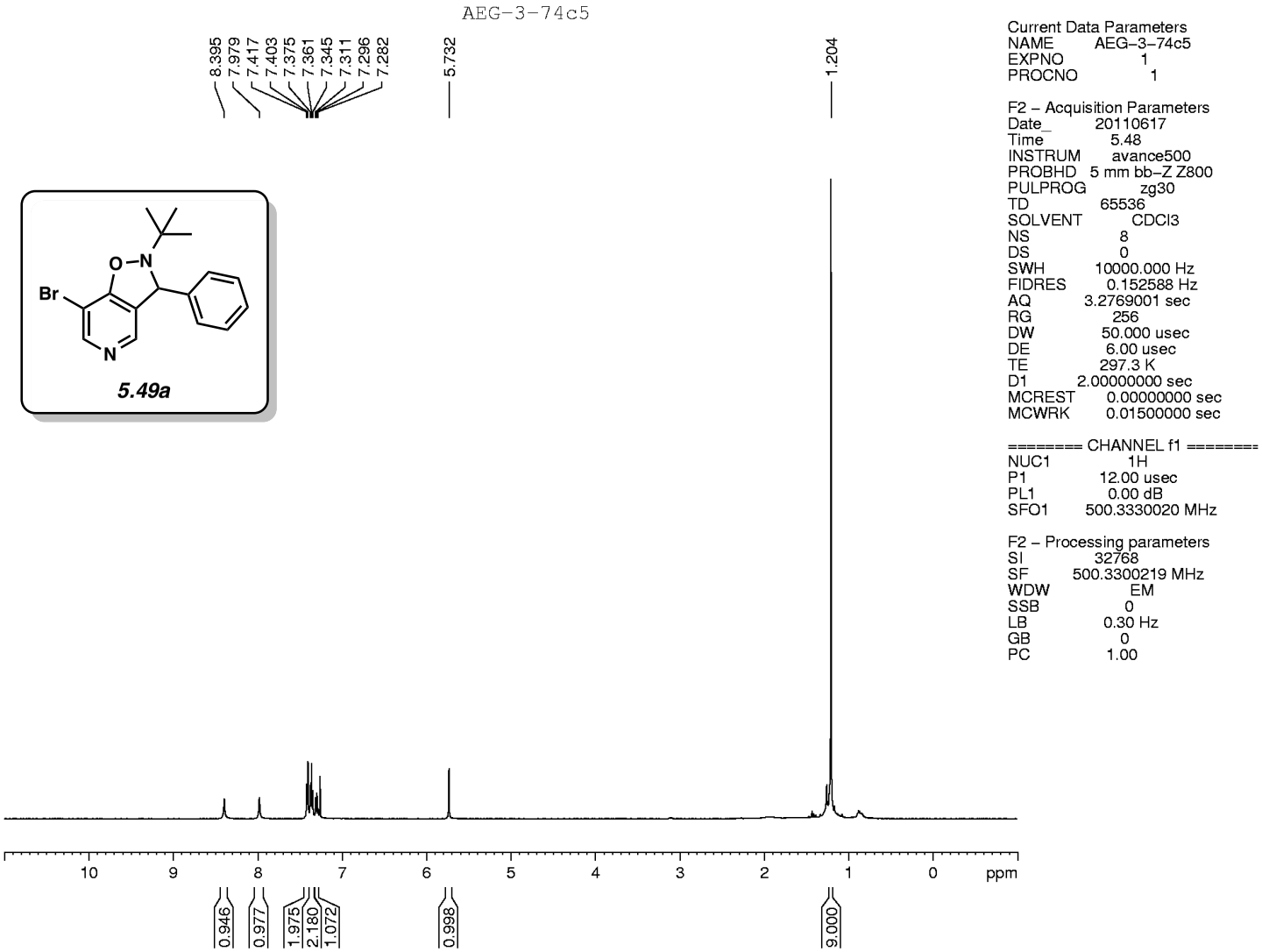



*Figure A3.61* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **5.49a**.

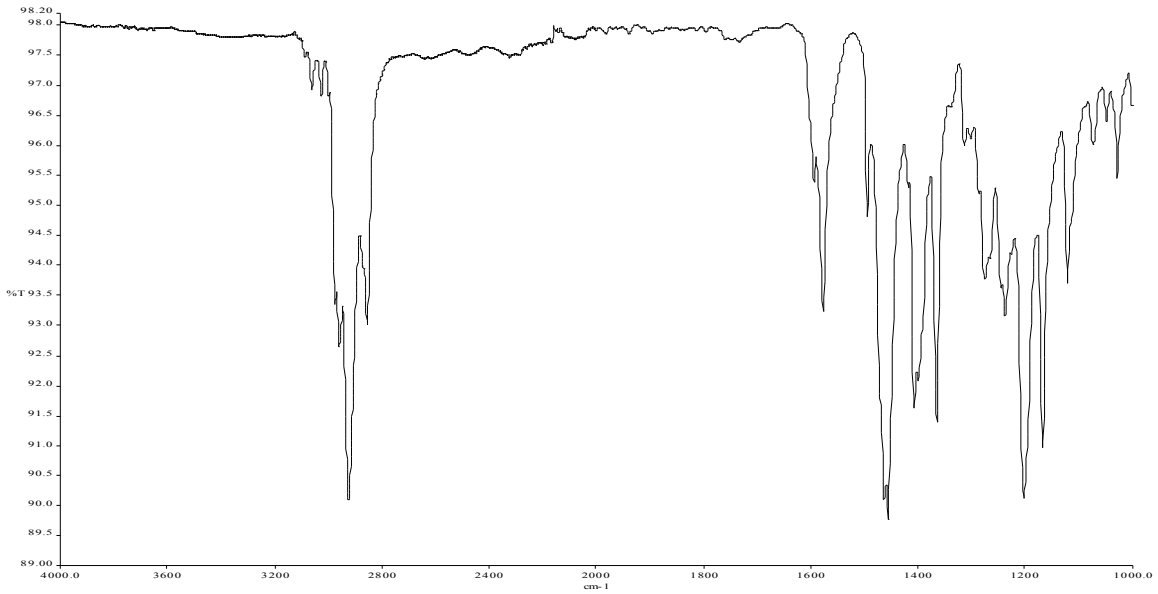



*Figure A3.62* Infrared spectrum of compound **5.49a**.

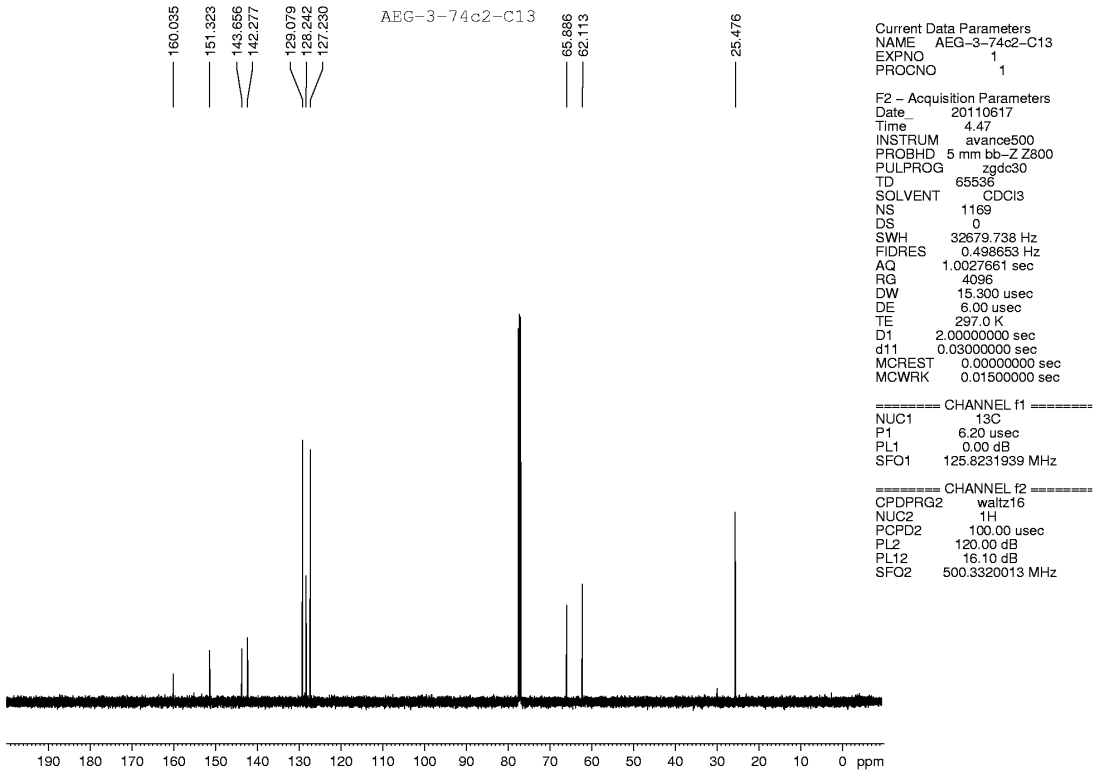



*Figure A3.63* $^{13}$C NMR (125 MHz, $CDCl_3$) of compound **5.49a**.

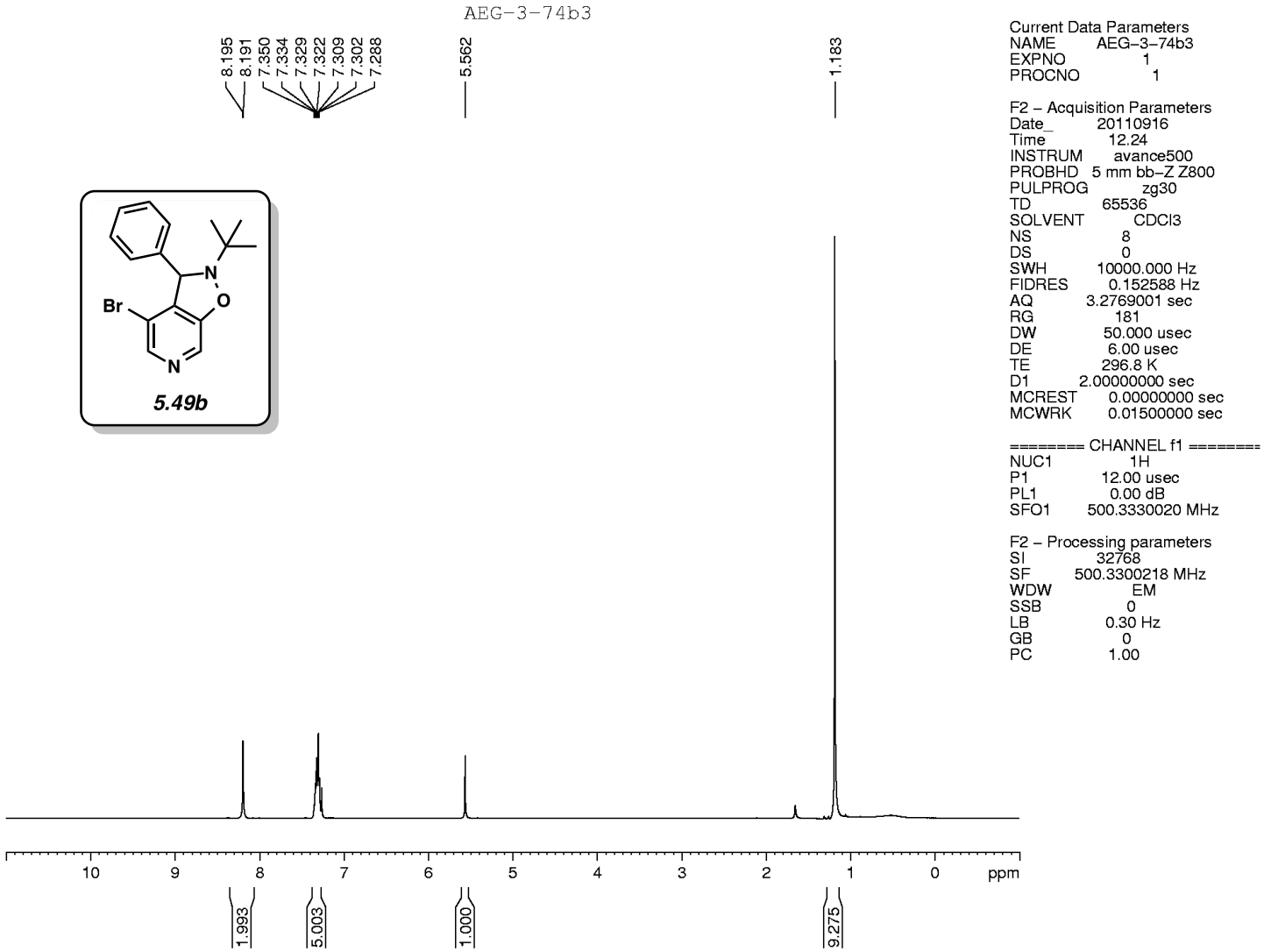



*Figure A3.64* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **5.49b**.

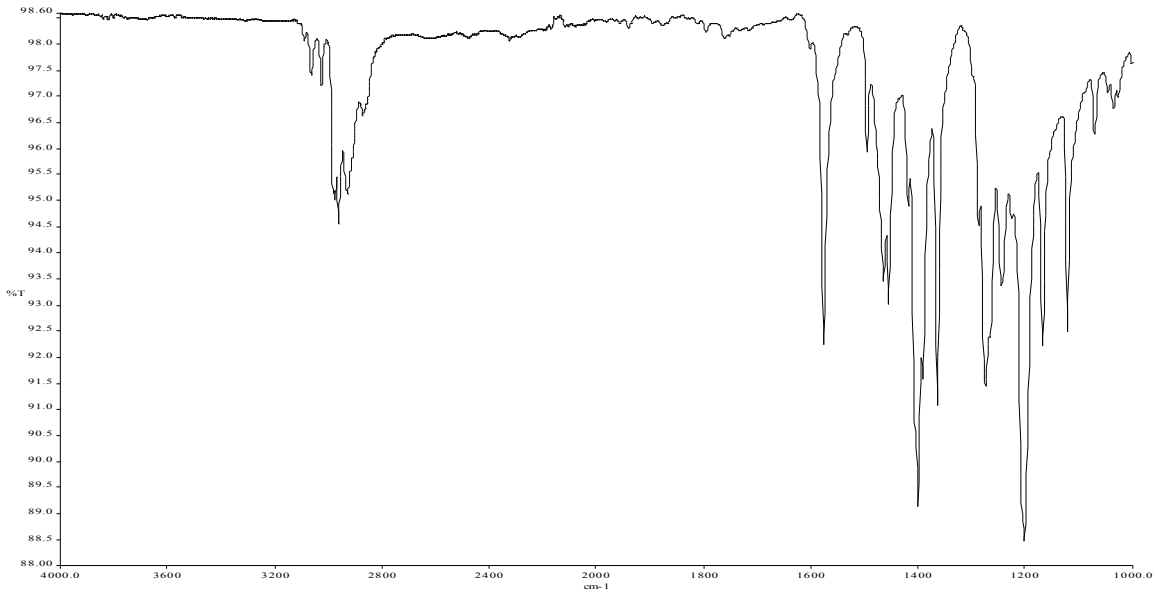



*Figure A3.65* Infrared spectrum of compound **5.49b**.

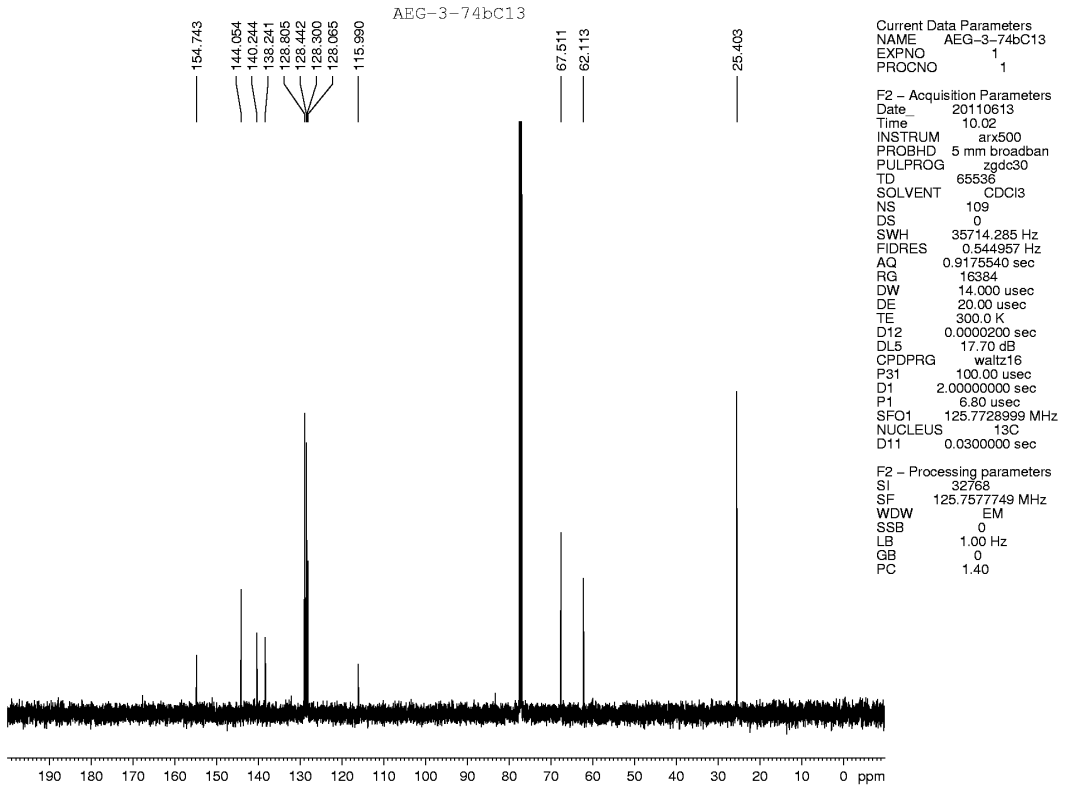



*Figure A3.66* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compound **5.49b**.

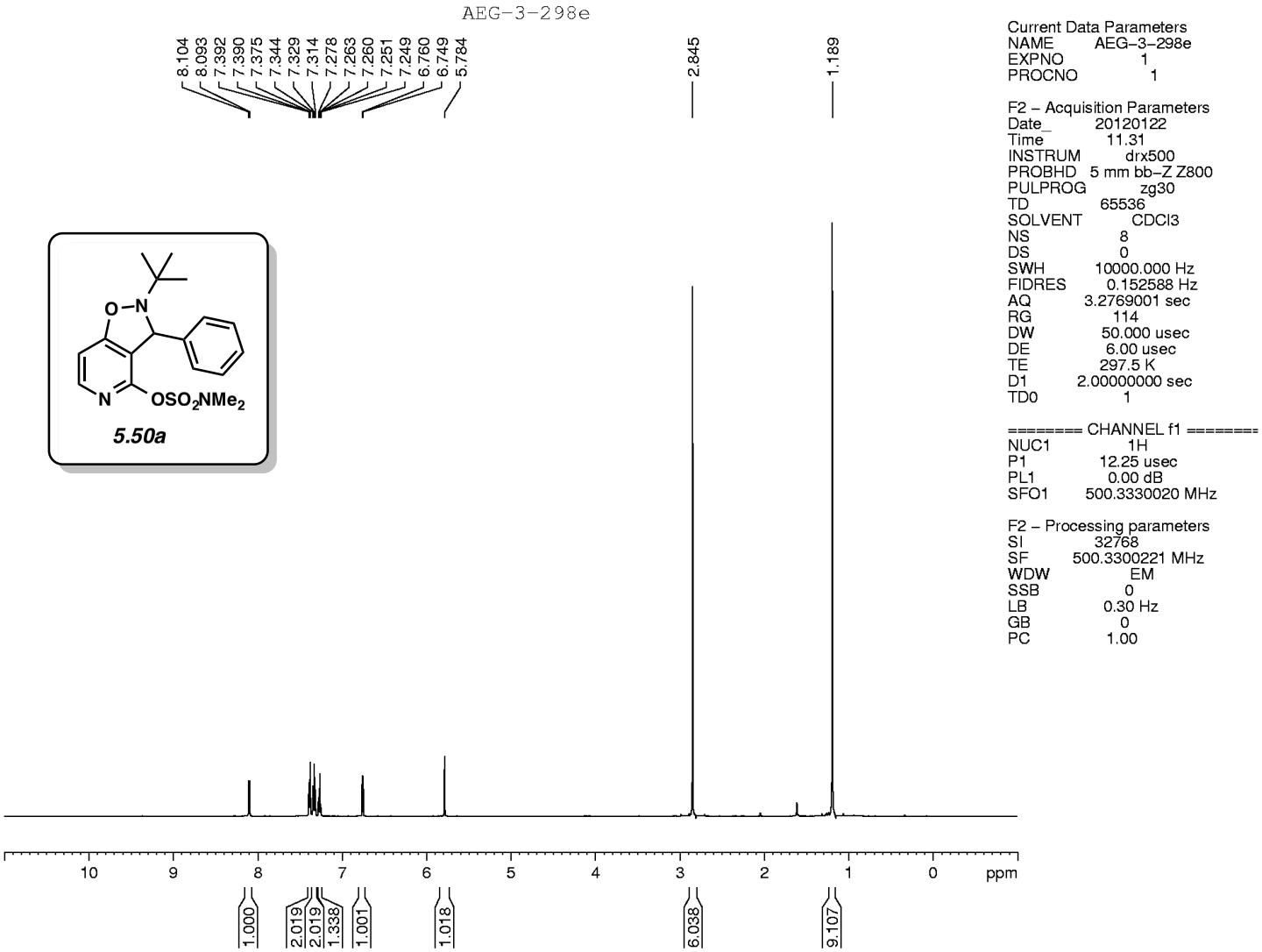



*Figure A3.67* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **5.50a**.

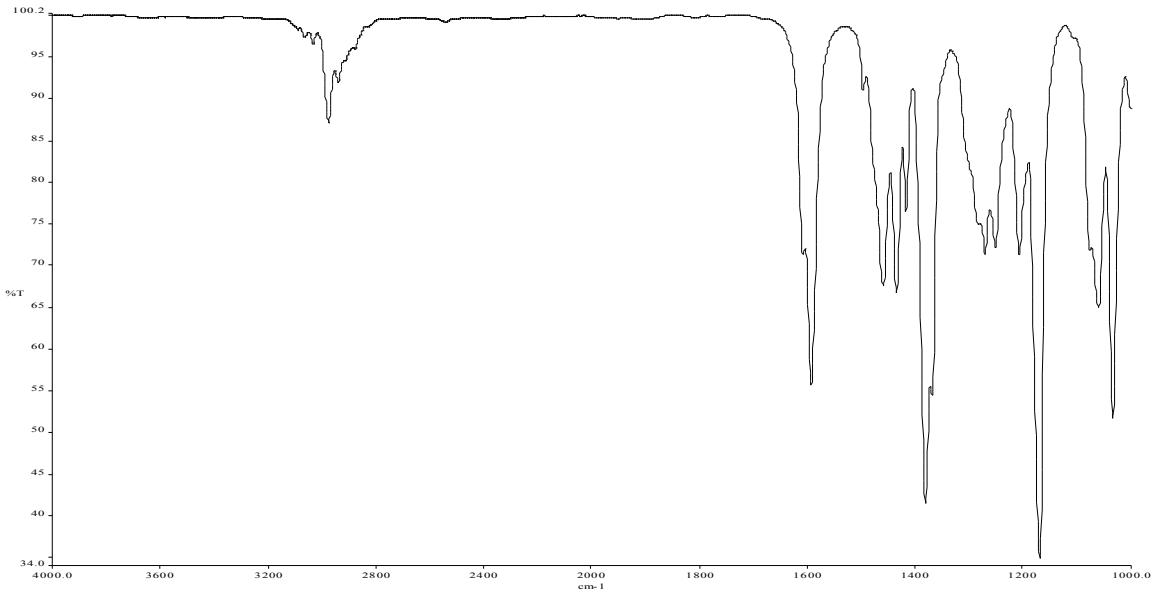



*Figure A3.68* Infrared spectrum of compound **5.50a**.

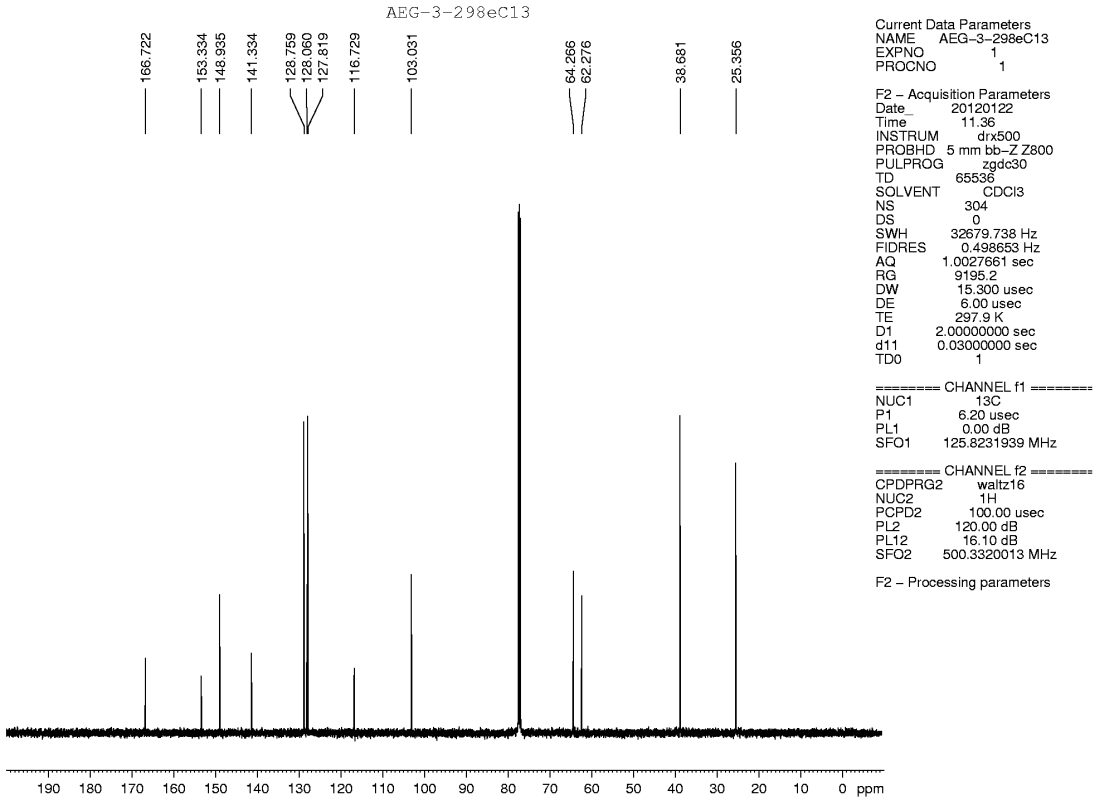



*Figure A3.69* $^{13}$C NMR (125 MHz, $CDCl_3$) of compound **5.50a**.

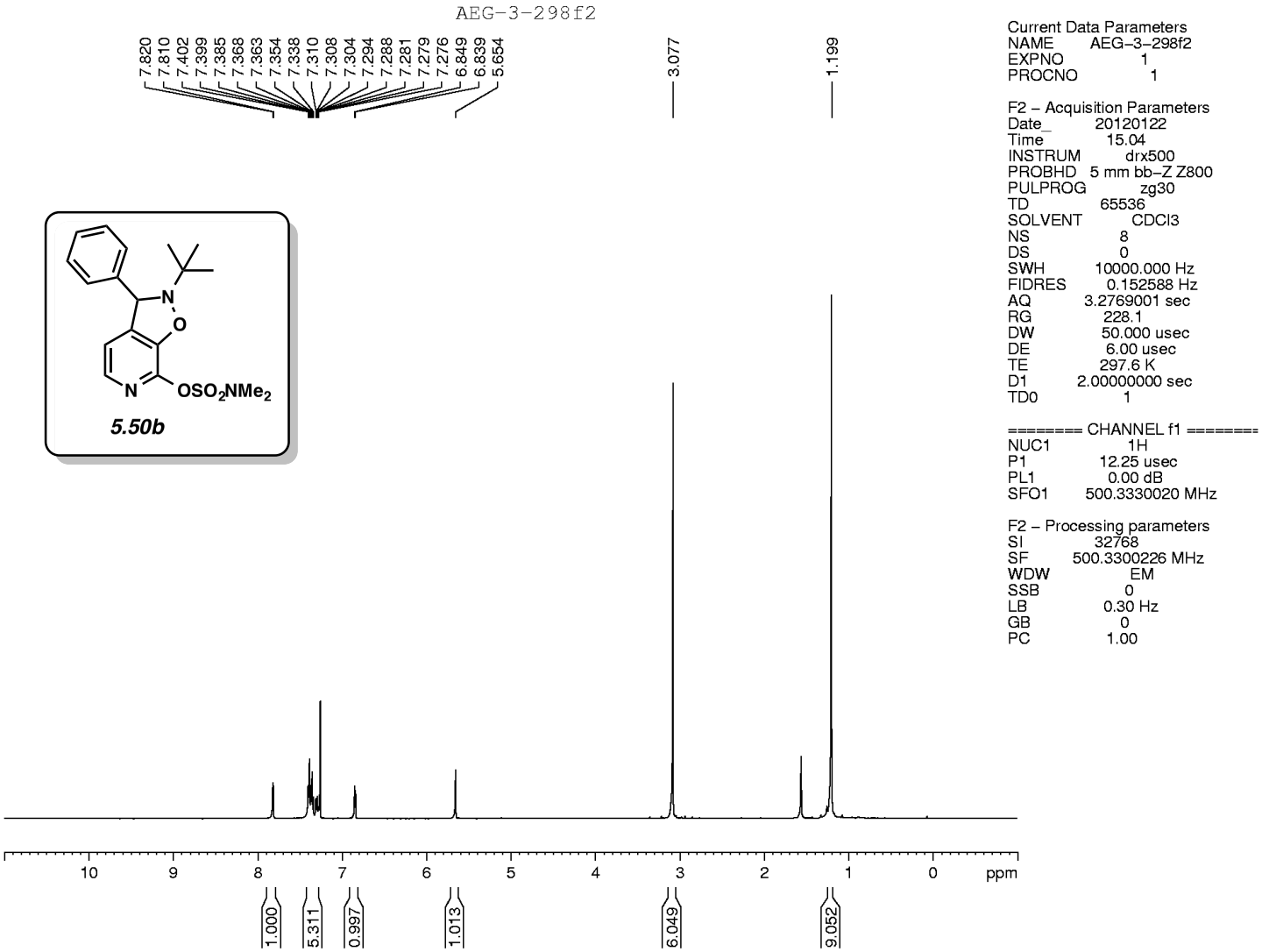



*Figure A3.70* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **5.50b**.

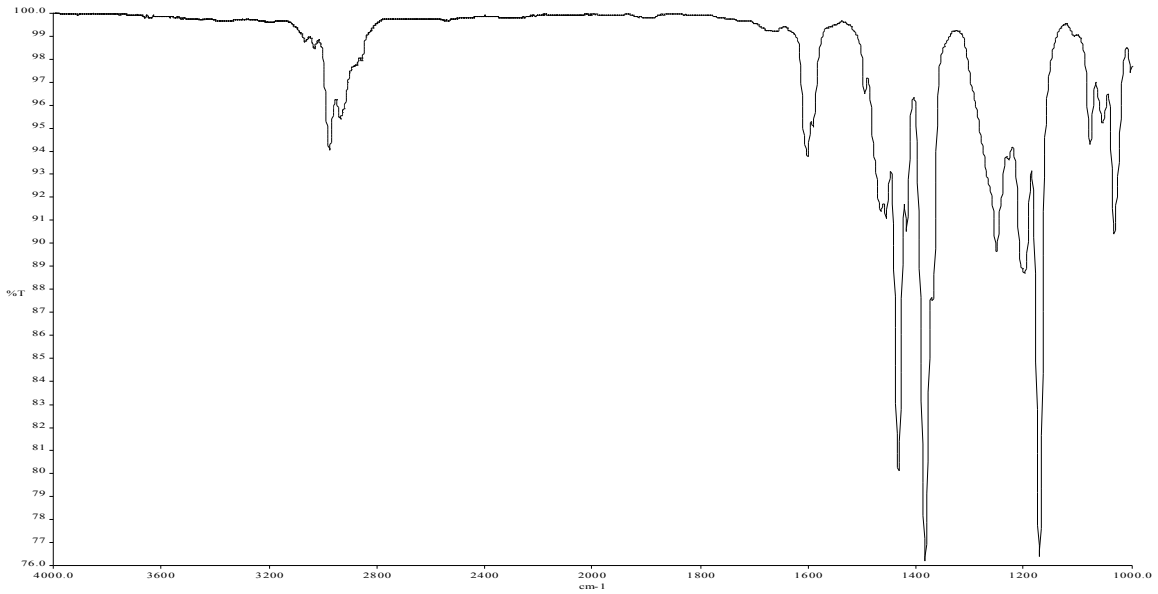



*Figure A3.71* Infrared spectrum of compound **5.50b**.

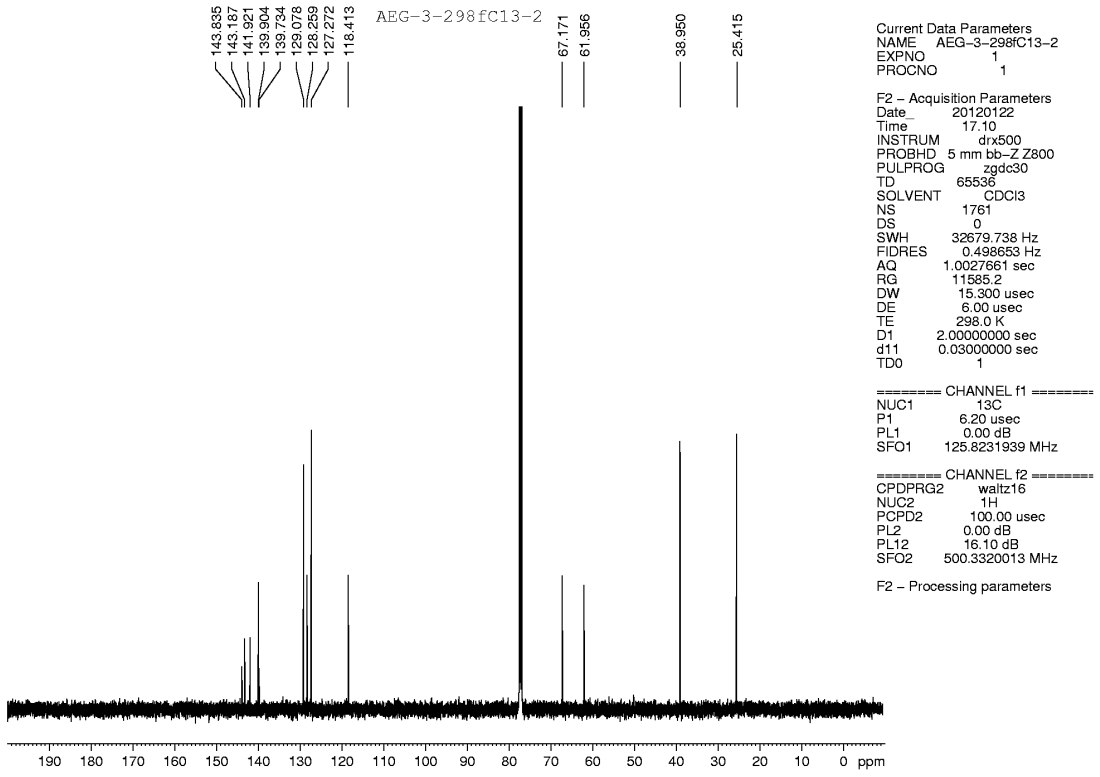



*Figure A3.72* $^{13}$C NMR (125 MHz, $CDCl_3$) of compound **5.50b**.

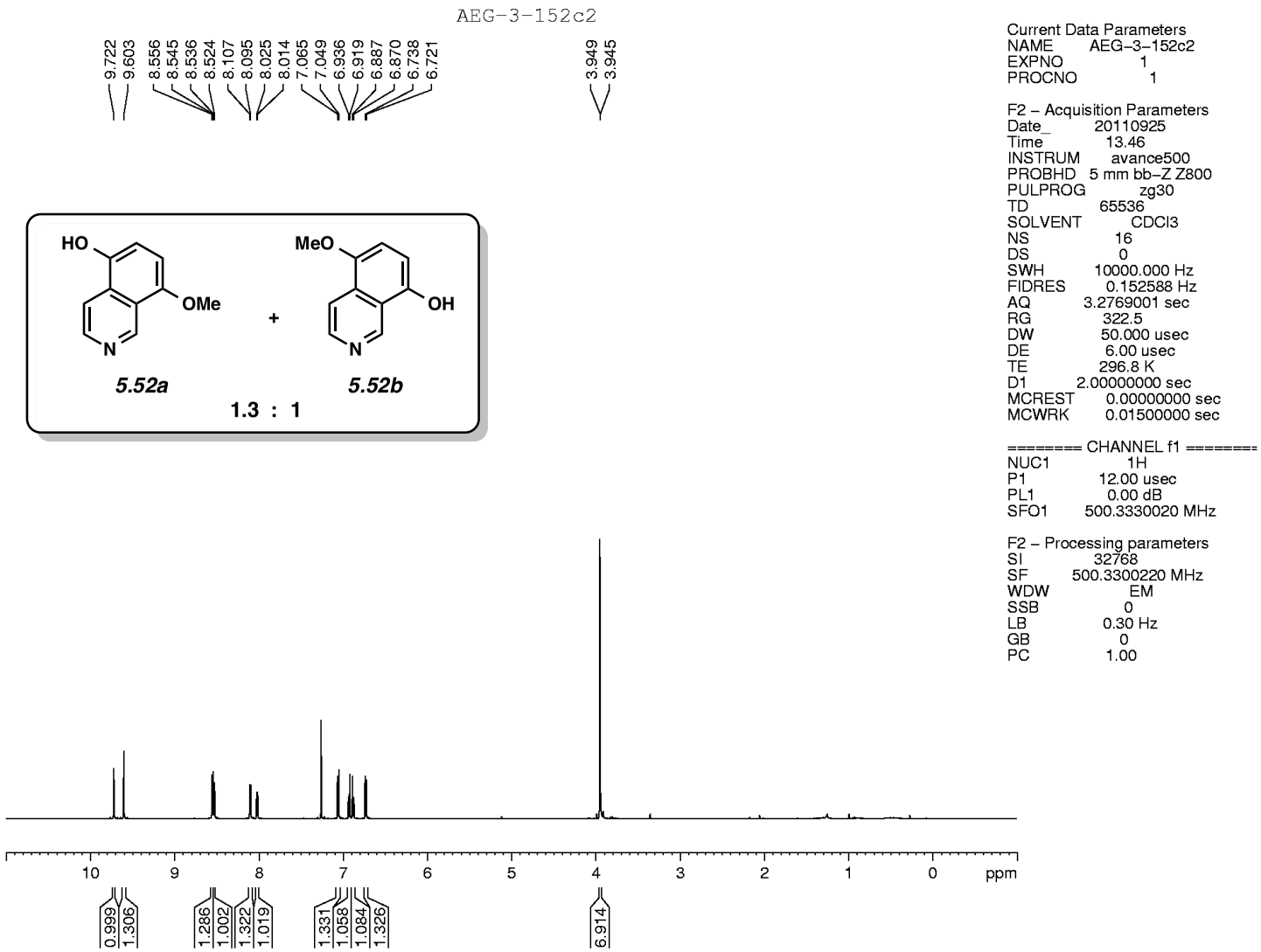



*Figure A3.73* $^{1}$H NMR (500 MHz, $CDCl_3$) of compounds **5.52a** and **5.52b**.

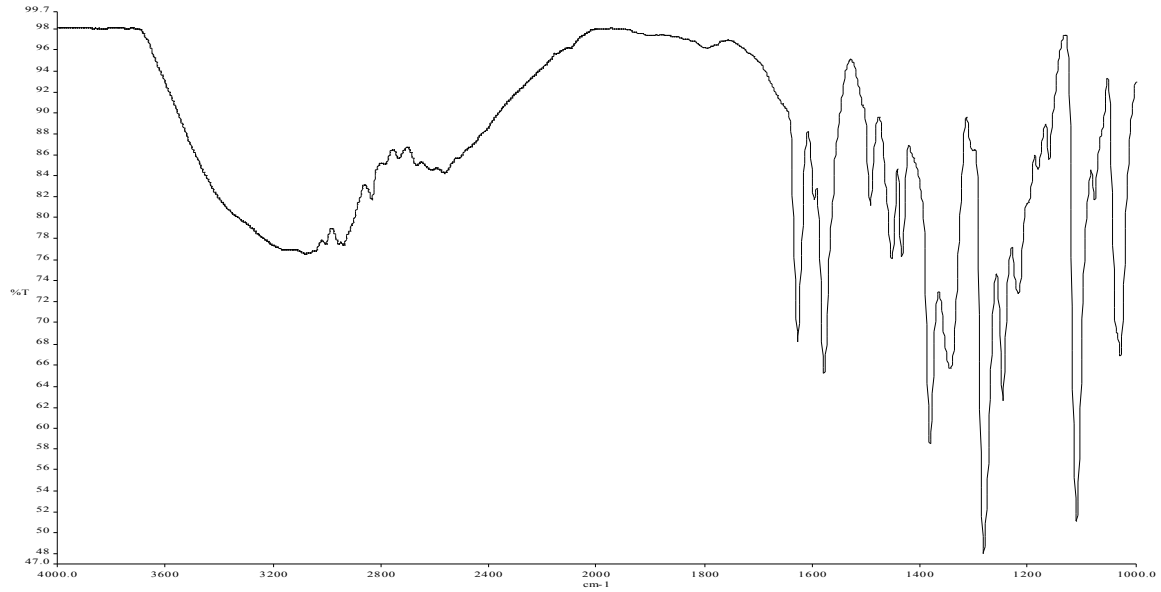



*Figure A3.74* Infrared spectrum of compounds **5.52a** and **5.52b**.

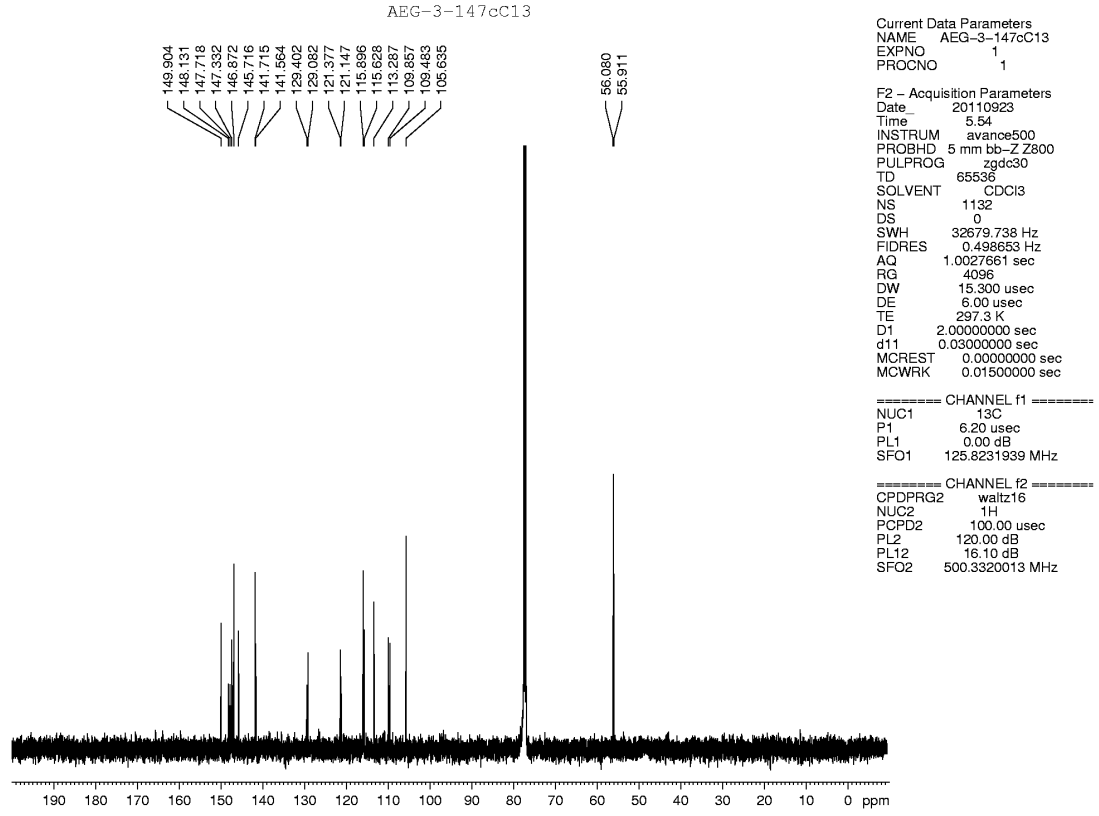



*Figure A3.75* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compounds **5.52a** and **5.52b**.

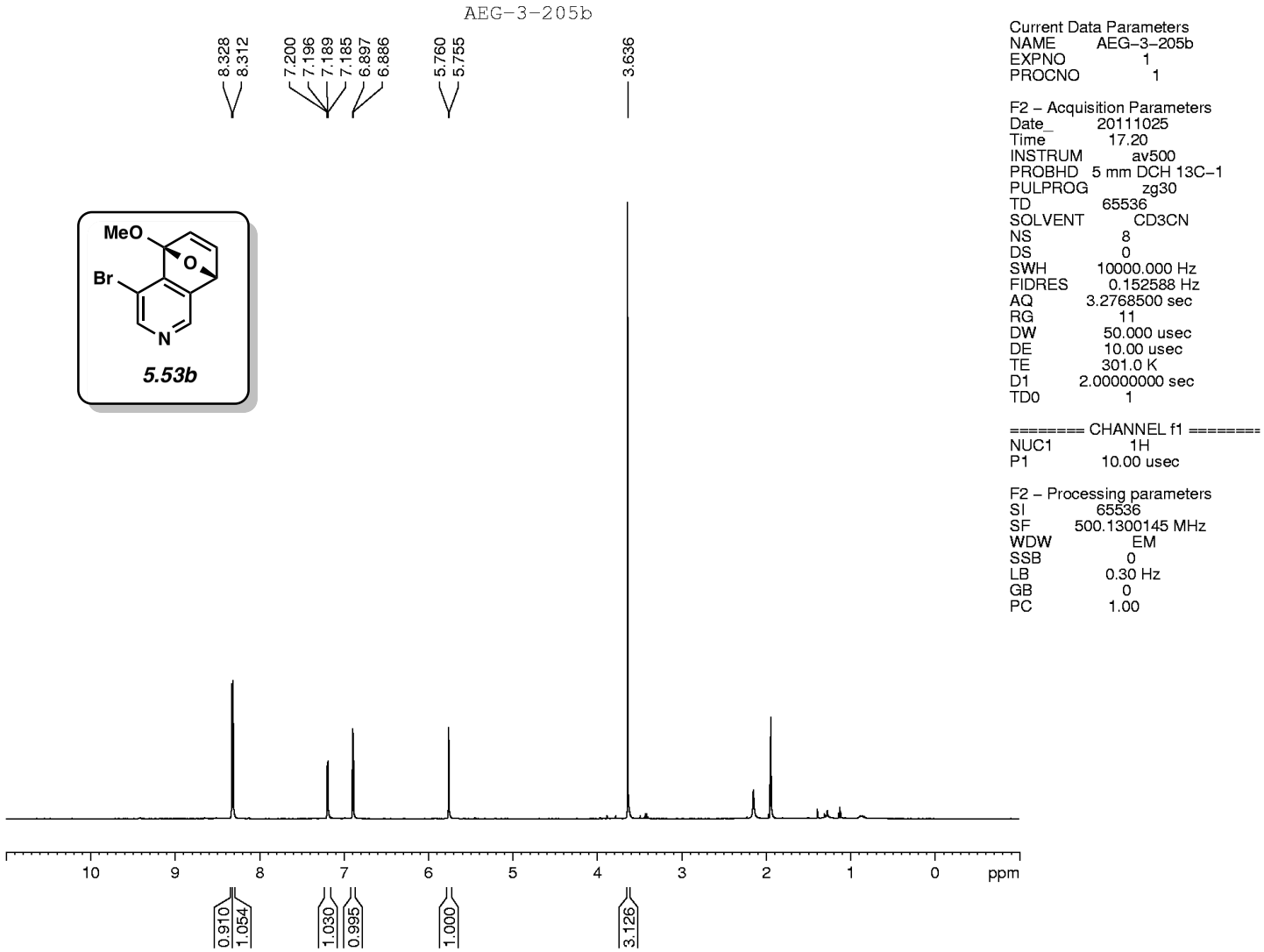



*Figure A3.76* $^{1}$H NMR (500 MHz, $CD_3CN$) of compound **5.53b**.

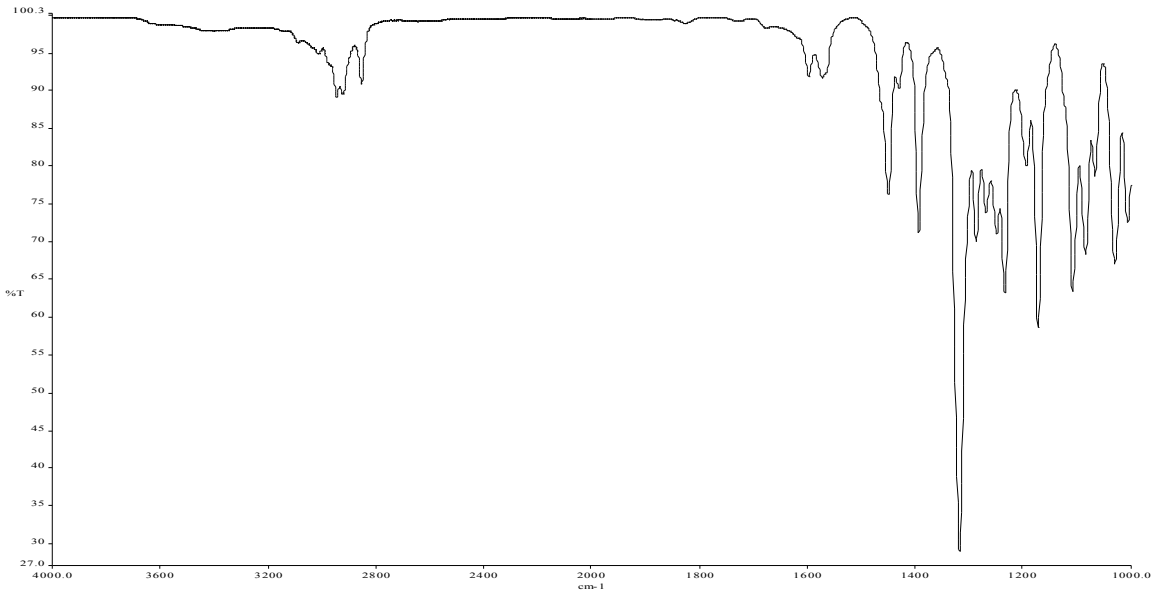



*Figure A3.77* Infrared spectrum of compound **5.53b**.

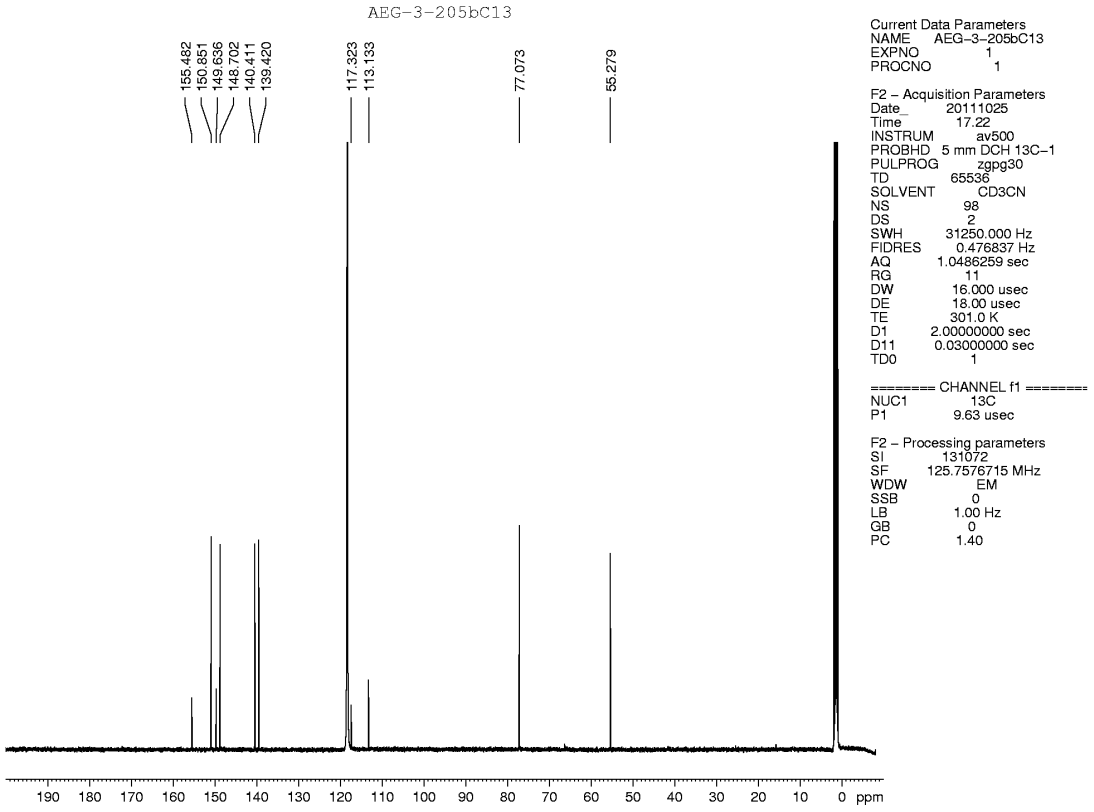



*Figure A3.78* $^{13}C$ NMR (125 MHz, $CD_3CN$) of compounds **5.53b**.

