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Total Synthesis of Welwitindolinone Natural Products

Author
Huters, Alexander David

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Total Synthesis of Welwitindolinone Natural Products

A dissertation submitted in partial satisfaction of the

requirements for the degree Doctor of Philosophy

in Chemistry

by

Alexander David Huters

2013

ABSTRACT OF THE DISSERTATION

Total Synthesis of Welwitindolinone Natural Products

by

Alexander David Huters

Doctor of Philosophy in Chemistry

University of California, Los Angeles, 2013

Professor Neil K. Garg, Chair

Chapter one provides a summary of efforts towards the syntheses of the welwitindolinones with bicyclo[4.3.1]decane cores. Emphasis is given to more recent approaches that have successfully assembled the bicyclic core of the natural products. Chapters two and three are a discussion of our studies relating to a model system of the welwitindolinone natural products. Chapter two focuses on the use of an aryne cyclization to assemble the bicyclo[4.3.1]decane framework of the welwitindolinones. Chapter three covers initial attempts to install the bridgehead nitrogen substituent present in the natural products in addition to the synthesis of a functionalized aryne cyclization substrate.

Chapters four and five present our total syntheses of the welwitindolinone natural products. The enantiospecific total syntheses of *N*-methylwelwitindolinone C isothiocyanate, *N*-

methylwelwitindolinone C isonitrile, 3-hydroxy-*N*-methylwelwitindolinone C isothiocyanate and 3-hydroxy-*N*-methylwelwitindolinone C isonitrile are detailed. The approach to these natural products features an aryne cyclization to construct the bicyclo[4.3.1]decane core of the molecules as well as a late-stage nitrene insertion reaction to install the bridgehead nitrogen substituent. The use of a deuterium kinetic isotope effect to improve the yield of the nitrene insertion is also presented. In addition, a computational method to predict the stereochemistry of a previously unconfirmed stereocenter in the hydroxylated natural products as well as experimental validation of the computational findings is discussed.

The dissertation of Alexander David Huters is approved.

Kendall N. Houk

Richard L. Weiss

Richard Wirz

Neil K. Garg, Committee Chair

University of California, Los Angeles

2013

For my parents, Ted Huters and Pauline Yu

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LIST OF ABBREVIATIONS

‡	transition state
$[a]_D$	specific rotation at wavelength of sodium D line
Ac	acetyl, acetate
AcOH	acetic acid
app.	apparent
aq.	aqueous
atm	atmosphere
B3LYP	Becke, 3-parameter, Lee–Yang–Parr (functional)
br	broad
Bu	butyl
i-Bu	isobutyl
t-Bu	*tert*-butyl
t-BuOH	*tert*-butyl alcohol
c	concentration for specific rotation measurements
°C	degrees Celsius
calc'd	calculated
CCDC	Cambridge Crystallographic Data Centre
CI	chemical ionization
d	doublet
dba	dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
dec	decomposition
DFT	density functional theorem
DMAP	4-dimethylaminopyridine
DMDO	dimethyldioxirane
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMP	Dess–Martin periodinane
DMSO	dimethyl sulfoxide
DTBP	2,6-di-*tert*-butylpyridine
EC_{50}	50% effective concentration

ee	enantiomeric excess
equiv	equivalent
ESI	electrospray ionization
Et	ethyl
FAB	fast atom bombardment
g	gram(s)
G	Gibbs free energy
gCOSY	gradient-selected Correlation Spectroscopy
h	hour(s)
HRMS	high resolution mass spectroscopy
HPLC	high performance liquid chromatography
hν	light
Hz	hertz
IBX	2-iodoxybenzoic acid
IMDA	intramolecular Diels–Alder
imid.	imidazole
IR	infrared (spectroscopy)
J	coupling constant
kcal/mol	kilocalories to mole ratio
KHMDS	potassium hexamethyldisilazide
λ	wavelength
L	liter
LiHMDS	lithium hexamethyldisilazide
m	multiplet or milli
m	meta
m/*z*	mass to charge ratio
μ	micro
MDR	multiple drug resistance
Me	methyl
MHz	megahertz
min	minute(s)
mol	mole(s)
MOM	methoxymethyl ether
mp	melting point
Ms	methanesulfonyl (mesyl)

MS	molecular sieves
μW	microwave
NCS	*N*-chlorosuccinimide
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
NMR	nuclear magnetic resonance
NOE	Nuclear Overhauser Effect
NOESY	Nuclear Overhauser Enhancement Spectroscopy
[O]	oxidation
p	para
π	pi
Ph	phenyl
pH	hydrogen ion concentration in aqueous solution
PhH	benzene
Piv	pivaloyl
PivCl	pivaloyl chloride
PPh_3	triphenylphosphine
ppm	parts per million
Pr	propyl
i-Pr	isopropyl
pyr	pyridine
q	quartet
rt	room temperature
R_f	retention factor
s	singlet or strong
t	triplet
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBS	*tert*-butyldimethylsilyl
TBSCl	*tert*-butyldimethylsilyl chloride
Tf	trifluoromethanesulfonyl (trifyl)
TFA	trifluoroacetic acid
TFEF	2,2,2-trifluoroethylformate
TFP	tri(2-furyl)phosphine
THF	tetrahydrofuran

TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMM	trimethylenemethane
TMS	trimethylsilyl
TMSCl	trimethylsilyl chloride
TMSOTf	trimethylsiyl triflate
Ts	*p*-toluenesulfonyl (tosyl)
TS	transition state
UV	ultraviolet
w	weak

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I would like to start by thanking Professor Neil Garg for being a wonderful advisor. His endless support and guidance over the years has meant very much to me. From his open door policy to his excitement and infectious joy of chemistry, he has really helped me to get through the rigors of a doctorate program. I am very appreciative of all the support and advice that he has willingly offered throughout my time at UCLA.

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Jain. He taught one of my organic chemistry lecture and laboratory courses and later on welcomed me as a member of his undergraduate research laboratory. He was always very excited about chemistry and concerned with student learning, and is one of the reasons why I decided to go to graduate school.

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grown stronger throughout my life. Matt has been my best friend and we have been able to share many common interests, be it our sports teams or books and television shows. Emily and her husband Trey Hatch have also brightened my life by providing me with two nephews, Henry and Max Hatch. I would also like to thank my extended family from my aunts and uncles to cousins and grandparents, all of whom have been very supportive of me. Finally, and most importantly, I would like to thank my parents, Ted Huters and Pauline Yu. Their unwavering love and assistance have helped to make me the man I am today and I am deeply grateful for all they have provided.

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Chapter 2 is a version of Tian, X.; Huters, A. D.; Douglas, C. J.; Garg, N. K. *Org. Lett.* **2009**, *11*, 2349–2351. Tian, Huters, and Douglas were responsible for experimental work.

Chapter 3 is currently unpublished work performed by Huters, A. D. and Quasdorf, K. W.

Chapter 4 is a version of Huters, A. D.; Quasdorf, K. W.; Styduhar, E. D.; Garg, N. K. *J. Am. Chem. Soc.* **2011**, *133*, 15797–15799. Huters, Quasdorf, and Styduhar were responsible for experimental work.

Chapter 5 is a version of Quasdorf, K. W.; Huters, A. D.; Lodewyk, M. W.; Tantillo, D. J Garg, N. K. *J. Am. Chem. Soc.* **2012**, *134*, 1396–1399. This work was done in collaboration with Michael W. Lodewyk and Dean J. Tantillo at the University of California, Davis. Quasdorf and Huters were responsible for experimental work. Lodewyk and Tantillo were responsible for computational work.

BIOGRAPHICAL SKETCH

Education:

University of California, Los Angeles, CA

- Graduate Research Assistant, July 2008 to current (PhD expected Spring 2013), GPA 3.98/4.00

University of California, Berkeley, CA

- Bachelor of Arts Degree in Biochemistry and Molecular Biology, December 2006, GPA 3.66/4.00

Professional and Academic Experience:

Graduate Research Assistant: University of California, Los Angeles, CA

- November 2008 to current (PhD expected Spring 2013)
- Completed the enantiospecific total synthesis of *N*-methylwelwitindolinone C isothiocyanate (MDR inhibitor) featuring an indolyne cyclization and late-stage nitrene insertion in the laboratory of Professor Neil K. Garg.
- Also achieved syntheses of *N*-methylwelwitindolinone C isonitrile, 3-hydroxy-*N*-methylwelwitindolinone C isothiocyanate, 3-hydroxy-*N*-methylwelwitindolinone C isonitrile, and *N*-methylwelwitindolinone D isonitrile in the Garg laboratory.

Teaching Assistant: University of California, Los Angeles, CA

- September 2008 to December 2009; April 2012 to June 2012
- Taught undergraduate organic chemistry laboratory classes of >20 students and taught discussion section for an undergraduate organic chemistry course and graduate level organic synthesis

Laboratory Research Assistant: University of California, Los Angeles, CA

- July 2007 to July 2008
- Conducted quantum mechanical studies of the transition states of aromatic Claisen rearrangements and Fischer indolizations and synthesized new coumarin-based substrates for enzyme design studies in the laboratory of Professor Kendall N. Houk.

Undergraduate Research Assistant: University of California, Berkeley, CA

- September 2004 to May 2006
- Led research on the development of fluorinated analogs of Oseltamivir (Tamiflu) to test for binding to viral neuraminidase in the laboratory of Professor Ahamindra Jain.

Honors and Awards:

- *Phi Beta Kappa*, 2006
- Dean's List, Spring 2005
- Golden Key Award Society Nominee, 2003 to 2006
- UCLA Division of Organic Chemistry ACS Travel Grant, 2010 (ACS/Anaheim 2011)
- Excellence in Second Year Academics and Research Award (UCLA), 2010
- Christopher S. Foote Fellowship in Organic Chemistry (UCLA), 2011–2012
- Glenn T. Seaborg Symposium Poster Session, First Place Prize (UCLA), 2011
- UCLA Division of Organic Chemistry ACS Travel Grant, 2011 (ACS/San Diego 2012)
- Roche Symposium: Excellence in Chemistry award (Roche, 2012)
- Bristol-Myers Squibb Graduate Student Fellowship, 2012–2013
- UCLA Dissertation Year Fellowship, 2012–2013
- Hanson–Dow Teaching Assistant Award (UCLA), 2012
- John Stauffer Fellowship (UCLA), 2012

Publications:

1. **Concise Synthesis of the Bicyclic Scaffold of *N*-Methylwelwitindolinone C Isothiocyanate via an Indolyne Cyclization.** Xia Tian, Alexander D. Huters, Colin J. Douglas, and Neil K. Garg. *Org. Lett.* **2009**, *11*, 2349–2351.
2. **Synthetic Studies Inspired by Vinigrol.** Alexander D. Huters and Neil K. Garg. *Chem. Eur. J.* **2010**, *16*, 8586–8595.
3. **Why Do Some Fischer Indolizations Fail?** Nihan Çelebi-Ölçüm, Ben W. Boal, Alexander D. Huters, Neil K. Garg, and K. N. Houk. *J. Am. Chem. Soc.* **2011**, *133,* 5752–5755.
4. **Total Synthesis of (–)-*N*-Methylwelwitindolinone C Isothiocyanate.** Alexander D. Huters, Kyle W. Quasdorf, Evan D. Styduhar, and Neil K. Garg. *J. Am. Chem. Soc.* **2011**, *133*, 15797–15799.
5. **Total Synthesis of Oxidized Welwitindolinones and (–)-*N*-Methylwelwitindolinone C Isonitrile.** Kyle W. Quasdorf, Alexander D. Huters, Michael W. Lodewyk, Dean J. Tantillo, and Neil K. Garg. *J. Am. Chem. Soc.* **2012**, *134*, 1396–1399.
6. **Total Syntheses of the Elusive Welwitindolinones with Bicyclo[4.3.1] Cores.** Alexander D. Huters, Evan D. Styduhar, and Neil K. Garg. *Angew. Chem., Int. Ed.* **2012**, *51*, 3758–3765.

Presentations:

1. **Tight-binding Fluorinated Inhibitors of Viral Neuraminidase.** Ahamindra Jain, Alexander D. Huters, Adam Weinstein, Daniel Kwan, and Nisha Sandesara. Poster, 232nd ACS National Meeting, San Francisco, CA, United States, September 10–14, 2006, MEDI-229.
2. **Progress Toward the Total Synthesis of *N*-Methylwelwitindolinone C Isothiocyanate.** Alexander D. Huters, Kyle W. Quasdorf, and Neil K. Garg. Poster, 241st ACS National Meeting, Anaheim, CA, United States, March 27–31, 2011, ORGN-747.
3. **Total Synthesis of (–)-*N*-Methylwelwitindolinone C Isothiocyanate.** Alexander D. Huters, Kyle W. Quasdorf, Evan D. Styduhar, and Neil K. Garg. Poster, UCLA Glenn T. Seaborg Symposium Poster Session, Los Angeles, CA, November 5, 2011.
4. **Total Synthesis of (–)-*N*-Methylwelwitindolinone C isothiocyanate.** Alexander D. Huters, Kyle W. Quasdorf, Evan D. Styduhar, and Neil K. Garg. Poster, 43rd Western Regional Meeting of the American Chemical Society, Pasadena, CA, United States, November 10–12, 2011, WRM-134.
5. **Total Synthesis of (–)-*N*-Methylwelwitindolinone C Isothiocyanate.** Alexander D. Huters, Kyle W. Quasdorf, Evan D. Styduhar, and Neil K. Garg. Poster, AstraZeneca Excellence in Chemistry Symposium, Waltham, MA, United States, December 6, 2011.
6. **Total Synthesis of (–)-*N*-Methylwelwitindolinone C Isothiocyanate.** Alexander D. Huters and Neil K. Garg. Oral Presentation, 243nd ACS National Meeting, San Diego, CA, United States, March 25–29, 2012, ORGN-248.
7. **Enantiospecific Total Synthesis of [4.3.1]-Bicyclic Welwitindolinones.** Alexander D. Huters and Neil K. Garg. Oral Presentation, Roche Excellence in Chemistry Symposium, Nutley, NJ, United States, May 21–22, 2012.
8. **Total Synthesis of Welwitindolinone Alkaloids.** Alexander D. Huters and Neil K. Garg. Poster, Gordon Research Conference – Natural Products, Andover, NH, United States, July 22–27, 2012.
9. **Enantiospecific Total Synthesis of [4.3.1]-Bicyclic Welwitindolinones.** Alexander D. Huters and Neil K. Garg. Oral Presentation, Division of Organic Chemistry Graduate Research Symposium, Boulder, CO, United States, July 26–29, 2012.
10. **Enantiospecific Total Synthesis of [4.3.1]-Bicyclic Welwitindolinones.** Alexander D. Huters and Neil K. Garg. Oral Presentation, Bristol-Myers Squibb Chemistry Symposium, Lawrenceville, NJ, United States, April 18–19, 2013.

CHAPTER ONE

Total Syntheses of the Elusive Welwitindolinones with Bicyclo[4.3.1]decane Cores

In part, adapted from: Alexander D. Huters, Evan D. Styduhar, and Neil K. Garg.

Angew. Chem. Int. Ed. **2012**, *51*, 3758–3765.

1.1 Abstract

The welwitindolinones with bicyclo[4.3.1]decane cores are a class of natural products that have attracted tremendous interest from the synthetic community due to their fascinating structures and promising biological profiles. More than fifteen laboratories worldwide have reported progress toward these elusive natural products. This chapter describes contemporary studies aimed at the total synthesis of these challenging targets, in addition to the two recently completed syntheses of welwitindolinones with bicyclo[4.3.1]decane cores reported by Rawal and Garg, respectively, in 2011. Both of the completed efforts rely on C4–C11 bond constructions in order to access the congested bicyclic framework of these elusive natural products.

1.2 Introduction

The welwitindolinones (**1.1**–**1.10**, Figure 1.1) are an enticing family of oxindole-containing natural products that have drawn substantial interest from the scientific community. In 1994, Moore and co-workers described the isolation of many of these natural products, which were produced by the blue-green algae Hapalosiphon welwitschii and Westiella intricata. The discovery of additional welwindolinones, generated from Fischerella muscicola and Fischerella major, was subsequently reported in 1999.[1] These natural products were found to exhibit a wide

range of biological activity, ranging from insecticidal or antimycotic properties, to the ability of **1.5** to reverse P-glycoprotein-mediated multiple drug resistance (MDR) to a variety of anti-cancer drugs in human cancer cell lines.[2] All of the welwitindolinones other than welwitindolinone A isonitrile (**1.1**) contain a 3,4-disubstituted oxindole with a bicyclo[4.3.1]decane core. In addition, these compounds feature a compact, yet heavily substituted cyclohexyl ring, where at least five of the six carbons on the ring are functionalized.

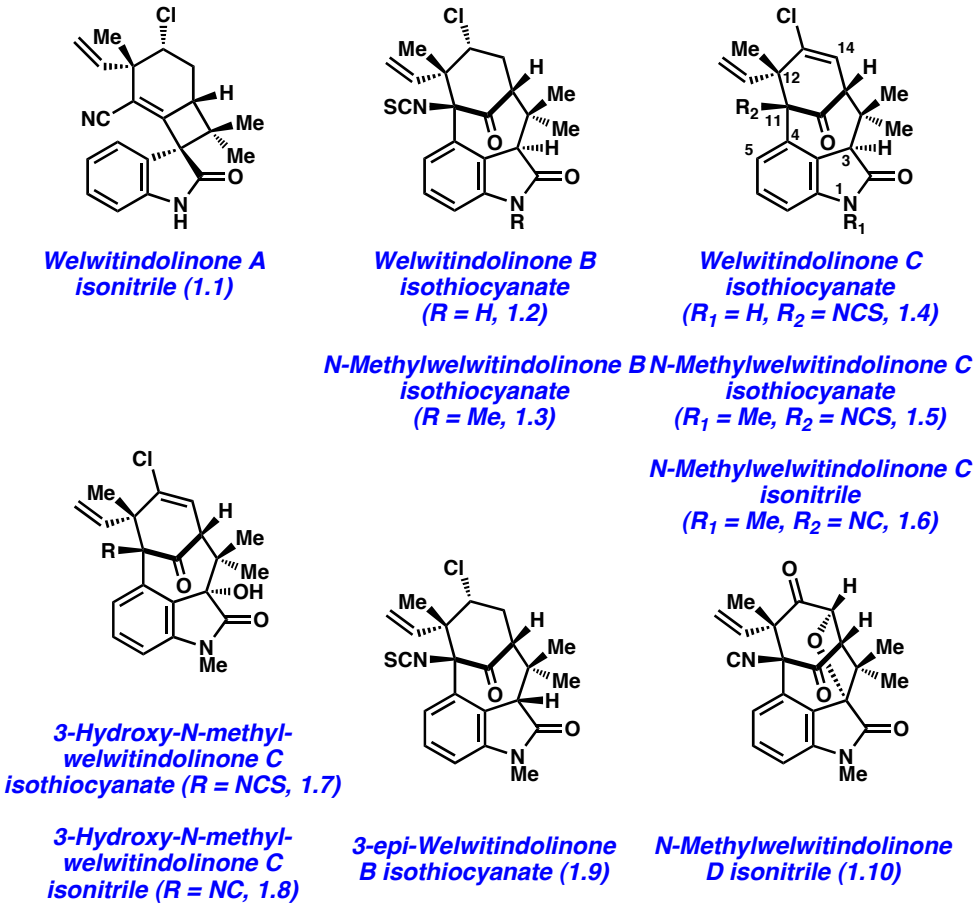


Figure 1.1. Welwitindolinone natural products **1.1**–**1.10**.

The combination of daunting structural features and promising biological activity have rendered the welwitindolinones attractive and highly sought after targets for total synthesis.

Since the initial isolation of the welwitindolinones in 1994, at least fifteen laboratories worldwide have sought to prepare these compounds by chemical synthesis.[3,4,5,6,7,8,9,10,11,12,13] Numerous dissertations and approaches toward these targets have been published (>20). The exhaustive synthetic efforts have led to two syntheses of welwitindolinone A isonitrile (**1.1**), reported by the Baran[14] and Wood[15] groups. However, relatively less success has been realized in synthesizing welwitindolinones with bicyclo[4.3.1]decane cores.

A summary of successful strategies toward the bicyclic welwitindolinone core is presented in Figure 1.2. These efforts can be categorized into four approaches based on the order of ring assembly. Using *Approach 1*, Funk[3] and Trost[4] have targeted bicycle **1.11** by late-stage introduction of the oxindole unit from bicyclo[4.3.1]decane **1.12**. Alternatively, *Approach 2* by Wood,[5] Martin,[6] and Menéndez,[7] relies on accessing bicycle **1.11** by final introduction of the cyclohexyl ring from precursor **1.13**. In turn, the 7-membered ring would be built from a simpler indole or oxindole starting material **1.14**. Shea's ambitious approach to **1.11** (*Approach 3*) features tandem construction of the 6- and 7-membered rings using an intramolecular Diels–Alder cycloaddition (**1.11** ⇒ **1.15** ⇒ **1.16**).[8] Finally, in *Approach 4*, Konopelski,[9] Simpkins,[10] Rawal,[11] and Garg,[12] targeted bicycle **1.11** from suitably functionalized cyclohexyl and indole precursors **1.17** and **1.18**, respectively.

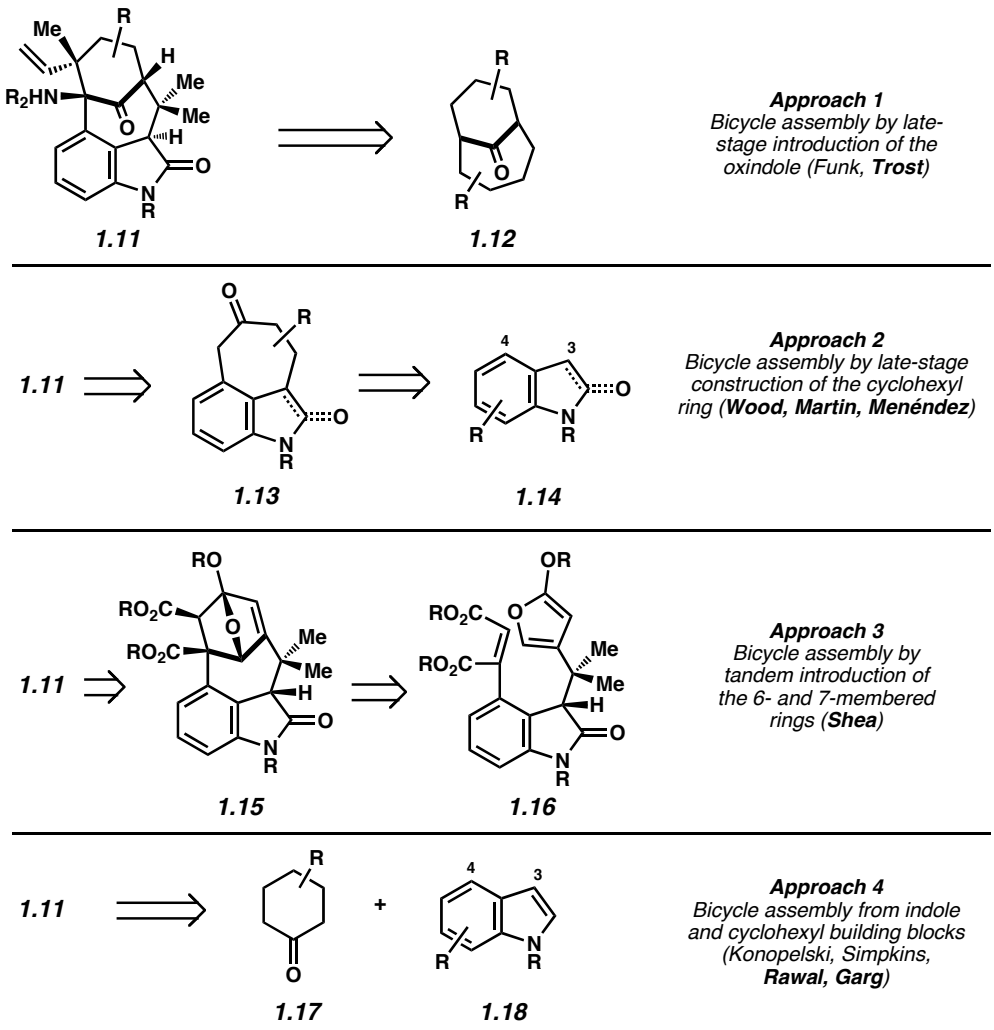


Figure 1.2. Synthetic approaches to the core scaffold of the welwitindolinone natural products with bicyclo[4.3.1]decane cores.

1.3 Recent Synthetic Studies Toward the Total Synthesis of the Welwitindolinones with Bicyclo[4.3.1]decane Cores

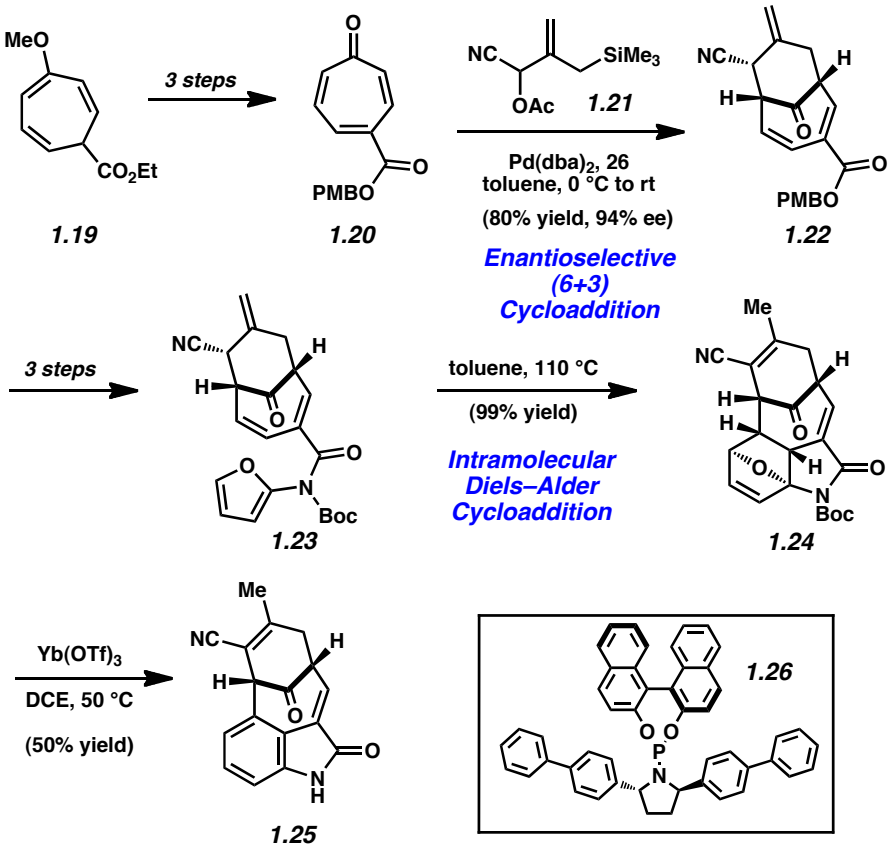
1.3.1 Late-Stage Assembly of the Oxindole

One elegant strategy to assemble the core structure of the welwitindolinones relies on late-stage appendage of the oxindole to a preformed bicyclo[4.3.1]decane intermediate, as recently reported by Trost.[4] In this approach, a series of cycloadditions were used to assemble the core, featuring a palladium-catalyzed trimethylenemethane (Pd-TMM) cycloaddition reaction

(Scheme 1.1). For this (6+3) cycloaddition, tropone **1.20** was selected for the acceptor molecule and allylsilane **1.21** was chosen for the donor. Tropone **1.20** was accessed in three steps from cycloheptatriene **1.19**. Upon reaction with allyl silane **1.21** in the presence of $Pd(dba)_2$ and phosphorous ligand **1.26**, the enantioselective (6+3) cycloaddition reaction occurred to deliver bicycle **1.22** in 94% ee. This impressive transformation is believed to proceed by way of an in situ generated π-allyl palladium intermediate.[16] The PMB ester **1.22** was then elaborated to amidofuran **1.23** in three steps. Upon heating **1.23** in toluene, a Diels–Alder cycloaddition occured to deliver oxabicycle **1.24**. Subsequent treatment with $Yb(OTf)_3$ unveiled oxindole **1.25**.

Although further elaboration of **1.25** has not yet been reported, this advanced species could possibly be used to access all of the welwitindolinones with bicyclo[4.3.1]decane cores. Additionally, Trost's approach elegantly highlights the utility of the (6+3) cycloaddition methodology for building complex architectures. The route to **1.25** also showcases the distinctive ability of Pd catalysis, and notably π-allyl palladium chemistry, to provide intricate structural frameworks with high enantiomeric excess.

Scheme 1.1

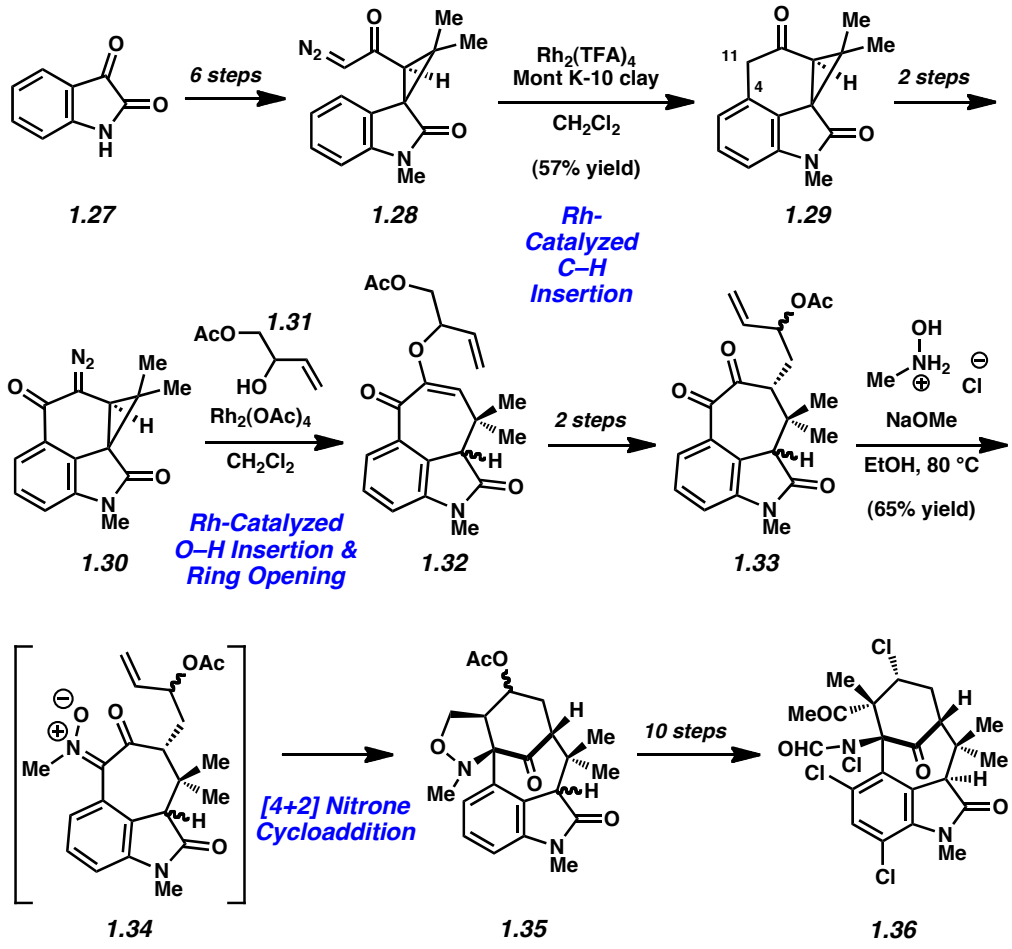


1.3.2 Late-Stage Construction of the Cyclohexyl Ring

Another attractive route toward construction of the bicyclo[4.3.1]decane core of the welwitindolinones relies on initial formation of the seven-membered ring followed by assembly of the cyclohexyl ring. As mentioned above, Wood, Martin, and Menéndez all designed their syntheses around this general strategy (Scheme 1.2). In Wood's route,[5b] isatin (**1.27**) was converted to diazoketone **1.28** using a six step sequence. The C4–C11 bond was then constructed through a rhodium-catalyzed C–H insertion[17] to provide tetracycle **1.29**. Further elaboration afforded diazoketone **1.30** over two steps. Subsequent treatment with $Rh_2(OAc)_4$ and allylic alcohol **1.31** initiated O–H insertion along with tandem ring expansion to furnish tricycle **1.32**,

which possesses the necessary 7-membered ring. Two additional steps allowed access to allylic acetate **1.33**. Upon treatment of **1.33** with *N*-methylhydroxylamine hydrochloride and sodium methoxide, [4+2] nitrone cycloaddition occurred to forge the bicyclo[4.3.1]decane scaffold. Presumably the conversion of **1.33** to cycloadduct **1.35** proceeds via intermediate **1.34**. After extensive experimentation, the authors were able to access alkyl chloride **1.36** from **1.35**.

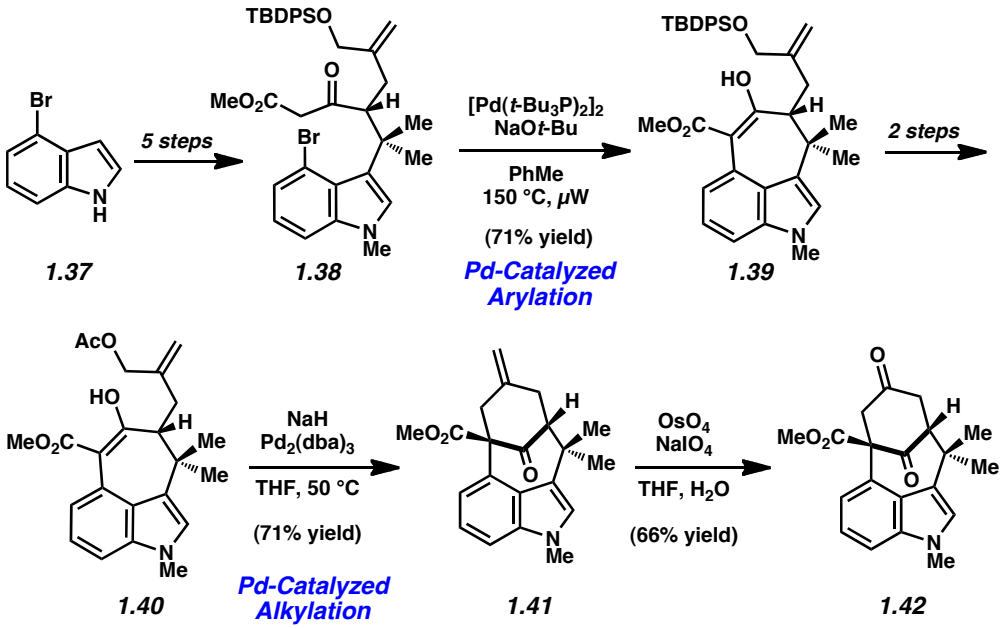
Scheme 1.2



Martin's efforts to construct the bicyclo[4.3.1]decane core through sequential installation of the seven- and six-membered rings are highlighted in Scheme 1.3.[6] Starting with 4-

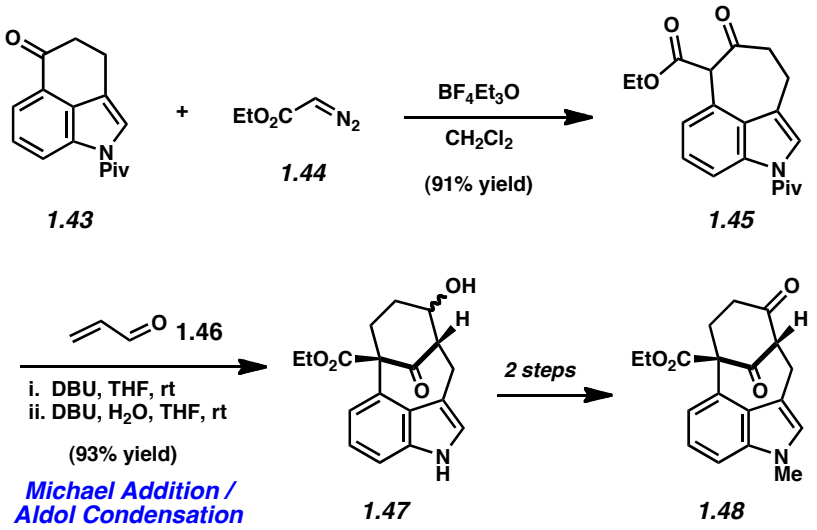
bromoindole (**1.37**), a five step sequence delivered β-ketoester **1.38**. Next, a palladium-catalyzed cyclization was employed to furnish **1.39**, which contains the necessary seven-membered ring. After elaborating to allylic acetate **1.40**, treatment with $Pd_2(dba)_3$ and sodium hydride provided bicycle **1.41** via intramolecular trapping of a π-allylpalladium intermediate. Lemieux–Johnson oxidation of the olefin furnished dione **1.42**, which possesses the welwitindolinone bicyclic core.

Scheme 1.3



As shown in Scheme 1.4, the Menéndez group also devised a very concise means to assemble the bicyclic structure of the welwitindolinones.[7] Kornfeld's ketone (**1.43**)[18] underwent ring expansion with ethyl diazoacetate (**1.44**) to deliver β-ketoester **1.45**. In turn, **1.45** was subjected to a one-pot, tandem Michael addition / aldol reaction using propenal (**1.46**) and DBU to yield keto alcohol **1.47**. Methylation of the indole nitrogen followed by oxidation of the alcohol provided indolyl bicycle **1.48**.

Scheme 1.4



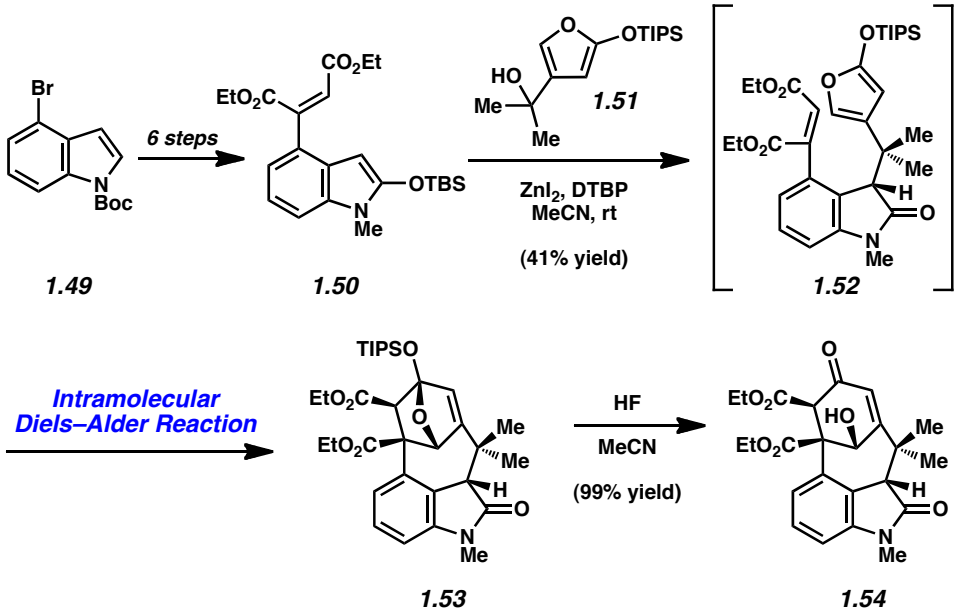
Each of the approaches discovered by Wood, Martin, and Menéndez provide smooth access to the bicyclic welwitinodolinone core, which sets the stage for late-stage elaboration. More importantly, lessons involving synthetic strategies and methods can be extracted from each group's efforts. Wood's use of C–H insertion chemistry (**1.28→1.29**, Scheme 1.2) and subsequent fragmentation chemistry to install the 7-membered ring, serves as a reminder that unconventional disconnections often provide exciting routes to complex structures. Wood's nitrone cycloaddition (**1.33→1.35**, Scheme 1.2) provides further support of this notion, and cleverly builds the 6-membered ring, while installing the troublesome C11 nitrogen substituent. Martin's approach to the welwitindolinones highlights the power of Pd-catalysis in building quaternary stereocenters and sterically congested frameworks by the assembly of carbon–carbon bonds (Scheme 1.3). The specific use of Pd-enolate chemistry provides an example of modern Pd catalysis greatly enabling complex molecule synthesis. Finally, Menéndez's application of a tandem Michael addition / aldol reaction (**1.45→1.47**, Scheme 1.4) to assemble the

welwitindolinone bicyclo[4.3.1]decane core demonstrates that classical chemistry may still provide simple, yet elegant solutions to challenging synthetic problems.

1.3.3 Tandem Assembly of the 7- and 6-Membered Rings

Another bold approach to the core of the welwitindolinones is to assemble the seven- and six-membered rings in a tandem process. To this end, Shea implemented a [4+2] cycloaddition to assemble the welwitindolinone bicycle (Scheme 1.5).[8b] Bromoindole **1.49** was elaborated to silylketene aminal **1.50** in six steps. In turn, **1.50** underwent a ZnI_2-promoted alkylation with silyloxyfuran **1.51** to deliver intermediate **1.52**, which immediately reacted in an intramolecular Diels–Alder (IMDA) cycloaddition to yield oxabicyclic oxindole **1.53**. Treatment of this compound with HF then unveiled ketoalcohol **1.54**. Shea's route is exceedingly concise, as it provides a highly functionalized oxindole-appended bicyclo[4.3.1]decane framework in only 8 steps from indole **1.49**. The approach not only highlights the utility of the IMDA reaction, but also demonstrates the effectiveness of cascade reactions for constructing complex architectures. Moreover, Shea's use of intermediates containing anti-Bredt olefins (i.e., **1.53**) reminds us that our commonly accepted rules concerning structure and stability are not insurmountable.

Scheme 1.5



1.3.4 Linkage of Cyclohexyl and Indole Building Blocks to Assemble the Bicyclo[4.3.1]decane Scaffold

An alternative approach to the formation of the bicyclic structure of the welwitindolinones is through the linkage of cyclohexyl and indole building blocks. Rawal[11b] and Garg[12b] have each reported recent efforts using this strategy, which have culminated in completed total syntheses. The details of these studies are described in depth in the subsequent sections of this chapter and chapter four of this dissertation.

1.4 Rawal's Total Synthesis of (±)-*N*-Methylwelwitindolinone D Isonitrile and Related Studies

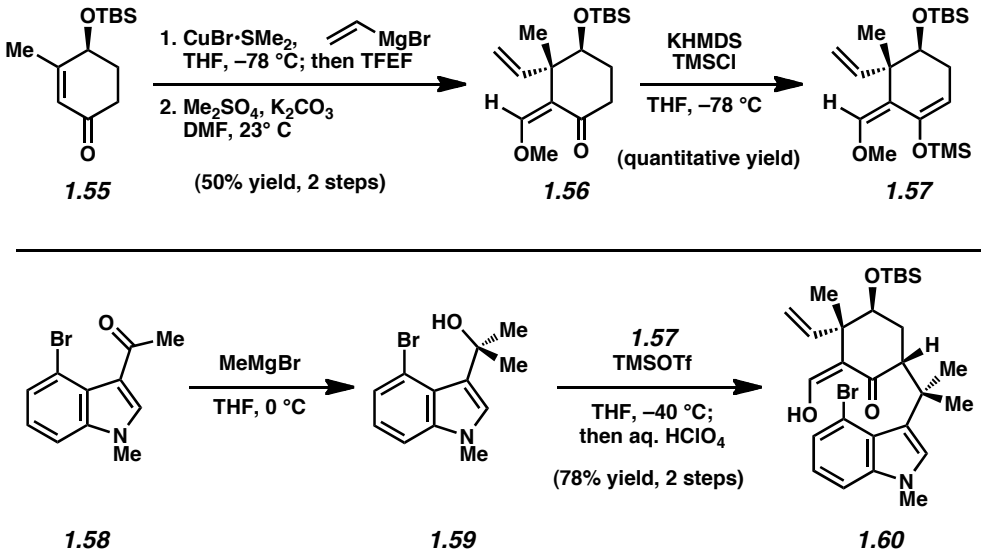
1.4.1 Assembly of the Bicyclo[4.3.1]decane Core

In 2011, Rawal reported the first total synthesis of any bicyclic welwitindolinone.[11b] Their synthetic route relies upon a palladium-catalyzed enolate coupling to form the key C4–C11 bond

found in the bicyclic welwitindolinones, as well as an uncommon aldoxime rearrangement to ultimately form the isonitrile moiety.

Starting from known enone **1.55**,[19] a sequence involving vinyl cuprate addition, quenching with 2,2,2-trifluoroethylformate (TFEF), and subsequent *O*-methylation provided the vinylogous ester **1.56** (Scheme 1.6).[20] Subsequent formation of TMS enol ether **1.57** proceeded smoothly to complete one of the coupling fragments. The remaining coupling partner was swiftly prepared from 4-bromo-*N*-methyl-3-acetyl indole (**1.58**). Treatment of ketone **1.58** with methylmagnesium bromide furnished tertiary alcohol **1.59**.[21] Upon reaction of **1.59** and crude silyl enol ether **1.57**, Lewis acid-mediated alkylative coupling occurred to provide vinylogous acid **1.60** as a single diastereomer.

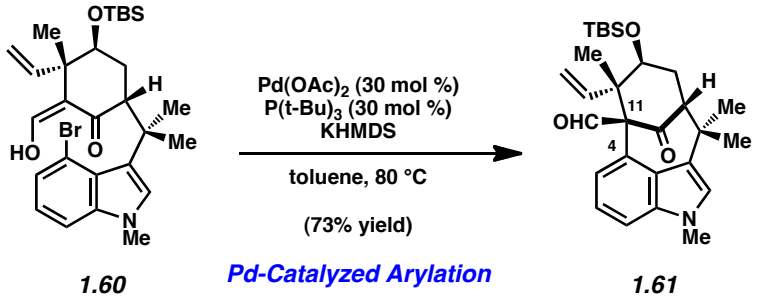
Scheme 1.6



It was expected that a palladium-catalyzed enolate coupling could be employed to forge the congested C4–C11 bond and build the critical bicyclo[4.3.1]decane framework (Scheme

1.7).[22] An exhaustive search of palladium sources, ligands, solvents, and bases revealed $Pd(OAc)_2$, tri-*tert*-butylphosphine, KHMDS, and toluene to be the optimal conditions for the desired transformation. At 80 °C, formation of bicycle **1.61** took place in 73% yield and set the stage for the completion of the total synthesis. It should be noted that Rawal has recently described a complementary method for assembling the C4–C11 bond in welwitindolinone model studies using a Mn-promoted oxidative cyclization.[11d]

Scheme 1.7



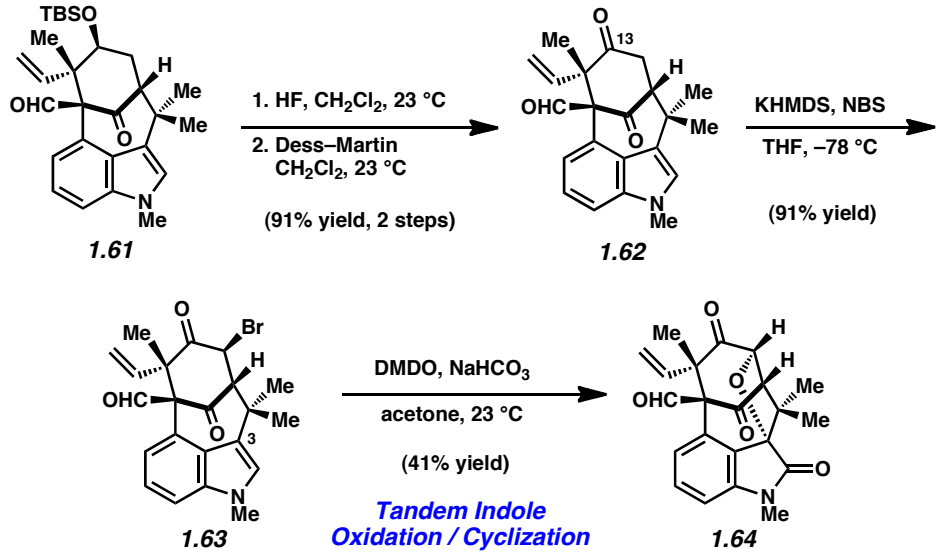
1.60 ***1.61***

1.4.2 Introduction of the Tetrahydrofuran Ring

Following formation of the bicycle, focus shifted to construction of the last ring of the natural product: the spiro-fused tetrahydrofuran. Desilylation of **1.61** followed by Dess–Martin oxidation smoothly delivered diketone **1.62** (Scheme 1.8). It was thought that α-bromination of the C13 ketone would provide a suitable intermediate to be intercepted by an in situ-generated 3-hydroxyoxindole moiety. Electrophilic bromination was expected to occur on the less hindered side of **1.62**, toward the one-carbon bridge of the bicycle, properly orienting the halide for subsequent displacement. Gratifyingly, regio- and stereoselective bromination occurred upon sequential treatment of ketone **1.62** with KHMDS and *N*-bromosuccinimide (NBS) to give bromodiketone **1.63**. Oxidation of the indole with dimethyldioxirane (DMDO) provided the

desired tetrahydrofuran-containing product **1.64**. This ambitious step presumably proceeds through the cyclization of a 3-hydroxy oxindole intermediate, just as the authors had intended.

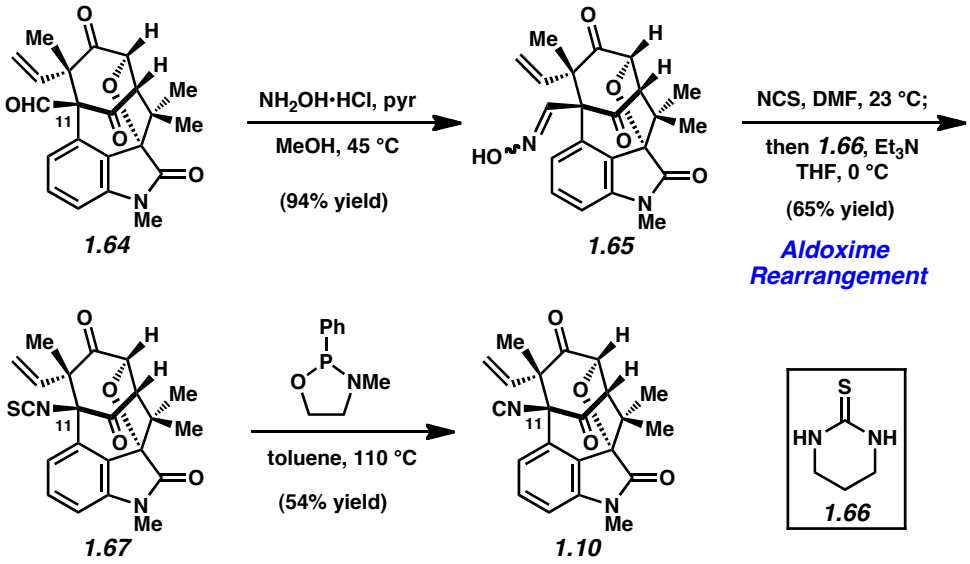
Scheme 1.8



1.4.3 Late-Stage Aldoxime Rearrangement and Completion of Total Synthesis

With the end in sight, the final obstacle was to convert the C11 aldehyde substituent to the desired isonitrile. To this end, Rawal and co-workers smoothly converted aldehyde **1.64** to oxime **1.65** (Scheme 1.9). Subsequent treatment of **1.65** with *N*-chlorosuccinimide (NCS) and propylenethiourea **1.66** gave isothiocyanate **1.67** in 65% yield.[23] Finally, desulfurization using *N*-methyl-*P*-phenyl-1,3,2-oxazaphospholidine delivered (±)-*N*-methylwelwitindolinone D isonitrile (**1.10**).[24] The last steps are notable in that both C11 isothiocyanate and isonitrile moieties are accessible, as these functional groups appear in all members of the bicyclic welwitindolinones (i.e., **1.2–1.10**).

Scheme 1.9



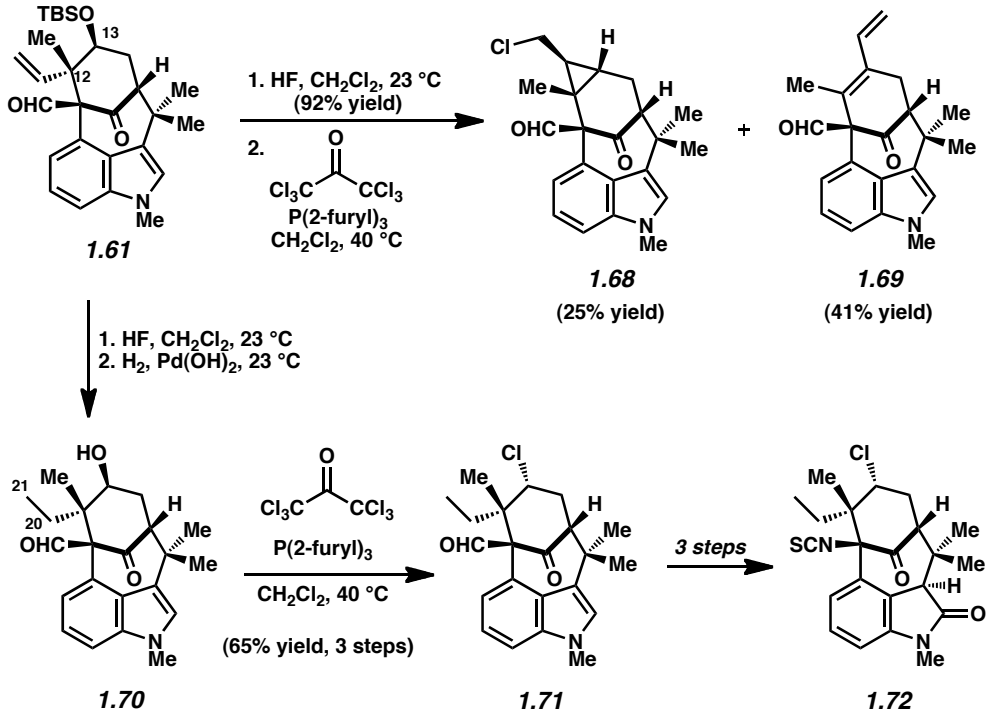
Rawal's elegant route to (±)-**1.10**, which proceeds in only 12 steps from enone **1.55**, provided the first total synthesis of a welwitindolinone with a bicyclo[4.3.1]decane core. The synthesis highlights the remarkable ability of Pd catalysis to build complex molecular frameworks, as seen similarly in the works of Trost and Martin, respectively. Notably, even very sterically congested systems, such as the vicinal quaternary stereocenters present in intermediate **1.61**, may be assembled by metal-catalyzed transformations. Rawal's use of a late-stage aldoxime rearrangement to install the bridgehead nitrogen substituent (**1.65→1.67**, Scheme 1.9) underscores the impressive utility of classic chemistry in a remarkably complex setting.

1.4.4 Unexpected Late-Stage Reactivity and the Synthesis of 20,21-Dihydro-*N*-methylwelwitindolinone B Isothiocyanate

Shortly after disclosing their synthesis of **1.10**, the Rawal group reported a concise approach to the unnatural compound 20,21-dihydro-*N*-methylwelwitindolinone B isothiocyanate.[11c] This route commenced with aldehyde **1.61**, an intermediate used in the

synthesis of (±)-**1.10** (Scheme 1.10). It was envisioned that installation of the alkyl chloride would be possible via nucleophilic displacement of an activated hydroxyl group. However, following desilylation of TBS ether **1.61**, treatment with tri(2-furyl)phosphine (TFP) and hexachloroacetone did not produce the desired alkyl chloride. Instead, methylcyclopropyl chloride **1.68** and diene **1.69** were seen as the major products.[25] The authors hypothesized that an interaction between the π-system of the vinyl group attached to C12 and an intermediate carbocation at C13 ultimately led to these undesired products. Thus, the offending vinyl group was removed by hydrogenation. Exposure of intermediate **1.70** to the same chlorination conditions then furnished **1.71**, containing the desired alkyl chloride. Indolyl aldehyde **1.71** was then elaborated to **1.72**, the unnatural dihydro derivative of *N*-methylwelwitindolinone B isothiocyanate through three additional steps. Although the natural product *N*-methylwelwitindolinone B isothiocyanate has yet to be synthesized, the formation of the undesired products **1.68** and **1.69** serves as a reminder of the unexpected side-reactions that often occur when manipulating intricate late-stage compounds.

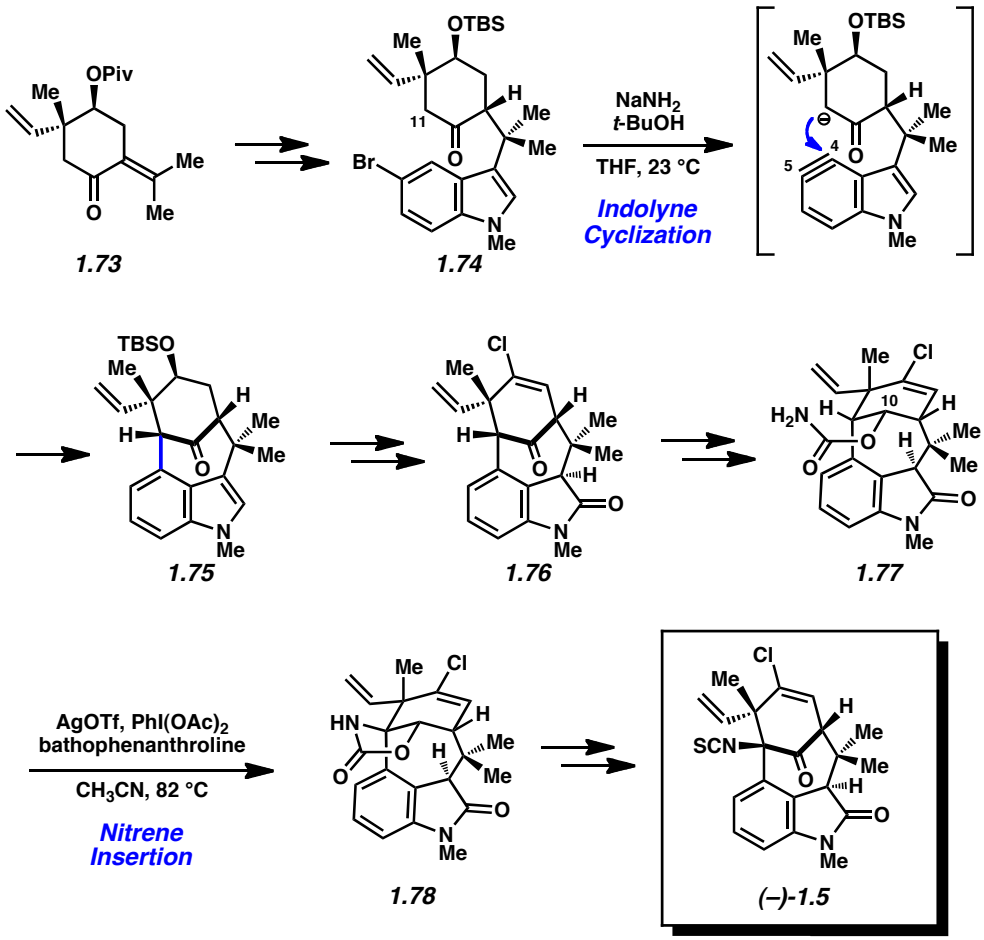
Scheme 1.10



1.5 Garg's Total Synthesis of (–)-*N*-Methylwelwitindolinone C Isothiocyanate

The Garg group reported the enantiospecific total synthesis of (–)-*N*-methylwelwitindolinone C isothiocyanate (**1.5**) in 2011.[12b] The route to the natural product is summarized in Scheme 1.11 and features a number of key transformations, including: (a) an iodine-catalyzed conjugate addition[26] to assemble the carbon framework of the natural product, (b) a challenging indolyne[27,28] cyclization to construct the C4–C11 bond of the bicycle (**1.74→1.75**), and (c) a late-stage nitrene insertion[29] to install the bridgehead nitrogen substituent (**1.77→1.78**). Full details of this total synthesis will be further discussed in chapter four of this dissertation.

Scheme 1.11



1.6 Conclusions

In summary, the bicyclic welwitindolinones have garnered tremendous attention from the chemical community because of their wide range of biological properties and challenging structural features. With the numerous laboratories working on these compounds worldwide, a variety of ambitious synthetic approaches have been disclosed. The combination of classical chemistry and new synthetic innovations has led to striking progress in the field, along with many lessons that may be useful in future synthetic studies. Beyond the ambitious approaches

and recently completed syntheses described here, it is certain that further breakthroughs in the welwitindolinone arena will be unveiled in due course.[30]

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CHAPTER TWO

Concise Synthesis of the Bicyclic Scaffold of *N*-Methylwelwitindolinone C Isothiocyanate via an Indolyne Cyclization

Xia Tian, Alexander D. Huters, Colin J. Douglas, and Neil K. Garg.

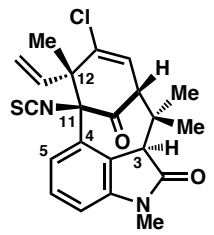
Org. Lett. **2009**, *11*, 2349–2351.

2.1 Abstract

A concise synthesis of the *N*-methylwelwitindolinone C isothiocyanate scaffold is disclosed. The approach relies on an indolyne cyclization to construct the bicyclo[4.3.1]decane ring system present in the natural product. Subsequent oxidation of the indole core occurs with excellent diastereoselectivity to afford oxindole **2.2**, the structure of which was confirmed by X-ray crystallographic analysis.

2.2 Introduction

N-Methylwelwitindolinone C isothiocyanate (**2.1**, Figure 2.1), was first isolated from the blue-green algae *Hapalosiphon welwitschii* in 1994 by Moore and co-workers.[1,2] **2.1** was found to reverse multiple drug resistance (MDR) to a variety of anti-cancer drugs, thus rendering it an attractive agent for the treatment of drug-resistant tumors.[3,4] The unique structural framework of **2.1**, coupled with its impressive biological profile, has attracted considerable attention from the synthetic community over the last decade.[5] Although numerous approaches to **2.1** have been reported,[6,7,8,9,10,11,12,13] a total synthesis of this unique target has remained elusive. In this chapter, we disclose a concise approach to the bicyclo[4.3.1]decane core of **2.1** using an indolyne cyclization.



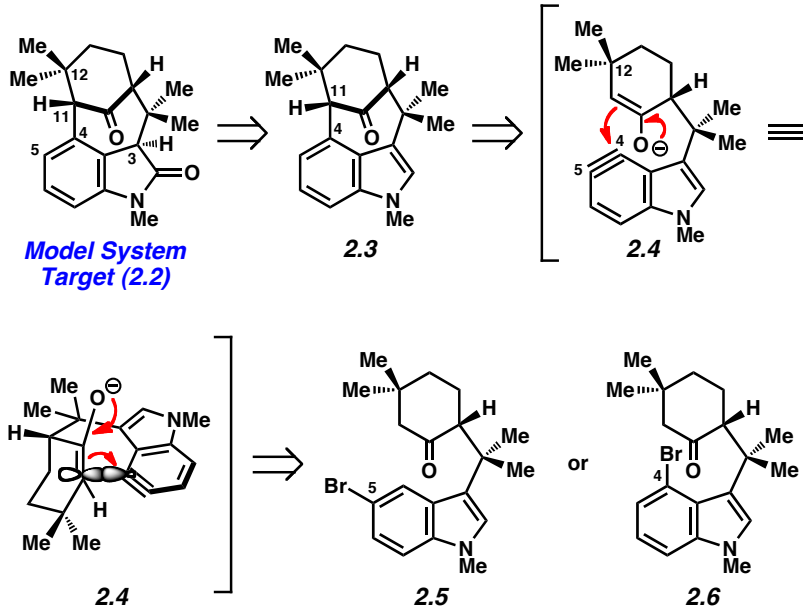
***N*-methylwelwitindolinone C isothiocyanate (2.1)**

Figure 2.1. *N*-Methylwelwitindolinone C isothiocyanate (**2.1**)

2.3 Retrosynthetic Analysis of Model System Target

With the aim of developing a concise route to the bicycle present in **2.1**, oxindole **2.2** was selected as a suitable model system target (Scheme 2.1). It was envisioned that oxindole **2.2** could be derived from indole precursor **2.3** through a diastereoselective oxidation reaction. In the key retrosynthetic disconnection, the C4–C11 bond of bicycle **2.3** would arise via a cyclization of an enolate onto an electrophilic indole, or indolyne[14,15,16] (see transition structure **2.4**). Although the enolate participating in this reaction would be adjacent to the congested C12 quaternary center, the desired cyclization seemed favorable given that the intermediate indolyne would be extremely reactive. Furthermore, the stereoelectronics for bicycle formation appeared optimal, as suggested in Scheme 2.1. Inspired by classic methods for aryne generation,[17] it was envisioned that the desired indolyne intermediate could be accessed in situ from either 5- or 4-brominated substrates, **2.5** or **2.6**, respectively.

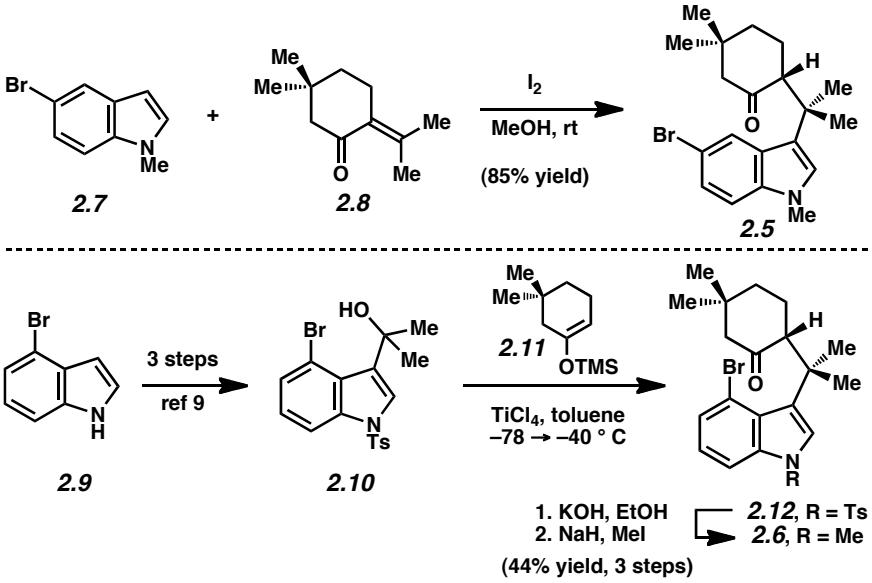
Scheme 2.1



2.4 Synthesis of Cyclization Precursors

Our synthetic routes to the desired cyclization precursors **2.5** and **2.6** are depicted in Scheme 2.2. To access 5-brominated substrate **2.5**, readily available 5-bromo-*N*-methylindole (**2.7**)[18] was allowed to react with enone **2.8**[19] in the presence of I_2 in MeOH following the general method described by Wang and co-workers.[20] This approach led to the single-step formation of the 5-brominated cyclization substrate **2.5** in 85% yield. Unfortunately, the analogous route to 4-brominated substrate **2.6** was less fruitful.[21] Nonetheless, substrate **2.6** could be prepared in six steps from 4-bromoindole following the robust approach developed by Rawal.[9] Thus, 4-bromoindole (**2.9**) was elaborated to known tertiary alcohol **2.10** over 3 steps.[9] Upon treatment of **2.10** with $TiCl_4$ and enoxysilane **2.11**,[22] Ts-indole **2.12** was obtained. Subsequently, a two-step detosylation / methyl protection sequence provided the desired substrate **2.6**.

Scheme 2.2

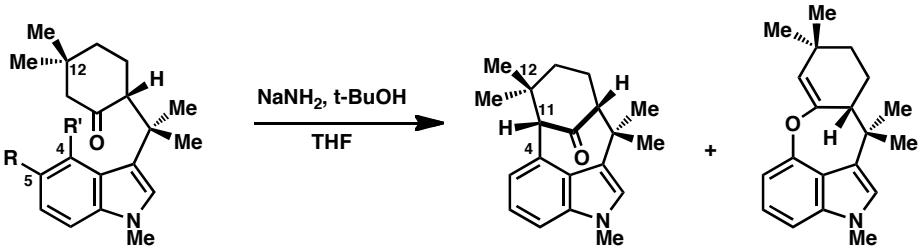


2.5 Indolyne Cyclization to Assemble the Bicyclo[4.3.1]decane Framework

Table 2.1 highlights the results of our efforts to effect the indolyne cyclization of substrates **2.5** and **2.6**. Gratifyingly, both substrates could be converted to the desired bicycle **2.3** upon reaction with $NaNH_2$/*t*-BuOH[23] in THF.[24] Although the yield is modest, several significant aspects of our cyclization results should be noted: a) the desired *C*-arylated product **2.3** is the major compound produced in the cyclizations, albeit with *O*-arylated product **2.13** being formed competitively;[25,26,27] b) 4-brominated substrate **2.6** requires higher temperatures to induce product formation; this result may be explained by the greater acidity of the C4 proton of substrate **2.5** in comparison to the C5 proton of **2.6**;[28] c) whereas the dehydrohalogenation of 5-bromo substrate **2.5** could plausibly lead to undesirable mixtures of 4,5- and 5,6-indolyne intermediates, formation of the desired 4,5-indolyne appears to be favored; d) the use of 5-brominated substrate **2.5** to access bicycle **2.3** is generally preferred, as the synthesis of **2.5** is concise, high-yielding, and ultimately begins with inexpensive 5-bromoindole.[29] Moreover, it is notable that a 5-

substituted substrate could be used as the synthetic precursor to the desired 4-substituted product. Our studies are the first to describe direct formation of the bicyclo[4.3.1]decane scaffold of **2.1** through assembly of the C4–C11 bond with an adjacent quaternary center at C12.

Table 2.1



2.5, R = Br, R' = H
2.6, R = H, R' = Br

2.3

2.13

substrate	temperature	yield[a]	ratio (***2.3***:***2.13***)
2.5	23 °C	56% (62%)	1.2:1
2.6	23 °C	no reaction	—
2.6	50 °C	64%	1:1

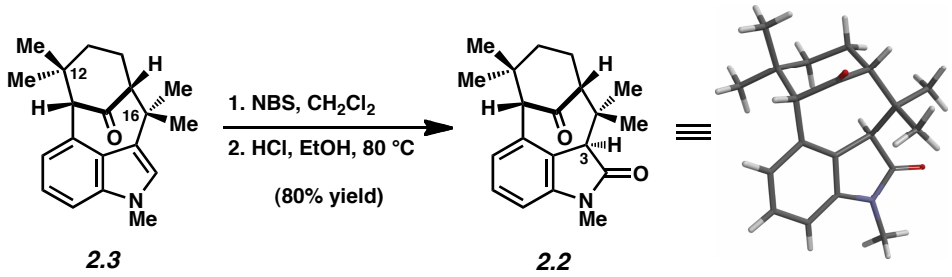
[a] combined isolated yield of **2.3** and **2.13**. Yield in parenthesis reflects yield based on recovered substrate

2.6 Oxidation to Model System Target

To date, most of the disclosed approaches to *N*-methylwelwitindolinone C isothiocyanate (**2.1**) plan for a late-stage diastereoselective indole oxidation to furnish the oxindole found in the natural product.[8,9,10,11,12] However, only two studies toward this goal have been documented,[10a,30] whereby attempted oxidation of model system substrates predominatly afforded the undesired epimers of the corresponding oxindole products. After extensive experimentation, we have found that bicyclic indole **2.3** can be cleanly converted to oxindole **2.2** through a two-step sequence involving treatment with NBS to afford the corresponding C-2 brominated indole, followed by HCl-promoted hydrolysis (Scheme 2.3). Fortunately, a single diastereomer of product was

obtained. X-ray diffraction studies revealed that **2.2** possessed the desired stereochemical configuration at C3, as shown below.

Scheme 2.3



2.3 ***2.2***

2.7 Conclusion

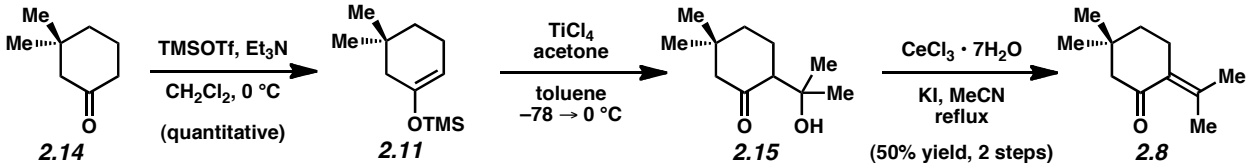
In summary, we have developed a concise approach to the bicyclic scaffold of *N*-methylwelwitindolinone C isothiocyanate (**2.1**). Our strategy involves an expedient synthesis of bromoindole **2.5**, an indolyne cyclization to forge the congested C4–C11 bond of bicycle **2.3**, and a diastereoselective oxidation to deliver oxindole **2.2**. Efforts to access related structures that possess a C11 nitrogen substituent, in addition to studies aimed at completing the total synthesis of **2.1**, will be discussed in the subsequent chapters of this dissertation.

2.8 Experimental Section

2.8.1 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 with the following exceptions. 4- and 5-bromoindole were obtained from VWR (manufactured by Combi-Blocks, Inc). Acetone was distilled from calcium sulfate at ambient pressure. *N*-bromosuccinimide was recrystallized from water. 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, ceric ammonium molybdate, and potassium permanganate staining. EMD silica gel 60 (particle size 0.040–0.063 mm) was used for flash column chromatography. ^{1}H NMR spectra were recorded on Bruker spectrometers (at 500 MHz) and are reported relative to deuterated solvent signals. Data for ^{1}H NMR spectra are reported as follows: chemical shift (d ppm), multiplicity, coupling constant (Hz) and integration. ^{13}C NMR spectra were recorded on Bruker Spectrometers (at 125 MHz). Data for ^{13}C NMR spectra are reported in terms of chemical shift. IR spectra were recorded on a Perkin-Elmer 100 spectrometer and are reported in terms of frequency of absorption (cm^{-1}). Melting points are uncorrected and were obtained on a Laboratory Devices Mel-Temp II. High resolution mass spectra were obtained from the UC Irvine Mass Spectrometry Facility.

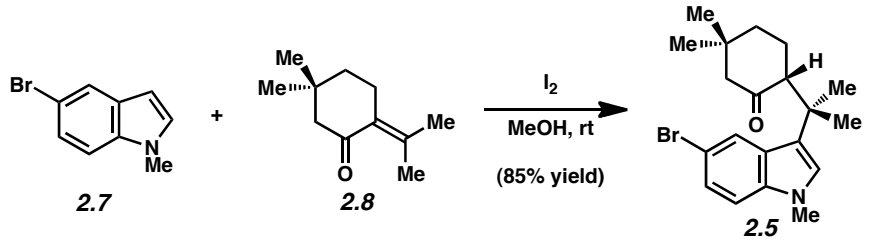
2.8.2 Experimental Procedures



Enone 2.8. Known enone **2.8** was prepared by a modification of the general method described by Marcantoni.[31] To a solution of 3,3-dimethylcyclohexanone **2.14** (0.718 mL, 5.18 mmol, 2.4 equiv) in CH_2Cl_2 (150 mL) at 0 °C was added triethylamine (1.00 mL, 7.34 mmol, 3.4 equiv) followed by TMSOTf (1.17 mL, 6.48 mmol, 3 equiv). The mixture was stirred for 30 min, then the reaction was quenched with a solution of saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL). The layers were separated and the aqueous layer was then extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to afford silyl enol ether **2.11** (quantitative yield) which could be used without further purification. Characterization data match those previously reported.[32] ^{1}H NMR (500 MHz, $CDCl_3$): d 4.84–4.82 (m, 1H), 2.05–2.00 (m, 2H), 1.77 (s, 2H), 1.26 (t, J = 6.4, 2H), 0.92 (s, 6H), 0.17 (s, 9H).

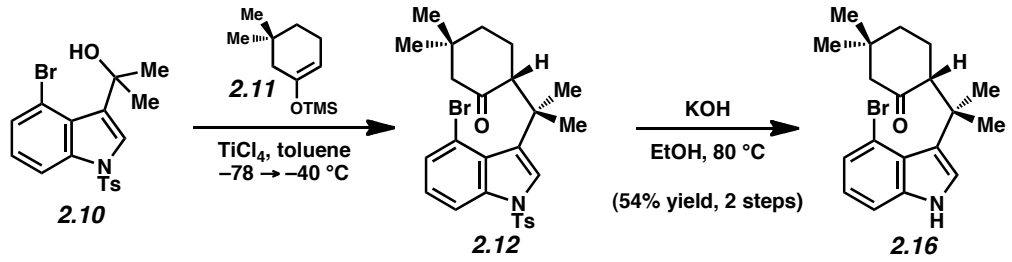
Silyl enol ether **2.11** was azeotropically dried by evaporation from benzene (3 mL) prior to use. To a solution of silyl enol ether **2.11** (28.6 mmol, 1 equiv) in CH_2Cl_2 (90 mL) at 0 °C was added acetone (2.30 mL, 31.4 mmol, 1.1 equiv) followed by $TiCl_4$ (3.31 mL, 30.0 mmol, 1.05 equiv) as a steady stream down the side of the flask. The mixture was stirred for 15 min and then quenched with ice cold $NaHSO_4$ (100 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 25 mL) and the combined organic layers dried over Na_2SO_4. Removal of the solvent under reduced pressure afforded crude cross aldol product **2.15**, which was used without purification.

To a heterogeneous solution of $CeCl_3 \bullet 7H_2O$ (17.7 g, 47.6 mmol, 2.5 equiv) and KI (8.00 g, 47.6 mmol, 2.5 equiv) in MeCN (150 mL) that had been refluxed for 12 h was added **2.15** neat at rt. The mixture was refluxed for 4 h, cooled to rt, and then filtered to remove solids. The filtrate was concentrated *in vacuo* to remove most of the organic solvent and then partitioned between a solution of $Na_2S_2O_3$ (50 mL) and Et_2O (50 mL). The aqueous layer was extracted with Et_2O (3 x 15 mL) and the combined organic layers dried over Na_2SO_4. The solvent was removed *in vacuo* and the crude residue was purified by flash chromatography (1:19 Et_2O:hexanes) to afford enone **2.8** (2.82 g, 50% yield over three steps). Enone **2.8**: R_f 0.78 (1:1 Hexanes:Et_2O); ^1H NMR (500 MHz, $CDCl_3$): d 2.46 (t, J = 6.5, 2H), 2.17 (s, 2H), 1.94 (s, 3H), 1.75 (s, 3H), 1.55 (t, J = 6.5, 2H), 0.95 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): d 204.1, 142.0, 131.1, 56.1, 37.4, 33.5 28.3, 26.0, 23.0, 22.1; IR (film): 2955, 2868, 1682, 1615, 1453, 1286 cm^{-1}; HRMS-ESI (m/z) [M + Na]$^+$ calcd for $C_{11}H_{18}ONa$, 189.1255; found, 189.1259.



Bromoindole 2.5. Bromoindole **2.5** was prepared following the general procedure reported by Wang et al.[20] with minor modifications. To enone **2.8** (0.50 g, 3.0 mmol, 1 equiv) was added 5-bromo-*N*-methylindole (**2.7**)[18] (0.95 g, 4.5 mmol, 1.5 equiv) followed by methanol (6.0 mL). The mixture was allowed to stir at 23 °C until homogenous, then I_2 (0.15 g, 0.60 mmol, 0.2 equiv) was added in two portions. The resulting mixture was stirred for 14 h, and then quenched with saturated aqueous $Na_2S_2O_3$ (20 mL). The resulting mixture was allowed to stir until the I_2 color disappeared. The mixture was extracted with Et_2O (5 x 10 mL). The combined organic layers

were dried with Na_2SO_4 and then concentrated to dryness *in vacuo*. Purification by flash chromatography (1:9 to 2:3 CH_2Cl_2:hexanes) provided bromoindole **2.5** (0.96 g, 85% yield) as a white foam. Bromoindole **2.5**: R_f 0.24 (1:1 CH_2Cl_2:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.81 (d, *J* = 2, 1H), 7.26 (dd, *J* = 8.5, 2, 1H), 7.15 (d, *J* = 8.5, 1H), 6.82 (s, 1H), 3.72 (s, 3H), 2.88 (dd, *J* = 9.5, 8.5, 1H), 2.29 (d, *J* = 12.5, 1H), 2.00 (dd, *J* = 12.3, 2.3, 1H), 1.63–1.60 (m, 2H), 1.59 (s, 3H), 1.53–1.50 (m, 1H), 1.48 (s, 3H), 1.45 (dd, *J* = 6, 3.5, 1H), 1.00 (s, 3H), 0.85 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 211.7, 136.3, 127.31, 127.27, 123.7, 123.3, 123.2, 111.7, 110.8, 56.9, 56.7, 38.8, 37.2, 36.3, 32.7, 31.6, 26.7, 25.7, 25.2, 23.4; IR (film): 2955, 1704, 1477, 1421, 1360, 1228 cm^{-1}; HRMS-ESI (*m/z*) [M + Na]$^+$ calcd for $C_{20}H_{26}BrNONa$, 398.1096; found, 398.1091.

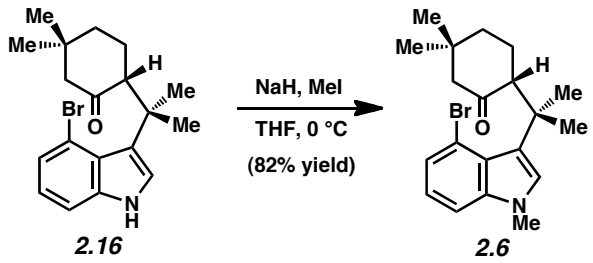


Indole **2.16**. Ts-indole **2.12** was prepared following the general procedure developed by Rawal.[9] To a solution of the silyl enol ether **2.11** and known tertiary alcohol **2.10**[9] (880 mg, 2.16 mmol, 1 equiv) in toluene (20 mL) at –78 °C was added $TiCl_4$ (0.523 mL, 4.74 mmol, 2.2 equiv) as a steady stream. The reddish brown mixture was allowed to warm to 0 °C over 1 h to facilitate stirring of the viscous reaction mixture. The reaction was quenched at 0 °C with saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL). The aqueous layer was extracted with EtOAc (3 x 25 mL). The combined organic layers washed with 1 M HCl (20 mL), then brine (20 mL), and then dried over Na_2SO_4. After removal of solvent, the crude residue was passed over a plug of

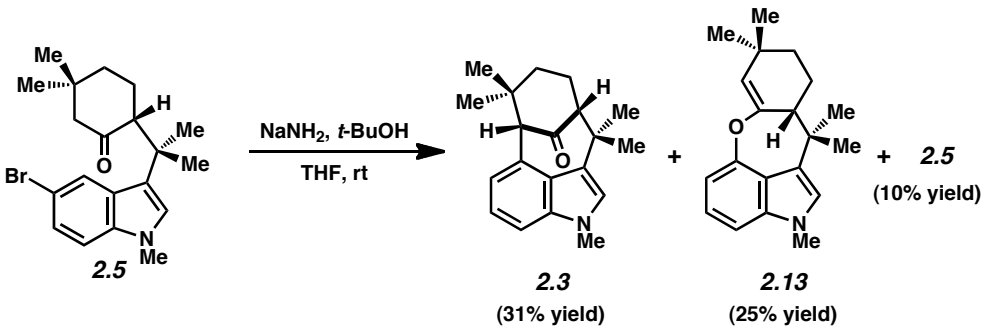
silica gel (5.5 x 2 cm**,** 1:1 mixture of hexane/ether) to afford Ts-indole **2.12**, which was used in the next step without further purification. An analytically pure sample of **2.12** was obtained by preparative thin layer chromatography (1:1 hexanes:Et_2O). Ts-indole **2.12**: R_f 0.25 (1:1 CH_2Cl_2:Hexanes); ^{1}H NMR (500 MHz, $CDCl_3$): d 8.00 (d, *J* = 8.2, 1H), 7.71 (d, *J* = 8.3, 2H), 7.57 (bs, 1H), 7.50 (d, *J* = 7.8, 1H), 7.22 (d, *J* = 8.3, 2H), 7.07 (dd, *J* = 8.2, 8.0, 1H), 3.96 (dd, *J* = 11.9, 5.9, 1H), 2.34 (s, 3H), 2.20 (d, *J* = 9.8, 1H), 1.98 (d, *J* = 11.0, 1H), 1.72 (s, 3H), 1.70–1.61 (m, 1H), 1.60–1.40 (m, 3H), 1.56 (s, 3H), 1.00 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): d 211.0, 145.0, 137.9, 134.5, 130.9, 129.9, 129.8, 128.9, 126.8, 125.6, 124.7, 113.6, 113.2, 57.0, 54.7, 38.8, 36.9, 36.3, 31.7, 25.5, 25.0, 21.5; IR (film) 2954, 1705, 1365, 1172 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{26}H_{30}NO_3SBrNa$, 538.1027; found, 538.1027.

To a solution of Ts-indole **2.12** (2.16 mmol, 1 equiv) in EtOH (20 mL) and THF (10 mL) at 23 °C was added powdered KOH (2.40 g, 43.2 mmol, 20 equiv). The mixture was heated to 50 °C and stirred for 1 h. The reaction was cooled to rt, then quenched with saturated aqueous NH_4Cl (10 mL) and brine (20 mL). The mixture was extracted with EtOAc (3 x 20 mL) and the combined organic layers were dried over Na_2SO_4. The crude residue was purified by flash chromatography (3:1:1 petroleum ether:CH_2Cl_2:Et_2O) to afford indole **2.16** as a white foam (422 mg, 54% yield over two steps). Indole **2.16**: R_f 0.43 (2:1:1 Hexanes:CH_2Cl_2:Et_2O); ^{1}H NMR (500 MHz, $CDCl_3$): d 8.50 (bs, 1H), 7.40 (d, *J* = 7.5, 1H), 7.30 (d, *J* = 8.0, 1H), 7.11 (s, 1H), 6.97 (dd, *J* = 7.8, 7.8, 1H), 4.15 (dd, *J* = 10.5, 7, 1H), 2.28 (dd, *J* = 6.4, 6.3, 1H), 1.99 (d, *J* = 9.5, 1H), 1.91–1.86 (m, 1H), 1.77 (s, 3H), 1.70–1.62 (m, 1H), 1.58 (s, 3H), 1.54–1.44 (m, 2H), 1.01 (s, 3H), 0.88 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): d 212.7, 139.4, 125.7, 125.4, 124.7, 123.6, 122.1, 113.5, 111.0, 57.3, 56.1, 40.8, 39.0, 37.9, 37.2, 31.7, 28.5, 25.1, 22.5; IR (film) 3350,

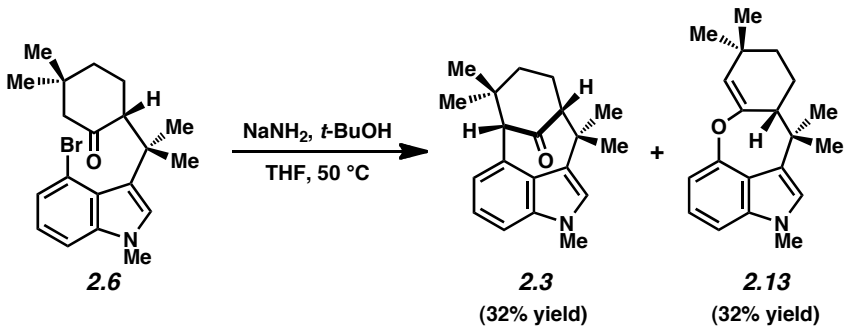
2953, 1693, 1025 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{19}H_{24}NOBrNa$, 384.0939; found, 384.0941.



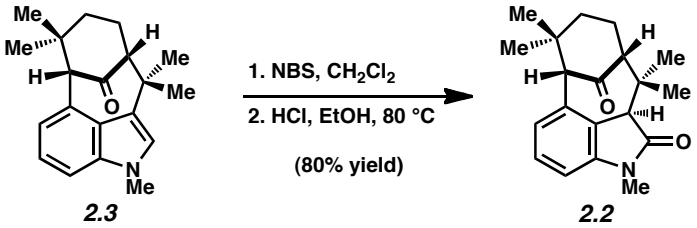
Methylindole 2.6. To a solution of **2.16** (90 mg, 0.25 mmol, 1 equiv) in THF (2 mL) at 0 °C was added NaH (8.0 mg, 0.32 mmol, 1.3 equiv). The mixture was stirred for 15 min and then MeI (19 μL, 0.30 mmol, 1.2 equiv) was added. After the reaction was stirred for 30 min, it was quenched with water (1 mL) and NH_4Cl (1 mL). The resulting mixture was extracted with EtOAc (3 x 20 mL) and the combined organic extracts were dried over Na_2SO_4. The crude residue was purified by flash chromatography (4:1 hexanes:Et_2O) to provide methylindole **2.6** as a clear oil (77 mg, 82%). Methylindole **2.6**: R_f 0.5 (1:1 hexanes:Et_2O); ^1H NMR (500 MHz, $CDCl_3$): d 7.39 (d, *J* = 7.5, 1H), 7.25 (d, *J* = 9, 1H), 7.01 (dd, *J* = 7.9, 7.9, 1H), 7.00 (s, 1H), 4.11 (dd, *J* = 9.2, 8.1, 1H), 3.73 (s, 3H), 2.26 (d, *J* = 10.4, 1H), 1.99–1.97 (m, 1H), 1.75 (s, 3H), 1.68–1.60 (m, 3H), 1.56 (s, 3H), 1.52–1.47 (m, 1H), 1.01 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): d 212.2, 139.7, 128.5, 125.3, 125.1, 124.0, 121.6, 113.7, 108.8, 57.3, 56.1, 39.0, 37.1, 35.9, 33.0, 31.7, 25.8, 25.0; IR (film) 2951, 1702, 1416 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{20}H_{26}NOBrNa$, 398.1096; found, 398.1090.



Bicycle 2.3 (from 2.5). In a glovebox, a 10 mL Schlenk tube was charged with $NaNH_2$ (521 mg, 13.4 mmol, 10.5 equiv). The Schlenk tube was removed from the glovebox, and THF (4 mL) and *t*-BuOH (425 μL, 4.45 mmol, 3.5 equiv) were added. The tube was sealed and heated to 40 °C for 1 h, then cooled to rt. A solution of methylindole **2.5** (480 mg, 1.27 mmol, 1 equiv) in THF (5 mL) was added, and the resulting mixture was stirred at 23 °C for 24 h. The reaction vessel was cooled to 0 °C, quenched with water (6 mL), then diluted with brine (6 mL) and Et_2O (6 mL). The aqueous layer was extracted with EtOAc (3 x 20 mL) and the combined organic extracts were dried over Na_2SO_4. Evaporation under reduced pressure afforded the crude product, which was further purified by flash chromatography (1:4 to 3:7 CH_2Cl_2:benzene) to provide bicycle **2.3** as a light brown solid (118 mg, 31%), *O*-arylated product **2.13** as a clear oil (96 mg, 25%), and recovered **2.5** (48 mg, 10%). Bicycle **2.3**: R_f 0.29 (1:1 CH_2Cl_2:benzene); ^{1}H NMR (500 MHz, $CDCl_3$): d 7.18 (dd, *J* = 8.1, 1.1, 1H), 7.15 (dd, *J* = 8.1, 8.1, 1H), 6.92 (s, 1H), 6.80 (d, *J* = 10, 1H), 3.72 (s, 3H), 3.57 (s, 1H), 2.55 (d, *J* = 7.7, 1H), 2.16–2.11 (m, 1H), 2.04–1.96 (m, 1H), 1.56 (s, 3H), 1.39 (ddd, *J* = 13.9, 13.9, 5.1, 1H), 1.09 (s, 6H), 0.90–0.86 (m, 1H), 0.61 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): d 214.7, 137.1, 127.8, 125.7, 125.0, 122.6, 121.3, 120.8, 107.5, 69.3, 59.3, 40.3, 36.1, 35.2, 32.7, 30.9, 29.4, 27.7, 26.9, 23.2; IR (film): 2957, 1684, 1543, 1451, 1421, 1234 cm^{-1}; m.p. 177.5–178.9 °C; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{20}H_{25}NONa$, 318.1834; found, 318.1830.



Bicycle 2.3 from methylindole 2.6. In a glovebox, a 10 mL Schlenk tube was charged with $NaNH_2$ (67 mg, 1.7 mmol, 9 equiv). The Schlenk tube was removed from the glovebox, and THF (1 mL) and *t*-BuOH (54 μL, 0.57 mmol, 3 equiv) were added. The tube was sealed and heated to 40 °C for 1 h, then cooled to rt. A solution of methylindole **2.6** (72 mg, 0.19 mmol, 1 equiv) in THF (1 mL) was added, and the resulting mixture was stirred at 50 °C for 24 h. The reaction vessel was cooled to 0 °C, quenched with water (3 mL), then diluted with brine (3 mL) and Et_2O (3 mL). The aqueous layer was extracted with EtOAc (3 x 20 mL) and the combined organic extracts were dried over Na_2SO_4. Evaporation under reduced pressure afforded the crude product, which was further purified by flash chromatography (1:4 to 3:7 CH_2Cl_2:benzene) to provide bicycle **2.3** as a light brown solid (18 mg, 32% yield) and *O*-arylated product **2.13** as a clear oil (17 mg, 32% yield).



Oxindole 2.2. To a solution of **2.3** (100 mg, 0.338 mmol, 1 equiv) in CH_2Cl_2 (2.5 mL) was added NBS (66 mg, 0.372 mmol, 1.1 equiv). After stirring for 15 min, solid $NaHCO_3$ (100 mg) was

added and the heterogeneous mixture was stirred for 5 min. The solution was passed over a plug of silica gel (2 inches in a pipette, eluting with 10 mL of 2:1:1 hexanes: CH_2Cl_2:Et_2O). The solvent was removed *in vacuo*, and the crude 2-bromoindole intermediate was used in the next step without further purification.

The crude material from above was suspended in ethanol (5 mL) and conc. HCl (5 mL), and the mixture was heated to 80 °C for 12 h. The light brown, homogeneous solution was cooled to rt, then poured onto 10 mL of ice cold water, and then $NaHCO_3$ (20 mL) was slowly added. Once gas evolution had ceased, the solution was extracted with EtOAc (5 x 15 mL) and the combined organic extracts were dried over Na_2SO_4. The crude residue was purified by flash chromatography (3:1:1 hexanes: CH_2Cl_2:Et_2O) to afford oxindole **2.2** as a white solid (85 mg, 80% yield). Crystals suitable for X-ray diffraction studies were obtained by evaporation of **2.2** from a mixture of CH_2Cl_2 and cyclohexane. Oxindole **2.2**: R_f 0.23 (3:1:1 hexanes:CH_2Cl_2:Et_2O); ^{1}H NMR (500 MHz, $CDCl_3$): d 7.17 (dd, *J* = 7.8, 7.8, 1H), 6.72 (d, *J* = 7.8, 1H), 6.69 (d, *J* = 7.7, 1H), 3.81 (s, 1H), 3.19 (s, 1H), 3.16 (s, 3H), 2.33–2.28 (m, 2H), 2.09 (dddd, *J* = 14.5, 13.5, 7.5, 5.5, 1H), 1.76 (ddd, *J* = 14.5, 14.5, 5.3, 1H), 1.59 (s, 3H), 1.33 (dd, *J* = 14.4, 5.7, 1H), 1.04 (s, 3H), 0.85 (s, 3H), 0.64 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): d 211.2, 175.2, 144.5, 132.4, 128.0, 126.4, 124.8, 106.6, 70.0, 60.6, 53.0, 40.5, 40.1, 33.1, 29.0, 27.2, 26.2, 26.1, 22.9, 22.7; IR (film): 2959, 2873, 1691, 1607, 1590, 1457 cm^{-1}; m.p. 185.7–186.5 °C; HRMS-ESI (*m*/*z*) [M + Na]$^+$ calcd for $C_{20}H_{25}NO_2Na$, 334.1783; found, 334.1780. CCDC deposition number 729161.

2.9 Notes and References

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(2) **2.1** has sometimes been referred to as 'welwistatin'; however, as originally defined in ref 3b, 'welwistatin' refers to the des-*N*-methyl analog of **2.1**.

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(4) At concentrations as low as 0.1 mM, **2.1** was found to greatly decrease the IC_{50} of vinblastine, taxol, actinomycin D, cochicines, and daunomycin in MCF-7/ADR drug-resistant breast carcinoma cells.

(5) For a review, see: Avendaño, C.; Menéndez, J. C. *Curr. Org. Synth.* **2004**, *1*, 65–82.

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(14) For seminal studies involving indolynes, see: (a) Julia, M.; Huang, Y.; Igolen, J. *C. R. Acad. Sci., Ser. C* **1967**, *265*, 110–112. (b) Igolen, J.; Kolb, A. *C. R. Acad. Sci., Ser. C* **1969**, *269*, 54–56. For related studies, see: (c) Julia, M.; Le Goffic, F. ; Igolen, J.; Baillarge, M. *C. R. Acad. Sci., Ser. C* **1967**, *264*, 118–120. (d) Julia, M.; Igolen, J.; Kolb, A. *C. R. Acad. Sci., Ser. C* **1971**, *273*, 1776–1777.

