STUDIES TOWARD THE
TOTAL SYNTHESIS OF XESTOCYCLAMINE A

By

Quinn Anderson Bumpers

Dissertation

Submitted to the Faculty of the

Graduate School of Vanderbilt University

in partial fulfillment of the requirements

for the degree of

DOCTOR OF PHILOSOPHY

in

Chemistry

June 30, 2021

Nashville, Tennessee

Approved:

Gary A. Sulikowski, Ph.D.

Craig W. Lindsley, Ph.D.

Steven D. Townsend, Ph.D.

Nathan D. Schley, Ph.D.

“Fanaticism consists in redoubling your efforts when you have forgotten your aim”

- *George Santayana*

ACKNOWLEDGEMENTS

I am thankful to my advisor Dr. Gary Sulikowski for his guidance and assistance throughout my graduate career. His expertise and knowledge of organic chemistry has inspired me from day one to pursue my education to its fullest. I am grateful for the freedom and support he has provided for me over the last six years.

I am grateful to my committee members Dr. Craig Lindsley, Dr. Nathan Schley, and Dr. Steven Townsend for their time invested in my education whether through didactic classes, committee meetings, or casual conversations. Furthermore, their mentorship within their own groups has produced excellent scientists whom I've had the pleasure of discussing and learning chemistry with.

Moreover, there are many current and former Sulikowski group members I would like to thank. Firstly, from very early on Dr. Katherine Chong and Dr. Robert Davis's mentorship taught me the type of scientist and person I wanted to become. Working beside Robby was especially rewarding, and I couldn't have asked for a better hoodmate and friend to endure all of graduate school's ups and downs. Next, Dr. Jennifer Benoy and Dr. Christopher Fullenkamp both made working in lab infinitely better and for which I'm grateful to have shared time with. I would like to highlight Dr. Jason Hudlicky, who's resilience, tenacity, and intellect never ceases to impress, and which I continually aim to match one day. Lastly, Alexander Allweil and Zachary Austin have traveled with me farthest down this road toward Ph.D. and now at the end, I am glad it ended with you two.

Outside of the Sulikowski lab, Dr. Daniel Jefferies, Dr. Benjamin Mueller, Dr. Lucas Thal, and Berkley Ellis all made Vanderbilt and Nashville a much happier place to live and who I look forward to many future adventures with! I would like to thank Dr. Donald Stec for assistance in conducting various NMR experiments which proved instrumental in my research. I must acknowledge the Synthesis Core who have shared space, time, and energy with our group and aided in my research and education as well. The BRET office, and specifically Kate Stuart, provided excellent advice, guidance, and critiques throughout my job application process.

Most importantly I would like to thank my family, both immediate and many relatives, for their endless love, support, and encouragement. I'm happy to announce that I will no longer respond to the annual question at Thanksgiving of "When do you graduate?" with a "Probably in another year". Kyle, playing games and catching up with you every week during my first years helped me more than you probably know. Mom, I really owe this all to you. Thank you for pushing me and always believing in me. I hope I made you and Dad proud. I wish he could've been here to see it.

TABLE OF CONTENTS

LIST OF TABLES

TABLE Page

LIST OF FIGURES

LIST OF SCHEMES

SCHEME Page

LIST OF ABBREVIATIONS

Ac	acetyl
Ac_2O	acetic anhydride
AcOH	acetic acid
AIBN	azobisisobutyronitrile
app	apparent
BBN	borabicyclo[3.3.1]nonane
BHT	butylated hydroxytoluene
Bn	benzyl
Boc	t-butyl carbamate
br	broad
BRSM	based on recovering starting material
Bu	butyl
Bz	benzoyl
°C	degrees Celsius
Cbz	carboxybenzyl
COSY	correlation spectroscopy
Cp	cyclopentadienyl
CSA	camphorsulfonic acid
d	doublet
DABCO	1,4-diazabicyclo[2.2.2]octane
DBN	diazabicyclononene
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexyl carbodiimide
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminum hydride
DIPEA	diisopropylethylamine
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	dimethyl formamide
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
DPPA	diphenylphosphoryl azide
dppf	1,1'-Bis(diphenylphosphino)ferrocene
Δ	heat
δ	chemical shift in ppm
ee	enantiomeric excess
ESI	electrospray ionization
Et	ethyl

Et_2O	diethyl ether
g	gram
HMBC	heteronuclear multiple bond correlation spectroscopy
HMDS	hexamethyldisilazide
HMPA	Hexamethylphosphoramide
HOMO	highest occupied molecular orbital
HPLC	high-pressure liquid chromatography
HSQC	Heteronuclear single quantum coherence spectroscopy
HRMS	high resolution mass spectrometry
i-Bu	isobutyl
ImH	imidazole
i-Pr	isopropyl
IR	infrared spectroscopy
J	coupling constant
KHMDS	potassium bis(trimethylsilyl)amide
L	liter
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LHMDS	lithium bis(trimethylsilyl)amide
LUMO	lowest unoccupied molecular orbital
M	molar concentration
m	milli, multiplet
*m*CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
MeCN	acetonitrile
MeI	methyl iodide
MeOH	methanol
MHz	megahertz
µ	micro
MMPP	magnesium monoperoxyphthalate
mol	mole
MS	molecular sieves
Ms	methanesulfonate
N	normal concentration
NBS	*N*-bromosuccinimide
n-BuLi	*n*-butyllithium
NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
OAc	acetoxy
Oxone	potassium peroxymonosulfate
p	pentet

Ph	phenyl
Piv	pivaloyl
PKS	polyketide synthase
PMB	*para*-methoxybenzyl
ppm	parts per million
PPTS	pyridinium *para*-toluenesulfonate
*p*TSA	*para*-toluenesulfonic acid
*p*TsOH	*para*-toluenesulfonic acid
pyr	pyridine
q	quartet
RCAM	ring closing alkyne metathesis
RCM	ring closing metathesis
Red-Al	sodium bis(2-methoxyethoxy)aluminumhydride
rt	room temperature
s	singlet
sept	septet
t	triplet
TBAF	tetra-*n*-butylammonium fluoride
TBAI	tetra-*n*-butylammonium iodide
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TBSCl	*tert*-butyldimethylsilyl chloride
t-BuOK	potassium *tert*-butoxide
TMEDA	Tetramethylethylenediamine
TES	triethylsilyl
TESCl	triethylsilyl chloride
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
Tf_2O	trifluoromethanesulfonic anhydride
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TIPSCl	triisopropylsilyl chloride
TMS	trimethylsilyl
TOCSY	total correlation spectroscopy
TRIS	tris(hydroxymethyl)aminomethane

CHAPTER I

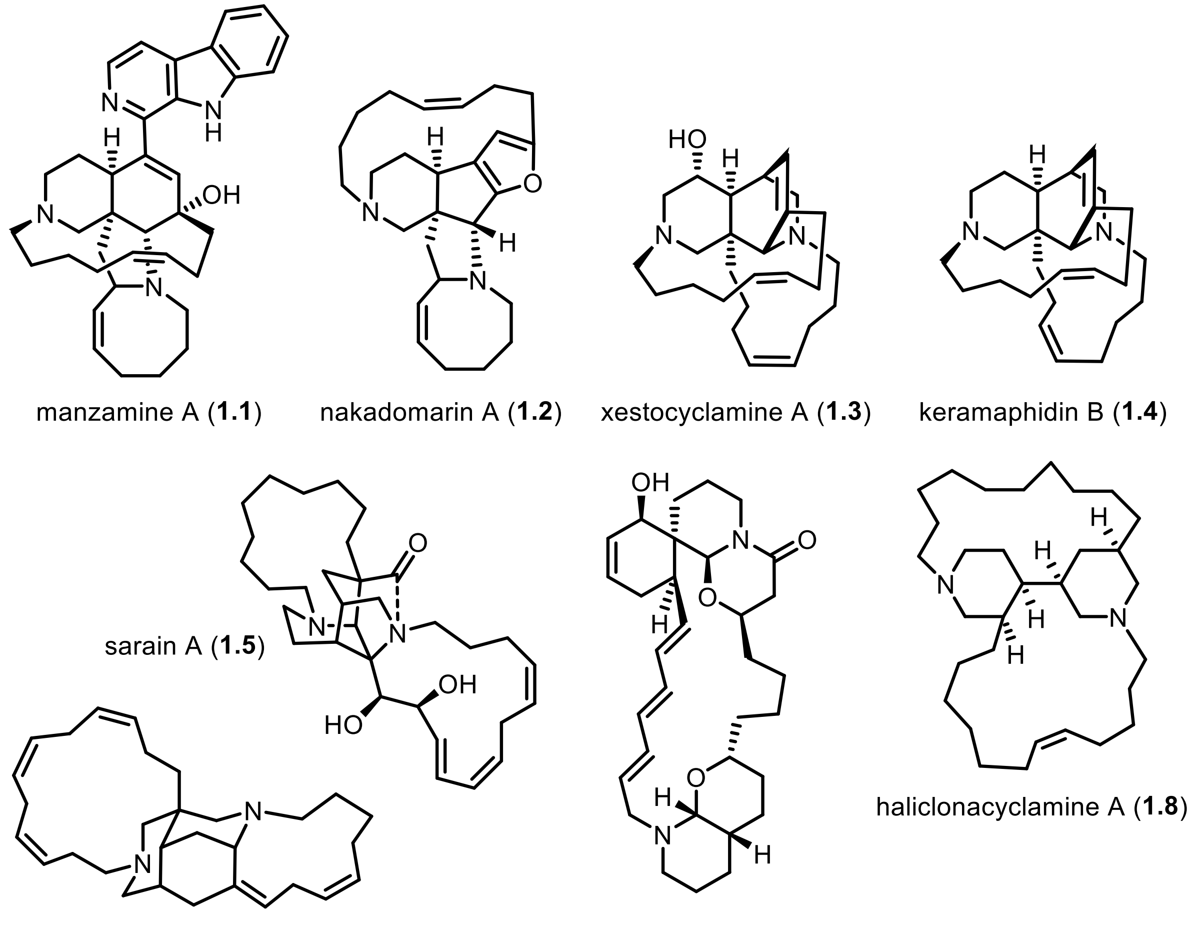
INTRODUCTION TO THE MANZAMINE ALKALOIDS: ISOLATION, STRUCTURE, AND ACTIVITY

Introduction to Marine Alkaloid Natural Products

Natural products have contributed significantly to drug discovery and the development of new medicines. As of 2019, reportedly 34% of approved small-molecule drugs between 1981-2019 were natural products (NP) or natural product derivatives.[1] Notably, these molecular scaffolds contain inherent biological activity as a result of their evolution within biological systems. Fortunately, the activity and interactions within their intended niche environments transcends into other systems including in whole organisms. Terrestrial sources have historically served as valuable assets for the discovery of new natural products, and indeed still do. However, the unintended rediscovery of previously reported natural products presents a growing challenge in the isolation of novel compounds.[2,3] As a result, the abundance of biological diversity within the ocean and its vast unexplored regions has presented a new arena brimming with a seemingly endless supply of novel molecular structures and biological activities.

Communal marine organisms have been postulated to produce such potent and diverse structures due to a variety of factors including high pressure conditions, the presence or absence of sunlight, and the challenge of partner-host interactions in aqueous environments. The emergence of evidence supporting secondary metabolites as a result of symbiotic relationships has reshaped the perspective of NP isolation and holds potential to impact future NP discovery through new methods (i.e. genome mining).[4–7] In 2017 it was reported for that year, 57% of marine natural products were sourced from marine microorganisms.[8]

An important class of secondary metabolites from these microorganisms are alkaloids, which are characterized by the presence of a basic nitrogen in a heterocyclic ring. One unique group of NPs are the manzamine alkaloids, sometimes referred to as the alkylpiperidine alkaloids. This family can be identified by their large macrocyclic rings, a di-nitrogenated polycyclic core, and a hypothetically shared biosynthetic origin (Figure **1.1**).



manzamine A (**1.1**) nakadomarin A (**1.2**) xestocyclamine A (**1.3**) keramaphidin B (**1.4**)

sarain A (**1.5**)

madangamine A (**1.6**) upenamide (**1.7**) haliclonacyclamine A (**1.8**)

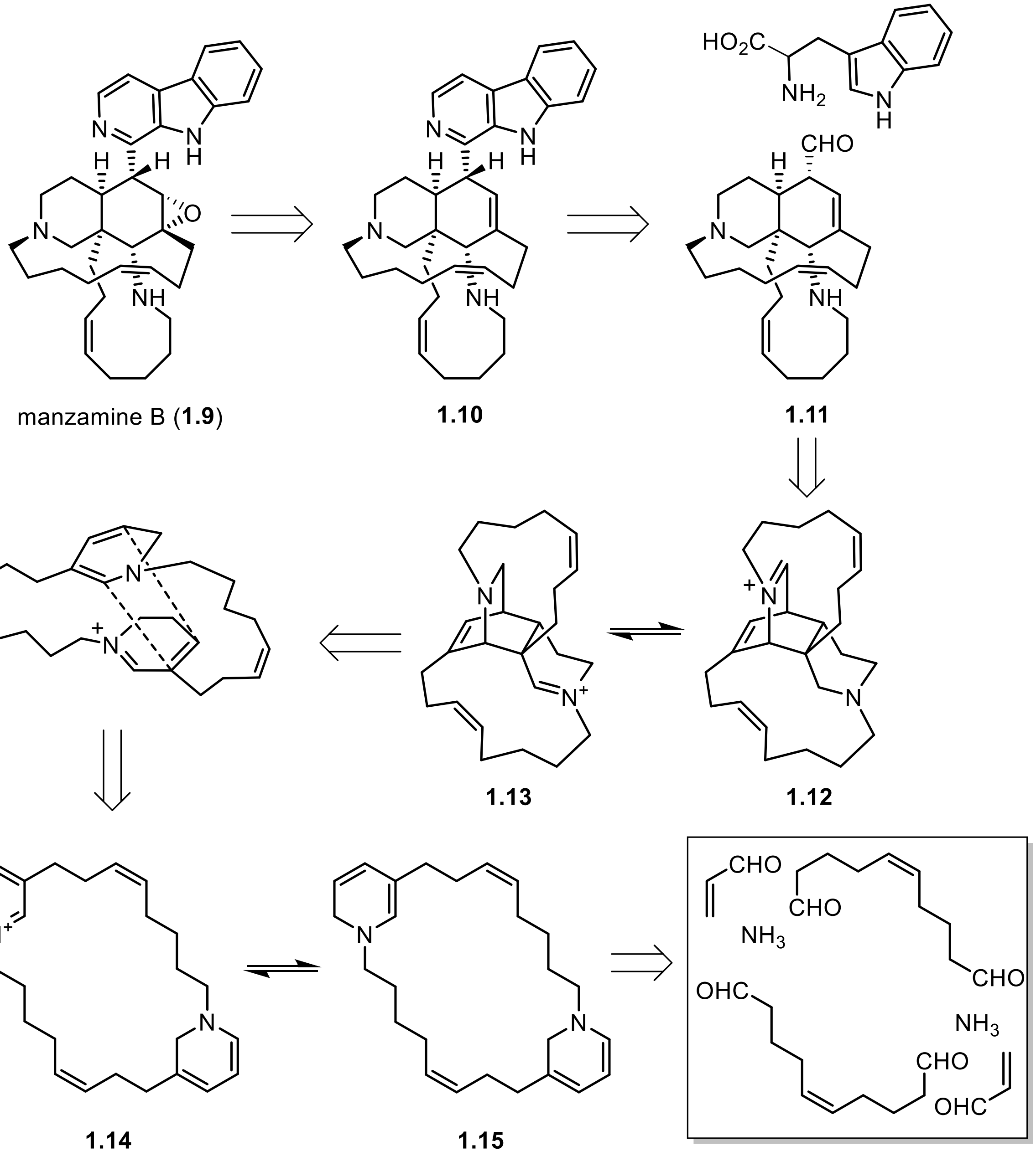
Figure 1.1 Representative collection of the manzamine alkaloids.

The earliest isolated member and namesake, manzamine A (**1.1**), was discovered in 1986 by Higa and coworkers from an Okinawan sponge *Haliclona* sp. and structurally characterized by X-ray diffraction of the hydrochloride salt.[9] Initial assays revealed significant activity against murine leukemia cell lines (IC_{50} = 0.07 μg/mL). Since then, more than 70 related alkaloids have been isolated from 16 species of marine sponges belonging to 5 families, with reported biological activities including cytotoxicity, kinase inhibition, antimicrobial, antimalarial, and antiviral activities.[10–12] In addition to their clinically relevant biological activity, their unprecedented and complex structures have spurned dozens of international groups to pursue synthetic approaches toward these natural products.[11,13,14]

Biomimetic Synthetic Approaches

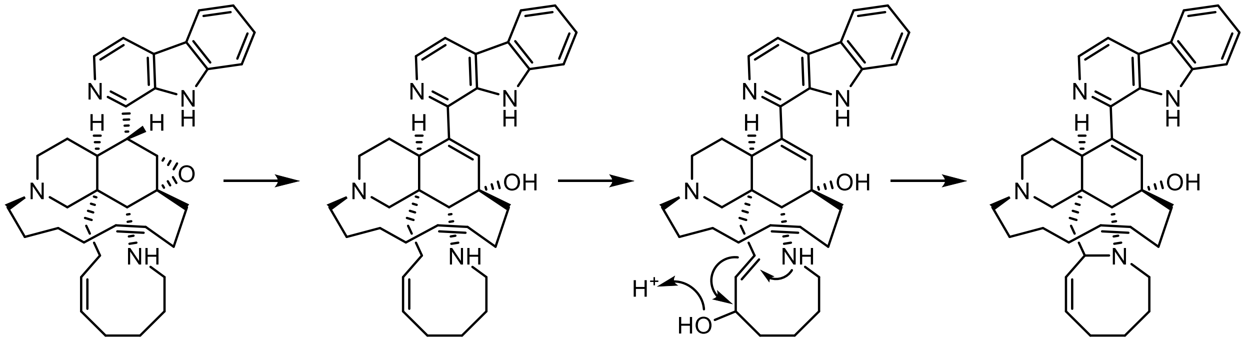
Baldwin Biosynthetic Proposal

In Higa and coworker's report of the manzamine alkaloids, the authors state: "the structure of manzamine A hydrochloride is unprecedented in nature. Moreover, its provenance is problematical as there appears to be no obvious biogenetic path."[9] Six years later, Baldwin and Whitehead put forth a hypothetical proposal on the biosynthesis of the manzamine alkaloids.[15] They postulated three simple building blocks would give rise to manzamines A, B, and C, and additionally postulated a biogenetic precursor for related family members, namely sarain, xestospongin, and petrosin. They proposed that reductive coupling of two equivalents of acrolein, ammonia, and a symmetrical C_{10} aldehyde unit would give rise to macrocycle **1.15** (Scheme **1.1**)**.** Protonation would generate **1.14** and induce a transannular Diels-Alder cycloaddition to afford iminium **1.13** which undergoes a redox equilibrium with **1.12**. Upon hydrolysis of **1.12,** the resulting aldehyde **1.11** would then undergo condensation with tryptophan and further cyclize in Pictet-Spengler type fashion and give rise to the β-carboline moiety in **1.10**. Further epoxidation would give rise to manzamine B, **1.9**.



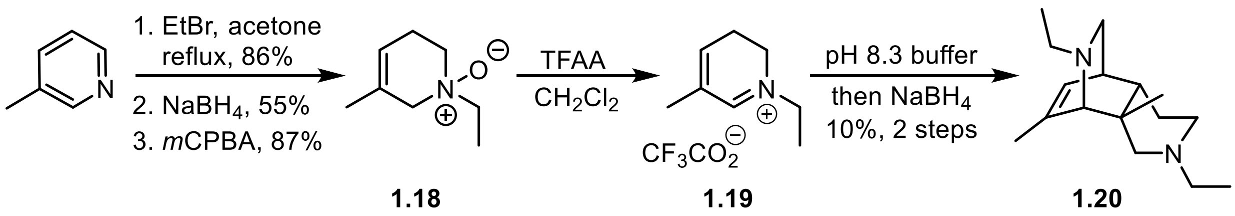
Scheme 1.1. The Baldwin and Whitehead proposal on the biosynthesis of manzamine B.

A notably important feature of their proposal is the symmetrical simplicity of the Diels-Alder cycloaddition which produces the correct regiochemical and stereochemical centers as a result from the endo isomer. Beginning from manzamine B, base-mediated opening of the epoxide would produce the resulting allylic alcohol. Oxidative transposition of the Southern alkene would give **1.16** (Scheme **1.2**)**.** Final acid-mediated cyclization of the secondary amine would generate the eight-membered ring seen in manzamine A. As time progressed and more alkaloids within the family were isolated, several hypothetical intermediates within the Baldwin proposal were identified, raising the impact of their speculative biosynthesis.



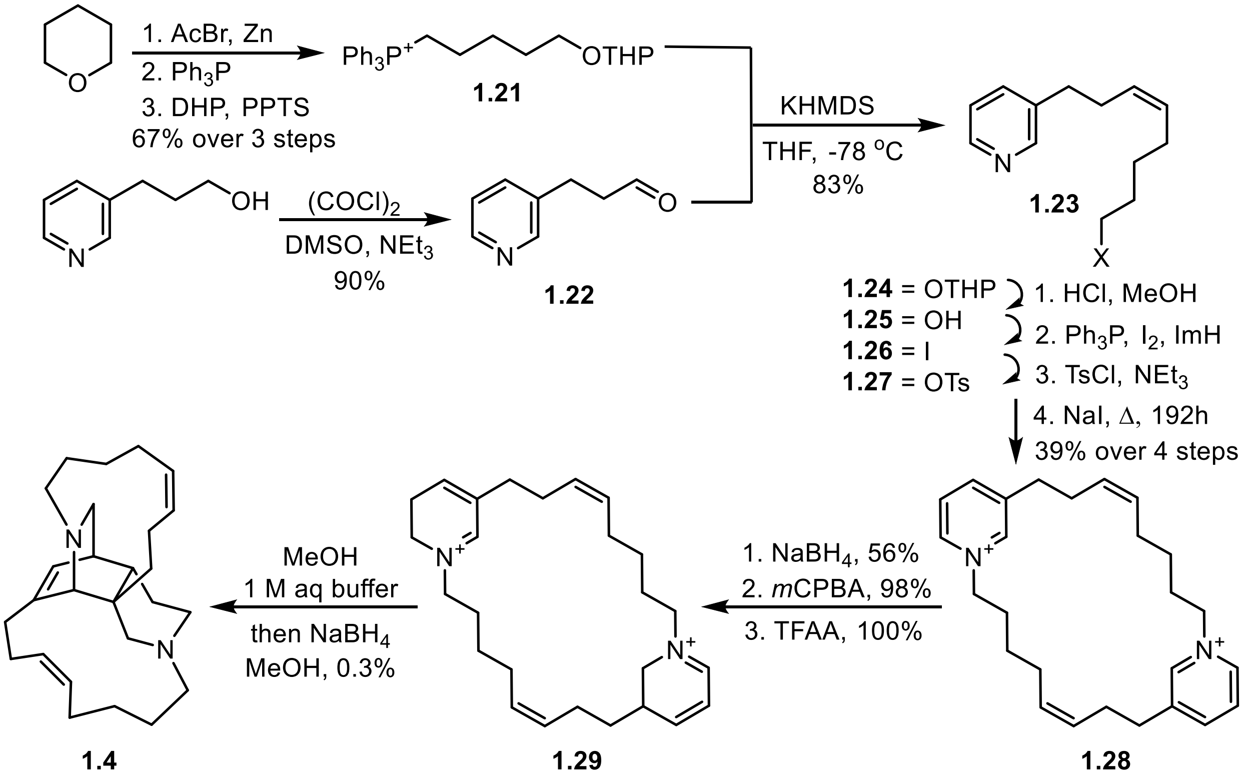
Scheme 1.2. The Baldwin and Whitehead proposal on the biosynthesis of manzamine A.

Baldwin and coworkers eventually evaluated their proposed transannular cycloaddition experimentally as summarized in two separate publications.[16,17] In the first study, the Baldwin group reported the use of a simple model system to access the bicyclic core (Scheme **1.3**) which the authors note "bears a clear resemblance to the central core of ingenamine, the ingamines, and keramaphidin B."[16] From 3-methyl pyridine, reduction of the alkylpyridinium with $NaBH_4$, and subsequent oxidation with *m*CPBA produces N-oxide **1.18**. Treatment with trifluoroacetic anhydride (TFAA) induces the Polonovski-Potier reaction to generate the iminium intermediate **1.19**. After extensive screening it was found treatment with pH 8.3 buffer and $NaBH_4$ revealed **1.20** in 10% yield over 2 steps.



Scheme 1.3. The Baldwin group's model study.

The authors note the major product isolated after treatment with $NaBH_4$ was the reduced tetrahydropyridine, but despite the poor yield, is still notably the first approach to access the keramaphidin bicyclic core via a Diels-Alder cycloaddition.

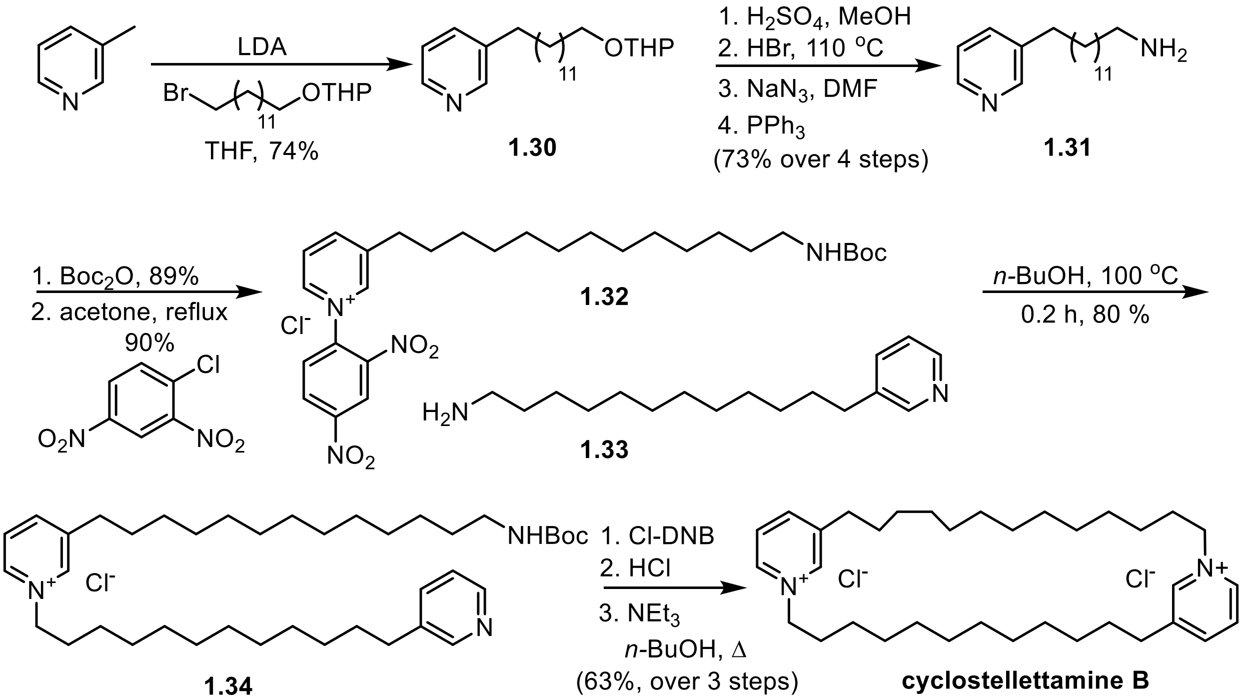


Scheme 1.4. The Baldwin group's approach toward the total synthesis of keramaphidin B.

In the Baldwin group's second report, the authors evaluated their proposed biomimetic transannular approach (Scheme **1.4**).[17] Treatment of tetrahydropyran with acetyl bromide and zinc followed by triphenylphosphine produced a phosphonium salt. Subsequent hydrolysis of the acetate and protection as the tetrahydropyranyl (THP) ether afforded **1.21**. Swern oxidation of commercially available 3-pyridinepropanol yielded aldehyde **1.22**. Wittig olefination with the ylide generated from **1.21** and KHMDS gave alkene **1.23**. Next, acid-mediated deprotection of THP ether and further reaction under Appel conditions furnished the alkyl iodide **1.26**. Although the alkyl iodide acted as an optimal leaving group for the cyclodimerization, **1.26** was prone to polymerization when concentrated after several hours. Furthermore, yields for the iodination proved to be inconsistent, and ultimately the alkyl iodide was converted to the more stable tosylate **1.27**. The cyclodimerization reaction was then conducted by dropwise addition of tosylate **1.27** to a refluxing solution of NaI in 2-butanone. Under these conditions the tosylate underwent an in-situ Finkelstein reaction and rapid S_N2 intermolecular displacement to form the dimeric species. The subsequent ring-closing reaction proceeded via an intramolecular S_N2 reaction under high dilution conditions. With the bis-pyridinium macrocycle in hand, reduction using $NaBH_4$, followed by treatment with *m*CPBA and trifluoroacetic anhydride (TFAA) induced the Polonovski-Potier reaction to arrive at iminium **1.29**. Now at the proposed hypothetical biosynthetic precursor for the key Diels-Alder cycloaddition, after extensive screening, the Baldwin group was only able to isolate the cycloadduct keramaphidin B in 0.3% yield. Ultimately, the authors attributed the low yield to the kinetic preference of **1.29** to undergo undesirable disproportionation side-reactions to the more stable tetrahydropyridine. They postulated that an in vivo Diels-Alderase could feasibly prevent this undesirable pathway and "mediate the conversion of bis-iminium salt to keramaphidin B."[17] Although there have been reports of Diels-Alderases[18–21], the failure of their transannular approach has led to another prominent biosynthetic proposal.

Marazano Biosynthetic Proposal

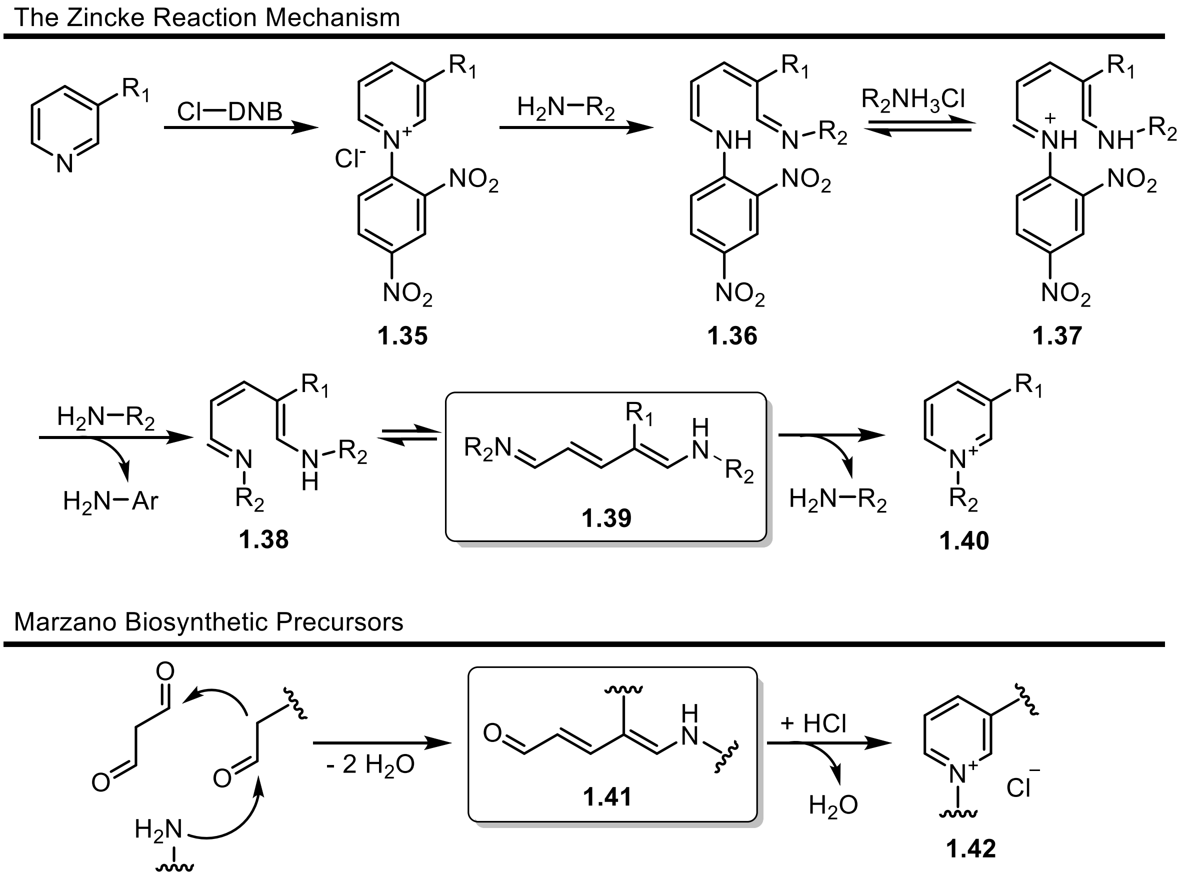
A year prior to the Baldwin group's report on their biomimetic synthesis, the Marazano group published the synthesis of cyclostellettamine B and other oligomeric pyridinium sponge macrocycles.[22] Perhaps most interestingly, the use of the Zincke reaction to access these pyridinium heterocycles led to the development of another alternative biosynthetic proposal to the manzamine alkaloids. Their synthesis begins from the alkylation of 3-picoline using LDA and an alkyl bromide to generate the elongated carbon chain in **1.30** (Scheme **1.5**). Next, acid catalyzed deprotection of the THP ether, and subsequent treatment with hydrobromic acid at elevated temperatures gave the alkyl bromide.



Scheme 1.5. The total synthesis of cyclostellettamine B by the Marazano group.

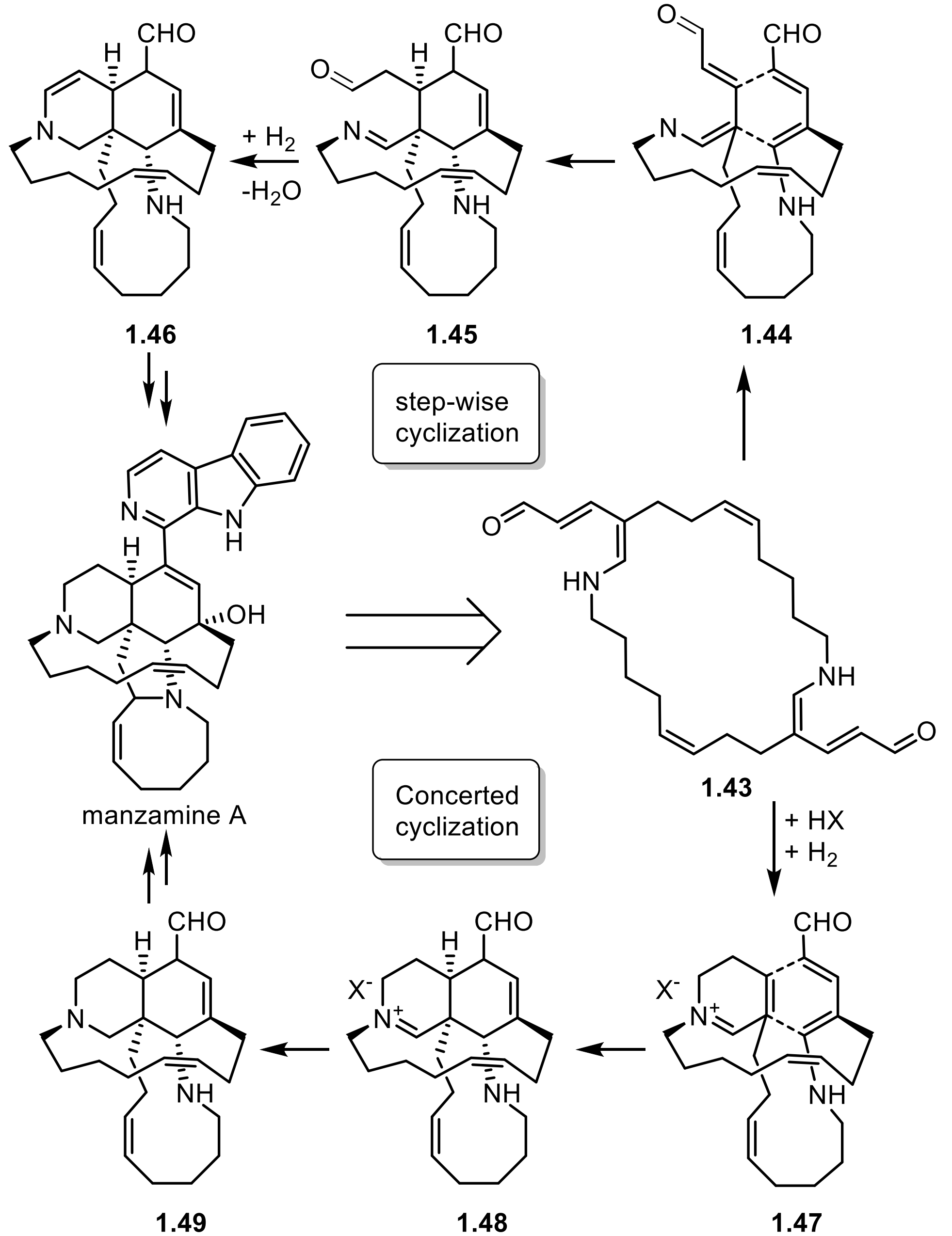
Azide displacement and a Staudinger reduction employing PPh_3 yielded primary amine **1.31** in 73% over four steps. Protection of the amine using Boc_2O followed by alkylation of the pyridine with 1-chloro-2,4-dinitrobenzene produced pyridinium **1.32**. Next the Zincke reaction was used to install the Southern fragment via treatment with amine **1.33**. Alkylation of the second pyridine with 1-chloro-2,4-dinitrobenzene, followed by *tert*-butyl carbamate deprotection and another Zincke reaction furnished the bis-pyridinium macrocycle cyclostellettamine B in 63% over 3 steps.

This methodology was then applied to synthesize other oligomeric species containing up to eight pyridinium heterocyclic rings. At this point the authors explicitly correlate the Zincke intermediate as a plausible biogenic precursor to the manzamines (Scheme **1.6**). Specifically, intermediate **1.39** provided valuable insight into a possible precursor for Baldwin's bis-pyridinium macrocyclic intermediate.



Scheme 1.6. Comparison of the Zincke Reaction and the Marzano Biosynthetic proposal.

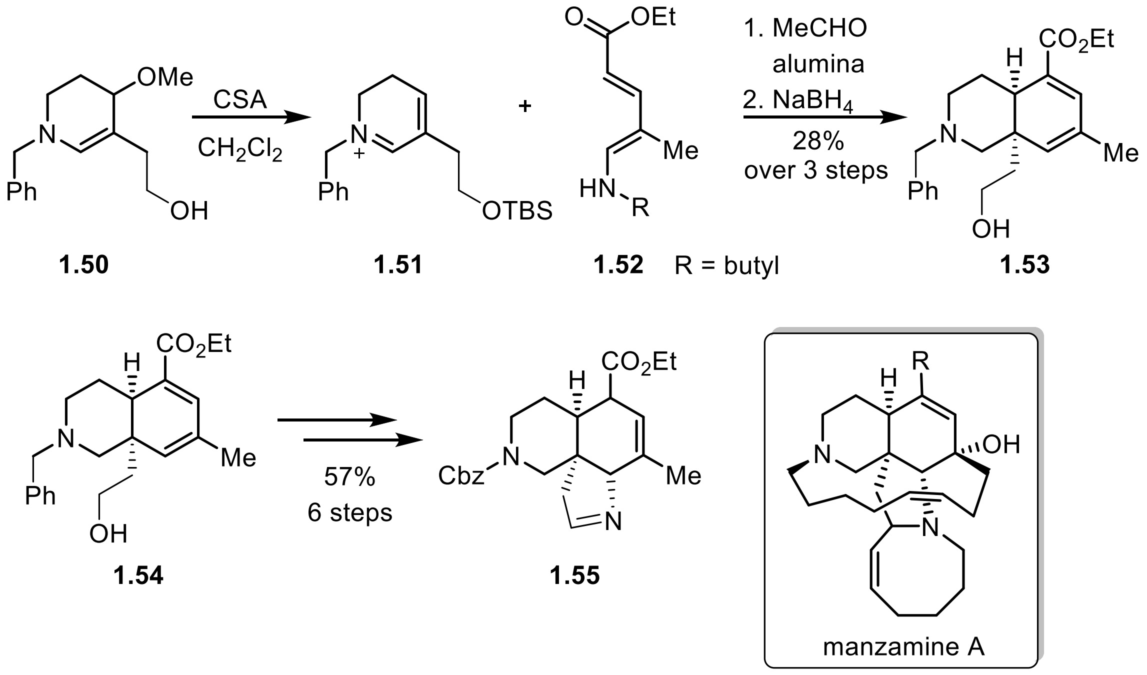
Marazano and coworkers postulated that 5-aminopentadienal **1.41** could arise from the condensation of an amine, aldehyde, and a malondialdehyde unit. Contrary to Baldwin's proposal of acrolein as the C_3 unit, Marazano states that malondialdehyde would be a more feasible biosynthetic intermediate and are well known as oxidative products of fatty acid catabolism.[23,24]



Scheme 1.7. The Marazano proposal on the biosynthesis of manzamine A.

Furthermore, whereas the Baldwin proposal suffered from disproportionation side reactions of the reactive iminium intermediate **1.14**, the aminopentadienal intermediates are well known to spontaneously and cleanly cyclize to the pyridinium heterocycles.[25]

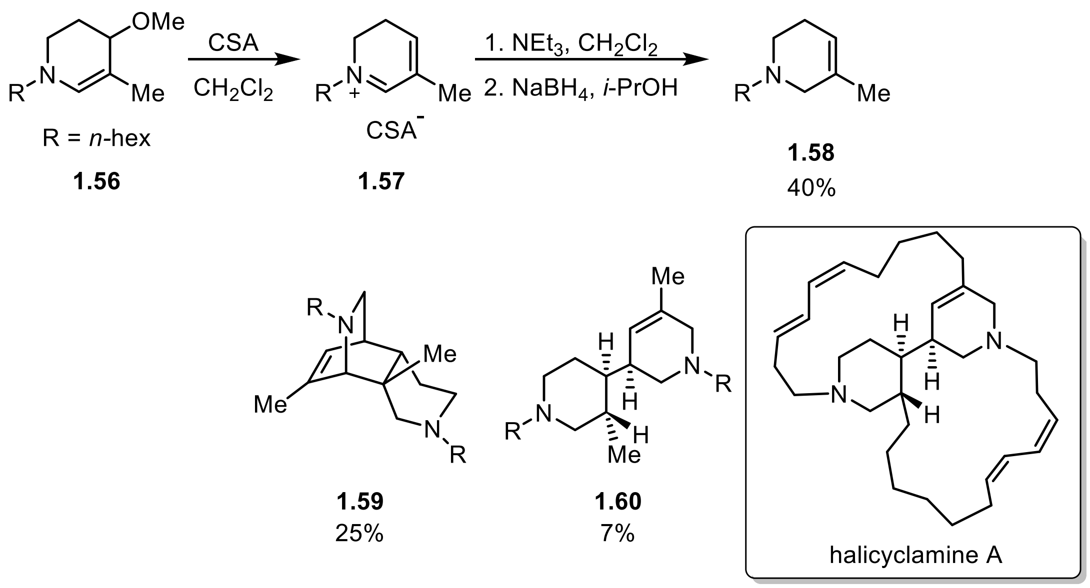
In their full proposed biosynthesis the Marazano group postulated two possible routes originating from the macrocyclic aminopentadienal species **1.43** (Scheme **1.7**). In the first route, after cyclization of the first iminium heterocycle, a concerted [4+2] cycloaddition proceeds to install the central core of **1.44**. Reduction of the resulting iminium and further elaboration then rapidly gives rise to manzamine A. Alternatively, in a stepwise fashion, a Michael-addition and tandem Mannich cyclization would also construct the manzamine skeleton. With a viable synthetic plan, the Marazano group went forward and tested their hypothesis using a model system (Scheme **1.8**).[26]



Scheme 1.8. The Marazano approach toward the ABC Ring of manzamine A.

Beginning from tetrahydropyridine **1.50** treatment with camphorsulfonic acid (CSA) gave dihydropyridinium salt **1.51** which was screened against a variety of substituted 5-aminopentadienals. Reaction with amine **1.52** gave the correctly substituted core and appeared to proceed in a stepwise manner. The authors suggested a possible intramolecular hydride migration originating from the butyl group to reduce the iminium moiety. Ultimately treatment with acetaldehyde and $NaBH_4$ induced elimination of the amino group to furnish diene **1.54**. Elaboration of the primary alcohol over the next 6 steps gave **1.55** in 57% yield and constructed the final central ring within the manzamine skeleton.

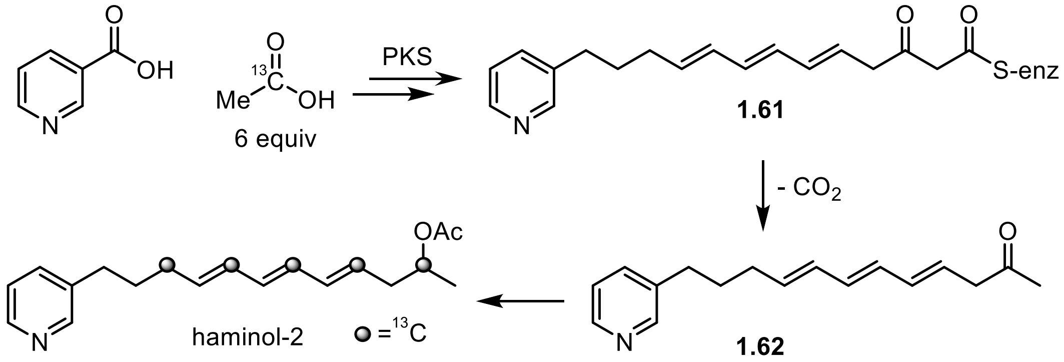
In addition to their proposal on the synthesis of the manzamines, in 1995 the Marazano group were first to draw a correlation between halicyclamine A, sarain A, and the manzamine alkaloids.[27,28] The authors reported a model system, remarkably similar to the Baldwin groups approach, which proceeded through the same dihydropyridine iminium intermediate **1.57** (Scheme **1.9**). Upon treatment with NEt_3 and $NaBH_4$ a mixture of tetrahydropyridine **1.58**, cycloadduct **1.59**, and the bis-piperidinyl species **1.60** were isolated. This provided the first experimental evidence for the formation of the halicyclamine core through a biomimetic approach but failed to confirm if formation proceeded through a fragmentation cascade or non-concerted mechanism.



Scheme 1.9. The Marazano group's biomimetic model studies.

In Vivo Evidence for Biosynthetic Proposals

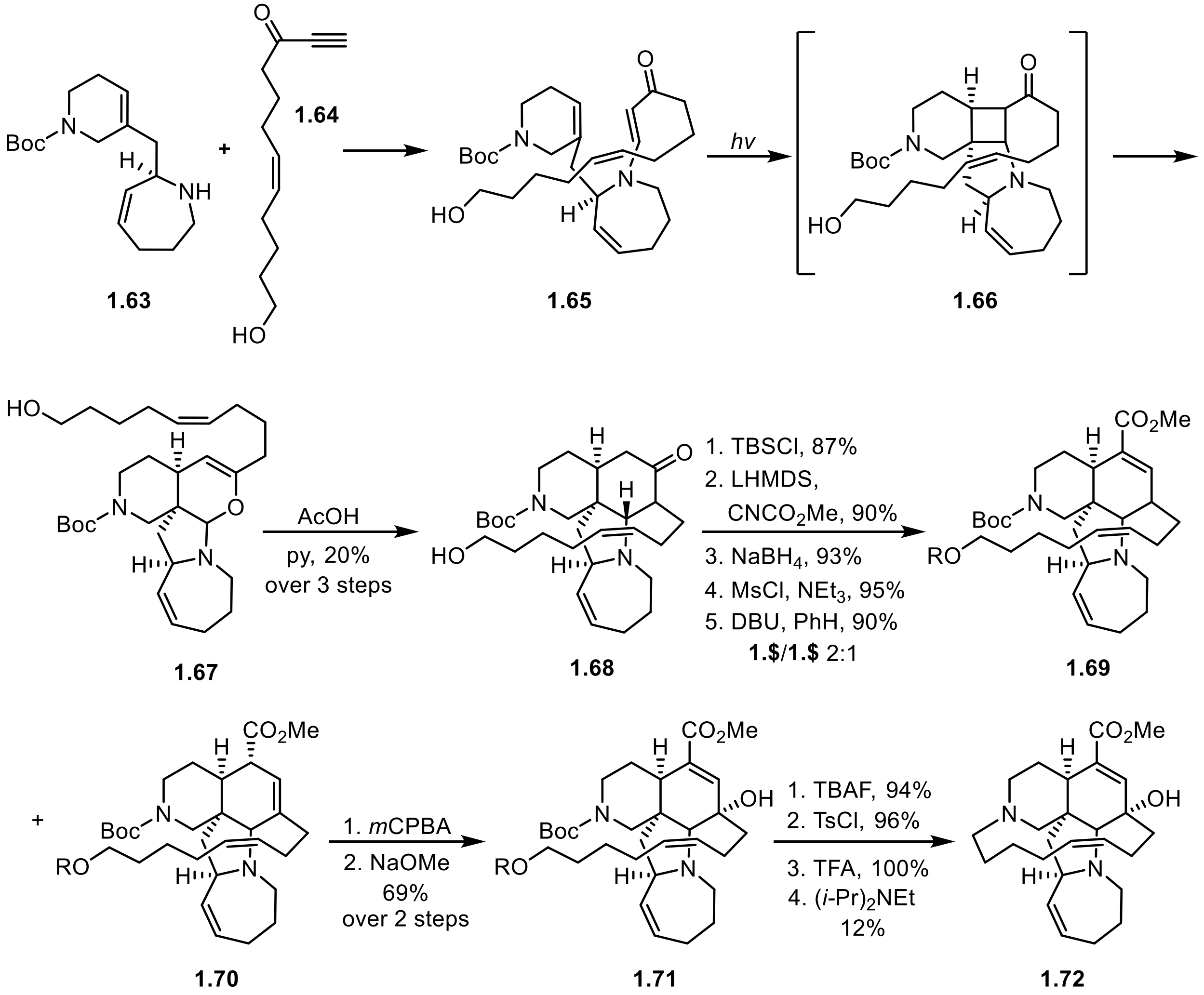
While the Baldwin and Marazano proposals were elegant hypothetical biosynthetic approaches, ultimately, they both lacked evidence to corroborate their proposed intermediates as secondary metabolites in vivo. This proved true until the Fontana group conducted pulse feeding studies of labeled intermediates using the Mediterranean mollusk *Haminoea orbignyana*, which are marine invertebrates known to produce the natural product, haminol-2, a member of the alkylpyridine alkaloids. Although structurally simple relative to the manzamine alkaloids, this provided the first insight into a legitimate biosynthetic pathway. In two separate experiments, the Fontana group injected these mollusks with [1-^{13}C] and [1,2-$^{13}C_2$] labeled acetate units, and then starved them for several days to induce secretion of alarm pheromones (Scheme **1.10**).[29] After which, isolation and analysis by ^{13}C NMR revealed incorporation of ^{13}C units in the alkyl chain. Another experiment in which [d$_4$] nicotinic acid was injected revealed complete incorporation of four deuterium isotopes as observed by an increase in *m/z* = 4 via LC-MS analysis. Secondly, ^{2}H NMR analysis corroborated complete retention of deuterium during the biosynthesis. Thus, the authors were able to conclude that haminol-2 are produced in *H. orbignyana* through a polyketide synthase pathway which used nicotinic acid as a novel PKS starter unit.[30]



Scheme 1.10. Fontana group's labeling study and biosynthesis of haminol-2.

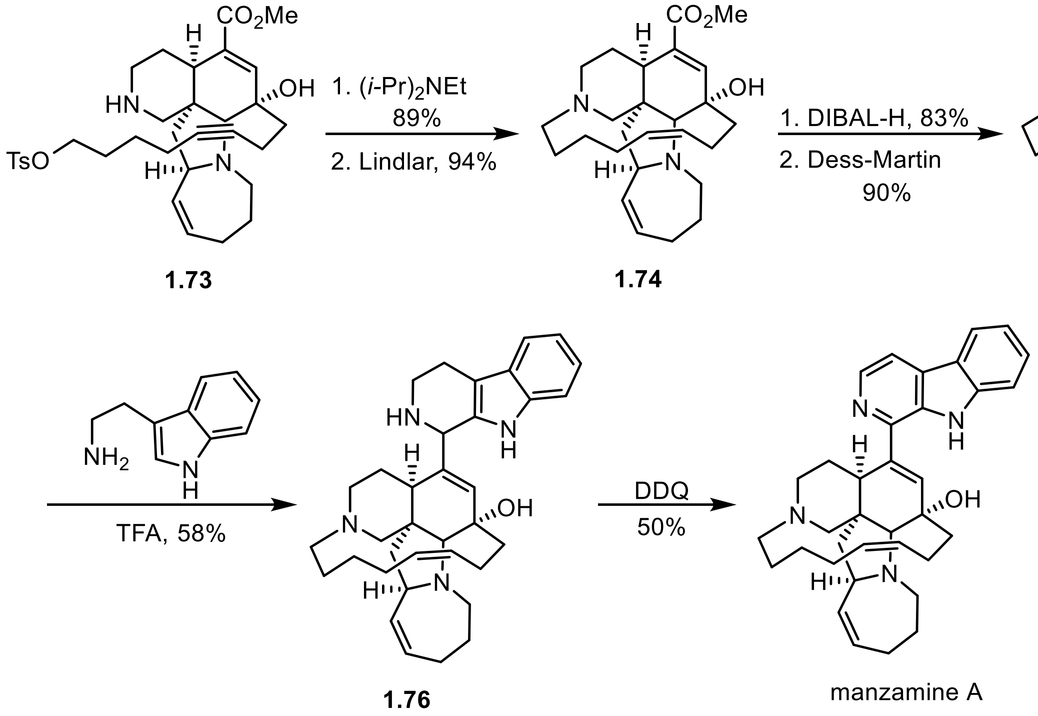
Winkler's Total Synthesis of Manzamine A, Ircinal A, and Ircinol A

The first total synthesis of manzamine A was reported in 1995 by the Winkler group, in which the authors utilized a [2+2] photocyclization/fragmentation strategy to rapidly access the tetracyclic core.[31] Optimization of this methodology resulted in the intramolecular photoaddition of **1.65** (Scheme **1.11**), generated from the Michael addition between **1.63** and **1.64**., to yield the intermediate cyclobutane **1.66**.[16] Spontaneous fragmentation in a retro-Mannich fashion and immediate O-alkylation gave hemiaminal **1.67**. When treated with AcOH and pyridine, a second fragmentation occurred and tautomerization led to C-alkylation and closure to tetracycle **1.68** as a single stereoisomer in 20% from **1.65**. Silyl protection of the primary alcohol followed by carboxylation of the kinetic enolate with Mander's reagent[34] produced the corresponding β-ketoester. Reduction of the ketone with $NaBH_4$, mesylation of the secondary alcohol, and elimination with DBU gave alkenes **1.69** and **1.70** as a separable mixture.



Scheme 1.11. Winkler's approach to the core of manzamine A.

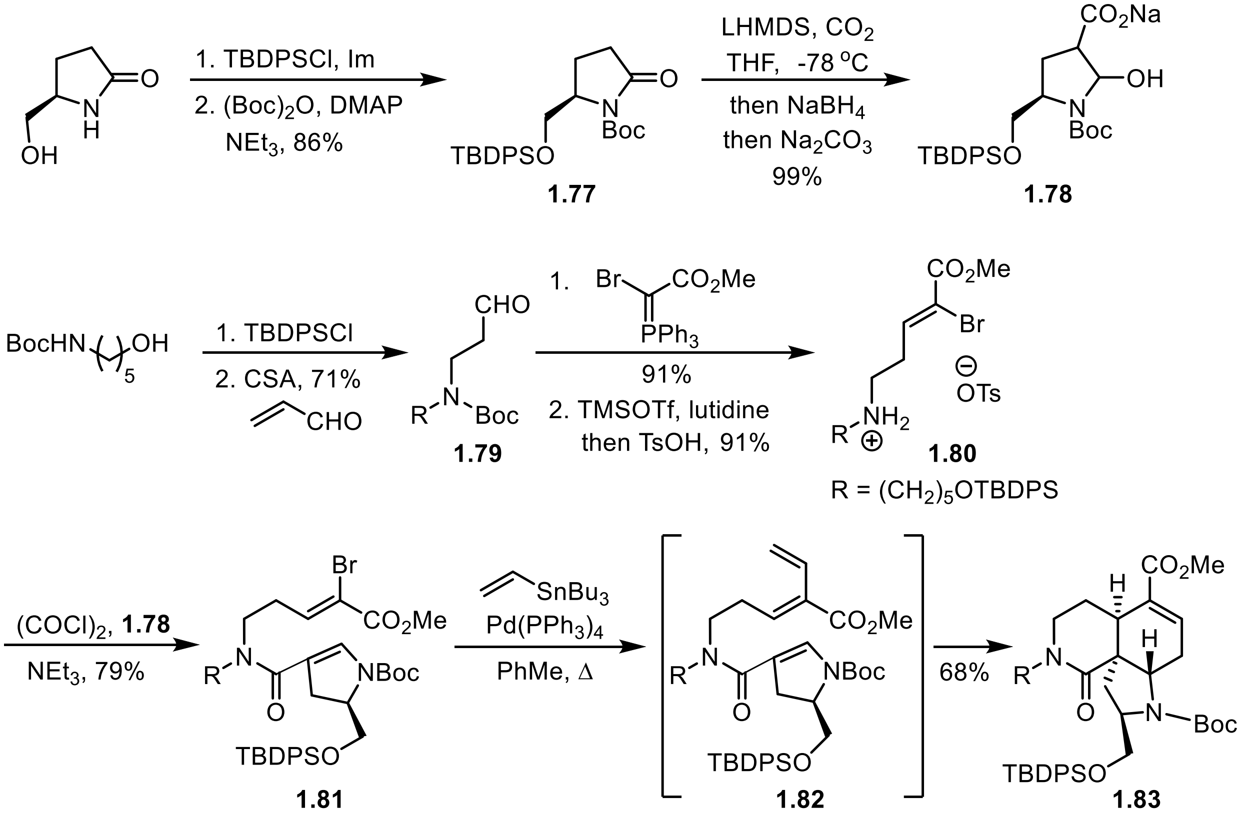
Epoxidation of **1.70** with *m*CPBA and base-promoted opening gave allylic alcohol **1.71** with the desired stereochemistry. Next, the authors noted closure of the macrocycle proved challenging. Deprotection of the primary alcohol with TBAF was followed by tosylation which occurred cleanly. However, upon deprotection of the secondary amine, subsequent treatment with Hünig's base resulted in formation of macrocycle **1.72** in 12% yield. Interestingly, the authors note that when the elaborated alkynyl substrate **1.73** was treated under the same conditions, the macrocycle was isolated in 89%. Semi-hydrogenation of the alkyne with Lindlar's catalyst[35] gave the Z-alkene isolated previously. Reduction of **1.74** with DIBAL-H produced the primary alcohol which was oxidized to aldehyde **1.75** with Dess-Martin's periodinane[36]. Treatment with tryptamine and TFA gave **1.76** via a Pictet-Spengler reaction. Further oxidation with DDQ installed the β-carboline moiety and completed manzamine A in 50% from **1.76**.



Scheme 1 12. Winkler's total synthesis of manzamine A.

Martin's Total Synthesis of Manzamine A, Ircinal A, and Ircinol A

Four years after the Winkler group reported the first total synthesis of manzamine A, the Martin group published an enantioselective total synthesis of manzamine A in which they accessed the final structure through ircinal A, similar to Winkler's approach.[37] However, their synthetic strategy, developed prior, intended to construct the tricyclic core via an intramolecular Diels-Alder cycloaddition employing N-acylated vinylogous ureas as the dienophile component.[38,39] To this end, synthesis of the dienophilic fragment began from commercially available pyroglutaminol, and silyl protection of the primary alcohol and Boc protection of the amine gave **1.77** (Scheme **1.13)**. Sequential deprotonation and carboxylation were followed by reduction with $NaBH_4$ to give alcohol **1.78**.

