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Enantiospecific Total Synthesis of Welwitindolinone Alkaloids

A dissertation submitted in partial satisfaction of the

requirements for the degree Doctor of Philosophy

in Chemistry

by

Evan Daniel Styduhar

2015

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ABSTRACT OF THE DISSERTATION

Enantiospecific Total Synthesis of Welwitindolinone Alkaloids

by

Evan Daniel Styduhar

Doctor of Philosophy in Chemistry

University of California, Los Angeles, 2015

Professor Neil K. Garg, Chair

Chapter one provides a summary of efforts towards the syntheses of the welwitindolinones with bicyclo[4.3.1]decane cores. Emphasis is given to more recent approaches that have successfully assembled the bicyclic core of the natural products. Chapters two, three, and four present our total syntheses of the welwitindolinone natural products. The enantiospecific total syntheses of *N*-methylwelwitindolinone C isothiocyanate, *N*-methylwelwitindolinone D isonitrile, and *N*-methylwelwitindolinone B isothiocyanate are detailed. The approach to these natural products features an aryne cyclization to construct the bicyclo[4.3.1]decane core of the molecules as well as a C–H nitrene insertion reaction to install the bridgehead nitrogen substituent. In chapter three, a dual C–H functionalization event installs the challenging ether linkage and allows for completion of (–)-*N*-methylwelwitindolinone D

isonitrile. Chapter four details a regio- and diastereoselective chlorinative oxabicyclic opening to enable the first total synthesis of *N*-methylwelwitindolinone B isothiocyanate.

The dissertation of Evan Daniel Styduhar is approved.

Kendall N. Houk

Tatiana Segura

Neil K. Garg, Committee Chair

University of California, Los Angeles

2015

For Kari, John, Drew, and Sonam

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LIST OF ABBREVIATIONS

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

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

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

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

ACKNOWLEDGEMENTS

I would like to start by thanking Professor Neil K. Garg, whose mentorship and guidance has no doubt helped shape me into the person I am today. From the very first step I set into Neil's laboratory, his infectious excitement for chemistry and endless amount of energy has enabled a creative, productive, and fun environment to carry out research in. Not only can I say that Neil has been a wonderful dissertation advisor, but also a great friend as well. For these reasons and many others, I am so very appreciative of Neil's support throughout my doctoral studies at UCLA and contribution to my scientific development.

I would also like to extend thanks to staff and faculty of the Department of Chemistry & Biochemistry at UCLA. Specifically, I would like to thank Professor Patrick Harran for teaching Strategy and Design in Organic Synthesis. His class was among one of my favorites at UCLA and gave me new perspective on how to approach total synthesis. Additionally, I would like to thank Professor Kendall N. Houk for his support as a member of my dissertation committee and also his willingness to help or advise at the drop of a hat. Lastly, I would like to thank my other committee members Professors Richard Weiss and Tatiana Segura.

I would also like to thank staff and faculty of the Department of Chemistry at Oregon State University. Specifically, I would like to thank Dr. Alexey Shvarev and Professor Rich Carter for allowing me to conduct research in their laboratories as an undergraduate student. Additionally, I would like to thank Professor Glenn Evans for his support and hilarious discussions during Physical Chemistry office hours.

I would like to extend my gratitude toward fellow members of the Garg laboratory that I have been fortunate to overlap with. There is no doubt in my mind that their encouragement,

jokes, and tough love has kept me together throughout the rigors of the program. Specifically, I would like most to recognize members of the Welwitindolinone project: Dr. Kyle Quasdorf, Dr. Alex Huters, Nick Weires, and Emma Baker for their camaraderie and technical support through even the toughest spells. We did great work, and I am very lucky to have been beside you all during those exciting times. Specifically, Kyle and Alex were excellent mentors when I first joined the project. Since then, I have passed on my life lessons to Nick Weires and Emma Baker, who have been absolutely instrumental in seeing the project to its end. Additionally, Dr. Travis McMahon (Machine) and Joyann Barber comprise my newer group of coworkers, which has been an equally rewarding experience. I am very lucky to have worked with such a talented and hard-working group of people.

Beyond those who I have directly worked alongside, I am indebted to a number of people in the Garg laboratory. Specifically, I would like to thank Dr. Adam Goetz for hiking trips and portmanteaus, and Dr. Stephen Ramgren for his sense of humor and lake trips. Adam and Stephen have served as intellectual beacons that I will forever strive toward, and I am very lucky to have met them. Additionally, I would like to thank Dr. Travis McMahon for his friendship and brewing skills, Nick Weires for his hilarious personality, incredible taste in music, and absolute chemical wizardry in the Wit B synthesis, Dr. Tehetena Mesganaw for her tough love and constant encouragement, Dr. Sarah Bronner for her continued friendship and kitty talks, and Tejas Shah for being a great friend all around. All other members of the Garg laboratory with whom I overlapped, including Professor Liansuo Zu, Dr. Alex Schammel, Dr. Ben Boal, Dr. Grace Chiou, Dr. Amanda Silberstein, Dr. Joel Smith, Noah Fine Nathel, Liana Hie, Jesus Moreno, Jose Medina, Mike Corsello, Elias Picazo, Junyong Kim, Lucas Morrill, and Bryan

Simmons, have all been amazing to work alongside and I look forward to crossing paths with them in the future.

Finally, I would like to thank my friends and family for their endless encouragement and support. Specifically, my parents Kari Boddington and John Styduhar have always remained supportive of my interests and allowed me to learn from making my own mistakes. Their unwavering love has helped to make me the person I am today and I am forever grateful for all they have provided. I also thank my brother Drew, who always has something in store for me during my visits home, with the most important being our multi-player, multi-hour long Starcraft games. Lastly, I thank Sonam Kumar for the wonderful years we have spent together. You are the smartest person I know and you challenge me every day. I cannot wait to see where life takes us, and knowing you will be at my side makes it all worth it. I love you.

Chapter 1 is a version of Huters, A. D.; Styduhar, E. D.; Garg, N. K. *Angew. Chem., Int. Ed.* **2012**, *51*, 3758–3765. Huters, Styduhar, and Garg were responsible for writing the manuscript.

Chapter 2 is a version of Huters, A. D.; Quasdorf, K. W.; Styduhar, E. D.; Garg, N. K. *J. Am. Chem. Soc.* **2011**, *133*, 15797–15799. Huters, Quasdorf, and Styduhar were responsible for experimental work.

Chapter 3 is a version of Styduhar, E. D.; Huters, A. D.; Weires, N. A.; Garg, N. K. *Angew. Chem., Int. Ed.* ***2013****, 52, 12422–12425*. Styduhar, Huters, and Weires were responsible for experimental work.

Chapter 4 is a version of Weires, N. A.; Styduhar, E. D.; Baker, E. L.; Garg, N. K. *J. Am. Chem. Soc.* **2014**, *136*, 14710–14713. Weires, Styduhar, and Baker were responsible for experimental work.

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- Completed an enantiospecific total synthesis of (–)-*N*-methylwelwitindolinone B isothiocyanate using a late-stage oxazolidinone cleavage event.
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Publications:

1. **Total Synthesis of (–)-*N*-Methylwelwitindolinone C Isothiocyanate.** Alexander D. Huters, Kyle W. Quasdorf, Evan D. Styduhar, and Neil K. Garg. *J. Am. Chem. Soc.* **2011**, *133*, 15797–15799 *(featured in C&E News)*.
2. **Total Syntheses of the Elusive Welwitindolinones with Bicyclo[4.3.1]decane Cores.** Alexander D. Huters, Evan D. Styduhar, and Neil K. Garg. *Angew. Chem. Int. Ed.* **2012**, *51*, 3758–3765.
3. **Enantiospecific Total Synthesis of *N*-Methylwelwitindolinone D Isonitrile.** Evan D. Styduhar, Alexander D. Huters, Nicholas A. Weires, and Neil K. Garg. *Angew. Chem. Int. Ed.* **2013**, *52*, 12422–12425. *Highlighted in*: *Synfacts* **2014**, *10*, 11.
4. **Total Synthesis of (–)-*N*-Methylwelwitindolinone B Isothiocyanate via a Chlorinative Oxabicycle Ring-Opening Strategy.** Nicholas A. Weires,[†] Evan D. Styduhar,[†] Emma L. Baker, and Neil K. Garg. *J. Am. Chem. Soc.* **2014**, *136*, 14710–14713. *Highlighted in*: *Synfacts* **2015**, *11*, 11.

Presentations:

1. **Progress Toward the Total Synthesis of *N*-Methylwelwitindolinone C Isothiocyanate.** Alexander D. Huters, Kyle W. Quasdorf, Evan D. Styduhar, Neil K. Garg. Poster, 241st ACS National Meeting, Anaheim, CA, United States, March, 2011, ORGN-4.
2. **Total Synthesis of *N*-Methylwelwitindolinone C Isothiocyanate.** Alexander D. Huters, Kyle W. Quasdorf, Evan D. Styduhar, Neil K. Garg. Poster, Glenn T. Seaborg Symposium, Los Angeles, CA, United States, November, 2011.
3. **Total Synthesis of *N*-Methylwelwitindolinone C Isothiocyanate.** Alexander D. Huters, Kyle W. Quasdorf, Evan D. Styduhar, Neil K. Garg. Poster, 43rd ACS Western Regional Meeting, Pasadena, CA, United States, November, 2011.
4. **Enantiospecific Total Synthesis of *N*-Methylwelwitindolinone D Isonitrile.** Evan D. Styduhar, Alexander D. Huters, Nicholas A. Weires, Neil K. Garg. Poster, Glenn T. Seaborg Symposium, Los Angeles, CA, United States, October, 2013.
5. **Enantiospecific Total Synthesis of *N*-Methylwelwitindolinone D Isonitrile.** Evan D. Styduhar, Alexander D. Huters, Nicholas A. Weires, Neil K. Garg. Oral Presentation, 248th ACS National Meeting, San Francisco, CA, United States, August, 2014, ORGN-60.

6. **Enantiospecific Total Synthesis of *N*-Methylwelwitindolinone D Isonitrile.** Evan D. Styduhar, Alexander D. Huters, Nicholas A. Weires, Neil K. Garg. Poster, UCLA Research Showcase, San Francisco, CA, United States, August, 2014.

7. **Total Synthesis of (–)-N-Methylwelwitindolinone B Isothiocyanate.** Evan D. Styduhar, Nicholas A. Weires, Emma L. Baker, Neil K. Garg. Poster, UCLA Seaborg Symposium, Los Angeles, CA, United States, November, 2014.

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CHAPTER ONE

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

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

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

1.1 Abstract

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

1.2 Introduction

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

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

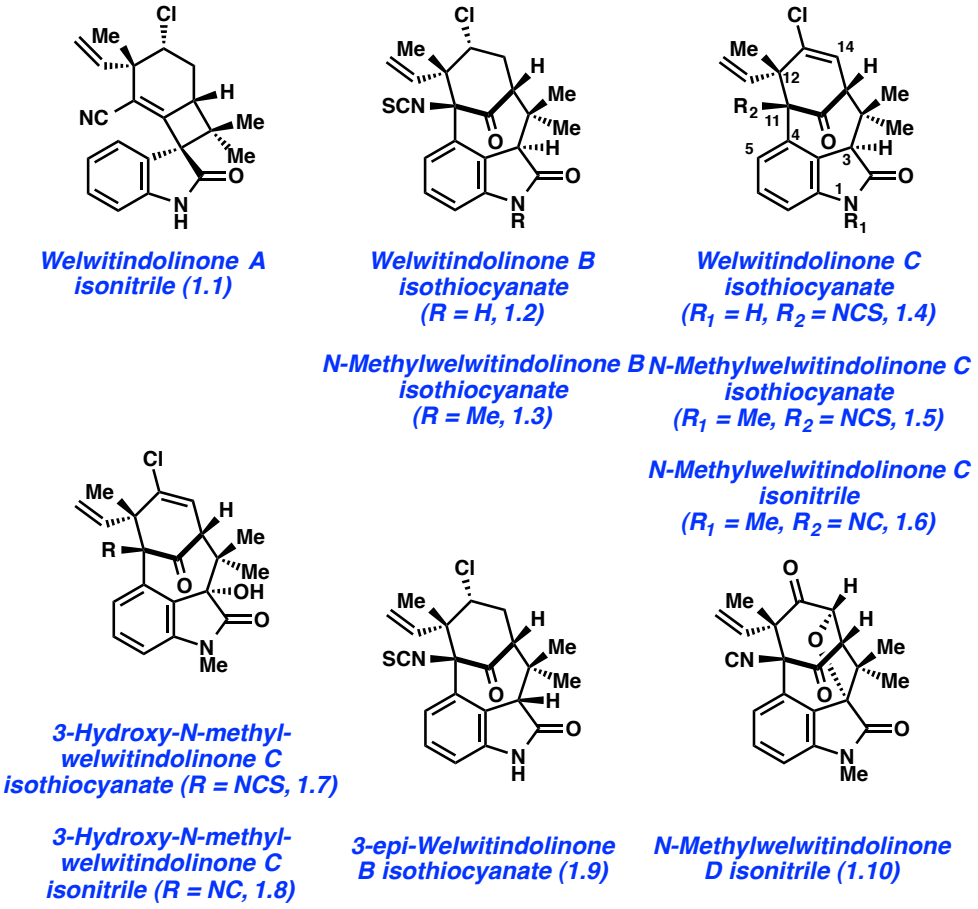


Figure 1.1. Welwitindolinone natural products **1.1**–**1.10**.

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

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

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

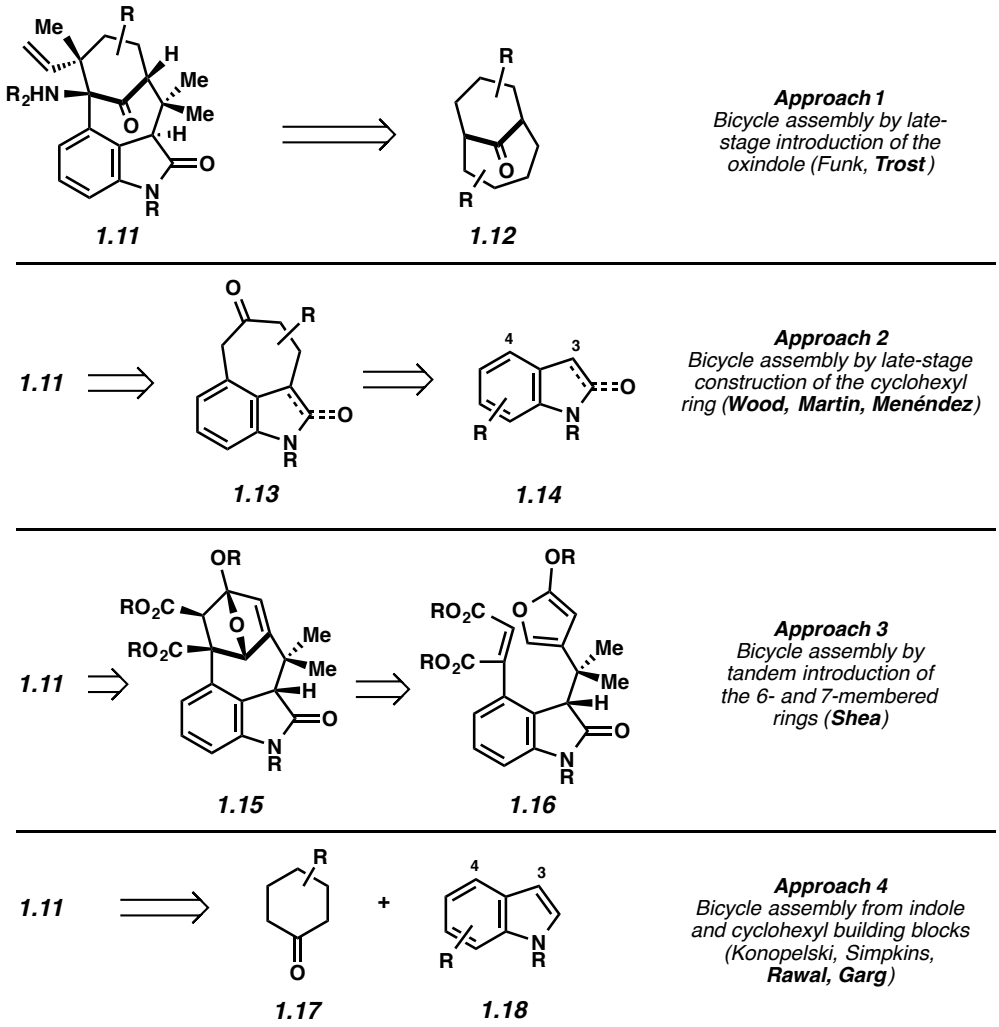


Figure 1.2. Synthetic approaches to the core scaffold of the welwitindolinone natural products with bicyclo[4.3.1]decane cores.

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

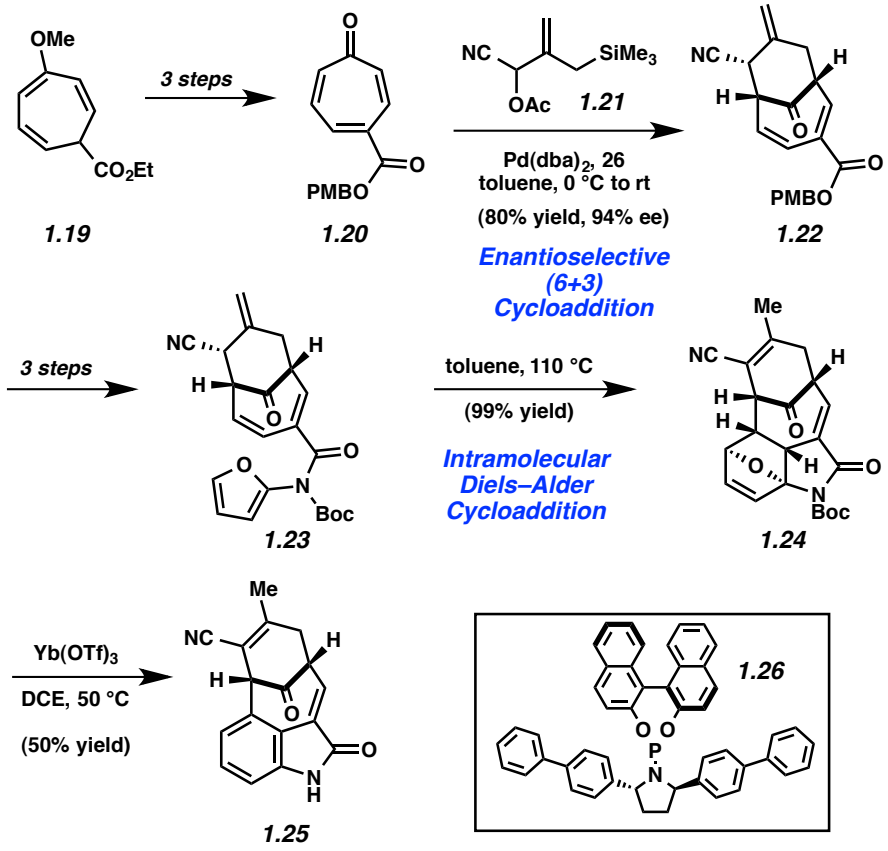
1.3.1 Late-Stage Assembly of the Oxindole

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

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

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

Scheme 1.1

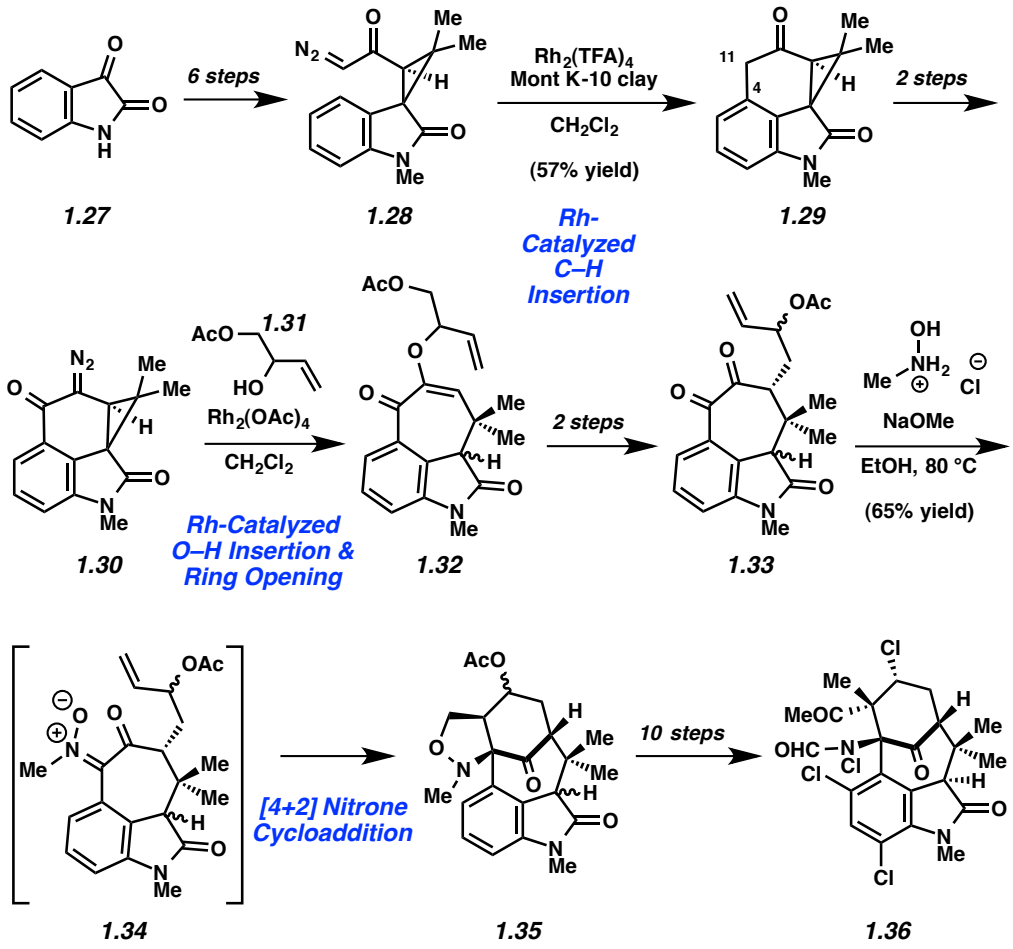


1.3.2 Late-Stage Construction of the Cyclohexyl Ring

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

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

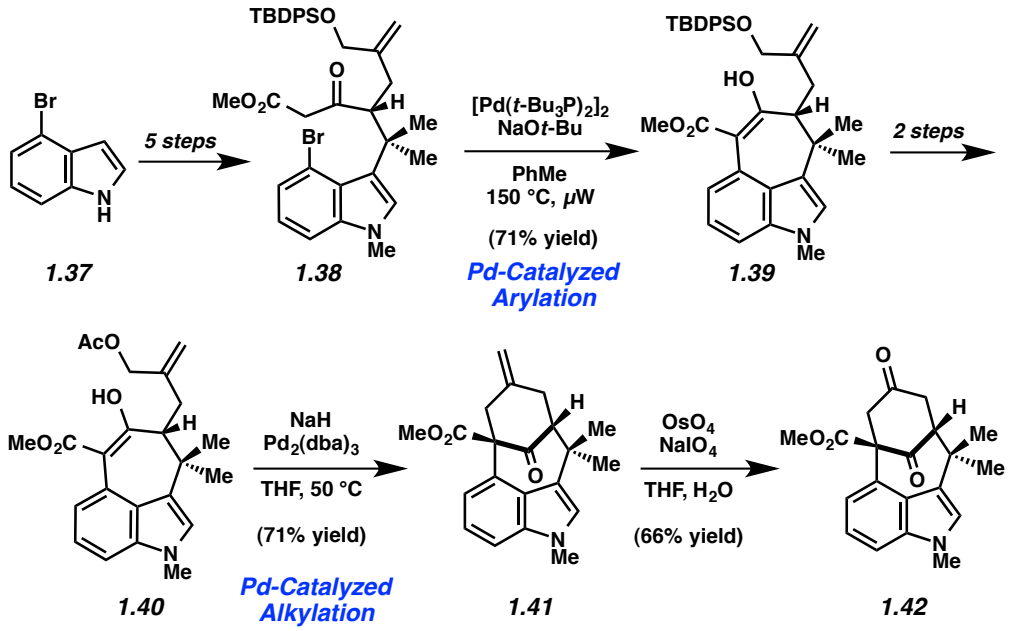
Scheme 1.2



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

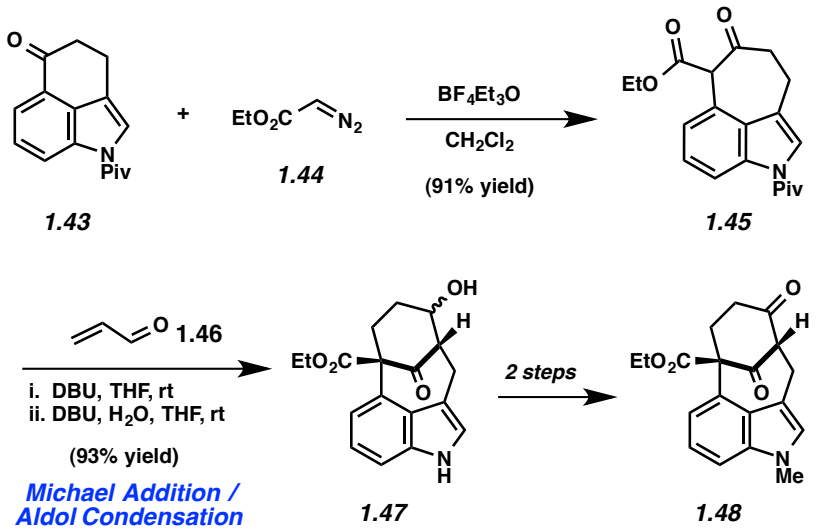
bromoindole (**1.37**), a five step sequence delivered β-ketoester **1.38**. Next, a palladium-catalyzed cyclization was employed to furnish **1.39**, which contains the necessary seven-membered ring. After elaborating to allylic acetate **1.40**, treatment with $Pd_2(dba)_3$ and sodium hydride provided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

Scheme 1.3



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

Scheme 1.4



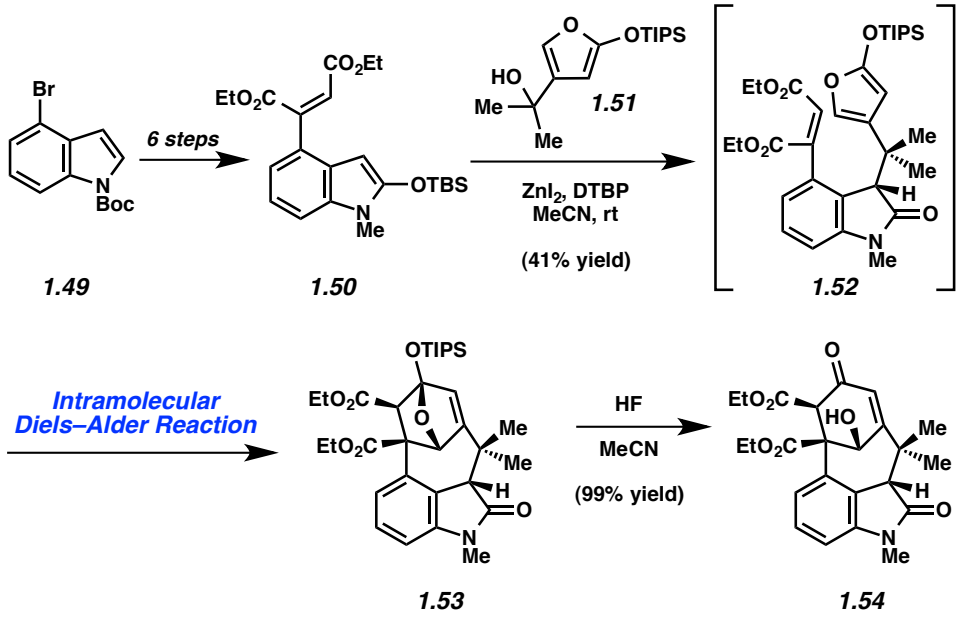
Each of the approaches discovered by Wood, Martin, and Menéndez provide smooth access to the bicyclic welwitinodolinone core, which sets the stage for late-stage elaboration. More importantly, lessons involving synthetic strategies and methods can be extracted from each group's efforts. Wood's use of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

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

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

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

Scheme 1.5



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

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

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

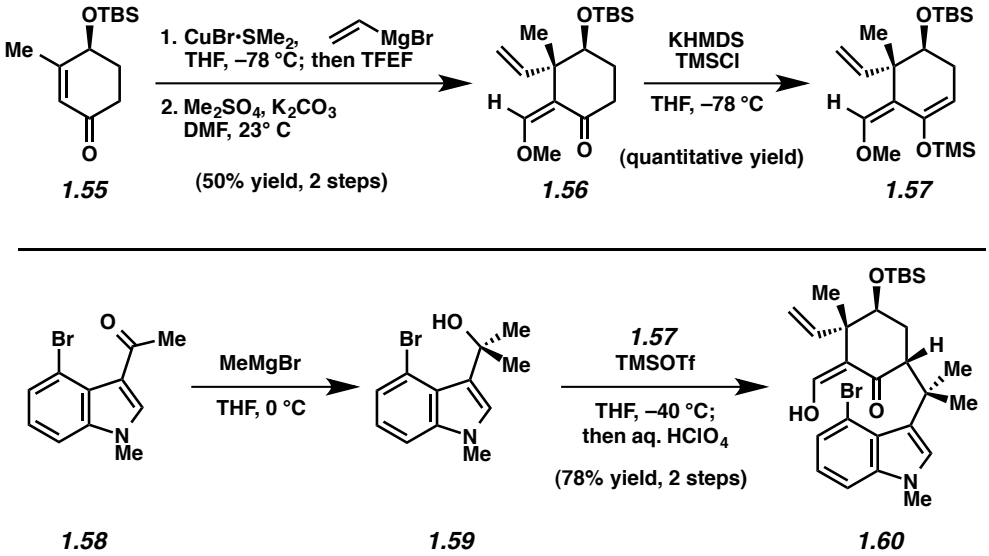
1.4.1 Assembly of the Bicyclo[4.3.1]decane Core

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

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

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

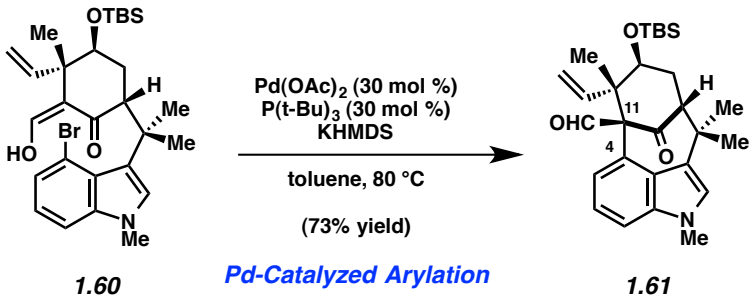
Scheme 1.6



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

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

Scheme 1.7



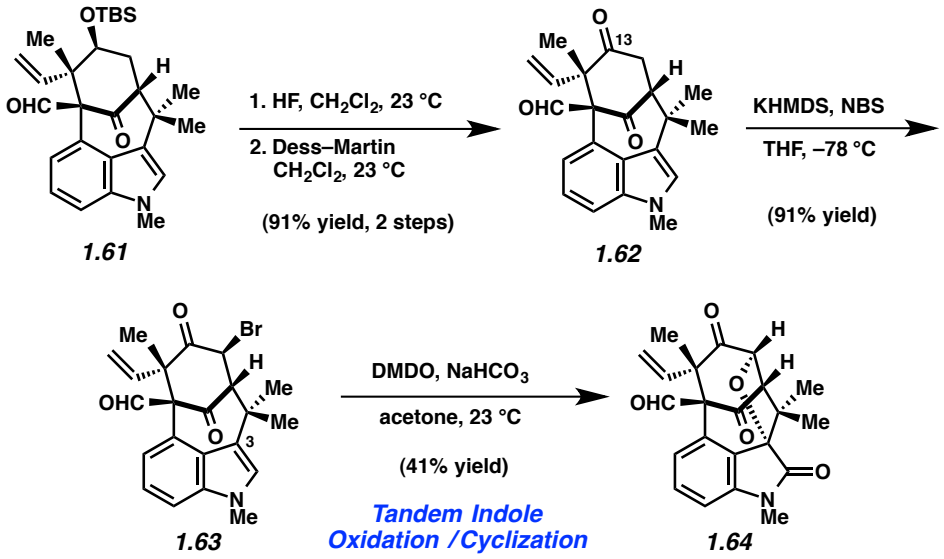
1.60 *1.61*

1.4.2 Introduction of the Tetrahydrofuran Ring

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

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

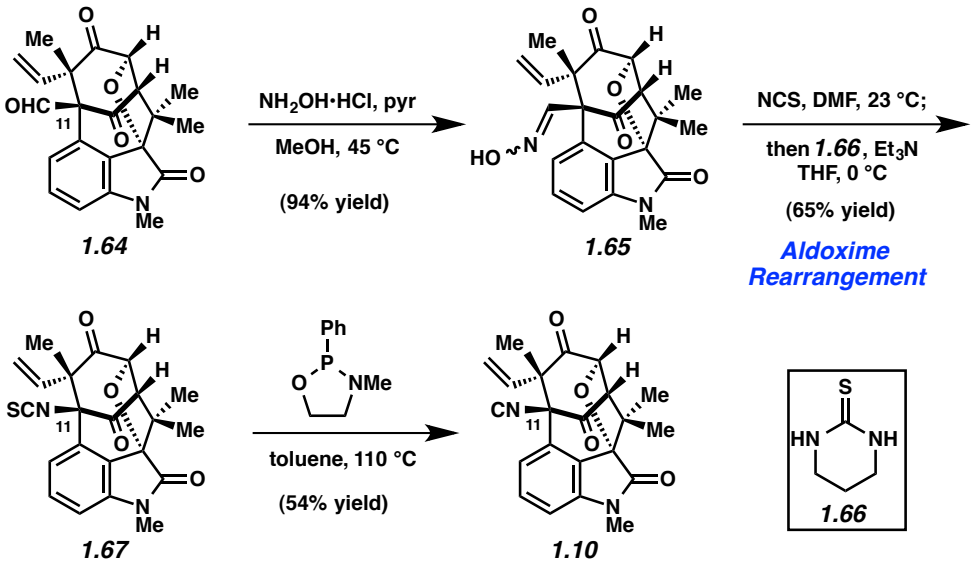
Scheme 1.8



1.4.3 Late-Stage Aldoxime Rearrangement and Completion of Total Synthesis

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

Scheme 1.9



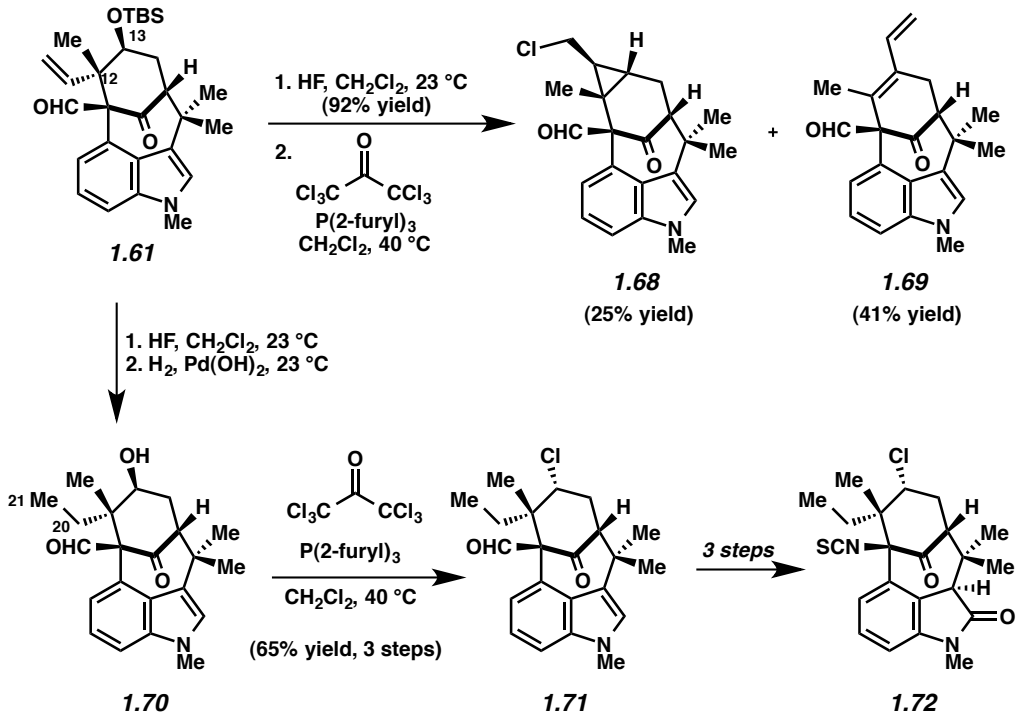
Rawal's elegant route to (±)-**1.10**, which proceeds in only 12 steps from enone **1.55**, provided the first total synthesis of a welwitindolinone with a bicyclo[4.3.1]decane core. The synthesis highlights the remarkable ability of Pd catalysis to build complex molecular frameworks, as seen similarly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

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

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

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

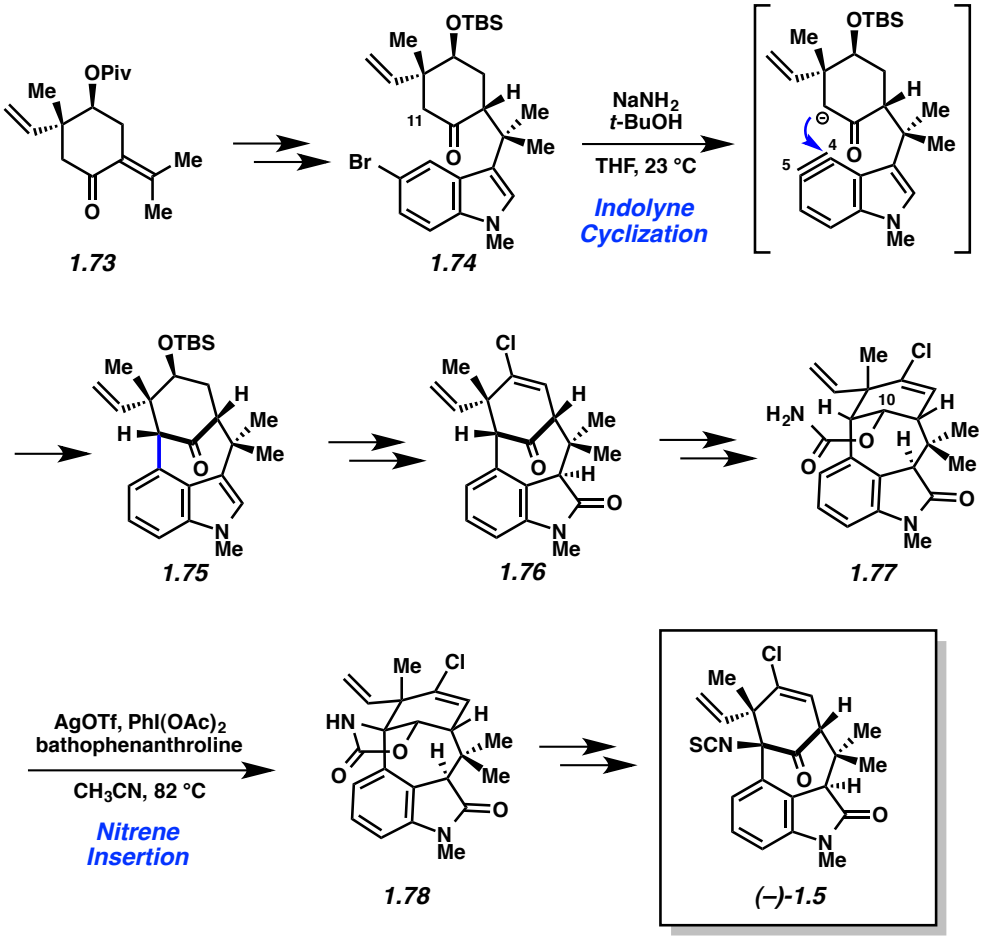
Scheme 1.10



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

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

Scheme 1.11



1.6 Conclusion

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

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

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CHAPTER TWO

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

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

2.1 Abstract

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

2.2 Introduction

The welwitindolinones are a unique class of natural products isolated from the blue-green algae *Hapalosiphon welwitschii* and *Westiella intricata*.[1] Ten welwitindolinones have been identified to date, nine of which possess bicyclo[4.3.1]decane cores (e.g., **2.1**–**2.3**, Figure 2.1).[2] Although compact in size, each of these natural products contains a dense array of functionality that has plagued synthetic efforts for nearly two decades. To date, more than ten laboratories have reported progress toward the bicyclic welwitindolinones.[3,4] Whereas these exhaustive efforts have resulted in several elegant methods for bicycle generation, completion of these targets has remained a formidable challenge. In fact, the only total synthesis of a welwitindolinone with a bicyclo[4.3.1]decane core was recently achieved by Rawal and co-workers, with their breakthrough synthesis of (±)-**2.3** in 2011.[5]

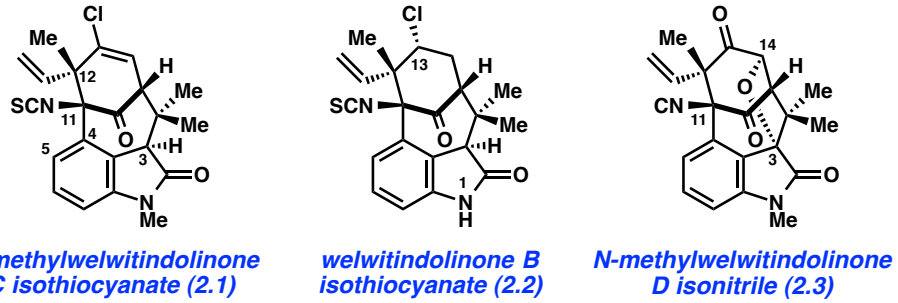


Figure 2.1. Welwitindolinones with bicyclo[4.3.1]decane cores **2.1–2.3**.

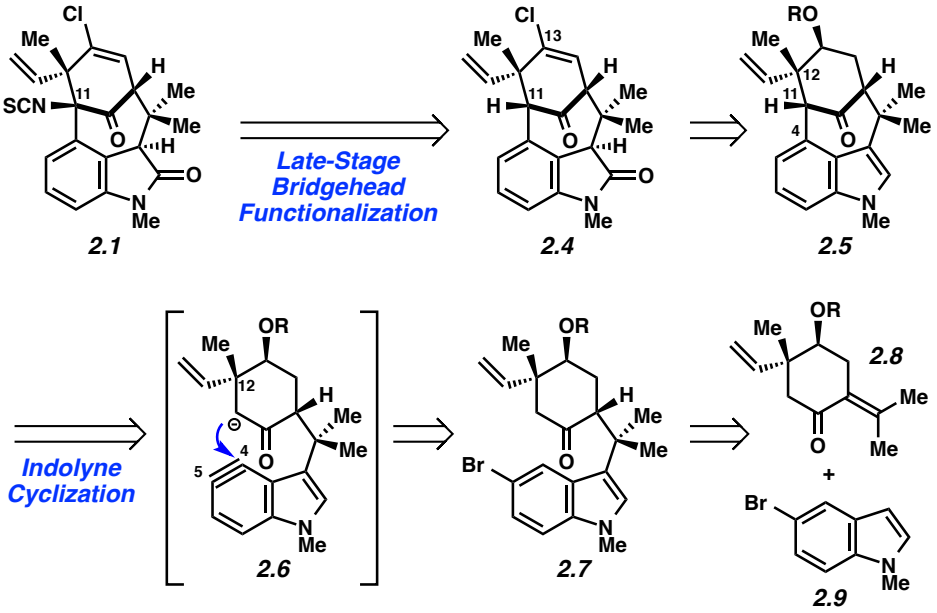
With the aim of synthesizing alkaloids **2.1**–**2.3** and other family members, we selected **2.1** as our initial synthetic target. Of note, welwitindolinone **2.1** was uniquely found to reverse P-glycoprotein-mediated multiple drug resistance (MDR) to a variety of anti-cancer drugs in human cancer cell lines, and is therefore a promising lead for the treatment of drug resistant tumors.[6] The densely functionalized bicyclic framework of **2.1** presents numerous synthetic challenges, including a 3,4-disubstituted oxindole, a heavily substituted cyclohexyl ring, and a bridgehead isothiocyanate substituent at C11. In this communication, we report the first total synthesis of (–)-*N*-methylwelwitindolinone C isothiocyanate (**2.1**).

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

Retrosynthetically, it was envisioned that **2.1** would be derived from bicycle **2.4** through late-stage functionalization of the C11 bridgehead position (Scheme 2.1). In turn, intermediate **2.4** would arise from indole precursor **2.5** by introduction of the vinyl chloride and oxindole moieties. In the key complexity generating step, the bicyclo[4.3.1]decane would be fashioned through intramolecular addition of an enolate onto an in situ-generated "indolyne" species (see transition structure **2.6**).[7] The use of an indolyne intermediate[8,9] was considered advantageous as the high reactivity of the aryne would permit the assembly of the congested C4–C11 bond linkage, where a tertiary center would be

introduced adjacent to the C12 quaternary stereocenter. Of note, the indolyne would be inherently electrophilic, representing an uncommon umpolung of the indole's typical reactivity. Bromoindole **2.7** was thought to be a suitable precursor to the desired indolyne via the classic dehydrohalogenation method for aryne generation. Finally, cyclohexyl derivative **2.8** and indole **2.9** were identified as suitable starting fragments.

Scheme 2.1

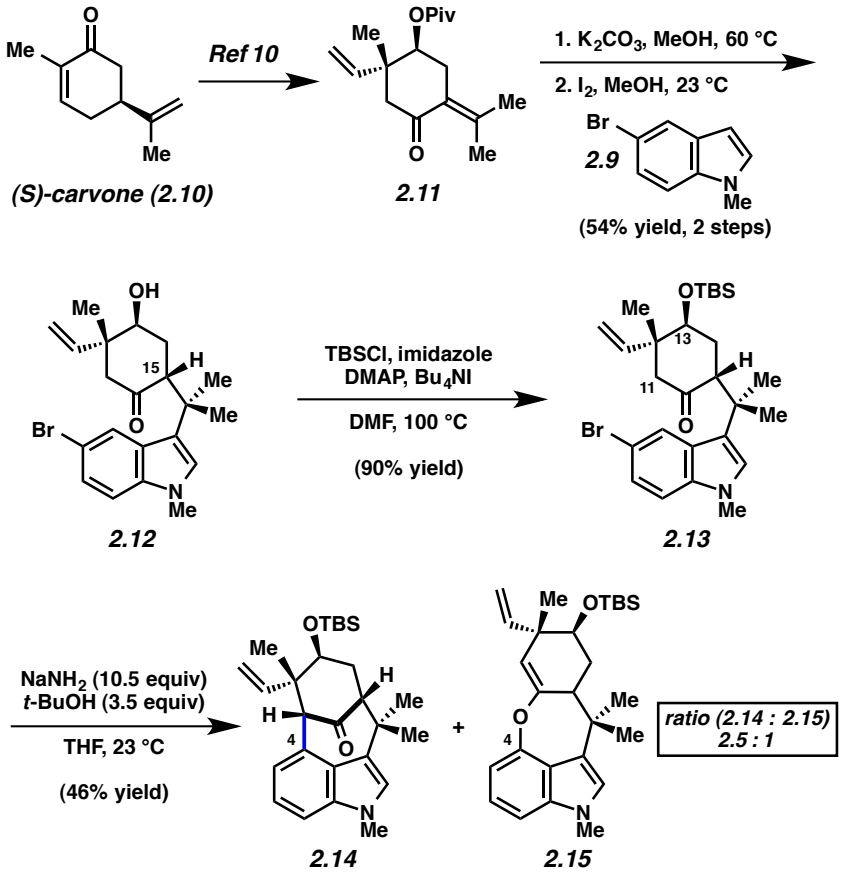


2.4 Construction of the Bicyclo[4.3.1]decane Framework

Our synthesis commenced with the concise preparation of the key bicyclo[4.3.1]decane scaffold (Scheme 2.2). (*S*)-Carvone (**2.10**) was elaborated to enone **2.11** using the robust five step procedure reported by Natsume in the enantiomeric series.[10] Subsequent pivalate cleavage, followed by I_2-promoted addition of bromoindole **2.9**,[11] furnished adduct **2.12** in 54% yield over two steps.[12] TBS-protection of **2.12** provided silylether **2.13**, which in turn was employed in the critical indolyne cyclization. To our delight, treatment of **2.13** with $NaNH_2$ and *t*-BuOH in THF at ambient

temperatures[3p,13] led to indolyne adducts **2.14** and **2.15** in a combined 46% yield (2.5 : 1 ratio).[14,15] Although *O*-arylated product **2.15** was observed,[16] the major product **2.14** possesses the desired bicyclo[4.3.1]decane framework of the natural product and is available in gram quantities.[17] Moreover, it was believed that bicycle **2.14** was suitably functionalized to allow for the ultimate completion of the natural product synthesis.

Scheme 2.2

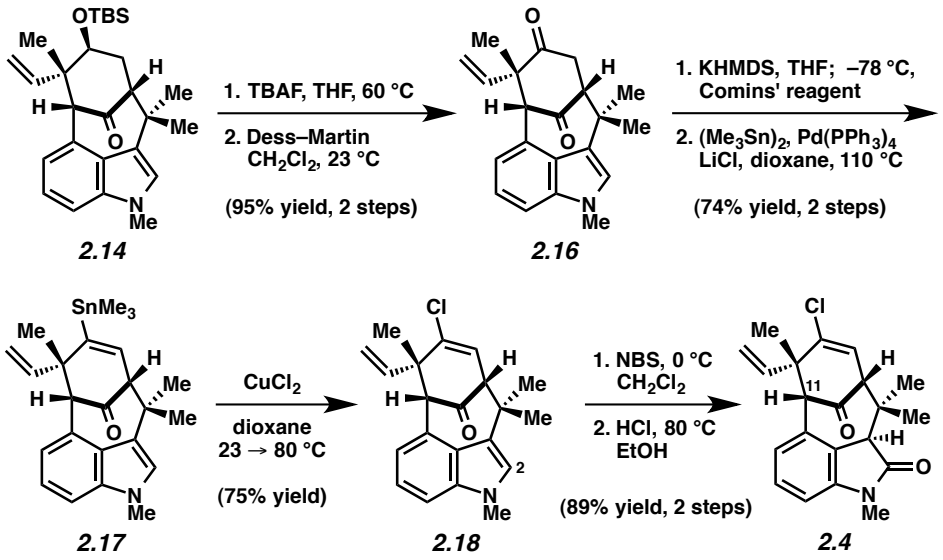


2.5 Introduction of the Vinyl Chloride and Oxindole Moieties

Having assembled the bicyclic framework of the natural product, we focused efforts on introduction of the vinyl chloride and oxindole moieties (Scheme 2.3). Desilylation of **2.14**, followed

by Dess–Martin oxidation, smoothly furnished diketone **2.16**. Subsequently, a sequence involving triflation and Pd-catalyzed stannylation provided vinyl stannane **2.17**.[18] Exposure of **2.17** to $CuCl_2$ in dioxane afforded vinyl chloride **2.18**.[19] To arrive at the necessary oxindole, a two-step procedure involving sequential C2 bromination and hydrolysis was employed to deliver late-stage intermediate **2.4**.[7]

Scheme 2.3

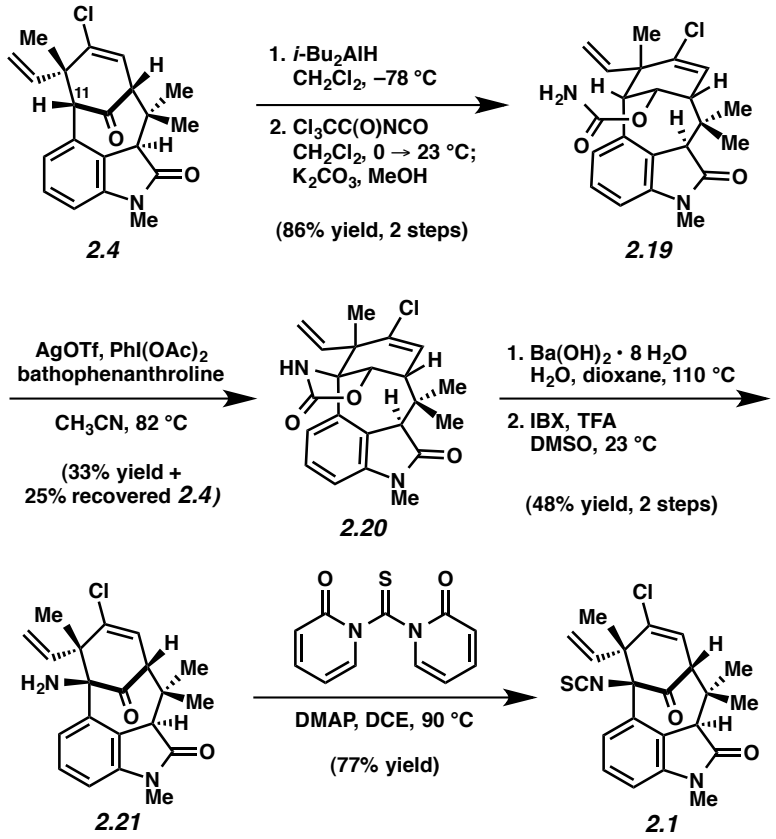


2.6 Completion of (–)-*N*-Methylwelwitindolinone C Isothiocyanate

With intermediate **2.4** lacking only the isothiocyanate substituent, we turned our attention to functionalization of the sterically congested C11 bridgehead position.[20] Unfortunately, attempts to substitute C11 through intermolecular processes were unsuccessful.[21] As a workaround, we postulated that an intramolecular nitrene C–H insertion might be more fruitful.[22,23] Ketone reduction of **2.4** proceeded efficiently using *i*-Bu_2AlH to furnish a secondary alcohol intermediate as a single diastereomer (Scheme 2.4). Subsequent carbamoylation furnished **2.19**,[23] the key substrate for the

critical C–H insertion reaction. The cyclization of carbamate **2.19** was attempted using a variety of reaction conditions that had previously been used to construct 5-membered oxazolidinones fused to cyclohexyl rings.[24] Although use of Rh catalysis furnished ketone **2.4** rather than the desired product **2.20**,[25] Ag catalysis[24b,c] was found to be more effective. Upon treatment of **2.19** with AgOTf, bathophenanthroline, and $PhI(OAc)_2$ in CH_3CN at elevated temperatures, the desired nitrene insertion took place to deliver oxazolidinone **2.20** as the major product. Ketone **2.4** was also recovered, and could be recycled through our synthetic route. Nonetheless, hydrolysis of **2.20** followed by IBX oxidation generated the penultimate intermediate **2.21**. With aminoketone **2.21** in hand, final introduction of the isothiocyanate[3m,26] furnished **2.1**. Spectral data for synthetic **2.1** was identical in all respects to that reported for the natural product.[1a,27]

Scheme 2.4



2.7 Conclusion

In summary, we have achieved the first total synthesis of (–)-*N*-methylwelwitindolinone C isothiocyanate (**2.1**). Our enantiospecific route proceeds in 17 steps from known carvone derivative **2.11** and features a number of key transformations, including: (a) an indolyne cyclization to assemble the bicyclo[4.3.1]decane framework, (b) late-stage introduction of the vinyl chloride and oxindole moieties, and (c) a nitrene insertion reaction to functionalize the sterically congested C11 bridgehead position. Our synthesis of (–)-**2.1** validates the use of indolynes as intermediates in complex molecule synthesis and provides a promising entryway to the other welwitindolinones with bicyclo[4.3.1]decane cores.

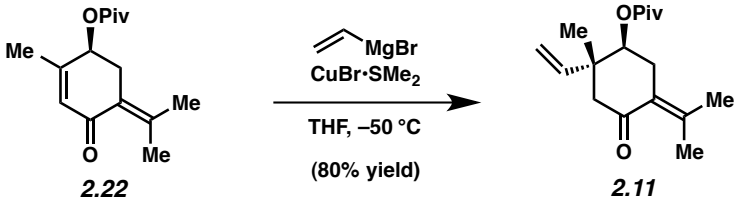
2.8 Experimental Section

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. (*S*)-Carvone was obtained from Aldrich. 5-bromoindole was obtained from Biosynth. $NaNH_2$ was obtained from Alfa Aesar. Comins' reagent was obtained from Aldrich. Hexamethylditin was obtained from Aldrich. Tetrakis(triphenylphosphine) palladium(0) was obtained from Strem. Anhydrous $CuCl_2$ was obtained from Aldrich. Trichloroacetyl isocyanate was obtained from Aldrich. AgOTf was obtained from Strem. Bathophenanthroline was obtained from Alfa Aesar. *O*,*O*-di(2-pyridinyl) thiocarbonate was obtained from Aldrich. 2-Iodoxybenzoic acid (IBX) and Dess–Martin periodinane were prepared from known literature procedures.[28,29] *t*-BuOH was distilled from CaH_2 and stored in a Schlenk tube prior to use. 1,4-dioxane was distilled from Na/benzophenone prior to use. 1,2-dichloroethane was distilled from P_2O_5 and stored in a Schlenk tube over 4Å molecular sieves prior to use. Unless stated otherwise, reactions were performed at room temperature (rt, approximately 23 °C). Thin-layer chromatography (TLC) was conducted with EMD gel 60 F254 pre-coated plates (0.25 mm) and visualized using a combination of UV, anisaldehyde, iodine, and potassium permanganate staining. Silicycle silica gel 60 (particle size 0.040–0.063 mm) was used for flash column chromatography. ^{1}H NMR spectra were recorded on Bruker spectrometers (500 MHz). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz), integration and are referenced to the residual solvent peak 7.26 ppm[30] for $CDCl_3$ and 5.32 ppm for CD_2Cl_2. ^{13}C NMR spectra are reported in terms of chemical shift (at 125 MHz) and are referenced to the residual solvent peak 77.16 ppm[30] for $CDCl_3$

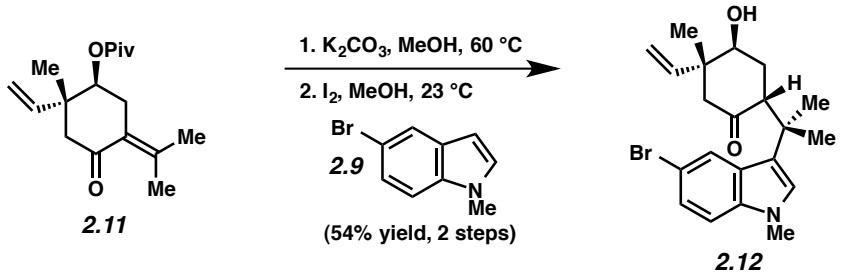
and 53.84 for CD_2Cl_2. IR spectra were recorded on a Perkin-Elmer 100 spectrometer and are reported in terms of frequency absorption (cm^{-1}). Optical rotations were measured with a Rudolph Autopol IV Automatic Polarimeter. Uncorrected melting points were measured with a Mel-Temp II melting point apparatus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

2.8.2 Experimental Procedures



Enone 2.11. Enone **2.11** was prepared using Natsume's procedure (originally performed in the enantiomeric series).[31] A flask was charged with $CuBr{\cdot}SMe_2$ (196 mg, 0.956 mmol, 0.1 equiv) followed by the addition of THF (90 mL). The resulting suspension was cooled to –50 °C and the vinyl magnesium bromide solution (1.0 M in THF, 28.7 mL, 28.7 mmol, 3.0 equiv) was added via syringe pump at a rate of 44.2 mL/hr. Once the addition was complete, a solution of **2.22**[31] (2.39 g, 9.56 mmol, 1.0 equiv) in THF (90 mL) was added via syringe pump at a rate of 86.0 mL/hr. After the addition of **2.22** was complete, the reaction was allowed to stir for 10 minutes and then quenched with a solution of saturated aqueous NH_4Cl (25 mL). The reaction vessel was then removed from the –50 °C bath, diluted with Et_2O (100 mL) and a solution of 1 M aqueous HCl (30 mL), and then allowed to warm to room temperature. The resulting mixture was vigorously stirred until all solids had dissolved. The resulting biphasic mixture was transferred to a separatory funnel and extracted with Et_2O (3 x 75 mL). The organic layers were combined, dried over $MgSO_4$, and evaporated under

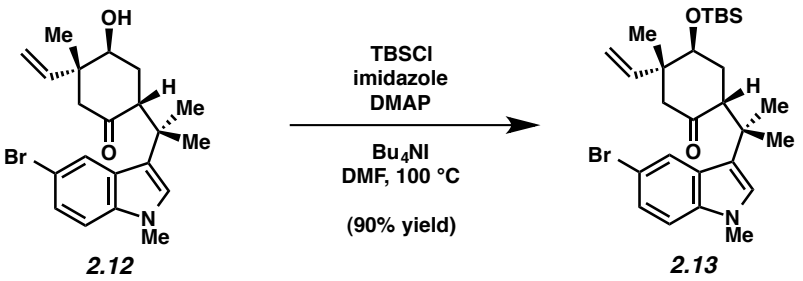
reduced pressure. The resulting residue was purified by flash chromatography (3:1 hexanes:Et_2O) to afford enone **2.11** (2.58 g, 80% yield) as a light yellow oil. Enone **2.11**: R_f 0.48 (3:1 hexanes:Et_2O); ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.76 (dd, *J* = 17.6, 10.7, 1H), 5.09 (d, *J* = 17.6, 1H), 5.09 (d, *J* = 10.7, 1H), 4.95 (t, *J* = 4.9, 1H), 2.70–2.66 (m, 2H), 2.54 (d, *J* = 15.8, 1H), 2.50 (d, *J* = 15.8, 1H), 2.02 (t, *J* = 1.6, 3H), 1.75 (s, 3H), 1.19 (s, 9H), 1.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 201.3, 177.9, 146.0, 142.8, 127.4, 114.7, 74.1, 49.2, 43.0, 39.2, 31.1, 27.2, 23.3, 22.6, 22.3; IR (film): 2975, 1720, 1679, 1480, 1280, 1215, 1157 cm^{-1}; HRMS-ESI (*m/z*) [M + Na]$^+$ calcd for $C_{17}H_{26}O_3Na$, 301.1780; found 301.1776; $[\alpha]^{24.5}_D$ +41.4° (*c* = 1.000, $CHCl_3$).



Indole 2.12. To a flask containing a solution of enone **2.11** (1.05 g, 3.79 mmol, 1.0 equiv) in MeOH (77.4 mL) was added K_2CO_3 (1.31 g, 9.47 mmol, 2.5 equiv) in one portion. The flask was fitted with a reflux condenser, flushed with N_2, and then allowed to stir at 60 °C. After 24 h, the reaction was cooled to room temperature and transferred to a separatory funnel with Et_2O (40 mL), H_2O (20 mL), and a solution of saturated aqueous NH_4Cl (20 mL). The resulting biphasic mixture was extracted with Et_2O (3 x 40 mL). The organic layers were combined, dried over $MgSO_4$, and evaporated under reduced pressure. The resulting crude residue was used in the subsequent reaction without further purification.

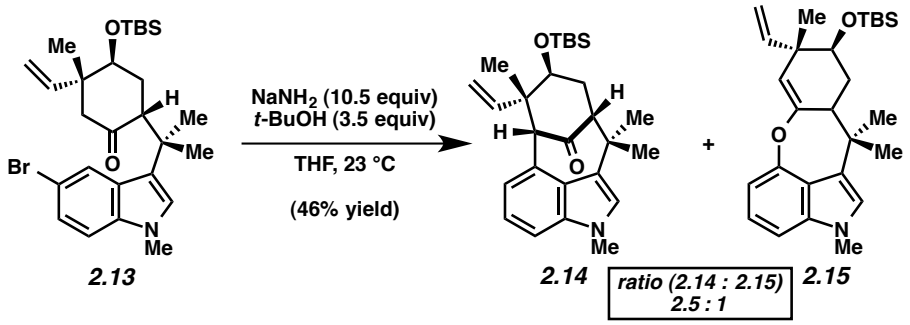
To a flask containing the crude residue from the previous step was added 5-bromo-*N*-methylindole[32] (1.23 g, 5.89 mmol, 1.5 equiv), followed by MeOH (7.82 mL). The resulting

suspension was stirred at room temperature until the mixture became homogeneous, and then iodine (198 mg, 0.78 mmol, 0.2 equiv) was added in one portion. The flask was flushed the N_2 and allowed to stir at room temperature. After 19 h, the reaction was quenched with a solution of saturated aqueous $Na_2S_2O_3$ (15 mL) and transferred to a separatory funnel with Et_2O (50 mL) and H_2O (15 mL). The resulting biphasic mixture was extracted with Et_2O (3 x 30 mL). The organic layers were combined, dried over $MgSO_4$, and evaporated under reduced pressure. The resulting residue was purified by flash chromatography (2:1:1 hexanes:CH_2Cl_2:Et_2O) to afford indole **2.12** (823 mg, 54% yield, over two steps) as a white solid. Indole **2.12**: mp: 71 ºC; R_f 0.43 (2:1:1 hexanes:CH_2Cl_2:Et_2O); ^{1}H NMR (500 MHz, CD_2Cl_2): δ 7.85, (d, *J* = 1.7, 1H), 7.26 (dd, *J* = 8.7, 1.7, 1H), 7.18 (d, *J* = 8.7, 1H), 6.82 (s, 1H), 5.64 (dd, *J* = 17.7, 10.9, 1H), 5.07 (d, *J* = 17.7, 1H), 5.05 (d, *J* = 10.9, 1H), 3.70 (s, 3H), 3.61 (br. s, 1H), 3.37 (dd, *J* = 12.7, 5.5, 1H), 2.71 (d, *J* = 13.7, 1H), 2.23 (dd, *J* = 13.7, 1.1, 1H), 1.82 (dt, *J* = 12.9, 2.4, 1H), 1.58 (s, 3H), 1.57–1.51 (m, 1H), 1.41 (s, 3H), 1.08 (s, 3H); ^{13}C NMR (125 MHz, CD_2Cl_2): δ 210.5, 144.1, 136.9, 127.9, 127.7, 124.1, 123.8, 123.6, 114.7, 112.0, 111.4, 72.8, 50.2, 48.7, 47.3, 36.6, 33.10, 33.08, 27.7, 24.6, 22.9; IR (film): 3463, 2966, 1703, 1479, 1214 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{21}H_{26}NO_2BrNa$, 426.1045; found 426.1044; $[\alpha]^{24.8}_D$ +76.2° (*c* = 1.000, $CHCl_3$).



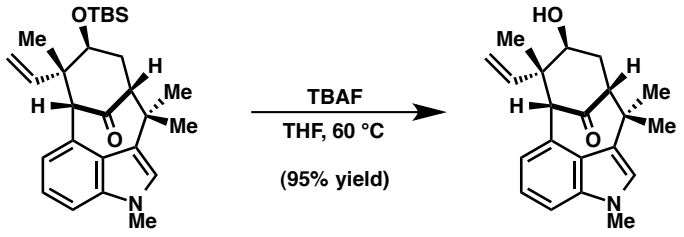
2.12 *2.13*

Silyl Ether 2.13. To a solution of indole **2.12** (3.84 g, 9.50 mmol, 1.0 equiv) in DMF (47.5 mL) was added imidazole (3.23 g, 47.5 mmol, 5 equiv), DMAP (1.17 g, 9.50 mmol, 1.0 equiv), tetrabutylammonium iodide (3.51 g, 9.50 mmol, 1.0 equiv), and TBSCl (4.30 g, 28.5 mmol, 3.0 equiv), all as solids in one portion. The flask was fitted with a reflux condenser, flushed with N_2, and then allowed to stir at 100 °C. After 12 h, the reaction was cooled to room temperature and transferred to a separatory funnel with EtOAc (75 mL), H_2O (30 mL), and a solution of saturated aqueous NH_4Cl (100 mL). The resulting biphasic mixture was extracted with EtOAc (4 x 75 mL). The organic layers were combined, washed with H_2O (1 x 20 mL), washed with brine (2 x 20 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The resulting residue was purified by flash chromatography (1:1 hexanes:Et_2O) to afford silyl ether **2.13** (4.43 g, 90% yield) as a white solid. Silyl ether **2.13**: mp: 117 ºC; R_f 0.68 (1:1 hexanes:Et_2O); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.79 (d, *J* = 1.8, 1H), 7.24 (dd, *J* = 8.7, 1.8, 1H), 7.12 (d, *J* = 8.7, 1H), 6.78 (s, 1H), 5.61 (dd, *J* = 17.6, 11.0, 1H), 5.07 (d, *J* = 17.6, 1H), 5.04 (d, *J* = 11.0, 1H), 3.70 (s, 3H), 3.56 (br. s, 1H), 3.27 (dd, *J* = 13.0, 5.4, 1H), 2.67 (d, *J* = 13.4, 1H), 2.16 (dd, *J* = 13.4, 0.9, 1H), 1.81 (dt, *J* = 13.4, 2.0, 1H), 1.63 (s, 3H), 1.61–1.59 (m, 1H), 1.38 (s, 3H), 1.00 (s, 3H), 0.86 (s, 9H), –0.04 (s, 3H), –0.42 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 211.0, 143.7, 136.5, 127.7, 127.3, 124.0, 123.71, 123.66, 114.7, 112.1, 110.9, 73.3, 50.4, 48.4, 48.1, 36.0, 33.3, 32.9, 26.5, 26.1, 25.6, 24.1, 18.2, –4.7, –5.1; IR (film): 2953, 2926, 2858, 1708, 1477, 1361, 1256, 1218, 1073 cm^{-1}; HRMS-ESI (*m/z*) [M + Na]$^+$ calcd for $C_{27}H_{40}NO_2BrSiNa$, 540.1909; found 540.1903; $[\alpha]^{22.7}_D$ +72.4° (*c* = 1.000, $CHCl_3$).



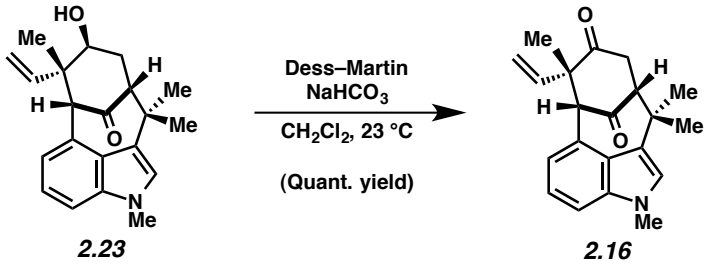
Bicycle 2.14. Inside of the glovebox, a flask was charged with $NaNH_2$ (2.13 g, 54.50 mmol, 10.5 equiv). The flask was then sealed and removed from the glovebox. THF (30.0 mL) was then added, followed by *t*-BuOH (1.75 mL, 18.20 mmol, 3.5 equiv). The resulting suspension was heated to 40 °C and stirred vigorously for 1 h. The reaction was cooled to room temperature and a solution of silyl ether **2.13** (2.68 g, 5.20 mmol, 1.0 equiv) in THF (22.0 mL) was added. After stirring at room temperature, the reaction was quenched via the dropwise addition of H_2O until no more gas evolution was observed. The reaction was then transferred to a separatory funnel with EtOAc (40 mL) and a solution of saturated aqueous NH_4Cl (40 mL). The resulting biphasic mixture was extracted with EtOAc (3 x 100 mL) and the organic layers were combined, dried over $MgSO_4$, and evaporated under reduced pressure. The resulting residue was purified by flash chromatography (100% benzene) to afford bicycle **2.14** (749 mg, 33% yield) as a light yellow oil and *O*-arylated product **2.15** (288 mg, 13% yield) as a clear oil. Bicycle **2.14**: R_f 0.56 (100% benzene); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.19 (d, *J* = 8.1, 1H), 7.13 (dd, *J* = 8.1, 7.3, 1H), 6.95 (s, 1H), 6.71 (d, *J* = 7.3, 1H), 4.96 (dd, *J* = 14.6, 4.6, 1H), 4.91–4.84 (m, 2H), 3.77 (s, 3H), 3.72 (dd, *J* = 11.0, 5.0, 1H), 3.60 (d, *J* = 1.5, 1H), 2.63 (d, *J* = 8.3, 1H), 2.21 (ddd, *J* = 14.5, 5.0, 1.8, 1H), 2.00 (ddd, *J* = 14.5, 8.3, 2.8), 1.57 (s, 3H), 1.18 (s, 3H), 1.07 (s, 3H), 0.72 (s, 9H), –0.21 (s, 3H), –0.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 212.4, 145.0, 137.4, 126.3, 126.2, 125.2, 122.6, 122.5, 121.1, 113.0, 108.1, 69.1, 69.0, 60.0, 49.8, 35.8, 35.7, 33.0, 32.1, 28.2, 25.9, 18.0, 16.8, –4.3, –4.8; IR (film): 2956, 2926,

1705, 1472, 1256, 1092 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{27}H_{39}NO_2SiNa$, 460.2648; found 460.2650; $[\alpha]^{24.9}_D$ +101.8° (*c* = 1.000, $CHCl_3$).



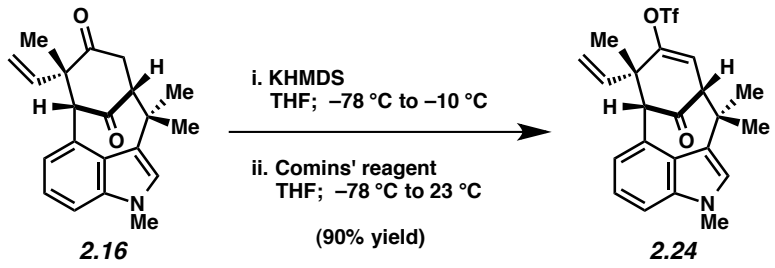
2.14 *2.23*

Alcohol 2.23. A flask was charged with bicycle **2.14** (848 mg, 1.94 mmol, 1.0 equiv) followed by the addition of THF (20 mL). A solution of TBAF (1.0 M in THF, 5.82 mL, 5.82 mmol, 3.0 equiv) was then added and the flask was fitted with a reflux condenser, flushed with N_2, and allowed to stir at 60 °C. After 12 h, the reaction was cooled to room temperature and transferred to a separatory funnel with EtOAc (30 mL) and a solution of 1 M aqueous $NaHSO_4$ (15 mL). The resulting biphasic mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure. The resulting residue was purified by flash chromatography (2:1 hexanes:EtOAc) to afford **2.23** (605 mg, 96% yield) as a white solid. **2.23**: R_f 0.25 (2:1 hexanes:EtOAc); ^1H NMR (500 MHz, $CDCl_3$): δ 7.20 (d, *J* = 8.2, 1H), 7.15 (dd, *J* = 8.2, 7.2, 1H), 6.96 (s, 1H), 6.72 (d, *J* = 7.2, 1H), 5.18–5.02 (m, 3H), 3.77 (s, 3H), 3.74 (ddd, *J* = 5.6, 3.0, 2.5, 1H), 3.67 (d, *J* = 1.5, 1H), 2.70 (d, *J* = 8.5, 1H), 2.42 (dd, *J* = 14.2, 5.6, 1H), 1.97 (ddd, *J* = 14.2, 8.5, 2.5, 1H), 1.61 (s, 3H), 1.18 (s, 3H), 1.08 (s, 3H).

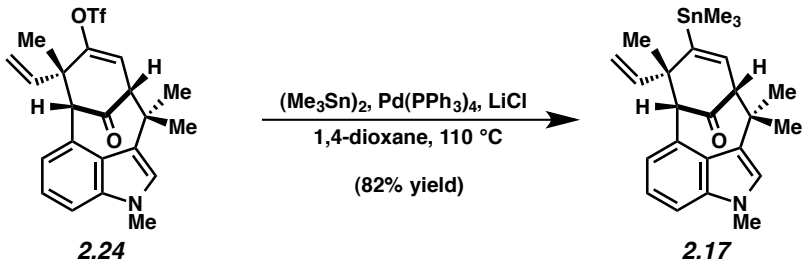


2.23 *2.16*

Diketone 2.16. A flask was charged with **2.23** (601 mg, 1.86 mmol, 1.0 equiv), $NaHCO_3$ (781 mg, 9.30 mmol, 5.0 equiv), and CH_2Cl_2 (37 mL). To the resulting suspension was added the Dess–Martin periodinane reagent (1.02 g, 2.42 mmol, 1.3 equiv) in one portion. The flask was flushed with N_2, and the reaction mixture was allowed to stir at room temperature. After 90 min, the reaction mixture was diluted with a solution of $NaHCO_3$ (1 g) and $Na_2S_2O_3$ (1 g) in H_2O (20 mL). The resulting biphasic mixture was vigorously stirred until both layers were no longer cloudy. The mixture was then transferred to a separatory funnel with EtOAc (50 mL) then extracted with EtOAc (3 x 50 mL). The organic layers were combined, dried over $MgSO_4$, and evaporated under reduced pressure. The resulting residue was purified by flash chromatography (2:1:1 hexanes:CH_2Cl_2:Et_2O) to afford diketone **2.16** (600 mg, quant. yield) as a white solid. Diketone **2.16**: mp: 194 ºC; R_f 0.48 (2:1:1 hexanes:CH_2Cl_2:Et_2O); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.20 (d, *J* = 8.4, 1H), 7.15 (dd, *J* = 8.4, 7.7, 1H), 6.94 (s, 1H), 6.80 (d, *J* = 7.7, 1H), 5.64 (dd, *J* = 17.4, 10.8, 1H), 5.21 (d, *J* = 10.8, 1H), 5.16 (d, *J* = 17.4, 1H), 3.90 (s, 1H), 3.75 (s, 3H), 3.00–2.87 (m, 3H), 1.51 (s, 3H), 1.47 (s, 3H), 1.17 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 209.9, 209.4, 139.3, 137.8, 127.1, 123.8, 123.5, 122.8, 121.1, 120.2, 114.8, 108.9, 68.9, 58.5, 56.3, 40.2, 37.4, 33.6, 33.1, 28.2, 22.2; IR (film): 2976, 2922, 1714, 1706, 1541, 1418, 1234 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{21}H_{23}NO_2Na$, 344.1627; found 344.1624; $[\alpha]^{25.1}_D$ +165.8° (*c* = 1.000, $CHCl_3$).

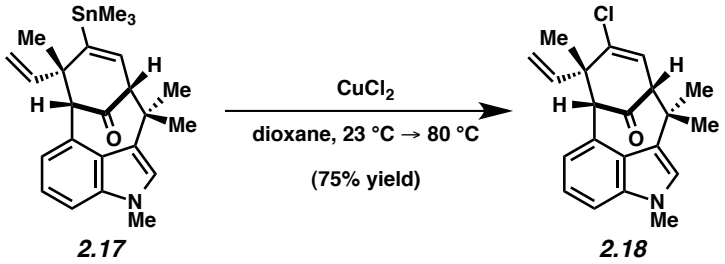


Vinyl Triflate 2.24. Inside of the glovebox, a flask was charged with solid KHMDS (327 mg, 1.65 mmol, 1.2 equiv). The flask was then sealed and removed from the glovebox. THF (7.0 mL) was added and the resulting solution was cooled to –78 °C. A solution of diketone **2.16** (440 mg, 1.37 mmol, 1.0 equiv) in THF (7.0 mL) was then added dropwise. Upon completion of the addition, the reaction was allowed to stir at –78 °C for 15 min, and was then warmed to –10 °C for 1 additional hour. The reaction vessel was then cooled to –78 °C and a solution of Comins' reagent (590 mg, 1.51 mmol, 1.1 equiv) in THF (3 mL) was added dropwise. After stirring at –78 °C for 45 min, the reaction mixture was warmed to room temperature and allowed to stir for an additional 15 min. The reaction was then quenched by the addition of a solution of saturated aqueous NH_4Cl (5 mL) and transferred to a separatory funnel with EtOAc (30 mL) and H_2O (20 mL). The resulting biphasic mixture was extracted with EtOAc (3 x 30 mL). The organic layers were combined, dried over $MgSO_4$, and evaporated under reduced pressure. The resulting residue was purified by flash chromatography (2:1:1 hexanes:CH_2Cl_2:Et_2O) to afford vinyl triflate **2.24** (555 mg, 90% yield) as a light yellow oil. Vinyl triflate **2.24**: R_f 0.64 (2:1:1 hexanes:CH_2Cl_2:Et_2O); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.23 (d, *J* = 8.2, 1H), 7.15 (dd, *J* = 8.2, 7.3, 1H), 6.92 (s, 1H), 6.75 (d, *J* = 7.3, 1H), 5.93 (d, *J* = 3.8, 1H), 5.24–5.17 (m, 3H), 3.80 (s, 1H), 3.76 (s, 3H), 3.15 (d, *J* = 3.8, 1H), 1.63 (s, 3H), 1.49 (s, 3H), 1.22 (s, 3H).



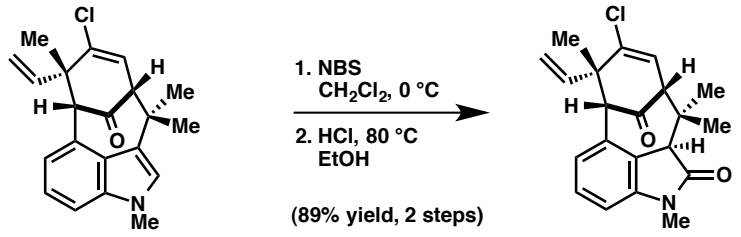
2.24 *2.17*

Vinyl Stannane 2.17. In the glovebox, a 20 mL scintillation vial was charged with $Pd(PPh_3)_4$ (59 mg, 0.051 mmol, 0.2 equiv), LiCl (258 mg, 6.51 mmol, 24 equiv), and hexamethylditin (254 μL, 1.23 mmol, 4.8 equiv). A separate 20 mL scintillation vial was charged with **2.24** (116 mg, 0.256 mmol, 1.0 equiv), followed by the addition of 1,4-dioxane (3.8 mL) which had been taken through three freeze-pump-thaw cycles prior to use. The resulting solution was then added to the vial containing the palladium catalyst, sealed, taken outside of the glovebox, and allowed to stir at 110 °C. After 20 h, the reaction was cooled to room temperature and filtered through a plug of silica gel topped with Celite. The filter cake was then washed with CH_2Cl_2 (15 mL), and the filtrate was evaporated under reduced pressure. The resulting residue was purified by flash chromatography (5:1 hexanes:Et_2O) to afford vinyl stannane **2.17** (97 mg, 82% yield) as a white solid. Vinyl stannane **2.17**: mp: 158 ºC; R_f 0.34 (5:1 hexanes:Et_2O); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.15 (d, J = 8.0, 1H), 7.10 (dd, J = 8.0, 7.0, 1H), 6.84 (s, 1H), 6.72 (d, J = 7.0, 1H), 5.93 (d, J = 3.2, $J_{H–Sn}$ = 72.0, 1H), 5.42 (dd, J = 17.7, 10.7, 1H), 5.07 (dd, J = 17.7, 1.1, 1H), 5.05 (dd, J = 10.7, 1.1, 1H), 3.73 (app. s, 4H), 2.93 (d, J = 3.2, 1H), 1.65 (s, 3H), 1.24 (s, 3H), 1.21 (s, 3H), –0.10 (s, $J_{H–Sn}$ = 52.7, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 211.9, 149.9, 145.4, 137.6, 135.5, 125.6, 125.5, 124.5, 122.9, 122.0, 120.5, 112.2, 107.8, 68.6, 61.8, 53.2, 37.1, 34.4, 33.0, 28.5, 25.7, –7.5; IR (film): 2973, 2919, 2875, 1703, 1454, 1420, 1371, 1255 cm^{-1}; HRMS-ESI (m/z) $[M + Na]^+$ calcd for $C_{24}H_{31}NOSnNa$, 492.1330; found 492.1327; $[\alpha]^{25.2}_D$ +46.6° (c = 1.000, $CHCl_3$).



2.17 *2.18*

Vinyl Chloride 2.18. A 20 mL scintillation vial was charged with vinyl stannane **2.17** (100 mg, 0.214 mmol, 1.0 equiv), and then transferred to the glovebox. Dioxane (4.27 mL) was added and to the resulting solution was added $CuCl_2$ (63 mg, 0.470 mmol, 2.2 equiv) in one portion. The vial was sealed and removed from the glovebox. The reaction mixture was allowed to stir at 23 °C for 30 min, and was then warmed to 80 °C. After 24 h, the reaction was diluted with brine (5 mL) and the resulting mixture was transferred to a separatory funnel with EtOAc (10 mL) and H_2O (5 mL). The resulting biphasic mixture was extracted with EtOAc (3 x 20 mL). The organic layers were combined, dried over $MgSO_4$, and evaporated under reduced pressure. The resulting residue was purified by preparative thin layer chromatography (benzene eluent) to afford vinyl chloride **2.18** (54 mg, 75% yield) as a white solid. Vinyl chloride **2.18**: mp: 83 ºC; R_f 0.27 (5:1 hexanes:Et_2O); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.20 (d, *J* = 8.4, 1H), 7.13 (dd, *J* = 8.4, 7.2, 1H), 6.89 (s, 1H), 6.76 (d, *J* = 7.2, 1H), 6.01 (d, *J* = 3.9, 1H), 5.27–5.12 (m, 3H), 3.82 (s, 1H), 3.75 (s, 3H), 3.02 (d, *J* = 3.9, 1H), 1.63 (s, 3H), 1.45 (s, 3H), 1.19 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 208.8, 142.2, 138.8, 137.7, 125.9, 124.31, 124.29, 124.2, 123.7, 121.4, 120.8, 113.8, 108.5, 68.6, 61.6, 51.9, 37.1, 34.0, 33.0, 28.3, 23.9; IR (film): 2970, 1716, 1450, 1418, 1368, 1255, 1152 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{21}H_{22}NOClNa$, 362.1288; found 362.1283; $[\alpha]^{22.8}_D$ +62.8° (*c* = 1.000, $CHCl_3$).