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(18) **2.7** is commercially available, or can be easily prepared in one step from inexpensive 5-bromoindole on multigram scale; see: Jiang, X.; Tiwari, A.; Thompson, M.; Chen, Z.; Cleary, T. P.; Lee, T. B. K. *Org. Proc. Res. Dev.* **2001**, *5*, 604–608.

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(24) Alternative basic conditions commonly used to promote aryne formation were unsuccessful (e.g., LDA, LHMDS, $Me_2Zn(TMP)Li$).

(25) Prolonged reaction times led to olefin isomerization of enol ether **2.13** to afford the corresponding tetrasubstituted olefin.

(26) Utilization of the TBS or TIPS enol ether derivatives of **2.5** did not lead to improvements in yield or selectivity for *C*-arylation.

(27) Variations in temperature, stoichiometry, and counterion did not lead to improvements in the conversion of **2.5** to **2.3**.

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APPENDIX ONE

Spectra Relevant to Chapter Two:

Concise Synthesis of the Bicyclic Scaffold of *N*-Methylwelwitindolinone C Isothiocyanate via and Indolyne Cyclization

Xia Tian, Alexander D. Huters, Colin J. Douglas, and Neil K. Garg.

Org. Lett. **2009**, *11*, 2349–2351.

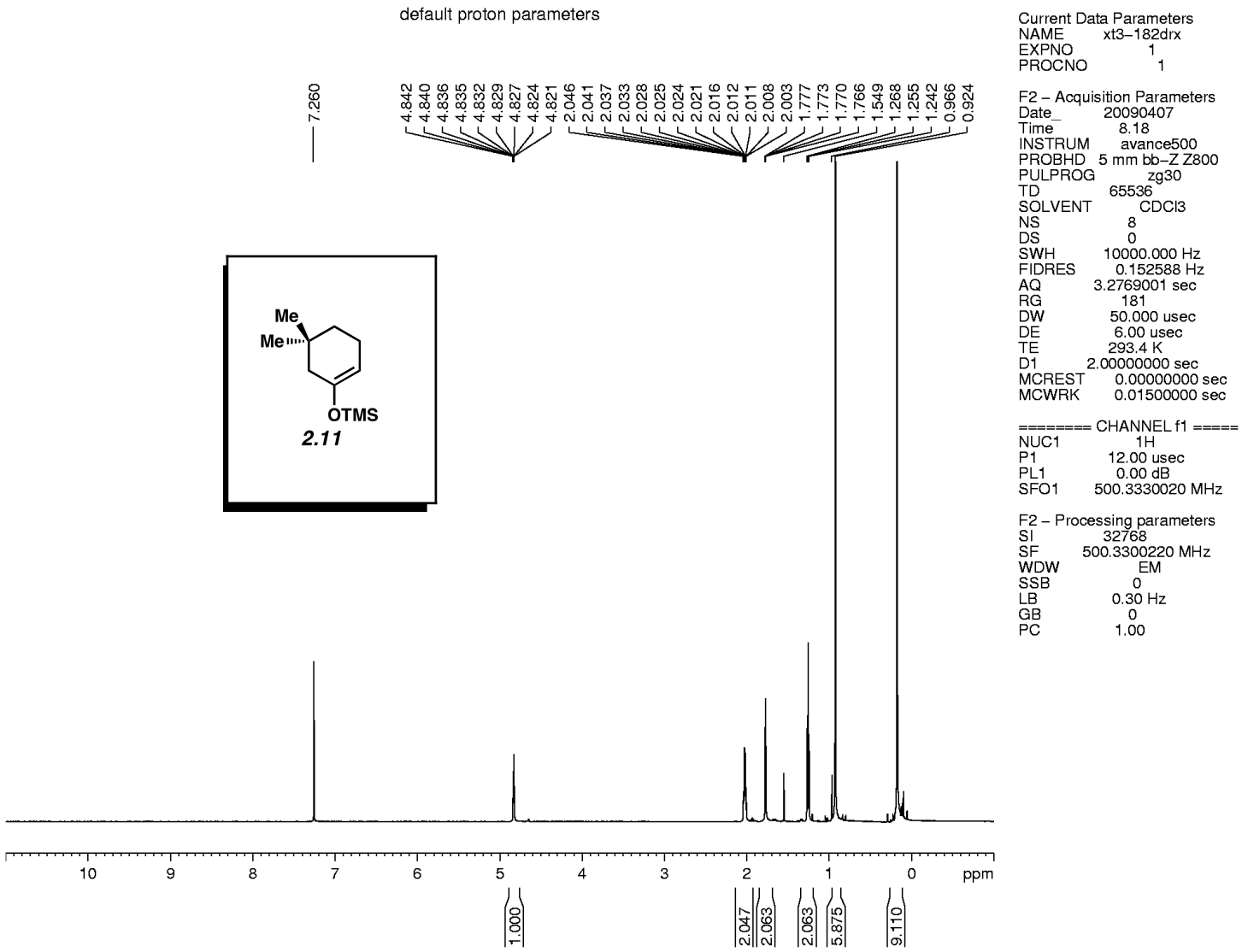

Figure A1.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **2.11**.

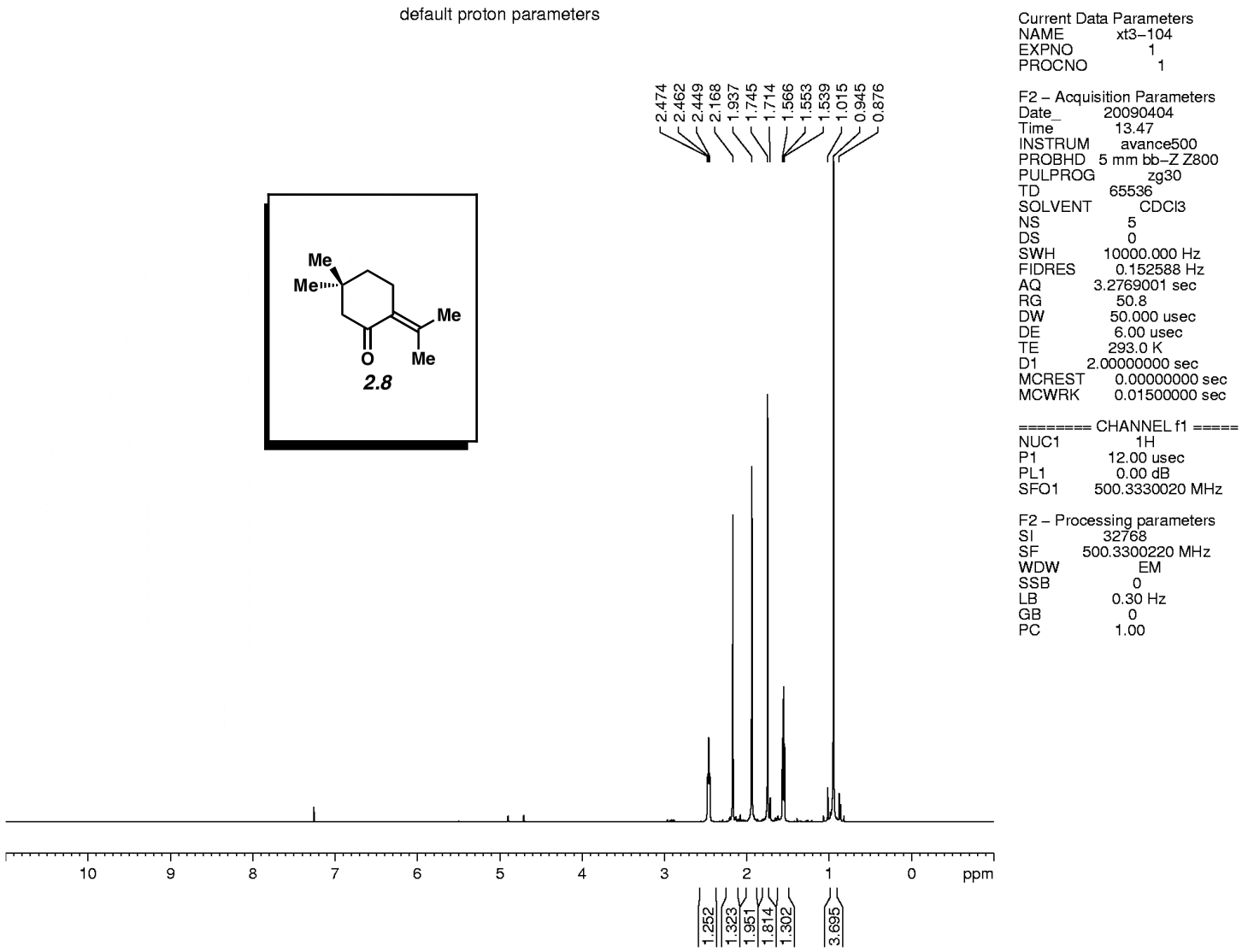

Figure A1.2 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **2.8**.

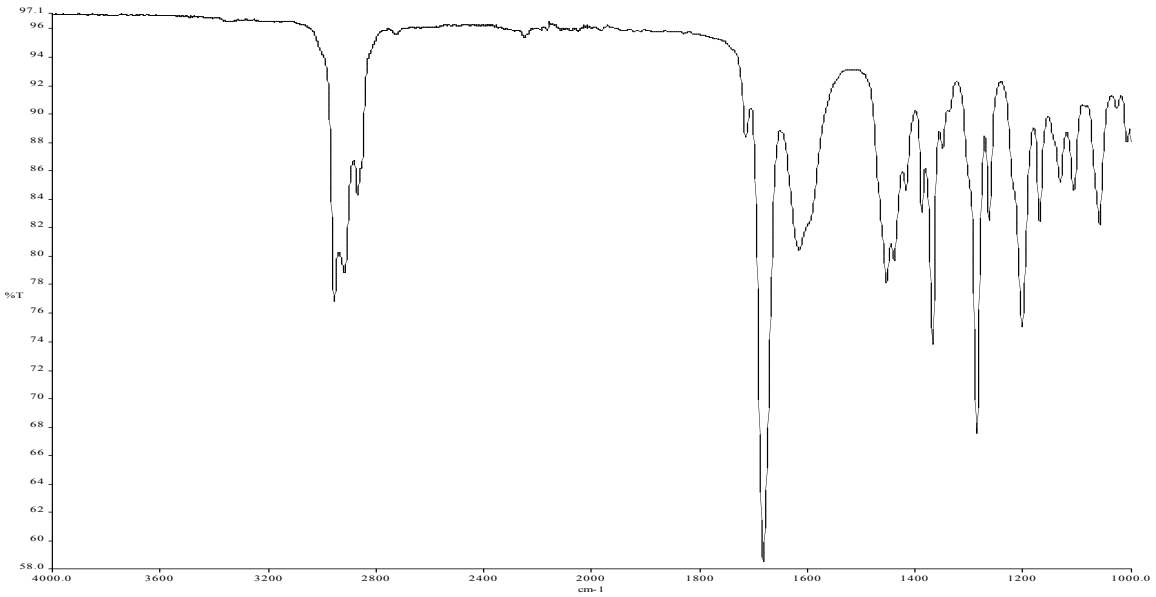

Figure A1.3 Infrared spectrum of compound **2.8**.

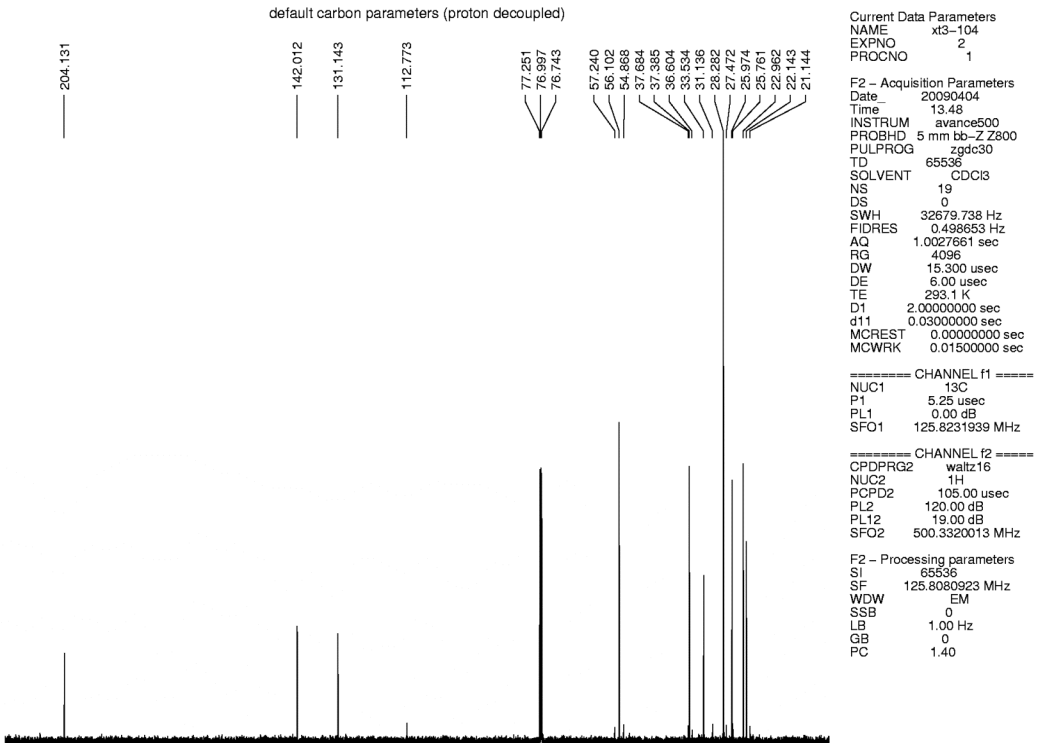

Figure A1.4 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **2.8**.

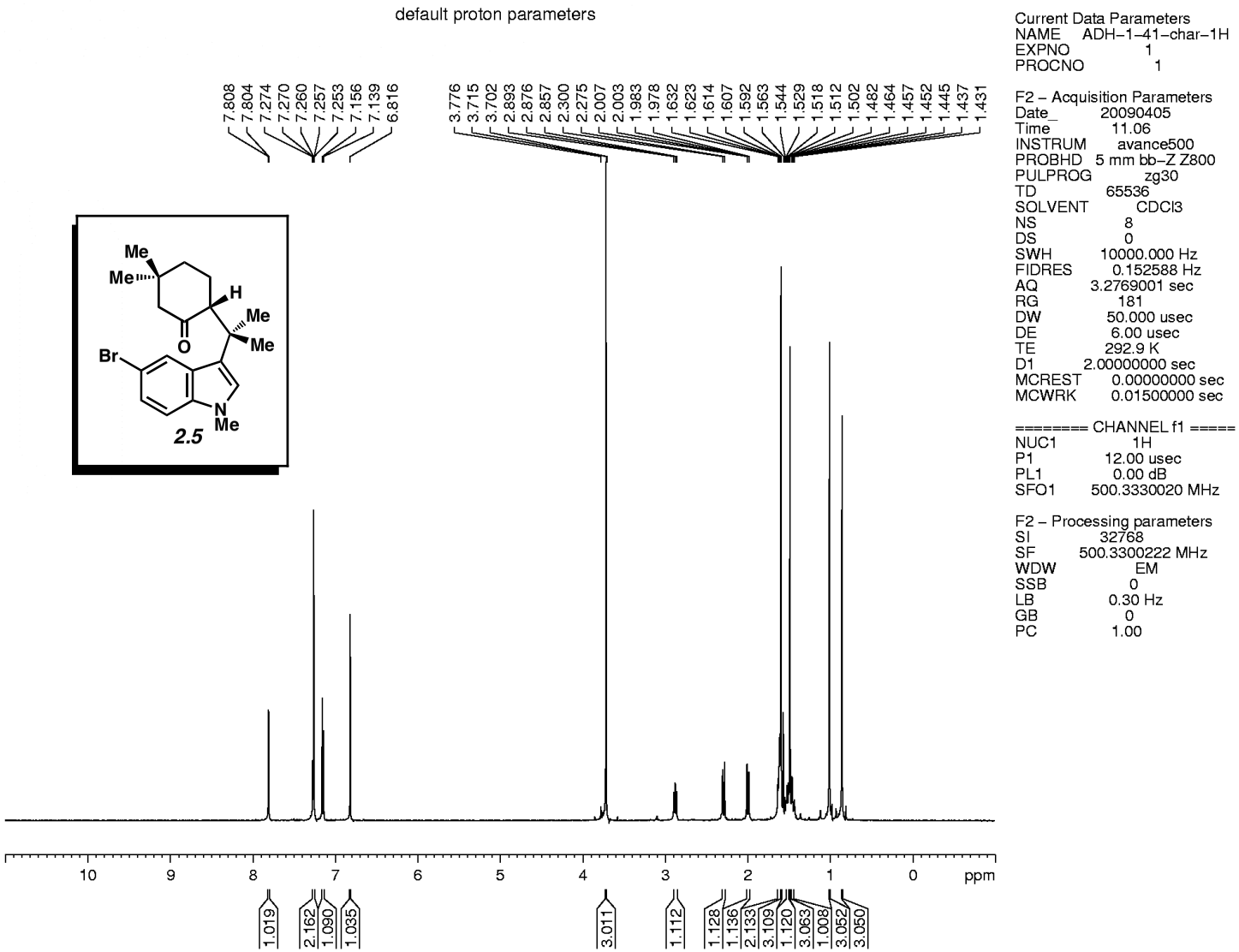

Figure A1.5 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **2.5**.

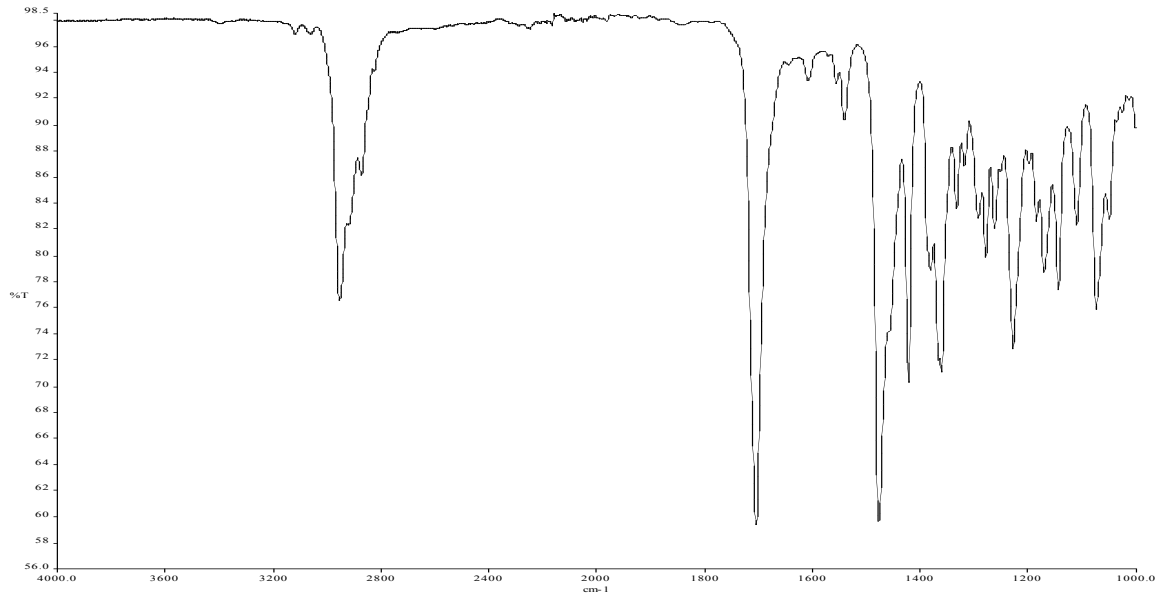

Figure A1.6 Infrared spectrum of compound **2.5**.

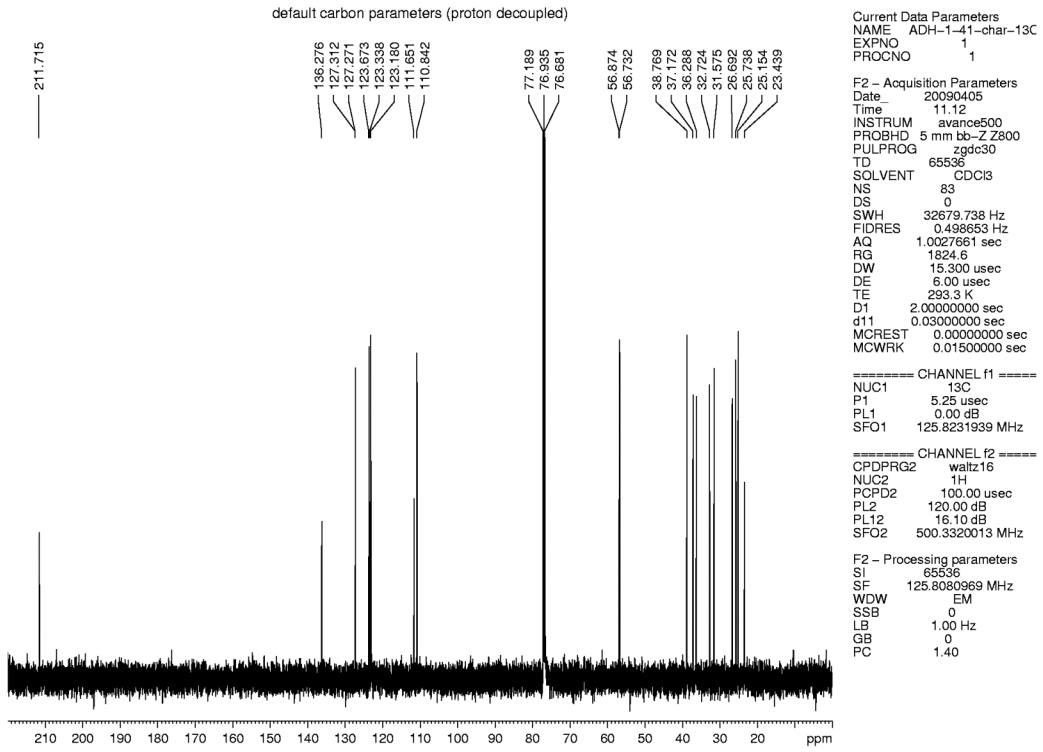

Figure A1.7 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **2.5**.

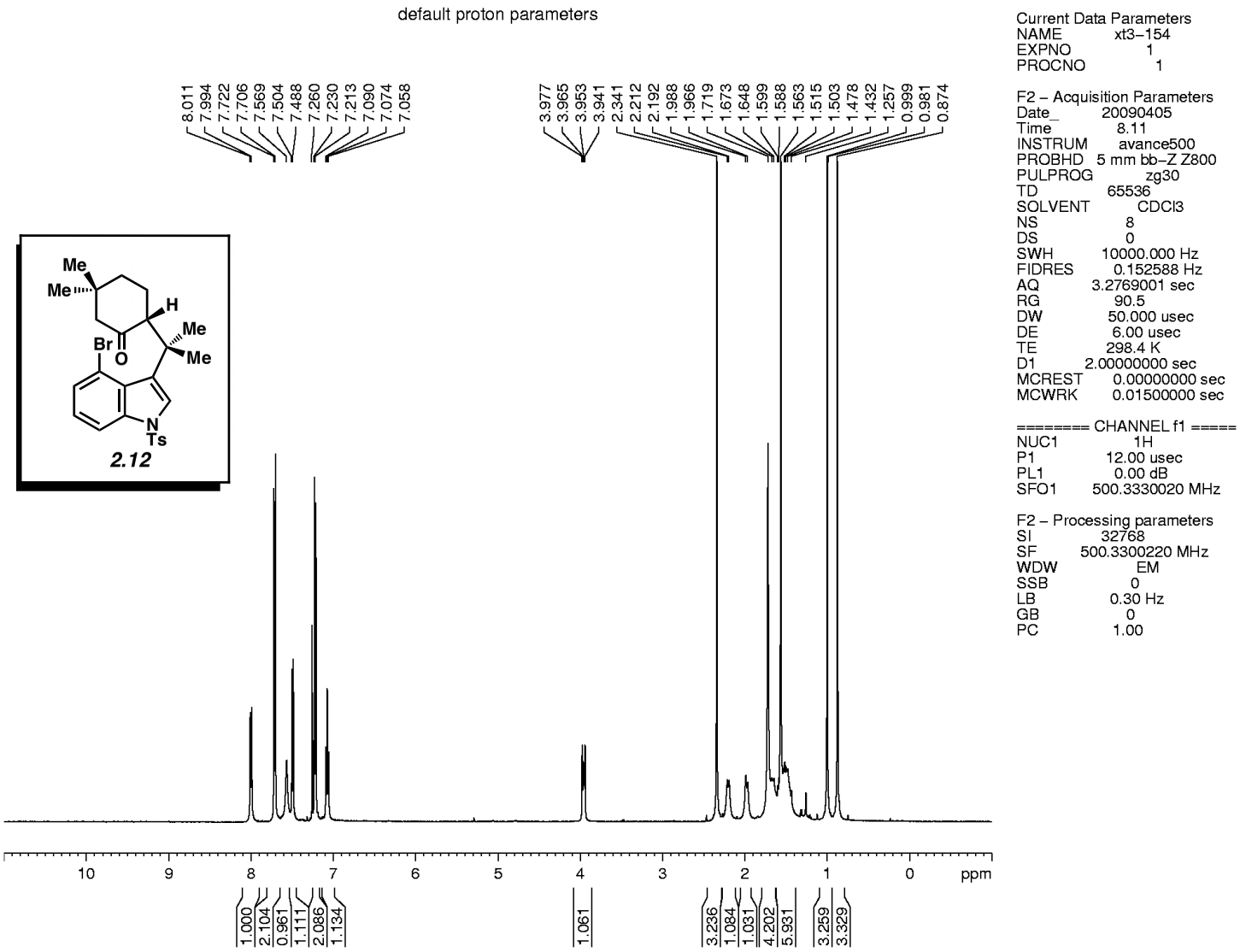

Figure A1.8 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **2.12**.

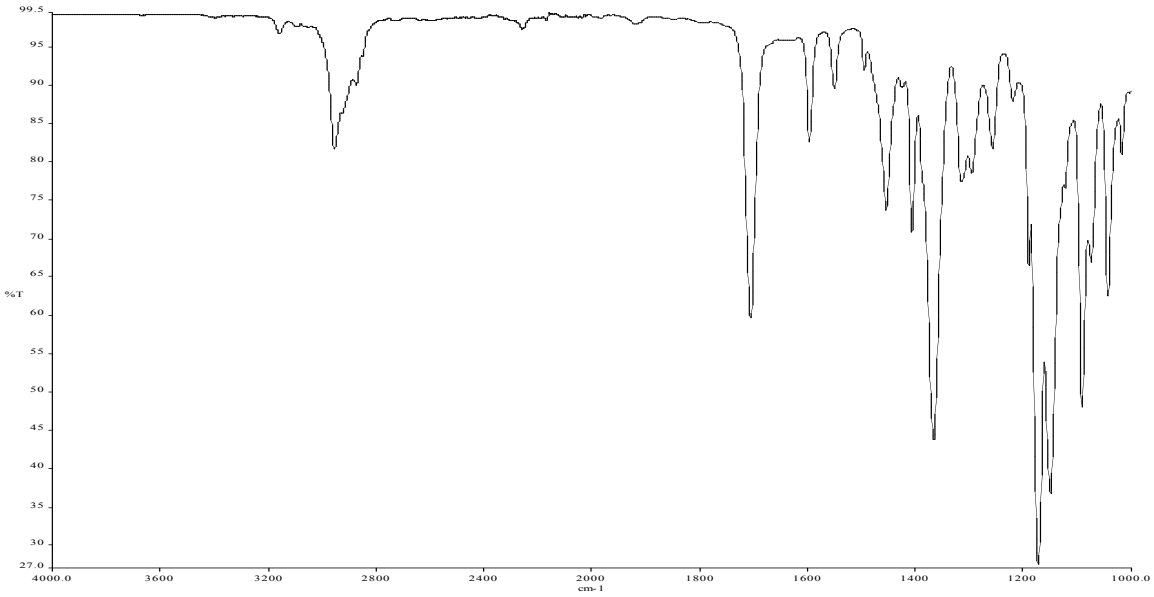

Figure A1.9 Infrared spectrum of compound **2.12**.

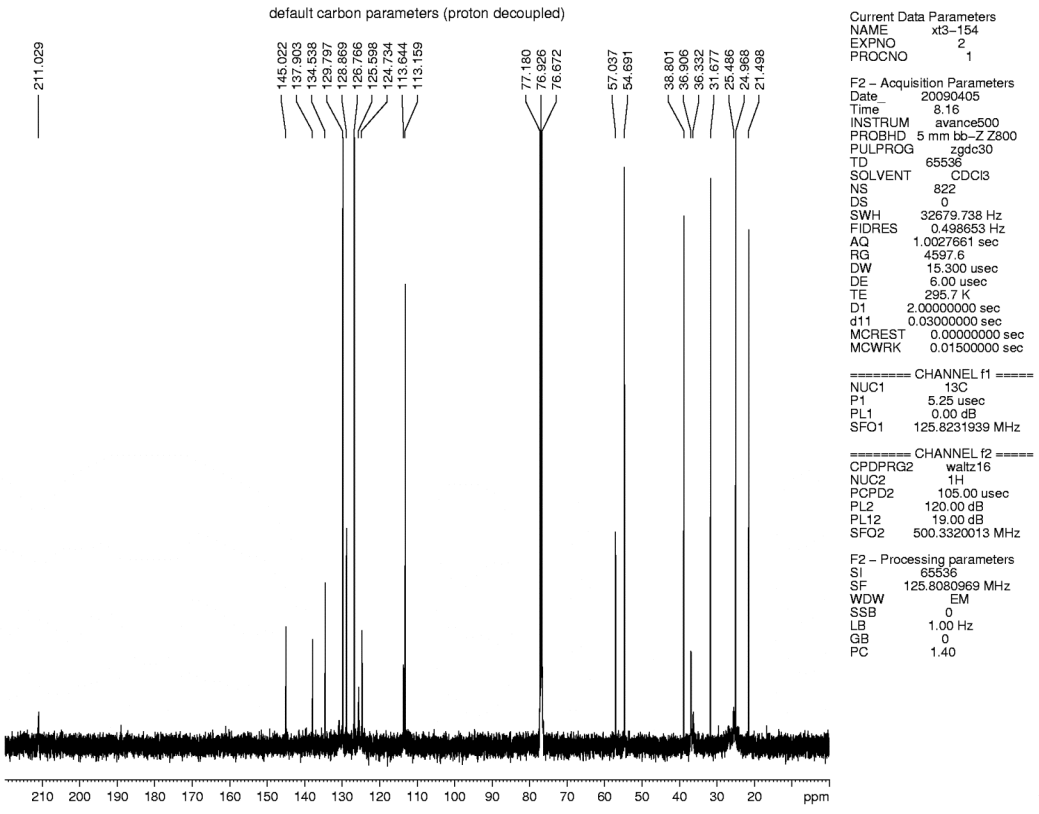

Figure A1.10 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **2.12**.

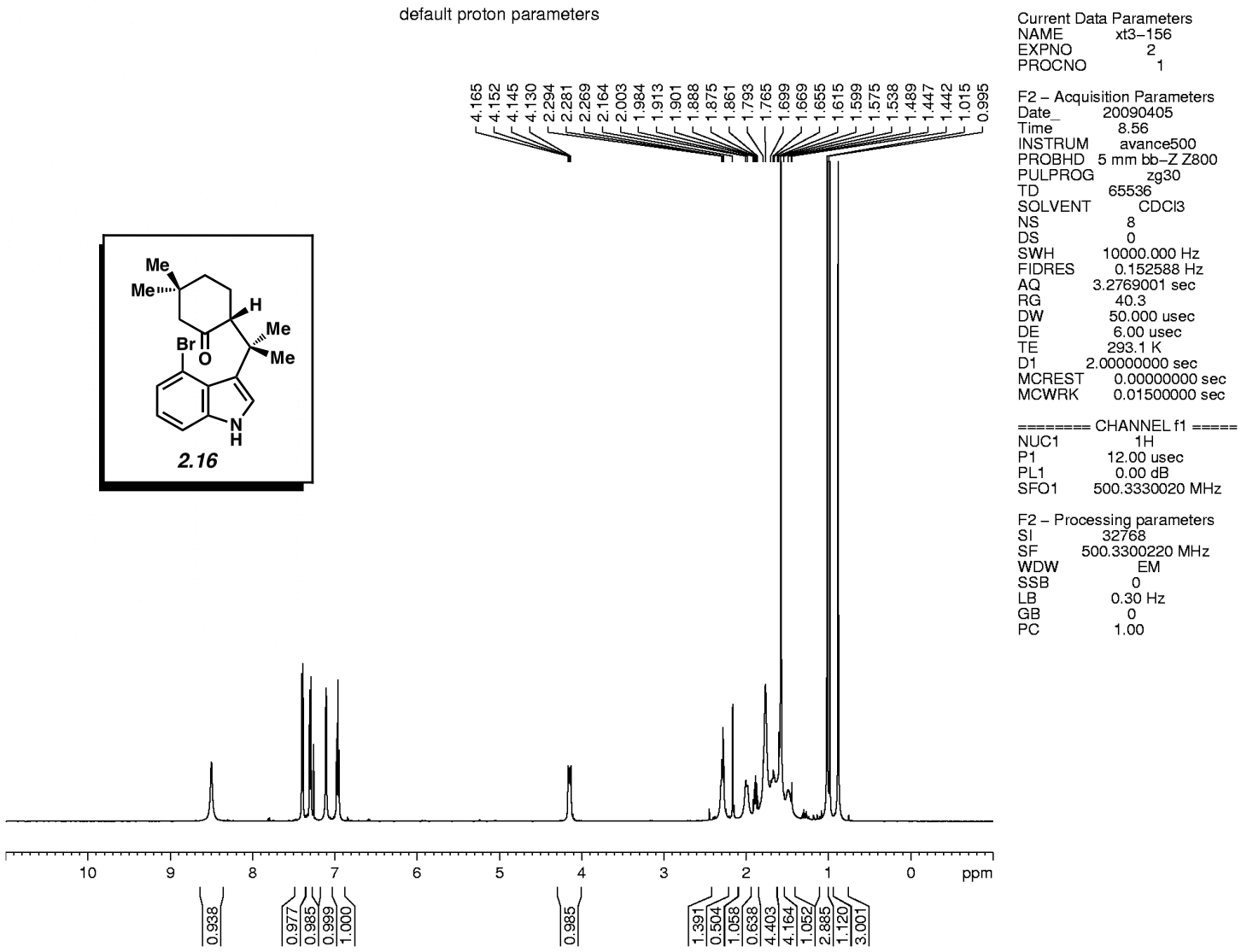

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Figure A1.11 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **2.16**.

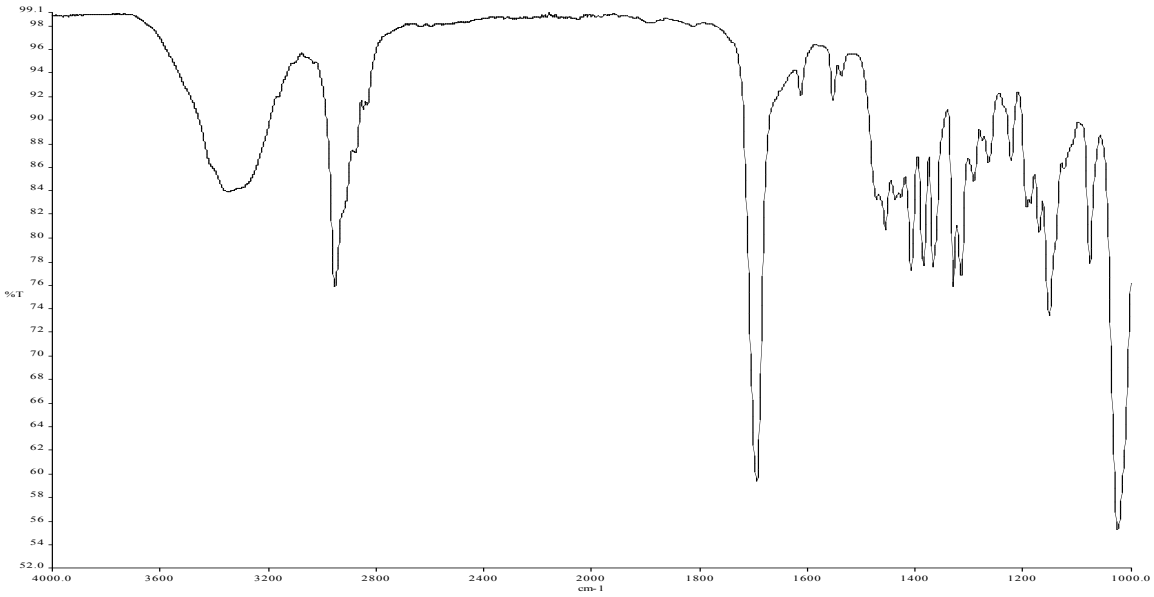


Figure A1.12 Infrared spectrum of compound **2.16**.

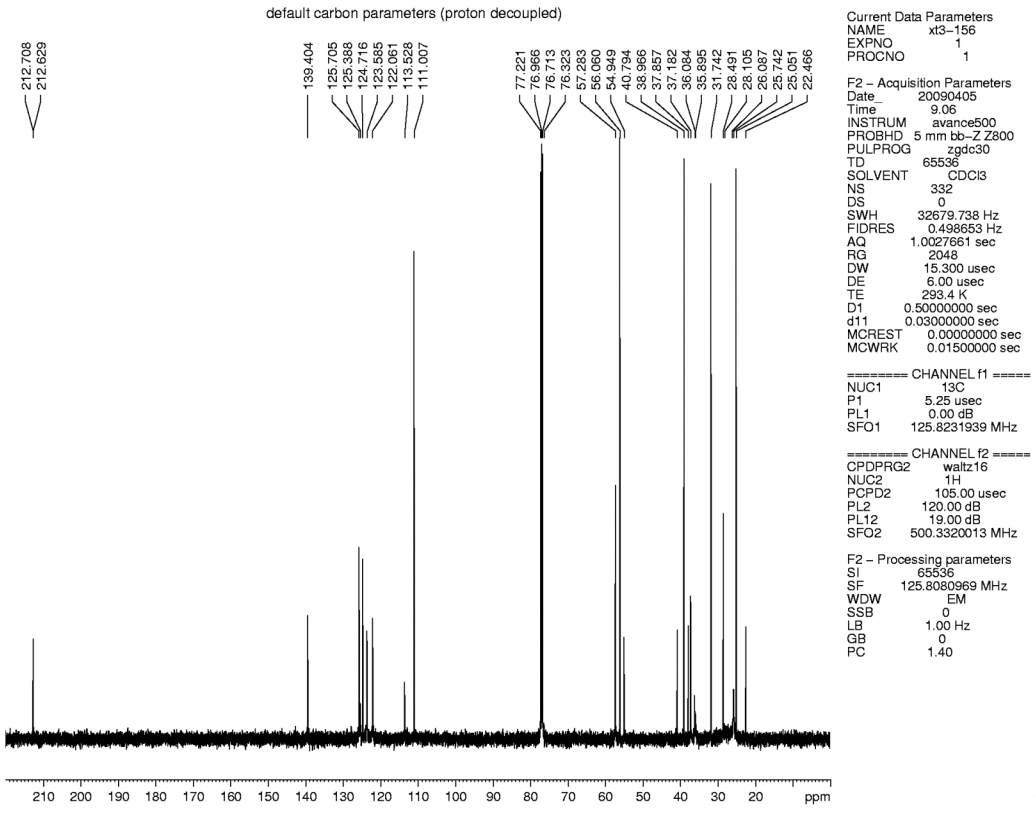


Figure A1.13 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **2.16**.

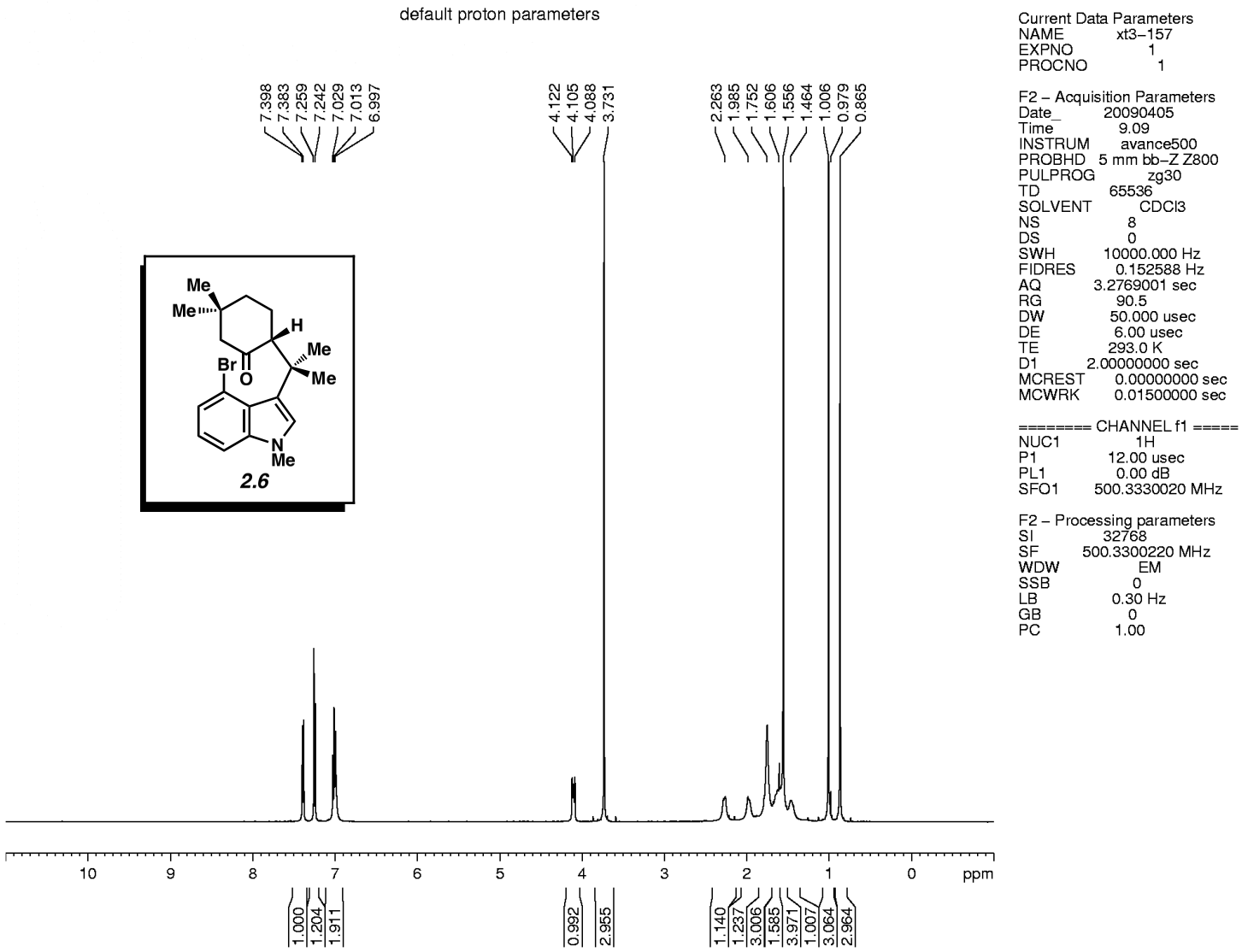


Figure A1.14 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **2.6**.

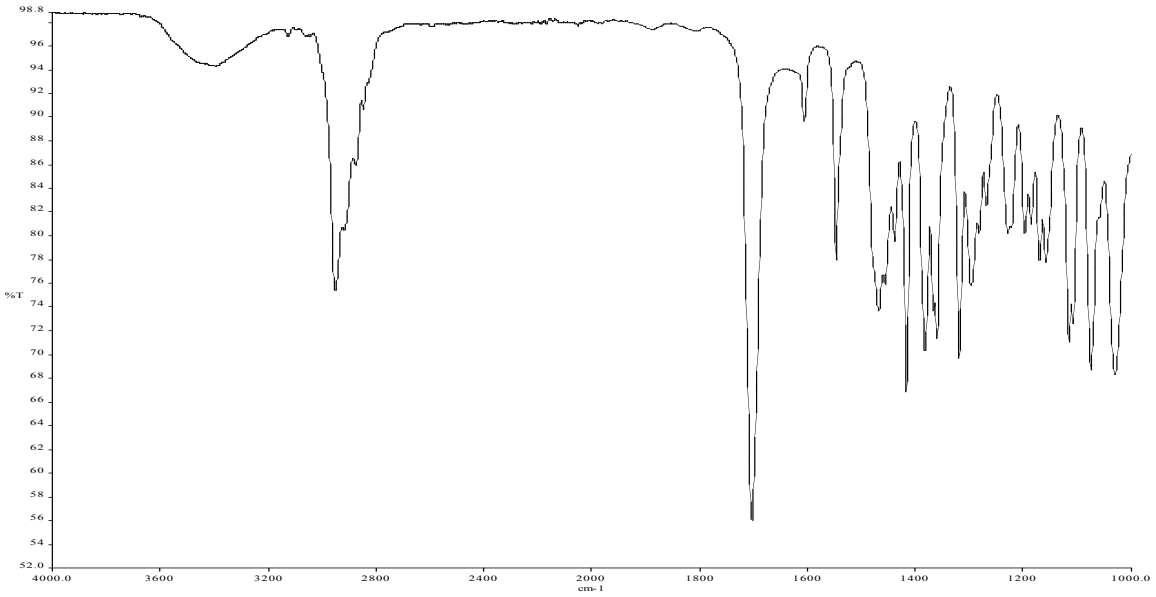


Figure A1.15 Infrared spectrum of compound **2.6**.

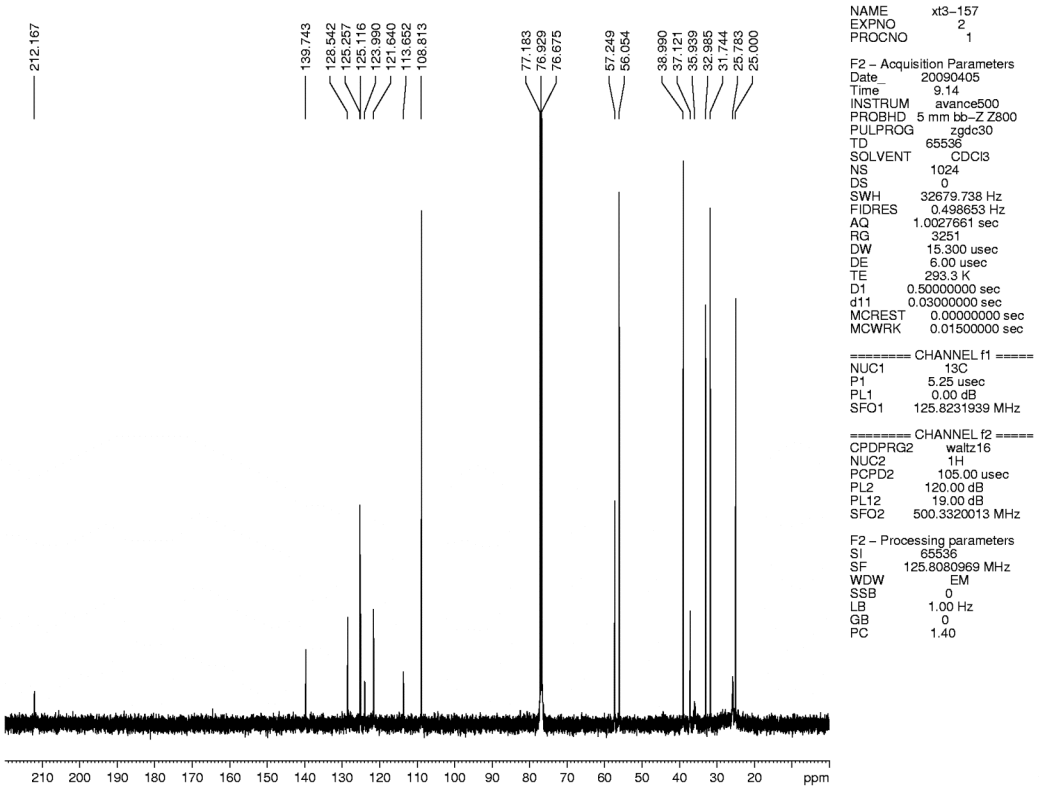


Figure A1.16 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **2.6**.

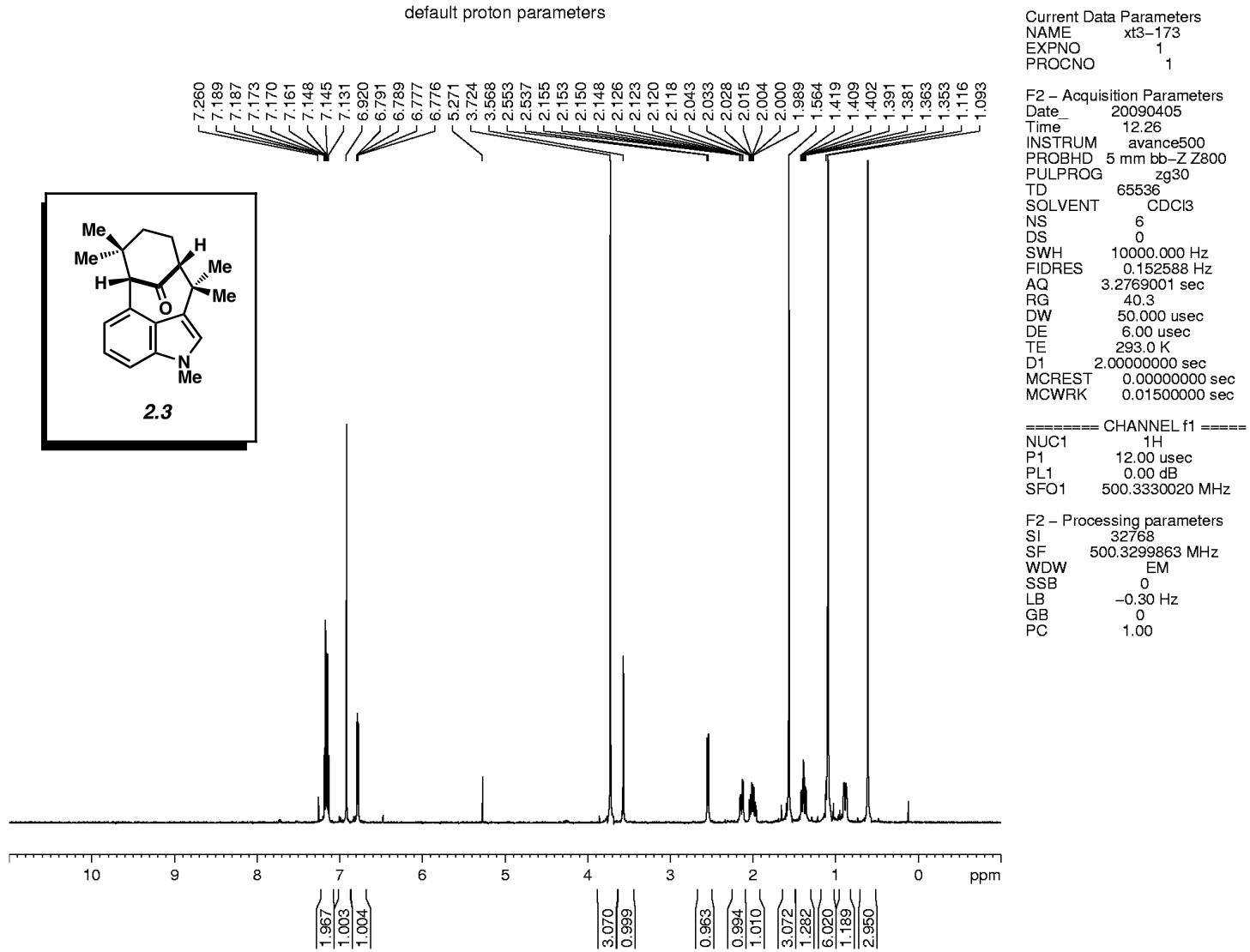


Figure A1.17 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **2.3**.

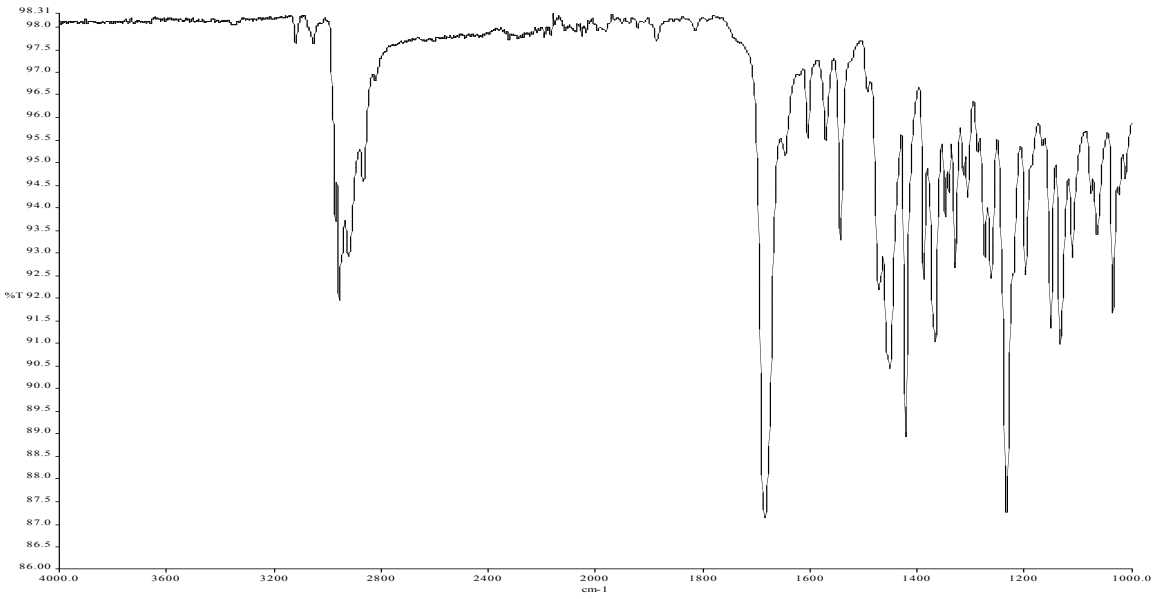


Figure A1.18 Infrared spectrum of compound **2.3**.

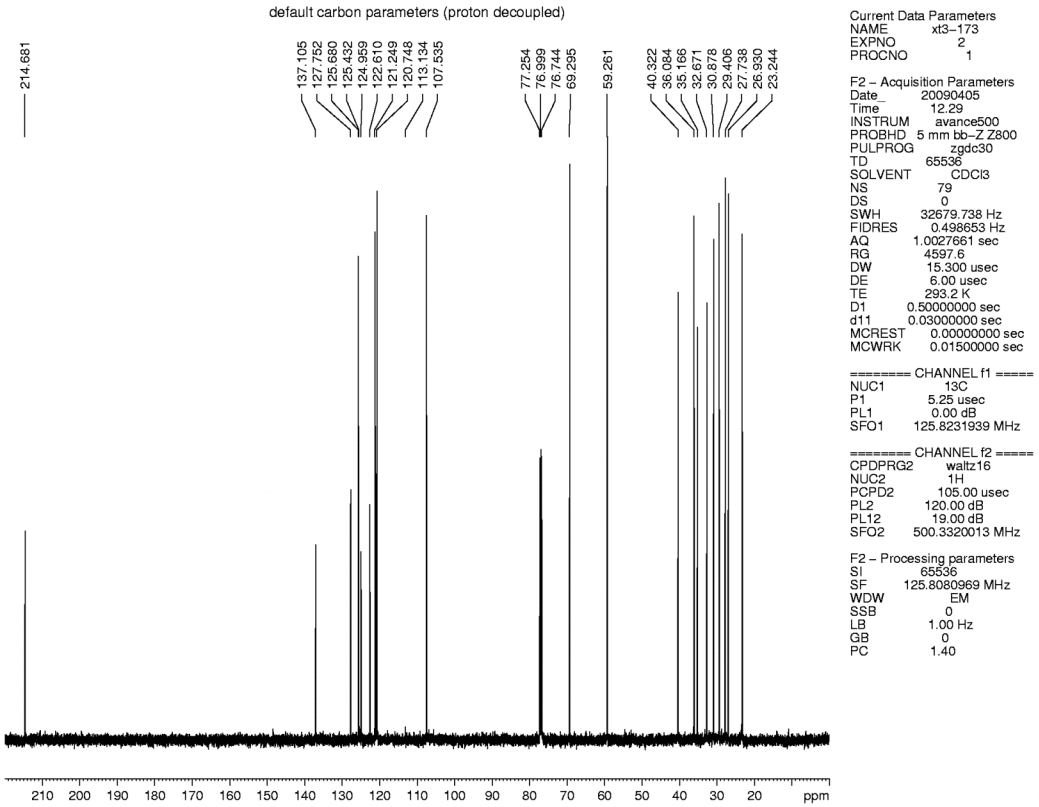


Figure A1.19 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **2.3**.

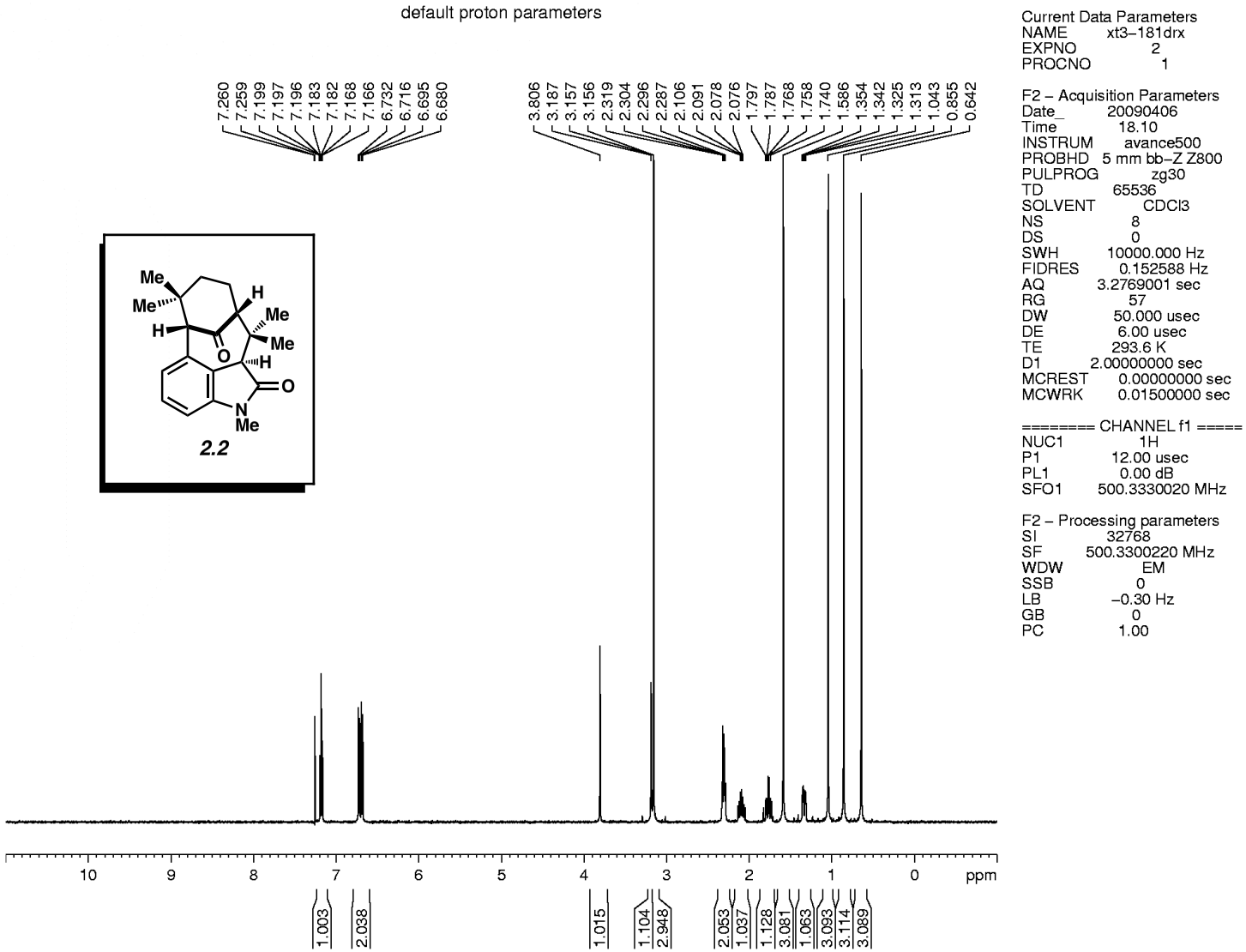


Figure A1.20 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **2.2**.

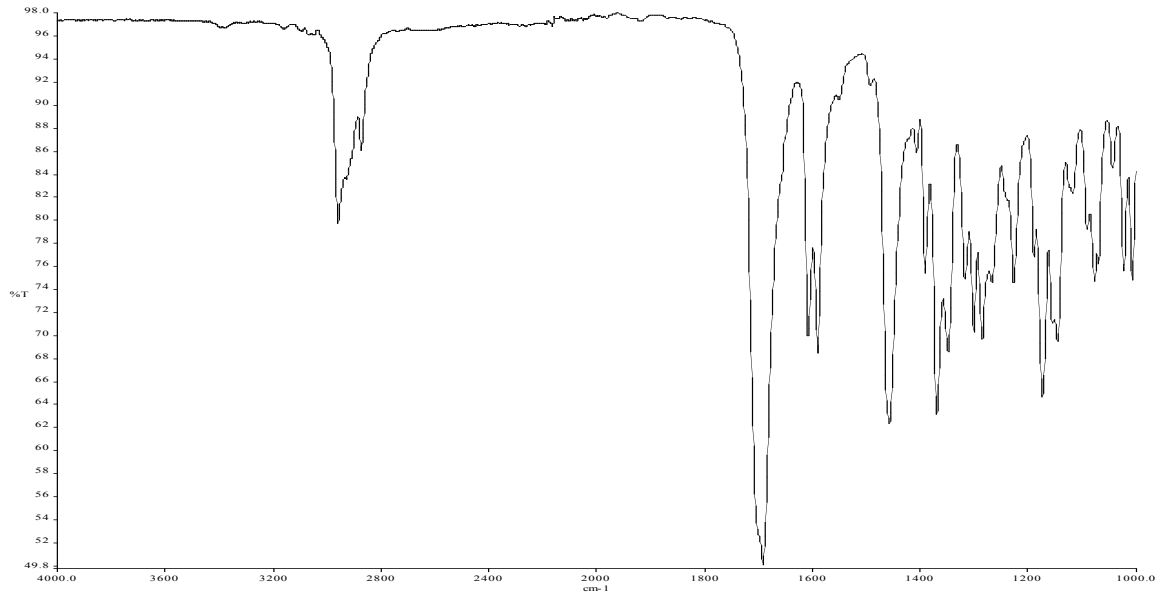


Figure A1.21 Infrared spectrum of compound **2.2**.

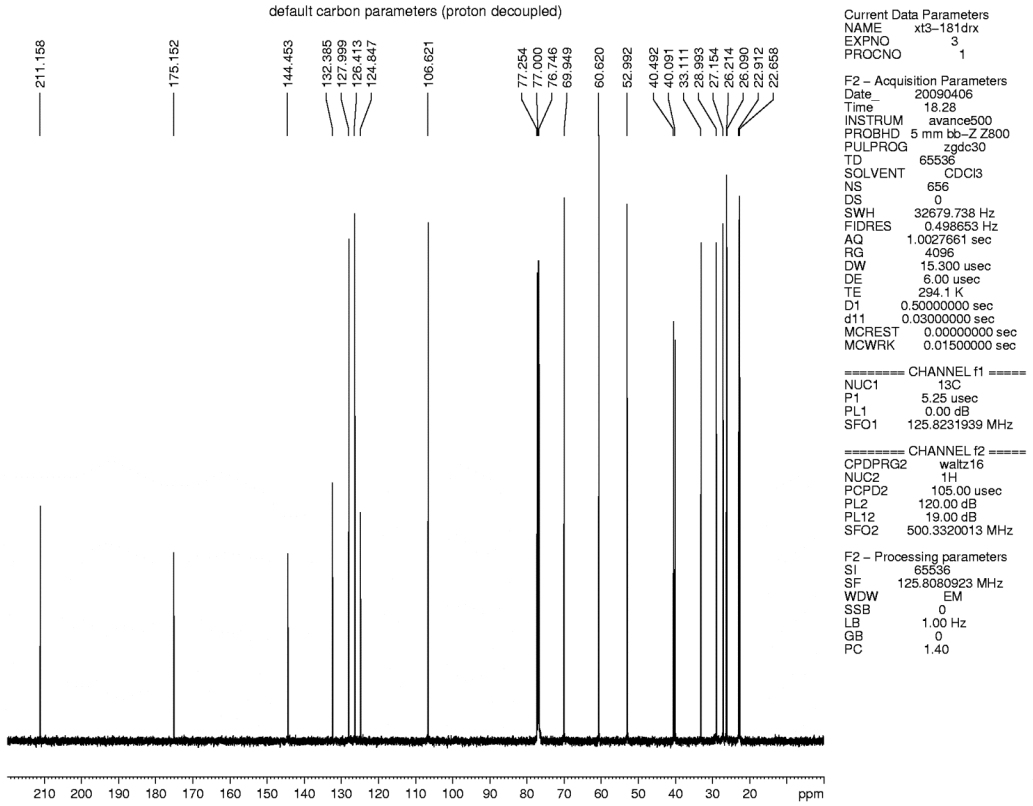


Figure A1.22 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **2.2**.

CHAPTER THREE

Initial Attempts to Install the Bridgehead Nitrogen Substituent and Synthesis of Cyclization Substrates Derived from (*R*)-Carvone

3.1 Abstract

This chapter covers efforts toward installing the bridgehead nitrogen substituent of the welwitindolinone natural products with bicyclo[4.3.1]decane cores. It also describes initial work towards designing an indolyne cyclization substrate with sufficient functionality in place to potentially complete a synthesis of *N*-methylwelwitindolinone C isothiocyanate.

3.2 Introduction

The welwitindolinones were initially isolated in 1994 by Moore and co-workers from the blue-green algae *Hapalosiphon welwitschii* and *Westiella intricata*.[1] Nine of the ten welwitindolinones contain a bicyclo[4.3.1]decane core (e.g. **3.1**–**3.3**, Figure 3.1). Some of these natural products have been shown to display impressive biological profiles.[2] The densely functionalized bicyclo[4.3.1]decane framework of the welwitindolinones and their promising biological profile have rendered these natural products highly sought after targets by the synthetic community.[3,4] While chapter two of this dissertation discussed an approach using an indolyne cyclization to assemble the bicyclo[4.3.1]decane scaffold of **3.1** using a model system, one challenge it did not address was how to install the C11 bridgehead nitrogen substituent. This chapter describes initial attempts to install the bridgehead substituent, as well as efforts toward the synthesis of a functionalized substrate aimed at a total synthesis of **3.1**.

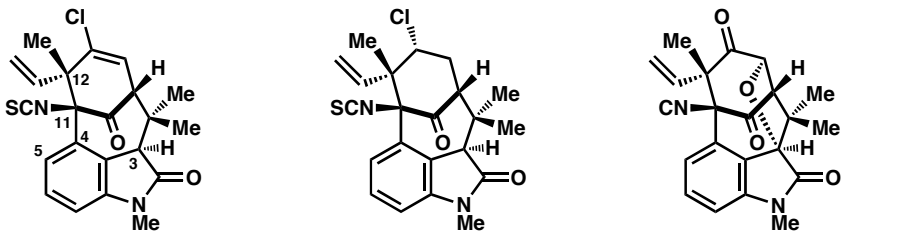
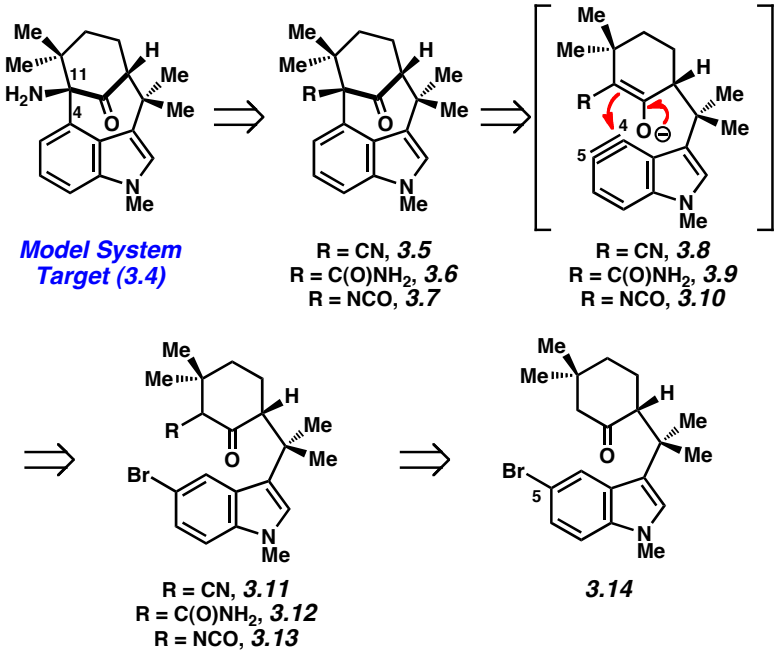


Figure 3.1. Representative welwitindolinone natural products (**3.1**–**3.3**)

3.3 Retrosynthetic Analysis of Model System Target with Bridgehead Substituent

After showing it was possible to assemble the bicyclo[4.3.1]decane core of **3.1** in earlier studies, efforts then turned to installing the requisite bridgehead nitrogen functionality.[3p] As such, aminoketone **3.4** was selected as a suitable model system target (Scheme 3.1). It was thought that aminoketone **3.4** could be accessed from any of three potential precursors **3.5**–**3.7** through a series of functional group interconversions. Following the key retrosynthetic disconnection outlined in chapter two of this dissertation, the C4–C11 bond of bicycles **3.5**–**3.7** would arise via an indolyne cyclization (see transition structures **3.8**–**3.10**). These indolyne intermediates were envisioned to be accessible from 5-brominated indoles **3.11**–**3.13**.[5] The 5-brominated indoles **3.11**–**3.13**, in turn, would be derived from functionalization of bromoindole **3.14**.

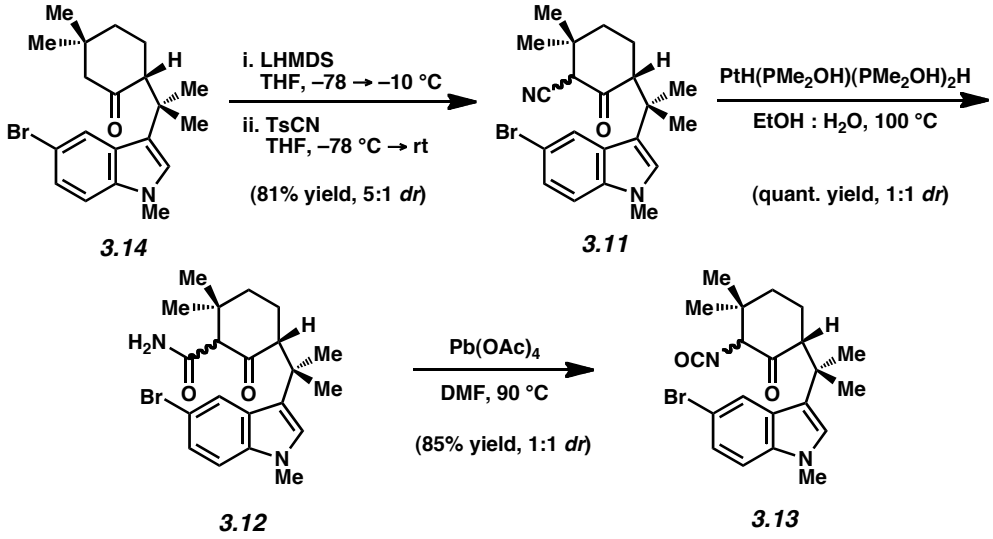
Scheme 3.1



3.4 Synthesis of Cyclization Precursors

The desired cyclization precursors **3.11**, **3.12**, and **3.13** were synthesized following a procedure developed by Greshock and Funk,[3i] which is depicted in Scheme 3.2. To access cyanoketone **3.11**, bromoindole **3.14** was lithiated with LHMDS. The resulting enolate underwent cyanation upon addition of *p*-toluenesulfonyl cyanide to provide **3.11** in 82% yield (5 : 1 ratio of diastereomers). Cyanoketone **3.11** was then hydrolyzed to provide amidoketone **3.12** in quantitative yield (1 : 1 ratio of diastereomers) upon treatment with Parkins catalyst.[6] **3.12** was subsequently converted to isocyanoketone **3.13** in 85% yield (1 : 1 ratio of diastereomers) through a modified Hofmann rearrangement using $Pb(OAc)_4$.[7]

Scheme 3.2



3.5 Indolyne Cyclization of Substrates with C11 Substituents

The results of the attempted indolyne cyclizations of substrates **3.11**–**3.13** are shown in Figure 3.2. Cyanoketone **3.11** only provided *O*-arylated product **3.15** in 52% yield upon treatment with $NaNH_2$/*t*-BuOH in THF.[8] Amidoketone **3.12** provided a mixture of products under the indolyne cyclization conditions. *O*-arylated product **3.16** was the major product isolated in 29% yield, with the corresponding alkene isomer **3.17** being formed as a minor component in 10% yield. *C*-arylated product **3.18** with the bicyclo[4.3.1]decane structure was formed in 12% yield, although it was lacking the key C11 substituent. Presumably, the product or an intermediate underwent deamidation under the reaction conditions. Reaction of isocyanoketone **3.13** under the indolyne cyclization conditions only afforded decomposition of starting material.[9] Due to the failure of these substrates to provide any of the desired C11 substituted bicyclo[4.3.1]decane products resulting from *C*-arylation, we decided to pursue a late-stage bridgehead functionalization to install the nitrogen functionality. Details of this approach are presented in chapter four of this dissertation.

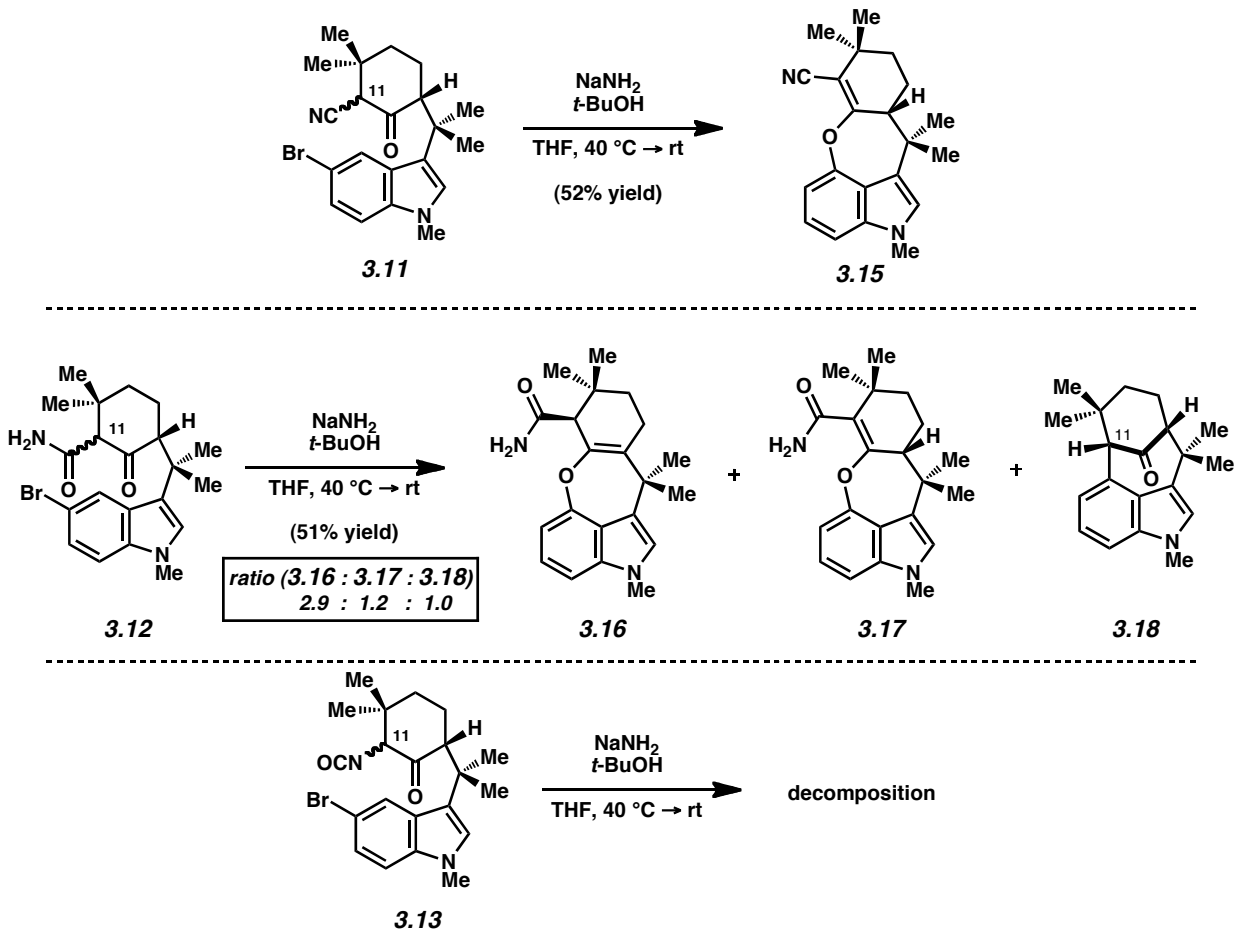


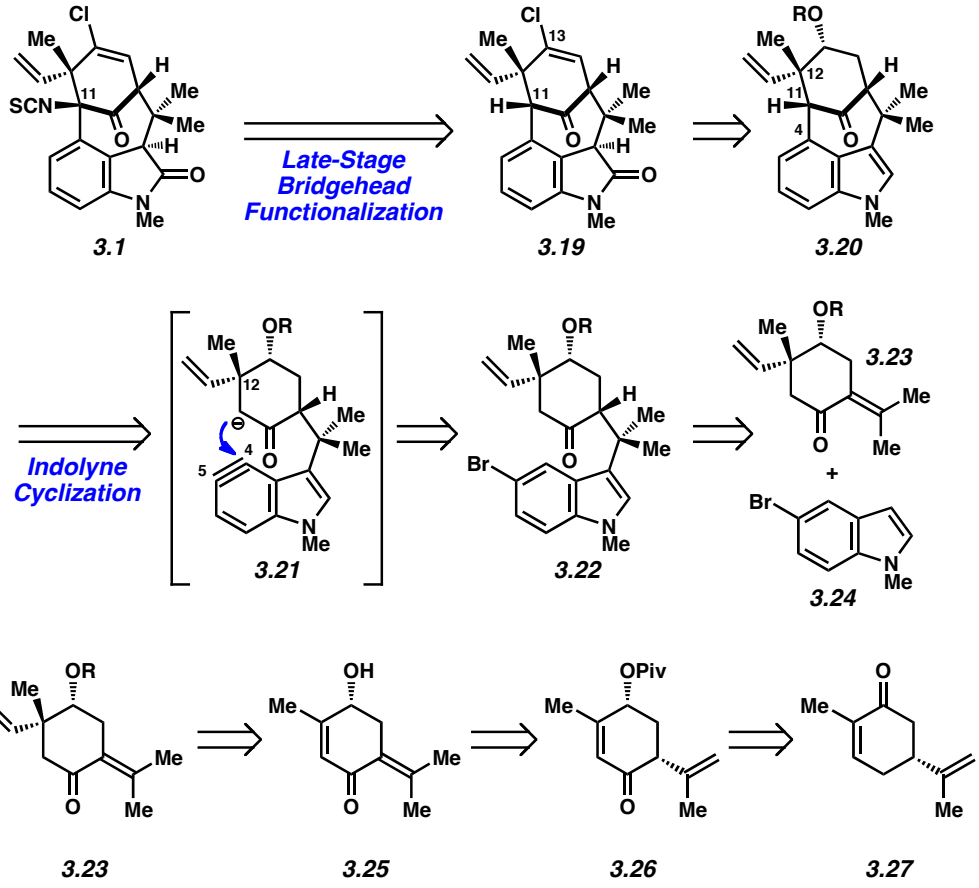
Figure 3.2. Indolyne cyclizations of functionalized substrates **3.11**–**3.13**.

3.6 Retrosynthetic Analysis of (–)-*N*-Methylwelwitindolinone C Isothiocyanate

With the goal of installing the required bridgehead nitrogen functionality at a later stage of the synthesis, efforts turned toward synthesis of a more functionalized cyclization substrate aimed at a synthesis of **3.1**. Retrosynthetically, this late-stage functionalization would lead to **3.1** being accessible from bicycle **3.19** as shown in Scheme 3.3. Bicycle **3.19**, in turn, would be derived from intermediate **3.20** through introduction of the vinyl chloride and oxindole moieties. The bicyclo[4.3.1]decane core of indole **3.20** would be assembled through an indolyne cyclization (see transition structure **3.21**) of bromoindole **3.22**. The carbon framework of the

natural product could be assembled through a coupling of 5-bromo-*N*-methylindole (**3.24**) and enone **3.23**. Cyclohexenone **3.23** could arise from dienone **3.25** through addition of the vinyl group. Dienone **3.25**, in turn, could be accessed from known pivaloate **3.26**, which is a derivative of (*R*)-carvone (**3.27**).

Scheme 3.3

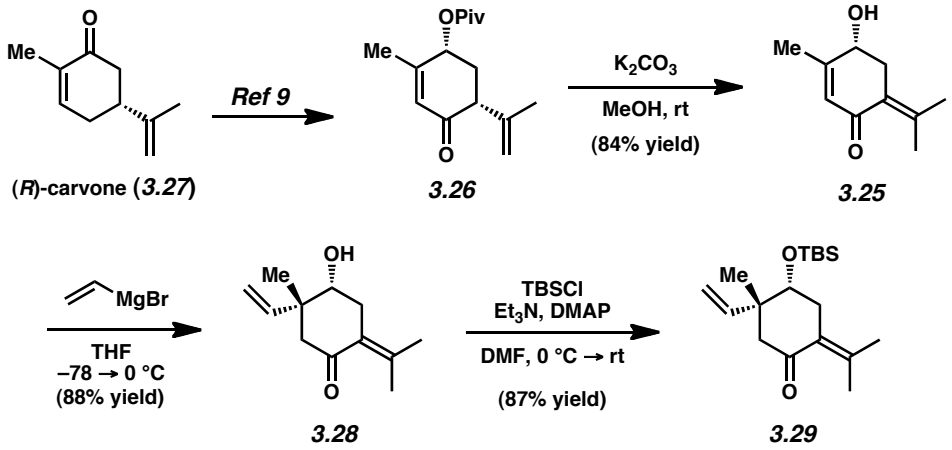


3.7 Synthesis of Functionalized Indolyne Cyclization Precursor

The synthesis of the indolyne cyclization precursor began with the preparation of enone **3.29** following a modification of a procedure described by Natsume and co-workers (Scheme 3.4).[10] (*R*)-Carvone (**3.27**) was elaborated in three steps to pivaloate **3.26**, which was then treated

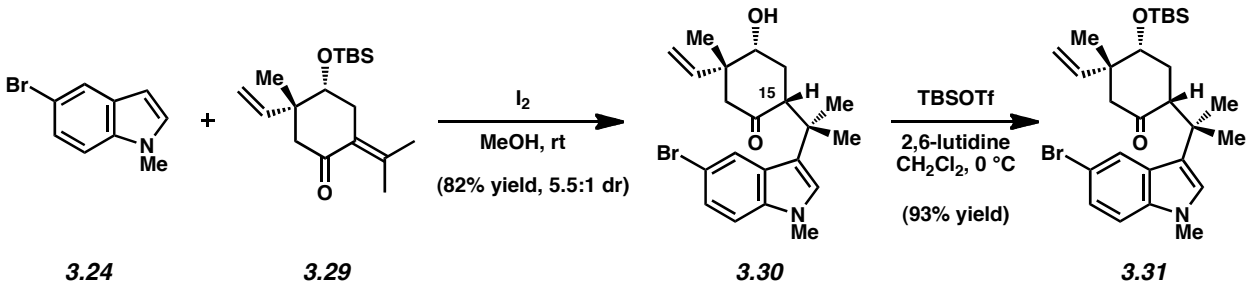
with K_2CO_3 in MeOH to effect pivaloyl group cleavage with concomitant alkene migration to furnish dienone **3.25** in 84% yield. Treatment of dienone **3.25** with vinyl Grignard produced an 84% yield of the desired 1,4-addition product **3.28** as a single diastereomer, a process that is likely guided by the adjacent hydroxyl group.[11] Protection of alcohol **3.28** with TBSCl yielded the target enone **3.29** in 87% yield.

Scheme 3.4



The next goal was to make a suitable substrate for the key indolyne cyclization. Enone **3.29** was coupled to 5-bromo-*N*-methylindole (**3.24**) catalyzed by I_2 in MeOH (Scheme 3.5).[12] These conditions afforded the desired bromoindole **3.30** in 82% yield as a 5.5:1 ratio of diastereomers at C15, which were separable by chromatography. The relative stereochemistry of the major diastereomer was confirmed by NOESY. Under the acidic conditions of I_2 and MeOH, the *tert*-butyldimethylsilyl group was removed; thus, alcohol **3.30** was then protected using TBSOTf to afford a 93% yield of silyl ether **3.31**. Attempts to utilize alcohol **3.28** in the conjugate addition led to a reduction in the diastereoselectivity for the desired bromoindole **3.30**.

Scheme 3.5

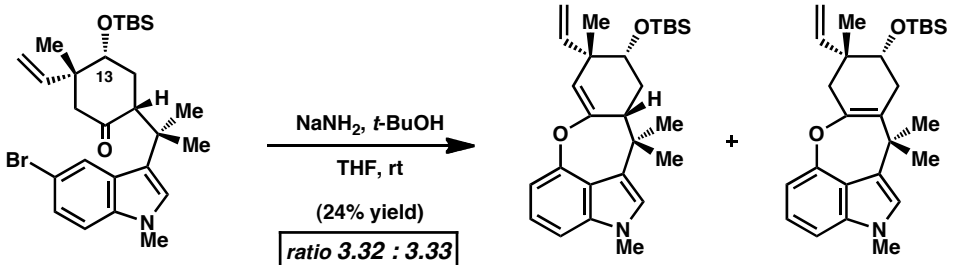


3.24 *3.29* *3.30* *3.31*

3.8 Indolyne Cyclization of Functionalized Precursor

With the more functionalized cyclization substrate **3.31** in hand, it was hoped that the indolyne cyclization would provide a bicyclo[4.3.1]decane intermediate suitable for finishing the total synthesis (Scheme 3.6). However, upon submission of silyl ether **3.31** to $NaNH_2$/*t*-BuOH in THF, the only arylated products obtained were those resulting from *O*-arylation to provide vinyl ether **3.32** and its alkene isomer **3.33**, in 24% total yield. It was initially thought that perhaps the bulky silyl ether was preventing the *C*-arylation from occuring.[13]

Scheme 3.6



3.31 *3.32* *3.33*

To explain the failure of silyl ether **3.31** to provide *C*-arylated indole **3.36**, the transition states of the cyclizations of model system bromoindole **3.14** and silyl ether **3.31** were compared

(Figure 3.3). While bromoindole **3.14** contains a pseudoaxial *tert*-butyl-like substituent at C15 en route to the C-arylated indole **3.18** (see transition structure **3.34**), silyl ether **3.31** contains the same pseudoaxial substituent at C15 as well as a second psuedoaxial substituent at C13 (see transition structure **3.35**). It is thus thought that this 1,3-diaxial interaction prevents the necessary conformation from being adopted en route to bicyclic indole **3.36**. It was hypothesized C13 epimer **3.37** would not have this 1,3-diaxial interaction (see transition structure **3.38**) and thus could undergo the desired *C*-arylation to occur to furnish bicyclic indole **3.39**.

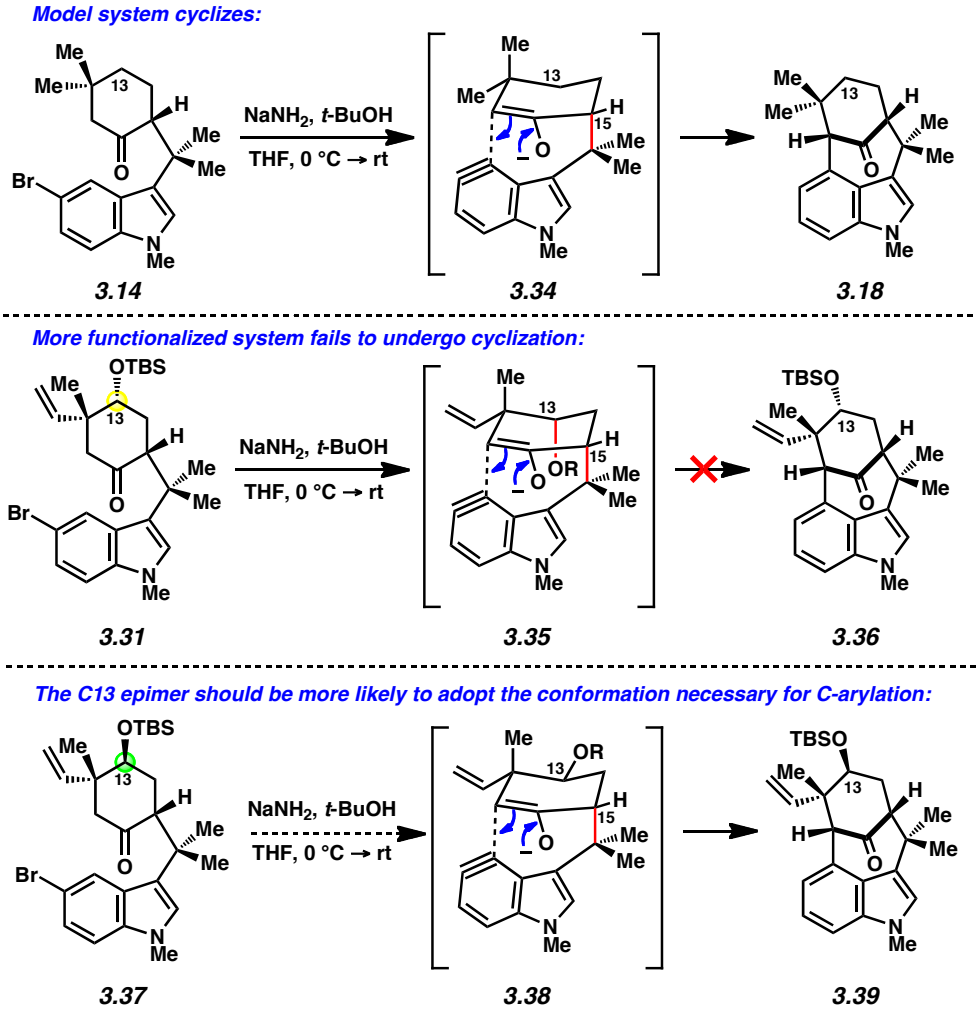
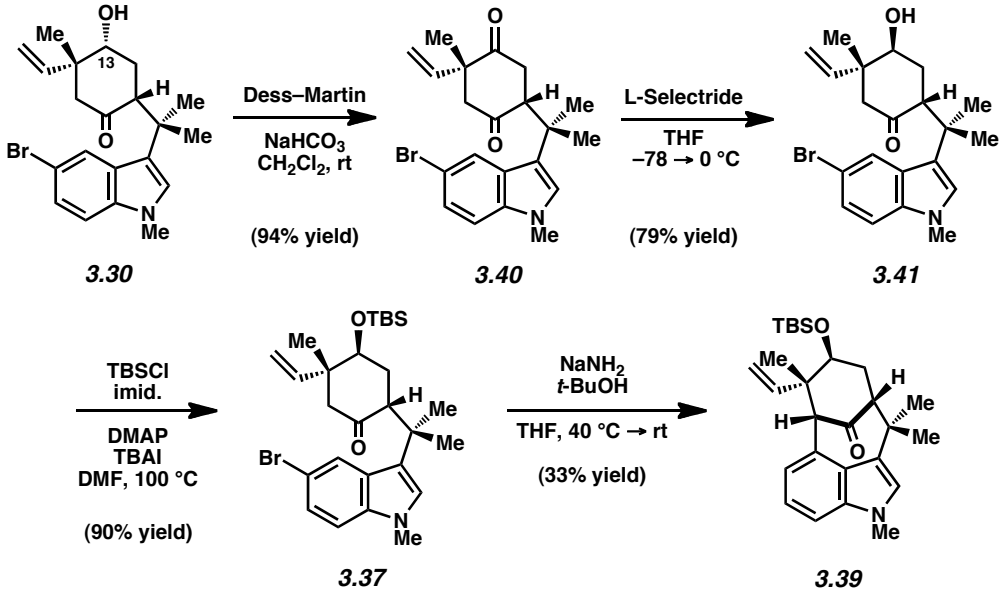


Figure 3.3. Rationale for **3.31** cyclization not providing **3.36** and alternative substrate **3.37**.

3.9 Synthesis of C13 Epimer for Indolyne Cyclization

To test the hypothesis, epimeric substrate **3.37** was prepared using the sequence shown in Scheme 3.7. Whereas attempts to invert the C13 stereocenter using Mitsunobu conditions failed, even under forcing conditions,[14] a two-step oxidation/reduction sequence was successful. Alcohol **3.30** was first oxidized with Dess–Martin periodinane to give diketone **3.40** in excellent yield. Diketone **3.40** was reduced with L-Selectride to furnish alcohol **3.41** in 79% yield, likely through equatorial approach of the bulky hydride reagent.[22] TBS protection of alcohol **3.41** provided silyl ether **3.37** in 90% yield. We were delighted to find that substrate **3.37** undergoes the desired indolyne cyclization to provide bicyclo[4.3.1]decane **3.39**. Further discussion of the cyclization and the completion of the synthesis of **3.1** are discussed in chapter four of this dissertation.

Scheme 3.7



3.10 Conclusion

In summary, we have attempted indolyne cyclizations in a model system that would provide a functional group handle at the bridgehead position in an effort to synthesize *N*-methylwelwitindolinone C isothiocyanate (**3.1**). Although these were unsuccessful, we have also explored indolyne cyclizations of more elaborate substrates to provide a functionalized bicyclo[4.3.1]decane scaffold. Although our initial attempt using substrate **3.31** was unsuccessful, a hypothesis explaining the failure of *C*-arylation has been made and was validated through the cyclization of epimeric substrate **3.37**. The use of indolyne cyclization product **3.39** toward the synthesis of welwitindolinone **3.1** is described in the following chapter of this dissertation.

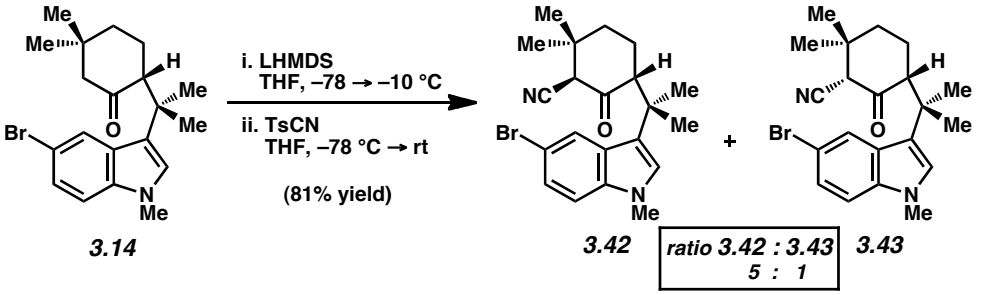
3.11 Experimental Section

3.11.1 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. *p*-Toluenesulfonyl cyanide and Parkins catalyst were obtained from Aldrich. 5-bromoindole was obtained from Biosynth. $NaNH_2$ was obtained from Alfa Aesar. (*R*)-Carvone was obtained from Aldrich. Dess–Martin periodinane was prepared from known literature procedures.[15,16] *t*-Butyldimethylsilyl triflate was distilled neat and stored in a Schlenk tube prior to use, *t*-BuOH was distilled from CaH_2 and stored in a Schlenk tube 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, ceric ammonium molybdate, and potassium permanganate staining. Silicycle silica gel 60 (particle size 0.040–0.063 mm) was used for flash column chromatography. ^{1}H NMR spectra were recorded on Bruker spectrometers (at 500 MHz) and are reported relative to deuterated solvent signals. Data for ^{1}H NMR spectra are reported as follows: chemical shift (d ppm), multiplicity, coupling constant (Hz) and integration. ^{13}C NMR spectra were recorded on Bruker Spectrometers (at 125 MHz). Data for ^{13}C NMR spectra are reported in terms of chemical shift. IR spectra were recorded on a Perkin-Elmer 100 spectrometer and are reported in terms of frequency of absorption (cm^{-1}). Melting points are uncorrected and were obtained on a Laboratory Devices Mel-Temp II. Optical rotations were

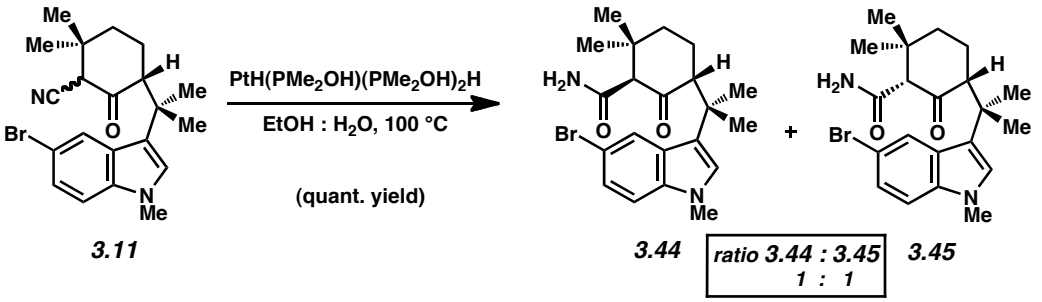
measured with a Rudolph Autopol IV Automatic Polarimeter. High resolution mass spectra were obtained from the UC Irvine Mass Spectrometry Facility.