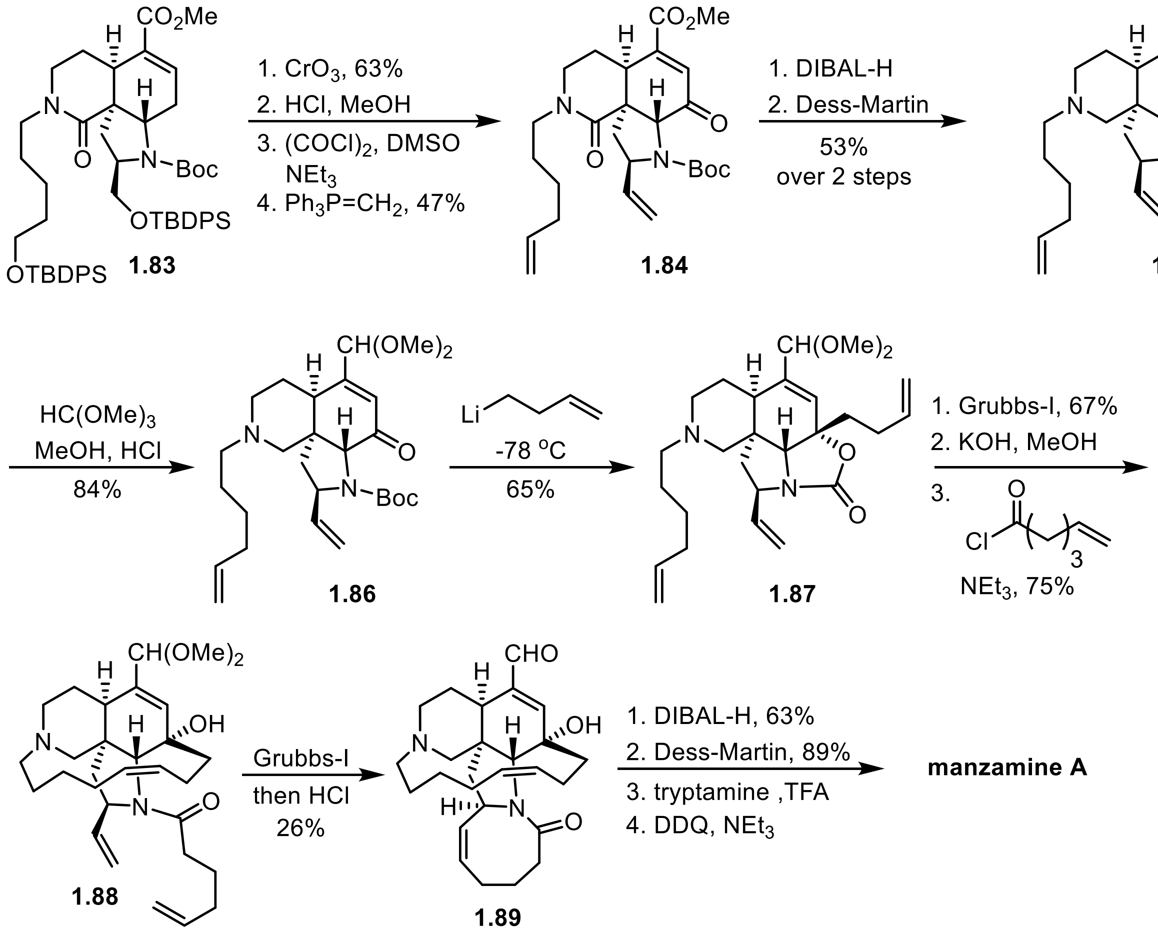


Scheme 1.13. Martin's approach to the core of manzamine A.

The authors noted the free carboxylic acid was unstable and storage as the sodium salt prevented any undesired decomposition. Simultaneously, synthesis of the diene fragment began from silylation of Boc-protected 5-aminopentan-1-ol. When further reacted with excess acrolein in the presence of CSA, aldehyde **1.79** was isolated in 71% yield. Wittig olefination proceeded with excellent selectivity for the Z-olefin and subsequent Boc deprotection with TMSOTf was followed by treatment with TsOH to afford **1.80** as the stable crystalline tosylate salt.

With both fragments in hand, acid **1.78** was reacted sequentially with $(COCl)_2$ and **1.80** to give vinylogous urea **1.81**. Now the key Stille/Diels Alder sequence was primed, and the vinyl bromide next underwent a Stille cross-coupling reaction. The resulting intermediate diene **1.82**, upon continued heating, gave the cyclized tricycle **1.83** as the sole isomer in 68%. It is interesting to note the selectivity and electron-withdrawing nature of the diene moiety in comparison to failed routes which employed electron-releasing dienes that produced low-yielding or isomeric mixtures. The authors noted the necessity of the vinylogous urea and how the inherent electron-richness facilitated the transformation in which the authors hypothesized was likely an inverse electron-demand Diels-Alder cycloaddition. Installation of the methyl ester proved essential for demonstrating the proposed effect.

Having successfully tested their hypothesis, the authors carried **1.83** forward and exposure to CrO_3 furnished the enone moiety (Scheme **1.14**). Acid-catalyzed global desilylation, Swern oxidation, and Wittig olefination gave the diolefin **1.84**. Reduction of the methyl ester and amide was achieved with DIBAL-H and oxidation with Dess-Martin periodinane produced aldehyde **1.85** that was then protected as the dimethyl acetal using trimethyl orthoformate and HCl in MeOH. At this point the authors attempted to construct the macrocyclic and eight-membered rings in a 5-step sequence which employed a double RCM cyclization strategy. Unfortunately, they observed ring formation with undesired connectivity in addition to a 1:1 mixture of *cis*/*trans* isomers. Therefore, the authors employed an alternative multistep and productive approach. From dimethyl acetal **1.86**, alkylation with 3-butenyllithium and careful quench produced cyclic carbamate **1.87**.



Scheme 1.14. Martin's total synthesis of manzamine A.

When reacted with Grubbs' first-generation catalyst, the macrocycle was obtained as an 8:1 mixture of Z and E olefins isolated in 67% yield. The absolute stereochemistry of the undesired E-isomer was established via X-ray crystallography. Subsequent hydrolysis and N-acylation of the Z-isomer gave the second RCM substrate precursor **1.88**. When treated with Grubbs' first-generation catalyst, **1.89** was isolated in 26% yield after acidic workup. Efforts to optimize this yield were unsuccessful and included protection of the tertiary alcohol and protonation of the amino groups. With limited supply of material, the authors hypothesized the low yield may be attributed to competitive metathesis pathways.

Conclusion to Chapter 1

In summary, the manzamine alkaloids possess a rich history and provide an excellent representation of the possibilities within marine natural products. Specifically, the discovery of dozens of alkaloids which exhibited biological activity pertinent to human health and also displayed molecular structures that spurned their synthetic pursuit from chemists across the globe, showcases the power these alkaloids have. The manzamine alkaloids have served as a sandbox which allowed the combination of synthetic chemistry and chemical biology to produce new biosynthetic proposals, investigations, and synthetic methodologies which in turn catalyzed new proposals and strategies. Such endeavors are worthwhile and exploratory in nature, and serve as a vehicle for growth and scientific advancement.

References

(1) Newman, D. J.; Cragg, G. M. *J. Nat. Prod.* **2020**, *83* (3), 770–803.

(2) Gwynn, M. N.; Portnoy, A.; Rittenhouse, S. F.; Payne, D. J. *Ann. N. Y. Acad. Sci.* **2010**, *1213* (1), 5–19.

(3) Kong, D. X.; Guo, M. Y.; Xiao, Z. H.; Chen, L. L.; Zhang, H. Y. *Chem. Biodivers.* **2011**, *8* (11), 1968–1977.

(4) Taylor, M. W.; Radax, R.; Steger, D.; Wagner, M. *Microbiol. Mol. Biol. Rev.* **2007**, *71* (2), 295–347.

(5) Liu, L.; Zheng, Y.-Y.; Shao, C.-L.; Wang, C.-Y. *Mar. Life Sci. Technol.* **2019**, *1* (1), 60–94.

(6) Flórez, L. V.; Biedermann, P. H. W.; Engl, T.; Kaltenpoth, M. *Nat. Prod. Rep.* **2015**, *32* (7), 904–936.

(7) Kelman, D.; Kashman, Y.; Hill, R. T.; Rosenberg, E.; Loya, Y. *Pure Appl. Chem.* **2009**, *81* (6), 1113–1121.

(8) Carroll, A. R.; Copp, B. R.; Davis, R. A.; Keyzers, R. A.; Prinsep, M. R. *Natural Product Reports* **2019**, 122–173.

(9) Sakai, R.; Higa, T.; Jefford, C. W.; Bernardinelli, G. *J. Am. Chem. Soc.* **1986**, *108* (20), 6404–6405.

(10) Duval, R.; Poupon, E. *Biomim. Org. Synth.* **2011**, *1*, 181–224.

(11) Nishida, A.; Nagata, T.; Nakagawa, M. *Top. Heterocycl. Chem.* **2006**, *5*, 255–280.

(12) Kubota, T.; Kurimoto, S.; Kobayashi, J. In *Alkaloids: Chemistry and Biology*; Academic Press Inc., **2020**; Vol. 84, 1–124.

(13) Magnier, E.; Langlois, Y. *Tetrahedron*. Pergamon **1998**, 6201–6258.

(14) Jana, S.; Mekonnen, H. G. *ChemistrySelect* **2018**, *3* (18), 5198–5206.

(15) Baldwin, J. E.; Whitehead, R. C. *Tetrahedron Lett.* **1992**, *33* (15), 2059–2062.

(16) Baldwin, J. E.; Claridge, T. D. .; Culshaw, A. J.; Heupel, F. A.; Smrcková, S.; Whitehead, R. C.

Tetrahedron Lett. **1994**, *35* (42), 7829–7832.

(17) Baldwin, J. E.; Claridge, T. D. W.; Culshaw, A. J.; Heupel, F. A.; Lee, V.; Spring, D. R.; Whitehead, R. C. *Chem. Eur. J.* **1999**, *5* (11), 3154–3161.

(18) Townsend, C. A. *ChemBioChem* **2011**, *12* (15), 2267–2269.

(19) Byrne, M. J.; Lees, N. R.; Han, L.-C.; van der Kamp, M. W.; Mulholland, A. J.; Stach, J. E. M.; Willis, C. L.; Race, P. R. *J. Am. Chem. Soc.* **2016**, *138* (19), 6095–6098.

(20) Klas, K.; Tsukamoto, S.; Sherman, D. H.; Williams, R. M. *J. Org. Chem.* **2015**, *80* (23), 11672–11685.

(21) Tan, D.; Jamieson, C. S.; Ohashi, M.; Tang, M.-C.; Houk, K. N.; Tang, Y. *J. Am. Chem. Soc.* **2019**, *141* (2), 769–773.

(22) Kaiser, A.; Billot, X.; Gateau-Olesker, A.; Marazano, C.; Das, B. C. *J. Am. Chem. Soc.* **1998**, *120* (32), 8026–8034.

(23) Esterbauer, H.; Schaur, R. J.; Zollner, H. *Free Radic. Biol. Med.* **1991**, *11* (1), 81–128.

(24) Gómez-Sánchez, A.; Hermosín, I.; Lassaletta, J.-M.; Maya, I. *Tetrahedron* **1993**, *49* (6), 1237–1250.

(25) Becher, J. *Synthesis (Stuttg).* **1980**, 08, 589–612.

(26) Herdemann, M.; Al-Mourabit, A.; Martin, M.-T.; Marazano, C. *J. Org. Chem.* **2002**, *67* (6), 1890–1897.

(27) Gil, L.; Baucherel, X.; Martin, M.-T.; Marazano, C.; Das, B. C. *Tetrahedron Lett.* **1995**, *36*

(35), 6231–6234.

(28) Gil, L.; Gateau-Olesker, A.; Marazano, C.; Das, B. C. *Tetrahedron Lett.* **1995**, *36* (5), 707–710.

(29) Cutignano, A.; Tramice, A.; De Caro, S.; Villani, G.; Cimino, G.; Fontana, A. *Angew. Chemie - Int. Ed.* **2003**, *42* (23), 2633–2636.

(30) Cutignano, A.; Cimino, G.; Giordano, A.; D'Ippolito, G.; Fontana, A. *Tetrahedron Lett.* **2004**, *45* (12), 2627–2629.

(31) Winkler, J. D.; Axten, J. M. *J. Am. Chem. Soc.* **1998**, *120* (25), 6425–6426.

(32) Winkler, J. D.; Siegel, M. G.; Stelmach, J. E. *Tetrahedron Lett.* **1993**, *34* (41), 6509–6512.

(33) Winkler, J. D.; Bowen, C. M.; Liotta, F. *Chem. Rev.* **1995**, *95* (6), 2003–2020.

(34) Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1983**, *24* (48), 5425–5428.

(35) Lindlar, H. *Helv. Chim. Acta* **1952**, *35* (2), 446–450.

(36) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48* (22), 4155–4156.

(37) Humphrey, J. M.; Liao, Y.; Ali, A.; Rein, T.; Wong, Y. L.; Chen, H. J.; Courtney, A. K.; Martin, S. F. *J. Am. Chem. Soc.* **2002**, *124* (29), 8584–8592.

(38) Martin, S. F.; Liao, Y.; Wong, Y.; Rein, T. *Tetrahedron Lett.* **1994**, *35* (5), 691–694.

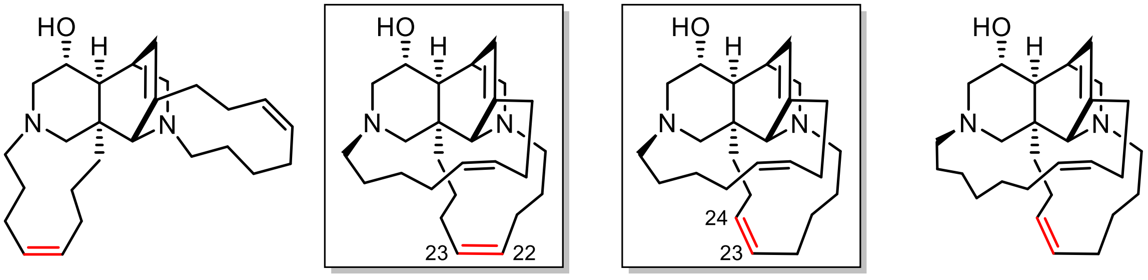
(39) Martin, S. F.; Rein, T.; Liao, Y. *Tetrahedron Lett.* **1991**, *32* (45), 6481–6484

CHAPTER II

SYNTHETIC APPROACHES OF XESTOCYCLAMINE A AND RELEVANT MANZAMINE ALKALOIDS

Introduction to Xestocyclamine A

Xestocyclamine A is a pentacyclic marine alkaloid in the manzamine alkaloid family first isolated from the sponge *Xestospongia* sp in 1993 by Crews et. al collected off the waters of Papua New Guinea.[40] Initial biological assays of xestocyclamine A revealed moderate inhibition against protein kinase C (IC_{50} = 4 μg/mL) and activity in whole cell IL-1 release assays (IC_{50} = 1 μM). Additionally, the authors state this activity appeared to be selective, as xestocyclamine A failed to display inhibition against related cancer-relevant targets such as protein tyrosine kinase (PTK) and inosine-5'-monophosphate dehydrogenase (IMPDH). Structurally, xestocyclamine A possesses several attractive synthetic challenges, namely the bicyclic [2.2.2] isoquinuclidine core, fused piperidine ring containing a chiral secondary alcohol, and two large flanking macrocyclic rings (Figure **2.1**). More importantly, structure elucidation of xestocyclamine A has remained challenging and has been repeatedly revised based on new NMR and structural evidence.



xestocyclamine A
original structure
1993
2.1

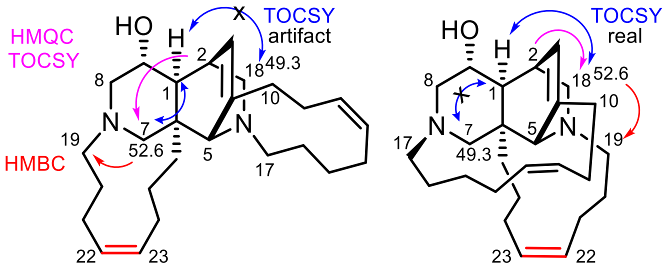
xestocyclamine A
revised structure
1994
2.2

xestocyclamine A
current proposed structure
2020
2.3

xestocyclamine B
original structure
1994
2.4

Figure 2.1 Proposed Structures of xestocyclamine A & B.

The original structure of xestocyclamine A (**2.1**) was proposed in 1993 from analysis of HRMS-EI and NMR data but was revised to **2.2** a year later upon further examination of new spectral data.[40] In 1994 the authors isolated xestocyclamine B (**2.4**), which aided in the identification of an artifact that previously led to a misassignment in the connectivity of the macrocyclic rings.[41] After characterization of xestocyclamine B was completed, reexamination of the xestocyclamine A ^{1}H-^{1}H TOCSY spectrum revealed the correlation between C1 and "C18" at 49.3 ppm to be an artifact. Further analysis demonstrated a TOCSY correlation between C1 and "C7" at 52.6 ppm, however this was inconsistent with spin-transfer across quaternary centers. Lastly, a HMBC correlation between the carbon at 52.6 ppm and C19 indicated that carbons C7 and C18 had been misassigned. Thus, the proton and carbon assignments of atoms C7 and C18 were switched, which produced the revised 1994 structure **2.2** with the correct macrocyclic connectivity.

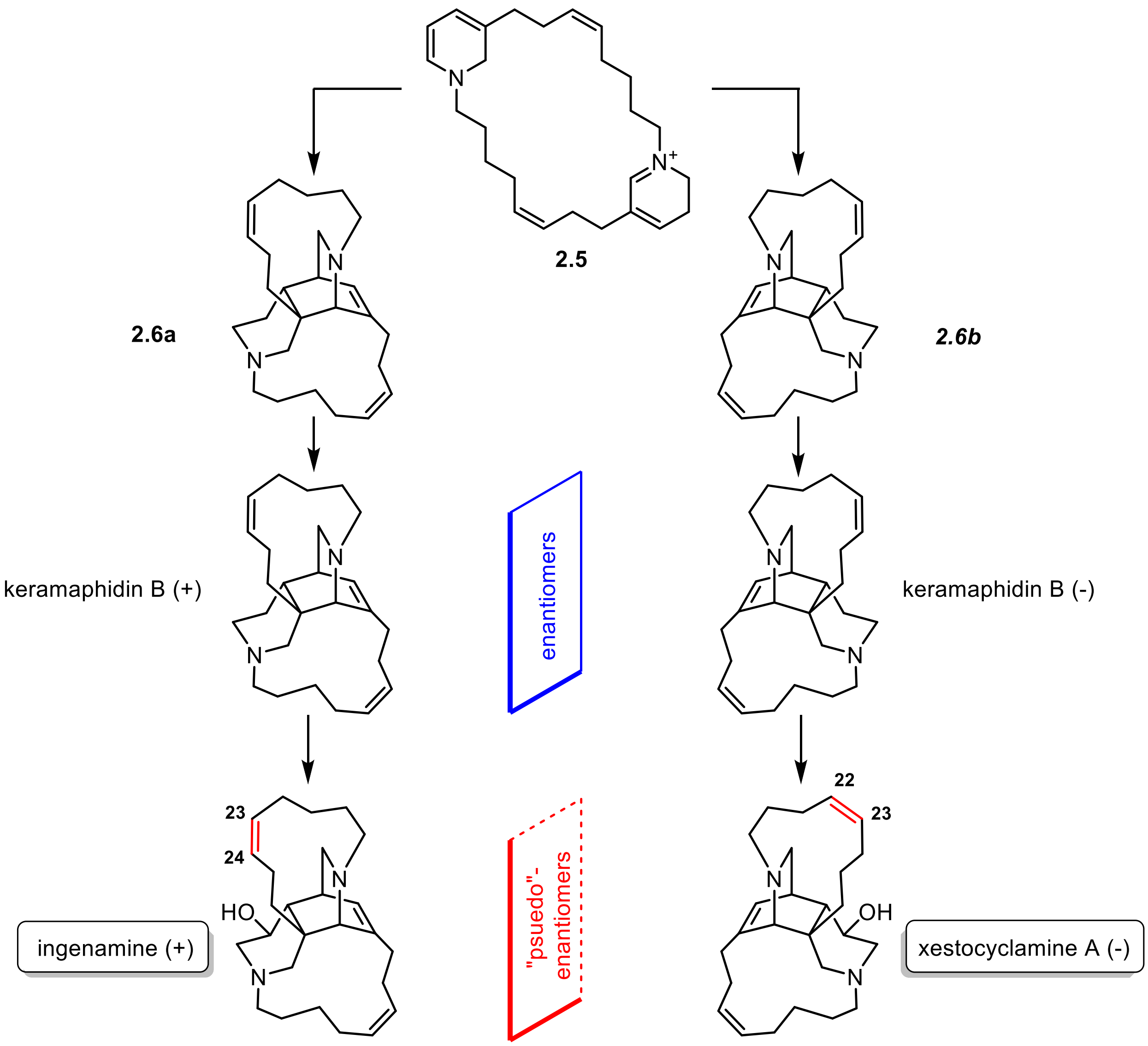


original structure
1993
2.1

revised structure
1994
2.2

Figure 2.1. Original and revised structures of xestocyclamine A.

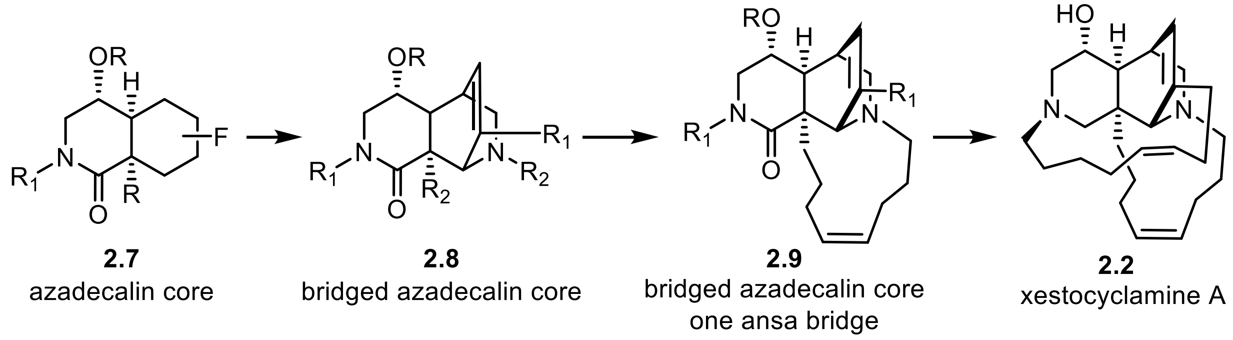
Thus, the revised 1994 or "nominal" structure **2.2** was thought to be correct until 2020, after a report from the Fürstner group revealed their synthetic sample of the completed natural product did not correlate with the isolation ^{1}H and ^{13}C NMR spectra.[42] X-ray crystallography of nominal xestocyclamine confirmed that the absolute stereochemistry and structure of nominal xestocyclamine A was correct, but a screen of deuterated solvents and titrated acid did not produce a matching spectrum. The authors then further investigated the biosynthetic pathway and other related natural products within the original Baldwin proposal. Xestocyclamine A appeared unique as the Δ22 unsaturation is uncommon in many of the manzamine alkaloids. Therefore, the authors hypothesized the true structure to share the more common Δ23 isomer. Whether or not if a "Diels-Alderase" plays a role in the proposed biosynthesis, a transannular cycloaddition could produce two possible enantiomers (Scheme **2.1**). Indeed, keramaphidin B has been isolated independently by the Andersen and Kobayashi groups as both the racemate and enantiomerically pure sample.[43–46] Furthermore, if ingenamine can be considered the "pseudo" enantiomer of xestocyclamine A, then the single difference is the Δ23 alkene which is common in both keramaphidins and other manzamine alkaloids. After further synthetic investigations, xestocyclamine A is now believed to be the enantiomer of ingenamine.



Scheme 2.1. Rational of certain manzamine alkaloids based on biosynthetic pathways.[42]

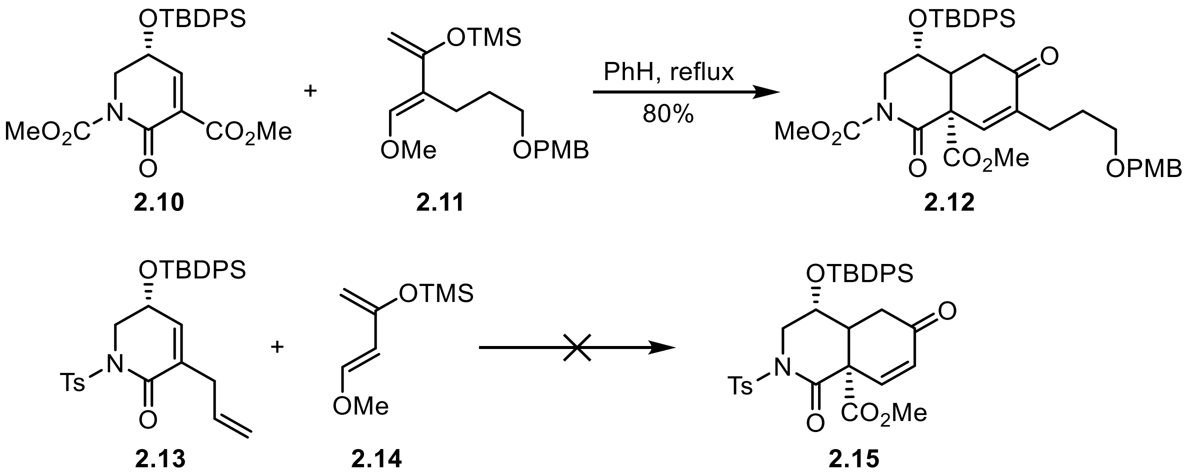
Danishefsky's Approach Towards Xestocyclamine A

The first published report toward the synthesis of xestocyclamine A came from Danishefsky and Gagnon who examined the construction of the azadecalin core via a Diels-Alder cycloaddition. Their synthetic strategy aimed to construct the azadecalin core prior to the bicyclic bridge and macrocyclic rings (Scheme **2.2**).[47]



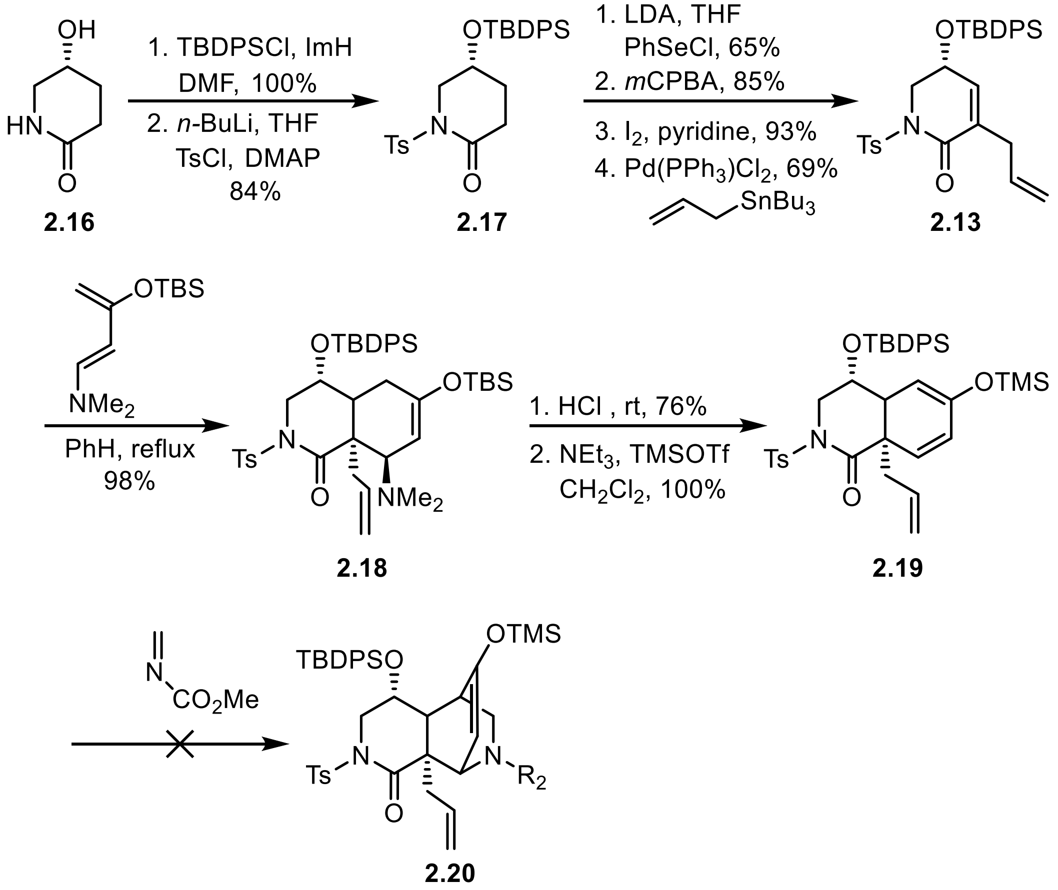
Scheme 2.2. Danishefsky's synthetic strategy. F = unspecified functionality.

The authors hoped to establish the azadecalin core of **2.7** with a Diels-Alder reaction and screened a variety of dienophiles for suitable reactivity (Scheme **2.3**). Early candidates included lactams **2.10** and **2.13**. The carbomethoxy group in **2.10** was an attractive activating group and reacted efficiently with the elaborated Danishefsky-type diene **2.11** to produce cycloadduct **2.12**. However, any attempt to reduce the methyl ester and functionalize the quaternary center failed. The elongated allylic handle in **2.13** offered better potential for functionalization, but lacked the activating effect of the carbomethoxy group. As a result, when reacted with diene **2.14**, the authors noted a lack of reactivity. However, when reacted with the more electron-releasing Rawal-Kozmin diene the authors were pleased to observe excellent reactivity.[48] Dienophile **2.13**



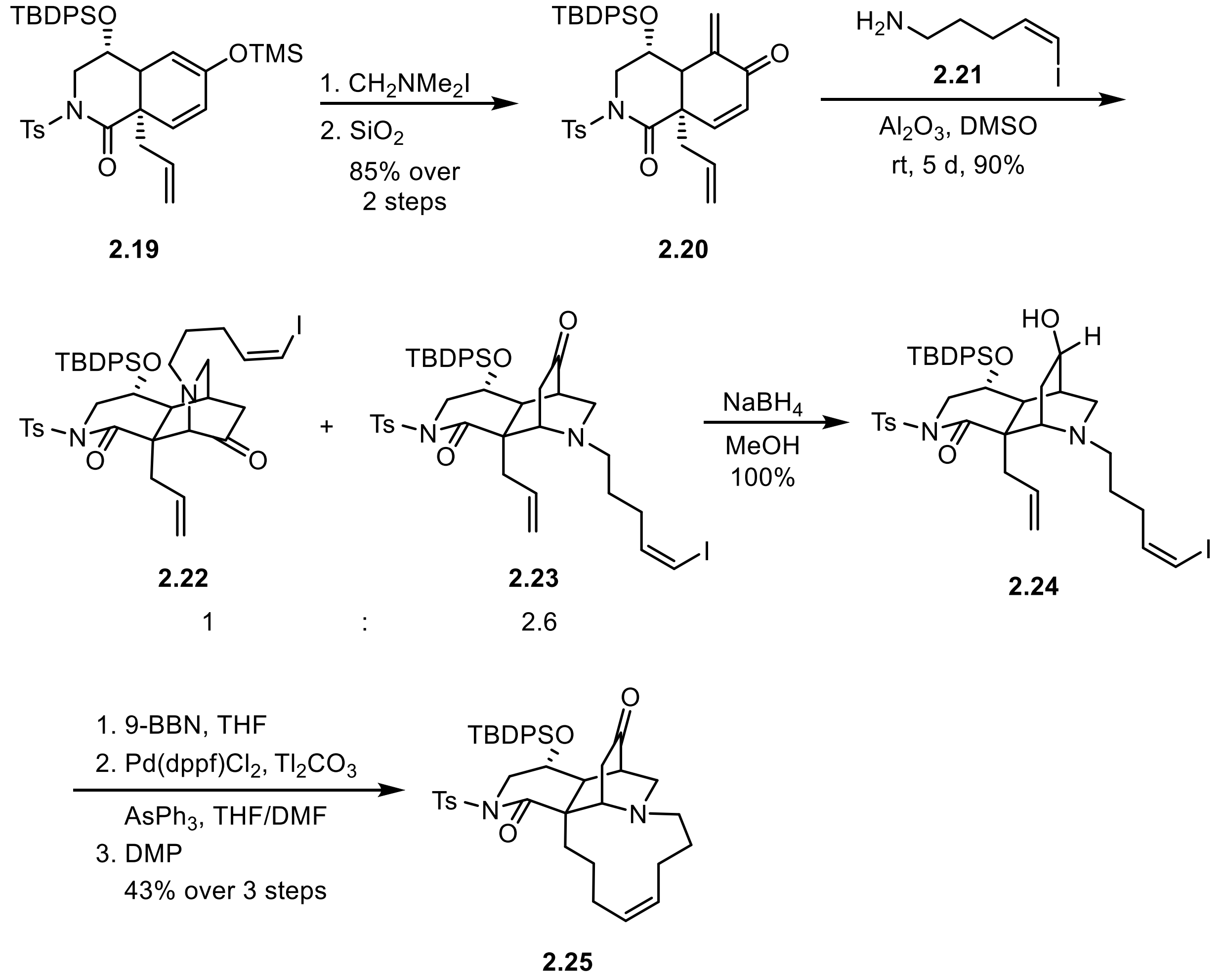
Scheme 2.3. Danishefsky's attempted Diels-Alder cycloadditions.

was synthesized in a straightforward manner from **2.16** (Scheme **2.4**). Access to the enantiomerically pure alcohol **2.16** was achieved in gram scale quantities from glutamic acid in a known 5-step sequence.[49] Silyl protection and subsequent tosylation of **2.16** afforded the bis-protected piperidine **2.17** in good yield. Next selenoxide elimination furnished the alkene and α-iodination followed by a Stille cross-coupling introduced the allylic handle.



Scheme 2.4. Danishefsky's synthesis of the azadecalin core.

With dienophile **2.13** in hand, treatment with Rawal-Kozmin diene in benzene at reflux generated cycloadduct **2.18** with excellent regio- and stereochemical control. Acid-mediated elimination and subsequent exposure to NEt_3 and TMSOTf yielded the silyl vinyl ether **2.19**. With the azadecalin core installed, the authors planned to introduce the bicycle with a heteronuclear Diels-Alder cycloaddition but failed to observe any formation of **2.20**.



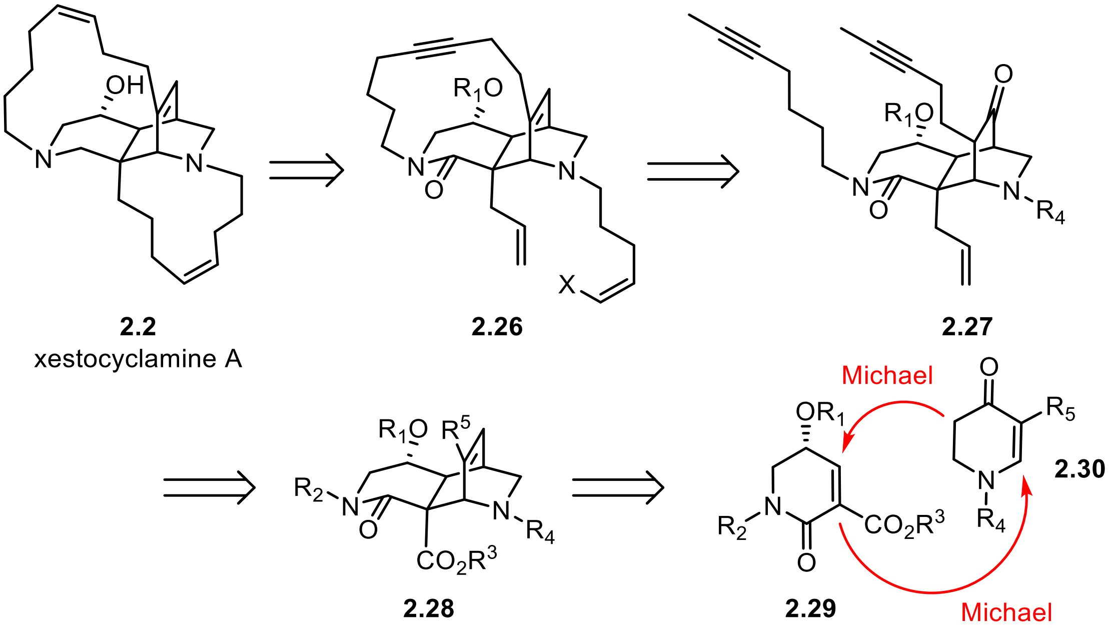
Scheme 2.5. Danishefsky's synthesis of the bicyclic core and macrocyclic ring.

With lack of reactivity, the authors sought to install the bridged bicyclic ring with an alternative strategy (Scheme **2.5**). Reaction of **2.19** with Eschenmoser's salt and stirring over acidic silica produced the exocyclic olefin **2.21**. Next, the key bond-forming reaction was performed when **2.21** was treated with amine **2.22** and weakly acidic aluminum oxide over 5 days. The tandem Michael addition proceeded in high yield but suffered from a lack of stereoselectivity and gave a mixture of desired: undesired isomers, **2.24**:**2.23**, in a 2.6: 1 ratio.

Now with the entire core set, Danishefsky and Gagnon proceeded to install the southern macrocycle. Taking advantage of the *cis*-vinyl iodide handle, the authors sought to functionalize the allylic handle and use a B-alkyl Suzuki cross-coupling to form the macrocyclic ring. Reduction of **2.24** with $NaBH_4$ produced alcohol **2.25**, which was then sequentially treated with 9-BBN, palladium catalyst, and Dess-Martin periodinane[36] to afford macrocycle **2.26**.

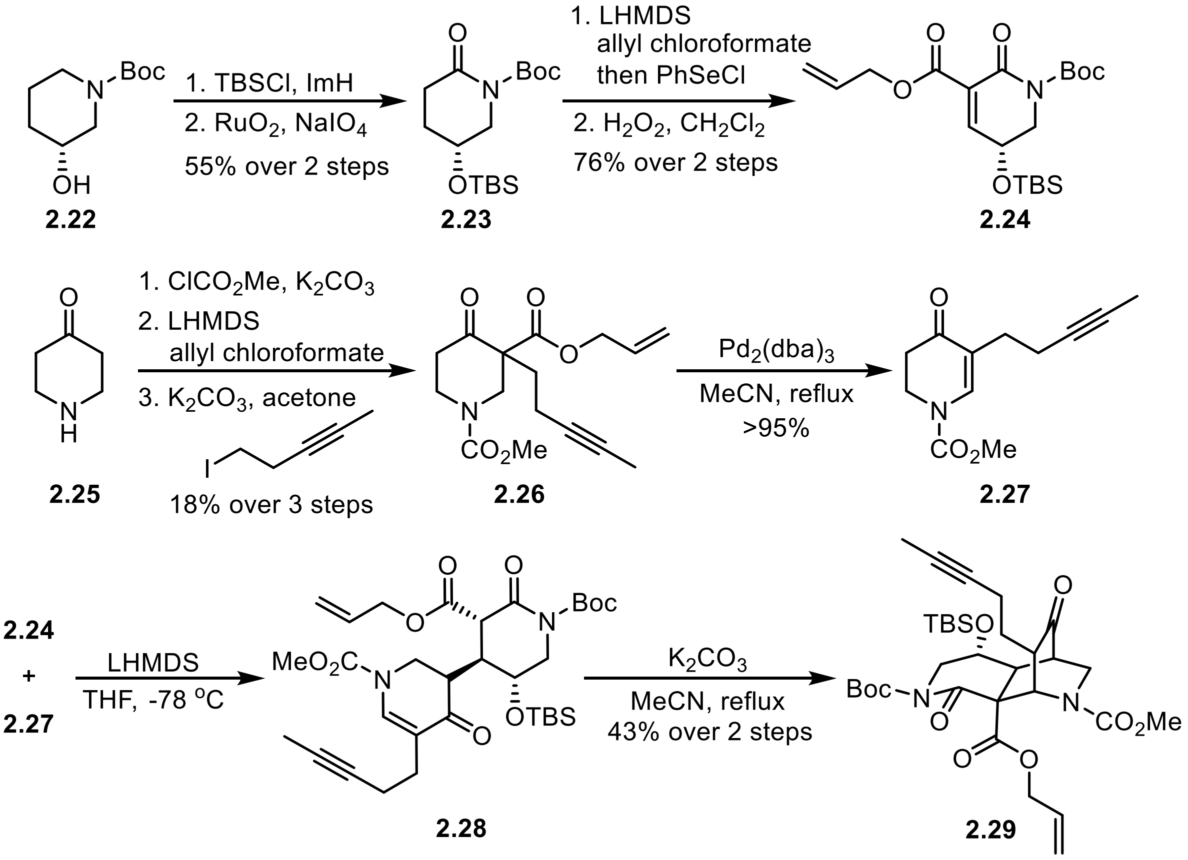
Fürstner Total Synthesis of Putative Xestocyclamine A

Recently the first total synthesis of xestocyclamine A was reported by the Fürstner and Meng in 2020.[42] However, as mentioned previously, the nominal structure failed to replicate spectra of an authentic sample and a new putative structure was synthetized.



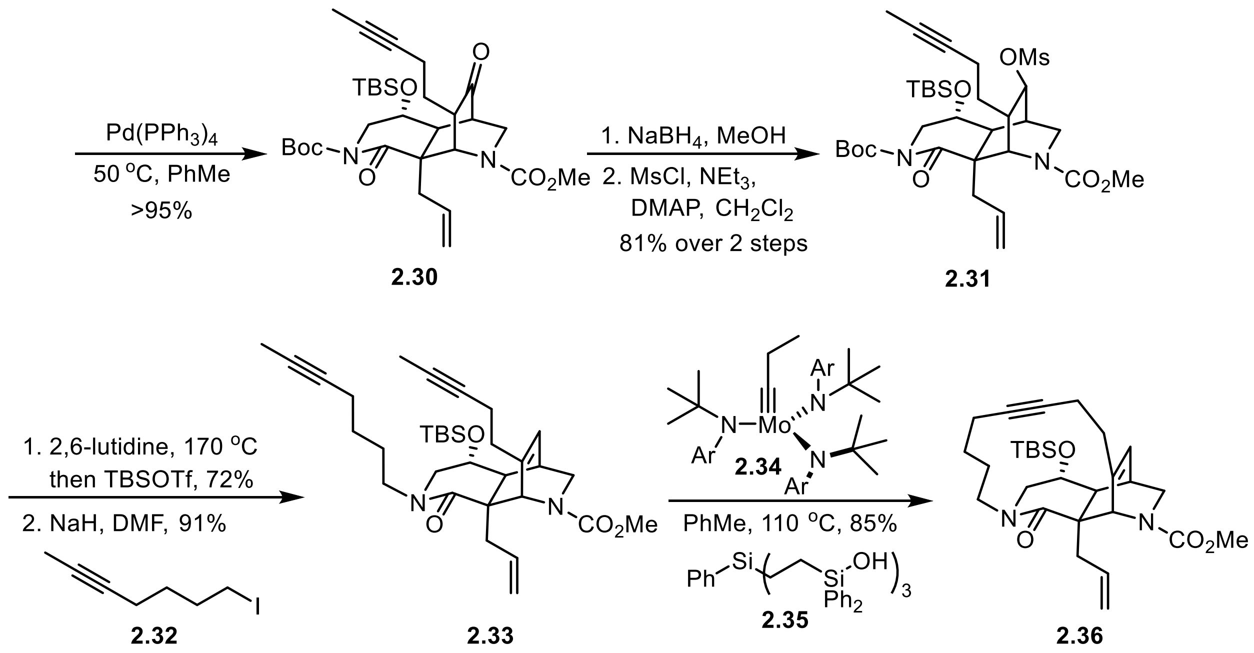
Scheme 2.6. Fürstner's retrosynthetic analysis of nominal xestocyclamine A.

The Fürstner group planned to reveal the Z-olefins in the macrocyclic rings with a combination of semi-reduction and B-alkyl Suzuki cross-coupling reactions (Scheme **2.6**). Intermediate **2.27** would be accessed with RCAM, Ring-Closing Alkyne Metathesis, chemistry heavily used in the Fürstner group. The central core of **2.28** would be set through tandem Michael additions from lactams **2.30** and **2.31**.



Scheme 2.7. Fürstner's approach to the bicyclic core of xestocyclamine A.

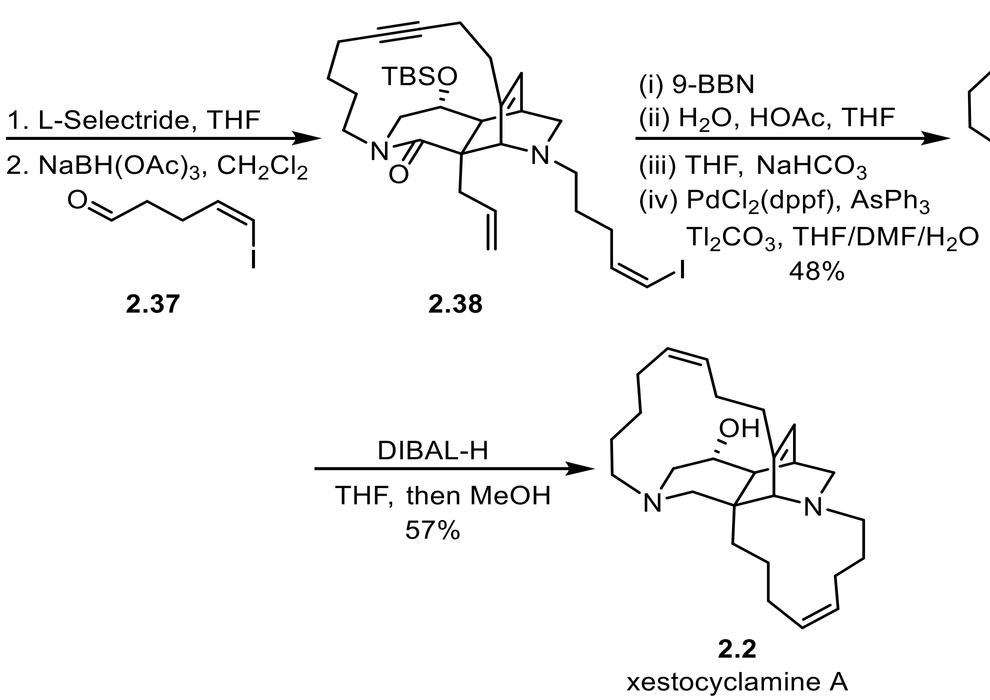
From the chiral alcohol **2.32**, silylation and subsequent regioselective C-H oxidation yielded lactam **2.33**. Upon enolate formation with LHMDS, alkylation and selenoxide elimination formed **2.34** in 76% over two steps. Synthesis of the other fragment began with **2.35** to form the carbamate and β-keto ester. Then treatment with K_2CO_3 and 5-iodopentyne gave **2.36** and introduced the alkynyl RCAM handle. Palladium-mediated decarboxylative dehydrogenation revealed **2.37** with no competitive reactivity. When lactams **2.34** and **2.37** were treated with LHMDS the double Michael addition was not observed and **2.38** was isolated. Further treatment with K_2CO_3 at reflux in acetonitrile induced the second conjugate addition to give **2.39**.



Scheme 2.8. Fürstner's approach to the northern macrocycle of xestocyclamine A.

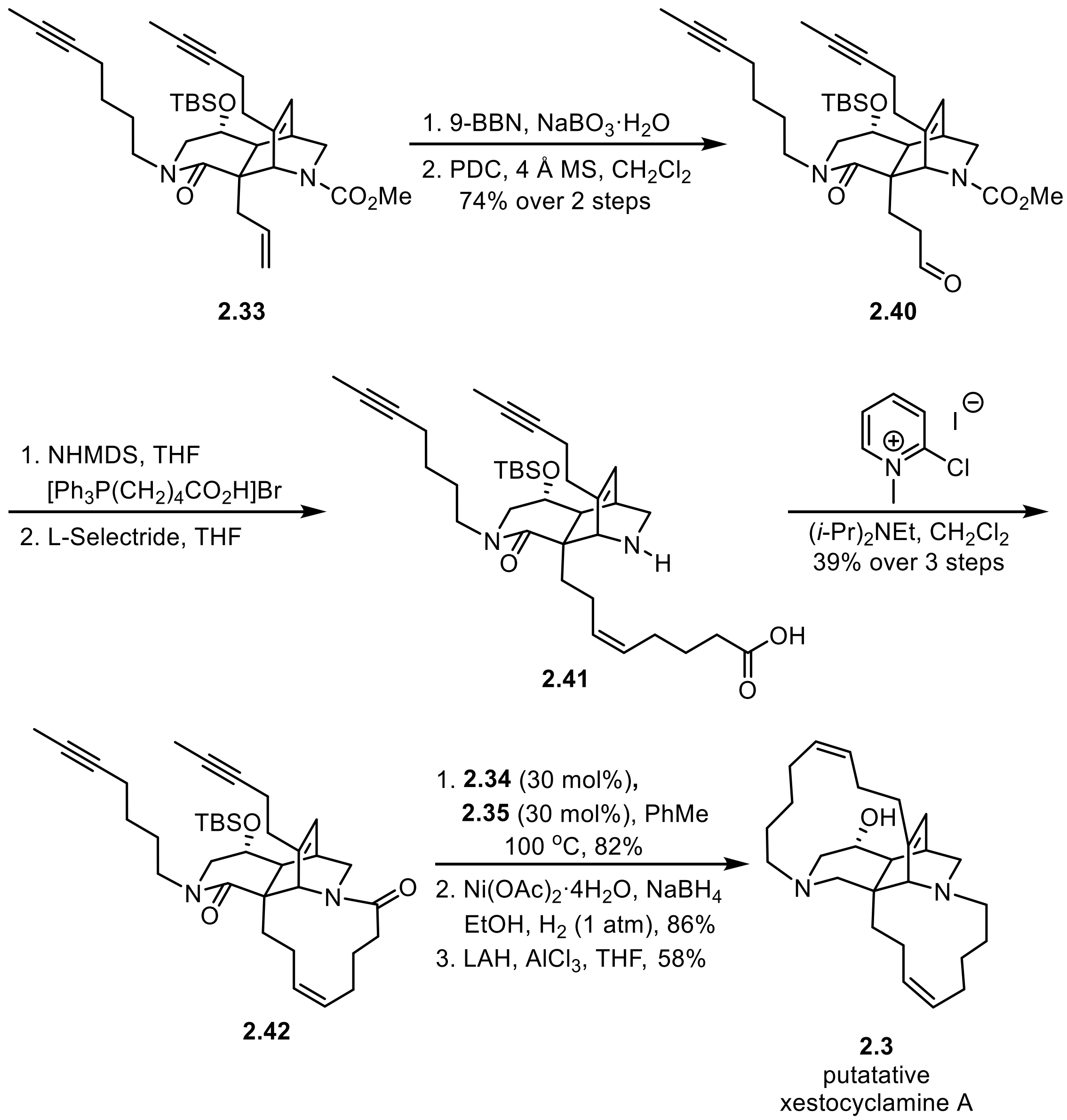
Palladium-catalyzed decarboxylative allylation installed the quaternary center of **2.40** in near quantitative yield. Reduction with $NaBH_4$ produced the secondary alcohol which was mesylated to afford **2.41**. Heat and 2,6-lutidine induced elimination of the mesylate and alkylation of the deprotected amine proceeded with NaH and alkyl iodide **2.42** to give **2.43**. With both alkynyl handles installed, the diyne was subjected to RCAM using molybdenum catalyst **2.44** and trisilanol ligand **2.45** to yield **2.46** in under 10 minutes. The structure of the macrocyclic ring was confirmed by X-ray diffraction.

Cleavage of the methyl carbamate was induced with L-Selectride and followed by reductive amination with aldehyde **2.47** to give the tertiary amine **2.48** (Scheme **2.9**). Next hydroboration with 2 equivalents of 9-BBN, selective hydrolysis of the vinyl borane, and cross-coupling successfully installed the southern macrocycle of **2.49** in 48% yield. Final reduction of the amide with DIBAL-H gave nominal xestocyclamine A.



Scheme 2.9. Fürstner's approach to the southern macrocycle of xestocyclamine A.

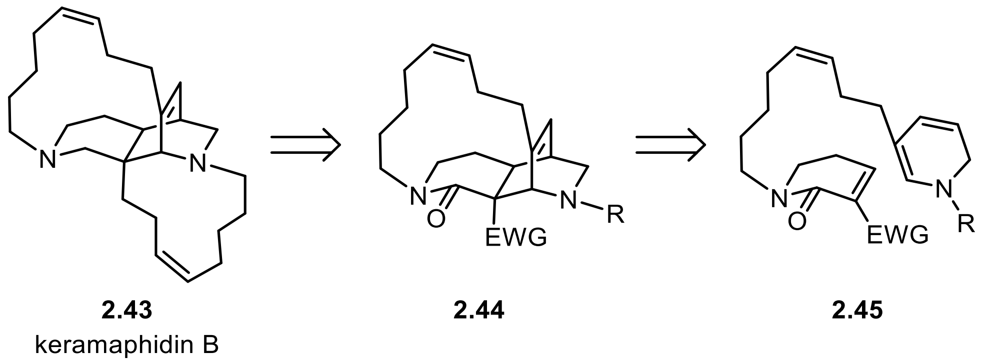
As the nominal structure of xestocyclamine A did not correlate with isolation data, the authors then went forward and synthesized the Δ23 isomer (Scheme **2.10**). Beginning with intermediate **2.43**, a hydroboration-oxidation sequence using 9-BBN and sodium perborate and subsequent treatment with PDC delivered aldehyde **2.50**. Next, Wittig olefination with the non-stabilized ylide afforded the Z-olefin and deprotection of the methyl carbamate with L-Selectride revealed the secondary amine **2.51**. When treated with Mukaiyama's reagent[50], macrocyclization gave the 11-membered lactam **2.52** in 39% yield over 3 steps. RCAM using catalyst **2.44** and ligand **2.45** installed the northern 13-membered macrocycle. Semi-reduction with nickel borohydride generated the Z-olefin and global reduction with in-situ generated AlH_3 furnished putative xestocyclamine.



Scheme 2.10. Fürstner's synthesis of putative xestocyclamine A.

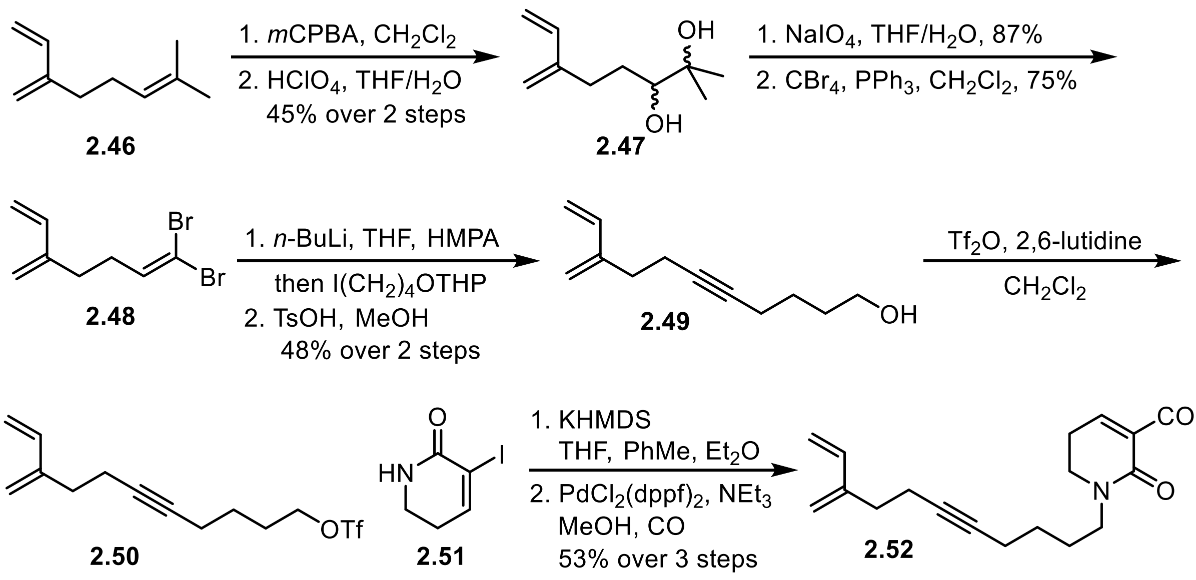
Nakada's Approach Toward Keramaphidin B

Recently the Nakada group reported a novel approach toward the construction of the bicyclic core in the manzamine alkaloids.[51] In their approach toward the total synthesis of keramaphidin B, the authors took inspiration from the Baldwin biosynthetic approach and envisioned a modified intramolecular Diels-Alder (IMDA) cycloaddition to access the central scaffold (Scheme **2.11**). Seeking to avoid the use of two unstable dihydropyridine macrocyclic intermediates, the authors sought to employ dihydropyridine and lactam moieties of **2.55** in an IMDA.



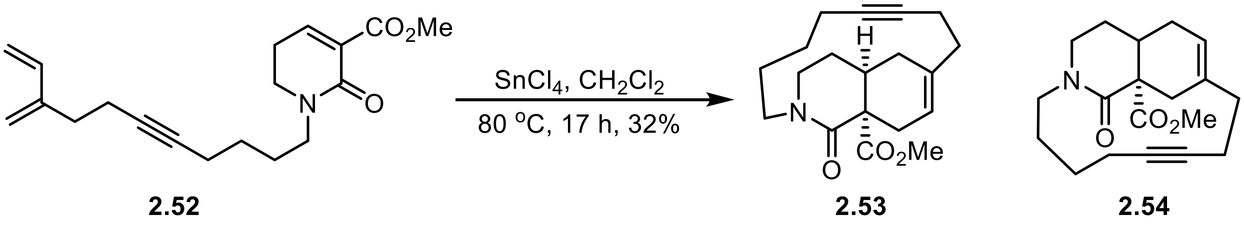
Scheme 2.11. Nakada's retrosynthetic analysis of keramaphidin B.

Synthesis of the IMDA precursor began from the epoxidation of commercially available myrcene with *m*CPBA followed by treatment with perchloric acid to give diol **2.57** (Scheme **2.12**). Oxidative cleavage with sodium periodate produced the resulting aldehyde which was immediately subjected to Corey-Fuchs conditions and the alkynyl lithiate quenched with iodoalkane. Reaction with *p*-toluenesulfonic acid furnished primary alcohol **2.59**. Triflation with Tf_2O and subsequent displacement with secondary amide **2.61** yielded the N-alkylated amide. Next palladium-catalyzed carbonylation furnished the methyl ester **2.62** and fully elongated IMDA precursor.



Scheme 2.12. Nakada's synthesis of IMDA precursor toward keramaphidin B.

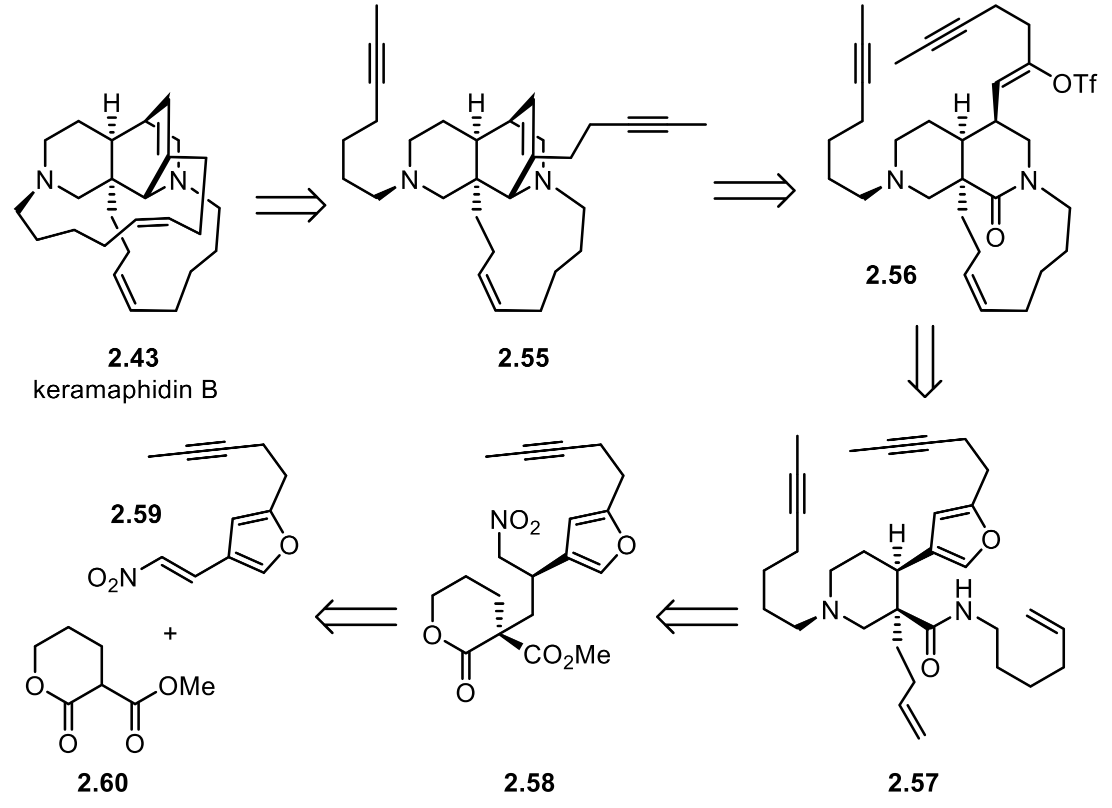
The penultimate intramolecular cyclization was nontrivial, and a variety of conditions were screened. In addition to the cyclized regioisomers, **2.53** and **2.54**, complex mixtures containing pyridinone intermediates were also characterized. Employment of stoichiometric Lewis acids such as: $MgBr_2$, $Zn(OTf)_2$, $ZnBr_2$, $InCl_3$, and $Cu(OTf)_2$ resulted in no reaction, inseparable mixtures, or trace product formation. Ultimately the authors found when **2.62** was treated with $SnCl_4$ and heat, the Type II IMDA cyclization proceeded in 32% to yield **2.63** (Scheme **2.13**). Unfortunately, **2.63** is the undesired regioisomer, and the yield of the desired isomer **2.64** was not reported.



