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An Interrupted Fischer Indolization Approach Toward the Akuammiline Alkaloids

Author
Boal, Ben Weston

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An Interrupted Fischer Indolization Approach Toward the Akuammiline Alkaloids

A dissertation submitted in partial satisfaction of the requirements for the degree Doctor of Philosophy in Chemistry

by

Ben Weston Boal

2012

ABSTRACT OF THE DISSERTATION

An Interrupted Fischer

Indolization Approach Toward the Akuammiline Alkaloids

by

Ben Weston Boal

Doctor of Philosophy in Chemistry

University of California, Los Angeles, 2012

Professor Neil K. Garg, Chair

Chapter one provides an overview of the history of the akuammiline alkaloids, including their isolation, structural features, biological activity, and biosynthesis. This chapter provides a discussion of synthetic efforts toward these intriguing alkaloids, in addition to detailed descriptions of several recently completed total syntheses. Chapter two discusses an efficient method to access the fused indoline ring system present in a multitude of bioactive molecules. The strategy involves the condensation of hydrazines with latent aldehydes to ultimately deliver indoline-containing products by way of an interrupted Fischer indolization sequence. The method is convergent, mild, operationally simple, broad in scope, and can be used to access enantioenriched products. In addition, the synthesis of furoindoline and pyrrolidinoindoline natural products is demonstrated by the concise formal total syntheses of physovenine and

debromoflustramine B. Chapter three explores the mechanisms of the Fischer indole synthesis and competing cleavage pathways with SCS-MP2/6-31G(d) and aqueous solvation calculations. Electron-donating substituents divert the reaction pathway to heterolytic *N–N* bond cleavage and preclude the acid-promoted [3,3]-sigmatropic rearrangement. Chapters four reports the total synthesis of (±)-aspidophylline A, one of many complex furoindoline-containing alkaloids that has not been synthesized previously. Our route features a number of key transformations, including a Heck cyclization to assemble the [3.3.1]-bicyclic scaffold, as well as a late-stage interrupted Fischer indolization to install the furoindoline and construct the natural product's pentacyclic framework.

The dissertation of Ben Weston Boal is approved.

Miguel A. García-Garibay

Louis Bouchard

Yi Tang

Neil K. Garg, Committee Chair

University of California, Los Angeles

2012

For my wife, Sarah Keiski

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LIST OF ABBREVIATIONS

‡	transition state
$[\alpha]_D$	specific rotation at wavelength of sodium D line
Ac	acetyl, acetate
acac	acetylacetonate
AcOH	acetic acid
app.	apparent
aq.	aqueous
atm	atmosphere
B3LYP	Becke, 3-parameter, Lee–Yang (functional)
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
bipyr	2,2'-bipyridine
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
br	broad
Bu	butyl
i-Bu	*iso*-butyl
n-Bu	butyl
t-Bu	*tert*-butyl
n-BuLi	butyl lithium
s-BuLi	*sec*-butyl lithium
t-BuLi	*tert*-butyl lithium
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
COD	1,5-cyclooctadiene
Cy	cyclohexyl
d	doublet
dba	dibenzylideneacetone
DCE	1,2-dichloroethane

dec	decomposition
DFT	density functional theorem
DIPEA	*N*,*N*-diisopropylethylamine
DMA	dimethylacetamide
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
DoM	directed ortho metalation
dppb	1,4-bis(diphenylphosphino)butane
dppe	1,2-bis(diphenylphosphino)ethane
dppf	1,1'-bis(diphenylphosphino)ferrocene
dppp	1,3-bis(diphenylphosphino)propane
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
IR	infrared (spectroscopy)
J	coupling constant
K_3PO_4	potassium phosphate (tribasic)
kcal/mol	kilocalories to mole ratio
KHMDS	potassium hexamethyldisilazane
λ	wavelength
L	liter

LANL2DZ	Los Alamos National Laboratory 2 double ζ (basis set)
LDA	lithium diisopropylamide
LiHMDS	lithium hexamethyldisilazane
m	multiplet or milli
m	meta
m/*z*	mass to charge ratio
μ	micro
Me	methyl
MHz	megahertz
min	minute(s)
mol	mole(s)
MOM	methoxymethyl ether
mp	melting point
Ms	methanesulfonyl (mesyl)
MS	molecular sieves
MW	microwave
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
NMR	nuclear magnetic resonance
NOE	Nuclear Overhauser Effect
NOESY	Nuclear Overhauser Enhancement Spectroscopy
[O]	oxidation
p	para
PCy_3	tricyclohexylphosphine
Ph	phenyl
pH	hydrogen ion concentration in aqueous solution
PhH	benzene
Piv	pivaloyl
PivCl	pivaloyl chloride
PPh_3	triphenylphosphine
ppm	parts per million
PP	protein phosphatase
Pr	propyl
i-Pr	isopropyl

pyr	pyridine
q	quartet
rt	room temperature
R_f	retention factor
s	singlet or strong
SEM	(trimethylsilyl)ethoxymethyl
t	triplet
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TBSCl	*tert*-butyldimethylsilyl chloride
Tf	trifluoromethanesulfonyl (trifyl)
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMDSO	tetramethyldisiloxane
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
TMSCl	trimethylsilyl chloride
Ts	*p*-toluenesulfonyl (tosyl)
TS	transition state
UV	ultraviolet
w	weak

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Chapter 2 is a version of Schammel, A. W.; Boal, B. W.; Zu, L.; Mesganaw, T.; Garg, N. K. *Tetrahedron* **2010**, *66*, 4687–4695. Schammel, Boal, Zu, and Mesganaw were responsible for experimental work.

Chapter 3 is a version of Çelebi-Ölçüm, N.; Boal, B. W.; Huters, A. D.; Garg, N. K.; Houk, K. N. *J. Am. Chem. Soc.* **2011**, *133*, 5752–5755.. This work was done in collaboration with Nihan Çelebi-Ölçüm and Kendall N. Houk from the University of California, Los Angeles. Boal was responsible for experimental work. Çelebi-Ölçüm, Huters, and Houk were responsible for computational work.

Chapter 4 is a version of Zu, L.; Boal, B. W.; Garg, N. K. *J. Am. Chem. Soc.* **2011**, *133*, 8877–8879. Zu and Boal were responsible for experimental work.

BIOGRAPHICAL SKETCH

Education:

University of Oregon, Eugene, OR

- Bachelor of Arts Degree in Chemistry, December 2006

Professional and Academic Experience:

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

- July 2007 to November 2012.
- Discovered convergent method for preparation of indoline-containing products.
- Completed the first total synthesis of the pentacyclic alkaloid aspidophylline A.
- Currently pursuing the synthesis of natural products in the Apocynaceae family of plants.

Undergraduate Research Assistant: University of Oregon, Eugene, OR

- September 2005 – June 2006
- Synthesized and tested the properties of polyaromatic organic light emitting diodes under the guidance of Professor Michael Haley.

Publications:

4. Zu, L.; Boal, B. W.; Garg, N. K. "Total Synthesis of (±)-Aspidophylline A." *J. Am. Chem. Soc.* **2011**, *133*, 8877–8879.

3. Çelebi-Ölçüm, N.; Boal, B. W.; Huters, A. D.; Garg, N. K.; Houk, K. N. "Why Do Some Fischer Indolizations Fail?" *J. Am. Chem. Soc*. **2011**, *133*, 5752–5755.

2. Schammel, A. W.; Boal, B. W.; Zu, L.; Mesganaw, T.; Garg, N. K. "Exploration of the Interrupted Fischer Indolization Reaction." *Tetrahedron* **2010**, *133*, 4687–4695.

1. Boal, B. W.; Schammel, A. W.; Garg, N. K. "An Interrupted Fischer Indolization Approach Toward Fused Indoline-Containing Natural Products." *Org. Lett*. **2009**, *11*, 3458–3461.

Posters or Presentations at Meetings or Conferences:

3. Gordon Conference in Heterocyclic Compounds, "Total Synthesis of (±)-Aspidophylline A" Newport, RI, June 26–July 1, 2011. Poster presentation.

2. ACS National Meeting and Exposition, "Total Synthesis of (±)-Aspidophylline A" Anaheim, CA, March 27 – 31, 2011. Poster presentation.

1. ACS National Meeting and Exposition, "An Interrupted Fischer Indolization Approach Toward Fused Indoline-Containing Natural Products" San Francisco, CA, March 11 – 25, 2010. Poster presentation.

CHAPTER ONE

Synthetic Studies of the Akuammiline Alkaloids

1.1 Abstract

The akuammiline alkaloids are a family of intricate natural products that have received considerable attention from chemists worldwide. This chapter provides an overview of the history of the akuammiline alkaloids, including their isolation, structural features, biological activity, and biosynthesis. In addition, this chapter provides a discussion of synthetic efforts toward these intriguing alkaloids, in addition to detailed descriptions of several recently completed total syntheses.

1.2 Introduction

1.2.1 Indoline Natural Products

The search for novel natural products has led to the isolation of a large number of structurally related indoline containing natural products. Such compounds are known for their intricate structures and interesting range of biological activity; as such, these natural products have captured the attention of synthetic chemists worldwide. A small sample of indoline-containing natural products is shown in Figure 1.1. Perophoramidine (**1.1**) was isolated in 2002,[1] and has been synthesized by Funk and Qin.[2,3] Psychotrimine (**1.2**) has been another popular target for synthesis since it's isolation in 2004.[4] It has succumbed to two total syntheses through elegant routes put forth by the Takayama and Baran laboratories, respectively.[5,6] Communesin B (**1.3**) is a member of the communesin family of natural products, which were isolated in 1993.[7] Since their isolation, the communesins have been intensely studied by synthetic chemists,[8,9] with

efforts culminating in several recent total synthesis.[10,11,12] Diazonamide A (**1.4**) is a secondary metabolite, which was isolated in 1991 from colonial marine ascidian *Diazona angulata*.[13] Diazonamide A shows promising bioactivity as a potent antimitotic agent in several human cancer cell lines.[14] Harran and coworkers have reported diazonamide A interacts with a form of ornithine δ-amino transferase (OAT) involved in controlling mitosis in cancer cells.[15] Further this inhibition of mitosis in cells using OAT does not induce the progressive retinal degeneration associated with loss of OAT enzymatic activity in rodents and humans.[16] Highlights in the synthetic literature[18] for this compound includes work by the Harran,[19] Macmillan,[20] and Nicolaou[21] laboratories. Lastly, bipleiophylline (**1.5**) is a recently isolated indoline-containing natural product that has yet to be synthesized.[22] Whereas these examples showcase the variety and complexity that is common amongst indoline natural products, this chapter focuses on a subset of natural products called the akuammiline alkaloids.

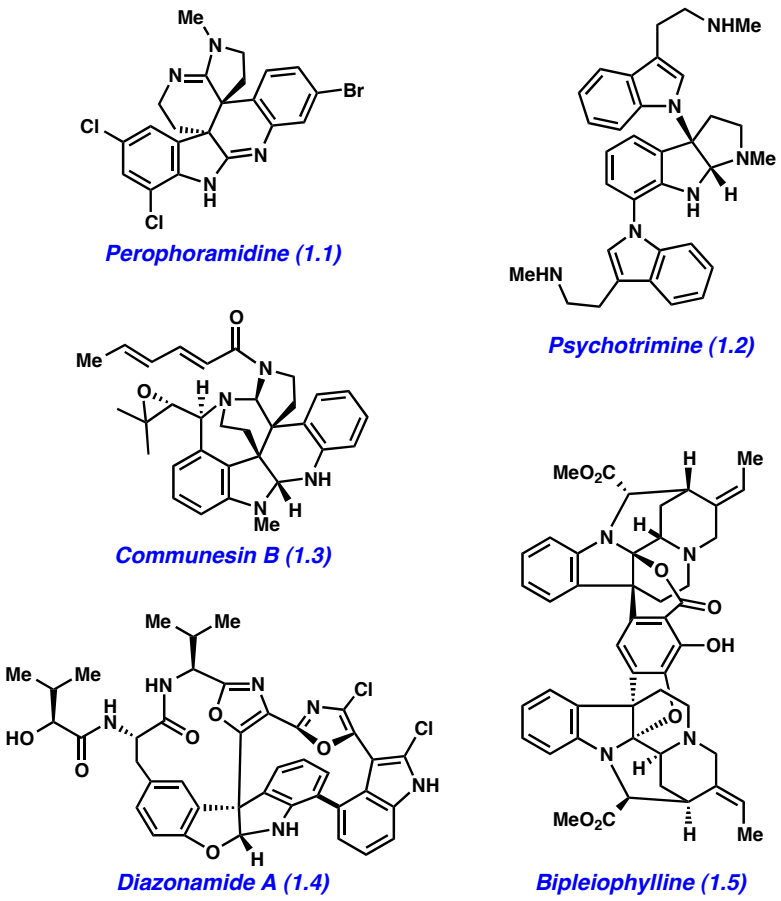


Figure 1.1. Representative structures of indoline alkaloids

1.2.2 Akuammiline Family of Natural Products

The akuammaline alkaloids are a particularly interesting family of natural products that have been isolated from plants predominantly found in Southeast Asia and Africa. In Figure 1.2, several akuammiline alkaloids are shown. Akuammiline[23] (**1.6**) and echitamine chloride[24,25,26] (**1.12**) were some of the earliest members isolated from this family. Later in the 1960's, the structures of strictamine[27] (**1.7**), picrinine[28] (**1.9**), and vincorine[29] (**1.11**) were elucidated. Very recently, new family members such as aspidophylline A[30] (**1.8**) and scholarisine A[31] (**1.13**) have been discovered. The akuammiline alkaloids are generally characterized by rigid polycyclic ring systems that contain: caged structures, a quaternary center, the indol(en)ine motif, and numerous

stereocenters. Seven-membered rings, which are typically difficult to synthesize, are seen in both vincorine (**1.11**) and echitamine chloride (**1.12**). Whereas structural complexity renders these molecules intriguing synthetic targets, the use of these molecules' parent plant species in traditional medicine also demonstrates their medical relevance.

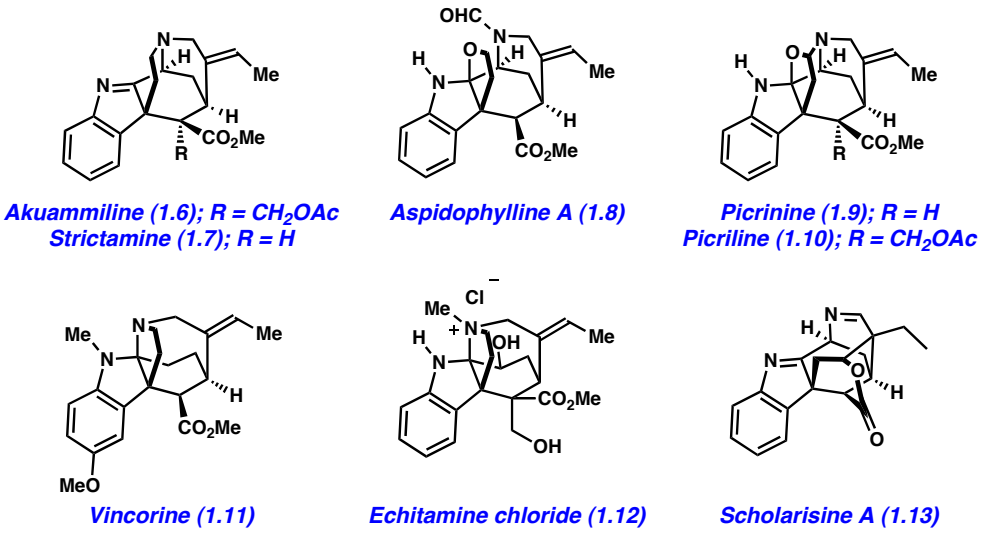


Figure 1.2. Representative akuammiline alkaloids

1.2.3 Biological Activity

The use of the akuammiline alkaloids in traditional medicine has prompted investigations of their bioactivities.[32] Aspidophylline A (**1.8**) was found to reverse drug resistance in resistant KB cells.30 Another akuammiline natural product with interesting biological activity is picriline (**1.10**). Picriline has been shown to selectively inhibit SGLT2,[33] a renal cortex membrane protein that regulates glucose reabsorption. SGLT2 was recently validated as a target for type-II diabetes intervention.[34] Perhaps the most biologically fascinating akuammiline alkaloid is echitamine chloride (**1.12**), as it has shown to be cytotoxic toward cancer cells with an unusually low overall toxicity.[35]

1.2.4 Biosynthesis

Although the biosynthesis of the akuammiline alkaloids has not been studied in detail, a plausible hypothesis has been proposed that relies upon a unique oxidative cyclization of geissoschizine, a common intermediate in the biosynthesis of several other alkaloid families (Figure 1.3). Beginning with the biosynthesis of picrinine (**1.9**) and aspidophylline A (**1.8**), it is thought that the initial steps of this biosynthetic pathway closely follow that of the strychnos and iboga alkaloids.[36] The biosynthesis starts with the coupling of tryptamine (**1.14**) and secologanine (**1.15**) to form 3α (S)-strictosidine (**1.16**). 3α (S)-strictosidine (**1.16**) then undergoes an intramolecular cyclization followed by an alkene isomerization to arrive at geissoschizine (**1.17**). Geissoschizine is a biogenetic precursor for a number of alkaloid families.[37] In the case of the akuammiline alkaloids, geissoschizine (**1.17**) undergoes an oxidative cyclization forming a bond between C7 and C16;[38] this is then followed by a deformylation arriving at strictamine (**1.7**).36 Further oxidation of strictamine at C5 (**1.7**) followed by a cyclization onto the indolenine moiety affords picrinine (**1.9**). Picrinine (**1.9**), in turn, undergoes a reduction at C5 followed by *N*-formylation to arrive at aspidophylline A (**1.8**). This reduction of C5 in picrinine (**1.9**) is interesting as it breaks the C–N bond that was present in the original tryptamine building block **1.14**.

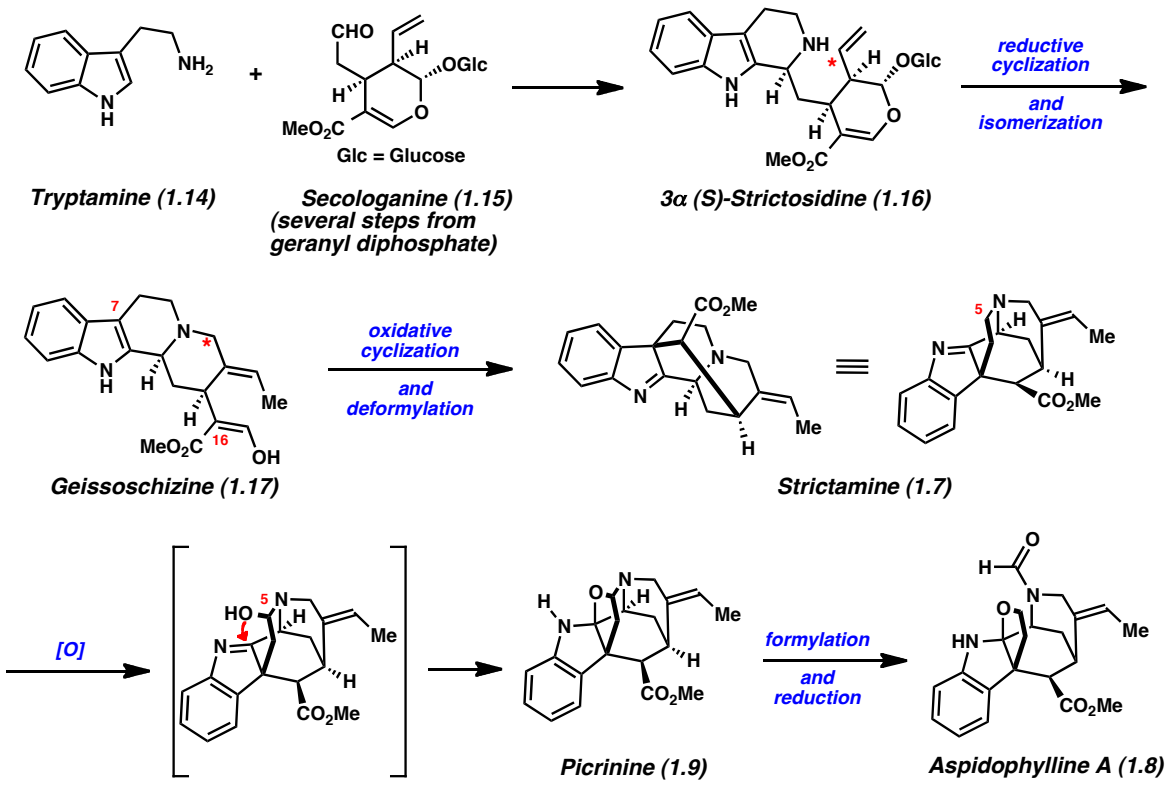


Figure 1.3. Proposed biosynthesis of picrinine (**1.9**) and aspidophylline A (**1.8**)

Picrinine and strictamine play key roles in the biosyntheses of scholarisine A and vincorine, respectively. The biosynthesis of scholarisine A (**1.13**) was hypothesized at the time of its isolation and begins with picrinine (**1.9**, Figure 1.4).[31] Picrinine (**1.9**) is expected to be in equilibrium with aldehyde **1.18**. This intermediate is thought to undergo an alkene isomerization to afford enamine **1.19**. This enamine would then attack the free aldehyde to form secondary alcohol **1.20**. Subsequent cyclization of the alcohol onto the proximal methyl ester with loss of methanol would afford scholarisine A (**1.13**). Similarly, vincorine (**1.11**) is closely related to strictamine (**1.7**), as shown in Figure 1.5. Rearrangement of strictamine (**1.7**), with reduction, could furnish **1.21**, which possesses a 7-membered ring. Subsequent oxidation and methylation of **1.21** would then provide vincorine (**1.11**).

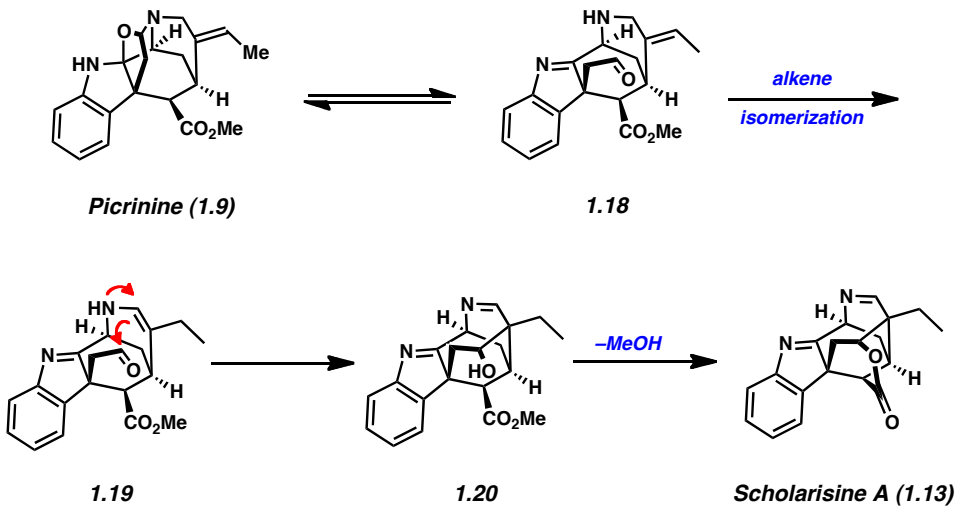


Figure 1.4. Proposed biosynthesis of scholarisine A (**1.13**)

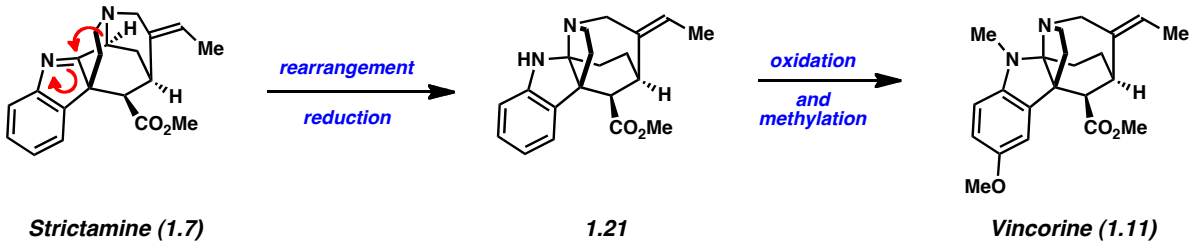


Figure 1.5. Proposed biosynthesis of vincorine (**1.11**)

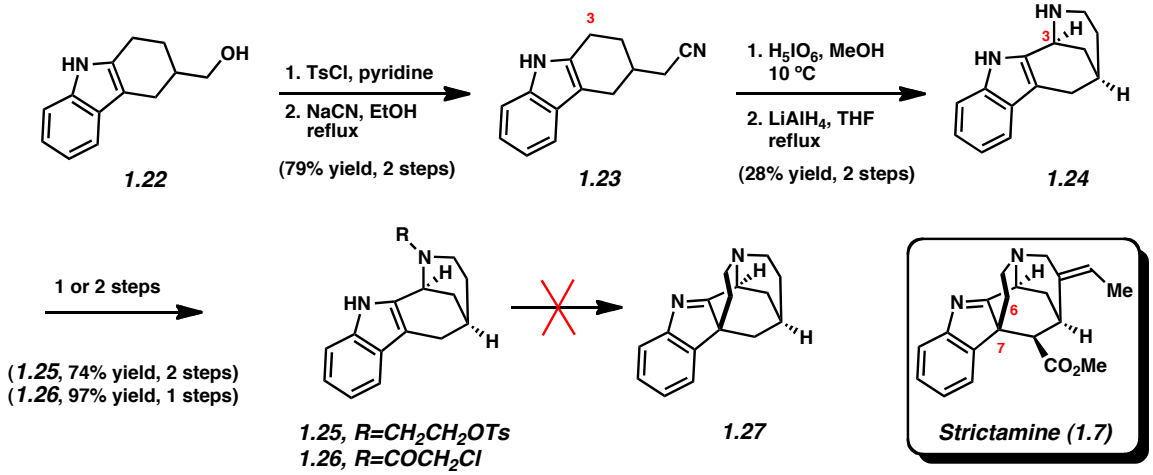
1.3 Progress Toward the Total Synthesis of Strictamine

1.3.1 Dolby's Efforts Toward the Strictamine Polycyclic Framework

In the early 1970's, the Dolby laboratory reported the first synthetic studies of the akuammiline natural products with their attempted synthesis of a strictamine model system (Scheme 1.1).[39] Their approach toward strictamine hinged on forming a bond between C6 and C7 at a late stage. To arrive at a substrate for this bond construction Dolby and coworkers synthesized amine **1.24** starting from known alcohol **1.22**. Alcohol 1.**22** was activated using *p*-toluenesulfonyl chloride, and the resulting alkyl tosylate was then displaced with sodium cyanide

to afford nitrile **1.23**. Using chemistry developed in the Dolby laboratory,[40] nitrile **1.23** was selectively oxidized at C3. This step was followed by a double reduction using lithium aluminum hydride to deliver the desired amine **1.24** in 28% yield over the two steps. Amine **1.24** was then further elaborated to two potential cyclization substrates: tosylate **1.25** and chloroacetamide **1.26**. Tosylate **1.25** was submitted to several sets of cyclization conditions, but the desired product **1.27** was not observed. Hypothesizing that substrate **1.25** could react unproductively to form an aziridinium ion if the electron rich nitrogen displaced the tosylate, the authors prepared the less electron-rich chloroacetamide substrate **1.26**. Unfortunately, efforts to employ acetamide **1.26** in the key C6–C7 bond forming event were also unsuccessful. After these admirable attempts by the Dolby laboratory, synthetic studies on the akuammaline alkaloids remained dormant for roughly 20 years.

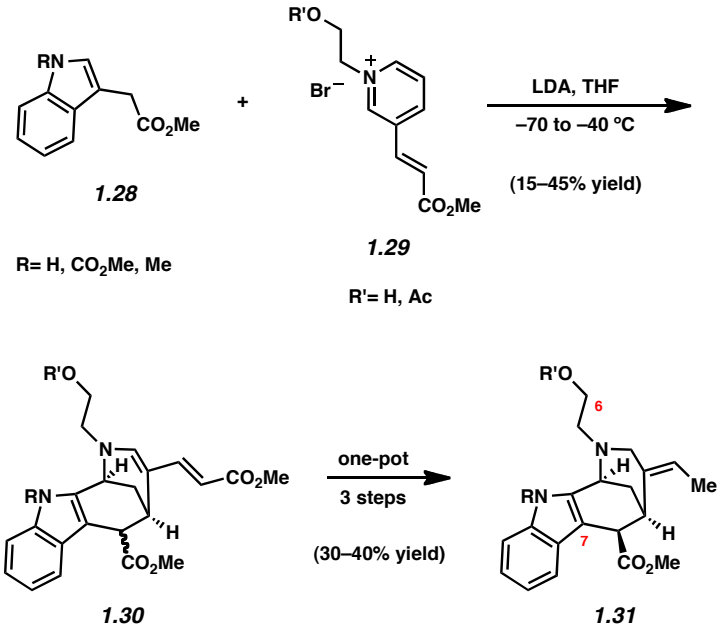
Scheme 1.1



1.3.2 Bosch and Bennasar's Progress Toward Strictamine

Likely influenced by the work of the Dolby group, the laboratories of Bosch and Bennasar took a similar approach in their synthetic efforts toward strictamine (**1.7**) where the C6–C7 bond would be fashioned at a late-stage (Scheme 1.2).[41] The authors targeted compound **1.31** for their desired cyclization and developed a rapid route to this key substrate. Using LDA to form the enolate of indole **1.28**, the addition of pyridinium salt **1.29** triggered a tandem nucleophilic addition/cyclization to form the [3.3.1] bicycle **1.30**.[42] Next, over a 3 step / one pot sequence, bicycle **1.30** was transformed to alkene **1.31**. Of note, **1.31** contains almost all of the strictamine functionality, except for the key C6–C7 bond.

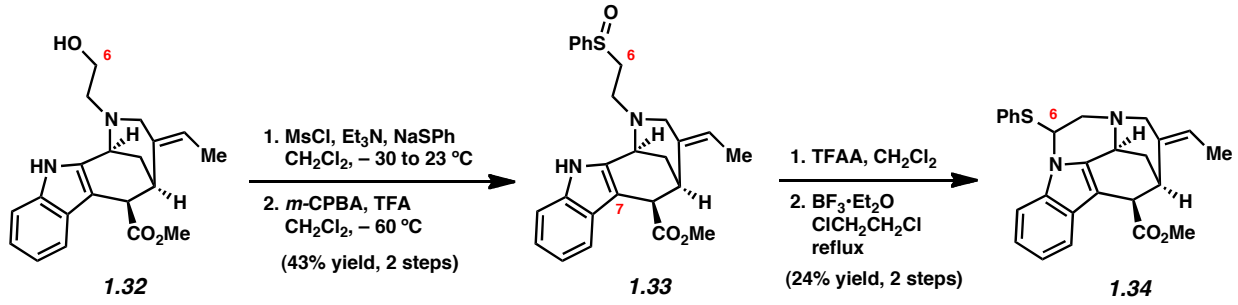
Scheme 1.2



After initial attempts to forge the desired C6–C7 linkage by activating the alcohol of derivative **1.32** as the tosylate or mesylate were deemed unsuccessful, the authors attempted to

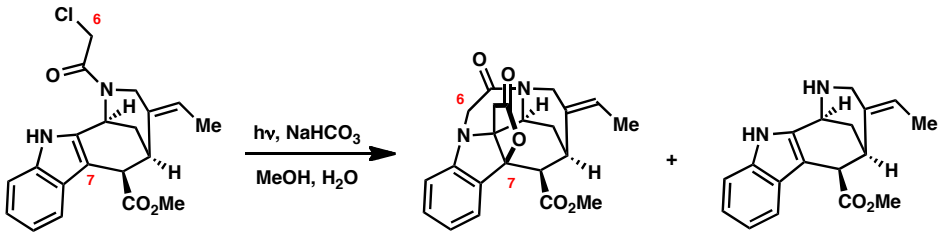
activate C6 through a Pummerer cyclization (Scheme 1.3).[43] To effect this transformation, they first converted alcohol **1.32** into sulfoxide **1.33**. Pummerer cyclization of sulfoxide **1.33** was conducted by treatment with trifluoroacetic anhydride (TFAA), followed by reaction with BF_3•Et_2O. Unfortunately, the only product observed was pentacycle **1.34**, which likely arises from the indole nitrogen attacking the presumed thiocarbenium intermediate. Further cyclization efforts using protected indole derivatives of **1.33** gave only decomposition products.[41]

Scheme 1.3



Bosch and Bennasar also attempted photocyclizations of chloroacetamides, such as **1.35** (Scheme 1.4).[44] Again, rather than desired cyclization occurring, reaction at the indole nitrogen appeared favorable as **1.36** formed as the only significant product. They attempted to circumvent this problem by protecting the indole nitrogen of **1.35**, but their efforts were met with similar decomposition pathways as seen in their earlier work.[41] Attempts to rearrange side products similar to **1.36** using a photo-Fries rearrangement were also unsuccessful.[45]

Scheme 1.4



1.35 *1.36* (10% yield) *1.37* (trace)

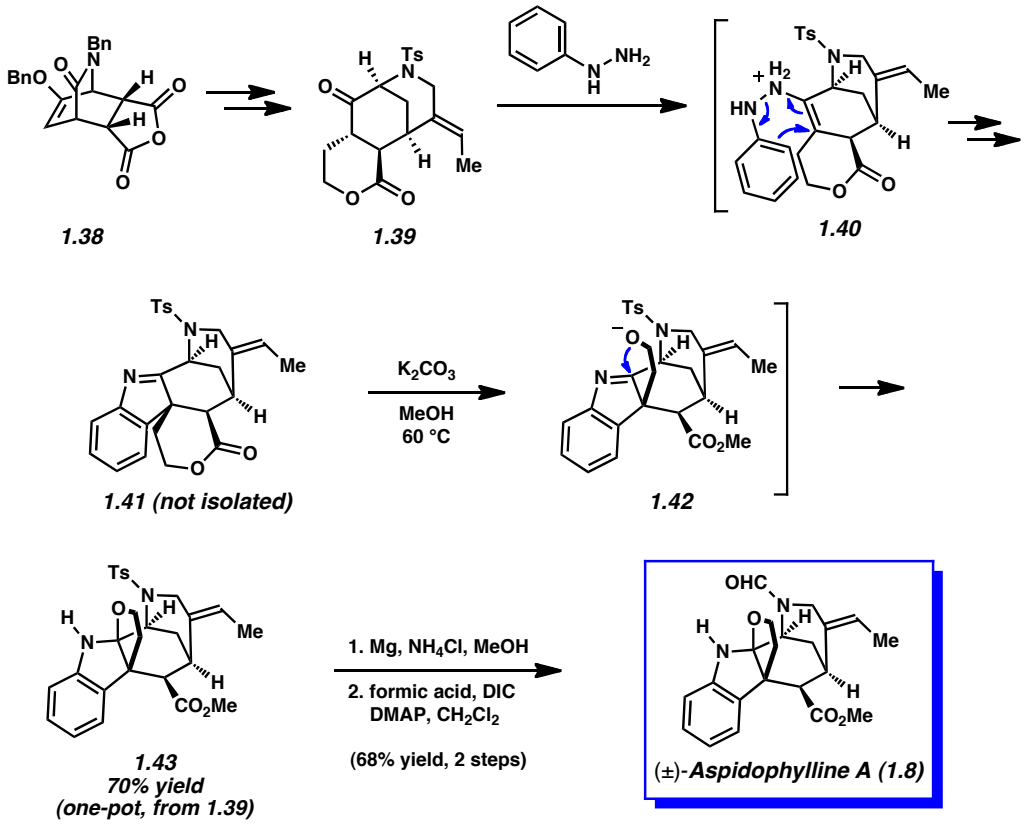
The seminal studies of Dolby and Bosch and Bennasar provide useful insights into the reactivity of these types of caged ring systems. When the indole nitrogen is unprotected, it is the preferred site of cyclization. However, even when the indole nitrogen is protected, cyclization to furnish the critical C6–C7 linkage is challenging. As suggested by Bosch and Bennasar,41[a] this difficulty is likely due to geometric factors, such as the distance between C6 and C7, the challenge in forming a congested quaternary center, and disfavorable transannular interactions encumbered in the desired cyclization transition states. Nonetheless, these results have laid the foundation for many of the contemporary studies in akuammiline alkaloid synthesis and have resulted in several completed total syntheses.

1.4 Total Synthesis of (±)-Aspidophylline A

In 2011, the Garg laboratory completed the first total synthesis of (±)-aspidophylline A (**1.8**).[46] The route to the pentacyclic alkaloid **1.8** is summarized in Scheme 1.5 and features a number of key transformations, including: (a) a copper-mediated oxidative bis(decarboxylation)[47] to furnish a [2.2.2]-bicyclic lactam, (b) a Heck cyclization[48] to assemble the natural product's [3.3.1]-bicyclic scaffold, and (c) a late-stage interrupted Fischer indolization reaction[49] to install the fused furoindoline and construct the natural product's full

pentacyclic framework (**1.39→1.43**). Full details of this total synthesis are discussed in Chapter 4 of this dissertation.

Scheme 1.5



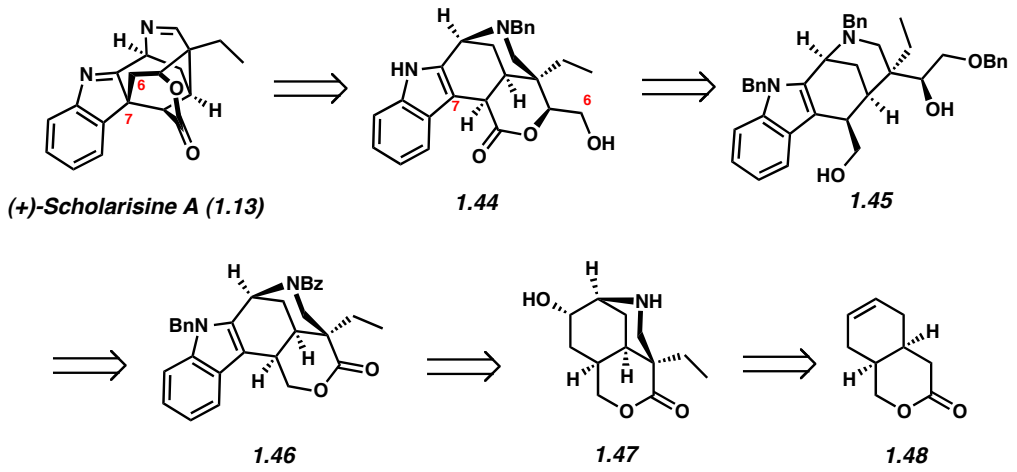
1.5 Total Synthesis of (+)-Scholarisine A

1.5.1 Retrosynthetic Analysis

In 2012, the Smith laboratory reported the first total synthesis of (+)-scholarisine A (**1.13**).[50] The retrosynthesis of (+)-scholarisine A (**1.13**) devised by Smith and coworkers is shown in Scheme 1.6. It was envisioned that (+)-scholarisine A (**1.13**) would be accessible from lactone **1.44**, which in turn would come from an oxidative cyclization of diol **1.45**. Diol **1.45**

was envisioned to arise from indole **1.46**. Further disconnection revealed alcohol **1.47** as an appropriate synthetic precursor, which would be prepared from known lactone **1.48**.[51]

Scheme 1.6

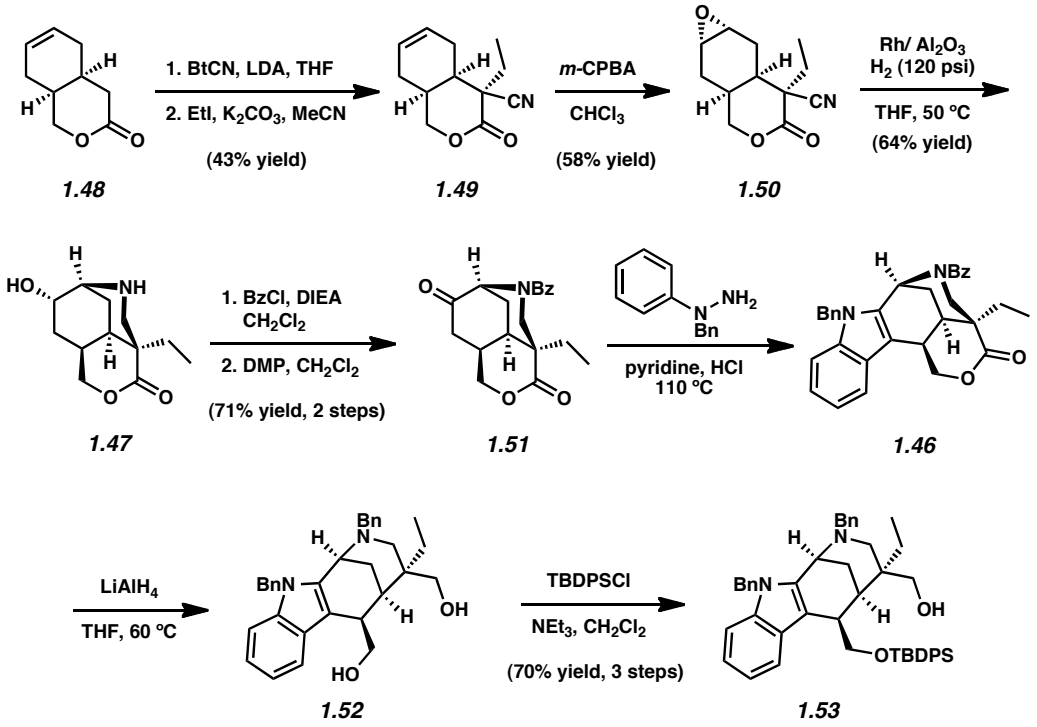


1.5.2 Forward Synthesis of (+)-Scholarisine A

The Smith laboratory's synthesis of intermediate **1.53** is shown in Scheme 1.7. The synthesis began with lactone **1.48**, which was synthesized in enantioenriched form from commercially available cis-4-cyclohexene-1,2-dicarboxylic anhydride in five steps, using a modification[52] of the known procedure.[51] Cyanation of lactone **1.48** with cyanobenzotriazole (BtCN) and lithium diisopropylamide (LDA), followed by a second alkylation using potassium carbonate and ethyl iodide, afforded alkene **1.49**. Epoxidation of alkene **1.49** led to a mixture of diastereomers, which upon recrystallization yielded nitrile **1.50** in a 58% yield. Nitrile **1.50** then underwent a reductive cyclization[53,54] with H_2 and rhodium on alumina to afford amine **1.47**, which possesses the desired [3.3.1]-bicycle of the natural product. Amine **1.47** was protected as the corresponding benzamide, and subsequent alcohol oxidation with Dess–Martin periodinane delivered ketone **1.51**. Treatment of ketone **1.51** with benzyl protected phenylhydrazine and HCl

in pyridine facilitated the Fischer indolization to provide indole **1.46**.[39,46] Of note, intermediate **1.46** possesses most of the scholarisine framework. Reduction of **1.46** with lithium aluminum hydride ($LiAlH_4$) simultaneously reduced the lactone and converted the benzamide into a benzyl protecting group, thus furnishing diol **1.52**. The more sterically accessible primary alcohol of diol **1.52** was then selectively protected to give **1.53** in 70% yield over the three steps.

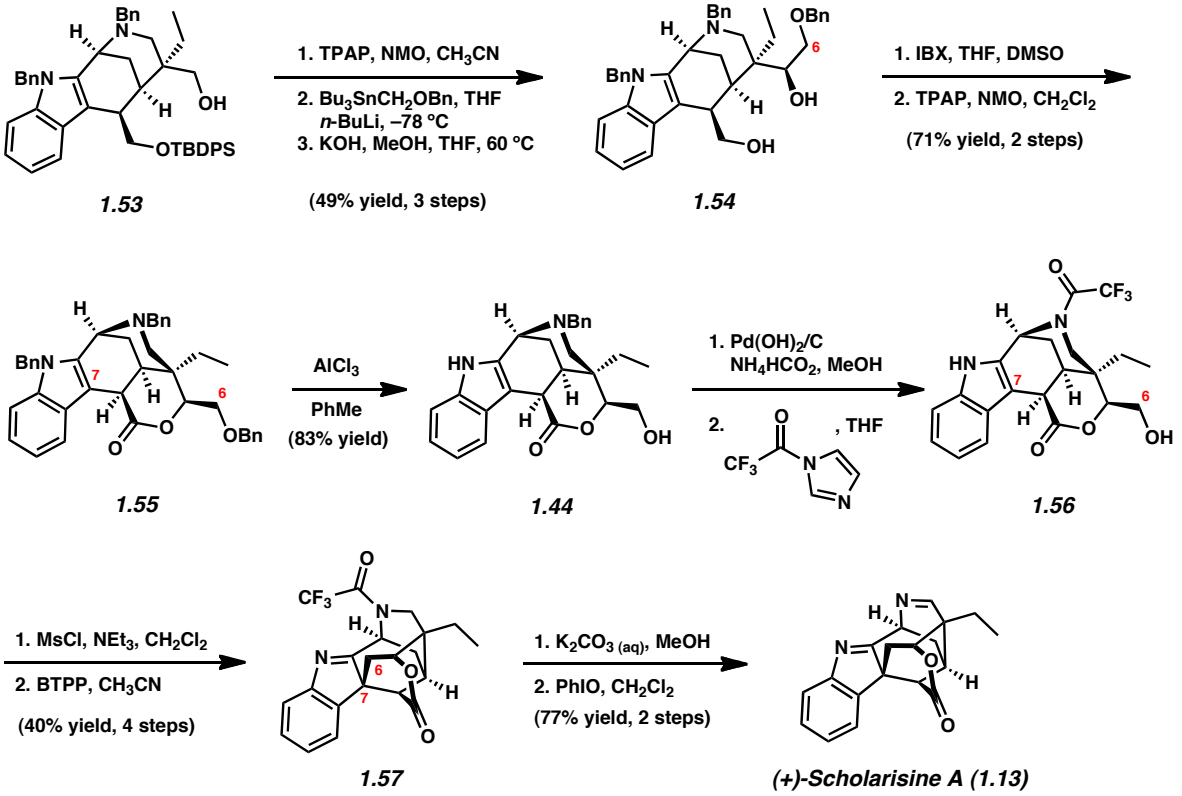
Scheme 1.7



The remaining steps of Smiths' synthesis of (+)-scholarisine A are shown in Scheme 1.8. The remaining goals included installing the lactone ring and introducing the C6 carbon. To this end, alcohol **1.53** was oxidized using tetrapropylammonium perruthenate (TPAP) and *N*-methyl-morpholine *N*-oxide (NMO) as a co-oxidant.[55] Subsequent addition of in situ-generated benzyloxymethyllithium,[56] followed by base-mediated desilylation afforded diol **1.54**. Next, diol

1.54 was exposed to 2-iodoxybenzoic acid (IBX) to provide an aldehyde intermediate.[57] The crude mixture of this reaction was then treated with TPAP and NMO to deliver **1.55**, which possesses the required lactone moiety. Of note, this stepwise oxidation avoided side products that were observed in attempts to affect direct oxidation of **1.54** to **1.55**. By forming the lactone, it was hypothesized that C7 and C6 would be in close enough proximity to eventually perform a crucial cyclization between these two sites. Following deprotection of the primary alcohol and indole nitrogen with aluminum trichloride, the key cyclization was attempted using intermediate **1.44**. However, activation of alcohol **1.44** was unsuccessful due to competitive cyclization of the benzyl amine onto C6. To mitigate this competitive cyclization, the nitrogen protecting group of **1.44** was exchanged to deliver trifluoroacetamide **1.56**. In the key bond forming sequence, the alcohol of **1.56** was activated with methanesulfonyl chloride (MsCl). Subsequent treatment of the resulting mesylate with *tert*-butyliminotri(pyrrolidino)-phosphorane (BTPP)[58] furnished indolenine **1.57** in a 40% yield (four steps from alcohol **1.44**). Removal of the trifluoroacetamide protecting group with potassium carbonate, followed by oxidation of the secondary amine using iodosobenzene (PhIO) provided (+)-scholarisine A (**1.13**).[59] Smith's synthetic sample was in complete accord with the natural material, and therefore confirmed the absolute stereochemical configuration of the natural product.

Scheme 1.8



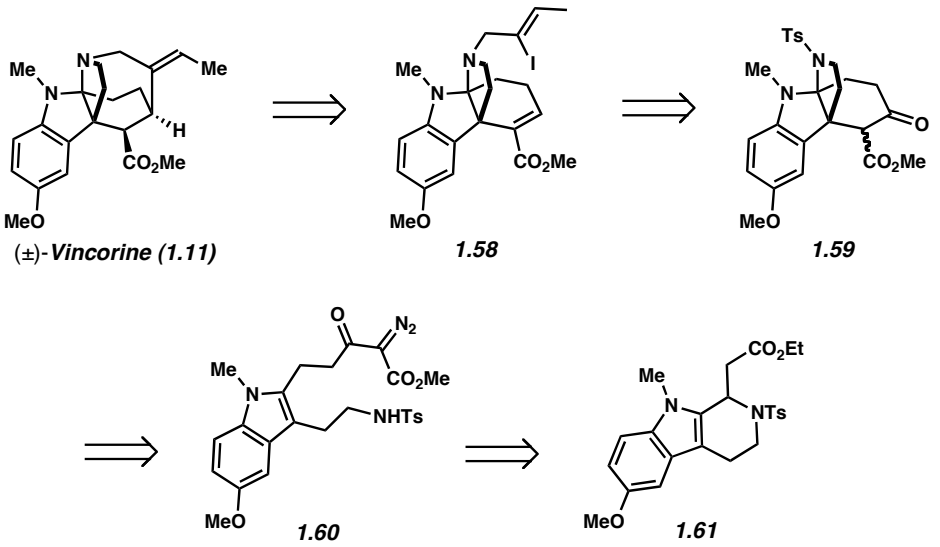
Smith's elegant synthesis of (+)-scholarisine A marks the first asymmetric synthesis of an akuammiline alkaloid. The longest linear reaction sequence to arrive at the intricate natural product structure is 20 steps from known lactone **1.48**. Highlights of the synthesis include a reductive cyclization of nitrile **1.50**, a Fischer indolization of ketone **1.51**, an oxidative lactonization of diol **1.54**, and an impressive late-stage intramolecular cyclization of alcohol **1.56** to forge the key C6–C7 bond.

1.6 Qin's Total Synthesis of (±)-Vincorine

1.6.1 Key Retrosynthetic Disconnections

Qin and coworkers reported the first total synthesis of (±)-vincorine (**1.11**) in 2009.[60] In Qin's initial retrosynthesis of (±)-vincorine, shown in Scheme 1.10, the seven membered ring observed in the natural product would be assembled by an intramolecular reductive Heck cyclization[48] of vinyl iodide **1.58**. Similar cyclizations were reported to close six membered rings in the total syntheses of minfiensine, a natural product structurally related to vincorine (**1.11**).[61] Vinyl iodide **1.58** was envisioned to arise from sulfonamide **1.59**, with sulfonamide **1.59** stemming from α-diazoketone **1.60**. In turn, α-diazoketone **1.60** would be obtained from known indole **1.61**, which can be readily prepared from commercially available material in one step.[62]

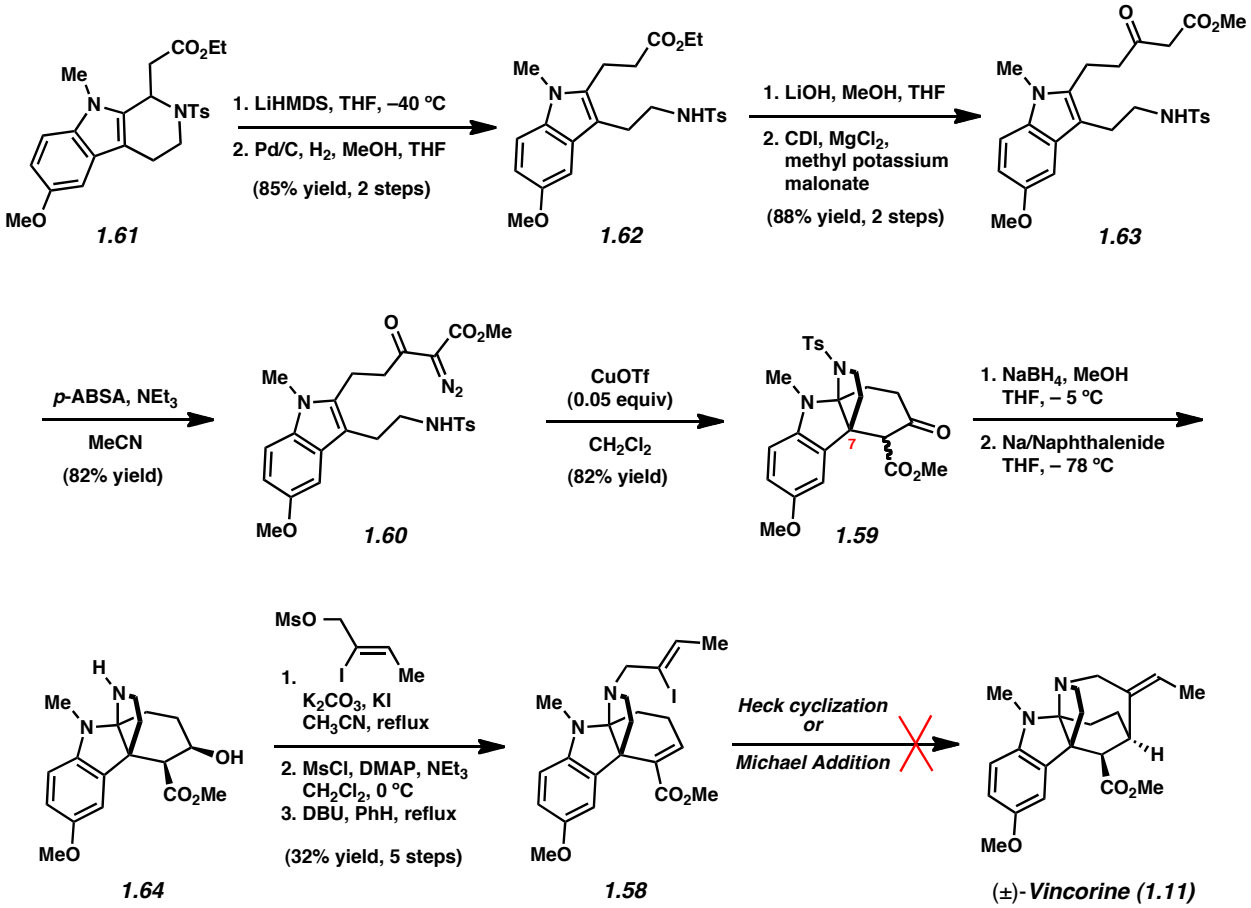
Scheme 1.9



1.6.2 Qin's Initial Route Toward (±)-Vincorine

Qin's initial efforts toward vincorine using the intramolecular Heck cyclization strategy are shown in Scheme 1.10. The synthesis began with the conversion of readily available intermediate **1.61**[62] into ester **1.62** over two steps. Ester **1.62** was then converted to β-keto ester **1.63**, which, in turn, underwent diazo transfer with *p*-acetamidobenzenesulfonyl azide (*p*-ABSA) to give α-diazoester **1.60**. Next, Qin installed the quaternary center at C7 via a cyclopropanation/fragmentation cascade sequence that they had successfully used in the synthesis of minfiensine.[63] In this cascade sequence 5 mol% of copper(I) triflate was added to α-diazoester 1.60, which furnished tetracyclic indoline **1.59** in 82% yield. The Qin laboratory forged ahead with tetracycle **1.59**, reduction of the ketone with sodium borohydride, followed by removal of the sulfonamide protecting group, delivered secondary amine **1.64**. Over three steps, amine 1.64 was transformed into reductive Heck cyclization precursor **1.58**. In attempts to access vincorine via the intramolecular reductive Heck cyclization, tetracyclic vinyl iodide **1.58** was subjected to a number of conditions that had been used previously in related Pd-catalyzed cyclizations. Despite extensive screening of palladium precatalysts, ligands, and bases, the desired pentacyclic ester **1.11** was not observed. Michael addition-type cyclizations and radical-based cyclizations of **1.58** were also tested.[60] Unfortunately, these attempts were also unsuccessful.

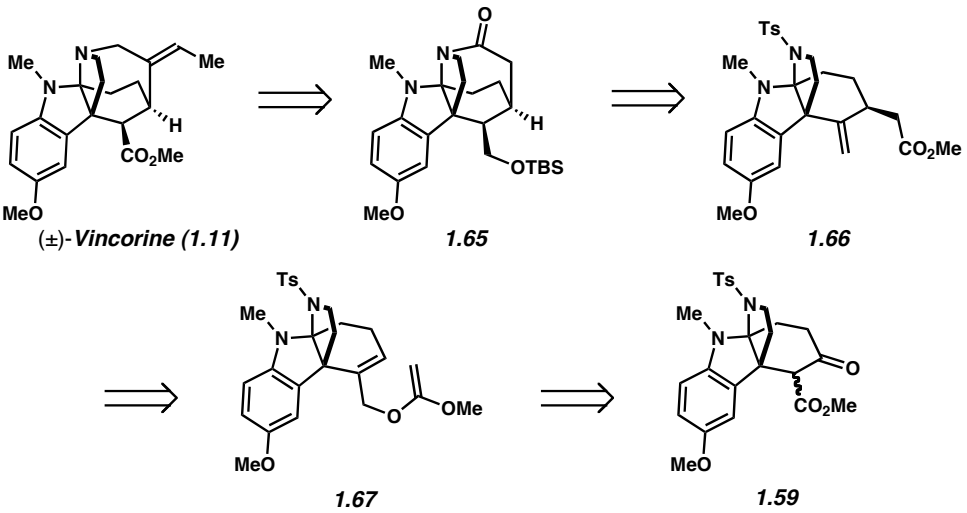
Scheme 1.10



1.6.3 Alternate Synthetic Route to (±)-Vincorine

The challenges encountered in the attempted late-stage introduction of the seven-membered ring using reductive Heck cyclization conditions prompted Qin's second generation approach to vincorine (Scheme 1.11). Retrosynthetically, the natural product would arise from amide **1.65**, which, in turn, would be derived from ester **1.66**. Thus, amide bond formation would be used to generate the challenging seven membered ring. Ester **1.66** was expected to come from a Claisen rearrangement of methyl ether **1.67**. Finally, methyl ether **1.67** would be obtained from **1.59**, which Qin's laboratory had accessed in their first generation approach (see Scheme 1.10).

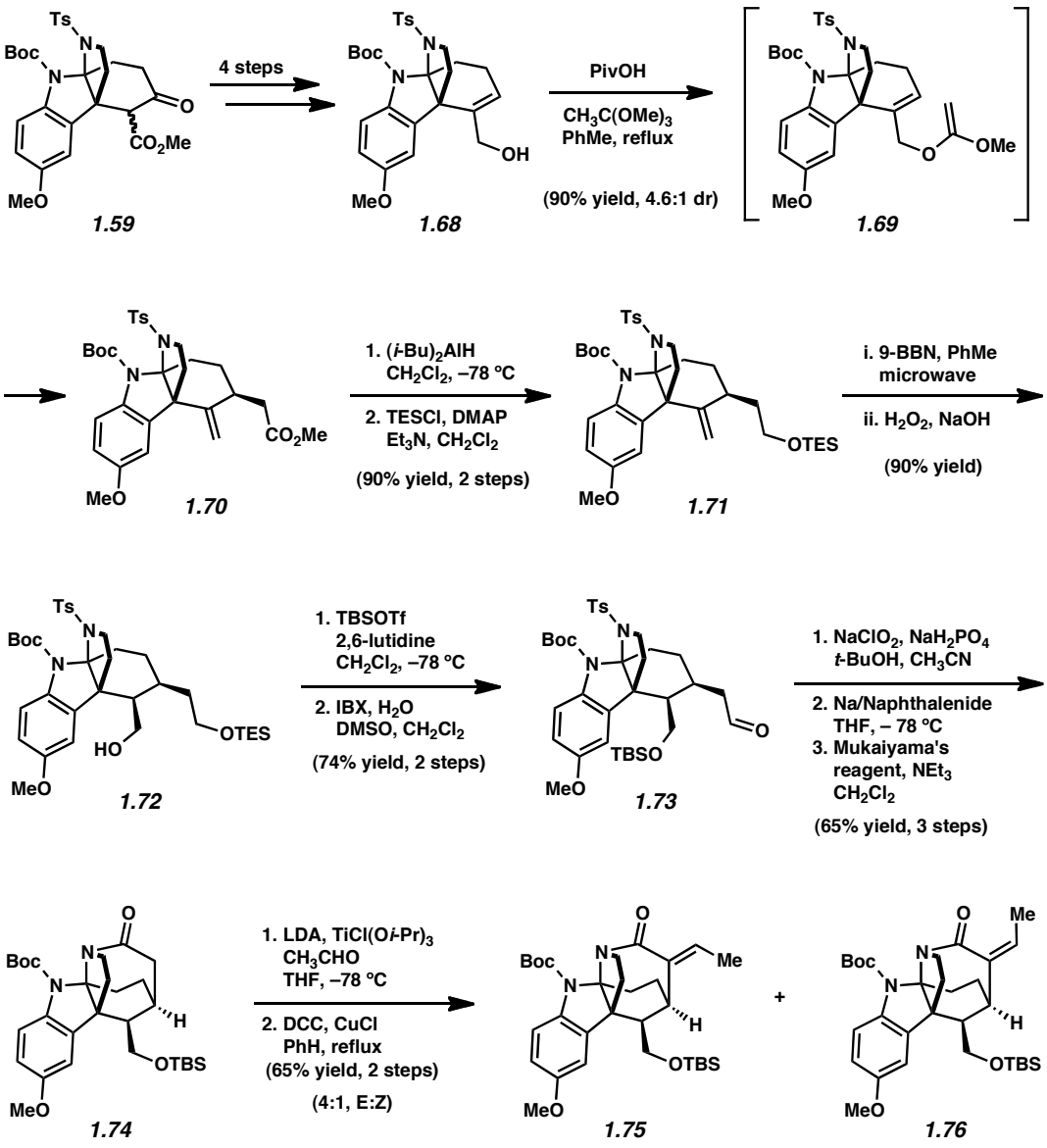
Scheme 1.11



Qin's approach to install the seven-membered ring proved viable, as shown in Scheme 1.12. Ester **1.59** was readily manipulated over four steps into allylic alcohol **1.68**. Upon treatment with pivalic acid and trimethyl orthoacetate, alcohol **1.68** was converted into ester **1.70**, presumably via intermediate methyl ether **1.69** undergoing Johnson–Claisen rearrangement.[64] Fortunately, the diastereomeric ratio of this process was 4.6:1 in favor of the desired diastereomer. The mixture of diastereomers was then separated via column chromatography, and the desired isomer **1.70** was taken forward. The synthesis continued with reduction of ester **1.70**, followed by protection of the resulting alcohol as the triethylsilyl ether. Alkene **1.71** was then hydroborated in a two-step process to give alcohol **1.72**. After protection of the primary alcohol as the TBS ether, the TES-protected alcohol was converted to the corresponding aldehyde by the action of IBX to afford aldehyde **1.73**. In the key three step sequence involving oxidation of the aldehyde, sulfonamide removal, and amide bond formation, **1.74** was obtained in 65% yield. With the critical seven membered ring in place, the exocyclic

olefin was installed to arrive at alkene **1.75**. The undesired isomeric alkene **1.76** was also observed; however, this byproduct could fortunately be removed by column chromatography.

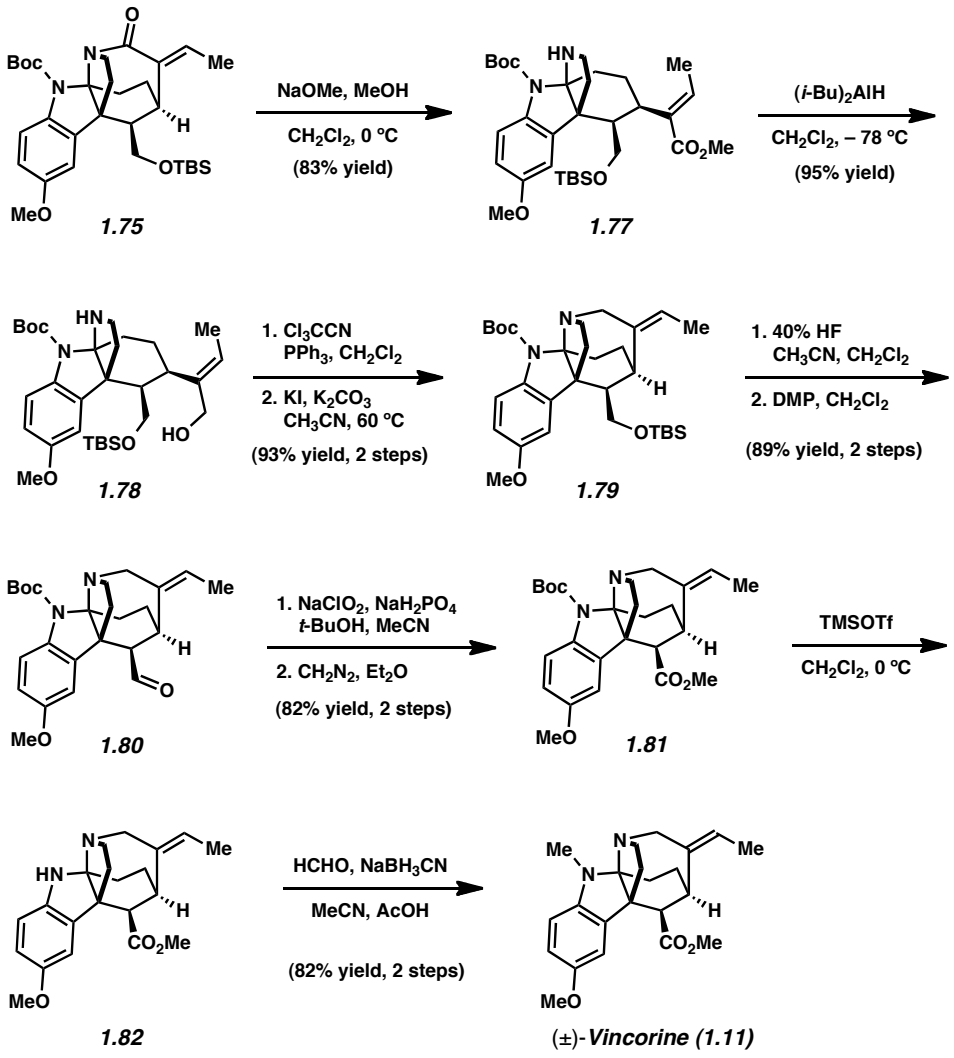
Scheme 1.12



The final steps of Qin's total synthesis of (±)-vincorine (**1.11**) are summarized in Scheme 1.13. Initial attempts at selectively reducing the amide in **1.75** were met with undesired alkene

reduction.[65] Therefore, Qin and coworkers resorted to opening the key seven-membered ring by methanolysis to furnish amino ester **1.77**. Subsequent ester reduction provided allylic alcohol **1.78**. To reconstruct the seven-membered ring, alcohol **1.78** was first transformed to the corresponding allylic chloride. Treatment of this intermediate with potassium iodide and potassium carbonate gave **1.79**, thus restoring the vincorine ring system, albeit now with more suitable oxidation states for further elaboration. A standard sequence was used to convert silylether **1.79** to aldehyde **1.80**, and the ensuing oxidation and methylation provided methyl ester **1.81** without event. In the final steps, Boc cleavage followed by *N*-methylation generated (±)-vincorine (**1.11**) in 82% yield.

Scheme 1.13



Qin's approaches toward vincorine reveal the challenges associated with assembling the natural product's core, while establishing one of few routes to akuammiline alkaloids. Both approaches relied on intermediate tetracycle **1.59**, which was synthesized using complexity-generating copper catalyzed cyclopropanation/fragmentation cascade.[63] Subsequent elaboration of tetracycle **1.59** to vinyl iodide **1.58** set the stage for an intramolecular Heck or Michael cyclizations that were deemed unsuccessful.[60] Greater success was seen in the second-generation approach to vincorine, where Qin and coworkers found two useful methods to construct the

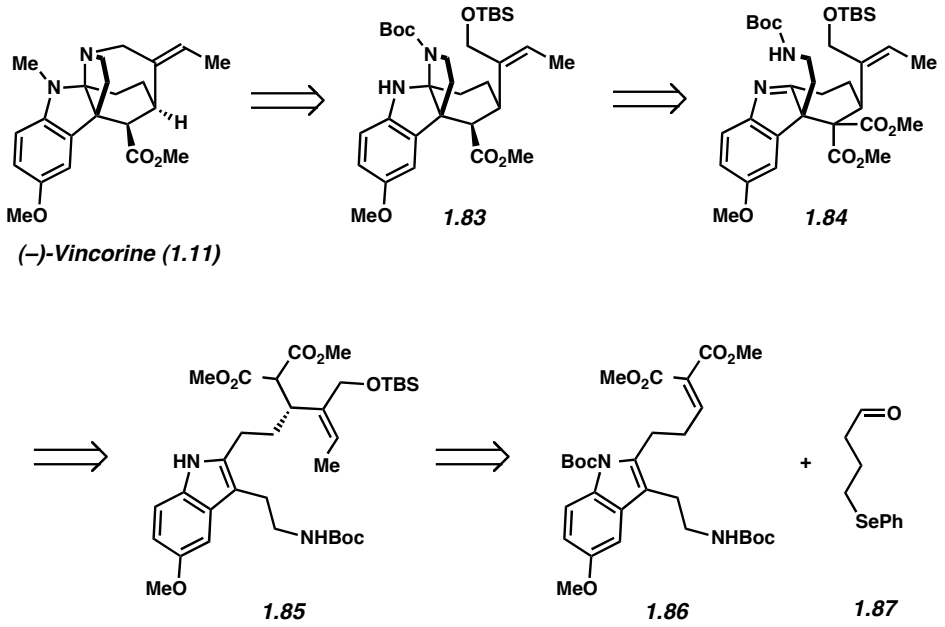
challenging 7-membered ring of the natural product. One of these methods, involving amine displacement of an alkyl iodide, ultimately enabled the total synthesis of (±)-vincorine (**1.11**). This seminal synthesis of (±)-vincorine (**1.11**) proceeded in 31 steps from indole **1.61** and was the first reported total synthesis of any akuammiline alkaloid.

1.7 Ma's Total Synthesis of (–)-Vincorine

1.7.1 Key Retrosynthetic Disconnections

Most recently, Ma and coworkers reported a concise enantiospecific synthesis of (–)-vincorine (**1.11**).[66] As shown in the retrosynthesis (Scheme 1.14), Ma and coworkers envisioned installing the seven membered ring of the natural product at a late stage, analogous to the approach of the Qin laoratory.60 As such, the natural product was thought to be accessible from pyrrolidinoindoline **1.83**. The fused indoline motif of **1.83** would come from cyclization of indolenine **1.84**, which in turn would be formed from an oxidative intramolecular coupling of diester **1.85**. The Ma laboratory had previously utilized a similar oxidative coupling strategy in their synthesis of communesin F.[67] Finally, it was envisioned that diester **1.85** could be derived from two simpler starting materials, malonate **1.86** and aldehyde **1.87**.

Scheme 1.14

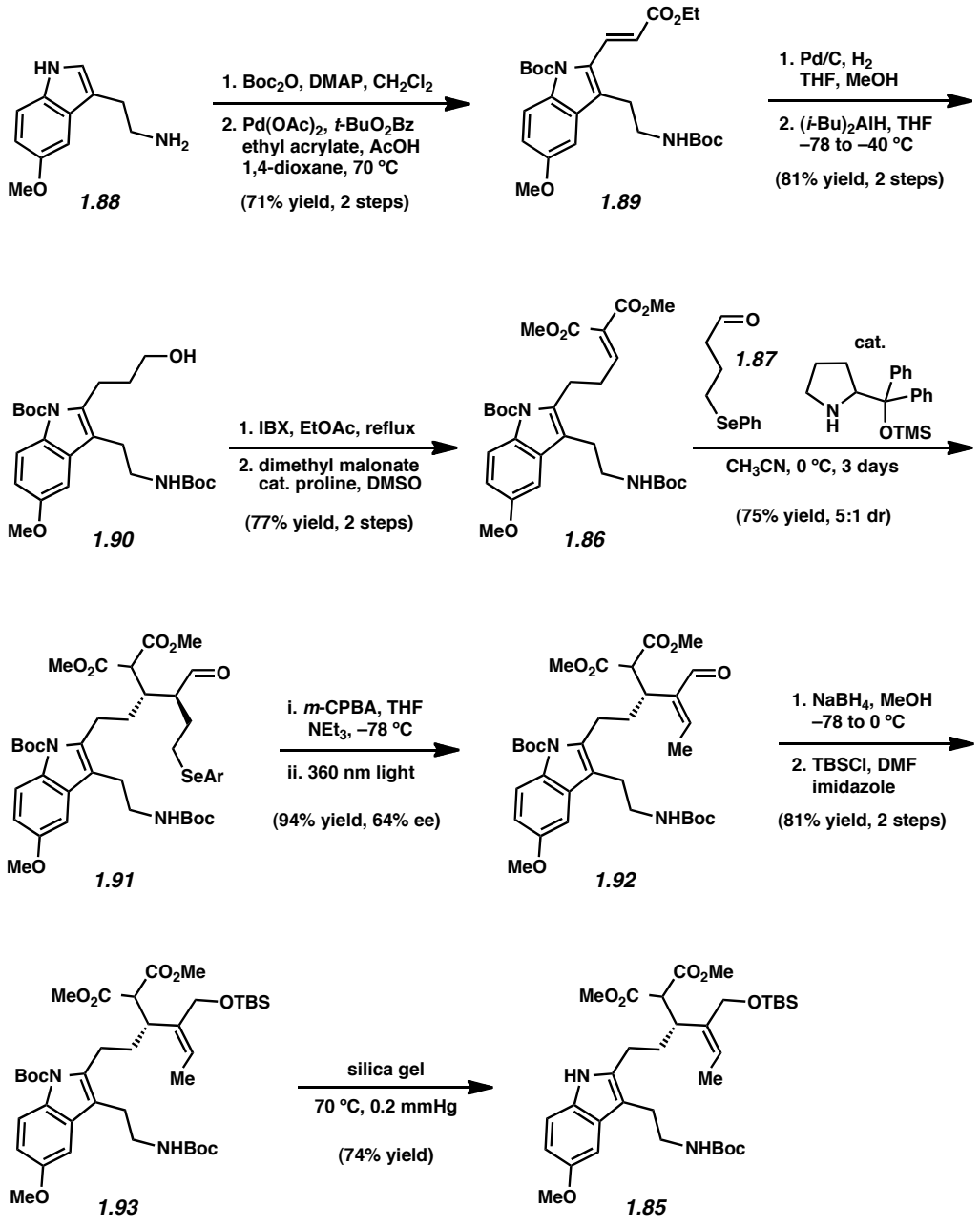


1.7.2 Ma's Total Synthesis of (–)-Vincorine

Ma's synthesis of the oxidative cyclization precursor **1.85** is summarized in Scheme 1.15. Boc-protection of 5-methoxytryptamine (**1.88**) followed by Pd-catalyzed coupling with acrylate afforded α,β-unsaturated ester **1.89**.[68] A two-step reduction sequence of ester **1.89** produced alcohol **1.90** in an 81% yield. After oxidation of alcohol **1.90** to the corresponding aldehyde, proline-mediated Knoevenagel condensation with dimethyl malonate gave malonate **1.86**.[69] Toward installing the ethylidine unit, the Ma laboratory elected to attempt an organocatalyzed enantioselective Michael addition of **1.87** using a proline derived catalyst on the basis of literature precedent.[70] Although both aldehyde **1.87** and malonate **1.86** were both more complex than substrates reported in the literature, the desired coupling proceeded smoothly to deliver selenide **1.91** in 75% yield as a 5:1 diastereomeric mixture. Next, this mixture of diastereomers was oxidized and eliminated with *m*-CPBA and triethylamine in a two step one pot procedure,[71]

which provided an initial 1.7:1 mixture of *E* and *Z* isomers. However, this ratio was improved to 30:1 by exposing the mixture to UV light (360 nm) for 16 hours. Unfortunately, Ma and coworkers report that the ee of the resulting aldehyde **1.92** was only 64%. The resulting aldehyde **1.92** was then converted to diester **1.85** using a straightforward three-step sequence.

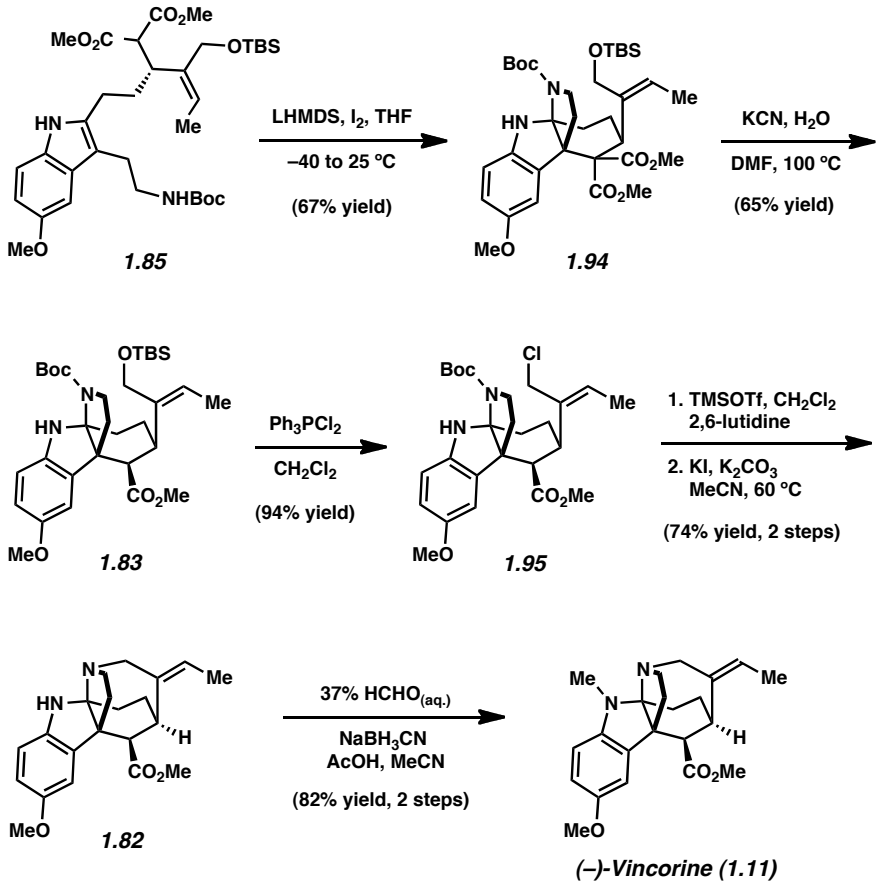
Scheme 1.15



Ma's completion of (–)-vincorine (**1.11**) is depicted in Scheme 1.16. Having established an efficient synthesis of diester **1.85**, the focus turned to forming the fused pyrrolidinoindoline of vincorine. To that end, diester **1.85** was oxidatively cyclized in the presence of lithium hexamethyldisilyazide (LiHMDS) and iodine.[67] Initial attempts at –78 °C gave minor amounts of

the desired indoline **1.94**, but when the reaction was started at –40 ºC and allowed to warm to room temperature, the yield improved to 67%. Starting the reaction at a higher temperature did not improve the yield. It should also be noted that the use of other oxidants such as Fe(III) salts, Cu(II) salts, or *N*-iodosuccinimide in place of iodine,[72] had detrimental effects on the reaction. Nonetheless, Krapcho decarboxylation[73] of diester **1.94** gave a single diastereomer of intermediate **1.83**, which was directly transformed to alkyl chloride **1.95** using triphenylphosphine dichloride.[74] Removal of the Boc group followed by cyclization promoted by potassium carbonate and potassium iodide afforded amine **1.82**, a known intermediate from Qin's synthesis.[60] Reductive amination of amine **1.82** with formaldehyde delivered (–)-vincorine (**1.11**).

Scheme 1.16



Ma's total synthesis of (–)-vincorine (**1.11**) is the first asymmetric route to this complex natural product. Key features of Ma's synthesis include the palladium-catalyzed C–H functionalization of indole **1.88**, the organocatalytic enantioselective Michael addition en route to intermediate **1.85**, the oxidative cyclization to form a quaternary center and two of the rings seen in the natural product (**1.11**), and the efficient late-stage assembly of the seven-membered ring. The approach to (–)-vincorine (**1.11**) proceeds in 18 steps from commercially available starting materials, and in an impressive overall yield of 5%.

1.8 Conclusions

Considering the use of akuammiline-containing plants as traditional medicines, coupled to the many modern achievements in total synthesis, the akuammiline alkaloids are perhaps best described as compounds with tremendously rich histories. Initial synthetic studies by Dolby in the 1970's and Bosch and Bennasar twenty years later helped lay the foundation for contemporary efforts. Several ambitious approaches toward akuammiline alkaloids have been examined, leading to four impressive total syntheses and several new synthetic innovations. It is certain that additional breakthroughs and total syntheses in the realm of akuammiline natural products will be forthcoming.

1.9 Notes and References

(1) Verbitski, S. M.; Mayne, C. L.; Davis, R. A.; Concepcion, G. P.; Ireland, C. M. *J. Org. Chem.* **2002**, *67*, 7124–7126.

(2) Fuchs, J. R.; Funk, R. L. *J. Am. Chem. Soc.* **2004**, *126*, 5068–5069.

(3) Wu, H.; Xue, F.; Xiao, X.; Qin Y. *J. Am. Chem. Soc.* **2010**, *132*, 14052–14054.

(4) Takayama, H.; Mori, I.; Kitajima, M.; Aimi, N.; Lajis, N. H. *Org. Lett.* **2004**, *6*, 2945–2948.

(5) Matsuda, Y.; Kitajima, M.; Takayama, H. *Org. Lett.* **2008**, *10*, 125–128.

(6) Newhouse, T.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 10886–10887.

(7) Numata, A.; Takahashi, C.; Ito, Y.; Takada, T.; Kawai, K.; Usami, Y.; Matsumura, E.; Imachi, M.; Ito, T.; Hasegawa, T. *Tetrahedron Lett.* **1993**, *34*, 2355–2358.

(8) For pertinent reviews, see: a) Siengalewicz, P.; Gaich, T.; Mulzer, J. *Angew. Chem. Int. Ed.* **2008**, *47*, 8170–8176. b) Zhang, D.; Song, H.; Qin, Y. *Acc. Chem. Res.* **2011**, *44*, 447–457. c) Zuo, Z.; Ma, D. *Isr. J. Chem.* **2011**, *51*, 434–441.

(9) For approaches to the communesin alkaloids, see: a) May, J. A.; Zeidan, R. K.; Stoltz, B. M. *Tetrahedron Lett.* **2003**, *44*, 1203–1205. b) Crawley, S. L.; Funk, R. L. *Org. Lett.* **2003**, *5*, 3169–3171. c) May, J. A.; Stoltz, B. M. *Tetrahedron* **2006**, *62*, 5262–5271. d) Yang, J.; Song, H.; Xiao, X.; Wang, J.; Qin, Y. *Org. Lett.* **2006**, *8*, 2187–2190. e) Crawley, S. L.; Funk, R. L. *Org. Lett.* **2006**, *8*, 3995–3998. f) Sabahi, A.; Novikov, A.; Rainier, J. D. *Angew. Chem., Int. Ed.* **2006**, *45*, 4317–4320. g) George, J. H.; Adlington, R. M. *Synlett* **2008**, 2093–2096. h) Schammel, A. W.; Chiou, G.; Garg, N. K. *Org. Lett.* **2012**, *Accepted*, DOI: 10.1021/ol302023q.

(10) Yang, J.; Wu, H.; Shen, L.; Qin, Y. *J. Am. Chem. Soc.* **2007**, *129*, 13794–13795.

(11) Liu, P.; Seo, J. H.; Weinreb, S. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 2000–2003.

(12) Zuo, Z.; Xie, W.; Ma, D. *J. Am. Chem. Soc.* **2010**, *132*, 13226–13228.

(13) Lindquist, N.; Fenical, W.; Van Duyne, G. D.; Clardy, J. *J. Am. Chem. Soc.* **1991**, *113*, 2303–2304.

(14) a) Cruz-Monserrate, Z.; Vervoort, H. C.; Bai, R.; Newman, D. J.; Howell, S. B.; Los, G.; Mullaney, J. T.; Williams, M. D.; Pettit, G. R.; Fenical, W.; Hamel, E. *Mol. Pharmacol.* **2003**, *63*, 1273–1280. b) Lindquist, N.; Fenical, W.; Van Duyne, G. D.; Clardy, J. *J. Am. Chem. Soc.* **1991**, *113*, 2303–2304.

(15) Williams, N. S.; Burgett, A. W. G.; Atkins, A. S.; Wang, X.; Harran, P. G.; McKnight, S. L. *Proc. Nat. Acad. Sci.* (USA) **2007**, *104*, 2074–2079.

(16) Wang, G.; Zhang, L.; Burgett, A. W. G.; Harran, P. G.; Wang, X. *Proc. Nat. Acad. Sci.* (USA) **2007**, *104*, 2068–2073.

(18) Lachia, M.; Moody, C. *Nat. Prod. Rep.* **2008**, *25*, 227–253.

(19) a) Burgett, A. W. G.; Li, Q.; Wei, Q.; Harran, P. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4961–4966. b) Li, J.; Jeong, S.; Esser, L.; Harran, P. G. *Angew. Chem., Int. Ed.* **2001**, *40*, 4765–4769. c) Li, J.; Burgett, A. W. G.; Esser, L.; Amezcua, C.; Harran, P. G. *Angew. Chem., Int. Ed.* **2001**, *40*, 4770–4773

(20) Knowles, R. R.; Carpenter, J.; Blakey, S. B.; Kayano, A.; Mangion, I. K.; Sinz, C. J.; MacMillan, D. W. C. *Chem. Sci.* **2011**, *2*, 308–311.

(21) Nicolaou, K. C.; Bella, M.; Chen, D. Y. -K.; Huang, X.; Ling, T.; Snyder, S. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 3495–3499.

(22) Kam, T. -S.; Tan, S. -J.; Ng, S. -W.; Komiyama, K. *Org. Lett.* **2008**, *10*, 3749–3752.

(23) Henry, T. A. *J. Chem. Soc.* **1932**, 2759–2768.

(24) Besanez, G. *Justus Liebigs Ann. Chem.* **1875**, *176*, 88–89.

(25) Hesse, O. *Justus Liebigs Ann. Chem.* **1875**, *176*, 326.

(26) a) Hamilton, J. A.; Hamor, T. A.; Robertson, J. M.; Sim, G. A. *Proc. Chem. Soc.* **1961**, 63–64. b) Manohar, H.; Ramaseshan, S. *Curr. Sci.* **1961**, *30*, 5–7.

(27) Schnoes, H. K.; Biemann, K.; Mokry, J.; Kompis, I.; Chatterjee, A.; Ganguli, G. *J. Org. Chem.* **1966**, *31*, 1641–1642.

(28) a) Chatterjee, A.; Mukherjee, B.; Ray, A. B.; Das, B. *Tetrahedron Lett*. **1965**, *6*, 3633–3637. b) Ghosh, R.; Roychowdhury, P.; Chattopadhyay, D.; Iitaka, Y. *Acta Crystallogr., Sect. C: Cryst. Struc. Commun.* **1988**, *44*, 2151–2154.

(29) a) Mokŕý, J.; Dúbravková, L.; Šefčovič, P. *Experientia* **1962**, *18*, 564–565. b) Mamatas-Kalamaras, S.; Sevenet, T.; Thal, C.; Potier, P. *Phytochemistry* **1975**, *14*, 1637–1639.

(30) Subramaniam, G.; Hiraku, O.; Hayashi, M.; Koyano, T.; Komiyama, K.; Kam, T. -S. *J. Nat. Prod.* **2007**, *70*, 1783–1789.

(31) Cai, X. -H.; Tan, Q. -G.; Liu, Y. -P.; Feng, T.; Du, Z. -Z.; Li, W. -Q.; Luo, X. -D. *Org. Lett.* **2008**, *10*, 577–580.

(32) a) Olivier-Bever, B. *J. Ethnopharmacol.* **1982**, *5*, 1–72. b) Ali, B. H.; Al-Qarawi, A. A.; Bashir, A. K.; Tanira, M. O. *Phytother. Res.* **2000**, *14*, 229–234. c) Subhadhirasakul, S.; Takayama, H.; Miyabe, Y.; Aimi, N.; Ponglux, D.; Sakai, S. -I. *Chem. Pharm. Bull.* **1994**, *42*, 2645–2646.

(33) Arai, H.; Hirasawa, Y.; Rahman, A.; Kusumawati, I.; Zaini, N. C.; Sato, S.; Aoyama, C.; Takeo, J.; Morita, H. *Bioorg. Med. Chem.* **2010**, *18*, 2152–2158.

(34) Meng, W.; Ellsworth, B. A.; Nirschl, A. A.; McCann, P. J.; Patel, M.; Girotra, R. N.; Wu, G.; Sher, P. M.; Morrison, E. P.; Biller, S. A.; Zahler, R.; Deshpande, P. P.; Pullockaran, A.; Hagan, D. L.; Morgan, N.; Taylor, J. R.; Obermeier, M. T.; Humphreys, W. G.; Khanna, A.; Discenza, L.; Robertson, J. G.; Wang, A.; Han, S.; Wetterau, J. R.; Janovitz, E. B.; Flint, O. P.; Whaley, J. M.; Washburn, W. N. *J. Med. Chem.* **2008**, *51*, 1145–1149.

(35) a) Karamajan, P.; Sekar, N.; Mathuram, V.; Govindasamy, S. *Biochem. Int.* **1991**, *25*, 491–498. b) Karamajan, P.; Sekar, N.; Govindasamy, S. *Med. Sci. Res.* **1995**, *23*, 237–239.

(36) Wenkert, E.; Wickberg, B. *J. Am. Chem. Soc.* **1965**, *87*, 1580–1589.

(37) a) Bisset, N. G. In *Indole and Biogenetically Related Alkaloids*; Phillipson, J. D., Zenk, M. H., Eds.; Academic Press: London, 1980; Chapter 3. b) Atta-ur-Rahman; Basha, A. *Biosynthesis of Indole Alkaloids*; Clarendon Press: Oxford, 1983.

(38) a) Britten, A. Z.; Smith, G. F. *J. Chem. Soc.* **1963**, 3850–3854. b) Britten, A.; Smith, G.; Spiteller, G. *Chem. Ind.* **1963**, 1492–1493. c) Ramirez, A.; Garcia-Rubio, S. *Curr. Med. Chem.* **2003**, *10*, 1891–1915. d) Llopart, C. C.; Joule, J. A. *ARKIVOC* **2004**, *x*, 20–38.

(39) a) Dolby, L. J.; Esfandiari, Z. *J. Org. Chem.* **1972**, *37*, 43–46. b) Dolby, L. J.; Nelson, S. J. *J. Org. Chem.* **1973**, *38*, 2882–2887.

(40) Dolby, L. J.; Booth, D. L. *J. Am. Chem. Soc.* **1966**, *88*, 1049–1051.

(41) a) Bennasar, M. -L.; Zulaica, E.; Ramírez, A.; Bosch, J. *J. Org. Chem.* **1996**, *61*, 1239–1251. b) Bennasar, M. -L.; Zulaica, E.; Ramírez, A.; Bosch, J. *Tetrahedron Lett.* **1996**, *37*, 6611–6614. c) Bennasar, M. -L.; Zulaica, E.; Ramírez, A.; Bosch, J. *Heterocycles* **1996**, *43*, 1959–1966. d) Bennasar, M. -L.; Zulaica, E.; Ramírez, A.; Bosch, J. *Tetrahedron* **1999**, *55*, 3117–3128.

(42) a) Bennasar, M. -L.; Zulaica, E.; Jiménez, J. -M.; Bosch, J. *J. Org. Chem.* **1993**, *58*, 7756–7767. b) Alvarez, M.; Salas, M.; de Veciana, A.; Lavilla, R.; Bosch, J. *Tetrahedron Lett.* **1990**, *31*, 5089–5092. c) Amat, M.; Linares, A.; Bosch. J. *J. Org. Chem.* **1990**, *55*, 6299–6312.

(43) a) Gallagher, T.; Magnus, P.; Huffman, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 4750–4757. b) Magnus, P.; Sear, N. L.; Kim. C. S.; Vicker, N. *J. Org. Chem.* **1992**, *57*, 70–78. c) Amat, M.; Bosch, J. *J. Org. Chem.* **1992**, *57*, 5792–5796.

(44) *Organic Photochemistry*; Padwa, A., Ed.; Marcel Dekker: New York, 1983; Vol. 6, Chapter 2.

(45) a) *The Chemistry of Acid Derivatives*; Patai, S., Ed.; Wiley: Chichester, 1992; Vol. 2, Part 2, Chapter 23. b) Lenz, G. R. *Synthesis* **1978**, 489–518. c) Campbell, A. L.; Lenz, G. R. *Synthesis* **1987**, 421–452.

(46) Zu, L.; Boal, B. W.; Garg, N. K. *J. Am. Chem. Soc.* **2011**, *133*, 8877–8879.

(47) a) Fessner, W. D.; Sedelmeier, G.; Spurr, P. R.; Rihs, G.; Prinzbach, H. *J. Am. Chem. Soc.* **1987**, *109*, 4626–4642. b) Snow, R. A.; Degenhardt, C. R.; Paquette, L. A. *Tetrahedron Lett.* **1976**, *17*, 4447–4450.

(48) a) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945–2963. b) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009–3066. c) Amatore, C.; Jutand, A. J. *Organomet. Chem.* **1999**, *576*, 254–278.

(49) a) Schammel, A. W.; Boal, B. W.; Zu, L.; Mesganaw, T.; Garg, N. K. *Tetrahedron* **2010**, *66*, 4687–4695. b) Boal, B. W.; Schammel, A. W.; Garg, N. K. *Org. Lett.* **2009**, *11*, 3458–3461. c) Çelebi-Ölçüm, N.; Boal, B. W.; Huters, A. D.; Garg, N. K.; Houk, K. N. *J. Am. Chem. Soc.*

2011, *133*, 5752–5755. d) Schammel, A. W.; Chiou, G.; Garg, N. K. *J. Org. Chem.* **2012**, *77*, 725–728.

(50) Adams, G. L.; Caroll, P. J.; Smith, A. B. *J. Am. Chem. Soc.* **2012**, *134*, 4037–4040.

(51) a) Danieli, B.; Lesma, G.; Mauro, M.; Palmisano, G.; Passarella, D. *J. Org. Chem.* **1995**, *60*, 2506–2513. b) Danieli, B.; Lesma, G.; Mauro, M.; Palmisano, G.; Passarella, D. *Tetrahedron* **1994**, *50*, 8837–8852. c) Danieli, B.; Lesma, G.; Mauro, M.; Palmisano, G.; Passarella, D. *Tetrahedron: Asymmetry* **1990**, *1*, 793–800.

(52) See Supporting Information of reference 50.

(53) Freifelder, M. *J. Am. Chem. Soc.* **1960**, *82*, 2386–2389.

(54) Schultz, R. J.; Staas, W. H.; Spurlock, L. A. *J. Org. Chem.* **1973**, *38*, 3091–3093.

(55) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639–666.

(56) Still, W. C. *J. Am. Chem. Soc.* **1978**, *100*, 1481–1487.

(57) Corey, E. J.; Palani, A. *Tetrahedron Lett.* **1995**, *36*, 7945–7948.

(58) Schwesinger, R.; Willaredt, J.; Schlemper, H.; Keller, M.; Schmitt, D.; Fritz, H. *Chem. Ber.* **1994**, *127*, 2435–2454.

(59) a) Muller, P.; Gilabert, D. *Tetrahedron* **1988**, *44*, 7171–7175. b) Larsen, J.; Jørgensen, K. A. *J. Chem. Soc., Perkin Trans. 2* **1992**, 1213–1217.

(60) Zhang, M.; Huang, X.; Shen, L.; Qin, Y. *J. Am. Chem. Soc.* **2009**, *131*, 6013–6020.

(61) a) Dounay, A. B.; Overman, L. E.; Wrobleski, A. D. *J. Am. Chem. Soc.* **2005**, *127*, 10186–10187. b) Dounay, A. B.; Humphreys, P. G.; Overman, L. E.; Wrobleski, A. D. *J. Am. Chem. Soc.* **2008**, *130*, 5368–5377. c) Shen, L.; Zhang, M.; Wu, Y.; Qin, Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 3618–3621.

(62) Vercauteren, J.; Lavaud, C.; Lévy, J.; Massiot, G. *J. Org. Chem.* **1984**, *49*, 2278–2279.

(63) a) He, B.; Song, H.; Du, Y.; Qin, Y. *J. Org. Chem.* **2009**, *74*, 298–304. b) Yang, J.; Wu, H.; Shen, L.; Qin, Y. *J. Am. Chem. Soc.* **2007**, *129*, 13794–13795. c) Song, H.; Yang, J.; Chen, W.; Qin, Y. *Org. Lett.* **2006**, *8*, 6011–6014. d) Yang, J.; Song, H.; Xiao, X.; Wang, J.; Qin, Y. *Org. Lett.* **2006**, *8*, 2187–2190.

(64) a) Schlama, T.; Baati, R.; Gouverneur, V.; Valleix, A.; Falck, J. R.; Mioskowski, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 2085–2087. b) Ng, F. W.; Lin, H.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2002**, *124*, 9812–9824. c) Birman, V. B.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2002**, *124*, 2080–2081. d) Kim, D.; Lee, J.; Shim, P. J.; Lim, J. I.; Jo, H.; Kim, S. *J. Org. Chem.* **2002**, *67*, 764–771. e) Shigeyama, T.; Katakawa, K.; Kogure, N.; Kitajima, M.; Takayama, H. *Org. Lett.* **2007**, *9*, 4069–4072.

(65) a) Borch, R. F. *Tetrahedron Lett.* **1968**, *9*, 61–65. b) Martin, S. F.; Clark, C. W.; Ito, M.; Mortimore, M. *J. Am. Chem. Soc.* **1996**, *118*, 9804–9805. c) Martin, S. F.; Chen, K. X.; Eary, C. T. *Org. Lett.* **1999**, *1*, 79–82. d) Deiters, A.; Chen, K.; Eary, C. T.; Martin, S. F. *J. Am. Chem. Soc.* **2003**, *125*, 4541–4550. e) Allin, S. M.; Thomas, C. I.; Doyle, K.; Elsegood, M. R. J. *J. Org. Chem.* **2005**, *70*, 357–359.

(66) Zi, W.; Xie, W.; Ma, D. *J. Am. Chem. Soc.* **2012**, *134*, 9126–9129.

(67) a) Zuo, Z.; Xie, W.; Ma, D. *J. Am. Chem. Soc.* **2010**, *132*, 13226–13228. b) Zuo, Z.; Ma, D. *Angew. Chem., Int. Ed.* **2011**, *50*, 12008–12011.

(68) Grimster, N. P.; Gauntlett, C.; Godfrey, C. R. A.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 3125–3129.

(69) Cardillo, G.; Fabbroni, S.; Gentilucci, L.; Gianotti, M.; Tolomelli, A. *Synth. Commun.* **2003**, *33*, 1587–1594.

(70) a) Zhao, G. -L.; Vesely, J.; Sun, J.; Christensen, K. E.; Bonneau, C.; Córdova, A. *Adv. Synth. Catal.* **2008**, *350*, 657–661. b) Wen, L.; Shen, Q.; Lu, L. *Org. Lett.* **2010**, *12*, 4655–4657. c) Chowdhury, R.; Ghosh, S. K. *Tetrahedron: Asymmetry* **2010**, *21*, 2696–2702.

(71) Callant, P.; Ongena, R.; Vandewalle, M. *Tetrahedron* **1981**, *37*, 2085–2089.

(72) a) Baran, P. S.; Richter, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 7450–7451. b) Baran, P. S.; Richter, J. M. *J. Am. Chem. Soc.* **2005**, *127*, 15394–15396. c) Baran, P. S.; Guerrero, C. A.; Ambhaikar , N. B.; Hafensteiner, B. D. *Angew. Chem., Int. Ed.* **2005**, *44*, 606–609.

(73) Krapcho, A. P.; Weimaster, J. F.; Eldridge, J. M.; Jahngen, E. G. E., Jr.; Lovey, A. J.; Stephens, W. P. *J. Org. Chem.* **1978**, *43*, 138–147.

(74) Aizpurua, J. M.; Cossio, F. P.; Palomo, C. *J. Org. Chem.* **1986**, *51*, 4941–4943.

CHAPTER TWO

Exploration of the Interrupted Fischer Indolization Reaction

Alex W. Schammel, Ben W. Boal, Liansuo Zu,

Tehetena Mesganaw, and Neil K. Garg.

Tetrahedron **2010**, *66*, 4687–4695.

2.1 Abstract

A convergent method to access the fused indoline ring system present in a multitude of bioactive molecules has been developed. The strategy involves the condensation of hydrazines with latent aldehydes to ultimately deliver indoline-containing products by way of an interrupted Fischer indolization sequence. The method is convergent, mild, operationally simple, broad in scope, and can be used to access enantioenriched products. In addition, our approach is amenable to the synthesis of furoindoline and pyrrolidinoindoline natural products as demonstrated by the concise formal total syntheses of physovenine and debromoflustramine B. The strategy will likely enable the synthesis of more complex targets such as the communesin alkaloids.

2.2 Introduction

The discovery of efficient methods to synthesize complex bioactive molecules continues to be a vital area of research.[1] A subset of compounds that have received substantial interest due to their medicinal properties and impressive structures are those that possess a fused indoline motif, of the type **2.1** (Figure 2.1 and Scheme 2.1). The simplest of these compounds are the acetylcholinesterase inhibitors physovenine (**2.2**) and physostigmine (**2.3**),[2,3] which are composed of basic furo- and pyrrolidinoindoline motifs, respectively (Figure 2.1). Numerous

relatives of pyrrolidinoindoline **2.1** have been isolated, including bis(prenylated) derivatives,[4] dimeric structures,[5] and compounds possessing a heteroatom substituent at C3 (e.g., **2.4**–**2.7**, respectively).[6,7] Beyond these compounds, a variety of more architecturally complex indoline containing natural products are known, such as the akuammiline alkaloids (e.g., **2.8**–**2.11**),[8,9] perophoramidine (**2.12**),[10] the communesins (e.g., **2.13**),[11] diazonamide A (**2.14**),[12] and bipleiophylline (**2.15**).[13] Many of these molecules possess interesting biological properties, which further enhance their appeal as targets for total synthesis.

The importance of indoline-containing compounds has prompted the development of a number of methods to access such motifs, with numerous studies particularly in the area of pyrrolidinoindoline synthesis. In most cases, the fused indoline ring systems **2.1** are constructed by cyclization of precursors of the type **2.16**, which in turn are derived from substituted indole[14] or oxindole[15] intermediates (Scheme 2.1). Herein, we report the development of a powerful cascade reaction that allows direct access to **2.1** (via **2.16**) from the coupling of two simple fragments.[16] The transformation is convergent, broad in scope, proceeds under mild reaction conditions, and can be used to synthesize a variety of natural product scaffolds.

Our approach to the indoline scaffold **2.1** of compounds **2.2**–**2.15** is inspired by the classic Fischer indole synthesis,[17,18] and is presented in Scheme 2.2. We envisioned that an arylhydrazine **2.17** and an α-disubstituted aldehyde **2.18** would react in the presence of acid to afford enamine intermediate **2.19**. Subsequent [3,3]-sigmatropic rearrangement and re-aromatization would provide aniline **2.20**, which in turn would cyclize with loss of NH_3 to furnish transient indolenine **2.16**. Intramolecular attack by a proximal heteroatom substituent (X=NR or O) would deliver the desired product **2.1**. This interrupted Fischer indolization process

would allow for the formation of three new bonds, two heterocyclic rings and two stereogenic centers, one of which is quaternary (C3).

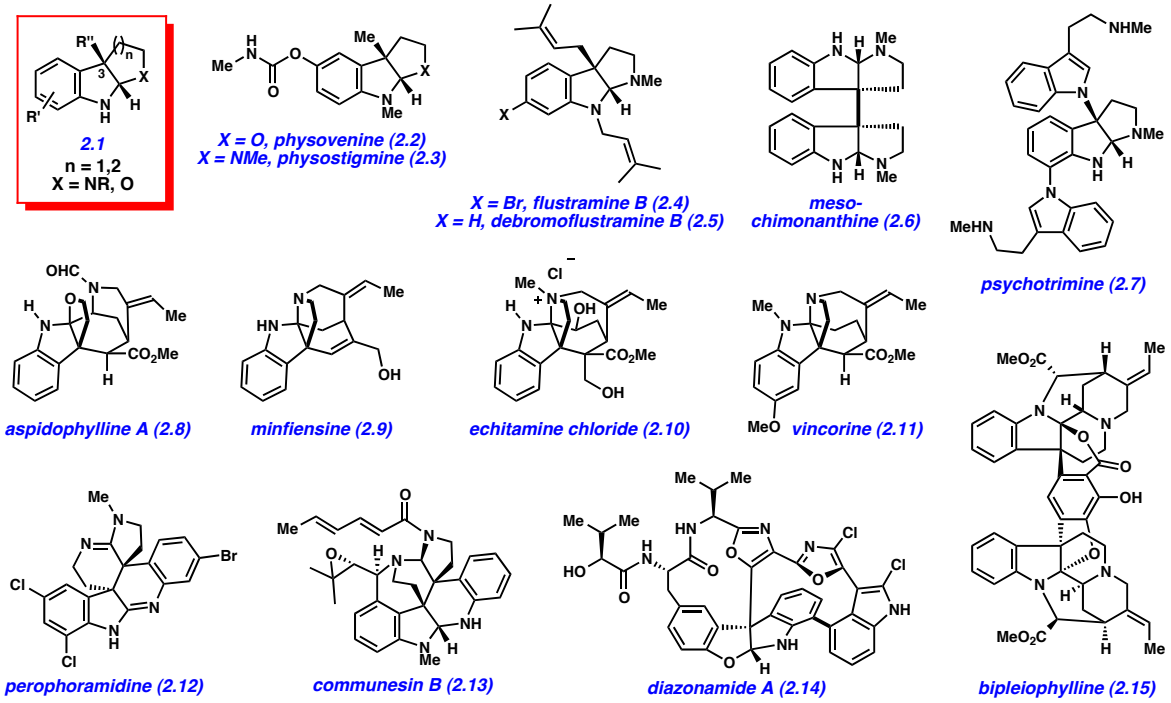
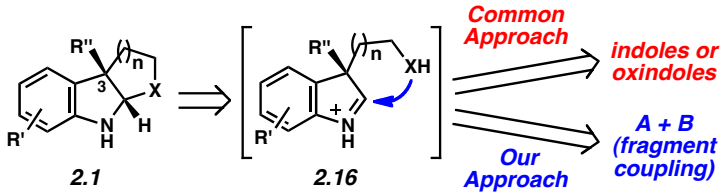


Figure 2.1. Parent indoline **2.1** and representative natural products **2.2**–**2.15**.

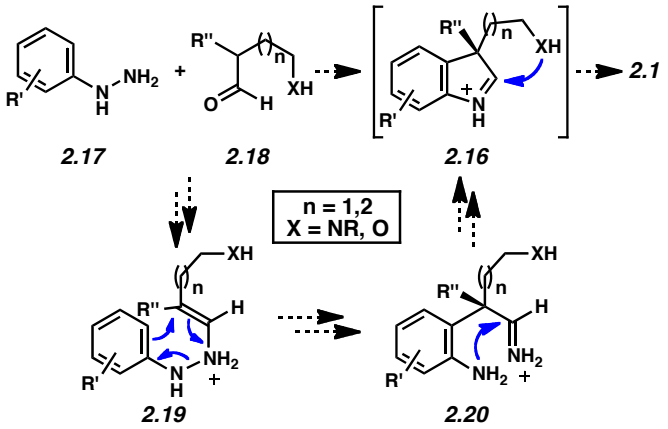
Scheme 2.1



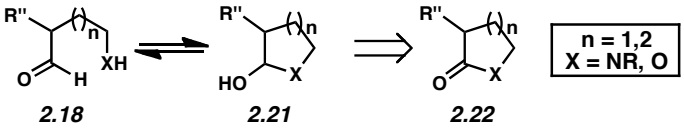
A key feature of our approach to **2.1** is the ready availability of starting materials **2.17** and **2.18**. The arylhydrazine coupling partners **2.17** could be easily prepared or accessed from

commercial sources.[19] Although the required α-branched aldehyde fragments **2.18** would not be obtainable commercially, isomeric lactols and hemiaminals **2.21** could likely serve as suitable aldehyde surrogates in the desired transformation (Scheme 2.3).[20,21] In turn, lactols and hemiaminals **2.21** could be accessed by reduction of readily available lactones or lactams **2.22**.[22]

Scheme 2.2



Scheme 2.3



Only scattered examples of the interrupted Fischer indolization process have been reported over the past fifty years.[23,24,25] Most notable are the seminal studies by Grandberg summarized in Figure 2.2.[23] In 1967, C2 substituted pyrrolidinoindoline **2.25** was prepared by reacting phenylhydrazine (**2.23**) and 5-chloro-3-methylpentan-2-one (**2.24**).[23a] However, this method is not applicable to the synthesis of furoindolines, or to the more complex ring systems

encountered in numerous natural products. It was later demonstrated that furoindolines could be accessed by the acid-promoted reaction of phenylhydrazines with α-disubstituted lactones.[23b] For example, reaction of hydrazine **2.26** and lactone **2.27** in HCl/*i*PrOH afforded furoindoline **2.28** in 22% yield. This method bears limitations, such as the modest yields of products, the use of strongly acidic conditions, and the constraint to furoindoline ring systems. Despite these laudable efforts, and those of others,[24,25] a general and mild method to access **2.1** using the interrupted Fischer indolization strategy outlined in Scheme 2.2 has remained elusive. Moreover, with the exception of our studies,[16] the notion that such a method could be used to prepare the indoline scaffold present in a multitude of complex biologically important compounds has not been realized.

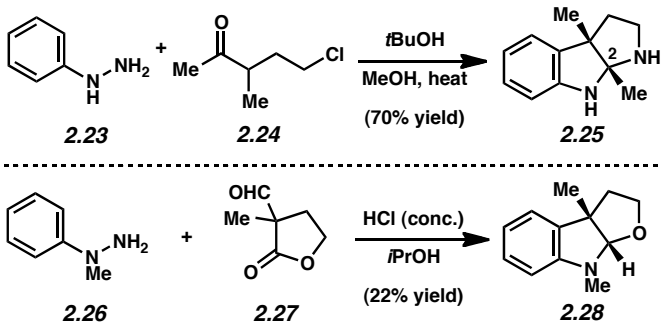
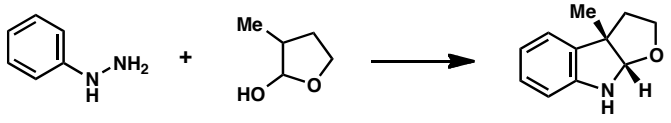


Figure 2.2. Grandberg's syntheses of pyrrolidinoindole **2.25** and furoindoline **2.28**.

2.3 Synthesis of Furoindolines

The feasibility of the proposed cascade reaction sequence of Scheme 2.2 was established in the context of furoindoline synthesis. Thus, the reaction between commercially available phenylhydrazine (**2.23**) and latent aldehyde **2.29** (1 equiv) was carried out under a variety of acidic conditions (Table 2.1). Lewis acids were examined and found to be ineffective (entries 1 and 2). However, use of *p*-toluenesulfonic acid, trifluoroacetic acid, or HCl each afforded the desired product **2.30** in modest yield (entries 3–5). Sulfuric acid-mediated reaction conditions were also explored, and ultimately provided the desired product in 87% yield (entry 6). Recognizing that a milder acid source would be more generally useful, acetic acid was examined. Although the use of glacial acetic acid afforded modest product yields (entry 7), employment of a 1:1 mixture of acetic acid and water at 60 °C furnished indoline **2.30** in 89% isolated yield (entry 8).[26]

Table 2.1. Survey of acids to promote furoindoline formation.



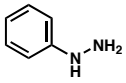
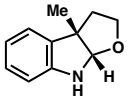
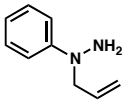
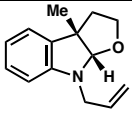
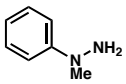
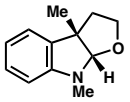
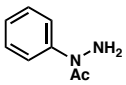
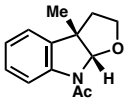
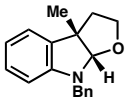
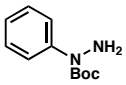
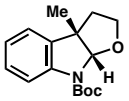
2.23 *2.29* *2.30*

entry	acid source	conditions	yield[a]
1	PCl_3	benzene, 60 °C	< 5%
2	$ZnCl_2$	EtOH, 100 °C	< 5%
3	TsOH	EtOH, H_2O, 60 °C	51%
4	TFA	CH_3CN, 60 °C	64%
5	5% HCl	CH_3CN, 60 °C	70%
6	4% H_2SO_4	CH_3CN, 60 °C	87%
7	AcOH	AcOH, 60 °C	52%
8	AcOH	1:1 AcOH/H_2O, 60 °C	89%[b]

[a] Unless otherwise noted, yields determined by ^{1}H NMR analysis.
[b] Isolated yield.

As shown in Table 2.2, a number of arylhydrazines bearing *N*-substitution were examined in the interrupted Fischer indolization reaction. In addition to parent arylhydrazine **2.23** (entry 1), *N*-methyl,[27] *N*-benzyl, and *N*-allyl substituted hydrazines were deemed competent coupling partners (entries 2–4). Interestingly, the use of *N*-acetyl and *N*-Boc phenylhydrazines (entries 5 and 6) led predominantly to the recovery of unreacted starting materials.

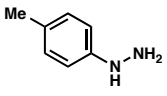
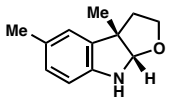
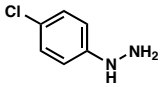
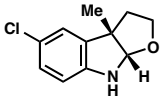
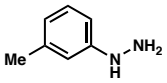
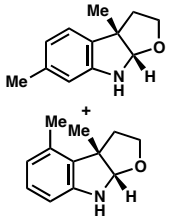
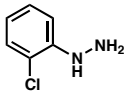
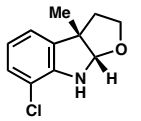
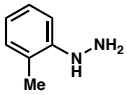
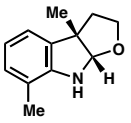
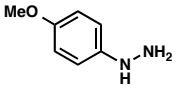
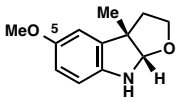
Table 2.2. Variation of the hydrazine *N*-substituent.

entry[a]	hydrazine	product	yield[c]	entry[a]	hydrazine	product	yield[c]
1			89%	4			60%
2[b]			70%	5			<5%
3			59%	6			<5%

[a] Conditions unless otherwise noted: lactol **2.29** (1 equiv), 1:1 AcOH/H_2O, 60 °C [b] AcOH as solvent. [c] Isolated yield.

Substitution on the aryl ring of the hydrazine component was also investigated (Table 2.3). It was found that para, meta, and ortho substituents were tolerated under the reaction conditions (entries 1–6). Importantly, use of chlorohydrazines furnished haloindolines (entries 4 and 5), which could be further functionalized by transition metal-catalyzed cross-coupling chemistry. Finally, the transformation proceeded smoothly with *p*-methoxyphenylhydrazine as a substrate, thus affording C5-oxygenated products in good yields (entry 6).[28]

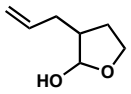
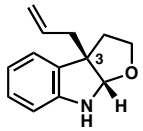
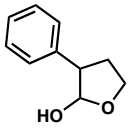
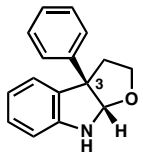
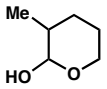
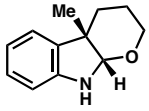
Table 2.3. Variation of the hydrazine aryl substituent.

entry[a]	hydrazine	product	yield[b]	entry[a]	hydrazine	product	yield[b]
1			60%	4			67%
2			75% (4 : 3)	5			60%
3			62%	6			75%

[a] Conditions unless otherwise noted: lactol **2.29** (1 equiv), 1:1 AcOH/H_2O, 60 °C. [b] Isolated yield.

The scope of the lactol component for furoindoline synthesis was examined in the interrupted Fischer indolization process (Table 2.4). Gratifyingly, allyl and phenyl substituents were tolerated, thus providing fused indolines with alternate C3 substitution (entries 1 and 2). Furthermore, the 6-membered homologue of the furoindoline framework was accessible using this methodology under our standard reaction conditions (entry 3).

Table 2.4. Variation of the lactol component.

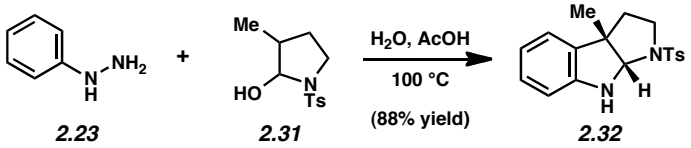
entry[a]	lactol	product	yield[b]
1			89%
2			75%
3			65%

[a] Conditions: hydrazine **2.23** (1 equiv), 1:1 AcOH/H_2O, 60 °C. [b] Isolated yield.

2.4 Synthesis of Pyrrolidinoindolines

Having established the viability of the interrupted Fischer indolization approach for the synthesis of furoindolines, we sought to develop the corresponding transformation that would enable the synthesis of pyrrolidinoindolines and related derivatives. Thus, hemiaminal **2.31** was prepared from the corresponding lactam following a known procedure, and then subjected to phenylhydrazine (**2.23**) in the presence of 1:1 H_2O/AcOH (Scheme 2.4). To our delight, the interrupted Fischer indolization reaction proceeded smoothly at 100 °C and delivered the desired indoline **2.32** in 88% yield.

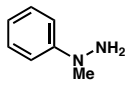
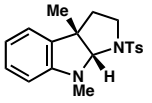
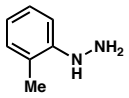
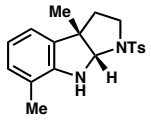
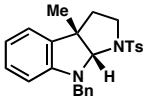
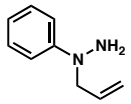
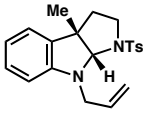
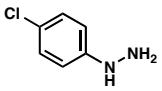
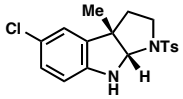
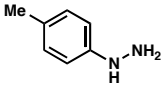
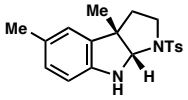
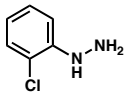
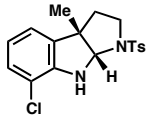
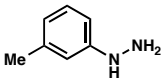
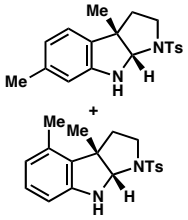
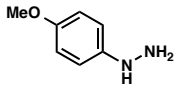
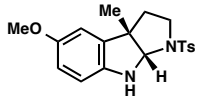
Scheme 2.4



2.23 *2.31* *2.32*

Analogous to our studies in the area of furoindoline synthesis, the interrupted Fischer indolization reaction was found to be an effective means to access a range of pyrrolidinoindolines. As shown in Table 2.5, a variety of arylhydrazines were tolerated in the transformation. Reactions of *N*-substituted arylhydrazines furnished the desired indoline products in good yield (entries 1–3), whereas a range of arylhydrazines bearing benzenoid substitution were deemed competent coupling partners (entries 4–9).

Table 2.5. Variation of the hydrazine component.

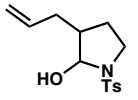
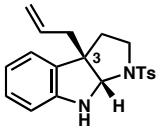
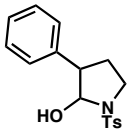
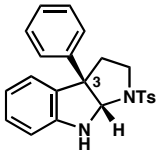
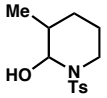
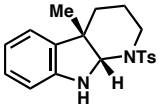
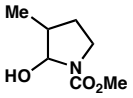
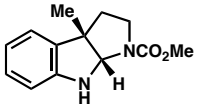
entry[a]	hydrazine	product	yield[d]	entry[a]	hydrazine	product	yield[d]
1[b]			81%	6			73%
2			83%				
3			70%	7			77%
4			71%	8			84%
5			55% (4 : 3)	9[c]			70%

[a] Conditions unless otherwise noted: hemiaminal **2.31** (1 equiv), 1:1 AcOH/H_2O, 100 °C. [b] 23 °C, AcOH as solvent. [c] 75 °C. [d] Isolated yield.

The scope of the hemiaminal component was also investigated (Table 2.6). C3-allylated and -phenylated pyrrolidinoindolines could be accessed without difficulty (entries 1 and 2). Of note, these pyrrolidinoindoline motifs are present in an array of medicinally important compounds, such as debromoflustramine B (**2.5**, Figure 2.1)[4a] and the hodgkinsine alkaloids.[29]

Furthermore, a 6-membered homologue was prepared in 81% yield (entry 3) reminiscent of the communesin and perophoramidine core structures. Finally, it was determined that a carbamylated hemiaminal could be employed in place of a sulfonamide (entry 4).

Table 2.6. Variation of the hemiaminal component.

entry[a]	hemiaminal	product	yield[b]
1			68%
2			70%
3			81%
4			88%

[a] Conditions: hydrazine **2.23** (1 equiv), 1:1 AcOH/H_2O, 100 °C. [b] Isolated yield.

As shown in Figure 2.3, the *N*-substituents of our pyrrolidinoindoline products can easily be manipulated. The sulfonamide group of **2.33** was removed upon treatment with Mg and NH_4Cl in MeOH[30] to provide pyrrolidinoindoline **2.34** in 77% yield.[31] Additionally, carbamate **2.35** was converted to the corresponding *N*-methylated product **2.36** when reacted with Red-Al. The latter of these results is particularly notable given that many pyrrolidinoindoline natural products possess this *N*-methylated substitution pattern (e.g., Figure 2.1, **2.3**–**2.7**).