3.11.2 Experimental Procedures



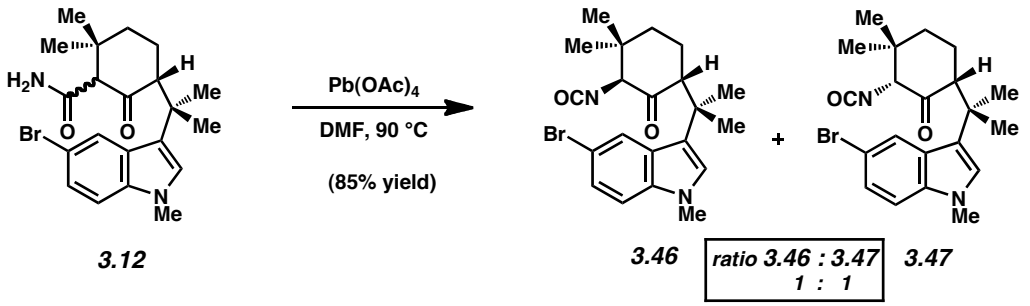
Cyanoketones 3.42 and 3.43. Inside of the glovebox, a flask was charged with solid LHMDS (234 mg, 1.40 mmol, 1.05 equiv). The flask was then sealed and removed from the glovebox. THF (7.0 mL) was added and the resulting solution was cooled to –78 °C. A solution of bromoindole **3.14** (500 mg, 1.33 mmol, 1.0 equiv) in THF (2 x 1.5 mL) was then added slowly down the side of the flask. Upon completion of the addition, the reaction was allowed to stir at –78 °C for 15 min, and was then warmed to –10 °C for 1 additional hour. The reaction vessel was then cooled to –78 °C and a solution of TsCN (314 mg, 1.73 mmol, 1.3 equiv) in THF (2 x 1.5 mL) was added dropwise. After stirring at –78 °C for 5 min, the reaction mixture was warmed to room temperature and allowed to stir for an additional 2 h. The reaction was then quenched by the addition of a solution of saturated aqueous NH_4OH (3 mL) and transferred to a separatory funnel with Et_2O (30 mL) and saturated aqueous NH_4Cl (30 mL). The resulting biphasic mixture was extracted with Et_2O (3 x 25 mL). The organic layers were combined and washed with brine (25 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The resulting residue was purified by flash chromatography (1:1 hexanes:Et_2O) to afford a mixture of

cyanoketones **3.42** and **3.43** (434 mg, 5:1 ratio **3.42** to **3.43**, 81% yield) as a yellow solid. These compounds were characterized as a mixture. Mp 135–136 °C; R_f 0.39 (1:1 hexanes:Et_2O); Cyanoketone **3.42**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.75 (d, *J* = 1.8, 1H), 7.27 (dd, *J* = 8.7, 1.8, 1H), 7.16 (d, *J* = 8.7, 1H), 6.85 (s, 1H), 3.72 (s, 3H), 3.45 (s, 1H), 2.89 (dd, *J* = 11.6, 5.9, 1H), 1.82–1.60 (m, 4H), 1.60 (s, 3H), 1.50 (s, 3H), 1.23 (s, 3H), 0.99 (s, 3H); Cyanoketone **3.43**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.88 (d, *J* = 1.7, 1H), 7.28 (dd, *J* = 8.7, 1.7, 1H), 7.15 (d, *J* = 8.7, 1H), 6.83 (s, 1H), 3.72 (s, 3H), 3.36 (dd, *J* = 11.4, 6.0, 1H), 2.96 (d, *J* = 1.4, 1H), 1.82–1.60 (m, 4H), 1.58 (s, 3H), 1.50 (s, 3H), 1.17 (s, 3H), 0.97 (s, 3H); ^{13}C NMR (41 of 42 observed, 125 MHz, $CDCl_3$): δ 202.9, 200.8, 136.5, 136.4, 127.9, 127.44, 127.41, 127.2, 124.3, 124.1, 123.5, 123.0, 122.2, 121.9, 116.8, 115.4, 112.4, 112.1, 111.3, 111.1, 57.05, 57.04, 55.6, 55.2, 41.4, 40.2, 38.6, 36.7, 36.5, 35.5, 33.0, 30.3, 28.3, 26.8, 26.3, 25.6, 25.5, 25.1, 24.6, 23.8, 21.5; IR (film): 2965, 2248, 1721, 1478, 1363, 1229, 1066 cm^{-1}; HRMS-ESI (*m/z*) [M + Na]$^+$ calcd for $C_{21}H_{25}N_2OBrNa$, 423.1048; found 423.1049.



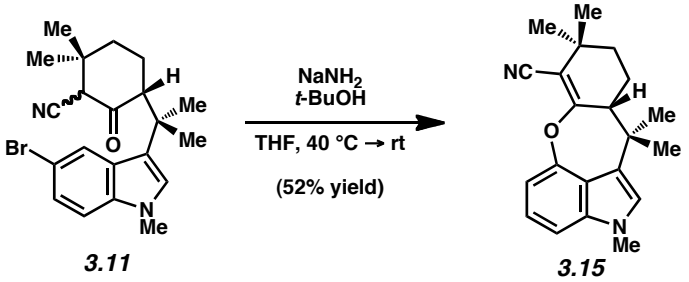
Amidoketones 3.44 and 3.45. In the glovebox, a 20 mL scintillation vial was charged with Parkins catalyst (4 mg, 0.009 mmol, 0.01 equiv). The vial was then sealed and removed from the glovebox. To the vial was then added a 4:1 solution of EtOH:H_2O (2.8 mL) and then cyanoketone **3.11** (374 mg, 0.932 mmol, 1 equiv) was quickly added. The vial was then sealed and allowed to stir at 100 °C. After 9 h, the reaction was cooled to room temperature and filtered

through a plug of silica gel (2 inches in a pipette, eluting with 10 mL EtOAc). The filtrate was then evaporated under reduced pressure to a mixture of amidoketones **3.44** and **3.45** (390 mg, 1:1 ratio **3.44** to **3.45**, quantitative yield) as a white solid. These compounds were characterized as a mixture. Mp 119–120 °C; Amidoketone **3.44**: R_f 0.39 (1:1 hexanes:Et_2O); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.86 (d, *J* = 1.7, 1H), 7.26 (dd, *J* = 8.7, 1.7, 1H), 7.13 (d, *J* = 8.7, 1H), 6.80 (s, 1H), 6.27 (bs, 1H), 5.36 (bs, 1H), 3.71 (s, 3H), 3.52–3.47 (m, 1H), 2.78 (s, 1H), 2.00–1.92 (m, 1H), 1.70–1.63 (m, 2H), 1.51 (s, 3H), 1.46 (s, 3H), 1.38–1.32 (m, 1H), 1.00 (s, 3H), 0.99 (s, 3H); Amidoketone **3.45**: R_f 0.39 (1:1 hexanes:Et_2O); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.80 (d, *J* = 1.8, 1H), 7.28 (dd, *J* = 8.7, 1.8, 1H), 7.15 (d, *J* = 8.7, 1H), 6.81 (s, 1H), 5.49 (bs, 1H), 3.72 (s, 3H), 3.32 (s, 1H), 3.07 (dd, *J* = 11.3, 6.3, 1H), 1.78–1.65 (m, 3H), 1.57 (s, 3H), 1.55–1.49 (m, 1H), 1.52 (s, 3H), 1.18 (s, 3H), 0.94 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 211.1, 210.9, 170.54, 170.46, 136.5, 136.4, 127.6, 127.5, 127.3, 127.2, 124.14, 124.09, 123.8, 123.4, 122.8, 122.7, 112.19, 112.18, 111.2, 110.9, 68.5, 67.9, 58.4, 56.0, 43.5, 41.2, 39.7, 36.6, 36.4, 35.5, 32.99, 32.96, 30.2, 28.1, 27.5, 27.3, 26.8, 26.5, 25.1, 24.5, 24.0, 21.4; IR (film): 3344, 2962, 1703, 1672, 1477, 1366, 1229 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{21}H_{27}N_2O_2BrNa$, 441.1154; found 441.1151.



Isocyanoketones 3.46 and 3.47. In the glovebox, a flask was charged with $Pb(OAc)_4$ (472 mg, 1.065 mmol, 1.4 equiv). The flask was then sealed and removed from the glovebox. To a separate flask fitted with an air condenser was added amidoketone **3.12** (319 mg, 0.761 mmol, 1.0 equiv). To this flask was added DMF (21 mL) followed by the $Pb(OAc)_4$, which was transferred using additional DMF (2 x 3 mL). The flask was then allowed to stir at 90 °C for 15 minutes. The reaction was cooled to room temperature and transferred to a separatory funnel with Et_2O (50 mL) and H_2O (10 mL). The resulting biphasic mixture was washed with H_2O (4 x 25 mL) and the aqueous layer was extracted with Et_2O (3 x 50 mL). The organic layers were combined and washed with brine (25 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The resulting residue was purified by flash chromatography (1:1 EtOAc:hexanes) to afford a mixture of isocyanoketones **3.46** and **3.47** (270 mg, 1:1 ratio **3.46** to **3.47**, 85% yield) as a yellow solid. These compounds were characterized as a mixture. Mp: 75–77 ºC; R_f 0.80 (1:1 EtOAc:hexanes); Isocyanoketone **3.46**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.86 (d, *J* = 1.7, 1H), 7.30 (dd, *J* = 8.7, 1.7, 1H), 7.16 (d, *J* = 8.7, 1H), 6.81 (s, 1H), 3.73 (s, 3H), 3.69 (s, 1H), 3.06–3.01 (m, 1H), 1.74–1.66 (m, 1H), 1.62–1.51 (m, 2H), 1.53 (s, 3H), 1.45 (s, 3H), 1.39–1.33 (m, 1H), 1.00 (s, 3H), 0.81 (s, 3H); Isocyanoketone **3.47**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.76 (d, *J* = 1.8, 1H), 7.28 (dd, *J* = 8.7, 1.8, 1H), 7.16 (d, *J* = 8.7, 1H), 6.85 (s, 1H), 3.81 (d, *J* = 1.1, 1H), 3.72 (s, 3H), 2.97–2.92 (m, 1H), 1.70–1.53 (m, 4H), 1.62 (s, 3H), 1.52 (s, 3H), 1.09 (s, 3H), 0.75 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 208.5, 205.2, 136.6, 136.5, 130.0, 129.5, 127.8, 127.6, 127.5, 127.3,

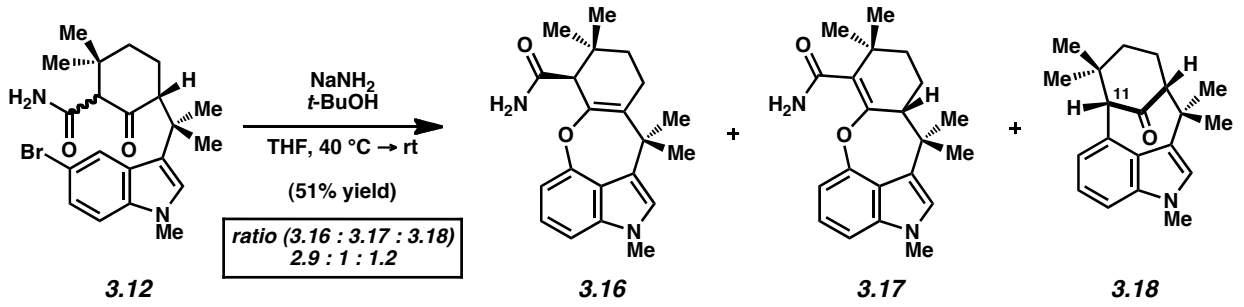
124.6, 124.1, 123.5, 123.1, 122.7, 121.0, 112.6, 112.1, 111.24, 111.18, 73.7, 72.5, 56.1, 55.9, 42.5, 39.1, 38.2, 37.9, 36.6, 36.2, 33.1, 33.0, 29.5, 28.9, 28.4, 26.5, 26.0, 25.5, 23.8, 23.6, 22.4, 19.5; IR (film): 2966, 2230, 1718, 1479, 1366, 1229 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{21}H_{25}N_2O_2BrNa$, 439.0997; found 439.0996.



3.11 *3.15*

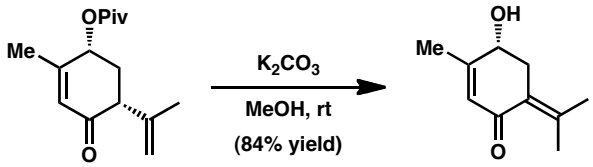
Vinyl Nitrile 3.15. Inside of the glovebox, a 4 mL Schlenk flask was charged with $NaNH_2$ (23.5 mg, 0.60 mmol, 10.5 equiv). The flask was then sealed and removed from the glovebox. Then *t*-BuOH (19.2 μL, 0.20 mmol, 3.5 equiv) in THF (0.40 mL) was then added. The resulting suspension was heated to 40 °C and stirred vigorously for 1 h. The reaction was cooled to room temperature and a solution of cyanoketone **3.11** (23.0 mg, 0.057 mmol, 1.0 equiv) in THF (2 x 0.20 mL) was added. After stirring at room temperature for 26 h, the reaction was quenched via the dropwise addition of brine (2 mL) followed by saturated aqueous NH_4Cl (2 mL). The reaction was then transferred to a test tube with EtOAc (3 mL). The resulting biphasic mixture was extracted with EtOAc (3 x 3 mL) and the organic layers were combined, dried over Na_2SO_4, and evaporated under reduced pressure. The resulting residue was purified by flash chromatography (1:1 EtOAc:hexanes) to afford vinyl nitrile **3.15** (9.5 mg, 52% yield) as a light yellow oil. Vinyl nitrile **3.15**: R_f 0.75 (1:1 EtOAc:hexanes); ^1H NMR (500 MHz, $CDCl_3$): δ 7.10 (dd, *J* = 8.1, 7.8, 1H), 6.93 (dd, *J* = 8.1, 0.5, 1H), 6.79 (dd, *J* = 7.8, 0.5, 1H), 6.63 (s, 1H), 3.70 (s, 3H), 3.23–3.20 (m, 1H), 2.36–2.22 (m, 2H), 1.55 (s, 3H), 1.54 (s, 3H), 1.54–1.49 (m, 1H), 1.36–

1.30 (m, 1H), 1.15 (s, 3H), 1.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 150.3, 142.2, 139.0, 131.1, 123.0, 122.3, 121.3, 119.2, 119.1, 106.9, 104.4, 44.8, 37.2, 33.4, 33.0, 32.7, 28.7, 26.9, 26.2, 25.7, 23.6; IR (film): 2966, 2240, 1582, 1494, 1314, 1238 cm^{-1}; HRMS-ESI (*m/z*) [M + Na]$^+$ calcd for $C_{21}H_{24}N_2ONa$, 343.1786; found 343.1782.



Aryne Cyclization Products 3.16, 3.17, and 3.18. Inside of the glovebox, a 4 mL Schlenk flask was charged with $NaNH_2$ (20.3 mg, 0.52 mmol, 10.5 equiv). The flask was then sealed and removed from the glovebox. Then *t*-BuOH (16.6 μL, 0.17 mmol, 3.5 equiv) in THF (0.40 mL) was then added. The resulting suspension was heated to 40 °C and stirred vigorously for 1 h. The reaction was cooled to room temperature and a solution of amidoketone **3.12** (20.8 mg, 0.050 mmol, 1.0 equiv) in THF (2 x 0.20 mL) was added. After stirring at room temperature for 24 h, the reaction was quenched via the dropwise addition of brine (2 mL) followed by saturated aqueous NH_4Cl (2 mL). The reaction was then transferred to a test tube with EtOAc (3 mL). The resulting biphasic mixture was extracted with EtOAc (3 x 3 mL) and the organic layers were combined, dried over Na_2SO_4, and evaporated under reduced pressure. The resulting residue was purified by preparative TLC (1:1 EtOAc:hexanes) to afford alkyl amide **3.16** (4.8 mg, 29% yield) as a light yellow oil, vinyl amide **3.17** (1.6 mg, 10% yield) as a light yellow oil, and known bicycle **3.18**[3p] (1.8 mg, 12% yield) as a light brown solid. Alkyl amide **3.16**: R_f 0.25 (1:1 EtOAc:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.04 (dd, *J* = 8.3, 7.7, 1H), 6.88 (dd, *J* = 8.3,

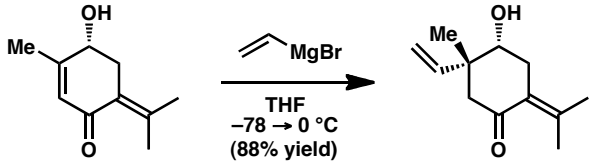
0.6, 1H), 6.63 (dd, *J* = 7.7, 0.6), 6.61 (s, 1H), 5.41 (bs, 1H), 5.17 (bs, 1H) 3.69 (s, 3H), 2.90 (s, 1H), 2.40–2.33 (m, 1H), 2.32–2.23, (m, 1H), 1.66–1.58 (m, 1H), 1.57 (s, 3H), 1.56 (s, 3H), 1.30–1.25 (m, 1H), 1.03 (s, 3H), 0.99, (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.4, 151.0, 148.1, 139.0, 130.8, 123.0, 122.9, 121.1, 119.2, 106.6, 103.9, 59.4, 37.1, 33.0, 32.3, 32.2, 29.5, 27.4, 27.3, 26.3, 23.7; IR (film): 3318, 3186, 2959, 1664, 1309, 1229 cm^{-1}; HRMS-ESI (*m/z*) [M + Na]$^+$ calcd for $C_{21}H_{26}N_2O_2Na$, 361.1892; found 361.1893. Vinyl amide **3.17**: R_f 0.29 (1:1 EtOAc:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.09 (dd, *J* = 8.3, 7.7, 1H), 6.94 (dd, *J* = 8.3, 0.5, 1H), 6.69 (s, 1H), 6.67 (dd, *J* = 7.7, 0.5), 5.62 (bs, 2H), 3.71 (s, 3H), 2.81 (dd, *J* = 7.4, 7.0, 1H), 1.91–1.85 (m, 2H), 1.64–1.58 (m, 1H), 1.44 (s, 3H), 1.44–1.38 (m, 1H), 1.38 (s, 3H), 1.29 (s, 3H), 1.21 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.9, 153.6, 149.2, 138.9, 127.0, 125.1, 122.9, 121.6, 118.0, 107.0, 104.1, 47.1, 37.3, 36.3, 33.7, 33.0, 29.2, 28.5, 27.9, 26.3, 23.0; IR (film): 3324, 3176, 2959, 1663, 1314, 1253 cm^{-1}; HRMS-ESI (*m/z*) [M + Na]$^+$ calcd for $C_{21}H_{26}N_2O_2Na$, 361.1892; found 361.1898.



3.26 ***3.25***

Dienone 3.25. To a solution of enone **3.26** (1.24 g, 4.95 mmol, 1 equiv) in methanol (20 mL) was added K_2CO_3 (1.71 g, 12.38 mmol, 2.5 equiv). The reaction was stirred for 5 h, then quenched by dropwise addition of AcOH until pH 7 (~1 mL). The methanol was removed *in vacuo* and the residue was partitioned between EtOAc (10 mL) and brine (20 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over Na_2SO_4. The solvent was removed *in vacuo* and the crude residue

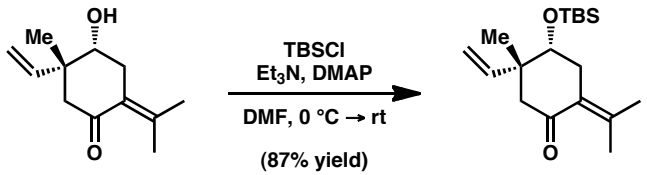
was purified by flash chromatography (1:4 to 2:3 EtOAc:hexanes) to yield dienone **3.25** (694 mg, 84% yield) as a yellow oil. Dienone **3.25**: Rf 0.34 (1:1 EtOAc:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.88 (s, 1H), 4.26 (dd, *J* = 6.9, 4.6, 1H), 2.96 (dd, *J* = 14.0, 4.6, 1H), 2.75 (dd, *J* = 14.0, 6.9, 1H), 2.12 (s, 3H), 2.03 (s, 3H), 1.90 (s, 3H), 1.76 (d, *J* =3.7, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 190.7, 159.2, 146.5, 129.7, 125.9, 69.5, 37.5, 23.0, 22.9, 20.3; IR (film): 3387, 2912, 1652, 1602, 1305, 1224 cm^{-1}; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{10}H_{14}O_2H$, 167.1072; found 167.1074; $[\alpha]^{22.5}_D$ +55.2° (*c* = 0.500, CH_2Cl_2).



3.25 ***3.28***

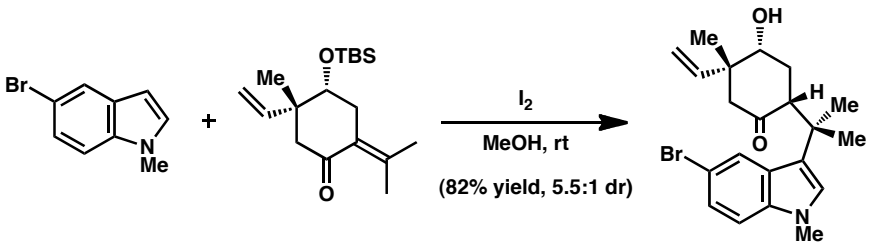
Enone 3.28. To dienone **3.25** (82 mg, 0.493 mmol, 1 equiv) in THF (3.32 mL) at –78 °C was added vinyl magnesium bromide (1 M in THF, 1.48 mL, 1.48 mmol, 3 equiv), dropwise over 10 min. The reaction was stirred at 0 °C for 3.5 h and then was quenched with saturated aqueous NH_4Cl (10 mL). The layers were separated and then the aqueous was extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (15 mL) and then dried over Na_2SO_4. The solvent was removed *in vacuo* and then the crude residue was purified by flash chromatography (1:4 EtOAc:hexanes) to afford enone **3.28** (84 mg, 88% yield) as a yellow oil. Enone **3.28**: R_f 0.27 (1:1 EtOAc:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.88 (dd, *J* = 17.6, 10.8, 1H), 5.21 (dd, *J* = 10.8, 0.8, 1H), 5.10 (dd, *J* = 17.6, 0.8, 1H), 3.77 (dd, *J* = 6.5, 4.5, 1H), 2.74 (d, *J* = 15.6, 1H), 2.72 (dd, *J* = 15.8, 4.5, 1H), 2.60 (dd, *J* = 15.8, 6.5, 1H), 2.20 (d, *J* = 15.6, 1H), 2.01 (s, 3H), 1.81 (s, 3H), 1.76 (bs, 1H), 1.10 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 201.8, 146.6, 141.8, 128.0, 115.7, 73.2, 48.4, 43.9, 33.9, 24.4, 23.6, 22.9; IR (film): 3446, 2966, 1673,

1589, 1277 cm^{-1}; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{12}H_{18}O_2H$, 195.1385; found 193.1390; $[\alpha]^{22.7}_D$ –19.2° (*c* = 0.500, CH_2Cl_2).



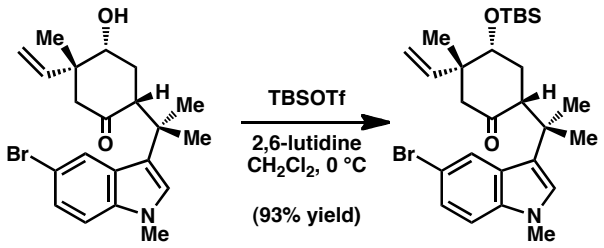
3.28 ***3.29***

Enone 3.29. To enone **3.28** (411 mg, 2.12 mmol, 1 equiv) in DMF (8.5 mL) at 0 °C was added Et_3N (870 μL, 6.35 mmol, 3 equiv) and DMAP (259 mg, 2.12 mmol. 1 equiv). TBSCl (957 mg, 6.35 mmol, 3 equiv) was added in one portion and mixture was stirred at rt for 66 h. The reaction was quenched with saturated aqueous NH_4Cl (20 mL) and then extracted with Et_2O (5 x 20 mL). The combined organic layers were washed consecutively with H_2O (20 mL) followed by brine (2 x 20 mL) and then dried over Na_2SO_4. The solvent was removed *in vacuo* and then the crude residue was purified by flash chromatography (1:5 Et_2O:hexanes) to provide enone **3.29** (566 mg, 87% yield) as a white solid. Enone **3.29**: mp: 55 ºC; R_f 0.81 (1:2 EtOAc:hexanes); ^1H NMR (500 MHz, $CDCl_3$): δ 5.97 (dd, *J* = 17.8, 11.0, 1H), 5.06 (d, *J* = 11.0, 1H), 4.98 (d, *J* = 17.8, 1H), 3.73 (dd, *J* = 8.1, 4.3, 1H), 2.74 (d, *J* = 15.8, 1H), 2.64 (dd, *J* = 15.3, 4.3, 1H), 2.41 (dd, *J* = 15.3, 8.1, 1H), 2.16 (d, *J* = 15.8, 1H), 2.01 (s, 3H), 1.77 (s, 3H), 1.05 (s, 3H), 0.89 (s, 9H), 0.07 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 202.3, 145.1, 142.4, 129.0, 113.9, 75.0, 49.6, 44.1, 35.5, 25.9, 25.4, 23.3, 22.7, 18.2, –4.1, –4.7; IR (film): 2929, 1683, 1472, 1253, 1088 cm^{-1}; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{18}H_{32}O_2SiH$, 309.2250; found 309.2247; $[\alpha]^{22.4}_D$ –20.2° (*c* = 1.000, CH_2Cl_2).



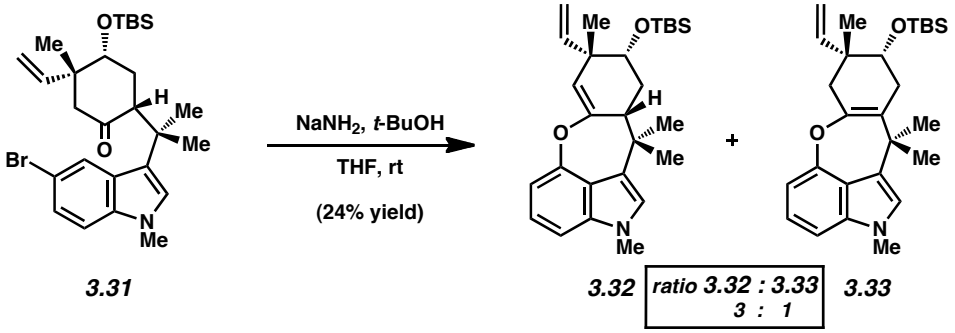
3.24 *3.29* *3.30*

Bromoindole 3.30. Bromoindole **3.30** was prepared following the general procedure reported by Wang et al. with minor modifications.[12] To enone **3.29** (137 mg, 0.44 mmol, 1 equiv) was added 5-bromo-*N*-methylindole (**3.24**)[17] (140 mg, 0.67 mmol, 1.5 equiv) followed by methanol (890 μL). The mixture was allowed to stir at 23 °C until homogeneous, then I_2 (23 mg, 0.089 mmol, 0.2 equiv) was added. The reaction was stirred for 12 h, and then quenched with saturated aqueous $Na_2S_2O_3$ (10 mL). The resulting mixture was allowed to stir until the I_2 color disappeared. The mixture was extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (20 mL) then dried over Na_2SO_4. The solvent was removed *in vacuo* and the crude residue was purified by flash chromatography (1:3 to 1:2 Et_2O:hexanes) to afford a single diastereomer of bromoindole **3.30** (127 mg, 69%) as a white solid. Bromoindole **3.30**: mp: 170–172 ºC; R_f 0.27 (1:1 Et_2O:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.78 (d, *J* = 1.7, 1H), 7.27 (dd, *J* = 8.7, 1.7, 1H), 7.15 (d, *J* = 8.7, 1H), 6.78 (s, 1H), 5.84 (dd, *J* = 17.7, 11.0, 1H), 5.24 (d, *J* = 11.0, 1H), 5.15 (d, *J* = 17.7, 1H), 3.74 (dd, *J* = 11.3, 4.1, 1H), 3.71 (s, 3H), 3.01 (dd, *J* = 13.2, 5.4, 1H), 2.41 (d, *J* = 14.0, 1H), 2.36 (d, *J* = 14.0, 1H), 1.68–1.61 (m, 1H), 1.62 (s, 3H), 1.60–1.51 (m, 1H), 1.48 (bs, 1H), 1.44 (s, 3H), 1.16 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 209.0, 138.8, 136.6, 127.5, 127.3 124.1, 123.21, 123.17, 117.3, 112.0, 111.2, 76.1, 54.8, 52.0, 45.9, 36.6, 33.9, 33.0, 27.2, 25.5, 22.9; IR (film): 3426, 2961, 1705, 1478, 1227 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{21}H_{26}NO_2BrNa$, 426.1045; found 426.1046; $[\alpha]^{22.4}_D$ +56.2° (*c* = 1.000, $CHCl_3$).



3.30 *3.31*

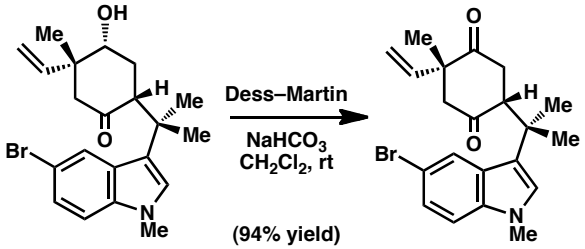
Silyl Ether 3.31. To bromoindole **3.30** (80 mg, 0.198 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) at 0 °C was added 2,6-lutidine (54 μL, 0.455 mmol, 2.3 equiv) followed by TBSOTf (100 μL, 0.435 mmol, 2.2 equiv), dropwise. The reaction was allowed to stir at rt for 1.5 h and then quenched with saturated aqueous NH_4Cl (10 mL). The layers were separated and then the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with brine (20 mL) and then dried over Na_2SO_4. The solvent was removed *in vacuo* and then the crude residue was purified by flash chromatography (1:3 Et_2O:hexanes) to afford silyl ether **3.31** (96 mg, 93% yield) as a white solid. Silyl ether **3.31**: mp: 105 ºC; R_f 0.75 (1:1 Et_2O:hexanes); ^1H NMR (500 MHz, $CDCl_3$): δ 7.79 (d, *J* = 1.7, 1H), 7.26 (dd, *J* = 8.7, 1.7, 1H), 7.14 (d, *J* = 8.7, 1H), 6.78 (s, 1H), 5.89 (dd, *J* = 17.9, 11.1, 1H), 5.10 (d, *J* = 11.2, 1H), 5.04 (d, *J* = 17.9, 1H), 3.70 (s, 3H), 3.65 (dd, *J* = 11.1, 3.8, 1H), 2.88 (dd, *J* = 13.6, 5, 1H), 2.50 (d, *J* = 14.5, 1H), 2.26 (d, *J* = 14.5, 1H), 1.61 (s, 3H), 1.56–1.48 (m, 1H), 1.42 (s, 3H), 1.41–1.35 (m, 1H), 1.05 (s, 3H), 0.71 (s, 9H), –0.15 (s, 3H), –0.40 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 208.9, 140.6, 136.6, 127.39, 127.38, 124.1, 123.5, 123.0, 115.3, 112.0, 111.1, 77.3, 54.9, 51.1, 46.4, 36.7, 34.0, 32.9, 27.3, 27.1, 25.8, 22.8, 18.1, –4.8, –5.0; IR (film): 2956, 2857, 1710, 1478, 1096 cm^{-1}; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{27}H_{40}NO_2BrSiH$, 518.2090; found 518.2088; $[\alpha]^{22.8}_D$ +26.8° (*c* = 1.000, CH_2Cl_2).



3.31 *3.32* ratio 3.32 : 3.33 = 3 : 1 *3.33*

Vinyl Ethers 3.32 and 3.33. Inside of the glovebox, a 4 mL schlenk flask was charged with $NaNH_2$ (50.9 mg, 1.31 mmol, 10.5 equiv). The flask was then sealed and removed from the glovebox. Then *t*-BuOH (41.6 μL, 0.44 mmol, 3.5 equiv) in THF (0.65 mL) was then added. The resulting suspension was heated to 40 °C and stirred vigorously for 1 h. The reaction was cooled to room temperature and a solution of silyl ether **3.31** (64.5 mg, 0.124 mmol, 1.0 equiv) in THF (2 x 0.33 mL) was added. After stirring at room temperature for 22 hours, the reaction was quenched via the dropwise addition of brine (2 mL) followed by saturated aqueous NH_4Cl (2 mL). The reaction was then transferred to a test tube with EtOAc (3 mL). The resulting biphasic mixture was extracted with EtOAc (3 x 3 mL) and the organic layers were combined, dried over Na_2SO_4, and evaporated under reduced pressure. The resulting residue was purified by flash chromatography (100% benzene) to afford a mixture of vinyl ethers **3.32** and **3.33** (13.2 mg, 3.3:1 ratio **3.32** to **3.33**, 24% yield) as a yellow oil. These compounds were characterized as a mixture. R_f 0.75 (100% benzene); Vinyl ether **3.32**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.10 (dd, *J* = 8.3, 7.7, 1H), 6.92 (dd, *J* = 8.3, 0.5, 1H), 6.67 (s, 1H), 6.65 (dd, *J* = 7.7, 0.5, 1H), 6.02 (dd, *J* = 17.6, 10.6, 1H), 5.26 (d, *J* = 1.7, 1H), 5.15 (dd, *J* = 10.6, 2.0, 1H), 5.11 (dd, *J* = 17.6, 2.0, 1H), 3.71 (s, 3H), 3.55 (dd, *J* = 11.2, 3.8, 1H), 2.93 (ddd, *J* = 11.1, 6.8, 1.7, 1H), 1.80–1.69 (m, 2H), 1.35 (s, 3H), 1.33 (s, 3H), 1.16 (s, 3H), 0.91 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H); Vinyl ether **3.33**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.07 (dd, *J* = 8.3, 7.6, 1H), 6.90 (dd, *J* = 8.3, 0.5, 1H), 6.64 (dd, *J*

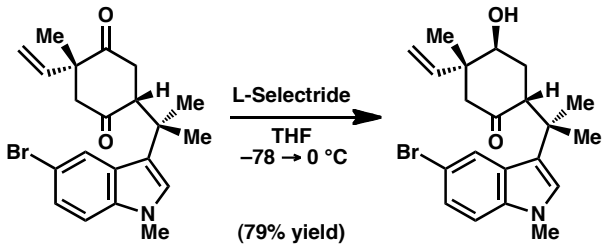
= 7.6, 0.5, 1H), 6.59 (s, 1H), 5.94 (dd, *J* = 17.9, 11.0, 1H), 5.06 (dd, *J* = 17.9, 1.5, 1H), 5.04 (dd, *J* = 11.0, 1.5, 1H), 3.69 (s, 3H), 3.47 (dd, *J* = 8.5, 5.3, 1H), 2.49 (d, *J* = 17.7, 1H), 2.35 (dd, *J* = 16.8, 5.3, 1H), 2.21 (d, *J* = 17.7, 1H), 2.10 (dd, *J* = 16.8, 8.5, 1H), 1.51 (s, 3H), 1.46 (s, 3H), 1.44 (s, 3H), 0.87 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (49 of 50 observed, 125 MHz, $CDCl_3$): δ 156.0, 150.7, 149.8, 147.8, 143.5, 141.2, 139.0, 138.9, 126.6, 125.7, 124.6, 123.7, 123.0, 122.7, 121.6, 120.8, 119.5, 118.3, 115.6, 114.5, 112.9, 107.1, 106.5, 103.7, 75.8, 74.3, 48.2, 44.4, 41.2, 39.6, 36.5, 36.0, 33.6, 32.98, 32.96, 32.7, 30.5, 30.0, 27.3, 26.04, 25.97, 25.94, 25.8, 25.2, 18.3, 18.2, –3.9, –4.0, –4.8; IR (film): 2956, 1581, 1495, 1315, 1258, 1080 cm^{-1}; HRMS-ESI (*m/z*) [M + H]$^+$ calcd for $C_{27}H_{39}NO_2SiH$, 438.2828; found 438.2825.



3.30 ***3.40***

Diketone 3.40. To alcohol **3.30** (120 mg, 0.298 mmol, 1.0 equiv) in CH_2Cl_2 (6 mL) was added $NaHCO_3$ (125 mg, 1.49 mmol, 5.0 equiv), followed by Dess-Martin periodinane (164 mg, 0.39 mmol, 1.3 equiv). The reaction was stirred for 1.5 h at rt and then was quenched with a saturated aqueous solution of $Na_2S_2O_3/NaHCO_3$ (1:1, 6 mL). The resulting mixture was allowed to stir until homogenous (10 min.), the layers were separated, and then the aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic phases were washed with brine (10 mL) then dried over Na_2SO_4. The solvent was removed *in vacuo* and the crude residue was purified by flash chromatography (1:1:5 Et_2O:CH_2Cl_2:hexanes) to afford diketone **3.40** (113 mg, 94% yield) as a white solid. Diketone **3.40**: mp: 85 ºC; R_f 0.54 (1:1:2 Et_2O:CH_2Cl_2:hexanes); ^{1}H NMR (500

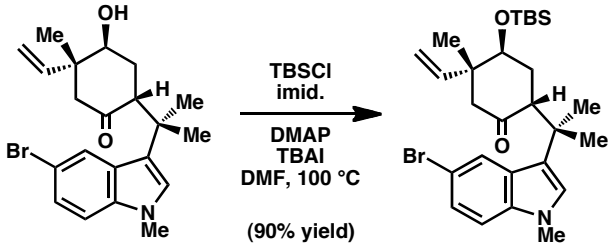
MHz, $CDCl_3$): δ 7.76 (d, *J* = 1.8, 1H), 7.28 (dd, *J* = 8.7, 1.8, 1H), 7.16 (d, *J* = 8.7, 1H), 6.79 (s, 1H), 5.83 (dd, *J* = 17.4, 10.7, 1H), 5.12 (d, *J* = 10.7, 1H), 5.05 (d, *J* = 17.4, 1H), 3.72 (s, 3H), 3.09 (dd, *J* = 12.8, 6.2, 1H), 2.85 (d, *J* = 13.6, 1H), 2.72 (dd, *J* = 15.1, 12.8, 1H), 2.47 (d, *J* = 13.6, 1H), 2.18 (dd, *J* = 15.1, 6.2, 1H), 1.64 (s, 3H), 1.47 (s, 3H), 1.16 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 210.8, 209.3, 140.5, 136.6, 127.5, 127.2, 124.6, 123.2, 120.8, 115.0, 112.6, 111.3, 54.0, 52.3, 51.0, 40.7, 38.1, 33.0, 27.6, 23.8, 23.7; IR (film): 2968, 1709, 1478, 1422, 1229 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{21}H_{24}NO_2BrNa$, 424.0888; found 424.0877; $[\alpha]^{23.0}_D$ +97.6° (*c* = 0.500, CH_2Cl_2).



3.40 ***3.41***

Alcohol 3.41. To diketone **3.40** (39 mg, 0.097 mmol, 1.0 equiv) in THF (2 mL) at –78 °C was added L-Selectride (1 M in THF, 126 μL, 0.126 mmol, 1.3 equiv), dropwise over 5 min. The resulting mixture was stirred at 0 °C for 1.5 h. The reaction was then cooled to –78 °C and treated with aqueous 10% NaOH (2 mL) and 30% H_2O_2 (2 mL) and then allowed to warm to rt with stirring for 30 min. The mixture was extracted with EtOAc (4 x 2 mL). The combined organics were washed with brine (2 mL), then dried by passage over silica (2 inches in a pipette, eluting with 10 mL EtOAc). The solvent was removed *in vacuo* then the crude residue was purified by flash chromatography (1:1:5 Et_2O:CH_2Cl_2:hexanes) to provide alcohol **3.41** (31 mg, 79% yield) as a white solid. Alcohol **3.41**: mp: 71 ºC; R_f 0.43 (2:1:1 hexanes:CH_2Cl_2:Et_2O); ^1H NMR (500 MHz, CD_2Cl_2): δ 7.85, (d, *J* = 1.7, 1H), 7.26 (dd, *J* = 8.7, 1.7, 1H), 7.18 (d, *J* = 8.7,

1H), 6.82 (s, 1H), 5.64 (dd, *J* = 17.7, 10.9, 1H), 5.07 (d, *J* = 17.7, 1H), 5.05 (d, *J* = 10.9, 1H), 3.70 (s, 3H), 3.61 (br. s, 1H), 3.37 (dd, *J* = 12.7, 5.5, 1H), 2.71 (d, *J* = 13.7, 1H), 2.23 (dd, *J* = 13.7, 1.1, 1H), 1.82 (dt, *J* = 12.9, 2.4, 1H), 1.58 (s, 3H), 1.57–1.51 (m, 1H), 1.41 (s, 3H), 1.08 (s, 3H); ^{13}C NMR (125 MHz, CD_2Cl_2): δ 210.5, 144.1, 136.9, 127.9, 127.7, 124.1, 123.8, 123.6, 114.7, 112.0, 111.4, 72.8, 50.2, 48.7, 47.3, 36.6, 33.10, 33.08, 27.7, 24.6, 22.9; IR (film): 3463, 2966, 1703, 1479, 1214 cm^{-1}; HRMS-ESI (*m/z*) [M + Na]$^+$ calcd for $C_{21}H_{26}NO_2BrNa$, 426.1045; found 426.1044; $[\alpha]^{24.8}_D$ +76.2° (*c* = 1.000, $CHCl_3$).



3.41 ***3.37***

Silyl Ether 3.37. To a solution of alcohol **3.41** (3.84 g, 9.50 mmol, 1.0 equiv) in DMF (47.5 mL) was added imidazole (3.23 g, 47.5 mmol, 5.0 equiv), DMAP (1.17 g, 9.50 mmol, 1.0 equiv), tetrabutylammonium iodide (3.51 g, 9.50 mmol, 1.0 equiv), and TBSCl (4.30 g, 28.5 mmol, 3.0 equiv), all as solids in one portion. The flask was fitted with a reflux condenser, flushed with N_2, and then allowed to stir at 100 °C. After 12 h, the reaction was cooled to room temperature and transferred to a separatory funnel with EtOAc (75 mL), H_2O (30 mL), and a solution of saturated aqueous NH_4Cl (100 mL). The resulting biphasic mixture was extracted with EtOAc (4 x 75 mL). The organic layers were combined, washed with H_2O (1 x 20 mL), washed with brine (2 x 20 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The resulting residue was purified by flash chromatography (1:1 hexanes:Et_2O) to afford silyl ether **3.37** (4.43 g, 90% yield) as a white solid. Silyl ether **3.37**: mp: 117 ºC; R_f 0.68 (1:1 Et_2O:hexanes); ^{1}H NMR (500

MHz, $CDCl_3$): δ 7.79 (d, *J* = 1.8, 1H), 7.24 (dd, *J* = 8.7, 1.8, 1H), 7.12 (d, *J* = 8.7, 1H), 6.78 (s, 1H), 5.61 (dd, *J* = 17.6, 11.0, 1H), 5.07 (d, *J* = 17.6, 1H), 5.04 (d, *J* = 11.0, 1H), 3.70 (s, 3H), 3.56 (br. s, 1H), 3.27 (dd, *J* = 13.0, 5.4, 1H), 2.67 (d, *J* = 13.4, 1H), 2.16 (dd, *J* = 13.4, 0.9, 1H), 1.81 (dt, *J* = 13.4, 2.0, 1H), 1.63 (s, 3H), 1.61–1.59 (m, 1H), 1.38 (s, 3H), 1.00 (s, 3H), 0.86 (s, 9H), –0.04 (s, 3H), –0.42 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 211.0, 143.7, 136.5, 127.7, 127.3, 124.0, 123.71, 123.66, 114.7, 112.1, 110.9, 73.3, 50.4, 48.4, 48.1, 36.0, 33.3, 32.9, 26.5, 26.1, 25.6, 24.1, 18.2, –4.7, –5.1; IR (film): 2953, 2926, 2858, 1708, 1477, 1361, 1256, 1218, 1073 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{27}H_{40}NO_2BrSiNa$, 540.1909; found 540.1903; $[\alpha]^{22.7}_D$ +72.4° (*c* = 1.000, $CHCl_3$).

3.12 Notes and References

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APPENDIX TWO

Spectra Relevant to Chapter Three:

Initial Attempts to Install the Bridgehead Nitrogen Substituent and Synthesis of Cyclization Substrate Derived from (*R*)-Carvone

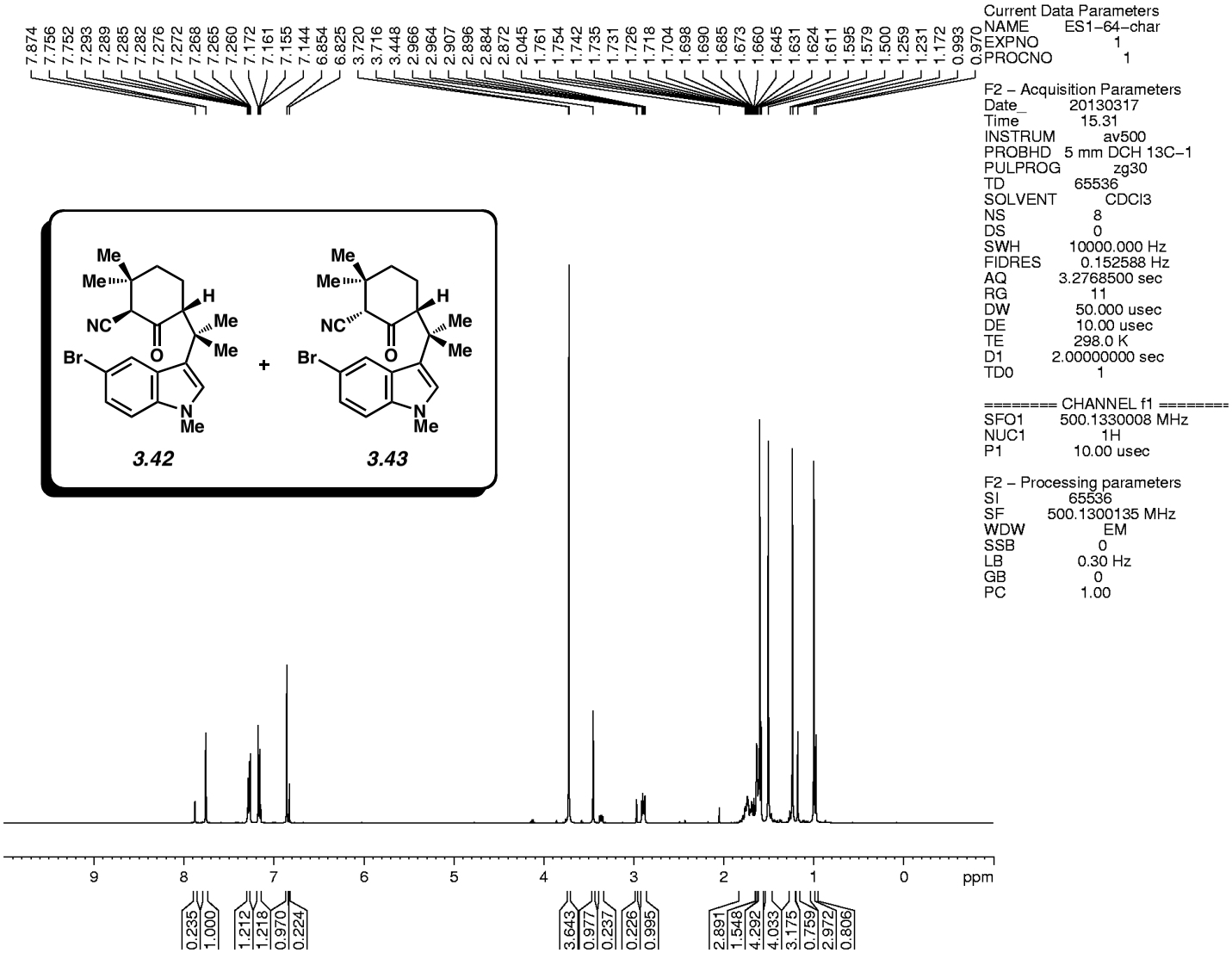


Figure A2.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compounds **3.42** and **3.43**.

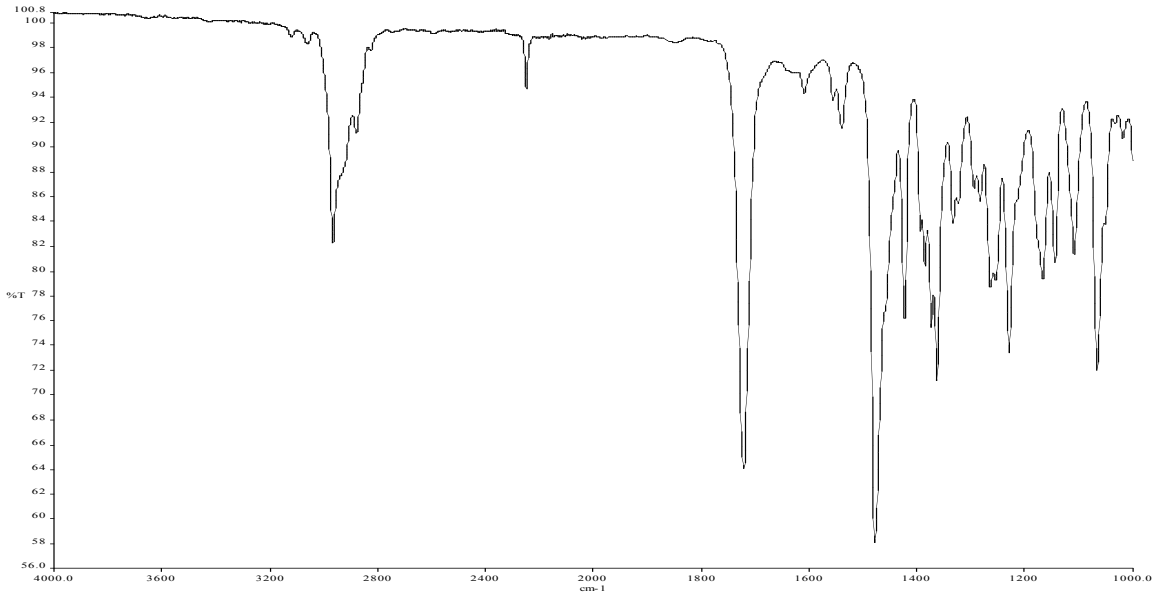


Figure A2.2 Infrared spectrum of compounds **3.42** and **3.43**.

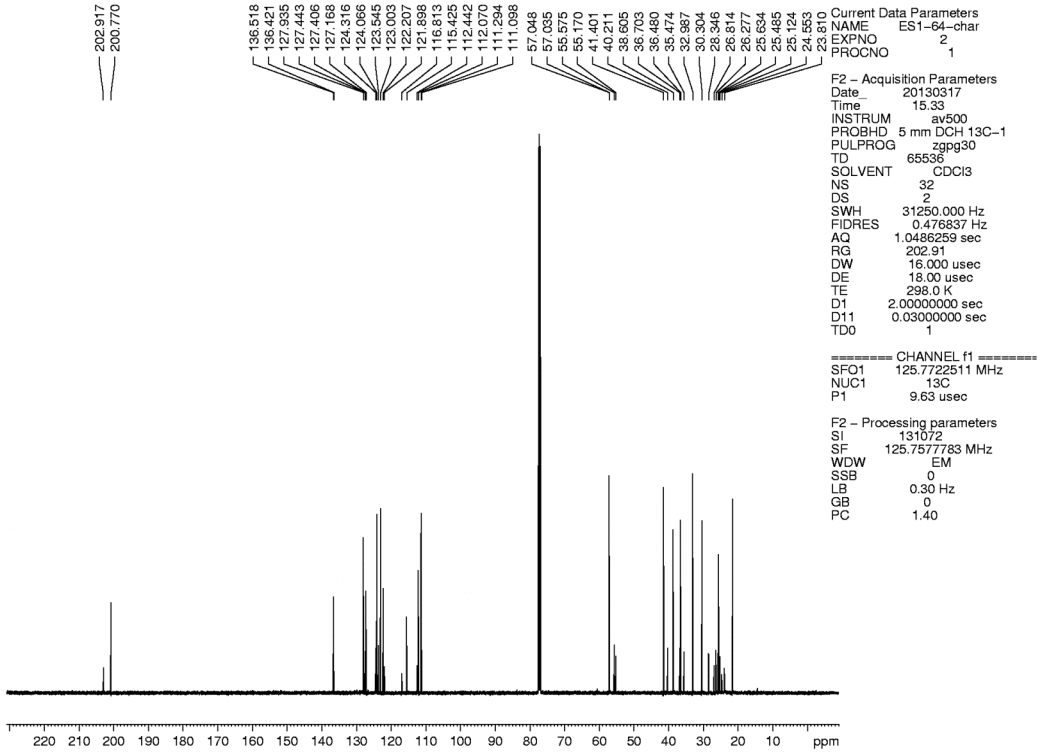


Figure A2.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compounds **3.42** and **3.43**.

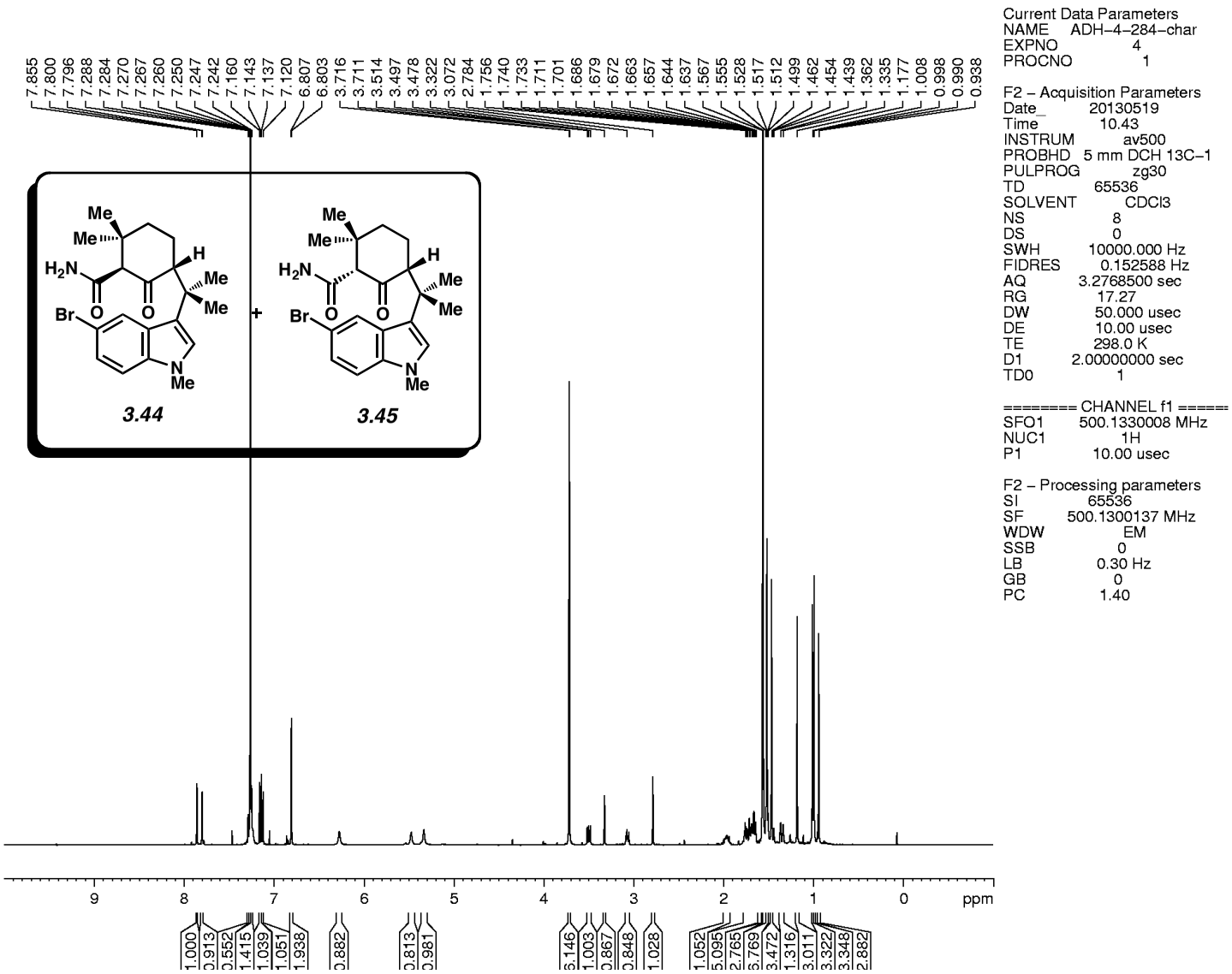


Figure A2.4 ^{1}H NMR (500 MHz, $CDCl_3$) of compounds **3.44** and **3.45**.

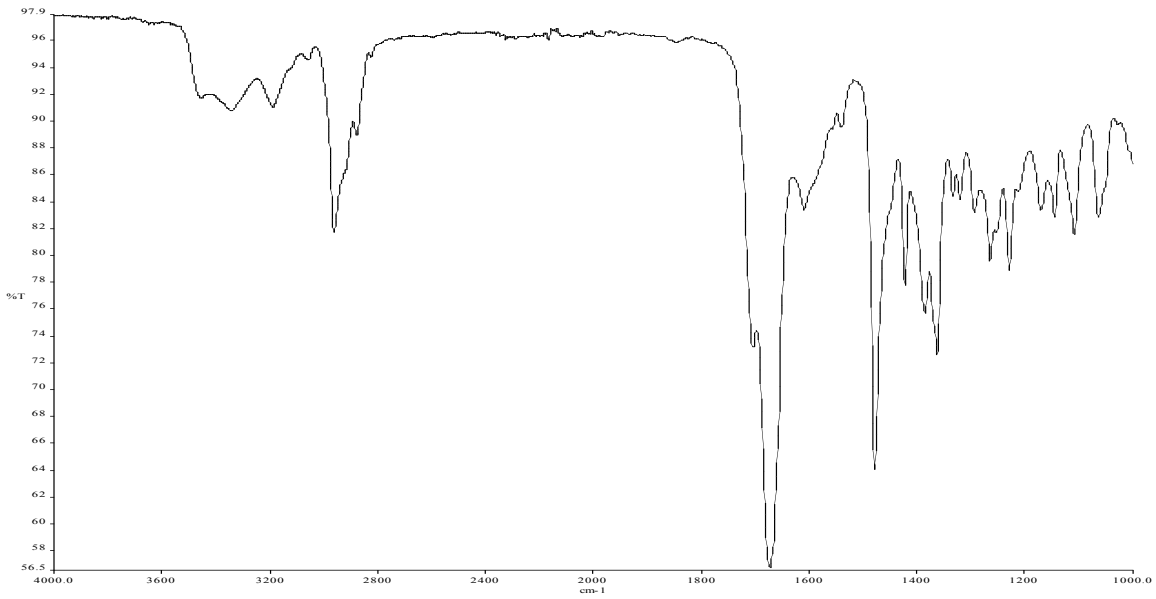


Figure A2.5 Infrared spectrum of compounds **3.44** and **3.45**.

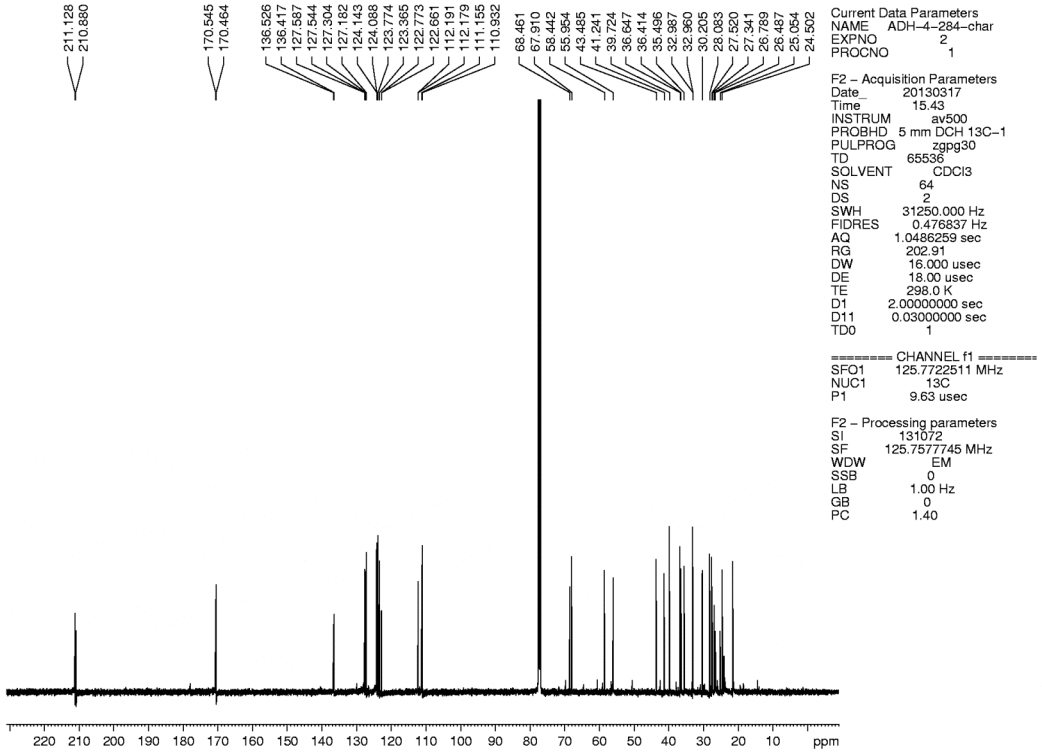


Figure A2.6 ^{13}C NMR (125 MHz, $CDCl_3$) of compounds **3.44** and **3.45**.

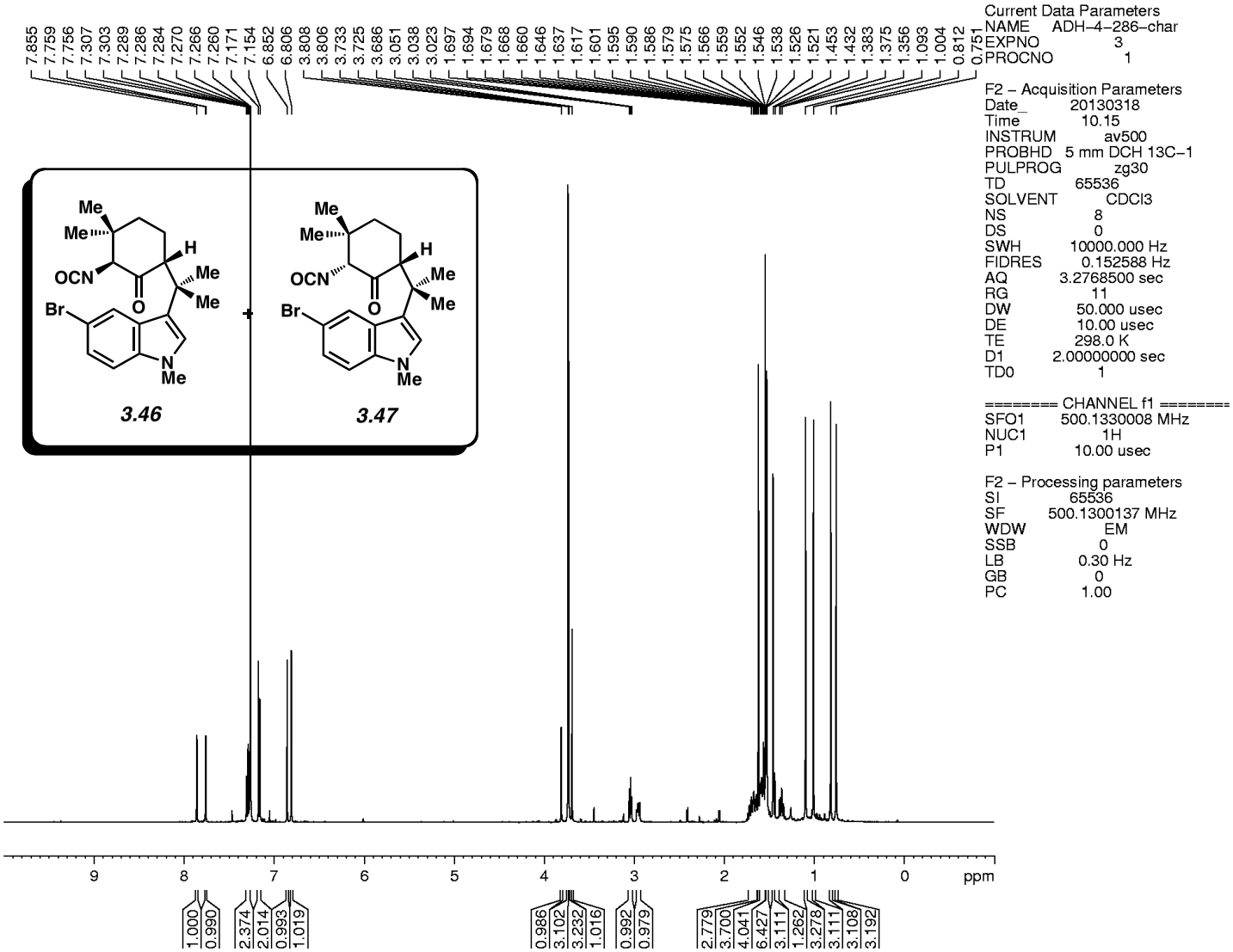


Figure A2.7 ^{1}H NMR (500 MHz, $CDCl_3$) of compounds **3.46** and **3.47**.

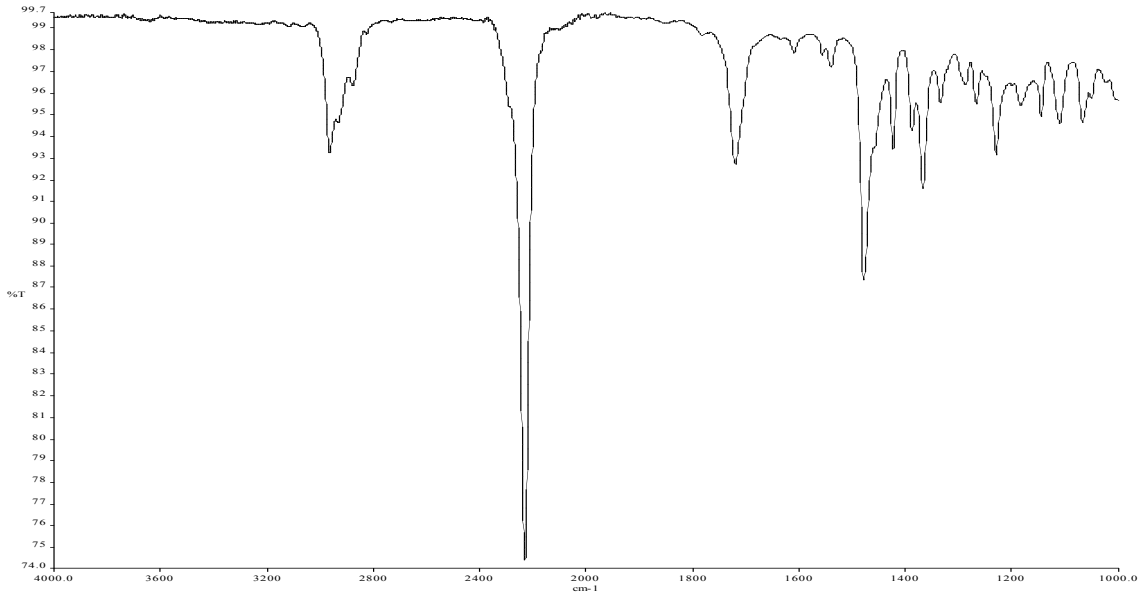


Figure A2.8 Infrared spectrum of compounds **3.46** and **3.47**.

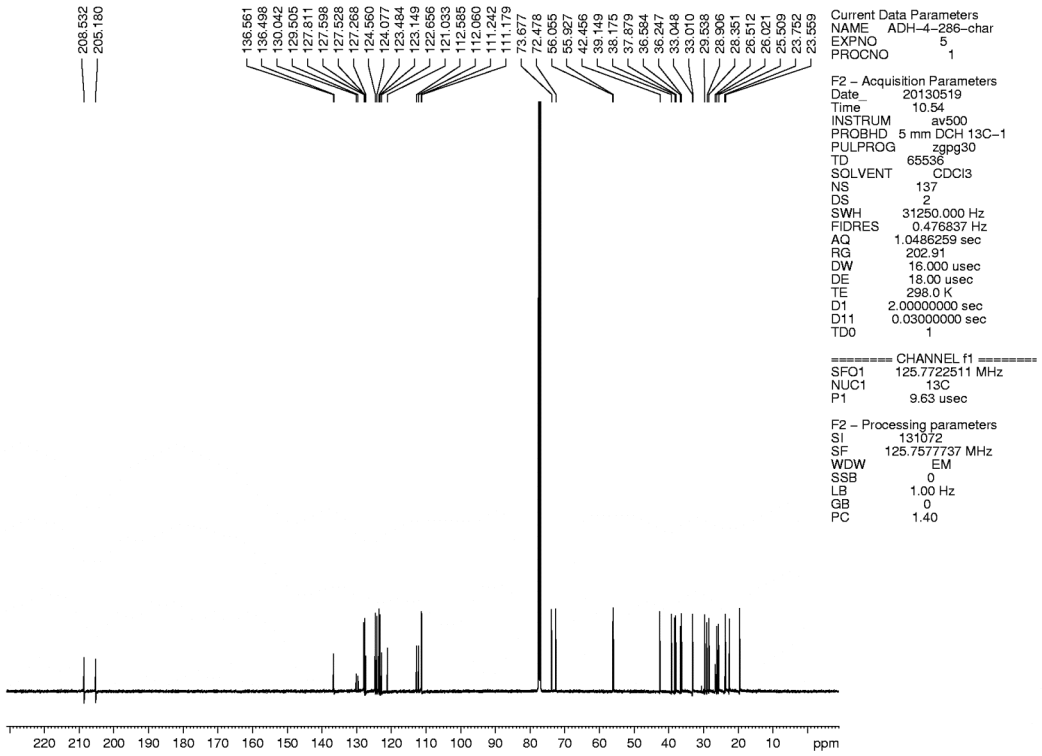


Figure A2.9 ^{13}C NMR (125 MHz, $CDCl_3$) of compounds **3.46** and **3.47**.

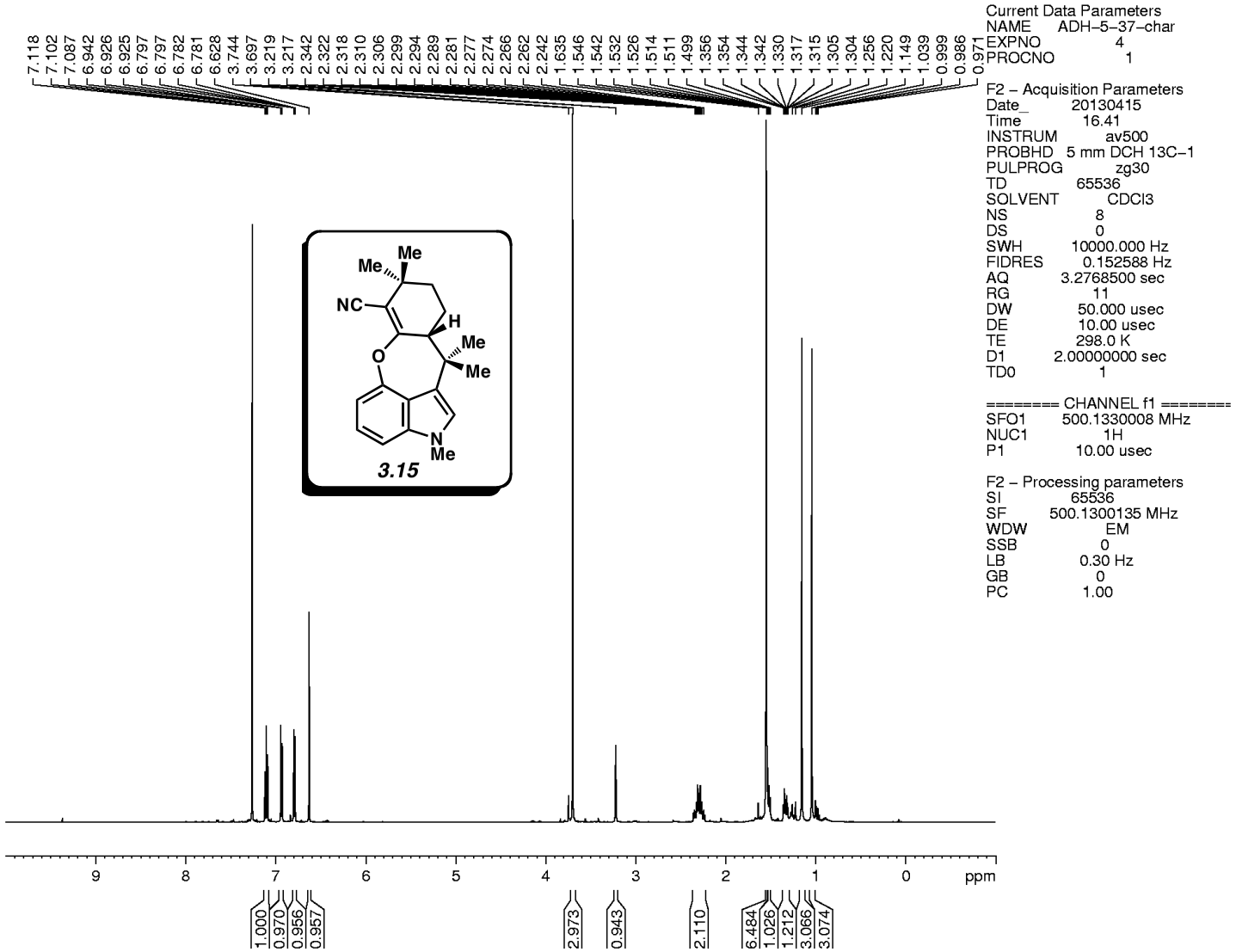


Figure A2.10 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.15**.

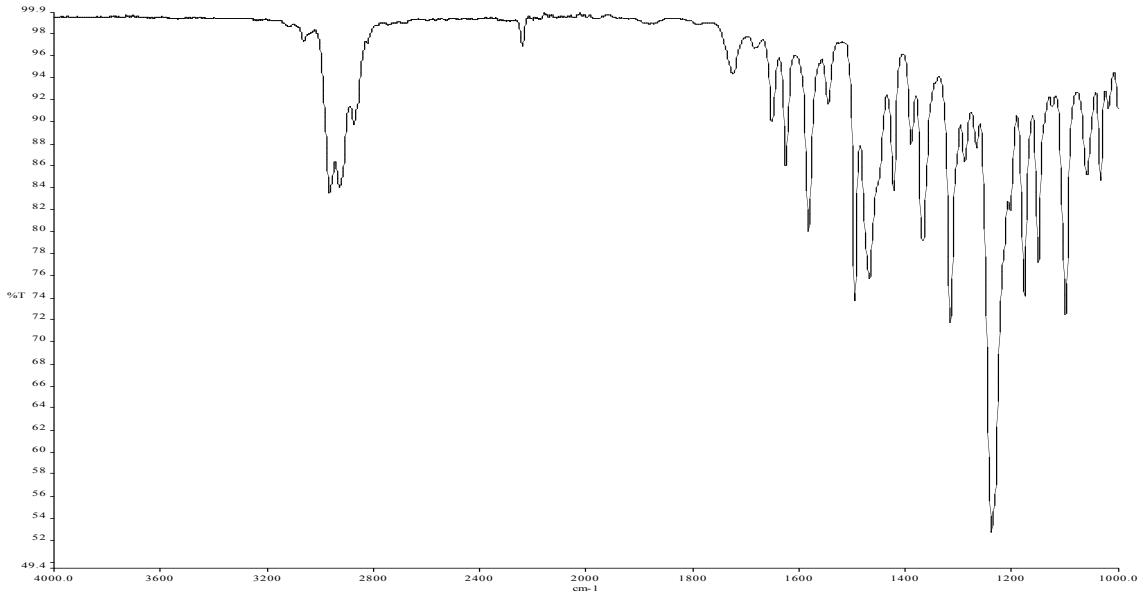


Figure A2.11 Infrared spectrum of compound **3.15**.

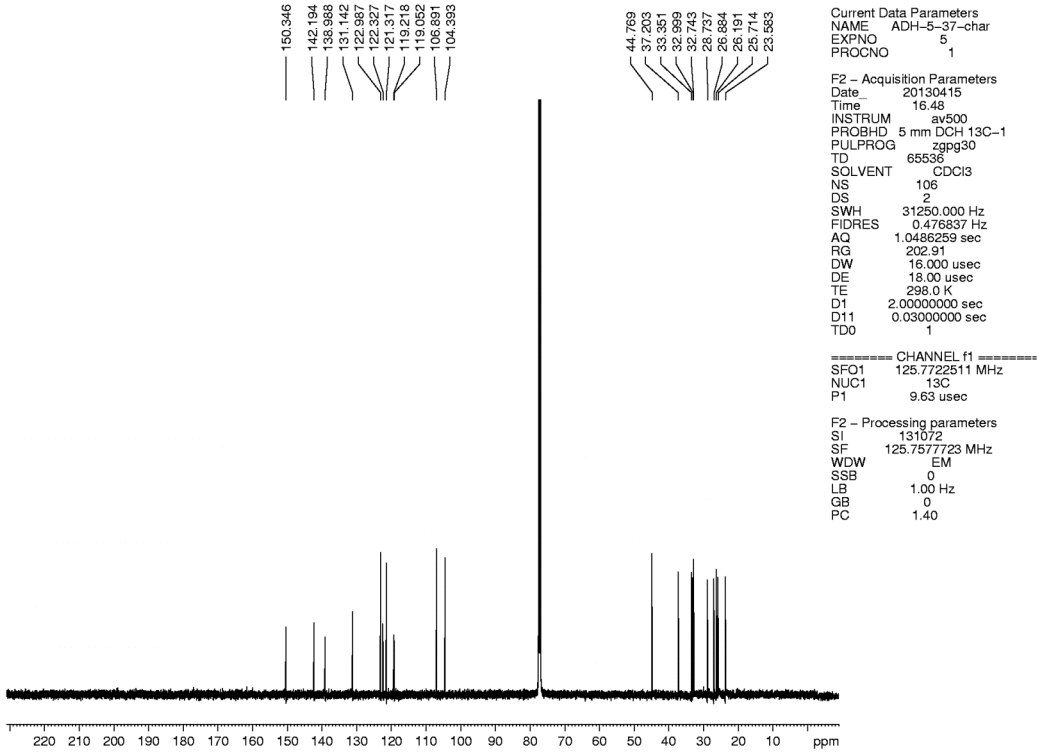


Figure A2.12 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **3.15**.

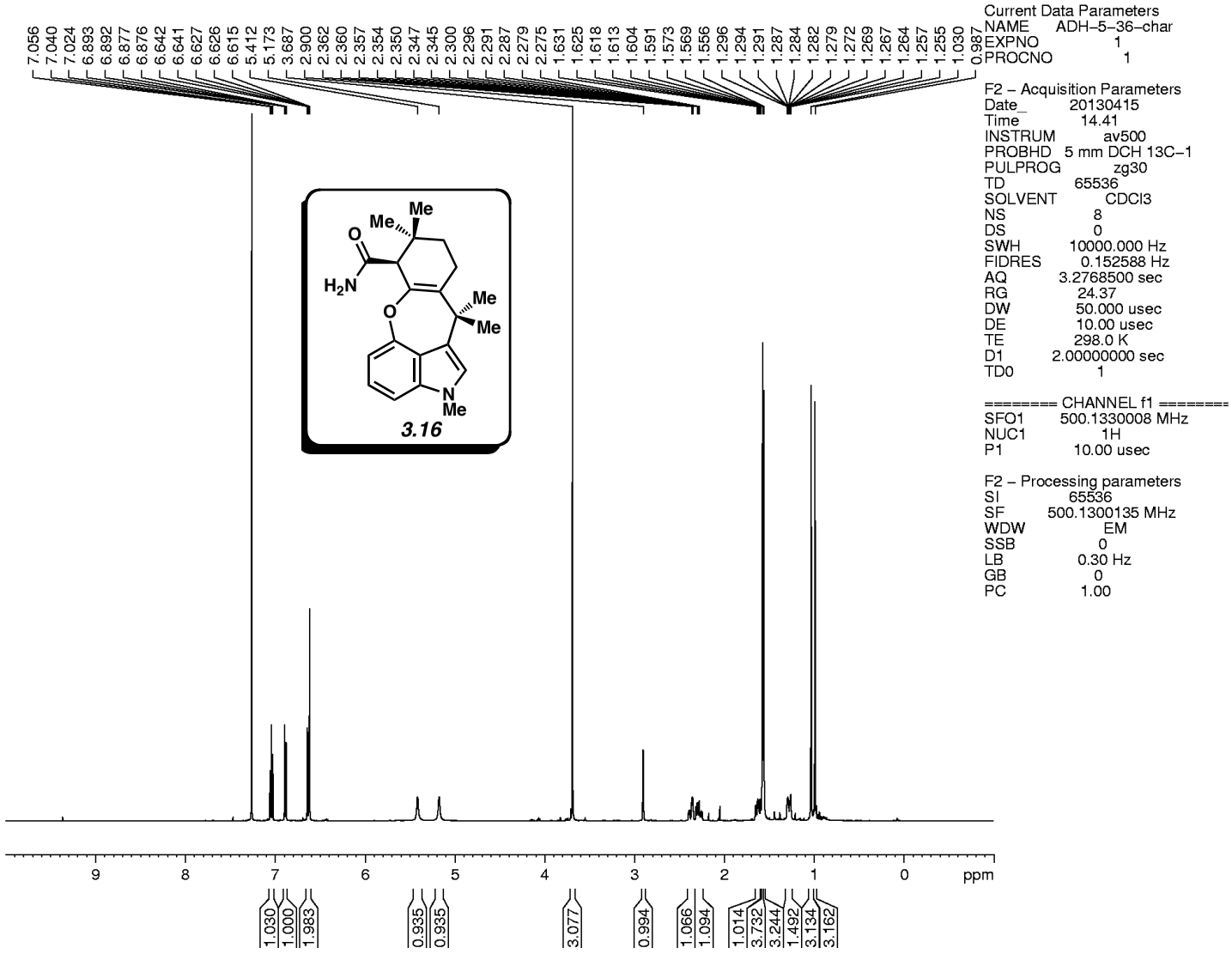


Figure A2.13 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.16**.

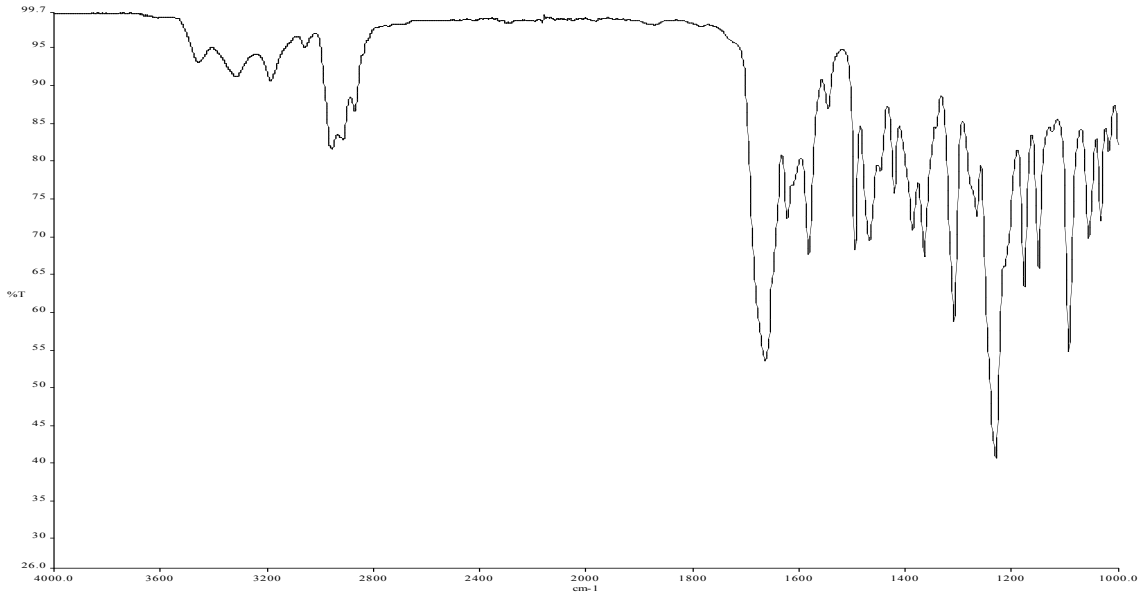


Figure A2.14 Infrared spectrum of compound **3.16**.

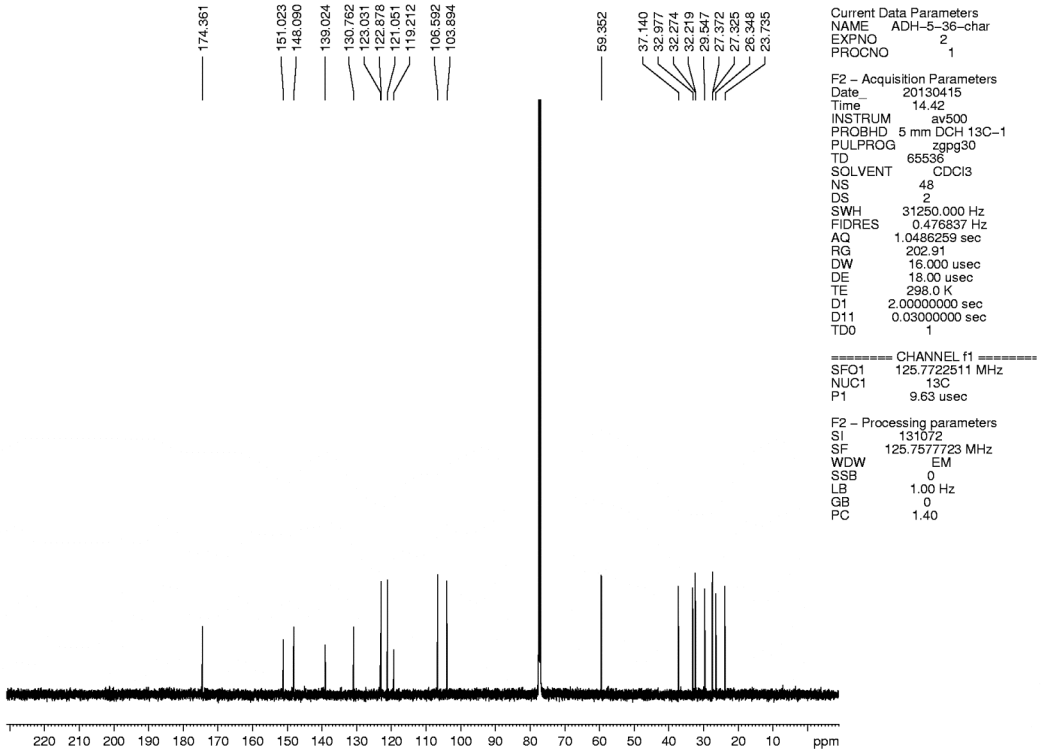


Figure A2.15 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **3.16**.

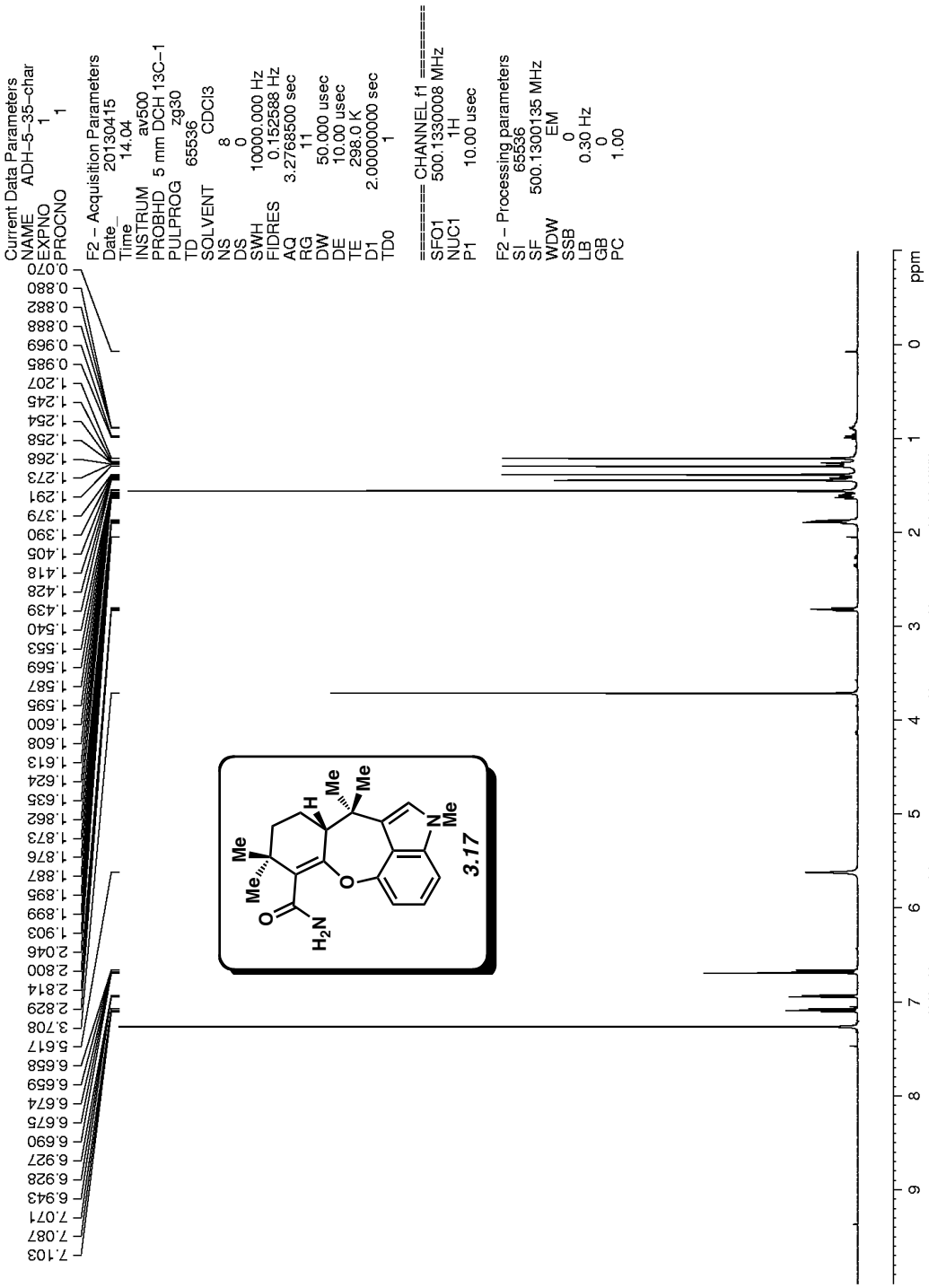


Figure A2.16 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.17**.

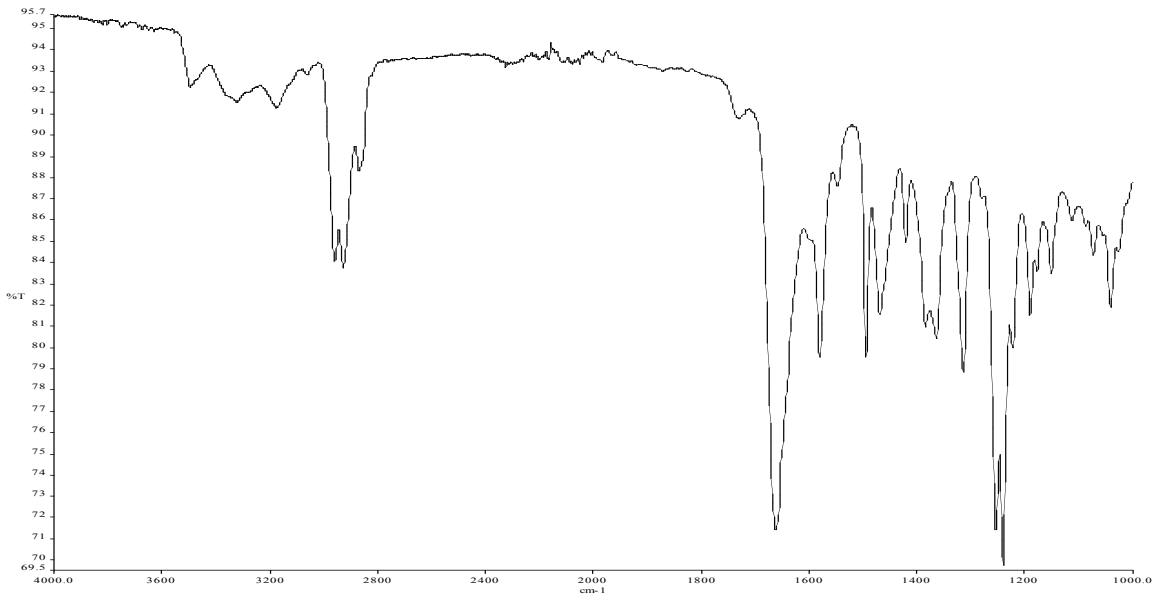


Figure A2.17 Infrared spectrum of compound **3.17**.

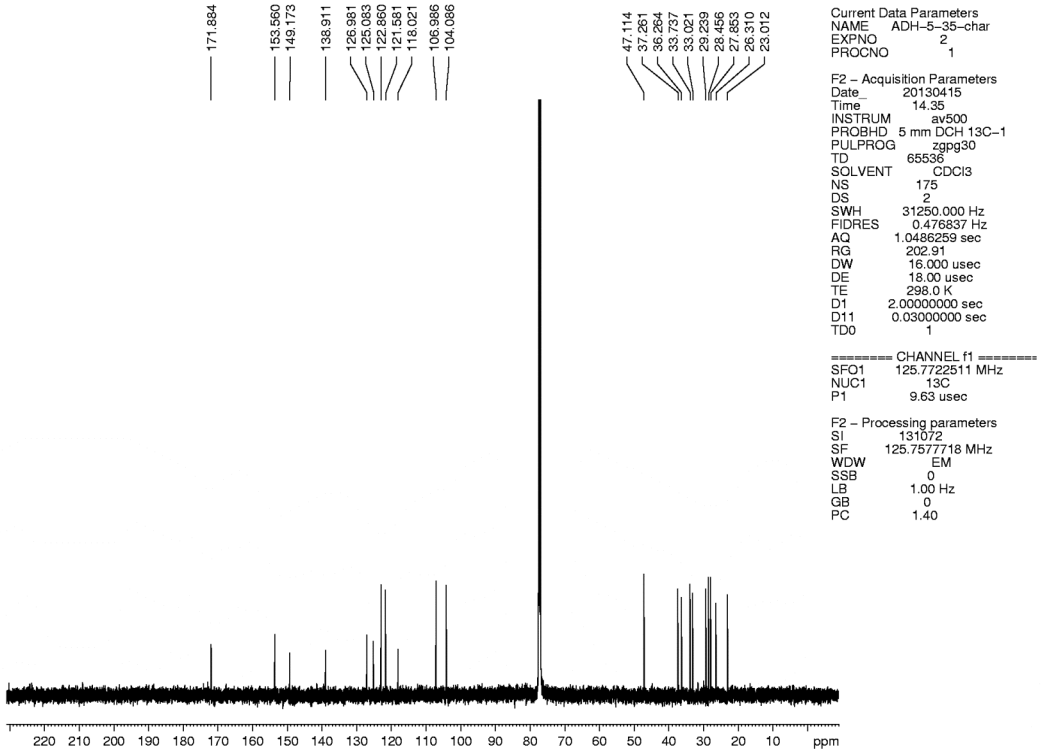


Figure A2.18 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **3.17**.