Scheme 2.13. Nakada's synthesis of IMDA precursor.

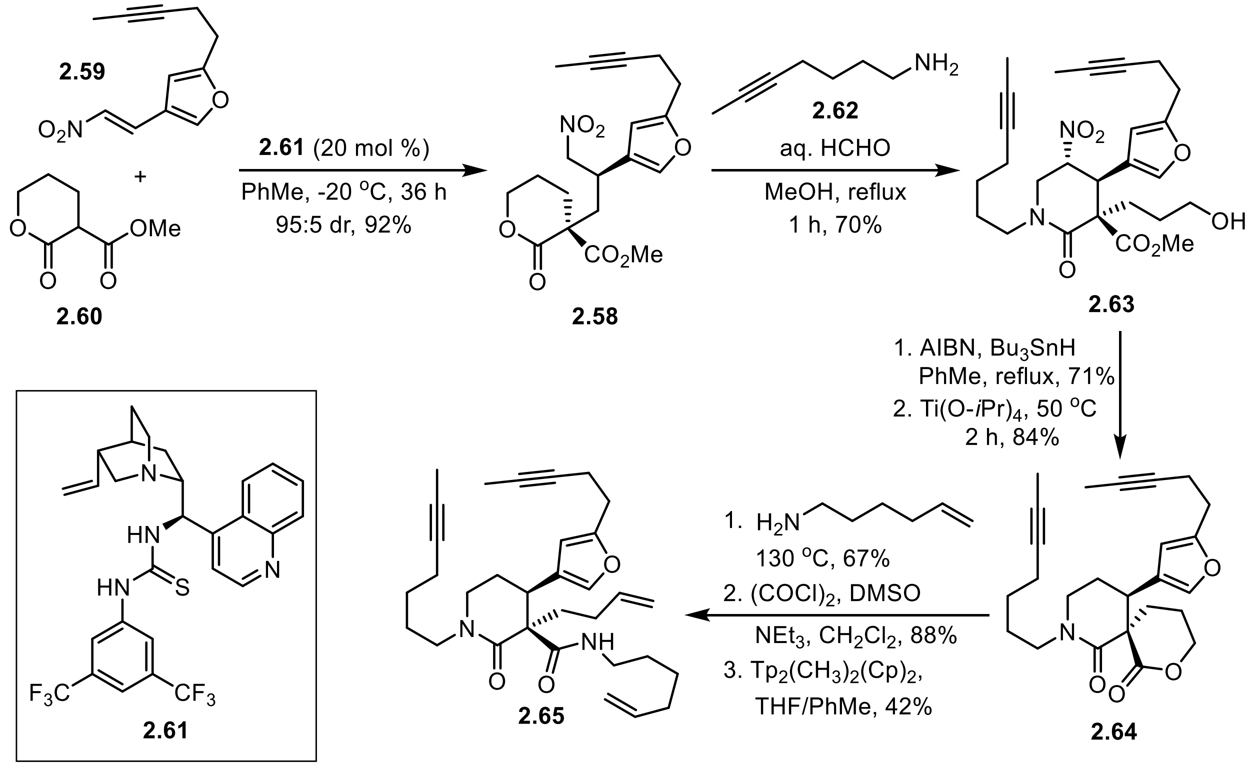
Dixon's Approach Toward Keramaphidin B

The Dixon group has reported the total synthesis of several manzamine alkaloids, namely: manzamine A, ircinal A, and nakadomarin A.[52,53] In 2016, the Dixon group published a report on the progress toward the total synthesis of keramaphidin B, in which the authors employ similar nitro-Mannich reactions and macrocyclization strategies in their retrosynthetic analysis as used in their previously named syntheses (Scheme **2.14**).[54]



Scheme 2.14. Dixon's retrosynthetic analysis of keramaphidin B.

The authors' immediately set out to install the stereochemistry of the quaternary center with a diastereoselective organocatalyzed Michael addition. When **2.69** and **2.70** were reacted in the presence of the cinchonine-derived organocatalyst **2.71**, nitroalkane **2.72** was isolated in 95:5 dr and 92% yield (Scheme **2.15**). Aminolysis of the δ-lactone with amine **2.73** was followed by treatment with aqueous formaldehyde and produced the resulting iminium which induced cyclization from the nitroalkane to give **2.74**. Radical-initiated reductive cleavage of the nitroalkane proceeded when heated in the presence of AIBN and Bu_3SnH. Subsequent Lewis acid catalyzed lactonization employing Ti(O-*i*Pr)$_4$ gave **2.75**. Aminolysis of the newly formed δ-lactone revealed the primary alcohol, which was then oxidized under Swern conditions and treated with Petasis reagent[55] to give alkene **2.76**. With both terminal olefin handles installed the authors plan to utilize ring-closing metathesis for the closure of the first macrocyclic ring.



Scheme 2.15. Dixon's synthetic approach towards keramaphidin B.

Conclusion to Chapter 2

The structure of xestocyclamine A has received considerable interest which can be attributed to its diverse functionality that includes its isoquinuclidine core, congested piperidine ring fusion, and large macrocyclic rings. While the structure of xestocyclamine A appears to have been fully validated, two syntheses from independent groups were required to do so, and notedly completed nearly 30 years after its isolation. Synthetic strategies toward xestocyclamine A and structurally related natural products were examined whose chemistry included: cycloadditions, Michael additions, Mannich reactions, cross-couplings, and RCM macrocyclizations.

References

(40) Rodriguez, J.; Peters, B. M.; Kurz, L.; Schatzman, R. C.; McCarley, D.; Lou, L.; Crews, P. *J. Am. Chem. Soc.* **1993**, *115* (22), 10436–10437.

(41) Rodríguez, J.; Crews, P. *Tetrahedron Lett.* **1994**, *35* (27), 4719–4722.

(42) Meng, Z.; Fürstner, A. *J. Am. Chem. Soc.* **2020**, *142* (27), 11703–11708.

(43) Kong, F.; Andersen, R. J. *Tetrahedron* **1995**, *51* (10), 2895–2906.

(44) Kobayashi, J.; Kawasaki, N.; Tsuda, M. *Tetrahedron Lett.* **1996**, *37* (45), 8203–8204.

(45) Kobayashi, J.; Tsuda, M.; Kawasaki, N.; Matsumoto, K.; Adachi, T. *Tetrahedron Lett.* **1994**, *35* (25), 4383–4386.

(46) Tsuda, M.; Inaba, K.; Kawasaki, N.; Honma, K.; Kobayashi, J. *Tetrahedron* **1996**, *52* (7), 2319–2324.

(47) Gagnon, A.; Danishefsky, S. J. *Angew. Chem. Int. ed.* **2002**, *41* (9), 1581–1584.

(48) Auerbach, K. G. *J. Hum. Lact.* **1989**, *5* (3), 121–121.

(49) Herdeis, C. *Synthesis (Stuttg).* **1986**, *1986* (03), 232–233.

(50) Narasaka, K.; Maruyama, K.; Mukaiyama, T. *Chem. Lett.* **1978**, *7* (8), 885–888.

(51) Nakada, M.; Shimoda, H.; Shibata, T.; Sekine, D. *Heterocycles* **2020**, *100* (1), 3.

(52) Jakubec, P.; Hawkins, A.; Felzmann, W.; Dixon, D. J. *J. Am. Chem. Soc.* **2012**, *134* (42), 17482–17485.

(53) Kyle, A. F.; Jakubec, P.; Cockfield, D. M.; Cleator, E.; Dixon, D. J. *Chem. Commun.* **2011**, *47* (36), 1–3.

(54) Jakubec, P.; Farley, A. J. M.; Dixon, D. J. *Beilstein J. Org. Chem.* **2016**, *12* (1), 1096–1100.

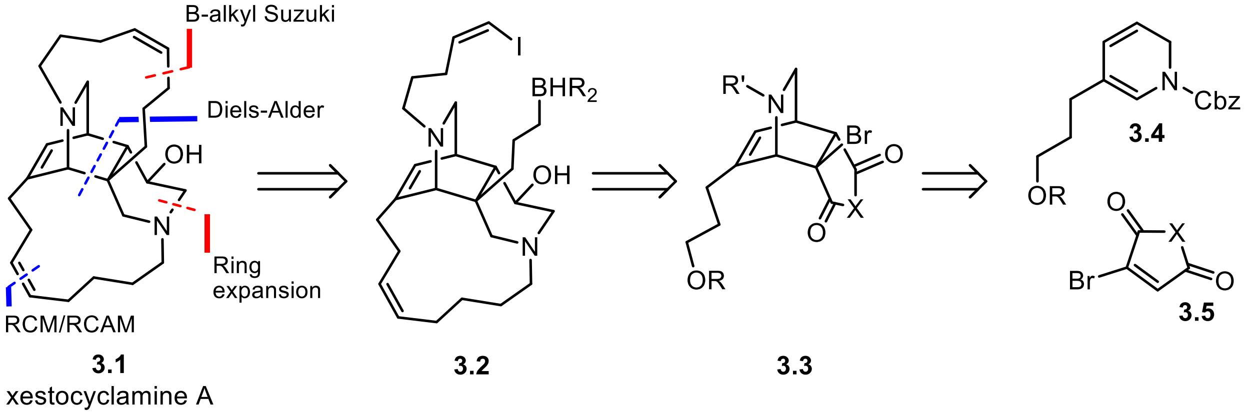
(55) Petasis, N. A.; Bzowej, E. I. *J. Am. Chem. Soc.* **1990**, *112* (17), 6392–6394.

CHAPTER III

SYNTHETIC ANALYSIS AND DEMONSTRATION OF [4+2] CYCLOADDITION

Retrosynthetic Analysis of Xestocyclamine A

It is important to consider xestocyclamine A's rich history concerning its proposed biosynthesis and previously employed synthetic strategies when developing a retrosynthetic plan. To this end, our synthetic strategy aimed to incorporate the same key disconnection as seen in the original Baldwin and Whitehead proposal.[15] The installation of the two central C-C bonds would be enabled via a Diels-Alder cycloaddition between a functionalized dihydropyridine **3.4** and suitable dienophile **3.5** (Scheme **3.1**). Such a cycloaddition would construct the central core in a single step and allow for a more robust and convergent strategy.



Scheme 3.1 First generation retrosynthetic analysis of xestocyclamine A, X = O; X = NR.

However, it is crucial to note the limited success of the transannular and intramolecular cyclization approaches used by the Baldwin and Nakada groups (Figure **3.1**). Therefore, an intermolecular cycloaddition appeared to offer the best reactivity. Furthermore, despite the apparent instability of dihydropyridines, there are several examples in the literature which have utilized them in natural product total syntheses or methodology studies.[27,56–64]

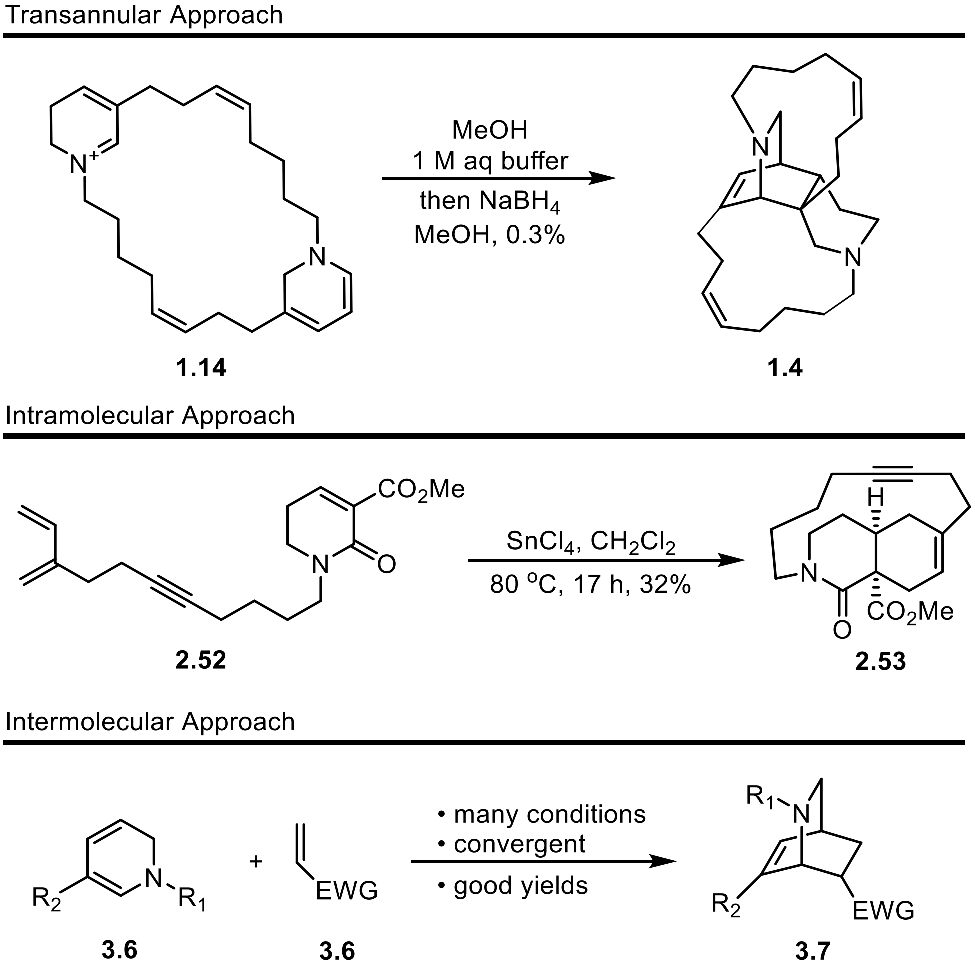
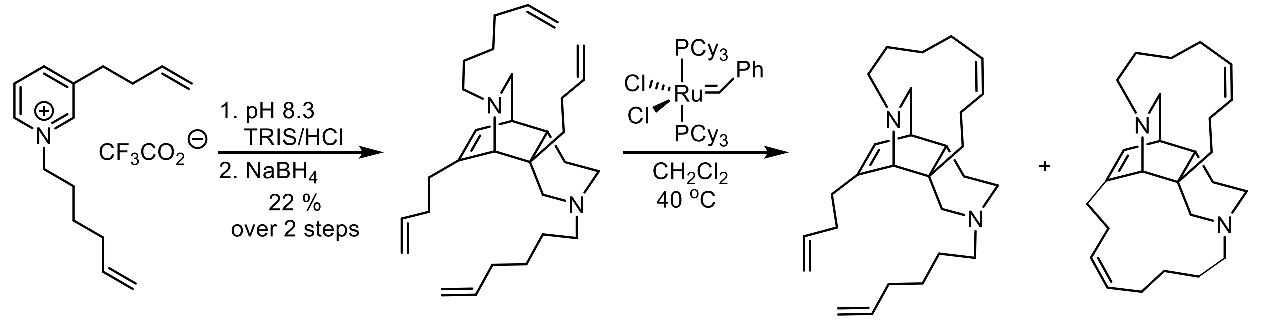


Figure 3.1 Cycloaddition strategies toward the core of manzamine alkaloids.

The two next most prominent obstacles involved synthesis of the large 13 and 11-membered macrocyclic rings containing Z-olefins. This presented a challenge with two possible variables, namely a macrocyclization strategy (e.g. Yamaguchi macrolactamization followed by lactam reduction) and an olefination strategy (e.g. Wittig olefination). While there are a multitude of many other possible approaches, our synthetic strategy planned on employing ring-closing metathesis (RCM) reactions for synthesis of at least one macrocycle. This disconnection across the C=C bond would solve both possible variables, macrocyclization and olefination, in a single step. Using the well-established Grubbs catalysts, including the Z-Selective Grubbs

Catalyst® C633, would offer a powerful method for synthesizing the Z-alkenes.[62–64]

We planned on exploring an alternative strategy for the second macrocycle as treatment of the terminal diolefin substrate with Grubbs catalyst in the presence of the first macrocycle may result in competitive ring-opening reactions. Indeed, this was observed in Martin's total synthesis of manzamine A, as described previously in (Scheme **1.14**).[38] Additionally, a double RCM cyclization proved less than ideal, as observed by the Baldwin group in their total synthesis of keramaphidin B (Scheme **3.2**).[17] In this case, reduction of pyridinium **3.8** lead to a Diels-Alder cycloaddition to afford cycloadduct **3.9.** When the tetraolefin **3.9** product was subjected to Grubbs Gen I catalyst, monocyclic product **3.10** and keramaphidin B were isolated in 10-20% and 2% yield, respectively. The low yields can be attributed to the obvious statistical possibility for undesired products which include: E/Z isomers, polymeric species, and macrocycles with incorrect connectivity.



3.8 **3.9** 10-20% **3.10** 2% **1.4** keramaphidin B

Scheme 3.2 Baldwin's double RCM approach toward the total synthesis of keramaphidin B.

Thus, we aimed to synthesize the second macrocycle through the use of a B-alkyl Suzuki cross-coupling reaction. This would allow a noncompetitive cyclization strategy and offer another convergence point to install a fully elaborated alkyl species from N-alkylation of the isoquinuclidine nitrogen. This B-alkyl Suzuki cross-coupling is also the same strategy Danishefsky and Gagnon used to install the first macrocyclic ring, as described previously in Scheme **2.16**.[47]

The last important structural challenge posed was the introduction of the quaternary center and fused piperidine ring. Fortunately, the employment of a unique α-halo dienophile would allow us to address both challenges. Notedly, use of such a dienophile has been successfully implemented by previous members of the Sulikowski lab.[60]

Dihydropyridines and Bromomaleic Anhydride: Diene and Dienophile

To this end, a 1,6-dihydropyridine with a substituent at the 3 position would produce the substituted isoquinuclidine core, presuming an *endo* selective cycloaddition, the desired stereochemistry would be obtained. Thus, a suitable dienophile was the last remaining requirement for this key transformation. Our initial investigations made use of bromomaleic anhydride, a commercially available and unique dienophile. which has seen little use in the literature.[56–58] Such a substrate would offer several advantages due to its inherent electronic properties. Firstly, the carbonyl moieties are well known to prefer the *endo* transition state in the Diels-Alder cycloaddition due to secondary orbital overlap, and would produce the desired stereoisomers. Secondly the electronegative nature of the bromine atom would create an inductive effect and generate partial positive charges on the alkene of the dienophile, and resultingly afford the correct regioisomers. Lastly, the bromine atom could serve as a functional group handle for installation of the congested quaternary center. We aimed to achieve this transformation via a radical-mediated Keck allylation.[59] In consideration of the radical intermediate, we intended for the rigid structure of the [2.2.2] bicyclic core to prevent epimerization to the more strained *trans* isomer. Fortunately, Wenzler and Sulikowski, demonstrated this strategy in their work toward the total synthesis of upenamide A, a related manzamine alkaloid.[60]

Wenzler and Sulikowski's Approach Toward the ABC Ring System of Upenamide

In 2016, the Sulikowski group published a report on the progress made toward the total synthesis of upenamide A.[60] In their retrosynthetic analysis (Figure **3.2**), the authors aimed to synthesize the C-ring system via a Diels-Alder cycloaddition between bromomaleic anhydride **3.13** and diene **3.14**.

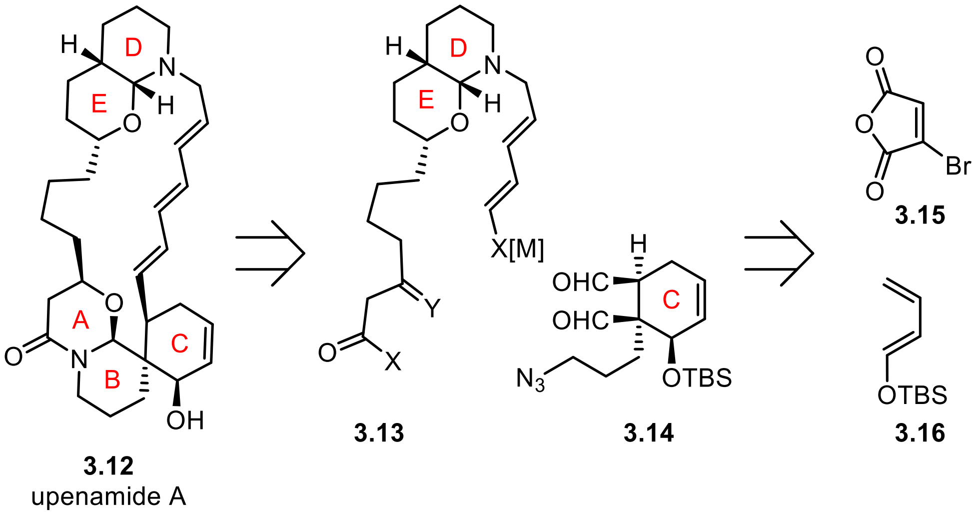
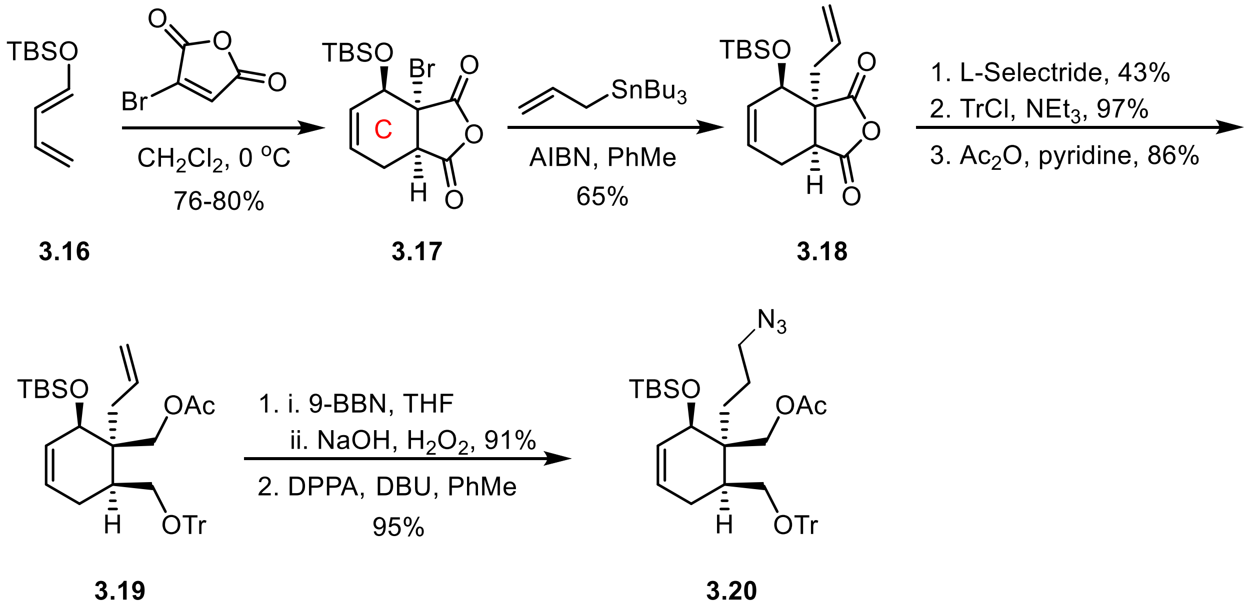


Figure 3.2 Wenzler and Sulikowski's retrosynthetic analysis of upenamide A.

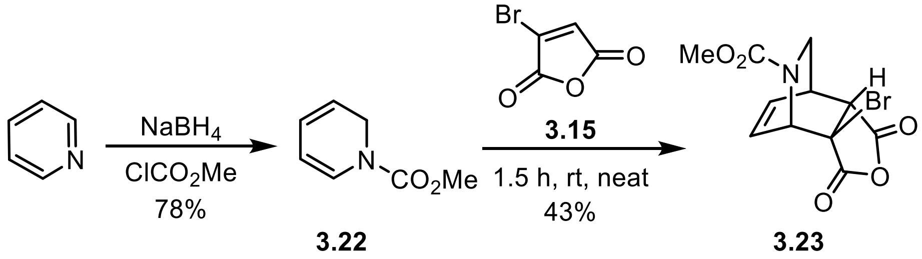
Indeed, when diene **3.14** was reacted with bromomaleic anhydride under mild reaction conditions, cycloadduct **3.15** was isolated as a crystalline solid in 76-80% yield as a single isomer (Scheme **3.3**). Radical mediated allylation was initiated with AIBN and produced **3.16** in 65% yield. Notedly, the β-epimer was observed in up to 23% yield. From anhydride **3.16**, reduction with L-Selectride generated the diol, from which, tritylation of the less sterically hindered alcohol was followed by acetylation of the second primary alcohol to give **3.17** in good yields. Hydroboration-oxidation of the allyl handle was successful when reacted with 9-BBN and basic peroxide. The resulting alcohol was displaced upon treatment with diphenylphosphoryl azide to give **3.18** in 86% over 2 steps.



Scheme 3.3 Synthesis of the C ring via a Diels-Alder cycloaddition and Keck allylation strategy.

First Generation Approach Toward Xestocyclamine A and Diene Substrates

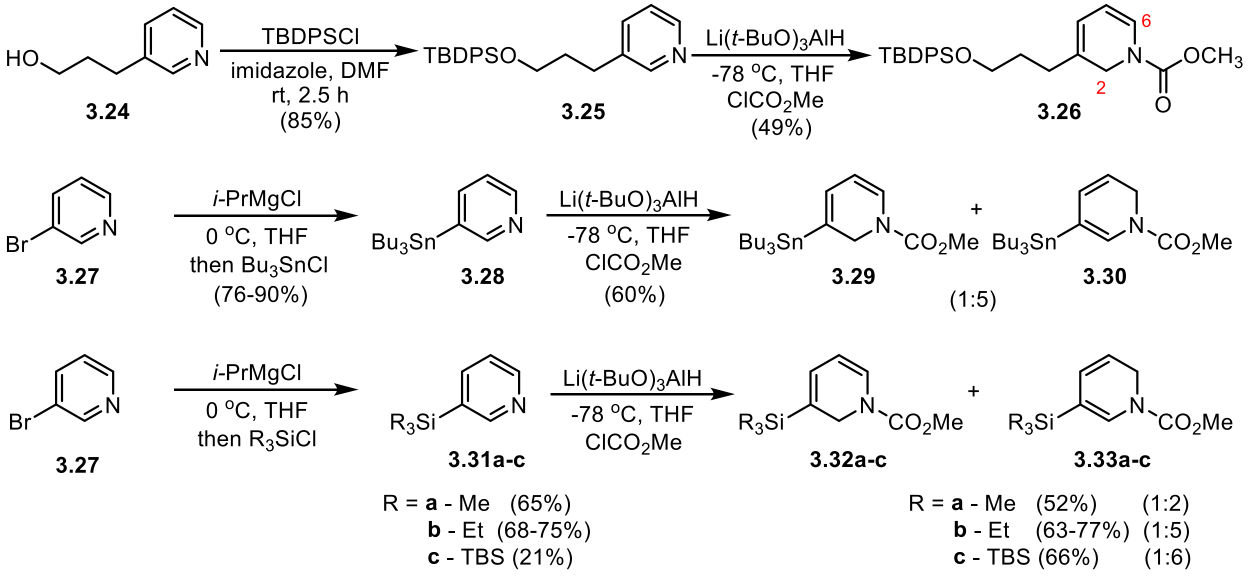
In consideration of the studies from Wenzler and Sulikowski, our first investigations aimed to test a simple model system (Scheme **3.4**). In contrast to highly reactive Danishefsky-type dienes such as **3.16** or **2.14**, dihydropyridines have seen far less use in the literature. Although the nitrogen atom is more electron-releasing than oxygen, nitrogens of dihydropyridines are typically connected to an electron-withdrawing group, thus lowering the diene HOMO. For example, carbamate protecting groups are often used to activate the pyridinium species and facilitate reduction to the dihydropyridine. However, this creates a second important structurally-related challenge, dihydropyridines are prone to oxidative elimination and in turn generate stabilized aromatic pyridines. Furthermore, the presence of oxygen, elevated temperatures, and basic conditions accelerate this decomposition. This became a crucial obstacle in future routes, but for the model system was of no concern. Synthesis of dihydropyridine **3.19** was straightforward and achieved in 78% yield upon treatment with conditions developed by Fowler.[61] Next, after a short screening of reaction conditions, it was found that under mild reaction conditions, cycloadduct **3.20** was isolated as a single isomer in 43% upon treatment with bromomaleic anhydride.



Scheme 3.4 Model system for dihydropyridines in the Diels-Alder reaction.

Trialkyl-Stannyl and Silyl Substituted 1,6-Dihydropyridines

With proof of concept in hand, we next focused on developing a synthesis for a 3-substitued dihydropyridine that would act as a functional handle for introduction of the Southern macrocyclic ring. However, 3-substitued pyridines are known to prefer reduction at the C2 position over the C6, leading to the undesired 1,6-dihydropyridine. This was demonstrated in Scheme **3.5** even when the alkyl-substituted pyridine **3.21** was treated with the bulky reducing agent, Li(*t*-OBu)$_3$AlH, where the undesired 1,2-dihydropyridine **3.22** was isolated in 49% rather than the 1,6-dihydropyridine isomer. In order to obtain the correct regioisomer, we next set forth synthesizing two series of trialkylstannyl and silyl substituted pyridines. This was chosen due to investigations by Sundberg and coworkers which demonstrated the effects of substituents and hydride sources on the reduction of substituted pyridines.[62] In their report, trialkylstannyl and trialkylsilyl pyridines produced the highest ratios of 1,6-dihydropyridines when treated with bulky reducing agents such as Li(*t*-BuO)$_3$AlH and K(*i*-OPr)$_3$BH. The preference for the 1,6-isomer was clearly shown to be guided by steric hindrance. In addition to their ability to dictate regioselectivity, both trialkylstannanes and silanes could potentially serve as cross-coupling partners post cycloaddition in Stille[63] and Hiyama[64] cross-coupling reactions, respectively. The two series of pyridines were accessed via magnesium-halogen exchange upon reaction between bromopyridine **3.24** and *i*-PrMgCl followed by quench with the metal chloride. Substituted pyridines **3.25** and **3.28a-c** were then reduced using Li(*t*-BuO)$_3$AlH to give a mixture of 1,2- and 1,6-dihydropyridines. In the stannyl series, **3.26:3.27** were obtain in a 1:5 ratio favoring the desired 1,6 isomer. In the silyl series, as steric bulk increased from trimethyl silyl **3.30a** to tert-butyl dimethyl silyl **3.30c**, the ratio of 1,6:1,2 isomers increased from 1:2 to 1:6. For both series, purification by flash chromatography resulted in protodemetallation. Two-dimensional TLC revealed both **3.26**/**2.27** and **3.29**/**330** were unstable towards silica, and thus were subsequently telescoped into the Diels-Alder cycloaddition upon workup. However, analysis of the crude reaction mixture by ^{1}H NMR revealed **3.27** and **3.30** again underwent protodemetallation. Adjustments in temperature, solvent, and equivalents did not prevent this from occurring.

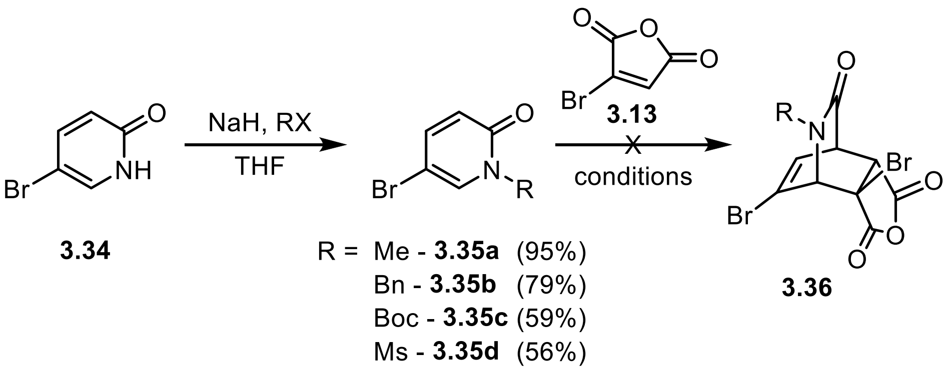


Scheme 3.5 Synthesis of trialkyl-stannyl and silyl 3-substituted pyridines

As the [4+2] cycloaddition progressed, formation of the oxidized pyridine ring was evident by NMR, and it became apparent that the proton source originated from the methylene of the dihydropyridine. In consideration of the lability of the trialkyl metal species and the propensity of dihydropyridines to undergo oxidative decomposition, we decided to develop a route towards a more stabilized diene.

Pyridones as Dihydropyridine Surrogates

In an attempt to mitigate rearomatization of the dihydropyridine we became interested in a functional group that could serve as a protecting group for the methylene of the dihydropyridine. In addition to avoiding vinyl metal species, we found substituted pyridones to be an attractive class of compounds capable of providing both benefits. Our initial studies aimed at functionalization of bromo-pyridone. Moreover, the vinyl bromide functional group could serve as a site for introduction of the Southern macrocycle (e.g. cross-coupling partner).

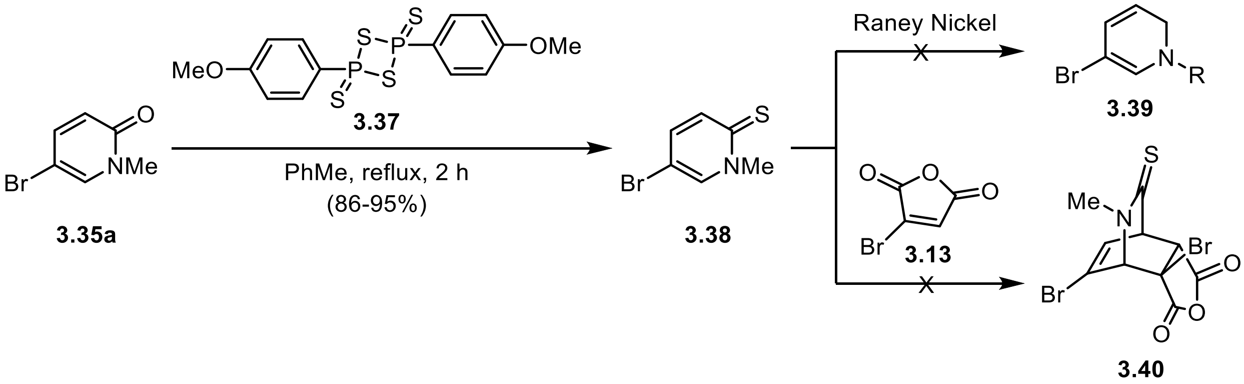


R = Me - **3.35a** (95%)
Bn - **3.35b** (79%)
Boc - **3.35c** (59%)
Ms - **3.35d** (56%)

entry	diene	eq. **3.15**	temperature	solvent	conditions	Result
1	**3.34**	4	110 °C	PhMe	-	Michael addn
2	**3.35a**	1.1	100 °C	PhMe	-	n.r.
3	**3.35a**	1.1	170 °C	xylenes	pressurized	decomposition
4	**3.35b**	1.1	100 °C	PhMe	-	n.r.
5	**3.35c**	1.1	100 °C	PhMe	-	decomposition
6	**3.35d**	1.1	100 °C	PhMe	-	decomposition
7	**3.35a**	1.1	0 °C	CH_2Cl_2	Et_2AlCl	decomposition
8	**3.35a**	1.1	rt	Et_2O	$LiClO_4$	n.r.
9	**3.35a**	1.1	rt	CH_2Cl_2	$Sc(OTf)_3$	n.r.
10	**3.35a**	1.1	0 °C	CH_2Cl_2	$AlCl_3$	decomposition

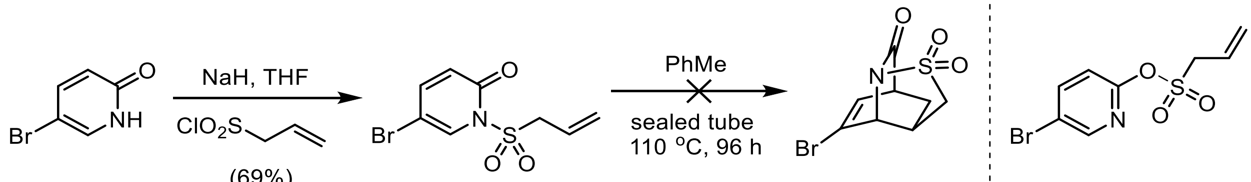
Table 3.1 Conditions screened for [4+2] between pyridones and bromomaleic anhydride

N-alkylation of pyridone **3.34** was affected upon treatment with NaH and the corresponding alkyl halide. N-alkylation was confirmed by the presence of a strong carbonyl stretch by IR spectroscopy. A small series of pyridones, **3.35a-d**, were synthesized with differing electronic characteristics in order to assess reactivity in the subsequent Diels-Alder reaction. A short screening of conditions was employed to test the reactivity of these pyridones as diene substrates (Table **3.1**). Alkylation of pyridone **3.34** prior to the cycloaddition was necessary, otherwise when reacted with bromomaleic anhydride **3.13**, a 1,4-addition was observed rather than the [4+2] cycloaddition (entry 1). When reacted under thermal conditions pyridones **3.35a-d** decomposed or failed to show any reactivity at all. Notedly, a pressurized system run in a sealed flask (entry 3) resulted in decomposition of both diene and dienophile with no cycloadduct formation observed. Lastly, **3.35a** was selected as the most electron rich diene, and then reacted with a variety of Lewis acid catalysts (entries 7-10). For entries 7 and 10, decomposition of the dienophile was observed. ^{1}H NMR analysis of entry 7 indicated conjugate addition of an ethyl moiety onto dienophile **3.13**. It became obvious that the electronics of the bromo-pyridones were very poor and thus hindered reactivity in the Diels-Alder reaction.



Scheme 3.6 Synthesis of thiopyridone and attempted cycloaddition and dethiolation.

In an attempt increase reactivity (i.e. raise the HOMO), we investigated the conversion of **3.35a** to thiopyridone **3.38**, which would serve as a less deactivating substituent. Lawesson's reagent[65] efficiently afforded thiopyridone upon reflux in toluene (Scheme **3.6**). Attempts at dethiolation of **3.38** using Raney nickel were unsuccessful and resulted in formation of a dimeric species by ^{1}H NMR and HPLC-MS but was not fully characterized. Additionally, thiopyridone **3.38** was also reacted with bromomaleic anhydride **3.13** and instead of cycloadduct formation, consumption of dienophile was observed. The disappearance of alkenyl peaks by ^{1}H NMR suggested 1,4-addition and thioalkylation of dienophile with **3.38**. Simultaneously another model system was investigated (Scheme **3.7**).



3.34 **3.41** **3.42** **3.43**

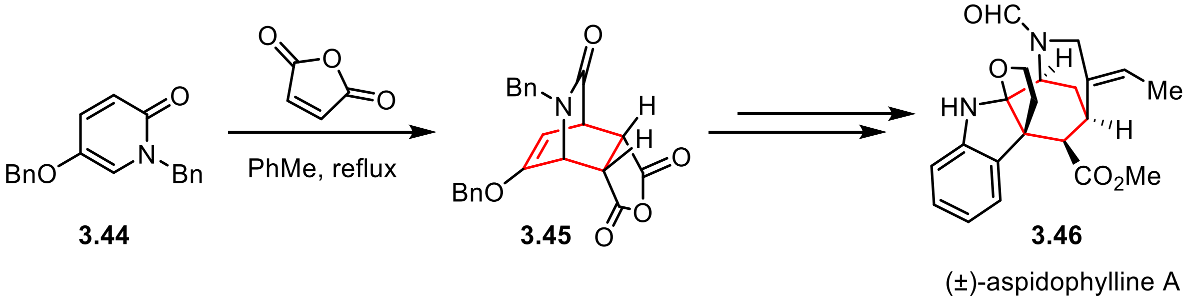
Scheme 3.7 Pyridone model system for intramolecular [4+2] cycloaddition

Due to the electron poor nature of pyridones, reactivity was very limited. In an attempt to compensate for this, we investigated an intramolecular [4+2] model system in an effort to gain an entropic advantage. Synthesis of sulfonamide **3.41** was readily achieved upon treatment of **3.34** with NaH and allylsulfonyl chloride. We hoped transitioning to a unimolecular reaction in addition to forming a 5-membered ring would provide a large enough entropic gain to overcome the evidently high activation barrier. However, after extended reaction times and high temperatures, formation of **3.42** was not observed. Monitoring by NMR and IR suggested aromatization and possible N to O migration of the sulfonamide moiety to give pyridine **3.43**. With the complete lack of reactivity from the bromo-pyridones, we decided to investigate more electron rich diene substrates.

Access to Alkoxy Substituted Pyridones via Aza-Achmatowicz Reaction

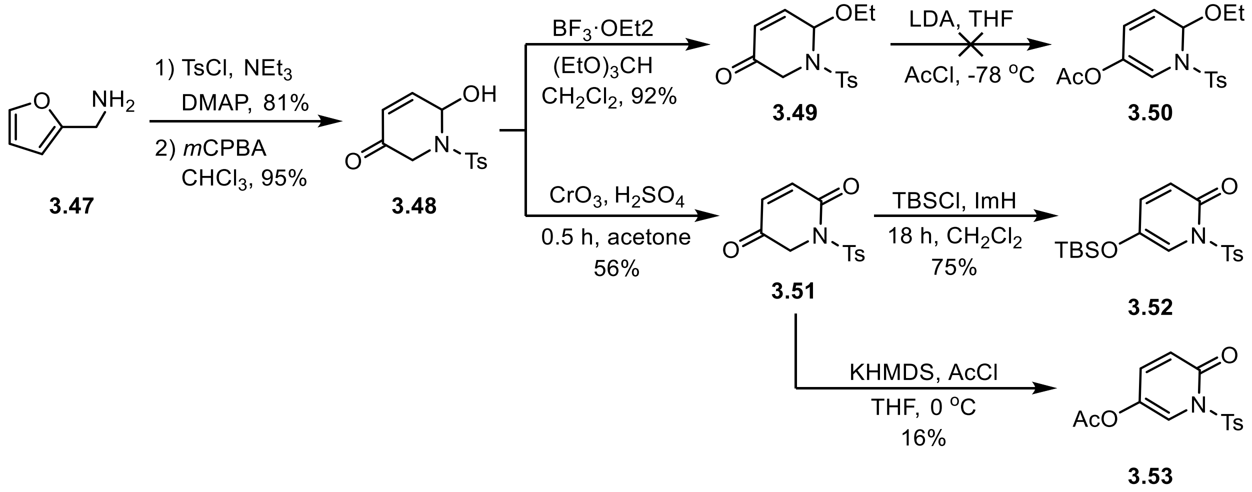
Upon searching the literature, an interesting alkoxy-substituted pyridone **3.44** was found in the total synthesis of aspidophylline A by Garg and coworkers (Scheme **3.8**).[66,67] [4+2] cycloaddition with maleic anhydride afforded cycloadduct **3.45** in a referenced 97% yield. With such a high yielding transformation and the electron-releasing nature of the benzyloxy substituent, we next aimed to synthesize such a diene and investigate its reactivity. Unfortunately, 5-alkoxy pyridones are not commercially available, and resultingly were required to be prepared in lab. Access to gram scale quantities was achieved through the use of the Aza-

Achmatowicz reaction, an oxidative rearrangement and cyclization of tosyl furfuryl amine (Scheme **3.9**). Admittedly, synthesis of the 3-alkoxy group was never achieved and rather our focus was aimed at investigating the silyl vinyl ether moiety, due to its ease of synthesis and stability.



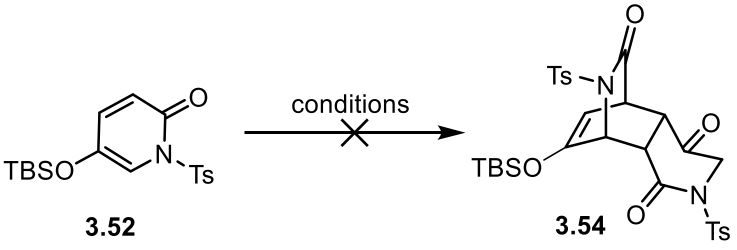
Scheme 3.8 Use of alkoxypyridone in Garg and coworkers' total synthesis of aspidophylline A.

Beginning from furfuryl amine **3.47**, tosylation produced the protected amine, which was necessary prior to treatment with *m*CPBA in order to prevent hydroxylamine formation. Subsequent reaction with *m*CPBA, induced the named Aza-Achmatowicz reaction to afford hemiaminal **3.48** in excellent yields. From the hemiaminal a variety of strategies were investigated to access the alkyoxy-substituted pyridones. Our first attempts began with synthesis of **3.49** under Lewis acid catalysis in the presence of triethyl orthoformate. We hoped removal of the free alcohol would allow formation of the corresponding enolate when deprotonated. Additionally, **3.49** would also lack the electron-withdrawing amide moiety. Unfortunately, when treated with LDA and AcCl, diene **3.50** was not formed and a complex mixture was observed. Presumably **3.49** underwent competitive deprotonation at the α and γ carbons. In a second effort, hemiaminal **3.48** was oxidized under Jones conditions[68] to generate 1,4 dione **3.51**. When reacted with TBSCl and imidazole, silyl vinyl ether **3.52** was isolated in 75% yield. Lastly, O-alkylation of **3.53** was achieved in low yield upon treatment with KHMDS and AcCl.



Scheme 3.9 Access to 5-hydroxy pyridone derivatives via Aza-Achmatowicz reaction.

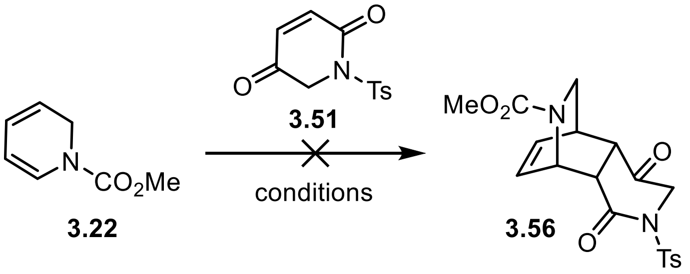
With gram scale quantities of **3.52** in hand we screened conditions against bromomaleic anhydride **3.13** (Table **3.2**). Under thermal heating, microwave irradiation, and pressurized conditions in a sealed flask (entries 1-4), only decomposition of **3.13** was observed. Changing the dienophile to benzoquinone, **3.55**, when reacted with pyridone **3.52** in a planetary ball mill or under sealed pressurized conditions (entries 5,6) resulted in decomposition or no reaction. Pyridone **3.53** was never synthesized in large enough quantities to investigate, and in consideration of the failure of **3.52**, the electronegative nature of the acetate deterred us from further studies. Again, with the lack of reactivity of pyridones as dienes we became interested in 1,4-dione **3.51** as a potential dienophile. As an alkene with two electron-withdrawing substituents inside a 6-membered ring, **3.51** could potentially install the piperidine ring of xestocyclamine through a Diels-Alder reaction.



entry	dienophile	eq.	temperature	solvent	conditions	Result
1	**3.15**	1	110 °C	PhMe	thermal	decomposition
2	**3.15**	1	100 °C	PhMe	microwave	decomposition
3	**3.15**	1.1	90 °C	CH_2Cl_2	sealed tube	n.r.
4	**3.15**	1.1	120 °C	CH_2Cl_2	sealed tube	decomposition
5	**3.55**	1.1	rt	-	ball milling	n.r.
6	**3.55**	1.1	90 °C	CH_2Cl_2	sealed tube	decomposition

Table 3.2 Screening of conditions for [4+2] cycloaddition employing vinyl silyl ether pyridones.

Thus, a short screen was investigated to assess its utility as a dienophile (Table **3.3**). Under thermal conditions (entry 1) both diene and dienophile were consumed upon reflux in toluene. ^{1}H NMR indicated tautomerization of 1,4-dione **3.51** and oxidation of dihydropyridine **3.22**.



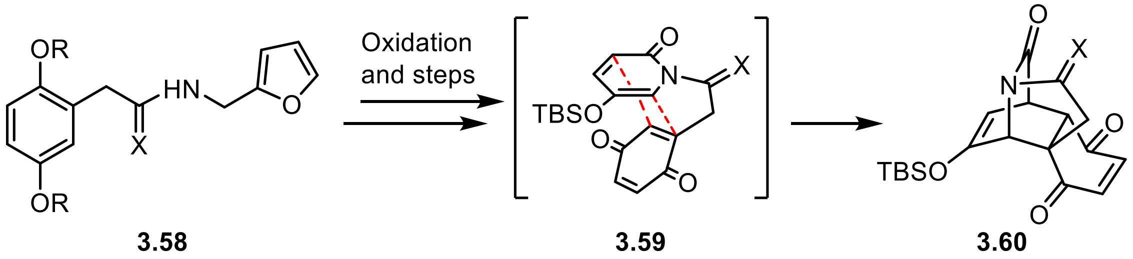
entry	diene	eq. **3.51**	temperature	solvent	conditions	Result
1	**3.22**	2	110 °C	PhMe	thermal	decomposition
2	**3.22**	2	100 °C	PhMe	microwave	decomposition
3	**3.22**	2	rt	CH_2Cl_2	-	decomposition
4	**3.22**	1	0 °C	CH_2Cl_2	-	decomposition
5	**3.57**	1.25	0 °C	CH_2Cl_2	-	95%

Table 3.3 Screening of conditions for [4+2] cycloaddition employing 1,4-diones.

Similar results were observed under microwave irradiation and milder conditions (entries 2-4). In a test reaction, **3.51** was able to undergo cycloaddition with cyclopentadiene, **3.57**, in 95% at

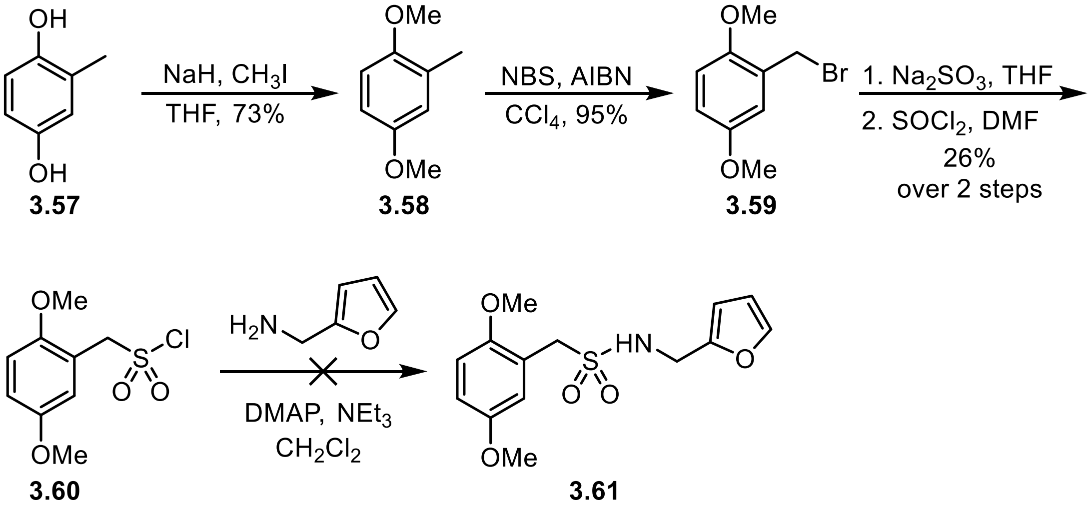
0 °C. Unfortunately, this reactivity was never translated into a system containing a dihydropyridine diene substrate.

In a continued effort to increase reactivity of these pyridones, we next sought to perform an intramolecular [4+2] cycloaddition. Inspired by Qi and coworkers,[69] we ambitiously envisioned installing a tethered furfuryl amine and benzoquinone, followed by an oxidative or photochemical-initiated Aza-Achmatowicz reaction and Diels-Alder sequence (Scheme **3.10**). We planned on synthesizing amide **3.58** from coupling of furfuryl amine and the corresponding carboxylic acid or sulfonyl chloride. Upon oxidative rearrangement, we intended to access the silyl vinyl ether **3.59** in a similar fashion as optimized previously (Scheme **3.10**).



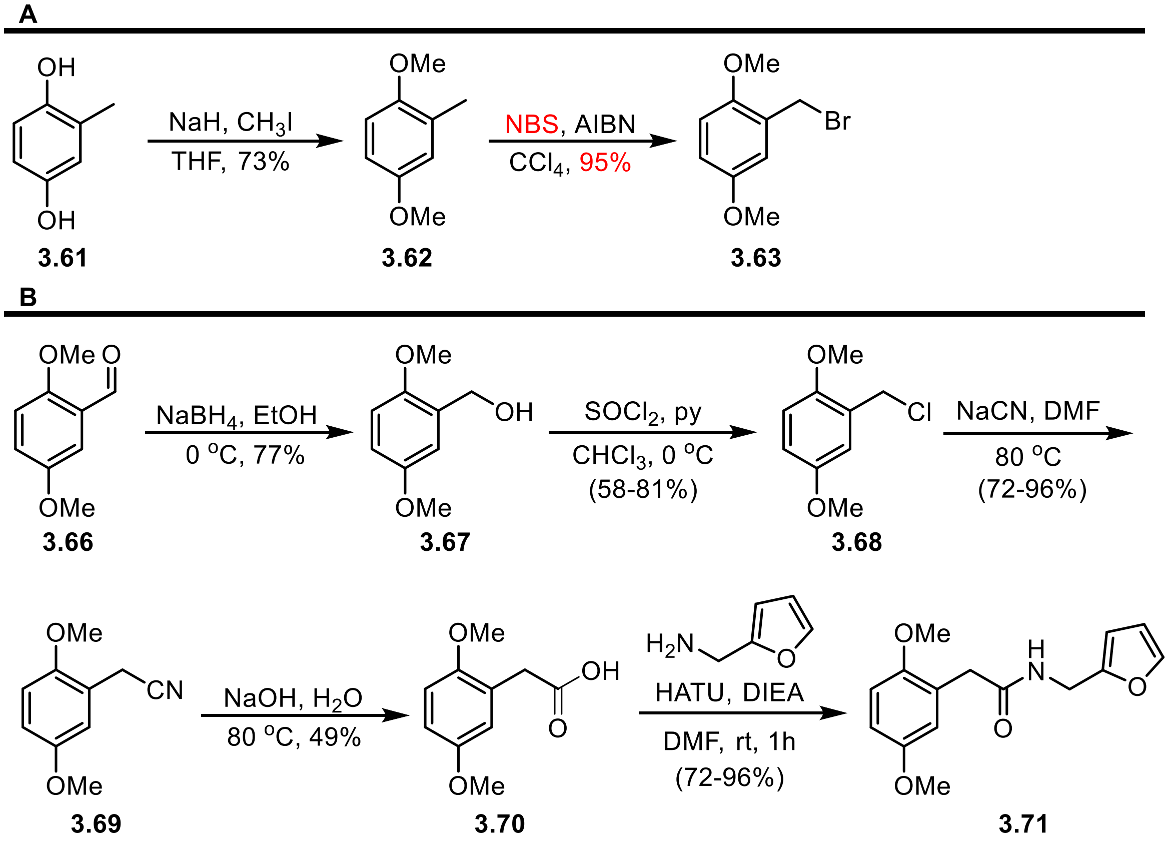
Scheme 3.10 Attempted intramolecular cascade to induce Aza-Achmatowicz/Diels-Alder reaction.

Our first efforts aimed at synthesizing the sulfonamide **3.61** (Scheme **3.11**). Beginning from 2-methyl 1,4-hydroxyquinone, **3.57**, bis-deprotonation with NaH was followed by methylation with CH_3I to give **3.58** in 73%. Benzylic bromination was next achieved upon reaction with NBS and AIBN in 95%. When treated with sodium sulfite, the sulfonic acid was formed in good yield, and was subsequently converted to **3.60** with thionyl chloride. However, we were unable to efficiently access sulfonamide **3.61** after employing a variety of coupling reagents. Next, we directed our attention towards the synthesis of the amide analogue **3.67** (Scheme **3.12**). Proceeding from the benzylic bromide **3.59**, displacement with NaCN was achieved in high yield upon moderate heating (Route A). We planned to hydrolyze the nitrile to the corresponding carboxylic acid, but while scaling up the route, upon use of NBS from a new supplier, we observed the formation of undesired dibrominated side-products. This led us to change routes and begin from the commercially available 2,6-dimethoxybenzaldehyde **3.62** (Route B). Reduction of the aldehyde with $NaBH_4$ was then followed by conversion to the alkyl chloride upon reaction with sulfonyl chloride. Displacement of the benzyl chloride **3.64** with NaCN was then followed by hydrolysis with NaOH and heat. Carboxylic acid **3.66** was then carried forward into the amide coupling with furfuryl amine. Activation of the acid with HATU and DIPEA gave the fully furnished amide **3.67** in up to 96% yield.



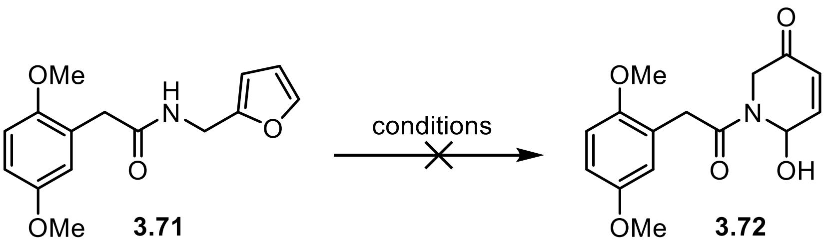
Scheme 3.11 Route to sulfonamide and Aza-Achmatowicz/Diels-Alder reaction cascade.

With amide **3.67** in hand, we next sought to induce the Aza-Achmatowicz/Diels-Alder cascade. Our initial strategy planned to approach the cascade in a step-wise manner in order to simplify analysis of the reaction mixture and fully characterize intermediates. However, in the presence of *m*CPBA, amide **3.67** failed to undergo oxidative rearrangement using the previously optimized conditions. With no formation of hemiaminal **3.68**, we screened a variety of oxidants (Table **3.4**).



Scheme 3.12 Route to amide and Aza-Achmatowicz/Diels-Alder reaction cascade.

Increasing equivalents of *m*CPBA failed to increase conversion of **3.67** to **3.68** (entries 1-3). Next, photochemical conditions were employed to produce singlet oxygen, which has previously been shown to initiate Achmatowicz rearrangements.[70] Notedly, the use of singlet oxygen in the Aza-Achmatowicz has not been reported in the literature, perhaps due to N-oxide formation. Regardless, irradiation by a medium-pressure mercury UV lamp at a range of temperatures were attempted (entries 4-6), but unsuccessful. Finally, a variety of common oxidants were investigated such as: *t*-BuOOH, magnesium monoperoxyphthalate (MMPP), dimethyldioxirane (DMDO), peracetic acid, and pyridinium chlorochromate (PCC) (entries 7-11). Unfortunately, in every entry we observed no oxidative rearrangement and only recovered starting material.