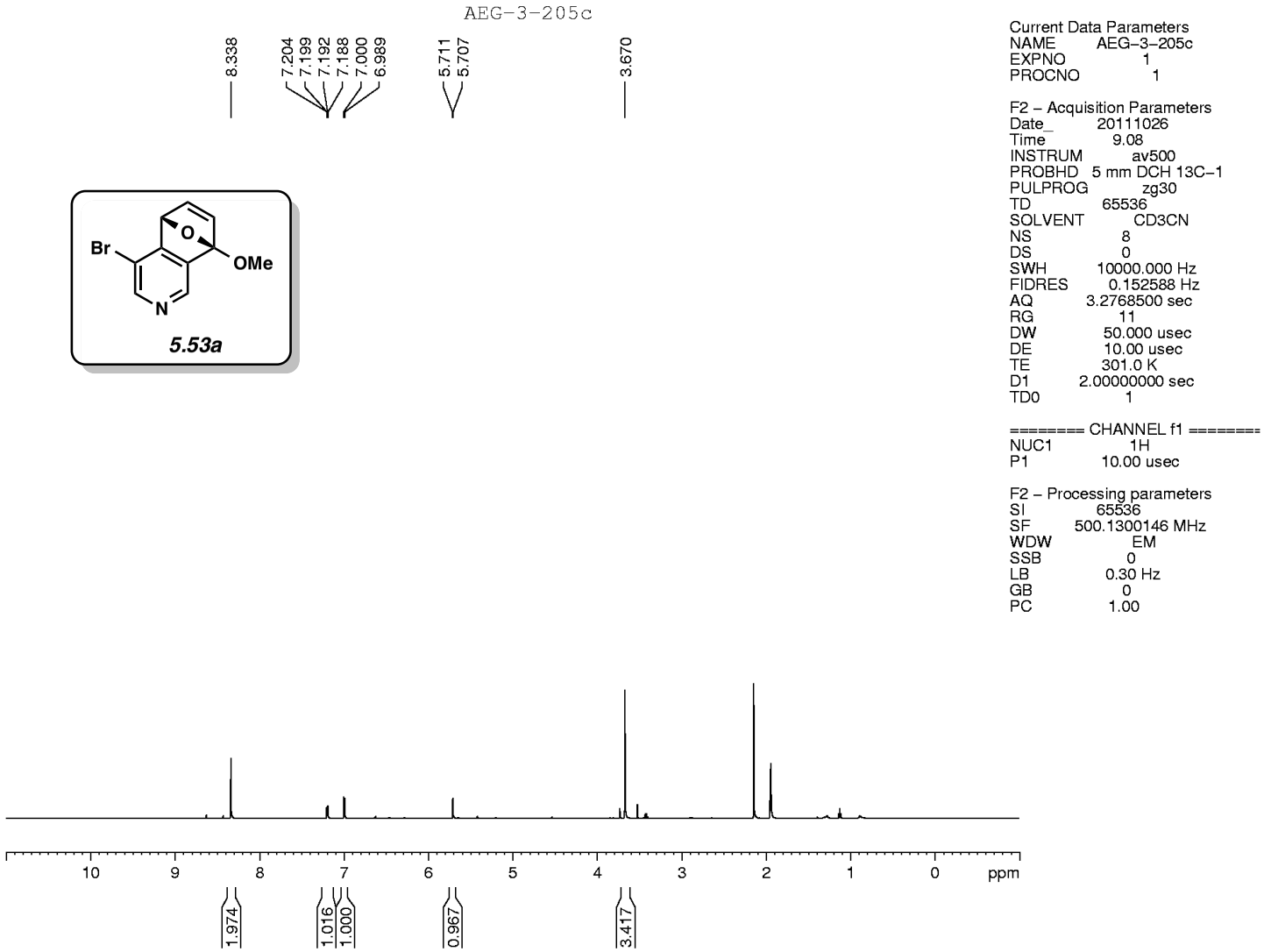



*Figure A3.79* $^{1}$H NMR (500 MHz, $CD_3CN$) of compound **5.53a**.

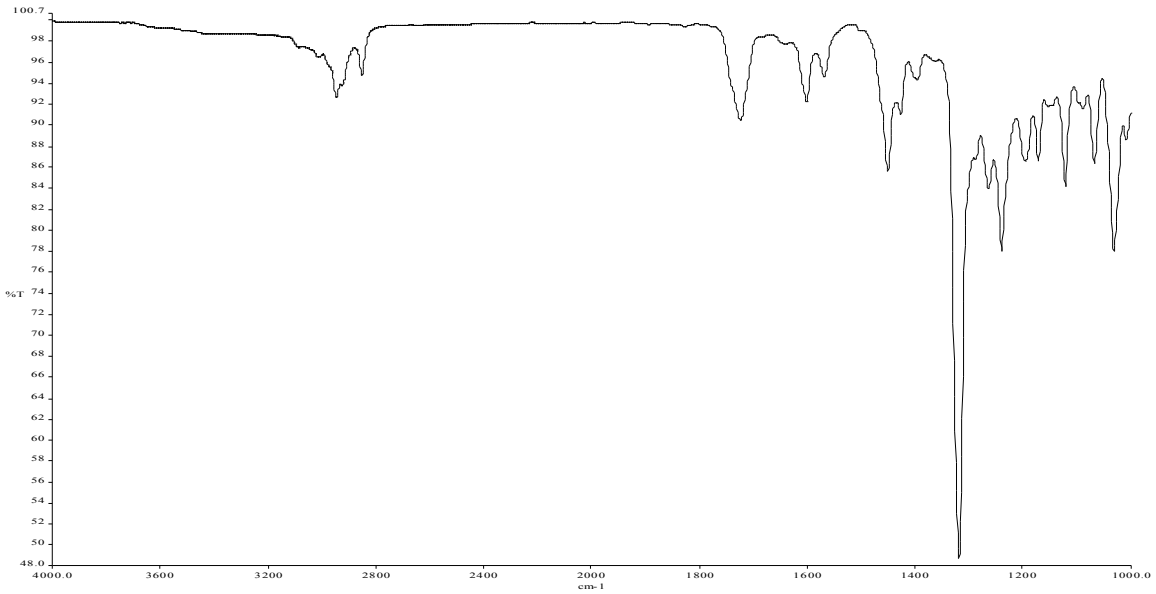



*Figure A3.80* Infrared spectrum of compound **5.53a**.

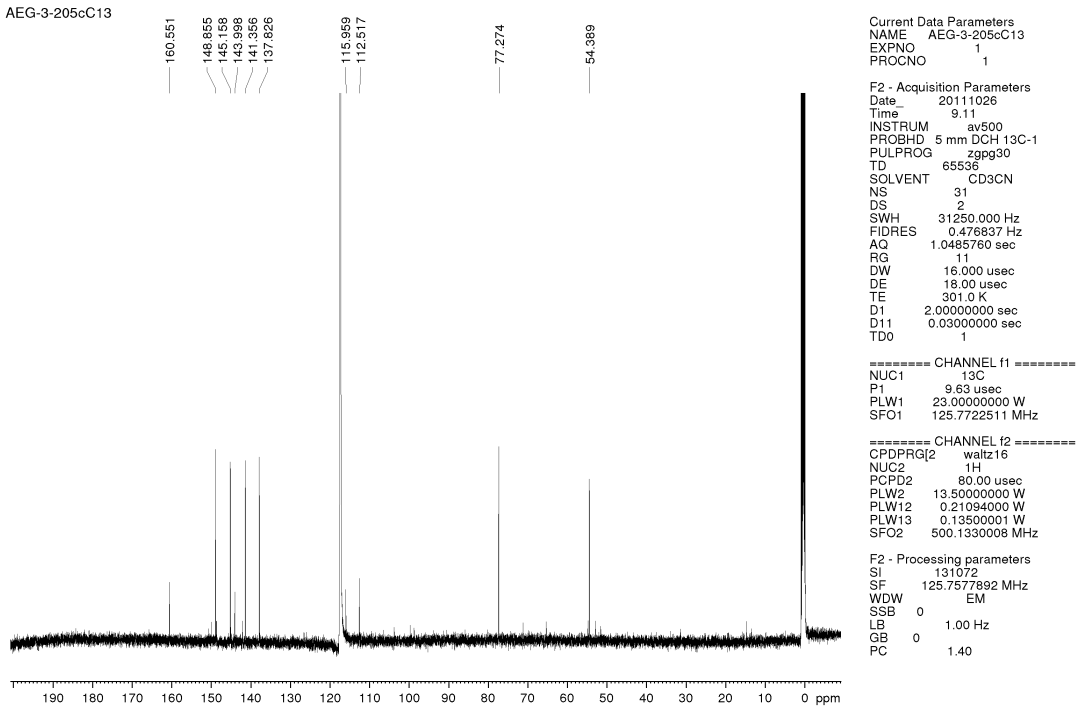



*Figure A3.81* $^{13}$C NMR (125 MHz, $CD_3CN$) of compounds **5.53a**.

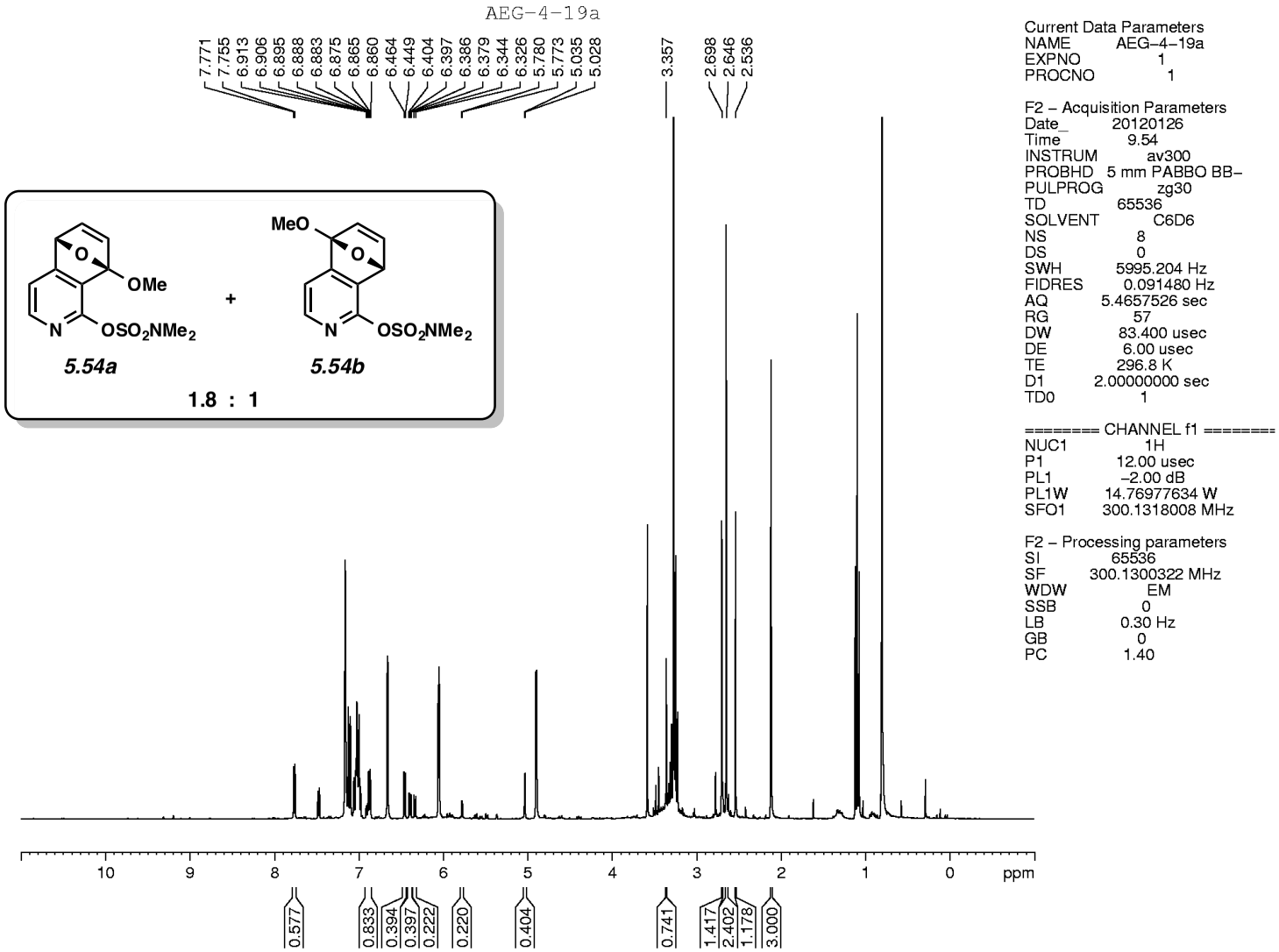



*Figure A3.82* $^{1}$H NMR (500 MHz, $C_6D_6$) of compounds **5.54a** and **5.54b**.

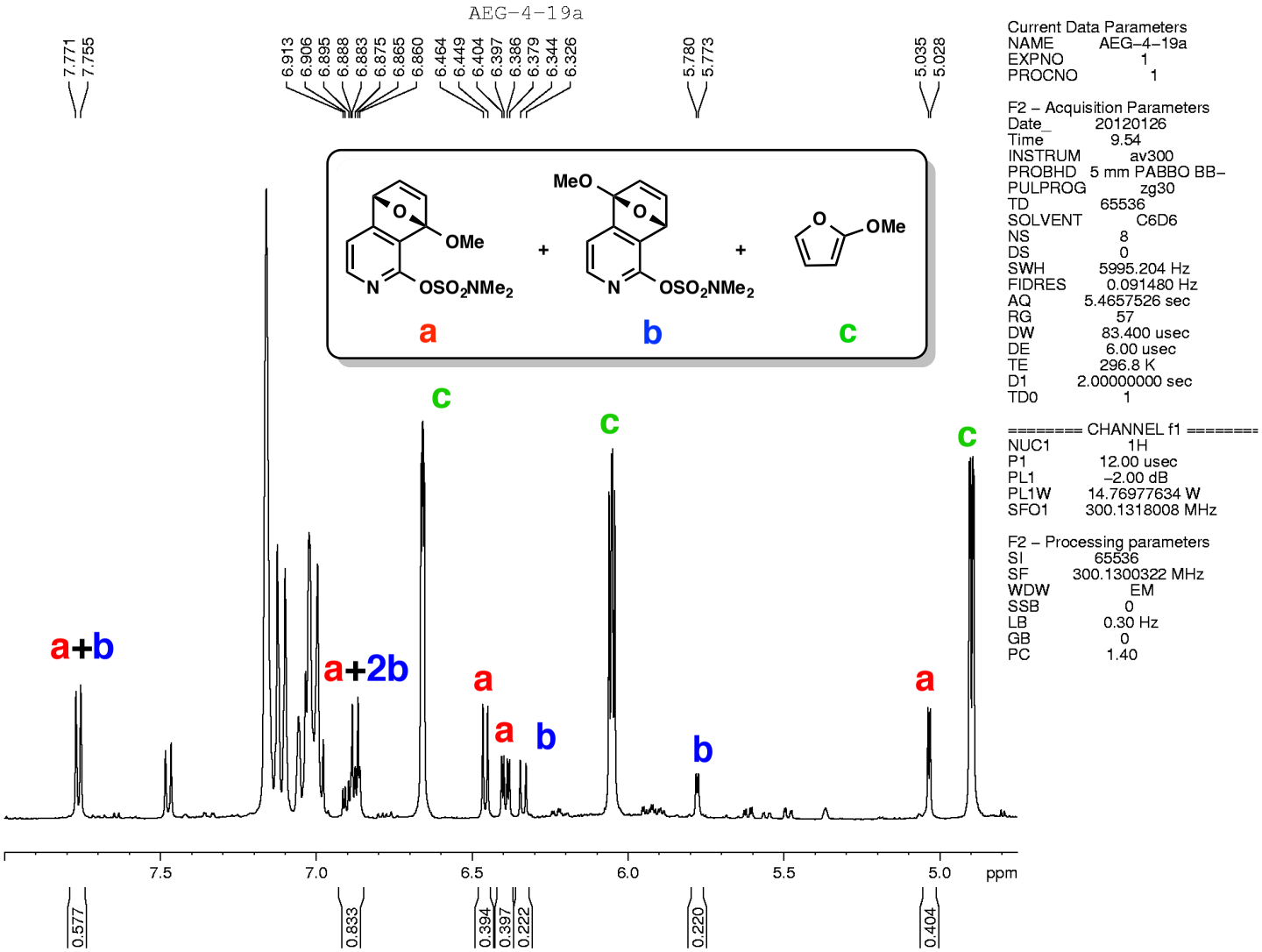



*Figure A3.83* $^{1}$H NMR (500 MHz, $C_6D_6$) of crude compounds **5.54a** and **5.54b**.

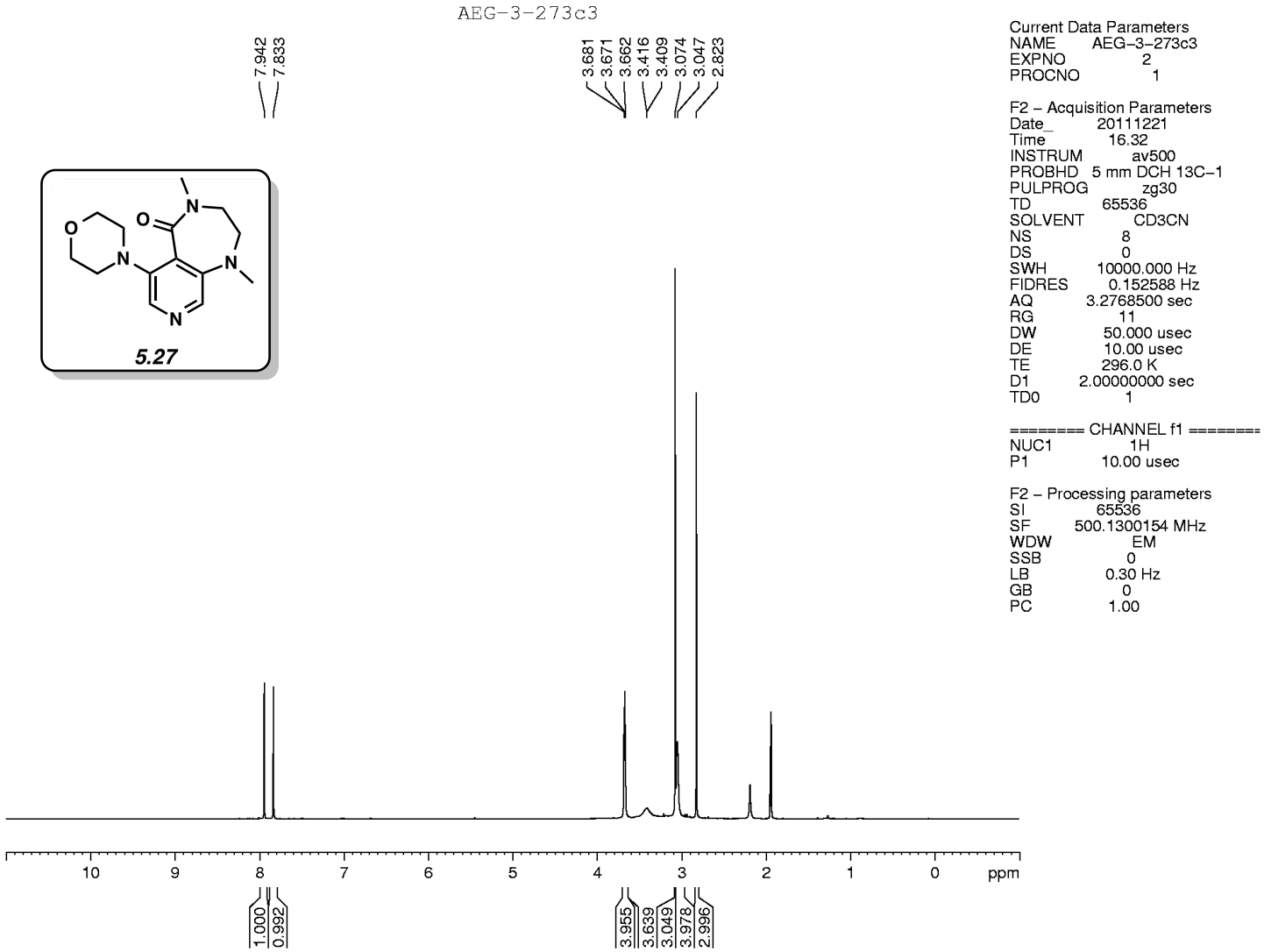



*Figure A3.84* $^{1}$H NMR (500 MHz, $CD_3CN$) of compound **5.27**.

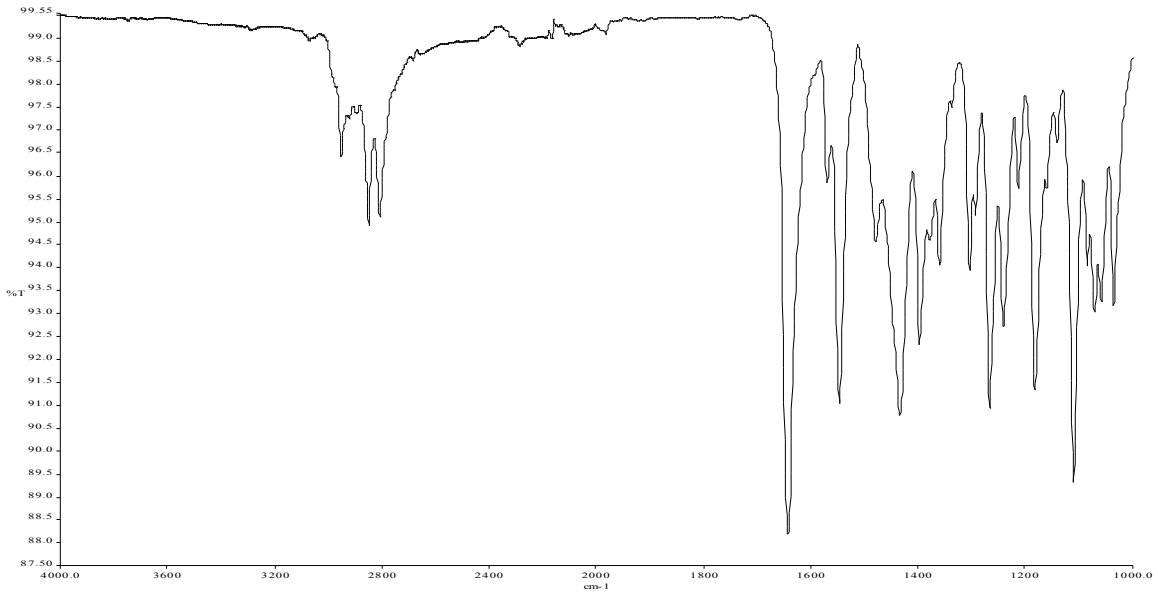



*Figure A3.85* Infrared spectrum of compound **5.27**.

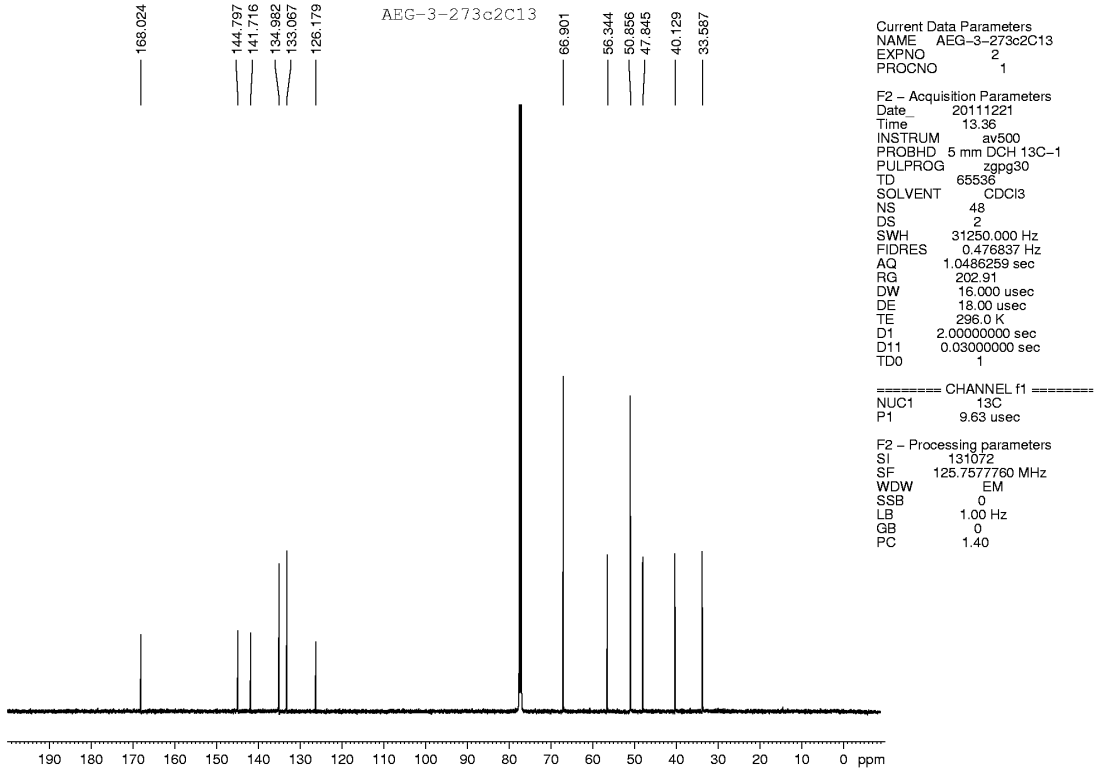



*Figure A3.86* $^{13}$C NMR (125 MHz, $CDCl_3$) of compounds **5.27**.

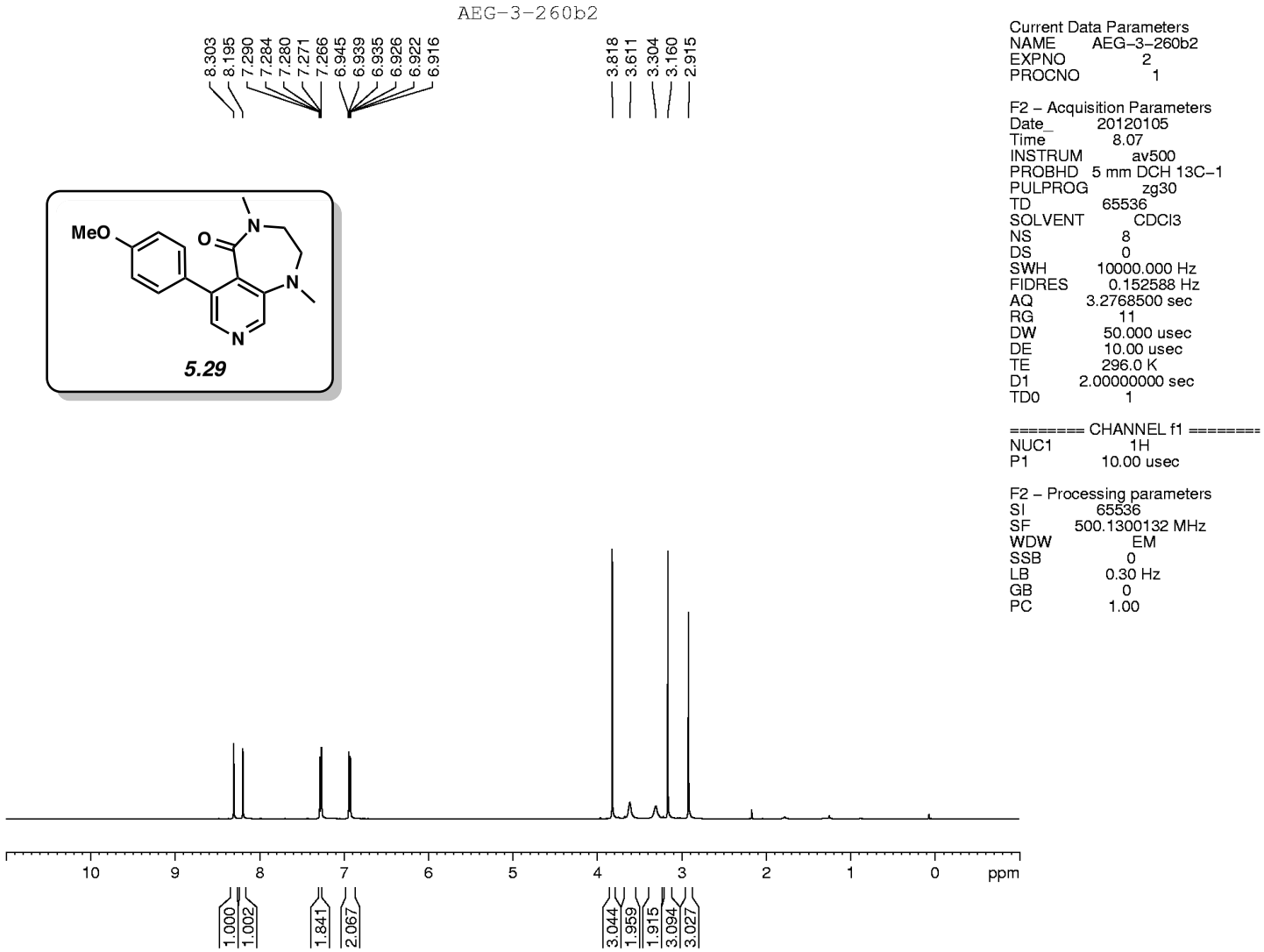



*Figure A3.87* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **5.29**.

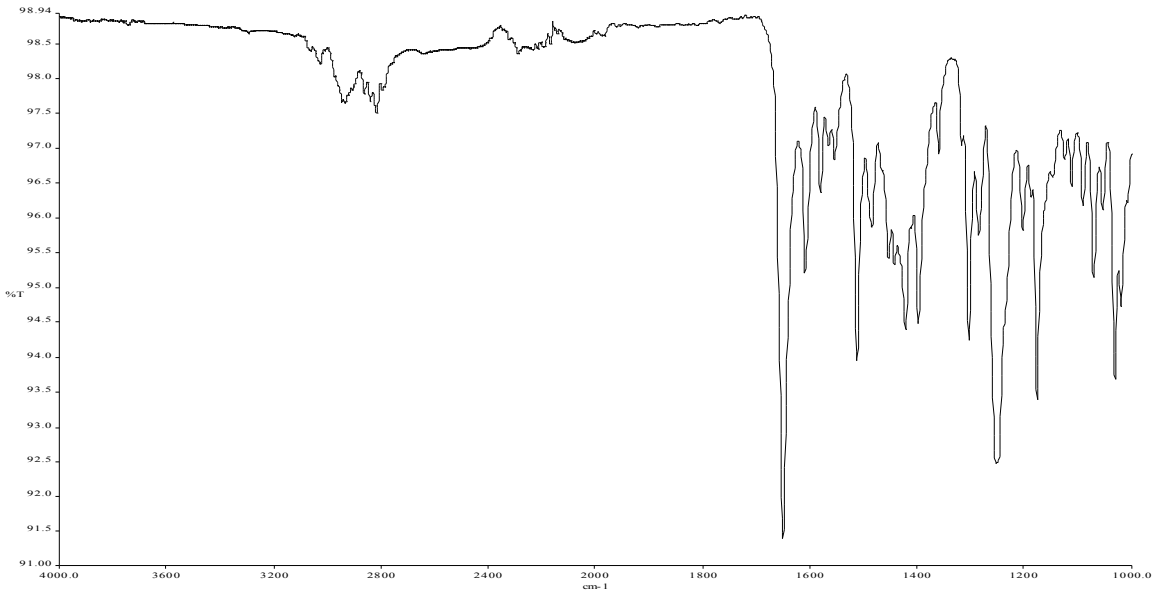



*Figure A3.88* Infrared spectrum of compound **5.29**.

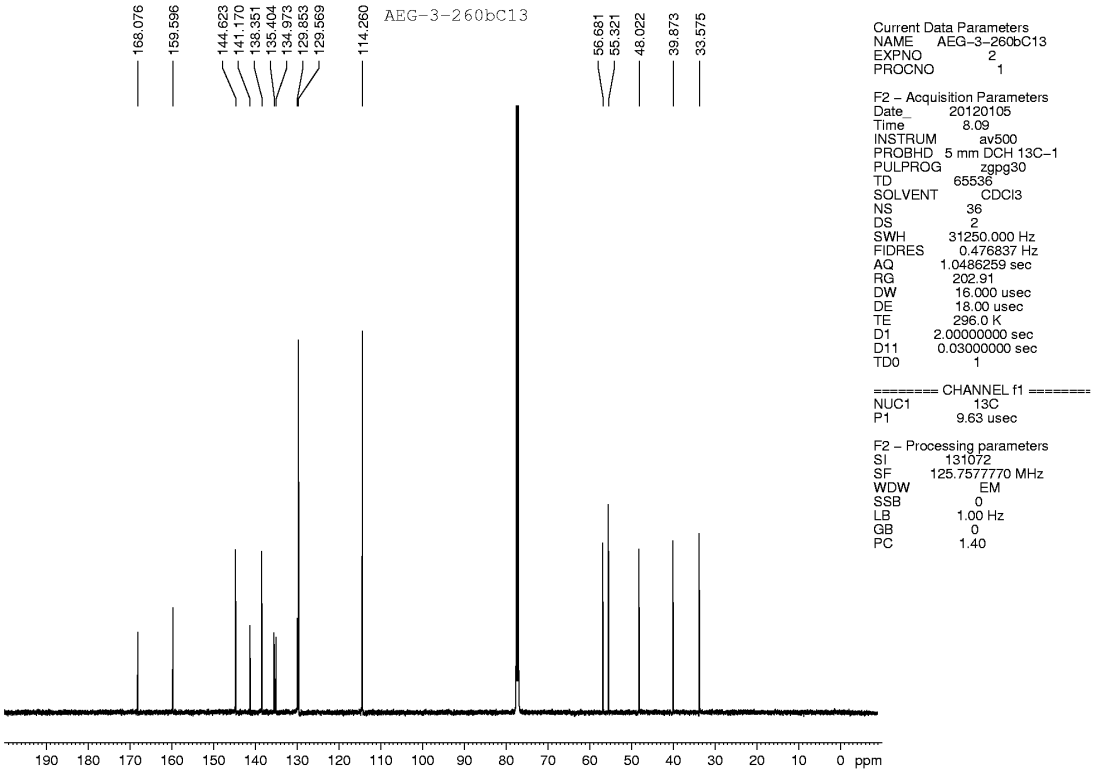



*Figure A3.89* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compounds **5.29**.

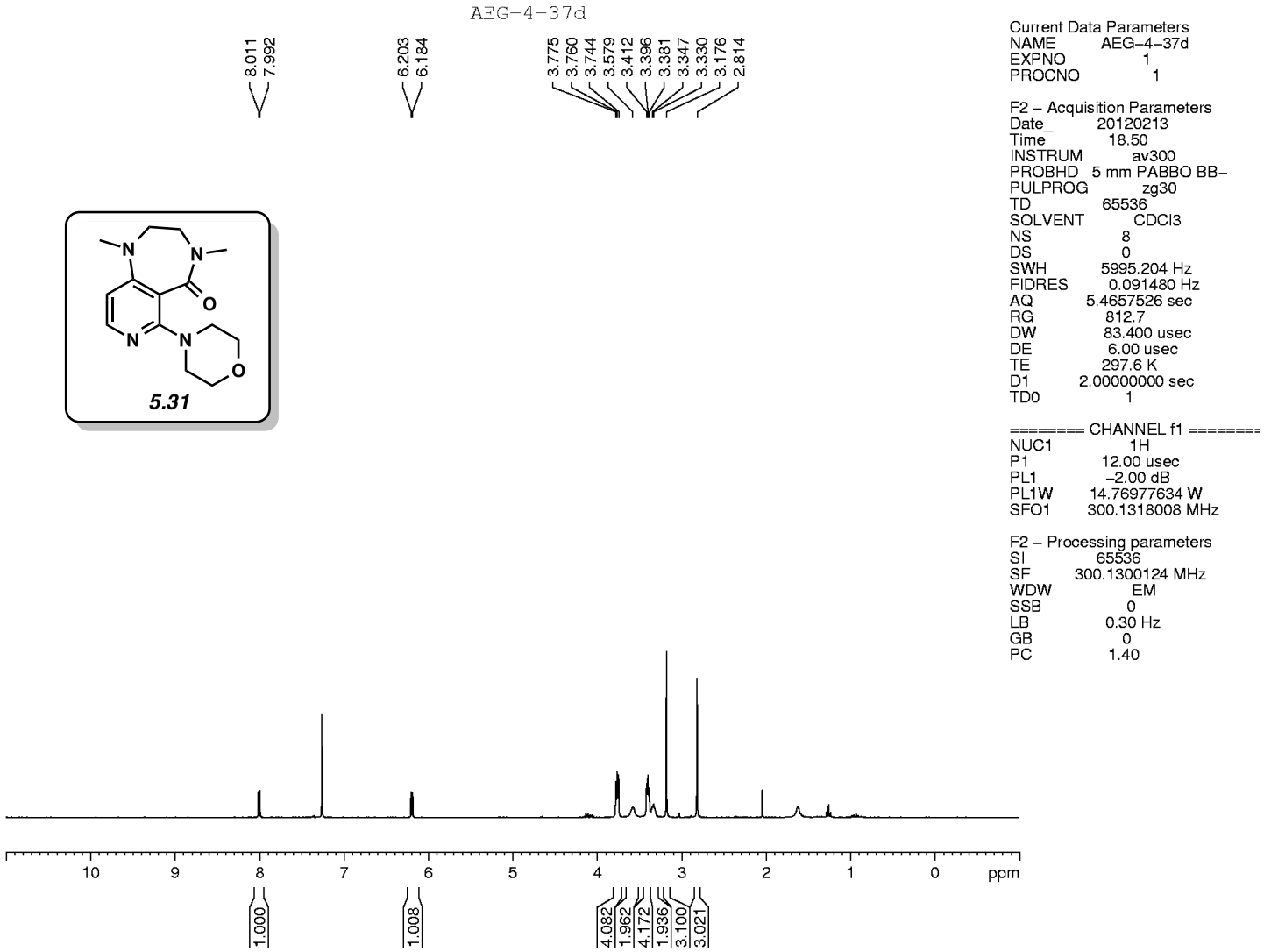



*Figure A3.90* $^{1}$H NMR (300 MHz, $CDCl_3$) of compound **5.31**.

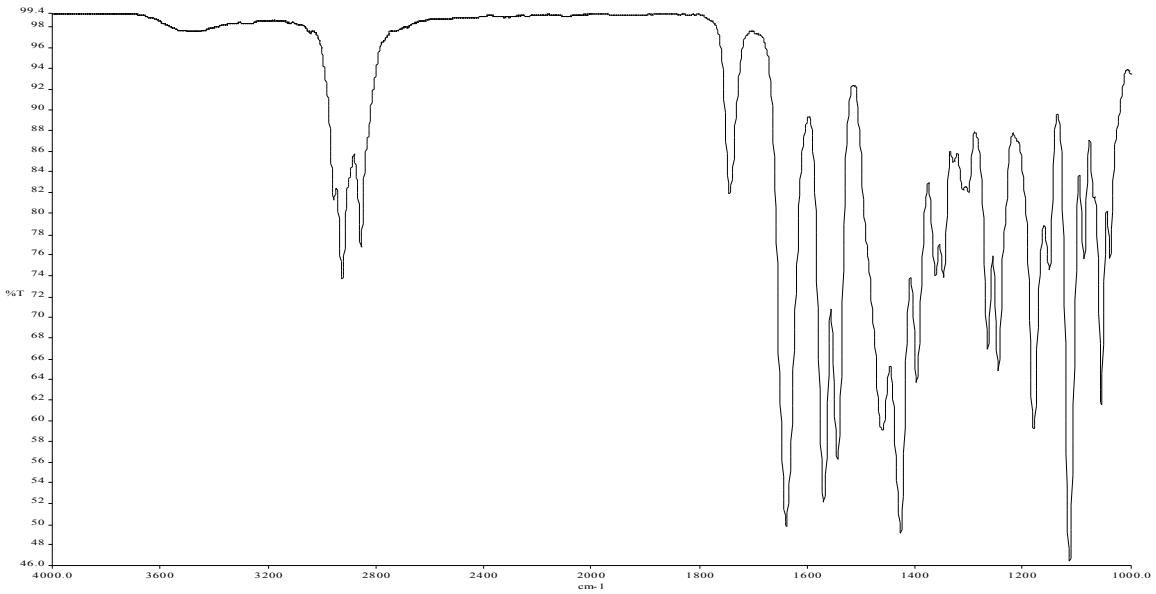



*Figure A3.91* Infrared spectrum of compound **5.31**.

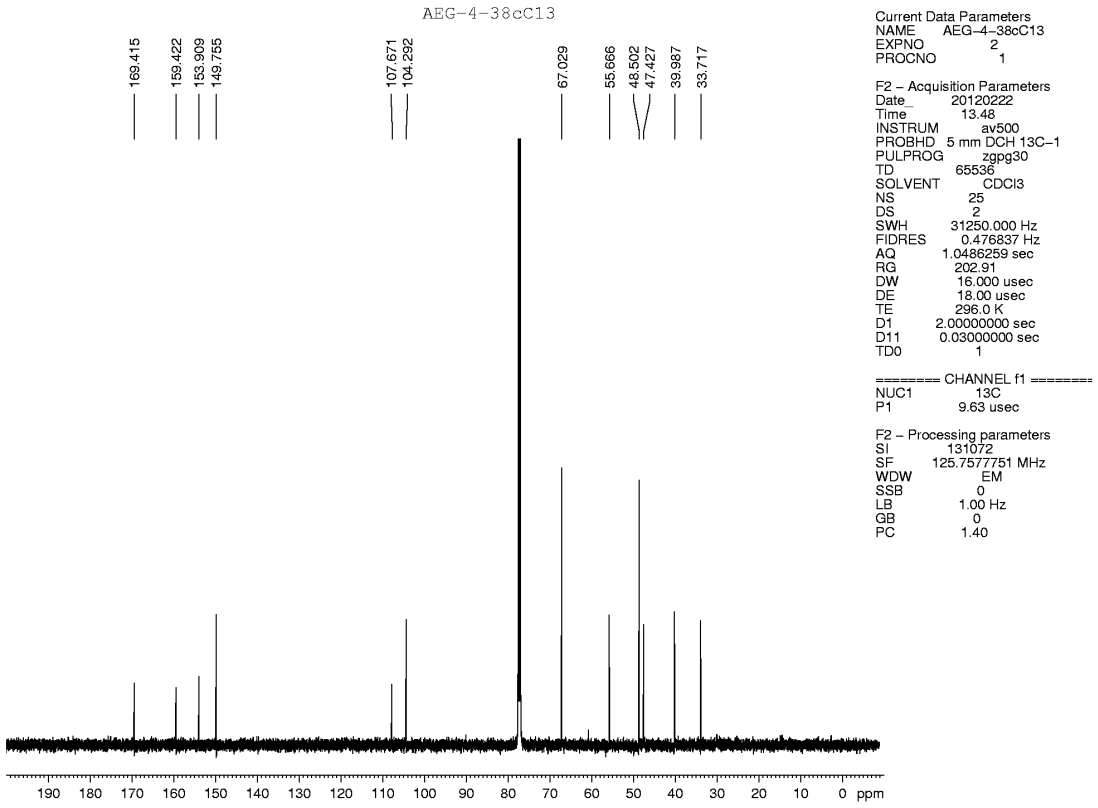



*Figure A3.92* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compounds **5.31**.

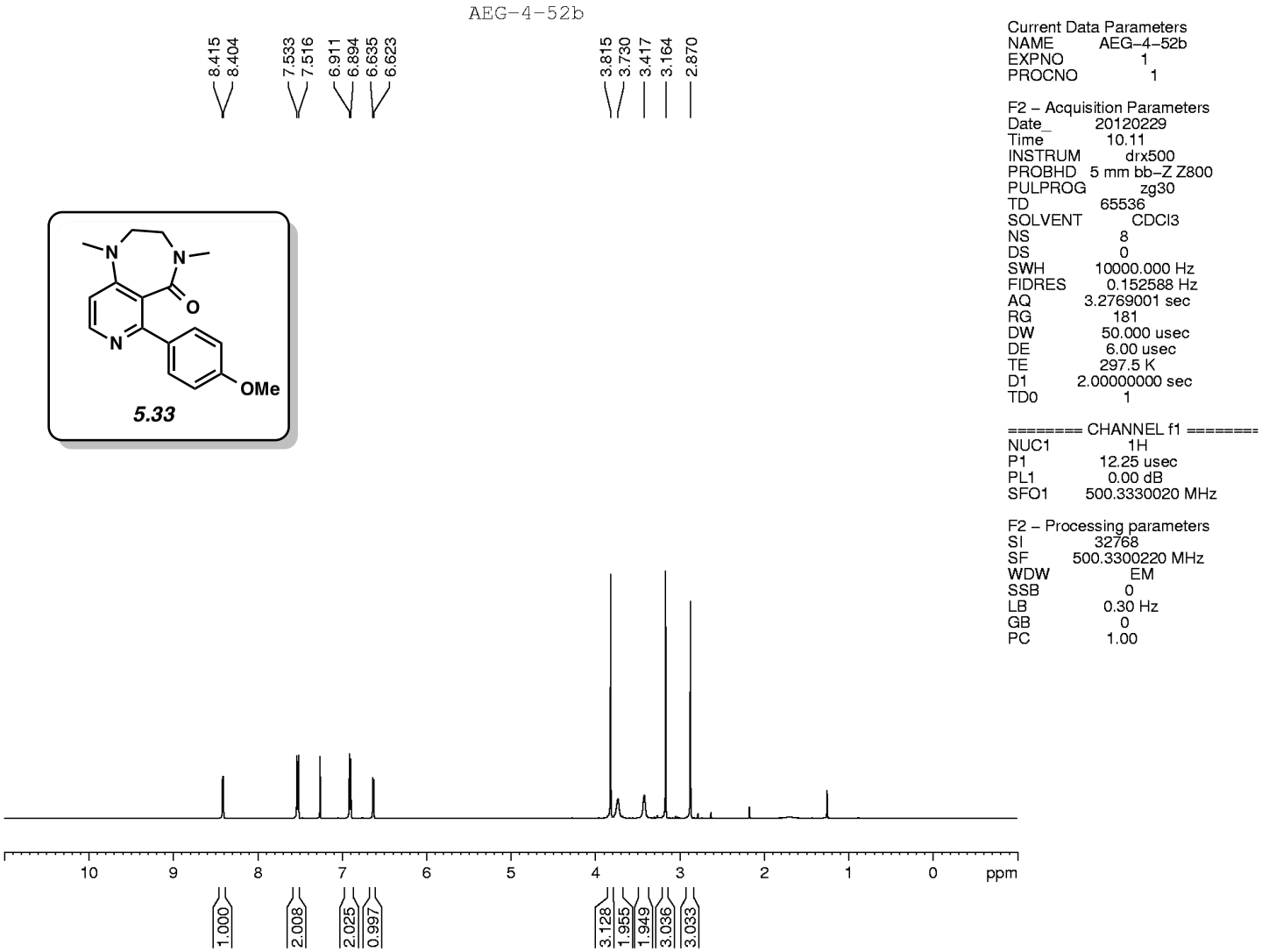



*Figure A3.93* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **5.33**.

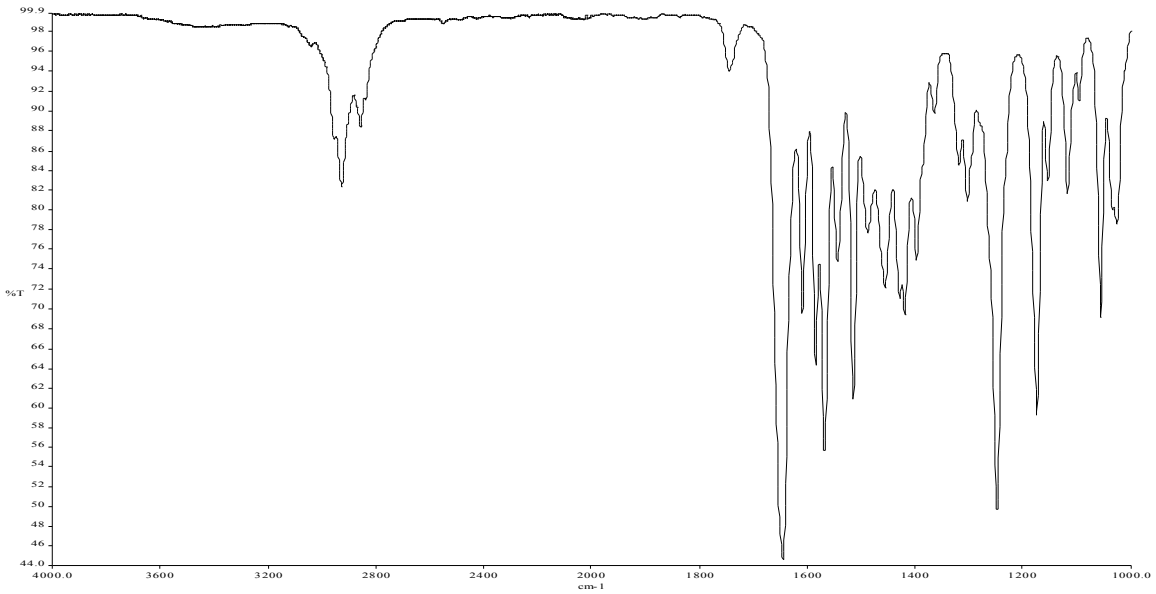



*Figure A3.94* Infrared spectrum of compound **5.33**.

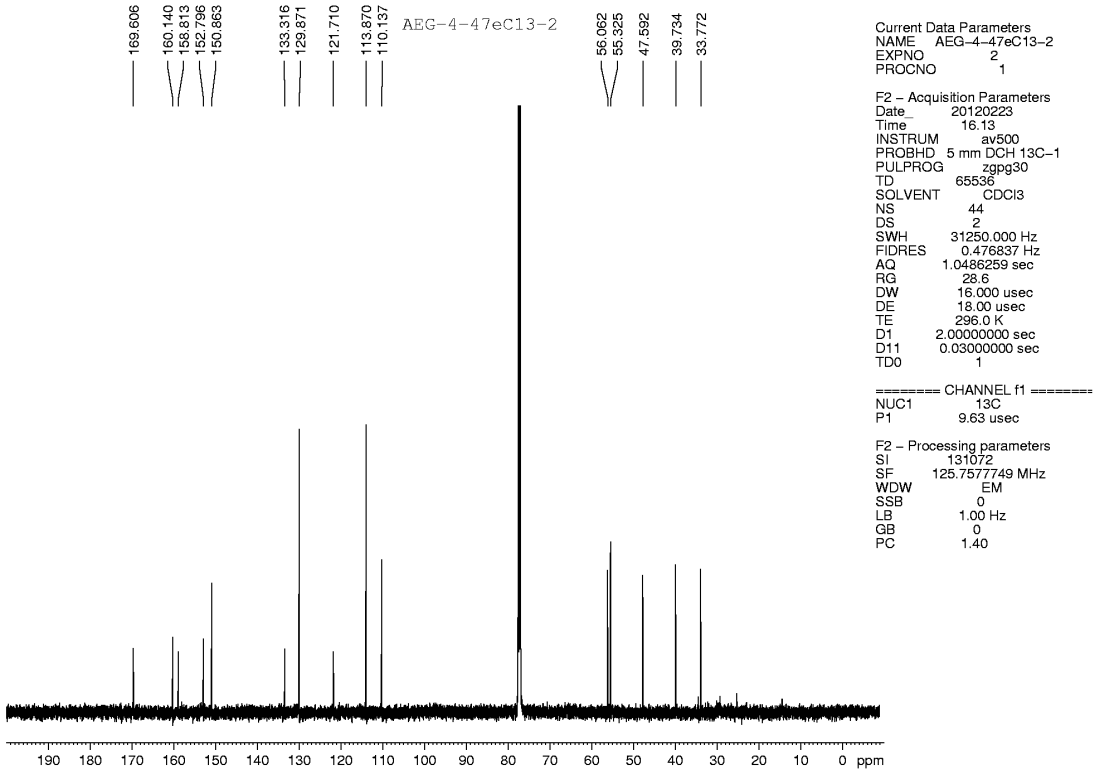



*Figure A3.95* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compounds **5.33**.

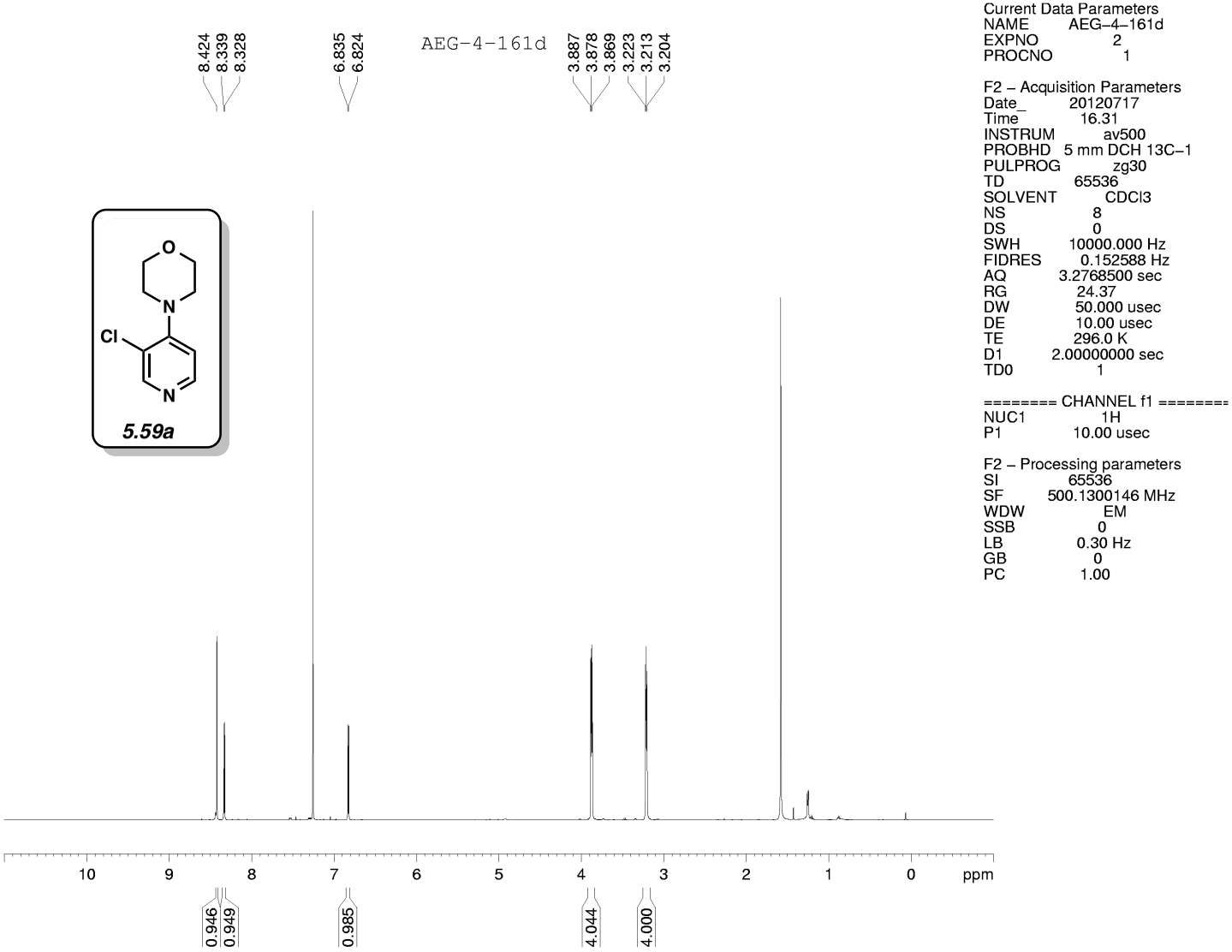



*Figure A3.96* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **5.59a**.