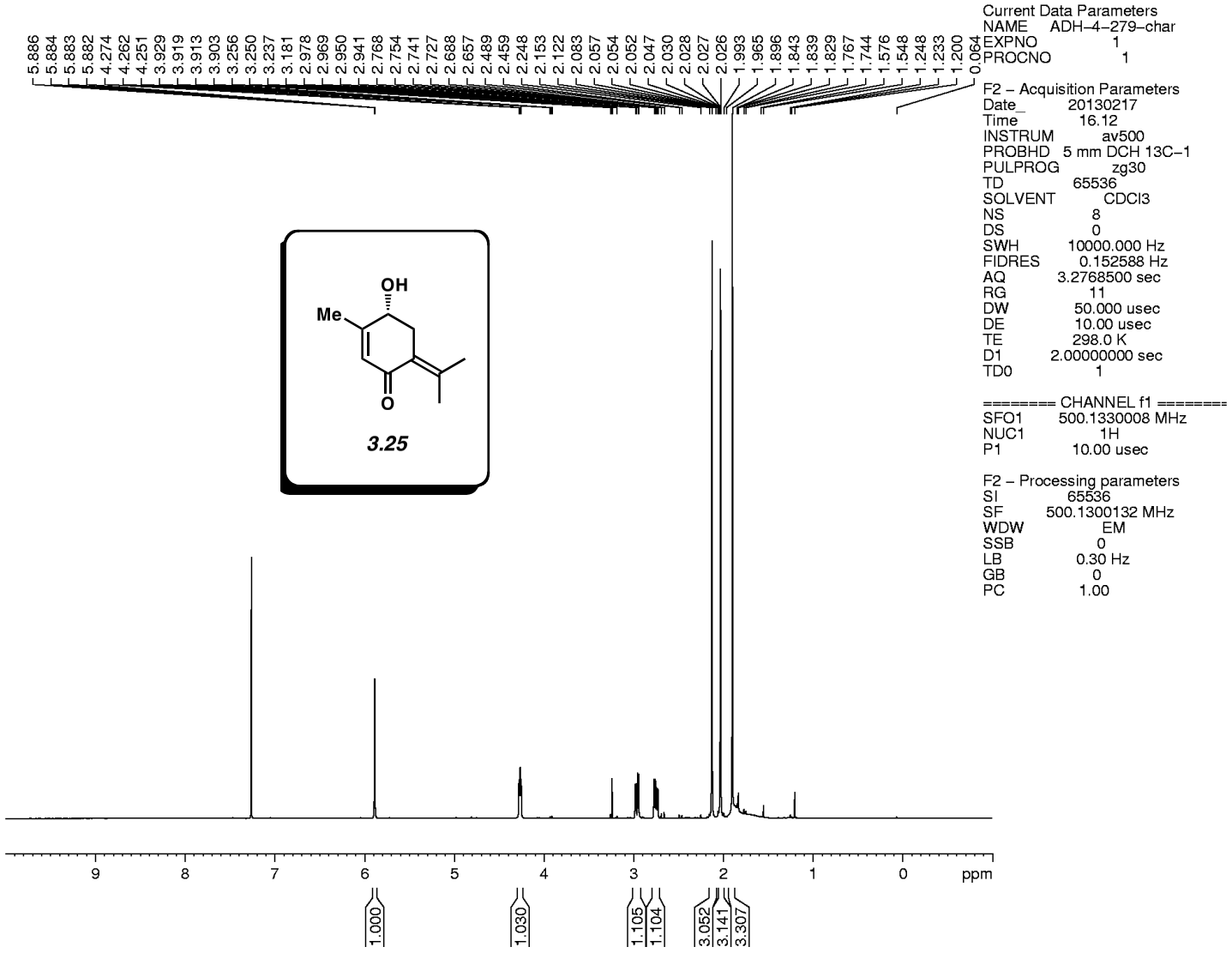


Figure A2.19 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.25**.

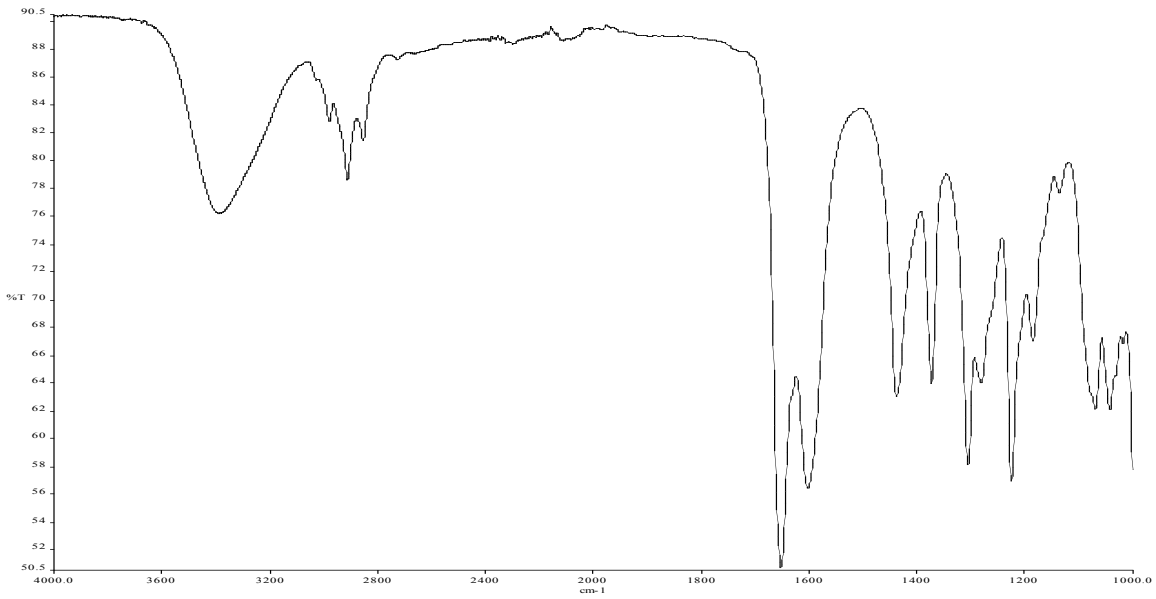


Figure A2.20 Infrared spectrum of compound **3.25**.

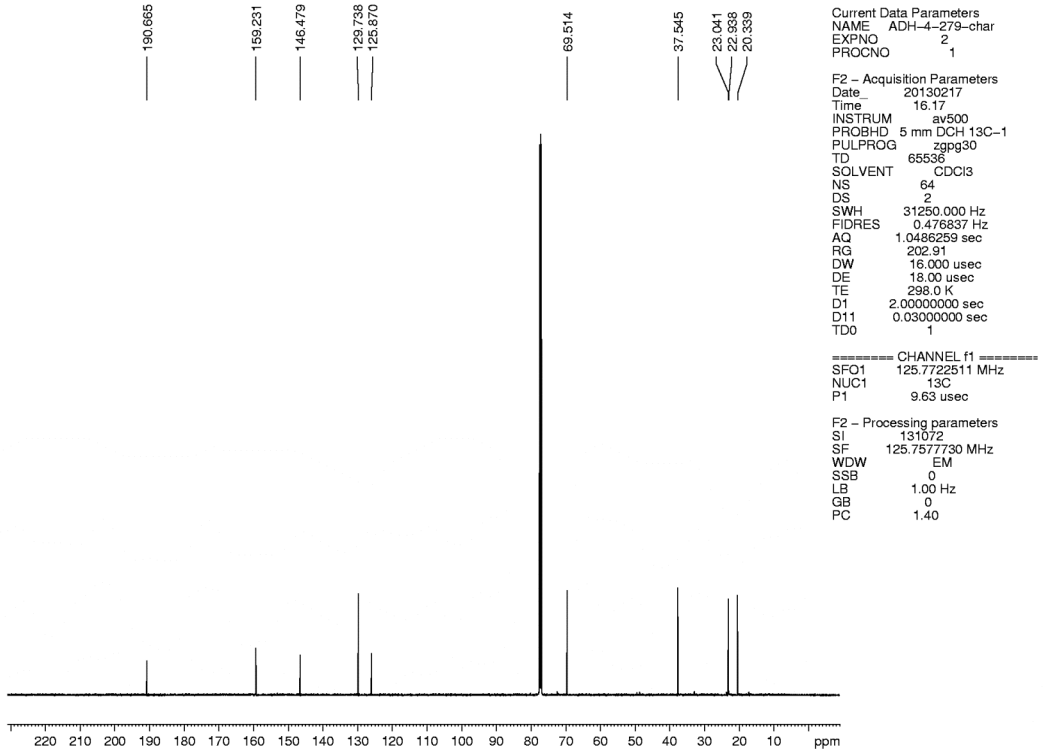
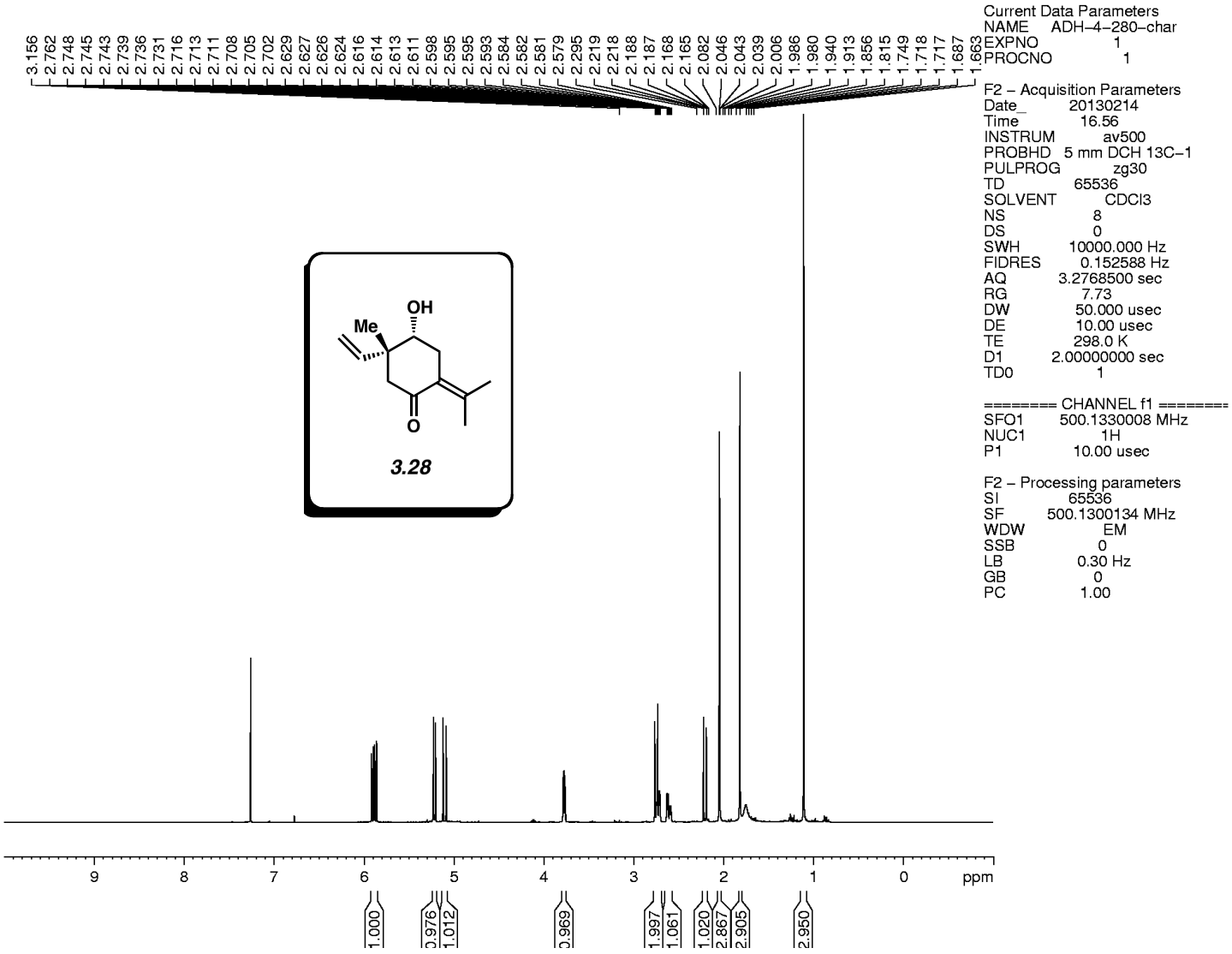


Figure A2.21 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **3.25**.



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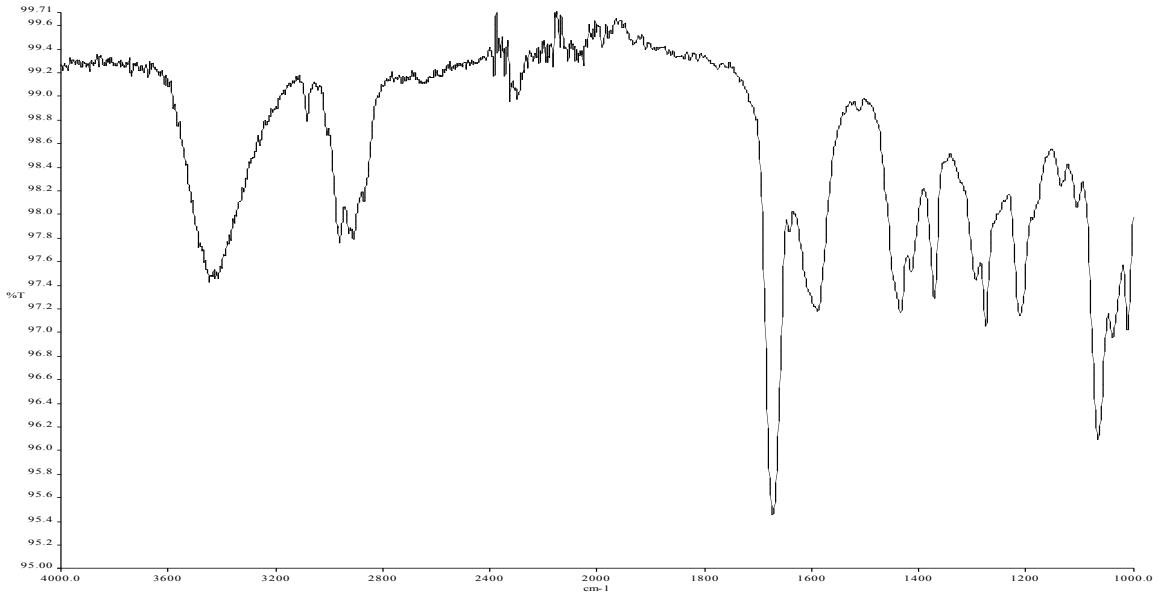


Figure A2.23 Infrared spectrum of compound **3.28**.

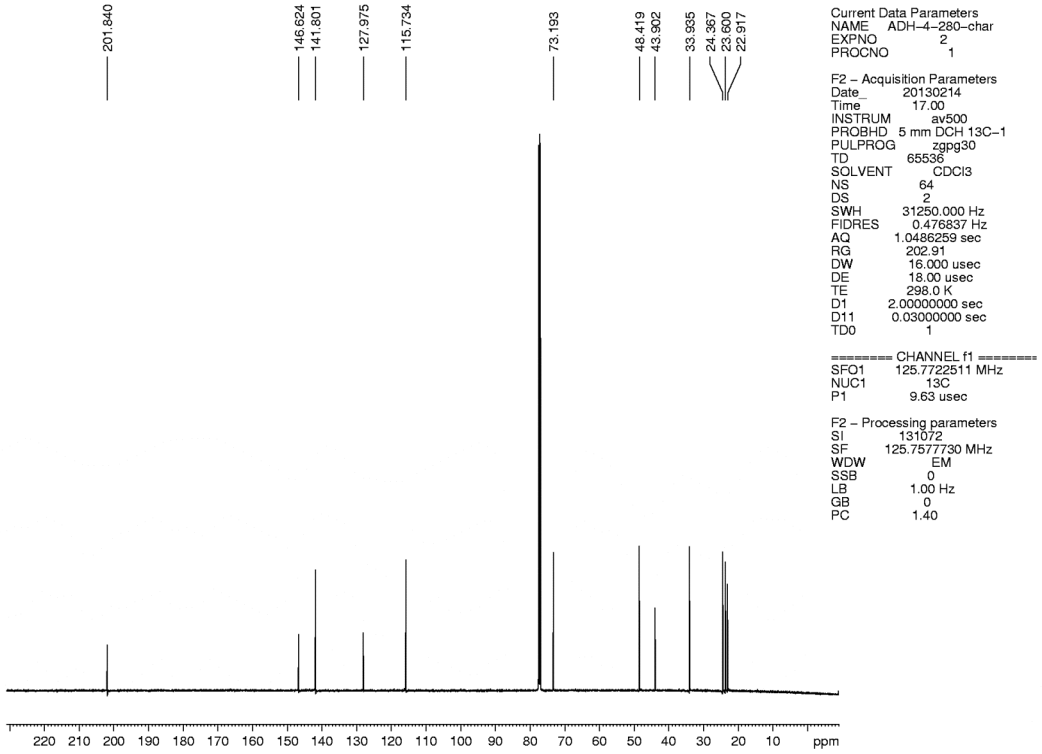
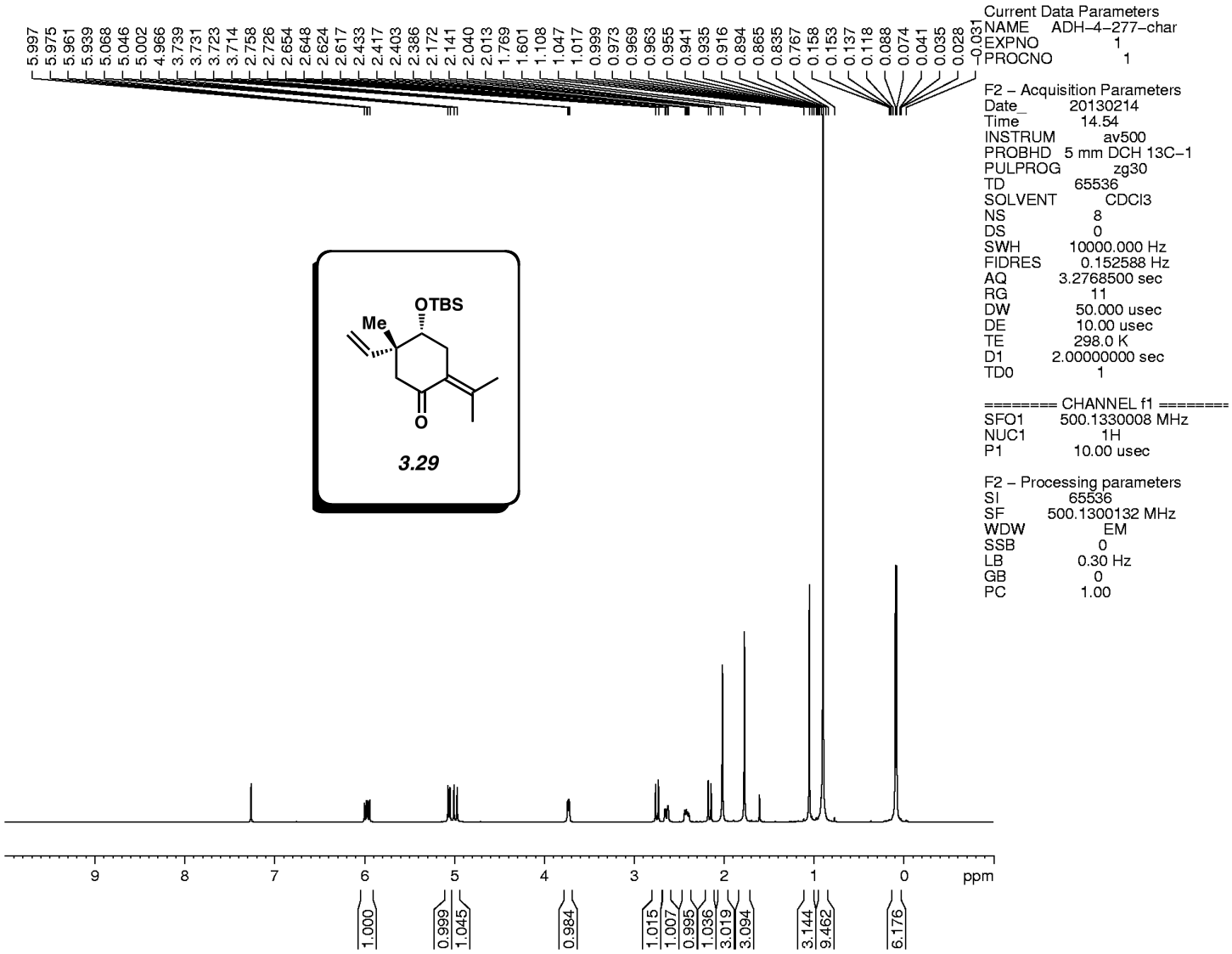


Figure A2.24 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **3.28**.



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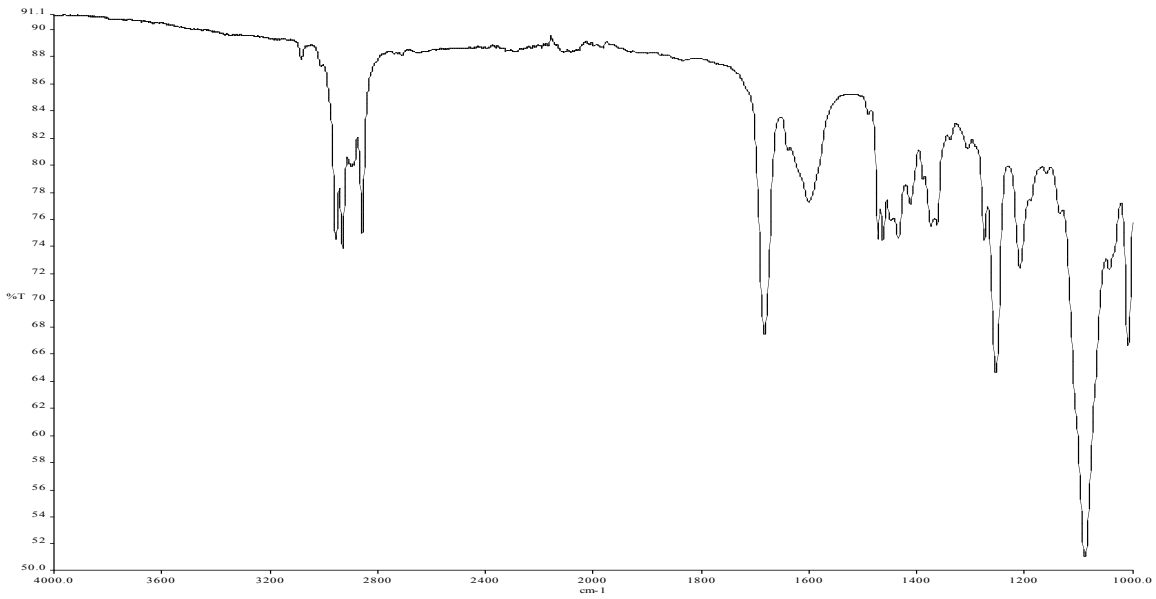


Figure 2.26 Infrared spectrum of compound **3.29**.

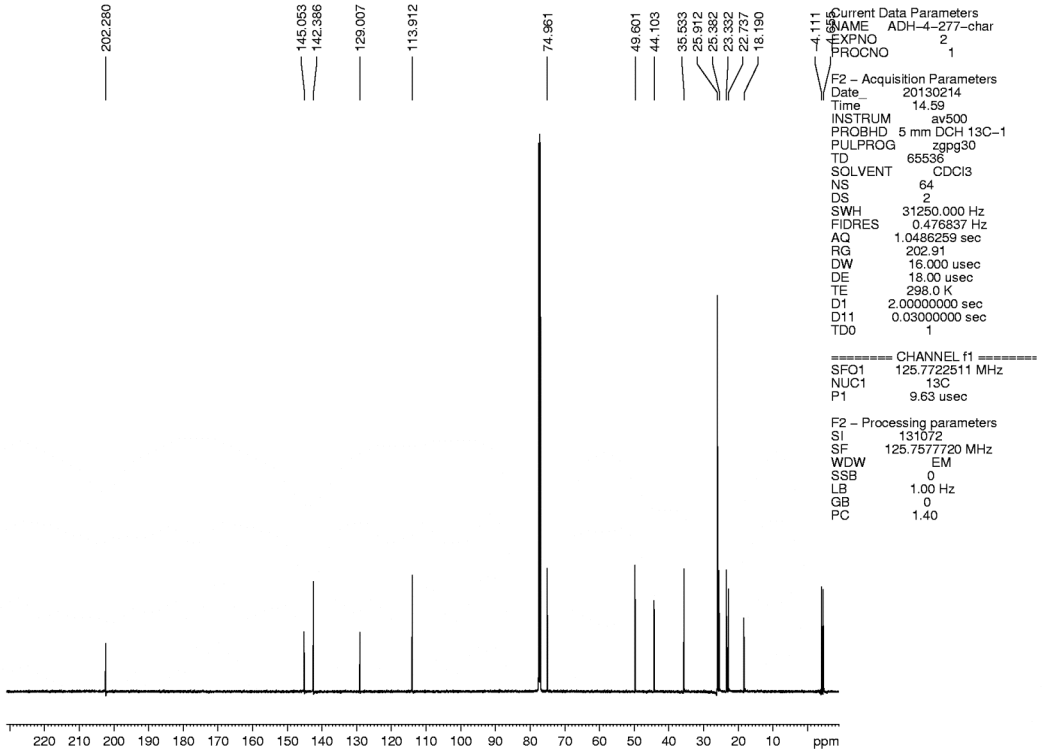
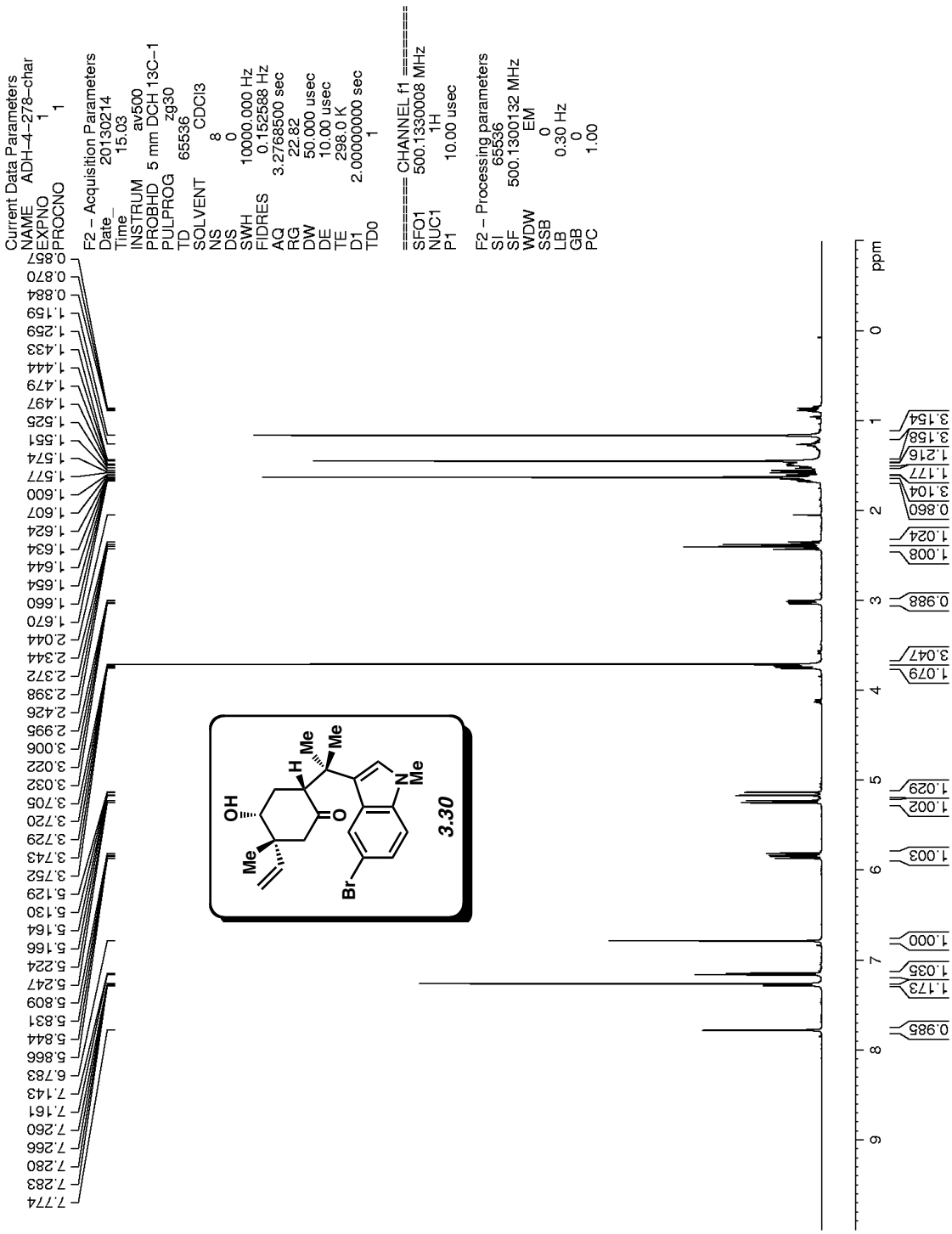


Figure A2.27 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **3.29**.



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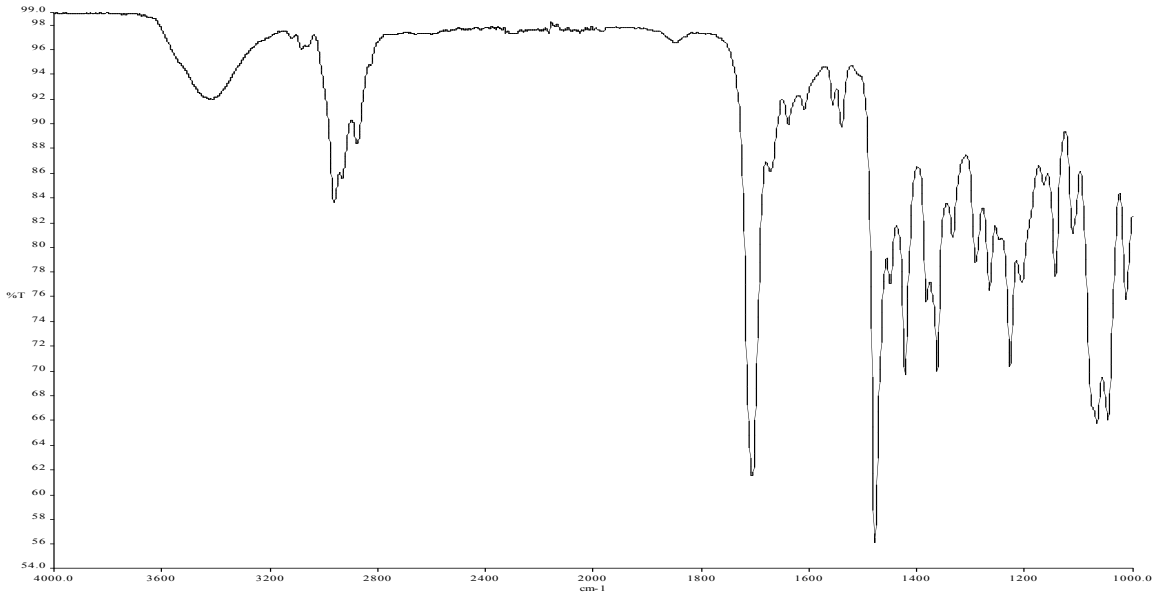
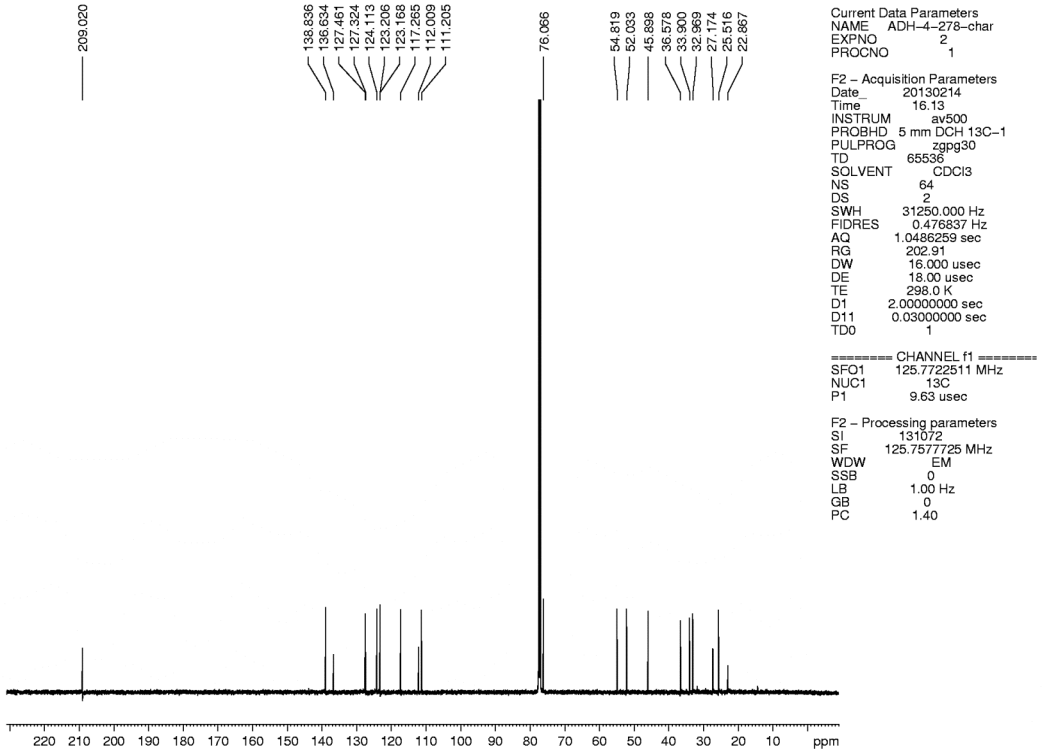


Figure A2.29 Infrared spectrum of compound **3.30**.



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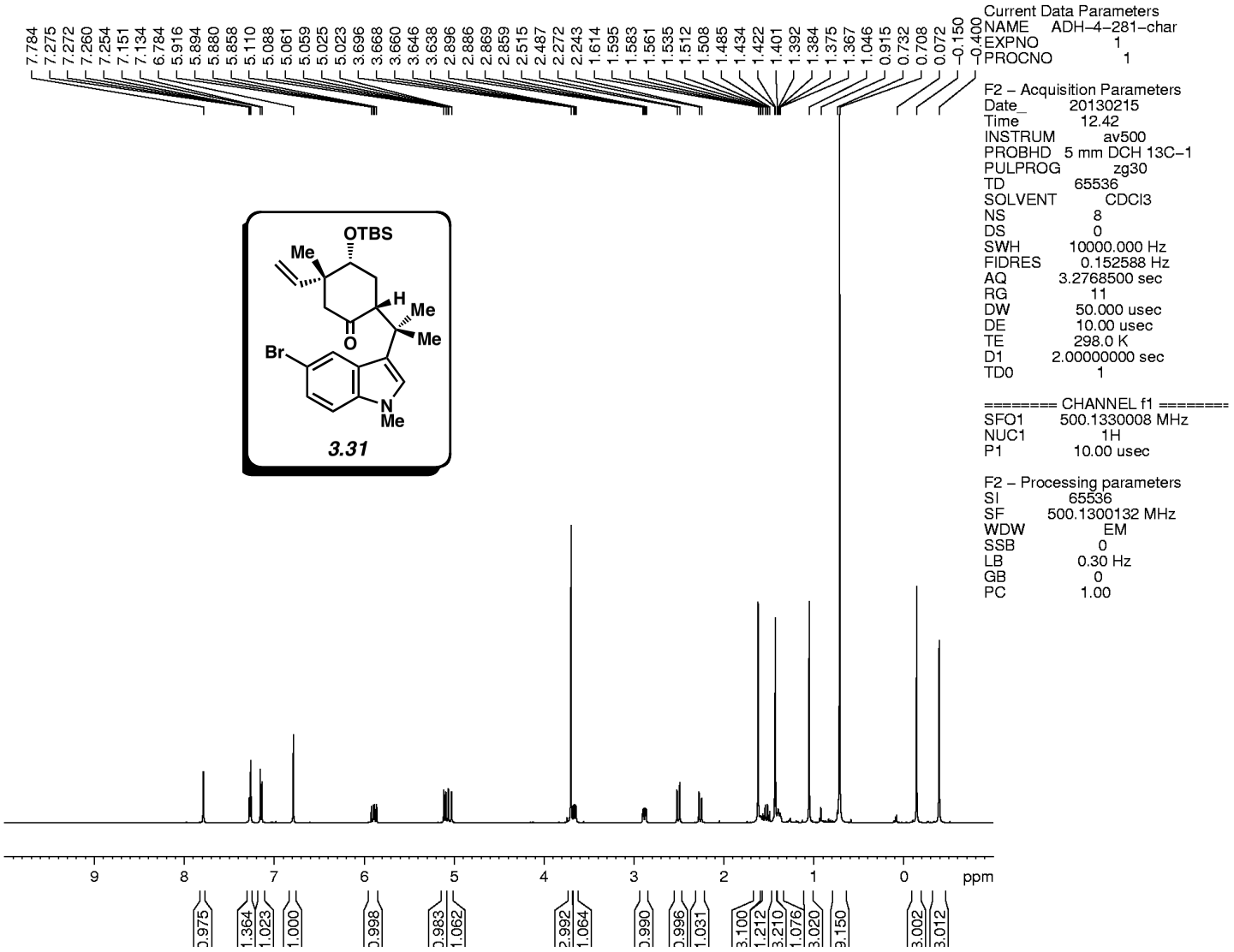

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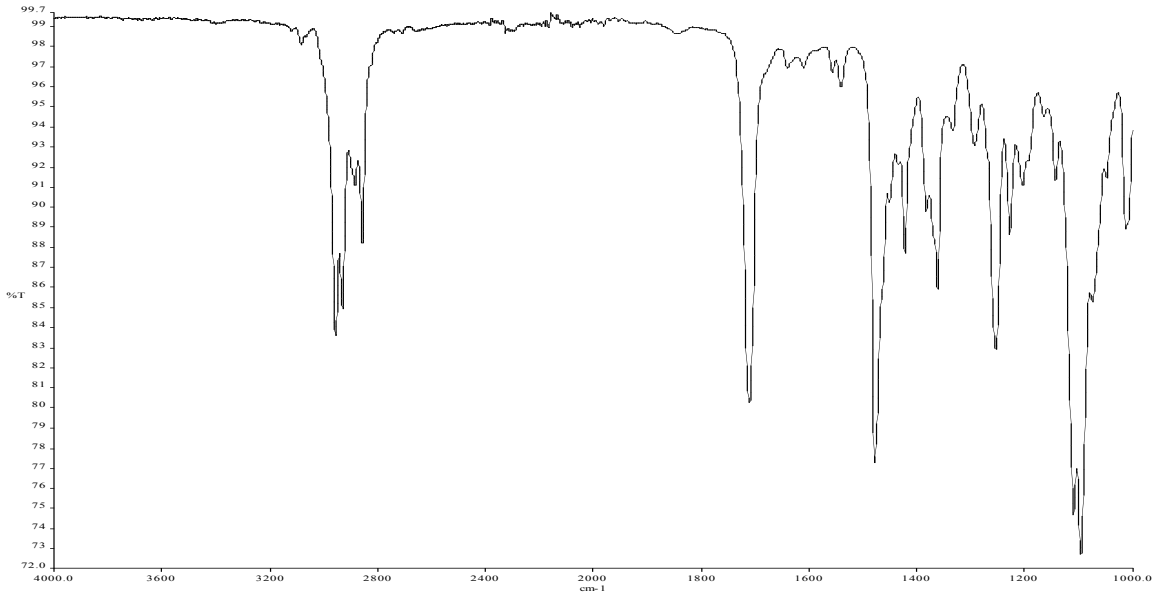


Figure A2.32 Infrared spectrum of compound **3.31**.

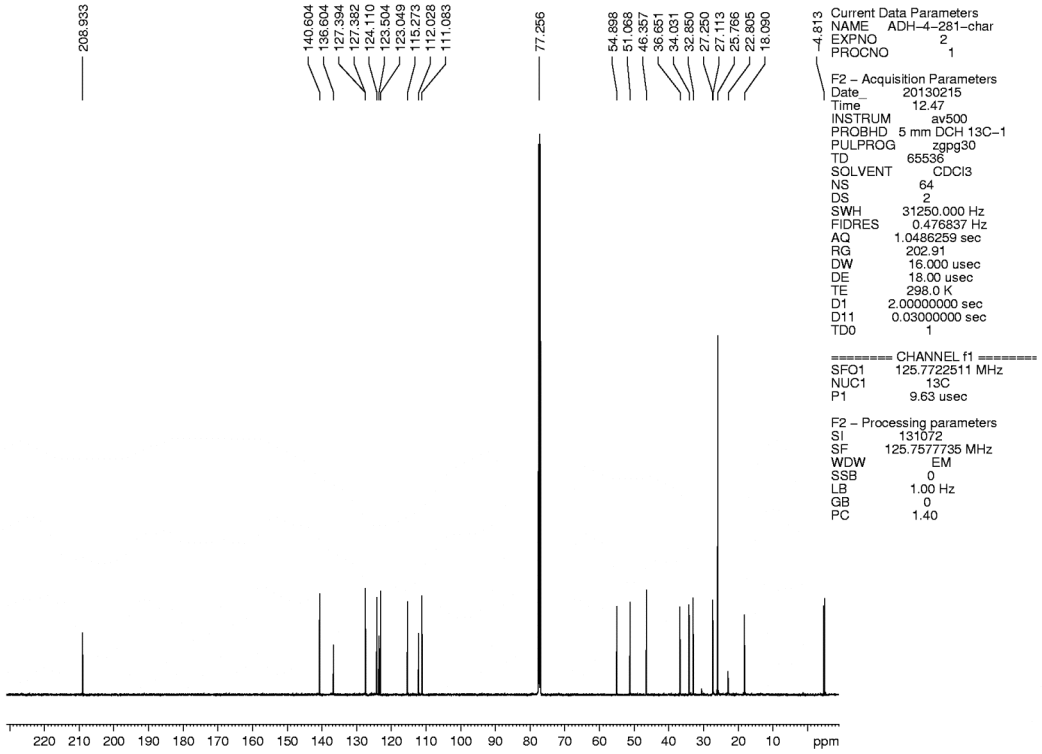


Figure A2.33 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **3.31**.

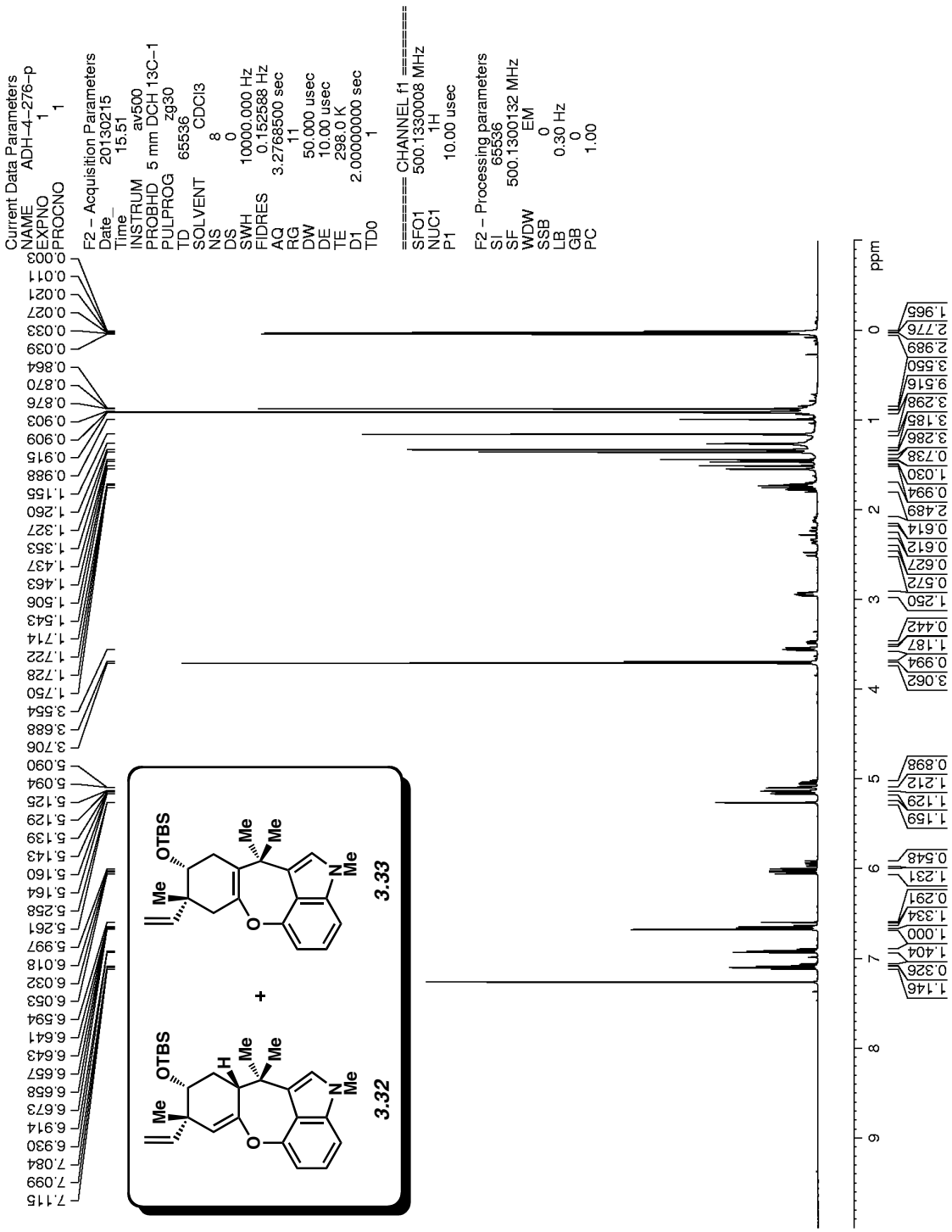


Figure A2.34 ^{1}H NMR (500 MHz, $CDCl_3$) of compounds **3.32** and **3.33**.

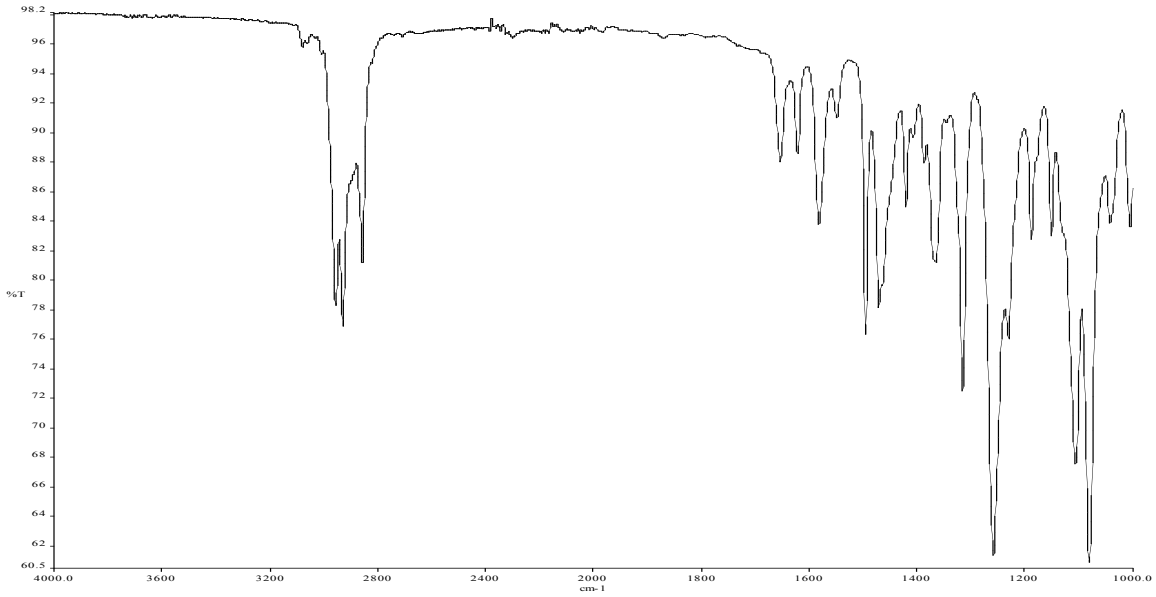


Figure A2.35 Infrared spectrum of compounds **3.32** and **3.33**.

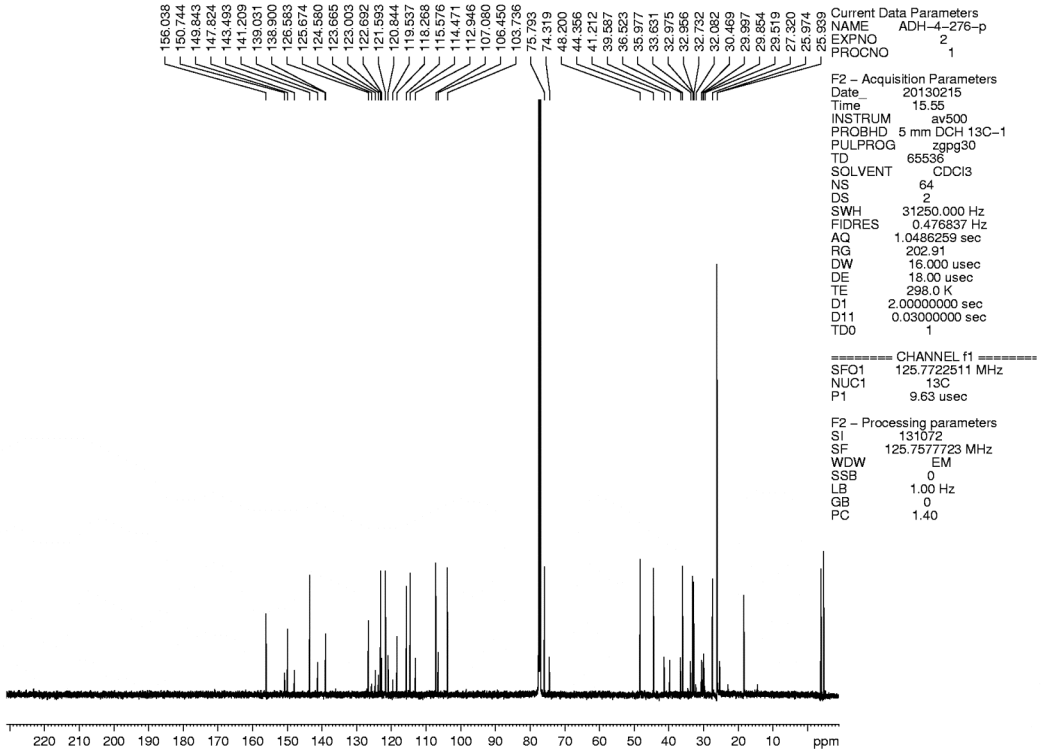


Figure A2.36 ^{13}C NMR (125 MHz, $CDCl_3$) of compounds **3.32** and **3.33**.

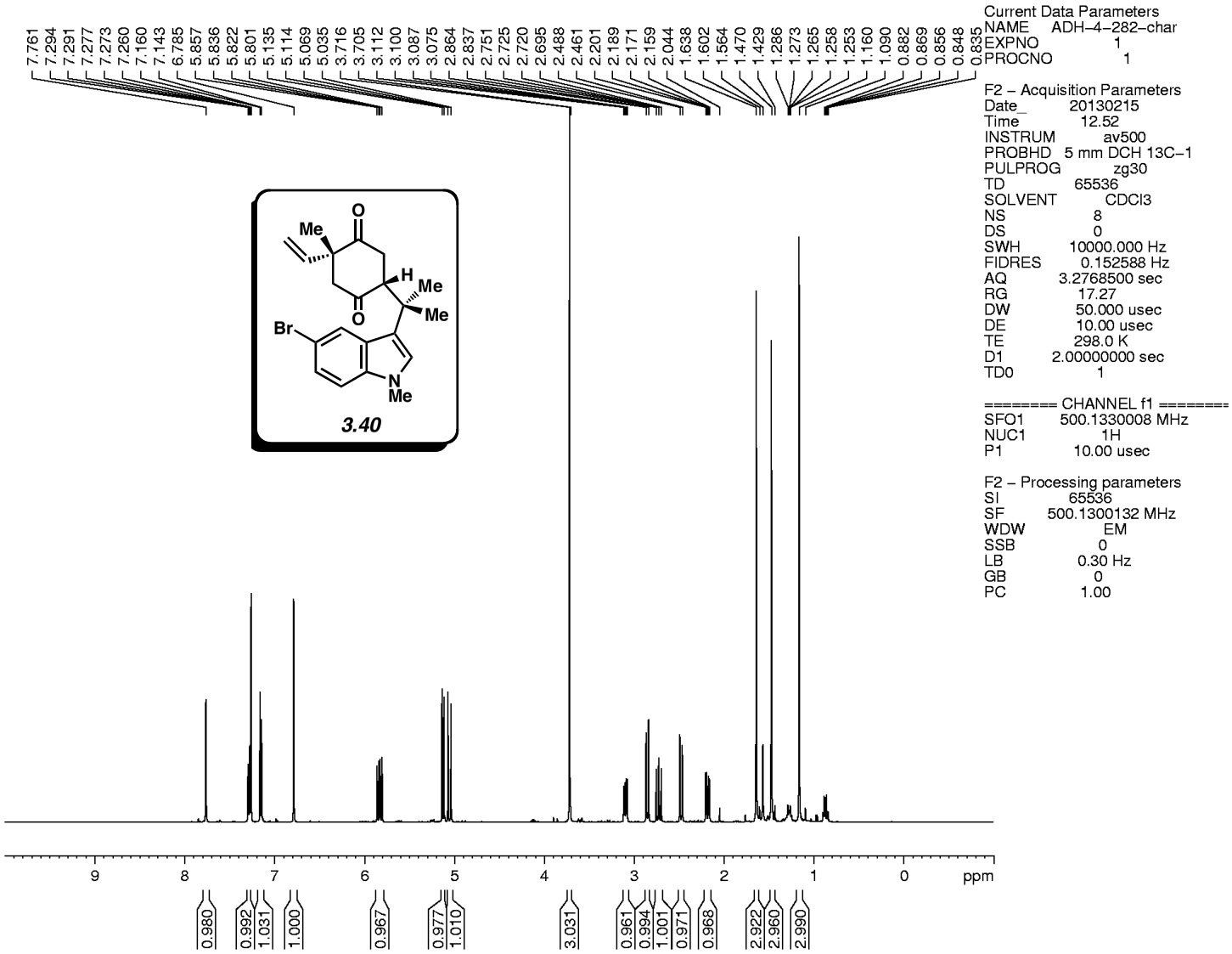


Figure A2.37 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.40**.

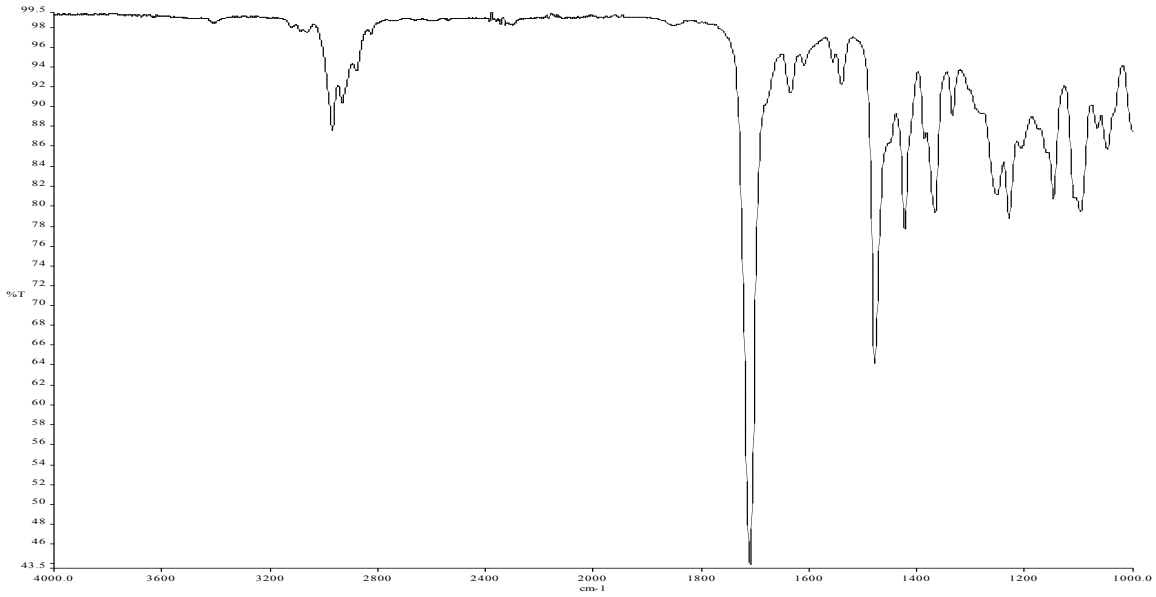


Figure A2.38 Infrared spectrum of compound **3.40**.

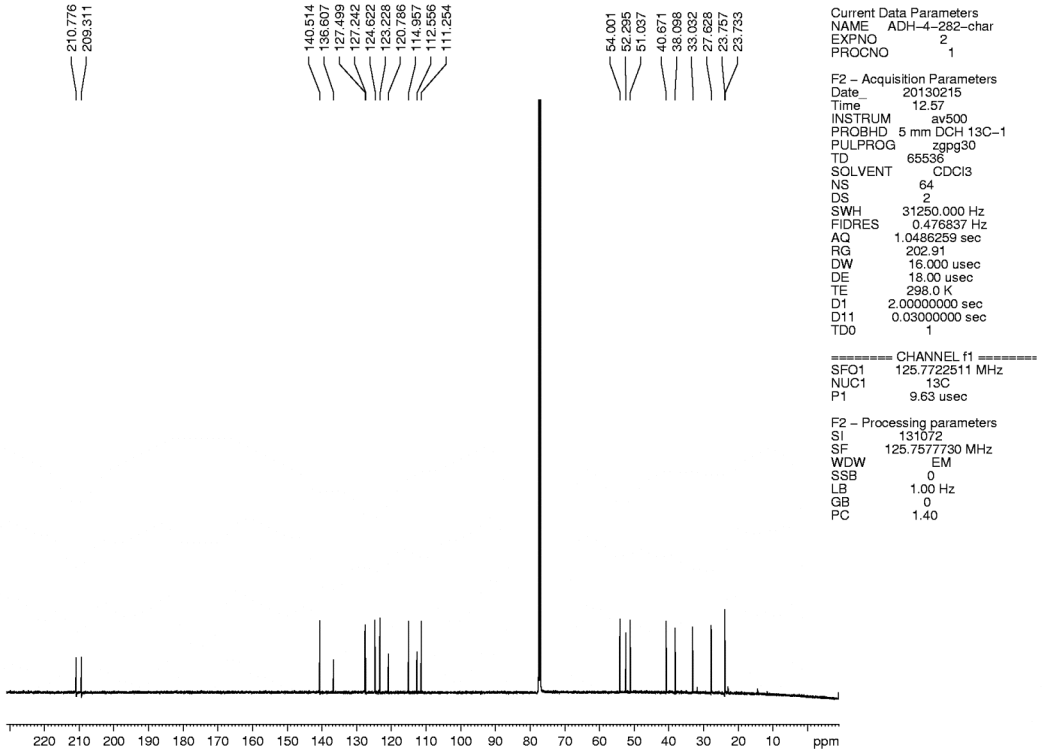
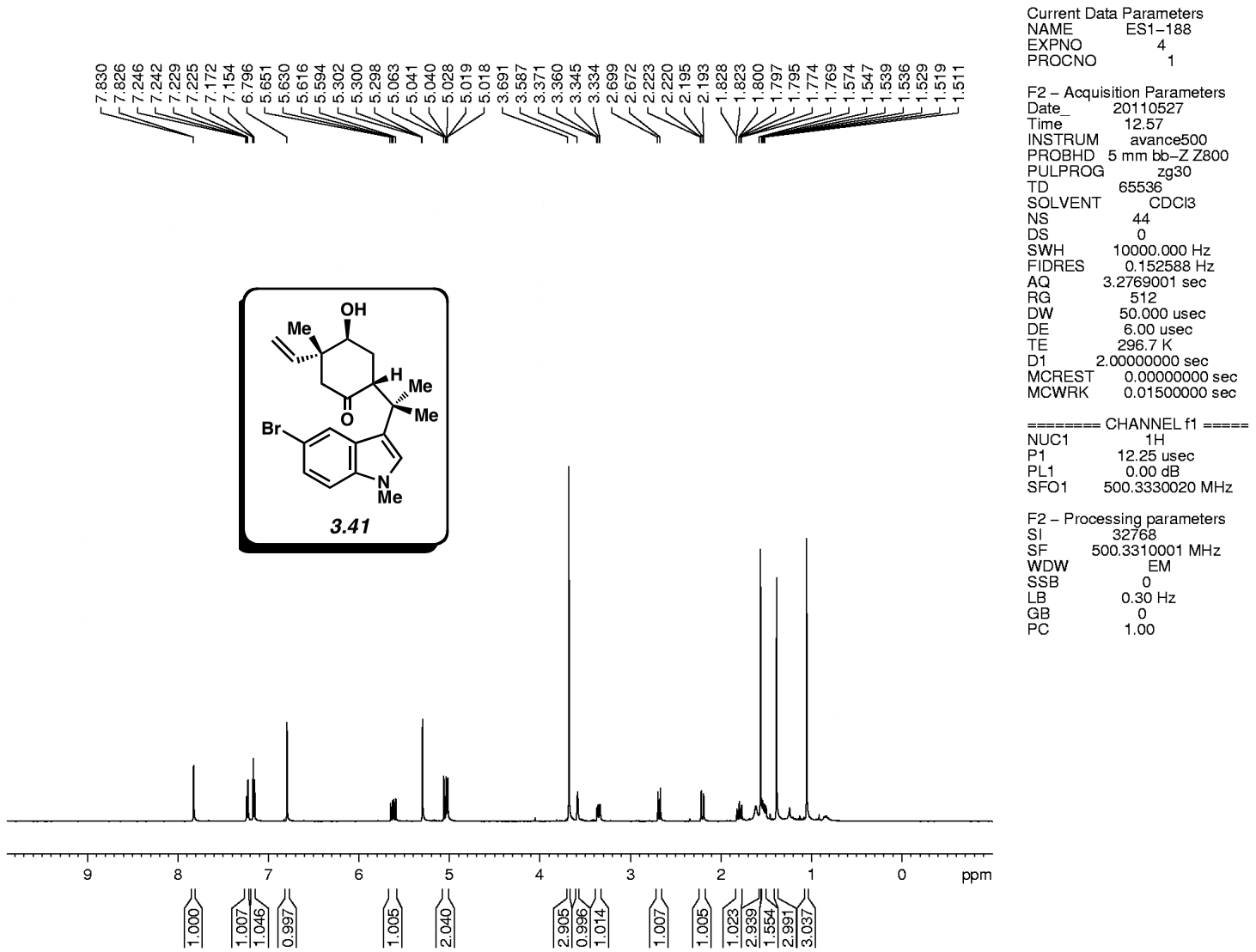


Figure A2.39 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **3.40**.



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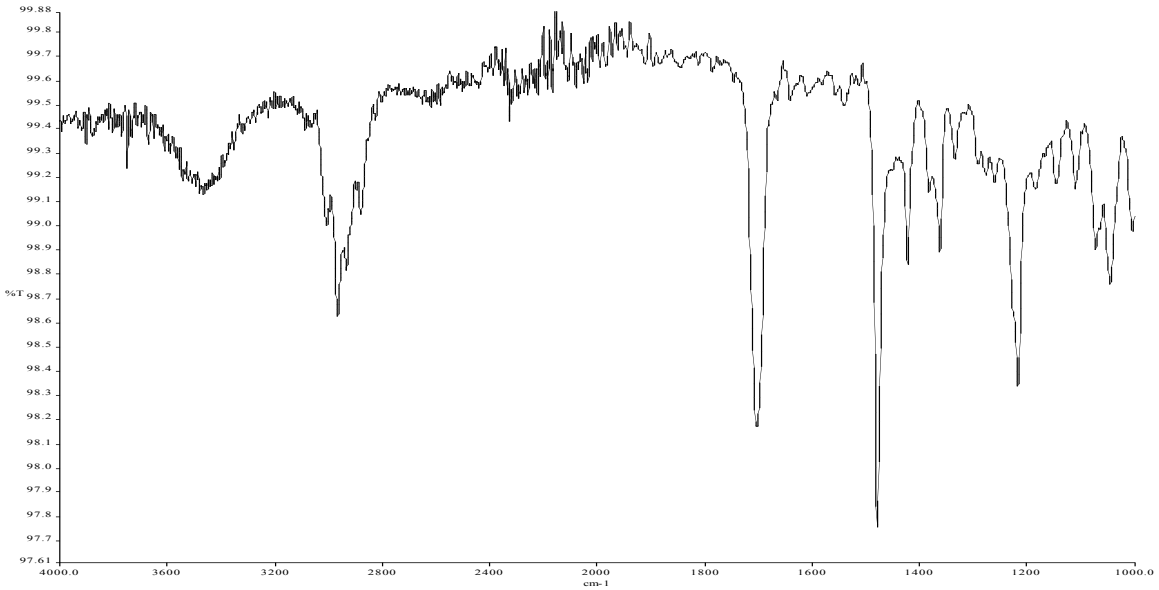


Figure A2.41 Infrared spectrum of compound **3.41**.

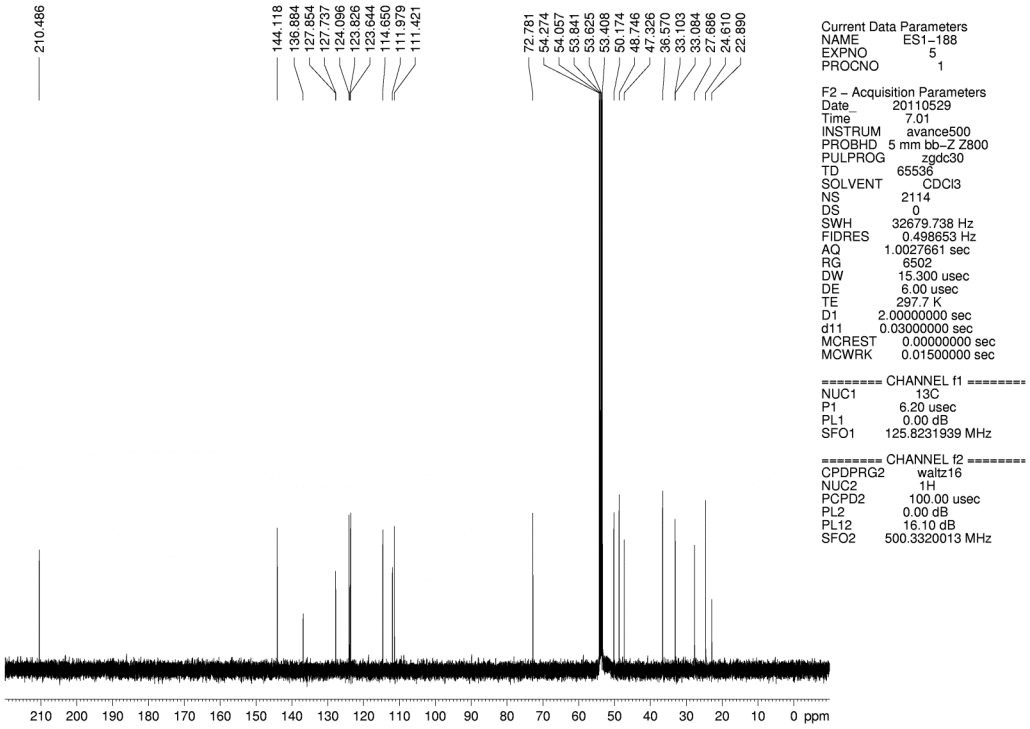


Figure A2.42 ^{13}C NMR (125 MHz, CD_2Cl_2) of compound **3.41**.

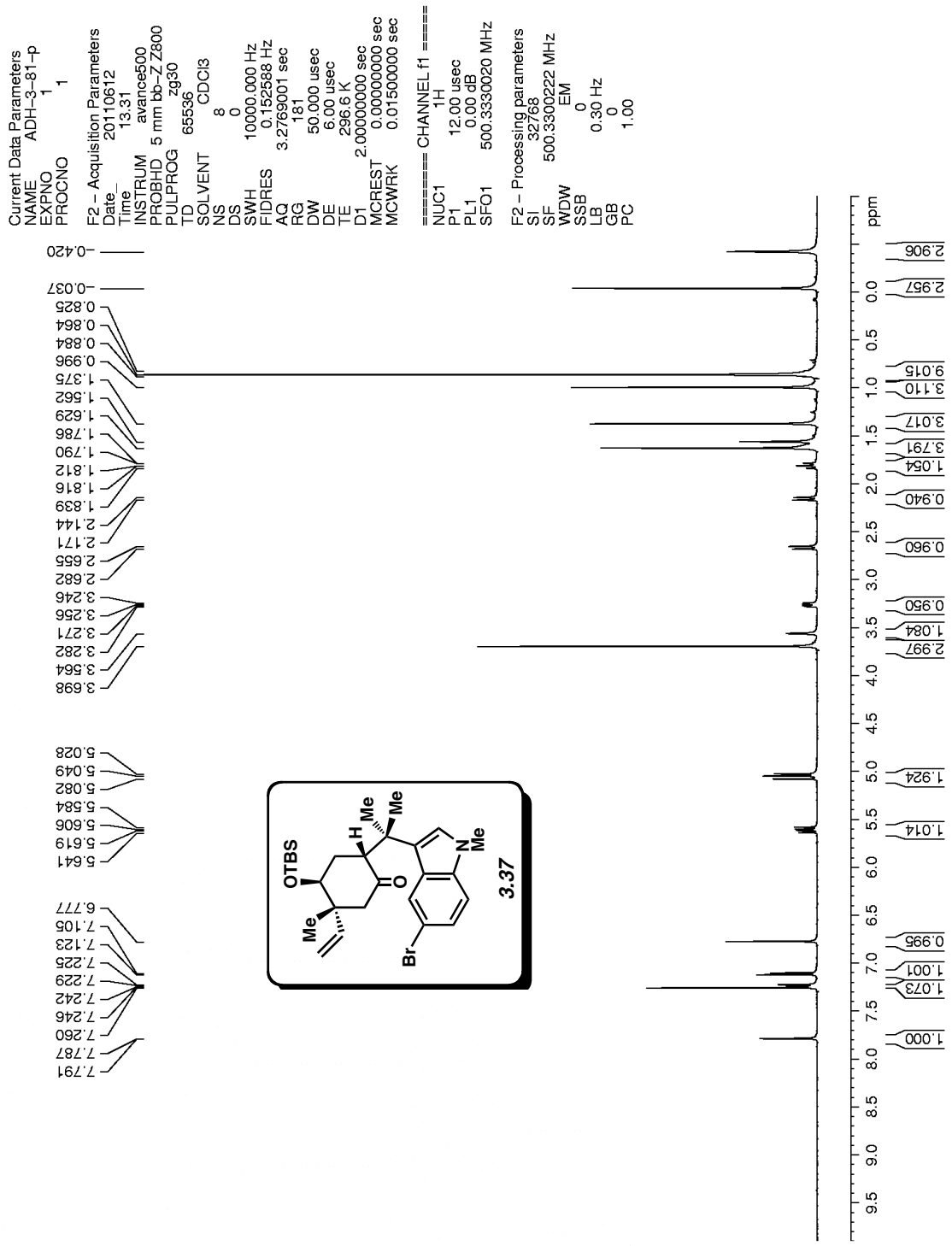


Figure A2.43 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.37**.

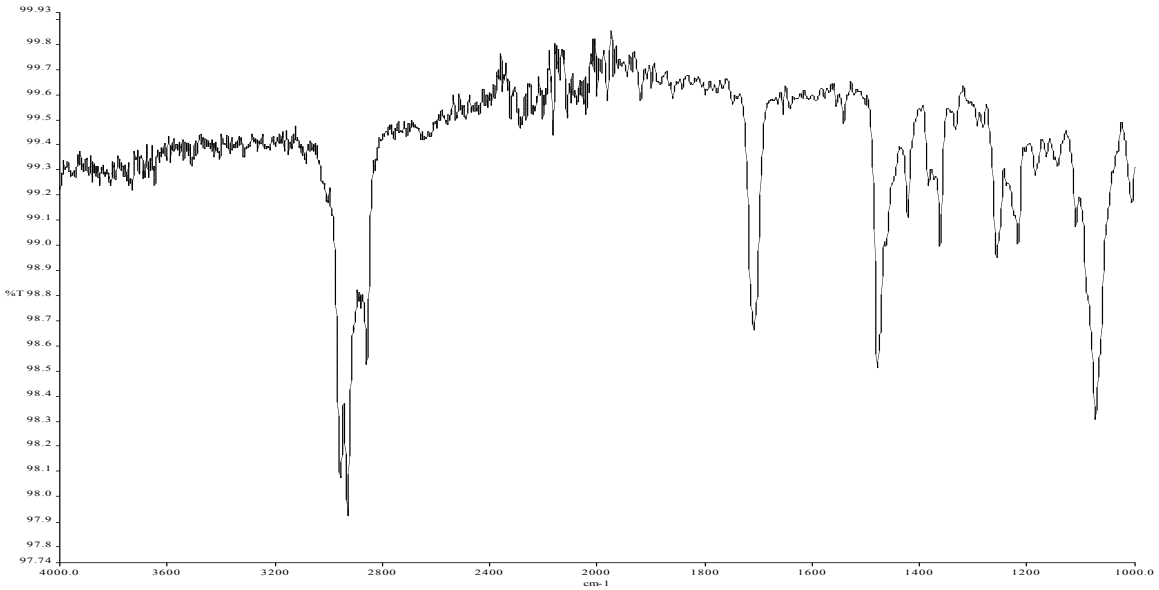


Figure A2.44 Infrared spectrum of compound **3.37**.

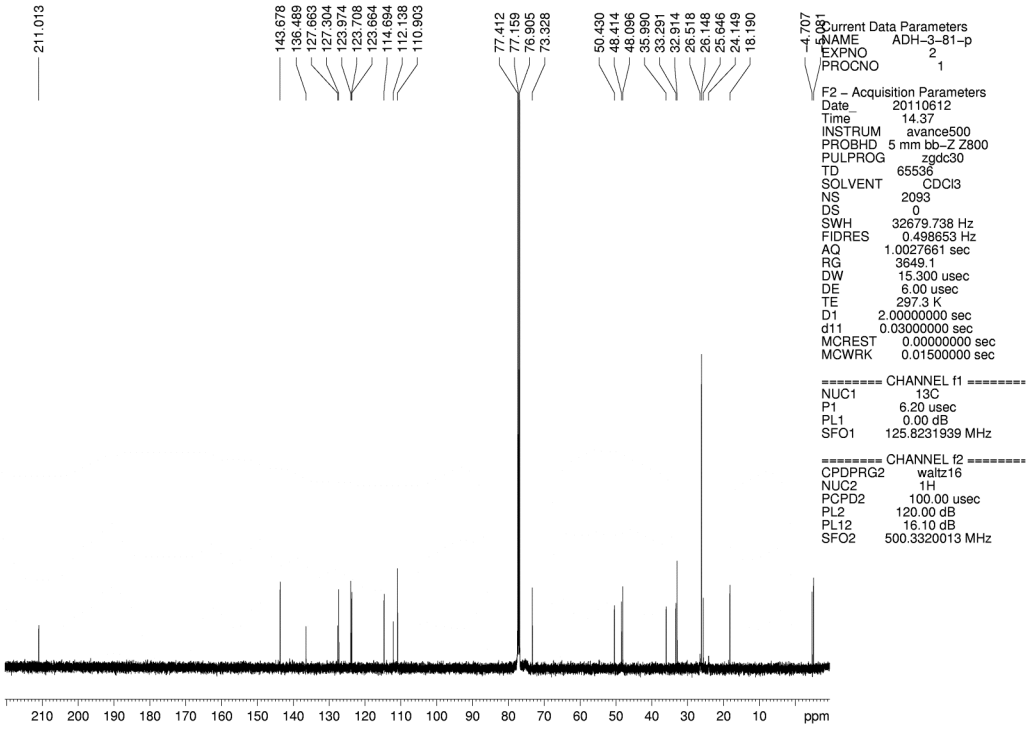


Figure A2.45 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **3.37**.

CHAPTER FOUR

Total Synthesis of (–)-*N*-Methylwelwitindolinone C Isothiocyanate

Alexander D. Huters, Kyle W. Quasdorf, Evan D. Styduhar, and Neil K. Garg.

J. Am. Chem. Soc. **2011**, *133*, 15797–15799.

4.1 Abstract

We report the first total synthesis of (–)-*N*-methylwelwitindolinone C isothiocyanate. Our route features a number of key transformations, including an indolyne cyclization to assemble the bicyclo[4.3.1]decane scaffold, as well as a late-stage intramolecular nitrene insertion to functionalize the C11 bridgehead carbon en route to the natural product.

4.2 Introduction

The welwitindolinones are a unique class of natural products isolated from the blue-green algae *Hapalosiphon welwitschii* and *Westiella intricata*.[1] Ten welwitindolinones have been identified to date, nine of which possess bicyclo[4.3.1]decane cores (e.g., **4.1**–**4.3**, Figure 4.1).[2] Although compact in size, each of these natural products contains a dense array of functionality that has plagued synthetic efforts for nearly two decades. To date, more than ten laboratories have reported progress toward the bicyclic welwitindolinones.[3,4] Whereas these exhaustive efforts have resulted in several elegant methods for bicycle generation, completion of these targets has remained a formidable challenge. In fact, the only total synthesis of a welwitindolinone with a bicyclo[4.3.1]decane core was recently achieved by Rawal and co-workers, with their breakthrough synthesis of (±)-**4.3** in 2011.[5]

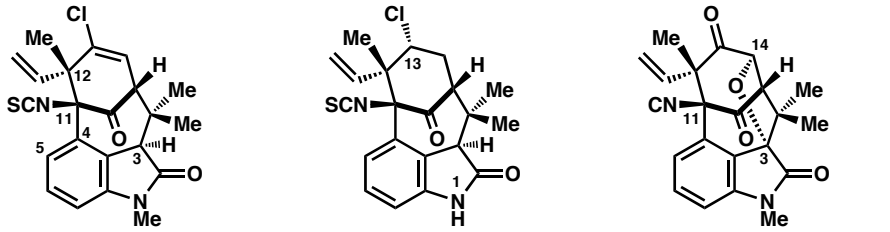


Figure 4.1. Welwitindolinones with bicyclo[4.3.1]decane cores **4.1–4.3**.

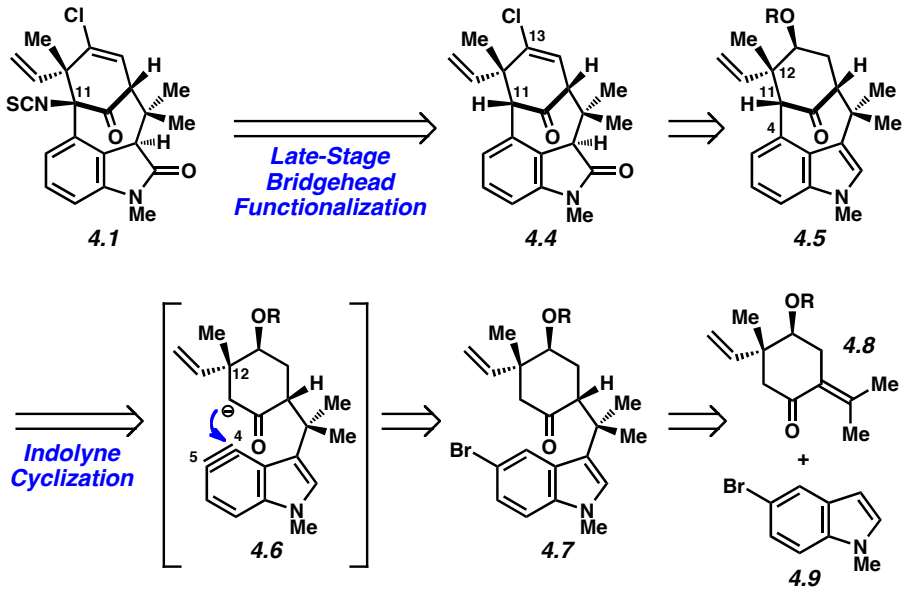
With the aim of synthesizing alkaloids **4.1**–**4.3** and other family members, we selected **4.1** as our initial synthetic target. Of note, welwitindolinone **4.1** was uniquely found to reverse P-glycoprotein-mediated multiple drug resistance (MDR) to a variety of anti-cancer drugs in human cancer cell lines, and is therefore a promising lead for the treatment of drug resistant tumors.[6] The densely functionalized bicyclic framework of **4.1** presents numerous synthetic challenges, including a 3,4-disubstituted oxindole, a heavily substituted cyclohexyl ring, and a bridgehead isothiocyanate substituent at C11. In this communication, we report the first total synthesis of (–)-*N*-methylwelwitindolinone C isothiocyanate (**4.1**).

4.3 Retrosynthetic Analysis of (–)-*N*-Methylwelwitindolinone C Isothiocyanate

Retrosynthetically, it was envisioned that **4.1** would be derived from bicycle **4.4** through late-stage functionalization of the C11 bridgehead position (Scheme 4.1). In turn, intermediate **4.4** would arise from indole precursor **4.5** by introduction of the vinyl chloride and oxindole moieties. In the key complexity generating step, the bicyclo[4.3.1]decane would be fashioned through intramolecular addition of an enolate onto an in situ-generated "indolyne" species (see transition structure **4.6**).[7] The use of an indolyne intermediate[8,9] was considered advantageous as the high reactivity of the aryne would permit the assembly of the congested C4–C11 bond

linkage, where a tertiary center would be introduced adjacent to the C12 quaternary stereocenter. Of note, the indolyne would be inherently electrophilic, representing an uncommon umpolung of the indole's typical reactivity. Bromoindole **4.7** was thought to be a suitable precursor to the desired indolyne via the classic dehydrohalogenation method for aryne generation. Finally, cyclohexyl derivative **4.8** and indole **4.9** were identified as suitable starting fragments.

Scheme 4.1

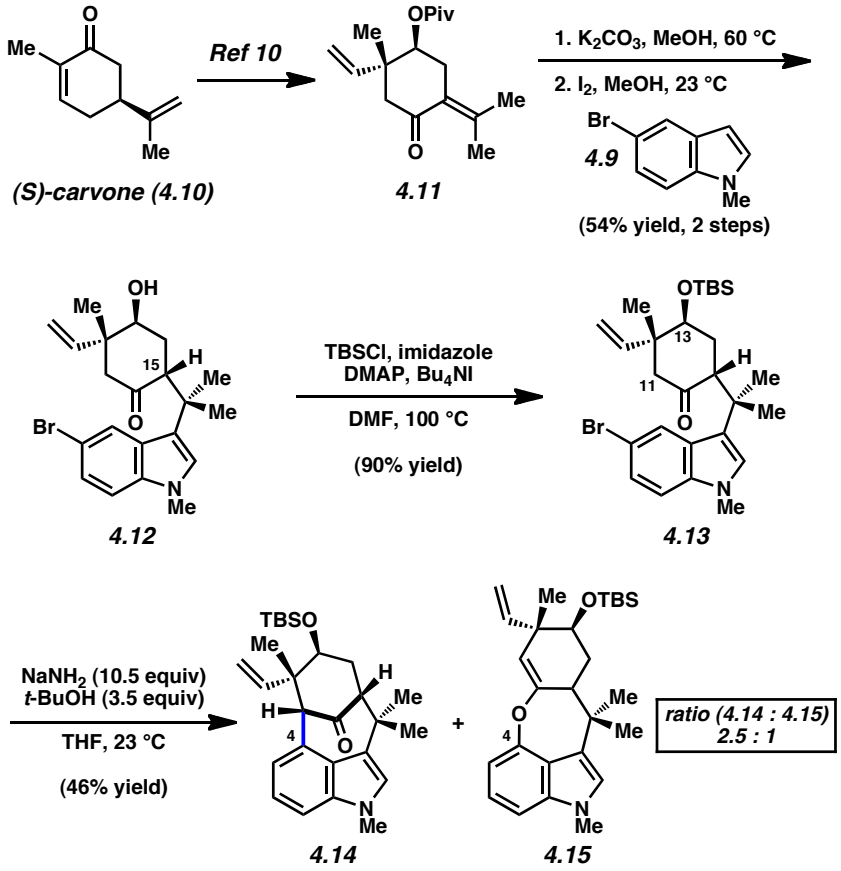


4.4 Construction of the Bicyclo[4.3.1]decane Framework

Our synthesis commenced with the concise preparation of the key bicyclo[4.3.1]decane scaffold (Scheme 4.2). (*S*)-Carvone (**4.10**) was elaborated to enone **4.11** using the robust five step procedure reported by Natsume in the enantiomeric series.[10] Subsequent pivalate cleavage, followed by I_2-promoted addition of bromoindole **4.9**,[11] furnished adduct **4.12** in 54% yield over two steps.[12] TBS-protection of **4.12** provided silylether **4.13**, which in turn was employed in the critical indolyne cyclization. To our delight, treatment of **4.13** with $NaNH_2$ and *t*-BuOH in THF

at ambient temperatures[3p,13] led to indolyne adducts **4.14** and **4.15** in a combined 46% yield (2.5 : 1 ratio).[14,15] Although *O*-arylated product **4.15** was observed,[16] the major product **4.14** possesses the desired bicyclo[4.3.1]decane framework of the natural product and is available in gram quantities.[17] Moreover, it was believed that bicycle **4.14** was suitably functionalized to allow for the ultimate completion of the natural product synthesis.

Scheme 4.2

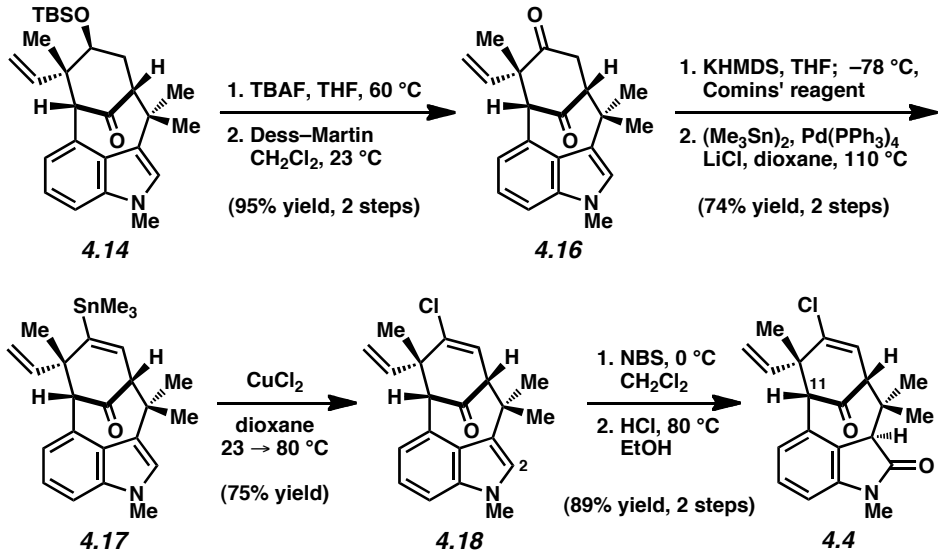


4.5 Introduction of the Vinyl Chloride and Oxindole Moieties

Having assembled the bicyclic framework of the natural product, we focused efforts on introduction of the vinyl chloride and oxindole moieties (Scheme 4.3). Desilylation of **4.14**,

followed by Dess–Martin oxidation, smoothly furnished diketone **4.16**. Subsequently, a sequence involving triflation and Pd-catalyzed stannylation provided vinyl stannane **4.17**.[18] Exposure of **4.17** to $CuCl_2$ in dioxane afforded vinyl chloride **4.18**.[19] To arrive at the necessary oxindole, a two-step procedure involving sequential C2 bromination and hydrolysis was employed to deliver late-stage intermediate **4.4**.[7]

Scheme 4.3

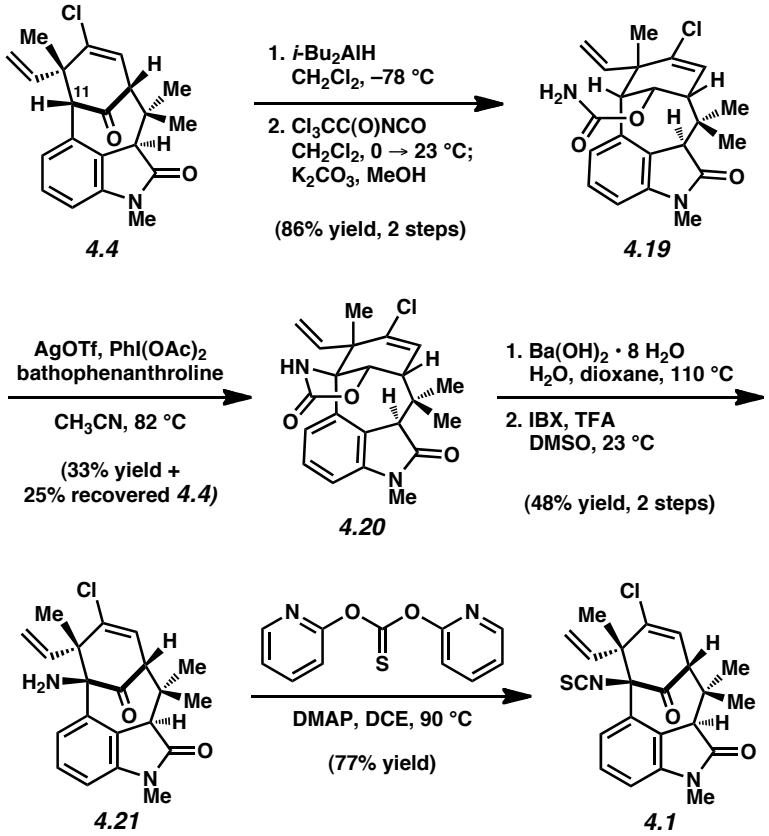


4.6 Completion of (–)-*N*-Methylwelwitindolinone C Isothiocyanate

With intermediate **4.4** lacking only the isothiocyanate substituent, we turned our attention to functionalization of the sterically congested C11 bridgehead position.[20] Unfortunately, attempts to substitute C11 through intermolecular processes were unsuccessful.[21] As a workaround, we postulated that an intramolecular nitrene C–H insertion might be more fruitful.[22,23] Ketone reduction of **4.4** proceeded efficiently using *i*-Bu_2AlH to furnish a secondary alcohol intermediate as a single diastereomer (Scheme 4.4). Subsequent carbamoylation

furnished **4.19**,[23] the key substrate for the critical C–H insertion reaction. The cyclization of carbamate **4.19** was attempted using a variety of reaction conditions that had previously been used to construct 5-membered oxazolidinones fused to cyclohexyl rings.[24] Although use of Rh catalysis furnished ketone **4.4** rather than the desired product **4.20**,[25] Ag catalysis[24b,c] was found to be more effective. Upon treatment of **4.19** with AgOTf, bathophenanthroline, and $PhI(OAc)_2$ in CH_3CN at elevated temperatures, the desired nitrene insertion took place to deliver oxazolidinone **4.20** as the major product. Ketone **4.4** was also recovered, and could be recycled through our synthetic route. Nonetheless, hydrolysis of **4.20** followed by IBX oxidation generated the penultimate intermediate **4.21**. With aminoketone **4.21** in hand, final introduction of the isothiocyanate[3m,26] furnished **4.1**. Spectral data for synthetic **4.1** was identical in all respects to that reported for the natural product.[1a,27]

Scheme 4.4



4.7 Conclusion

In summary, we have achieved the first total synthesis of (–)-*N*-methylwelwitindolinone C isothiocyanate (**4.1**). Our enantiospecific route proceeds in 17 steps from known carvone derivative **4.11** and features a number of key transformations, including: (a) an indolyne cyclization to assemble the bicyclo[4.3.1]decane framework, (b) late-stage introduction of the vinyl chloride and oxindole moieties, and (c) a nitrene insertion reaction to functionalize the sterically congested C11 bridgehead position. Our synthesis of (–)-**4.1** validates the use of indolynes as intermediates in complex molecule synthesis and provides a promising entryway to the other welwitindolinones with bicyclo[4.3.1]decane cores.

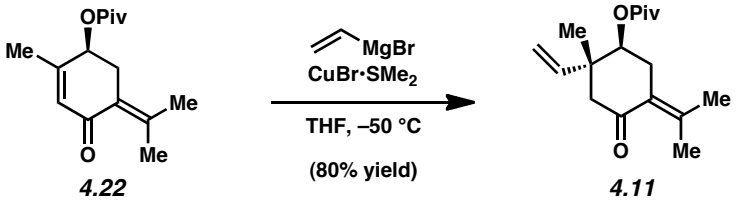
4.8 Experimental Section

4.8.1 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 available reagents were used as received unless otherwise specified. (*S*)-Carvone was obtained from Aldrich. 5-bromoindole was obtained from Biosynth. $NaNH_2$ was obtained from Alfa Aesar. Comins' reagent was obtained from Aldrich. Hexamethylditin was obtained from Aldrich. Tetrakis(triphenylphosphine) palladium(0) was obtained from Strem. Anhydrous $CuCl_2$ was obtained from Aldrich. Trichloroacetyl isocyanate was obtained from Aldrich. AgOTf was obtained from Strem. Bathophenanthroline was obtained from Alfa Aesar. *O*,*O*-di(2-pyridinyl) thiocarbonate was obtained from Aldrich. 2-Iodoxybenzoic acid (IBX) and Dess–Martin periodinane were prepared from known literature procedures.[28,29] *t*-BuOH was distilled from CaH_2 and stored in a Schlenk tube prior to use. 1,4-dioxane was distilled from Na/benzophenone prior to use. 1,2-dichloroethane was distilled from P_2O_5 and stored in a Schlenk tube over 4Å molecular sieves prior to use. 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, and potassium permanganate staining. Silicycle silica gel 60 (particle size 0.040–0.063 mm) was used for flash column chromatography. ^{1}H NMR spectra were recorded on Bruker spectrometers (500 MHz). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz), integration and are referenced to the residual solvent peak 7.26 ppm[30] for $CDCl_3$ and 5.32 ppm for CD_2Cl_2. ^{13}C NMR spectra are reported in terms of chemical shift (at 125 MHz) and are referenced to the

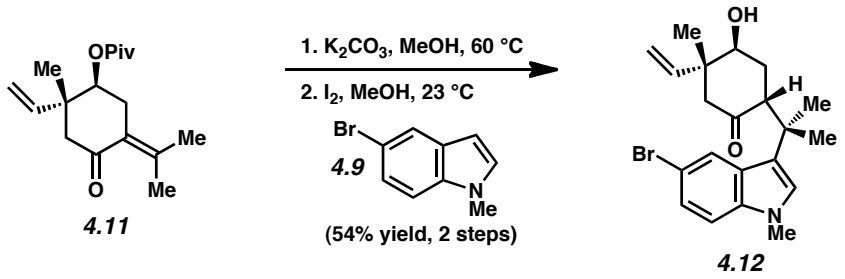
residual solvent peak 77.16 ppm[30] for $CDCl_3$ and 53.84 for CD_2Cl_2. IR spectra were recorded on a Perkin-Elmer 100 spectrometer and are reported in terms of frequency absorption (cm^{-1}). Optical rotations were measured with a Rudolph Autopol IV Automatic Polarimeter. Uncorrected melting points were measured with a Mel-Temp II melting point apparatus and a Fluke 50S thermocouple. High resolution mass spectra were obtained from the UC Irvine Mass Spectrometry Facility.

4.8.2 Experimental Procedures



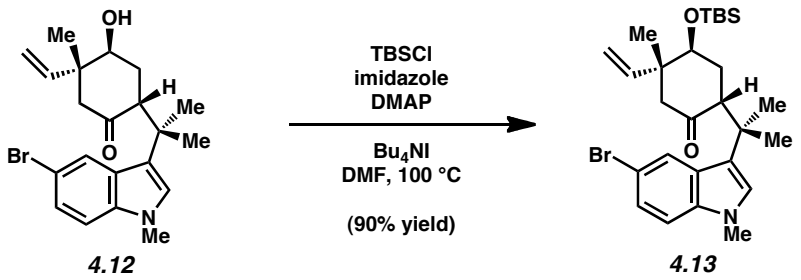
Enone 4.11. Enone **4.11** was prepared using Natsume's procedure (originally performed in the enantiomeric series).[31] A flask was charged with $CuBr{\cdot}SMe_2$ (196 mg, 0.956 mmol, 0.1 equiv) followed by the addition of THF (90 mL). The resulting suspension was cooled to –50 °C and the vinyl magnesium bromide solution (1.0 M in THF, 28.7 mL, 28.7 mmol, 3.0 equiv) was added via syringe pump at a rate of 44.2 mL/hr. Once the addition was complete, a solution of **4.22**[31] (2.39 g, 9.56 mmol, 1.0 equiv) in THF (90 mL) was added via syringe pump at a rate of 86.0 mL/hr. After the addition of **4.22** was complete, the reaction was allowed to stir for 10 minutes and then quenched with a solution of saturated aqueous NH_4Cl (25 mL). The reaction vessel was then removed from the –50 °C bath, diluted with Et_2O (100 mL) and a solution of 1 M aqueous HCl (30 mL), and then allowed to warm to room temperature. The resulting mixture was vigorously stirred until all solids had dissolved. The resulting biphasic mixture was

transferred to a separatory funnel and extracted with Et_2O (3 x 75 mL). The organic layers were combined, dried over $MgSO_4$, and evaporated under reduced pressure. The resulting residue was purified by flash chromatography (3:1 hexanes:Et_2O) to afford enone **4.11** (2.58 g, 80% yield) as a light yellow oil. Enone **4.11**: R_f 0.48 (3:1 hexanes:Et_2O); ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.76 (dd, *J* = 17.6, 10.7, 1H), 5.09 (d, *J* = 17.6, 1H), 5.09 (d, *J* = 10.7, 1H), 4.95 (t, *J* = 4.9, 1H), 2.70–2.66 (m, 2H), 2.54 (d, *J* = 15.8, 1H), 2.50 (d, *J* = 15.8, 1H), 2.02 (t, *J* = 1.6, 3H), 1.75 (s, 3H), 1.19 (s, 9H), 1.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 201.3, 177.9, 146.0, 142.8, 127.4, 114.7, 74.1, 49.2, 43.0, 39.2, 31.1, 27.2, 23.3, 22.6, 22.3; IR (film): 2975, 1720, 1679, 1480, 1280, 1215, 1157 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{17}H_{26}O_3Na$, 301.1780; found 301.1776; $[\alpha]^{24.5}_D$ +41.4° (*c* = 1.000, $CHCl_3$).