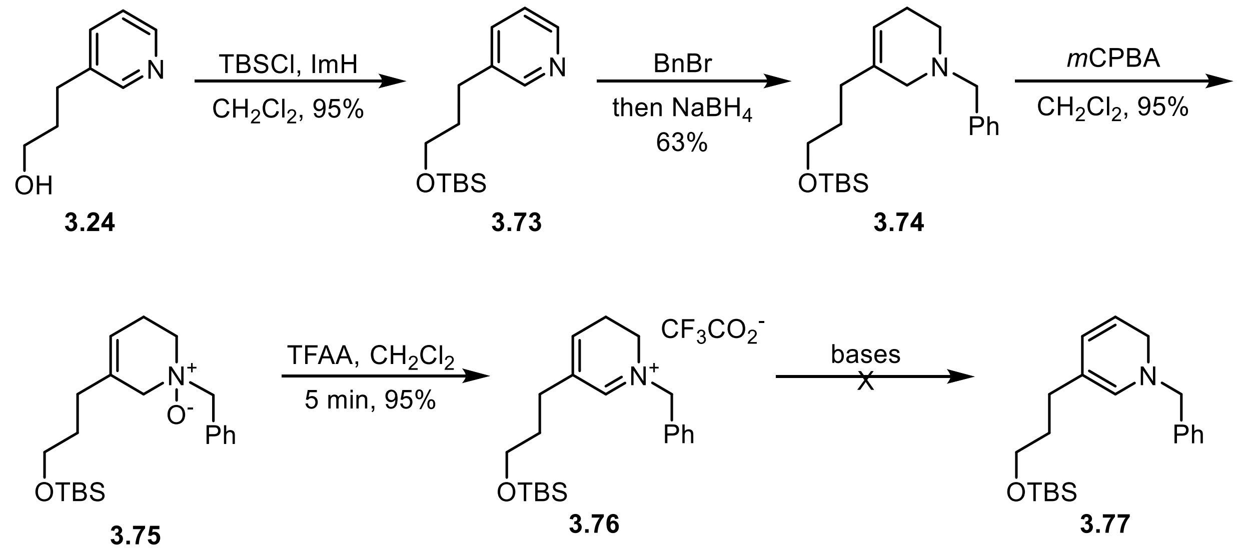


entry	eq. [Ox]	oxidant	solvent	temperature	Result
1	1.5	*m*CPBA	$CHCl_3$	0 °C	n.r.
2	2	*m*CPBA	$CHCl_3$	0 °C	n.r.
3	2.5	*m*CPBA	$CHCl_3$	0 °C	n.r.
4	-	$^1O_2$, rose bengal	CH_2Cl_2	-78 °C	n.r.
5	-	$^1O_2$, rose bengal	CH_2Cl_2	0 °C	n.r.
6	-	$^1O_2$, rose bengal	CH_2Cl_2	rt	n.r.
7	2.5	*t*-BuOOH	CH_2Cl_2	rt	n.r.
8	2.5	MMPP	CH_2Cl_2	rt	n.r.
9	1.5	DMDO	acetone	rt	n.r.
10	1.2	peracetic acid	CH_2Cl_2	rt	n.r.
11	2	PCC	CH_2Cl_2	rt	n.r.

Table 3.4 Attempts at Aza-Achmatowicz for the Diels-Alder cascade from amide **3.67**

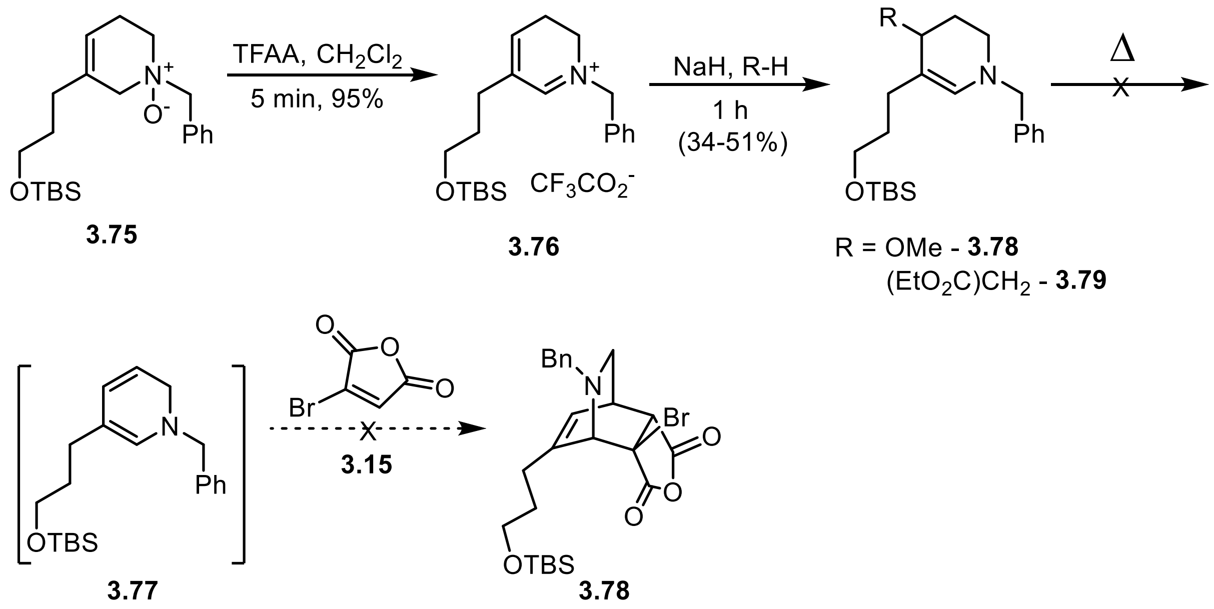
Alkyl-Substituted Pyridines and the Polonovski-Potier Reaction

Having fully experienced the complete lack of reactivity of pyridones, we next pursued modification of alkyl-substituted pyridines due to their more electron-releasing nature and literature precedence. From commercially available 3-propanol pyridine **3.21**, silylation of the alcohol was performed with imidazole and TBSCl, from which reduction of the benzyl pyridinium with $NaBH_4$ yielded tetrahydropyridine **3.70** in 63% yield. Next oxidation of the amine was achieved in excellent yields upon subjection to *m*CPBA. From the resulting N-oxide **3.71**, reaction with trifluoroacetic anhydride induced the Polonovski-Potier reaction to provide the iminium **3.72**.[71] We planned to isomerize **3.72** upon deprotonation to give the desired dihydropyridine **3.73**. After a short screening of bases, we found **3.72** exhibited remarkable sensitivity towards air, heat, and basic conditions. A variety of bases were used such as: alkoxides (KO*t*-Bu), sterically hindered amines (Hünig's base, DBU), irreversible kinetic bases (NaH), and mild basic alumina. Upon reaction with **3.72** a complex mixture of aromatic compounds was observed with no formation of diene **3.73**.



Scheme 3.13 Attempted Polonovski-Potier reaction to access dihydropyridines.

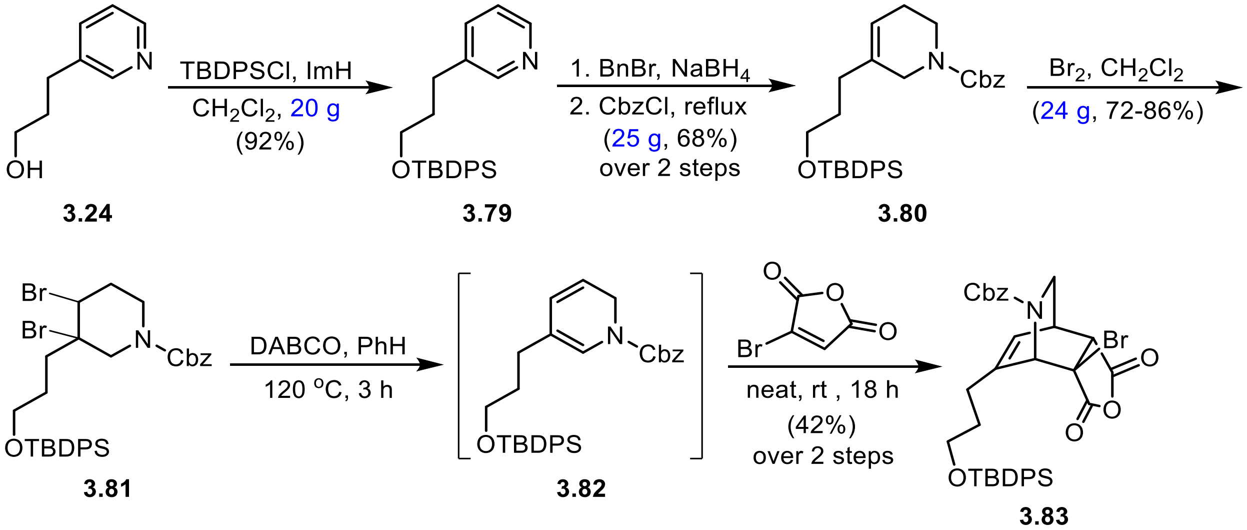
In an attempt to modulate the reactivity of **3.72**, we next investigated trapping the iminium species as the enamine upon conjugate addition of methoxide or diethylmalonate (Scheme **3.14**). The resulting enamines **3.74** and **3.75**, have been previously shown to undergo elimination upon heating to release the conjugate base and generate dienes such as **3.73** *in situ.*[72,73] Enamines **3.74** and **3.75** were isolated in poor yields due to their instability toward silica, but were then carried forward into the elimination. A variety of 2-step and one pot procedures were attempted in the presence or absence of bromomaleic anhydride **3.13**, but formation of diene **3.73** or cycloadduct **3.76** were not observed.



Scheme 3.14 Trapping of reactive α,β-unsaturated iminium species.

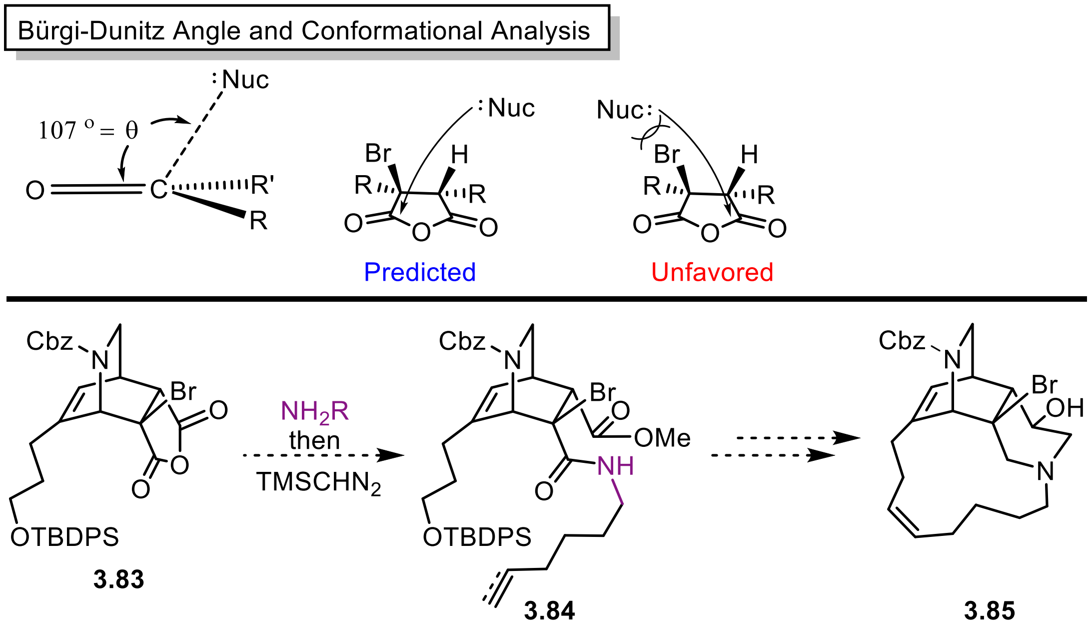
Diels-Alder Cycloaddition between Dihydropyridine and Bromomaleic anhydride

Due to the electron-richness of alkyl-substituted dihydropyridines and their more frequent use in the literature, we decided to pursue a pathway developed by the Fukuyama group in order to access the elusive 3-alkyl dihydropyridine intermediate.[74] Beginning from commercially available 3-propanol pyridine **3.21**, silylation with TBDPSCl was necessary as smaller protecting groups (e.g. TBS) were found to be labile in later steps. From the protected alcohol **3.22** reduction of the benzyl pyridinium with two equivalents of $NaBH_4$ was followed by protecting group exchange with benzyl chloroformate. Loss of benzyl chloride from the intermediate ammonium salt allowed for this transformation in a single step. Use of the benzyl carbamate was necessary as in the following step, when reacted with bromine, undesired side-products were observed, likely due to N-halogenation. From tetrahydropyridine **3.77**, dibromination occurred cleanly and required no further purification. Now posed for the bis-elimination to the desired diene, considerable optimization was required to afford **3.79** as a single isomer. Ultimately it was found that when **3.78** was reacted with DABCO under elevated temperatures in a sealed flask and static vacuum, diene **3.79** was formed as a single isomer. Subjection to other bases, solvents, and non-pressurized or lower temperatures resulted in a mixture of mono-, di-, and exocyclic alkenes. Isolation of **3.79** by flash chromatography proved impossible due to its silica and air sensitivity. Amid optimization of the elimination, several decomposition studies were conducted. Three aliquots of diene **3.79** were taken and placed under separate conditions. The first reaction revealed that heating at 120 °C overnight resulted in full conversion to the aromatic pyridine. The second aliquot was left open to air overnight and also showed the same oxidative decomposition. Lastly, the third aliquot was left at room temperature under vacuum and showed no appreciable decomposition for several days.



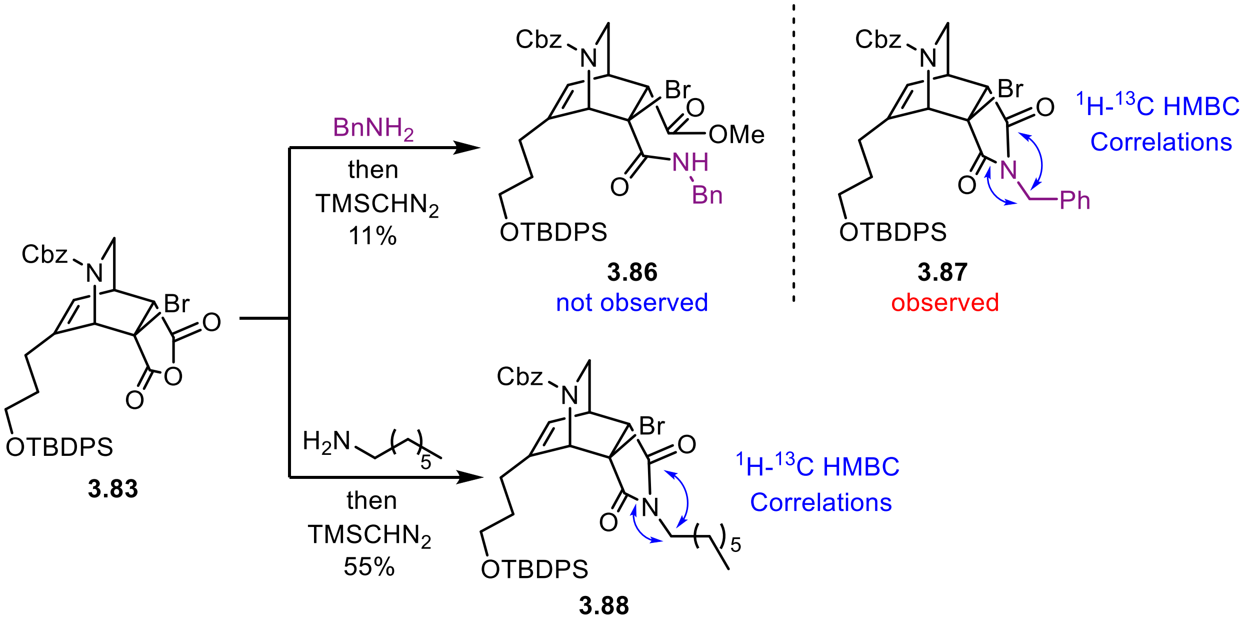
Scheme 3.15 Successful cycloaddition between alkyl dihydropyridine and bromomaleic anhydride.

Further studies and attempts to telescope **3.79** into the Diels-Alder reaction without an aqueous workup were unsuccessful. Upon addition of bromomaleic anhydride, consumption of dienophile was observed without conversion of diene **3.79**. It appears DABCO serves as a Michael-donor and sequesters dienophile from the [4+2] cycloaddition. Regardless, it was ultimately found that the previously optimized conditions (Scheme **3.4**) produced cycloadduct **3.80** in 42% over two steps as a single isomer (Scheme **3.15**). From **3.80** we next planned to investigate opening of the anhydride with an amine in order to determine if we could gain selectivity upon nucleophilic addition. Based upon the Bürgi-Dunitz trajectory, approach of the incoming amine would greatly influence regioselectivity.[75] We hypothesized nucleophilic addition may occur towards the carbonyl adjacent to the quaternary center, due to the steric hindrance of the endo bromine substituent toward the other carbonyl (Scheme **3.16**). However, we were also aware the adjacent quaternary center may completely block addition to the adjacent carbonyl. Regardless, we hoped to gain some selectivity which would allow us to proceed from **3.81** using functional group interconversions and ring closing metathesis to arrive at macrocycle **3.82**.



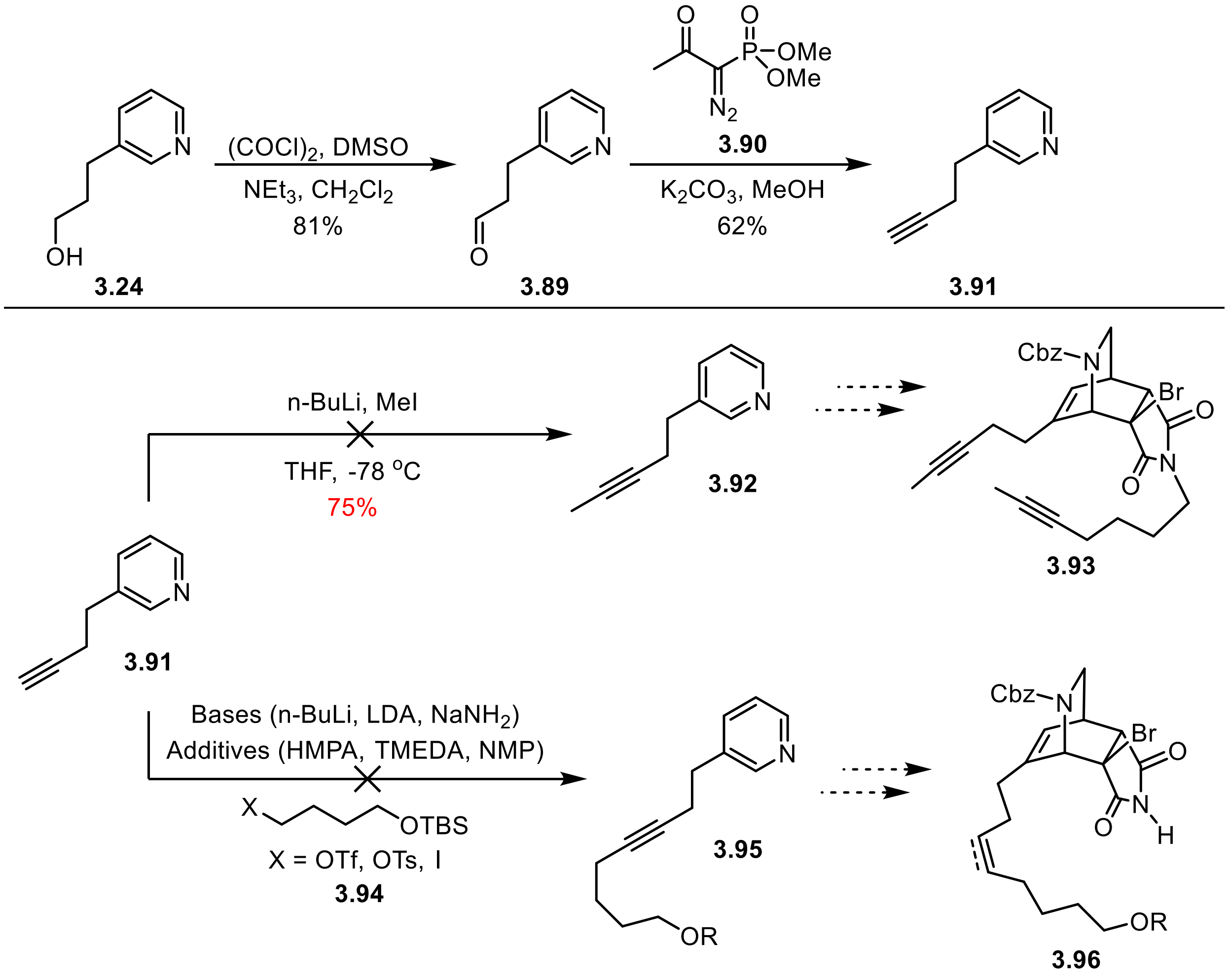
Scheme 3.16 Conformational analysis of Burgi-Dunitz angle and nucleophile trajectory.

When cycloadduct **3.80** was first treated with benzyl amine followed by $TMSCHN_2$, we anticipated formation of methyl ester **3.83** but were surprised to isolate imide **3.84** (Scheme **3.17**). Formation of the 5-membered imide was confirmed via ^1H-^{13}C HMBC-correlations, and in hindsight is likely highly favored due to the close proximity of the endo substituents. This ring closure was also observed when treated with heptylamine which produced **3.85** in 55% yield. Attempts were made without a $TMSCHN_2$ quench, with HCl amine salts, and other solvent systems, but all failed to prevent imide formation.



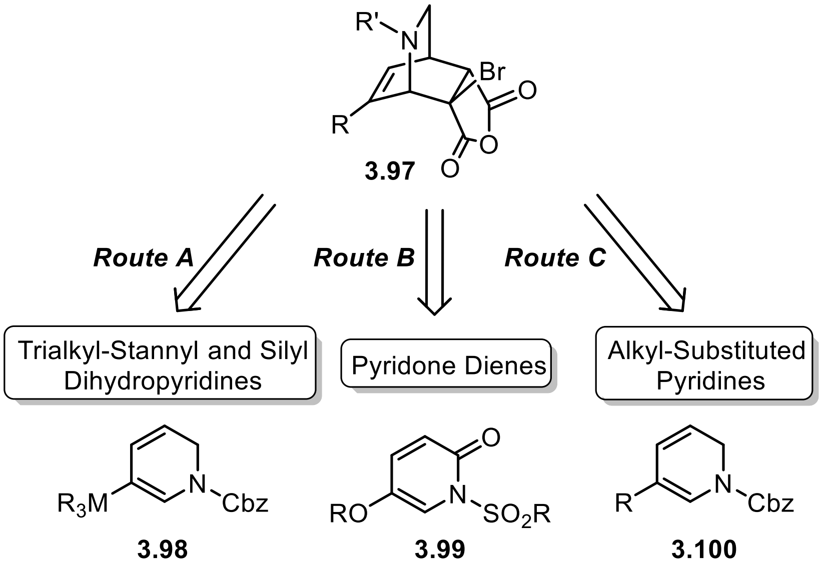
Scheme 3.17 Opening of anhydride and formation of imide.

However serendipitous, we believed formation of the imide could be used to our synthetic advantage. Firstly, use of an imide would introduce the second nitrogen of xestocyclamine A's core. Second, N-alkylation of the imide would install the alkyl handle for construction of the southern macrocyclic ring while offering a more convergent strategy. Furthermore, imides typically show better silica stability than their anhydride analogues, which was a challenge encountered in the purification of cycloadduct **3.80**. With these factors in mind, we next planned to proceed with the new imide dienophile containing an alkynyl handle to later facilitate RCAM. Moving forward, we first began by installing the alkyne on the diene. However, alkyne metathesis requires terminal methyl groups in order to prevent C-H insertion from Mo or W alkylidene catalysts and subsequent undesirable side reactions. Thus beginning from 3-propanol pyridine **3.21,** Swern oxidation[76] provided aldehyde **3.86** in 81% yield (Scheme **3.18**). Next when reacted with Bestmann-Ohira reagent[77,78], **3.87**, the homologated alkyne **3.88** was generated.



Scheme 3.18 Failed alkylation of alkyne for RCAM substrates

Alkylation with *n*-BuLi and methyl iodide was first successful, but suddenly stopped providing full conversion of **3.89** and instead afforded an inseparable mixture of starting material and product. Deprotonation followed by deuterium quench demonstrated successful deprotonation, but increased equivalents, higher temperatures, and freshly distilled MeI failed to restore the original reactivity. With our initial goal to access RCAM precursor **3.90** showing limited success, we decided to investigate another alternative closure of the southern macrocycle. Next, we envisioned alkylation of the terminal alkyne to install a fully elaborated species which would enable macrolactamization by displacement of an activated leaving group. Unfortunately, we observed similar problems, where deprotonation occurred but alkylation failed. Upon encountering this obstacle, a variety of bases (*n*-BuLi, LDA, $NaNH_2$), additives (HMPA, TMEDA, NMP), and leaving groups (OTf, OTs, I) were screened with no formation of **3.92** observed. With no hint of success or reactivity, we decided to abandon formation of an alkynyl RCAM substrate and instead focus on pursuit of a terminal alkene RCM precursor.

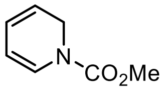


Scheme 3.19 Summary of routes used to access cycloadduct **3.97**

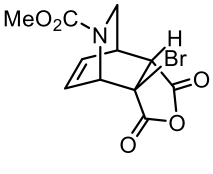
Conclusion to Chapter 3

After considerable setbacks and unforeseen transformations, we were able to access the advanced intermediate, cycloadduct **3.97**. Three main routes were employed which comprised of trialkyl-stannyl and silyl substituted pyridines (Route A), pyridones as dihydropyridine surrogates (Route B), and alkyl-substituted dihydropyridines (Route C). From the cycloadduct nucleophilic opening of the anhydride with amines resulted in immediate imide formation. Investigations into alkynyl RCAM substrates were unsuccessful and encouraged future directions toward alkenyl RCM substrates.

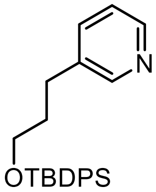
Experimental Methods



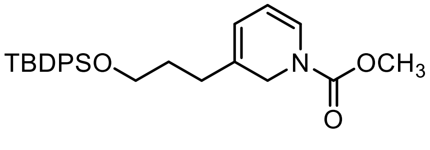
3.22: To a cooled suspension of $NaBH_4$ (1.12 g, 29.7 mmol) in MeOH (25 mL) at -78 °C was added pyridine (2 mL, 24.7 mmol) dropwise. The reaction mixture was maintained at -78 °C for 30 min, then methyl chloroformate (2.5 mL, 32.2 mmol) was added by syringe pump over 1 h. The reaction mixture was stirred at -78 °C for 2 additional hours, warmed to room temperature, poured over ice and extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine (30 mL), dried (Na_2SO_4), and concentrated *in vacuo* to give 2.70 g (78%) of dihydropyridine **3.22** as a yellow oil which was used without further purification. ^1H NMR (400 MHz, $CDCl_3$) δ 6.78-6.64 (dd, *J* = 49.8, 7.6 Hz, 1H), 5.83 (m, 1H), 5.53-5.47 (m, 1H), 5.17-5.11 (m, 1H), 4.36 (bs, 1H), 3.77 (s, 3H).



3.23: To bromomaleic anhydride (1.7 mL, 18.0 mmol) was added **3.22** (1 g, 7.2 mmol) neat. The resulting reaction mixture was stirred at room temperature for 1.5 h and then purified by flash chromatography (silica gel, gradient elution, 0-30% EtOAc in hexanes) to afford 970 mg (92%) of cycloadduct **3.23** as a red oil: R*f* 0.3 (7:3 hexanes/EtOAc); ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.55 (m, 2H), 5.40-5.20 (m, 1H), 3.78 (d, *J* = 8.2 Hz, 3H), 3.54 (d, *J* = 10.9 Hz, 1H), 3.47 (m, 1H), 3.40 (m, 1H), 3.17 (m, 1H); ^{13}C NMR (400 MHz, CDCl$_3$) δ 168.2, 168.0, 167.1, 166.9, 155.3, 133.6, 133.1, 132.6, 132.0, 53.2, 53.1, 52.9, 52.8, 52.1, 51.6, 44.6, 44.4, 34.1, 33.8.

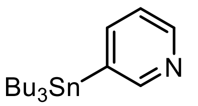


3.25: To a solution of 3-propanolpyridine (10.0 g, 72.9 mmol) and imidazole (7.44 g, 109 mmol) in CH$_2$Cl$_2$ (243 mL) at 0 °C, was added TBDPSCl (20 mL, 76.5 mmol). The reaction mixture was allowed to warm to room temperature and maintained for 18 h. The mixture was then diluted with water (200 mL) and extracted with EtOAc (3 x 100 mL). The combined organic extracts were washed with brine (100 mL), dried (MgSO$_4$), and concentrated *in vacuo*. The resulting residue was purified via flash column chromatography (silica gel, gradient elution, 0-20% EtOAc in hexanes) to afford 25.25 g (92%) of pyridine **3.25** as a colorless oil: Rf 0.3 (4:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.45 (m, 2H), 7.66 (m, 4H), 7.39 (m, 7H), 7.19 (dd, *J* = 7.5, 5.0 Hz, 1H), 3.69 (t, *J* = 6.2 Hz, 2H), 2.74 (t, *J* = 7.7 Hz, 2H), 1.87 (m, 2H), 1.08 (s, 9H); ^{13}C NMR (400 MHz, CDCl$_3$) δ 149.8, 147.0, 137.4, 136.0, 135.5, 133.7, 129.6, 127.6, 123.2, 62.6, 33.7, 29.1, 26.8, 19.2.

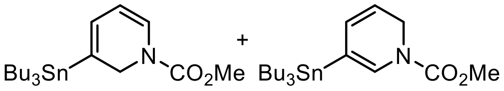


3.26: To a cooled solution of **3.25** (500 mg, 1.33 mmol) in THF (2.7 mL) at -78 °C was added methyl chloroformate (0.11 mL, 1.46 mmol) dropwise. The solution was maintained at -78 °C for 30 min, then Li(*t*-BuO)$_3$AlH (1.1 M in THF, 2.53 mL, 2.79 mmol) was added by syringe pump over 1 h. The reaction mixture was stirred for 1 h at -78 °C, warmed to room temperature for 1 h, and poured over ice. Saturated aq.

Rochelle's salt was added and extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), and concentrated *in vacuo* to give 283 mg (49%) of dihydropyridine **3.26** as a yellow oil that was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66-7.38 (m, 15H), 6.70-6.55 (dd, *J* = 51.4, 7.5 Hz, 1H), 5.56 (d, *J* = 5.3 Hz, 1H), 5.11 (m, 1H), 4.22 (m, 1H), 3.78 (s, 3H), 3.68 (m, 2H), 2.10 (m, 2H), 1.72 (m, 4H), 1.06 (s, 9H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 135.6, 129.6, 129.6, 127.7, 127.6, 123.0, 116.0, 105.2, 63.2, 62.7, 53.1, 46.9, 46.7, 33.8, 31.1, 29.5, 29.2, 26.9, 26.6.

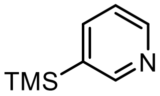


3.28: To a solution of 3-bromopyridine (2.0 mL, 10.4 mmol) in THF (20.8 mL) was added *i*-PrMgCl (2 M in THF, 10.4 mL, 20.8 mmol) dropwise. The reaction mixture was stirred at room temperature for 2 h, then cooled to 0 ^{o}C and Bu_3SnCl (5.9 mL, 21.6 mmol) added dropwise. The reaction was allowed to warm to room temperature and stir overnight. Mixture was poured over water and extracted with EtOAc (3 x 25 mL). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The resulting residue was purified via flash column chromatography (silica gel, gradient elution, 0-10% EtOAc in hexanes) to afford 6.93 g (90%) of pyridine **3.28** as a colorless oil: R_f 0.3 (9:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (m, 1H), 8.51 (m, 1H), 7.74 (m, 1H), 7.23 (m, 1H), 1.54 (m, 2H), 1.33 (m, 6H), 1.10 (m, 6H), 0.88 (t, *J* = 7.4 Hz, 9H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 155.8, 148.9, 144.2, 137.0, 123.8, 28.9, 27.2, 13.5, 9.5.

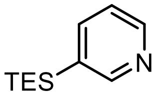


3.29,3.30: To a solution of **3.28** (577 mg, 1.56 mmol) in THF (5.0 mL) at -78 ^{o}C was added methyl chloroformate (0.13 mL, 1.72 mmol) dropwise. The solution was maintained at -78 ^{o}C for 30 min, then Li(*t*-

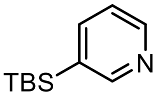
BuO)$_3$AlH (1.1 M in THF, 2.53 mL, 2.79 mmol) was added by syringe pump over 1 h. The reaction mixture was stirred for 3.5 h at -78 ^{o}C, warmed to room temperature for 1 h, and poured over ice. Saturated aq. Rochelle's salt was added and extracted with EtOAc (3 x 15 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), and concentrated *in vacuo* to give 400 mg (60%) as a mixture of dihydropyridine **3.29** and **3.30** as a yellow oil that was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.65-6.51 (m, 1H), 5.83 (m, 1H), 5.20 (m, 1H), 4.29 (bs, 2H), 3.77 (s, 3H), 1.50 (m, 10H), 1.30 (m, H), 1.06 (s, 23H).



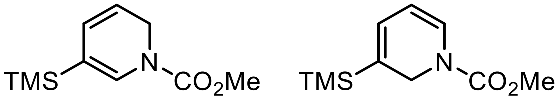
3.31a: To a solution of 3-bromopyridine (2.8 mL, 28.7 mmol) in THF (29 mL) was added *i*-PrMgCl (2 M in THF, 14.4 mL, 28.7 mmol) dropwise. The reaction mixture was stirred at room temperature for 2 h, then cooled to 0 ^{o}C and TMSCl (4.0 mL, 31.6 mmol) added dropwise. The reaction was allowed to warm to room temperature and stir overnight. Mixture was poured over water and extracted with Et_2O (3 x 25 mL). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The resulting residue was purified via flash column chromatography (silica gel, gradient elution, 0-10% EtOAc in hexanes) to afford 2.82 g (65%) of pyridine **3.31a** as a yellow oil: R_f 0.3 (9:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (bs, 1H), 8.57 (dd, *J* = 4.9, 1.8 Hz, 1H), 7.77 (dt, *J* = 7.5, 1.8 Hz, 1H), 7.24 (m, 1H), 0.30 (s, 9H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 153.9, 149.9, 141.0, 123.2, -1.4.



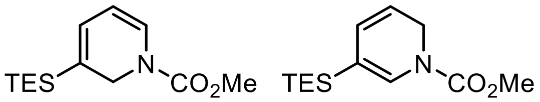
3.31b: To a solution of 3-bromopyridine (1.0 mL, 10.2 mmol) in THF (10 mL) was added *i*-PrMgCl (2 M in THF, 5.1 mL, 10.2 mmol) dropwise. The reaction mixture was stirred at room temperature for 2 h, then cooled to 0 ^{o}C and TESCl (1.90 mL, 11.3 mmol) added dropwise. The reaction was allowed to warm to room temperature and stir for 48 h. The mixture was poured over water and extracted with Et_2O (3 x 25 mL). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The resulting residue was purified via flash column chromatography (silica gel, gradient elution, 0-10% EtOAc in hexanes) to afford 1.35 g (68%) of pyridine **3.31b** as a yellow oil: R_f 0.3 (9:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (bs, 1H), 8.53 (m, 1H), 7.73 (m, 1H), 7.23 (m, 1H), 0.94 (m, 9H), 0.80 (m, 6H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 154.3,149.6, 141.9, 132.2, 123.1, 7.1, 3.0.



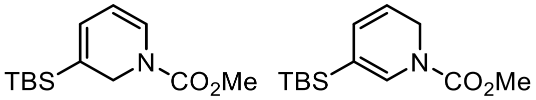
3.31c: To a solution of 3-bromopyridine (1.5 mL, 15.4 mmol) in THF (15 mL) was added *i*-PrMgCl (2 M in THF, 7.7 mL, 15.4 mmol) dropwise. The reaction mixture was stirred at room temperature for 2 h, then cooled to 0 °C and TBSCl (2.32 g, 15.4 mmol) added. The reaction was allowed to warm to room temperature and stir for 48 h. Mixture was poured over water and extracted with Et_2O (3 x 25 mL). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The resulting residue was purified via flash column chromatography (silica gel, gradient elution, 0-10% EtOAc in hexanes) to afford 611 mg (21%) of pyridine **3.31c** as a yellow oil: R_f 0.3 (9:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (bs, 1H), 8.57 (dd, *J* = 4.9, 1.8 Hz, 1H), 7.77 (dt, *J* = 7.4, 1.8 Hz, 1H), 7.25 (dd, *J* = 7.4, 4.9, 1.8 Hz, 1H), 0.89 (m, 9H), 0.30 (m, 6H).



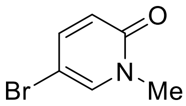
3.32a/3.32a: To a solution of **3.31a** (400 mg, 2.64 mmol) in THF (4.1 mL) at -78 °C was added methyl chloroformate (0.22 mL, 2.90 mmol) dropwise. The solution was maintained at -78 °C for 30 min, then Li(*t*-BuO)$_3$AlH (1.1 M in THF, 4.0 mL, 1.65 mmol) was added by syringe pump over 1 h. The reaction mixture was stirred for 4 h at -78 °C, warmed to room temperature for 1 h, and poured over ice. Saturated aq. Rochelle's salt was added and extracted with Et$_2$O (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried (MgSO$_4$), and concentrated *in vacuo* to give 411 mg (52%) as a mixture of dihydropyridine **3.32a** and **3.32a** as a yellow oil that was used without further purification. ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.82-6.69 (m, 1H), 5.86 (m, 1H), 5.50 (m, 1H), 4.32 (bs, 2H), 3.79 (s, 3H), 0.10 (s, 9H).



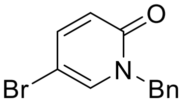
3.32b/3.32b: To a solution of **3.31b** (200 mg, 1.03 mmol) in THF (2.1 mL) at -78 °C was added methyl chloroformate (0.10 mL, 1.24 mmol) dropwise. The solution was maintained at -78 °C for 30 min, then Li(*t*-BuO)$_3$AlH (1.1 M in THF, 1.96 mL, 2.16 mmol) was added by syringe pump over 1 h. The reaction mixture was stirred for 4 h at -78 °C, warmed to room temperature for 1 h, and poured over ice. Saturated aq. Rochelle's salt was added and extracted with Et$_2$O (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried (MgSO$_4$), and concentrated *in vacuo* to give 168 mg (53%) as a mixture of dihydropyridine **3.32b** and **3.32b** as a yellow oil that was used without further purification. ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.80-6.66 (m, 1H), 5.83 (m, 1H), 5.50 (m, 1H), 4.32 (m, 2H), 3.78 (s, 3H), 0.95 (m, 16H), 0.60 (m, 10H).



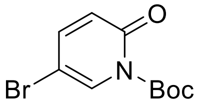
3.32c/3.32c: To a solution of **3.31c** (486 mg, 2.51 mmol) in THF (5 mL) at -78 °C was added methyl chloroformate (0.21 mL, 2.76 mmol) dropwise. The solution was maintained at -78 °C for 30 min, then Li(*t*-BuO)$_3$AlH (1.1 M in THF, 9.1 mL, 10.0 mmol) was added by syringe pump over 1 h. The reaction mixture was stirred for 4 h at -78 °C, warmed to room temperature for 1 h, and poured over ice. Saturated aq. Rochelle's salt was added and extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), and concentrated *in vacuo* to give 430 mg (56%) as a mixture of dihydropyridine **3.32c** and **3.32c** as a yellow oil that was used without further purification. ^1H NMR (400 MHz, $CDCl_3$) δ 6.82-6.68 (m, 1H), 5.88 (m, 1H), 5.50 (m, 1H), 4.32 (m, 2H), 3.79 (s, 3H), 0.88 (s, 9H), 0.07 (s, 6H).



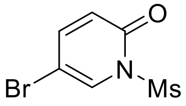
3.35a: To a cooled suspension of NaH (60% in mineral oil, 46 mg, 1.89 mmol) in THF (9.5 mL) at 0 °C was added a solution of 5-bromopyridin-2(1H)-one (300 mg mL, 1.72 mmol) in THF (5.7 mL) dropwise. The solution was maintained at 0 °C for 1 h, and then MeI (0.21 mL, 3.44 mmol) was added dropwise. The mixture was allowed to warm to room temperature and stir overnight. The reaction was quenched with water (30 mL) and extracted with EtOAc (3 x 15 mL). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The resulting residue was purified via flash column chromatography (silica gel, gradient elution, 0-10% MeOH in CH_2Cl_2) to afford 323 mg (>95%) of pyridone **3.35a** as a light-yellow solid: R_f 0.4 (9:1 CH_2Cl_2/MeOH); IR (film) 3053, 2948, 1661, 1586, 1529 cm^{-1}, ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 2.7 Hz, 1H), 7.34 (dd, *J* = 9.6, 2.7 Hz, 1H), 6.48 (d, *J* = 9.6 Hz, 1H), 3.51 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 161.4, 142.4, 138.0, 121.8, 97.5, 37.6.



3.35b: To a cooled suspension of NaH (60% in mineral oil, 50 mg, 2.06 mmol) in THF (4 mL) at 0 °C was added a solution of 5-bromopyridin-2(1H)-one (300 mg mL, 1.72 mmol) in THF (5 mL) dropwise. The solution was maintained at 0 °C for 1 h, and then BnBr (0.41 mL, 3.44 mmol) was added dropwise. The mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched with water (20 mL) and extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The resulting residue was purified via flash column chromatography (silica gel, gradient elution, 0-5% MeOH in CH_2Cl_2) to afford 359 mg (79%) of pyridone **3.35b** as a light-yellow solid: R_f 0.3 (95:5 CH_2Cl_2/MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.27 (m, 7H), 6.53 (dd, *J* = 9.6, 1.6 Hz, 1H), 5.10 (bs, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 161.0, 142.4, 136.9, 135.6, 129.0, 128.3, 128.2, 122.3, 98.0, 52.0.

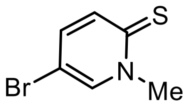


3.35c: To a cooled suspension of NaH (60% in mineral oil, 50 mg, 2.06 mmol) in THF (5 mL) at 0 °C was added a solution of 5-bromopyridin-2(1H)-one (300 mg mL, 1.72 mmol) in THF (4 mL) dropwise. The solution was maintained at 0 °C for 1 h, and then a solution of Boc_2O (750 mg, 3.44 mmol) in THF (1 mL) was added dropwise. The mixture was allowed to warm to room temperature and stir overnight. The reaction was quenched with water (20 mL) and extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The resulting residue was purified via flash column chromatography (silica gel, gradient elution, 0-20% EtOAc in hexanes) to afford 279 mg (59%) of pyridone **3.35c** as a yellow oil: R_f 0.3 (8:2 hexanes/EtOAc); IR (film) 3050, 2986, 1755, 1689, 1607 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 2.6 Hz, 1H), 7.25 (m, 1H), 6.43 (d, *J* = 9.3 Hz, 1H), 1.62 (s, 9H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 142.9, 132.8, 124.8, 27.7.

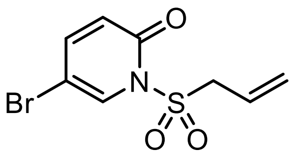


3.35d: To a cooled suspension of NaH (60% in mineral oil, 50 mg, 2.06 mmol) in THF (4 mL) at 0 °C was added a solution of 5-bromopyridin-2(1H)-one (300 mg mL, 1.72 mmol) in THF (5 mL) dropwise. The solution was maintained at 0 °C for 1 h, and then

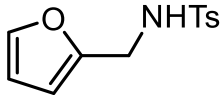
MsCl (0.27 mL, 3.44 mmol) was added dropwise. The mixture was allowed to warm to room temperature and stir overnight. The reaction was quenched with water (20 mL) and extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The resulting residue was purified via flash column chromatography (silica gel, gradient elution, 0-30% EtOAc in hexanes) to afford 241 mg (56%) of pyridone **3.35d** as a white solid: R_f 0.2 (7:3 hexanes/EtOAc); IR (film) 3063, 2931, 1681, 1594, 1528 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 2.3 Hz, 1H), 7.42 (d, *J* = 9.7, 2.3 Hz, 1H), 6.52 (d, *J* = 9.7 Hz, 1H), 3.62 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 159.5, 145.0, 130.5, 124.2, 99.3, 41.9.



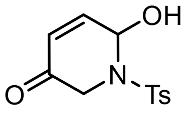
3.38: To a solution of **3.35a** (150 mg, 0.80 mmol) in PhMe (3.2 mL) was added Lawesson's reagent (323 mg, 0.80 mmol) in one portion. Reaction mixture was heated at reflux for 2 h, cooled to room temperature and concentrated *in vacuo*. The resulting residue was purified via flash column chromatography (silica gel, gradient elution, 0-5% MeOH in CH_2Cl_2) to afford 163 mg (>95%) of thiopyridone **3.38** as a light-yellow solid: R_f 0.2 (CH_2Cl_2); ^1H NMR (400 MHz, $(CD_3)_2CO$ δ 8.28 (d, *J* = 2.2 Hz, 1H), 7.42 (d, *J* = 9.3 Hz, 1H), 7.37 (dd, *J* = 9.3, 2.2 Hz, 1H), 3.91 (s, 3H); ^{13}C NMR (400 MHz, $(CD_3)_2CO$ δ 179.6, 141.9, 136.0, 135.9, 104.4, 45.0.



3.39: To a cooled suspension of NaH (60% in mineral oil, 76 mg, 3.16 mmol) in THF (6 mL) at 0 °C was added a solution of 5-bromopyridin-2(1H)-one (500 mg mL, 2.87 mmol) in THF (19 mL) dropwise. The solution was maintained at 0 °C for 1 h, and then propene sulfonyl chloride (807 mg, 5.74 mmol) was added dropwise. The mixture was allowed to warm to room temperature and stir overnight. The reaction was quenched with water (20 mL) and extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The resulting residue was purified via flash column chromatography (silica gel, gradient elution, 0-20% EtOAc in hexanes) to afford 552 mg (69%) of sulfonamide **3.39** as a yellow oil: R_f 0.3 (8:2 hexanes/EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, *J* = 2.5 Hz, 1H), 7.92 (d, *J* = 8.6, 2.5 Hz, 1H), 7.05 (d, *J* = 8.6 Hz, 1H), 6.02 (ddt, *J* = 17.1, 9.9, 7.2 Hz, 1H), 5.55 (m, 2H), 4.36 (s, *J* = 7.2 Hz, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 156.1, 149.0, 142.9, 125.4, 123.7, 118.6, 117.2, 57.5.

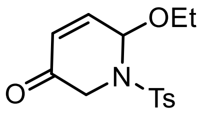


3.47.5: To a cooled solution of furfurylamine (3.06 g, 31.5 mmol), NEt_3 (8.8 mL, 63 mmol), and DMAP (2.3 g, 18.9 mmol) in CH_2Cl_2 (100 mL) at 0 °C was added a solution of TsCl (6.31 g, 33.1 mmol) in CH_2Cl_2 (70 mL) by cannula. The reaction mixture was allowed to warm to room temperature and stir for 1.5 h. Reaction was quenched with water (150 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The resulting residue was purified via flash column chromatography (silica gel, CH_2Cl_2) to afford 5.91 g (81%) of **3.47.5** as a white solid: R_f 0.3 (CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.1 Hz, 1H), 7.28 (d, *J* = 8.1 Hz, 1H), 7.25 (m, 1H), 6.22 (dd, *J* = 3.2, 1.8 Hz, 1H), 6.09 (d, *J* = 3.2 Hz, 1H), 4.67 (m, 1H), 4.18 (d, *J* = 6.0 Hz, 2H), 2.42 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 179.6, 141.9, 136.0, 135.9, 104.4, 45.0.

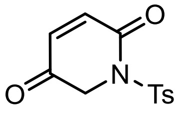


3.48: To a solution of **3.47.5** (150 mg, 0.597 mmol) in $CHCl_3$ (1.5 mL) at 0 °C was added a solution of *m*CPBA (155 mg, 0.895 mmol) in $CHCl_3$ (1.5 mL) by cannula. Reaction mixture was allowed to warm to room temperature and stir for 3 h. Reaction was quenched with water (10 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$), and concentrated *in vacuo* to afford 145 mg

(91%) of **3.48** as a white solid that was used without further purification: R$_f$ 0.3 (CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.3 Hz, 1H), 7.32 (d, *J* = 8.3 Hz, 1H), 6.91 (dd, *J* = 10.2, 5.0 Hz, 1H), 6.07 (m, 1H), 5.99 (m, 1H), 4.05 (m, 2H), 3.16 (m, 1H), 2.42 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 191.4, 144.5, 143.7, 135.4, 130.0, 128.1, 127.2, 73.0, 48.1, 21.5.

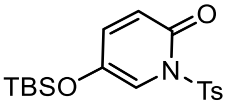


3.49: To a solution of **3.48** (398 mg, 1.49 mmol) in CH_2Cl_2 (7.5 mL) at 0 °C was added triethyl orthoformate (0.5 mL 2.98 mmol) and $BF_3 \bullet OEt_2$ (0.04 mL, 0.30 mmol) sequentially. Reaction mixture was maintained at 0 °C and stirred for 1.5 h. Reaction was quenched with $NaHCO_3$ (10 mL) and extracted with Et_2O (3 x 5 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$), and concentrated *in vacuo* to afford 406 mg (92%) of **3.49** as an orange oil that was used without further purification: R$_f$ 0.3 (7:3 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.3 Hz, 1H), 7.26 (d, *J* = 8.3 Hz, 1H), 6.79 (dd, *J* = 10.3, 4.7 Hz, 1H), 5.85 (d, *J* = 10.3 Hz, 1H), 5.62 (d, *J* = 4.7 Hz, 1H), 4.09 (dd, *J* = 81.0, 18.5 Hz, 2H), 3.94-3.64 (dddt, *J* = 89.7, 9.5, 7.1, 7.1 Hz, 2H), 2.40 (s, 3H), 1.24 (t, *J* = 7.1 Hz, 3H) 4.05 (m, 2H), 3.16 (m, 1H), 2.42 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 191.6, 144.1, 142.8, 135.8, 129.9, 128.1, 127.0, 79.0, 64.6, 48.6, 21.5, 14.8.

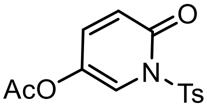


3.51: To a cooled solution of crude **3.49** (761 mg) in acetone (20 mL) at 0 °C was added Jones reagent (2.9 M CrO_3, 1.03 mL, 2.98 mmol). Reaction mixture was stirred for 20 min at 0 °C, filtered, and concentrated *in vacuo.* The resulting residue was dissolved in EtOAc (15 mL) and washed with water (15 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated *in vacuo* to afford 544 mg (69% over 2 steps) of dione **3.59** as a white solid that was used without further purification: R$_f$ 0.3 (95:5 CH_2Cl_2/MeOH); ^{1}H NMR (400 MHz $CDCl_3$) δ 7.97 (d,

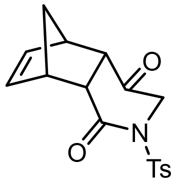
J = 8.3 Hz, 1H), 7.36 (d, J = 8.3 Hz, 1H), 6.74 (dd, J = 18.3, 10.3 Hz, 1H), 4.66 (s, 2H), 2.45 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$ δ 188.7, 159.3, 145.9, 139.8, 137.5, 134.3, 129.6, 129.1, 127.1, 53.5, 21.7.



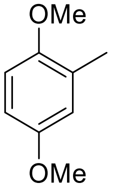
3.52: To a cooled solution of **3.47** (150 mg, 0.561 mmol) and imidazole (95 mg, 1.403 mmol) in CH_2Cl_2 (2.8 mL) at 0 °C was added TBSCl (101 mg, 0.673 mmol). The mixture was allowed to warm to room temperature and stir overnight. The reaction was quenched with water (30 mL) and extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$), and concentrated *in vacuo.* The resulting residue was purified via flash column chromatography (silica gel, gradient elution, 0-30% EtOAc in hexanes) to afford 159 g (75%) of silyl vinyl ether **3.52** as a light-yellow oil: R_f 0.3 (7:3 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 8.3 Hz, 2H), 7.64 (d, J = 3.0 Hz, 1H), 7.34 (d, J = 8.3 Hz, 2H), 7.07 (dd, J = 9.8, 3.0 Hz, 1H), 6.32 (d, J = 9.8 Hz, 1H), 2.44 (s, 3H), 0.98 (s, 9H), 0.21 (s, 6H).



3.53: To a cooled solution of **3.47** (53 mg, 0.20 mmol) THF (1 mL) at 0 °C was added KHMDS (0.5 M in THF, 0.44 mL, 0.23 mmol) dropwise. The reaction mixture was maintained at 0 °C for 0.5 h, then AcCl (0.02 mL, 0.22 mmol) was added and stirred at 0 °C for 1 h. Reaction was quenched with water (5 mL) and extracted with EtOAc (3 x 5 mL). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$), and concentrated in *vacuo*. The resulting residue was purified via flash column chromatography (silica gel, gradient elution, 0-5% MeOH in CH_2Cl_2) to afford 10 mg (16%) of acetate **3.53** as a white solid: R_f 0.3 (95:5 CH_2Cl_2/MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (m, 2H), 7.35 (d, J = 8.3 Hz, 2H), 7.18 (dd, J = 9.8, 3.0 Hz, 1H), 6.40 (d, *J* = 9.8 Hz, 1H), 2.44 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (400 MHz, CDCl$_3$ δ 138.8, 130.1, 129.6, 123.3, 21.8, 20.7.

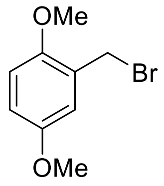


3.57: To a cooled solution of **3.51** (251 mg, 0.945 mmol) in CH$_2$Cl$_2$ (3.1 mL) at 0 °C was added freshly distilled cyclopentadiene (0.06 mL, 0.756 mmol). Reaction mixture was maintained at 0 °C for 2 h and then allowed to warm to room temperature and stir for 1 h. Reaction was concentrated *in vacuo* and the resulting residue was purified via flash column chromatography (silica gel, gradient elution, 0-3% MeOH in CH$_2$Cl$_2$) to afford 250 mg (>95%) of cycloadduct **3.57** as a white solid: R$_f$ 0.3 (1:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.85 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 8.3 Hz, 2H), 6.17 (dd, *J* = 5.7, 2.7 Hz, 1H), 5.92 (dd, *J* = 5.7, 2.7 Hz, 1H), 4.24 (d, *J* = 3.4 Hz, 2H), 3.45 (m, 2H), 3.29-3.12 (ddd, *J* = 53.2, 9.7, 3.9 Hz, 2H), 2.44 (s, 3H), 1.52-1.36 (m, 2H); ^{13}C NMR (400 MHz, CDCl$_3$ δ 169.6, 145.3, 136.1, 135.2, 129.3, 128.8, 54.4, 50.6, 49.0, 49.0, 48.1, 46.1, 21.6.

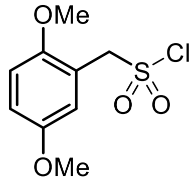


3.62: To a cooled suspension of NaH (60% in mineral oil, 725 mg, 30.2 mmol) in THF (9 mL) at 0 °C was added a solution methylhydroquinone (1.50 g, 12.1 mmol) in THF (15 mL) by cannula. The solution was maintained at 0 °C for 0.5 h, and then MeI (1.9 mL, 30.2 mmol) was added dropwise. The mixture was allowed to warm to room temperature and stir overnight. The reaction was quenched with water (30 mL) and extracted with EtOAc (3 x 15 mL). The combined organic extracts were washed with brine (30 mL), dried (MgSO$_4$), and concentrated *in vacuo*. The resulting residue was purified via flash column chromatography (silica gel, gradient elution, 0-10% EtOAc in hexanes) to afford 1.35 g (73%) of **3.62** as a light-yellow oil:

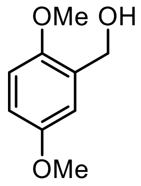
R_f 0.3 (9:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.73 (m, 3H), 3.79 (s, 3H), 3.76 (s, 3H), 2.21 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 153.3, 152.0, 127.8, 117.0, 110.9, 110.6, 55.8, 55.6, 16.3.



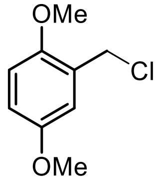
3.63: A solution of **3.62** (285 mg, 1.87 mmol), NBS (367 mg, 2.06 mmol), and AIBN (31 mg, 0.19 mmol) in CCl_4 (5.2 mL) was heated at 70 °C for 3 h in a sealed tube. The reaction mixture was then cooled to room temperature and washed with brine (2 x 10 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The resulting residue was purified via flash column chromatography (silica gel, gradient elution, 0-5% Et_2O in hexanes) to afford 430 mg (>95%) of **3.63** as a white solid: R_f 0.5 (9:1 hexanes/Et_2O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.82 (m, 3H), 4.54 (s, 2H), 3.85 (s, 3H), 3.77 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 153.3, 151.6, 126.9, 116.3, 115.0, 112.1, 56.1, 55.7, 28.8.



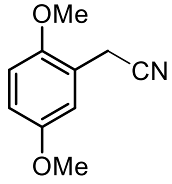
3.64: A solution of **3.63** (50 mg, 0.216 mmol) and Na_2SO_3 (27 mg, 0.216 mmol) in water (0.9 mL) was heated at reflux for 18 h. Reaction mixture was cooled to room temperature and concentrated *in vacuo*. The resulting solid was dissolved in CH_2Cl_2 (1 mL), then DMF (0.1 mL) and $SOCl_2$ (0.02 mL, 0.237 mmol) were added sequentially. Reaction mixture was heated at 40 °C for 1 h. The mixture was then diluted with water (5 mL) and extracted with Et_2O (3 x 5 mL). The combined organic extracts were washed with water (3 x 5 mL), brine (2 x 10 mL), dried ($MgSO_4$), and concentrated *in vacuo* to give 21 mg (39%) of **3.64** as a white solid that was used without further purification; ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 6.95 (m, 3H), 4.66 (s, 2H), 3.83 (s, 3H), 3.76 (s, 3H); ^{13}C NMR (400 MHz, $(CD_3)_2CO$) δ 116.3, 114.6, 112.1, 55.6, 55.0, 41.2.



3.67: To a cooled suspension of NaBH$_4$ (683 mg, 18.1 mmol) in EtOH (36 mL) at 0 ^{o}C was added a solution of (2,5-dimethoxyphenyl)methanol (3.0 g, 18.1 mmol) in EtOH (36 mL) by cannula. Reaction mixture was maintained at 0 ^{o}C for 0.5 h then poured over ice water (100 mL) and extracted with EtOAc (3 x 15 mL). The combined organic extracts were washed with brine (20 mL), dried (MgSO$_4$), and concentrated *in vacuo* to give 2.33 g (77%) of **3.67** as a yellow oil that was used without further purification; ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.80 (m, 3H), 4.65 (bs, 2H), 3.82 (s, 3H), 3.77 (s, 3H); ^{13}C NMR (400 MHz, CDCl$_3$) δ 114.8, 113.0, 111.1, 62.1, 55.8.

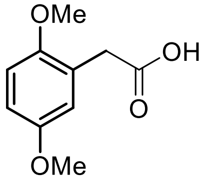


3.68: To a cooled solution of **3.67** (300 mg, 1.78 mmol) and pyridine (0.16 mL, 1.96 mmol) in CHCl$_3$ (3.6 mL) at 0 ^{o}C was added SOCl$_2$ (0.14 mL, 1.87 mmol) was added dropwise. Reaction mixture was maintained at 0 ^{o}C for 0.5 h then quenched with water (10 mL) and extracted with EtOAc (3 x 5 mL). The combined organic extracts were washed with brine (10 mL), dried (MgSO$_4$), and concentrated *in vacuo* to give 193 mg (58%) of **3.68** as a white solid that was used without further purification; ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.84 (m, 3H), 4.64 (s, 2H), 3.84 (s, 3H), 3.78 (s, 3H).

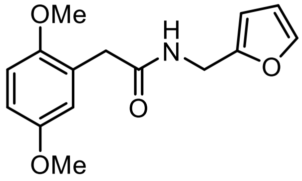


3.69: A solution of **3.68** (399 mg, 2.14 mmol) and NaCN (126 mg, 2.57 mmol) in DMF (8.6 mL) was heated at 80 ^{o}C for 2 h. Reaction mixture was diluted with water (15 mL) and extracted with Et$_2$O (3 x 5 mL). The combined organic extracts were washed with water (2 x 10 mL), brine (10 mL), dried (MgSO$_4$), and concentrated *in vacuo* to give 363 mg (>95%) of **3.69** as a white solid that was used without further purification; ^{1}H NMR

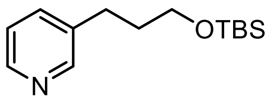
(400 MHz, $CDCl_3$) δ 6.82 (m, 3H), 3.81 (s, 3H), 3.78 (s, 3H), 3.66 (s, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 153.6, 150.8, 119.4, 117.9, 115.3, 113.7, 111.3, 55.8, 55.7, 18.6.



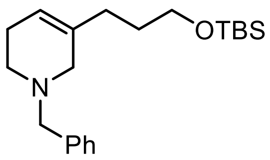
3.70: To a solution of NaOH (45 mg, 1.13 mmol) in water (1.4 mL) was added **3.69** (50 mg, 0.282 mmol). Reaction mixture was heated at 80 °C for 8 h and cooled to room temperature. Mixture was acidified to pH 3 upon addition of 1 N solution of HCl and extracted with EtOAc (3 x 5 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The resulting residue was purified via flash column chromatography (silica gel, gradient elution, 0-50% EtOAc in hexanes) to afford 27 mg (49%) of **3.70** as a white solid: R_f 0.3 (1:1 hexanes/EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 6.79 (m, 3H), 3.80 (s, 3H), 3.76 (s, 3H), 3.65 (s, 2H) ^{13}C NMR (400 MHz, $CDCl_3$) δ 153.5, 151.5, 123.2, 117.1, 113.1, 111.6, 56.1, 55.6, 35.9.