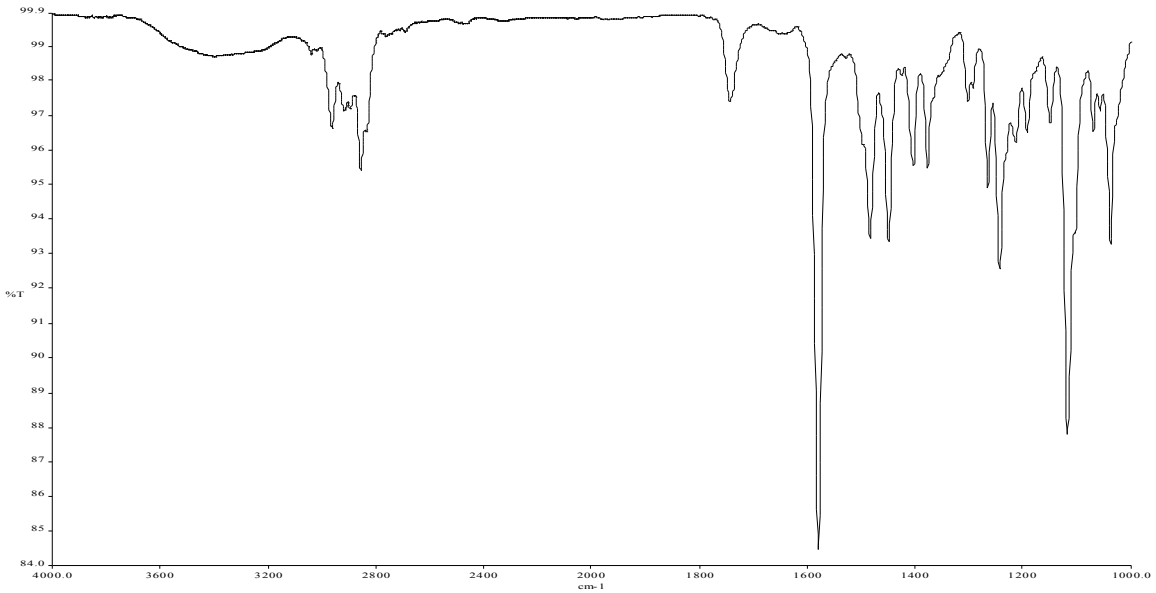



*Figure A3.97* Infrared spectrum of compound **5.59a**.

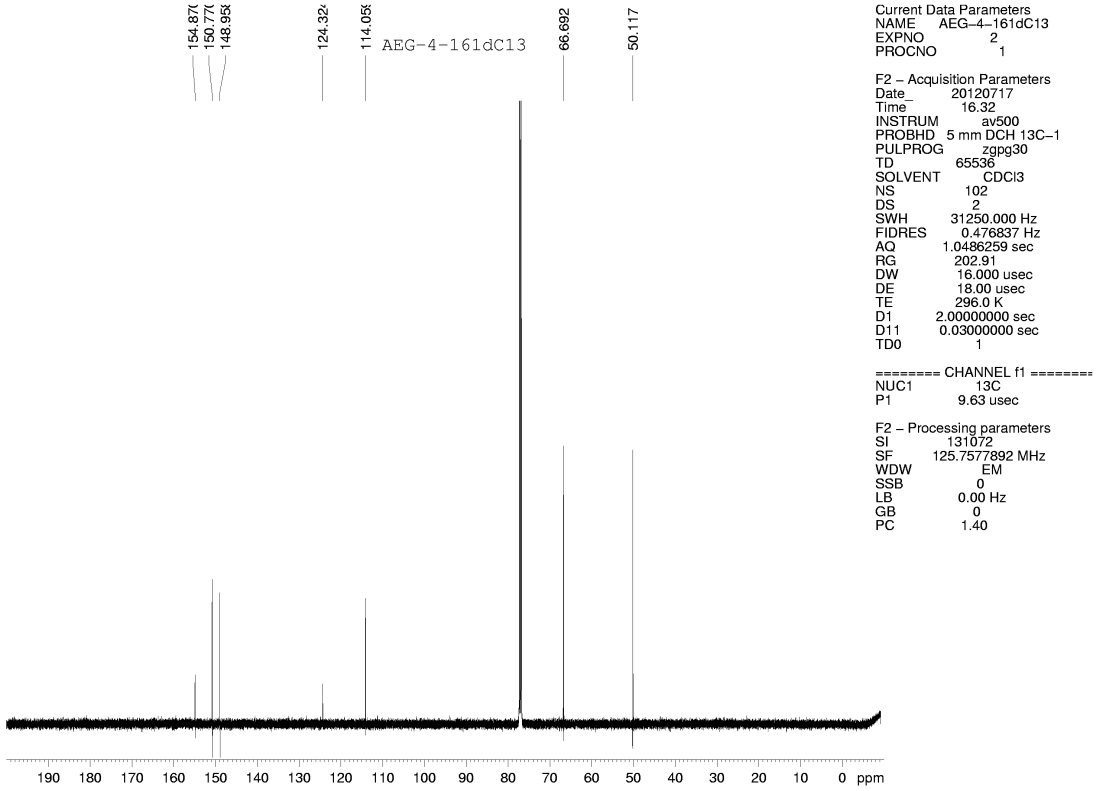



*Figure A3.98* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compounds **5.59a**.

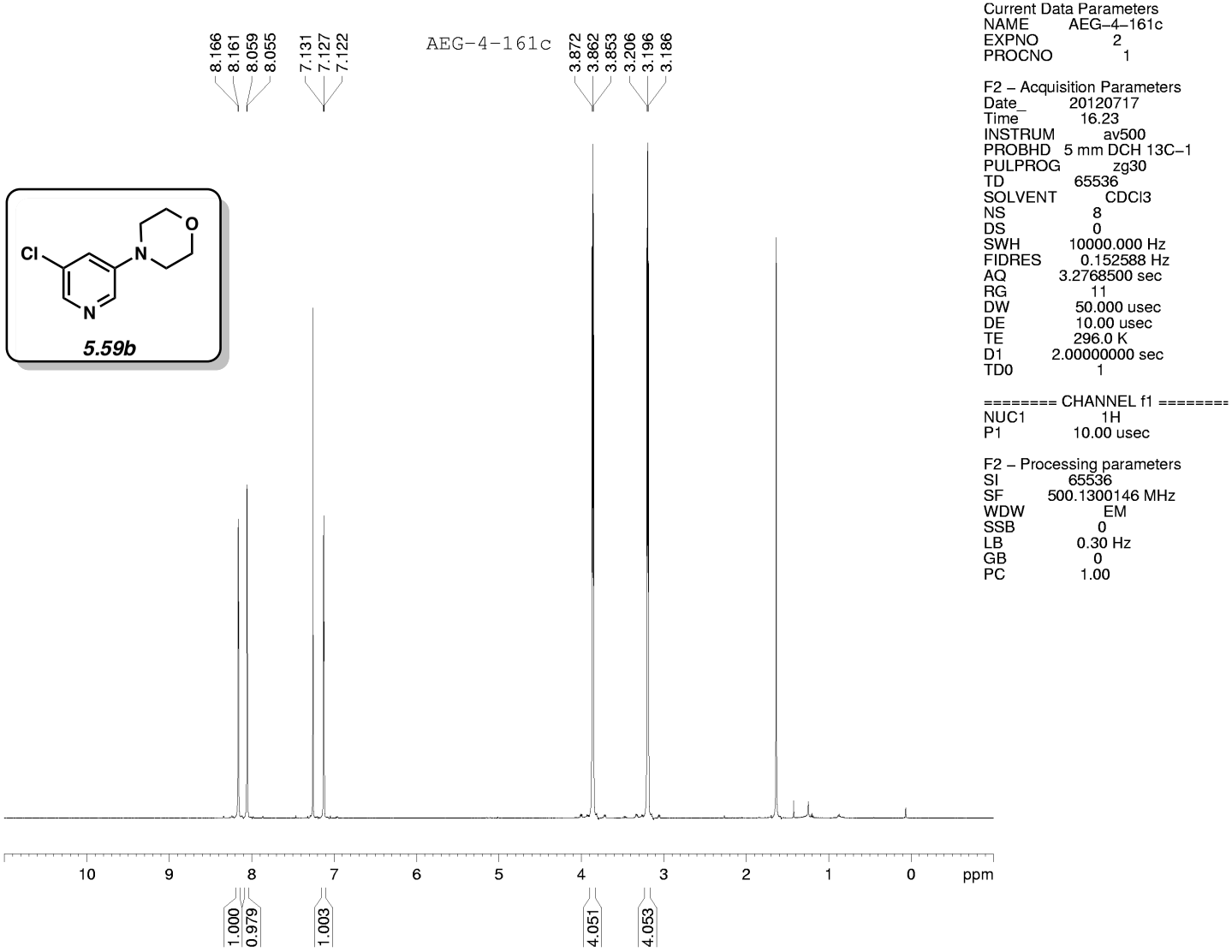



*Figure A3.99* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **5.59b**.

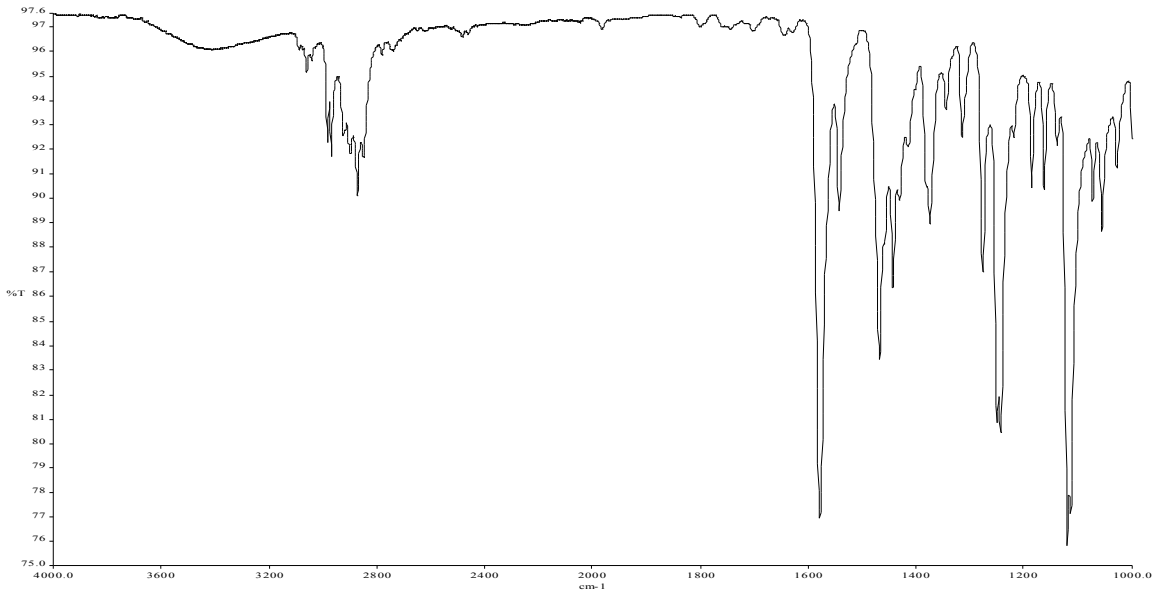



*Figure A3.100* Infrared spectrum of compound **5.59b**.

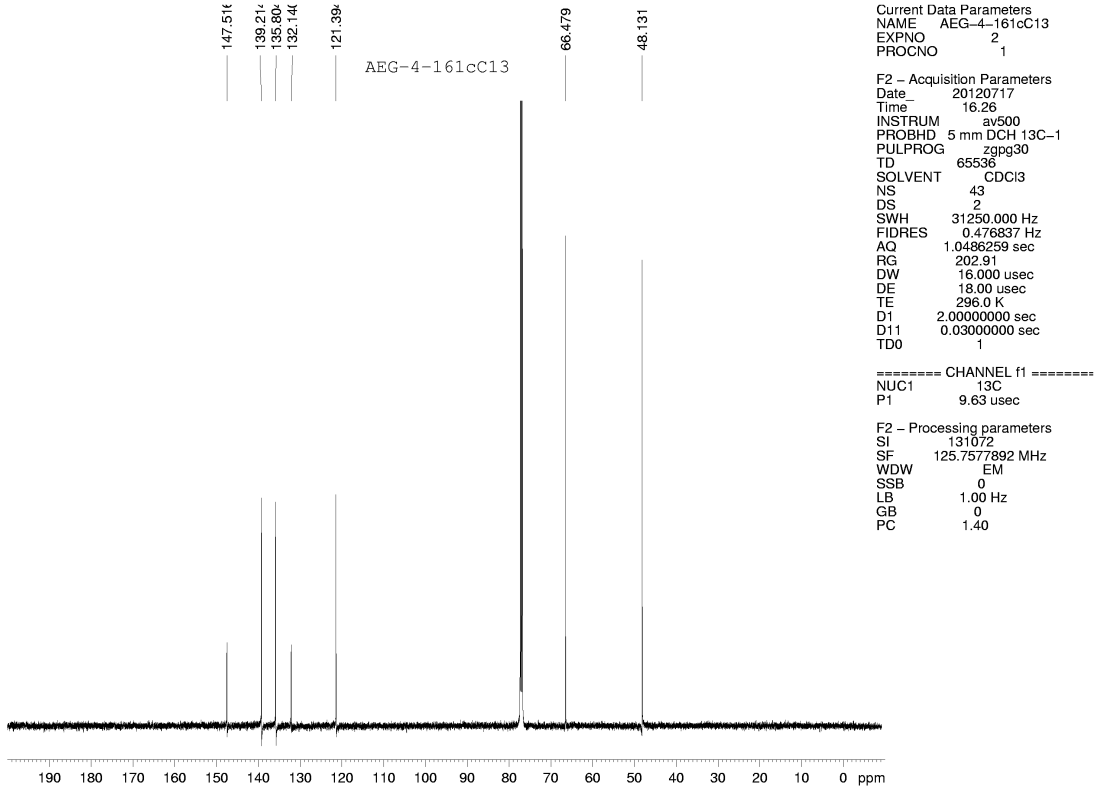



*Figure A3.101* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compounds **5.59b**.

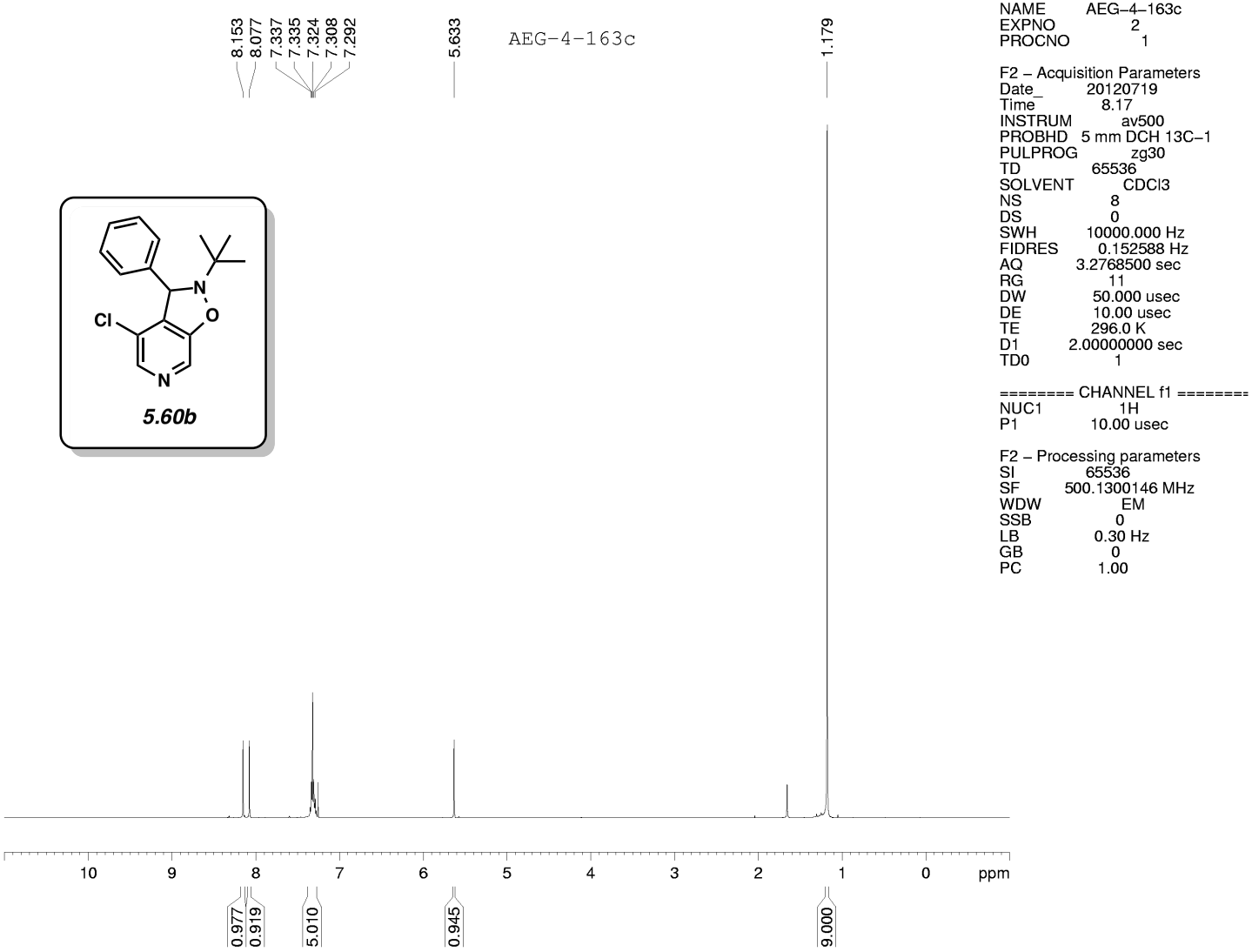



*Figure A3.102* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **5.60b**.

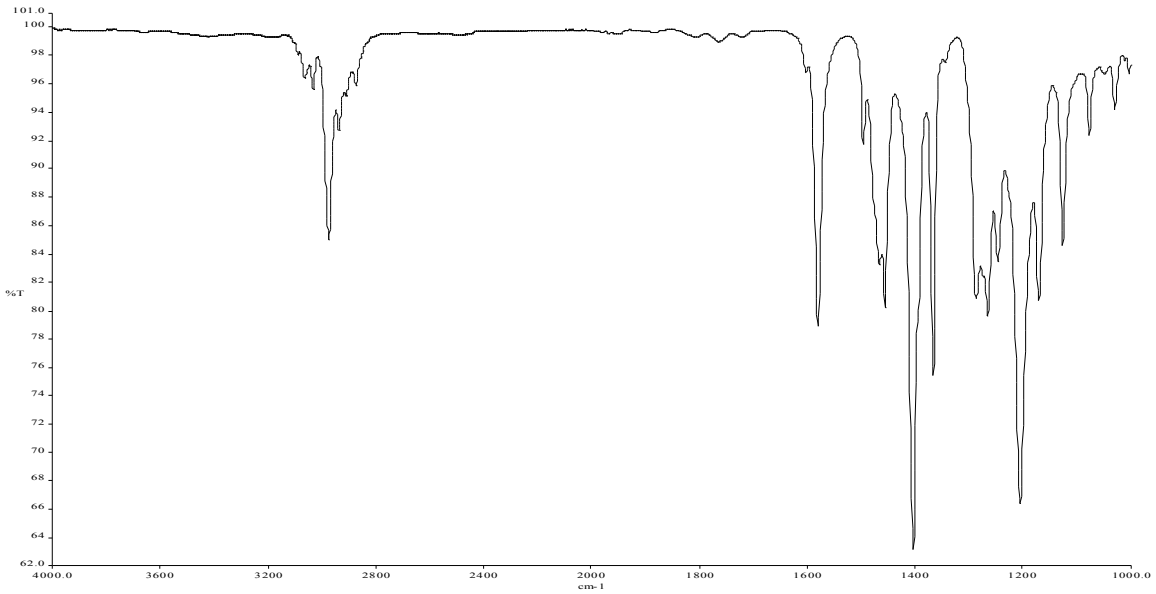



*Figure A3.103* Infrared spectrum of compound **5.60b**.

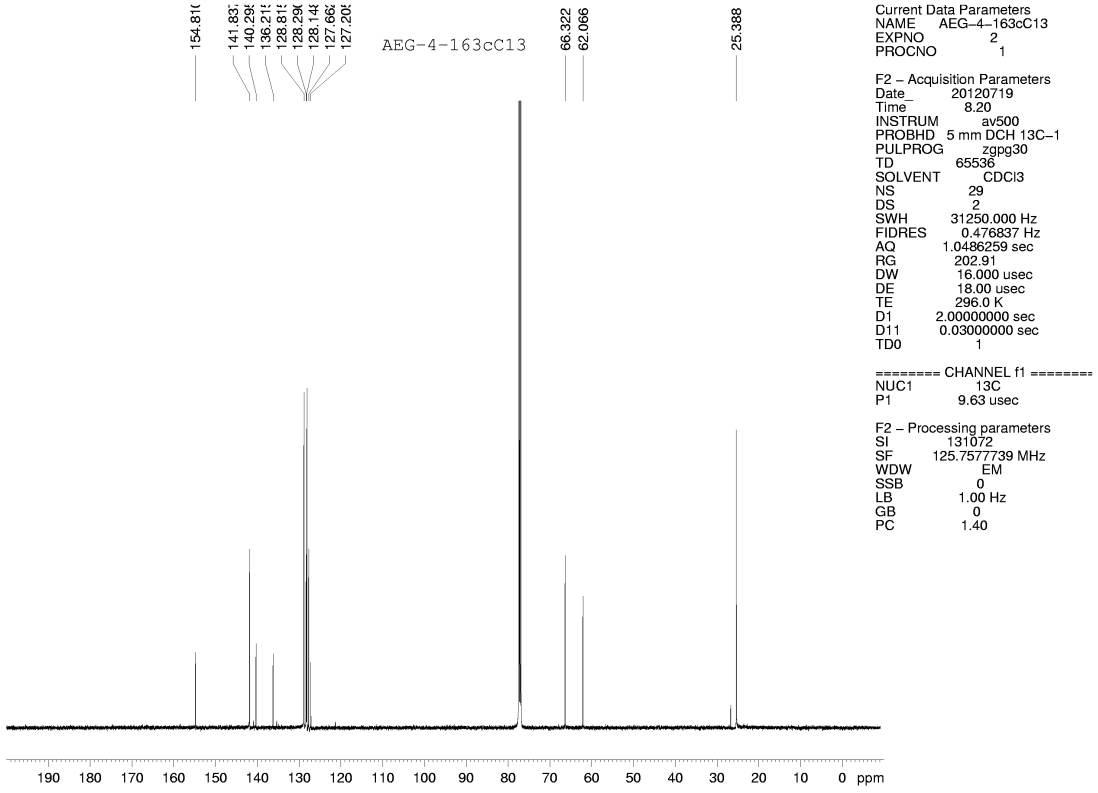



*Figure A3.104* $^{13}C$ NMR (125 MHz, $CDCl_3$) of compounds **5.60b**.

# CHAPTER SIX

## Concise Enantiospecific Total Synthesis of Tubingensin A

Goetz, A. E.; Silberstein, A. L.; Corsello, M. A.; Garg, N. K.

*J. Am. Chem. Soc.* **2014**, *136,* 3036–3039.

### 6.1 Abstract

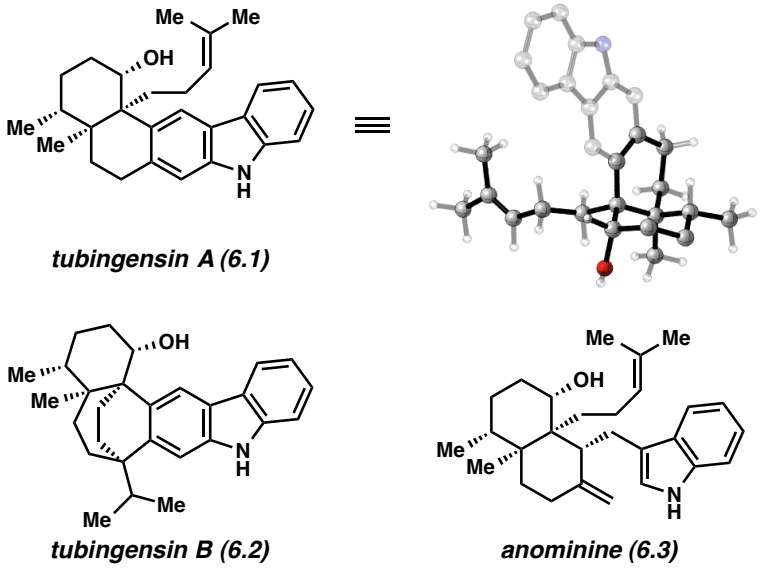
We report the enantiospecific total synthesis of (+)-tubingensin A. Our synthesis features an aryne cyclization to efficiently introduce the vicinal quaternary stereocenters of the natural product and proceeds in only 9 steps (longest linear sequence) from known compounds.

### 6.2 Introduction

Carbazole-containing natural products have long provided a fruitful area for scientific discovery.[1] The complex alkaloid tubingensin A (**6.1**),[2] and its structural isomer tubingensin B (**6.2**),[3] are members of this class that were isolated from the fungus *Aspergillus tubingensis* by Gloer and coworkers in 1989 (Figure 6.1). Compounds **6.1** and **6.2** are both postulated to arise biosynthetically from the indole diterpenoid anominine (**6.3**),[4] and have been shown to display antiviral, anticancer, and insecticidal activity.[2,3] Structurally, tubingensin A (**6.1**) possesses a disubstituted carbazole that is fused to a densely functionalized *cis*-decalin framework.[5] Moreover, the decalin core contains four contiguous stereocenters, two of which are vicinal quaternary centers. With regard to synthetic efforts toward tubingensin A (**6.1**), Bonjoch and coworkers reported an approach to assemble the natural product's scaffold,[6] and Li and Nicolaou

recently completed an elegant bio-inspired total synthesis of **6.1** that proceeds in 23 linear steps from a cyclohexyl precursor.[4a]

*Figure 6.1. Tubingensin A and Related Natural Products*

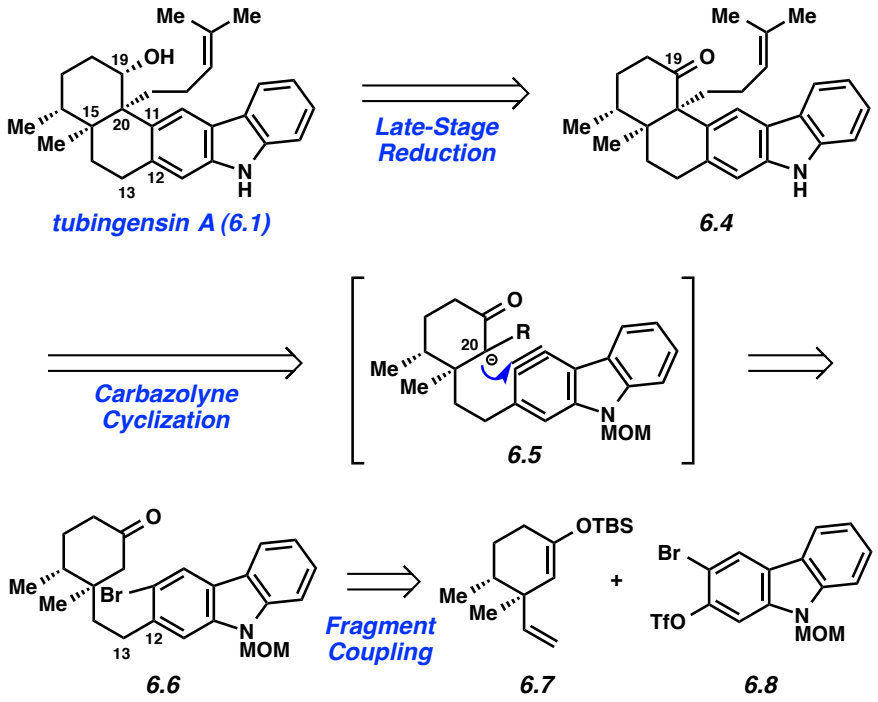



Given our interest in assembling congested scaffolds using heterocyclic aryne intermediates,[7,8] we questioned if the vicinal quaternary stereocenters of tubingensin A (**6.1**) could be introduced using aryne cyclization methodology. Although arynes have been used in an array of interesting trapping experiments,[9] their use in the assembly of sterically congested linkages is limited.[8a,c, 10] Furthermore, to our knowledge arynes have not previously been employed for the introduction of vicinal quaternary stereocenters. In this communication, we report the use of a late-stage carbazolyne cyclization to efficiently construct the tubingensin A framework. Our approach not only demonstrates that arynes can be used for the assembly of challenging molecular scaffolds, but also provides (+)-**6.1** in just 9 steps (longest linear sequence) from known compounds.

Our retrosynthetic analysis for the synthesis of tubingensin A (**6.1**) is shown in Scheme 6.1. It was envisioned that the natural product would arise by late-stage reduction of ketone **6.4**.

This intermediate could be constructed through a key carbazolyne[11] cyclization (see transition structure **5**). If successful, this transformation would fashion the challenging vicinal quaternary stereocenters and provide the *cis*-decalin framework of the natural product. Ketone **6.6**, the precursor to potential carbazolyne cyclization substrates, would ultimately arise from the coupling of two simple fragments, cyclohexyl derivative **6.7** and carbazole triflate **6.8**.

*Scheme 6.1. Retrosynthesis of Tubingensin A*

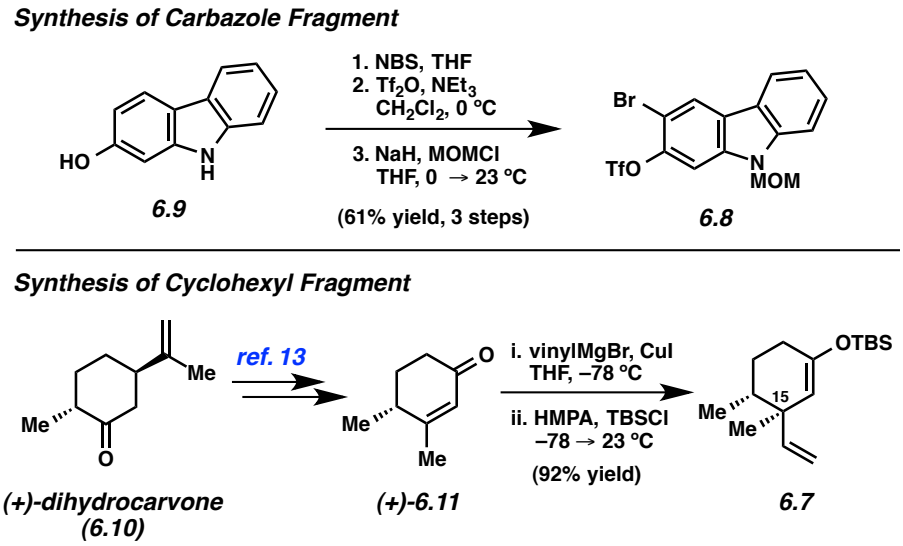



## 6.3 Synthesis of Tubingensin A

The key coupling partners were prepared in a straightforward manner (Figure 6.2). Commercially available hydroxycarbazole **6.9** was brominated using a known procedure.[12] Subsequent *O*-triflation and *N*-protection afforded **6.8** in 61% yield over three steps. The synthesis of cyclohexyl fragment **6.7** began from commercially available (+)-dihydrocarvone (**6.10**), which was elaborated to enone **6.11** using a known 3-step procedure.[13] Vinyl cuprate

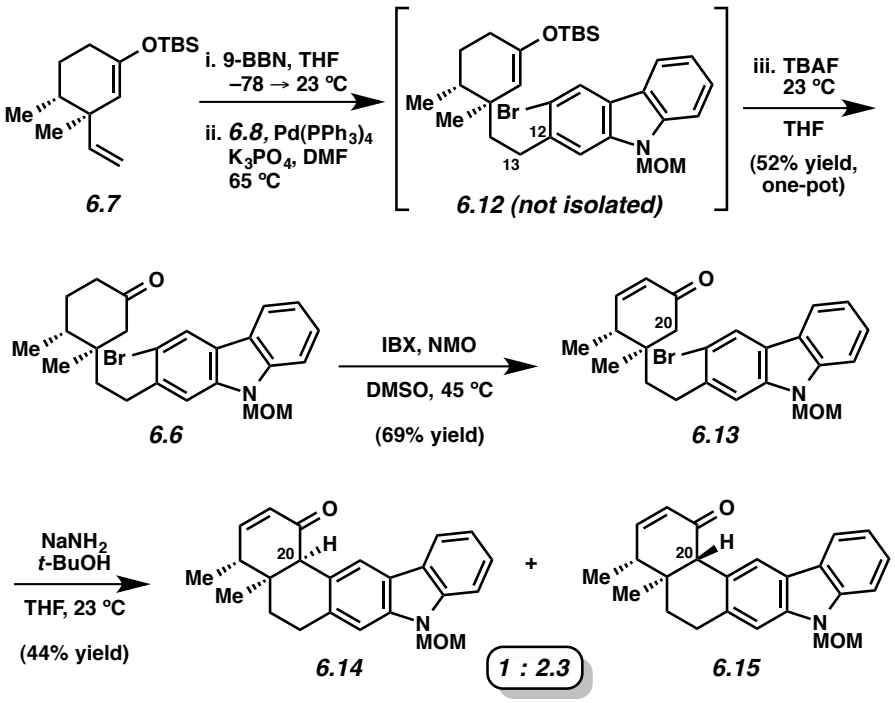
addition and trapping of the resulting enolate furnished silyl enol ether **6.7** as a single diastereomer.[14]

*Figure 6.2. Preparation of Coupling Fragments **6.7** and **6.8***



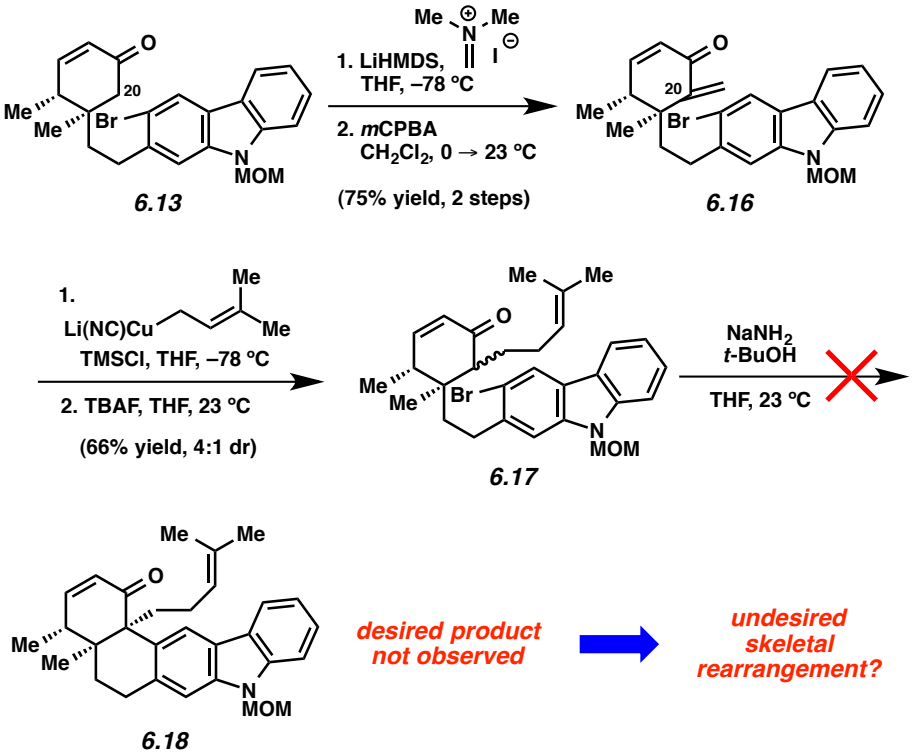

With cyclohexyl fragment **6.7** and carbazole triflate **6.8** in hand, we pursued their coupling and the ensuing carbazolyne cyclization (Scheme 6.2). Treatment of **6.7** with 9-BBN[15] led to chemoselective hydroboration of the terminal olefin. Subsequent Pd-catalyzed cross-coupling[16] with **6.8** proceeded smoothly to generate coupled product **6.12**. Addition of TBAF to the reaction mixture then delivered ketone **6.6**. The highly optimized conversion of **6.7** and **6.8** to **6.6** in one-pot[17] provides a rare example of a silyl enol ether being employed as a ketone protecting group in a complex setting.[14,18] In order to control regioselectivity of enolate formation in the forthcoming carbazolyne cyclization,[19] ketone **6.6** was oxidized to enone **6.13** using IBX and NMO.[20] To our delight, exposure of enone **6.13** to $NaNH_2$ and *t*-BuOH in THF[8c,21] facilitated the desired cyclization and afforded C20-epimeric products **6.14** and **6.15** in 44% combined yield (1 to 2.3 ratio, respectively). We hypothesize that **6.14** forms kinetically as the major product, but is prone to epimerization under the reaction conditions.[22]

*Scheme 6.2. Testing the Desired Aryne Cyclization*



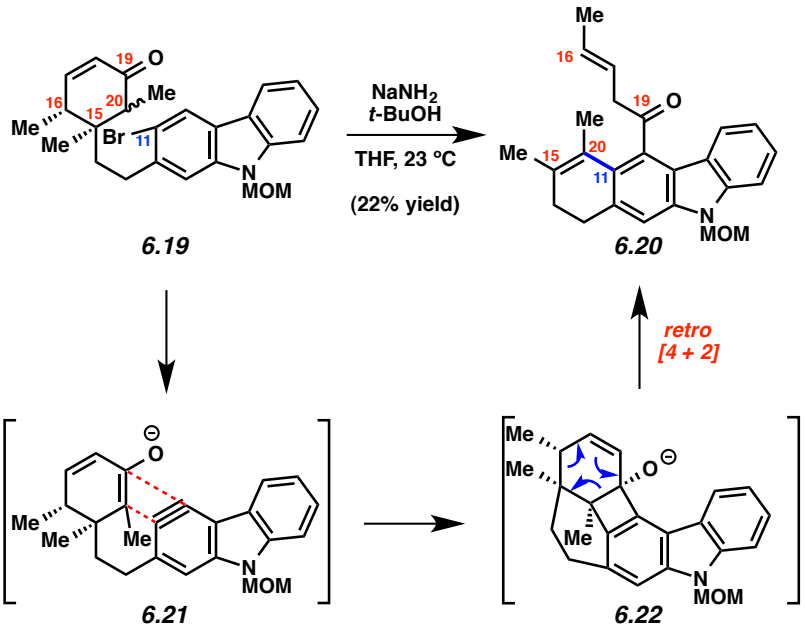

Having demonstrated the feasibility of the carbazolyne cyclization, we next prepared a C20 substituted substrate to test if the method could be used to forge the critical vicinal quaternary stereocenters (Scheme 6.3). Sequential treatment of enone **6.13** with LiHMDS and Eschenmoser's salt led to C20 alkylation.[23] Exposure of the crude adduct to *m*CPBA furnished enone **6.16**.[23] Addition of prenylcuprate[24] provided **6.17** as an inconsequential mixture of diastereomers. Unfortunately, attempts to effect the carbazolyne cyclization of substrate **6.17** were unsuccessful. Analysis of the major product suggested that a skeletal rearrangement had occurred, rather than the desired formation of **6.18**.

*Scheme 6.3. Attempted Cyclization of C20 Substituted Enone* ***6.17***




In order to identify the skeletal rearrangement product, we prepared the simpler C20 methylated substrate **6.19**, and exposed it to aryne cyclization conditions (Scheme 6.4). The major product obtained was analogous to that formed in the attempted cyclization of **6.17**. Interestingly, although the desired C11–C20 linkage was intact, a bond was unexpectedly formed between the carbazole and C19. In addition, the C15–C16 and C19–C20 linkages had been severed. 2D NMR analysis eventually revealed the rearranged structure to be compound **6.20**. We propose that the desired enolate-carbazolyne intermediate indeed undergoes cyclization, but the resulting anion cyclizes onto C19, analogous to C–C aryne insertion reactions of 1,3-dicarbonyls (see transition structure **6.21**).[10e,25] A subsequent retro Diels–Alder reaction, as shown in transition structure **6.22**, and protonation yields **6.20**.

*Scheme 6.4. Undesired Cyclization/Fragmentation of Substrate* ***6.19***

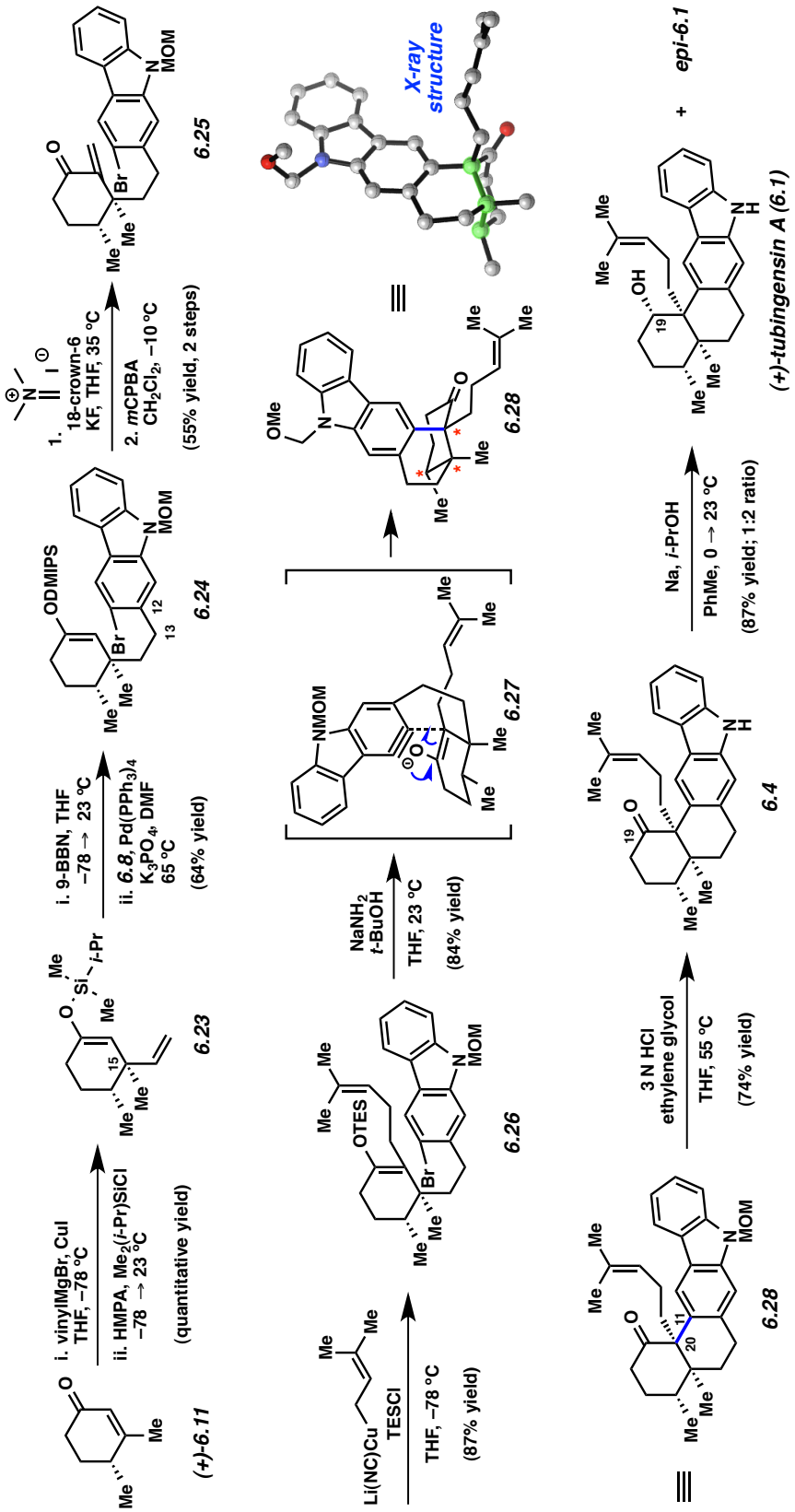



As the attempted cyclization indeed led to the desired C11–C20 bond formation, we postulated that a modified substrate might be more likely to undergo the desired transformation without rearrangement. Specifically, we envisioned that a substrate lacking the alkene in the six-membered ring could not suffer from the retro [4+2] cycloaddition, and would thus not be prone to cyclohexyl ring fragmentation.[26] Therefore, we elected to prepare enol ether **6.26** (Scheme 6.5). In contrast to enone substrates **6.13** and **6.17**, the selectivity for C20 enolate formation for the critical carbazolyne cyclization would be dictated by the controlled formation of **6.26** as a single enol ether isomer.

The design and synthesis of substrate **6.26** ultimately proved fruitful and enabled an efficient enantiospecific total synthesis of tubingensin A (**6.1**), which is summarized in Scheme 5.[27] Vinyl cuprate addition to enone **6.11**, followed by trapping with $Me_2$(*i*-Pr)SiCl (DMIPSCl), gave enol ether **6.23**. Next, a one-pot hydroboration/Suzuki coupling (analogous to that described previously) afforded the desired coupled product **6.24** in 64% yield. Using the labile

DMIPS enol ether, enone **6.25** was generated via a two-step sequence.[28] Subsequent cuprate addition and trapping with TESCl supplied aryne cyclization precursor **6.26**. Fortuitously, in the key step, aryne cyclization delivered the desired product **6.28** in 84% yield and established the vicinal quaternary centers with complete diastereoselectivity. The structure of **6.28** was verified by X-ray crystallography. Only two steps remained in order to complete the total synthesis: *N*-deprotection and ketone reduction. The removal of the MOM group of **6.28** provided ketone **6.4** smoothly. However, reduction proved more challenging. An array of reducing agents were examined, all of which gave the undesired C19 epimer as the major product.[29] The best conditions using Na/*i*-PrOH delivered a 1:2 ratio of tubingensin A (**6.1**) and its C19 epimer. It should be noted that oxidation of epi-**6.1** gives **6.4**, so the undesired epimer can be readily recycled.[30] Nonetheless, synthetic (+)-**6.1** was found to be identical to an authentic sample in all respects.

*Scheme 6.5. Completed Synthesis of Tubingesin A*



## 6.4 Conclusion

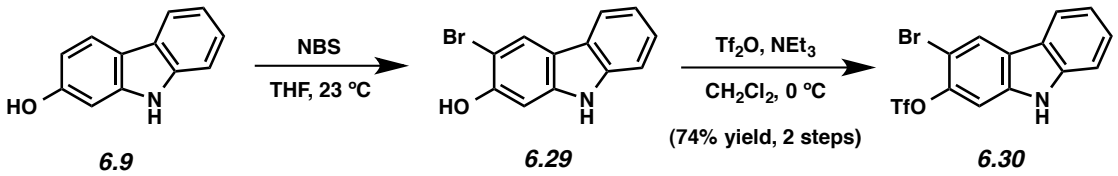
In summary, we have achieved a concise enantiospecific total synthesis of tubingensin A (**1**). Our synthesis features an aryne cyclization to efficiently introduce the vicinal quaternary stereocenters of the natural product and proceeds in only 9 steps (longest linear sequence) from known compounds. Further efforts to probe the use of arynes for the assembly of challenging molecular scaffolds are currently underway in our laboratory.

## 6.5 Experimental Section

**6.5.1 Materials and Methods**. Unless stated otherwise, reactions were conducted in flame-dried glassware under an atmosphere of nitrogen using anhydrous solvents (either freshly distilled or passed through activated alumina columns). All commercially obtained reagents were used as received unless otherwise specified. The following reagents were distilled prior to use: chlorotrimethylsilane (TMSCl, distilled over $CaH_2$), chlorotriethylsilane (TESCl, distilled over $CaH_2$), chlorodimethylisopropylsilane (DMIPSCl), hexamethylphosphoramide (HMPA, distilled over $CaH_2$ and stored over 4Å molecular sieves), trifluoromethanesulfonic anhydride ($Tf_2O$), isopropyl alcohol (*i*-PrOH, distilled over CaO after refluxing overnight). 2-Iodoxybenzoic acid (IBX) was prepared following the procedure reported by Frigerio et al.[31] Prenyl tri(*n*-butyl)stannane was prepared using prenyl bromide according to the general procedure of Keck et al. and distilled prior to use.[32] Methyl iodide (MeI) was passed over basic Brockman Grade I 58 Å activated alumina immediately prior to use. 18-Crown-6 was recrystallized from acetonitrile and stored in a glovebox. *N*,*N*-Dimethylmethyleneiminium iodide (Eschenmoser's salt) was purchased from Sigma–Aldrich and stored inside a glovebox. $Pd(PPh_3)_4$ was purchased from Strem and stored inside a glovebox at –20 °C. Karstedt's catalyst was purchased as a 2% solution

in xylene from Sigma–Aldrich and stored inside a glovebox. Reaction temperatures were controlled using an IKAmag temperature modulator, and unless stated otherwise, reactions were performed at room temperature (rt, approximately 23 °C). Thin-layer chromatography (TLC) was conducted with EMD gel 60 F254 pre-coated plates (0.25 mm) and visualized using a combination of UV, anisaldehyde, iodine, vanillin, ninhydrin, and potassium permanganate staining. SiliCycle Siliaflash P60 (particle size 0.040–0.063 mm), was used for flash column chromatography. $^{1}$H NMR and 2D-NMR spectra were recorded on Bruker spectrometers (at 300 MHz or 500 MHz) and are reported relative to deuterated solvent signals. Data for $^{1}$H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz), and integration. $^{13}$C NMR spectra were recorded on Bruker Spectrometers (at 75 or 125 MHz). Data for $^{13}$C NMR spectra are reported in terms of chemical shift, and when necessary, multiplicity, coupling constant (Hz) and carbon type. IR spectra were recorded on a Perkin-Elmer 100 spectrometer and are reported in terms of frequency of absorption ($cm^{-1}$). High resolution mass spectra were obtained from the UC Irvine Mass Spectrometry Facility and the UCLA Molecular Instrumentation Center. Melting points were determined using a DigiMelt MPA160 melting point apparatus. Images in Figure 6.1 and Scheme 6.5 were created using CYLview.[33]

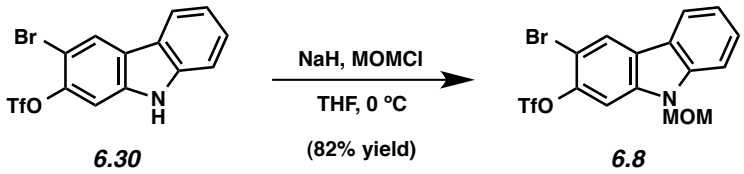
### 6.5.2 Preparative Procedures.




**Bromotriflate 6.30**. Known compound **6.29** was prepared using a modification of the procedure reported by Erra–Balsells.[12] To a mixture of 2-hydroxycarbazole (**6.9**, 3.50 g, 19.10 mmol, 1 equiv) in THF (110 mL) was added NBS (3.63 g, 20.40 mmol, 1.07 equiv) as a solution in THF (90 mL) over 13 min. After stirring for 10 min, silica gel (~30 mL) was added and the mixture was concentrated under reduced pressure. The resulting material was loaded onto a column and purified by flash chromatography (4:1:1 Benzene:$CH_2Cl_2$:$Et_2O$) to provide **6.29** as an off-white solid. Spectral data match those previously reported.[12] All material was carried on to the subsequent triflation step.

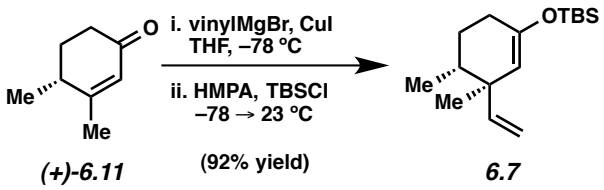
To a suspension of **6.29** in $CH_2Cl_2$ (210 mL) was added $NEt_3$ (8.0 mL, 57.56 mmol, 3 equiv) and the reaction was cooled to 0 ºC. Triflic anhydride (3.5 mL, 20.84 mmol, 1.1 equiv) was added dropwise over 3 min. The reaction was stirred for 25 min, quenched with sat. aq. $NaHCO_3$ (125 mL) and then allowed to warm to room temperature. The layers were separated and the aqueous layer was extracted with $CH_2Cl_2$ (2 x 75 mL). The combined organic layers were dried over $MgSO_4$. Evaporation under reduced pressure afforded crude product, which was further purified by flash chromatography (6:1 Hexanes:EtOAc) to provide **6.30** (5.59 g, 74% yield, 2 steps) as a white solid. Mp: 124–126 ºC; $R_f$ 0.27 (6:1 Hexanes:EtOAc); $^1$H NMR (500 MHz, $C_6D_6$): δ 7.83 (s, 1H), 7.56 (d, *J* = 7.9, 1H), 7.28 (app. t, *J* = 7.7, 1H), 7.09 (app. t, *J* = 7.6, 1H), 6.91 (dd, *J* = 8.1, 0.8, 1H), 6.89 (s, 1H), 6.26 (br s, 1H); $^{13}$C NMR (125 MHz, $C_6D_6$): δ

144.4, 140.7, 138.1, 127.3, 125.2, 124.3, 121.6, 121.1, 120.8, 119.5 (q, $J$ = 321Hz, $CF_3$), 111.0, 105.3, 105.2; IR (film): 3376, 1605, 1429, 1209, 1130 $cm^{-1}$; HRMS-ESI ($m/z$) $[M - H]^-$ calcd for $C_{13}H_6BrF_3NO_3S$, 391.9204; found, 391.9204.



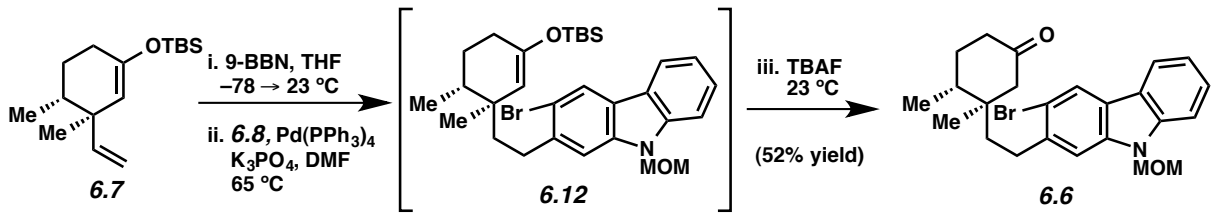
*6.30* *6.8*

***N*-MOM-Carbazole 6.8**. To a solution of carbazole **6.30** (7.11 g, 18.04 mmol, 1 equiv) in THF (100 mL) at 0 ºC was added NaH (60% dispersion in mineral oil, 941.2 mg, 23.53 mmol, 1.3 equiv) in two portions. (*Caution: The reaction is exothermic and releases hydrogen gas. Make sure that the reaction is cooled and properly ventilated to prevent pressure buildup*). After 10 min, MOMCl (1.8 mL, 23.70 mmol, 1.3 equiv) was added dropwise over 1 min. The reaction was stirred for 20 min, quenched with $H_2O$ (150 mL) and diluted with $CH_2Cl_2$ (150 mL). The layers were separated, and the aqueous layer was extracted with $CH_2Cl_2$ (2 x 100 mL). The combined organic layers were dried over $MgSO_4$. Evaporation under reduced pressure afforded the crude product, which was purified by flash chromatography (3:1 Hexanes:$Et_2O$) to provide **6.8** (6.49 g, 82% yield) as a white solid. Mp: 84–86 ºC; $R_f$ 0.37 (3:1 Hexanes:$Et_2O$); $^1H$ NMR (500 MHz, $CDCl_3$): δ 8.32 (s, 1H), 8.04 (d, $J$ = 7.8, 1H), 7.59–7.51 (m, 3H), 7.34 (ddd, $J$ = 8.0, 5.5, 2.5, 1H), 5.65 (s, 2H), 3.30 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 144.6, 141.8, 139.4, 127.7, 125.1, 124.5, 121.5, 121.3, 120.9, 118.9 (q, $J$ = 321, $CF_3$), 109.7, 106.3, 104.3, 74.5, 56.5; IR (film): 2927, 1596, 1420, 1208, 1130, 1113 $cm^{-1}$; HRMS-ESI ($m/z$) $[M + NH_4]^+$ calcd for $C_{15}H_{15}BrF_3N_2O_4S$, 454.98825; found, 454.98625.