Indole 4.12. To a flask containing a solution of enone **4.11** (1.05 g, 3.79 mmol, 1.0 equiv) in MeOH (77.4 mL) was added K_2CO_3 (1.31 g, 9.47 mmol, 2.5 equiv) in one portion. The flask was fitted with a reflux condenser, flushed with N_2, and then allowed to stir at 60 °C. After 24 h, the reaction was cooled to room temperature and transferred to a separatory funnel with Et_2O (40 mL), H_2O (20 mL), and a solution of saturated aqueous NH_4Cl (20 mL). The resulting biphasic mixture was extracted with Et_2O (3 x 40 mL). The organic layers were combined, dried over $MgSO_4$, and evaporated under reduced pressure. The resulting crude residue was used in the subsequent reaction without further purification.

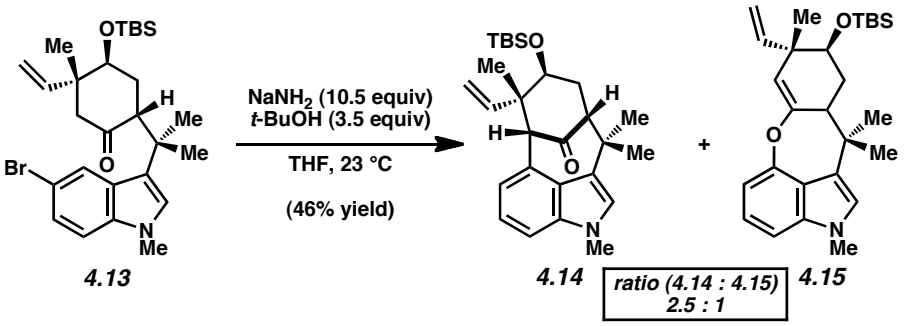
To a flask containing the crude residue from the previous step was added 5-bromo-*N*-methylindole[32] (1.23 g, 5.89 mmol, 1.5 equiv), followed by MeOH (7.82 mL). The resulting suspension was stirred at room temperature until the mixture became homogeneous, and then iodine (198 mg, 0.78 mmol, 0.2 equiv) was added in one portion. The flask was flushed the N_2 and allowed to stir at room temperature. After 19 h, the reaction was quenched with a solution of saturated aqueous $Na_2S_2O_3$ (15 mL) and transferred to a separatory funnel with Et_2O (50 mL) and H_2O (15 mL). The resulting biphasic mixture was extracted with Et_2O (3 x 30 mL). The organic layers were combined, dried over $MgSO_4$, and evaporated under reduced pressure. The resulting residue was purified by flash chromatography (2:1:1 hexanes:CH_2Cl_2:Et_2O) to afford indole **4.12** (823 mg, 54% yield, over two steps) as a white solid. Indole **4.12**: mp: 71 ºC; R_f 0.43 (2:1:1 hexanes:CH_2Cl_2:Et_2O); ^{1}H NMR (500 MHz, CD_2Cl_2): δ 7.85, (d, *J* = 1.7, 1H), 7.26 (dd, *J* = 8.7, 1.7, 1H), 7.18 (d, *J* = 8.7, 1H), 6.82 (s, 1H), 5.64 (dd, *J* = 17.7, 10.9, 1H), 5.07 (d, *J* = 17.7, 1H), 5.05 (d, *J* = 10.9, 1H), 3.70 (s, 3H), 3.61 (br. s, 1H), 3.37 (dd, *J* = 12.7, 5.5, 1H), 2.71 (d, *J* = 13.7, 1H), 2.23 (dd, *J* = 13.7, 1.1, 1H), 1.82 (dt, *J* = 12.9, 2.4, 1H), 1.58 (s, 3H), 1.57–1.51 (m, 1H), 1.41 (s, 3H), 1.08 (s, 3H); ^{13}C NMR (125 MHz, CD_2Cl_2): δ 210.5, 144.1, 136.9, 127.9, 127.7, 124.1, 123.8, 123.6, 114.7, 112.0, 111.4, 72.8, 50.2, 48.7, 47.3, 36.6, 33.10, 33.08, 27.7, 24.6, 22.9; IR (film): 3463, 2966, 1703, 1479, 1214 cm^{-1}; HRMS-ESI (*m/z*) [M + Na]$^+$ calcd for $C_{21}H_{26}NO_2BrNa$, 426.1045; found 426.1044; $[\alpha]^{24.8}_D$ +76.2° (*c* = 1.000, $CHCl_3$).



4.12 *4.13*

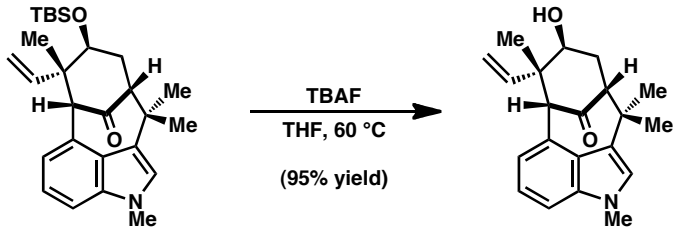
Silyl Ether 4.13. To a solution of indole **4.12** (3.84 g, 9.50 mmol, 1.0 equiv) in DMF (47.5 mL) was added imidazole (3.23 g, 47.5 mmol, 5 equiv), DMAP (1.17 g, 9.50 mmol, 1.0 equiv), tetrabutylammonium iodide (3.51 g, 9.50 mmol, 1.0 equiv), and TBSCl (4.30 g, 28.5 mmol, 3.0 equiv), all as solids in one portion. The flask was fitted with a reflux condenser, flushed with N_2, and then allowed to stir at 100 °C. After 12 h, the reaction was cooled to room temperature and transferred to a separatory funnel with EtOAc (75 mL), H_2O (30 mL), and a solution of saturated aqueous NH_4Cl (100 mL). The resulting biphasic mixture was extracted with EtOAc (4 x 75 mL). The organic layers were combined, washed with H_2O (1 x 20 mL), washed with brine (2 x 20 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The resulting residue was purified by flash chromatography (1:1 hexanes:Et_2O) to afford silyl ether **4.13** (4.43 g, 90% yield) as a white solid. Silyl ether **4.13**: mp: 117 ºC; R_f 0.68 (1:1 hexanes:Et_2O); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.79 (d, *J* = 1.8, 1H), 7.24 (dd, *J* = 8.7, 1.8, 1H), 7.12 (d, *J* = 8.7, 1H), 6.78 (s, 1H), 5.61 (dd, *J* = 17.6, 11.0, 1H), 5.07 (d, *J* = 17.6, 1H), 5.04 (d, *J* = 11.0, 1H), 3.70 (s, 3H), 3.56 (br. s, 1H), 3.27 (dd, *J* = 13.0, 5.4, 1H), 2.67 (d, *J* = 13.4, 1H), 2.16 (dd, *J* = 13.4, 0.9, 1H), 1.81 (dt, *J* = 13.4, 2.0, 1H), 1.63 (s, 3H), 1.61–1.59 (m, 1H), 1.38 (s, 3H), 1.00 (s, 3H), 0.86 (s, 9H), –0.04 (s, 3H), –0.42 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 211.0, 143.7, 136.5, 127.7, 127.3, 124.0, 123.71, 123.66, 114.7, 112.1, 110.9, 73.3, 50.4, 48.4, 48.1, 36.0, 33.3, 32.9, 26.5, 26.1, 25.6, 24.1, 18.2, –4.7, –5.1; IR (film): 2953, 2926, 2858, 1708, 1477, 1361, 1256, 1218,

1073 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{27}H_{40}NO_2BrSiNa$, 540.1909; found 540.1903; $[\alpha]^{22.7}_D$ +72.4° (*c* = 1.000, $CHCl_3$).



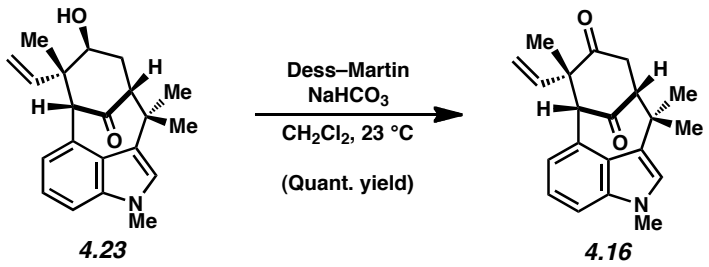
Bicycle 4.14. Inside of the glovebox, a flask was charged with $NaNH_2$ (2.13 g, 54.50 mmol, 10.5 equiv). The flask was then sealed and removed from the glovebox. THF (30.0 mL) was then added, followed by *t*-BuOH (1.75 mL, 18.20 mmol, 3.5 equiv). The resulting suspension was heated to 40 °C and stirred vigorously for 1 h. The reaction was cooled to room temperature and a solution of silyl ether **4.13** (2.68 g, 5.20 mmol, 1.0 equiv) in THF (22.0 mL) was added. After stirring at room temperature, the reaction was quenched via the dropwise addition of H_2O until no more gas evolution was observed. The reaction was then transferred to a separatory funnel with EtOAc (40 mL) and a solution of saturated aqueous NH_4Cl (40 mL). The resulting biphasic mixture was extracted with EtOAc (3 x 100 mL) and the organic layers were combined, dried over $MgSO_4$, and evaporated under reduced pressure. The resulting residue was purified by flash chromatography (100% benzene) to afford bicycle **4.14** (749 mg, 33% yield) as a light yellow oil and *O*-arylated product **4.15** (288 mg, 13% yield) as a clear oil. Bicycle **4.14**: R_f 0.56 (100% benzene); ^1H NMR (500 MHz, $CDCl_3$): δ 7.19 (d, *J* = 8.1, 1H), 7.13 (dd, *J* = 8.1, 7.3, 1H), 6.95 (s, 1H), 6.71 (d, *J* = 7.3, 1H), 4.96 (dd, *J* = 14.6, 4.6, 1H), 4.91–4.84 (m, 2H), 3.77 (s, 3H), 3.72 (dd, *J* = 11.0, 5.0, 1H), 3.60 (d, *J* = 1.5, 1H), 2.63 (d, *J* = 8.3, 1H), 2.21 (ddd, *J* = 14.5, 5.0, 1.8,

1H), 2.00 (ddd, J = 14.5, 8.3, 2.8), 1.57 (s, 3H), 1.18 (s, 3H), 1.07 (s, 3H), 0.72 (s, 9H), –0.21 (s, 3H), –0.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 212.4, 145.0, 137.4, 126.3, 126.2, 125.2, 122.6, 122.5, 121.1, 113.0, 108.1, 69.1, 69.0, 60.0, 49.8, 35.8, 35.7, 33.0, 32.1, 28.2, 25.9, 18.0, 16.8, –4.3, –4.8; IR (film): 2956, 2926, 1705, 1472, 1256, 1092 cm^{-1}; HRMS-ESI (m/z) [M + Na]$^+$ calcd for $C_{27}H_{39}NO_2SiNa$, 460.2648; found 460.2650; $[\alpha]^{24.9}_D$ +101.8° (c = 1.000, $CHCl_3$).



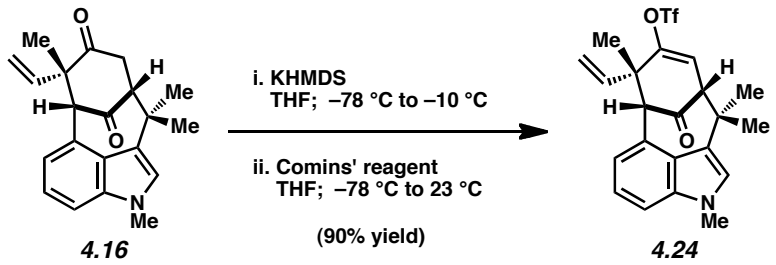
4.14 *4.23*

Alcohol 4.23. A flask was charged with bicycle **4.14** (848 mg, 1.94 mmol, 1.0 equiv) followed by the addition of THF (20 mL). A solution of TBAF (1.0 M in THF, 5.82 mL, 5.82 mmol, 3.0 equiv) was then added and the flask was fitted with a reflux condenser, flushed with N_2, and allowed to stir at 60 °C. After 12 h, the reaction was cooled to room temperature and transferred to a separatory funnel with EtOAc (30 mL) and a solution of 1 M aqueous $NaHSO_4$ (15 mL). The resulting biphasic mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure. The resulting residue was purified by flash chromatography (2:1 hexanes:EtOAc) to afford **4.23** (605 mg, 96% yield) as a white solid. **4.23**: R_f 0.25 (2:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.20 (d, J = 8.2, 1H), 7.15 (dd, J = 8.2, 7.2, 1H), 6.96 (s, 1H), 6.72 (d, J = 7.2, 1H), 5.18–5.02 (m, 3H), 3.77 (s, 3H), 3.74 (ddd, J = 5.6, 3.0, 2.5, 1H), 3.67 (d, J = 1.5, 1H), 2.70 (d, J = 8.5, 1H), 2.42 (dd, J = 14.2, 5.6, 1H), 1.97 (ddd, J = 14.2, 8.5, 2.5, 1H), 1.61 (s, 3H), 1.18 (s, 3H), 1.08 (s, 3H).

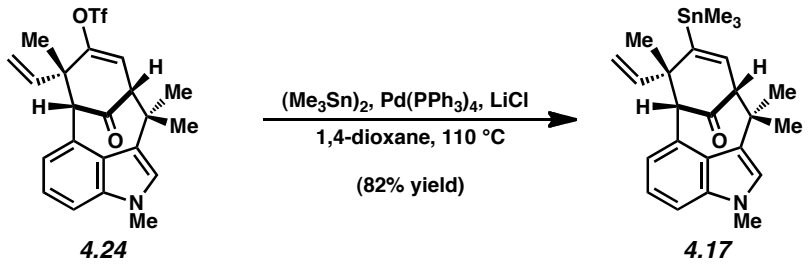


4.23 *4.16*

Diketone 4.16. A flask was charged with **4.23** (601 mg, 1.86 mmol, 1.0 equiv), $NaHCO_3$ (781 mg, 9.30 mmol, 5.0 equiv), and CH_2Cl_2 (37 mL). To the resulting suspension was added the Dess–Martin periodinane reagent (1.02 g, 2.42 mmol, 1.3 equiv) in one portion. The flask was flushed with N_2, and the reaction mixture was allowed to stir at room temperature. After 90 min, the reaction mixture was diluted with a solution of $NaHCO_3$ (1 g) and $Na_2S_2O_3$ (1 g) in H_2O (20 mL). The resulting biphasic mixture was vigorously stirred until both layers were no longer cloudy. The mixture was then transferred to a separatory funnel with EtOAc (50 mL) then extracted with EtOAc (3 x 50 mL). The organic layers were combined, dried over $MgSO_4$, and evaporated under reduced pressure. The resulting residue was purified by flash chromatography (2:1:1 hexanes:CH_2Cl_2:Et_2O) to afford diketone **4.16** (600 mg, quant. yield) as a white solid. Diketone **4.16**: mp: 194 ºC; R_f 0.48 (2:1:1 hexanes:CH_2Cl_2:Et_2O); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.20 (d, *J* = 8.4, 1H), 7.15 (dd, *J* = 8.4, 7.7, 1H), 6.94 (s, 1H), 6.80 (d, *J* = 7.7, 1H), 5.64 (dd, *J* = 17.4, 10.8, 1H), 5.21 (d, *J* = 10.8, 1H), 5.16 (d, *J* = 17.4, 1H), 3.90 (s, 1H), 3.75 (s, 3H), 3.00–2.87 (m, 3H), 1.51 (s, 3H), 1.47 (s, 3H), 1.17 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 209.9, 209.4, 139.3, 137.8, 127.1, 123.8, 123.5, 122.8, 121.1, 120.2, 114.8, 108.9, 68.9, 58.5, 56.3, 40.2, 37.4, 33.6, 33.1, 28.2, 22.2; IR (film): 2976, 2922, 1714, 1706, 1541, 1418, 1234 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{21}H_{23}NO_2Na$, 344.1627; found 344.1624; $[\alpha]^{25.1}_D$ +165.8° (*c* = 1.000, $CHCl_3$).

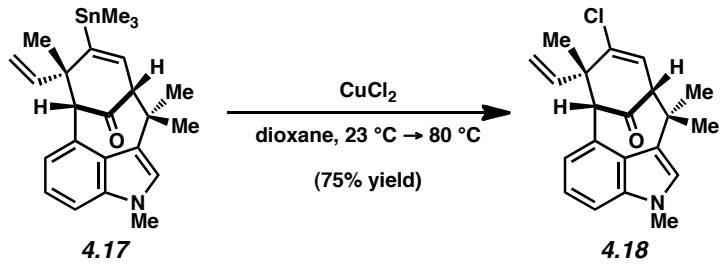


Vinyl Triflate 4.24. Inside of the glovebox, a flask was charged with solid KHMDS (327 mg, 1.65 mmol, 1.2 equiv). The flask was then sealed and removed from the glovebox. THF (7.0 mL) was added and the resulting solution was cooled to –78 °C. A solution of diketone **4.16** (440 mg, 1.37 mmol, 1.0 equiv) in THF (7.0 mL) was then added dropwise. Upon completion of the addition, the reaction was allowed to stir at –78 °C for 15 min, and was then warmed to –10 °C for 1 additional hour. The reaction vessel was then cooled to –78 °C and a solution of Comins' reagent (590 mg, 1.51 mmol, 1.1 equiv) in THF (3 mL) was added dropwise. After stirring at –78 °C for 45 min, the reaction mixture was warmed to room temperature and allowed to stir for an additional 15 min. The reaction was then quenched by the addition of a solution of saturated aqueous NH_4Cl (5 mL) and transferred to a separatory funnel with EtOAc (30 mL) and H_2O (20 mL). The resulting biphasic mixture was extracted with EtOAc (3 x 30 mL). The organic layers were combined, dried over $MgSO_4$, and evaporated under reduced pressure. The resulting residue was purified by flash chromatography (2:1:1 hexanes:CH_2Cl_2:Et_2O) to afford vinyl triflate **4.24** (555 mg, 90% yield) as a light yellow oil. Vinyl triflate **4.24**: R_f 0.64 (2:1:1 hexanes:CH_2Cl_2:Et_2O); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.23 (d, J = 8.2, 1H), 7.15 (dd, J = 8.2, 7.3, 1H), 6.92 (s, 1H), 6.75 (d, J = 7.3, 1H), 5.93 (d, J = 3.8, 1H), 5.24–5.17 (m, 3H), 3.80 (s, 1H), 3.76 (s, 3H), 3.15 (d, J = 3.8, 1H), 1.63 (s, 3H), 1.49 (s, 3H), 1.22 (s, 3H).



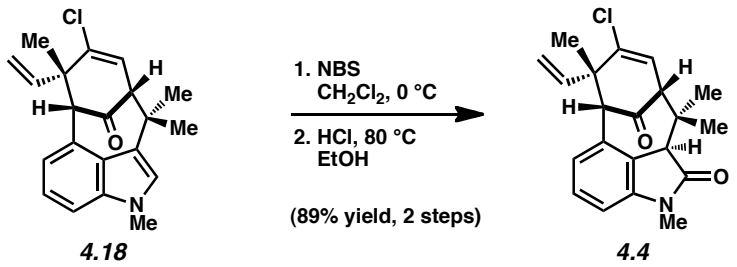
4.24 *4.17*

Vinyl Stannane 4.17. In the glovebox, a 20 mL scintillation vial was charged with $Pd(PPh_3)_4$ (59 mg, 0.051 mmol, 0.2 equiv), LiCl (258 mg, 6.51 mmol, 24 equiv), and hexamethylditin (254 μL, 1.23 mmol, 4.8 equiv). A separate 20 mL scintillation vial was charged with **4.24** (116 mg, 0.256 mmol, 1.0 equiv), followed by the addition of 1,4-dioxane (3.8 mL) which had been taken through three freeze-pump-thaw cycles prior to use. The resulting solution was then added to the vial containing the palladium catalyst, sealed, taken outside of the glovebox, and allowed to stir at 110 °C. After 20 h, the reaction was cooled to room temperature and filtered through a plug of silica gel topped with Celite. The filter cake was then washed with CH_2Cl_2 (15 mL), and the filtrate was evaporated under reduced pressure. The resulting residue was purified by flash chromatography (5:1 hexanes:Et_2O) to afford vinyl stannane **4.17** (97 mg, 82% yield) as a white solid. Vinyl stannane **4.17**: mp: 158 ºC; R_f 0.34 (5:1 hexanes:Et_2O); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.15 (d, J = 8.0, 1H), 7.10 (dd, J = 8.0, 7.0, 1H), 6.84 (s, 1H), 6.72 (d, J = 7.0, 1H), 5.93 (d, J = 3.2, J_{H-Sn} = 72.0, 1H), 5.42 (dd, J = 17.7, 10.7, 1H), 5.07 (dd, J = 17.7, 1.1, 1H), 5.05 (dd, J = 10.7, 1.1, 1H), 3.73 (app. s, 4H), 2.93 (d, J = 3.2, 1H), 1.65 (s, 3H), 1.24 (s, 3H), 1.21 (s, 3H), –0.10 (s, J_{H-Sn} = 52.7, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 211.9, 149.9, 145.4, 137.6, 135.5, 125.6, 125.5, 124.5, 122.9, 122.0, 120.5, 112.2, 107.8, 68.6, 61.8, 53.2, 37.1, 34.4, 33.0, 28.5, 25.7, –7.5; IR (film): 2973, 2919, 2875, 1703, 1454, 1420, 1371, 1255 cm^{-1}; HRMS-ESI (m/z) [M + Na]$^+$ calcd for $C_{24}H_{31}NOSnNa$, 492.1330; found 492.1327; $[\alpha]^{25.2}_D$ +46.6° (c = 1.000, $CHCl_3$).



4.17 *4.18*

Vinyl Chloride 4.18. A 20 mL scintillation vial was charged with vinyl stannane **4.17** (100 mg, 0.214 mmol, 1.0 equiv), and then transferred to the glovebox. Dioxane (4.27 mL) was added and to the resulting solution was added $CuCl_2$ (63 mg, 0.470 mmol, 2.2 equiv) in one portion. The vial was sealed and removed from the glovebox. The reaction mixture was allowed to stir at 23 °C for 30 min, and was then warmed to 80 °C. After 24 h, the reaction was diluted with brine (5 mL) and the resulting mixture was transferred to a separatory funnel with EtOAc (10 mL) and H_2O (5 mL). The resulting biphasic mixture was extracted with EtOAc (3 x 20 mL). The organic layers were combined, dried over $MgSO_4$, and evaporated under reduced pressure. The resulting residue was purified by preparative thin layer chromatography (benzene eluent) to afford vinyl chloride **4.18** (54 mg, 75% yield) as a white solid. Vinyl chloride **4.18**: mp: 83 ºC; R_f 0.27 (5:1 hexanes:Et_2O); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.20 (d, *J* = 8.4, 1H), 7.13 (dd, *J* = 8.4, 7.2, 1H), 6.89 (s, 1H), 6.76 (d, *J* = 7.2, 1H), 6.01 (d, *J* = 3.9, 1H), 5.27–5.12 (m, 3H), 3.82 (s, 1H), 3.75 (s, 3H), 3.02 (d, *J* = 3.9, 1H), 1.63 (s, 3H), 1.45 (s, 3H), 1.19 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 208.8, 142.2, 138.8, 137.7, 125.9, 124.31, 124.29, 124.2, 123.7, 121.4, 120.8, 113.8, 108.5, 68.6, 61.6, 51.9, 37.1, 34.0, 33.0, 28.3, 23.9; IR (film): 2970, 1716, 1450, 1418, 1368, 1255, 1152 cm^{-1}; HRMS-ESI (*m/z*) [M + Na]$^+$ calcd for $C_{21}H_{22}NOClNa$, 362.1288; found 362.1283; $[\alpha]^{22.8}_D$ +62.8° (*c* = 1.000, $CHCl_3$).

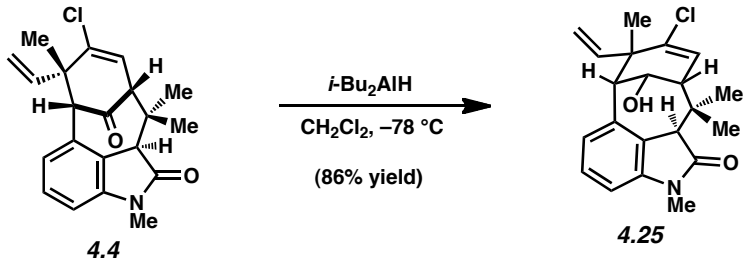


4.18 *4.4*

Oxindole 4.4. To a solution of vinyl chloride **4.18** (46 mg, 0.136 mmol, 1.0 equiv) in CH_2Cl_2 (2.75 mL) at 0 °C was added NBS (24.3 mg, 0.136 mmol, 1.0 equiv) in one portion. The reaction vial was flushed with N_2, and allowed to stir at 0 °C. After 25 min, solid $NaHCO_3$ (46 mg) was added in one portion. The reaction was removed from the 0 °C bath, and allowed to stir at room temperature for 5 min. The resulting suspension was filtered through a plug of silica gel (CH_2Cl_2 eluent, 10 mL). Evaporation under reduced pressure provided the crude brominated product, which was used in the subsequent step without further purification.

To the crude product was added absolute ethanol (1.5 mL) and concentrated aqueous HCl (1.5 mL). After heating to 80 °C for 14 h, the the reaction was cooled to room temperature and transferred to a separatory funnel with H_2O (10 mL) and EtOAc (20 mL). To the funnel was added solid $NaHCO_3$ until no more gas evolution was observed. The resulting biphasic mixture was extracted with EtOAc (3 x 20 mL) and the organic layers were combined, dried over $MgSO_4$, and evaporated under reduced pressure. The resulting residue was purified by flash chromatography (2:1:1 hexanes:CH_2Cl_2:Et_2O) to afford oxindole **4.4** (42.8 mg, 89% yield) as a white solid. Oxindole **4.4**: mp: 193 °C; R_f 0.40 (2:1:1 hexanes:CH_2Cl_2:Et_2O); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.19 (dd, *J* = 7.9, 7.9, 1H), 6.71 (d, *J* = 7.9, 1H), 6.60 (d, *J* = 7.9, 1H), 6.16 (d, *J* = 5.1, 1H), 5.37 (dd, *J* = 17.4, 10.6, 1H), 5.13 (d, *J* = 17.4, 1H), 5.09 (d, *J* = 10.6, 1H), 3.81 (s, 1H), 3.52 (d, *J* = 1.4, 1H), 3.18 (s, 3H), 2.93 (dd, *J* = 5.1, 1.4, 1H), 1.62 (s, 3H), 1.47 (s, 3H), 0.73 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 204.7, 175.4, 144.7, 141.4, 140.3, 130.5, 128.6,

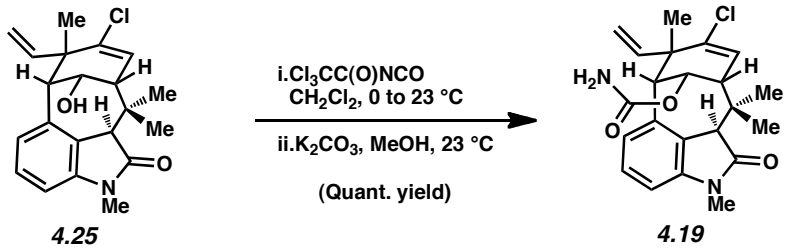
127.1, 124.6, 123.9, 115.4, 107.3, 68.8, 63.8, 52.0, 51.9, 41.7, 26.4, 25.8, 25.6, 21.4; IR (film): 2966, 2922, 1700, 1609, 1595, 1465 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{21}H_{22}NO_2ClNa$, 378.1237; found 378.1248; $[\alpha]^{23.4}_D$ –132.8° (*c* = 1.000, $CHCl_3$).



4.4 *4.25*

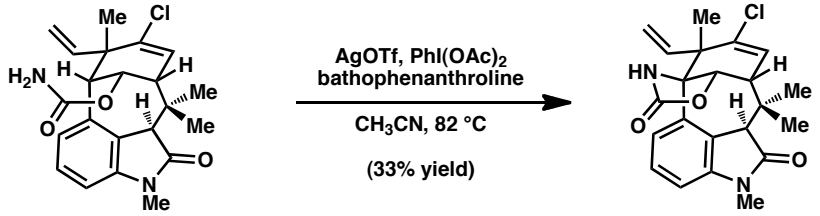
Alcohol 4.25. To a solution of oxindole **4.4** (43.0 mg, 0.121 mmol, 1.0 equiv) in CH_2Cl_2 (4.00 mL) at –78 °C was added a solution of *i*-Bu_2AlH (1.0 M in hexanes, 145 μL, 0.145 mmol, 1.2 equiv) dropwise. After stirring at –78 °C for 1 h, an additional portion of *i*-Bu_2AlH (1.0 M in hexanes, 24 μL, 0.024 mmol, 0.2 equiv) was added. After stirring at –78 °C for 1 h, a third portion of *i*-Bu_2AlH (1.0 M in hexanes, 24 μL, 0.024 mmol, 0.2 equiv) was added and the mixture was allowed to stir at –78 °C for 1 h. At this time, a final portion of *i*-Bu_2AlH (1.0 M in hexanes, 48 μL, 0.048 mmol, 0.4 equiv) was added. After 30 min, the reaction was quenched at –78 °C with a solution of saturated aqueous NH_4Cl (1 mL) and Rochelle's salt (1 mL). The mixture was stirred at room temperature for 1 h, transferred to a separatory with EtOAc (20 mL) and a solution of saturated aqueous NH_4Cl (20 mL), and extracted with EtOAc (3 x 20 mL). The organic layers were combined, dried over $MgSO_4$, and evaporated under reduced pressure. The resulting residue was purified by flash chromatography (1:1:1 hexanes:CH_2Cl_2:Et_2O) to afford alcohol **4.25** (37.2 mg, 86% yield) as a white solid. Alcohol **4.25**: R_f 0.12 (2:1:1 hexanes:CH_2Cl_2:Et_2O); ^1H NMR (500 MHz, $CDCl_3$): δ 7.17 (dd, *J* = 7.8, 7.7, 1H), 6.70 (d, *J* = 7.8, 1H), 6.68 (d, *J* = 7.7, 1H), 6.19 (d, *J* = 6.7, 1H), 5.23 (dd, *J* = 17.4, 10.7, 1H), 5.03 (dd, *J* =

17.4, 0.7, 1H), 4.89 (dd, *J* = 10.7, 0.7, 1H), 4.59–4.55 (app. t, *J* = 4.9, 1H), 3.62 (s, 1H), 3.18 (s, 3H), 3.14 (dd, *J* = 4.9, 1.0, 1H), 2.58 (ddd, *J* = 6.7, 5.4, 1.0, 1H), 1.57 (s, 3H), 1.53 (s, 3H), 0.95 (s, 3H).



Carbamate 4.19. To a solution of **4.25** (78 mg, 0.218 mmol, 1.0 equiv) in CH_2Cl_2 (2.2 mL) at 0 °C was added trichloroacetyl isocyanate (27 μL, 0.229 mmol, 1.05 equiv) in a dropwise manner. The resulting mixture was allowed to stir at 0 °C for 5 min, and then at room temperature for 20 min. The solvent was evaporated under reduced pressure. To the resulting residue was added MeOH (4.4 mL) and solid K_2CO_3 (165 mg, 1.19 mmol, 5.5 equiv) in one portion. The reaction was flushed with N_2 and left to stir at room temperature for 90 min. The reaction was diluted with EtOAc (3 mL) and H_2O (1 mL) and the resulting biphasic mixture was transferred to a test tube with EtOAc (2 mL) and brine (2 mL). After extracting with EtOAc (3 x 3 mL), the organic layers were combined, dried over $MgSO_4$, and evaporated under reduced pressure. The resulting residue was purified by flash chromatography (1:1 hexanes:EtOAc) to afford carbamate **4.19** (90 mg, quant. yield) as a white solid. Carbamate **4.19**: mp: 135 ºC; R_f 0.41 (1:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.13 (dd, *J* = 7.8, 7.7, 1H), 6.68 (d, *J* = 7.7, 1H), 6.61 (d, *J* = 7.8, 1H), 6.18 (d, *J* = 6.8, 1H), 5.47 (dd, *J* = 5.3, 4.8, 1H), 5.19 (dd, *J* = 17.3, 10.6, 1H), 5.04 (dd, *J* = 17.3, 0.8, 1H), 4.91 (dd, *J* = 10.6, 0.8, 1H), 4.41 (br. s, 2H), 3.62 (s, 3H), 3.18 (s, 3H), 3.15 (d, *J* = 4.8, 1H), 2.78 (dd, *J* = 6.8, 5.3, 1H), 1.61 (s, 3H), 1.52 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (125

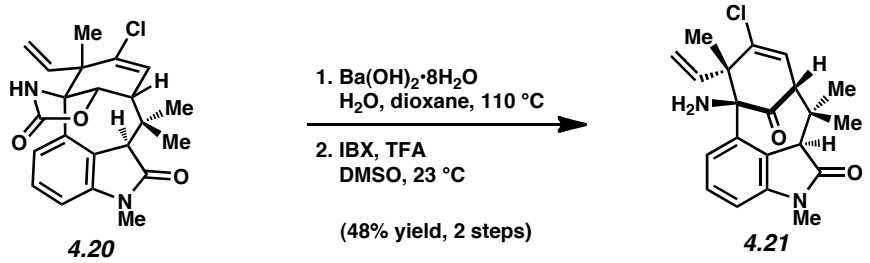
MHz, $CDCl_3$): δ 176.3, 155.9, 144.3, 141.2, 141.0, 136.9, 127.7, 127.3, 126.4, 125.7, 114.7, 106.6, 72.7, 55.9, 52.6, 50.6, 49.0, 38.7, 28.0, 26.3, 26.2, 22.7; IR (film): 3497, 3341, 2936, 1730, 1698, 1609, 1470, 1341, 1066 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{22}H_{25}N_2O_3ClNa$, 423.1451; found 423.1459; $[\alpha]^{23.0}_D$ –166.4° (*c* = 1.000, $CHCl_3$).



4.19 *4.20*

Oxazolidinone 4.20. A 20 mL scintillation vial containing CH_3CN and a separate 20 mL scintillation vial charged with bathophenanthroline (24.1 mg, 0.0750 mmol, 0.5 equiv) were transferred into the glovebox. AgOTf (19.2 mg, 0.0750 mmol, 0.5 equiv) and CH_3CN (4.30 mL) were added to the vial containing the bathophenanthroline, and the resulting suspension was allowed to stir at room temperature for 20 min. Next, a third 20 mL scintillation vial containing carbamate **4.19** (55 mg, 0.150 mmol, 1.0 equiv) and $PhI(OAc)_2$ (96.4 mg, 0.300 mmol, 2.0 equiv) was transferred into the glovebox and the AgOTf/bathophenanthroline suspension was added to this vial. The vial was then sealed, removed from the glovebox, and the resulting mixture was allowed to stir at 82 °C. After 24 h, the reaction was cooled to room temperature and filtered through a plug of silica gel (EtOAc eluent, 50 mL). The filtrate was evaporated under reduced pressure, and the resulting residue was purified by preparative thin layer chromatography (2:1 benzene:EtOAc) to afford oxazolidinone **4.20** (18 mg, 33% yield) as a white solid and recovered oxindole **4.4** (12 mg, 25% yield) as a white solid. Oxazolidinone **4.20**: mp: 329 ºC; R_f 0.35 (2:1 benzene:EtOAc); ^1H NMR (500 MHz, $CDCl_3$): δ 7.55 (br. s, 1H), 7.15

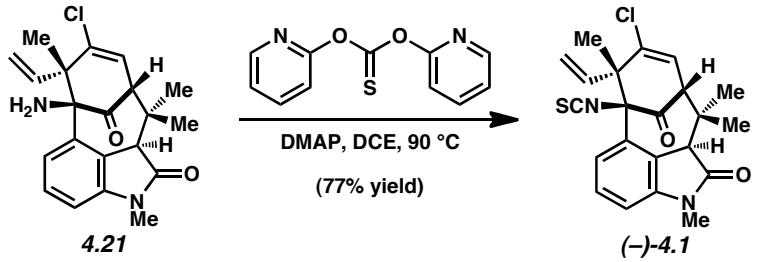
(dd, J = 8.3, 7.6, 1H), 6.72 (d, J = 8.3, 1H), 6.71 (d, J = 7.6, 1H), 6.29 (d, J = 5.8, 1H), 5.19–5.05 (m, 3H), 5.02 (d, J = 6.5, 1H), 3.62 (s, 1H), 3.19 (s, 3H), 2.98 (dd, J = 6.5, 5.8, 1H), 1.65 (s, 3H), 1.56 (s, 3H), 1.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.9, 159.2, 144.2, 141.2, 140.6, 136.8, 128.2, 126.0, 125.5, 124.0, 116.4, 107.4, 81.3, 69.9, 54.2, 52.1, 49.6, 38.7, 27.4, 26.4, 22.0, 20.2; IR (film): 3270, 1755, 1686, 1612, 1460, 1202, 1152 cm^{-1}; HRMS-ESI (m/z) [M + Na]$^+$ calcd for $C_{22}H_{23}N_2O_3ClNa$, 421.1295; found 421.1289; $[\alpha]^{25.5}_D$ –109.4° (c = 1.000, $CHCl_3$).



Aminoketone 4.21. A Schlenk tube was charged with oxazolidinone **4.20** (15 mg, 0.0376 mmol, 1.0 equiv) and $Ba(OH)_2{\cdot}8H_2O$ (59 mg, 0.188 mmol, 5.0 equiv). The reaction vessel was then evacuated and backfilled with N_2 five times. A 2:1 mixture of 1,4-dioxane:H_2O (1.4 mL) that had been taken through seven freeze-pump-thaw cycles prior to use was then added and the Schlenk tube. The vessel was sealed, and then transferred to the glovebox where the reaction was allowed to stir at 110 °C. After 16 h, the Schlenk tube was removed from the glovebox and the contents were transferred to a test tube with EtOAc (6 mL), H_2O (1 mL), and brine (1 mL). The resulting biphasic mixture was extracted with EtOAc (3 x 4 mL). The organic layers were combined, dried over $MgSO_4$, and evaporated under reduced pressure to afford the crude product, which was used directly in the subsequent reaction.

To the crude residue was added DMSO (1.4 mL) and TFA (3 μL, 0.0413 mmol, 1.1 equiv). The resulting solution was allowed to stir at room temperature for 2 min. IBX (53 mg,

0.188 mmol, 5 equiv) was then added in one portion, and the vial was flushed with N_2. After stirring at room temperature for 20 h, the reaction mixture transferred with EtOAc (3 mL) to a test tube containing a solution of aqueous K_2CO_3 (1 mL, concentration of 50 mg/mL). The resulting biphasic mixture was extracted with EtOAc (5 x 3 mL) and the organic layers were combined, dried over $MgSO_4$, and evaporated under reduced pressure. The resulting residue was purified by preparative thin layer chromatography (1:1 hexanes:EtOAc) to afford aminoketone **4.21** (6.7 mg, 48% yield, over two steps) as an amorphous solid. Aminoketone **4.21**: R_f 0.42 (1:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34 (d, *J* = 8.4, 1H), 7.27 (dd, *J* = 8.4, 7.6, 1H), 6.75 (d, *J* = 7.6, 1H), 6.18 (d, *J* = 4.2, 1H), 5.44 (dd, *J* = 17.3, 10.9, 1H), 5.22 (d, *J* = 10.9, 1H), 5.17 (d, *J* = 17.3, 1H), 3.82 (s, 1H), 3.18 (s, 3H), 3.15 (d, *J* = 4.2, 1H), 1.71 (br. s, 2H), 1.69 (s, 3H), 1.31 (s, 3H), 0.78 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 207.4, 174.7, 144.1, 140.6, 138.9, 135.2, 128.2, 124.2, 123.8, 123.7, 116.2, 107.7, 71.8, 62.8, 56.7, 53.8, 40.0, 26.4, 25.9, 21.6, 20.6; IR (film): 2973, 1709, 1698, 1609, 1583, 1457 cm^{-1}; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{21}H_{24}N_2O_2Cl$, 371.1526; found 371.1516; $[\alpha]^{23.8}_D$ –70.2° (*c* = 1.000, $CHCl_3$).



(–)-*N*-Methylwelwitindolinone C Isothiocyanate (4.1). To solution of aminoketone **4.21** (5.0 mg, 0.0135 mmol, 1.0 equiv) in 1,2-dichloroethane (540 μL) was added DMAP (0.8 mg, 0.0067 mmol, 0.5 equiv) and *O*,*O*-di(2-pyridinyl) thiocarbonate (15.7 mg, 0.067 mmol, 5 equiv) in one portion. The reaction vial was flushed with N_2 and then allowed to stir at 90 °C. After 14 h, the

reaction was cooled to room temperature and then passed over a plug of silica gel (EtOAc eluent, 20 mL). The filtrate was evaporated under reduced pressure. The resulting residue was purified by preparative thin layer chromatography (9:1 benzene:EtOAc) to afford **(–)-4.1** (4.3 mg, 77% yield) as an amorphous solid. (–)-*N*-Methylwelwitindolinone C isothiocyanate **(4.1)**: R_f 0.81 (1:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30 (dd, *J* = 8.4, 7.8, 1H), 7.18 (dd, *J* = 8.4, 0.9, 1H), 6.79 (dd, *J* = 8.4, 0.9, 1H), 6.17 (d, *J* = 4.4, 1H), 5.35 (dd, *J* = 16.8, 10.6, 1H), 5.29–5.17 (m, 2H), 3.73 (s, 1H), 3.24 (d, *J* = 4.4, 1H), 3.17 (s, 3H) 1.68 (s, 3H), 1.47 (s, 3H), 0.80 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 196.3, 174.1, 144.5, 140.7, 138.7, 137.2, 130.1, 128.6, 124.7, 123.3, 122.5, 117.7, 108.5, 83.8, 61.7, 57.0, 53.1, 40.8, 26.4, 25.7, 22.2, 21.4; IR (film): 2970, 2932, 2041, 1712, 1609, 1460, 1341 cm^{-1}; HRMS-ESI (*m*/*z*) $[M + Na]^+$ calcd for $C_{22}H_{21}N_2O_2SClNa$, 435.0910; found 435.0899; $[\alpha]^{23.6}_D$ –223.9° (*c* = 0.77, CH_2Cl_2).[33]

4.9 Notes and References

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(7) For a model system study of this transformation, see ref 3p.

(8) For seminal indolyne studies, see: (a) Julia, M.; Huang, Y.; Igolen, J. *C. R. Acad. Sci., Ser. C* **1967**, *265*, 110–112. (b) Igolen, J.; Kolb, A. *C. R. Acad. Sci., Ser. C* **1969**, *269*, 54–56. (c) Julia, M.; Le Goffic, F.; Igolen, J.; Baillarge, M. *Tetrahedron Lett.* **1969**, *10*, 1569–1571. For related studies, see: (d) Julia, M.; Goffic, F. L.; Igolen, J.; Baillarge, M. *C. R. Acad. Sci., Ser. C* **1967**, *264*, 118–120. (e) Julia, M.; Igolen, J.; Kolb, M. *C. R. Acad. Sci., Ser. C* **1971**, *273*, 1776–1777.

(9) For recent indolyne studies, see: (a) Bronner, S. M.; Bahnck, K. B.; Garg, N. K. *Org. Lett.* **2009**, *11*, 1007–1010. (b) Cheong, P. H.-Y.; Paton, R. S.; Bronner, S. M.; Im, G.-Y.; Garg, N. K.; Houk, K. N. *J. Am. Chem. Soc*. **2010**, *132*, 1267–1269. (c) Im, G.-Y.; 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. (d) Bronner, S. M.; Goetz, A. E.; Garg, N. K. *J. Am. Chem. Soc*. **2011**, *133*, 3832–3835. (e) Buszek, K. R.; Luo, D.; Kondrashov, M.; Brown, N.; VanderVelde, D. *Org. Lett*. **2007**, *9*, 4135–4137. (f) Brown, N.; Luo, D.; VanderVelde, D.; Yang, S.; Brassfield, A.; Buszek, K. R. *Tetrahedron Lett.* **2009**, *50*, 63–65. (g) Buszek, K. R.; Brown, N.; Luo, D. *Org. Lett.* **2009**, *11*, 201–204. (h) Brown, N.; Luo, D.; Decapo, J. A.; Buszek, K. R. *Tetrahedron Lett.* **2009**, *50*, 7113–7115. (i) Garr, A. N.; Luo, D.; Brown, N.; Cramer, C. J.; Buszek, K. R.; VanderVelde, D. *Org. Lett.* **2010**, *12*, 96–99. (j) Thornton, P. D.; Brown, N.; Hill, D.; Neunswander, B.; Lushington, G. H.; Santini, C.; Buszek, K. R. *ACS Comb. Sci*. **2011**, *13*, 443–448. (k) Nguyen, T. D.; Webster, R.; Lautens, M. *Org. Lett.* **2011**, *13*, 1370–1373.

(10) Sakagami, M.; Muratake, H.; Natsume, M. *Chem*. *Pharm*. *Bull*. **1994**, *42*, 1393–1398.

(11) Wang, S.-Y.; Ji, S.-J.; Loh, T.-P. *Synlett* **2003**, *15*, 2377–2379.

(12) The C15 epimer of **4.12** was also obtained in 22% yield. Upon treatment of this compound with DBU in heated toluene, a separable mixture of **4.12** and epi-**4.12** is readily obtained.

(13) Caubere, P. *Acc. Chem. Res.* **1974**, *7*, 301–308.

(14) Variations in reaction conditions (e.g., temperature, stoichiometry, counterion, etc.) did not lead to improvements in the conversion of **4.13** to **4.14**.

(15) The remaining balance of mass in the indolyne cyclization is largely attributed to aminoindole products, which presumably form by intermolecular addition of $^{-}NH_2$ to the indolyne intermediate. Attempts to suppress this undesired reaction pathway have been unsuccessful.

(16) *O*-arylated product **4.15** is often isolated with small amounts of the isomeric tetrasubstituted olefin.

(17) Interestingly, the C13 epimer of substrate **4.13** does not undergo conversion to the corresponding bicyclo[4.3.1]decane.

(18) Wulff, W. D.; Peterson, G. A.; Bauta, W. E.; Chan, K.-S.; Faron, K. L.; Gilbertson, S. R.; Kaesler, R. W.; Yang, D. C.; Murray, C. K. *J. Org. Chem*. **1986**, *51*, 277–279.

(19) Simpkins, S. M. E.; Kariuki, B. M.; Aricó, C. S.; Cox, L. R. *Org. Lett*. **2003**, *5*, 3971–3974.

(20) Exhaustive efforts to effect indolyne cyclization of substrates bearing *N*- or *C*-substituents at C11 were unsuccessful, thus preventing earlier installation of the C11 bridgehead functionality.

(21) Intermolecular functionalization methods that were tested include bridgehead enolate chemistry, nitrene insertion reactions, and radical halogenations.

(22) (a) Davies, H. M. L.; Manning, J. R. *Nature* **2008**, *451*, 417–424. (b) Collet, F.; Lescot, C.; Liang, C.; Dauban, P. *Dalton Trans.* **2010**, *39*, 10401–10413.

(23) For an elegant late-stage nitrene insertion in natural product total synthesis, see: Hinman, A.; Du Bois, J. *J. Am. Chem. Soc.* **2003**, *125*, 11510–11511.

(24) For intramolecular nitrene C–H insertion reactions using carbamate substrates, see: (a) Espino, C. G.; Du Bois, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 598–600. (b) Li, Z.; Capretto, D.

A.; Rahaman, R.; He, C. *Angew. Chem., Int. Ed.* **2007**, *46*, 5184–5186. (c) Cui, Y.; He, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 4210–4212.

(25) Ketone **4.4** likely forms by a pathway involving initial insertion into the α C–H bond; for related observations, see: Hinman, A. W. Ph.D. Dissertation, Stanford University, Stanford, CA, 2004.

(26) Kim, S.; Yi, K. Y. *J. Org. Chem.* **1986**, *51*, 2613–2615.

(27) A sample of natural **4.1** was not available for direct comparison.

(28) Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem.* **1999**, *64*, 4537–4538.

(29) Niu, C.; Pettersson, T.; Miller, M. J. *J. Org. Chem.* **1996**, *61*, 1014–1022.

(30) For compound **4.1** the ^{1}H NMR residual solvent peak is set to 7.24 ppm and the ^{13}C NMR residual solvent peak is set to 77.0 ppm to match the reference values set in the isolation paper.

(31) Sakagami, M.; Muratake, H.; Natsume, M. *Chem*. *Pharm*. *Bull*. **1994**, *42*, 1393–1398.

(32) **4.9** is commercially available, or can be easily prepared in one step from 5-bromoindole on multigram scale; see: Jiang, X.; Tiwari, A.; Thompson, M.; Chen, Z.; Cleary, T. P.; Lee, T. B. K. *Org. Proc. Res. Dev*. **2001**, *5*, 604–608.

(33) Reported values for specific rotations can be highly variable; for a pertinent discussion, see: Gawley, R. E. *J. Org. Chem.* **2006**, *71*, 2411–2416.

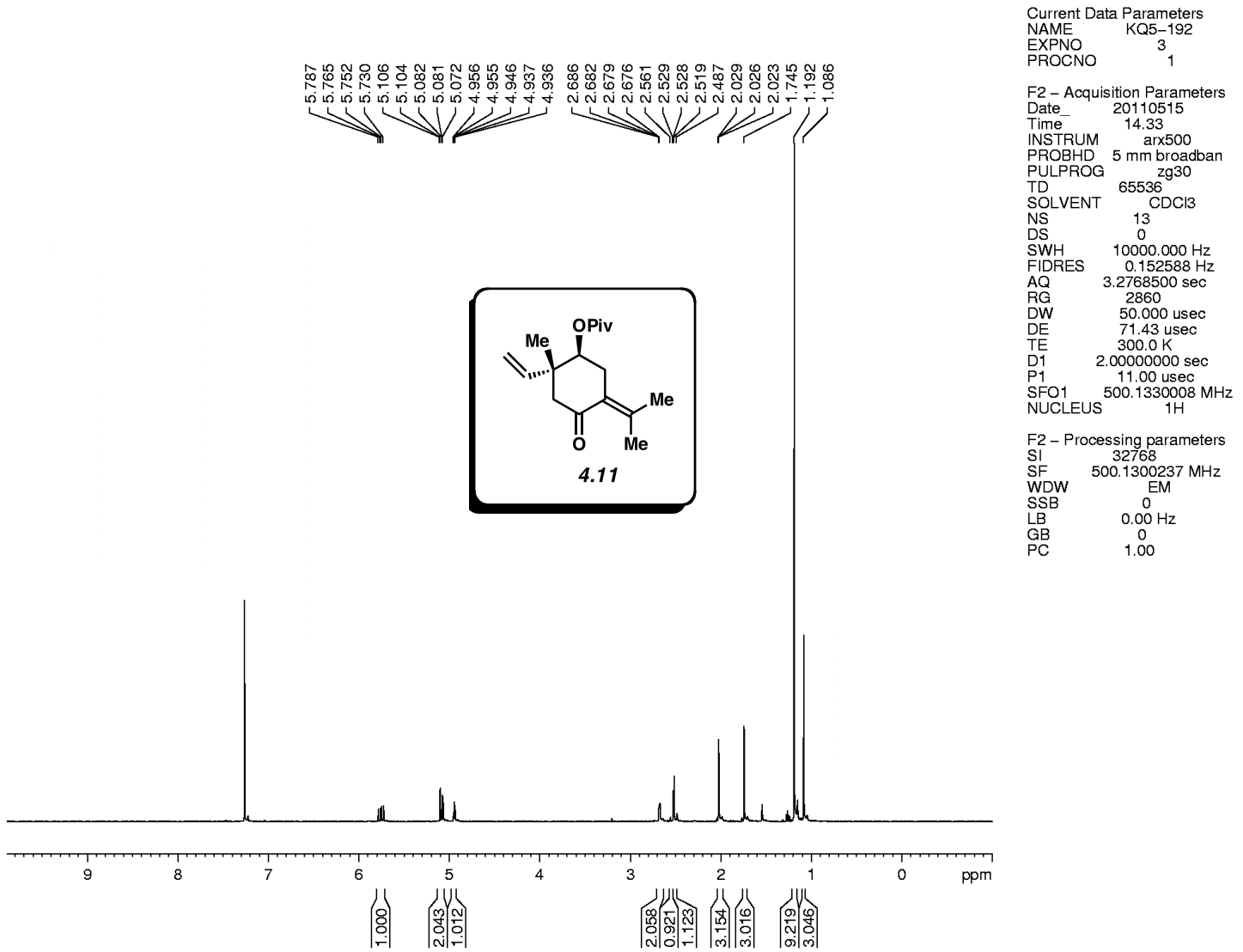
APPENDIX THREE

Spectra Relevant to Chapter Four:

Total Synthesis of (–)-*N*-Methylwelwitindolinone C Isothiocyanate

Alexander D. Huters, Kyle W. Quasdorf, Evan D. Styduhar, and Neil K. Garg.

J. Am. Chem. Soc. **2011**, *133*, 15797–15799.



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NAME KQ5–192
EXPNO 3
PROCNO 1

F2 – Acquisition Parameters
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Time 14.33
INSTRUM arx500
PROBHD 5 mm broadban
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 13
DS 0
SWH 10000.000 Hz
FIDRES 0.152588 Hz
AQ 3.2768500 sec
RG 2860
DW 50.000 usec
DE 71.43 usec
TE 300.0 K
D1 2.00000000 sec
P1 11.00 usec
SFO1 500.1330008 MHz
NUCLEUS 1H

F2 – Processing parameters
SI 32768
SF 500.1300237 MHz
WDW EM
SSB 0
LB 0.00 Hz
GB 0
PC 1.00

Figure A3.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.11**.

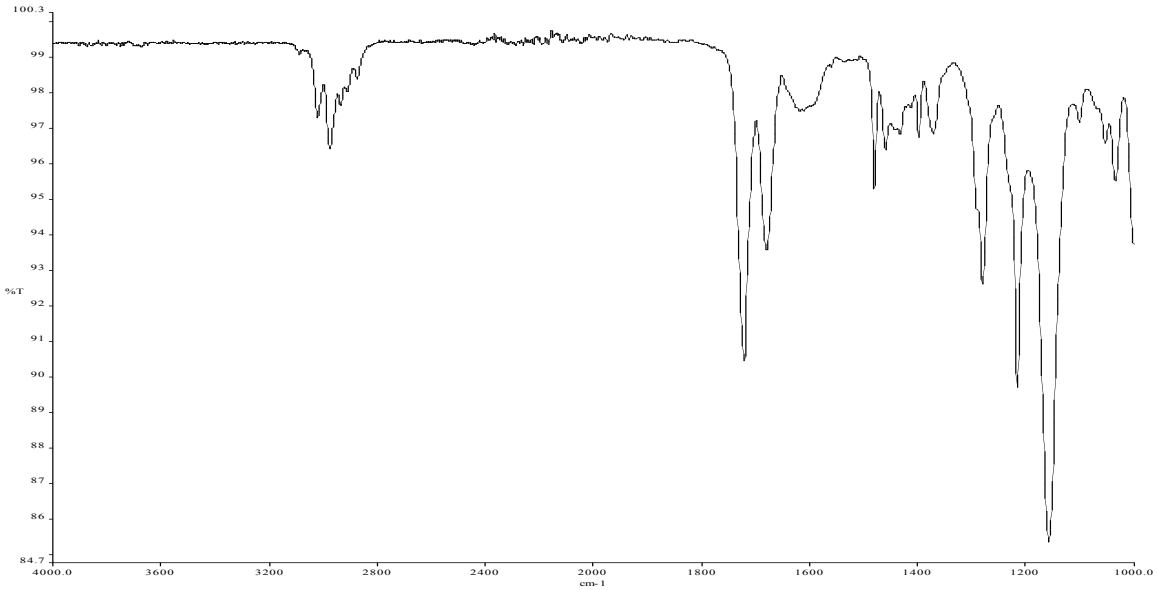


Figure A3.2 Infrared spectrum of compound **4.11**.

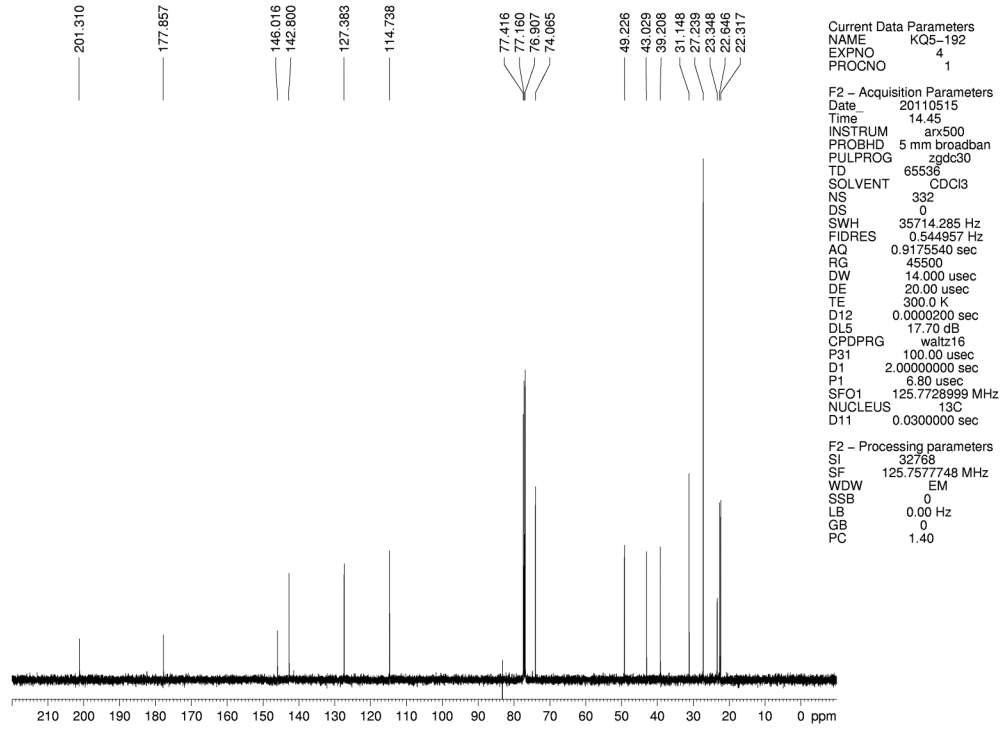
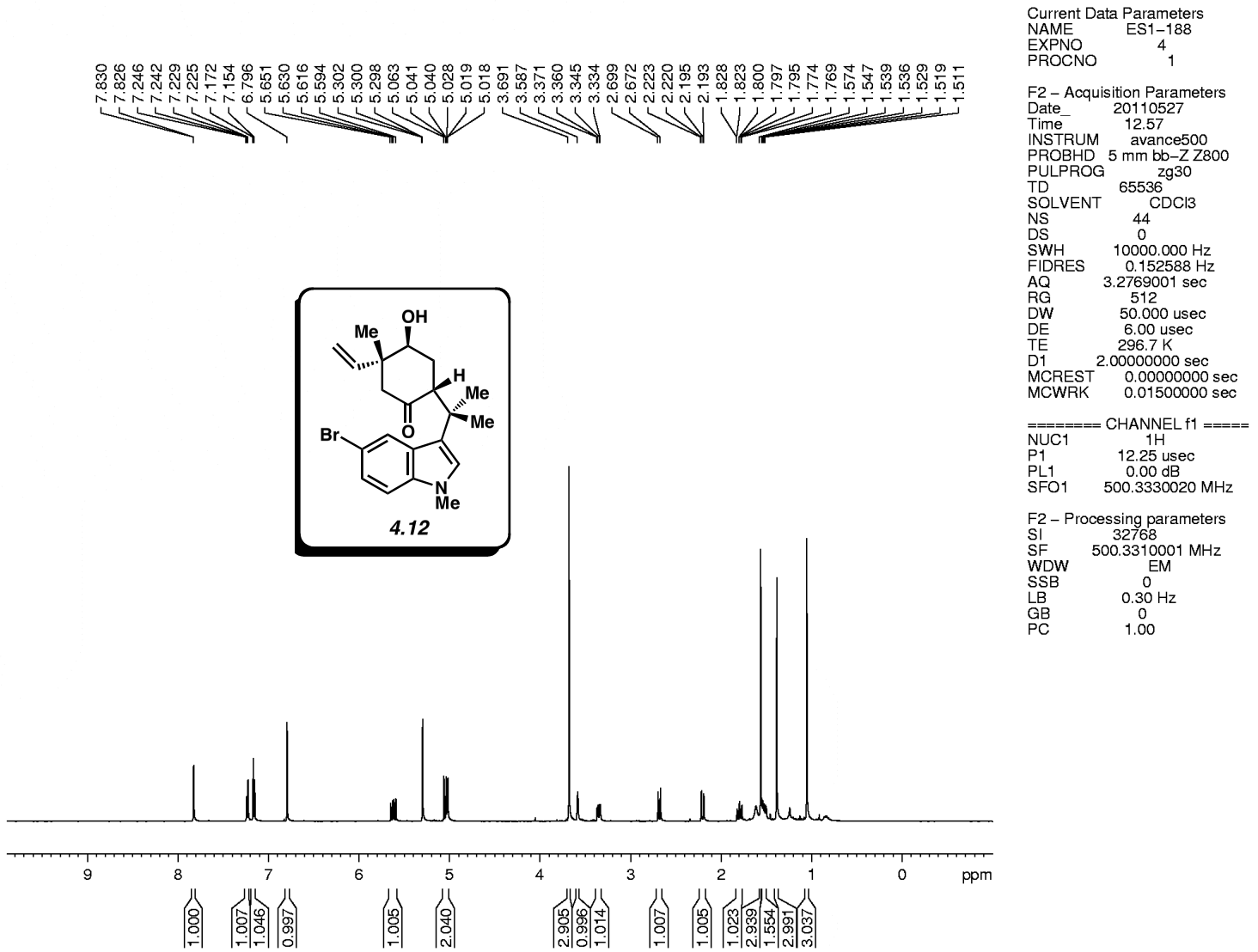


Figure A3.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4.11**.



Current Data Parameters
NAME ES1–188
EXPNO 4
PROCNO 1

F2 – Acquisition Parameters
Date_ 20110527
Time 12.57
INSTRUM avance500
PROBHD 5 mm bb–Z Z800
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 44
DS 0
SWH 10000.000 Hz
FIDRES 0.152588 Hz
AQ 3.2769001 sec
RG 512
DW 50.000 usec
DE 6.00 usec
TE 296.7 K
D1 2.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

======== CHANNEL f1 =====
NUC1 1H
P1 12.25 usec
PL1 0.00 dB
SFO1 500.3330020 MHz

F2 – Processing parameters
SI 32768
SF 500.3310001 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

Figure A3.4 ^{1}H NMR (500 MHz, CD_2Cl_2) of compound **4.12**.

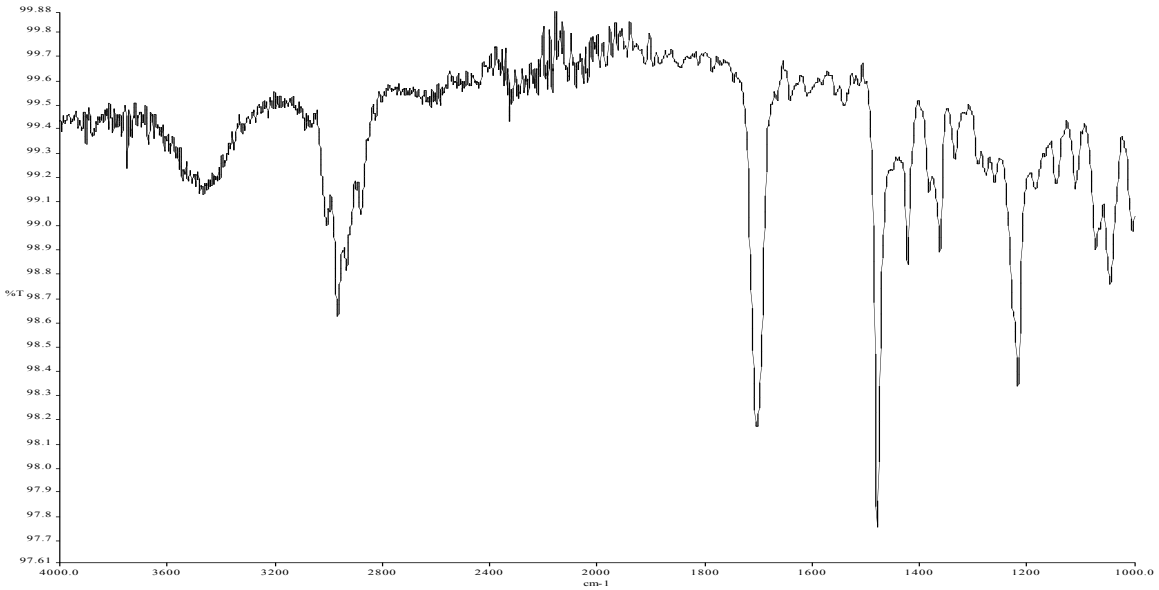


Figure A3.5 Infrared spectrum of compound **4.12**.

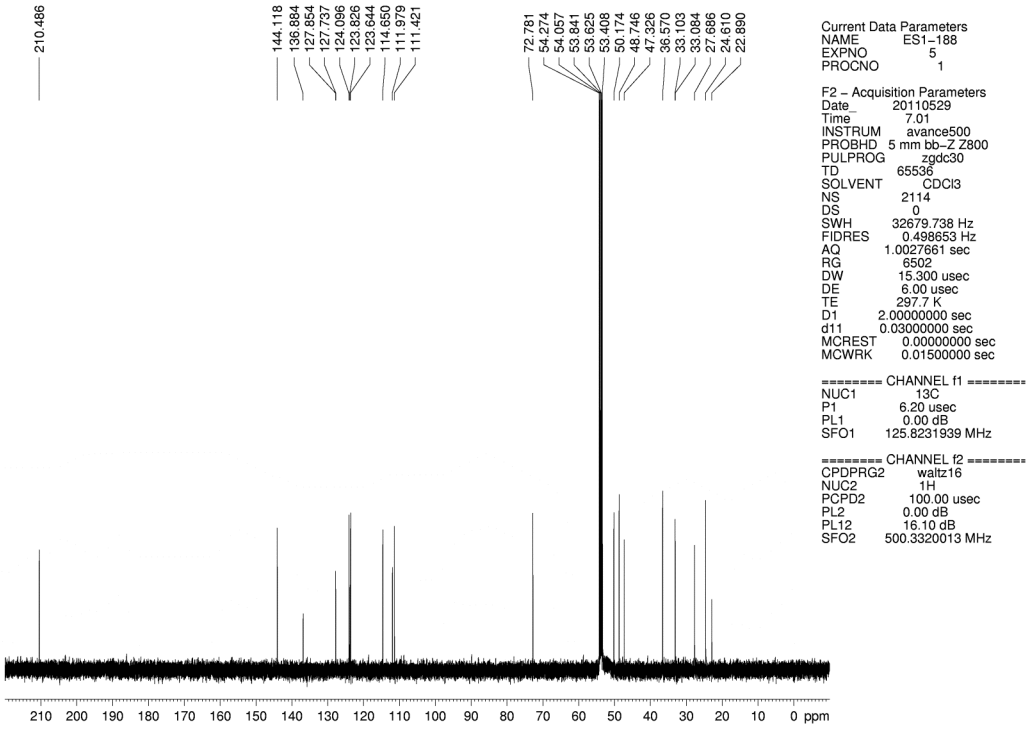


Figure A3.6 ^{13}C NMR (125 MHz, CD_2Cl_2) of compound **4.12**.

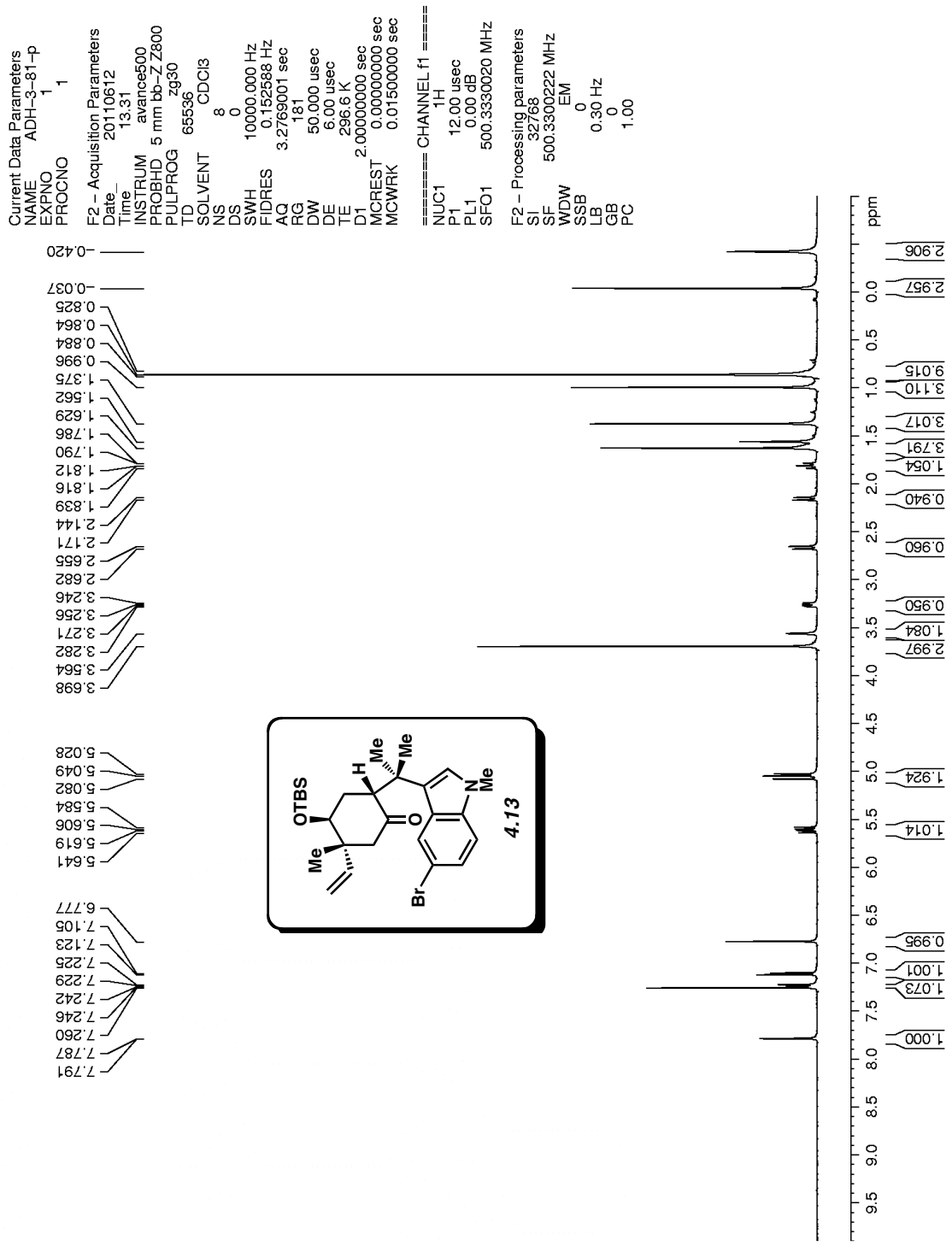


Figure A3.7 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.13**.

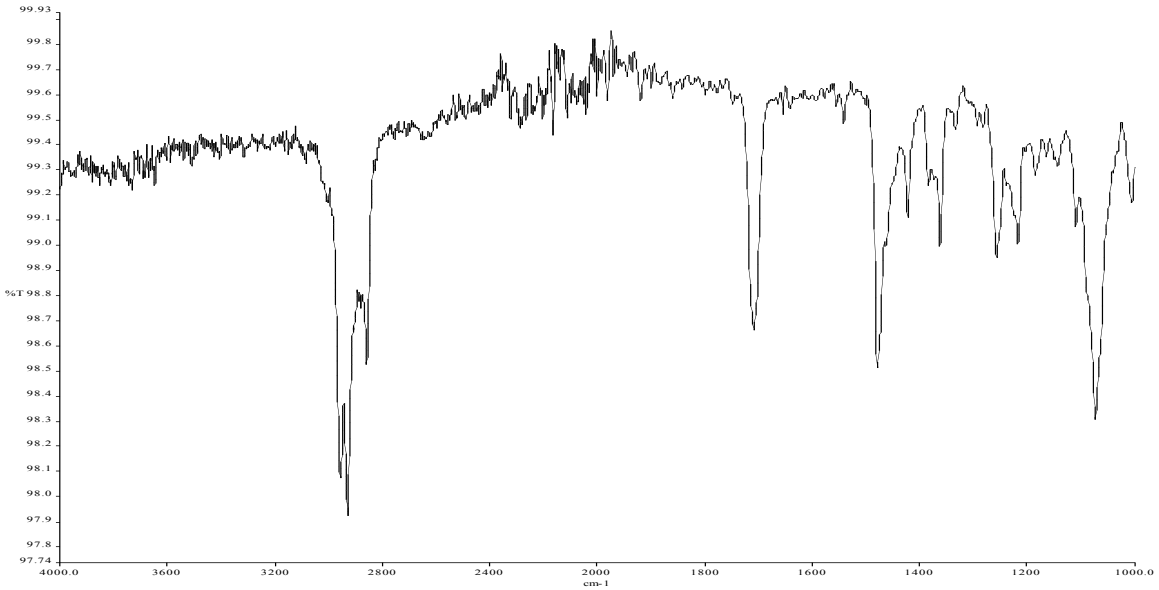


Figure A3.8 Infrared spectrum of compound **4.13**.

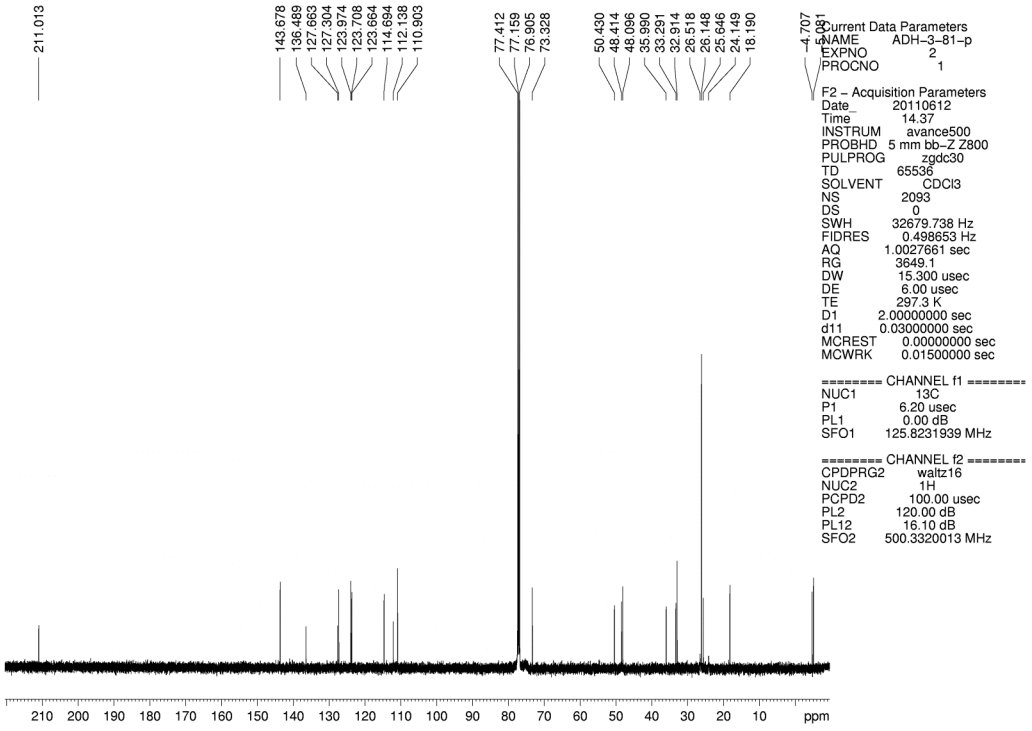


Figure A3.9 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4.13**.

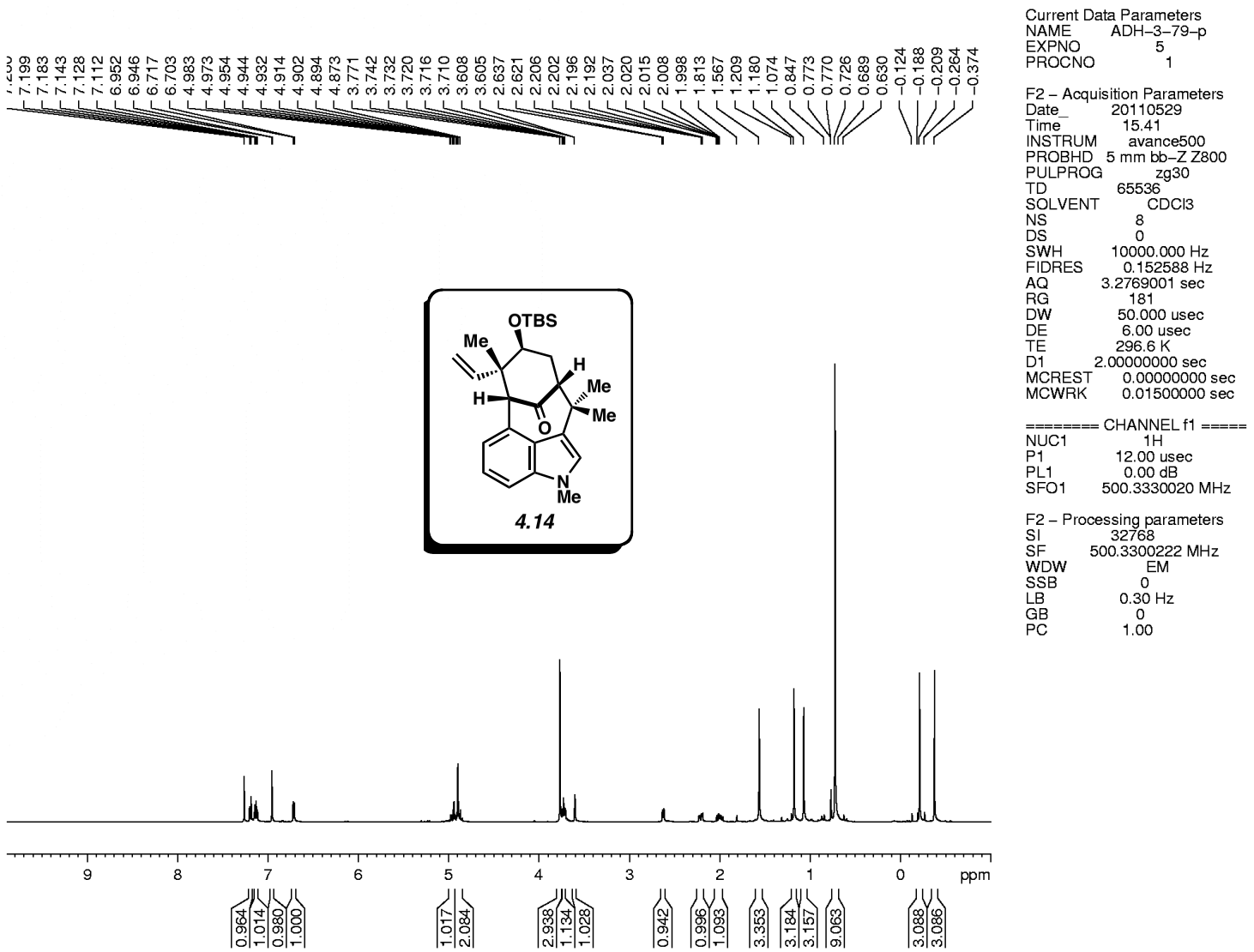


Figure A3.10 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.14**.

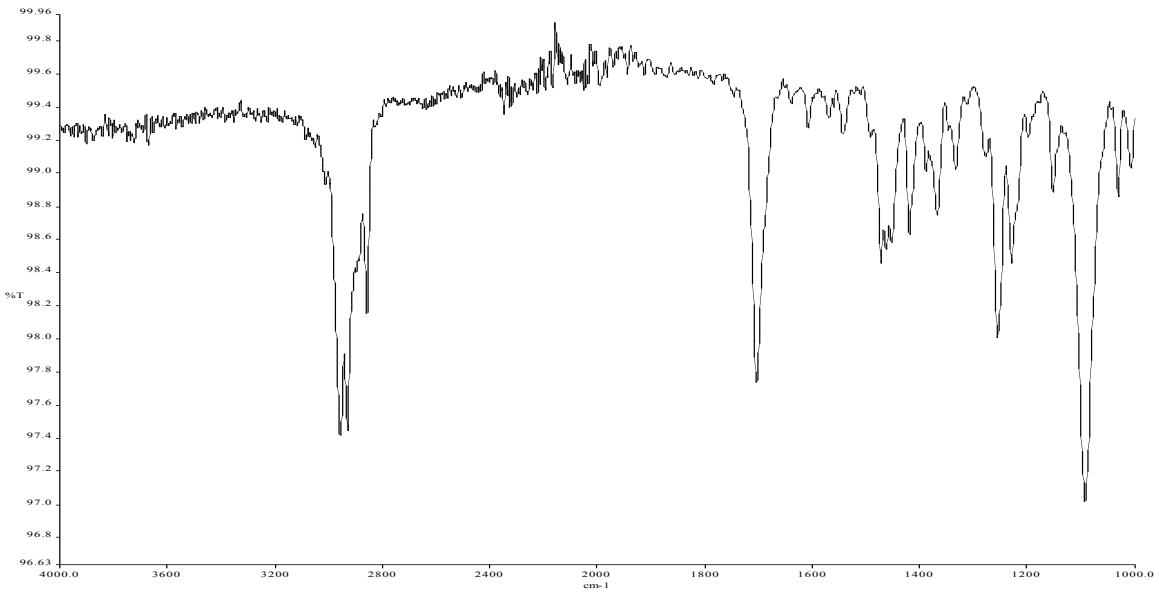


Figure A3.11 Infrared spectrum of compound **4.14**.

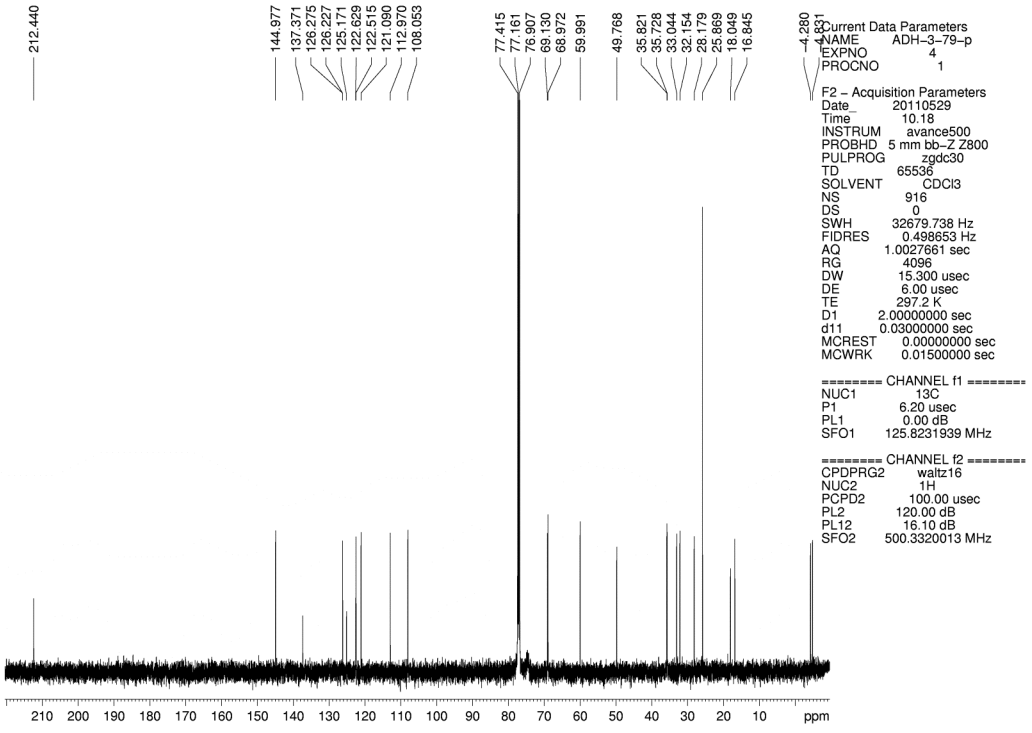
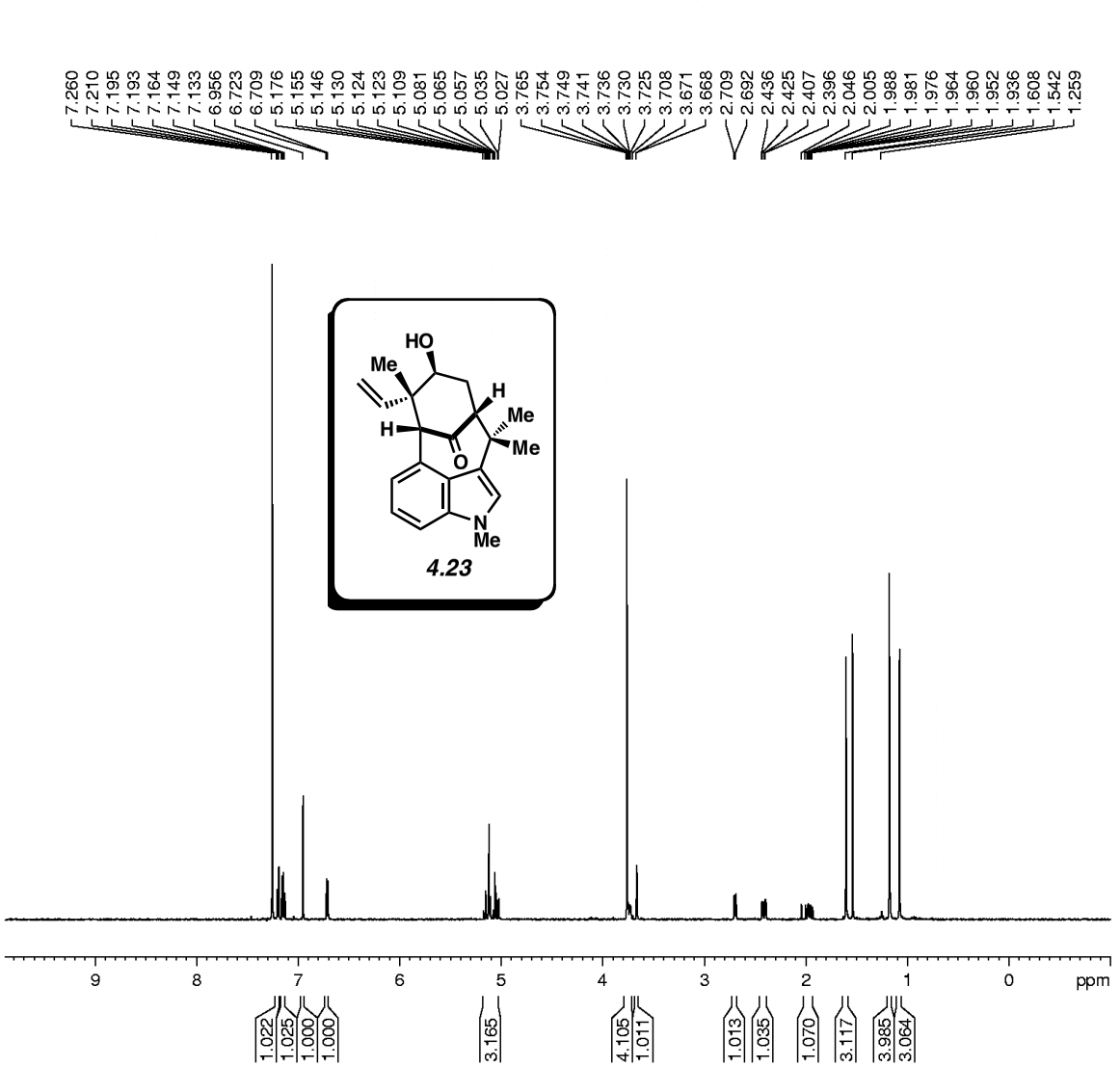


Figure A3.12 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4.14**.



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EXPNO 1
PROCNO 1

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PULPROG zg30
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SOLVENT CDCl3
NS 8
DS 0
SWH 10000.000 Hz
FIDRES 0.152588 Hz
AQ 3.2768500 sec
RG 4096
DW 50.000 usec
DE 71.43 usec
TE 300.0 K
D1 2.00000000 sec
P1 11.00 usec
SFO1 500.1330008 MHz
NUCLEUS 1H

F2 – Processing parameters
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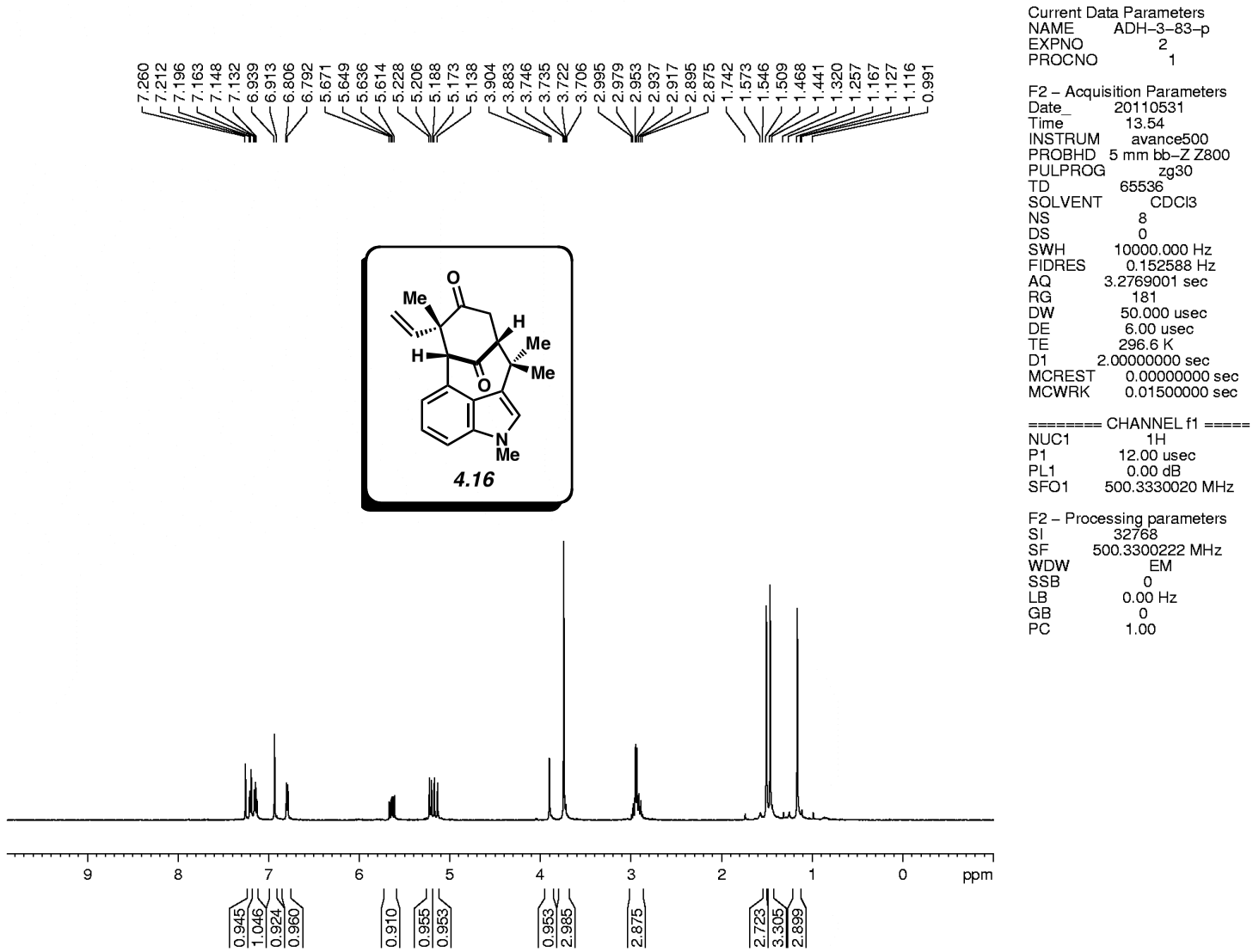
SF 500.1300237 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

Figure A3.13 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.23**.



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PROCNO 1

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NS 8
DS 0
SWH 10000.000 Hz
FIDRES 0.152588 Hz
AQ 3.2769001 sec
RG 181
DW 50.000 usec
DE 6.00 usec
TE 296.6 K
D1 2.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

======== CHANNEL f1 =====
NUC1 1H
P1 12.00 usec
PL1 0.00 dB
SFO1 500.3330020 MHz

F2 – Processing parameters
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SF 500.3300222 MHz
WDW EM
SSB 0
LB 0.00 Hz
GB 0
PC 1.00

Figure A3.14 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.16**.

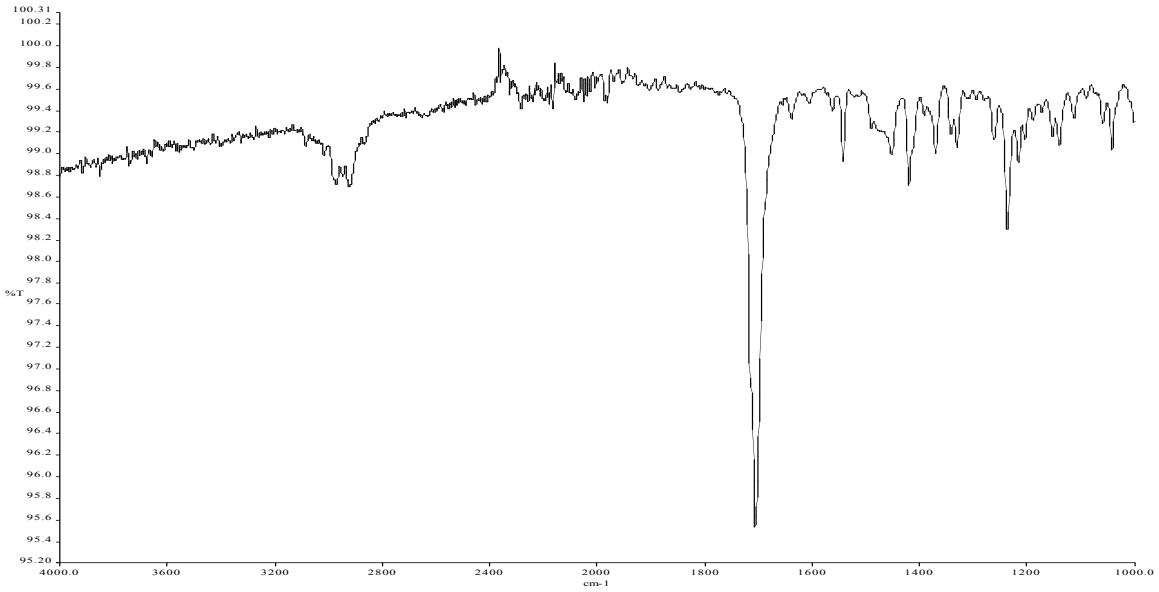


Figure A3.15 Infrared spectrum of compound **4.16**.