3.71: To a solution of **3.70** (381 mg, 1.94 mmol) in DMF (9.7 mL) was added HATU (886 mg, 2.33 mmol), DIPEA (1.01 mL, 5.83 mmol), and furfurylamine (0.19 mL, 2.136 mmol) sequentially. Reaction mixture was stirred at room temperature for 0.5 h, diluted with water (20 mL), and extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with water (5 x 5 mL), brine (10 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The resulting residue was purified via flash column chromatography (silica gel, gradient elution, 0-50% EtOAc in hexanes) to afford 513 mg (96%) of amide **3.71** as a white solid: R_f 0.3 (1:1 hexanes/EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 7.31 (br s, 1H), 6.82 (m, 3H), 6.29-6.11 (m, 3H), 4.38 (d, *J* = 5.7 Hz, 2H), 3.76 (app. d, *J* = 2.3 Hz, 6H), 3.55 (s, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 170.8, 153.7, 151.5, 151.2, 141.9, 124.4, 116.9, 113.3, 111.7, 110.3, 106.8, 55.8, 55.6, 38.9, 36.5.

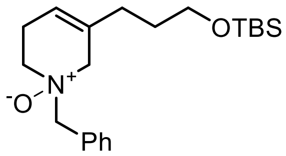


3.73: To a cooled solution of 3-propanolpyridine (4.7 mL, 36.5 mmol) and imidazole (3.7 g, 54.8 mmol) in CH_2Cl_2 (36 mL) at 0 °C, was added a solution of TBSCl (6.6 g, 43.8 mmol) in CH_2Cl_2 (36 mL) was added by cannula. The reaction mixture was allowed to warm to room temperature and maintained for 18 h. The mixture was then diluted with water (100 mL) and extracted with EtOAc (3 x 30 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The resulting residue was purified via flash column chromatography (silica gel, gradient elution, 0-20% EtOAc in hexanes) to afford 8.78 g (96%) of pyridine **3.73** as a colorless oil: R_f 0.3 (8:2 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, *J* = 1.9 Hz, 2H), 8.43 (dd, *J* = 4.8, 1.4 Hz, 1H), 7.50 (m, 1H), 7.19 (dd, *J* = 7.7, 4.8 Hz, 1H), 3.63 (t, *J* = 6.2 Hz, 2H), 2.69 (t, *J* = 7.9 Hz, 2H), 1.83 (m, 2H), 0.90 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 150.0, 147.2, 135.9, 123.3, 61.9, 34.0, 29.2, 25.9, -5.3.

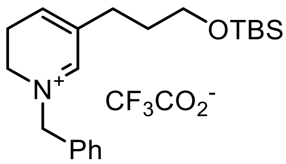


3.74: To a solution of **3.73** (1.0 g, 3.98 mmol) in CH_2Cl_2 (4 mL) was added BnBr (0.5 mL, 4.2 mmol) and the mixture was stirred at room temperature overnight. The reaction mixture was then added dropwise to a cooled suspension of $NaBH_4$ (166 mg, 4.38 mmol) in EtOH (13 mL) and maintained at 0 °C for 3 h. Reaction was then quenched with water (20 mL) and extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The resulting residue was purified via flash column chromatography (silica gel, gradient elution, 0-10% EtOAc in hexanes) to afford 869 mg (63%) of tetrahydropyridine **3.74** as a yellow oil: R_f 0.3 (8:2 hexanes/EtOAc); ^{1}H NMR (400

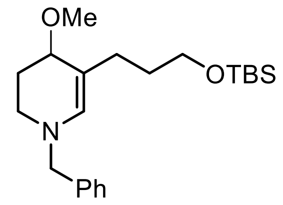
MHz, $CDCl_3$) δ 7.30 (m, 5H), 5.46 (bs, 1H), 3.59 (app t, *J* = 6.4 Hz, 4H), 2.88 (bs, 2H), 2.50 (m, 2H), 2.13 (bs, 2H), 1.96 (t, *J* = 7.3 Hz, 2H), 1.61 (m, 2H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 129.2, 128.2, 118.9, 62.8, 31.4, 30.8, 26.0, -5.3.



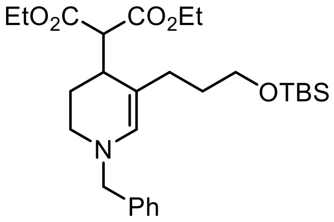
3.75: To a cooled solution of **3.74** (200 mg, 0.58 mmol) in CH_2Cl_2 (1.2 mL) at 0 °C was added a solution of *m*CPBA (129 mg, 0.75 mmol) in CH_2Cl_2 (0.75 mL) dropwise. Reaction mixture was maintained at 0 °C for 15 min, quenched with a saturated aq. solution of $KHCO_3$, and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$), and concentrated *in vacuo* to give 185 mg (88%) of N-Oxide **3.75** as a yellow oil that was used without further purification: R_f 0.3 (7:3 hexanes/EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 7.58-7.37(m, 5H), 5.58 (bs, 1H), 4.34 (bs, 2H), 3.73-3.40 (m, 4H), 3.41 (s, 1H), 3.26 (m, 2H), 2.68-2.28 (m, 2H), 2.00 (t, *J* = 7.2 Hz, 2H), 1.58 (m, 2H), 0.86 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 132.4, 132.1, 130.1, 129.4, 128.4, 117.6, 71.5, 66.9, 62.2, 61.3, 30.9, 30.2, 25.8, 23.2, 18.2, -5.4.



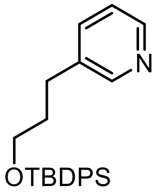
3.76: To a solution of **3.75** (100 mg, 0.28 mmol) in CH_2Cl_2 (1.4 mL) was added TFAA (0.04 mL, 0.30 mmol) dropwise. Reaction mixture was stirred for 5 min at room temperature and used without further purification or workup. ^1H NMR (400 MHz, CD_2Cl_2) δ 8.46 (s, 1H), 7.48 (m, 5H), 6.80 (bs, 1H), 5.06 (s, 2H), 3.76 (t, *J* = 9.6 Hz, 2H), 3.64 (t, *J* = 5.9 Hz, 4H), 2.69 (m, 2H), 2.43 (t, *J* = 7.4 Hz, 2H), 1.69 (m, 2H), 0.88 (s, 9H), 0.05 (s, 6H).



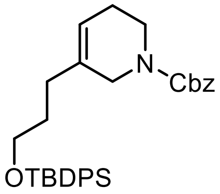
3.78: To a solution of **3.75** (207 mg, 0.57 mmol) in CH_2Cl_2 (1.9 mL) was added TFAA (0.09 mL, 0.63 mmol) dropwise. Reaction mixture was stirred for 5 min at room temperature and then a solution of NaOMe (0.5 M, 2.5 mL, 1.3 mmol) was added dropwise. Solution was stirred at room temperature for 30 min, quenched with water (10 mL), and extracted with EtOAc (3 x 5 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$), and concentrated *in vacuo* to give 121 mg (57%) of enamine **3.78** as a yellow oil that was used without further purification: R_f 0.3 (95:5 CH_2Cl_2/MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (m, 5H), 5.94 (s, 1H), 4.03-3.90 (dd, *J* = 37.4, 14.4 Hz, 2H), 3.60 (m, 5H), 3.33 (s, 3H), 2.72 (m, 2H), 1.98 (m, 2H), 1.60 (m, 2H), 0.90 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 138.7, 135.4, 128.5, 128.3, 127.3, 108.2, 73.1, 63.2, 59.6, 55.8, 42.3, 32.5, 29.0, 26.6, 26.2, -5.1.



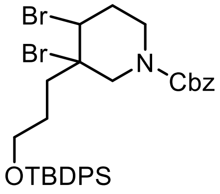
3.79: To a solution of **3.75** (25 mg, 0.069 mmol) in CH_2Cl_2 (0.6 mL) was added TFAA (0.01 mL, 0.077 mmol) dropwise. Reaction mixture was stirred for 5 min at room temperature and then a solution of sodium diethyl malonate (0.3 M, 0.5 mL, 1.52 mmol) was added dropwise. Solution was stirred at room temperature for 30 min and concentrated *in vacuo*. The resulting residue was purified via flash column chromatography (silica gel, gradient elution, 0-10% EtOAc in hexanes) to afford 12 mg (34%) of enamine **3.79** as yellow oil: R_f 0.3 (9:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (m, 5H), 5.89 (s, 1H), 4.15 (m, 4H), 3.95 (s, 2H), 3.58 (t, *J* = 6.4 Hz, 2H), 3.48 (d, *J* = 7.3 Hz, 1H), 2.95 (m, 1H), 2.75 (m, 2H), 1.90 (m, 4H), 1.67-1.51 (m, 2H), 1.25 (dt, *J* = 17.0, 7.1 Hz, 6H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 169.3, 168.5, 138.6, 134.2, 129.8, 129.1, 128.8, 128.4, 128.1, 127.7, 127.2, 106.6, 62.8, 61.3, 61.1, 59.5, 55.7, 53.5, 43.6, 33.6, 31.9, 29.3, 26.1, 26.0, 26.0, 18.4, 14.2, 14.1, -5.2.



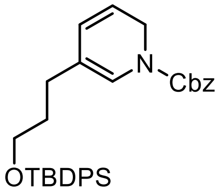
3.80: To a cooled solution of 3-propanolpyridine (10.0 g, 72.9 mmol) and imidazole (7.445 g, 109.4 mmol) in CH_2Cl_2 (243 mL) at 0 °C, was added TBDPSCl (20 mL, 76.5 mmol). Reaction mixture was allowed to warm to room temperature and stir for 18 h. The mixture was then diluted with water (200 mL), and extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The resulting residue was purified via flash chromatography (silica gel, gradient elution, 0-20% EtOAc in hexanes) to afford 25.3 g (92%) of pyridine **3.80** as colorless oil: R_f 0.3 (8:2 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (m, 2H), 7.66 (m, 4H), 7.39 (m, 7H), 7.18 (dd, *J* = 7.5, 5 Hz, 1H), 3.69 (t, *J* = 6.2 Hz, 2H), 2.73 (t, *J* = 7.7 Hz, 2H), 1.86 (m, 2H), 1.07 (s, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 150.0, 147.2, 135.7, 135.5, 129.5, 127.6, 123.1, 62.6, 33.7, 29.1, 26.8.



3.81: To a solution of **3.80** (2.00 g, 5.32 mmol) in CH_2Cl_2 (11 mL) was added benzyl bromide (0.67 mL, 5.59 mmol). Solution was stirred for 18 h at room temperature. Reaction mixture was then diluted with EtOH (3 mL) and added dropwise via cannula to a cooled suspension of $NaBH_4$ (201 mg, 5.32 mmol) in EtOH (18 mL) at 0 °C. Reaction mixture was maintained at 0 °C for 1 h, quenched with water (20 mL), and extracted with EtOAc (3 x 10 mL). The combined organics were washed with water (2 x 10 mL), brine (1 x 10 mL), dried ($MgSO_4$), and conc. *in vacuo*. Residue was dissolved in benzene (21 mL) and benzyl chloroformate (50% wt/sol) (1.52 mL, 10.64 mmol) added. Reaction mixture was heated at reflux for 3 h, cooled to room temperature, and conc. *in vacuo.* The resulting residue was purified via flash chromatography (silica gel, gradient elution, 0-10% EtOAc in hexanes) to afford 1.74 g (64%) of tetrahydropyridine **3.81** as colorless oil: R_f 0.3 (9:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (m, 4H), 7.37 (m, 11H), 5.50 (s, 1H), 5.16 (s, 2H), 3.82 (s, 2H), 3.66 (t, J = 6.1 Hz, 2H), 3.49 (t, J = 6.1 Hz, 2H), 2.08 (s, 4H), 1.68 (s, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 155.4, 136.9, 135.5, 133.9, 129.5, 128.4, 127.9, 127.8, 127.5, 119.4, 119.0, 66.9, 63.2, 46.0, 40.6, 40.3, 30.8, 30.5, 26.8, 24.9, 24.6, 19.1.

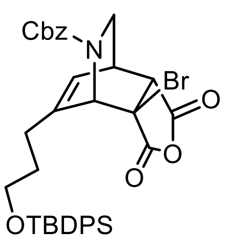


3.82: To a cooled solution of **3.81** (2.43 g, 4.73 mmol) in CH_2Cl_2 (19 mL) at 0 °C was added bromine (0.27 mL, 5.21 mmol) dropwise. Reaction mixture was maintained at 0 °C for 5 min, quenched with a saturated solution of $Na_2S_2O_3$ (30 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The combined organics were washed with brine (20 mL), dried ($MgSO_4$), and concentrated *in vacuo* to give 2.77 g (87%) of dibromo **3.82** as a viscous yellow oil that was used without further purification: R_f 0.3 (9:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (m, 4H), 7.37 (m, 11H), 5.17 (s, 2H), 4.59 (s, 1H), 4.16 (m, 2H), 3.72 (m, 2H), 3.36 (m, 2H), 2.78 (m, 2H), 1.94 (m, 4H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 155.1, 135.4, 134.7, 133.7, 128.4, 128.0, 127.9, 127.6, 70.4, 67.4, 63.1, 56.1, 56.1, 50.9, 39.2, 37.4, 27.2, 26.8, 19.1.

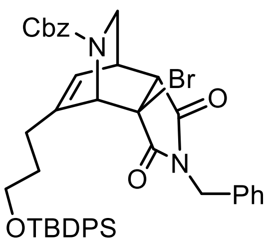


3.83: To a solution of **3.82** (300 mg, 0.445 mmol) in benzene (1.8 mL) was added DABCO (100 mg, 0.890 mmol). The mixture was heated immediately at 120 °C for 3 h under static vacuum (ca. 0.01 torr). The reaction mixture was cooled to room temperature, filtered, and the filtrate diluted with water (10 mL), and extracted with EtOAc (3 x 5 mL). The combined organic extracts were washed with brine (1 x 15 mL), dried

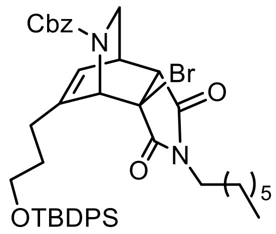
(Na_2SO_4), and concentrated *in vacuo*. Residue was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (m, 4H), 7.37 (m, 11H), 6.54 (d, J = 38.6 Hz, 1H), 5.78 (d, J = 9.8 Hz, 1H), 5.54 (m, 1H), 5.20 (s, 2H), 4.31 (s, 2H), 3.66 (m, 2H), 2.13 (m, 2H), 1.65 (m, 2H), 1.05 (s, 9H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 135.6, 129.6, 128.6, 128.2, 128.1, 127.7, 127.6, 125.0, 120.9, 119.7, 67.6, 62.9, 43.4, 31.6, 28.6, 26.9.



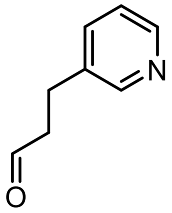
3.84: Crude oil of **3.83** was transferred to an oven-dried sealed flask, which was sparged with argon for 5 minutes. Bromomaleic anhydride (0.08 mL, 0.89 mmol) was added, and the reaction mixture stirred at room temperature for 18 h under static vacuum (ca. 0.01 torr). Mixture was then purified via flash chromatography (silica gel, gradient elution, 0-20% EtOAc in hexanes) to afford 128 mg (42%) of cycloadduct **3.84** as a red oil: R_f 0.3 (8:2 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (m, 4H), 7.37 (m, 11H), 5.90 (dd, J = 5.2, 12.4 Hz, 1H), 5.09 (m, 3H), 3.57 (m, 1H), 3.46 (m, 2H), 3.34 (m, 1H), 3.30 (m, 1H), 3.01 (dd, J = 10.8, 35.5 Hz, 1H), 2.24 (m, 2H), 1.60 (m, 2H), 1.04 (s, 9H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 168.2, 166.8, 155.1, 146.4, 135.5, 133.6, 130.0, 129.6, 128.5, 128.3, 128.2, 127.9, 127.6, 124.3, 67.6, 62.1, 55.8, 55.1, 53.5, 45.2, 34.1, 29.9, 29.0, 20.8, 19.1.



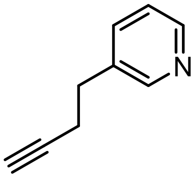
3.87: To a solution of **3.84** (100 mg, 0.145 mmol) in CH_2Cl_2 (0.32 mL) was added benzylamine (0.04 mL, 0.348 mmol). Reaction mixture was stirred at room temperature for 2 h then concentrated *in vacuo*. The residue was taken up in MeOH (0.2 mL) and PhH (0.7 mL) to which $TMSCHN_2$ (2M in hexanes, 0.09 mL, 0.189 mmol) was added. Reaction was stirred at room temperature for 30 min and concentrated *in vacuo*. The resulting residue was purified via flash chromatography (silica gel, gradient elution, 0-20% EtOAc in hexanes) to give 13 mg (11%) of imide **3.87** as a colorless oil: R_f 0.3 (8:2 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61-7.24 (m, 20H), 5.50 (t, *J* = 7.6 Hz, 1H), 5.15 (m, 1H), 5.01 (d, *J* = 64.3 Hz, 1H), 4.56 (m, 2H), 3.51-3.30 (m, 3H), 3.19 (m, 1H), 3.09 (dd, *J* = 6.7, 2.8 Hz, 1H), 2.98 (ddd, J = 33.7, 10.7, 2.3 Hz, 1H), 1.98-1.85 (m, 2H), 1.82-1.40 (m, 2H), 1.26 (m, 2H), 1.04 (s, 9H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 174.4, 174.3, 172.6, 155.4, 154.8, 145.6, 145.0, 136.5, 136.3, 135.7, 134.9, 133.9, 129.8, 129.8, 128.7, 128.6, 128.4, 128.3, 128.2, 128.0, 127.8, 123.9, 123.7, 67.7, 67.5, 62.5, 62.4, 57.1, 57.0, 56.6, 53.2, 45.9, 45.6, 43.2, 34.4, 34.2, 29.7, 29.0, 28.9, 27.0, 19.3.



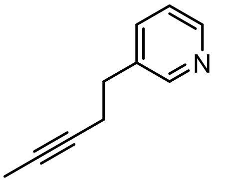
3.88: To a solution of **3.84** (25 mg, 0.036 mmol) in CH_2Cl_2 (0.5 mL) was added heptylamine (0.01 mL, 0.040 mmol). Reaction mixture was stirred at room temperature for 1 h then concentrated *in vacuo*. The residue was taken up in MeOH (0.5 mL) to which $TMSCHN_2$ (2M in hexanes, 0.04 mL, 0.072 mmol) was added. Reaction was stirred at room temperature for 30 min and concentrated *in vacuo*. The resulting residue was purified via flash chromatography (silica gel, gradient elution, 0-20% EtOAc in hexanes) to give 16 mg (55%) of imide **3.88** as a colorless oil: R_f 0.3 (8:2 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61-7.28 (m, 15H), 5.73 (m, 1H), 5.17-4.99 (m, 3H), 3.63-3.41 (m, 5H), 3.23 (m, 1H), 3.08-2.97 (m, 2H), 2.18 (m, 2H), 1.74-1.46 (m, 5H), 1.26 (m, 12H), 1.03 (s, 9H), 0.86 (m, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 174.8, 174.6, 173.0, 172.8, 155.4, 154.8, 145.8, 145.2, 136.6, 136.3, 135.7, 133.8, 129.8, 128.6, 128.4, 128.3, 128.0, 127.8, 124.1, 123.8, 67.7, 62.5, 62.4, 57.2, 57.1, 56.5, 53.3, 53.2, 46.0, 45.7, 39.6, 34.3, 34.1, 31.8, 29.9, 29.4, 29.2, 28.9, 27.4, 27.0, 26.7, 22.7, 19.3, 14.2.



3.89: To a cooled solution of oxalyl chloride (1.4 mL, 16.0 mmol) in CH_2Cl_2 (36 mL) at -65 °C was added a solution of DMSO (2.3 mL, 32.9 mmol) in CH_2Cl_2 (8 mL) dropwise and stirred for 2 min. A solution of 3-pyridinepropanol (2.0 g, 14.6 mmol) in CH_2Cl_2 (58 mL) was added and the mixture maintained at -65 °C for 15 min. Then NEt_3 (10.2 mL, 72.9 mmol) was added, and the reaction stirred at -65 °C for 5 min, warmed to room temperature for 30 min. The reaction mixture was quenched with water (60 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The resulting residue was purified via flash chromatography (silica gel, gradient elution, 0-5% MeOH in CH_2Cl_2) to give 1.62 g (82%) of aldehyde **3.89** as a yellow oil: R_f 0.3 (95:5 CH_2Cl_2/MeOH);^{1}H NMR (400 MHz, $CDCl_3$) δ 9.83 (s, 1H), 8.47 (m, 2H), 7.52 (m, 1H), 7.22 (dd, *J* = 7.7, 4.3 Hz, 1H), 2.96 (t, *J* = 7.4 Hz, 2H), 2.82 (t, *J* = 7.4 Hz, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 200.6, 150.0, 148.0, 136.0, 123.6, 45.0, 25.3.



3.91: To a suspension of **3.89** (500 mg, 3.70 mmol) and K_2CO_3 (1.02 g , 7.40 mmol) in MeOH (3.7 mL) was added a solution of Bestmann-Ohira reagent (782 mg, 4.07 mmol) in MeOH (3.7 mL) dropwise. Reaction mixture was maintained at room temperature and stirred for 18 h. Mixture was diluted with water (15 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The resulting residue was purified via flash chromatography (silica gel, gradient elution, 0-5% MeOH in CH_2Cl_2) to give 301 mg (62%) of alkyne **3.91** as a light-yellow oil: R_f 0.3 (95:5 CH_2Cl_2/MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (m, 2H), 7.57 (m, 1H), 7.23 (dd, *J* = 7.7, 4.8 Hz, 1H), 2.84 (t, *J* = 7.3 Hz, 2H), 2.51 (td, *J* = 7.3, 2.6 Hz, 2H), 1.99 (t, *J* = 2.6 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 149.9, 147.9, 135.8, 135.5, 123.2, 82.8, 69.6, 31.7, 20.2.



3.92: To a cooled solution of **3.91** (100 mg, 0.76 mmol) in THF (3 mL) at -20 °C was added *n*-BuLi (2.5 M in THF, 0.3 mL, 0.76 mmol) dropwise. Reaction mixture was stirred at -20 °C for 20 min and then MeI (0.05 mL, 0.84 mmol) was added dropwise. Reaction stirred at -20 °C for 5 min, and then allowed to warm to room temperature and stir for 0.5 h. Reaction mixture was quench with a saturated aq. solution of NH_4Cl (10 mL) and extracted with EtOAc (3 x 5 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The resulting residue was purified via flash chromatography (silica gel, gradient elution, 0-5% MeOH in CH_2Cl_2) to give 83 mg (75%) of **3.92** as a brown oil: R_f 0.3 (95:5 CH_2Cl_2/MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (m, 2H), 7.51 (m, 1H), 7.18 (m, 1H), 2.75 (m, 2H), 2.40 (m, 2H), 1.72 (m, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 150.1, 147.8, 136.2, 135.9, 123.3, 77.7, 77.0, 32.5, 3.4 .

References

(56) Apponyi, M. A.; Bowie, J. H.; Skelton, B. W.; White, A. H. *Aust. J. Chem.* **2002**, *55* (5), 343.

(57) Burgess, K. L.; Lajkiewicz, N. J.; Sanyal, A.; Yan, W.; Snyder, J. K. *Org. Lett.* **2005**, *7* (1), 31–34.

(58) Stevens-Cullinane, L.; Lucas, N. T.; Hawkins, B. C. *European J. Org. Chem.* **2014**, *2014* (22), 4767–4772.

(59) Keck, G.; Yates, J. *J. Am. Chem. Soc.* **1984**, *104* (1), 5829–5831.

(60) Wenzler, M. E.; Melancon, B. J.; Sulikowski, G. A. *Tetrahedron Lett.* **2016**, *57* (30), 3252–3253.

(61) Fowler, F. W. *J. Org. Chem.* **1972**, *37* (9), 1321–1323.

(62) Sundberg, R. J.; Hamilton, G.; Trindle, C. *J. Org. Chem.* **1986**, *51* (19), 3672–3679.

(63) Stille, J. K. *Angew. Chemie Int. Ed. English* **1986**, *25* (6), 508–524.

(64) Hatanaka, Y.; Hiyama, T. *J. Org. Chem.* **1988**, *53* (4), 918–920.

(65) Pedersen, B. S.; Scheibye, S.; Nilsson, N. H.; Lawesson, S.-O. *Bull. des Sociétés Chim. Belges* **2010**, *87* (3), 223–228.

(66) Zu, L.; Boal, B. W.; Garg, N. K. *J. Am. Chem. Soc.* **2011**, *133* (23), 8877–8879.

(67) Herdeis, Claus; Hartke, C. *Heterocycles* **1989**, *29* (2), 287–296.

(68) Bowden, K.; Heilbron, I. M.; Jones, E. R. H.; Weedon, B. C. L. *J. Chem. Soc.* **1946**, No. 0, 39.

(69) Zhang, L.; Zhang, Y.; Li, W.; Qi, X. *Angew. Chemie* **2019**, *131* (15), 5042–5045.

(70) Deska, J.; Thiel, D.; Gianolio, E. *Synthesis (Stuttg).* **2015**, *47* (22), 3435–3450.

(71) Ahond, A.; Cave, A.; Kan-Fan, C.; Husson, H. P.; De Rostolan, J.; Potier, P. *J. Am. Chem. Soc.* **1968**, *90* (20), 5622–5623.

(72) Dos Santos, D. C.; De Freitas Gil, R. P.; Gil, L.; Marazano, C. *Tetrahedron Lett.* **2001**, *42* (35), 6109–6111.

(73) Maia, A.; Freitas-Gil, R.; Gil, L.; Marazano, C. *Lett. Org. Chem.* **2004**, *1* (2), 168–170.

(74) Reding, M. T.; Fukuyama, T. **1999**, No. 7, 973–976.

(75) B:urgi, H. B.; Dunitz, J. D.; Lehn, J. M.; Wipff, G. *Tetrahedron* **1974**, *30* (12), 1563–1572.

(76) Mancuso, A. J.; Swern, D. *Synthesis (Stuttg).* **1981**, *1981* (03), 165–185.

(77) Müller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett* **1996**, *1996* (06), 521–522.

(78) Ohira, S. *Synth. Commun.* **1989**, *19* (3–4), 561–564.

Appendix A.3: Spectra Relevant to Chapter 3

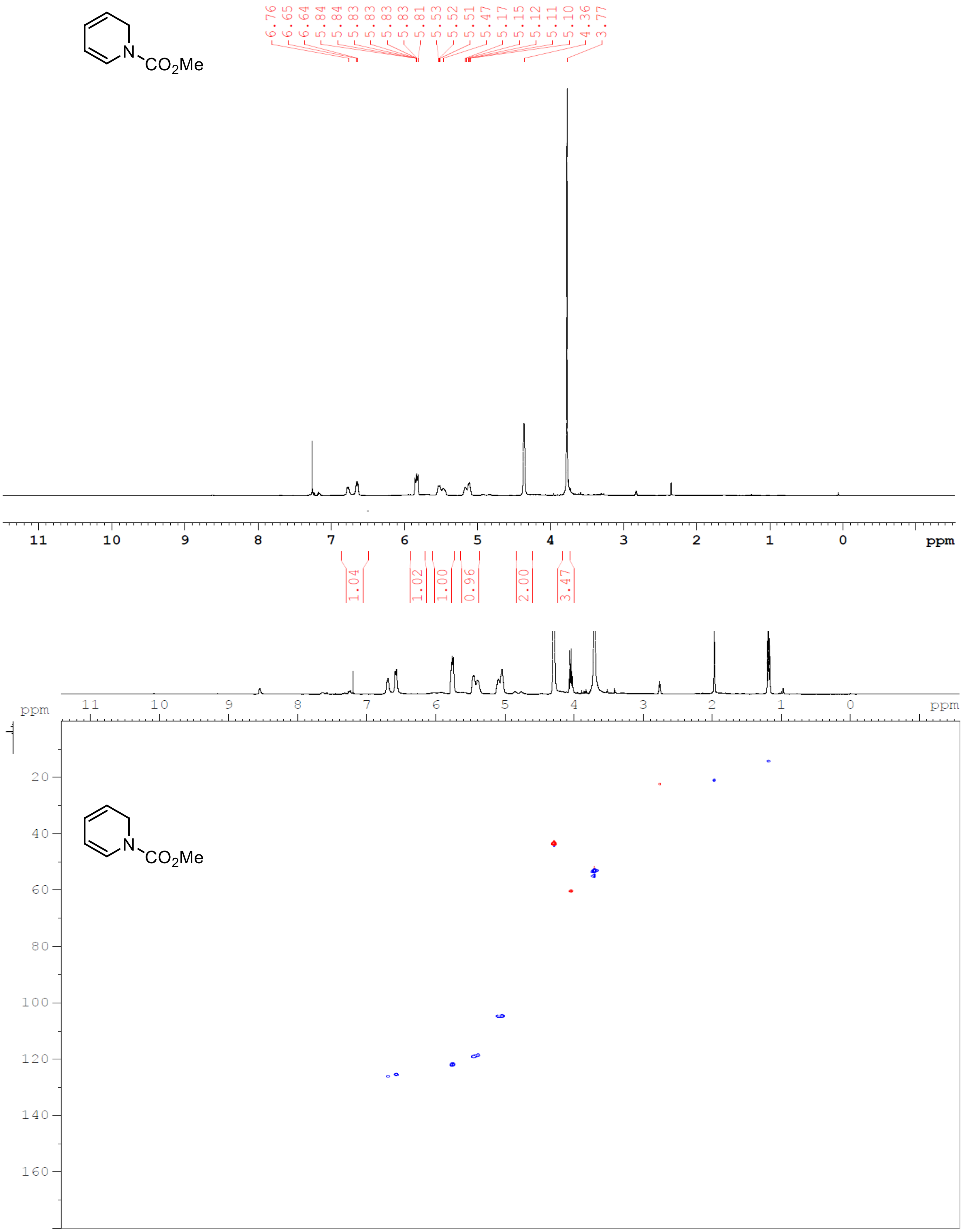


Figure A.3.1 ^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (400 MHz, CDCl$_3$) of **3.22**

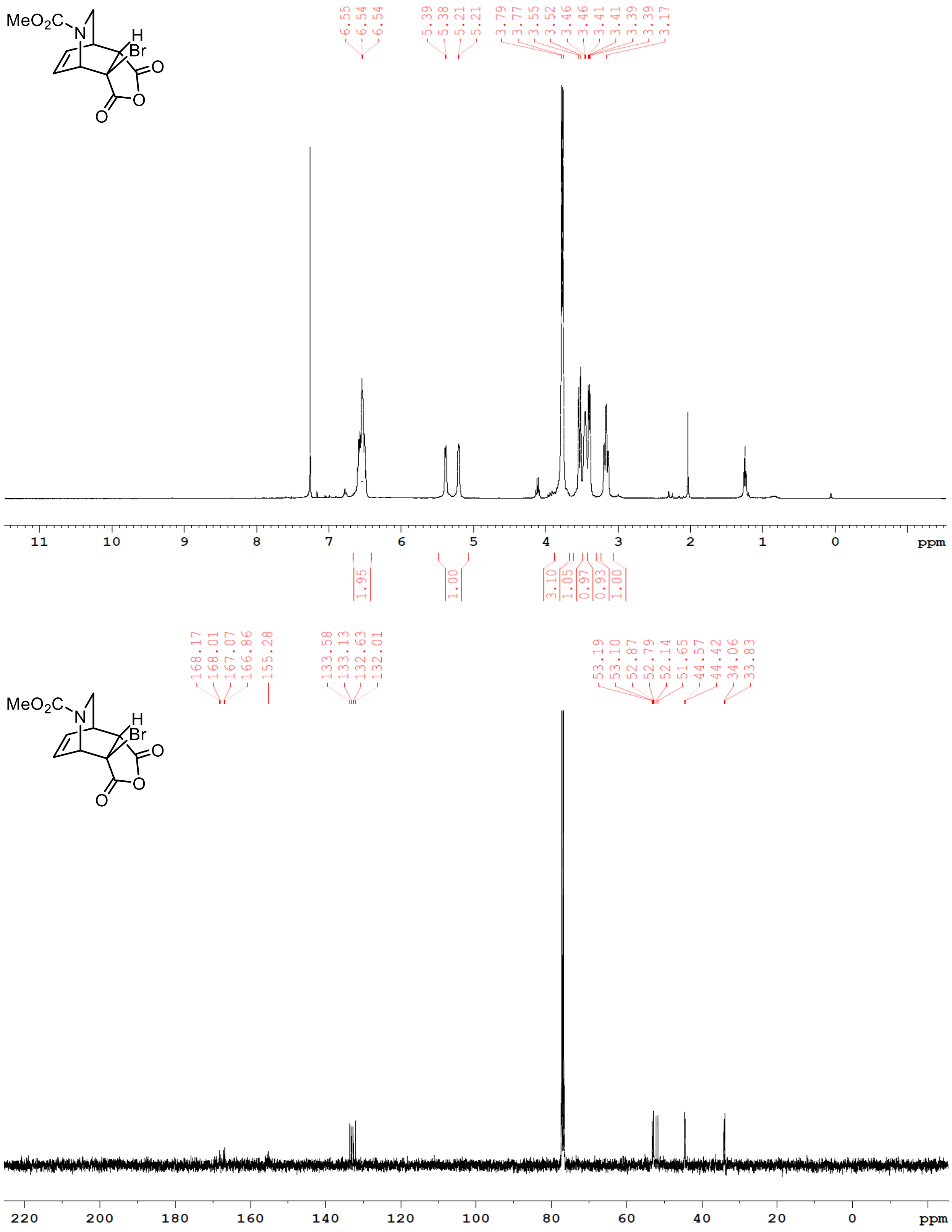


Figure A.3.2 ^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (400 MHz, CDCl$_3$) of **3.23**

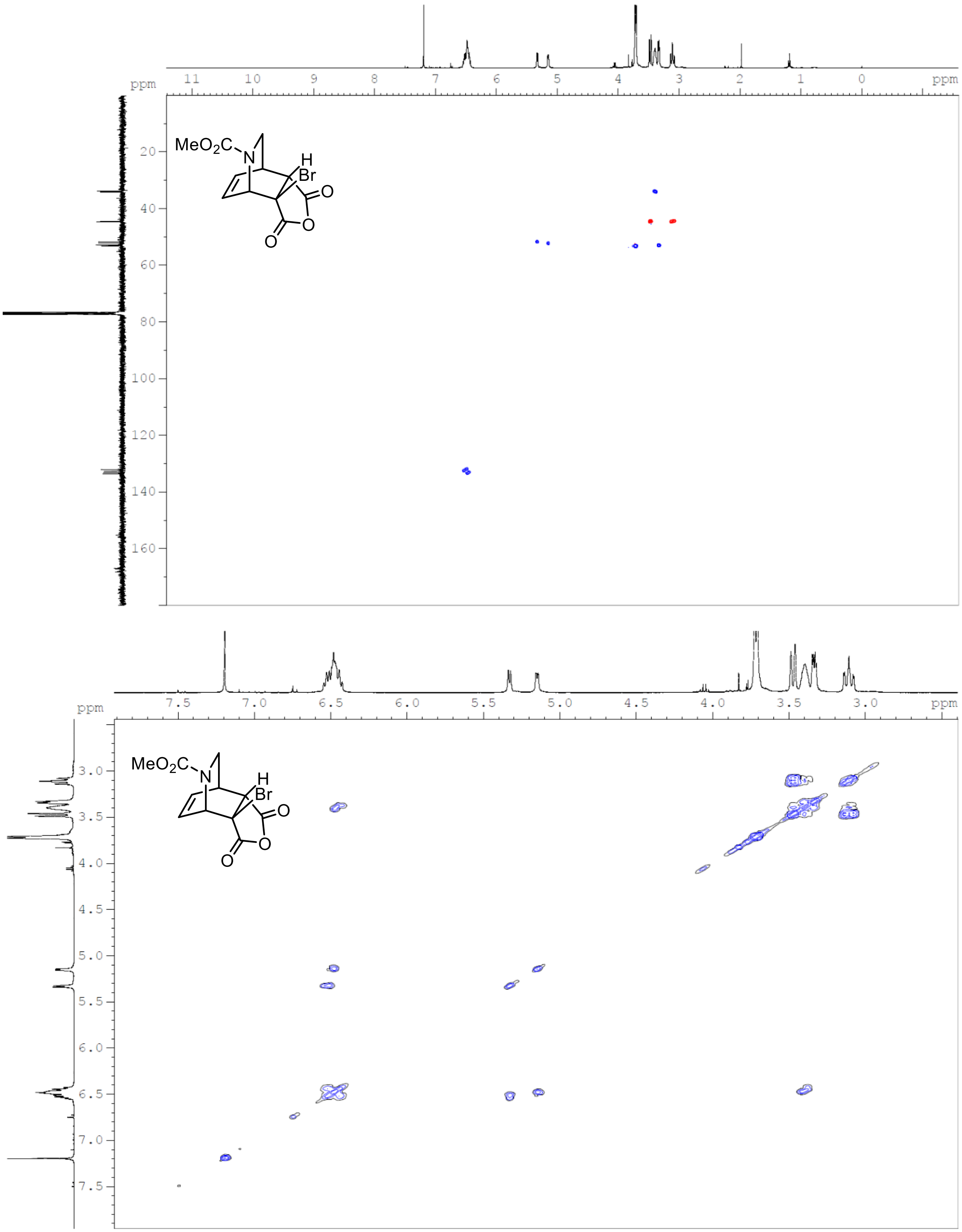


Figure A.3.3 HSQC NMR (400 MHz, CDCl$_3$) and COSY NMR (400 MHz, CDCl$_3$) of **3.23**

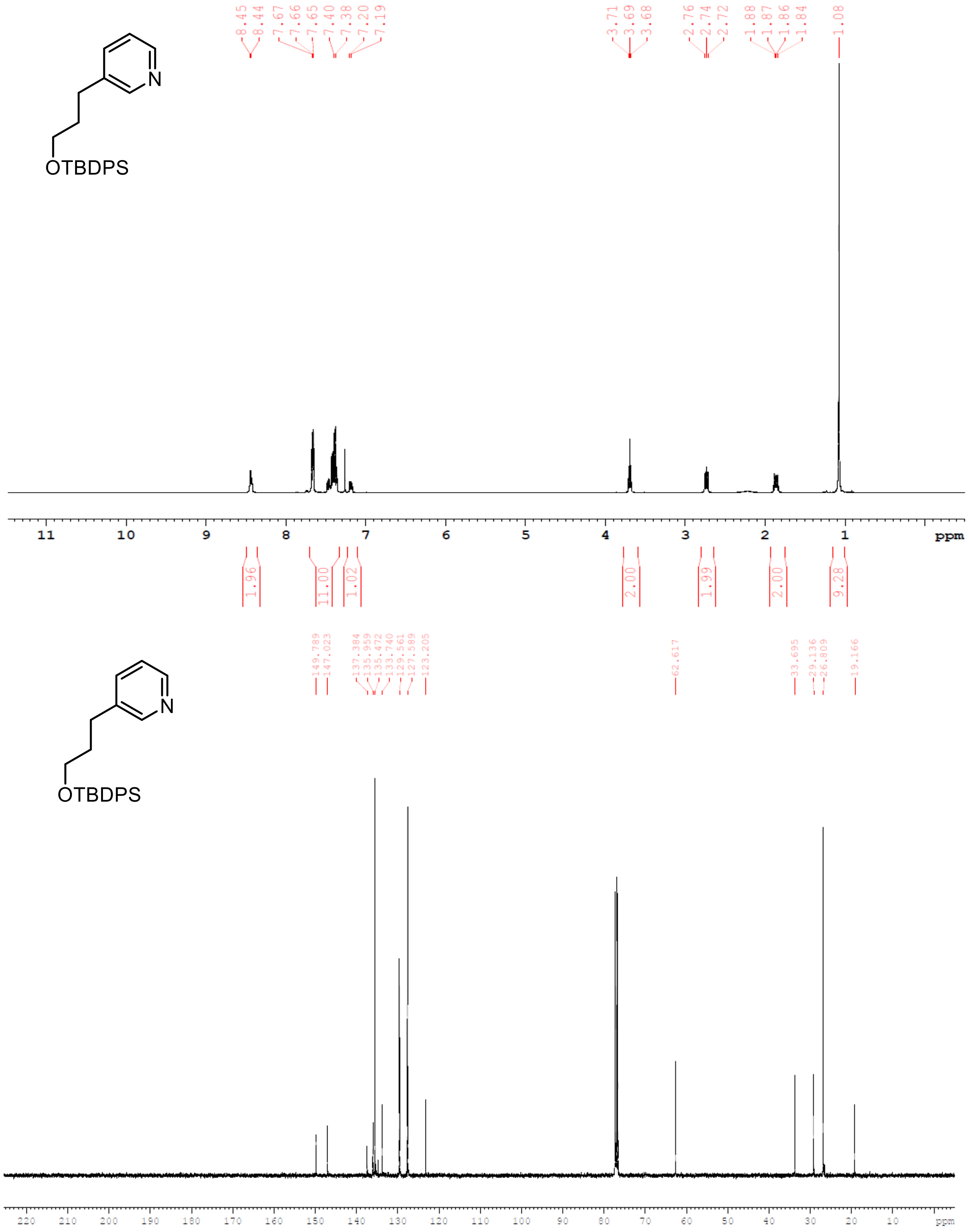


Figure A.3.4 ^{1}H NMR (400 MHz, $CDCl_3$) and HSQC NMR (400 MHz, $CDCl_3$) of **3.25**

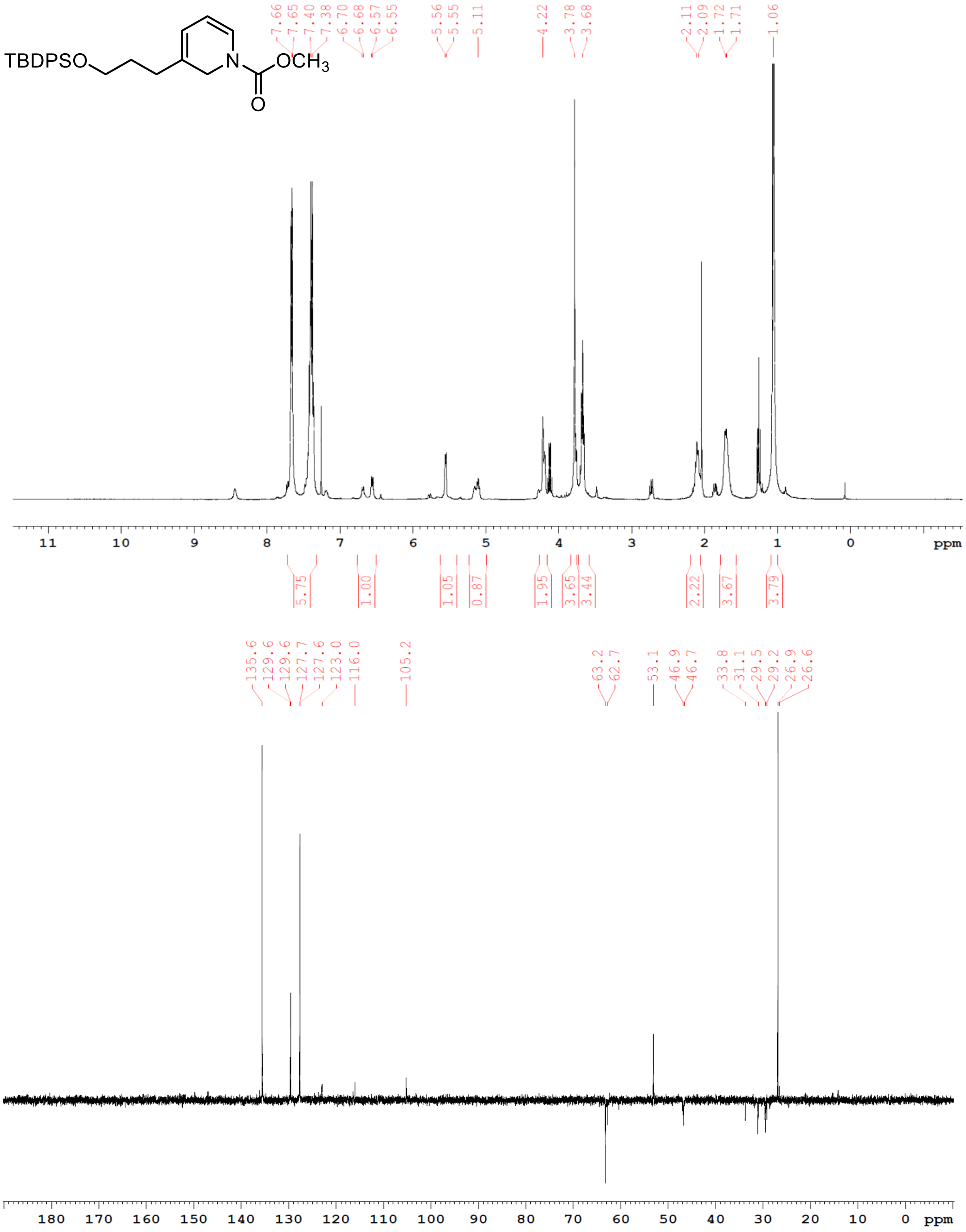


Figure A.3.5 ^{1}H NMR (400 MHz, CDCl$_3$) and DEPT-135 NMR (400 MHz, CDCl$_3$) of **3.26**

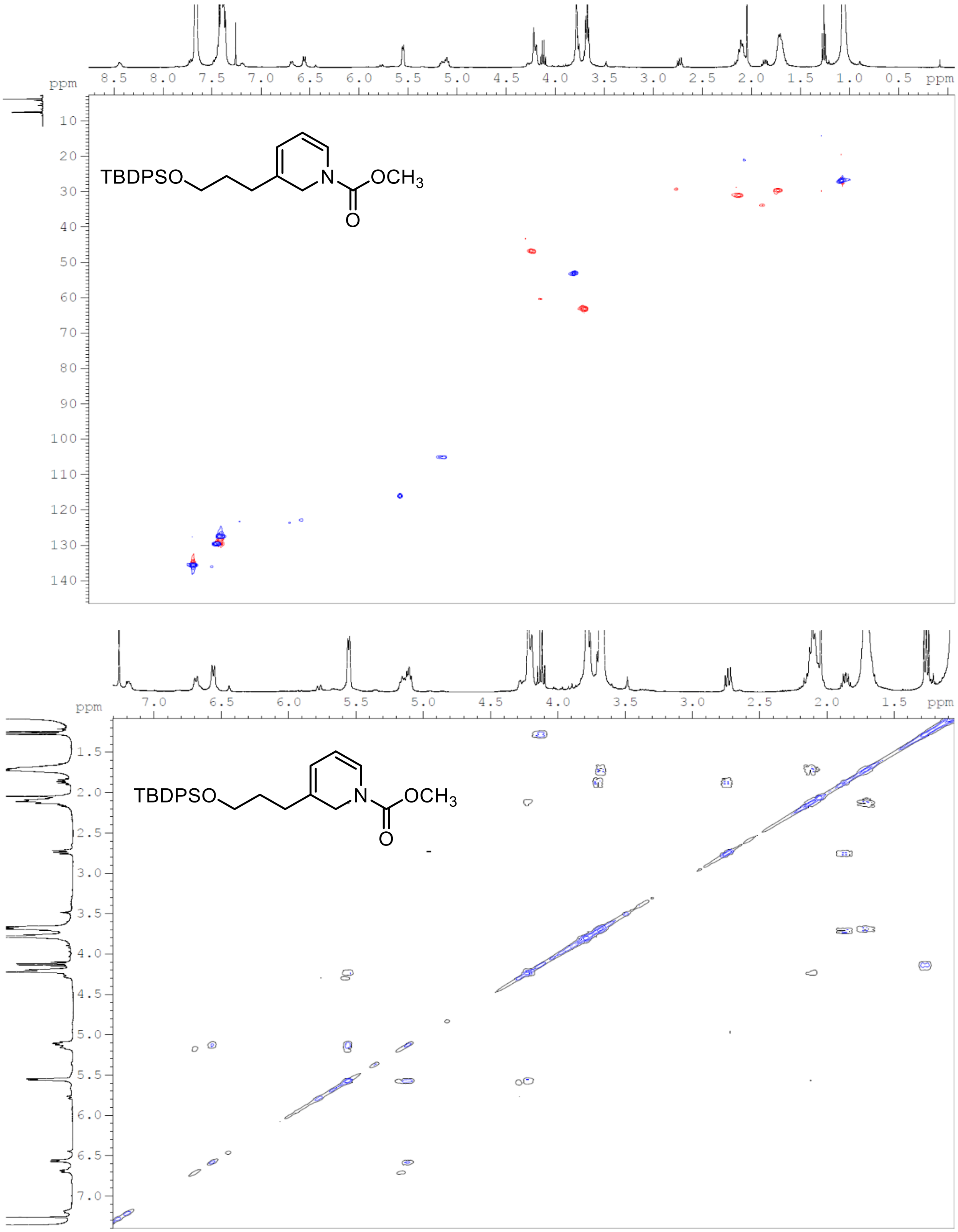


Figure A.3.6 HSQC NMR (400 MHz, $CDCl_3$) and COSY NMR (400 MHz, $CDCl_3$) of **3.26**

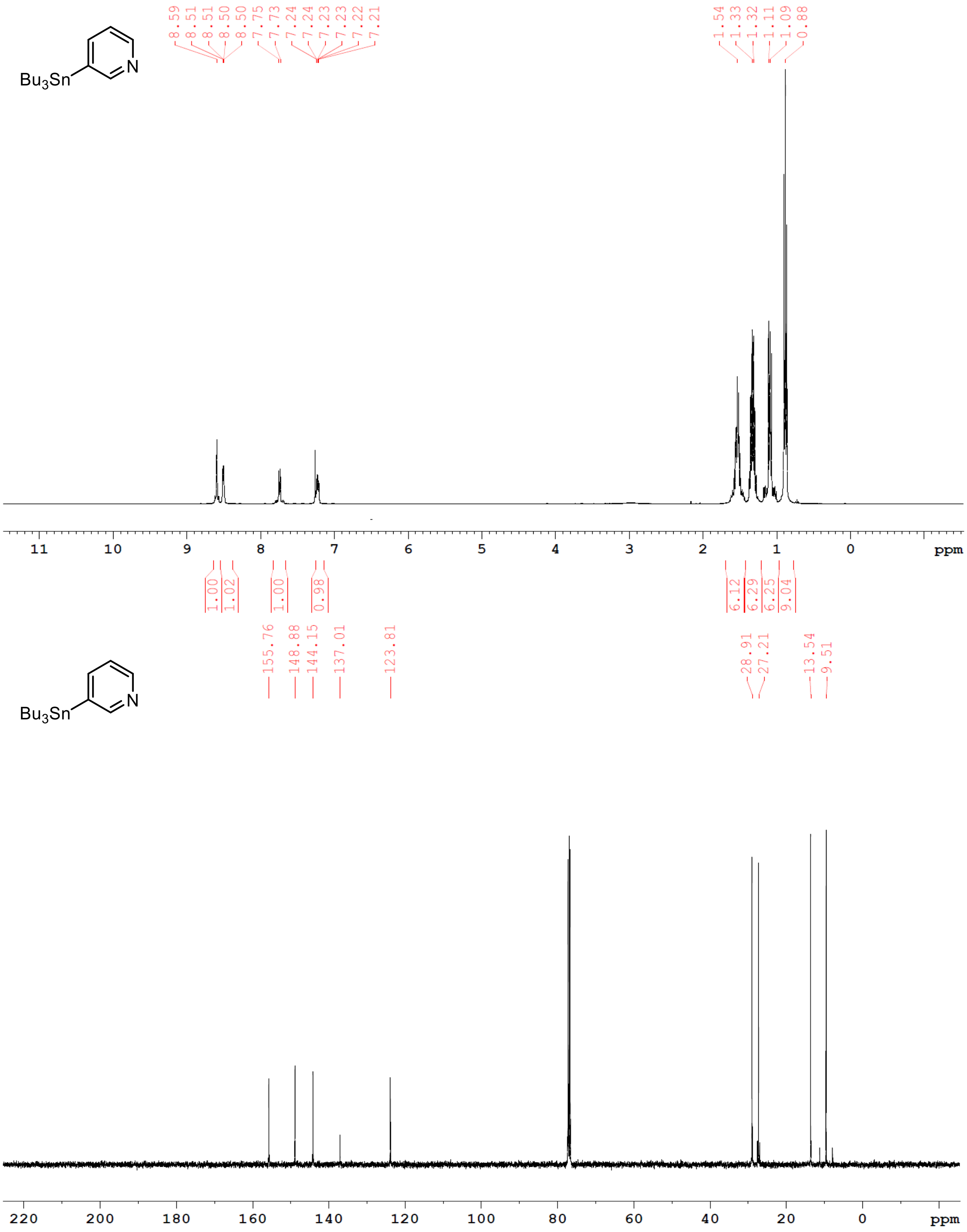


Figure A.3.7 ^{1}H NMR (400 MHz, CDCl$_3$) and HSQC NMR (400 MHz, CDCl$_3$) of **3.28**

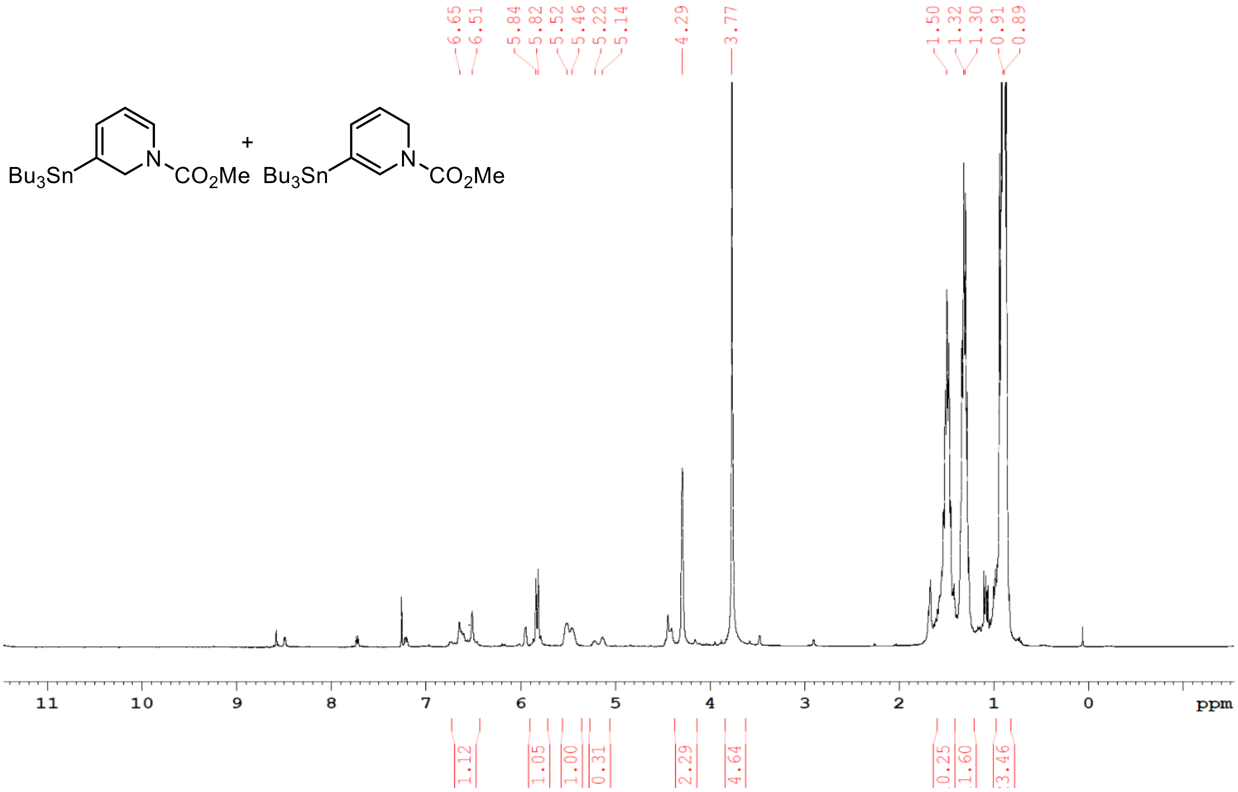


Figure A.3.8 ^{1}H NMR (400 MHz, CDCl$_3$) of **3.29** and **3.30**

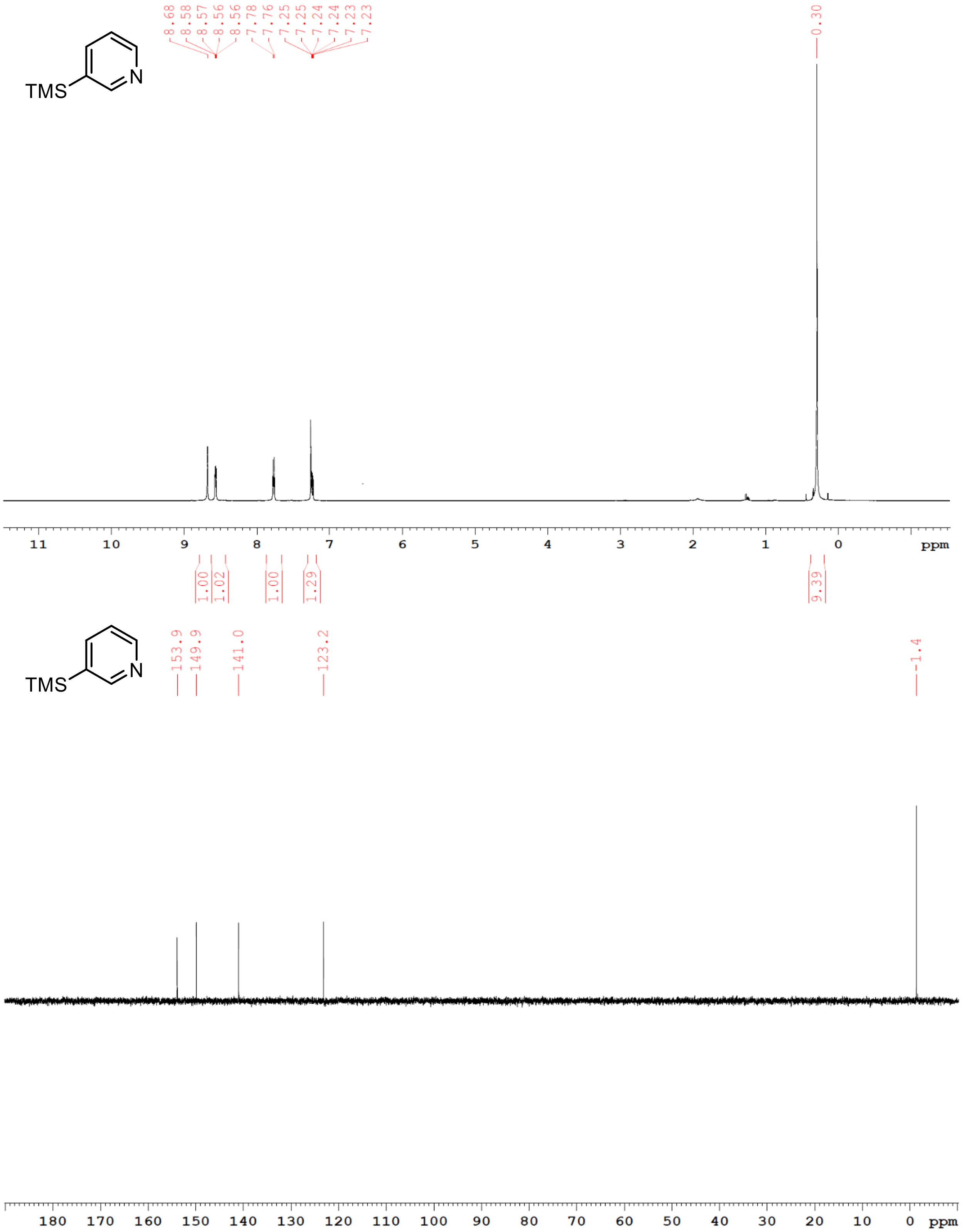


Figure A.3.9 ^{1}H NMR (400 MHz, CDCl$_3$) and DEPT-135 NMR (400 MHz, CDCl$_3$) of **3.31a**