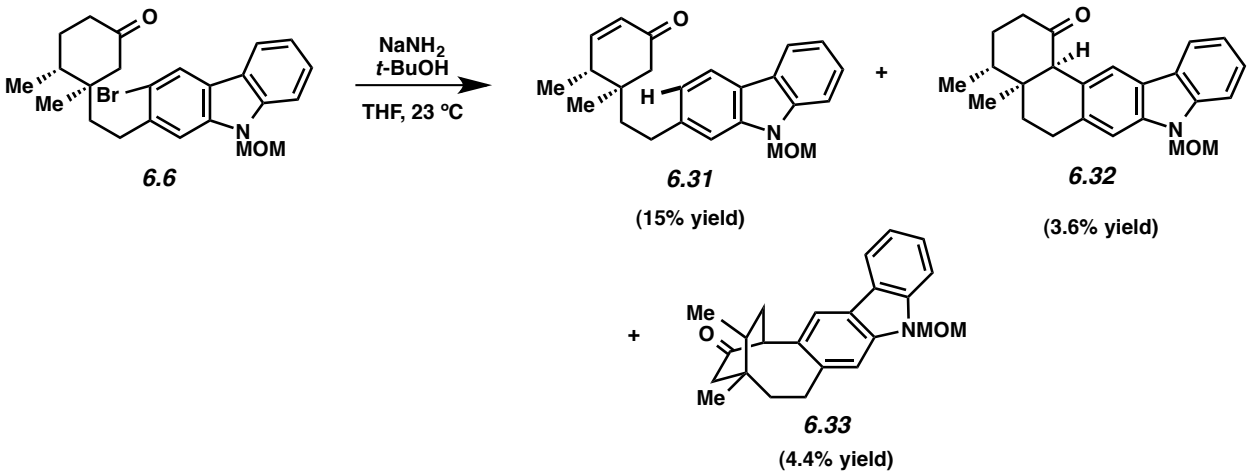

*(+)-6.11* *6.7*

**Silyl Enol Ether 6.7**. To a flask charged with CuI (1.53 g, 8.052 mmol, 2 equiv) was added THF (50 mL). The mixture was cooled to –78 ºC and vinyl magnesium bromide (1.0 M in THF, 16.1 mL, 16.10 mmol, 4 equiv) was added dropwise over 10 min. The reaction was warmed to –10 ºC for 25 min, then recooled to –78 ºC. Enone **(+)-6.11** (500 mg, 4.026 mmol, 1 equiv) was added dropwise over 10 min as a solution in THF (11 mL). HMPA (11.2 mL, 64.42 mmol, 16 equiv) and TBSCl (1.27 g, 8.46 mmol, 2.1 equiv) were then added to the reaction mixture as a solution in THF (6 mL). The reaction was warmed to room temperature and stirred overnight. The reaction was quenched with $H_2O$ (30 mL) and diluted with $Et_2O$ (30 mL). The layers were separated and the aqueous layer was filtered over celite, which was washed with $Et_2O$ (300 mL). The combined organic layers were washed with brine (30 mL) and the resulting aqueous layer was extracted with $Et_2O$ (2 x 20 mL). The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified via flash chromatography (19:1 Hexanes: $NEt_3$) to afford **6.7** (982 mg, 92% yield) as a yellow oil. $R_f$ 0.55 (Hexanes); $^1$H NMR (500 MHz, $C_6D_6$): δ 5.80 (dd, *J* = 17.4, 10.5, 1H), 5.06 (dd, *J* = 17.4, 1.6, 1H), 5.00 (dd, *J* = 10.5, 1.6, 1H), 4.77 (s, 1H), 1.92–2.09 (m, 2H), 1.35–1.51 (m, 3H), 0.99 (s, 9H), 0.97 (s, 3H), 0.82 (d, *J* = 6.5, 3H), 0.150 (s, 3H), 0.147 (s, 3H); $^{13}$C NMR (125 MHz, $C_6D_6$): δ 150.5, 149.1, 112.7, 111.7, 41.6, 36.9, 29.6, 27.3, 25.9, 21.1, 18.3, 15.6, –4.17, –4.26; IR (thin film) 2929, 2858, 1663, 1363, 1192 cm$^{-1}$. HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{16}H_{31}OSi$, 267.2144; found 267.2131. $[\alpha]_D^{23}$ –19.3º (*c* = 0.10, EtOAc).




**Ketone 6.6**. A vial charged with silyl enol ether **6.7** (50.0 mg, 0.188 mmol, 2 equiv) was cooled to –78 ºC. 9-BBN (0.5 M in THF, 0.43 mL, 0.216 mmol, 2.3 equiv) was then added dropwise. The reaction was allowed to warm to room temperature and stirred for 5 h. To a separate vial was added $Pd(PPh_3)_4$ (22.0 mg, 0.019 mmol, 0.2 equiv) in the glovebox. The vial was removed, DMF (0.38 mL) was added, and the solution was sparged with $N_2$ for 10 min. $K_3PO_4$ (29.9 mg, 0.141 mmol, 1.5 equiv) and carbazole **6.8** (41.2 mg, 0.094 mmol, 1 equiv) were then added to the DMF solution. The THF solution was then added to the DMF mixture and the reaction was heated to 65 ºC for 24 h. The reaction was cooled to room temperature and TBAF (1.0 M in THF, 0.47 mL, 0.47 mmol, 5 equiv) was added. After stirring for 20 min, the reaction was quenched with brine (5 mL) and EtOAc (5 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 5 mL). The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. The compound was purified by flash chromatography (4:1 Hexanes:EtOAc) to afford **6.6** (21.8 mg, 52% yield) as a clear oil. $R_f$ 0.39 (2:1 hexanes:EtOAc); $^1$H NMR (500 MHz, $CDCl_3$): d 8.21 (s, 1H), 7.99 (app. d, *J* = 7.6, 1H), 7.51 (d, *J* = 8.2, 1H), 7.47 (ddd, *J* = 8.3, 7.0, 1.2, 1H), 7.35 (s, 1H), 7.27 (ddd, *J* = 8.2, 7.1, 1.2, 1H), 5.65 (s, 2H), 3.29 (s, 3H), 2.87 (m, 2H), 2.53 (d, *J* = 13.2, 1H), 2.37–2.39 (m, 2H), 2.28 (d, *J* = 13.2, 1H), 1.92–2.00 (m, 2H), 1.59–1.76 (m, 3H), 1.02 (d, *J* = 7.3, 3H), 0.89 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): 212.5, 141.2, 140.2, 139.3, 126.6, 124.5, 123.7, 122.5, 120.53, 120.51, 115.4, 110.6, 109.4, 74.4, 56.3, 52.4, 42.8, 41.13, 41.09, 37.1, 31.5, 30.9, 19.1, 15.2; IR (thin film): 2957, 1708, 1602,

1451, 1241 $cm^{-1}$; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{24}H_{28}BrNO_2Na$, 464.1201; found 464.1188. $[\alpha]_D^{23}$ +12.0° (*c* = 0.10, $CHCl_3$).

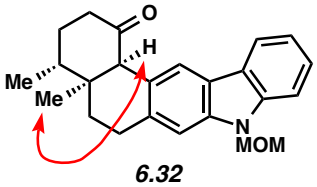



**Aryne products 6.31, 6.32, and 6.33**. To a vial inside the glovebox was added $NaNH_2$ (44.5 mg, 1.14 mmol, 10.7 equiv) and the solid was crushed into a powder. The vial was removed from the glovebox and THF (2.1 mL) was added, followed by *t*-BuOH (36.5 μL, 0.382 mmol, 3.6 equiv). The vial was placed in a heating block at 40 °C and stirred for 1 h. After cooling to room temperature under $N_2$, ketone **6.6** (47.4 mg, 0.107 mmol, 1 equiv) was added as a solution in THF (1.5 mL). The vial containing **6.6** was then washed with additional THF (600 μL) and the resulting solution was added to the reaction mixture. The resulting solution was stirred at 23 °C for 3 h, then quenched with $H_2O$ (1 mL) and diluted with EtOAc (10 mL), and sat. aq. $NH_4Cl$ (3 mL). The layers were separated, and the aqueous layer extracted with EtOAc (2 x 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to afford the crude products. The crude material was further purified by preparative thin layer chromatography (2:1 Hexanes:EtOAc) to afford compounds **6.31** (5.8 mg, 15% yield), **6.32** (1.4 mg, 3.6% yield), and **6.33** (1.7 mg, 4.4% yield) as colorless oils. **6.31**: $R_f$ 0.29 (2:1

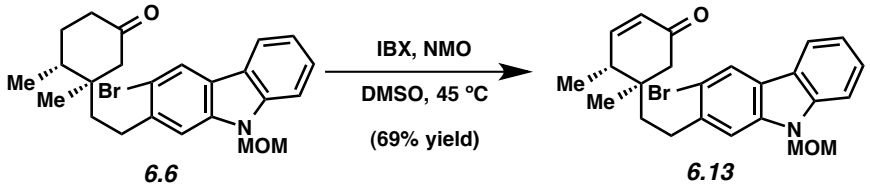
Hexanes:EtOAc); $^{1}$H NMR (500 MHz, $CDCl_3$): δ 8.04 (d, *J* = 7.8, 1H), 7.98 (d, *J* = 8.0, 1H), 7.53 (d, *J* = 8.2, 1H), 7.44 (ddd, *J* = 8.2, 7.2, 1.1, 1H), 7.32 (s, 1H), 7.28–7.24 (m, 1H), 7.09 (dd, *J* = 8.0, 1.2, 1H), 6.68 (dd, *J* = 10.1, 3.0, 1H), 6.01 (dd, *J* = 10.1, 2.4, 1H), 5.68 (s, 2H), 3.31 (s, 3H), 2.83–2.71 (m, 2H), 2.63–2.56 (m, 1H), 2.48 (d, *J* = 15.8, 1H), 2.42 (d, *J* = 15.8, 1H), 1.87–1.74 (m, 2H), 1.14 (d, *J* = 7.5, 3H), 1.01 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 200.1, 154.8, 141.1, 141.0, 140.9, 128.1, 125.8, 123.6, 121.8, 120.9, 120.5, 120.3, 120.1, 109.2, 108.9, 74.3, 56.3, 48.9, 43.5, 39.8, 39.3, 31.2, 20.2, 14.4; IR (film): 2932, 1675, 1604, 1460, 1326, 1065 $cm^{-1}$; HRMS-ESI (*m/z*) $[M + NH_4]^+$ calcd for $C_{24}H_{31}N_2O_2$, 379.23800; found, 379.23730; $[\alpha]_D^{23}$ –16.7° (*c* = 0.10, $CHCl_3$). **6.32**: $R_f$ 0.53 (2:1 Hexanes:EtOAc); $^{1}$H NMR (500 MHz, $CDCl_3$): δ 7.97 (app. d, *J* = 7.8, 1H), 7.56 (s, 1H), 7.49 (app. d, *J* = 8.0, 1H), 7.43 (ddd, *J* = 8.2, 7.1, 1.1, 1H), 7.32 (s, 1H), 7.23 (ddd, *J* = 7.9, 7.0, 0.9, 1H), 5.64 (s, 2H), 3.53 (bs, 1H), 3.31 (s, 3H), 3.15 (m, 1H), 3.00 (dd, *J* = 17.6, 4.3, 1H), 2.52 (m, 1H), 2.29 (m, 1H), 2.11 (m, 1H), 2.02 (ddd, *J* = 13.8, 5.7, 2.1, 1H), 1.74 (m, 2H), 1.53 (m, 1H), 1.00 (s, 3H), 0.96 (d, *J* = 6.4, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 214.6, 141.2, 139.9, 133.8, 126.1, 125.4, 123.4, 122.8, 120.5, 120.2, 119.3, 109.6, 109.1, 74.4, 63.0, 56.3, 39.0, 38.9, 33.7, 31.2, 30.1, 26.4, 21.1, 14.8; IR (film): 2922, 2855, 1702, 1462, 1240, 1065 $cm^{-1}$; HRMS-ESI (*m/z*) $[M + NH_4]^+$ calcd for $C_{24}H_{31}N_2O_2$, 379.23800; found, 379.23720; $[\alpha]_D^{23}$ +27.3° (*c* = 0.10, $CHCl_3$). **6.33**: $R_f$ 0.42 (2:1 Hexanes:EtOAc); $^{1}$H NMR (500 MHz, $CDCl_3$): δ 8.01 (app. d, *J* = 7.9, 1H), 7.78 (s, 1H), 7.51 (app. d, *J* = 8.5, 1H), 7.44 (ddd, *J* = 8.2, 7.2, 1.1, 1H), 7.25 (app. t, *J* = 7.1, 1H), 7.22 (s, 1H), 5.64 (d, *J* = 1.2, 2H), 3.95 (app. t, *J* = 3.1, 1H), 3.30 (s, 3H), 3.04 (ddd, *J* = 16.0, 13.3, 3.8, 1H), 2.80 (dt, *J* = 16.0, 4.0, 1H), 2.55 (d, *J* = 17.2, 1H), 2.32 (d, *J* = 17.2, 1H), 1.89 (m, 3H), 1.81 (m, 1H), 1.70 (m, 1H), 1.03 (s, 3H), 0.91 (d, *J* = 7.1, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 217.4, 141.1, 139.9, 137.7, 132.8, 126.0, 123.2, 122.6, 122.0, 120.3, 120.1, 110.8, 109.3, 74.4, 56.3, 56.0, 49.6, 48.7, 41.1, 35.2, 34.4, 32.0, 28.7,

18.4; IR (film): 2920, 2848, 1709, 1473, 1238, 1065 $cm^{-1}$; HRMS-ESI (*m/z*) $[M + NH_4]^+$ calcd for $C_{24}H_{31}N_2O_2$, 379.23800; found, 379.23724; $[\alpha]_D^{23}$ +50.0° (*c* = 0.10, $CHCl_3$).

The stereochemistry of decalin **6.32** was verified by NOESY (500MHz, $CDCl_3$), as the following correlation was observed:



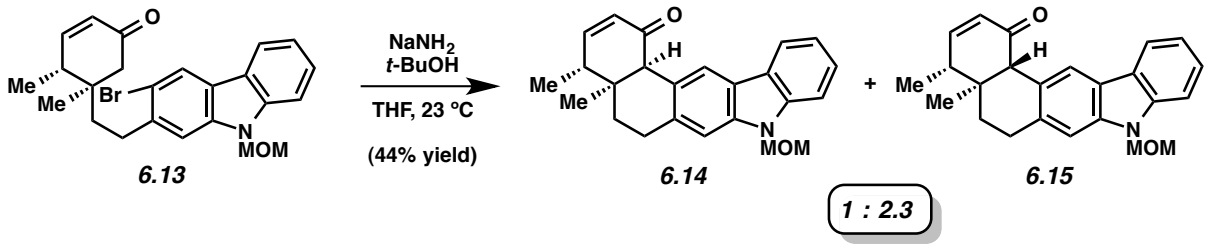

***6.32***




***6.6*** ***6.13***

**Enone 6.13**. *Note: The reaction shown here was found to give variable yields when carried out on larger scale*. Two separate vials were each charged with IBX[31] (372.2 mg, 1.33 mmol, 2.5 equiv), *N*-methylmorpholine-*N*-oxide (160.9 mg, 1.37 mmol, 2.6 equiv) and DMSO (1.8 mL). The vials were capped and heated to 45 °C. After stirring for 15 min, during which time the IBX mixture became homogenous. The IBX solutions were transferred to two vials each of which had been charged with ketone **6.6** (234.2 mg, 0.529 mmol, 1 equiv). The vials were heated to 45 °C for 19 h. The reactions were cooled to room temperature and quenched with a 1:1 mixture of sat. aq. $NaHCO_3$:sat. aq. $Na_2S_2O_3$ (1.5 mL each), combined, and further diluted with EtOAc (40 mL), and $H_2O$ (13 mL). The layers were separated and the aq. layer was extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over $MgSO_4$. Evaporation under reduced pressure afforded the crude product which was purified by flash chromatography (2:1 Hexanes:EtOAc) to

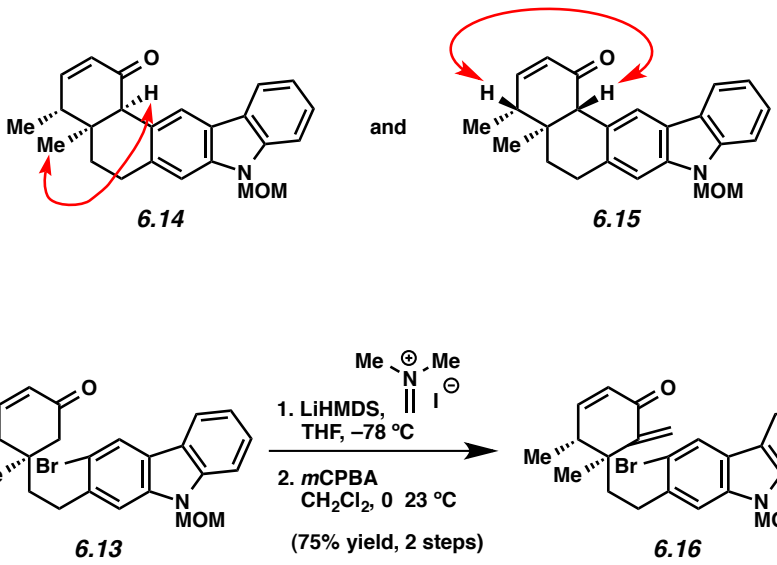
give **6.13** as a white, amorphous solid (321.8 mg, 69% yield). $R_f$ 0.32 (2:1 Hexanes:EtOAc); $^1$H NMR (500 MHz, $CDCl_3$): δ 8.21 (s, 1H), 7.99 (ddd, *J* = 7.8, 1.2, 0.8, 1H), 7.52 (app. dt, *J* = 8.2, 0.9, 1H), 7.47, (ddd, *J* = 8.2, 7.0, 1.2, 1H), 7.36 (s, 1H), 7.27 (ddd, *J* = 7.9, 6.9, 1.0, 1H), 6.70 (dd, *J* = 10.1, 3.0, 1H), 6.02, (dd, *J* = 10.1, 2.5, 1H), 5.65 (s, 2H), 3.29 (s, 3H), 2.93–2.81 (m, 2H), 2.63 (app. ddt, *J* = 14.8, 7.4, 2.8, 1H), 2.53 (d, *J* = 15.8, 1H), 2.46 (*J* = 15.8, 1H), 1.82–1.69 (m, 2H), 1.16 (d, *J* = 7.4, 3H), 1.03 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): (23 of 24 C) δ 200.2, 154.8, 141.2, 140.2, 139.0, 128.1, 126.6, 124.5, 123.7, 122.5, 120.5, 115.4, 110.6, 109.4, 74.3, 56.3, 49.0, 41.8, 39.9, 39.1, 32.0, 20.1, 14.5; IR (film): 2956, 1673, 1453, 1241, 1110 $cm^{-1}$; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{24}H_{26}BrNO_2Na$, 462.1045; found, 462.1045. $[\alpha]_D^{23}$ –6.8° (*c* = 1.0, $CHCl_3$).




**Cyclized products 6.14 and 6.15**. To a vial inside the glovebox was added $NaNH_2$ (40.9 mg, 1.05 mmol, 10.3 equiv) and the solid was crushed into a powder. The vial was removed from the glovebox and THF (1.6 mL) added, followed by *t*-BuOH (35 μL, 0.366 mmol, 3.6 equiv). The vial was placed in a heating block at 40 ºC and stirred for 1 h. After cooling to room temperature under $N_2$, enone **6.13** (44.8 mg, 0.105 mmol, 1 equiv) was added as a solution in THF (1.2 mL). The vial containing **6.13** was then washed with additional THF (400 μL) and the resulting solution was added to the reaction mixture. The resulting solution was stirred at 23 ºC for 3 h, then quenched with $H_2O$ (2 mL) and diluted with EtOAc (10 mL), and sat. aq. $NH_4Cl$ (1 mL).

The layers were separated, and the aqueous layer extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to afford the crude products. The crude material was further purified by preparative thin layer chromatography (3:2 Hexanes:EtOAc) to afford compounds **6.14** and **6.15** (16.1 mg, 44% yield) as an inseparable mixture of diastereomers (1 : 2.3 ratio of **6.14** : **6.15**). These compounds were characterized as a mixture. $R_f$ 0.51 (3:2 Hexanes:EtOAc); **6.15(major)**: $^1$H NMR (500 MHz, $CDCl_3$): δ 8.33 (s, 1H), 8.07 (d, *J* = 7.8, 1H), 7.48 (d, *J* = 8.2, 1H), 7.44–7.40 (m, 1H), 7.27 (s, 1H), 7.25–7.21 (m, 1H), 6.52 (dd, *J* = 10.1, 1.9, 1H), 6.17 (dd, *J* = 10.0, 3.2, 1H), 5.64 (s, 2H), 4.00 (s, 1H), 3.29 (s, 3H), 3.23–3.05 (m, 1H), 2.95 (ddd, *J* = 17.1, 5.2, 2.0, 1H), 2.75–2.64 (m, 1H), 2.09–2.02 (m, 1H), 1.78 (td, *J* = 13.0, 5.3, 1H), 1.17 (d, *J* = 7.5, 3H), 0.86 (s, 3H); **6.14(minor)**: $^1$H NMR (500 MHz, $CDCl_3$): δ 8.00 (d, *J* = 7.7, 1H), 7.72 (s, 1H), 7.47 (d, *J* = 8.0, 1H), 7.44–7.40 (m, 1H), 7.30 (s, 1H), 7.25–7.21 (m, 1H), 6.49 (dd, *J* = 10.1, 2.3, 1H), 6.06 (dd, *J* = 10.0, 2.9, 1H), 5.62 (s, 2H), 3.49 (s, 1H), 3.30 (s, 3H), 3.23–3.05 (m, 2H), 2.75–2.64 (m, 1H), 2.09–2.02 (m, 1H), 1.69–1.62 (m, 1H), 1.13 (d, *J* = 7.5, 3H), 1.08 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 200.9, 199.6, 154.3, 150.6, 141.20, 141.15, 140.0, 139.7, 134.8, 133.8, 130.0, 127.3, 125.9, 125.7, 124.0, 123.6, 123.3, 123.2, 122.7, 122.5, 122.2, 120.61, 120.58, 120.1, 120.0, 119.7, 109.4, 109.0, 108.9, 108.7, 74.32, 74.26, 59.2, 56.7, 56.3, 56.2, 44.6, 41.8, 39.4, 34.4, 33.4, 32.8, 26.92, 26.87, 21.8, 14.0, 13.8, 12.5; IR (film): 2966, 2930, 1685, 1671, 1473, 1460, 1330, 1239, 1062 $cm^{-1}$; HRMS-ESI (*m/z*) $[M - H]^-$ calcd for $C_{24}H_{24}NO_2$, 358.18125; found, 358.18067.

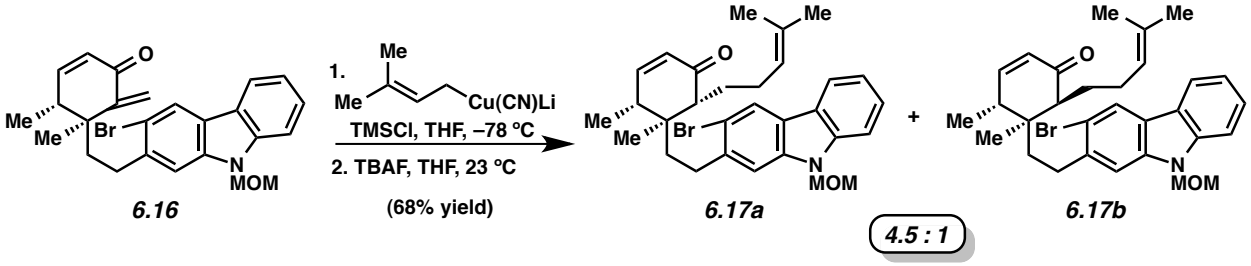
The relative stereochemistry of **6.14** and **6.15** was verified by NOESY (500MHz, $CDCl_3$), as the following correlations were observed:




**Dienone 6.16**. To a solution of enone **6.13** (245.9 mg, 0.558 mmol, 1 equiv) in THF (1.9 mL) at –78 °C was added LiHMDS (148.3 mg, 0.886 mmol, 1.6 equiv) as a solution in THF (1.5 mL). After 10 min, the enolate mixture was warmed to room temperature over 10 min. In a separate flask, Eschenmoser's salt (207.1 mg, 1.12 mmol, 2 equiv) was suspended in THF (1.5 mL) and cooled to –78 °C. The solution containing the enolate of **6.13** was added dropwise to the Eschenmoser's salt suspension over 3 min. The reaction was warmed to room temperature and stirred for 2.5 h. The reaction was quenched with brine (4 mL) and diluted with $H_2O$ (15 mL) and EtOAc (40 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 x 30 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to afford the crude adduct, which was used in the subsequent step without further purification.

The crude adduct was dissolved in $CH_2Cl_2$ (2.8 mL) and cooled to 0 °C. *m*-CPBA (68%, 280.6 mg, 1.11 mmol, 2 equiv) was added and the reaction was stirred for 3 min before warming to room temperature. After an additional 15 min, the reaction was diluted with EtOAc (40 mL) and sat. aq. $NaHCO_3$ (20 mL). The layers were separated, and the aqueous layer was extracted

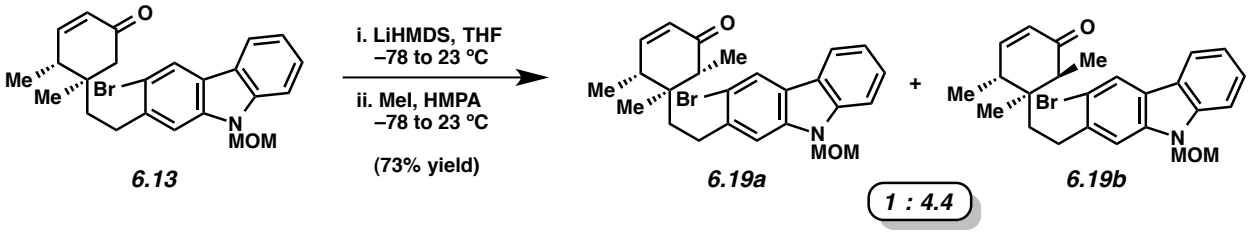
with EtOAc (2 x 25 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to afford the crude product. This compound was further purified by flash chromatography (2.5:1 Hexanes:EtOAc) to provide **6.16** (190.1 mg, 75% yield, 2 steps) as a white solid. Mp: 143–144 ºC; $R_f$ 0.37 (2.5:1 Hexanes:EtOAc); $^1$H NMR (500 MHz, $CDCl_3$): δ 8.17 (s, 1H), 7.97 (app. dt, *J* = 7.7, 0.8, 1H), 7.50 (app. dt, *J* = 8.2, 0.8, 1H), 7.45 (ddd, *J* = 8.2, 7.1, 1.1, 1H), 7.27 (s, 1H), 7.25 (ddd, *J* = 7.9, 7.1, 0.9, 1H) 6.96 (dd, *J* = 10.0, 5.8, 1H), 6.28 (d, *J* = 0.9, 1H), 6.11 (d, *J* = 10.0, 1H), 5.62 (s, 2H), 5.42 (app. t, *J* = 1.0, 1H), 3.27 (s, 3H), 2.83, (app. td, *J* = 13.0, 4.8, 1H), 2.64 (app. td, *J* = 12.9, 4.7, 1H), 2.43 (app. p, *J* = 6.7, 1H), 2.02 (app. td, *J* = 13.2, 4.7, 1H), 1.78 (app. td, *J* = 13.2, 4.8, 1H), 1.35 (s, 3H), 1.07 (d, *J* = 7.1, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): (24 of 25 C) δ 189.2, 155.2, 148.9, 141.1, 140.2, 139.0, 127.9, 126.5, 124.4, 123.6, 122.4, 121.8, 120.4, 115.3, 110.6, 109.4, 74.3, 56.3, 44.4, 41.7, 40.8, 32.9, 21.3, 15.9; IR (film): 2934, 1668, 1603, 1470, 1452, 1242 $cm^{-1}$; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{25}H_{26}BrNO_2Na$, 474.1045; found, 474.1042. $[\alpha]_D^{23}$ +24.9º (*c* = 1.0, $CHCl_3$).




**Enones 6.17a and 6.17b.** Compounds **6.17a** and **6.17b** were prepared following the general procedure of Lipshutz.[24] A vial charged with CuCN (35.1 mg, 0.392 mmol, 3.6 equiv) was evacuated, backfilled with $N_2$ a total of three times, and then taken into the glovebox. Lithium chloride (18.4 mg, 0.434 mmol, 3.9 equiv) was added and the vial was removed from the

glovebox. To a separate vial was added prenyl tri(*n*-butyl)stannane (prepared following the procedure of Keck et al,[32] 130 μL, 0.364 mmol, 3.3 equiv). To each vial was added THF (450 μL) and both were cooled to –78 ºC. Once at –78 ºC, *n*-butyllithium (2.20 M in hexanes, 150 μL, 0.330 mmol, 3 equiv) was added to the vial containing stannane, causing the solution to turn bright yellow. After 10 min, the yellow lithiate solution was transferred to the vial containing CuCN and the resulting brown mixture was stirred for 10 min. TMSCl (55 μL, 0.433 mmol, 3.9 equiv) was then added to the brown cuprate solution, followed by enone **6.16** (49.7 mg, 0.110 mmol, 1 equiv) as a solution in THF (600 μL) over 2 min. The vial from which the enone solution was taken was then washed with additional THF (300 μL) and the resulting solution was added to the reaction mixture. After stirring for 1 h, the reaction was quenched with sat. aq. $NH_4Cl$ (700 μL) and the reaction was warmed to room temperature. The mixture was diluted with $H_2O$ (4 mL) and EtOAc (15 mL). The layers were separated and the aqueous layer extracted with EtOAc (2 x 15 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was redissolved in THF (700 μL) and TBAF (1.0 M in THF, 550 μL, 0.550 mmol, 5 equiv) was added. After stirring for 5 min, the reaction was diluted with $H_2O$ (8 mL) and EtOAc (15 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to afford a crude mixture of diastereomeric products. These compounds were purified by flash chromatography (4:1 Hexanes:EtOAc) to give a 4.5:1 mixture of homoprenylated diastereomers **6.17a** and **6.17b** (39.2 mg, 68% yield) as a colorless oil. Analytical samples of **6.17a** and **6.17b** were obtained by preparative thin layer chromatography (3:1 Hexanes:EtOAc). **6.17a(major diastereomer)**: $R_f$ 0.37 (4:1 Hexanes:EtOAc); $^1$H NMR (500 MHz, $CDCl_3$): δ 8.22 (s, 1H), 8.00 (app. d, $J$ = 8.0, 1H), 7.53

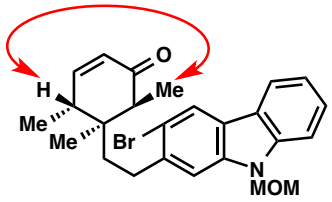
(app. d, *J* = 8.1, 1H), 7.48 (ddd, *J* = 8.2, 7.0, 1.2, 1H), 7.35 (s, 1H), 7.28 (app. t, *J* = 7.6, 1H), 6.55 (dd, *J* = 10.1, 2.1, 1H), 6.00 (dd, *J* = 10.1, 3.0, 1H), 5.65 (s, 2H), 5.31 (app. t, *J* = 7.4, 1H), 3.10 (s, 3H), 2.99 (m, 2H), 2.79 (td, *J* = 13.1, 4.6, 1H), 2.48 (d, *J* = 9.7, 1H), 2.39 (m, 1H), 2.10 (m, 1H), 1.84 (m, 2H), 1.75 (m, 1H), 1.74 (s, 3H), 1.69 (s, 3H), 1.53 (m, 1H), 1.19 (d, *J* = 7.5, 3H), 0.74 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 202.6, 152.5, 141.2, 140.3, 139.2, 132.4, 128.4, 126.6, 124.9, 124.4, 123.7, 122.4, 120.53, 120.51, 115.3, 110.4, 109.4, 74.3, 56.3, 53.9, 44.6, 38.2, 37.9, 31.6, 28.3, 25.9, 23.8, 18.0, 16.3, 15.0; IR (film): 2966, 2929, 1675, 1451, 1241, 1111, 1060 cm$^{-1}$; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{30}H_{36}BrNO_2Na$, 544.1827; found, 544.1829. $[\alpha]_D^{23}$ –106.5° (*c* = 0.2, $CHCl_3$). **6.17b(minor diastereomer)**: $R_f$ 0.30 (4:1 Hexanes:EtOAc); $^1$H NMR (500 MHz, $CDCl_3$): δ 8.22 (s, 1H), 8.00 (app. d, *J* = 7.51, 1H), 7.52 (app. d, *J* = 8.2, 1H), 7.47 (ddd, *J* = 8.1, 7.1, 1.0, 1H), 7.34 (s, 1H), 7.27 (app. t, *J* = 7.5, 1H), 6.49 (app. d, *J* = 9.7, 1H), 5.90 (dd, *J* = 10.1, 2.5, 1H), 5.66 (s, 2H), 5.18 (app. t, *J* = 7.2, 1H), 3.30 (s, 3H), 2.81 (dd, *J* = 9.6, 8.0, 2H), 2.55 (m, 1H), 2.31 (app. d, *J* = 9.9, 1H), 2.03 (m, 2H), 1.85 (m, 2H), 1.76 (m, 1H), 1.71 (s, 3H), 1.65 (s, 3H), 1.53 (m, 1H), 1.08 (d, *J* = 7.3, 3H), 1.07 (s, 3H); $^{13}$C NMR (125 MHz, $CD_3CN$): δ 203.6, 153.6, 142.0, 141.2, 140.3, 132.9, 127.4, 126.6, 125.02, 124.96, 124.2, 123.0, 121.3, 121.2, 115.5, 112.0, 110.7, 74.8, 56.4, 55.8, 42.2, 38.8 (2 carbons by HSQC), 31.4, 26.8, 26.6, 25.8, 19.8, 17.9, 14.0; IR (film): 2963, 2930, 1676, 1451, 1242, 1111 cm$^{-1}$; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{30}H_{36}BrNO_2Na$, 544.1827; found, 544.1817. $[\alpha]_D^{23}$ +16.0° (*c* = 0.1, $CHCl_3$).



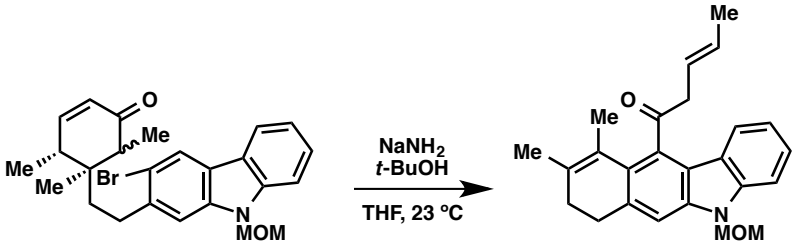

**Methylated compounds 6.19a and 6.19b**. To a solution of LiHMDS (40.3 mg, 0.241 mmol, 1.7 equiv) in THF (500 μL) at –78 ºC was added enone **6.13** (62.7 mg, 0.142 mmol, 1 equiv) as a solution in THF (200 μL). The vial containing the enone solution was then washed with additional THF (200 μL) and the resulting solution was added to the reaction mixture. The reaction was warmed to room temperature and stirred for 1 h. After recooling to –78 ºC, MeI (27 μL, 0.434 mmol, 3.1 equiv) was added, followed by HMPA (100 μL, 0.575 mmol, 4 equiv). The reaction was immediately allowed to warm to room temperature over 1 h. After 89 h, the reaction was quenched with sat. aq. $NH_4Cl$ (1 mL) and diluted with $H_2O$ (2 mL) and EtOAc (5 mL). The layers were separated, and the aqueous layer extracted with EtOAc (3 x 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to afford the crude products, which were purified by flash chromatography (3:1 Hexanes:EtOAc), to give **6.19a** and **6.19b** (47.4 mg, 73% yield) as a 1 : 4.4 mixture of diastereomers. An analytical sample of the major diastereomer was obtained by preparative thin layer chromatography (3:1 Hexanes:EtOAc). **6.19b**: $R_f$ 0.21 (3:1 Hexanes:EtOAc); $^1$H NMR (500 MHz, $CDCl_3$): δ 8.21 (s, 1H), 7.99 (d, *J* = 7.8, 1H), 7.52 (d, *J* = 8.2, 1H), 7.47 (ddd, *J* = 8.2, 7.1, 1.2, 1H), 7.34 (s, 1H), 7.27 (ddd, *J* = 7.9, 7.1, 1.1, 1H), 6.61 (dd, *J* = 10.1, 2.4, 1H), 5.93 (dd, *J* = 10.1, 2.3, 1H), 5.66 (s, 2H), 3.29 (s, 3H), 2.87–2.77 (m, 2H), 2.63–2.56 (m, 1H), 2.52 (q, *J* = 7.2, 1H), 1.82–1.69 (m, 2H), 1.20 (d, *J* = 7.1, 3H), 1.12 (d, *J* = 7.4, 3H), 1.10 (s, 3H); $^{13}$C NMR (125 MHz, $CD_3CN$): δ 203.6, 154.1, 142.0, 141.3, 140.4, 127.4, 126.9, 125.0, 124.2, 123.0, 121.3, 121.2, 115.5, 112.1,

110.7, 74.8, 56.4, 49.9, 41.6, 38.0, 37.8, 31.7, 20.5, 13.9, 11.0; IR (film): 2965, 2937, 1676, 1470, 1451, 1242, 1111, 1061 $cm^{-1}$; HRMS-ESI (*m/z*) $[M + NH_4]^+$ calcd for $C_{25}H_{32}BrN_2O_2$, 471.16417; found, 471.16228; $[\alpha]_D^{23}$ –12.7° (*c* = 0.10, $CHCl_3$).

The stereochemistry of the major diastereomer was confirmed by NOESY (500MHz, $CDCl_3$), as the following interaction was observed:



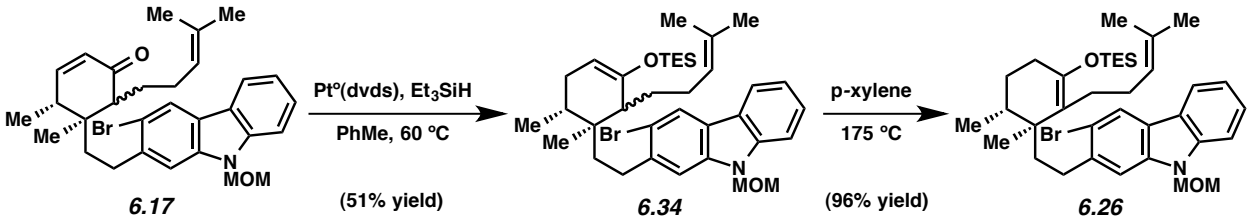

***6.19b***




***6.19*** ***6.20***

**Rearranged product 6.20**. Inside the glovebox, a vial was charged with $NaNH_2$ (37.9 mg, 0.972 mmol, 11 equiv) and the solid was crushed into a powder. The vial was removed from the glovebox and THF (1.75 mL) was added, followed by *t*-BuOH (31 μL, 0.324 mmol, 3.7 equiv). The vial was placed in a heating block at 40 °C and stirred for 1 h. After cooling to room temperature under $N_2$, enone **6.19** (40.1 mg, 0.088 mmol, 1 equiv) was added as a solution in THF (1.5 mL). The vial containing **6.19** was then washed with additional THF (500 μL) and the resulting solution was added to the reaction mixture. The reaction was stirred at room temperature for 3.5 h, then quenched with $H_2O$ (5 mL) and diluted with EtOAc (10 mL). The

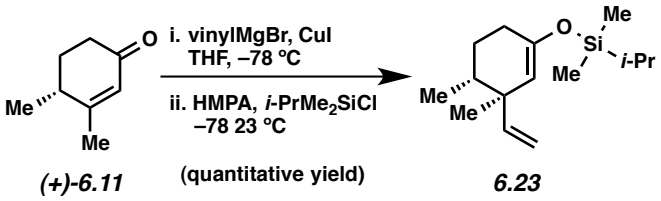
layers were separated, and the aqueous layer extracted with EtOAc (2 x 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to afford the crude products. The crude material was further purified by preparative thin layer chromatography (2:1 Hexanes:EtOAc) to afford **6.20** (7.3 mg, 22% yield) as a light yellow oil. $R_f$ 0.49 (2:1 Hexanes:EtOAc); $^1$H NMR (500 MHz, $CD_2Cl_2$): δ 7.76 (d, *J* = 7.6, 1H), 7.52 (d, *J* = 8.0, 1H), 7.42 (app. t, *J* = 7.7, 1H), 7.37 (s, 1H), 7.16 (app. t, *J* = 7.6, 1H), 5.82–5.73 (m, 1H), 5.66 (s, 2H), 5.62–5.53 (m, 1H), 3.56 (br s, 2H), 3.29 (s, 3H), 2.84 (t, *J* = 7.2, 2H), 2.22 (br s, 2H), 2.01 (s, 3H), 1.97 (s, 3H), 1.71 (dd, *J* = 6.3, 1.2, 3H); $^{13}$C NMR (125 MHz, $CD_2Cl_2$): δ 209.4, 141.3, 139.1, 137.8, 135.4, 131.7, 130.0, 128.3, 126.0, 125.2, 123.4, 122.4, 121.8, 120.4, 117.3, 109.5, 108.8, 74.4, 56.4, 49.1, 31.4, 31.0, 20.8, 18.5, 18.2; IR (film): 2931, 2889, 1699, 1595, 1474, 1332, 1065 cm$^{-1}$; HRMS-ESI (*m/z*) [M + $NH_4$]$^+$ calcd for $C_{25}H_{31}N_2O_2$, 391.23800; found, 391.23684.




**Silyl Enol Ether 6.26**. To a solution of Karstedt's catalyst (~2 wt. % in xylene, 30 μL, 2.6 μmol, 0.1 equiv) at room temperature, was added $Et_3SiH$ (440 μL, 2.75 mmol, 35 equiv) and the mixture was stirred for 10 min. To this mixture was added enone **6.17** (41.2 mg, 0.079 mmol, 1 equiv) as a solution in toluene (1 mL). The vial from which the enone was taken was washed with additional toluene (600 μL) and the resulting solution was added to the reaction mixture. The reaction was heated to 60 °C for 2.5 h, then cooled to room temperature and filtered by

passage through a pad of celite (95:5 $Et_2O$:$NEt_3$ eluent). Concentration under reduced pressure afforded the crude silyl enol ether product, which was further purified by flash chromatography (10:1 Hexanes:EtOAc w/ 2% $NEt_3$) to give the less-substituted silyl enol ether **6.34** (25.5 mg, 51% yield), which was used for the subsequent isomerization.

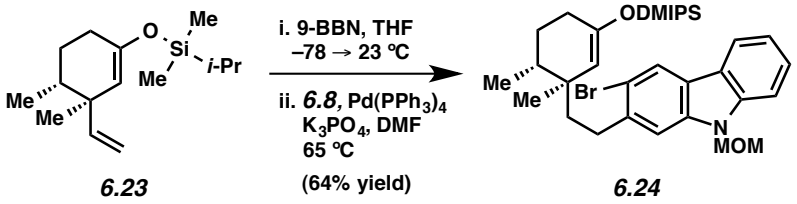
Silyl enol ether **6.34** (11.5 mg, 0.018 mmol) was transferred to a flame-dried Schlenk vessel using 3 portions of anhydrous *p*-xylene (1.8 mL total, *p*-xylene was sparged with $N_2$ for ~15 min before use). The Schlenk vessel was sealed under $N_2$ and placed in an oil bath maintained at 175 ºC. After 23 h, the reaction was cooled to room temperature and concentrated under reduced pressure to afford the crude product, which was further purified by flash chromatography (10:1 Hexanes:EtOAc w/ 2% $NEt_3$) to give **6.26** (11.0 mg, 96% yield) as a colorless oil. Spectral data matches that reported on page 686 of this dissertation.



*(+)-6.11* *6.23*

**Silyl Enol Ether 6.23**. To a flask charged with CuI (1.53 g, 8.052 mmol, 2 equiv) was added THF (50 mL). The mixture was cooled to –78 ºC and vinyl magnesium bromide (1.0 M, 16.1 mL, 16.10 mmol, 4 equiv) was added dropwise over ten min. The reaction was warmed to –10 ºC for 25 min, then recooled to –78 ºC. Enone **(+)-6.11** (500 mg, 4.03 mmol, 1 equiv) was then added dropwise as a solution in THF (11 mL) over 15 min. HMPA (11.2 mL, 64.42 mmol, 16 equiv) and DMIPSCl (1.33 mL, 8.46 mmol, 2.1 equiv) were then added to the reaction mixture as a solution in THF (6 mL). The reaction was then allowed to warm to room temperature and was stirred for 12 h. The reaction was recooled to 0 ºC and quenched with $NEt_3$ (10 mL). The

mixture was allowed to stir for 1 h and then diluted with $H_2O$ (30 mL) and $Et_2O$ (30 mL). The layers were separated and the aqueous layer was filtered over celite, which was washed with $Et_2O$ (300 mL). The organic layer was washed with brine (30 mL) and the aqueous layer was back-extracted with $Et_2O$ (2 x 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified via flash chromatography (19:1 Hexanes: $NEt_3$) to afford **6.23** (1.01 g, quantitative yield) as a yellow oil. $R_f$ 0.30 (Hexanes); $^1$H NMR (300 MHz, $C_6D_6$): δ 5.80 (dd, *J* = 17.4, 10.5, 1H), 5.05 (dd, *J* = 17.4, 1.5, 1H), 5.00 (dd, *J* = 10.5, 1.5, 1H), 4.75 (s, 1H), 1.92–2.14 (m, 2H), 1.31–1.56 (m, 4H), 1.01 (d, *J* = 6.5, 6H), 0.97 (s, 3H), 0.81 (d, *J* = 6.4, 3H), 0.14 (s, 6H); $^{13}$C NMR (125 MHz, $C_6D_6$): δ 151.0, 149.7, 112.9, 112.3, 42.2, 37.4, 30.2, 27.8, 21.7, 17.5, 16.1, 15.8, –2.79, –2.82; IR (film): 2958, 2927, 2866, 1663, 1463, 1370, 1189 cm$^{-1}$; HRMS-ESI (*m/z*) [M + H]$^+$ calcd for $C_{15}H_{29}OSi$, 253.1988; found, 253.1987. $[\alpha]_D^{23}$ –8.0° (*c* = 0.1, EtOAc).

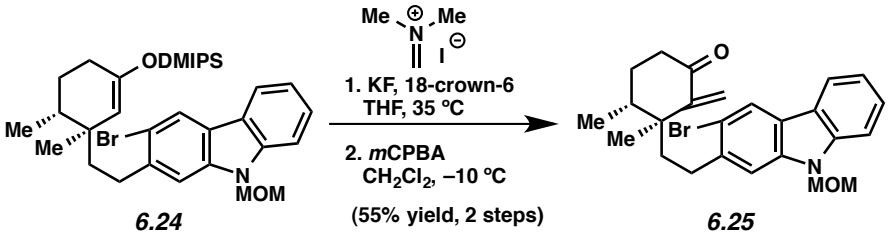


*6.23* *6.24*

**Coupled Silyl Enol Ether 6.24**. A vial charged with silyl enol ether **6.23** (552.2 mg, 2.19 mmol, 2 equiv) was cooled to –78 °C. 9-BBN (0.5 M in THF, 5.3 mL, 2.65 mmol, 2.4 equiv) was then added dropwise over 5 min. The reaction was allowed to warm to room temperature and stirred for 5 h. To a separate vial was added $Pd(PPh_3)_4$ (252.8 mg, 0.219 mmol, 0.2 equiv) in the glovebox. The vial was removed, DMF (4.5 mL) was added, and the solution was sparged with $N_2$ for 10 min. $K_3PO_4$ (349.3 mg, 1.65 mmol, 1.5) and carbazole **6.8** (480.6 mg, 1.10 mmol, 1 equiv) were added to the DMF solution. The THF solution was then added to the DMF mixture

and the reaction was heated to 65 ºC for 24 h. The reaction was then allowed to cool to room temperature, quenched with $NEt_3$ (2.5 mL), and diluted with $H_2O$ (20 mL) and EtOAc (30 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 x 30 mL). The combined organic layers were washed with brine (25 mL), dried over $Na_2SO_4$, and concentrated under reduced pressure. The compound was purified by flash chromatography (20:2:1 Hexanes:Acetone:$NEt_3$) to afford **6.24** (379.6 mg, 64% yield) as a yellow oil. $R_f$ 0.45 (20:2:1 Hexanes:Acetone:$NEt_3$); $^1$H NMR (300 MHz, $CD_3CN$): δ 8.26 (s, 1H), 8.03 (d, J = 7.7, 1H), 7.58 (d, J = 8.6, 1H), 7.50 (s, 1H), 7.46 (ddd, *J* = 8.4, 7.2, 1.2, 1H), 7.24 (ddd, *J* = 8.0, 7.2, 1.0, 1H), 5.64 (s, 2H), 4.81 (d, *J* = 1.7, 1H), 3.23 (s, 3H), 2.80 (m, 2H), 2.04–2.08 (m, 1H), 1.68–1.80 (m, 3H), 1.45–1.60 (m, 4H), 0.99 (m, 6H), 0.92 (d, *J* = 6.9, 3H), 0.88 (s, 3H), 0.17 (s, 6H); $^{13}$C NMR (125 MHz, $C_6D_6$): δ 150.7, 141.5, 140.7, 140.6, 126.5, 124.8, 123.9, 122.9, 120.8, 120.6, 115.9, 114.1, 111.0, 109.6, 74.0, 55.5, 43.0, 38.2, 34.0, 33.2, 30.4, 28.0, 23.6, 17.14, 17.13, 15.7, 15.4, –3.11, –3.14; IR (film): 2925, 2864, 1665, 1450, 1241, 1111, 1067 cm$^{-1}$; HRMS-ESI (*m/z*) [M + $NH_4$]$^+$ calcd for $C_{29}H_{44}BrN_2O_2Si$, 559.23224; found, 559.23499. $[\alpha]_D^{23}$ –12.0º (*c* = 0.1, EtOAc).

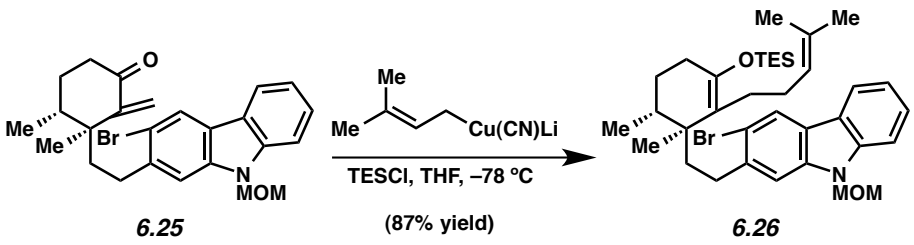
*NOTE: The purification reported above typically gave compound* **6.24** *with a purity of ~70–75% according to $^1$H-NMR analysis with an external standard, despite $^1$H-NMR not showing impurities. Nonetheless, this material was used in the subsequent step without further purification.*




**Enone 6.25**. To a vial inside the glovebox containing silyl enol ether **6.24** (63.7 mg, 0.117 mmol, 1 equiv) were added 18-crown-6 (123.4 mg, 0.467 mmol, 4 equiv), Eschenmoser's salt (215.4 mg, 1.16 mmol, 10 equiv), and KF (27.2 mg, 0.468 mmol, 4 equiv). The vial was removed from the glovebox, THF (1.3 mL) was added, and the mixture was warmed to 35 ºC for 14 h. The reaction was then cooled to room temperature and diluted with EtOAc (10 mL), brine (5 mL), and $H_2O$ (5 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over $Na_2SO_4$ and concentrated under reduced pressure to afford the crude adduct, which was used without further purification.

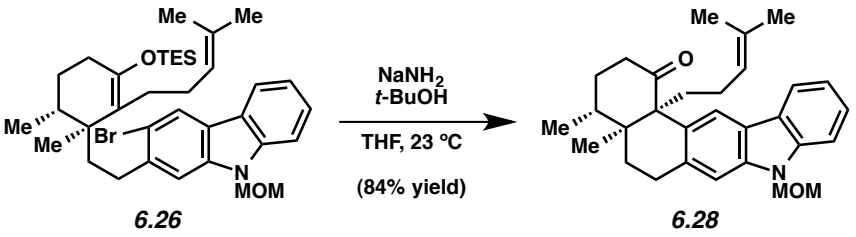
The crude adduct was dissolved in $CH_2Cl_2$ (2.0 mL) and cooled to –10 ºC. *m*-CPBA (75%, 52.2 mg, 0.233 mmol, 2 equiv) was added and the reaction was stirred for 30 min at –10 ºC. The reaction was diluted with sat. aq. $NaHCO_3$ (5 mL) and EtOAc (10 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 x 15 mL). The combined organic layers were dried over $Na_2SO_4$ and concentrated under reduced pressure to afford the crude product. Purification by flash chromatography (5:1 Hexanes:EtOAc) provided **6.25** (29.2 mg, 55% yield, 2 steps) as a colorless oil. $R_f$ 0.14 (5:1 Hexanes:EtOAc); $^1$H NMR (500 MHz, $CD_3CN$): δ 8.28 (s, 1H), 8.06 (app. dt, *J* = 7.6, 1.0, 1H), 7.60 (app. d, *J* = 8.3, 1H), 7.51 (s, 1H), 7.48 (ddd, *J* = 8.3, 7.1, 1.2, 1H), 7.26 (ddd, *J* = 7.9, 7.2, 0.9, 1H) 5.83 (d, *J* = 1.4, 1H), 5.68 (s, 2H), 5.33 (d, *J* = 1.3, 1H), 3.24 (s, 3H), 2.83 (m, 2H), 2.51 (ddd, *J* = 17.3, 9.0, 7.0, 1H), 2.39, (app. dt, *J* = 17.2, 6.1, 1H), 2.18 (m, 1H), 2.05 (m, 1H), 1.77 (m, 3H), 1.18 (s, 3H), 1.09 (d, *J* = 7.0, 3H); $^{13}$C NMR (125 MHz, $CD_3CN$): δ 203.7, 154.4, 142.0, 141.3, 140.2, 127.4, 125.0, 124.1,

123.0, 121.3, 121.2, 119.0, 115.5, 112.0, 110.7, 74.8, 56.4, 45.0, 41.3, 37.7, 35.9, 32.2, 27.2, 22.5, 15.6; IR (film): 2938, 1691, 1603, 1470, 1452, 1242, 1112 $cm^{-1}$; HRMS-ESI (*m/z*) [M + $NH_4$]$^+$ calcd for $C_{25}H_{32}BrN_2O_2$, 471.1635; found, 471.1642. $[\alpha]_D^{23}$ +28.0° (*c* = 0.1, EtOAc).