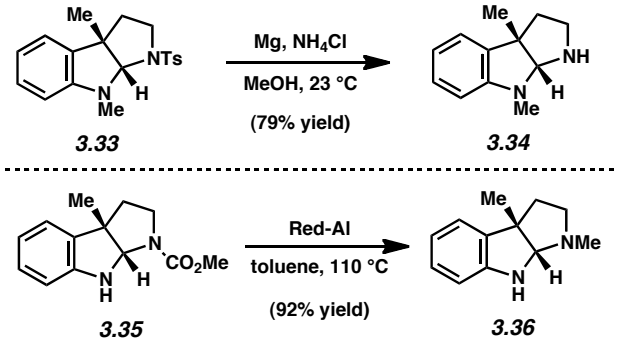
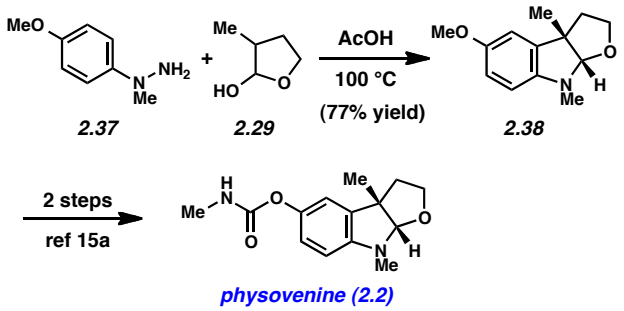


Figure 2.3. Manipulation of the *N*-substituent.

2.5. Formal Total Syntheses of Physovenine and Debromoflustramine B, and Assembly of the Communesin Indoline Scaffold

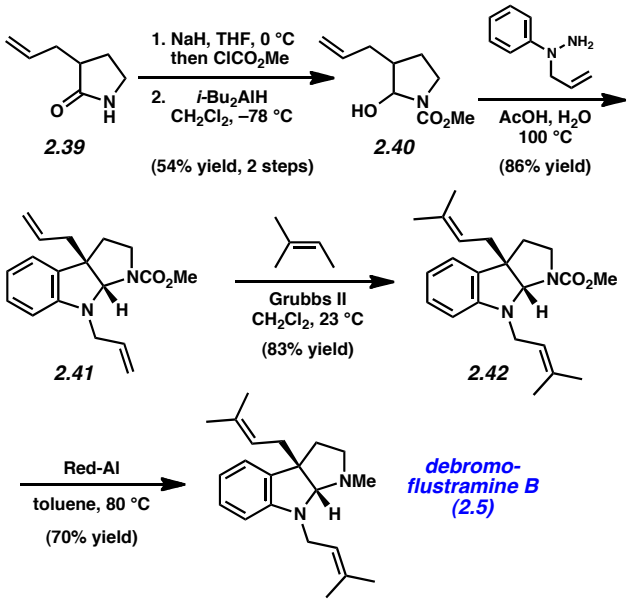
Having developed a powerful means to synthesize fused indoline ring systems, we examined the scope and limitations of our methodology in more complex settings. As shown in Scheme 2.5, the newly discovered transformation has been utilized to achieve a concise formal total synthesis of the furoindoline natural product physovenine (**2.2**).[32] Reaction of hydrazine **2.37**[33] with lactol **2.29** in AcOH furnished furoindoline **2.38** in 77% yield, which has previously been converted to physovenine (**2.2**) in two additional steps.[15a] Although asymmetric routes to intermediate **2.38** have previously been reported, our single step route to (±)-**2.38** is substantially shorter (one step compared to 7,[15a] or 18[32g] steps). Furthermore physovenine (**2.2**) can be optically resolved, on preparative scale, using column chromatography with cellulose triacetate.[32o]

Scheme 2.5



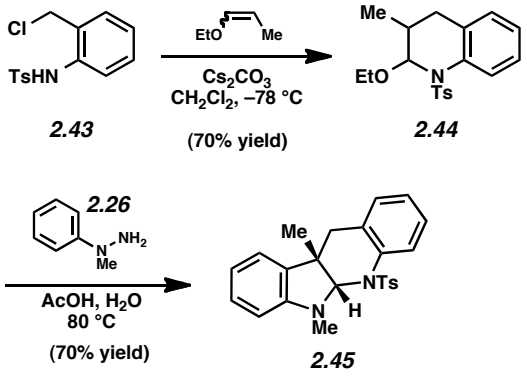
The interrupted Fischer indolization reaction could also be used to complete a formal total synthesis of the pyrrolidinoindoline natural product debromoflustramine B (**2.5**) (Scheme 2.6).[34] Pyrrolidinone **2.39**[35] was elaborated to hemiaminal **2.40** using a standard two-step sequence. Treatment of **2.40** with 1-allyl-1-phenylhydrazine in H_2O/AcOH at 100 °C facilitated the key condensation/sigmatropic rearrangement to deliver bis(allylated)pyrrolidinoindoline **2.41**. In turn, **2.41** was reacted with 2-methyl-2-butene in the presence of Grubbs' second generation catalyst to afford bis(prenylated) derivative **2.42**,[36] which was converted to **2.5** by reduction with Red-Al.

Scheme 2.6



Finally, we explored the scope and limitations of our methodology in the context of the communesin natural products (Scheme 2.7).[37] Known sulfonamide **2.43**[38] was reacted with 1-ethoxypropene in the presence of Cs_2CO_3 to afford hetero-Diels–Alder product **2.44**, following the general procedure described by Corey.[38] Exposure of **2.44** to *N*-methyl phenylhydrazine (**2.26**) in 1:1 AcOH/H_2O delivered indoline **2.45**, which possesses the tetracyclic 6,5,6,6-ring system of the communesin alkaloids.[39] As noted earlier, the previously described [3,3]-sigmatropic rearrangement strategies for the synthesis of fused indoline ring systems are not amenable to this complex scaffold.

Scheme 2.7

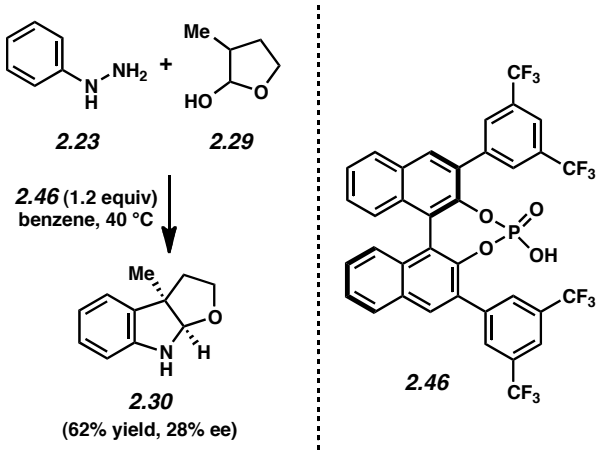


2.6. Access to Enantioenriched Indoline Products

Having demonstrated that the interrupted Fischer indolization reaction provides an effective means to access indoline scaffolds, we hoped to uncover a variant that would give access to enantioenriched indoline products. The most appealing scenario to achieve this goal would involve asymmetric catalysis. Thus, efforts were put forth to carry out the interrupted Fischer indolization reaction in the presence of chiral non-racemic phosphoric acids.[40]

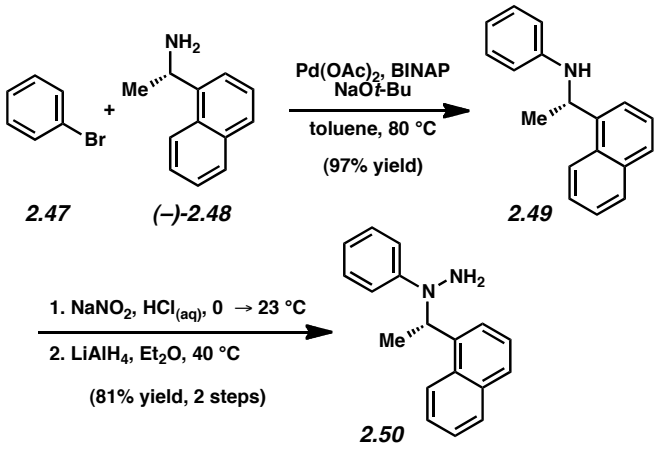
As shown in Scheme 2.8, this asymmetric transformation proved challenging. Despite an extensive survey of reaction conditions (e.g., variations in substrates, phosphoric acid promoter, stoichiometry, solvent, and temperature), only modest levels of enantioselectivity could be obtained. For example, reaction of hydrazine **2.23** and lactol **2.29** in the presence of 1.2 equivalents of phosphoric acid **2.46** (prepared from (*R*)-BINOL)[41] in benzene at 40 °C provided furoindoline **2.30** in 62% yield and 28% ee.[42] Similar results were obtained when hemiaminal substrates were employed in place of lactols.

Scheme 2.8



Given the difficulty in achieving a reagent or catalyst-controlled asymmetric interrupted Fischer indolization, we turned to the development of an auxiliary-based approach.[43] Following precedent from Nishida and co-workers in the synthesis of a pyrrolidinoindoline derivative, enantioenriched arylhydrazine **2.50** was prepared (Scheme 2.9).[25e] Bromobenzene (**2.47**) was coupled with commercially available enantioenriched amine (–)-**2.48** under Pd catalysis to provide aniline **2.49**. Using a standard protocol, aniline **2.49** was converted to the targeted hydrazine **2.50** in 81% yield over two steps.

Scheme 2.9



The utility of arylhydrazine **2.50** in our interrupted Fischer indolization process was evaluated in the context of furoindoline synthesis (Figure 2.4).[44] Gratifyingly, the reaction of **2.50** and lactol **2.29** proceeded smoothly under a variety of acidic conditions. When the reaction was carried out in the presence of 3 equivalents of chloroacetic acid in benzene at 40 °C, an 80% yield of diastereomeric indoline products **2.51** and **2.52** was obtained (d.r.=2.4:1).[45] The isomers were easily separable using conventional flash column chromatography on silica gel. The major isomer **2.51** was treated with $Pd(OH)_2$ and 1,4-cyclohexadiene in EtOH to remove the auxiliary and deliver optically enriched indoline **2.30**.[46] The ee of **2.30** was found to be 97%,[22] thus demonstrating that our methodology can be utilized to access enantioenriched products. The absolute configuration of **2.30** was determined based on correlation to known data,[32c] and was found to be as depicted in Figure 2.4.

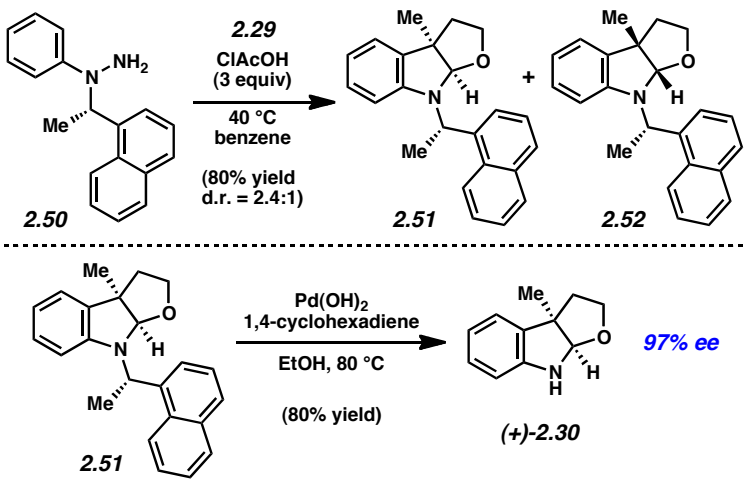


Figure 2.4. Synthesis of enantioenriched **2.30**.

2.7. Conclusions

In summary, we have developed an efficient method to access the fused indoline ring systems present in a variety of natural products. Our interrupted Fischer indolization strategy involves the condensation of readily available hydrazines with latent aldehydes to deliver indoline-containing products by way of a tandem [3,3]-sigmatropic rearrangement / cyclization cascade sequence. The method is convergent, mild, operationally simple, broad in scope, and can be used to access enantioenriched products. In addition, our approach is amenable to the synthesis of furoindoline and pyrrolidinoindoline natural products as demonstrated by the concise formal total syntheses of physovenine and debromoflustramine B. We expect that the interrupted Fischer indolization strategy will enable the synthesis of more complex targets such as the communesins and akuammiline alkaloids. Such studies in the realm of natural product synthesis are currently underway in our laboratory.

2.8 Experimental Section

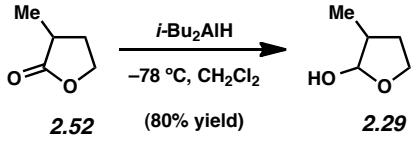
2.8.1 Materials and Methods

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 available reagents were used as received unless otherwise specified. α-Methyl-γ-butyrolactone, γ-butyrolactone, and α-methyl-γ-valerolactone were obtained from VWR (manufactured by TCI). 2-Piperidinone, 2-pyrrolidinone, *o*-tolylhydrazine hydrochloride, *p*-tolylhydrazine hydrochloride, and 4-chlorophenylhydrazine hydrochloride were obtained from VWR (manufactured by Alfa-Aesar). Sodium *t*-butoxide and *m*-tolylhydrazine hydrochloride were obtained from VWR (manufactured by Acros Organics). 37% concentrated hydrochloric acid was obtained from VWR (manufactured by EMD). Acetic acid was also obtained from VWR. 2-Chlorophenylhydrazine was obtained from Oakwood. *p*-Methoxyphenylhydrazine hydrochloride, ethyl 2-phenylacetate, 2-methyl-2-butene, diisobutylaluminium hydride, lithium aluminum hydride, Red-Al, sodium hydride, methyl iodide (MeI), *n*-butyllithium, LHMDS, NaHMDS, chloroacetic acid, 1,4-cyclohexadiene, palladium hydroxide (20% wt on carbon), and methyl chloroformate were obtained from Sigma-Aldrich. Palladium acetate and racemic BINAP were obtained from Strem Chemicals. Bromobenzene and sodium nitrite were obtained from Fisher. *(S)*-1-(Naphthyl)ethylamine and *(R)*-bi-2-naphthol were obtained from TCI America. Grubbs' second generation catalyst was obtained from Materia. Methyl iodide and allyl bromide were passed over basic Brockman Grade I 58 Å activated alumina prior to use. Diisopropylamine was distilled over CaH_2 prior to use. Chiral phosphoric acid **2.46** was prepared according to a known method.[47] Reaction temperatures were controlled using an IKAmag temperature modulator, and unless stated otherwise, reactions were

performed at room temperature (rt, approximately 23 °C). Thin-layer chromatography (TLC) was conducted with EMD gel 60 F254 pre-coated plates (0.25 mm) and visualized using a combination of UV, anisaldehyde, iodine, 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 300 MHz, 400 MHz, or 500 MHz) and are reported relative to deuterated solvent signals. Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz) and integration. ^{13}C NMR spectra are reported in terms of chemical shift. For mixtures of diastereomers, the major diastereomer is reported with the minor diastereomer in parentheses for both ^{1}H NMR and ^{13}C NMR spectra. IR spectra were recorded on a Perkin-Elmer 100 spectrometer and are reported in terms of frequency absorption (cm^{-1}). High resolution mass spectra were obtained from the UC Irvine Mass Spectrometry Facility. Determination of enantiopurity was carried out on a Mettler Toledo SFC (supercritical fluid chromatography) using a Chiral AS-H column.

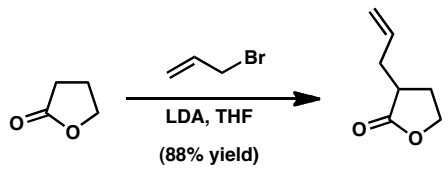
2.8.2 Experimental Procedures

A. Synthesis of Lactols



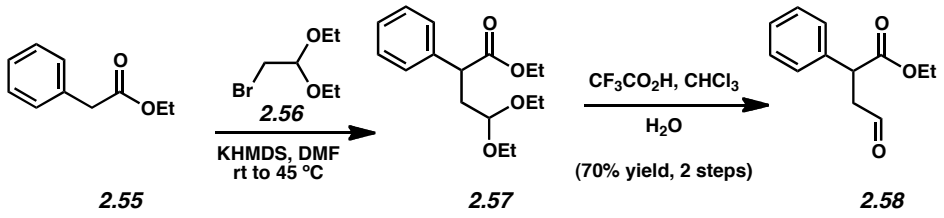
2.52 *2.29*

Lactol 2.29. Lactol **2.29** was prepared following a known procedure, with minor modifications.[48] Diisobutylaluminum hydride (1.0 M solution in hexanes, 33 mL, 33 mmol) was added dropwise over 30 min via syringe pump to a solution of α-methyl-γ-butyrolactone **2.52** (2.83 mL, 29.97 mmol, 1 equiv) in CH_2Cl_2 (36 mL) at –78 ºC. The resulting solution was stirred at –78 ºC for 0.5 h, and then quenched at –78 ºC with EtOAc. The reaction was warmed to 23 ºC, and then poured into a solution of sat. aq. Na–K tartrate (150 mL). The resulting mixture was vigorously stirred until both the aqueous and organic layers were clear (2 h). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (4 x 100 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to afford the crude product. Purification by flash chromatography (2:1 Et_2O:hexanes) produced lactol **2.29** (2.45 g, 80% yield, 67:33 mixture of diastereomers) as a yellow oil. R_f 0.5 (2:1 Et_2O:hexanes); ^1H NMR (500 MHz, $CDCl_3$): δ 5.11 (5.27) (dd, *J* = 2.0, 1.0, 1H), 4.05 (4.10) (ddd, *J* = 8.5, 8.5, 2.5, 1H), 3.97 (3.82) (ddd, *J* = 8.0, 8.0, 2.5, 1H), 2.55 (2.37) (d, *J* = 3.5, 1H), 2.18–2.27 (1.98–2.03) (m, 2H), 1.51–1.56 (1.72–1.77) (m, 1H), 1.04 (1.10) (d, *J* = 7.0, 3H). Spectral data match those previously reported.[48]



2.53 *2.54*

Lactone 2.54. Lactone **2.54** was prepared following a known procedure, with minor modifications.[49] To a stirred solution of diisopropylamine (1.65 mL, 11.6 mmol) in THF (23 mL) at 0 ºC, *n*-BuLi was added dropwise over 5 min (2.43 M in hexanes, 4.80 mL, 11.6 mmol). The resulting solution was cooled to –78 ºC for 0.5 h. γ-butyrolactone **2.53** (0.893 mL, 1 g, 11.6 mmol) was added dropwise over 2 min at –78 ºC, and the resulting solution was stirred for 1 h. Allyl bromide (1.01 mL, 11.6 mmol) was added dropwise over 2 min, and the resulting mixture was stirred for 1 h at –78 ºC. The reaction was warmed to –15 ºC and quenched with a solution of sat. aq. $NaHCO_3$ (10 mL). The reaction was then warmed to 23 ºC and diluted with Et_2O (50 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 x 50 mL). The combined organic layers were dried over Na_2SO_4. Evaporation of the solvent under reduced pressure afforded the crude lactone **2.54** (1.29 g, 88% yield), which was used in the subsequent step without further purification. R_f 0.3 (1:1 EtOAc:hexanes); ^{1}H NMR (400 MHz, $CDCl_3$); 5.77 (ddt, J = 16.8, 10.0, 6.8, 1H), 5.09–5.21 (m, 2H), 4.40 (ddd, J = 8.8, 8.8, 3.2, 1H), 4.20 (ddd, J = 9.2, 9.2, 6.8, 1H), 2.58–2.69 (m, 2H), 2.30–2.40 (m, 1H), 2.26–2.31 (m, 1H), 1.97–2.03 (m, 1H). Spectral data match those previously reported.[49]

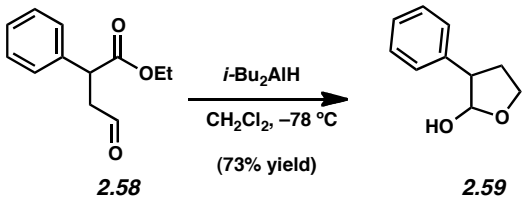


2.55 *2.57* *2.58*

Aldehyde 2.58. Aldehyde **2.58** was prepared following a known procedure, with minor modifications.[50] To a solution of KHMDS (0.5 M in toluene, 33.0 mL, 16.5 mmol) in DMF (40 mL) was added a solution of ethyl 2-phenylacetate **2.55** (2.4 mL, 15 mmol) in DMF (10 mL) at 23 ºC. The resulting solution was stirred for 10 min, and then bromoacetaldehyde diethylacetal **2.56** (2.53 mL, 16.5 mmol) was added dropwise over 3 min. After 10 min, the reaction was heated to 45 ºC for 3 h. The reaction was then cooled to 0 ºC and quenched with a solution of sat. aq. NH_4Cl (5 mL). The reaction was diluted with water (45 mL), and extracted with hexanes (3 x 50 mL). The combined organic layers were washed with water (3 x 25 mL) and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure afforded crude ester **2.57**, which was used in the subsequent step without further purification.

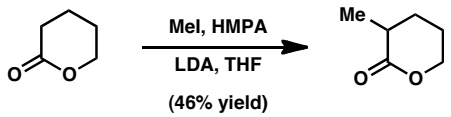
Ester **2.57** was suspended in water (7.5 mL) and cooled to 0 ºC. A 1:1 mixture of trifluoroacetic acid and chloroform (90 mL) was added and the resulting solution was stirred for 2 h. The reaction was then quenched with a solution of 1 M aqueous potassium carbonate (110 mL). Solid potassium carbonate was added until the pH of the solution was 10. The solution was diluted with CH_2Cl_2 (200 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL) and dried over Na_2SO_4. Purification by flash chromatography (4:1 Petroleum Ether:EtOAc) provided aldehyde **2.58** (2.16 g, 70% yield) as a yellow oil. R_f 0.05 (1:3 EtOAc:hexanes); ^1H NMR (400 MHz, $CDCl_3$): δ 9.78 (s, 1H), 7.25–7.35 (m, 5H), 4.07–4.20 (m,

3H), 3.39 (dd, *J* = 18.4, 10.8, 1H), 2.80 (dd, *J* = 18.4, 4.7, 1H), 1.20 (t, *J* = 7.2, 3H). Spectral data match those previously reported.[50]



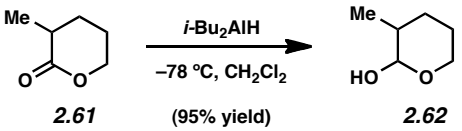
2.58 *2.59*

Lactol 2.59. Lactol **2.59** was prepared using the general procedure described by Schmitt et al.[48] Diisobutylaluminum hydride (1.0 M in hexanes, 3.64 mL, 3.64 mmol) was added dropwise over 10 min to a solution of ester **2.58** (300 mg, 1.45 mmol) in CH_2Cl_2 (30 mL) at –78 ºC. The resulting solution was stirred at –78 ºC for 30 min, and then quenched at –78 ºC with EtOAc (3 mL). The reaction was warmed to 23 ºC, and then poured into a solution of sat. aq. Na–K tartrate salt (50 mL). The resulting mixture was vigorously stirred until both the aqueous and organic layers were clear (2 h). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were dried over Na_2SO_4. Evaporation of the solvent under reduced pressure afforded the crude product. Purification by flash chromatography (1:1 hexanes:EtOAc) provided lactol **2.59** (174 mg, 73% yield, 80:20 mixture of diastereomers) as a faint yellow oil. R_f 0.5 (1:1 EtOAc:hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22–7.36 (7.22–7.36) (m, 5H), 5.45 (5.51) (t, *J* = 2.8, 1H), 4.19 (4.01) (ddd, *J* = 8.4, 7.2, 1.2, 1H), 4.13 (4.29) (ddd, *J* = 12.8, 8.4, 4.8, 1H), 3.34 (3.34) (ddd, *J* = 8.0, 6.4, 2.0, 1H), 2.97 (2.97) (d, *J* = 3.2, 1H), 2.45–2.59 (2.45–2.59) (m, 1H), 1.99–2.01 (2.02–2.04) (m, 1H). Spectral data match those previously reported.[51]



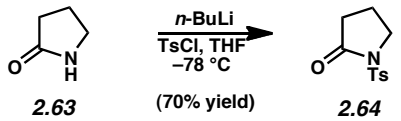
2.60 *2.61*

Lactone 2.61. Lactone **2.61** was prepared following a known procedure, with minor modifications.[52] To a stirred solution of diisopropylamine (1.72 mL, 12.2 mmol) in THF (23 mL) at 0 ºC, a solution of *n*-BuLi in hexanes (2.74 M, 7 mL, 12.2 mmol) was added dropwise over 5 min. The resulting solution was cooled to –78 ºC for 1.5 h. A solution of δ-valerolactone **2.60** (1.0 g, 10 mmol), HMPA (2.18 g, 12.2 mmol), and THF (11 mL) was added dropwise over 3 min at –78 ºC, and the resulting solution was stirred for 1 h. Methyl iodide (1.48 g, 10.5 mmol) was added dropwise over 2 min, and the resulting mixture was stirred for 2 h at –78 ºC. The reaction was quenched with solution of sat. aq. NH_4Cl solution (5 mL). The reaction was diluted with Et_2O (50 mL), and the layers were separated. The aqueous layer was extracted with Et_2O (4 x 50 mL). The combined organic layers were dried over Na_2SO_4. Evaporation of the solvent under reduced pressure afforded the crude product. Purification by flash chromatography (1:1 Et-OAc:hexanes) produced lactone **2.61** (528 mg, 46% yield). R_f 0.5 (1:1 EtOAc:hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.32 (m, 2H), 2.53–2.62 (m, 1H), 2.11 (ddd, J = 11.2, 6.8, 4.4, 1H), 1.83–1.96 (m, 2H), 1.41–1.57 (m, 1H), 1.26 (d, J = 7.2, 3H). Spectral data match those previously reported.[52]

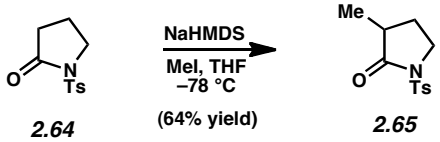


Lactol 2.62. Lactol **2.62** was prepared following the general procedure described by Schmitt et al.[48] A solution of diisobutylaluminum hydride (1.0 M in hexanes, 5.1 mL, 5.1 mmol) was added dropwise over 7 min to a solution of α-methyl-δ-valerolactone **2.61** (528 mg, 4.59 mmol) in CH_2Cl_2 (15 mL) at –78 ºC. The resulting solution was stirred at –78 ºC for 30 min, and then quenched with EtOAc (2 mL). The reaction was warmed to 23 ºC, and then poured into a solution of sat. aq. Na–K tartrate (125 mL). The resulting mixture was vigorously stirred until both the aqueous and organic layers were clear (2 h). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (4 x 100 mL). The combined organic layers were dried over Na_2SO_4. Evaporation of the solvent under reduced pressure afforded the crude product. Purification by flash chromatography (2:1 Et_2O:hexanes) afforded lactol **2.62** (510 mg, 95% yield, 67:33 mixture of diasteromers). R_f 0.3 (2:1 Et_2O:hexanes); ^1H NMR (300 MHz, $CDCl_3$): δ 4.33 (4.99) (d, J = 7.5, 1H), 3.90–4.04 (3.89–3.95) (m, 1H), 3.51 (3.58) (ddd, J = 12.0, 10.2, 3.1, 1H), 2.72 (2.37) (d, J = 3.3, 1H), 1.79–1.87 (1.79–1.87) (m, 1H) 1.42–1.63 (1.42–1.63) (m, 2H), 1.18–1.28 (1.18–1.28) (m, 2H), 0.98 (0.92) (d, J = 6.6, 3H). Spectral data match those previously reported.[53]

B. Synthesis of Hemiminals

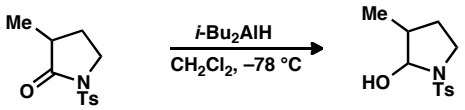


Ts-Lactam 2.64. Ts-lactam **2.64** was prepared following the general procedure described by Dake et al.[54] To a solution of 2-pyrrolidinone **2.63** (3.0 mL, 38.9 mmol) in THF (50 mL) at –78 °C, *n*-BuLi (2.55 M in hexanes, 16.0 mL, 41.0 mmol) was added dropwise over 6 min. The reaction was stirred at –78 °C for 1.5 h, then a solution of TsCl (7.95 g, 40.88 mmol) in THF (25 mL), was added dropwise over 20 min. The bath was removed after 20 min, and warmed to 23 °C over 1 h, and then quenched with sat. aq. NH_4Cl (30 mL). The layers were separated and the aqueous portion was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The resulting yellow solid was recrystallized from hexanes (50 mL) to afford Ts-Lactam **2.64** (6.55 g, 70% yield) as a white amorphous solid. R_f 0.2 (2:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.92 (d, *J* = 8.5, 2H), 7.33 (d, *J* = 8.0, 2H), 3.89 (t, *J* = 7.0, 2H), 2.43 (s, 3H) 2.42 (t, *J* = 8.0, 2H), 2.07 (p, *J* = 7.0, 2H). Data match those previously reported.[55]



Methylated Lactam 2.65. Methylated lactam **2.65** was prepared following a known procedure with slight modifications.[56] To a solution of Ts-lactam **2.64** (6.57 g, 27.4 mmol) in THF (135 mL) at –78 °C, NaHMDS (1.0 M in hexanes, 29 mL, 29 mmol) was added dropwise over 10 min. Following addition, the reaction mixture was stirred for 1 h, then methyl iodide (2.56 mL,

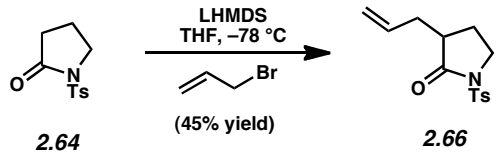
41.1 mmol) was added dropwise over 2 min. After 1.5 h, the reaction was quenched with a solution of sat. aq. NH_4Cl (100 mL) at –78 °C, and warmed to 23 °C. The layers were separated and the resulting aqueous layer was extracted with EtOAc (4 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The resulting residue was purified by flash chromatography (4:1 → 2:1 hexanes:EtOAc) affording methylated lactam **2.65** as a white amorphous powder (4.44 g, 64% yield). R_f 0.5 (2:1 hexanes:EtOAc); ^1H NMR (500 MHz, $CDCl_3$): δ 7.92 (d, *J* = 8.0, 2H), 7.33 (d, *J* = 8.0, 2H), 3.95 (ddd, *J* = 9.5, 8.5, 2.5, 1H), 3.68 (ddd, *J* = 10.0, 9.5, 7.0, 1H), 2.26–2.50 (m, 1H), 2.43 (s, 3H), 2.22–2.28 (m, 1H), 1.66–1.74 (m, 1H), 1.14 (d, *J* = 7.0, 3H). Spectral data match those previously reported.[56]



2.65 *2.31*

Hemiaminal 2.31. Hemiaminal **2.31** was prepared following the general procedure by Schmitt et al.[48] To a solution of methylated lactam **2.65** (1.28 g, 5.06 mmol) in CH_2Cl_2 (17 mL) at –78 °C, *i*-Bu_2AlH (1.0 M in hexanes, 15.2 mL, 15.2 mmol) was added dropwise over 5 min. After stirring for 1 h, the reaction mixture was quenched with a solution of sat. aq. NH_4Cl (50 mL) at –78 °C. The mixture was warmed to 23 °C and transferred to a 500 mL Erlenmeyer flask, with sat. aq. Na–K tartrate (100 mL) and EtOAc (50 mL). The reaction mixture was then stirred for 1 h at 23 °C. The layers were separated, and the aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (50 mL), 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 provide hemiaminal **2.31** (1.23 g, 96% yield, 65:35 mixture of

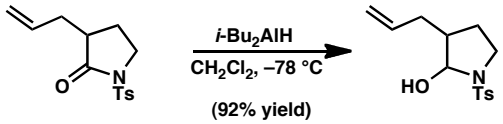
diastereomers) as a clear viscous oil. R_f 0.2 (8:1:1 hexanes:Et_2O:CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.74 (7.74) (d, *J* = 8.0, 2H), 7.32 (7.31) (d, *J* = 8.0, 2H), 4.97 (5.22) (t, *J* = 2.5, 1H), 3.49–3.56 (3.49–3.56) (m, 1H), 3.22 (3.03) (ddd, *J* = 9.5, 9.5, 7.0, 1H), 3.11 (2.83) (d, *J* = 2.5, 1H), 2.43 (2.42) (s, 3H), 2.14–2.21 (2.14–2.21) (m, 1H), 1.80–1.87 (1.80–1.87) (m, 1H), 1.36–1.42 (1.36–1.42) (m, 1H), 0.71 (1.04) (d, *J* = 7.0, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.7 (143.5), 135.5 (135.8), 129.7 (129.7), 127.2, (127.1), 84.8 (90.0), 46.7 (46.0), 40.6 (39.2), 30.3 (30.0), 21.5 (21.5), 15.8 (12.8); IR (film): 3491, 2970, 2879, 1598, 1335, 1161 cm^{-1}; HRMS-ESI (*m*/*z*) $[M + Na]^+$ calcd for $C_{12}H_{17}NO_3SNa$, 278.0827; found, 278.0818.



2.64 *2.66*

Allylated pyrrolidinone 2.66. To a solution of hexamethyldisilazane (2.58 mL, 12.4 mmol) in THF (12 mL) at 0 °C, *n*-BuLi (2.38 M in hexanes, 5.2 mL, 12.4 mmol) was added dropwise over 5 min and stirred for 40 min. The resulting mixture was then added dropwise over 10 min to a solution of **2.64** (2.83 g, 11.8 mmol) in anhydrous THF (40 mL) at –78 °C. The reaction stirred for 1 h 10 min, then allyl bromide (1.03 mL, 11.8 mmol) was added dropwise over 2 min. The reaction was warmed to 23 °C over 1 h, and quenched with sat. aq. NH_4Cl (50 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The crude residue was purified by flash chromatography (5:1 → 2:1 hexanes:EtOAc) to afford allylated pyrrolidinone **2.66** (1.49 g, 45% yield) as a white amorphous solid. R_f 0.4 (3:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.91 (d, *J* = 8.5, 2H), 7.32 (d, *J* = 8.5, 2H), 5.62 (ddt, *J* = 16.0, 10.0, 7.0, 1H), 5.03 (dd, *J* = 16.0, 1.0, 1H), 5.00 (dd, *J* = 7.0, 2.0, 1H), 3.92 (ddd, *J*

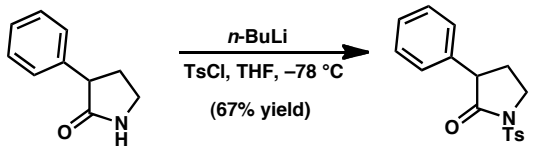
= 10.0, 9.0, 3.0 1H), 3.69 (ddd, *J* = 10.0, 9.0, 7.5, 1H), 2.44–2.50 (m, 2H), 2.43 (s, 3H), 2.16–2.22 (m, 1H), 2.09–2.14 (m, 1H), 1.77 (ddd, *J* = 13.0, 9.0, 9.0, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.8, 145.4, 135.3, 134.3, 129.8, 128.2, 117.9, 45.6, 42.9, 34.5, 24.3, 21.9; IR (neat): 3084, 2890, 1726, 1596, 1354, 1114 cm^{-1}; HRMS-ESI (*m*/*z*) $[M + Na]^+$ calcd for $C_{14}H_{17}NO_3SNa$, 302.0827; found, 302.0832.



2.66 *2.67*

Hemiaminal 2.67. To a solution of lactam **2.66** (1.38 g, 4.93 mmol) in CH_2Cl_2 (16 mL) at –78 °C, *i*-Bu_2AlH (1.0 M in hexanes, 14.8 mL, 14.8 mmol) was added dropwise over 8 min. After stirring for 1 h, the reaction was quenched with a solution of sat. aq. NH_4Cl (50 mL) at –78 °C. The mixture was warmed to 23 °C and transferred to a 500 mL Erlenmeyer flask with sat. aq. Na–K tartrate (100 mL) and EtOAc (50 mL). The reaction mixture was then stirred for 1 h at 23 °C. The layers were separated, and the aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (50 mL), 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 provide hemiaminal **2.67** (1.28 g, 92% yield, 65:35 mixture of diastereomers) as a clear viscous oil. R_f 0.1 (4:1:1 hexanes:Et_2O:CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$); δ 7.71–7.75 (7.71–7.75) (m, 2H), 7.28–7.33 (7.28–7.33) (m, 2H), 5.59 (5.74) (ddt, *J* = 17.0, 10.0, 7.0, 1H), 5.07 (5.30) (t, *J* = 2.0, 1H), 4.96 (4.96) (t, *J* = 9.5, 1H), 4.81 (5.02) (dd, *J* = 17.0, 1.5, 1H), 3.48–3.53 (3.48–3.53) (m, 1H), 3.41 (3.23) (s, 1H), 3.28 (3.07) (d, *J* = 2.5, 1H) 3.18 (3.02) (td, *J* = 9.5, 7.0, 1H), 2.42 (2.41) (s, 3H), 2.13–2.18 (2.13–2.18) (m, 1H) 2.08–2.30 (2.08–2.30) (m, 1H) 1.62–1.68 (1.73–1.81) (m, 1H), 1.44–1.50 (1.44–1.50) (m, 1H); ^{13}C NMR

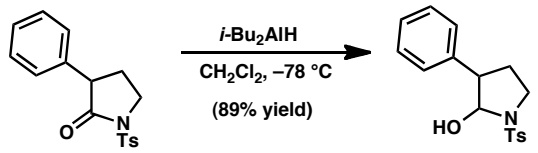
(125 MHz, $CDCl_3$): δ 143.9 (143.7), 136.5 (136.0), 135.9 (135.5), 130.0 (130.0), 127.3 (127.3), 117.1 (116.4), 88.2 (83.9), 46.7 (46.3), 45.8 (44.7), 34.9 (32.8), 28.6 (28.05), 21.7 (21.7); IR (film): 3488, 2950, 1598, 1331, 1158 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{14}H_{19}NO_3SNa$, 304.0983; found, 304.0984.



2.68 *2.69*

Ts-Lactam 2.69. Ts-pyrrolidinone **2.69** was prepared using the general procedure described by Dake et al.[54] To a solution of pyrrolidinone **2.68** (385 mg, 2.39 mmol) in THF (12 mL) at –78 °C, *n*-BuLi was added dropwise over 2 min. The reaction was stirred at –78 °C for 50 min, then a solution of TsCl (478 mg, 2.507 mmol) in THF (2 mL) was added dropwise over 2 min. The reaction mixture was stirred for 1 h 15 min, then quenched with sat. aq. NH_4Cl (20 mL) at –78 °C and warmed to 23 °C. The layers were separated and the resulting aqueous layer was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, and then concentrated *in vacuo*. The resulting crude product was purified by flash chromatography (6:1 → 5:1 hexanes:EtOAc) affording Ts-lactam **2.69** (506 mg, 67% yield) as a white amorphous powder. R_f 0.5 (3:1 hexanes:EtOAc); ^1H NMR (500 MHz, $CDCl_3$): δ 7.95 (d, *J* = 7.0, 2H), 7.35 (d, *J* = 6.5, 2H), 7.23–7.30 (m, 3H), 7.09–7.11 (m, 2H), 4.07 (ddd, *J* = 8.0, 3.5, 3.5, 1H), 3.84 (ddd, *J* = 7.5, 7.0, 1.5 1H), 3.67 (t, *J* = 9.5, 1H), 2.49–2.52 (m, 1H), 2.44 (s, 3H), 2.19–2.27 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.5, 145.5, 137.0, 135.2, 129.9, 129.0, 128.4, 128.0, 127.8, 49.3, 45.5, 27.8, 21.9; IR (neat): 3707, 3681, 2973,

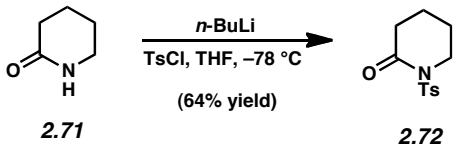
2923, 2865, 2826, 1734, 1346, 1032 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{17}H_{17}NO_3SNa$, 338.0827; found, 338.0821.



2.69 *2.70*

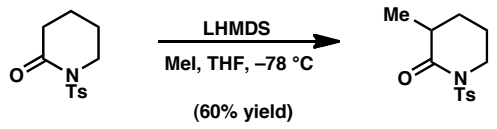
Hemiaminal 2.70. Hemiaminal **2.70** was prepared following the general procedure described by Schmitt et al.[48] To a solution of Ts-lactam **2.69** (428 mg, 1.36 mmol) in anhydrous CH_2Cl_2 (12 mL) at –78 °C, *i*-Bu_2AlH (1.0 M in hexanes, 4 mL, 4.07 mmol) was added dropwise over 2 min. After stirring for 1 h 20 min, the reaction mixture was quenched with sat. aq. NH_4Cl (25 mL) at –78 °C. The mixture was warmed to 23 °C and transferred to a 250 mL Erlenmeyer flask, with EtOAc (30 mL), and sat. aq. Na–K tartrate (50 mL). The resulting mixture was stirred vigorously for 20 min. The layers were separated and the aqueous layer was extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with water (20 mL), brine (20 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The resulting crude product was purified by flash chromatography (2:1:1 hexanes:Et_2O:CH_2Cl_2) affording hemiaminal **2.70** (382 mg, 89% yield, 67:33 mixture of diastereomers) as a clear viscous oil. R_f 0.2 (6:1:1 hexanes:Et_2O:CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$): δ 7.73 (7.85) (d, *J* = 8.5, 2H), 7.30–7.45 (7.30–7.45) (m, 4H), 7.16–7.25 (7.16–7.25) (m, 2H), 7.00–7.19 (m, 1H), 5.44 (5.58) (t, *J* = 2.5, 1H), 3.68 (3.68) (td, *J* = 10.0, 7.0, 1H), 3.47–3.55 (3.30–3.35) (m, 1H), 3.43 (2.71) (d, *J* = 2.0, 1H), 3.34 (3.11) (ddd, *J* = 7.0, 7.0, 4.0, 1H), 2.45 (2.44) (s, 3H), 2.37 (2.52) (ddd, *J* = 7.0, 6.5, 5.0, 1H), 1.89 (2.21) (td, *J* = 7.5, 7.5, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.0 (143.9), 139.9 (136.7), 136.2 (136.0), 130.0 (130.0), 128.9 (128.8), 128.6 (127.6), 127.5 (127.3), 127.3 (127.2), 90.0 (84.4), 51.8 (50.2), 46.9

(46.5), 30.5 (27.6), 21.8 (21.8); IR (film): 3482, 2889, 2254, 1598, 1333, 1155 cm^{-1}; HRMS-ESI (*m*/*z*) $[M + Na]^+$ calcd for $C_{17}H_{19}NO_3SNa$, 340.0983; found, 340.0984.



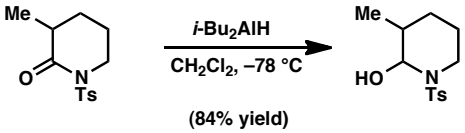
2.71 *2.72*

Ts-lactam 2.72. Ts-lactam **2.72** was prepared using a known procedure with minor modifications.[54] To a solution of piperidinone **2.71** (2.73 g, 27.5 mmol) in anhydrous THF (35 mL) at –78 °C, *n*-BuLi (2.59 M in hexanes, 11.2 mL, 28.9 mmol) was added dropwise over 4 min. The reaction was stirred at –78 °C for 1 h, then a solution of TsCl (5.51 g, 28.9 mmol) in THF (30 mL) was added dropwise over 18 min. The bath was then removed and the reaction was warmed to 23 °C. After 1 h 30 min, the reaction was quenched with sat. aq. NH_4Cl (50 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The resulting crude product was purified by recrystallization (75:10 hexanes:EtOAc) to afford Ts-lactam **2.72** (4.46 g, 64% yield) as a white crystalline solid. R_f 0.4 (2:1 hexanes: EtOAc); ^1H NMR (500 MHz, $CDCl_3$): δ 7.91 (d, *J* = 8.5, 2H), 7.31 (d, *J* = 8.0, 2H), 3.91 (t, *J* = 6.0, 2H), 2.42 (s, 3H), 2.41 (t, *J* = 7.0, 2H), 1.88–1.93 (m, 2H), 1.75–1.80 (m, 2H). Spectral data match those previously reported.[57]



2.72 *2.73*

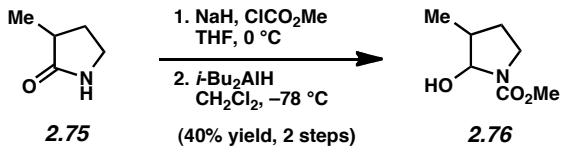
Methylated Lactam 2.73. Methylated lactam **2.73** was prepared following the general procedure described by Padwa et al.[56] To a solution of lactam **2.72** (2.01 g, 7.93 mmol) in THF (40 mL) at –78 °C, LHMDS (1.0 M in hexanes, 8.33 mL, 8.33 mmol) was added dropwise over 5 min and was stirred for 55 min. Methyl iodide (0.47 mL, 7.53 mmol) was added dropwise over 1 min, and the reaction was allowed to warm to 23 °C. After 1 h the reaction was quenched with sat. aq. NH_4Cl (30 mL). The layers were separated, and the resulting aqueous layer extracted with EtOAc (3 x 30 mL). The combined organic layers were then washed with brine (20 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The resulting crude product was purified by flash chromatography (6:1:1 → 3:1:1 hexanes:Et_2O:CH_2Cl_2) to afford methylated lactam **2.73** (1.27 g, 60% yield) as a white amorphous solid. R_f 0.4 (3:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.4, 2H), 7.30 (d, *J* = 8.4, 2H), 3.85–4.02 (m, 2H), 2.42 (s, 3H), 2.36–2.49 (m, 1H), 1.80–2.03 (m, 3H), 1.40–1.57 (m, 1H), 1.14 (d, *J* = 6.9, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.7, 144.4, 136.2, 129.2, 128.4, 46.7, 38.5, 28.4, 22.4, 21.6, 16.3; IR (neat): 2873, 1688, 1597, 1349, 1164 cm^{-1}; HRMS-ESI (*m*/*z*) $[M + Na]^+$ calcd for $C_{13}H_{17}NO_3SNa$, 290.0827; found, 290.0823.



2.73 *2.74*

Hemiaminal 2.74. To a solution of methylated lactam **2.73** (1.22 g, 4.56 mmol) in anhydrous CH_2Cl_2 (15 mL) at –78 °C, *i*-Bu_2AlH (1.0 M in hexanes, 13.7 mL, 13.7 mmol) was added

dropwise over 5 min. After stirring for 40 min, the reaction mixture was quenched with sat. aq. NH_4Cl (50 mL) at –78 °C. The mixture was warmed to 23 °C, and transferred to a 250 mL Erlenmeyer flask with EtOAc (50 mL) and sat. aq. Na–K tartrate (50 mL). The reaction mixture was stirred vigorously for 1 h. The layers were separated and the aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The resulting crude product was purified by flash chromatography (2:1:1 hexanes:Et_2O:CH_2Cl_2) affording hemiaminal **2.74** (1.03 g, 84% yield, 82:18 mixture of diastereomers). R_f 0.1 (4:1:1 hexanes:Et_2O:CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.73 (7.73) (d, *J* = 8.0, 2H), 7.17 (7.17) (d, *J* = 8.0, 2H), 5.32 (5.15) (t, *J* = 3.0, 1H), 3.50–3.57 (3.50–3.57) (m, 1H), 2.99 (3.11) (ddd, *J* = 12.5, 12.5, 3.0, 1H), 2.42 (2.42) (s, 3H), 2.11 (2.16) (dd, *J* = 4.0, 1.0, 1H), 1.69–1.75 (1.69–1.75) (m, 2H), 1.55–1.63 (1.55–1.63) (m, 1H), 1.39–1.47 (1.39–1.47) (m, 2H), 0.94 (0.94) (d, *J* = 7.0, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.4 (143.2), 136.9 (135.1), 129.7 (129.7), 129.6 (129.5), 127.2 (127.1), 81.1 (79.8), 39.4 (43.2), 26.3 (25.2), 21.4 (23.2) 20.8 (20.8), 17.7 (17.7); IR (film): 3519, 3352, 1596, 1449, 1324, 1146 cm^{-1}; HRMS-ESI (*m/z*) [M + Na]$^+$ calcd for $C_{13}H_{19}NO_3SNa$, 292.0983; found, 292.0975.



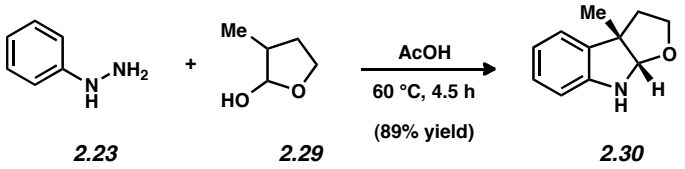
2.75 *2.76*

Hemiaminal 2.76. To a suspension of NaH (73 mg, 3.03 mmol) in THF (5 mL) at 0 °C was added a solution of known pyrrolidinone **2.75**[58] (100 mg, 1.01 mmol) in THF (5 mL). Following the addition, the reaction mixture was stirred for 30 min, then methyl chloroformate (156 μL, 2.02 mmol) was added over 30 sec and the reaction was warmed to 23 °C. After 10 min, the reaction mixture was quenched with a solution of sat. aq. NH_4Cl (5 mL) and the layers were

separated. The aqueous layer was extracted with Et_2O (3 x 25 mL). The combined organic layers were washed with brine (25 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to afford the crude product, which was used in the subsequent step without further purification.

To a solution of the crude product in CH_2Cl_2 (5 mL) at –78 °C was added *i*-Bu_2AlH (1.0 M in hexanes, 1.1 mL) and the resulting mixture was stirred for 0.5 h. The reaction mixture was quenched with EtOAc (0.1 mL) at – 78 °C, warmed to 23 °C, then transferred to a mixture of Na–K tartrate (50 mL) and Et_2O (25 mL). After stirring vigorously for 2.5 h, the reaction mixture was extracted with Et_2O (3 x 30 mL). The combined organic layers were washed with brine (2 x 50 mL), dried over Na_2SO_4, and evaporated to dryness. Purification by flash chromatography (1:1:1 → 0:1:1 hexanes:CH_2Cl_2:Et_2O) furnished hemiaminal **2.76** as a yellow oil (64 mg, 40% yield, 2 steps, 59:41 mixture of diastereomers). R_f 0.2 (1:1 hexanes: Et_2O); ^{1}H NMR (500 MHz, $CDCl_3$ @ 345K) δ 5.25 (5.25) (m, 1H), 5.01 (5.01) (s, 1H), 3.70 (3.70) (s, 3H), 3.52 (3.23) (t, *J* = 9.5, 1H), 3.34–3.45 (3.34–3.35) (m, 1H), 2.04–2.15 (1.71–1.79) (m, 1H), 2.04–2.15 (2.04–2.15) (m, 1H), 1.84–1.89 (1.43–1.48) (m, 1H), 1.07 (1.04) (d, *J* = 6.0, 3H); ^{13}C NMR (125 MHz, CD_3CN @ 345K) δ 129.6 (129.6), 117.5 (117.5), 83.8 (88.9), 52.8 (52.9), 45.6 (46.4), 39.8 (41.9), 13.6 (17.1); IR (film): 3421, 2961, 2885, 1683, 1450, 1379, 1121 cm^{-1}; HRMS-ESI (*m*/*z*) $[M+Na]^+$ calcd for $C_7H_{13}NO_3Na$, 182.0793; found, 182.0789.

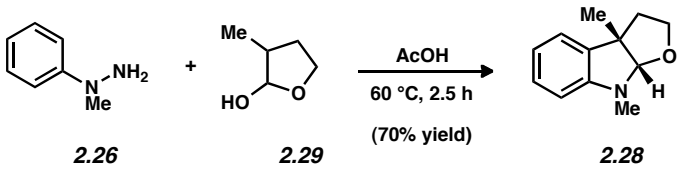
C. Synthesis of Furoindolines



2.23 *2.29* *2.30*

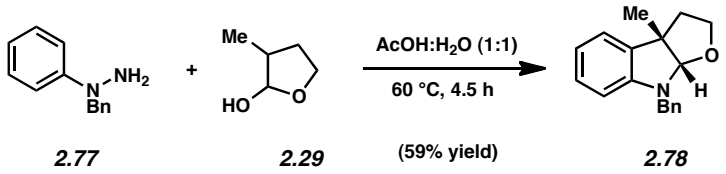
Representative Procedure (Reacting phenylhydrazine (2.23) with lactol 2.29 is used as an example, Table 2.2, entry 1). Lactol **2.29** (126 mg, 1.22 mmol) was dissolved in a 1:1 mixture of acetic acid and water (6 mL). Phenylhydrazine (**2.23**) (0.121 mL, 1.23 mmol) was added to the resulting mixture. The reaction was heated to 60 ºC for 4.5 h, then cooled to 23 ºC, and quenched with a solution of sat. aq. $NaHCO_3$ (15 mL). The resulting mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were dried over $MgSO_4$. Evaporation of the solvent under reduced pressure afforded the crude product. Purification by flash chromatography (7:1 hexanes:EtOAc) afforded indoline **2.30** (196 mg, 89% yield). R_f 0.7 (1:1 EtOAc:hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.08 (d, *J* = 7.2, 1H), 7.05 (t, *J* = 7.5, 1H), 6.76 (t, *J* = 7.5, 1H), 6.59 (d, *J* = 7.8, 1H), 5.28 (s, 1H), 3.96 (ddd, *J* = 8.4, 7.2, 1.8, 1H), 3.56 (ddd, *J* = 10.8, 8.4, 5.1, 1H), 2.13 (ddd, *J* = 11.7, 5.4, 1.5, 1H), 2.07 (ddd, *J* = 11.7, 7.2, 4.2, 1H), 1.47 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.8, 133.9, 127.9, 122.9, 118.8, 108.8, 99.5, 67.3, 53.8, 41.4, 24.7; IR (film): 2967, 2845, 1611, 1486, 1265, 1055 cm^{-1}; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{11}H_{14}NO$, 176.1075; found 176.1078.

Any modifications of the conditions shown in this representative procedure are specified in the following schemes, which depict all of the condensation reactions in Tables 2.2–2.4.



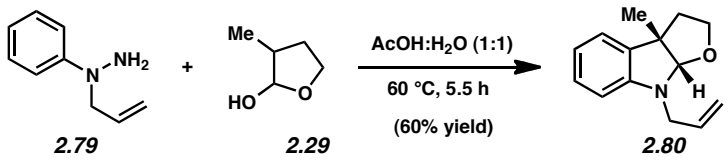
2.26 *2.29* *2.28*

Indoline 2.28 (Table 2.2, entry 2). Purification by flash chromatography (4:1 hexanes:EtOAc) afforded indoline **2.28** as a orange oil (70% yield). R_f 0.5 (3:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.10 (t, *J* = 8.0, 1H), 7.06 (d, *J* = 7.5, 1H), 6.69 (t, *J* = 7.5, 1H), 6.38 (d, *J* = 8.0, 1H), 5.09 (s, 1H), 3.95 (ddd, *J* = 7.5, 7.5, 1.5, 1H), 3.45 (ddd, *J* = 8.5, 6.0, 2.5, 1H), 2.94 (s, 3H), 2.13–2.16 (m, 1H), 2.06 (ddd, *J* = 11.8, 7.5, 2.5, 1H), 1.48 (s, 3H). Spectral data match those previously reported.[59]

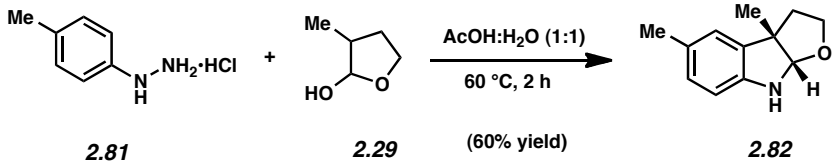


2.77 *2.29* *2.78*

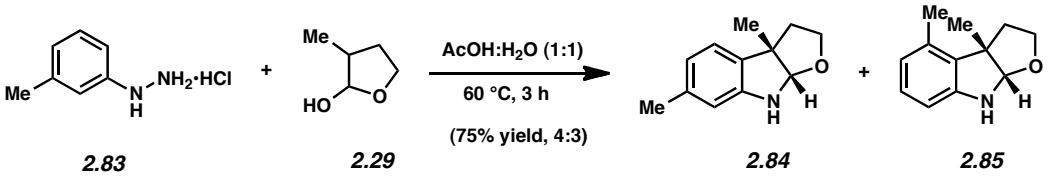
Indoline 2.78 (Table 2.2, entry 3). Purification by flash chromatography (6:1 → 4:1 hexanes:EtOAc) afforded indoline **2.78** as a yellow oil (59% yield). R_f 0.6 (6:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45–7.52 (m, 4H), 7.39 (t, *J* = 7.0, 1H), 7.23 (d, *J* = 6.5, 1H), 7.19 (t, *J* = 7.5, 1H), 6.86 (t, *J* = 7.5, 1H), 6.49 (d, *J* = 8.0, 1H), 5.35 (s, 1H), 4.71 (d, *J* = 16.0, 1H), 4.66 (d, *J* = 16.0, 1H), 4.13 (t, *J* = 7.5, 1H), 3.72 (ddd, *J* = 11.5, 8.5, 5.0, 1H), 2.33 (dd, *J* = 5.0, 2.0, 1H), 2.22 (ddd, *J* = 11.5, 7.5, 7.0, 1H), 1.64 (s, 3H). Spectral data match those previously reported.[60]



Indoline 2.80 (Table 2.2, entry 4). Purification by flash chromatography (10:1 hexanes:EtOAc) furnished indoline **2.80** as a yellow oil (60% yield). R_f 0.4 (4:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.07 (t, *J* = 5.0, 2H), 6.70 (t, *J* = 7.0, 1H), 6.39 (d, *J* = 8.0, 1H), 5.86–5.90 (m, 1H), 5.27 (dd, *J* = 17.5, 1.5, 1H), 5.17–5.18 (m, 2H), 3.94–3.98 (m, 3H), 3.51 (ddd, *J* = 14.0, 9.0, 5.5, 1H), 2.15–2.18 (m, 1H), 2.04–2.09 (m, 1H), 1.48 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.5, 134.3, 134.1, 127.8, 122.5, 117.3, 116.3, 105.2, 103.6, 67.0, 52.2, 47.2, 41.8, 25.0; IR (film): 3054, 2960, 2866, 1606, 1490, 1030, 1007 cm^{-1}; HRMS-ESI (*m*/*z*) $[M+H]^+$ calcd for $C_{14}H_{18}NO$, 216.1388; found, 216.1391.

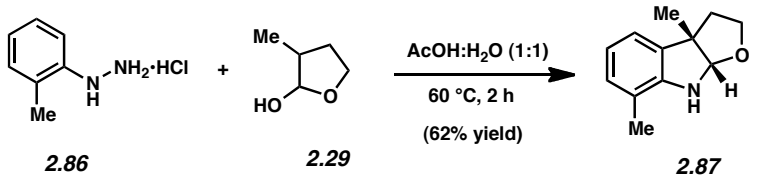


Indoline 2.82 (Table 2.3, entry 1). Purification by flash chromatography (3:1 hexanes:EtOAc) afforded indoline **2.82** as a brown oil (60% yield). R_f 0.3 (3:1 hexanes:EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.90 (s, 1H), 6.86 (d, *J* = 8.0, 1H), 6.50 (d, *J* = 8.0, 1H), 5.26 (s, 1H), 4.50 (bs, 1H), 3.94 (ddd, *J* = 8.5, 8.4, 1.2, 1H), 3.56 (ddd, *J* = 5.6, 5.2, 1.2, 1H), 2.27 (s, 3H), 2.16 (dd, *J* = 7.0, 4.0, 1H), 2.07 (ddd, *J* = 11.6, 11.2, 7.2, 1H), 1.46 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 146.7, 134.3, 128.4, 128.3, 123.7, 108.3, 100.0, 67.4, 53.9, 41.5, 24.8, 20.8; IR (film): 3357, 2961, 2868, 1617, 1494, 1265 cm^{-1}; HRMS-ESI (*m*/*z*) $[M + H]^+$ calcd for $C_{12}H_{16}NO$, 190.1232; found, 190.1226.



2.83 *2.29* *2.84* *2.85*

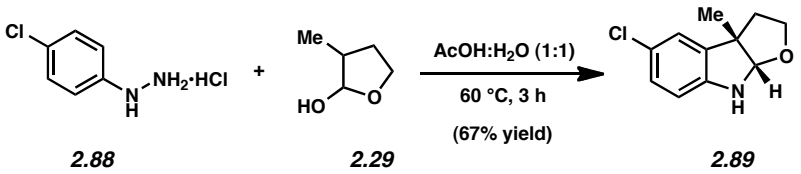
Indolines 2.84 and 2.85 (Table 2.3, entry 2). Purification by flash chromatography (10:1 → 5:1 hexanes:EtOAc) furnished indolines **2.84** and **2.85** as an orange oil (75% yield, 4:3). R_f 0.3 (4:1 hexanes:EtOAc); **2.84** ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.98 (m, 1H), 6.60 (d, *J* = 7.5, 1H), 6.44 (s, 1H), 5.29 (s, 1H), 4.57 (s, 1H), 3.96 (m, 1H), 3.62 (m, 1H), 2.36 (s, 3H), 2.17 (dd, *J* = 12.0, 5.0, 1H), 2.07 (m, 1H), 1.55 (s, 3H); **2.85** ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.98 (m, 1H), 6.55 (d, *J* = 7.5, 1H), 6.45 (d, *J* = 8.0, 1H), 5.24 (s, 1H), 4.57 (s, 1H), 3.96 (m, 1H), 3.62 (m, 1H), 2.29 (s, 3H), 2.07 (m, 2H), 1.48 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.5, 148.4, 143.5, 143.4, 138.3, 136.1, 135.4, 133.5, 130.1, 129.7, 129.5, 128.3, 127.2, 127.0, 121.9, 121.6, 120.0, 110.3, 107.3, 85.2, 84.9, 54.5, 53.8, 47.5, 47.3, 37.9, 36.4, 24.5, 23.1, 21.4, 18.0; IR (film): 3392, 2960, 2867, 1618, 1596, 1450, 1334, 1156 cm^{-1}; HRMS-ESI (*m*/*z*) $[M+Na]^+$ calcd for $C_{12}H_{15}NONa$, 212.1051; found, 212.1049.



2.86 *2.29* *2.87*

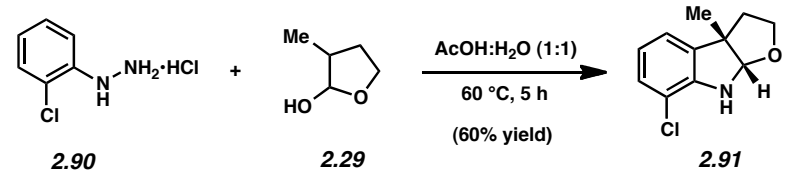
Indoline 2.87 (Table 2.3, entry 3) Purification by flash chromatography (3:1 hexanes:EtOAc) afforded indoline **2.87** as a brown oil (62% yield). R_f 0.4 (3:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.94 (d, *J* = 7.6, 1H), 6.90 (d, *J* = 7.6, 1H), 6.72 (t, *J* = 7.6, 1H), 5.31 (s, 1H), 4.41 (bs, 1H), 3.95 (ddd, *J* = 7.2, 6.8, 2.0, 1H), 3.57 (ddd, *J* = 5.2, 5.2, 3.6, 1H), 2.18 (ddd, *J* = 6.4, 5.6, 1.6, 1H), 2.15 (s, 3H), 2.08 (ddd, *J* = 11.6, 11.2, 7.2, 1H), 1.47 (s, 3H); ^{13}C NMR (125

MHz, $CDCl_3$): δ 147.5, 133.5, 128.9, 120.4, 119.2, 117.8, 99.6, 67.4, 54.2, 41.6, 24.9, 16.7; IR (film): 3707, 3681, 3352, 2981, 2923, 1602, 1467 cm^{-1}; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{12}H_{16}NO$, 190.1232; found, 190.1228.



2.88 *2.29* *2.89*

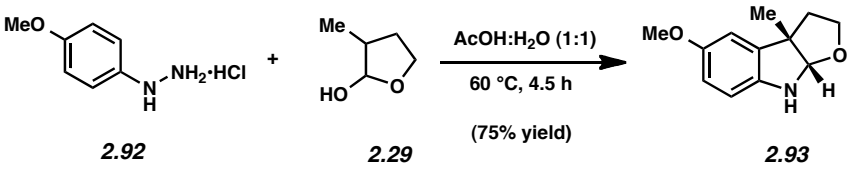
Indoline 2.89 (Table 2.3, entry 4) Purification by flash chromatography (5:95 MeOH:CH_2Cl_2) afforded indoline **2.89** as a red oil (67% yield). R_f 0.2 (3:1 hexanes:EtOAc); ^1H NMR (500 MHz, $CDCl_3$): δ 7.02 (s, 1H), 7.00 (d, *J* = 8.0, 1H), 6.49 (d, *J* = 8.4, 1H), 5.27 (s, 1H), 4.56 (bs, 1H), 3.96 (ddd, *J* = 7.2, 3.2, 2.0, 1H), 3.55 (ddd, *J* = 8.8, 5.2, 5.2, 1H), 2.15 (ddd, *J* = 6.8, 5.2, 1.6, 1H), 2.07 (ddd, *J* = 11.2, 7.2, 0.6, 1H), 1.46 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.6, 136.0, 127.8, 123.4, 123.3, 109.0, 99.9, 67.4, 54.0, 41.4, 24.7; IR (film): 3697, 3681, 2967, 1607, 1479, 1264, 1033 cm^{-1}; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{11}H_{13}NOCl$, 210.0686; found, 210.0680.



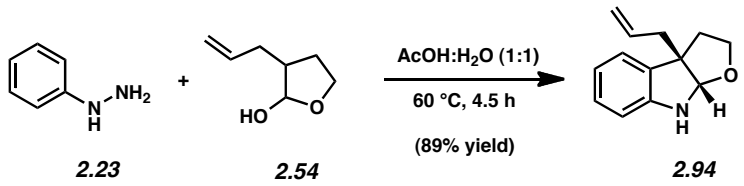
2.90 *2.29* *2.91*

Indoline 2.91 (Table 2.3, entry 5). Purification by flash chromatography (3:1 hexanes:EtOAc) afforded indoline **2.91** as a red oil (60% yield). R_f 0.4 (3:1 hexanes:EtOAc); ^1H NMR (500 MHz, $CDCl_3$): δ 7.10 (d, *J* = 8.0, 1H), 7.01 (d, *J* = 7.5, 1H), 6.73 (t, *J* = 7.5, 1H), 5.33 (s, 1H), 4.8 (s, 1H), 3.97 (ddd, *J* = 7.5, 6.0 1.0, 1H), 3.62 (ddd, *J* = 7.5, 5.5 2.0, 1H), 2.21 (ddd, *J* = 8.0, 5.5, 1.0, 1H), 2.13 (ddd, *J* = 8.0, 6.0, 2.0, 1H), 1.53 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.9,

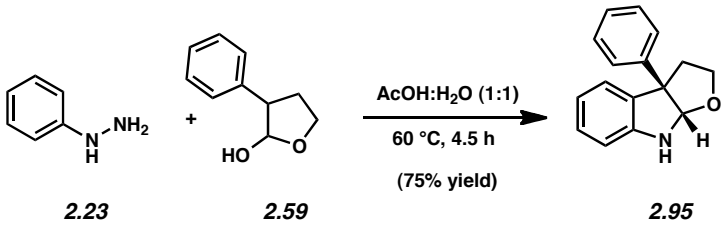
135.5, 127.6, 121.2, 119.6, 113.4, 99.1, 67.5, 55.0, 41.5, 24.6; IR (neat): 3681, 3431, 2967, 2844, 1609, 1473, 1265, 1034 cm^{-1}; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{11}H_{13}NOCl$, 210.0686; found, 210.0686.



Indoline 2.93 (Table 2.3, entry 6). Purification by flash chromatography (3:1 hexanes:EtOAc) afforded indoline **2.93** as a orange oil (75% yield). R_f 0.5 (2:98 MeOH:CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$): δ 6.70 (d, *J* = 2.4, 1H), 6.63 (dd, *J* = 8.4, 2.4, 1H), 6.53 (d, *J* = 8.4, 1H), 5.27 (s, 1H), 3.95 (ddd, *J* = 7.2, 2.1, 1.5, 1H), 3.76 (s, 3H), 3.56 (ddd, *J* = 8.4, 5.4, 5.1), 2.05–2.20 (m, 2H), 1.47 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.8, 142.9, 135.8, 112.7, 110.0, 109.1, 100.4, 67.4, 55.9, 54.3, 41.4, 24.7; IR (neat): 3342, 2961, 1735, 1664, 1486, 1235, 1038 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{12}H_{15}NO_2Na$, 228.1001; found, 228.1002.

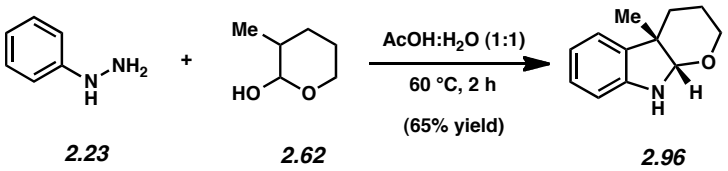


Indoline 2.94 (Table 2.4, entry 1). Purification by flash chromatography (4:1 hexanes:EtOAc) afforded indoline **2.94** as a brown oil (89% yield). R_f 0.4 (6:1 hexanes:EtOAc); ^1H NMR (500 MHz, $CDCl_3$): δ 7.07 (t, *J* = 7.5, 1H), 7.05 (d, *J* = 7.5, 1H), 6.75 (t, *J* = 7.5, 1H), 6.58 (d, *J* = 7.5, 1H), 5.70 (m, 1H), 5.64 (s, 1H), 5.08 (dd, *J* = 17.0, 1.0, 1H), 5.05 (dd, *J* = 10.0, 1.0, 1H), 3.95 (ddd, *J* = 8.5, 6.5, 1.5, 1H)), 3.56 (ddd, *J* = 10.5, 8.5, 5.5, 1H), 2.62 (dd, *J* = 13.0, 6.0, 1H), 2.49 (dd, *J* = 14.0, 8.0, 1H), 2.11–2.49 (m, 2H). Spectral data match those previously reported.[61]



2.23 *2.59* *2.95*

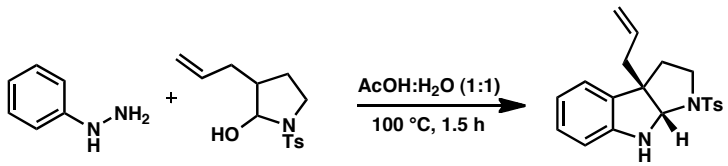
Indoline 2.95 (Table 2.4, entry 2). Purification by flash chromatography (9:1 hexanes:EtOAc) afforded indoline **2.95** as an off white solid (75% yield). R_f 0.5 (3:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39–7.33 (m, 5H), 7.14 (t, *J* =8.0, 1H), 7.07 (d, *J* = 7.0, 1H), 6.80 (t, *J* = 7.0, 1H), 6.71 (d, *J* = 7.5, 1H), 5.65 (s, 1H), 4.68 (bs, 1H), 4.18–4.22 (m, 1H), 3.72 (ddd, *J* = 11.5, 8.5, 4.5, 1H), 2.80 (ddd, *J* = 11.5, 7.5, 7.5, 1H), 2.57 (dd, *J* = 12.0, 4.5, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.4, 144.0, 132.6, 128.6, 128.4, 126.7, 126.1, 124.6, 119.3, 108.7, 100.5, 68.3, 62.3, 40.5; IR (film): 3708, 3681, 3351, 2973, 2923, 2844, 1606, 1484, 1033 cm^{-1}; HRMS-ESI (*m*/*z*) [M + H]$^+$ calcd for $C_{16}H_{16}NO$, 238.1232; found, 238.1230.



2.23 *2.62* *2.96*

Indoline 2.96 (Table 2.4, entry 3). Purification by flash chromatography (6:1 hexanes:EtOAc) afforded indoline **2.96** as a orange solid (65% yield). R_f 0.6 (3:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): 7.07 (t, *J* = 7.5, 1H), 7.05 (d, *J* = 7.5, 1H), 6.80 (t, *J* = 7.5, 1H), 6.70 (d, *J* = 7.5, 1H), 4.73 (s, 1H), 4.31 (bs, 1H), 3.75 (ddd, *J* = 11.0, 4.0, 1.5, 1H), 3.45 (ddd, *J* = 11.0, 9.0, 3.5, 1H), 2.19 (td, *J* = 14.0, 4.0, 1H), 1.77 (ddd, *J* =14.0, 11.5 5.0, 1H), 1.41–1.54 (m, 2H), 1.18 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.4, 134.8, 127.5, 121.8, 119.3, 109.9, 95.2, 62.5, 43.5, 30.7, 26.6, 21.8; IR (neat) 3310, 2909, 1609, 1466, 1211, 1065, 1021 cm^{-1}; HRMS-ESI (*m*/*z*) [M + H]$^+$ calcd for $C_{12}H_{16}NO$, 190.1232; found, 190.1228.

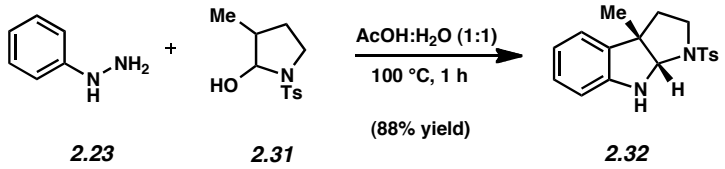
D. Synthesis of Pyrrolidinoindolines



2.23 *2.67* *2.97*

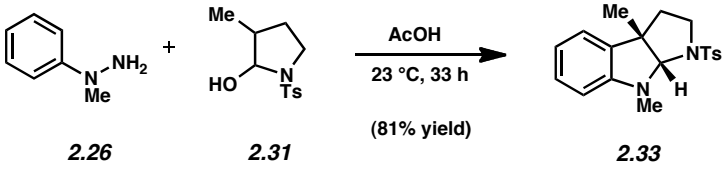
Representative Procedure (Reacting phenylhydrazine (2.23) with hemiaminal 2.67 is used as an example). Indoline 2.97 (Table 2.6, entry 1). Hemiaminal **2.67** (105 mg, 0.37 mmol) was dissolved in a 1:1 mixture of acetic acid and water (1.8 mL). Phenylhydrazine (**2.23**) (0.036 mL, 0.36 mmol) was added to the resulting mixture. The reaction was heated to 100 °C for 1 h 40 min, cooled to 23 °C, and then diluted with Et_2O (20 mL). The reaction mixture was quenched with sat. aq. $NaHCO_3$ (20 mL), and the layers were separated. The aqueous layer was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, and concentrated *in vacuo* to afford crude indoline **2.97**. Purification by flash chromatography (18:1:1 benzene:Et_2O:CH_2Cl_2) afforded indoline **2.97** as a yellow oil (68% yield). R_f 0.6 (8:1:1 benzene:Et_2O:CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.75 (d, *J* = 8.0, 2H), 7.32 (d, *J* = 8.0, 2H), 7.08 (t, *J* = 7.5, 1H), 7.00 (d, *J* = 7.0, 1H), 6.75 (t, *J* = 7.5, 1H), 6.62 (d, *J* = 7.5, 1H), 5.55 (ddt, *J* = 16.8, 10.0, 7.5, 1H), 5.13 (s, 1H), 4.96–5.00 (m, 2H), 4.84 (s, 1H), 3.43 (ddd, *J* = 10.0, 8.0, 2.0, 1H), 3.13 (ddd, *J* = 10.5, 10.5, 6.0, 1H), 2.44 (s, 3H), 2.31 (m, 2H), 2.07 (ddd, *J* = 6.5, 6.0, 2.0, 1H), 1.84 (ddd, *J* = 10.5, 8.0, 6.5, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.1, 143.7, 136.4, 133.5, 131.4, 130.0, 128.8, 127.3, 123.2, 119.3, 118.8, 109.7, 82.7, 58.0, 47.6, 42.3, 36.2, 21.7; IR (neat): 3391, 3076, 1611, 1485, 1337, 1160 cm^{-1}; HRMS-ESI (*m/z*) $[M+Na]^+$ calcd for $C_{20}H_{22}N_2O_2SNa$, 377.1300; found, 377.1298.

Any modifications of the conditions shown in this representative procedure are specified in the following schemes, which depict all Table 2.5 and Table 2.6 condensation reactions.



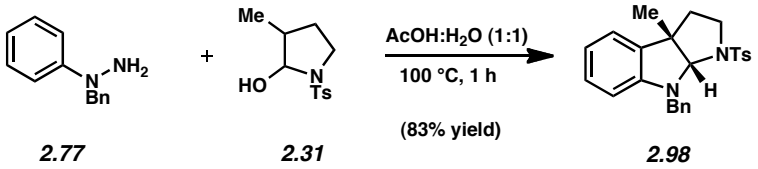
2.23 *2.31* *2.32*

Indoline 2.32 (Scheme 2.4). Purification by filtration afforded indoline **2.32** as a yellow solid (88% yield). R_f 0.4 (1:1 hexanes:Et_2O); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.74 (d, *J* = 8.5, 2H), 7.31 (d, *J* = 8.0, 2H), 7.08 (t, *J* = 6.5, 1H), 7.00 (d, *J* = 7.0, 1H), 6.75 (t, *J* = 7.0, 1H), 6.62 (d, *J* = 8.0, 1H), 5.02 (s, 1H), 4.86 (bs, 1H), 3.40 (ddd, *J* =10.5, 7.5, 2.0, 1H), 3.13 (ddd *J* = 10.5, 10.0, 6.0, 1H), 2.42 (s, 3H), 2.15 (ddd, *J* = 6.5, 6.0, 2.5, 1H), 1.77 (ddd *J* = 10.5, 8.0 2.5, 1H), 1.27 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.5, 143.7, 136.4, 133.2, 130.0, 128.6, 127.3, 122.5, 119.5, 109.8, 84.9, 54.4, 47.8, 38.2, 24.7, 21.7; IR (neat): 3387, 2965, 1610, 1329, 1156; HRMS-ESI (*m*/*z*) $[M+Na]^+$ calcd for $C_{18}H_{20}N_2O_2SNa$, 351.1143; found, 351.1142.



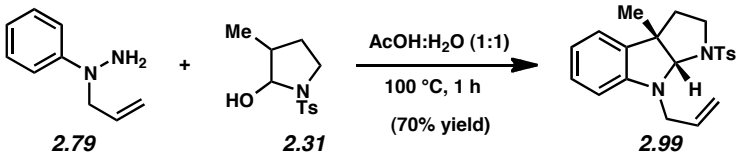
2.26 *2.31* *2.33*

Indoline 2.33 (Table 2.5, entry 1). Purification by flash chromatography (6:1 → 4:1 hexanes:Et_2O) affording indoline **2.33** (81% yield) as a yellow foam. R_f 0.5 (2:1 hexanes:Et_2O); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.79 (d, *J* = 8.0, 2H), 7.34 (d, *J* = 8.0, 2H), 7.10 (t, *J* = 7.5, 1H), 6.92 (d, *J* = 7.0, 1H), 6.66 (t, *J* = 7.0, 1H), 6.40 (d, *J* = 8.0, 1H), 5.13 (s, 1H), 3.55 (ddd, *J* = 7.0, 5.5, 2.5, 1H), 3.07 (ddd, *J* = 12.0, 11.0, 5.5, 1H), 3.01 (s, 3H), 2.45 (s, 3H), 1.93 (ddd, *J* = 6.5, 5.5, 2.0, 1H), 1.39 (ddd, *J* = 12.0, 11.0, 7.5, 1H), 1.14 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 150.2, 143.8, 136.8, 133.2, 129.9, 128.6, 127.4, 122.0, 117.7, 106.0, 91.2, 53.2, 48.6, 39.6, 31.5, 24.5, 21.7; IR (neat): 2936, 2868, 1609, 1492, 1341, 1153 cm^{-1}; HRMS-ESI (*m*/*z*) $[M + Na]^+$ calcd for $C_{19}H_{22}N_2O_2SNa$, 365.1300; found, 365.1291.



2.77 *2.31* *2.98*

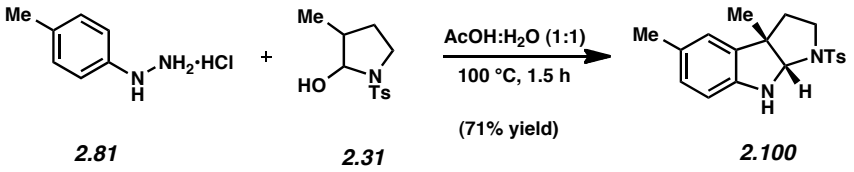
Indoline 2.98 (Table 2.5, entry 2). Purification by flash chromatography (10:1:1 → 8:1:1 hexanes:Et_2O:CH_2Cl_2) afforded indoline **2.98** as a white solid (83% yield). R_f 0.8 (2:1:1 hexanes:Et_2O:CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.71 (d, *J* = 8.5, 2H), 7.29–7.35 (m, 4H), 7.21–7.26 (m, 3H), 7.02 (t, *J* = 8.0, 1H), 6.94 (d, *J* = 7.0, 1H), 6.65 (t, 7.5, 1H), 6.32 (d, *J* = 8.0, 1H), 5.27 (s, 1H), 4.75 (d, *J* = 16.5 1H), 4.61 (d, *J* = 16.5, 1H), 3.62 (ddd, *J* = 7.0, 5.0, 1.5, 1H), 3.14 (ddd, *J* =12.0, 11.5, 5.5, 1H), 2.44 (s, 3H), 1.97 (ddd, *J* = 12.5, 5.5, 2.0, 1H), 1.41 (ddd, *J* = 12.0, 11.5, 7.0, 1H), 1.14 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$); δ 149.3 149.2, 143.5, 143.4 138.6, 136.7, 132.8, 129.7, 128.3, 127.1, 127.1, 126.7, 122.1, 106.0, 89.5, 53.3, 48.2, 48.0, 39.8, 25.1, 21.4; IR (neat): 3062, 2924, 1605, 1489, 1343, 1155 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{25}H_{26}N_2O_2SNa$, 441.1613; found, 441.1623.



2.79 *2.31* *2.99*

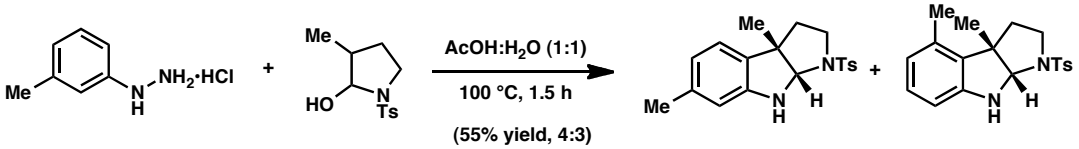
Indoline 2.99 (Table 2.5, entry 3). Purification by flash chromatography (10:1 hexanes:EtOAc) afforded indoline **2.99** (70% yield) as a yellow oil. R_f 0.5 (4:1 hexanes:EtOAc ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.0, 2H), 7.35 (d, *J* = 8.0, 2H), 7.08 (t, *J* = 7.5, 1H), 6.93 (d, *J* = 7.5, 1H), 6.65 (t, *J* = 7.5, 1H), 6.42 (d, *J* = 8.0, 1H), 5.86–5.91 (m, 1H), 5.29 (dd, *J* = 17.0, 1.5, 1H), 5.23 (s, 1H), 5.19 (dd, *J* = 10.5, 1.5, 1H), 4.18 (dd, *J* = 17.0, 6.0, 1H), 4.03 (dd, *J* = 16.5, 4.5, 1H), 3.58 (ddd, *J* = 12.0, 7.5, 2.5, 1H), 3.13 (ddd, *J* = 16.5, 11.0, 6.0, 1H), 2.46 (s, 3H), 1.95 (ddd, *J* = 12.5, 6.0, 2.5, 1H), 1.41 (ddd, *J* = 16.0, 10.5, 7.0, 1H), 1.13 (s, 3H); ^{13}C NMR (125

MHz, $CDCl_3$) δ 148.9, 143.6, 136.7, 133.6, 133.0, 129.7, 128.3, 127.2, 122.0, 117.3, 116.4, 106.2, 89.3, 53.1, 48.1, 46.6, 39.7, 24.8, 21.5; IR (film): 3682, 2966, 2845, 1607, 1490, 1346, 1158, 1054 cm^{-1}; HRMS-ESI (*m/z*) $[M+Na]^+$ calcd for $C_{21}H_{24}N_2O_2SNa$, 391.1456; found, 391.1442.



2.81 *2.31* *2.100*

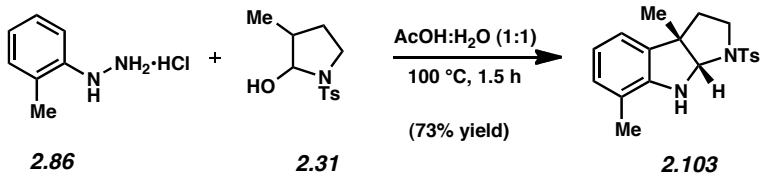
Indoline 2.100 (Table 2.5, entry 4). Purification by flash chromatography (6:1:1 hexanes:Et_2O:CH_2Cl_2) afforded indoline **2.100** as a yellow foam (71% yield). R_f 0.4 (4:1:1 hexanes:Et_2O:CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$): δ 7.73 (d, *J* = 8.0, 2H), 7.31 (d, *J* = 8.0, 2H), 6.88 (d, *J* = 7.5, 1H), 6.81 (s, 1H), 6.53 (d, *J* = 7.5, 1H), 5.00 (s, 1H), 4.70 (bs, 1H), 3.40 (ddd, *J* = 10.5, 8.0, 2.5, 1H), 3.13 (ddd, *J* = 10.5, 10.5, 6.0, 1H), 2.43 (s, 3H), 2.16 (s, 3H), 2.14 (ddd, *J* = 12.5, 6.0, 2.5, 1H), 1.77 (ddd, *J* = 12.5, 10.5, 8.0, 1H), 1.26 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 146.1, 143.6, 136.4, 133.4, 129.9, 128.9, 128.8, 127.3, 123.1, 109.7, 85.2, 54.4, 47.8, 38.1, 24.7, 21.7, 21.0; IR (film): 3395, 2962, 2924, 1617, 1598, 1494, 1334, 1156 cm^{-1}; HRMS-ESI (*m/z*) $[M+Na]^+$ calcd for $C_{19}H_{22}N_2O_2SNa$, 365.1300; found, 365.1305.



2.83 *2.31* *2.101* *2.102*

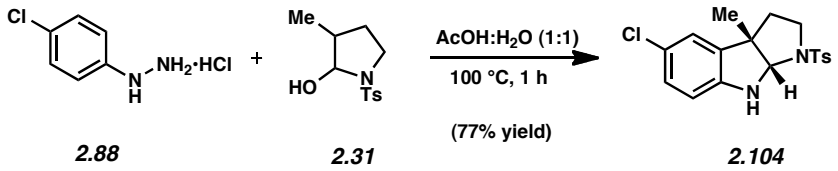
Indolines 2.101 and 2.102 (Table 2.5, entry 5). Purification by flash chromatography (5:1 hexanes:EtOAc) furnished indolines **2.101** and **2.102** as a dark red oil (55% yield, 4:3). R_f 0.3 (4:1 hexanes:EtOAc); **2.101** ^1H NMR (500 MHz, $CDCl_3$) δ 7.34 (d, *J* = 6.0, 2H), 7.33 (d, *J* = 7.5,

2H), 6.89 (d, *J* = 5.0, 1H), 6.58 (d, *J* = 7.0, 1H), 6.46 (s, 1H), 5.01 (s, 1H), 3.41 (ddd, *J* = 14.0, 4.0, 2.0, 1H), 3.15 (ddd, *J* = 10.5, 10.0, 6.5, 1H), 2.45 (s, 6H), 2.39 (ddd, *J* = 12.0, 6.0, 4.0, 1H), 2.13 (ddd, *J* = 11.0, 5.0, 1.0, 1H), 1.27 (s, 3H); **2.102** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, *J* = 5.0, 2H), 7.75 (d, *J* = 5.0, 2H), 6.98 (t, *J* = 8.0, 1H), 6.53 (d, *J* = 7.5, 1H), 6.47 (d, *J* = 7.0, 1H), 4.90 (s, 1H), 3.33 (ddd, *J* = 11.0, 6.0, 4.0, 1H), 3.21 (ddd, *J* = 10.0, 9.5, 6.0, 1H), 2.28 (s, 6H), 1.75–1.80 (m, 2H), 1.34 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.7, 148.6, 143.7, 143.6, 138.5, 136.3, 135.7, 133.7, 130.1, 129.7, 128.5, 127.4, 127.2, 122.1, 121.8, 120.2, 110.5, 107.5, 85.5, 85.1, 54.5, 53.8, 47.7, 47.5, 38.1, 36.6, 24.8, 23.3, 21.7, 21.6, 18.3; IR (film): 3392, 2960, 2867, 1618, 1596, 1450, 1334, 1156 cm^{-1}; HRMS-ESI (*m*/*z*) [M+Na]$^{+}$ calcd for $C_{19}H_{22}N_2O_2SNa$, 365.1300; found, 365.1294.



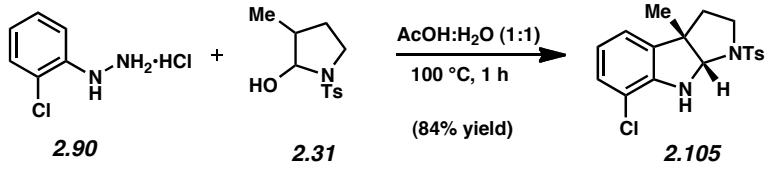
2.86 *2.31* *2.103*

Indoline 2.103 (Table 2.5, entry 6). Purification by flash chromatography (6:1:1 → 4:1:1 hexanes:Et_2O:CH_2Cl_2) afforded indoline **2.103** as a yellow foam (73% yield). R_f 0.4 (2:1:1 hexanes:Et_2O:CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.74 (d, *J* = 8.5, 2H), 7.32 (d, *J* = 8.5, 2H), 6.91 (d, *J* = 7.5, 1H), 6.86 (d, *J* = 7.5, 1H), 6.70 (t, *J* = 7.5, 1H), 5.07 (s, 1H), 4.62 (bs, 1H), 3.40 (ddd, *J* = 10.5, 8.0, 2.5, 1H), 3.13 (ddd, *J* = 10.5, 10.5, 6.0, 1H), 2.44 (s, 3H), 2.12–2.17 (m, 4H), 1.79 (ddd, *J* = 12.5, 10.5, 8.0, 1H), 1.27 (s, 3H); ^{13}C NMR (500 MHz, $CDCl_3$): δ 146.6, 143.3, 136.2, 132.2, 129.5, 129.1, 127.0, 119.5, 119.3, 118.8, 84.4, 54.3, 47.9, 37.9, 24.4, 21.3, 16.4; IR (film): 3383, 2957, 1598, 1464, 1339, 1156 cm^{-1}; HRMS-ESI (*m*/*z*) [M+Na]$^{+}$ calcd for $C_{19}H_{22}N_2O_2SNa$, 365.1300; found, 365.1303.



2.88 *2.31* *2.104*

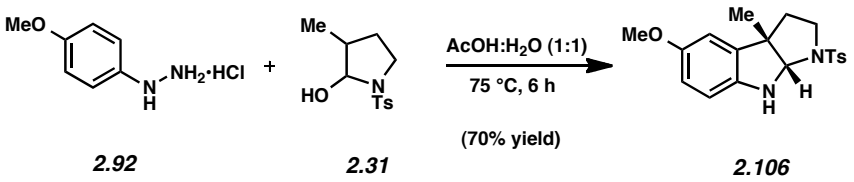
Indoline 2.104 (Table 2.5, entry 7). Purification by flash chromatography (6:1:1 hexanes:Et_2O:CH_2Cl_2) afforded indoline **2.104** as yellow solid (77% yield). R_f 0.2 (4:1:1 hexanes:Et_2O:CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$): δ 7.73 (d, *J* = 8.0, 2H), 7.32 (d, *J* = 8.0, 2H), 7.02 (d, *J* = 8.5, 1H), 6.95 (s, 1H), 6.53 (d, *J* = 8.5, 1H), 5.01 (s, 1H), 4.90 (s, 1H), 3.40 (ddd, *J* = 10.5, 8.5, 2.5, 1H), 3.14 (ddd, *J* = 10.5, 10.0, 6.0, 1H), 2.42 (s, 3H), 2.12 (ddd, *J* = 12.5, 6.0, 2.5, 1H), 1.77 (ddd, *J* = 12.5, 10.0, 8.0, 1H), 1.25 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.1, 143.9, 136.2, 135.1, 130.0, 128.4, 127.3, 123.9, 122.9, 110.5, 85.2, 54.5, 47.7, 38.0, 24.5, 21.7; IR (film): 3394, 2964, 1607, 1482, 1432, 1334, 1157, 1093 cm^{-1}; HRMS-ESI (*m*/*z*) $[M+Na]^+$ calcd for $C_{18}H_{19}ClN_2O_2SNa$, 385.0753; found, 385.0749.



2.90 *2.31* *2.105*

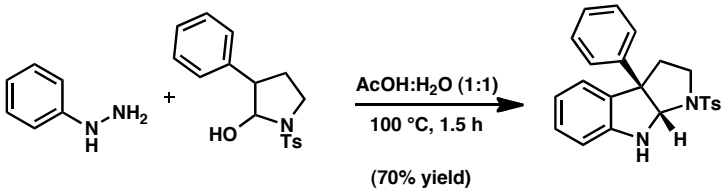
Indoline 2.105 (Table 2.5, entry 8). Purification by flash chromatography (6:1:1 → 4:1:1 hexanes:Et_2O:CH_2Cl_2) afforded indoline **2.105** as a yellow foam (84% yield). R_f 0.6 (2:1:1 hexanes:Et_2O:CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$): δ 7.74 (d, *J* = 8.5, 2H), 7.31 (d, *J* = 8.0, 2H), 7.05 (d, *J* = 8.0, 1H), 6.88 (d, *J* = 7.5, 1H), 6.67 (t, *J* = 7.5, 1H), 5.14 (s, 1H), 5.04 (s, 1H), 3.45 (ddd, *J* = 10.5, 8.0, 2.5, 1H), 3.08 (ddd, *J* = 10.5, 8.0, 2.5, 1H), 2.43 (s, 3H), 2.14 (ddd, *J* = 12.5, 6.0, 2.5, 1H), 1.84 (ddd, *J* = 12.5, 10.0, 8.0, 1H), 1.29 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.5, 143.9, 136.3, 134.8, 129.8, 128.3, 127.4, 120.8, 120.3, 114.9, 84.3, 55.6, 47.7,

38.4, 24.7, 21.7; IR (film): 3393, 2958, 1608, 1460, 1338, 1158, 1033 cm^{-1}; HRMS-ESI (*m/z*) $[M+Na]^+$ calcd for $C_{18}H_{19}ClN_2O_2SNa$, 385.0753; found, 385.0751.



2.92 *2.31* *2.106*

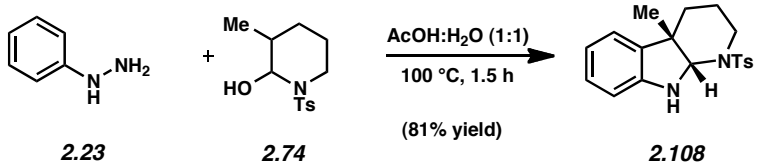
Indoline 2.106 (Table 2.5, entry 9). Purification by flash chromatography (12:1:1 → 8:1:1 benzene:Et_2O:CH_2Cl_2) afforded indoline **2.106** as a yellow foam (70% yield). R_f 0.4 (10:1:1 benzene:Et_2O:CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$): δ 7.73 (d, *J* = 8.0, 2H), 7.31 (d, *J* = 8.0, 2H), 6.63 (dd, *J* = 8.5, 2.5 2H), 6.55 (d, *J* = 8.5, 1H), 4.99 (s, 1H), 4.64 (s, 1H), 3.37 (s, 3H), 3.41 (ddd, *J* = 10.5, 8.0, 2.5, 1H), 3.13 (ddd, *J* = 10.5, 10.5, 6.0, 1H), 2.43 (s, 3H), 2.13 (ddd, *J* = 12.5, 6.0, 2.0, 1H), 1.75 (ddd, *J* = 12.5, 10.5, 8.0, 1H), 1.31 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.8, 143.4, 142.0, 136.0, 134.5, 129.6, 127.0, 112.9, 110.1, 109.3, 85.3, 55.8, 54.4, 47.4, 37.6, 24.2, 21.4; IR (film); 3382, 2974, 2832, 1499, 1435, 1226, 1032 cm^{-1}; HRMS-ESI (*m/z*) $[M+Na]^+$ calcd for $C_{19}H_{22}N_2O_3SNa$, 381.1249; found, 381.1244.



2.23 *2.70* *2.107*

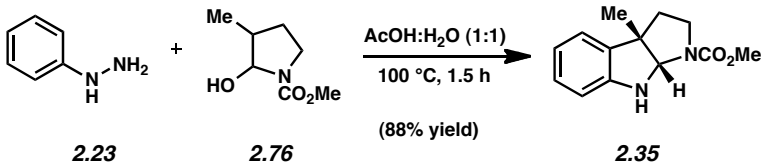
Indoline 2.107 (Table 2.6, entry 2). Purification by filtration, and rinsing with EtOAc afforded analytically pure indoline **2.107** as a white solid (70% yield); R_f 0.2 (3:1 hexanes:EtOAc); ^1H NMR (300 MHz, d_6 DMSO): δ 7.76 (d, *J* = 8.1, 2H), 7.37 (d, *J* = 7.8, 2H), 7.17–7.23 (m, 3H), 6.98–7.06 (m, 3H), 6.58–6.68 (m, 3H), 5.41 (s, 1H), 3.64 (dd, *J* = 10.2, 7.2, 1H), 2.87–2.95 (m,

1H), 2.38 (s, 3H), 2.03–2.35 (m, 1H) 1.99–2.01 (m, 1H); ^{13}C NMR (125 MHz, d_6 DMSO): δ 149.3, 143.7, 143.4, 136.0, 131.4, 129.8, 128.5, 128.3, 127.0, 126.7, 125.3, 123.7, 118.1, 109.1, 85.2, 61.5, 47.9, 37.0, 21.0; IR (neat): 3365, 2889, 1332, 1154 cm^{-1}; HRMS-ESI (*m*/*z*) [M+Na]$^+$ calcd for $C_{23}H_{22}N_2O_2SNa$, 413.1300; found, 412.1303.



2.23 *2.74* *2.108*

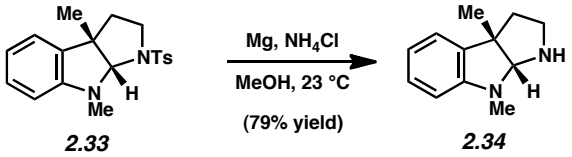
Indoline 2.108 (Table 2.6, entry 3). Purification by flash chromatography (10:1:1 → 6:2:2 hexanes:Et_2O:CH_2Cl_2) afforded indoline **2.108** as a white solid (81% yield). R_f 0.6 (3:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.75 (d, *J* = 8.5, 2H), 7.35 (d, *J* = 8.5, 2H), 7.03 (t, *J* = 7.5, 1H), 6.96 (d, *J* = 6.5, 1H), 6.75 (t, *J* = 7.5, 1H), 6.58 (d, *J* = 8.0, 1H), 5.17 (s, 1H), 4.00 (s, 1H), 3.66–3.70 (m, 1H), 3.14–3.21 (m, 1H), 2.42 (s, 3H) 1.49–1.61 (m, 4H), 1.27 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.1, 143.8, 137.5, 136.6, 130.11, 127.9, 127.3, 121.9, 119.7, 110.1, 78.0, 42.4, 40.4, 33.6, 22.4, 21.8, 20.3; IR (neat): 3351, 2962, 2930, 1610, 1454, 1336, 1148 cm^{-1}; HRMS-ESI (*m*/*z*) [M+Na]$^+$ calcd for $C_{19}H_{22}N_2O_2SNa$, 365.1300; found, 365.1291.



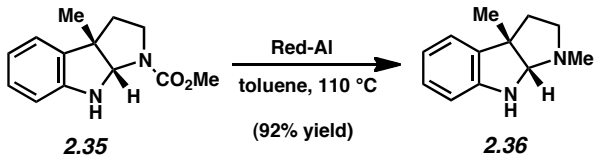
2.23 *2.76* *2.35*

Indoline 2.35 (Table 2.6, entry 4). Purification by flash chromatography (5:1 → 4:1 hexanes:EtOAc) furnished indoline **2.35** (88% yield) as an off white amorphous solid. R_f 0.3 (3:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$ @ 330K): δ 7.06–7.07 (m, 2H), 6.77 (t, *J* = 7.0,

1H), 6.60 (d, *J* = 8.0, 1H), 5.10 (s, 1H), 4.92 (br s, 1H), 3.75 (s, 3H), 3.68–3.72 (m, 1H), 3.12–3.17 (m, 1H), 2.24–2.28 (m, 1H), 2.04–2.10 (m, 1H), 1.45 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$ @ 330K): δ 155.8, 148.9, 133.7, 128.4, 122.6, 119.2, 109.5, 82.7, 53.0, 52.3, 46.0, 37.5, 24.6; IR (neat): 3352, 2956, 1698, 1609, 1456, 1382, 1113, 1056 cm^{-1}; HRMS-ESI (*m*/*z*) $[M+Na]^+$ calcd for $C_{13}H_{16}N_2O_2Na$, 255.1109; found, 255.1115.



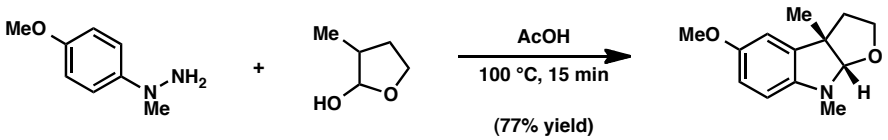
Indoline 2.34 (Figure 2.3). To a solution of indoline **2.33** (62.1 mg, 0.1700 mmol) in methanol (8.5 mL) was added magnesium turnings (413 mg, 17.00 mmol) and ammonium chloride (909 mg, 17.00mmol). The reaction was sonicated for 2 h and then filtered over celite. The filtrate was diluted with CH_2Cl_2 (50 mL), washed with sat. aq. $NaHCO_3$ (3 x 30 mL), and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$, and concentrated *in vacuo* to afford crude indoline **2.34**. Purification by flash chromatography (3% → 8% MeOH:CH_2Cl_2) afforded indoline **2.34** (25 mg, 79% yield) as an orange oil. R_f 0.1 (EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.08 (td, *J* = 7.5, 1.0, 1H), 7.02 (dd, *J* = 7.5, 1.0, 1H), 6.66 (td, *J* = 7.0, 0.5, 1H), 6.35 (d, *J* = 7.5, 1H), 4.86 (br s, 1H), 4.56 (s, 1H), 3.11 (ddd, *J* = 7.0, 7.0, 2.5, 1H), 2.87 (s, 3H), 2.78 (ddd, *J* = 10.5, 10.5, 6.0, 1H), 2.05 (ddd, *J* = 7.5, 6.0, 2.5, 1H), 1.86 (ddd, *J* = 10.5, 7.0, 2.0, 1H), 1.45 (s, 3H). Spectral data match those previously reported.[62]



2.35 *2.36*

Indoline 2.36. To a solution of indoline **2.35** (10 mg, 0.043 mmol) in toluene (2 mL) was added Red-Al (65% w/w in toluene, 134 μL, 0.431 mmol) and the resulting mixture was heated to 110 °C. After 1h, the reaction was cooled to 23 °C, and quenched with EtOAc (3 mL). The reaction mixture was poured into a solution of sat. aq. Na–K tartrate (50 mL) and EtOAc (25 mL) and stirred vigorously for 2 h. The layers were separated, and the aqueous layer was extracted with EtOAc (2 x 25 mL) and CH_2Cl_2 (25 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure to afford crude indoline **2.36**. Purification by flash chromatography (5% → 15% MeOH:CH_2Cl_2) afforded indoline **2.36** (7.5 mg, 92% yield) as an off white solid. R_f 0.1 (10% MeOH/ 90% EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.06-7.02 (m, 2H), 6.74 (t, *J* = 7.5, 6.5, 1H), 6.60 (d, *J* = 8.0, 1H), 4.40 (s, 1H), 4.0 (bs, 1H), 2.72 (ddd, *J* = 9.25, 5.5, 5.5, 1H), 2.64 (ddd, *J* = 7.5, 7.5, 7.5, 1H), 2.46 (s, 3H), 2.01 (m, 2H), 1.46 (s, 3H). Spectral data matches those previously reported.[63]

E. Formal Total Synthesis of Physovenine.

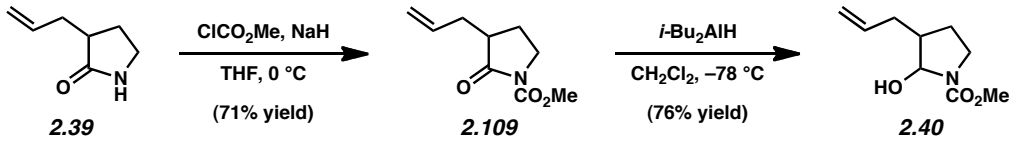


2.37 *2.29* *2.38*

Indoline 2.38. Hydrazine **2.37** was prepared[64] immediately before use. A solution of hydrazine **2.37** (85 mg, 0.559 mmol) and lactol **2.29** (57 mg, 0.559 mmol) in AcOH (3 mL) was stirred at 23 ºC for 10 min and then heated at 100 °C for 15 min. The reaction was then cooled to 23 °C

and quenched with sat. aq. $NaHCO_3$ (100 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, and concentrated *in vacuo* to afford the crude product. Purification by flash chromatography (9:1 hexanes:EtOAc) furnished indoline **2.38** as an orange oil (94 mg, 77% yield). R_f 0.8 (1:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.74 (s, 1H), 6.71 (d, *J* = 8.0, 1H), 6.34 (d, *J* = 8.5), 5.08 (s, 1H), 3.99 (ddd, *J* = 8.5, 8.5, 1.5, 1H), 3.80 (s, 3H), 3.52 (ddd, *J* = 8.5, 5.5, 5.5, 1H), 2.93 (s, 3H), 2.17 (ddd, *J* = 7.0, 4.5, 1.0, 1H), 2.09 (ddd, *J* = 12.0, 11.0, 7.5, 1H), 1.54 (s, 3H). Spectral data match those previously reported.[65]

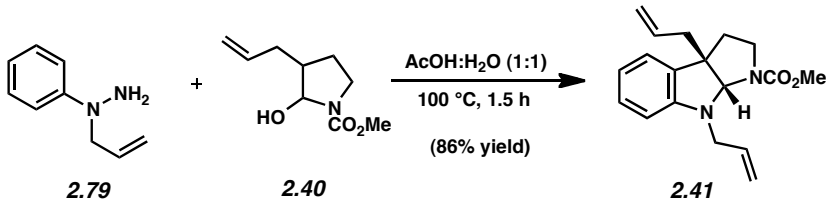
F. Total Synthesis of Debromoflustramine B



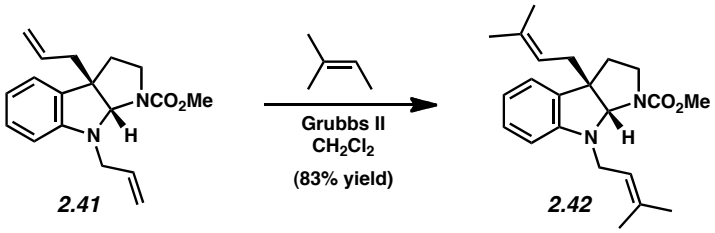
Hemiaminal 2.40. To a suspension of NaH (288 mg, 7.21 mmol) in THF (23 mL) was added a solution of known pyrrolidinone[66] **2.39** (820 mg, 6.56 mmol) in THF (10 mL) at 0 °C. Following the addition, the reaction mixture was stirred for 0.5 h, then methyl chloroformate (535 μL, 7.21 mmol) was added over 30 sec and the reaction was warmed to 23 °C. After 1 h, the reaction mixture was quenched with a solution of sat. aq. NH_4Cl (15 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (40 mL), dried over $MgSO_4$ and evaporated under reduced pressure. The resulting residue was purified by flash chromatography (3:1 → 2:1 hexanes:EtOAc) to afford intermediate **2.109** (858 mg, 71% yield) as a yellow oil. R_f 0.2 (2:1 hexanes:EtOAc); ^{1}H NMR

(500 MHz, $CDCl_3$): δ 5.76 (dddd, *J* = 20.0, 17.0, 10.0, 7.0, 1H), 5.08–5.12 (m, 1H), 5.06–5.08 (m, 1H). 3.85 (s, 3H), 3.78–3.83 (m, 1H), 3.60–3.66 (m, 1H), 2.57–2.66 (m, 2H), 2.13–2.23 (m, 2H); 1.74 (ddd, *J* = 22.5, 13.0, 4.0, 1H); ^{13}C NMR (125 MHz, CD_3CN): δ 174.9, 152.1, 134.4, 117.3, 53.3, 44.3, 42.9, 34.4, 23.3; IR (film): 1789, 1720, 1439, 1370, 1289, 1188 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_9H_{13}NO_3Na$, 206.0793; found 206.0796.

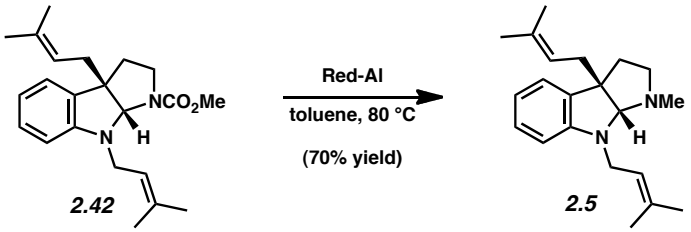
To a solution of intermediate **2.109** (730 mg, 3.98 mmol) in CH_2Cl_2 (15 mL) at –78 °C, *i*-Bu_2AlH (1.0 M solution in hexanes, 6 mL, 5.98 mmol) was added at –78 °C dropwise over 3 min. After stirring for 1 h, the reaction mixture was quenched with a solution of sat. aq. NH_4Cl (20 mL) at –78 °C. The mixture was warmed to 23 °C and transferred to a 250 mL Erlenmeyer flask, with sat. aq. Na–K tartrate (100 mL) and CH_2Cl_2 (40 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 40 mL). The combined organic layers were washed with brine (40 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The resulting residue was purified by flash chromatography (2:1:1 hexanes: CH_2Cl_2:Et_2O) to afford hemiaminal **2.40** (562 mg, 76% yield) as a yellow oil. R_f 0.2 (2:1 hexanes:EtOAc); ^1H NMR (500 MHz, $CDCl_3$): δ 5.80–5.92 (5.80–5.92) (m, 1H), 5.25 (5.42) (br s, 1H) 5.05–5.09 (4.97–5.04) (m, 2H), 3.66 (3.65) (s, 3H), 3.44–3.51 (3.39–3.43) (m, 1H), 3.22 (3.22) (ddd, *J* = 10.4, 7.1, 7.1, 1H), 2.29–2.35 (m, 1H), 2.08–2.18 (2.08–2.18) (m, 1H), 1.99–2.07 (1.99–2.07) (m, 1H), 1.89–1.94 (1.89–1.94) (m, 1H), 1.69–1.75 (1.57–1.60) (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.5 (156.5), 138.5 (137.7), 116.1 (116.9), 82.7 (87.0), 52.8 (52.8), 46.1 (45.5), 45.1 (47.0), 33.8 (37.0), 28.3 (28.9); IR (film): 3697, 3420, 2953, 1685, 1642, 1453, 1381, 1195, 1060 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_9H_{15}NO_3Na$, 208.0950; found 208.0953.



Indoline 2.41. Hemiaminal **2.40** (45 mg, 0.243 mmol) and aryl hydrazine **2.79** (47 mg, 0.291 mmol) were dissolved in a1:1 mixture of AcOH:H_2O (1.2 mL). The reaction was heated to 100 °C for 1.5 h. The reaction mixture was cooled to 23 °C, diluted with EtOAc (15 mL), quenched with sat. aq. $NaHCO_3$ (20 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford crude indoline **2.41**. Purification by flash chromatography (6:1 hexanes:EtOAc) afforded indoline **2.41** (62.4 mg, 86% yield) as a yellow oil. R_f 0.6 (2:1 hexanes:EtOAc); ^{1}H NMR: (500 MHz, $CDCl_3$ @ 330K): δ 7.05 (td, *J* = 7.5, 1.0, 1H), 7.01 (dd, *J* = 7.5, 1.0, 1H), 6.66 (t, *J* = 7.5, 1H), 6.38 (d, *J* = 8.0, 1H), 5.83 (td, *J* = 10.5, 6.0, 1H), 5.66 (td, *J* = 10.0, 7.0, 1H), 5.41 (s, 1H), 5.23 (dd, *J* = 17.0, 1.0), 5.04–5.25 (m, 3H), 4.02–4.04 (m, 2H), 3.76–3.87 (m, 1H), 3.72 (s, 3H), 3.09 (ddd, *J* = 10.0, 7.0, 7.0, 1H), 2.54 (dd, *J* = 13.5, 7.5, 1H), 2.43 (dd, *J* = 13.5, 7.5, 1H), 2.00–2.12 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$ @ 330K): δ 150.0, 134.4, 133.7, 132.1, 128.2, 122.6, 118.1, 117.2, 117.1, 115.6, 106.1, 84.4, 52.1, 48.5, 45.2, 43.1, 37.4, 37.3; IR (film): 2952, 1694, 1606, 1491, 1449, 1387, 1033 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{18}H_{22}N_2O_2Na$, 321.1579; found 321.1576.



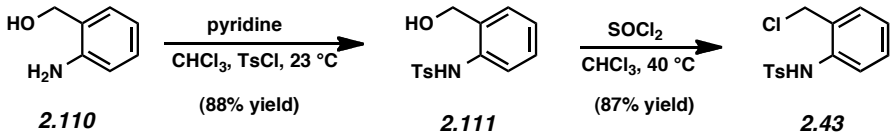
Bis(prenylated) Indoline 2.42. To a solution of Grubbs' second generation catalyst (0.168 g, 0.196 mmol) in CH_2Cl_2 (5 mL) was added, simultaneously, a solution of indoline **2.41** (0.590 g, 1.99 mmol) in CH_2Cl_2 (5 mL) and 2-methyl-2-butene (2.0 M solution in THF, 39 mL, 79.4 mmol) over 10 min. The reaction was stirred at 23 °C for 20 h, and the reaction mixture was concentrated under reduced pressure to afford crude indoline **2.42**. Purification by flash chromatography (3% → 5% EtOAc:hexanes) afforded prenylated indoline **2.42** (0.585 g, 83% yield) as a brown oil. R_f 0.8 (2:1 hexanes:EtOAc); ^{1}H NMR: (500 MHz, $CDCl_3$ @ 330K): δ 7.05 (td, *J* = 7.5, 1.0, 1H), 6.97 (d, *J* = 7.5, 1H), 6.64 (t, *J* = 7.0, 1H), 6.38 (d, *J* = 8.0, 1H), 5.32 (s, 1H), 5.19 (br t, *J* = 5.5, 1H), 5.07 (br t, *J* = 7.0, 1H), 3.97–4.14 (m, 1H), 3.60–3.80 (m, 1H), 3.73 (s, 3H), 3.07 (ddd, *J* = 8.0, 7.5, 1.5, 1H), 2.39 (d, *J* = 7.5, 2H), 1.99–2.06 (m, 2H), 1.75 (s, 3H), 1.70 (s, 3H), 1.69 (s, 4H), 1.56 (s, 3H); ^{13}C NMR: (125 MHz, $CDCl_3$ @ 330K): δ 150.1, 134.3, 133.5, 133.1, 128.0, 122.4, 121.4, 119.4, 117.1, 117.0, 106.2, 84.4, 52.0, 45.3, 44.0, 43.9, 37.0, 36.9, 25.6, 25.4, 17.8, 17.7; IR (film): 2929, 1698, 1605, 1447, 1383, 1211 cm^{-1}; HRMS-ESI (*m*/*z*) $[M + Na]^+$ calcd for $C_{22}H_{30}N_2O_2Na$, 377.2205; found 377.2205.



2.42 *2.5*

Debromoflustramine B (2.5). To a solution of bis(prenylated) indoline **2.42** (38 mg, 0.107 mmol) in toluene (1 mL) was added Red-Al (65% w/w in toluene, 100 μL, 0.321 mmol) and the resulting mixture was heated at 80 °C. After 1 h, the reaction was cooled to 23 °C, and transferred to a 125 mL Erlenmeyer flask with CH_2Cl_2 (20 mL), and quenched with a solution of sat. aq. Na–K tartrate (20 mL). The resulting mixture was vigorously stirred for 7 h. The layers were separated, and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford the crude indoline (**2.5**). Purification by flash chromatography (3:1 → 2:1 hexanes:EtOAc) afforded debromoflustramine B (**2.5**) (23.5 mg, 70% yield) as a yellow oil. R_f 0.2 (2:1 hexanes:EtOAc), ^{1}H NMR: (500 MHz, $CDCl_3$): δ 7.09 (t, *J* = 7.5, 1H), 7.02 (d, *J* = 7.0, 1H), 6.70 (t, *J* = 7.5, 1H), 6.47 (d, *J* = 8.0, 1H), 5.22 (br t, *J* = 6.0, 1H), 5.01 (br t, *J* = 7.0, 1H), 4.35 (s, 1H), 3.98 (dd, *J* = 16.0, 5.5, 1H), 3.85 (dd, *J* = 16.0, 7.0, 1H), 2.75 (ddd, *J* = 6.0, 5.5, 2.5, 1H), 2.60 (ddd, *J* = 9.5, 9.0, 6.5, 1H), 2.54 (s, 3H), 2.47–2.48 (m, 2H), 2.11 (ddd, *J* = 7.5, 7.5, 2.5, 1H), 1.95–1.99 (m, 1H), 1.76 (s, 3H), 1.75 (s, 3H), 1.70 (s, 3H), 1.63 (s, 3H). Spectral data match those previously reported.[67]

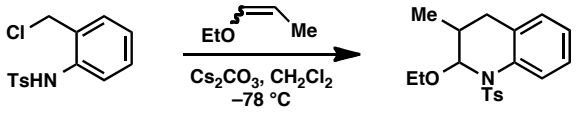
G. Synthesis of the Communesin Indoline Scaffold



Aminobenzyl chloride 2.43. Aminobenzyl chloride **2.43** was prepared following the general procedure by Fonesca et al.[68] To a solution of aminobenzyl alcohol **2.110** (1.62 g, 13.15 mmol) in $CHCl_3$ (60 mL) was added pyridine (1.17 mL, 14.46 mmol) dropwise over 2 min. The reaction was stirred for 25 min, and a solution of TsCl (2.38 g, 12.49 mmol) in $CHCl_3$ (20 mL) was added dropwise over 13 min. After 2.5 h, the reaction was quenched with sat. aq. NH_4Cl (30 mL). The layers were separated and the aqueous layer extracted with $CHCl_3$ (3 x 30 mL). The combined organic layers were then washed with brine (30 mL) and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure afforded crude aminobenzyl alcohol **2.111** (3.22 g, 88% yield), which was used in the subsequent transformation without further purification. R_f 0.3 (1:1 hexanes:EtOAc); ^1H NMR (500 MHz, $CDCl_3$): δ 7.91 (s, 1H), 7.64 (d, J = 8.0, 2H), 7.43 (d, J = 8.0, 1H), 7.24–7.27 (m, 1H), 7.21 (d, J = 8.0, 2H), 7.06–7.10 (m, 1H), 4.39 (s, 2H), 2.38 (s, 3H). Spectral data match those previously reported.[38]

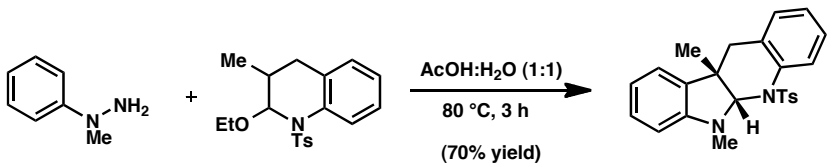
To a solution of thionyl chloride (981 μL, 13.93 mmol) in $CHCl_3$ (5 mL), was added a solution of benzyl alcohol **2.111** (3.22 g, 11.6 mmol) in $CHCl_3$ (60 mL) over 1 min. The reaction was heated to 40 °C for 11 h, cooled to 23 °C, then poured into ice water (30 mL). The layers were separated and the aqueous layer was extracted with $CHCl_3$ (3 x 40 mL). The combined organic layers were washed with brine (30 mL), and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure afforded crude chloroaniline **2.43** (2.98 g, 87% yield) as a brown solid, which was used in the subsequent transformation without further purification. R_f 0.5 (3:1

hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70 (d, *J* = 8.0, 2H), 7.39 (d, *J* = 8.5, 1H), 7.34 (t, *J* = 8.0, 2H), 7.26–7.30 (m, 2H), 7.22 (td, *J* = 7.5, 1.0, 1H), 6.84 (bs, 1H), 4.31 (s, 2H), 2.40 (s, 3H). Spectral data match those previously reported.[68]



2.43 (70% yield) *2.44*

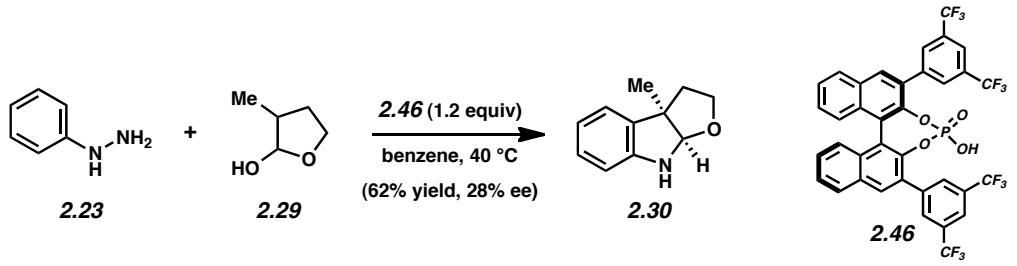
***N,O*-acetal 2.44.** *N,O*-acetal **2.44** was prepared following the general procedure described by Corey et al.[38] To a mixture of Cs_2CO_3 (716 mg, 2.20 mmol), ethyl 1-propenyl ether (mixture of *cis* and *trans*) (975 μL, 8.79 mmol) in CH_2Cl_2 (3 mL) at –78 °C, was added a solution of chloroaniline **2.43** (260 mg, 0.879 mmol) in CH_2Cl_2 (7.5 mL) over 24 min via syringe pump. The reaction stirred for 9 min at –78 °C, and then warmed to 23 °C for 5 h. The reaction was filtered through celite and the solvent was evaporated under reduced pressure. Purification by flash chromatography (5:1 hexanes:EtOAc) afforded *N,O*-acetal **2.44** as an off-white solid (212 mg, 70% yield, 77:23 mixture of diastereomers). R_f 0.6 (3:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.88 (7.88) (d, *J* = 8.0, 1H), 7.48 (7.48) (d, *J* = 8.0, 2H), 7.41 (7.64) (d, *J* = 8.0, 1H), 7.17 (7.15) (d, *J* = 8.0, 2H), 7.03 (7.24) (t, *J* = 7.5, 1H), 6.97 (7.11) (t, *J* = 7.5, 1H), 5.43 (5.23) (d, *J* = 2.5, 1H), 3.77 (3.96) (dq, *J* = 10.0, 7.0, 3.0), 3.62 (3.70) (dq, *J* = 10.0, 7.0, 3.0) 2.57 (2.60) (d, *J* = 12.5, 1H), 2.48 (2.45) (d, *J* = 6.5, 1H), 2.35 (2.36) (s, 3H), 1.47–1.54 (1.83–1.90) (m, 1H), 1.12 (1.21) (t, *J* = 7.5, 3H), 1.01 (d, *J* = 7.0, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.5 (136.8), 136.4 (134.9), 133.5 (134.6), 129.4 (129.2), 129.0 (128.8), 127.2 (127.2), 126.9 (126.9), 126.1 (126.2), 124.3 (123.8), 87.2 (91.8), 63.2 (63.2), 39.2 (39.2), 32.2 (32.2), 30.5 (30.5), 21.4 (19.3), 17.3 (17.3), 14.5 (14.8); IR (neat): 2973, 2924, 2878, 1598, 1490, 1456, 1379, 1332, 1158, 1088 cm^{-1}; HRMS-ESI (*m/z*) $[M+Na]^+$ calcd for $C_{19}H_{23}NO_3SNa$, 368.1296; found, 368.1289.