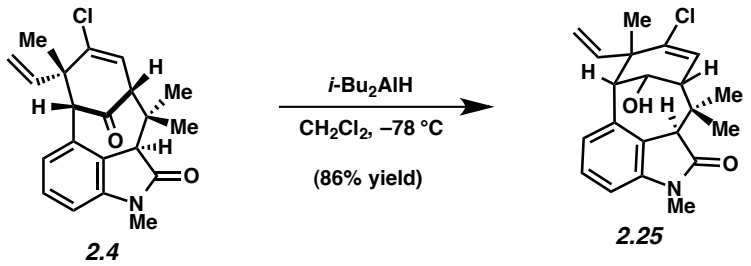


2.18 *2.4*

Oxindole 2.4. To a solution of vinyl chloride **2.18** (46 mg, 0.136 mmol, 1.0 equiv) in CH_2Cl_2 (2.75 mL) at 0 °C was added NBS (24.3 mg, 0.136 mmol, 1.0 equiv) in one portion. The reaction vial was flushed with N_2, and allowed to stir at 0 °C. After 25 min, solid $NaHCO_3$ (46 mg) was added in one portion. The reaction was removed from the 0 °C bath, and allowed to stir at room temperature for 5 min. The resulting suspension was filtered through a plug of silica gel (CH_2Cl_2 eluent, 10 mL). Evaporation under reduced pressure provided the crude brominated product, which was used in the subsequent step without further purification.

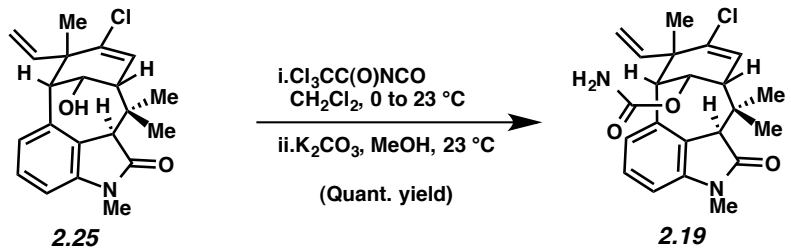
To the crude product was added absolute ethanol (1.5 mL) and concentrated aqueous HCl (1.5 mL). After heating to 80 °C for 14 h, the the reaction was cooled to room temperature and transferred to a separatory funnel with H_2O (10 mL) and EtOAc (20 mL). To the funnel was added solid $NaHCO_3$ until no more gas evolution was observed. The resulting biphasic mixture was extracted with EtOAc (3 x 20 mL) and the organic layers were combined, dried over $MgSO_4$, and evaporated under reduced pressure. The resulting residue was purified by flash chromatography (2:1:1 hexanes:CH_2Cl_2:Et_2O) to afford oxindole **2.4** (42.8 mg, 89% yield) as a white solid. Oxindole **2.4**: mp: 193 ºC; R_f 0.40 (2:1:1 hexanes:CH_2Cl_2:Et_2O); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.19 (dd, *J* = 7.9, 7.9, 1H), 6.71 (d, *J* = 7.9, 1H), 6.60 (d, *J* = 7.9, 1H), 6.16 (d, *J* = 5.1, 1H), 5.37 (dd, *J* = 17.4, 10.6, 1H), 5.13 (d, *J* = 17.4, 1H), 5.09 (d, *J* = 10.6, 1H), 3.81 (s, 1H), 3.52 (d, *J* = 1.4, 1H), 3.18 (s, 3H), 2.93 (dd, *J* = 5.1, 1.4, 1H), 1.62 (s, 3H), 1.47 (s, 3H), 0.73 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 204.7, 175.4, 144.7, 141.4, 140.3, 130.5, 128.6, 127.1, 124.6, 123.9, 115.4, 107.3, 68.8,

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



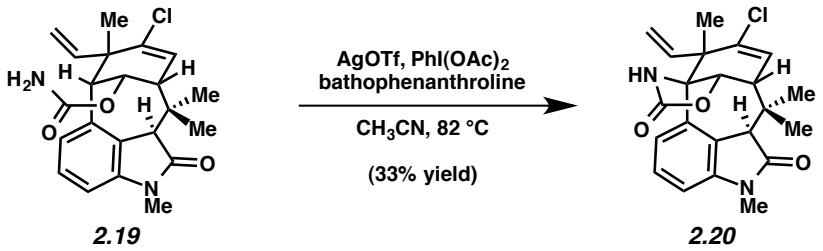
Alcohol 2.25. To a solution of oxindole **2.4** (43.0 mg, 0.121 mmol, 1.0 equiv) in CH_2Cl_2 (4.00 mL) at –78 °C was added a solution of *i*-Bu_2AlH (1.0 M in hexanes, 145 μL, 0.145 mmol, 1.2 equiv) dropwise. After stirring at –78 °C for 1 h, an additional portion of *i*-Bu_2AlH (1.0 M in hexanes, 24 μL, 0.024 mmol, 0.2 equiv) was added. After stirring at –78 °C for 1 h, a third portion of *i*-Bu_2AlH (1.0 M in hexanes, 24 μL, 0.024 mmol, 0.2 equiv) was added and the mixture was allowed to stir at –78 °C for 1 h. At this time, a final portion of *i*-Bu_2AlH (1.0 M in hexanes, 48 μL, 0.048 mmol, 0.4 equiv) was added. After 30 min, the reaction was quenched at –78 °C with a solution of saturated aqueous NH_4Cl (1 mL) and Rochelle's salt (1 mL). The mixture was stirred at room temperature for 1 h, transferred to a separatory with EtOAc (20 mL) and a solution of saturated aqueous NH_4Cl (20 mL), and extracted with EtOAc (3 x 20 mL). The organic layers were combined, dried over $MgSO_4$, and evaporated under reduced pressure. The resulting residue was purified by flash chromatography (1:1:1 hexanes:CH_2Cl_2:Et_2O) to afford alcohol **2.25** (37.2 mg, 86% yield) as a white solid. Alcohol **2.25**: R_f 0.12 (2:1:1 hexanes:CH_2Cl_2:Et_2O); ^1H NMR (500 MHz, $CDCl_3$): δ 7.17 (dd, *J* = 7.8, 7.7, 1H), 6.70 (d, *J* = 7.8, 1H), 6.68 (d, *J* = 7.7, 1H), 6.19 (d, *J* = 6.7, 1H), 5.23 (dd, *J* = 17.4, 10.7, 1H), 5.03 (dd, *J* = 17.4, 0.7, 1H), 4.89 (dd, *J* = 10.7, 0.7, 1H), 4.59–4.55 (app. t, *J* = 4.9, 1H), 3.62 (s, 1H),

3.18 (s, 3H), 3.14 (dd, *J* = 4.9, 1.0, 1H), 2.58 (ddd, *J* = 6.7, 5.4, 1.0, 1H), 1.57 (s, 3H), 1.53 (s, 3H), 0.95 (s, 3H).



Carbamate 2.19. To a solution of **2.25** (78 mg, 0.218 mmol, 1.0 equiv) in CH_2Cl_2 (2.2 mL) at 0 °C was added trichloroacetyl isocyanate (27 μL, 0.229 mmol, 1.05 equiv) in a dropwise manner. The resulting mixture was allowed to stir at 0 °C for 5 min, and then at room temperature for 20 min. The solvent was evaporated under reduced pressure. To the resulting residue was added MeOH (4.4 mL) and solid K_2CO_3 (165 mg, 1.19 mmol, 5.5 equiv) in one portion. The reaction was flushed with N_2 and left to stir at room temperature for 90 min. The reaction was diluted with EtOAc (3 mL) and H_2O (1 mL) and the resulting biphasic mixture was transferred to a test tube with EtOAc (2 mL) and brine (2 mL). After extracting with EtOAc (3 x 3 mL), the organic layers were combined, dried over $MgSO_4$, and evaporated under reduced pressure. The resulting residue was purified by flash chromatography (1:1 hexanes:EtOAc) to afford carbamate **2.19** (90 mg, quant. yield) as a white solid. Carbamate **2.19**: mp: 135 ºC; R_f 0.41 (1:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.13 (dd, *J* = 7.8, 7.7, 1H), 6.68 (d, *J* = 7.7, 1H), 6.61 (d, *J* = 7.8, 1H), 6.18 (d, *J* = 6.8, 1H), 5.47 (dd, *J* = 5.3, 4.8, 1H), 5.19 (dd, *J* = 17.3, 10.6, 1H), 5.04 (dd, *J* = 17.3, 0.8, 1H), 4.91 (dd, *J* = 10.6, 0.8, 1H), 4.41 (br. s, 2H), 3.62 (s, 3H), 3.18 (s, 3H), 3.15 (d, *J* = 4.8, 1H), 2.78 (dd, *J* = 6.8, 5.3, 1H), 1.61 (s, 3H), 1.52 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.3, 155.9, 144.3, 141.2, 141.0, 136.9, 127.7, 127.3, 126.4, 125.7, 114.7, 106.6, 72.7, 55.9, 52.6, 50.6, 49.0, 38.7, 28.0, 26.3,

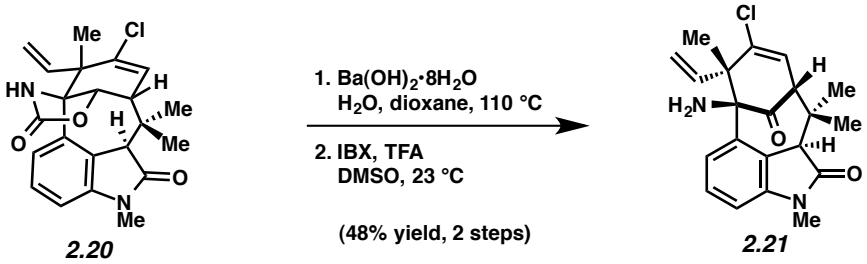
26.2, 22.7; IR (film): 3497, 3341, 2936, 1730, 1698, 1609, 1470, 1341, 1066 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{22}H_{25}N_2O_3ClNa$, 423.1451; found 423.1459; $[\alpha]^{23.0}_D$ –166.4° (*c* = 1.000, $CHCl_3$).



2.19 ***2.20***

Oxazolidinone 2.20. A 20 mL scintillation vial containing CH_3CN and a separate 20 mL scintillation vial charged with bathophenanthroline (24.1 mg, 0.0750 mmol, 0.5 equiv) were transferred into the glovebox. AgOTf (19.2 mg, 0.0750 mmol, 0.5 equiv) and CH_3CN (4.30 mL) were added to the vial containing the bathophenanthroline, and the resulting suspension was allowed to stir at room temperature for 20 min. Next, a third 20 mL scintillation vial containing carbamate **2.19** (55 mg, 0.150 mmol, 1.0 equiv) and $PhI(OAc)_2$ (96.4 mg, 0.300 mmol, 2.0 equiv) was transferred into the glovebox and the AgOTf/bathophenanthroline suspension was added to this vial. The vial was then sealed, removed from the glovebox, and the resulting mixture was allowed to stir at 82 °C. After 24 h, the reaction was cooled to room temperature and filtered through a plug of silica gel (EtOAc eluent, 50 mL). The filtrate was evaporated under reduced pressure, and the resulting residue was purified by preparative thin layer chromatography (2:1 benzene:EtOAc) to afford oxazolidinone **2.20** (18 mg, 33% yield) as a white solid and recovered oxindole **2.4** (12 mg, 25% yield) as a white solid. Oxazolidinone **2.20**: mp: 329 ºC; R_f 0.35 (2:1 benzene:EtOAc); ^1H NMR (500 MHz, $CDCl_3$): δ 7.55 (br. s, 1H), 7.15 (dd, *J* = 8.3, 7.6, 1H), 6.72 (d, *J* = 8.3, 1H), 6.71 (d, *J* = 7.6, 1H), 6.29 (d, *J* = 5.8, 1H), 5.19–5.05 (m, 3H), 5.02 (d, *J* = 6.5, 1H), 3.62 (s, 1H), 3.19 (s,

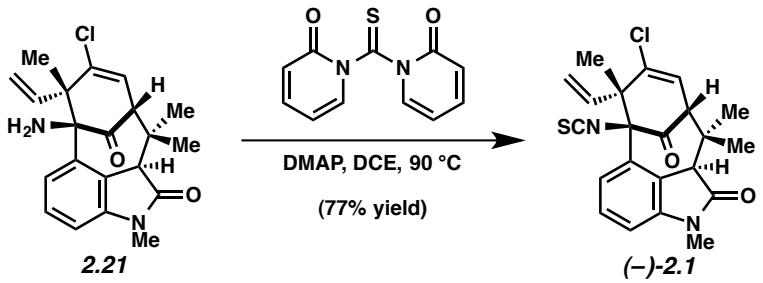
3H), 2.98 (dd, J = 6.5, 5.8, 1H), 1.65 (s, 3H), 1.56 (s, 3H), 1.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.9, 159.2, 144.2, 141.2, 140.6, 136.8, 128.2, 126.0, 125.5, 124.0, 116.4, 107.4, 81.3, 69.9, 54.2, 52.1, 49.6, 38.7, 27.4, 26.4, 22.0, 20.2; IR (film): 3270, 1755, 1686, 1612, 1460, 1202,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



Aminoketone 2.21. A Schlenk tube was charged with oxazolidinone **2.20** (15 mg, 0.0376 mmol, 1.0 equiv) and $Ba(OH)_2{\cdot}8H_2O$ (59 mg, 0.188 mmol, 5.0 equiv). The reaction vessel was then evacuated and backfilled with N_2 five times. A 2:1 mixture of 1,4-dioxane:H_2O (1.4 mL) that had been taken through seven freeze-pump-thaw cycles prior to use was then added and the Schlenk tube. The vessel was sealed, and then transferred to the glovebox where the reaction was allowed to stir at 110 °C. After 16 h, the Schlenk tube was removed from the glovebox and the contents were transferred to a test tube with EtOAc (6 mL), H_2O (1 mL), and brine (1 mL). The resulting biphasic mixture was extracted with EtOAc (3 x 4 mL). The organic layers were combined, dried over $MgSO_4$, and evaporated under reduced pressure to afford the crude product, which was used directly in the subsequent reaction.

To the crude residue was added DMSO (1.4 mL) and TFA (3 μL, 0.0413 mmol, 1.1 equiv). The resulting solution was allowed to stir at room temperature for 2 min. IBX (53 mg, 0.188 mmol, 5 equiv) was then added in one portion, and the vial was flushed with N_2. After stirring at room

temperature for 20 h, the reaction mixture transferred with EtOAc (3 mL) to a test tube containing a solution of aqueous K_2CO_3 (1 mL, concentration of 50 mg/mL). The resulting biphasic mixture was extracted with EtOAc (5 x 3 mL) and the organic layers were combined, dried over $MgSO_4$, and evaporated under reduced pressure. The resulting residue was purified by preparative thin layer chromatography (1:1 hexanes:EtOAc) to afford aminoketone **2.21** (6.7 mg, 48% yield, over two steps) as an amorphous solid. Aminoketone **2.21**: R_f 0.42 (1:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34 (d, *J* = 8.4, 1H), 7.27 (dd, *J* = 8.4, 7.6, 1H), 6.75 (d, *J* = 7.6, 1H), 6.18 (d, *J* = 4.2, 1H), 5.44 (dd, *J* = 17.3, 10.9, 1H), 5.22 (d, *J* = 10.9, 1H), 5.17 (d, *J* = 17.3, 1H), 3.82 (s, 1H), 3.18 (s, 3H), 3.15 (d, *J* = 4.2, 1H), 1.71 (br. s, 2H), 1.69 (s, 3H), 1.31 (s, 3H), 0.78 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 207.4, 174.7, 144.1, 140.6, 138.9, 135.2, 128.2, 124.2, 123.8, 123.7, 116.2, 107.7, 71.8, 62.8, 56.7, 53.8, 40.0, 26.4, 25.9, 21.6, 20.6; IR (film): 2973, 1709, 1698, 1609, 1583, 1457 cm^{-1}; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{21}H_{24}N_2O_2Cl$, 371.1526; found 371.1516; $[\alpha]^{23.8}_D$ –70.2° (*c* = 1.000, $CHCl_3$).



(–)-*N*-Methylwelwitindolinone C Isothiocyanate (2.1). To solution of aminoketone **2.21** (5.0 mg, 0.0135 mmol, 1.0 equiv) in 1,2-dichloroethane (540 μL) was added DMAP (0.8 mg, 0.0067 mmol, 0.5 equiv) and 1,1′-thiocarbonyldi-2(1H)-pyridone (15.7 mg, 0.067 mmol, 5 equiv) in one portion. The reaction vial was flushed with N_2 and then allowed to stir at 90 °C. After 14 h, the reaction was cooled to room temperature and then passed over a plug of silica gel (EtOAc eluent, 20 mL). The

filtrate was evaporated under reduced pressure. The resulting residue was purified by preparative thin layer chromatography (9:1 benzene:EtOAc) to afford **(–)-2.1** (4.3 mg, 77% yield) as an amorphous solid. (–)-*N*-Methylwelwitindolinone C isothiocyanate (**2.1**): R_f 0.81 (1:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30 (dd, *J* = 8.4, 7.8, 1H), 7.18 (dd, *J* = 8.4, 0.9, 1H), 6.79 (dd, *J* = 8.4, 0.9, 1H), 6.17 (d, *J* = 4.4, 1H), 5.35 (dd, *J* = 16.8, 10.6, 1H), 5.29–5.17 (m, 2H), 3.73 (s, 1H), 3.24 (d, *J* = 4.4, 1H), 3.17 (s, 3H) 1.68 (s, 3H), 1.47 (s, 3H), 0.80 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 196.3, 174.1, 144.5, 140.7, 138.7, 137.2, 130.1, 128.6, 124.7, 123.3, 122.5, 117.7, 108.5, 83.8, 61.7, 57.0, 53.1, 40.8, 26.4, 25.7, 22.2, 21.4; IR (film): 2970, 2932, 2041, 1712, 1609, 1460, 1341 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{22}H_{21}N_2O_2SClNa$, 435.0910; found 435.0899; $[\alpha]^{23.6}_D$ –223.9° (*c* = 0.77, CH_2Cl_2).[33]

2.9 Notes and References

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

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

(9) For recent indolyne studies, see: (a) Bronner, S. M.; Bahnck, K. B.; Garg, N. K. *Org. Lett*. **2009**, *11*, 1007–1010. (b) Cheong, P. H.-Y.; Paton, R. S.; Bronner, S. M.; Im, G.-Y.; Garg, N. K.;

Houk, K. N. *J. Am. Chem. Soc*. **2010**, *132*, 1267–1269. (c) Im, G.-Y.; Bronner, S. M.; Goetz, A. E.; Paton, R. S.; Cheong, P. H.-Y.; Houk, K. N.; Garg, N. K. *J. Am. Chem. Soc*. **2010**, *132*, 17933–17944. (d) Bronner, S. M.; Goetz, A. E.; Garg, N. K. *J. Am. Chem. Soc*. **2011**, *133*, 3832–3835. (e) Buszek, K. R.; Luo, D.; Kondrashov, M.; Brown, N.; VanderVelde, D. *Org. Lett*. **2007**, *9*, 4135–4137. (f) Brown, N.; Luo, D.; VanderVelde, D.; Yang, S.; Brassfield, A.; Buszek, K. R. *Tetrahedron Lett.* **2009**, *50*, 63–65. (g) Buszek, K. R.; Brown, N.; Luo, D. *Org. Lett.* **2009**, *11*, 201–204. (h) Brown, N.; Luo, D.; Decapo, J. A.; Buszek, K. R. *Tetrahedron Lett.* **2009**, *50*, 7113–7115. (i) Garr, A. N.; Luo, D.; Brown, N.; Cramer, C. J.; Buszek, K. R.; VanderVelde, D. *Org. Lett.* **2010**, *12*, 96–99. (j) Thornton, P. D.; Brown, N.; Hill, D.; Neunswander, B.; Lushington, G. H.; Santini, C.; Buszek, K. R. *ACS Comb. Sci*. **2011**, *13*, 443–448. (k) Nguyen, T. D.; Webster, R.; Lautens, M. *Org. Lett.* **2011**, *13*, 1370–1373.

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

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

(12) The C15 epimer of **4.12** was also obtained in 22% yield. Upon treatment of this compound with DBU in heated toluene, a separable mixture of **2.12** and epi-**2.12** is readily obtained.

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

(14) Variations in reaction conditions (e.g., temperature, stoichiometry, counterion, etc.) did not lead to improvements in the conversion of **2.13** to **2.14**.

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

(16) *O*-arylated product **2.15** is often isolated with small amounts of the isomeric tetrasubstituted olefin.

(17) Interestingly, the C13 epimer of substrate **2.13** does not undergo conversion to the corresponding bicyclo[4.3.1]decane.

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

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

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

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

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

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

(24) For intramolecular nitrene C–H insertion reactions using carbamate substrates, see: (a) Espino, C. G.; Du Bois, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 598–600. (b) Li, Z.; Capretto, D. A.; Rahaman, R.; He, C. *Angew. Chem., Int. Ed.* **2007**, *46*, 5184–5186. (c) Cui, Y.; He, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 4210–4212.

(25) Ketone **2.4** likely forms by a pathway involving initial insertion into the α C–H bond; for related observations, see: Hinman, A. W. Ph.D. Dissertation, Stanford University, Stanford, CA, 2004.

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

(27) A sample of natural **2.1** was not available for direct comparison.

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

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

(30) For compound **2.1** the ^{1}H NMR residual solvent peak is set to 7.24 ppm and the ^{13}C NMR residual solvent peak is set to 77.0 ppm to match the reference values set in the isolation paper.

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

(32) **2.9** is commercially available, or can be easily prepared in one step from 5-bromoindole on multigram scale; see: Jiang, X.; Tiwari, A.; Thompson, M.; Chen, Z.; Cleary, T. P.; Lee, T. B. K. *Org. Proc. Res. Dev*. **2001**, *5*, 604–608.

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

APPENDIX ONE

Spectra Relevant to Chapter Two:

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

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

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

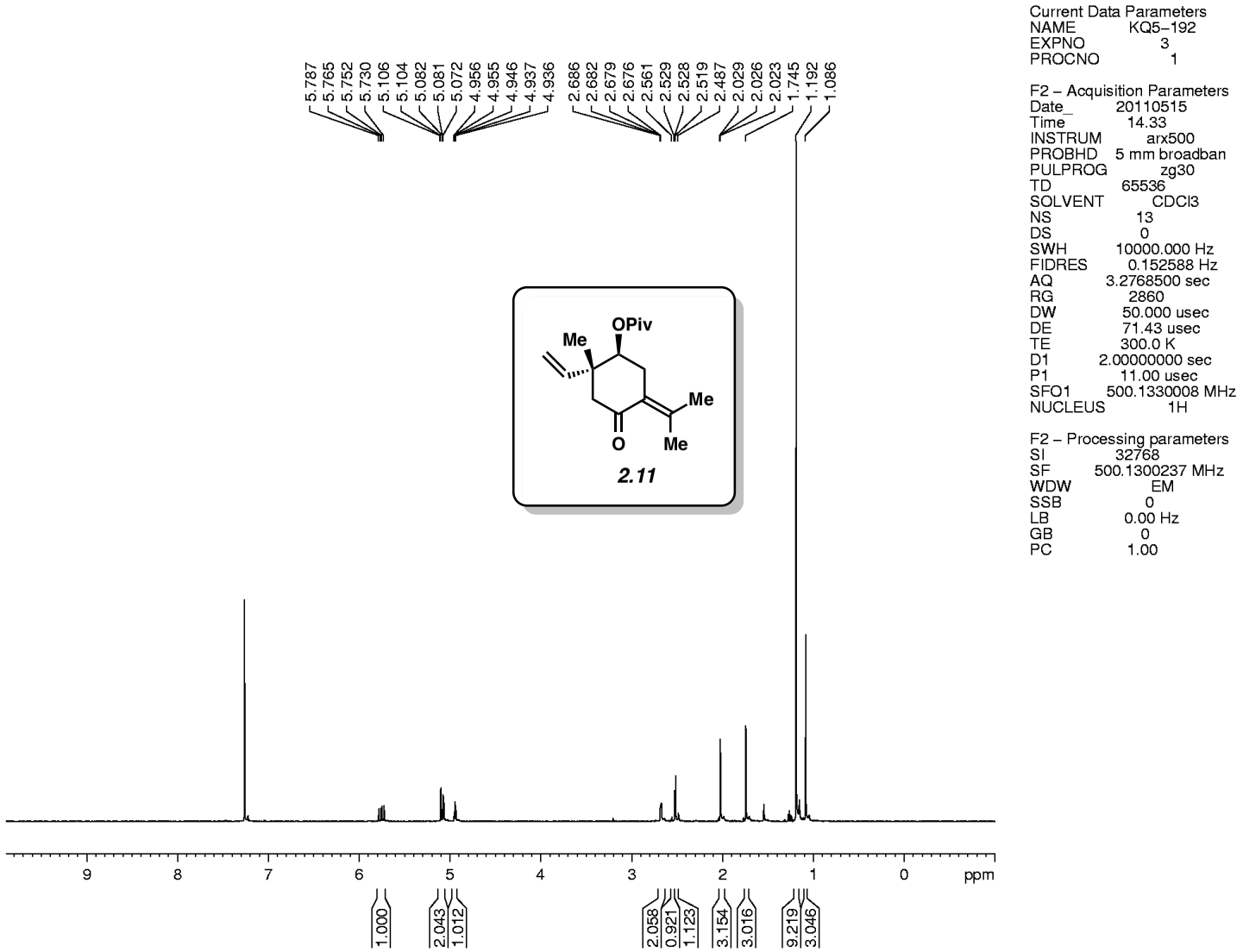


Figure A1.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **2.11**.

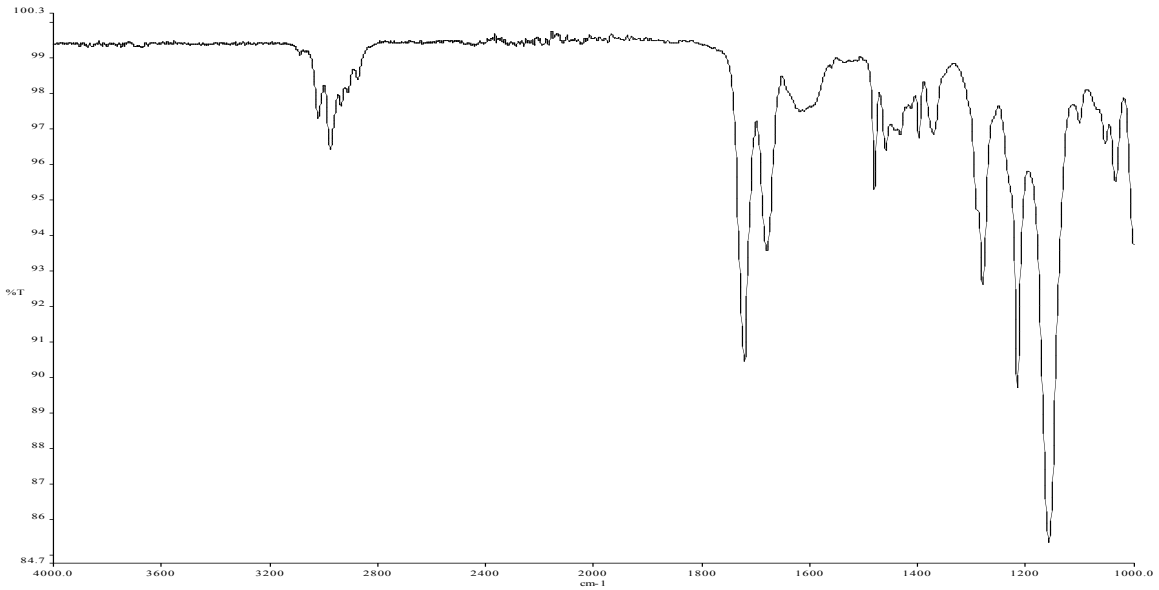


Figure A1.2 Infrared spectrum of compound **2.11**.

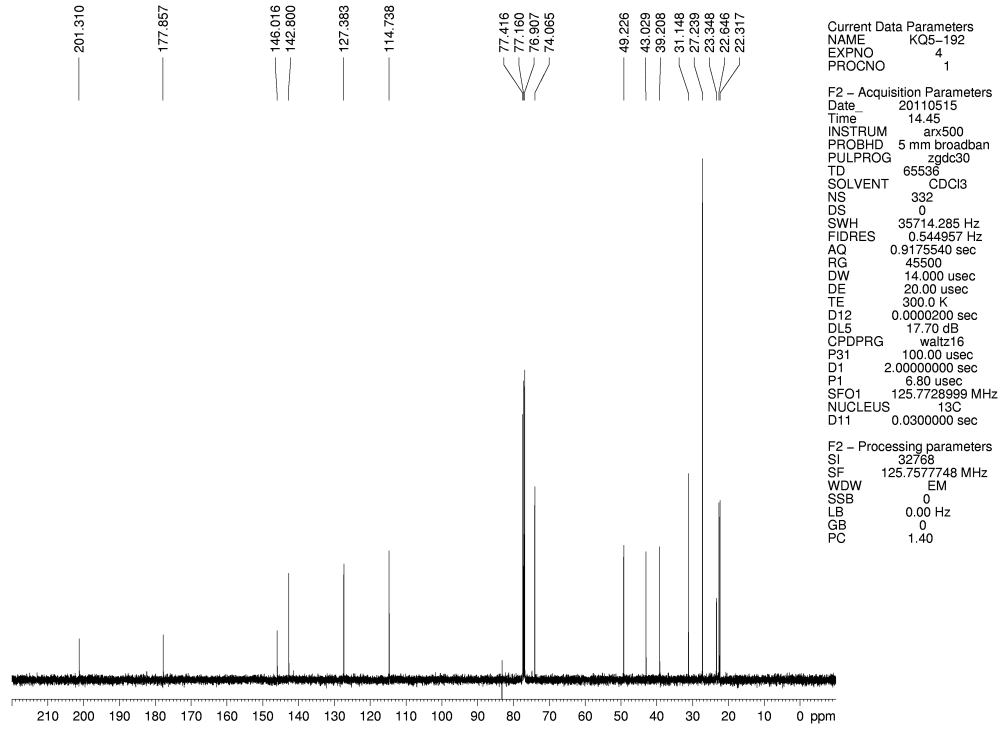
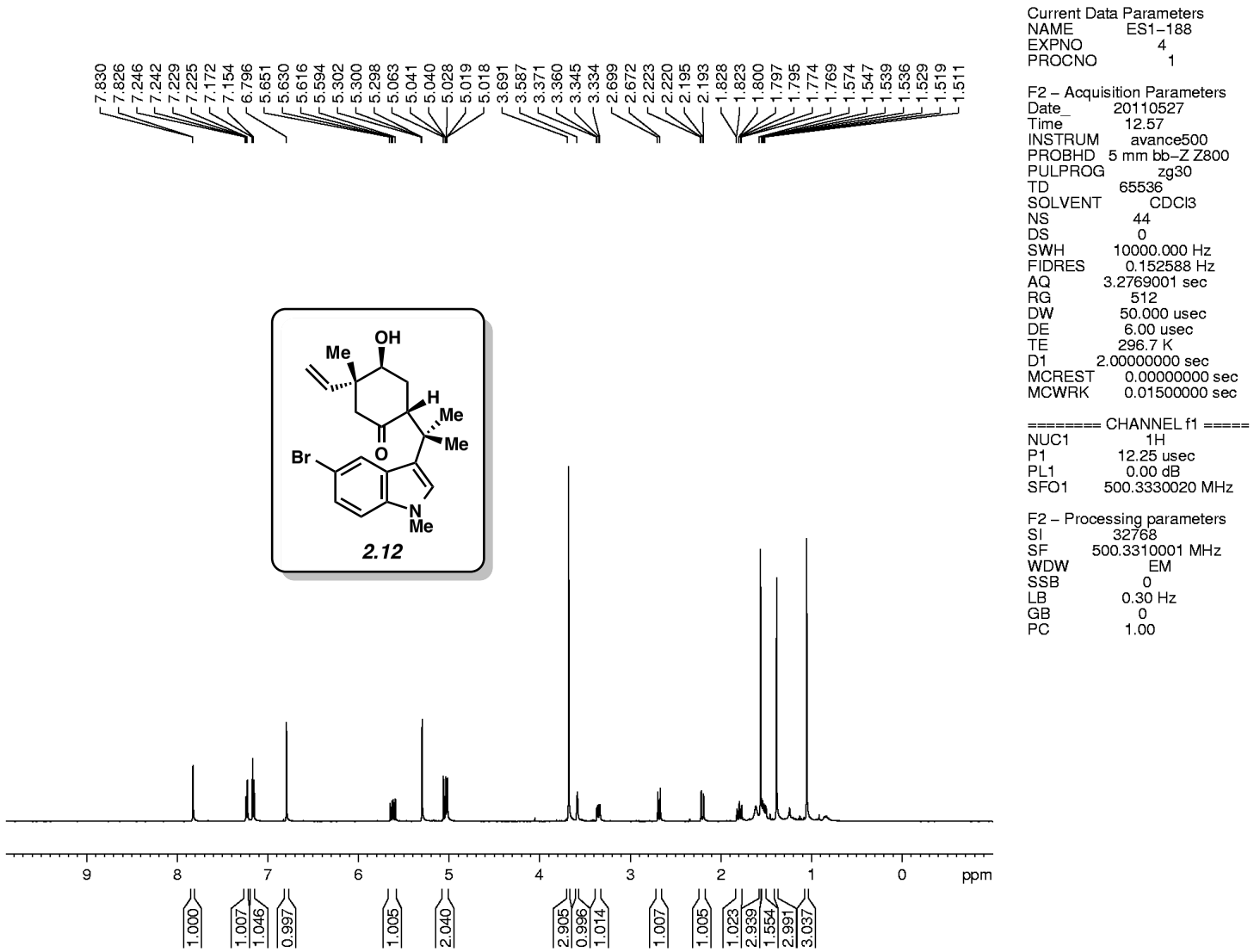


Figure A1.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **2.11**.



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EXPNO 4
PROCNO 1

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

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

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

Figure A1.4 ^{1}H NMR (500 MHz, CD_2Cl_2) of compound **2.12**.

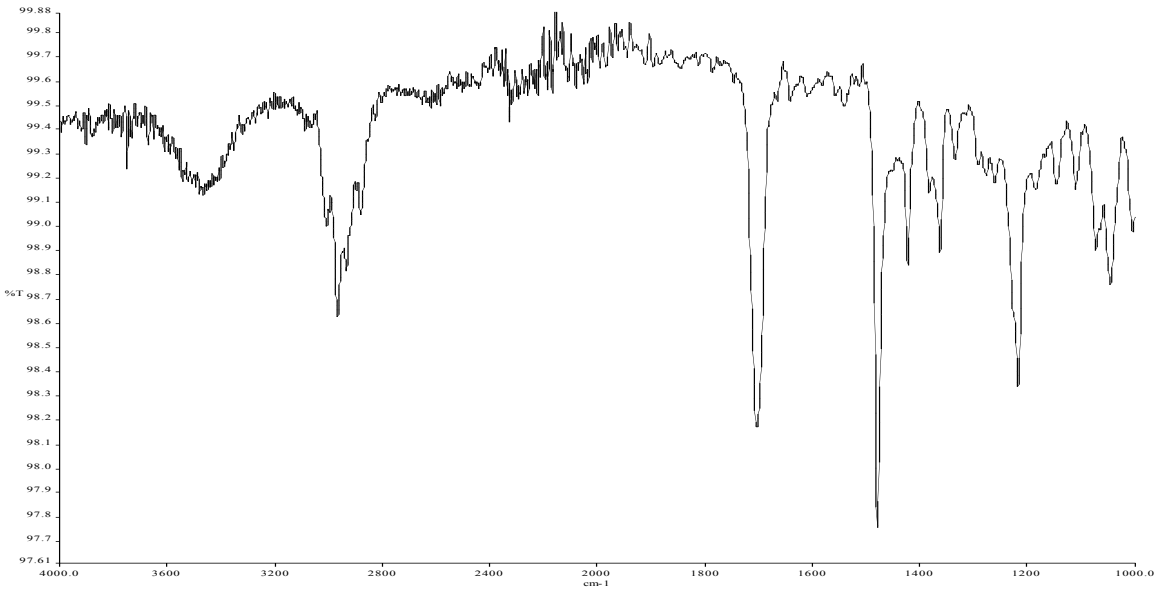


Figure A1.5 Infrared spectrum of compound **2.12**.

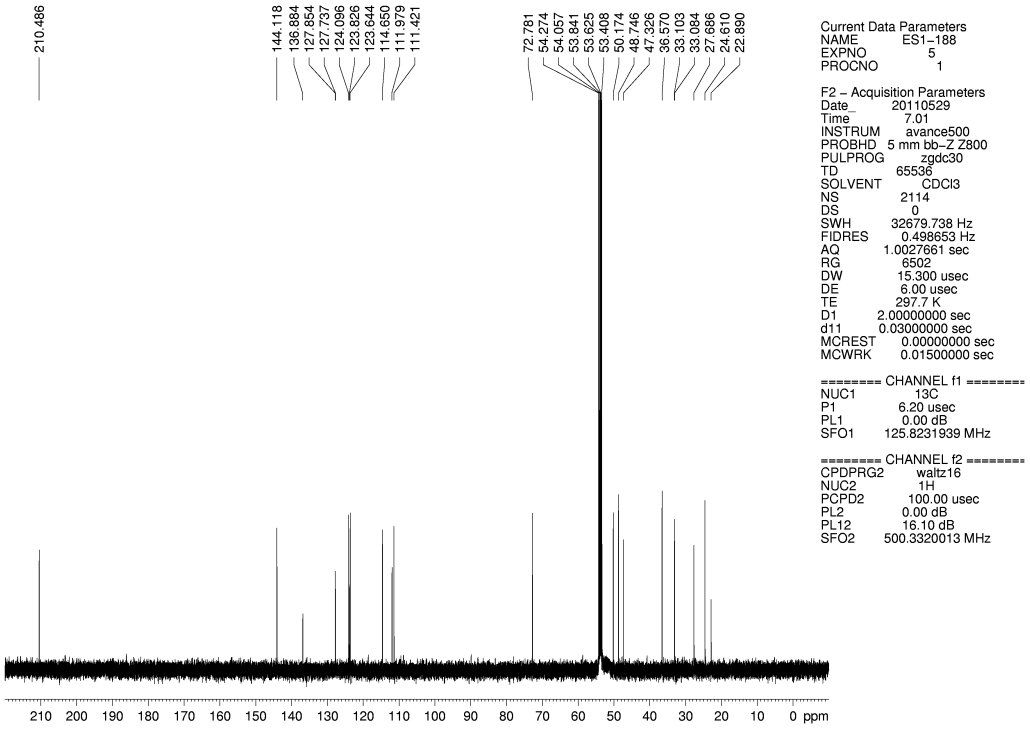


Figure A1.6 ^{13}C NMR (125 MHz, CD_2Cl_2) of compound **2.12**.

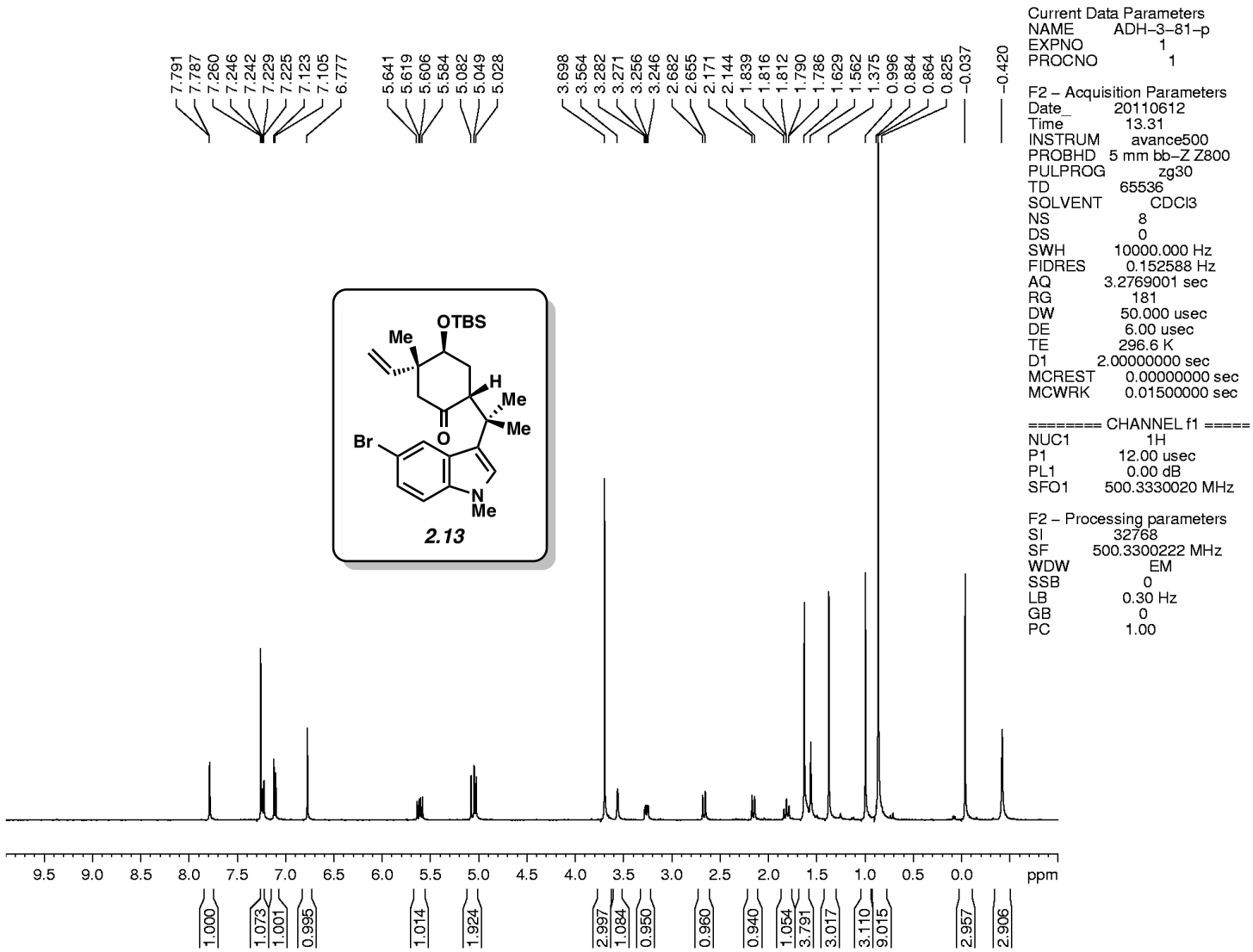


Figure A1.7 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **2.13**.

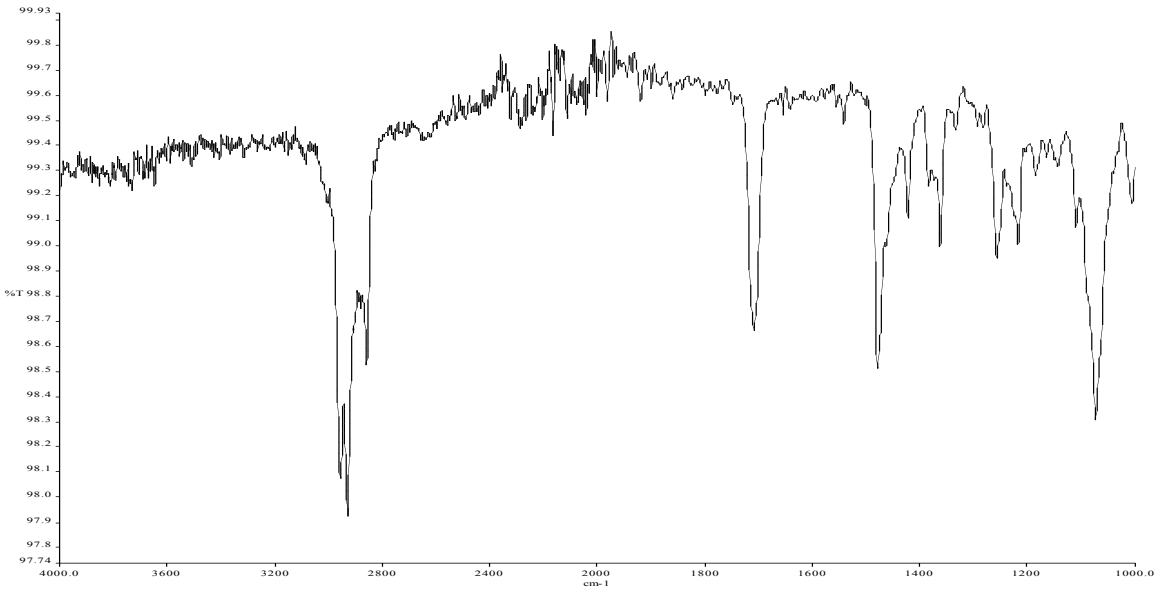


Figure A1.8 Infrared spectrum of compound **2.13**.

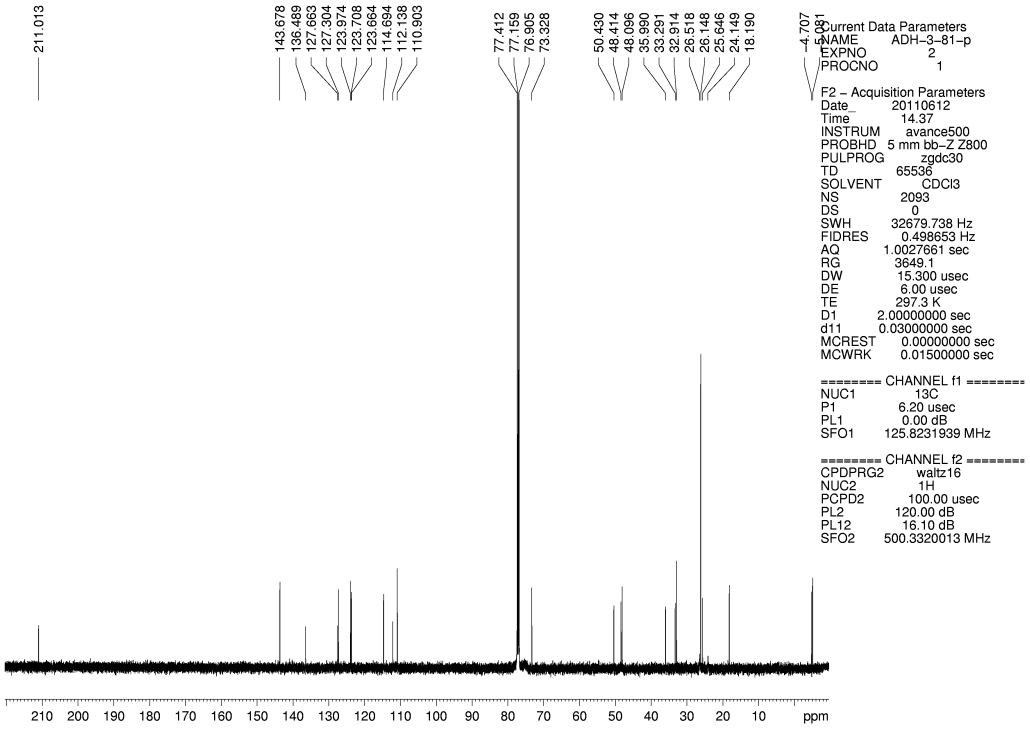
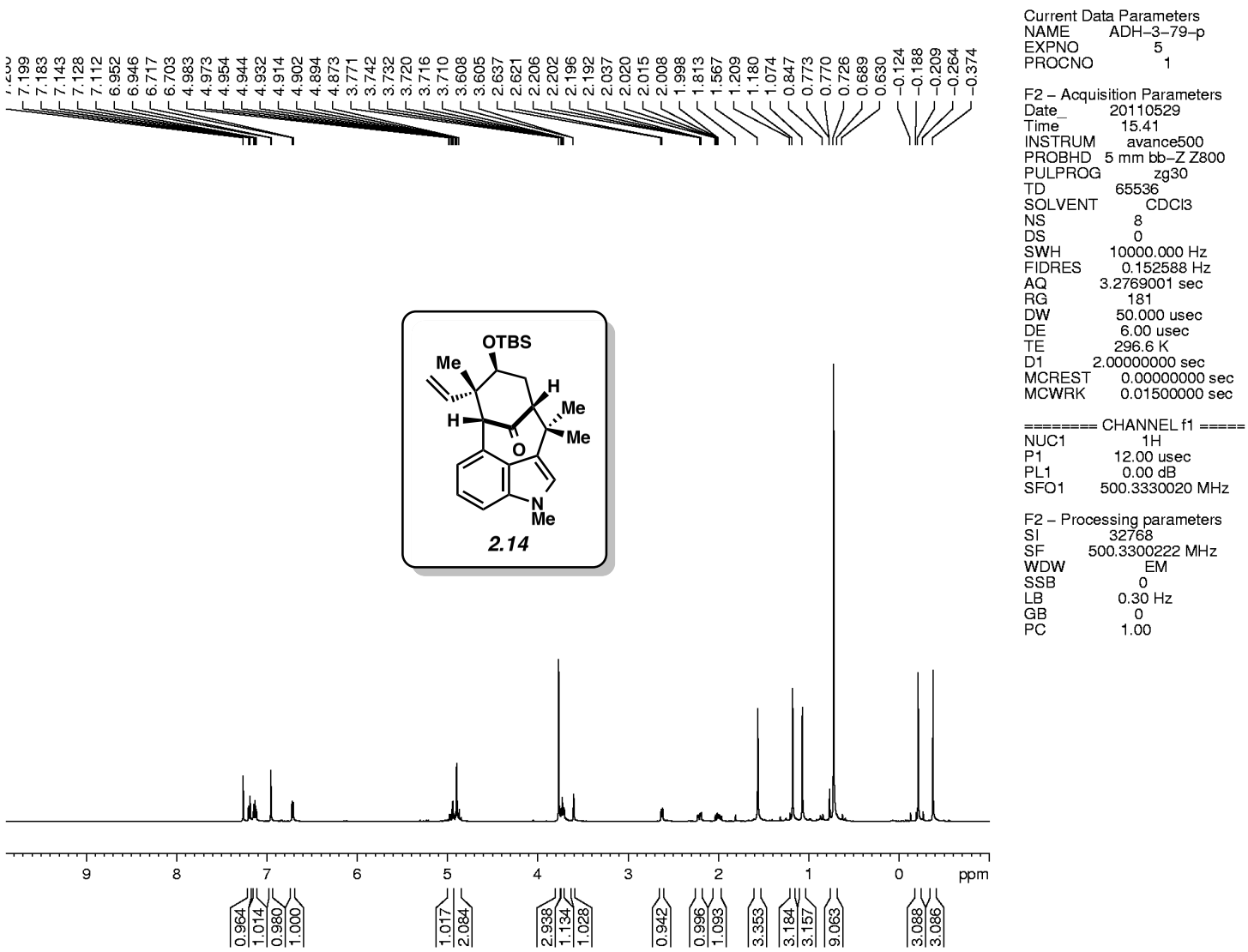


Figure A1.9 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **2.13**.



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PROCNO 1

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TD 65536
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NS 8
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SWH 10000.000 Hz
FIDRES 0.152588 Hz
AQ 3.2769001 sec
RG 181
DW 50.000 usec
DE 6.00 usec
TE 296.6 K
D1 2.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

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

F2 – Processing parameters
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SF 500.3300222 MHz
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SSB 0
LB 0.30 Hz
GB 0
PC 1.00

Figure A1.10 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **2.14**.

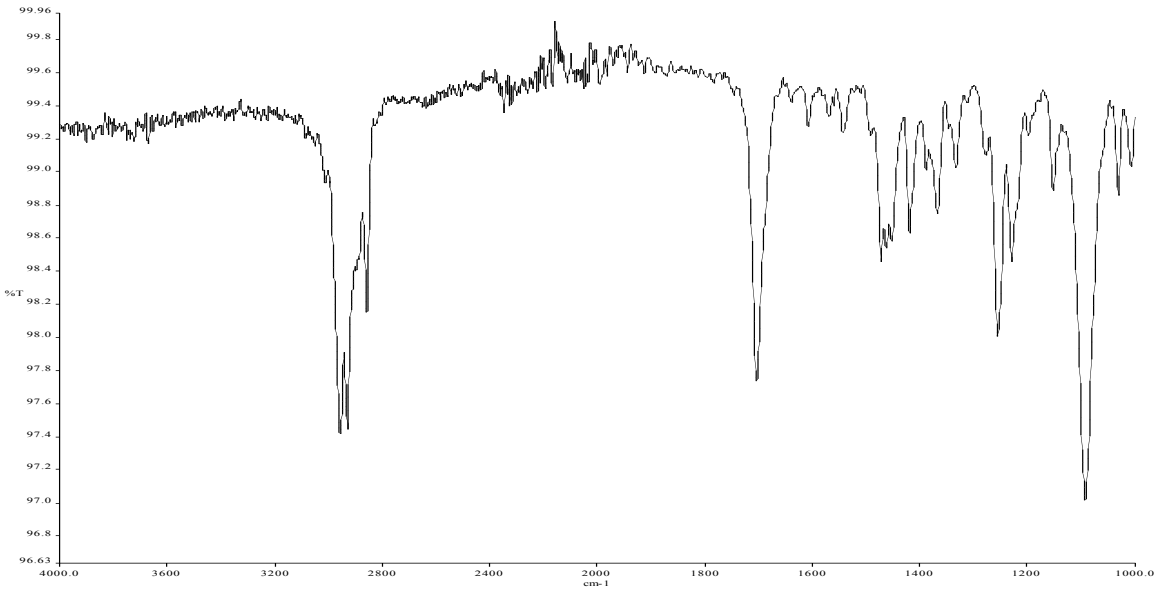


Figure A1.11 Infrared spectrum of compound **2.14**.

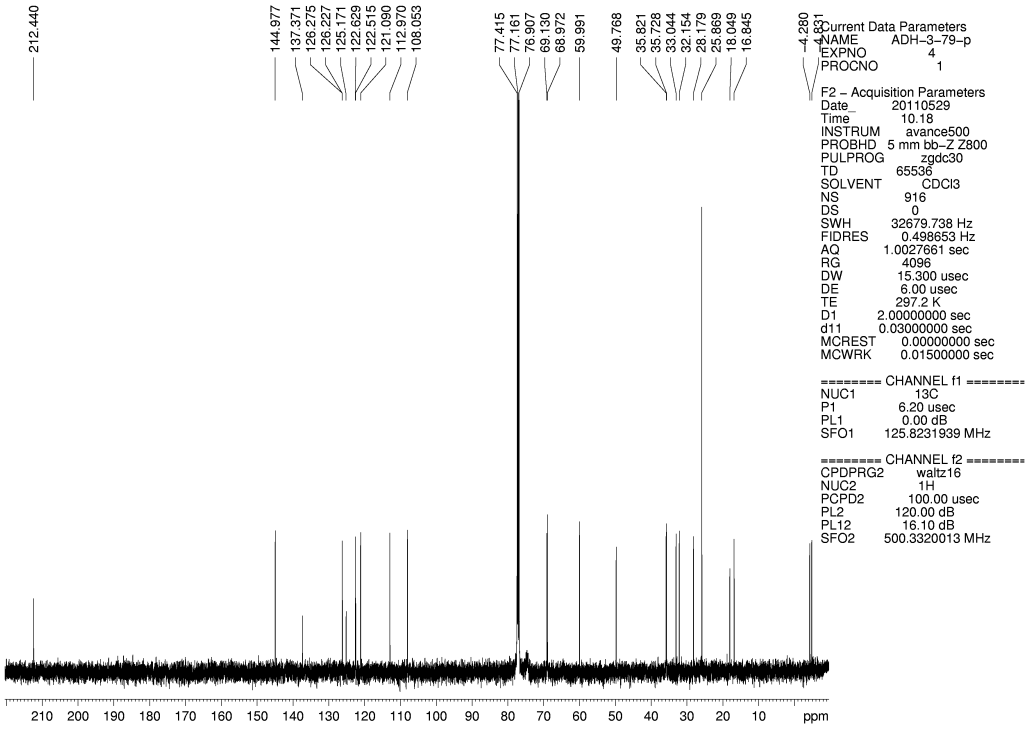
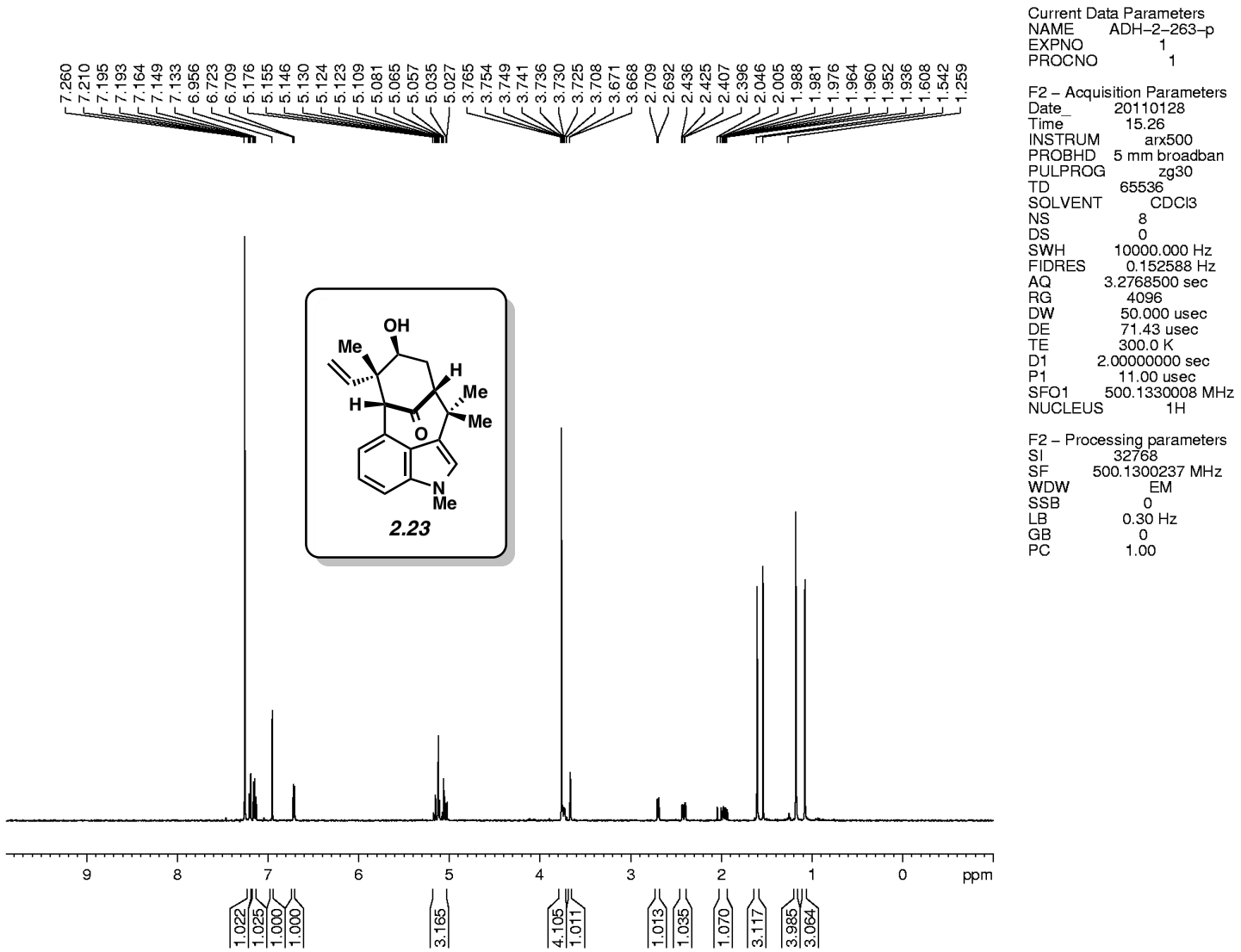


Figure A1.12 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **2.14**.



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EXPNO 1
PROCNO 1

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PROBHD 5 mm broadban
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 8
DS 0
SWH 10000.000 Hz
FIDRES 0.152588 Hz
AQ 3.2768500 sec
RG 4096
DW 50.000 usec
DE 71.43 usec
TE 300.0 K
D1 2.00000000 sec
P1 11.00 usec
SFO1 500.1330008 MHz
NUCLEUS 1H

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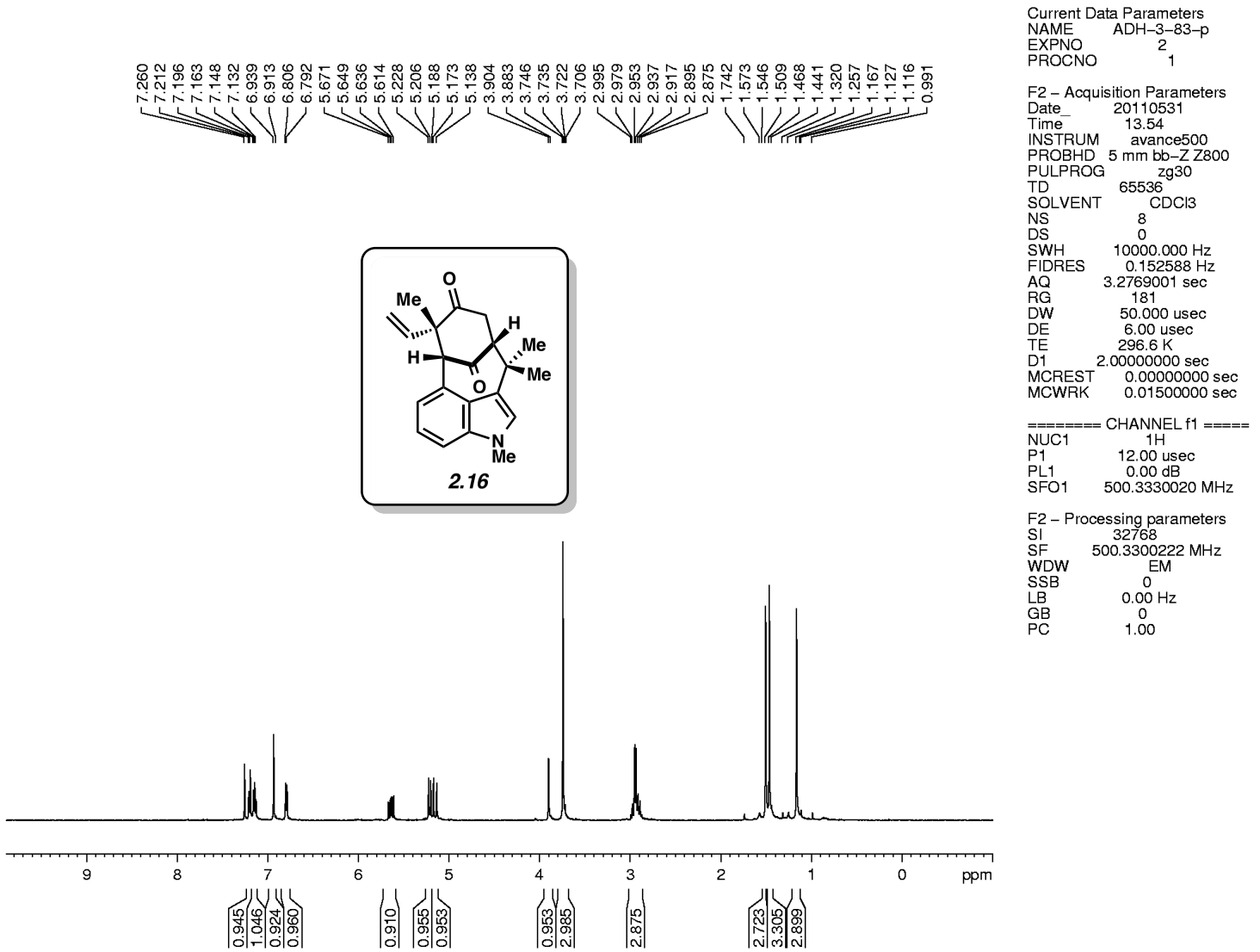
LB 0.30 Hz
GB 0
PC 1.00

Figure A1.13 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **2.23**.



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

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

F2 – Processing parameters
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GB 0
PC 1.00

Figure A1.14 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **2.16**.

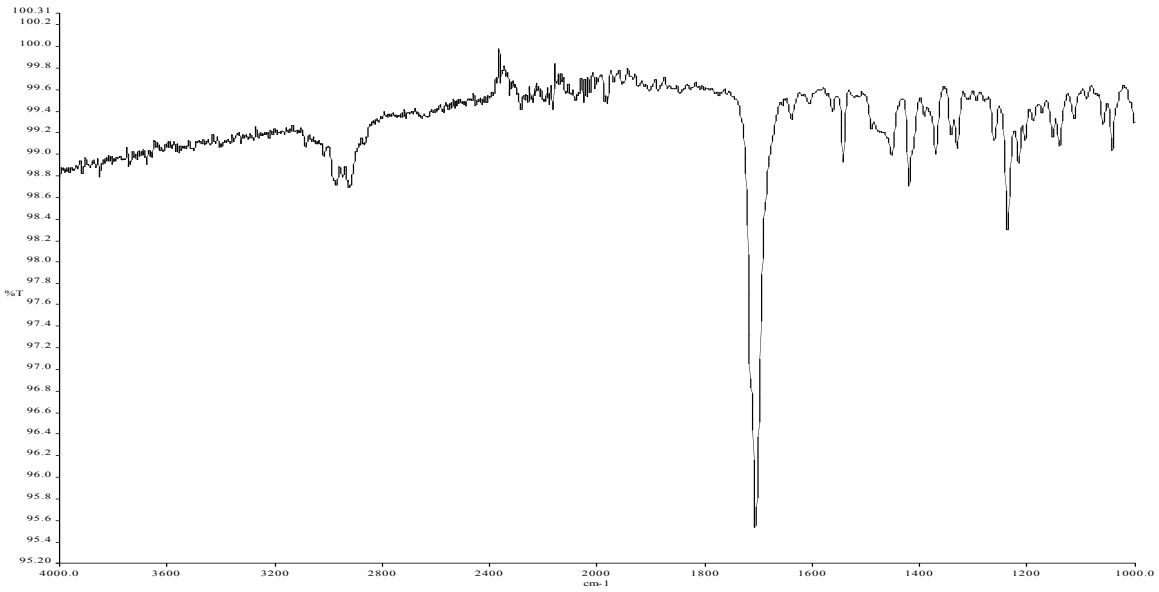


Figure A1.15 Infrared spectrum of compound **2.16**.

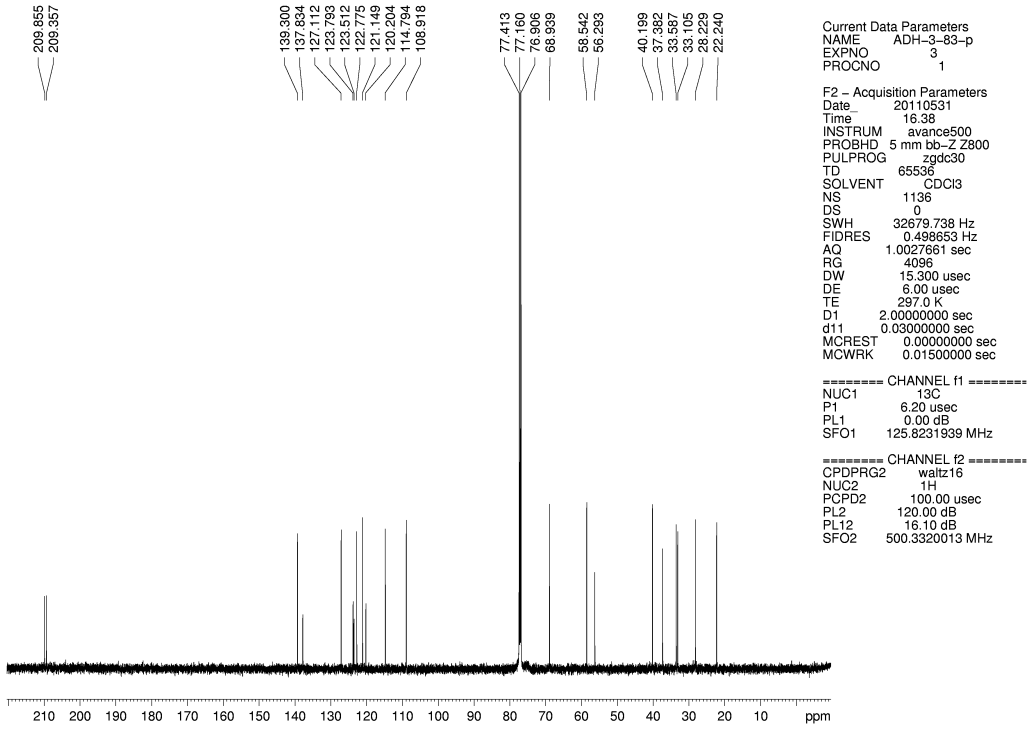
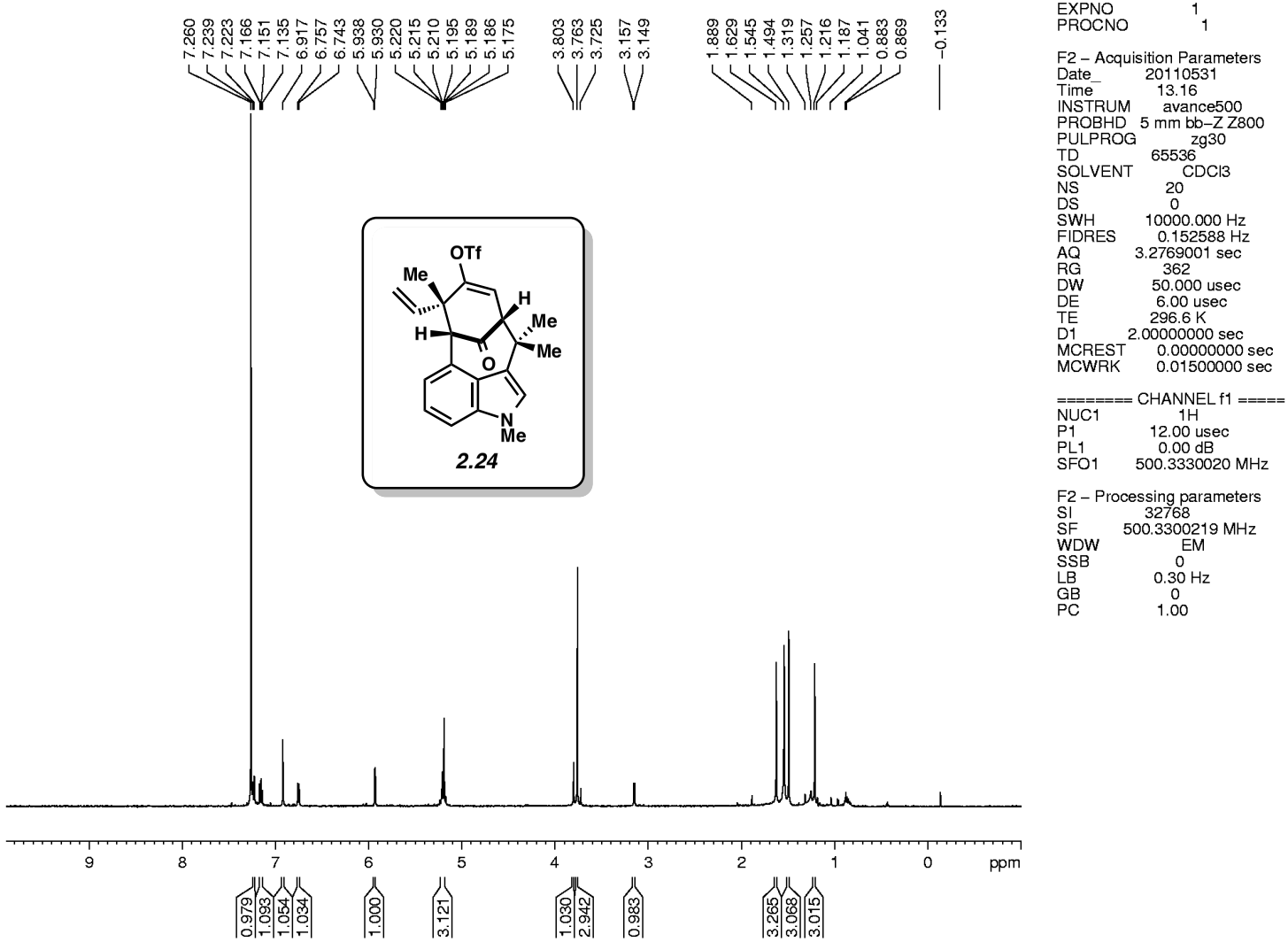


Figure A1.16 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **2.16**.



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PROCNO 1

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TD 65536
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NS 20
DS 0
SWH 10000.000 Hz
FIDRES 0.152588 Hz
AQ 3.2769001 sec
RG 362
DW 50.000 usec
DE 6.00 usec
TE 296.6 K
D1 2.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

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

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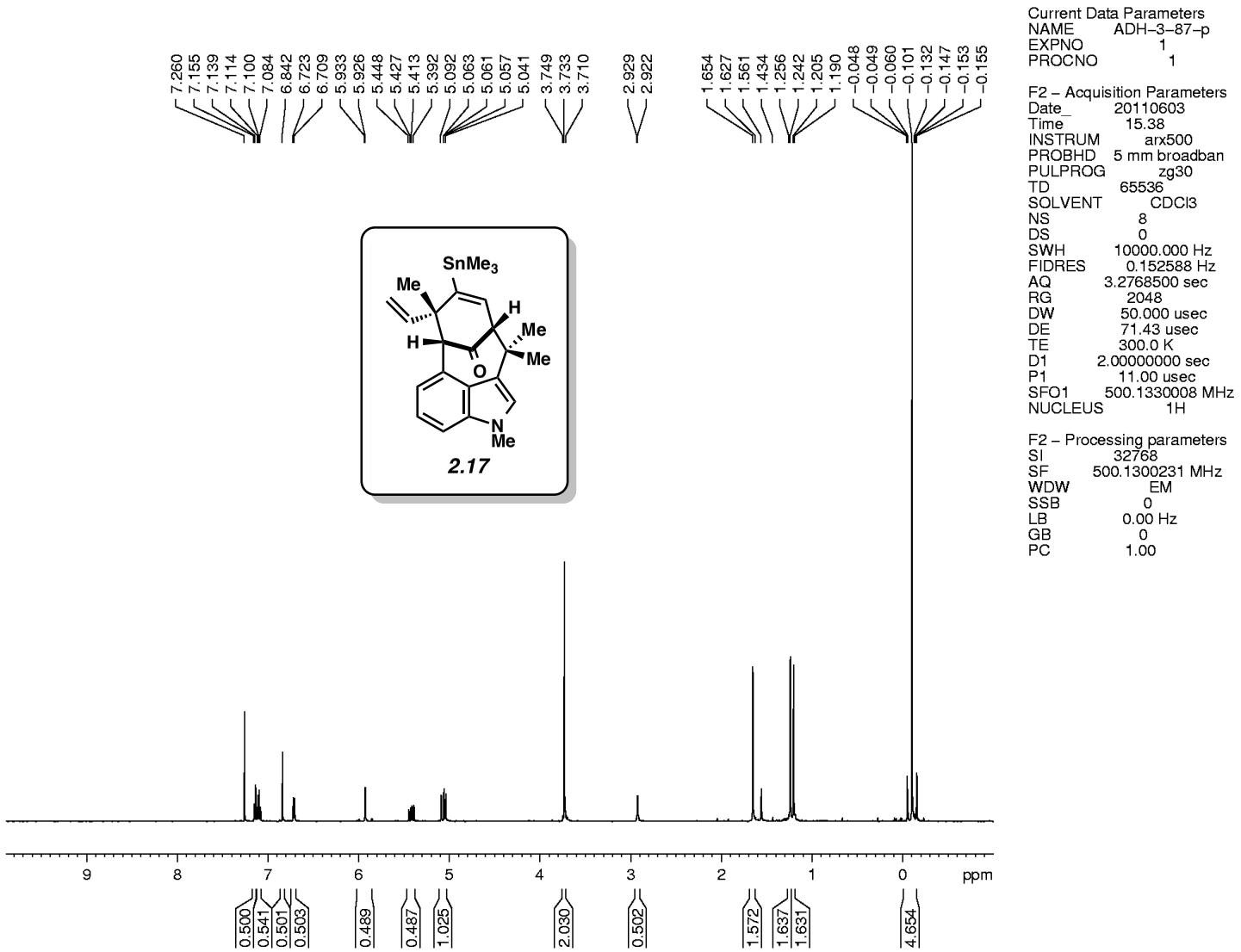
LB 0.30 Hz
GB 0
PC 1.00

Figure A1.17 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **2.24**.



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PROCNO 1

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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 500.1300231 MHz
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LB 0.00 Hz
GB 0
PC 1.00

Figure A1.18 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **2.17**.

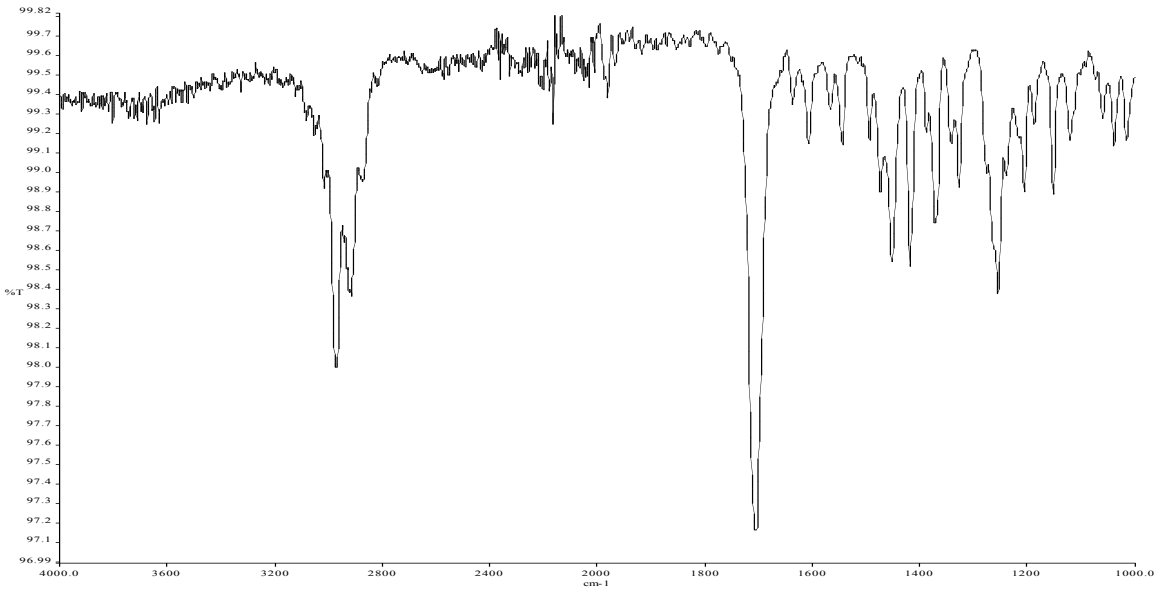


Figure A1.19 Infrared spectrum of compound **2.17**.

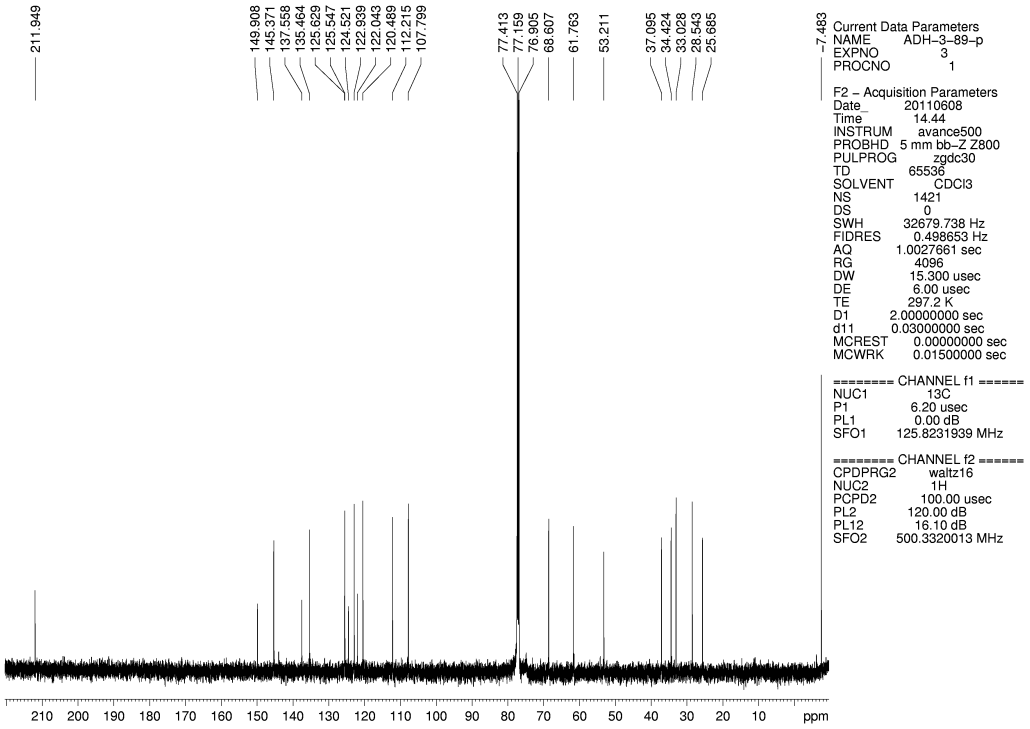
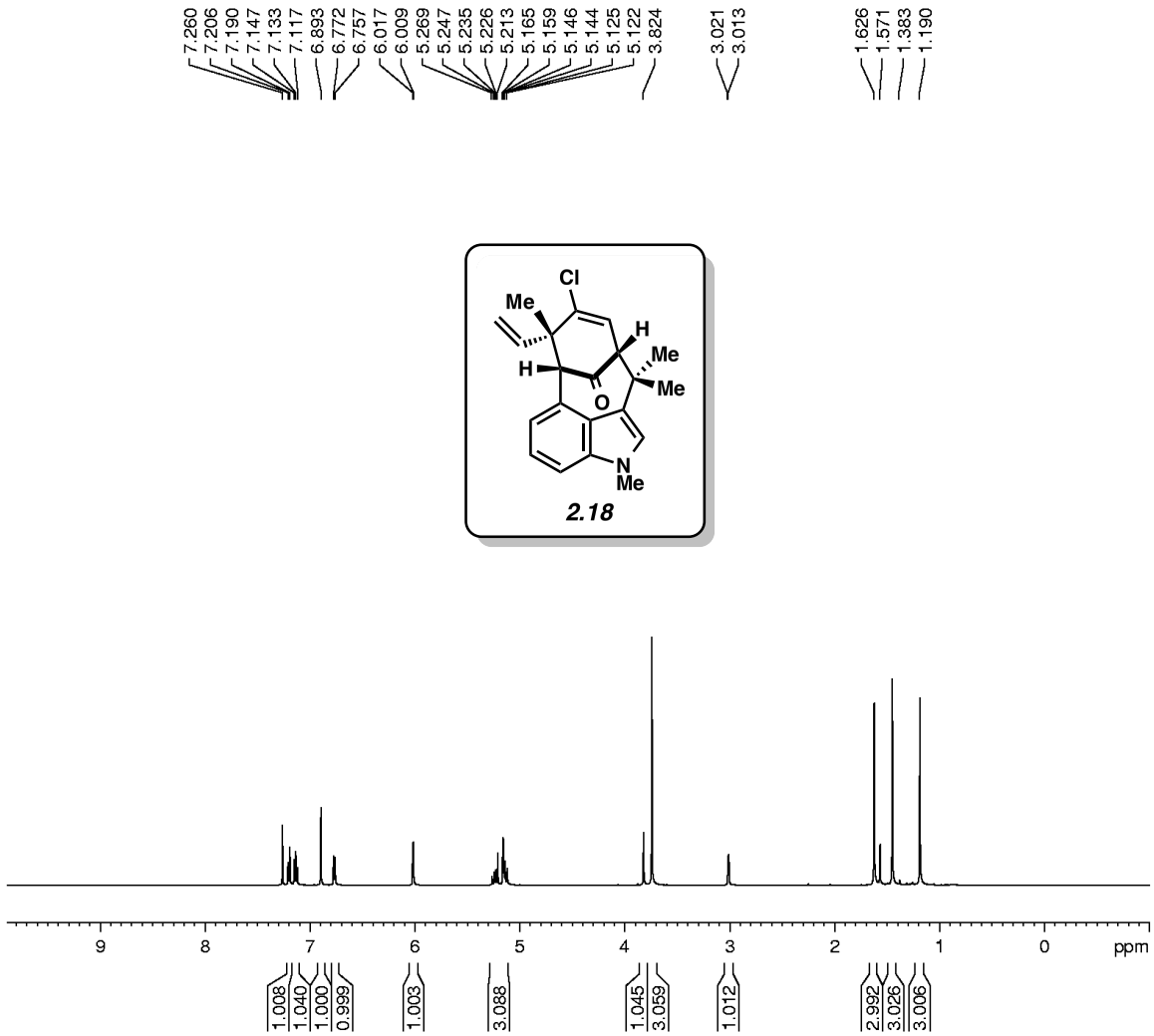


Figure A1.20 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **2.17**.



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PROCNO 1

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SWH 10000.000 Hz
FIDRES 0.152588 Hz
AQ 3.2769001 sec
RG 143.7
DW 50.000 usec
DE 6.00 usec
TE 296.8 K
D1 2.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

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

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

Figure A1.21 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **2.18**.

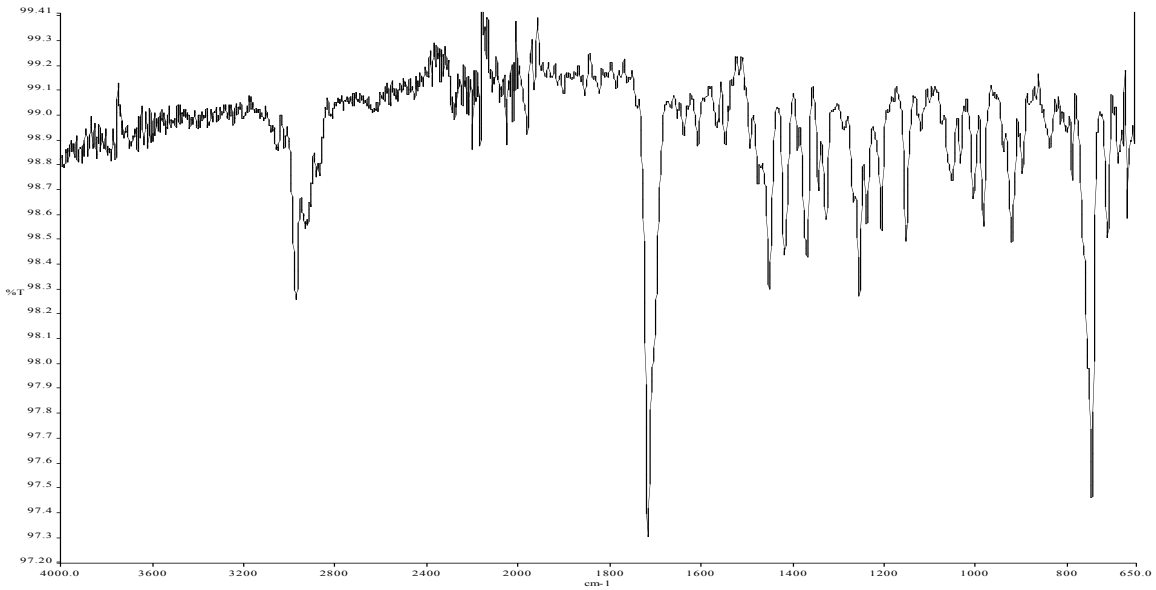


Figure A1.22 Infrared spectrum of compound **2.18**.