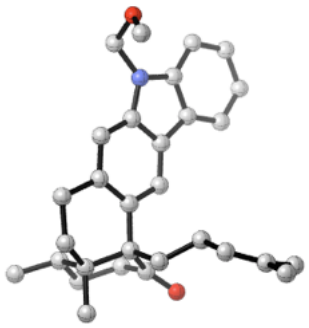

**Silyl Enol Ether 6.26**. Compound **6.26** was prepared following the general procedure of Lipshutz.[Error! Bookmark not defined.] A vial was charged with CuCN (36.7 mg, 0.410 mmol, 3.5 equiv) and lithium chloride (18.4 mg, 0.433 mmol, 3.7 equiv) inside a glovebox and then the vial was removed from the glovebox. To this vial was added THF (0.5 mL) and the mixture was allowed to stir at 23 ºC for 5 min, until the solids fully dissolved. The pale green solution was then cooled to –78 ºC. To a separate vial was added prenyl tri(*n*-butyl)stannane (prepared following the procedure of Keck et al,[32] 133.6 μL, 0.374 mmol, 3.2 equiv). To the stannane was added THF (0.5 mL) and the solution immediately cooled to –78 ºC. Once at –78 ºC, *n*-butyllithium (2.40 M in hexanes, 141.3 μL, 0.339 mmol, 2.9 equiv) was added to the vial containing stannane, causing the solution to turn bright yellow. After 30 min, the yellow lithiate solution was transferred to the vial containing CuCN via chilled cannulation. To the resulting brown mixture was added TESCl (72.7 μL, 0.433 mmol, 3.7 equiv) and the solution was allowed to stir cold. After 20 min, enone **6.25** (53.0 mg, 0.117 mmol, 1 equiv) as a solution in THF (1.0 mL) was added slowly via syringe. The vial from which the enone solution was taken was then washed with additional THF (0.2 mL) and the resulting solution was added to the reaction mixture. After stirring for 1 h, the reaction

was quenched with triethylamine (0.5 mL) and sat. aq. $NaHCO_3$ (1 mL), and then warmed to room temperature. The mixture was diluted with $H_2O$ (5 mL) and EtOAc (6 mL). The layers were separated and the aqueous layer was extracted with EtOAc (4 x 6 mL). The combined organic layers were dried over $Na_2SO_4$ and concentrated under reduced pressure to deliver the crude product. Purification by flash chromatography (10:1 Hexanes:EtOAc, 2% $Et_3N$) gave **6.26** (64.9 mg, 87% yield) as a colorless oil. $R_f$ 0.77 (3:1 Hexanes:EtOAc); $^1H$ NMR (500 MHz, $CD_2Cl_2$): δ 8.22 (s, 1H), 8.01 (app. d, *J* = 7.6, 1H), 7.54 (app. d, *J* = 8.1, 1H), 7.47 (ddd, *J* = 8.2, 7.1, 1.1, 1H), 7.39 (s, 1H), 7.27 (app. t, *J* = 7.6, 1H), 5.65 (s, 2H), 5.19 (app. t, *J* = 7.0, 1H), 3.29 (s, 3H), 2.84 (td, *J* = 13.1, 4.8, 1H), 2.56 (td, *J* = 13.1, 4.6, 1H), 2.34 (m, 2H), 2.24 (m, 1H), 2.06 (m, 2H), 1.86 (m, 3H), 1.73 (m, 2H), 1.69 (s, 3H), 1.66 (m, 1H), 1.61 (s, 3H), 1.03 (t, *J* = 7.8, 9H), 0.98 (d, *J* = 6.8, 3H), 0.95 (s, 3H), 0.72 (q, *J* = 7.8, 6H); $^{13}C$ NMR (125 MHz, $CD_2Cl_2$): δ 146.7, 141.4, 140.8, 140.7, 131.0, 126.7, 126.0, 124.3, 123.5, 122.7, 121.5, 120.6, 120.58, 115.7, 110.7, 109.8, 74.6, 56.4, 41.5, 39.1, 34.0, 32.7, 30.7, 28.7, 27.6, 27.5, 25.8, 21.8, 17.9, 16.5, 7.1, 6.2; IR (film): 2956, 1711, 1657, 1603, 1451, 1241 $cm^{-1}$; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{36}H_{53}BrNO_2Si$, 638.3023; found, 638.3044. $[\alpha]_D^{23}$ –56.0° (*c* = 0.1, EtOAc).

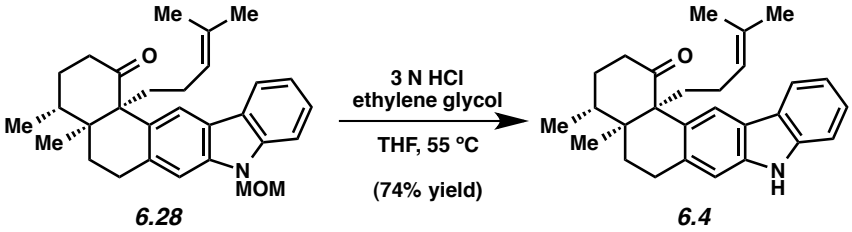



**Decalin 6.28**. To a 20-mL vial inside the glovebox was added $NaNH_2$ (41.5 mg, 1.064 mmol, 11 equiv) and the solid was crushed into a powder. The vial was removed from the glovebox and THF (2.0 mL) was added, followed by *t*-BuOH (29.6 μL, 0.309 mmol, 3.2 equiv). The vial was

placed in a heating block at 40 ºC and stirred for 1 h. After cooling to room temperature under $N_2$, silyl enol ether **6.26** (61.8 mg, 0.097 mmol, 1 equiv) was added as a solution in THF (1.0 mL). The vial containing **6.26** was then washed with additional THF (1.0 mL) and the resulting solution was added to the reaction mixture. The reaction was stirred at 23 ºC for 3 h, quenched with $H_2O$ (3 mL), and then diluted with EtOAc (10 mL) and sat. aq. $NH_4Cl$ (4 mL). The layers were separated, and the aqueous layer extracted with EtOAc (3 x 8 mL). The combined organic layers were dried over $Na_2SO_4$ and concentrated under reduced pressure to afford the crude product. Purification by flash chromatography (8:1 Hexanes:EtOAc) gave **6.28** (36.0 mg, 84% yield) as a white solid. Crystals suitable for X-ray diffraction studies (CCDC 984476) were obtained using a sample of racemic **6.28** by vapor diffusion ($CHCl_3$/Heptanes). Mp: 177 ºC (*rac*.); $R_f$ 0.39 (8:1 Hexanes:EtOAc); $^1$H NMR (500 MHz, $CDCl_3$): δ 7.96 (d, *J* = 7.7, 1H), 7.49 (d, *J* = 8.1, 1H), 7.43 (ddd, *J* = 8.2, 7.1, 1.1, 1H), 7.31 (s, 2H), 7.23 (ddd, *J* = 7.9, 7.0, 1.0, 1H), 5.66–5.61 (m, 2H), 4.96 (app. dt, *J* = 7.1, 1.4, 1H), 3.34 (s, 3H), 3.17–3.02 (m, 2H), 2.87–2.78 (m, 1H), 2.26 (dt, *J* = 12.8, 3.3, 1H), 2.22–1.99 (m, 4H), 1.76 (ddd, *J* = 14.5, 7.1, 1.3, 1H), 1.70–1.63 (m, 2H), 1.56 (s, 3H), 1.45 (s, 3H), 1.44–1.36 (m, 1H), 1.21–1.11 (m, 1H), 0.91 (d, *J* = 6.8, 3H), 0.85 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 215.7, 141.2, 139.7, 133.9, 131.5, 129.7, 126.0, 125.2, 123.6, 121.9, 121.8, 120.4, 120.1, 109.4, 109.1, 74.4, 61.4, 56.4, 43.8, 39.7, 33.5, 32.2, 32.1, 28.5, 26.3, 25.8, 25.4, 17.8, 16.2, 15.8; IR (film): 2959, 2928, 1697, 1474, 1241 cm$^{-1}$; HRMS-ESI (*m/z*) [M + H]$^+$ calcd for $C_{30}H_{38}NO_2$, 444.28971; found, 444.28781. $[\alpha]_D^{23}$ +80.0º (*c* = 0.10, $CHCl_3$).

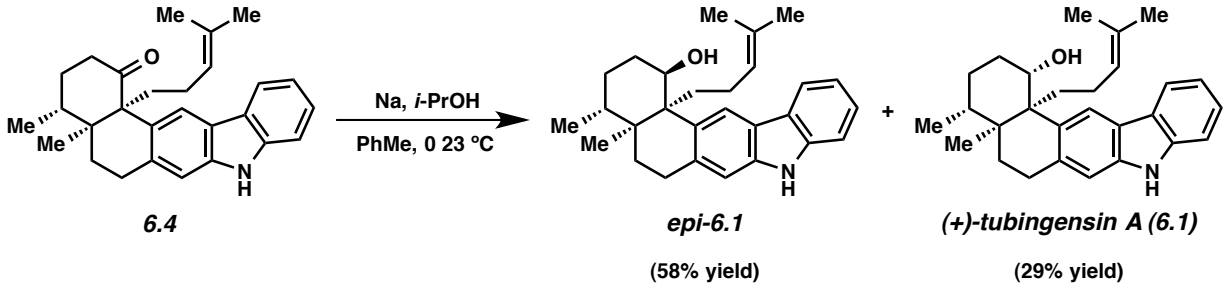


**X-ray structure of 6.28**




**Ketone 6.4.** To a solution of **6.28** (11.2 mg, 0.025 mmol, 1 equiv) in THF (2 mL) was added ethylene glycol (100 μL, 1.79 mmol, 72 equiv) and 3 N HCl (250 μL, 0.750 mmol, 30 equiv). The reaction was capped and heated to 55 °C. After 20.5 h the reaction was cooled to room temperature and diluted with $Et_2O$ (20 mL) and sat. aq. $NaHCO_3$ (5 mL). The layers were separated, and the aqueous layer was extracted with $Et_2O$ (2 x 15 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to provide the crude product. Purification by flash chromatography (5:1 Hexanes:EtOAc) provided **6.4** (7.5 mg, 74% yield) as an amorphous white solid. $R_f$ 0.66 (Benzene eluent); $^1H$ NMR (500 MHz, $CDCl_3$): δ 7.96 (d, *J* = 8.1, 1H), 7.88 (s, 1H), 7.39–7.35 (m, 2H), 7.30 (s, 1H), 7.21–7.17 (m, 2H), 5.00–4.94 (m, 1H), 3.14–2.98 (m, 2H), 2.90–2.80 (m, 1H) 2.26 (dt, *J* = 12.9, 3.2, 1H), 2.22–1.98 (m, 4H), 1.77–1.71 (m, 1H), 1.70–1.62 (m, 2H), 1.57 (s, 3H), 1.45 (s, 3H), 1.43–1.37 (m, 1H), 1.21–

1.11 (m, 1H), 0.90 (d, $J$ = 6.8, 3H), 0.85 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 215.8, 140.0, 138.7, 133.6, 131.4, 129.1, 125.8, 125.2, 123.5, 121.9, 121.7, 120.4, 119.5, 110.60, 110.57, 61.4, 43.7, 39.7, 33.5, 32.2, 32.1, 28.5, 26.2, 25.8, 25.4, 17.8, 16.2, 15.8 IR (film): 3411, 2960, 2928, 1689, 1466, 1243 cm$^{-1}$; HRMS-ESI ($m/z$) [M + H]$^+$ calcd for $C_{28}H_{34}NO$, 400.26349; found, 400.26270; $[\alpha]_D^{23}$ +104.7° ($c$ = 0.10, $CHCl_3$).




**Tubingensin A (6.1) and *epi*-Tubingensin A (*epi*-6.1).** To a solution of ketone **6.4** (5.7 mg, 0.014 mmol, 1 equiv) in toluene (950 μL) was added *i*-PrOH (90 μL, 1.18 mmol, 84 equiv), and the reaction was cooled to 0 ºC. Sodium metal (11.1 mg, 0.483 mmol, 35 equiv), after being briefly immersed in hexanes to remove any mineral oil, was added to the reaction. After 2 h the reaction was warmed to room temperature and stirred for an additional 1 h. The reaction was quenched with sat. aq. $NH_4Cl$ (2 mL) and diluted with $H_2O$ (2 mL) and $Et_2O$ (10 mL). The layers were separated, and the aqueous layer was extracted with $Et_2O$ (2 x 10 mL). The combined organic layers were dried over $MgSO_4$. Evaporation of the solvent under reduced pressure afforded the crude products, which were purified by preparative thin layer chromatography (8:1:1 Hexanes:$CH_2Cl_2$:Acetone) to afford **6.1** (1.7 mg, 29% yield) and ***epi*-6.1** (3.3 mg, 58% yield) as colorless oils. **Tubingensin A (6.1)**: $R_f$ 0.55 (benzene eluent); $^1$H NMR (500 MHz,

$CDCl_3$): δ 8.00 (d, *J* = 7.8, 1H), 7.94 (s, 1H), 7.81 (s, 1H), 7.39–7.44 (m, 2H), 7.19 (ddd, *J* = 7.7, 5.8, 1.8, 1H), 7.14 (s, 1H), 5.03 (app. t, *J* = 6.9, 1H), 4.98 (s, 1H), 3.07–2.98 (m, 1H), 2.90 (dd, *J* = 17.5, 6.7, 1H), 2.13–1.97 (m, 3H), 1.84–1.65 (m, 5H), 1.60 (s, 3H), 1.59–1.50 (m, 3H), 1.44 (s, 3H), 1.23 (s, 3H), 1.20–1.16 (m, 1H), 0.86 (d, *J* = 5.9, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 140.1, 138.0, 135.3, 132.6, 131.7, 125.5, 125.2, 123.9, 121.5, 119.9, 119.3, 118.6, 110.8, 110.6, 71.5, 47.4, 38.9, 35.0, 32.7, 29.7, 29.5, 27.2, 25.8, 25.5, 23.2, 18.5, 17.8, 16.4; IR (film): 3413, 2928, 1612, 1467, 1242 cm$^{-1}$; HRMS-ESI (*m/z*) [M – H]$^-$ calcd for $C_{28}H_{34}NO$, 400.26349; found, 400.26387; $[\alpha]_D^{23}$ +14.0° (*c* = 0.10, $CHCl_3$). ***epi*-Tubingensin A (*epi*-6.1)**: $R_f$ 0.55 (benzene eluent); $^1$H NMR (500 MHz, $C_6D_6$): δ 9.43 (s, 1H), 8.13 (d, *J* = 7.8, 1H), 7.32 (ddd, *J* = 8.2, 7.0, 1.1, 1H), 7.13 (ddd, *J* = 8.0, 7.0, 1.0, 1H), 7.07, (app. dt, *J* = 8.1, 0.8, 1H), 6.86 (s, 1H), 6.54 (s, 1H), 5.2–5.14 (m, 1H), 3.90 (dd, *J* = 12.7, 3.7, 1H), 2.99–2.90 (m, 1H), 2.85 (dd, *J* = 17.3, 7.2, 1H), 2.47–2.38 (m, 1H), 2.17–2.07 (m, 1H), 2.00–1.90 (m, 3H), 1.80–1.66 (m, 2H), 1.60 (s, 3H), 1.56–1.48 (m, 1H), 1.44 (s, 3H), 1.40–1.33 (m, 1H), 1.29–1.17 (m, 3H), 0.89 (s, 3H), 0.73 (d, *J* = 6.9, 3H); $^{13}$C NMR (125 MHz, $C_6D_6$): δ 140.5, 138.5, 135.4, 132.2, 130.4, 126.7, 125.3, 124.9, 123.2, 122.4, 120.7, 119.5, 110.5, 110.1, 77.5, 49.6, 41.0, 39.1, 32.3, 32.2, 30.7, 29.8, 27.8, 27.0, 25.8, 17.8, 16.6, 16.4; IR (film): 3411, 2927, 1612, 1490, 1465, 1242; HRMS-ESI (*m/z*) [M – H]$^-$ calcd for $C_{28}H_{34}NO$, 400.26349; found, 400.26470; $[\alpha]_D^{23}$ +24.7° (*c* = 0.10, $CHCl_3$).

## 6.6 Notes and References


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(26) Although this strategy would not preclude the corresponding cyclobutyl ring formation, it was plausible that such an intermediate would fragment to give the desired carbazolyne cyclization product.

(27) Alternatively, **6.26** could be derived from **6.17**; see Section 6.5.2 for details.

(28) Analogous attempts to employ TBS ether **6.12** were unsuccessful.

(29) Reduction of **6.4** with $LiAlH_4$ provided a ~1:7.7 mixture favoring *epi*-**6.1**. Attempts to reduce **6.28** with sodium naphthalenide gave a ~1:5 ratio favoring the undesired epimer, while borohydride reducing agents (e.g., L-Selectride, $NaBH_4$) were found to be unreactive. Meerwein–Ponndorf–Verley reduction was also unsuccessful.

(30) Dess–Martin oxidation of *epi*-**6.1** gives **6.4** (60% yield, unoptimized). Exhaustive efforts to effect Mitsunobu inversion of *epi*-**6.1** failed.

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# APPENDIX FOUR

## Spectra Relevant to Chapter Six:

## Concise Enantiospecific Total Synthesis of Tubingensin A

Adam E. Goetz, Amanda L. Silberstein, Michael A. Corsello, Neil K. Garg

*J. Am. Chem. Soc.* **2014**, *136*, 3036–3039.

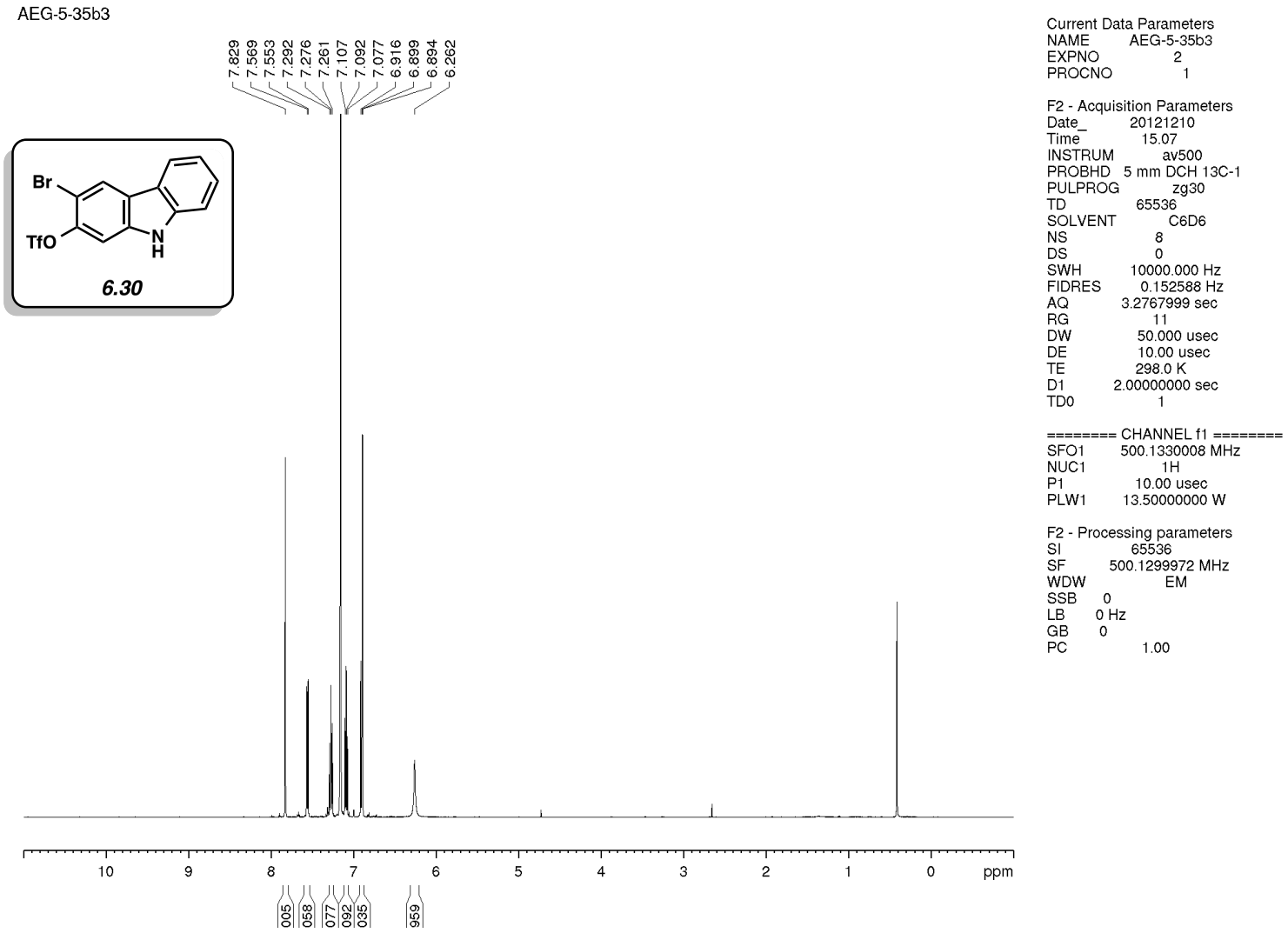



*Figure A4.1* $^{1}$H NMR (500 MHz, $C_6D_6$) of compound **6.30**.

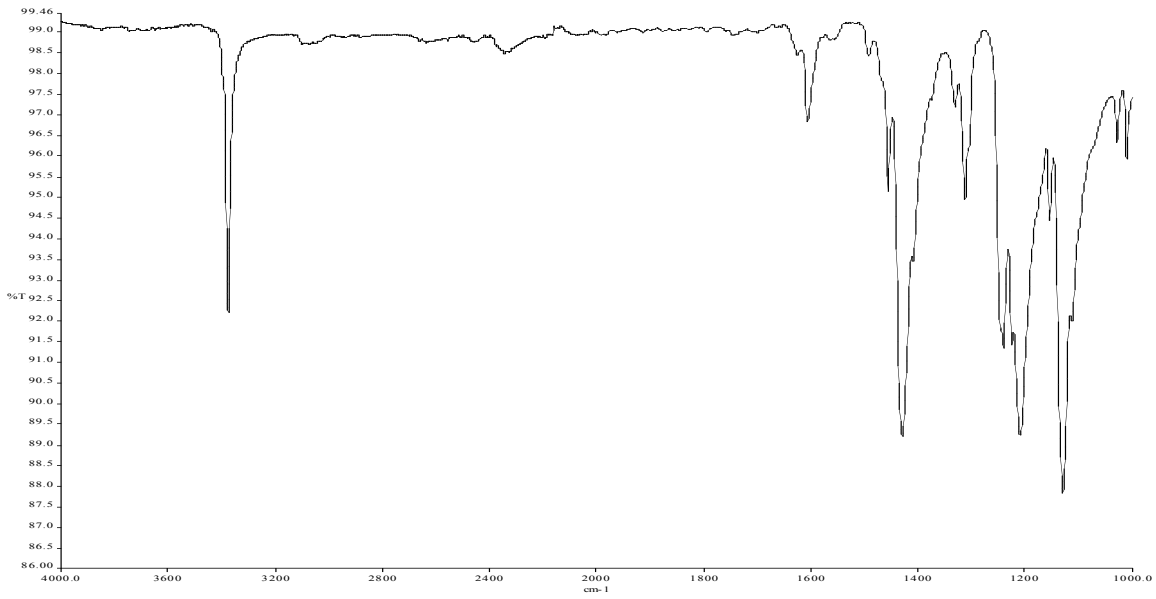



*Figure A4.2* Infrared spectrum of compound **6.30**.

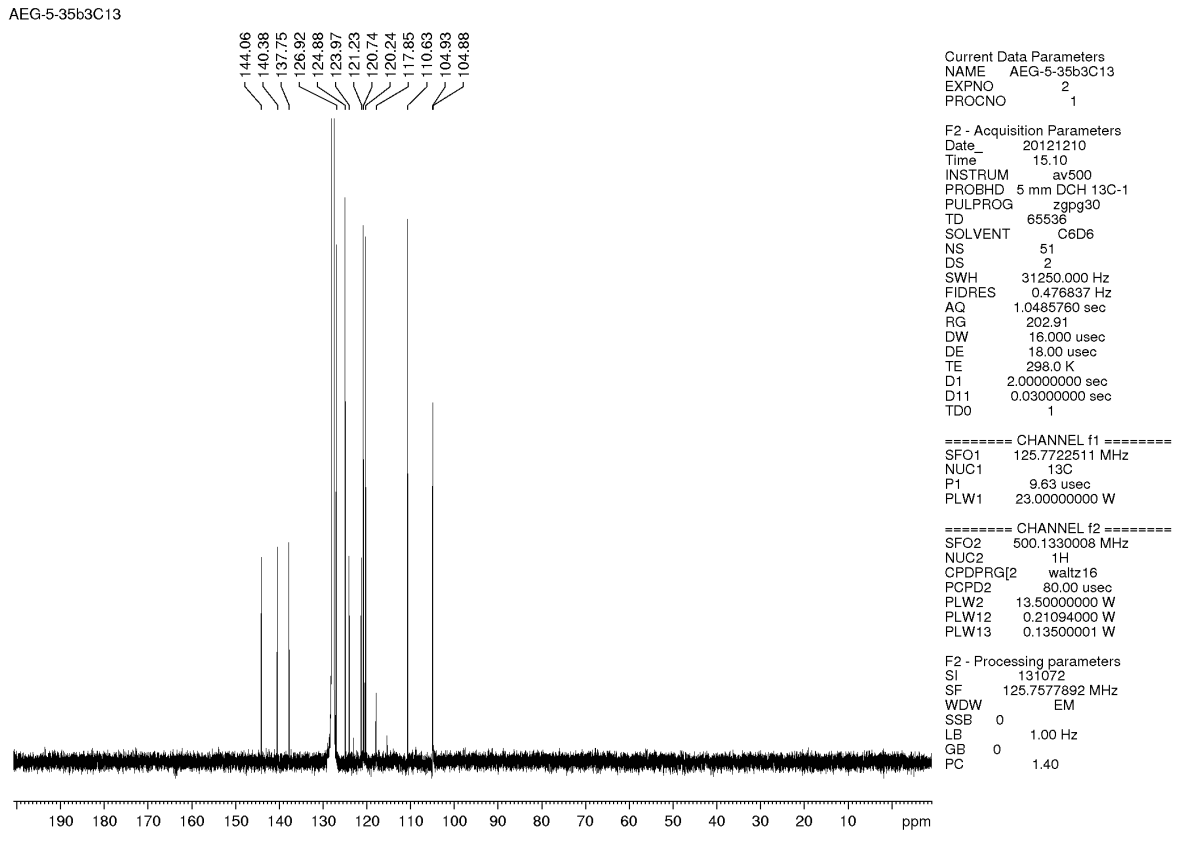



*Figure A4.3* $^{13}$C NMR (125 MHz, $C_6D_6$) of compound **6.30**.

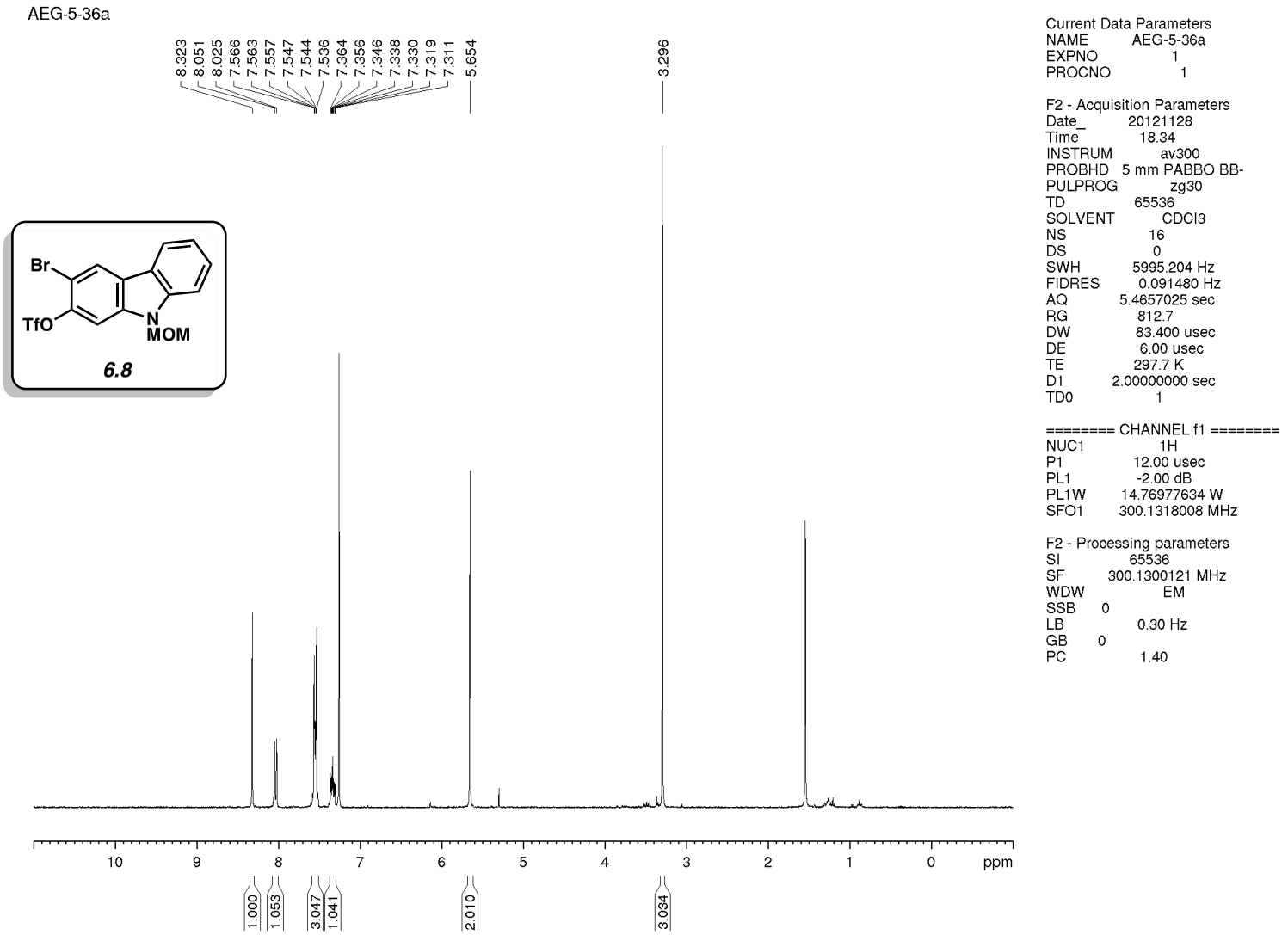



*Figure A4.4* $^{1}$H NMR (300 MHz, $CDCl_3$) of compound **6.8**.

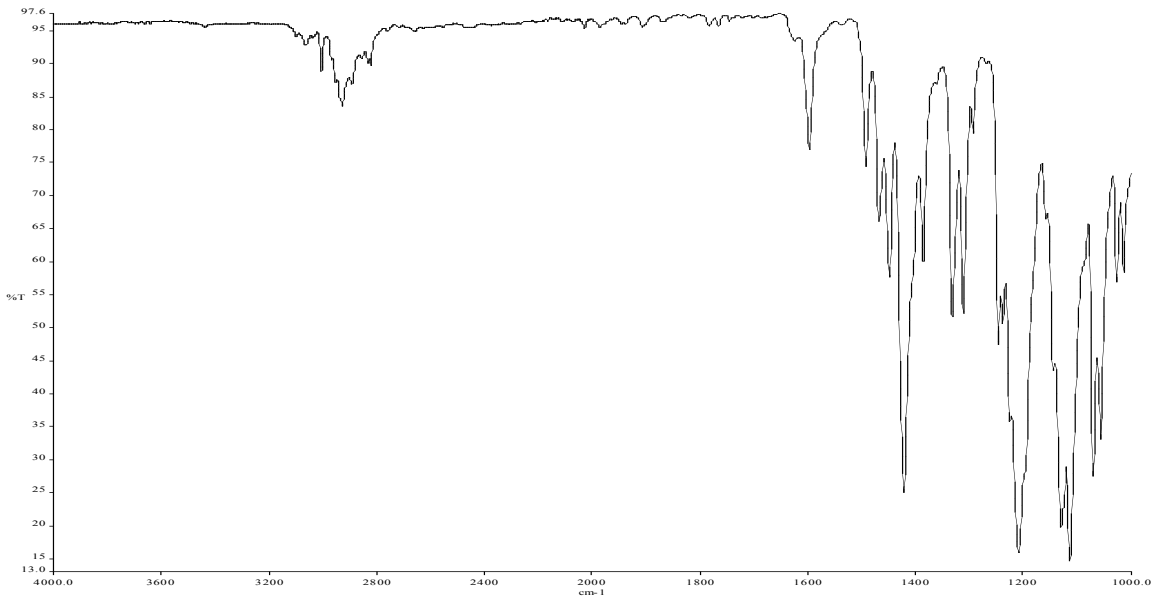



*Figure A4.5* Infrared spectrum of compound **6.8**.

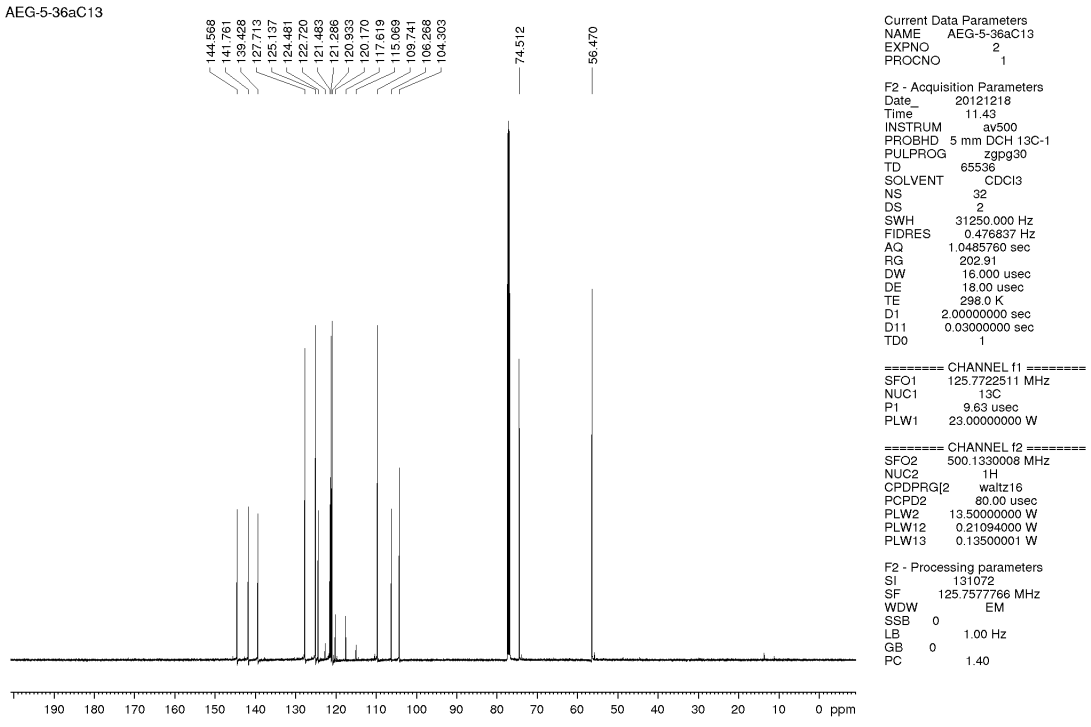



*Figure A4.6* $^{13}$C NMR (125 MHz, $CDCl_3$) of compound **6.8**.

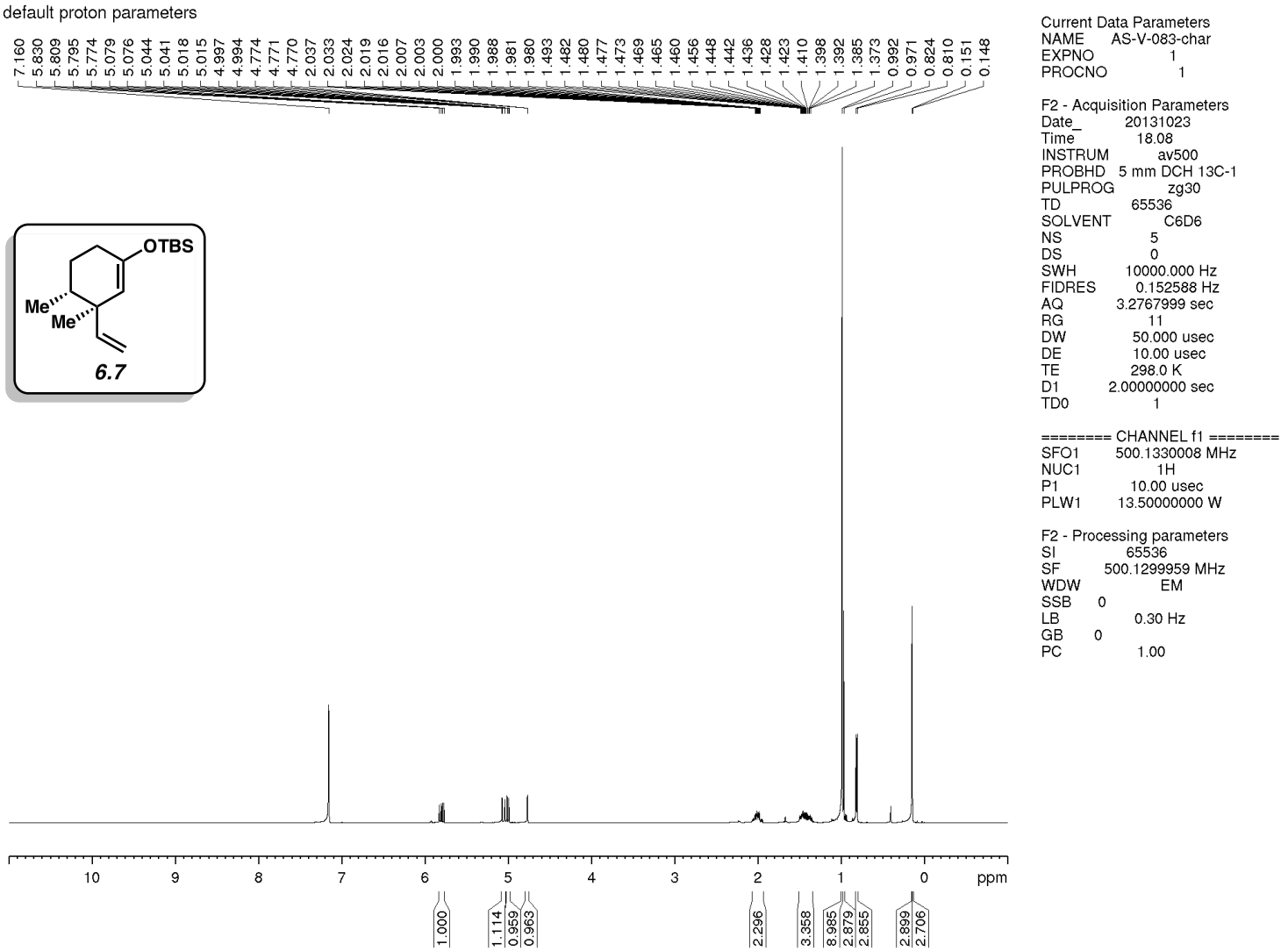



*Figure A4.7* $^{1}$H NMR (500 MHz, $C_6D_6$) of compound **6.7**.

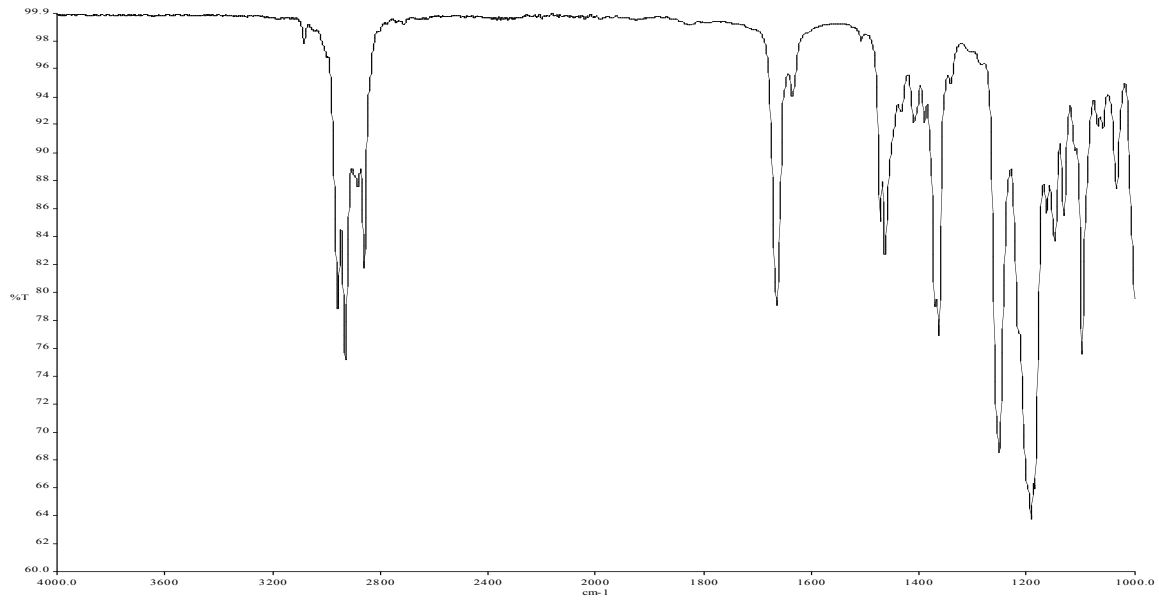



*Figure A4.8* Infrared spectrum of compound **6.7**.

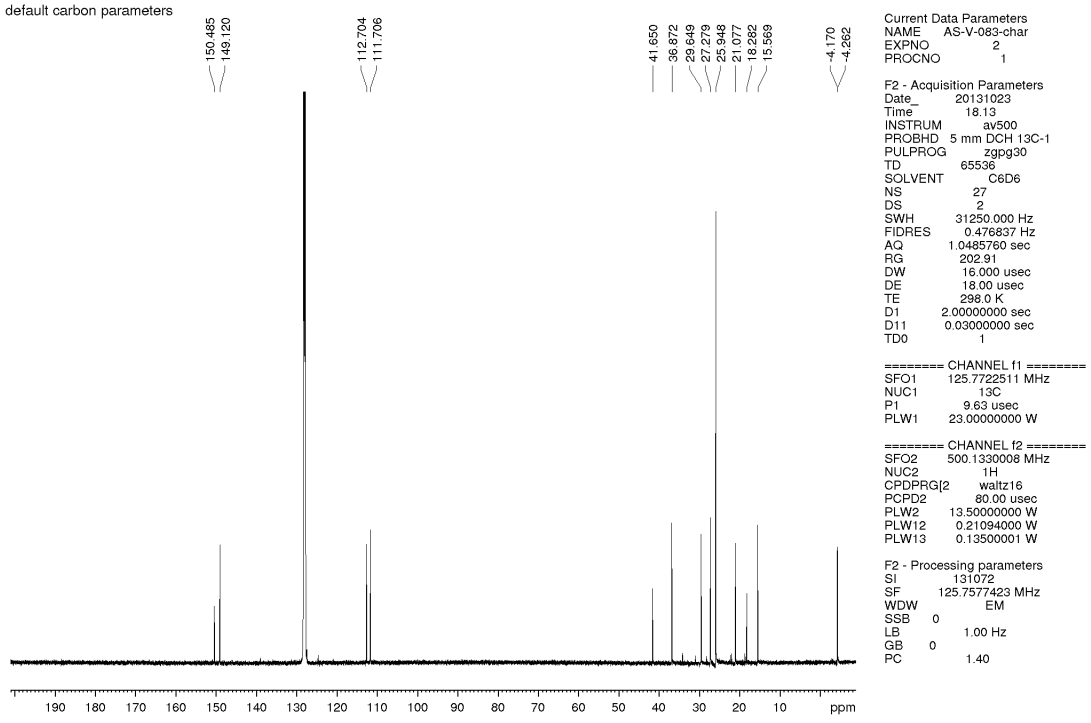



*Figure A4.9* $^{13}$C NMR (125 MHz, $C_6D_6$) of compound **6.7**.

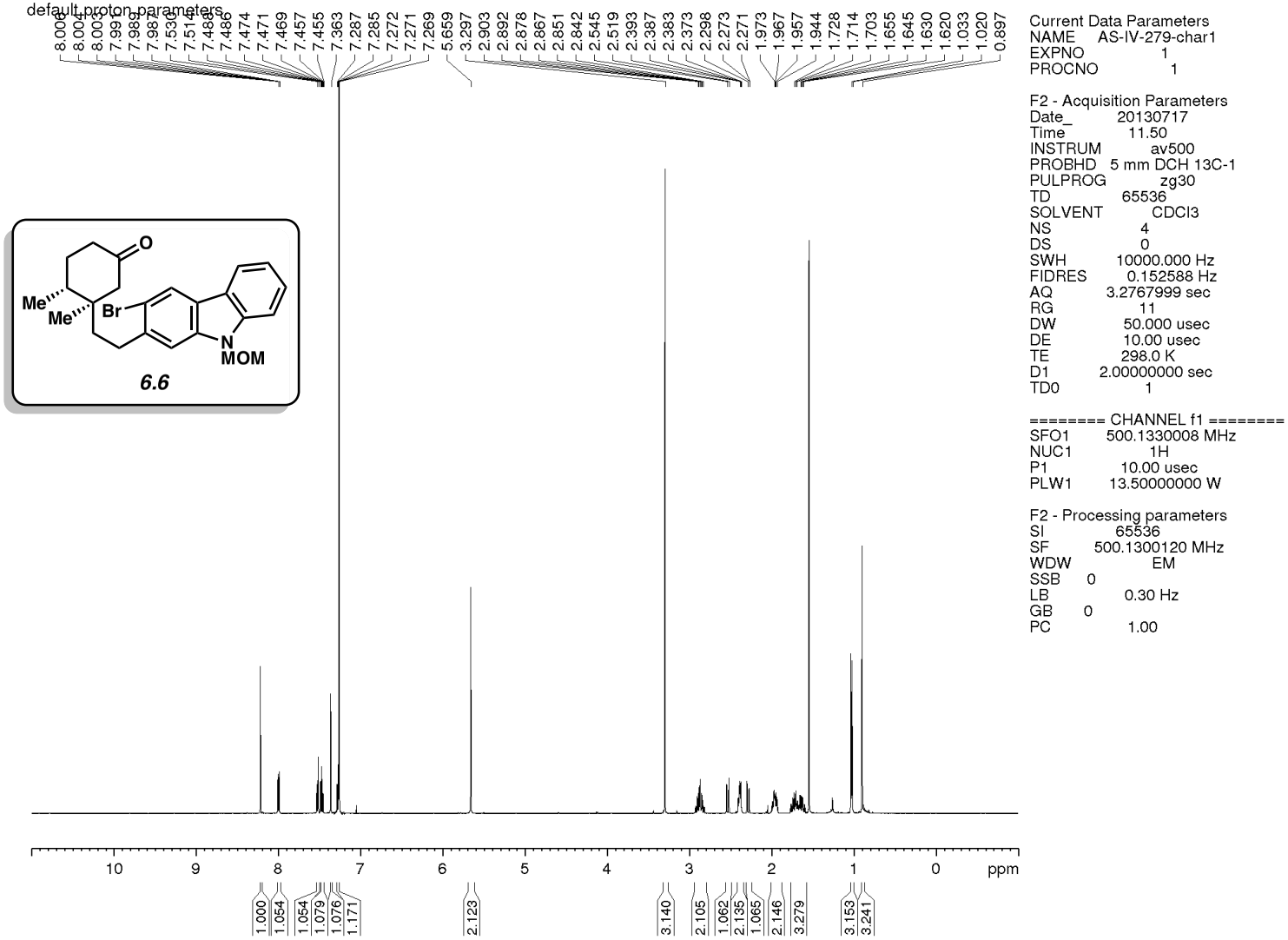



*Figure A4.10* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **6.6**.

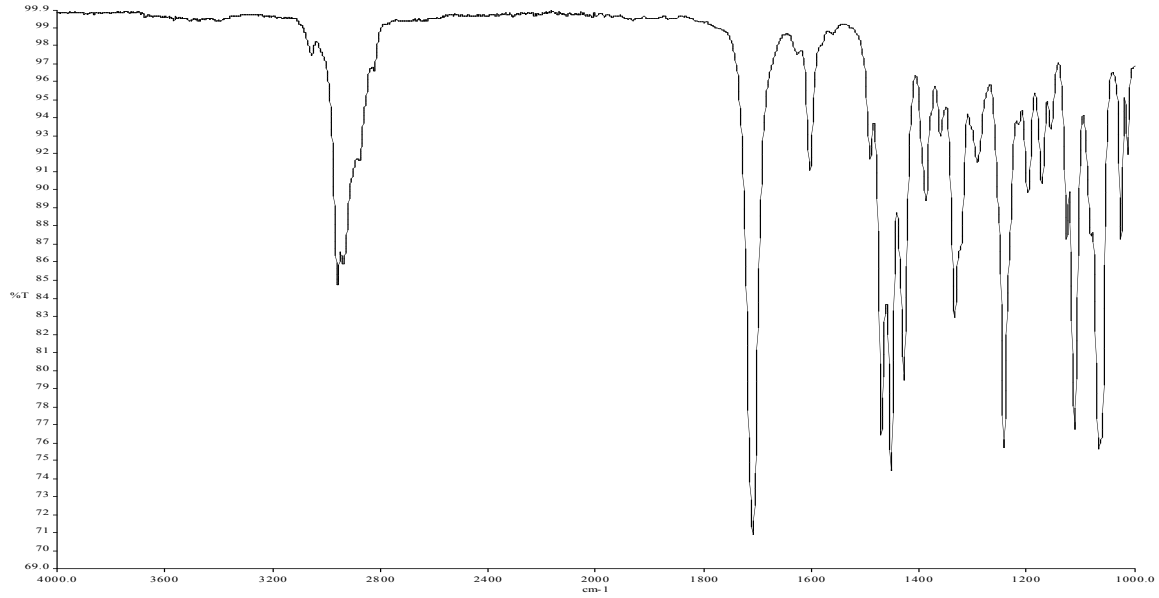



*Figure A4.11* Infrared spectrum of compound **6.6**.

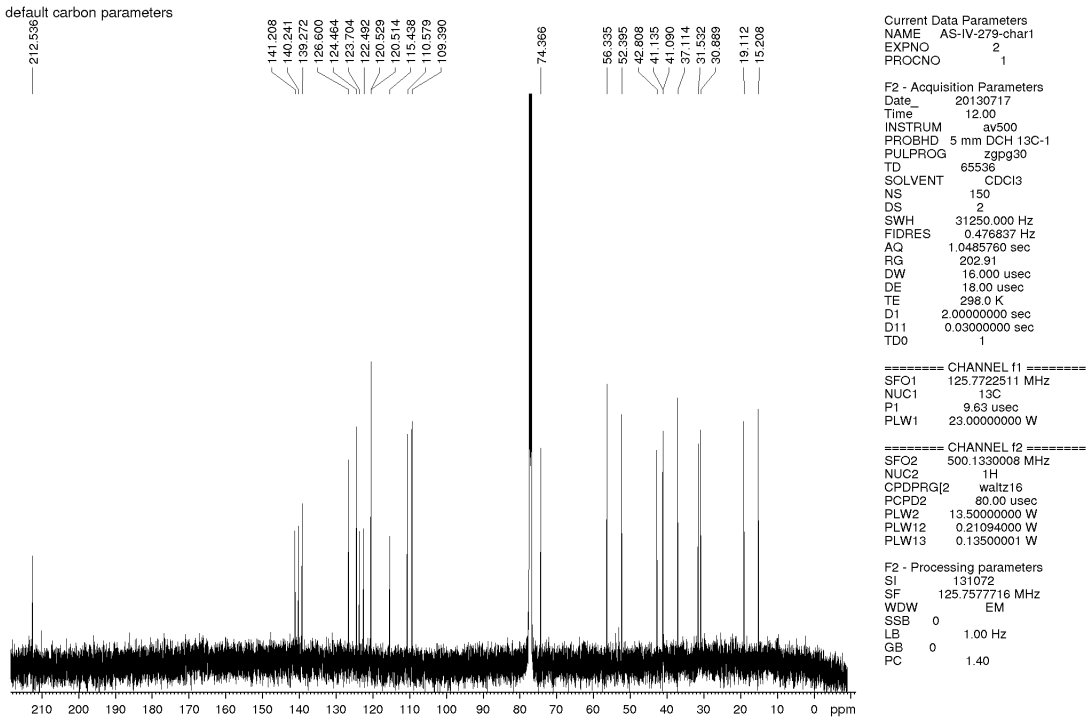



*Figure A4.12* $^{13}$C NMR (125 MHz, $CDCl_3$) of compound **6.6**.

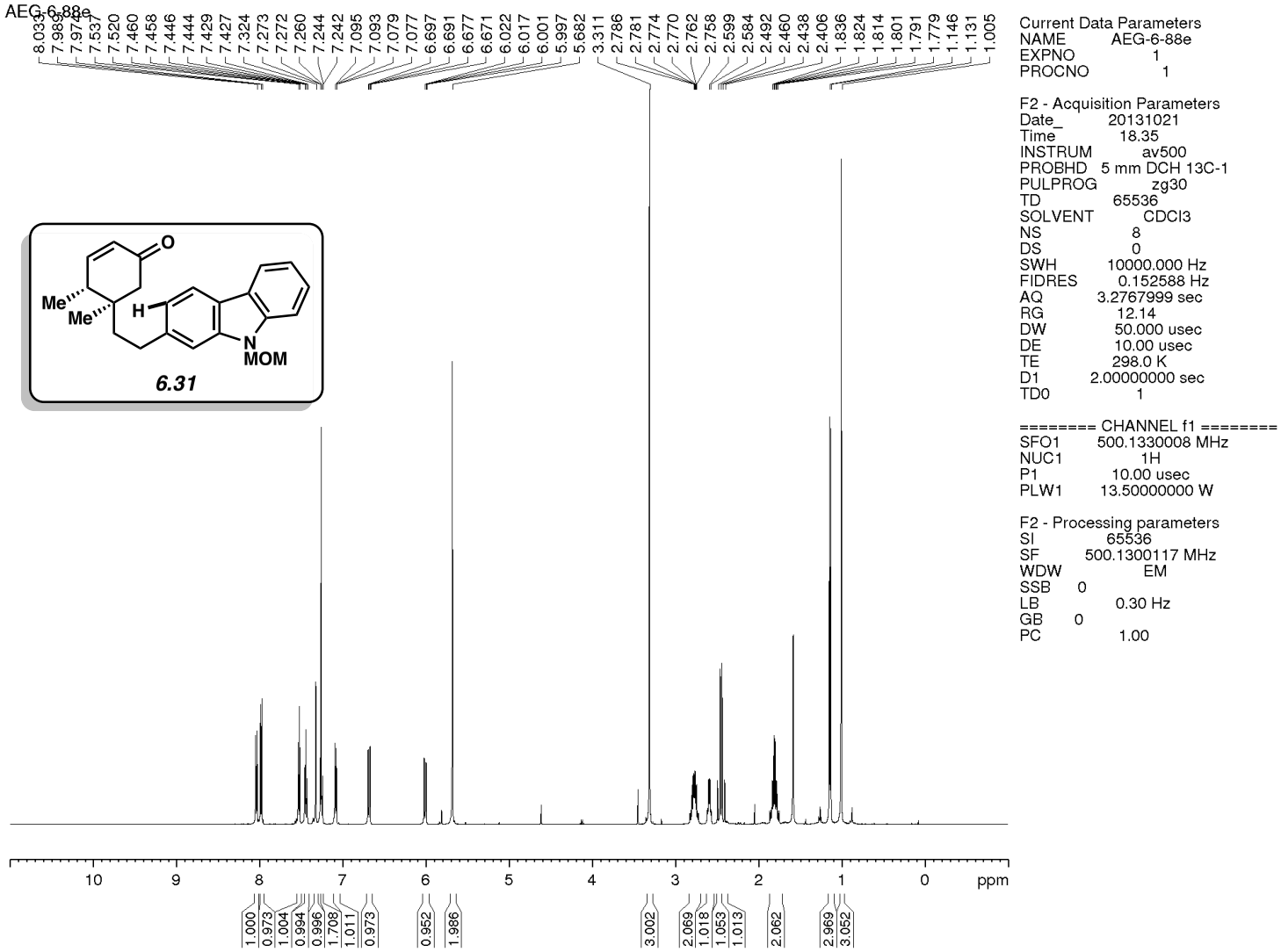



*Figure A4.13* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **6.31**.