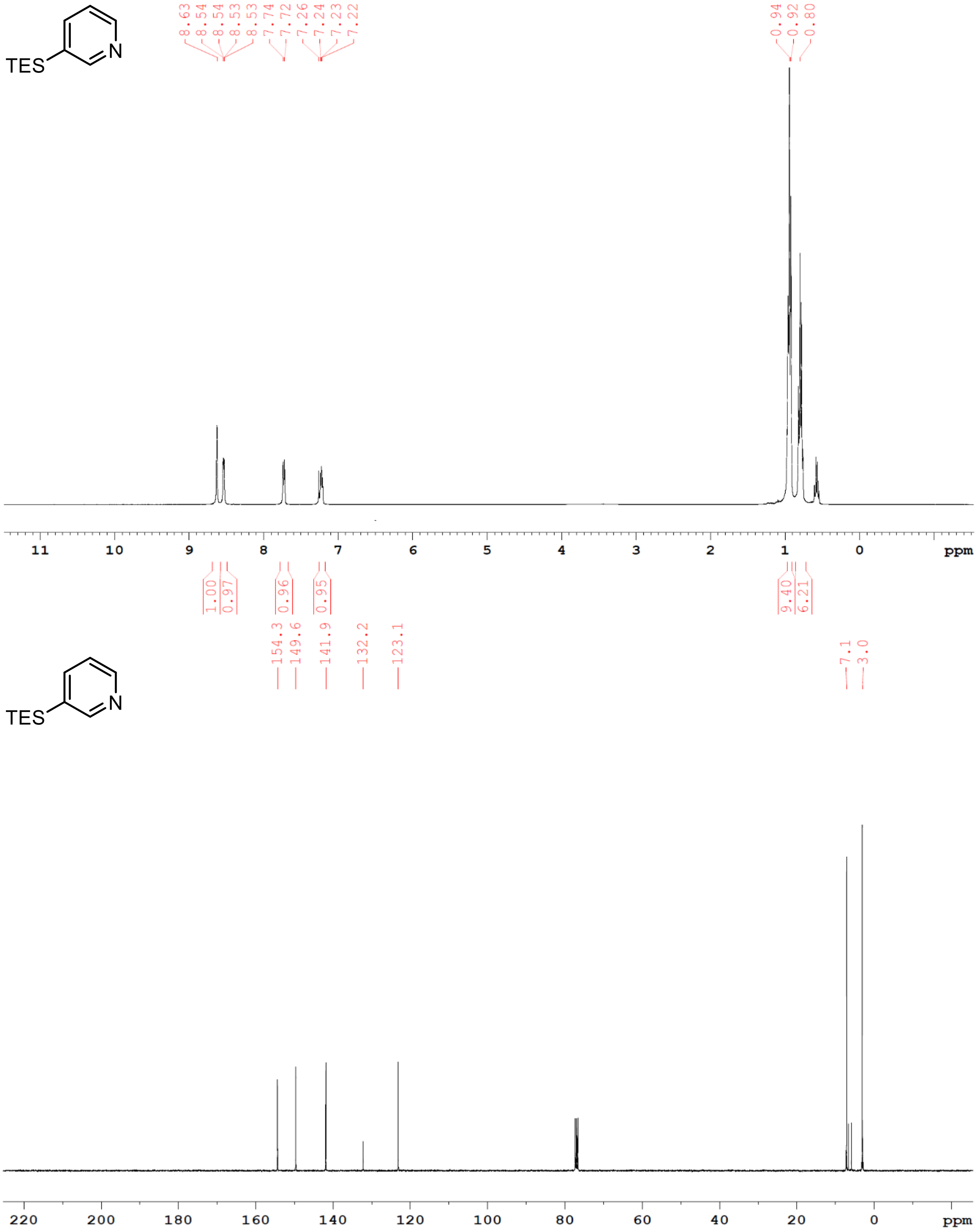


Figure A.3.10 ^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (400 MHz, CDCl$_3$) of **3.31b**

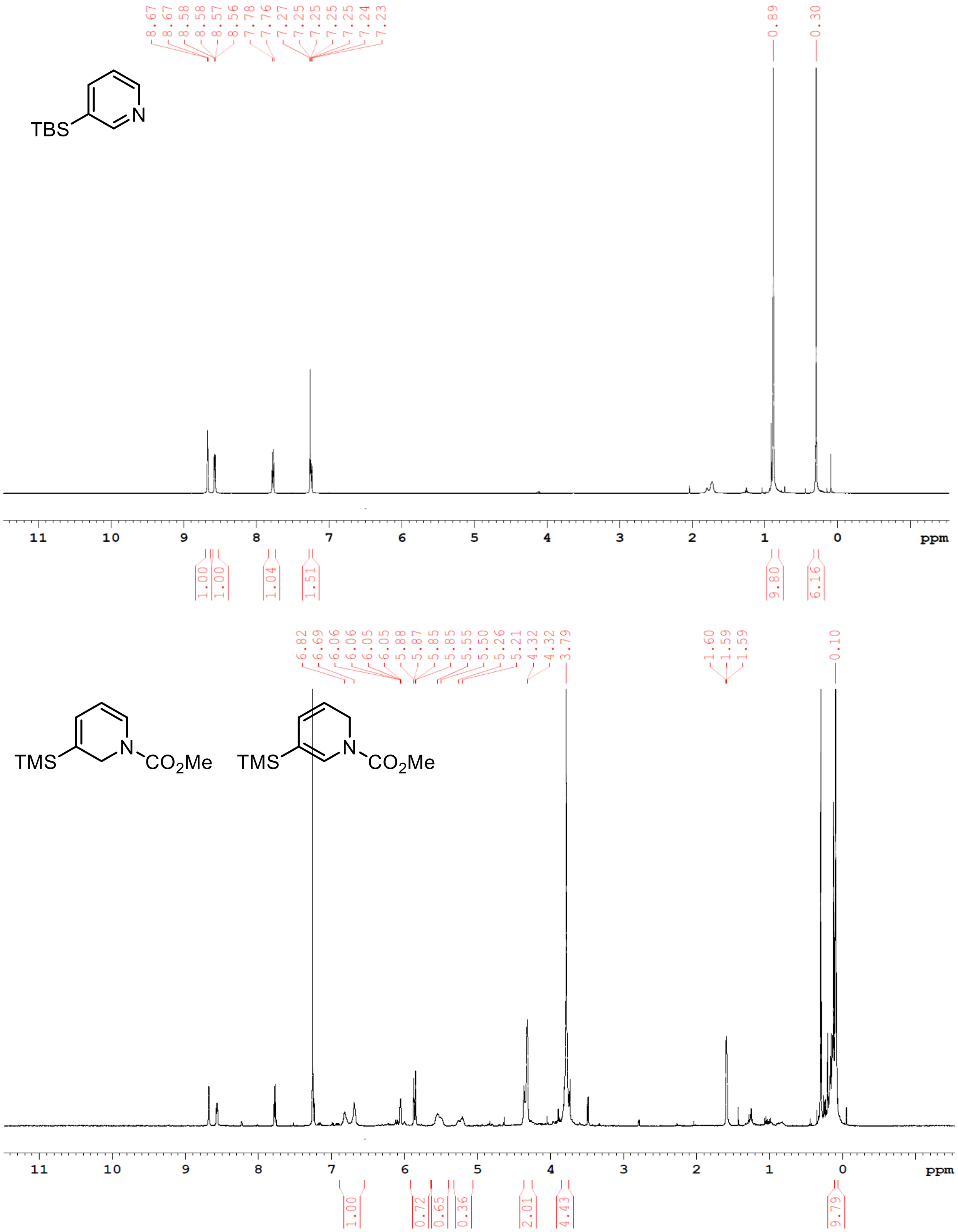


Figure A.3.11 ^{1}H NMR (400 MHz, CDCl$_3$) of **3.31c** and **3.32a/3.32a**

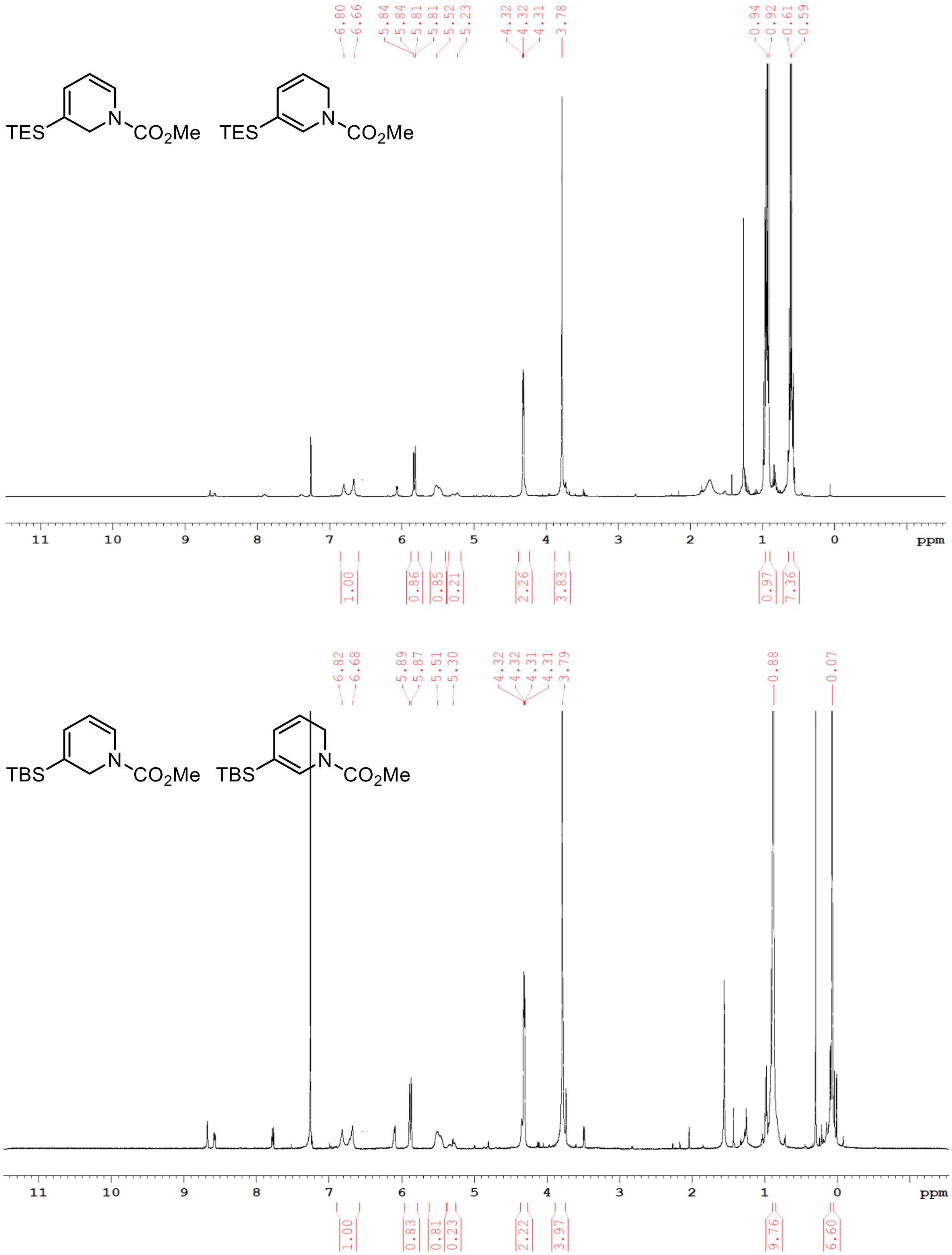


Figure A.3.12 ^{1}H NMR (400 MHz, CDCl$_3$) of **3.32b/3.32b** and **3.32c/3.32c**

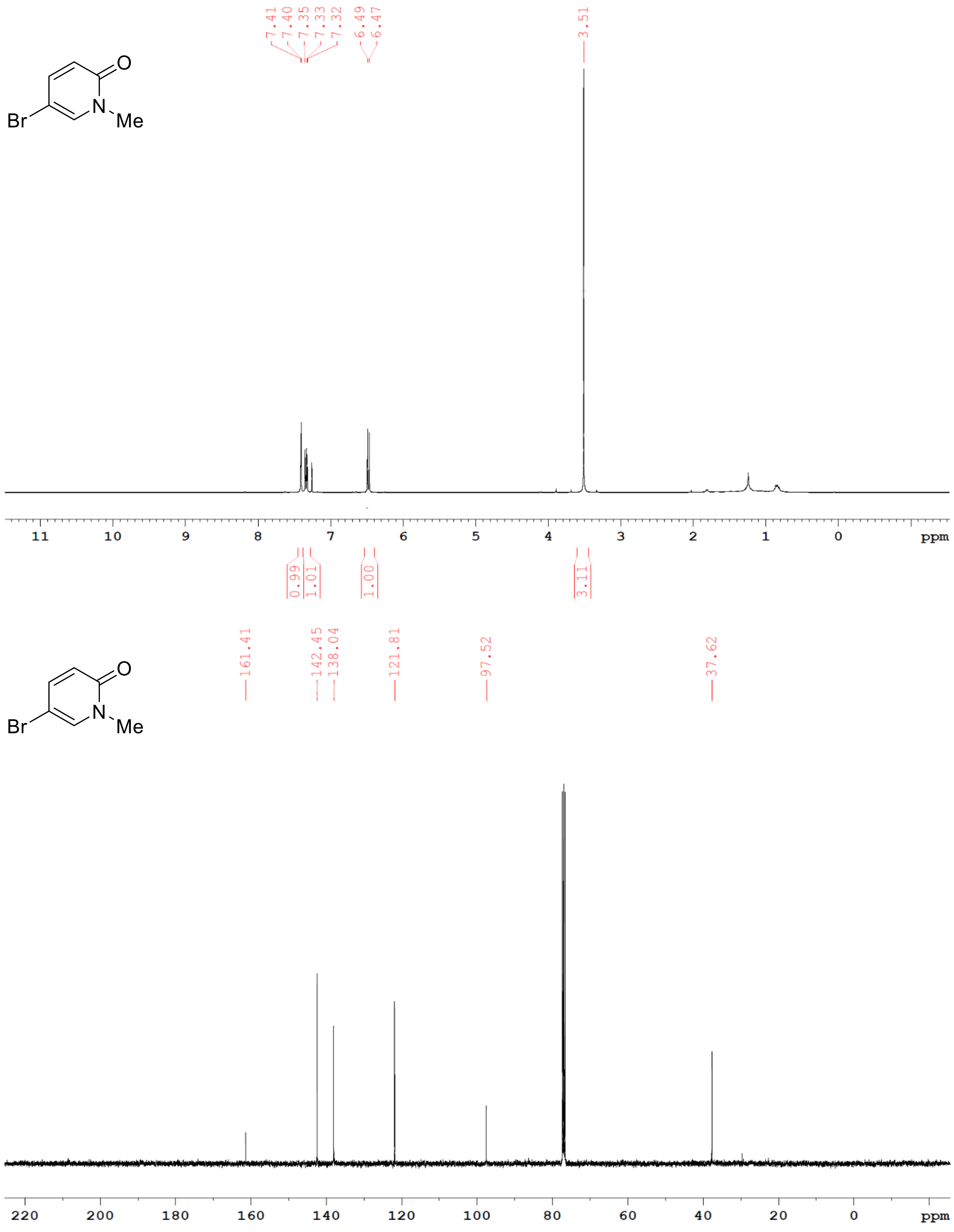


Figure A.3.13 ^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (400 MHz, CDCl$_3$) of **3.35a**

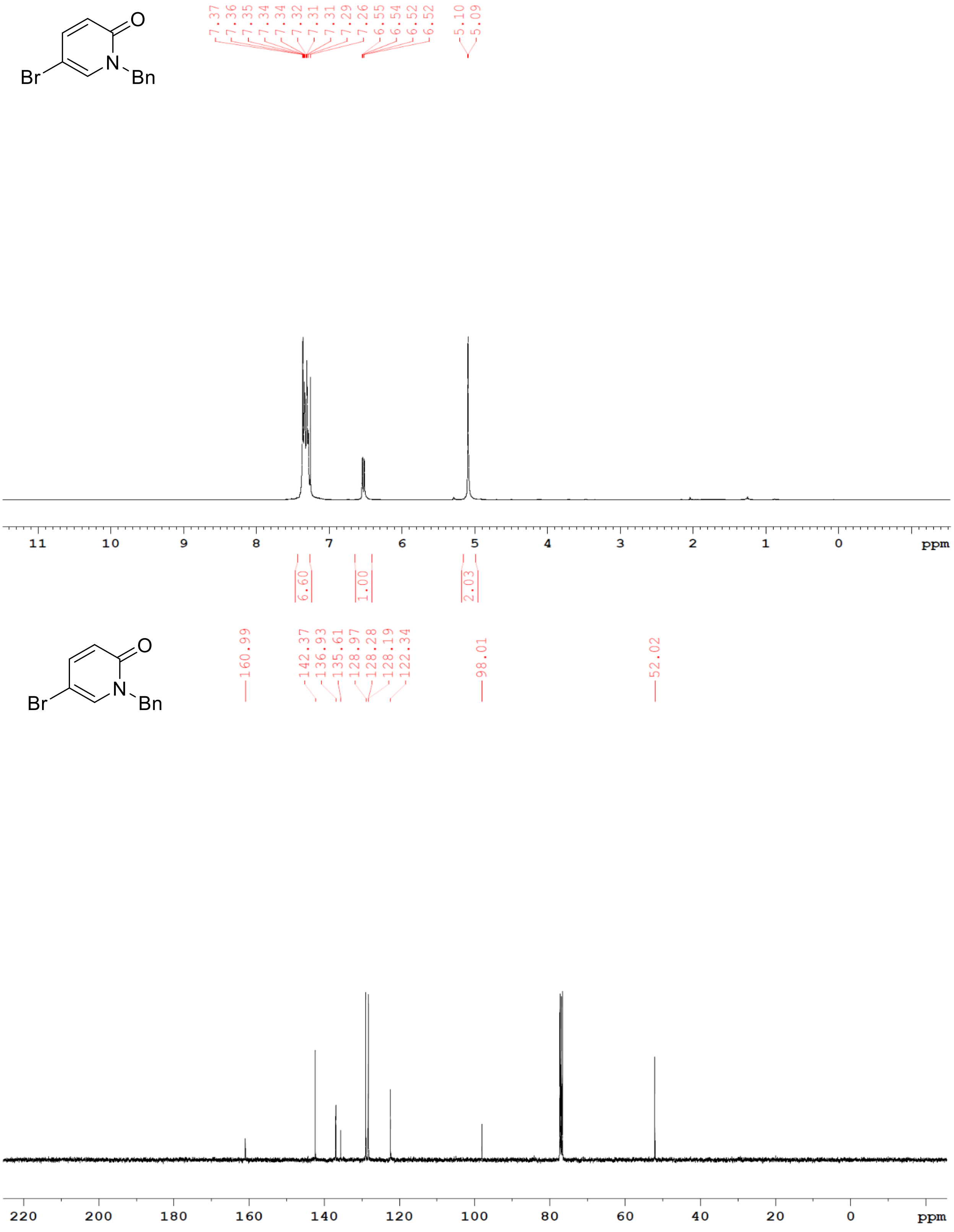


Figure A.3.14 ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (400 MHz, $CDCl_3$) of **3.35b**

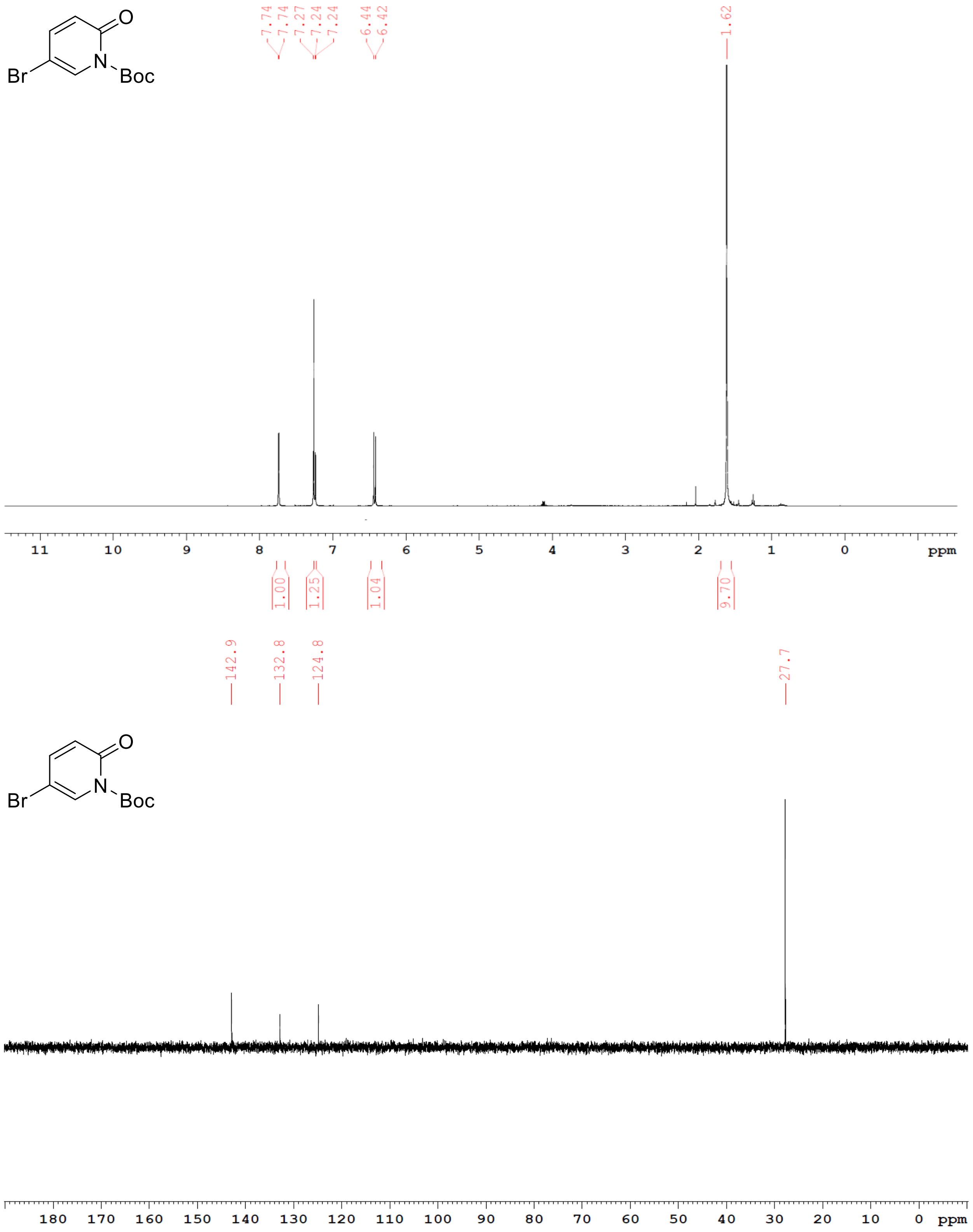


Figure A.3.15 ^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (400 MHz, CDCl$_3$) of **3.35c**

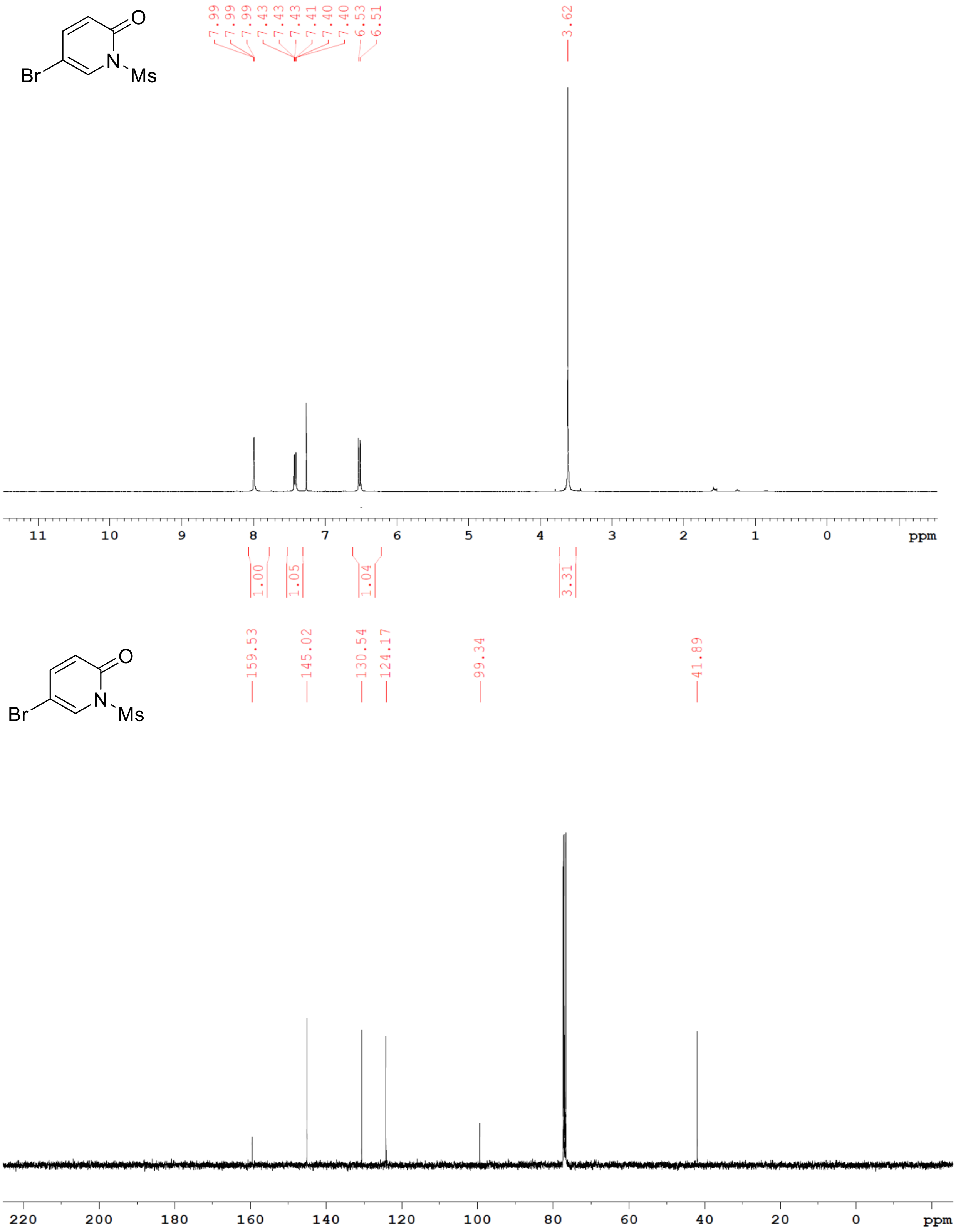


Figure A.3.16 ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (400 MHz, $CDCl_3$) of **3.35d**

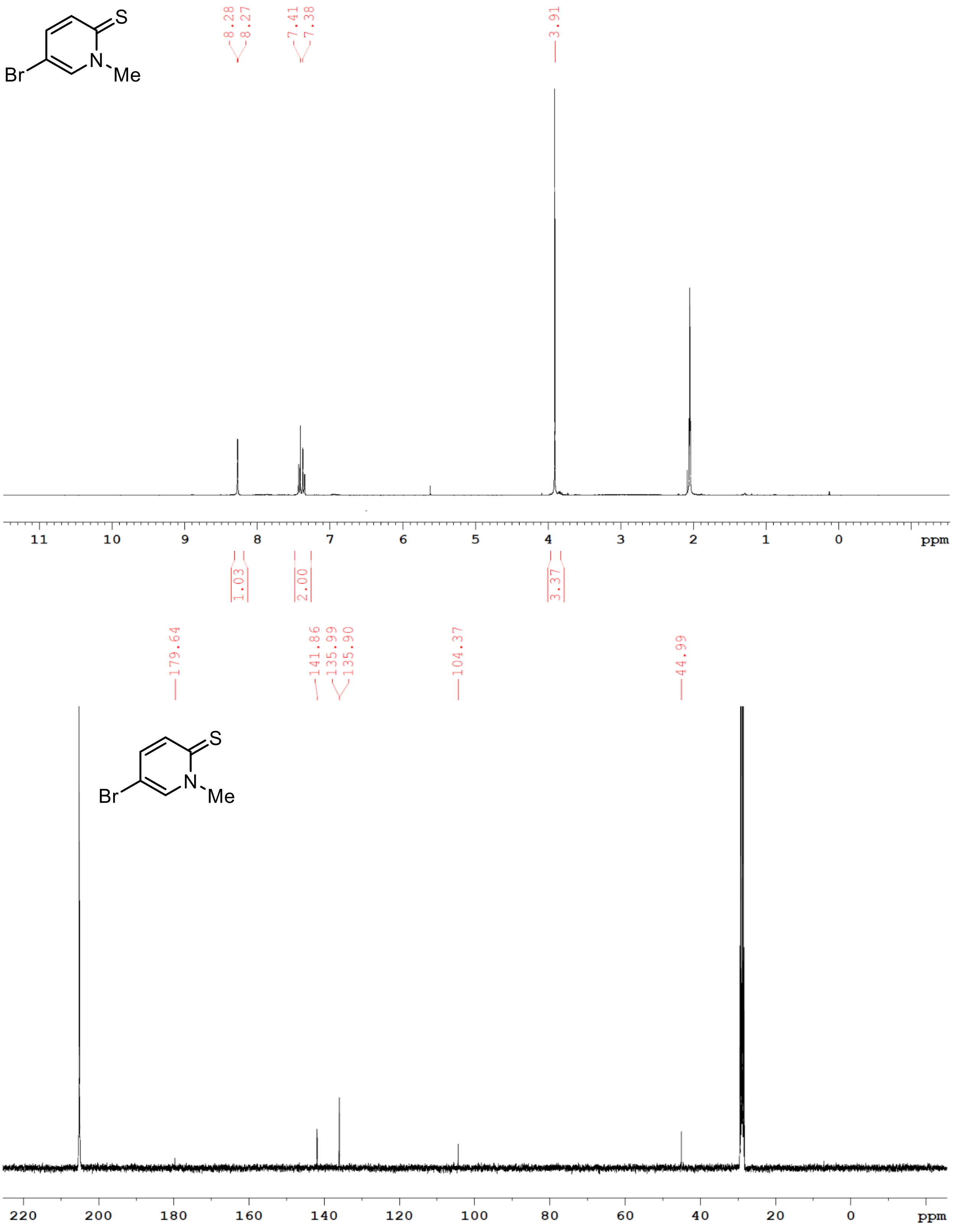


Figure A.3.17 ^{1}H NMR (400 MHz, $(CD_3)_2CO$ and ^{13}C NMR (400 MHz, $(CD_3)_2CO$ of **3.38**

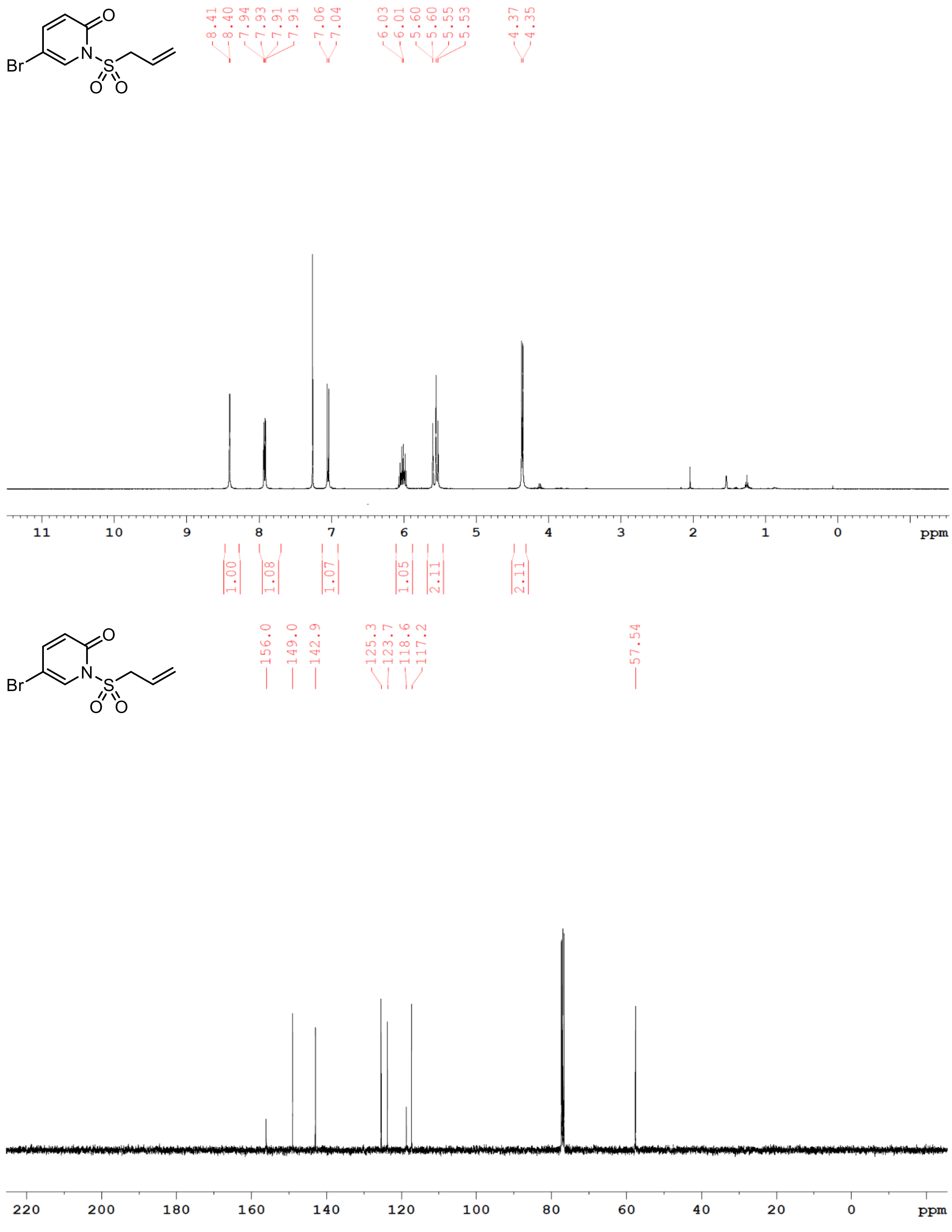


Figure A.3.18 ^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (400 MHz, CDCl$_3$) of **3.41**

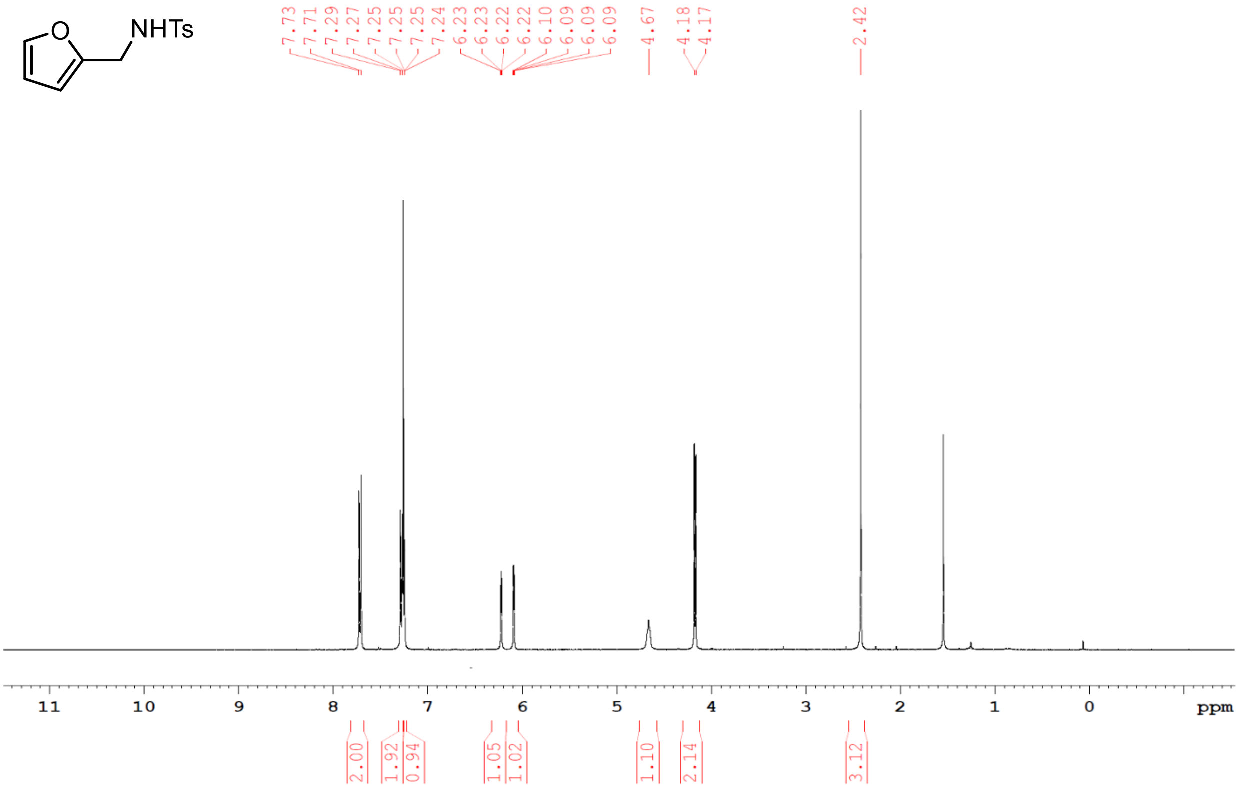


Figure A.3.19 ^{1}H NMR (400 MHz, CDCl$_3$) of **3.47.5**

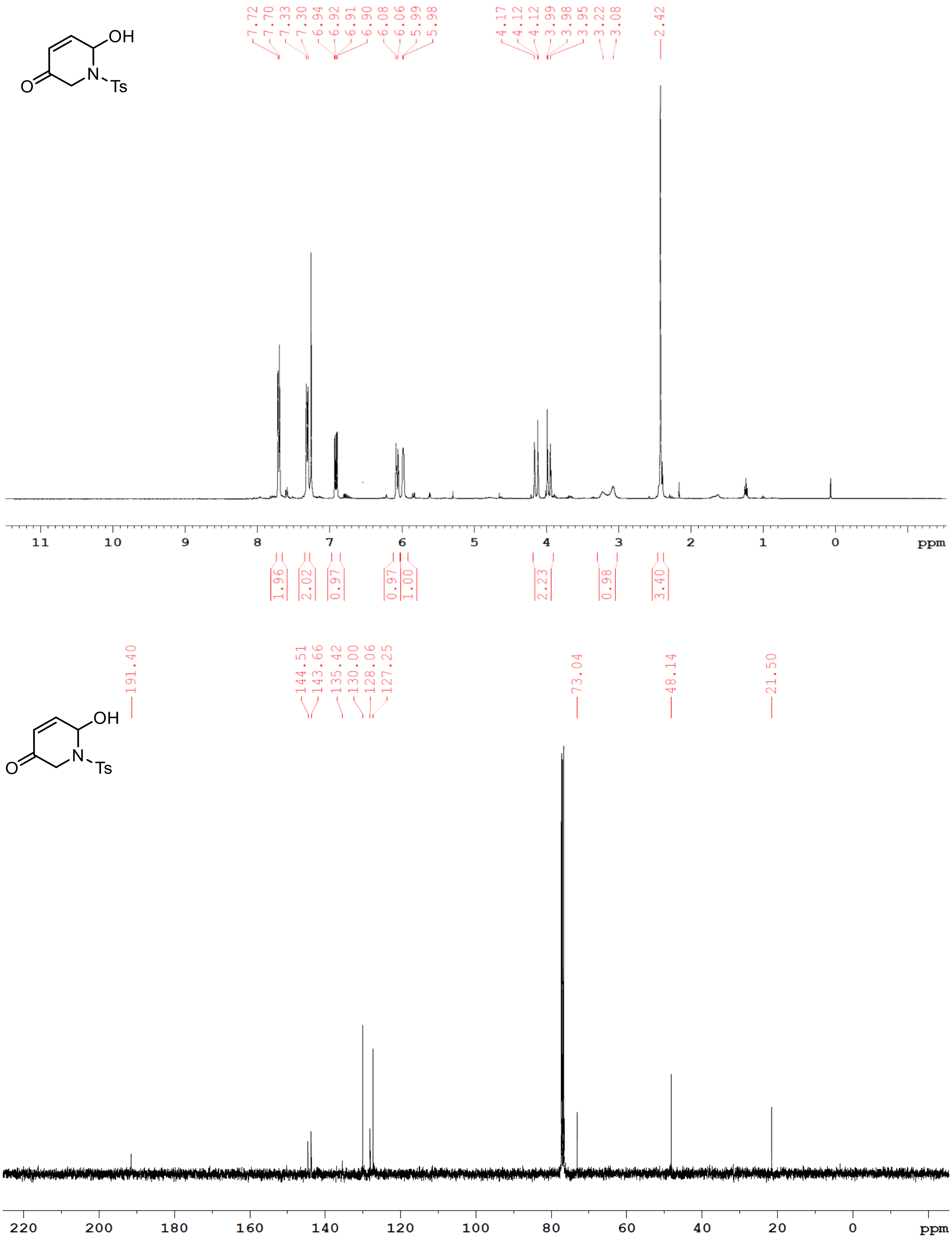


Figure A.3.20 ^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (400 MHz, CDCl$_3$) of **3.48**

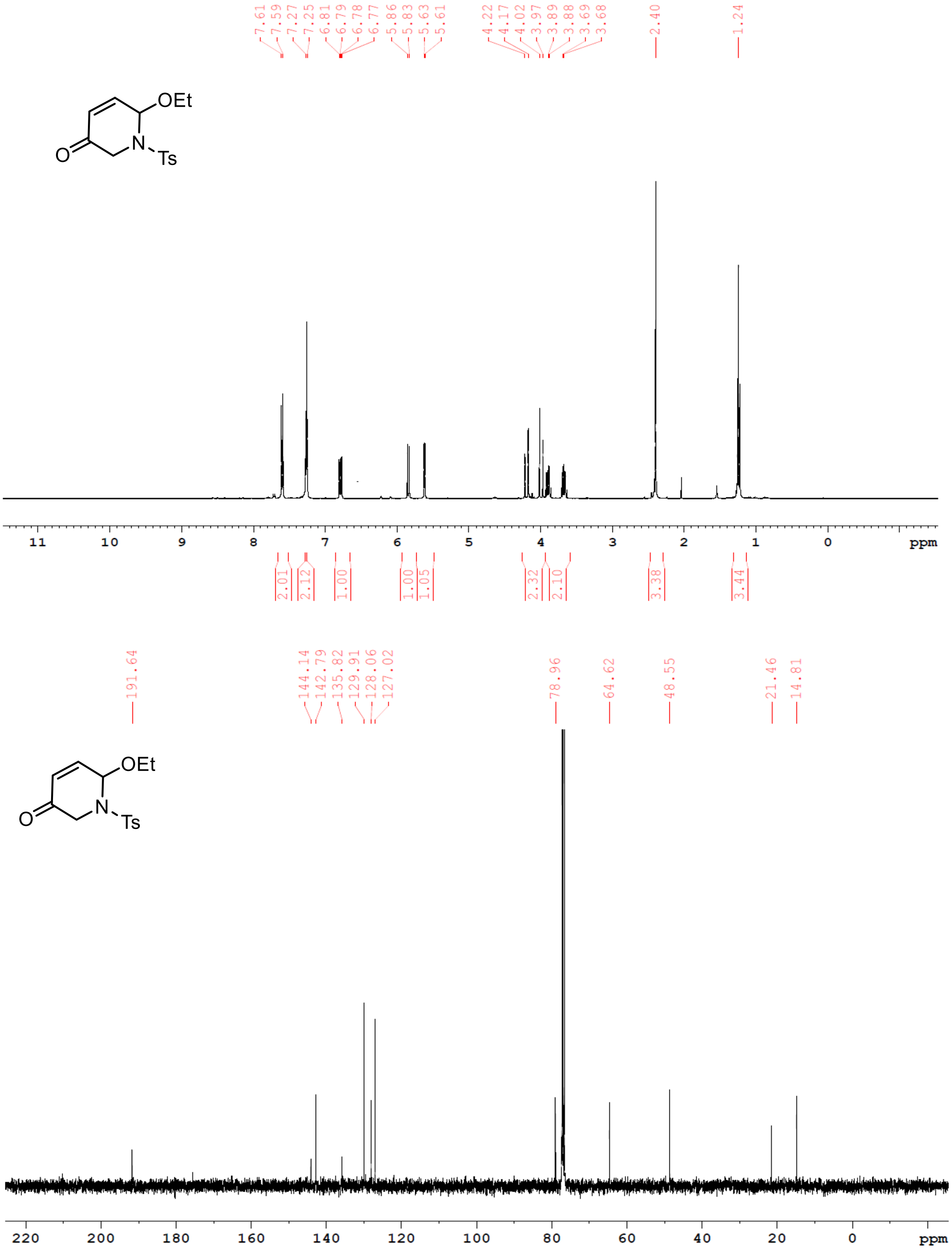


Figure A.3.21 ^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (400 MHz, CDCl$_3$) of **3.49**

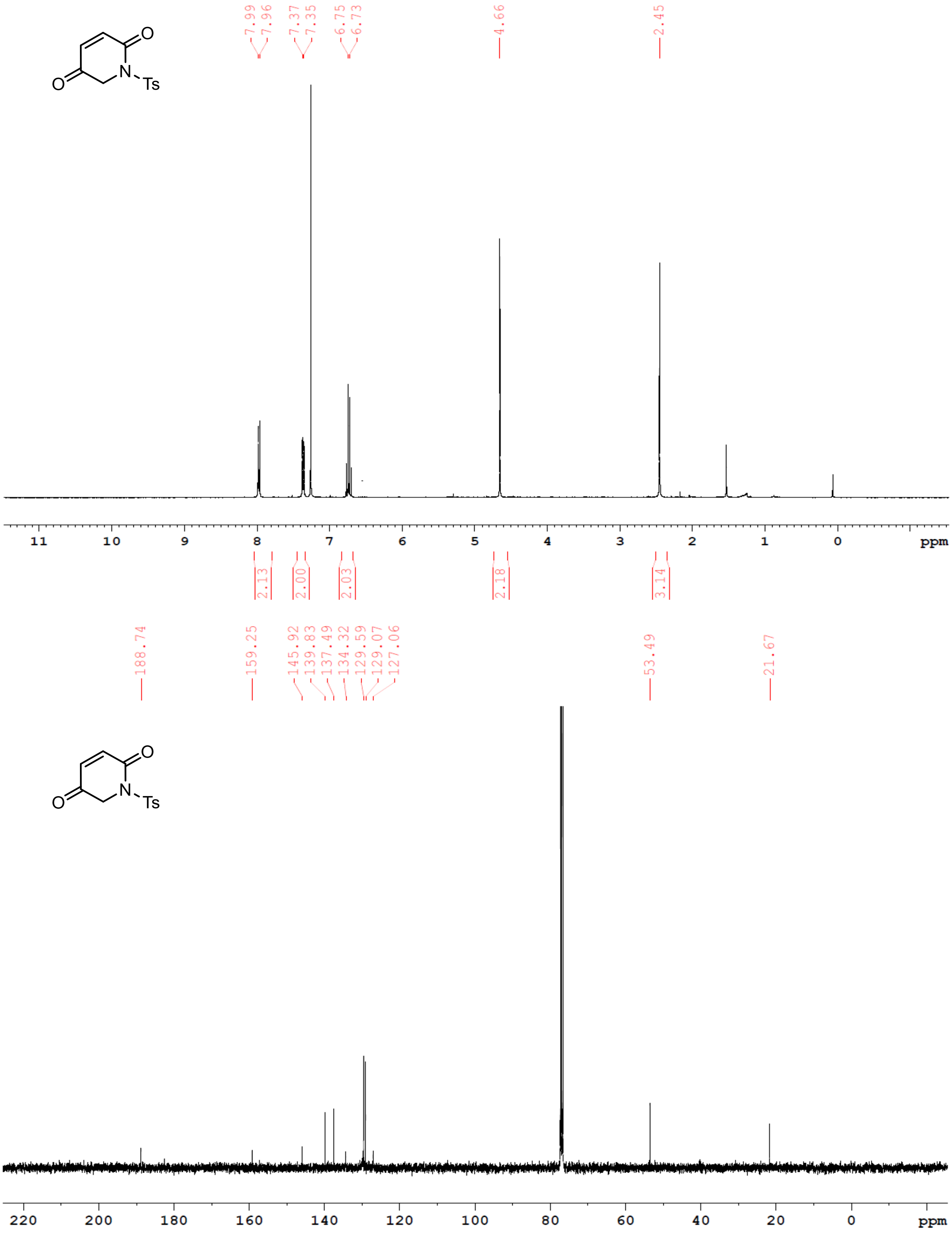


Figure A.3.22 ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (400 MHz, $CDCl_3$) of **3.51**

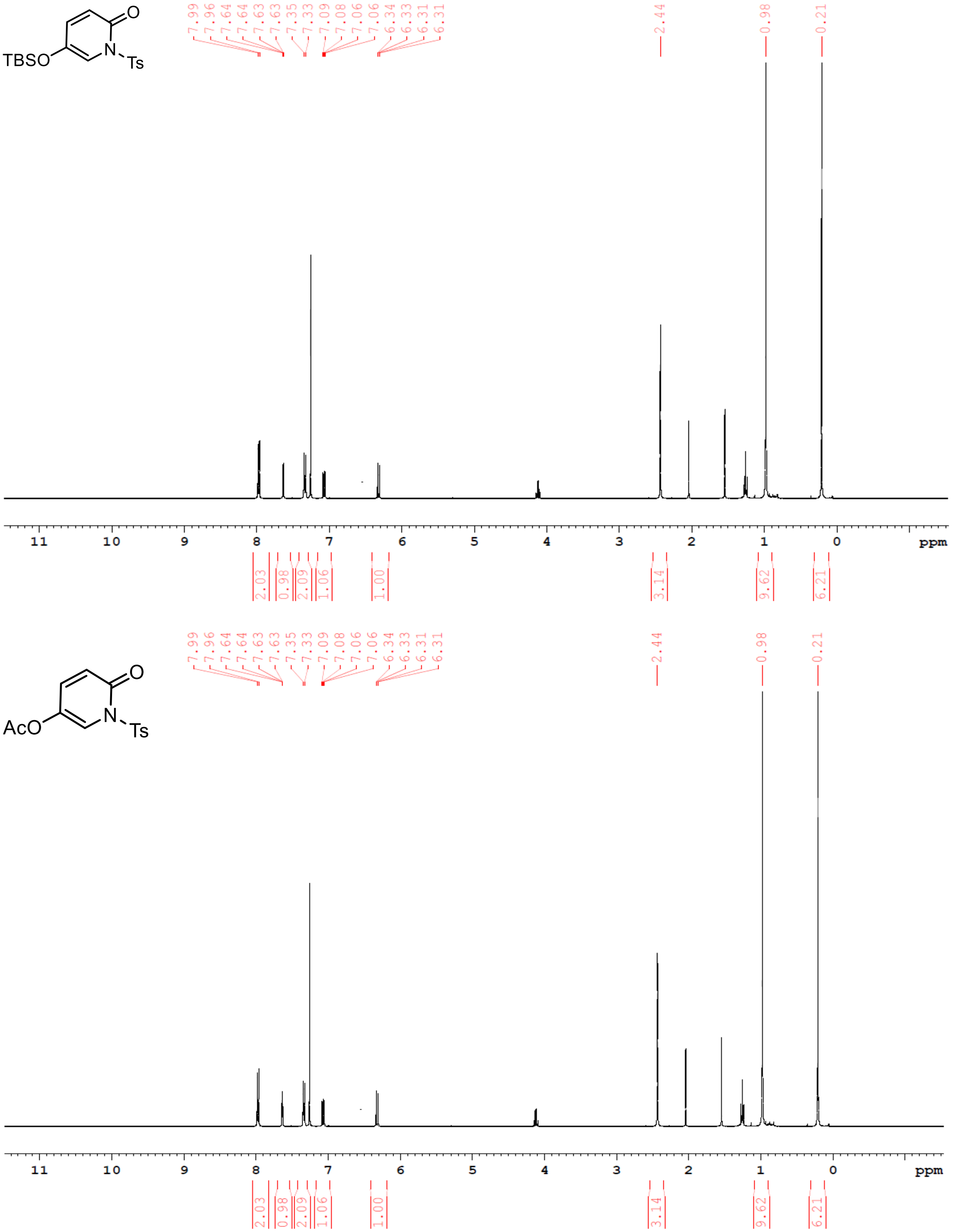


Figure A.3.23 ^{1}H NMR (400 MHz, $CDCl_3$) of **3.52** and **3.53**

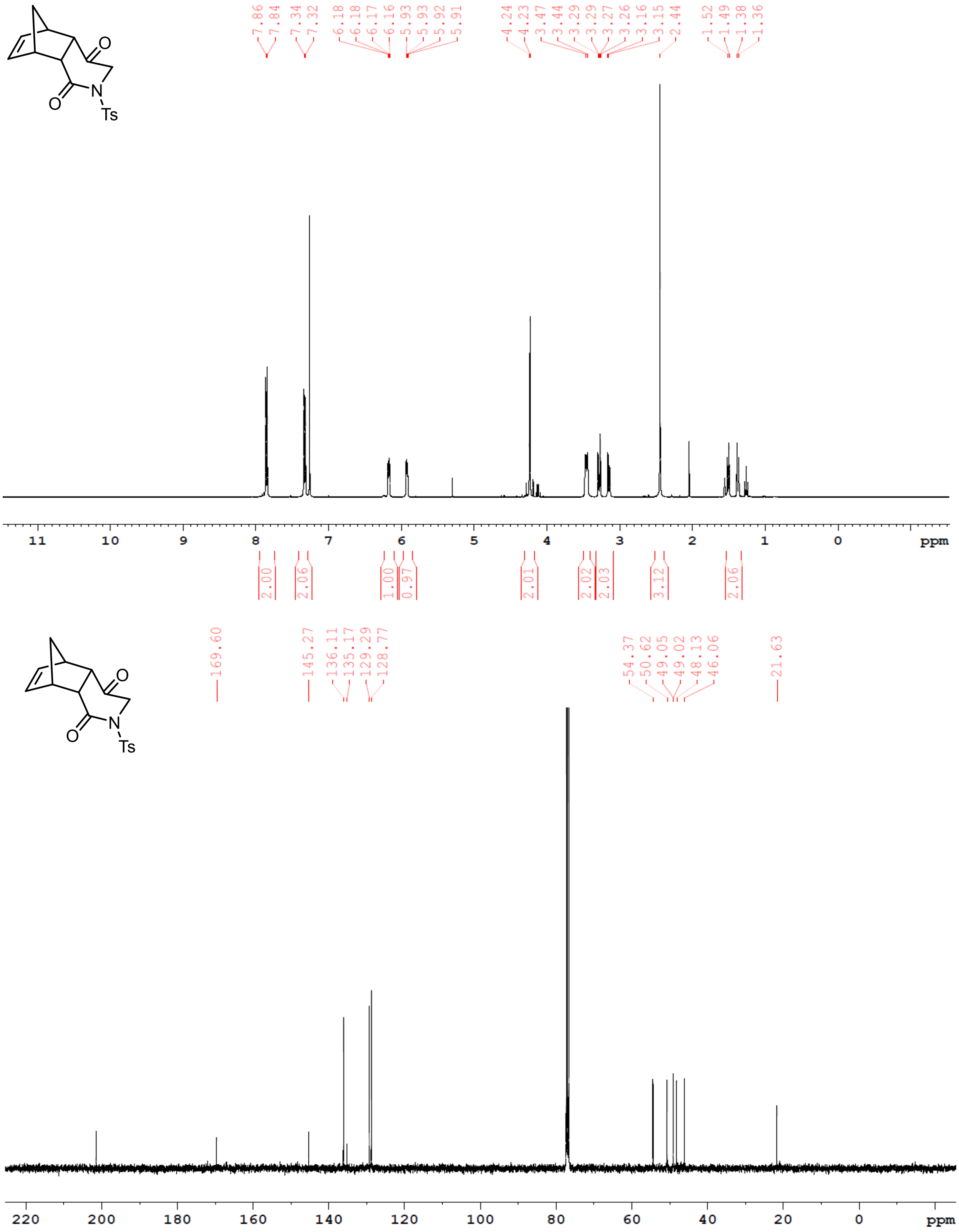


Figure A.3.24 ^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (400 MHz, CDCl$_3$) of **3.57**

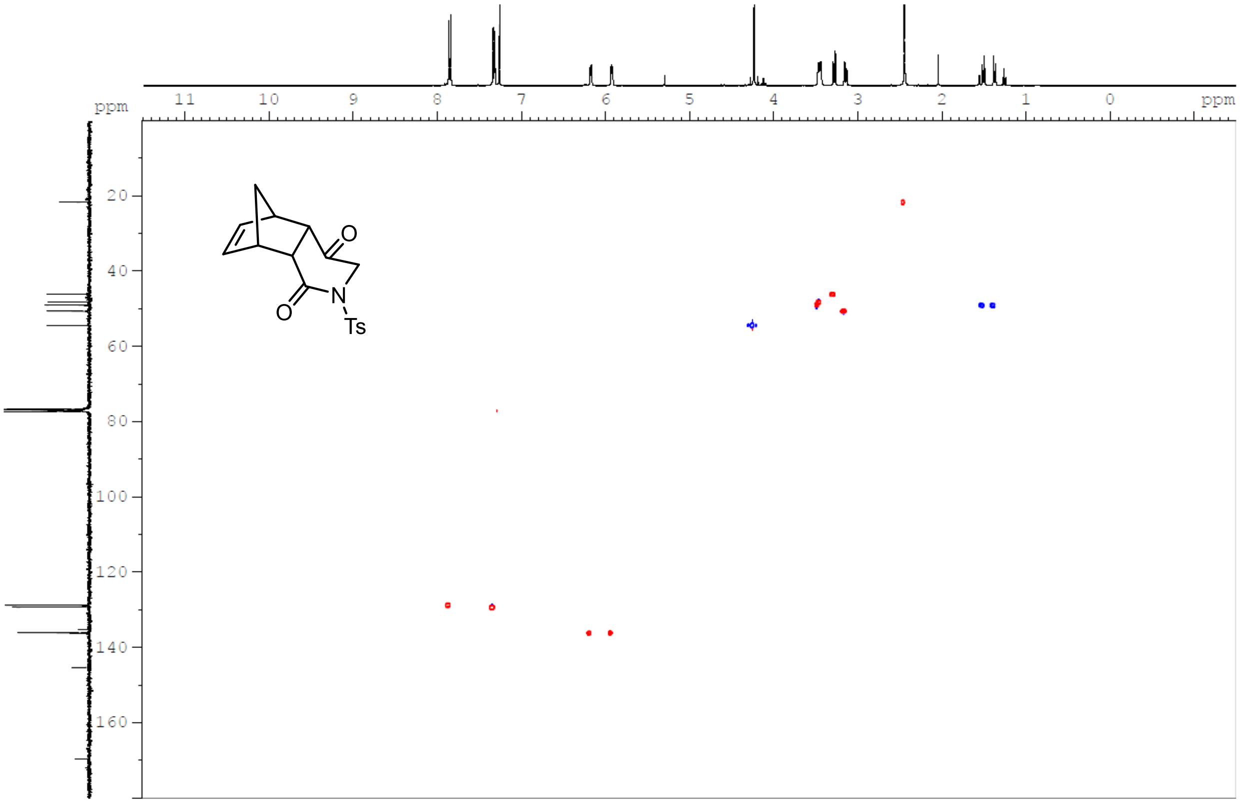


Figure A.3.25 HSQC NMR (400 MHz, $CDCl_3$) of **3.57**

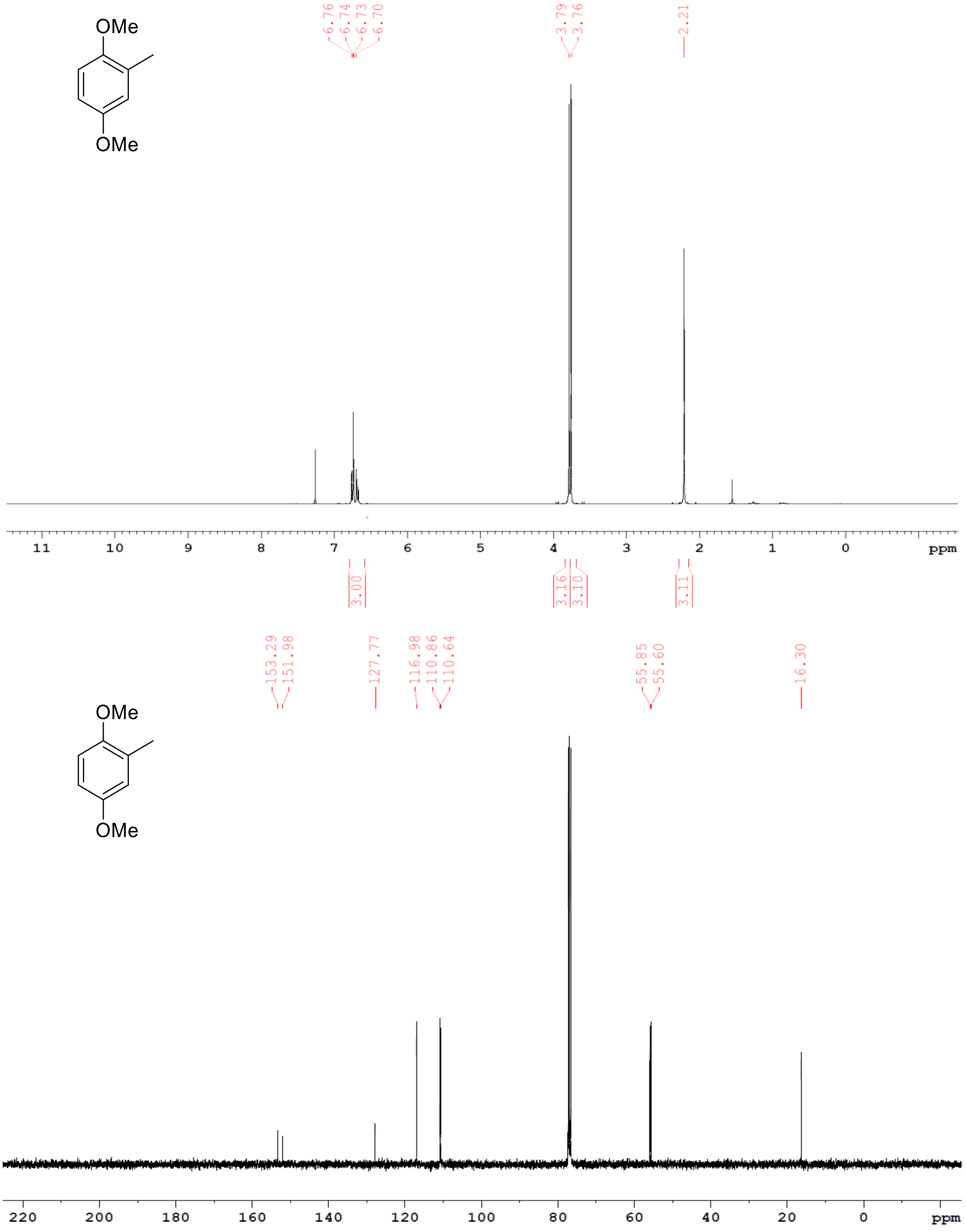


Figure A.3.26 ^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (400 MHz, CDCl$_3$) of **3.62**