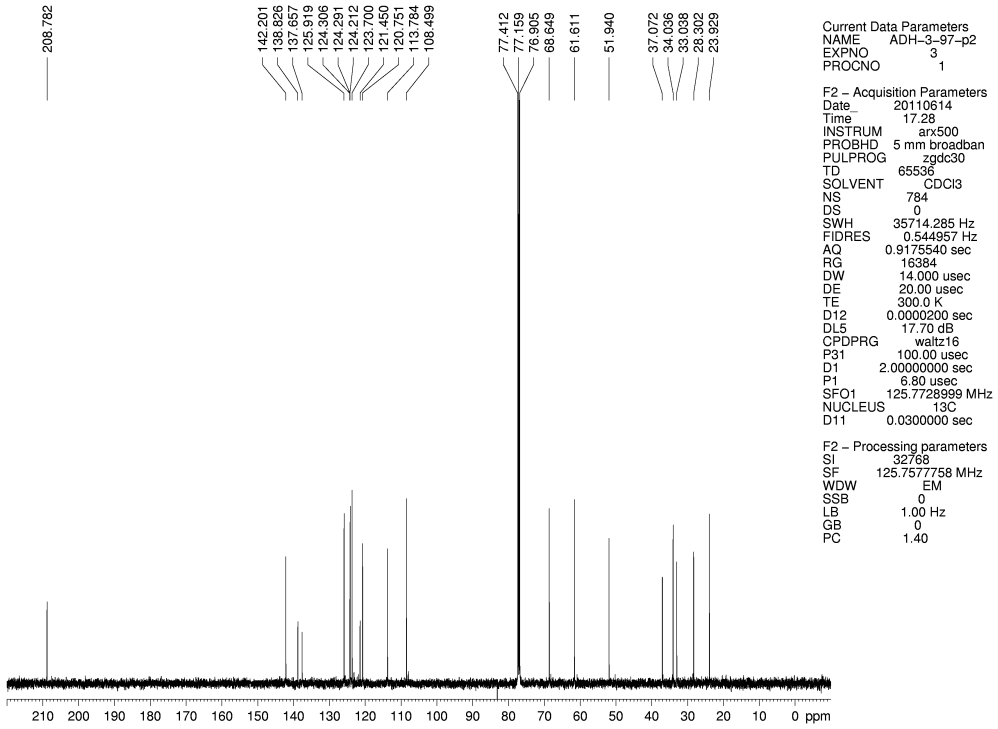


Figure A1.23 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **2.18**.

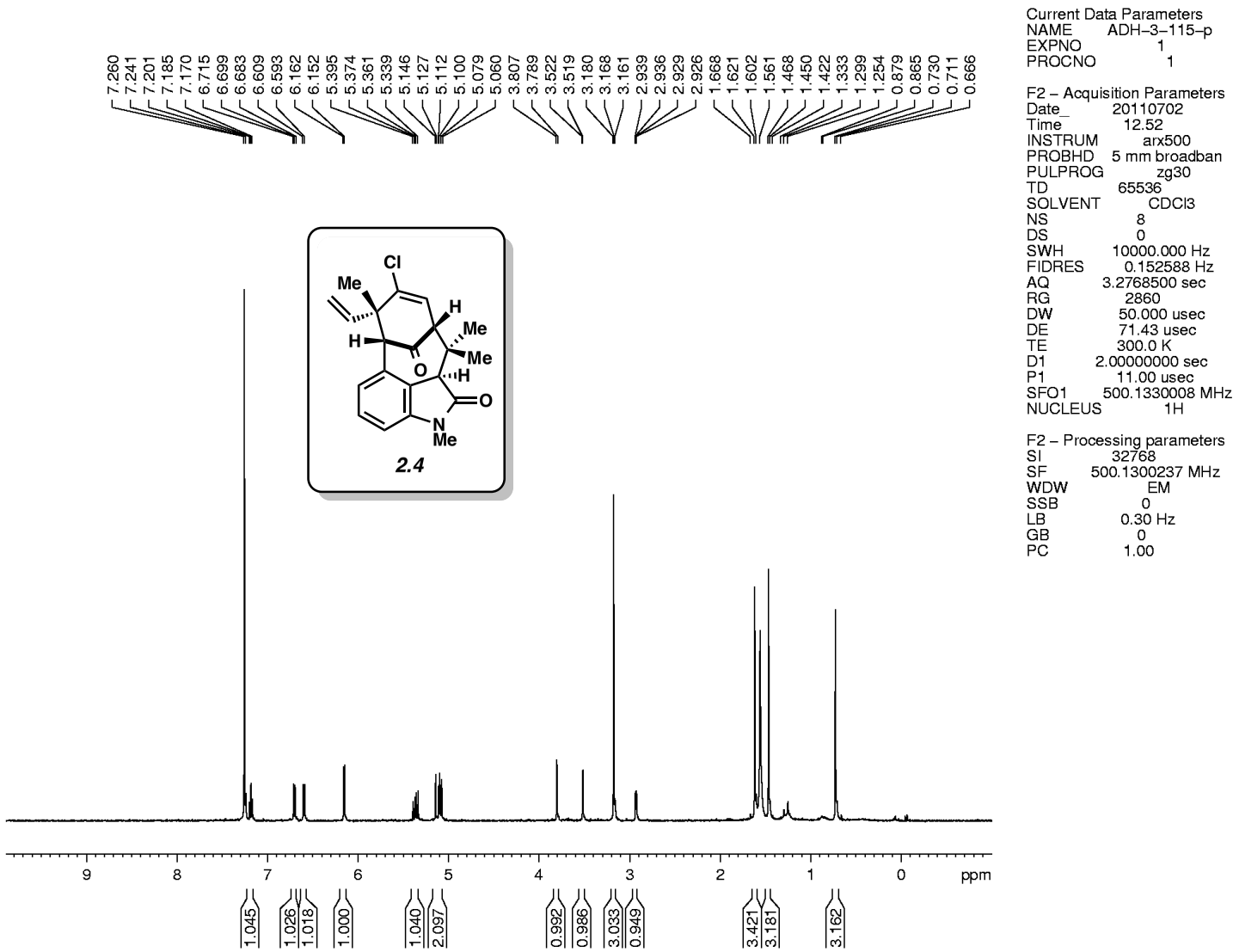


Figure A1.24 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **2.4**.

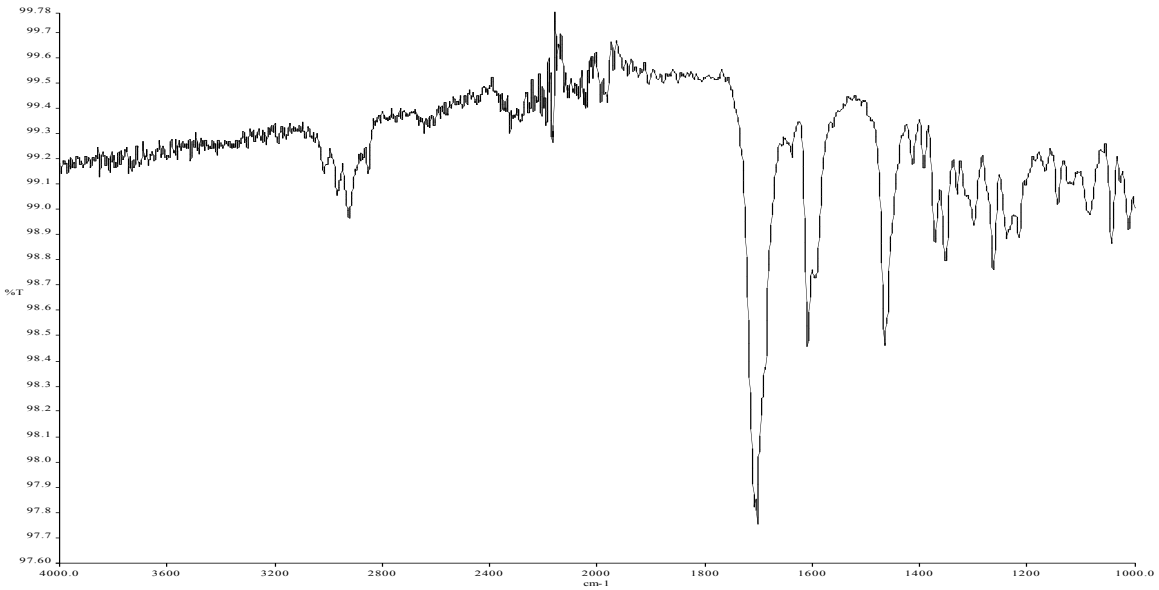


Figure A1.25 Infrared spectrum of compound **2.4**.

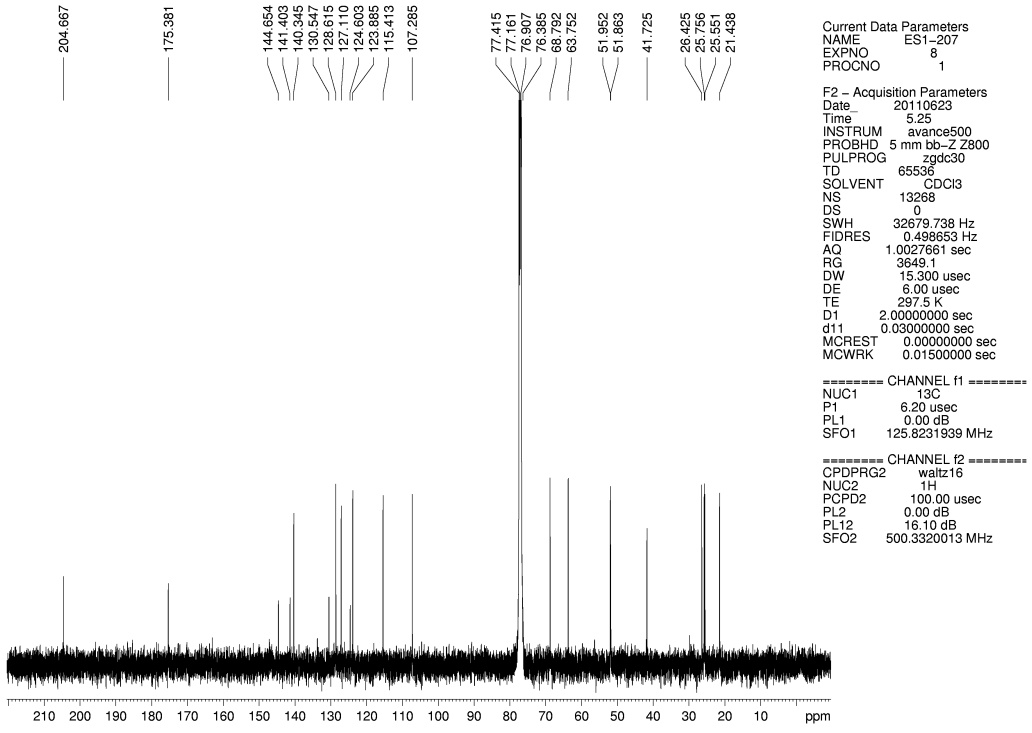
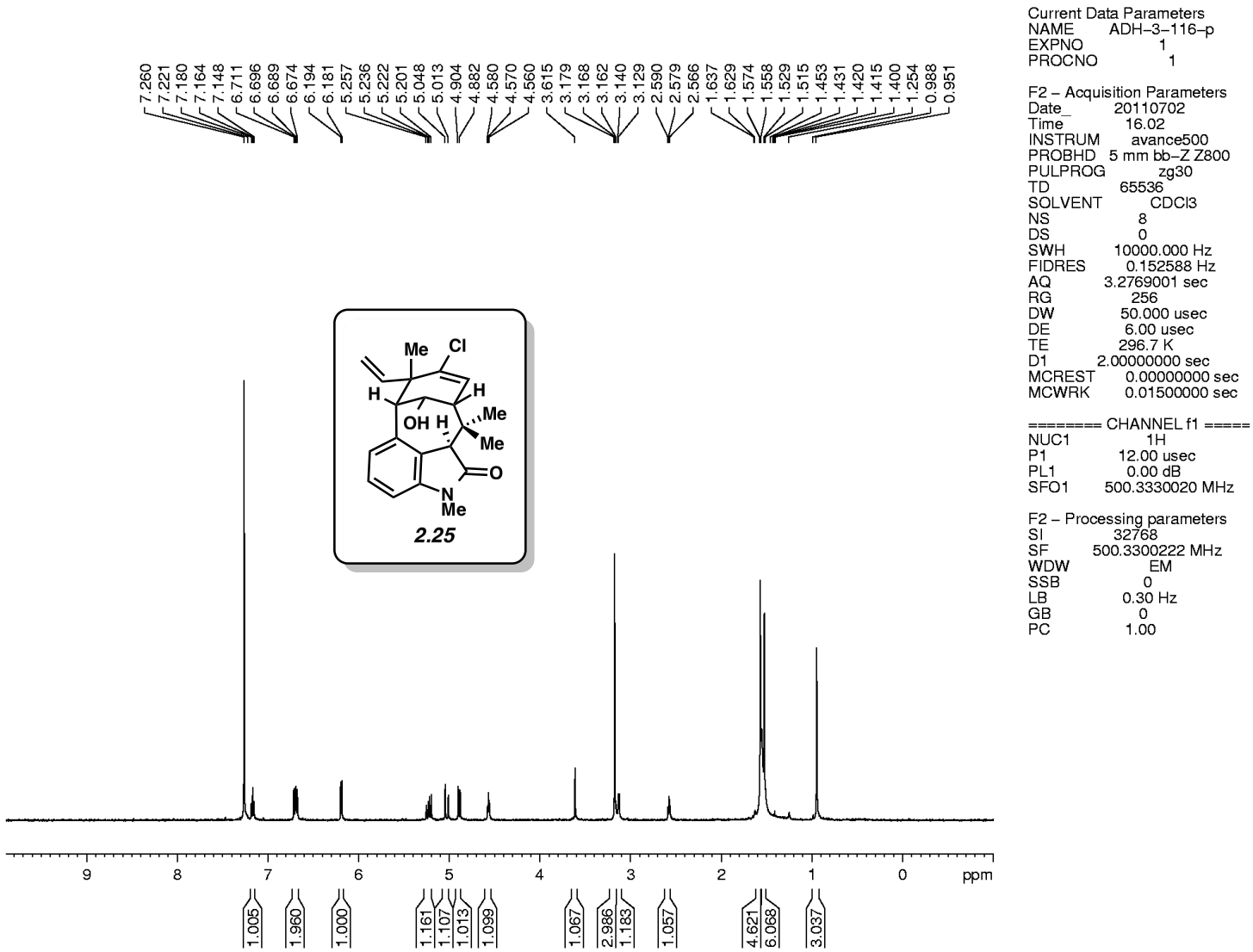


Figure A1.26 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **2.4**.



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PROCNO 1

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FIDRES 0.152588 Hz
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RG 256
DW 50.000 usec
DE 6.00 usec
TE 296.7 K
D1 2.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

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PL1 0.00 dB
SFO1 500.3330020 MHz

F2 – Processing parameters
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SF 500.3300222 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

Figure A1.27 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **2.25**.

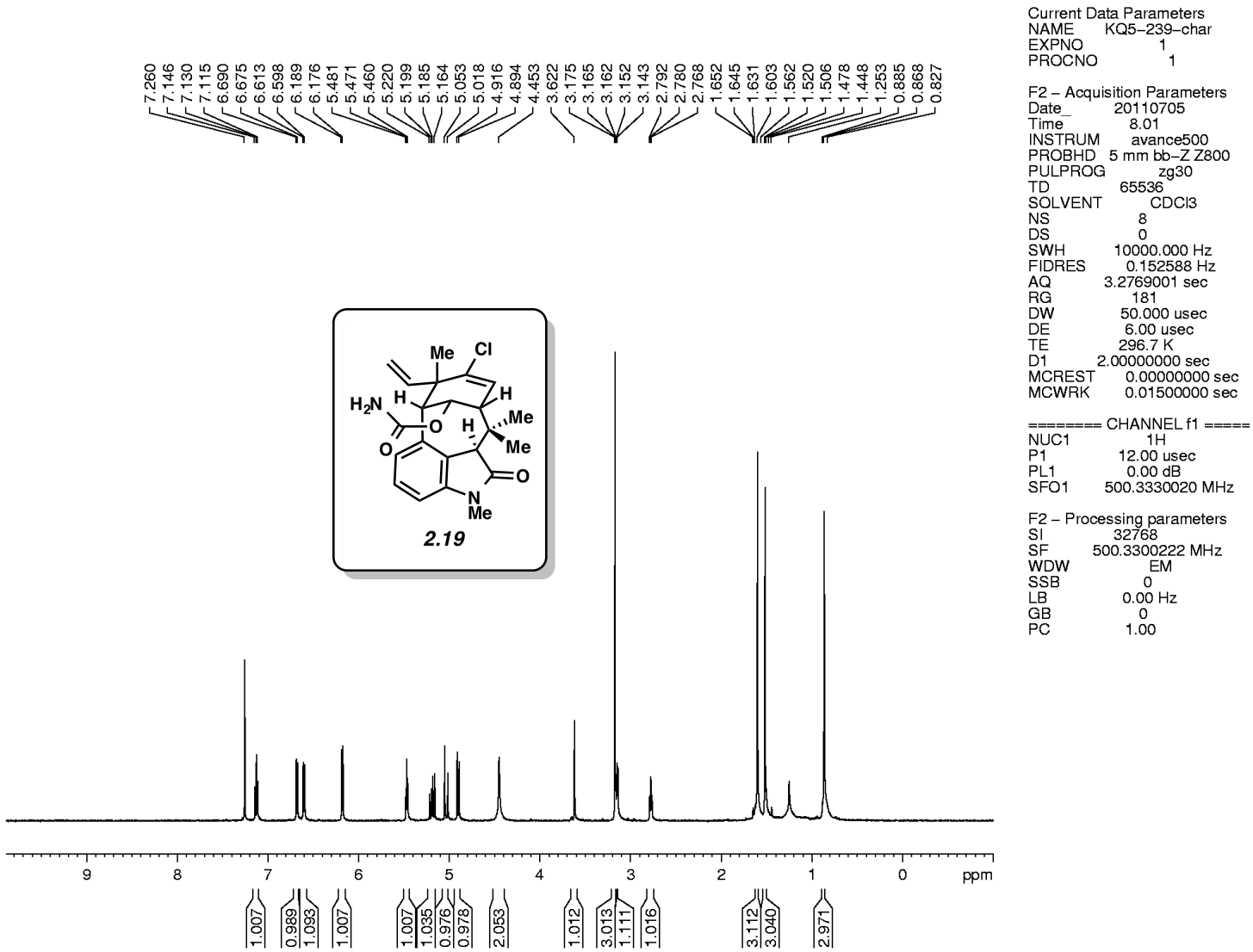


Figure A1.28 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **2.19**.

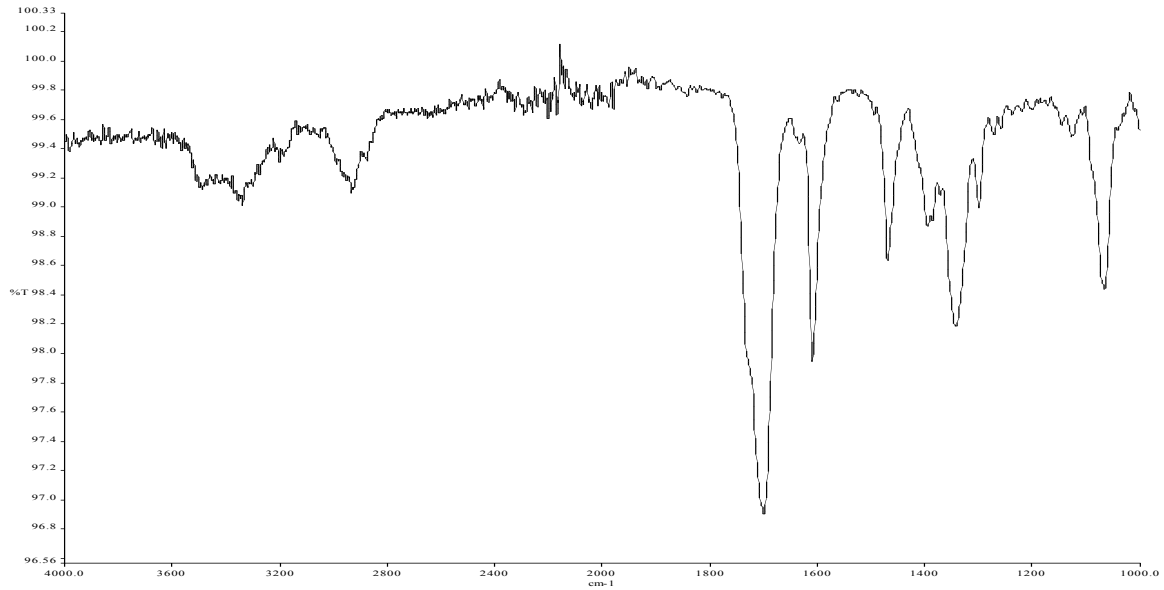


Figure A1.29 Infrared spectrum of compound **2.19**.

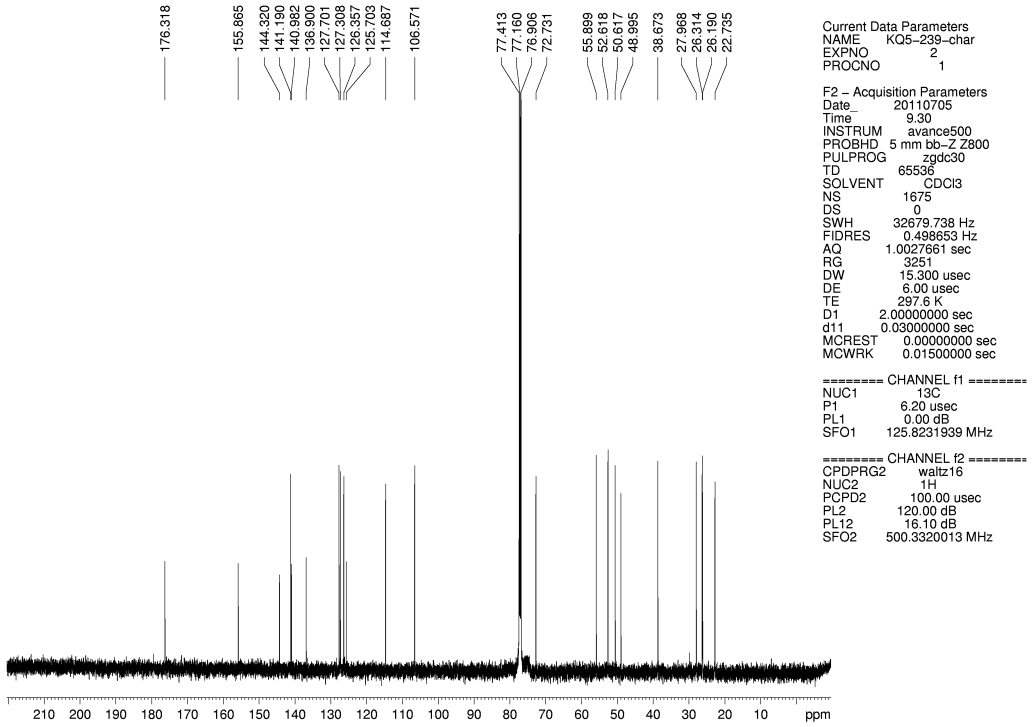
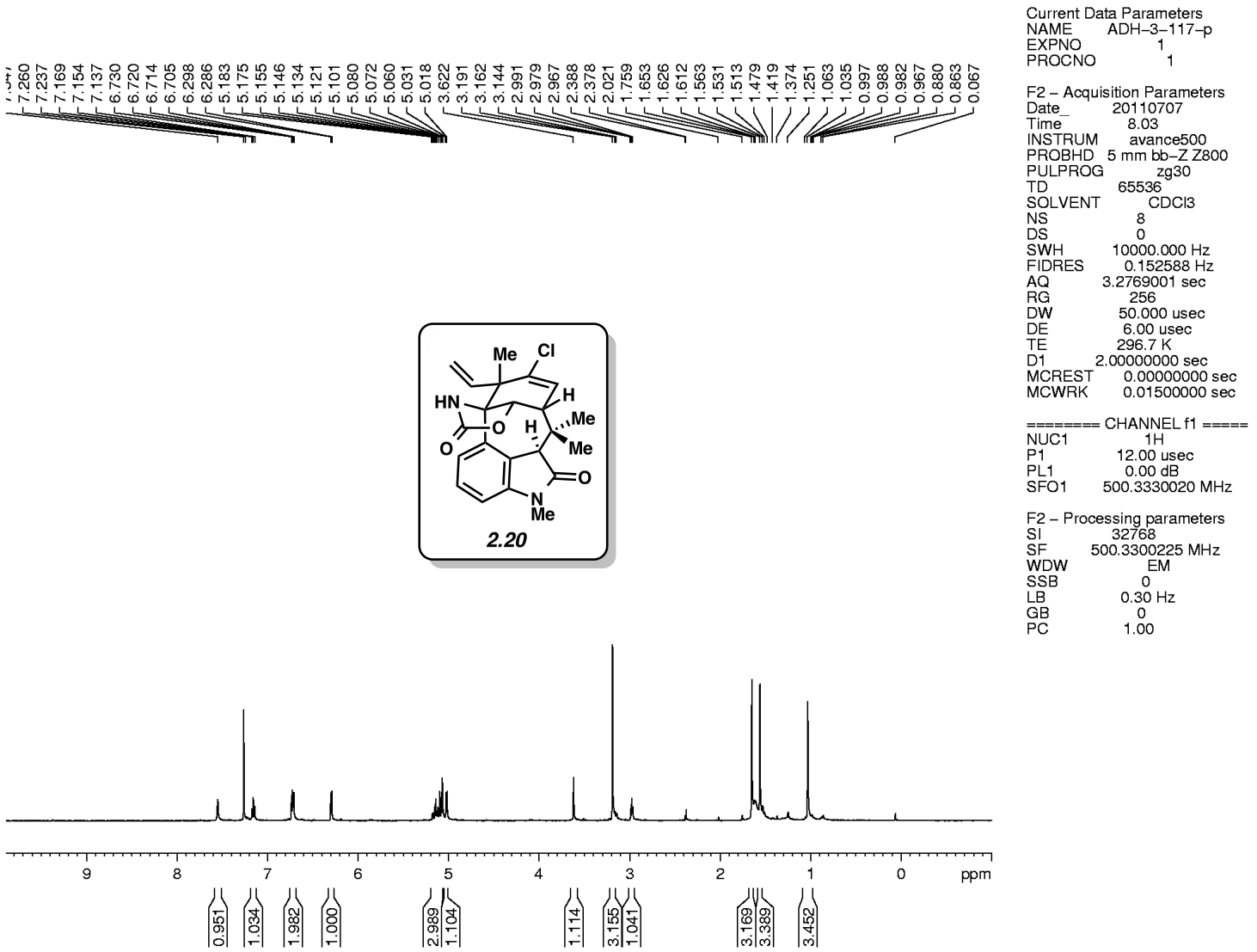


Figure A1.30 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **2.19**.



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PROCNO 1

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SWH 10000.000 Hz
FIDRES 0.152588 Hz
AQ 3.2769001 sec
RG 256
DW 50.000 usec
DE 6.00 usec
TE 296.7 K
D1 2.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

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

F2 – Processing parameters
SI 32768
SF 500.3300225 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

Figure A1.31 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **2.20**.

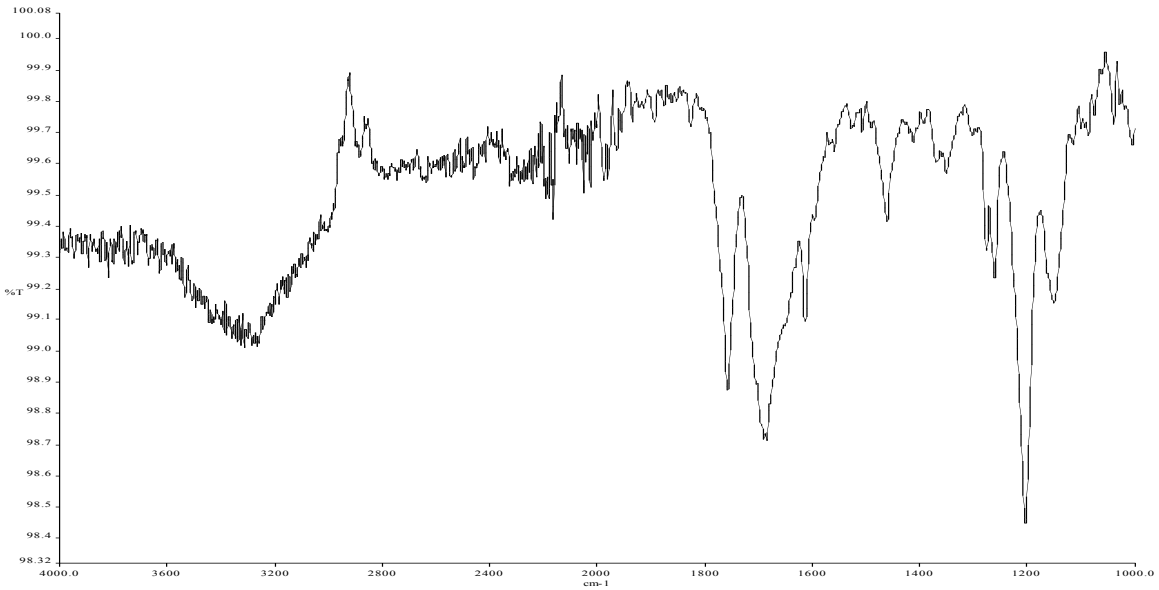


Figure A1.32 Infrared spectrum of compound **2.20**.

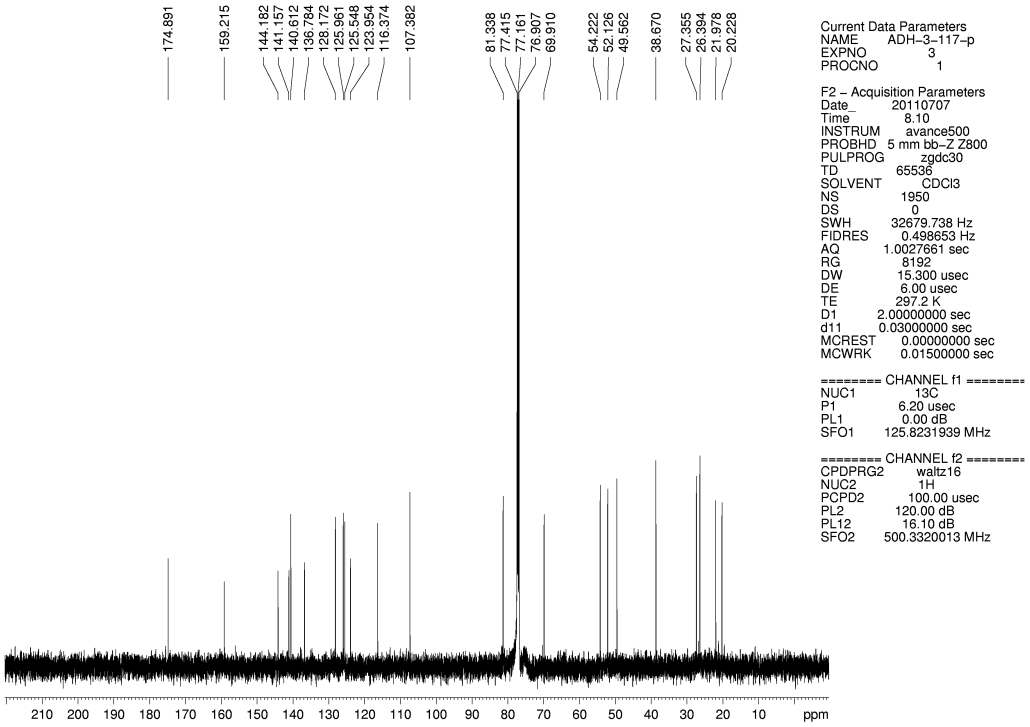
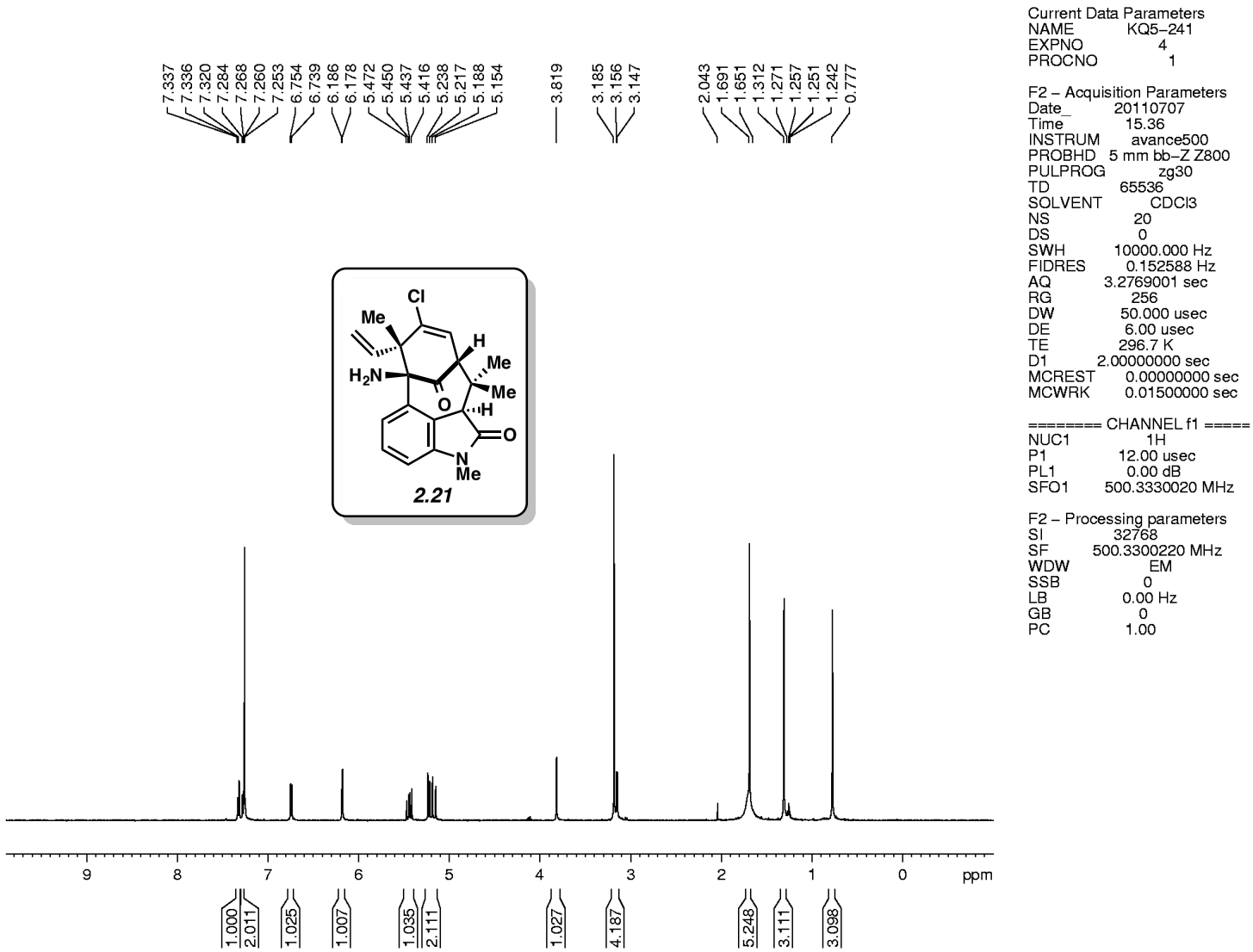


Figure A1.33 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **2.20**.



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EXPNO 4
PROCNO 1

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

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

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

Figure A1.34 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **2.21**.

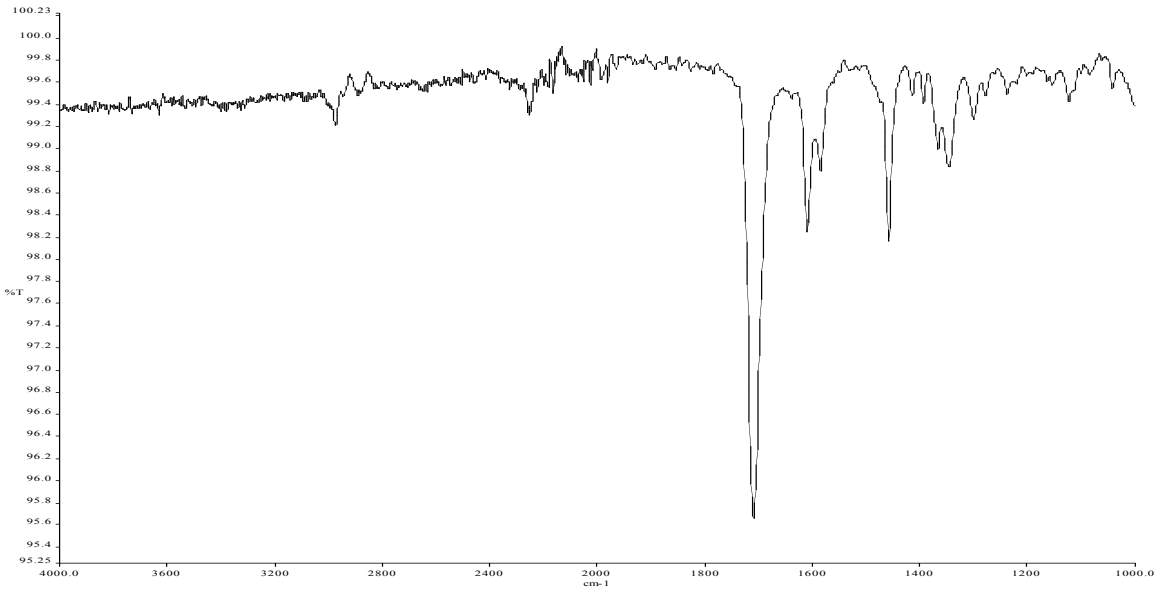


Figure A1.35 Infrared spectrum of compound **2.21**.

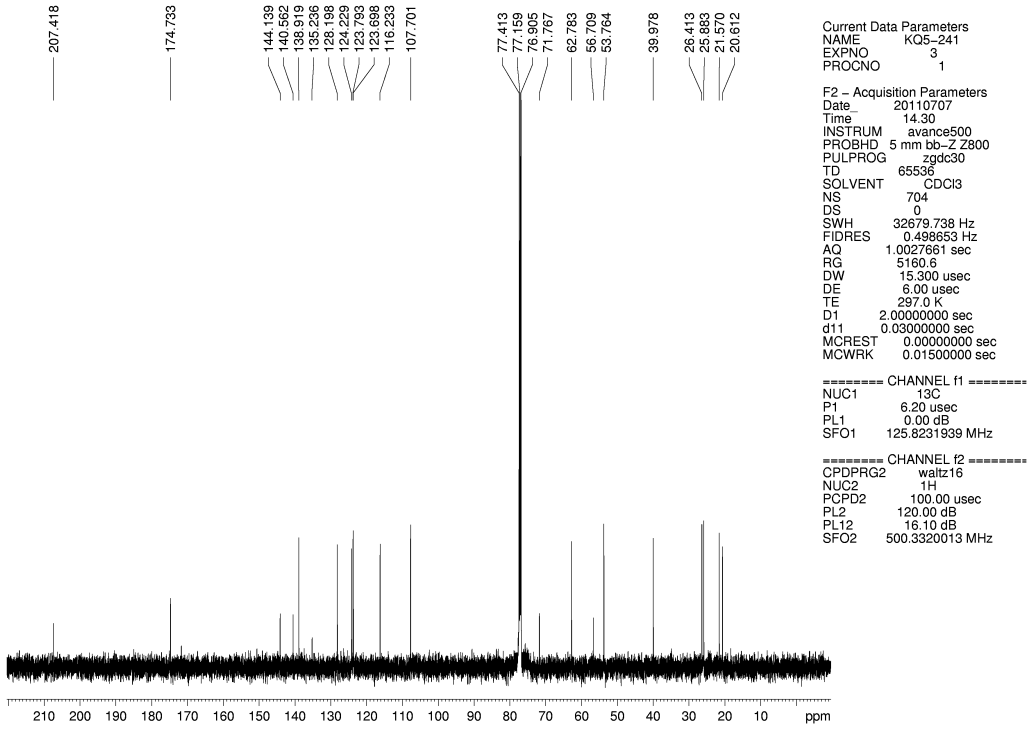
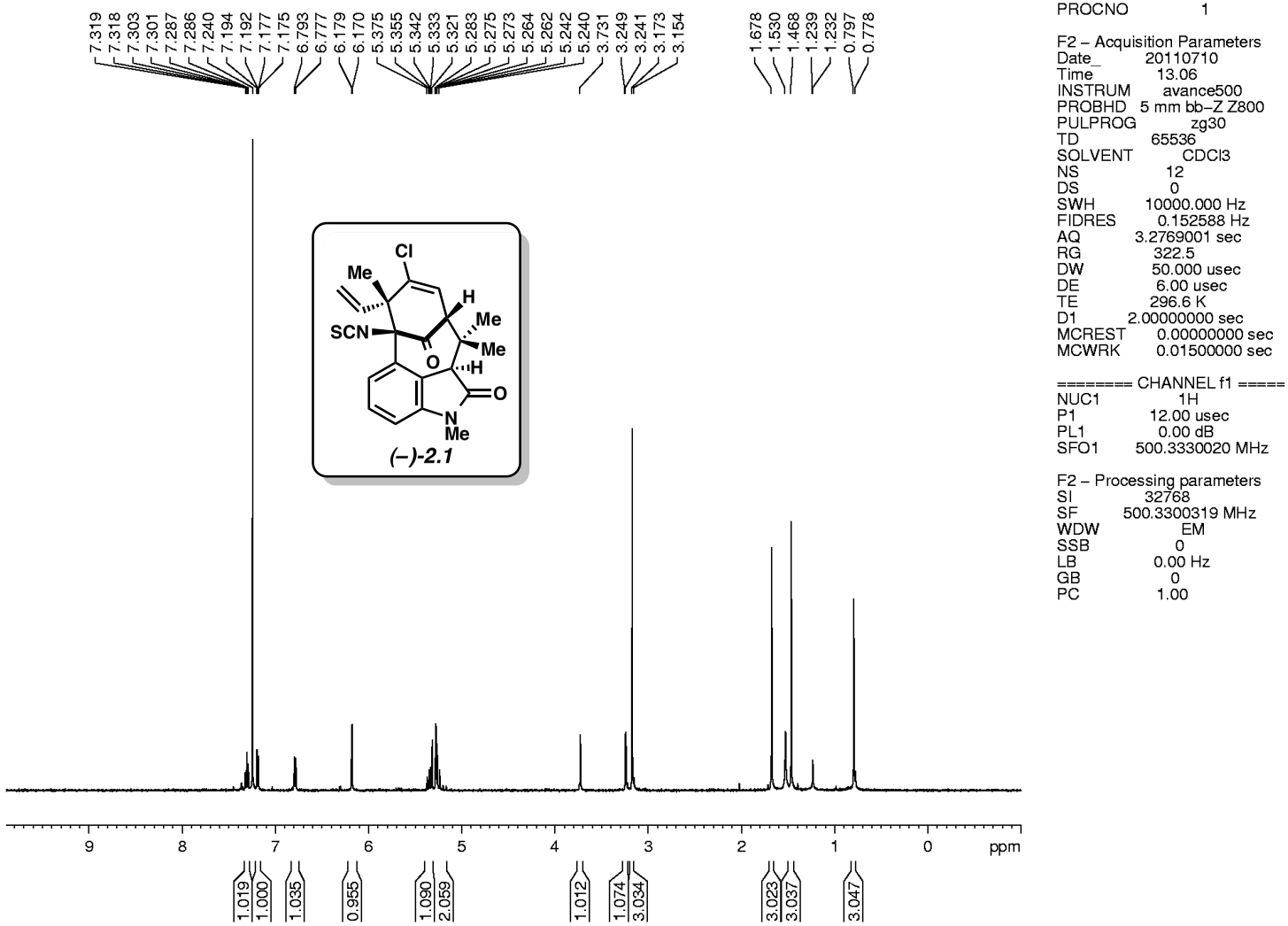


Figure A1.36 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **2.21**.



Current Data Parameters
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PROCNO 1

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FIDRES 0.152588 Hz
AQ 3.2769001 sec
RG 322.5
DW 50.000 usec
DE 6.00 usec
TE 296.6 K
D1 2.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

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

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

Figure A1.37 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **2.1**.

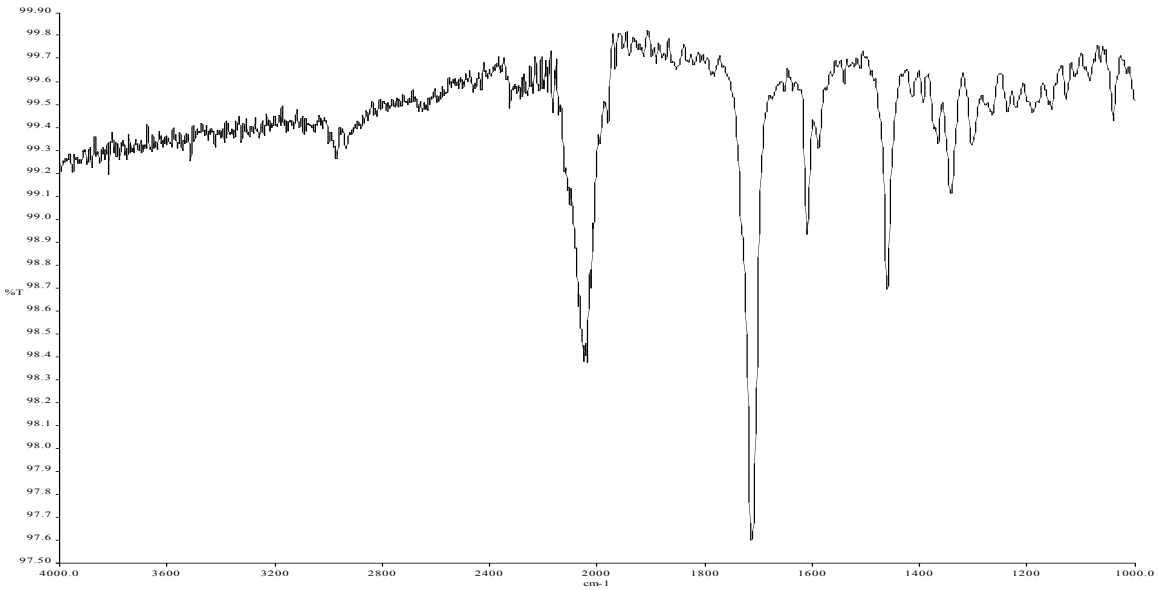


Figure A1.38 Infrared spectrum of compound **2.1**.

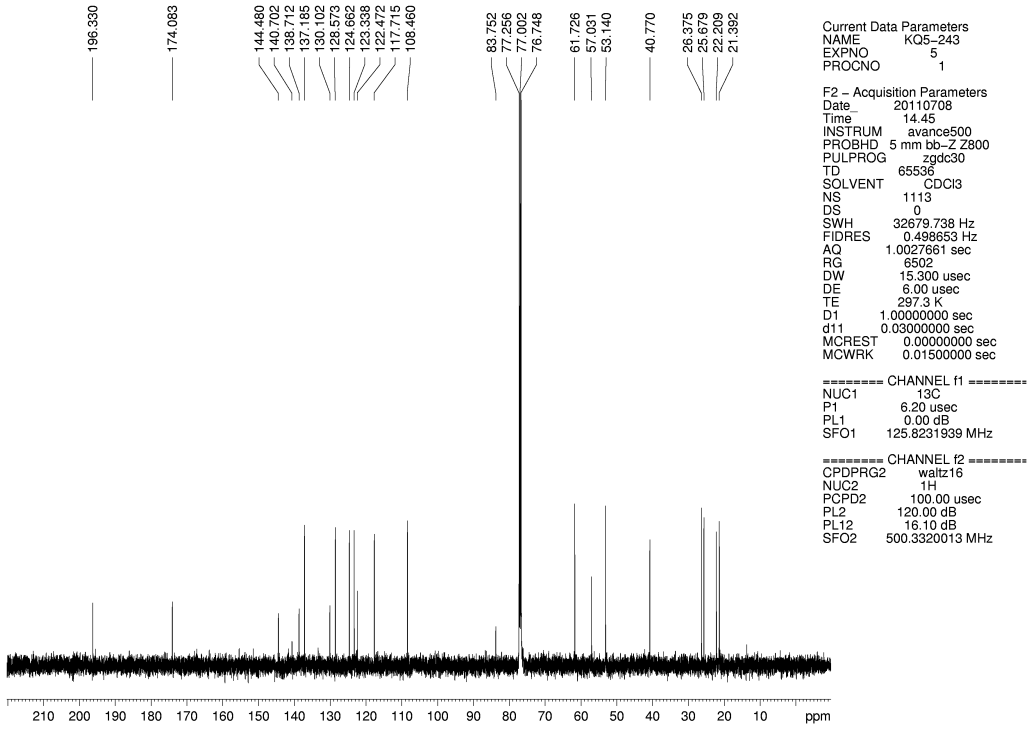


Figure A1.39 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **2.1**.

CHAPTER THREE

Enantiospecific Total Synthesis of *N*-Methylwelwitindolinone D Isonitrile

Evan D. Styduhar, Alexander D. Huters, Nicholas A. Weires, and Neil K. Garg.

Angew. Chem. Int. Ed. **2013**, *52*, 12422–12425.

3.1 Abstract

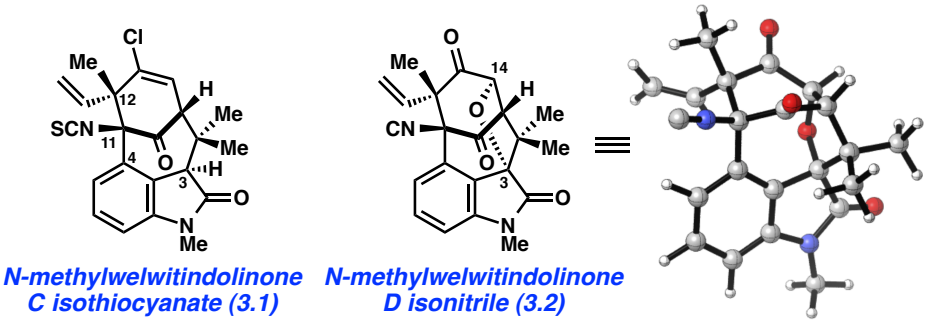
The total synthesis of *N*-methylwelwitindolinone D isonitrile has been achieved in 17 steps from a readily available carvone derivative. The route features a double C–H functionalization event involving a keto oxindole substrate to introduce the tetrahydrofuran ring of the natural product.

3.2 Introduction

The welwitindolinone family of natural products (e.g., **3.1**–**3.2**, Figure 3.1) has attracted tremendous attention from the synthetic community over the past two decades.[1,2,3,4,5] Interest in these compounds stems from their promising biological profiles, in addition to their compact, yet daunting structures. Synthetic efforts toward the welwitindolinones have led to at least ten methods for building the bicyclo[4.3.1] core that is common to most of these natural products.[1,4] However, the sheer difficulty associated with late-stage manipulations has plagued most synthetic routes and only a few completed syntheses have been reported in recent years.[5]

One exceptionally challenging synthetic target is *N*-methylwelwitindolinone D isonitrile (**3.2**).[6,7] The compound possesses five stereocenters, two quaternary carbons, and a heavily substituted cyclohexyl ring. Compared to other related family members, **3.2** also possesses an ether linkage between C3 and C14. Thus, a successful synthesis of **3.2** would not only have to

assemble the congested oxindole-fused bicyclo[4.3.1] framework, but would also have to allow for introduction of the ethereal linkage on the sterically congested face of the bicycle. Highlights of synthetic efforts toward **3.2** include the Wood group's assembly of the spirocyclic oxindole[8] and Rawal's elegant total synthesis of (±)-**3.2** in 2011.[5a] Herein, we report our synthetic forays toward **3.2**, which culminate in an enantiospecific synthesis.



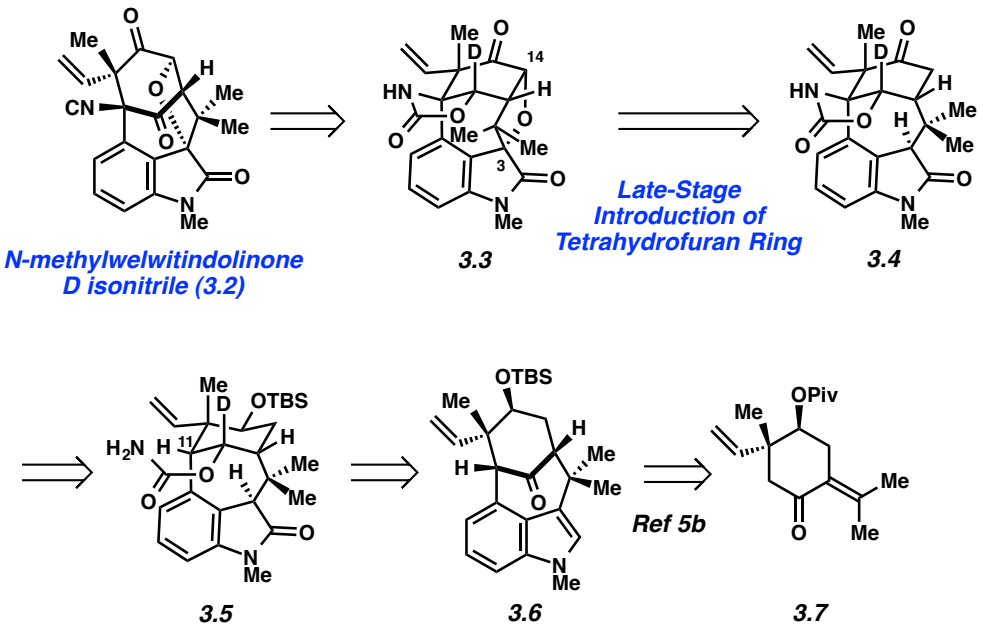
***N*-methylwelwitindolinone C isothiocyanate (3.1)** **N-methylwelwitindolinone D isonitrile (3.2)**

Figure 3.1. Welwitindolinones **3.1** and **3.2**.

3.3 Retrosynthetic Analysis of *N*-Methylwelwitindolinone D Isonitrile

Our retrosynthetic plan for the synthesis of **3.2** is presented in Scheme 3.1. The natural product would be accessed from **3.3** via late-stage manipulations. In a key disconnection, the tetrahydrofuran ring would be installed from keto-oxindole derivative **3.4**. Of note, the ability to elaborate **3.4** to **3.3** would hinge on our ability to perform chemoselective and diastereoselective manipulations adjacent to the two carbonyls. The cyclic carbamate was thought to be accessible using an intramolecular nitrene insertion reaction[9] involving oxindole substrate **3.5**. Substrate **3.5** would be derived from ketone **3.6**, which in turn can be readily prepared from known carvone derivative **3.7**[10] in just four steps using our previously established procedure involving an indolyne cyclization.[5b,11]

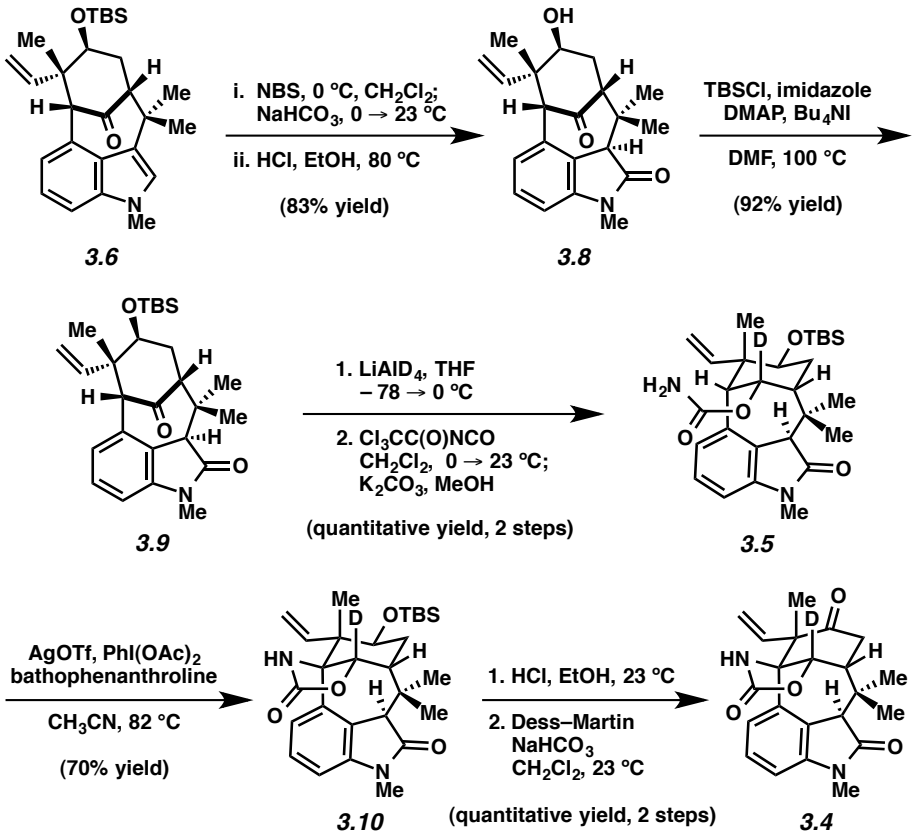
Scheme 3.1



3.4 Elaboration of Bicycle to Keto Oxindole

Our approach toward implementing the retrosynthetic plan is highlighted in Scheme 3.2. Indole **3.6** was converted to oxindole **3.8** using a one-pot oxidation/hydrolysis sequence. As the acidic conditions led to desilylation, reprotection of the alcohol was necessary to provide **3.9**. Deuteride reduction and carbamoylation proceeded without event to furnish **3.5** in quantitative yield. Exposure of **3.5** to Ag-promoted nitrene insertion conditions[12,5e] furnished **3.10** in 70% yield. Note that attempts to use the proteo analog of **3.5** gave only 44% yield of the corresponding insertion product, along with 19% of recovered ketone **3.9**. Consistent with our previous findings on an alternate substrate,[5e] the strategic use of deuterium minimizes an undesirable competitive reaction, thus giving synthetically useful yields of the desired insertion product **3.10**. From **3.10**, a standard deprotection/oxidation sequence delivered key intermediate **3.4**.

Scheme 3.2

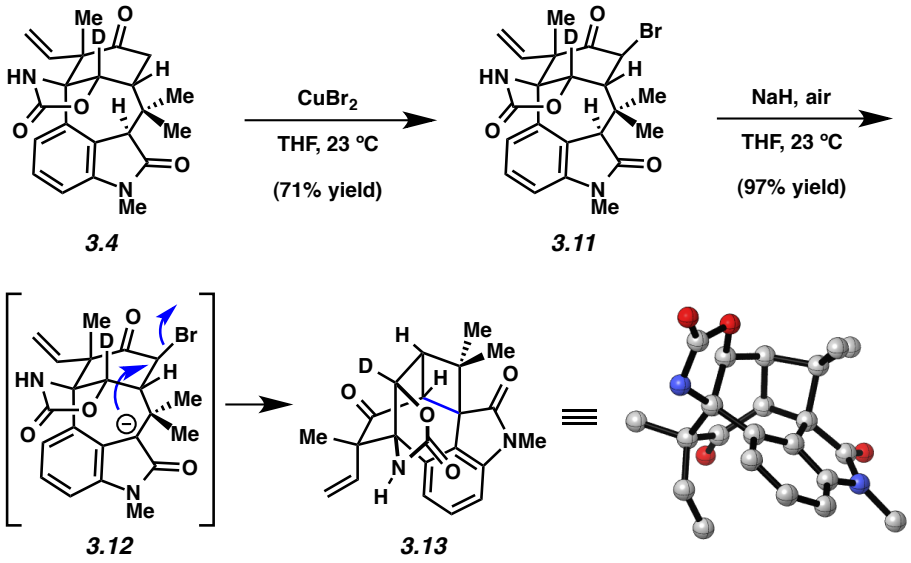


3.5 Unexpected Formation of Spirocyclobutane

Many attempts to introduce the tetrahydrofuran ring from **3.4** were put forth. Unfortunately, efforts toward site-selective functionalization of one carbonyl over the other via enol ethers were unsuccessful. After considerable experimentation, it was found that the keto carbonyl could be α-functionalized first upon treatment of **3.4** with $CuBr_2$ in THF at ambient temperature to yield **3.11** as a single diastereomer (Scheme 3.3). It was hoped that C3 oxidation would provide an alcohol intermediate that would cyclize to give the necessary tetrahydrofuran ring. However, upon treatment of **3.11** with C3 oxidation conditions,[5b] the desired oxidation and cyclization did not occur. Instead, we unexpectedly obtained cyclobutane **3.13** in high yield,

presumably through direct cyclization of the oxindole enolate (see transition structure **3.12**).[13] X-ray analysis of a single crystal of **3.13** validated our structural assignment.[14,7]

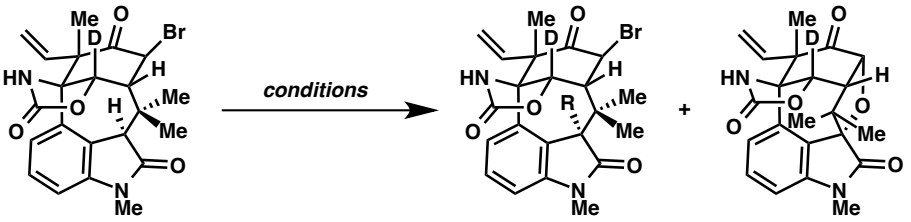
Scheme 3.3



3.6 Conversion of Bromoketone to Acetate and Cyclized Product

As a workaround, we opted to introduce a protected hydroxyl group directly onto C3 of substrate **3.11**. $Mn(OAc)_3$ Was deemed a potential reagent for selective C3 acetoxylation, based on its use in benzylic acetoxylation reactions.[15] Treatment of oxindole **3.11** with $Mn(OAc)_3$ in AcOH at 80 °C provided acetoxylated product **3.14** (Table 3.1, entry 1). Interestingly, when the corresponding reaction was conducted at 150 °C, we obtained a 53% yield of **3.3**, which possesses the desired tetrahydrofuran ring. Alternatively, **3.3** could also be prepared in one-pot by performing the acetoxylation at 80 °C, removing the volatiles, and exposing the crude intermediate to K_2CO_3 in MeOH and H_2O at 70 °C.

Table 3.1



Entry	Conditions	Conversion to products 3.14 (%)	3.3 (%)
1	$Mn(OAc)_3$ (4.0 equiv), AcOH, 80 °C	74	0
2	$Mn(OAc)_3$ (4.0 equiv), AcOH, 150 °C	2	53
3	$Mn(OAc)_3$ (4.0 equiv), AcOH, 80 °C; K_2CO_3, MeOH, H_2O, 70 °C	0	56

3.7 Double C–H Functionalization of Keto Oxindole to Install the Tetrahydrofuran Ring

We also explored the feasibility of directly converting keto oxindole **3.4** to **3.3** (Figure 3.2). Of note, the Wood research group was able to elegantly install a tetrahydrofuran ring from a keto oxindole substrate using basic conditions and O_2.[8] Despite the modest yield, this key precedent laid the groundwork for additional experimentation. To our delight, we found that simple exposure of **3.4** to tetrabutylammonium fluoride (TBAF) in acetonitrile in the presence of air efficiently delivered **3.3**.[16] In previous studies, we[17] and others[18] have found that TBAF/air can facilitate C3 oxidation of oxindoles containing the welwitindolinone scaffold, but the use of TBAF/air to build an ethereal linkage via double C-H functionalization was unknown. Notably, the use of other bases in place of TBAF, such as K_2CO_3 and Cs_2CO_3, also promoted the formation of **3.3**, albeit in lower yields. It is likely that this efficient method for introducing the tetrahydrofuran ring proceeds by initial diastereoselective C3 oxidation, followed by

cyclization.[19] Related C3-peroxy compounds have been observed in our studies[20] and in those of the Wood research group.[8]

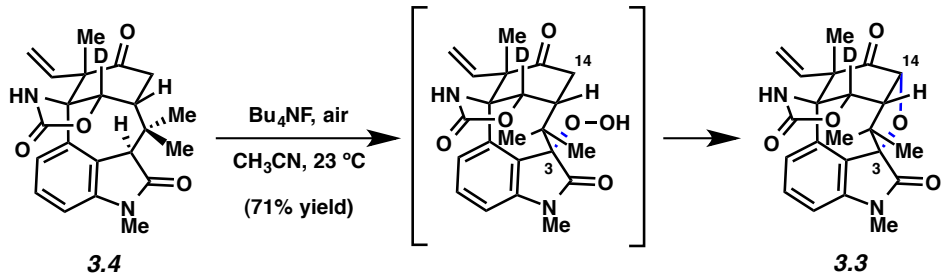
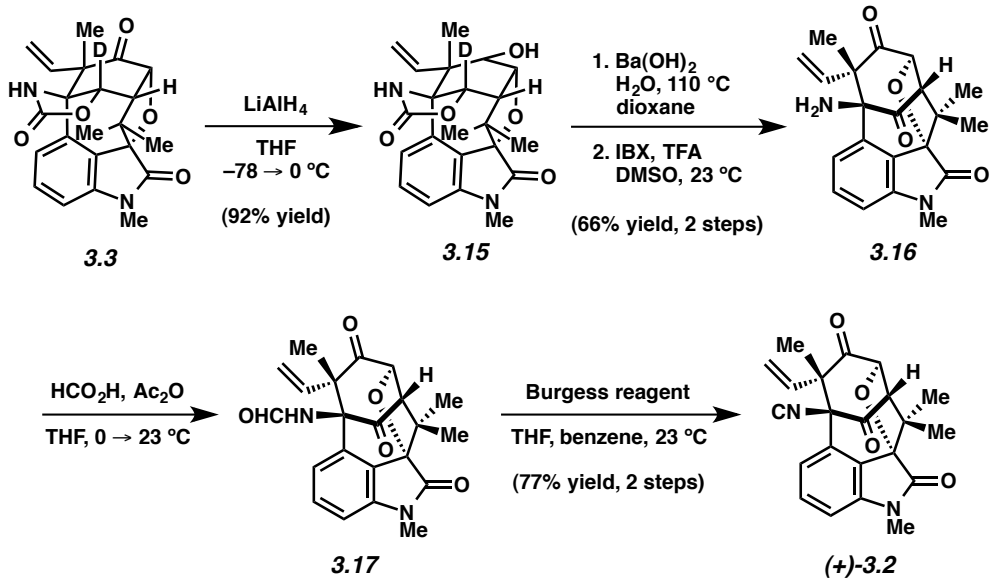


Figure 3.2. Double C–H functionalization of substrate **3.4**.

3.8 Completion of (+)-*N*-Methylwelwitindolinone D Isonitrile

To complete the total synthesis, it remained to elaborate the cyclic carbamate to the ketone and isonitrile functional groups present in **3.2** (Scheme 3.4). Unexpectedly, attempted hydrolysis of **3.3** led to cyclohexyl ring fragmentation, a process that was attributed to the reactivity of the ketone. To circumvent this, ketone **3.3** was reduced to alcohol **3.15** with $LiAlH_4$. Fortunately, upon exposure of **3.15** to hydrolysis conditions, cyclohexyl ring fragmentation was not observed. Hydrolysis gave the desired diol intermediate, which was oxidized with IBX to provide diketone **3.16**. Finally, formylation provided **3.17**, which was directly exposed to standard dehydration conditions to deliver (+)-**3.2**.

Scheme 3.4



3.9 Conclusion

In summary, we have completed the enantiospecific total synthesis of *N*-methylwelwitindolinone D isonitrile. Several unexpected hurdles, including the formation of the unusual cyclobutane-containing compound **3.13**, were overcome en route to the natural product. Our total synthesis features a double C-H functionalization event of keto oxindole **3.4** to introduce the tetrahydrofuran ring of **3.2** and is achieved in 17 steps from readily available carvone derivative **3.7**.

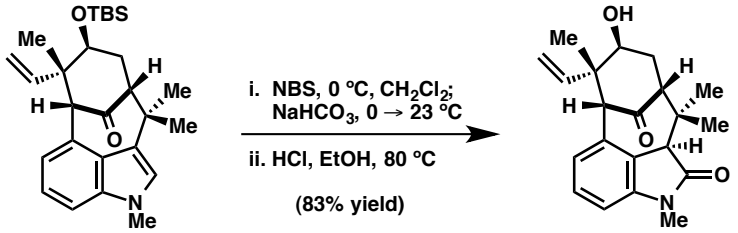
3.10 Experimental Section

3.10.1 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. $Mn(OAc)_3$ (dried *in vacuo* over P_2O_5) and $LiAlD_4$ were obtained from Acros. AgOTf and $CuBr_2$ were obtained from Strem. Bathophenanthroline was obtained from Alfa Aesar. 2-Iodoxybenzoic acid (IBX)[21] and Dess–Martin periodinane[22] were prepared from known literature procedures. 1,4-dioxane was distilled from Na/benzophenone and stored in a Schlenk tube prior to use. Unless stated otherwise, reactions were performed at room temperature (RT, approximately 23 °C). Thin-layer chromatography (TLC) was conducted with EMD gel 60 F254 pre-coated plates (0.25 mm) and visualized using a combination of UV, anisaldehyde, iodine, and potassium permanganate staining. Silicycle silica gel 60 (particle size 0.040–0.063 mm) was used for flash column chromatography. ^{1}H NMR spectra were recorded on Bruker spectrometers (500 MHz). Data for ^{1}H spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz), integration and are referenced to the residual solvent peak 7.26 ppm for $CDCl_3$, 5.32 ppm for CD_2Cl_2, 4.79 ppm for D_2O, and 1.94 ppm for CD_3CN. Data for ^{2}H NMR spectra are reported as follows: chemical shift (δ ppm, at 77 MHz), multiplicity, coupling constant, integration and are referenced to the residual solvent peak 7.26 ppm for $CDCl_3$. ^{13}C NMR spectra are reported in terms of chemical shift (at 125 MHz) and are referenced to the residual solvent peak 118.26 ppm for CD_3CN, 77.16 ppm for $CDCl_3$, and 53.84 for CD_2Cl_2. IR spectra were recorded on a Perkin-Elmer 100 spectrometer and are reported in terms of frequency absorption (cm^{-1}). Optical rotations were measured with a Rudolph Autopol III

Automatic Polarimeter. Uncorrected melting points were measured using a Mel-Temp II melting point apparatus with a Fluke 50S thermocouple and a Digimelt MPA160 melting point apparatus. High resolution mass spectra were obtained from the UC Irvine Mass Spectrometry Facility.

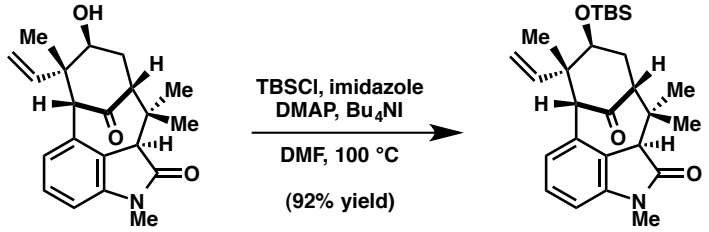
3.10.2 Experimental Procedures



3.6 *3.8*

Oxindole 3.8. To a solution of indole **3.6**[5b] (200 mg, 0.457 mmol, 1.0 equiv) in CH_2Cl_2 (9.2 mL) at 0 ºC was added NBS (82.0 mg, 0.462 mmol, 1.01 equiv) in one portion. The reaction vial was flushed with N_2, and allowed to stir at 0 ºC. After 15 min, solid $NaHCO_3$ (200 mg, 100 wt %) was added in one portion. The reaction was removed from the 0 ºC bath and allowed to stir at room temperature for 5 min. The resulting suspension was evaporated under reduced pressure. Absolute ethanol (9.2 mL) and concentrated aqueous HCl (9.2 mL) were added. After heating to 80 ºC for 17 h, the reaction was cooled to room temperature and transferred to a separatory funnel with H_2O (15 mL) and EtOAc (15 mL). To the funnel was added solid $NaHCO_3$ until gas evolution was no longer observed. The resulting biphasic mixture was extracted with EtOAc (3 x 15 mL) and the organic layers were combined, dried over $MgSO_4$, and evaporated under reduced pressure. The resulting residue was purified by flash chromatography (1:1:1 hexanes:CH_2Cl_2:Et_2O) to afford oxindole **3.8** (130 mg, 83% yield) as a brown solid. Oxindole **3.8**: mp: 203.2 ºC; R_f 0.23 (1:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.22 (dd, *J* =

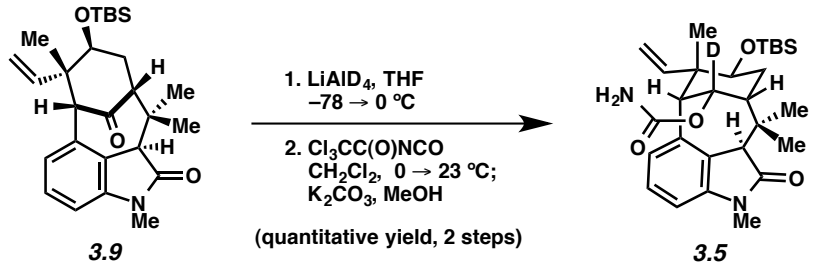
7.8, 7.7, 1H), 6.73 (d, *J* = 7.7, 1H), 6.67 (d, *J* = 7.8, 1H), 5.56 (dd, *J* = 17.5, 10.9, 1H), 5.22 (d, *J* = 10.9, 1H), 5.19 (d, *J* = 17.5, 1H), 4.22 (ddd, *J* = 12.2, 5.6, 2.8, 1H), 3.73 (s, 1H), 3.32 (d, *J* = 1.4, 1H), 3.19 (s, 3H), 2.59 (dd, *J* = 14.9, 5.6, 1H) 2.53 (d, *J* = 8.2, 1H), 2.07 (ddd, *J* = 14.9, 12.2, 8.2, 1H), 1.65 (s, 3H), 1.58 (d, *J* = 2.8, 1H), 1.17 (s, 3H), 0.68 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, 20 of 21 observed): δ 208.3, 174.9, 144.8, 142.0, 130.7, 128.5, 127.2, 125.2, 116.6, 107.2, 68.4, 68.2, 62.2, 53.5, 50.1, 40.2, 30.0, 26.4, 26.3, 22.6; IR (film): 1703, 1687, 1611, 1588, 1461 cm^{-1}; HRMS-ESI (*m/z*) [M + Na]$^+$ calcd for $C_{21}H_{25}NO_3Na$, 362.1732; found 362.1737; $[\alpha]^{25.2}_D$ +6.60° (*c* = 1.000, $CHCl_3$).



3.8 ***3.9***

Silyl ether 3.9. To a solution of oxindole **3.8** (609 mg, 1.80 mmol, 1.0 equiv) in DMF (18.0 mL) was added imidazole (611 mg, 8.97 mmol, 5.0 equiv), DMAP (219 mg, 1.79 mmol, 1.0 equiv), and tetrabutylammonium iodide (663 mg, 1.79 mmol, 1.0 equiv). The resulting solution was stirred at room temperature for 5 min, and then TBSCl (809 mg, 5.37 mmol, 3.0 equiv) was added in one portion. The flask was fitted with a reflux condenser, flushed with N_2, and then heated to 100 °C. After 25 h, the reaction mixture was cooled to room temperature and transferred to a separatory funnel with EtOAc (50 mL), H_2O (20 mL), and a solution of saturated aqueous NH_4Cl (20 mL). The resulting biphasic mixture was extracted with EtOAc (3 x 50 mL). The organic layers were combined, washed with H_2O (3 x 50 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The resulting residue was purified by flash chromatography

(9:1 hexanes:EtOAc) to afford silyl ether **3.9** (746 mg, 92% yield) as a white solid. Silyl ether **3.9**: mp: 184.5 ºC; R_f 0.64 (2:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.21 (dd, *J* = 7.9, 7.7, 1H), 6.73 (d, *J* = 7.7, 1H), 6.66 (d, *J* = 7.9, 1H), 5.40 (dd, *J* = 17.5, 10.8, 1H), 5.15–5.00 (m, 2H), 4.17 (dd, *J* = 11.6, 5.5, 1H), 3.62 (s, 1H), 3.26 (s, 1H), 3.21 (s, 3H), 2.47 (d, *J* = 8.2, 1H), 2.40 (dd, *J* = 15.1, 5.5, 1H), 2.10 (ddd, *J* = 15.1, 11.6, 8.2, 1H), 1.62 (s, 3H), 1.17 (s, 3H), 0.82 (s, 9H), 0.67 (s, 3H), 0.04 (s, 3H), -0.09 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, 24 of 25 observed): δ 208.6, 175.0, 144.6, 143.6, 131.2, 128.4, 127.4, 124.9, 114.6, 107.1, 70.0, 69.2, 62.5, 53.7, 50.3, 40.1, 32.0, 26.4, 25.8, 22.4, 18.1, 16.1, -3.8, -4.4; IR (film): 1707, 1689, 1609, 1590, 1465 cm^{-1}; HRMS-ESI (*m/z*) [M + Na]$^+$ calcd for $C_{27}H_{39}NO_3SiNa$, 476.2597; found 476.2600; $[\alpha]^{26.1}_D$ +12.60° (*c* = 1.000, $CHCl_3$).

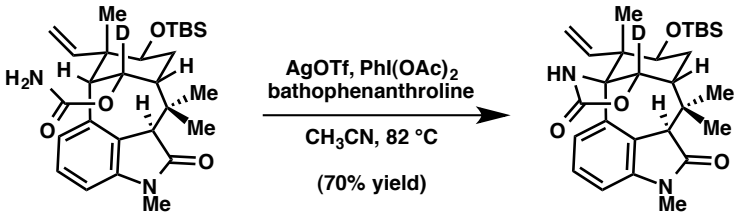


Carbamate 3.5. To a solution of silyl ether **3.9** (178 mg, 0.393 mmol, 1.0 equiv) in THF (13.0 mL) at –78 °C was added a solution of $LiAlD_4$ (1.0 M in THF, 1.18 mL, 1.18 mmol, 3.0 equiv) in a dropwise manner. After stirring at –78 °C for 20 min, the solution was then allowed to warm to 0 ºC. After 20 min, the reaction was quenched at 0 °C with slow addition of a saturated aqueous solution of Rochelle's salt (10 mL), and then allowed to warm to 23 ºC. The resulting biphasic mixture was stirred at room temperature for 1 h, transferred to a separatory funnel with EtOAc (25 mL) and H_2O (20 mL), and extracted with EtOAc (3 x 25 mL). The organic layers

were combined, dried over $MgSO_4$, and evaporated under reduced pressure. The resulting residue was used in the subsequent step without further purification.

To a flask containing the crude residue from the previous step was added CH_2Cl_2 (7.85 mL), cooled to 0 ºC, followed by addition of trichloroacetyl isocyanate (58 μL, 0.490 mmol, 1.25 equiv) in a dropwise manner. The resulting mixture was allowed to stir at 0 °C for 5 min, and then at room temperature for 20 min. The solvent was evaporated under reduced pressure. To the resulting residue was added MeOH (7.85 mL) followed by solid K_2CO_3 (298 mg, 2.16 mmol, 5.5 equiv) in one portion. The reaction was flushed with N_2 and left to stir at room temperature for 80 min. The reaction was quenched with saturated aqueous NH_4Cl (7 mL), and the resulting biphasic mixture was transferred to a separatory funnel with EtOAc (25 mL) and H_2O (20 mL). After extracting with EtOAc (3 x 25 mL), the organic layers were combined, dried over $MgSO_4$, and evaporated under reduced pressure. The resulting residue was purified by flash chromatography (2:1 hexanes:EtOAc) to afford carbamate **3.5** (203 mg, quant. yield, over two steps) as a white solid. Carbamate **3.5**: mp: 106.1 ºC; R_f 0.47 (1:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.15 (ddd, *J* = 7.8, 7.7, 0.7, 1H), 6.70 (dd, *J* = 7.7, 0.7, 1H), 6.63 (d, *J* = 7.8, 1H), 5.23 (dd, *J* = 17.4, 10.7, 1H), 5.03 (dd, *J* = 17.4, 1.3, 1H), 4.93 (dd, *J* = 10.7, 1.3, 1H), 4.34 (s, 2H), 4.03 (dd, *J* = 12.5, 5.1, 1H), 3.60 (s, 1H), 3.20 (s, 3H), 2.83 (s, 1H) 2.30 (ddd, *J* = 15.0, 5.1, 1.9, 1H), 2.25 (d, *J* = 6.1, 1H), 1.98 (ddd, *J* = 15.0, 12.5, 6.1, 1H), 1.58 (s, 3H), 1.36 (s, 3H), 0.88 (s, 3H), 0.82 (s, 9H), 0.03 (s, 3H), -0.12 (s, 3H); ^{2}H NMR (77 MHz, $CDCl_3$) δ 5.51 (br. s, 1D); ^{13}C NMR (125 MHz, $CDCl_3$): δ 175.8, 156.1, 146.3, 144.6, 138.1, 128.6, 127.4, 125.3, 113.7, 106.3, 74.5 (t, J_{C-D} = 22.1), 70.9, 56.8, 55.9, 49.0, 48.9, 37.3, 32.4, 29.2, 26.3, 25.9, 24.3, 18.1, 17.1, -3.8, -4.3; IR (film): 2956, 2923, 2857, 1728, 1701, 1607, 1596, 1463 cm^{-1}; HRMS-

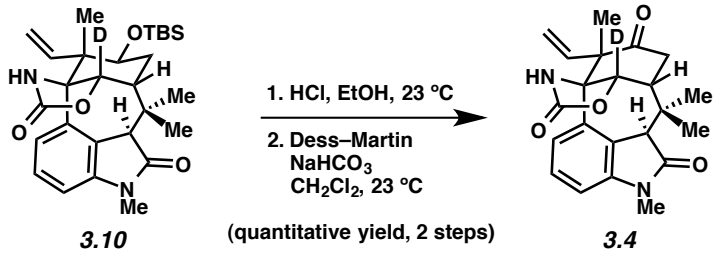
ESI (*m/z*) $[M + Na]^+$ calcd for $C_{28}H_{41}N_2O_4SiDNa$, 522.2874; found 522.2872; $[\alpha]^{26.5}_D$ +11.40° (*c* = 1.000, $CHCl_3$).



3.5 ***3.10***

Oxazolidinone 3.10. A 1-dram vial containing CH_3CN, a second 1-dram vial charged with bathophenanthroline (10.6 mg, 0.0319 mmol, 0.5 equiv), and a third 1-dram vial containing carbamate **3.5** (33.0 mg, 0.0660 mmol, 1.0 equiv) and $PhI(OAc)_2$ (42.5 mg, 0.132 mmol, 2.0 equiv) were transferred into the glovebox. AgOTf (8.5 mg, 0.033 mmol, 0.5 equiv) and CH_3CN (950 μL) were added to the vial containing the bathophenanthroline, and the resulting suspension was allowed to stir at room temperature for 20 min. Next, CH_3CN (950 μL) was added to the vial containing the carbamate, and the AgOTf/bathophenanthroline suspension was also added to this vial. The vial was then sealed, removed from the glovebox, and the resulting mixture was heated to 82 °C. After 24 h, the reaction was cooled to room temperature and filtered by passage over a plug of silica gel (EtOAc eluent, 10 mL). The filtrate was evaporated under reduced pressure, and the resulting residue was purified by preparative thin layer chromatography (2:1 hexanes:EtOAc) to afford oxazolidinone **3.10** (23 mg, 70% yield) as a yellow solid and recovered silyl ether **3.9** (2 mg, 7% yield) as a white solid. Oxazolidinone **3.10**: mp: 288.0 ºC (decomp.); R_f 0.50 (1:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.21 (app t, *J* = 8.0, 1H), 6.77–6.73 (m, 2H), 6.54 (s, 1H), 5.19–5.09 (m, 3H), 3.87 (dd, *J* = 11.7, 5.2, 1H), 3.47 (s, 1H), 3.22 (s, 3H), 2.44 (d, *J* = 6.7, 1H), 2.31 (dd, *J* = 15.2, 5.2, 1H), 2.01 (ddd, *J* = 15.2, 11.7,

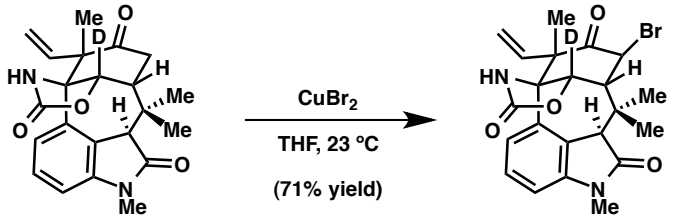
6.7, 1H), 1.60 (s, 3H), 1.33 (s, 3H), 0.96 (s, 3H), 0.80 (s, 9H), 0.00 (s, 3H), -0.16 (s, 3H); ^{2}H NMR (77 MHz, $CDCl_3$) δ 4.97 (br. s, 1D); ^{13}C NMR (125 MHz, $CDCl_3$, 25 of 26 observed): δ 174.8, 159.1, 144.1, 144.0, 137.6, 128.0, 125.9, 124.7, 116.3, 107.4, 72.2, 69.9, 55.2, 49.9, 46.8, 37.7, 32.3, 28.0, 26.4, 25.8, 22.8, 18.1, 12.9, -3.8, -4.4; IR (film): 1758, 1708, 1691, 1607, 1590, 1461 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{28}H_{39}N_2O_4SiDNa$, 520.2718; found 520.2719; $[\alpha]^{27.0}_D$ +1.40° (*c* = 1.000, $CHCl_3$).