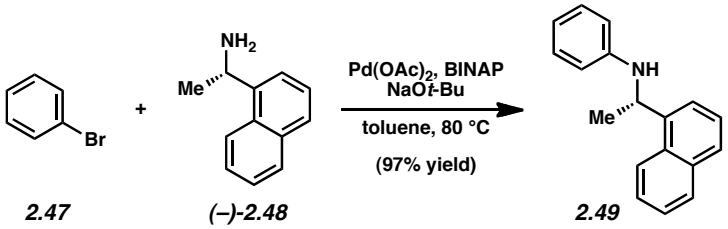
2.26 *2.44* *2.45*

Indoline 2.45. *N,O*-acetal **2.44** (68.7 mg, 0.199 mmol) was dissolved in a 1:1 mixture of AcOH and H_2O (1.3 mL). Aryl hydrazine **2.26** (22.5 μL, 0.195 mmol) was then added and the reaction was heated at 80 °C for 3 h. The reaction was allowed to cool to 23 °C, and then diluted to a volume of 20 mL with EtOAc. The reaction was quenched with sat. aq. $NaHCO_3$ (20 mL), and the layers were separated. The resulting aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, and concentrated *in vacuo* to afford the crude product. Purification by flash chromatography (12:1:1 hexanes:Et_2O:CH_2Cl_2) afforded indoline **2.45** as a white solid (55 mg, 70% yield). R_f 0.8 (2:1:1 hexanes:Et_2O:CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): 7.53 (d, *J* = 8.0, 1H), 7.45 (d, *J* = 8.0, 2H), 7.21 (d, *J* = 8.0, 2H), 7.10 (t, *J* = 7.5, 1H), 6.97 (t, *J* = 7.5, 1H), 6.86 (t, *J* = 7.5, 1H), 6.76 (d, *J* = 7.0, 2H), 6.72 (d, *J* = 7.0, 1H), 6.44 (t, *J* = 7.0, 1H), 5.63 (s, 1H), 2.96 (s, 3H), 2.49 (d, *J* = 14.5, 1H), 2.41 (s, 3H), 1.59 (d, *J* = 14, 1H), 1.26 (s, 3H). Spectral data match those previously reported.[30]

H. Access to Enantioenriched Indoline Products

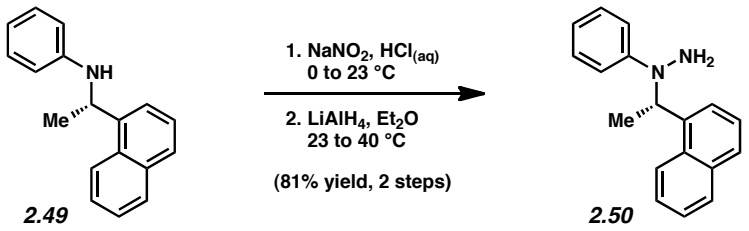


Indoline 2.30. Phosphoric acid **2.46** (70 mg, 0.094 mmol) was added to a solution of lactol **2.29** (7.7 mg, 0.075 mmol), phenyl hydrazine **2.23** (8.1 mg, 0.075 mmol) in benzene (0.40 mL). The reaction was stirred at 40 °C for 36 h. The reaction mixture was cooled to 23 °C and purified by flash chromatography (5:1 hexanes:EtOAc) to furnish furoindoline **2.30** (8.0 mg, 62% yield, 28% ee). $[\alpha]_D^{23.8}$ +16.0 (*c* 0.01, $CHCl_3$), SFC (CHIRALPAK AS-H, CO_2/MeOH = 9/10, flow 1.5 mL/min, at 23 °C, detection at 254 nm) t_R 3.06 min (major) and t_R 4.43 min (minor). The enantiomer formed in excess is believed to have the *(R,R)* configuration based on correlation to known data.[69]



Aniline 2.49. To a mixture of racemic BINAP (0.393 g, 0631 mmol), palladium acetate (0.129 g, 0.573 mmol) and sodium *tert*-butoxide (0.771 g, 8.02 mmol) was added α-naphthylethyl amine (–)-**2.48** (1.11 mL, 6.89 mmol), bromobenzene (**2.47**) (0.602 mL, 5.73 mmol) and toluene (23 mL). The mixture was deoxygenated by sparging with N_2 for 1 h and then heated at 80 °C for 12 h. After cooling to 23 °C, the reaction mixture was diluted with Et_2O (23 mL), filtered over celite and concentrated under reduced pressure. The crude product was purified by flash

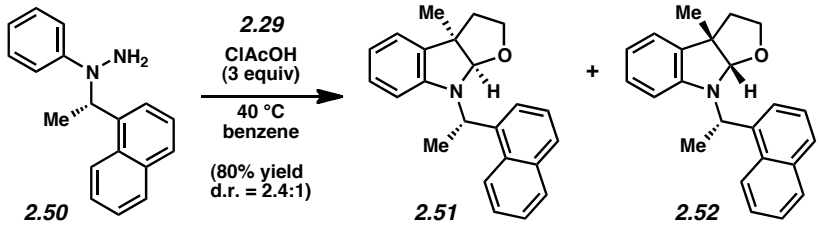
chromatography (5:1 hexanes:EtOAc) to afford aniline **2.49** (1.65 g, 97% yield) as a yellow oil. R_f 0.4 (hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.5, 1H), 7.93 (d, *J* = 8.0, 1H), 7.77 (d, *J* = 8.5, 1H), 7.68 (d, *J* = 7.0, 1H), 7.53–7.61 (m, 2H), 7.43 (t, *J* = 8.0, 1H), 7.09 (t, *J* = 8.0, 2H), 6.66 (t, *J* = 7.5, 1H), 6.51 (d, *J* = 8.0, 2H), 5.32 (q, *J* = 12.0, 6.5, 1H), 4.18 (s, 1H), 1.69 (d, *J* = 6.5, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.3, 140.1, 134.3, 130.9, 129.4, 127.7, 126.3, 126.1, 125.6, 122.8, 122.8, 122.5, 117.4, 113.4, 49.7, 23.8; IR (film): 3707, 3411, 2973, 2845, 1601, 1503, 1318, 1257, 1055 cm^{-1}; HRMS-ESI (*m/z*) $[M+H]^+$ calcd for $C_{18}H_{18}N$, 248.1439; found 248.1435; $[\alpha]_D^{24.1}$ +150.8 (*c* 0.01, $CHCl_3$).



Aryl Hydrazine 2.50. A solution of sodium nitrite (0.597 g, 8.65 mmol) in water (5 mL) was added dropwise to a mixture of aniline **2.49** (1.07 g, 4.32 mmol) and concentrated hydrochloric acid (37% yield, 1 mL) at 0 °C. The reaction mixture was warmed to 23 °C, stirred for 12 h, poured into water (50 mL) and then extracted with benzene (3 x 20 mL). The combined organic layers were dried over Na_2SO_4 and evaporated to dryness to afford the crude nitrosylated product as an orange oil. The crude product was used in the subsequent step without further purification.

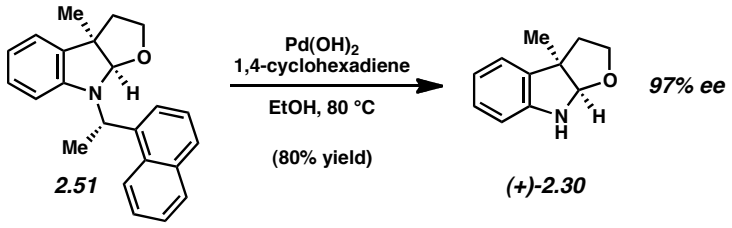
To a solution of the crude product in diethyl ether (45 mL) was added $LiAlH_4$ (0.343 g, 9.03 mmol) and the reaction was heated at reflux for 3.5 h. The reaction vessel was cooled to 23 °C and quenched by the dropwise addition of sat. aq. NH_4Cl until gas evolution subsided (ca. 15 mL). The reaction mixture was filtered over Celite, washed with ether (3 x 15 mL), and dried over Na_2SO_4, and evaporated to dryness. Purification by flash chromatography (3:2

benzene:hexanes → 4:1 benzene:EtOAc) afforded aryl hydrazine **2.50** (0.915 g, 81% yield, 2 steps) as a light yellow foam. R_f 0.5 (3:1 hexanes:EtOAc) ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07, (d, *J* = 8.5, 1H), 7.89 (d, *J* = 7.5, 1H), 7.84 (d, *J* = 8.0, 1H), 7.59 (d, *J* = 7.5, 1H), 7.45–7.52 (m, 3H), 7.34 (t, *J* = 9.0, 2H), 7.23 (d, *J* = 8.0, 2H), 6.84 (t, *J* = 7.5, 2H), 5.84 (q, *J* = 13.0, 6.5, 1H), 3.12 (s, 2H), 1.64 (d, *J* = 7.0, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.7, 136.9, 134.1, 132.1, 129.5, 128.9, 128.6, 126.7, 126.0, 125.3, 125.1, 124.0, 118.1, 113.4, 54.9, 12.4; IR (neat): 2979, 1586, 1485, 1358, 1286, 1160 cm^{-1}; HRMS-ESI (*m/z*) $[M+H]^+$ calcd for $C_{18}H_{19}N_2$, 263.1548; found 263.1533; $[\alpha]_D^{24.4}$ –112.3 (*c* 0.01, $CHCl_3$).



Indoline Diastereomers 2.51 and 2.52. To a mixture of aryl hydrazine **2.50** (52.4 mg, 0.20 mmol), lactol **2.29** (20.6 mg, 0.20 mmol), and benzene (1 mL) was added chloroacetic acid (56.7 mg, 0.60 mmol). The resulting mixture was heated at 40 °C for 24 h. The reaction mixture was cooled to 23 °C, diluted with CH_2Cl_2 (20 mL), washed with sat. aq. $NaHCO_3$ (5 mL) and extracted with CH_2Cl_2 (10 mL). The combined organic layers were dried over $MgSO_4$ and evaporated to dryness. Purification by flash chromatography (15:1 → 10:1 hexanes:EtOAc) afforded a mixture of diastereomers as an orange solid (53.0 mg, 80% yield, 2.4:1 dr). To separate the diastereomers the mixture was repurified by flash chromatography, under the same conditions. The stereochemical configurations of **2.51** and **2.52** were inferred after the conversion of **2.51** to (+)-**2.30**. Indoline **2.51** R_f 0.5 (4:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (d, *J* = 8.0, 1H), 7.96 (d, *J* = 7.5, 1H), 7.82 (t, *J* = 8.0, 2H), 7.60 (t, *J* = 7.0, 2H),

7.56 (t, *J* = 7.5, 1H), 7.49 (t, *J* = 8.0, 1H), 7.11 (d, *J* = 7.5, 1H), 6.91 (t, *J* = 7.5, 1H), 6.03 (d, *J* = 7.5, 1H), 5.65 (s, 1H), 5.56 (q, *J* = 7.0, 1H), 4.03 (t, *J* = 8.0, 1H), 3.70–3.75 (m, 1H), 2.28 (dd, *J* = 11.5, 4.5, 1H), 2.27 (m, 1H), 1.86 (d, *J* = 6.5, 3H), 1.58 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.1, 139.4, 134.5, 133.9, 130.8, 129.1, 127.8, 127.5, 125.9, 125.8, 125.2, 123.6, 122.5, 122.4, 117.3, 106.0, 101.4, 66.7, 52.3, 51.7, 41.9, 25.8, 19.0; IR (neat): 3046, 2963, 2852, 1606, 1594, 1487, 1459, 1395, 1298, 1236, 1013 cm^{-1}; HRMS-ESI (*m/z*) [M + Na]$^+$ calcd for $C_{23}H_{23}NONa$, 352.1677; found 352.1686; $[\alpha]_D^{24.4}$ +125.4 (*c* 0.01, $CHCl_3$). Indoline **2.52**: R_f 0.5 (4:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.5, 1H), 7.90 (d, *J* = 8.0, 1H), 7.84 (d, *J* = 8.5, 1H), 7.74 (d, *J* = 7.5, 1H), 7.45–7.54 (m, 3H), 7.14 (t, *J* = 8.0, 1H), 7.10 (d, *J* = 7.0, 1H), 6.75 (d, *J* = 7.0, 1H), 6.51 (d, *J* = 7.5, 1H), 5.52 (q, *J* = 7.0, 1H), 4.69 (s, 1H), 3.93 (t, *J* = 7.5, 1H), 3.53 (ddd, *J* = 13.0, 8.5, 4.5, 1H), 2.18 (dd, *J* = 12.0, 4.5, 1H), 1.98 (ddd, *J* = 11.5, 11.5, 7.0, 1H), 1.90 (d, *J* = 6.5, 3H), 1.24 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.8, 136.3, 134.7, 133.8, 131.7, 128.7, 128.1, 128.0, 126.2, 125.5, 125.4, 124.2, 123.2, 122.7, 117.3, 105.0, 101.0, 67.0, 52.2, 49.3, 41.2, 24.7, 18.1; IR (film): 3681, 2973, 2845, 1605, 1487, 1215, 1059 cm^{-1}; HRMS-ESI (*m/z*) [M + Na]$^+$ calcd for $C_{23}H_{23}NONa$, 352.1677; found 352.1680; $[\alpha]_D^{24.2}$ –54.6 (*c* 0.01, $CHCl_3$).



Indoline (+)-2.30. Indoline **2.51** (32.9 mg, 0.1 mmol), 1,4-cyclohexadiene (80.0 mg, 1.0 mmol), palladium hydroxide (20% wt on carbon, 10.0 mg) in ethanol (1 mL) was heated at 80 °C for 6 h. The reaction mixture was cooled to 23 °C, filtered through celite, washed with CH_2Cl_2 (10 mL),

and the solvent was removed under reduced pressure. Purification by flash chromatography (5:1 hexanes:EtOAc) furnished furoindoline (+)-**2.30** (14.0 mg, 80% yield, 97% ee). $[\alpha]_D^{24.3}$ +124.5 (*c* 0.01, $CHCl_3$), SFC (CHIRALPAK AS-H, CO_2/MeOH = 9/10, flow 1.5 mL/min, at 23 °C, detection at 254 nm) t_R 3.06 min (major) and t_R 4.43 min (minor). The absolute configuration of **30** was determined based on correlation to known data.[59]

2.9 Notes and References

(1) (a) Hudlicky, T.; Reed, J. W. *The Way of Synthesis*; Wiley–VCH, Weinheim, 2007. (b) Wender, P. A.; Verman, V. A.; Paxton, T. J.; Pillow, T. H. *Acc. Chem. Res*. **2008**, *41*, 40–49.

(2) For a review of these alkaloids, see: Takano, S.; Ogasawara, K. *Alkaloids* **1989**, *36*, 225–251.

(3) Physostigmine (**2.3**) has been used to treat glaucoma, Alzheimer's disease, and myasthenia gravis. For a pertinent review, see: Triggle, D. J.; Mitchell, J. M.; Filler, R. *CNS Drug Rev*. **1998**, *4*, 87–136.

(4) (a) Carle, J. S.; Christophersen, C. *J. Am. Chem. Soc.* **1979**, *101*, 4012–4013. (b) Holst, P. B.; Anthoni, U.; Christophersen, C.; Nielsen, P. H. *J. Nat. Prod*. **1994**, *57*, 997–1000.

(5) For a pertinent review, see: Steven, A.; Overman, L. E. *Angew. Chem. Int. Ed*. **2007**, *46*, 5488–5508.

(6) (a) Nakao, Y.; Yeung, B. K. S.; Yoshida, W. Y.; Scheuer, P. J.; Kelly-Borges, M. *J. Am. Chem. Soc*. **1995**, *117*, 8271–8272. (b) Yeung, B. K. S.; Nakao, Y.; Kinnel, R. B.; Carney, J. R.; Yoshida, W. Y.; Scheuer, P. J.; Kelly-Borges, M. *J. Org. Chem.* **1996**, *61*, 7168–7173. (c) Nakao, Y.; Kuo, J.; Yoshida, W. Y.; Kelly, M.; Scheuer, P. J. *Org. Lett*. **2003**, *5*, 1387–1390. (d) Takayama, H.; Mori, I.; Kitajima, M.; Aimi, N.; Lajis, N. H. *Org. Lett.* **2004**, *6*, 2945–2948.

(7) For synthetic studies, see: (a) Newhouse, T.; Baran, P. S. *J. Am. Chem. Soc*. **2008**, *130*, 10886–10887. (b) Newhouse, T.; Lewis, C. A.; Baran, P. S. *J. Am. Chem. Soc*. **2009**, *131*, 6360–6361. (c) Marsden, S. P.; Watson, E. L.; Raw, S. A. *Org. Lett*. **2008**, *10*, 2905–2908. (d) Toumi, M.; Couty, F.; Marrot, J.; Evano, G. *Org. Lett.* **2008**, *10*, 5027–5030. (e) Espejo,

V. R.; Rainier, J. D. *J. Am. Chem. Soc.* **2008**, *130*, 12894–12895. f) Matsuda, Y.; Kitajima, M.; Takayama, H. *Org. Lett*. **2008**, *10*, 125–128.

(8) (a) Subramaniam, G.; Hiraku, O.; Hayashi, M.; Koyano, T.; Komiyama, K.; Kam, T.-S. *J. Nat. Prod*. **2007**, *70*, 1783–1789. (b) Jagetia, G.; Baliga, M. S.; Venkatesh, P.; Ulloor, J. N.; Mantena, S. K.; Genebriera, J.; Mathuram, V. J. *Pharm. Pharmacol.* **2005**, *57*, 1213–1219. (c) Ramírez, A.; García-Rubio, S. *Curr. Med. Chem*. **2003**, *10*, 1891–1915.

(9) For pertinent total syntheses, see: (a) Dounay, A. B.; Humphreys, P. G.; Overman, L. E.; Wrobleski, A. D. *J. Am. Chem. Soc.* **2008**, *130*, 5368–5377. (b) Shen, L.; Zhang, M.; Wu, Y.; Qin, Y. *Angew. Chem. Int. Ed.* **2008**, *47*, 3618–3621. (c) Jones, S. B.; Simmons, B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2009**, *131*, 13606–13607. (d) Zhang, M.; Huang, X.; Shen, L.; Qin, Y. *J. Am. Chem. Soc.* **2009**, *131*, 6013–6020.

(10) For isolation, see: (a) Verbitski, S. M.; Mayne, C. L.; Davis, R. A.; Concepcion, G. P.; Ireland, C. M. *J. Org. Chem*. **2002**, *67*, 7124–7126. For the total synthesis of (±)-**12**, see: (b) Fuchs, J. R.; Funk, R. L. *J. Am. Chem. Soc.* **2004**, *126*, 5068–5069.

(11) (a) Numata, A.; Takahashi, C.; Ito, Y.; Takada, T.; Kawai, K.; Usami, Y.; Matsumura, E.; Imachi, M.; Ito, T.; Hasegawa, T. *Tetrahedron Lett*. **1993**, *34*, 2355–2358. (b) Jadulco, R.; Edrada, R. A.; Ebel, R.; Berg, A.; Schaumann, K.; Wray, V.; Steube, K.; Proksch, P. *J. Nat. Prod.* **2004**, *67*, 78–81. For a comprehensive review, see: (c) Siengalewicz, P.; Gaich, T.; Mulzer, J. *Angew. Chem. Int. Ed.* **2008**, *47*, 8170–8176.

(12) For biological studies, see: (a) Williams, N. S.; Burgett, A. W. G.; Atkins, A. S.; Wang, X.; Harran, P. G.; McKnight, S. L. *Proc. Natl. Acad. Sci. U.S.A.* **2007**, *104*, 2074–2079. (b) Wang, G.; Shang, L.; Burgett, A. W. G.; Harran, P. G.; Wang, X. *Proc. Natl. Acad. Sci.*

U.S.A. **2007**, *104*, 2068–2073. For a review of synthetic studies, see: (c) Lachia, M.; Moody, C. J. *Nat. Prod. Rep*. **2008**, *25*, 227–253.

(13) Kam, T.-S.; Tan, S.-J.; Ng, S.-K.; Komiyama, K. *Org. Lett*. **2008**, *10*, 3749–3752.

(14) For examples of pyrrolidinoindoline and furoindoline syntheses from substituted indoles, see: (a) Depew, K. M.; Marsden, S. P.; Zatorska, D.; Zatorski, A.; Bornmann, W. G.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 11953–11963. (b) Austin, J. F.; Kim, S. G.; Sinz, C. J.; Xiao, W. J.; MacMillan, D. W. C. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5482–5487. (c) Movassaghi, M.; Schmidt, M. A. *Angew. Chem. Int. Ed.* **2007**, *46*, 3725–3728. (d) Kim, J.; Ashenhurst, J. A.; Movassaghi, M. *Science* **2009**, *324*, 238–241.

(15) For examples of pyrrolidinoindoline and furoindoline syntheses from substituted oxindoles, see: (a) Matsuura, T.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6500–6503. (b) Trost, B. M.; Zhang, Y. *J. Am. Chem. Soc.* **2006**, *128*, 4590–4591.

(16) For a preliminary communication describing this chemistry, see: Boal, B. W.; Schammel, A. W.; Garg, N. K. *Org. Lett*. **2009**, *11*, 3458–3461.

(17) For reviews, see: (a) Robinson, B. *Chem. Rev.* **1963**, *63*, 373–401. (b) Robinson, B. *Chem. Rev.* **1969**, *69*, 227–250.

(18) (a) Fischer, E.; Jourdan, F. *Ber.* **1883**, *16*, 2241–2245. (b) Fischer, E.; Hess, O. *Ber.* **1884**, *17*, 559–568.

(19) Hydrazines could be employed in either free-base form or as the hydrochloric acid salts.

(20) All lactol and hemiaminal substrates were employed as an inconsequential mixture of diastereomers.

(21) Lactols and hemiaminals have previously been employed in modifications of the Fischer indole synthesis, see: (a) Campos, K. R.; Woo, J. C. S.; Lee, S.; Tillyer, R. D. *Org. Lett.* **2004**, *6*, 79–82. (b) Brodfuehrer, P. R.; Chen, B.-C.; Sattelberg, T. R.; Smith, P. R.; Reddy, J. P.; Stark, D. R.; Quinlan, S. L.; Reid, J. G.; Thottathil, J. K.; Wang, S. *J. Org. Chem*. **1997**, *62,* 9192–9202. (c) Adachi, H.; Palaniappan, K. K.; Ivanov, A. A.; Bergman, N.; Gao, Z.-G.; Jacobson; K. A. *J. Med. Chem.* **2007**, *50*, 1810–1827.

(22) See Section 2.8.

(23) (a) Grandberg, I. I.; Zuyanova, T. I.; Afonina, N. I.; Ivanova, T. A. *Dokl. Akad. Nauk SSSR* **1967**, *176,* 583–585. For a synthesis of furoindolines, albeit in modest yield, see: (b) Grandberg, I. I.; Tokmakov, G. P. *Khim. Geterotsikl. Soedin*. **1975**, 207–210.

(24) Takano, et al., has synthesized a pyrrolidinoindoline product using an interrupted Fischer indolization reaction; see: (a) Takano, S.; Moriya, M.; Iwabuchi, Y.; Ogasawara, K. *Chem. Lett*. **1990**, 109–112. (b) Takano, S.; Ogasawara, K.; Iwabuchi, R.; Moriya, M. JP 03112989 A 19910514, 1991.

(25) For other examples, see: (a) Tsuji, R.; Nakagawa, M.; Nishida, A. *Heterocycles* **2002**, *58*, 587–593. (b) Britten, A. Z.; Bardsley, W. G.; Hill, C. M. *Tetrahedron* **1971**, *27*, 5631–5639. (c) Rosenmund, P.; Sadri, E. *Liebigs Ann. Chem.* **1979**, 927–943. (d) Rosenmund, P.; Gektidis, S.; Brill, H.; Kalbe, R. *Tetrahedron Lett.* **1989**, *30*, 61–62. (e) Nishida, A.; Ushigome, S.; Sugimoto, A.; Arai, S. *Heterocycles* **2005**, *66*, 181–185.

(26) For the use of H_2O/AcOH to facilitate the Fischer indole synthesis, see: (a) Desaty, D.; Keglević, D. *Croat. Chem. Acta* **1964**, *36*, 103–109. (b) Keglević, D.; Stojanac, N.; Desaty, D. *Croat. Chem. Acta* **1961***, 33*, 83–88.

(27) Interestingly, the reaction between *N*-methylphenylhydrazine (**2.26**) and lactol **2.29** in 1:1 H_2O/AcOH leads to the desired product, albeit with significant (ca. 20–30%) formation of *NH* furoindoline **2.30**.

(28) Use of *p*-(trifluoromethyl)phenylhydrazine as a substrate afforded low yields of product.

(29) Guéritte-Voegelein, F.; Sévenet, T.; Pusset, J.; Adeline, M.-T.; Gillet, B.; Beloiel, J.-C.; Guénard, D.; Potier, P.; Rasolonjanahary, R.; Kordon, C. *J. Nat. Prod*. **1992**, *55*, 923–930.

(30) May, J. A.; Stoltz, B. M. *Tetrahedron* **2006**, *62*, 5262–5271.

(31) The *N*-sulfonyl group of pyrrolidinoindoline products could also be removed using Na_2K–SG(1), a solid-supported alkali metal reagent developed by SiGNa Chemistry, Inc.; see: Nandi, P.; Redko, M. Y.; Petersen, K.; Dye, J. L.; Lefenfeld, M.; Vogt, P. F.; Jackson, J. E. *Org. Lett.* **2008**, *10*, 5441–5444.

(32) For syntheses of **2.2**, see ref 15a and the following: (a) Kulkarni, M. G.; Dhondge, A. P.; Borhade, A. S.; Gaikwad, D. D.; Chavhan, S. W.; Shaikh, Y. B.; Nigdale, V. B.; Desai, M. P.; Birhade, D. R.; Shinde, M. P. *Eur. J. Org. Chem.* **2009**, 3875–3877. (b) Shao, Z.; Zhang, H. *Youji Huaxue* **2005**, *25*, 282–289. (c) Sunazuka, T.; Yoshida, K.; Kojima, N.; Shirahata, T.; Hirose, T.; Handa, M.; Yamamoto, D.; Harigaya, Y.; Kuwajima, I.; Omura, S. *Tetrahedron Lett.* **2005**, *46*, 1459–1461. (d) Zhang, T. Y.; Zhang, H. *Tetrahedron Lett.* **2002**, *43*, 1363–1365. (e) Morales-Ríos, M. S.; Santos-Sánchez, N. F.; Joseph-Nathan, P. *J. Nat. Prod.* **2002**, *65*, 136–141. (f) Tanaka, K.; Taniguchi, T.; Ogasawara, K. *Tetrahedron Lett.* **2001**, *42*, 1049–1052. g) ElAzab, A. S.; Taniguchi, T.; Ogasawara, K. *Org. Lett.* **2000**, *2*, 2757–2759. (h) Ishibashi, H.; Kobayashi, T.; Machida, N.; Tamura, O. *Tetrahedron* **2000**, *56*, 1469–1473. (i) Node, M.; Hao, X.-J.; Nishide, K.; Fuki, K. *Chem. Pharm. Bull.*

1996, *44*, 715–719. (j) Yu, Q. S.; Lu, B. Y. *Heterocycles* **1994**, *39*, 519–525. (k) Morales-Ríos, M. S.; Santos-Sánchez, N. F.; Fragoso-Vázquez, M. J.; Alagille, D.; Villagómez-Ibarra, J. R.; Joseph-Nathan, P. *Tetrahedron* **2003**, *59*, 2843–2853. (l) Clark, A. J.; Jones, K. *Tetrahedron* **1992**, *48*, 6875–6882. (m) Horne, S.; Taylor, N.; Collins, S.; Rodrigo, R. *J. Chem. Soc. Perkin Trans. 1* **1991**, *12*, 3047–3051. (n) Takano, S.; Moriya, M.; Ogasawara, K. *J. Org. Chem.* **1991**, *56*, 5982–5984. (o) Yu, Q.; Liu, C.; Brzostowska, M.; Chrisey, L.; Brossi, A.; Greig, N. H.; Atack, J. R.; Soncrant, T. T.; Rapoport, S. I.; Radunz, H. *Helv. Chim. Acta* **1991**, *74*, 761–766. (p) Luo, Y.; Yu, Q.; Chrisey, L.; Brossi, A. *Heterocycles* **1990**, *31*, 283–287. (q) Shishido, K.; Azuma, T.; Shibuya, M. *Tetrahedron Lett.* **1990**, *31*, 219–220. (r) Shishido, K.; Shitara, E.; Komatsu, H.; Hiroya, K.; Fukumoto, K.; Kametani, T. *J. Org. Chem.* **1986**, *51*, 3007–3011. (s) Tadamasa, O. *Tetrahedron Lett.* **1971**, *12*, 4391–4392. (t) Dale, F. J.; Robinson, B. *J. Pharm. Pharmacol.* **1970**, *22*, 889–896. (u) Longmore, R. B.; Robinson, B. *Chem. Commun.* **1967**, *32*, 2184–2192.

(33) Srivastava, S.; Ruane, P. H.; Toscano, J. P.; Sullivan, M. B.; Cramer, C. J.; Chiapperino, D.; Reed, E. C.; Falvey, D. E. *J. Am. Chem. Soc.* **2000**, *122*, 8271–8278.

(34) For syntheses of **2.5**, see ref 14d and the following: (a) Rivera-Becerril, E.; Joseph-Nathan, P.; Pérez-Álvarez, V. M.; Morales-Ríos, M. S. *J. Med. Chem.* **2008**, *51*, 5271–5284. (b) Cardoso, A. S. P.; Marques, M. M. B.; Srinivasan, N.; Prabhakar, S.; Lobo, A. M. *Tetrahedron* **2007**, *63*, 10211–10225. (c) Miyamoto, H.; Okawa, Y.; Nakazaki, A.; Kobayashi, S. *Tetrahedron Lett.* **2007**, *48*, 1805–1808. (d) López-Alvarado, P.; Caballero, E.; Avendaño, C.; Menéndez, J. C. *Org. Lett.* **2006**, *8*, 4303–4306. (e) Dix, A. V.; Meseck, C. M.; Lowe, A. J.; Mitchell, M. O. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2522–2524. (f)

Morales-Ríos, M. S.; Rivera-Becerril, E.; Joseph-Nathan, P. *Tetrahedron: Asymmetry* **2005**, *16*, 2493–2499. (g) Tan, G. H.; Zhu, X.; Ganesan, A. *Org. Lett.* **2003**, *5*, 1801–1803. (h) Cardoso, A. S.; Srinivasan, N.; Lobo, A. M.; Prabhakar, S. *Tetrahedron Lett.* **2001**, *42*, 6663–6666. (i) Morales-Ríos, M. S.; Suárez-Castillo, O. R.; Trujillo-Serrato, J. J.; Joseph-Nathan, P. *J. Org. Chem.* **2001**, *66*, 1186–1192. (j) Morales-Ríos, M. S.; Suárez-Castillo, O. R.; Joseph-Nathan, P. *J. Org. Chem.* **1999**, *64*, 1086–1087. (k) Somei, M.; Yamada, F.; Izumi, T.; Nakajou, M. *Heterocycles* **1997**, *45*, 2327–2330. (l) Jensen, J.; Anthoni, U.; Christophersen, C.; Nielsen, P. H. *Acta Chem. Scand*. **1995**, *49*, 68–71. (m) Bruncko, M.; Crich, D.; Samy, R. *J. Org. Chem.* **1994**, *59*, 5543–5549. (n) Muthusubramanian, P.; Carle, J. S.; Christophersen, C. *Acta Chem. Scand*. Ser. B **1983**, *B37*, 803–807.

(35) Khoukhi, N.; Vaultier, M.; Carrié, R. *Tetrahedron* **1987**, *43*, 1811–1822.

(36) **2.42** has previously been converted to debromoflustramine B (**2.5**) by reduction with $LiAlH_4$; see ref 34e.

(37) For the total synthesis of communesin F, see: Yang, J.; Wu, H.; Shen, L.; Qin, Y. *J. Am. Chem. Soc.* **2007**, *129*, 13794–13795.

(38) Steinhagen, H.; Corey, E. J. *Angew. Chem. Int. Ed*. **1999**, *38*, 1928–1931.

(39) Indoline **2.45** has previously been prepared by an intermolecular aza-Diels–Alder strategy; see ref 30.

(40) (a) Terada, M. *Chem. Commun.* **2008**, 4097–4112. (b) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2006**, *45*, 1520–1543.

(41) Akiyama, T.; Morita, H.; Itoh, J.; Fuchibe, K. *Org. Lett*. **2005**, *7*, 2583–2585.

(42) The enantiomer formed in excess is believed to have the (*R,R*) configuration, as depicted in Scheme 2.8, based on correlation to known data (see ref 32c).

(43) Takano has shown that a proximal stereogenic center can be used to induce diastereoselectivity in a Fischer indolization reaction; see ref 24a.

(44) Nishida has utilized **2.50** to synthesize an optically enriched pyrrolidinone, albeit in modest yield; see ref 25e.

(45) The stereochemical configurations of **2.51** and **2.52** were inferred after the conversion of **2.51** to (+)-**2.30**.

(46) **2.30** can be converted to physovenine (**2.2**) in four steps; see ref 32c.

(47) Akiyama, T.; Morita, H.; Itoh, J.; Fuchibe, K. *Org. Lett.* **2005**, *7*, 2583–2585.

(48) Schmitt, A.; Reißig, H. *Chem. Ber.* **1995**, *128*, 871–876.

(49) Walton, R.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1991**, *113*, 5791–5799.

(50) Neilsen, T.; Meldal, M. *J. Org. Chem.* **2004**, *69*, 3765–3773.

(51) Adickles, H. W.; Politzer, I. R.; Meyers, A. I. *J. Am. Chem. Soc.* **1969**, *91*, 2155–2156.

(52) Oikawa, M.; Oikawa, H.; Ichihara, A. *Tetrahedron Lett.* **1993**, *34*, 4797–4800.

(53) Feldman, K. S.; Wrobleski, M. L. *J. Org. Chem.* **2000**, *65*, 8659–8668.

(54) Dake, G. R.; Fenster, M. D.; Hurley, P. B.; Partick, B. O. *J. Org. Chem.* **2004***, 69*, 5668–5675.

(55) Morimoto, T.; Fujioka, M.; Fuji, K.; Tsutsumi, K.; Kakiuchi, K. *J. Organomet. Chem.* **2007***, 692*, 625–634.

(56) Padwa, A.; Kissel, W. S.; Eidell, C. K. *Can. J. Chem.* **2001**, *79*, 1681–1693.

(57) Filippis, A.; Pardo, D. G.; Cossy, J. *Tetrahedron* **2004**, *60*, 9756–9768.

(58) Khoukhi, N.; Vaultier, M.; Carrie, R. *Tetrahedron* **1987**, *43*, 1811–1822.

(59) Morales-Ríos, M. S.; Santos-Sánchez, N. F.; Pérez-Rojas, N. A.; Joeseph-Nathan, P. *Magn. Reson. Chem.* **2004**, *42*, 973–976.

(60) Grandberg, T. *Chem. Heterocycl. Compd. (N. Y., NY, U. S.)* **1975**, *11*, 176.

(61) Trost, B. M.; Quancard, J. *J. Am. Chem. Soc.* **2006**, *128*, 6314–6315.

(62) Mekael, M. K. G.; Heingartner, H. *Helv. Chim. Acta* **2003**, *86*, 2805–2813.

(63) Santos, P. F.; Srinivasan, N.; Almeida, P. S.; Lobo, A. M.; Prabhakar, S. *Tetrahedron* **2005**, *61*, 9147–9156.

(64) Srivastava, S.; Ruane, P. H.; Toscano, J. P.; Sullivan, M. B.; Cramer, C. J.; Chiapperino, D.; Reed, E. C.; Falvey, D. E. *J. Am. Chem. Soc.* **2000**, *122*, 8271–8278.

(65) Horne, S.; Taylor, N.; Collins, S.; Russell, R. *J. Chem. Soc., Perkin Trans. 1* **2001**, *12*, 3047–3052.

(66) Lee, H-L.; Aubé, J. *Tetrahedron* **2007**, *63*, 9007–9015.

(67) Morales-Ríos, M. S.; Suárez-Castillo, O. R.; Trujillo-Serrato, J. J.; Joeseph-Nathan, P. *J. Org. Chem.* **2001**, *66*, 1186–1192.

(68) Fonesca, M. H.; Eibler, E.; Zabel, M.; Koenig, B. *Tetrahedron: Asymmetry* **2003**, *14*, 1989–1994.

(69) Sunazuka, T.; Yoshida, K.; Kojima, N.; Shirahata, T.; Hirose, T.; Handa, M.; Yamamoto, D.; Harigaya, Y.; Kuwajima, I.; Omura, S. *Tetrahedron Lett.* **2005**, *46*, 1459–1461.

APPENDIX ONE

Spectra Relevant to Chapter Two:

Exploration of the Interrupted Fischer Indolization Reaction

Alex W. Schammel, Ben W. Boal, Liansuo Zu, Tehetena Mesganaw, and Neil K. Garg.

Tetrahedron **2010**, *66*, 4687–4695.

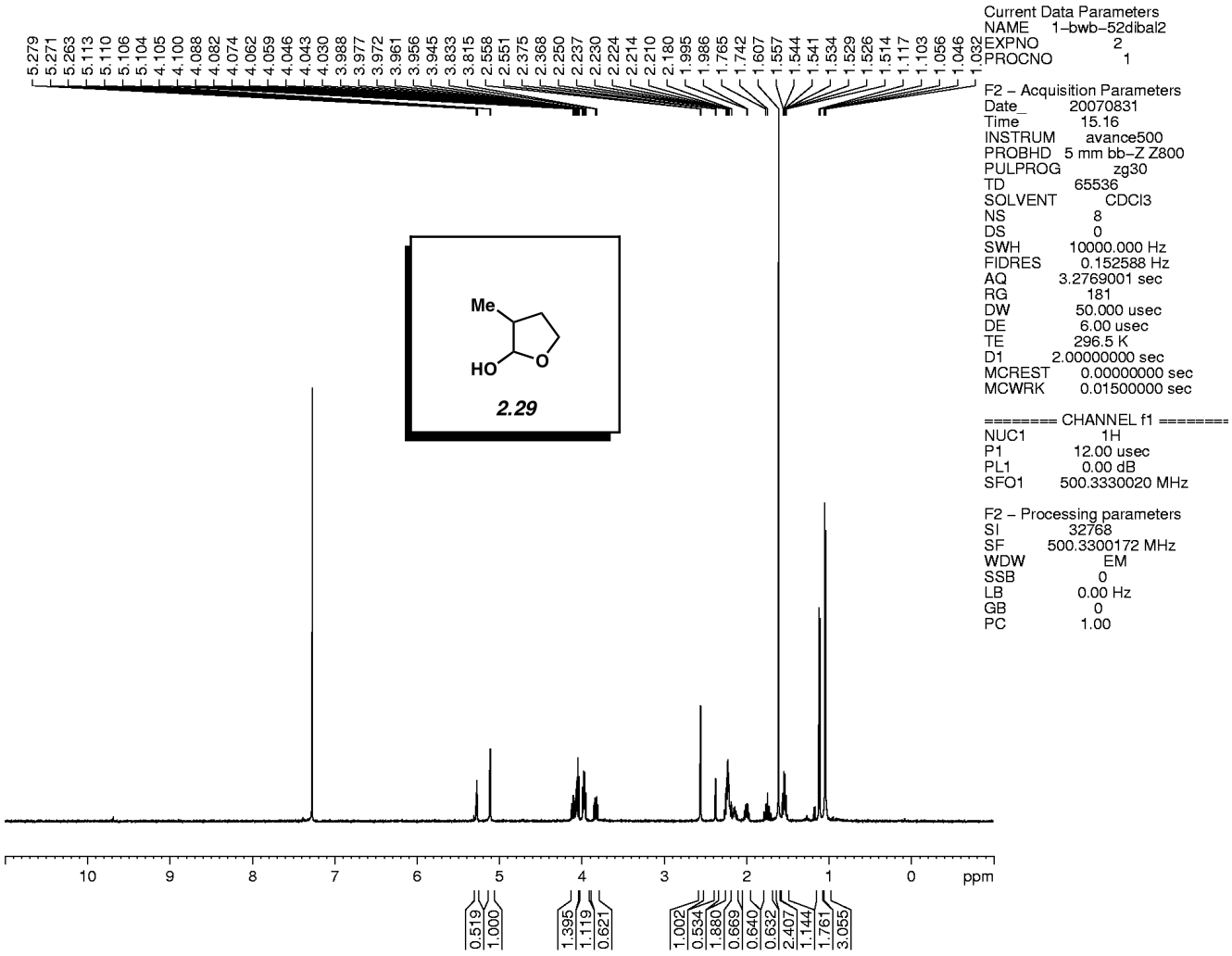


Figure A1.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **2.29**.

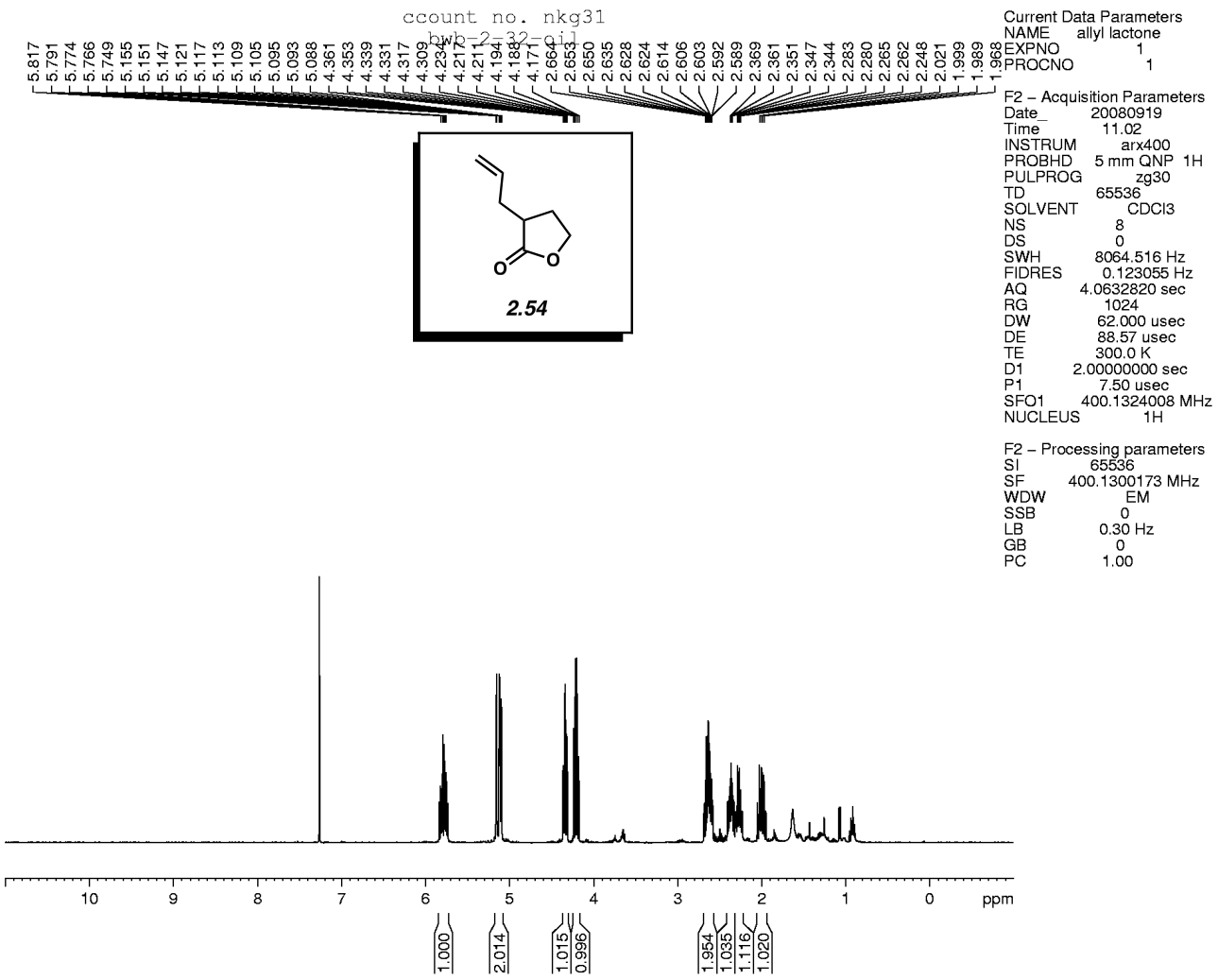


Figure A1.2 ^{1}H NMR (400 MHz, $CDCl_3$) of compound **2.54**.

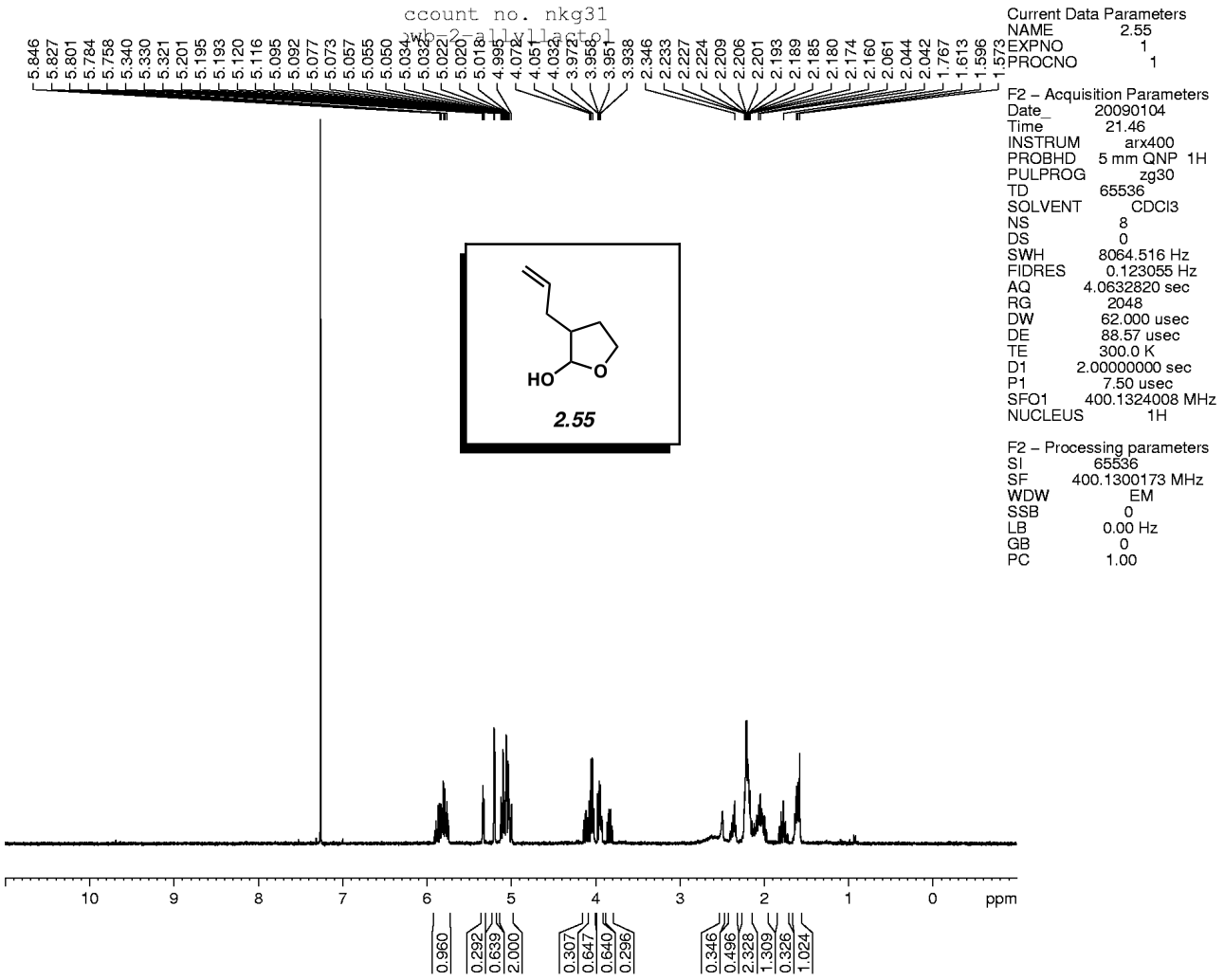


Figure A1.3 ^{1}H NMR (400 MHz, $CDCl_3$) of compound **2.55**.

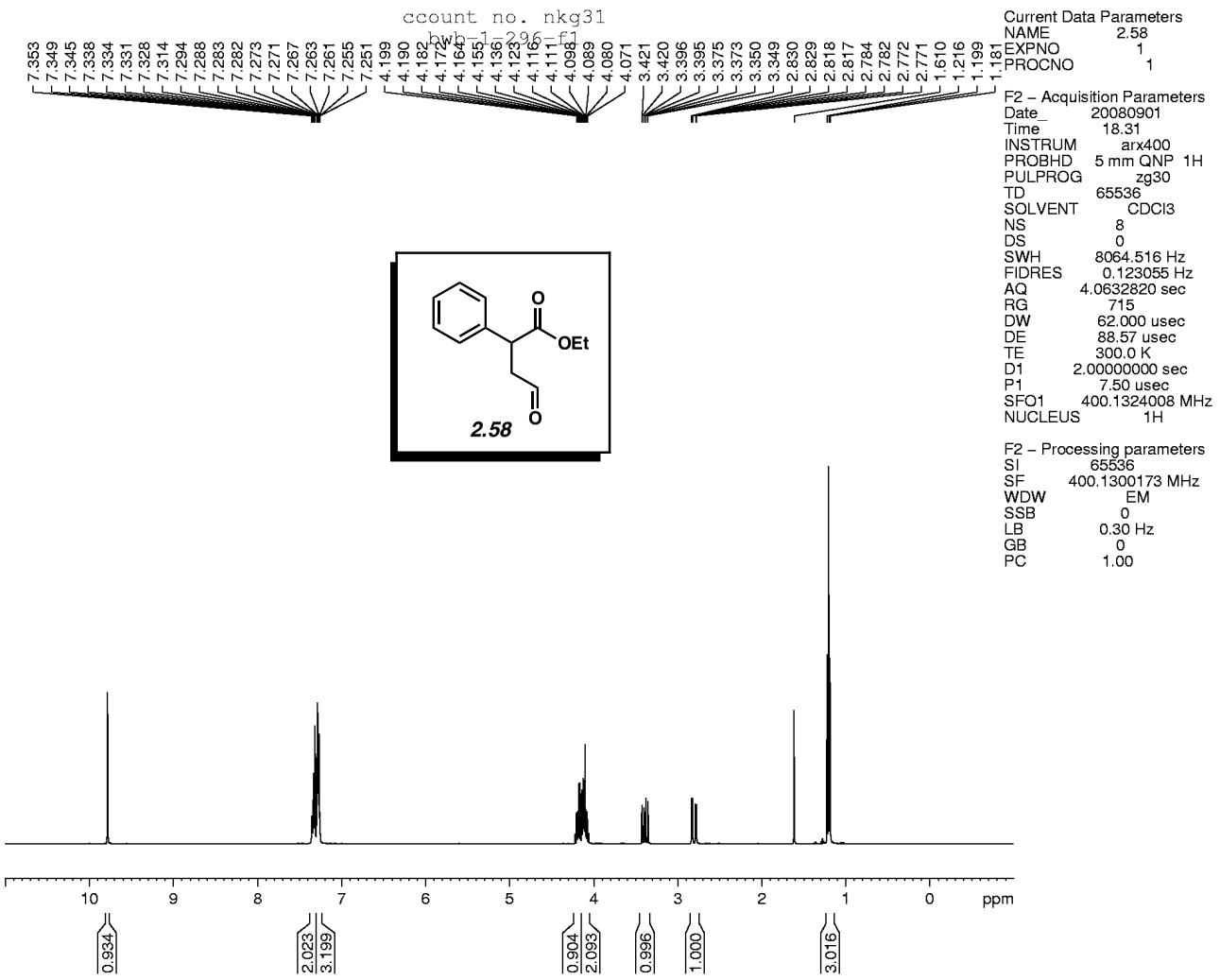


Figure A1.4 ^{1}H NMR (400 MHz, $CDCl_3$) of compound **2.58**.

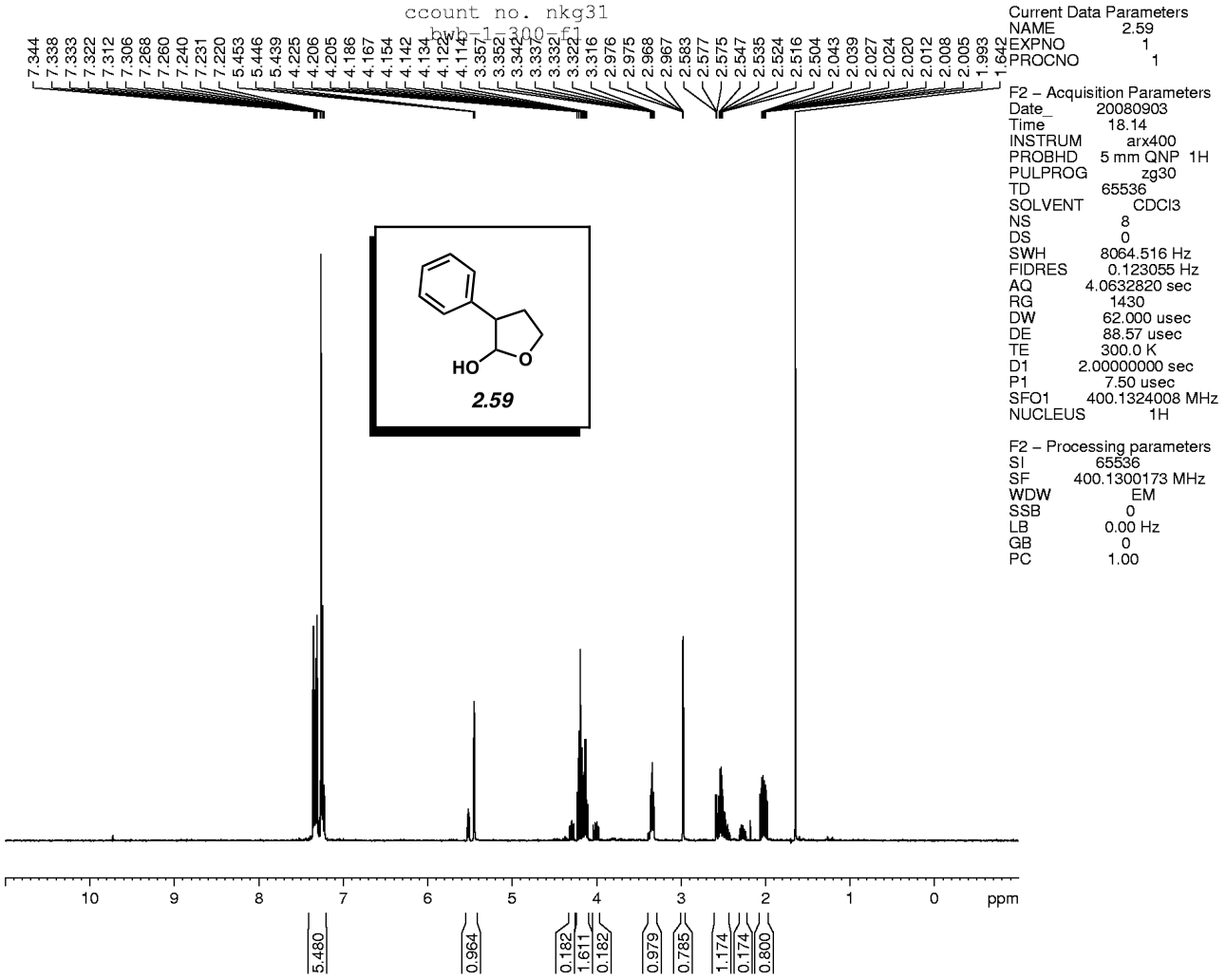


Figure A1.5 ^{1}H NMR (400 MHz, $CDCl_3$) of compound **2.59**.

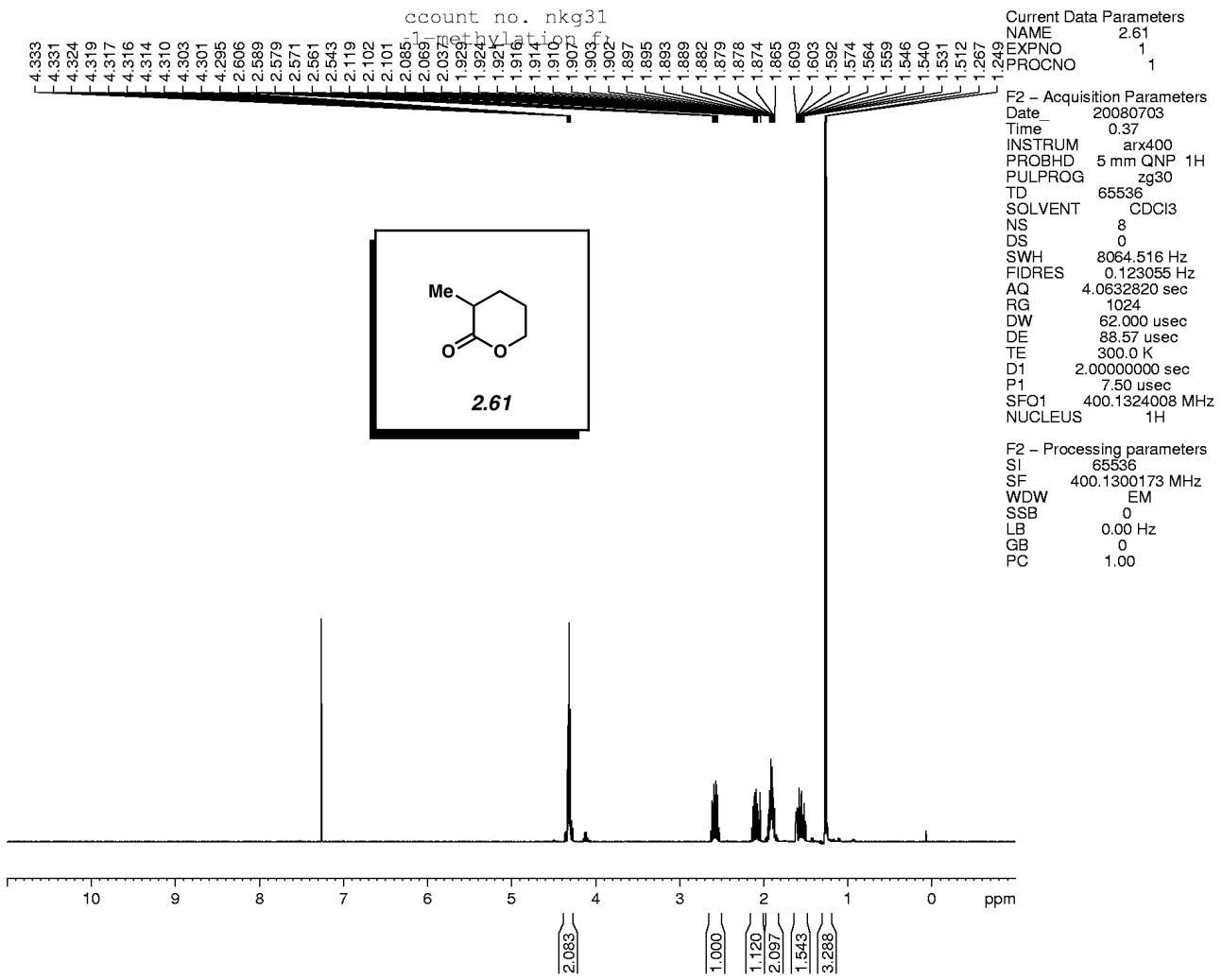


Figure A1.6 ^{1}H NMR (400 MHz, $CDCl_3$) of compound **2.61**.

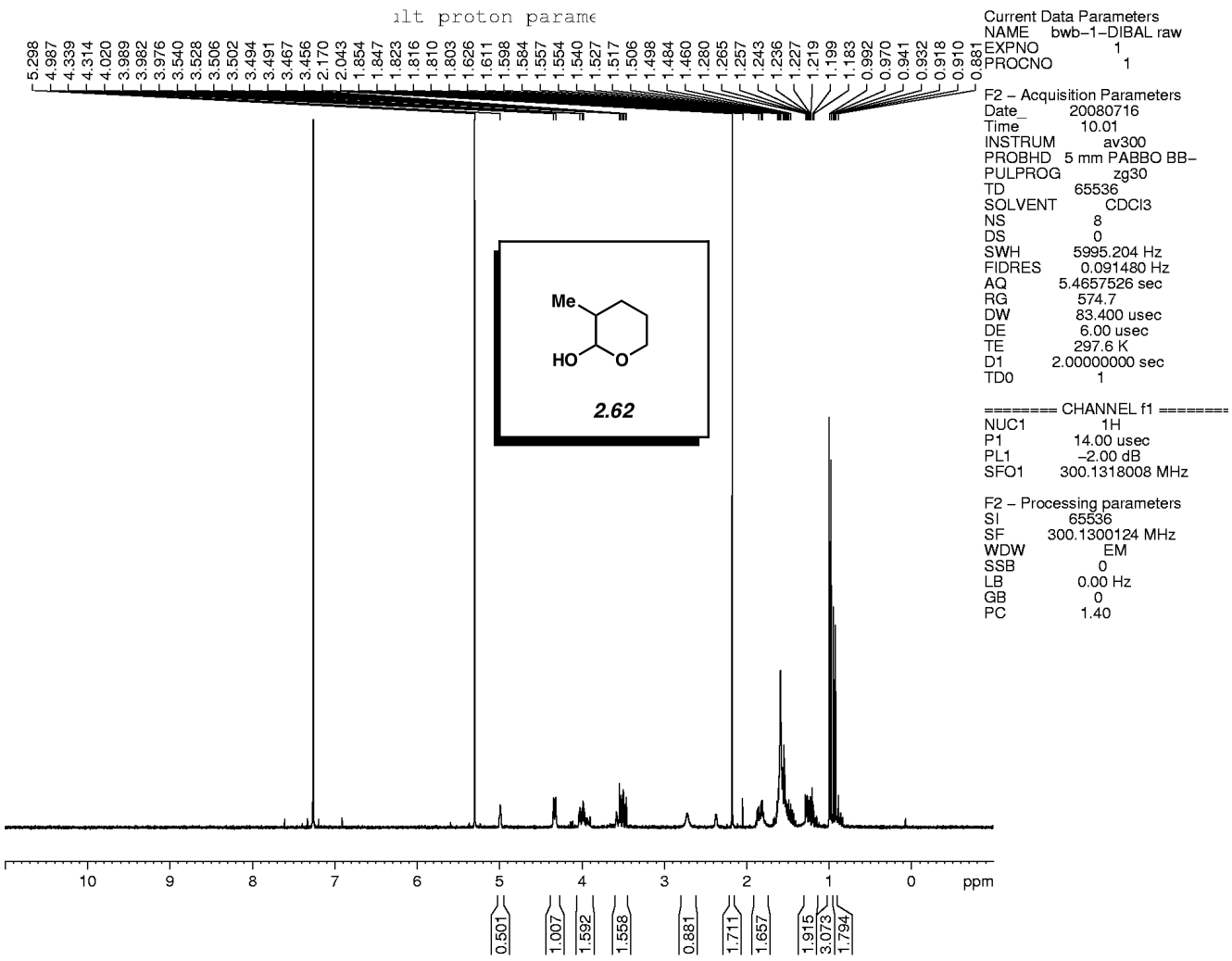


Figure A1.7 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **2.62**.

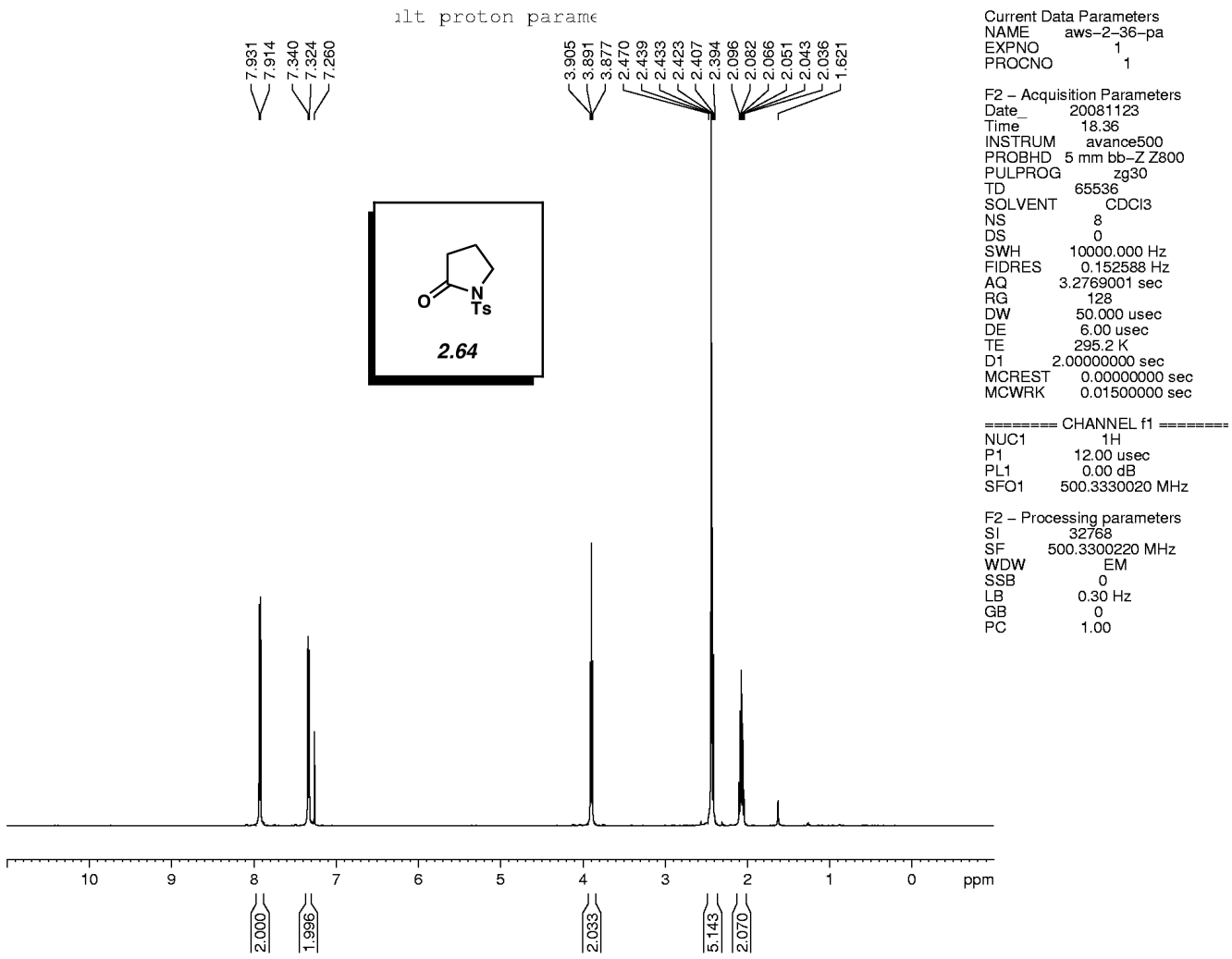


Figure A1.8 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **2.64**.

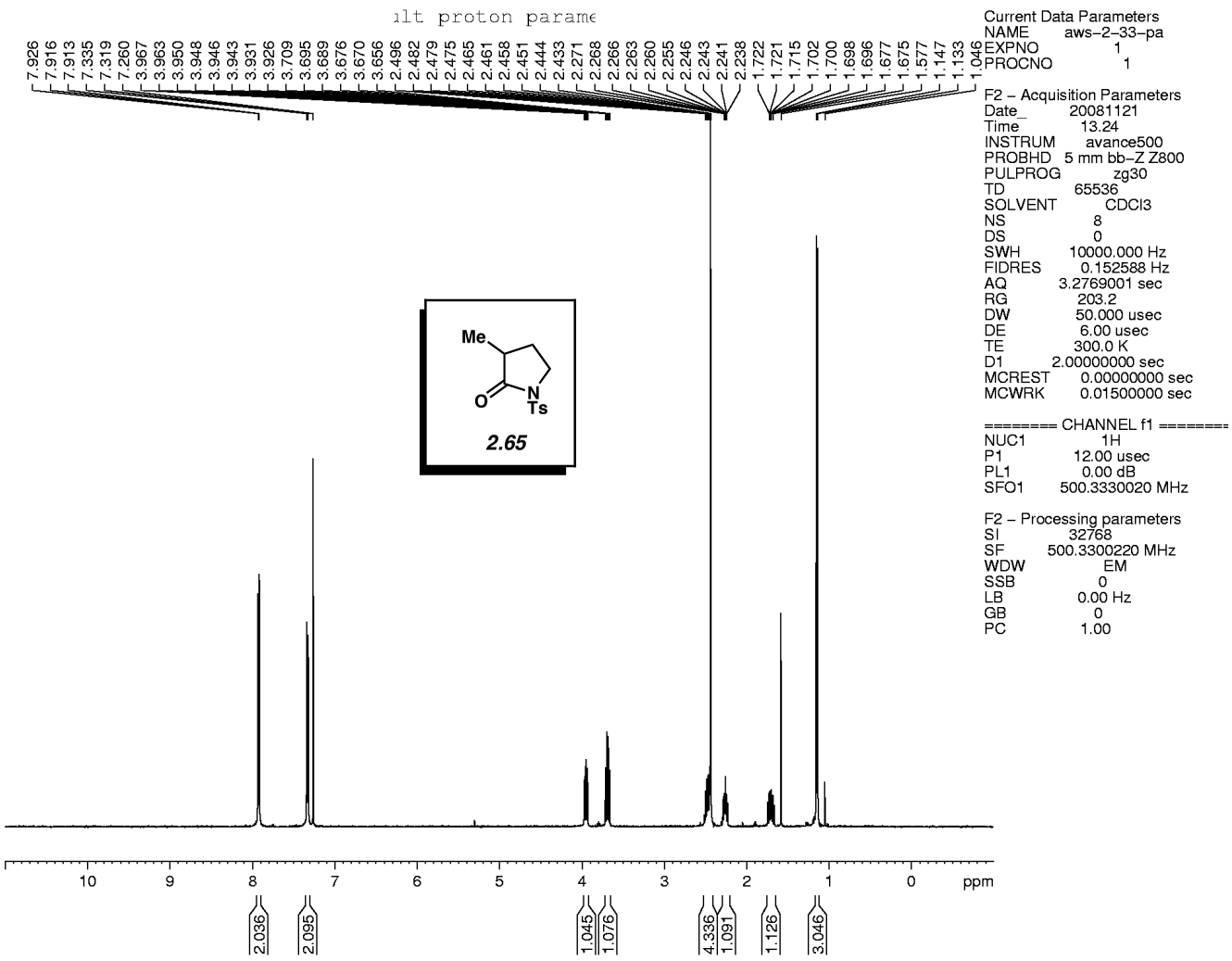


Figure A1.9 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **2.65**.

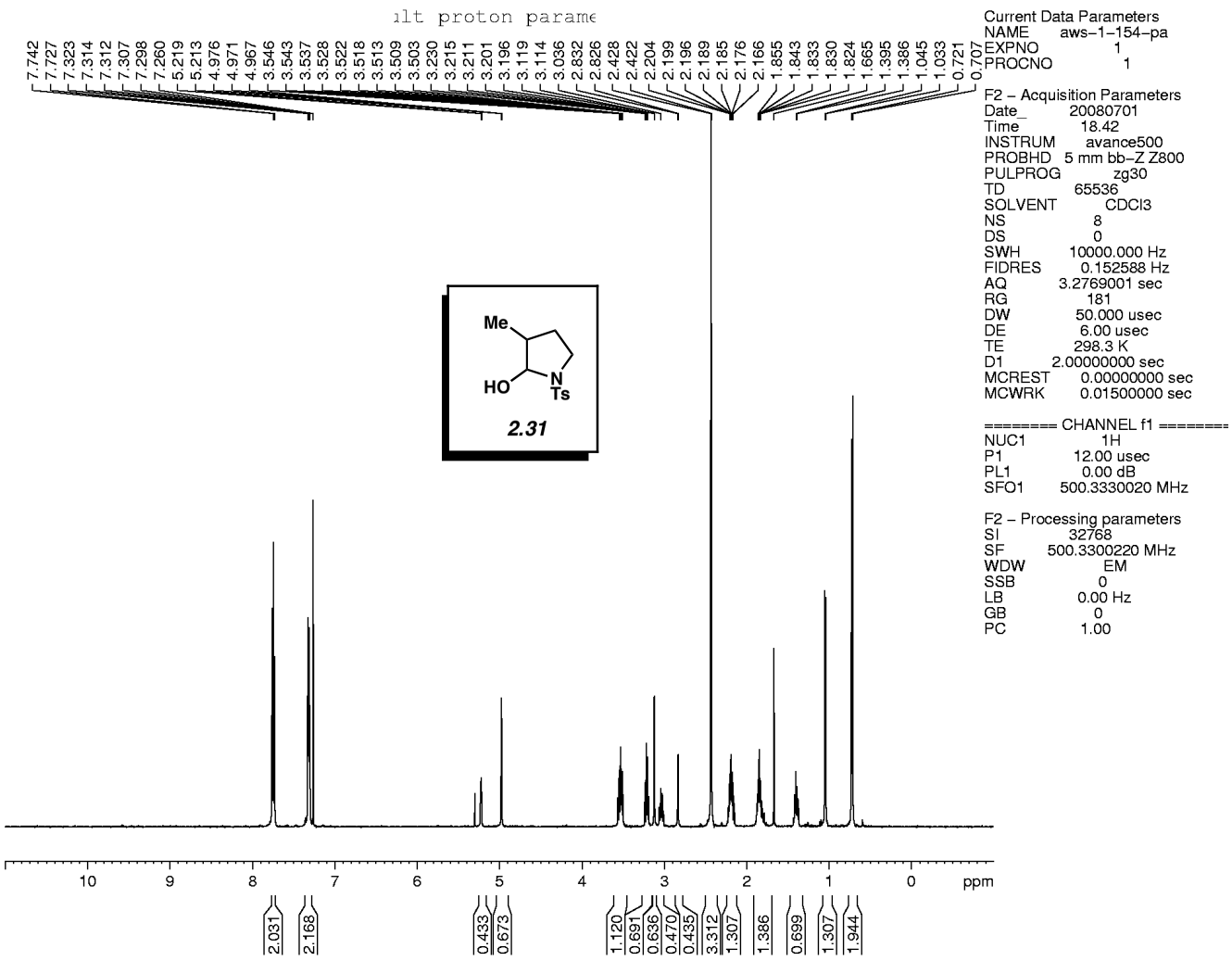


Figure A1.10 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **2.31**.

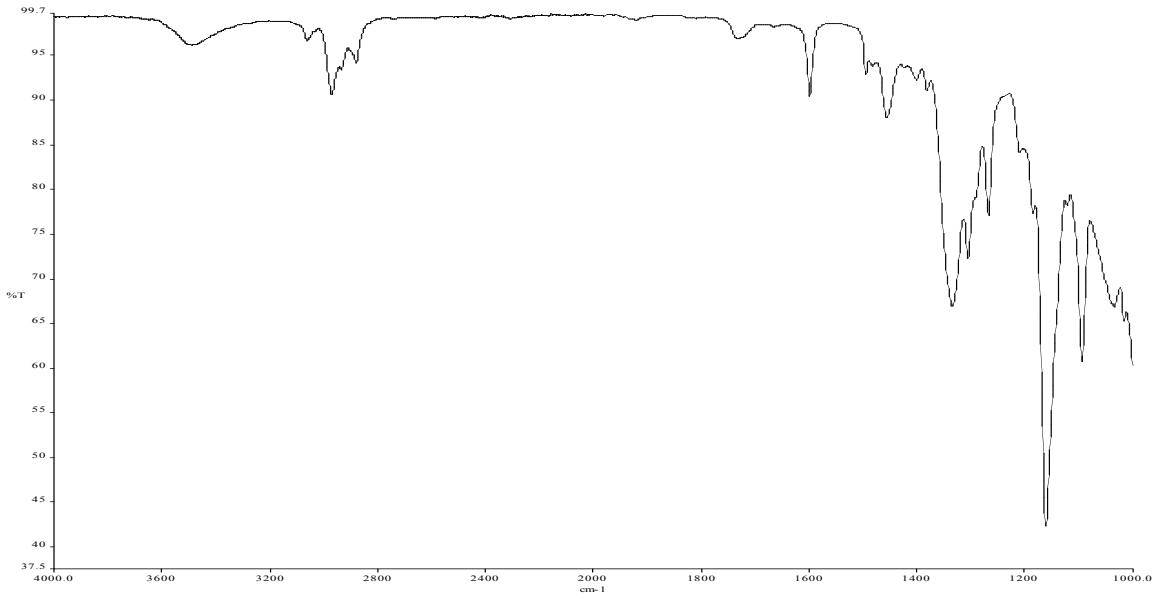


Figure A1.11 Infrared spectrum of compound **2.31**.

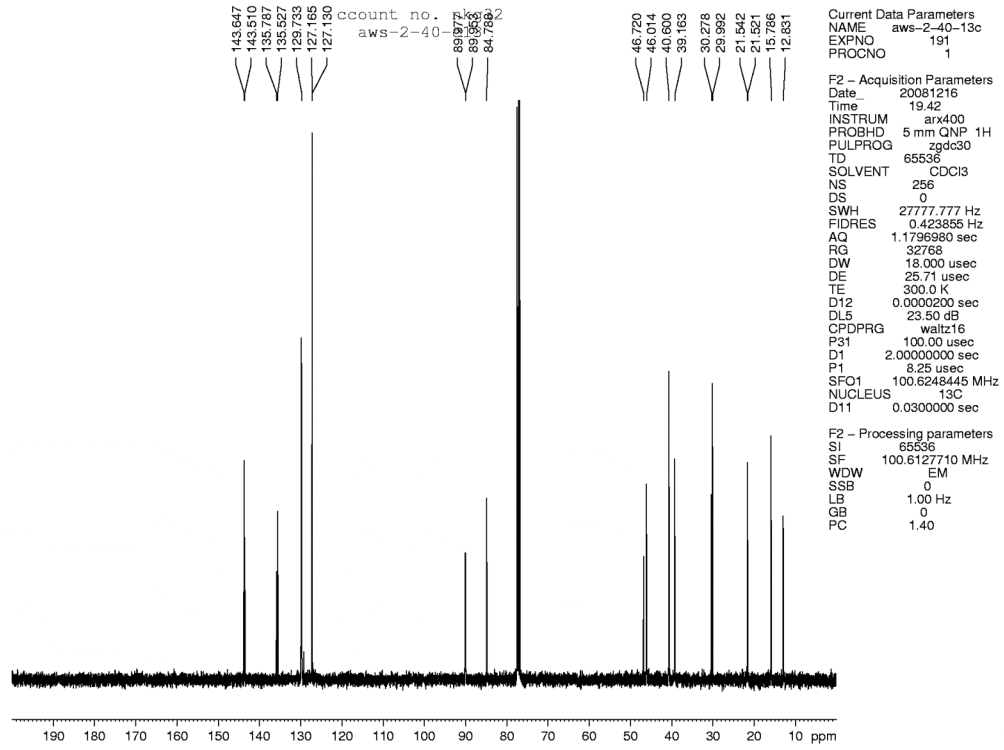


Figure A1.12 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **2.31**.

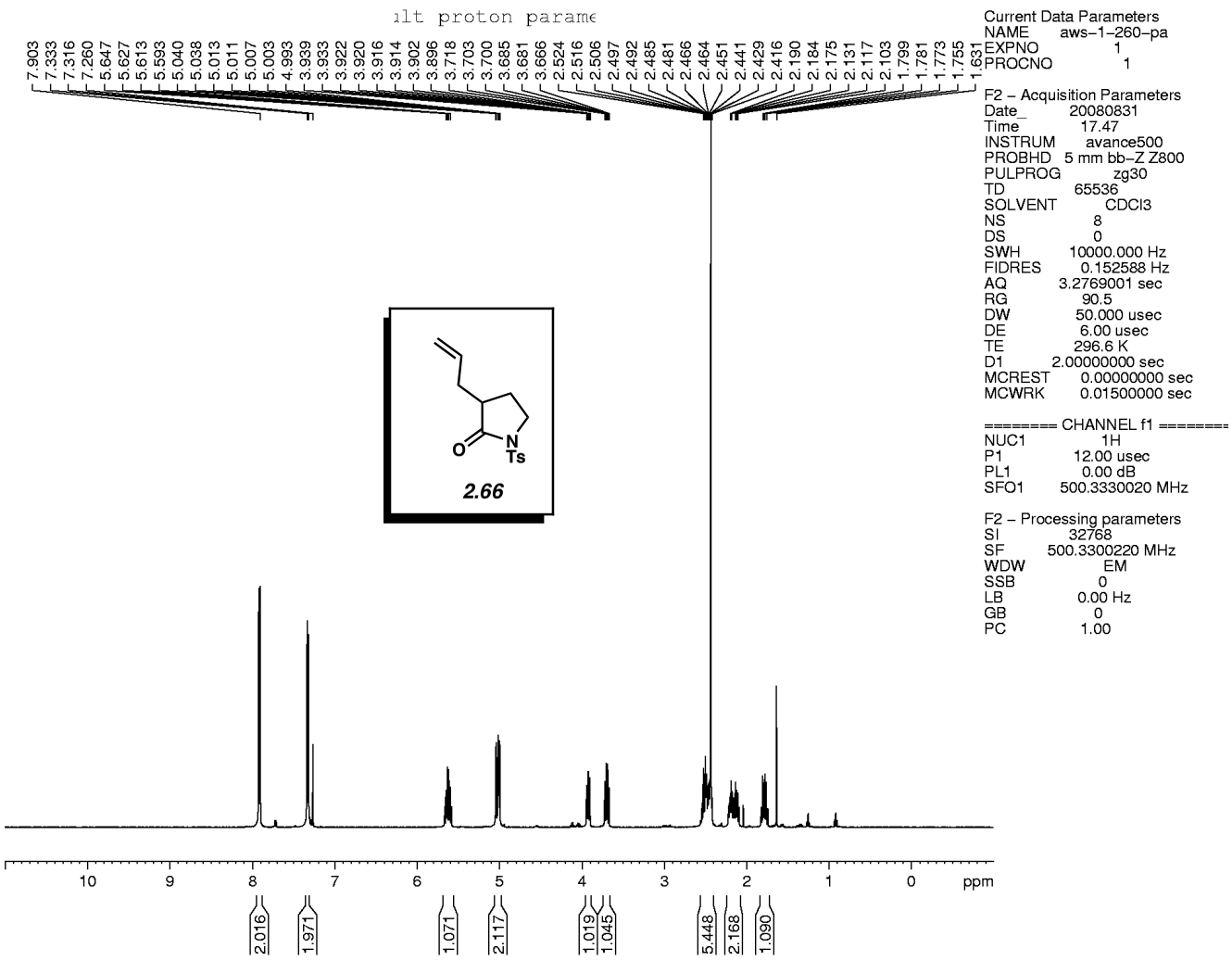


Figure A1.13 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **2.66**.

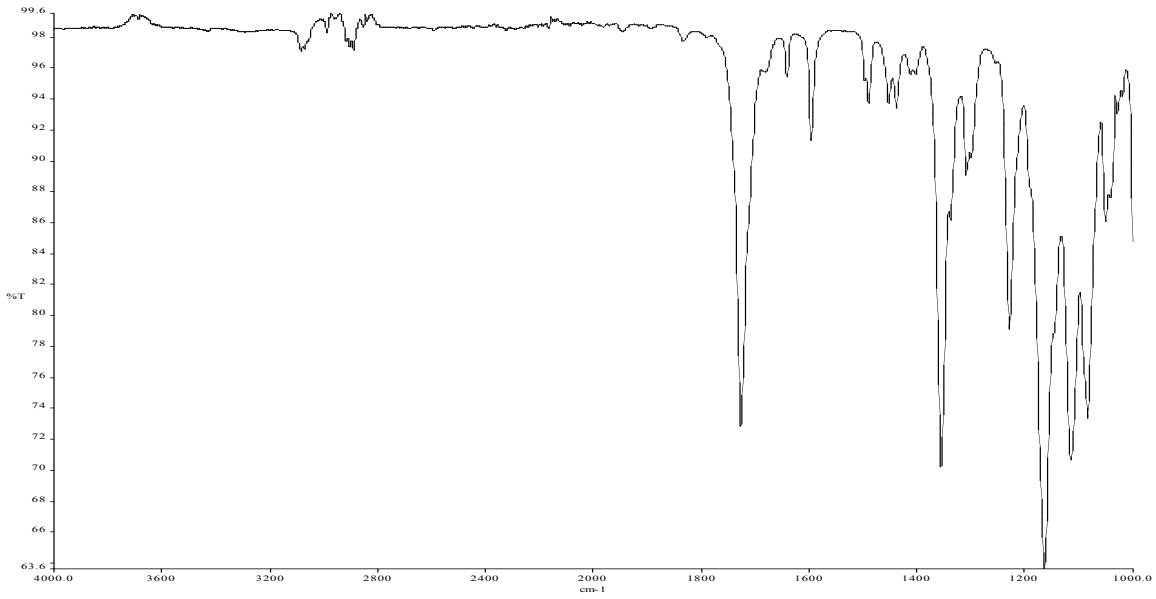


Figure A1.14 Infrared spectrum of compound **2.66**.

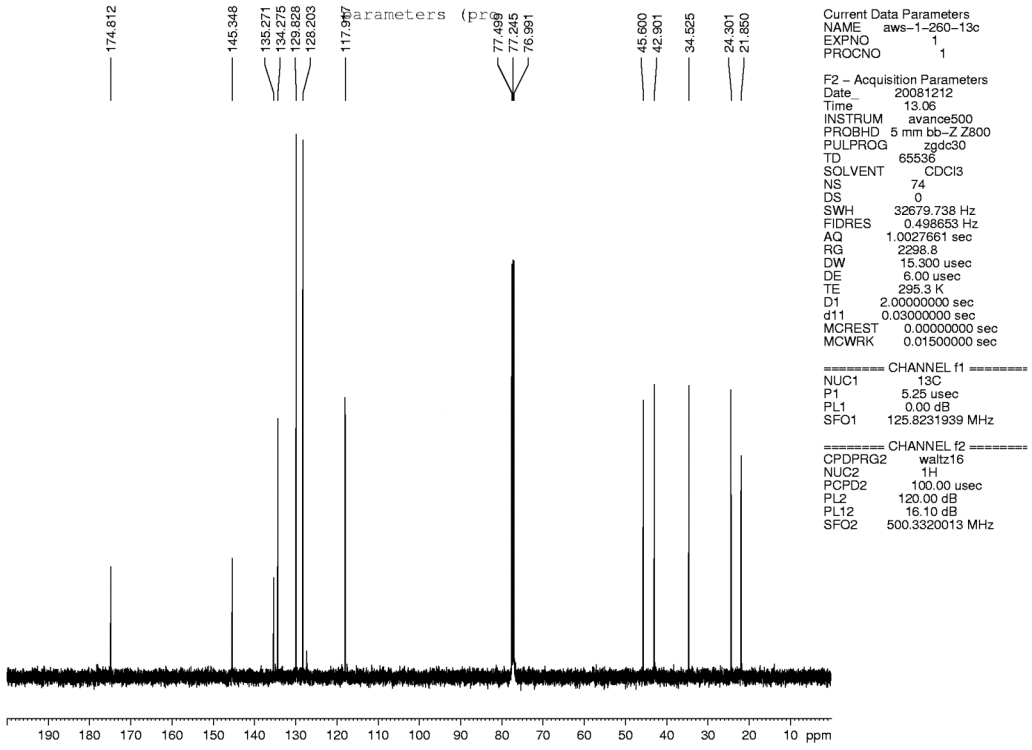


Figure A1.15 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **2.66**.

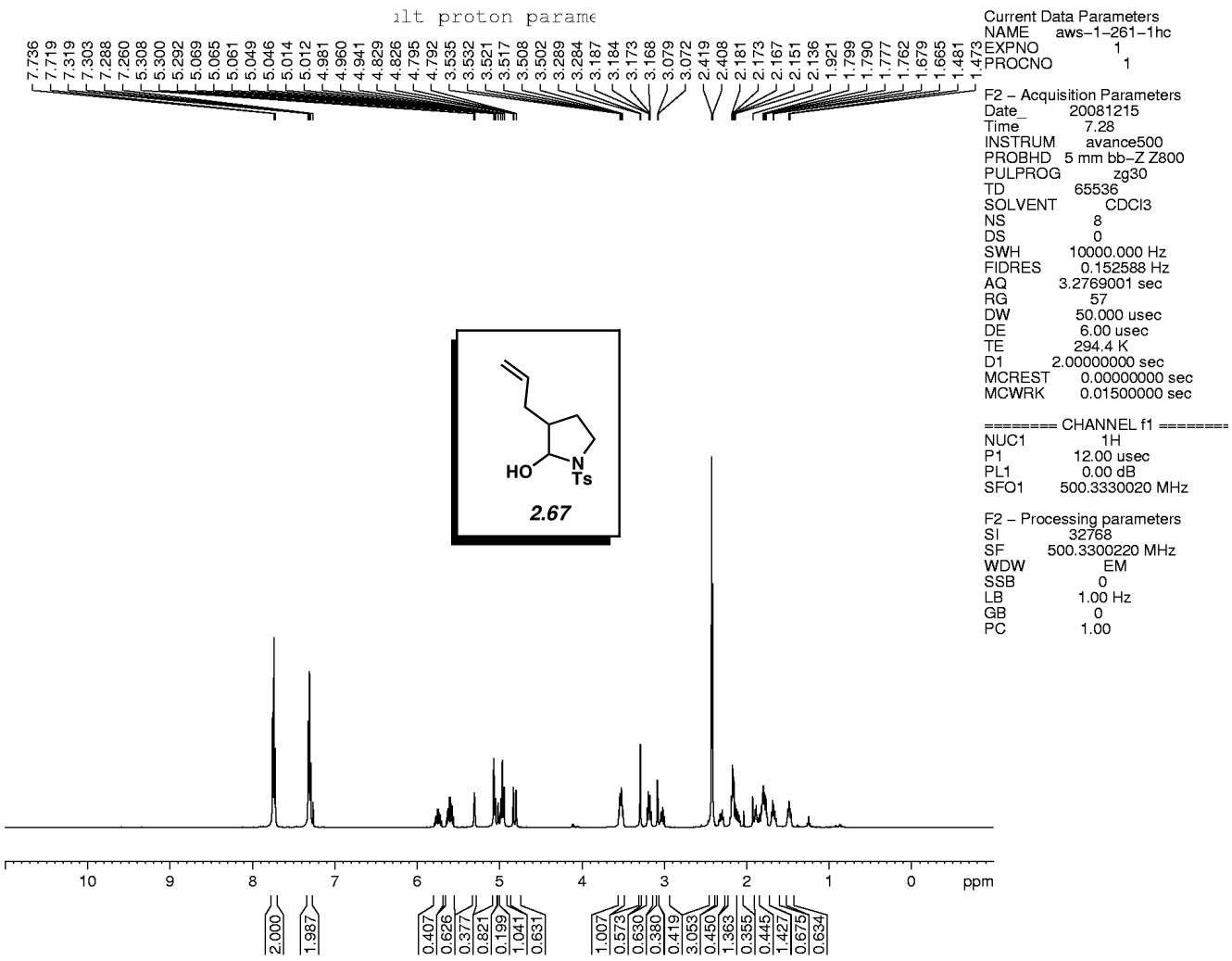


Figure A1.16 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **2.67**.

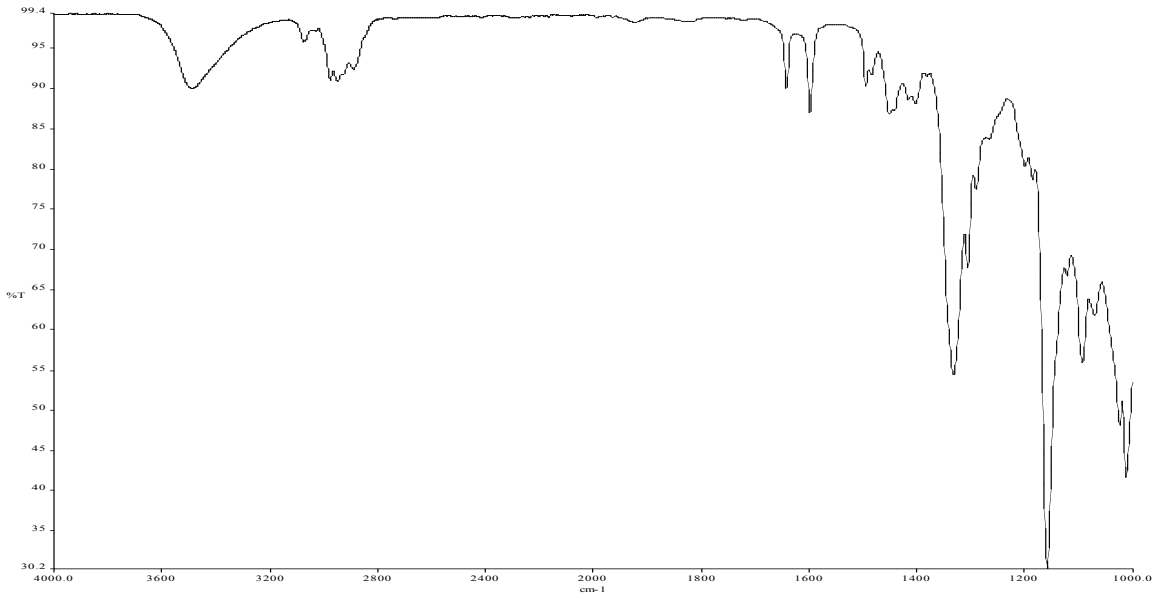


Figure A1.17 Infrared spectrum of compound **2.67**.

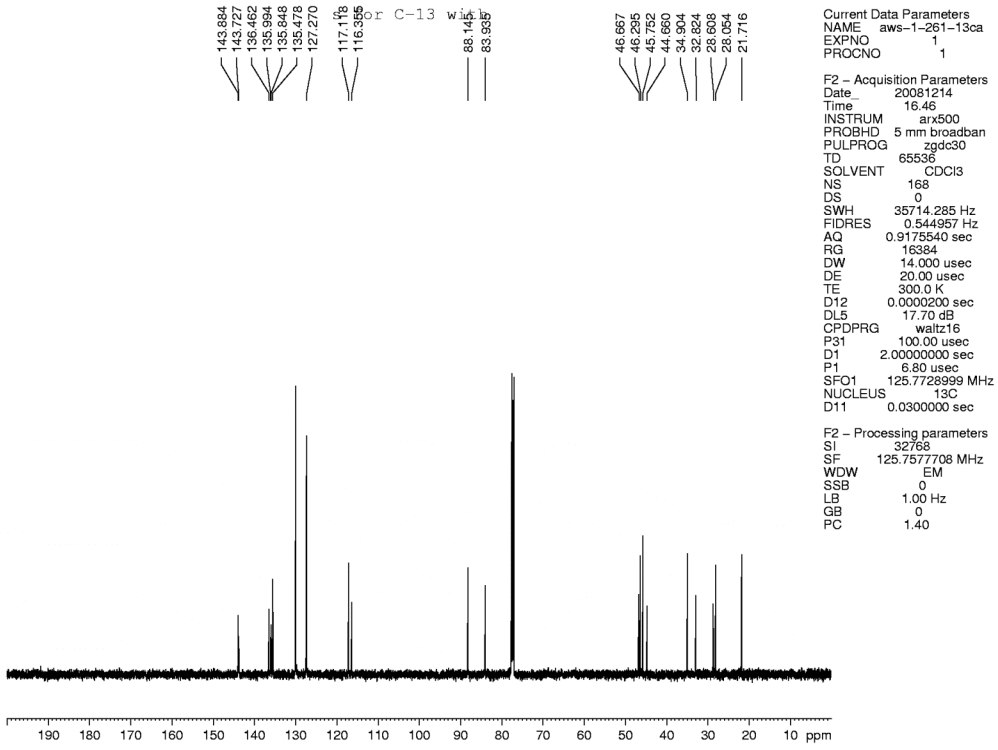


Figure A1.18 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **2.67**.

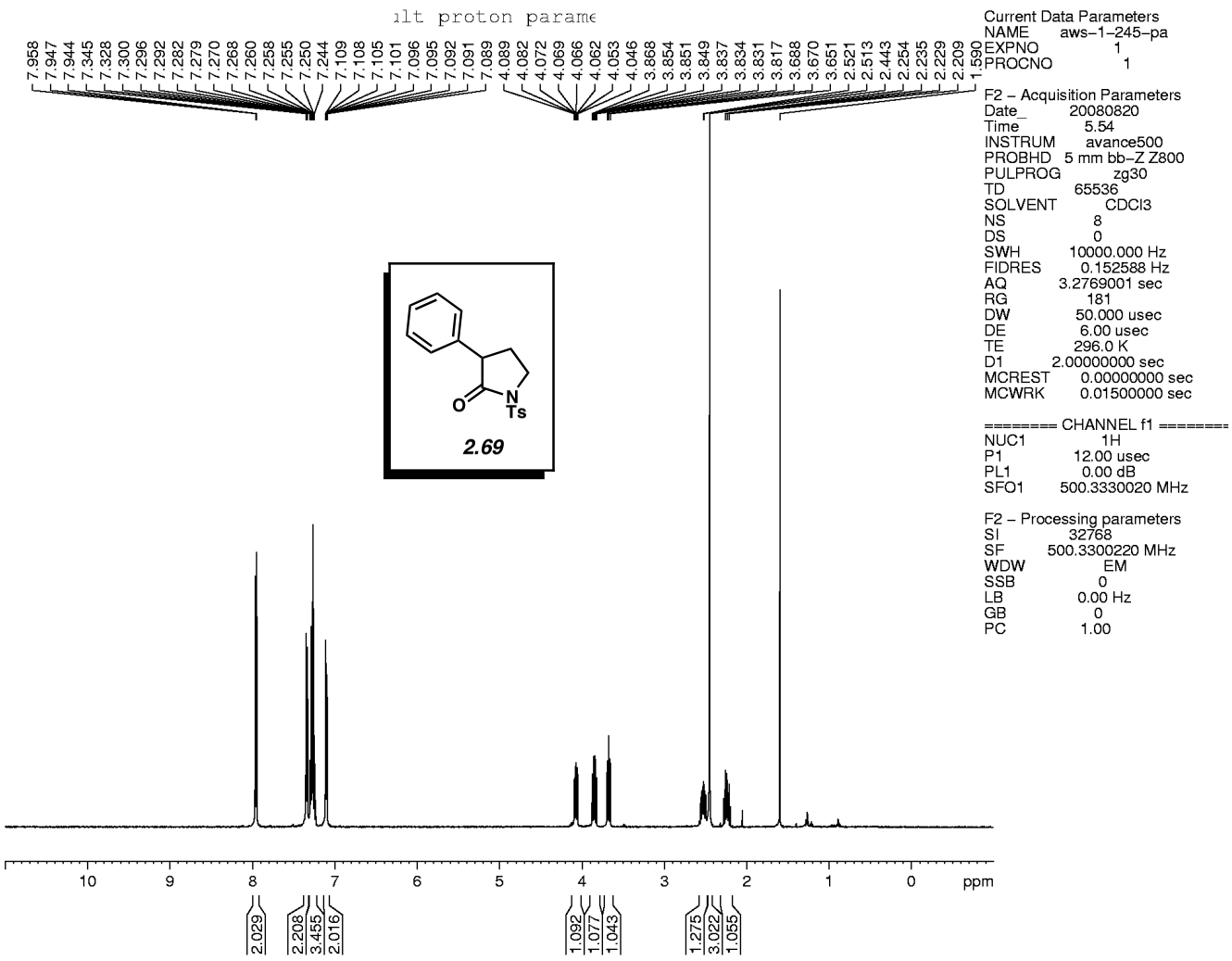


Figure A1.19 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **2.69**.

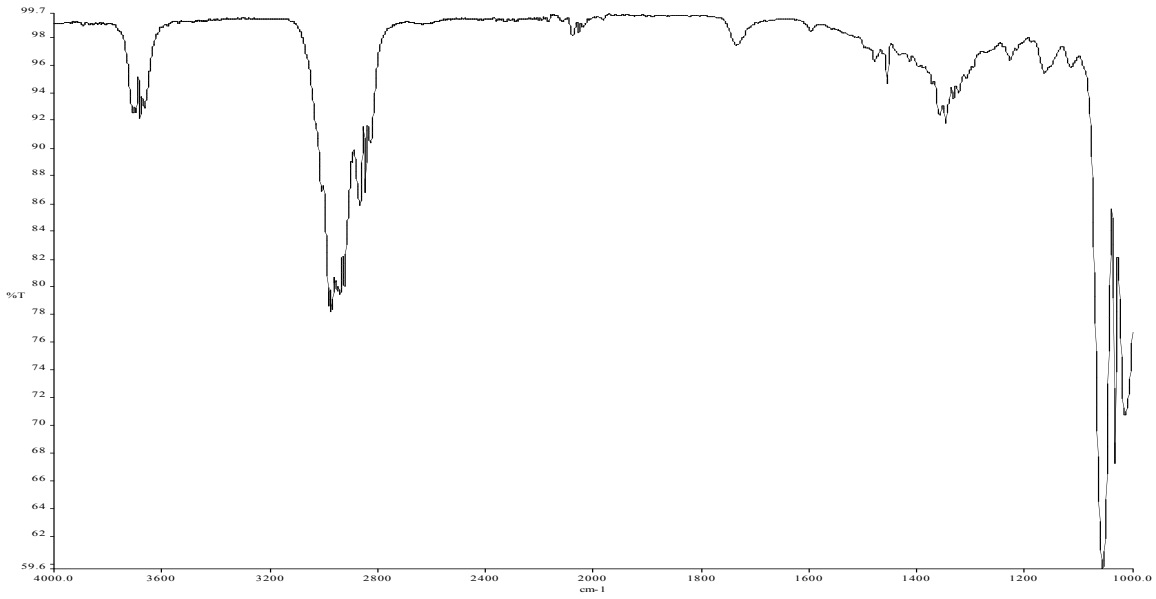


Figure A1.20 Infrared spectrum of compound **2.69**.

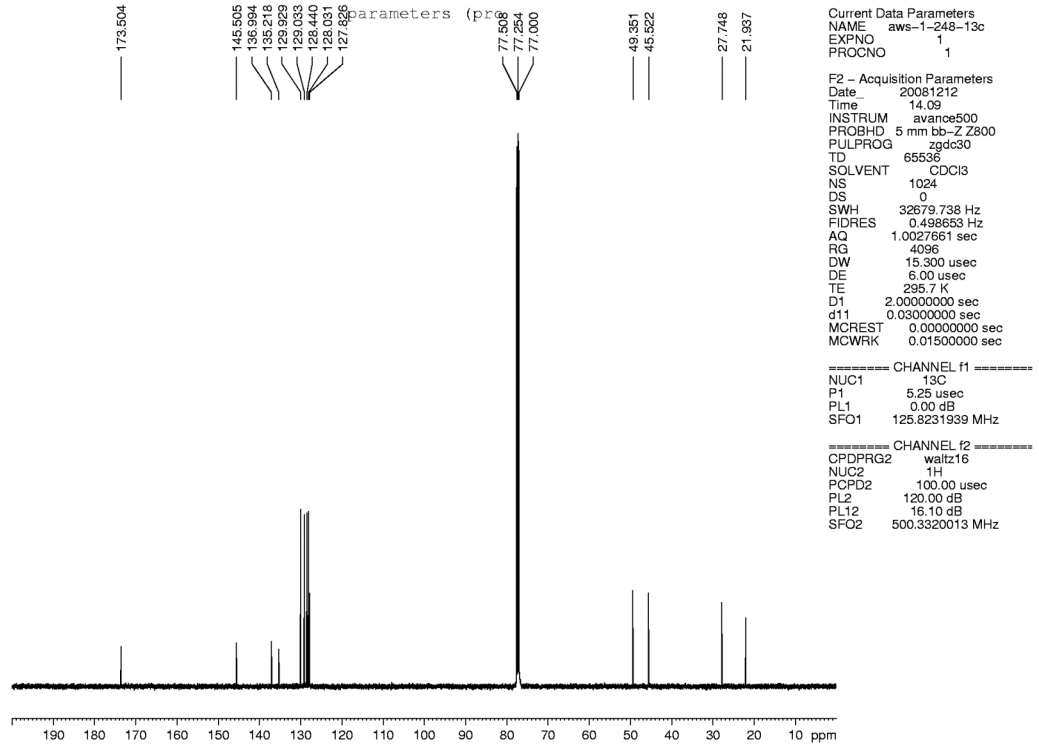


Figure A1.21 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **2.69**.

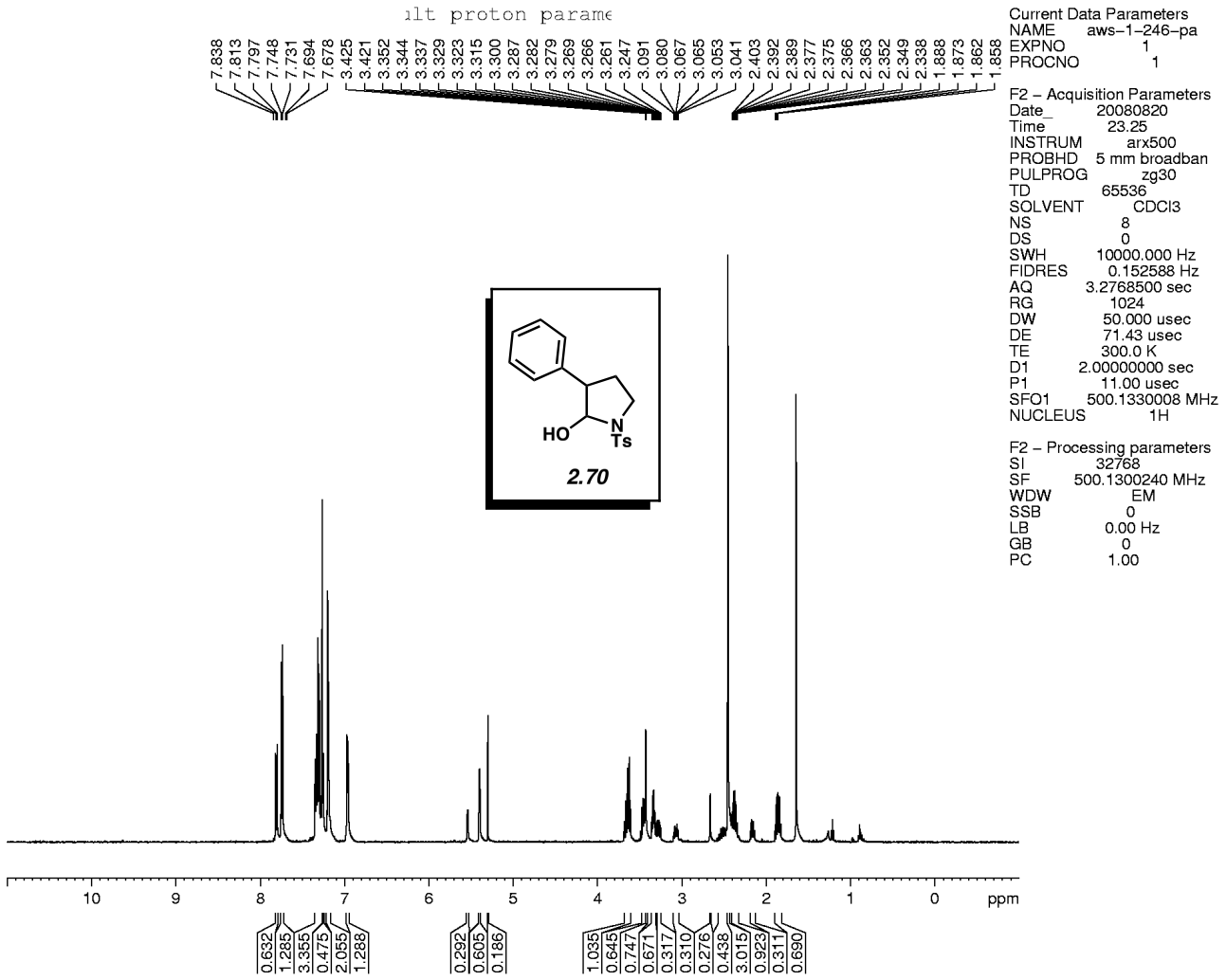


Figure A1.22 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **2.70**.

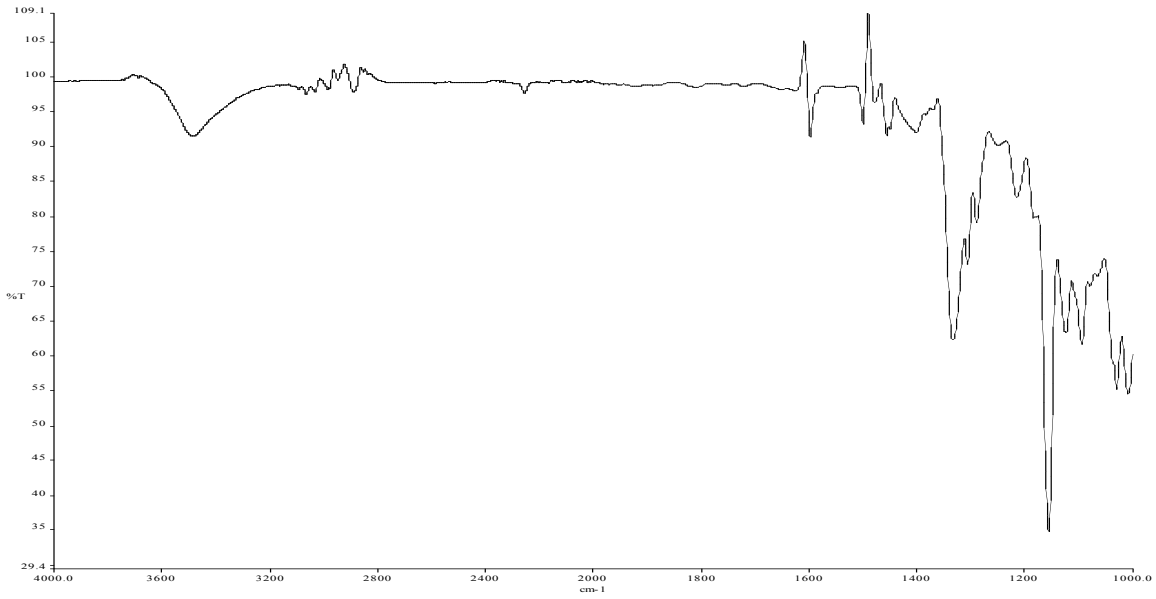


Figure A1.23 Infrared spectrum of compound **2.70**.

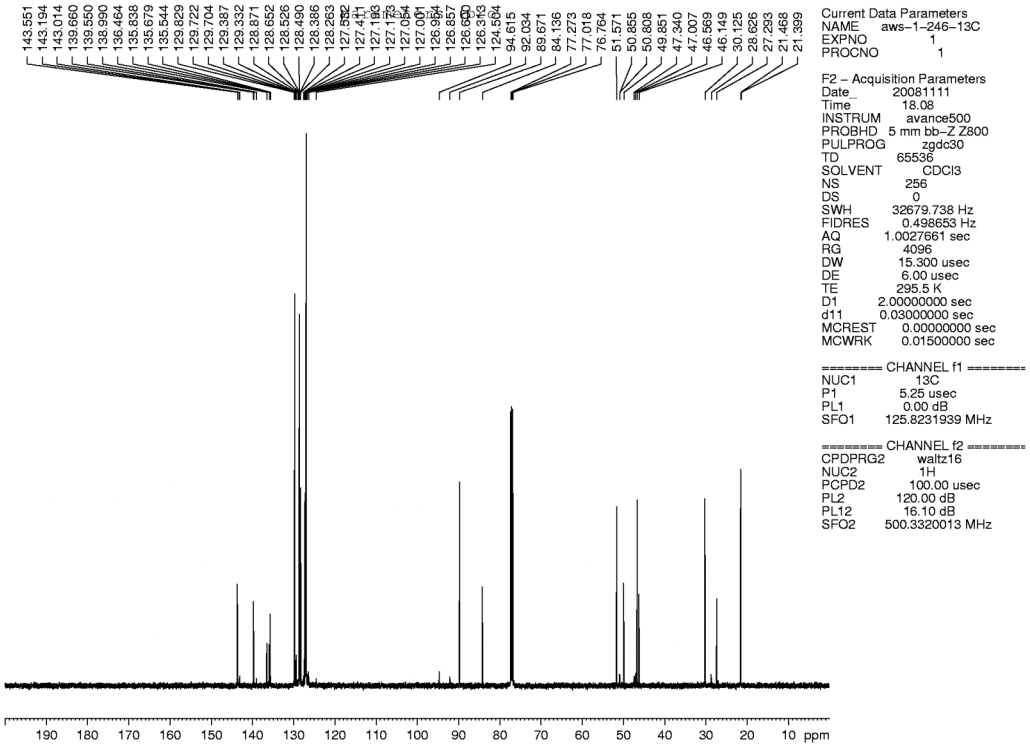


Figure A1.24 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **2.70**.

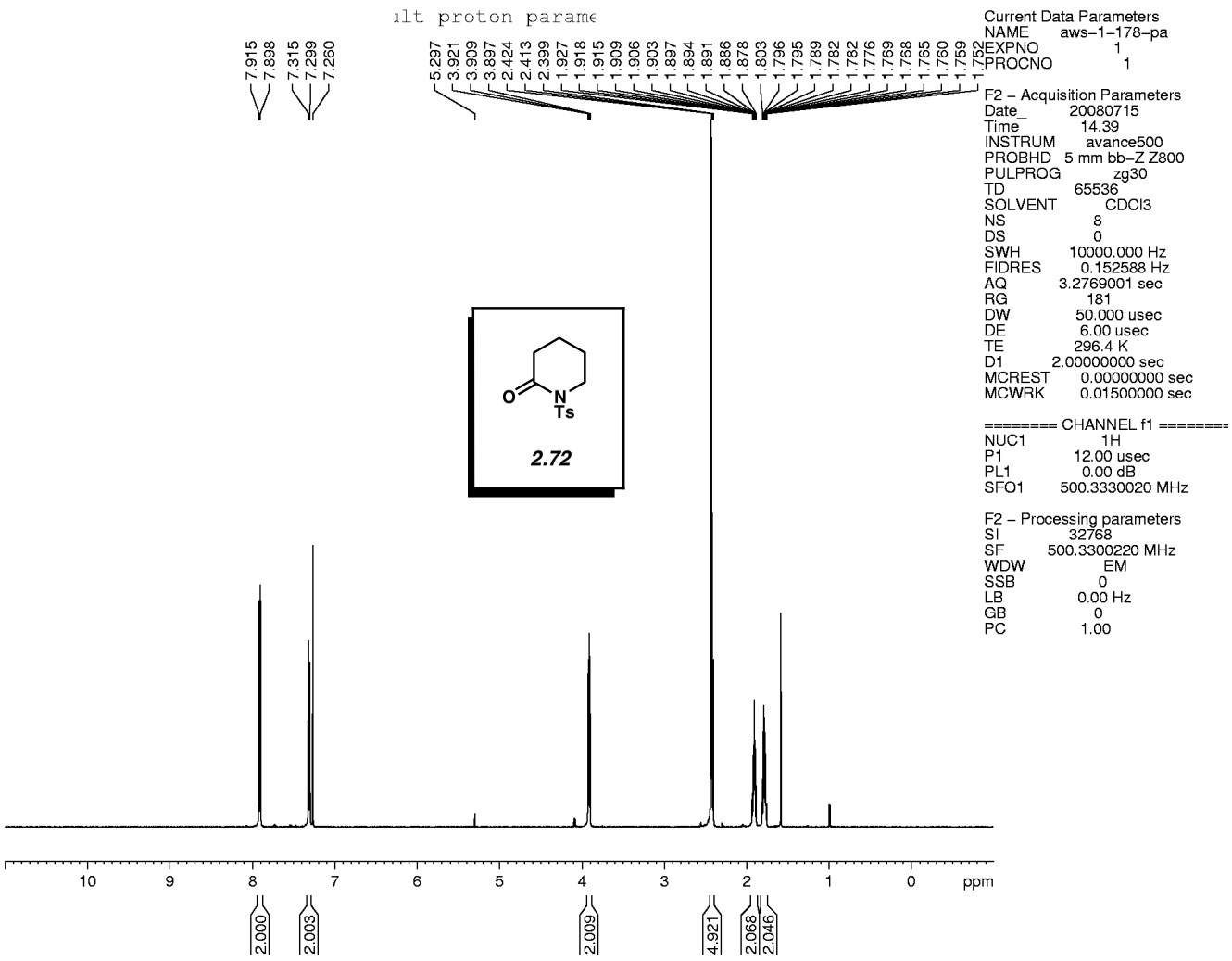


Figure A1.25 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **2.72**.

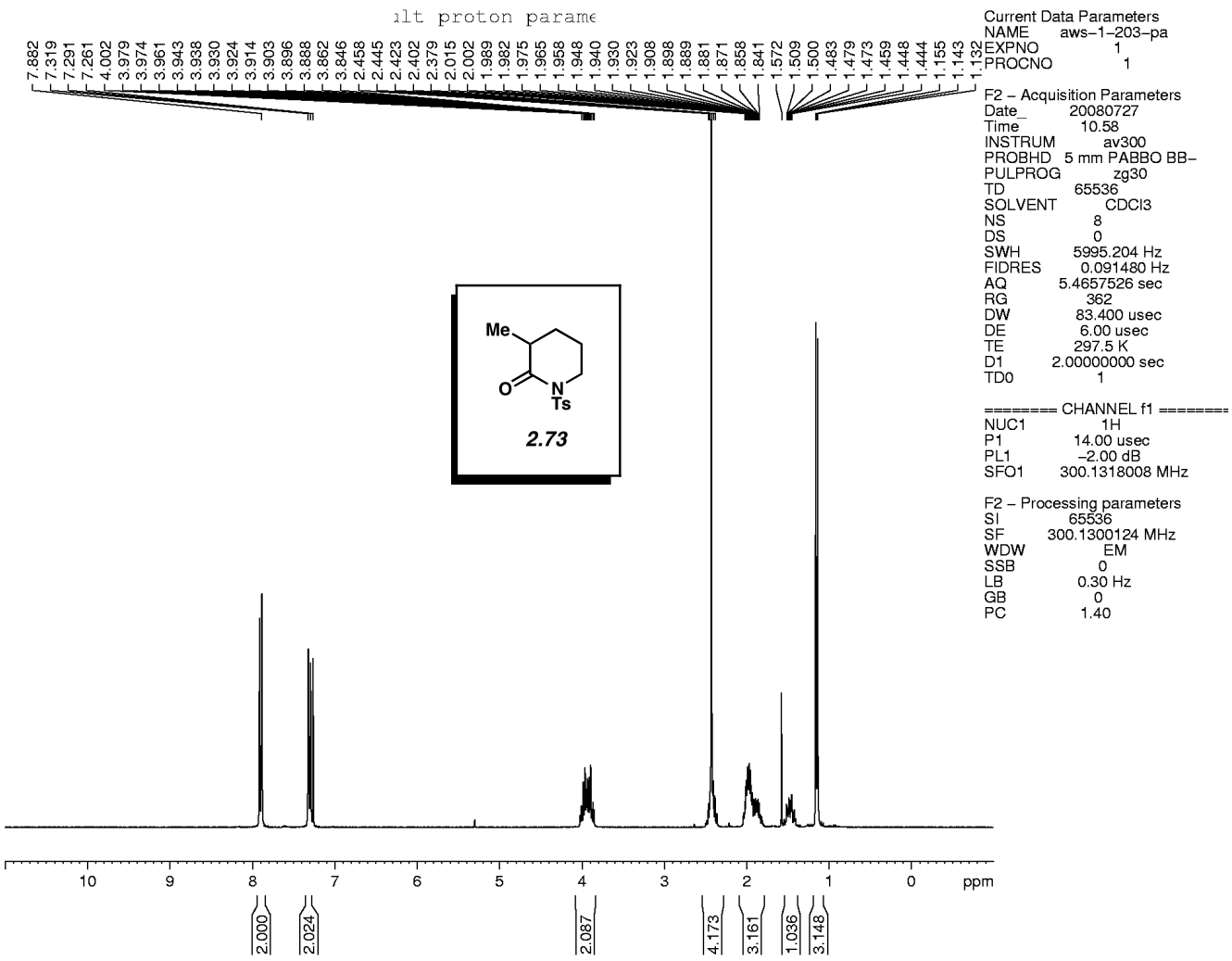


Figure A1.26 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **2.73**.