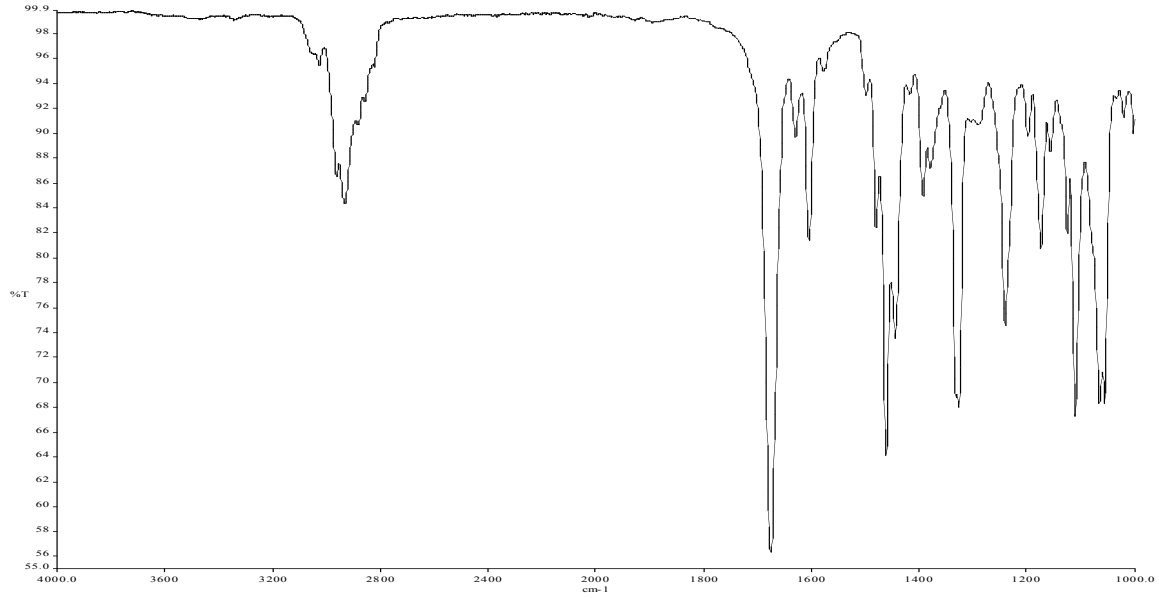



*Figure A4.14* Infrared spectrum of compound **6.31**.

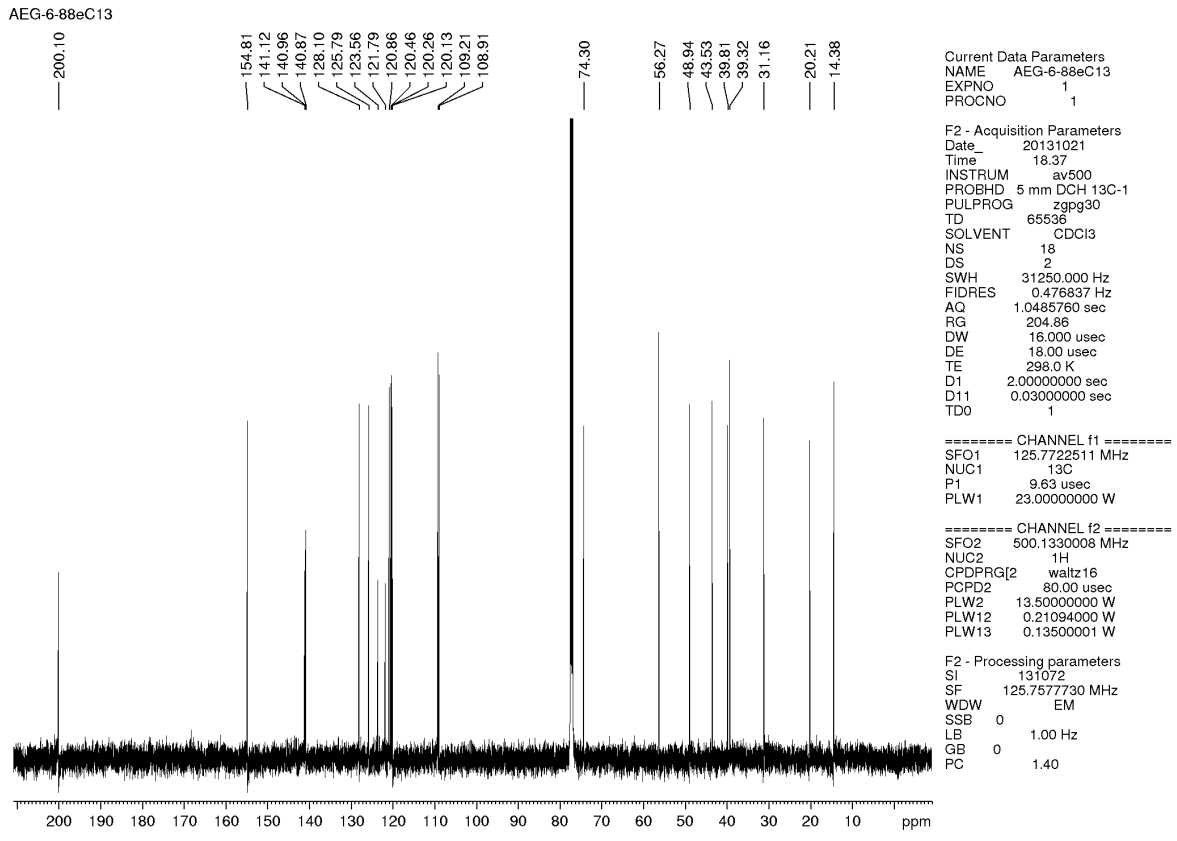



*Figure A4.15* $^{13}$C NMR (125 MHz, $CDCl_3$) of compound **6.31**.

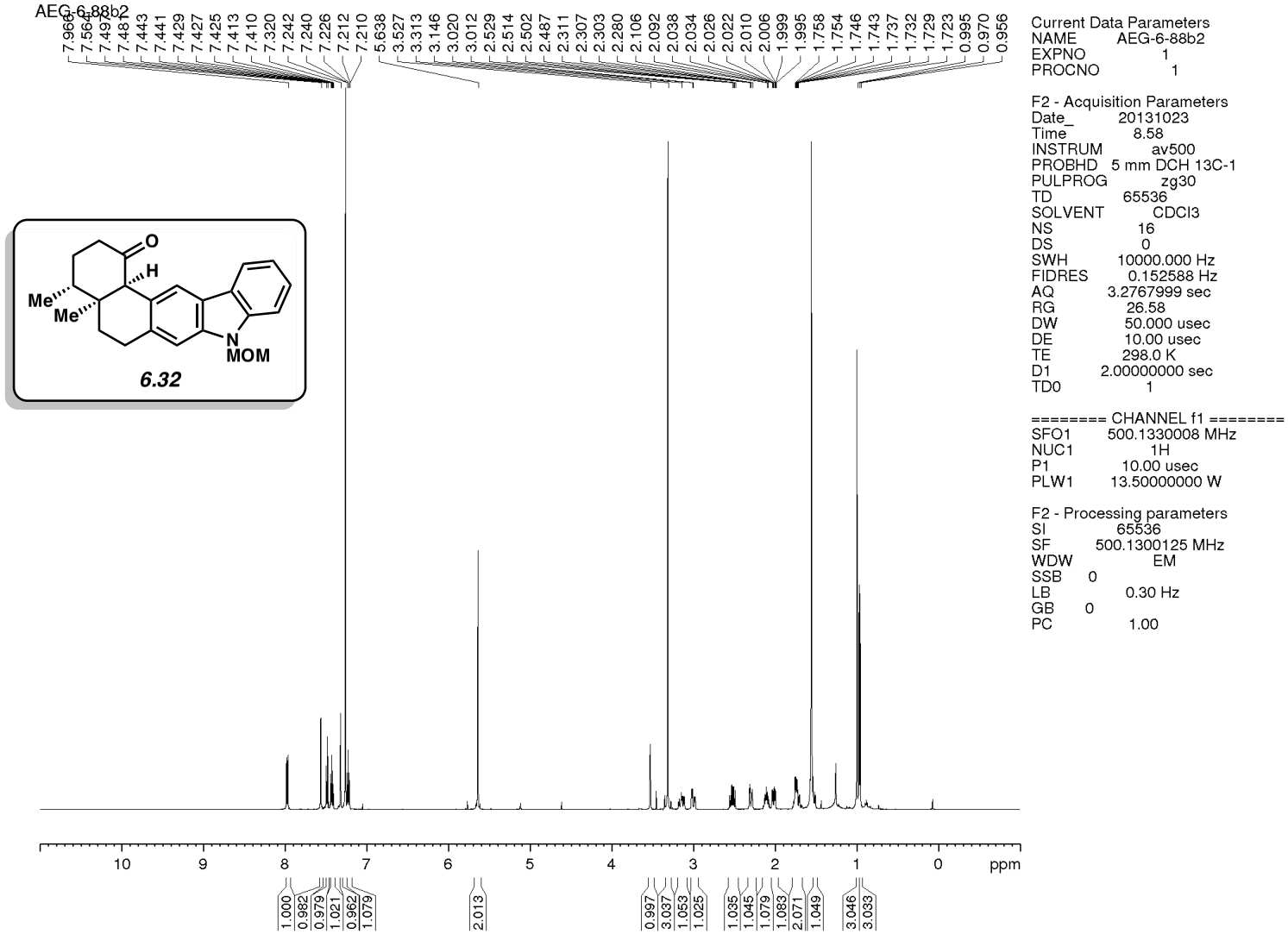



*Figure A4.16* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **6.32**.

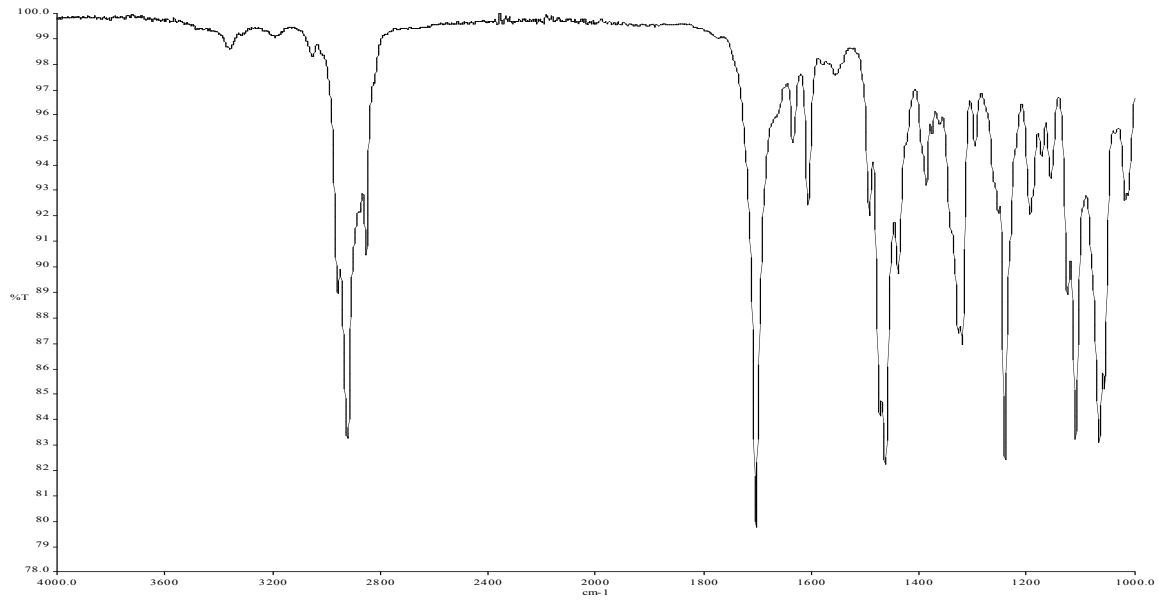



*Figure A4.17* Infrared spectrum of compound **6.32**.

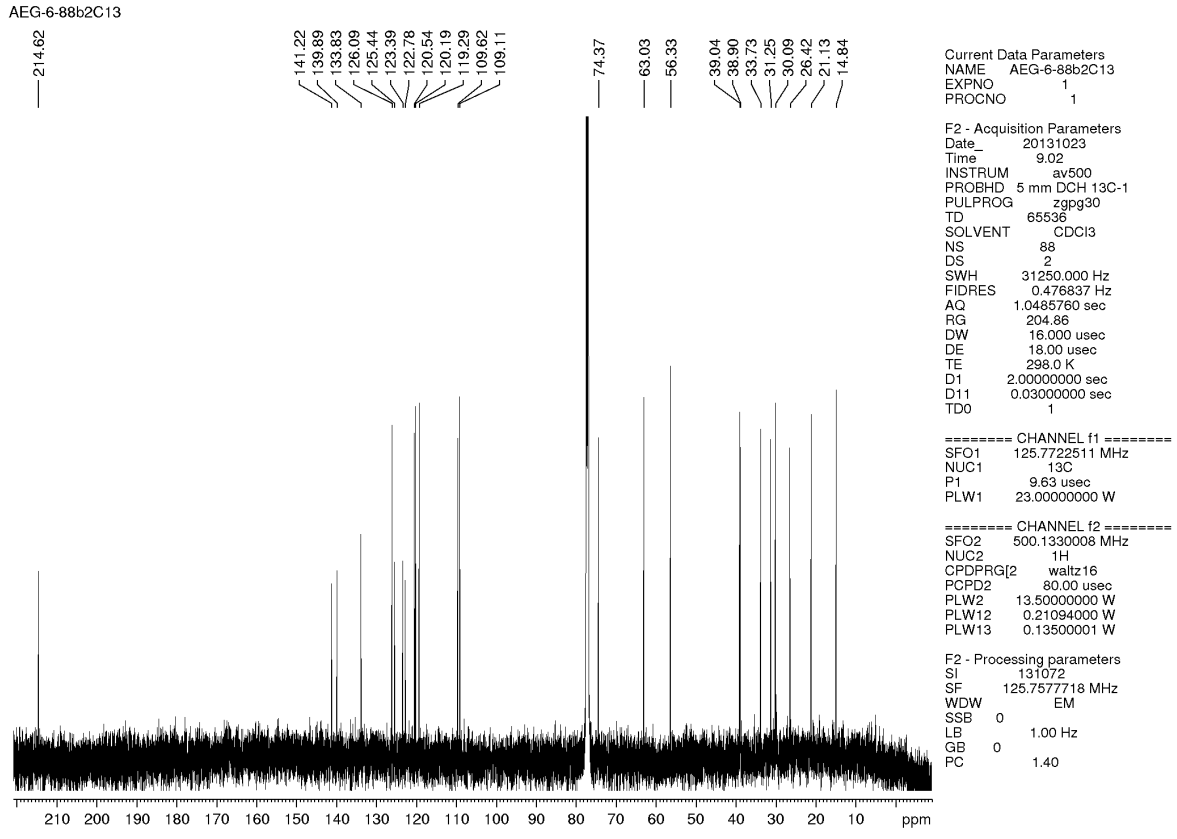



*Figure A4.18* $^{13}$C NMR (125 MHz, $CDCl_3$) of compound **6.32**.

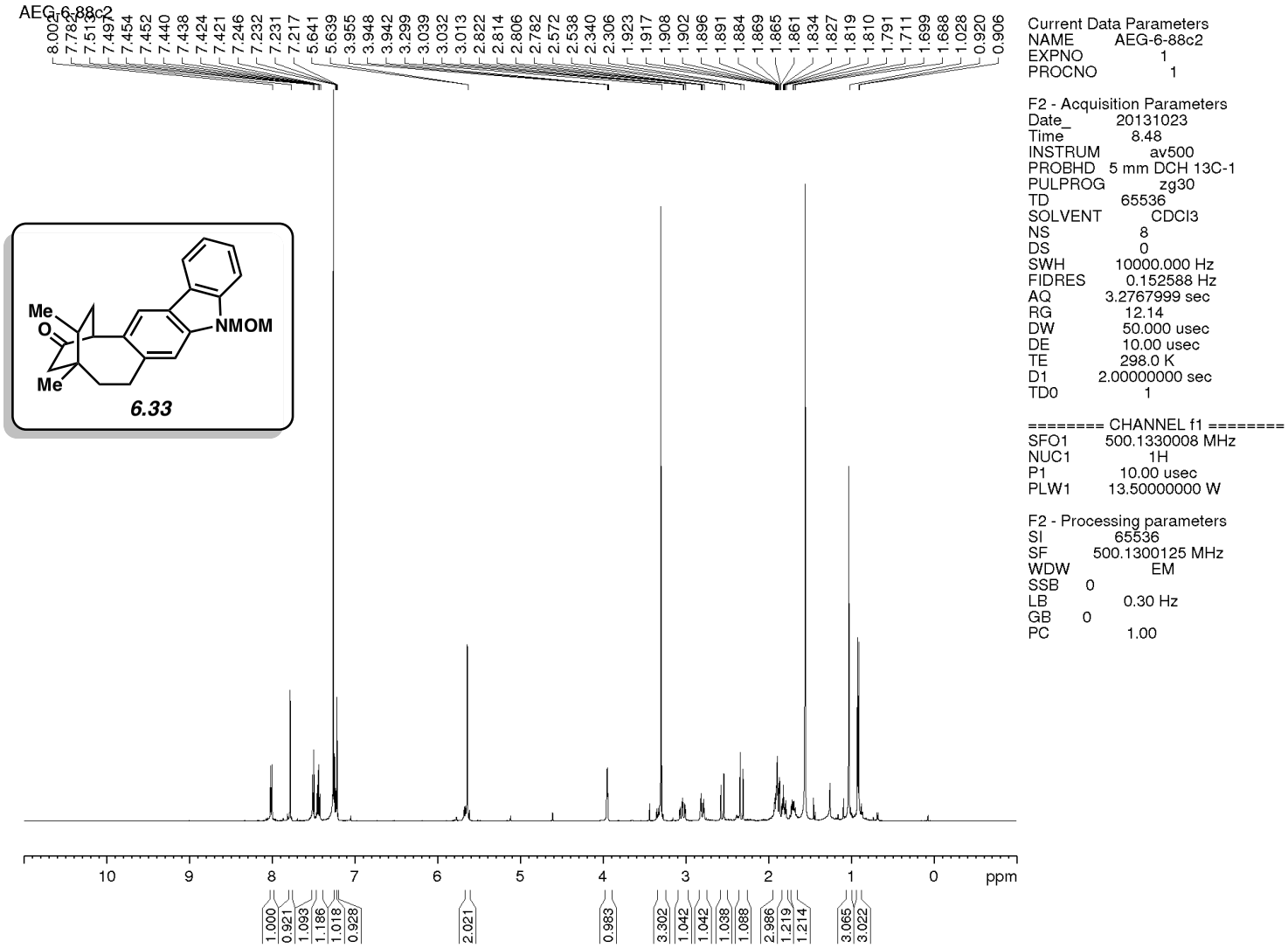



*Figure A4.19* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **6.33**.

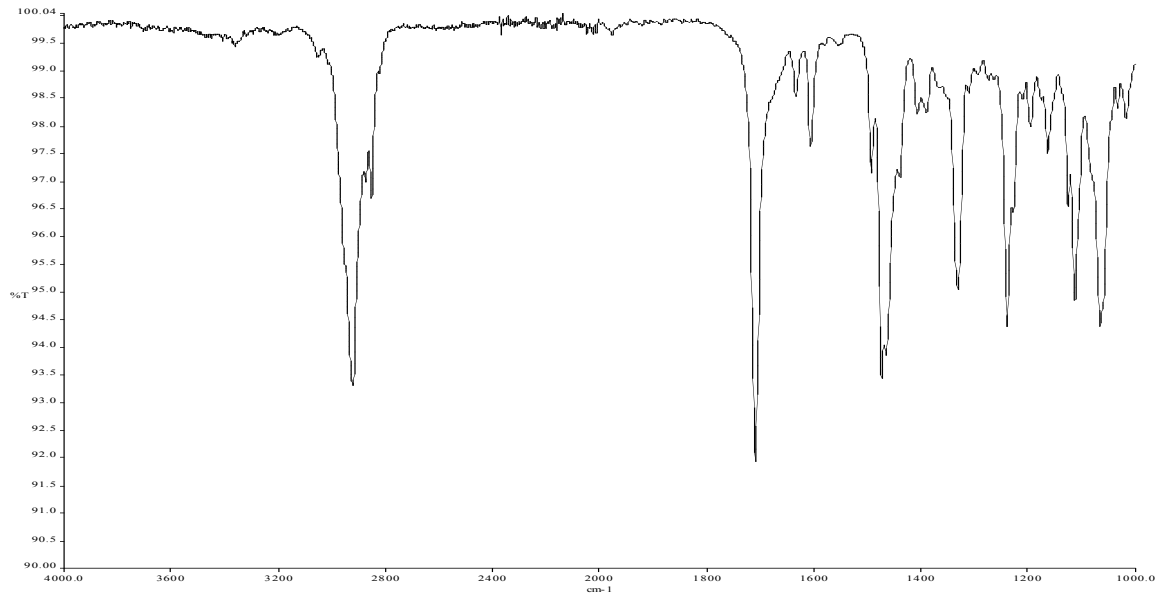



*Figure A4.20* Infrared spectrum of compound **6.33**.

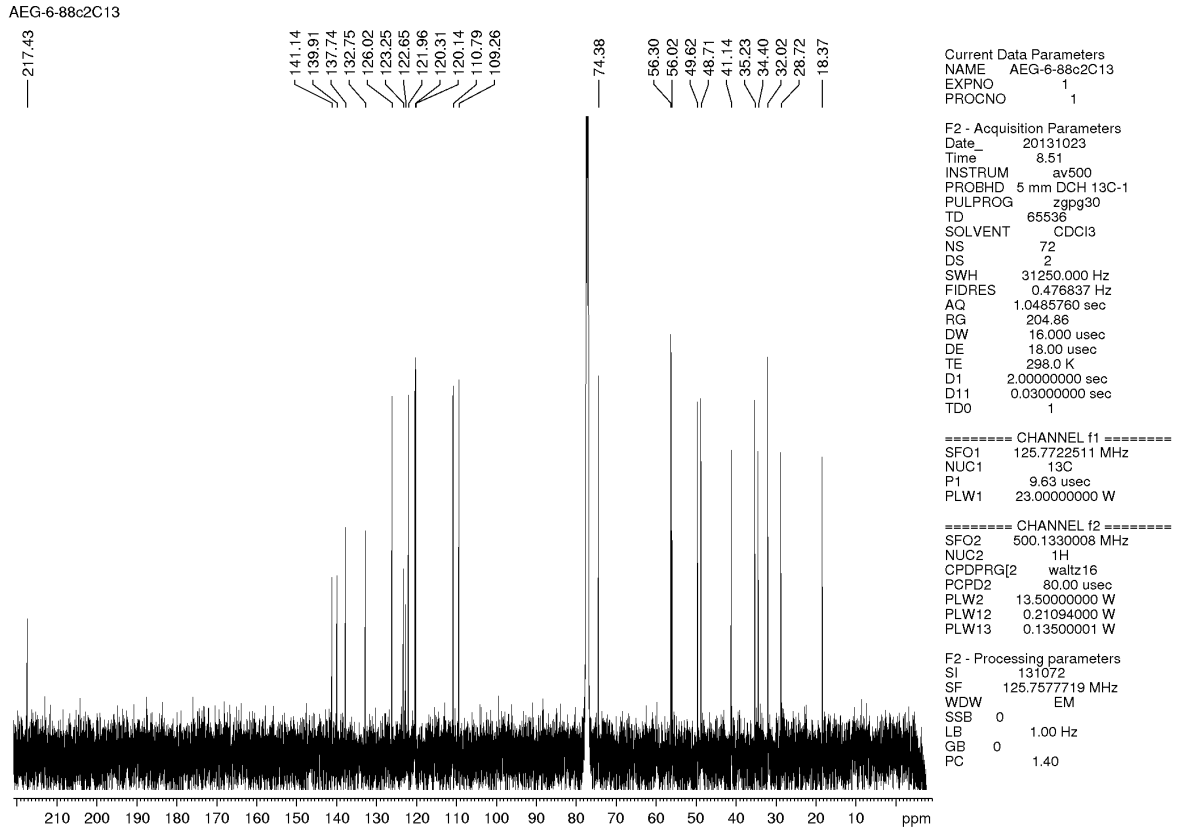



*Figure A4.21* $^{13}$C NMR (125 MHz, $CDCl_3$) of compound **6.33**.

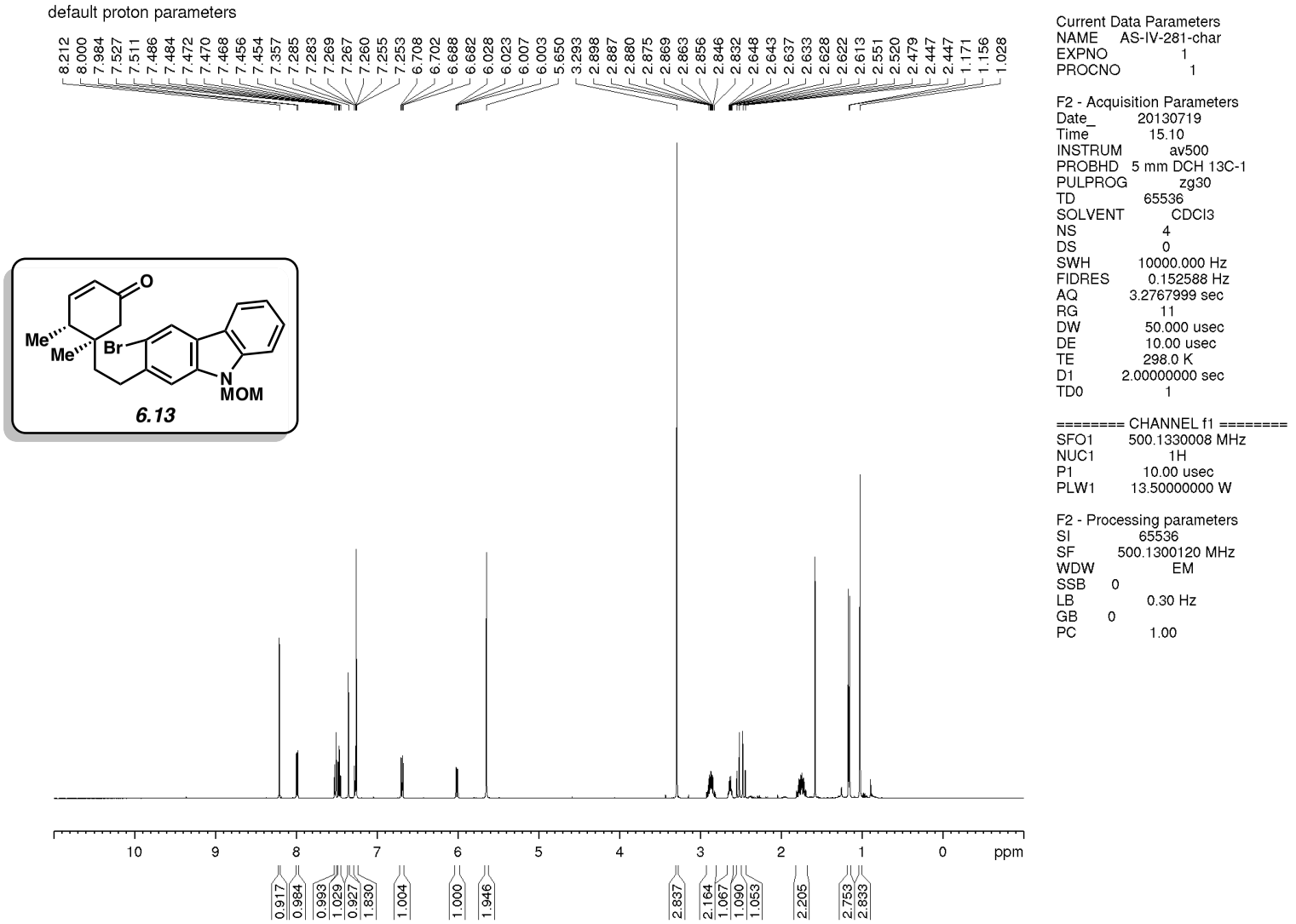



*Figure A4.22* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **6.13**.

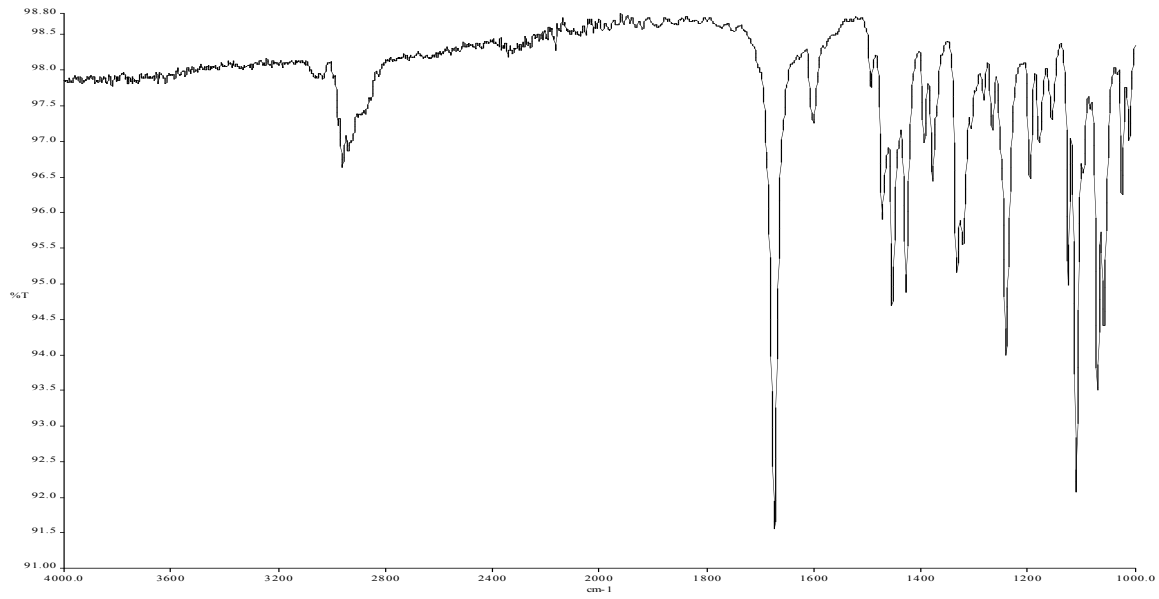



*Figure A4.23* Infrared spectrum of compound **6.13**.

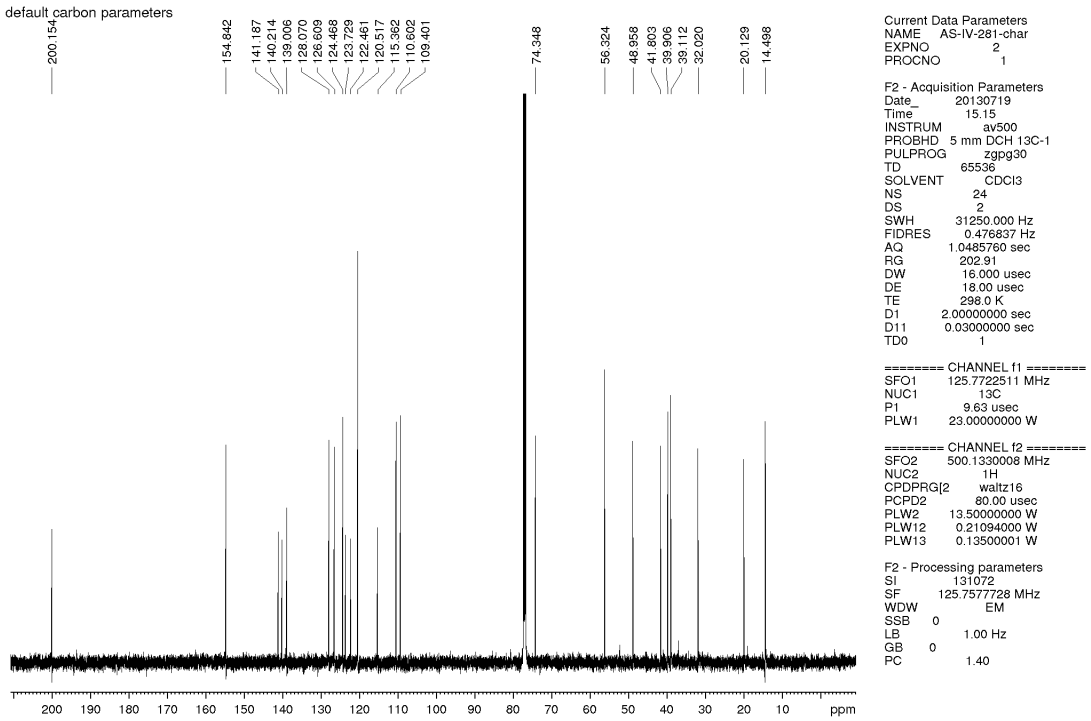



*Figure A4.24* $^{13}$C NMR (125 MHz, $CDCl_3$) of compound **6.13**.

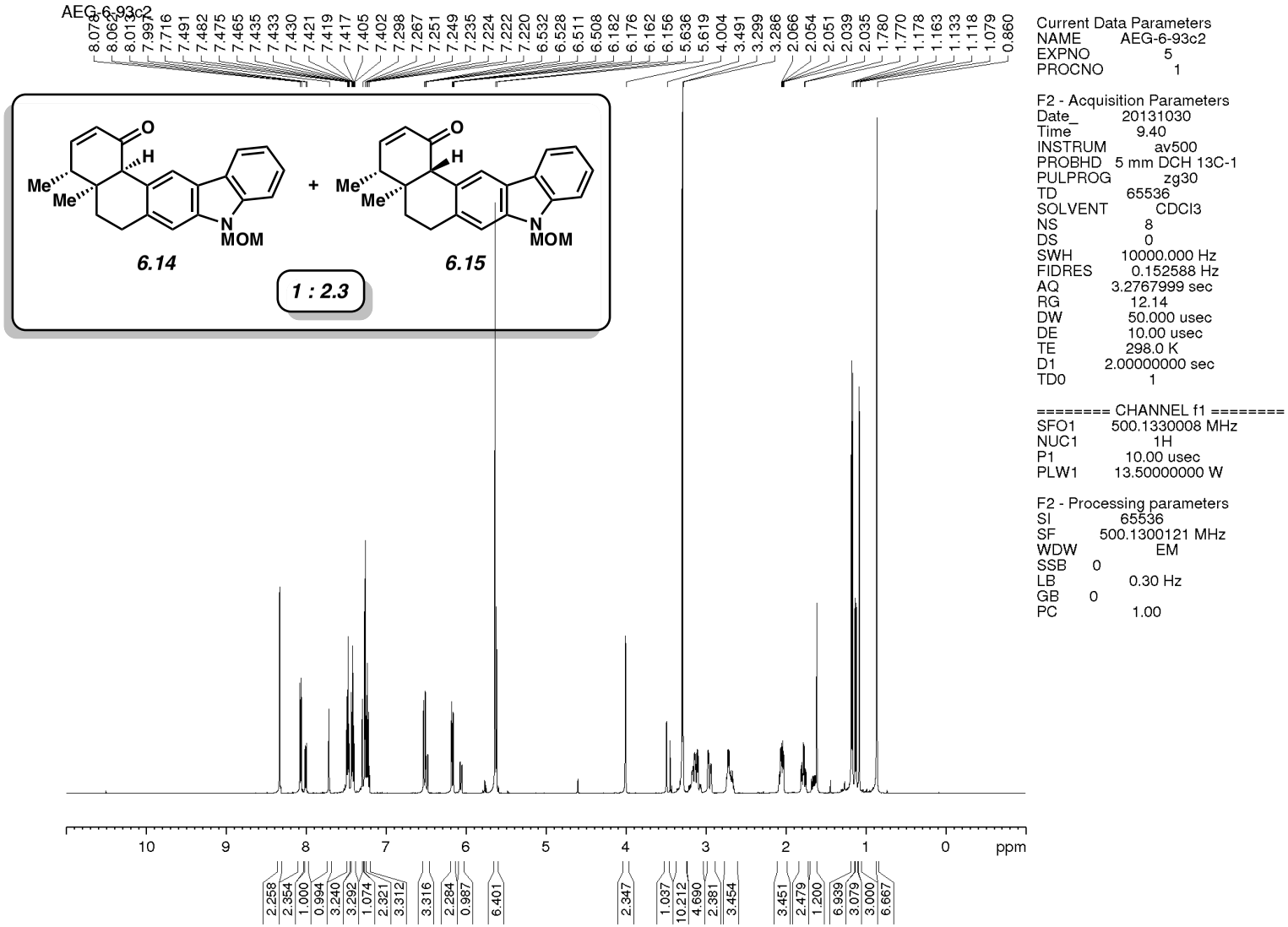



*Figure A4.25* $^{1}$H NMR (500 MHz, $CDCl_3$) of compounds **6.14** amd **6.15**.

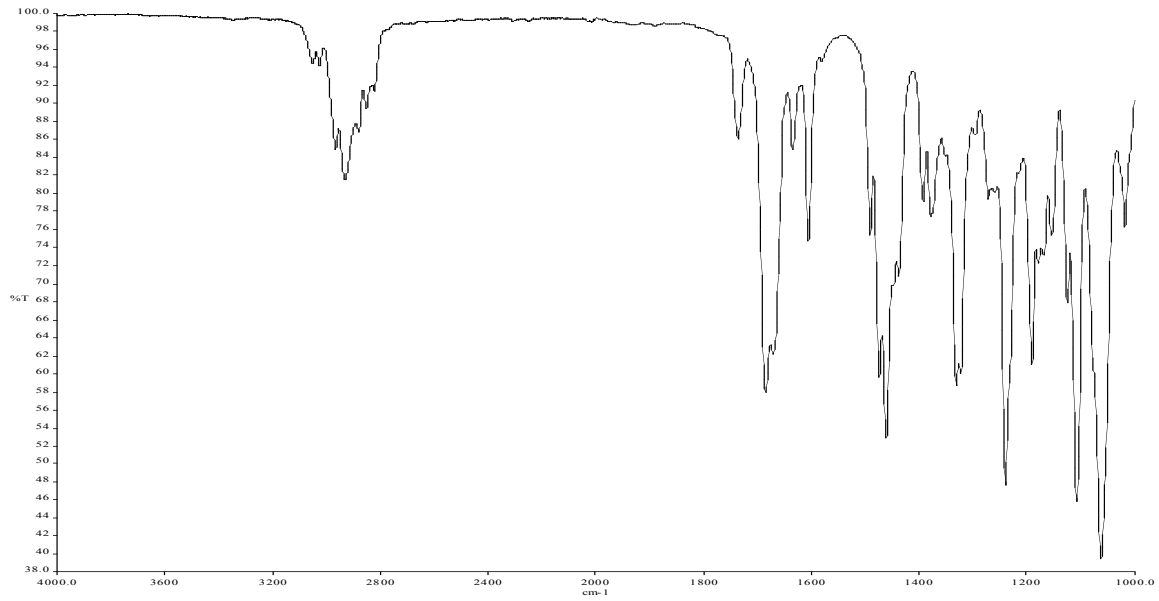



*Figure A4.26* Infrared spectrum of compounds **6.14** and **6.15**.

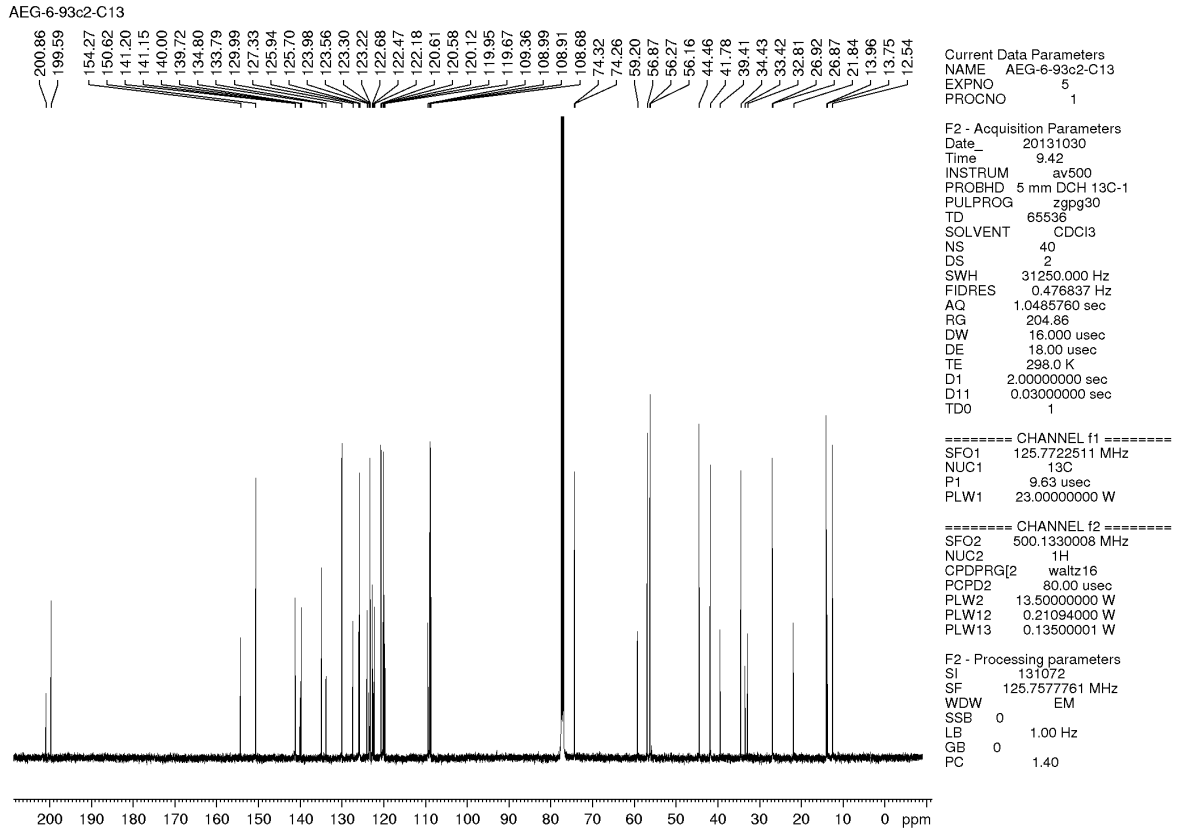



*Figure A4.27* $^{13}$C NMR (125 MHz, $CDCl_3$) of compounds **6.14** and **6.15**.

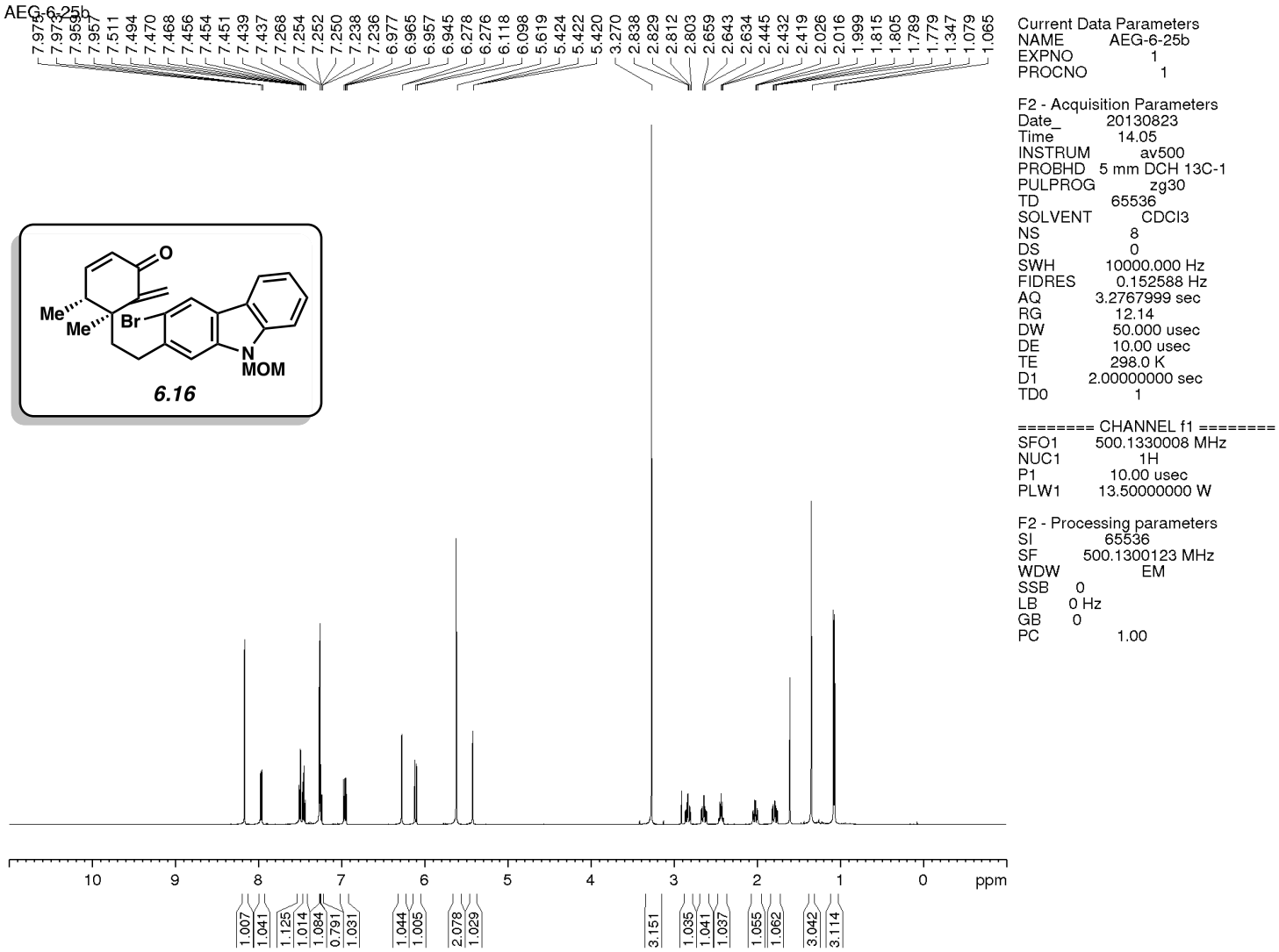



*Figure A4.28* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **6.16**.

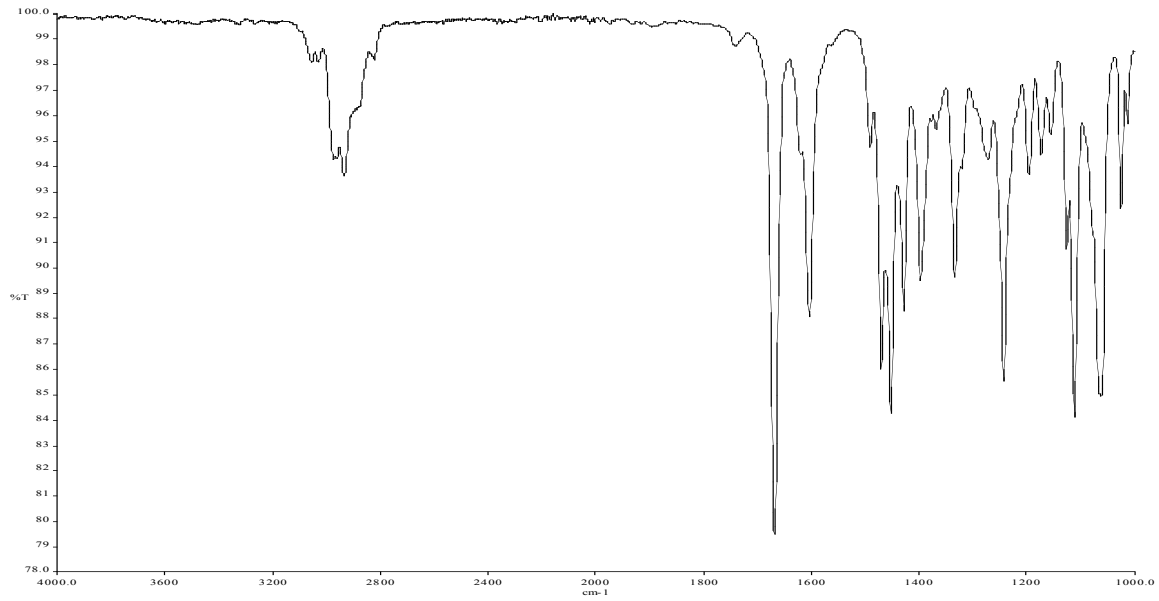



*Figure A4.29* Infrared spectrum of compound **6.16**.

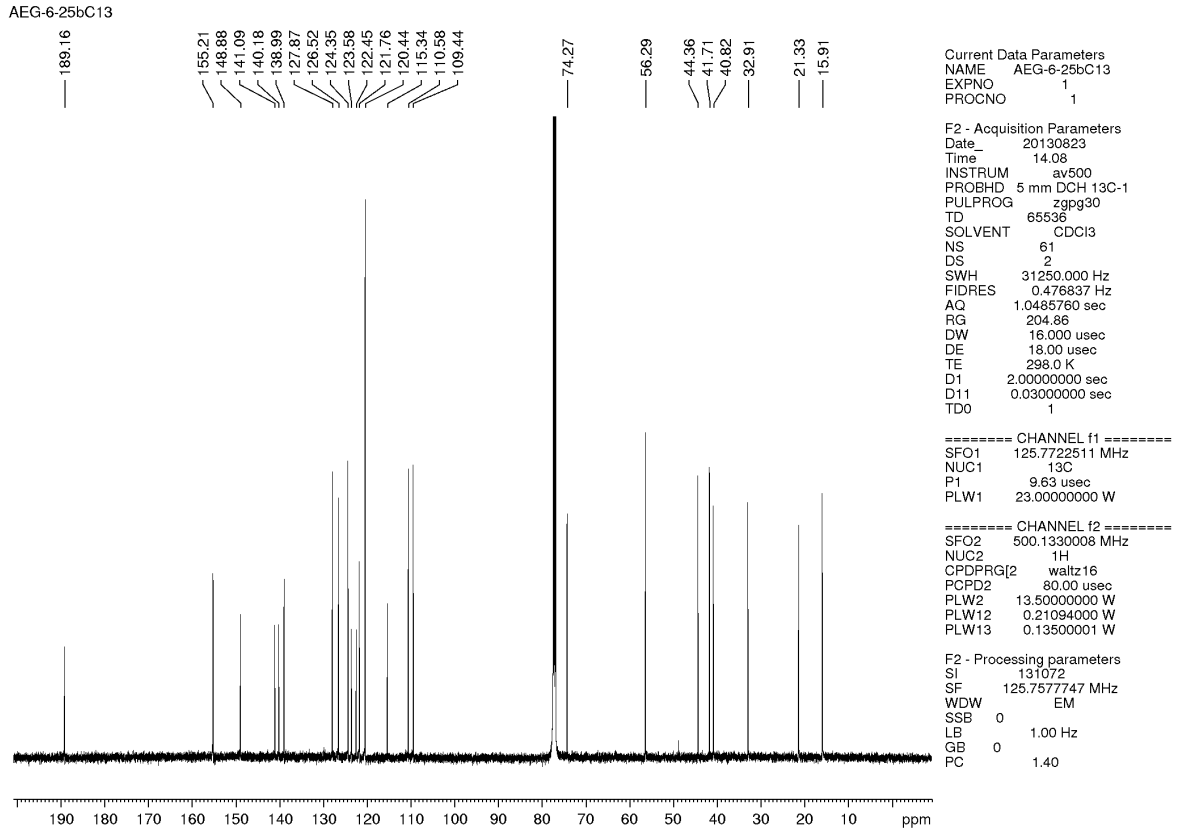



*Figure A4.30* $^{13}$C NMR (125 MHz, $CDCl_3$) of compound **6.16**.