Ketone 3.4. A flask was charged with oxazolidinone **3.10** (576 mg, 1.16 mmol, 1.0 equiv), absolute ethanol (23.0 mL), and concentrated aqueous HCl (23.0 mL). After stirring at 23 ºC for 1 h, the reaction mixture was transferred to a separatory funnel with H_2O (50 mL) and EtOAc (50 mL). To the funnel was added solid $NaHCO_3$ until no more gas evolution was observed. The resulting biphasic mixture was extracted with EtOAc (3 x 50 mL) and the organic layers were combined, dried over $MgSO_4$, and evaporated under reduced pressure. The resulting residue was used in the subsequent step without further purification.

To a flask containing the crude product from the previous step was added solid $NaHCO_3$ (487 mg, 5.80 mmol, 5.0 equiv) in one portion. The reaction vessel was flushed with N_2, and then CH_2Cl_2 (11.6 mL) was added. To the resulting suspension was added the Dess–Martin periodinane reagent (645 mg, 1.52 mmol, 1.3 equiv) in one portion. The flask was flushed with N_2, and the reaction mixture was allowed to stir at room temperature. After 1 h, the reaction

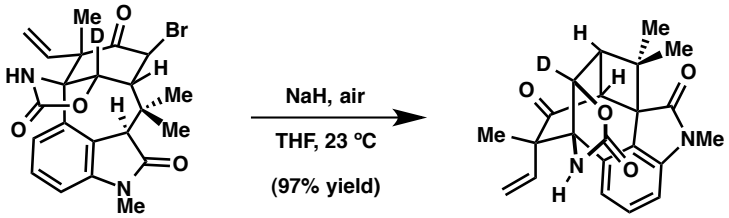
mixture was diluted with a 1:1 mixture of saturated aqueous $NaHCO_3$ and saturated aqueous $Na_2S_2O_3$ (10.0 mL). The resulting biphasic mixture was vigorously stirred until both layers appeared clear. The mixture was then transferred to a separatory funnel with EtOAc (30 mL) and H_2O (30 mL), and then extracted with EtOAc (3 x 30 mL). The organic layers were combined, dried over $MgSO_4$, and evaporated under reduced pressure. The resulting residue was purified by flash chromatography (1:1 hexanes:EtOAc) to afford ketone **3.4** (454 mg, quant. yield, over two steps) as a yellow solid. Ketone **3.4**: mp: 293.5 ºC; R_f 0.42 (1:3 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.20 (app t, *J* = 8.0, 1H), 7.10 (s, 1H), 6.77–6.73 (m, 2H), 5.34 (dd, *J* = 17.6, 10.9, 1H), 5.22–5.16 (m, 2H), 3.34 (s, 1H), 3.18 (s, 3H), 3.17–3.06 (m, 2H), 2.86–2.82 (m, 1H), 1.62 (s, 3H), 1.56 (s, 3H), 0.92 (s, 3H); ^{2}H NMR (77 MHz, $CDCl_3$) δ 5.45 (br. s, 1D); ^{13}C NMR (125 MHz, $CDCl_3$, 21 of 22 observed): δ 209.8, 174.3, 159.3, 144.5, 137.9, 136.0, 128.5, 124.3, 123.4, 116.8, 108.0, 70.8, 57.4, 51.9, 48.2, 40.2, 38.4, 27.3, 26.5, 22.5, 19.8; IR (film): 1760, 1752, 1689, 1611, 1590 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{22}H_{23}N_2O_4DNa$, 404.1696; found 404.1700; $[\alpha]^{27.3}_D$ –26.67° (*c* = 0.870, $CHCl_3$).



3.4 *3.11*

Bromoketone 3.11. A 1-dram vial was charged with ketone **3.4** (50.0 mg, 0.131 mmol, 1.0 equiv) and transferred into the glovebox. $CuBr_2$ (59.0 mg, 0.264 mmol, 2.0 equiv) was then added and the vial was removed from the glovebox. THF (2.1 mL) was added and the reaction vial was sealed and left to stir at room temperature. After 19 h, the reaction mixture was filtered

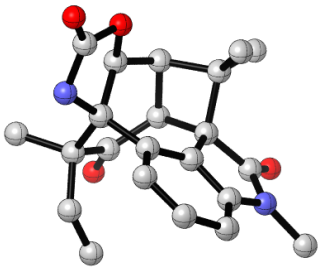
by passage over a plug of celite (THF eluent, 10 mL). The filtrate was collected in a test tube, diluted with H_2O (5 mL), and then extracted with $CHCl_3$ (3 x 5 mL). The organic layers were combined, dried over $MgSO_4$, and evaporated under reduced pressure. The resulting residue was adsorbed onto silica gel (2 mL) and purified by flash chromatography (4:1 hexanes:acetone) to afford bromoketone **3.11** (42.5 mg, 71% yield) as a white solid. Bromoketone **3.11**: mp: 273.0 ºC (decomp.); R_f 0.62 (1:3 hexanes:EtOAc); ^{1}H NMR (500 MHz, CD_3CN): δ 7.32 (ddd, J = 8.2, 7.6, 0.8, 1H), 7.21 (s, 1H), 6.89–6.84 (m, 2H), 5.27–5.19 (m, 1H), 5.12–5.03 (m, 2H), 3.10 (s, 3H), 3.05 (s, 2H), 1.87 (s, 3H), 1.59 (s, 3H), 0.81 (s, 3H); ^{2}H NMR (77 MHz, $CDCl_3$) δ 5.87 (br. s, 1D); ^{13}C NMR (21 of 22 observed, 125 MHz, CD_3CN): δ 204.9, 173.3, 157.4, 144.7, 138.3, 136.2, 128.4, 123.7, 122.8, 115.8, 108.0, 70.5, 58.2, 56.0, 50.4, 46.8, 38.7, 25.84, 25.75, 23.3, 21.5; IR (film): 1762, 1702, 1607, 1464 cm^{-1}; HRMS-ESI (m/z) [M + Na]$^+$ calcd for $C_{22}H_{22}O_4DN_2BrNa$, 484.0784; found 484.0809; $[\alpha]^{25.8}_D$ +179.20° (c = 1.000, $CHCl_3$).

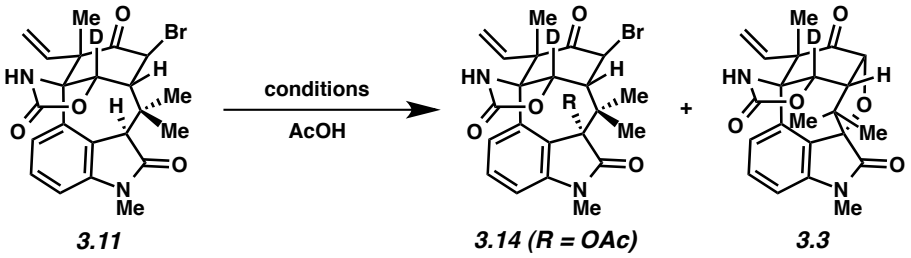


3.11 *3.13*

Cyclobutane 3.13. To a solution of bromoketone **3.11** (4.0 mg, 0.0087 mmol, 1.0 equiv) in THF (870 μL) was added NaH (60% dispersion in mineral oil, 1.7 mg, 0.043 mmol, 5.0 equiv) in one portion. The reaction vial was then opened to air for 10 seconds, sealed and left to stir at room temperature. After 2 h, the reaction mixture was filtered by passage over a plug of silica gel (EtOAc eluent, 6 mL). The filtrate was evaporated under reduced pressure, and the resulting residue was purified by flash chromatography (2:1 hexanes:EtOAc) to afford cyclobutane **3.13**

(3.3 mg, 97% yield) as a white solid. Crystals suitable for X-ray diffraction studies (CCDC 960226) were obtained by concentration of **3.13** from a mixture of $CHCl_3$ and pentane. Cyclobutane **3.13**: mp: 284.0 ºC; R_f 0.51 (1:3 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27 (app t, *J* = 8.0, 7.8, 1H), 6.88 (d, *J* = 8.0, 1H), 6.79 (d, *J* = 7.8, 1H), 6.42 (s, 1H), 5.09–5.02 (m, 2H), 4.90 (dd, *J* = 17.7, 10.8, 1H), 4.00 (d, *J* = 7.4, 1H), 3.17 (s, 3H), 3.09 (d, *J* = 7.4, 1H), 1.49 (s, 3H), 1.41 (s, 3H), 0.68 (s, 3H); ^{2}H NMR (77 MHz, $CDCl_3$) δ 5.33 (br. s, 1D); ^{13}C NMR (125 MHz, $CDCl_3$): δ 206.7, 172.3, 159.2, 142.9, 137.2, 135.5, 128.9, 124.6, 120.3, 117.4, 108.5, 80.4 (t, J_{C-D} = 21.6), 69.3, 61.1, 57.4, 46.0, 45.3, 41.6, 26.7, 26.1, 21.1, 18.7; IR (film): 1758, 1710, 1607, 1469 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{22}H_{21}O_4DN_2Na$, 402.1540; found 402.1540; $[\alpha]^{27.3}_D$ –94.00° (*c* = 0.500, $CHCl_3$).

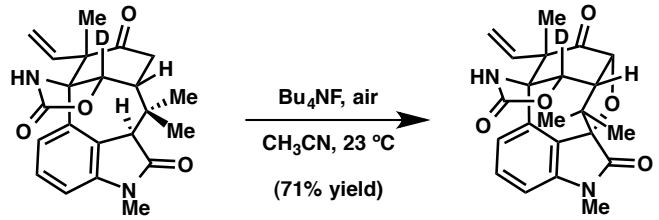




General Procedure for Acetoxyoxindole 3.14 + Ether 3.3 From Table 3.1. A 1-dram vial charged with bromoketone **3.11** (5.0 mg, 0.011 mmol, 1.0 equiv) was transferred into the glovebox. $Mn(OAc)_3$ was added and the vial was removed from the glovebox. AcOH (1.1 mL) was then added and the reaction vial was sealed and left to stir at the indicated temperature. For

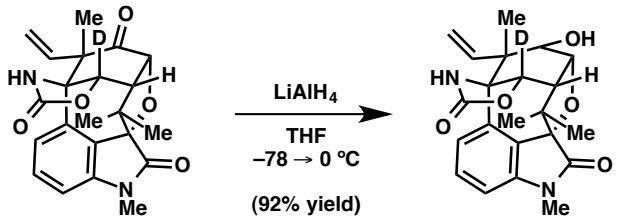
entries 1–2, after stirring for 24 h the reaction mixture was cooled to room temperature, transferred to a test tube with $CHCl_3$ (2 mL) and aqueous 2M HCl (1 mL), and then extracted with $CHCl_3$ (3 x 2 mL). The organic layers were combined, washed with saturated aqueous $NaHCO_3$ (2 x 2 mL), H_2O (2 x 2 mL), and then dried over $MgSO_4$ and evaporated under reduced pressure. The resulting residue was purified by preparative thin layer chromatography (1:1 $CHCl_3$:EtOAc) to afford acetoxyoxindole **3.14** and/or ether **3.3** as white solids. For entry 3, after stirring for 24 h the reaction mixture was cooled to room temperature and concentrated under reduced pressure. To the resulting residue was added a 1:1 mixture of MeOH:H_2O (1.1 mL) and solid K_2CO_3 (3.8 mg, 0.272 mmol, 25.0 equiv) in one portion. The reaction vial was flushed with N_2, sealed and allowed to stir at 70 ºC. After 19 h, the reaction mixture was cooled to room temperature, diluted with H_2O (2 mL) and transferred to a test tube with $CHCl_3$ (2 mL). The resulting biphasic mixture was extracted with $CHCl_3$ (3 x 2 mL). The organic layers were combined, dried over $MgSO_4$, and evaporated under reduced pressure. The resulting residue was purified by preparative thin layer chromatography (1:1 $CHCl_3$:EtOAc) to afford ether **3.3** (2.4 mg, 56% yield) as a white solid. Acetoxyoxindole **3.14**: mp: 283.0 ºC (decomp.); R_f 0.65 (1:3 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31 (app t, J = 8.0, 1H), 6.94 (s, 1H), 6.80–6.76 (m, 2H), 5.37 (s, 1H), 5.31 (d, J = 17.0, 1H), 5.21 (d, J = 10.7, 1H), 5.01 (dd, J = 17.0, 10.7, 1 H), 3.20 (s, 3H), 3.04 (s, 1H), 1.91 (s, 3H), 1.88 (s, 3H), 1.64 (s, 3H), 1.02 (s, 3H); ^{2}H NMR (77 MHz, $CDCl_3$) δ 5.87 (br. s, 1D); ^{13}C NMR (23 of 24 observed, 125 MHz, $CDCl_3$): δ 203.1, 171.4, 168.9, 158.4, 145.9, 137.3, 136.5, 131.0, 124.7, 122.6, 118.0, 108.2, 84.3, 70.4, 58.2, 56.3, 48.9, 41.2, 27.1, 25.3, 22.7, 22.6, 21.4; IR (film): 1762, 1732, 1712, 1611, 1597, 1463 cm^{-1}; HRMS-ESI (m/z) $[M + Na]^+$ calcd for $C_{24}H_{24}O_6DN_2BrNa$, 540.0856; found 540.0858; $[\alpha]^{26.9}_D$ – 18.40° (c = 1.000, $CHCl_3$). Ether **3.3**: mp: 317.0 ºC (decomp.); R_f 0.53 (1:3 hexanes:EtOAc); ^{1}H

NMR (500 MHz, $CDCl_3$): δ 7.67 (s, 1H), 7.25 (app t, J = 7.9, 1H), 6.93 (dd, J = 7.9, 0.64, 1H), 6.81 (dd, J = 7.9, 0.64, 1H), 5.22 (dd, J = 17.2, 10.7, 1H), 4.96–4.89 (m, 2H), 4.78 (d, J = 10.7, 1H), 3.30 (d, J = 7.5, 1H), 3.23 (s, 3H), 1.45 (s, 3H), 1.42 (s, 3H), 1.02 (s, 3H); ^{2}H NMR (77 MHz, $CDCl_3$) δ 4.69 (br. s, 1D); ^{13}C NMR (125 MHz, $CDCl_3$): δ 205.2, 171.9, 158.7, 142.8, 137.6, 136.3, 130.4, 126.6, 122.3, 116.4, 108.6, 88.8, 83.3, 81.4 (t, J_{C-D} = 22.6), 70.2, 59.4, 51.4, 48.9, 26.9, 25.4, 21.2, 19.6; IR (film): 1774, 1724, 1710, 1605 cm^{-1}; HRMS-ESI (m/z) $[M + Na]^+$ calcd for $C_{22}H_{21}O_5DN_2Na$, 418.1489; found 418.1476; $[\alpha]^{21.3}_D$ –157.20° (c = 1.000, $CHCl_3$).



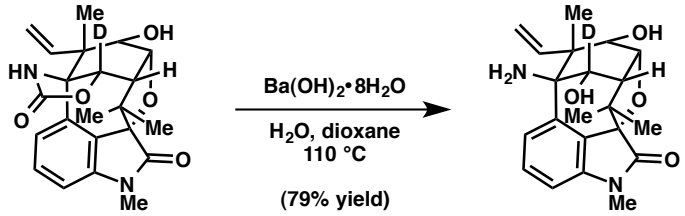
3.4 *3.3*

Ether 3.3. To a solution of ketone **3.4** (30 mg, 0.079 mmol, 1.0 equiv) in CH_3CN (7.9 mL) was added Bu_4NF (1.0 M in THF, 236 μL, 0.236 mmol, 3.0 equiv) in a dropwise manner. The reaction mixture was stirred for 1 min, then opened to air for 30 seconds. The reaction vessel was sealed and left to stir at room temperature. After 2 h, the reaction was quenched with a solution of saturated aqueous NH_4Cl (5 mL). The resulting mixture was transferred to a separatory funnel with EtOAc (10 mL) and H_2O (10 mL). The resulting biphasic mixture was extracted with EtOAc (3 x 10 mL). The organic layers were combined, dried over $MgSO_4$, and evaporated under reduced pressure. The crude residue was purified by flash chromatography (1:1 hexanes:EtOAc) to afford ether **3.3** (22 mg, 71% yield) as a white solid.



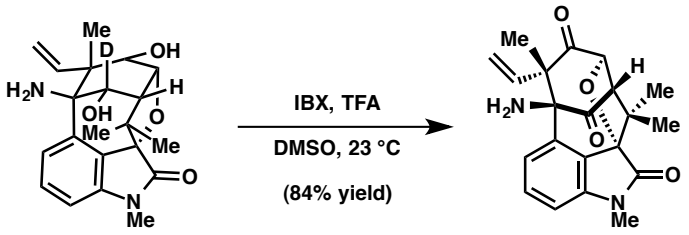
3.3 *3.15*

Alcohol 3.15. To a solution of ether **3.3** (9.4 mg, 0.024 mmol, 1.0 equiv) in THF (2.3 mL) at –78 ºC was added $LiAlH_4$ (1.0 M in THF, 24 μL, 0.024 mmol, 1.0 equiv) in a dropwise manner. After 5 min, the reaction mixture was warmed to 0 ºC. After 20 min, the reaction was quenched at 0 °C with slow addition of a saturated aqueous solution of Rochelle's salt (3.0 mL) and then allowed to warm to 23 ºC. The mixture was stirred at room temperature for 30 min, and then transferred to a separatory funnel with EtOAc (10 mL) and H_2O (10 mL). The resulting biphasic mixture was extracted with EtOAc (3 x 10 mL). The organic layers were combined, dried over $MgSO_4$, and evaporated under reduced pressure. The resulting residue was purified by preparative thin layer chromatography (1:2 $CHCl_3$:EtOAc) to afford alcohol **3.15** (8.7 mg, 92% yield) as a white solid. Alcohol **3.15**: mp: 263.0 ºC; R_f 0.15 (1:3 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.60 (s, 1H), 7.19 (app t, *J* = 7.9, 1H), 6.82 (d, *J* = 7.9, 1H), 6.77 (d, *J* = 7.9, 1H), 5.21 (dd, *J* = 17.4, 10.8, 1 H), 5.09–5.03 (m, 2H), 4.94 (d, *J* = 10.8, 1H), 3.72 (dd, *J* = 11.1, 2.0, 1H), 3.22 (s, 3H), 3.02 (d, J = 7.5, 1H), 2.02 (d, J = 11.1, 1 H), 1.43 (s, 3H), 1.41 (s, 3H), 0.94 (s, 3H); ^{2}H NMR (77 MHz, $CDCl_3$) δ 4.79 (br. s, 1D); ^{13}C NMR (21 of 22 observed, 125 MHz, $CDCl_3$): δ 173.0, 159.4, 142.4, 139.0, 136.4, 130.2, 126.9, 122.4, 117.9, 108.2, 87.3, 82.0, 76.1, 70.9, 49.2, 48.7, 48.3, 26.8, 25.6, 21.3, 19.6; IR (film): 1752, 1722, 1603, 1462 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{22}H_{23}O_5DN_2Na$, 420.1646; found 420.1631; $[\alpha]^{24.1}_D$ – 49.20° (*c* = 1.000, $CHCl_3$).



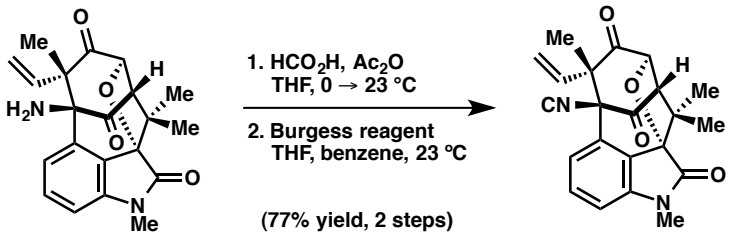
3.15 *3.18*

Aminodiol 3.18. A Schlenk tube was charged with alcohol **3.15** (7.30 mg, 0.0184 mmol, 1.0 equiv) and $Ba(OH)_2 \cdot 8H_2O$ (46.3 mg, 0.147 mmol, 8.0 equiv). The reaction vessel was then evacuated and backfilled with N_2 three times. A 2:1 mixture of 1,4-dioxane:H_2O (634 μL) that had been taken through six freeze-pump-thaw cycles prior to use was then added to the Schlenk tube. The vessel was then sealed and allowed to stir at 110 °C. After 21 h, the contents of the Schlenk tube were transferred to a separatory funnel with EtOAc (5 mL) and H_2O (5 mL). The resulting biphasic mixture was extracted with EtOAc (3 x 5 mL). The organic layers were combined, dried over Na_2SO_4, and evaporated under reduced pressure. The resulting residue was purified by preparative thin layer chromatography (3:1 $CHCl_3$:MeOH) to afford **3.18** (5.4 mg, 79% yield) as a white solid. Aminodiol **3.18**: R_f 0.12 (9:1 $CHCl_3$:MeOH); ^{1}H NMR (500 MHz, D_2O, 22 of 25 observed): δ 7.37 (app t, J = 8.3, 1H), 7.18 (d, J = 8.3, 1H), 7.02 (d, J = 8.2, 1H), 5.50 (dd, J = 17.6, 11.0, 1H), 4.96 (dd, J = 7.3, 1.8, 1 H), 4.92 (d, J = 17.6, 1H), 3.88 (d, J = 1.8, 1H), 3.23 (s, 3H), 2.83 (d, J = 7.3, 1H), 1.91 (s, 2H), 1.37 (s, 3H), 1.28 (s, 3H), 0.85 (s, 3H).



3.18 *3.16*

Aminodiketone 3.16. To a solution of **3.18** (5.4 mg, 0.014 mmol, 1.0 equiv) in DMSO (500 μL) was added TFA (1.2 μL, 0.016 mmol, 1.10 equiv). The mixture was stirred at room temperature. After 5 min, IBX (20.4 mg, 0.0728 mmol, 5.0 equiv) was added in one portion and the vial was flushed with N_2. After stirring at room temperature for 20 h, the reaction mixture transferred to a separatory funnel with a solution of aqueous K_2CO_3 (5 mL, concentration of 50 mg/mL) and EtOAc (5 mL). The resulting biphasic mixture was extracted with EtOAc (3 x 5 mL) and the organic layers were combined, dried over Na_2SO_4, and evaporated under reduced pressure. The resulting residue was purified by preparative thin layer chromatography (9:1 $CHCl_3$:MeOH) to afford aminodiketone **3.16** (4.5 mg, 84% yield) as a white solid. Aminodiketone **3.16**: mp: 190–191 ºC; R_f 0.73 (9:1 CH_3Cl:MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35 (dd, *J* = 8.2, 7.6, 1H), 7.29 (dd, *J* = 8.2, 1.0, 1H), 6.80 (dd, *J* = 7.6, 1.0, 1H), 5.64 (dd, *J* = 17.4, 10.7, 1H), 5.40 (d, *J* = 10.7, 1 H), 5.21 (d, *J* = 17.4, 1H), 4.93 (d, *J* = 7.6, 1H), 3.49 (d, *J* = 7.6, 1H), 3.20 (s, 3H), 2.04 (br. s, 2H), 1.59 (s, 3H), 1.19 (s, 3H), 0.78 (s, 3H); ^{13}C NMR (21 of 22 observed, 125 MHz, $CDCl_3$): δ 204.9, 204.4, 170.2, 143.6, 134.8, 134.8, 130.3, 125.8, 124.2, 118.9, 108.9, 86.5, 79.4, 69.4, 62.5, 62.1, 52.4, 26.9, 25.3, 20.0, 17.6; IR (film): 1718, 1609, 1582, 1459, 1366 cm^{-1}; HRMS-ESI (*m*/*z*) [M + Na]$^+$ calcd for $C_{21}H_{22}O_4DN_2Na$, 389.1477; found 389.1469; $[\alpha]^{22.9}_D$ +29.20° (*c* = 1.000, $CHCl_3$).



3.16 *(+)-3.2*

(+)-*N*-Methylwelwitindolinone D Isonitrile (3.2). A 1-dram vial was charged with 96% formic acid (0.100 mL) and acetic anhydride (0.100 mL). The resulting mixture was stirred at 60 °C for 1 h. The reaction vessel was cooled to room temperature and 39 μL of the 96% formic acid/acetic anhydride mixture was added to a solution of aminodiketone **3.16** (4.2 mg, 0.010 mmol, 1.0 equiv) in THF (765 μL) at 0 °C. The reaction was then warmed to room temperature. After 2 h, the reaction mixture was transferred to a test tube with EtOAc (2 mL) and a solution of saturated aqueous $NaHCO_3$ (1 mL). The resulting biphasic mixture was extracted with EtOAc (4 x 2 mL). The organic layers were combined, dried over $MgSO_4$, and evaporated under reduced pressure to afford the crude product, which was used directly in the subsequent reaction.

To a vial containing the crude product from the previous step was added THF (600 μL) and benzene (600 μL), followed by Burgess reagent (3.5 mg, 0.011 mmol, 1.0 equiv). The vial was flushed with N_2 and allowed to stir at room temperature for 40 min. An additional amount of Burgess reagent (3.5 mg, 0.015 mol, 1.0 equiv) was then added, and the reaction was allowed to stir at room temperature for 10 min. The reaction was then filtered by passage over a plug of silica gel (EtOAc eluent, 10 mL). The filtrate was evaporated under reduced pressure, and the resulting residue was purified by preparative thin layer chromatography (1:1 hexanes:EtOAc) to afford (+)-**3.2** (3.3 mg, 77% yield, 2 steps) as a white solid. Spectral data for ^{1}H NMR, ^{13}C NMR, and IR for synthetic **3.2** was consistent with literature reports.[2b] (+)-*N*-Methylwelwitindolinone D isonitrile (**3.2**): mp: 156 ºC; R_f 0.50 (1:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, CD_2Cl_2): δ 7.45

(dd, J = 8.3, 7.9, 1H), 7.29 (dd, J = 8.3, 0.7, 1H), 6.93 (dd, J = 7.9, 0.7, 1H), 5.48 (dd, J = 16.3, 10.6, 1H), 5.43 (dd, J = 10.6, 1.5, 1H), 5.35 (dd, J = 16.3, 1.5, 1H), 4.92 (d, J = 7.5, 1H), 3.57 (d, J = 7.5, 1H), 3.19 (s, 3H), 1.55 (s, 3H), 1.39 (s, 3H), 0.80 (s, 3H); ^{13}C NMR (125 MHz, CD_2Cl_2): δ 201.3, 192.8, 169.9, 165.5, 144.4, 133.0, 131.4, 126.8, 125.8, 124.0, 120.6, 110.5, 86.7, 81.1, 79.7, 62.0, 61.7, 53.6, 27.1, 25.0, 20.1, 19.8; IR (film): 2980, 2940, 2139, 1730, 1609, 1592, 1463, 1366, 1344 cm^{-1}; HRMS-ESI (m/z) [M + Na]$^+$ calcd for $C_{22}H_{20}N_2O_4Na$, 399.1321; found 399.1322; $[\alpha]^{22.3}_D$ +4.30° (c = 0.37, CH_2Cl_2). Note: This specific rotation differs from that reported for the natural product ($[\alpha]_D$ –30°, c = 0.37, CH_2Cl_2). This is most likely due to a tabulation error in the isolation report as: (a) the synthesis begins with (S)-carvone >96%+ ee, (b) the specific rotation of bicycle **3.6** in this synthesis is consistent with that of material used in previous syntheses of welwitindolinones,[5b,e] and (c) our specific rotation data has given consistent results across a range of samples and concentrations. Although the sign of rotation differs, the compound we have prepared is assumed to be the natural occurring enantiomer due to its biosynthetic relationship to the *N*-methylweltindolinone C series of natural products, whose absolute configuration have previously been established.[5]

3.11 Notes and References

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(7) Image prepared using CYLview: C. Y. Legault, CYLview, 1.0b; Université de Sherbrooke: Québec, Montreal, Canada, 2009; http://www.cylview.org.

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(14) CCDC 960226 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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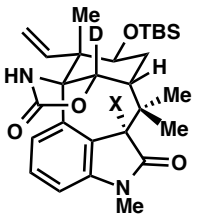
(16) For recent alkaloid syntheses that feature the strategic use of indole oxidation chemistry, see: (a) Han, S.; Movassaghi, M. *J. Am. Chem. Soc.* **2011**, *133*, 10768. (b) Qi, X.; Bao, H.; Tambar, U. K. *J. Am. Chem. Soc.* **2011**, *133*, 10050.

(17) Huters, A. D.; Quasdorf, K. W.; Garg, N. K. University of California, Los Angeles, CA. Unpublished work, **2010**.

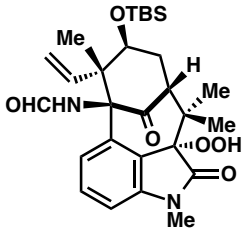
(18) Buckley, B. R.; Fernández D.-R., B. *Tetrahedron Lett.* **2013**, *54*, 843.

(19) Treatment of **3.4** with 3.0 equiv TBAF and 50.0 equiv MeOD in CH_3CN under an atmosphere of N_2 at ambient temperature gave 40% deuterium incorporation at C3 after 10 min, whereas treatment under the same conditions for 1 h gave 50% deuterium incorporation at C3 and 25% deuterium incorporation at C14.

(20) Efforts to isolate the putative peroxy species (Figure 3.2) have been unsuccessful; however, we have isolated several related compounds, such as **3.19** and **3.20**, by oxidation of the corresponding oxindoles.



3.19, X = OOH



3.20

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

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

APPENDIX TWO

Spectra Relevant to Chapter Three:

Enantiospecific Total Synthesis of *N*-Methylwelwitindolinone D Isonitrile

Evan D. Styduhar, Alexander D. Huters, Nicholas A. Weires, and Neil K. Garg.

Angew. Chem. Int. Ed. **2013**, *52*, 12422–12425.

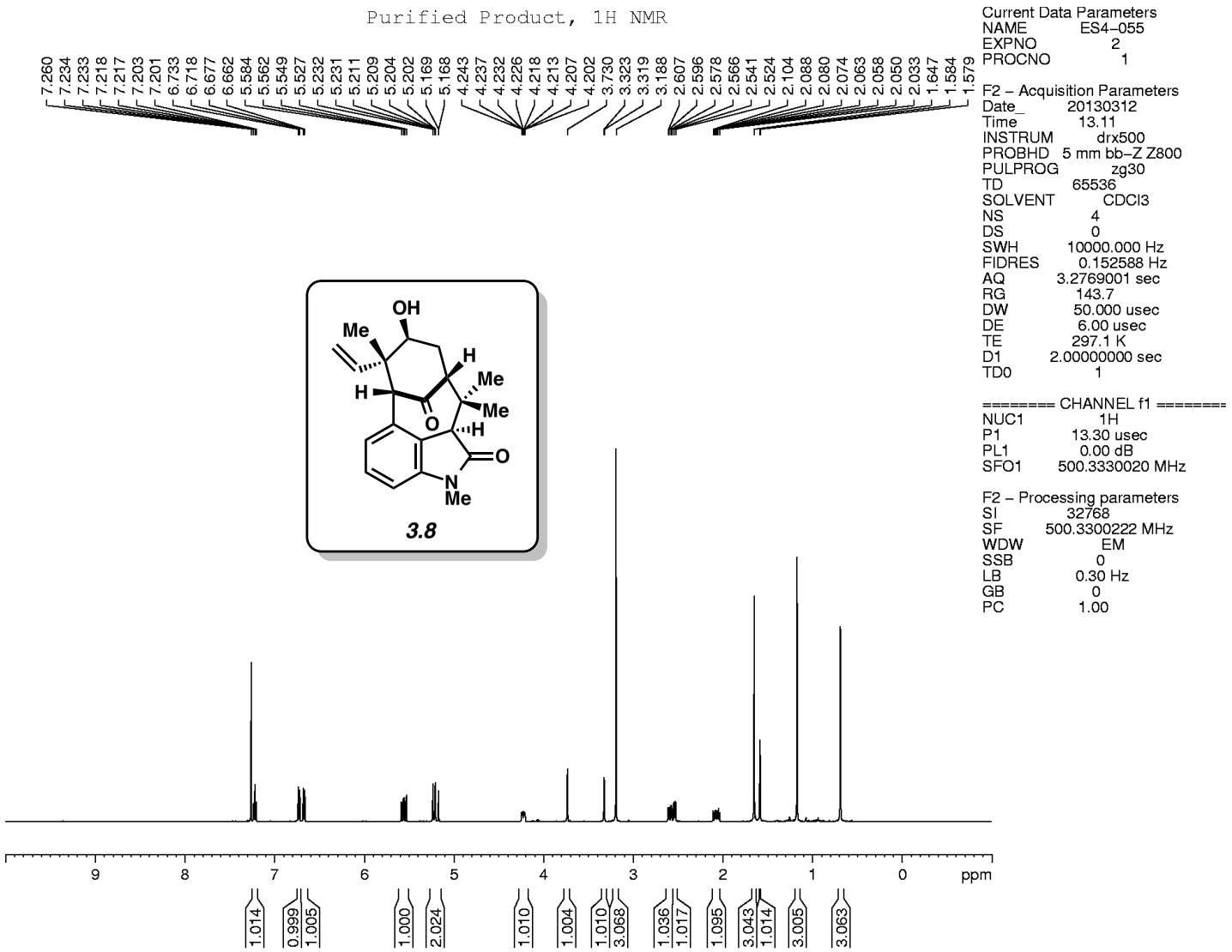


Figure A2.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.8**.

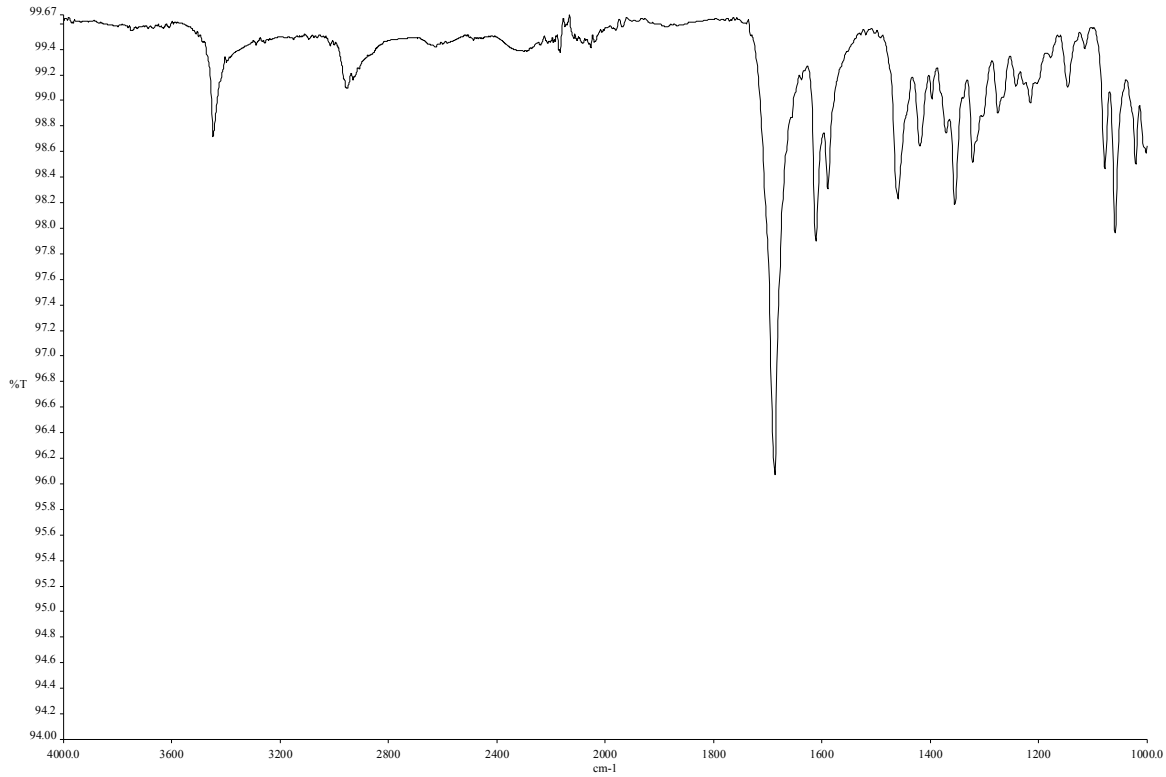


Figure A2.2 Infrared spectrum of compound **3.8**.

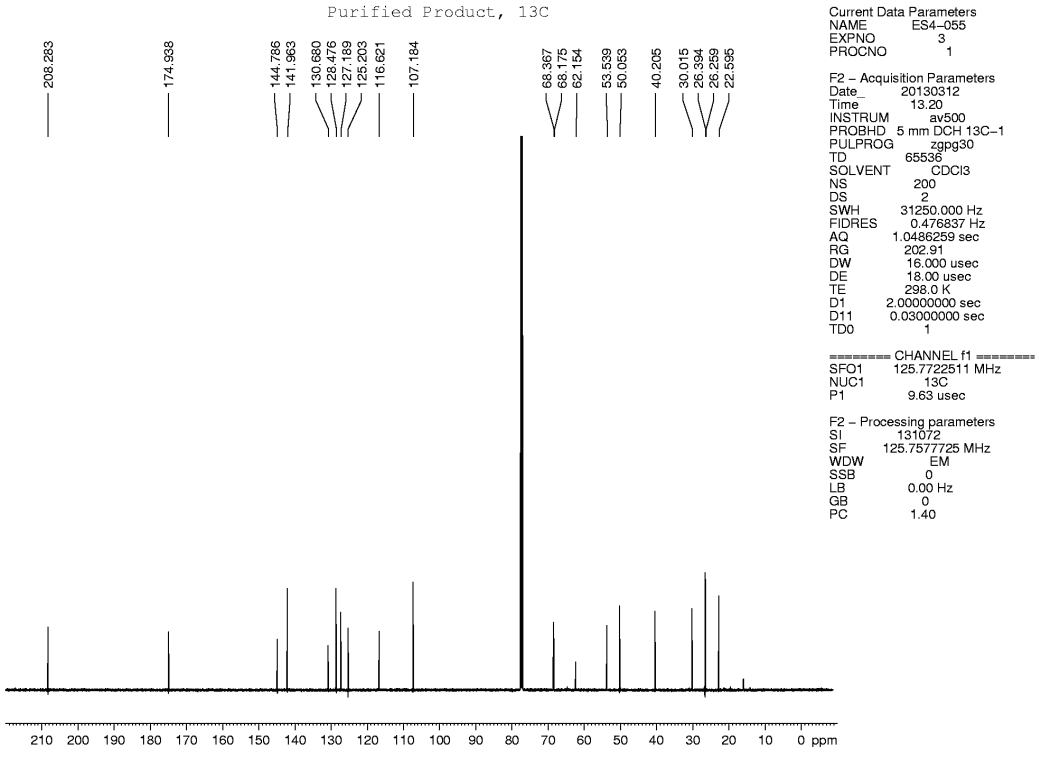


Figure A2.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **3.8**.

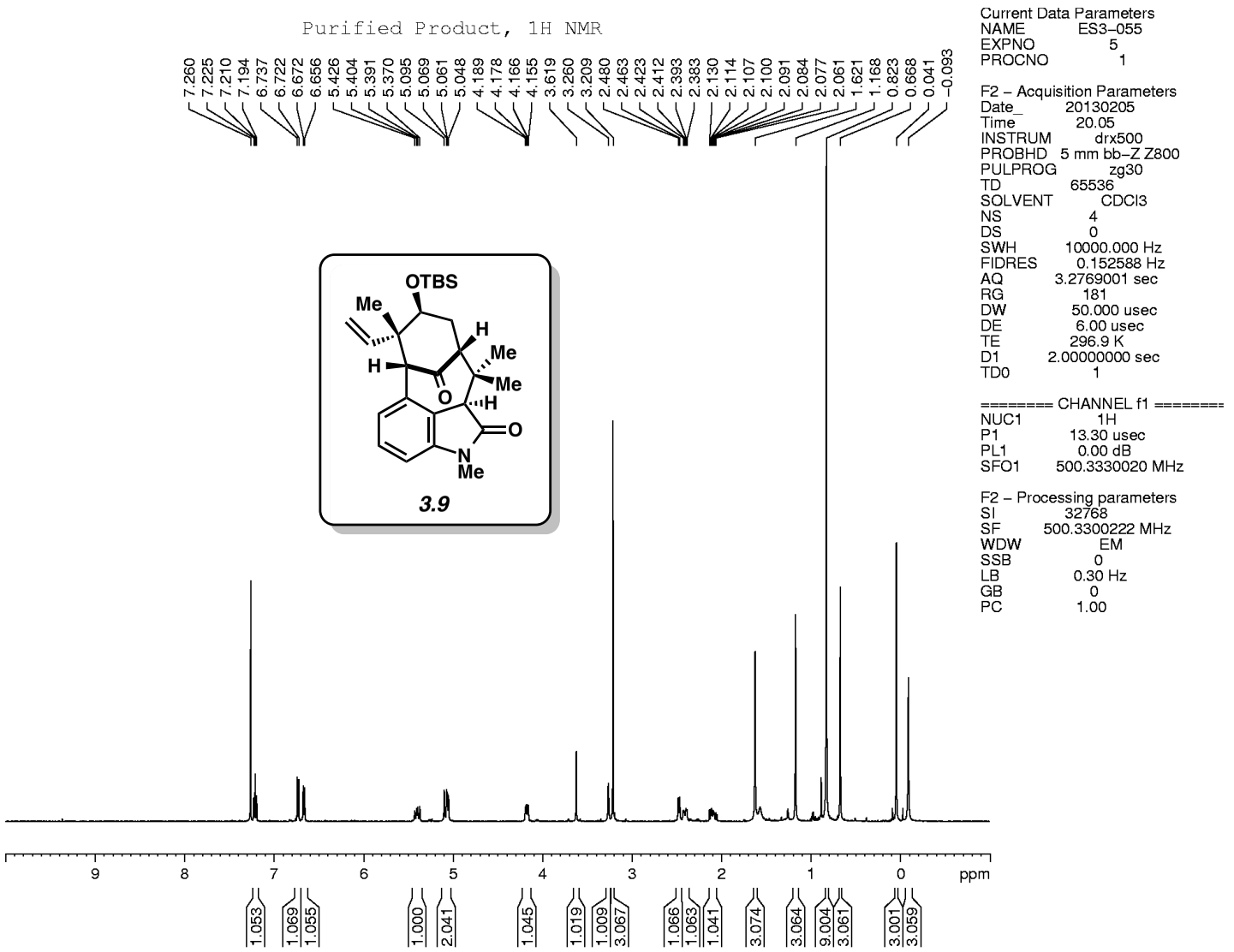


Figure A2.4 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.9**.

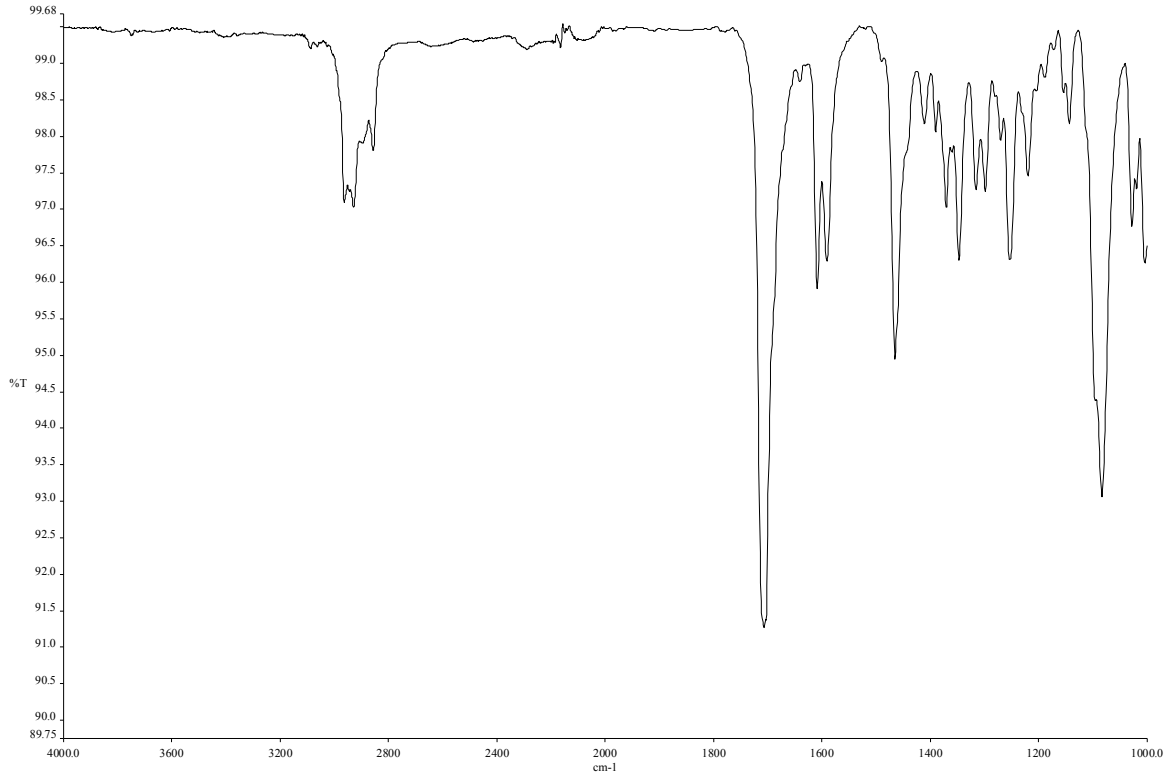


Figure A2.5 Infrared spectrum of compound **3.9**.

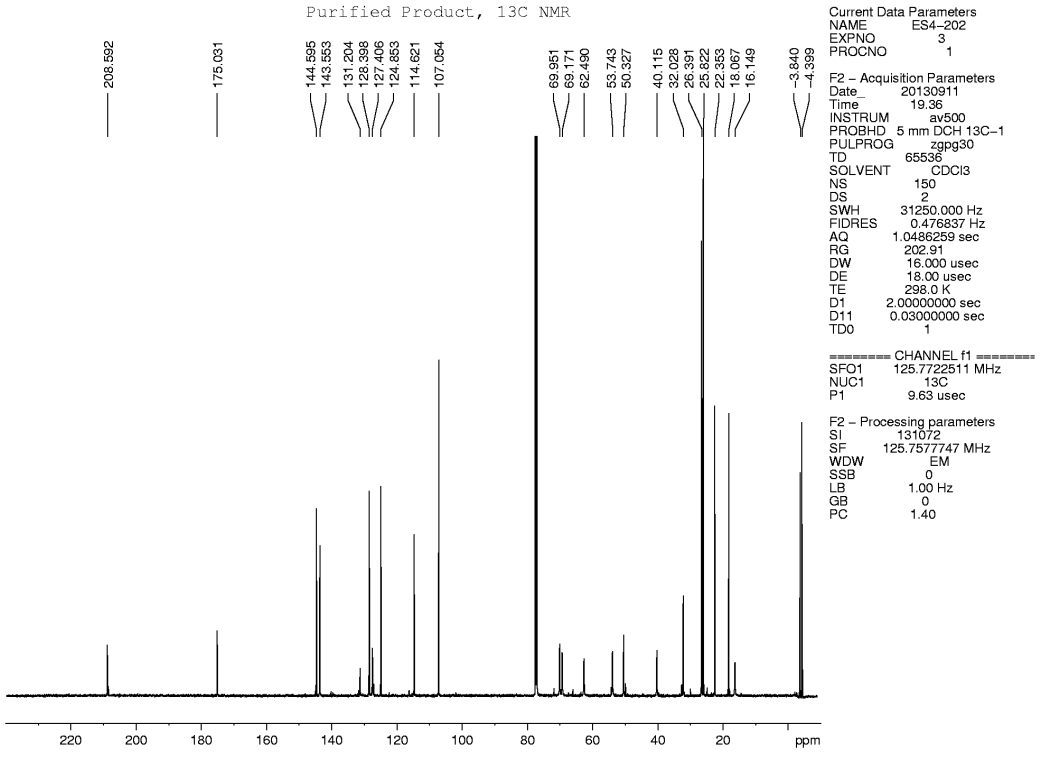


Figure A2.6 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **3.9**.

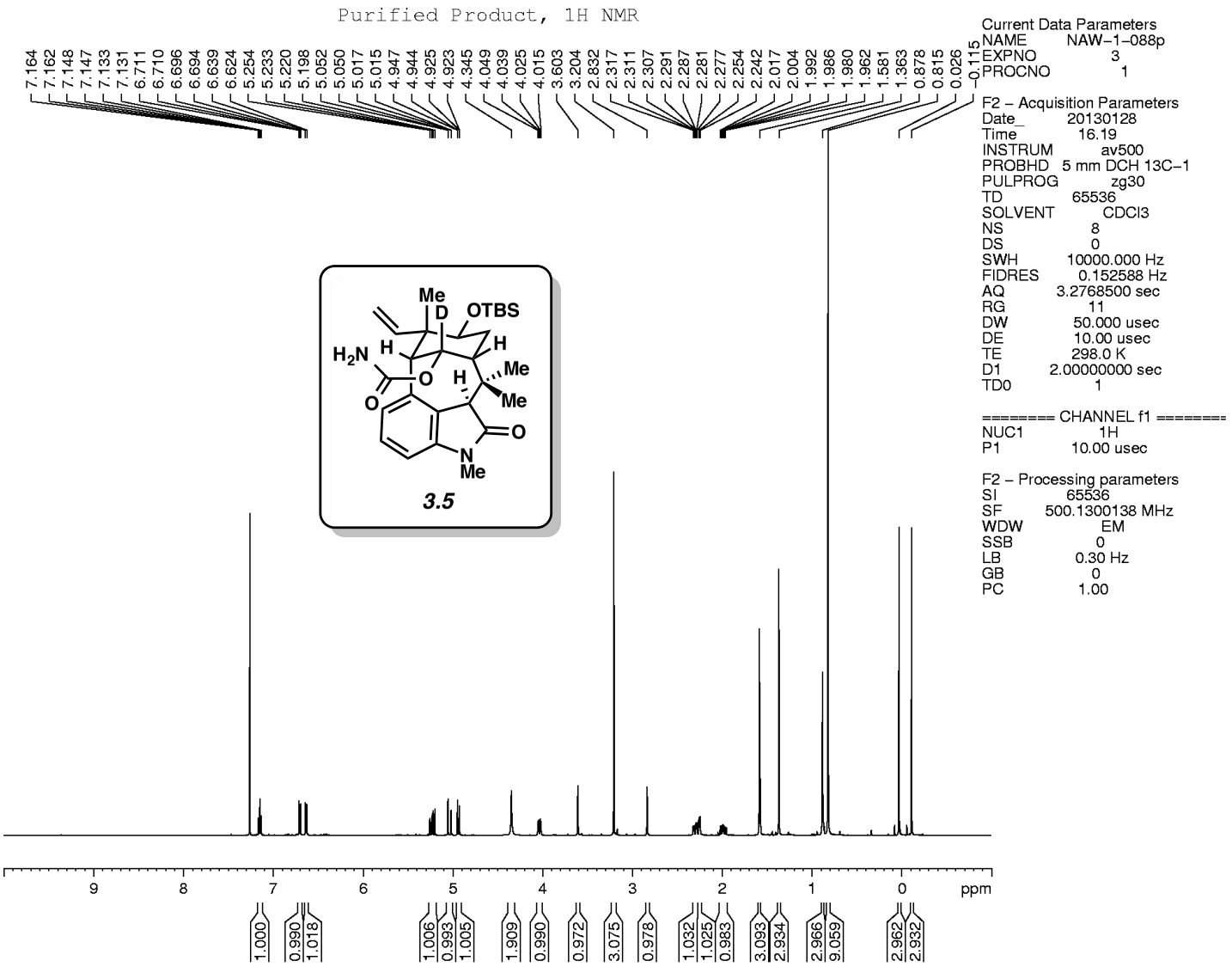


Figure A2.7 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.5**.

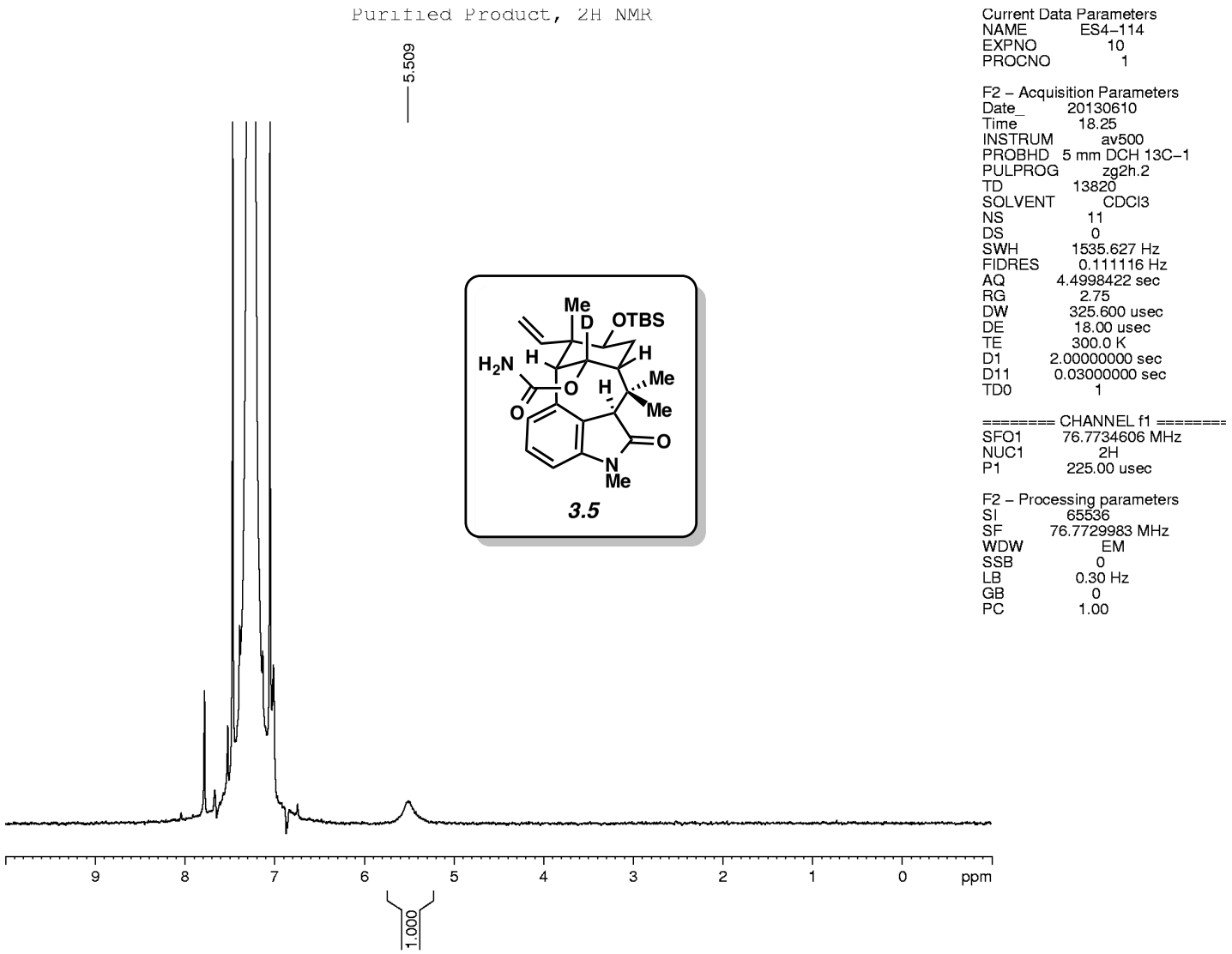


Figure A2.8 ^{2}H NMR (77 MHz, $CDCl_3$) of compound **3.5**.

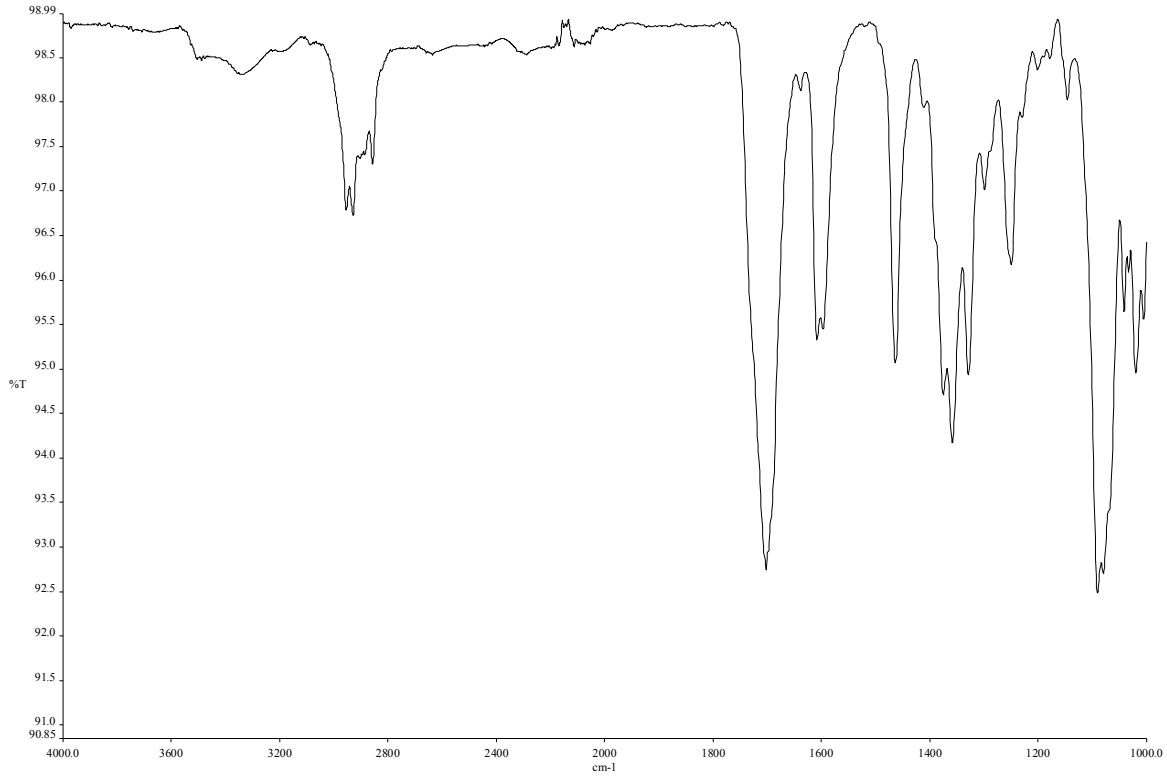


Figure A2.9 Infrared spectrum of compound **3.5**.

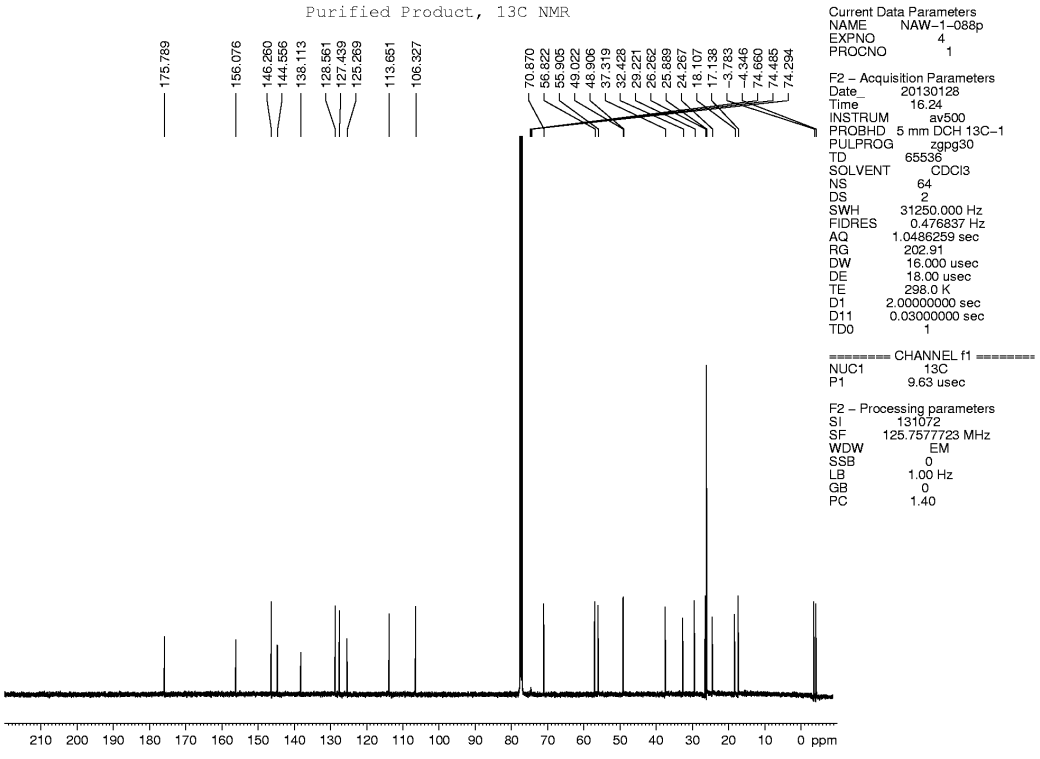


Figure A2.10 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **3.5**.

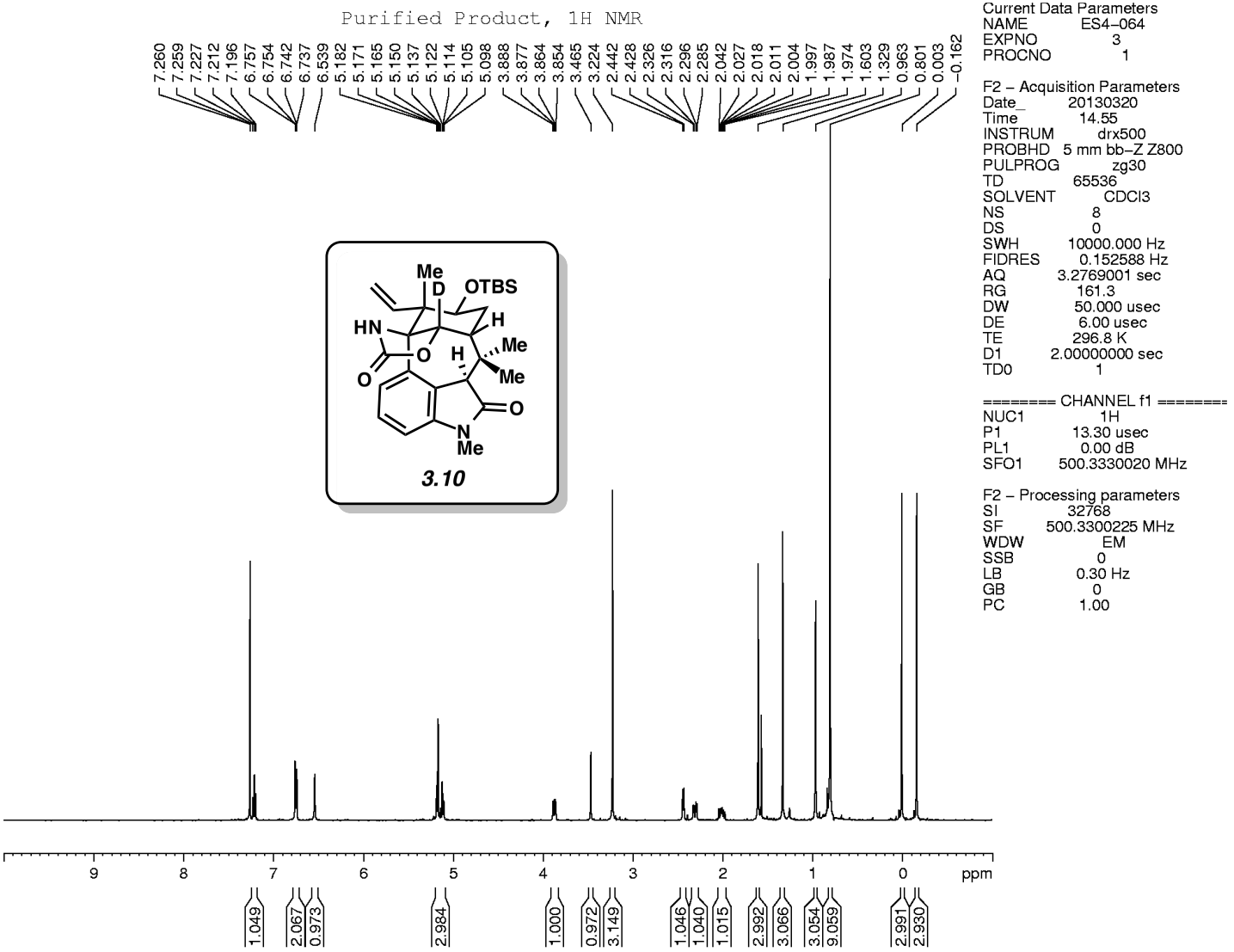


Figure A2.11 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.10**.

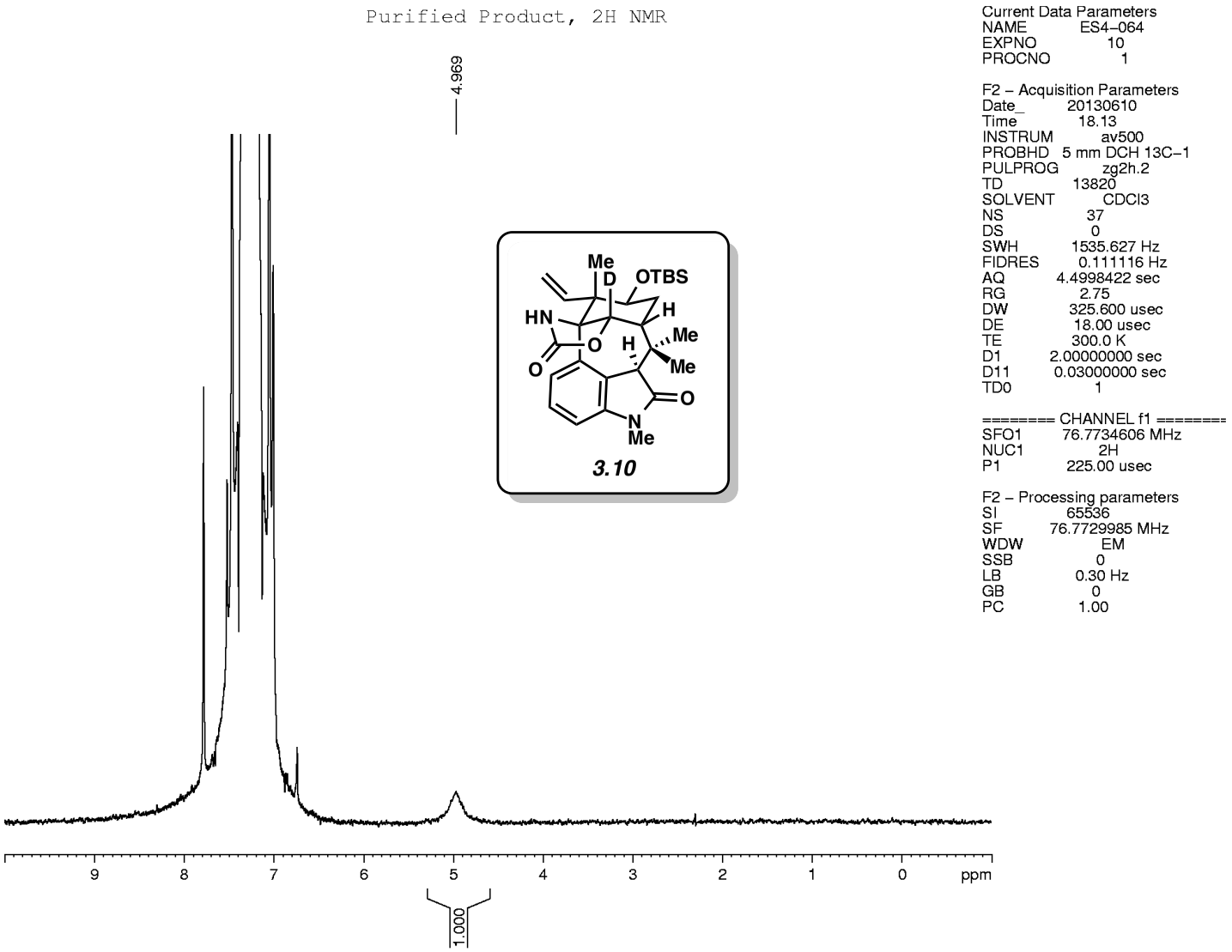


Figure A2.12 ^{2}H NMR (77 MHz, $CDCl_3$) of compound **3.10**.

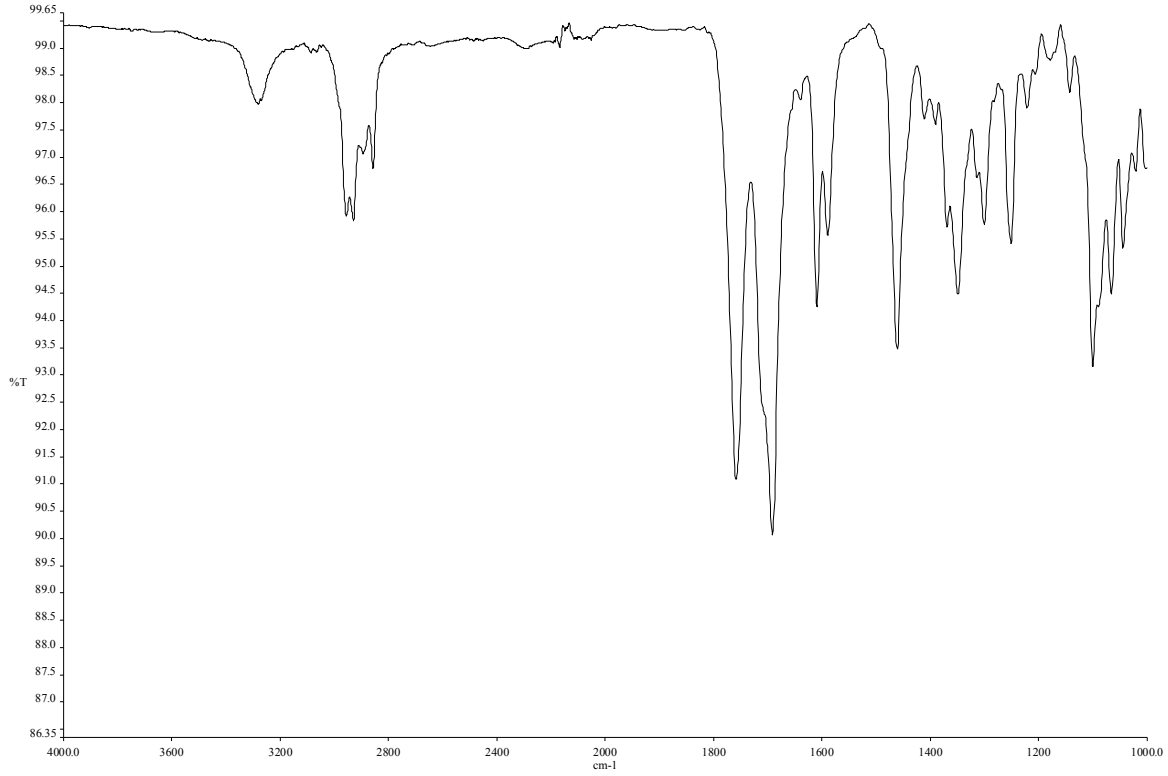


Figure A2.13 Infrared spectrum of compound **3.10**.

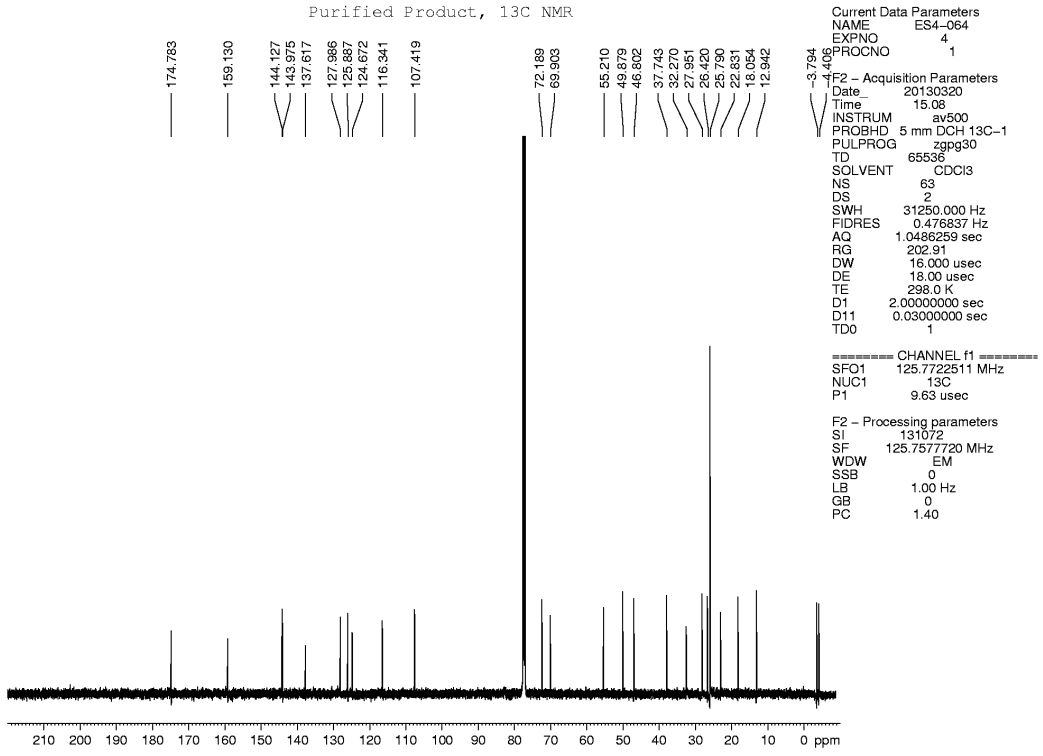


Figure A2.14 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **3.10**.

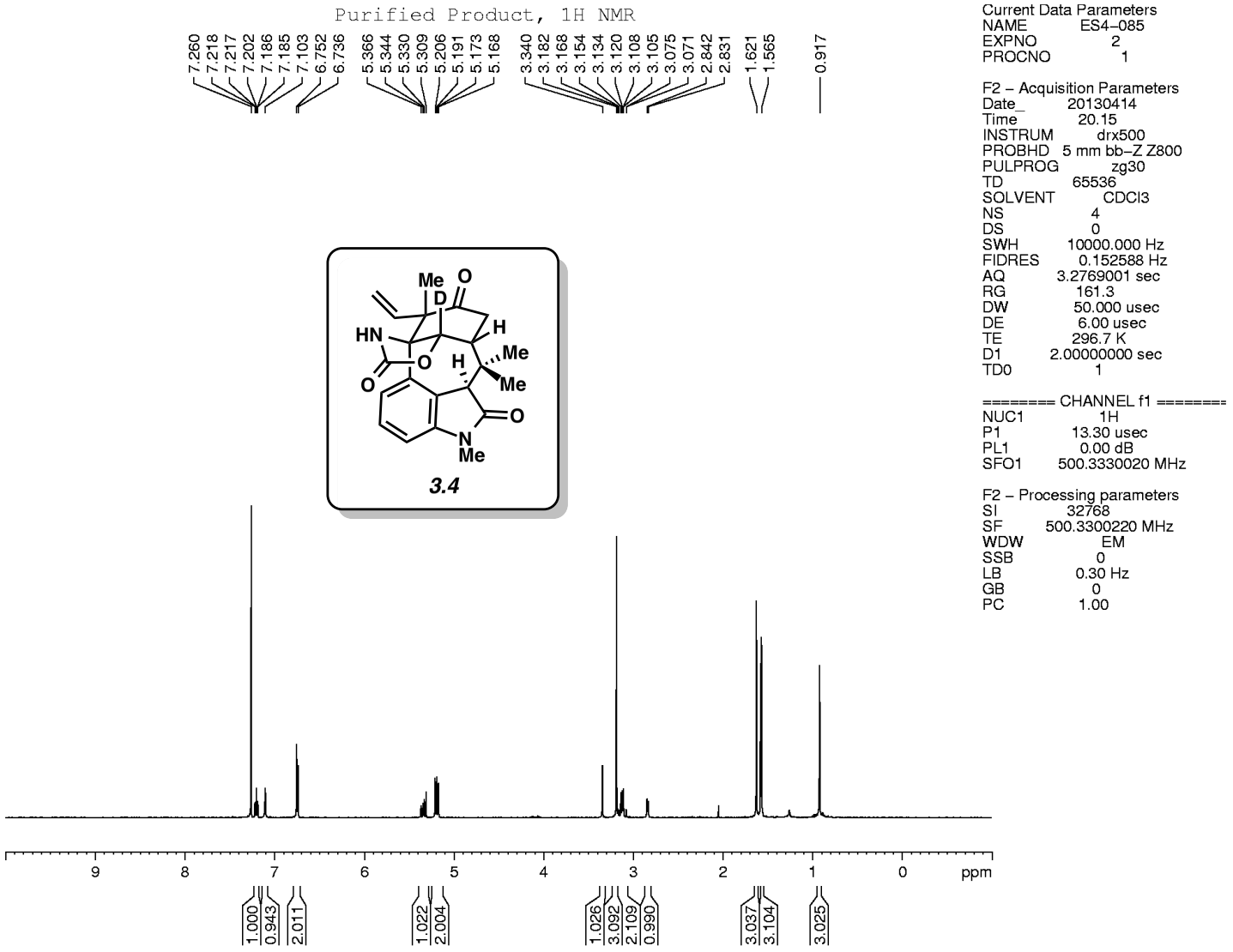


Figure A2.15 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.4**.

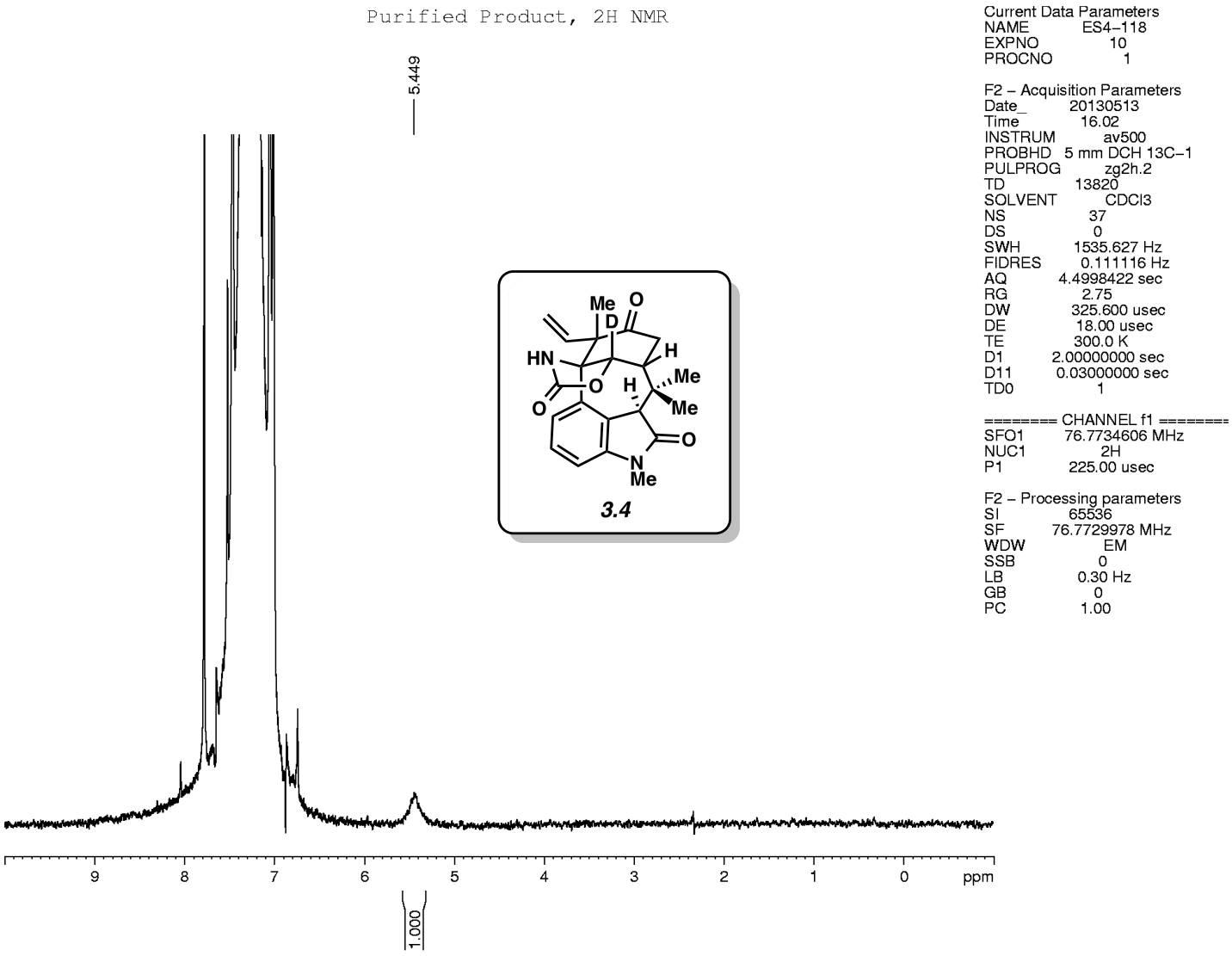


Figure A2.16 ^{2}H NMR (77 MHz, $CDCl_3$) of compound **3.4**.

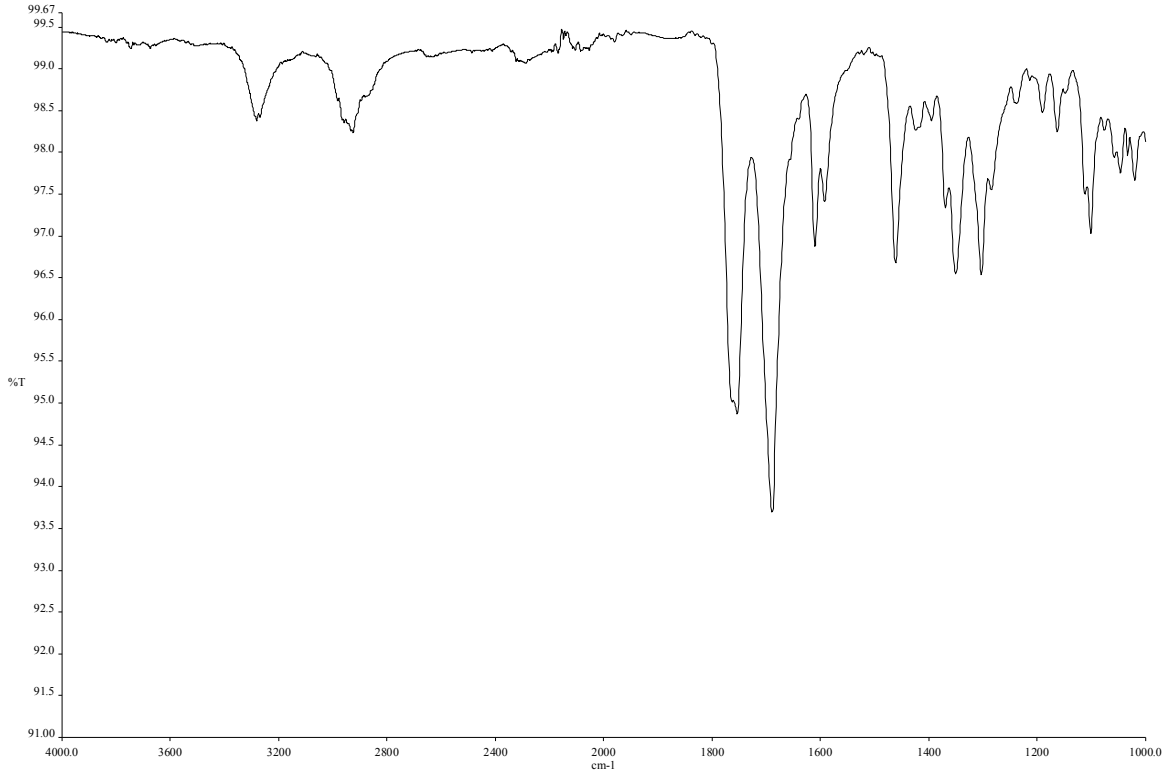


Figure A2.17 Infrared spectrum of compound **3.4**.

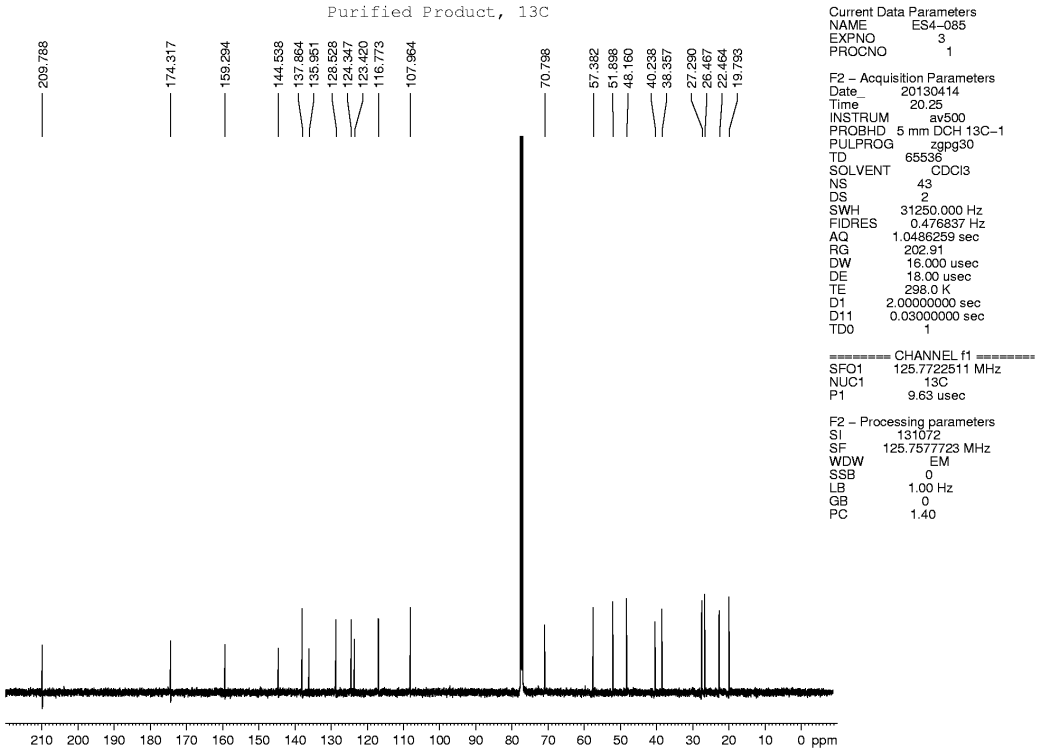


Figure A2.18 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **3.4**.