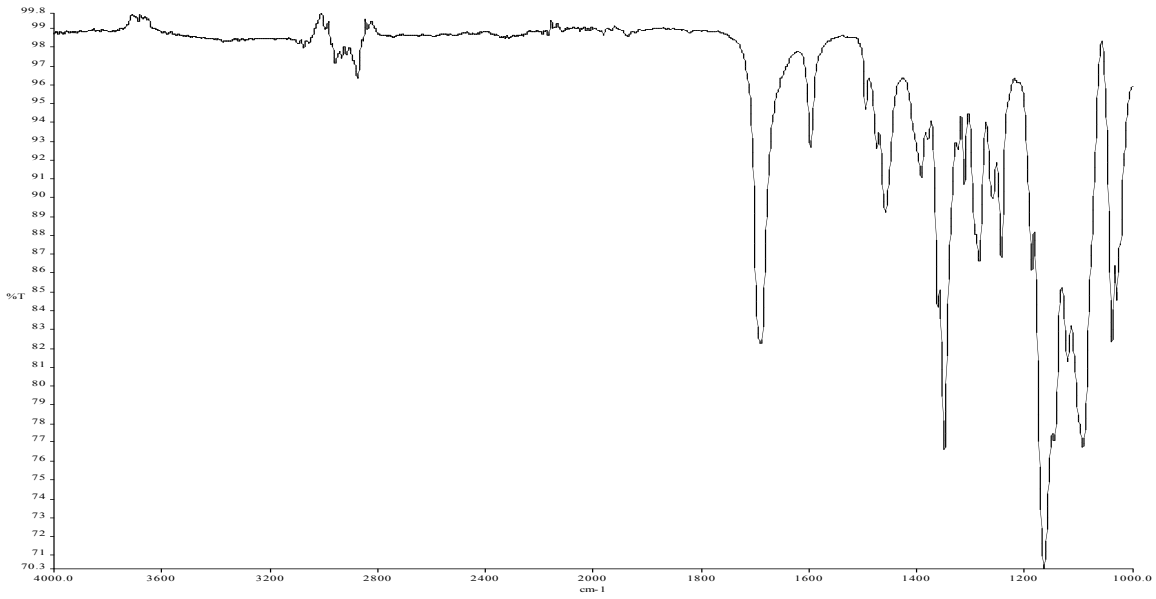


Figure A1.27 Infrared spectrum of compound **2.73**.

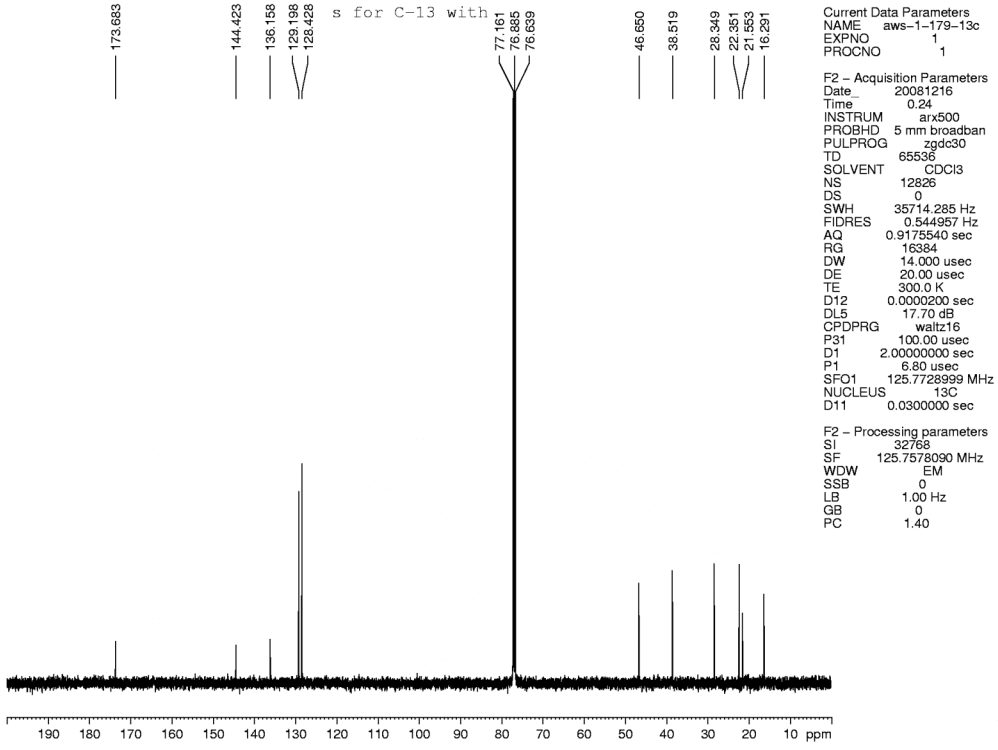


Figure A1.28 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **2.73**.

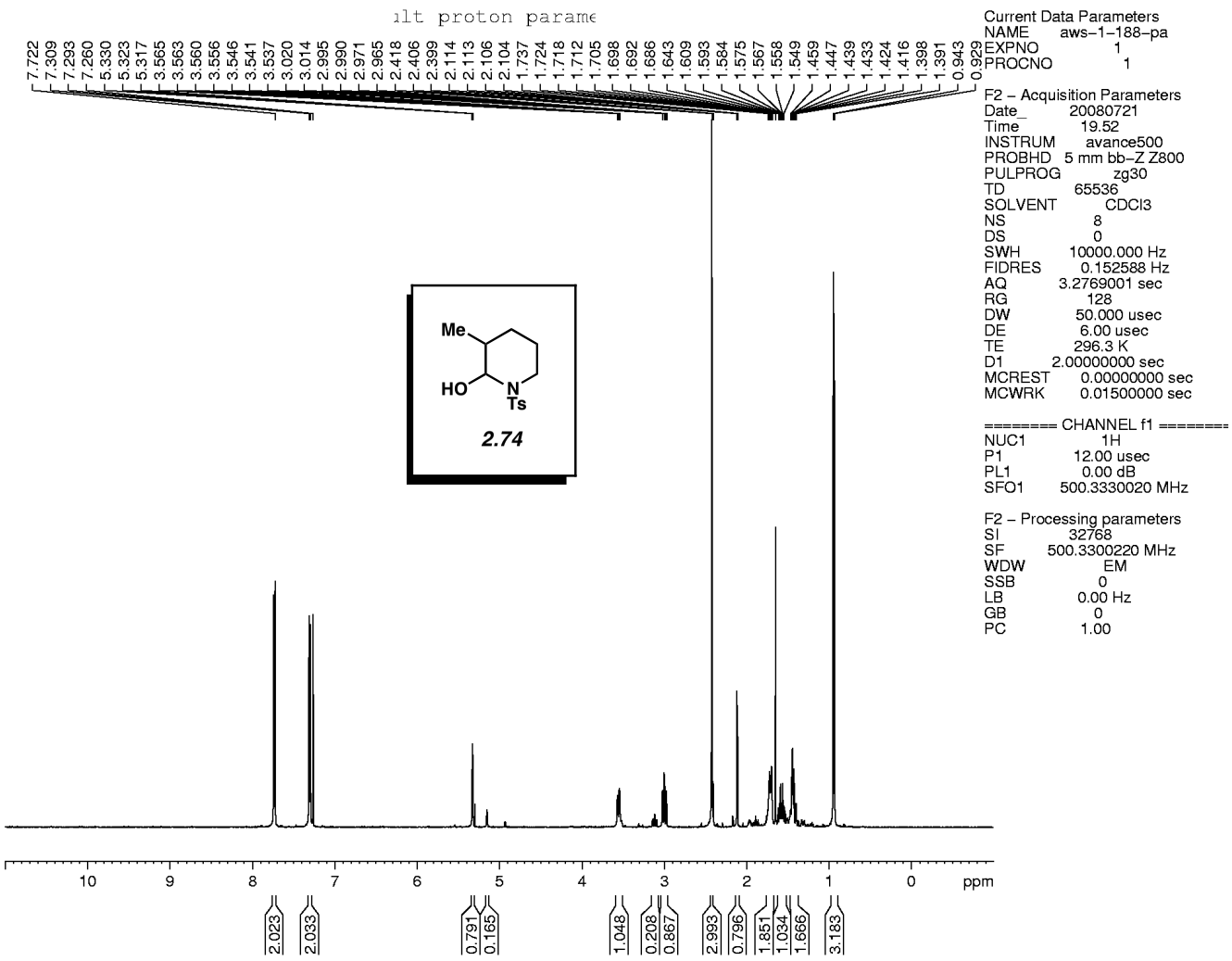


Figure A1.29 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **2.74**.

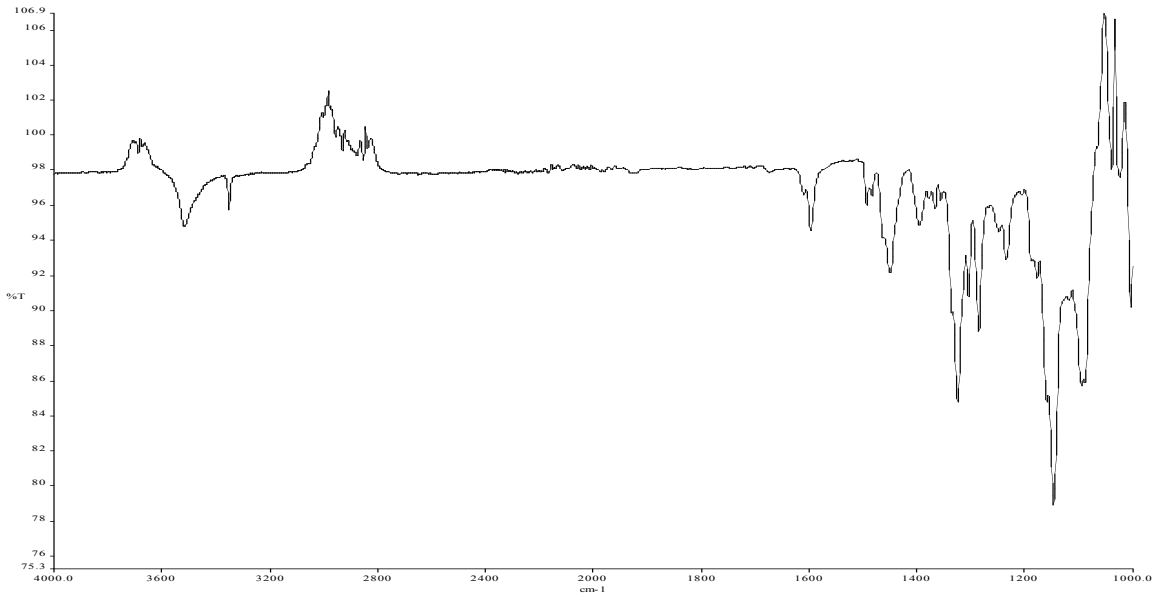


Figure A1.30 Infrared spectrum of compound **2.74**.

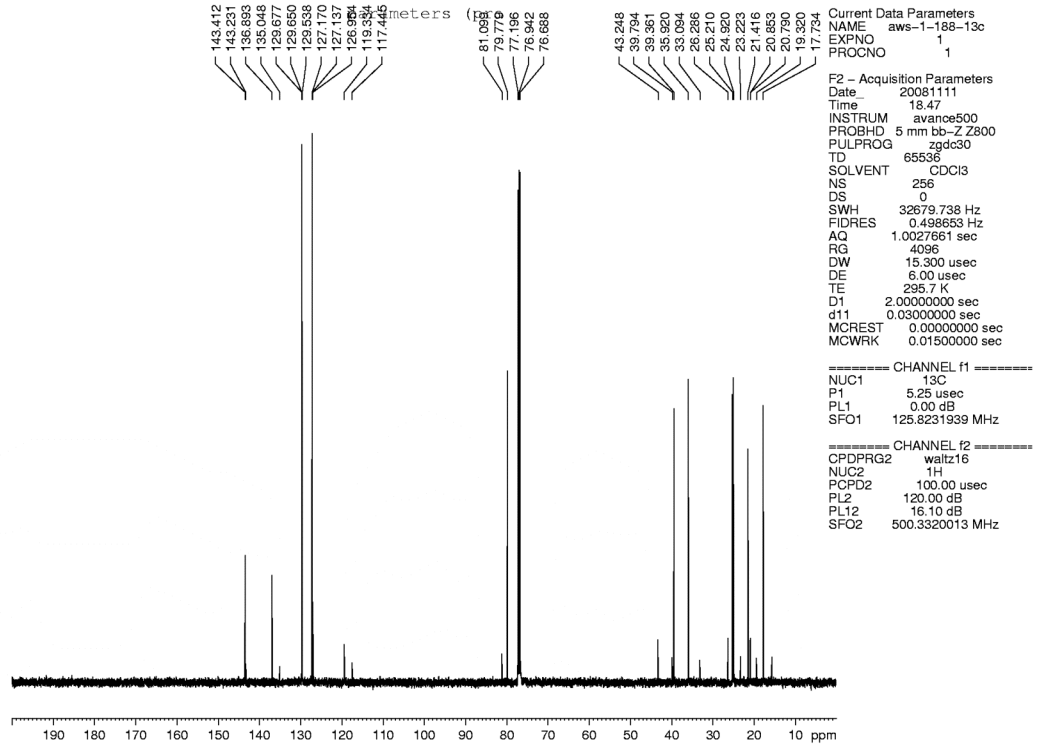


Figure A1.31 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **2.74**.

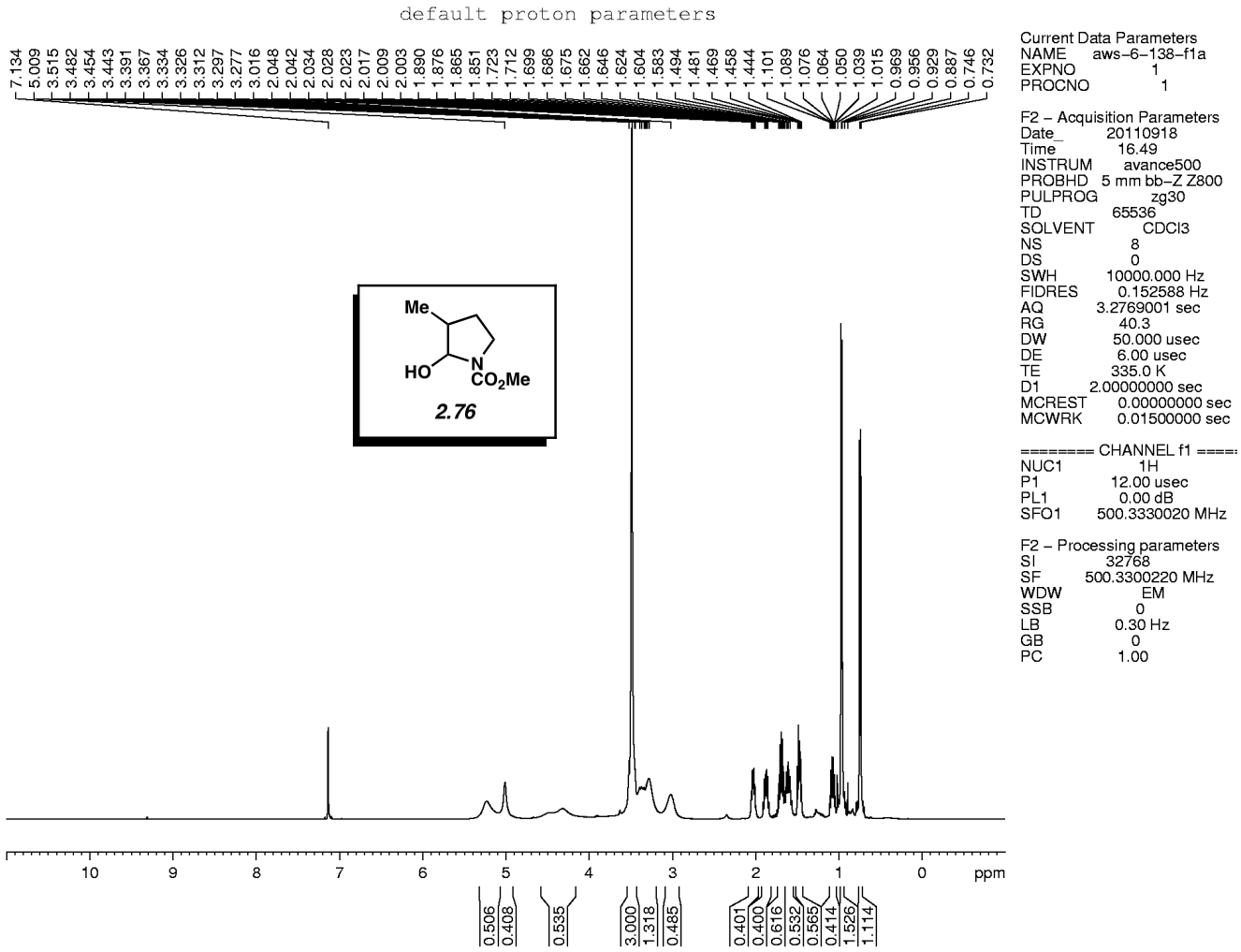


Figure A1.32 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **2.76**.

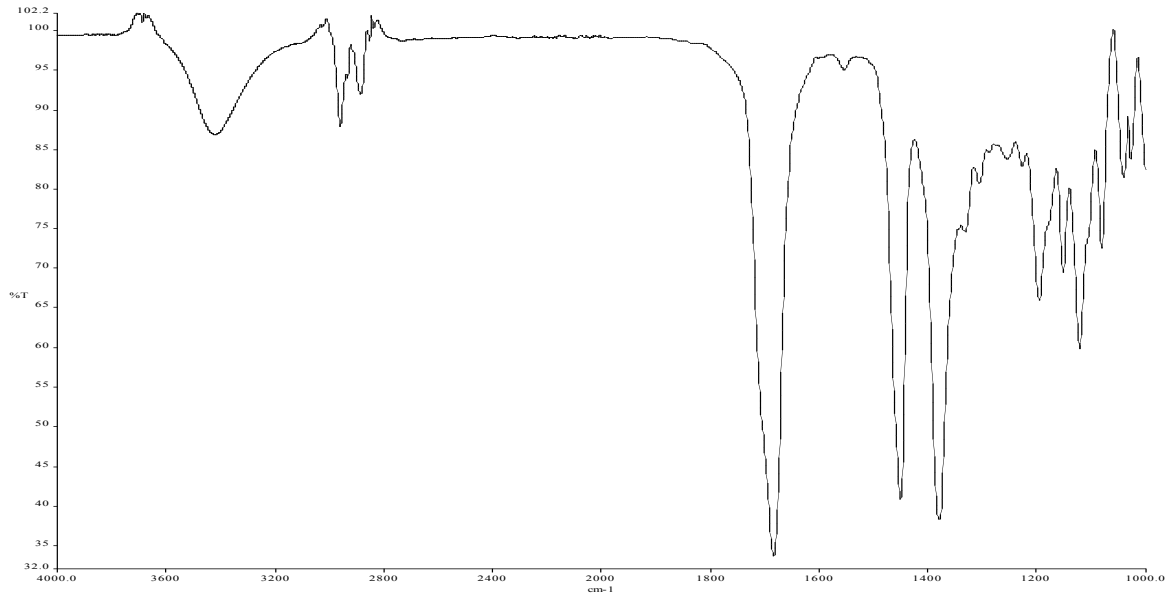


Figure A1.33 Infrared spectrum of compound **2.76**.

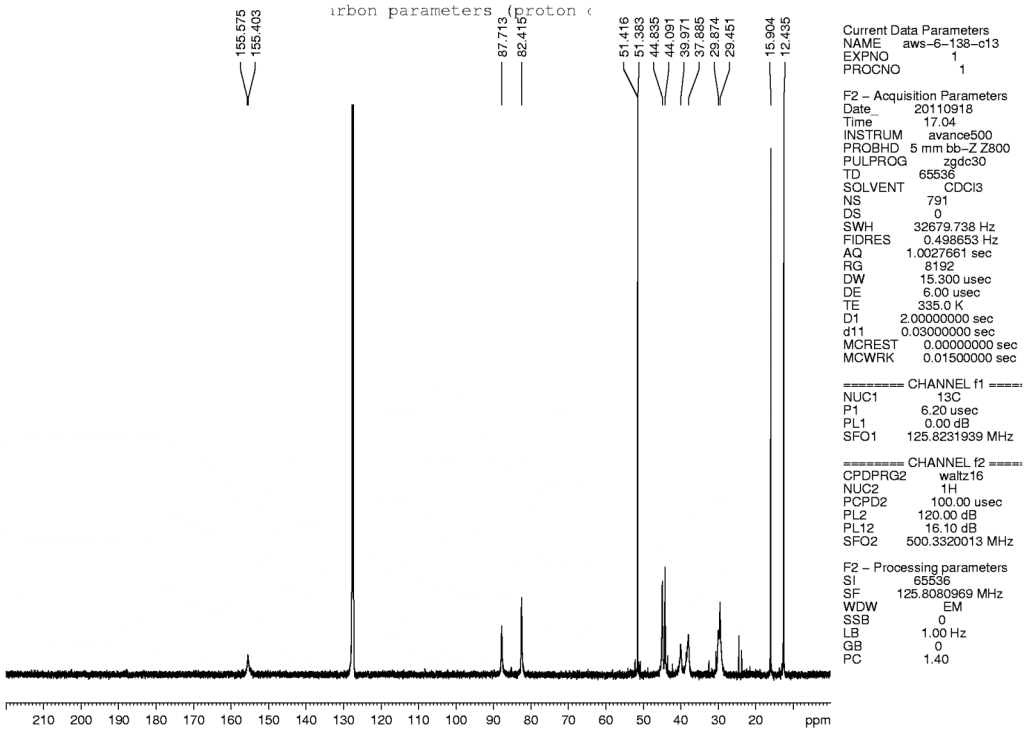


Figure A1.34 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **2.76**.

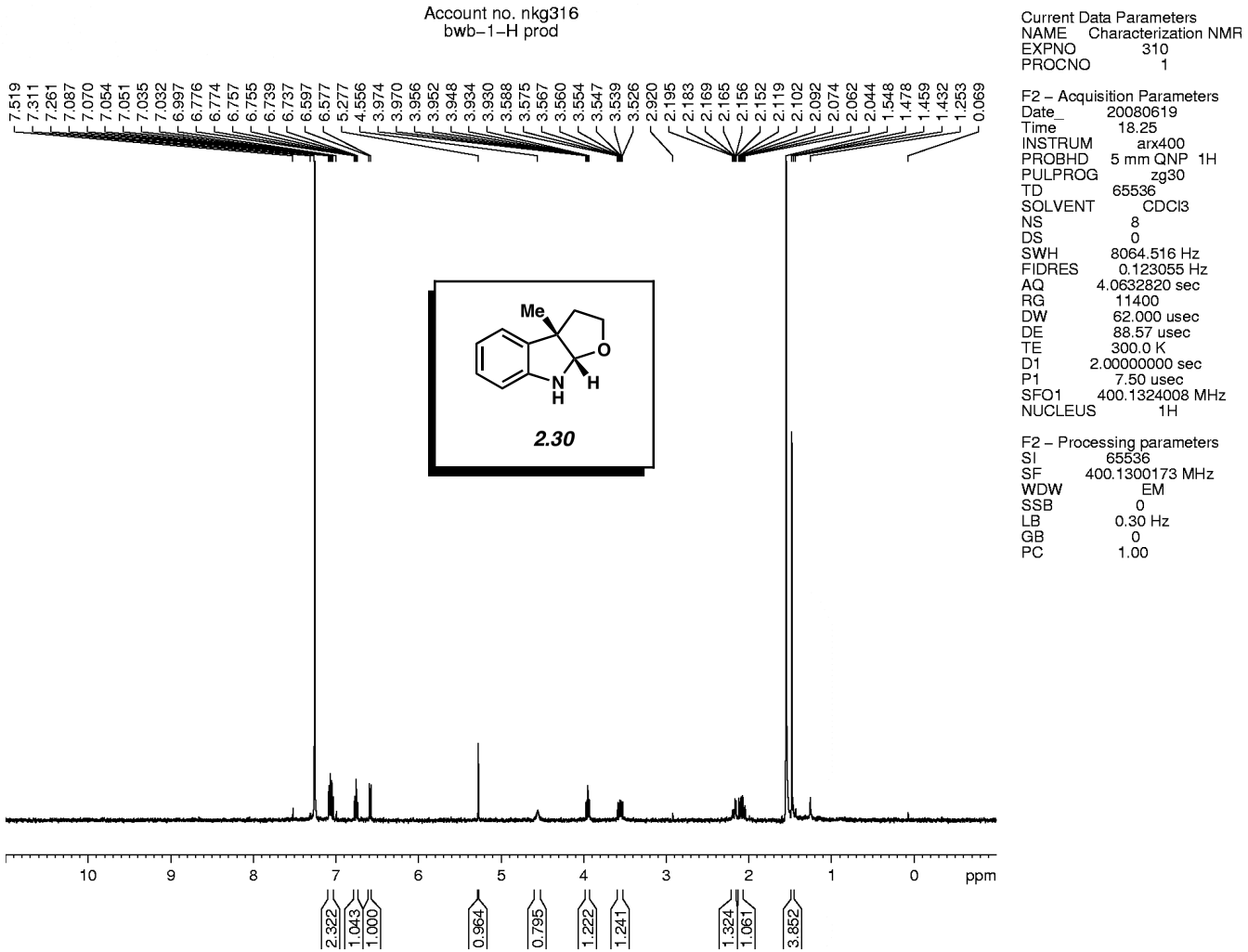


Figure A1.35 ^{1}H NMR (400 MHz, $CDCl_3$) of compound **2.30**.

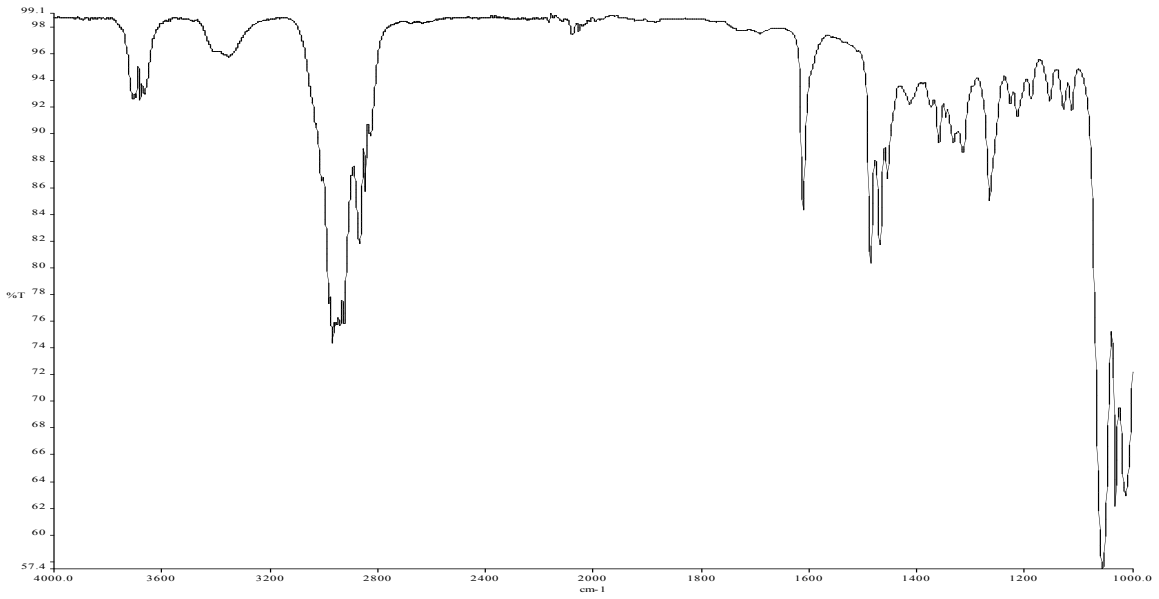


Figure A1.36 Infrared spectrum of compound **2.30**.

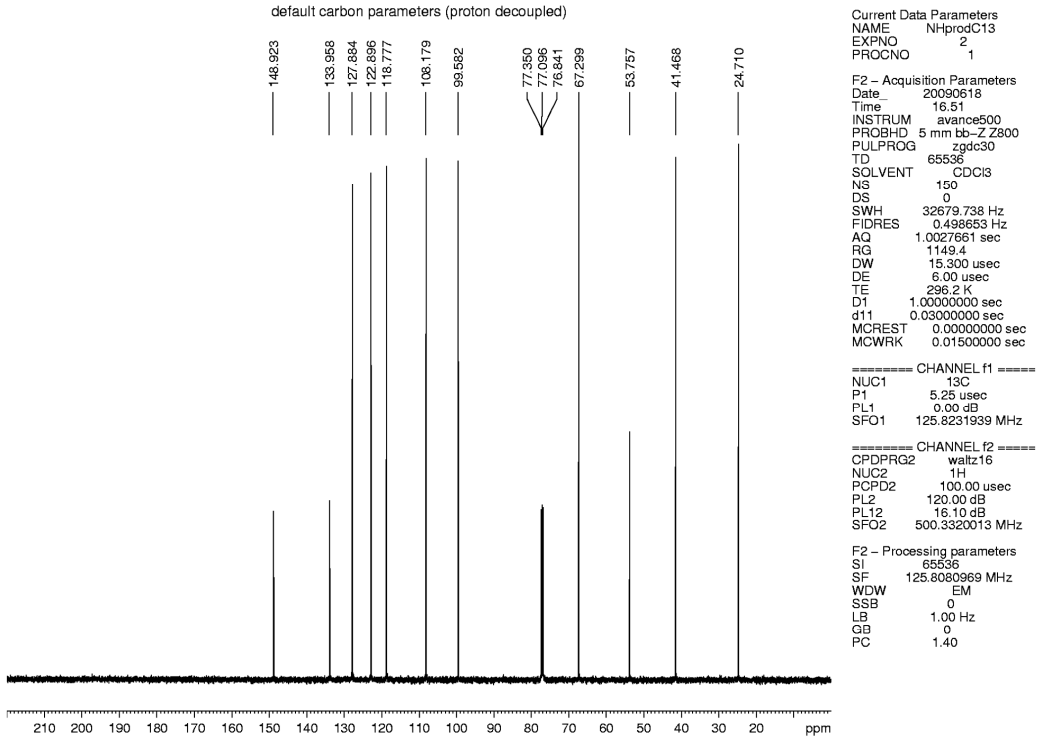


Figure A1.37 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **2.30**.

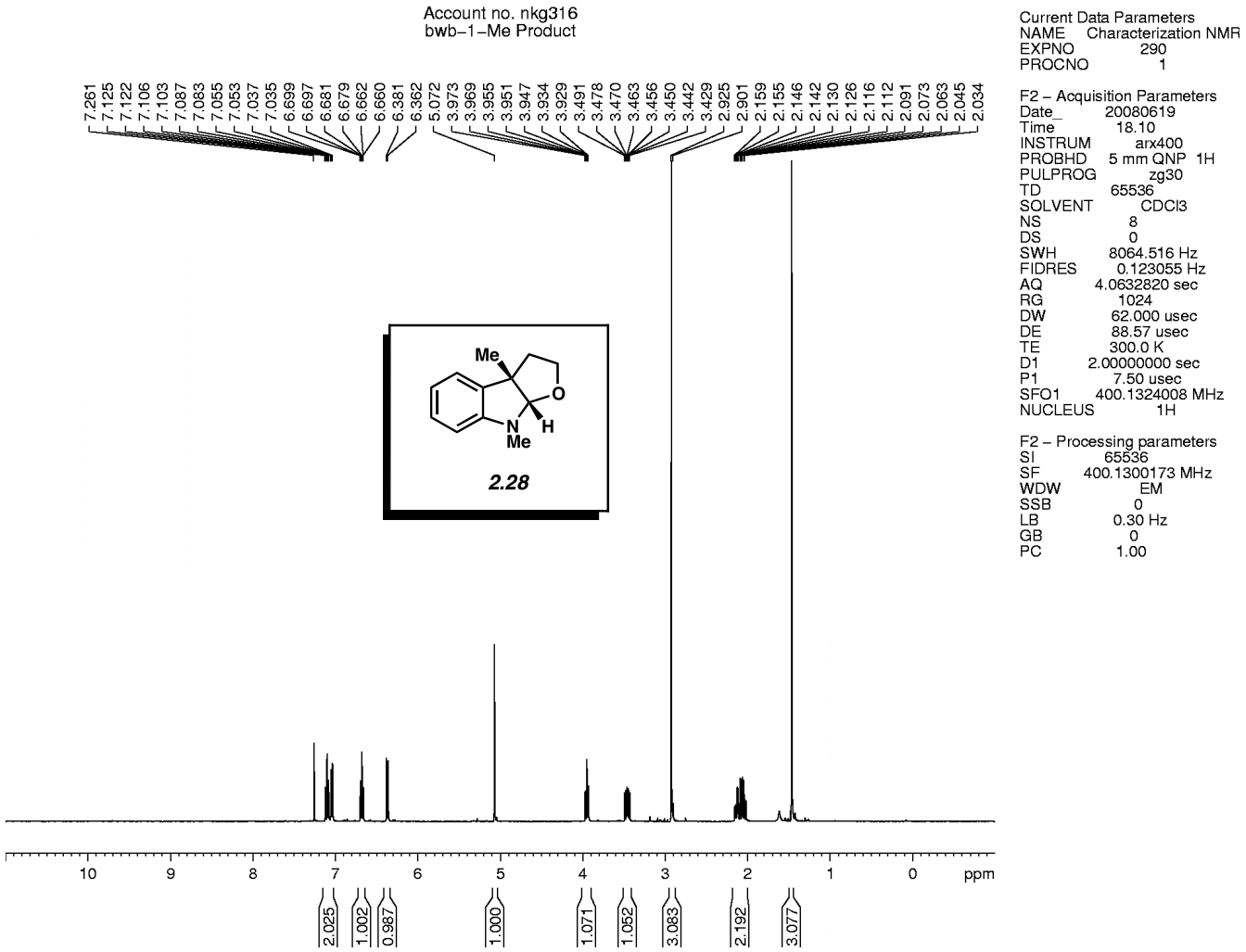
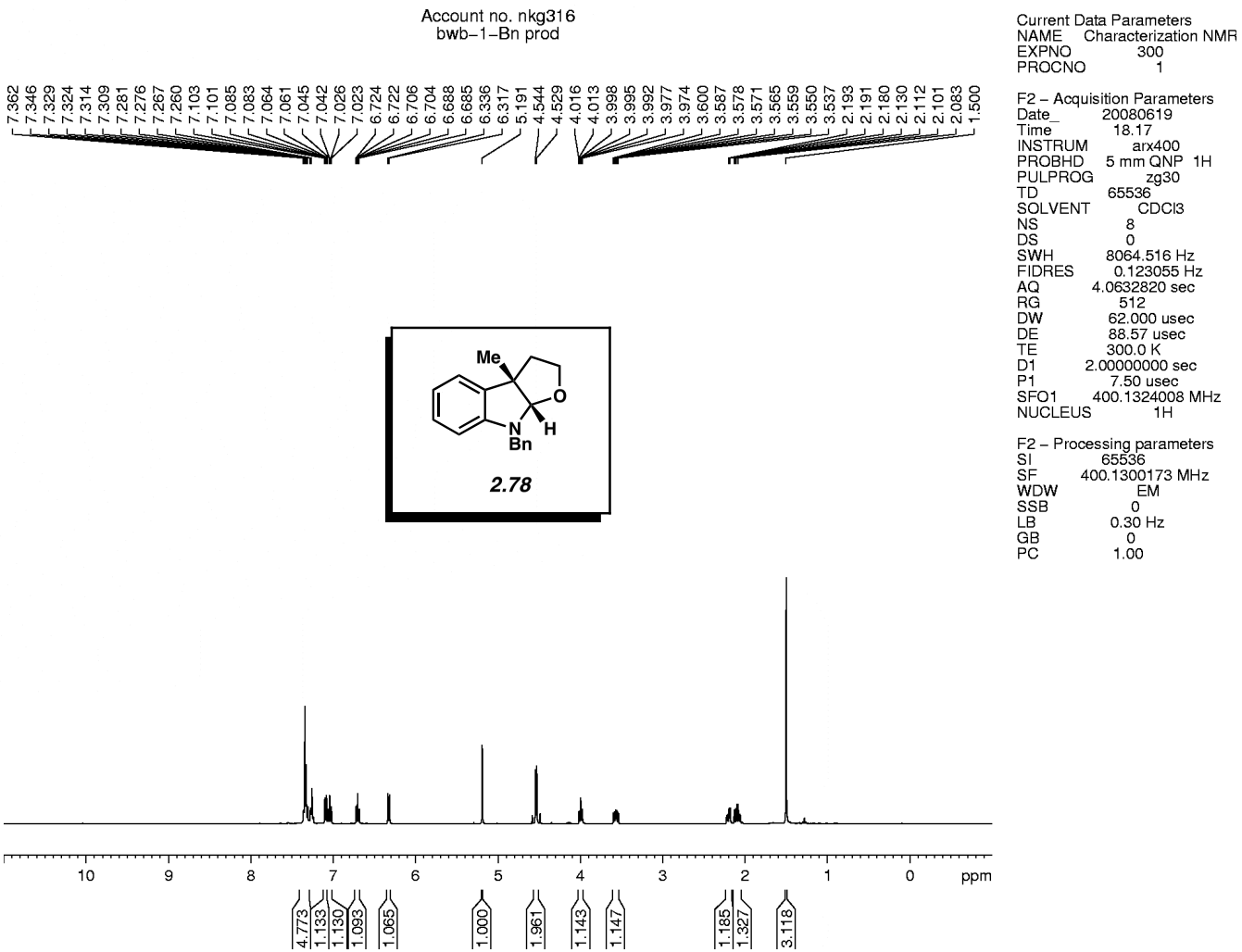


Figure A1.38 ^{1}H NMR (400 MHz, $CDCl_3$) of compound **2.28**.



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FIDRES 0.123055 Hz
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NUCLEUS 1H

F2 – Processing parameters
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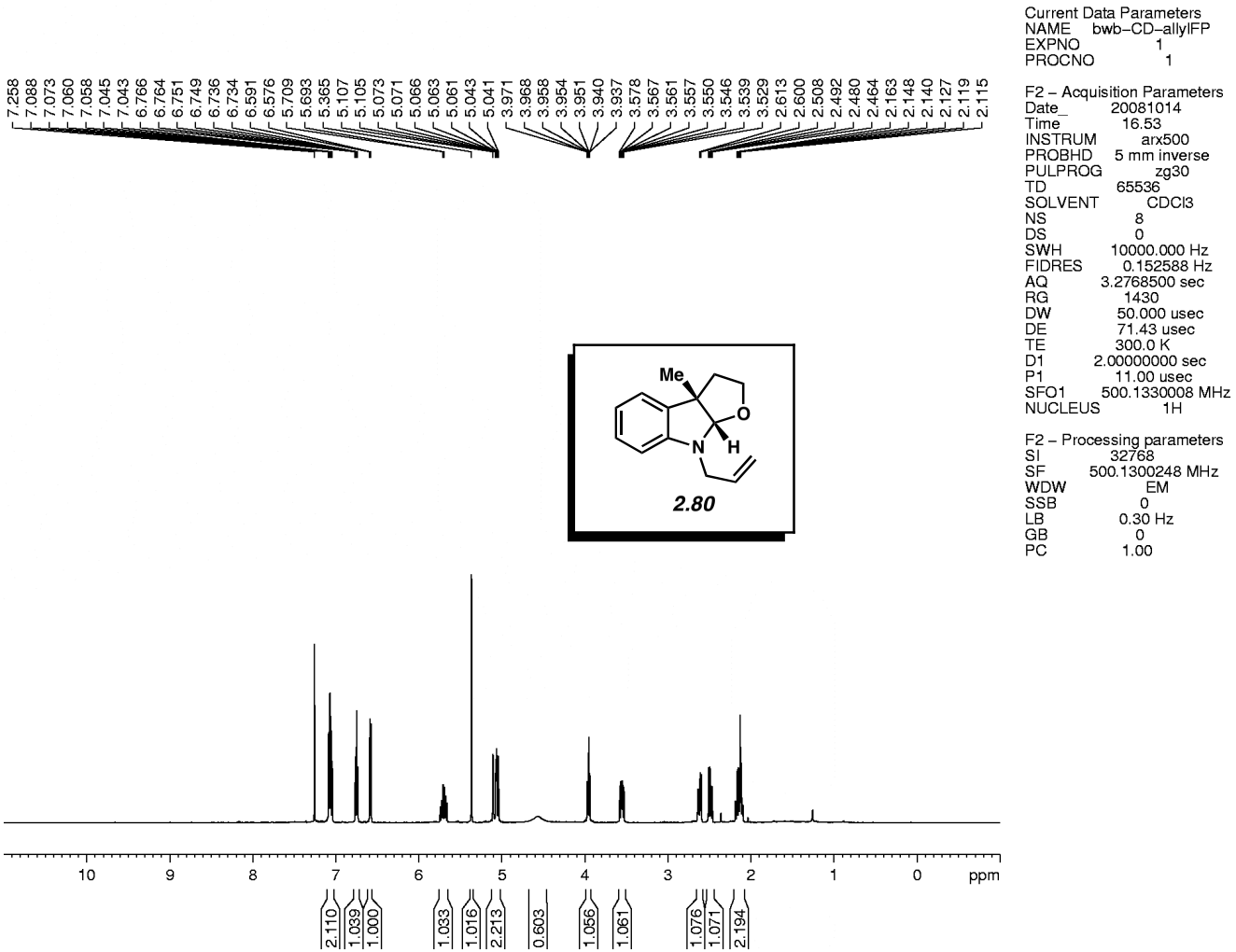
Figure A1.39 ^{1}H NMR (400 MHz, $CDCl_3$) of compound **2.78**.



Current Data Parameters
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PROCNO 1

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D1 2.00000000 sec
P1 11.00 usec
SFO1 500.1330008 MHz
NUCLEUS 1H

F2 – Processing parameters
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LB 0.30 Hz
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Figure A1.40 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **2.80**.

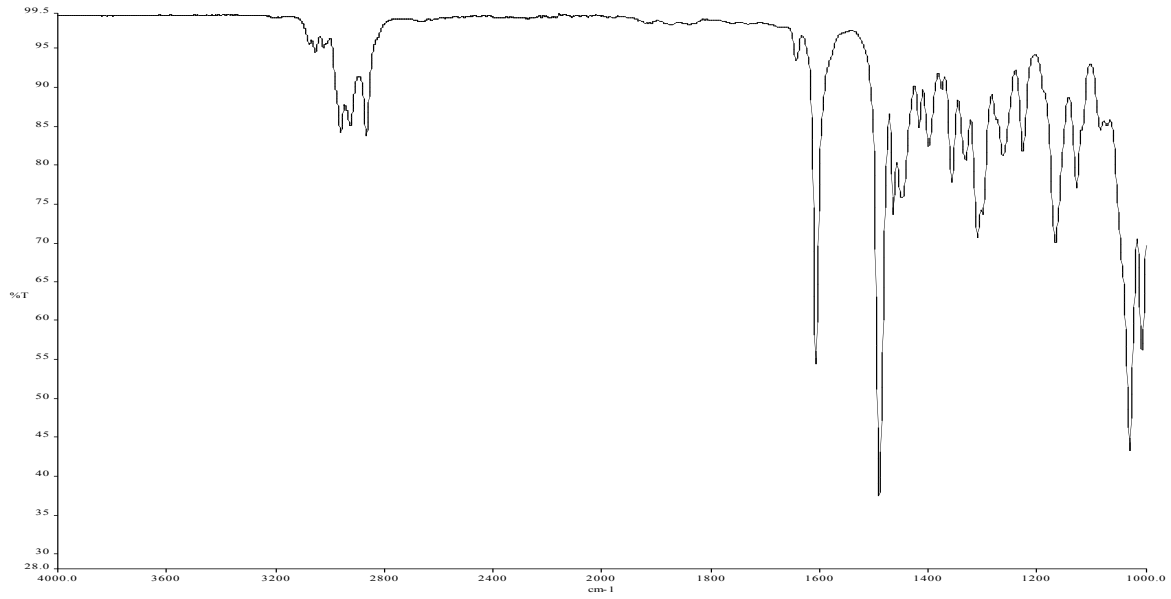


Figure A1.41 Infrared spectrum of compound **2.80**.

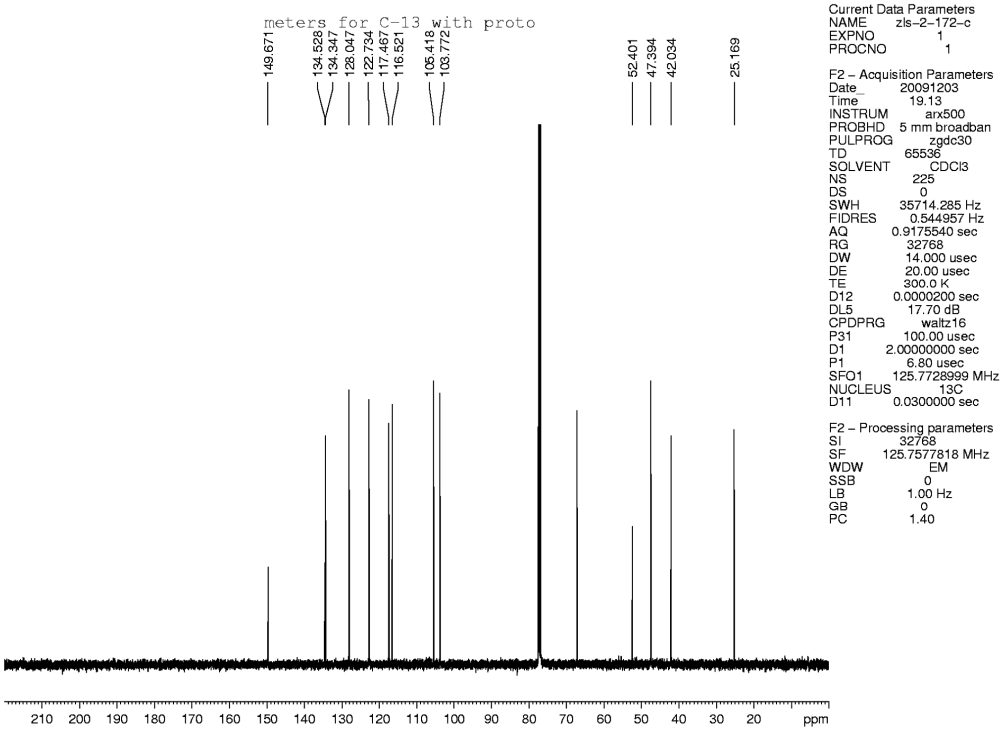


Figure A1.42 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **2.80**.

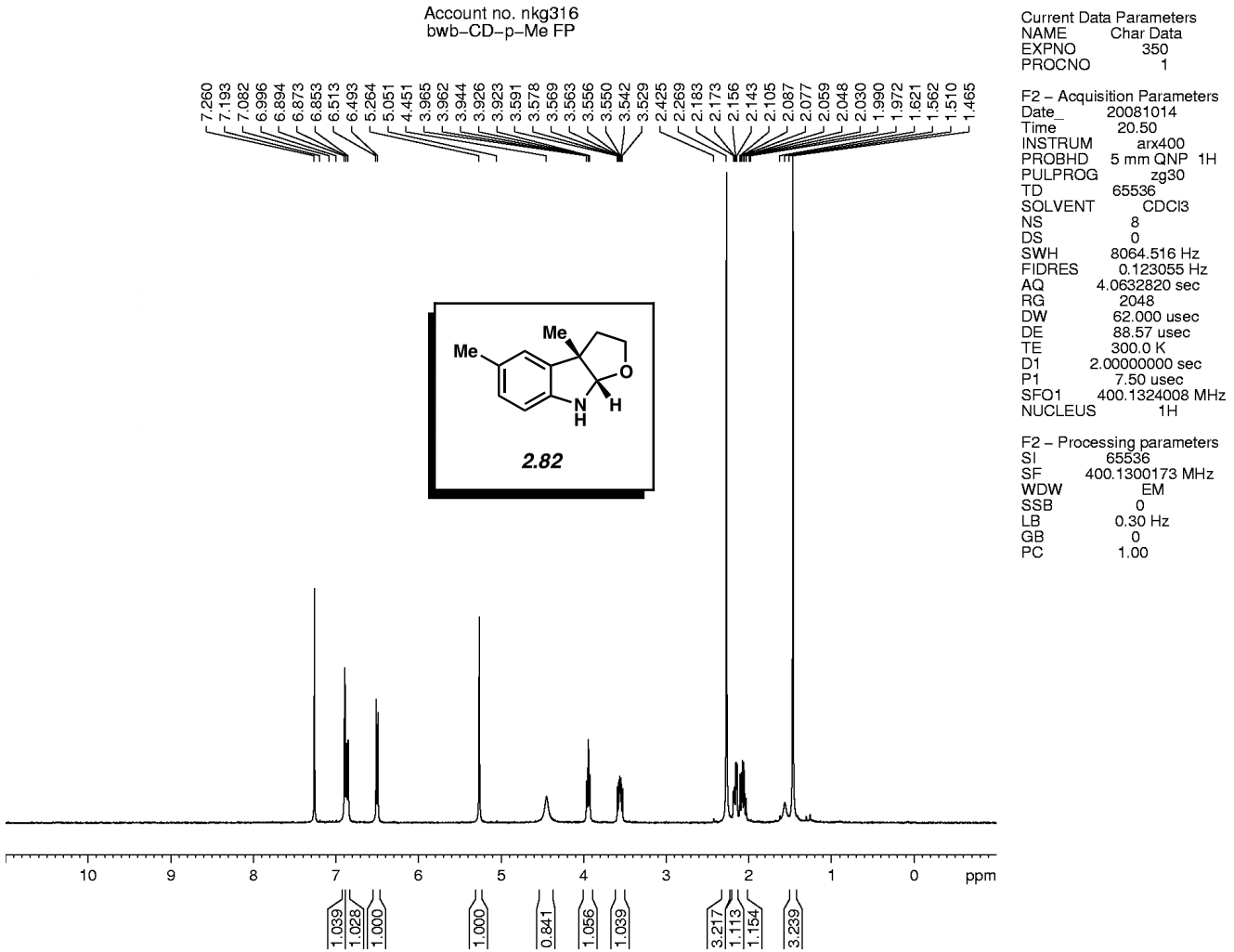


Figure A1.43 ^{1}H NMR (400 MHz, $CDCl_3$) of compound **2.82**.

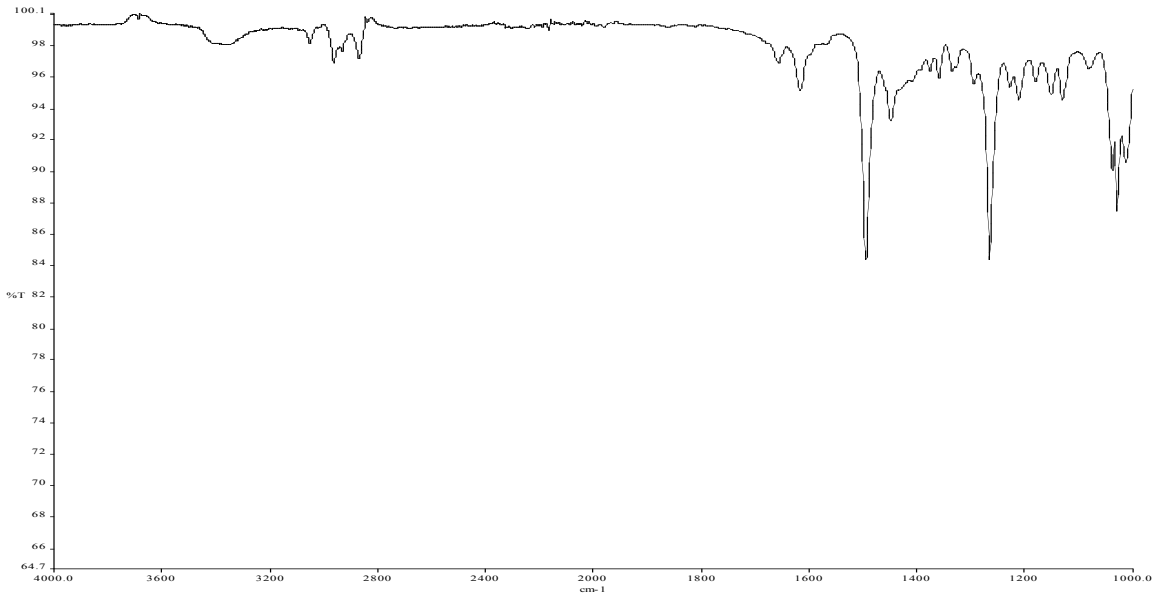


Figure A1.44 Infrared spectrum of compound **2.82**.

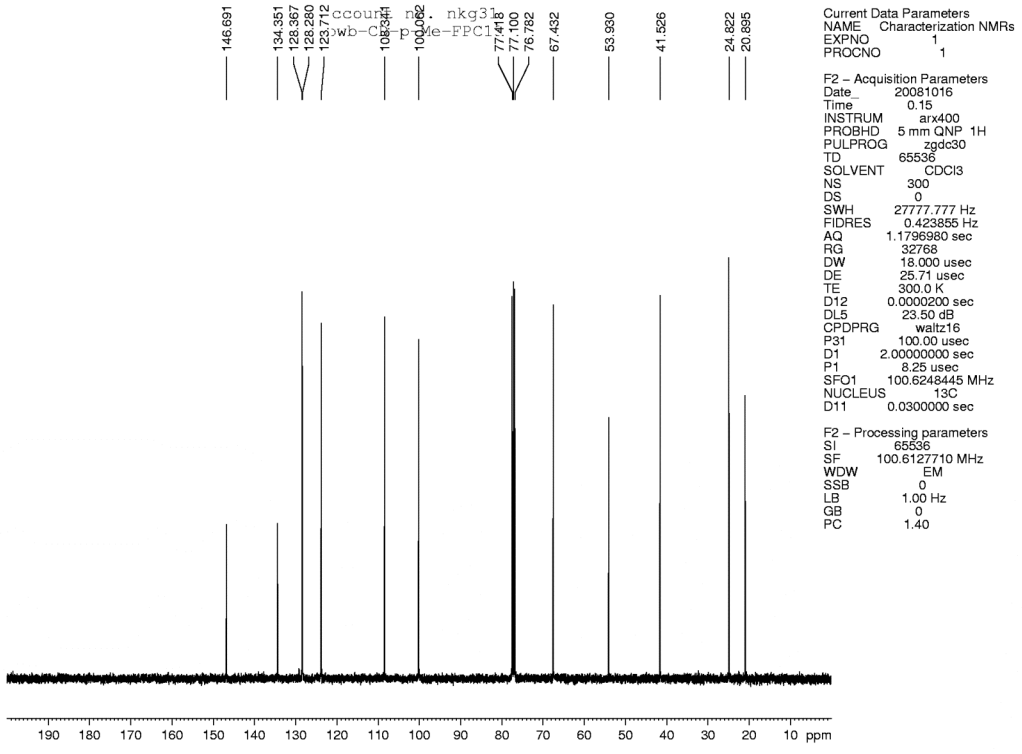


Figure A1.45 ^{13}C NMR (100 MHz, $CDCl_3$) of compound **2.82**.

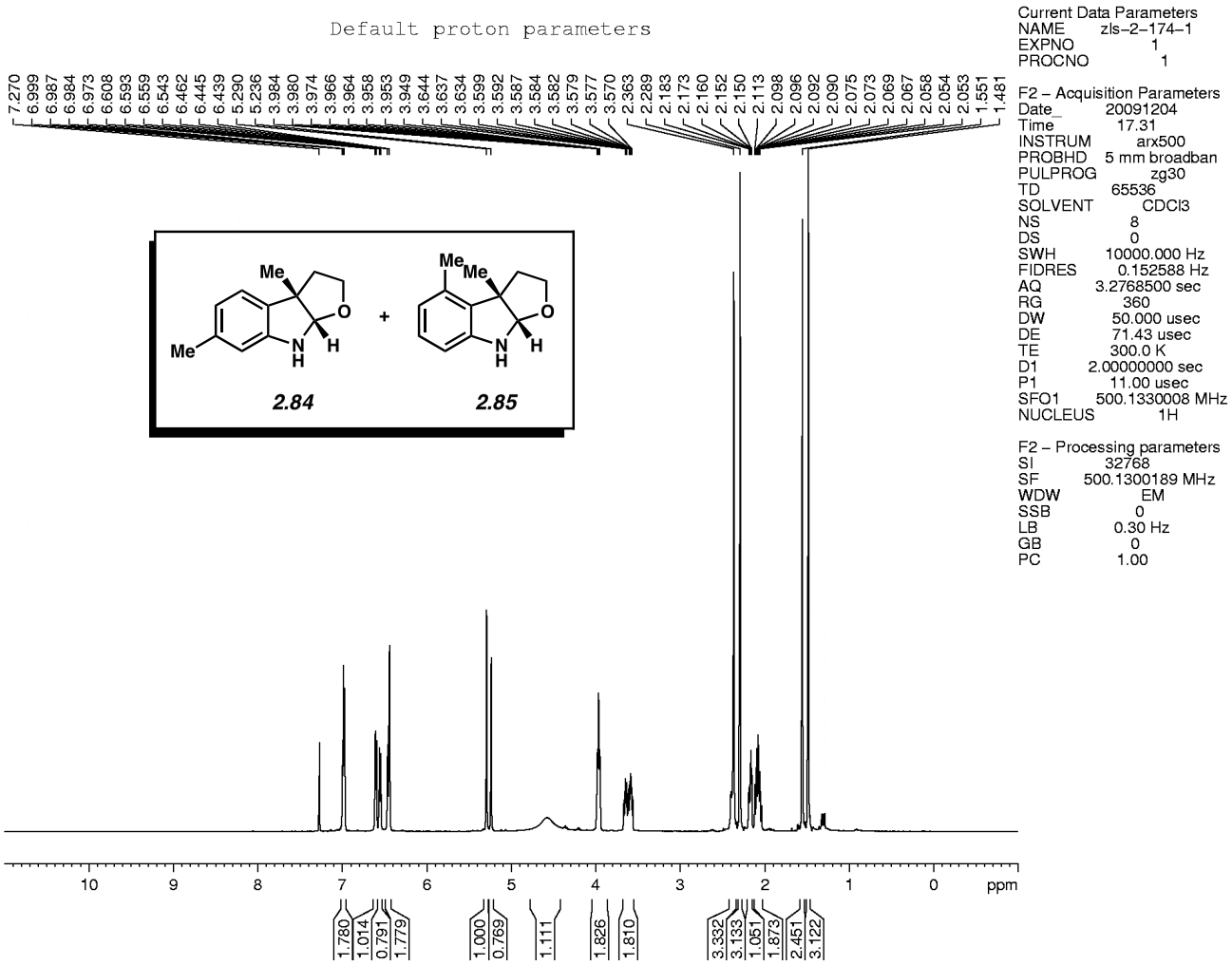


Figure A1.46 ^{1}H NMR (500 MHz, $CDCl_3$) of compounds **2.84** and **2.85**.

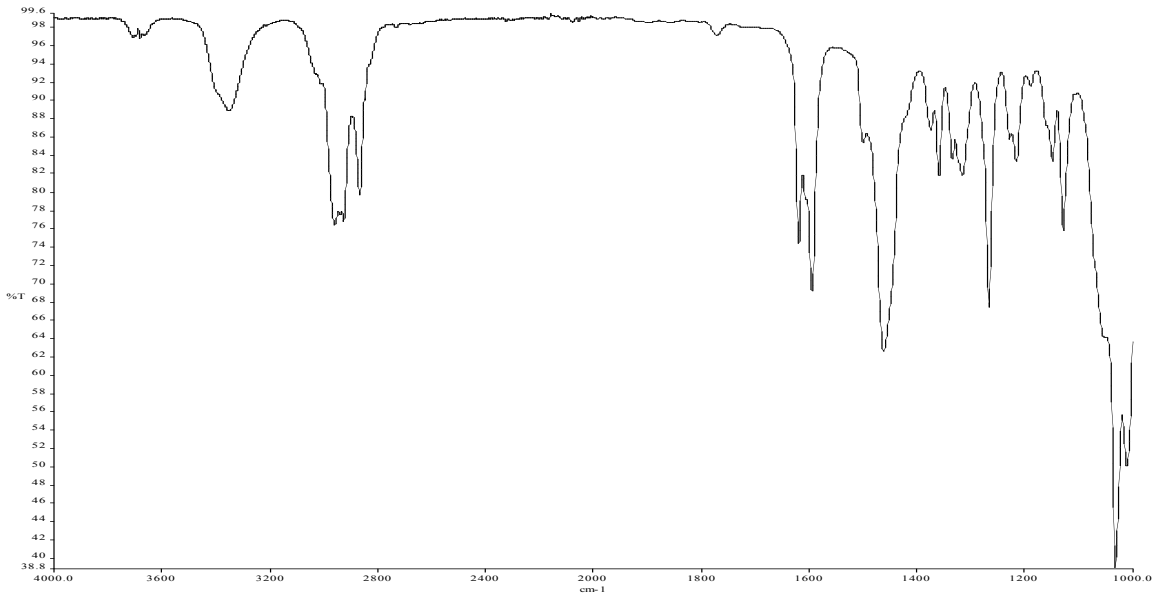


Figure A1.47 Infrared spectrum of compounds **2.84** and **2.85**.

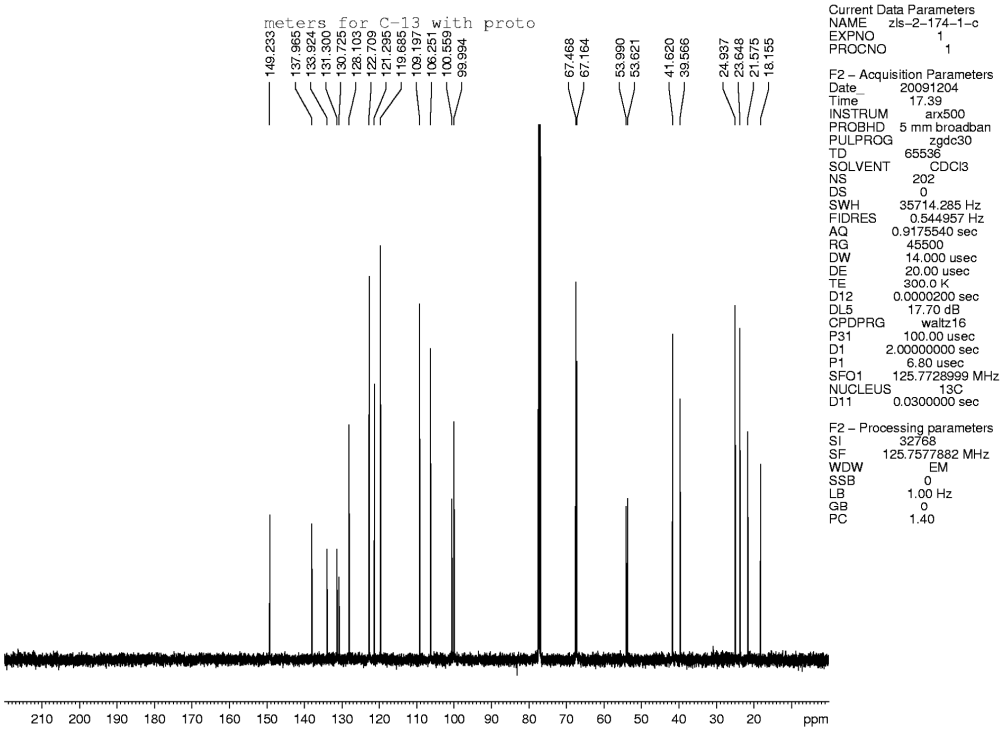


Figure A1.48 ^{13}C NMR (125 MHz, $CDCl_3$) of compounds **2.84** and **2.85**.

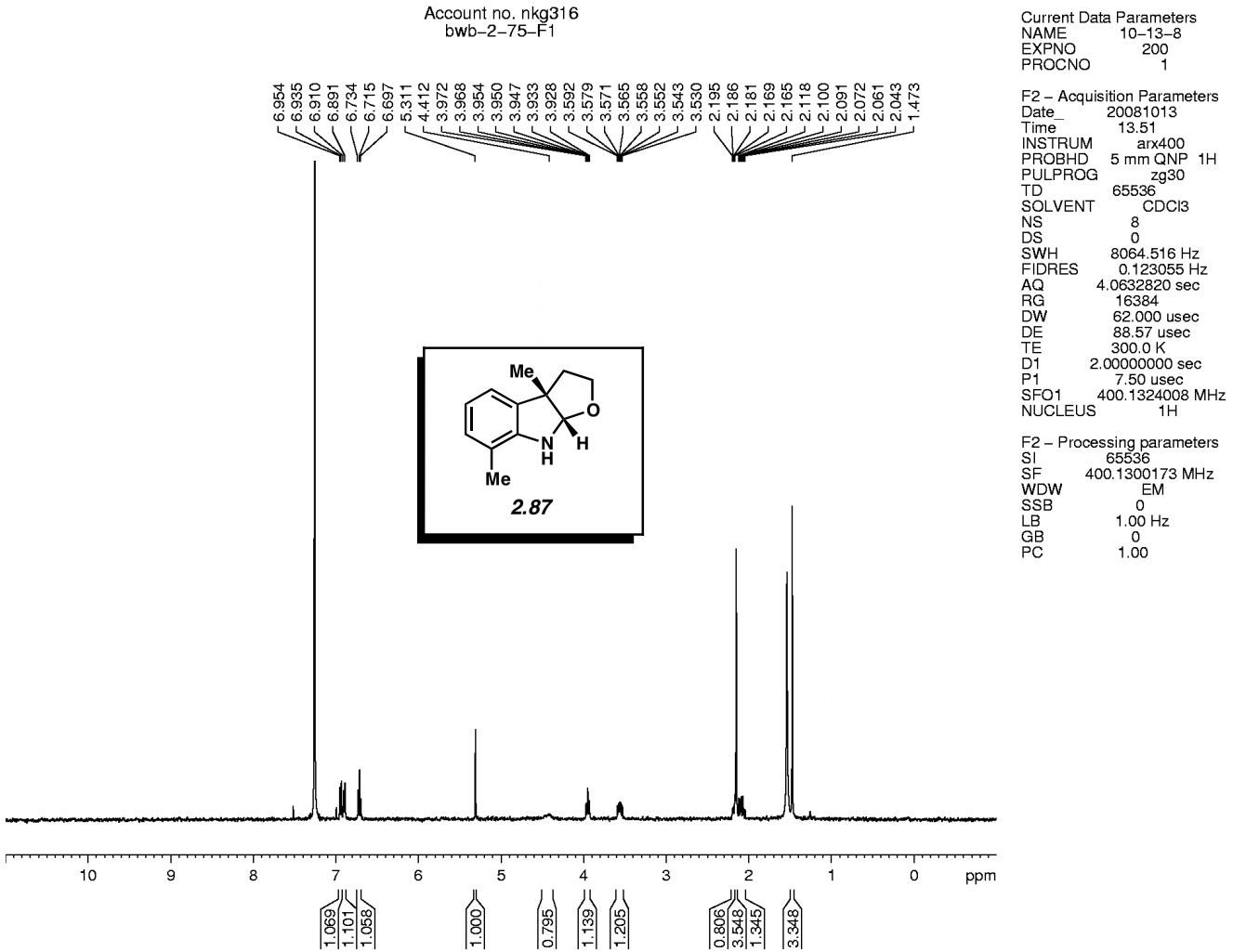


Figure A1.49 ^{1}H NMR (400 MHz, $CDCl_3$) of compound **2.87**.

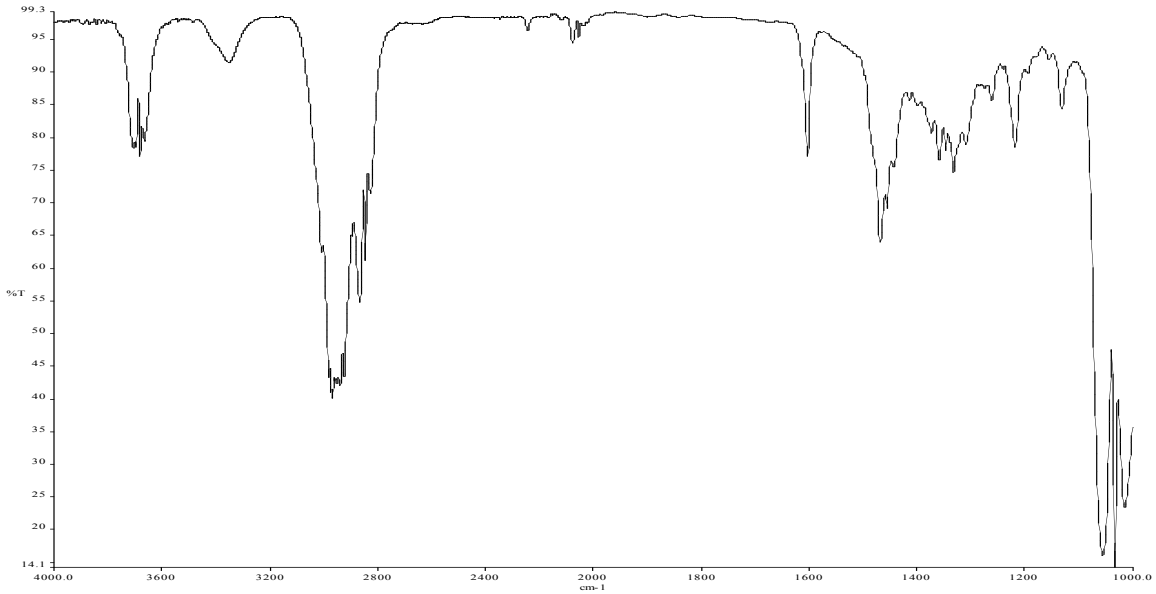


Figure A1.50 Infrared spectrum of compound **2.87**.

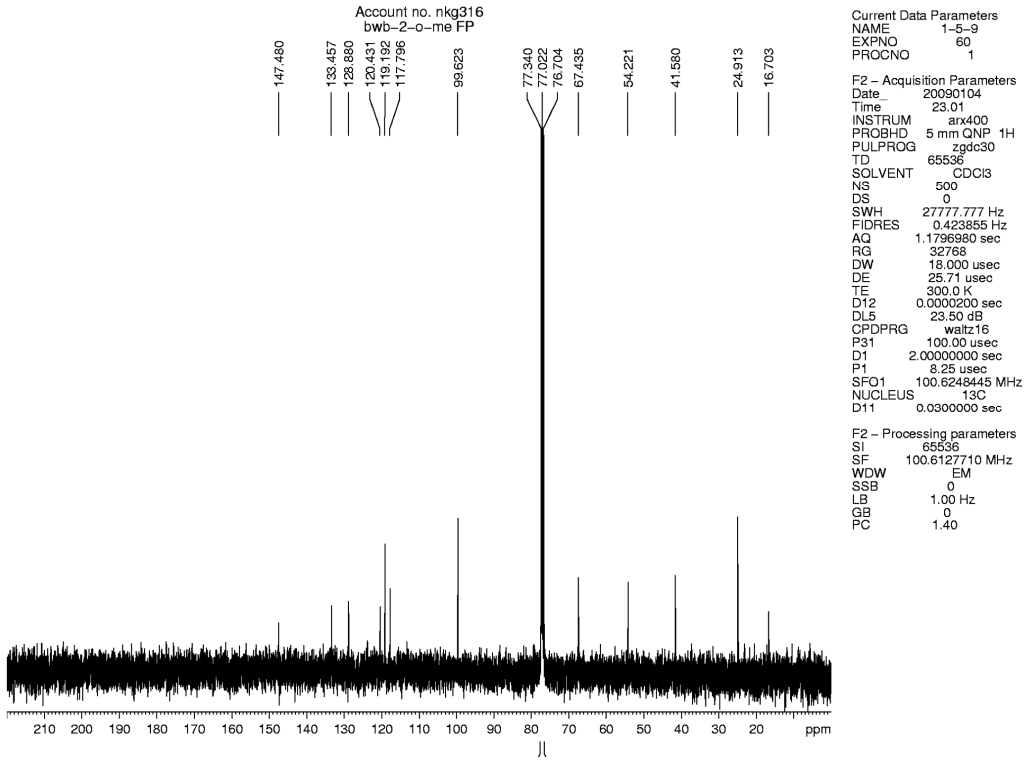


Figure A1.51 ^{13}C NMR (100 MHz, $CDCl_3$) of compound **2.87**.

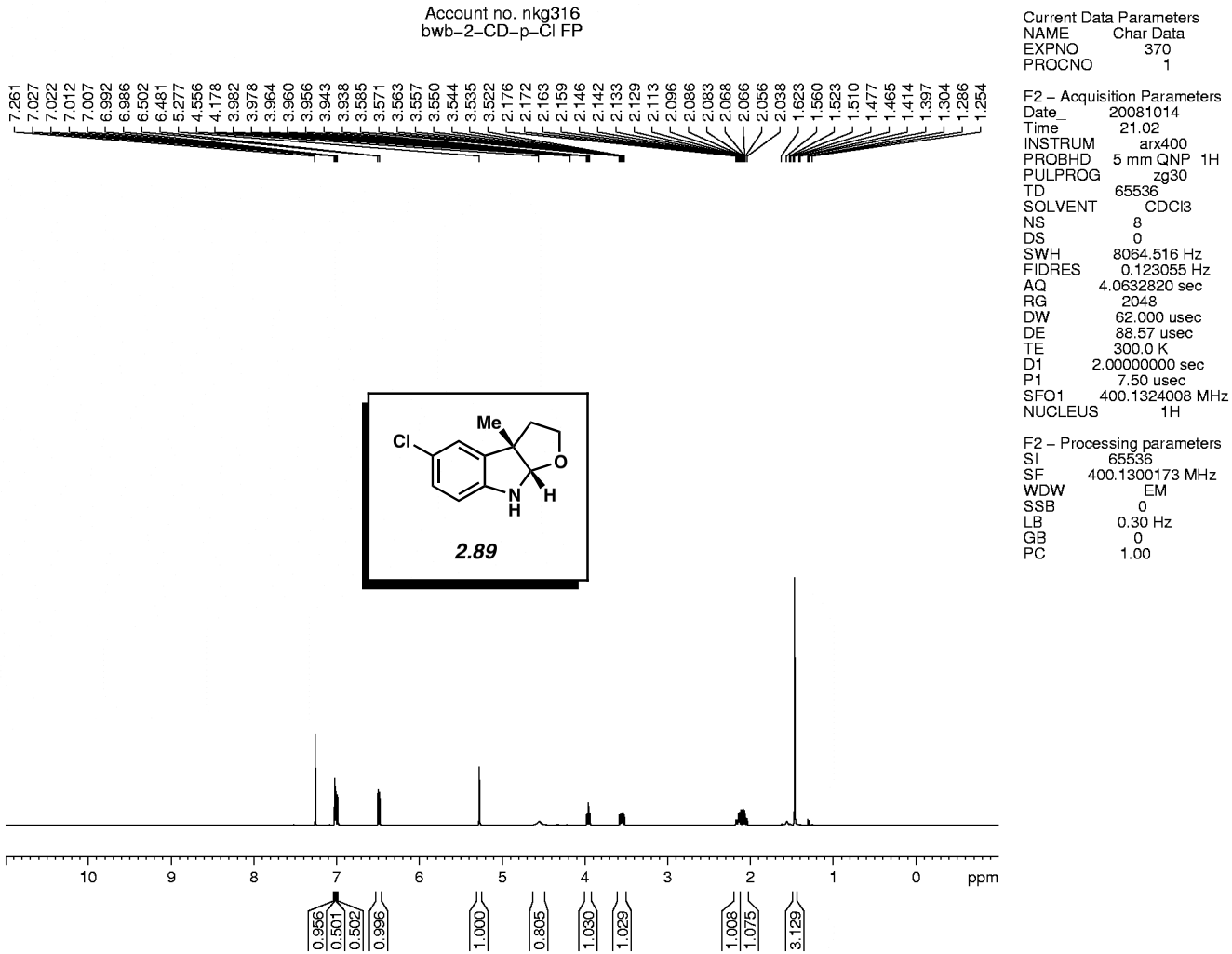


Figure A1.52 ^{1}H NMR (400 MHz, $CDCl_3$) of compound **2.89**.

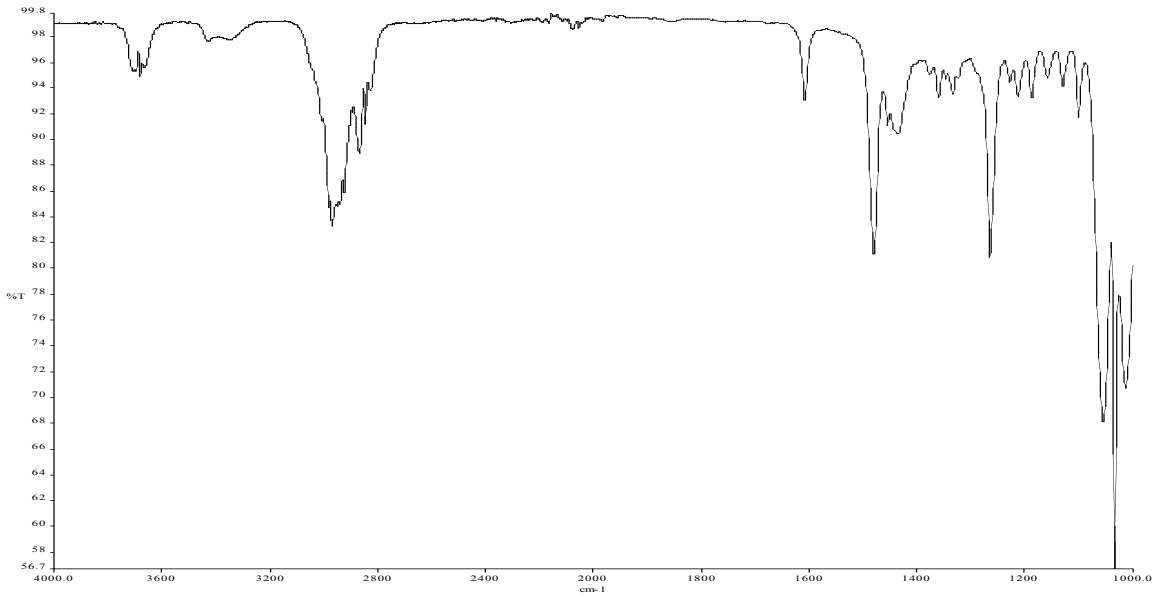
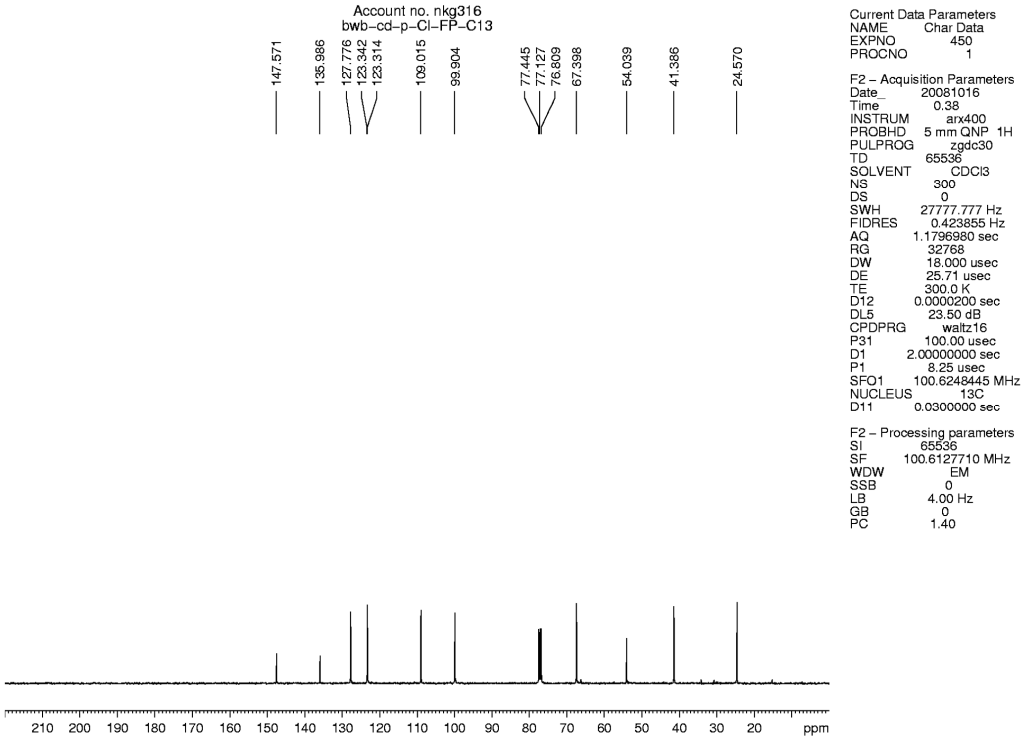


Figure A1.53 Infrared spectrum of compound **2.89**.



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DE 25.71 usec
TE 300.0 K
D12 0.0000200 sec
DL5 23.50 dB
CPDPRG waltz16
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P1 8.25 usec
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NUCLEUS 13C
D11 0.0300000 sec

F2 – Processing parameters
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GB 0
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Figure A1.54 ^{13}C NMR (100 MHz, $CDCl_3$) of compound **2.89**.

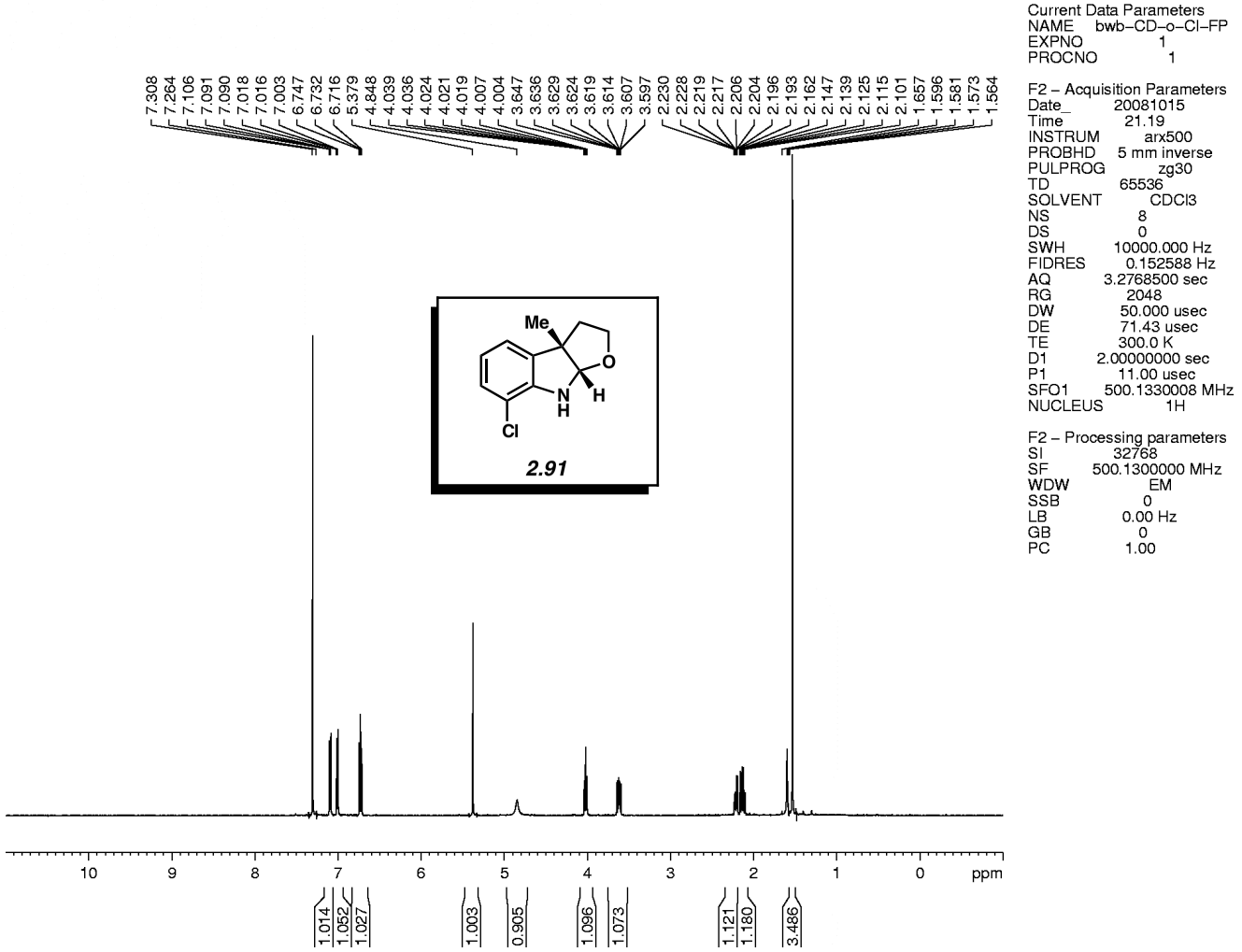


Figure A1.55 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **2.91**.

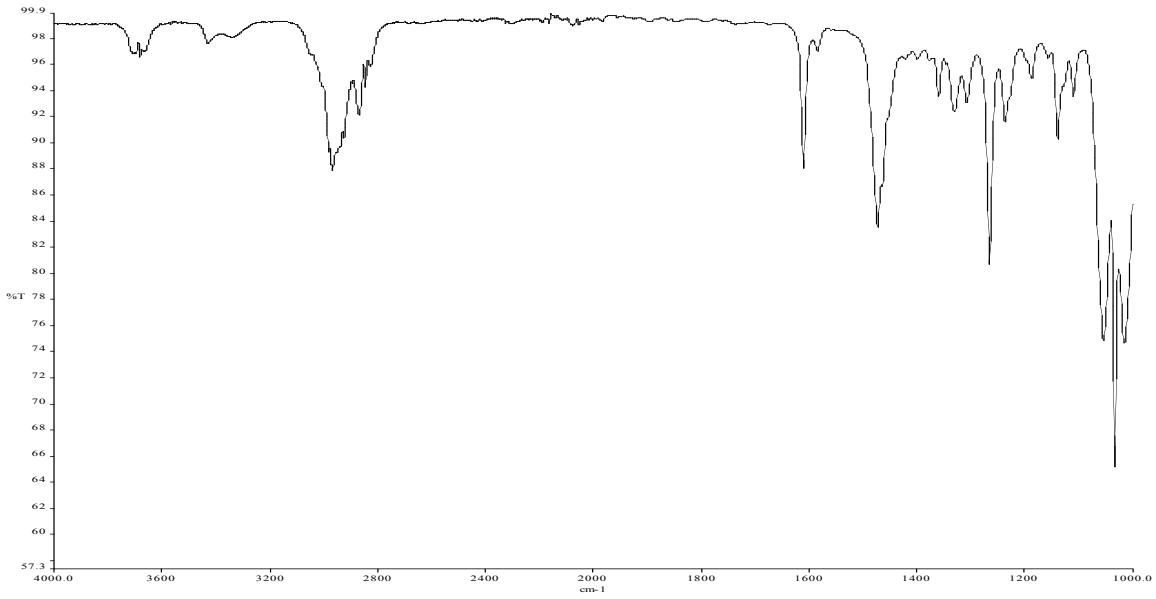


Figure A1.56 Infrared spectrum of compound **2.91**.

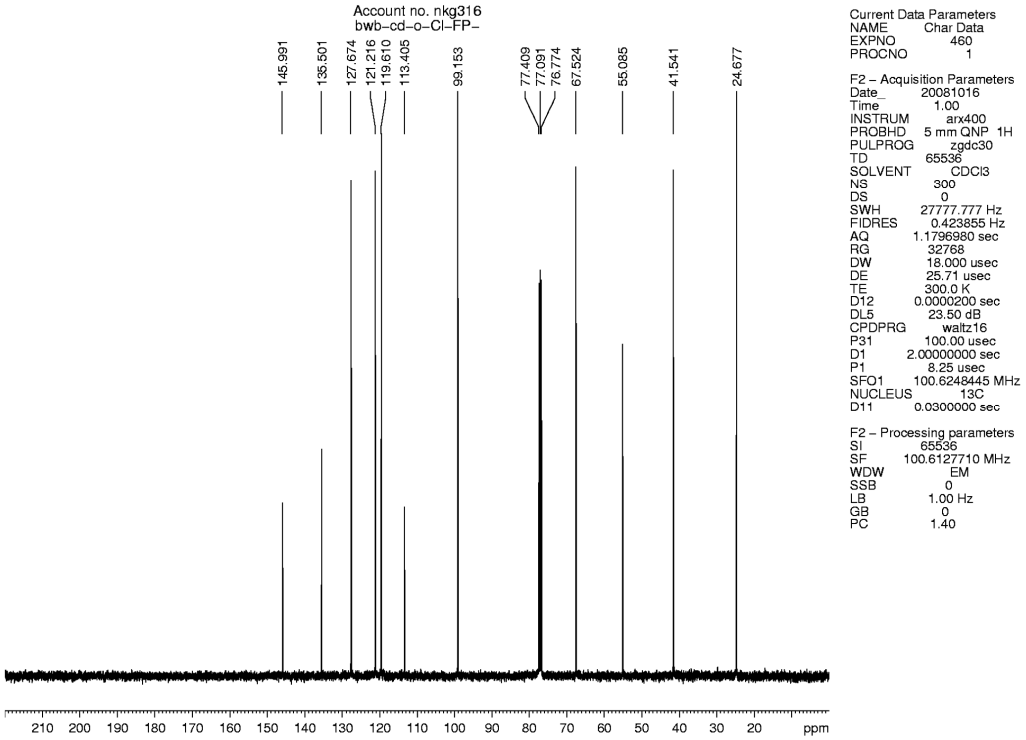


Figure A1.57 ^{13}C NMR (100 MHz, $CDCl_3$) of compound **2.91**.

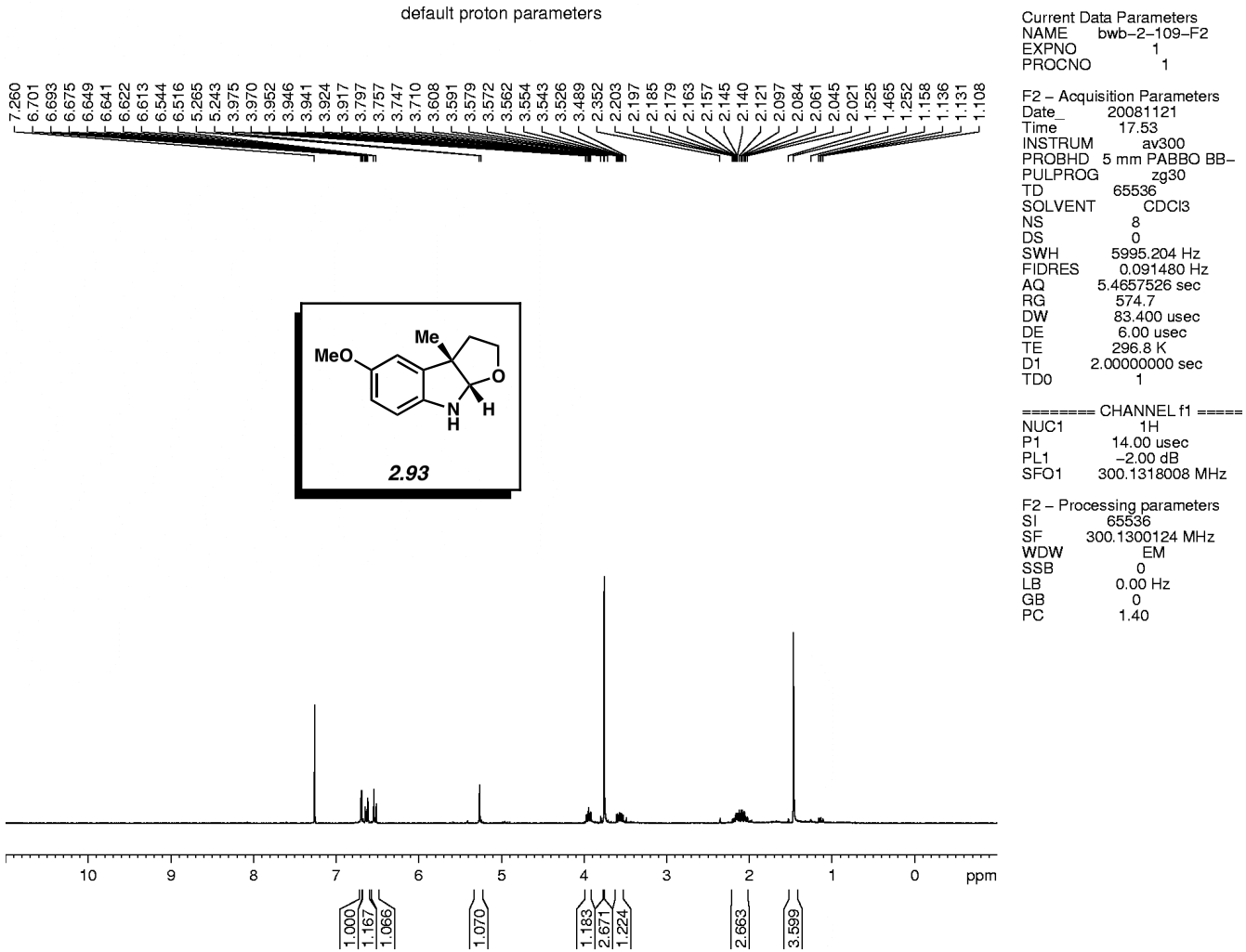


Figure A1.58 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **2.93**.

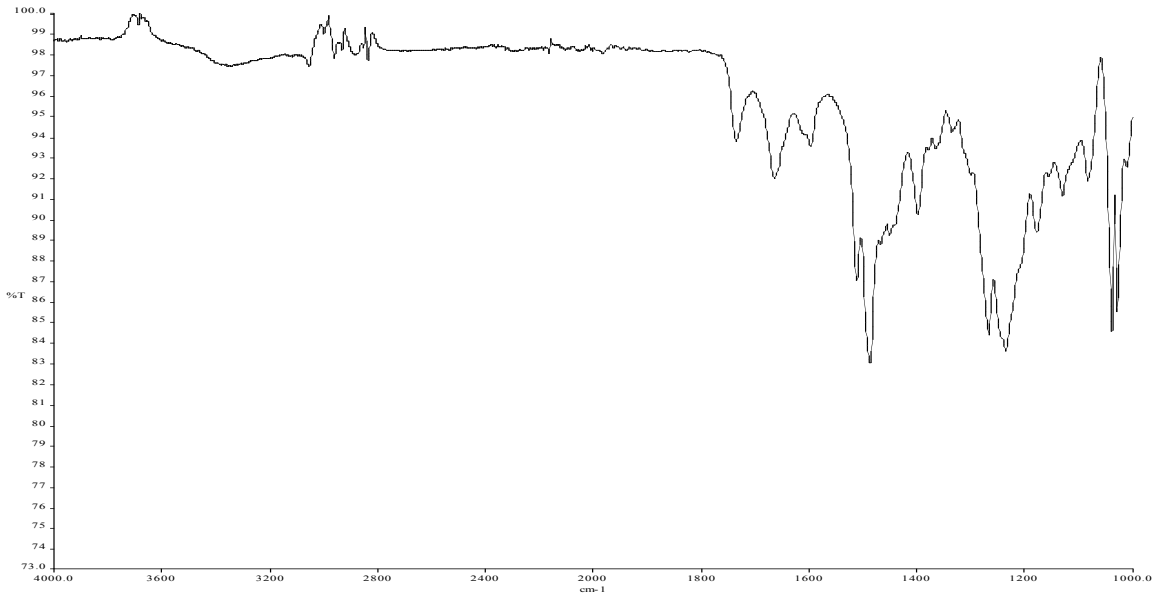


Figure A1.59 Infrared spectrum of compound **2.93**.

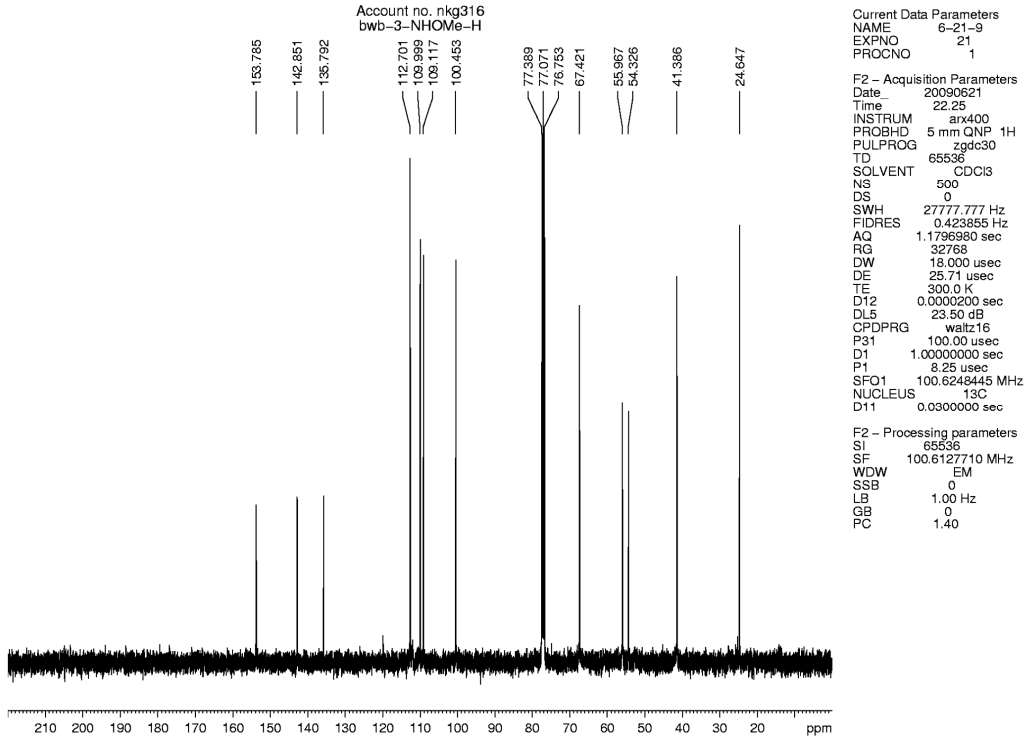


Figure A1.60 ^{13}C NMR (100 MHz, $CDCl_3$) of compound **2.93**.

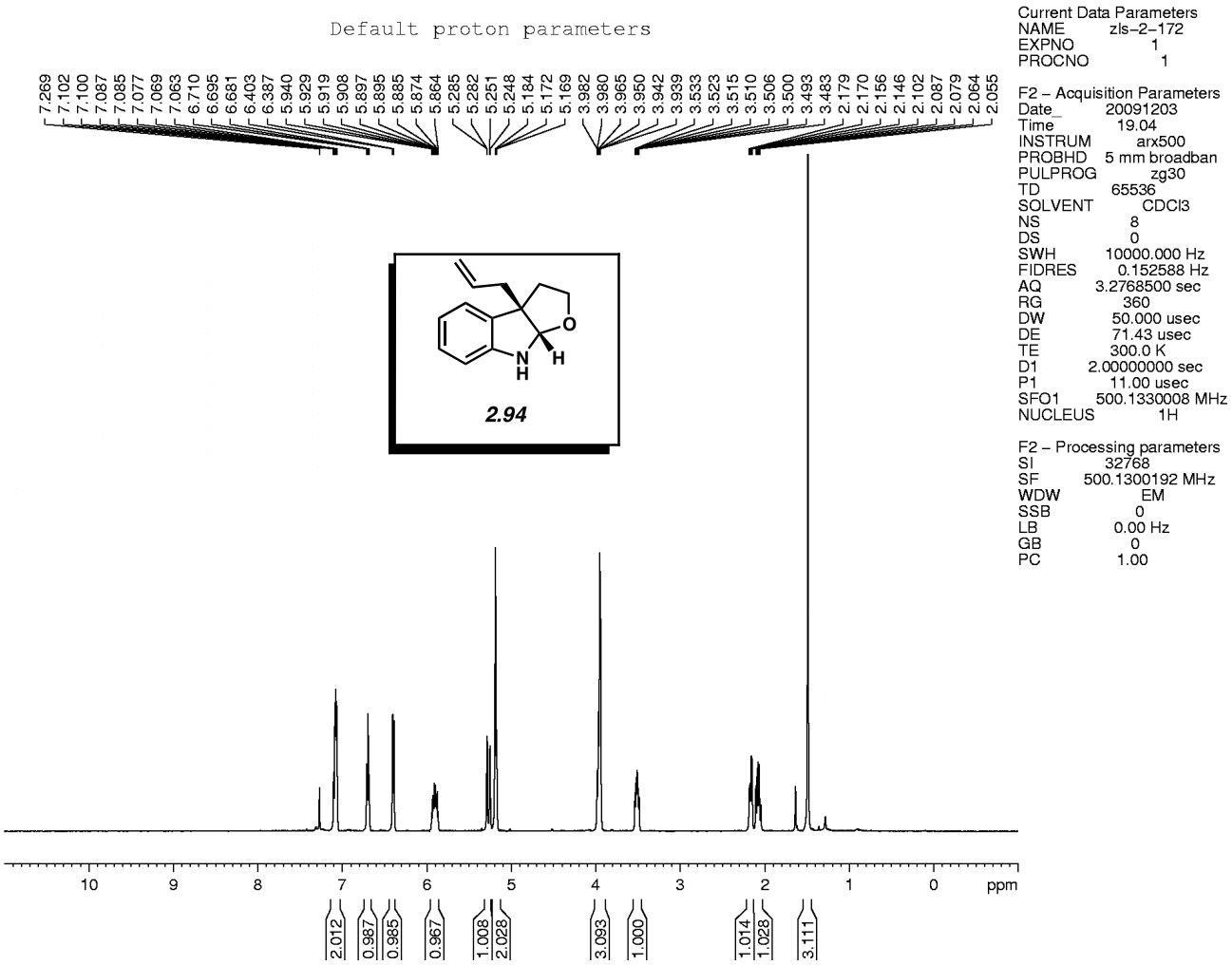


Figure A1.61 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **2.94**.

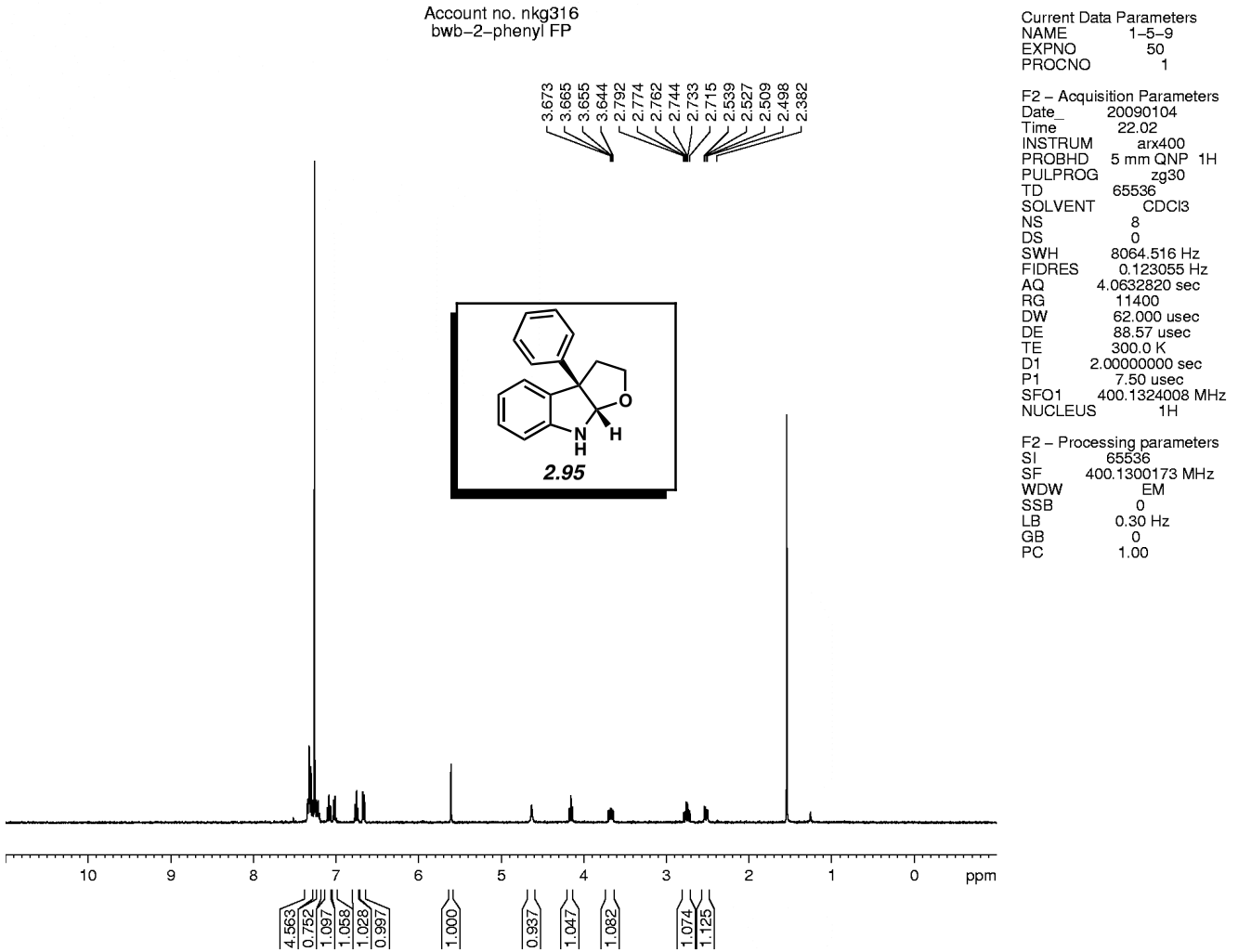


Figure A1.62 ^{1}H NMR (400 MHz, $CDCl_3$) of compound **2.95**.

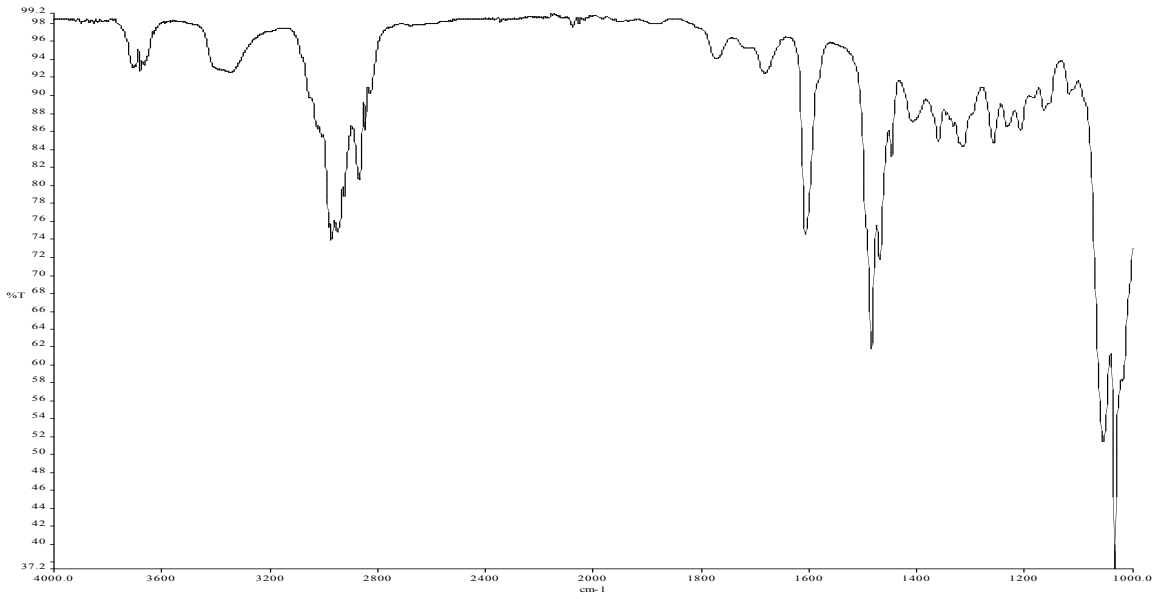


Figure A1.63 Infrared spectrum of compound **2.95**.

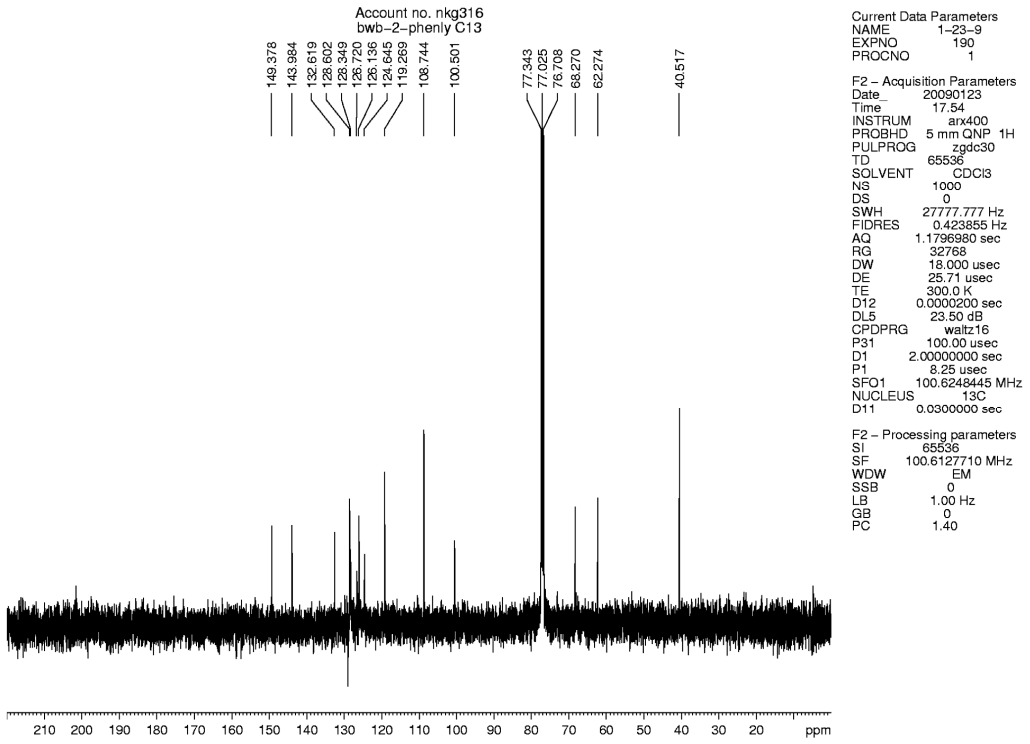


Figure A1.64 ^{13}C NMR (100 MHz, $CDCl_3$) of compound **2.95**.

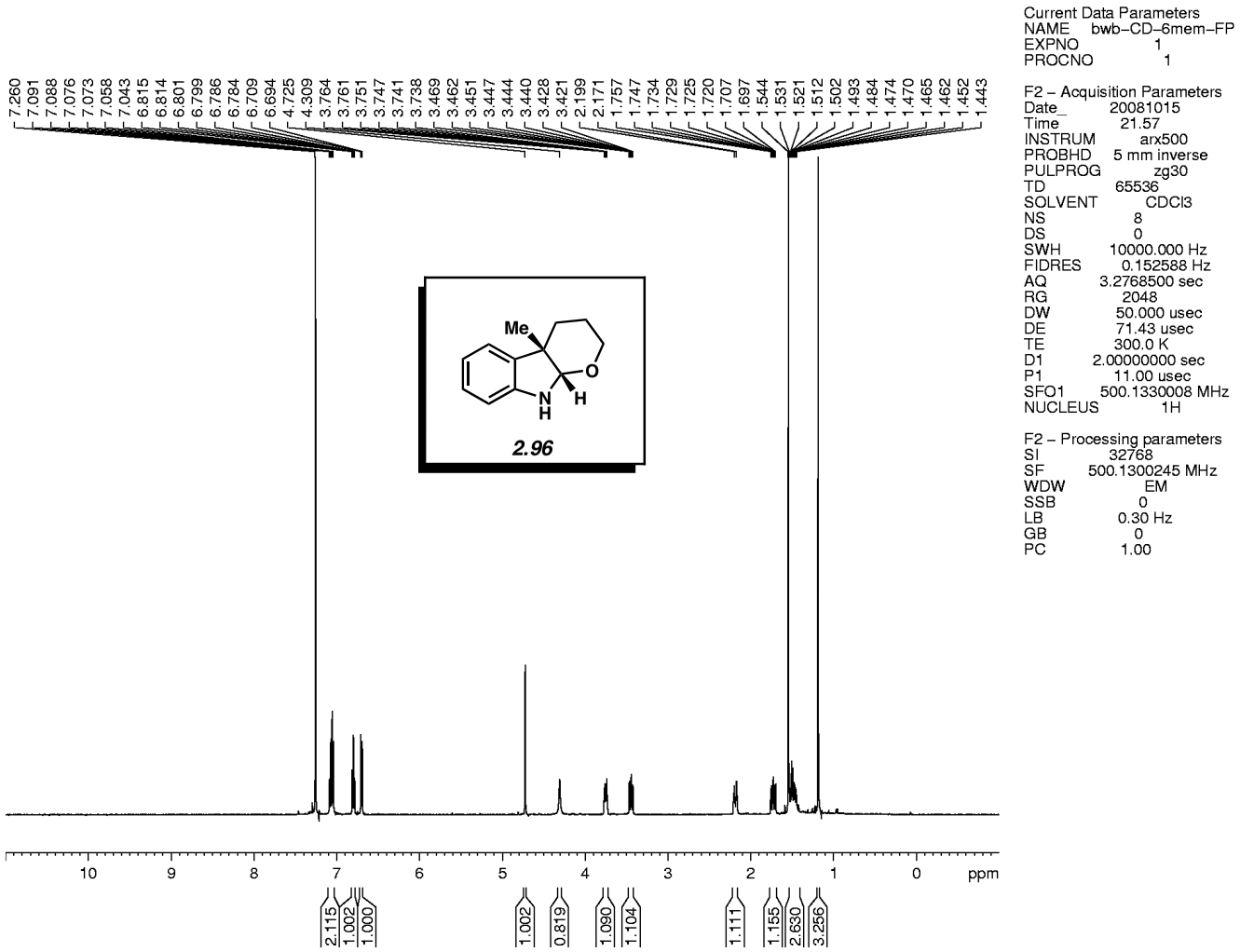


Figure A1.65 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **2.96**.

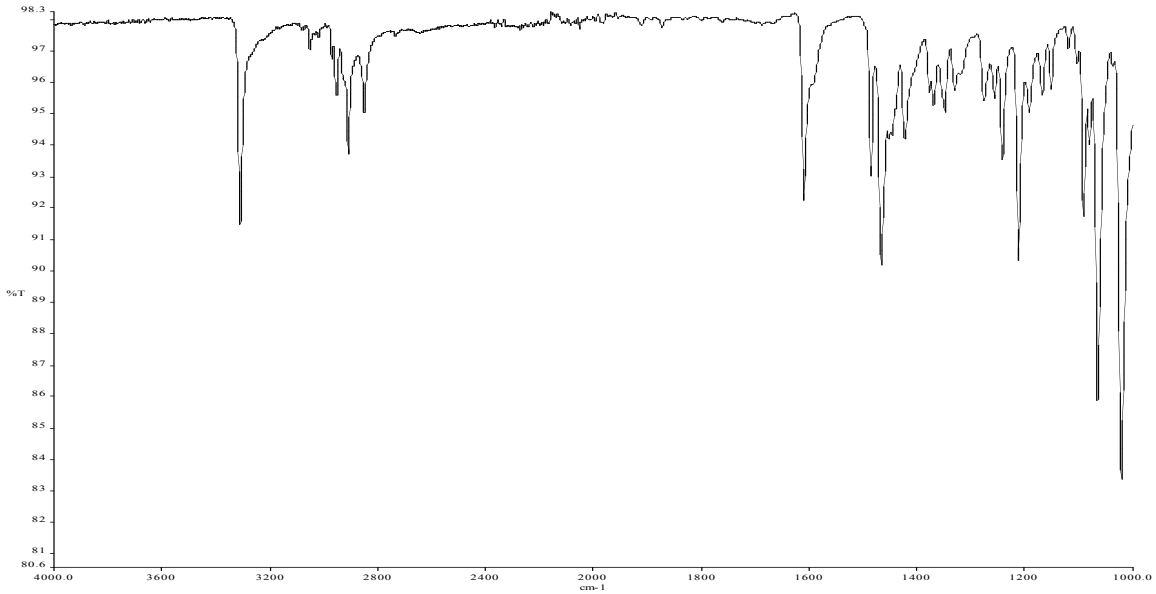


Figure A1.66 Infrared spectrum of compound **2.96**.

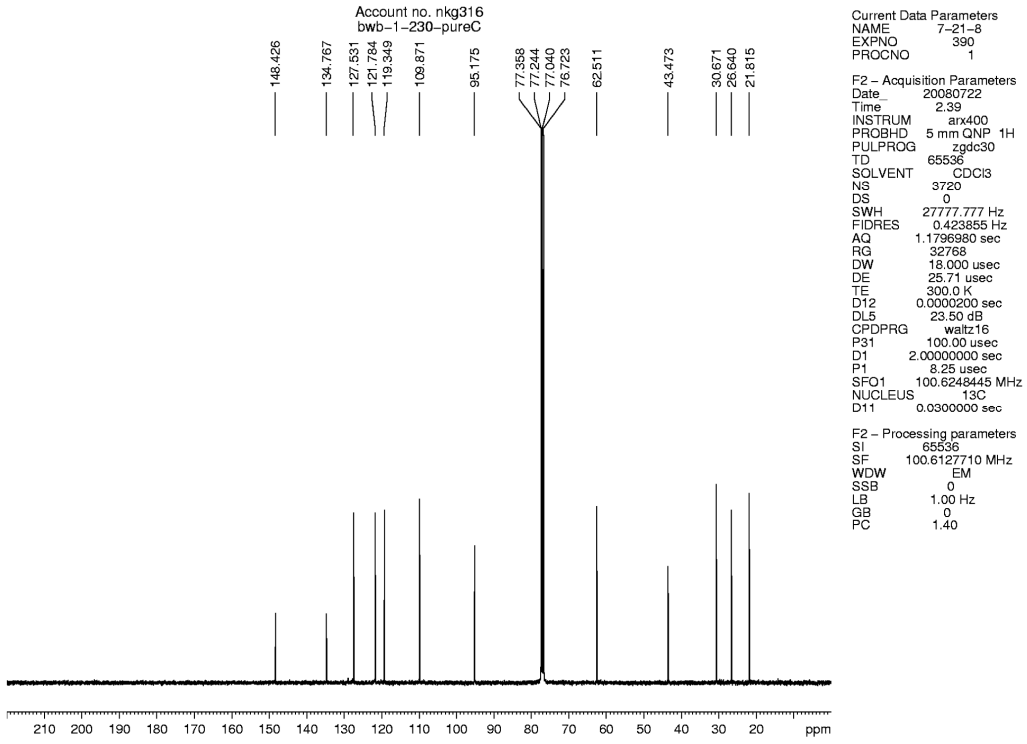


Figure A1.67 ^{13}C NMR (100 MHz, $CDCl_3$) of compound **2.96**.

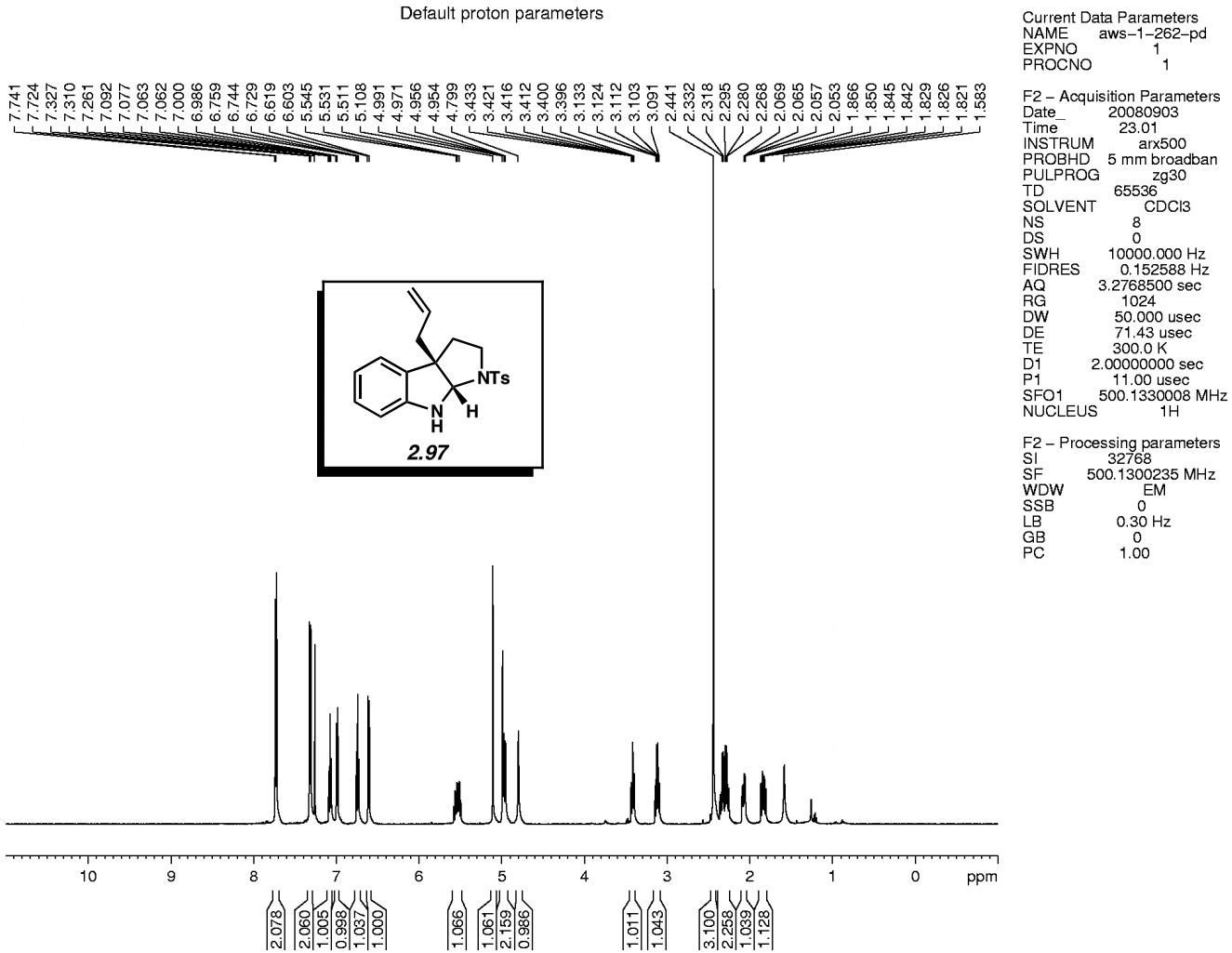


Figure A1.68 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **2.97**.