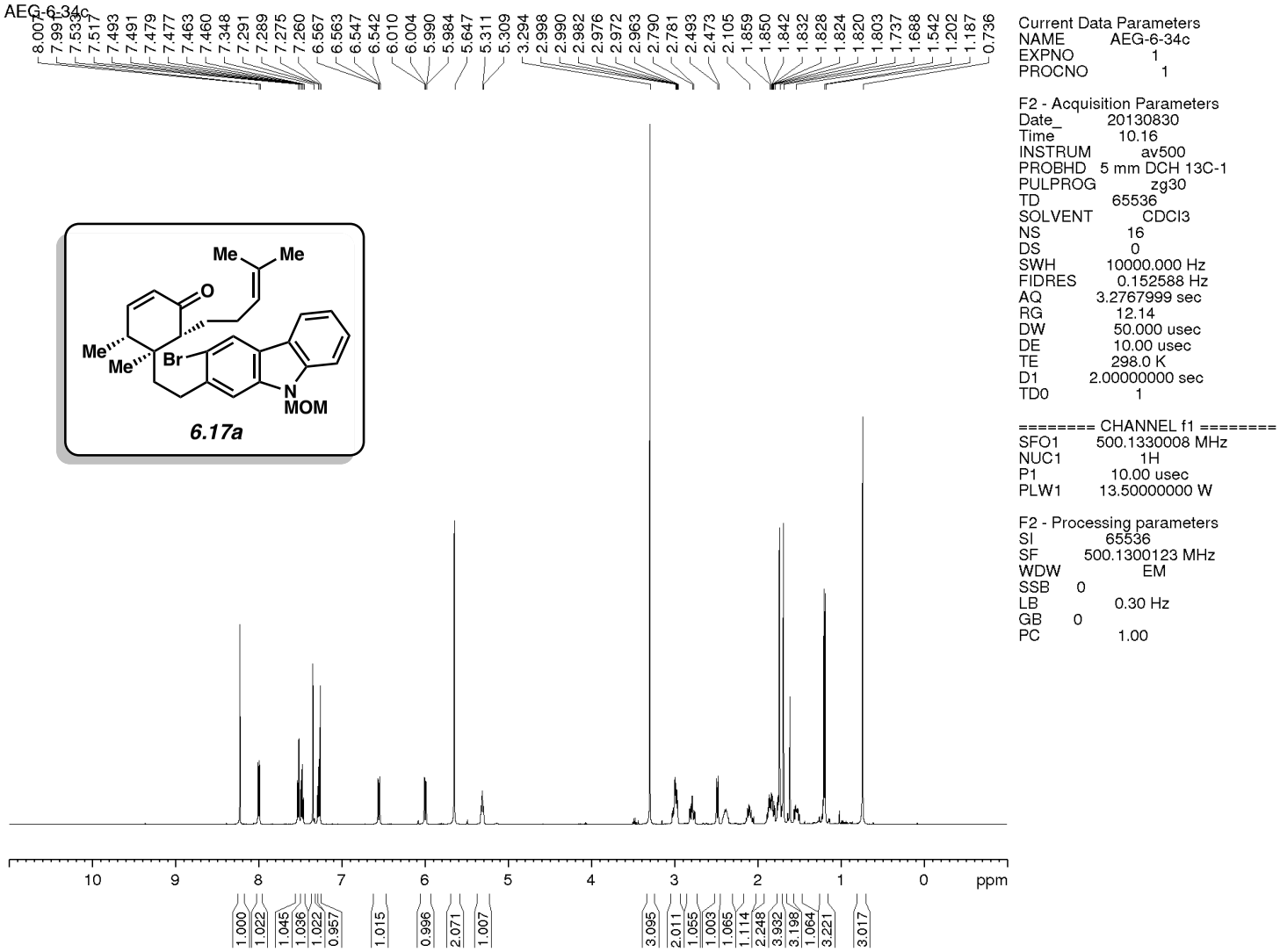



*Figure A4.31* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **6.17a**.

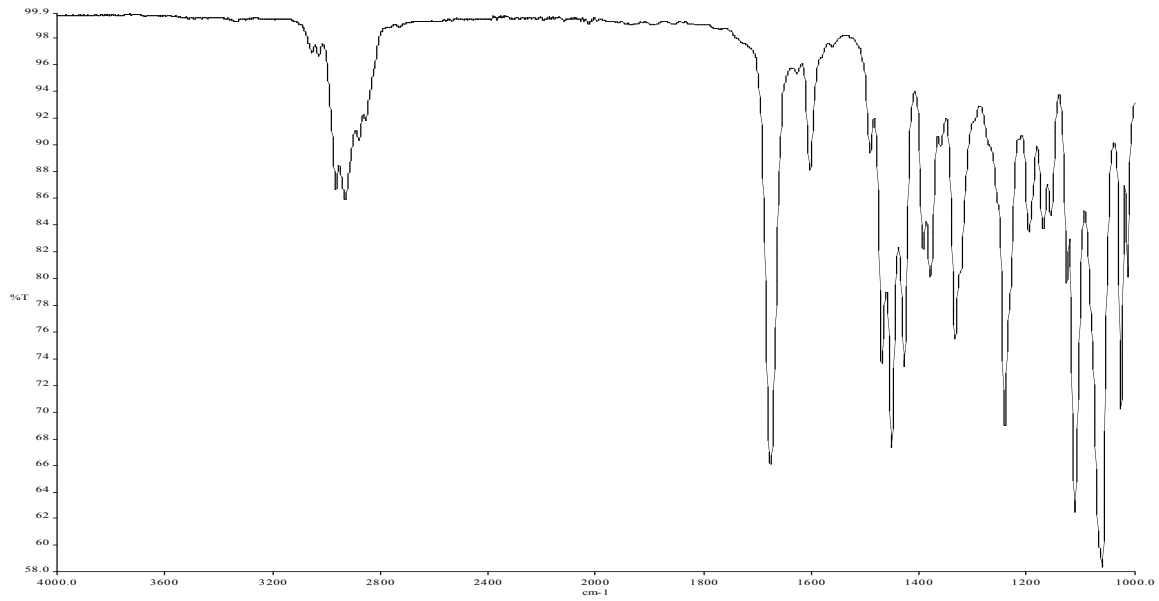



*Figure A4.32* Infrared spectrum of compound **6.17a**.

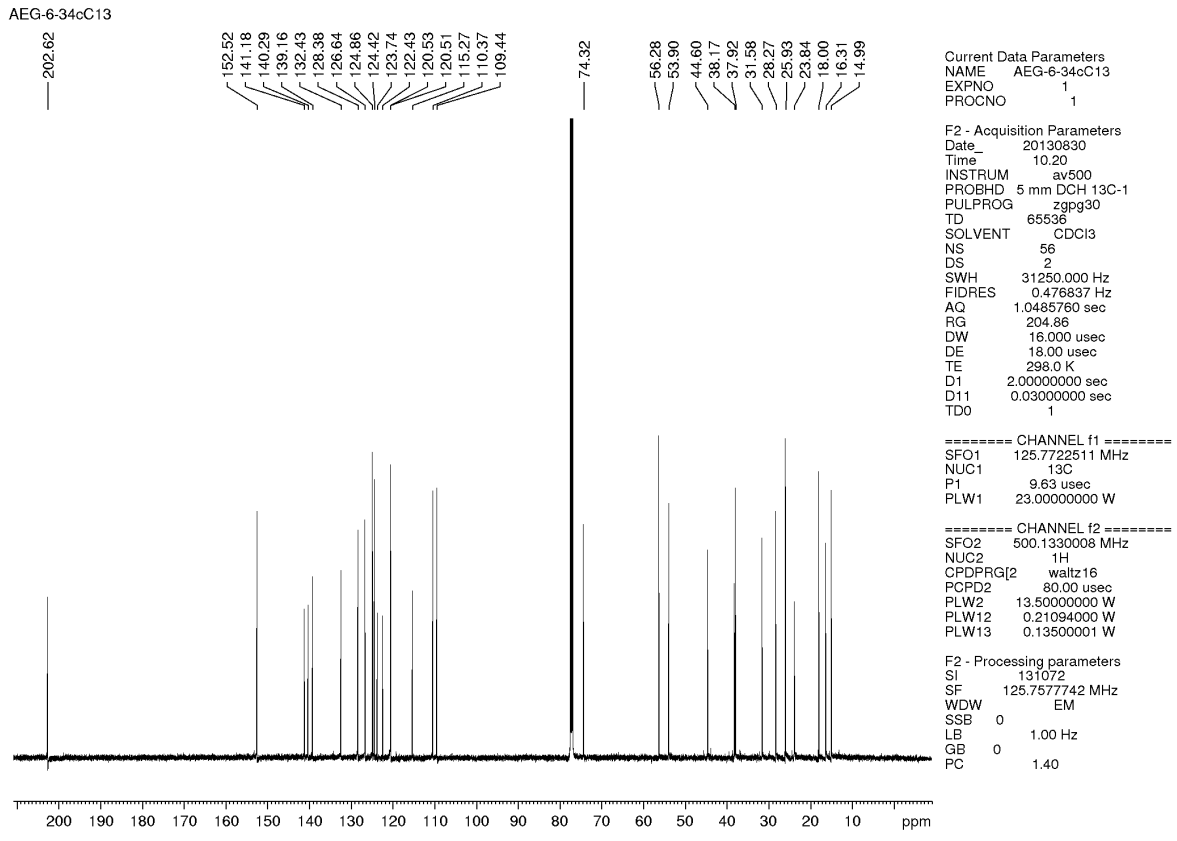



*Figure A4.33* $^{13}$C NMR (125 MHz, $CDCl_3$) of compound **6.17a**.

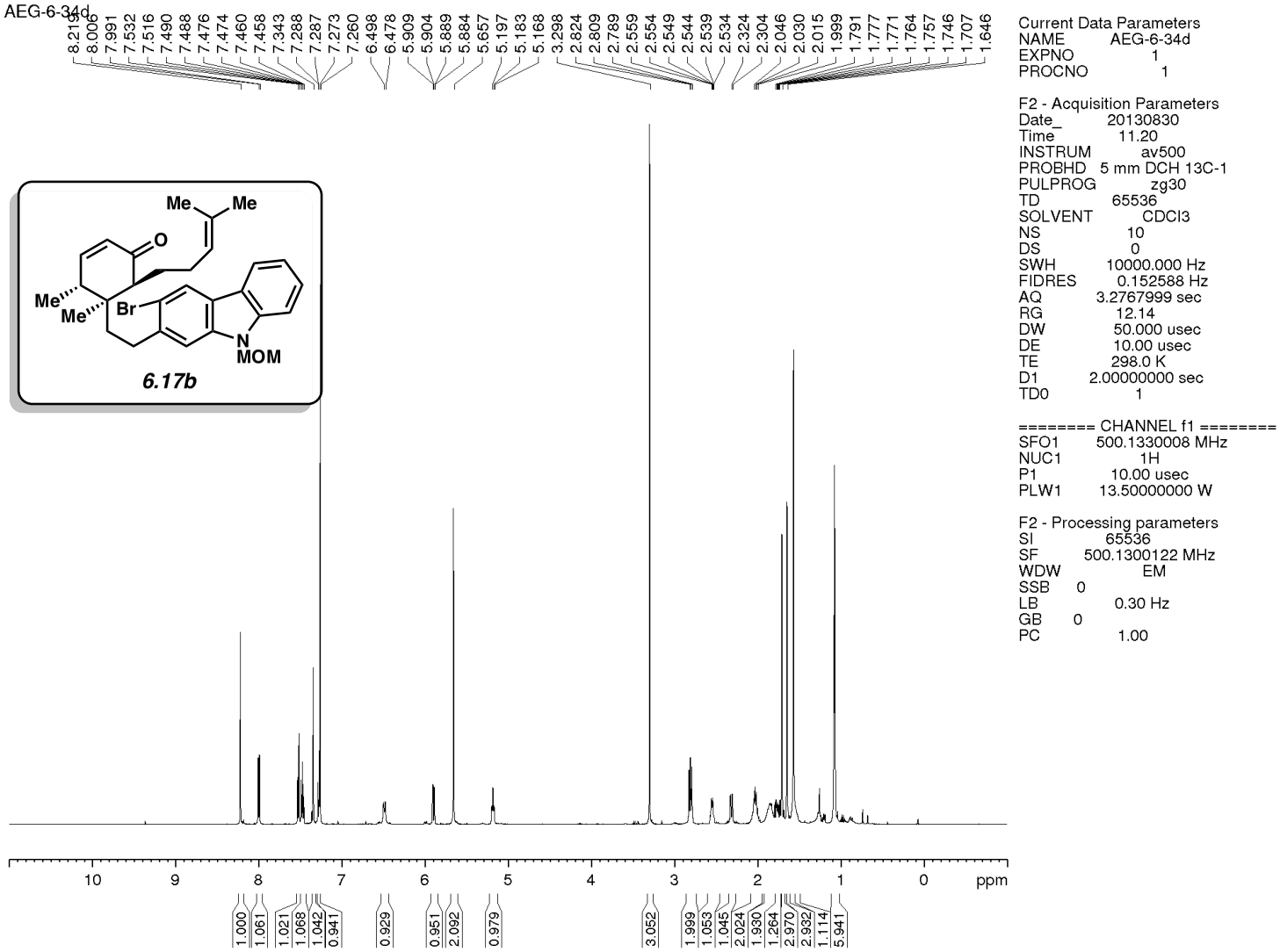



*Figure A4.34* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **6.17b**.

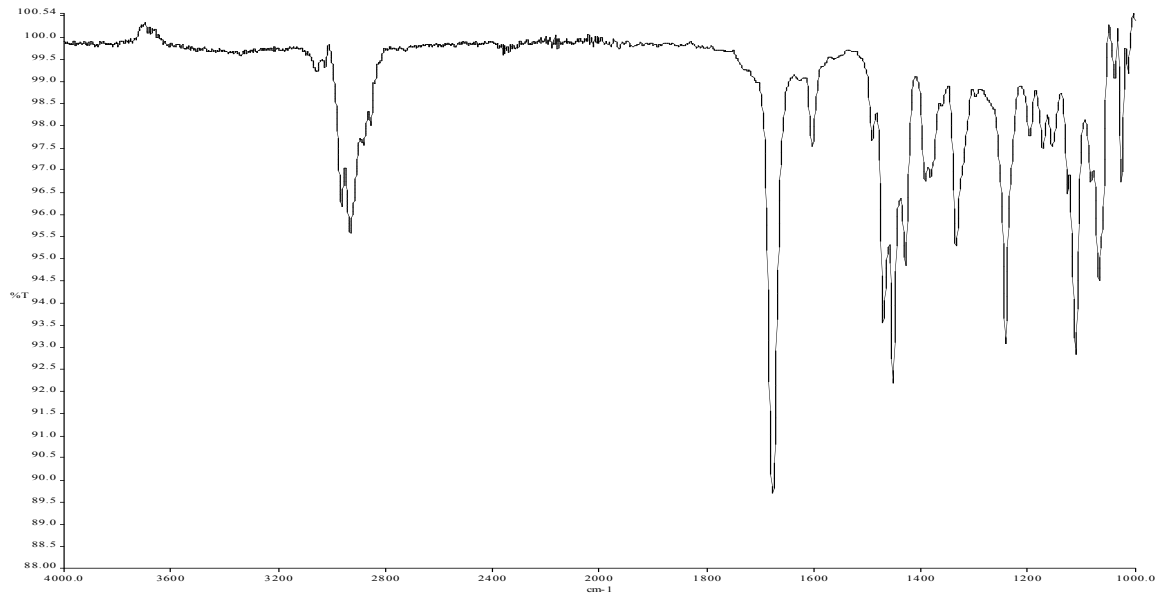



*Figure A4.35* Infrared spectrum of compound **6.17b**.

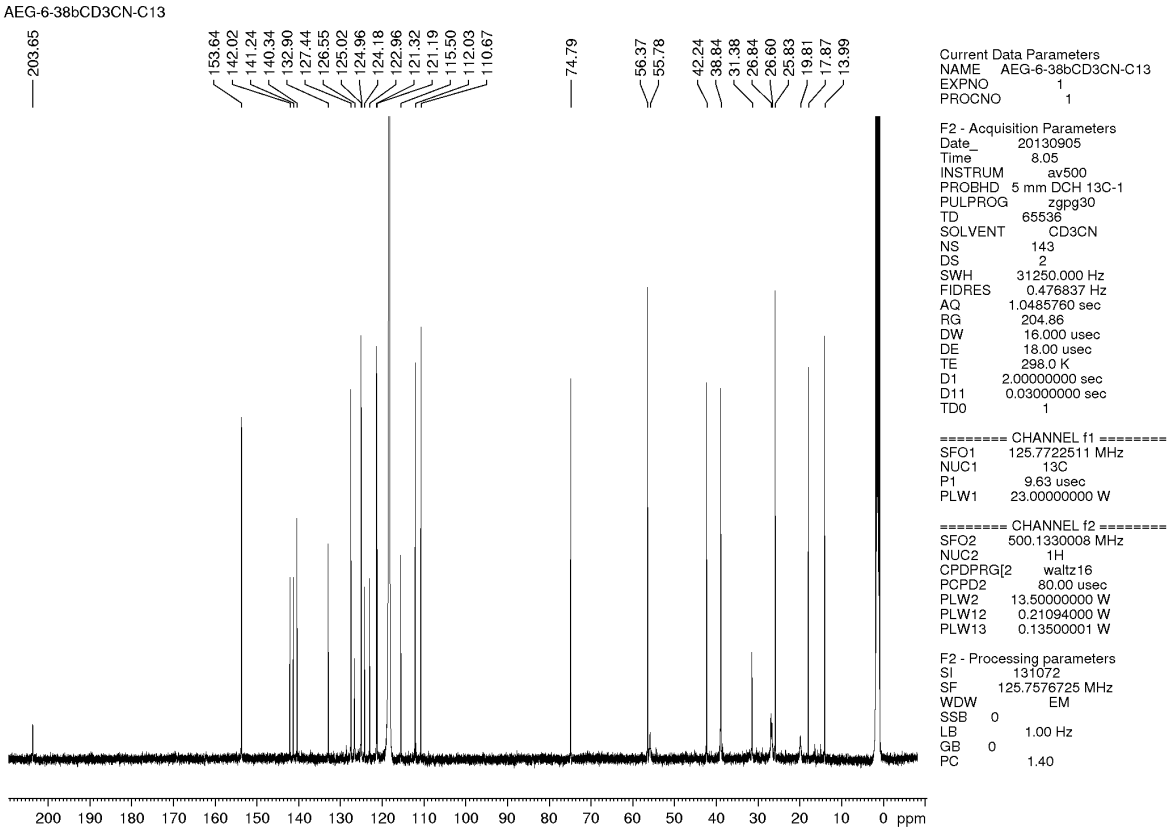



*Figure A4.36* $^{13}$C NMR (125 MHz, $CD_3CN$) of compound **6.17b**.

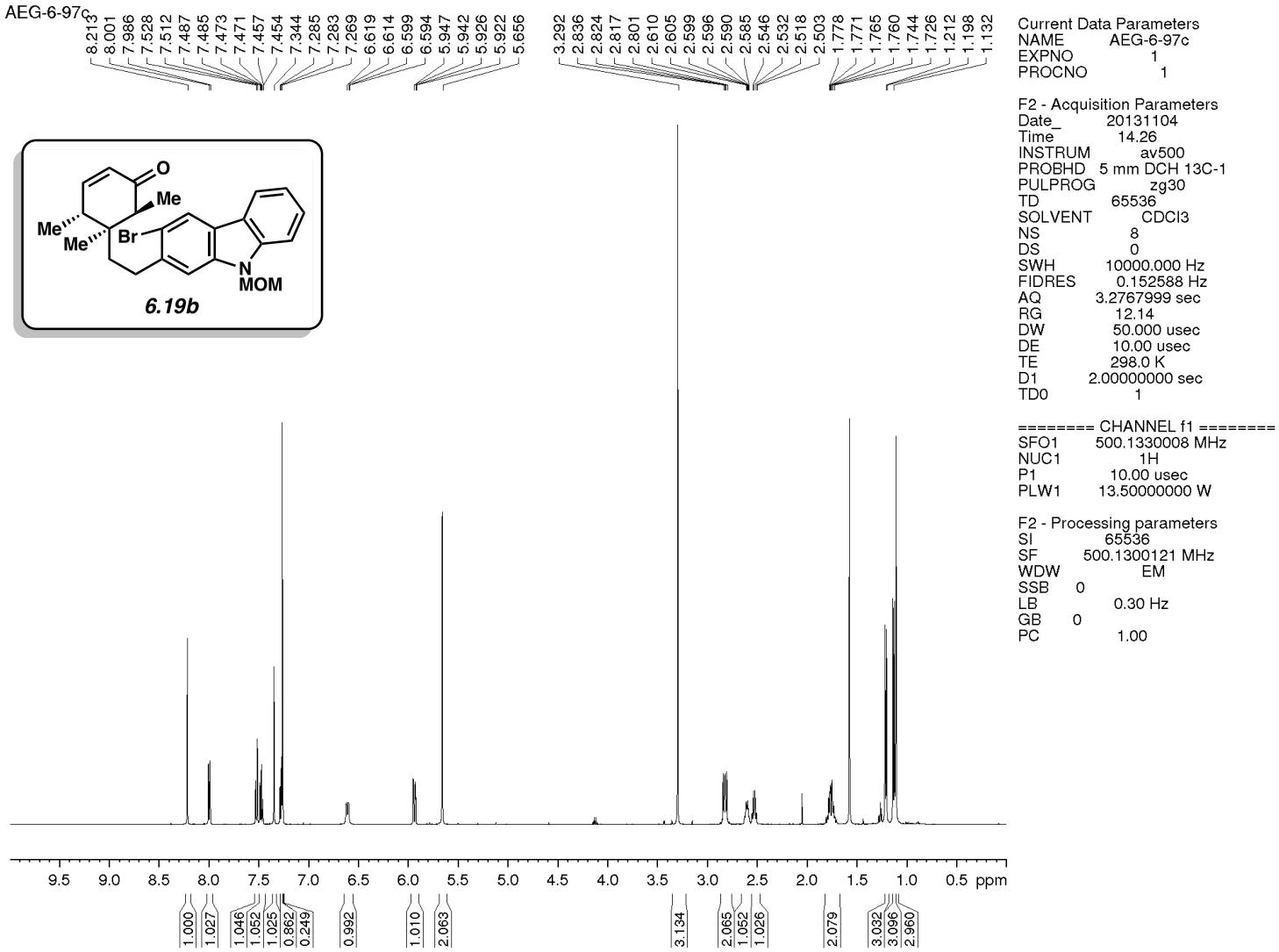



*Figure A4.37* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **6.19b**.

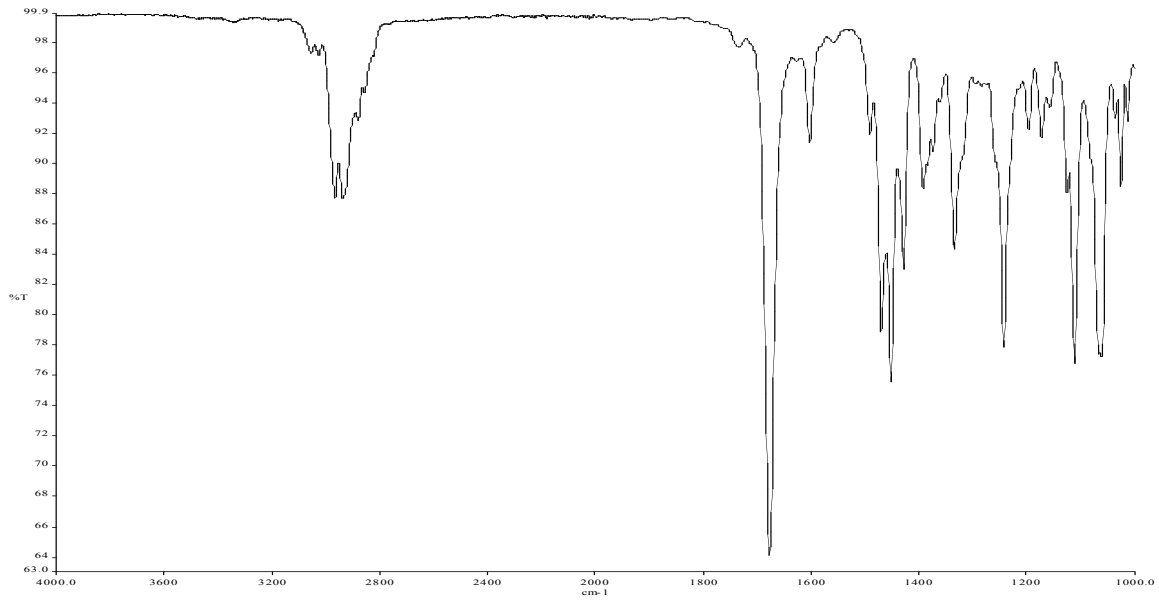



*Figure A4.38* Infrared spectrum of compound **6.19b**.

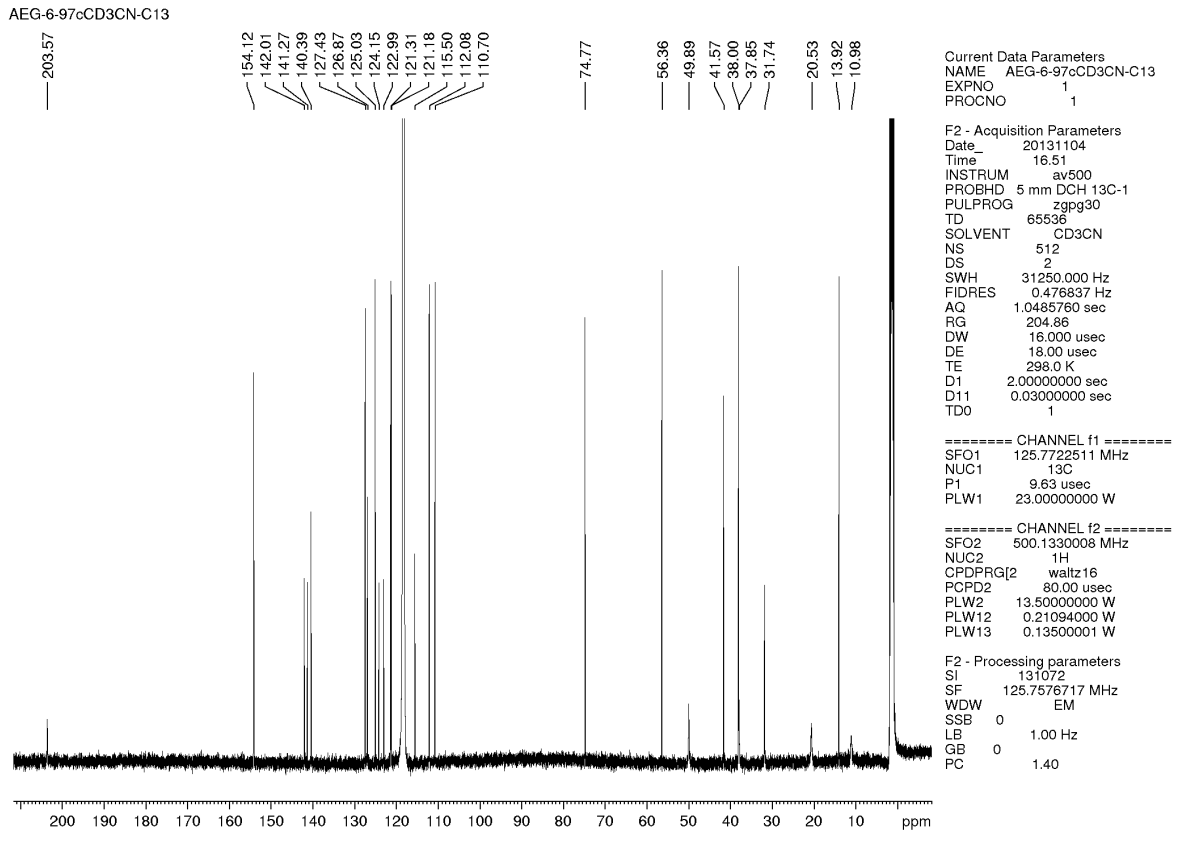



*Figure A4.39* $^{13}$C NMR (125 MHz, $CD_3CN$) of compound **6.19b**.

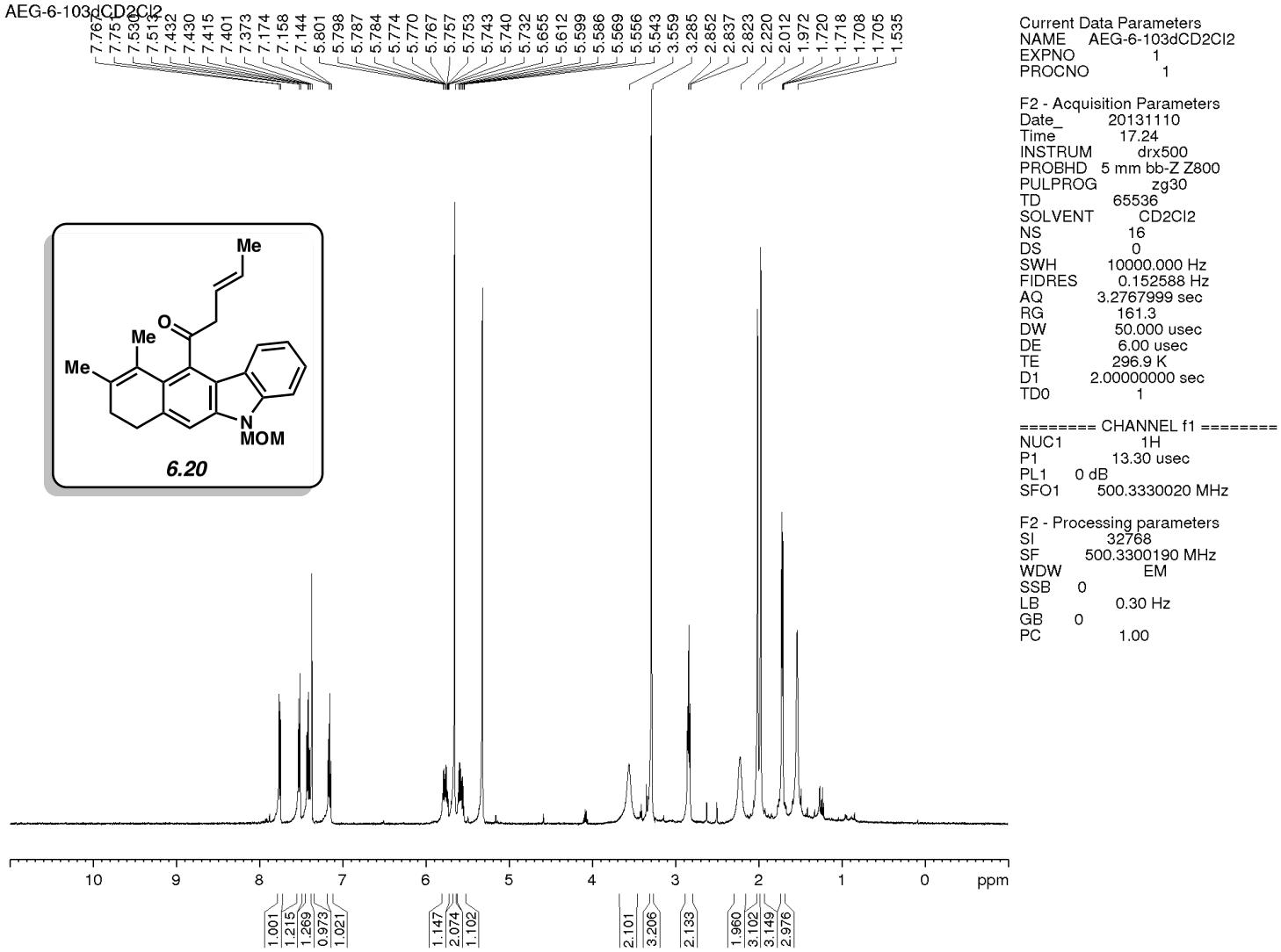



*Figure A4.40* $^1$H NMR (500 MHz, $CD_2Cl_2$) of compound **6.20**.

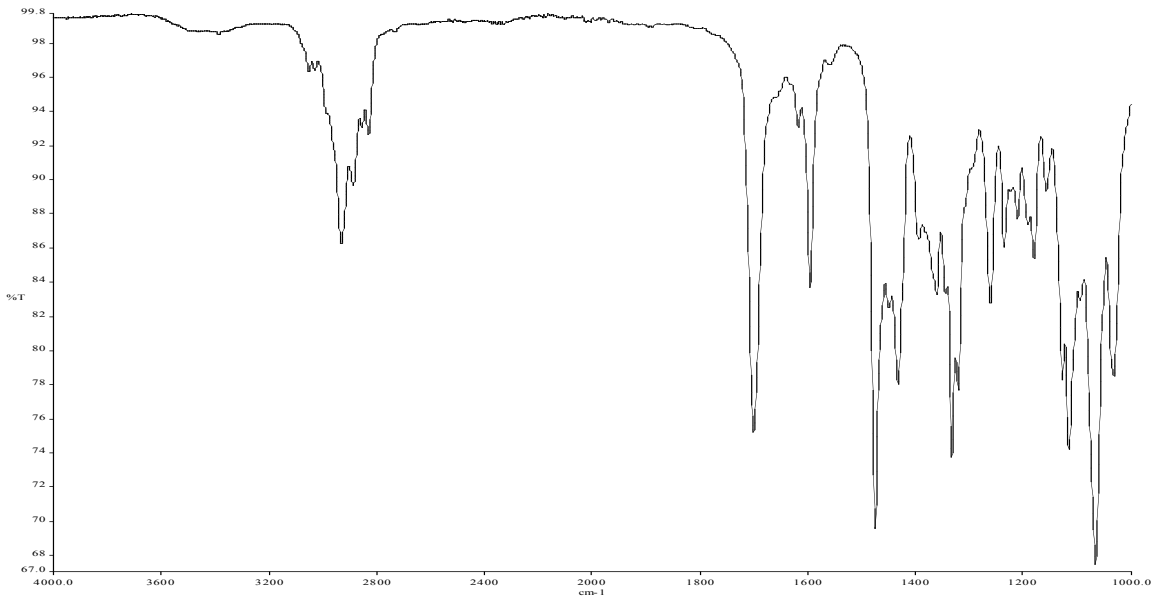



*Figure A4.41* Infrared spectrum of compound **6.20**.

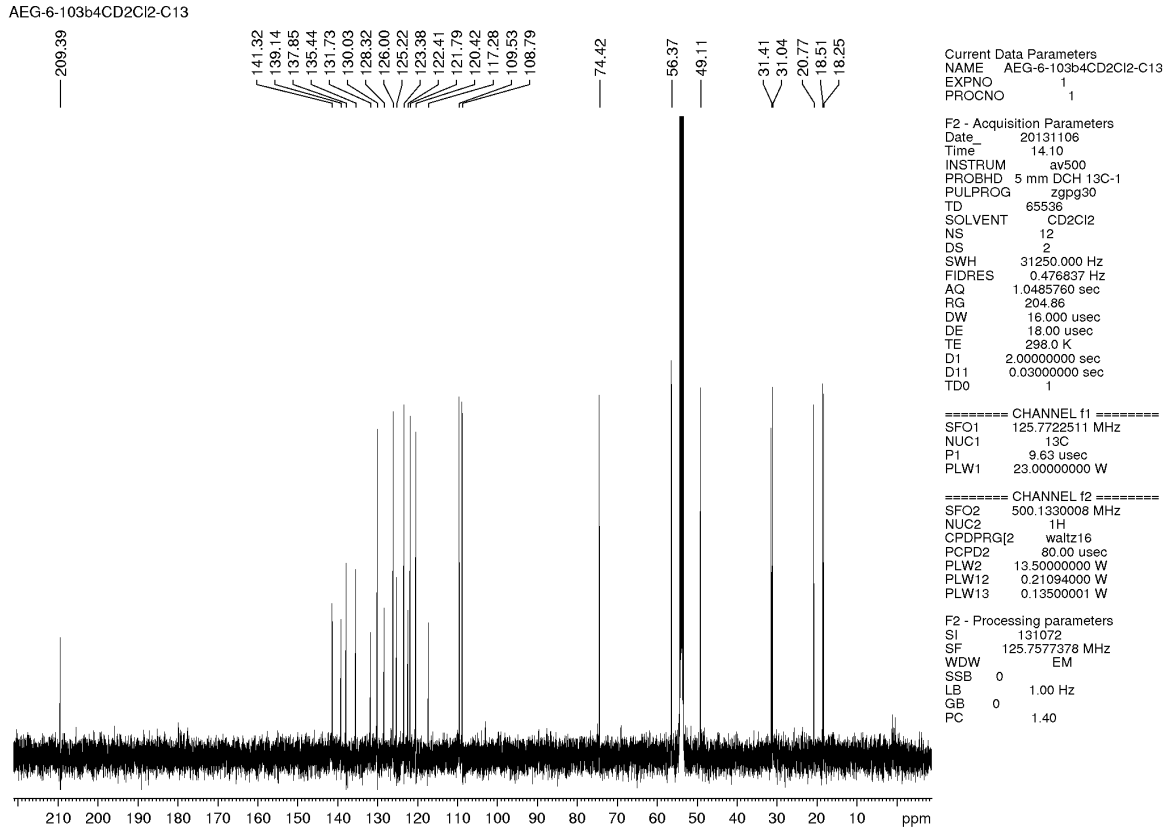



*Figure A4.42* $^{13}$C NMR (125 MHz, $CD_2Cl_2$) of compound **6.20**.

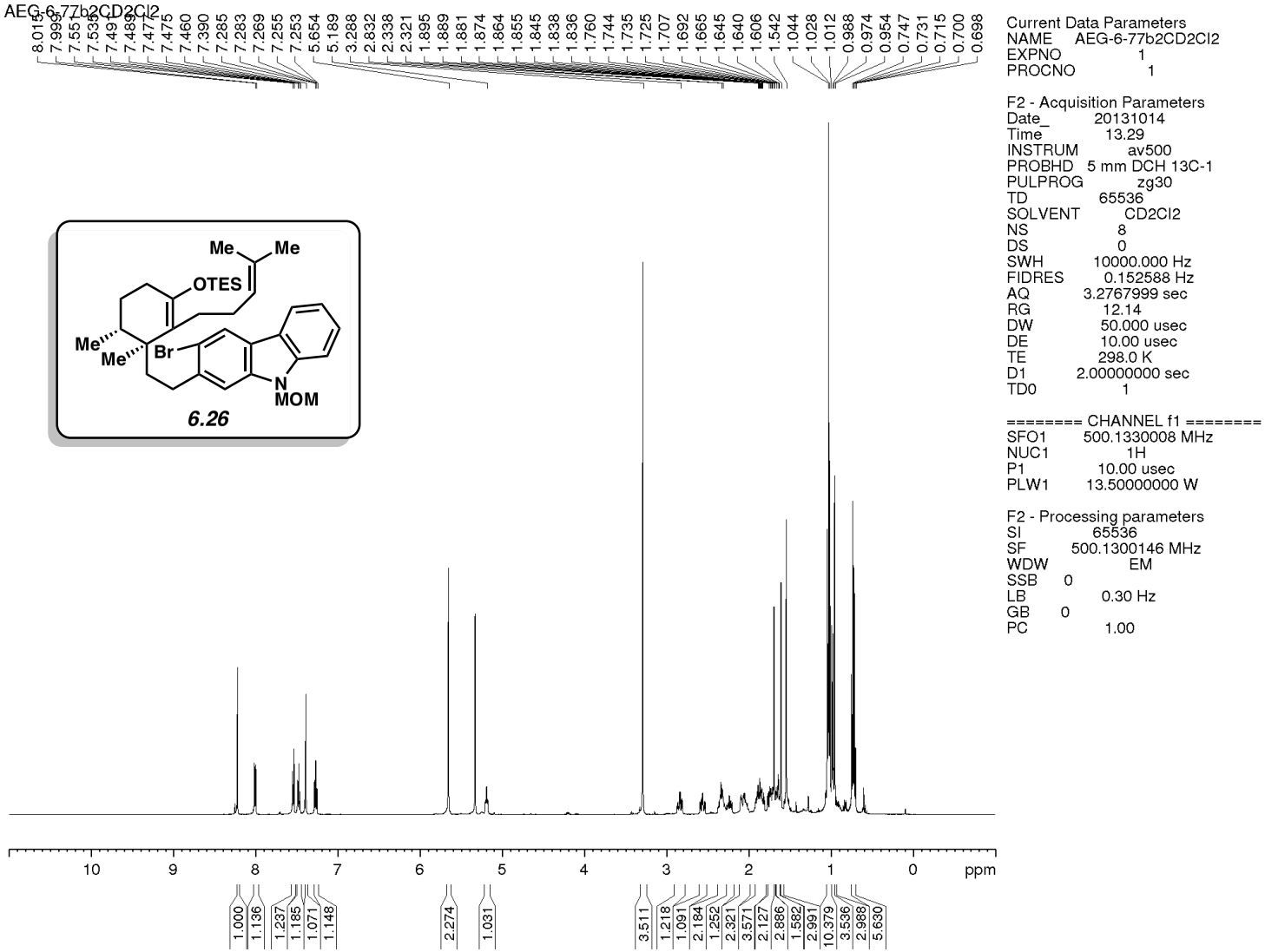



*Figure A4.43* $^1$H NMR (500 MHz, $CD_2Cl_2$) of compound **6.26**.

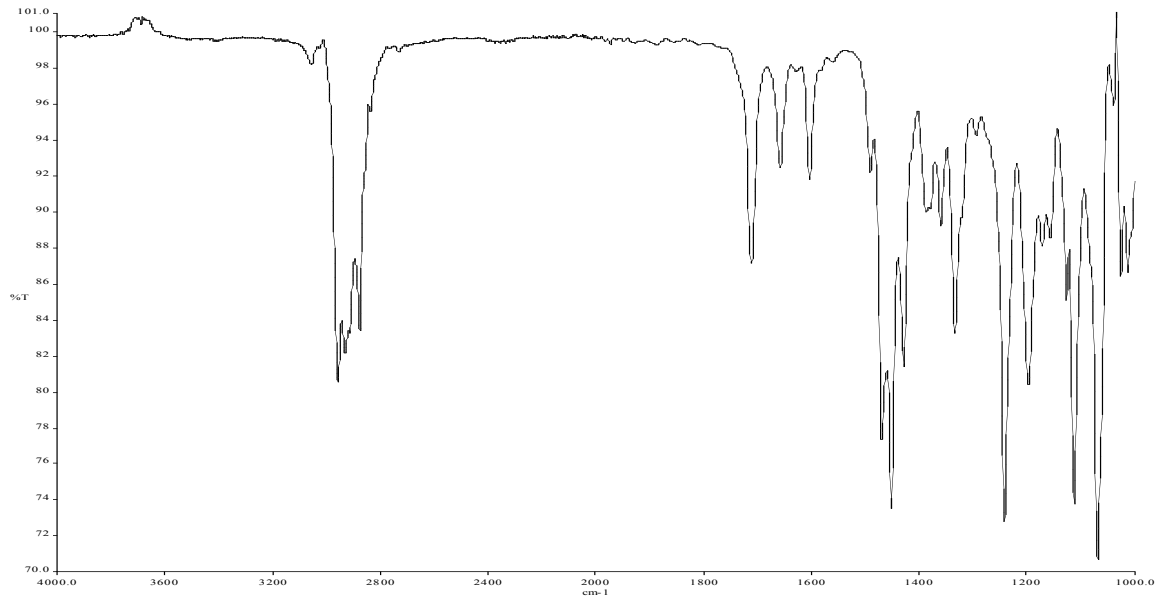



*Figure A4.44* Infrared spectrum of compound **6.26**.

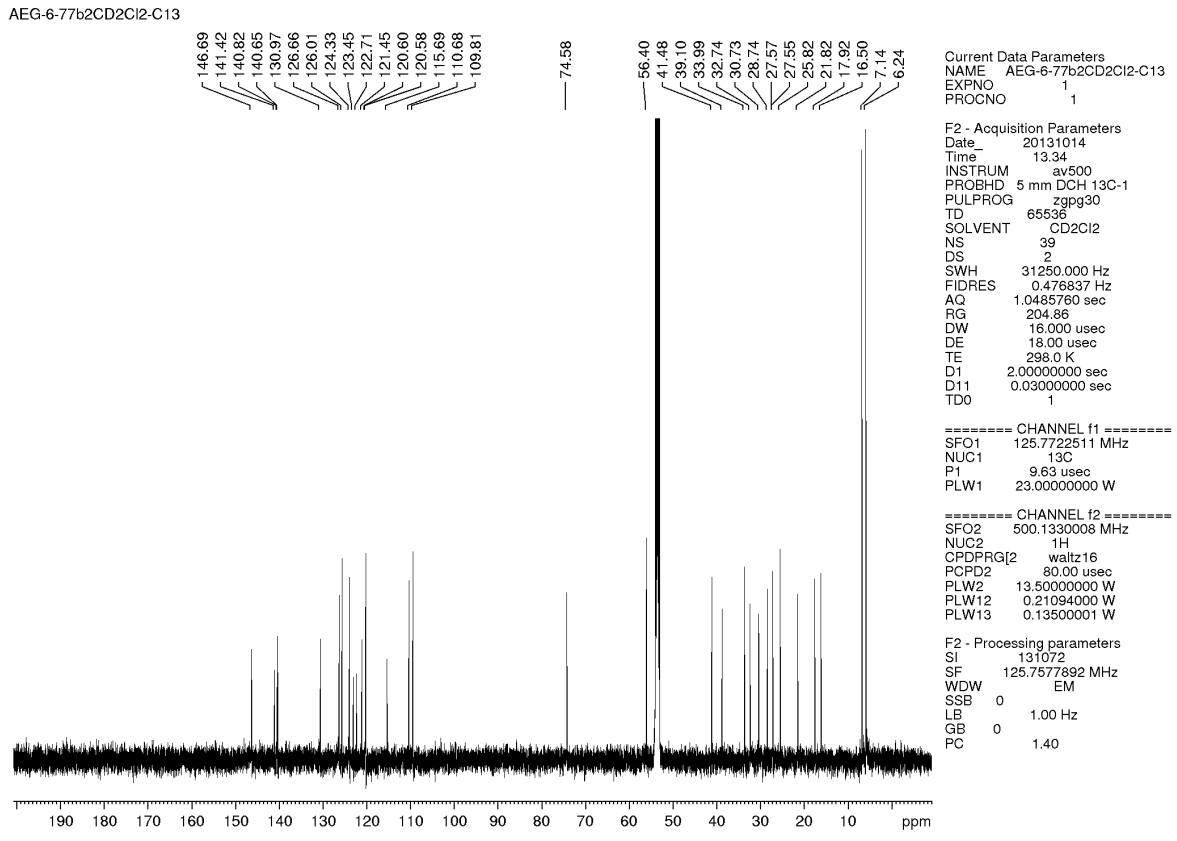



*Figure A4.45* $^{13}$C NMR (125 MHz, $CD_2Cl_2$) of compound **6.26**.

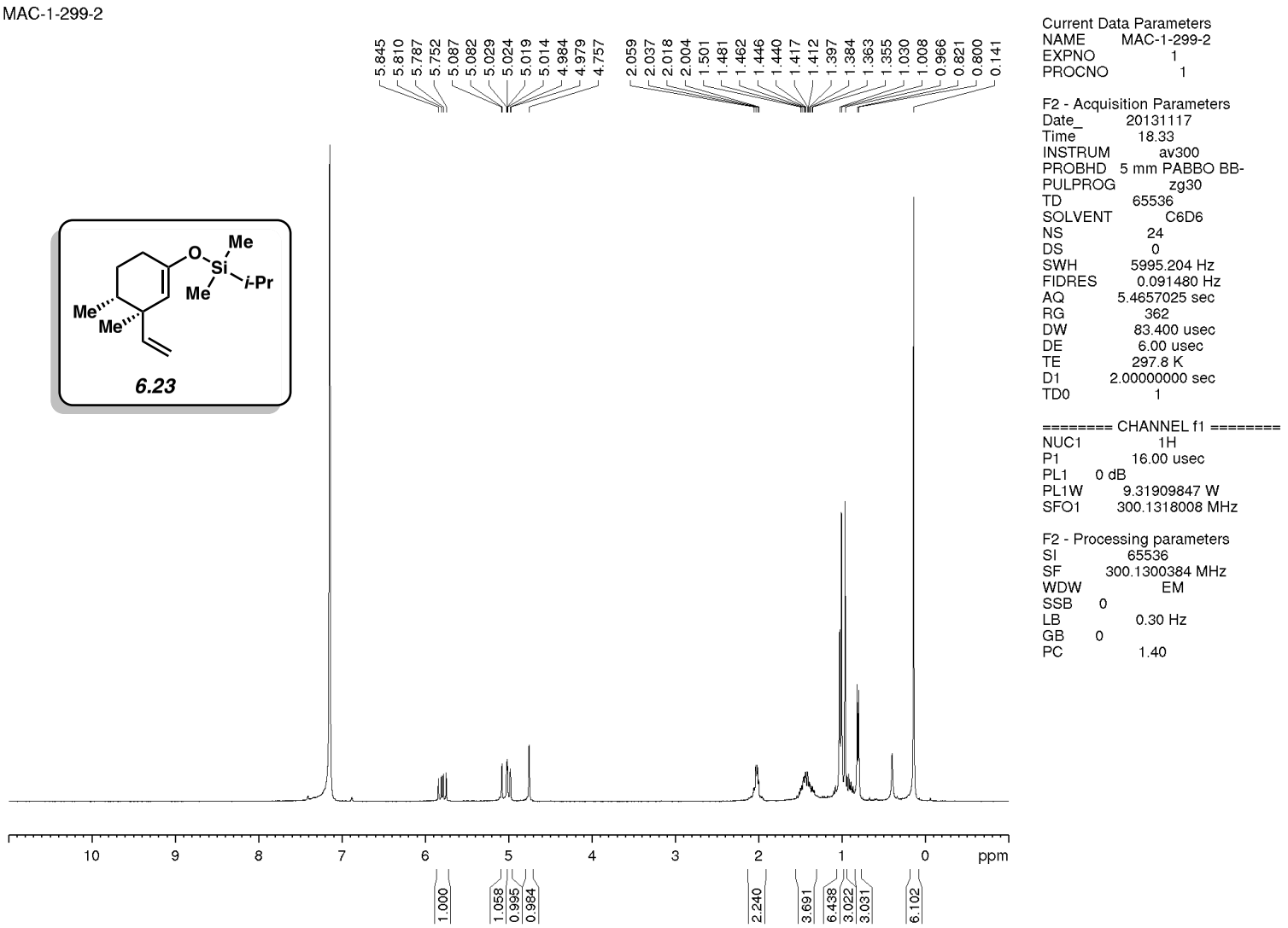



*Figure A4.46* $^1$H NMR (300 MHz, $C_6D_6$) of compound **6.23**.

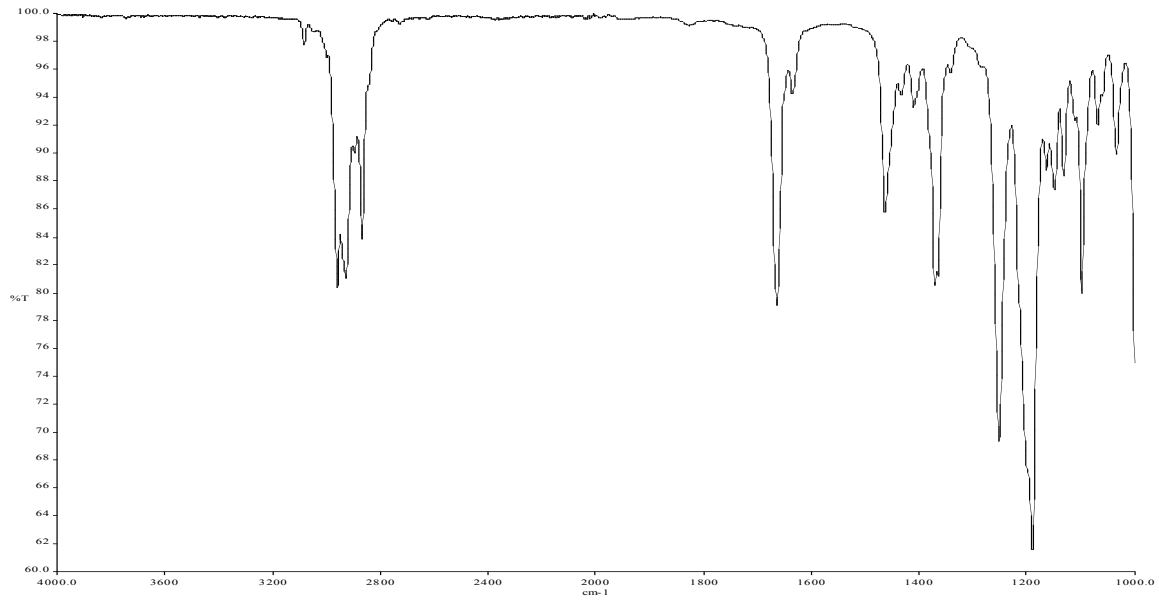



*Figure A4.47* Infrared spectrum of compound **6.23**.

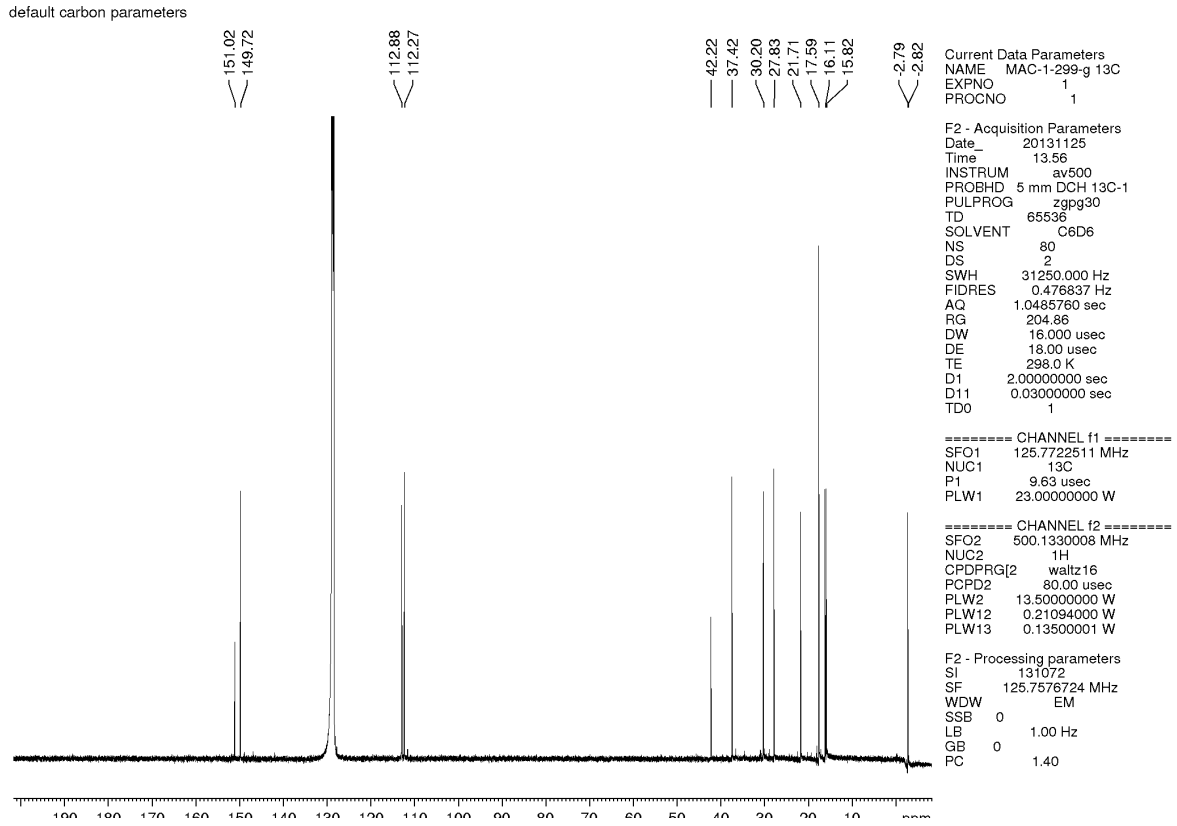



*Figure A4.48* $^{13}$C NMR (125 MHz, $C_6D_6$) of compound **6.23**.