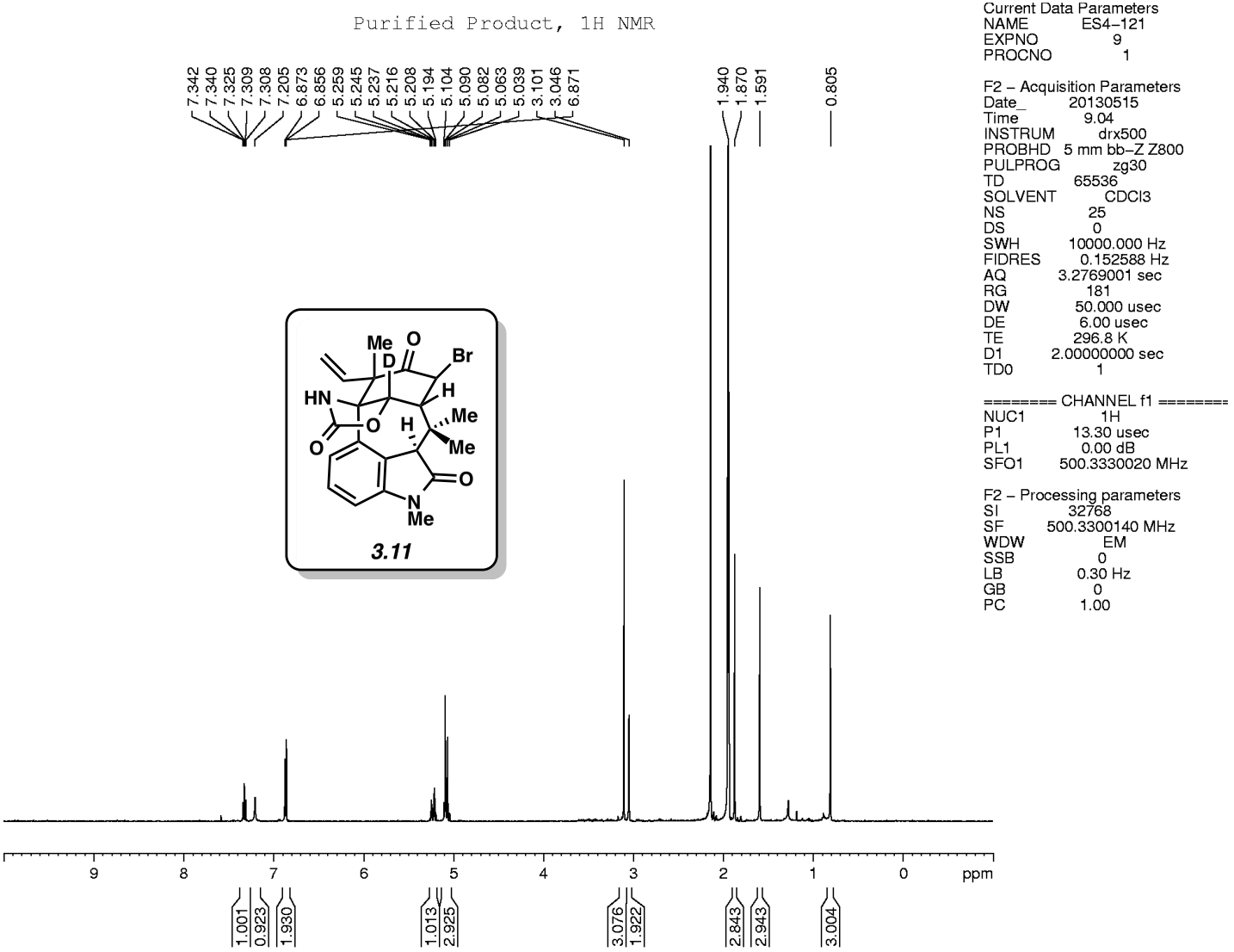


Figure A2.19 ^{1}H NMR (500 MHz, CD_3CN) of compound **3.11**.

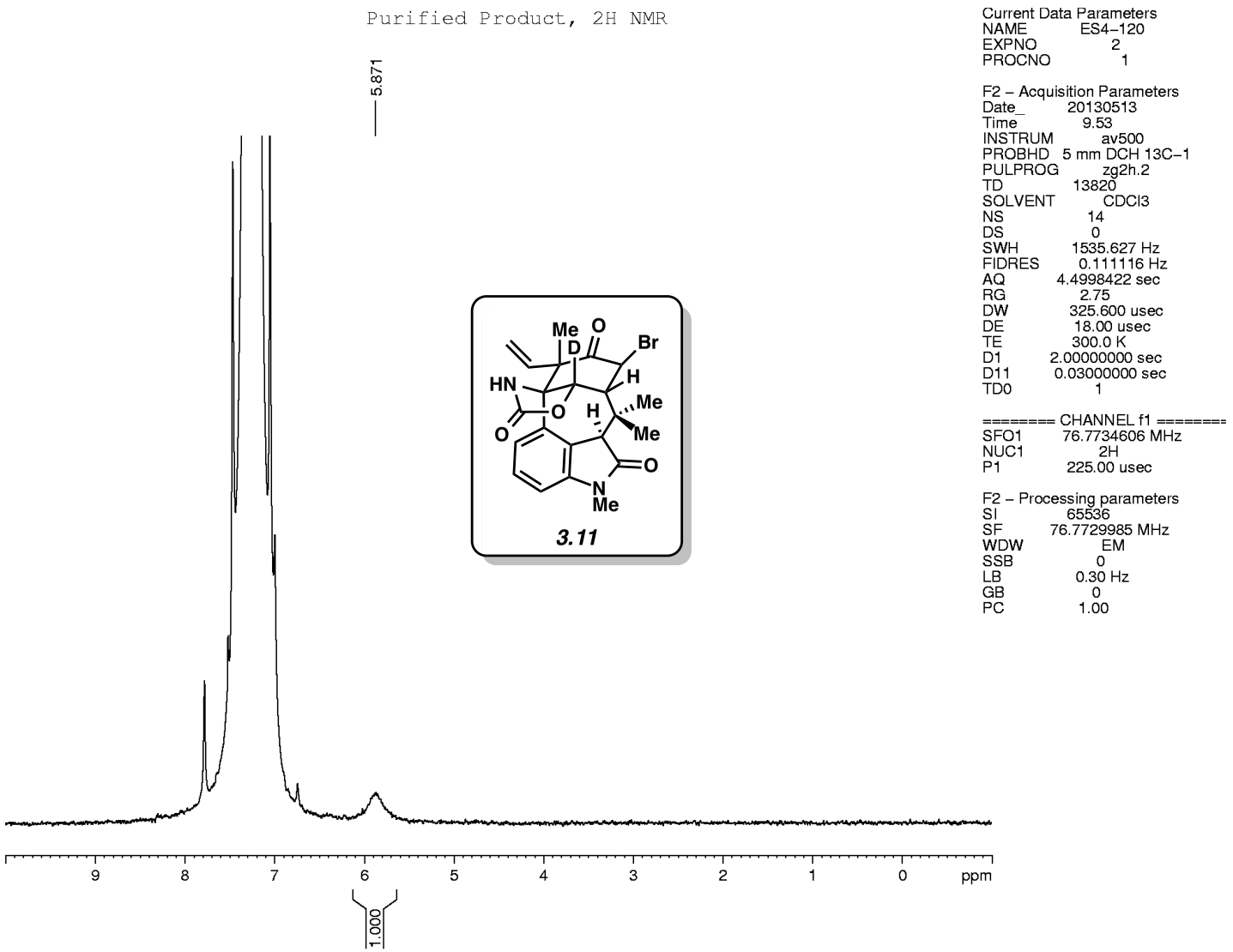


Figure A2.20 ^{2}H NMR (77 MHz, $CDCl_3$) of compound **3.11**.

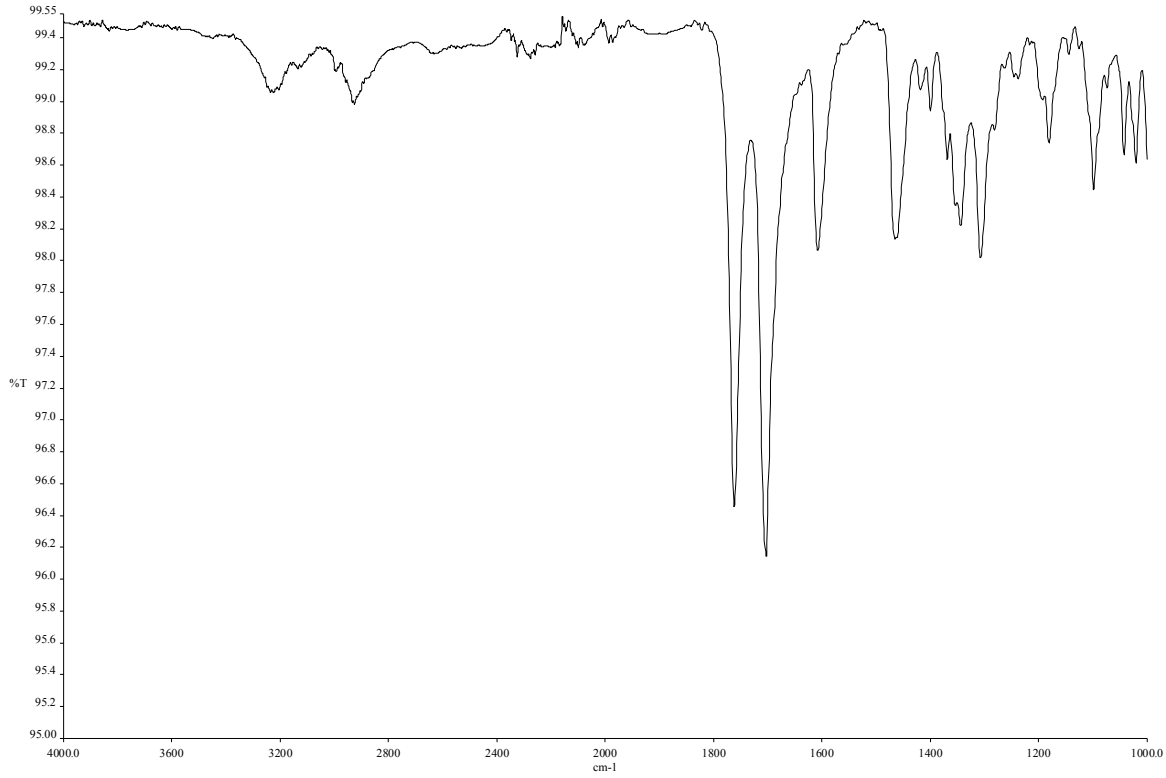


Figure A2.21 Infrared spectrum of compound **3.11**.

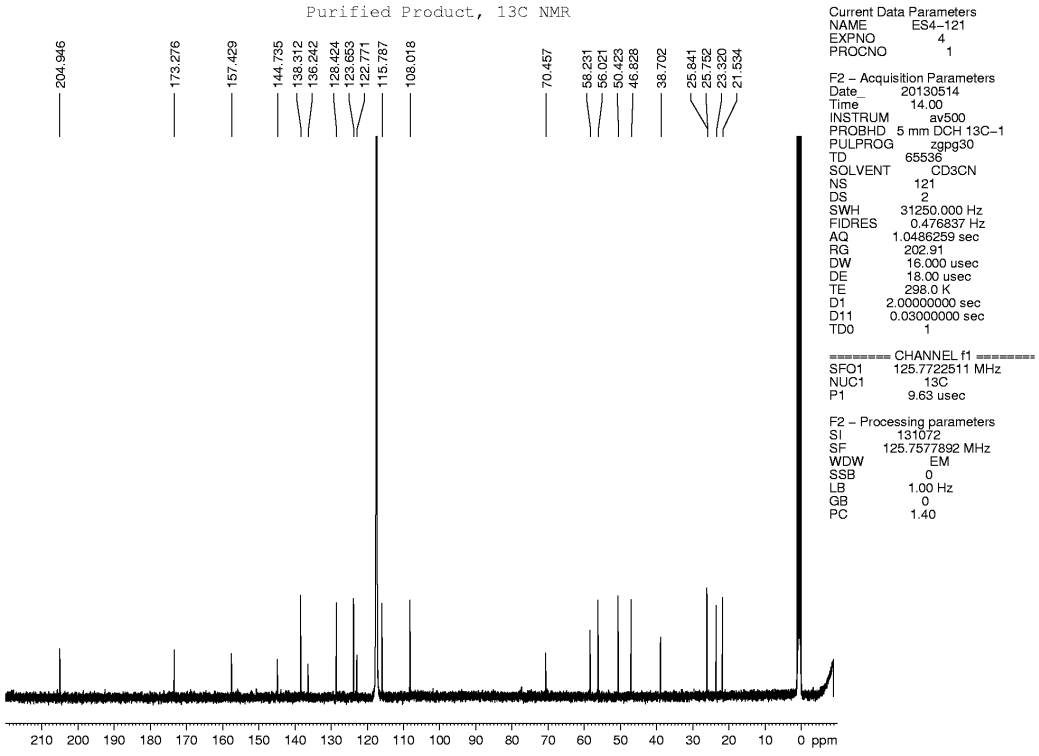


Figure A2.22 ^{13}C NMR (125 MHz, CD_3CN) of compound **3.11**.

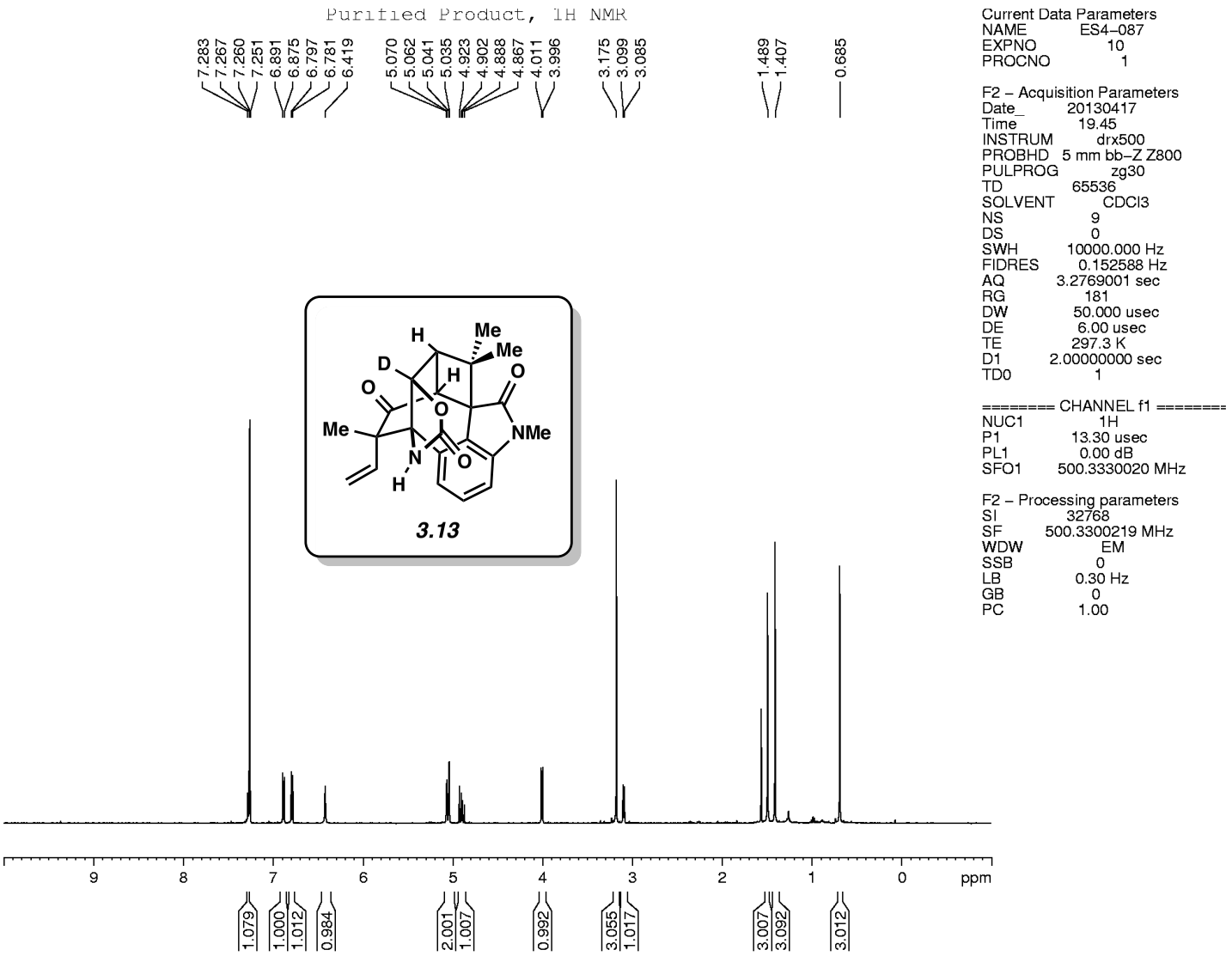


Figure A2.23 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.13**.

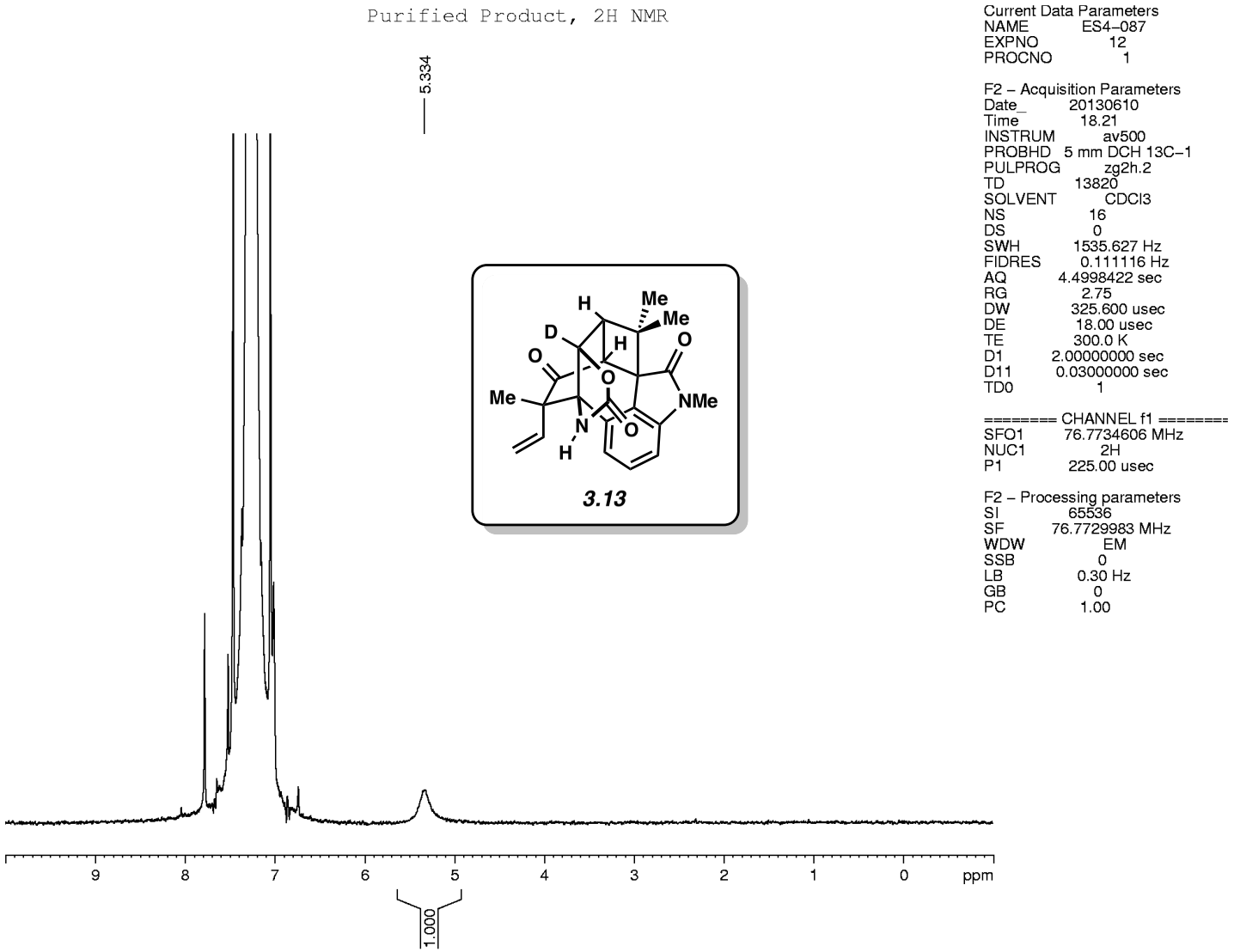


Figure A2.24 ^{2}H NMR (77 MHz, $CDCl_3$) of compound **3.13**.

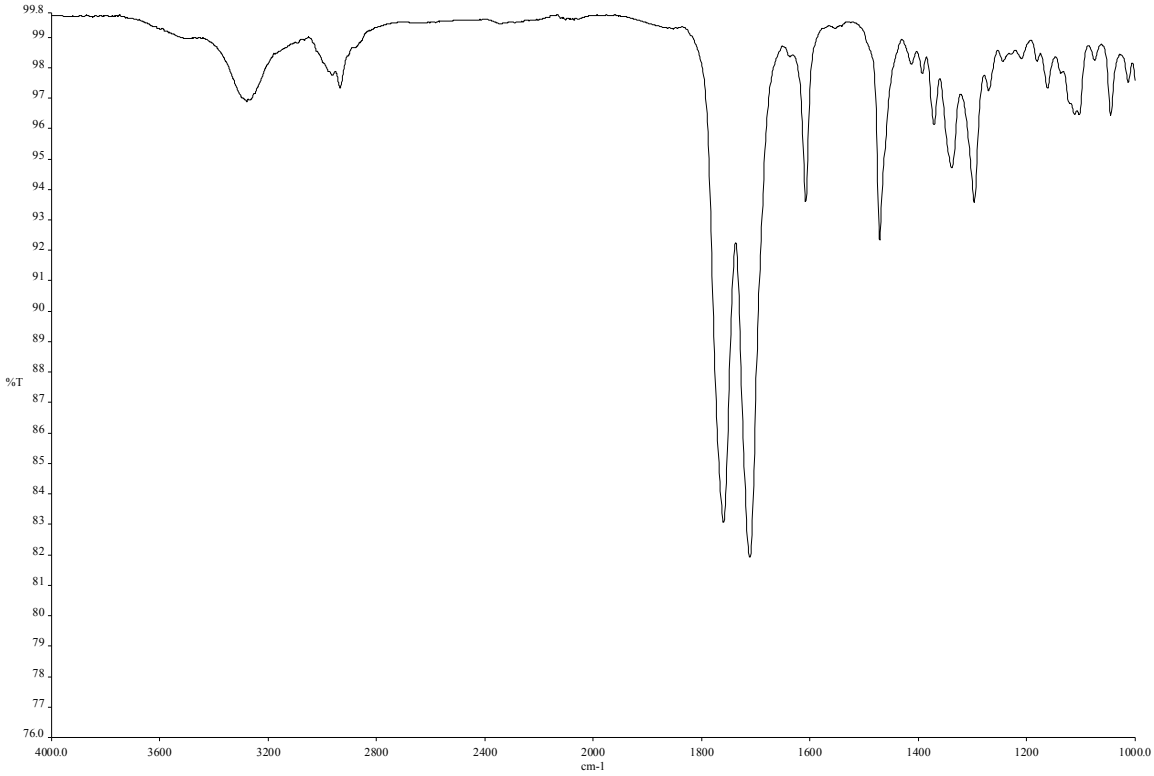


Figure A2.25 Infrared spectrum of compound **3.13**.

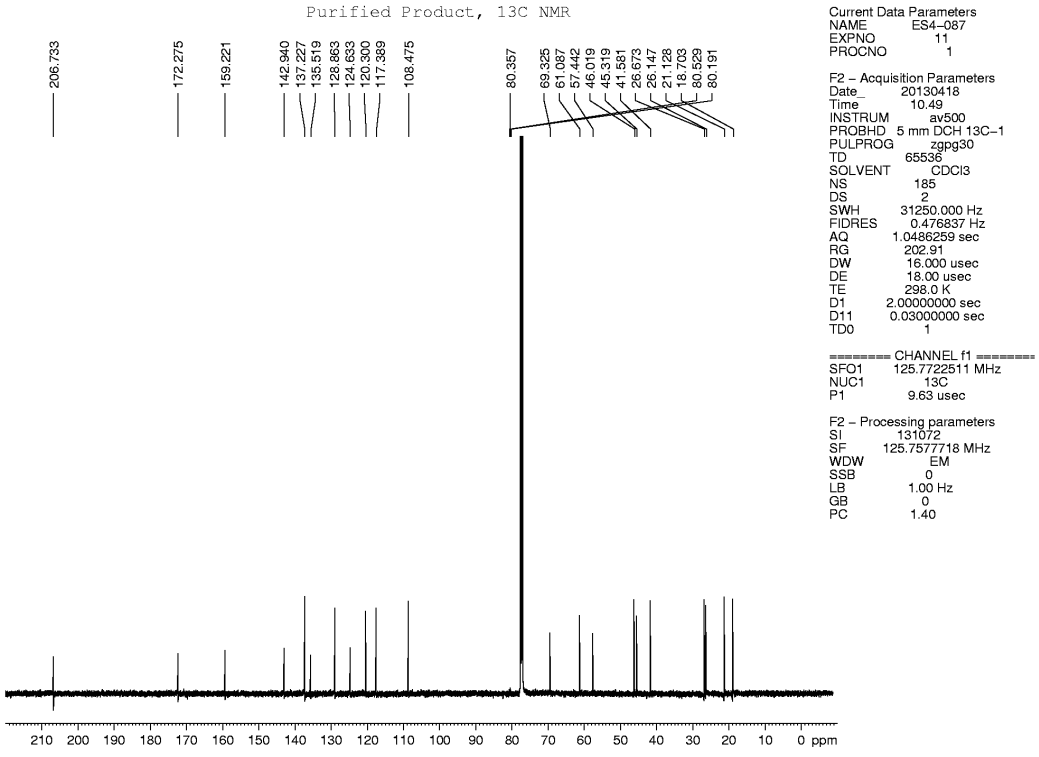


Figure A2.26 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **3.13**.

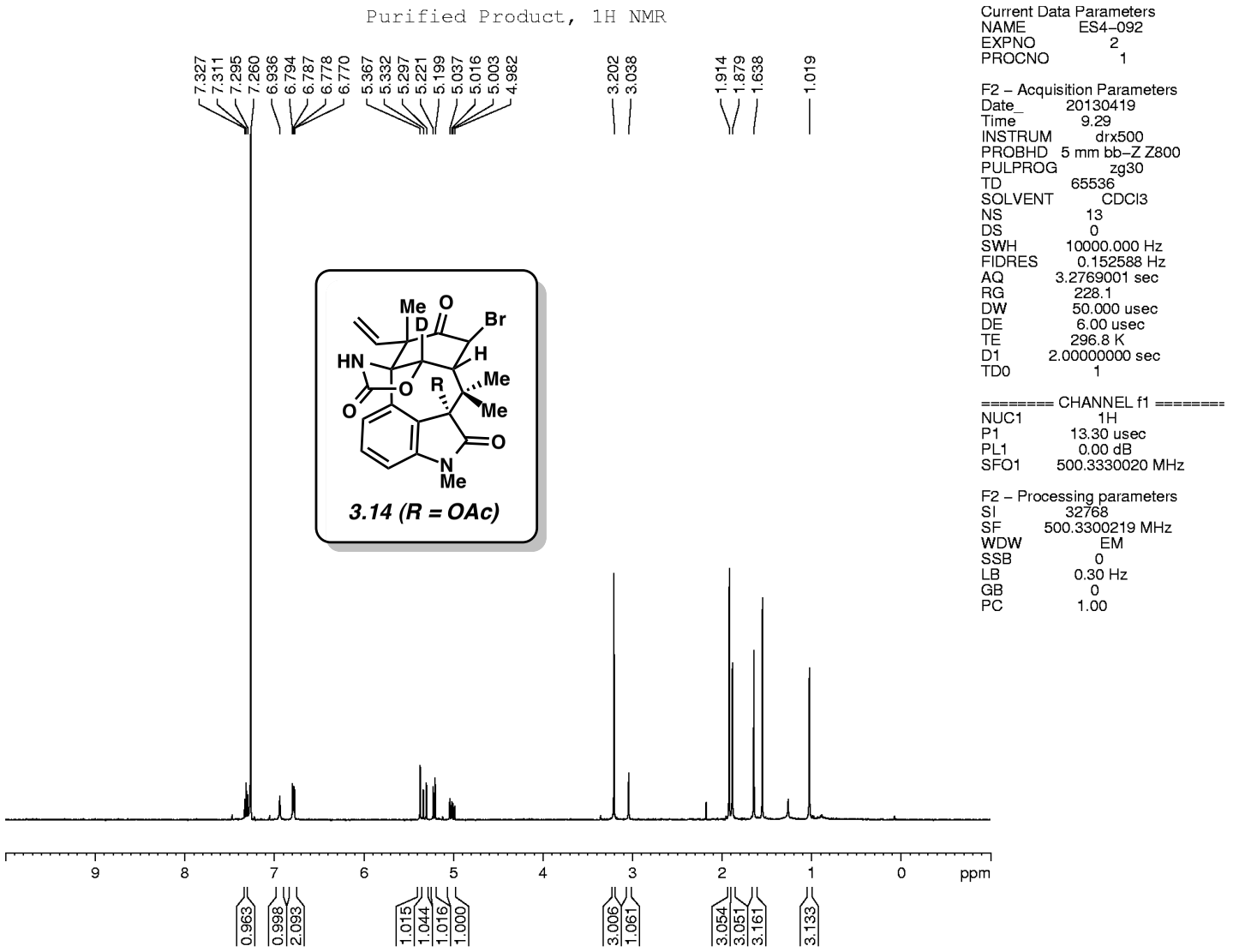


Figure A2.27 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.14**.

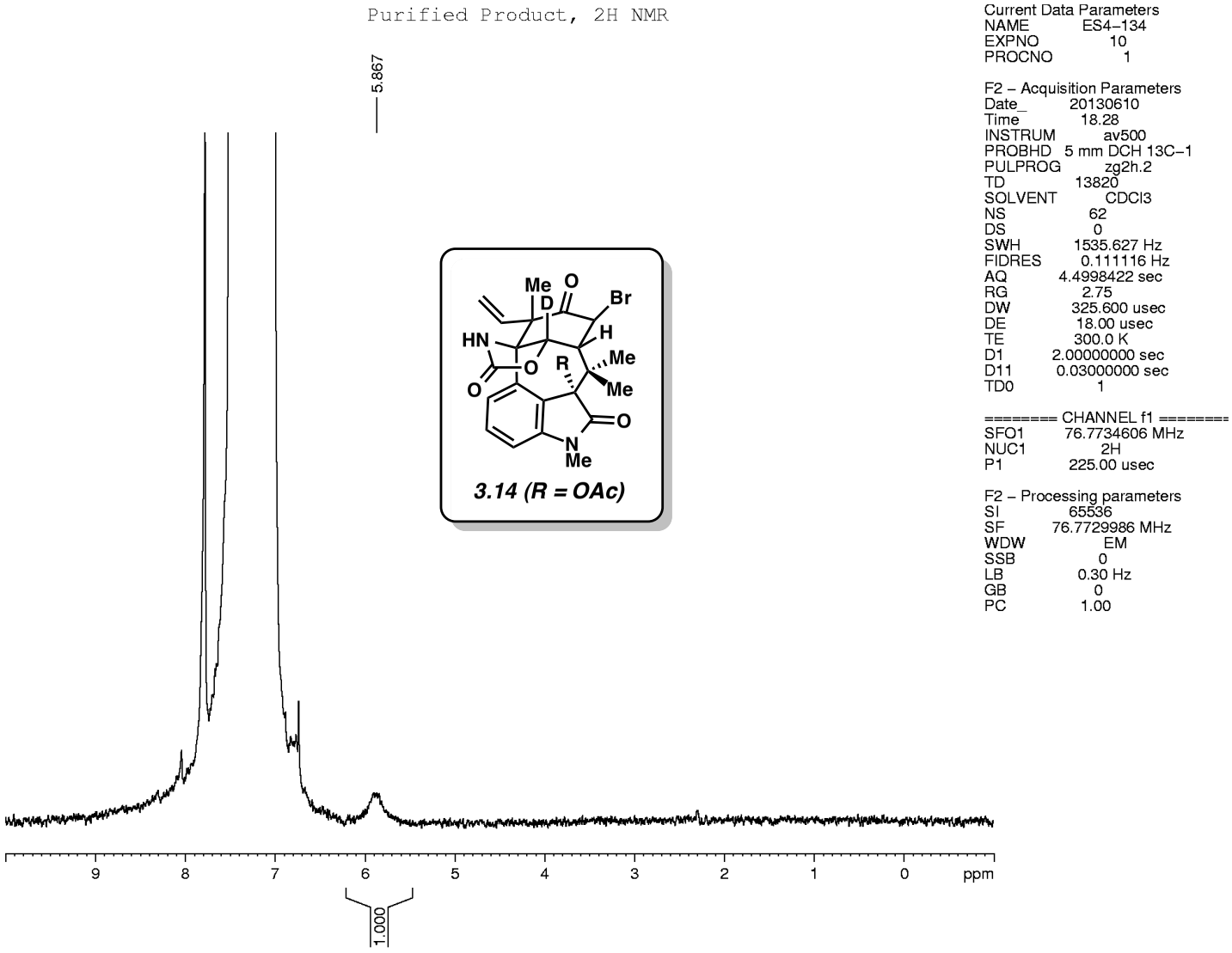


Figure A2.28 ^{2}H NMR (77 MHz, $CDCl_3$) of compound **3.14**.

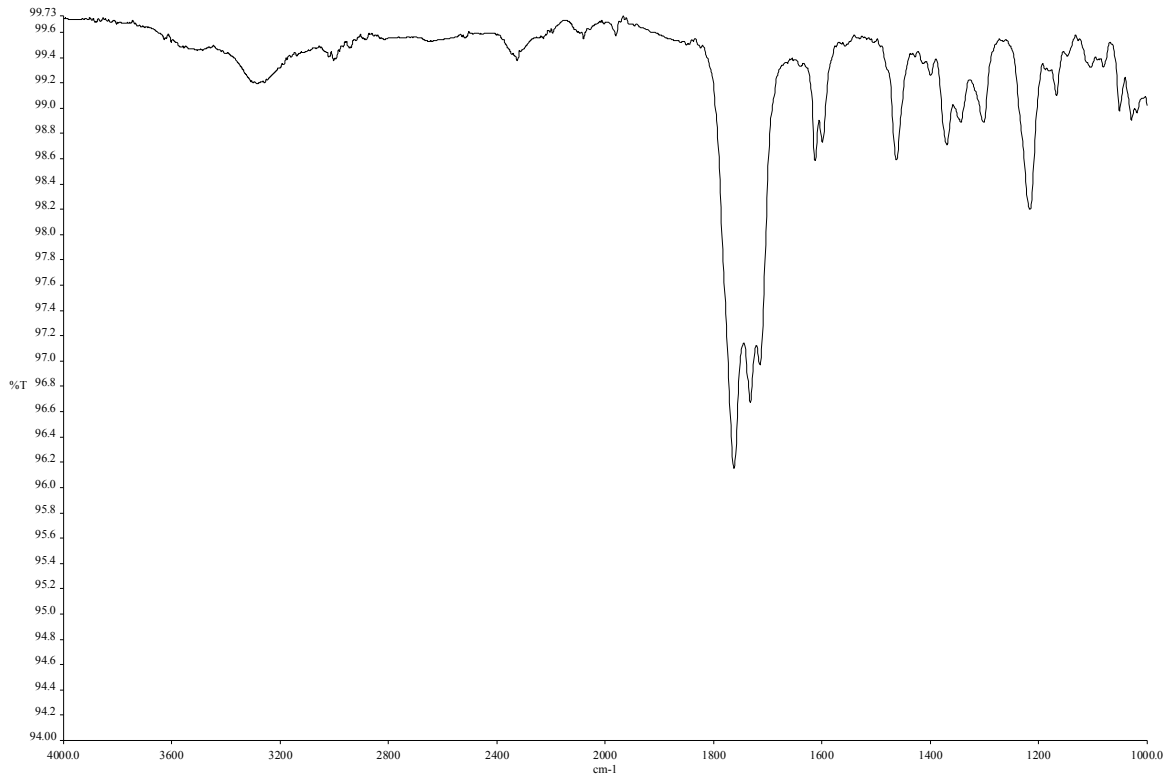


Figure A2.29 Infrared spectrum of compound **3.14**.

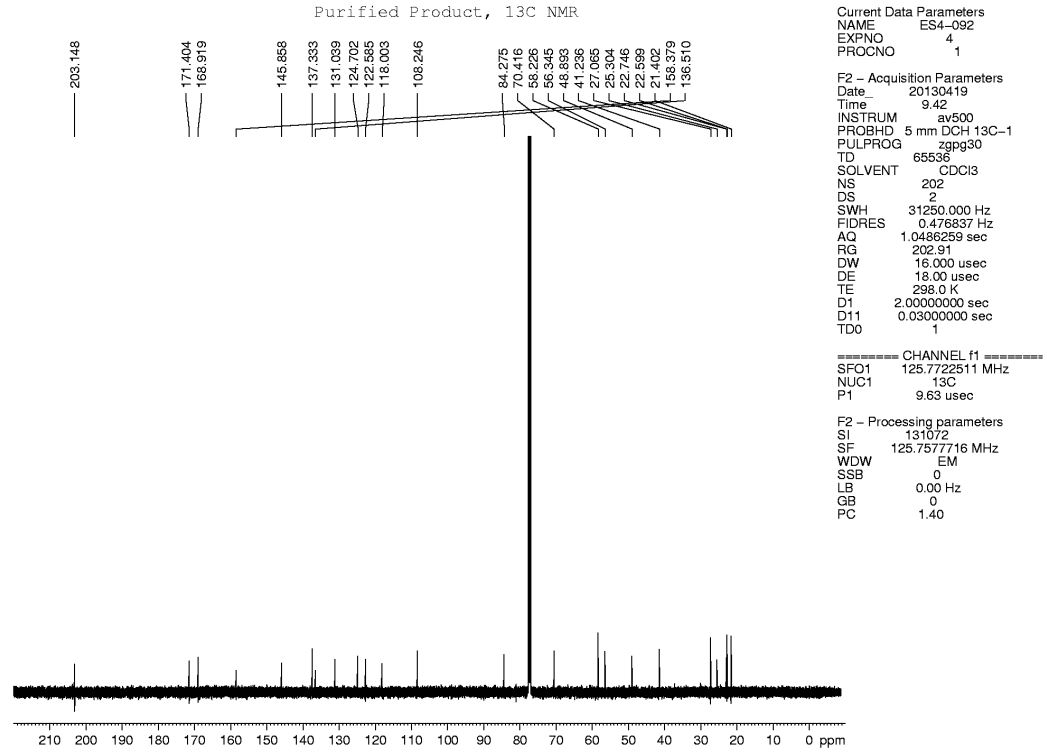


Figure A2.30 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **3.14**.

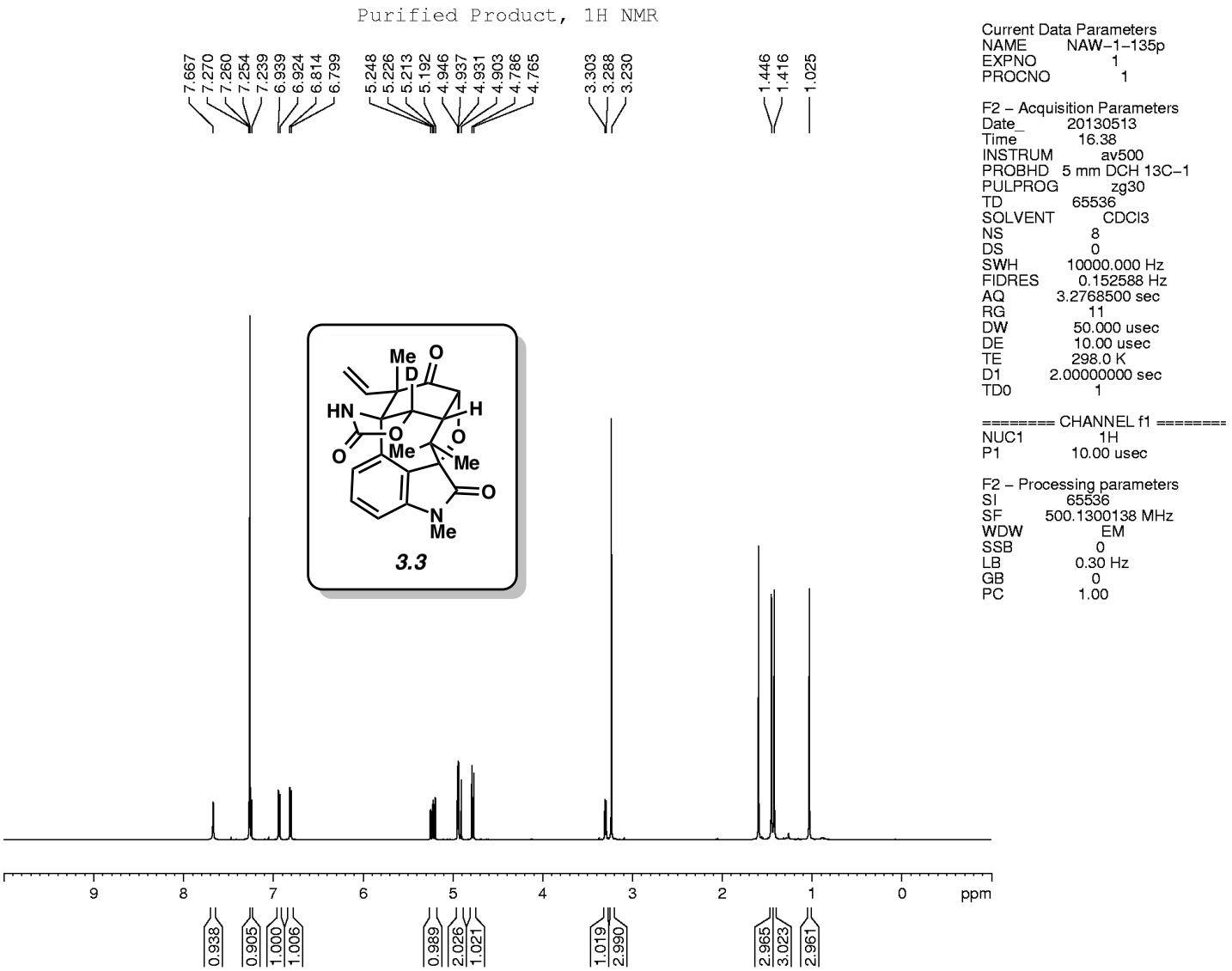


Figure A2.31 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.3**.

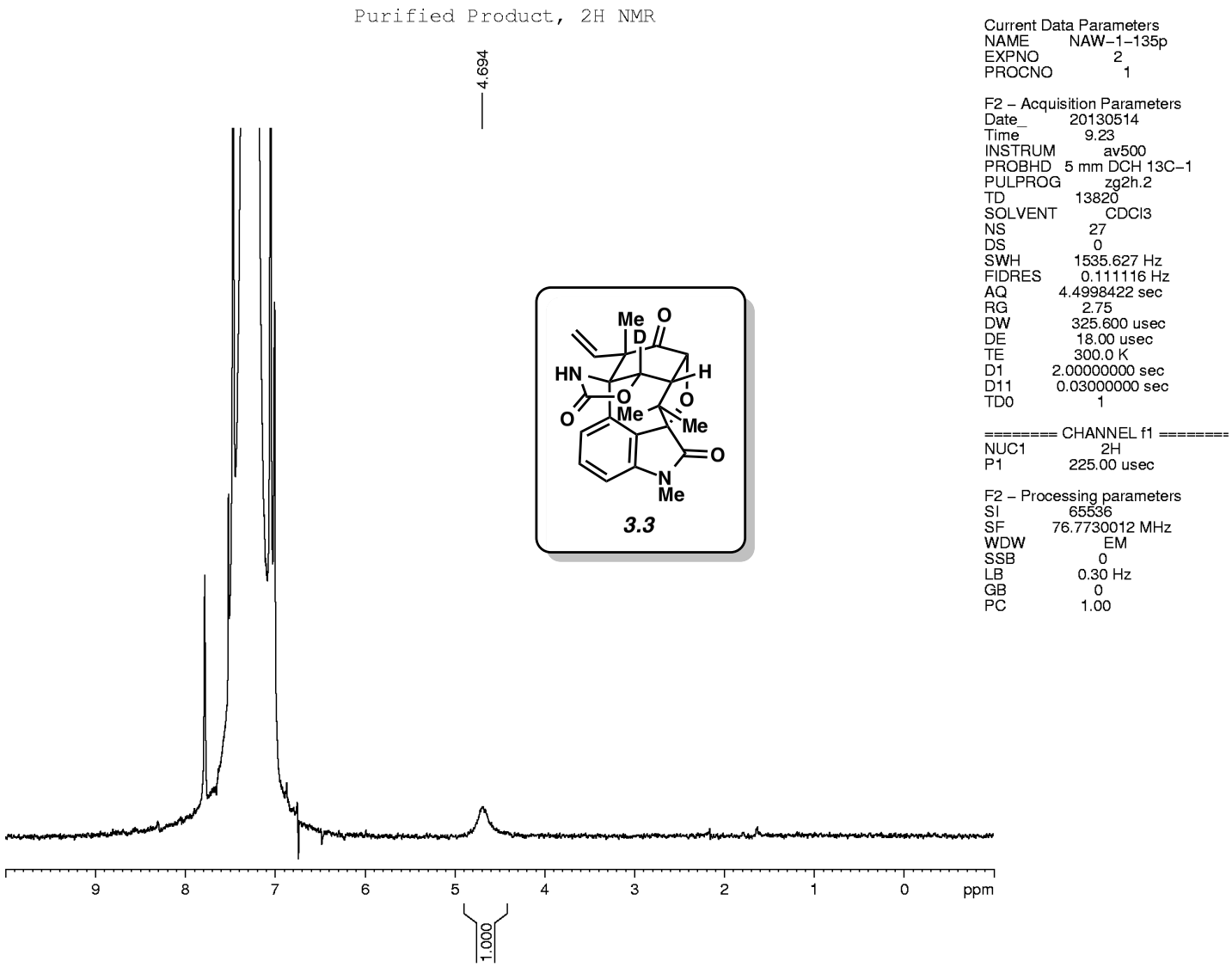


Figure A2.32 ^{2}H NMR (77 MHz, $CDCl_3$) of compound **3.3**.

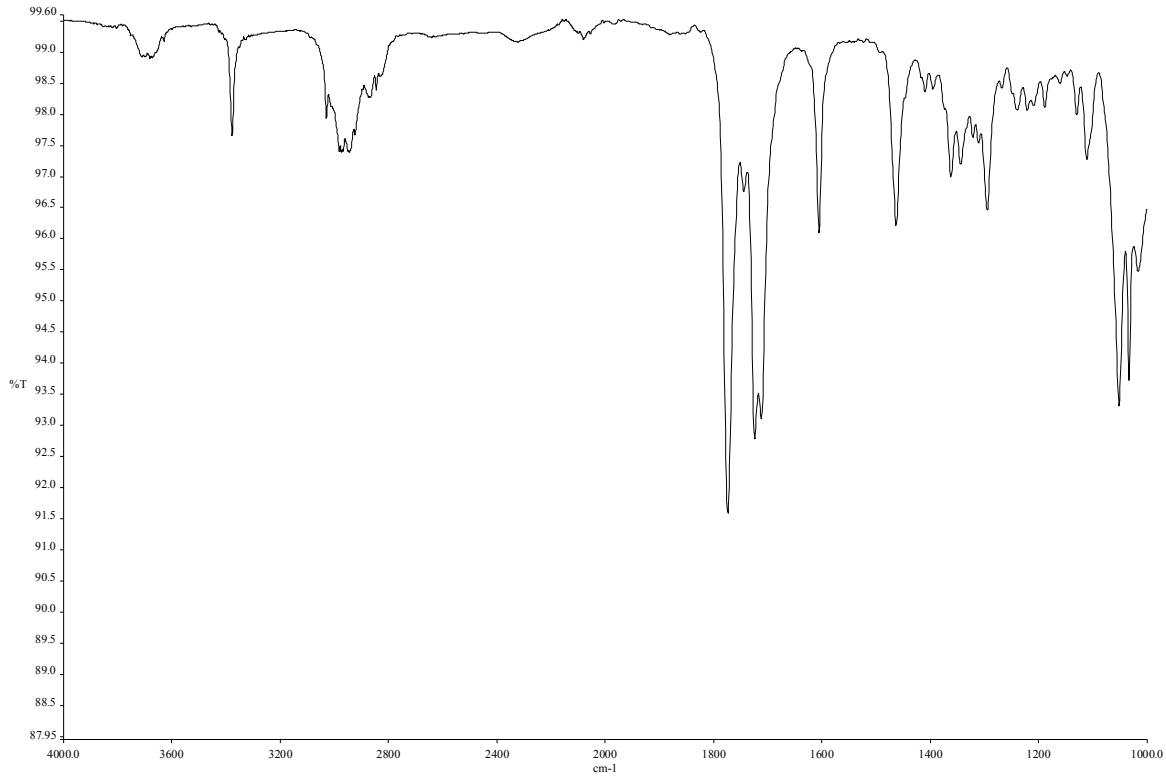


Figure A2.33 Infrared spectrum of compound **3.3**.

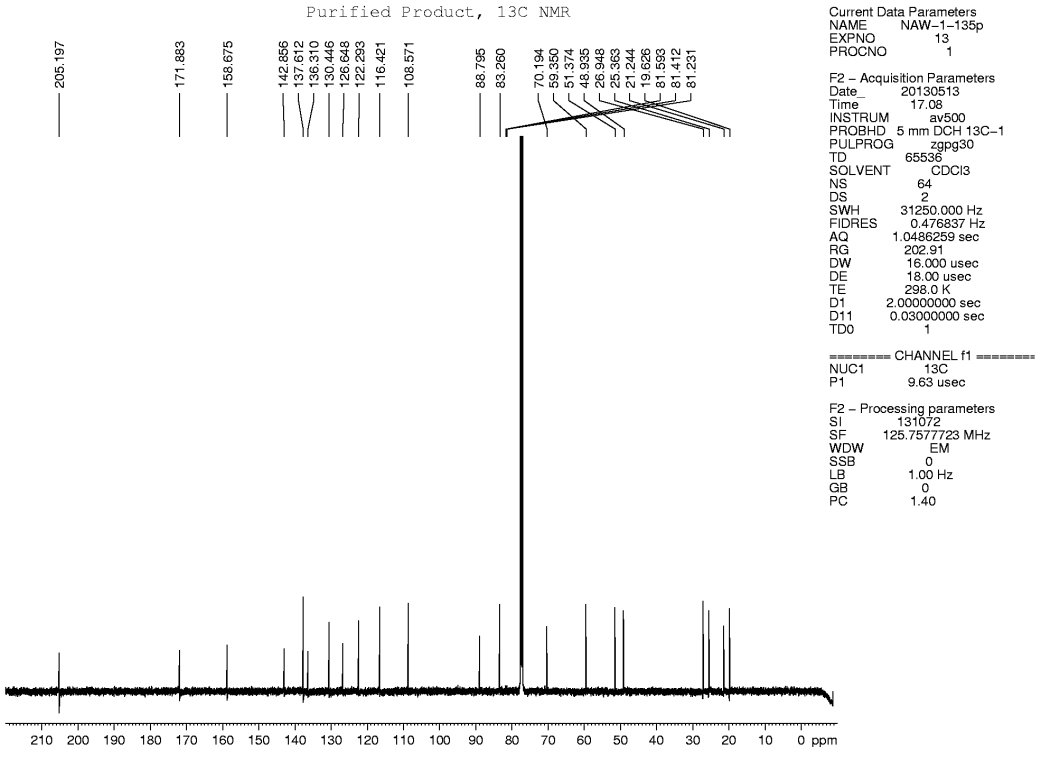


Figure A2.34 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **3.3**.

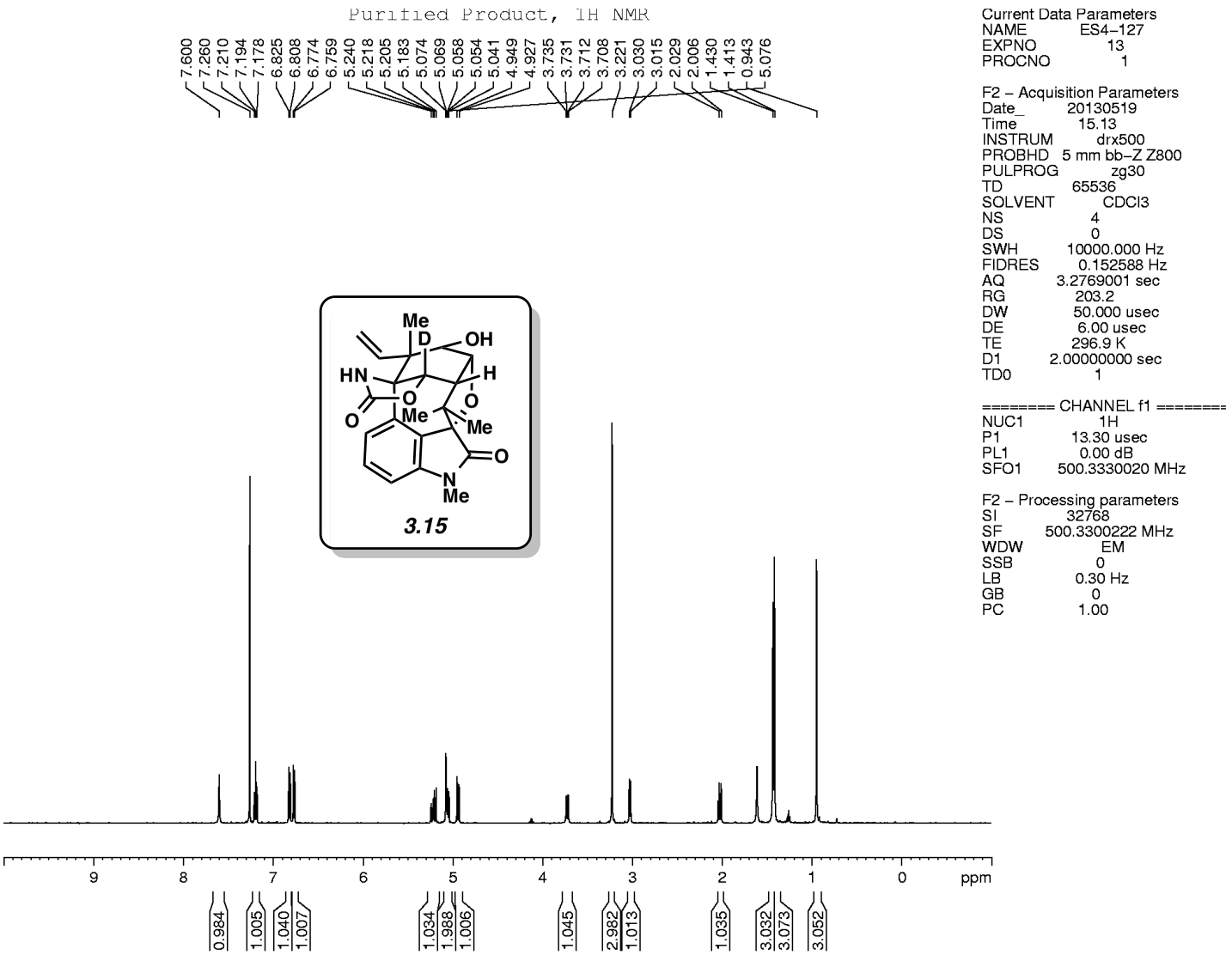


Figure A2.35 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.15**.

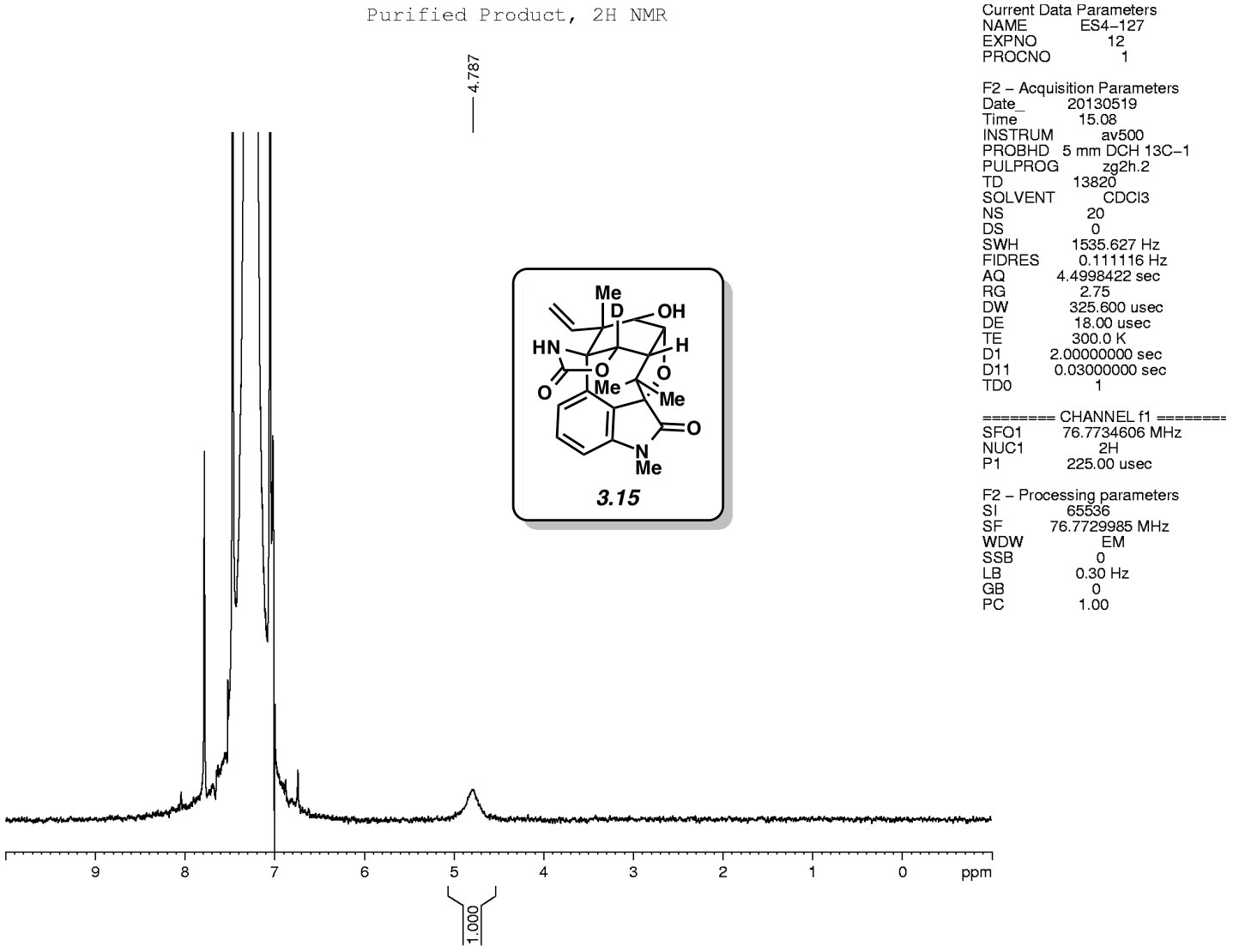


Figure A2.36 ^{2}H NMR (77 MHz, $CDCl_3$) of compound **3.15**.

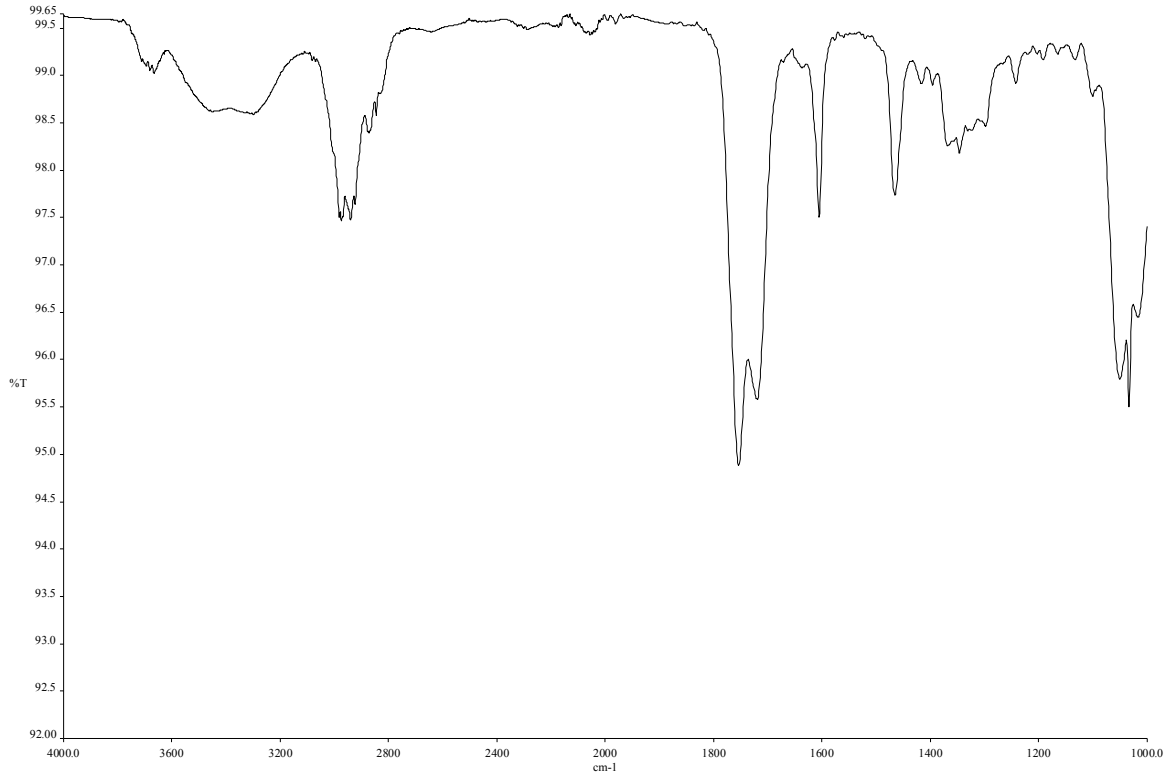


Figure A2.37 Infrared spectrum of compound **3.15**.

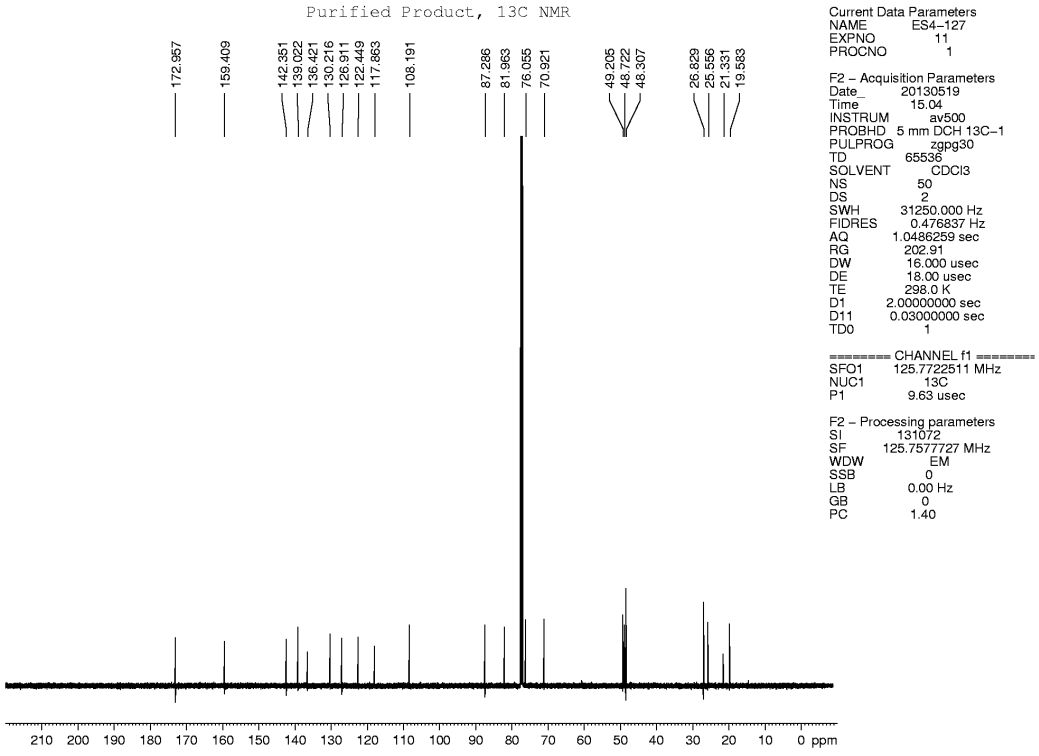


Figure A2.38 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **3.15**.

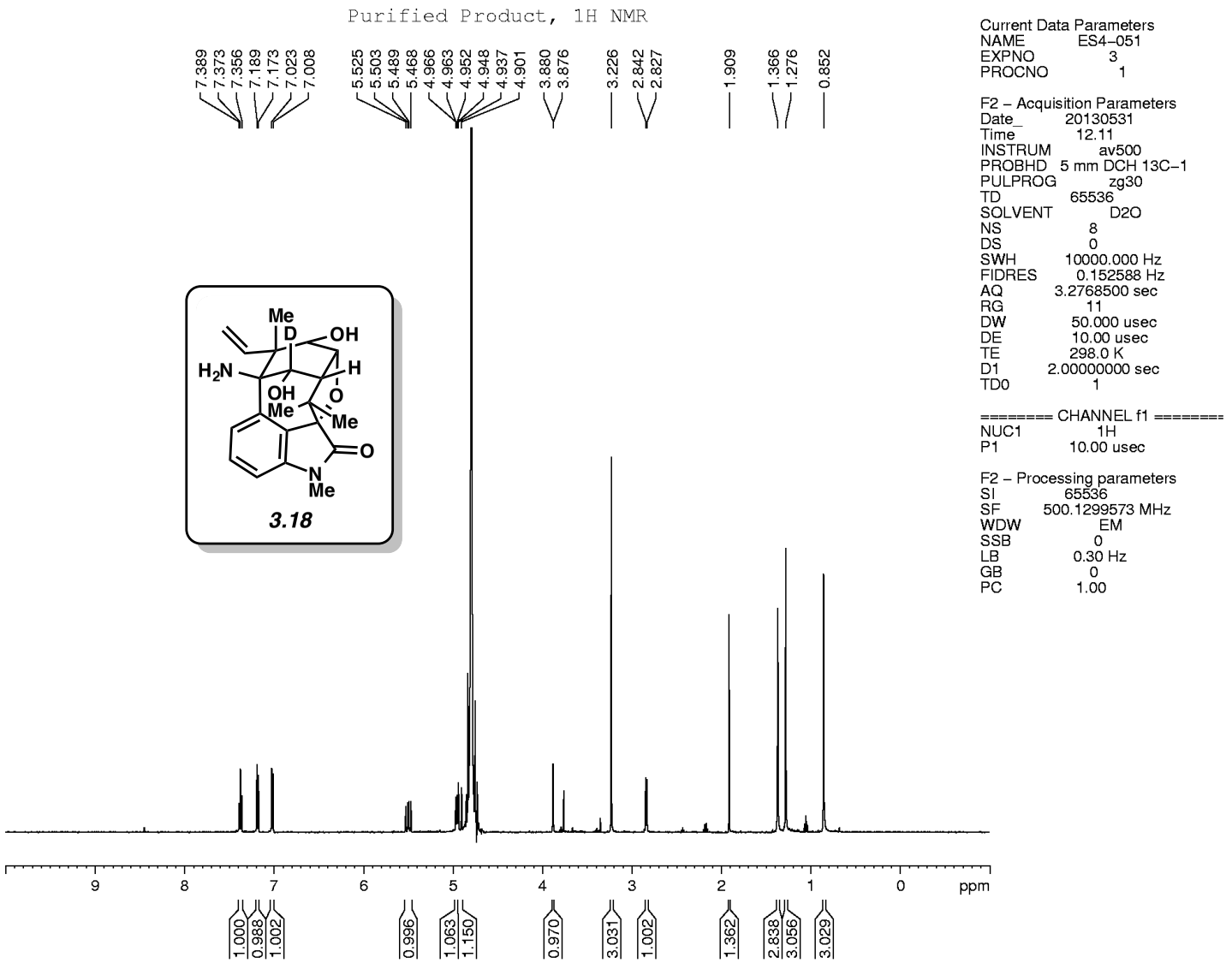


Figure A2.39 ^{1}H NMR (500 MHz, D_2O) of compound **3.18**.

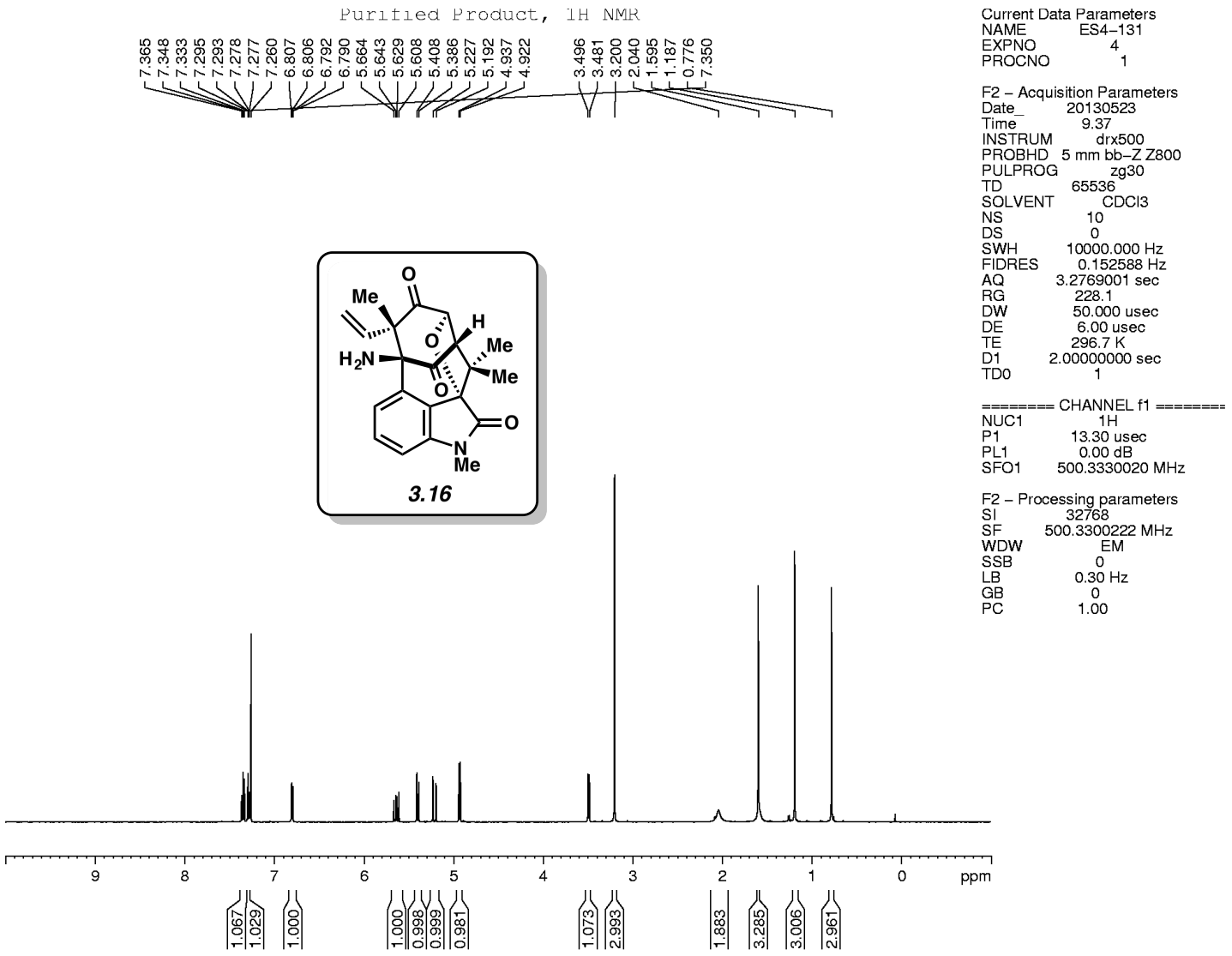


Figure A2.40 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.16**.

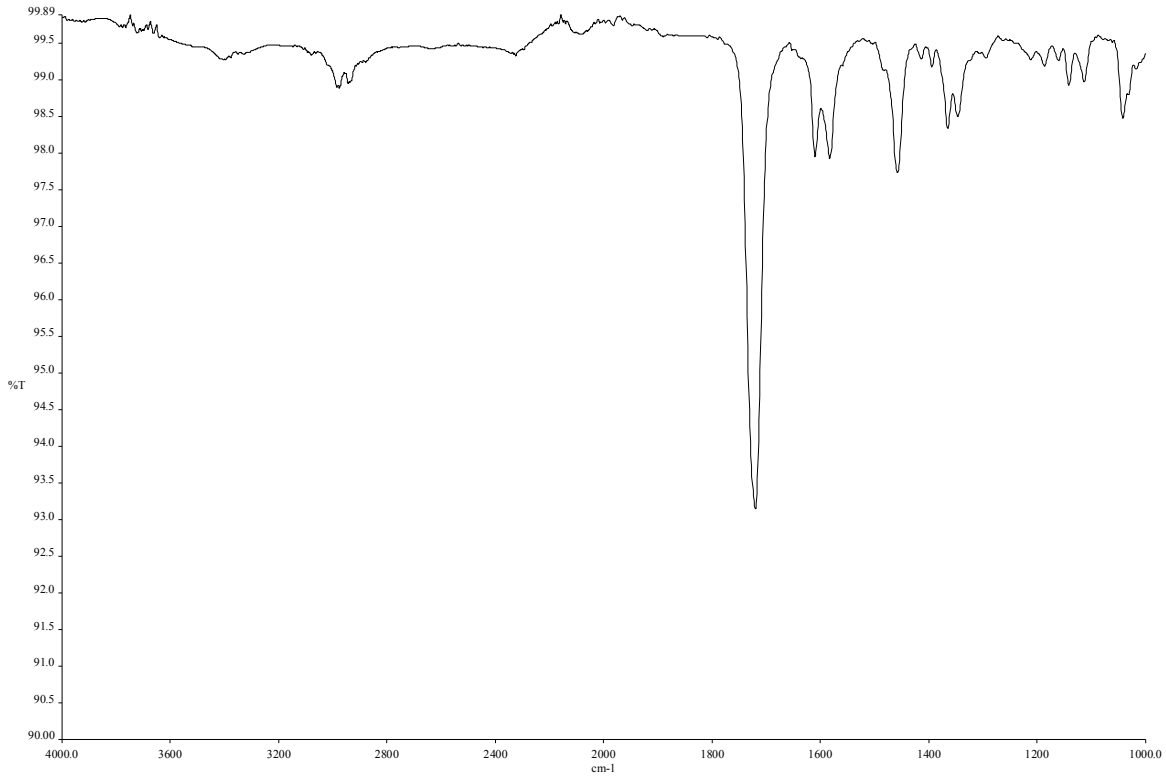


Figure A2.41 Infrared spectrum of compound **3.16**.

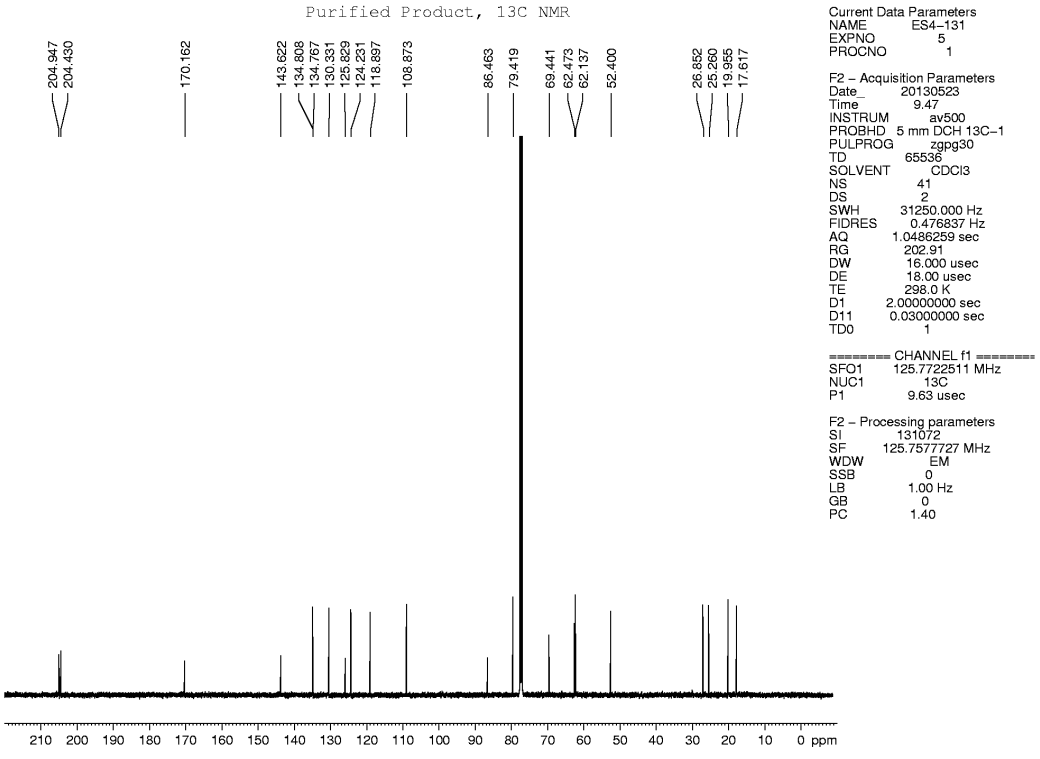


Figure A2.42 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **3.16**.

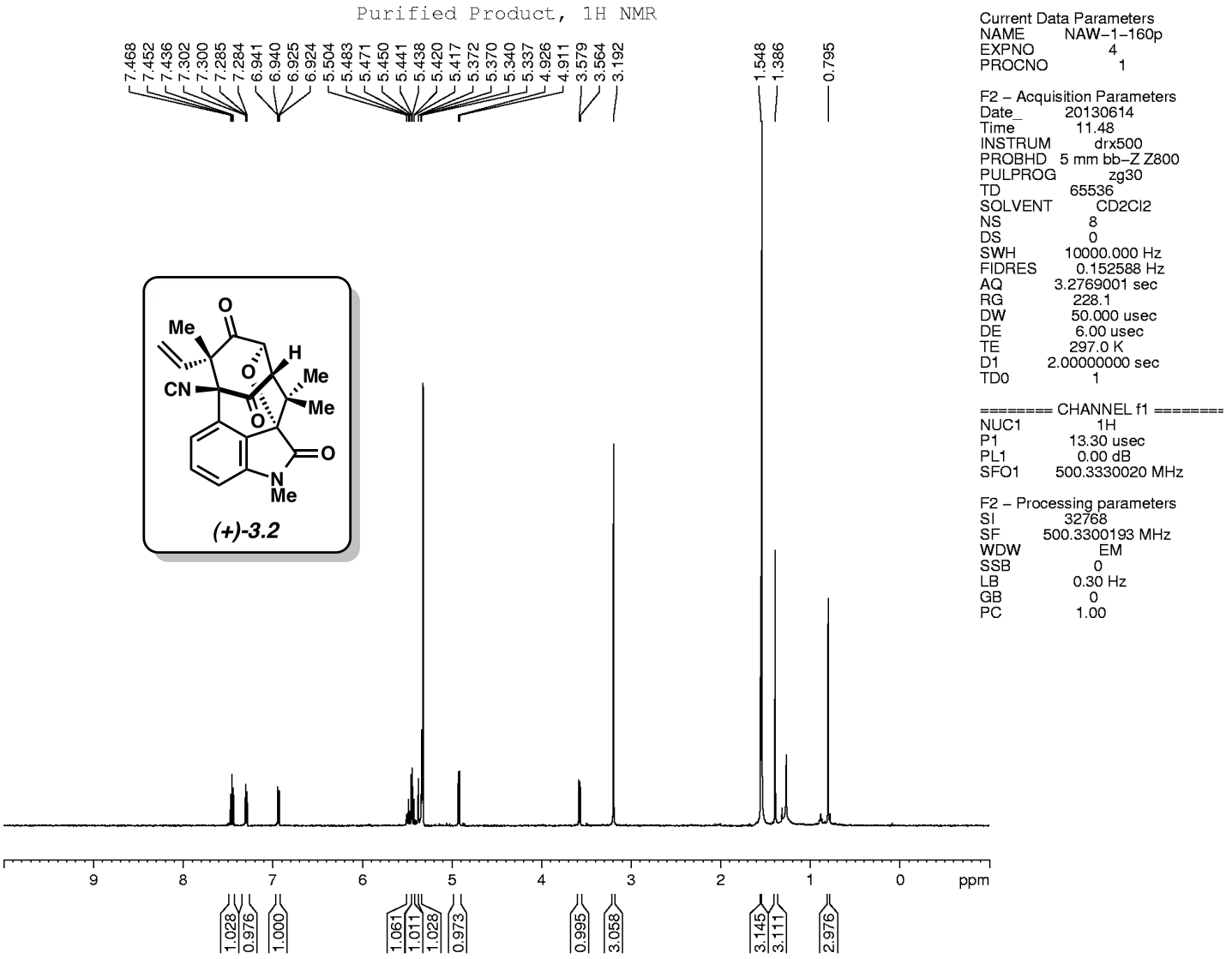


Figure A2.43 ^{1}H NMR (500 MHz, CD_2Cl_2) of compound **3.2**.

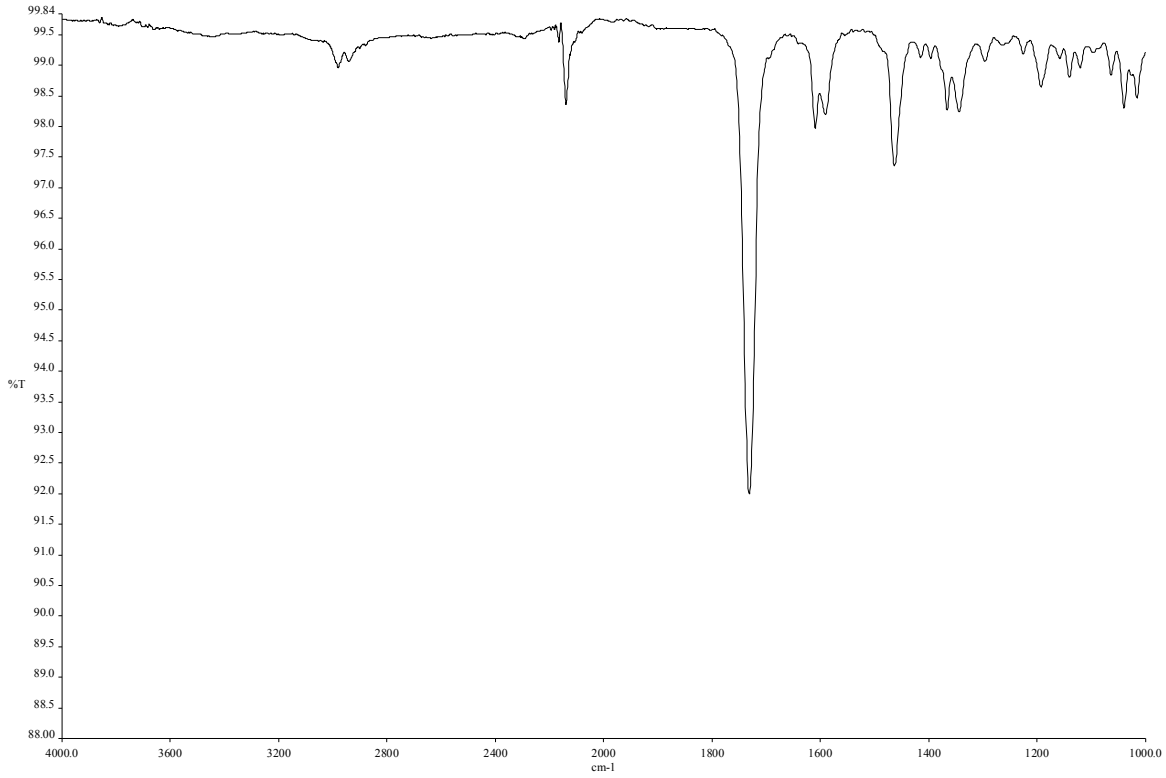


Figure A2.44 Infrared spectrum of compound **3.2**.

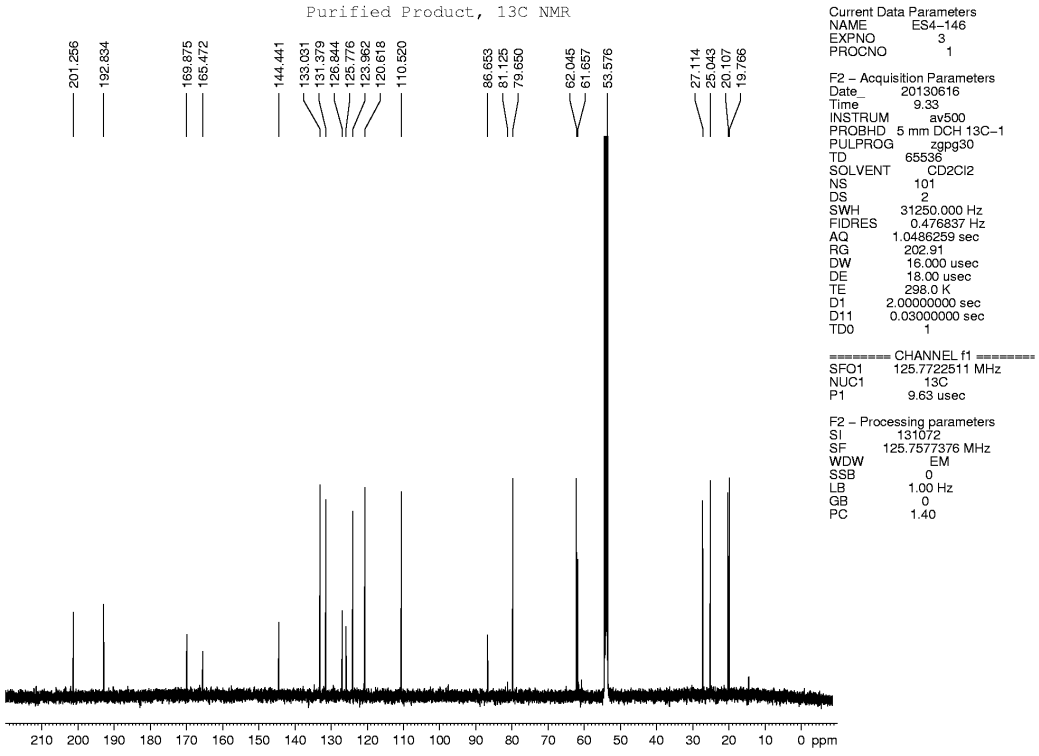


Figure A2.45 ^{13}C NMR (125 MHz, CD_2Cl_2) of compound **3.2**.