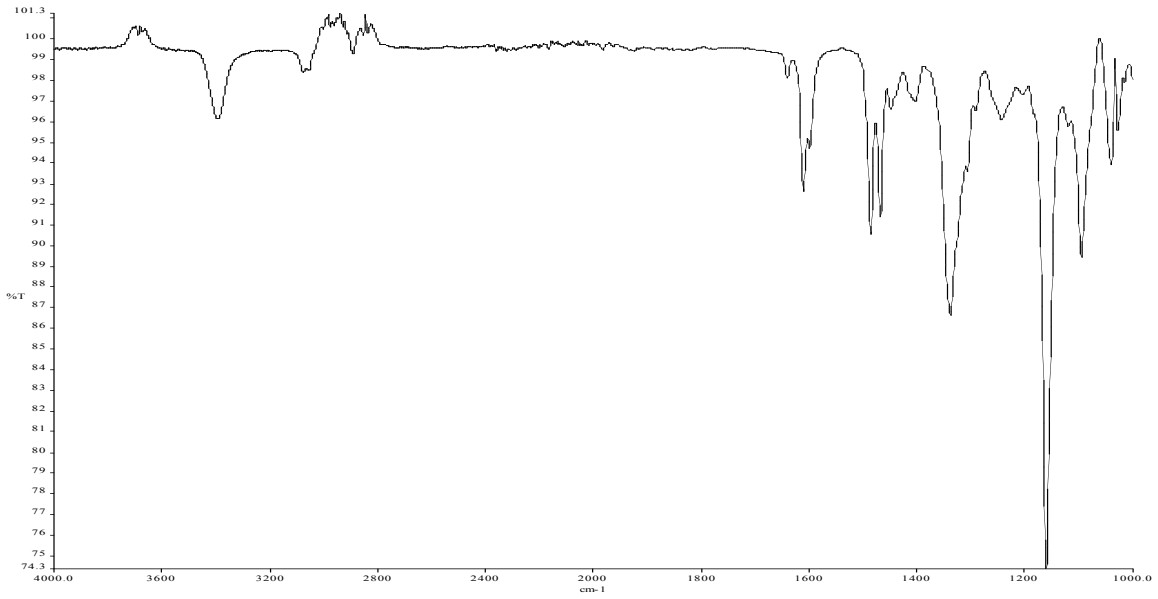


Figure A1.69 Infrared spectrum of compound **2.97**.

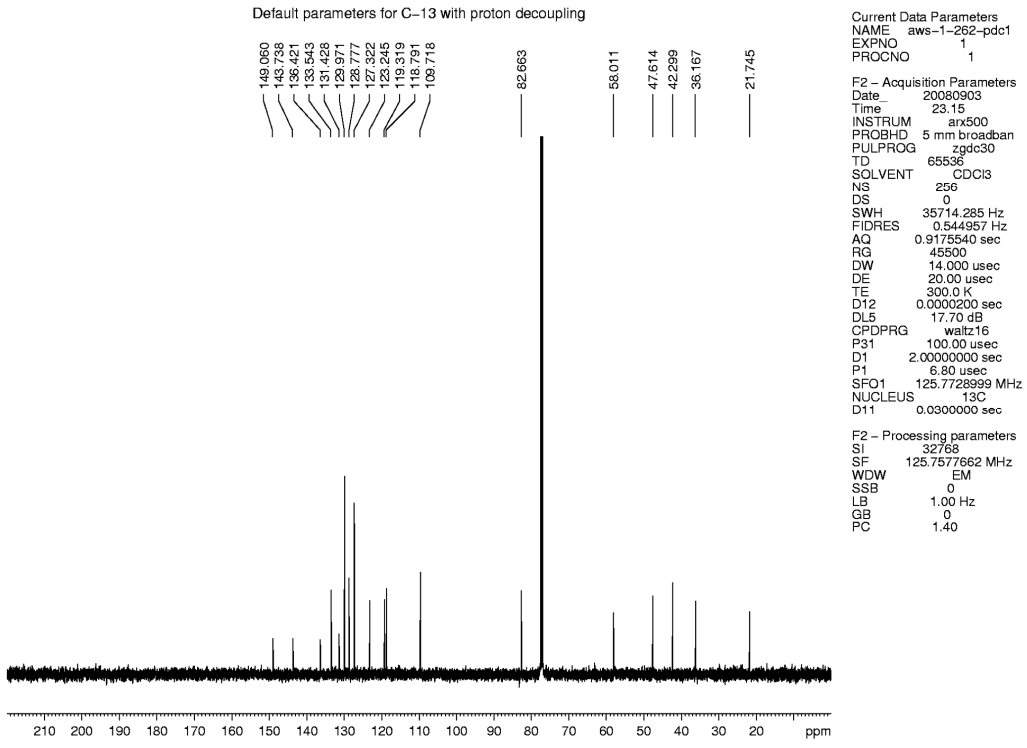


Figure A1.70 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **2.97**.

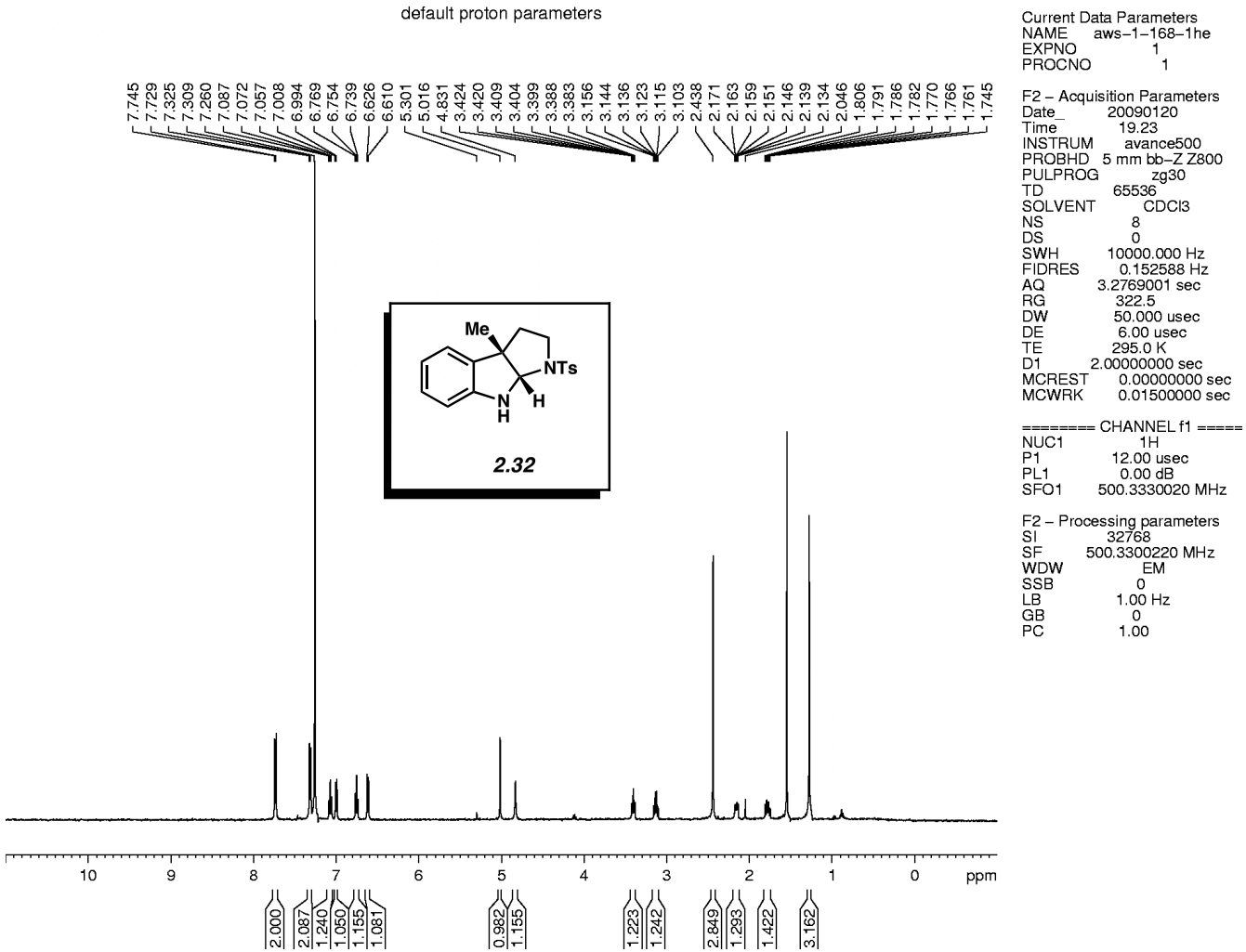


Figure A1.71 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **2.32**.

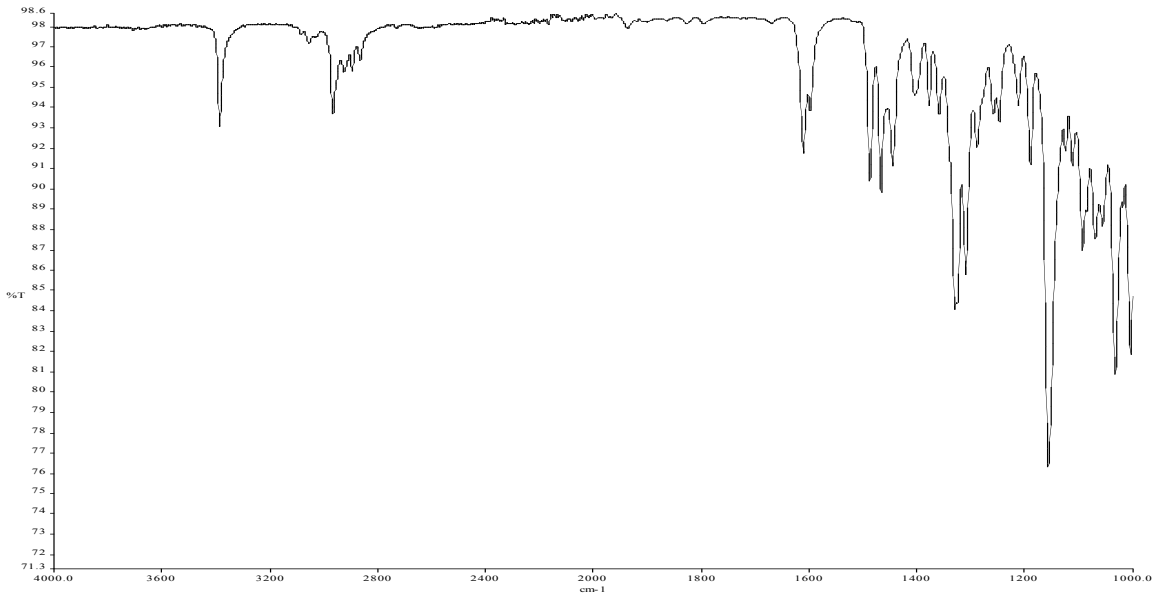


Figure A1.72 Infrared spectrum of compound **2.32**.

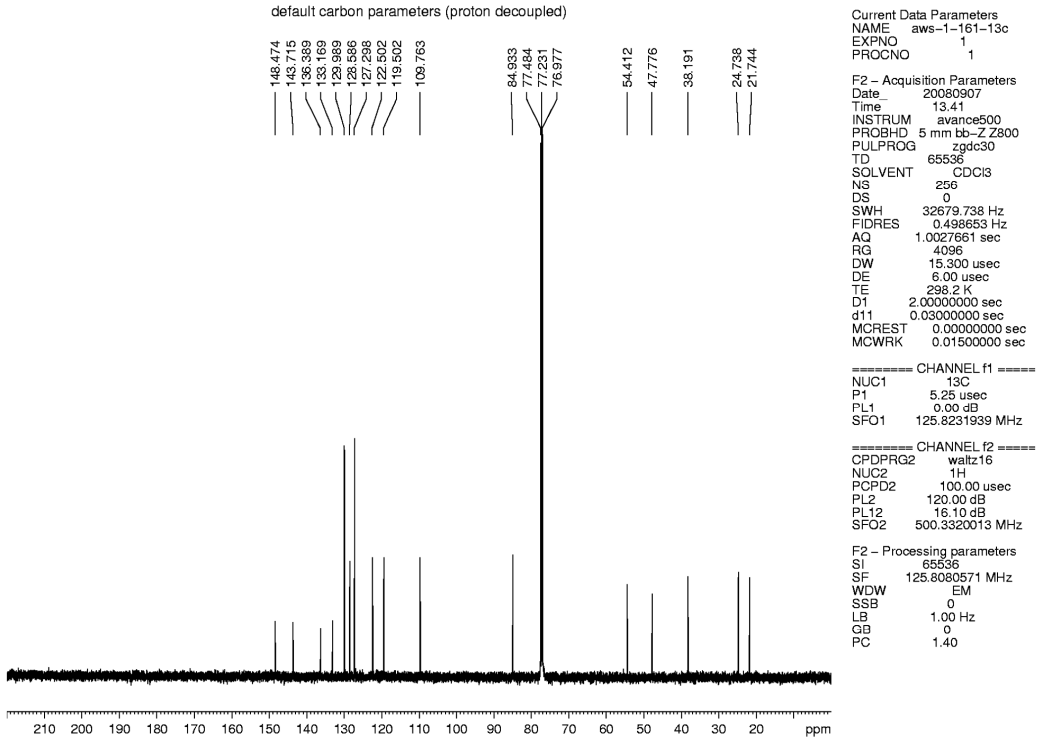


Figure A1.73 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **2.32**.

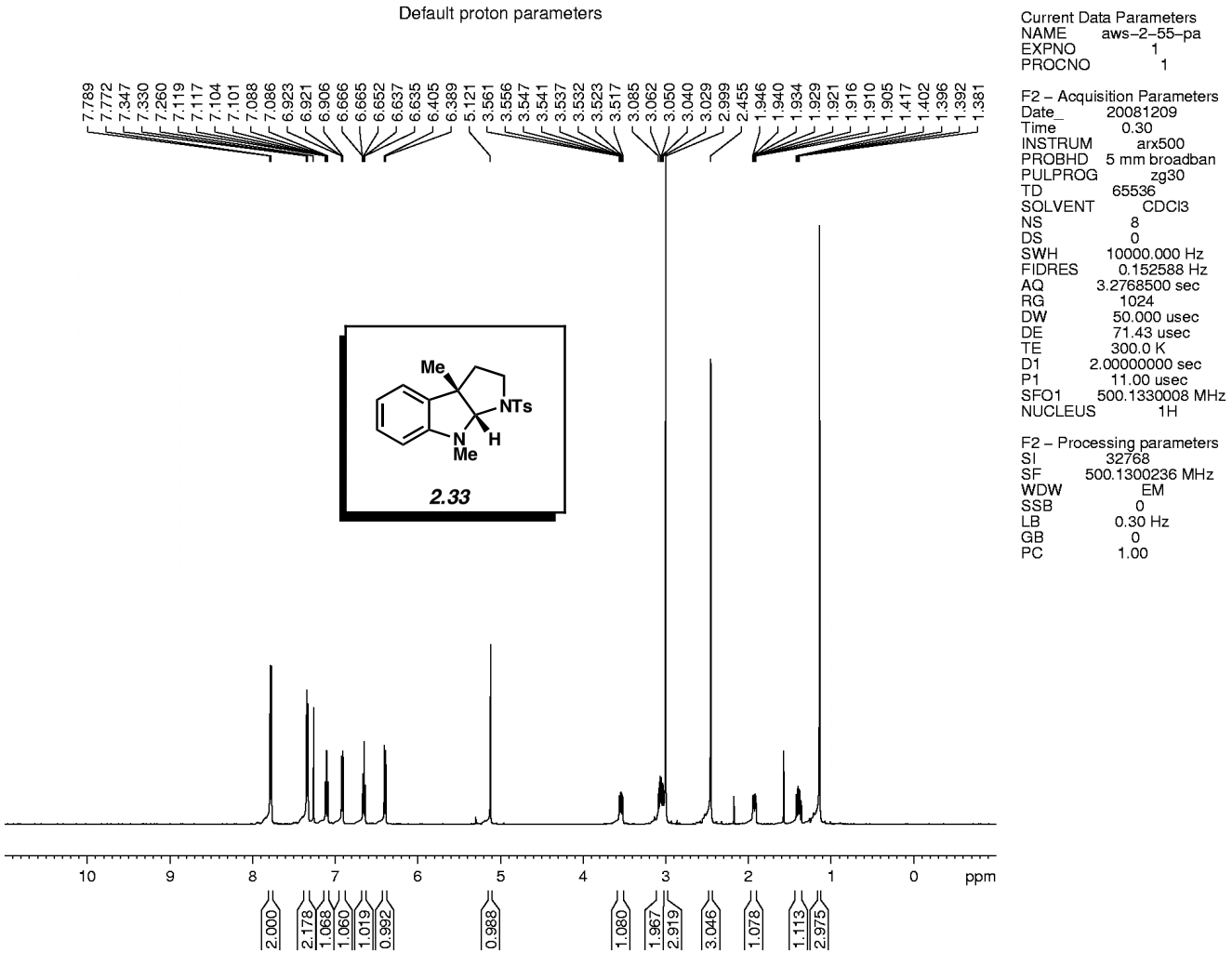


Figure A1.74 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **2.33**.

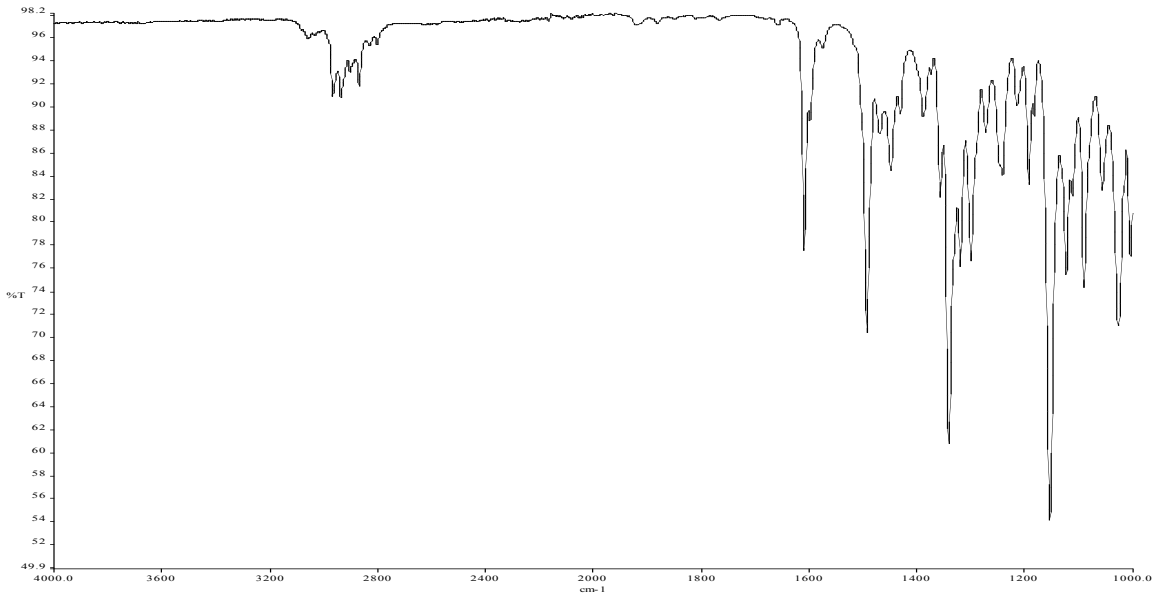


Figure A1.75 Infrared spectrum of compound **2.33**.

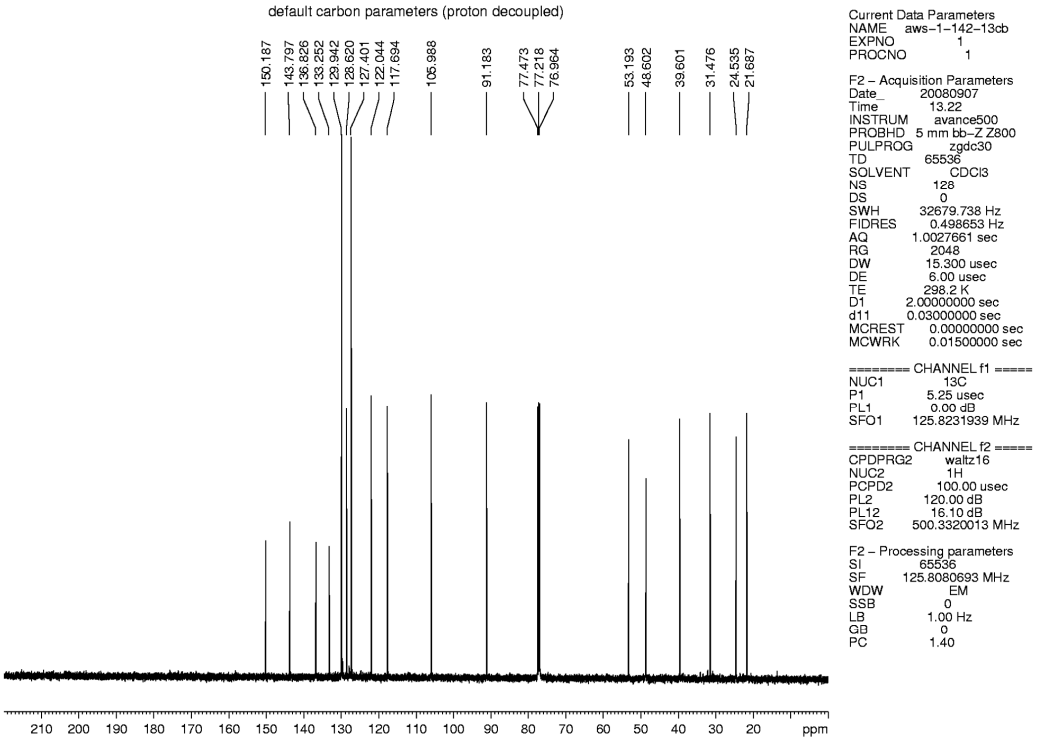


Figure A1.76 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **2.33**.

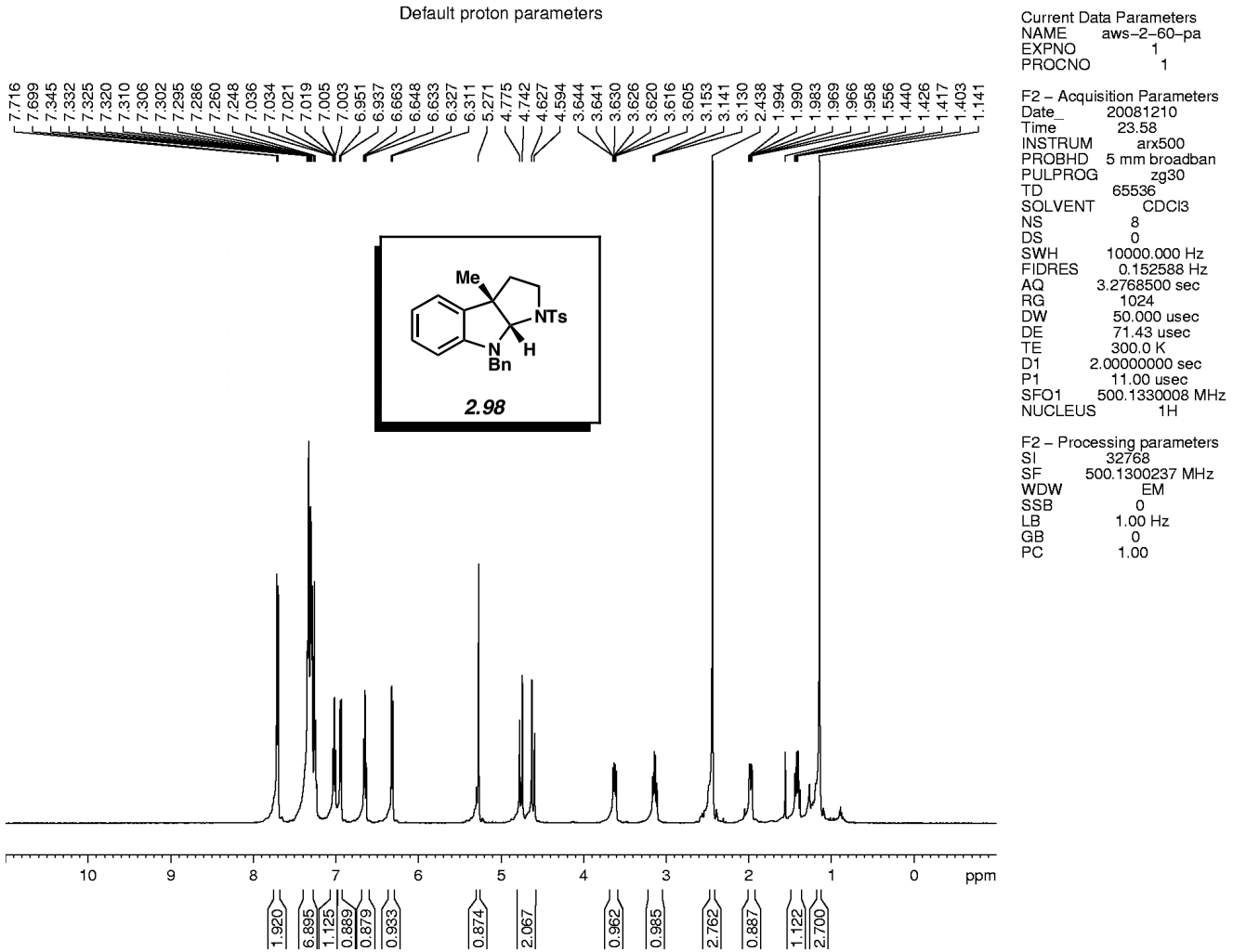


Figure A1.77 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **2.98**.

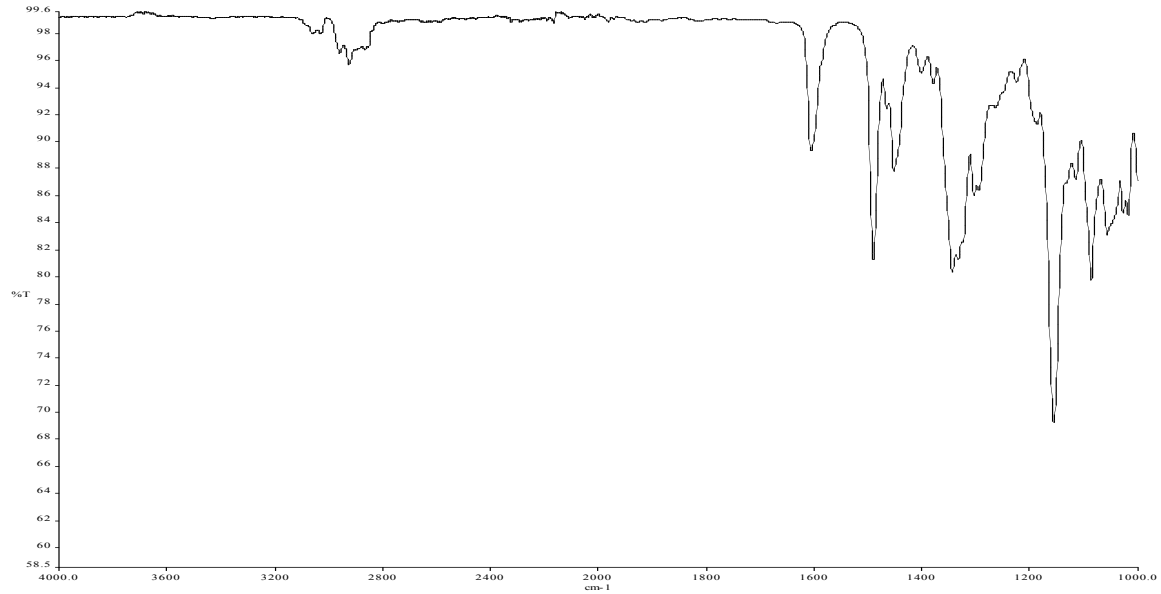


Figure A1.78 Infrared spectrum of compound **2.98**.

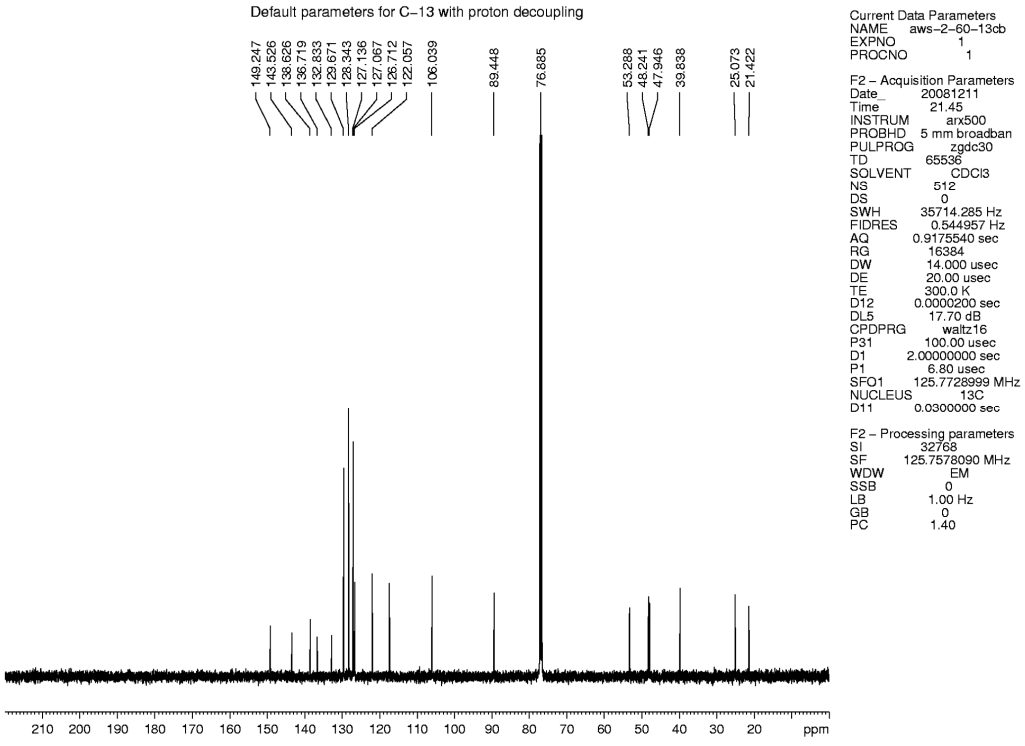


Figure A1.79 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **2.98**.

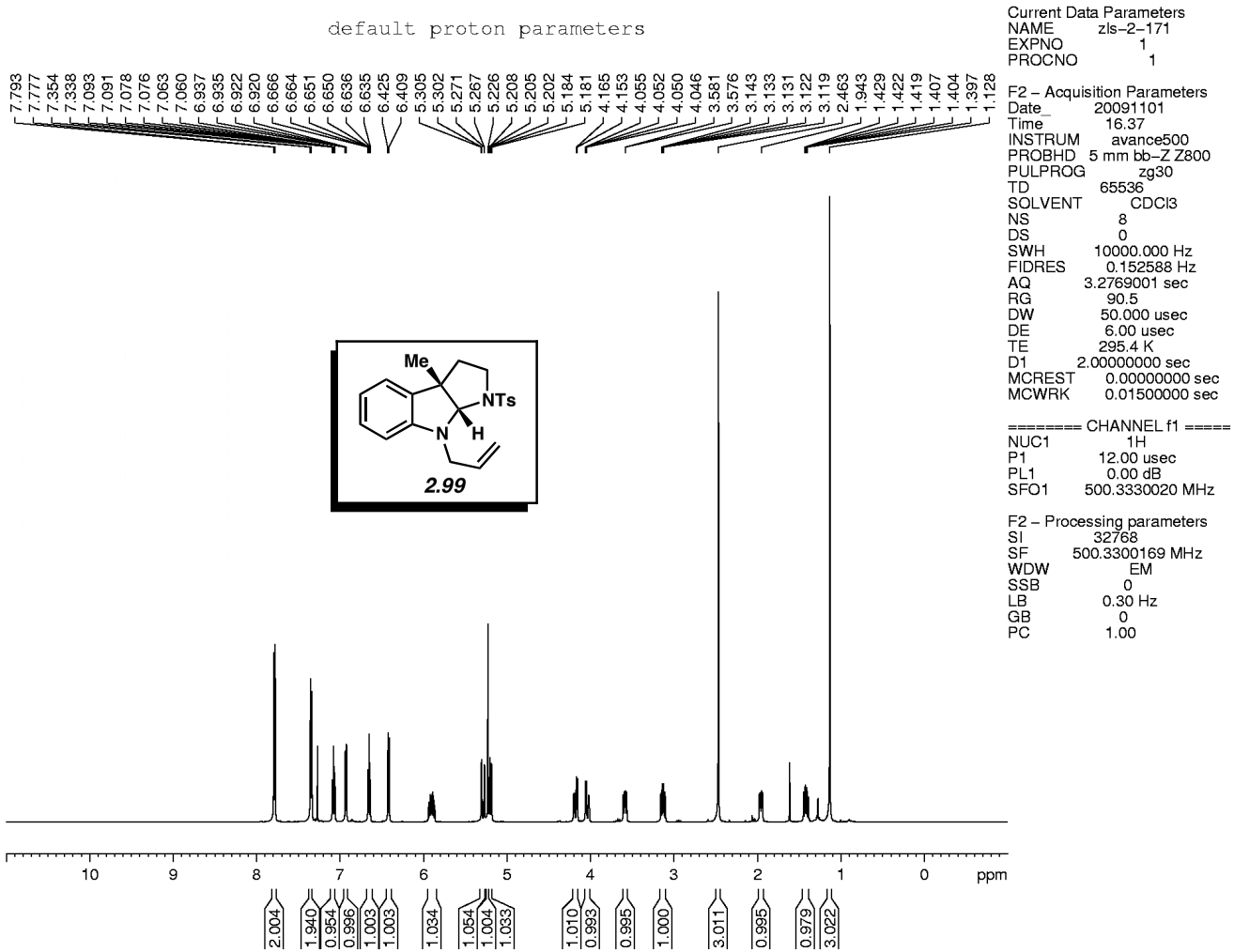


Figure A1.80 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **2.99**.

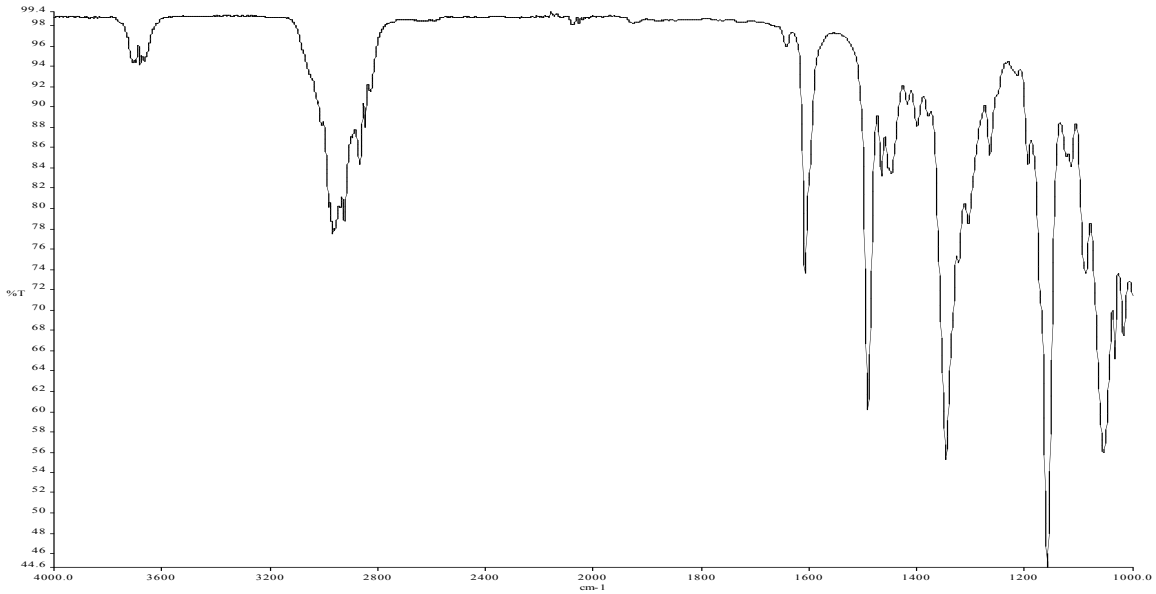


Figure A1.81 Infrared spectrum of compound **2.99**.

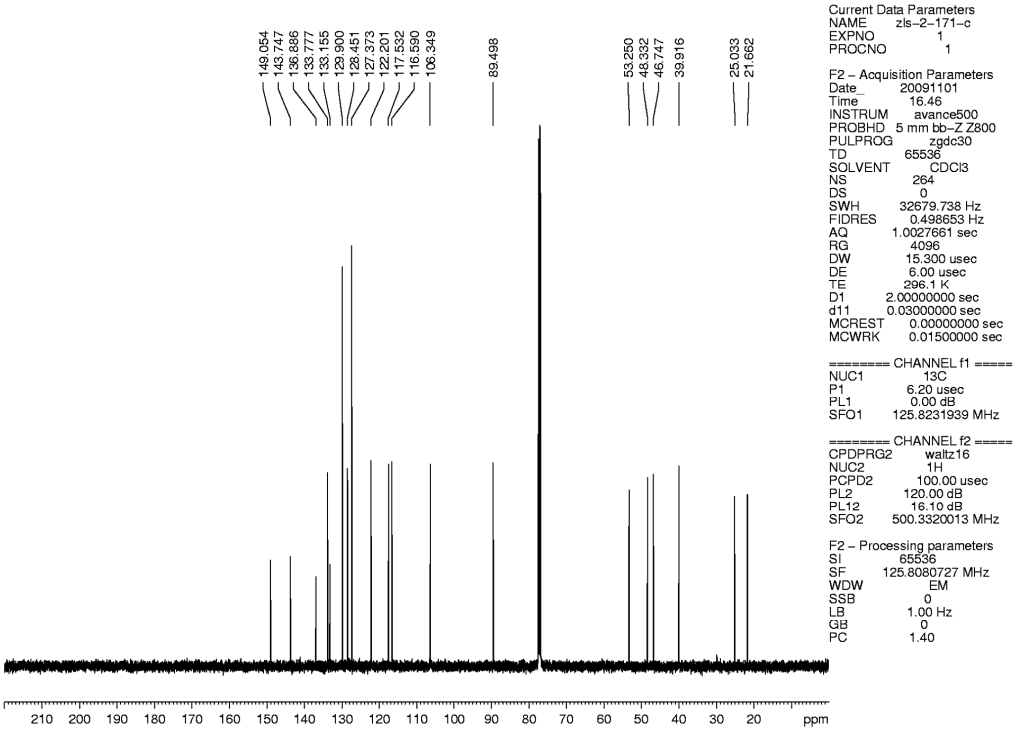


Figure A1.82 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **2.99**.

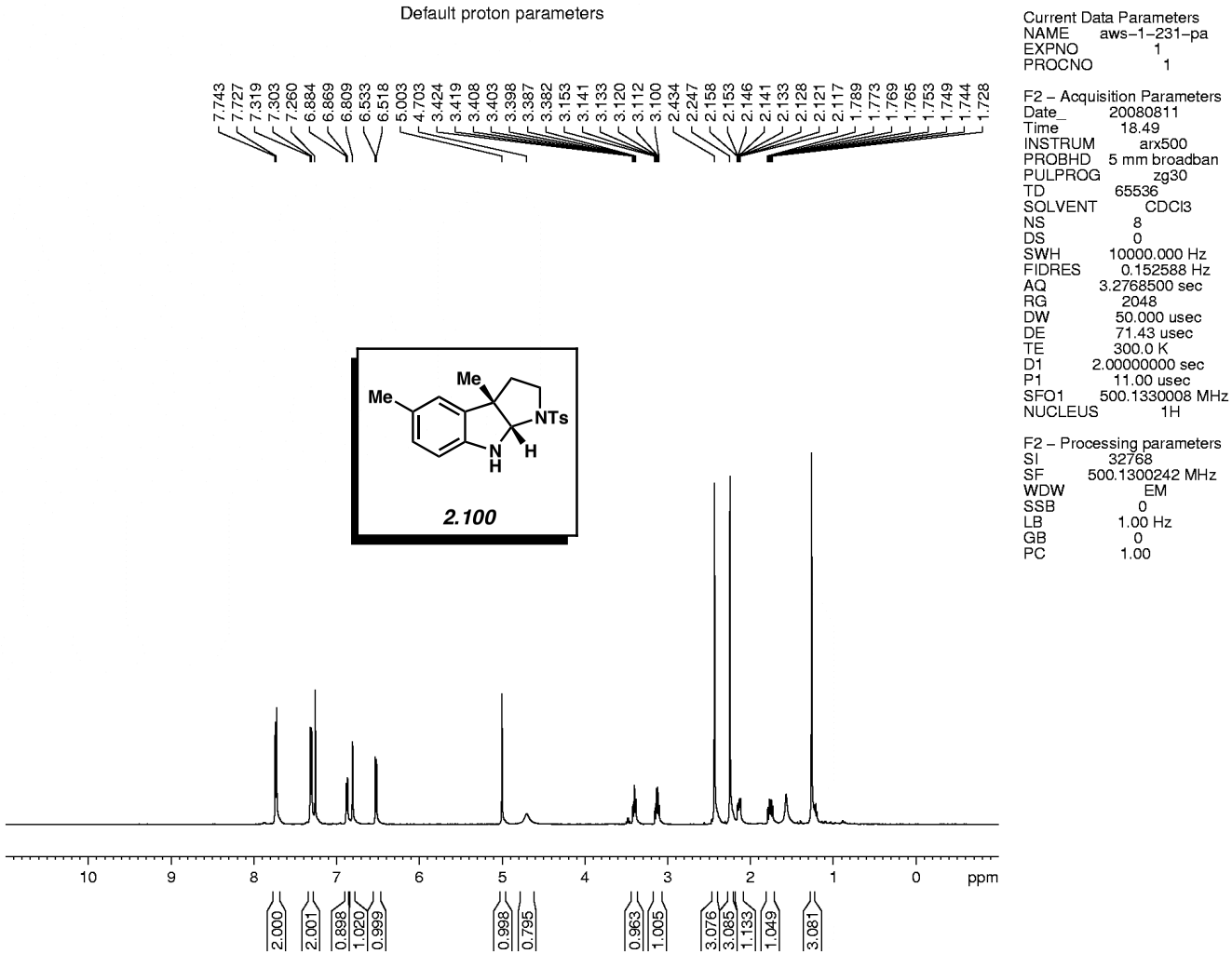


Figure A1.83 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **2.100**.

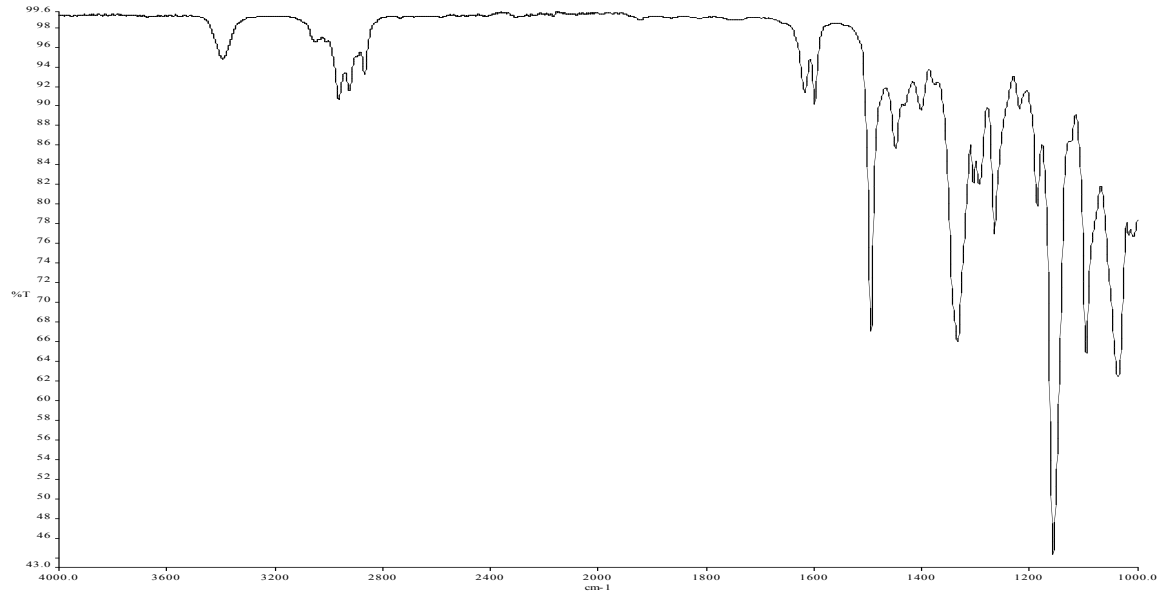


Figure A1.84 Infrared spectrum of compound **2.100**.

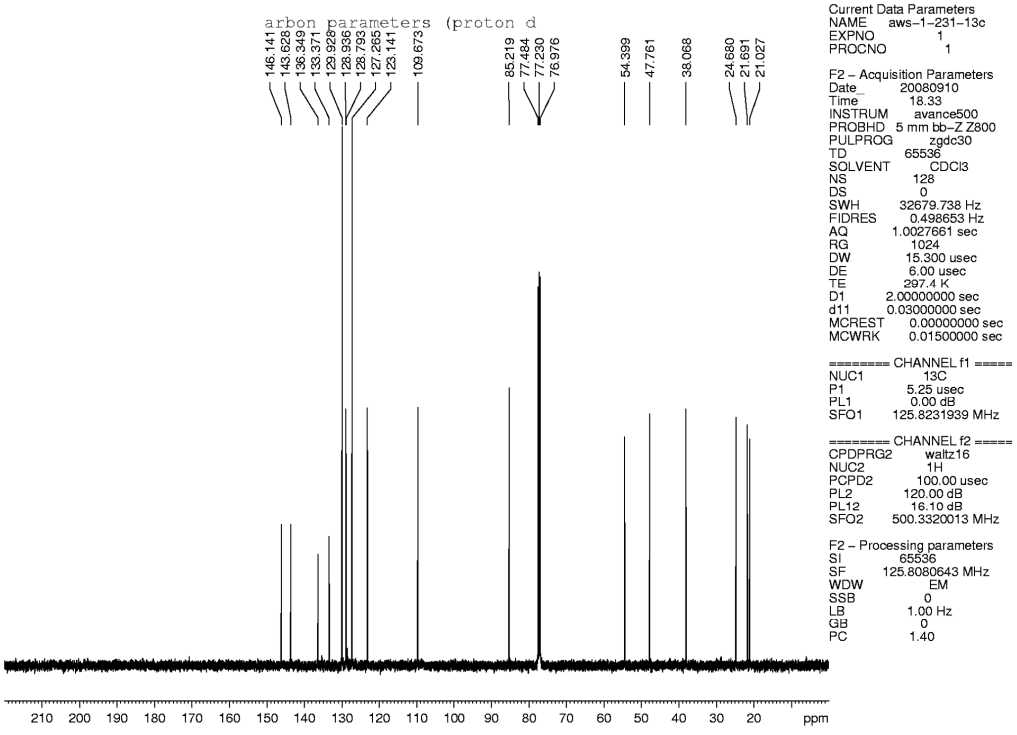


Figure A1.85 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **2.100**.

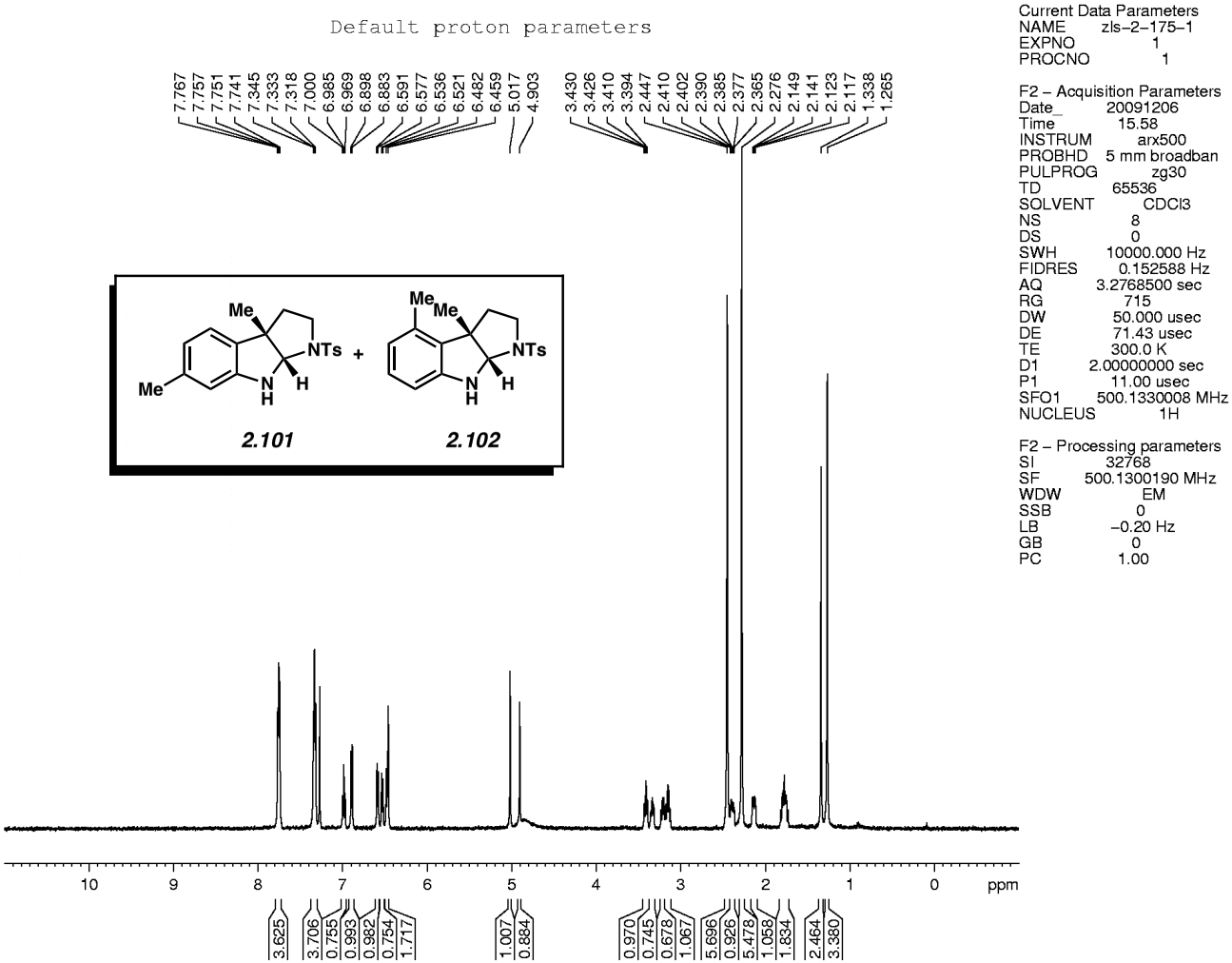


Figure A1.86 ^{1}H NMR (500 MHz, $CDCl_3$) of compounds **2.101** and **2.102**.

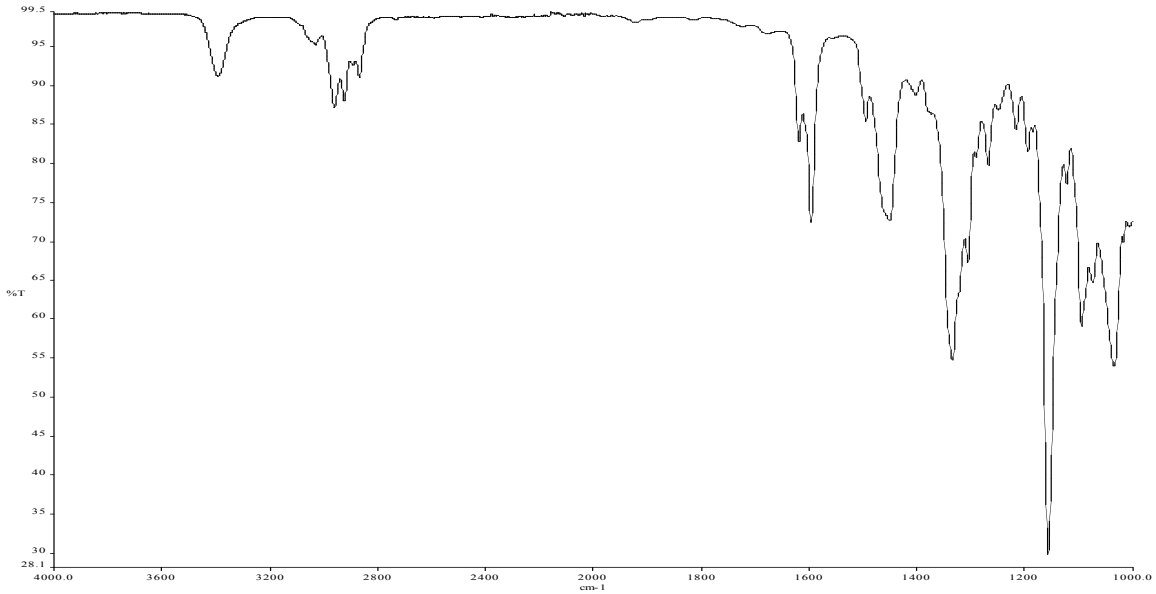


Figure A1.87 Infrared spectrum of compounds **2.101** and **2.102**.

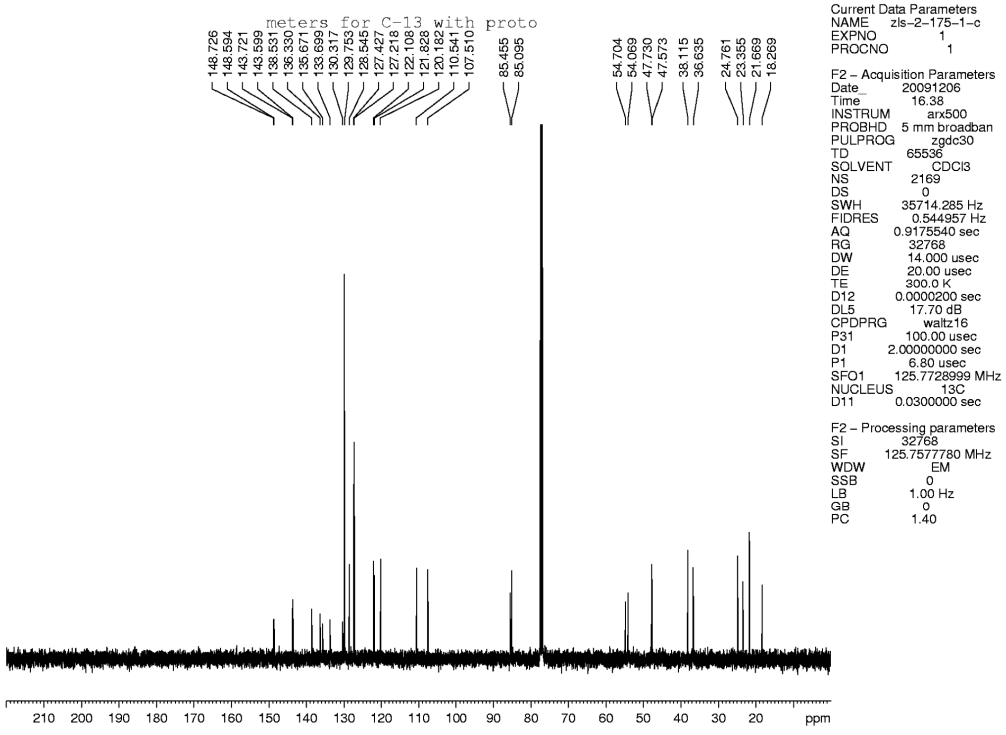


Figure A1.88 ^{13}C NMR (125 MHz, $CDCl_3$) of compounds **2.101** and **2.102**.

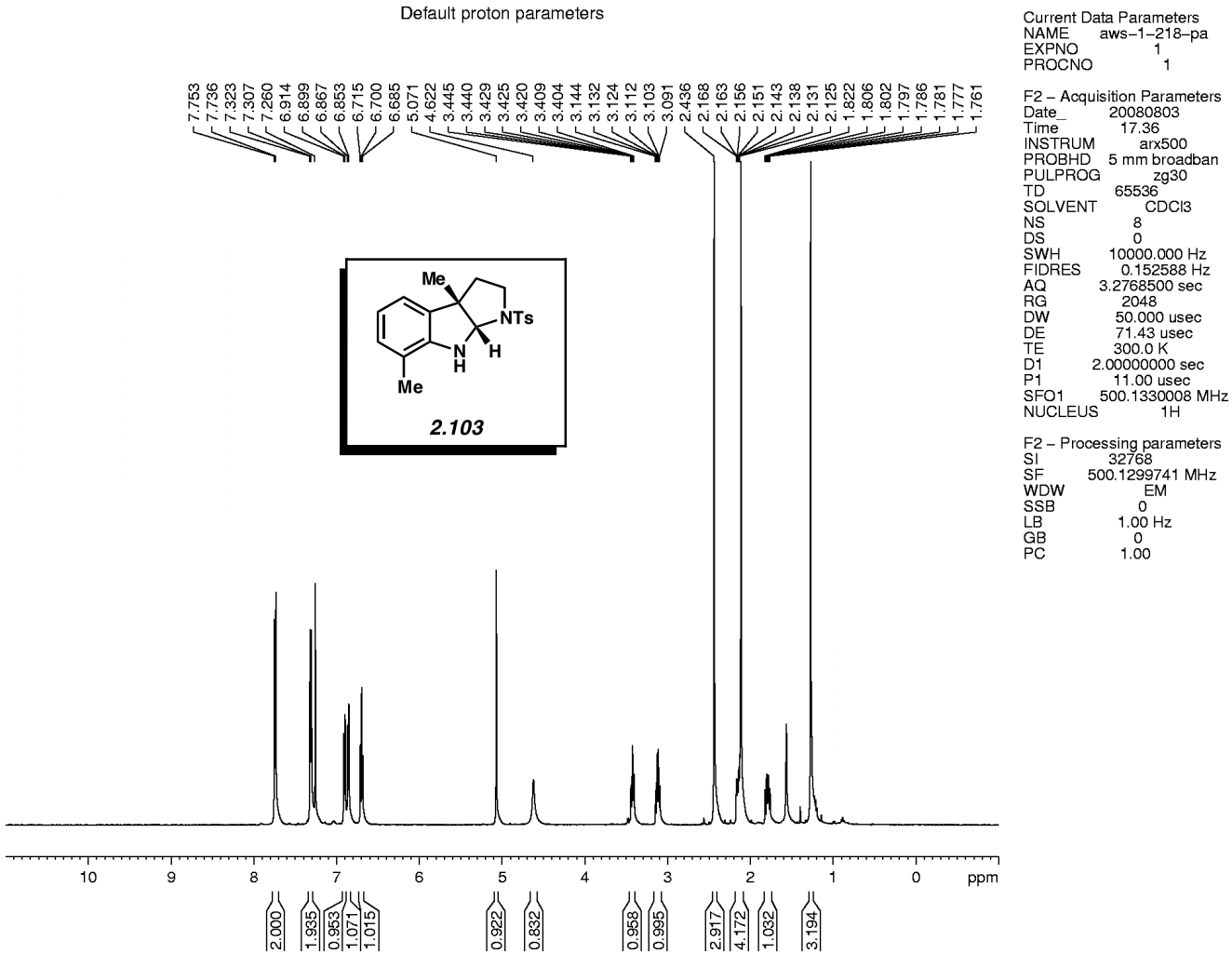


Figure A1.89 ^{1}H NMR (500 MHz, $CDCl_3$) of compounds **2.103**.

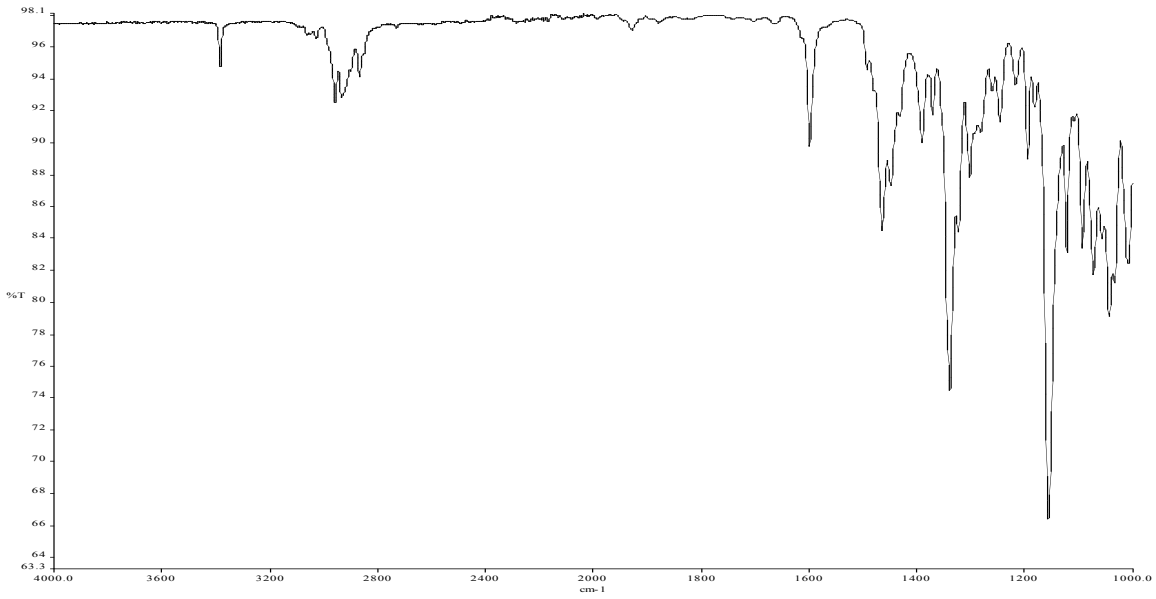


Figure A1.90 Infrared spectrum of compounds **2.103**.

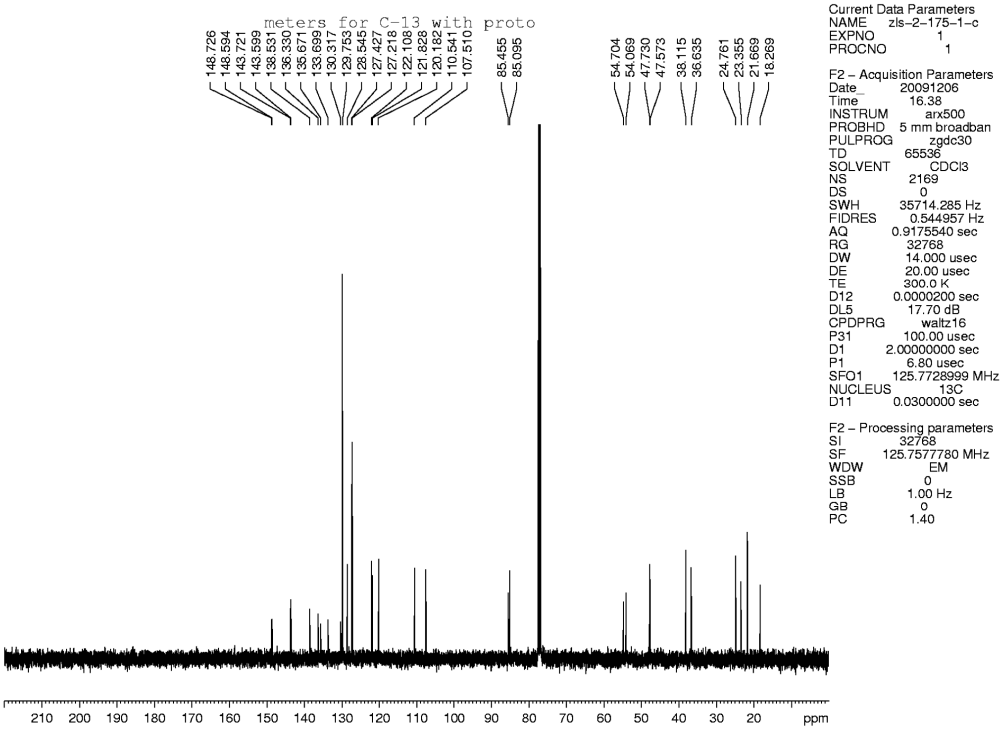


Figure A1.91 ^{13}C NMR (125 MHz, $CDCl_3$) of compounds **2.103**.

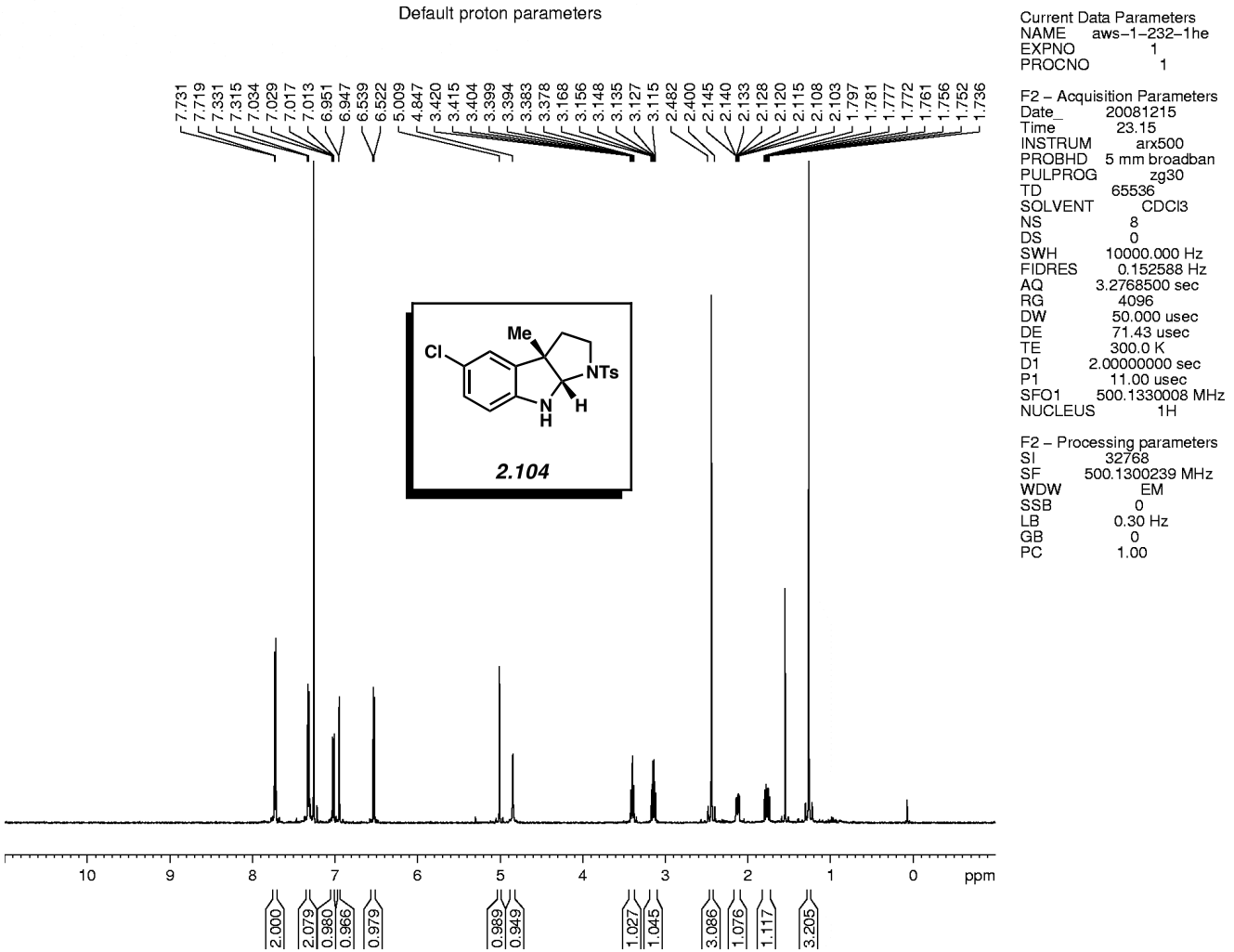


Figure A1.92 ^{1}H NMR (500 MHz, $CDCl_3$) of compounds **2.104**.

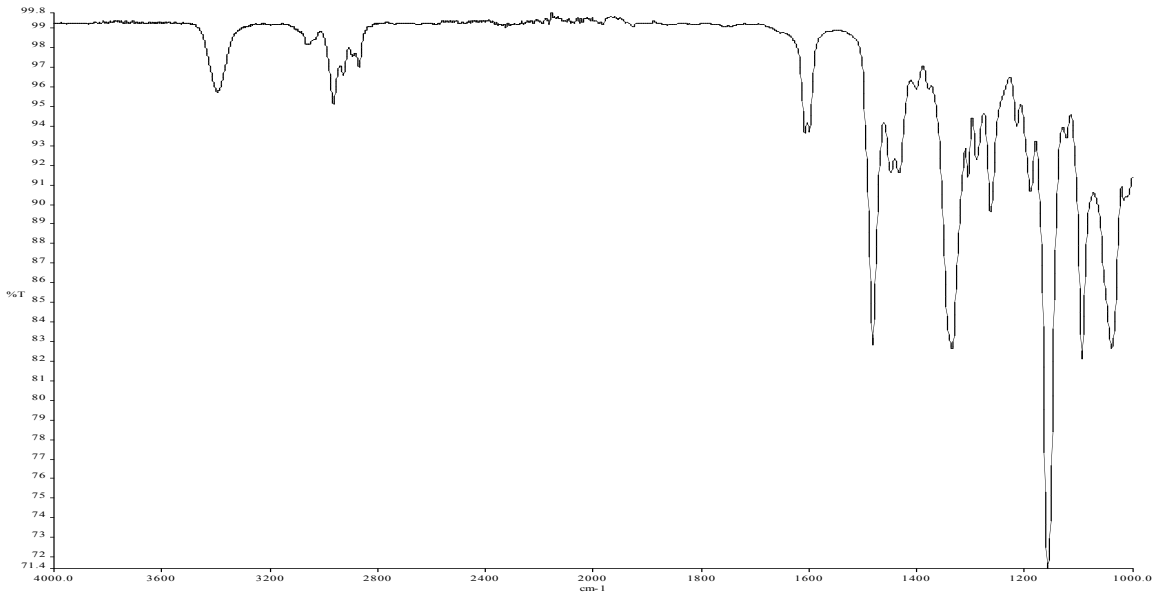


Figure A1.93 Infrared spectrum of compounds **2.104**.

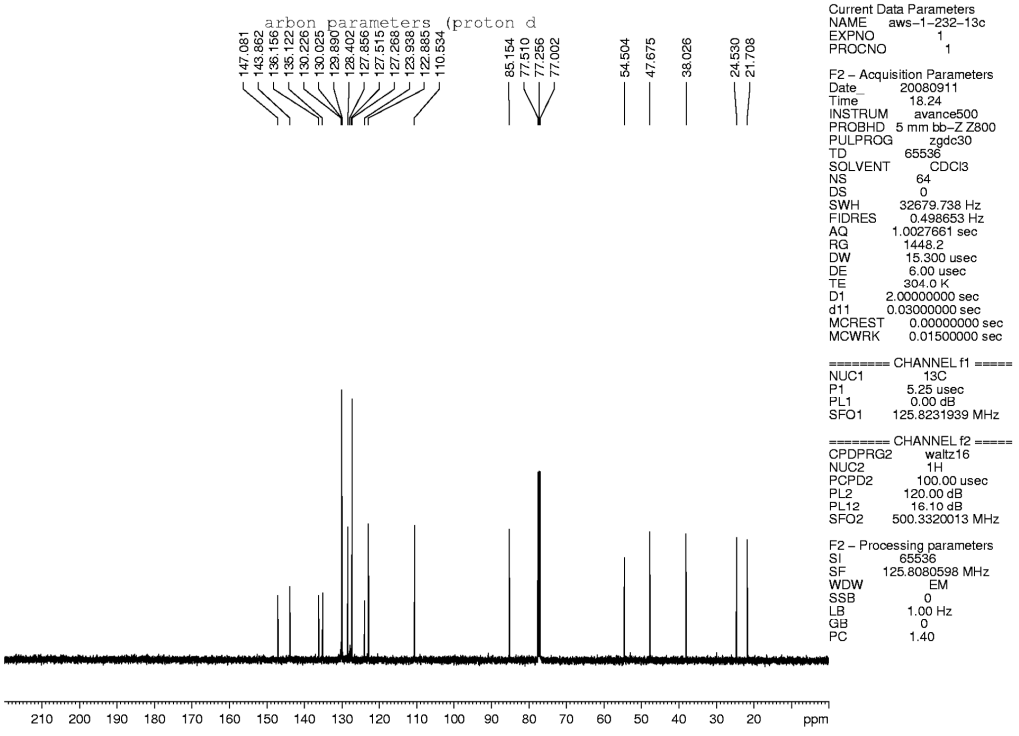


Figure A1.94 ^{13}C NMR (125 MHz, $CDCl_3$) of compounds **2.104**.

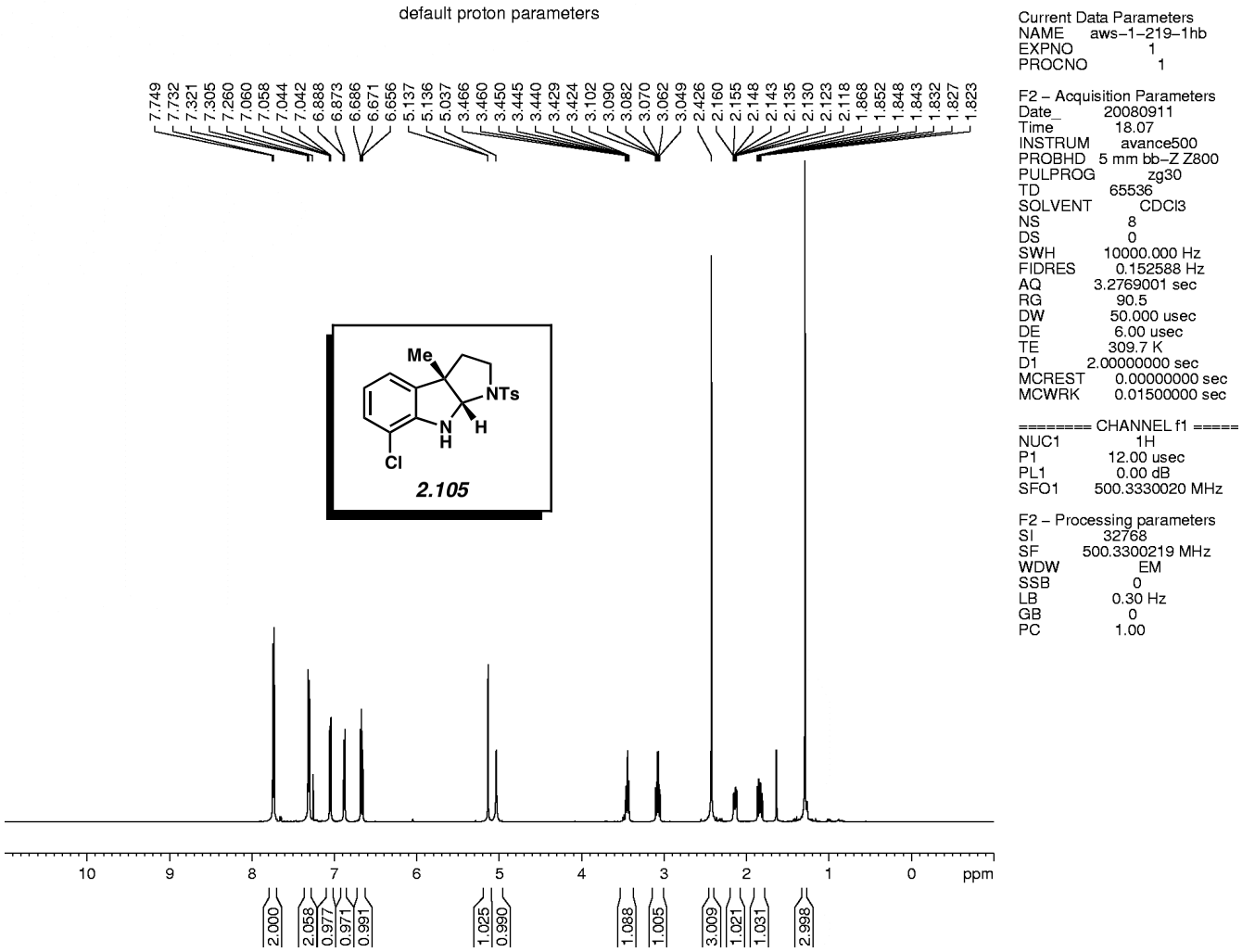


Figure A1.95 ^{1}H NMR (500 MHz, $CDCl_3$) of compounds **2.105**.

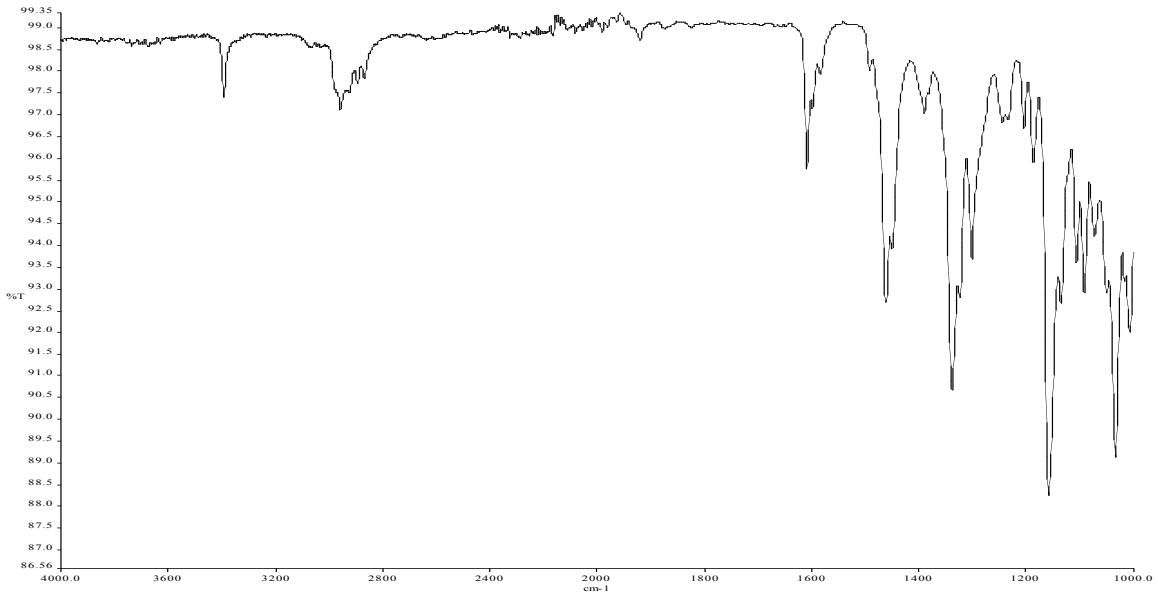


Figure A1.96 Infrared spectrum of compounds **2.105**.

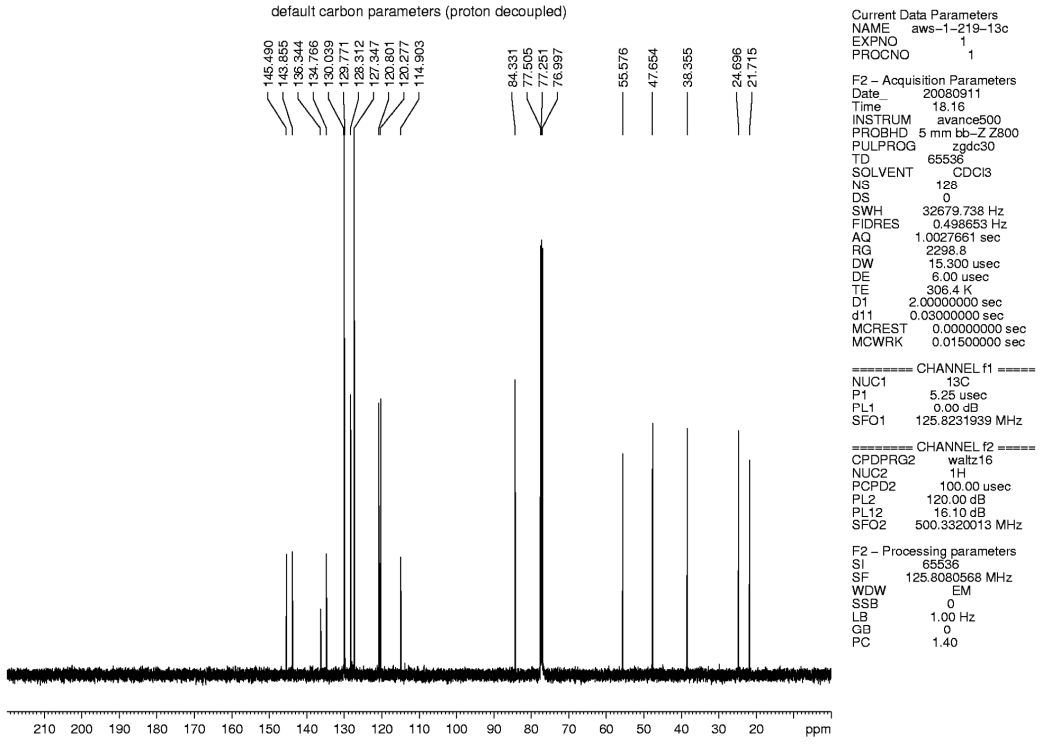


Figure A1.97 ^{13}C NMR (125 MHz, $CDCl_3$) of compounds **2.105**.

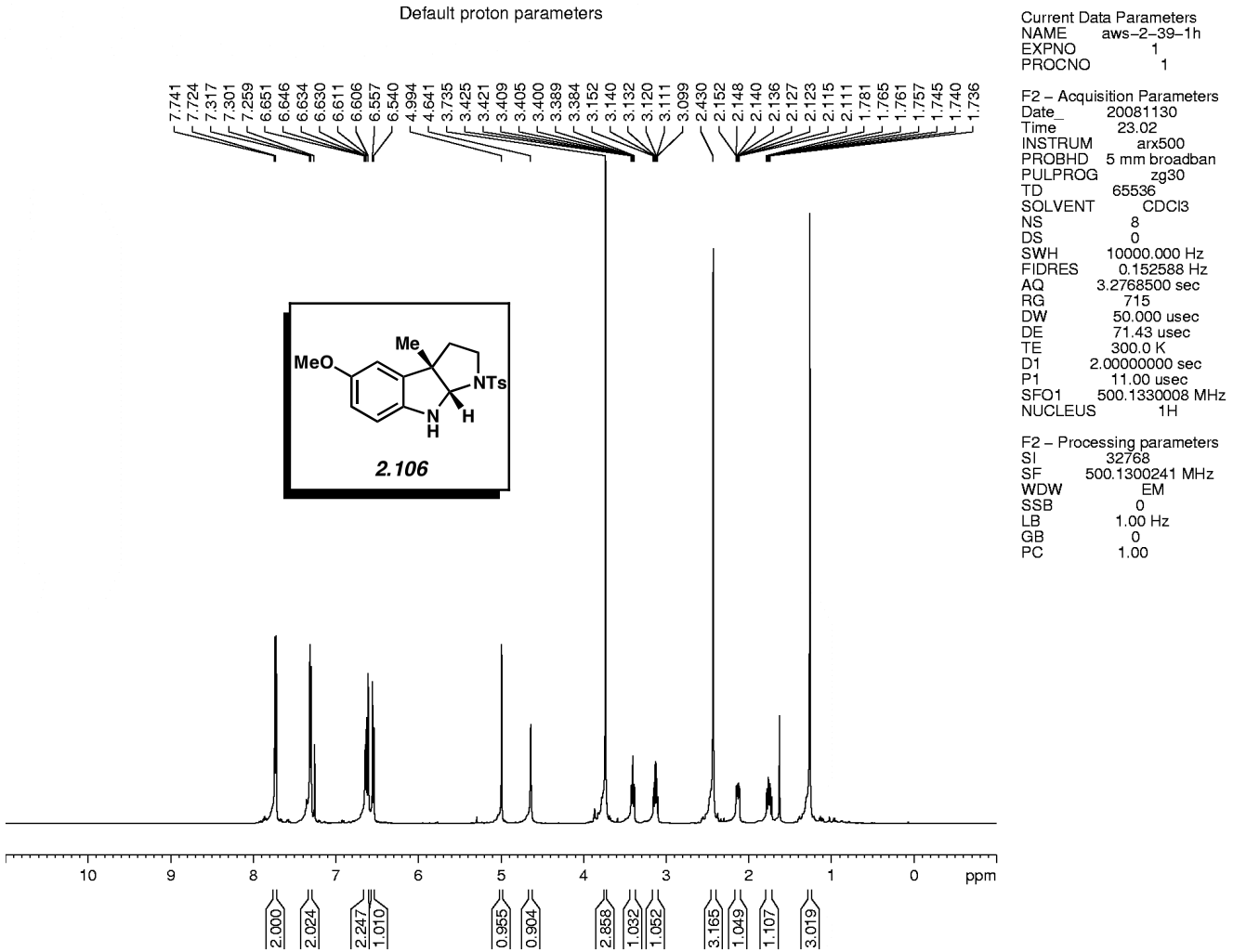


Figure A1.98 ^{1}H NMR (500 MHz, $CDCl_3$) of compounds **2.106**.

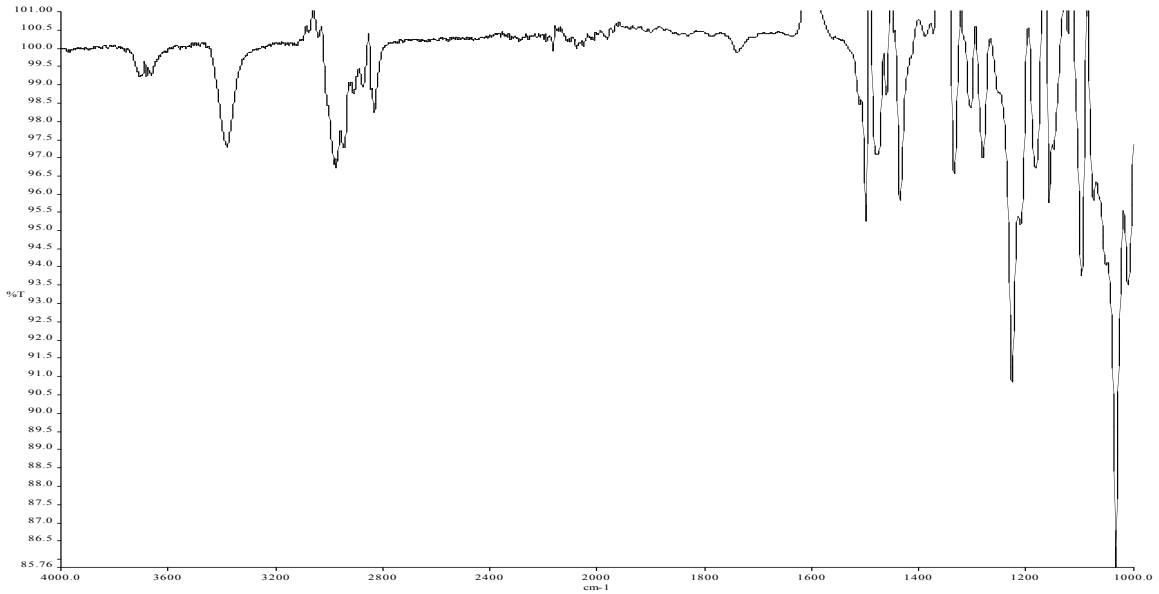


Figure A1.99 Infrared spectrum of compounds **2.106**.

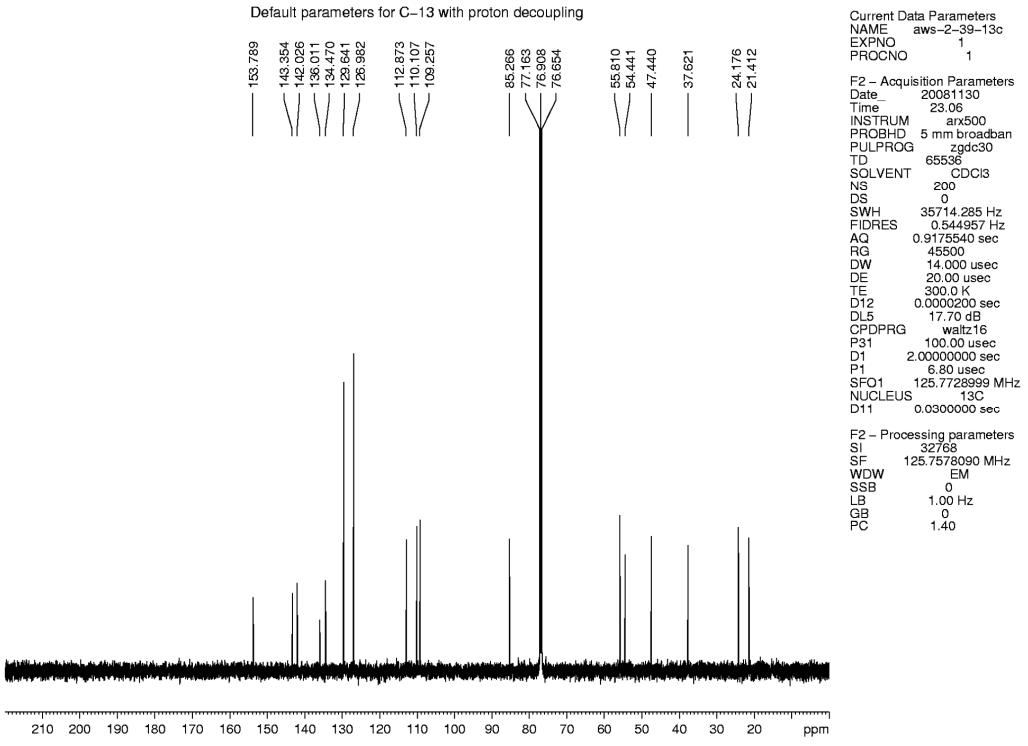


Figure A1.100 ^{13}C NMR (125 MHz, $CDCl_3$) of compounds **2.106**.

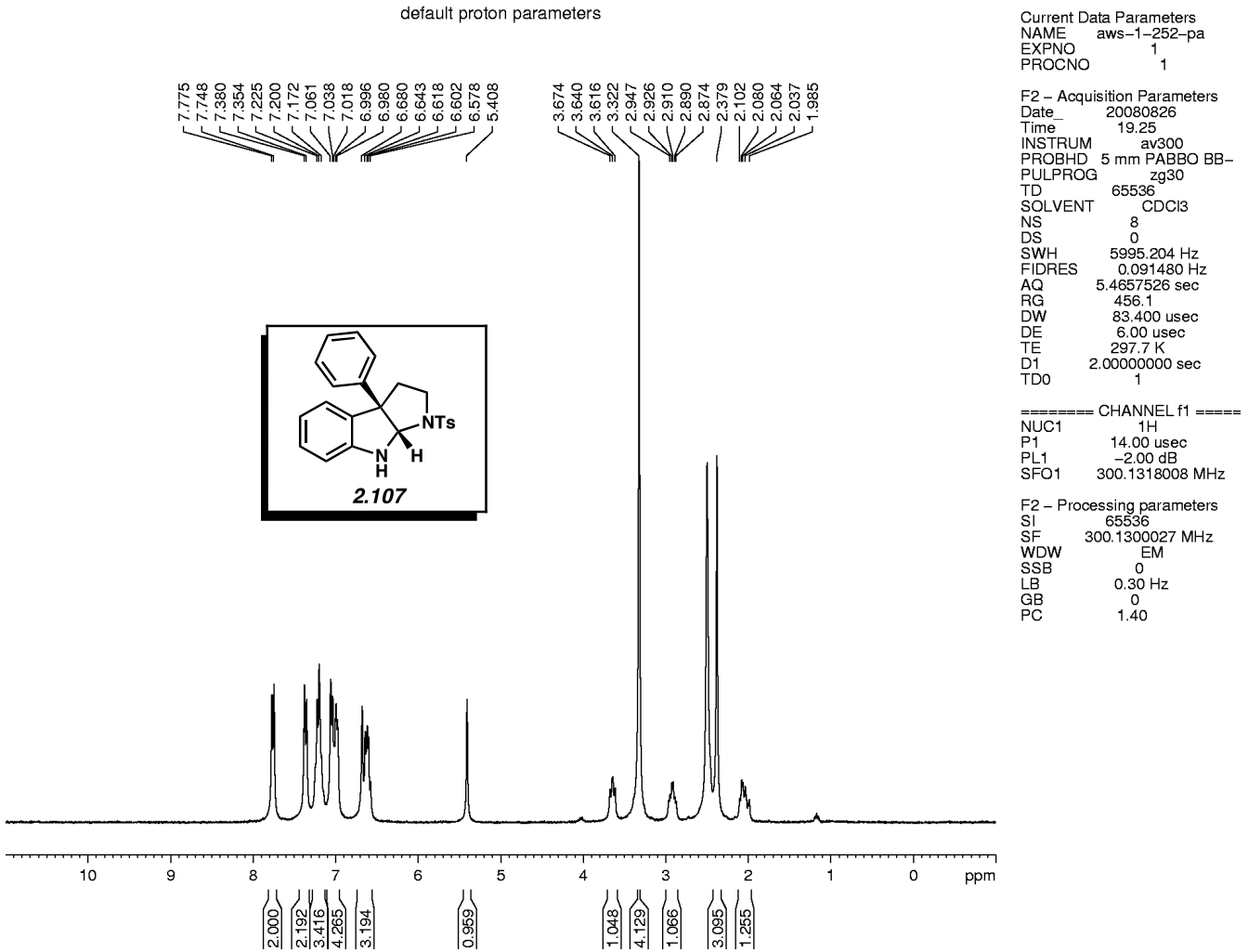


Figure A1.101 ^{1}H NMR (300 MHz, $CDCl_3$) of compounds **2.107**.

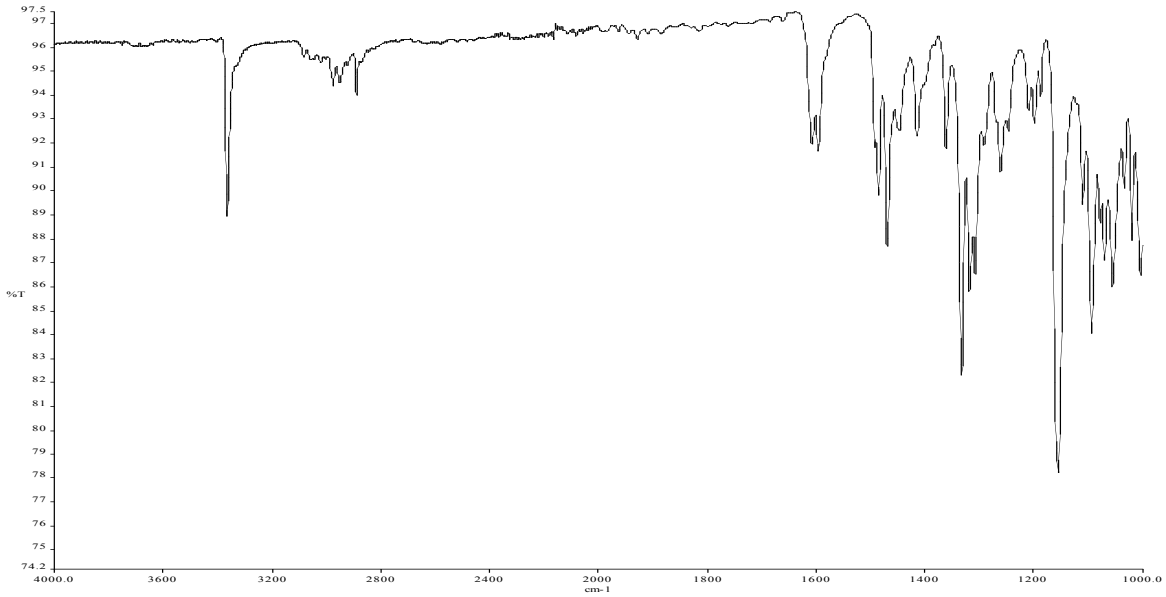


Figure A1.102 Infrared spectrum of compounds **2.107**.

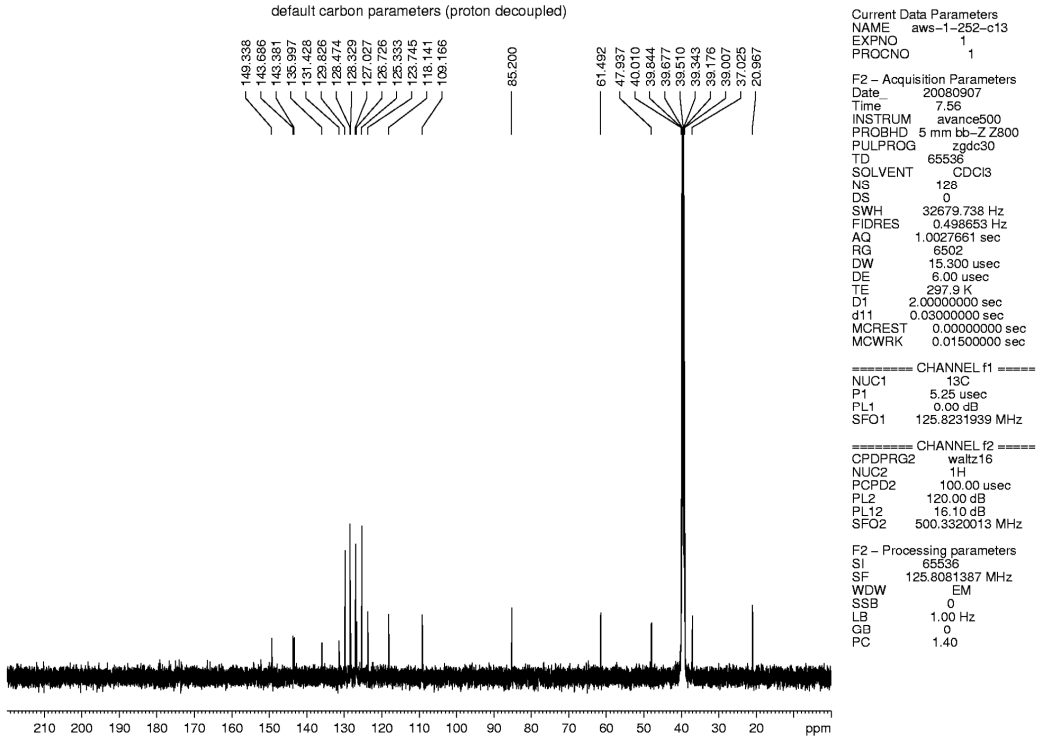


Figure A1.103 ^{13}C NMR (125 MHz, $CDCl_3$) of compounds **2.107**.

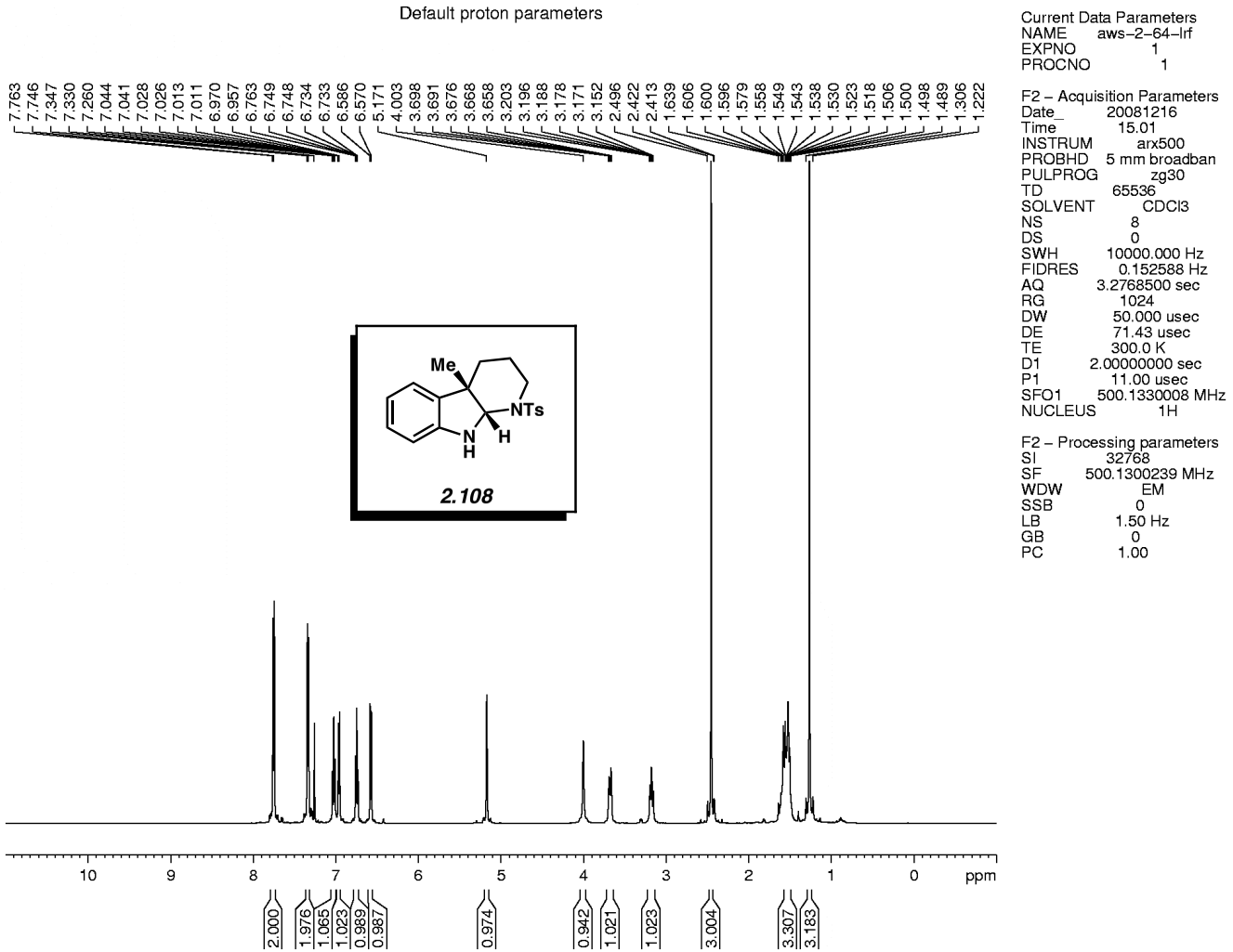


Figure A1.104 ^{1}H NMR (500 MHz, $CDCl_3$) of compounds **2.108**.

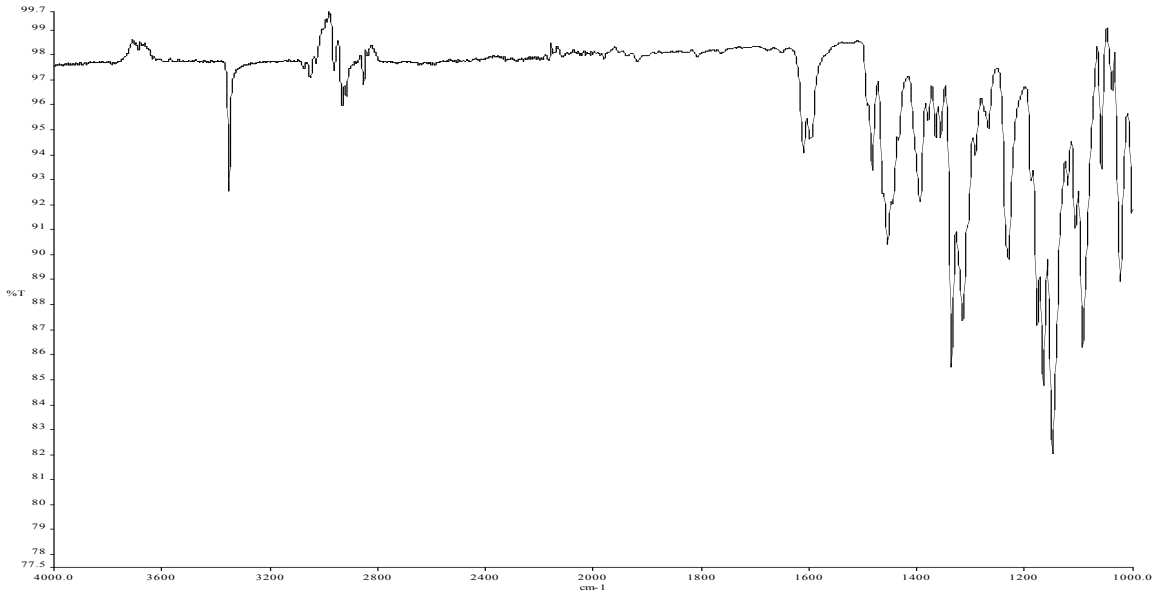


Figure A1.105 Infrared spectrum of compounds **2.108**.

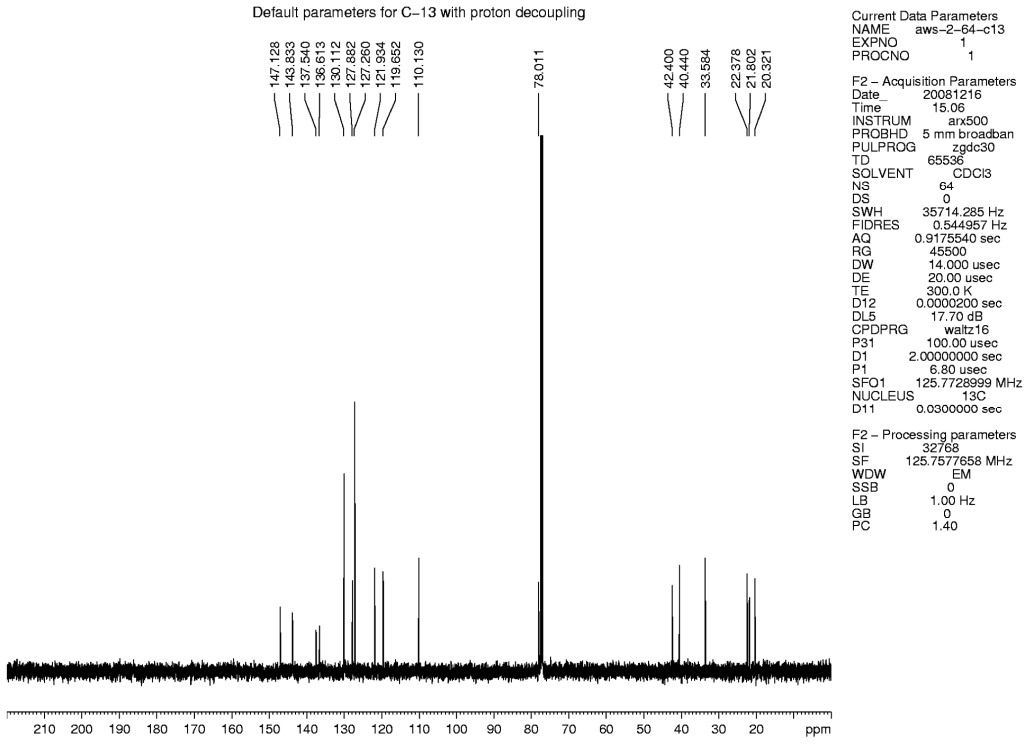


Figure A1.106 ^{13}C NMR (125 MHz, $CDCl_3$) of compounds **2.108**.

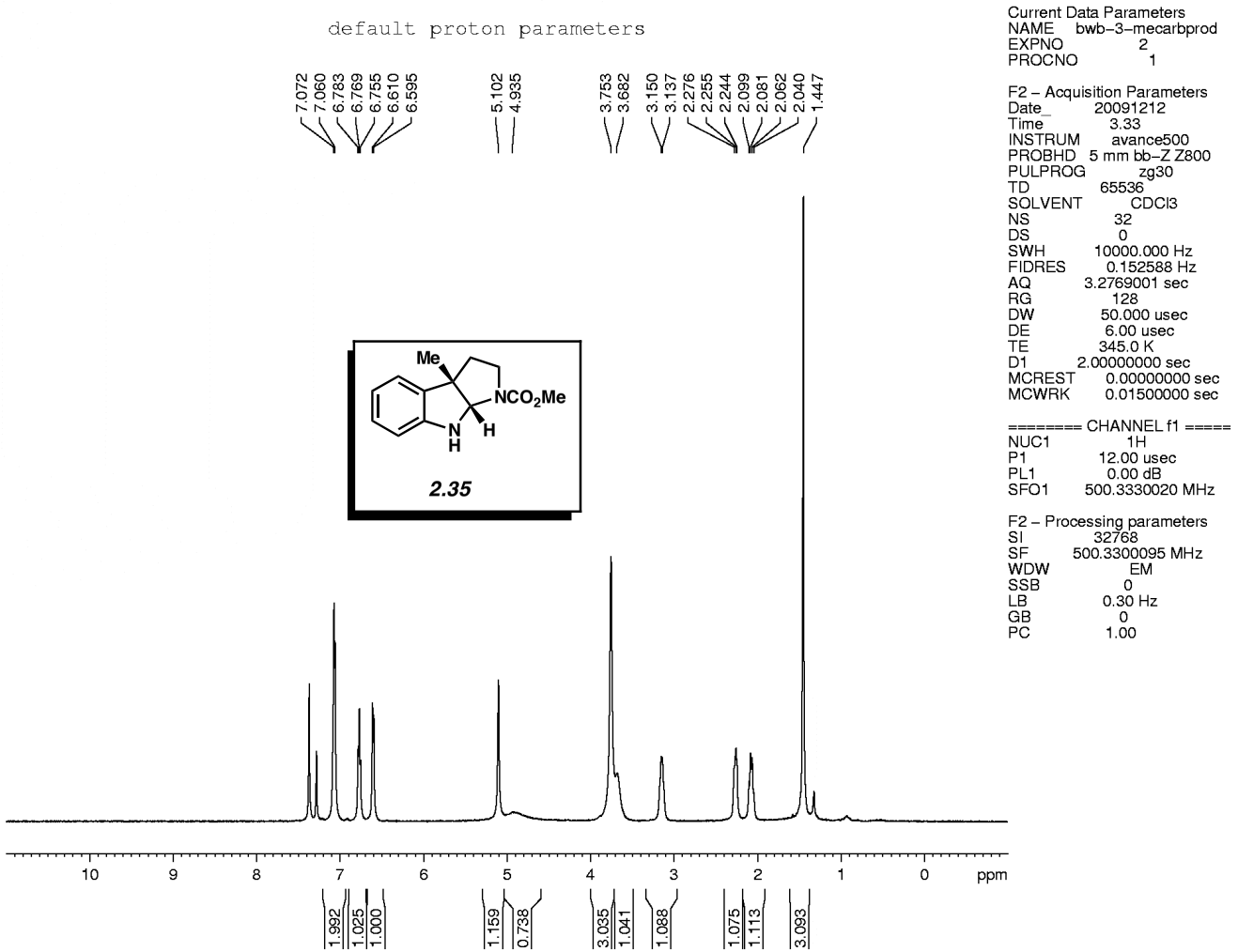


Figure A1.107 ^{1}H NMR (500 MHz, $CDCl_3$) of compounds **2.35**.

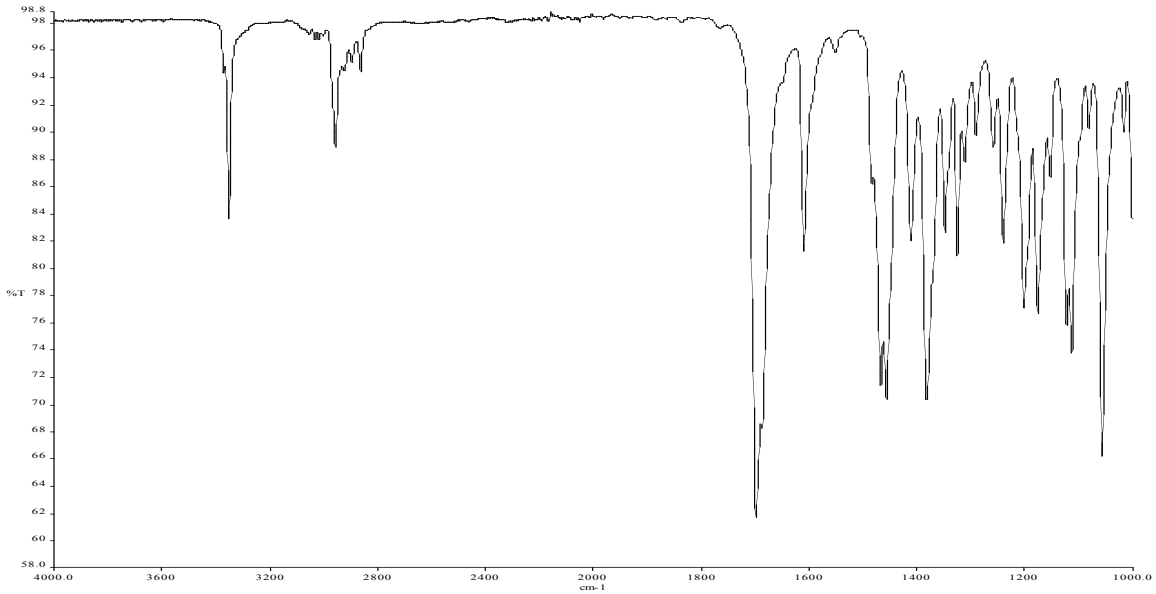


Figure A1.108 Infrared spectrum of compounds **2.35**.

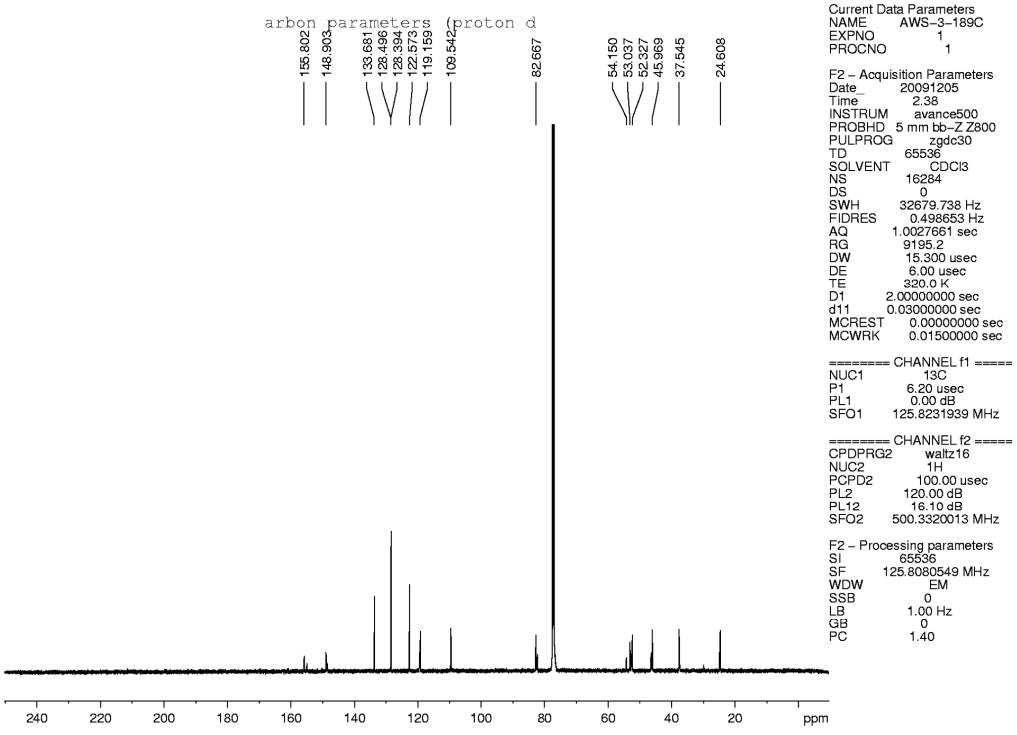


Figure A1.109 ^{13}C NMR (125 MHz, $CDCl_3$) of compounds **2.35**.

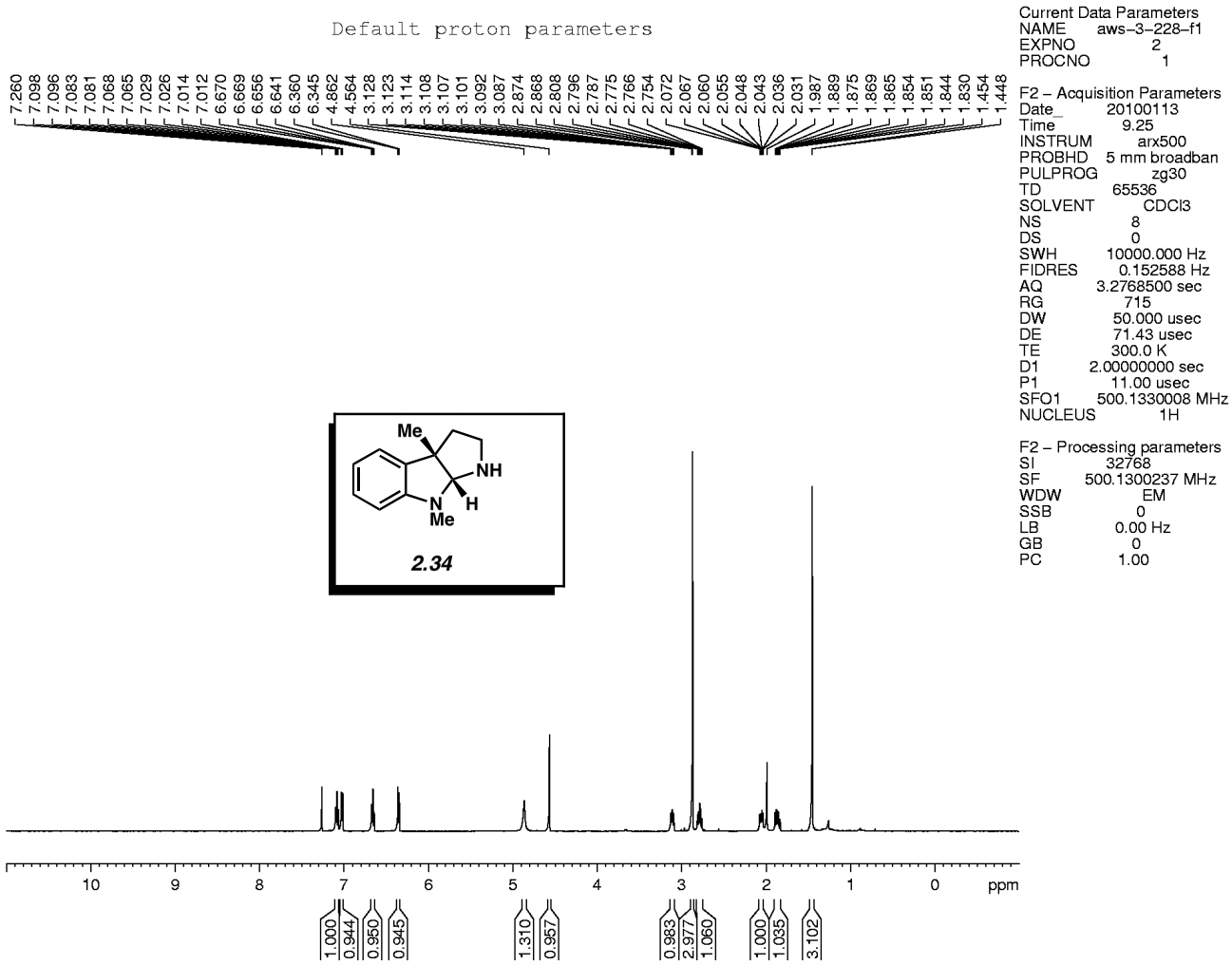


Figure A1.110 ^{1}H NMR (500 MHz, $CDCl_3$) of compounds **2.34**.

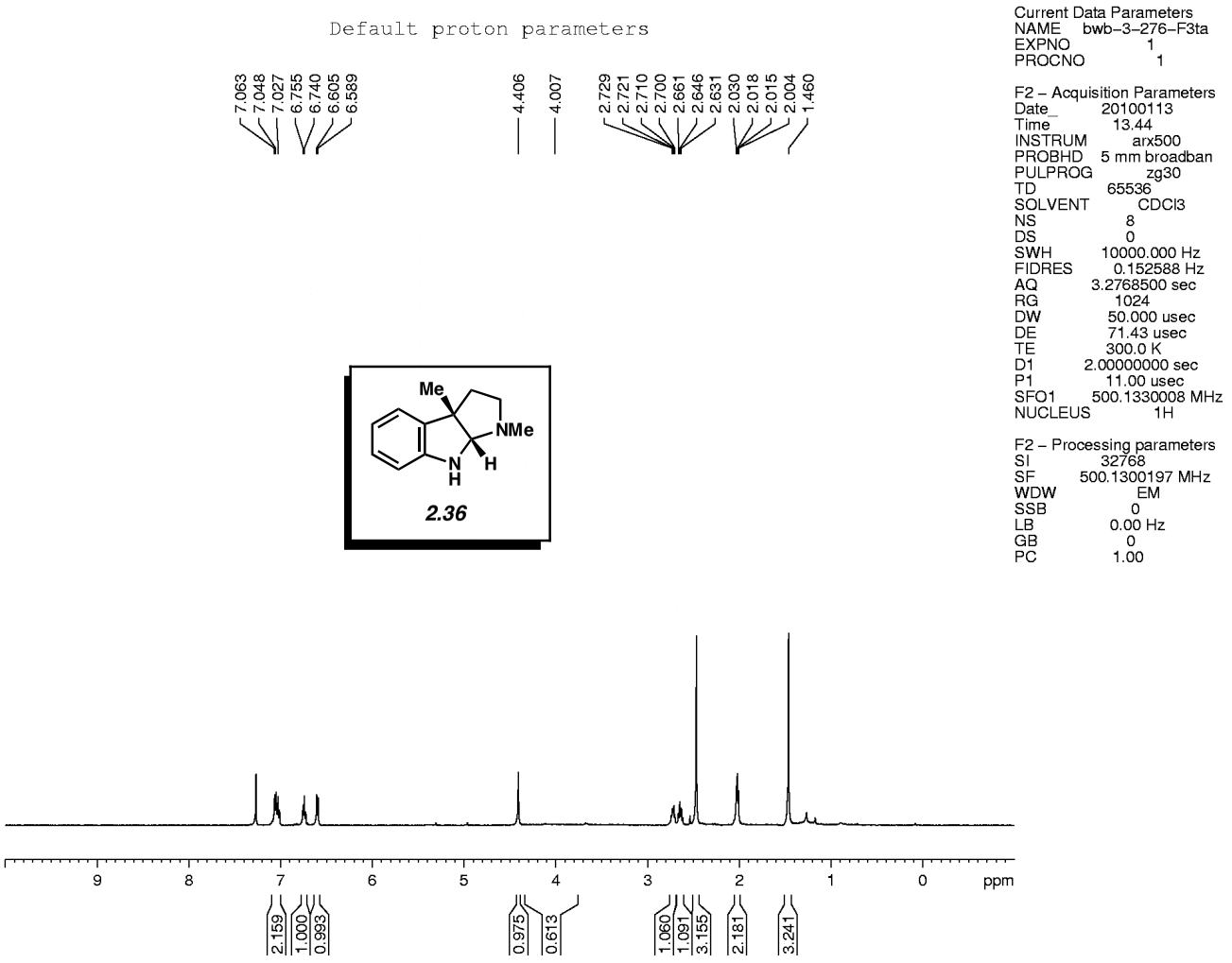


Figure A1.111 ^{1}H NMR (500 MHz, $CDCl_3$) of compounds **2.36**.