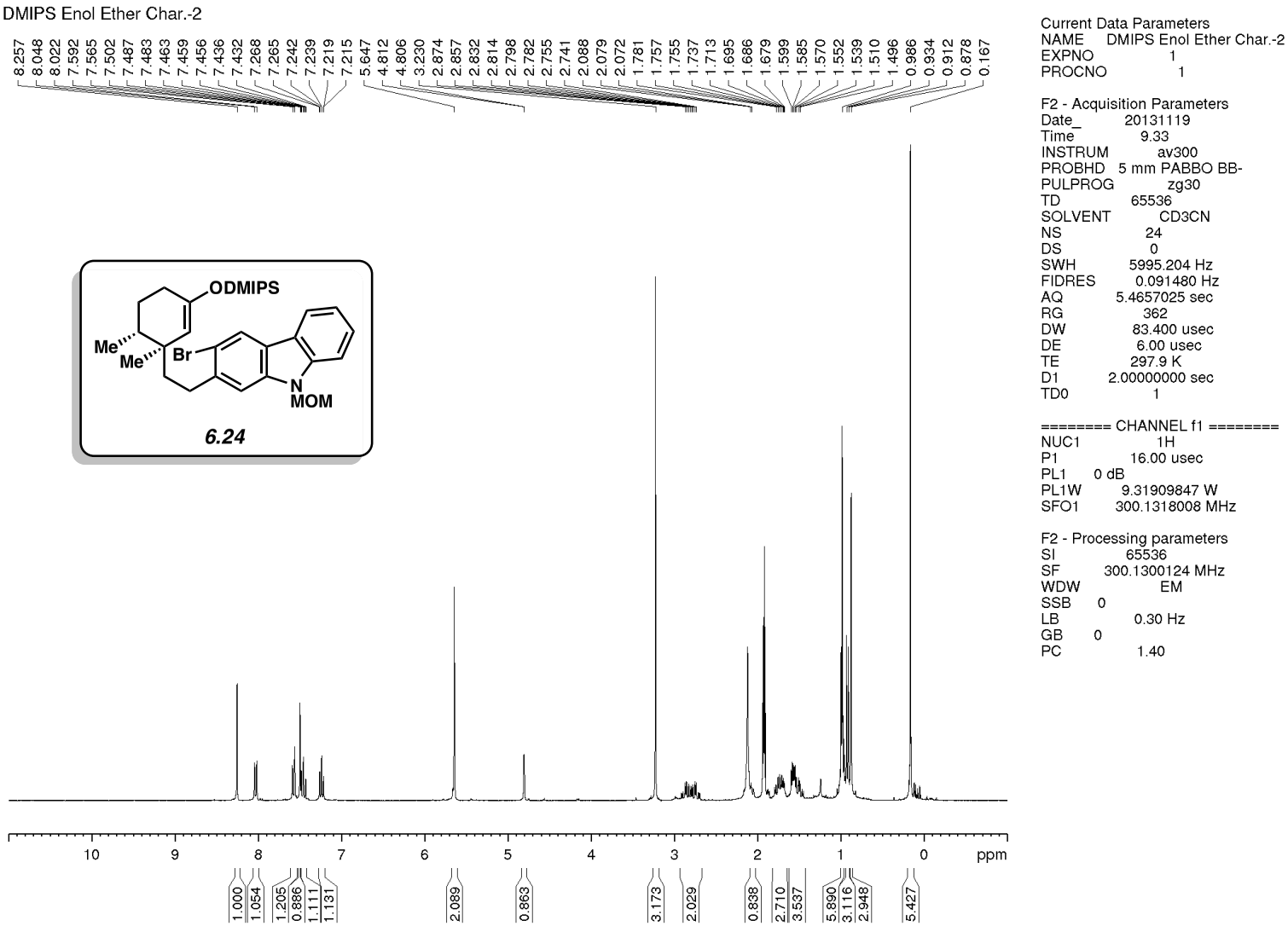



*Figure A4.49* $^{1}$H NMR (300 MHz, $CD_3CN$) of compound **6.24**.

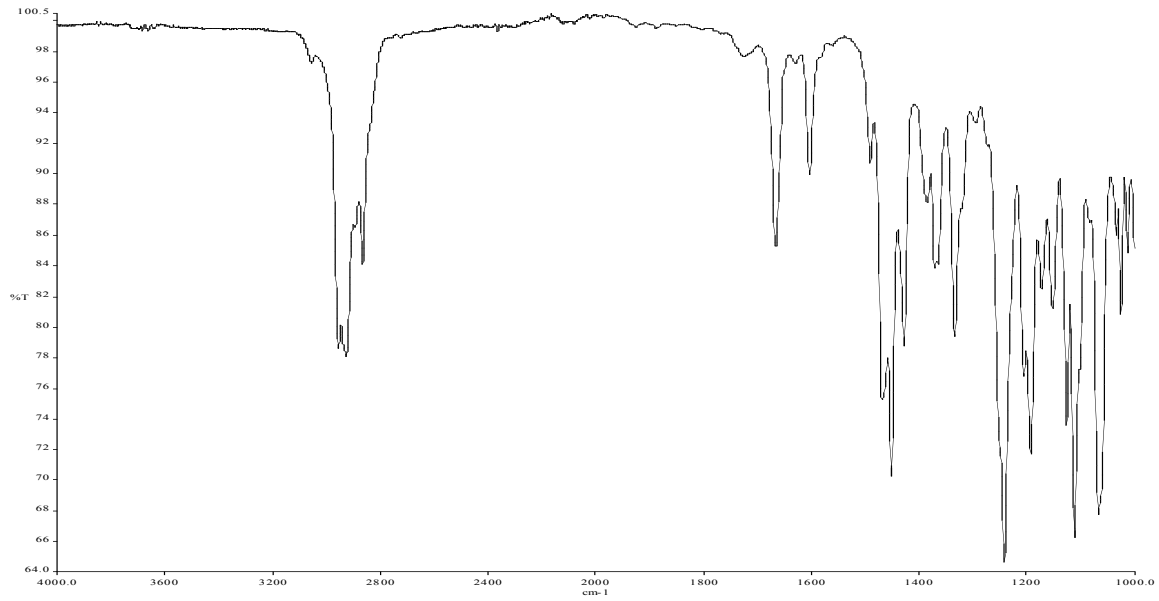



*Figure A4.50* Infrared spectrum of compound **6.24**.

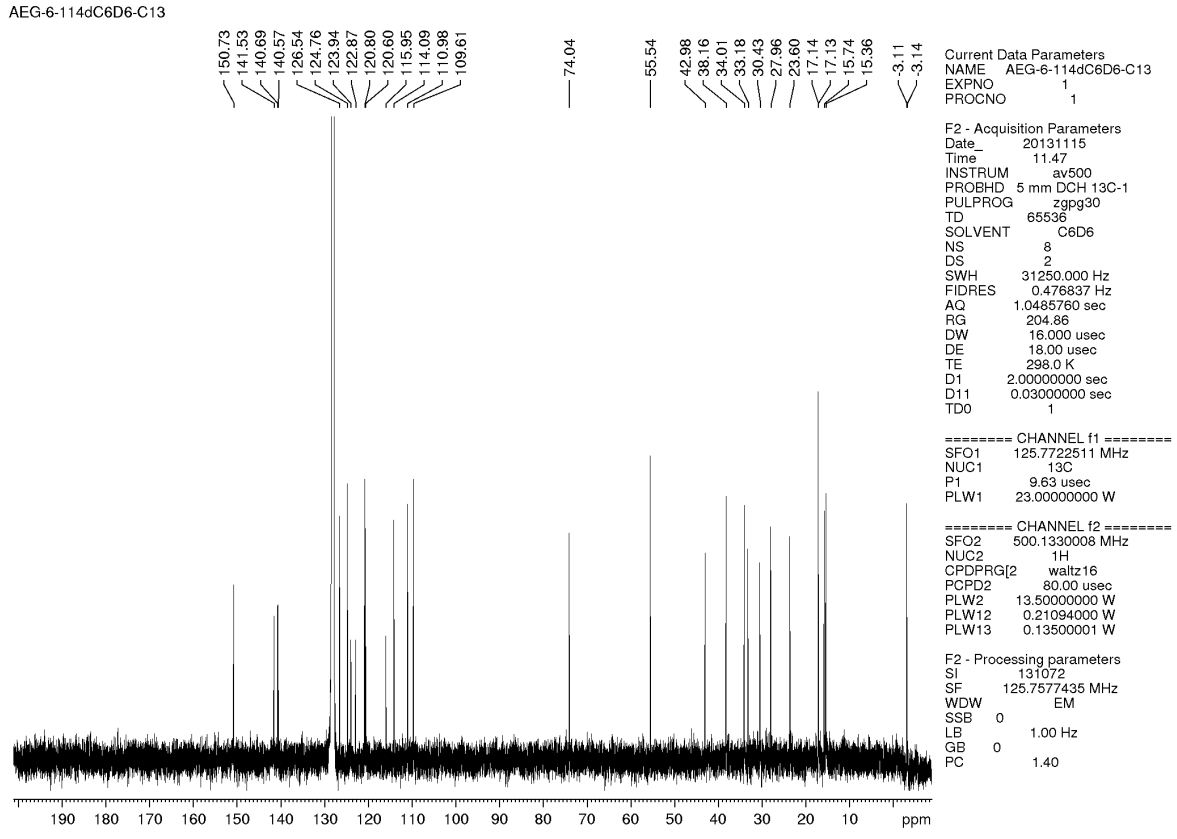



*Figure A4.51* $^{13}$C NMR (125 MHz, $C_6D_6$) of compound **6.24**.

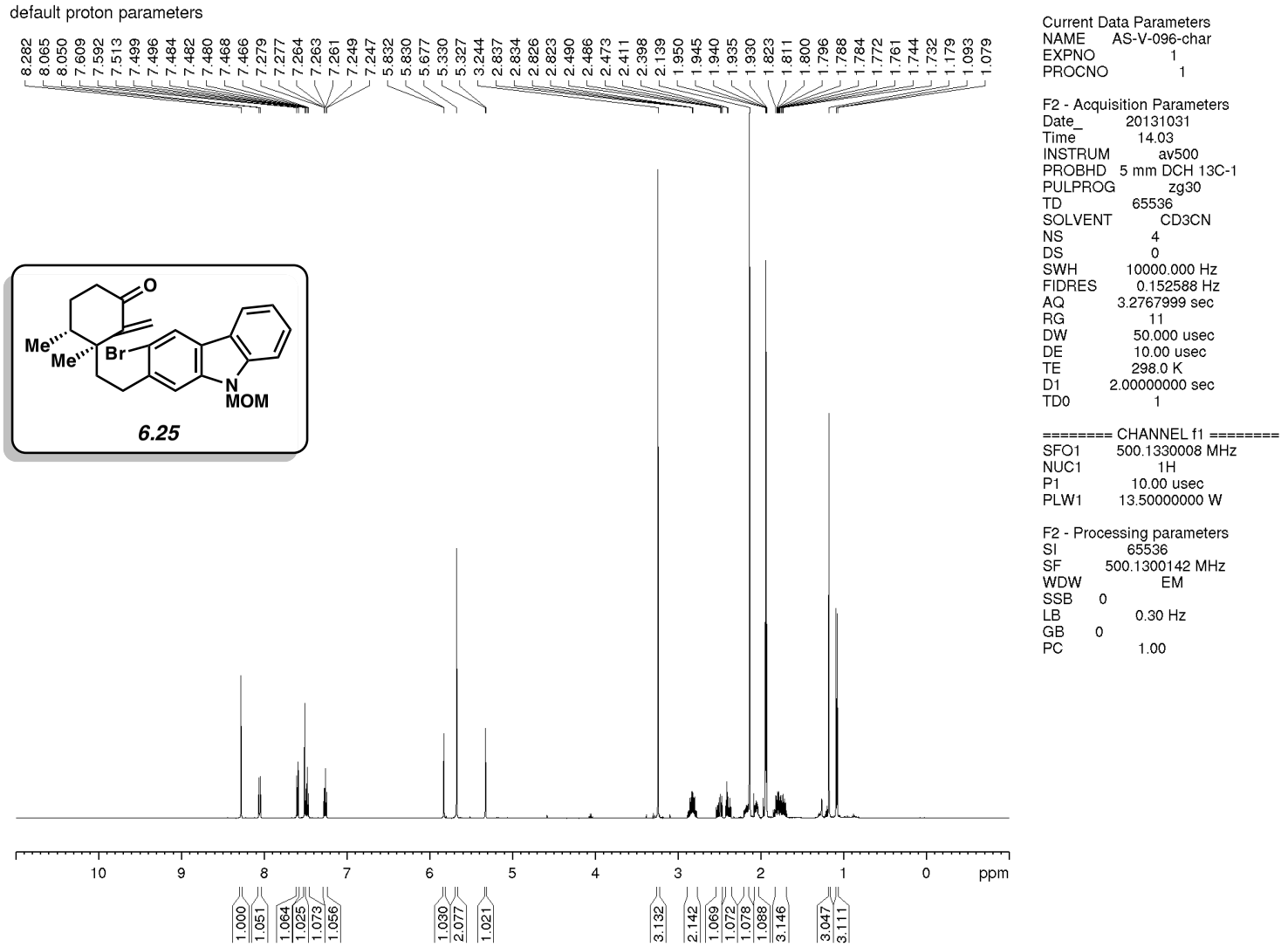



*Figure A4.52* $^{1}$H NMR (500 MHz, $CD_3CN$) of compound **6.25**.

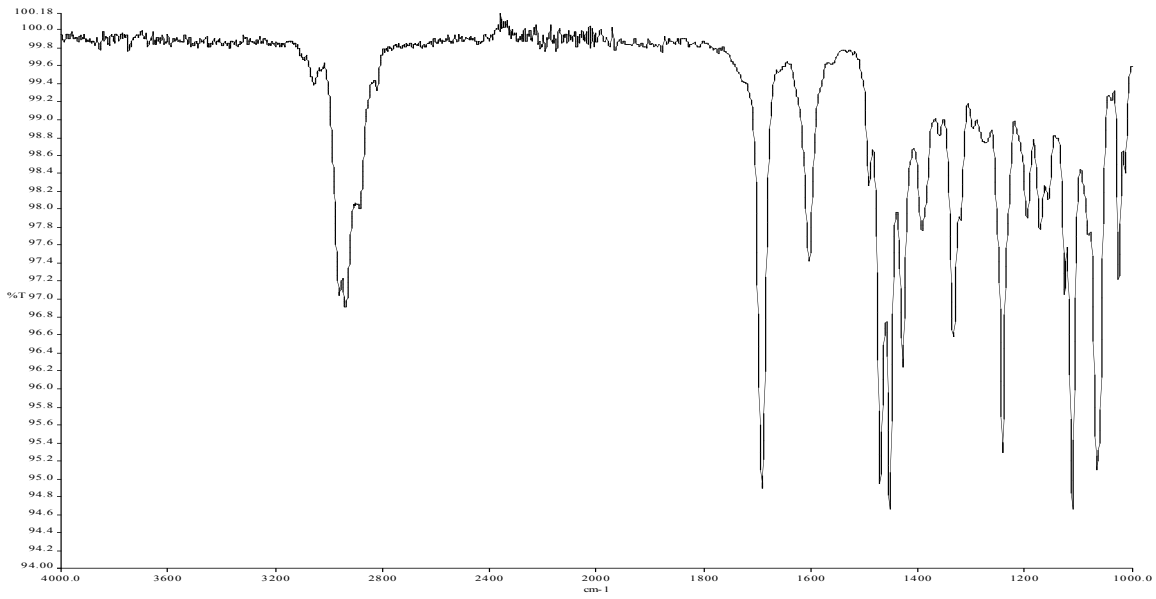



*Figure A4.53* Infrared spectrum of compound **6.25**.

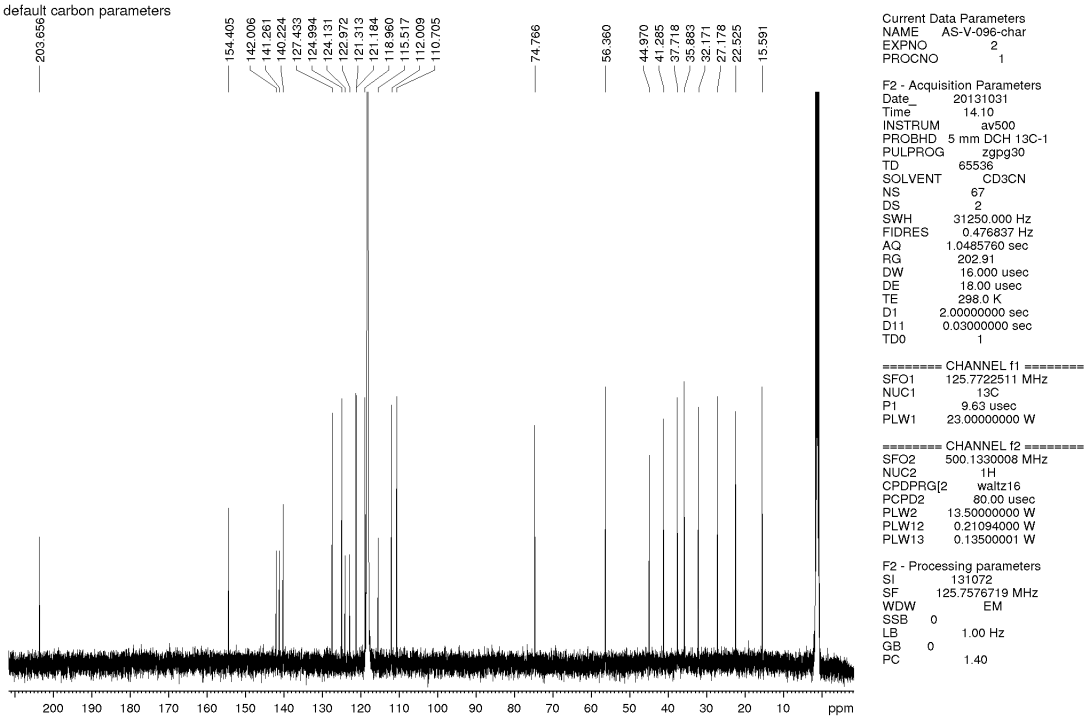



*Figure A4.54* $^{13}$C NMR (125 MHz, $CD_3CN$) of compound **6.25**.

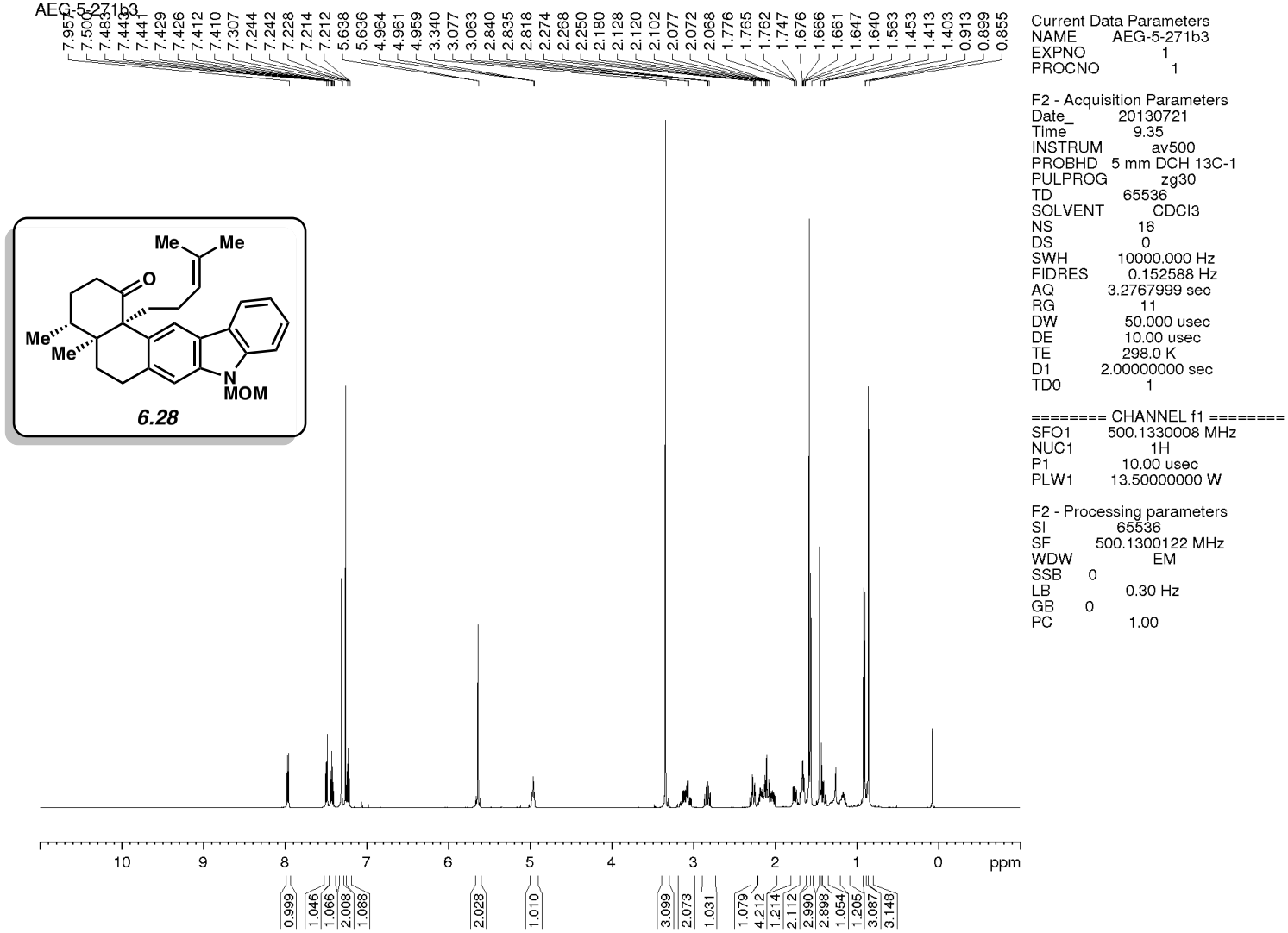



*Figure A4.55* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **6.28**.

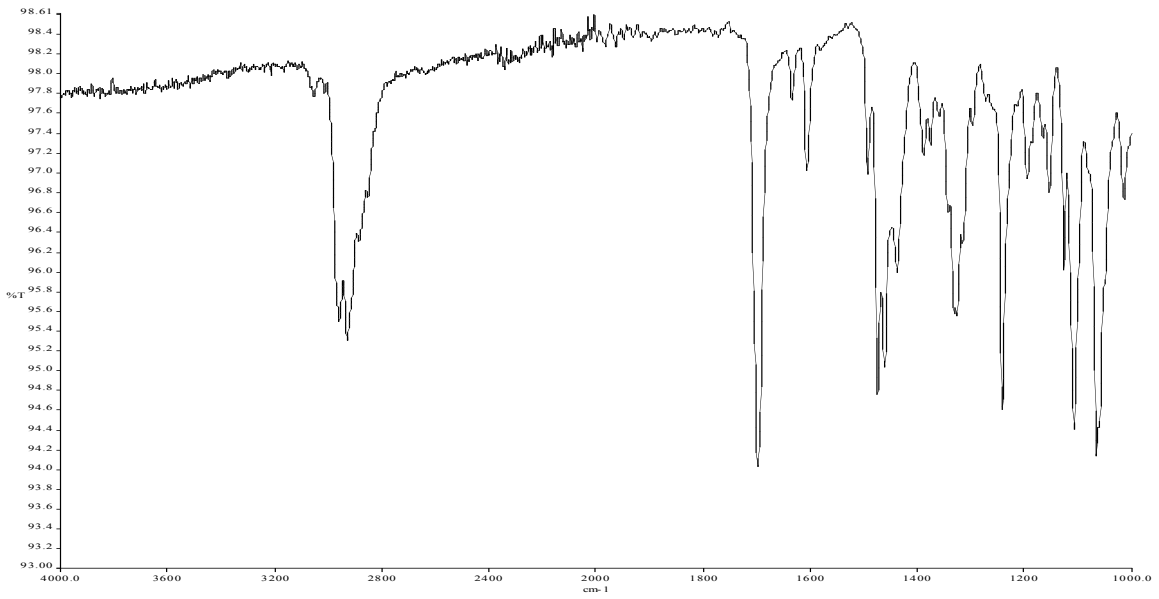



*Figure A4.56* Infrared spectrum of compound **6.28**.

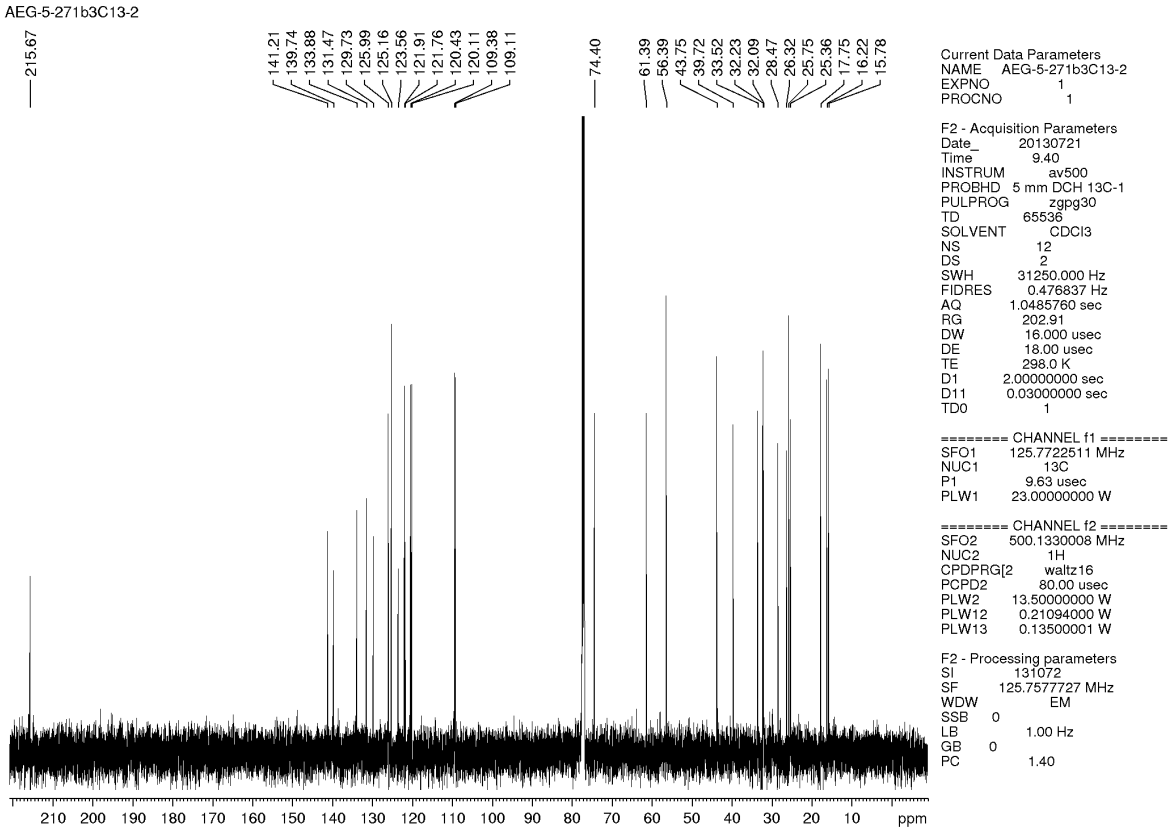



*Figure A4.57* $^{13}$C NMR (125 MHz, $CDCl_3$) of compound **6.28**.

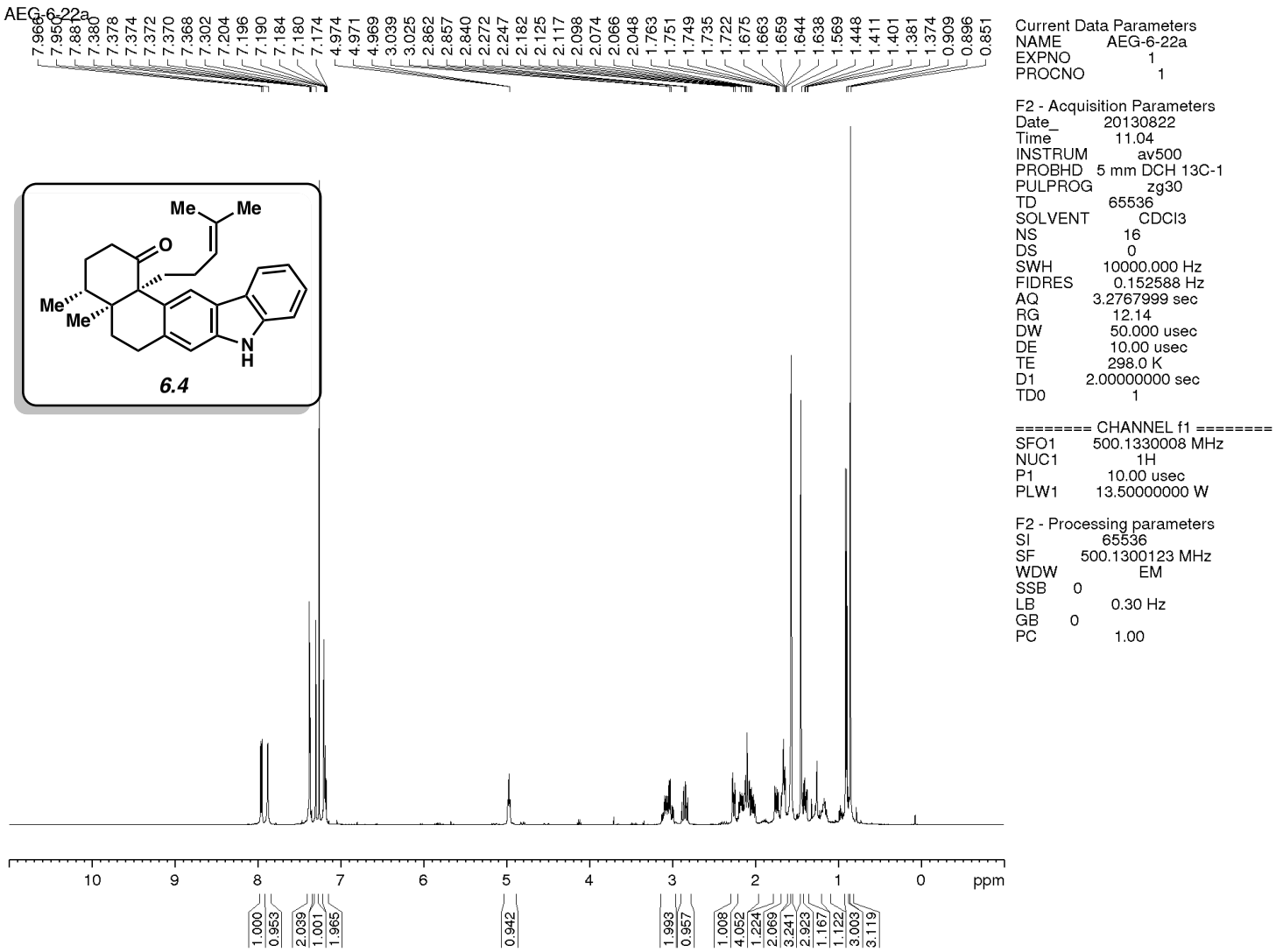



*Figure A4.58* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **6.4**.

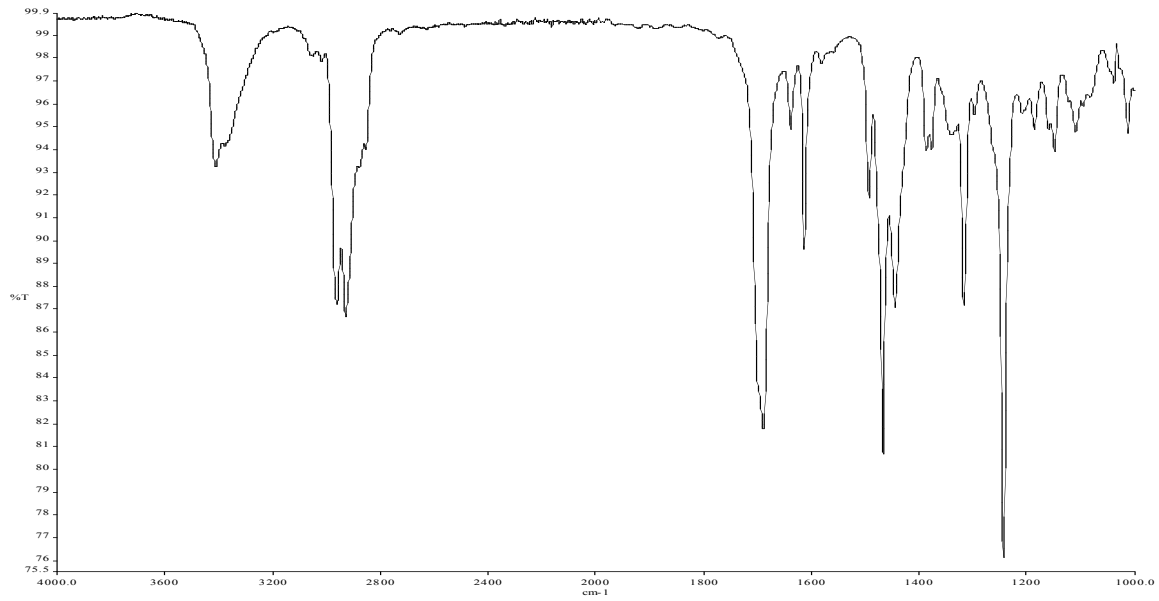



*Figure A4.59* Infrared spectrum of compound **6.4**.

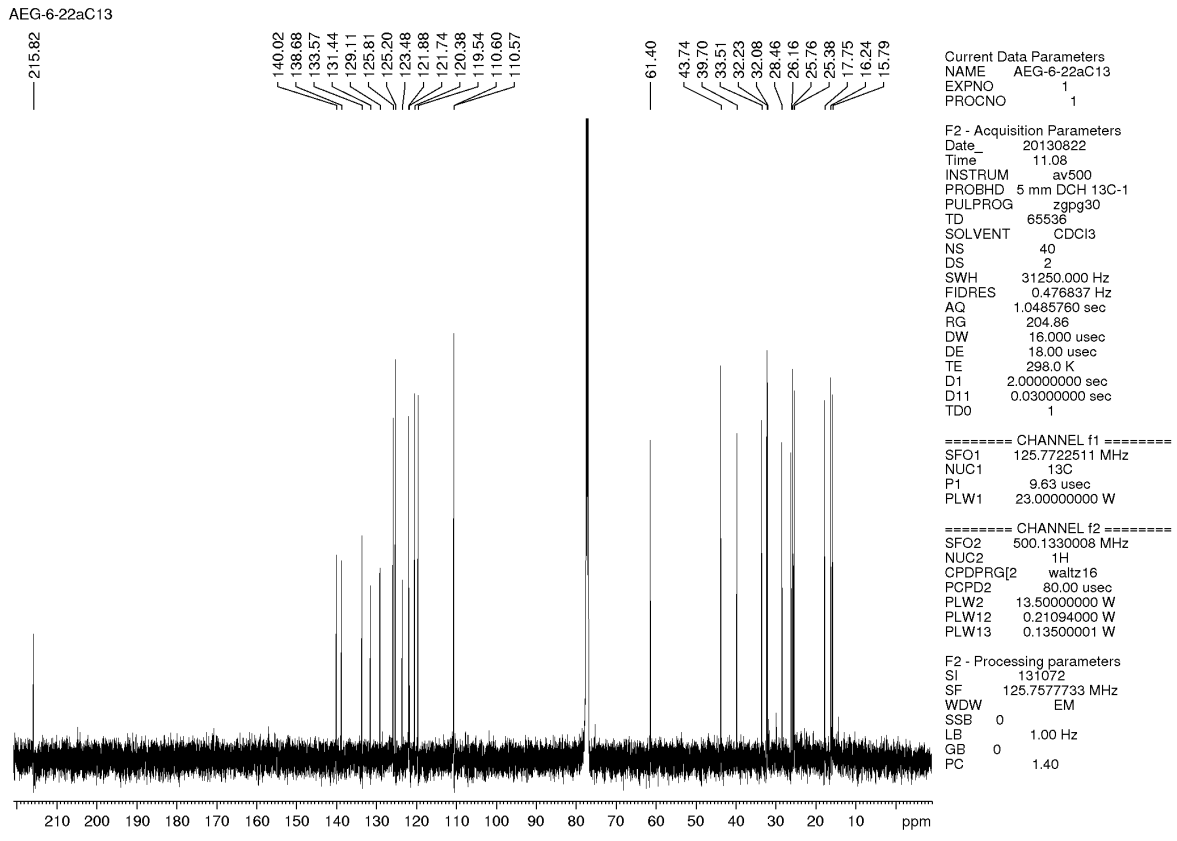



*Figure A4.60* $^{13}$C NMR (125 MHz, $CDCl_3$) of compound **6.4**.

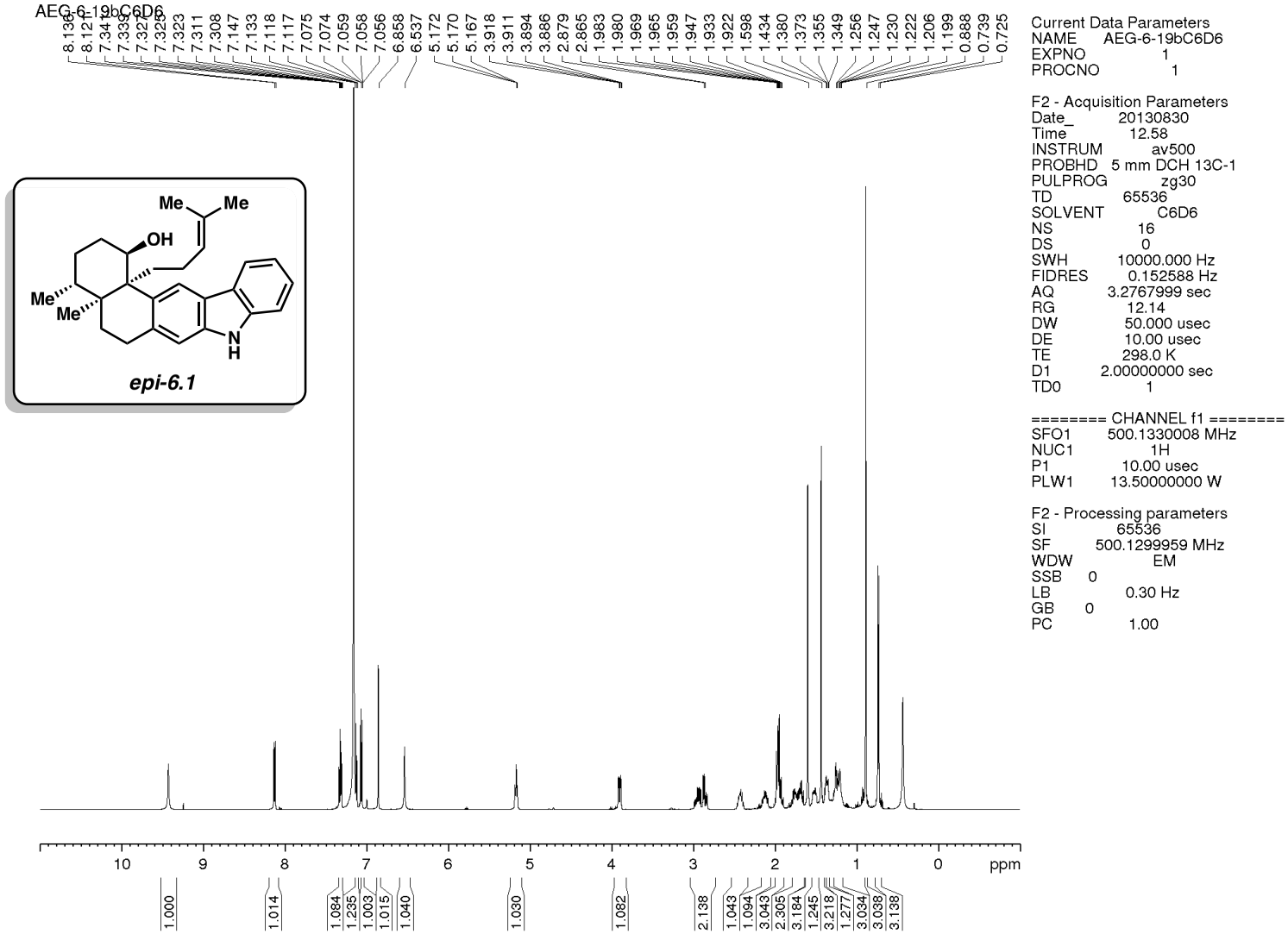



*Figure A4.61* $^{1}$H NMR (500 MHz, $C_6D_6$) of compound **epi-6.1**.

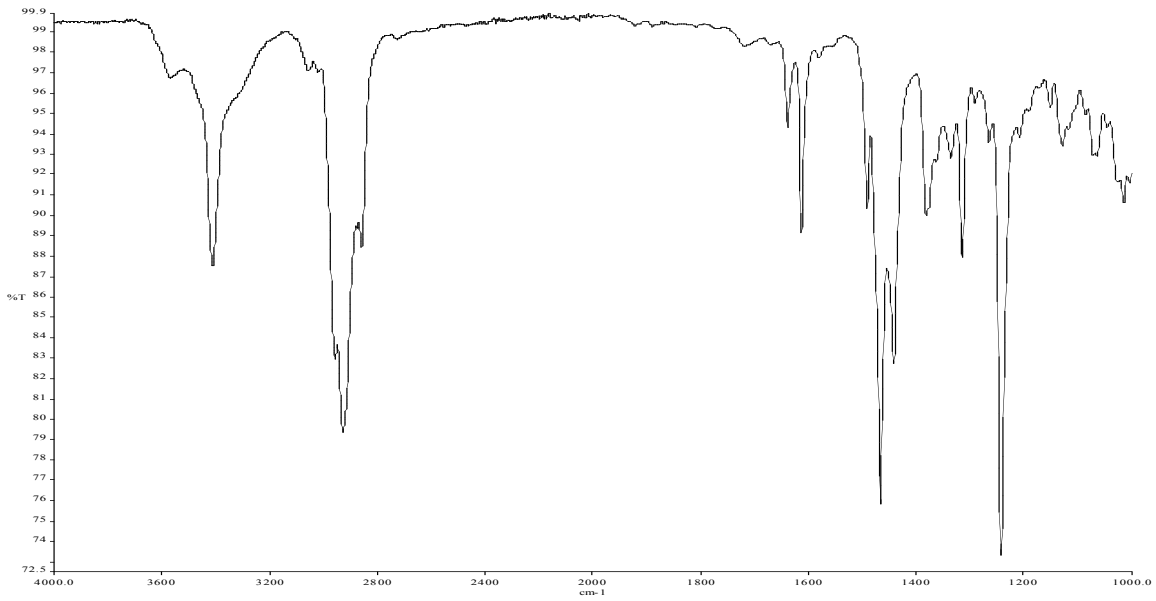



*Figure A4.62* Infrared spectrum of compound **epi-6.1**.

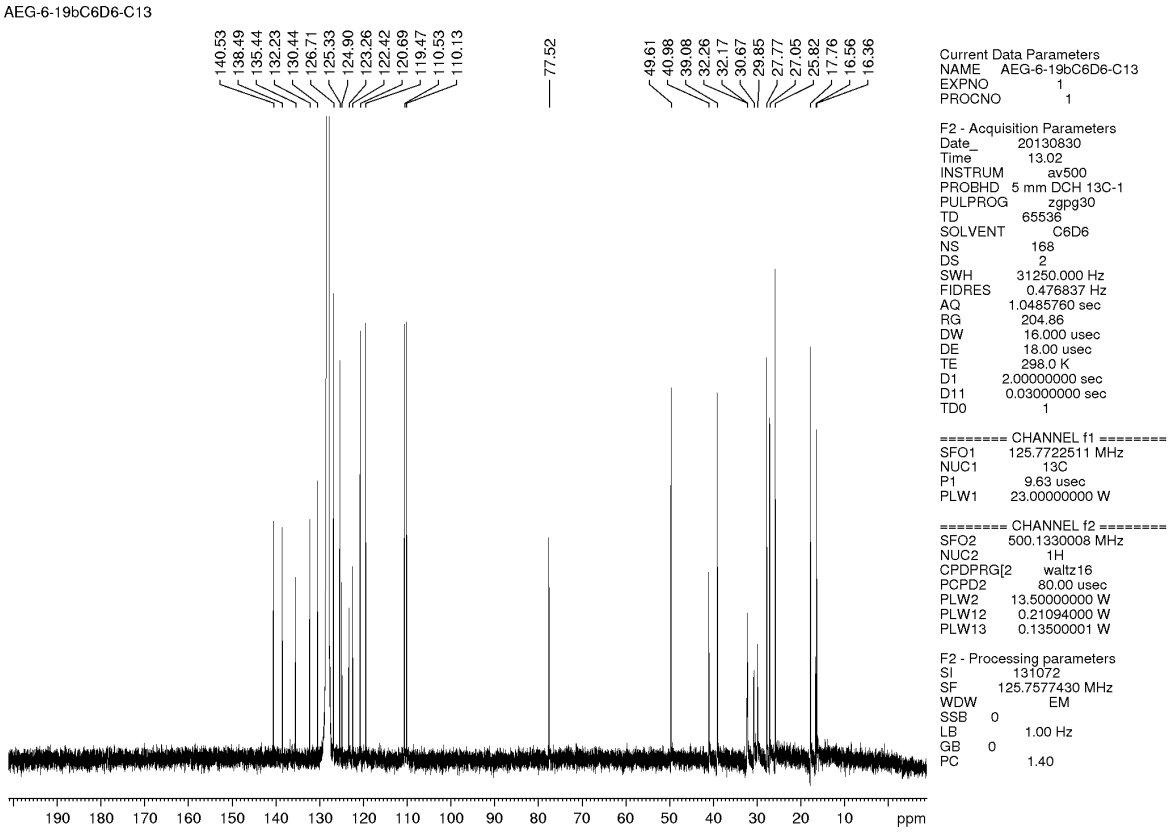



*Figure A4.63* $^{13}$C NMR (125 MHz, $C_6D_6$) of compound **epi-6.1**.

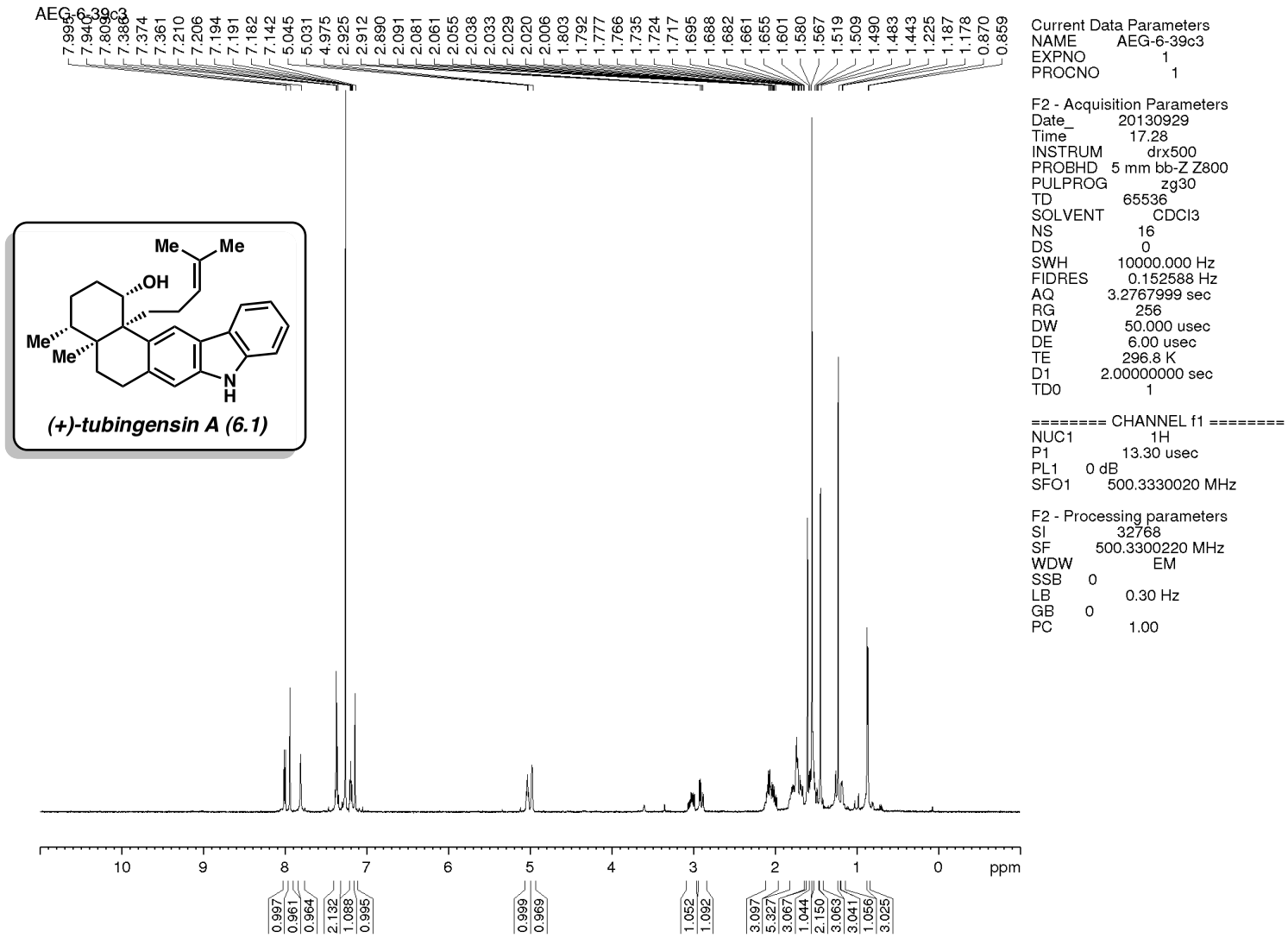



*Figure A4.64* $^{1}$H NMR (500 MHz, $CDCl_3$) of compound **6.1**.

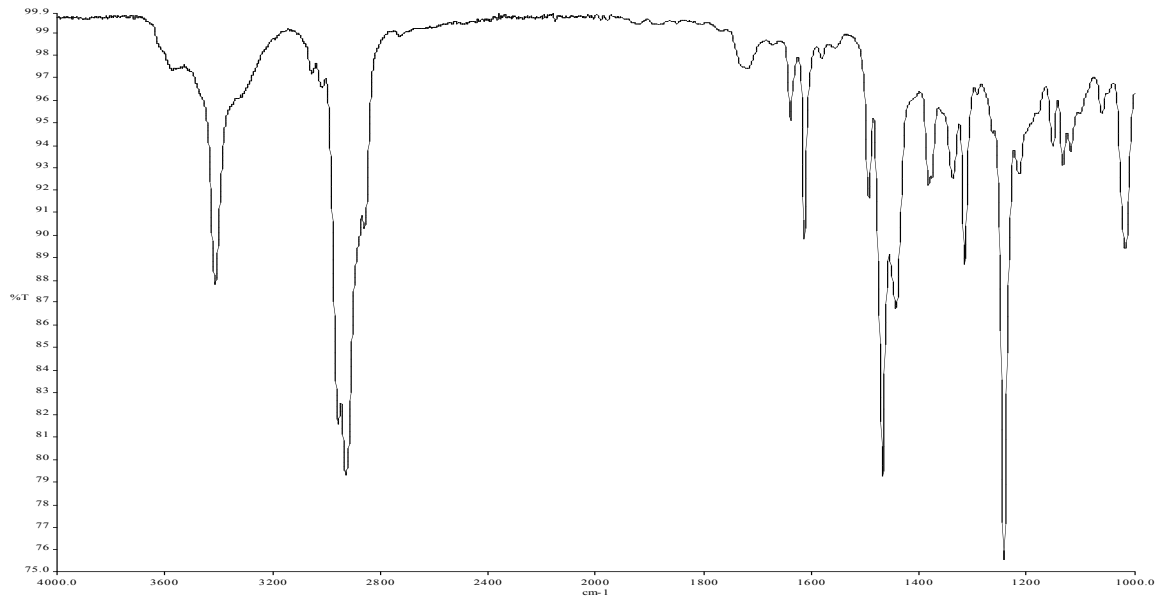



*Figure A4.65* Infrared spectrum of compound **6.1**.

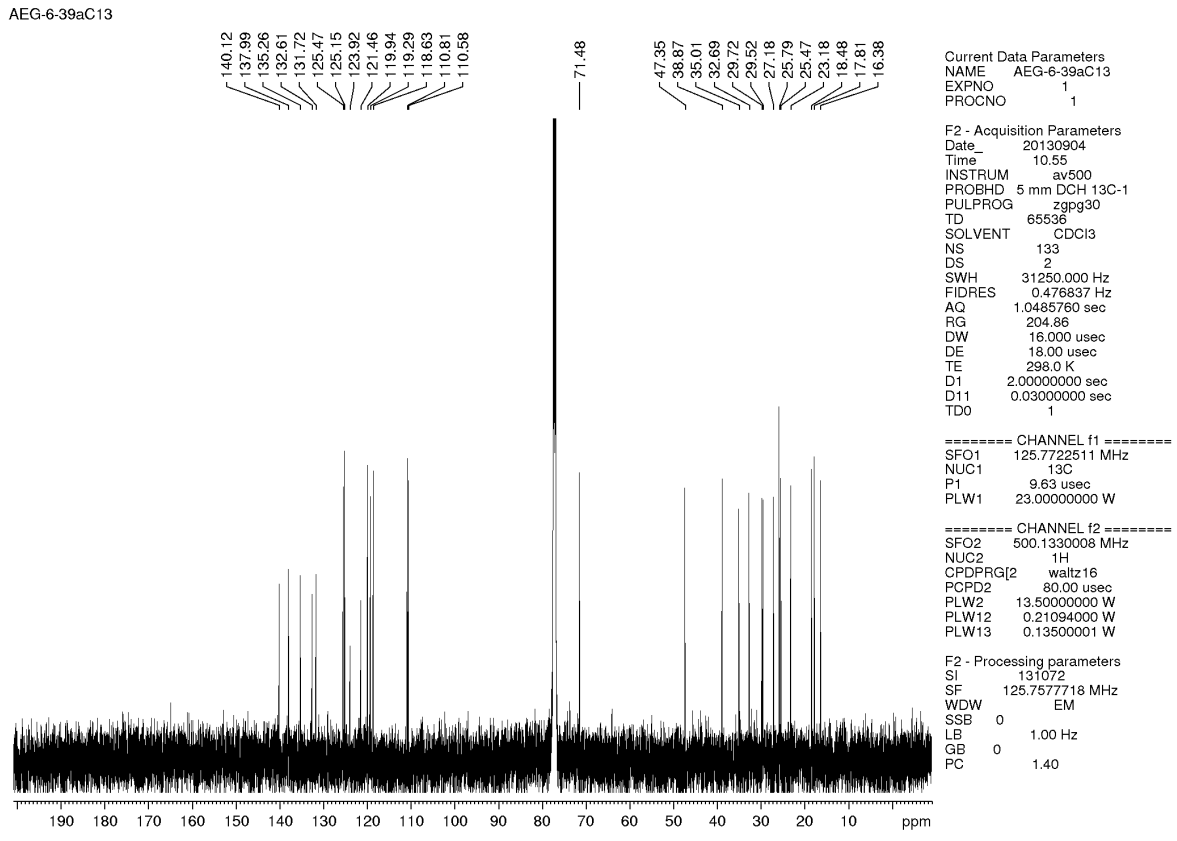



*Figure A4.66* $^{13}$C NMR (125 MHz, $CDCl_3$) of compound **6.1**.