CHAPTER FOUR

Total Synthesis of (–)-*N*-Methylwelwitindolinone B Isothiocyanate via a Chlorinative Oxabicyclic Ring-Opening Strategy

Nicholas A. Weires, Evan D. Styduhar, Emma L. Baker, and Neil K. Garg.

J. Am. Chem. Soc. **2014**, *136*, 14710–14713.

4.1 Abstract

The first total synthesis of *N*-methylwelwitindolinone B isothiocyanate is reported. The route features several key steps, including a regio- and diastereoselective chlorinative oxabicycle ring-opening reaction to introduce the challenging alkyl chloride motif.

4.2 Introduction

The total synthesis of indole alkaloids continues to be a fruitful area of scientific pursuit. One particular class of molecules that has provided an exciting arena of chemical discovery is the welwitindolinone natural products, wherein the majority of congeners contain a [4.3.1]-bicyclic core (e.g., **4.2**–**4.4**, Figure 4.1).[1,2] Since Moore's first isolation report in 1994,[3] roughly 25 manuscripts describing efforts toward these complex structures have appeared from many research groups worldwide.[2b,4] The majority of initially reported studies established a variety of methods for assembling the [4.3.1]-bicyclic core and subsequent efforts have focused on completing the total syntheses. Towards this latter end, the most recent publications describe formal,[5] as well as total syntheses of **4.3**, **4.4**, and C3-oxidized variants of **4.3**.[6,7]

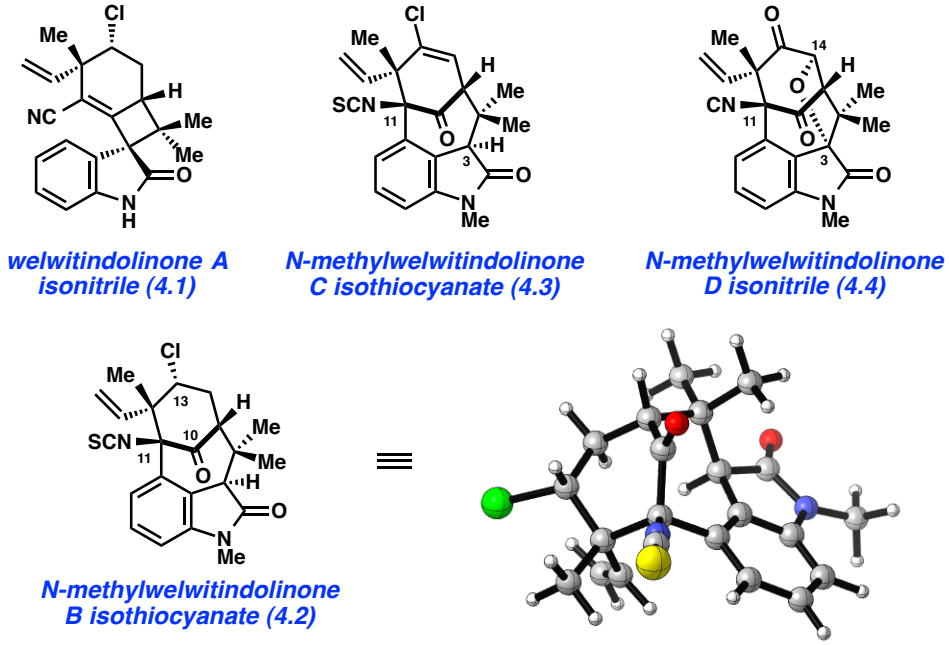


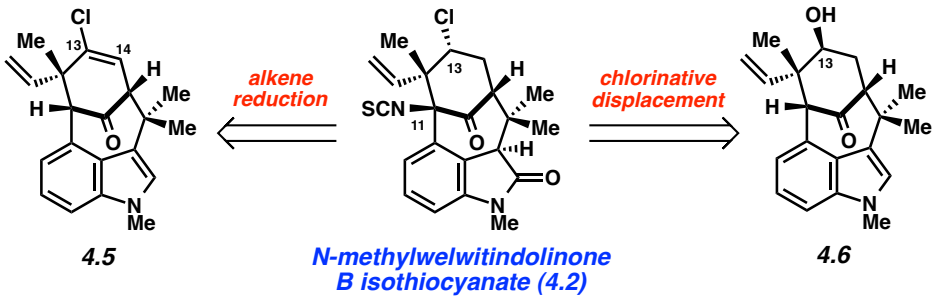
Figure 4.1. Welwitindolinones **4.1–4.4**.

Although [4.3.1]-bicyclic welwitindolinones in the C- and D- 'series' have been synthesized (e.g., **4.3** and **4.4**), compounds in the B- 'series' (e.g., **4.2**) have yet to be prepared by total synthesis.[4u,y] Structurally, **4.2** is quite similar to **4.3** with the key difference being a variation in the oxidation state at C13.[8,9] However, this seemingly simple change is deceptive, as the alkyl chloride resides on the more congested face of the [4.3.1]-bicycle, adjacent to a quaternary center,[10] and thus presents a formidable challenge with regard to synthesis. In addition to this subtle feature, the alkyl chloride in these systems is prone to undergo a variety of undesirable side-reactions under basic reaction conditions.[4y,11] Herein, we describe our efforts toward (–)-**4.2** and the first total synthesis of this elusive natural product.

4.3 Initial Approaches Toward Installation of the Alkyl Chloride

In our initial efforts, we considered several approaches to **4.2** that ultimately proved unsuccessful (Scheme 4.1). In what can be considered the most direct assault, we envisioned **4.2** as arising from C13–14-reduction of **4.5** or a related derivative. However, attempts to realize this strategy were thwarted by the facile reduction of the terminal olefin.[12] We also pursued a strategy wherein the alkyl chloride would derive from alcohol **4.6** by activation and chlorination with stereochemical inversion. Similar to the observations made by Rawal,[4u] we found that the proximal vinyl group underwent formal migration to C13 upon activation of the alcohol.[13] Even in the absence of the vinyl group, the chlorination is known to be difficult and only proceeds under specialized conditions,[4u] as the necessary approach of a chloride nucleophile is somewhat hampered by the steric congestion of the bicyclic scaffold.[14]

Scheme 4.1



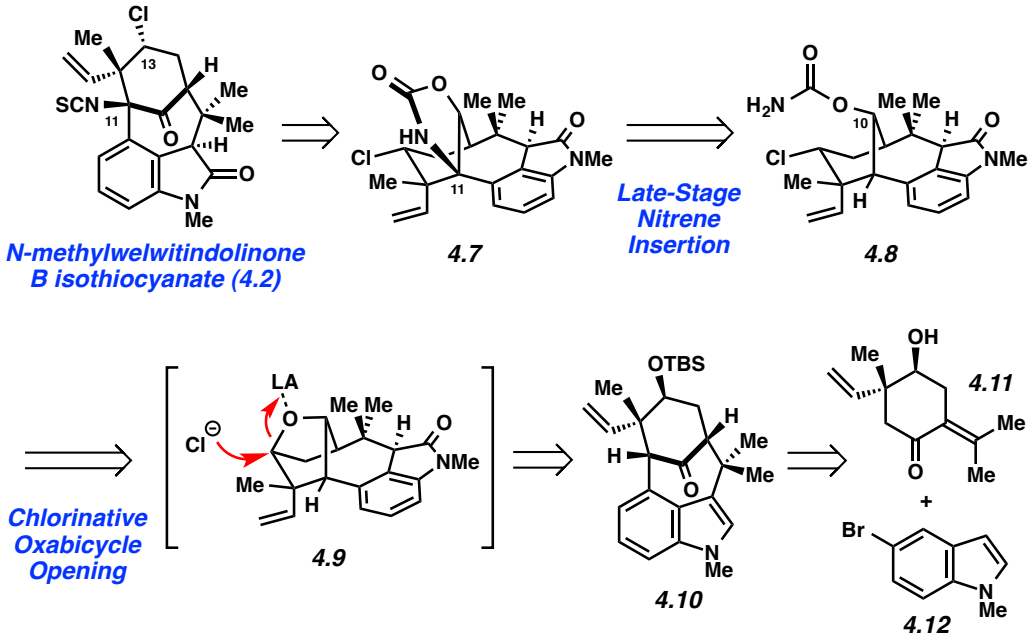
4.5 — *N-methylwelwitindolinone B isothiocyanate (4.2)* — *4.6*

4.4 Modified Retrosynthetic Plan for the Total Synthesis of (–)-*N*-Methylwelwitindolinone B Isothiocyanate

After numerous failed attempts to advance late-stage intermediates from our previous synthesis, we devised the alternative retrosynthetic plan highlighted in Scheme 4.2. In this revised approach, it was envisioned that **4.2** would arise from oxazolidinone **4.7** by late-stage

cleavage of the carbamate and further manipulation, all in the presence of the sensitive alkyl chloride. In turn, oxazolidinone **4.7** would derive from nitrene insertion of carbamate **4.8**.[15] We have previously studied related insertion reactions for C11 functionalization of welwitindolinone scaffolds, but in all prior cases the substrates possessed the opposite stereochemical configuration at C10.[7] Thus, the attempted nitrene insertion of **4.8** would serve as an opportunity to probe the generality of this method for C11 functionalization. In a critical transformation, we sought to introduce the alkyl chloride of **4.8** by performing a regio- and diastereoselective chlorinative ring-opening of an oxabicycle-containing intermediate (see transition structure **4.9**). This transformation, largely inspired by Shea's seminal studies,[4y] could provide a solution to the challenge faced earlier. Namely, the necessary approach of the chloride appeared favorable, owing to the restricted conformation of the oxabicycle unit.[16] Importantly, the oxabicycle was envisioned to be readily available from indole **4.10**, which would be accessed from enantioenriched carvone derivative **4.11** and indole **4.12** in three steps using our previously established procedure involving an indolyne cyclization.[7a,17]

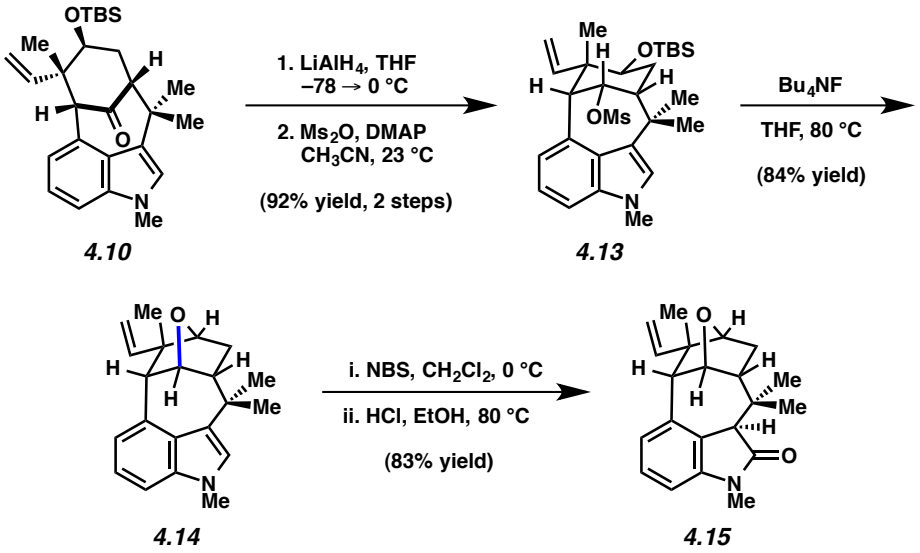
Scheme 4.2



4.5 Construction of Oxabicycle and Chlorination Studies

To implement the plan illustrated in Scheme 4.2, we first targeted construction of oxabicycle **4.15** (Scheme 4.3). To this end, ketone **4.10** was elaborated to mesylate **4.13** in two steps involving reduction with $LiAlH_4$ followed by sulfonylation. Upon treatment of **4.13** with Bu_4NF in THF at 80 °C, desilylation readily occurred with concomitant cyclization to afford oxabicycle **4.14** in 84% yield. Subsequently, a one-pot oxidation / hydrolysis protocol was used to elaborate **4.14** to the corresponding oxindole **4.15**, which was formed as a single diastereomer.

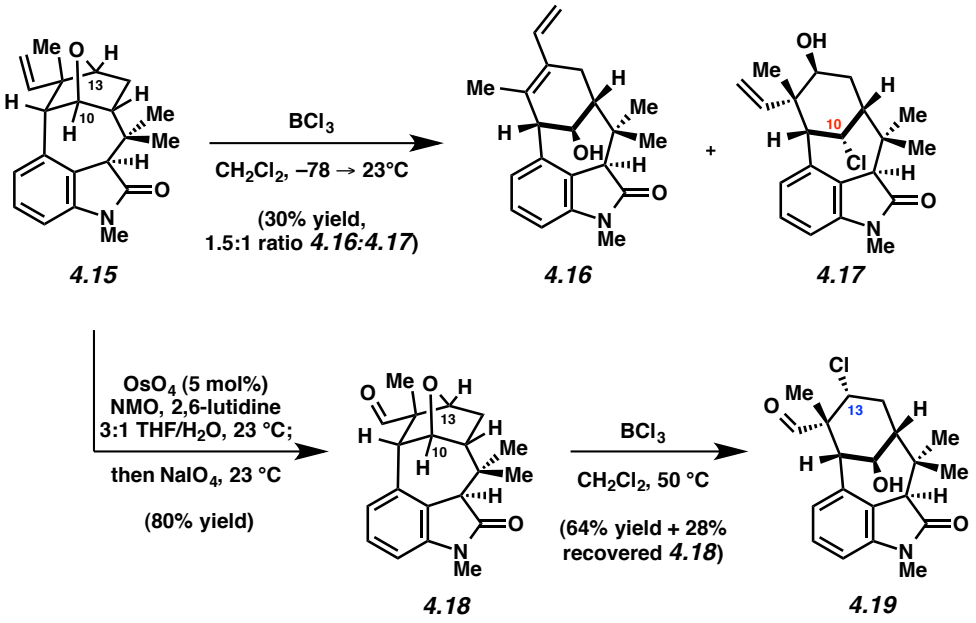
Scheme 4.3



4.10 *4.13* *4.14* *4.15*

With rapid access to oxabicycle **4.15**, we were poised to attempt the key chlorinative ring-opening reaction (Scheme 4.4).[18] We surveyed several conditions that have previously been used for related transformations such as $ZnCl_2$ and acetyl chloride,[19] ethanolic HCl,[20] and $TiCl_4$.[21] Although the use of most reaction conditions led to the recovery of starting material or decomposition, treatment of **4.15** with BCl_3[22] led to consumption of the substrate with opening of the oxabicycle. Unfortunately, the two products obtained were **4.16**, which had undergone formal vinyl migration, and **4.17**, an unproductive constitutional isomer of the desired product, which forms as a result of undesired chloride attack at C10 (rather than C13). In hope of avoiding the vinyl migration, and to perturb the electronic environment at C13,[4u] alkene **4.15** was exposed to modified oxidative cleavage conditions,[23] which furnished aldehyde **4.18**. To our delight, treatment of **4.18** with BCl_3 in CH_2Cl_2 at 50 °C delivered the desired chlorinated product **4.19** in 64% yield. Of note, **4.19** was obtained as a single diastereomer and the analogous undesired regioisomer was not observed.[24]

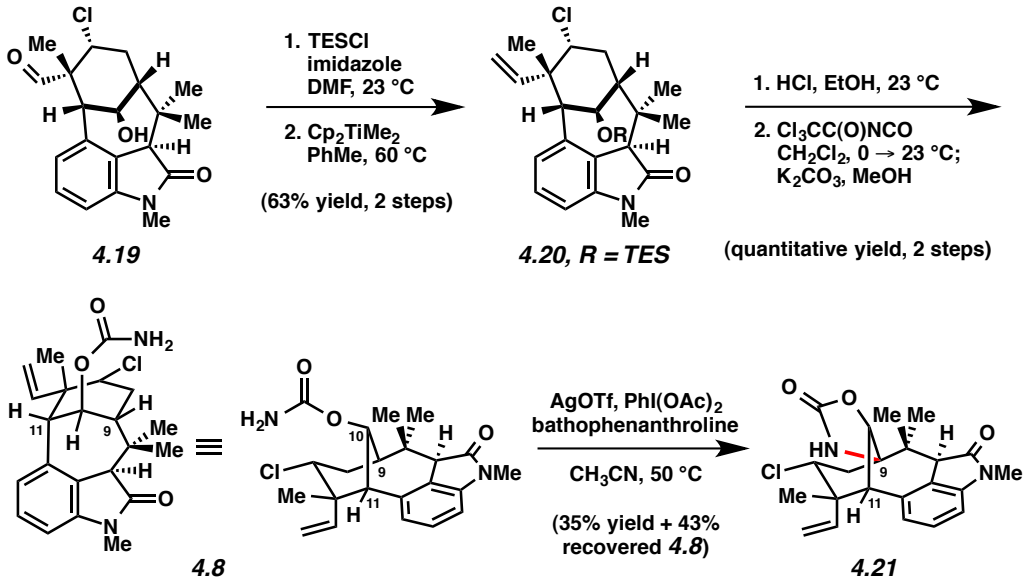
Scheme 4.4



4.6 Attempted Introduction of the C11 Bridgehead Nitrogen Substituent

Having introduced the alkyl chloride, we turned our attention to installing the C11 nitrogen substituent via the key nitrene insertion reaction (Scheme 4.5). The requisite substrate for this transformation (**4.8**), was accessed from **4.19** in four steps that began with conversion to silyl ether **4.20** using a protection / olefination sequence.[25] Deprotection of **4.20** followed by carbamoylation delivered the nitrene insertion substrate **4.8** in quantitative yield over two steps. As mentioned above, our previous studies of related nitrene insertion reactions were performed on substrates epimeric at C10.[7] Although these prior attempts routinely delivered the desired C11-functionalized products, Ag-[26] or Rh-promoted[27] nitrene insertion reactions of **4.8** were regrettably found to predominantly furnish **4.21**, the product of nitrene insertion into the C9–H bond.[28]

Scheme 4.5

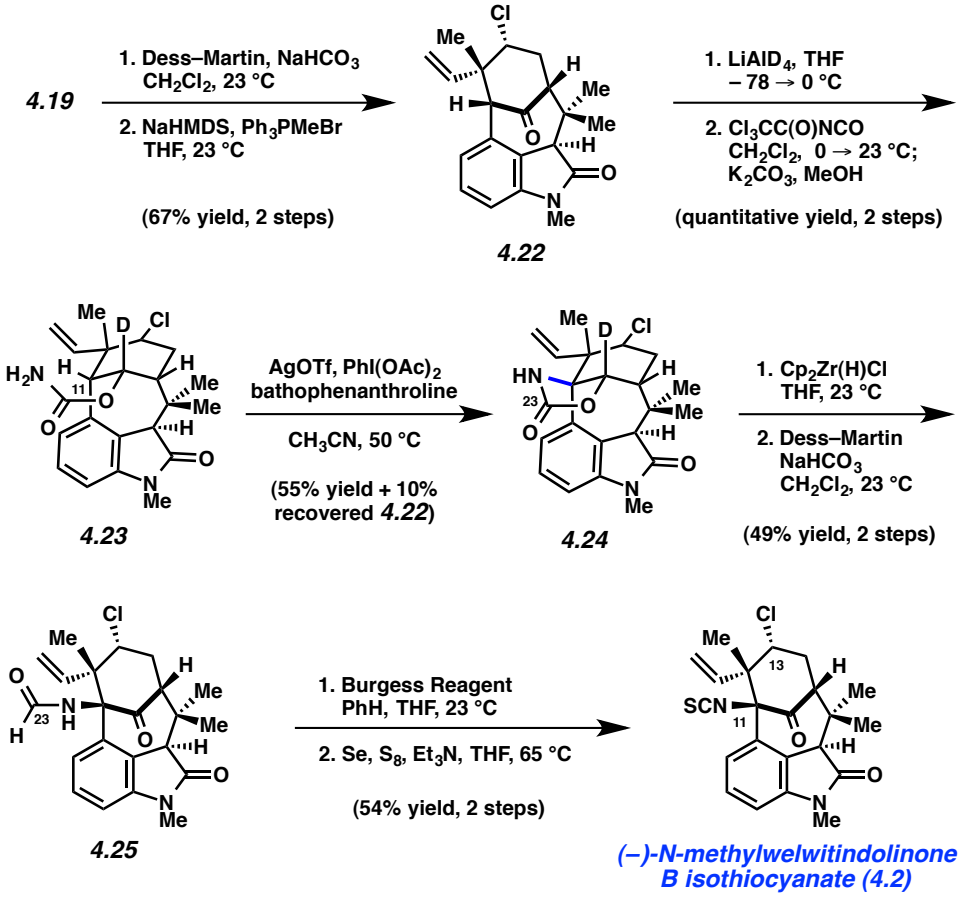


4.7 Nitrene Insertion, Oxazolidinone Cleavage, and Completion of (–)-*N*-Methylwelwitindolinone B Isothiocyanate

To test if the formation of **4.21** was strictly an artifact of the stereochemical configuration, we prepared the corresponding C10 epimer of nitrene insertion substrate **4.8** (Scheme 4.6). To that end, oxidation of alcohol **4.19**, followed by Wittig olefination, afforded ketone **4.22**. Subsequent reduction of **4.22** with $LiAlD_4$[29] occurred with complete diastereoselectivity to furnish an alcohol intermediate, which was carbamoylated to provide **4.23**. Fortunately, carbamate **4.23** proved to be a viable substrate for the desired nitrene insertion reaction; upon treatment of **4.23** with AgOTf, $PhI(OAc)_2$, and bathophenanthroline in CH_3CN at 50 °C, we obtained the C11 functionalized product **4.24** in 55% yield with 10% recovered **4.22**. The dichotomy regarding the nitrene products derived from substrates **4.8** and **4.23** underscores the subtleties often seen in late-stage manipulations in total synthesis. Moreover, the successful

formation of **4.24** is noteworthy in that He's Ag-based nitrene insertion conditions[26] tolerate the sensitive alkyl chloride unit.

Scheme 4.6



From insertion product **4.24**, all that remained to complete the total synthesis of **4.2** was cleavage of the carbamate, followed by oxidation and *N*-functionalization. Despite previously having success with carbamate hydrolysis on related compounds, we found that treatment of **4.24** with $Ba(OH)_2$ led to decomposition of the alkyl chloride. This led us to develop a milder means for cleaving the carbamate. Prompted by Snieckus' recent report of cleaving *N*,*N*-dialkylcarbamate derivatives of phenols,[30] cyclic carbamate **4.24** was exposed to Schwartz'

reagent in THF (Scheme 4.6). Gratifyingly, the carbamate was cleaved selectively to give an amidoalcohol intermediate, where C23 of **4.24** had conveniently been retained as a formyl group on the bridgehead nitrogen. Oxidation of the alcohol intermediate delivered **4.25**. With the chloride still intact, dehydration with Burgess reagent and sulfurization[31] afforded (–)-*N*-methylwelwitindolinone B isothiocyanate (**4.2**). Analytical data for (–)-**4.2** were found to be identical to that of the natural material in all respects.

4.8 Conclusion

In summary, we have completed the first total synthesis of (–)-*N*-methylwelwitindolinone B isothiocyanate (**4.2**) in 15 steps from indolyne cyclization product **4.10**. Critical to the success of our enantiospecific route is the use of a regio- and diastereoselective chlorinative oxabicycle ring-opening reaction to introduce the challenging alkyl chloride. To complete the synthesis, a number of steps were taken, including substrate-specific installation of the C11 nitrogen substituent and oxazolidinone cleavage, all of which proceeded in the presence of the alkyl chloride motif. With our completed synthesis of (–)-**4.2**, all structural classes of the welwitindolinones are now accessible by synthetic chemistry.

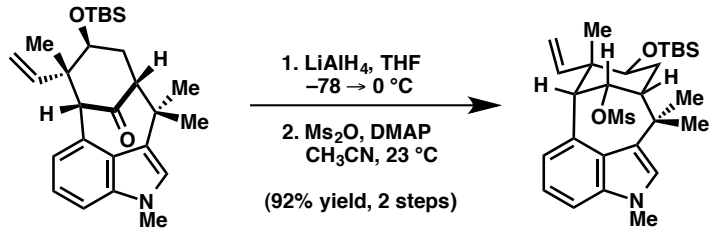
4.9 Experimental Section

4.9.1 Materials and Methods

Unless stated otherwise, reactions were conducted in flame-dried glassware under an atmosphere of nitrogen using anhydrous solvents (either freshly distilled or passed through activated alumina columns). All commercially available reagents were used as received unless otherwise specified. $LiAlD_4$ was obtained from Acros. AgOTf and Schwartz' reagent were obtained from Strem. Bathophenanthroline and selenium metal were obtained from Alfa Aesar. Ms_2O and BCl_3 were obtained from Aldrich. Petasis reagent[32] and Dess–Martin periodinane[33] were prepared from known literature procedures. 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. ^1H and 2D NMR spectra were recorded on Bruker spectrometers (500 MHz). Data for ^1H spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz), integration and are referenced to the residual solvent peak 7.26 ppm for $CDCl_3$ and 7.16 for C_6D_6. Data for ^2H NMR spectra are reported as follows: chemical shift (δ ppm, at 77 MHz), multiplicity, coupling constant, integration and are referenced to the residual solvent peak 7.26 ppm for $CDCl_3$. ^{13}C NMR spectra are reported in terms of chemical shift (at 125 MHz) and are referenced to the residual solvent peak 77.16 ppm for $CDCl_3$.[34] IR spectra were recorded on a Perkin-Elmer 100 spectrometer and a JASCO 4100 spectrometer and are reported in terms of frequency absorption (cm^{-1}). Optical rotations were measured with a Rudolph Autopol III Automatic Polarimeter. Uncorrected melting points were measured using a Mel-Temp II melting point apparatus with a

Fluke 50S thermocouple and a Digimelt MPA160 melting point apparatus. High resolution mass spectra were obtained from the UC Irvine Mass Spectrometry Facility and the UCLA Molecular Instrumentation Center.

4.9.2 Experimental Procedures

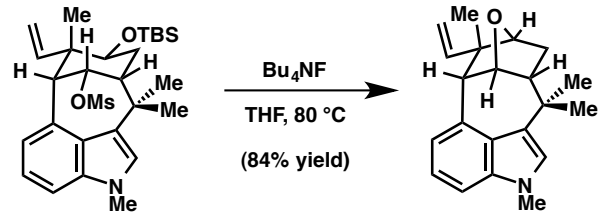


4.10 *4.13*

Mesylate 4.13. To a solution of indole **4.10**[7a] (500 mg, 1.14 mmol, 1.0 equiv) in THF (38.0 mL) at –78 °C was added a solution of $LiAlH_4$ (1.0 M in THF, 3.44 mL, 3.44 mmol, 3.0 equiv) in a dropwise manner. After stirring at –78 °C for 5 min, the solution was then allowed to warm to 0 ºC. After 20 min, the reaction was quenched at 0 °C with slow addition of a saturated solution of aqueous Rochelle's salt (30 mL), and then allowed to warm to 23 ºC. The resulting biphasic mixture was stirred at room temperature for 30 min, transferred to a separatory funnel with EtOAc (30 mL) and H_2O (30 mL), and extracted with EtOAc (3 x 20 mL). The organic layers were combined, dried over Na_2SO_4, and evaporated under reduced pressure. The resulting residue was used in the subsequent step without further purification.

To a flask containing the crude product (382 mg, 0.87 mmol, 1.0 equiv) from the previous step was added DMAP (637 mg, 5.22 mmol, 6.0 equiv) and Ms_2O (409 mg, 2.35 mmol, 2.7 equiv) as solids. The flask was flushed with N_2, to which CH_3CN (7.77 mL) was then added and the reaction mixture was allowed to stir at room temperature. After 2 h the reaction was filtered by passage through a plug of silica gel (5:1 hexanes:EtOAc eluent) to afford mesylate

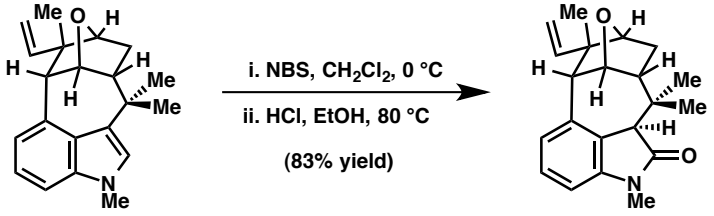
4.13 (413 mg, 92% yield, over two steps) as a white foam. Mesylate **4.13**: mp: 71.5 ºC; R_f 0.53 (5:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.17 (dd, *J* = 8.1, 0.6, 1H), 7.06 (dd, *J* = 8.1, 7.2, 1H), 6.95 (s, 1H), 6.66 (d, *J* = 7.1, 1H), 5.79 (app t, *J* = 5.8, 1H), 4.92 (dd, *J* = 17.5, 1.1, 1H), 4.78 (dd, *J* = 11.0, 1.1, 1H), 4.44 (dd, *J* = 17.4, 10.9, 1H), 4.77 (s, 3H), 3.64 (dd, *J* = 12.3, 4.2, 1H), 3.33 (d, *J* = 5.4, 1H), 2.85 (s, 3H), 2.55–2.48 (m, 1H), 2.18 (ddd, *J* = 14.7, 4.0, 2.7, 1H), 1.95 (ddd, *J* = 14.7, 12.4, 5.6, 1H), 1.57 (s, 3H), 1.42 (s, 3H), 1.36 (s, 3H), 0.73 (s, 9H), –0.16 (s, 3H), –0.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 146.8, 136.7, 130.5, 126.4, 125.7, 124.4, 124.2, 120.5, 112.5, 107.8, 82.4, 68.2, 57.7, 49.2, 48.7, 40.5, 39.1, 37.4, 33.0, 32.8, 32.0, 25.9, 18.0, 16.1, -4.0, -4.6; IR (film): 2952, 2895, 1607, 1533, 1472 cm^{-1}; HRMS-ESI (*m/z*) [M + H]$^+$ calcd for $C_{28}H_{44}NO_4SSi$, 518.27603; found 518.27472; $[\alpha]^{21.6}_D$ +59.60° (*c* = 1.000, $CHCl_3$).



4.13 *4.14*

Oxabicycle 4.14. To a Schlenk tube containing a solution of mesylate **4.13** (118 mg, 0.23 mmol, 1.0 equiv) in THF (5.8 mL) was added TBAF (1.0 M in THF, 681 μL, 0.68 mmol, 3.0 equiv) in a dropwise manner. The Schlenk tube was then sealed and heated to 80 °C. After 21 h, the solution was then allowed to cool to 23 ºC and then filtered by passage over a plug of silica gel (EtOAc eluent, 30 mL). The filtrate was concentrated and the resulting residue was purified by flash chromatography (9:1 hexanes:EtOAc) to afford oxabicycle **4.14** (56 mg, 84% yield) as a white solid. Oxabicycle **4.14**: mp: 108.8 ºC; R_f 0.66 (3:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.16–7.08 (m, 2H), 6.91 (s, 1H), 6.72 (d, *J* = 6.4, 1H), 4.93 (app t, *J* = 4.4, 1H), 4.75–

4.71 (m, 1H), 4.65–4.59 (m, 1H), 4.55–4.52 (m, 1H), 4.16 (d, *J* = 6.1, 1H), 3.75 (s, 3H), 3.46 (d, *J* = 5.3, 1H), 2.44–2.34 (m, 1H), 1.89–1.83 (ddd, *J* = 23.8, 11.8, 6.3, 1H), 1.64–1.60 (dd, *J* = 12.4, 8.5, 1H), 1.43 (s, 3H), 1.37 (s, 3H), 1.23 (s, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 140.7, 137.4, 131.3, 126.2, 124.6, 122.0, 121.5, 120.5, 114.3, 107.3, 87.2, 82.2, 59.8, 55.7, 53.0, 35.9, 34.9, 32.9, 28.7, 28.4, 27.5; IR (film): 2962, 2904, 2864, 1632, 1541, 1456 cm^{-1}; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{21}H_{26}NO$, 308.20144; found 308.20022; $[\alpha]^{21.4}_D$ +115.40° (*c* = 1.000, $CHCl_3$).

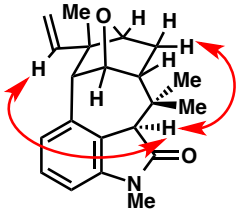


4.14 ***4.15***

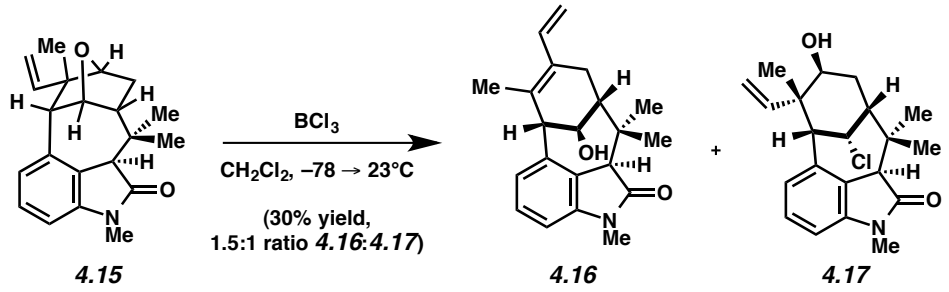
Oxindole 4.15. To a solution of indole **4.14** (137 mg, 0.44 mmol, 1.0 equiv) in CH_2Cl_2 (8.2 mL) at 0 ºC was added NBS (80.0 mg, 0.45 mmol, 1.01 equiv) in one portion. The reaction vial was flushed with N_2, and allowed to stir at 0 ºC. After 15 min, solid $NaHCO_3$ (137 mg, 100 wt %) was added in one portion. The reaction was removed from the 0 ºC bath and allowed to stir at room temperature for 5 min. The resulting suspension was then evaporated under reduced pressure. Absolute ethanol (7.0 mL) and concentrated aqueous HCl (7.0 mL) were added. After heating to 80 ºC for 2 h, the reaction mixture was cooled to room temperature and transferred to a separatory funnel with H_2O (14 mL) and EtOAc (14 mL). To the separatory funnel was slowly added solid $NaHCO_3$ until gas evolution was no longer observed. The resulting biphasic mixture was extracted with EtOAc (3 x 14 mL) and the organic layers were combined, dried over Na_2SO_4, and evaporated under reduced pressure. The resulting residue was purified by flash

chromatography (9:1 hexanes:EtOAc) to afford oxindole **4.15** (120 mg, 83% yield) as a white solid. Oxindole **4.15**: mp: 138.4 ºC; R_f 0.59 (1:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.19 (ddd, *J* = 7.8, 7.8, 0.6, 1H), 6.76 (d, *J* = 7.5, 1H), 6.70 (d, *J* = 7.7, 1H), 5.53 (dd, *J* = 17.9, 11.2, 1H), 4.96 (dd, *J* = 11.2, 1.2, 1H), 4.84 (dd, *J* = 17.9, 1.2, 1H), 4.47 (app t, *J* = 5.0, 1H), 4.38 (d, *J* = 5.8, 1H), 3.46 (s, 1H), 3.19 (s, 3H), 3.02 (d, *J* = 4.5, 1H), 2.31–2.22 (m, 1H), 2.11 (dd, *J* = 12.9, 6.6, 1H), 1.98 (ddd, *J* = 12.2, 12.2, 5.8, 1H), 1.43 (s, 3H), 1.35 (s, 3H), 0.73 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$: δ 176.6, 144.2, 140.6, 134.3, 128.1, 126.5, 126.2, 116.4, 106.6, 87.0, 80.8, 60.3, 56.5, 51.2, 49.9, 37.0, 31.9, 27.8, 27.6, 26.3, 23.2; IR (film): 2962, 1703, 1605, 1469, 1324 cm^{-1}; HRMS-ESI (*m/z*) [M + H]$^+$ calcd for $C_{21}H_{26}NO_2$, 324.19635; found 324.19514; $[\alpha]^{21.4}_D$ +28.20° (*c* = 1.000, $CHCl_3$).

The structure of **4.15** was confirmed by a 2D-NOESY experiment, as the following interactions were observed:



4.15



4.15 ***4.16*** ***4.17***

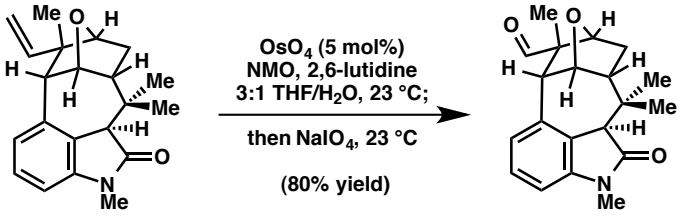
Diene 4.16 and Alkyl Chloride 4.17. A solution of oxindole **4.15** (6.1 mg, 0.019 mmol, 1.0 equiv) in CH_2Cl_2 (1.89 mL) was cooled to –78 °C. A solution of BCl_3 (1.0 M in CH_2Cl_2, 145.4

μL, 0.14 mmol, 7.7 equiv) was added in a dropwise manner. The resulting solution was allowed to stir at –78 °C. After 30 min, the solution was then allowed to warm to 0 ºC. After 2 h the solution was then warmed to room temperature. After 4 h the reaction was quenched with addition of a saturated aqueous solution of $NaHCO_3$ (1 mL) and transferred to a separatory funnel with EtOAc (6 mL) and H_2O (4 mL), and extracted with EtOAc (3 x 3 mL). The organic layers were combined, dried over Na_2SO_4, and evaporated under reduced pressure. The resulting residue was purified by preparative thin layer chromatography (1:1 hexanes:EtOAc) to afford diene **4.16** (1.1 mg, 18% yield) and alkyl chloride **4.17** (0.8 mg, 12% yield) as amorphous solids.

Diene **4.16**: R_f 0.60 (1:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.21 (ddd, *J* = 7.8, 7.8, 0.6, 1H), 6.91 (d, *J* = 7.3, 1H), 6.76 (dd, *J* = 17.2, 11.0, 1H), 6.67 (d, *J* = 7.8, 1H), 5.32 (d, *J* = 17.2, 1H), 5.09 (d, *J* = 11.1, 1H), 4.24 (br. s, 1H), 3.32 (s, 1H), 3.25 (s, 1H), 3.14 (s, 3H), 2.73 (d, *J* = 18.7, 1H), 2.56 (dd, *J* = 18.7, 7.9, 1H), 2.02 (d, *J* = 7.9, 1H), 1.79 (d, *J* = 6.7, 1H), 1.68 (s, 3H), 1.54 (s, 3H), 0.73 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.4, 144.4, 135. 8, 134.0, 128.9, 128.1, 126.6, 126.4, 123.5, 112.9, 106.4, 67.5, 54.4, 50.9, 49.1, 39.0, 28.0, 26.1, 22.5, 21.2, 17.8; IR (film): 3412, 2969, 1690, 1608, 1470 cm^{-1}; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{21}H_{26}NO_2$, 324.19635; found 324.19417; $[\alpha]^{21.4}_D$ –264.00° (*c* = 0.150, $CHCl_3$).

Alkyl chloride **4.17**: R_f 0.52 (1:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$, 25 of 26 observed): δ 7.16 (ddd, *J* = 7.8, 7.8, 0.7, 1H), 6.68 (dd, *J* = 7.8, 0.7, 1H), 6.65 (d, *J* = 7.7, 1H), 5.31 (dd, *J* = 17.4, 10.7, 1H), 5.12 (dd, *J* = 17.4, 1.0, 1H), 5.03 (dd, *J* = 10.7, 1.0, 1H), 4.69 (br. s, 1H), 4.12 (dd, *J* = 10.3, 7.1, 1H), 3.57 (s, 1H), 3.20–3.18 (m, 1H), 3.17 (s, 3H), 2.37–2.32 (m, 2H), 2.28–2.25 (m, 1H), 1.67 (s, 3H), 1.57 (s, 3H), 0.89 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 175.2, 146.3, 145.0, 138.7, 128.0, 126.8, 124.1, 114.8, 106.8, 69.7, 59.3, 58.2, 56.8, 54.8, 46.5, 39.4, 27.3, 26.3, 25.3, 23.3, 19.0; IR (film): 3451, 2962, 2872, 1699, 1609 cm^{-1}; HRMS-ESI

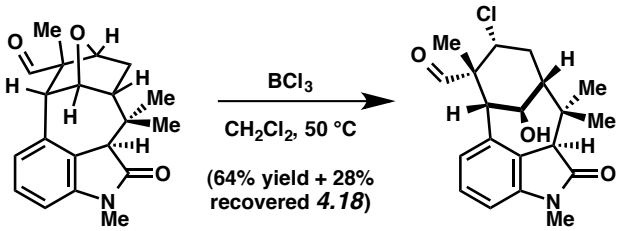
(*m/z*) $[M + H]^+$ calcd for $C_{21}H_{27}ClNO_2$, 360.17303; found 360.17087; $[\alpha]^{21.2}_D$ –9.00° (*c* = 0.400, $CHCl_3$).



4.15 ***4.18***

Aldehyde 4.18. To a solution of oxindole **4.15** (45 mg, 0.14 mmol, 1.0 equiv) in a 3:1 mixture of THF/H_2O (1.4 mL) was added 2,6-lutidine (32 μL, 0.28 mmol, 2.0 equiv), OsO_4 (20 mg/mL in H_2O, 84 μL, 0.007 mmol, 0.05 equiv), and NMO (65 mg, 0.56 mmol, 4.0 equiv). The resulting solution was flushed with N_2 and stirred at room temperature. After 19 h, solid $NaIO_4$ (89 mg, 0.42 mmol, 3.0 equiv) was added in one portion and the reaction mixture was stirred at room temperature. After 13 min, the reaction mixture was quenched with a saturated aqueous solution of $Na_2S_2O_3$ (1 mL) and stirred vigorously at room temperature. After 30 min the resulting mixture was transferred to a test tube with EtOAc (5 mL) and H_2O (5 mL). The resulting biphasic mixture was extracted with EtOAc (3 x 3 mL). The organic layers were combined, dried over Na_2SO_4, and evaporated under reduced pressure. The resulting residue was purified by preparative thin layer chromatography (3:1 hexanes:EtOAc) to afford aldehyde **4.18** (36 mg, 80% yield) as a white solid. Aldehyde **4.18**: mp: 181.1 ºC; R_f 0.53 (1:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.17 (s, 1H), 7.24 (dd, *J* = 7.7, 7.7, 1H), 6.89 (d, *J* = 7.7, 1H), 6.74 (d, *J* = 7.8, 1H), 4.55 (t, *J* = 4.9, 1H), 4.47 (d, *J* = 5.0, 1H), 3.26 (s, 1H), 3.18–3.16 (m, 4H), 2.37–2.29 (m, 1H), 2.16–2.07 (m, 2H), 1.43 (s, 3H), 1.37 (s, 3H), 0.74 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 204.6, 175.9, 144.7, 131.8, 128.8, 125.65, 125.60, 107.4, 84.6, 81.0, 59.1, 58.9,

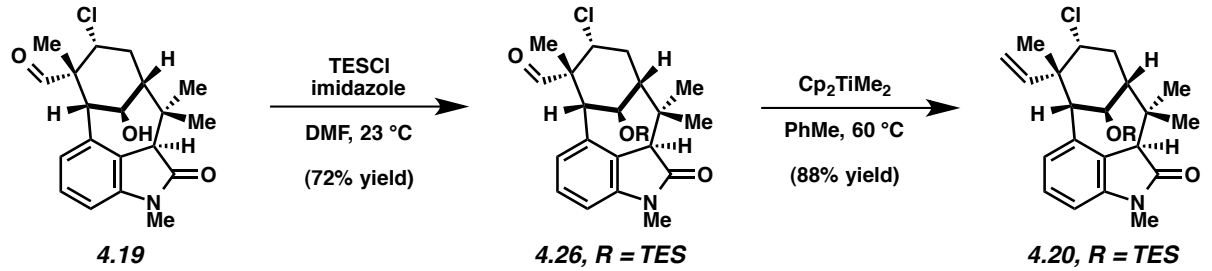
56.0, 49.3, 36.9, 282, 27.5, 26.4, 25.4, 23.2; IR (film): 2959, 2928, 1708, 1606, 1470 cm^{-1}; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{20}H_{24}NO_3$, 326.17562; found 326.17443; $[\alpha]^{21.6}_D$ +23.80° (*c* = 1.000, $CHCl_3$).



4.18 *4.19*

Alkyl Chloride 4.19. To a scintillation vial containing oxindole **4.18** (19.3 mg, 0.059 mmol, 1.0 equiv) was added a solution of BCl_3 (1.0 M in CH_2Cl_2, 178.2 μL, 0.178 mmol, 3.0 equiv) in a dropwise manner. The reaction vial was then sealed and heated to 50 °C. After 2 h, the solution was then allowed to cool to 23 ºC and quenched with addition of a saturated aqueous solution of $NaHCO_3$ (1 mL) and transferred to a separatory funnel with EtOAc (6 mL) and H_2O (6 mL), and extracted with EtOAc (3 x 3 mL). The organic layers were combined, dried over Na_2SO_4, and evaporated under reduced pressure. The resulting residue was purified by preparative thin layer chromatography (1:1 hexanes:EtOAc) to afford alkyl chloride **4.19** (13.7 mg, 64% yield) as a white solid and recovered oxindole **4.18** (5.4 mg, 28% yield). Alkyl chloride **4.19**: mp: 176.4 ºC; R_f 0.42 (1:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.29 (s, 1H), 7.18 (dd, *J* = 7.7, 7.7, 1H), 6.75 (d, *J* = 7.7, 1H), 6.70 (d, *J* = 7.8, 1H), 5.13–5.04 (m, 1H), 4.18 (s, 1H), 3.47 (s, 1H), 3.24–3.21 (m, 1H), 3.16 (s, 3H), 2.61–2.56 (m, 2H), 2.20–2.16 (m, 1H) 1.90 (s, 1H), 1.58 (s, 3H), 1.56 (s, 3H), 0.88 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 200.3, 175.8, 144.9, 133.8, 128.9, 125.1, 124.8, 107.5, 69.6, 61.8, 57.4, 53.8, 51.6, 50.5, 39.5, 31.3, 26.4, 26.1, 25.9, 22.8;

IR (film): 3443, 2967, 1689, 1609, 1594 cm^{-1}; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{20}H_{25}ClNO_3$, 362.15230; found 362.15085; $[\alpha]^{23.0}_D$ +59.60° (*c* = 1.000, $CHCl_3$).

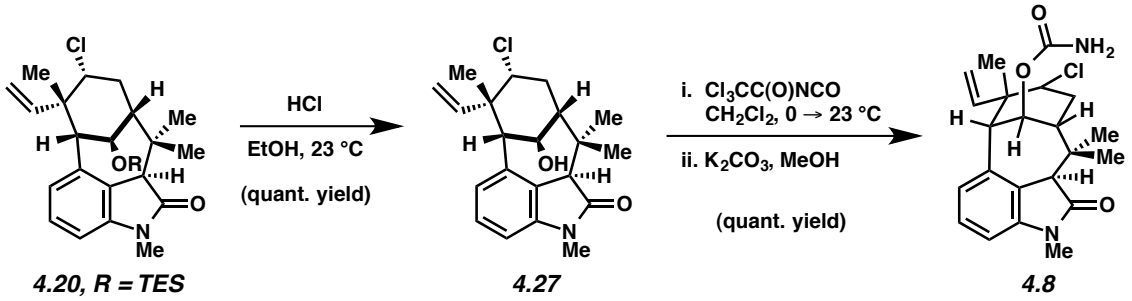


4.19 ***4.26, R = TES*** ***4.20, R = TES***

Silyl Ether 4.20. To a solution of **4.19** (18.8 mg, 0.052 mmol, 1.0 equiv) in DMF (944 μL) was added imidazole (35.3 mg, 0.52 mmol, 3.0 equiv). The reaction vial was then purged with N_2 and TESCl (26.2 μL, 0.156 mmol, 3.0 equiv) was added in a dropwise manner. The resulting solution was stirred at room temperature. After 1 h the reaction was quenched by addition of a saturated aqueous solution of $NaHCO_3$ (2 mL) and transferred to a separatory funnel with EtOAc (6 mL) and H_2O (4 mL). After extracting with EtOAc (3 x 3 mL), the organic layers were combined, dried over Na_2SO_4, and evaporated under reduced pressure. The resulting residue was purified by preparative thin layer chromatography (1:1 hexanes:EtOAc) to afford **4.26** (18 mg, 72% yield) as an amorphous solid. **4.26**: R_f 0.69 (1:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.30 (s, 1H), 7.18 (ddd, *J* = 7.8, 7.7, 0.65, 1H), 6.72 (d, *J* = 7.6, 1H), 6.70 (d, *J* = 7.8, 1H), 5.12–5.03 (m, 1H), 4.10–4.04 (m, 1H), 3.46 (s, 1H), 3.16 (s, 3H), 3.14–3.10 (m, 1H), 2.61–2.51 (m, 2H), 2.19–2.11 (m, 1H), 1.55 (s, 3H), 1.54 (s, 3H), 0.96 (t, *J* = 7.9, 9H), 0.86 (s, 3H), 0.59 (q, *J* = 7.9, 6H).

To a vial containing **4.26** (17.9 mg, 0.038 mmol, 1.0 equiv) was added the Petasis reagent (1.0 M in PhMe, 444 μL, 0.444 mmol, 11.8 equiv) in the absence of light. The reaction vessel was then sealed and heated to 60 °C. After 4.5 h the reaction was cooled to room temperature and filtered by passage over a plug of silica gel (3:1 hexanes:EtOAc eluent, 15 mL). The filtrate

was evaporated under reduced pressure and the resulting residue was purified by preparative thin layer chromatography (3:1 hexanes:EtOAc) to afford silyl ether **4.20** (15.6 mg, 88% yield) as an amorphous solid. Silyl Ether **4.20**: R_f 0.57 (3:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.14 (dd, *J* = 7.7, 7.7, 1H), 6.65 (d, *J* = 7.6, 1H), 6.62 (d, *J* = 7.6, 1H), 5.65 (dd, *J* = 17.2, 10.9, 1H), 5.15 (dd, *J* = 12.7, 4.5, 1H), 4.85 (dd, *J* = 17.3, 0.9, 1H), 4.80 (d, *J* = 11.1, 1H), 4.04 (br. s, 1H), 3.46 (s, 1H), 3.17 (s, 3H), 3.12–3.08 (m, 1H), 2.43–2.34 (m, 1H), 2.19–2.03 (m, 2H), 1.51 (s, 3H), 1.50 (s, 3H), 0.96 (t, *J* = 7.9, 9H), 0.85 (s, 3H), 0.58 (q, *J* = 7.8, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.2, 144.5, 138.6, 138.3, 128.0, 125.5, 124.4, 115.0, 106.3, 70.0, 65.3, 60.7, 54.8, 50.6, 44.4, 39.7, 31.5, 29.7, 26.3, 25.9, 22.6, 7.1, 4.9; IR (film): 2956, 2912, 1708, 1610, 1597 cm^{-1}; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{27}H_{41}ClNO_2Si$, 474.25951; found 474.25746; $[\alpha]^{21.0}_D$ –1.40° (*c* = 1.000, $CHCl_3$).

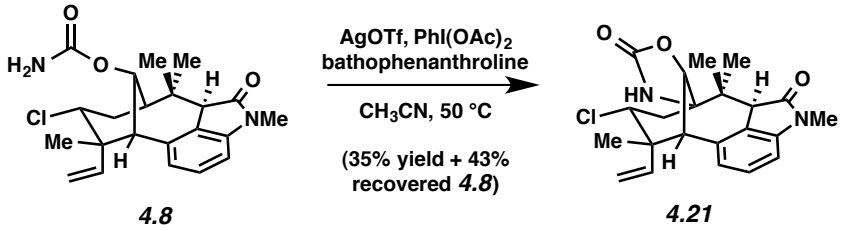


Carbamate 4.8. A flask was charged with silyl ether **4.20** (5.4 mg, 0.011 mmol, 1.0 equiv), followed by the addition of absolute ethanol (542 μL) and concentrated aqueous HCl (542 μL). The solution was then allowed to stir at room temperature. After 20 min, the reaction mixture was transferred to a separatory funnel with EtOAc (6 mL). To the funnel was added a saturated aqueous solution of $NaHCO_3$ (5 mL) slowly until gas evolution was no longer observed. The resulting biphasic mixture was extracted with EtOAc (3 x 3 mL) and the organic layers were combined, dried over Na_2SO_4, and evaporated under reduced pressure. The resulting residue was

purified by preparative thin layer chromatography (1:1 hexanes:EtOAc) to afford **4.27** (4.1 mg, quant. yield) as an amorphous solid. Alcohol **4.27**: R_f 0.18 (3:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.14 (dd, *J* = 7.7, 7.7, 1H), 6.67–6.63 (m, 2H), 5.64 (dd, *J* = 17.3, 11.0, 1H), 5.14 (dd, *J* = 12.8, 4.5, 1H), 4.87 (dd, *J* = 17.2, 0.8, 1H), 4.81 (d, *J* = 11.1, 1H), 4.15 (s, 1H), 3.47 (s, 1H), 3.17 (s, 3H), 2.42 (ddd, *J* = 14.7, 10.8, 5.3,1H), 2.21–2.07 (m, 2H), 1.54 (s, 3H), 1.52 (s, 3H), 0.85 (s, 3H).

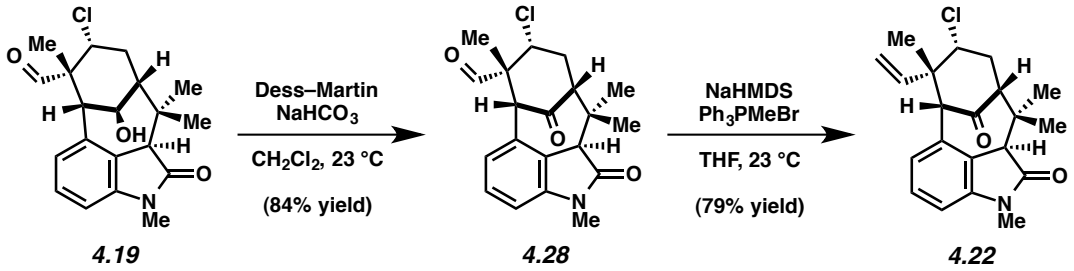
To a solution of **4.27** (4.1 mg, 0.011 mmol, 1.0 equiv) in CH_2Cl_2 (228 μL) at 0 °C was added trichloroacetyl isocyanate (1.7 μL, 0.0142 mmol, 1.25 equiv) in a dropwise manner. The resulting mixture was allowed to stir at 0 °C for 5 min, and then at room temperature for 30 min. The solvent was evaporated under reduced pressure. To the resulting residue was added MeOH (228 μL) followed by addition of solid K_2CO_3 (8.6 mg, 0.0626 mmol, 5.5 equiv) in one portion. The reaction was flushed with N_2 and left to stir at room temperature. After 1 h, the reaction was quenched with a saturated aqueous solution of NH_4Cl (1 mL), and the resulting biphasic mixture was transferred to a separatory funnel with EtOAc (6 mL) and H_2O (4 mL). After extracting with EtOAc (3 x 3 mL), the organic layers were combined, dried over Na_2SO_4, and evaporated under reduced pressure. The resulting residue was purified by preparative thin layer chromatography (1:1 hexanes:EtOAc) to afford carbamate **4.8** (4.6 mg, quant. yield) as an amorphous solid. Carbamate **4.8**: R_f 0.44 (1:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.15 (dd, *J* = 7.8, 7.8, 1H), 6.70–6.63 (m, 2H), 5.62 (dd, *J* = 17.2, 10.8, 1H), 5.14–5.09 (m, 1H), 4.88 (dd, *J* = 17.2, 0.7, 1H), 4.84 (d, *J* = 11.0, 1H), 4.77 (dd, *J* = 12.7, 4.7, 1H), 4.66 (s, 2H), 3.47 (s, 1H), 3.28–3.25 (m, 1H), 3.18 (s, 3H), 2.44–2.34 (m, 1H), 2.23–2.13 (m, 2H), 1.53, (s, 3H), 1.50 (s, 3H), 0.93 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 175.9, 155.3, 144.5, 137.9, 137.0, 128.2, 125.7, 124.4, 115.6, 106.7, 73.2, 64.6, 57.0, 51.1, 50.7, 44.1, 39.7, 31.0, 29.4, 26.4, 25.7, 22.3; IR (film): 3489,

3348, 2966, 1694, 1610 cm^{-1}; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{22}H_{28}ClN_2O_3$, 403.17885; found 403.17618; $[\alpha]^{23.4}_D$ –89.33° (*c* = 1.000, $CHCl_3$).



Oxazolidinone 4.21. A 1-dram vial containing CH_3CN, a second 1-dram vial charged with bathophenanthroline (3.8 mg, 0.011 mmol, 1.0 equiv), and a third 1-dram vial containing carbamate **4.8** (4.6 mg, 0.011 mmol, 1.0 equiv) and $PhI(OAc)_2$ (14.7 mg, 0.046 mmol, 4.0 equiv) were transferred into the glovebox. AgOTf (2.9 mg, 0.011 mmol, 1.0 equiv) and CH_3CN (200 μL) were added to the vial containing the bathophenanthroline, and the resulting suspension was allowed to stir at room temperature for 20 min. Next, CH_3CN (126 μL) was added to the vial containing the carbamate, and the AgOTf/bathophenanthroline suspension was also added to this vial. The vial was then sealed, removed from the glovebox, and the resulting mixture was heated to 50 °C. After 20.5 h, the reaction was cooled to room temperature and filtered by passage over a plug of celite (EtOAc eluent, 10 mL). The filtrate was evaporated under reduced pressure, and the resulting residue was purified by preparative thin layer chromatography (1:2:2 PhH:CH_2Cl_2:Et_2O) to afford oxazolidinone **4.21** (1.6 mg, 35% yield) as an amorphous solid and recovered carbamate **4.8** (2 mg, 43% yield). Oxazolidinone **4.21**: R_f 0.43 (1:2:2 PhH:Et_2O:CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.21 (dd, *J* = 7.8, 7.8, 1H), 6.75–6.68 (m, 2H), 5.77 (s, 1H), 5.39 (dd, *J* = 17.1, 10.8, 1H), 5.02 (d, *J* = 17.2, 1H), 4.94 (d, *J* = 10.8, 1H) 4.71 (d, *J* = 2.0, 1H), 4.62 (dd, *J* = 13.7, 3.6, 1H), 3.59 (s, 1H), 3.46 (s, 1H), 3.20 (s, 3H), 2.67

(app t, J = 14.3, 1H), 2.19 (dd, J = 14.7, 3.6, 1H), 1.61 (s, 3H), 1.58 (s, 3H), 0.95 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.2, 158.0, 144.7, 137.9, 136.4, 128.7, 126.7, 123.0, 116.0, 107.3, 78.7, 67.5, 61.7, 53.6, 52.7, 44.4, 41.3, 40.2, 28.3, 26.5, 21.1, 17.8; IR (film): 3268, 2975, 1754, 1702, 1610 cm^{-1}; HRMS-ESI (m/z) [M + H]$^+$ calcd for $C_{22}H_{26}ClN_2O_3$, 401.16320; found 401.16188; $[\alpha]^{20.5}_D$ +68.60° (c = 1.000, $CHCl_3$).

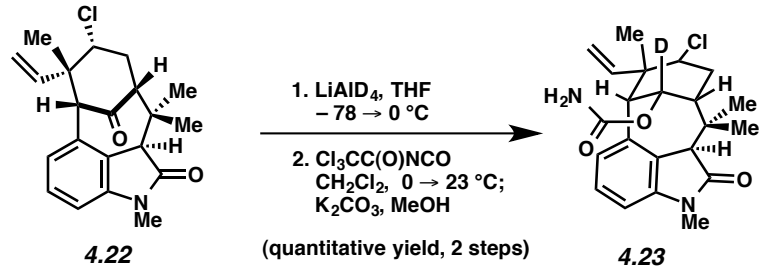


4.19 *4.28* *4.22*

Ketone 4.22. A flask containing alkyl chloride **4.19** (15.1 mg, 0.042 mmol, 1.0 equiv) was added solid $NaHCO_3$ (17.5 mg, 0.054 mmol, 5.0 equiv) in one portion. The reaction vessel was flushed with N_2, and then CH_2Cl_2 (834 μL) was added. To the resulting suspension was added the Dess–Martin periodinane reagent (23.0 mg, 0.21 mmol, 1.3 equiv) in one portion. The flask was flushed with N_2, and the reaction mixture was allowed to stir at room temperature. After 1 h, the reaction mixture was diluted with a 1:1 mixture of saturated aqueous $NaHCO_3$ and saturated aqueous $Na_2S_2O_3$ (1.0 mL). The resulting biphasic mixture was vigorously stirred until both layers appeared clear. The mixture was then transferred to a separatory funnel with EtOAc (6 mL) and H_2O (4 mL), and then extracted with EtOAc (3 x 3 mL). The organic layers were combined, dried over Na_2SO_4, and evaporated under reduced pressure. The resulting residue was purified by preparative thin layer chromatography (1:1 hexanes:EtOAc) to afford **4.28** (12.6 mg, 84% yield) as a white foam. Keto aldehyde **4.28**: R_f 0.88 (1:3 hexanes:EtOAc); ^{1}H NMR (500 MHz, C_6D_6): δ 9.06 (d, J = 1.2, 1H), 6.76 (ddd, J = 7.8, 7.8, 0.8, 1H), 6.33 (d, J = 7.6, 1H), 6.00

(d, J = 7.5, 1H), 3.41 (d, J = 2.2, 1H), 3.40 (s, 1H), 3.35 (ddd, J = 13.5, 4.5, 0.9, 1H), 2.84 (m, 1H), 2.52 (s, 3H), 2.28–2.21 (m, 1H), 1.93 (ddd, J = 14.6, 10.7, 4.6, 1H), 1.40 (s, 3H), 1.13 (s, 3H), 0.70 (s, 3H).

To a vial containing methyltriphenylphosphonium bromide (373 mg, 1.04 mmol, 15.0 equiv) was added THF (1.7 mL). The reaction vessel was cooled to 0 °C and NaHMDS (1.0 M in THF, 836 μL, 0.84 mmol, 12.0 equiv) was added in a dropwise manner. The vial was allowed to warm to room temperature and left to stir for 20 min. A solution of **4.28** (25.0 mg, 0.070 mmol, 1.0 equiv) in THF (2.4 mL) was added dropwise in three portions and the reaction was left to stir at room temperature. After 30 min the reaction was quenched with the addition of a saturated aqueous solution of NH_4Cl (5 mL). The resulting biphasic mixture was transferred to a separatory funnel with EtOAc (15 mL) and H_2O (10 mL). After extracting with EtOAc (3 x 15 mL), the organic layers were combined, dried over $MgSO_4$, and evaporated under reduced pressure. The resulting crude mixture was filtered by passage over a plug of silica gel (1:1 hexanes:EtOAc, 40 mL). The filtrate was evaporated under reduced pressure and resulting residue was purified by flash chromatography (7:1 hexanes:EtOAc) to afford ketone **4.22** (77.4 mg, 79% yield) as a white solid. Ketone **4.22**: mp: 110.4 ºC; R_f 0.67 (1:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.21 (dd, J = 7.7, 7.7, 1H), 6.70 (d, J = 7.6, 1H), 6.68 (d, J = 7.7, 1H), 5.82 (dd, J = 17.4, 11.1, 1H), 5.00–4.95 (m, 2H), 3.99 (dd, J = 12.1, 3.6, 1H), 3.72 (s, 1H), 3.61 (d, J = 2.0, 1H), 3.19 (s, 3H), 2.75–2.64 (m, 2H), 2.54–2.47 (m, 1H), 1.55 (s, 3H), 1.48 (s, 3H), 0.71 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 207.6, 175.3, 144.6, 136.2, 132.1, 129.0, 125.2, 124.4, 117.9, 107.3, 68.9, 64.5, 62.5, 50.9, 48.6, 41.8, 32.6, 29.7, 26.5, 25.0, 22.2; IR (film): 1702, 1607, 1591, 1465 cm^{-1}; HRMS-ESI (m/z) $[M + H]^+$ calcd for $C_{21}H_{25}ClNO_2$, 358.15738; found 358.15590; $[\alpha]^{23.4}_D$ +12.0° (c = 1.000, $CHCl_3$).

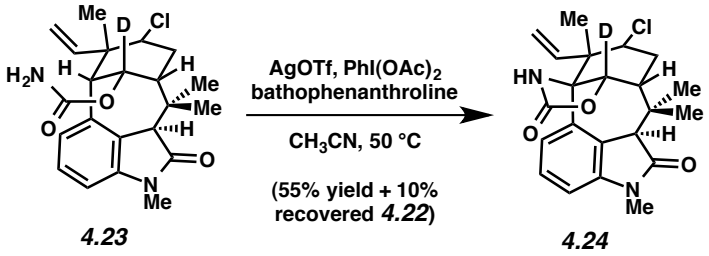


4.22 *4.23*

Carbamate 4.23. To a solution of ketone **4.22** (87 mg, 0.244 mmol, 1.0 equiv) in THF (24.4 mL) at –78 °C was added a solution of $LiAlD_4$ (1.0 M in THF, 731 μL, 0.731 mmol, 3.0 equiv) in a dropwise manner. After stirring at –78 °C for 10 min, the solution was then allowed to warm to 0 ºC. After 12 min, the reaction was quenched at 0 °C with slow addition of a saturated solution of aqueous Rochelle's salt (10 mL), and then allowed to warm to 23 ºC. The resulting biphasic mixture was stirred at room temperature for 1 h, transferred to a separatory funnel with EtOAc (10 mL) and H_2O (10 mL), and extracted with EtOAc (3 x 10 mL). The organic layers were combined, dried over $MgSO_4$, and evaporated under reduced pressure. The resulting residue was used in the subsequent step without further purification.

To a flask containing the crude residue from the previous step was added CH_2Cl_2 (4.9 mL). The reaction vessel was cooled to 0 ºC and trichloroacetyl isocyanate (36.3 μL, 0.305 mmol, 1.25 equiv) was added in a dropwise manner. The resulting mixture was allowed to stir at 0 °C for 5 min, and then at room temperature for 20 min. The solvent was evaporated under reduced pressure. To the resulting residue was added MeOH (4.9 mL) and solid K_2CO_3 (185 mg, 1.34 mmol, 5.5 equiv) in one portion. The reaction was flushed with N_2 and left to stir at room temperature for 1 h. The reaction was quenched by the addition of a solution of saturated aqueous NH_4Cl (5.0 mL), and the resulting biphasic mixture was transferred to a separatory funnel with EtOAc (10 mL) and H_2O (10 mL). After extracting with EtOAc (3 x 10 mL), the organic layers were combined, dried over $MgSO_4$, and evaporated under reduced pressure. The

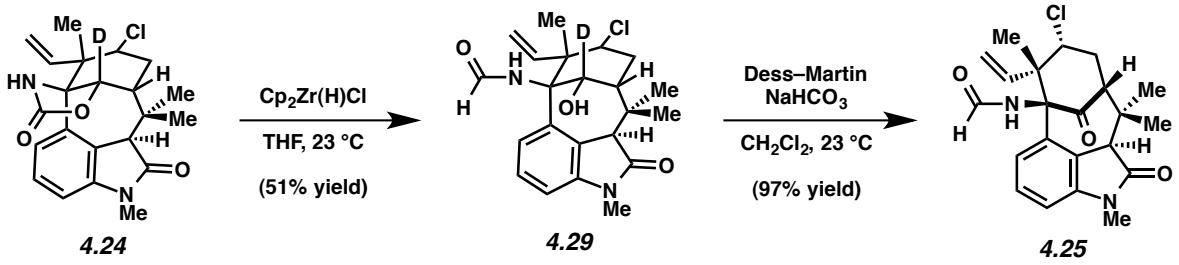
resulting residue was purified by flash chromatography (2:1 → 1:1 hexanes:EtOAc) to afford carbamate **4.23** (98 mg, quantitative yield, over two steps) as a white solid. Carbamate **4.23**: mp: 102.8 ºC; R_f 0.56 (2:1 EtOAc:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.14 (dd, *J* = 7.7, 7.7, 1H), 6.68 (d, *J* = 7.6, 1H), 6.61 (d, *J* = 7.7, 1H), 5.72 (dd, *J* = 17.1, 10.9, 1H), 4.87–4.84 (m, 2H), 4.47–4.4 (m, 3H), 3.69 (s, 1H), 3.19 (s, 3H), 3.14 (s, 1H), 2.54–2.46 (m, 2H), 2.39–2.29 (m, 1H), 1.51 (s, 3H), 1.45 (s, 3H), 0.90 (s, 3H); ^{2}H NMR (77 MHz, $CDCl_3$) δ 5.43 (br. s, 1D); ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.3, 155.8, 144.3, 137.9, 137.5, 127.8, 126.5, 125.3, 116.1, 106.6, 64.1, 56.1, 51.5, 46.6, 46.3, 39.1, 33.0, 29.0, 26.7, 26.4, 24.0; IR (film): 1724, 1701, 1607, 1467, 1376, cm^{-1}; HRMS-ESI (*m*/*z*) $[M + H]^+$ calcd for $C_{22}H_{27}DClN_2O_3$, 404.18512; found 404.18342; $[\alpha]^{24.3}_D$ –3.20° (*c* = 1.000, $CHCl_3$).



4.23 ***4.24***

Oxazolidinone 4.24. A 1-dram vial containing CH_3CN, a second 1-dram vial charged with bathophenanthroline (13 mg, 0.039 mmol, 1.0 equiv), and a third 1-dram vial containing carbamate **4.23** (15.8 mg, 0.039 mmol, 1.0 equiv) and $PhI(OAc)_2$ (50 mg, 0.157 mmol, 4.0 equiv) were transferred into the glovebox. AgOTf (10 mg, 0.039 mmol, 1.0 equiv) and CH_3CN (550 μL) were added to the vial containing the bathophenanthroline, and the resulting suspension was allowed to stir at room temperature for 20 min. Next, CH_3CN (550 μL) was added to the vial containing the carbamate, and the AgOTf/bathophenanthroline suspension was also added to this vial. The vial was then sealed, removed from the glovebox, and the resulting mixture was heated

to 50 °C. After 24 h, the reaction was cooled to room temperature and filtered by passage over a plug of silica gel (EtOAc eluent, 10 mL). The filtrate was evaporated under reduced pressure, and the resulting residue was purified by preparative thin layer chromatography (2:1:1 benzene:Et_2O:CH_2Cl_2) to afford oxazolidinone **4.24** (8.7 mg, 55% yield) as a white solid and recovered ketone **4.22** (1 mg, 10% yield). Oxazolidinone **4.24**: mp: 183.2 ºC; R_f 0.32 (1:2:2 benzene:Et_2O:CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.76 (s, 1H), 7.09 (dd, *J* = 7.9, 7.9, 1H), 6.69 (d, *J* = 7.8, 1H), 6.66 (d, *J* = 8.2, 1H), 5.54 (dd, *J* = 17.3, 10.7, 1H), 5.06 (d, *J* = 17.3, 1H), 5.00 (d, *J* = 10.9, 1H), 4.38–4.32 (m, 1H), 3.97 (s, 1H), 3.21 (s, 3H), 2.71–2.60 (m, 2H), 2.55–2.45 (m, 1H), 1.57 (s, 3H), 1.52 (s, 3H), 1.11 (s, 3H); ^{2}H NMR (77 MHz, $CDCl_3$) δ 4.91 (br. s, 1D); ^{13}C NMR (125 MHz, $CDCl_3$): δ 175.1, 159.5, 143.6, 138.7, 137.5, 128.2, 125.3, 124.1, 115.9, 107.0, 70.3, 63.1, 53.3, 47.9, 45.5, 38.2, 32.3, 27.1, 26.4, 23.3, 21.0; IR (film): 1748, 1703, 1683, 1610, 1591 cm^{-1}; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{22}H_{25}DClN_2O_3$, 402.16947; found 402.16849; $[\alpha]^{23.1}_D$ +8.20° (*c* = 1.000, $CHCl_3$).

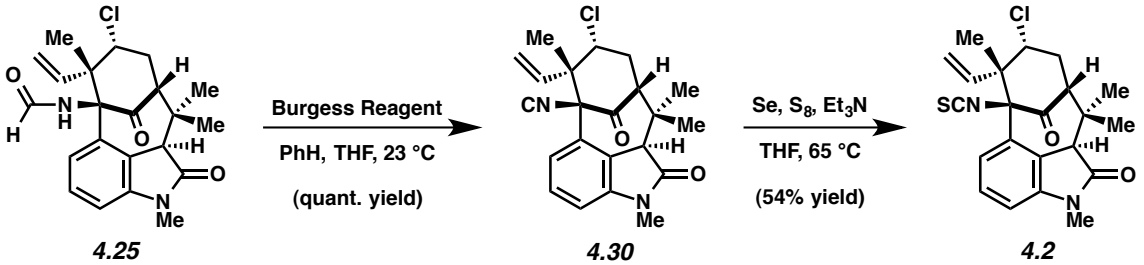


Formamide 4.25. Two 1-dram vials were charged with **4.24** (7.0 mg, 0.017 mmol, 1.0 equiv each) and taken into the glovebox. Each reaction vessel was charged with Schwartz' reagent (5.9 mg, 0.023 mmol, 1.3 equiv each) and THF (1.74 mL each), which had previously been taken through six freeze-pump-thaw cycles, was added. The reaction vessels were sealed and left to stir at room temperature. After 14 h, the reaction vials were removed from the glovebox and

quenched with saturated aqueous solution of NH_4Cl (1 mL) for each vial. The resulting biphasic mixtures were transferred to a test tube with EtOAc (2 mL) and brine (1 mL). After extracting with EtOAc (3 x 2 mL). The organic layers were combined, dried over $MgSO_4$, and evaporated under reduced pressure. The resulting residue was purified by preparative thin layer chromatography (1:1 hexanes:acetone) to afford **4.29**[35] (7.2 mg, 51% yield) as a white solid and recovered oxazolidinone **4.24** (3.1 mg, 22% yield). **4.29**: R_f 0.09 (1:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$):[36] 8.3–8.25 (m, 1.36H), 7.95 (s, 0.47H), 7.31–7.27 (m, 1.25H), 6.96 (d, *J* = 8.2, 0.41H), 6.87 (d, *J* = 8.1, 1H), 6.78-6.73 (m, *J* = 8.3, 2.0H), 6.22 (s, 1H), 6.10 (d, *J* = 11.2, 0.41H), 5.92 (dd, *J* = 17.8, 11.4, 1H), 5.88-5.80 (m, 0.87H), 5.05–4.97 (m, 0.8H), 4.94–4.85 (m, 3H), 4.79 (dd, *J* = 9.9, 5.5, 1H), 4.48 (dd, *J* = 9.2, 5.2, 0.5H), 4.33 (d, *J* = 8.2, 5.7, 0.38H), 4.20 (s, 0.36H), 4.10 (s, 0.38H), 4.06 (s, 1H), 3.23–3.19 (m, 5.7H), 2.73–2.49 (m, 4.5H), 2.44–2.36 (m, 1.5H), 1.57 (s, 3H), 1.56 (s, 3.5H), 1.52 (s, 4.4H), 1.50 (s, 1.71H), 1.23 (s, 1.34H), 1.18 (s, 3H), 0.95 (s, 1.4H).

A 1-dram vial was charged with **4.29** (5.2 mg, 0.013 mmol, 1.0 equiv) and solid $NaHCO_3$ (5.4 mg, 0.065 mmol, 5.0 equiv) in one portion. The reaction vessel was flushed with N_2, and then CH_2Cl_2 (260 μL) was added. To the resulting suspension was added the Dess–Martin periodinane reagent (7.1 mg, 0.017 mmol, 1.3 equiv) in one portion. The flask was flushed with N_2, and the reaction mixture was allowed to stir at room temperature. After 1 h, the reaction mixture was diluted with a 1:1 mixture of saturated aqueous $NaHCO_3$ and saturated aqueous $Na_2S_2O_3$ (1.0 mL). The resulting biphasic mixture was vigorously stirred until both layers appeared clear. The mixture was then transferred to a test tube with EtOAc (2 mL) and brine (2 mL), and then extracted with EtOAc (3 x 2 mL). The organic layers were combined, dried over $MgSO_4$, and evaporated under reduced pressure. The resulting residue was purified by flash

chromatography (5:1 → 3:1 hexanes:acetone) to afford formamide **4.25** (5.0 mg, 97% yield) as a white solid. formamide **4.25**: mp: 213.3 ºC; R_f 0.41 (3:1 EtOAc:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$ at –44 °C):[37] δ 8.21 (d, *J* = 1.1, 0.25H), 7.53 (d, *J* = 12.0, 1H), 7.32 (dd, *J* = 8.1, 7.9, 1.25H), 7.02 (d, *J* = 8.1, 1H), 7.00 (d, *J* = 8.3, 0.25H), 6.82 (d, *J* = 7.5, 1H), 6.79 (d, *J* = 7.5, 0.25H), 6.38 (dd, *J* = 17.3, 11.0, 0.25H), 6.28 (dd, *J* = 17.3, 10.7, 1H), 5.78 (s, 0.25H), 5.73 (d, *J* = 11.5, 1H), 5.51 (d, *J* = 11.2, 0.25H), 5.48 (d, *J* = 11.0, 1H), 5.42–5.30 (m, 1.25H), 4.40 (s, 1H), 4.32 (s, 0.25H), 4.24 (d, *J* = 7.4, 1H), 4.19 (d, *J* = 7.1, 0.25H), 3.22 (s, 3H), 3.21 (s, 0.75H), 3.20–3.14 (m, 1H), 3.08–2.90 (m, 2.6H), 2.81 (d, *J* = 17.4, 1H), 2.75 (d, *J* = 16.4, 0.25H), 1.68 (s, 3H), 1.63 (s, 0.75H), 1.28 (s, 3.75H), 0.98 (s, 0.75H), 0.87 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 202.8, 174.3, 167.3, 144.0, 137.2, 133.7, 128.4, 126.7, 124.8, 118.2, 108.1, 71.5, 62.2, 60.2, 55.0, 49.8, 38.2, 31.8, 26.3, 26.1, 22.9, 20.9; IR (film): 2967, 2932, 1696, 1609, 1585 cm^{-1}; HRMS-ESI (*m/z*) [M + H]$^+$ calcd for $C_2H_{26}ClN_2O_3$, 401.16320; found 401.16143; $[\alpha]^{22.4}_D$ +9.60° (*c* = 1.000, $CHCl_3$).



(–)-*N*-Methylwelwitindolinone B Isothiocyanate (4.2). To a solution of formamide **4.25** (3.3 mg, 0.008 mmol, 1.0 equiv) in 1:1 THF/PhH (660 μL) was added Burgess reagent (2.0 mg, 0.008 mmol, 1.0 equiv). The reaction vessel was purged with N_2, sealed and left to stir at room temperature. After stirring for 1 h, an additional portion of Burgess reagent (0.5 mg, 0.002 mmol,

0.25 equiv) was added. After stirring at room temperature for 30 min, a final portion of Burgess reagent (0.5 mg, 0.002 mmol, 0.25 equiv) was added and the resulting solution was stirred at room temperature. After 25 min the reaction was filtered by passage over a plug of silica gel (EtOAc eluent, 6 mL). The filtrate was evaporated under reduced pressure and the resulting residue was purified by flash chromatography (5:1:1 hexanes:Et_2O:CH_2Cl_2) to afford **4.30** (3.2 mg, quant. yield) as a white solid. **4.30**: R_f 0.55 (1:1:1 hexanes:Et_2O:CH_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6): δ 7.41 (d, *J* = 8.3, 1H), 6.86 (dd, *J* = 8.0, 8.0, 1H), 6.04 (d, *J* = 7.7, 1H), 5.82 (dd, *J* = 17.2, 11.0, 1H), 4.95–4.81 (m, 2H), 3.83 (s, 1H), 3.43 (dd, *J* = 6.4, 6.2, 1H), 2.55 (s, 3H), 2.36 (dd, *J* = 9.9, 3.6, 1H), 2.19–2.11 (m, 1H), 1.91–1.81 (m, 1H), 1.46 (s 3H), 1.26 (s, 3H), 0.75 (s, 3H).

To two 1-dram vials containing **4.30** (2.9 mg, 0.008 mmol, 1.0 equiv each) was added powdered Se (1.8 mg, 0.023 mmol, 3.0 equiv each) and S_8 (1.9 mg, 0.590 mmol, 76.4 equiv each). The reaction vessels were purged with N_2 and to each vessel was added THF (584 μL, previously sparged with N_2 for 20 min) and NEt_3 (81 μL, 0.590 mmol, 26.4 equiv), which were then sealed and heated to 65 °C. After 17 h the reaction vials were cooled to room temperature and filtered by passage over a plug of silica gel (EtOAc eluent, 6 mL). The filtrate was evaporated under reduced pressure and the resulting residue was purified by preparative thin layer chromatography (1:1:1 hexanes:Et_2O:CH_2Cl_2) to afford (–)-**4.2** (3.4 mg, 54% yield) as a white solid. (–)-*N*-Methylwelwitindolinone B isothiocyanate (**4.2**): mp: 186.4 ºC; R_f 0.61 (1:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34 (ddd, *J* = 8.3, 0.8, 1H), 7.25 (dd, *J* = 8.3, 0.9, 1H), 6.80 (d, *J* = 7.7, 1H), 5.99 (dd, *J* = 17.5, 11.1, 1H), 5.22–5.15 (m, 2H), 4.17 (app t, *J* = 6.3, 1H), 4.13 (s, 1H), 3.20 (s, 3H), 2.95 (app t, *J* = 7.2, 1H), 2.78 (app t, *J* = 6.5, 1H), 1.62 (s 3H), 1.48 (s, 3H), 0.83 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 198.6, 174.3, 144.1, 139.6,

136.4, 131.2, 128.8, 123.9, 122.6, 118.1, 108.3, 83.5, 62.5, 60.2, 53.3, 52.9, 39.8, 31.5, 26.4, 25.4, 24.1, 22.5; IR (film): 2969, 2933, 2049, 1710, 1607, 1587, 1460 cm^{-1}; HRMS-ESI (*m/z*) [M + H]$^+$ calcd for $C_{22}H_{24}ClN_2O_2S$, 415.12470; found 415.12245; $[\alpha]^{20.9}_D$ –133.71° (*c* = 0.071, CH_2Cl_2).[38]

4.10 Notes and References

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(6) (a) Bhat, V.; Allan, K. M.; Rawal, V. H. *J. Am. Chem. Soc.* **2011**, *133*, 5798. (b) Allan, K. M.; Kobayashi, K.; Rawal, V. H. *J. Am. Chem. Soc.* **2012**, *134*, 1392.

(7) (a) Huters, A. D.; Quasdorf, K. W.; Styduhar, E. D.; Garg, N. K. *J. Am. Chem. Soc.* **2011**, *133*, 15797. (b) Quasdorf, K. W.; Huters, A. D.; Lodewyk, M. W.; Tantillo, D. J.; Garg, N. K. *J. Am. Chem. Soc.* **2012**, *134*, 1396. (c) Styduhar, E. D.; Huters, A. D.; Weires, N. A.; Garg, N. K. *Angew. Chem. Int. Ed.* **2013**, *52*, 12422.

(8) The 3D representation of **4.2** was obtained using B3LYP/6-31G* calculations (geometry optimization), using MacSpartan software.

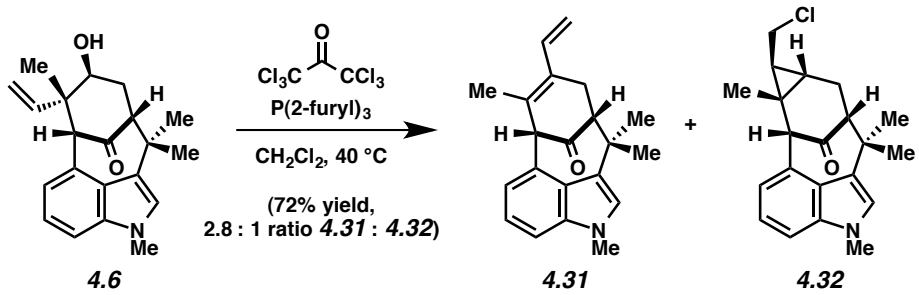
(9) Image prepared using CYLview: Legault, C. Y. CYLview, 1.0b; Université de Sherbrooke: Québec, Montreal, Canada, 2009; http://www.cylview.org.

(10) Related natural products, such as **4.1**, also bear a similar motif where an alkyl chloride resides adjacent to a quaternary center, albeit not on a [4.3.1]-bicyclic scaffold. For elegant approaches to this motif, see ref 2.

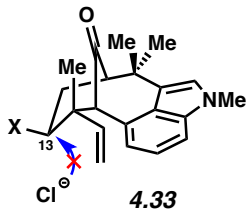
(11) Huters, A. D.; Styduhar, E. D.; Weires, N. A.; Garg, N. K. University of California, Los Angeles, CA, **2012**, unpublished work.

(12) In related studies, efforts to reduce the vinyl chloride in compounds lacking the terminal olefin either led to recovery of starting material or over-reduction to cyclohexyl compounds lacking the chloride.

(13) Subjection of **4.6** to Rawal's chlorination conditions resulted in vinyl migration and cyclopropanation products **4.31** and **4.32**; see ref 4u.



(14) As seen in transition structure **4.33** below, approach of the chloride is obstructed, whereas the vinyl group is poised to react at C13.



(15) For a review on C–N bond forming reactions involving C(sp^3)–H bonds, see: Jeffrey, J. L.; Sarpong, R. *Chem. Sci.* **2013**, *4*, 4092.