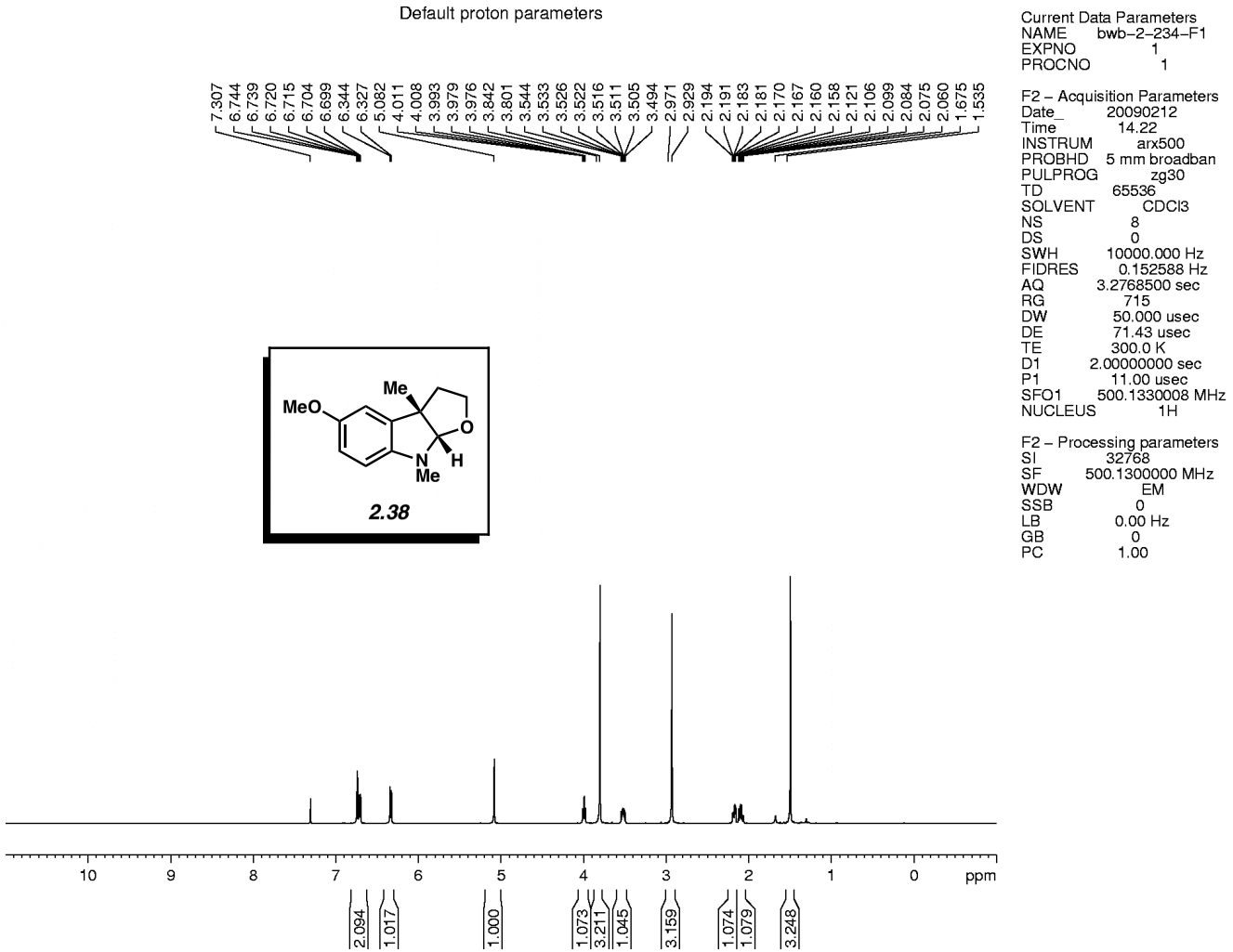


Figure A1.112 ^{1}H NMR (500 MHz, $CDCl_3$) of compounds **2.38**.

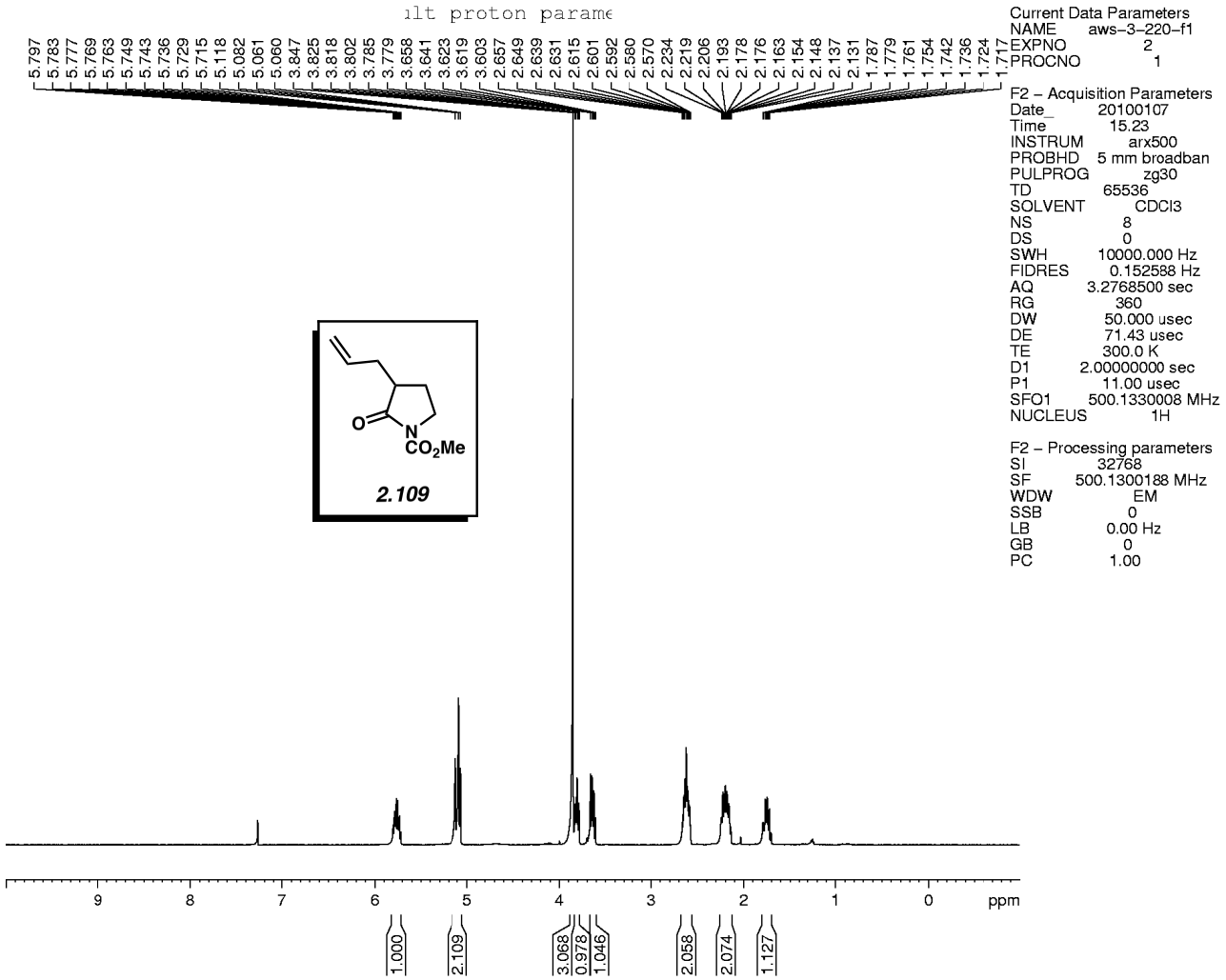


Figure A1.113 ^{1}H NMR (500 MHz, $CDCl_3$) of compounds **2.109**.

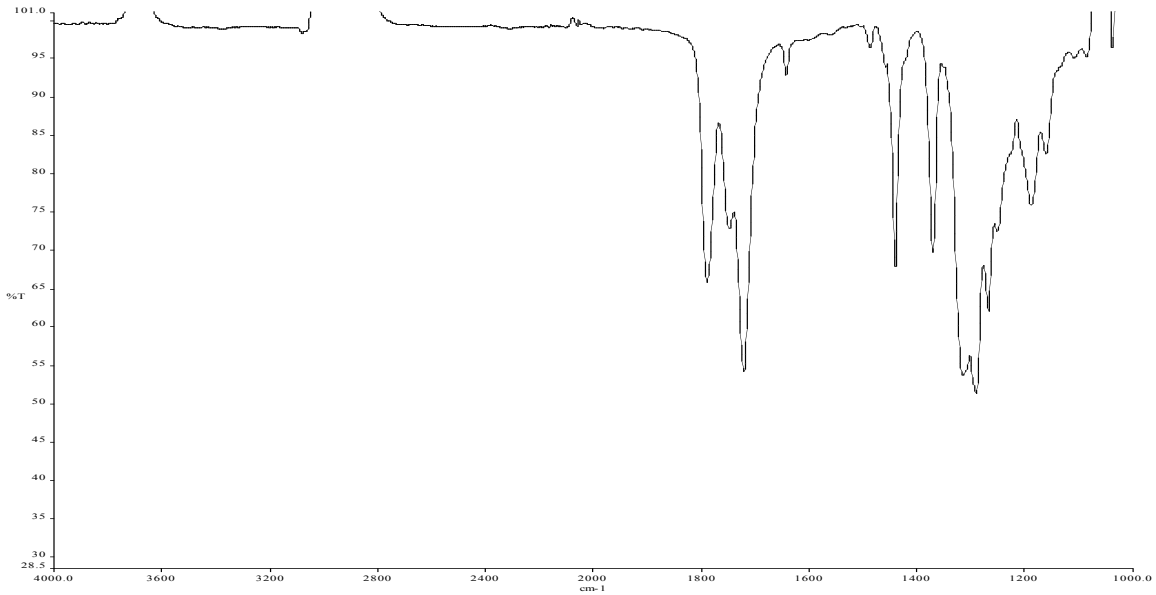


Figure A1.114 Infrared spectrum of compounds **2.109**.

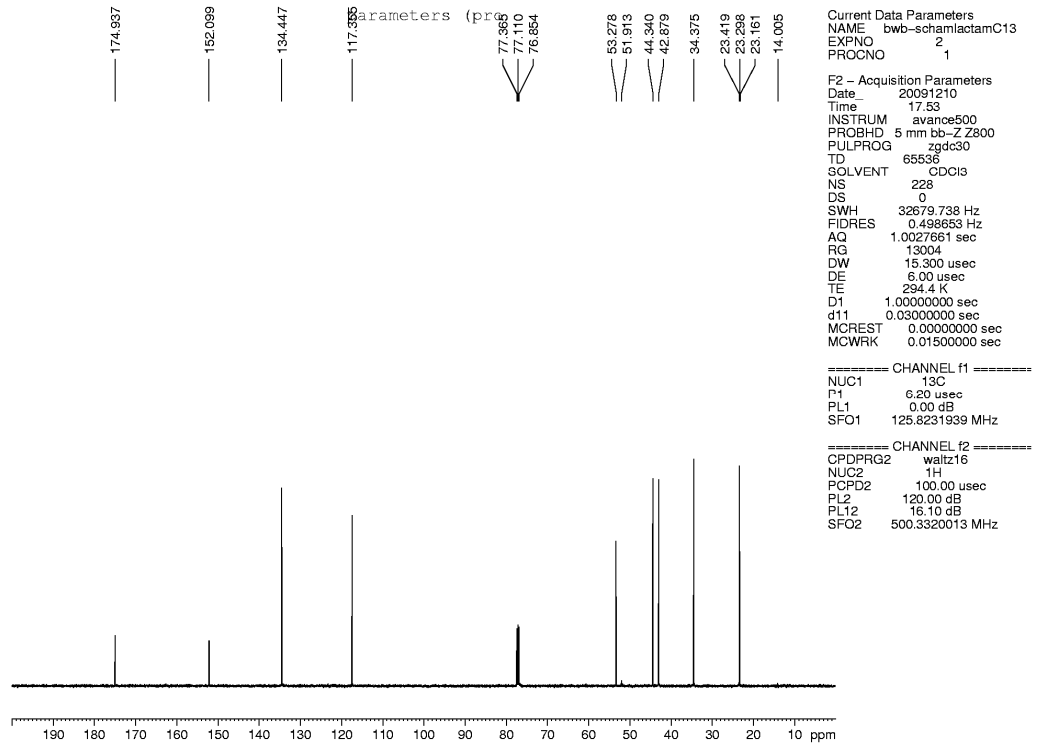


Figure A1.115 ^{13}C NMR (125 MHz, $CDCl_3$) of compounds **2.109**.

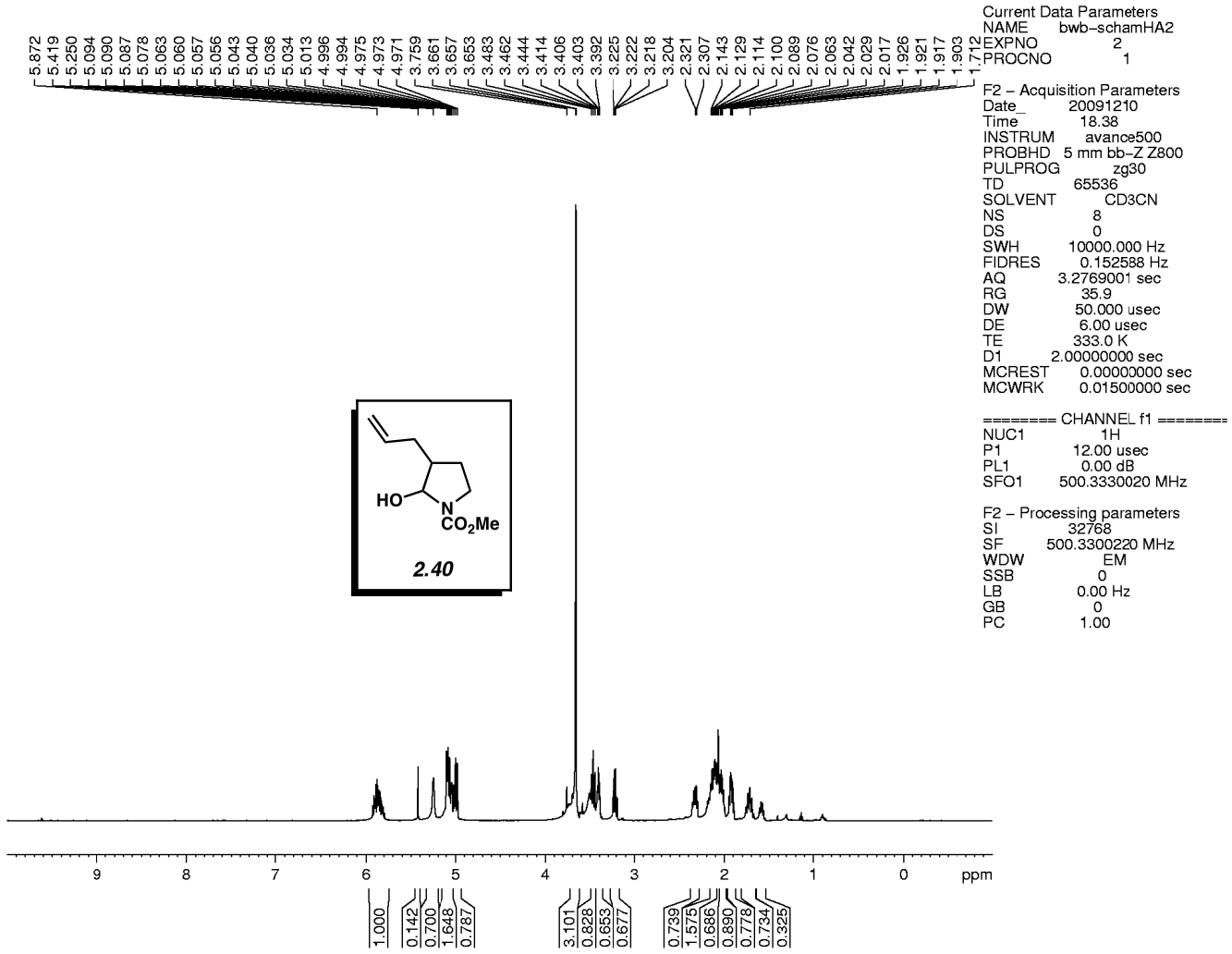


Figure A1.116 ^{1}H NMR (500 MHz, CD_3CN) of compounds **2.40**.

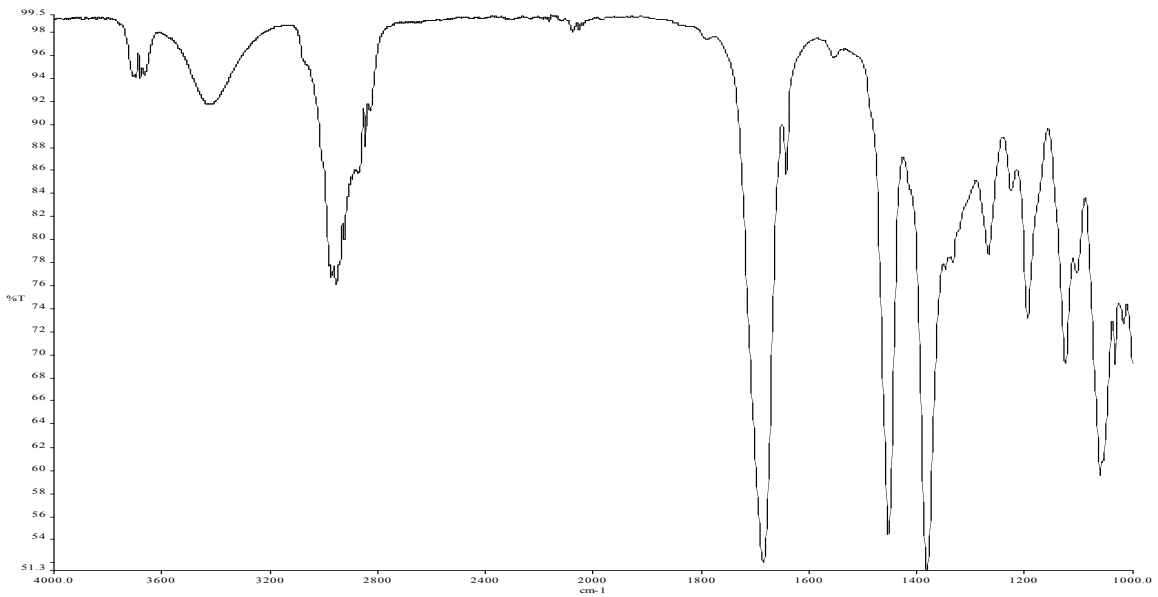


Figure A1.117 Infrared spectrum of compounds **2.40**.

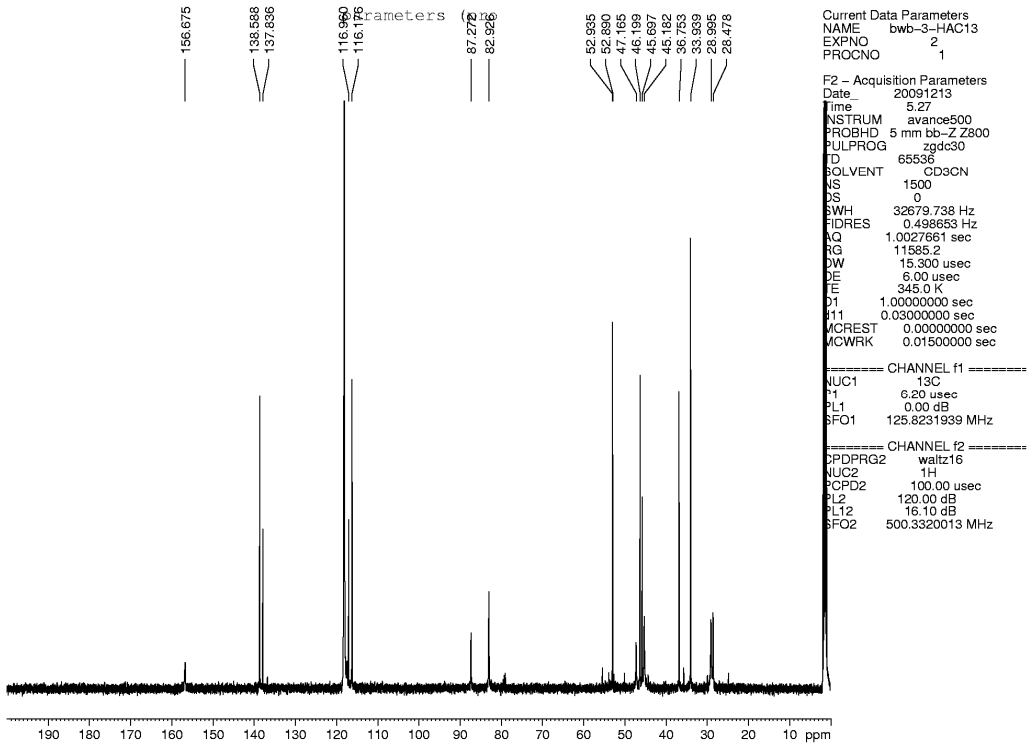


Figure A1.118 ^{13}C NMR (125 MHz, CD_3CN) of compounds **2.40**.

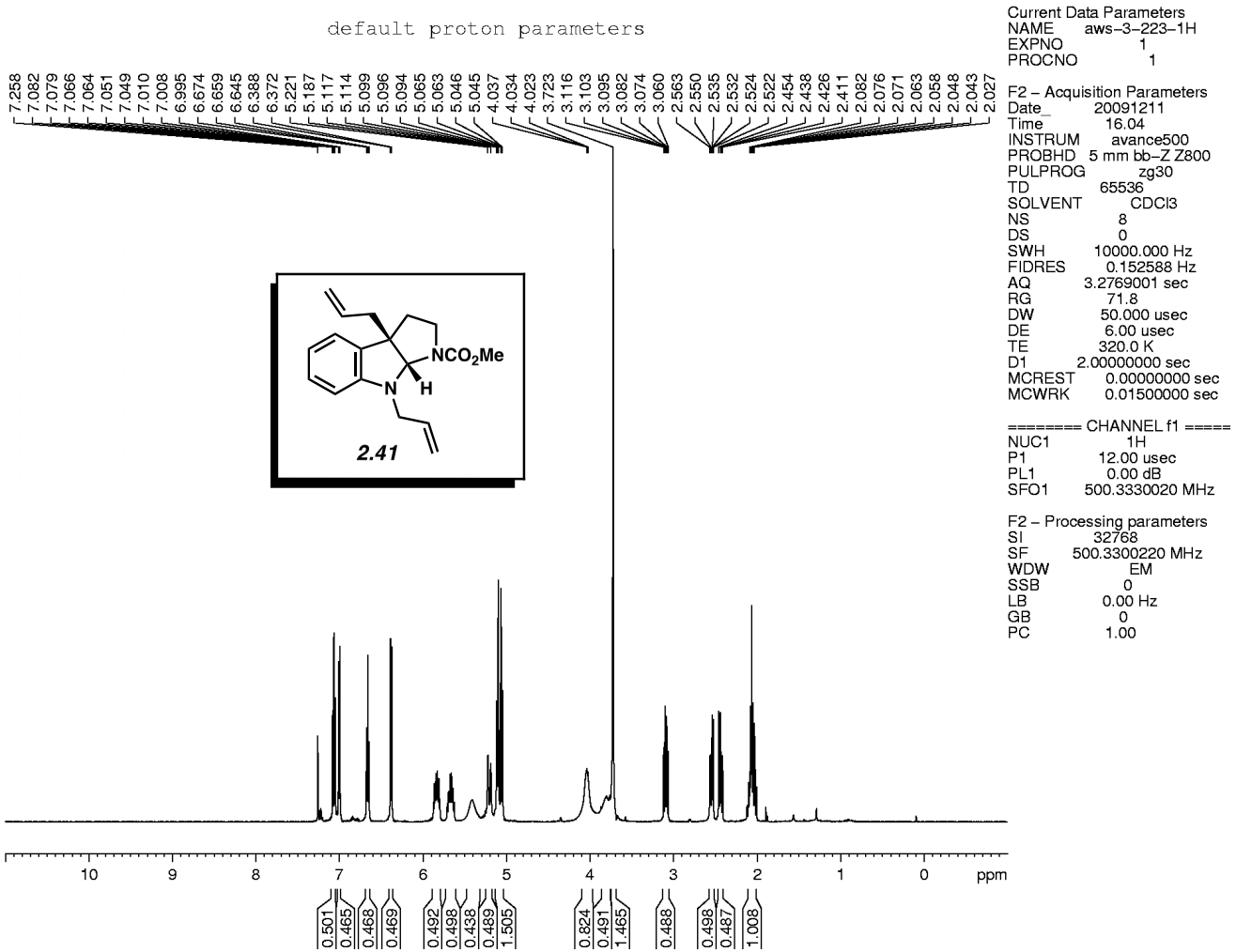


Figure A1.119 ^{1}H NMR (500 MHz, $CDCl_3$) of compounds **2.41**.

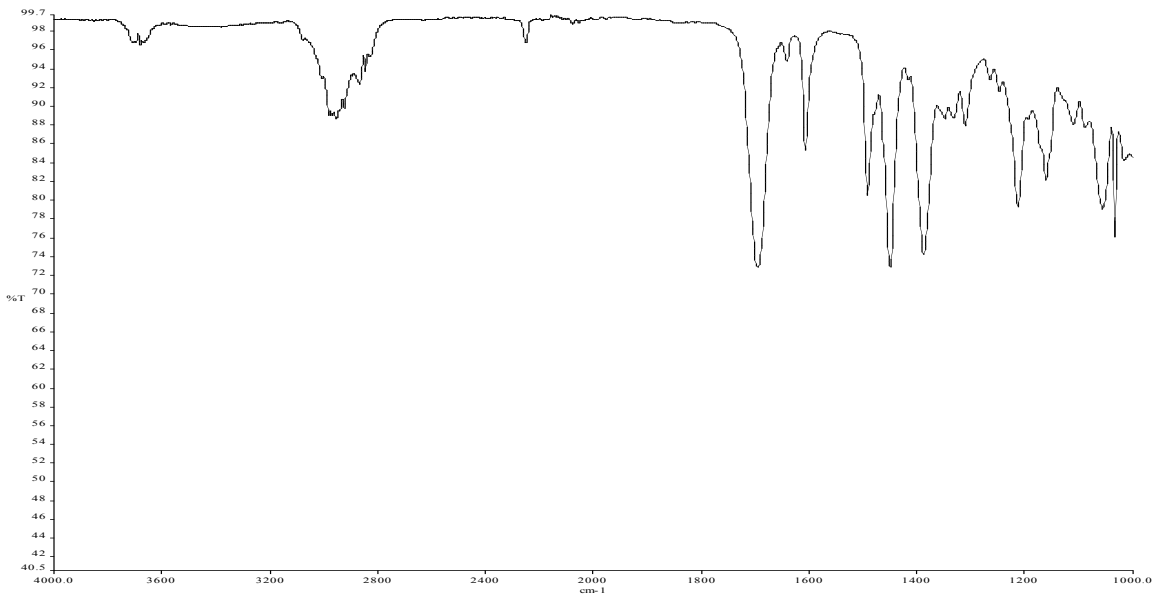


Figure A1.120 Infrared spectrum of compounds **2.41**.

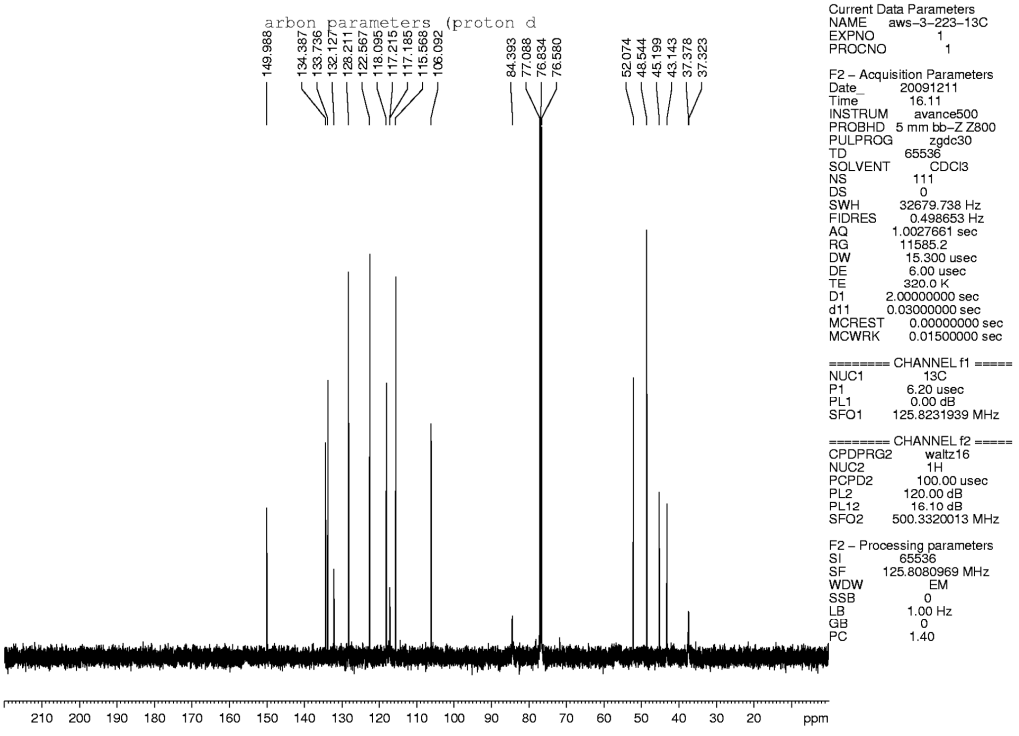


Figure A1.121 ^{13}C NMR (125 MHz, $CDCl_3$) of compounds **2.41**.

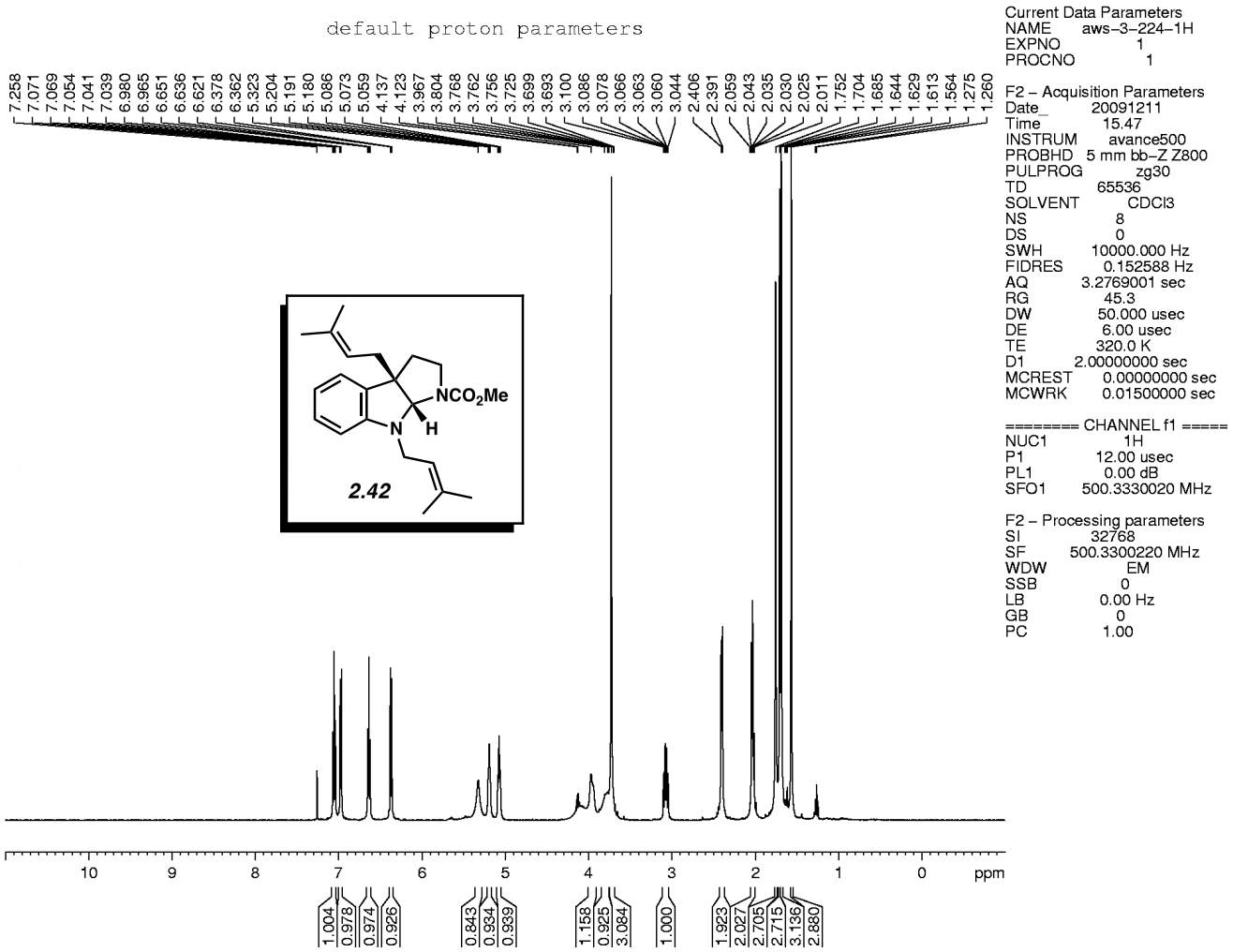


Figure A1.122 ^{1}H NMR (500 MHz, $CDCl_3$) of compounds **2.42**.

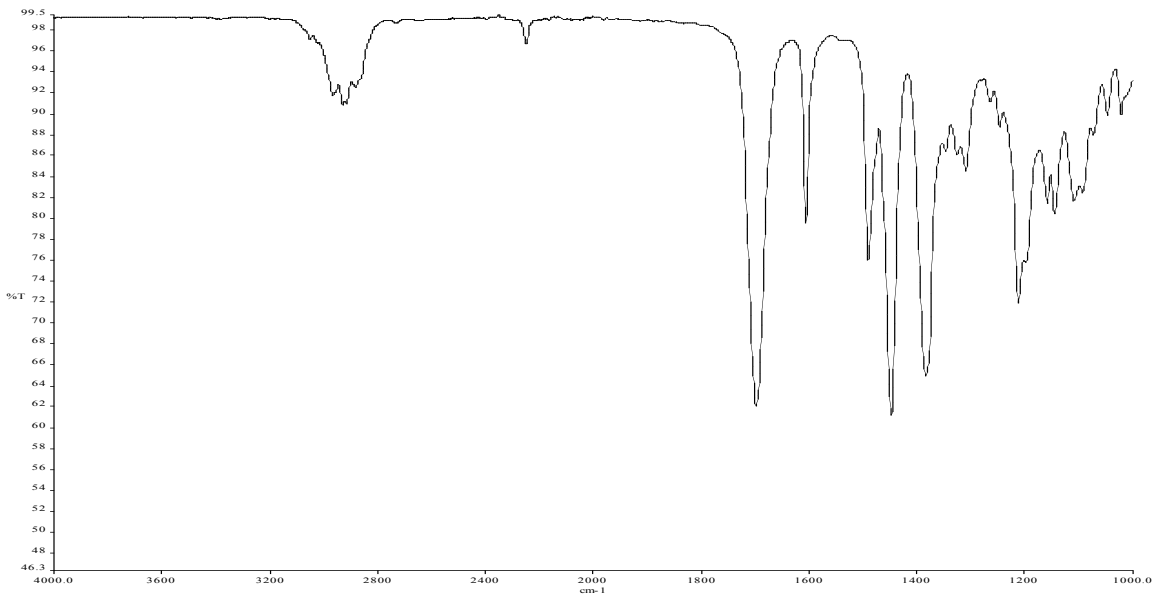


Figure A1.123 Infrared spectrum of compounds **2.42**.

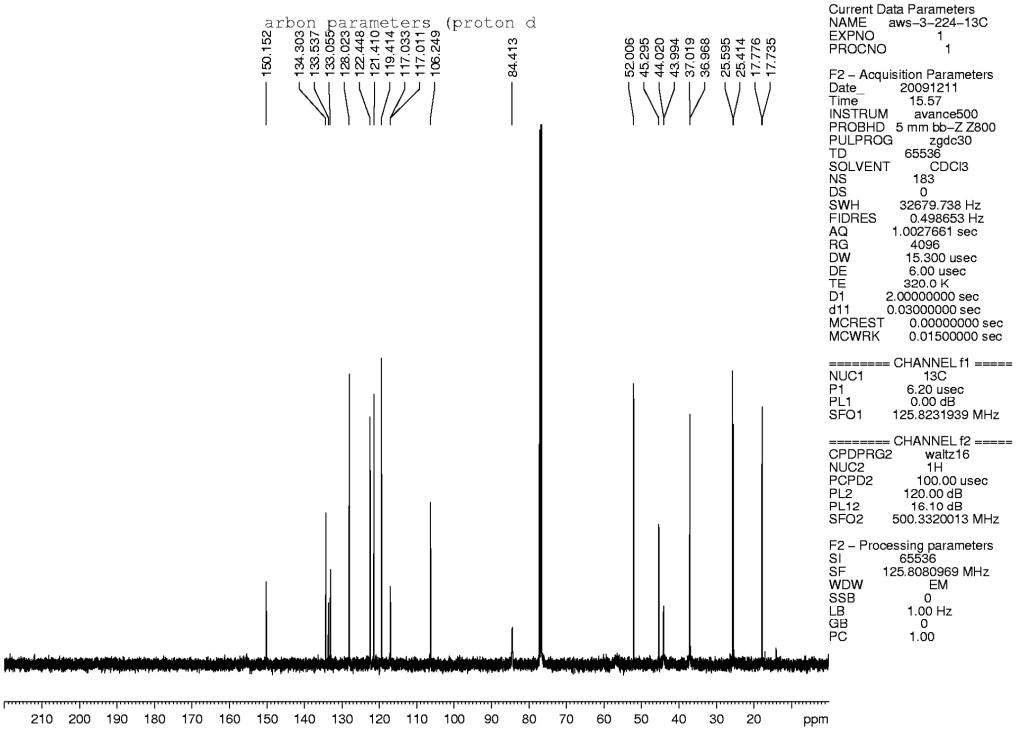


Figure A1.124 ^{13}C NMR (125 MHz, $CDCl_3$) of compounds **2.42**.

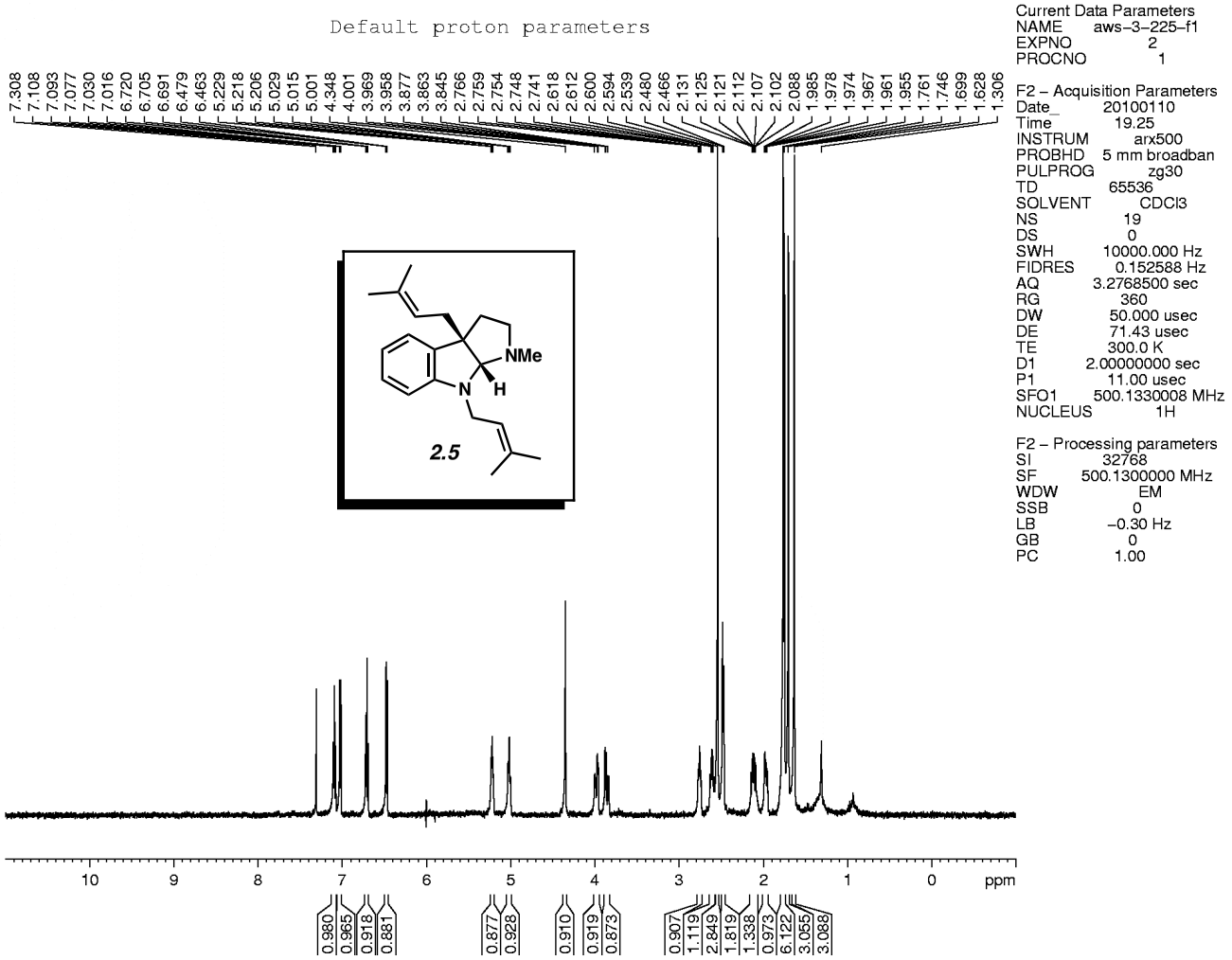


Figure A1.125 ^{1}H NMR (500 MHz, $CDCl_3$) of compounds **2.5**.

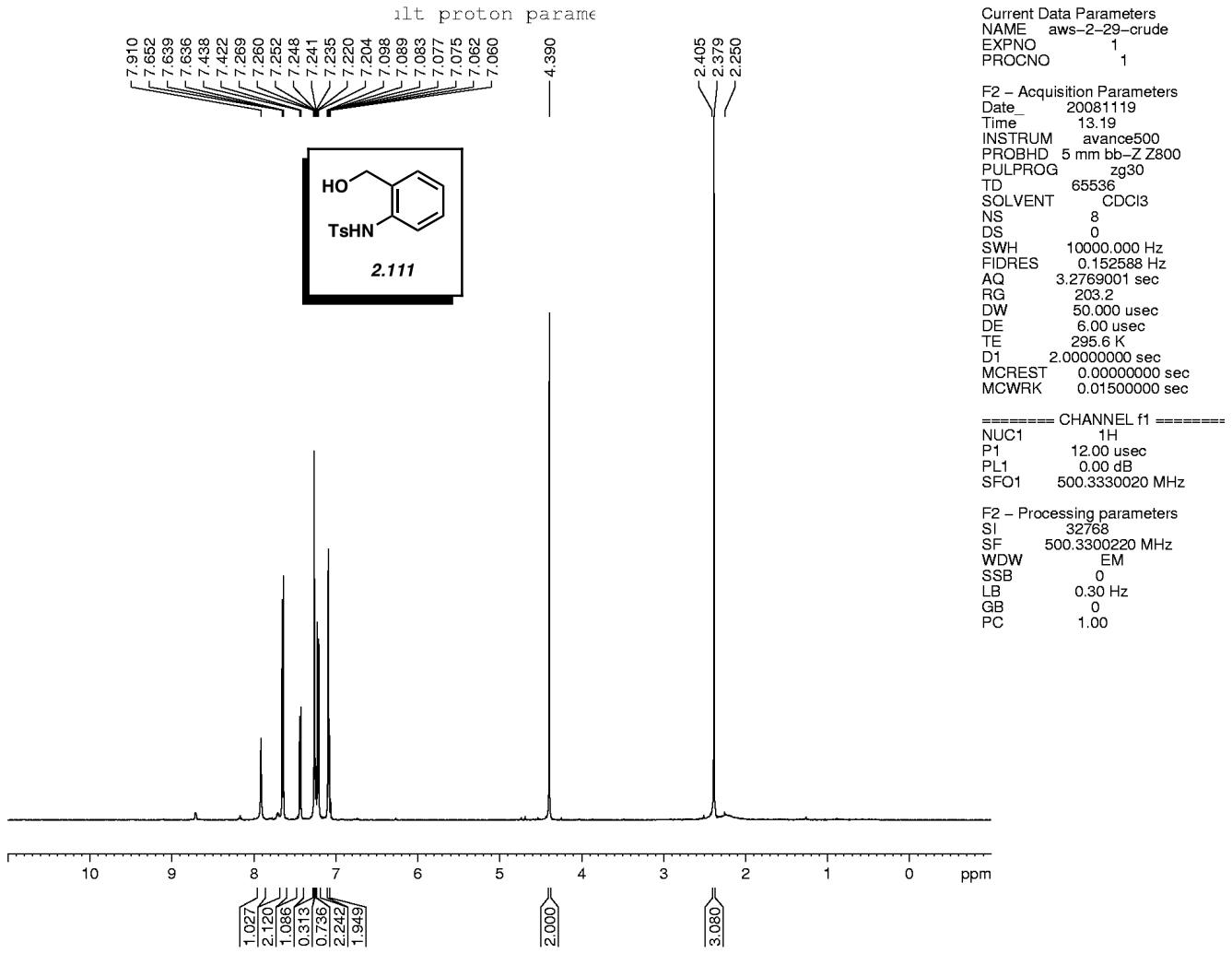


Figure A1.126 ^{1}H NMR (500 MHz, $CDCl_3$) of compounds **2.111**.

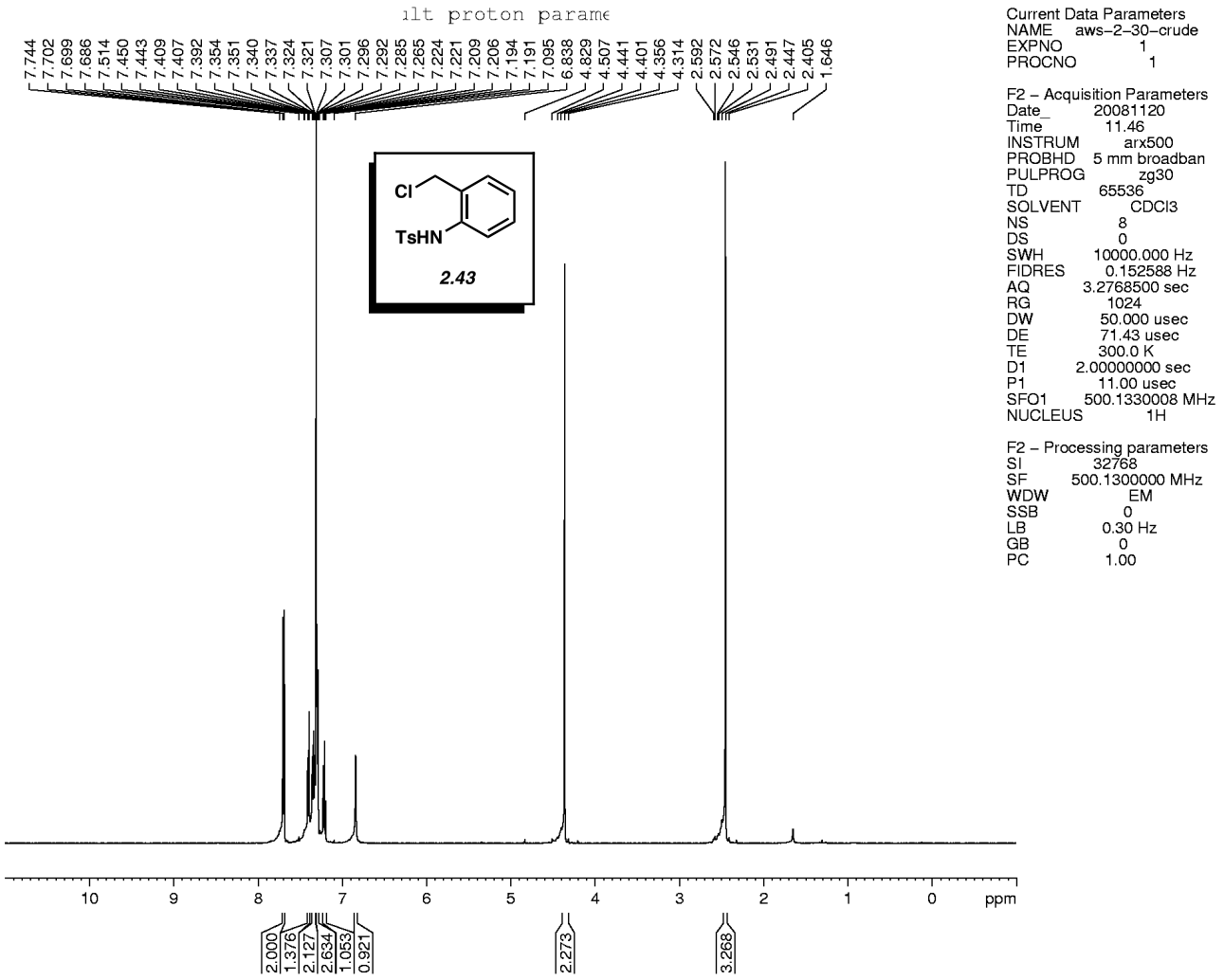


Figure A1.127 ^{1}H NMR (500 MHz, $CDCl_3$) of compounds **2.43**.

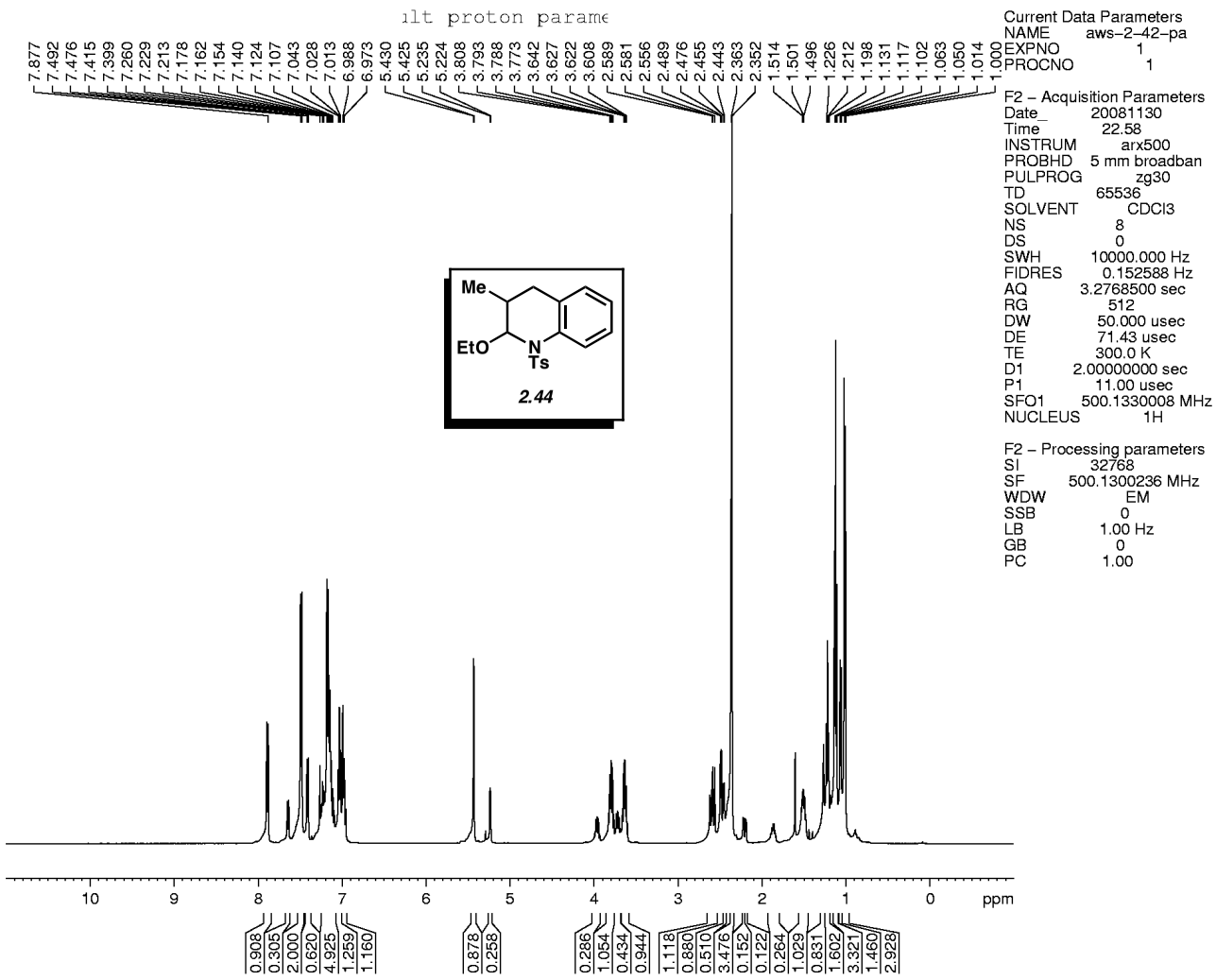


Figure A1.128 ^{1}H NMR (500 MHz, $CDCl_3$) of compounds **2.44**.

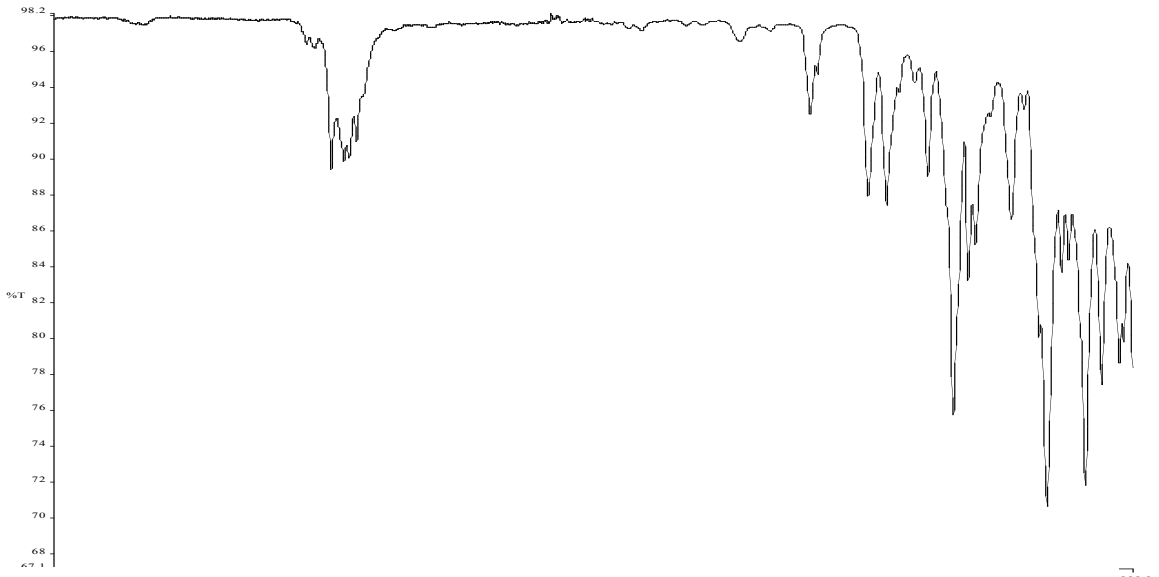


Figure A1.129 Infrared spectrum of compounds **2.44**.

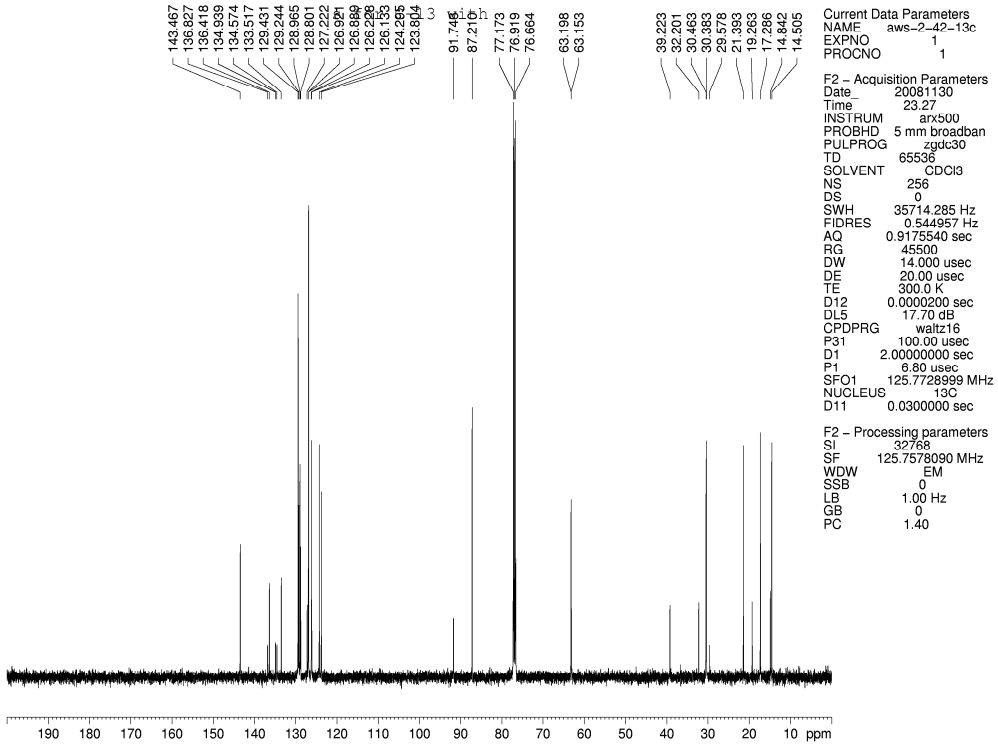
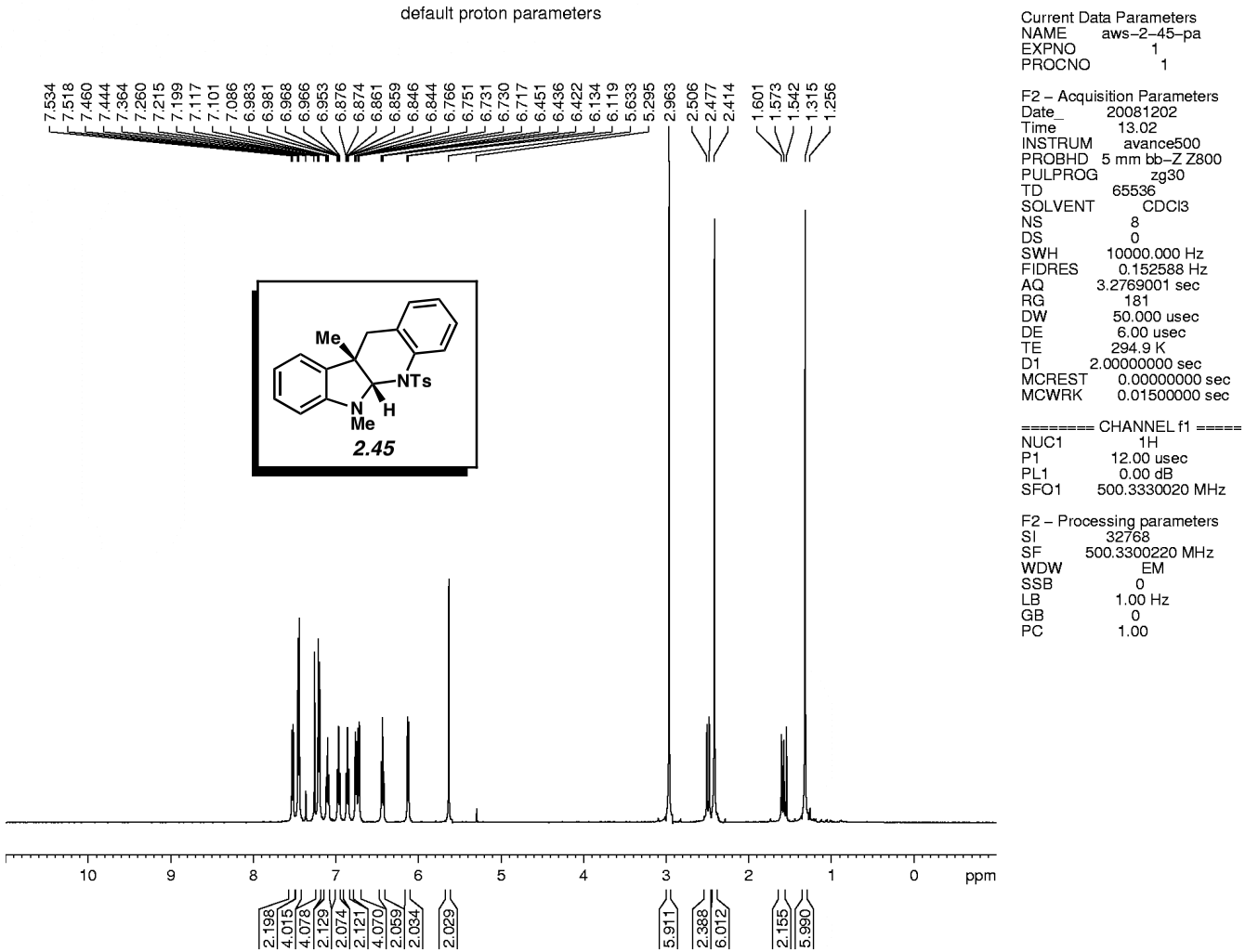


Figure A1.130 ^{13}C NMR (125 MHz, $CDCl_3$) of compounds **2.44**.



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F2 – Processing parameters
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GB 0
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Figure A1.131 ^{1}H NMR (500 MHz, $CDCl_3$) of compounds **2.45**.

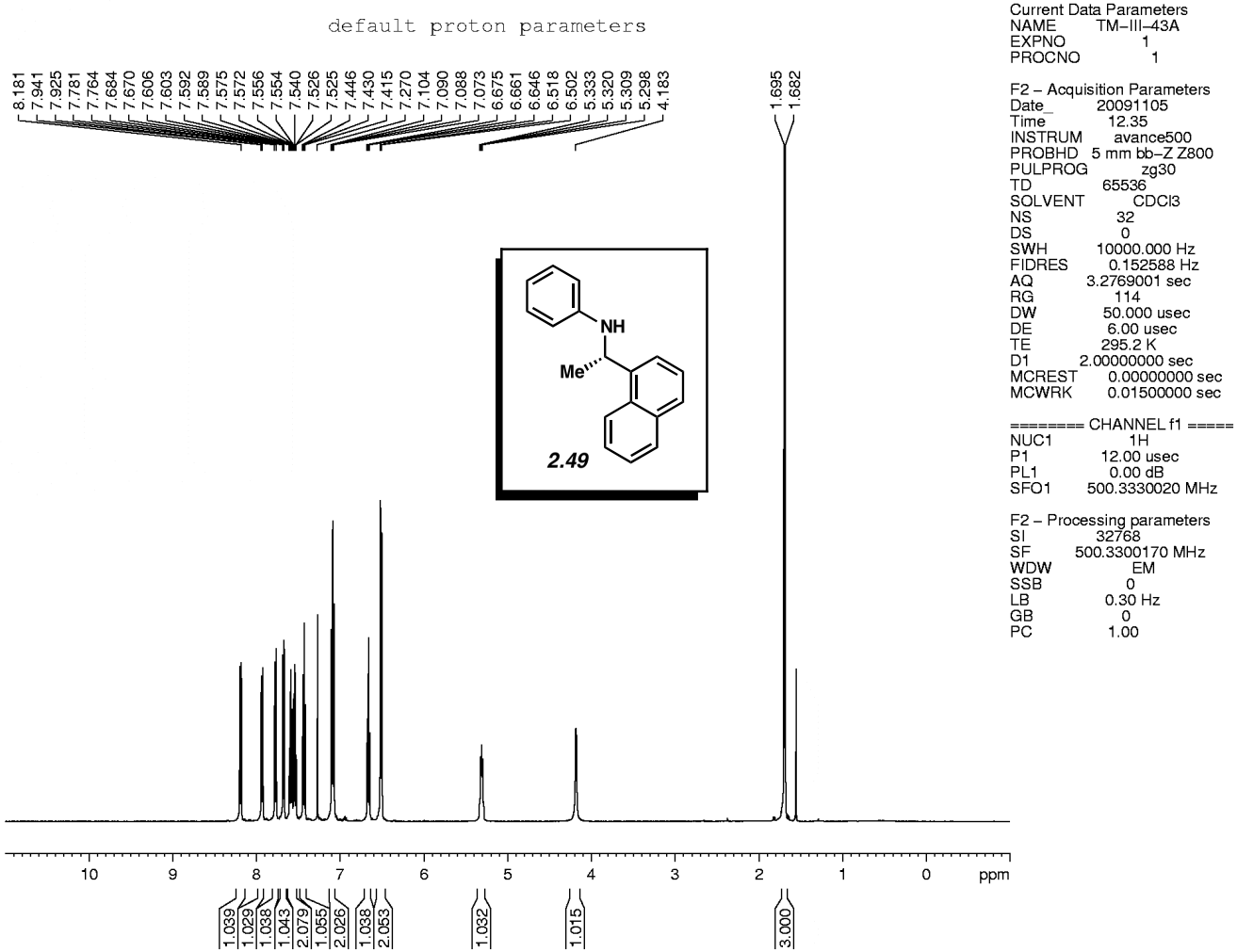


Figure A1.132 ^{1}H NMR (500 MHz, $CDCl_3$) of compounds **2.49**.

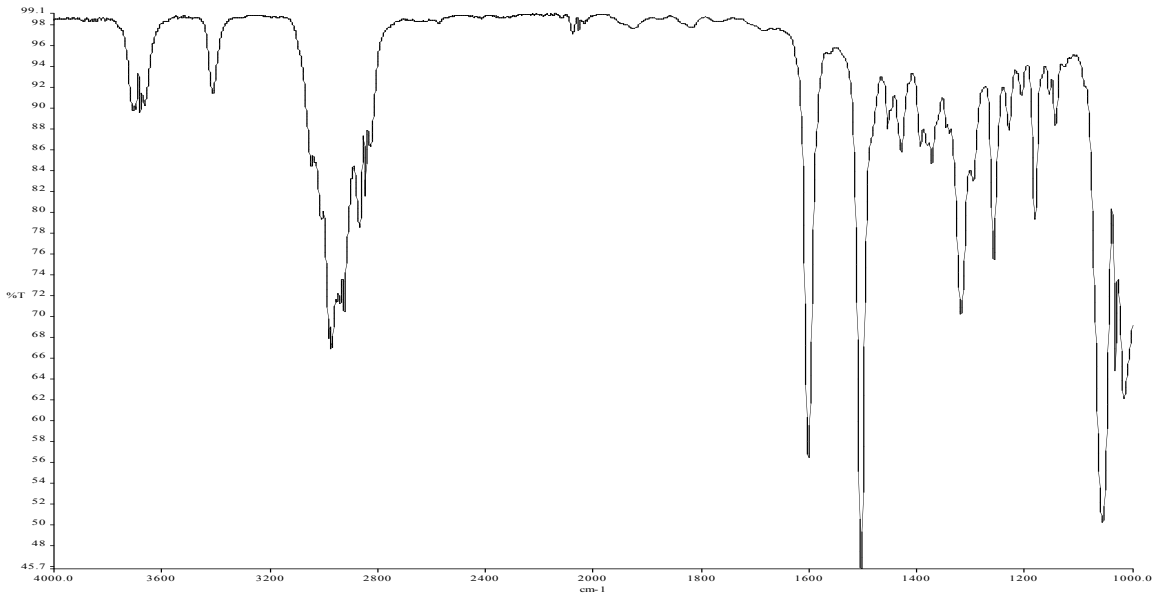


Figure A1.133 Infrared spectrum of compounds **2.49**.

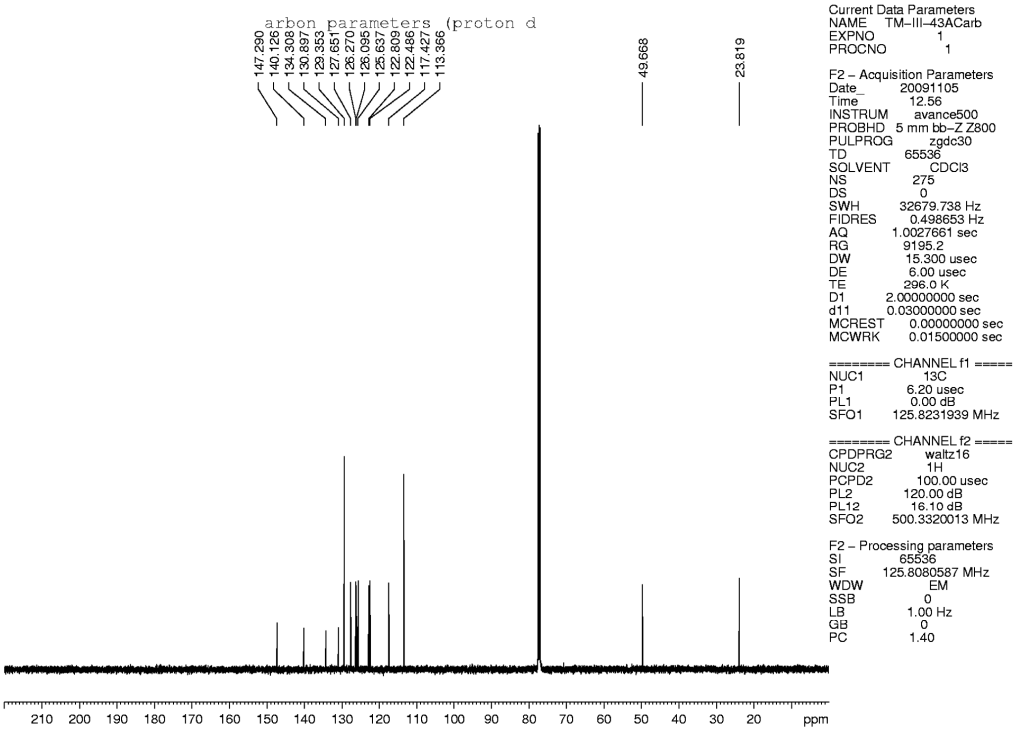


Figure A1.134 ^{13}C NMR (125 MHz, $CDCl_3$) of compounds **2.49**.

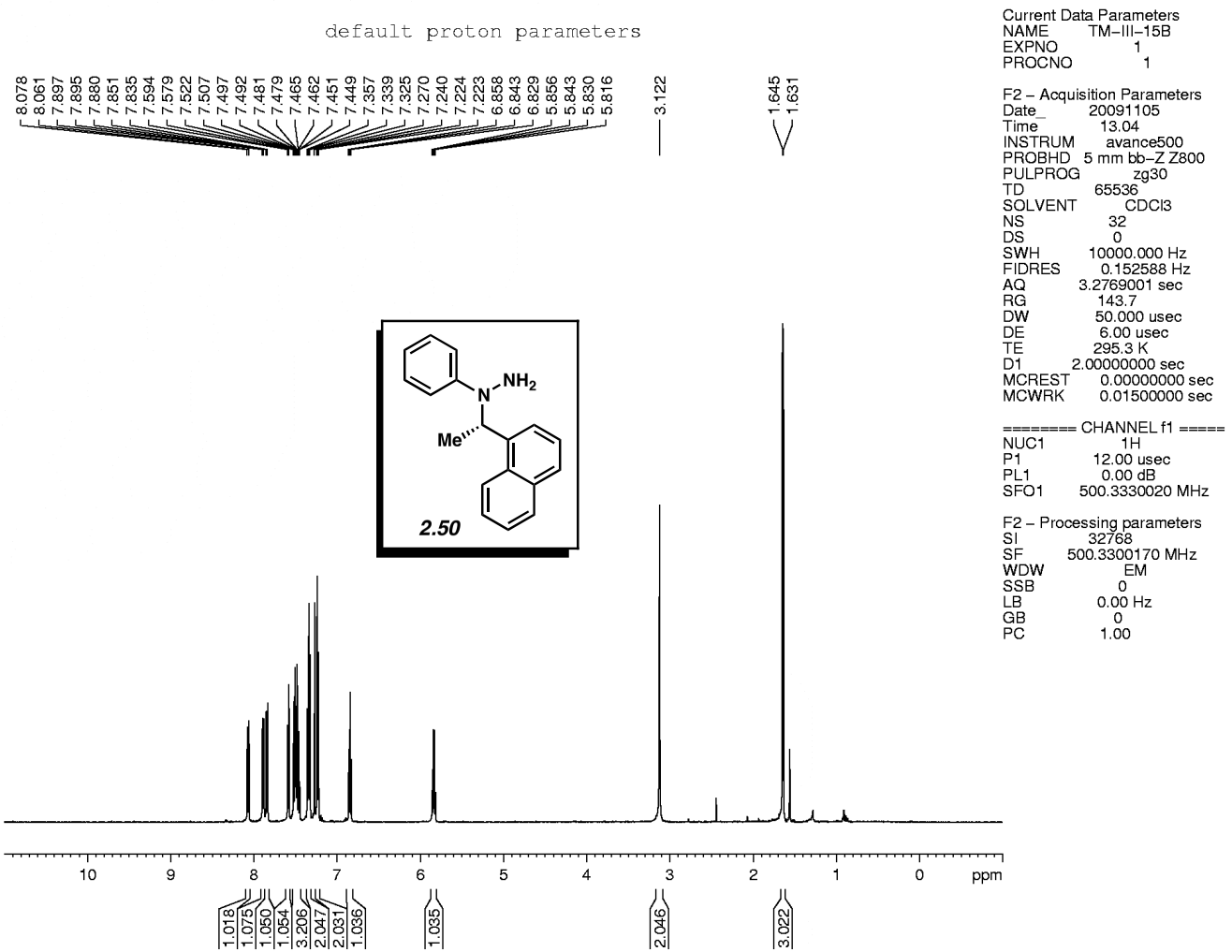


Figure A1.135 ^{1}H NMR (500 MHz, $CDCl_3$) of compounds **2.50**.

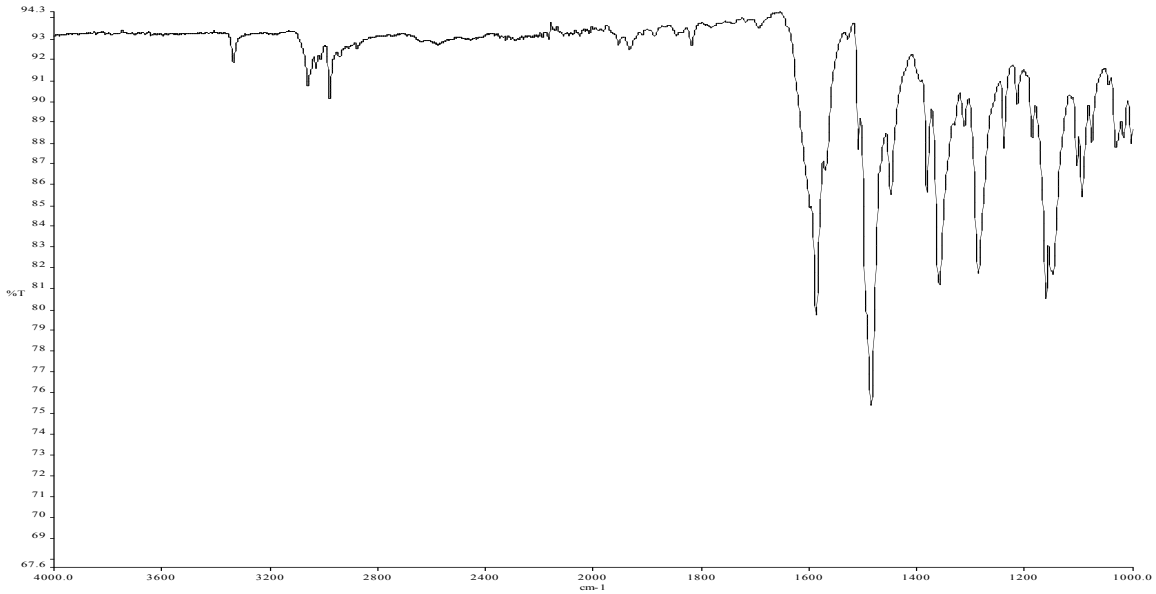


Figure A1.136 Infrared spectrum of compounds **2.50**.

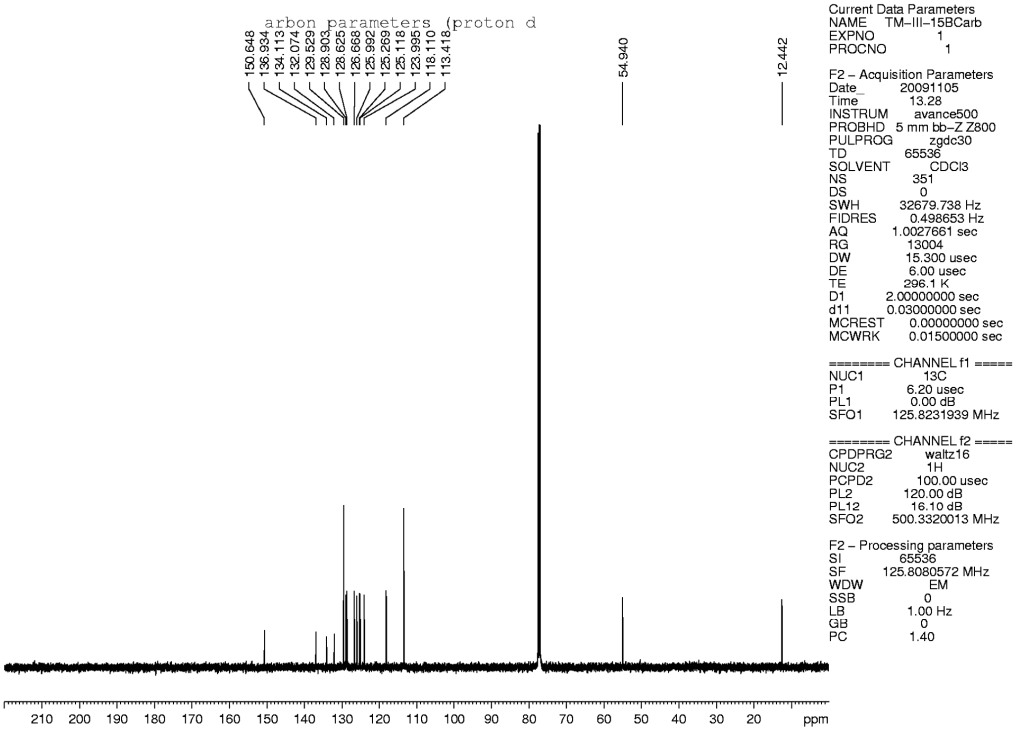


Figure A1.137 ^{13}C NMR (125 MHz, $CDCl_3$) of compounds **2.50**.

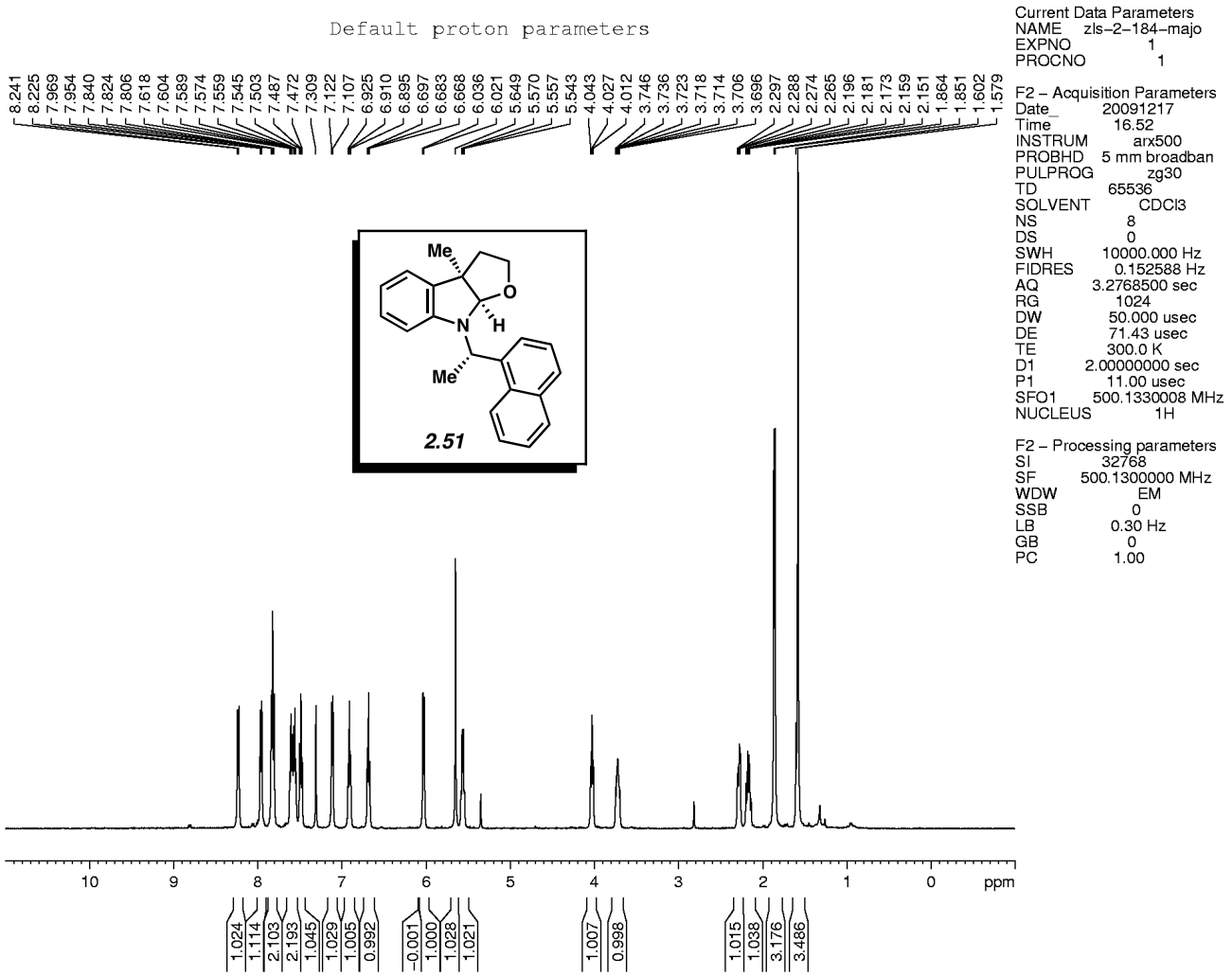


Figure A1.138 ^{1}H NMR (500 MHz, $CDCl_3$) of compounds **2.51**.

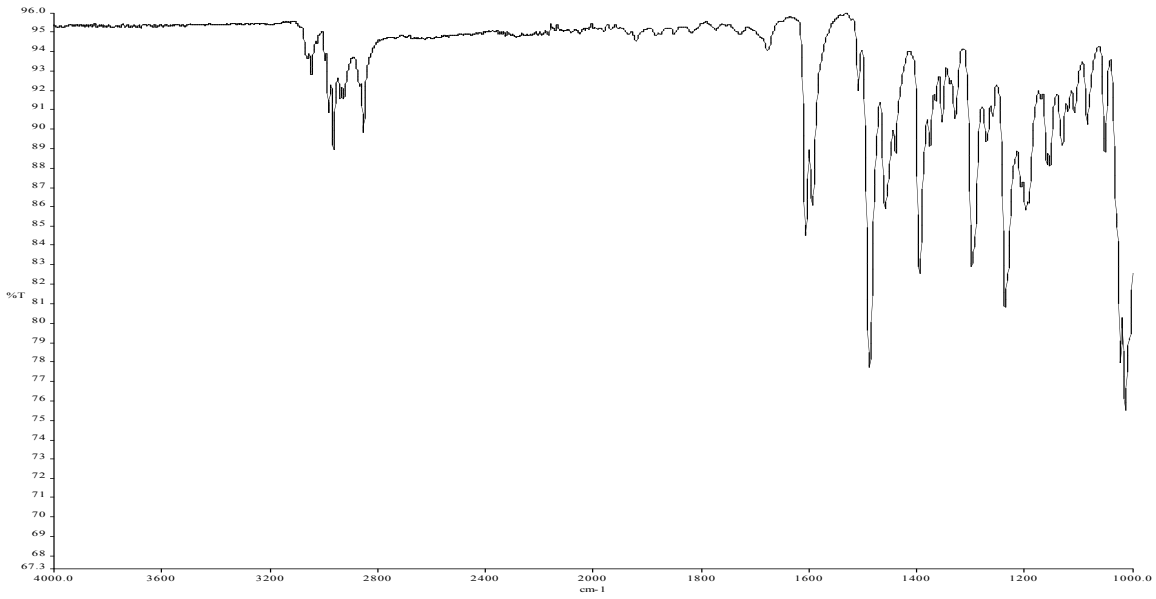


Figure A1.139 Infrared spectrum of compounds **2.51**.

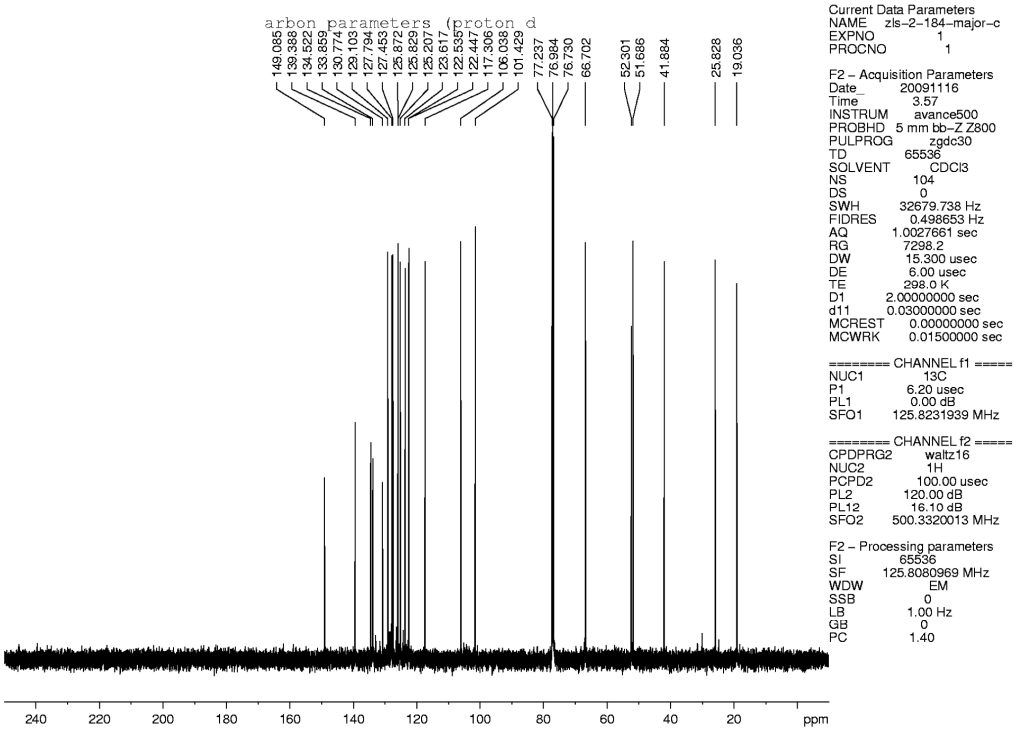


Figure A1.140 ^{13}C NMR (125 MHz, $CDCl_3$) of compounds **2.51**.

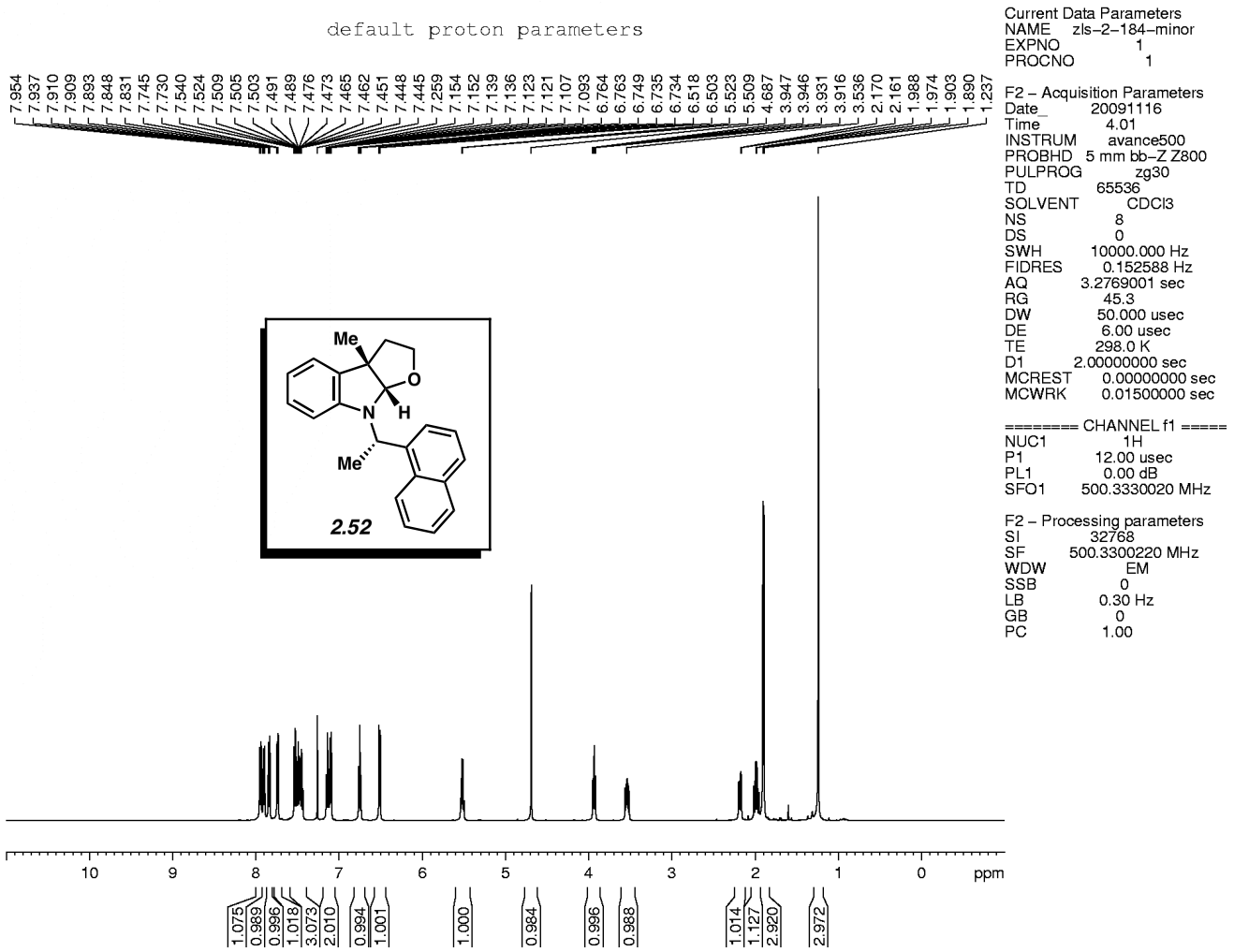


Figure A1.141 ^{1}H NMR (500 MHz, $CDCl_3$) of compounds **2.52**.

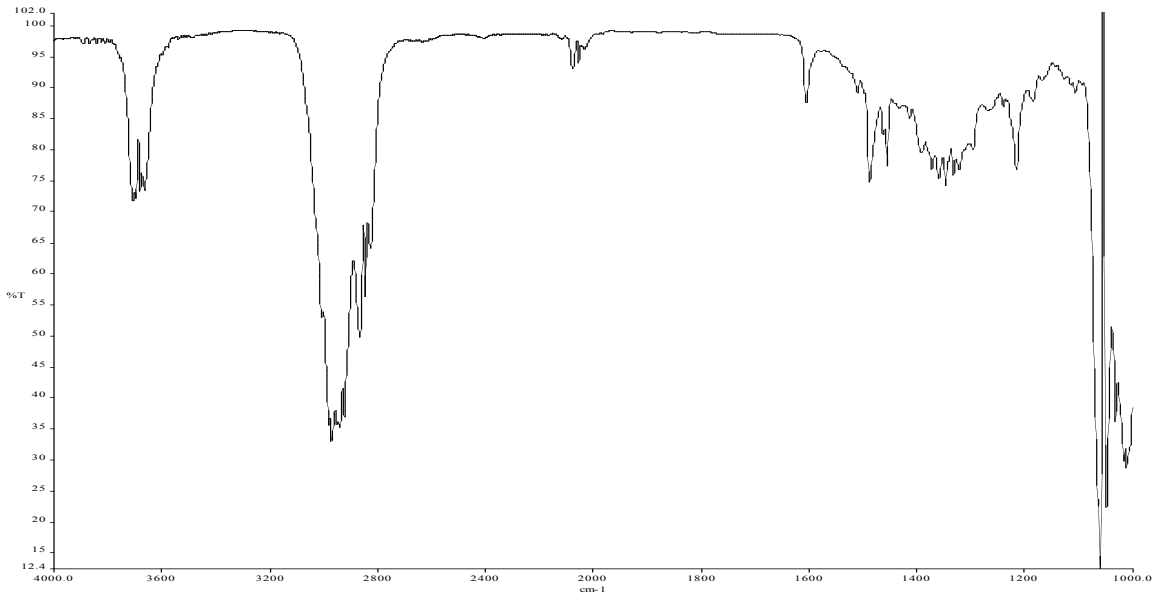


Figure A1.142 Infrared spectrum of compounds **2.52**.

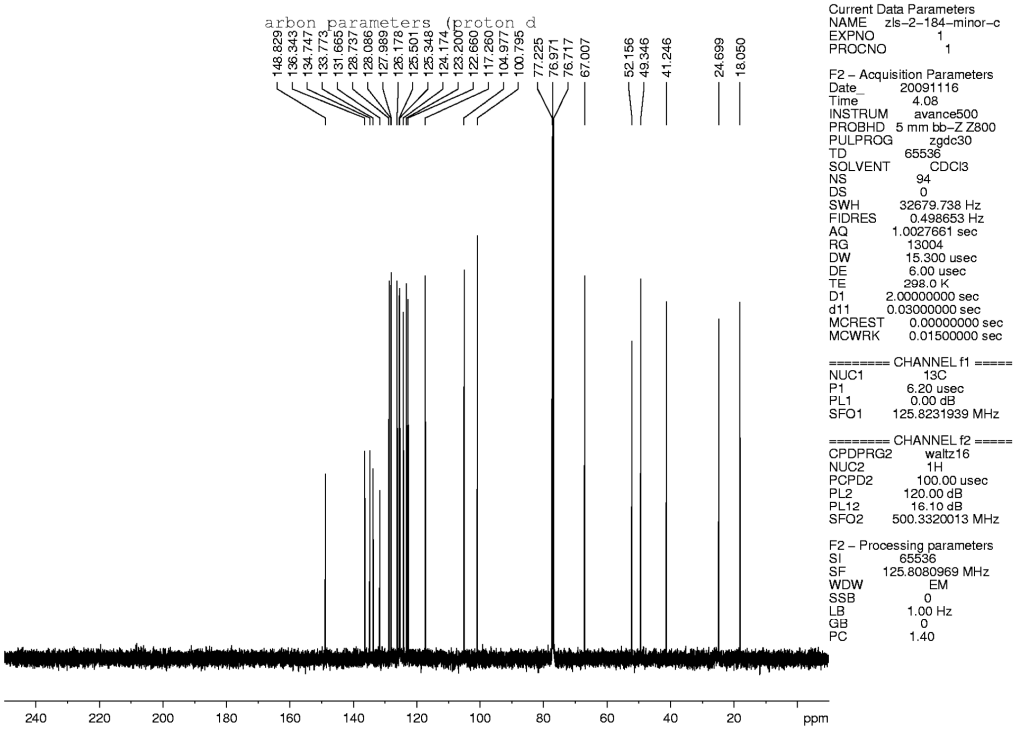


Figure A1.143 ^{13}C NMR (125 MHz, $CDCl_3$) of compounds **2.52**.

CHAPTER THREE

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.

3.1 Abstract

The mechanisms of the Fischer indole synthesis and competing cleavage pathways were explored with SCS-MP2/6-31G(d) and aqueous solvation calculations. Electron-donating substituents divert the reaction pathway to heterolytic *N–N* bond cleavage and preclude the acid-promoted [3,3]-sigmatropic rearrangement.

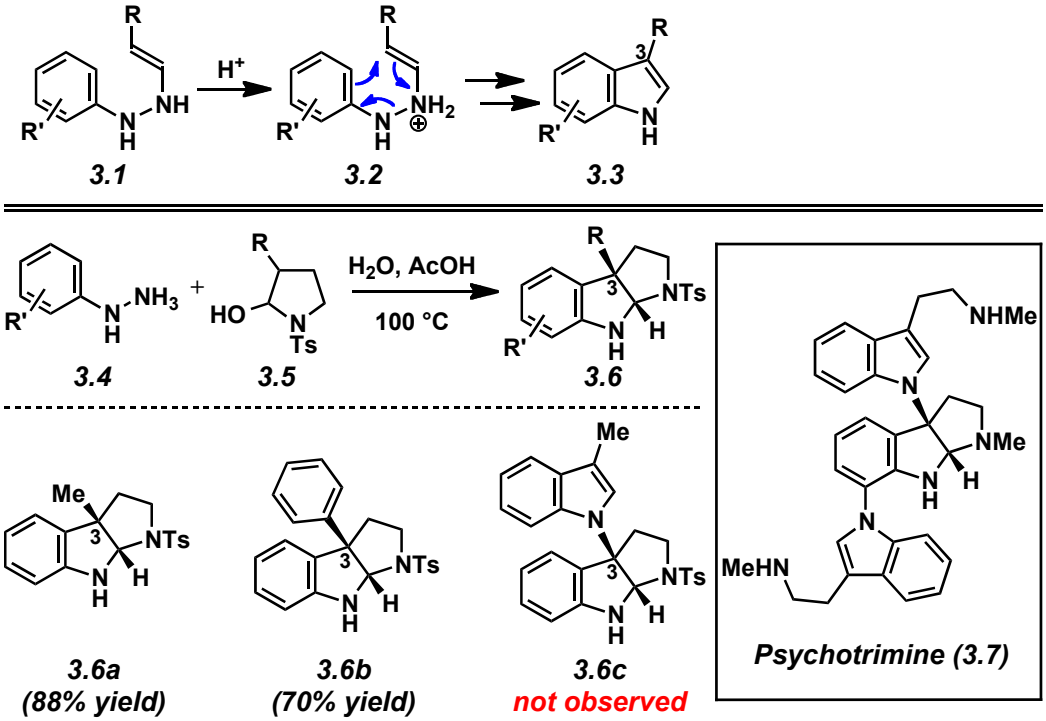
3.2 Introduction

Indole derivatives continue to receive substantial interest due to their wide range of biological activity.[1,2,3,4,5] The Fischer indole synthesis[6] remains among the most widely used approaches to indoles, with more than 700 reports over the last 15 years.[5] Despite the extensive application of the Fischer indole sequence, certain substitution patterns cause the reaction to fail.

A notable challenge for the Fischer indolization reaction is the synthesis of C3 *N*-substituted indoles (**3.1→3.3**, Scheme 3.1). Various 3-aminoindole derivatives display antimalarial, anti-muscarinic, anti-bacterial, anti-viral, anti-plasmoidal, and anti-hyperglycemic activities and are attractive pharmacological targets.[7,8] However, to date, there are no examples of 3-aminoindole synthesis by the Fischer method, and the corresponding preparation of *N*-(indol-3-yl)amides[9,10,11,12]and 3-pyrazolylindoles[13,14] proceeds poorly in the presence of protic acids. While the use of Lewis-acids (e.g., $ZnCl_2$ or $ZnBr_2$) improves the efficiency of cyclizations,[9] the question remains: Why do these Fischer indolizations fail?

We have encountered similar difficulties in efforts to synthesize complex indoline-containing natural products using the interrupted Fischer indolization cascade[15] (**3.4+3.5→3.6**, Scheme 3.1). Reactions between aryl hydrazines **3.4** and latent aldehydes **3.5** delivered 3-alkyl and 3-aryl substituted pyrrolidindolines, **3.6a** and **3.6b**, in good yields,[15] but the transformation failed en route to 3-indolyl pyrrolidindoline, **3.6c**, intended to be a model study for the synthesis of psychotrimine[16,17] (**3.7**) and related alkaloids.

Scheme 3.1

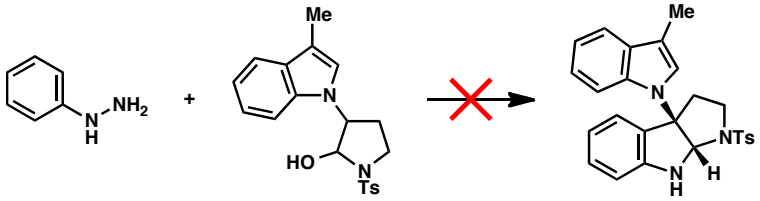


3.3 Failed Experimental Interrupted Fischer Indolization

Table 3.1 shows a sampling of our unsuccessful interrupted Fischer indolization attempts of substrate **3.5c**. Phenylhydrazine was employed in initial experiments. Acetic acid-based conditions, commonly used for the interrupted Fischer indolization reaction, gave none of the

desired indoline product (entries 1–2). Similarly, the use of stronger acids typically used to promote Fischer indole synthesis was also unsuccessful (entries 3–6).[18] All of these experiments gave rise to two significant byproducts: 3-methylindole and aniline. Comparable results were obtained when treating arylhydrazone derivatives of **3.5c** under acidic conditions. Despite being a widely utilized process, many essential mechanistic details underlying the acid-promoted Fischer indolization remain unclear. Previous computational investigations on the mechanism of the Fischer indole reaction are limited to semiempirical methods,[19] and the effect of substituents on the possible competing pathways has not yet been addressed. Here, we report the first computational study on the mechanism of the Fischer indole reaction using accurate quantum mechanical methods, and demonstrate that substituents on the starting carbonyl compound play a pivotal role in the success or failure of the Fischer indole synthesis. We also show that the commonly used B3LYP method fails to reproduce the concerted nature of the acid-promoted 3,4-diaza-Cope rearrangement.

Table 3.1. Interrupted Fischer Indolization Attempts with **3.5c**



3.5c *3.6c*

Entry	Conditions
1	1:1 AcOH/H_2O, rt to 110°C
2	AcOH, rt to 100 °C
3	TFA, $C_2H_4Cl_2$, rt to 80°C
4	$HCl_{(aq)}$, CH_3CN, rt to 120 °C
5	$H_2SO_{4(aq)}$, CH_3CN, rt to 120 °C
6	TsOH, *t*-BuOH, rt to 80 °C
7	ClAcOH, PhMe, rt to 170 °C
8	ClAcOH, MeOH, rt to 80 °C
9	PPTS, MeOH, rt to 80 °C

3.4 Initial Computational Studies

We first studied the parent unsubstituted rearrangement using different levels of theory, including CBS-QB3, B3LYP, SCS-MP2, MP2 and M06-2X with Gaussian 09.[20] Solvation effects were taken into account in geometry optimizations and in energy calculations using the SMD model.[21] B3LYP favors *N–N* bond cleavage, without *C–C* bond formation, for the protonated species and failed to predict the concerted nature of the sigmatropic rearrangement transition states upon substitution. These results and a detailed comparison of all methods are given in the Supporting Information. In the text, we discuss results obtained at the SCS-MP2/6-31G(d)(water)//MP2/6-31G(d)(water) level of theory, which provide the best results in test calculations. Figure 3.1 shows the free energies of the ene-hydrazine intermediates and [3,3]-sigmatropic rearrangement transition states relative to the phenylhydrazone for both the thermal

and acid-catalyzed (Nα-protonated and Nβ-protonated) pathways. In the thermal reaction, ene-hydrazine intermediate **3.9** lies 17.5 kcal/mol higher in energy than phenylhydrazone **3.8**. The rearrangement transition state (**t-TS**) is concerted, but asynchronous with a very high activation barrier of 43.7 kcal/mol. Protonation of either nitrogen gives earlier transition states, increased asynchronicity, and a substantial decrease in the activation energy by 11-13 kcal/mol. Stabilization of the ene-hydrazine intermediates due to protonation (**3.9a** and **3.9b**) is less significant ($\Delta\Delta G$ = 3.1 kcal/mol). Overall, the Nβ-protonated pathway is favored by 1.5 kcal/mol and yields the rearranged product **3.10b** in a concerted fashion. M06-2X significantly overestimated the barrier of the [3,3]-sigmatropic rearrangement by ~6-10 kcal/mol (see SI).

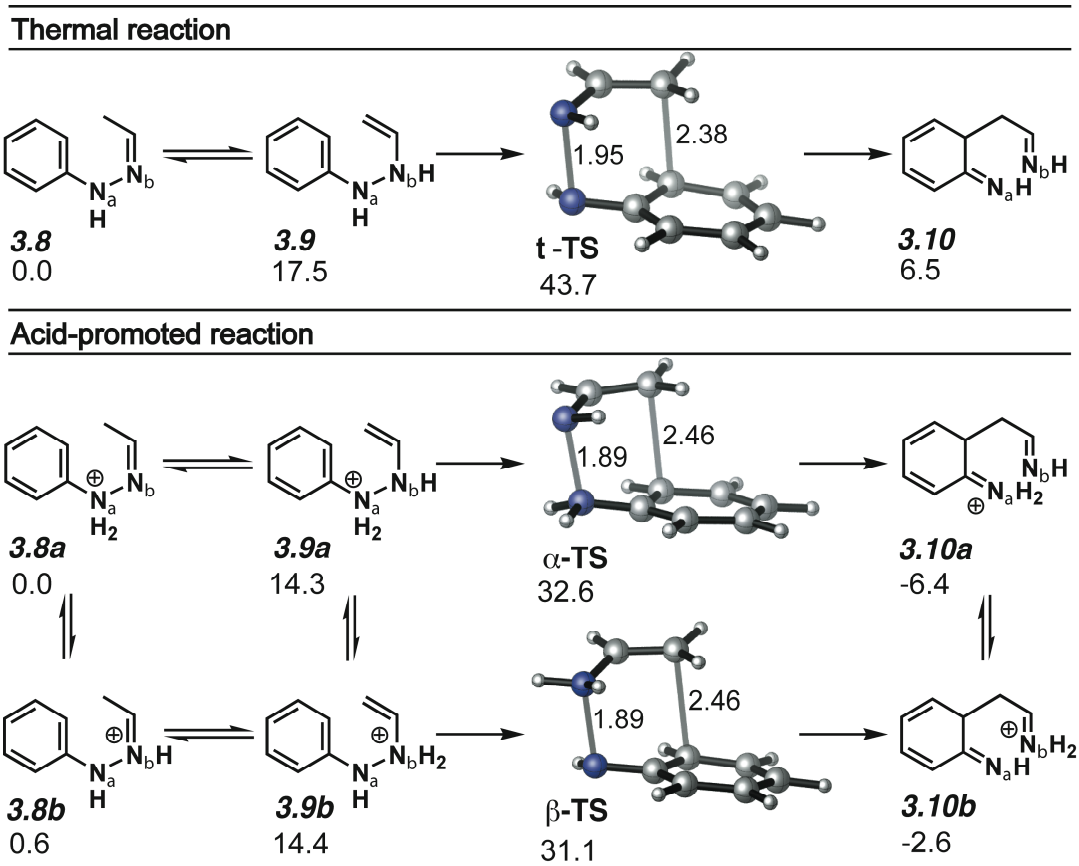


Figure 3.1. Free energies (ΔG, in kcal/mol) for the transformation of hydrazone to imine for the thermal and acid-promoted reaction [SCS-MP2/6-31G(d)(water)//MP2-6-31G(d)(water)].

3.5 Substituent Effects

The influence of various substituents was evaluated computationally (Table 3.2). A single methyl substituent (entry 2) led to additional stabilization of both ene-hydrazine intermediates ($\Delta\Delta G \approx 4$ kcal/mol) and [3,3]-sigmatropic rearrangement transition states ($\Delta\Delta G \approx 6$ kcal/mol) compared to the parent reaction (entry 1). The energies of protonated ene-hydrazines are essentially identical, and the **β-TS** is still favored over the **α-TS**. The favorable [3,3]-sigmatropic rearrangement of the monomethylated substrate (entry 2) is consistent with experimental data on Fischer indole synthesis.[5] Condensation of phenylhydrazines with 3-substituted hemiaminals or lactols, the so-called interrupted Fischer indolization strategy,[15] involves disubstituted phenylhydrazone intermediates. We find that the second substituent further stabilizes the intermediates and transition states by 1-3 kcal/mol (entry 3) compared to the monomethyl substituted reaction. The Nα- and Nβ-protonated pathways have comparable energies (Figure 3.2).

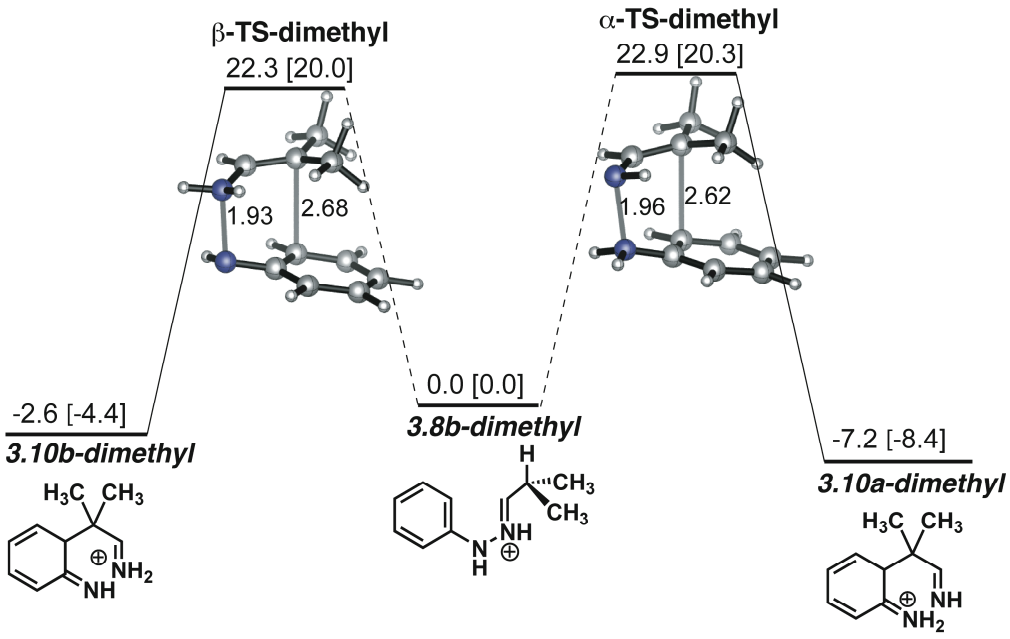


Figure 3.2. Energy profile (Δ*G*[Δ*H*], in kcal/mol) for the acid-promoted transformation of dimethyl substituted hydrazone.

Table 3.2. Substituent Effects on the Free Energy (Enthalpy)[a] Profile [SCS-MP2/6-31G(d)(water)//MP2/6-31G(d)(water)]

Entry	Substituents	3.8a	3.9a	**α-TS**	3.8b	3.9b	**β-TS**
1	R_1: H, R_2: H	0.0 (0.0)	14.3 (14.1)	32.6 (30.3)	0.6 (0.6)	14.4 (14.3)	**31.1 (28.7)**[b]
2	R_1: CH_3, R_2: H	0.0 (0.0)	10.6 (10.3)	26.1 (23.9)	0.5 (0.4)	10.7 (10.7)	**24.7 (22.8)**[b]
3	R_1: CH_3, R_2: CH_3	0.2 (0.0)	9.3 (8.7)	**22.9 (20.3)**[b]	0.0 (0.0)	8.7 (7.7)	**22.3 (20.0)**[b]
4	R_1: Indolyl, R_2: CH_3	0.0 (0.0)	9.2 (8.8)	**18.0 (16.5)**[c]	2.2 (2.7)	9.0 (9.3)	21.2 (19.3)
5	R_1: CH_3, R_2: N(H)acetyl	0.0 (0.0)	7.3 (7.6)	**18.5 (17.7)**[c]	1.1 (1.5)	7.4 (8.5)	19.6 (17.9)

[a]Free energies (enthalpies in parenthesis) are given relative to phenylhydrazone in kcal/mol. [b]Favored transition state involves [3,3]-sigmatropic rearrangement. [c] Favored transition state leads to *N-N* bond cleavage products.

3.6 Nitrogen Substituents

The reaction profile obtained with the indolyl-substituent, on the other hand, is completely different (entry 4 Table 3.1, and Figure 3.3). The **α-TS-indolyl** (ΔG = 18.0 kcal/mol) is noticeably lower in energy than **β-TS-indolyl** (ΔG = 21.2 kcal/mol), but the favored transition state is not that of a [3,3]-sigmatropic rearrangement (Figure 3.3). Instead, the intrinsic reaction coordinate (IRC) gives the stable p-complex, **3.11**. In solution, this complex will dissociate, forming aniline and iminylcarbocation **3.12**. Therefore, for the indolyl substituted reaction, the Nα-protonated pathway leads to dissociation rather than rearrangement in solution. This suggests that the iminylcarbocation, formed by the heterolytic *N–N* bond cleavage, is stabilized by the electron-donating indolyl substituent, and this is responsible for the failure of the Fischer indolization for this substitution pattern. In place of an indolyl substituent, an acylated amine was evaluated (entry 5). Similarly, heterolytic *N–N* bond cleavage was favored over [3,3]-sigmatropic rearrangement. This result explains why the acid-catalyzed Fischer indolization of amide-containing substrates has proved challenging.[9-14]

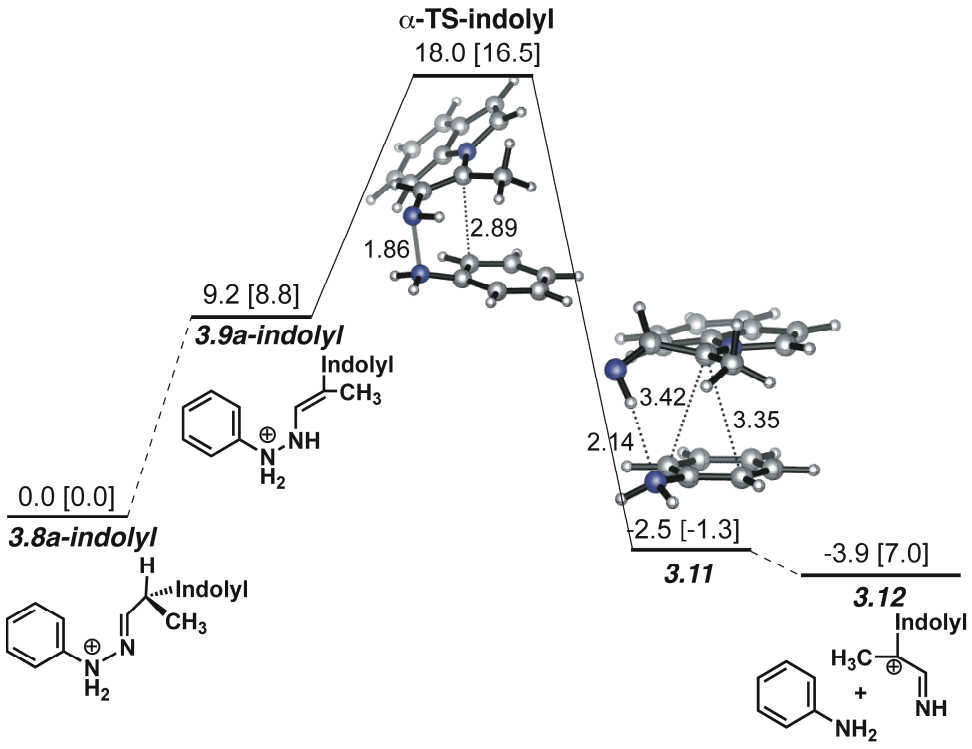


Figure 3.3. Energy profile (Δ*G*[Δ*H*], in kcal/mol) for the acid-promoted transformation of indolyl substituted hydrazone.

To better understand this behavior, we calculated the heterolytic bond dissociation enthalpies of Nα- and Nβ-protonated ene-hydrazine intermediates (Table 3.3). As highlighted by entries 1-5, substantial weakening of the *N–N* bond occurs in **3.9a**with more electron-donating substituents on the terminal alkene. The activation barriers of the Nα-protonated species are lowered, and the transition states became more dissociative. The dissociative character of the weak *N–N* bond eventually precludes the [3,3]-sigmatropic rearrangement, and the ene-hydrazine intermediate collapses to aniline and a stabilized iminylcarbocation. The heterolytic *N–N* bond cleavage leads to side reactions rather than the Fischer indolization. These results are in accord with our experimental observations, and experimental findings by Mann and Cook.[22] Previous studies of substituent effects on the Cope rearrangement and related 3,3-sigmatropic shifts

indicate that substituents that stabilize either associative or dissociative transition states accelerate the concerted rearrangement.[23] Extreme stabilization of the dissociative transition state can eventually lead to dissociation, as was noted previously for amido-Cope rearrangements.[24]

Table 3.3. Bond Dissociation Enthalpies (BDE) of Protonated Ene-hydrazines [SCS-MP2/6-31G(d)(water)//MP2/6-31G(d)(water)]

Entry	Substituents	**BDE-3.9*a*[a]**	**BDE-3.9*b*[a]**
1	R_1: H R_2: H	47.1 (36.3)	34.2 (23.6)
2	R_1: CH_3 R_2: H	31.0 (19.8)	35.9 (25.1)
3	R_1: CH_3 R_2: CH_3	20.7 (9.7)	38.1 (26.0)
4	R_1: Indolyl R_2: H	0.0 (-10.1)	32.3 (21.2)
5	R_1: Indolyl R_2: CH_3	-1.8(-13.2)	33.2 (21.5)
6	R_1: CH_3 R_2: N(H)acetyl	1.0(-10.7)	36.4 (25.8)
7	R_1: H R_2: N(H)acetyl	8.9 (-2.6)	34.9 (23.7)
8	R_1:N(H)acetyl R_2:acetyl	10.7 (0.4)	22.4 (10.9)

[a]Relative enthalpies of *N-N* bond cleavage of the corresponding ene-hydrazine intermediate (ΔH, kcal/mol). Relative free energies (ΔG, kcal/mol) are given in parenthesis.

In contrast to electron-donating substituents, electron-withdrawing groups weaken the *N–N* bond in **3.9b**, and stabilize the *N–N* bond in **3.9a** (Table 3.3, entry 8 vs. 6). This suggests that changing the amino substituent to amido would somewhat disfavor the competing dissociative pathway. Indeed, the *N*-acyl group notably increases the strength of the *N–N* bond in the Nα-protonated ene-hydrazines compared to indolyl (Table 3.3, entries 4 and 7). However, the bond dissociation enthalpy is still low (8.9 kcal/mol) compared to the case with only alkyl substituents (31.0 kcal/mol). These results explain in part the relatively poor yields obtained in the acid-

catalyzed Fischer indole synthesis of 3-amido indoles.[10] Disubstitution with an amido and alkyl group is predicted to be detrimental for the Nα-protonated rearrangement (Table 3.3, entry 6).

3.7 Conclusions

Electron-donating substituents weaken the *N–N* bond in the Nα-protonated ene-hydrazine and lower the activation energy for the rearrangement step. However, excessive stabilization of heterolytic *N–N* bond cleavage precludes the products of the [3,3]-sigmatropic rearrangement, leading to the dissociation of the ene-hydrazine intermediate. This eventually translates to lower yields, or even to the failure of cyclization. Bond dissociation enthalpies are excellent guides to determine the feasibility of the cleavage process. Beyond providing an explanation for the failure of certain Fischer indolization reactions, we expect these findings will enable the judicious design of synthetic routes that employ aza-[3,3]-sigmatropic rearrangements.

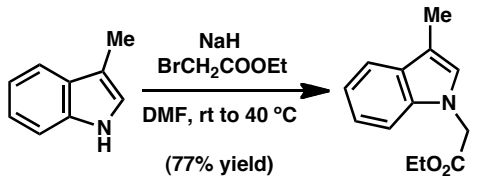
3.8 Experimental Section

3.8.1 Materials and Methods

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. *tert*-butyldimethylsilyl chloride was obtained from Oakwood. 3-methylindole, and 4-dimethylaminopyridine were obtained from VWR (manufactured by Alfa-Aesar). Sodium hydride, ethyl 2-bromoacetate, bis(trimethylsilyl)amine, bromoacetonitrile, sodium borohydride, 4-toluenesulfonyl chloride, tetra-*n*-butylammonium fluoride, 2-iodobenzoic acid, Oxone and lithium aluminum hydride were obtained from Sigma-Aldrich. 2-Iodoxybenzoic acid was prepared from a known literature procedure.[25] 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 (at 300 MHz, 400 MHz, or 500 MHz) and are reported relative to deuterated solvent signals. Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz) and integration. ^{13}C NMR spectra are reported in terms of chemical shift (at 100 MHz, 125 MHz). For mixtures of diastereomers, the major diastereomer is reported with the minor diastereomer in parentheses for both ^{1}H NMR and ^{13}C NMR spectra. IR spectra were recorded on a Perkin-Elmer

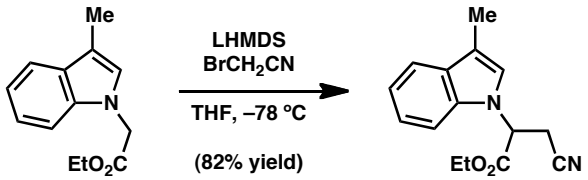
100 spectrometer and are reported in terms of frequency absorption (cm^{-1}). High resolution mass spectra were obtained from the UC Irvine Mass Spectrometry Facility.