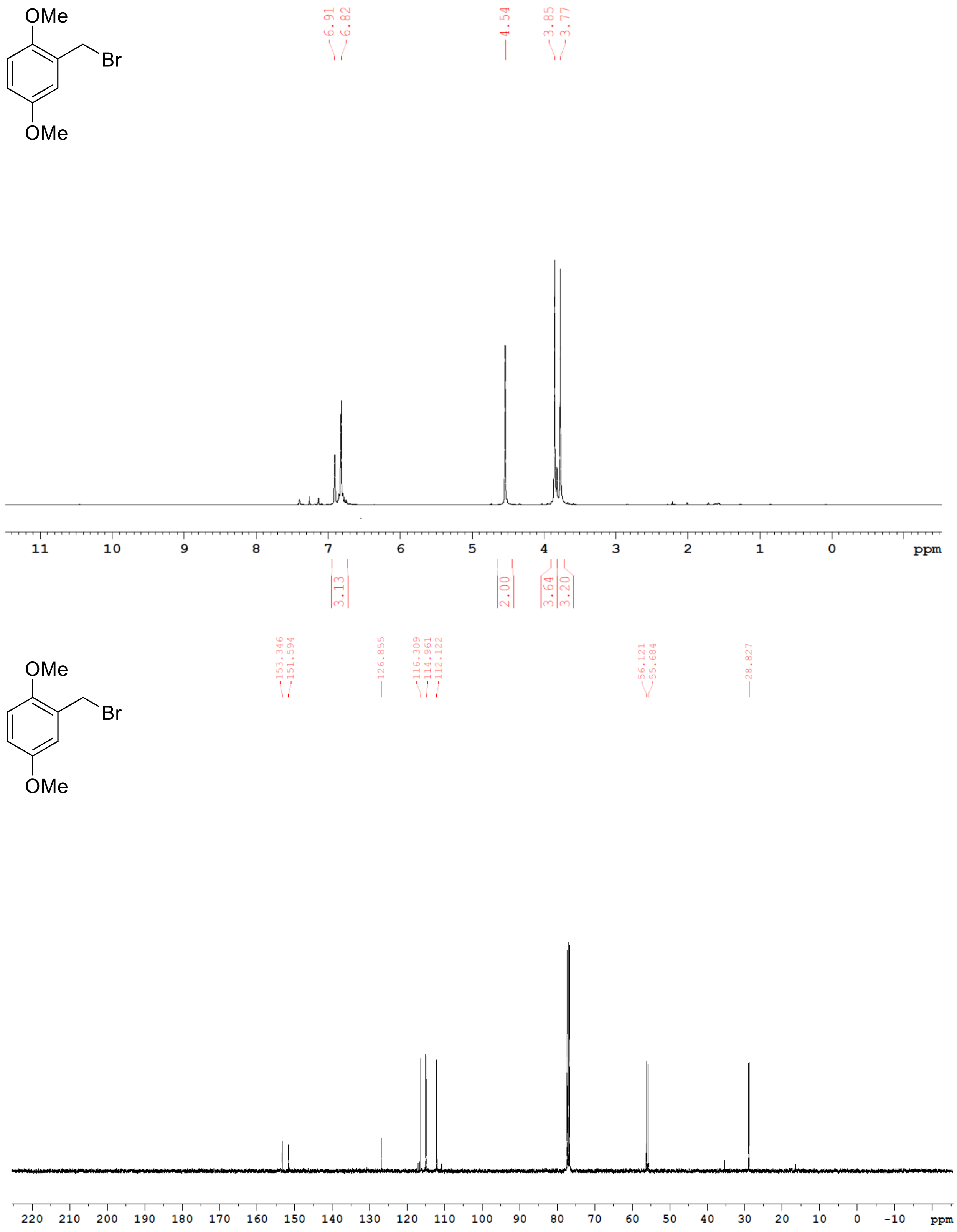


Figure A.3.27 ^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (400 MHz, CDCl$_3$) of **3.63**

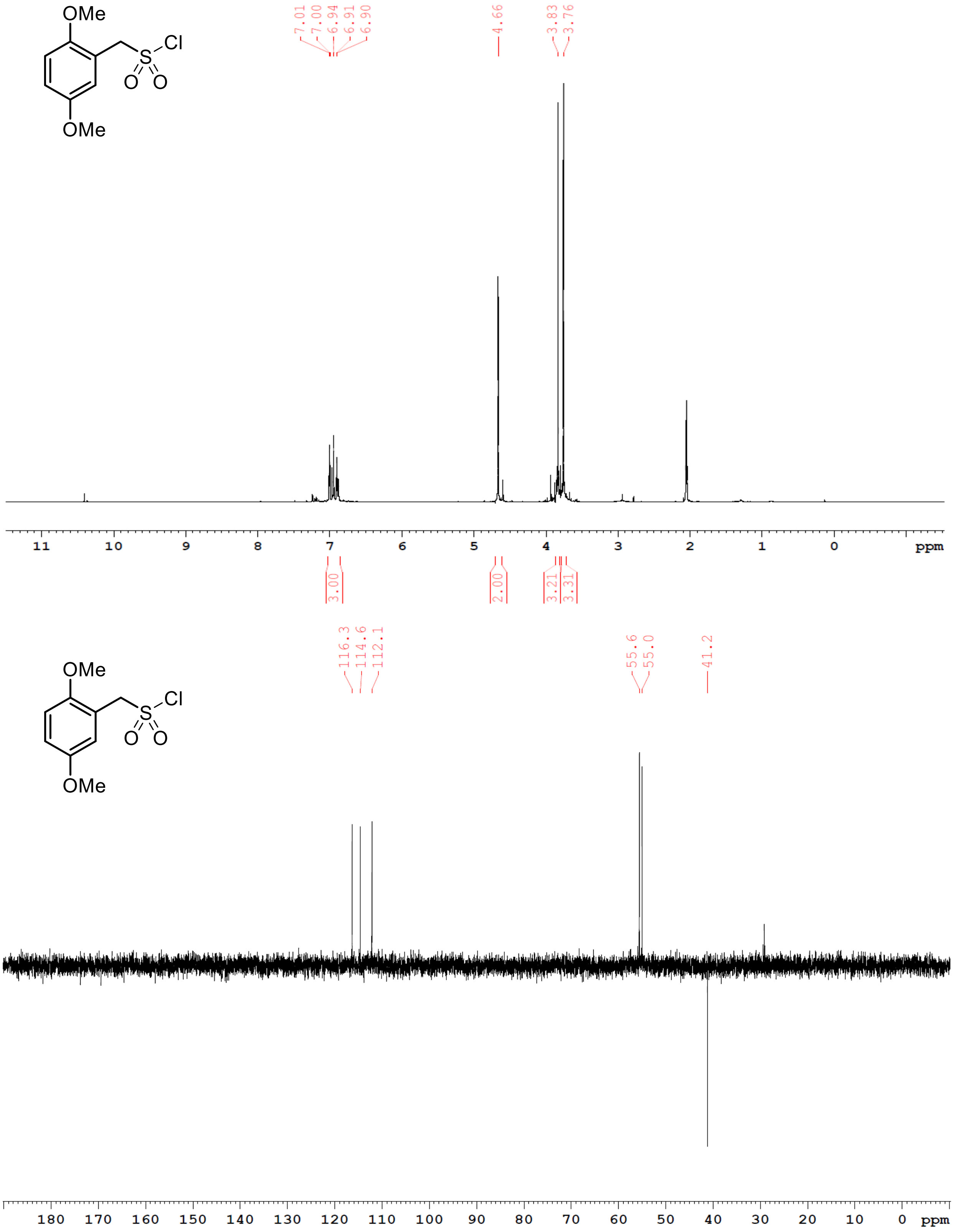


Figure A.3.28 ^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (400 MHz, CDCl$_3$) of **3.63**

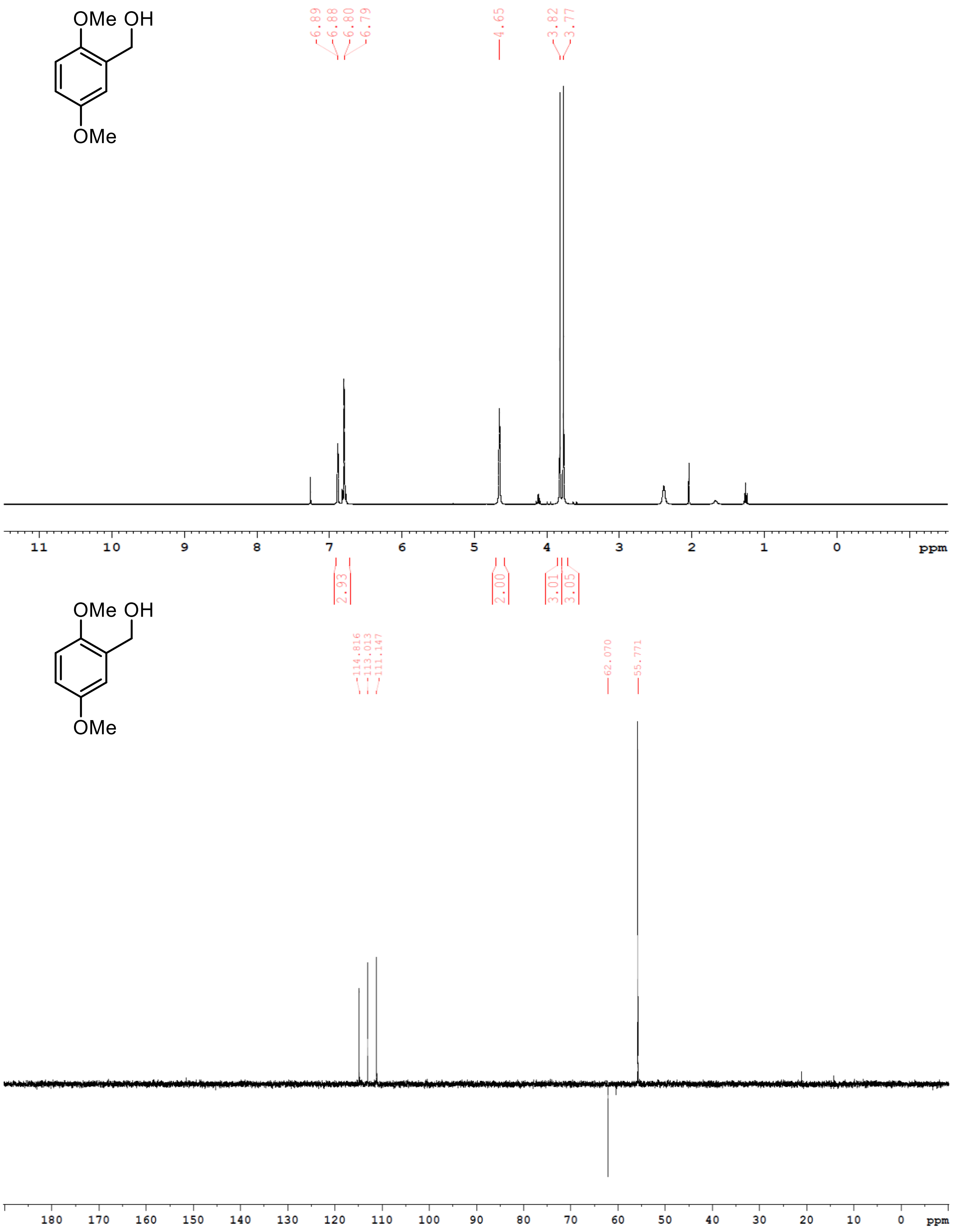


Figure A.3.29 ^{1}H NMR (400 MHz, CDCl$_3$) and DEPT-135 NMR (400 MHz, CDCl$_3$) of **3.67**

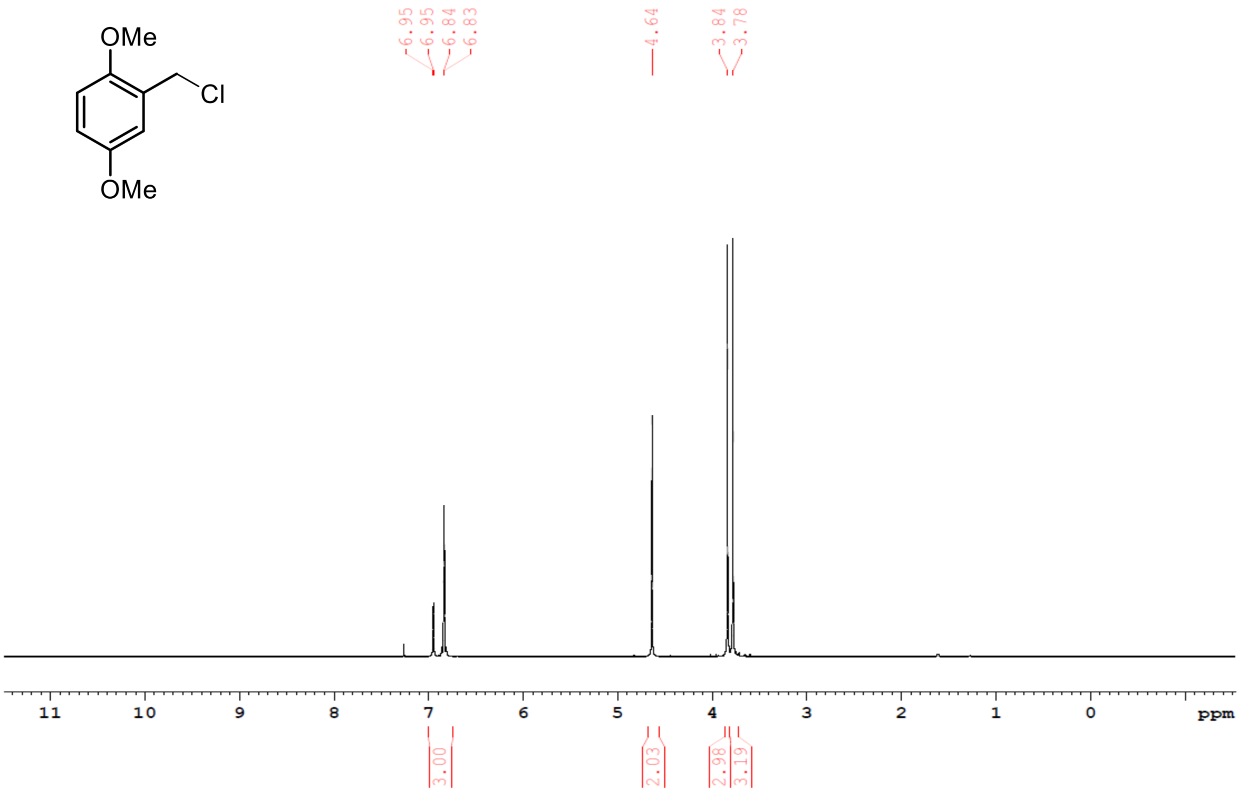


Figure A.3.30 ^{1}H NMR (400 MHz, CDCl$_3$) of **3.68**

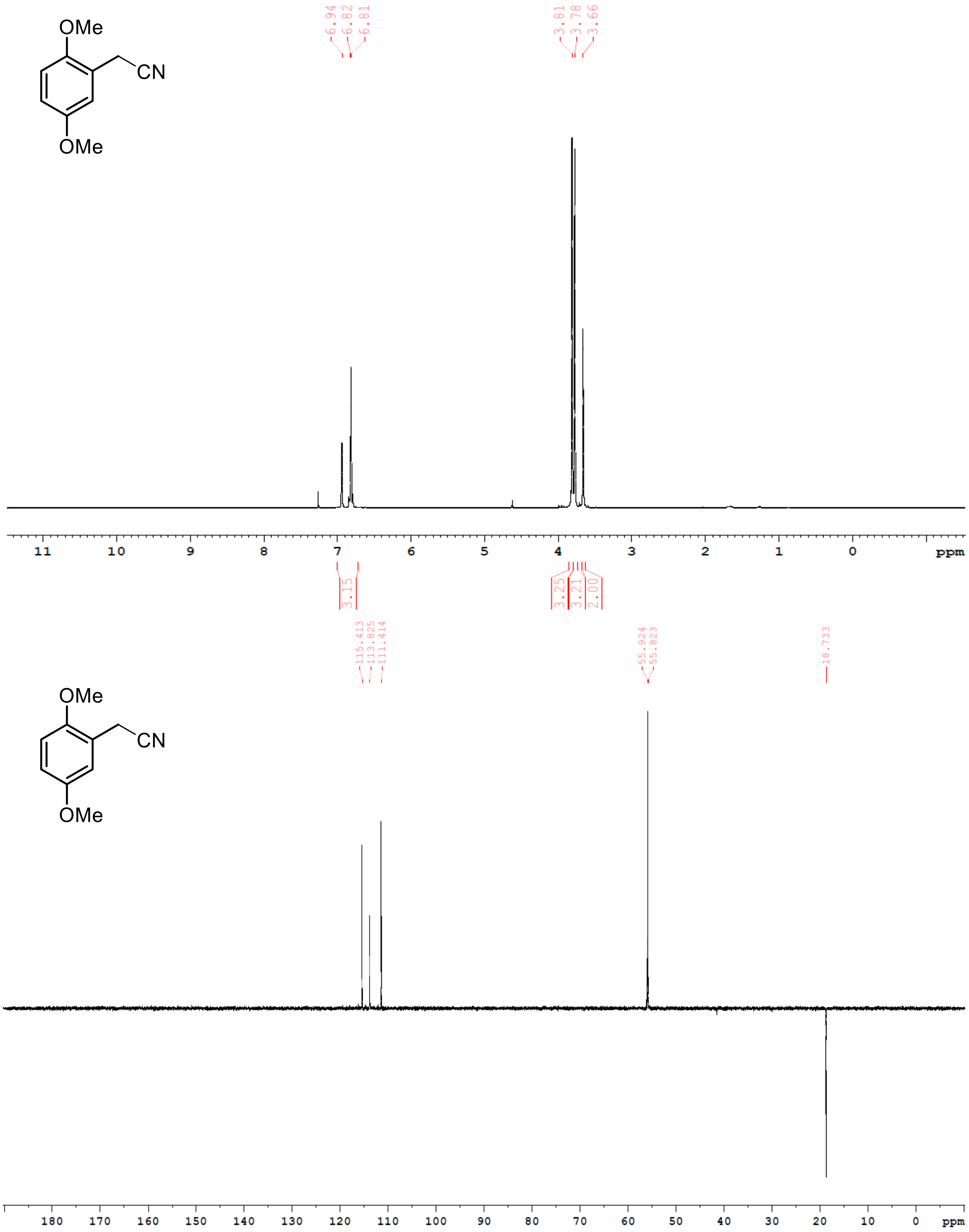


Figure A.3.31 ^{1}H NMR (400 MHz, $CDCl_3$) and DEPT-135 NMR (400 MHz, $CDCl_3$) of **3.69**

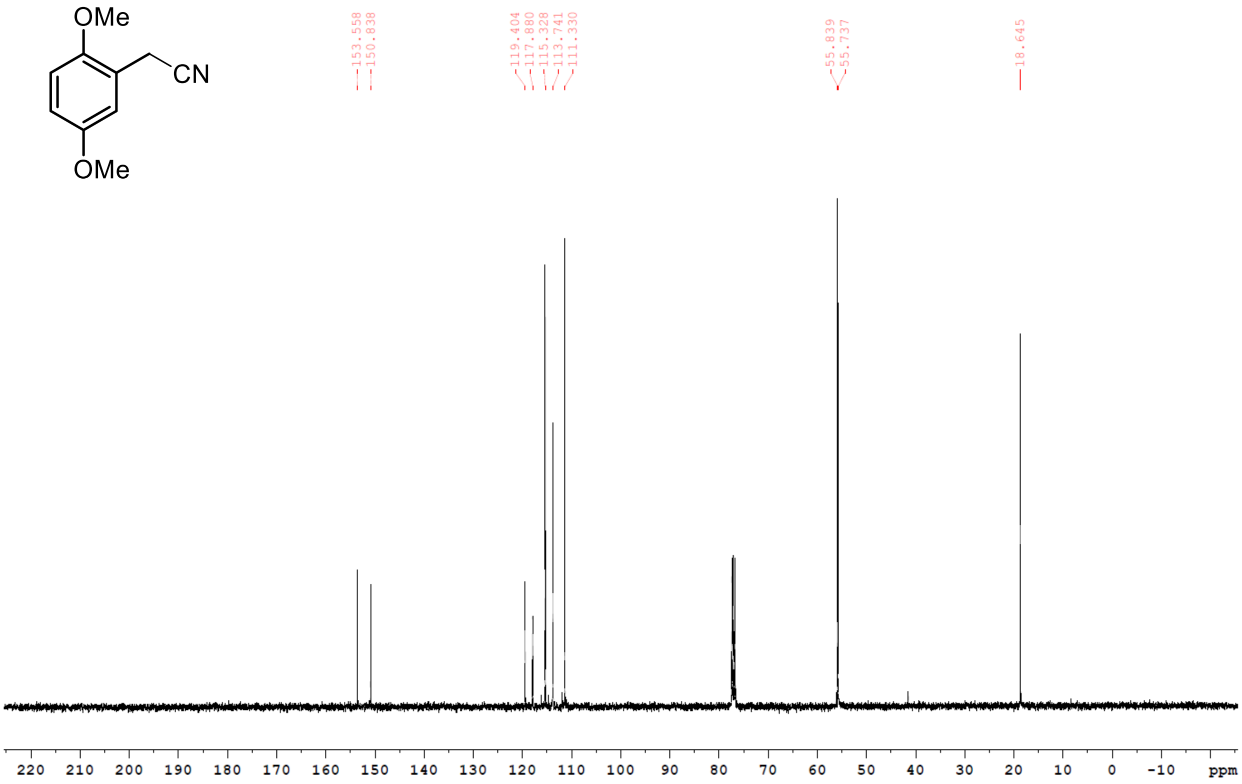


Figure A.3.32 ^{13}C NMR (400 MHz, $CDCl_3$) of **3.69**

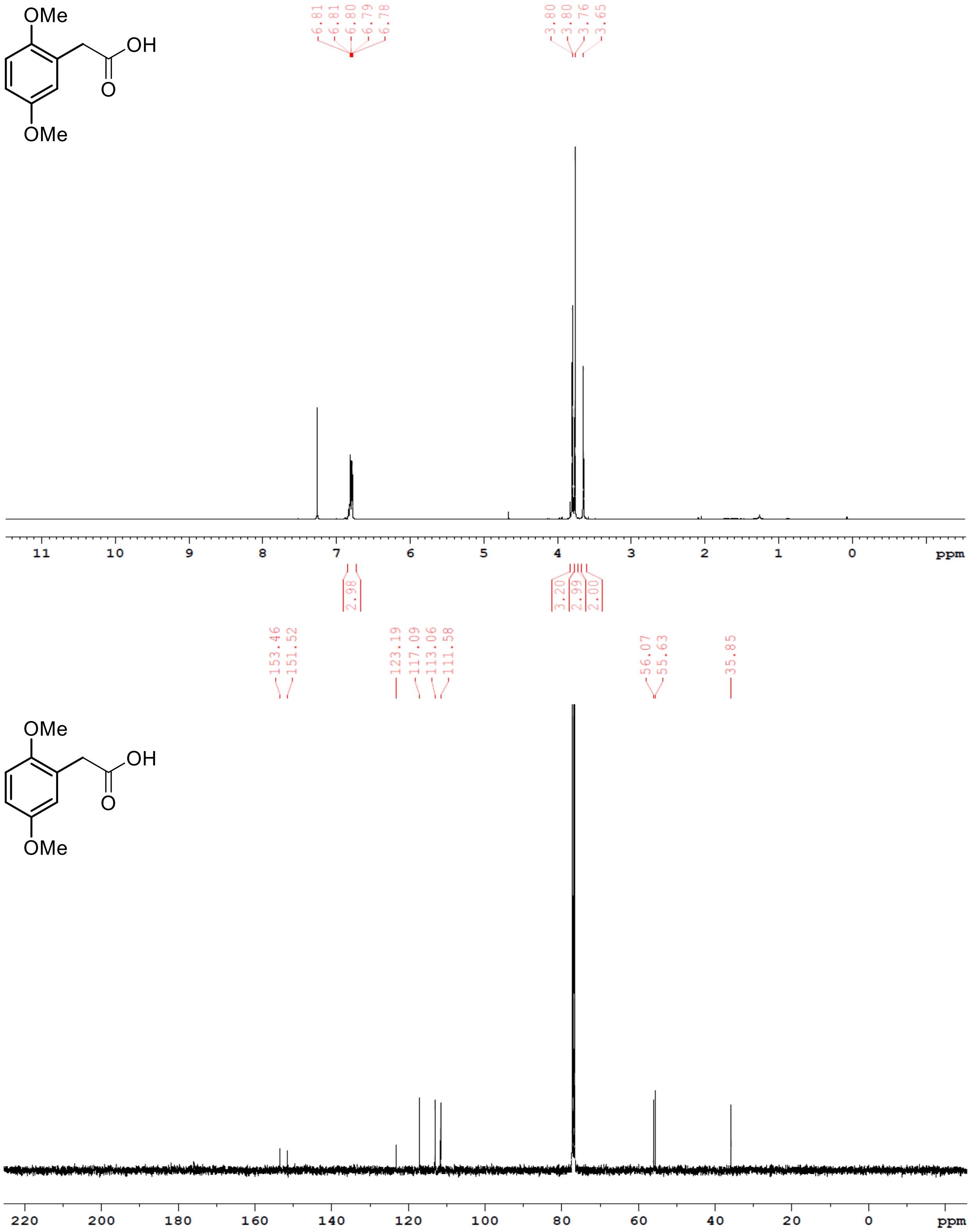


Figure A.3.33 ^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (400 MHz, CDCl$_3$) of **3.70**

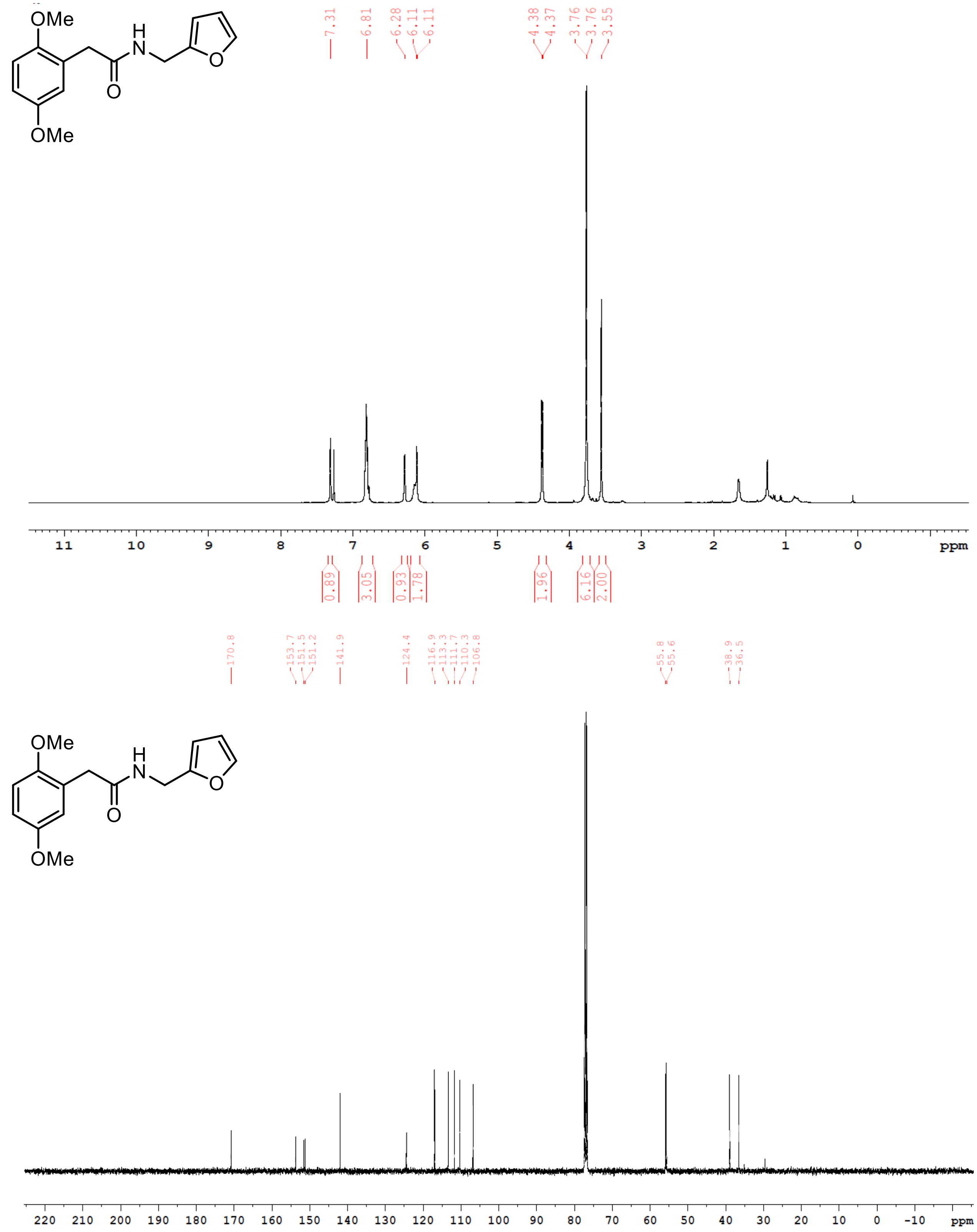


Figure A.3.34 ^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (400 MHz, CDCl$_3$) of **3.71**

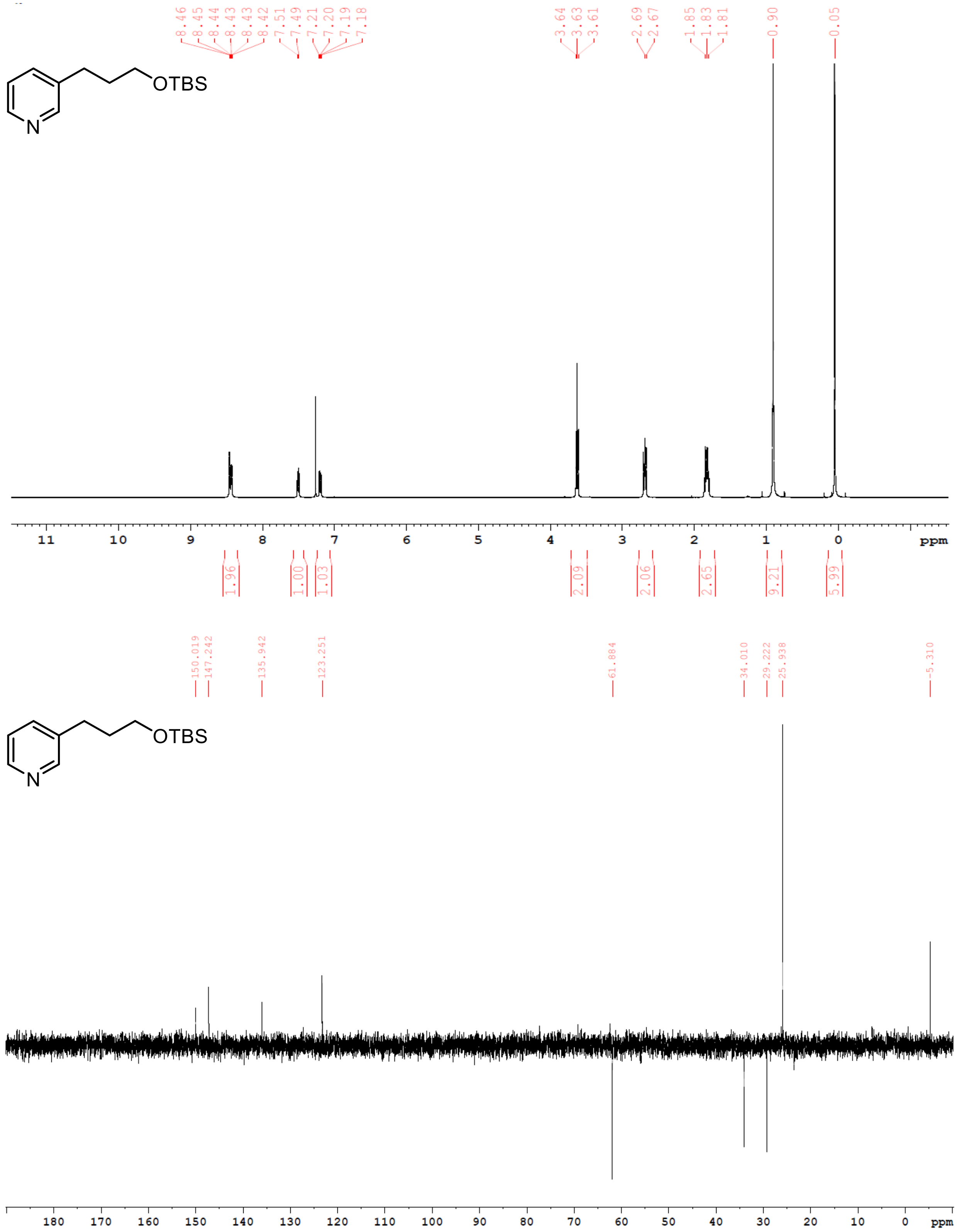


Figure A.3.35 ^{1}H NMR (400 MHz, CDCl$_3$) and DEPT-135 NMR (400 MHz, CDCl3) of **3.73**

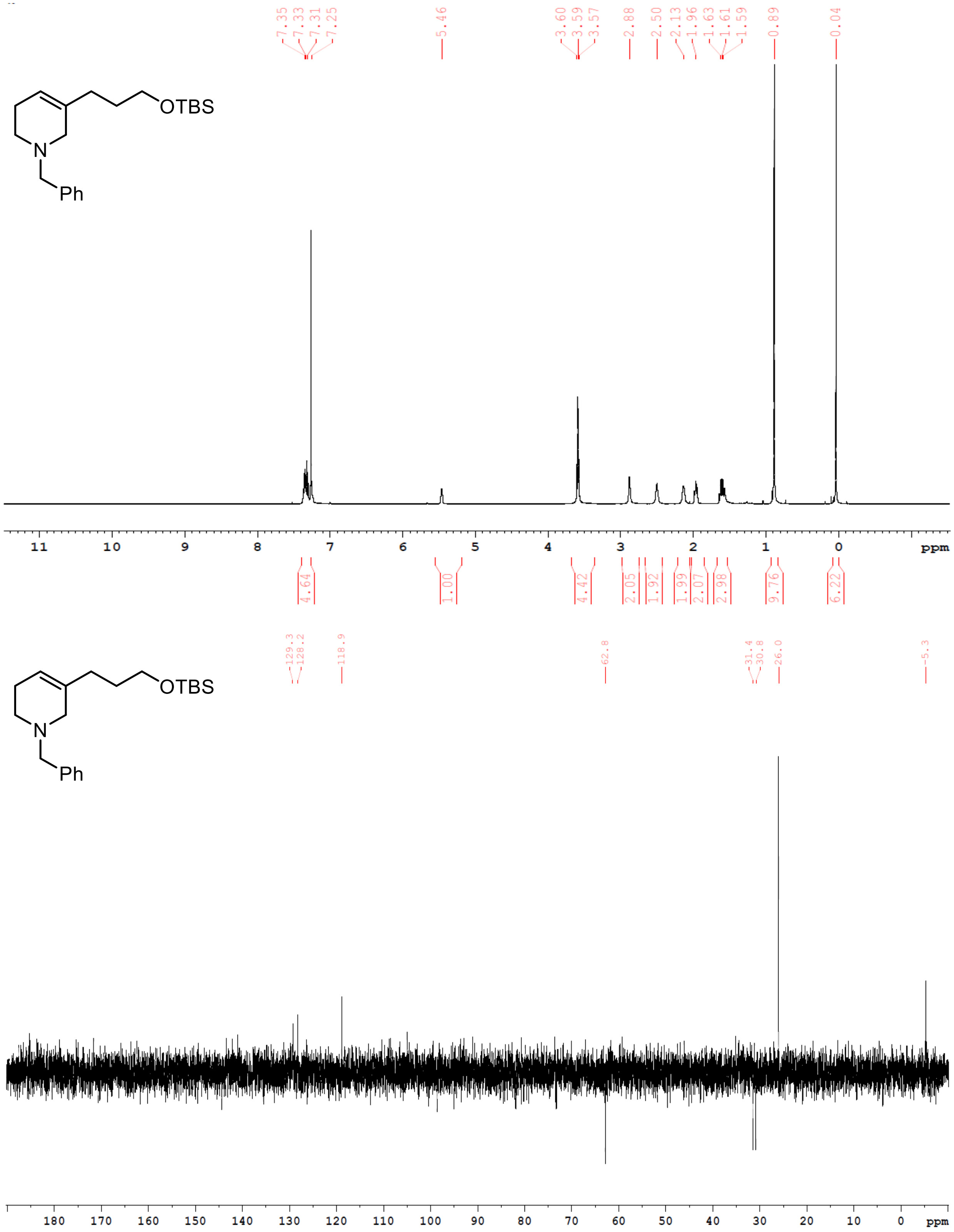


Figure A.3.36 ^{1}H NMR (400 MHz, CDCl$_3$) and DEPT-135 NMR (400 MHz, CDCl3) of **3.74**

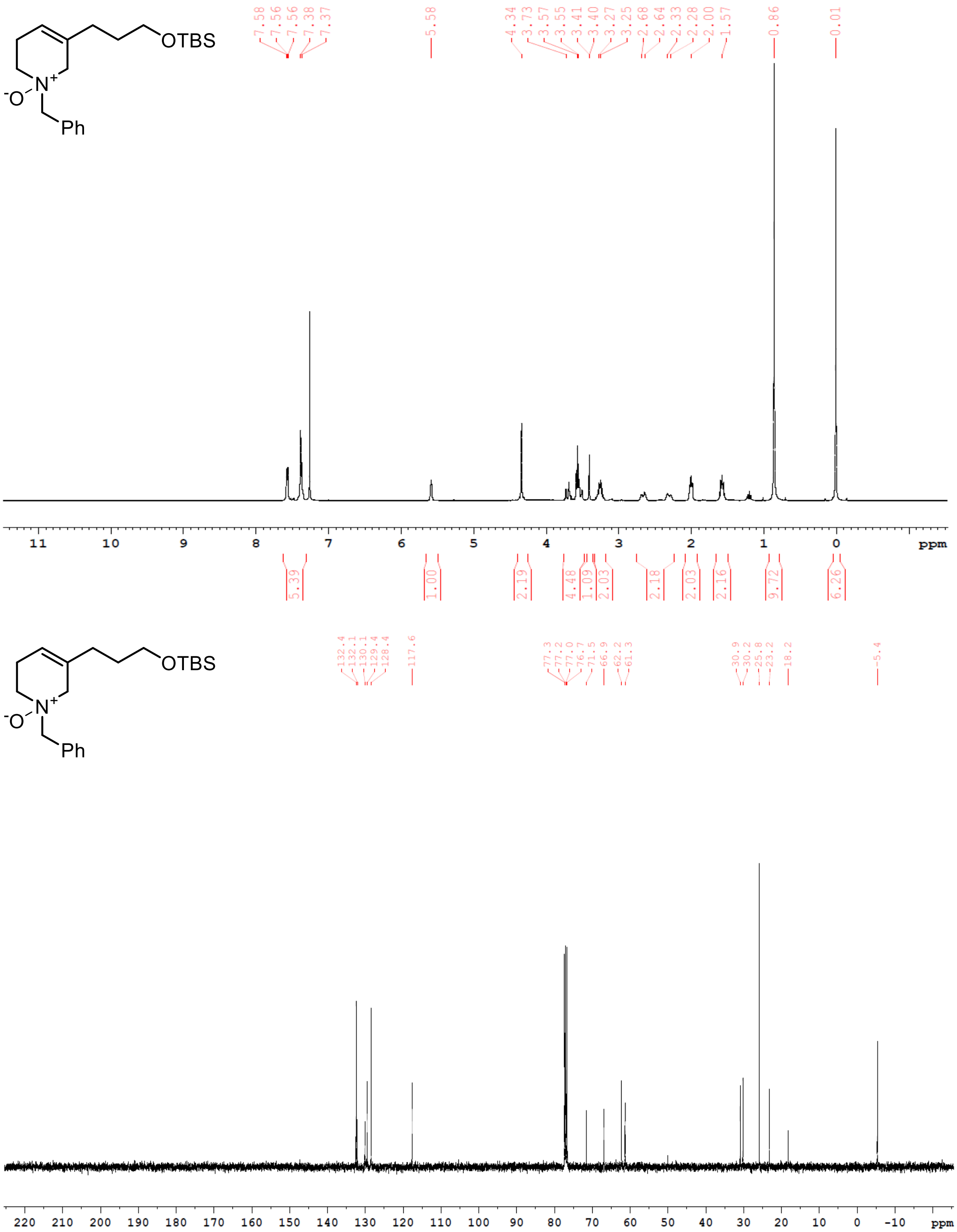


Figure A.3.37 ^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (400 MHz, CDCl$_3$) of **3.75**

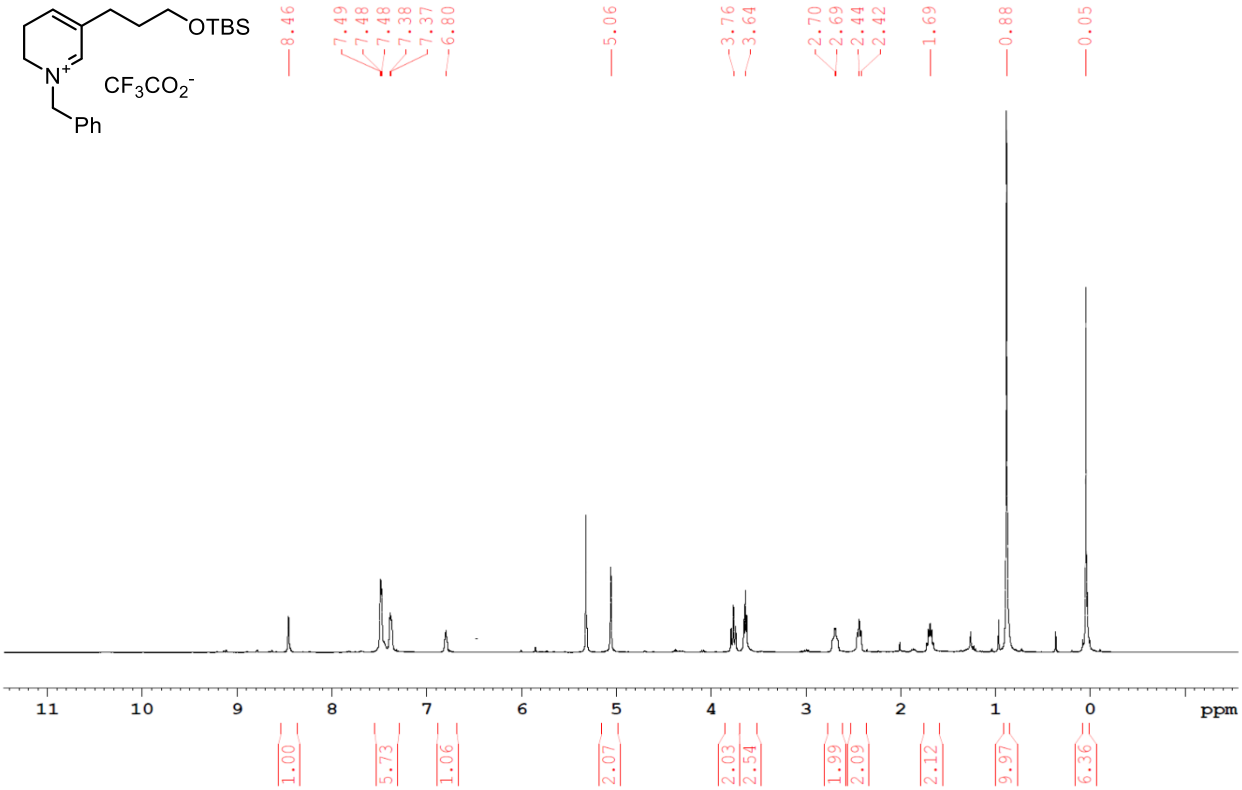


Figure A.3.38 ^{1}H NMR (400 MHz, CD_2Cl_2) of **3.76**

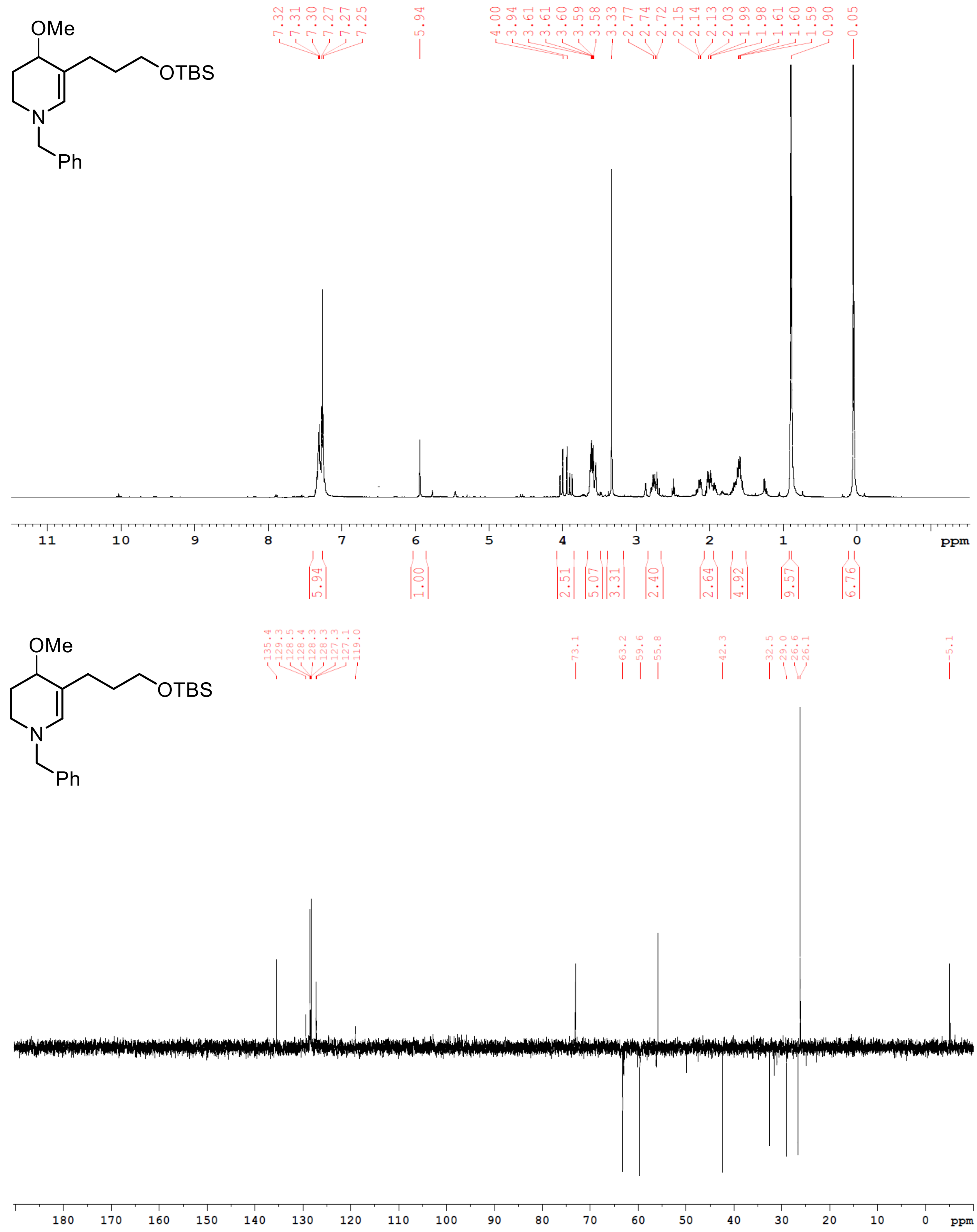


Figure A.3.39 ^{1}H NMR (400 MHz, $CDCl_3$) and DEPT-135 NMR (400 MHz, $CDCl_3$) of **3.78**

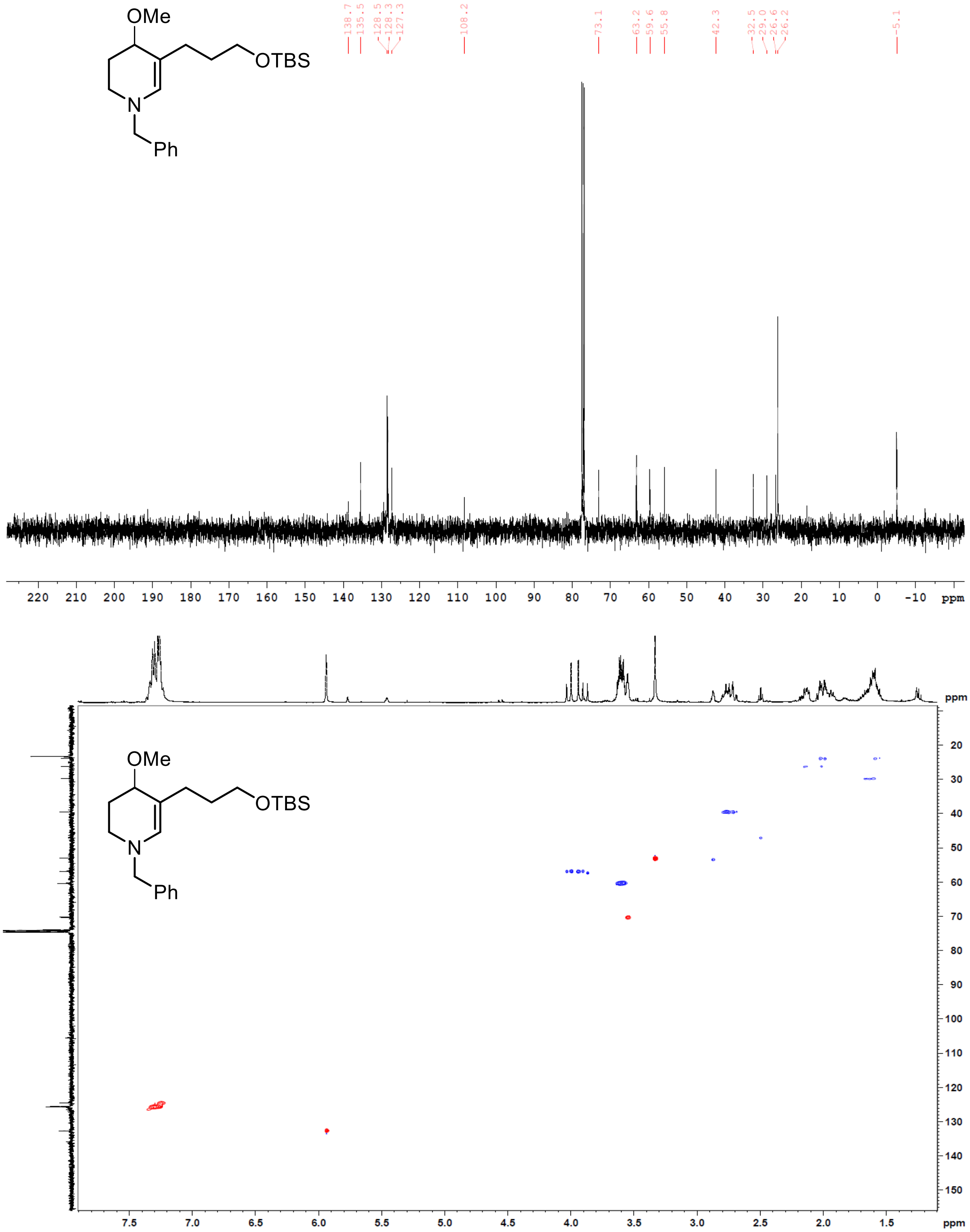


Figure A.3.40 ^{13}C NMR (400 MHz, CDCl$_3$) and HSQC NMR (400 MHz, CDCl$_3$) of **3.78**

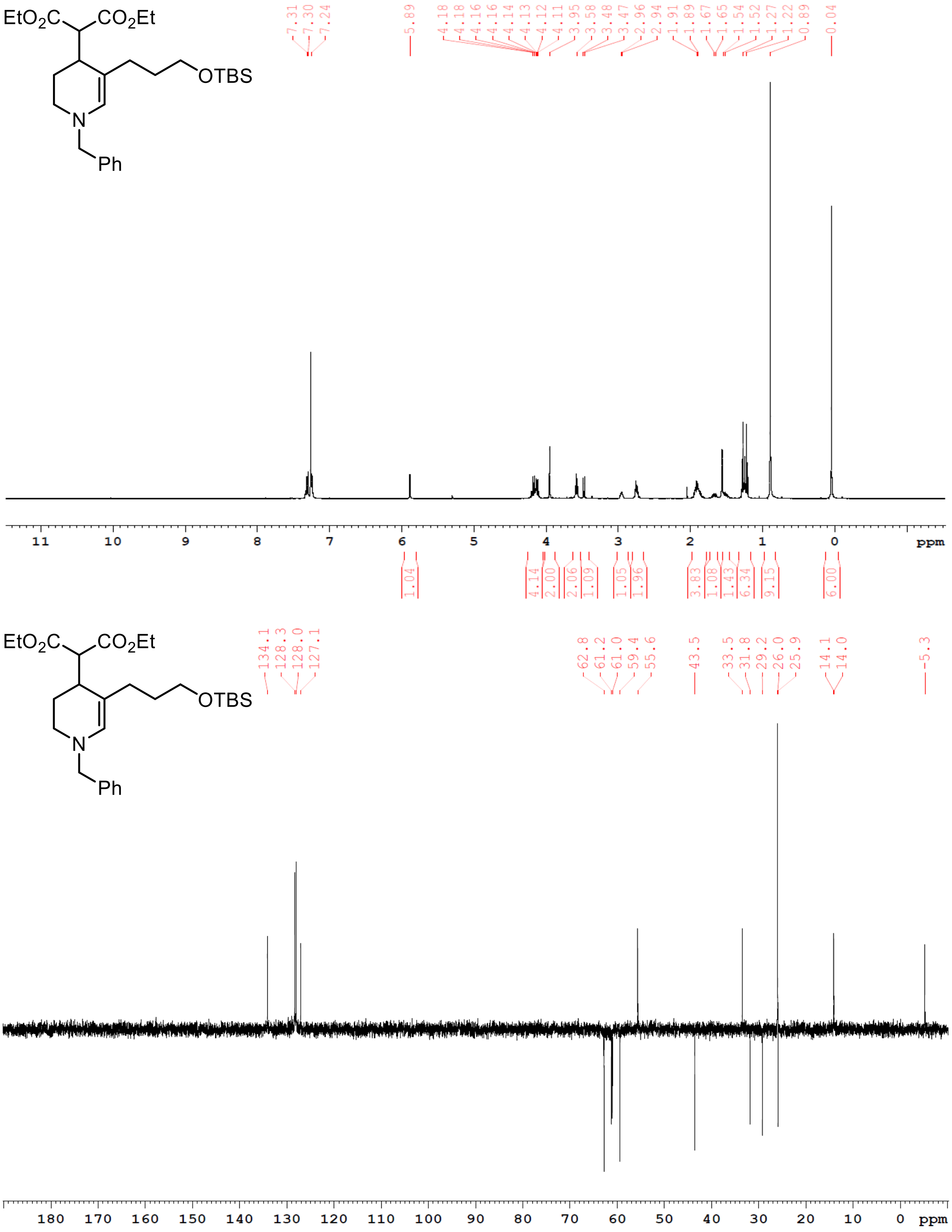


Figure A.3.41 ^{1}H NMR (400 MHz, CDCl$_3$) and DEPT-135 NMR (400 MHz, CDCl$_3$) of **3.79**