(16) Although this strategy would not preclude the possibility of vinyl group migration, it was anticipated that the ease of chlorination would be considerably greater. As such, it was hoped that the necessary chlorinative displacement could compete with the undesired vinyl group migration.

(17) For reviews of indolynes and other heterocyclic arynes, see: (a) Bronner, S. M.; Goetz, A. E.; Garg, N. K. *Synlett* **2011**, 2599. (b) Goetz, A. E.; Garg, N. K. *J. Org. Chem.* **2014**, *79*, 846.

(18) Attempts to achieve the chlorinative ring opening of indolo-oxabicycle **4.14** resulted in undesired byproducts and decomposition.

(19) Treatment of **4.15** with $ZnCl_2$ and acetyl chloride resulted in the acetylated derivative of **4.17** in ca. 40% yield; see: Clive, D. L. J.; Sannigrahi, M.; Hisaindee, S. *J. Org. Chem.* **2001**, *66*, 954.

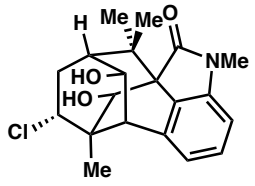
(20) MaloneyHuss, K. E.; Portoghese, P. S. *J. Org. Chem.* **1990**, *55*, 2957.

(21) Delaney, P. A.; Johnstone, R. A. W.; Entwistle, I. D. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1855.

(22) Koreeda, M.; Gopalaswamy, R. *J. Am. Chem. Soc.* **1995**, *117*, 10595.

(23) Wensheng, Y.; Mei, Y.; Kang, Y.; Hua, Z.; Jin, Z. *Org. Lett.* **2004**, *6*, 3217.

(24) Compound **4.34** (single diastereomer, unassigned) commonly forms as a minor byproduct of this transformation, presumably by way of an intramolecular aldol reaction.



4.34

(25) All attempts to directly olefinate aldehyde **4.19** were unsuccessful. Attempts to olefinate **4.26** using Wittig olefination protocols led to aldol reaction (i.e., the TES ether analog of compound **4.34**; see ref 24).

(26) (a) Li, Z.; Capretto, D. A.; Rahaman, R.; He, C. *Angew. Chem. Int. Ed.* **2007**, *46*, 5184. (b) Cui, Y.; He, C. *Angew. Chem. Int. Ed.* **2004**, *43*, 4210.

(27) Espino, C. G.; Du Bois, J. *Angew. Chem. Int. Ed.* **2001**, *40*, 598.

(28) Use of the sulfamate derivative of **4.8** under Rh-catalysis also facilitated C9 insertion.

(29) We also carried out the corresponding sequence with $LiAlH_4$, which gave the proteo derivative of carbamate **4.23**. When employed in the nitrene insertion reaction, we obtained a

1:1.4 ratio of desired insertion product to ketone **4.22**. Consistent with our previous findings on alternate substrates, the strategic use of deuterium minimizes an undesirable competitive reaction, thus giving synthetically useful yields of the desired nitrene insertion product; see ref 7b, c.

(30) Morin, J.; Zhao, Y.; Snieckus, V. *Org. Lett.* **2013**, *15*, 4102.

(31) Nishikawa, K.; Umezawa, T.; Garson, M. J.; Matsuda, F. *J. Nat. Prod.* **2012**, *75*, 2232.

(32) Payack, J. F.; Hughed, D. L.; Cai, D.; Cottrell, I. F.; Verhoeven, T. R. *Org. Synth.* **2002**, *79*, 19.

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

(34) For compound **4.2** the ^{13}C NMR residual solvent peak is set to 77.0 ppm to match the reference values set in the isolation paper.

(35) In our studies, products containing a formamide often assume a mixture of rotamers by ^{1}H NMR.

(36) **4.29** Was obtained as a 2.8:1.3:1 mixture of rotamers. These data represent empirically obtained chemical shifts and coupling constants from the ^{1}H NMR spectrum.

(37) Formamide **4.25** was obtained as a 4:1 mixture of rotamers. These data represent empirically obtained chemical shifts and coupling constants from the ^{1}H NMR spectrum.

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

APPENDIX THREE

Spectra Relevant to Chapter Four:

Total Synthesis of (–)-*N*-Methylwelwitindolinone B Isothiocyanate via a Chlorinative Oxabicyclic Ring-Opening Strategy

Nicholas A. Weires, Evan D. Styduhar, Emma L. Baker, and Neil K. Garg.

J. Am. Chem. Soc. **2014**, *136*, 14710–14713.

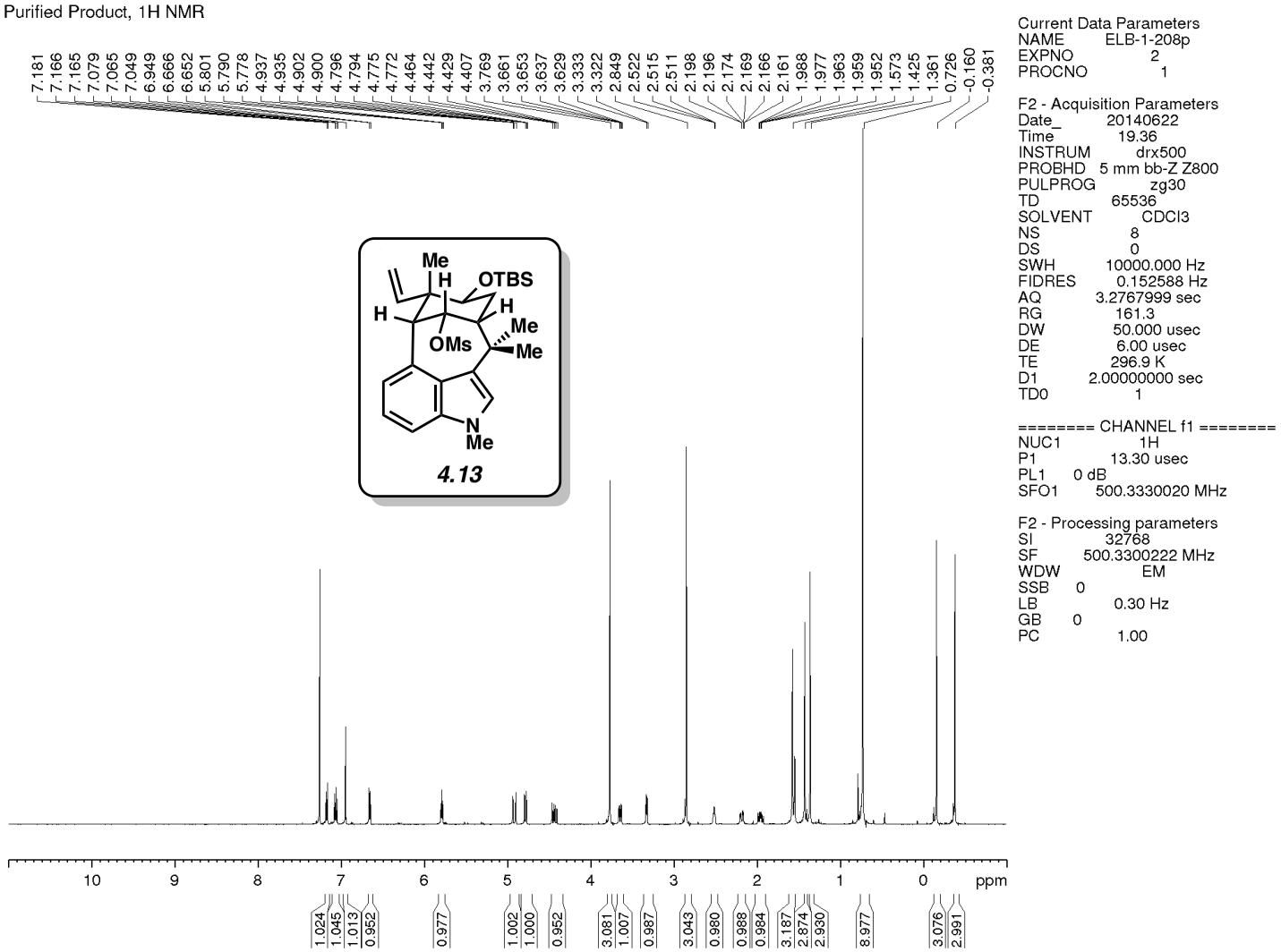


Figure A3.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.13**.

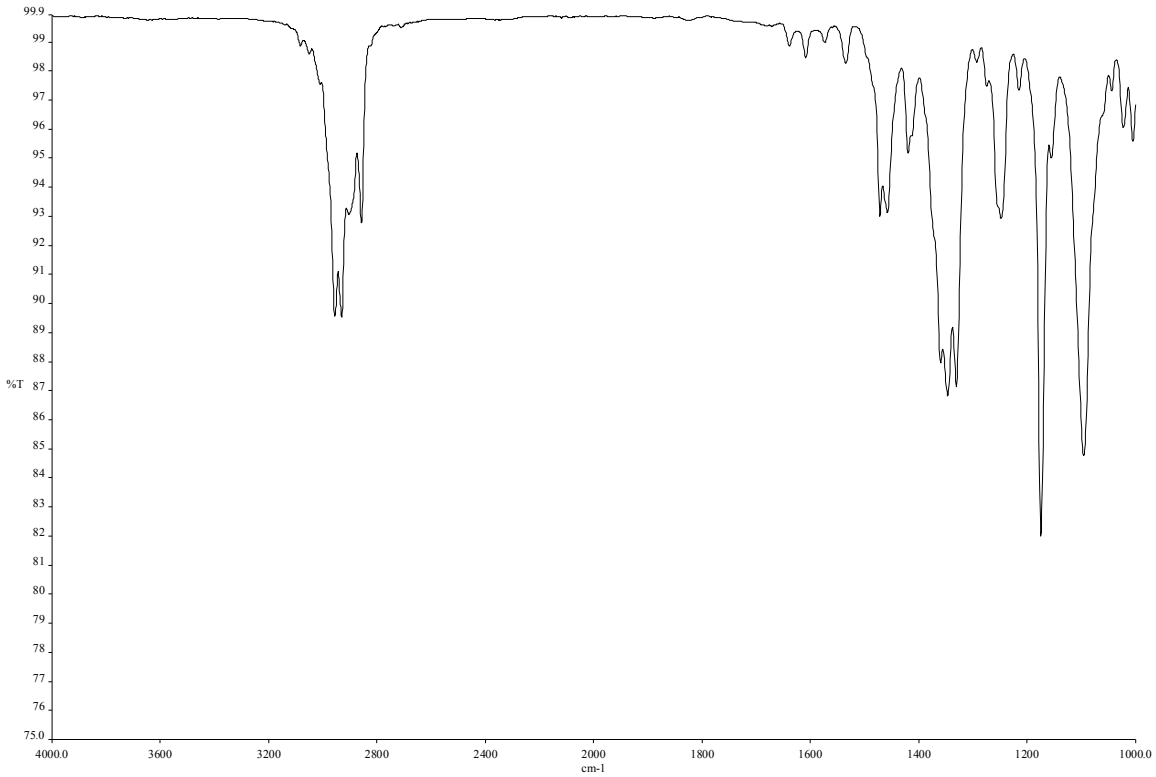


Figure A3.2 Infrared spectrum of compound **4.13**.

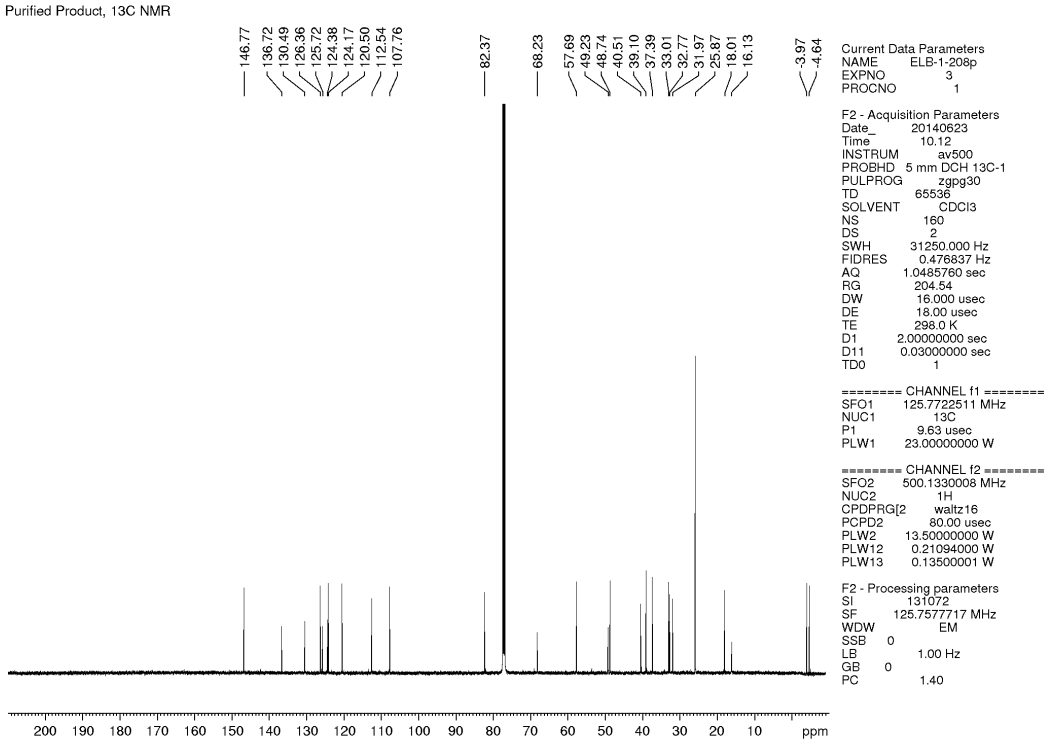


Figure A3.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4.13**.

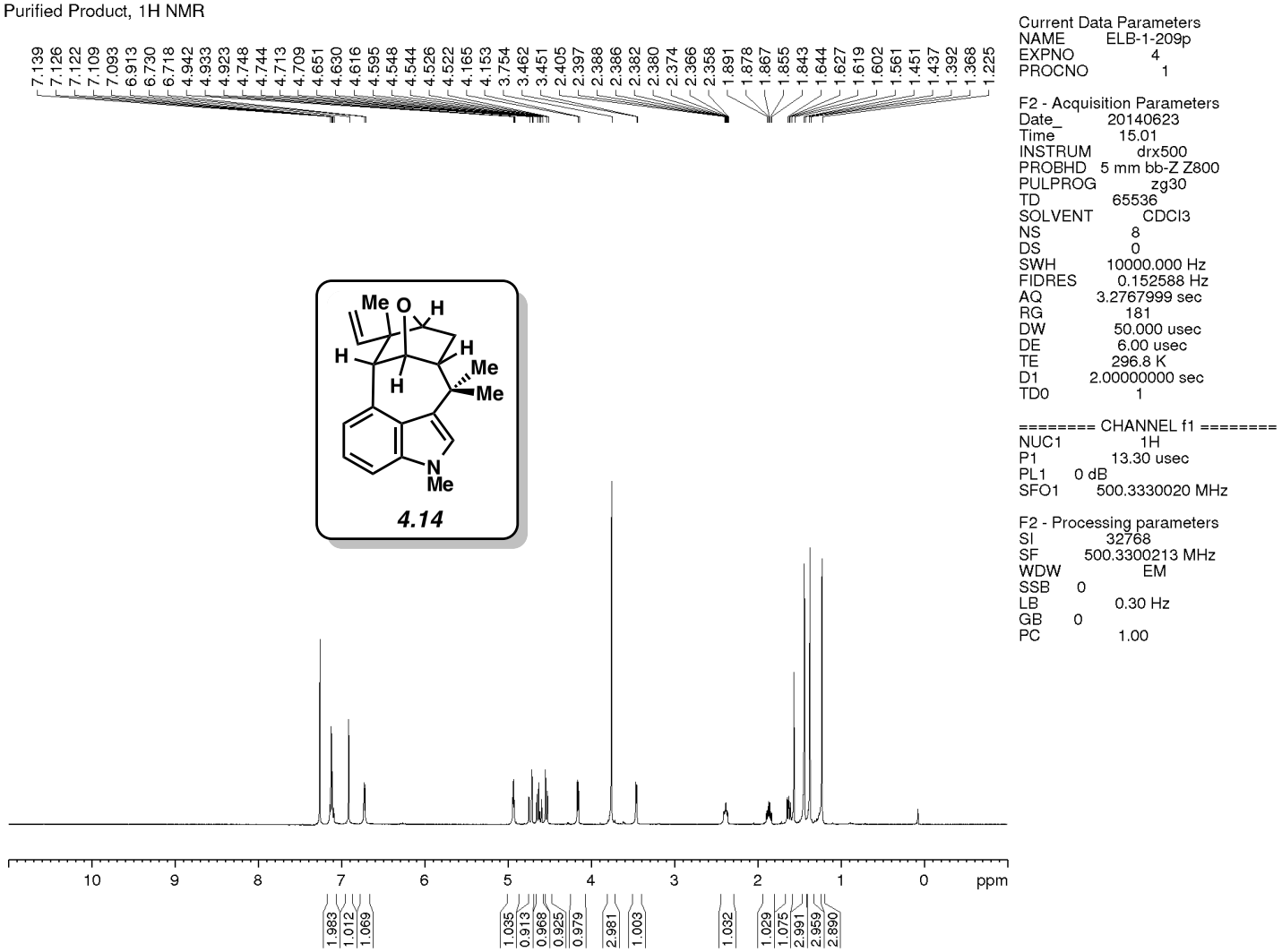


Figure A3.4 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.14**.

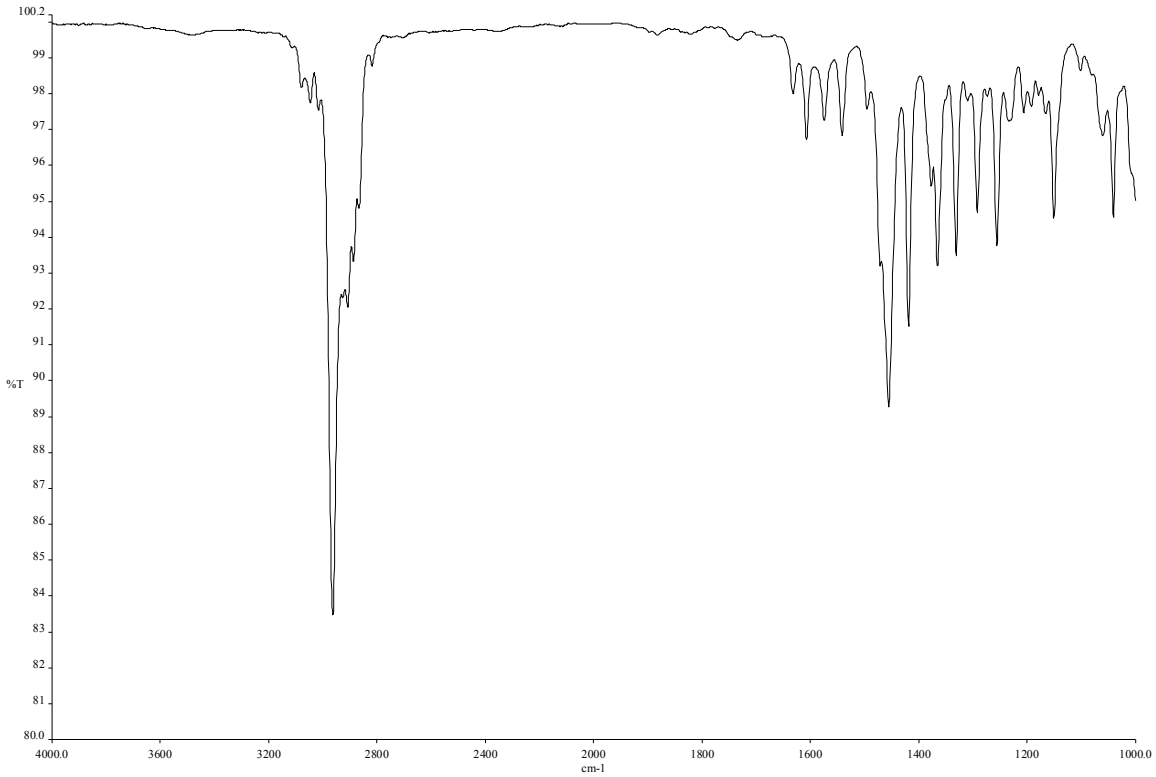


Figure A3.5 Infrared spectrum of compound **4.14**.

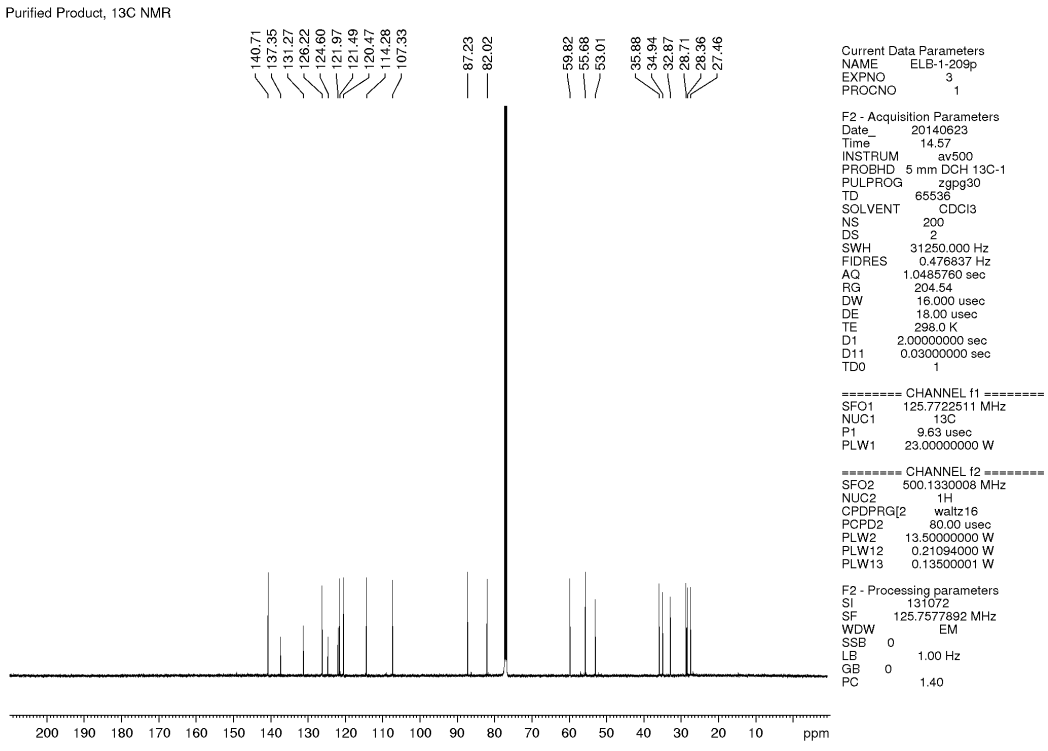


Figure A3.6 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4.14**.

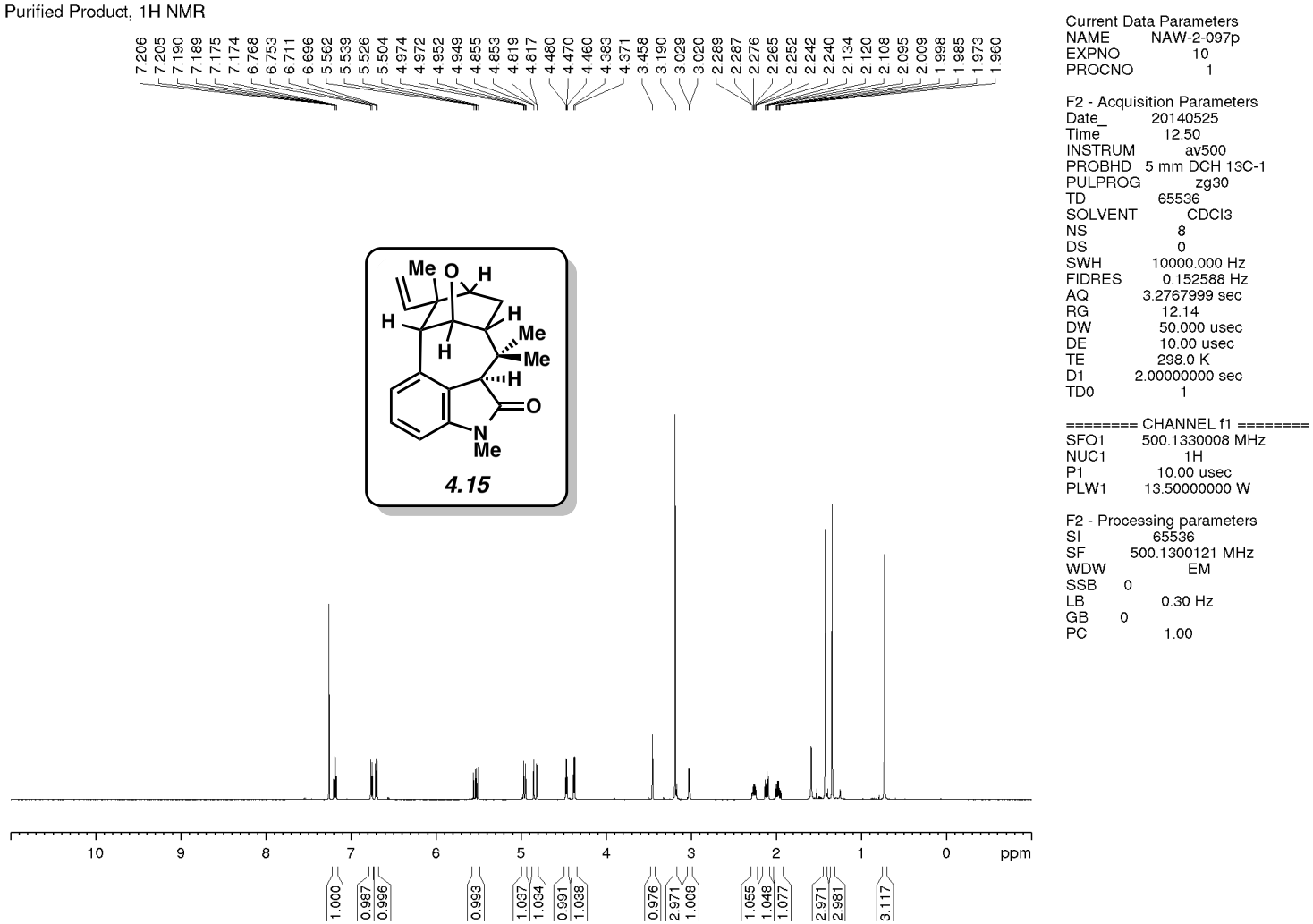


Figure A3.7 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.15**.

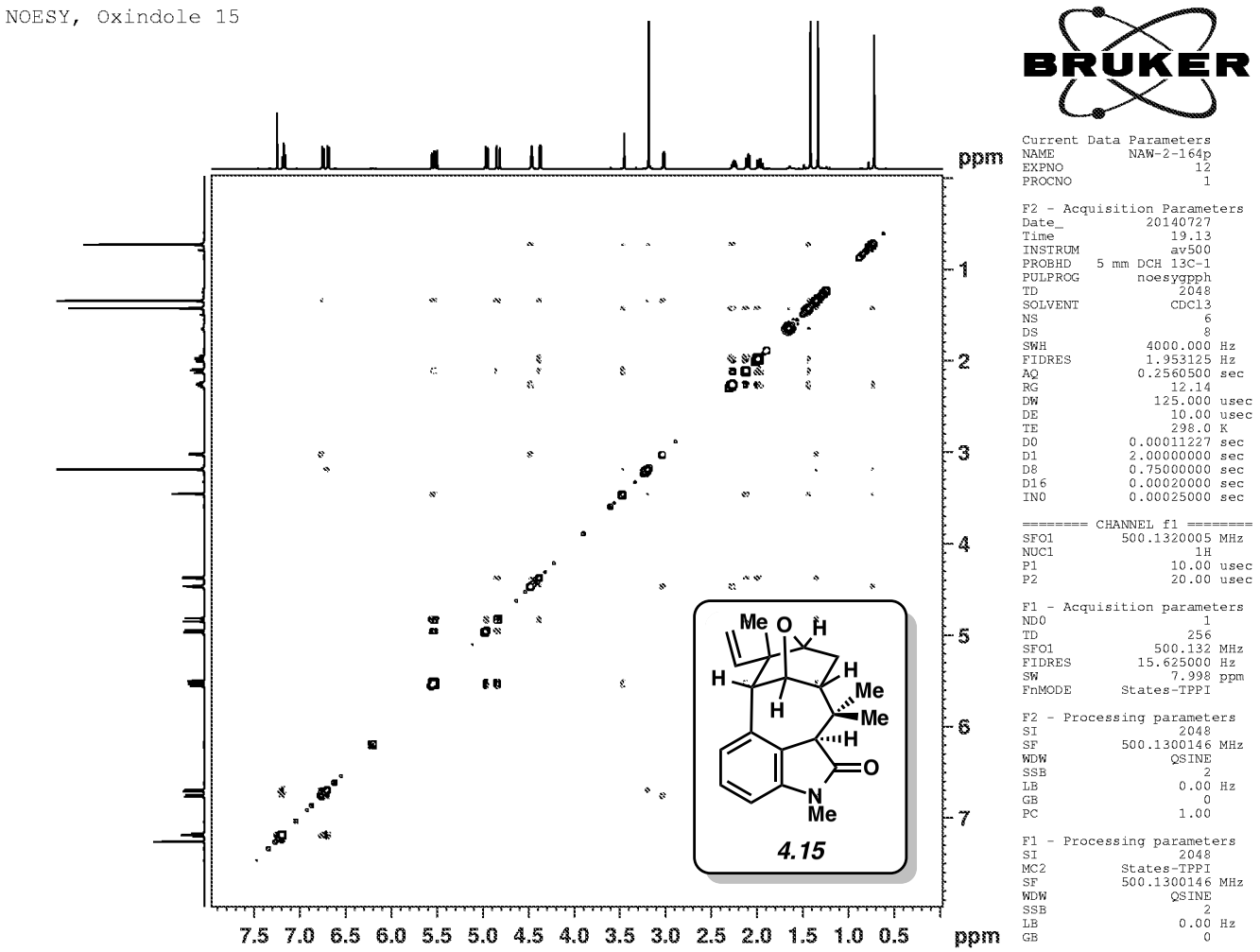


Figure A3.8 2D-NOESY NMR (500 MHz, $CDCl_3$) of compound **4.15**.

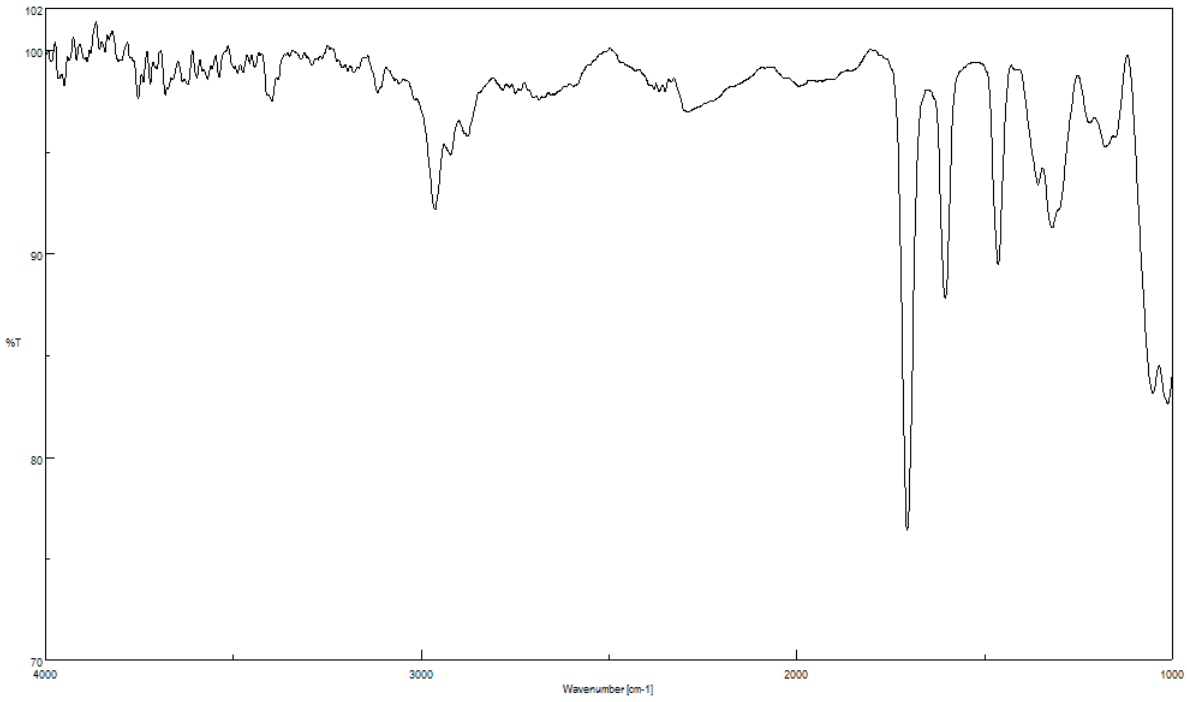


Figure A3.9 Infrared spectrum of compound **4.15**.

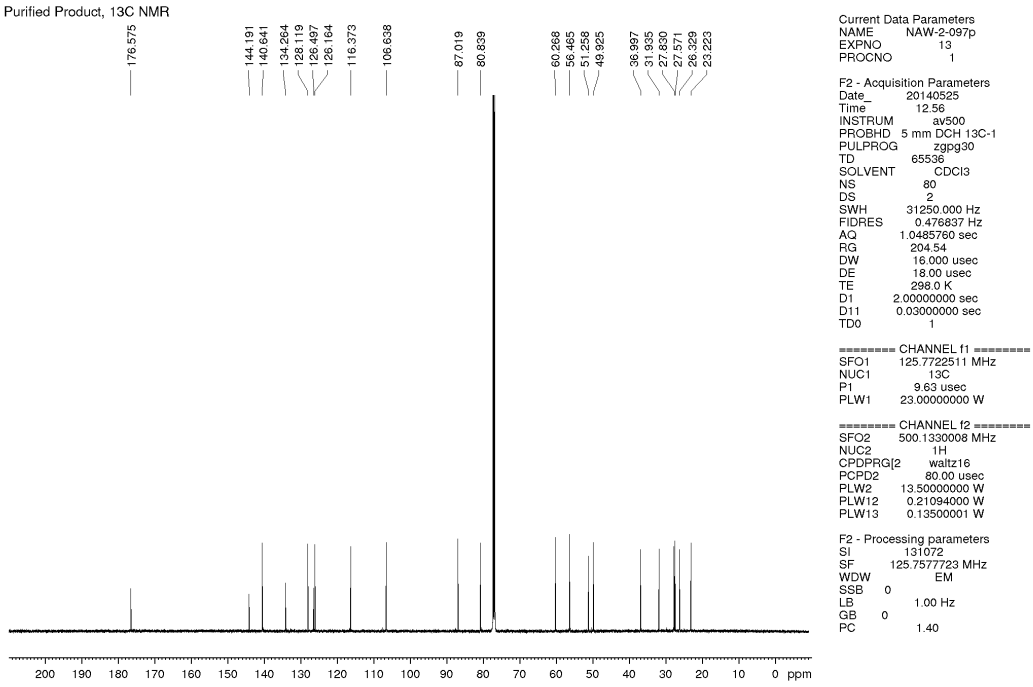


Figure A3.10 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4.15**.

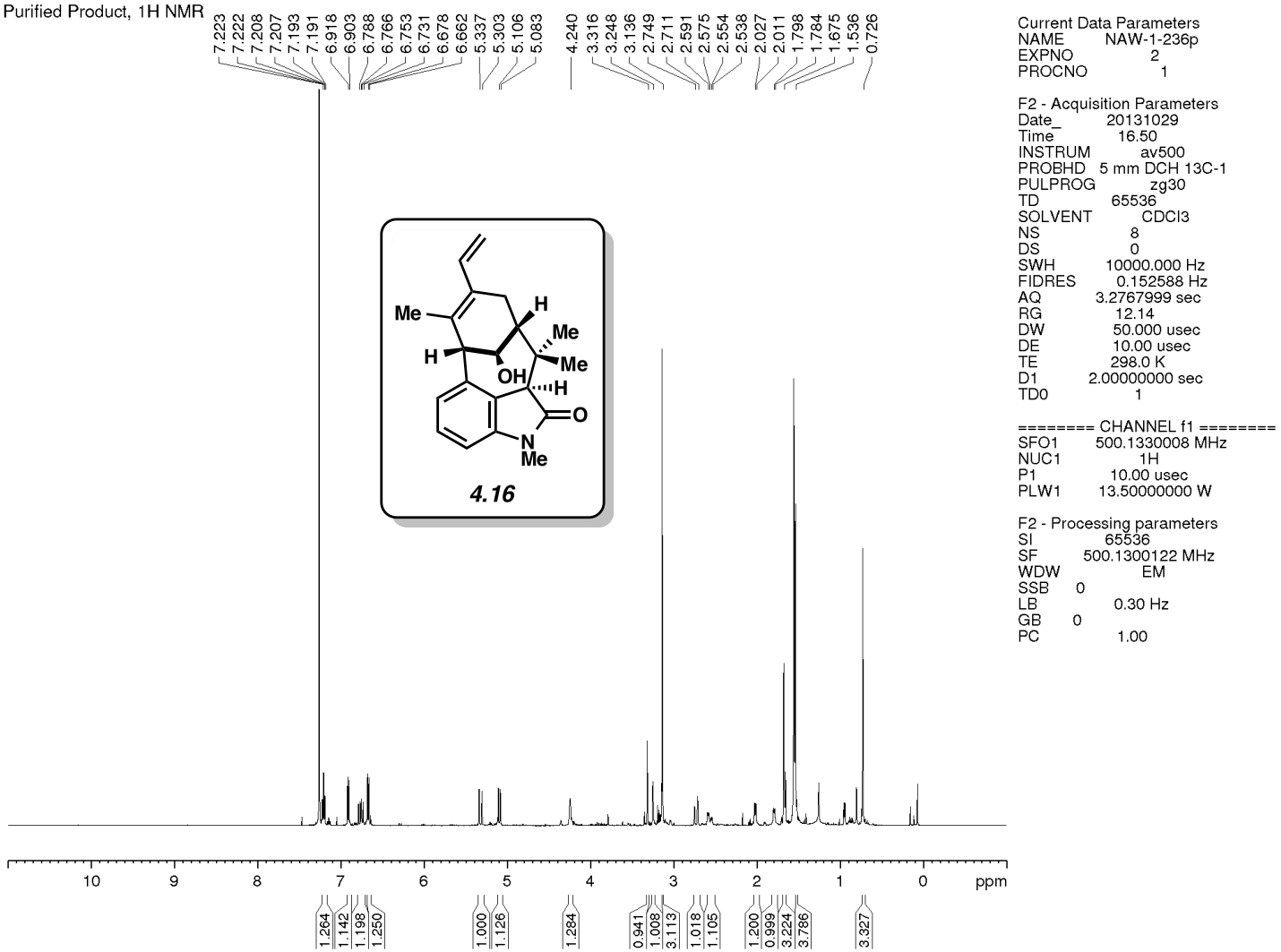


Figure A3.11 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.16**.

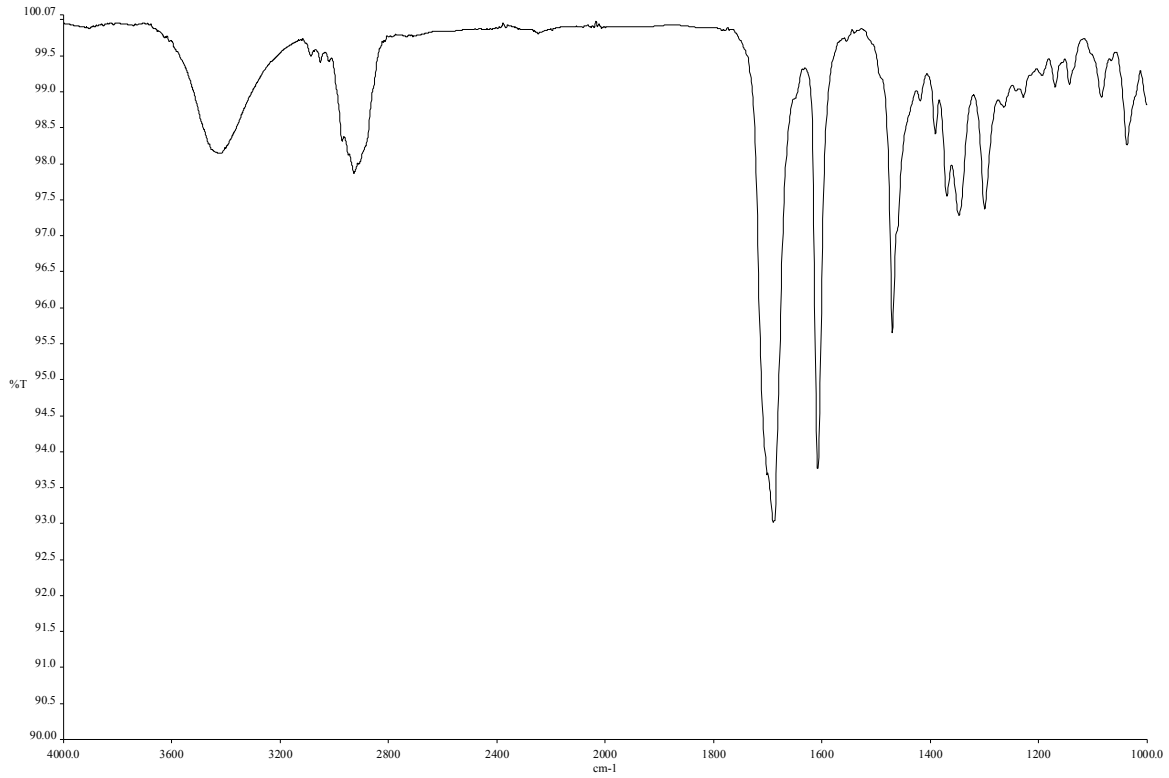


Figure A3.12 Infrared spectrum of compound **4.16**.

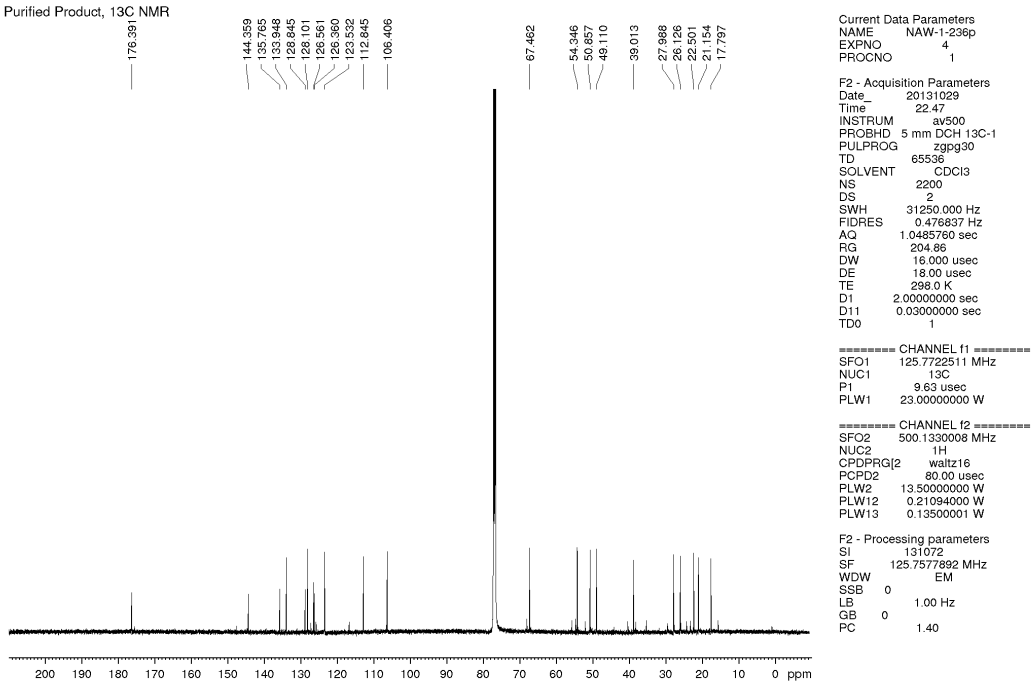


Figure A3.13 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4.16**.

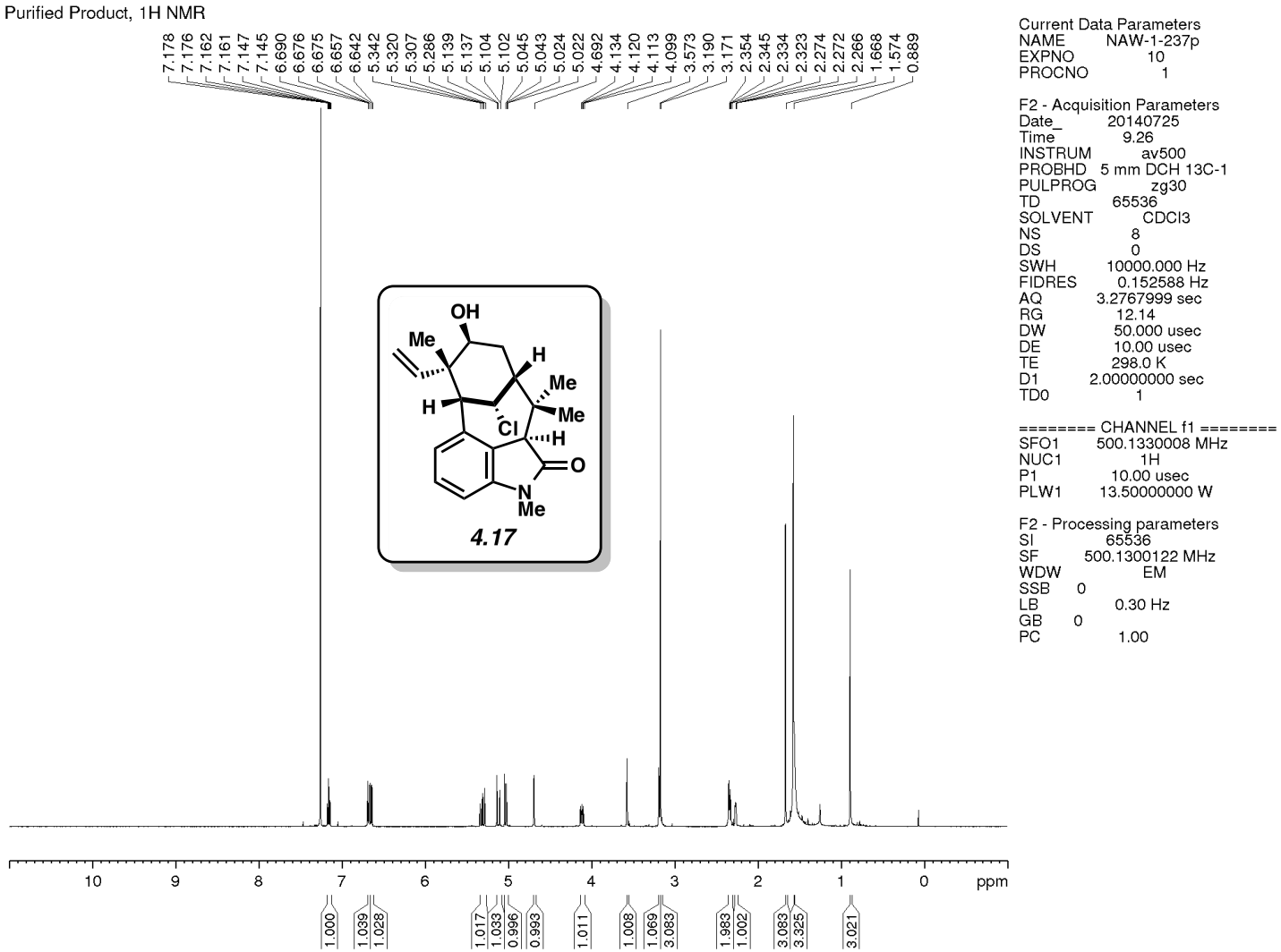


Figure A3.14 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.17**.

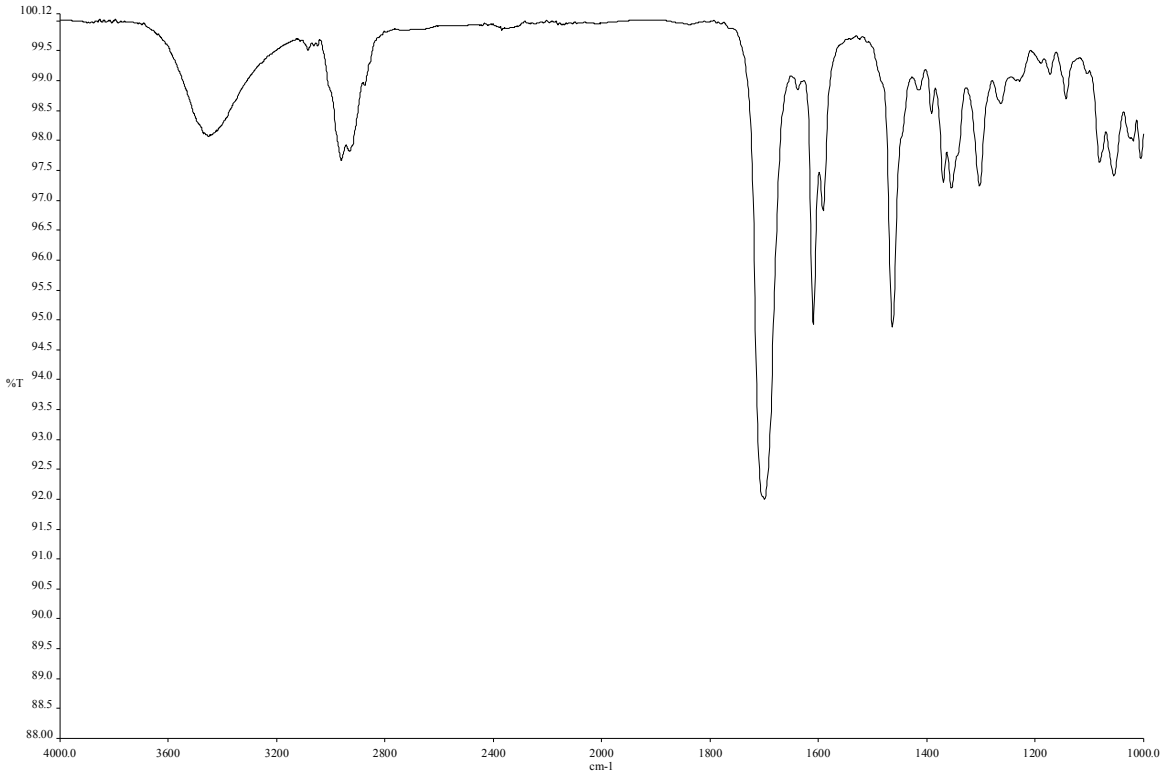


Figure A3.15 Infrared spectrum of compound **4.17**.

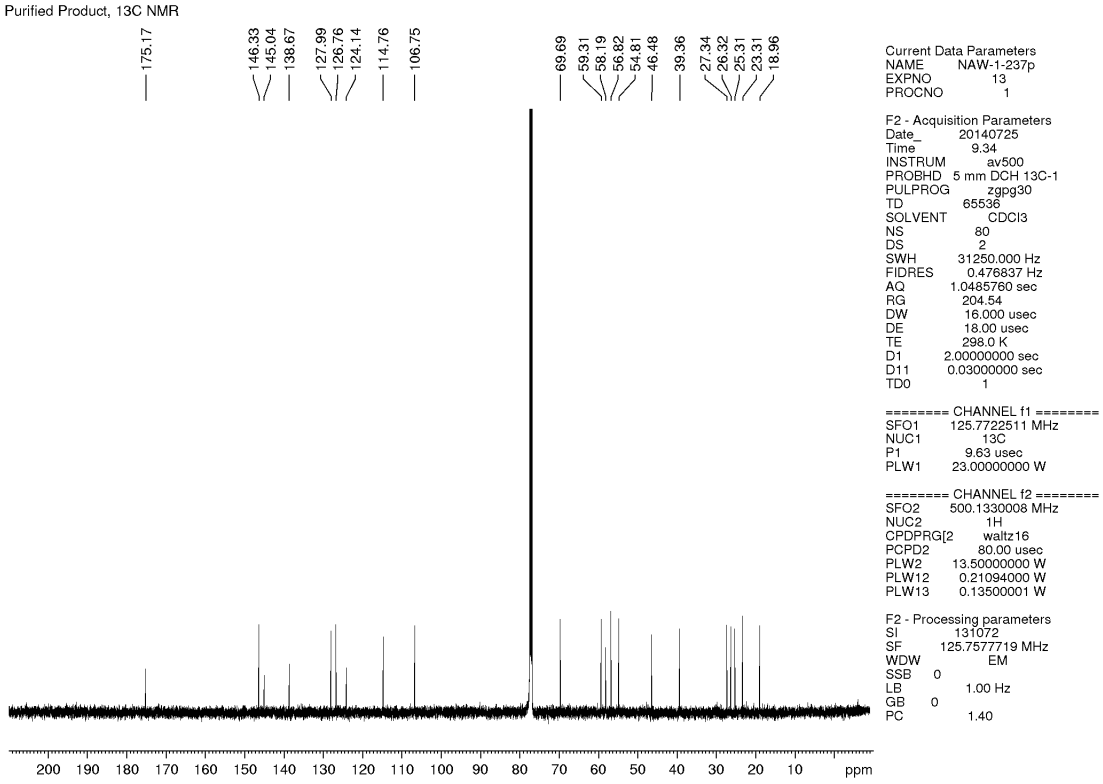


Figure A3.16 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4.17**.

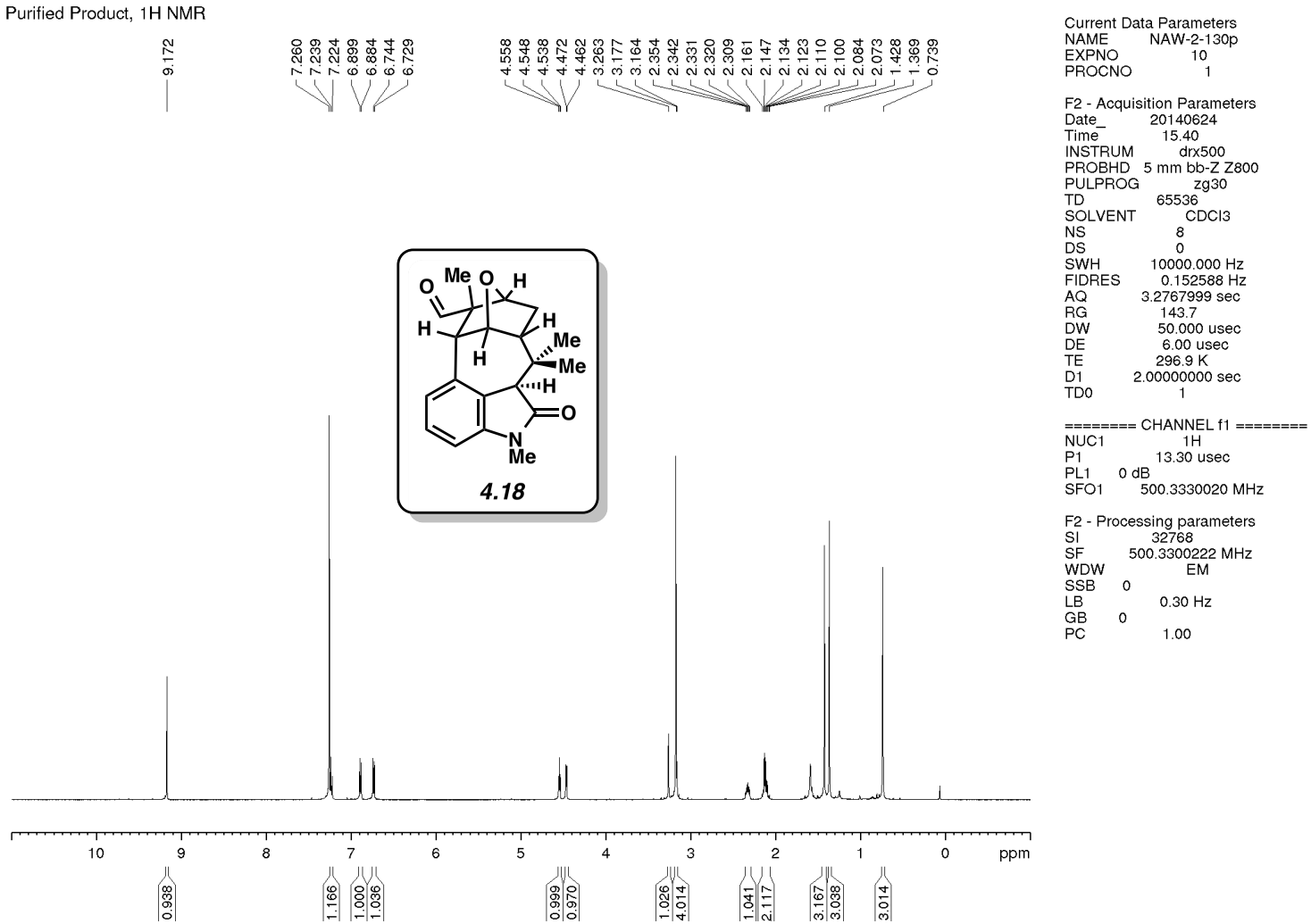


Figure A3.17 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.18**.

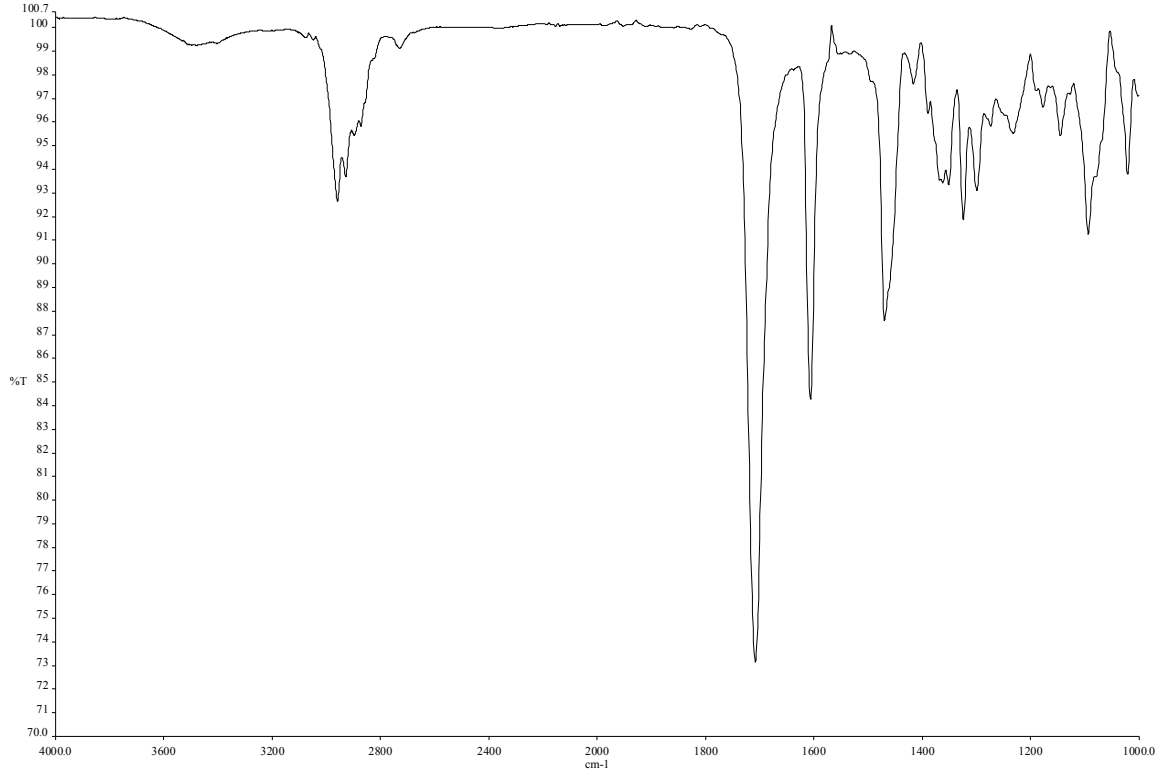


Figure A3.18 Infrared spectrum of compound **4.18**.

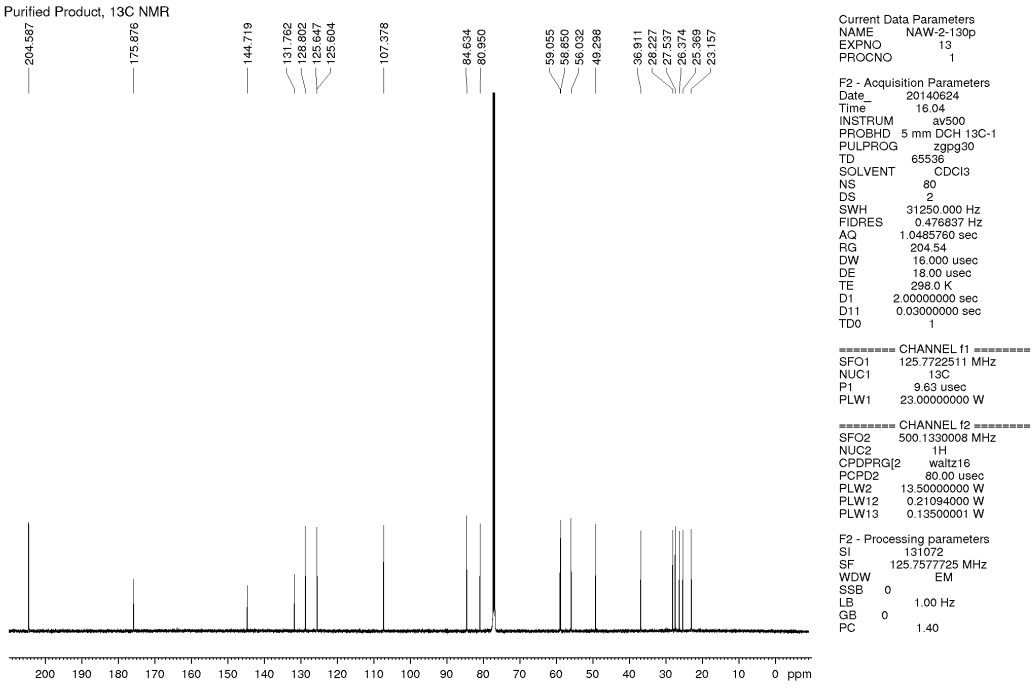


Figure A3.19 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4.18**.

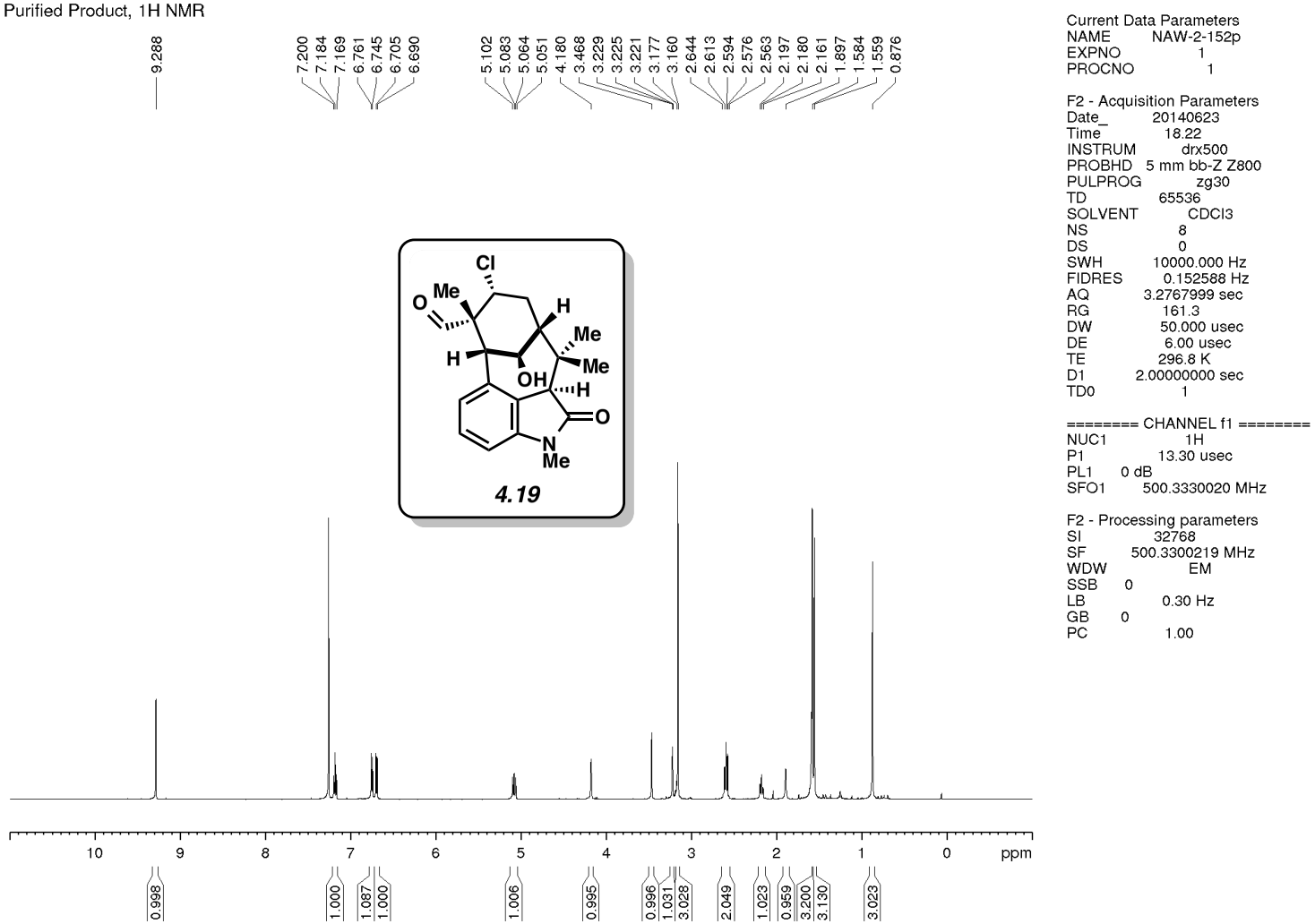


Figure A3.20 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.19**.

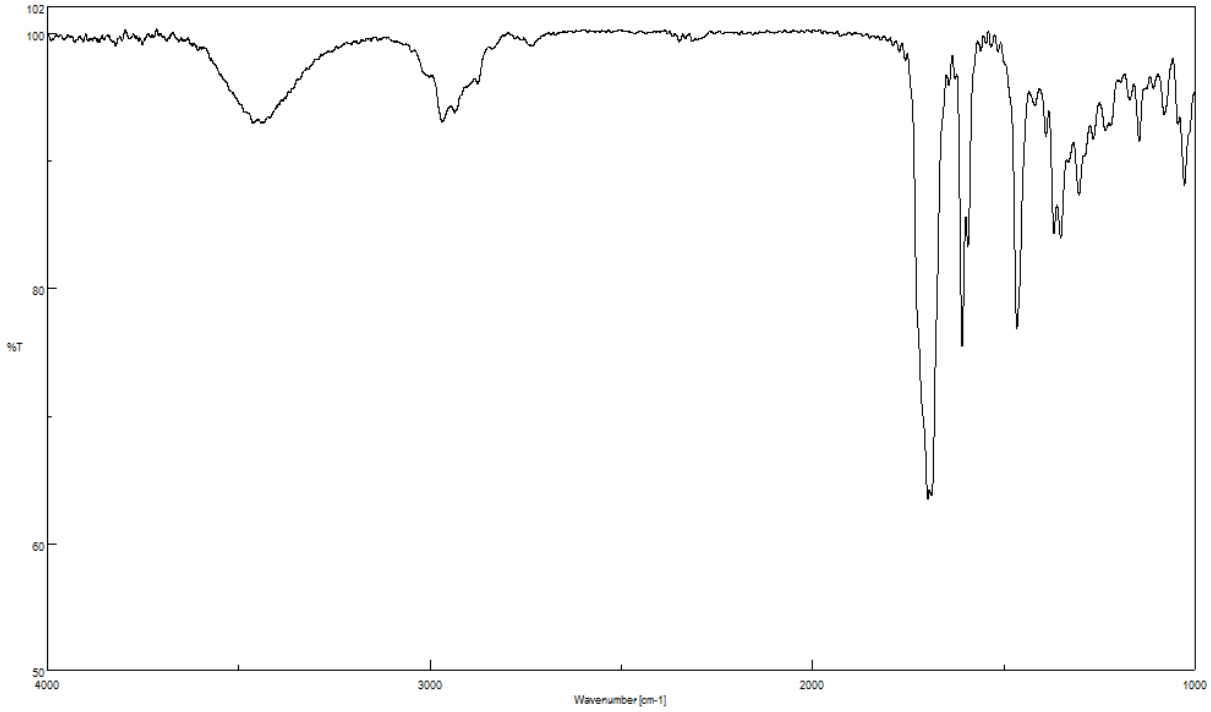


Figure A3.21 Infrared spectrum of compound **4.19**.

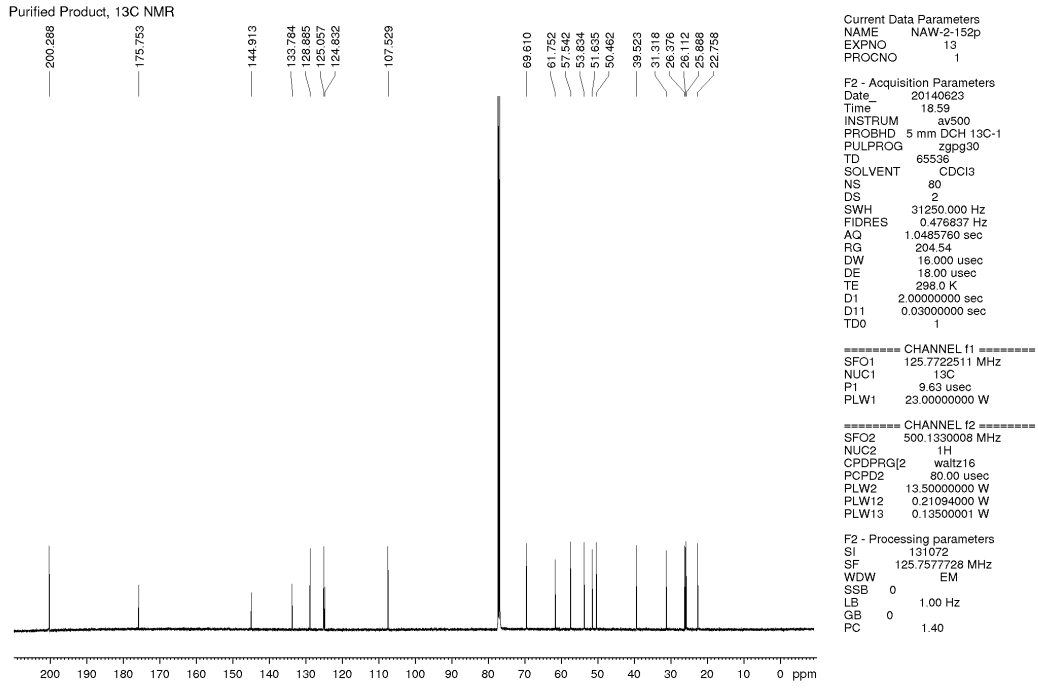


Figure A3.22 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4.19**.

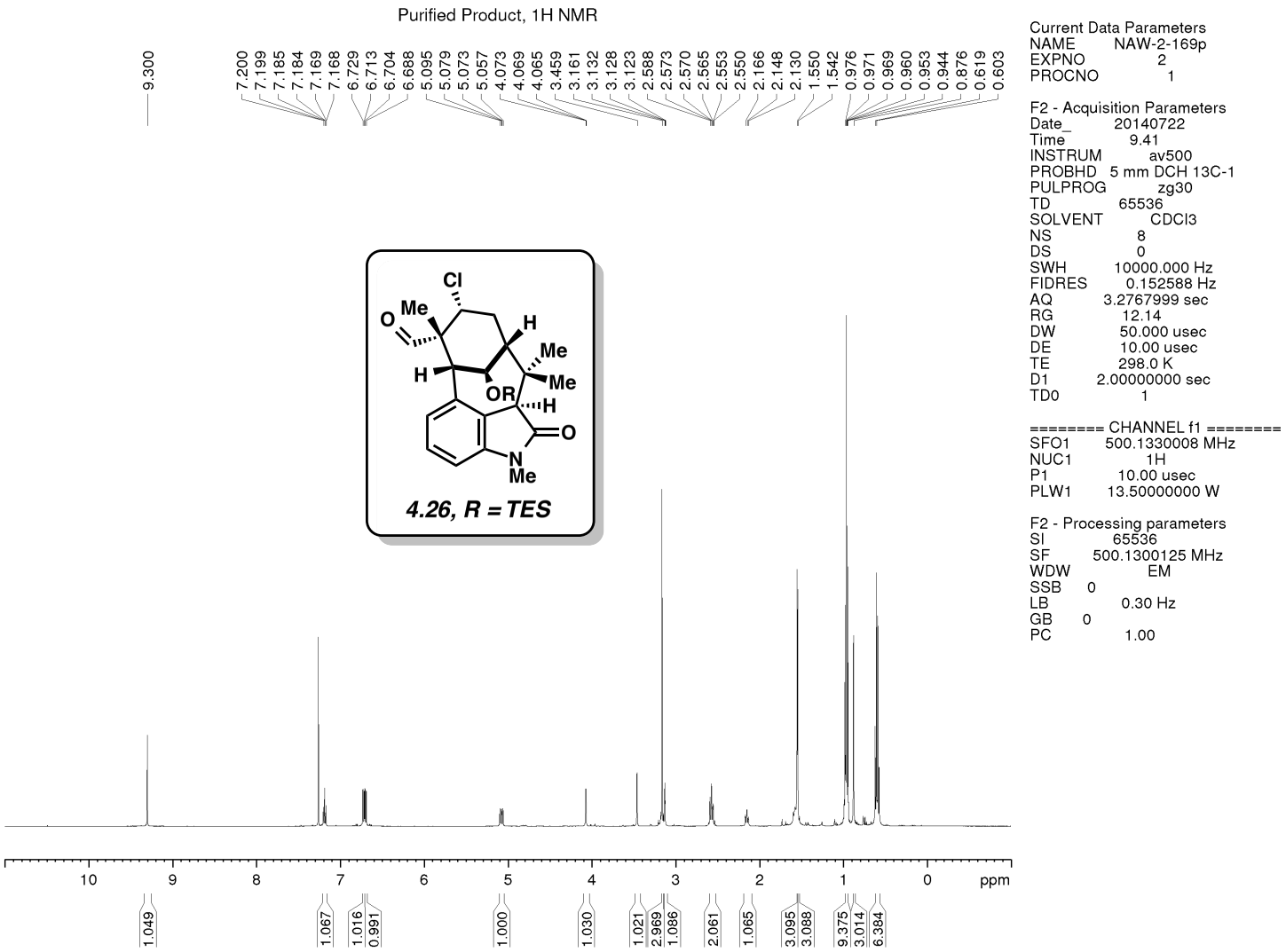


Figure A3.23 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.26**.

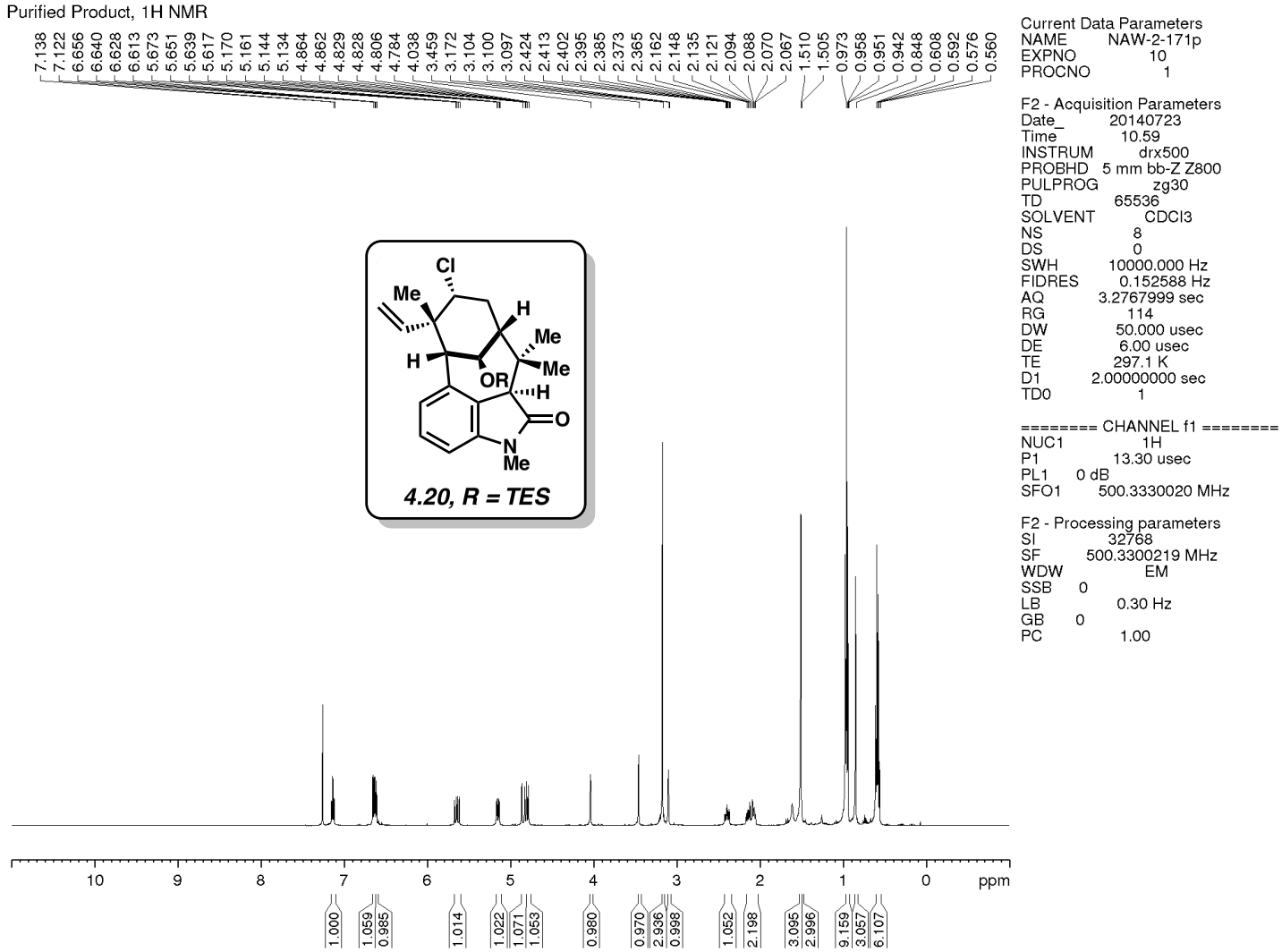


Figure A3.24 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.20**.

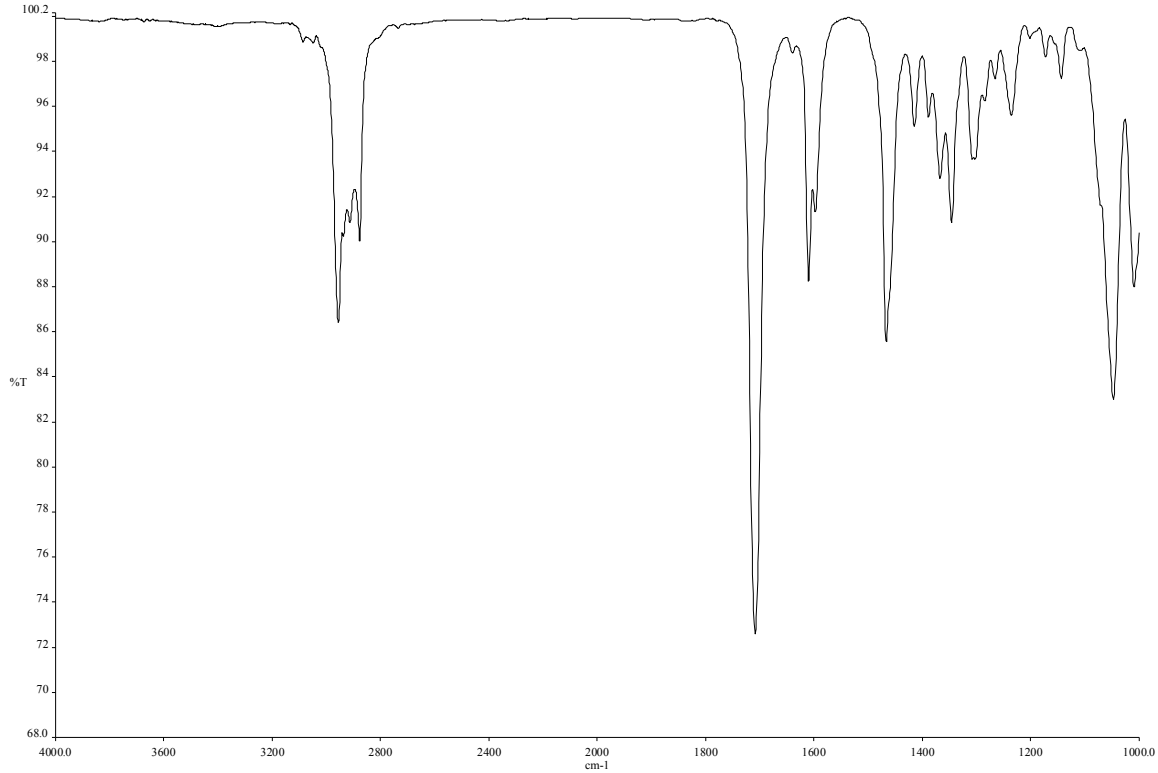


Figure A3.25 Infrared spectrum of compound **4.20**.

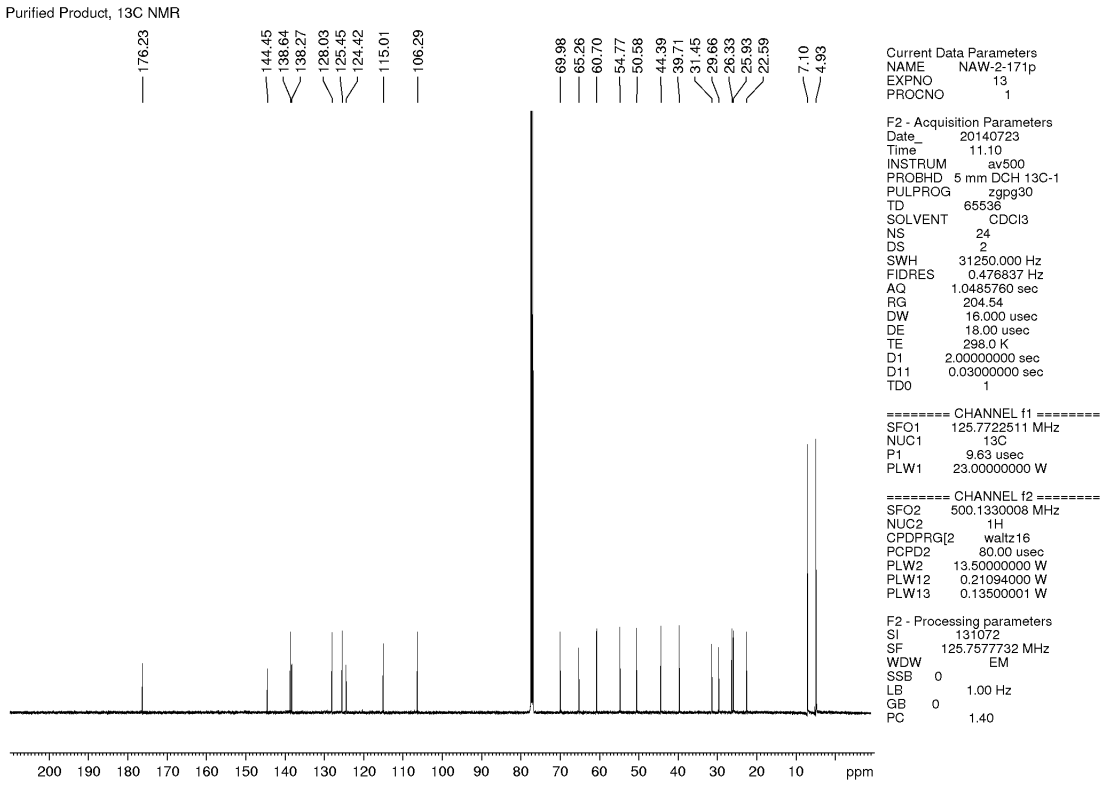


Figure A3.26 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4.20**.