3.8.2 Experimental Procedures



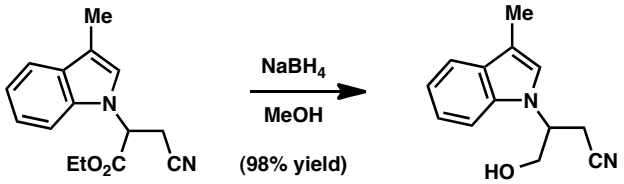
3.13 *3.14*

Ester 3.14. To a suspension of NaH (988 mg, 41.2 mmol) in DMF (90 mL) at rt was added a solution of 3-methylindole (**3.13**) (4.5 g, 34 mmol) in DMF (30 mL) dropwise over 10 min. Following the addition, the reaction mixture was stirred for 30 min at rt, then ethyl bromoacetate (535 μL, 7.21 mmol) was added dropwise over 5 min. After stirring for 30 min at rt, the reaction was warmed to 40 °C. After 1 h, the reaction mixture was cooled to rt and poured into deionized water (200 mL). The solution was diluted with EtOAc (100 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 100 mL). The organic layers were combined, dried over Na_2SO_4, and evaporated under reduced pressure. The resulting residue was purified by flash chromatography (3:1 → 1:1 hexanes:benzene) to afford ester **3.14** (5.78 g, 77% yield) as a pink oil. R_f 0.3 (1:1 hexanes:benzene); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, J = 7.6, 1H), 7.4–7.2 (m, 3H), 6.93 (s, 1H), 4.82 (s, 2H), 4.29 (q, J = 7.2, 2H), 2.44 (s, 3H), 1.35 (t, J = 7.2, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.0, 137.0, 129.1, 126.2, 122.1, 119.3, 119.2, 111.6, 108.9, 61.6, 47.7, 14.3, 9.7; IR (film): 3053, 2981, 2919, 1749, 1735, 1467, 1187 cm^{-1}; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{13}H_{16}NO_2$, 218.1181; found 218.1190.



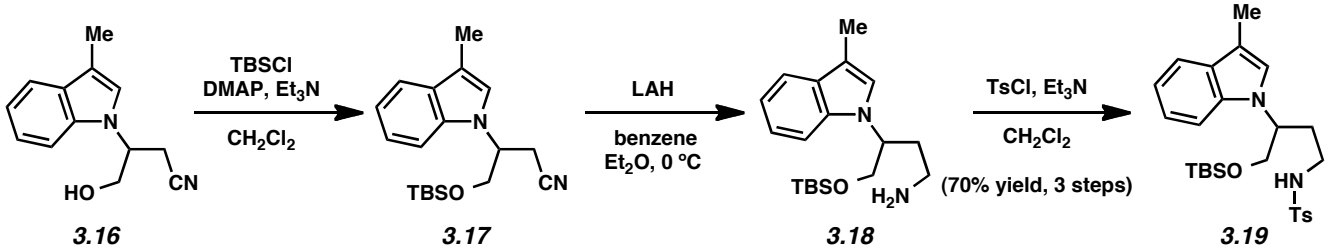
3.14 *3.15*

Nitrile 3.15. To a solution of bis(trimethylsilyl)amine (0.321 mL, 1.46 mmol) in THF (9 mL) was added a solution of *n*-butyllithium in hexanes (2.6 M, 0.58 mL, 1.46 mmol) at 0 °C. Following the addition, the reaction mixture was stirred for 15 min at 0 ºC, then cooled to –78 °C. A solution of ester **3.14** (300 mg, 1.45 mmol) in THF (5 mL) was added dropwise over 3 min at –78 ºC and the resulting solution was stirred for 1 h. Bromoacetonitrile (0.202 mL, 2.90 mmol) was added dropwise over 2 min, and the resulting mixture was stirred for 1 h at –78 ºC. The reaction mixture was quenched with a solution of sat. aq. NH_4Cl (3 mL) and warmed to rt. The reaction mixture was poured into brine (20 mL). The solution was diluted with CH_2Cl_2 (30 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 30 mL). The combined organic layers were washed with brine (40 mL), dried over Na_2SO_4, and evaporated under reduced pressure. The resulting residue was purified by flash chromatography (6:1 → 4:1 → 3:1 hexanes:EtOAc) to afford nitrile **3.15** (305 mg, 82% yield) as a yellow oil. R_f 0.3 (3:1 hexanes:EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, *J* = 8.0, 1H), 7.3–7.2 (m, 2H), 7.17 (t, *J* = 4.0, 1H), 6.94 (s, 1 H), 5.26 (dd, *J* = 7.2, 6.8, 1H), 4.26 (q, *J* = 7.2, 2H), 3.22 (dd, *J* = 16.8, 6.8, 1H), 3.08 (dd, *J* = 16.8, 7.2, 1H), 2.32 (s, 3 H), 1.23 (t, *J* = 7.2, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.7, 135.8, 129.3, 122.7, 122.4, 119.9, 119.5, 116.0, 113.4, 108.5, 62.7, 54.7, 20.9, 13.9, 9.5; IR (film): 2980, 2865, 1738, 1463, 1033 cm^{-1}; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{15}H_{17}N_2O_2$, 279.1110; found 279.1100.



3.15 *3.16*

Alcohol 3.16. To a solution of nitrile **3.15** (4.856 g, 18.86 mmol) in MeOH (100 mL) at rt was added sodium borohydride (3 x 1.00 g portions, 75.4 mmol) over 15 min. After 10 min, the reaction mixture was poured into brine (200 mL). The solution was diluted with EtOAc (100 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 100 mL). The organic layers were combined, dried over Na_2SO_4, and evaporated under reduced pressure. The resulting residue was purified by flash chromatography (9:1 CH_2Cl_2:EtOAc) to afford alcohol **3.16** (3.953 g, 98% yield) as an amorphous white solid. R_f 0.2 (9:1 CH_2Cl_2:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.59 (d, *J* = 7.5, 1H), 7.30 (d, *J* = 8.5, 1H), 7.26 (t, *J* = 8, 1H), 7.16 (t, *J* = 8.5, 1H), 7.05 (s, 1H), 4.80 (dd, *J* = 12, 5.5, 1H), 4.12 (dd, *J* = 11, 5.5, 2H), 3.02 (dd, *J* = 17, 7, 1H), 2.94 (dd, *J* = 17, 7, 1H), 2.33 (s, 3H), 1.71 (t, *J* = 5.5, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 136.2, 128.9, 122.2, 121.3, 119.6, 119.4, 116.7, 112.8, 108.6, 63.2, 52.9, 20.2, 9.6; IR (film): 3440, 2921, 2853, 1461 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $NaC_{13}H_{14}N_2O$, 237.1004; found 237.0996.



3.16 *3.17* *3.18* *3.19*

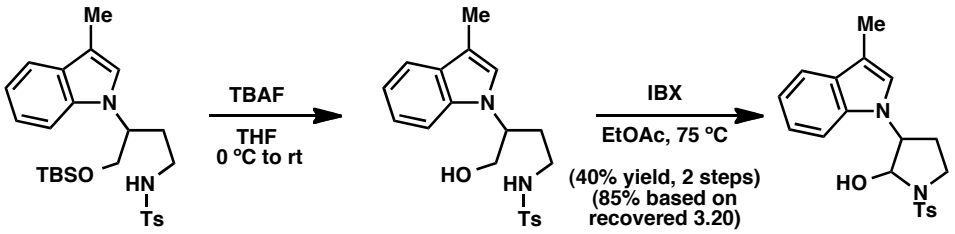
Sulfonamide 3.19. To a solution of *tert*-butyldimethylsilyl chloride (177 mg, 1.18 mmol) and 4-dimethylaminopyridine (5.0 mg, 0.04 mmol) in DMF (1.5 mL) was added a solution of alcohol

3.16 (84 mg, 0.39 mmol) and triethylamine (0.151 mL, 1.18 mmol) in DMF (1.5 mL). After 3 h, the reaction mixture was poured into a solution of sat. aq. NH_4Cl (25 mL). The solution was diluted with Et_2O (30 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (2 x 30 mL). The organic layers were combined and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure afforded crude silylether **3.17**, which was used in the subsequent step without further purification.

To a suspension of lithium aluminum hydride (690 mg, 18.1 mmol) in Et_2O (90 mL) was added a solution of silylether **3.17** (5.957 g, 18.09 mmol) in benzene (90 mL) at 0 °C. After 10 min, the reaction mixture was quenched with a solution of sat. aq. NH_4Cl (15 mL) and Celite (40 g) was added. The reaction was warmed to rt and poured into a fritted funnel. The filter cake was washed with EtOAc (3 x 100 mL). The organic layers were combined and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure afforded crude amine **3.18**, which was used in the subsequent step without further purification.

To a solution of amine **3.18** (103 mg, 0.31 mmol) and triethylamine (0.063 mL, 0.460 mmol) in CH_2Cl_2 (1 mL) was added 4-toluenesulfonyl chloride (89 mg, 0.46 mmol). After 1 h, the reaction mixture was poured into brine (10 mL). The solution was diluted with CH_2Cl_2 (10 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). The organic layers were combined, dried over Na_2SO_4, and evaporated under reduced pressure. The resulting residue was purified by flash chromatography (6:1:1 → 4:1:1 hexanes:CH_2Cl_2:Et_2O) to afford sulfonamide **3.19** (103 mg, 70% yield) as an orange solid. R_f 0.5 (4:1:1 hexanes:CH_2Cl_2:Et_2O); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.56–7.54 (m, 3H), 7.25–7.15 (m, 4H), 7.10 (t, *J* = 7, 1H), 6.89 (s, 1H), 4.40 (d, *J* = 5.0, 1H), 4.27 (t, *J* = 6, 5, 1H), 3.78 (dd, *J* = 5, 2, 2H), 2.87 (dd, *J* = 12.5, 6.0, 1H), 2.75 (dd, *J* = 13.5, 6, 1H), 2.39 (s, 3H), 2.29 (s, 3H), 2.21 (dd,

J = 13.5, 8, 1H), 2.09 (dd, J = 12.5, 8, 1H), 0.83 (s, 9H), –0.07 (s, 3H), –0.09 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.2, 136.5, 136.4, 129.6, 128.5, 126.9, 122.6, 121.4, 118.9, 118.7, 111.0, 109.0, 65.6, 54.4, 40.3, 31.2, 25.7, 21.4, 18.1, 9.6, –5.7, –5.8; IR (film): 3280, 2953, 2928, 2857, 1460, 1325, 1157 cm^{-1}; HRMS-ESI (m/z) [M + Na]$^+$ calcd for $NaC_{26}H_{38}N_2O_3SSi$, 509.2270; found 509.2259.



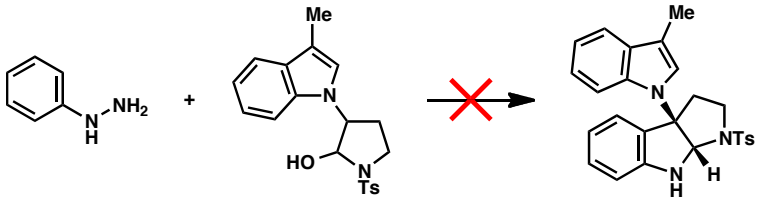
3.19 ***3.20*** ***3.5c***

Hemiaminal 3.5c. To a solution of sulfonamide **3.19** (2.3 g, 4.73 mmol) in THF (20 mL) was added a solution of tetra-*n*-butylammonium fluoride in THF (1 M, 9.47 mL, 9.47 mmol) at 0 °C. Following the addition, the reaction mixture was stirred for 1 h, and then warmed to rt. After 30 min, the reaction mixture poured into brine (200 mL). The solution was diluted with EtOAc (100 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 100 mL). The organic layers were combined and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure afforded crude alcohol **3.20**, which was used in the subsequent step without further purification.

To a solution of alcohol **3.20** (261 mg, 0.70 mmol) in EtOAc (20 mL) was added 2-iodoxybenzoic acid (196 mg, 0.70 mmol) in THF (10 mL) at rt.[26] Following the addition, the reaction was heated to 75 °C. After 1 h, the reaction mixture was cooled to rt and then filtered over plug of silica gel (EtOAc eluent, 3 x 50 mL). The volatiles were removed under reduced pressure and the resulting residue was purified by flash chromatography (99:1 CH_2Cl_2: MeOH)

to afford hemiaminal **3.5c** (122 mg, 40% yield) as a yellow oil and **3.20** (117 mg, 45% yield) as a white solid. R_f 0.3 (99:1 CH_2Cl_2:MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.59(7.82) (d, *J* = 10.5, 2H), 7.50(7.56) (d, *J* = 10, 1H), 7.25(7.20) (d, *J* = 9.5, 1H) 7.20(7.36) (d, *J* = 10.5, 2H) 7.20–7.15 (m, 2H), 6.15(7.08) (s, 1H), 5.51(5.61) (s, 1H), 4.81(4.57) (dd, *J* = 8, 6, 1H), 3.81(3.62) (dd, *J* = 11.5, 4.5, 1H), 3.50(3.38) (dd, *J* = 20.5, 10.5, 1H), 2.65(3.38) (dd, *J* = 22.5, 11.5, 1H), 2.20(2.72) (ddd, *J* = 11.5, 8.5, 4, 1H), 2.44(2.47) (s, 3H), 2.09(2.20) (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.0(143.9), 136.7(136.1), 135.2(135.8), 129.9(129.8), 129.0(128.8), 127.4(127.0), 123.5(122.0), 121.8(120.9), 119.5(119.4), 119.3(119.1), 111.4(111.2), 109.3(108.6), 87.9(80.6), 61.3(57.3), 46.3(43.8), 28.6(29.7), 21.6(26.6), 9.5(9.7); IR (film): 3480, 2920, 1598, 1463, 1339, 1161 cm^{-1}; HRMS-ESI (*m*/*z*) [M + Na]$^+$ calcd for $NaC_{20}H_{23}N_2O_3S$, 393.1249; found 393.1254.

Attempted Fischer Indolization of Substrate 3.5c.[27, 28, 29, 30, 31, 32]



3.5c ***3.6c***

Entry	Conditions
1	1:1 AcOH/H_2O, rt to 110°C
2	AcOH, rt to 100 °C
3	TFA, $C_2H_4Cl_2$, rt to 80°C
4	$HCl_{(aq)}$, CH_3CN, rt to 120 °C
5	$H_2SO_{4(aq)}$, CH_3CN, rt to 120 °C
6	TsOH, *t*-BuOH, rt to 80 °C
7	ClAcOH, PhMe, rt to 170 °C
8	ClAcOH, MeOH, rt to 80 °C
9	PPTS, MeOH, rt to 80 °C

3.9 Notes and References

(1) *Indoles*; Sundberg, R. J., Ed.; Academic Press: London, 1996.

(2) Sundberg, R. J. In *Best Synthetic Methods, Indoles*; Academic Press: New York, 1996; pp 7–11.

(3) Joule, J. A. Indole and its Derivatives. In *Science of Synthesis: Houben-Weyl Methods of Molecular Transformations*; Thomas, E. J., Ed.; George Thieme Verlag: Stuttgart, Germany, 2000; Category 2, Vol. 10, Chapter 10.13.

(4) Gribble, G. W. *J. Chem. Soc. Perkin Trans. 1* **2000**, 1045–1075.

(5) Humprey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875–2911.

(6) (a) Fischer, E.; Jourdan, F. *Ber. Dtsch. Chem. Ges.* **1883**, *16*, 2241–2245. (b) Fischer, E.; Hess, O. *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 559–568.

(7) Görlitzer, K.; Kramer, C.; Meyer, H.; Walter, A. D.; Jomaa, H.; Wiesner, J. *Pharmazie* **2004**, *59*, 243–250.

(8) Arzel, E.; Rocca, P.; Grellier, P.; Labaed, M.; Frappier, F.; Guritte, F.; Gaspard, C.; Marsais, F.; Godard, A.; Queguiner, G. *J. Med. Chem.* **2001**, *44*, 949–960.

(9) Pews-Davtyan, A.; Tillack, A.; Schmöle, A.-C.; Ortinau, S.; Frech, M. J.; Rolfs, A.; Beller, M. *Org. Biomol. Chem.* **2010**, *8*, 1149–1153.

(10) Przheval'skii, N. M.; Skvortsova, N. S.; Magedov, I. V. *Chem. Het. Comp.* **2002**, *38*, 1055–1061.

(11) Trudell, M. L.; Fukada, N.; Cook, J. M. *J. Org. Chem.* **1987**, *52*, 4293–4296.

(12) Robinson, R.; Thornby, S. *J. Chem. Soc.* **1926**, 3144.

(13) Mohamed, M. H.; Abdel-Khalik, M. M.; Elnagdi, M. H. *J. Heterocyclic Chem.* **2001**, *38*, 685–689.

(14) Przheval'skii, N. M.; Skvortsova, N. S.; Magedov, I. V. *Khim. Geterotsikl. Soed*. **2004**, *11*, 1662–1669.

(15) (a) Boal, B. W.; Schammel, A. W.; Garg, N. K. *Org. Lett.* **2009**, *11*, 3458–3461. (b) Schammel, A. W.; Boal, B. W.; Zu, L.; Mesganaw, T.; Garg, N. K. *Tetrahedron* **2010**, *66*, 4687–4695

(16) For psychotrimine isolation studies, see: Takayama, H.; Mori, I.; Kitajima, M.; Aimi, N.; Lajis, N. H. *Org. Lett.* **2004**, *6*, 2945–2948.

(17) For synthetic studies involving psychotrimine and related alkaloids, see: (a) Newhouse, T.; Baran, P. S. *J. Am. Chem. Soc*. **2008**, *130*, 10886–10887. (b) Newhouse, T.; Lewis, C. A.; Baran, P. S. *J. Am. Chem. Soc*. **2009**, *131*, 6360–6361. (c) Marsden, S. P.; Watson, E. L.; Raw, S. A. *Org. Lett*. **2008**, *10*, 2905–2908. (d) Toumi, M.; Couty, F.; Marrot, J.; Evano, G. *Org. Lett.* **2008**, *10*, 5027–5030. (e) Espejo, V. R.; Rainier, J. D. *J. Am. Chem. Soc.* **2008**, *130*, 12894–12895. (f) Matsuda, Y.; Kitajima, M.; Takayama, H. *Org. Lett*. **2008**, *10*, 125–128. (g) Takahashi, N.; Ito, T.; Matsuda, Y.; Kogure, N.; Kitajima, M.; Takayama, H. *Chem. Commun.* **2010**, *46*, 2501–2503. (h) Newhouse, T.; Lewis, C. A.; Eastman, K. J.; Baran, P. S. *J. Am. Chem. Soc.* **2010**, *132*, 7119–7137. (i) Espejo, V. R.; Rainier, J. D. *Org. Lett.* **2010**, *12*, 2154–2157. (j) Benkovics, T.; Guzei, I. A.; Yoon, T. P. *Angew. Chem., Int. Ed.* **2010**, *49*, 9153–9157.

(18) Employing substituted aryl hydrazines (e.g., *p*-OMe or *o*-Cl) did not lead to improvements.

(19) Kereselidze, Dz. A; Samsoniya, Sh. A.; Tsikoliya, M. A. *Khim. Geterotsikl. Soed*. **1995**, *8*, 1092–1103.

(20) Frisch, M. J. et al. *Gaussian 09, Revision A.2*; Gaussian, Inc., Wallingford CT, 2009.

(21) Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. *J. Phys. Chem. B* **2009**, *113*, 6378–6396.

(22) Mann and Hinton (Mann, F. G.; Hinton, I. G. *J. Chem. Soc.* **1959**, 599–610.) reported that phenylhydrazone of 2-methyl-4-oxo-1,2,3,4-tetrahydroisoquinoline gave the 2-methyl-4-aminoisoquinolium salt when heated in ethanolic hydrogen chloride, preventing the successful application of the Fischer indolization reaction. Cook and co-workers[10] obtained 4-amino-b-carboline derivatives along with Fischer indole products from the reaction of 2-benzoyl-4-oxo-1,2,3,4-tetrahydro-b-carboline with phenylhydrazine in ethanolic hydrogen chloride.

(23) (a) Hrovat, D. A.; Chen, J. G.; Houk, K. N.; Borden, W. T. *J. Am. Chem. Soc.* **2000**, *122*, 7456–7460. (b) Hrovat, D. A.; Beno, B. R.; Lange, H.; Yoo, H. Y.; Houk, K. N.; Borden, W. T. *J. Am. Chem. Soc.* **1999**, *121*, 10529–10537. (c) Hrovat, D. A.; Borden, W. T.; Vance, R. L.; Rondan, N. G.; Houk, K. N.; Morokuma, K. *J. Am. Chem. Soc.* **1990**, *112*, 2018–2019.

(24) Yoo, H. Y.; Houk, K. N.; Lee, J. K.; Scialdone, M. A.; Meyers, A. I. *J. Am. Chem. Soc*. **1998**, *120*, 205–206.

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

(26) More, J. D.; Finney, N. S. *Org. Lett.* **2002**, *4*, 3001–3003.

(27) In all cases desired product **3.6c** was not observed; 3-methylindole and aniline formed under all reaction conditions.

(28) For the use of H_2O/AcOH to facilitate the Fischer indole synthesis, see: (a) Desaty, D.; Kegleviæ, D. *Croat. Chem. Acta* **1964**, *36*, 103–109.(b) Kegleviæ, D.; Stojanac, N.; Desaty, D. *Croat. Chem. Acta* **1961**, *33*, 83–88.

(29) For the use of trifluoroacetic acid in the Fischer indole synthesis, see: Cheng, Y.; Chapman, K. T. *Tetrahedron Lett.* **1997**, *38*, 1497–1500.

(30) For the use of hydrochloric acid in the Fischer indole synthesis, see: Trudell, M. L.; Lifer, S. L.; Tan, Y. C.; Martin, M. J.; Deng, L.; Skolnick, P.; Cook, J. M. *J. Med. Chem.* **1990**, *33*, 2412–2420.

(31) For the use of sulfuric acid in the Fischer indole synthesis, see: Campos, K. R.; Woo, J. C. S.; Lee, S.; Tillyer, R. D. *Org. Lett.* **2004**, *6*, 79–82.

(32) For the use of *p*-toluenesulfonic acid in the Fischer indole synthesis, see: Ueda, H.; Satoh, H.; Matsumoto, K.; Sugimoto, K.; Fukuyama, T.; Tokuyama, H. *Angew. Chem. Int. Ed.* **2009**, *48*, 7600–7603.

APPENDIX TWO

Spectra Relevant to Chapter Three:

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.

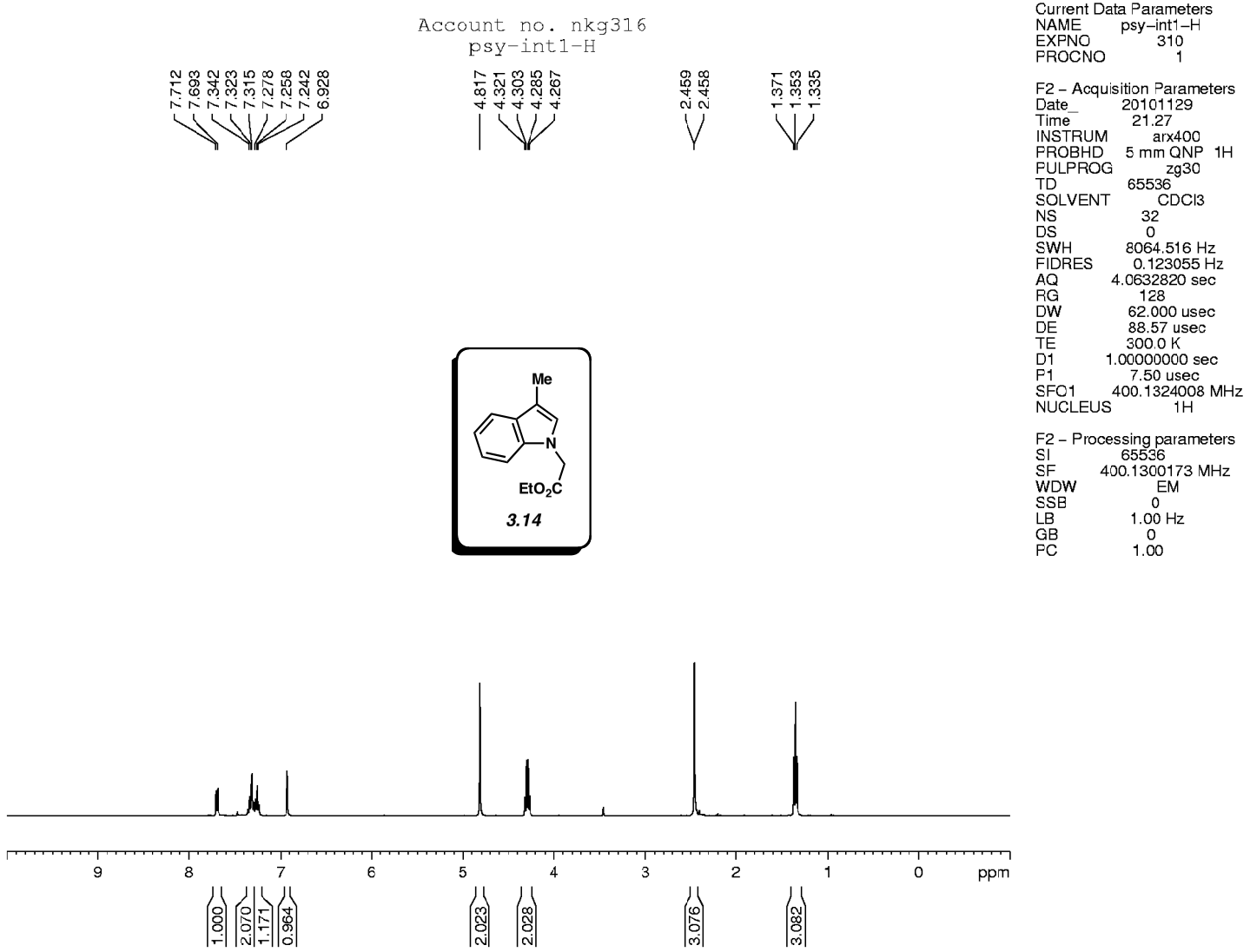


Figure A2.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.14**.

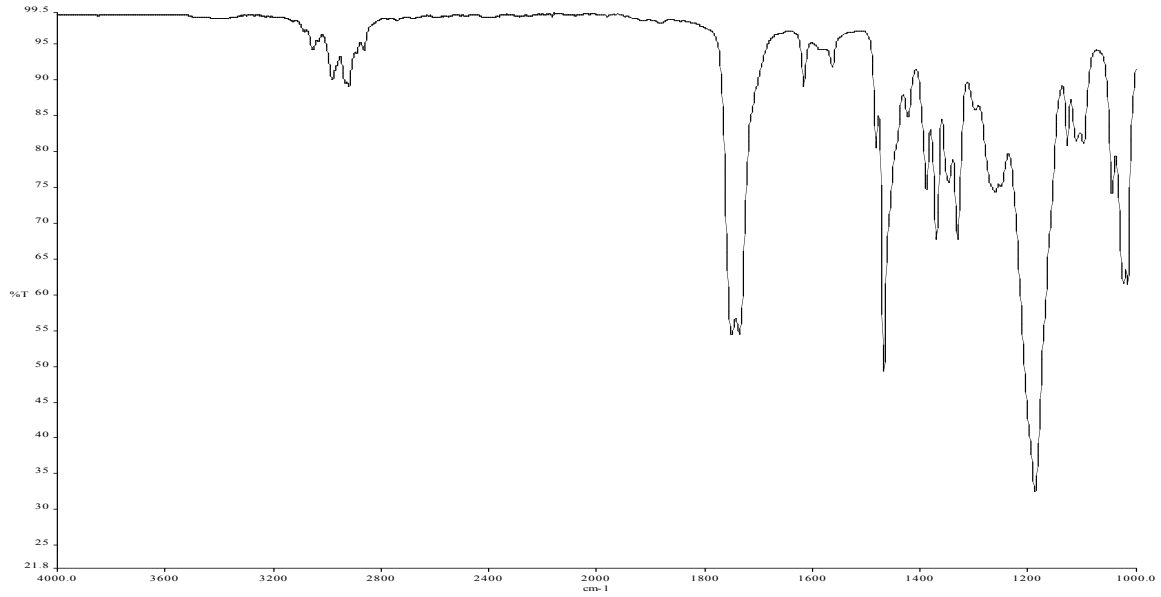


Figure A2.2 Infrared spectrum of compound **3.14**.

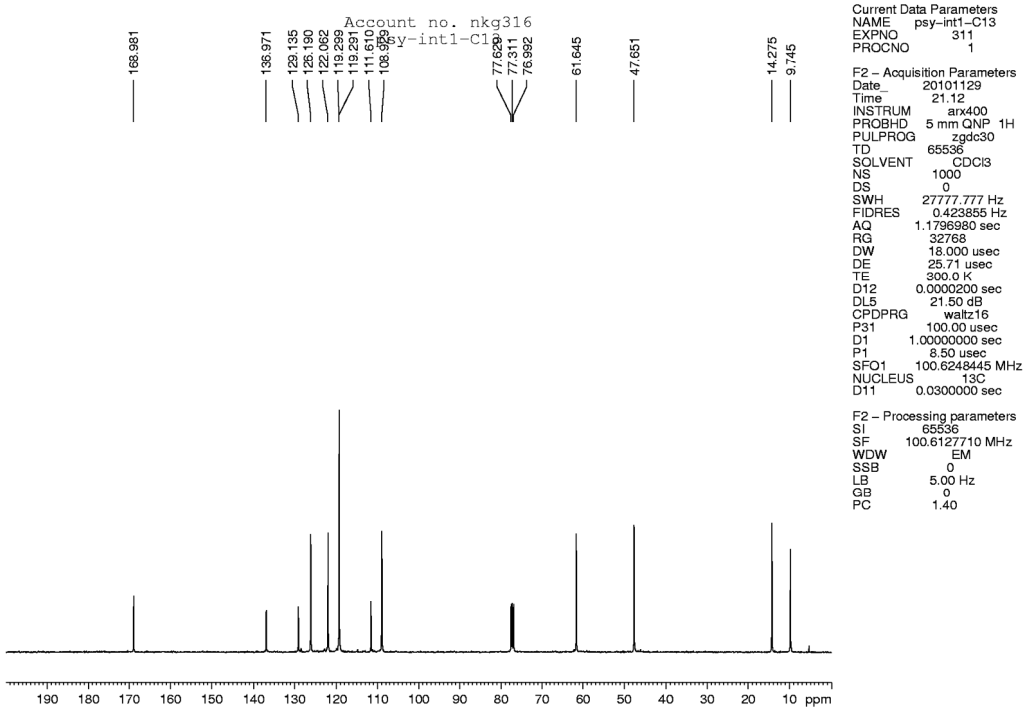


Figure A2.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **3.14**.

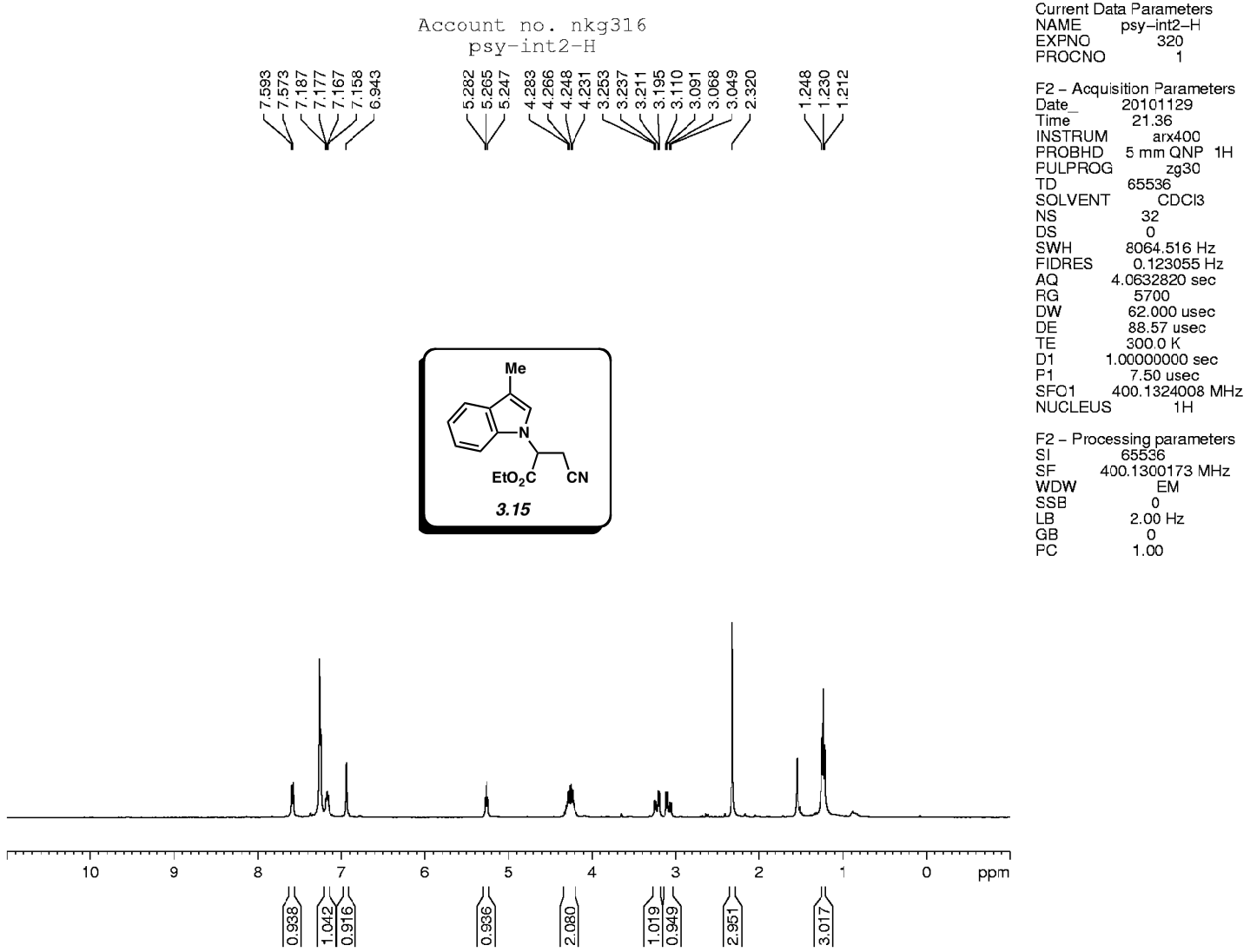


Figure A2.4 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.15**.

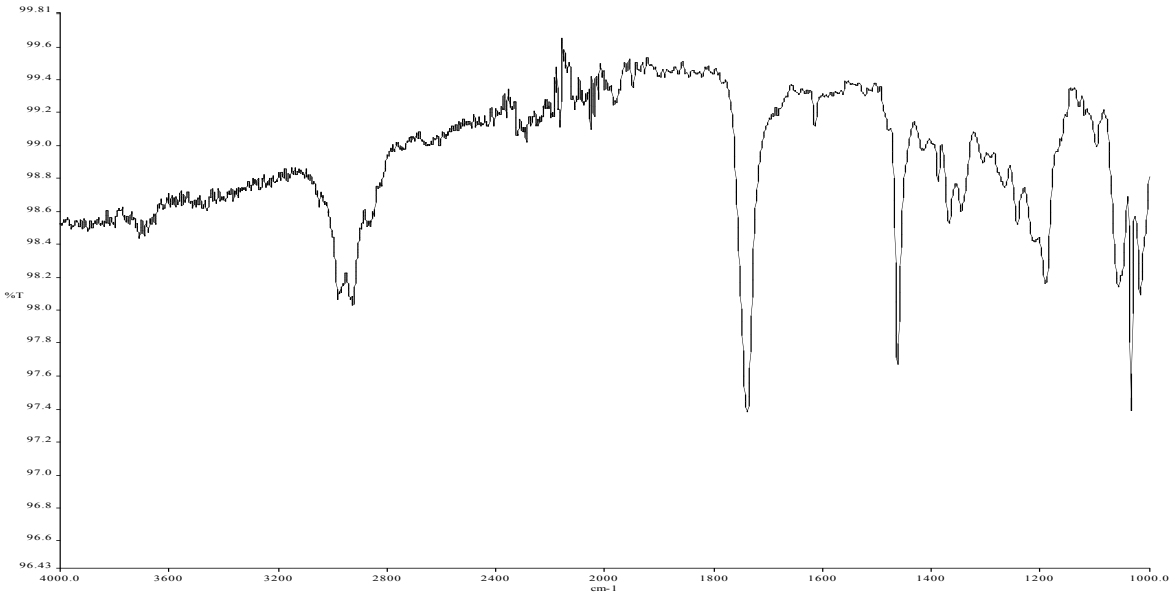


Figure A2.5 Infrared spectrum of compound **3.15**.

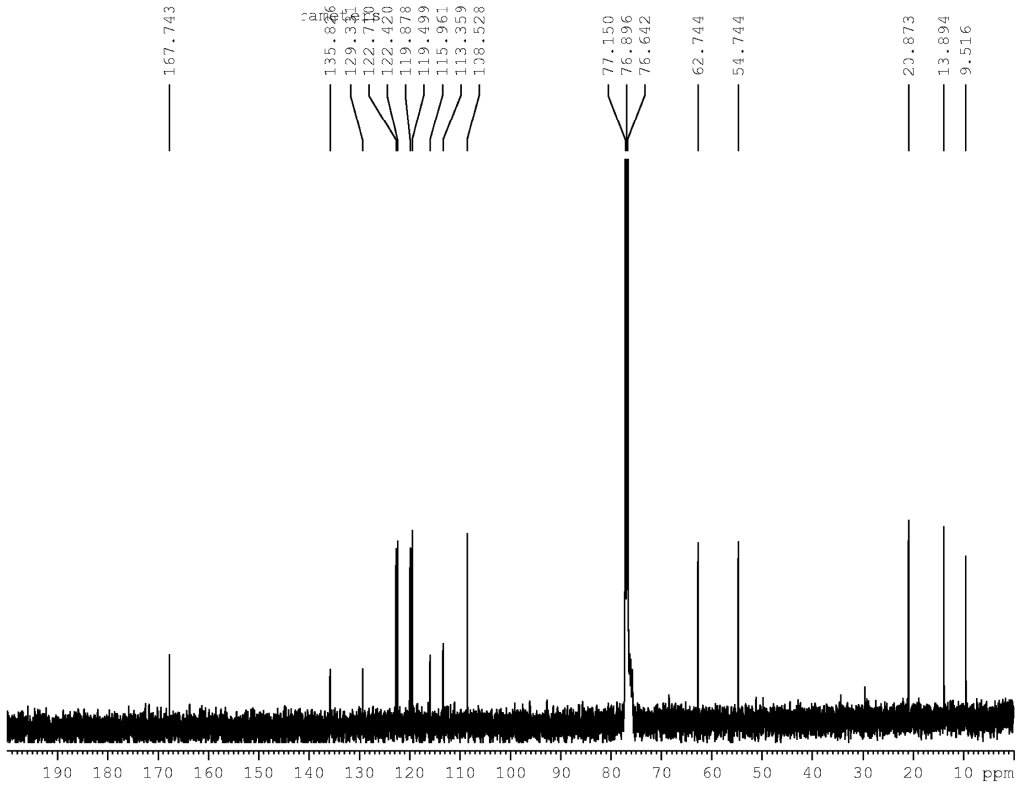


Figure A2.6 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **3.15**.

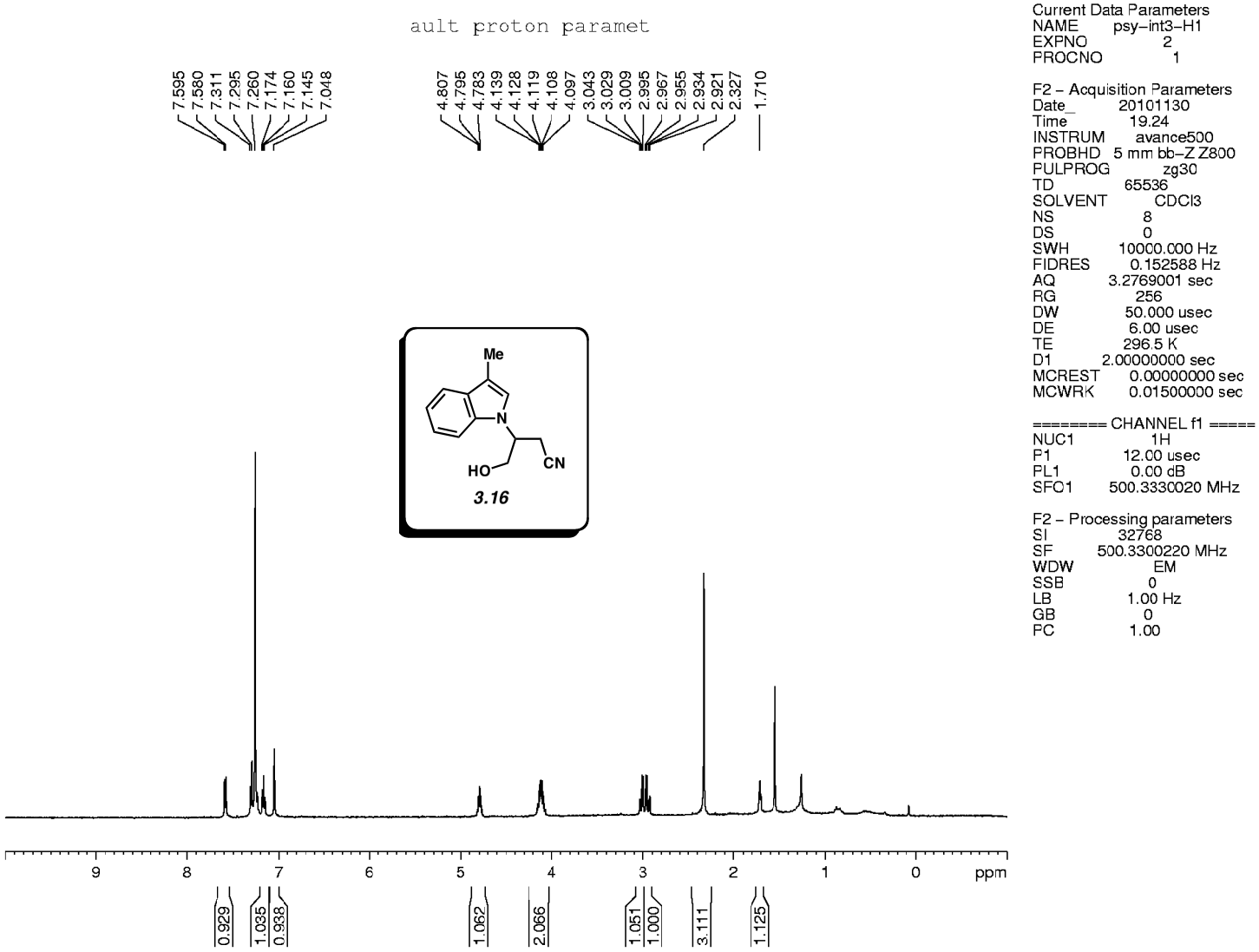


Figure A2.7 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.16**.

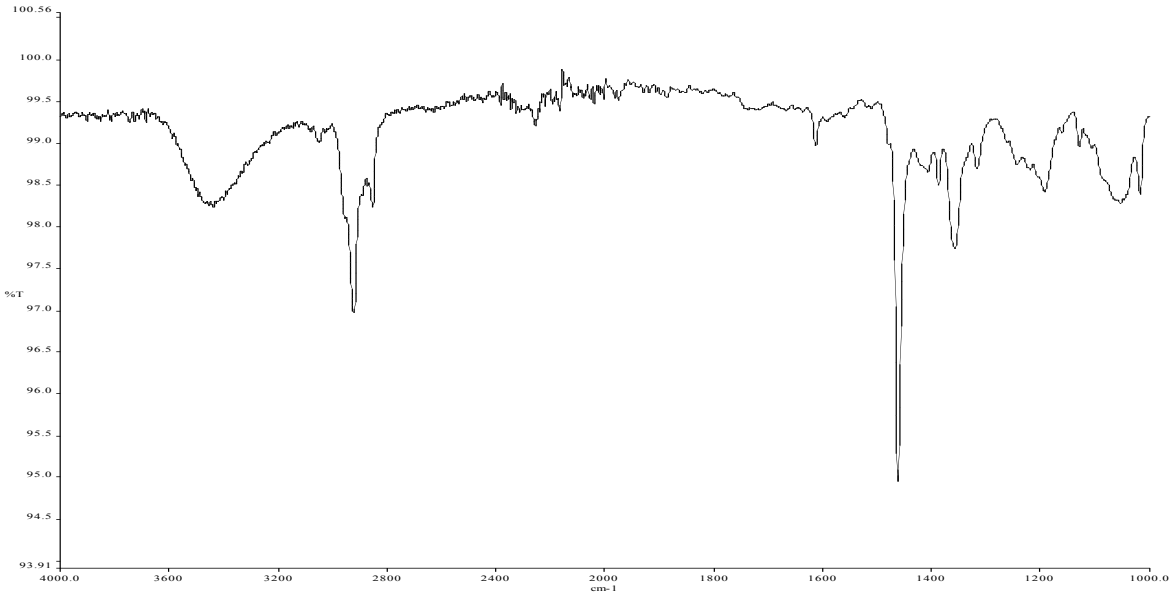


Figure A2.8 Infrared spectrum of compound **3.16**.

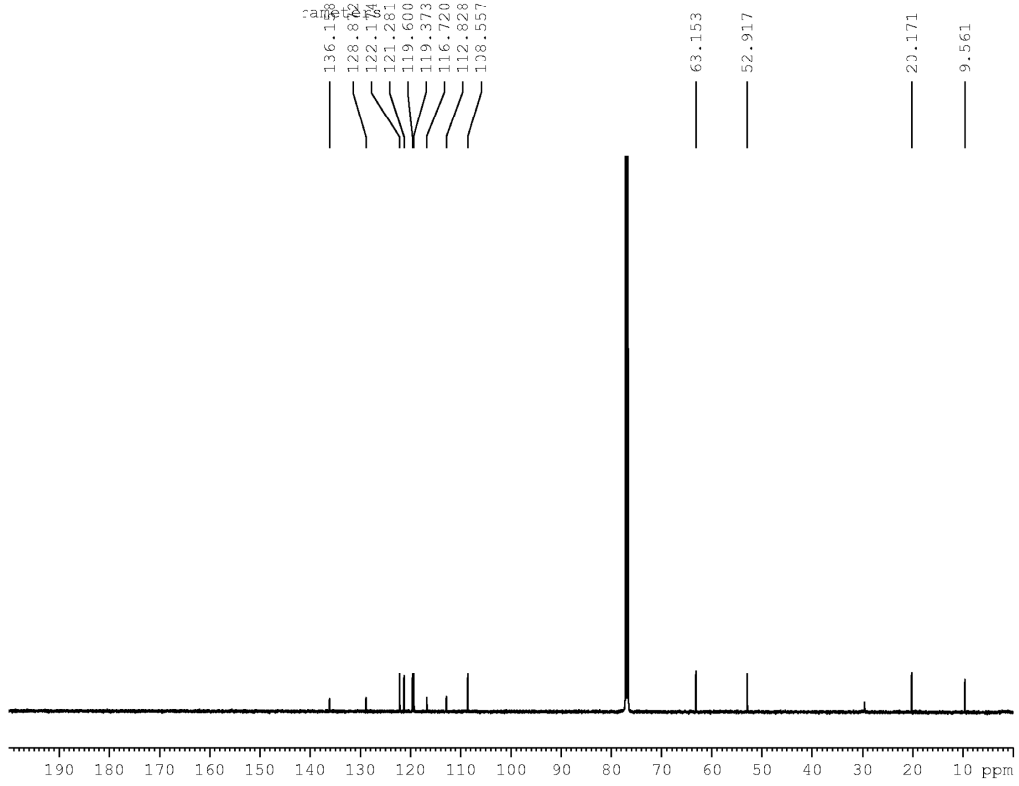


Figure A2.9 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **3.16**.

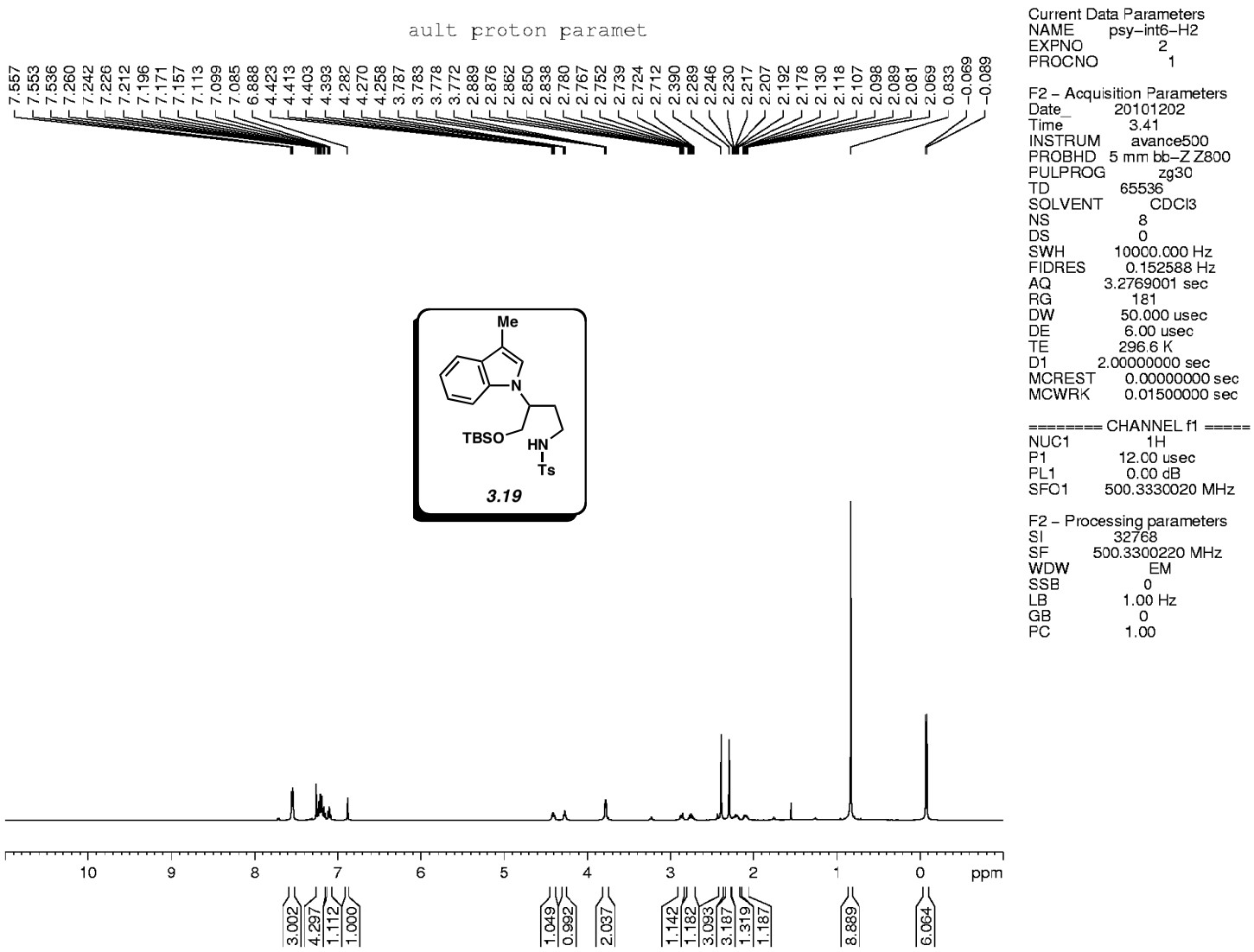


Figure A2.10 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.19**.

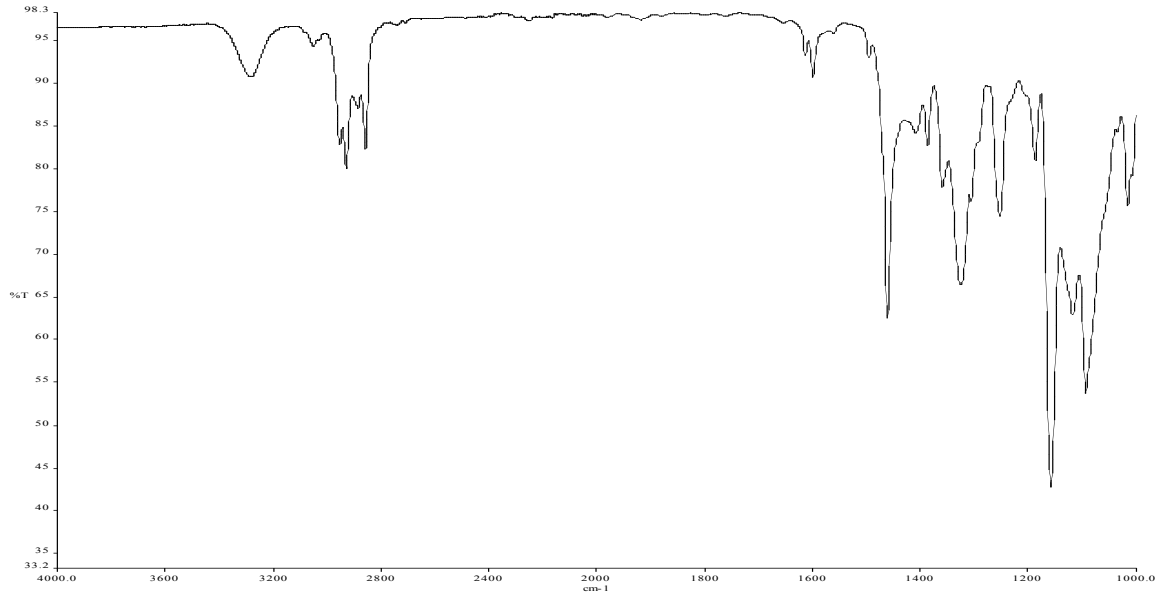


Figure A2.11 Infrared spectrum of compound **3.19**.

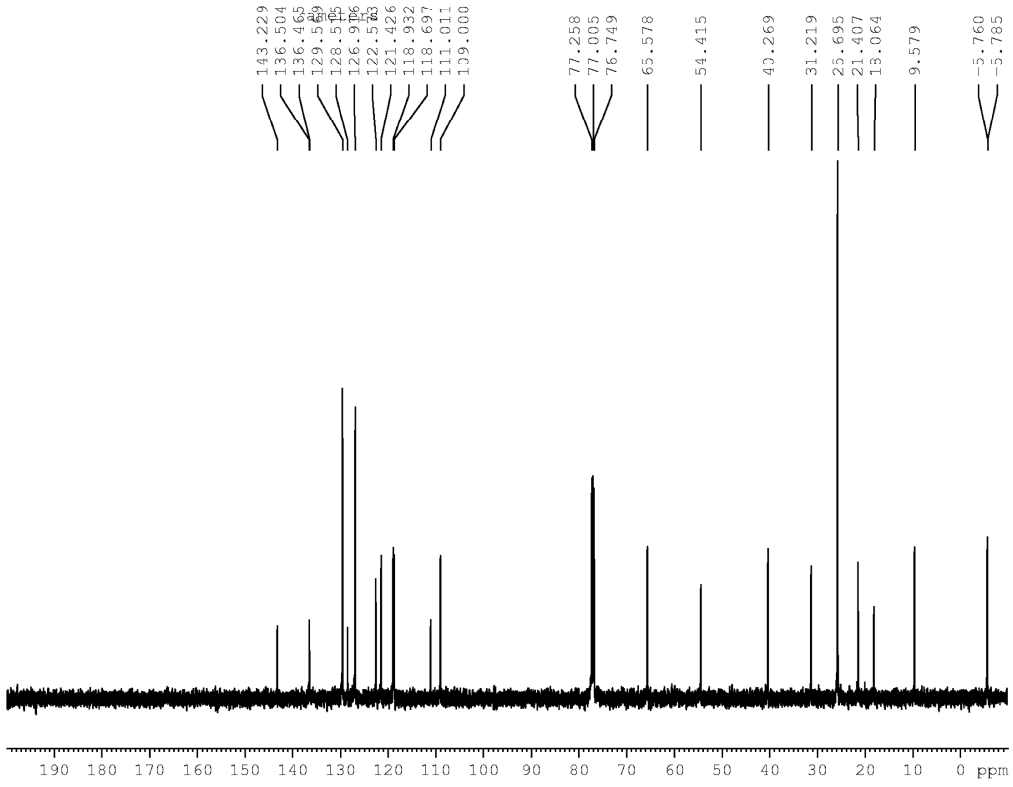


Figure A2.12 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **3.19**.

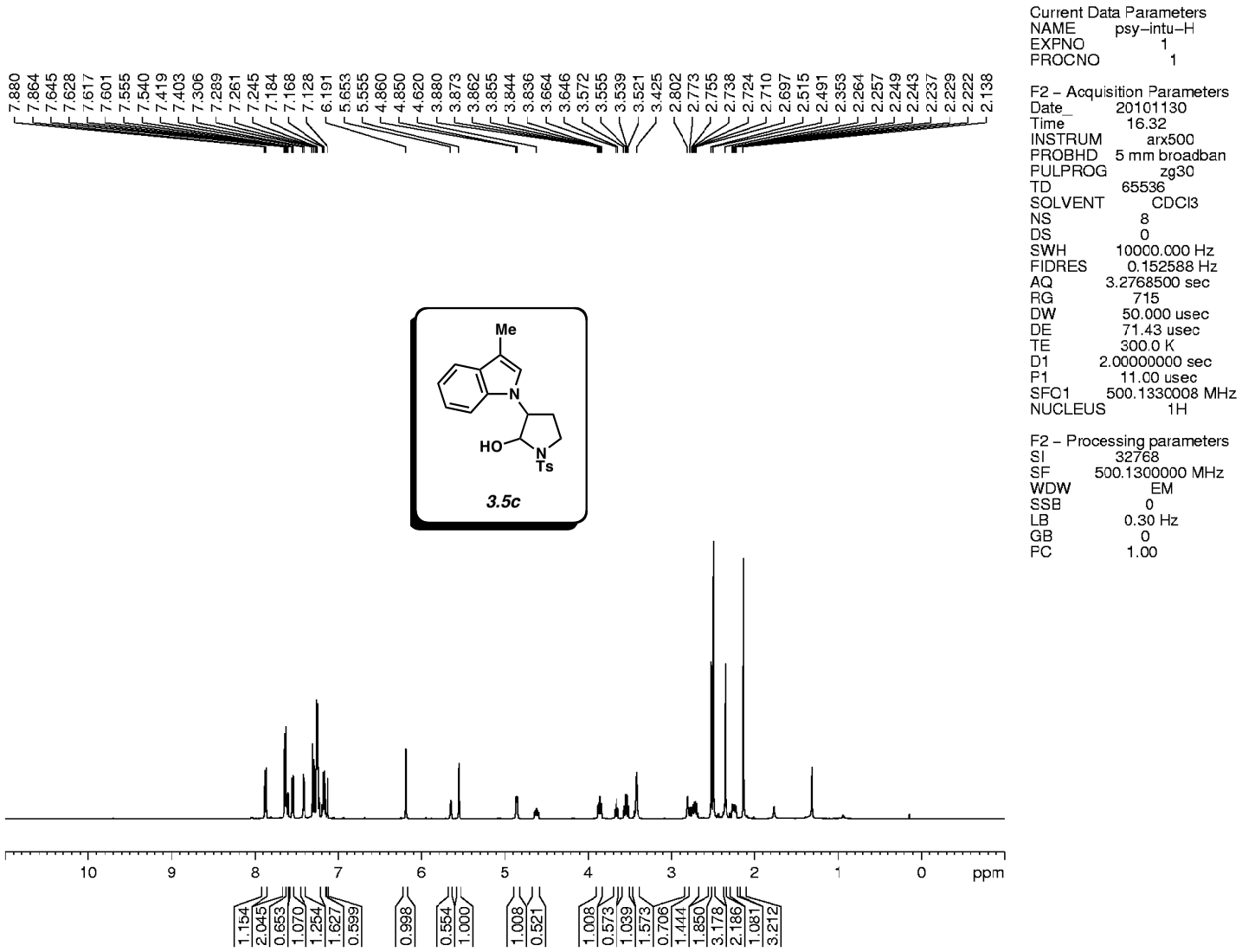


Figure A2.13 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.5c**.

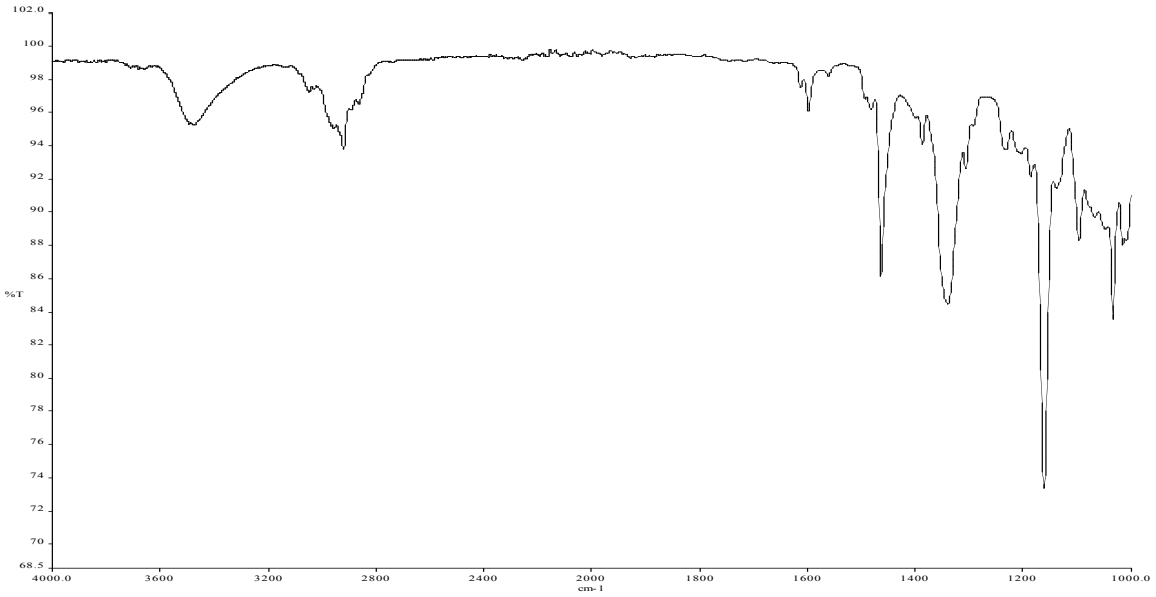


Figure A2.14 Infrared spectrum of compound **3.5c**.

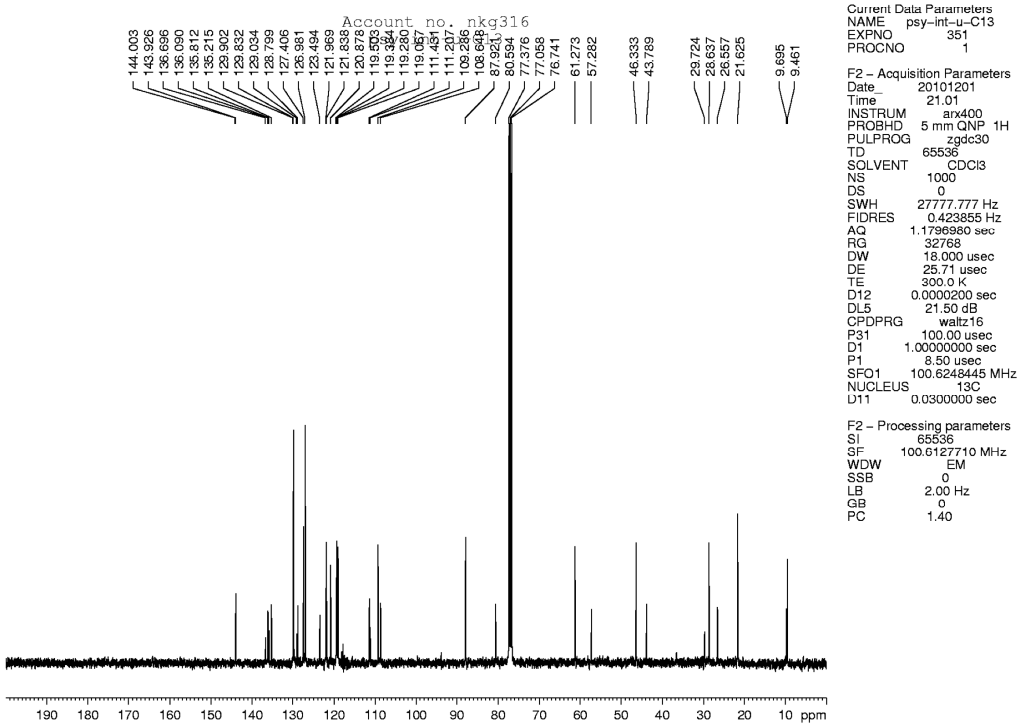


Figure A2.15 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **3.5c**.

CHAPTER FOUR

Total Synthesis of (±)-Aspidophylline A

Liansuo Zu, Ben W. Boal, and Neil K. Garg

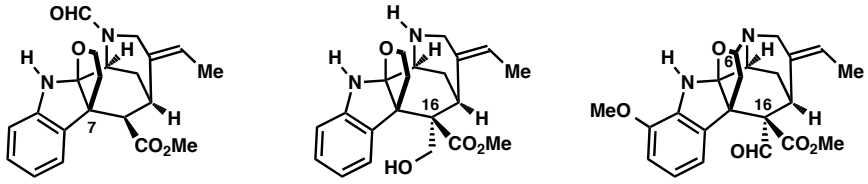
J. Am. Chem. Soc. **2011**, *133*, 8877–8879.

4.1 Abstract

We report the total synthesis of (±)-aspidophylline A, one of many complex furoindoline-containing alkaloids that has not been synthesized previously. Our route features a number of key transformations, including a Heck cyclization to assemble the [3.3.1]-bicyclic scaffold, as well as a late-stage interrupted Fischer indolization to install the furoindoline and construct the natural product's pentacyclic framework.

4.2 Introduction

For decades, indole alkaloids isolated from natural sources have captivated the attention of synthetic chemists, leading to innovations in synthetic methodology and stunning achievements in total synthesis.[1] One particularly rich source of indole alkaloids is the Apocynaceae family of plants, predominantly found in Southeast Asia.2 Natural products isolated from these plants are characterized by intricate polycyclic structures and a range of biological activity.[2,3] Alkaloids **4.1**–**4.3** (Figure 4.1) are representatives of more than 20 molecules in this family that possess a furoindoline motif, none of which have been synthesized previously.



Aspidophylline A (4.1) *Aspidodasycarpine (4.2)* *Vincarinine (4.3)*

Figure 4.1. Furoindoline alkaloids **4.1–4.3** from the Apocynaceae plants.

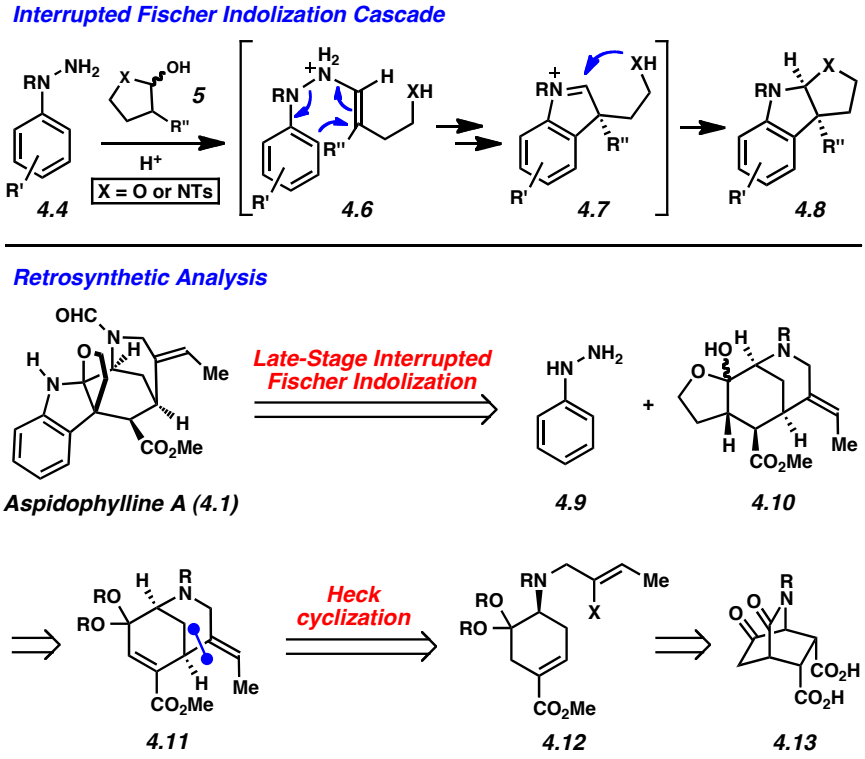
With the ultimate goal of preparing alkaloids **4.1**–**4.3** and other family members, we selected aspidophylline A (**4.1**) as our initial synthetic target. Aspidophylline A (**4.1**) was isolated by Kam and coworkers in 2007, and was found to reverse drug resistance in resistant KB cells.[3] The intricate pentacyclic framework of **4.1** presents many synthetic challenges, including the tricyclic furoindoline motif, a densely substituted cyclohexyl ring, containing 5-contiguous stereogenic centers, and a bridged [3.3.1]-bicycle. In this communication, we report the first total synthesis of (±)-aspidophylline A (**4.1**).

4.3 Interrupted Fischer Indolization Cascade and Retrosynthetic Analysis of (±)-Aspidophylline A.

Our approach to **4.1** is inspired, in part, by our laboratory's previously described approach to fused indoline ring systems.[4] Specifically, we demonstrated that reactions between aryl hydrazines **4.4** and latent aldehydes **4.5** under acidic conditions provide basic furoindoline and pyrrolidinoindoline scaffolds **4.8** (Figure 4.2). The transformation, termed the "interrupted Fischer indolization", proceeds via a charge-accelerated rearrangement/cyclization cascade (see transition structures **4.6** and **4.7**).[4] We envisioned that such a process could be used to access the pentacyclic framework of aspidophylline A if a late-stage diastereoselective variant[5] employing phenylhydrazine (**4.9**) and hemiketal **4.10** was deemed feasible. The implementation of this

endgame strategy would not only serve to assemble the aspidophylline A scaffold, but would also validate our interrupted Fischer indolization methodology in a complex setting. It was anticipated that hemiketal **4.10** could be prepared from bicycle **4.11**, the product of Heck cyclization of cyclohexylamine **4.12**.[6,7] Finally, cyclohexylamine **4.12** would be derived from [2.2.2]-bicyclic lactam **4.13**, an intermediate believed to be accessible from readily available known compounds.[8]

Scheme 4.1

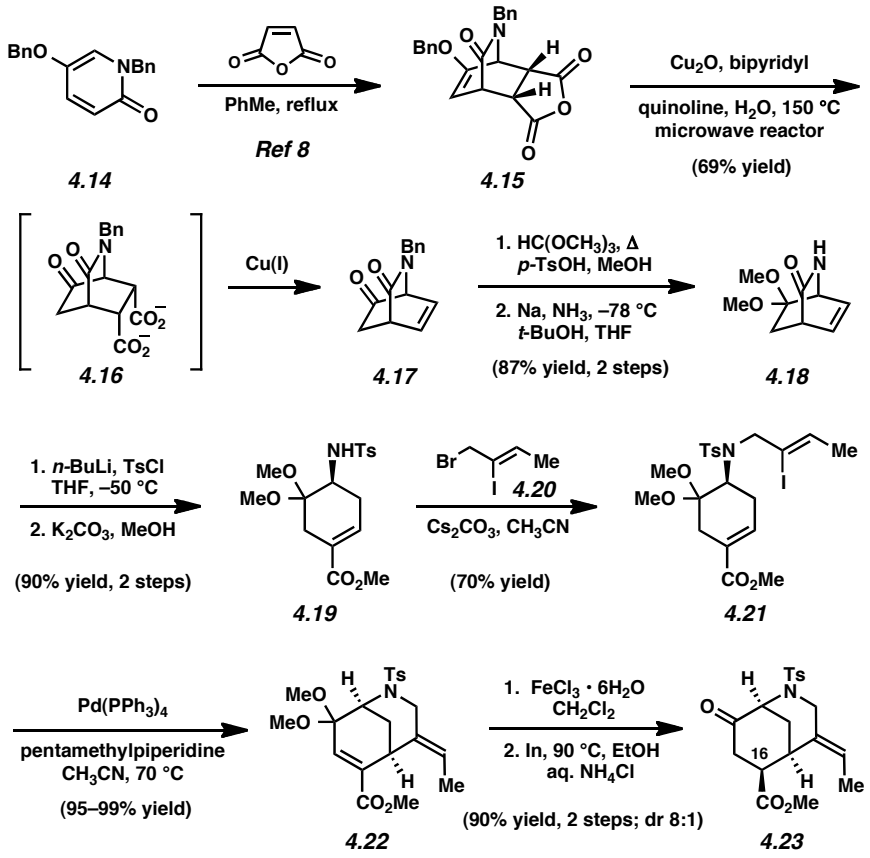


4.4 Construction of the [3.3.1]-Bicyclic Framework

Our synthesis commenced with the assembly of aspidophylline A's [3.3.1]-bicyclic motif (Scheme 4.2). Thermal Diels–Alder reaction between pyridinone **4.14** and maleic anhydride furnished known bicycle **4.15**,[8] which was available in multigram quantities. Microwave

irradiation of **4.15** with Cu_2O and bipyridyl in a quinoline/water mixture delivered alkene **4.17**. The transformation of **4.15** to **4.17** likely proceeds by enol ether and anhydride hydrolysis to furnish intermediate **4.16**, followed by Cu(I)-promoted oxidative bis(decarboxylation).[9] Ketal protection and removal of the Bn protecting group provided lactam **4.18**, which in turn, underwent *N*-tosylation and methanolysis to provide a,b-unsaturated ester **4.19**. Subsequent alkylation with allylic bromide **4.20**[10] provided vinyl iodide **4.21**, the necessary substrate for Heck cyclization. Upon treatment of substrate **4.21** with Pd(0) under Vanderwal's conditions,[7] bicycle **4.22** was obtained in quantitative yield. Ketal deprotection and olefin reduction furnished ketoester **4.23** as a mixture of C16 diastereomers (dr 8:1).

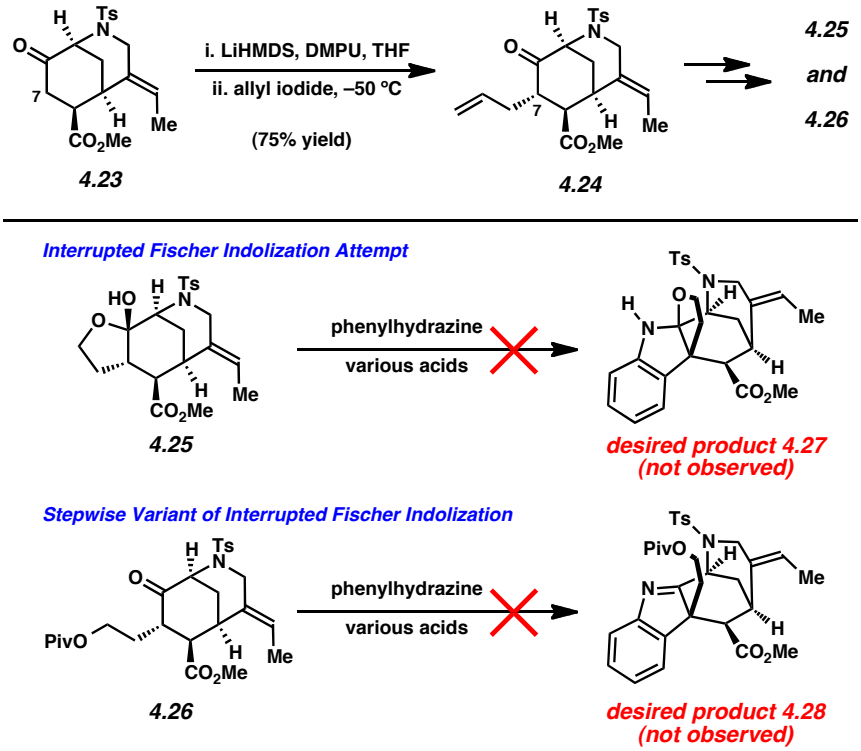
Scheme 4.2



4.5 Initial Interrupted Fischer Indolization Attempts

Having assembled the desired [3.3.1]-bicycle, we turned our attention to introducing a C7 substituent en route to the desired interrupted Fischer indolization substrate. Although the lithium enolate of **4.23** was found to be unreactive toward various electrophiles, enolate alkylation proceeded smoothly with allyl iodide at –50 °C. The resulting product **4.24** was isolated as a single diastereomer and served as a versatile intermediate en route to the desired hemiketal **4.25**[11] and an alternate substrate, ketone **4.26**.[12] Unfortunately, the critical interrupted Fischer indolization proved challenging. In fact, both direct and stepwise variants of this key step (using substrates **4.25** and **4.26**, respectively) failed to deliver either of the desired products, pentacycle **4.27** or tetracycle **4.28**.[13,14]

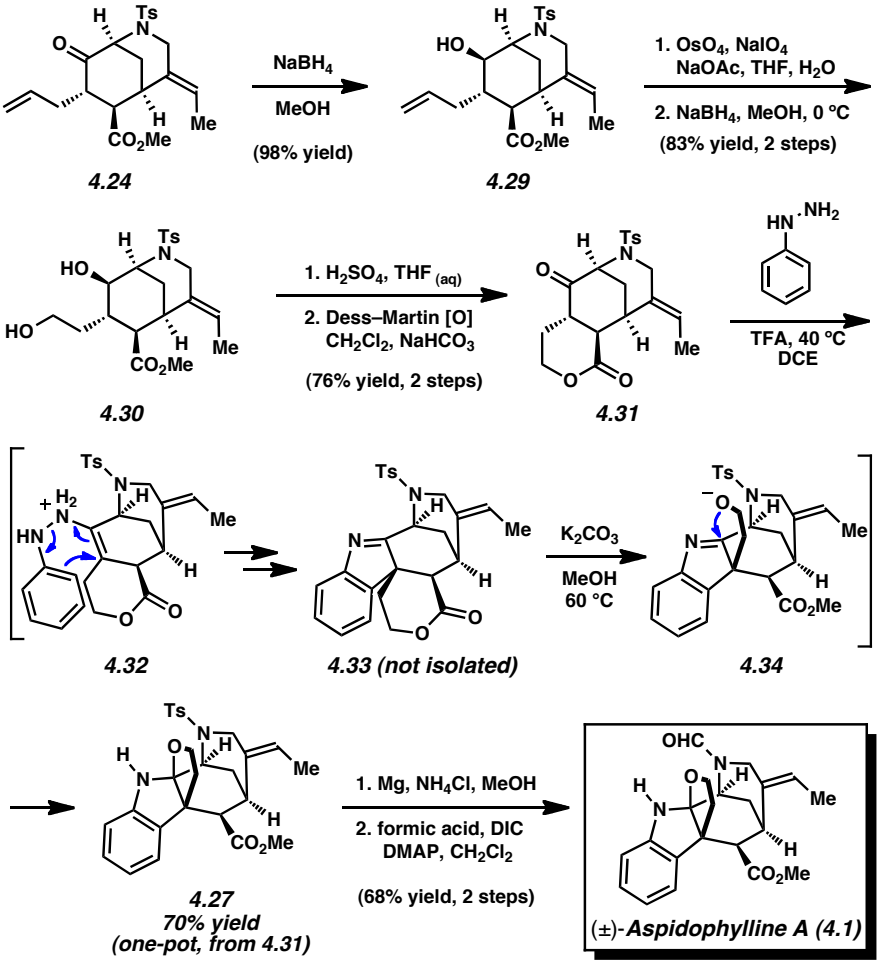
Scheme 4.3



4.6 Completion of (±)-Aspidophylline A

Hypothesizing that the [3,3]-sigmatropic rearrangement of substrate **4.26** was sluggish,[14,15] we sought to prepare a more rigid substrate for use in the key step. The targeted substrate, lactone **4.31**, was prepared following the sequence shown in Scheme 4.4. Diastereoselective reduction of allyl ketone **4.24** provided alcohol **4.29**,[16] which underwent oxidative cleavage[17] and reduction to furnish diol **4.30**. Acid-promoted lactonization, followed by Dess–Martin oxidation, delivered ketoester **4.31**. Much to our delight, ketoester **4.31** proved to be an excellent substrate for Fischer indolization. Upon reaction with phenylhydrazine in the presence of TFA in dichloroethane at 40 °C, intermediate **4.33** was generated, presumably via transition structure **4.32**. Removal of solvent, followed by addition of K_2CO_3 in MeOH with heating led to lactone methanolysis and cyclization (see transition structure **4.34**) to afford pentacycle **4.27**. This one-pot sequence leads to the introduction of three rings by assembly of one C–C bond and two C–heteroatom bonds, all with complete diastereoselectivity. Removal of the tosyl protecting group of **4.27**, followed by formylation, furnished aspidophylline A (**4.1**). Synthetic **4.1** was found to be indistinguishable from an authentic sample of the natural product by NMR, mass spectrometric, and chromatographic comparisons.[3,18]

Scheme 4.4



4.7 Conclusions

In summary, we have achieved the first total synthesis of aspidophylline A (**4.1**), one of many complex furoindoline-containing alkaloids that has not been synthesized previously. Our route to **4.1** proceeds in 18 steps from known Diels–Alder adduct **4.15** and features a number of key transformations, including: (a) an oxidative bis(decarboxylation) to furnish [2.2.2]-bicyclic lactam **4.17**, (b) a Heck cyclization to assemble the natural product's [3.3.1]-bicyclic scaffold, and (c) a late-stage interrupted Fischer indolization to install the furoindoline and construct the full pentacyclic framework of **4.1**. Our synthesis of (±)-aspidophylline A (**4.1**) validates the

interrupted Fischer indolization approach to intricate indoline-containing natural products and sets the stage for future synthetic endeavors.

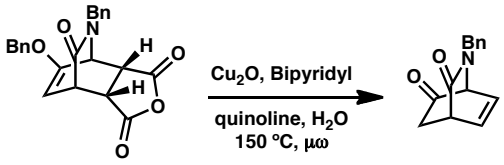
4.8 Experimental Section

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. Tetrakis(triphenylphosphane)palladium(0) was obtained from Strem. Cesium carbonate, trimethoxymethane, phenylhydrazine, and 4-dimethylaminopyridine were obtained from VWR (manufactured by Alfa-Aesar). Bipyridyl was obtained from VWR (manufactured by TCI). Quinoline, 4-methylbenzenesulfonic acid monohydrate (*p*-TsOH•H_2O), sodium metal, *n*-butyllithium (hexanes solution), 2-butyn-1-ol, 1,2,2,6,6-pentamethylpiperidine, indium metal, lithium bis(trimethylsilyl)amide (LiHMDS), 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU), sodium borohydride, osmium tetroxide, magnesium metal powder, formic acid, *N,N*'-diisopropylcarbodiimide (DIC), 2-iodobenzoic acid, and Oxone® were obtained from Sigma Aldrich. Phenylhydrazine was purified by column chromatography (10:1→ 1:1 Benzene:EtOAc) and recrystallized from pet. ether/ benzene. 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU) was distilled from calcium hydride before use. 2-Iodoxybenzoic acid (IBX) and Dess–Martin periodinane were prepared from known literature procedures.[19,20] Allyl iodide was prepared from a known literature procedure[21] and used immediately after purification. Bromide **4.20** was prepared from a known procedure.[22,23] Unless stated otherwise, reactions were performed at room temperature (rt, approximately 23 °C).

Anhydride **4.15** was made from a known procedure.[24] Microwave-assisted reactions were performed in Discover model equipped with an Explorer autosampler from CEM. 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 (at 300 MHz, 400 MHz, or 500 MHz) and are reported relative to deuterated solvent signals. Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz) and integration. ^{13}C NMR spectra are reported in terms of chemical shift (at 100 MHz or 125 MHz). For mixtures of diastereomers or rotational isomers, the major diastereomer is reported with the minor diastereomer in parentheses for both ^{1}H NMR and ^{13}C NMR spectra. IR spectra were recorded on a Perkin-Elmer 100 spectrometer and are reported in terms of frequency absorption (cm^{-1}). 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

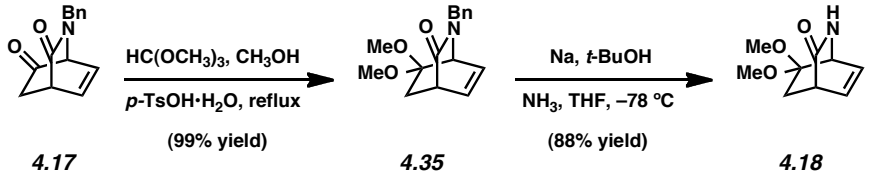


4.15 (69% yield) *4.17*

Alkene 4.17. To a mixture of anhydride **4.15** (40.0 mg, 0.103 mmol), copper oxide (32.0 mg, 0.226 mmol), and bipyridyl (18.0 mg, 0.113 mmol) in quinoline (1.0 mL) was added deionized H_2O (20 μL, 1.03 mmol). The reaction was heated to 150 ºC for 25 min in a microwave reactor.[25] The reaction was poured into an aqueous solution of HCl (1 M, 15 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The organic layers were combined, dried over Na_2SO_4, and evaporated under reduced pressure. The resulting residue was purified by flash chromatography (2:1→ 1:1 hexanes:EtOAc) to afford alkene **4.17** (15.6 mg, 69% yield) as an orange solid. Alkene **4.17**: mp: 88–90 ºC; R_f 0.20 (1:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36–7.28 (m, 3H), 7.18–7.13 (m, 2H), 6.70 (ddd, *J* = 9.0, 6.0, 1.5, 1H), 6.44 (ddd, *J* = 9.0, 6.0, 2.0, 1H), 4.86 (d, *J* = 15.0, 1H), 4.30 (d, *J* = 15.0, 1H), 4.15(dd, *J* =6.0, 2.0, 1H), 3.77 (ddd, *J* = 5.0, 3.0, 2.5, 1H), 2.42 (dd, *J* = 18.0, 2.5, 1H), 2.13 (dd, *J* = 18.0, 3.0, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 200.2, 170.5, 136.9, 135.7, 129.1, 128.7, 128.7, 127.9, 64.8, 48.6, 44.6, 32.0; IR (film): 3467, 3031, 2923, 1736, 1671, 1445, 1419, 1240, 1156 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{14}H_{13}NO_2Na$, 250.0844; found 250.0845.

Alkene 4.17 (batch processing procedure). Twenty-four microwave reaction tubes were charged using the procedure described above (using anhydride **4.15**, 40.0 mg, 0.103 mmol per tube). The reaction vessels were placed in the microwave's autosampler rack, and then each was heated to 150 ºC for 25 min in the microwave reactor. The reactions were combined poured into

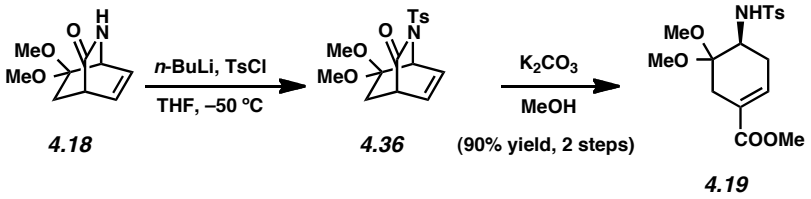
an aqueous solution of HCl (1 M, 150 mL) and extracted with CH_2Cl_2 (3 x 100 mL). The organic layers were combined, dried over Na_2SO_4, and evaporated under reduced pressure. The resulting residue was purified by flash chromatography (2:1→ 1:1 hexanes:EtOAc) to afford alkene **4.17**. This procedure was consistently repeated more than ten times to give multigram quantities of **4.17** (280-386 mg, 50–69% yield, per batch) as an orange solid.



Amide 4.18. To a solution of alkene **4.17** (2.04 g, 8.99 mmol) and trimethoxymethane (20.0 mL, 182 mmol) in methanol (80 mL) was added 4-methylbenzenesulfonic acid monohydrate (*p*–TsOH•H_2O) (855 mg, 4.50 mmol). The resulting mixture was heated to reflux. After 14 h, the reaction mixture was cooled to rt, excess methanol was removed under reduced pressure, and the reaction mixture was poured into a solution of sat. aq. $NaHCO_3$ (200 mL). The mixture was diluted with CH_2Cl_2 (50 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 and evaporated under reduced pressure. The resulting residue was purified by flash chromatography (2:1→ 1:1 hexanes:EtOAc) to afford ketal **4.35** (2.42 g, 99% yield) as an orange oil. Ketal **4.35**: mp: 71–72 ºC; R_f 0.20 (1:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32–7.25 (m, 3H), 7.12 (d, *J* = 7.5, 2H), 6.44 (dd, *J* = 7.0, 6.0, 1H), 6.29 (dd, *J* = 7.0, 5.5, 1H), 5.22 (d, *J* = 15.5, 1H), 4.01 (d, *J* = 5.5, 1H), 3.90 (d, *J* = 15.5, 1H), 3.49–3.47 (m, 1H), 3.20 (s, 3H), 3.13 (s, 3H), 2.01 (dd, *J* = 13.0, 1.5, 1H), 1.64 (dd, *J* = 13.0, 2.5, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.5, 136.8, 132.6, 131.3, 128.5, 127.8, 127.2, 107.2, 57.8, 49.4, 49.0, 48.4, 44.4, 33.8; IR (film): 3474, 2945, 2834,

1672, 1451, 1096, 1052 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{16}H_{19}NO_3Na$, 296.1263; found 296.1268.

A solution of ketal **4.35** (3.11 g, 11.4 mmol) and *tert*-butanol (0.20 mL, 3.45 mmol) in THF (40 mL) was added dropwise to a solution of sodium metal (786 mg, 34.2 mmol) in NH_3 (30 mL) at –78 °C. After 30 min, the reaction mixture was quenched with a solution of sat. aq. NH_4Cl (15 mL) at –78 ºC. The reaction was warmed to rt and poured into brine (20 mL). The solution was diluted with EtOAc (50 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure. The resulting residue was purified by flash chromatography (100:0→ 90:10 CH_2Cl_2:MeOH) to afford amide **4.18** (1.84 g, 88% yield) as a beige solid. Amide **4.18**: mp: 160–162 ºC; R_f 0.1 (1:1 hexanes:EtOAc); ^1H NMR (500 MHz, $CDCl_3$): δ 7.38 (s, 1H), 6.45 (s, 2H), 4.24 (s, 1H), 3.30 (s, 1H), 3.25 (s, 3H), 3.19 (s, 3H), 1.69 (d, *J* = 12.5, 1H), 1.26 (d, *J* = 12.5, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.4, 132.7, 131.8, 106.9, 53.3, 49.1, 49.0, 44.3, 34.1; IR (film): 3242, 2946, 1683, 1638, 1618, 1451, 1131, 1063 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_9H_{13}NO_3Na$, 206.0793; found 206.0796.

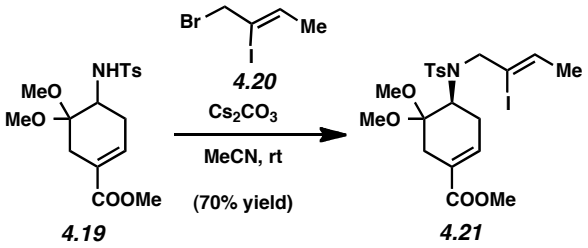


4.18 *4.36* (90% yield, 2 steps) *4.19*

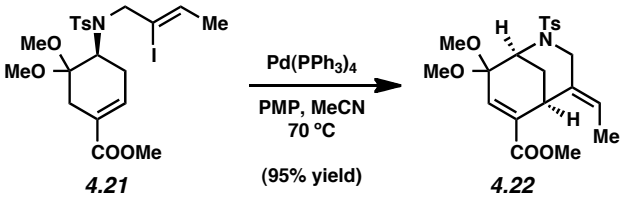
Ester 4.19. To a solution of amide **4.18** (1.10 g, 6.00 mmol) in THF (100 mL) was added a solution of *n*-butyllithium in hexanes (2.4 M, 3.50 mL, 8.40 mmol) at –50 °C. Following the addition, the reaction mixture was stirred for 30 min, and then a solution of 4-toluenesulfonyl chloride (1.72 g, 9.00 mmol) in THF was added dropwise over 10 min at –50 ºC. After 1 h, the reaction mixture was quenched with a solution of sat. aq. NH_4Cl (50 mL) at –50 ºC. The resulting mixture was warmed to rt and then diluted with EtOAc (50 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 x 50 mL). The organic layers were combined and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure afforded crude sulfonamide **4.36**, which was used in the subsequent step without further purification.

To a solution of crude sulfonamide **4.36** in MeOH (30 mL) at rt was added potassium carbonate (2.07 g, 15.0 mmol). After 12 h, excess methanol was removed under reduced pressure, and the resulting solution was poured into a solution of sat. aq. NH_4Cl (50 mL). The solution was diluted with CH_2Cl_2 (50 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The organic layers were combined, dried over Na_2SO_4, and evaporated under reduced pressure. The resulting residue was purified by flash chromatography (5:1→ 2:1 hexanes:EtOAc) to afford ester **4.19** (1.95 g, 90% yield, 2 steps) as an orange solid. Ester **4.19**: mp: 120–122 ºC; R_f 0.25 (2:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.74 (d, *J* = 8.0, 2H), 7.28 (d, *J* = 8.0, 2H), 6.75 (s, 1H), 4.85 (s, 1H), 3.70 (s, 3H), 3.51 (s, 1H), 3.08 (s, 3H), 2.94 (s, 3H), 2.69 (d, *J* = 18.5, 1H), 2.54 (d, *J* = 19.5, 1H), 2.42 (d, *J* = 19.5, 1H), 2.41 (s, 3H), 2.27 (d, *J* = 18.5, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.4, 143.4, 137.0, 136.1, 129.5,

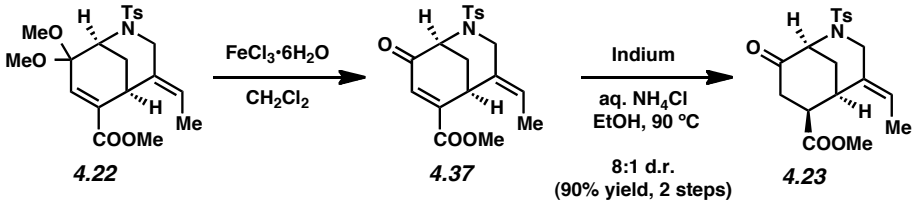
127.1, 126.5, 99.2, 51.6, 49.8, 48.3, 47.7, 30.1, 28.4, 21.4; IR (film): 3271, 2952, 1713, 1437, 1331, 1262, 1161, 1059 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{17}H_{23}NO_6SNa$, 392.1144; found 392.1149.



Iodide 4.21. To a suspension of ester **4.19** (1.95 g, 5.29 mmol) and cesium carbonate (3.42 g, 10.5 mmol) in MeCN (50 mL) at rt was added bromide **4.20** (4.11 g, 15.8 mmol). After stirring for 64 h, the excess MeCN was removed under reduced pressure. The residue was poured into deionized water (50 mL), and the resulting mixture was diluted with CH_2Cl_2 (100 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 100 mL). The organic layers were combined, dried over Na_2SO_4, and evaporated under reduced pressure. The resulting residue was purified by flash chromatography (10:1 → 5:1 hexanes:EtOAc) to afford iodide **4.21** (2.24 g, 70% yield) as a white solid. Iodide **4.21**: mp: 76–80 ºC; R_f 0.40 (2:1 hexanes:EtOAc); ^1H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, *J* = 8.5, 2H), 7.32 (d, *J* = 8.5, 2H), 6.81 (s, 1H), 6.24 (q, *J* = 6.5, 1H), 4.37 (s, 1H), 4.17 (d, *J* = 18.0, 1H), 3.91 (d, *J* = 18.0, 1H), 3.74 (s, 3H), 3.32 (s, 3H), 3.16 (s, 3H), 2.65 (d, *J* = 15.0, 1H), 2.51 (d, *J* = 15.0, 1H), 2.51 (d, *J* = 19.0, 1H), 2.45 (s, 3H), 2.00 (d, *J* = 19.0, 1H), 1.79 (d, *J* = 6.5, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.2, 143.4, 137.5, 136.9, 131.5, 129.5, 127.6, 127.4, 104.6, 99.5, 56.2, 54.4, 51.7, 48.9, 48.7, 30.1, 28.7, 21.4, 20.9; IR (film): 2950, 1713, 1436, 1342, 1263, 1159, 1090, 1065 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{21}H_{28}NO_6SINa$, 572.0580; found 572.0565.



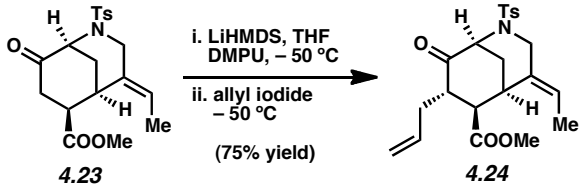
Ester 4.22. A solution of iodide **4.21** (470 mg, 0.850 mmol), 1,2,2,6,6-pentamethylpiperidine (PMP) (460 μL, 2.55 mmol), and tetrakis(triphenylphosphine)palladium (200 mg, 0.170 mmol) in MeCN (60 mL) was sparged with nitrogen for 25 min. The reaction mixture was then heated to 70 ºC. After 3 h, the reaction vessel was cooled to rt, and the excess solvent was removed under reduced pressure. The residue was diluted with CH_2Cl_2 (100 mL) and deionized water (50 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 100 mL). The organic layers were combined, dried over Na_2SO_4, and evaporated under reduced pressure. Purification by flash chromatography (10:1 → 5:1 hexanes:EtOAc) afforded ester **4.22** (340 mg, 95% yield) as an orange solid. Ester **4.22**: mp: 137–140 ºC; R_f 0.40 (2:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.69 (d, J = 8.5, 2H), 7.24 (d, J = 8.5, 2H), 6.97 (s, 1H), 5.33 (q, J = 6.5, 1H), 4.29 (s, 1H), 4.03 (d, J = 15.5, 1H), 3.84 (d, J = 15.5, 1H), 3.70 (s, 3H), 3.66 (s, 1H), 3.40 (s, 3H), 3.29 (s, 3H), 2.41 (s, 3H), 1.81 (d, J = 13.0, 1H), 1.58 (d, J = 6.5, 3H), 1.28 (d, J = 13.0, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.6, 142.9, 138.0, 136.6, 134.0, 129.5, 129.2, 127.4, 122.5, 96.3, 52.5, 51.9, 49.0, 48.9, 46.9, 30.2, 29.4, 21.4, 12.4; IR (film): 2950, 1721, 1438, 1345, 1329, 1247, 1159 cm^{-1}; HRMS-ESI (m/z) [M + Na]$^+$ calcd for $C_{21}H_{27}NO_6SNa$, 444.1457; found 444.1454.



Ketone 4.23. To a solution of ester **4.22** (1.40 g, 3.30 mmol) in CH_2Cl_2 (50 mL) at rt was added iron(III) chloride hexahydrate (0.782 g, 6.60 mmol). After 30 min, the reaction mixture was poured into a solution of sat. aq. $NaHCO_3$ (50 mL) and diluted with CH_2Cl_2 (100 mL). The layers were separated, and the organic layer was washed with a solution of sat. aq. $NaHCO_3$ (50 mL). The organic layer was dried over Na_2SO_4, and then evaporated under reduced pressure. Purification by flash chromatography (4:1 hexanes:EtOAc) gave ketone **4.37** (1.18 g, 99% yield) as a beige solid. Ketone **4.37**: mp: 112–113 ºC; R_f 0.40 (2:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.68 (d, *J* = 8.0, 2H), 7.28 (d, *J* = 8.0, 2H), 6.73 (s, 1H), 5.66 (q, *J* = 7.0, 1H), 4.53 (s, 1H), 4.13 (d, *J* = 14.0, 1H), 4.11 (s, 1H), 3.79 (s, 3H), 3.45 (d, *J* = 14.0, 1H), 2.41 (s, 3H), 2.25 (d, *J* = 13.5, 1H), 2.12 (d, *J* = 13.5, 1H), 1.81 (d, *J* = 7.0, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): 194.0, 165.4, 148.1, 143.4, 135.6, 133.2, 129.7, 127.7, 127.6, 125.4, 55.4, 52.7, 46.3, 33.8, 30.6, 21.4, 12.8; IR (film): 2954, 1722, 1685, 1437, 1347, 1243, 1159 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{19}H_{21}NO_5SNa$, 398.1038; found 398.1032.

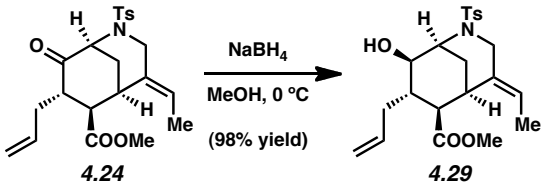
To a solution of ketone **4.37** (1.18 g, 3.14 mmol) in a mixture of sat. aq. NH_4Cl (20 mL) and EtOH (20 mL) was added indium (0.771 g, 6.28 mmol). The reaction vessel was heated to 90 ºC for 2 h. The reaction was diluted with CH_2Cl_2 (100 mL) and a solution of sat. aq. $NaHCO_3$ (100 mL) was added. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 100 mL). The organic layers were combined, dried over Na_2SO_4, and evaporated under reduced pressure. The resulting residue was purified by flash chromatography (2:1 hexanes:EtOAc) to afford ketone **4.23** (1.12 g, 91% yield) as an orange solid. Ketone **4.23** was

obtained as a mixture of diastereomers (8:1 d.r.) the major diastereomer being the one depicted. An analytical sample of the major diastereomer was obtained by column chromatography. Ketone **4.23**: mp: 65–70 ºC; R_f 0.45 (2:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.63 (d, *J* = 8.0, 2H), 7.28 (d, *J* = 8.0, 2H), 5.61 (q, *J* = 6.5, 1H), 4.38 (s, 1H), 4.24 (d, *J* = 14.0, 1H), 3.73 (d, *J* = 14.0, 1H), 3.63 (s, 3H), 3.39 (d, *J* = 4.0, 1H), 3.04 (ddd, *J* = 12.0, 4.0, 2.5, 1H), 2.41–2.30 (m, 5H), 2.15 (d, *J* = 14.0, 1H), 2.04 (d, *J* = 14.0, 1H), 1.60 (d, *J* = 6.5, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 204.4, 171.9, 143.8, 134.2, 129.5, 127.6, 124.1, 77.15, 57.9, 51.9, 49.3, 45.9, 40.4, 33.5, 29.9, 21.4, 12.3; IR (film): 2993, 2959, 2925, 2304, 1735, 1351, 1153 cm^{-1}; HRMS-ESI (*m/z*) [M + Na]$^+$ calcd for $C_{19}H_{23}NO_5SNa$, 400.1195; found 400.1198.



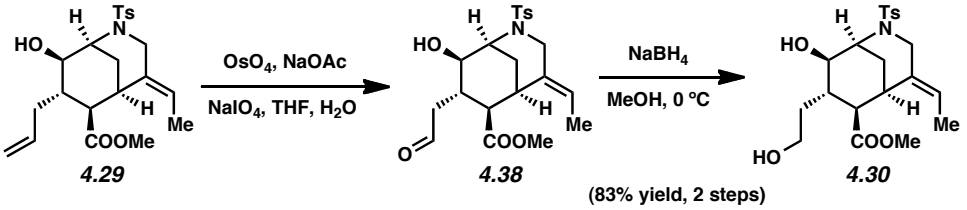
Alkene 4.24. To a solution of ketone **4.23** (100 mg, 0.270 mmol, 8:1 dr) in THF (1 mL) at –50 ºC was added a solution of LiHMDS (53 mg, 0.32 mmol) in THF (500 μL), followed by the addition of DMPU (1 mL). After 30 min, allyl iodide (30 μL, 0.33 mmol) was added at –50 ºC. Following 1 h, an additional aliquot of allyl iodide (20 μL, 0.20 mmol) was added at –50 ºC. After 30 min, the reaction was quenched with a solution of sat. aq. NH_4Cl (1 mL) and warmed to rt. The reaction mixture was poured into deionized H_2O (3 mL) and the resulting mixture was diluted with Et_2O (4 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 x 4 mL). The combined organic layers were washed with H_2O (4 x 5mL), dried over Na_2SO_4, and evaporated under reduced pressure. The resulting residue was purified by flash chromatography (5:1→ 2:1 hexanes:EtOAc) to afford a single diastereomer of alkene **4.24** (83

mg, 75% yield) as a clear oil. R_f 0.55 (2:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.61 (d, *J* = 8.0, 2H), 7.28 (d, *J* = 8.0, 2H), 5.59 (q, *J* = 6.5, 1H), 5.43–5.35 (m, 1H), 4.86 (d, *J* = 10.5, 1H), 4.82 (d, *J* = 10.5, 1H), 4.42 (s, 1H), 4.26 (d, *J* = 14.0, 1H), 3.83 (d, *J* = 14.0, 1H), 3.61 (s, 3H), 3.32 (s, 1H), 2.78 (dd, *J* = 11.5, 5.0, 1H), 2.43–2.41 (m, 4H), 2.14–1.94 (m, 4H), 1.56 (d, *J* = 6.5, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 205.5, 171.7, 143.7, 134.8, 134.2, 130.0, 129.5, 127.7, 123.5, 117.0, 58.6, 51.8, 51.5, 49.2, 48.5, 33.8, 32.9, 30.9, 21.4, 12.2; IR (film): 2983, 2956, 2921, 1733, 1717, 1598, 1437, 1351, 1161, 1095 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{20}H_{27}NO_5SNa$, 440.1508; found 440.1515.



Alcohol 4.29. To a solution of alkene **4.24** (80.0 mg, 0.190 mmol) in MeOH (1.0 mL) at 0 °C was added sodium borohydride (11.0 mg, 0.290 mmol). After 5 min, the reaction mixture was quenched with a solution of sat. aq. $NaHCO_3$ (20 mL) and diluted with CH_2Cl_2 (20 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were dried over Na_2SO_4 and evaporated under reduced pressure. The resulting residue was purified by flash chromatography (2:1 hexanes:EtOAc) to afford alcohol **4.29** (78 mg, 98% yield) as a white solid. Alcohol **4.29**: mp: 118–125 ºC; R_f 0.15 (2:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.68 (d, *J* = 8.0, 2H), 7.27 (d, *J* = 8.0, 2H), 5.81–5.73 (m, 1H), 5.40 (q, *J* = 6.5, 1H), 5.03 (s, 1H), 5.00 (d, *J* = 5.5, 1H), 4.19 (m, 2H), 4.18 (s, 1H), 4.10 (d, *J* = 2.0, 1H), 3.59 (s, 3H), 3.54–3.50 (m, 1H), 3.09 (d, *J* = 4.0, 1H), 2.68 (d, *J* = 7.0, 1H), 2.59 (dd, *J* = 11.5, 4.5, 1H), 2.41 (s, 3H), 2.39–2.28 (m, 3H), 1.56 (d, *J* = 16.0, 1H),

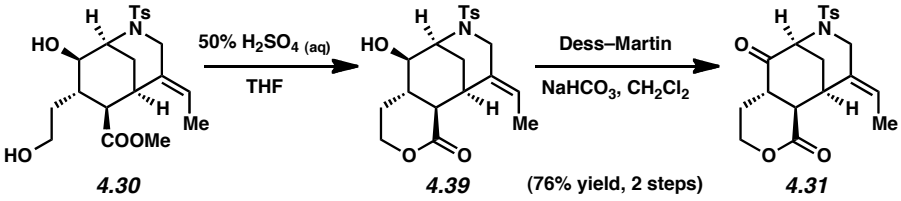
1.44 (d, J = 6.5, 3H), 1.39 (ddd, J = 16.0, 4.0, 3.5, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.6, 143.3, 137.1, 134.7, 131.1, 129.6, 126.9, 121.8, 117.6, 72.1, 52.9, 51.4, 50.3, 48.8, 40.4, 36.1, 31.4, 30.6, 21.4, 12.0; IR (film): 3519, 2956, 2868, 1734, 1598, 1445, 1327, 1158 cm^{-1}; HRMS-ESI (m/z) [M + Na]$^+$ calcd for $C_{20}H_{29}NO_5SNa$, 442.1664; found 442.1678.



Diol 4.30. To a solution of alcohol **4.29** (75 mg, 0.18 mmol) and NaOAc (88.6 mg, 1.08 mmol) in THF (0.6 mL) and H_2O (1.2 mL) was added a solution of osmium tetroxide (89 mg, 0.04 mmol) in *tert*-butanol (183 μL). After 10 min, sodium periodate (116 mg, 0.54 mmol) was added. After stirring for 4 h, the reaction mixture was quenched with a solution of sat. aq. $NaHCO_3$ (20 mL) and diluted with CH_2Cl_2 (20 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were dried over Na_2SO_4 and evaporated under reduced pressure to afford crude aldehyde **4.38**, which was used in the subsequent step without further purification.

To a solution of aldehyde **4.38** (75 mg, 0.18 mmol) in MeOH (1 mL) was added sodium borohydride (10 mg, 0.27 mmol) at 0 °C. After 5 min, the reaction mixture was quenched with a solution of sat. aq. $NaHCO_3$ (20 mL) and diluted with CH_2Cl_2 (20 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were dried over Na_2SO_4, and evaporated under reduced pressure. The resulting residue was purified by flash chromatography (19:80:1 hexanes:EtOAc:MeOH) to afford diol **4.30** (62 mg, 83% yield) as a white solid. Diol **4.30**: mp: 111–116 ºC; R_f 0.10 (2:1 hexanes:EtOAc); ^{1}H

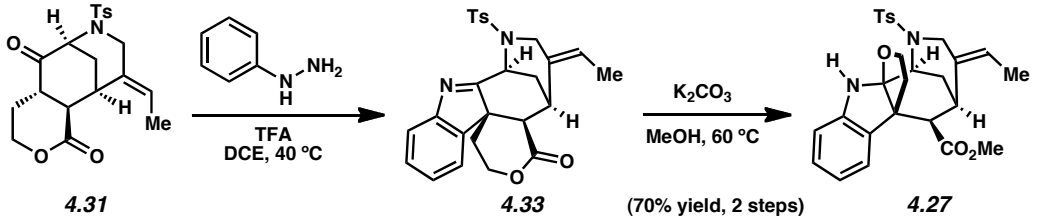
NMR (300 MHz, $CDCl_3$): δ 7.68 (d, *J* = 8.0, 2H), 7.27 (d, *J* = 8.0, 2H), 5.43 (q, *J* = 11.5, 1H), 4.22–4.18 (m, 2H), 4.10–4.06 (m, 1H), 3.71–3.68 (m, 2H), 3.62 (s, 3H), 3.59–3.54 (m, 2H), 3.48–3.42 (m, 1H), 3.12 (dd, *J* = 7.5, 4.0, 1H), 2.54 (dd, *J* = 12, 4.5, 1H), 2.42 (s, 3H), 2.35–2.27 (m, 1H), 1.64–1.59 (m, 3H), 1.45–1.37 (m, 4H) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.0, 143.5, 137.2, 130.9, 129.8, 127.0, 122.2, 74.7, 61.7, 52.7, 51.8, 51.5, 50.4, 40.7, 39.8, 31.5, 30.7, 21.5, 12.2; IR (film):3371, 2950, 1733, 1437, 1327, 1158 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{21}H_{29}NO_6SNa$, 446.1613; found 446.1615.



Lactone 4.31. To a solution of diol **4.30** (55 mg, 0.13 mmol) in THF (0.5 mL) was added a solution of 50% aqueous H_2SO_4 (0.5 mL). After stirring at rt for 30 min, the reaction mixture was quenched with a solution of sat. aq. $NaHCO_3$ (10 mL) and diluted with CH_2Cl_2 (20 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were dried over Na_2SO_4 and evaporated under reduced pressure to afford crude alcohol **4.39**, which was used in the subsequent step without further purification.

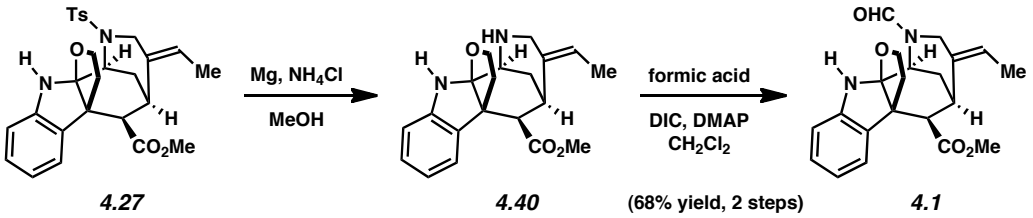
To a solution of alcohol **4.39** (44 mg, 0.11 mmol) and sodium bicarbonate (92.4 mg, 1.10 mmol) in CH_2Cl_2 (2.2 mL) at rt was added Dess–Martin Periodinane (140 mg, 0.330 mmol). After 2 h, the reaction mixture was quenched with a solution of sat. aq. $NaHCO_3$ (20 mL) and diluted with CH_2Cl_2 (20 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were dried over Na_2SO_4 and evaporated under reduced pressure. The resulting residue was purified by flash chromatography (2:1

hexanes:EtOAc) to afford lactone **4.31** (40 mg, 76% yield, 2 steps) as a white solid. Lactone **4.31**: mp: 180–190 ºC dec; R_f 0.40 (2:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.62 (d, *J* = 7.0, 2H), 7.30 (d, *J* = 7.0, 2H), 5.70 (q, *J* = 7.0, 1H), 4.37 (s, 1H), 4.30 (ddd, *J* = 10.5, 6.0, 4.5, 1H), 4.23 (d, *J* = 14.5, 1H), 4.10 (ddd, *J* = 10.5, 5.5, 5.0, 1H), 3.99 (d, *J* = 14.5, 1H), 3.54 (s, 1H), 2.57 (dd, *J* = 14.0, 3.0, 1H), 2.48–2.43 (m, 1H), 2.41 (s, 3H), 2.09 (d, *J* = 14.0, 1H), 1.97 (d, *J* = 14.0, 1H), 1.94–1.89 (m, 1H), 1.80 (d, *J* = 7.0, 3H), 1.80–1.75 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 204.1, 168.7, 144.0, 134.1, 129.6, 128.0, 127.6, 126.4, 67.5, 58.6, 50.2, 49.5, 45.1, 34.4, 28.4, 22.1, 21.4, 13.4; IR (film): 2924, 2864, 1720, 1597, 1328, 1161 cm^{-1}; HRMS-ESI (*m*/*z*) $[M + Na]^+$ calcd for $C_{20}H_{23}NO_5SNa$, 412.1195; found 412.1203.



Furoindoline 4.27. A solution of lactone **4.31** (35 mg, 0.090 mmol), phenylhydrazine (13 μL, 0.14 mmol), and trifluoroacetic acid (35 μL, 0.45 mmol) in DCE (4.5 mL) was degassed by the freeze-pump-thaw method until gas evolution was no longer observed. The reaction mixture was heated to 40 ºC for 16 h, and then cooled to rt. Evaporation of the solvent under reduced pressure afforded crude imine **4.33**. MeOH (2 mL) and potassium carbonate (125 mg, 0.90 mmol) were added to the reaction vessel and the resulting mixture was heated to 60 ºC for 30 min. After cooling to rt, the reaction mixture was diluted with brine (20 mL) and CH_2Cl_2 (20 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were dried over Na_2SO_4, and then evaporated under reduced pressure. The resulting residue was purified by column chromatography (4:1 hexanes:EtOAc) to afford

furoindoline **4.27** (30.5 mg, 70% yield, 2 steps) as a white solid. Furoindoline **4.27**: mp: 130–132 ºC; R_f 0.30 (2:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.72 (d, *J* = 8.5, 2H), 7.27 (d, *J* = 8.5, 2H), 7.09–7.06 (m, 2H), 6.76 (app. t, *J* = 7.0, 1H), 6.62 (d, *J* = 7.5, 1H), 5.53 (q, *J* = 7.0, 1H), 4.49–4.47 (m, 2H), 3.97 (d, *J* = 15.0, 1H), 3.88 (d, *J* = 15.0, 1H), 3.70 (s, 3H), 3.58 (t, *J* = 8.0, 1H), 3.38 (ddd, *J* = 6.0, 5.5, 2.5, 1H), 3.28 (d, *J* = 3.5, 1H), 2.91 (d, *J* = 4.5, 1H), 2.75 (ddd, *J* = 13.0, 8.5, 5.0, 1H), 2.48 (dd, *J* = 13.5, 5.5, 1H), 2.42 (s, 3H), 2.04 (d, *J* = 13.5, 1H), 1.86 (dt, *J* = 13.5, 3.5, 1H), 1.56 (d, *J* = 7.0, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.0, 146.4, 142.5, 137.3, 135.9, 129.7, 129.0, 128.2, 127.5, 124.2, 122.8, 119.7, 109.1, 101.9, 68.2, 54.1, 53.7, 53.1, 51.5, 47.8, 35.6, 31.2, 29.7, 21.4, 12.6; IR (film): 3361, 2950, 2872, 1740, 1610, 1469, 1326, 1159 cm^{-1}; HRMS-ESI (*m*/*z*) [M + Na]$^+$ calcd for $C_{27}H_{30}N_2O_5SNa$, 517.1773; found 517.1793.



Aspidophylline A (4.1). To a solution of furoindoline **4.27** (10 mg, 0.020 mmol) and NH_4Cl (129 mg, 2.40 mmol) in MeOH (2 mL) was added magnesium metal powder (58.0 mg, 2.40 mmol). The resulting mixture was sonicated for 1 h, and then additional magnesium metal powder (58.0 mg, 2.40 mmol) was added. After 1 h of further sonication, a final portion of magnesium metal powder (29.0 mg, 1.20 mmol) was added to the reaction mixture. The reaction mixture was sonicated for an additional 0.5 h, quenched with a solution of sat. aq. $NaHCO_3$ (10 mL) and then diluted with H_2O (10 mL) and EtOAc (20 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 x 20 mL). The organic layers were combined and

dried over Na_2SO_4. Evaporation of the solvent under reduced pressure afforded crude amine **4.40**, which was used in the subsequent step without further purification.

To a solution of *N*,*N*′-diisopropylcarbodiimide (DIC) (3.0 mg, 0.020 mmol) and 4-dimethylaminopyridine (DMAP) (0.5 mg, 0.01 mmol) in CH_2Cl_2 (0.1 mL) at 0 ºC was added formic acid (1.4 mg, 0.03 mmol). After 15 min, this solution was added to a solution of the crude amine **4.40** in CH_2Cl_2 (0.1 mL) at rt. After 1 h, the reaction mixture was quenched with a solution of sat. aq. $NaHCO_3$ (10 mL) and diluted with CH_2Cl_2 (20 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were dried over Na_2SO_4 and evaporated under reduced pressure to afford the crude product. Purification by flash chromatography (1:2 hexanes:EtOAc) provided (±)-Aspidophylline A (**4.1**) (5 mg, 68% yield). Synthetic **4.1** was found to be spectroscopically identical to a natural sample of **4.1** obtained from Prof. T.-S. Kam (see comparison ^{1}H NMR spectra), and exists as a mixture of two amide rotational isomers(17 to 1). R_f 0.30 (1:2 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.15(8.13) (s, 1H), 7.10–7.07(7.09–7.06) (m, 2H), 6.79(6.76) (app. t, *J* = 7.5, 1H), 6.67(6.60) (d, *J* = 7.5, 1H), 5.61(5.58) (q, *J* = 7.0, 1H), 4.41(4.54) (s, 1H), 4.29(4.14) (d, *J* = 17.5, 1H), 4.07(4.05) (d, *J* = 17.5, 1H), 3.96–3.92(4.03–3.99) (m, 1H), 3.90(3.87) (s, 1H), 3.71(3.74) (s, 3H), 3.57(3.49) (dd, *J* = 17.5, 8.0, 1H), 3.42(3.11) (d, *J* = 3.5, 1H), 2.86(2.74) (d, *J* = 4.5, 1H), 2.70–2.67(2.50–2.46) (m, 2H), 2.19(1.98) (d, *J* = 13.5, 1H), 2.01(1.78) (dt, *J* = 13.5, 3.5, 1H), 1.60(1.62) (d, *J* = 7.0, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.9(172.1), 164.3(161.8), 146.2(146.6), 135.7(135.9), 129.1(130.4), 128.3(128.2), 124.2(123.8), 122.9(122.9), 120.3(119.6), 110.0(108.5), 102.0(101.1), 69.1(68.0), 53.8(54.3), 53.6(53.8), 51.5(49.5), 44.4(47.9), 34.3(36.9), 30.5(31.15), 30.1(29.6), 12.7(12.5); IR (film): 3303, 2920, 2872, 1740, 1652, 1609, 1468, 1432, 1157 cm^{-1}; HRMS-ESI (*m*/*z*) $[M + Na]^+$

calcd for $C_{21}H_{24}N_2O_4Na$, 391.1634; found 391.1625.

4.9 Notes and References

(1) (a) For a review describing recent indole functionalization methodology, see: Bandini, M.; Eichholzer, A. *Angew. Chem. Int. Ed.* **2009**, *48*, 9608–9644. (b) For a review of recent indole alkaloid syntheses, see: Bronner, S. M.; Im, G.-Y. J.; Garg, N. K. Indoles and Indolizidines. In *Heterocycles in Natural Product Synthesis*; Majumdar, K. C.; Chattopadhyay, S. K., Eds.; Wiley–VCH, 2011; pp 221–266.

(2) For reviews, see: (a) Kam, T.-S. In Alkaloids: Chemical and Biological Perspective; Pelletier, S. W., Ed.; Pergamon: Amsterdam, 1999; Vol. 14, pp 285–435. (b) Kam, T.-S.; Choo, Y. M. In The Alkaloids; Cordell G. A., Ed.; Academic Press: Amsterdam, 2006; Vol. 63, pp 181–337.

(3) For recent isolation reports, see: (a) Subramaniam, G.; Hiraku, O.; Hayashi, M.; Koyano, T.; Komiyama, K.; Kam, T.-S. *J. Nat. Prod.* **2007**, *70*, 1783–1789. (b) Subramaniam, G.; Kam, T.-S. *Helv. Chim. Acta* **2008**, *91*, 930–937.

(4) (a) Çelebi-Ölçüm, N.; Boal, B. W.; Huters, A. D.; Garg, N. K.; Houk, K. N. *J. Am. Chem. Soc.* **2011**, *133*, 5752–5755. (b) Boal, B. W.; Schammel, A. W.; Garg, N. K. *Org. Lett.* **2009**, *11*, 3458–3461. (c) Schammel, A. W.; Boal, B. W.; Zu, L.; Mesganaw, T.; Garg, N. K. *Tetrahedron (Special Issue)* **2010***, 66*, 4687–4695.

(5) For an impressive late-stage Fischer indolization in natural product synthesis, see: Ueda, H.; Satoh, H.; Matsumoto, K.; Sugimoto, K.; Fukuyama, T.; Tokuyama, H. *Angew. Chem. Int. Ed.* **2009**, *48*, 7600–7603.