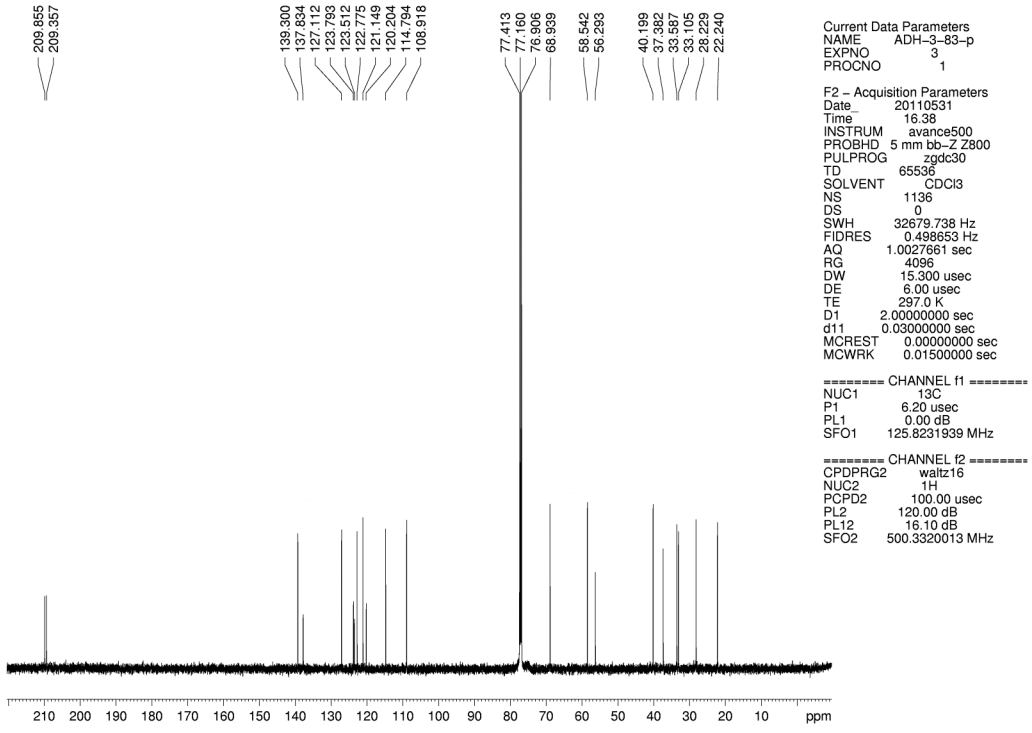
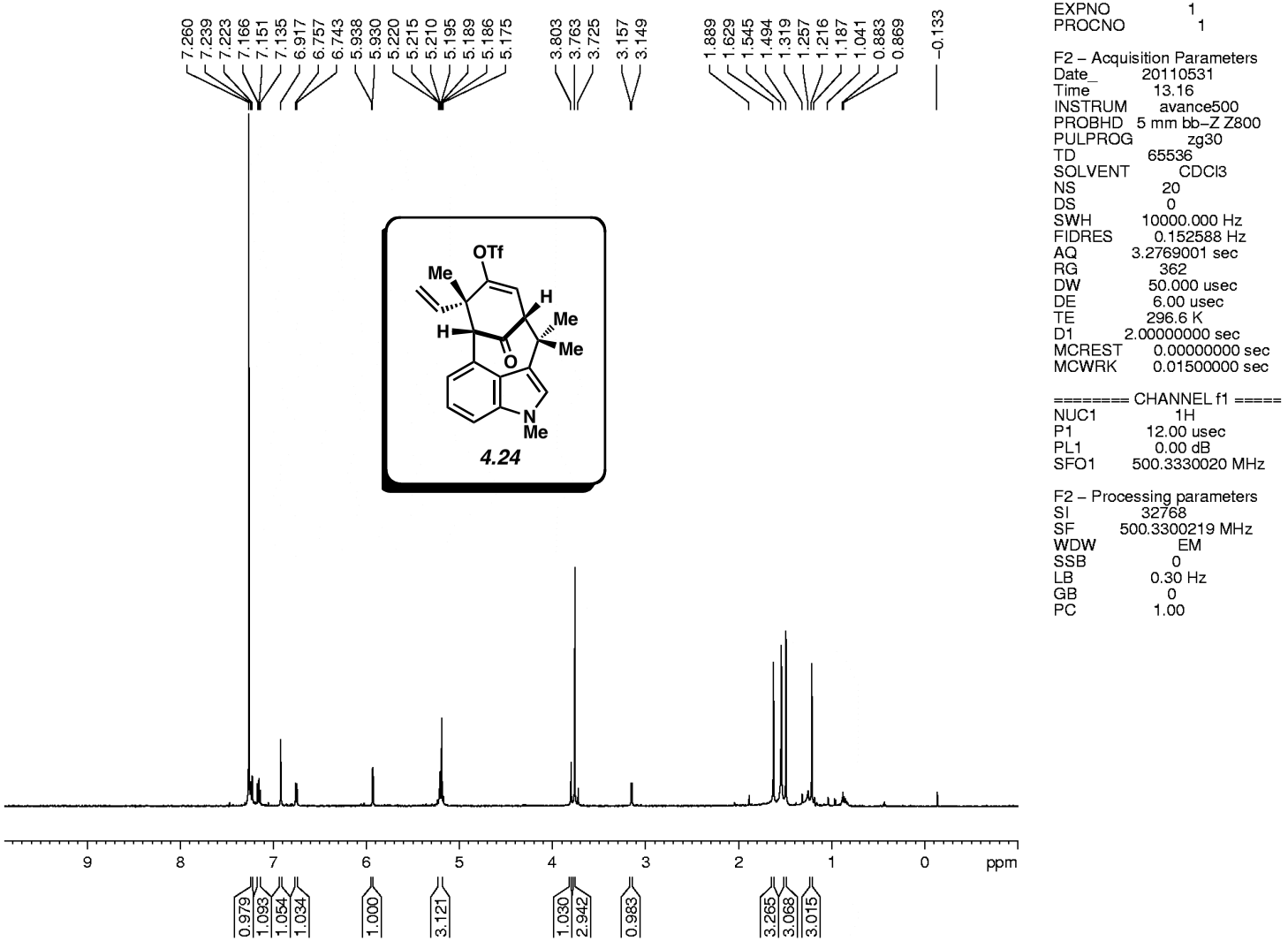


Figure A3.16 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4.16**.



Current Data Parameters
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EXPNO 1
PROCNO 1

F2 – Acquisition Parameters
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PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 20
DS 0
SWH 10000.000 Hz
FIDRES 0.152588 Hz
AQ 3.2769001 sec
RG 362
DW 50.000 usec
DE 6.00 usec
TE 296.6 K
D1 2.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

======== CHANNEL f1 =====
NUC1 1H
P1 12.00 usec
PL1 0.00 dB
SFO1 500.3330020 MHz

F2 – Processing parameters
SI 32768
SF 500.3300219 MHz
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LB 0.30 Hz
GB 0
PC 1.00

Figure A3.17 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.24**.

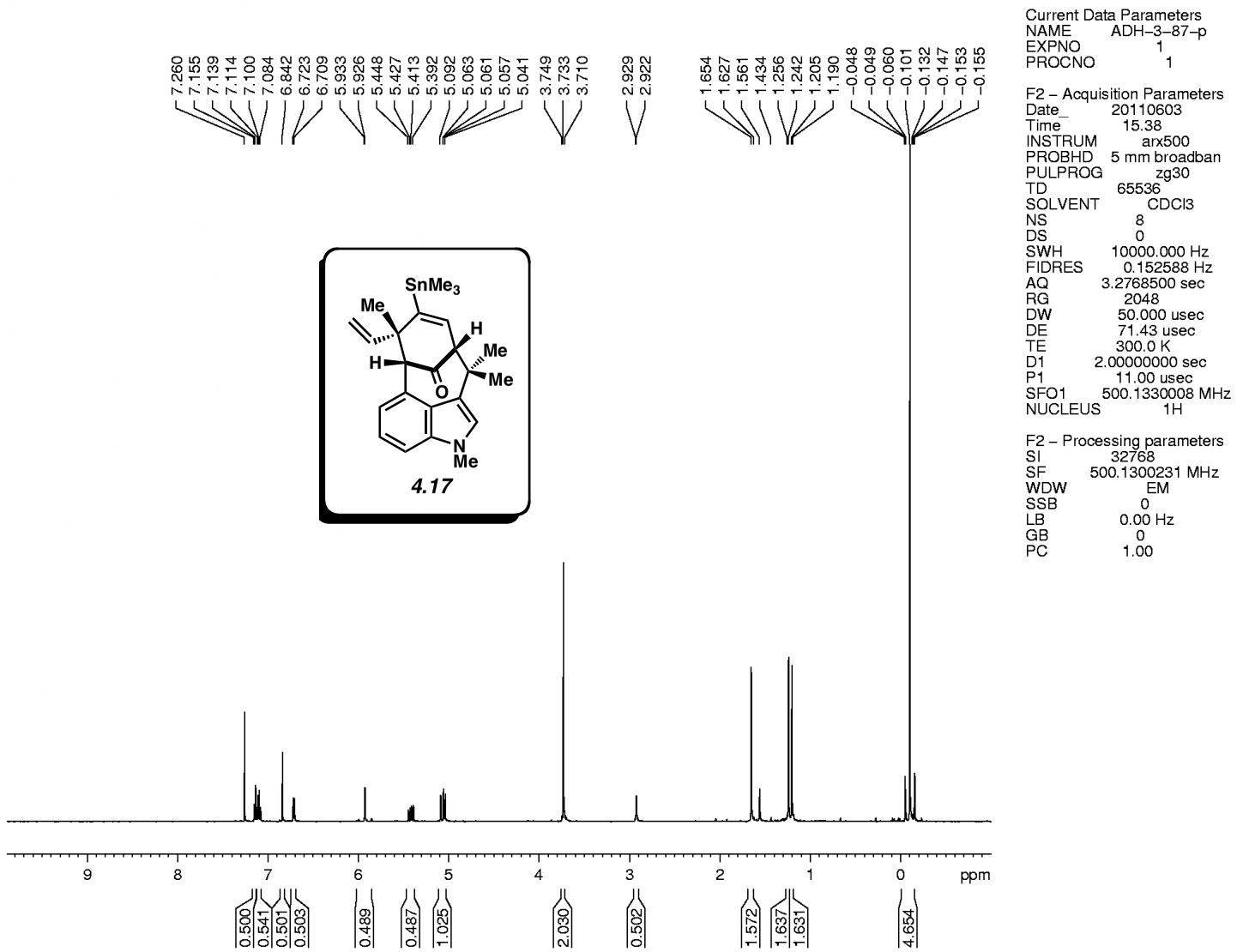


Figure A3.18 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.17**.

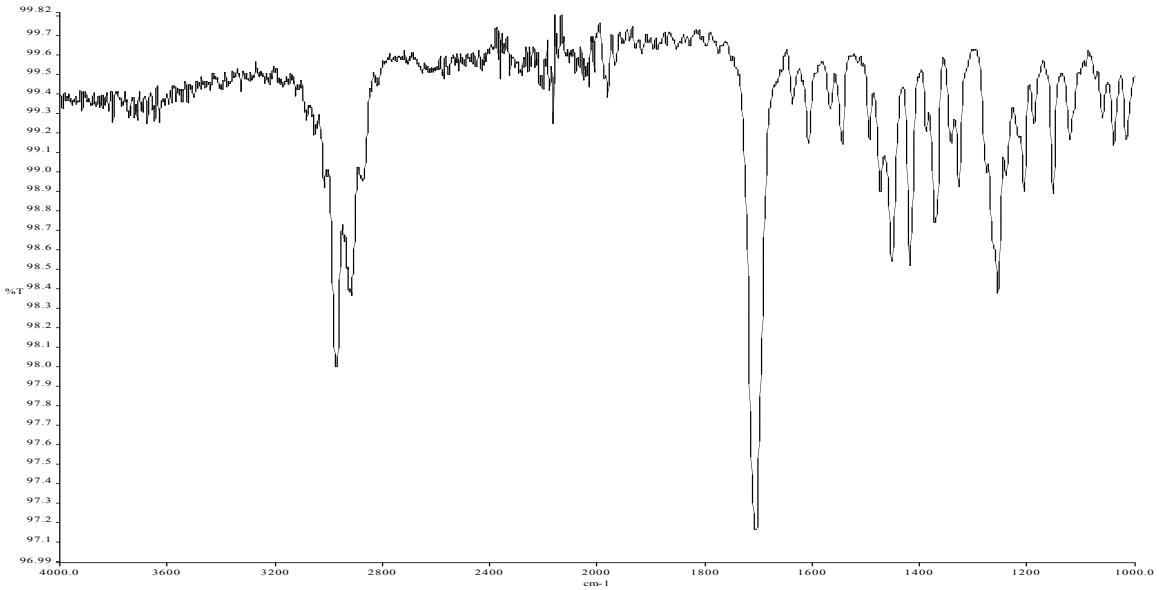


Figure A3.19 Infrared spectrum of compound **4.17**.

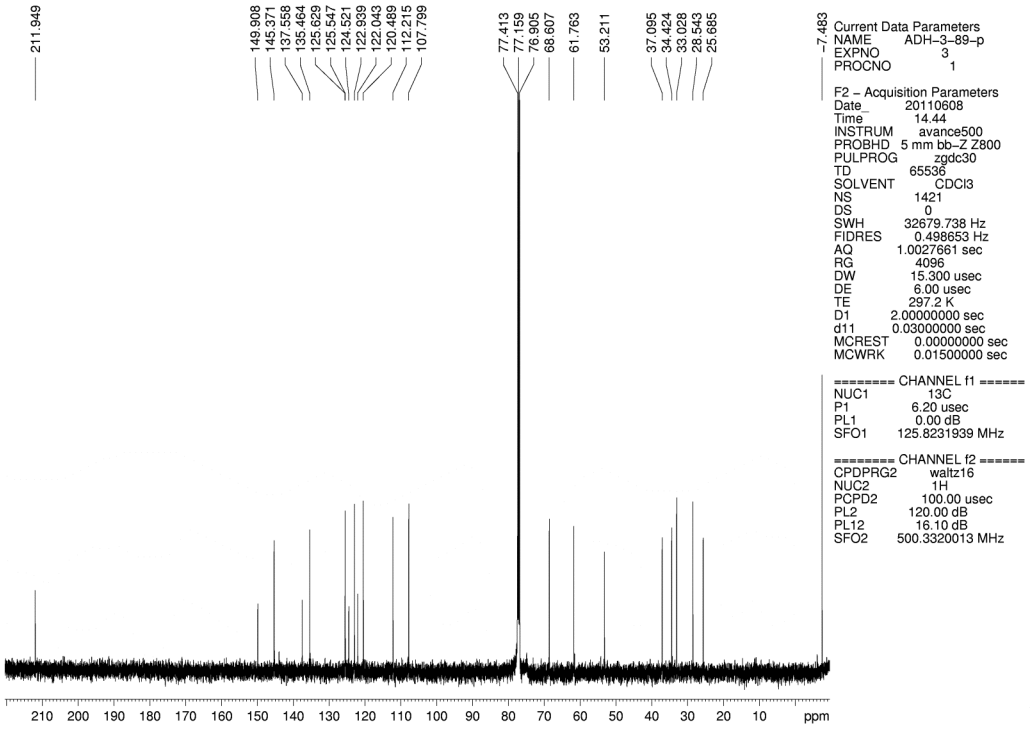
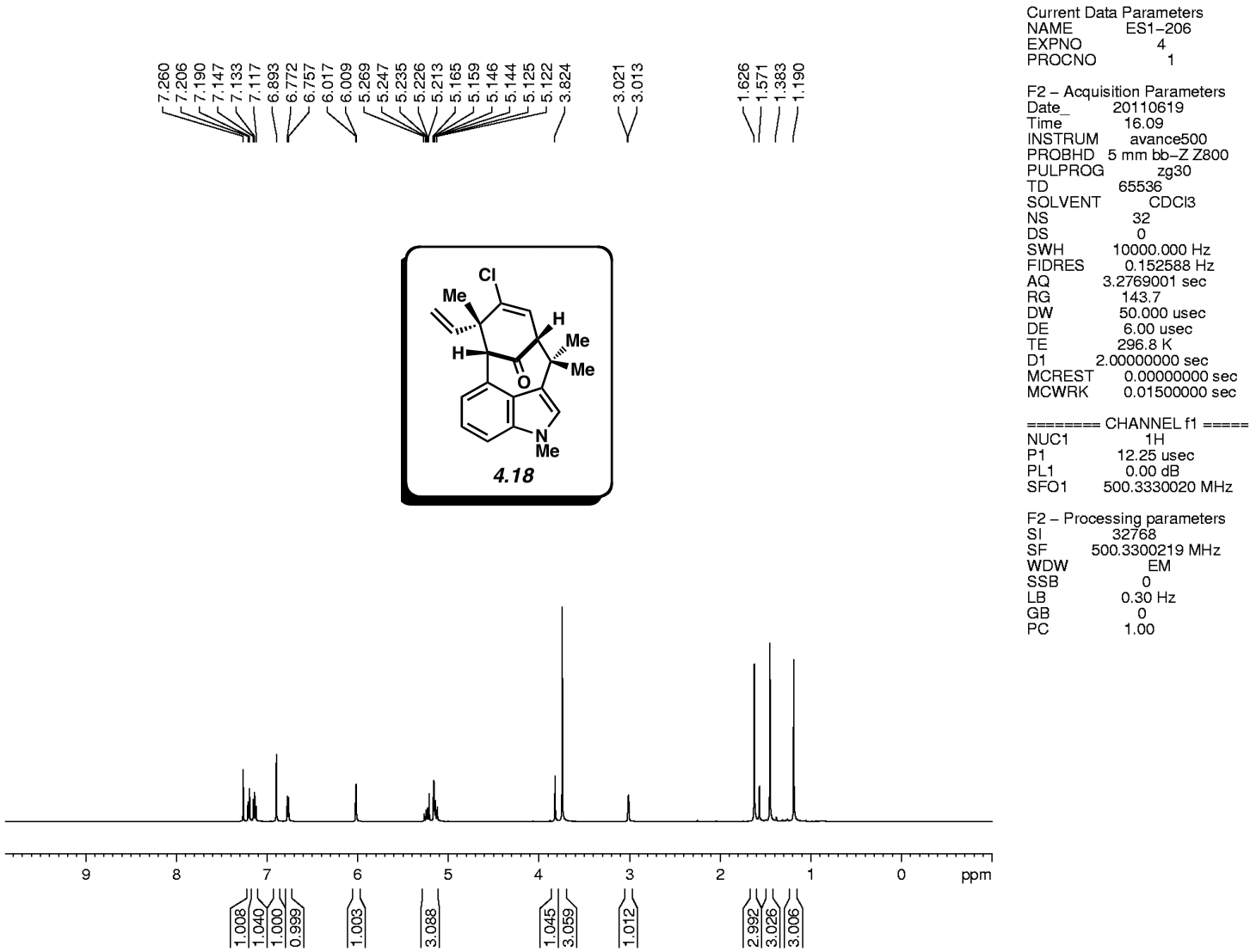


Figure A3.20 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4.17**.



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PROCNO 1

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FIDRES 0.152588 Hz
AQ 3.2769001 sec
RG 143.7
DW 50.000 usec
DE 6.00 usec
TE 296.8 K
D1 2.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

======== CHANNEL f1 =====
NUC1 1H
P1 12.25 usec
PL1 0.00 dB
SFO1 500.3330020 MHz

F2 – Processing parameters
SI 32768
SF 500.3300219 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

Figure A3.21 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.18**.

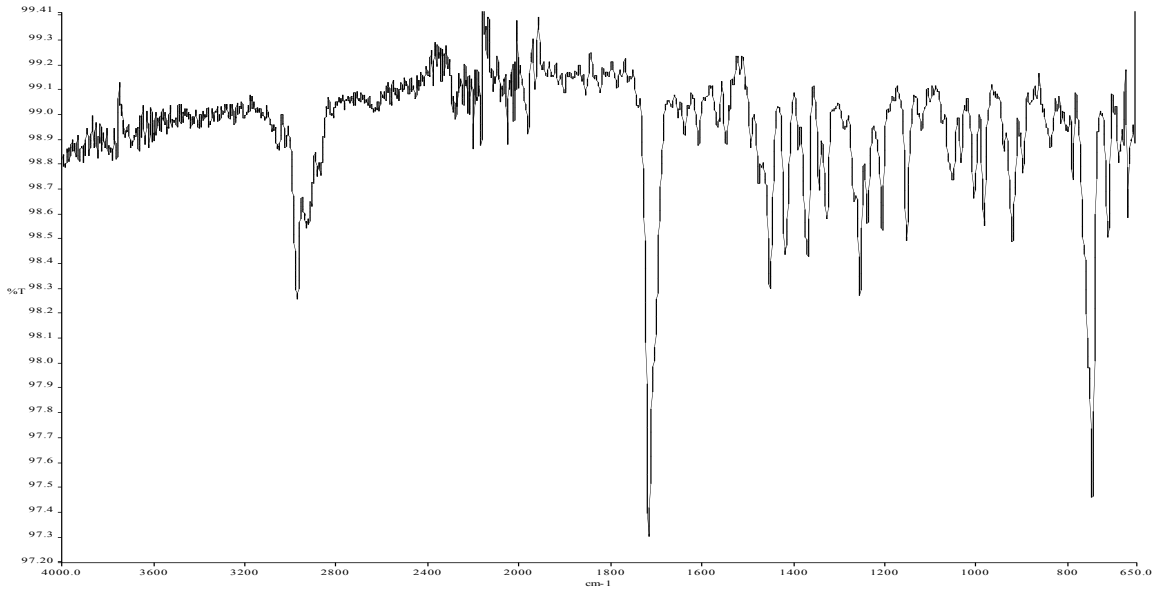


Figure A3.22 Infrared spectrum of compound **4.18**.

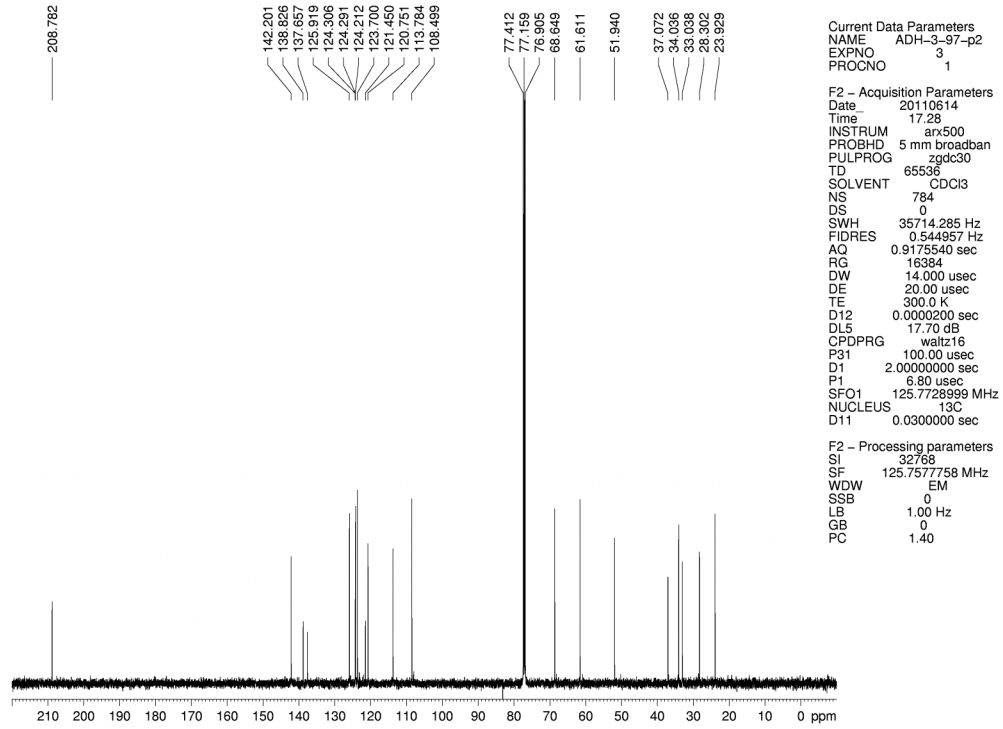
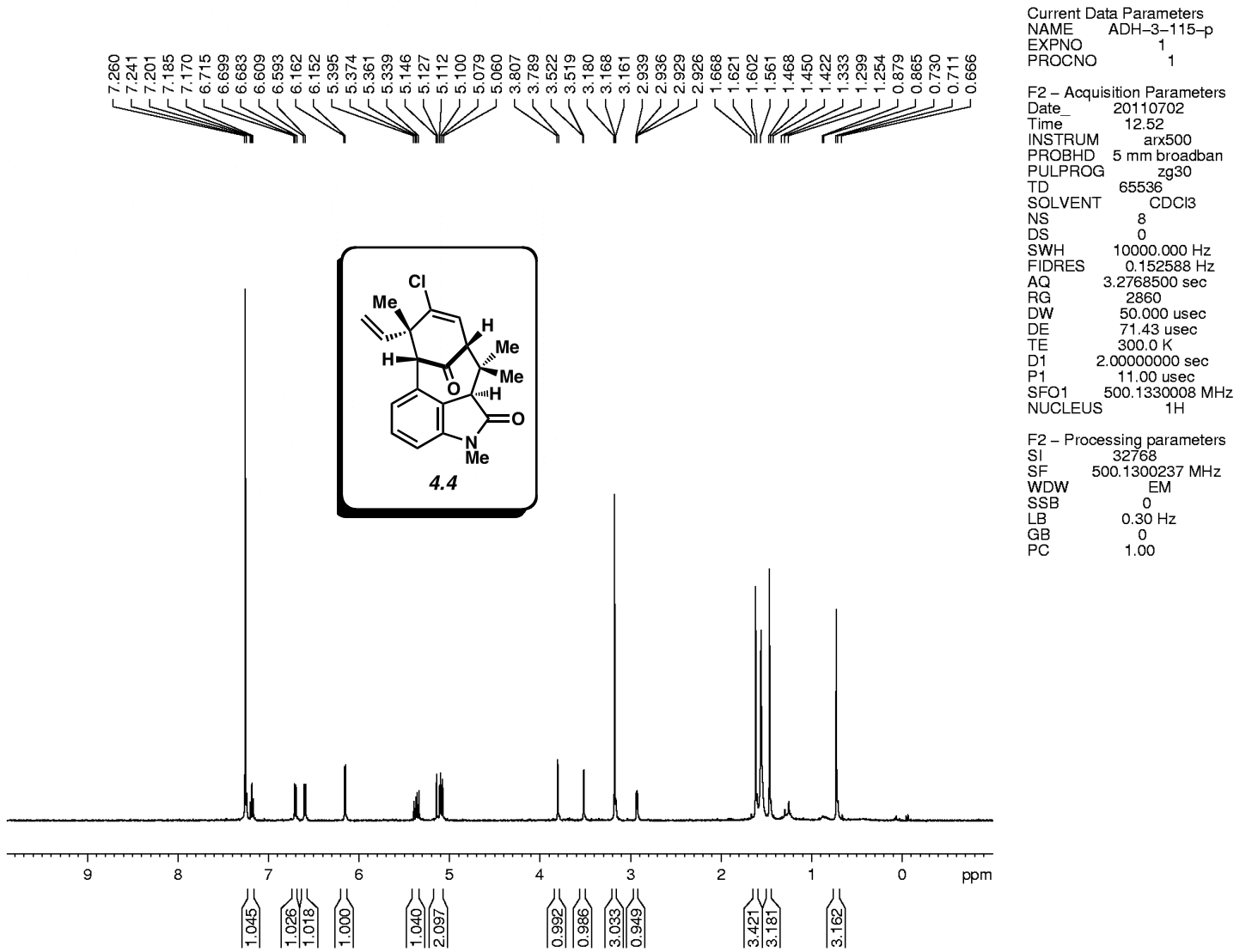


Figure A3.23 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4.18**.



Current Data Parameters
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PROCNO 1

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SOLVENT CDCl3
NS 8
DS 0
SWH 10000.000 Hz
FIDRES 0.152588 Hz
AQ 3.2768500 sec
RG 2860
DW 50.000 usec
DE 71.43 usec
TE 300.0 K
D1 2.00000000 sec
P1 11.00 usec
SFO1 500.1330008 MHz
NUCLEUS 1H

F2 – Processing parameters
SI 32768
SF 500.1300237 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

Figure A3.24 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.4**.

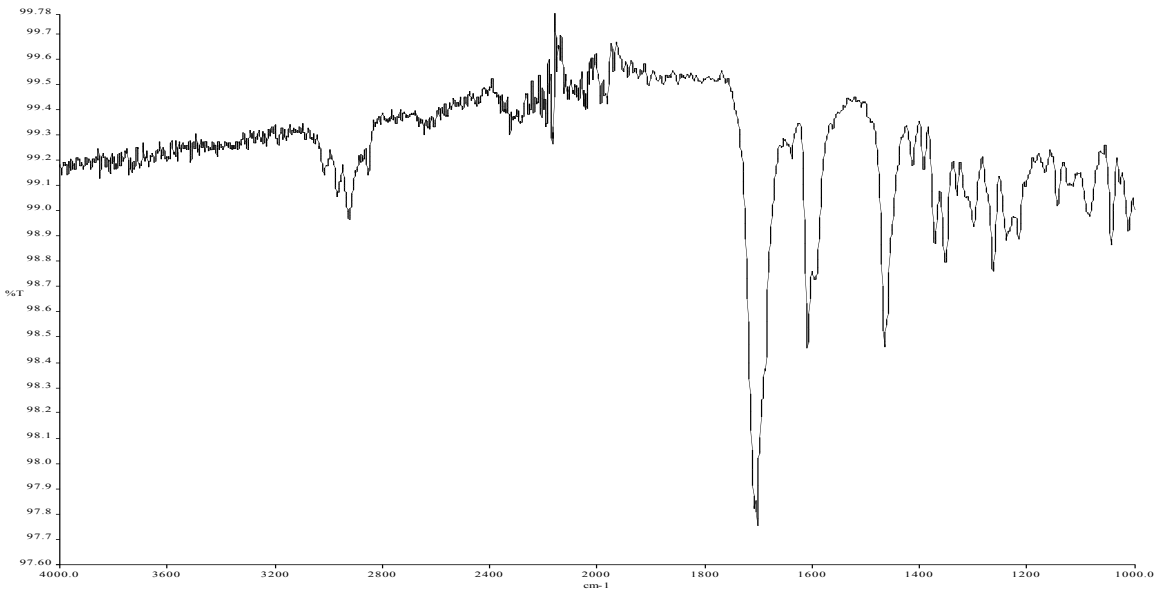


Figure A3.25 Infrared spectrum of compound **4.4**.

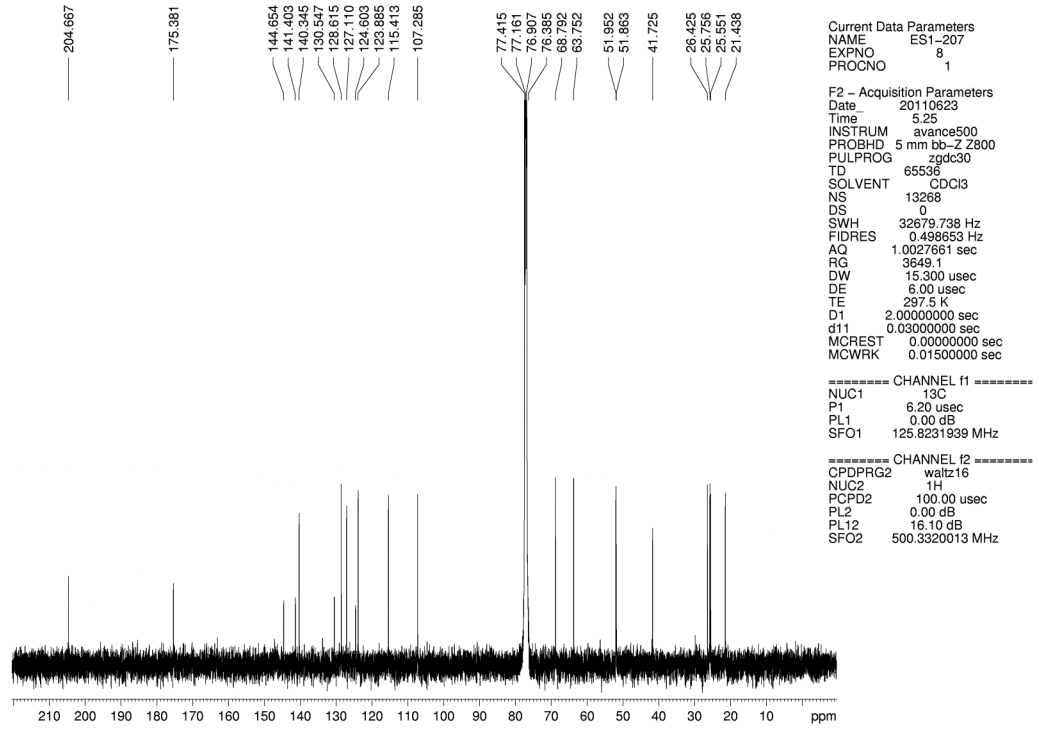
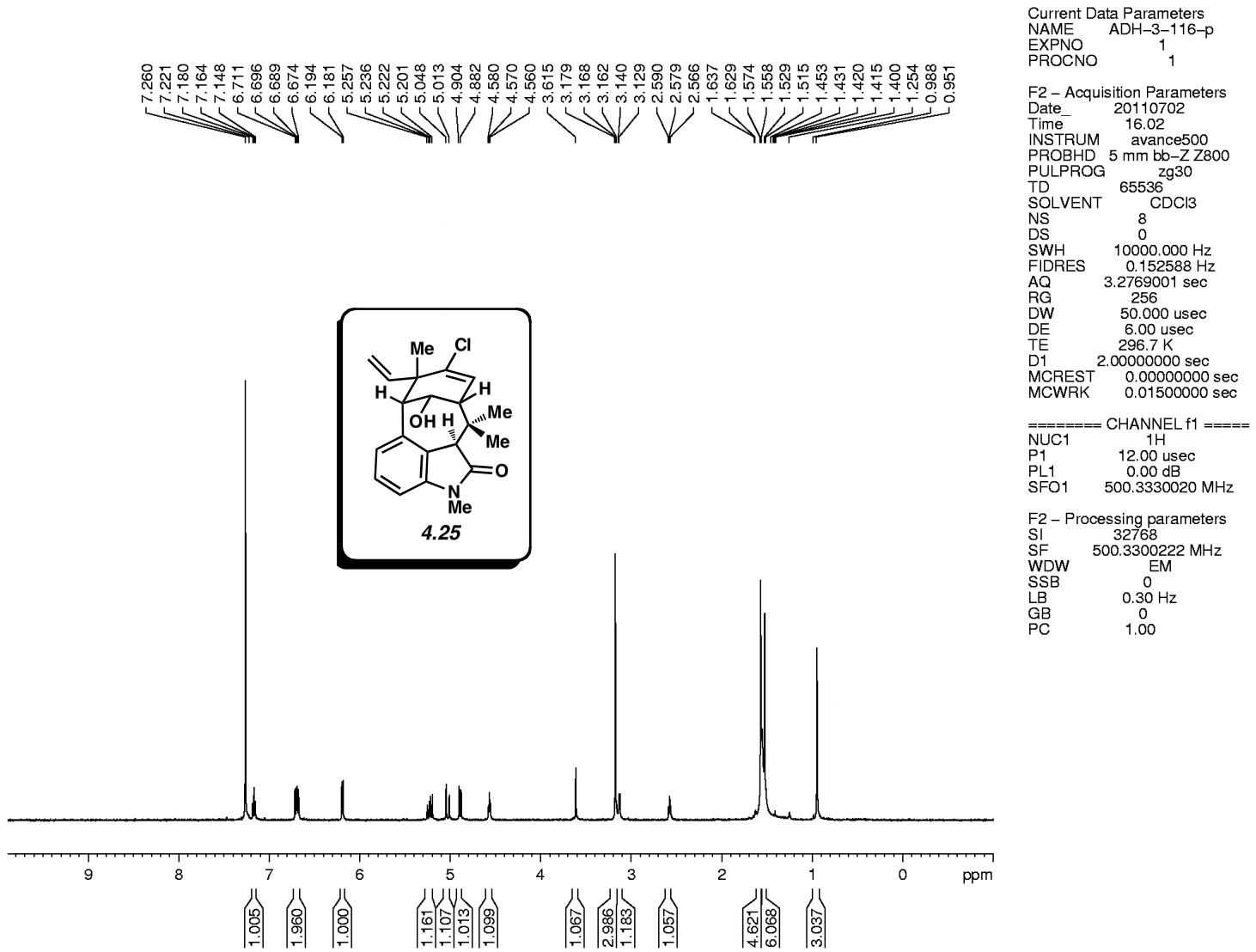


Figure A3.26 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4.4**.



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PROCNO 1

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RG 256
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DE 6.00 usec
TE 296.7 K
D1 2.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

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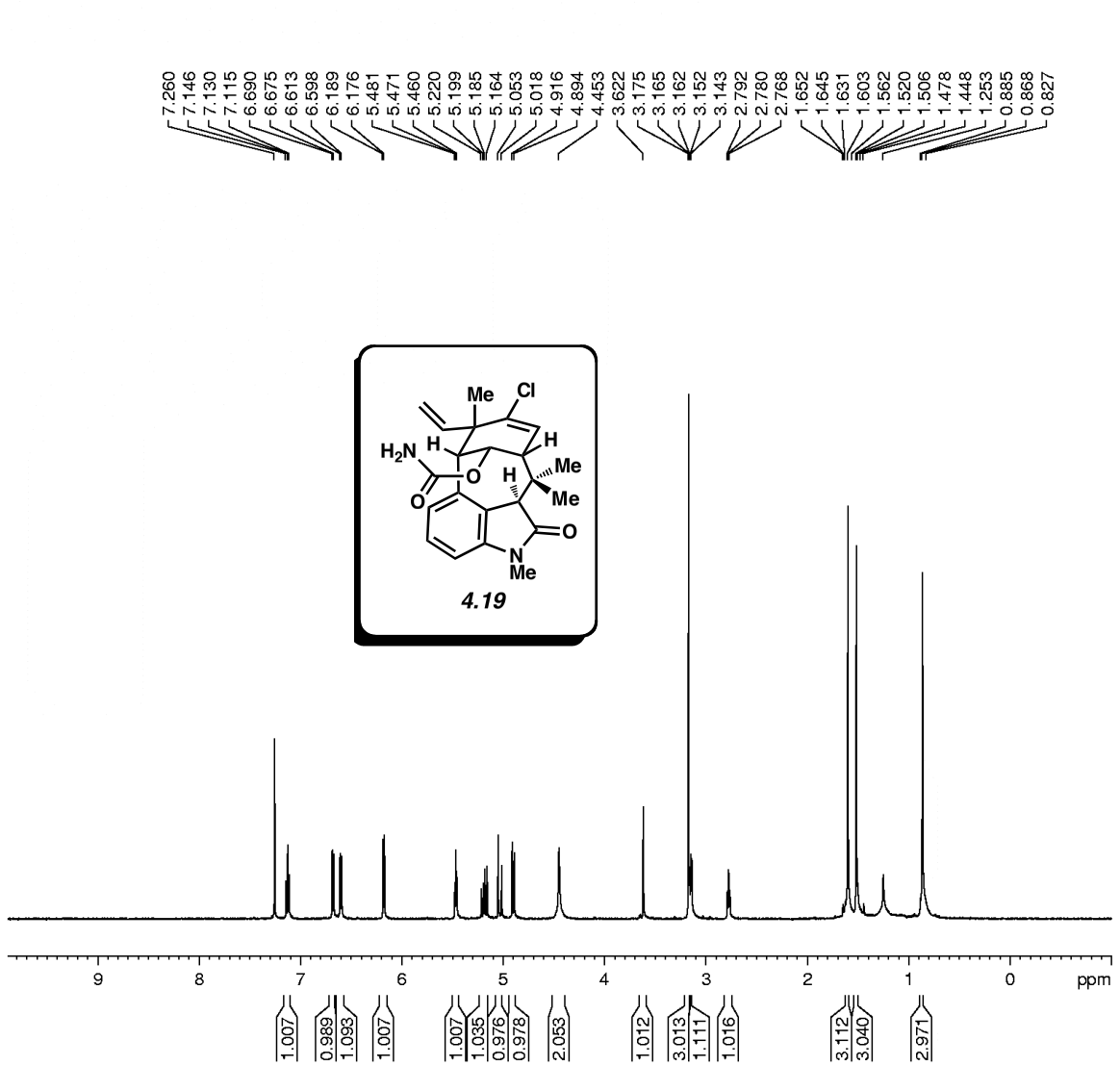
GB 0
PC 1.00

Figure A3.27 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.25**.



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PROCNO 1

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FIDRES 0.152588 Hz
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======== CHANNEL f1 =====
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P1 12.00 usec
PL1 0.00 dB
SFO1 500.3330020 MHz

F2 – Processing parameters
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GB 0
PC 1.00

Figure A3.28 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.19**.

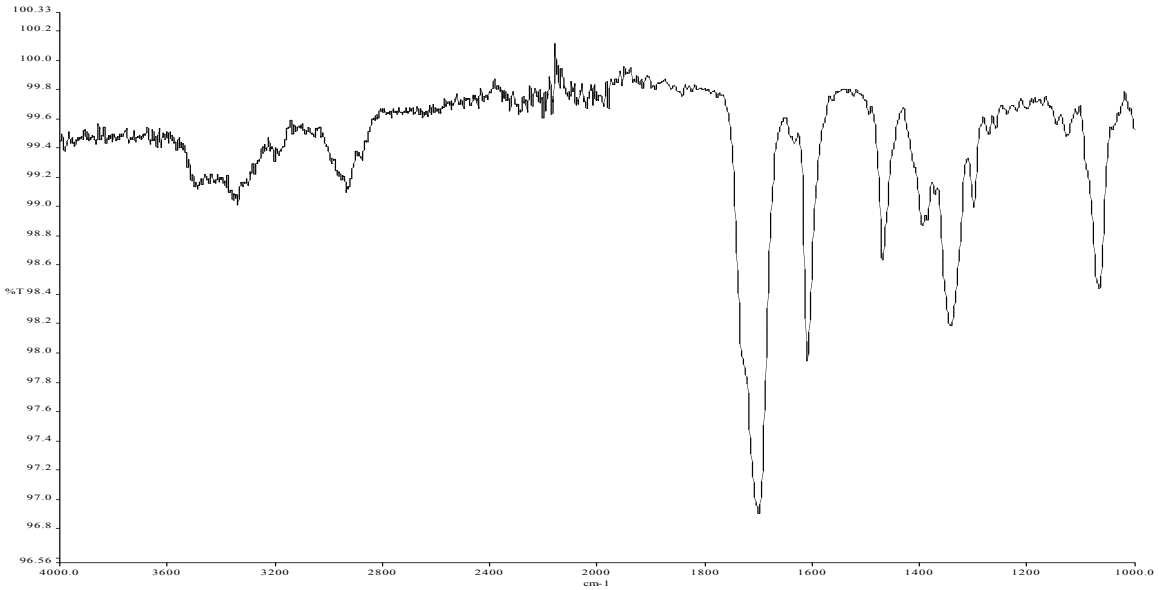


Figure A3.29 Infrared spectrum of compound **4.19**.

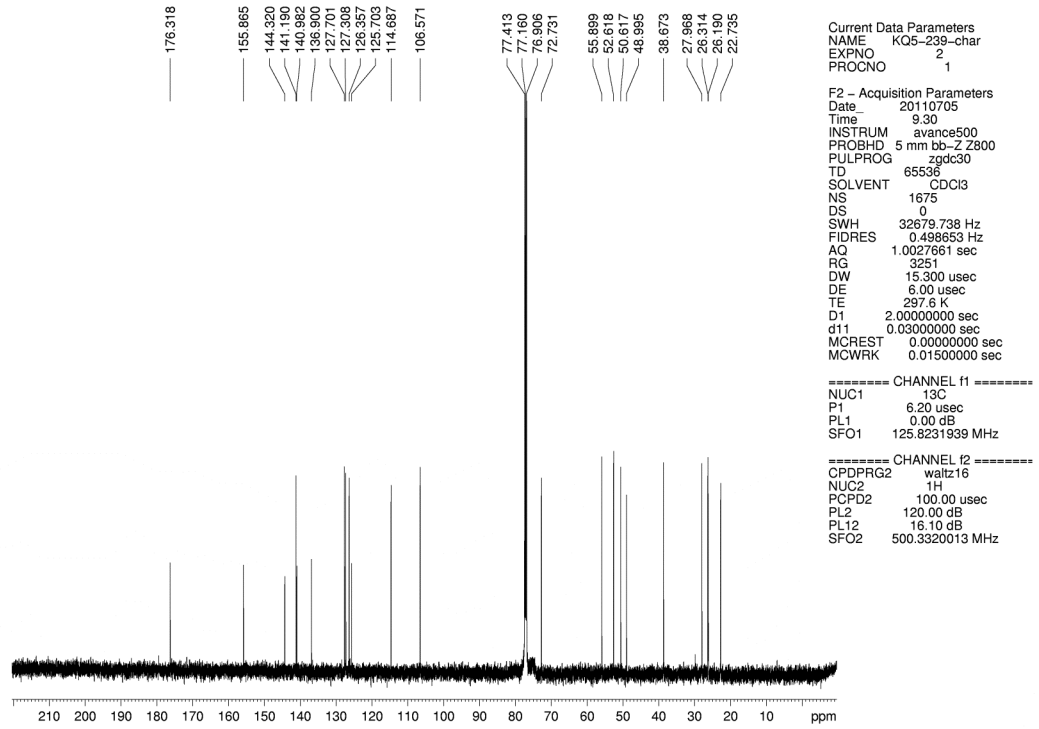
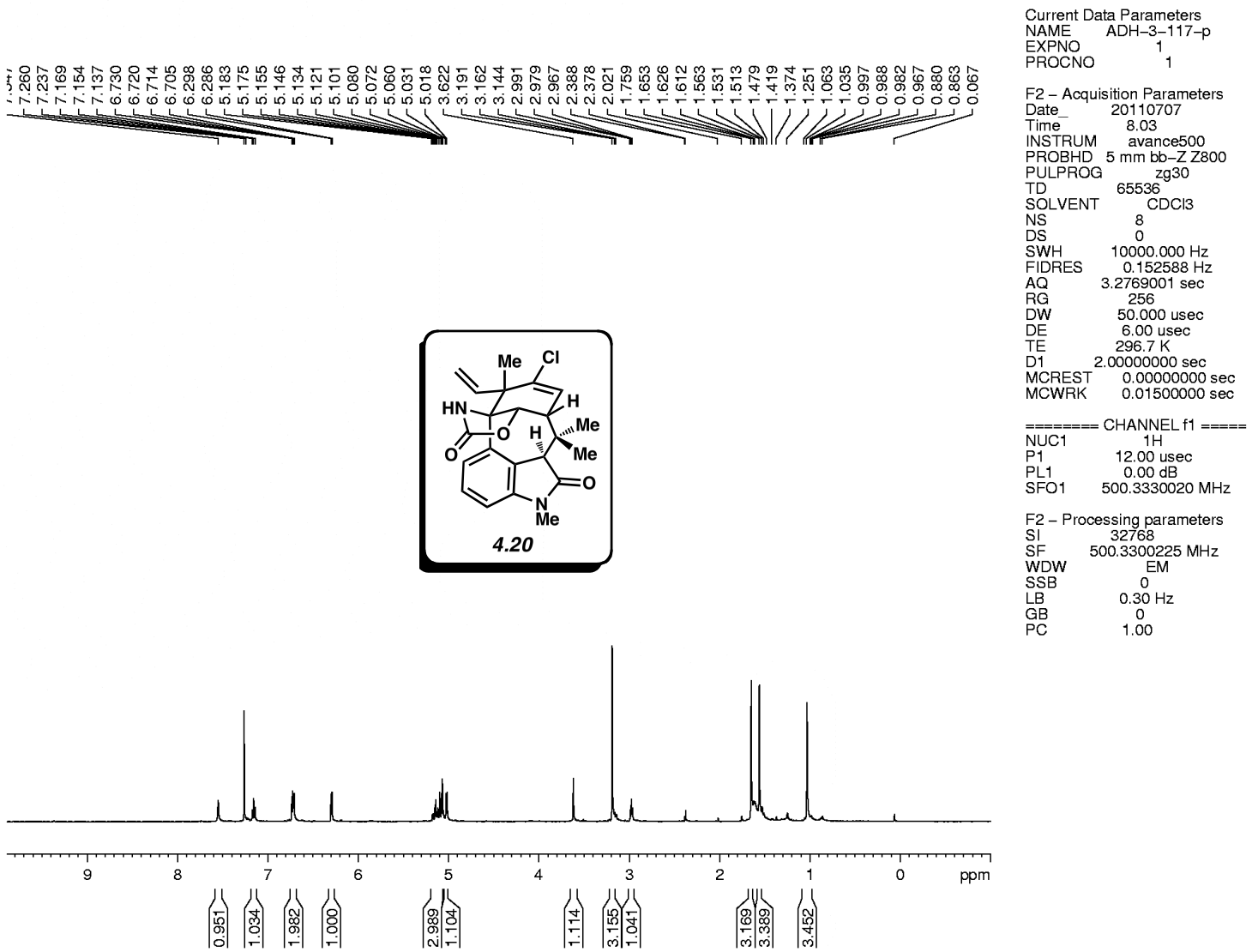


Figure A3.30 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4.19**.



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PROCNO 1

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FIDRES 0.152588 Hz
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DE 6.00 usec
TE 296.7 K
D1 2.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

======== CHANNEL f1 =====
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P1 12.00 usec
PL1 0.00 dB
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F2 – Processing parameters
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SF 500.3300225 MHz
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GB 0
PC 1.00

Figure A3.31 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.20**.

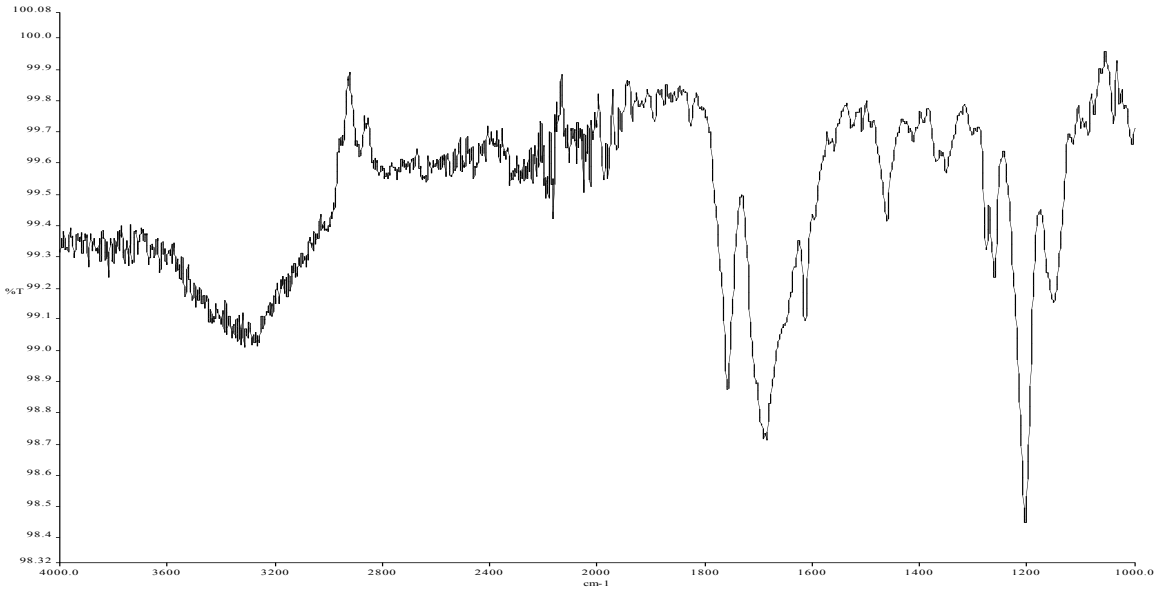


Figure A3.32 Infrared spectrum of compound **4.20**.

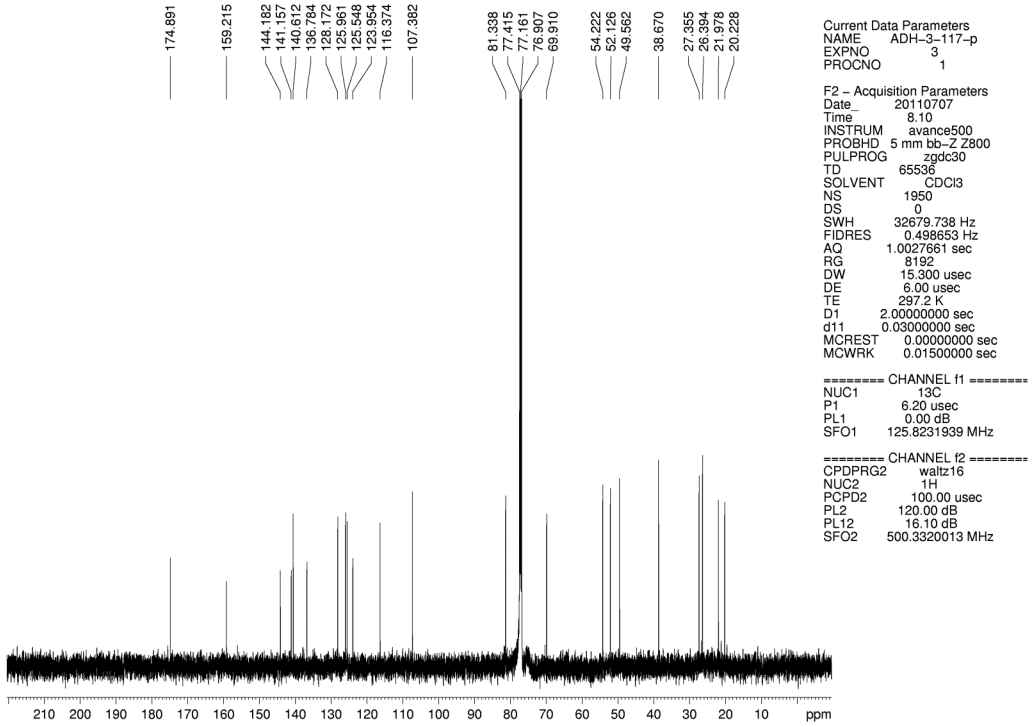
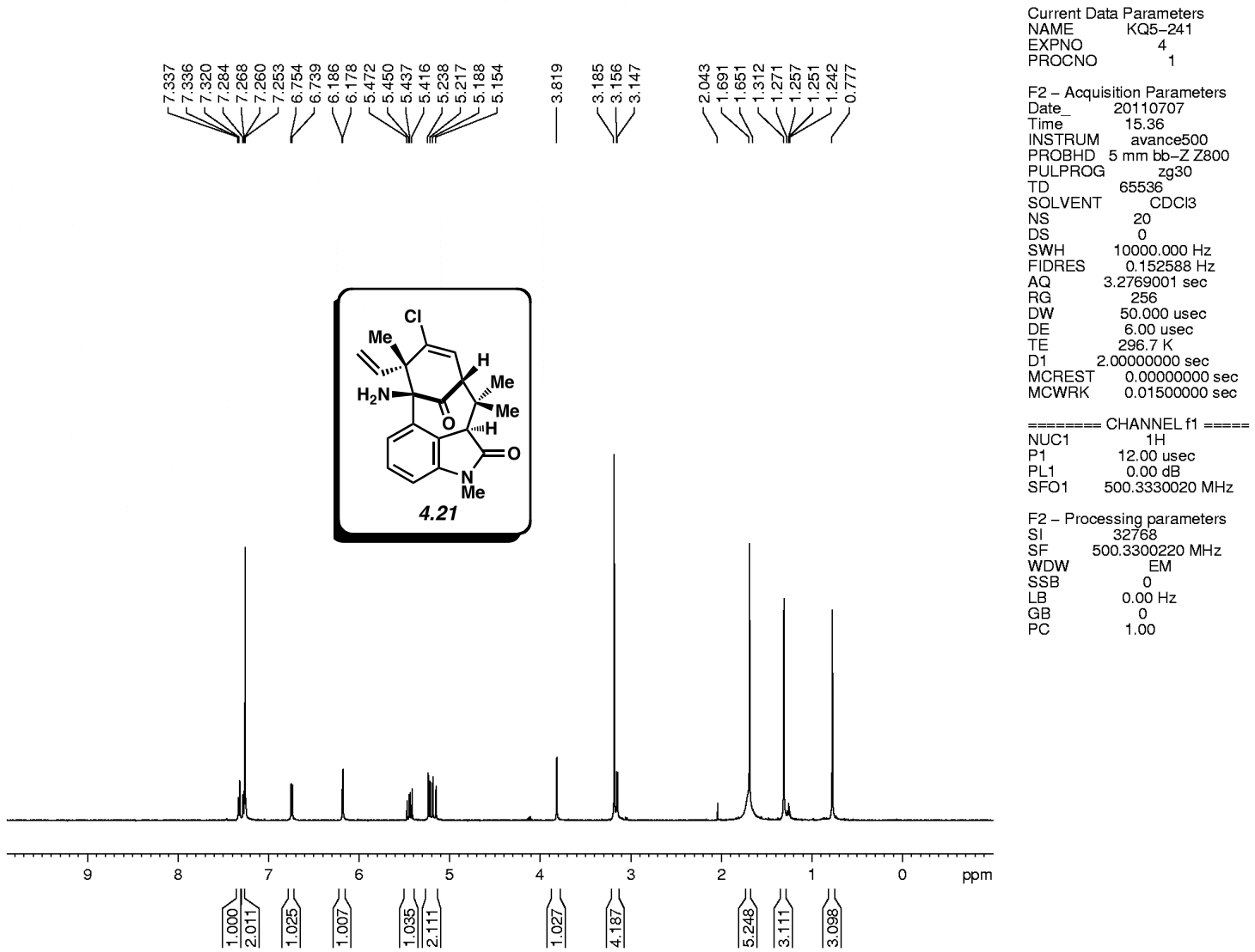


Figure A3.33 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4.20**.



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PROCNO 1

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TD 65536
SOLVENT CDCl3
NS 20
DS 0
SWH 10000.000 Hz
FIDRES 0.152588 Hz
AQ 3.2769001 sec
RG 256
DW 50.000 usec
DE 6.00 usec
TE 296.7 K
D1 2.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

======== CHANNEL f1 =====
NUC1 1H
P1 12.00 usec
PL1 0.00 dB
SFO1 500.3330020 MHz

F2 – Processing parameters
SI 32768
SF 500.3300220 MHz
WDW EM
SSB 0
LB 0.00 Hz
GB 0
PC 1.00

Figure A3.34 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.21**.

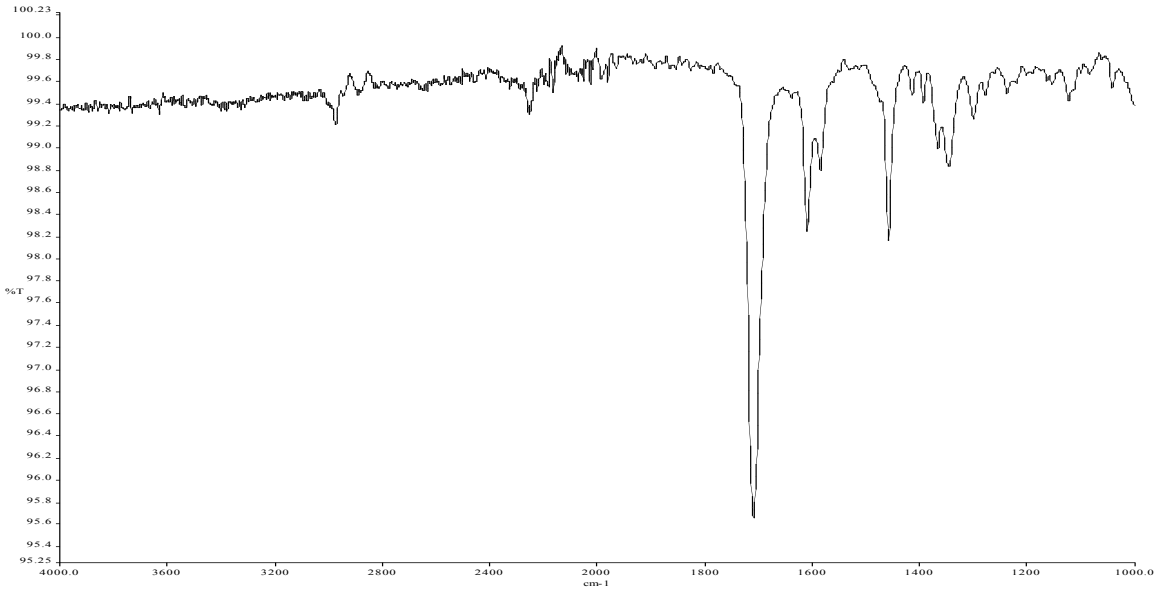


Figure A3.35 Infrared spectrum of compound **4.21**.

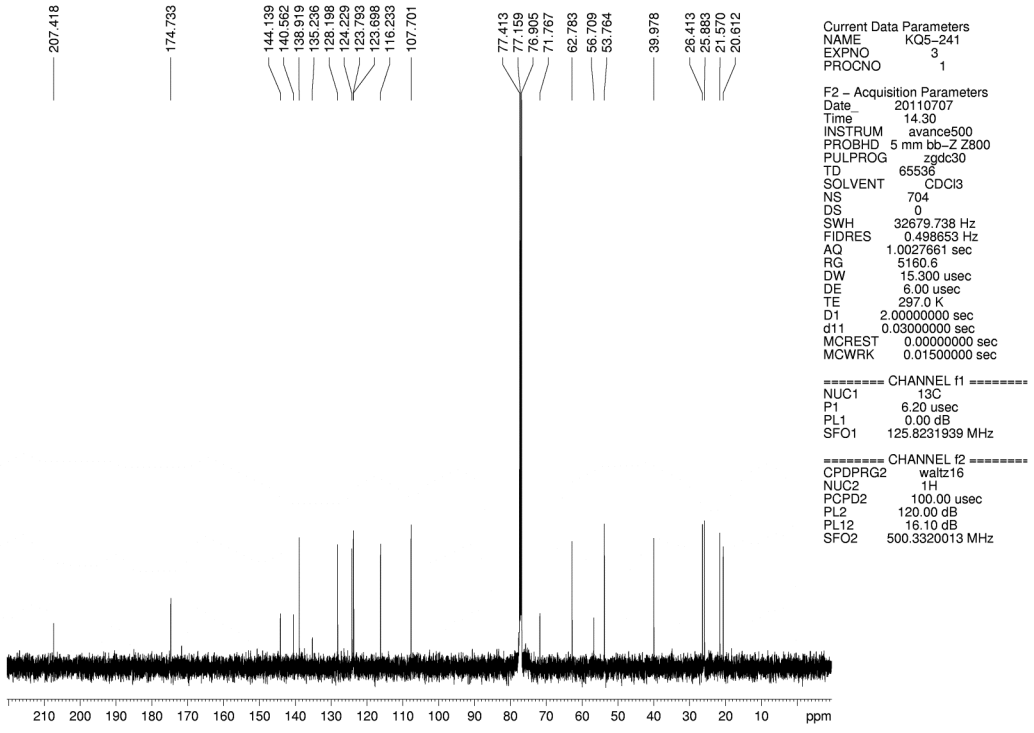
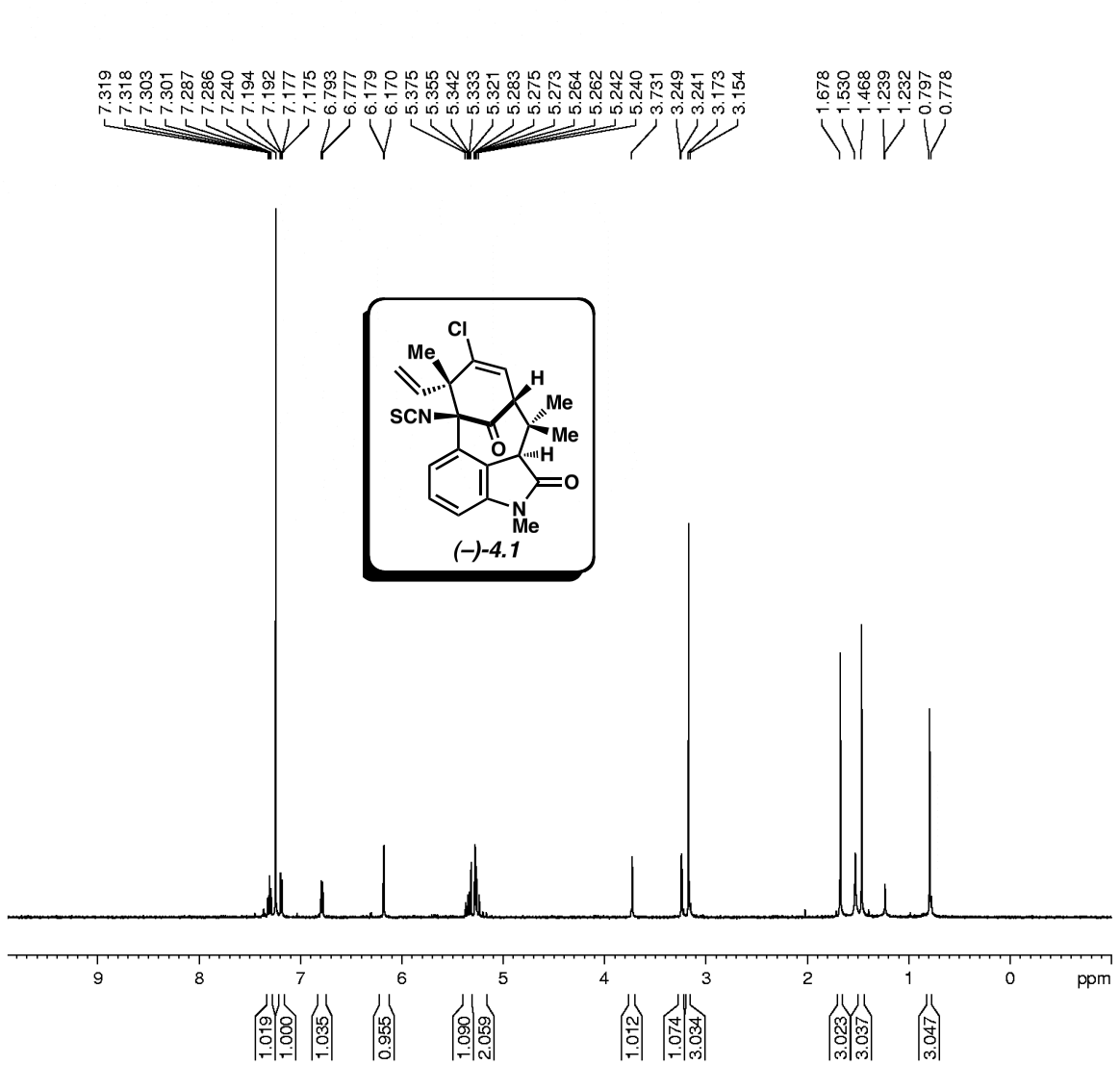


Figure A3.36 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4.21**.



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PROCNO 1

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TD 65536
SOLVENT CDCl3
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DS 0
SWH 10000.000 Hz
FIDRES 0.152588 Hz
AQ 3.2769001 sec
RG 322.5
DW 50.000 usec
DE 6.00 usec
TE 296.6 K
D1 2.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

======== CHANNEL f1 =====
NUC1 1H
P1 12.00 usec
PL1 0.00 dB
SFO1 500.3330020 MHz

F2 – Processing parameters
SI 32768
SF 500.3300319 MHz
WDW EM
SSB 0
LB 0.00 Hz
GB 0
PC 1.00

Figure A3.37 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.1**.

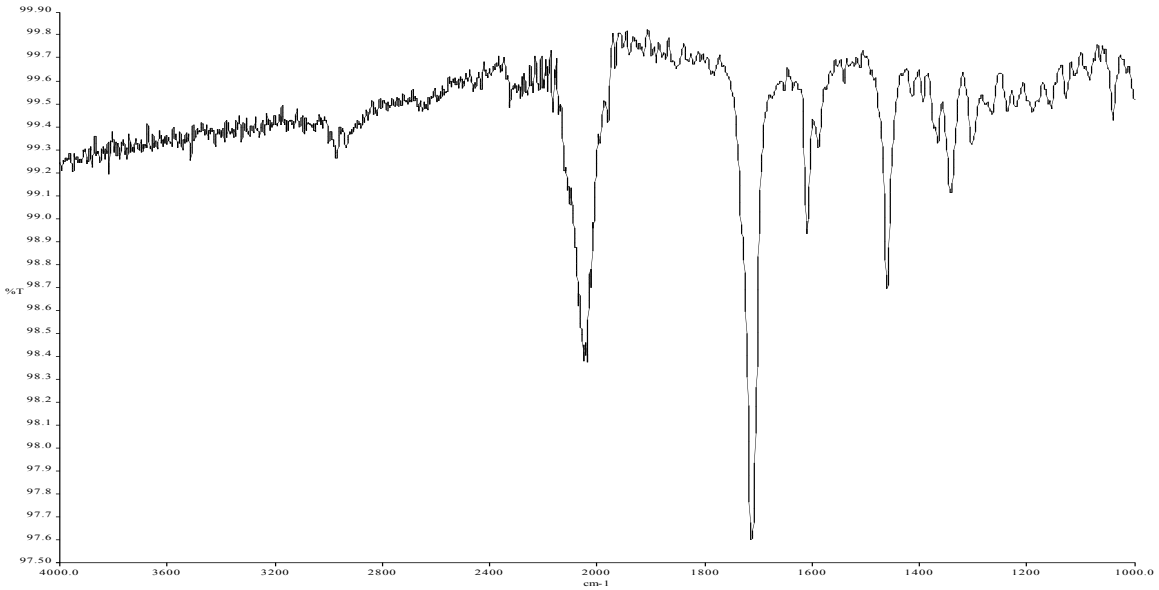


Figure A3.38 Infrared spectrum of compound **4.1**.

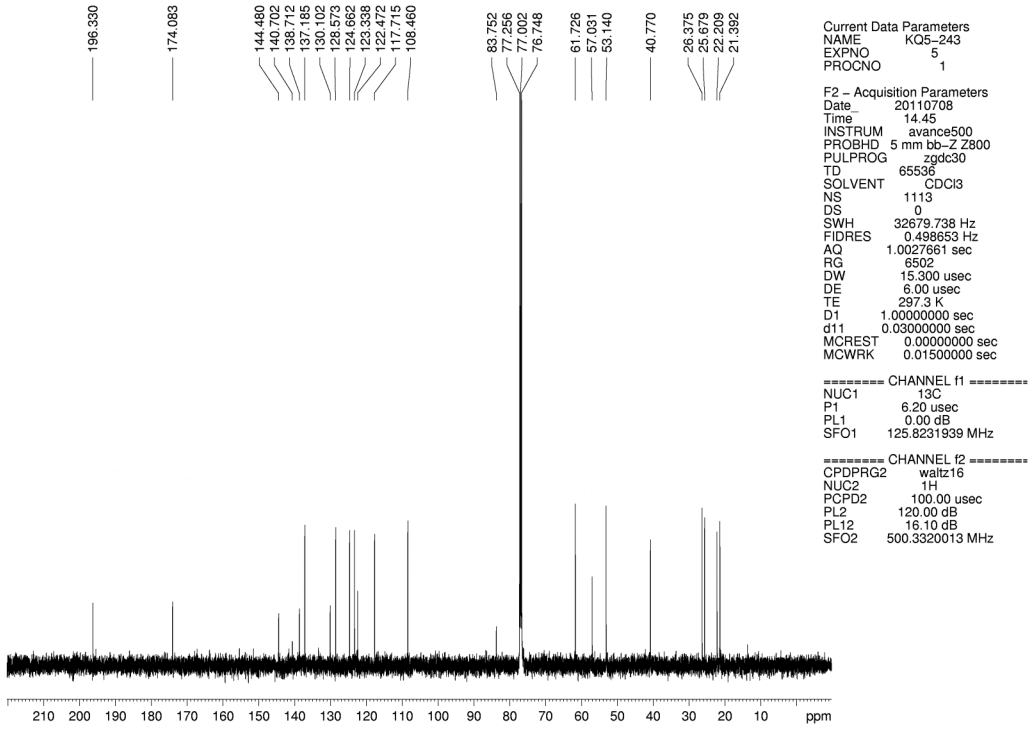


Figure A3.39 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4.1**.

CHAPTER FIVE

Total Synthesis of Oxidized Welwitindolinones and (–)-*N*-Methylwelwitindolinone C Isonitrile

Kyle W. Quasdorf, Alexander D. Huters, Michael W. Lodewyk, Dean J. Tantillo, and Neil K. Garg.

J. Am. Chem. Soc. **2012**, *134*, 1396–1399.

5.1 Abstract

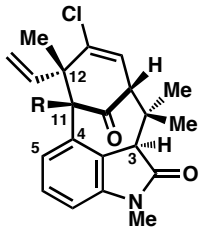
We report the total synthesis of (–)-*N*-methylwelwitindolinone C isonitrile, in addition to the total syntheses of the 3-hydroxylated welwitindolinones. Our routes to these elusive natural products feature the strategic use of a deuterium kinetic isotope effect to improve the efficiency of a late-stage nitrene insertion reaction. We also provide a computational prediction for the stereochemical configuration at C3 of the hydroxylated welwitindolinones, which was confirmed by experimental studies.

5.2 Introduction

Since their isolation reports in 1994 and 1999,[1] the welwitindolinone natural products have captivated synthetic chemists worldwide.[2] To date, nine welwitindolinones with bicyclo[4.3.1]decane frameworks have been discovered (e.g., **5.1**–**5.5**, Figure 5.1), some of which show promising activity for the treatment of drug resistant cancer cells.[3] The dense array of functional groups that decorate the compact structure of these targets has taunted chemists for nearly two decades. More than fifteen laboratories have reported progress toward these intriguing natural products, resulting in many elegant approaches to the bicyclic core.[4,5] The strategies used by our laboratory and Rawal's, respectively, have recently facilitated the first two

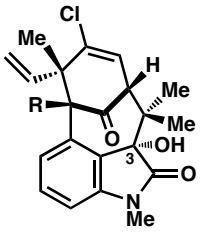
syntheses of these elusive natural products.[6,7] However, syntheses of several challenging members of the welwitindolinone family of natural products have not been reported.[8]

In this communication, we report the total syntheses of three natural products in the welwitindolinone C series: (–)-**5.2**, (–)-**5.3** and (–)-**5.4**. The latter two of these targets represent the so-called "oxidized welwitindolinones", whose configuration at C3 had not been unambiguously defined. We also describe the strategic manipulation of a kinetic isotope effect to improve the efficiency of a challenging C–H activation / nitrene-insertion reaction, which takes place late-stage in the total syntheses to forge a critical C–N bond.



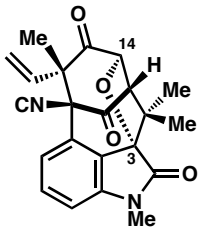
N-methylwelwitindolinone C isothiocyanate (5.1); R = -NCS

N-methylwelwitindolinone C isonitrile (5.2); R = -NC



C3-hydroxy-*N*-methylwelwitindolinone C isothiocyanate (5.3); R = -NCS

C3-hydroxy-*N*-methylwelwitindolinone C isonitrile (5.4); R = -NC



N-methylwelwitindolinone D isonitrile (5.5)

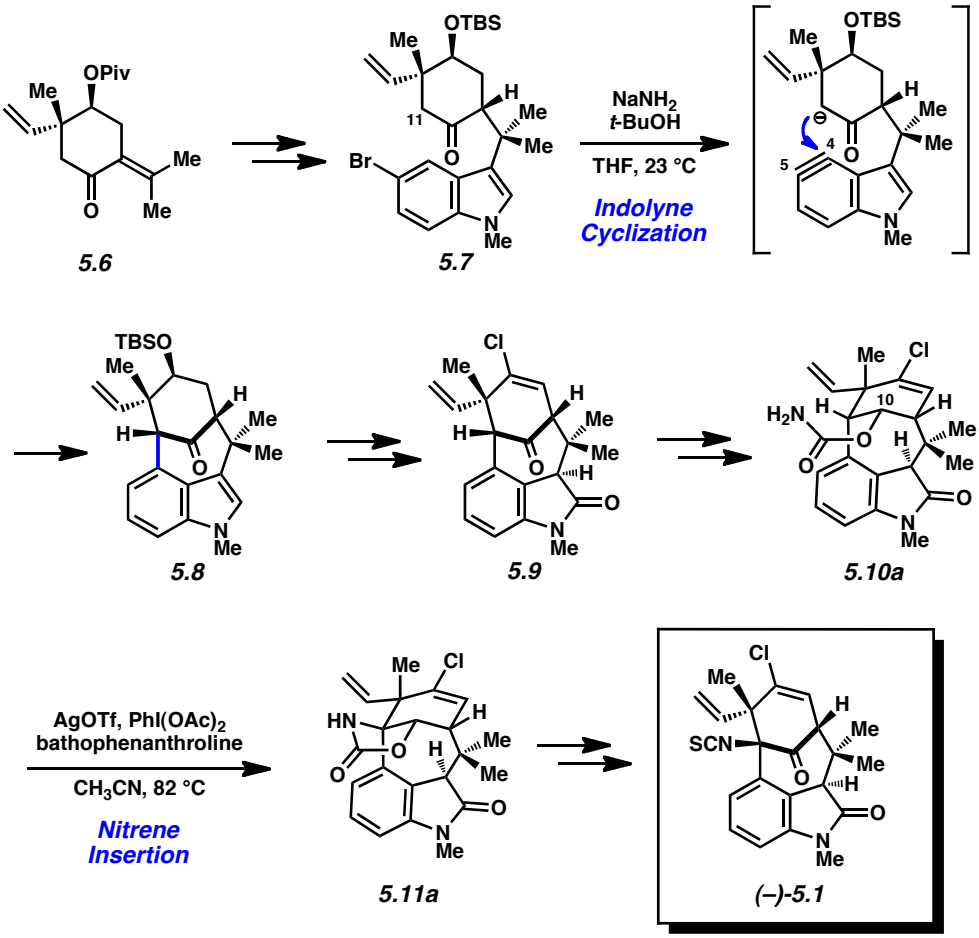
Figure 5.1. Welwitindolinones **5.1–5.5**.

5.3 Previous Total Synthesis of (–)-*N*-Methylwelwitindolinone C Isothiocyanate

A summary of our recent total synthesis of (–)-**5.1**[7] is shown in Scheme 5.1. Known carvone derivative **5.6** was elaborated to bromoindole **5.7** over three synthetic steps. Subsequent treatment of **5.7** with $NaNH_2$ and *t*-BuOH in THF facilitated an indolyne cyclization to afford **5.8**, which possesses the desired bicyclo[4.3.1]decane. Bicycle **5.8** was elaborated to ketone **5.9**, which lacked only the isothiocyanate functional group. Thus, ketone **5.9** was readily converted to

carbamate **5.10a** the substrate for a critical nitrene C–H insertion reaction.[9,10,11] We were delighted to find that the desired C–H functionalization took place to afford **5.11a** upon exposure of substrate **5.10a** to the Ag-promoted conditions described by He.[11b,c] Insertion product **5.11a** could be elaborated to the elusive natural product (–)-**5.1** over three additional transformations.

Scheme 5.1



5.4 Optimization of Nitrene Insertion

In order to facilitate syntheses of the remaining natural products in the welwitindolinone C series, we sought to first improve the efficiency of the late-stage nitrene insertion reaction (i.e.,

5.10a→5.11a, Scheme 5.1), which had proceeded in a modest 33% yield. It was noted that a major byproduct of the insertion step was ketone **5.9**, which presumably formed through the undesired insertion of the intermediate nitrene species into the C10 C–H bond.[12] We hypothesized that replacing the problematic hydrogen with deuterium would subdue the undesired insertion process, thereby favoring the desired functionalization event.[13] The deuterated substrate **5.10b** was readily prepared by a sequence involving reduction of ketone **5.9** with super deuteride, followed by carbamoylation (Figure 5.2). We were delighted to find that exposure of this substrate to our optimal reaction conditions for nitrene insertion furnished the desired product **5.11b** in 60% yield, while the formation of ketone **5.9** was diminished. The strategic use of a deuterium kinetic isotope effect in total synthesis is rare,[14] and the present study marks the first use of this approach to facilitate a C–H functionalization event en route to natural products.

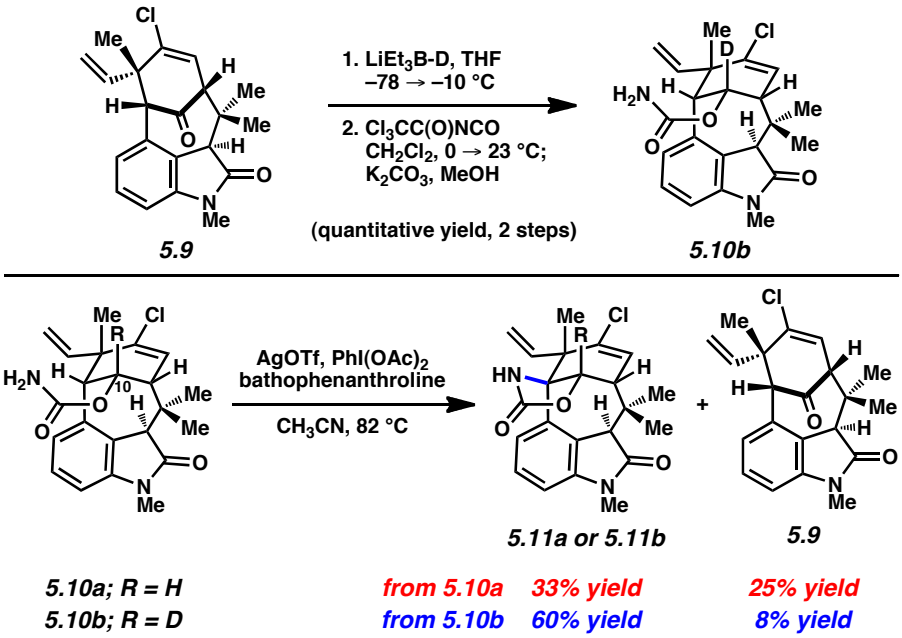
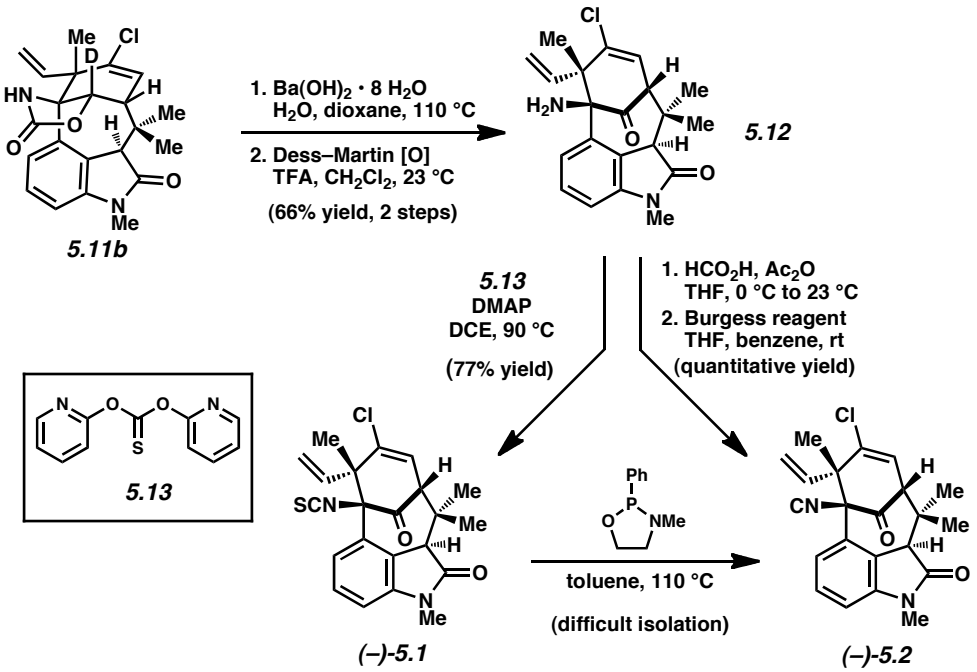


Figure 5.2. Nitrene insertion of substrates **5.10a** and **5.10b.**

5.5 Syntheses of *N*-Methylwelwitindolinone C Isothiocyanate and *N*-Methylwelwitindolinone Isonitrile

With improved access to a C11 *N*-functionalized product, we explored elaboration of **5.11b** to several welwitindolinone natural products. Hydrolysis of the carbamate, followed by Dess–Martin oxidation, proceeded smoothly to furnish aminoketone **5.12** (Scheme 5.2). Subsequent elaboration of **5.12** delivered *N*-methylwelwitindolinone C isothiocyanate (–)-**5.1** as we have shown previously.[6] Subsequently, exposure of this natural product to Rawal's desulfurization conditions provided (–)-*N*-methylwelwitindolinone isonitrile (**5.2**) as the major product.[6] Unfortunately, purification of the crude natural product proved difficult.[15] As a workaround, aminoketone **5.12** was subjected to sequential formylation[4s] and dehydration[4m] to afford the desired natural product (–)-**5.2** in 88% yield.[16] Spectral data for synthetic (–)-**5.2** was in accord with that provided for natural (–)-**5.2** in the isolation report.[1a]

Scheme 5.2



5.6 Syntheses of the C3-Hydroxylated Welwitindolinones

We next pursued total syntheses of the C3-hydroxylated welwitindolinones, the two oxidized welwitindolinones that had not been synthesized previously. Furthermore, the stereochemical configuration of these natural products at C3 had not been rigorously established spectroscopically, but rather, had been assigned based on analogy to the non-hydroxylated welwitindolinone natural products.[17] In our first attempts toward these natural products, aminoketone **5.12** was treated with various bases, with the reaction vessels being under standard atmospheric conditions to allow for air-oxidation. Although the corresponding C3 oxidized product was formed and could be manipulated further, low yields and irreproducibility hampered our efforts. However, direct oxidation of the non-hydroxylated natural products was found to be a more fruitful strategy (Figure 5.3). It should be noted that related aerobic oxidations of oxindoles have been reported,[18] including an impressive example in the context of the welwitindolinones.[19] Treatment of (–)-*N*-methylwelwitindolinone C isonitrile (**5.2**) with NaH in the presence of air, provided (–)-3-hydroxy-*N*-methylwelwitindolinone C isonitrile (**5.4**). Similarly, oxidation of (–)-*N*-methylwelwitindolinone C isothiocyanate (**5.1**) delivered (–)-3-hydroxy-*N*-methylwelwitindolinone C isonitrile (**5.3**). Both oxidations occurred selectively to furnish single diastereomers of hydroxylated products, while leaving the sensitive C11 functional groups undisturbed.

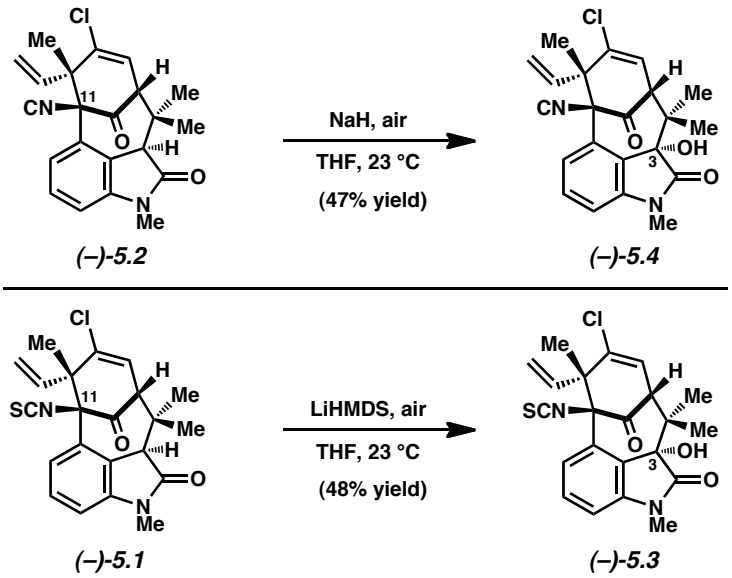


Figure 5.3. Total synthesis of oxidized welwitindolinones **5.3** and **5.4**.

5.7 Computational and Experimental Studies to Establish the Stereochemistry of the C3-Hydroxylated Welwitindolinones

For each of the natural products synthesized, our synthetic samples matched the natural materials by spectroscopic means.[1b,20] However, for the hydroxylated welwitindolinones, the C3 stereochemistry remained to be unambiguously established. Since computational predictions for ^{1}H and ^{13}C NMR chemical shifts have proven valuable in elucidating stereochemical configurations of natural products,[21,22] we calculated the ^{1}H and ^{13}C NMR chemical shifts for the C3 epimers of welwitindolinones **5.3** and **5.4** (Figure 5.4).[23] In both cases, the computed chemical shifts for the C3(*S*) diastereomer matched the experimental data better than did the computed shifts for the C3(*R*) diastereomer. For example, although computed ^{13}C shifts for **5.4** and *epi*-**5.4** deviated from the experimental shifts by similar amounts (mean absolute deviations (MADs) of 2.13 and 2.69 ppm, with largest outliers off by 5.59 and 5.34 ppm for **5.4** and *epi*-**5.4**, respectively), computed ^{1}H shifts for **5.4** matched the experimental values much more closely than did computed shifts for *epi*-**5.4** (MADs of 0.08 (0.05 without the OH proton included) and

0.36 ppm (0.34 without the OH proton included), with largest C–H outliers off by 0.13 and 0.79 ppm for **5.4** and *epi*-**5.4**, respectively). Similar results were obtained for **5.3**.[23] We therefore propose that the stereochemical configuration at C3 is *S* in **5.3** and **5.4**, in accord with the hypothesis made by the isolation chemists.[1]

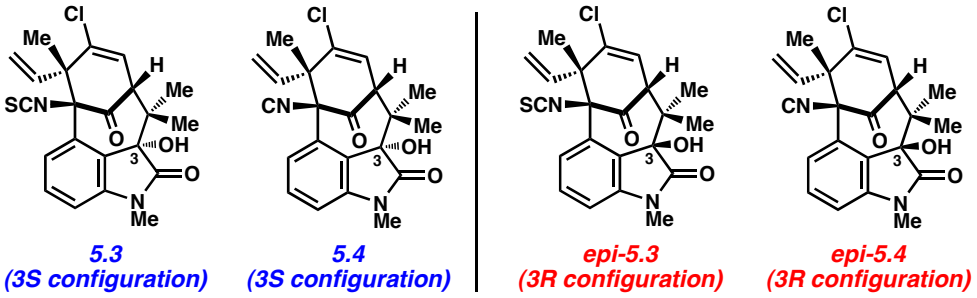
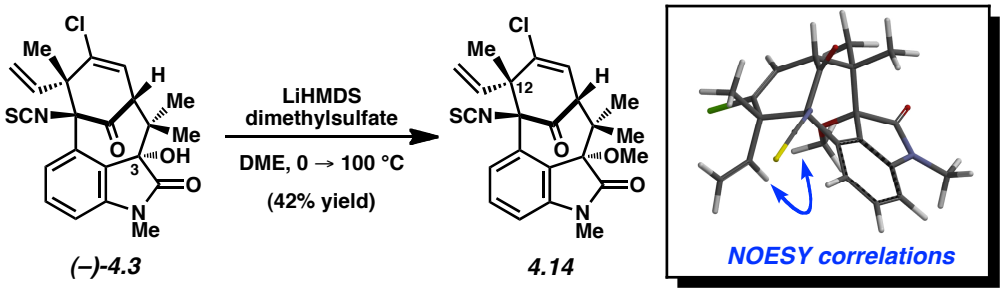


Figure 5.4. Structures of **5.3** and **5.4**, in addition to C3 epimers, and summary of computational findings.

To provide evidence for this stereochemical assignment, (–)-3-hydroxy-*N*-methylwelwitindolinone C isothiocyanate (**5.3**) was treated with LiHMDS and dimethylsulfate (Scheme 5.3). Despite the severely hindered nature of the tertiary alcohol, methylation proceeded to provide ether **5.14**. 2D-NOESY experiments of **5.14** showed correlations between the methoxy protons and the protons of the vinyl group at C12, thus supporting the proposed C3(*S*) configuration.[24] This result further validates the promising use of computational chemistry to establish stereochemical assignments on complex molecules.[21,22]

Scheme 5.3



5.8 Conclusion

In summary, we have completed the total syntheses of several elusive welwitindolinone natural products. Our routes to these natural products feature the strategic use of a deuterium kinetic isotope effect to improve the efficiency of a late-stage nitrene insertion reaction. We also provide a computational prediction for the stereochemical configuration at C3 of the hydroxylated welwitindolinones **5.3** and **5.4**. This prediction was confirmed by experimental studies. Our findings are expected to facilitate the total syntheses of other welwitindolinone natural products, while demonstrating the utility of computational chemistry in elucidating stereochemical assignments and the strategic manipulation of kinetic isotope effects in total synthesis.

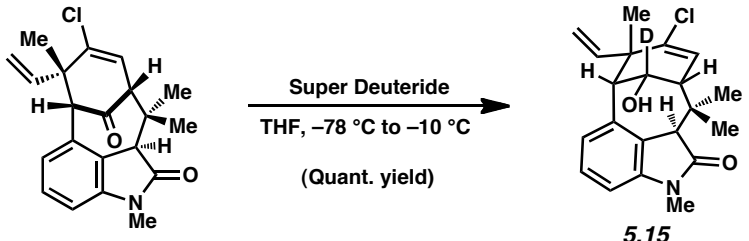
5.9 Experimental Section

5.9.1 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 available reagents were used as received unless otherwise specified. (*S*)-carvone was obtained from Aldrich. 5-bromoindole was obtained from Biosynth. $NaNH_2$ was obtained from Alfa Aesar. Comins' reagent was obtained from Aldrich. Hexamethylditin was obtained from Aldrich. Tetrakis(triphenylphosphine)palladium(0) was obtained from Strem. Anhydrous $CuCl_2$ was obtained from Aldrich. Trichloroacetyl isocyanate was obtained from Aldrich. $LiEt_3BD$ ("super deuteride") was obtained from Aldrich. AgOTf was obtained from Strem. Bathophenanthroline was obtained from Alfa Aesar. *O*,*O*-di(2-pyridinyl) thiocarbonate was obtained from Aldrich. 2-Iodoxybenzoic acid (IBX) and Dess–Martin periodinane were prepared from known literature procedures.[25,26] *t*-BuOH was distilled from CaH_2 and stored in a Schlenk tube prior to use. 1,4-dioxane was distilled from Na/benzophenone prior to use. 1,2-dichloroethane was distilled from P_2O_5 and stored in a Schlenk tube over 4Å molecular sieves prior to use. 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, and potassium permanganate staining. Silicycle silica gel 60 (particle size 0.040–0.063 mm) was used for flash column chromatography. ^{1}H NMR spectra were recorded on Bruker spectrometers (500 MHz). Data for ^{1}H spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz), integration and are referenced to the residual solvent peak 7.26 ppm for $CDCl_3$ and 5.32 ppm for CD_2Cl_2. Data for ^{2}H NMR spectra are

reported as follow: chemical shift (δ ppm, at 77 MHz), multiplicity, coupling constant, integration and are referenced to the residual solvent peak 7.26 ppm for $CDCl_3$. ^{13}C NMR spectra are reported in terms of chemical shift (at 125 MHz) and are referenced to the residual solvent peak 77.16 ppm for $CDCl_3$, 53.84 for CD_2Cl_2, and 128.06 for C_6D_6. IR spectra were recorded on a Perkin-Elmer 100 spectrometer and are reported in terms of frequency absorption (cm^{-1}). Optical rotations were measured with a Rudolph Autopol IV Automatic Polarimeter. Uncorrected melting points were measured with a Mel-Temp II melting point apparatus and a Fluke 50S thermocouple. High resolution mass spectra were obtained from the UC Irvine Mass Spectrometry Facility.

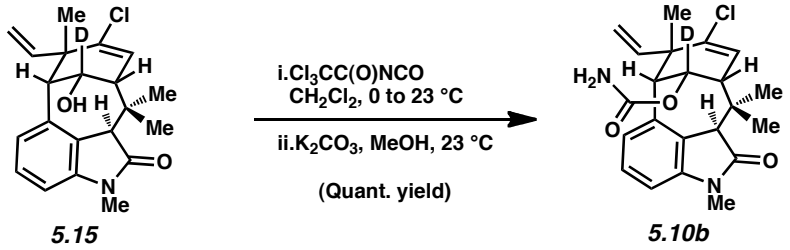
5.9.2 Experimental Procedures



5.9 *5.15*

Alcohol 5.15. To a solution of ketone **5.9**[7] (367 mg, 1.03 mmol, 1.0 equiv) in THF (34.0 mL) at -–78 °C was added a solution of $LiEt_3BD$ ("super deuteride", 1.0 M in THF, 1.13 mL, 1.13 mmol, 1.1 equiv) in a dropwise manner. After stirring at –78 °C for 10 min the reaction was warmed to –10 °C and stirred for an additional 1 h. The reaction was then quenched with the addition of MeOH (5 mL) and warmed to room temperature. The resulting mixture was transferred to a separatory funnel with EtOAc (50 mL), H_2O (15 mL), and brine (25 mL). The resulting biphasic mixture was extracted with EtOAc (3 x 50 mL), the organic layers were combined, dried over

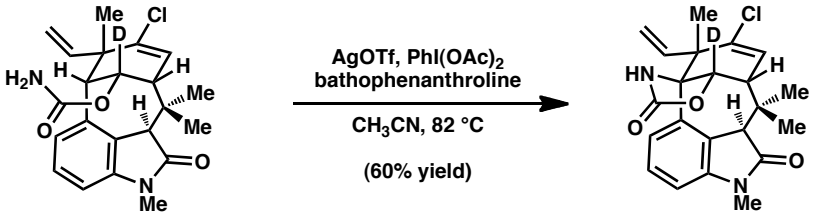
$MgSO_4$, and evaporated under reduced pressure. The resulting residue was purified by flash chromatography (1:1:1 hexanes:CH_2Cl_2:Et_2O) to afford alcohol **5.15** (370 mg, quant. yield) as a white solid. Alcohol **5.15**: R_f 0.12 (2:1:1 hexanes:CH_2Cl_2:Et_2O); ^1H NMR (500 MHz, $CDCl_3$): δ 7.17 (ddd, *J* = 7.8, 7.7, 0.9, 1H), 6.70 (d, *J* = 7.8, 0.9 1H), 6.68 (d, *J* = 7.7, 1H), 6.19 (d, *J* = 6.7, 1H), 5.23 (dd, *J* = 17.4, 10.7, 1H), 5.03 (dd, *J* = 17.4, 0.7, 1H), 4.89 (dd, *J* = 10.7, 0.7, 1H), 3.62 (s, 1H), 3.18 (s, 3H), 3.13 (d, *J* = 0.9, 1H), 2.57 (dd, *J* = 6.7, 0.9, 1H), 1.57 (s, 3H), 1.53 (s, 3H), 0.95 (s, 3H).