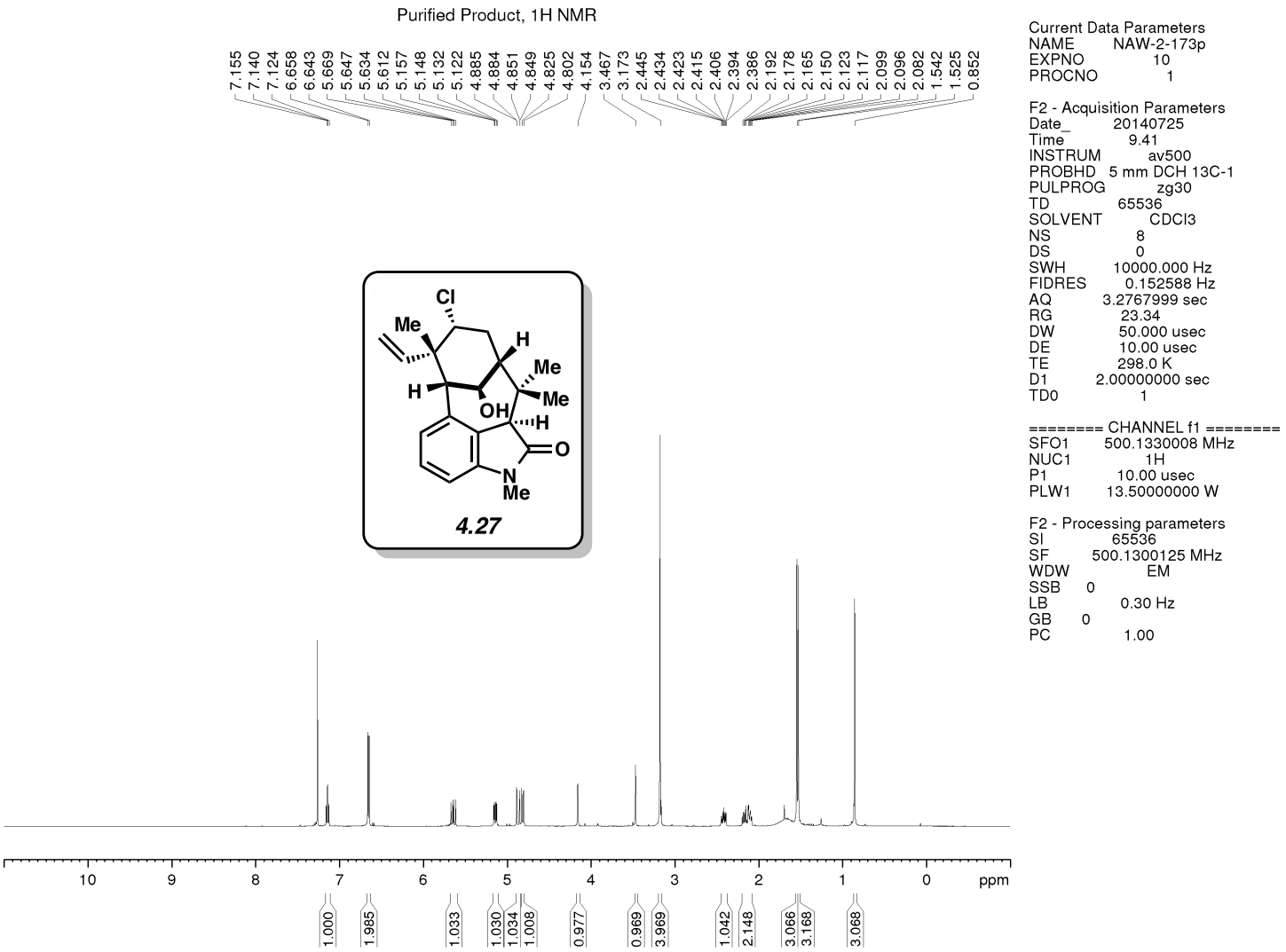


Figure A3.27 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.27**.

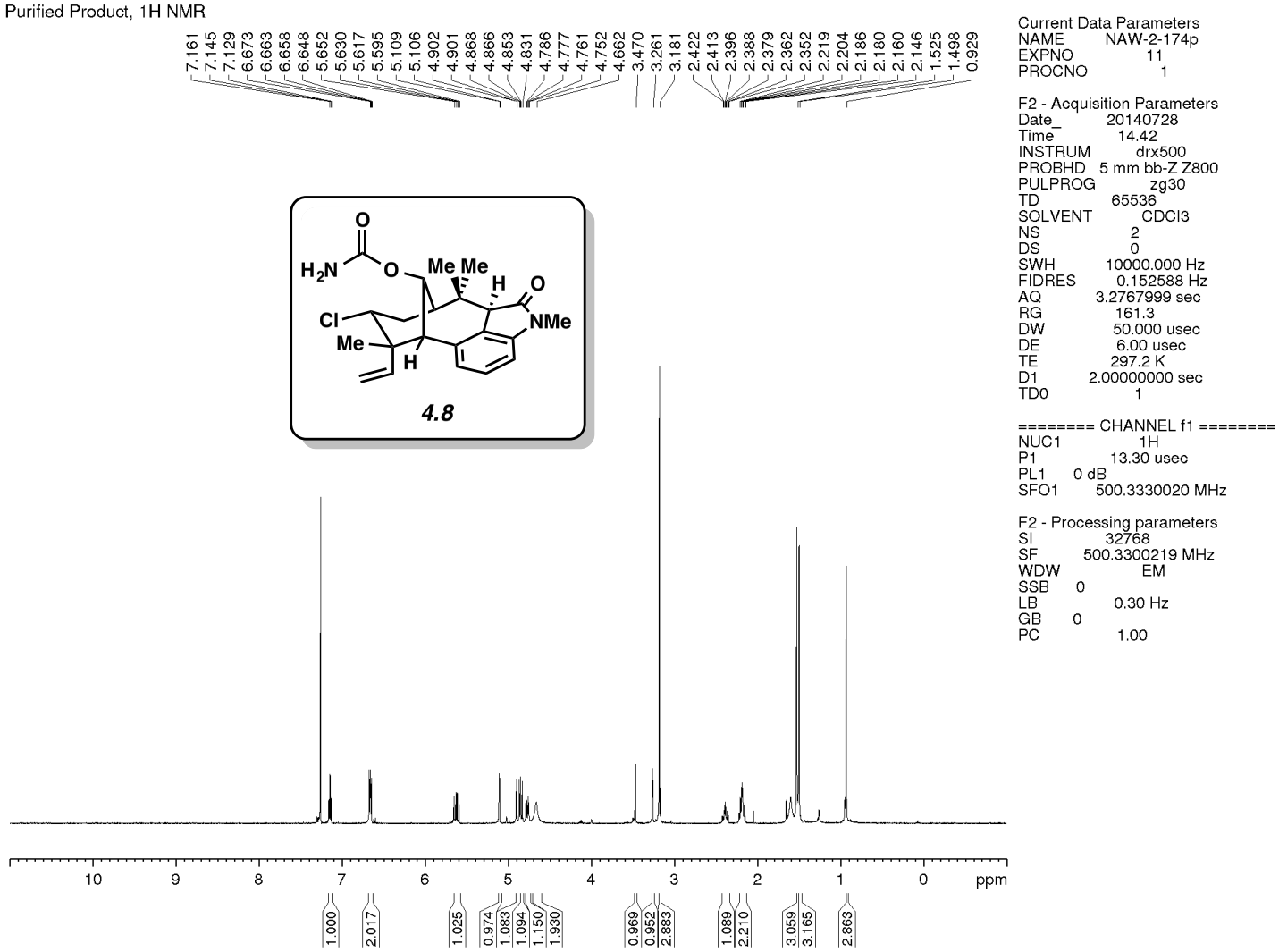


Figure A3.28 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.8**.

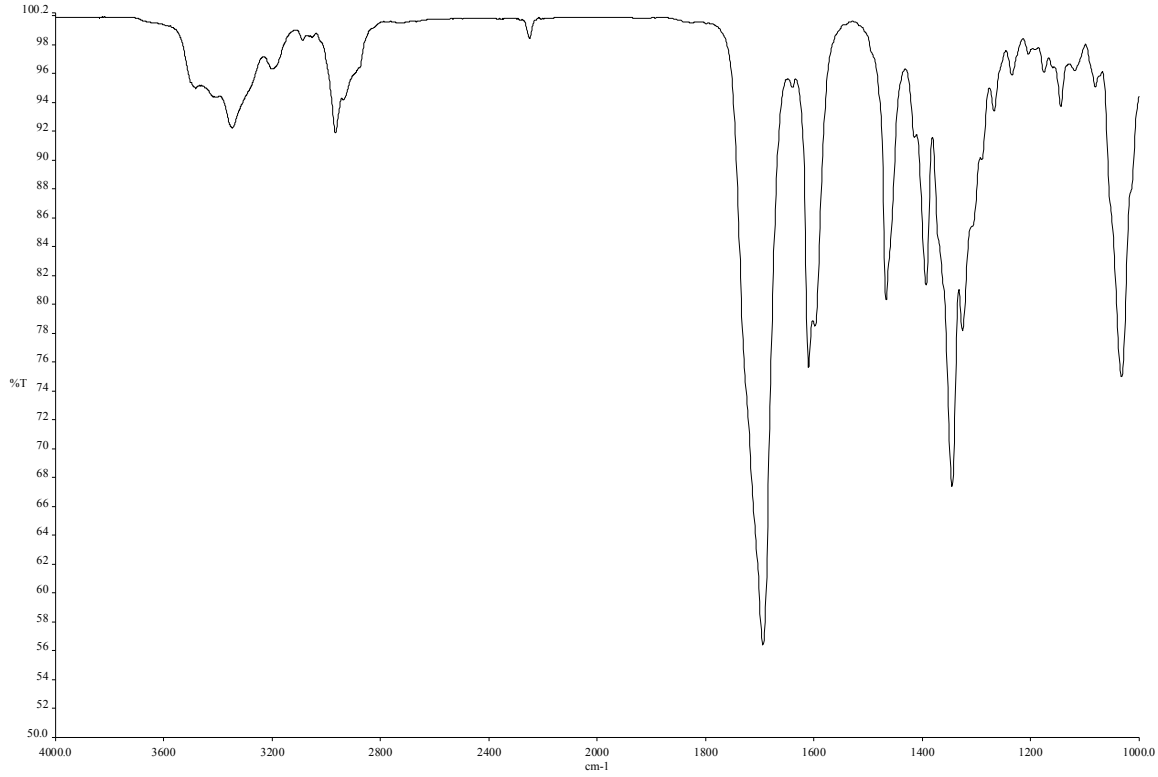


Figure A3.29 Infrared spectrum of compound **4.8**.

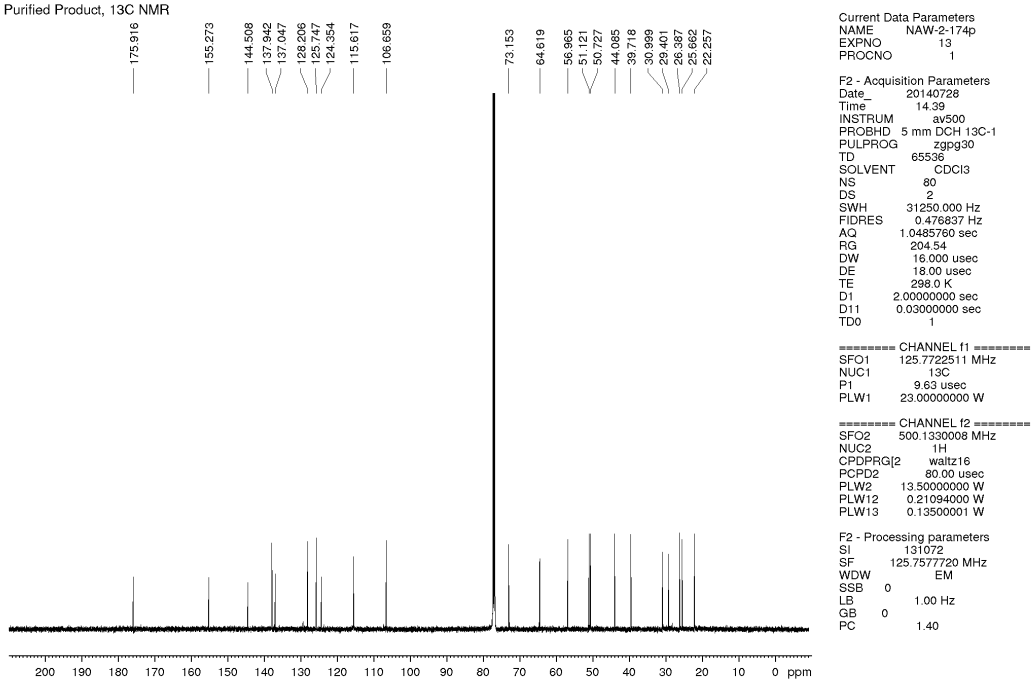


Figure A3.30 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4.8**.

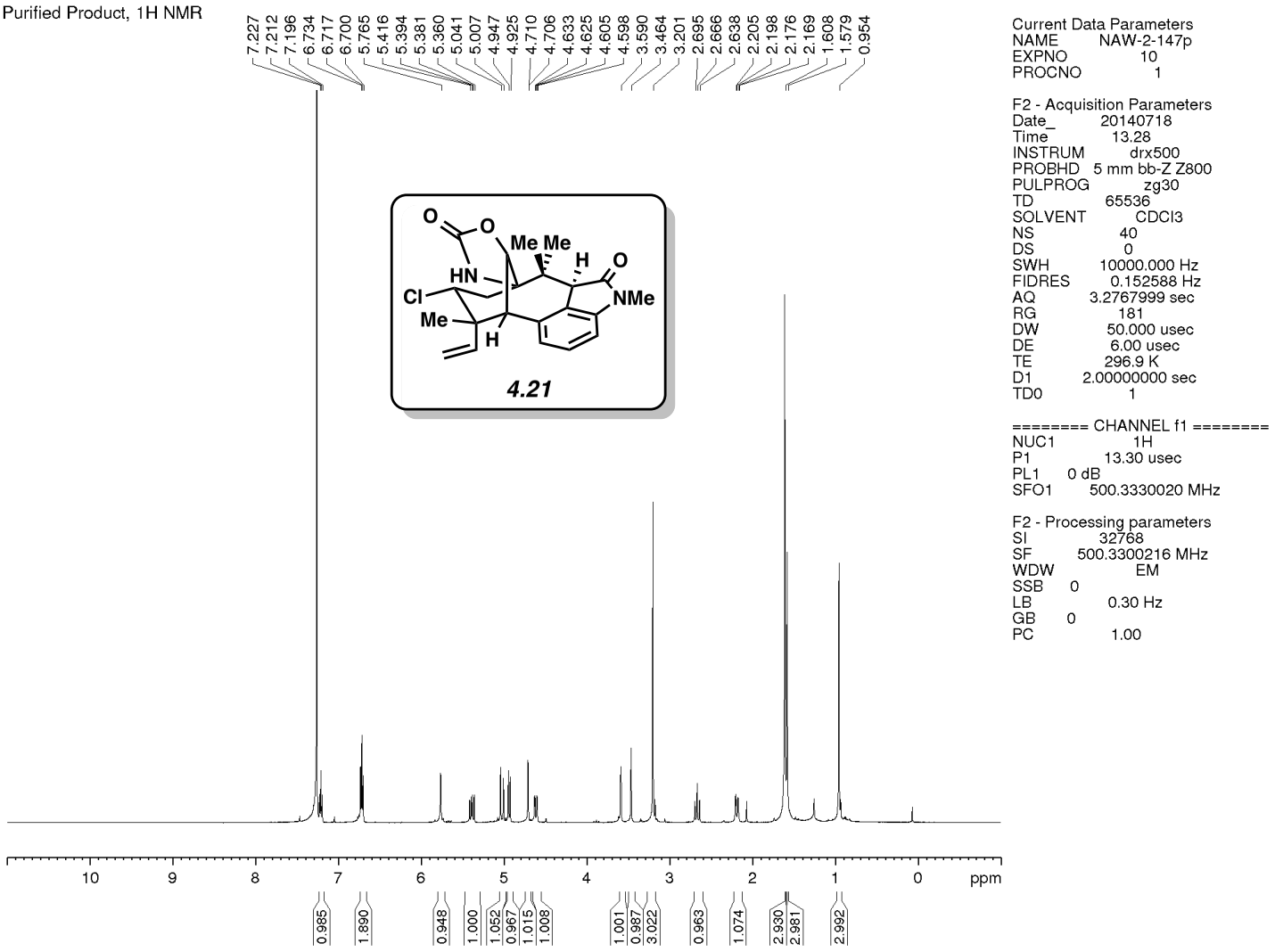


Figure A3.31 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.21**.

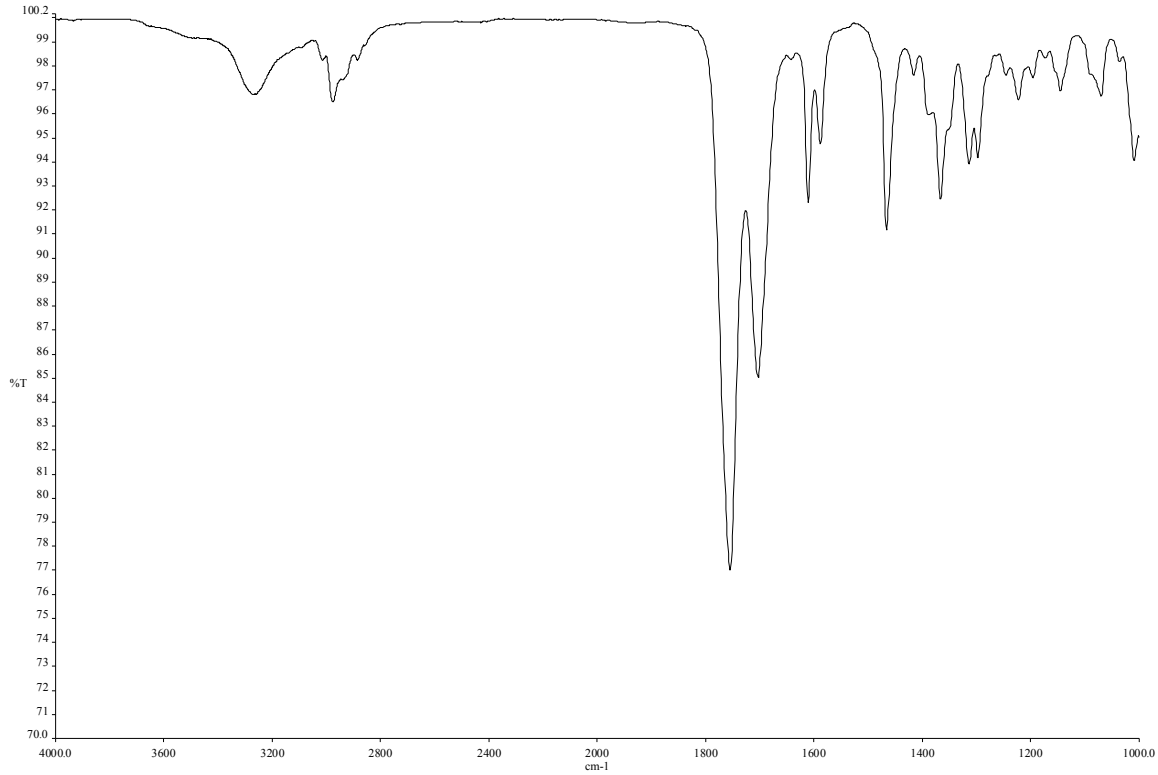


Figure A3.32 Infrared spectrum of compound **4.21**.

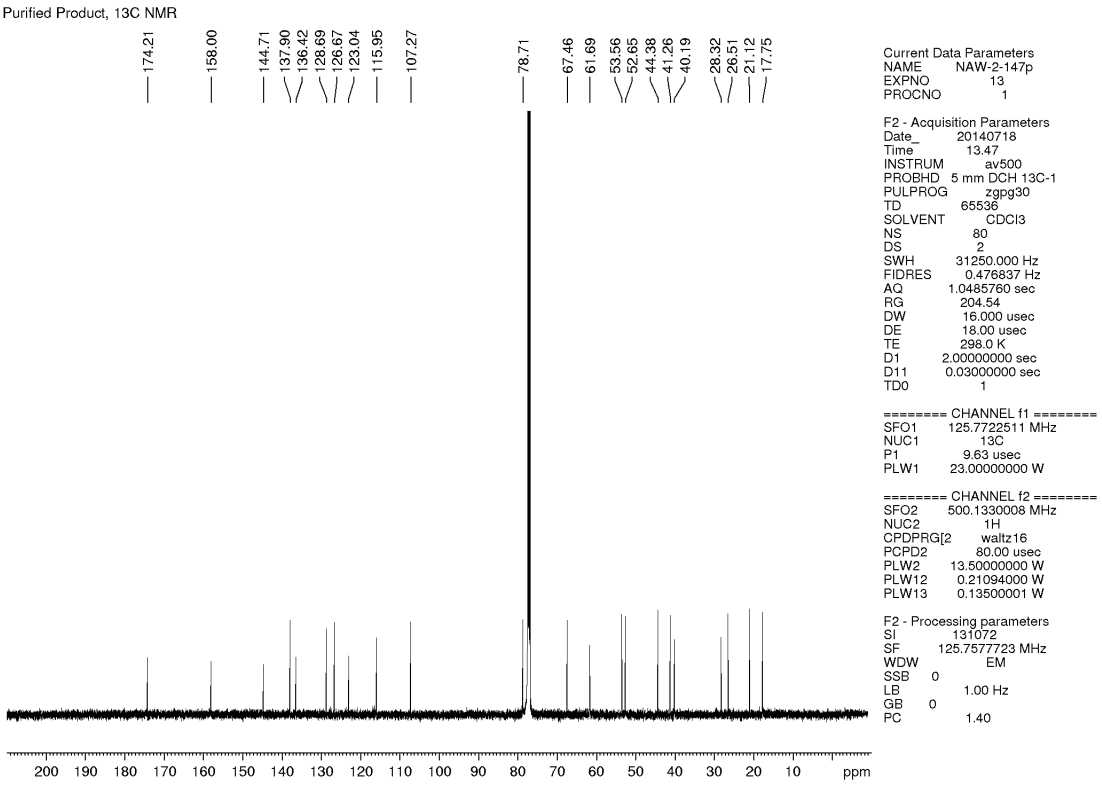


Figure A3.33 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4.21**.

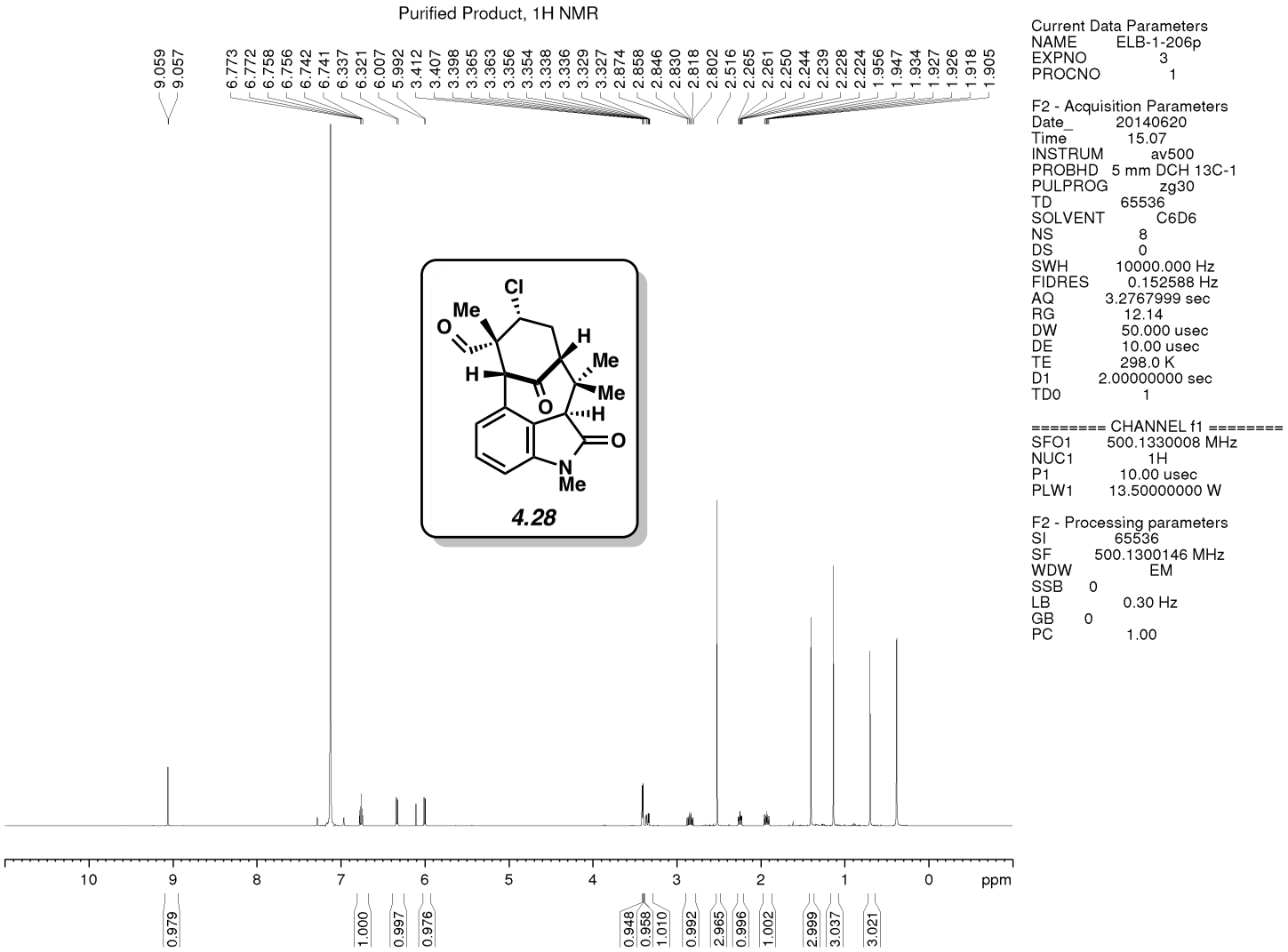


Figure A3.34 ^{1}H NMR (500 MHz, C_6D_6) of compound **4.28**.

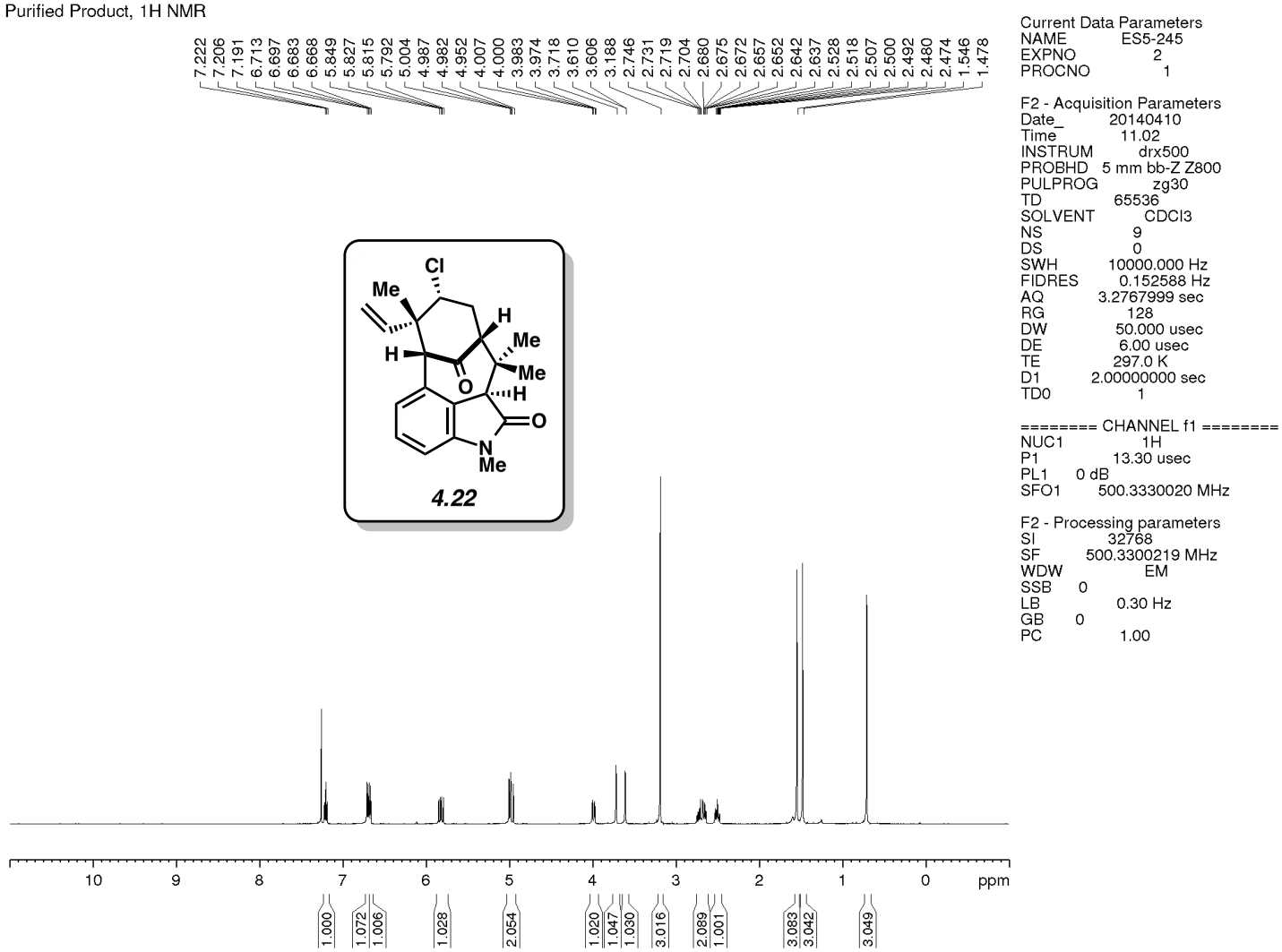


Figure A3.35 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.22**.

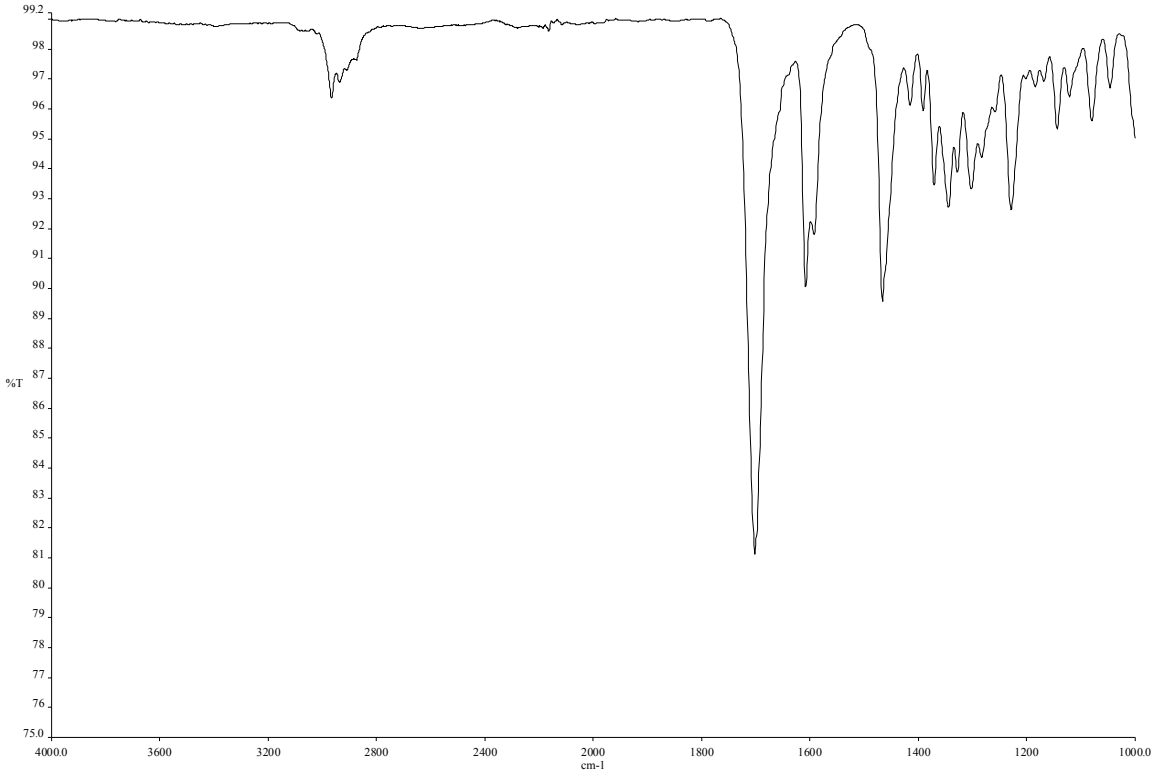


Figure A3.36 Infrared spectrum of compound **4.22**.

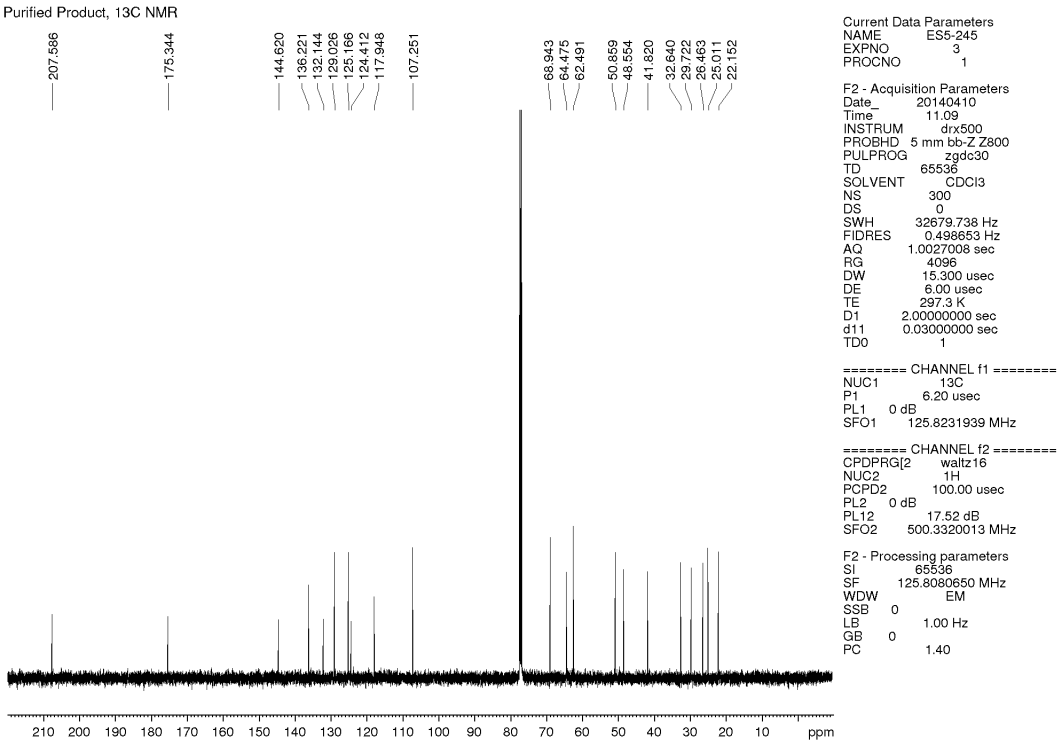


Figure A3.37 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4.22**.

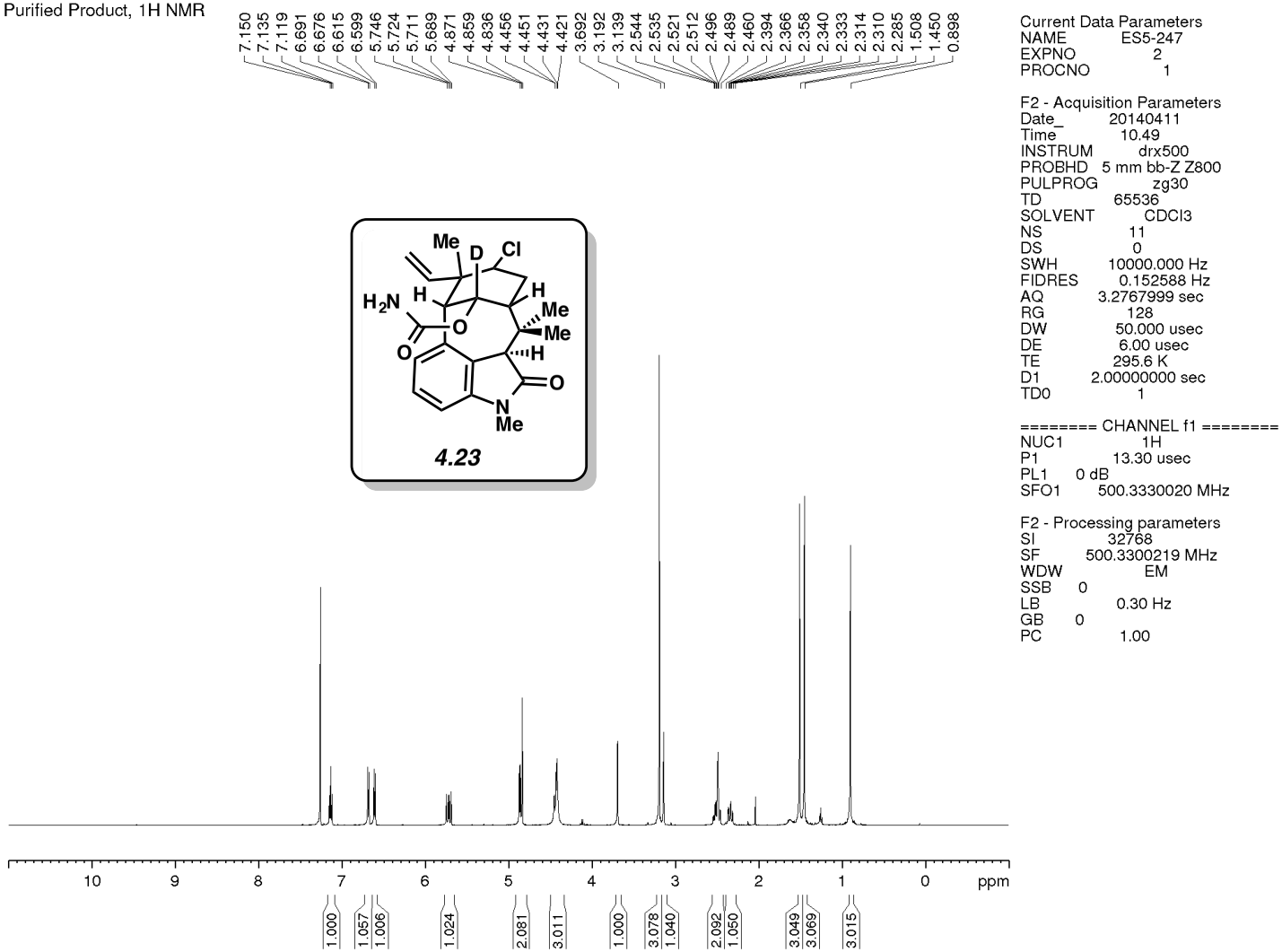


Figure A3.38 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.23**.

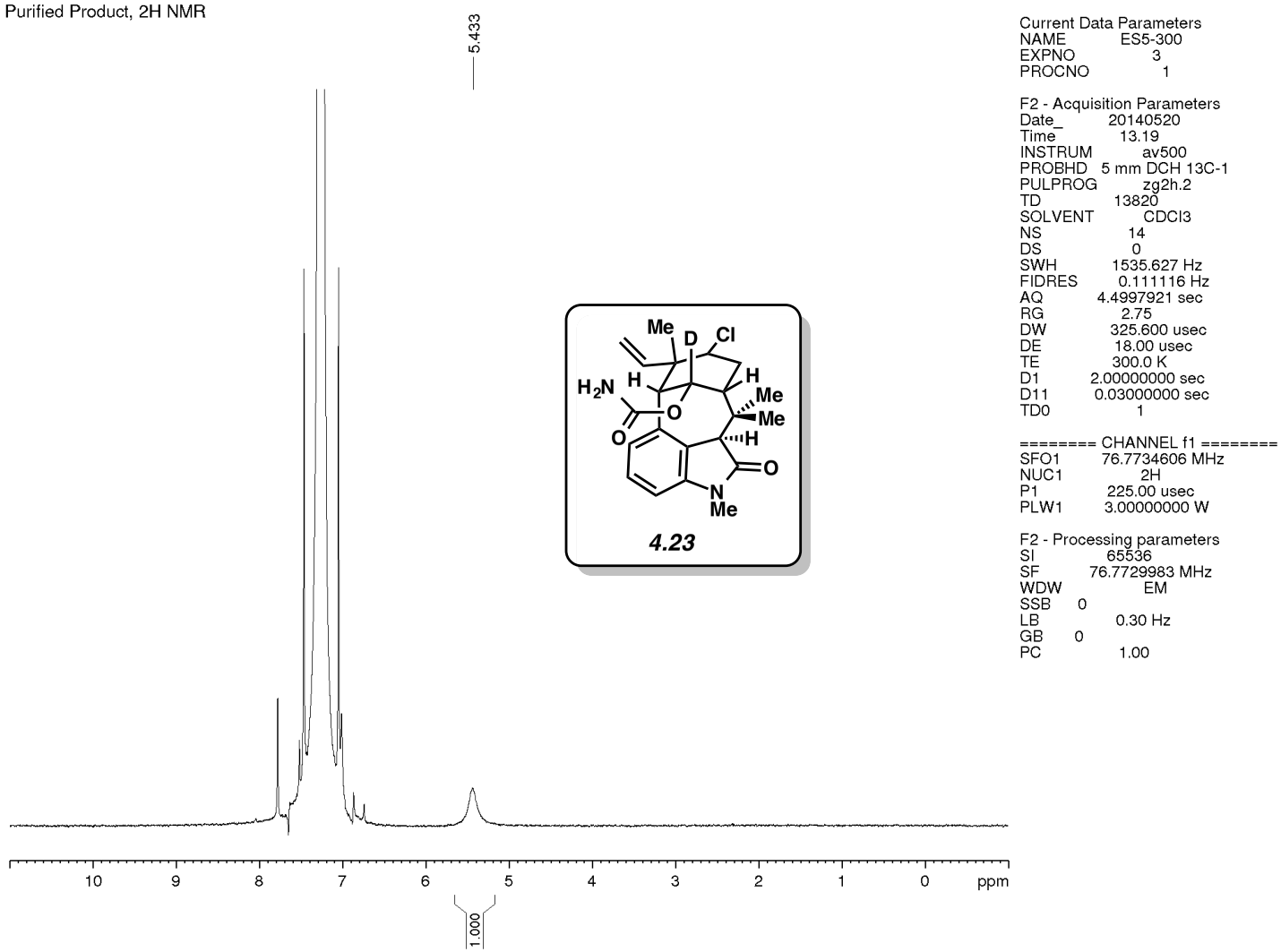


Figure A3.39 ^{2}H NMR (77 MHz, $CDCl_3$) of compound **4.23**.

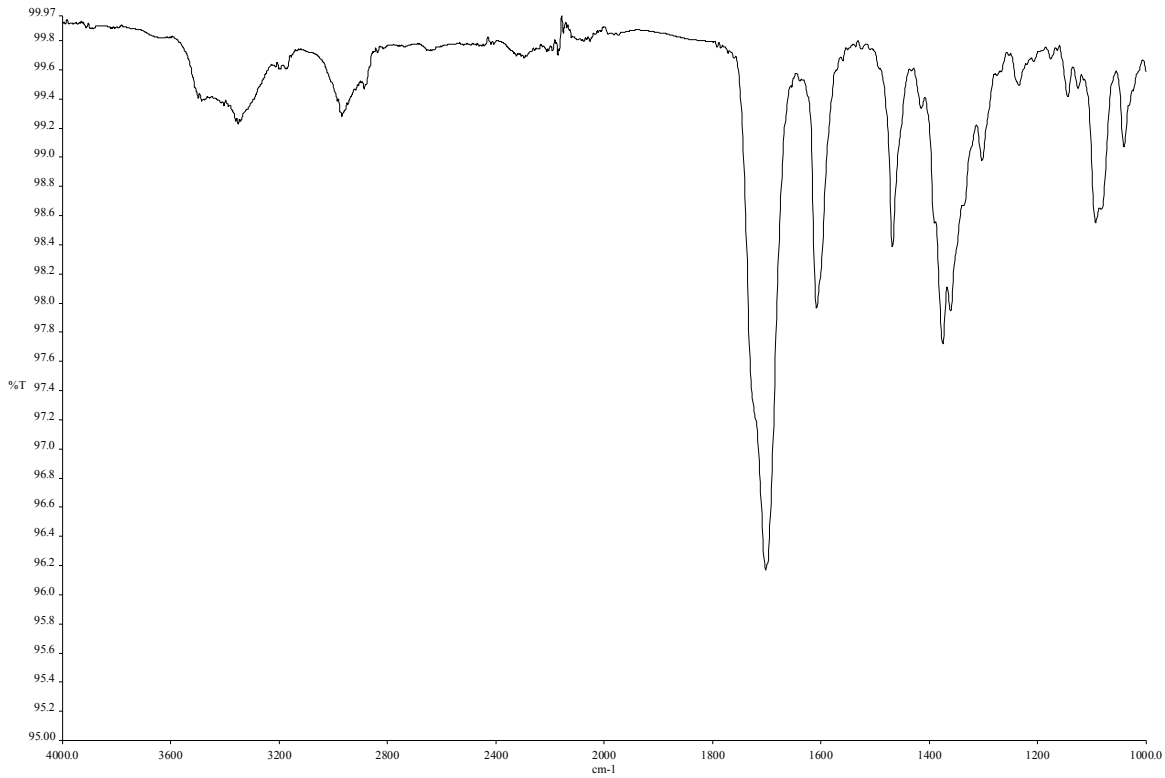


Figure A3.40 Infrared spectrum of compound **4.23**.

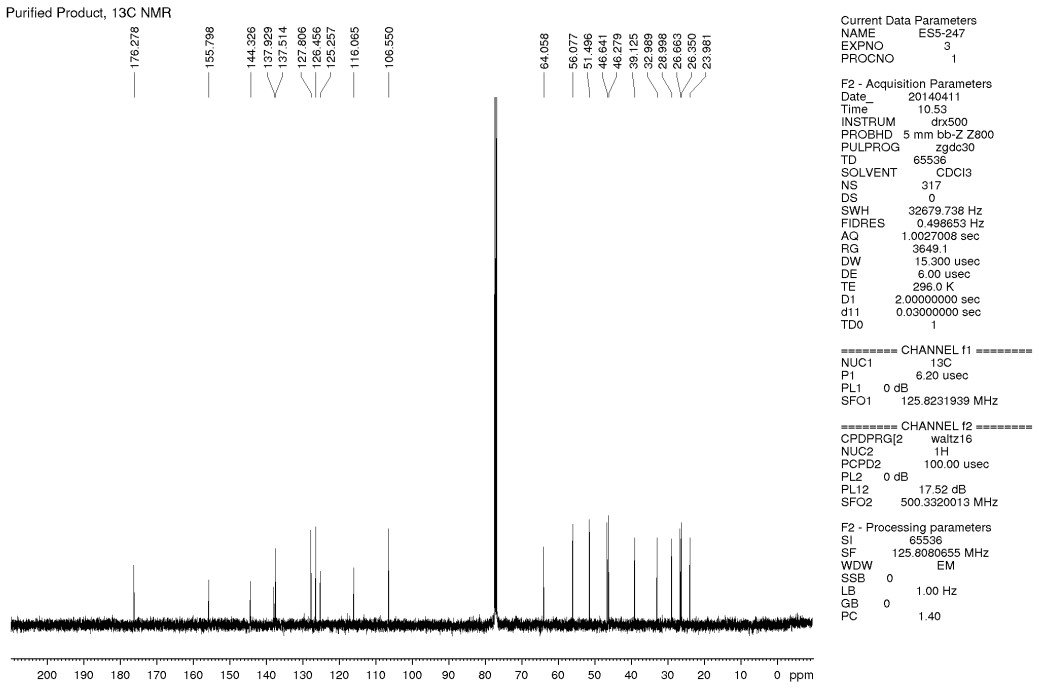


Figure A3.41 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4.23**.

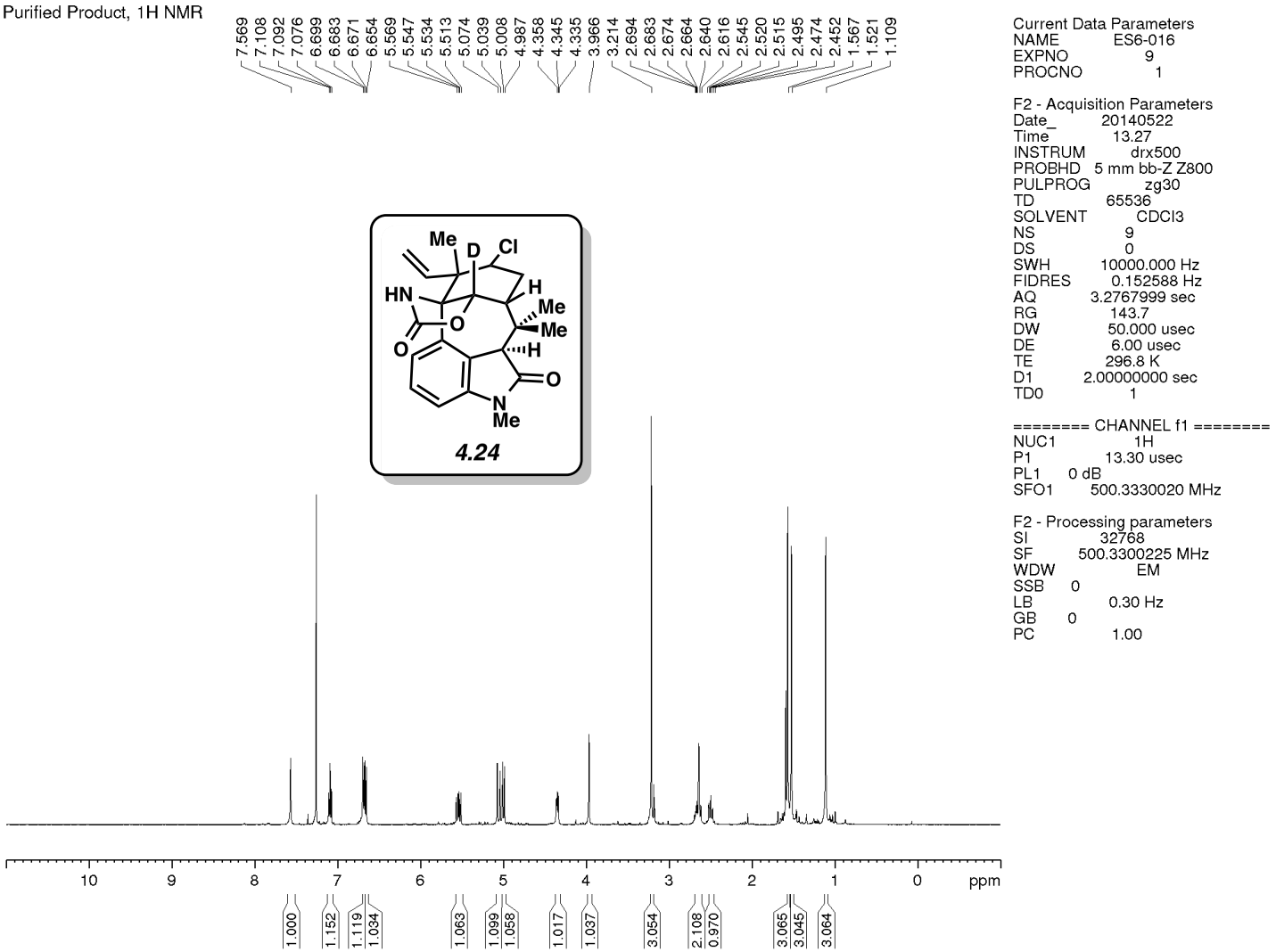


Figure A3.42 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.24**.

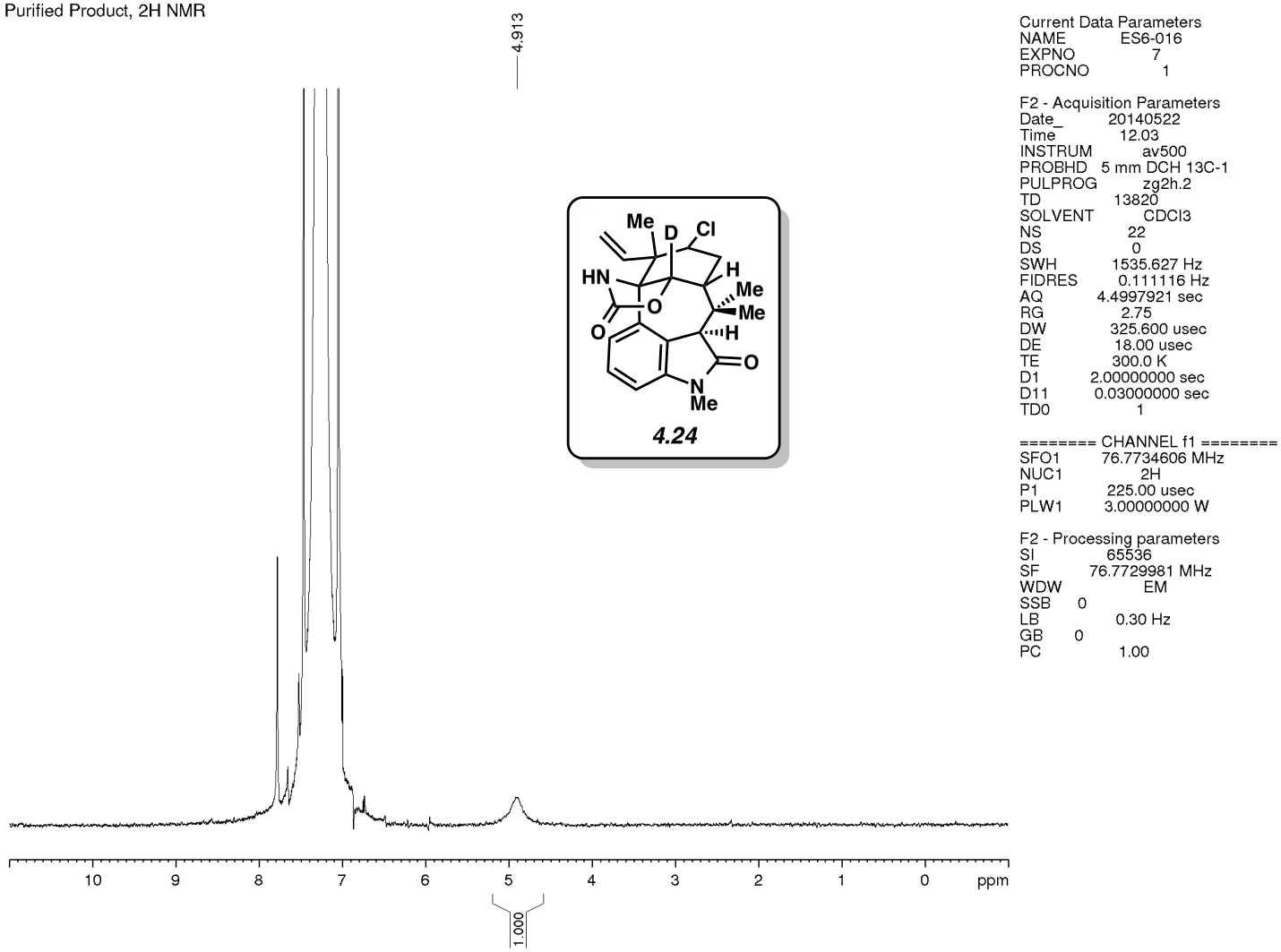


Figure A3.43 ^{2}H NMR (77 MHz, $CDCl_3$) of compound **4.24**.

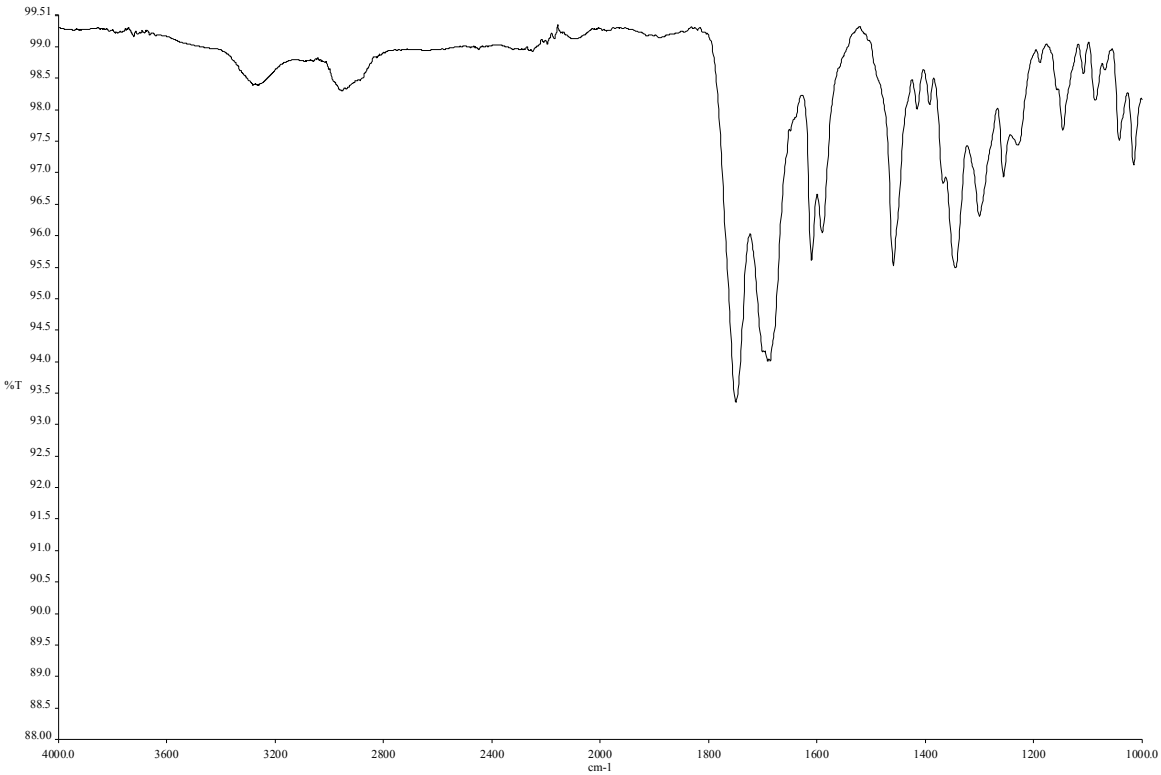


Figure A3.44 Infrared spectrum of compound **4.24**.

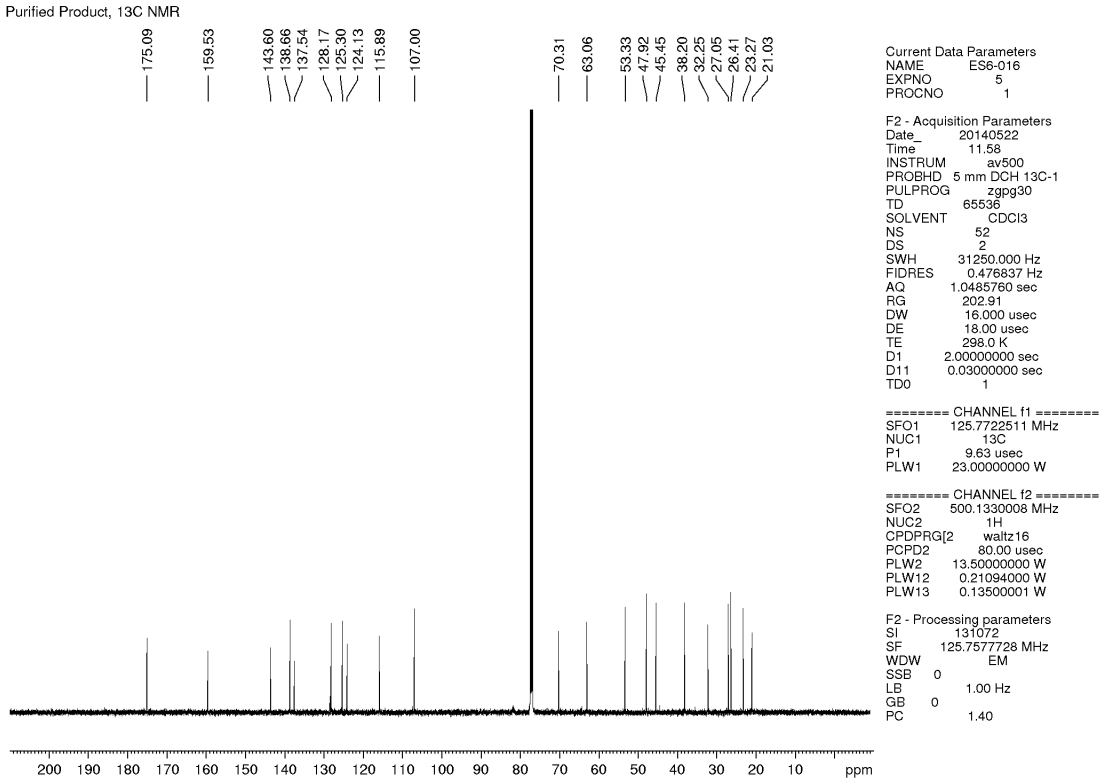


Figure A3.45 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4.24**.

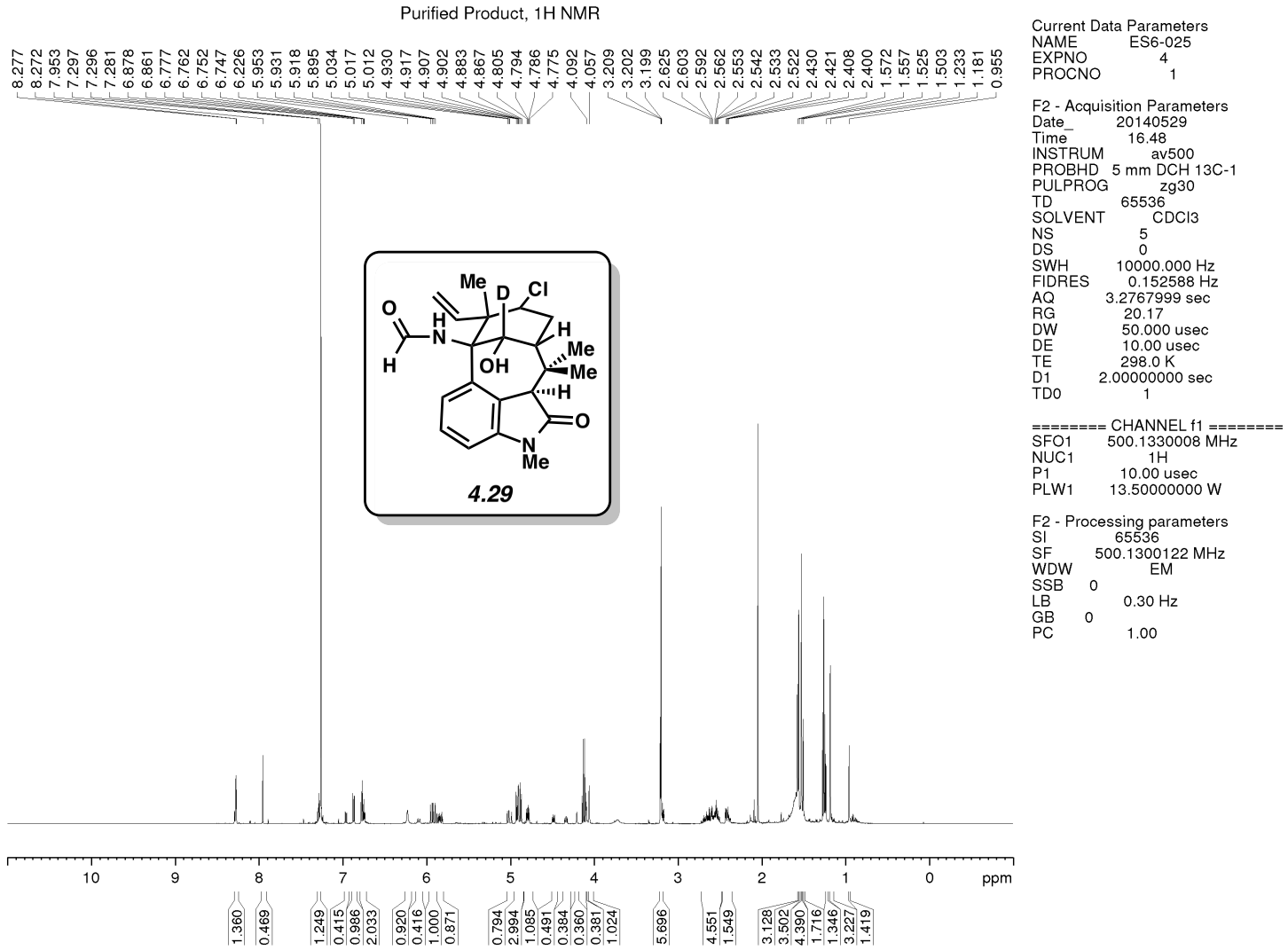


Figure A3.46 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.29**.

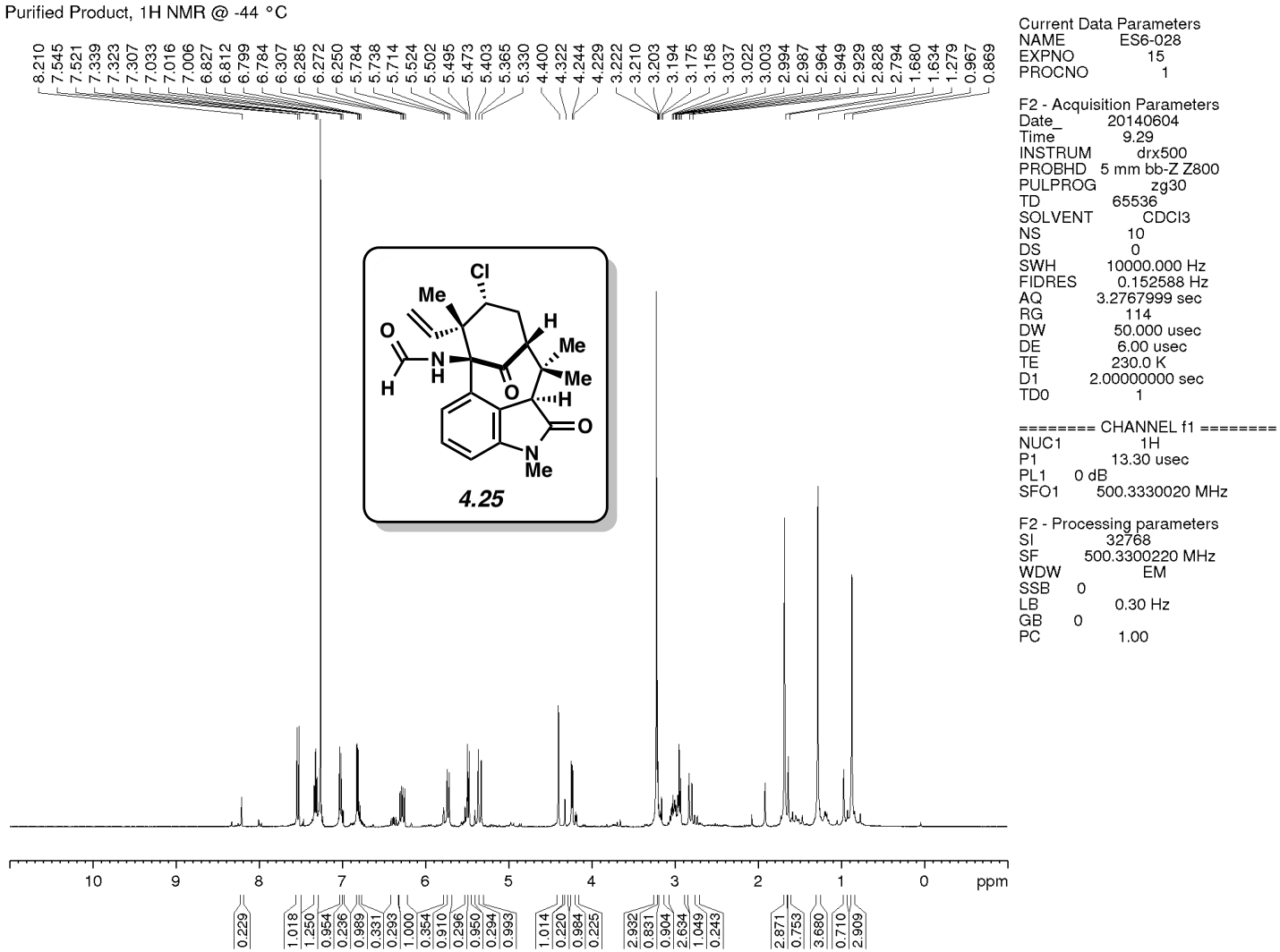


Figure A3.47 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.25**.

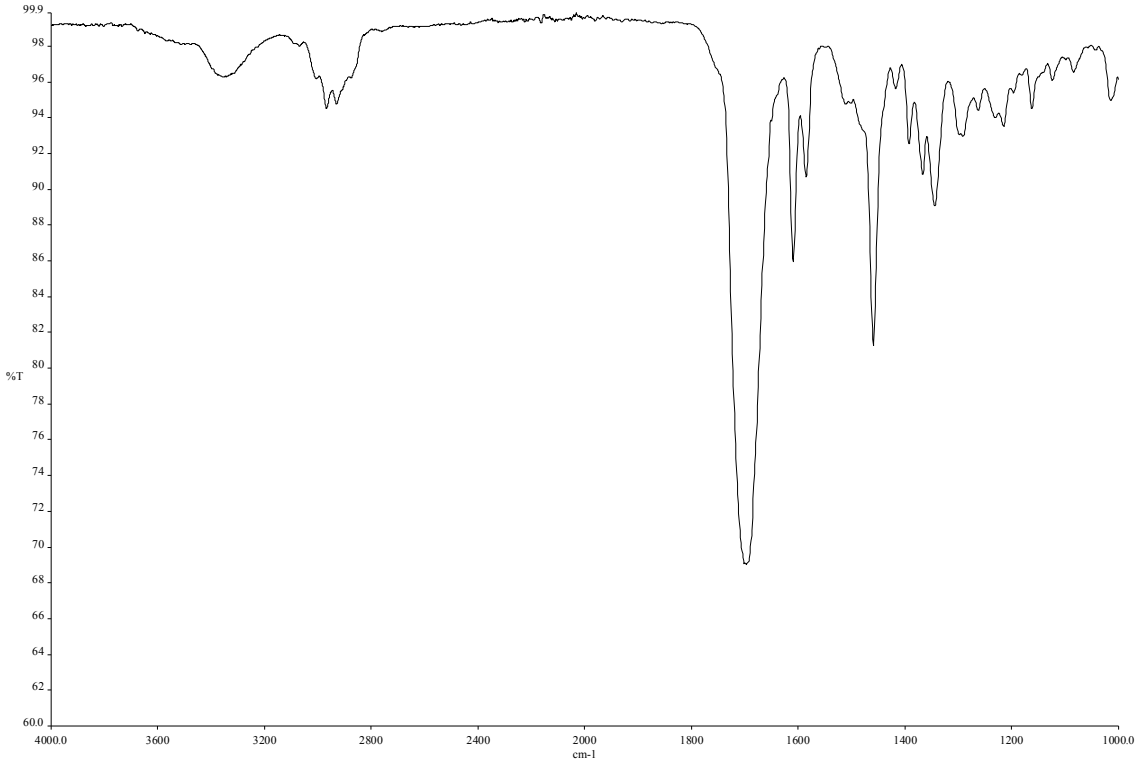


Figure A3.48 Infrared spectrum of compound **4.25**.

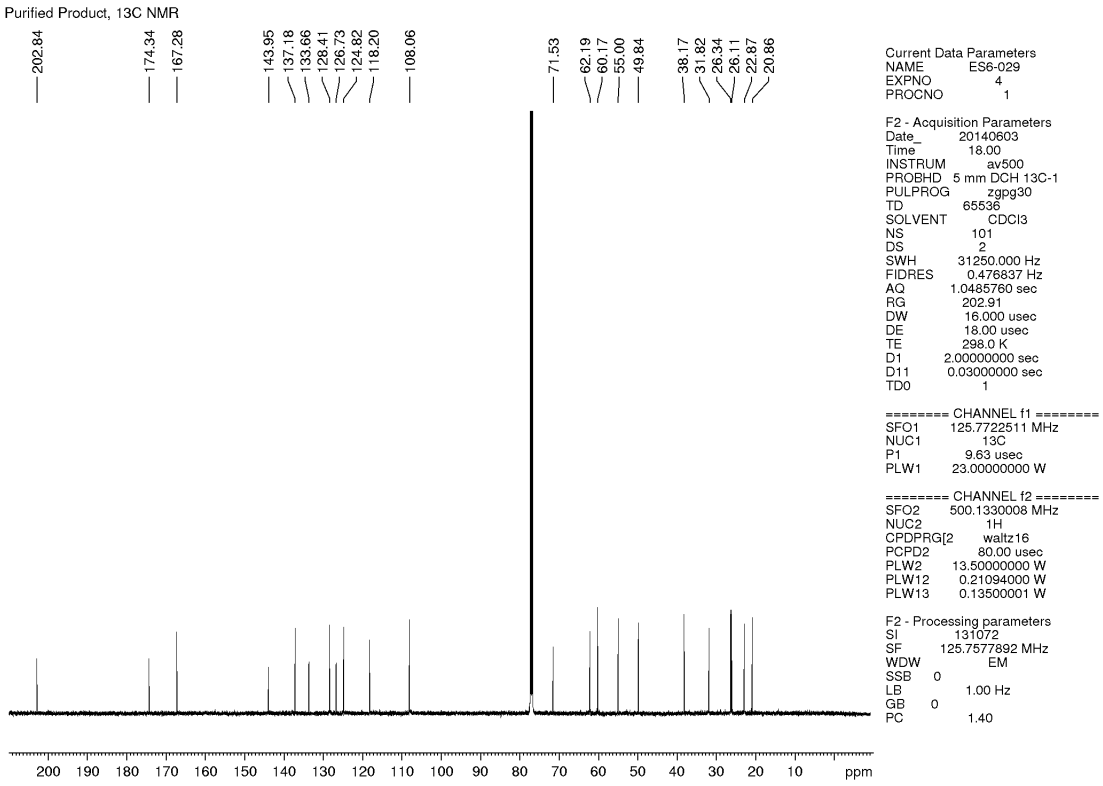


Figure A3.49 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4.25**.

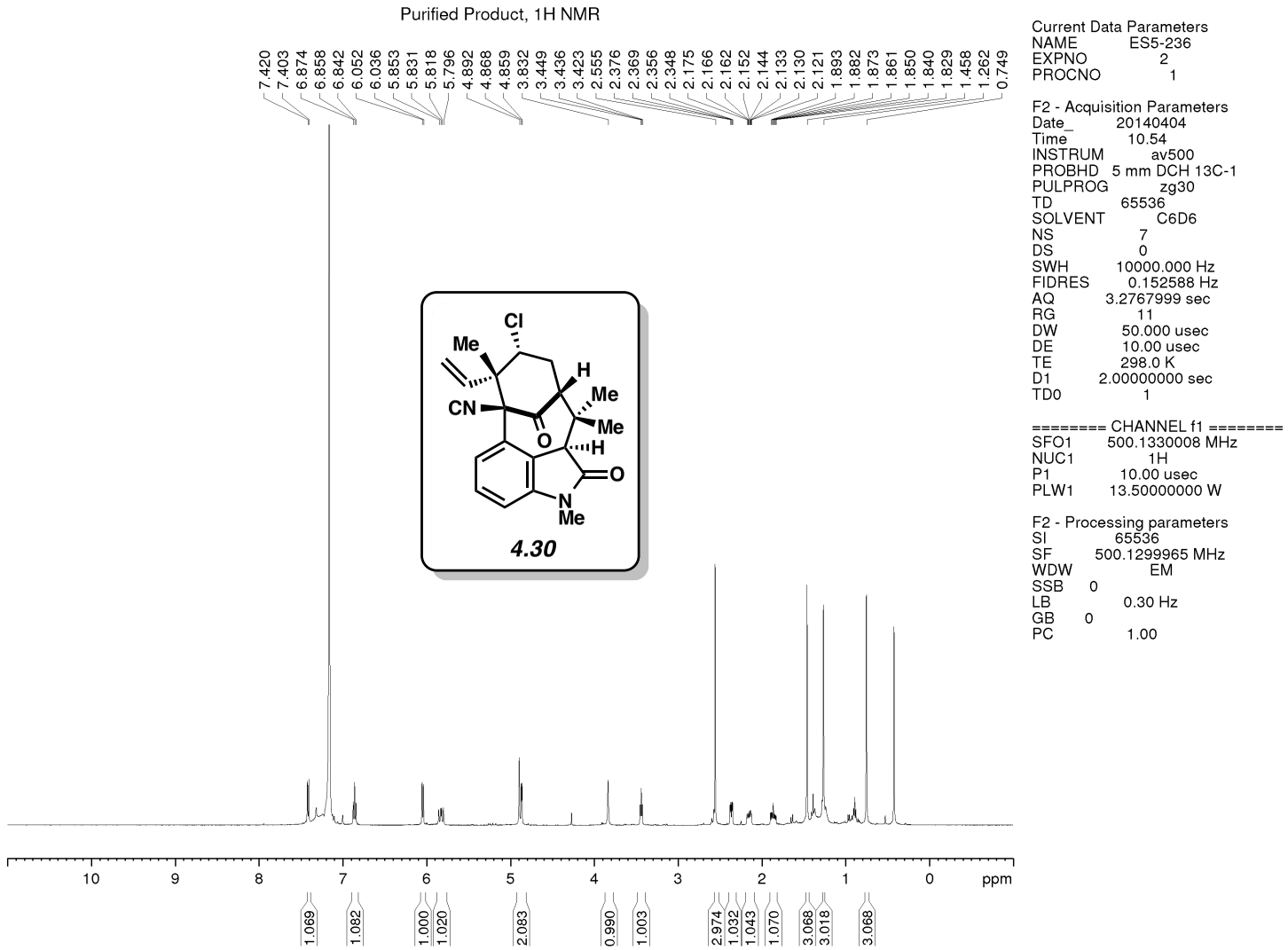


Figure A3.50 ^{1}H NMR (500 MHz, C_6D_6) of compound **4.30**.

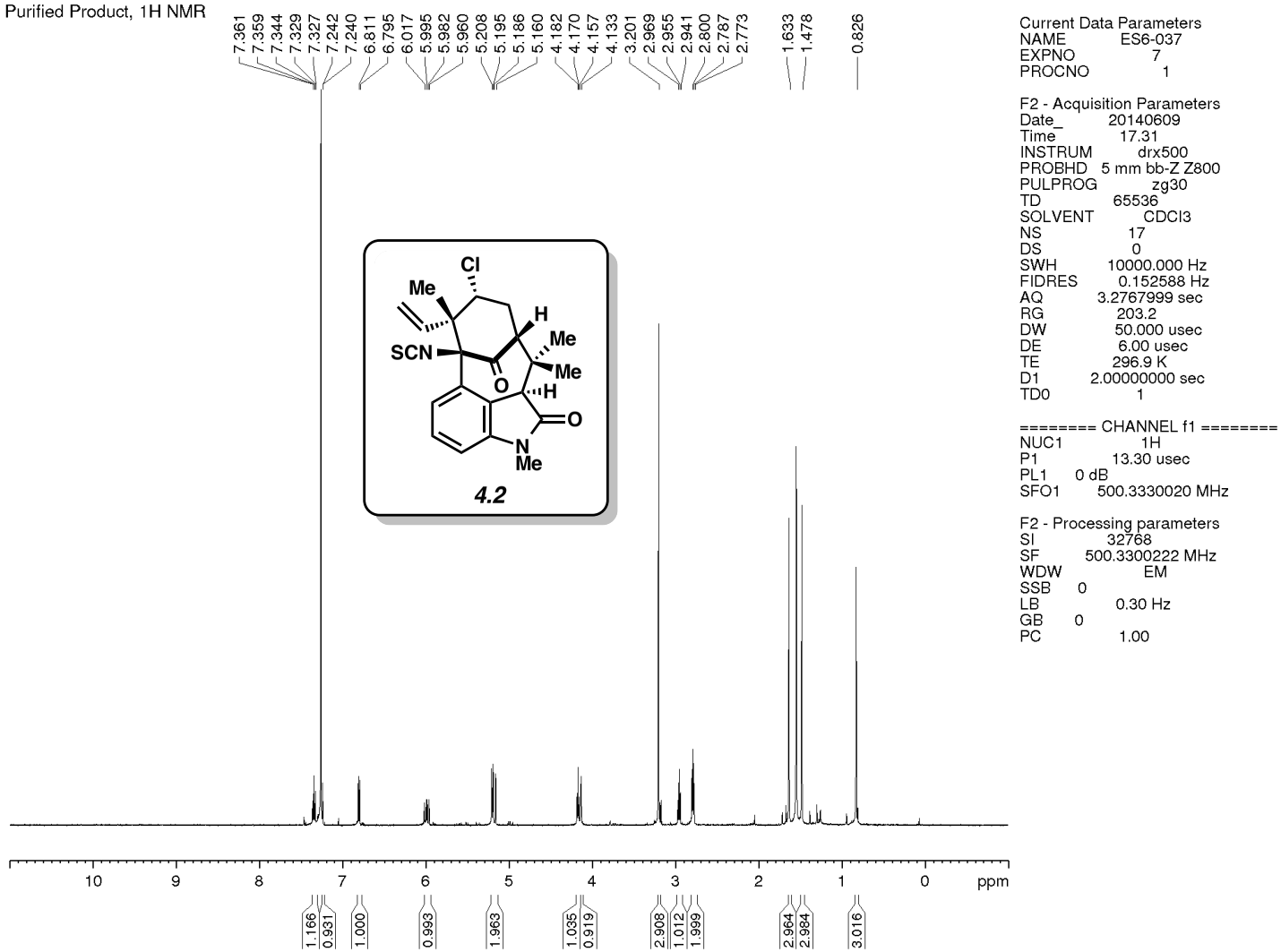


Figure A3.51 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.2**.

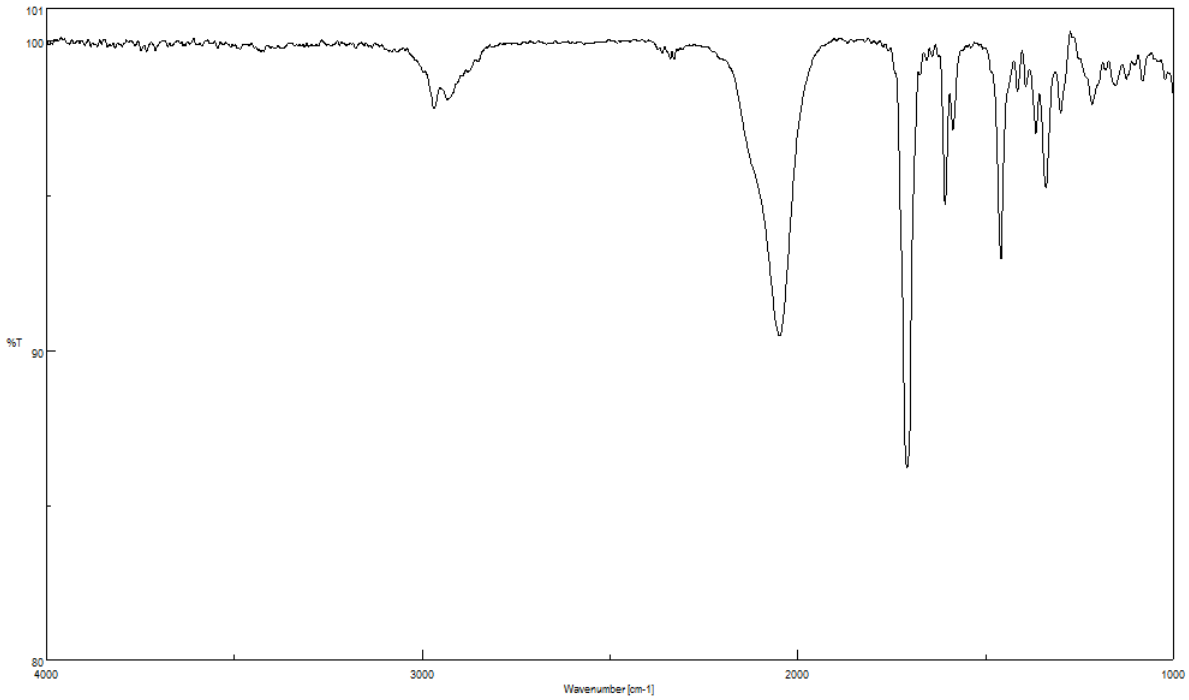


Figure A3.52 Infrared spectrum of compound **4.2**.

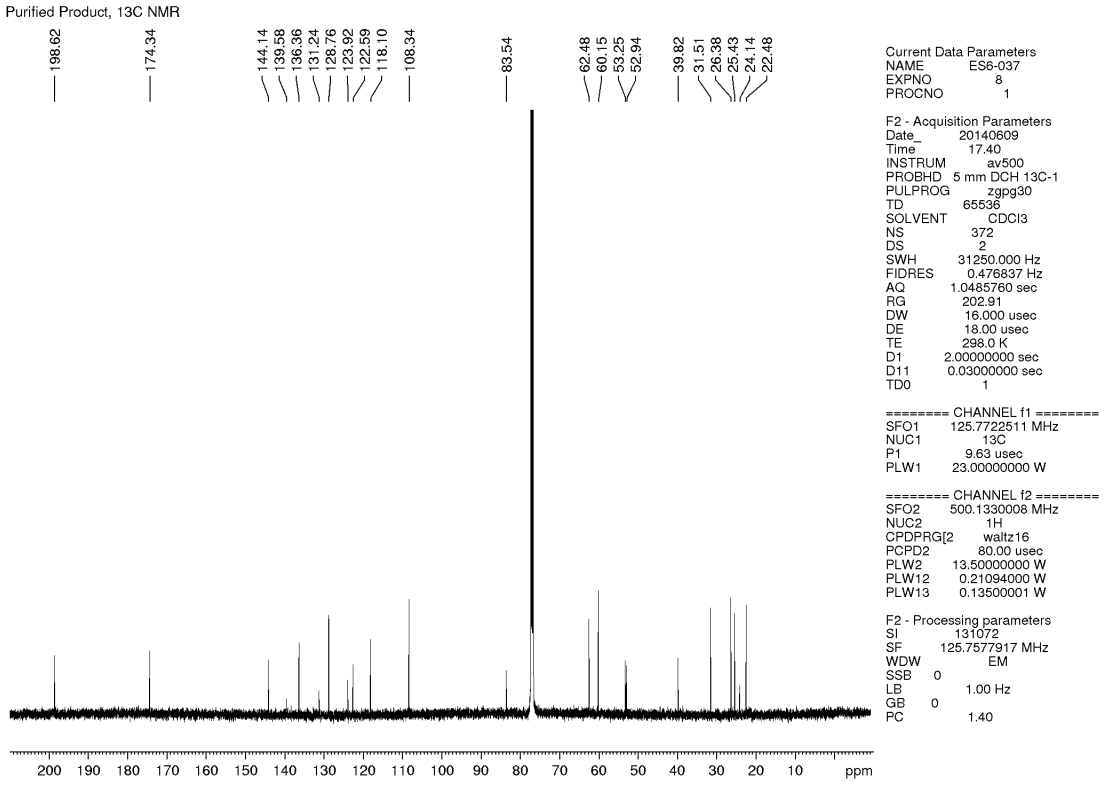


Figure A3.53 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4.2**.