(6) For reviews of the Heck reaction, see: (a) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945–2963. (b) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev*. **2000**, *100*, 3009–3066. (c) Amatore, C.; Jutand, A. *J. Organomet. Chem.* **1999**, *576*, 254–278.

(7) For the use of the Heck reaction in the synthesis of *Strychnos* alkaloids, see: (a) Rawal, V. H.; Michoud, C.; Monestel, R. F. *J. Am. Chem. Soc.* **1993**, *115*, 3030–3031. (b) Rawal, V. H.; Iwasa, S. *J. Org. Chem.* **1994**, *59*, 2685–2686. (c) Martin, D. B. C.; Vanderwal, C. D. *J. Am. Chem. Soc.* **2009**, *131*, 3472–3473.

(8) Herdeis, C.; Hartke, C. *Heterocycles* **1989**, *29*, 287–296.

(9) (a) Fessner, W. D.; Sedelmeier, G.; Spurr, P. R.; Rihs, G.; Prinzbach, H. *J. Am. Chem. Soc.* **1987**, *109*, 4626–4642. (b) Snow, R. A.; Degenhardt, C. R.; Paquette, L. A. *Tetrahedron Lett.* **1976**, *17*, 4447–4450.

(10) (a) Ensley, H. E.; Buescher, R. R.; Lee K. *J. Org. Chem.* **1982**, *47*, 404–408. (b) Sole, D.; Diaba, F.; Bonjoch, J. *J. Org. Chem.* **2003**, *68*, 5746–5749.

(11) The conversion of **4.24** to **4.25** was achieved through a sequence involving: a) ketone protection as the cyclic ketal, b) oxidative cleavage of the terminal olefin, c) reduction of the corresponding aldehyde, and d) acid-mediated ketal deprotection.

(12) The conversion of **4.24** to **4.26** was achieved through a sequence involving: a) ketone protection as the cyclic ketal, b) oxidative cleavage of the terminal olefin, c) reduction of the corresponding aldehyde, d) Piv-protection of the resulting alcohol, and e) acid-mediated ketal deprotection.

(13) Under a variety of interrupted Fischer indolization conditions, substrate **4.25** underwent facile dehydration to the corresponding dihydrofuran.

(14) Although ketone **4.26** underwent condensation with phenylhydrazine under several interrupted Fischer indolization conditions, no evidence of [3,3]-sigmatropic rearrangement was detected.

(15) Ketone **4.23**, a substrate without the C7-sidechain, readily underwent Fischer indolization upon treatment with phenylhydrazine and various acids. The factors that influence the likelihood of [3,3]-sigmatropic rearrangement in this series of compounds are currently under investigation. 16 A more concise approach involving oxidative cleavage of the terminal olefin in **4.24** led to substantial decomposition.

(17) Sabahi, A.; Novikov, A.; Rainier, J. D. *Angew. Chem. Int. Ed.* **2006**, *45*, 4317–4320.

(18) Aspidophylline A was isolated as a 17:1 mixture of formamide rotamers.

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

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

(21) Varlamov, A. V.; Boltukhina, E. V.; Zubkov, F. I.; Nikitina, E. V.; Turchin, K. F. *J. Heterocycl. Chem.* **2006**, *43*, 1479–1495.

(22) Ensley, H. E.; Buescher, R. R.; Lee K. *J. Org. Chem.* **1982**, *47*, 404–408.

(23) Sole, D.; Diaba, F.; Bonjoch, J. *J. Org. Chem.* **2003**, *68*, 5746–5749.

(24) Herdeis, C.; Hartke, C. *Heterocycles* **1989**, *29*, 287–296.

(25) Variable yields were obtained using conventional heating or microwave on larger scale. Nonetheless, multigram quantities of **4.15** were readily processed using a microwave reactor equipped with an autosampler (see batch processing procedure).

APPENDIX THREE

Spectra Relevant to Chapter Four:

Total Synthesis of (±)-Aspidophylline A
Liansuo Zu, Ben W. Boal, and Neil K. Garg

J. Am. Chem. Soc. **2011**, *133*, 8877–8879.

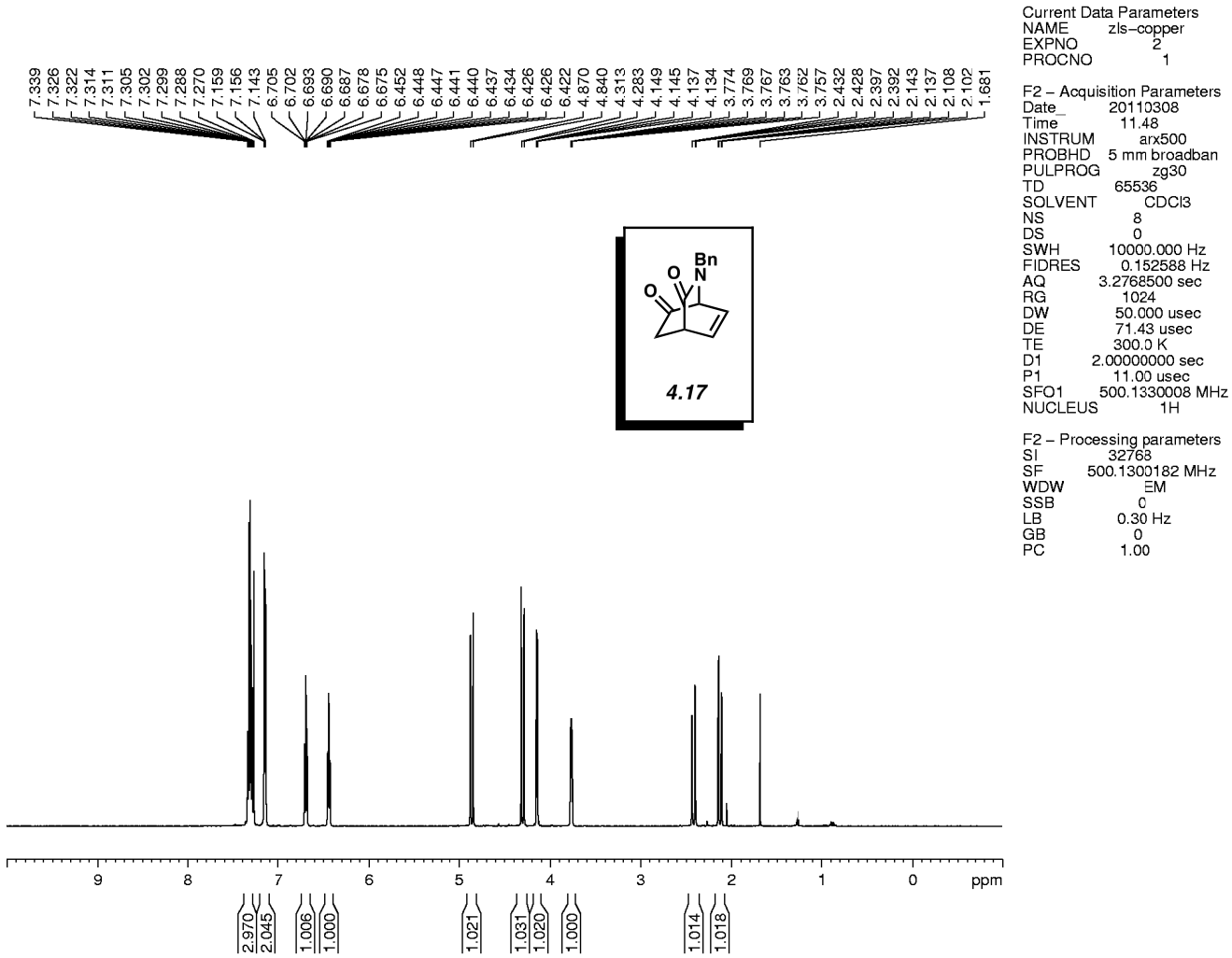


Figure A3.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.17**.

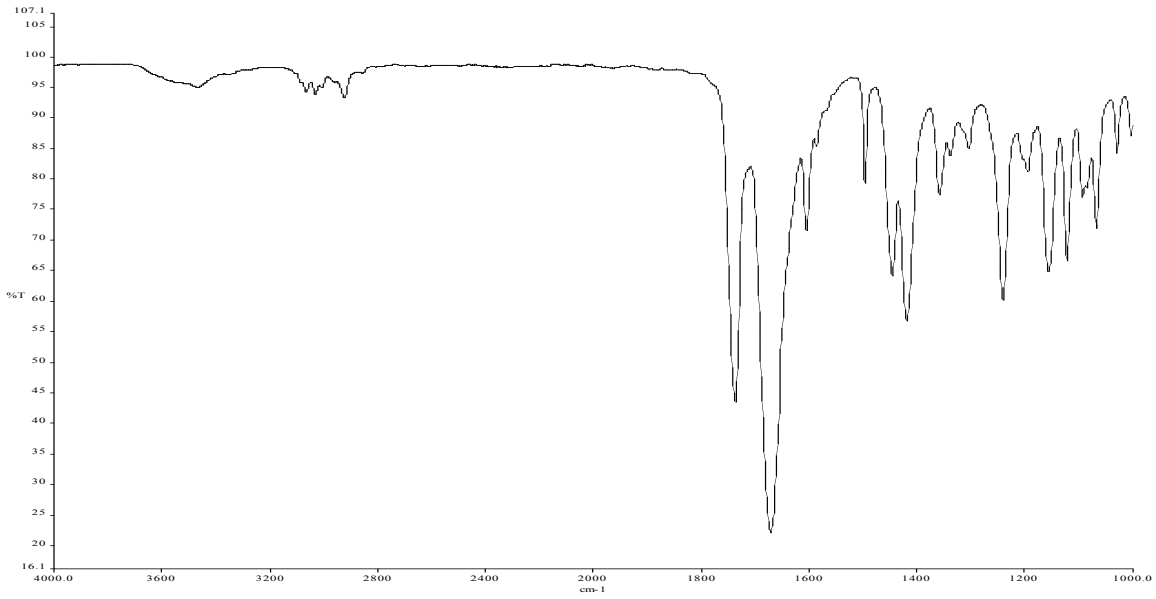


Figure A3.2 Infrared spectrum of compound **4.17**.

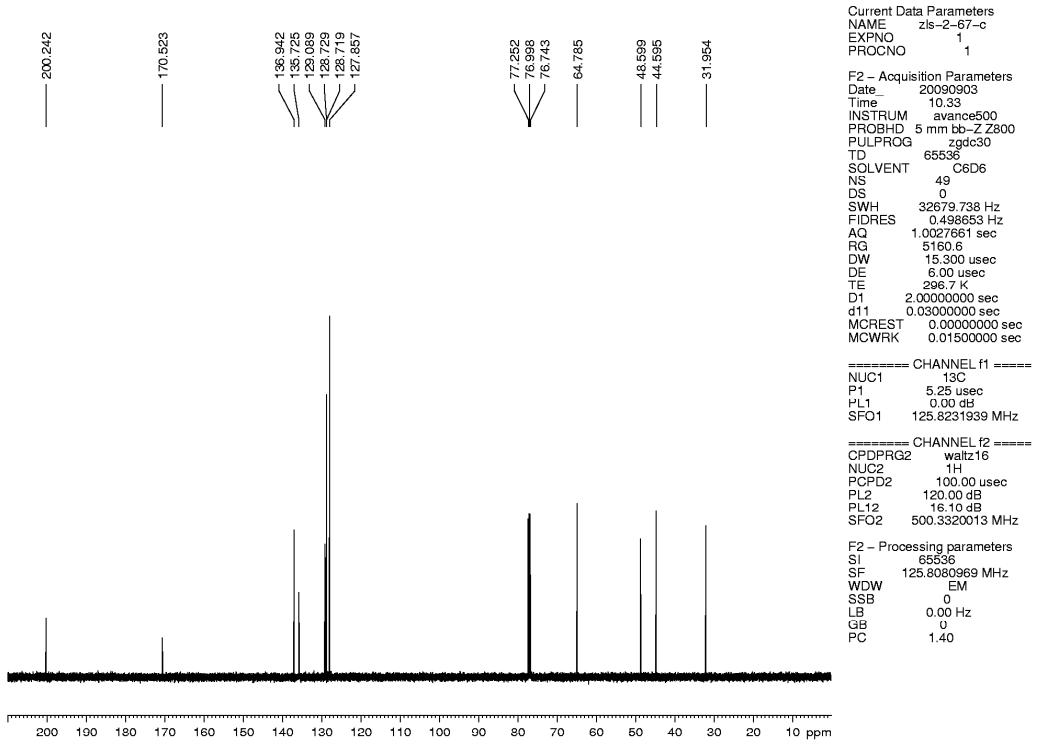


Figure A3.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4.17**.

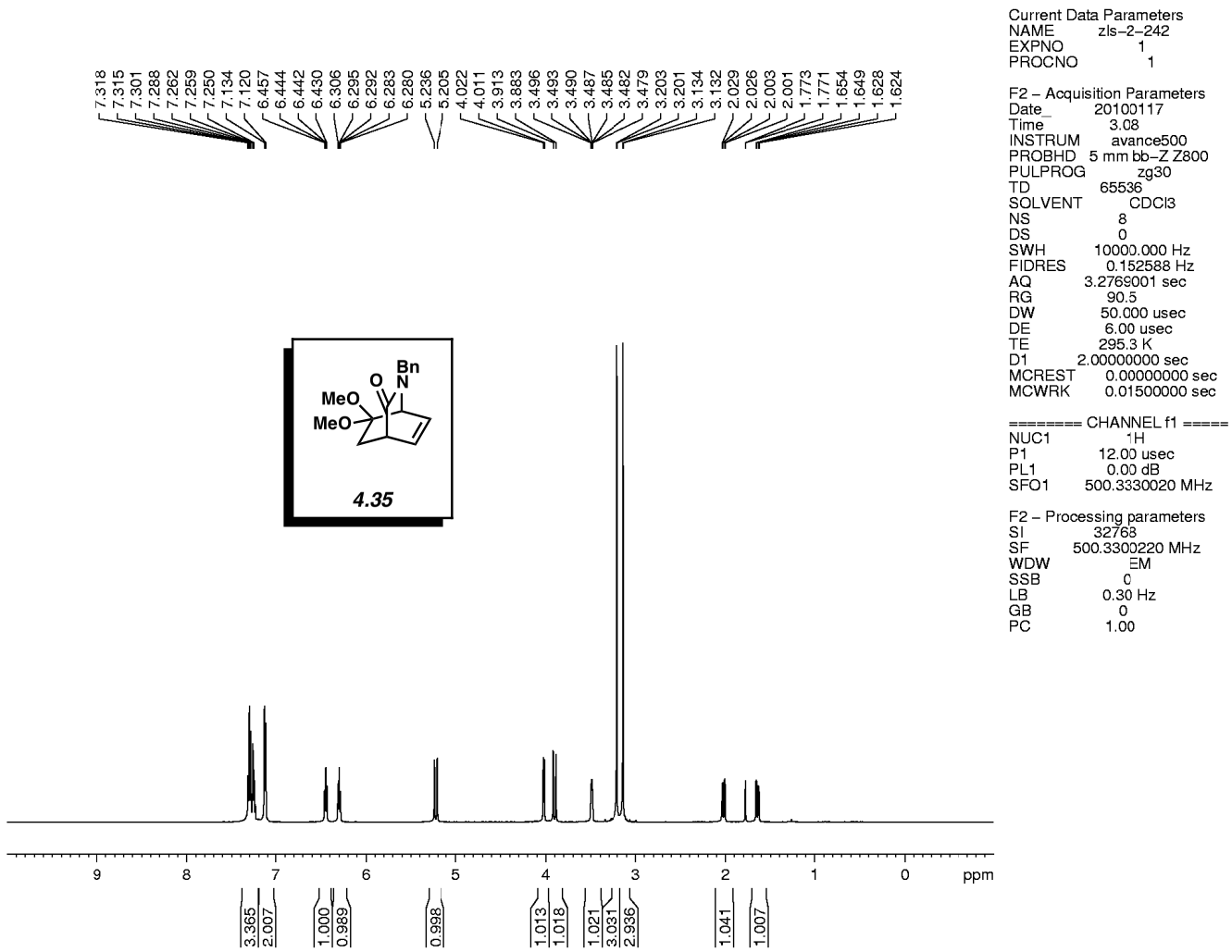


Figure A3.4 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.35**.

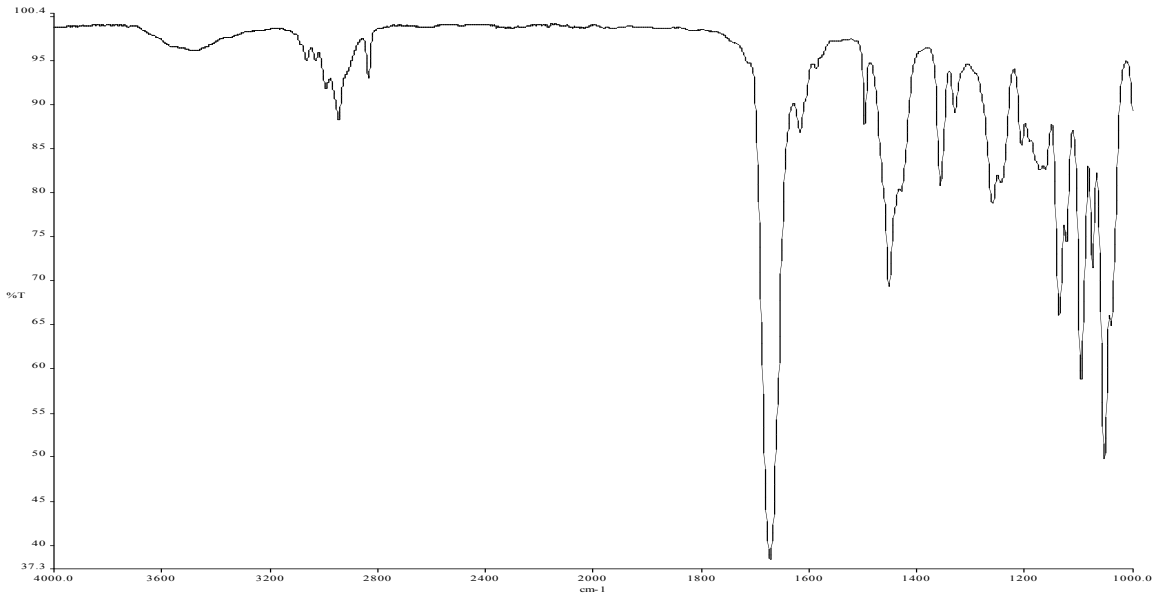


Figure A3.5 Infrared spectrum of compound **4.35**.

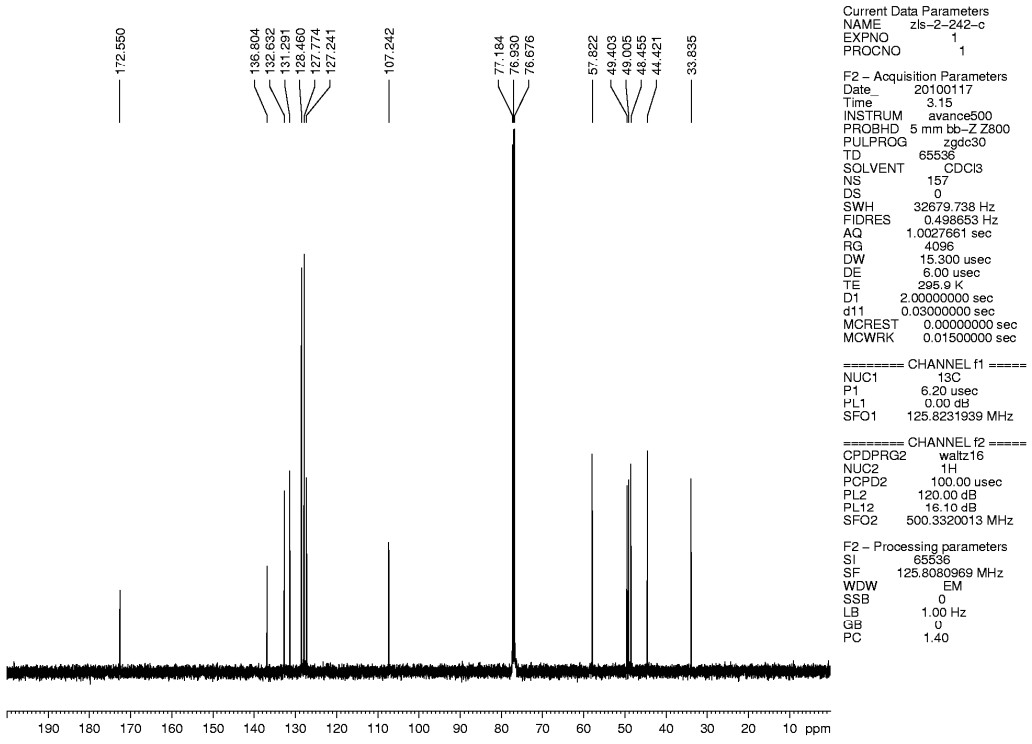


Figure A3.6 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4.35**.

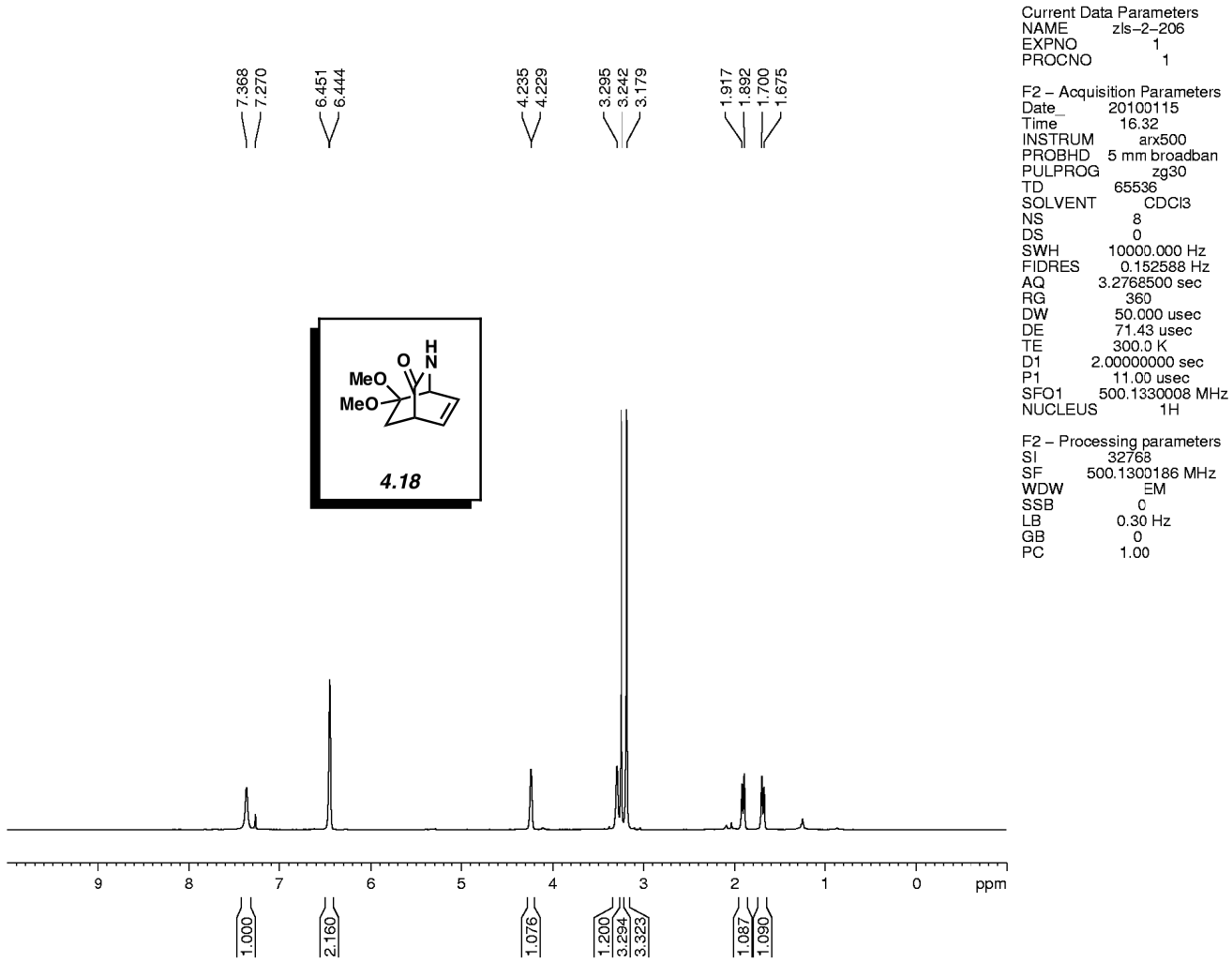


Figure A3.7 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.18**.

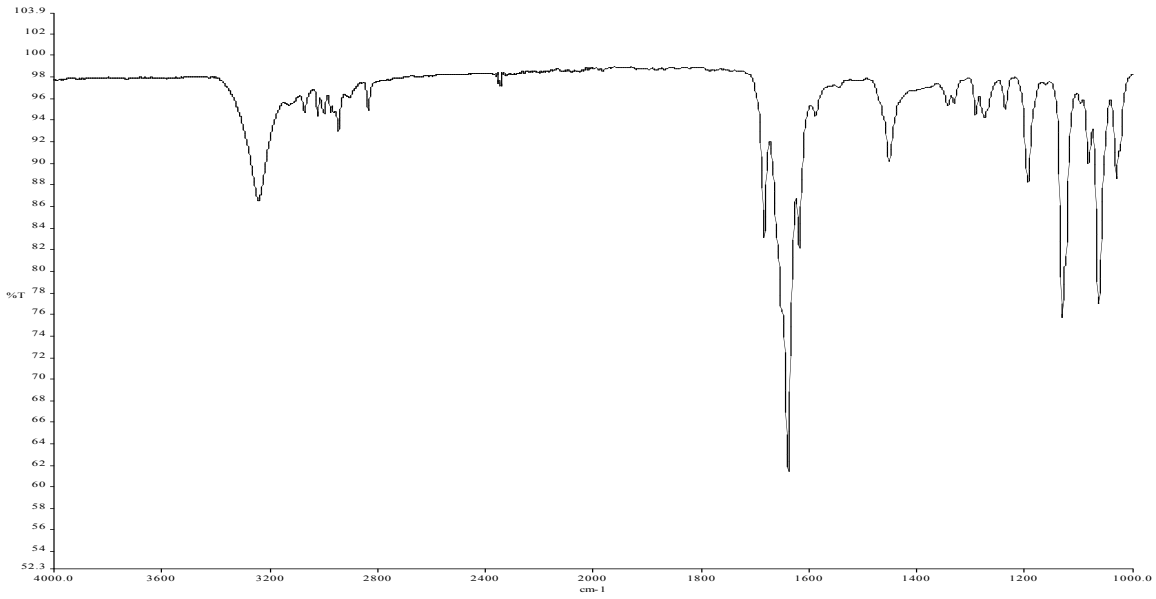


Figure A3.8 Infrared spectrum of compound **4.18**.

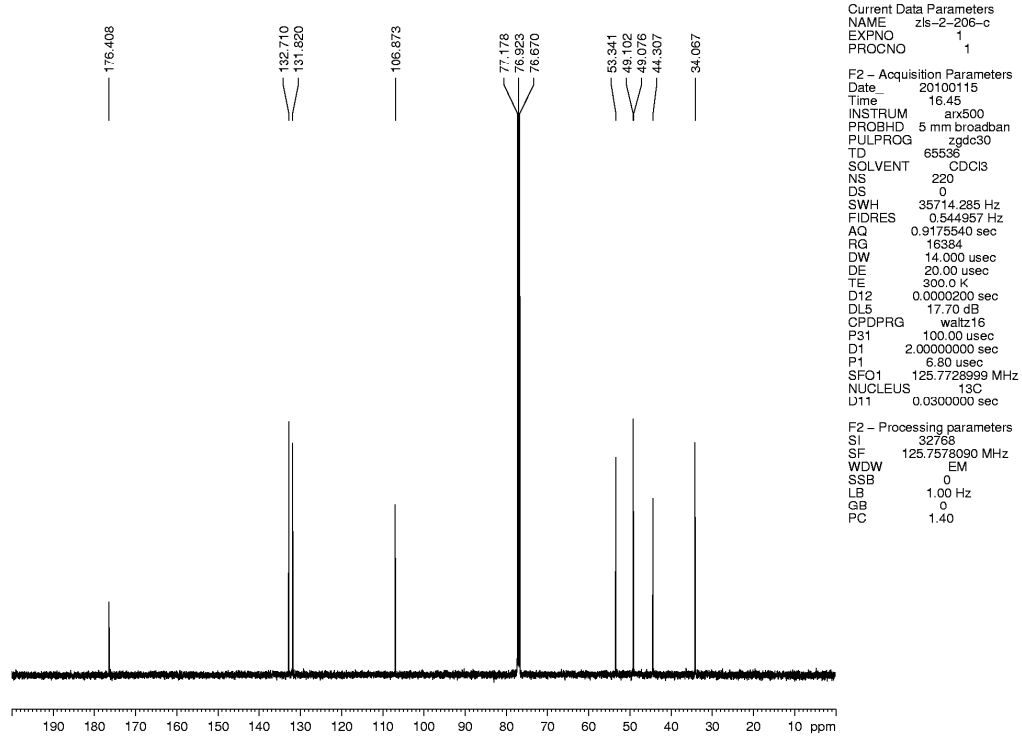


Figure A3.9 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4.18**.

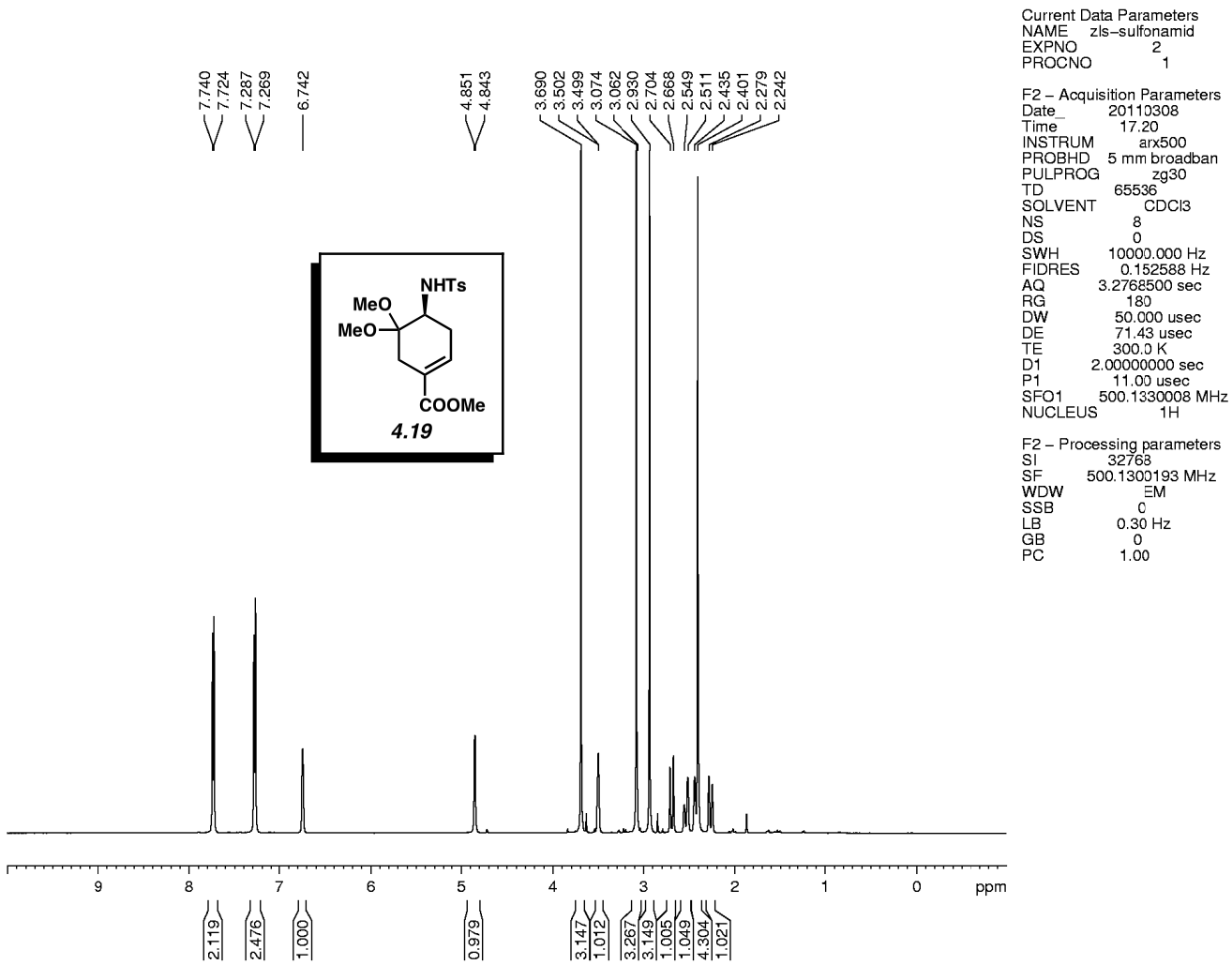


Figure A3.10 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.19**.

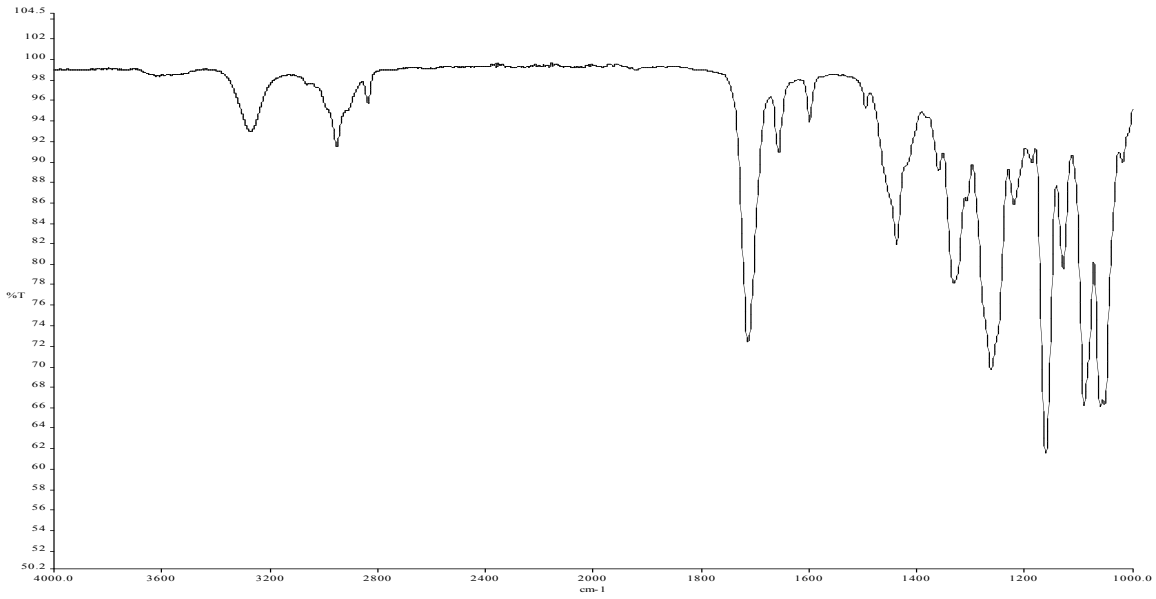


Figure A3.11 Infrared spectrum of compound **4.19**.

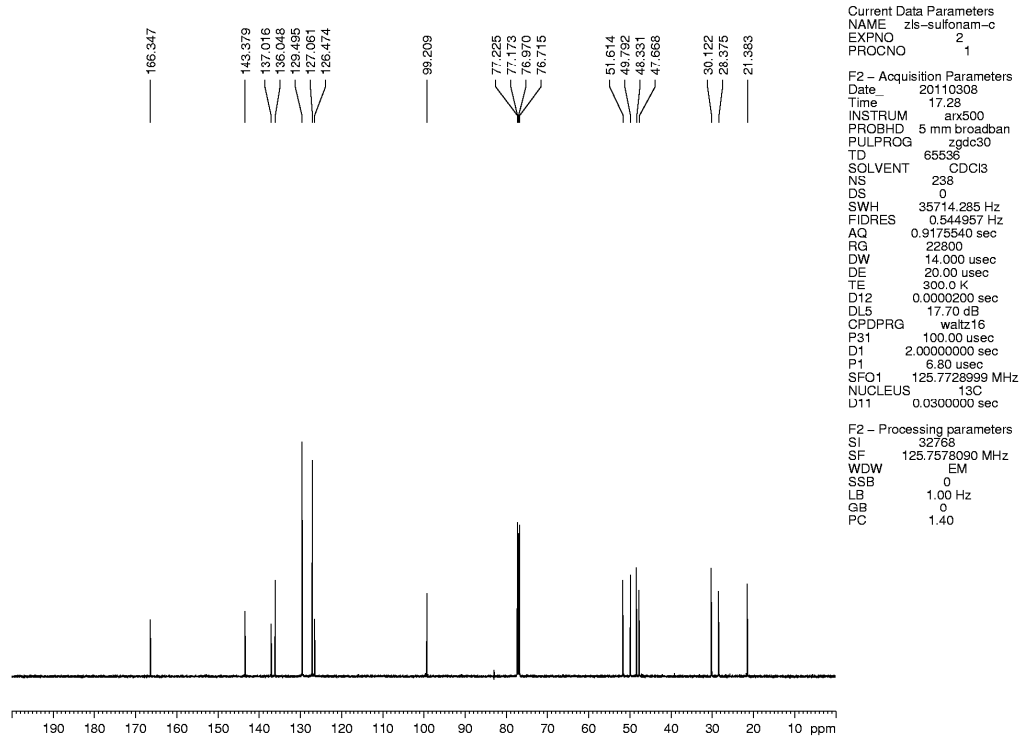


Figure A3.12 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4.19**.

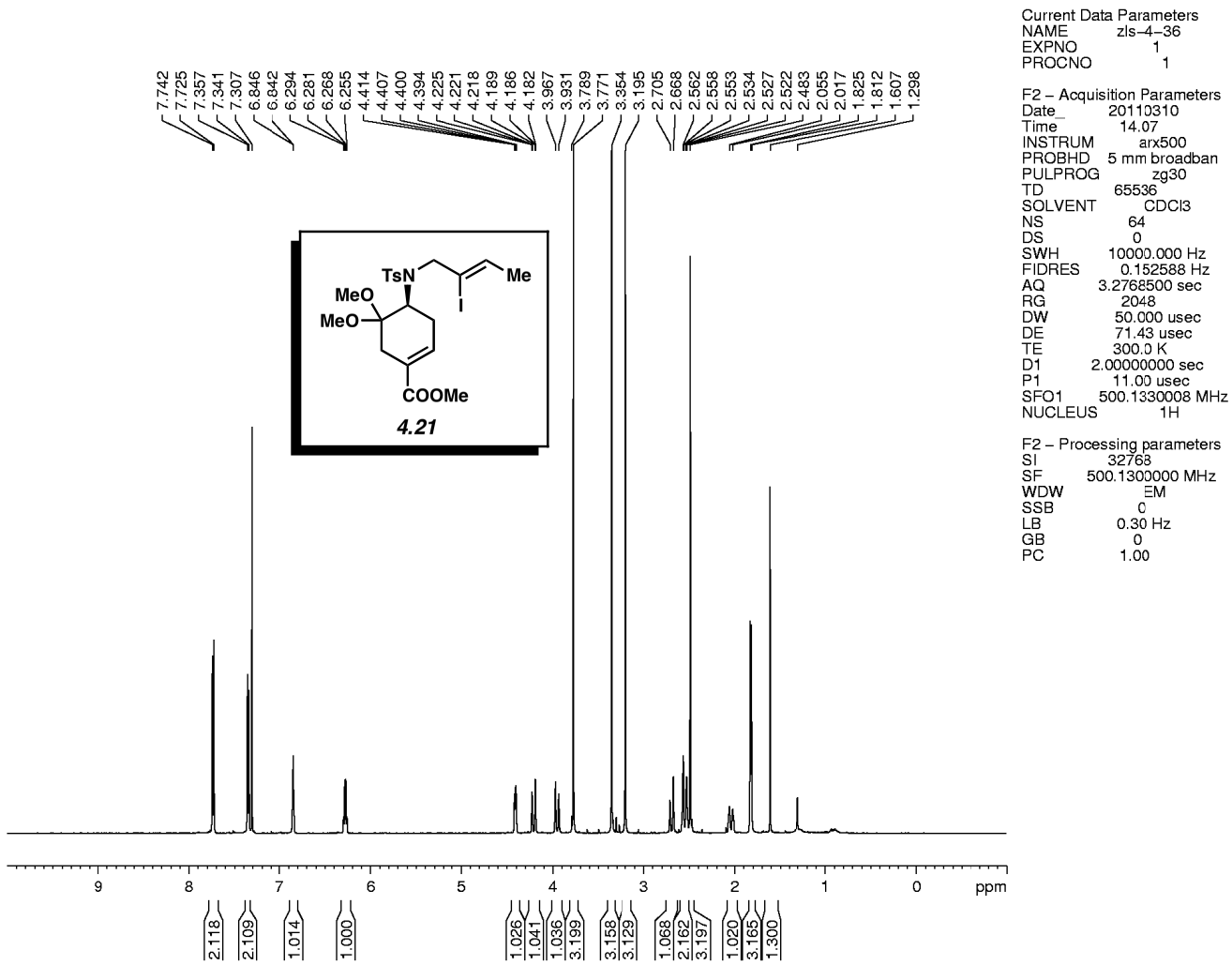


Figure A3.13 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.21**.

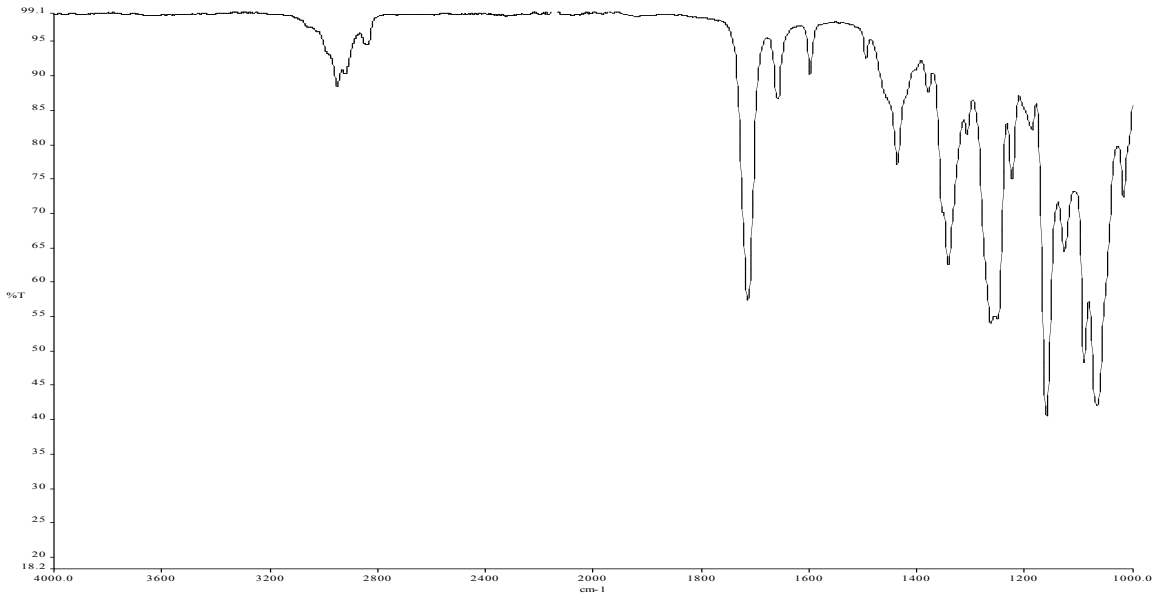


Figure A3.14 Infrared spectrum of compound **4.21**.

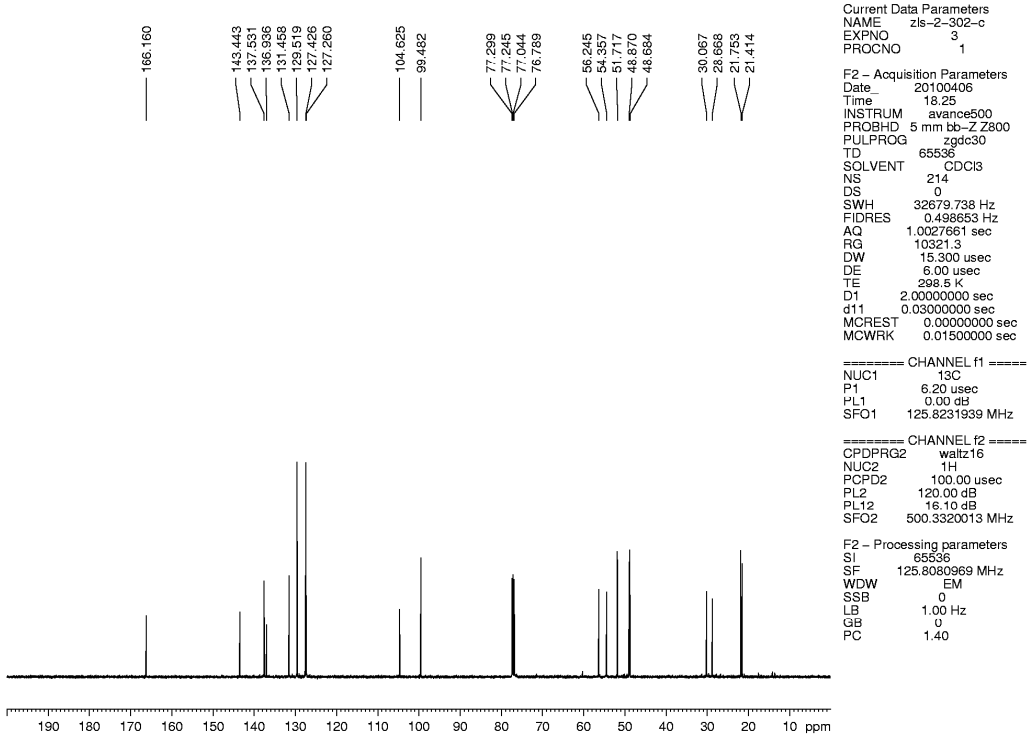


Figure A3.15 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4.21**.

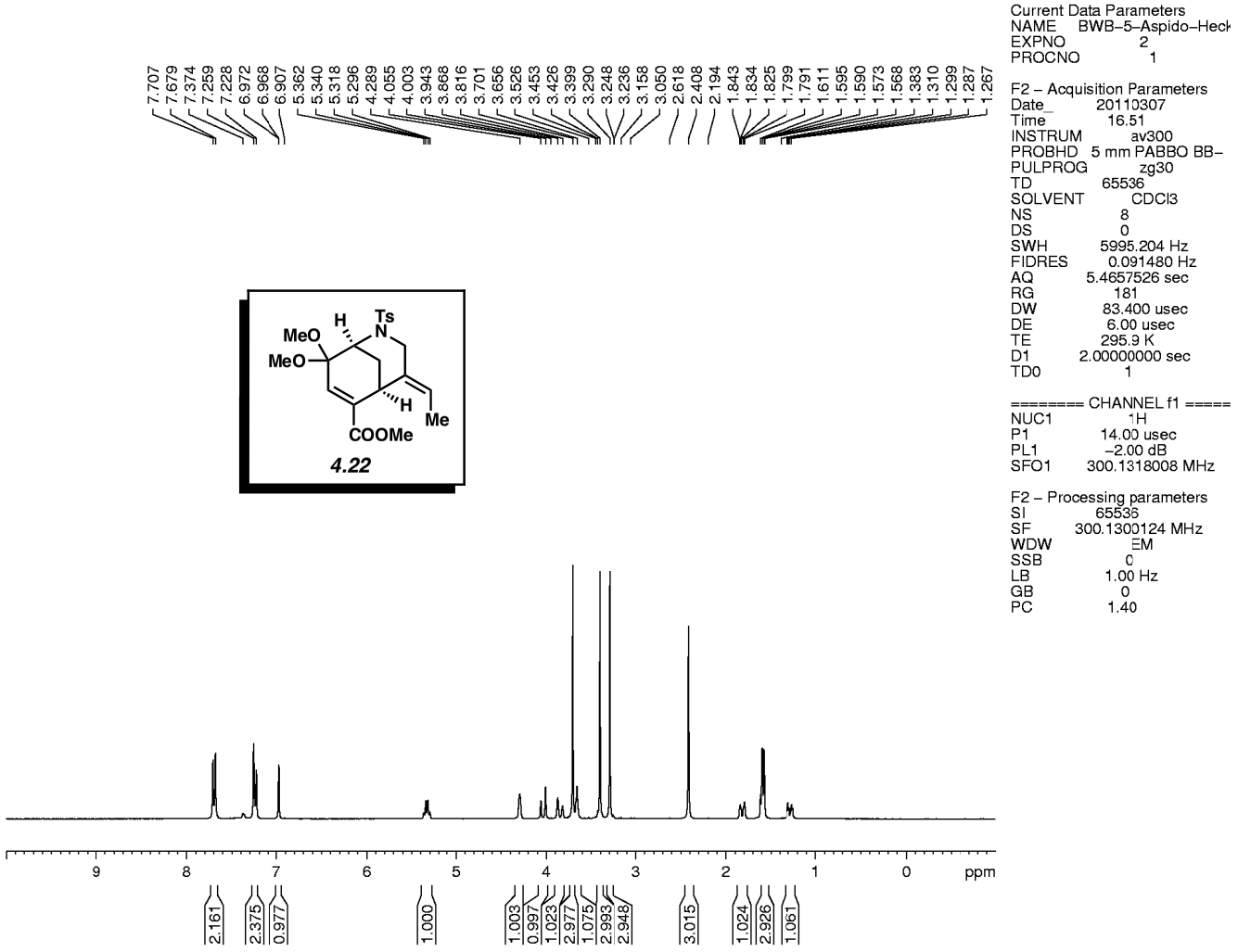


Figure A3.16 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **4.22**.

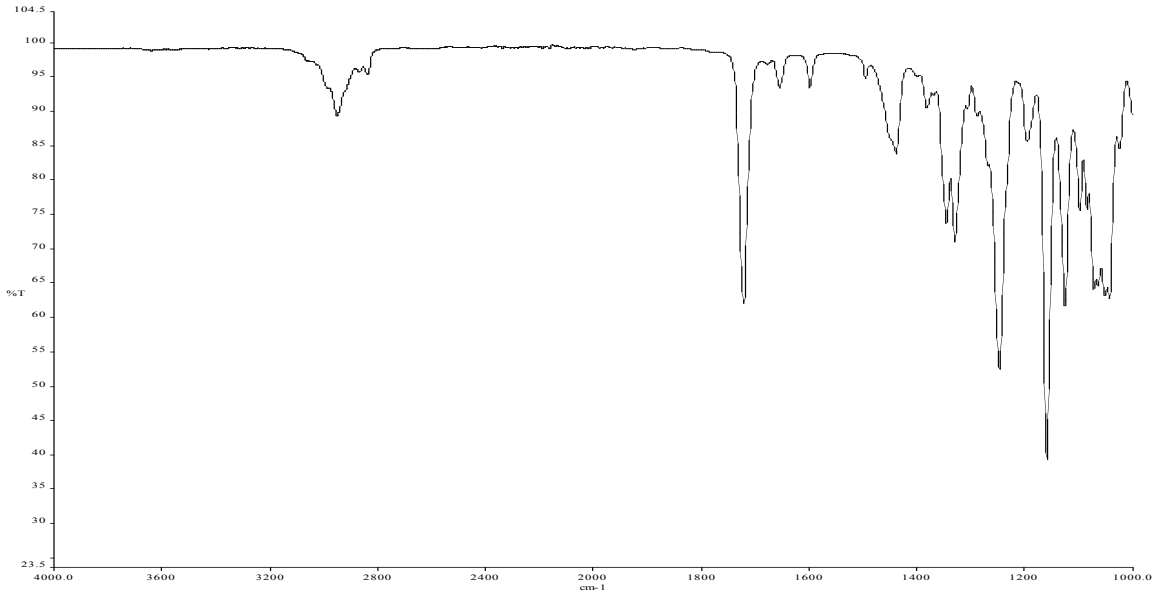


Figure A3.17 Infrared spectrum of compound **4.22**.

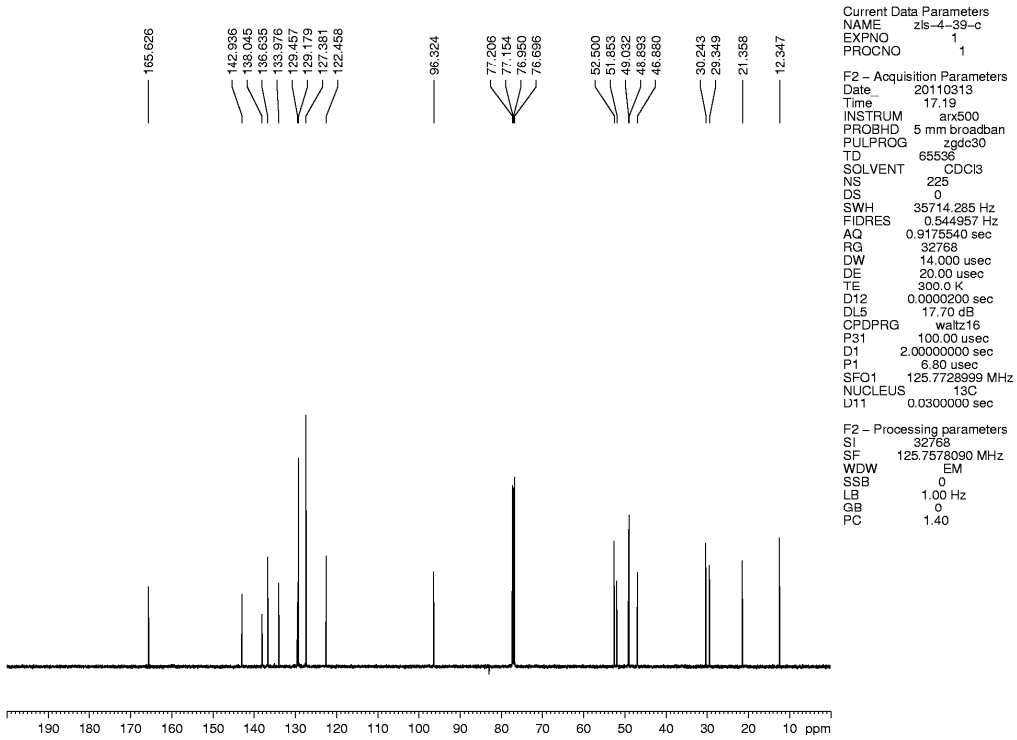


Figure A3.18 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4.22**.

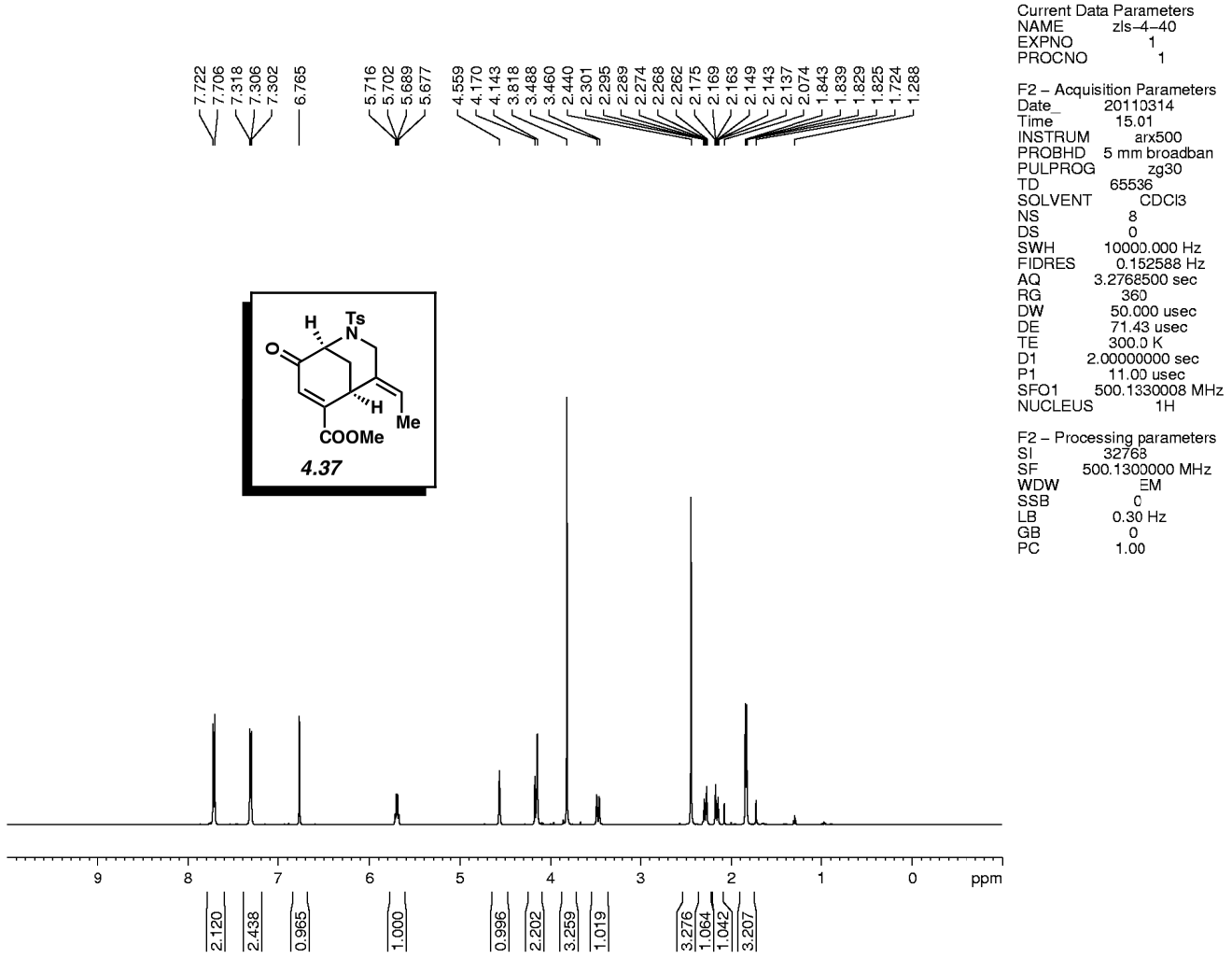


Figure A3.19 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.37**.

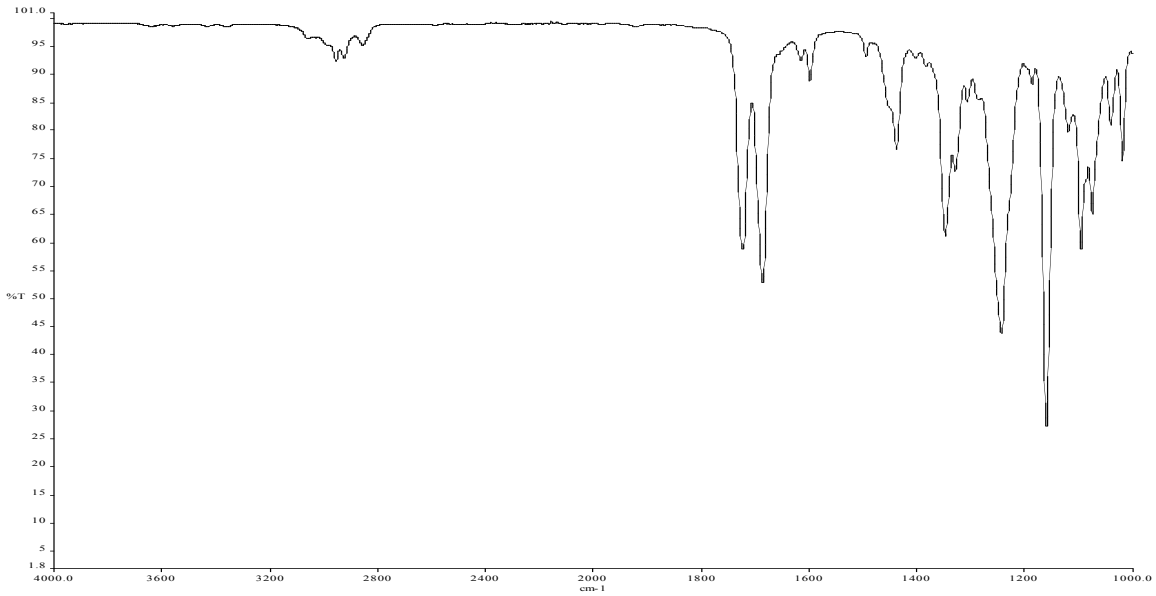


Figure A3.20 Infrared spectrum of compound **4.37**.

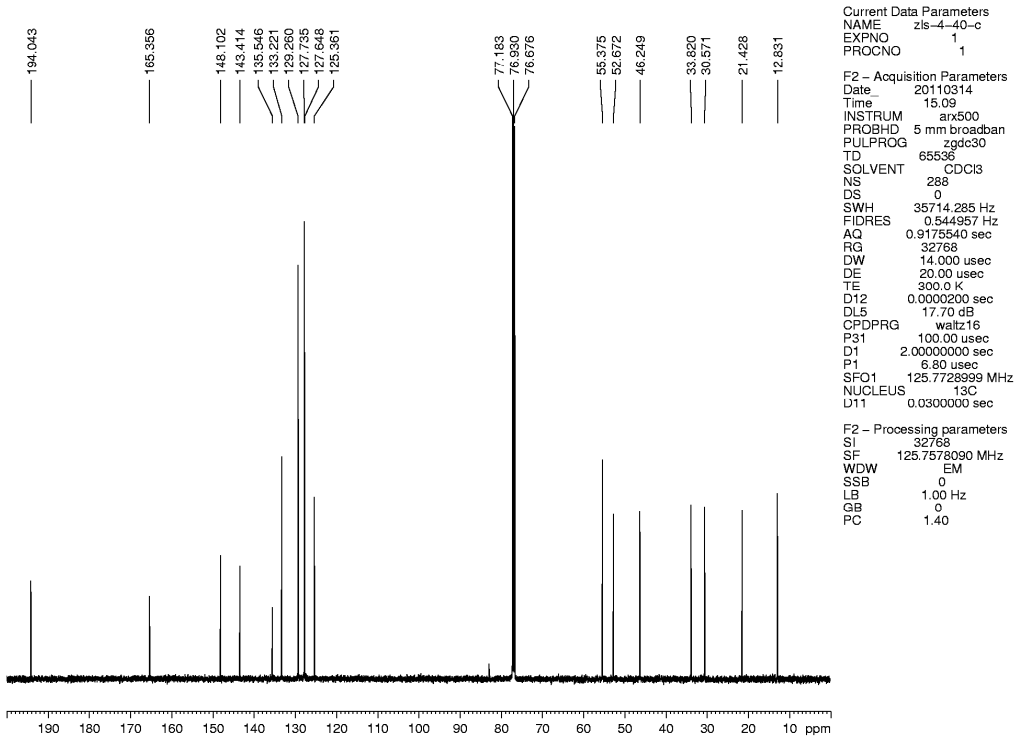


Figure A3.21 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4.37**.

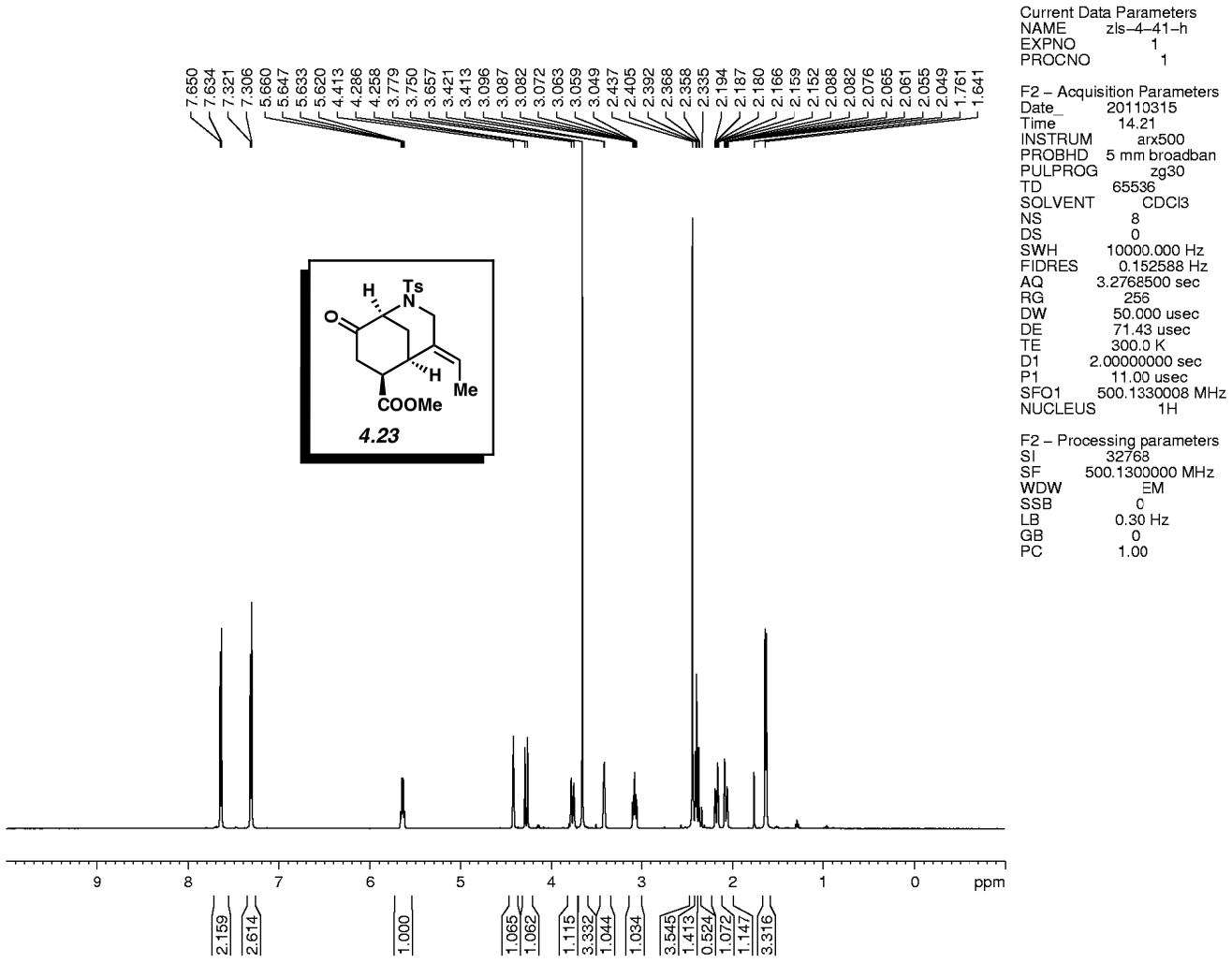


Figure A3.22 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.23**.

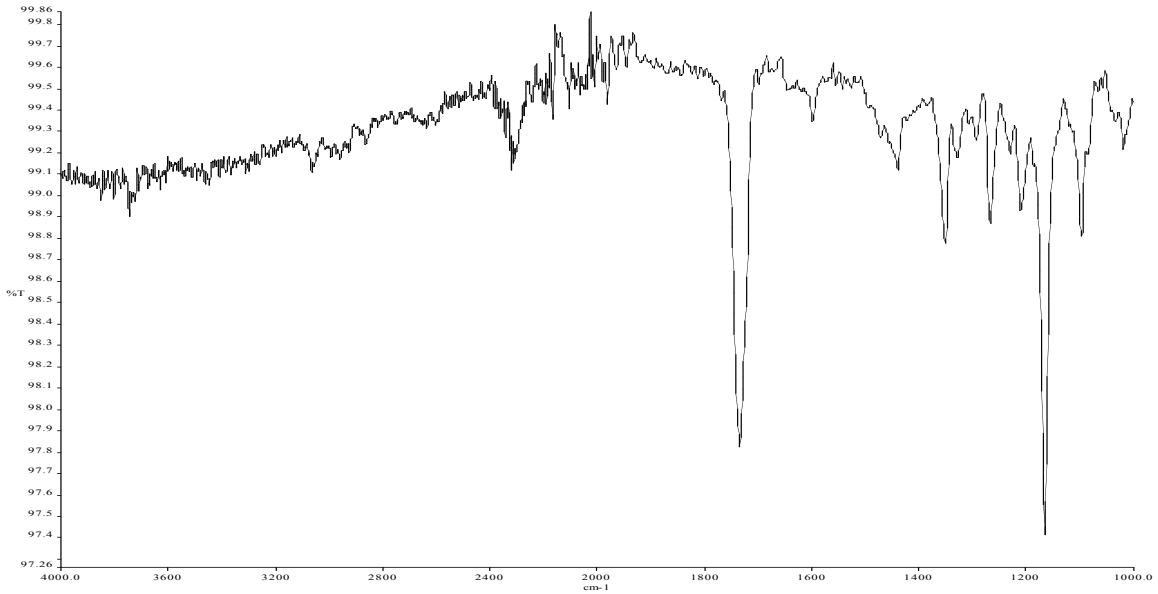


Figure A3.23 Infrared spectrum of compound **4.23**.

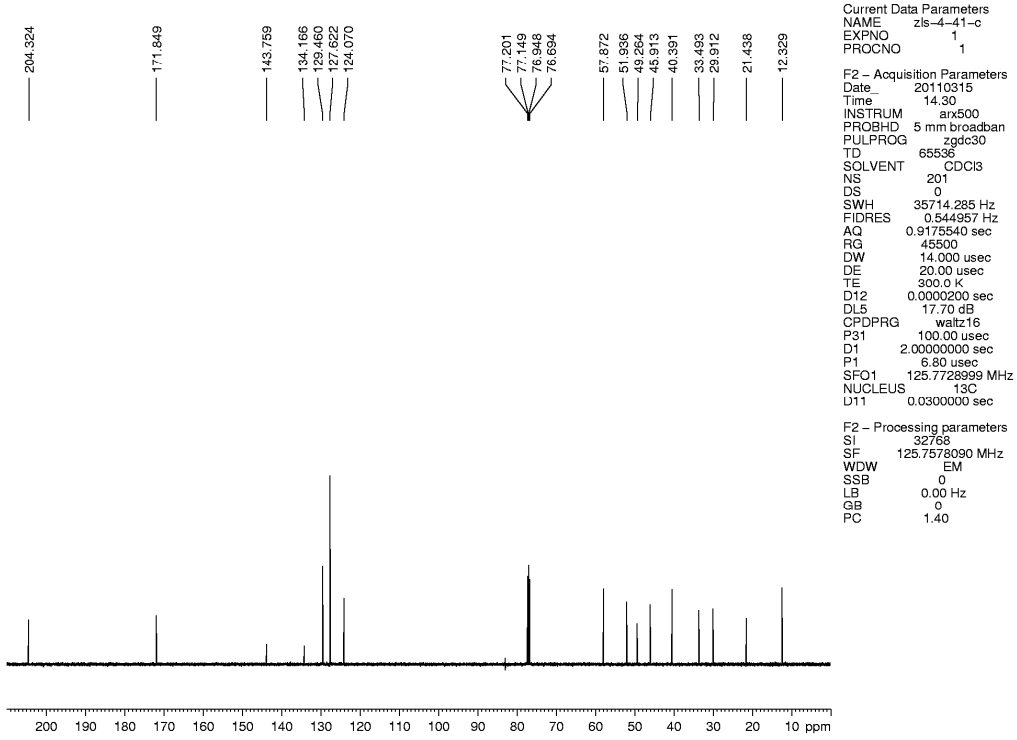


Figure A3.24 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4.23**.

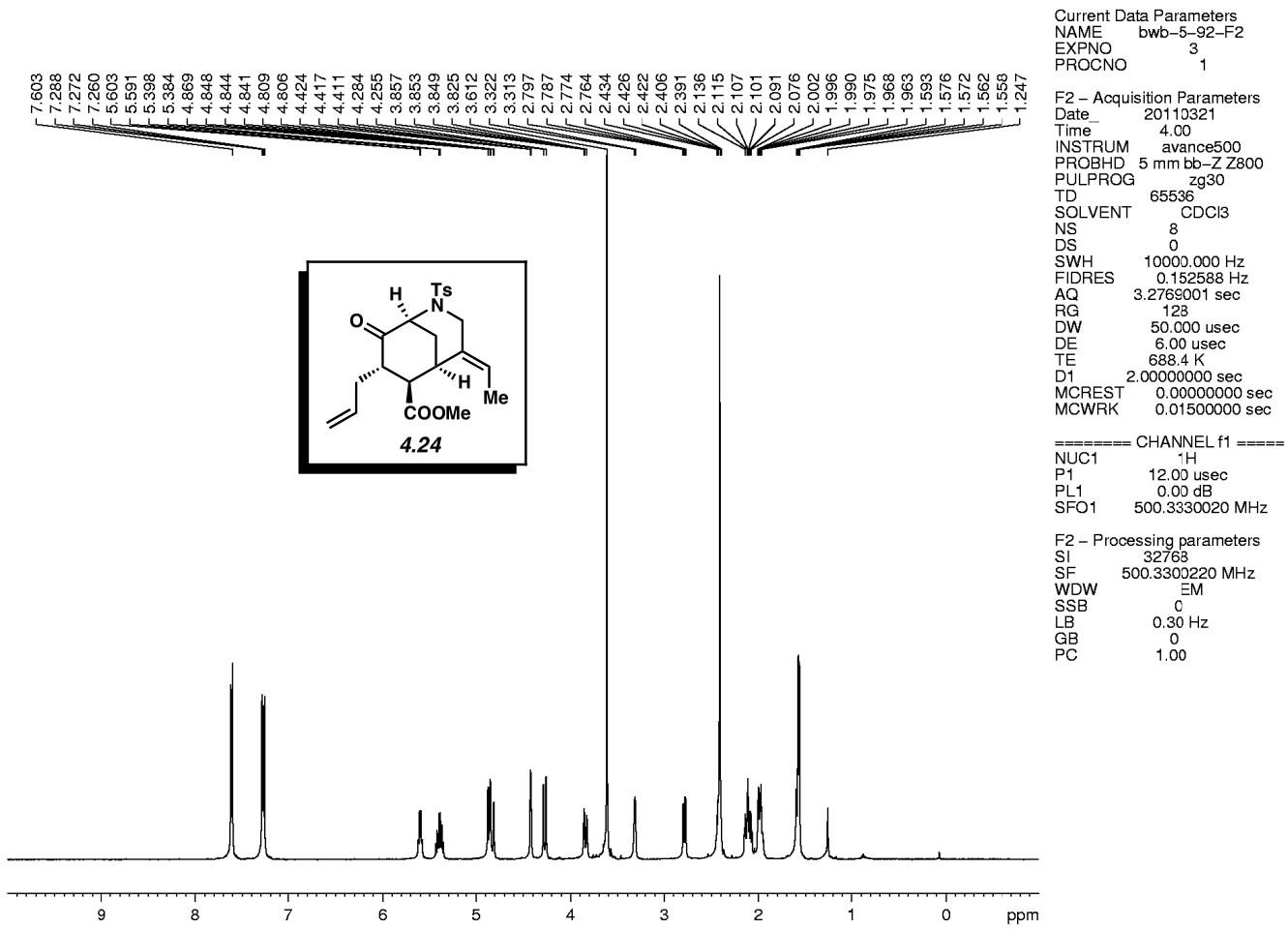


Figure A3.25 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.24**.

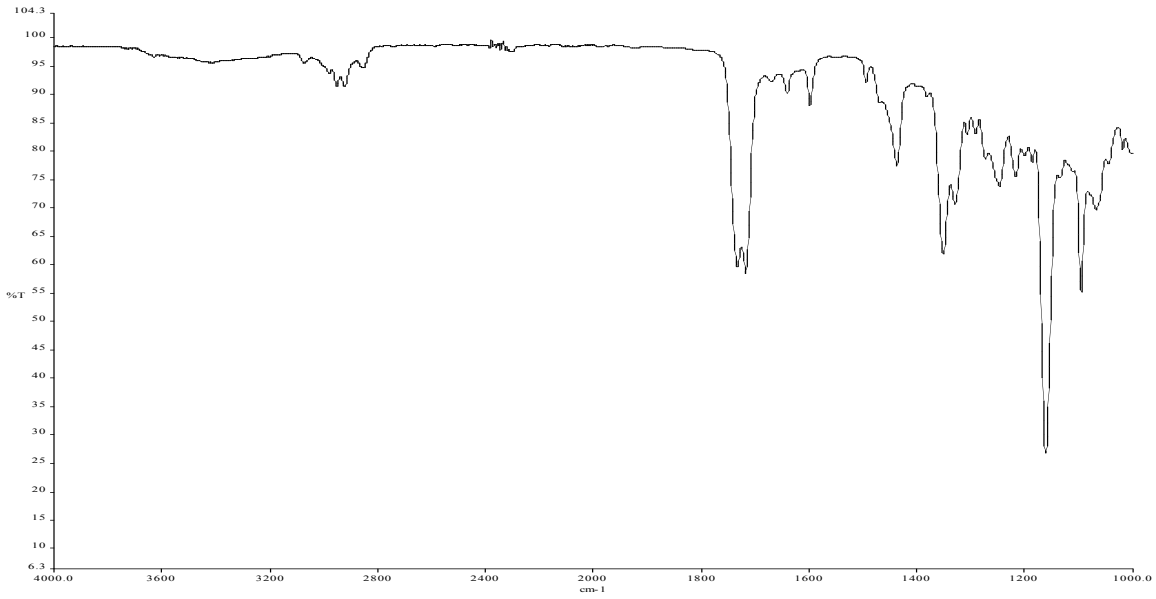


Figure A3.26 Infrared spectrum of compound **4.24**.

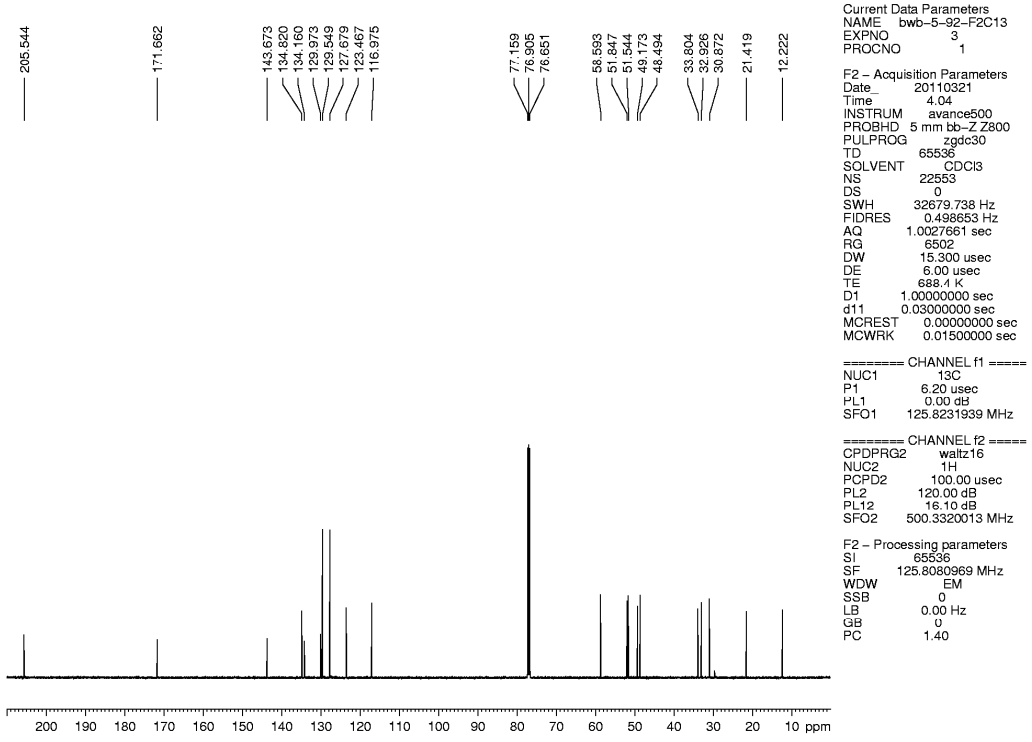


Figure A3.27 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4.24**.

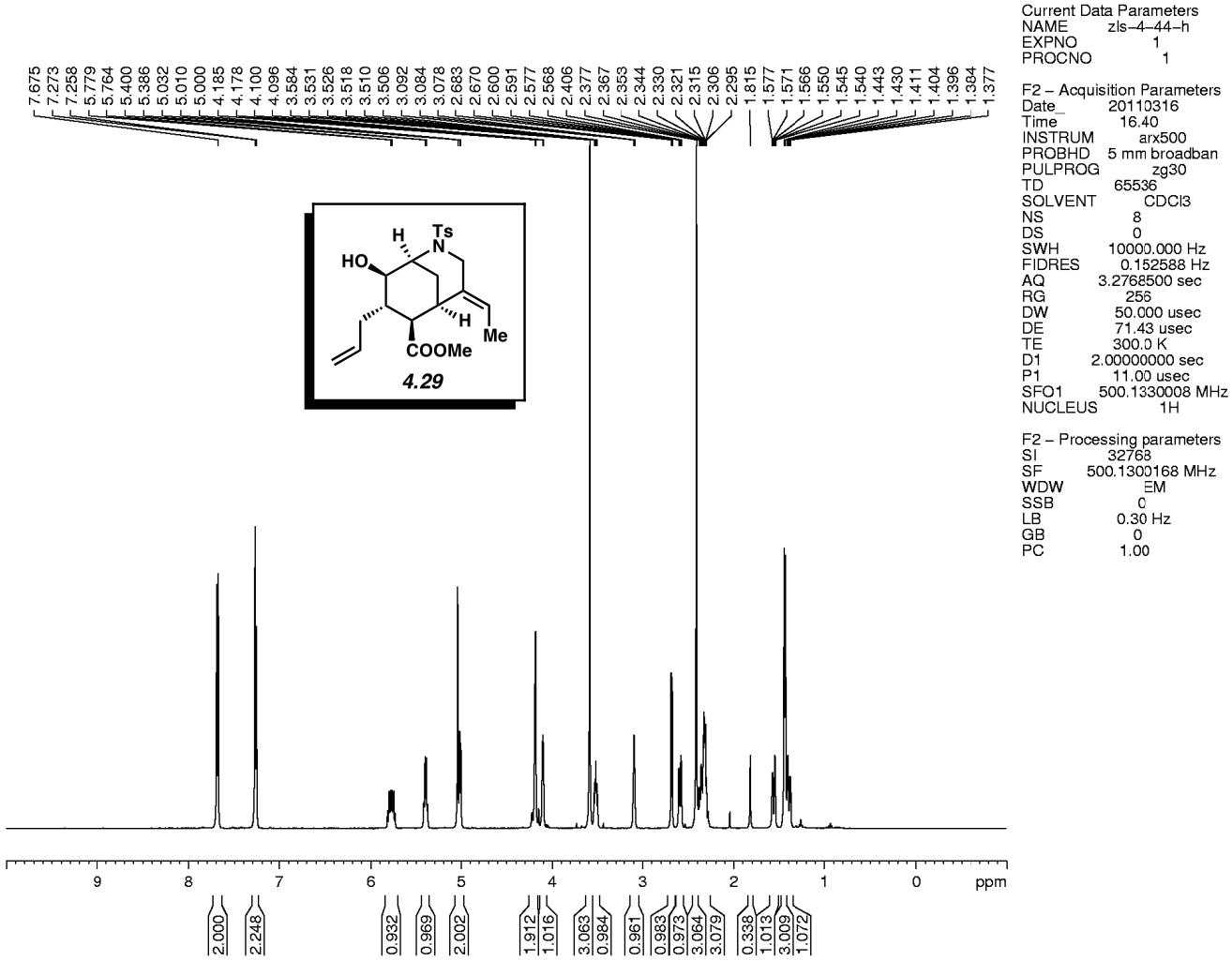


Figure A3.28 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.29**.

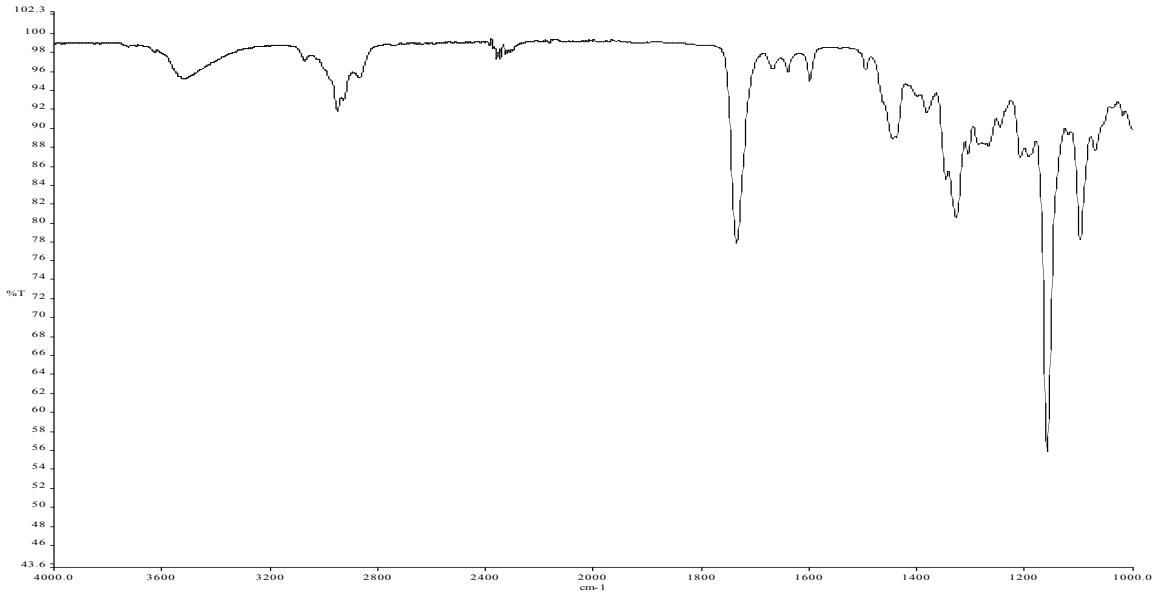


Figure A3.29 Infrared spectrum of compound **4.29**.

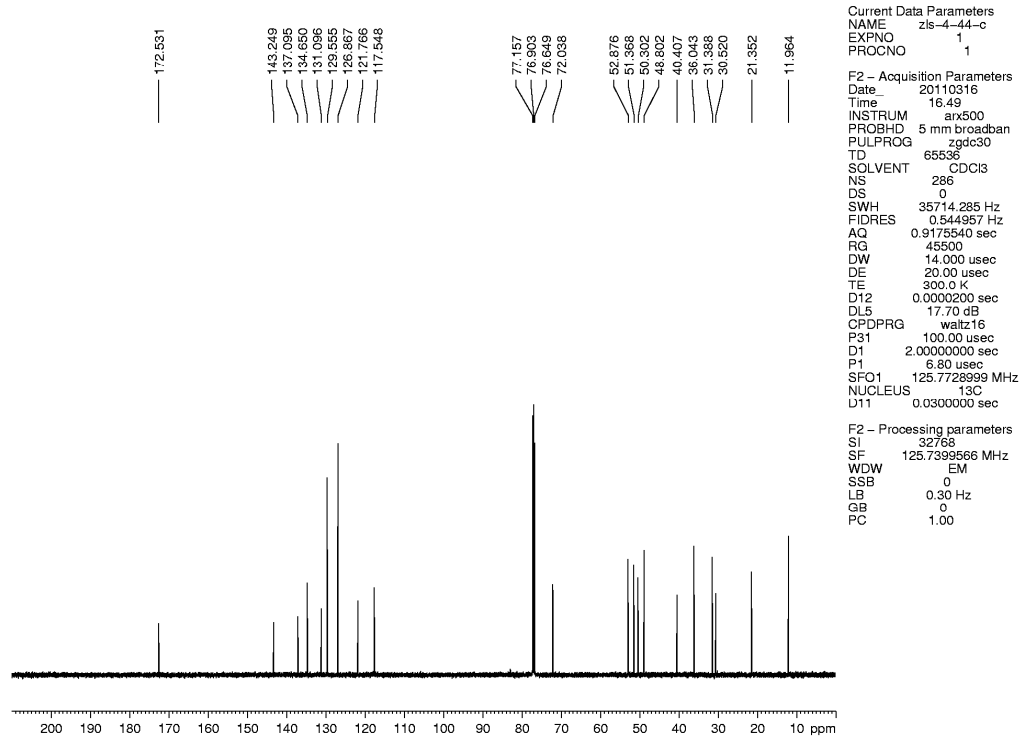


Figure A3.30 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4.29**.

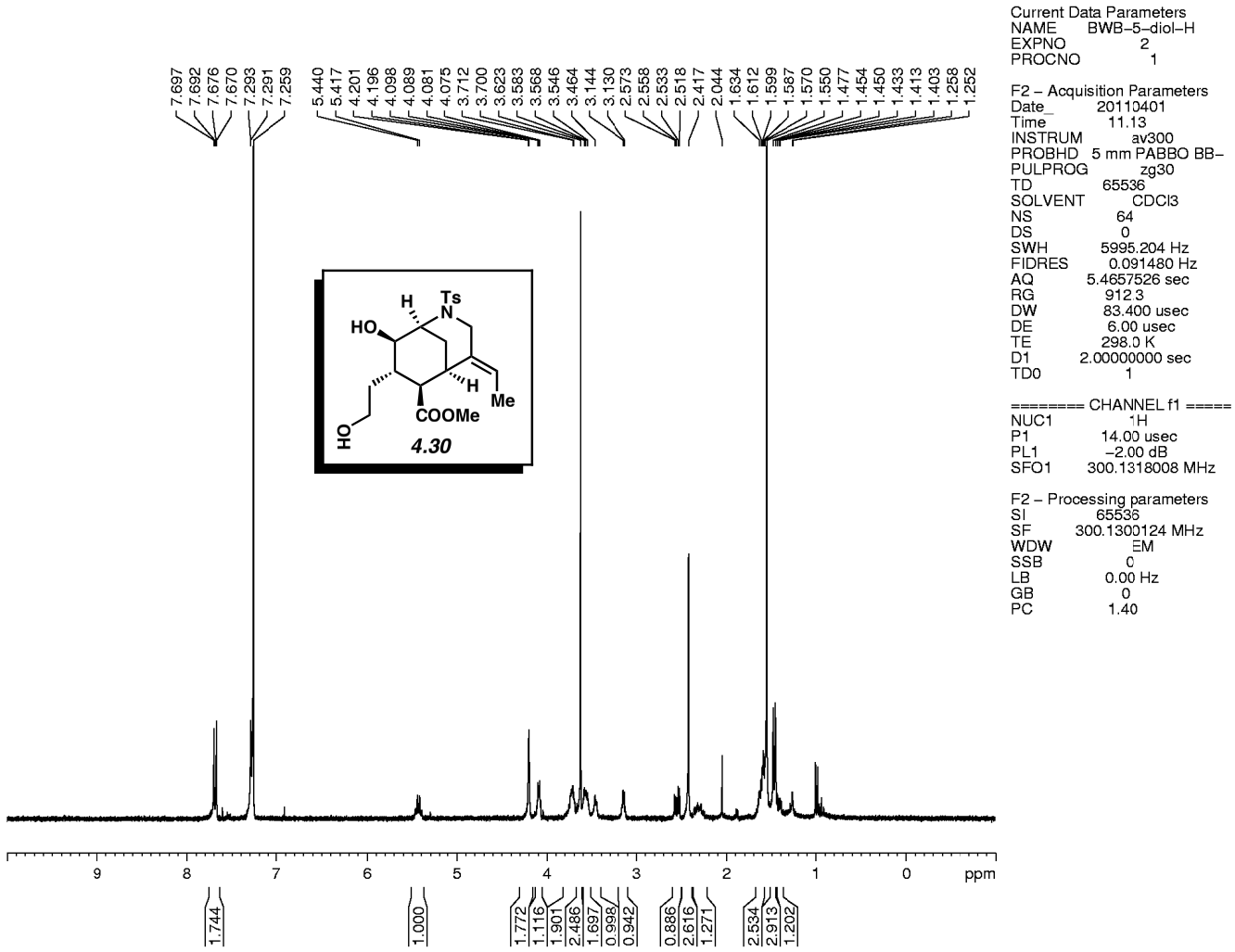


Figure A3.31 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.30**.

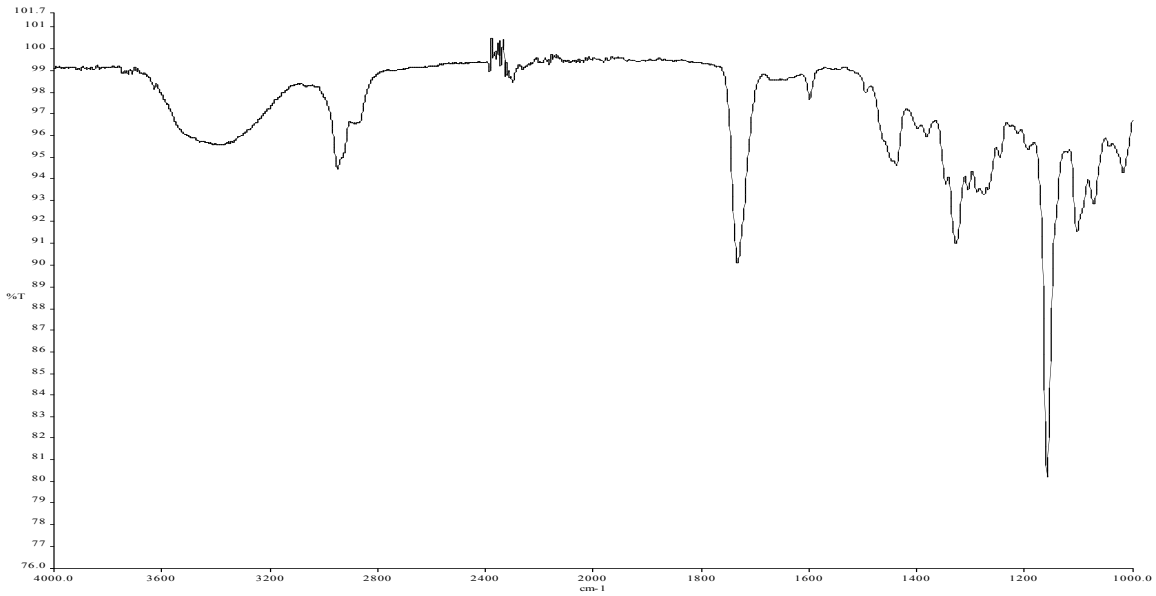


Figure A3.32 Infrared spectrum of compound **4.30**.

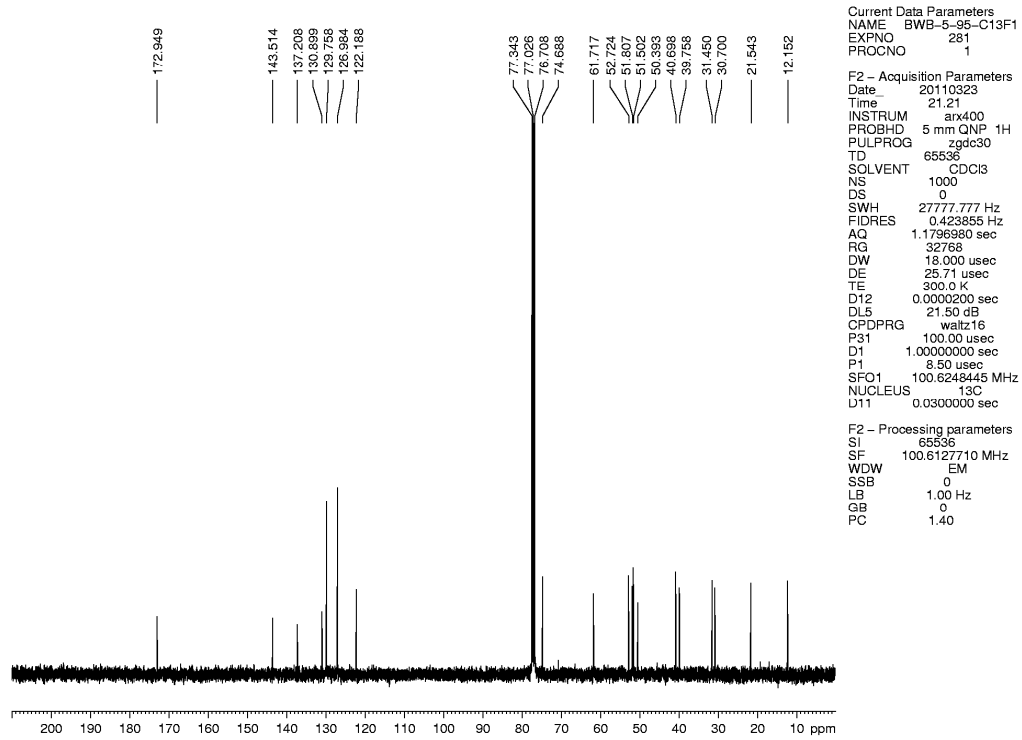


Figure A3.33 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4.30**.

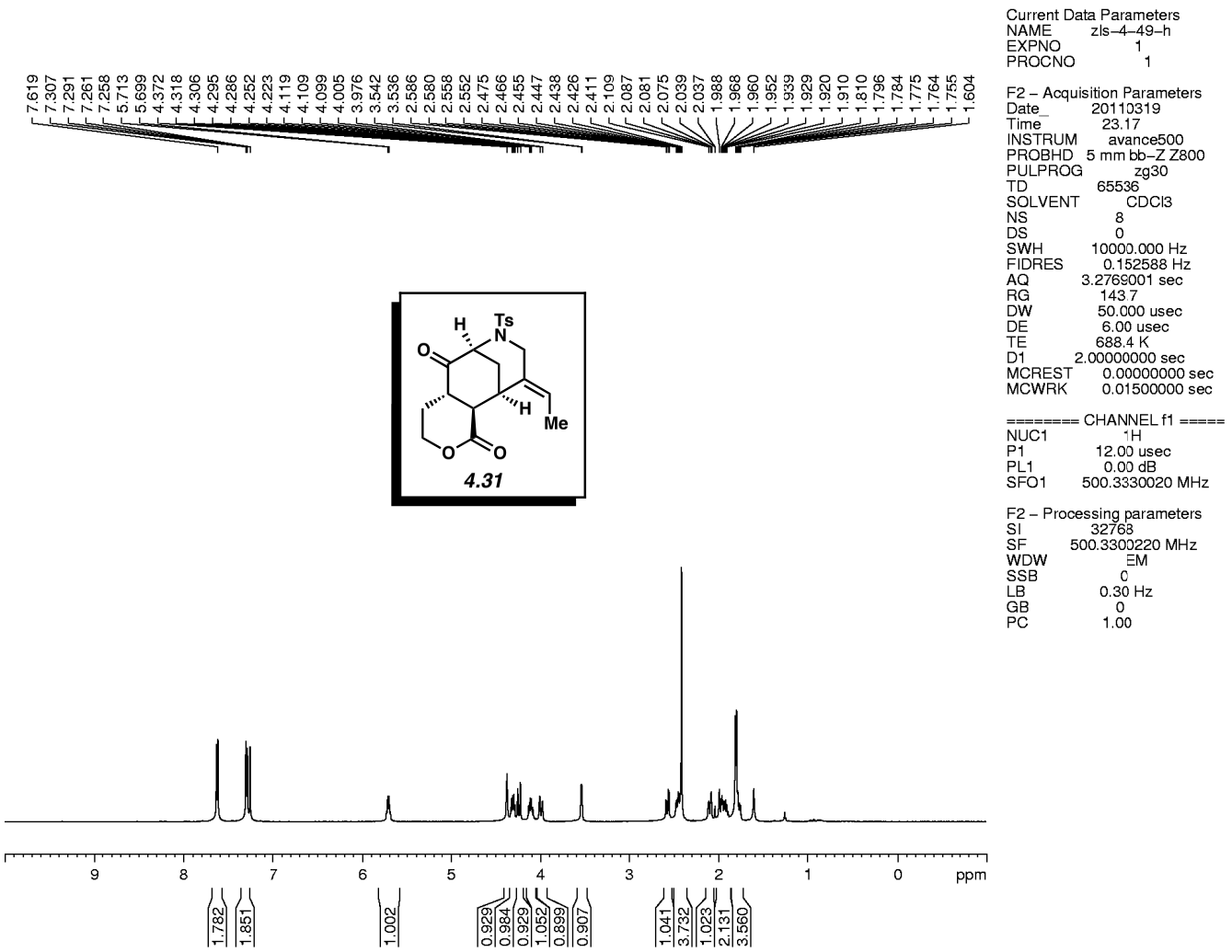


Figure A3.34 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.31**.

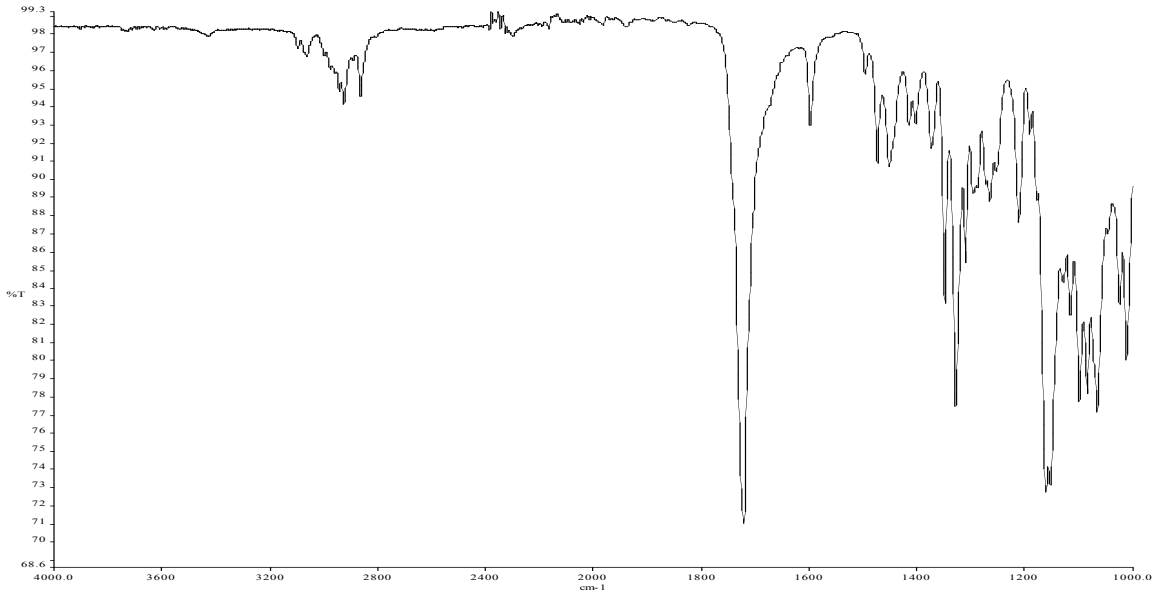


Figure A3.35 Infrared spectrum of compound **4.31**.

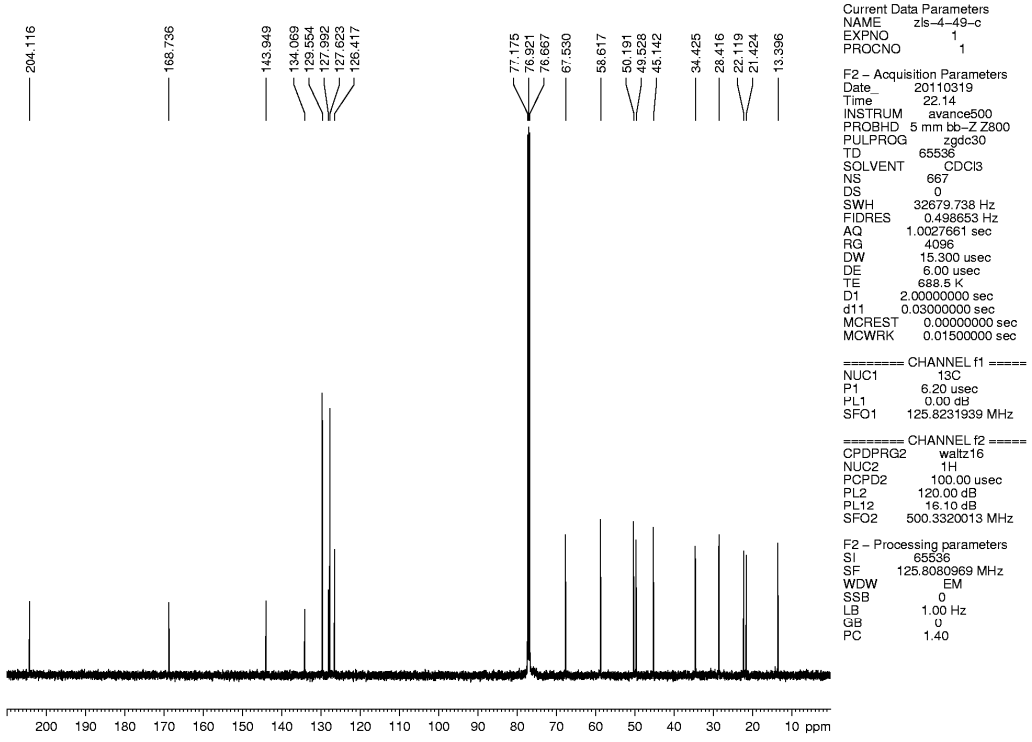


Figure A3.36 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4.31**.

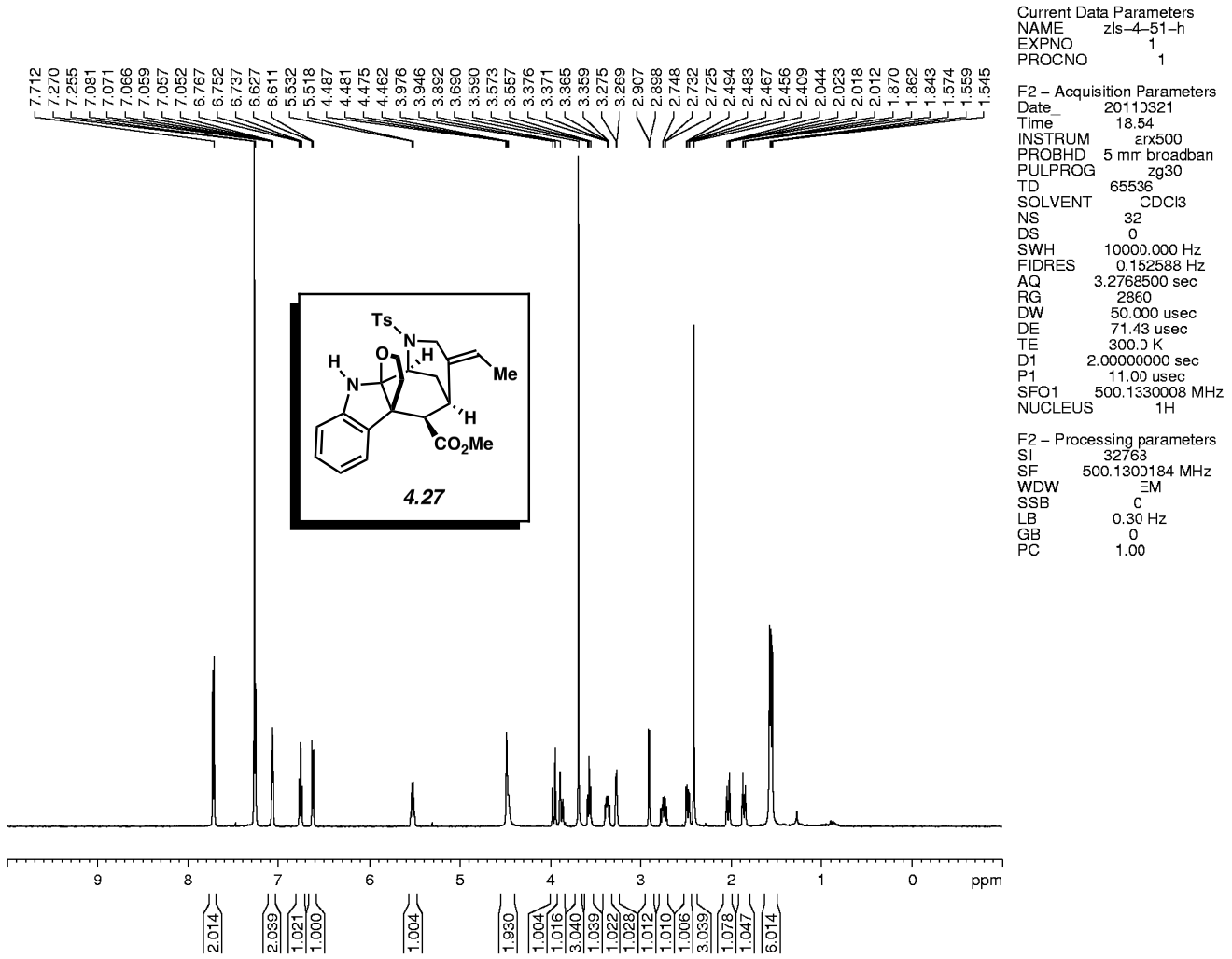


Figure A3.37 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.27**.

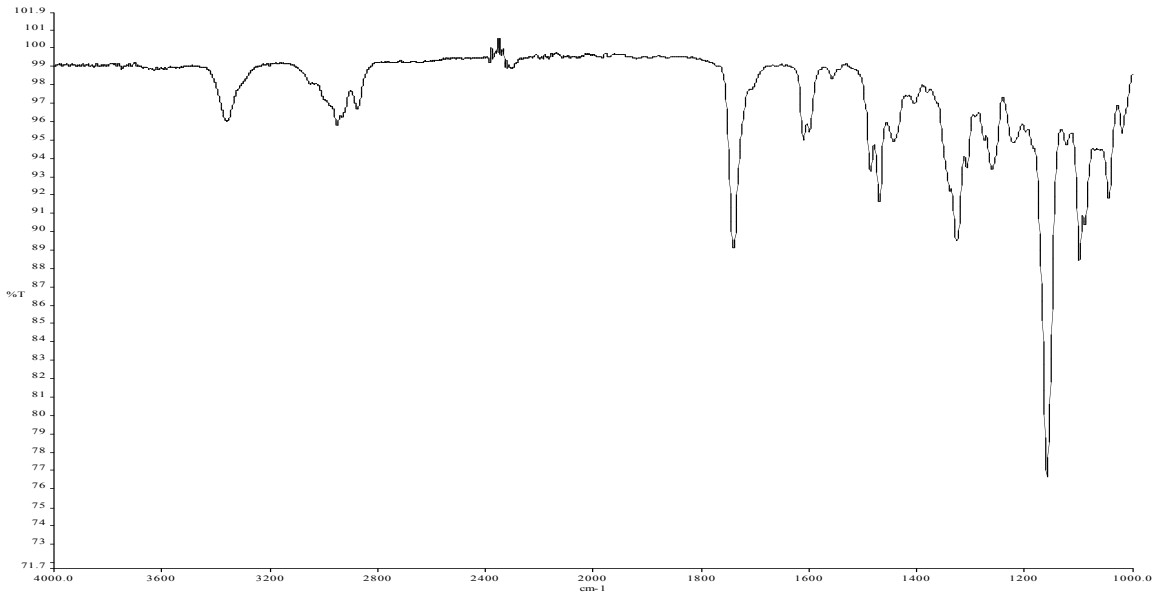


Figure A3.38 Infrared spectrum of compound **4.27**.

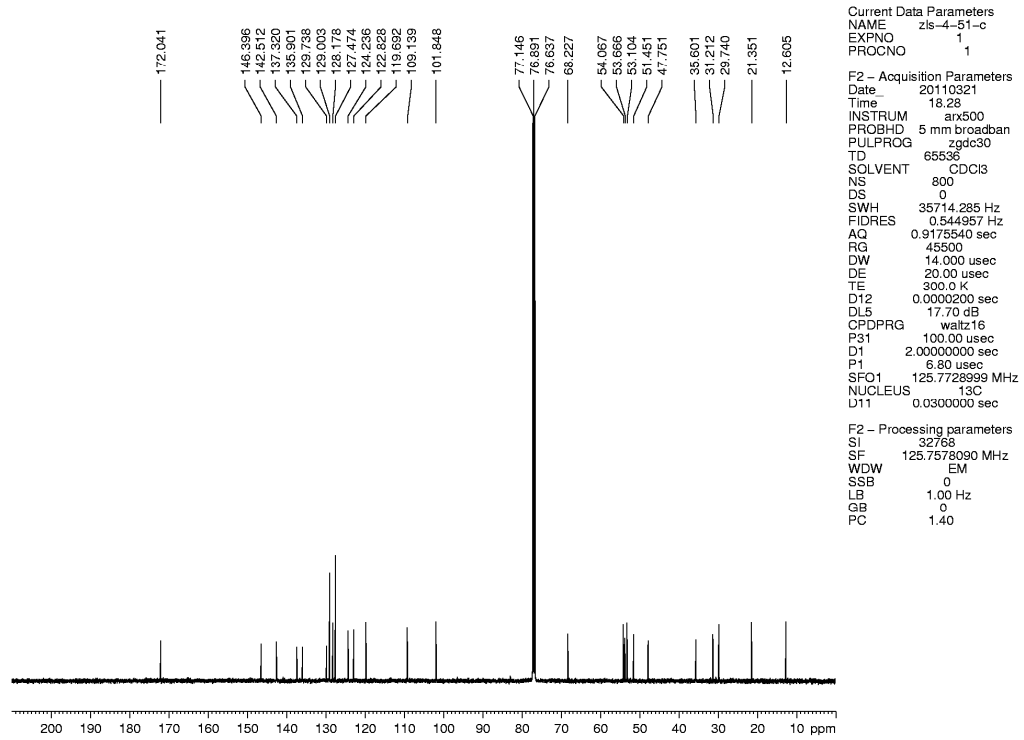
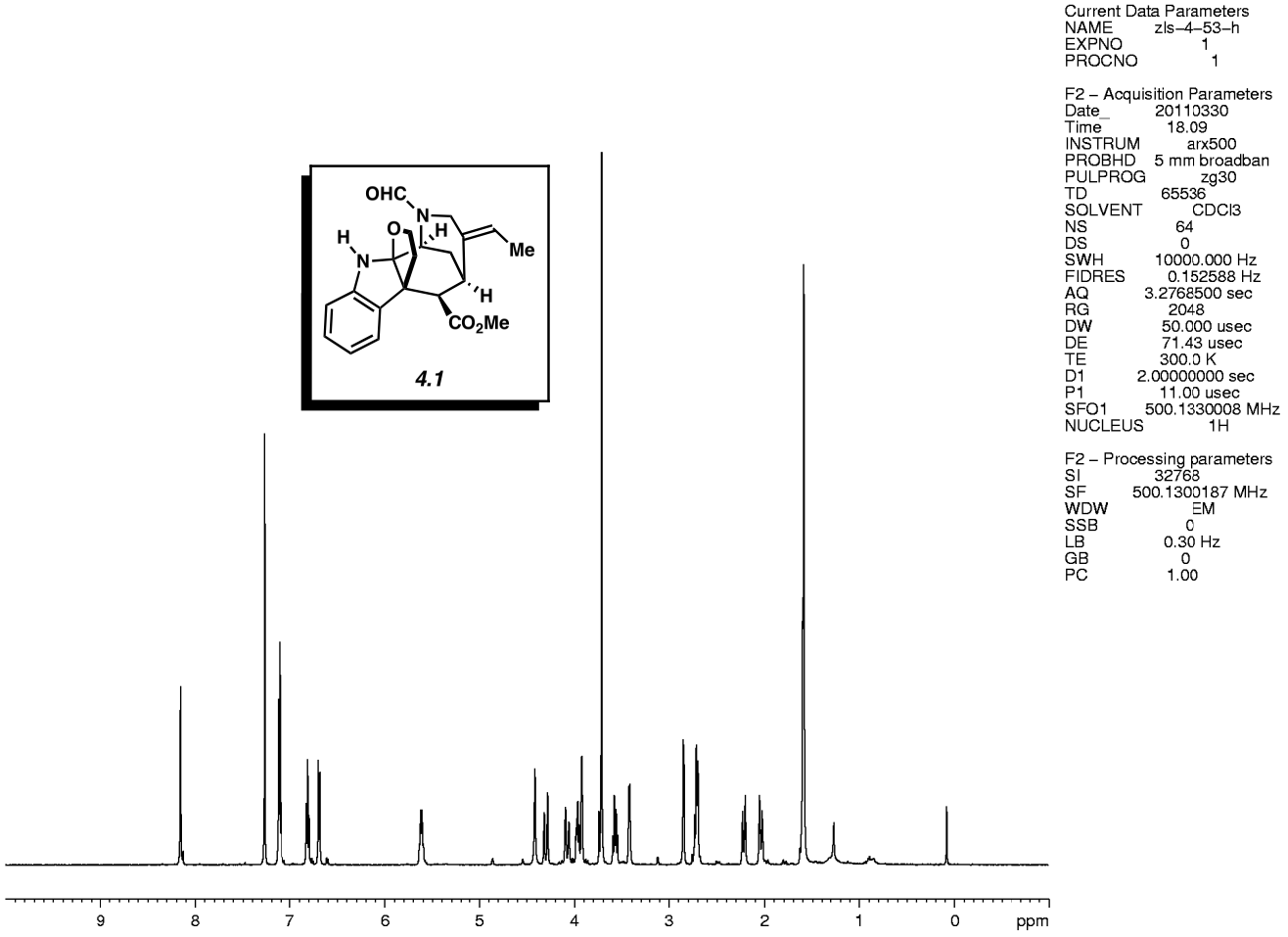


Figure A3.39 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4.27**.



Current Data Parameters
NAME zls–4–53–h
EXPNO 1
PROCNO 1

F2 – Acquisition Parameters
Date_ 20110330
Time 18.09
INSTRUM arx500
PROBHD 5 mm broadban
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 64
DS 0
SWH 10000.000 Hz
FIDRES 0.152588 Hz
AQ 3.2768500 sec
RG 2048
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 500.1300187 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

Figure A3.40 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.1**.

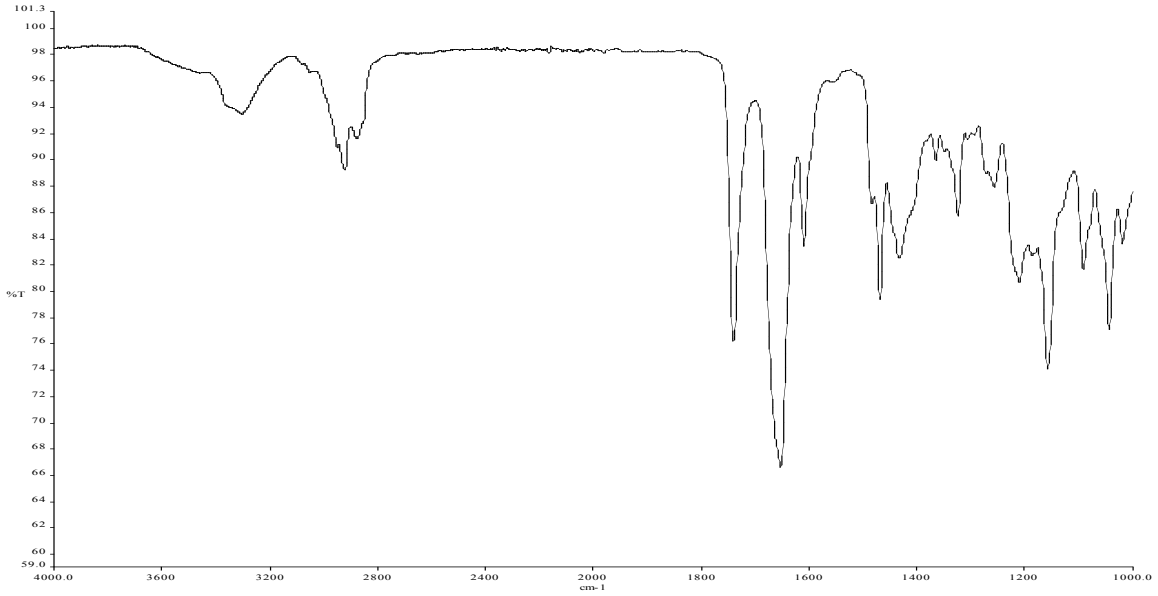


Figure A3.41 Infrared spectrum of compound **4.1**.

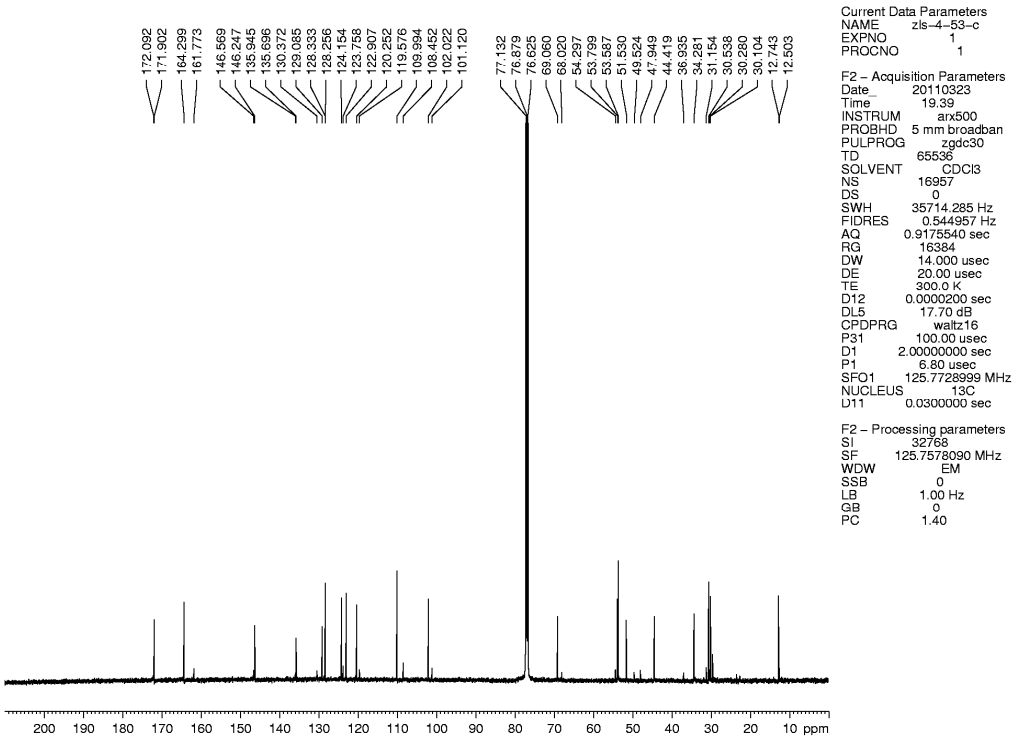


Figure A3.42 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4.1**.