5.15 ***5.10b***

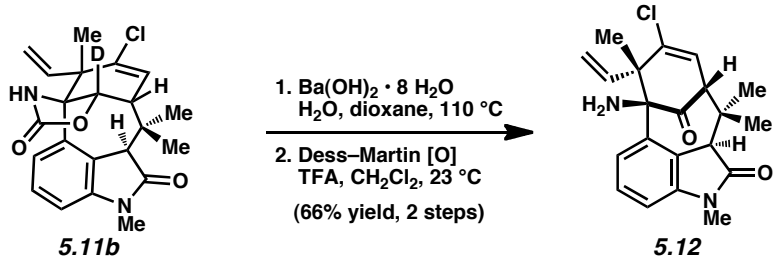
Carbamate 5.10b. To a solution of **5.15** (370 mg, 1.03 mmol, 1.0 equiv) in CH_2Cl_2 (21.0 mL) at 0 °C was added trichloroacetyl isocyanate (129 μL, 1.08 mmol, 1.05 equiv) in a dropwise manner. The resulting mixture was stirred at 0 °C for 5 min, and then at room temperature for an additional 20 min. The solvent was evaporated under reduced pressure. To the resulting residue was added MeOH (21.0 mL) and solid K_2CO_3 (784 mg, 5.67 mmol, 5.5 equiv) in one portion. The reaction was flushed with N_2 and left to stir at room temperature for 3.5 h. The reaction was quenched with a saturated aqueous NH_4Cl solution (50 mL) and the resulting biphasic mixture was transferred to a separatory funnel with EtOAc (50 mL) and H_2O (25 mL). After extracting with EtOAc (3 x 50 mL), the organic layers were combined, dried over $MgSO_4$, and evaporated under reduced pressure. The resulting residue was purified by flash chromatography (1:1 hexanes:EtOAc) to afford carbamate **5.10b** (416 mg, quant. yield) as a white solid. Carbamate

5.10b: mp: 135 ºC; R_f 0.41 (1:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.13 (dd, *J* = 7.8, 7.7, 1H), 6.68 (d, *J* = 7.7, 1H), 6.61 (d, *J* = 7.8, 1H), 6.18 (d, *J* = 6.7, 1H), 5.19 (dd, *J* = 17.3, 10.6, 1H), 5.04 (dd, *J* = 17.3, 0.8, 1H), 4.91 (dd, *J* = 10.6, 0.8, 1H), 4.46 (br. s, 2H), 3.62 (s, 3H), 3.17 (s, 3H), 3.14 (s,1H), 2.77 (dd, *J* = 6.7, 0.9, 1H), 1.60 (s, 3H), 1.52 (s, 3H), 0.87 (s, 3H); ^{2}H NMR (77 MHz, $CDCl_3$) δ 5.48 (br. s, 1D); ^{13}C NMR (21 of 22 observed, 125 MHz, $CDCl_3$): δ 176.3, 155.9, 144.3, 141.2, 141.0, 136.9, 127.7, 127.3, 126.4, 125.7, 114.7, 106.6, 55.8, 52.6, 50.6, 49.0, 38.7, 28.0, 26.3, 26.2, 22.7; IR (film): 3493, 3351, 2929, 2875, 1723, 1698, 1609, 1469, 1375, 1084 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{22}H_{24}DN_2O_3ClNa$, 424.1514; found 424.1504; $[\alpha]^{24.2}_D$ –151.0° (*c* = 1.000, CH_2Cl_2).



Oxazolidinone 5.11b. A 20 mL scintillation vial containing CH_3CN and two separate 20 mL scintillation vials each charged with bathophenanthroline (40.1 mg, 0.124 mmol, 0.5 equiv) were transferred into the glovebox. AgOTf (32.0 mg, 0.124 mmol, 0.5 equiv) and CH_3CN (7.00 mL) were added to each vial containing the bathophenanthroline, and the resulting suspensions were stirred at room temperature for 20 min. Next, two additional 20 mL scintillation vials each containing carbamate **5.10b** (100 mg, 0.249 mmol, 1.0 equiv) and $PhI(OAc)_2$ (160 mg, 0.498 mmol, 2.0 equiv) were transferred into the glovebox and a AgOTf/bathophenanthroline suspension was added to each of these vials. The vials were then sealed, removed from the glovebox, and the resulting mixtures were allowed to stir at 82 °C. After 24 h, the reactions were

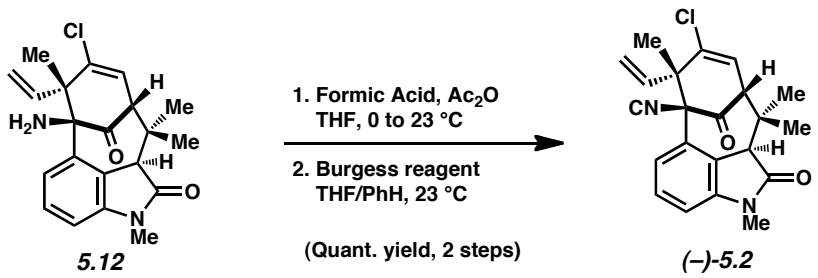
cooled to room temperature and combined then filtered through a plug of silica gel (EtOAc eluent, 50 mL). The filtrate was evaporated under reduced pressure, and the resulting residue was purified by flash chromatography (4:1 benzene:EtOAc) to afford oxazolidinone **5.11b** (59.3 mg, 60% yield) as a white solid and recovered ketone **5.9** (7.0 mg, 8% yield) as a white solid. Oxazolidinone **5.11b**: mp: 329 ºC; R_f 0.35 (2:1 benzene:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.53 (br. s, 1H), 7.15 (ddd, *J* = 8.3, 7.6, 0.7 1H), 6.72 (d, *J* = 8.3, 1H), 6.71 (d, *J* = 7.6, 1H), 6.29 (d, *J* = 5.9, 1H), 5.19–5.05 (m, 3H), 3.62 (s, 1H), 3.19 (s, 3H), 2.97 (d, *J* = 5.9, 1H), 1.65 (s, 3H), 1.56 (s, 3H), 1.04 (s, 3H); ^{2}H NMR (77 MHz, $CDCl_3$) δ 5.02 (br. s, 1D); ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.9, 159.2, 144.2, 141.1, 140.6, 136.8, 128.2, 125.9, 125.5, 123.9, 116.4, 107.4, 80.9 (t, $J_{C–D}$ = 21.9), 69.8, 54.2, 52.1, 49.4, 38.6, 27.3, 26.4, 22.0, 20.2; IR (film): 3280, 2997, 1757, 1707, 1610, 1460, 1346 cm^{-1}; HRMS-ESI (*m/z*) [M + Na]$^+$ calcd for $C_{22}H_{22}DN_2O_3ClNa$, 422.1358; found 422.1357; $[\alpha]^{25.2}_D$ –147.6° (*c* = 1.000, CH_2Cl_2).



Aminoketone 5.12. A Schlenk tube was charged with oxazolidinone **5.11b** (20 mg, 0.050 mmol, 1.0 equiv) and $Ba(OH)_2$· 8 H_2O (79 mg, 0.250 mmol, 5.0 equiv). The reaction vessel was then evacuated and backfilled with N_2 five times. A 2:1 mixture of 1,4-dioxane:H_2O (1.9 mL) that had been taken through seven freeze-pump-thaw cycles prior to use was then added to the Schlenk tube. The vessel was sealed, and the reaction vessel was heated to 110 °C. After 14 h, the reaction was cooled to room temperature, and the contents were transferred to a test tube with

EtOAc (6 mL), H_2O (3 mL), and brine (3 mL). The resulting biphasic mixture was extracted with EtOAc (5 x 5 mL). The organic layers were combined, dried over $MgSO_4$, and evaporated under reduced pressure to afford the crude product, which was used directly in the subsequent reaction.

To the crude residue was added CH_2Cl_2 (1.1 mL) and TFA (4.2 μL, 0.0413 mmol, 1.1 equiv). The resulting solution was stirred at room temperature for 2 min. Dess–Martin periodinane (28 mg, 0.065 mmol, 1.3 equiv) was then added in one portion, and the vial was flushed with N_2. After stirring at room temperature for 17 h, the reaction was diluted with a 1:1 mixture of saturated aqueous solutions of $NaHCO_3$ and $Na_2S_2O_3$ (2 mL). The resulting biphasic mixture was vigorously stirred until both layers were no longer cloudy. The resulting mixture was transferred to a test tube with EtOAc (2 mL). After extracting with EtOAc (4 x 2 mL), the organic layers were combined, dried over $MgSO_4$, and evaporated under reduced pressure. The resulting residue was purified by flash chromatography (4:1 hexanes:EtOAc) to afford aminoketone **5.12** (12.3 mg, 66% yield, over two steps) as an amorphous solid. Aminoketone **5.12**: R_f 0.42 (1:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34 (d, *J* = 8.4, 1H), 7.27 (dd, *J* = 8.4, 7.6, 1H), 6.75 (d, *J* = 7.6, 1H), 6.18 (d, *J* = 4.2, 1H), 5.44 (dd, *J* = 17.3, 10.9, 1H), 5.22 (d, *J* = 10.9, 1H), 5.17 (d, *J* = 17.3, 1H), 3.82 (s, 1H), 3.18 (s, 3H), 3.15 (d, *J* = 4.2, 1H), 1.71 (br. s, 2H), 1.69 (s, 3H), 1.31 (s, 3H), 0.78 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 207.4, 174.7, 144.1, 140.6, 138.9, 135.2, 128.2, 124.2, 123.8, 123.7, 116.2, 107.7, 71.8, 62.8, 56.7, 53.8, 40.0, 26.4, 25.9, 21.6, 20.6; IR (film): 2973, 1709, 1698, 1609, 1583, 1457 cm^{-1}; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{21}H_{24}N_2O_2Cl$, 371.1526; found 371.1516; $[\alpha]^{23.8}_D$ –70.2° (*c* = 1.000, $CHCl_3$).

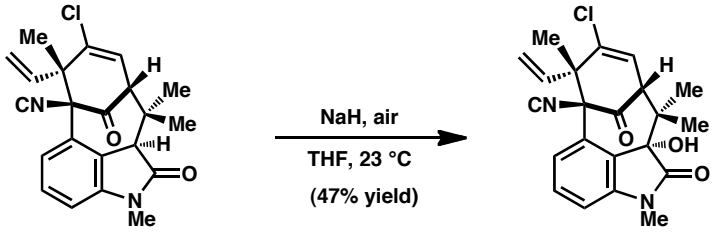


5.12 *(–)-5.2*

(–)-*N*-Methylwelwitindolinone Isonitrile (5.2). A 1-dram vial was charged with 96% formic acid (0.100 mL) and acetic anhydride (0.100 mL), and then stirred at 60 °C for 1 h. The reaction vessel was cooled to room temperature and 68 μL of the 96% formic acid/acetic anhydride mixture was added to a solution of aminoketone **5.12** (7.5 mg, 0.0203 mmol, 1 equiv) in THF (450 μL) at 0 °C. The reaction was stirred at 0 °C for 5 minutes, and then warmed to room temperature. After stirring for an additional 30 minutes, the reaction mixture was then transferred to a test tube containing EtOAc (1 mL) and a saturated solution of aqueous $NaHCO_3$ (1 mL). The resulting biphasic mixture was extracted with EtOAc (3 x 3 mL). The organic layers were combined, dried over $MgSO_4$, and evaporated under reduced pressure to afford the crude product, which was used directly in the subsequent reaction.

To the crude residue was added THF (1 mL) and benzene (1 mL), followed by the addition of Burgess reagent (12 mg, 0.0406 mmol, 2 equiv). The vial was flushed with N_2 and allowed to stir at room temperature for 1 h. The reaction was then filtered through a plug of silica gel (EtOAc eluent, 20 mL). The filtrate was evaporated under reduced pressure, and the resulting residue was purified by prep TLC (1:1 hexanes:EtOAc) to afford (–)-**5.2** (7.8 mg, quant. yield) as an amorphous solid. (–)-*N*-Methylwelwitindolinone C isonitrile (**5.2**). Spectral data for synthetic **5.2** was consistent with literature reports[1b]: R_f 0.60 (1:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33 (ddd, J = 8.5, 7.7, 0.9, 1H), 7.27 (dd, J = 8.5, 0.9, 1H), 6.81 (dd, J = 7.7, 0.9, 1H), 6.18 (d, J = 4.4, 1H), 5.37–5.30 (m, 3H), 3.73 (s, 1H), 3.23 (d, J = 4.4, 1H), 3.18 (s, 3H), 1.68 (s,

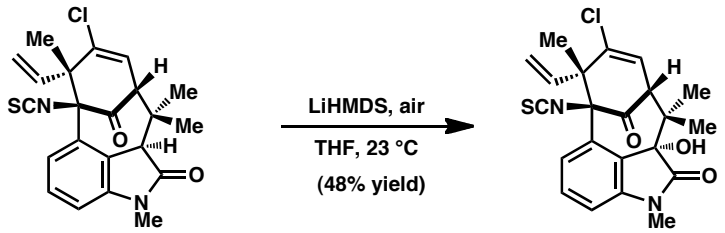
3H), 1.53 (s, 3H), 0.79 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 193.4, 173.9, 163.5, 144.5, 138.3, 136.2, 128.7, 127.7, 124.6, 123.3, 122.8, 118.3, 108.8, 81.9, 61.6, 55.6, 53.2, 40.7, 26.4, 25.6, 22.6, 21.3; IR (film): 2969, 2141, 1735, 1711, 1609, 1587, 1460, 1341 cm^{-1}; HRMS-ESI (*m*/*z*) [M + Na]$^+$ calcd for $C_{22}H_{21}N_2O_2ClNa$, 403.1189; found 403.1178; $[\alpha]^{24.2}_D$ –90.4° (*c* = 0.25, CH_2Cl_2).[27]



(–)-5.2 *(–)-5.4*

(–)-3-Hydroxy-*N*-Methylwelwitindolinone C Isonitrile (5.4). To a solution of (–)-**5.2** (7.8 mg, 0.0205 mmol, 1.0 equiv) in THF (1.1 mL) was added NaH (60% dispersion in mineral oil, 4.0 mg, 0.103 mmol, 5 equiv) in one portion. The vial was sealed under ambient atomospheric conditions and allowed to star at room temperature. After 2.5 h, the reaction was filtered through a plug of silica gel (EtOAc eluent, 20 mL). The filtrate was evaporated under reduced pressure and the resulting residue was purified by prep TLC (1:1 hexanes:EtOAc) to afford (–)-**5.4** (3.8 mg, 47% yield) as an amorphous solid. (–)-3-Hydroxy-*N*-methylwelwitindolinone C isonitrile (**5.4**). Spectral data for synthetic **5.4** was consistent with literature reports[1b]: R_f 0.46 (1:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, CD_2Cl_2): δ 7.44 (dd, *J* = 8.2, 7.6, 1H), 7.33 (dd, *J* = 8.2, 0.9, 1H), 6.89 (dd, *J* = 7.6, 0.9, 1H), 6.40 (d, *J* = 4.6, 1H), 5.50 (dd, *J* = 17.2, 10.4, 1H), 5.40 (dd, *J* = 17.2, 0.8 1H), 5.37 (dd, *J* = 10.4, 0.8 1H), 3.18 (d, *J* = 4.6, 1H), 3.15 (s, 3H), 1.71 (s, 3H), 1.56 (s, 3H), 0.81 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6): δ 192.6, 173.2, 166.5, 145.1, 137.4, 132.8, 130.3, 128.8, 126.4, 126.00, 125.98, 117.8, 109.2, 82.3, 80.2, 60.6, 55.4, 42.3, 25.6, 22.6,

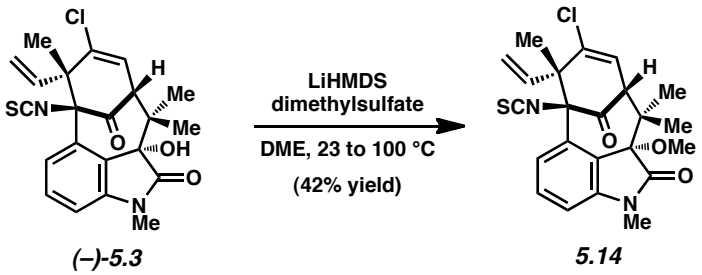
22.0, 20.8; IR (film): 3395, 2973, 2922, 2142, 1723, 1610, 1587, 1459 cm^{-1}; HRMS-ESI (*m/z*) [M + Na]$^+$ calcd for $C_{22}H_{21}N_2O_3ClNa$, 419.1138; found 419.1137; $[\alpha]^{23.1}_D$ –90.0° (*c* = 0.4, CH_2Cl_2).[27]



(–)-5.1 *(–)-5.3*

(–)-3-Hydroxy-*N*-Methylwelwitindolinone C Isothiocyanate (5.3). A 1-dram vial was charged with (–)-**5.1** (2.4 mg, 0.0058 mmol, 1.0 equiv) and then sealed under ambient atmospheric conditions. THF (300 μL) was then added, followed by the dropwise addition of 100 μL of an 11 mg/mL solution of LiHMDS in THF. The reaction was stirred at room temperature for 6 h, and then another 50 μL of the LiHMDS solution was added. After an additional 90 minutes, another 50 μL of the LiHMDS solution was added and the reaction was stirred for an additional 14 h. The reaction was then filtered through a plug of silica gel (EtOAc eluent, 20 mL). The filtrate was evaporated under reduced pressure and the resulting residue was purified by prep TLC (1:1 hexanes:EtOAc) to afford (–)-**5.3** (1.2 mg, 48% yield) as an amorphous solid. (–)-3-hydroxy-*N*-methylwelwitindolinone C isothiocyanate (**5.3**)[20]: R_f 0.46 (1:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, CD_2Cl_2): δ 7.41 (dd, *J* = 8.4, 7.6, 1H), 7.25 (dd, *J* = 8.4, 0.9, 1H), 6.87 (dd, *J* = 7.6, 0.9, 1H), 6.40 (d, *J* = 4.5, 1H), 5.48 (dd, *J* = 17.5, 10.2, 1H), 5.33–5.29 (m, 2H), 3.21 (d, *J* = 4.5, 1H), 3.14 (s, 3H), 1.71 (s, 3H), 1.50 (s, 3H), 0.81 (s, 3H); ^{13}C NMR (125 MHz, CD_2Cl_2): δ 196.3, 173.7, 145.5, 140.7, 138.0, 133.8, 130.7, 130.6, 126.2, 126.1, 125.9, 117.9, 109.7, 84.5, 80.6, 61.1, 57.1, 42.9, 26.6, 22.9, 21.7, 21.2; IR (film): 3399, 2966, 2929, 2044, 1721, 1610, 1585,

1457 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{22}H_{21}N_2O_3SClNa$, 451.0859; found 451.0860; $[\alpha]^{25.2}_D$ –206.0° (*c* = 1.00, CH_2Cl_2).[27]



(–)-5.3 *5.14*

Methyl Ether 5.14. To a stirred solution of (–)-**5.3** (2.3 mg, 0.0054 mmol, 1.0 equiv) in DME (200 μL) was added 100 μL of a 10 mg/mL solution of LiHMDS in DME. The reaction was stirred at room temperature for 1 h. Dimethylsulfate (10.2 μL, 0.107 mmol, 20 equiv) was added and the reaction was heated to 100 °C. After 24 h, the reaction was cooled to room temperature and filtered through a plug of silica gel (EtOAc eluent, 20 mL). The filtrate was evaporated under reduced pressure and the resulting residue was purified by prep TLC (2:1:1 hexanes:CH_2Cl_2:Et_2O) to afford **5.14** (1.0 mg, 42% yield) as an amorphous solid. Methyl ether **5.14**: R_f 0.58 (1:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41 (dd, *J* = 8.5, 7.9, 1H), 7.32 (dd, *J* = 8.5, 0.9, 1H), 6.82 (dd, *J* = 7.9, 0.9, 1H), 6.31 (d, *J* = 4.4, 1H), 5.46 (dd, *J* = 17.5, 10.1, 1H), 5.34 (d, *J* = 17.5, 1H), 5.34 (d, *J* = 10.1, 1H), 3.19 (s, 3H), 3.16 (d, *J* = 4.4, 1H), 1.70 (s, 3H), 1.49 (s, 3H), 0.81 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 196.3, 172.0, 145.7, 140.7, 137.9, 132.3, 131.1, 130.7, 126.7, 126.1, 122.1, 117.7, 108.6, 85.2, 84.4, 61.1, 56.6, 51.3, 43.7, 26.1, 22.9, 21.62, 21.55; IR (film): 2916, 2050, 1725, 1607, 1583, 1455 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{23}H_{23}N_2O_3SClNa$, 465.1016; found 465.1028; $[\alpha]^{25.2}_D$ –118.7° (*c* = 0.15, CH_2Cl_2).

5.9.3 Computational Data

Computed NMR Chemical Shift Data

Table 5.1. Comparison of Experimental and Computed NMR Chemical Shifts for Structure **5.4**.

^{13}C NMR Chemical Shifts (ppm)				^{1}H NMR Chemical Shifts (ppm)			
Nucleus #[a]	Expt.[b]	Computed[c] Original	Computed[c] C3 epimer	Nucleus #[a]	Expt.[b]	Computed[c] Original	Computed[c] C3 epimer
N CH_3	26.60	24.75	24.68	*N* CH_3	3.15	3.02	3.00
2	173.60	171.48	172.62	OH	2.65	2.20	1.96
3	80.60	80.47	80.08	5	7.33	7.20	7.37
4	128.40	129.46	132.98	6	7.44	7.39	7.36
5	126.20	124.05	123.51	7	6.89	6.82	6.78
6	130.80	128.65	128.49	14	6.40	6.40	5.83
7	110.00	108.52	108.75	15	3.18	3.22	3.09
8	145.50	144.64	143.77	17	1.71	1.66	0.94
9	126.40	126.15	127.18	18	0.81	0.77	1.60
10	193.60	196.02	198.73	19	1.55	1.55	1.36
11	82.00	82.13	77.56	20	5.49	5.48	6.25
12	55.50	60.92	60.84	21 *E*	5.34	5.36	5.65
13	133.30	140.06	142.36	21 *Z*	5.40	5.40	5.58
14	126.00	128.32	127.63				
15	61.00	61.60	59.56				
16	42.80	48.39	47.55				
17	22.80	19.42	21.41				
18	21.20	21.49	21.51				
19	22.10	20.56	20.48				
20	137.10	139.50	140.61				
21	118.40	118.25	120.00				
23	164.30	168.17	166.42				
	CMAD[d]	**2.13**	**2.69**		**CMAD[d]**	**0.08**	**0.36**

[a]See page 316. [b]Data taken from isolation report; see reference 1b. [c]Conformationally averaged values – see page 317. Largest outliers are indicated in red. Note that higher than average errors are expected for the carbon atom bearing a chlorine atom (C13) – due to heavy-atom effects, and for the hydroxyl proton – due to concentration-dependent hydrogen bonding.[20] [d]CMAD = corrected mean absolute deviation and is computed as $\frac{1}{n}\sum_{i}^{n}|\delta_{comp} - \delta_{exp}|$ where δ_{comp} refers to the scaled computed chemical shifts.

Note: For the C3 epimer structure, a modest improvement in the match to experimental data is found if the C17 and C18 methyl protons are switched in their experimental assignments

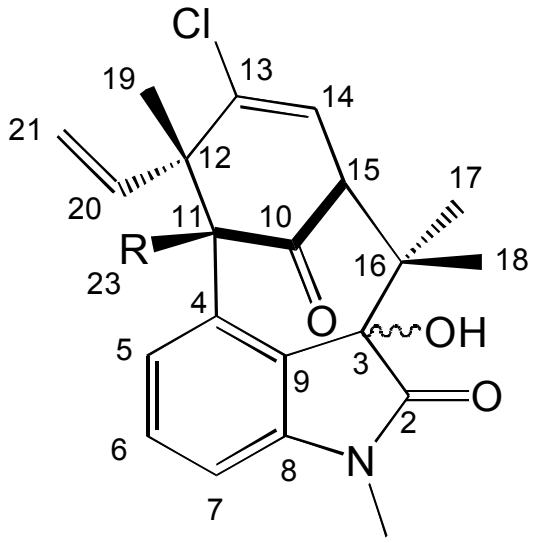
(CMAD = 0.26 ppm). This amount of improvement is not sufficient to change our overall conclusion.

Table 5.2. Comparison of Experimental and Computed NMR Chemical Shifts for Structure **5.3**.

^{13}C NMR Chemical Shifts (ppm)				^{1}H NMR Chemical Shifts (ppm)			
Nucleus #[a]	Expt.[b]	Computed[c] Original	Computed[c] C3 epimer	Nucleus #[a]	Expt.[b]	Computed[c] Original	Computed[c] C3 epimer
N CH_3	26.60	24.89	24.57	*N* CH_3	3.14	3.02	3.01
2	173.70	172.44	173.12	OH	*not obsv.*		
3	80.60	80.37	79.50	5	7.25	7.14	7.38
4	130.60	132.41	132.88	6	7.41	7.30	7.26
5	126.20	124.24	123.93	7	6.87	6.83	6.73
6	130.70	128.78	127.83	14	6.40	6.34	5.87
7	109.70	108.20	108.22	15	3.21	3.20	3.29
8	145.50	144.63	144.49	17	1.71	1.62	0.96
9	125.90	125.36	126.44	18	0.81	0.79	1.61
10	196.30	198.52	201.21	19	1.50	1.49	1.38
11	84.50	86.70	82.20	20	5.48	5.42	6.30
12				21 *E*	5.33–5.29	5.25	5.56
	57.10	61.87	60.36				
13				21 *Z*	5.33–5.29	5.30	5.42
	133.80	140.56	143.45				
14	126.10	126.98	127.83				
15	61.10	60.63	59.72				
16	42.90	48.15	47.78				
17	22.90	19.33	21.88				
18	21.70	21.38	21.69				
19	21.70	19.95	20.29				
20	138.00	141.57	142.17				
21	117.90	116.31	118.28				
23	140.60	144.85	146.31				
	CMAD[d]	**2.25**	**2.50**		**CMAD[d]**	**0.06**	**0.33**

[a] See page 316). [b] Data obtained from Prof Philip Williams (University of Hawaii); see ref 20. [c]Lowest energy conformation – see page 317). Largest outliers are indicated in red. Note that higher than average errors are expected for the carbon atom bearing a chlorine atom (C13) – due to heavy-atom effects, and for the hydroxyl proton – due to concentration-dependent hydrogen bonding.[20] [d]CMAD = corrected mean absolute deviation and is computed as $\frac{1}{n}\sum_{i}^{n}|\delta_{comp} - \delta_{exp}|$ where δ_{comp} refers to the scaled computed chemical shifts. Where the experimental value is a range, the mean value is used.

Atom #'s used in Tables 5.1 & 5.2, taken from reference **1b**.



Methods

General

Calculations (geometry optimization, frequency, and NMR chemical shift) were performed on C3-hydroxyl-N-methylwelwitindolinone C isonitrile (structure **5.4**) and its C3 epimer, as well as C3-hydroxyl-N-methylwelwitindolinone C isothiocyanate (structure **5.3**) and its C3 epimer.

Calculations were performed with GAUSSIAN09.[28] Geometries were optimized in the gas-phase using the B3LYP/6-31+G(d,p)[29] level of theory. Frequency calculations (at 298.15 K) at the same level of theory were used to confirm the nature of all stationary points as minima and also provided values for computed free energies. NMR single point calculations (GIAO)[30] were performed on these geometries at the mPW1PW91/6-311+G(d,p)[31] level of theory in an implicit chloroform solvent continuum (SMD[32] method).

Conformational Analysis

For structure **5.4** and its C3 epimer, nine candidate conformers (three conformations of the vinyl group and three conformations of the hydroxyl group) for each epimer were subjected to geometry optimization. This resulted in four unique conformers for structure **5.4** and six unique conformers of its C3 epimer. For both epimers, Boltzmann-weighted averaging of the computed chemical shifts based on the relative computed free energies at 298.15 K of each conformer was performed, using the equation below to determine relative populations.

$$\frac{P_i}{P_j} = e^{\frac{-(E_i - E_j)}{RT}}$$

P_i = population of conformer *i* relative to lowest energy conformer *j*
E_i, E_j = computed free energies (in J/mol)
R = molar gas constant (8.314510 J mol^{-1} K^{-1})
T = 298.15 K

The relative populations were then converted to Boltzmann-weighting factors by means of a set of linear equations.

Although only one conformer of the ring system seemed to be likely, both epimers of structure **5.4** were subjected to a conformational search (in Spartan'10).[33] As expected, only a single conformation of the ring system was found in each case.

For the isothiocyanate structure **5.3**, the major contributing (lowest energy) conformer of isonitrile structure **5.4** was converted into the corresponding isothiocyanate, and subjected to geometry optimization, followed by frequency and NMR chemical shift calculations (for both epimers).

Empirical Scaling of Computed NMR Chemical Shifts

Computed chemical shifts are commonly scaled empirically in order to remove systematic error that results from a variety of sources. The scaling factors themselves are generally determined by comparison of computed NMR data with known experimental chemical shifts for large databases of molecules. These factors (slope and intercept from a best fit line) are specific for each level of theory used computationally. We have generated numerous such scaling factors for ^{1}H and ^{13}C chemical shifts utilizing a database originally compiled by Rablen and co-workers and have made them available on our web site at http://cheshirenmr.info.

One of our preferred methods for obtaining high quality computed chemical shifts at reasonable costs is to use mPW1PW91/6-311+G(2d,p) NMR calculations (with the SMD chloroform continuum model) on B3LYP/6-31+G(d,p) geometries. After scaling, this method produces average errors (CMAD's) of 0.11-0.15 ppm for ^{1}H and 1.8-2.5 ppm for ^{13}C on diverse sets of small organic molecules. Details and numerous references on linear regression methods applied to computed chemical shifts can be found in our review paper.[22]

The specific scaling factors used in this study are given below and are applied to the computed NMR isotropic shielding constants by way of the equation shown.

δ = computed chemical shift relative to TMS
σ = computed isotropic shielding constant
m = slope, b = intercept

$$\delta = \frac{b - \sigma}{m}$$

DP4 Probability Analysis

For further support of our assignment to the C3(*S*) diastereomer for isonitrile structure **5.4**, we utilized the DP4 probability analysis of Smith and Goodman.[34] When both possible epimers were compared to the experimental data, the analysis suggested a 67.5% probability of C3(*S*) being correct based on the ^{13}C data, a 100% probability based on the ^{1}H data, and a 100% probability based on both sets of data.

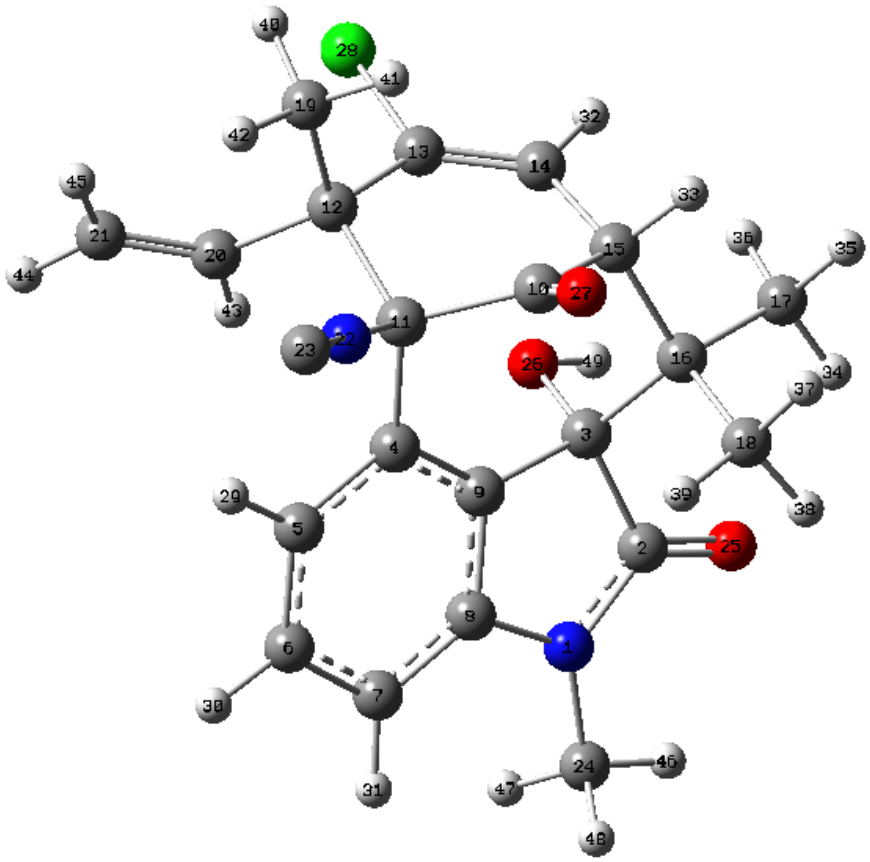
Energies, coordinates, and NMR isotropic shielding constants

Structure 5.4, conformer 1

Sum of electronic and thermal free energies = -1645.99519 H

Center Number	Atomic Number	Coordinates (Angstroms) X	Y	Z
1	7	-3.380511	0.751109	-0.617354
2	6	-3.108729	-0.579788	-0.477610
3	6	-1.576958	-0.739243	-0.229973
4	6	0.100593	1.342374	0.224316
5	6	0.166355	2.747156	0.083118
6	6	-0.926998	3.509133	-0.308650
7	6	-2.164939	2.908981	-0.547955
8	6	-2.224961	1.528726	-0.433403
9	6	-1.115549	0.717867	-0.099250
10	6	0.911574	-0.488942	1.794213
11	6	1.361546	0.651230	0.832091
12	6	2.441035	0.080430	-0.232322
13	6	1.991257	-1.302366	-0.688458
14	6	1.114541	-2.103441	-0.085843
15	6	0.340831	-1.738622	1.154370
16	6	-1.226129	-1.694004	0.949197
17	6	-1.694972	-3.141817	0.675179
18	6	-1.918249	-1.203489	2.239070
19	6	3.813867	-0.103077	0.460532
20	6	2.502368	1.034876	-1.415368
21	6	3.497088	1.873522	-1.710270
22	7	2.033204	1.616907	1.637432
23	6	2.586836	2.357422	2.363512
24	6	-4.681175	1.269742	-0.999762
25	8	-3.902935	-1.495419	-0.652588
26	8	-1.090993	-1.225047	-1.496027
27	8	1.040237	-0.387499	2.994192
28	17	2.810643	-1.908346	-2.135113
29	1	1.094865	3.254364	0.304017
30	1	-0.819288	4.585337	-0.400957
31	1	-3.037307	3.497044	-0.810138
32	1	0.936332	-3.087914	-0.503238
33	1	0.500607	-2.520825	1.907413
34	1	-2.776929	-3.181623	0.543748
35	1	-1.426114	-3.773261	1.528812
36	1	-1.231478	-3.576643	-0.214547
37	1	-1.578758	-1.786674	3.099890
38	1	-3.002030	-1.330487	2.154846
39	1	-1.711653	-0.151953	2.456298
40	1	4.498705	-0.599373	-0.230537
41	1	3.714525	-0.727653	1.352535
42	1	4.252712	0.847527	0.762572
43	1	1.626966	1.010046	-2.060573
44	1	3.429437	2.518753	-2.581112
45	1	4.403556	1.951460	-1.119072
46	1	-5.361472	0.421841	-1.084425
47	1	-4.622074	1.785227	-1.964582
48	1	-5.056951	1.965669	-0.242570
49	1	-1.689279	-1.931402	-1.787016

2	C	Isotropic =	5.3824	29	H	Isotropic =	23.9179
3	C	Isotropic =	101.9705	30	H	Isotropic =	23.7070
4	C	Isotropic =	49.7929	31	H	Isotropic =	24.3199
5	C	Isotropic =	55.7165	32	H	Isotropic =	24.8577
6	C	Isotropic =	51.0288	33	H	Isotropic =	28.2880
7	C	Isotropic =	72.1794	34	H	Isotropic =	29.1701
8	C	Isotropic =	34.1558	35	H	Isotropic =	30.8685
9	C	Isotropic =	53.9450	36	H	Isotropic =	30.0279
10	C	Isotropic =	-20.0573	37	H	Isotropic =	30.5775
11	C	Isotropic =	100.0258	38	H	Isotropic =	30.8627
12	C	Isotropic =	122.5598	39	H	Isotropic =	31.4457
13	C	Isotropic =	39.6653	40	H	Isotropic =	30.0039
14	C	Isotropic =	51.8523	41	H	Isotropic =	30.6930
15	C	Isotropic =	121.7132	42	H	Isotropic =	29.6167
16	C	Isotropic =	135.6107	43	H	Isotropic =	25.8003
17	C	Isotropic =	166.2994	44	H	Isotropic =	25.9664
18	C	Isotropic =	164.0007	45	H	Isotropic =	25.8850
19	C	Isotropic =	165.0069	46	H	Isotropic =	27.5588
20	C	Isotropic =	39.3145	47	H	Isotropic =	28.9537
21	C	Isotropic =	62.5941	48	H	Isotropic =	28.9597
23	C	Isotropic =	9.4942	49	H	Isotropic =	29.4283
24	C	Isotropic =	160.3779				

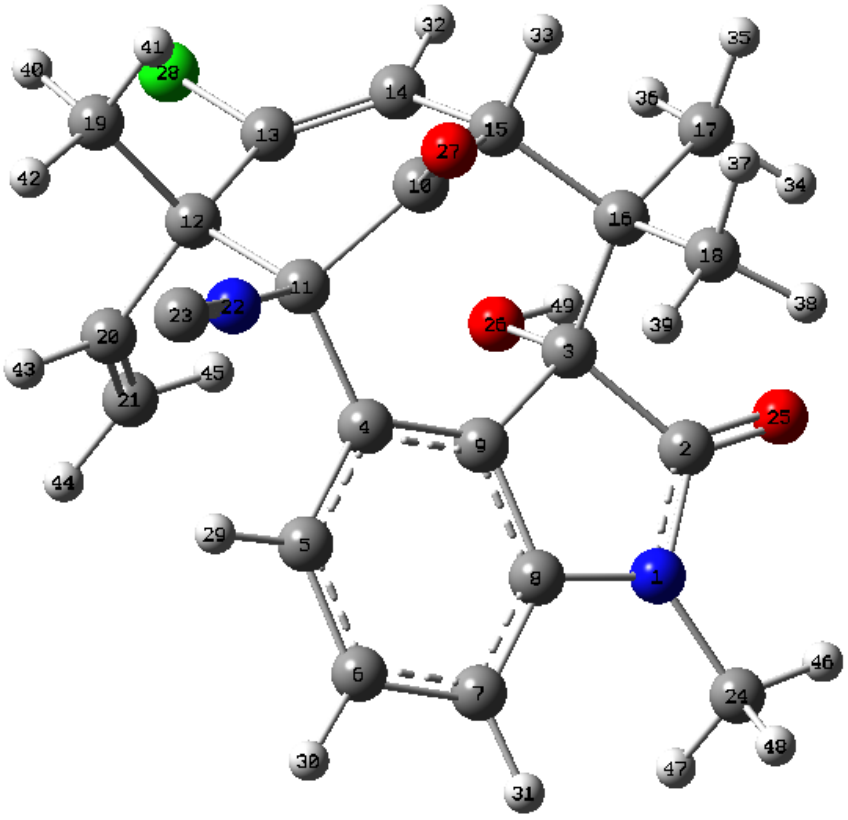


Structure 5.4, conformer 2

Sum of electronic and thermal free energies = -1645.992378 H

Center Number	Atomic Number	Coordinates (Angstroms) X	Y	Z
1	7	-3.389910	0.411641	-0.584188
2	6	-2.965521	-0.872239	-0.398840
3	6	-1.427194	-0.846062	-0.141642
4	6	0.012876	1.426251	0.172806
5	6	-0.088399	2.823398	-0.011922
6	6	-1.268385	3.441804	-0.404375
7	6	-2.431329	2.695800	-0.605917
8	6	-2.329062	1.322773	-0.445527
9	6	-1.129801	0.657371	-0.101630
10	6	1.030557	-0.187507	1.832779
11	6	1.356655	0.894958	0.758969
12	6	2.436090	0.330558	-0.322514
13	6	2.169786	-1.147259	-0.573941
14	6	1.396904	-1.962253	0.142545
15	6	0.567402	-1.538793	1.325806
16	6	-0.991904	-1.665159	1.111119
17	6	-1.311230	-3.169442	0.949863
18	6	-1.738553	-1.147243	2.358981
19	6	3.869594	0.421973	0.274214
20	6	2.371154	1.204721	-1.566937
21	6	1.672684	0.966313	-2.677686
22	7	1.980856	1.972917	1.454311
23	6	2.499432	2.806413	2.101395
24	6	-4.742986	0.763434	-0.974618
25	8	-3.645808	-1.880969	-0.539796
26	8	-0.879667	-1.372703	-1.364425
27	8	1.169300	0.037695	3.014619
28	17	3.113201	-1.882915	-1.883336
29	1	0.776650	3.444181	0.173272
30	1	-1.286911	4.519781	-0.530763
31	1	-3.369095	3.170462	-0.871934
32	1	1.366618	-3.013474	-0.122288
33	1	0.786676	-2.220689	2.157072
34	1	-2.383033	-3.328798	0.826617
35	1	-0.982069	-3.705397	1.846601
36	1	-0.803240	-3.618029	0.092046
37	1	-1.359121	-1.638557	3.259701
38	1	-2.806525	-1.374337	2.280869
39	1	-1.625833	-0.069313	2.502672
40	1	4.565784	-0.076892	-0.403155
41	1	3.926828	-0.068257	1.250262
42	1	4.188723	1.458815	0.387579
43	1	2.951041	2.123283	-1.491520
44	1	1.689639	1.674541	-3.500899
45	1	1.066322	0.074939	-2.805571
46	1	-5.322154	-0.159042	-1.024872
47	1	-4.746801	1.248298	-1.956963
48	1	-5.193416	1.438110	-0.239220
49	1	-1.404343	-2.153019	-1.604425

2	C	Isotropic =	4.9313	29	H	Isotropic =	23.8898
3	C	Isotropic =	101.8846	30	H	Isotropic =	23.7819
4	C	Isotropic =	47.7504	31	H	Isotropic =	24.3539
5	C	Isotropic =	56.1850	32	H	Isotropic =	24.8360
6	C	Isotropic =	50.5833	33	H	Isotropic =	28.3687
7	C	Isotropic =	72.3931	34	H	Isotropic =	29.2774
8	C	Isotropic =	34.0780	35	H	Isotropic =	30.8967
9	C	Isotropic =	54.5485	36	H	Isotropic =	29.9107
10	C	Isotropic =	-19.4205	37	H	Isotropic =	30.6386
11	C	Isotropic =	98.4760	38	H	Isotropic =	30.9444
12	C	Isotropic =	120.3660	39	H	Isotropic =	31.4424
13	C	Isotropic =	39.7763	40	H	Isotropic =	29.7032
14	C	Isotropic =	48.9210	41	H	Isotropic =	30.6575
15	C	Isotropic =	121.5678	42	H	Isotropic =	29.9034
16	C	Isotropic =	135.6714	43	H	Isotropic =	25.7159
17	C	Isotropic =	166.5375	44	H	Isotropic =	26.1295
18	C	Isotropic =	164.1755	45	H	Isotropic =	26.4239
19	C	Isotropic =	158.0736	46	H	Isotropic =	27.5589
20	C	Isotropic =	40.9847	47	H	Isotropic =	28.9945
21	C	Isotropic =	54.8881	48	H	Isotropic =	28.9520
23	C	Isotropic =	7.6178	49	H	Isotropic =	29.4036
24	C	Isotropic =	160.4337				

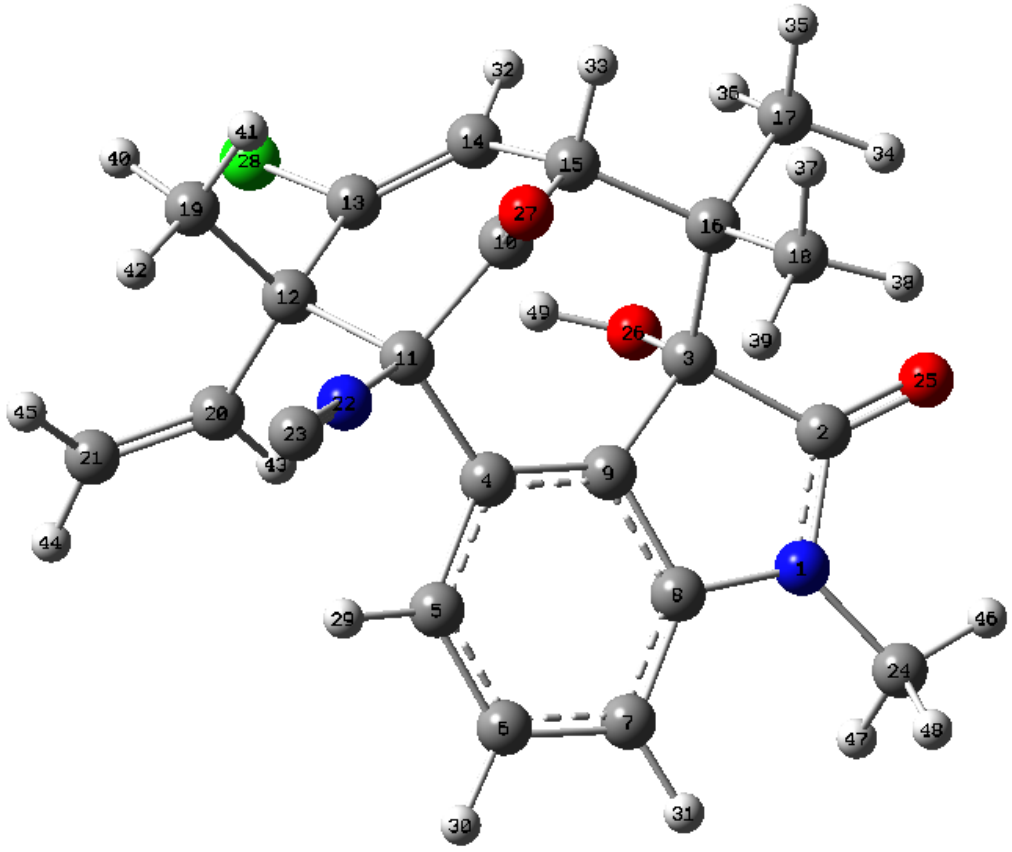


Structure 5.4, conformer 3

Sum of electronic and thermal free energies = -1645.993819 H

Center Number	Atomic Number	Coordinates (Angstroms) X	Y	Z
1	7	-3.368932	0.825648	-0.629677
2	6	-3.157544	-0.516396	-0.430269
3	6	-1.615809	-0.722439	-0.255060
4	6	0.110041	1.315147	0.269538
5	6	0.216937	2.720030	0.145044
6	6	-0.846054	3.511664	-0.269219
7	6	-2.092278	2.944669	-0.546407
8	6	-2.196843	1.566140	-0.436883
9	6	-1.116419	0.723442	-0.077750
10	6	0.893998	-0.610775	1.760484
11	6	1.349943	0.587841	0.876648
12	6	2.449760	0.069134	-0.194197
13	6	1.964466	-1.253081	-0.780820
14	6	1.076899	-2.090895	-0.235152
15	6	0.318438	-1.813115	1.038195
16	6	-1.251673	-1.752414	0.852265
17	6	-1.730562	-3.171703	0.473467
18	6	-1.918724	-1.347152	2.184506
19	6	3.784465	-0.234372	0.531732
20	6	2.603352	1.114144	-1.288207
21	6	3.654511	1.911392	-1.484484
22	7	2.010776	1.505779	1.742841
23	6	2.556233	2.206743	2.513309
24	6	-4.666021	1.390904	-0.949739
25	8	-4.017924	-1.377950	-0.464930
26	8	-1.278846	-1.185915	-1.578005
27	8	1.025223	-0.591597	2.963826
28	17	2.785009	-1.759528	-2.265224
29	1	1.151272	3.201081	0.398496
30	1	-0.709502	4.585596	-0.349512
31	1	-2.941161	3.557803	-0.827679
32	1	0.888501	-3.043511	-0.719605
33	1	0.487428	-2.651677	1.725197
34	1	-2.816004	-3.189593	0.373942
35	1	-1.437135	-3.875270	1.260605
36	1	-1.313172	-3.510827	-0.476299
37	1	-1.562267	-1.983655	2.999523
38	1	-3.002208	-1.472190	2.108315
39	1	-1.710453	-0.310705	2.465781
40	1	4.481365	-0.696440	-0.171052
41	1	3.625627	-0.926805	1.362777
42	1	4.242145	0.670104	0.931887
43	1	1.750170	1.203559	-1.957080
44	1	3.652028	2.630787	-2.297749
45	1	4.544204	1.883991	-0.864411
46	1	-5.377827	0.566846	-1.006027
47	1	-4.632832	1.908513	-1.914460
48	1	-4.985630	2.095613	-0.174126
49	1	-0.322909	-1.100994	-1.701002

2	C	Isotropic =	8.2332	29	H	Isotropic =	23.9698
3	C	Isotropic =	100.9151	30	H	Isotropic =	23.7605
4	C	Isotropic =	52.2624	31	H	Isotropic =	24.4222
5	C	Isotropic =	56.4224	32	H	Isotropic =	24.6004
6	C	Isotropic =	51.0441	33	H	Isotropic =	28.2420
7	C	Isotropic =	72.3600	34	H	Isotropic =	28.9353
8	C	Isotropic =	34.2295	35	H	Isotropic =	30.8612
9	C	Isotropic =	52.2202	36	H	Isotropic =	29.6794
10	C	Isotropic =	-19.6241	37	H	Isotropic =	30.4989
11	C	Isotropic =	100.3225	38	H	Isotropic =	30.7159
12	C	Isotropic =	122.0071	39	H	Isotropic =	31.5247
13	C	Isotropic =	36.0314	40	H	Isotropic =	30.1151
14	C	Isotropic =	50.0042	41	H	Isotropic =	30.6694
15	C	Isotropic =	121.3573	42	H	Isotropic =	29.6456
16	C	Isotropic =	135.2910	43	H	Isotropic =	25.8986
17	C	Isotropic =	165.0367	44	H	Isotropic =	25.7683
18	C	Isotropic =	163.3592	45	H	Isotropic =	25.7723
19	C	Isotropic =	166.0095	46	H	Isotropic =	27.5553
20	C	Isotropic =	40.3261	47	H	Isotropic =	28.9550
21	C	Isotropic =	61.0648	48	H	Isotropic =	29.0701
23	C	Isotropic =	9.3674	49	H	Isotropic =	29.2466
24	C	Isotropic =	160.7578				

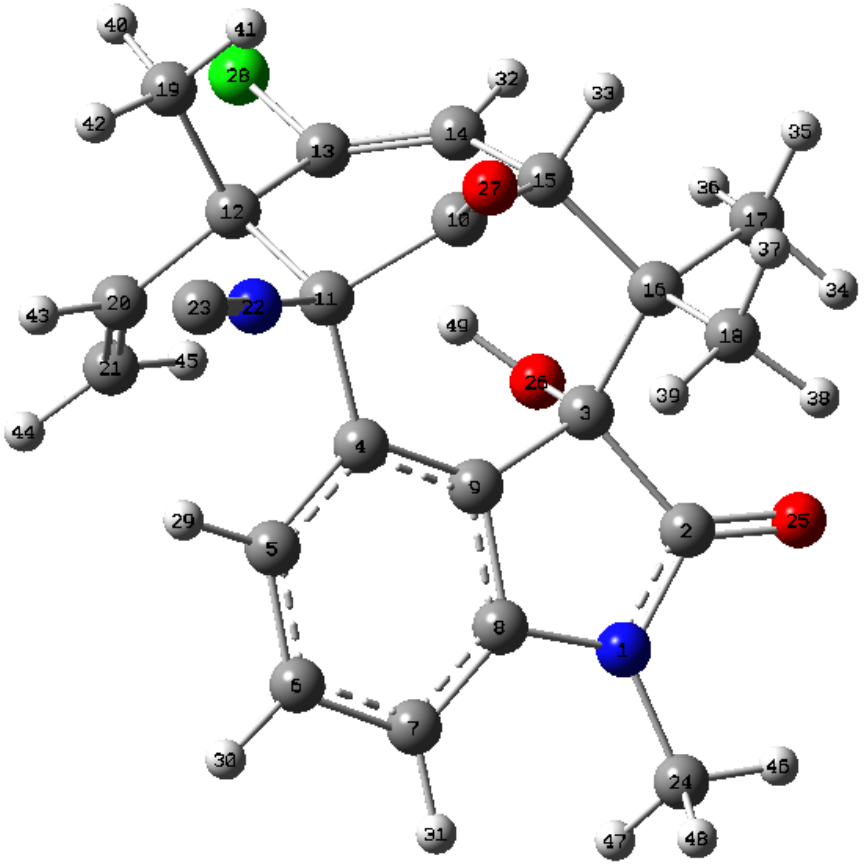


Structure 5.4, conformer 4

Sum of electronic and thermal free energies = -1645.990807 H

Center Number	Atomic Number	Coordinates (Angstroms) X	Y	Z
1	7	-3.383740	0.566778	-0.610315
2	6	-3.053866	-0.749632	-0.404647
3	6	-1.502026	-0.816780	-0.214802
4	6	0.041698	1.369611	0.272369
5	6	0.019676	2.777398	0.141515
6	6	-1.111888	3.469606	-0.267287
7	6	-2.302822	2.791942	-0.538165
8	6	-2.281883	1.410361	-0.422782
9	6	-1.130076	0.669650	-0.061469
10	6	0.985067	-0.440706	1.799880
11	6	1.344407	0.756735	0.872524
12	6	2.471665	0.293020	-0.205474
13	6	2.119896	-1.097394	-0.718871
14	6	1.302069	-1.977261	-0.128904
15	6	0.502608	-1.706429	1.120501
16	6	-1.064392	-1.781722	0.924539
17	6	-1.419350	-3.245934	0.582480
18	6	-1.770669	-1.396033	2.241871
19	6	3.848229	0.151181	0.507979
20	6	2.589793	1.375056	-1.266159
21	6	2.063455	1.389910	-2.491065
22	7	1.949458	1.746286	1.702698
23	6	2.450688	2.501879	2.451465
24	6	-4.725876	1.012629	-0.932908
25	8	-3.833050	-1.685569	-0.439157
26	8	-1.108252	-1.282675	-1.518983
27	8	1.118726	-0.370258	3.001027
28	17	3.064853	-1.681170	-2.100933
29	1	0.906429	3.344477	0.387287
30	1	-1.072432	4.551192	-0.351229
31	1	-3.204506	3.324865	-0.818126
32	1	1.228235	-2.977031	-0.544828
33	1	0.731191	-2.503770	1.838738
34	1	-2.499142	-3.360044	0.484947
35	1	-1.066253	-3.902404	1.385728
36	1	-0.973398	-3.569377	-0.359684
37	1	-1.371713	-1.981726	3.075163
38	1	-2.840486	-1.607855	2.163737
39	1	-1.645868	-0.339626	2.496583
40	1	4.568505	-0.279372	-0.191013
41	1	3.779438	-0.504005	1.381016
42	1	4.225967	1.121416	0.832729
43	1	3.160923	2.240385	-0.934546
44	1	2.211380	2.246374	-3.141755
45	1	1.480996	0.570431	-2.899529
46	1	-5.360630	0.127838	-0.989069
47	1	-4.738278	1.530177	-1.898183
48	1	-5.108798	1.686745	-0.158694
49	1	-0.151893	-1.164749	-1.608721

2	C	Isotropic =	8.2386	29	H	Isotropic =	23.9665
3	C	Isotropic =	100.8098	30	H	Isotropic =	23.7824
4	C	Isotropic =	50.6591	31	H	Isotropic =	24.4111
5	C	Isotropic =	55.8937	32	H	Isotropic =	24.4481
6	C	Isotropic =	51.4584	33	H	Isotropic =	28.2770
7	C	Isotropic =	72.3683	34	H	Isotropic =	28.9619
8	C	Isotropic =	34.4162	35	H	Isotropic =	30.8492
9	C	Isotropic =	52.3402	36	H	Isotropic =	29.6213
10	C	Isotropic =	-19.4601	37	H	Isotropic =	30.5030
11	C	Isotropic =	99.3093	38	H	Isotropic =	30.7587
12	C	Isotropic =	119.5882	39	H	Isotropic =	31.5047
13	C	Isotropic =	36.6404	40	H	Isotropic =	29.7433
14	C	Isotropic =	46.8267	41	H	Isotropic =	30.5658
15	C	Isotropic =	121.3607	42	H	Isotropic =	29.8611
16	C	Isotropic =	135.3283	43	H	Isotropic =	25.4891
17	C	Isotropic =	165.1747	44	H	Isotropic =	26.0009
18	C	Isotropic =	163.5269	45	H	Isotropic =	26.6548
19	C	Isotropic =	159.0525	46	H	Isotropic =	27.5470
20	C	Isotropic =	42.1685	47	H	Isotropic =	28.9975
21	C	Isotropic =	56.4925	48	H	Isotropic =	29.0701
23	C	Isotropic =	8.0406	49	H	Isotropic =	29.0085
24	C	Isotropic =	160.7613				

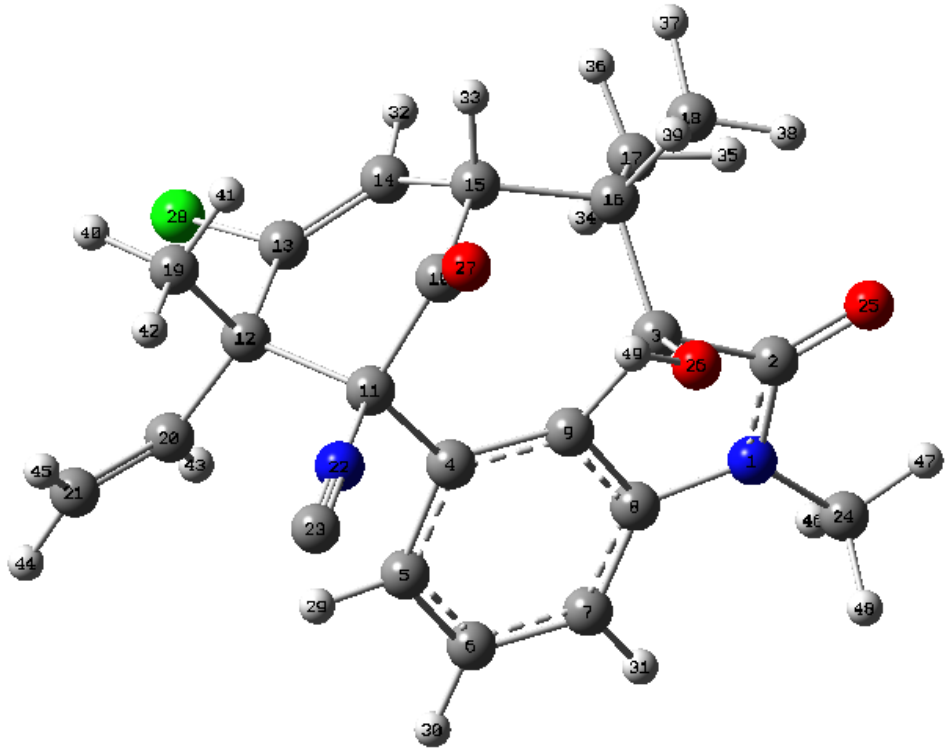


Structure 5.4, C3 epimer, conformer 1

Sum of electronic and thermal free energies = -1645.990153 H

Center Number	Atomic Number	Coordinates (Angstroms) X	Y	Z
1	7	-3.288099	1.175668	-0.492135
2	6	-3.342285	-0.126122	-0.051393
3	6	-1.919172	-0.517146	0.467896
4	6	0.216887	1.116132	0.417828
5	6	0.574596	2.469902	0.244971
6	6	-0.328608	3.404260	-0.250180
7	6	-1.640543	3.038434	-0.570087
8	6	-2.007208	1.721176	-0.330716
9	6	-1.109312	0.751089	0.163076
10	6	0.677127	-1.267257	1.184698
11	6	1.289584	0.140867	0.966776
12	6	2.575046	-0.092689	0.000328
13	6	2.049458	-0.793428	-1.248061
14	6	0.990422	-1.602758	-1.280469
15	6	0.181495	-1.977392	-0.064002
16	6	-1.406789	-1.847788	-0.199949
17	6	-1.804230	-1.873909	-1.691333
18	6	-2.052391	-3.058982	0.505371
19	6	3.567136	-1.054323	0.705381
20	6	3.251073	1.220955	-0.359613
21	6	4.341876	1.730577	0.216459
22	7	1.754250	0.642592	2.213633
23	6	2.123883	1.053143	3.252223
24	6	-4.450401	1.908166	-0.958184
25	8	-4.337098	-0.828475	-0.041046
26	8	-2.162345	-0.633914	1.873909
27	8	0.582003	-1.758320	2.292595
28	17	3.012929	-0.604441	-2.717114
29	1	1.565825	2.796251	0.528119
30	1	-0.012579	4.435246	-0.376291
31	1	-2.349097	3.766197	-0.949937
32	1	0.745583	-2.103865	-2.209250
33	1	0.362853	-3.043980	0.123176
34	1	-1.454774	-0.989199	-2.233915
35	1	-2.890367	-1.935564	-1.783427
36	1	-1.388636	-2.758513	-2.183704
37	1	-1.801792	-3.972569	-0.046034
38	1	-3.138164	-2.948786	0.529867
39	1	-1.696158	-3.173178	1.531216
40	1	4.421744	-1.229297	0.047779
41	1	3.103579	-2.019656	0.922715
42	1	3.929574	-0.637874	1.646851
43	1	2.788680	1.770696	-1.173443
44	1	4.746011	2.680106	-0.121828
45	1	4.868284	1.245979	1.031658
46	1	-4.286205	2.289523	-1.971632
47	1	-5.294088	1.217278	-0.961382
48	1	-4.673133	2.747444	-0.289889
49	1	-1.356329	-0.880342	2.350000

2	C	Isotropic =	8.1779	29	H	Isotropic =	23.7702
3	C	Isotropic =	101.0505	30	H	Isotropic =	23.7763
4	C	Isotropic =	47.8541	31	H	Isotropic =	24.4329
5	C	Isotropic =	57.3462	32	H	Isotropic =	25.3772
6	C	Isotropic =	51.2848	33	H	Isotropic =	28.2214
7	C	Isotropic =	71.9486	34	H	Isotropic =	31.0741
8	C	Isotropic =	35.1191	35	H	Isotropic =	30.3962
9	C	Isotropic =	50.6689	36	H	Isotropic =	30.6682
10	C	Isotropic =	-31.7935	37	H	Isotropic =	30.6696
11	C	Isotropic =	103.2573	38	H	Isotropic =	29.3534
12	C	Isotropic =	123.3461	39	H	Isotropic =	29.7256
13	C	Isotropic =	36.3752	40	H	Isotropic =	30.2138
14	C	Isotropic =	53.0628	41	H	Isotropic =	30.9754
15	C	Isotropic =	124.3429	42	H	Isotropic =	29.6424
16	C	Isotropic =	136.0421	43	H	Isotropic =	24.9394
17	C	Isotropic =	162.8294	44	H	Isotropic =	25.6098
18	C	Isotropic =	161.6207	45	H	Isotropic =	25.7081
19	C	Isotropic =	164.8084	46	H	Isotropic =	29.0151
20	C	Isotropic =	39.1842	47	H	Isotropic =	27.6030
21	C	Isotropic =	59.8987	48	H	Isotropic =	29.0021
23	C	Isotropic =	10.1194	49	H	Isotropic =	29.7586
24	C	Isotropic =	160.7944				

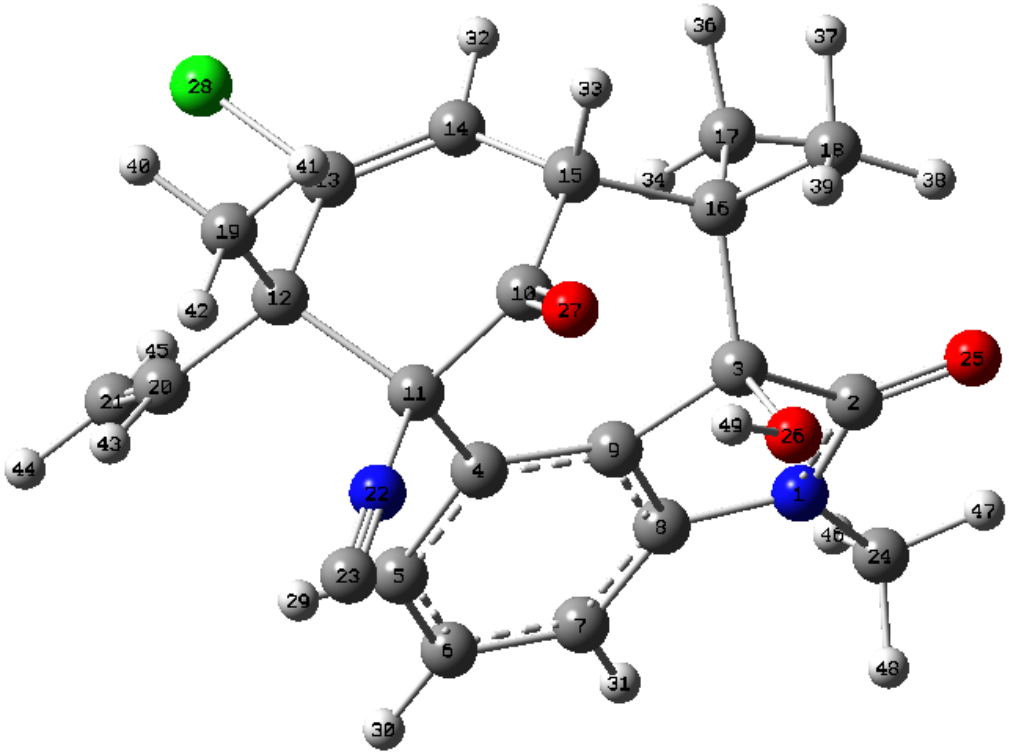


Structure 5.4, C3 epimer, conformer 2

Sum of electronic and thermal free energies = -1645.984941 H

Center Number	Atomic Number	Coordinates (Angstroms) X	Y	Z
1	7	-3.278393	1.117972	-0.533461
2	6	-3.310383	-0.209469	-0.178852
3	6	-1.902906	-0.587507	0.389296
4	6	0.185832	1.105916	0.535168
5	6	0.498441	2.480029	0.471956
6	6	-0.414085	3.416622	-0.001700
7	6	-1.694216	3.031209	-0.411083
8	6	-2.023780	1.689516	-0.276956
9	6	-1.117140	0.717749	0.196082
10	6	0.678948	-1.295351	1.201769
11	6	1.266480	0.132206	1.075058
12	6	2.607114	-0.025916	0.162271
13	6	2.176542	-0.689437	-1.139566
14	6	1.130719	-1.511176	-1.253244
15	6	0.261511	-1.951592	-0.102602
16	6	-1.317902	-1.862164	-0.319460
17	6	-1.631250	-1.813554	-1.830465
18	6	-1.963050	-3.129295	0.280033
19	6	3.588562	-1.007686	0.872083
20	6	3.341014	1.300907	0.055371
21	6	3.389177	2.161408	-0.962656
22	7	1.668367	0.584181	2.365535
23	6	1.977950	0.945099	3.441586
24	6	-4.440003	1.843416	-1.011636
25	8	-4.279727	-0.942319	-0.263731
26	8	-2.211929	-0.787911	1.773533
27	8	0.548325	-1.842008	2.279464
28	17	3.272230	-0.583978	-2.525662
29	1	1.463443	2.821562	0.813100
30	1	-0.129282	4.463551	-0.041017
31	1	-2.410581	3.759099	-0.775830
32	1	0.969213	-2.010491	-2.201256
33	1	0.466678	-3.020853	0.041535
34	1	-1.277141	-0.890238	-2.301119
35	1	-2.708330	-1.897056	-1.988036
36	1	-1.163913	-2.657356	-2.347271
37	1	-1.653516	-4.002908	-0.305300
38	1	-3.051393	-3.051544	0.248445
39	1	-1.661113	-3.290452	1.316941
40	1	4.477093	-1.126810	0.246868
41	1	3.145988	-1.995540	1.023409
42	1	3.899830	-0.615425	1.842892
43	1	3.899484	1.542858	0.957834
44	1	3.981398	3.068289	-0.877126
45	1	2.857633	2.015263	-1.895536
46	1	-4.242538	2.286829	-1.993526
47	1	-5.261236	1.130562	-1.092827
48	1	-4.718029	2.636531	-0.308601
49	1	-1.420214	-1.020993	2.279312

2	C	Isotropic =	8.5407	29	H	Isotropic =	23.7140
3	C	Isotropic =	100.7337	30	H	Isotropic =	23.8762
4	C	Isotropic =	48.2975	31	H	Isotropic =	24.4155
5	C	Isotropic =	56.1226	32	H	Isotropic =	25.3406
6	C	Isotropic =	52.0942	33	H	Isotropic =	28.1967
7	C	Isotropic =	72.0936	34	H	Isotropic =	31.0889
8	C	Isotropic =	35.5088	35	H	Isotropic =	30.4055
9	C	Isotropic =	50.9200	36	H	Isotropic =	30.6679
10	C	Isotropic =	-31.9216	37	H	Isotropic =	30.7191
11	C	Isotropic =	103.7739	38	H	Isotropic =	29.3263
12	C	Isotropic =	120.9632	39	H	Isotropic =	29.6950
13	C	Isotropic =	38.4030	40	H	Isotropic =	29.8207
14	C	Isotropic =	50.6647	41	H	Isotropic =	30.8758
15	C	Isotropic =	123.5190	42	H	Isotropic =	29.8531
16	C	Isotropic =	137.1848	43	H	Isotropic =	25.2441
17	C	Isotropic =	162.7858	44	H	Isotropic =	25.4090
18	C	Isotropic =	161.7333	45	H	Isotropic =	26.1240
19	C	Isotropic =	159.8194	46	H	Isotropic =	29.0313
20	C	Isotropic =	43.5803	47	H	Isotropic =	27.5970
21	C	Isotropic =	52.4288	48	H	Isotropic =	29.0234
23	C	Isotropic =	9.4675	49	H	Isotropic =	29.7756
24	C	Isotropic =	160.9283				

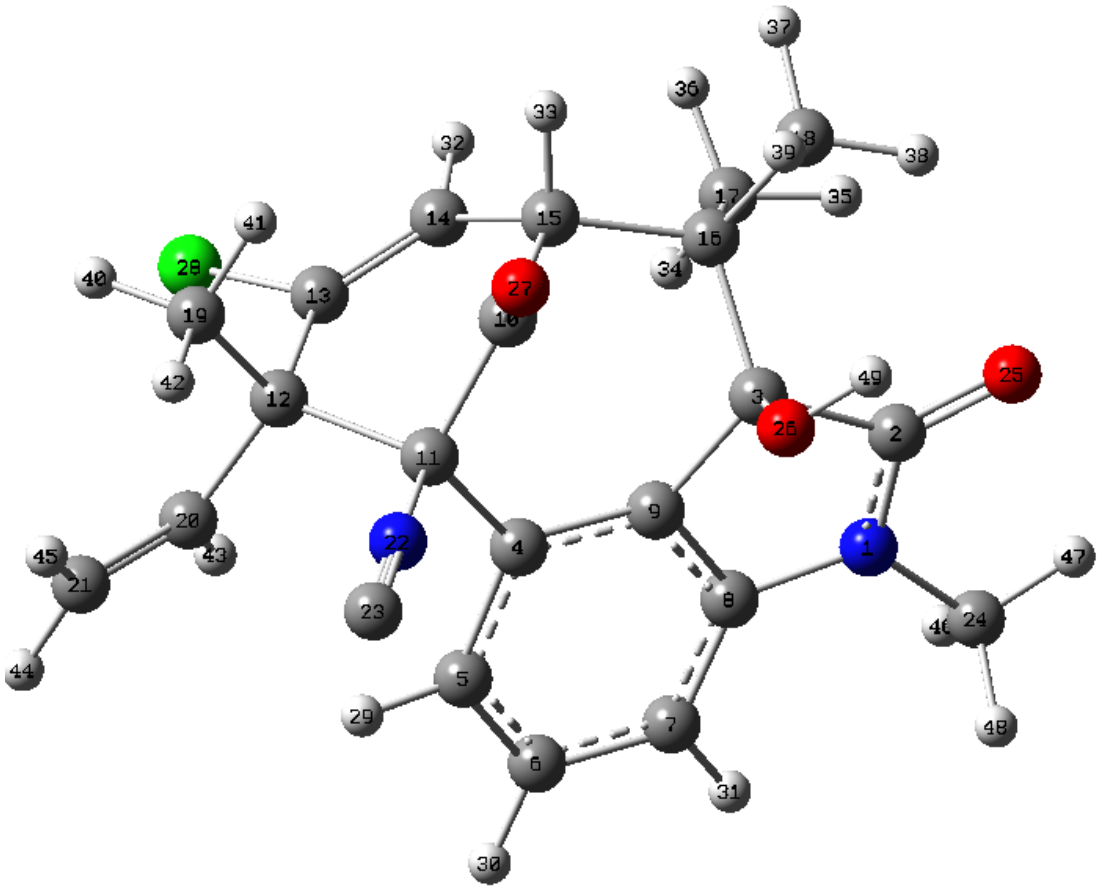


Structure 5.4, C3 epimer, conformer 3

Sum of electronic and thermal free energies = -1645.993218 H

Center Number	Atomic Number	Coordinates (Angstroms) X	Y	Z
1	7	-3.304913	1.158080	-0.473247
2	6	-3.343767	-0.124220	0.012860
3	6	-1.900808	-0.526113	0.438143
4	6	0.202583	1.098414	0.441505
5	6	0.549857	2.458531	0.300853
6	6	-0.349169	3.394542	-0.201661
7	6	-1.654658	3.030875	-0.552499
8	6	-2.016782	1.709150	-0.335573
9	6	-1.114512	0.741754	0.146499
10	6	0.712752	-1.342329	1.145440
11	6	1.262646	0.108362	0.982553
12	6	2.560517	-0.074405	0.005008
13	6	2.038092	-0.733226	-1.267192
14	6	0.977493	-1.539015	-1.335178
15	6	0.165346	-1.970739	-0.137086
16	6	-1.410666	-1.832481	-0.278582
17	6	-1.827944	-1.804664	-1.763284
18	6	-2.052035	-3.069296	0.389982
19	6	3.578225	-1.040036	0.666839
20	6	3.217110	1.261431	-0.309193
21	6	4.289669	1.774829	0.297376
22	7	1.719682	0.579075	2.241375
23	6	2.085755	0.958664	3.292619
24	6	-4.488163	1.905444	-0.858646
25	8	-4.346060	-0.811932	0.151027
26	8	-1.913560	-0.658144	1.862321
27	8	0.831333	-1.960728	2.176980
28	17	3.004922	-0.490953	-2.728440
29	1	1.529805	2.790146	0.614743
30	1	-0.036243	4.429139	-0.304160
31	1	-2.360881	3.764169	-0.926083
32	1	0.737318	-2.002744	-2.285010
33	1	0.350153	-3.045699	-0.012173
34	1	-1.474030	-0.906708	-2.279741
35	1	-2.916945	-1.848538	-1.846404
36	1	-1.430496	-2.676692	-2.291910
37	1	-1.805258	-3.964359	-0.191192
38	1	-3.141320	-2.978058	0.419119
39	1	-1.671232	-3.222910	1.403675
40	1	4.445008	-1.142476	0.009787
41	1	3.150534	-2.030982	0.826388
42	1	3.914830	-0.662151	1.634015
43	1	2.757918	1.825543	-1.114875
44	1	4.680780	2.740848	-0.008234
45	1	4.811897	1.277404	1.107423
46	1	-4.380090	2.298264	-1.874694
47	1	-5.337383	1.222389	-0.820208
48	1	-4.662884	2.738110	-0.167863
49	1	-2.611489	-1.284980	2.106659

2	C	Isotropic =	4.5082	29	H	Isotropic =	23.7408
3	C	Isotropic =	102.2206	30	H	Isotropic =	23.7433
4	C	Isotropic =	46.4347	31	H	Isotropic =	24.3823
5	C	Isotropic =	56.3911	32	H	Isotropic =	25.4292
6	C	Isotropic =	51.1940	33	H	Isotropic =	28.4365
7	C	Isotropic =	71.9627	34	H	Isotropic =	31.0058
8	C	Isotropic =	35.0494	35	H	Isotropic =	30.6109
9	C	Isotropic =	52.6692	36	H	Isotropic =	30.6921
10	C	Isotropic =	-22.5454	37	H	Isotropic =	30.6963
11	C	Isotropic =	104.8751	38	H	Isotropic =	29.5775
12	C	Isotropic =	122.4370	39	H	Isotropic =	29.9092
13	C	Isotropic =	36.5446	40	H	Isotropic =	30.3197
14	C	Isotropic =	52.0920	41	H	Isotropic =	30.9179
15	C	Isotropic =	123.7915	42	H	Isotropic =	29.7019
16	C	Isotropic =	136.4725	43	H	Isotropic =	24.9580
17	C	Isotropic =	164.0214	44	H	Isotropic =	25.6285
18	C	Isotropic =	164.0273	45	H	Isotropic =	25.6935
19	C	Isotropic =	164.9704	46	H	Isotropic =	28.9284
20	C	Isotropic =	38.3761	47	H	Isotropic =	27.6248
21	C	Isotropic =	60.1109	48	H	Isotropic =	29.0147
23	C	Isotropic =	11.2619	49	H	Isotropic =	29.5616
24	C	Isotropic =	160.4922				

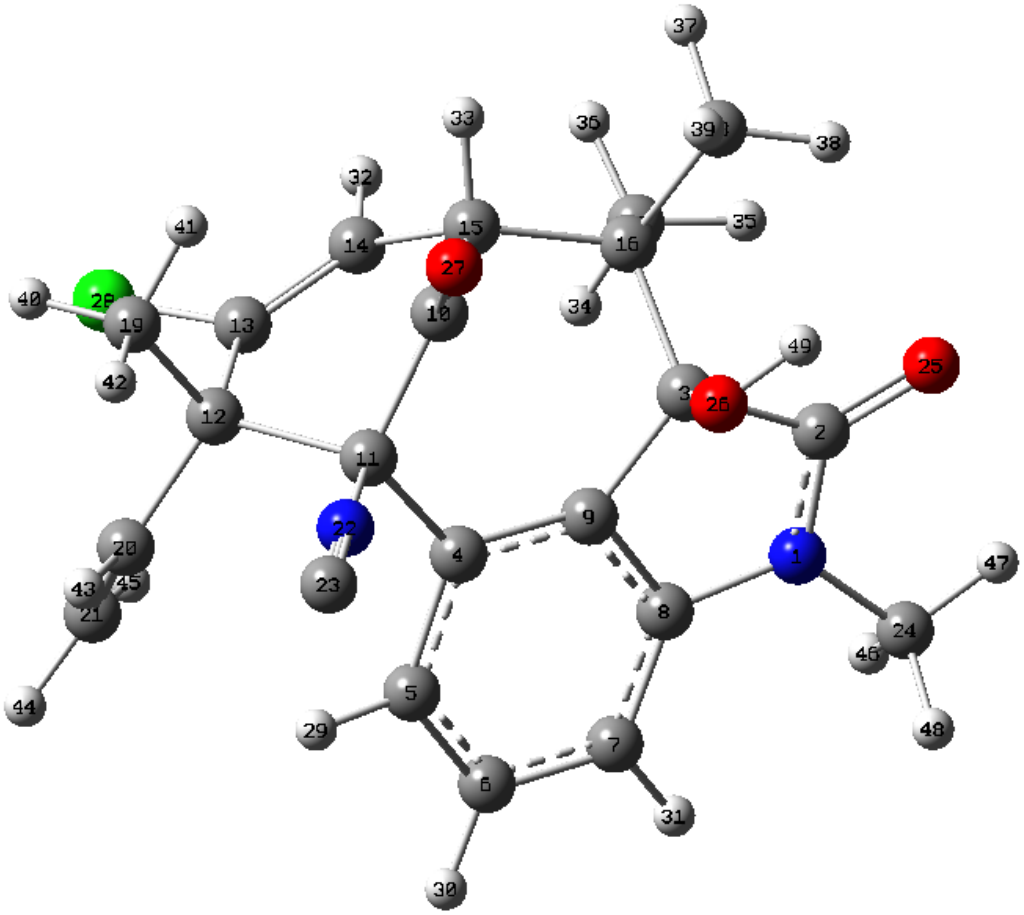


Structure 5.4, C3 epimer, conformer 4

Sum of electronic and thermal free energies = -1645.987825 H

Center Number	Atomic Number	Coordinates (Angstroms) X	Y	Z
1	7	-3.296992	1.098062	-0.519742
2	6	-3.317437	-0.210481	-0.111600
3	6	-1.884018	-0.593435	0.359311
4	6	0.167951	1.087122	0.557247
5	6	0.468669	2.464755	0.525766
6	6	-0.438472	3.403086	0.042077
7	6	-1.709896	3.021859	-0.399926
8	6	-2.034115	1.677458	-0.287498
9	6	-1.123219	0.709965	0.176459
10	6	0.714456	-1.368430	1.162040
11	6	1.234122	0.098595	1.090693
12	6	2.587794	-0.006527	0.172366
13	6	2.166070	-0.632158	-1.150719
14	6	1.121171	-1.449679	-1.302106
15	6	0.245808	-1.942975	-0.174963
16	6	-1.320668	-1.840181	-0.402156
17	6	-1.650628	-1.730027	-1.905135
18	6	-1.963149	-3.132190	0.150963
19	6	3.600765	-0.983010	0.844450
20	6	3.295345	1.337588	0.109250
21	6	3.360863	2.218882	-0.890052
22	7	1.625594	0.519045	2.392415
23	6	1.929422	0.848788	3.479734
24	6	-4.483964	1.831598	-0.919345
25	8	-4.301992	-0.935598	-0.063345
26	8	-1.957268	-0.806376	1.772259
27	8	0.808081	-2.034886	2.165788
28	17	3.272247	-0.483221	-2.526924
29	1	1.419198	2.810462	0.901120
30	1	-0.157996	4.451844	0.025838
31	1	-2.423665	3.754808	-0.759696
32	1	0.969832	-1.914653	-2.269756
33	1	0.455063	-3.017670	-0.091631
34	1	-1.288388	-0.794356	-2.343013
35	1	-2.731464	-1.790928	-2.056824
36	1	-1.202105	-2.559204	-2.460985
37	1	-1.657828	-3.982723	-0.468039
38	1	-3.054361	-3.070632	0.122706
39	1	-1.636281	-3.339575	1.173934
40	1	4.498186	-1.032525	0.222334
41	1	3.198684	-1.992566	0.946629
42	1	3.887046	-0.623190	1.835406
43	1	3.824146	1.570334	1.031876
44	1	3.936363	3.132432	-0.768057
45	1	2.859783	2.084733	-1.841219
46	1	-4.339782	2.288596	-1.903624
47	1	-5.310886	1.122067	-0.964380
48	1	-4.720173	2.615082	-0.190315
49	1	-2.645567	-1.466065	1.947961

2	C	Isotropic =	4.8033	29	H	Isotropic =	23.7027
3	C	Isotropic =	101.9481	30	H	Isotropic =	23.8476
4	C	Isotropic =	47.3036	31	H	Isotropic =	24.3863
5	C	Isotropic =	54.9469	32	H	Isotropic =	25.4145
6	C	Isotropic =	52.1010	33	H	Isotropic =	28.4066
7	C	Isotropic =	72.2651	34	H	Isotropic =	31.0133
8	C	Isotropic =	35.5006	35	H	Isotropic =	30.6263
9	C	Isotropic =	52.9277	36	H	Isotropic =	30.6721
10	C	Isotropic =	-22.4746	37	H	Isotropic =	30.6941
11	C	Isotropic =	105.2378	38	H	Isotropic =	29.5224
12	C	Isotropic =	119.2896	39	H	Isotropic =	29.8903
13	C	Isotropic =	38.7276	40	H	Isotropic =	29.9140
14	C	Isotropic =	49.9270	41	H	Isotropic =	30.7893
15	C	Isotropic =	122.8680	42	H	Isotropic =	29.8884
16	C	Isotropic =	137.0406	43	H	Isotropic =	25.2216
17	C	Isotropic =	163.9270	44	H	Isotropic =	25.4410
18	C	Isotropic =	164.2834	45	H	Isotropic =	26.1526
19	C	Isotropic =	160.3357	46	H	Isotropic =	28.9489
20	C	Isotropic =	42.8063	47	H	Isotropic =	27.6230
21	C	Isotropic =	53.4203	48	H	Isotropic =	29.0286
23	C	Isotropic =	10.6569	49	H	Isotropic =	29.5085
24	C	Isotropic =	160.6551				

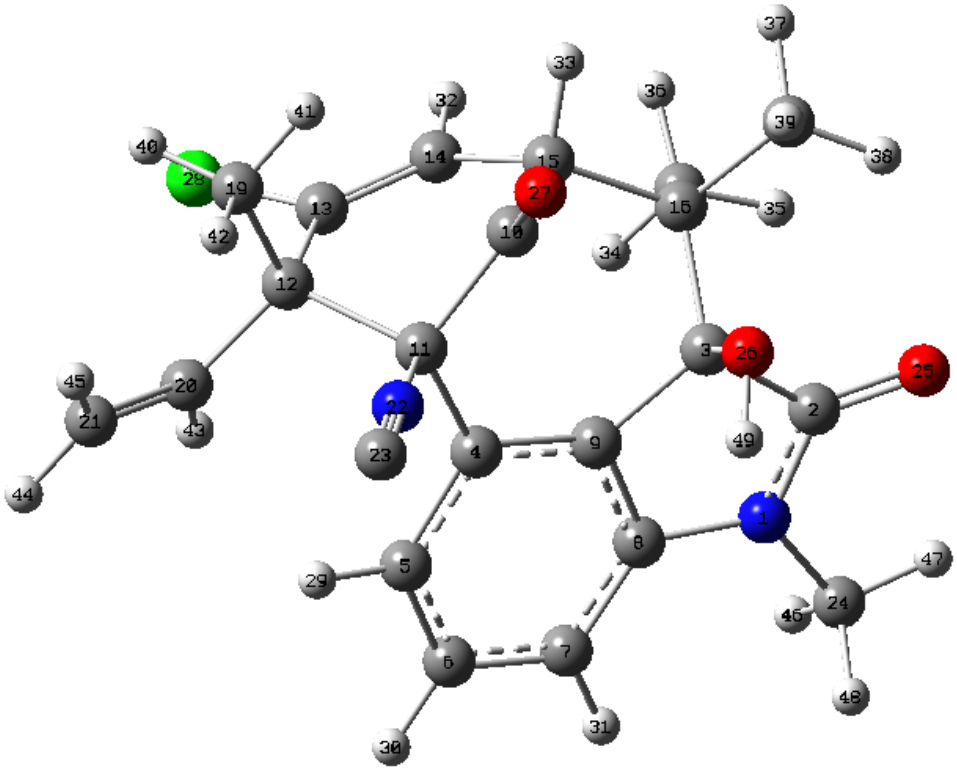


Structure 5.4, C3 epimer, conformer 5

Sum of electronic and thermal free energies = -1645.991068 H

Center Number	Atomic Number	Coordinates (Angstroms) X	Y	Z
1	7	-3.316210	1.144844	-0.470852
2	6	-3.353000	-0.145626	0.016414
3	6	-1.900274	-0.530040	0.456442
4	6	0.195691	1.110009	0.426253
5	6	0.535916	2.470473	0.269947
6	6	-0.371177	3.397256	-0.235857
7	6	-1.677562	3.024701	-0.573098
8	6	-2.033824	1.702602	-0.342798
9	6	-1.122774	0.741996	0.142090
10	6	0.725498	-1.322317	1.175416
11	6	1.263098	0.131843	0.975234
12	6	2.556738	-0.062327	-0.003870
13	6	2.036001	-0.767570	-1.251864
14	6	0.981869	-1.583705	-1.293192
15	6	0.165831	-1.980456	-0.085158
16	6	-1.411863	-1.842012	-0.237032
17	6	-1.816382	-1.832304	-1.725165
18	6	-2.065012	-3.064028	0.447132
19	6	3.592983	-0.991378	0.680623
20	6	3.190944	1.272471	-0.365900
21	6	4.266338	1.816945	0.207755
22	7	1.721041	0.632824	2.223792
23	6	2.081051	1.038479	3.267421
24	6	-4.496318	1.870426	-0.902808
25	8	-4.354671	-0.833775	0.108351
26	8	-1.897460	-0.778516	1.865497
27	8	0.880065	-1.916681	2.215989
28	17	3.001830	-0.566105	-2.720418
29	1	1.517588	2.808976	0.570713
30	1	-0.063227	4.431928	-0.351967
31	1	-2.388990	3.750671	-0.951099
32	1	0.747195	-2.079790	-2.227923
33	1	0.342733	-3.052577	0.068531
34	1	-1.453253	-0.945486	-2.255049
35	1	-2.904431	-1.874170	-1.816303
36	1	-1.419353	-2.715718	-2.234178
37	1	-1.807241	-3.967991	-0.116408
38	1	-3.151829	-2.961174	0.463288
39	1	-1.713413	-3.182768	1.473244
40	1	4.452775	-1.107859	0.016800
41	1	3.178446	-1.980092	0.881730
42	1	3.937337	-0.574397	1.628771
43	1	2.712322	1.806697	-1.180794
44	1	4.640389	2.777977	-0.133001
45	1	4.808607	1.349899	1.022736
46	1	-4.369044	2.238269	-1.926233
47	1	-5.338560	1.178550	-0.866659
48	1	-4.697542	2.719456	-0.239400
49	1	-1.981566	0.058863	2.343130

2	C	Isotropic =	5.1952	29	H	Isotropic =	23.6966
3	C	Isotropic =	102.1608	30	H	Isotropic =	23.7777
4	C	Isotropic =	46.0600	31	H	Isotropic =	24.4347
5	C	Isotropic =	56.4614	32	H	Isotropic =	25.3922
6	C	Isotropic =	50.9654	33	H	Isotropic =	28.3243
7	C	Isotropic =	72.0633	34	H	Isotropic =	31.0289
8	C	Isotropic =	35.4876	35	H	Isotropic =	30.5817
9	C	Isotropic =	52.2471	36	H	Isotropic =	30.7290
10	C	Isotropic =	-21.8691	37	H	Isotropic =	30.7986
11	C	Isotropic =	105.0030	38	H	Isotropic =	29.4384
12	C	Isotropic =	122.2357	39	H	Isotropic =	29.6777
13	C	Isotropic =	36.8419	40	H	Isotropic =	30.2849
14	C	Isotropic =	51.7461	41	H	Isotropic =	30.8969
15	C	Isotropic =	123.6310	42	H	Isotropic =	29.7062
16	C	Isotropic =	136.1821	43	H	Isotropic =	24.9935
17	C	Isotropic =	163.9169	44	H	Isotropic =	25.6372
18	C	Isotropic =	163.1060	45	H	Isotropic =	25.7188
19	C	Isotropic =	165.0023	46	H	Isotropic =	28.9835
20	C	Isotropic =	38.3576	47	H	Isotropic =	27.5879
21	C	Isotropic =	60.6279	48	H	Isotropic =	29.0337
23	C	Isotropic =	11.3981	49	H	Isotropic =	30.5600
24	C	Isotropic =	160.7619				

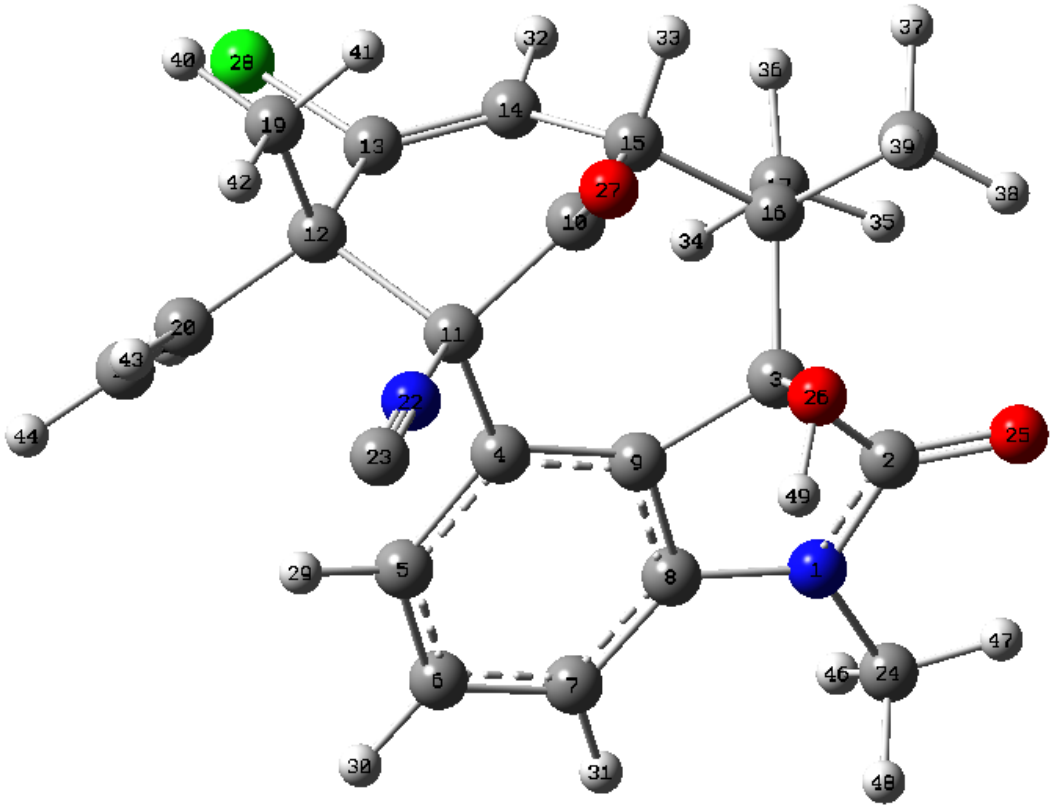


Structure 5.4, C3 epimer, conformer 6

Sum of electronic and thermal free energies = -1645.986160 H

Center Number	Atomic Number	Coordinates (Angstroms) X	Y	Z
1	7	-3.312624	1.070087	-0.517719
2	6	-3.323492	-0.246966	-0.110163
3	6	-1.880062	-0.604648	0.379318
4	6	0.156962	1.103937	0.542283
5	6	0.443307	2.484536	0.495961
6	6	-0.476925	3.408969	0.009569
7	6	-1.747298	3.010784	-0.419833
8	6	-2.058333	1.663388	-0.294924
9	6	-1.133600	0.707541	0.171626
10	6	0.735897	-1.340861	1.196557
11	6	1.236535	0.133516	1.082426
12	6	2.584691	0.023322	0.157121
13	6	2.167810	-0.661675	-1.137978
14	6	1.133465	-1.497661	-1.257865
15	6	0.255063	-1.954172	-0.117195
16	6	-1.312905	-1.858185	-0.354434
17	6	-1.630140	-1.772956	-1.861439
18	6	-1.962419	-3.137148	0.220416
19	6	3.624972	-0.902505	0.857785
20	6	3.258600	1.380226	0.032286
21	6	3.287376	2.220559	-1.003236
22	7	1.631285	0.589556	2.372781
23	6	1.930996	0.948564	3.451996
24	6	-4.497128	1.778340	-0.965471
25	8	-4.301112	-0.975325	-0.109797
26	8	-1.933180	-0.927604	1.772579
27	8	0.869596	-1.978865	2.213930
28	17	3.274935	-0.554405	-2.518122
29	1	1.393378	2.843624	0.859876
30	1	-0.206985	4.460228	-0.019166
31	1	-2.470221	3.732707	-0.783612
32	1	0.991383	-2.002287	-2.206844
33	1	0.458766	-3.026367	-0.000361
34	1	-1.261198	-0.847576	-2.316215
35	1	-2.709337	-1.836217	-2.020688
36	1	-1.179506	-2.614846	-2.395392
37	1	-1.640594	-3.999269	-0.374910
38	1	-3.051135	-3.069846	0.176867
39	1	-1.667942	-3.302582	1.258096
40	1	4.515211	-0.960810	0.226305
41	1	3.244144	-1.914013	1.008749
42	1	3.916936	-0.494254	1.828047
43	1	3.794607	1.662499	0.936979
44	1	3.840698	3.152754	-0.929232
45	1	2.777150	2.032186	-1.940362
46	1	-4.335374	2.210442	-1.958528
47	1	-5.313299	1.056398	-1.011084
48	1	-4.762161	2.579062	-0.265378
49	1	-2.081707	-0.121526	2.286962

2	C	Isotropic =	5.6260	29	H	Isotropic =	23.7169
3	C	Isotropic =	101.7692	30	H	Isotropic =	23.8617
4	C	Isotropic =	46.8953	31	H	Isotropic =	24.4447
5	C	Isotropic =	54.4966	32	H	Isotropic =	25.3600
6	C	Isotropic =	51.9572	33	H	Isotropic =	28.2891
7	C	Isotropic =	72.3771	34	H	Isotropic =	31.0062
8	C	Isotropic =	36.0630	35	H	Isotropic =	30.6048
9	C	Isotropic =	52.3668	36	H	Isotropic =	30.7046
10	C	Isotropic =	-21.6655	37	H	Isotropic =	30.8278
11	C	Isotropic =	105.1827	38	H	Isotropic =	29.3924
12	C	Isotropic =	119.2166	39	H	Isotropic =	29.6543
13	C	Isotropic =	39.0046	40	H	Isotropic =	29.9060
14	C	Isotropic =	49.4286	41	H	Isotropic =	30.7720
15	C	Isotropic =	122.6971	42	H	Isotropic =	29.9302
16	C	Isotropic =	136.9722	43	H	Isotropic =	25.2462
17	C	Isotropic =	163.8095	44	H	Isotropic =	25.4644
18	C	Isotropic =	163.3482	45	H	Isotropic =	26.2006
19	C	Isotropic =	160.5311	46	H	Isotropic =	28.9944
20	C	Isotropic =	43.0063	47	H	Isotropic =	27.5786
21	C	Isotropic =	53.1354	48	H	Isotropic =	29.0435
23	C	Isotropic =	10.8252	49	H	Isotropic =	30.5209
24	C	Isotropic =	160.9110				

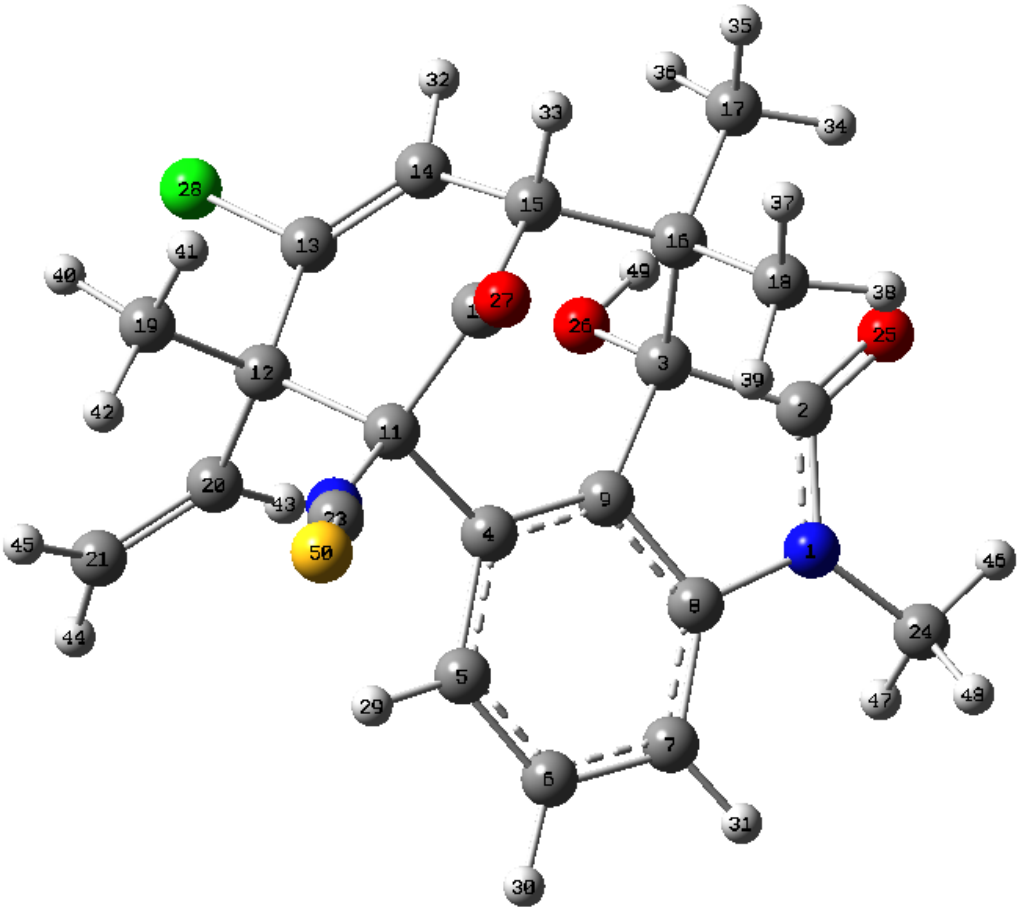


Structure 5.3

Sum of electronic and thermal free energies = -2044.228627 H

Center Number	Atomic Number	Coordinates (Angstroms) X	Y	Z
1	7	3.491312	-1.137705	-0.667141
2	6	3.468337	-0.007255	0.098748
3	6	1.986878	0.464263	0.228362
4	6	-0.133580	-0.961406	-0.663930
5	6	-0.448307	-2.047557	-1.512488
6	6	0.528610	-2.836392	-2.106567
7	6	1.883265	-2.602645	-1.856977
8	6	2.193617	-1.523155	-1.044414
9	6	1.225434	-0.665468	-0.473704
10	6	-0.926198	0.041919	1.521845
11	6	-1.341403	-0.285430	0.058195
12	6	-1.939853	1.036289	-0.661648
13	6	-1.153515	2.259394	-0.206882
14	6	-0.324087	2.348248	0.831109
15	6	0.033732	1.196340	1.733996
16	6	1.559826	0.785272	1.692658
17	6	2.368264	1.966387	2.277266
18	6	1.797448	-0.449467	2.587994
19	6	-3.404688	1.245858	-0.205723
20	6	-1.813324	0.867272	-2.169007
21	6	-2.805218	0.640241	-3.031626
22	7	-2.400780	-1.249285	0.099800
23	6	-3.026178	-1.987924	0.812450
24	6	4.713110	-1.784422	-1.109825
25	8	4.449019	0.604419	0.503796
26	8	1.928088	1.619649	-0.628398
27	8	-1.377734	-0.588383	2.453942
28	17	-1.455073	3.726927	-1.150965
29	1	-1.488757	-2.280390	-1.692551
30	1	0.230614	-3.658003	-2.750493
31	1	2.653856	-3.237184	-2.280203
32	1	0.129295	3.307096	1.055940
33	1	-0.141596	1.501619	2.773437
34	1	3.432782	1.731081	2.308767
35	1	2.026890	2.166259	3.298657
36	1	2.244315	2.887411	1.701496
37	1	1.399713	-0.274079	3.591868
38	1	2.870180	-0.644828	2.683311
39	1	1.317164	-1.351718	2.199932
40	1	-3.775657	2.193237	-0.602938
41	1	-3.467205	1.285730	0.885515
42	1	-4.056144	0.443475	-0.552501
43	1	-0.795340	0.940058	-2.545759
44	1	-2.595628	0.529276	-4.091361
45	1	-3.845373	0.563052	-2.732652
46	1	5.550706	-1.247887	-0.663214
47	1	4.797453	-1.744513	-2.201407
48	1	4.734444	-2.830131	-0.786015
49	1	2.712081	2.160658	-0.443242
50	16	-3.967455	-3.023543	1.559218

2	C	Isotropic =	4.8855	29	H	Isotropic =	23.9984
3	C	Isotropic =	101.8740	30	H	Isotropic =	23.8156
4	C	Isotropic =	47.0518	31	H	Isotropic =	24.3353
5	C	Isotropic =	55.6586	32	H	Isotropic =	24.8723
6	C	Isotropic =	50.8762	33	H	Isotropic =	28.3058
7	C	Isotropic =	72.5542	34	H	Isotropic =	29.2384
8	C	Isotropic =	34.1863	35	H	Isotropic =	30.8878
9	C	Isotropic =	54.4800	36	H	Isotropic =	29.9737
10	C	Isotropic =	-22.5835	37	H	Isotropic =	30.5709
11	C	Isotropic =	95.1988	38	H	Isotropic =	30.8818
12	C	Isotropic =	121.3605	39	H	Isotropic =	31.3575
13	C	Isotropic =	38.4718	40	H	Isotropic =	30.0976
14	C	Isotropic =	52.7774	41	H	Isotropic =	30.6923
15	C	Isotropic =	122.6604	42	H	Isotropic =	29.7414
16	C	Isotropic =	135.8042	43	H	Isotropic =	25.8781
17	C	Isotropic =	166.1601	44	H	Isotropic =	26.0590
18	C	Isotropic =	164.0081	45	H	Isotropic =	26.0025
19	C	Isotropic =	165.5144	46	H	Isotropic =	27.5723
20	C	Isotropic =	37.4105	47	H	Isotropic =	28.9626
21	C	Isotropic =	64.0130	48	H	Isotropic =	28.9522
23	C	Isotropic =	33.9484	49	H	Isotropic =	29.4462
24	C	Isotropic =	160.3097				



Structure 5.3, C3 epimer

Sum of electronic and thermal free energies = -2044.226582 H

Center Number	Atomic Number	Coordinates (Angstroms) X	Y	Z
1	7	3.508897	0.034700	1.185185
2	6	3.461453	0.331733	-0.153051
3	6	1.966000	0.401803	-0.582116
4	6	-0.111304	0.205516	1.063527
5	6	-0.435091	0.191248	2.437306
6	6	0.537608	0.016818	3.417095
7	6	1.890944	-0.110910	3.081768
8	6	2.214182	-0.013667	1.736157
9	6	1.242227	0.135284	0.728037
10	6	-0.725084	0.459204	-1.433944
11	6	-1.250533	0.387511	0.031499
12	6	-2.314605	-0.848701	0.005622
13	6	-1.550717	-2.067344	-0.500202
14	6	-0.494633	-2.028799	-1.313731
15	6	0.069515	-0.759401	-1.906174
16	6	1.641233	-0.566342	-1.772568
17	6	2.342801	-1.921963	-1.550555
18	6	2.151556	0.042890	-3.098071
19	6	-3.443991	-0.532057	-1.008790
20	6	-2.897771	-1.117065	1.385510
21	6	-4.077035	-0.690080	1.842611
22	7	-1.968062	1.577656	0.363280
23	6	-2.174575	2.717022	0.037974
24	6	4.738606	0.001779	1.955649
25	8	4.422504	0.567687	-0.872661
26	8	1.697331	1.770336	-0.903737
27	8	-1.030153	1.365191	-2.175190
28	17	-2.213061	-3.648178	-0.059791
29	1	-1.461894	0.344490	2.738410
30	1	0.241807	-0.000457	4.461714
31	1	2.651105	-0.228044	3.846218
32	1	-0.072017	-2.964162	-1.662136
33	1	-0.123922	-0.810457	-2.985629
34	1	2.085865	-2.370219	-0.585513
35	1	3.427262	-1.794094	-1.598822
36	1	2.068332	-2.632093	-2.336814
37	1	2.038672	-0.692049	-3.902375
38	1	3.211259	0.303132	-3.027751
39	1	1.576691	0.928942	-3.382477
40	1	-4.158028	-1.358859	-1.016138
41	1	-3.055202	-0.406748	-2.020645
42	1	-3.973162	0.383702	-0.737975
43	1	-2.282292	-1.729326	2.037431
44	1	-4.399704	-0.946336	2.847548
45	1	-4.757634	-0.080157	1.258455
46	1	4.831705	-0.949218	2.489822
47	1	5.568994	0.110459	1.257192
48	1	4.765071	0.824457	2.679261
49	1	2.335551	2.059062	-1.573813
50	16	-2.567777	4.231745	-0.213587

2	C	Isotropic =	4.1786	29	H	Isotropic =	23.7346
3	C	Isotropic =	102.7844	30	H	Isotropic =	23.8586
4	C	Isotropic =	46.5561	31	H	Isotropic =	24.4441
5	C	Isotropic =	55.9890	32	H	Isotropic =	25.3803
6	C	Isotropic =	51.8771	33	H	Isotropic =	28.1997
7	C	Isotropic =	72.5350	34	H	Isotropic =	30.9148
8	C	Isotropic =	34.3350	35	H	Isotropic =	30.6643
9	C	Isotropic =	53.3429	36	H	Isotropic =	30.6711
10	C	Isotropic =	-25.4087	37	H	Isotropic =	30.7396
11	C	Isotropic =	99.9395	38	H	Isotropic =	29.5377
12	C	Isotropic =	122.9421	39	H	Isotropic =	29.8480
13	C	Isotropic =	35.4253	40	H	Isotropic =	30.2733
14	C	Isotropic =	51.8841	41	H	Isotropic =	30.9084
15	C	Isotropic =	123.6216	42	H	Isotropic =	29.6995
16	C	Isotropic =	136.1963	43	H	Isotropic =	24.9076
17	C	Isotropic =	163.4768	44	H	Isotropic =	25.7231
18	C	Isotropic =	163.6791	45	H	Isotropic =	25.8722
19	C	Isotropic =	165.1487	46	H	Isotropic =	28.9125
20	C	Isotropic =	36.7707	47	H	Isotropic =	27.5861
21	C	Isotropic =	61.9335	48	H	Isotropic =	29.0421
23	C	Isotropic =	32.4181	49	H	Isotropic =	29.5902
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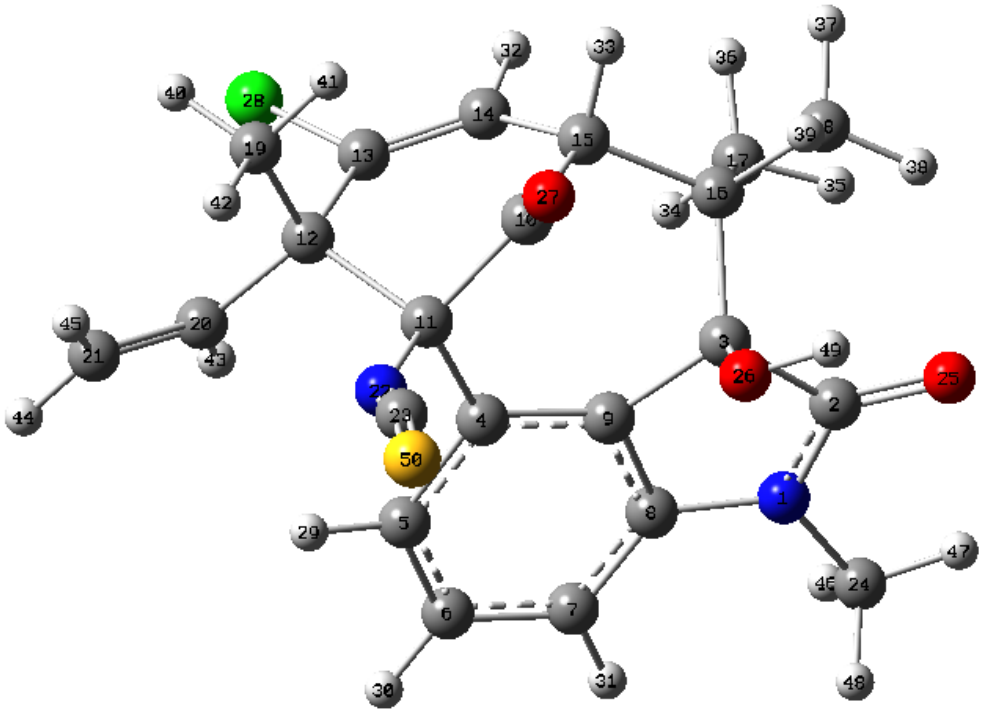

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(15) Rawal and co-workers have recently achieved this transformation; see reference 8.

(16) Moore and co-workers have shown that (–)-**5.2** can be converted to (–)-**5.4** and (–)-**5.5**, albeit in low yield (5% and 3% yield, respectively) using a photooxidation procedure. Thus, the synthesis of (–)-**5.2** also constitutes formal total syntheses of (–)-**5.4** and (–)-**5.5**.

(17) The C3 stereochemical configuration of **5.4** was assigned based on this compound having similar ^{1}H NMR and CD spectra in comparison to **5.2**. Further support was obtained by the

experiment described in reference 16. The C3 configuration of **5.3** was assigned by analogy to **5.4**. See reference 1b.

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APPENDIX FOUR

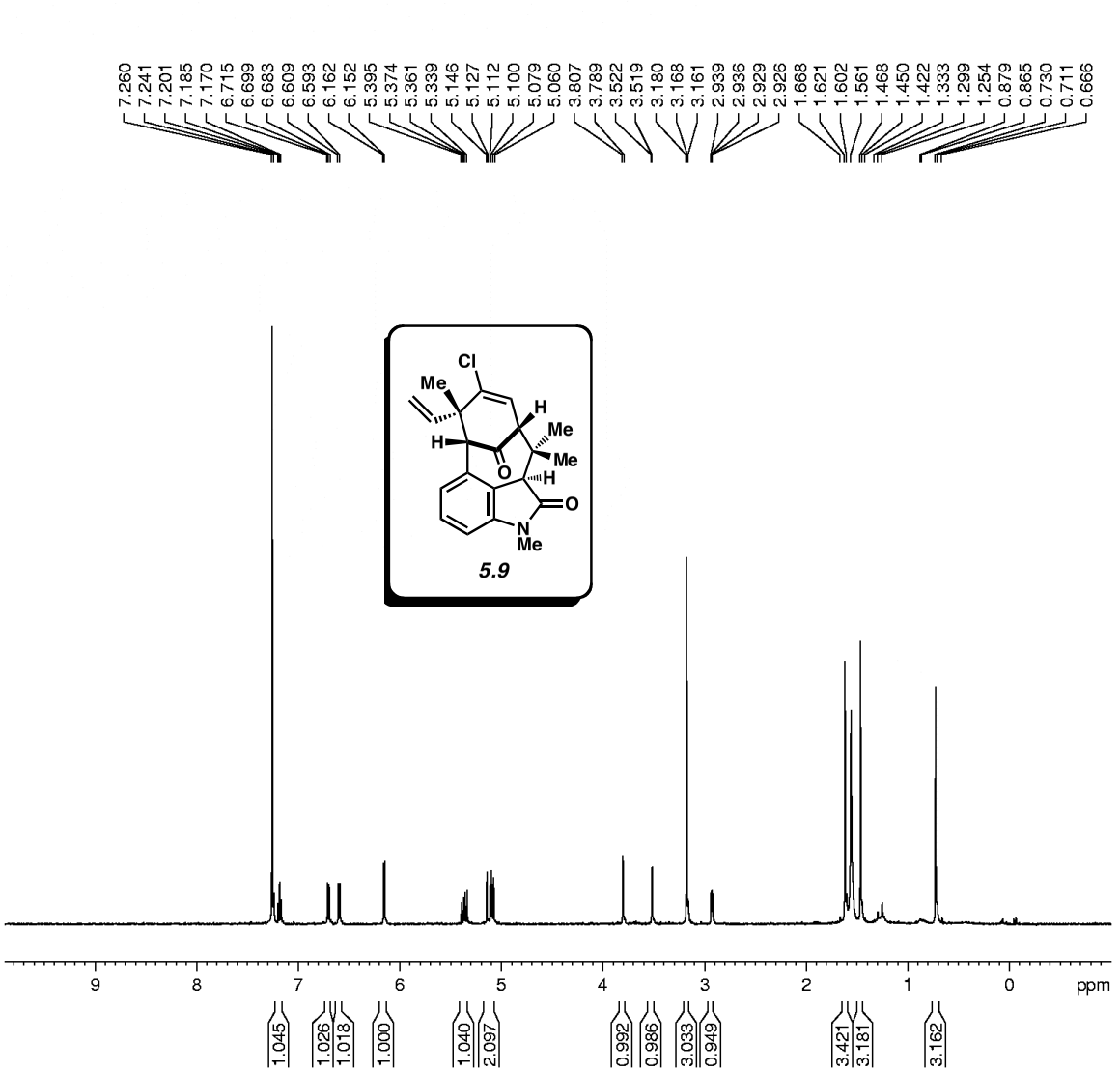
Spectra Relevant to Chapter Five:

Total Synthesis of Oxidized Welwitindolinones and

(–)-*N*-Methylwelwitindolinone C Isonitrile

Kyle W. Quasdorf, Alexander D. Huters, Michael W. Lodewyk, Dean J. Tantillo, and Neil K. Garg.

J. Am. Chem. Soc. **2012**, *134*, 1396–1399.



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PROCNO 1

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AQ 3.2768500 sec
RG 2860
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Figure A4.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **5.9**.

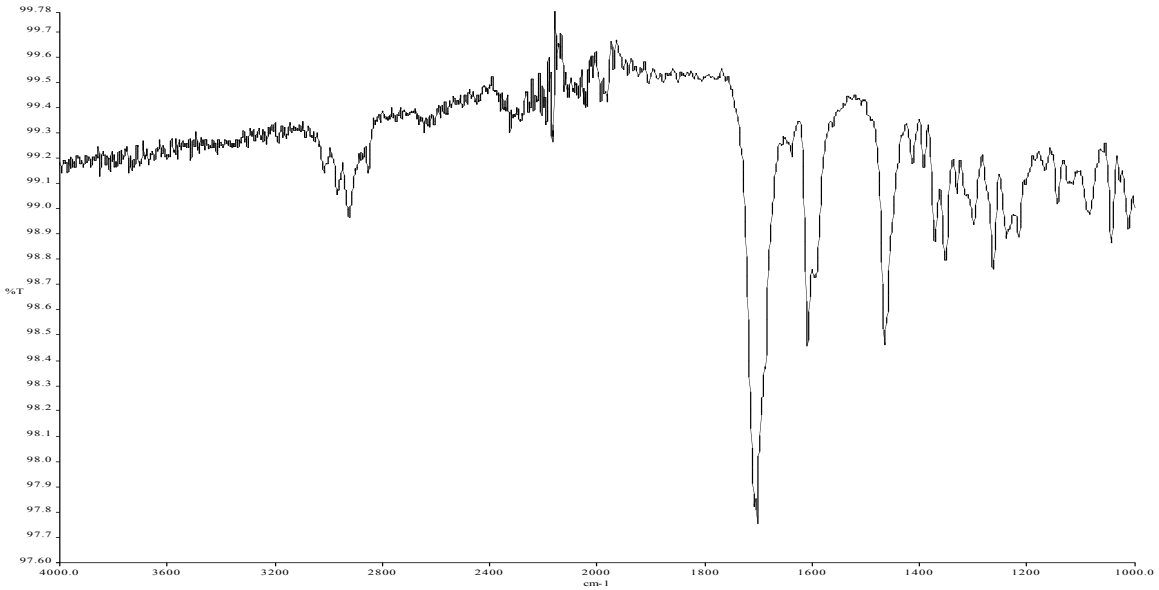


Figure A4.2 Infrared spectrum of compound **5.9**.

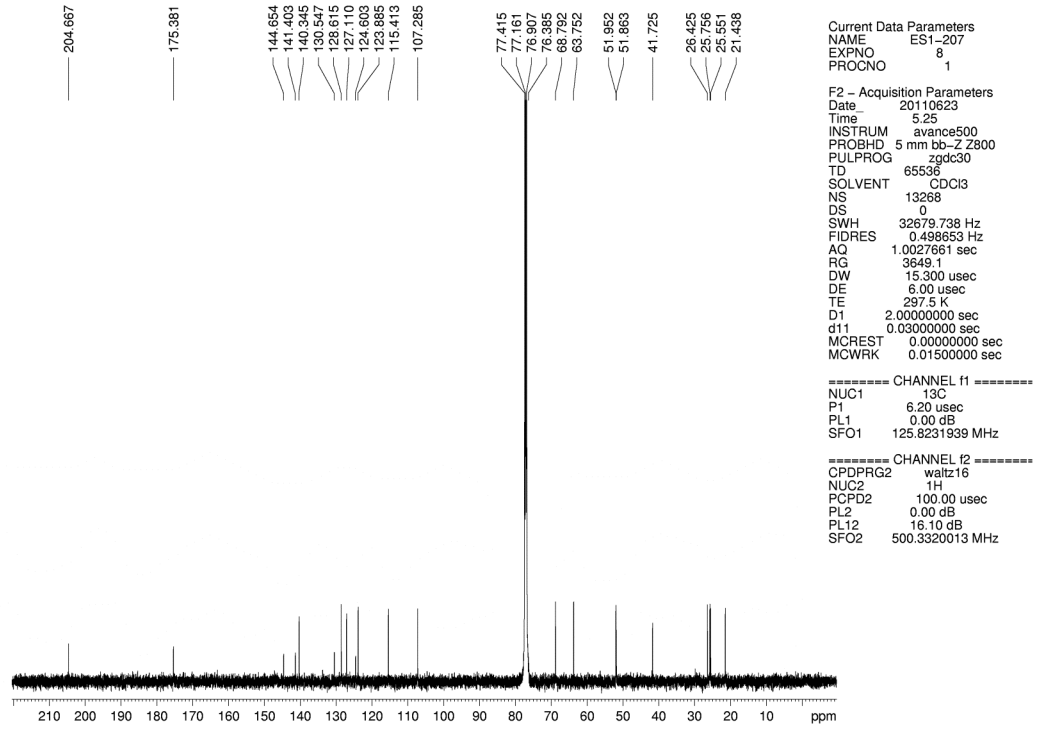


Figure A4.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **5.9**.

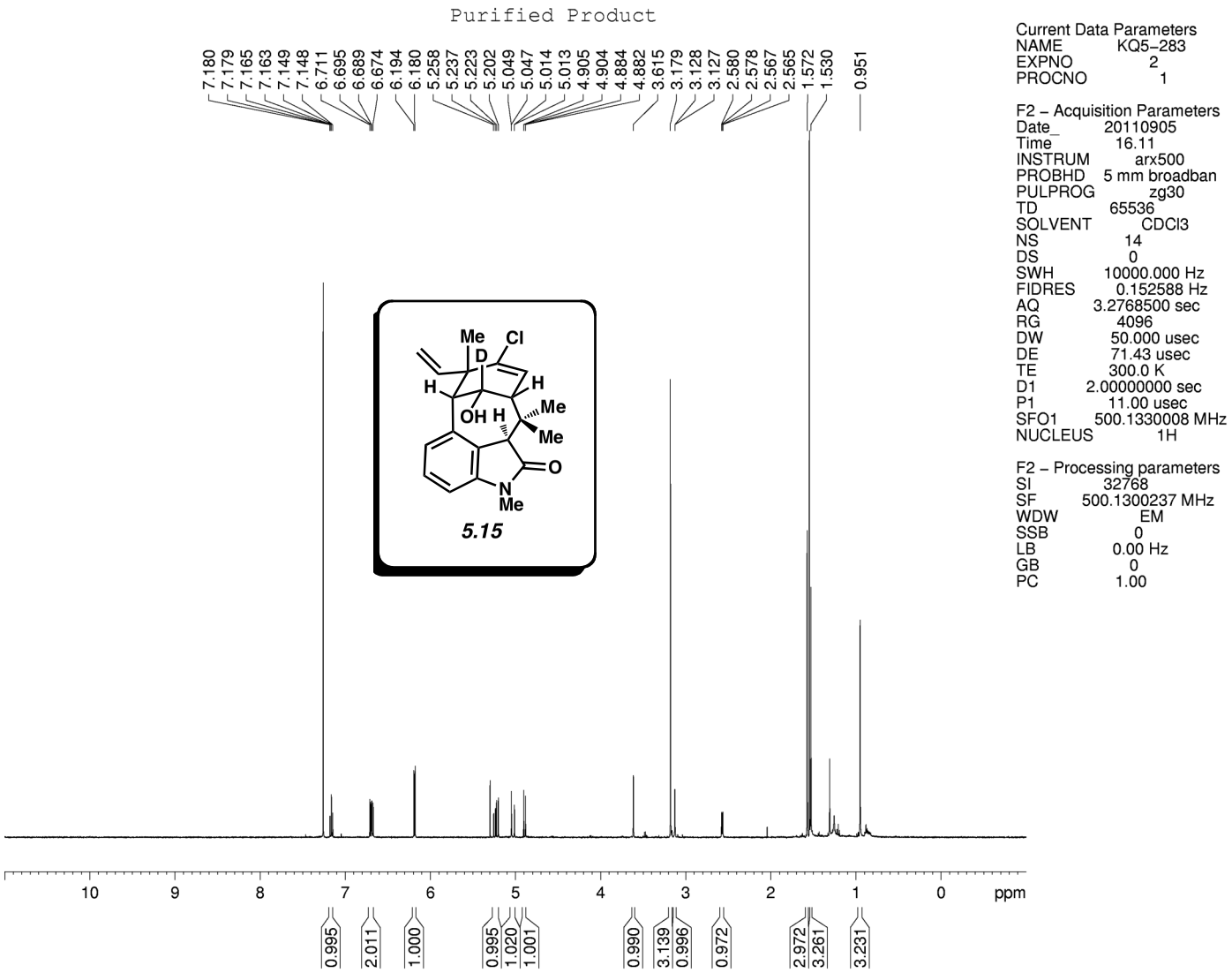


Figure A4.4 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **5.15**.

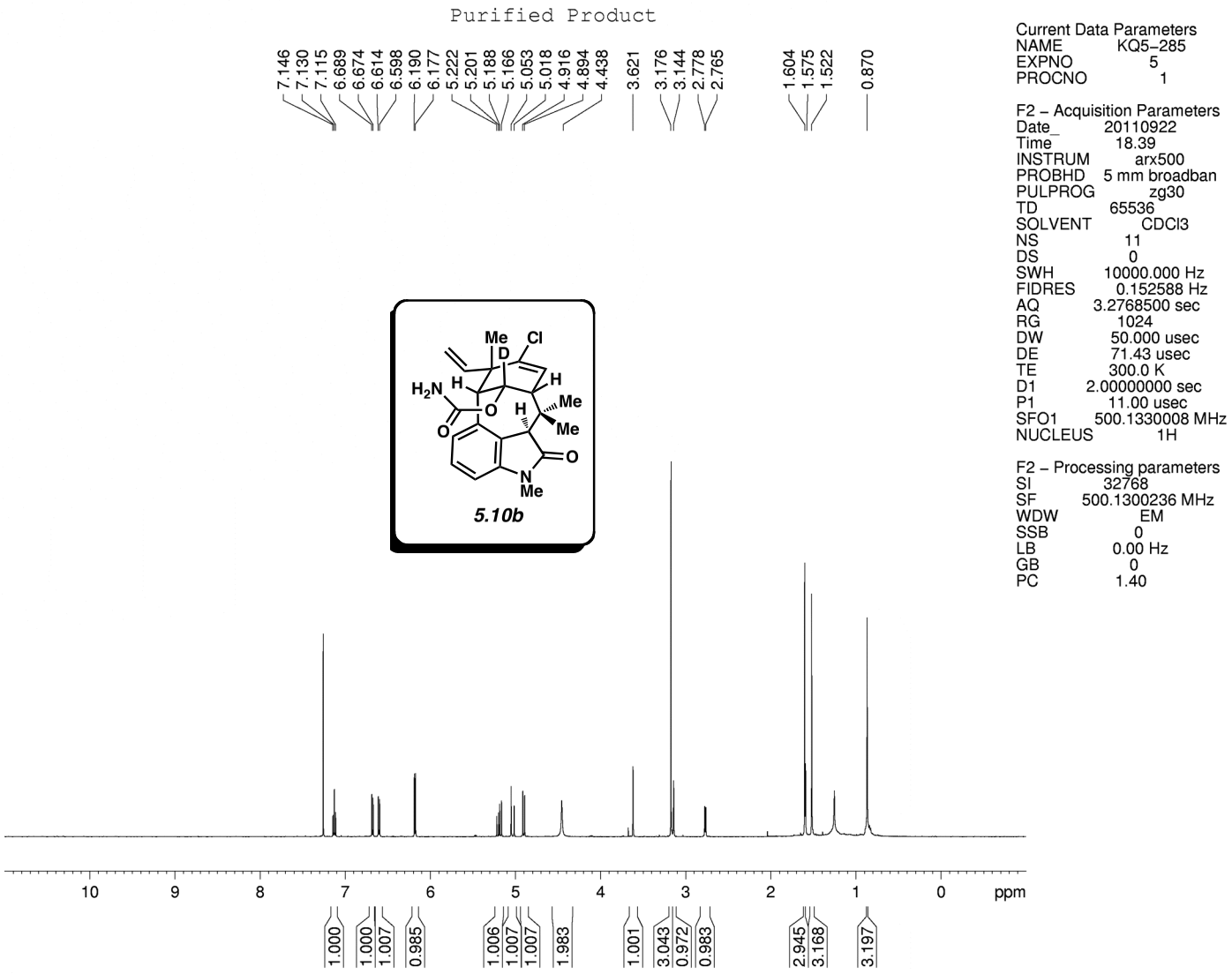


Figure A4.5 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **5.10b**.

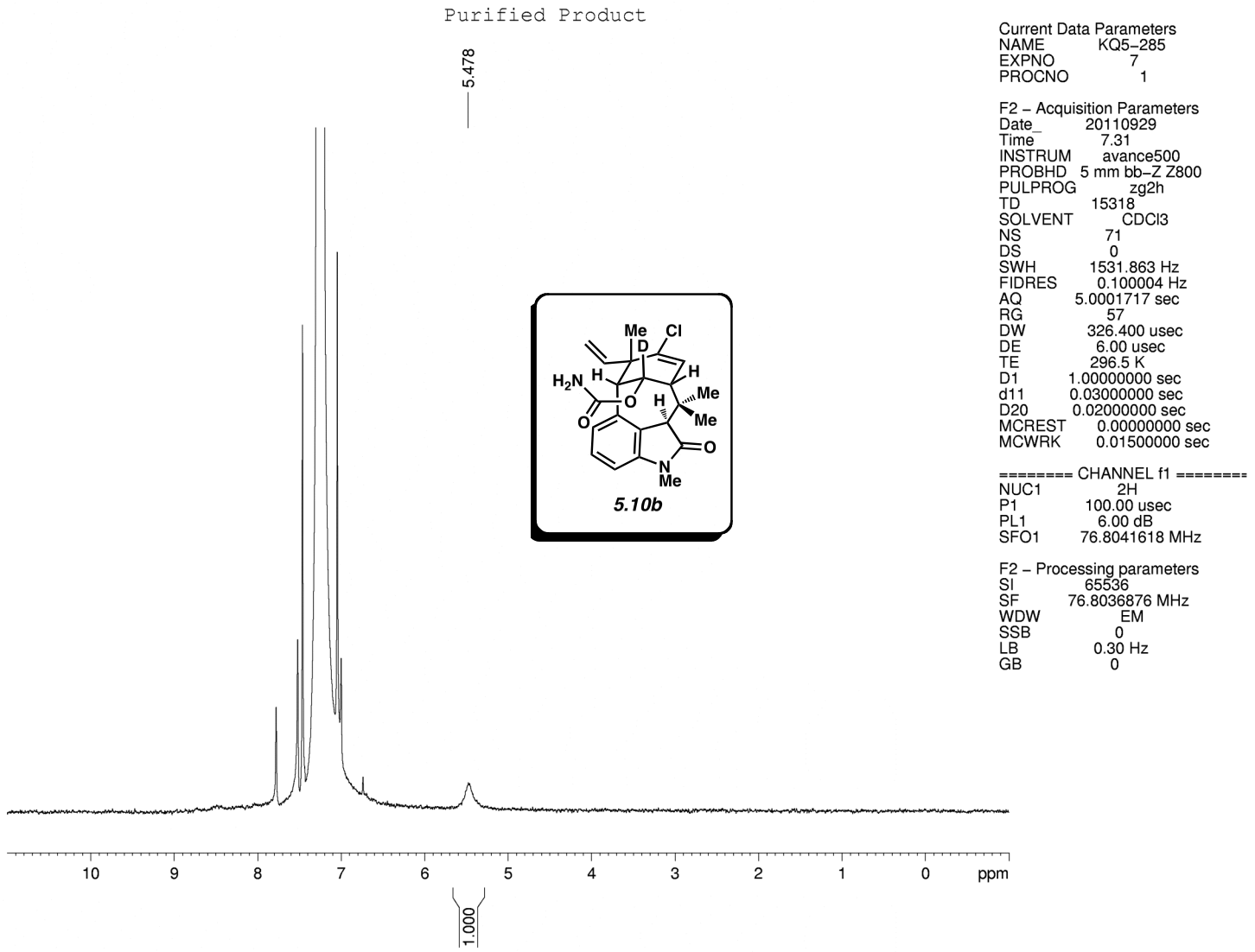


Figure A4.6 ^{2}H NMR (77 MHz, $CDCl_3$) of compound **5.10b**.

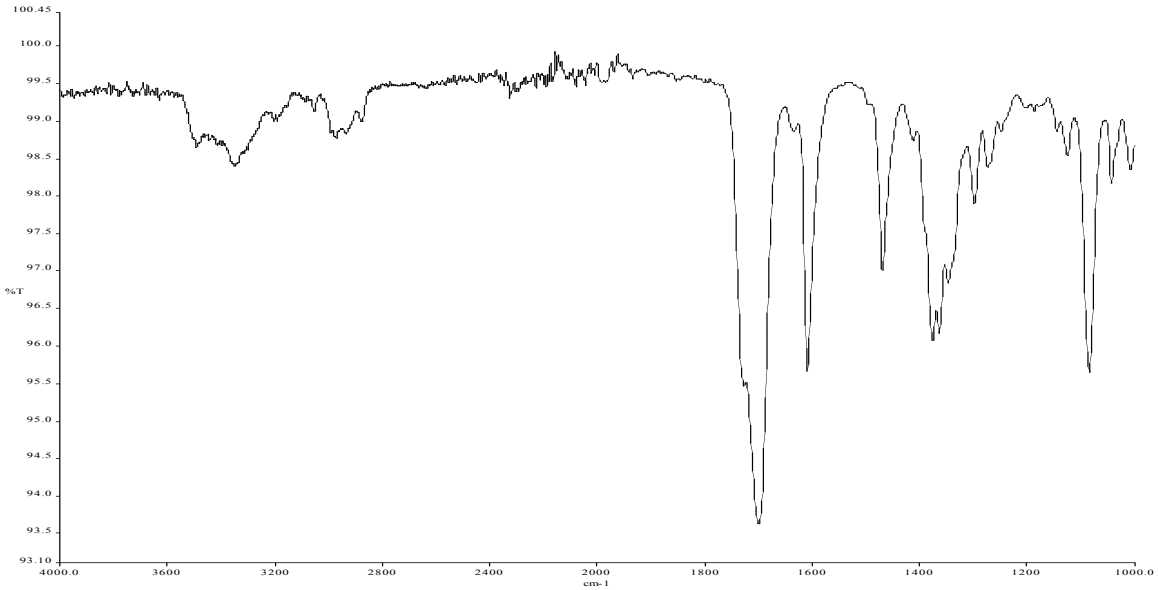


Figure A4.7 Infrared spectrum of compound **5.10b**.

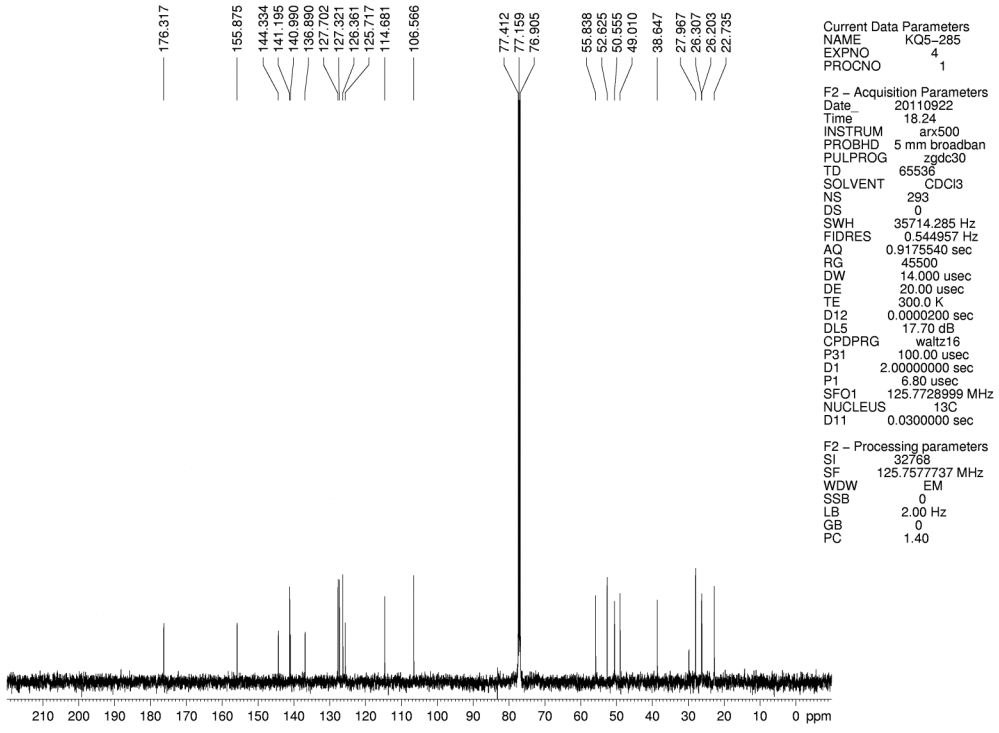


Figure A4.8 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **5.10b**.

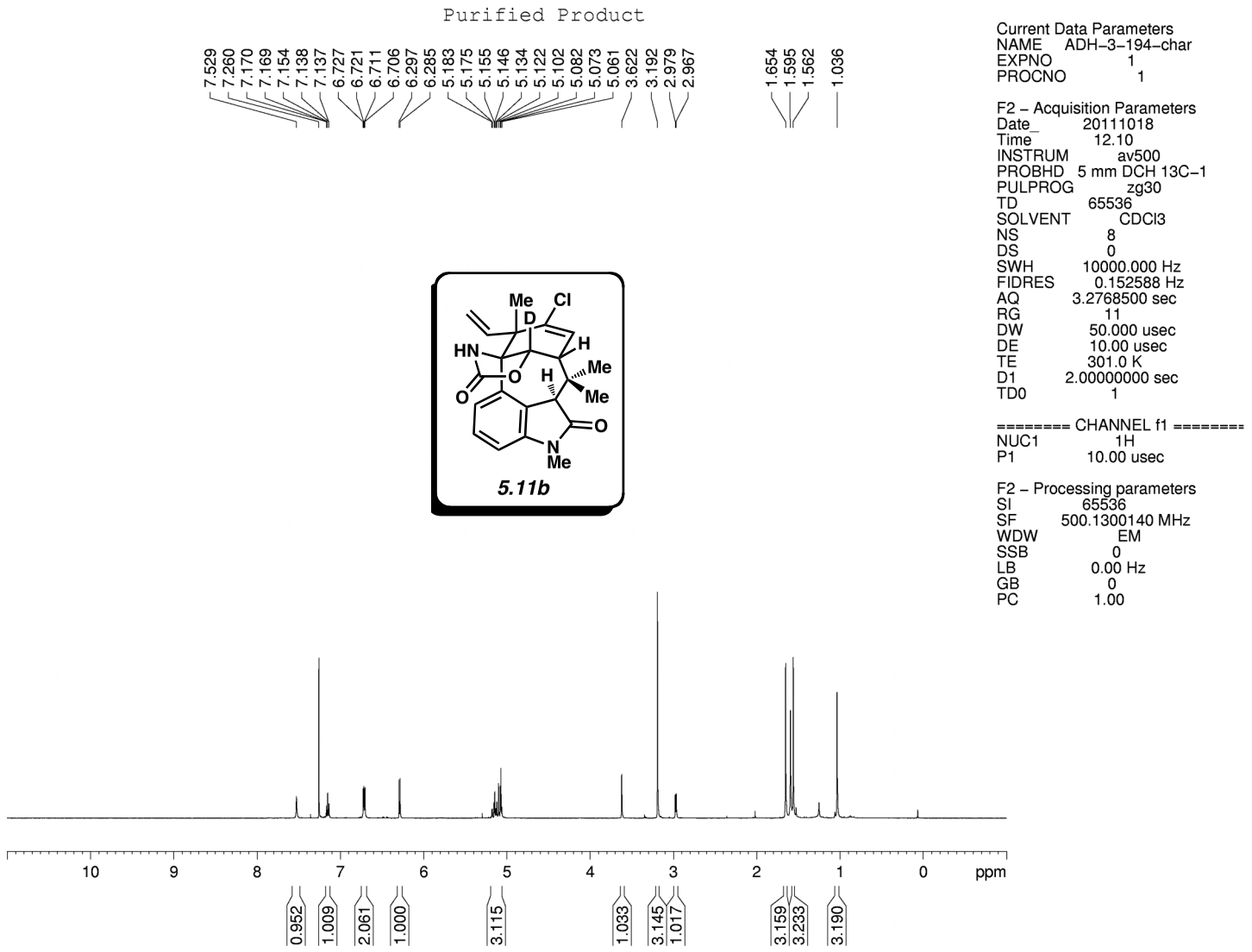


Figure A4.9 ^{1}H NMR (500 MHz, $CDCl_3$) of compounds **5.11b**.

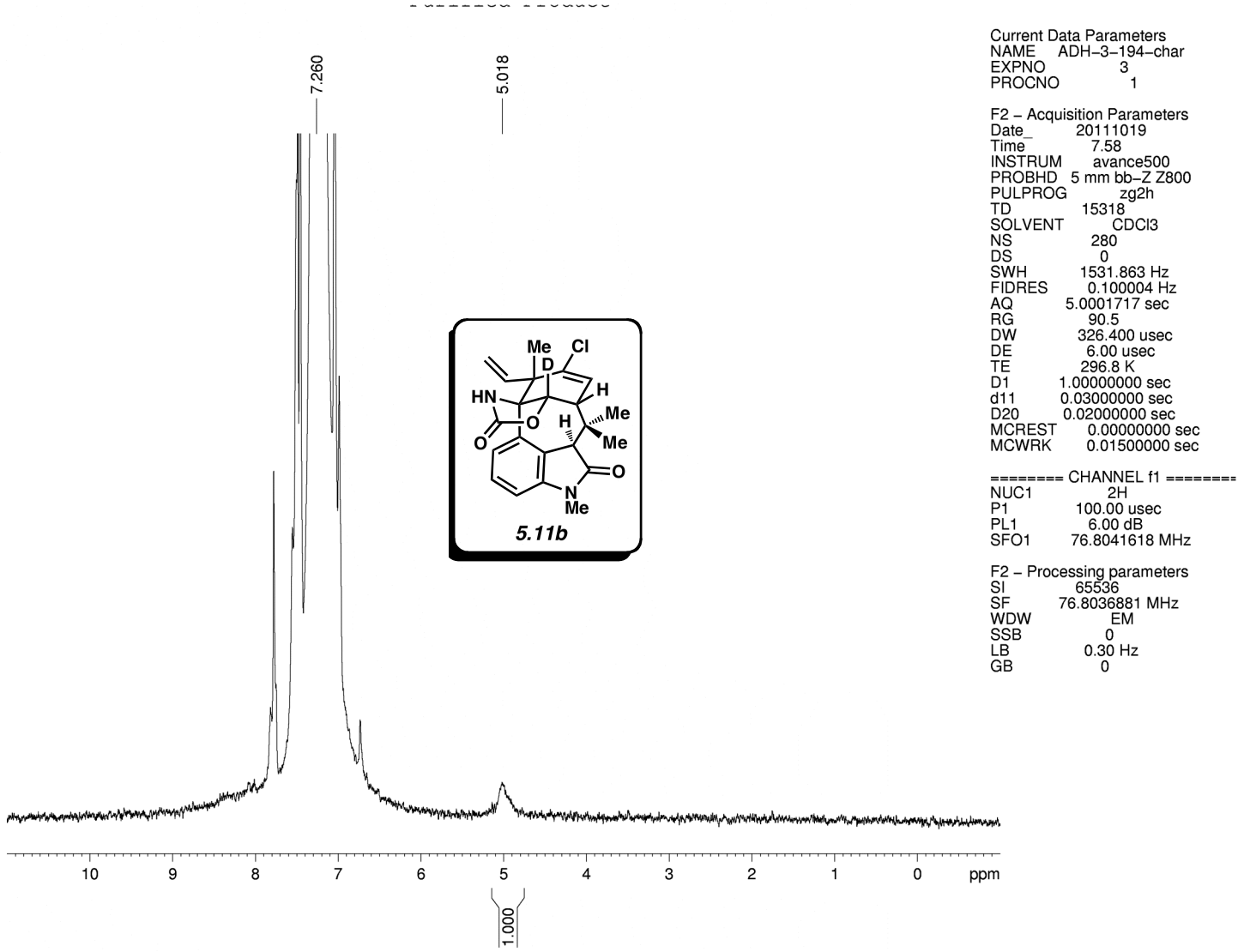


Figure A4.10 ^{2}H NMR (77 MHz, $CDCl_3$) of compound **5.11b**.

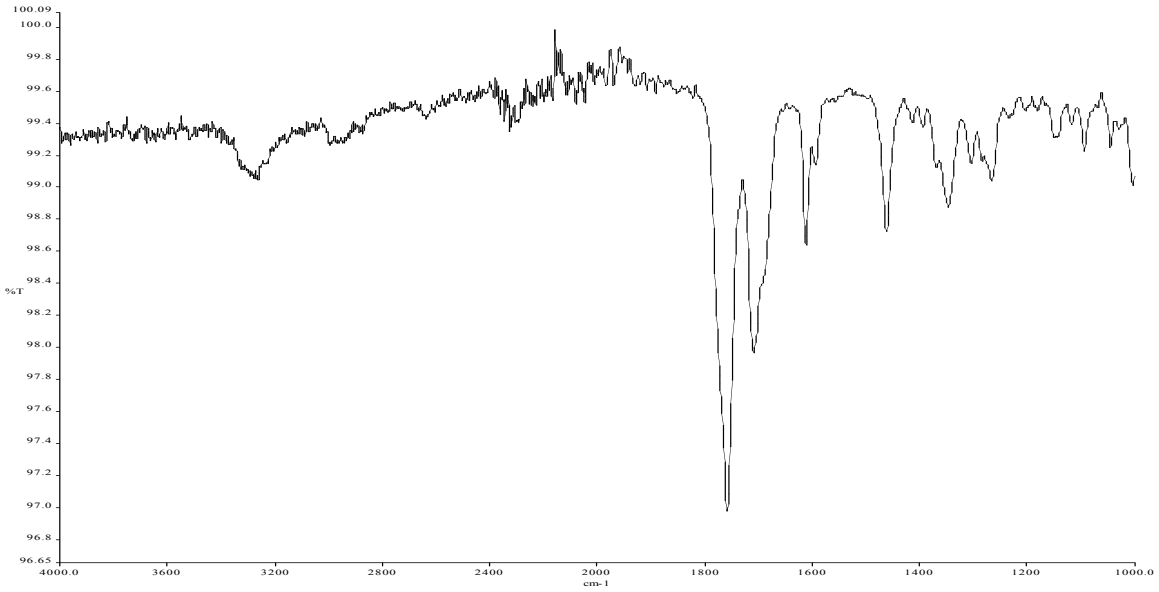


Figure A4.11 Infrared spectrum of compound **5.11b**.

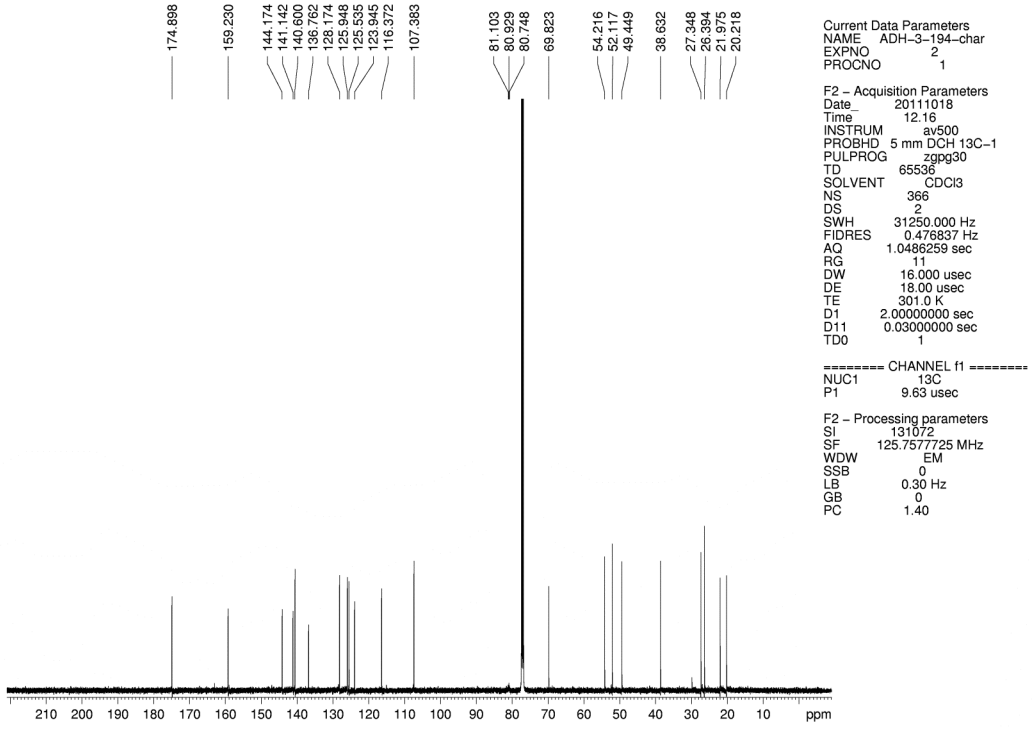
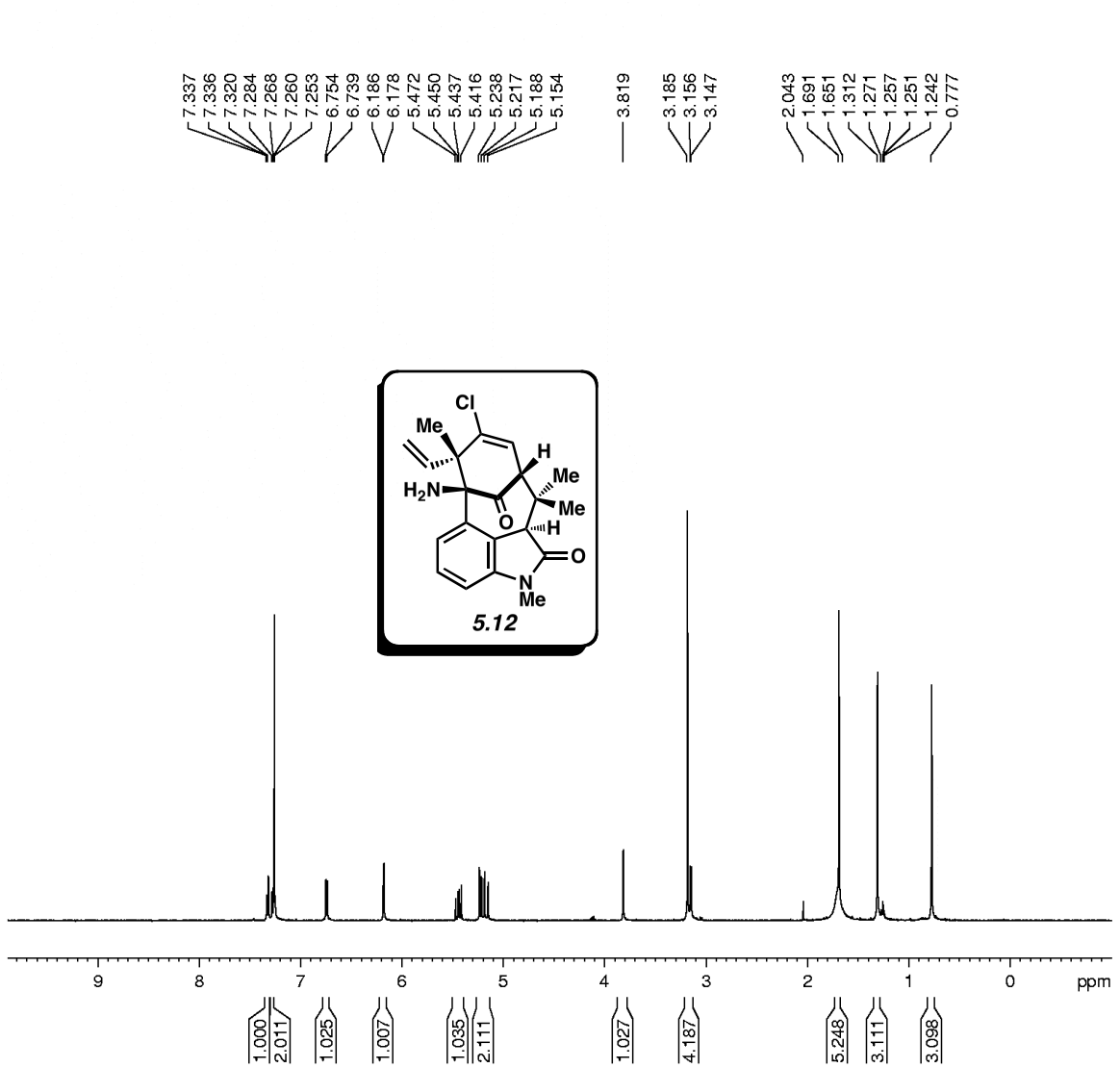


Figure A4.12 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **5.11b**.



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EXPNO 4
PROCNO 1

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PROBHD 5 mm bb–Z Z800
PULPROG zg30
TD 65536
SOLVENT CDCl3
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DS 0
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FIDRES 0.152588 Hz
AQ 3.2769001 sec
RG 256
DW 50.000 usec
DE 6.00 usec
TE 296.7 K
D1 2.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

======== CHANNEL f1 =====
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P1 12.00 usec
PL1 0.00 dB
SFO1 500.3330020 MHz

F2 – Processing parameters
SI 32768
SF 500.3300220 MHz
WDW EM
SSB 0
LB 0.00 Hz
GB 0
PC 1.00

Figure A4.13 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **5.12**.

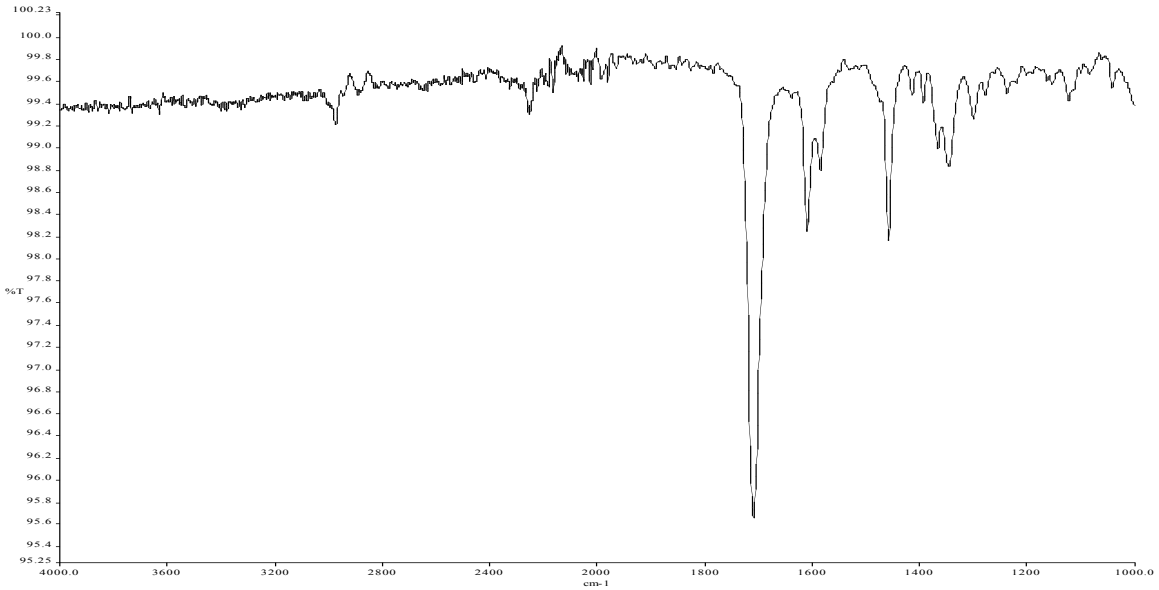

Figure A4.14 Infrared spectrum of compound **5.12**.

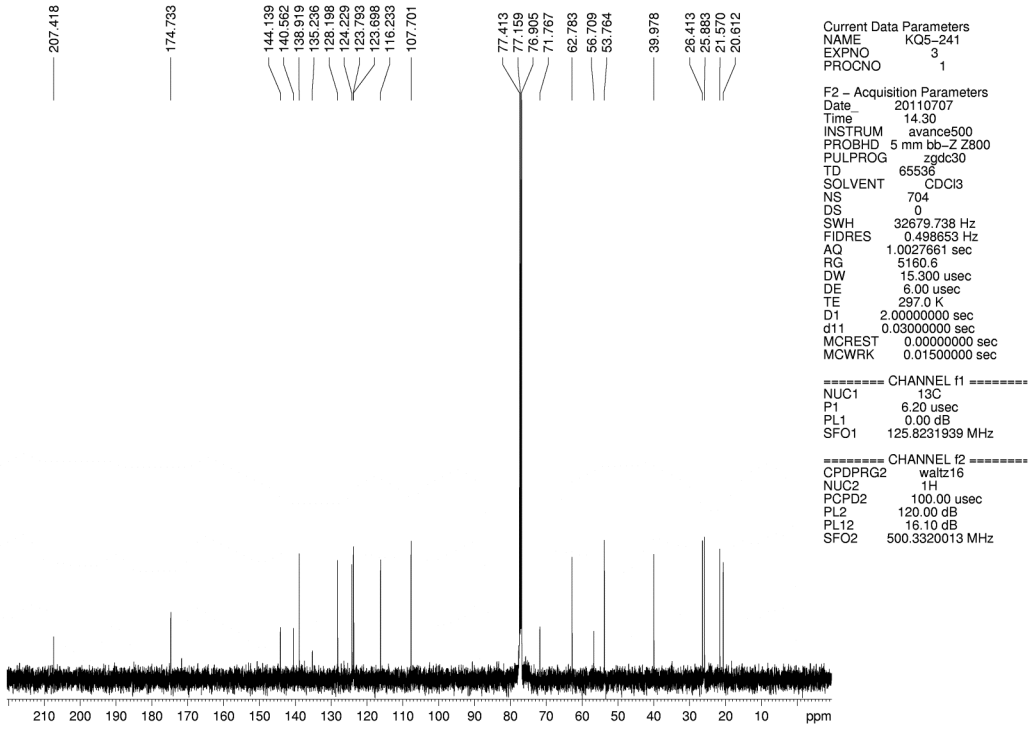

Figure A4.15 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **5.12**.

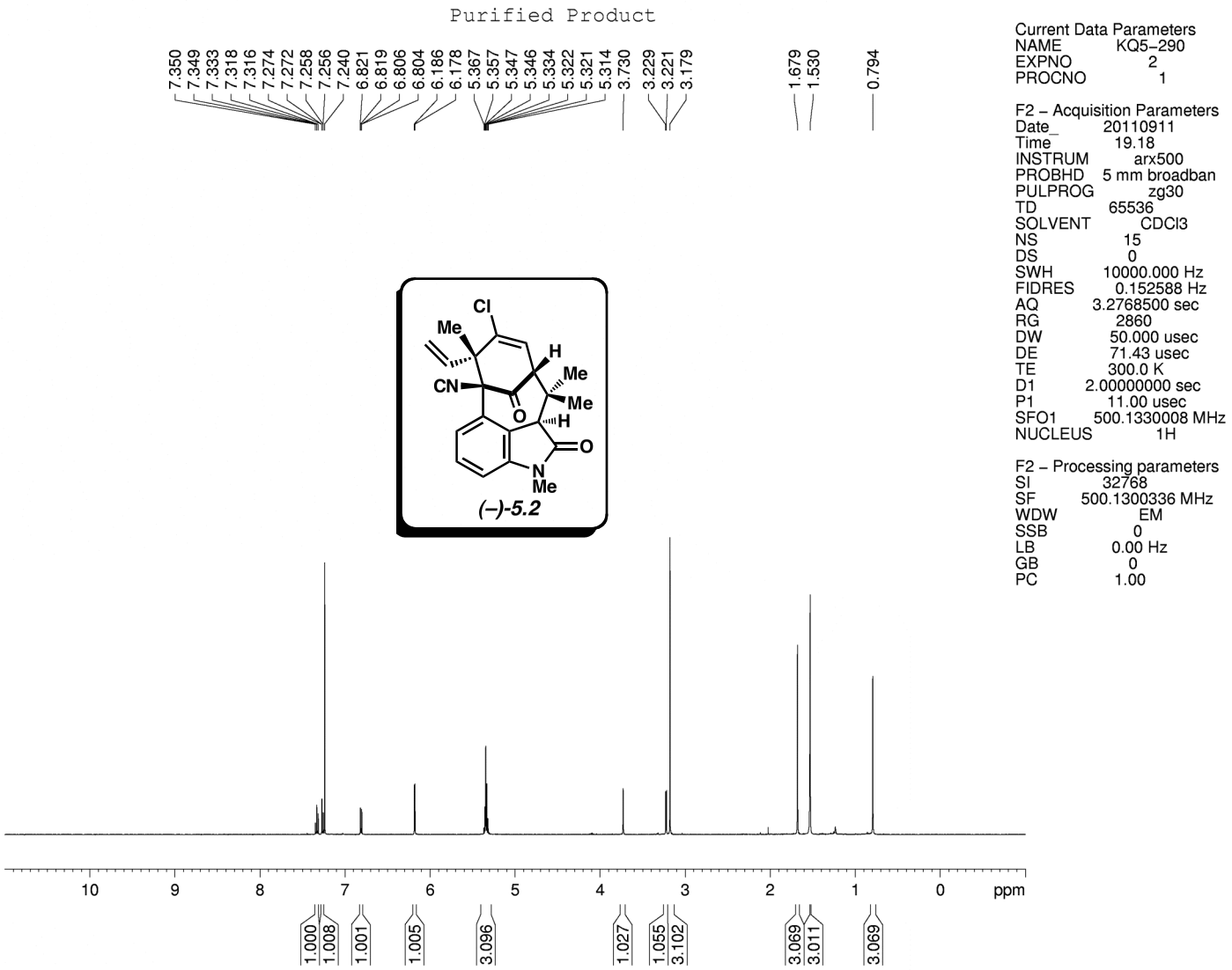

Figure A4.16 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **5.2**.

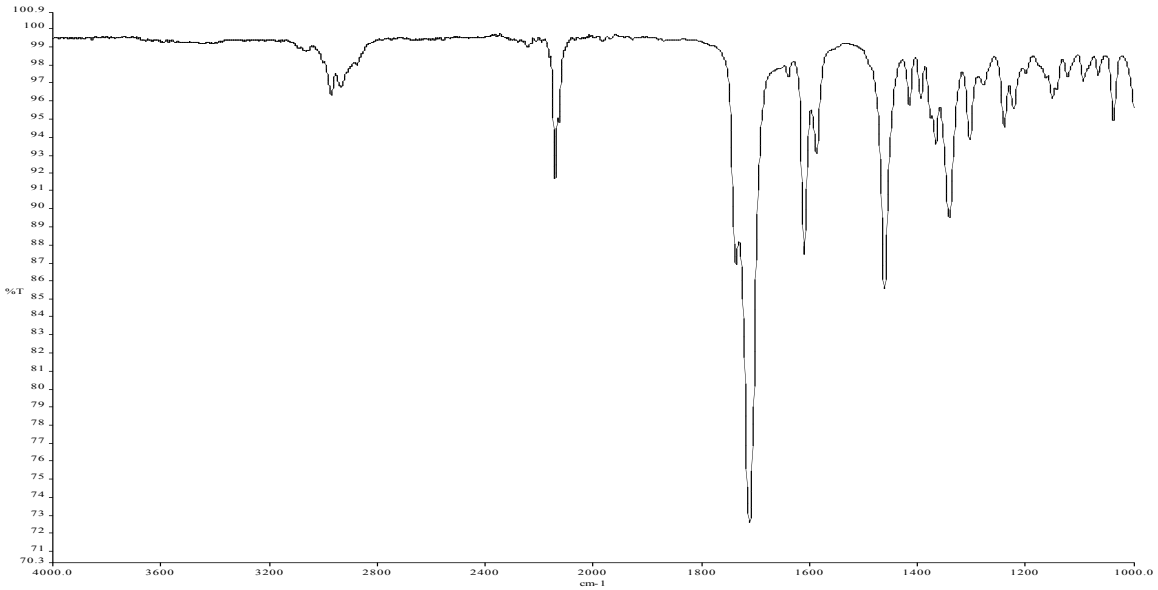

Figure A4.17 Infrared spectrum of compound **5.2**.

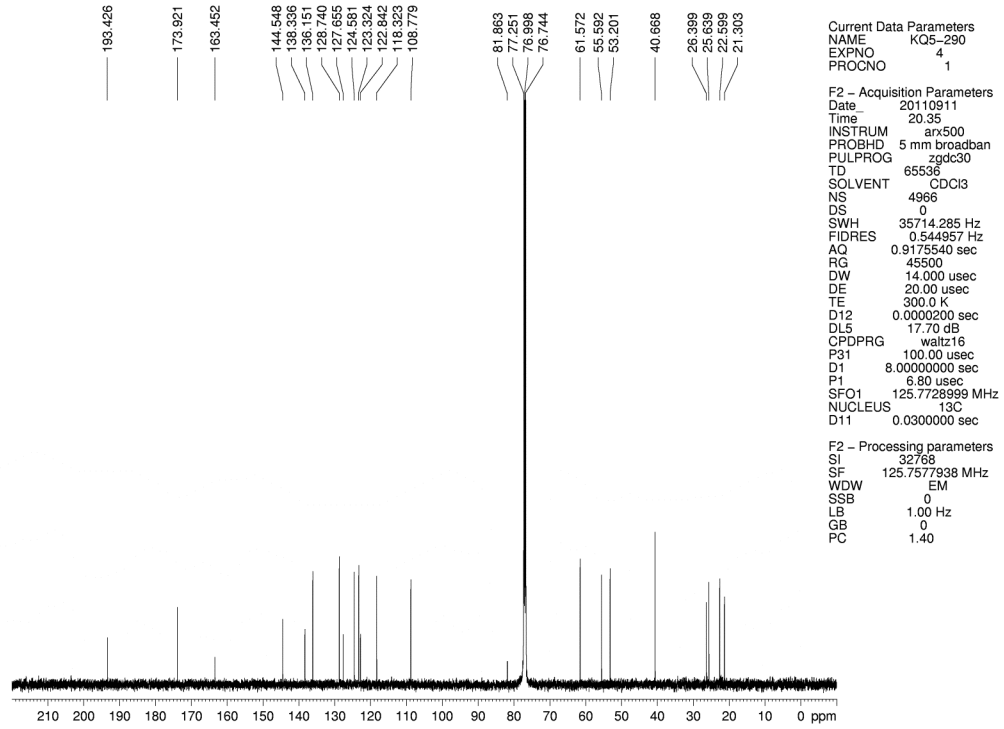

Figure A4.18 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **5.2**.

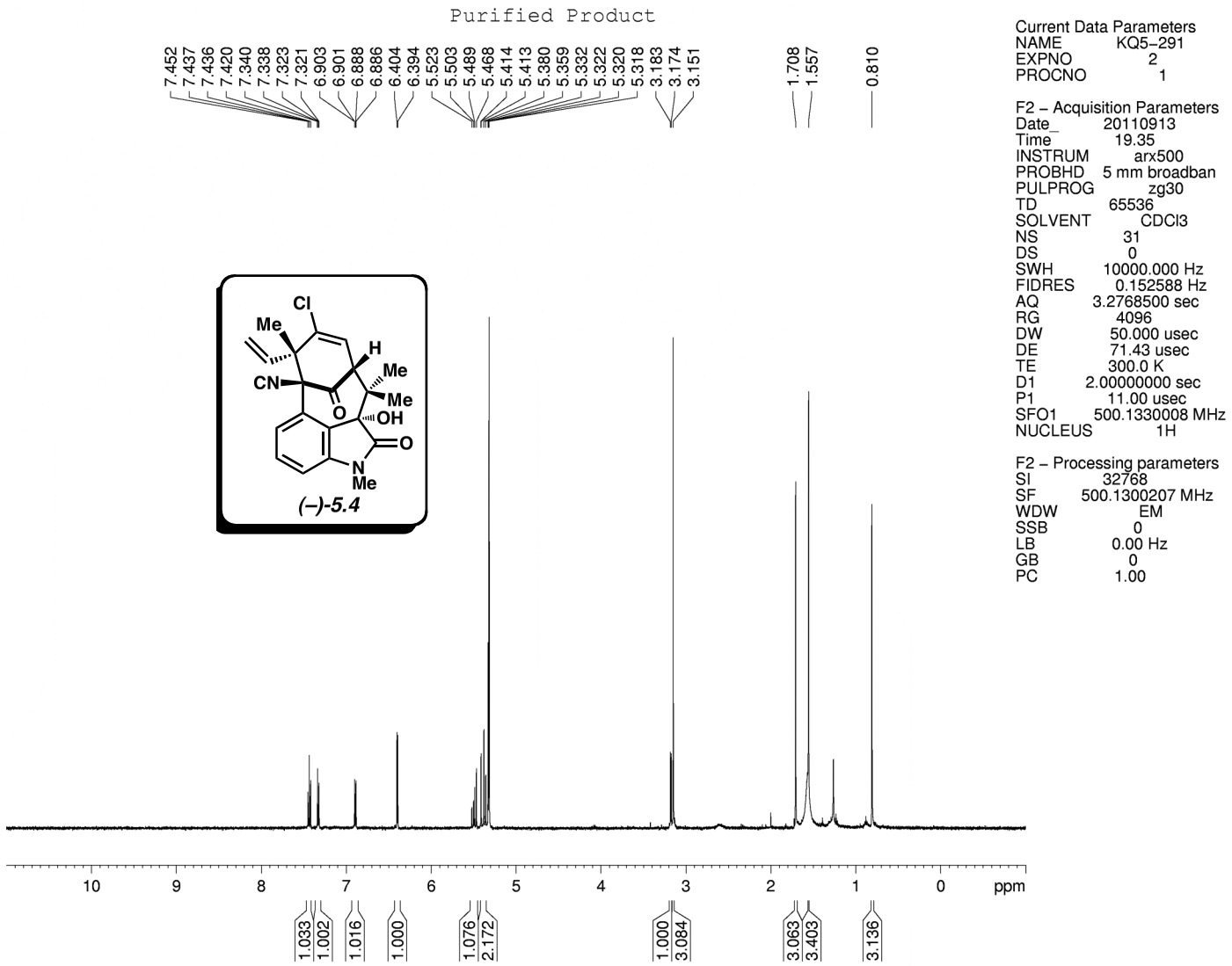

Figure A4.19 ^{1}H NMR (500 MHz, CD_2Cl_2) of compound **5.4**.

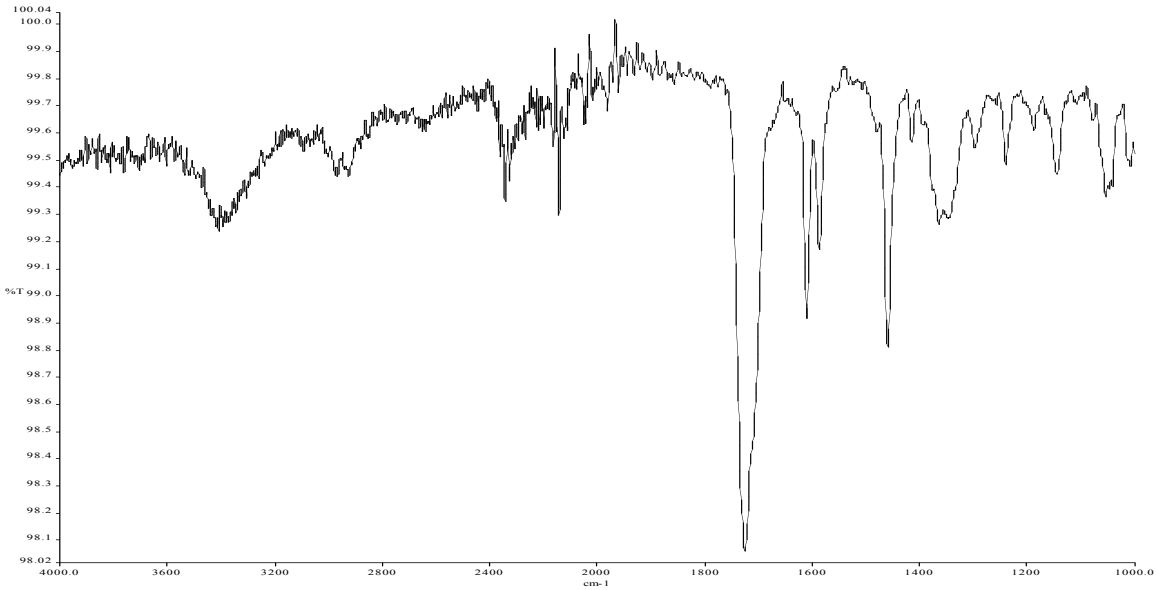

Figure A4.20 Infrared spectrum of compound **5.4**.

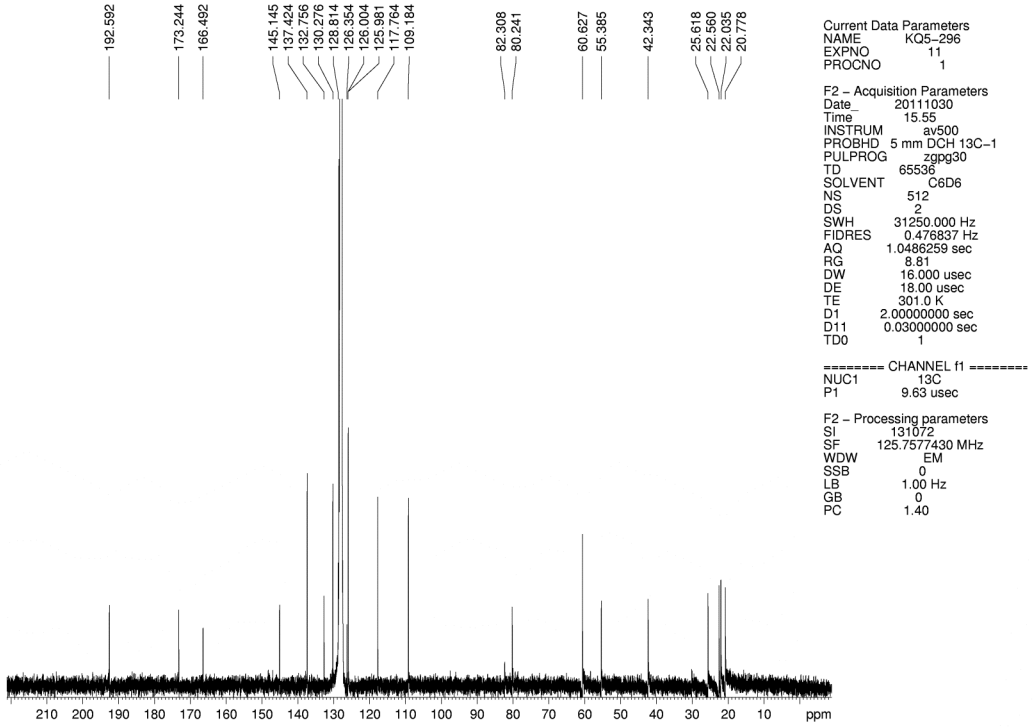

Figure A4.21 ^{13}C NMR (125 MHz, C_6D_6) of compound **5.4**.

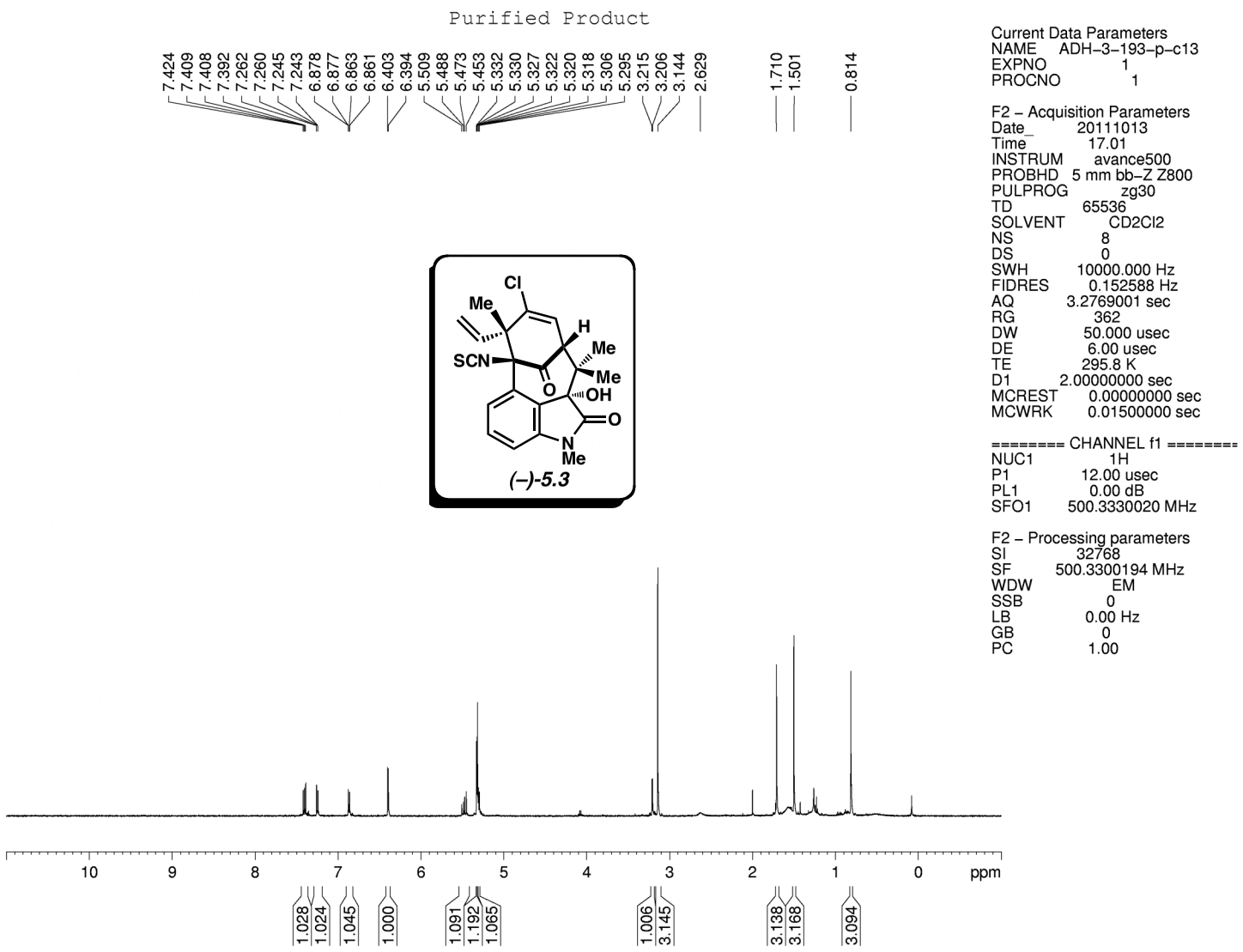

Figure A4.22 ^{1}H NMR (500 MHz, CD_2Cl_2) of compound **5.3**.

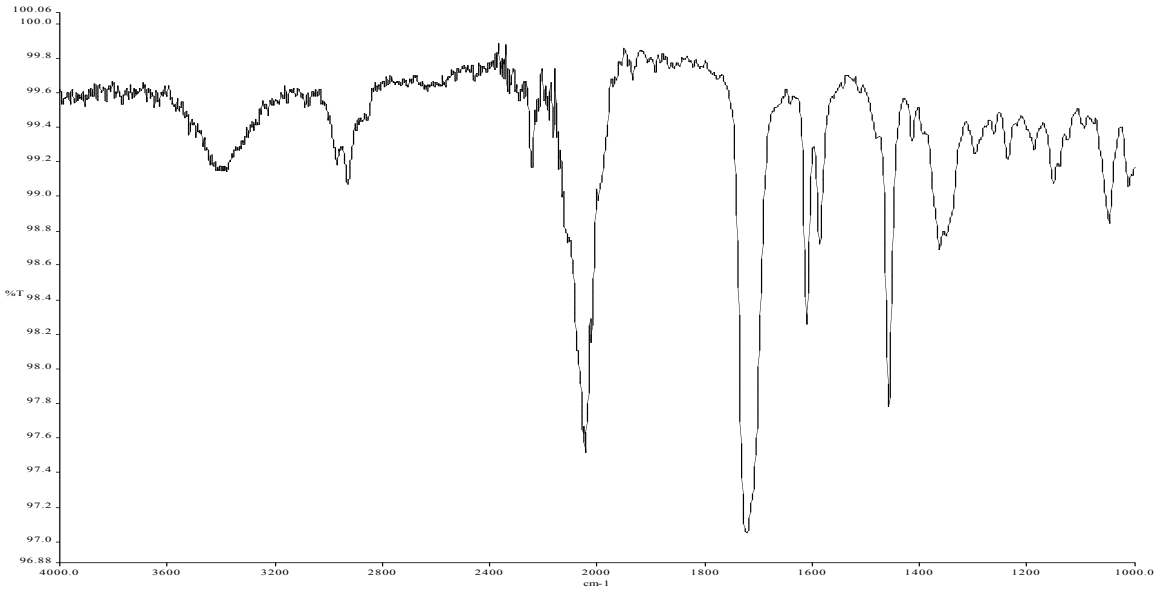

Figure A4.23 Infrared spectrum of compound **5.3**.

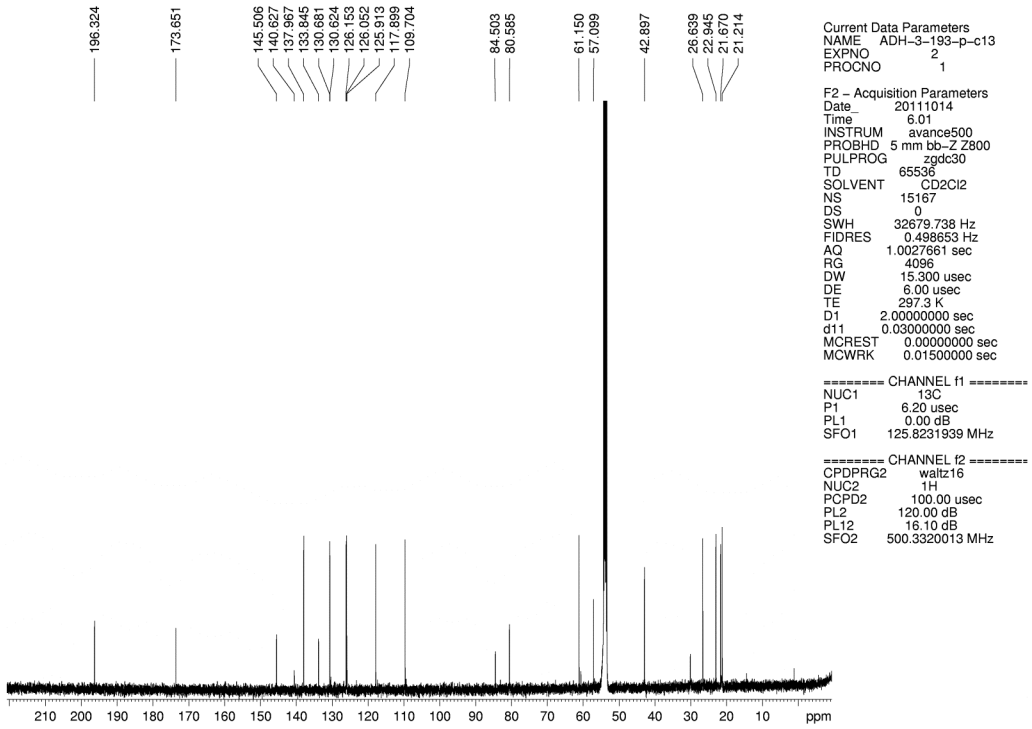

Figure A4.24 ^{13}C NMR (125 MHz, CD_2Cl_2) of compound **5.3**.

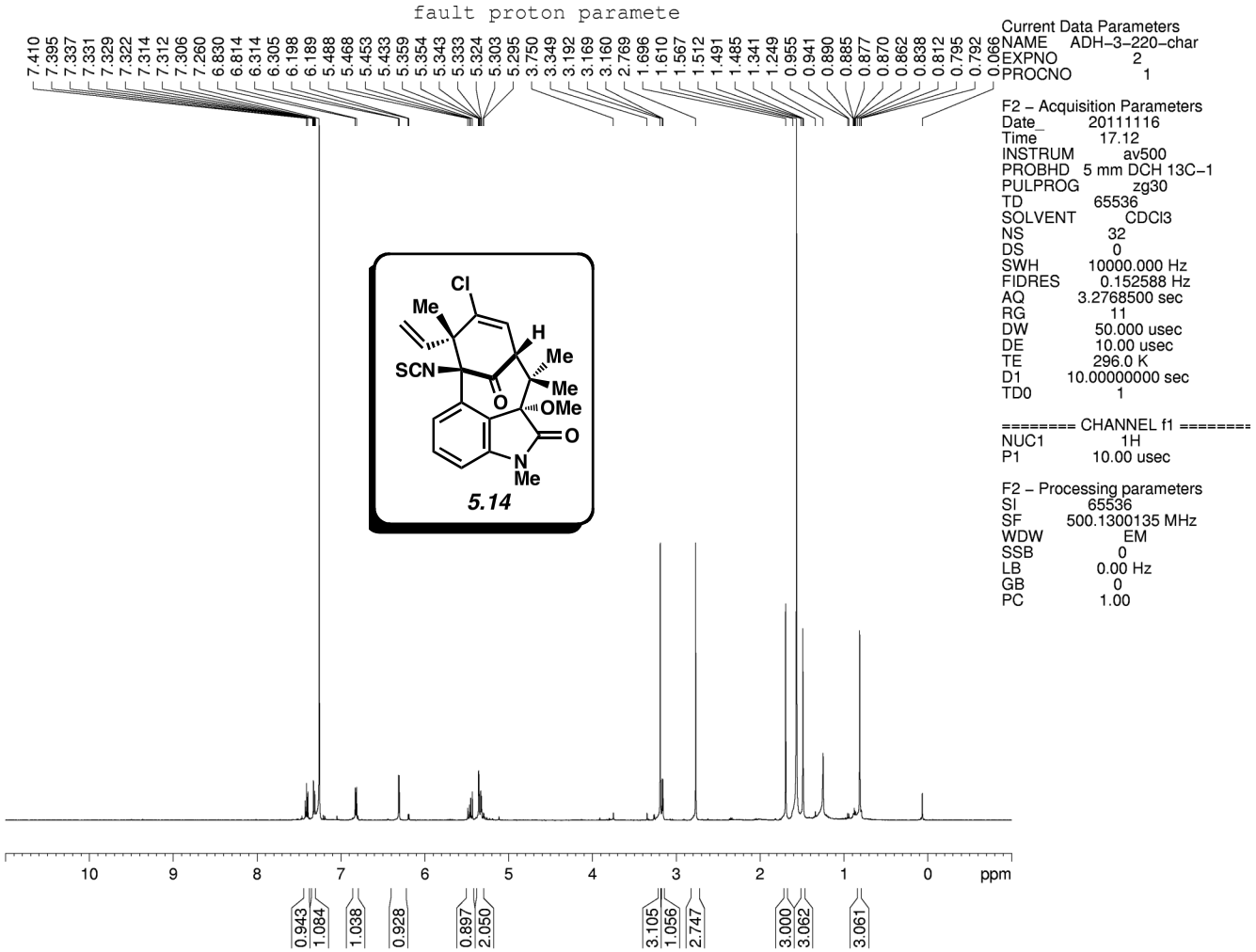

Figure A4.25 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **5.14**.

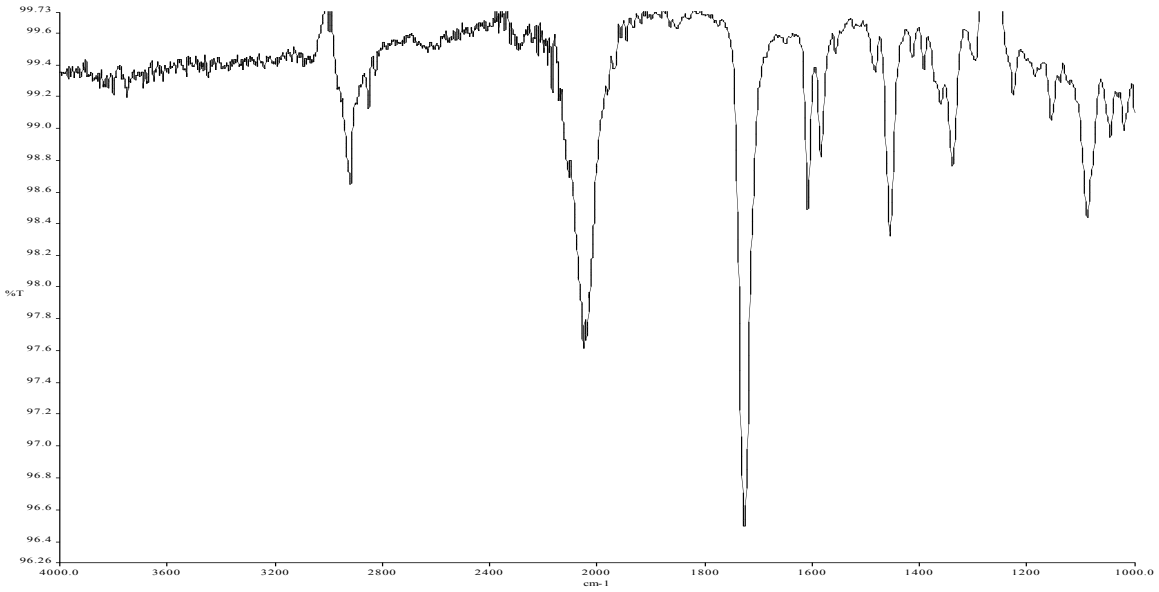

Figure A4.26 Infrared spectrum of compound **5.14**.

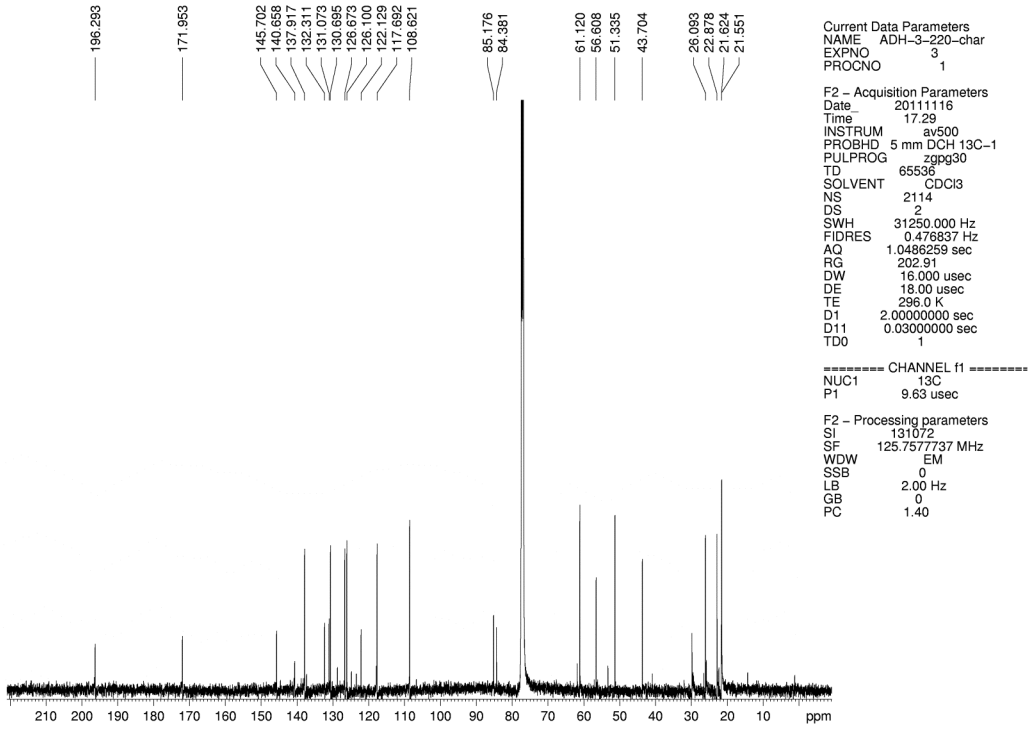

Figure A4.27 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **5.14**.