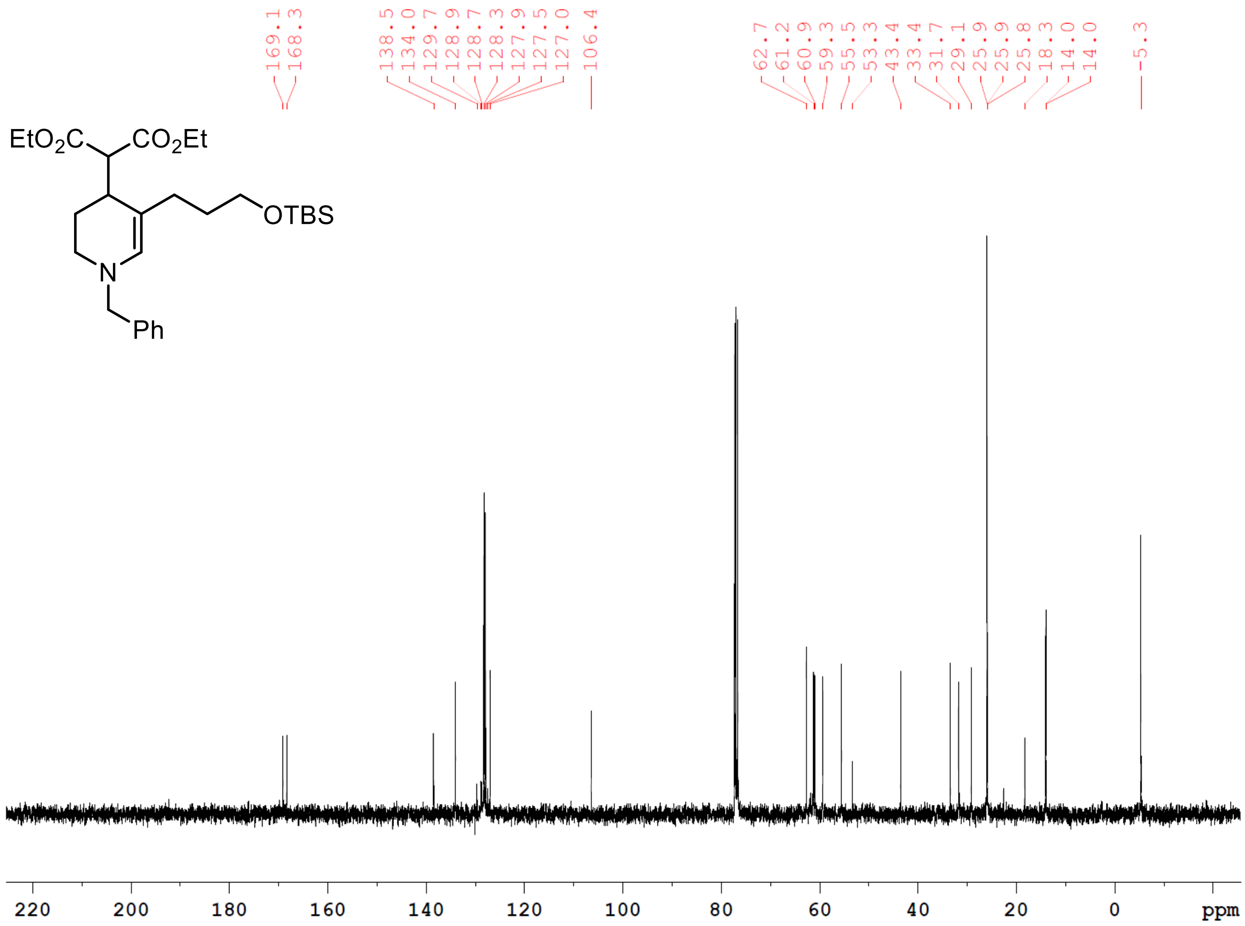


Figure A.3.42 ^{13}C NMR (400 MHz, CDCl$_3$) of **3.79**

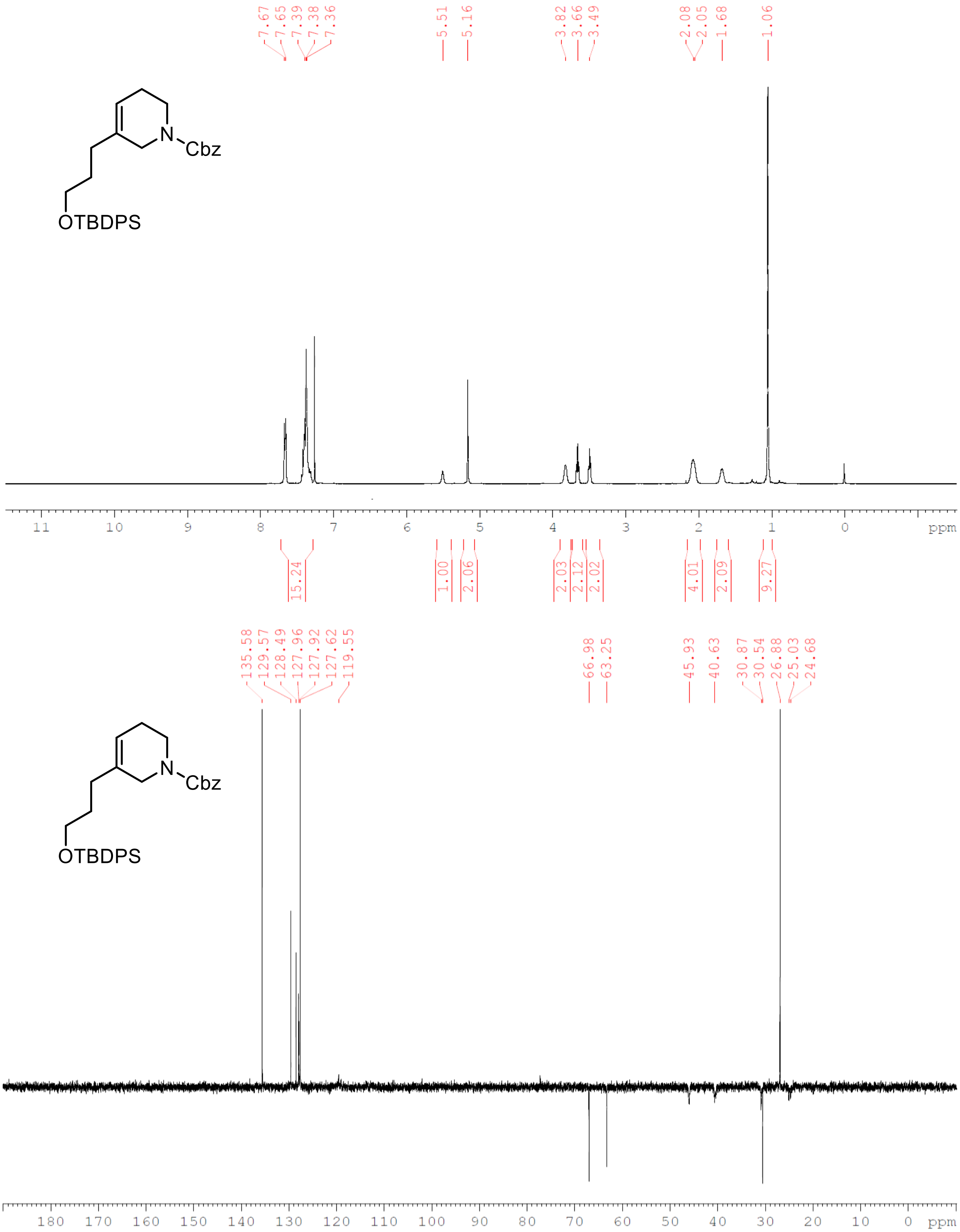


Figure A.3.43 ^{1}H NMR (400 MHz, CDCl$_3$) and DEPT-135 NMR (400 MHz, CDCl$_3$) of **3.81**

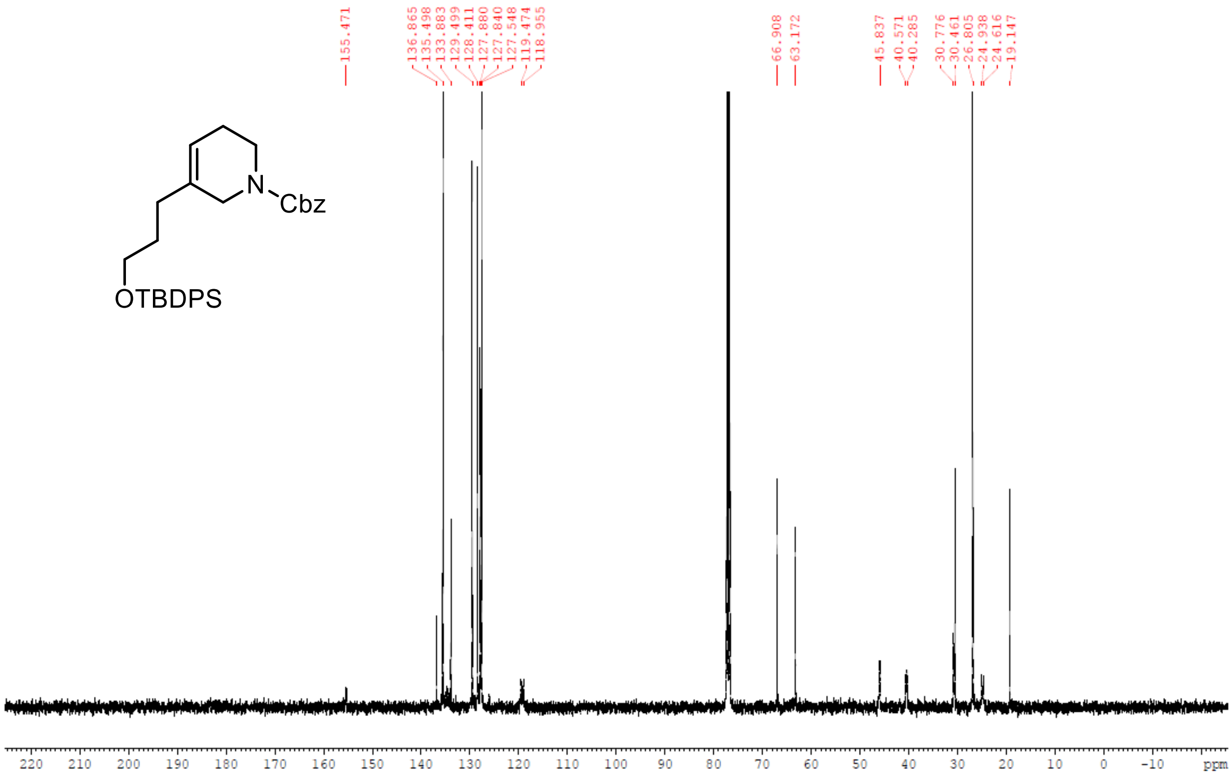


Figure A.3.44 ^{13}C NMR (400 MHz, CDCl$_3$) of **3.81**

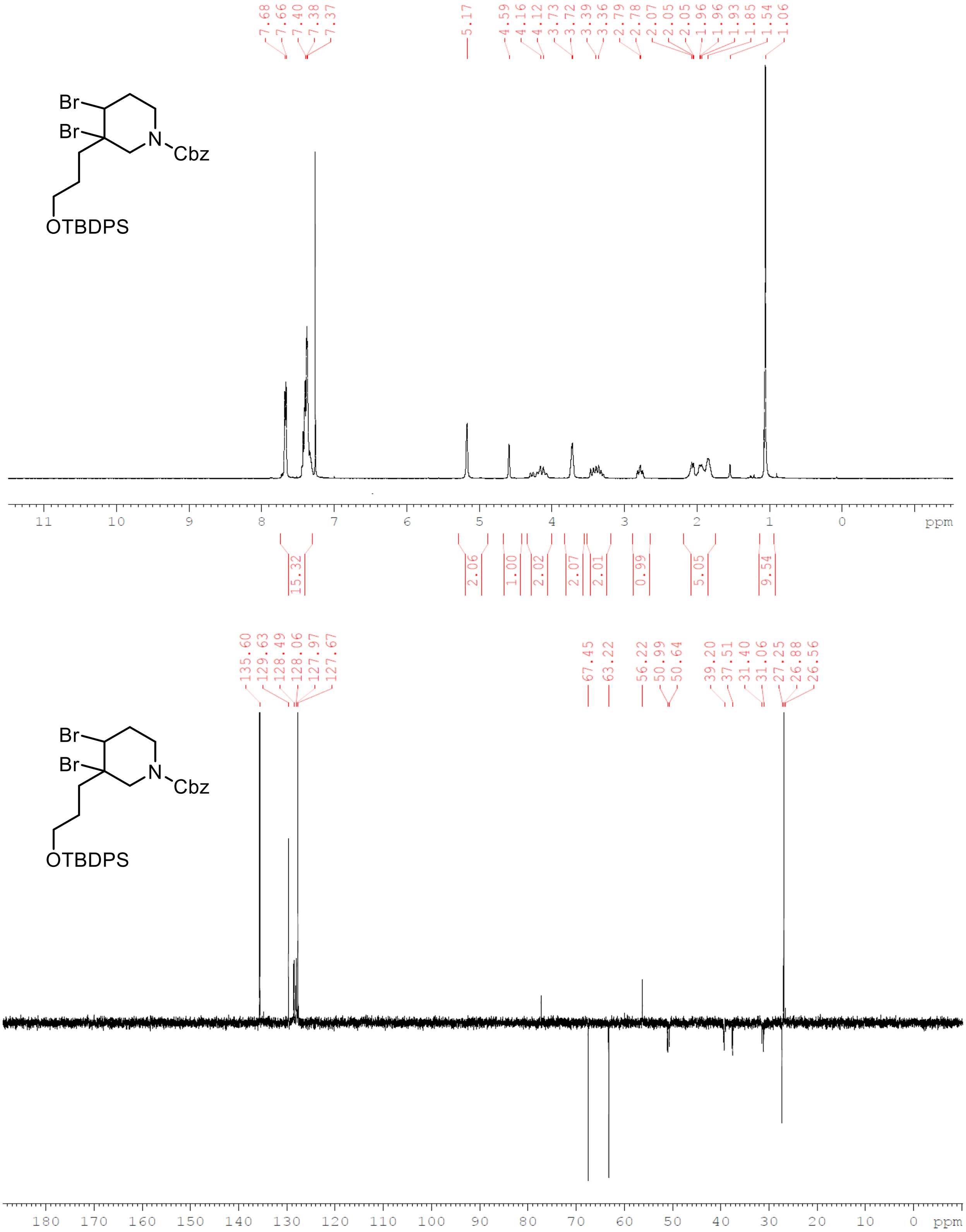


Figure A.3.45 ¹H NMR (400 MHz, $CDCl_3$) and DEPT-135 NMR (400 MHz, $CDCl_3$) of **3.82**

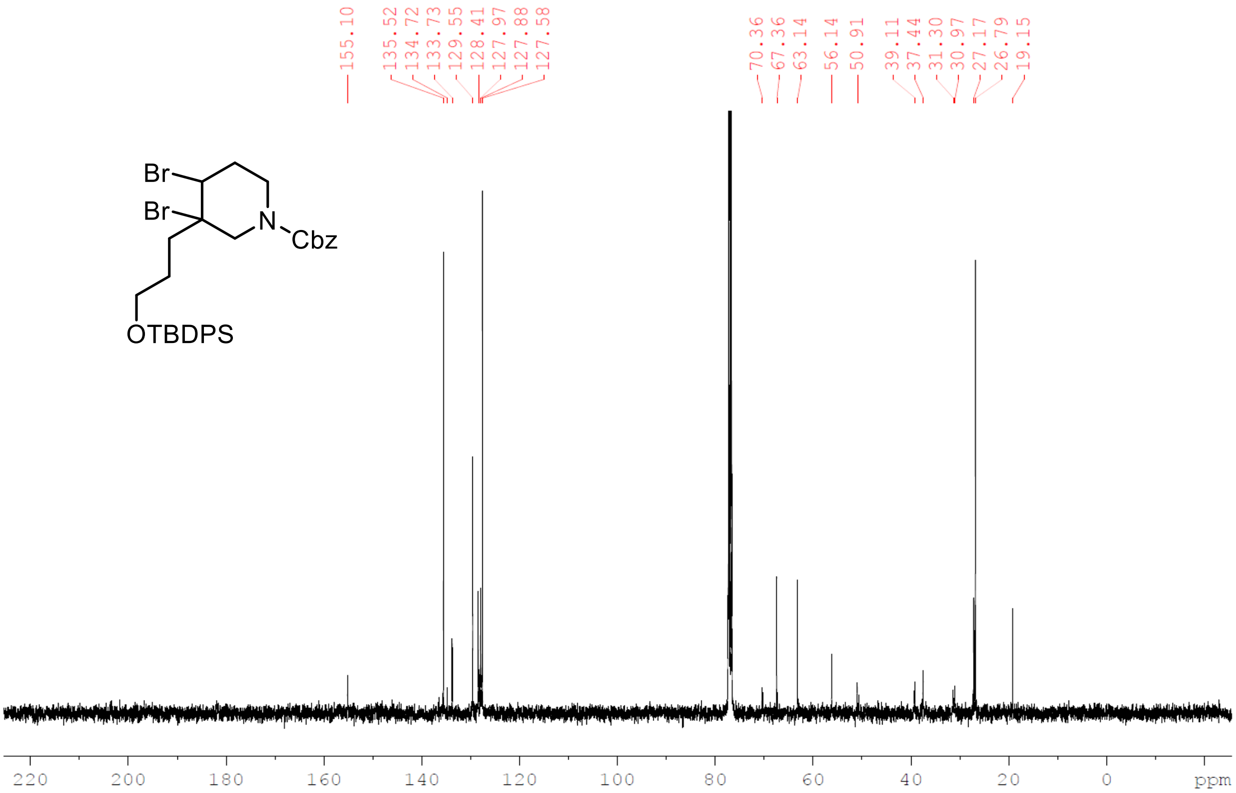


Figure A.3.46 ^{13}C NMR (400 MHz, $CDCl_3$) of **3.82**

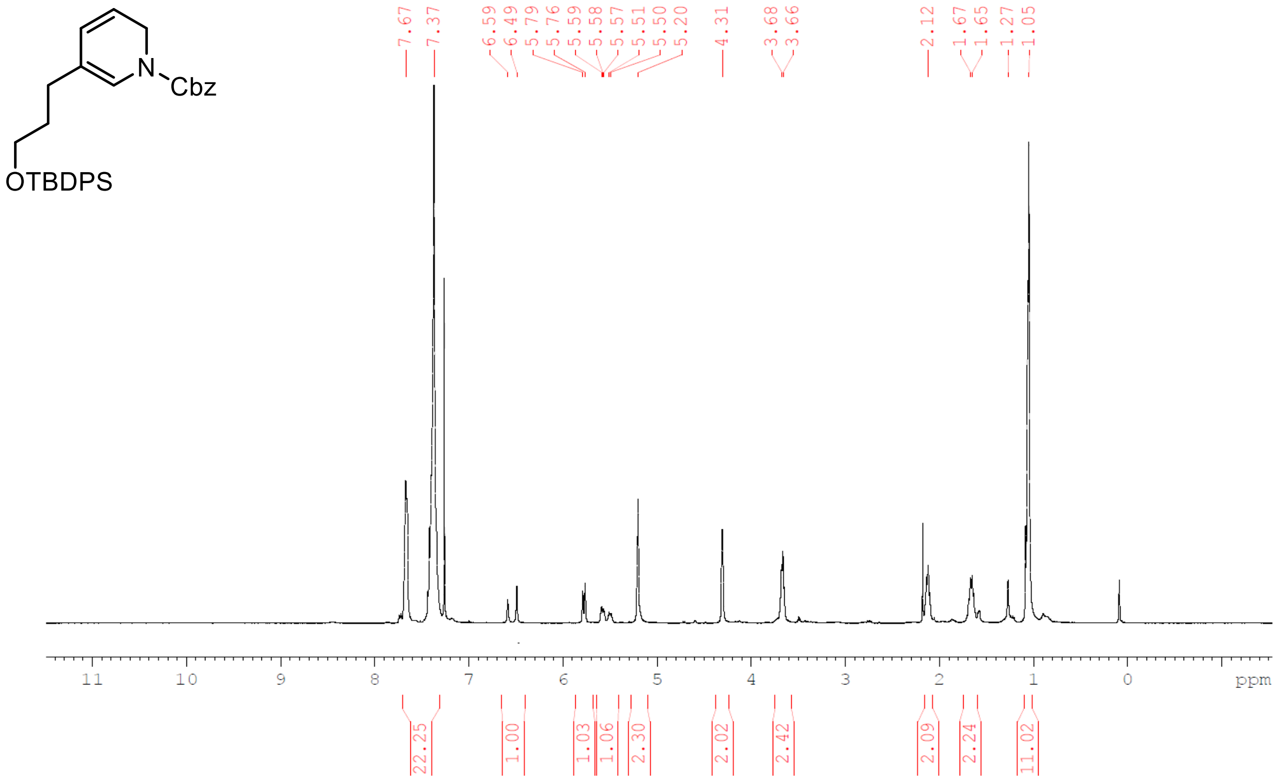


Figure A.3.47 ^{1}H NMR (400 MHz, CDCl$_3$) of **3.83**

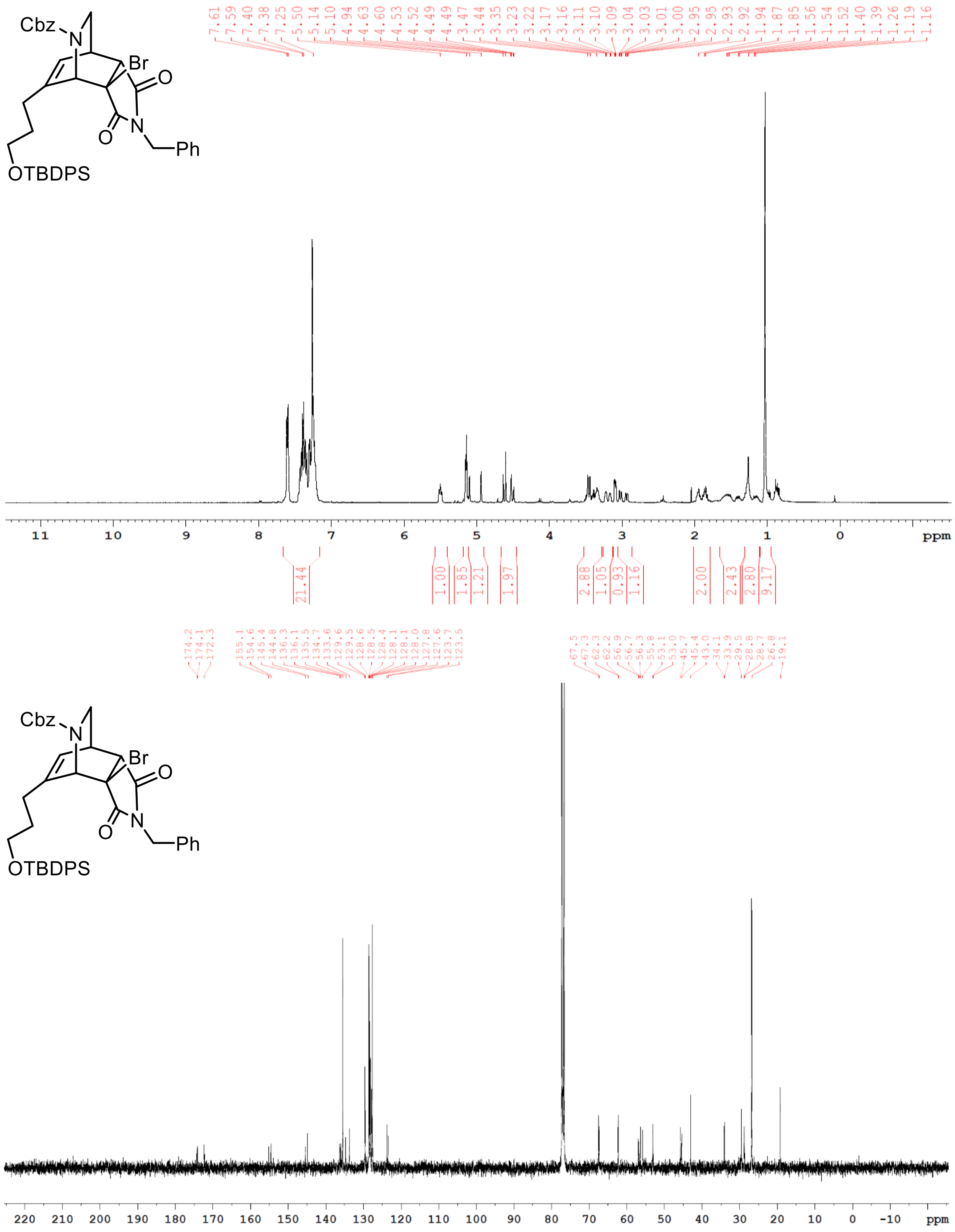


Figure A.3.48 ^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (400 MHz, CDCl$_3$) of **3.87**

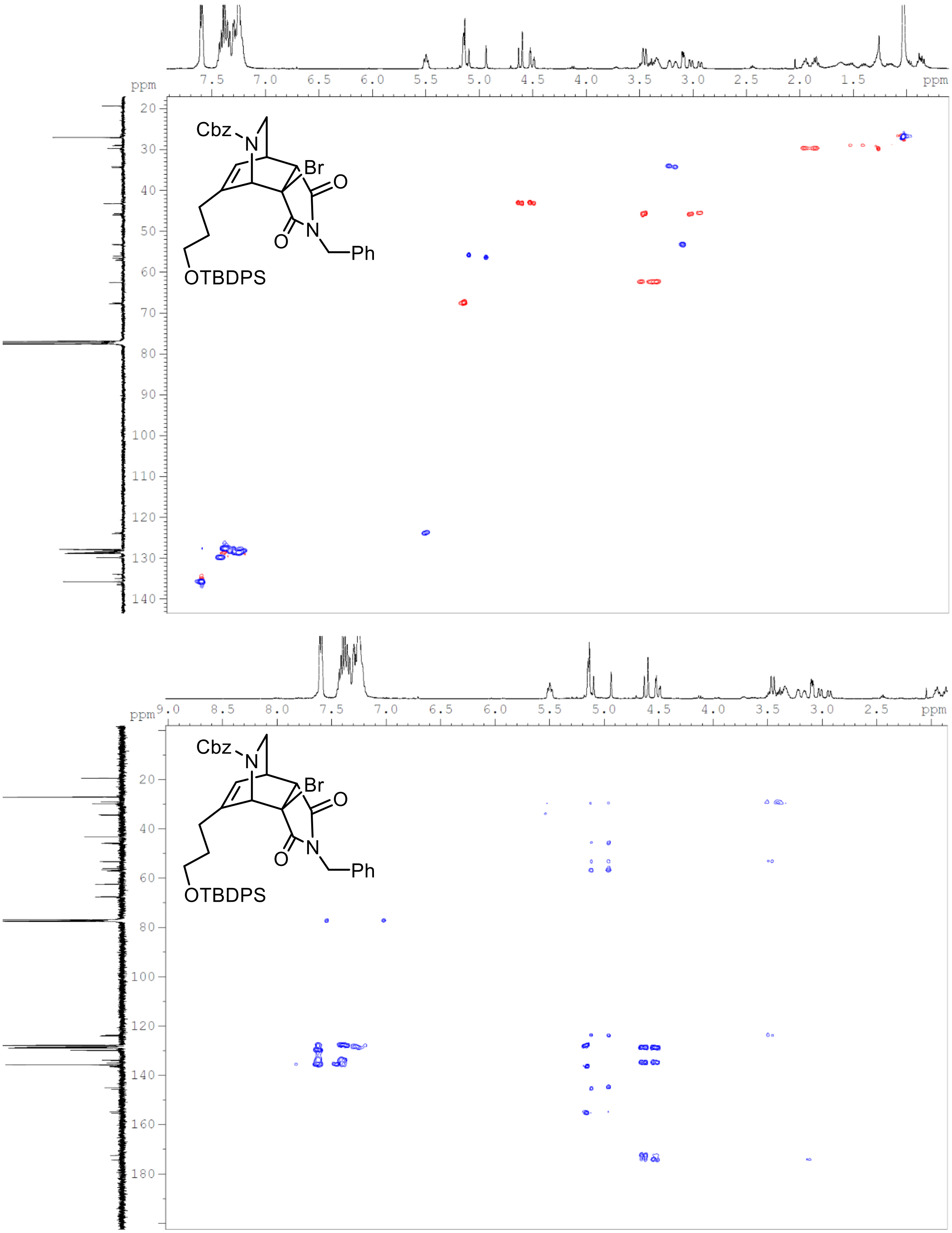


Figure A.3.49 HSQC NMR (400 MHz, $CDCl_3$) and HMBC NMR (400 MHz, $CDCl_3$) of **3.87**

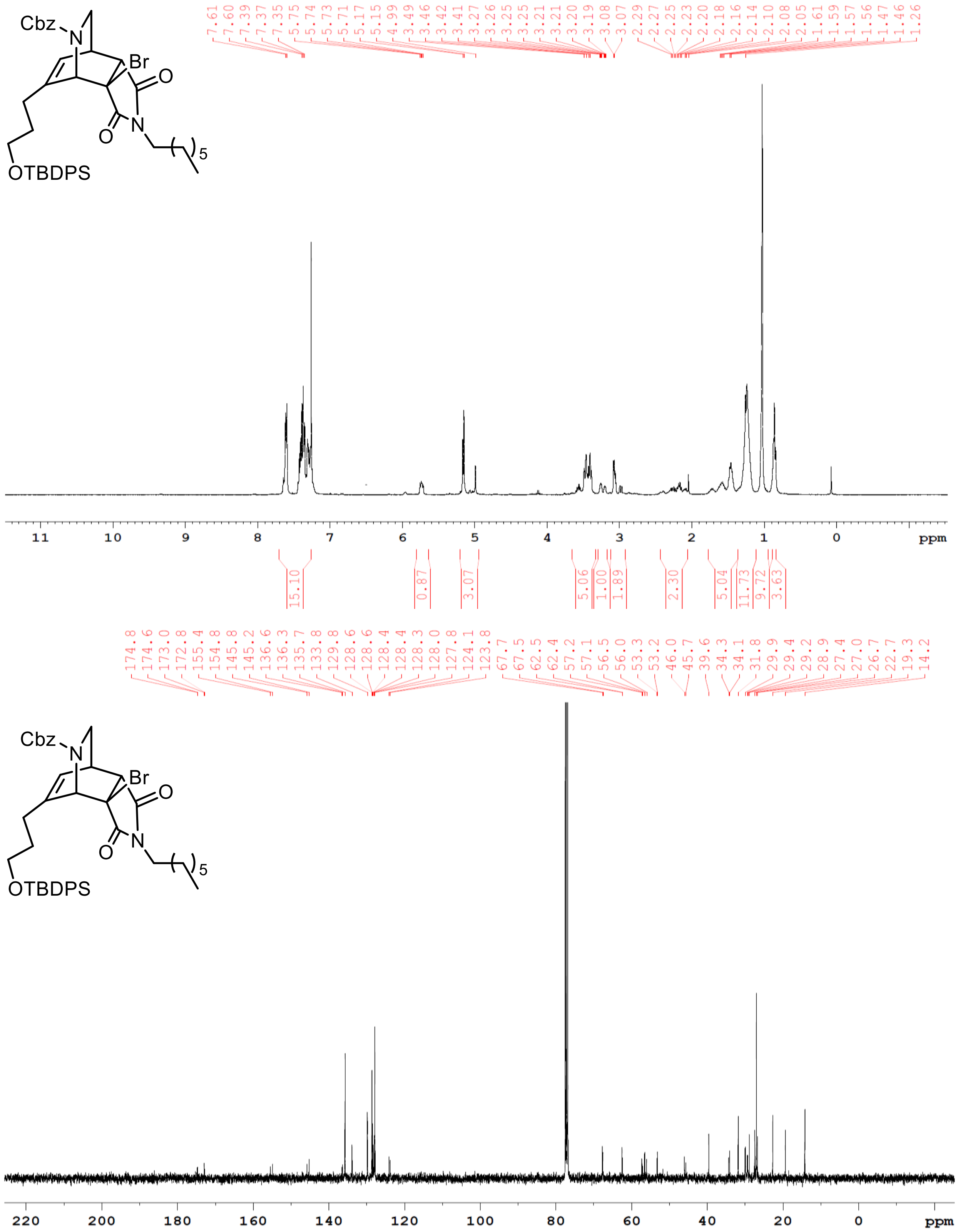


Figure A.3.50 ^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (400 MHz, CDCl$_3$) of **3.88**

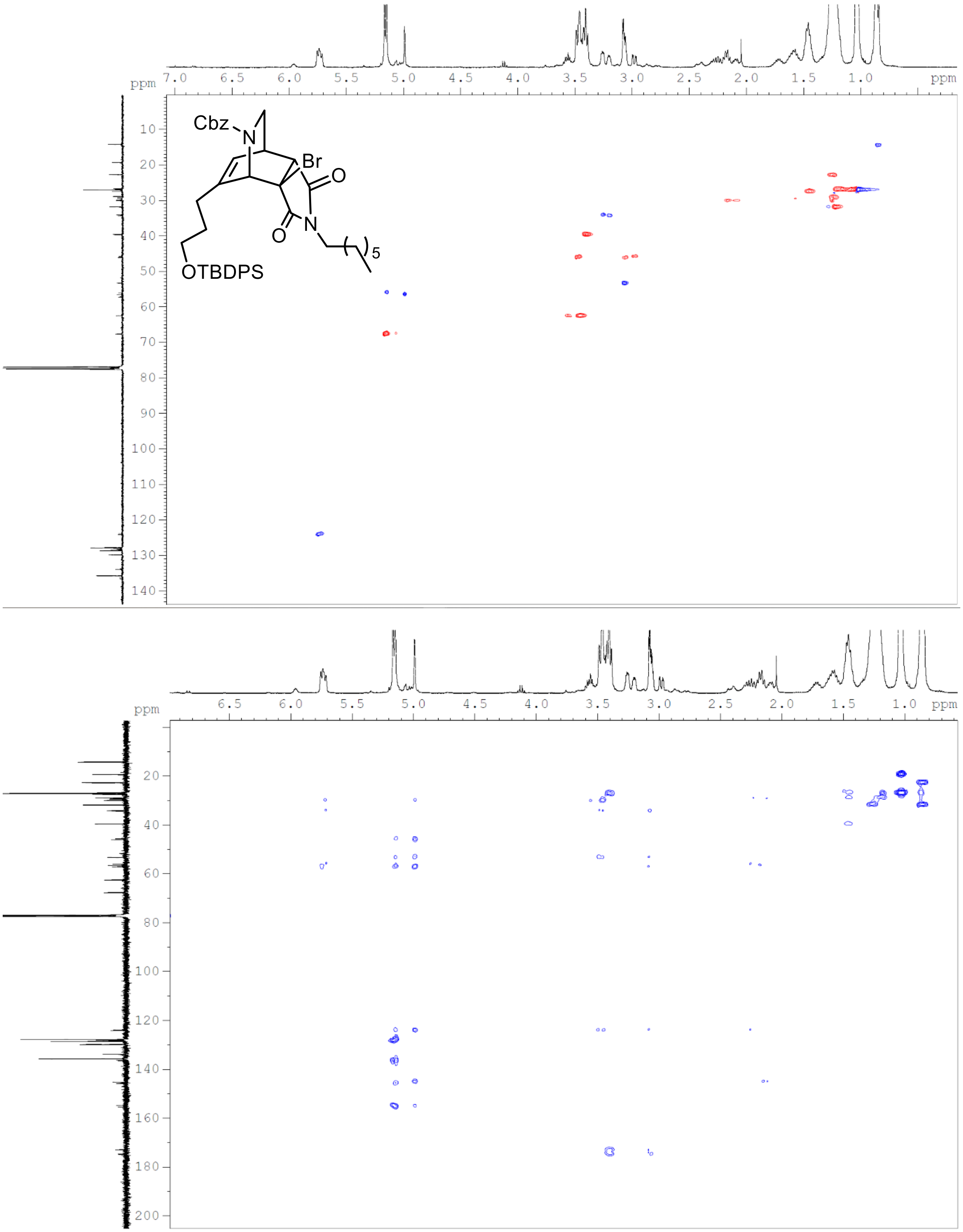


Figure A.3.51 HSQC NMR (400 MHz, $CDCl_3$) and HMBC NMR (400 MHz, $CDCl_3$) of **3.88**

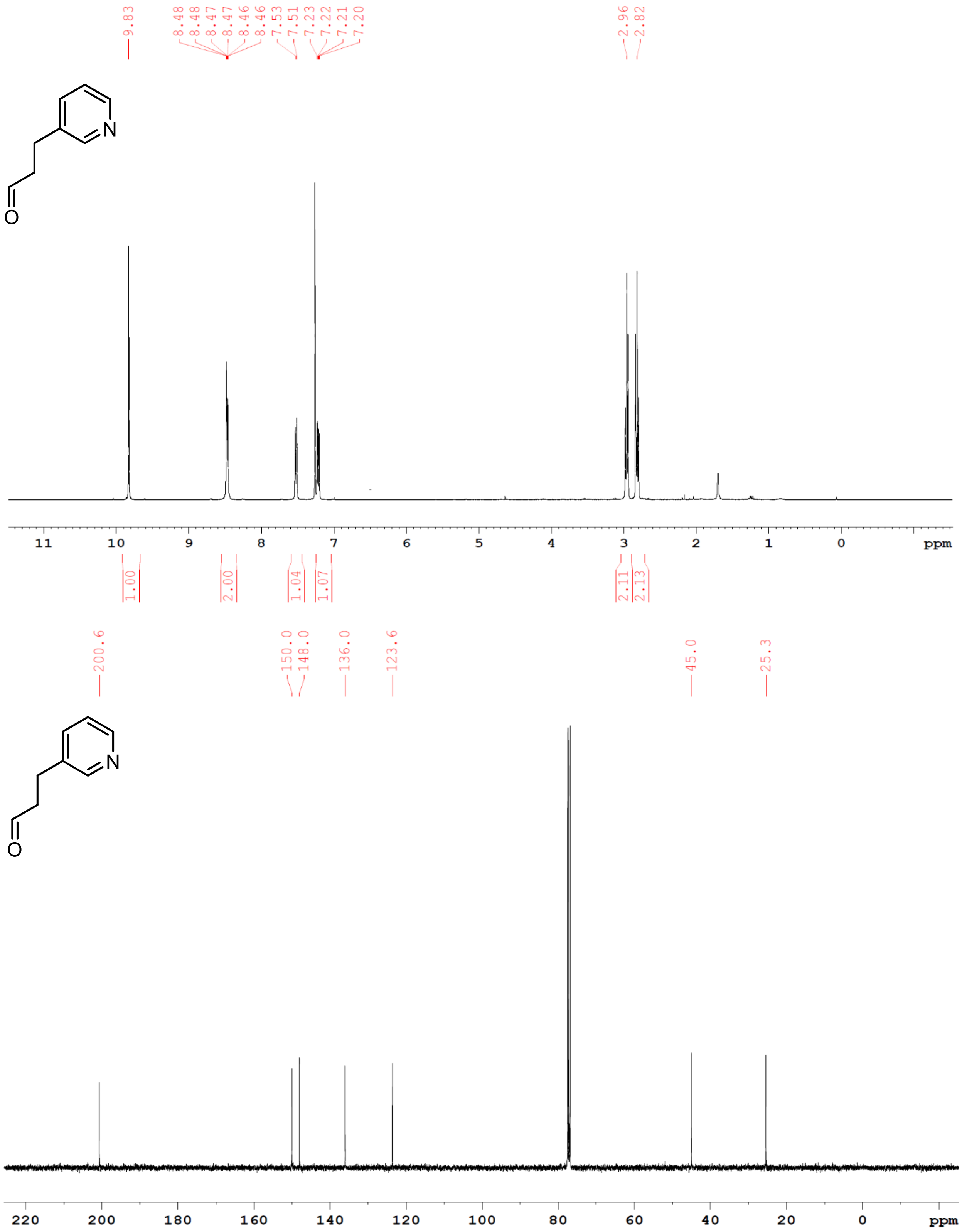


Figure A.3.52 ^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (400 MHz, CDCl$_3$) of **3.89**

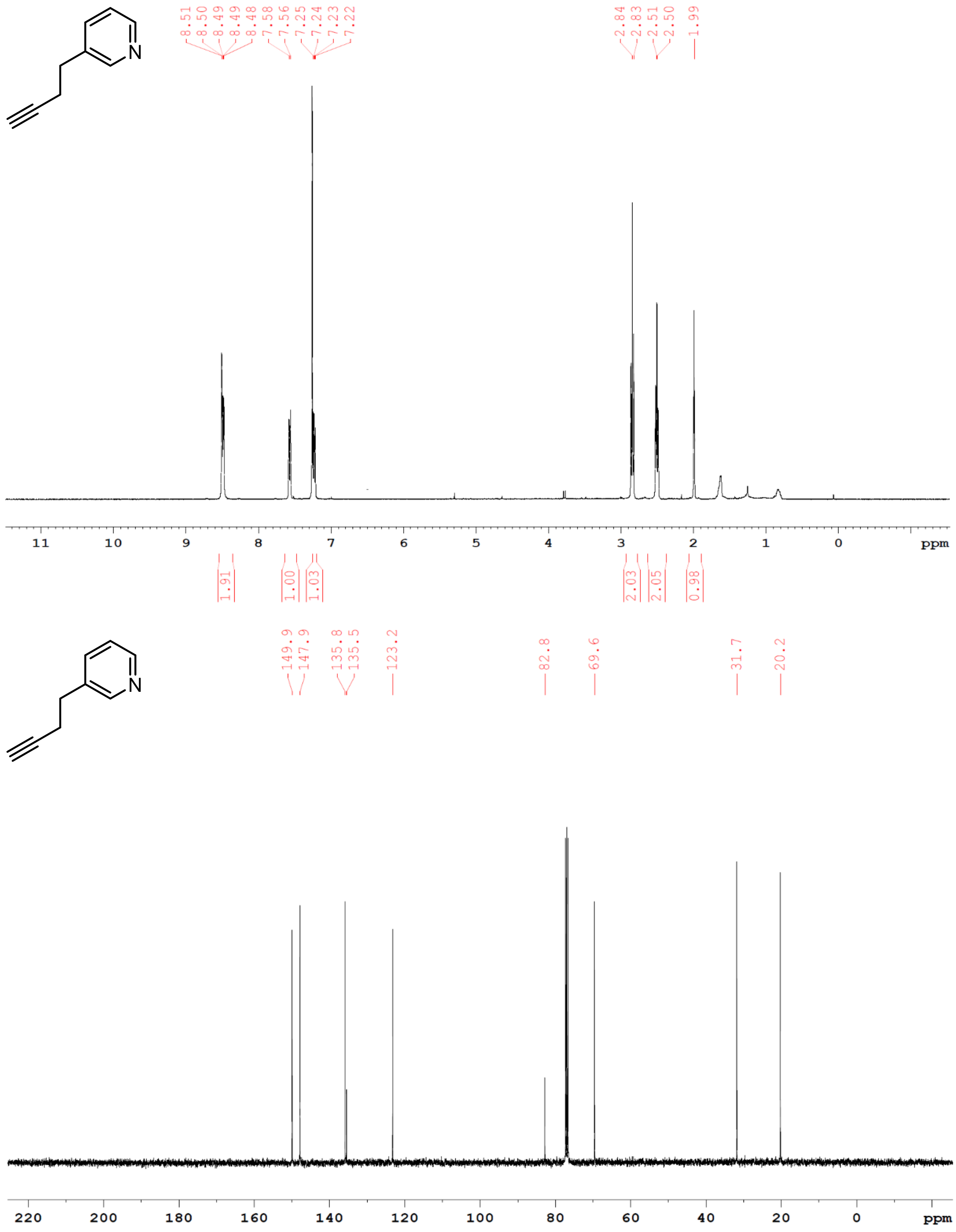


Figure A.3.53 ^{1}H NMR (400 MHz, $CDCl_3$) and DEPT-135 NMR (400 MHz, $CDCl_3$) of **3.91**

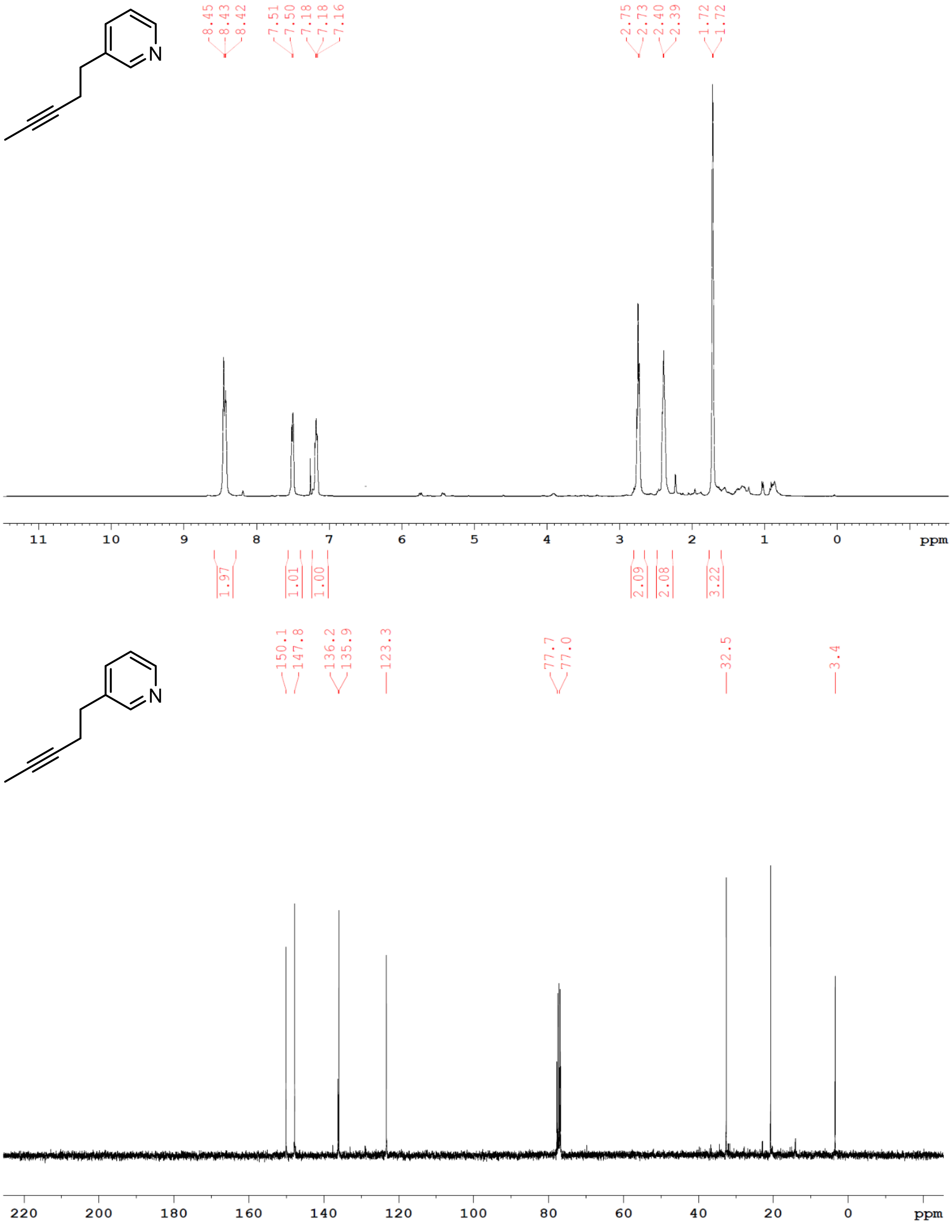
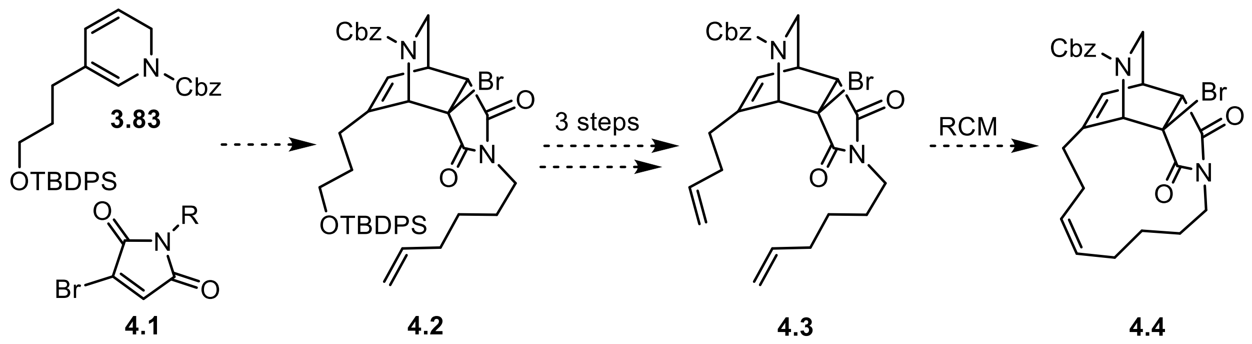


Figure A.3.54 ^{1}H NMR (400 MHz, $CDCl_3$) and DEPT-135 NMR (400 MHz, $CDCl_3$) of **3.92**

PROGRESS TOWARD THE TOTAL SYNTHESIS OF XESTOCYCLAMINE FROM AN ADVANCED BICYCLIC INTERMEDIATE

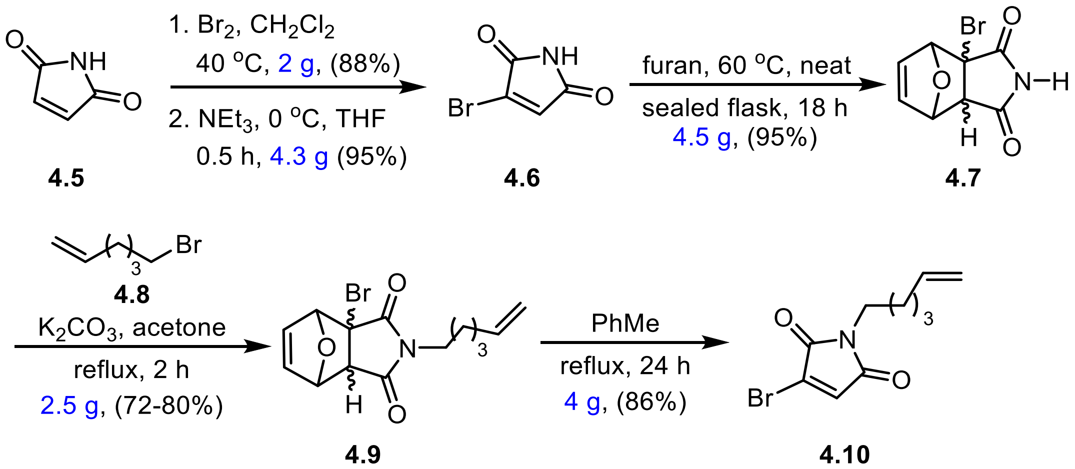
A Ring-Closing Metathesis Approach Toward the Southern Macrocycle

After success of the Diels-Alder reaction, functionalization of the anhydride proved challenging and resulted in the adoption of a new maleimide dienophile. Moving forward with the nitrogen analogue, our future goal focused on installation of the Southern macrocycle (Scheme **4.1**) and required preparation of an N-alkylated bromomaleimide.



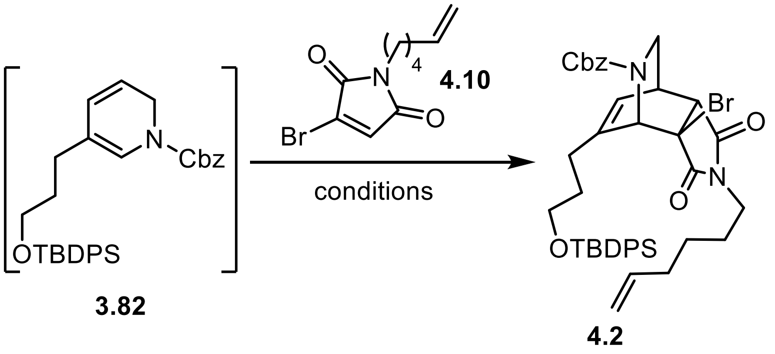
Scheme 4.1 Synthetic strategy toward the southern macrocycle.

Synthesis of the N-alkylated bromomaleimides was straightforward and routinely conducted on gram scale in reproducibly high yields. Beginning from maleimide **4.5**, a dibromination and elimination sequence was performed to afford bromomaleimide **4.6** in excellent yields which required no purification (Scheme **4.2**). Next, imide **4.6** was reacted with furan to induce a Diels-Alder reaction that generated an inconsequential mixture of diastereomers prior to N-alkylation under basic conditions which give **4.9**. Notedly, extended reaction times at reflux would equilibrate the *exo* to *endo* isomer. More importantly, reaction with furan was necessary as the cycloadduct served as a protecting group which prevented competitive Michael additions toward the reactive bromomaleimide under basic conditions. Deprotection occurred readily above 100 °C in an open vessel to give **4.10** in 86% yield.



Scheme 4.2 Synthesis of N-alkyl bromomaleimides.

With dienophile in hand, we examined the ability of N-alkyl bromomaleimide **4.10** to engage in the Diels-Alder cycloaddition and we were surprised to observe no reactivity using previously optimized conditions (Scheme **3.15**). A wide variety of conditions were then screened to optimize this transformation (Table **4.1**). In summary, early studies showed microwave irradiation and thermal heating produced the cycloadduct in 29-31% yields (entries 1, 2). It was found that increasing equivalents of diene **3.82** and antioxidant additives such as BHT increased the yield to 47% (entries 3, 4). Employing milder temperatures (65 °C) further raised the yield to 58% while extended reaction times led to a decrease (entries 5-7). Next, a variety of Lewis acids were screened, of which the Co- and Cr-salen catalysts, **4.12a-c** were of the most interest (entries 8-11). Such Co and Cr-salen complexes were developed by the Jacobson group and have been employed by Rawal and coworkers in catalysis of 1,2-dihydropyridines and 1-amino-3-siloxy- 1,3-butadienes in Diels-Alder reactions.[79–81]

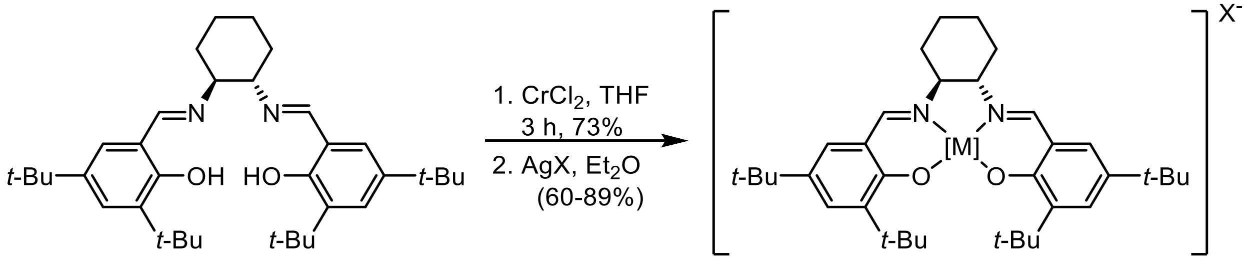


entry	eq. **3.82**	eq. **4.10**	temperature	solvent	class	conditions	Result
1	1	1	120 °C	PhH	microwave	4 h	29%
2	1	1	80 °C	PhH	thermal	18 h	31%
3	3	1	80 °C	PhH	thermal	18 h	42%
4	3	1	80 °C	PhH	thermal	BHT, 18 h	47%
5	3	1	65 °C	PhH	thermal	BHT, 18 h	58%
6	3	1	65 °C	PhH	thermal	BHT, 24 h	56%
7	3	1	65 °C	PhH	thermal	BHT, 48 h	46%
8	3	1	rt	acetone	Lewis acid	**4.12a**,11 d	32%[a]
9	3	1	rt	acetone	Lewis acid	**4.12b**, 8 d	39%[a]
10	3	1	rt	CH_2Cl_2	Lewis acid	**4.12b**, 8 d	46%[a]
11	3	1	rt	acetone	Lewis acid	**4.12c**, 5 d	28%[a]
12	3	1	rt	CH_2Cl_2	Lewis acid	**4.12b**, 3 d	decomp[b]
13	1	1	0 °C	CH_2Cl_2	Lewis acid	ZnI_2 1 eq.	decomp
14	1	1	0 °C	CH_2Cl_2	Lewis acid	$ZnBr_2$, 1 eq.	decomp
15	1	1	0 °C	CH_2Cl_2	Lewis acid	$ZnCl_2$, 1 eq.	decomp
16	1	1	0 °C	CH_2Cl_2	Lewis acid	$AlCl_3$, 1 eq.	decomp
17	1	1	0 °C	CH_2Cl_2	Lewis acid	$AlEt_2Cl$, 1 eq.	decomp

[a] 0.1 equivalents of **4.12a-c** were used, [b] 1 equivalent of **4.12b** was used.

Table 4.1 Screening of conditions employing maleimide dienophile.

Preparation of **4.12a-c** commenced with chelation of the chromium metal ion with the readily available Schiff base **4.11**. Precipitation of AgCl then generated the triflate and hexafluoroantimonate salts. The cobalt complex **4.12a** was also readily available and we were pleased to find that when **4.12a-b** were charged to the Diels-Alder reaction, cycloadduct **4.2** was isolated in 32% and 39% yields (entries 8, 9). A simple solvent change with **4.12b** to CH_2Cl_2 increased the yield to 46% (entry 10). Meanwhile triflate salt **4.12c** and stoichiometric equivalents led to lower yields or decomposition of substrate, respectively (entries 11, 12). Due to the extended reaction times, we were interested if **4.12a-c** were catalyzing the reaction enantioselectively and therefore measured the optical rotation of cycloadduct **4.2**. The measured $[\alpha]_D^{24}$ + 0.1° failed to confirm if **4.2** was isolated as an enantiopure compound. Analysis by chiral-HPLC was never pursued, but regardless, while interesting, the extended reaction times became unamendable to creating a productive synthetic route and catalysts **4.12a-c** were not pursued further. Finally and unremarkably, other Lewis acids such as: zinc halides, $AlCl_3$, and $AlEt_2Cl$ resulted in decomposition of substrate (entries 13-17).



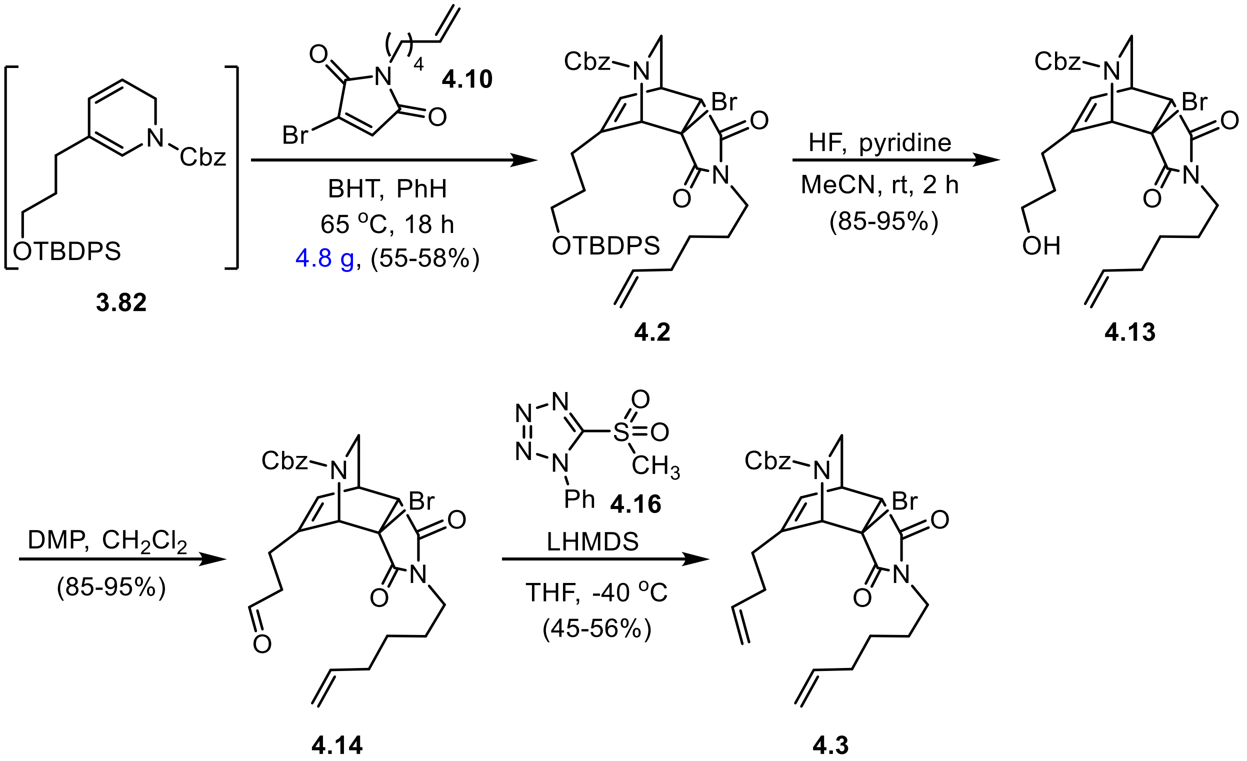
4.11

4.12a - [M] = Co
4.12b - [M] = Cr, X = SbF_6
4.12c - [M] = Cr, X = OTf

Scheme 4.3 Synthesis of metal-salen catalysts.

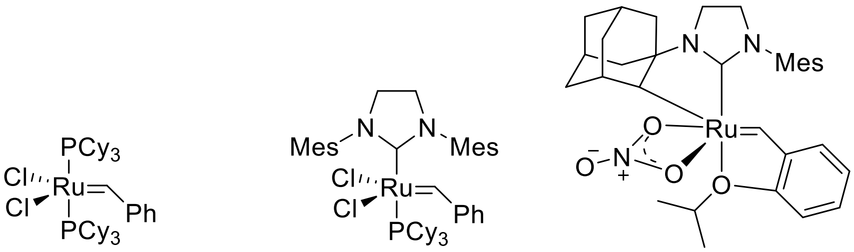
With thermal conditions optimized to yield **4.2** in 58%, we now gained access to a scalable route enabling access to gram quantities of cycloadduct **4.2.** The next objective focused on installation of the southern macrocyclic ring and would require a second alkenyl handle. Thus, desilylation with HF·pyridine afforded alcohol **4.13** in good yields and was necessary as TBAF gave incomplete conversion (Scheme **4.4**). Oxidation to aldehyde **4.14** was achieved using Dess-Martin periodinane from which a seemingly trivial olefination would then give alkene **4.3**. However, when reacted with ylides such as $Ph_3P{=}CH_2$, decomposition of substrate was observed.

Interestingly when reacted with stabilized ylides such as $Ph_3P{=}CHCO_2Et$, the *trans*-alkene **4.15** was isolated in 75% yield under identical reaction conditions. Presumably the unstabilized ylide's stronger nucleophilic character resulted in addition at the imide or carbamate carbonyl. Lombardo conditions[82] utilizing I_2CH_2, Zn, and Ti(O-*i*-Pr)$_4$ systems failed to show any reactivity. Fortunately, Julia-Lythgoe[83,84] and Julia Kocienski[85] olefinations provided the terminal alkene **4.3** in modest yields. When reacted with methyl sulfone **4.16** at -40 °C, the olefin was isolated in 45-56%.



Scheme 4.4 Synthesis of alkenyl RCM precursor.

With the RCM precursor **4.3** in hand, the terminal diolefin was first subjected to Grubbs 1st and 2nd generation catalysts, **4.17** and **4.18**, respectively to give macrocycle **4.20** (Scheme **4.5**). Surprisingly a single isomer was observed by ^1H NMR and LCMS. However, assignment of the olefin geometry proved impossible due to complex rotameric peaks caused by the benzyl carbamate. Fortunately, our next step was to examine introduction of the Northern macrocycle starting with removal of the Cbz group. Standard deprotection of Cbz-groups occurs readily under hydrogenolytic conditions, but also resulted in reduction of both alkenes. Other reagents such as Raney Ni, or $Pd(OH)_2$ similarly resulted in hydrogenation of the alkenes. Non-hydrogenolytic conditions such as $Pd(OAc)_2$, Et_3SiH, NEt_3 or TMSI both failed to generate the secondary amine. Ultimately the Lewis acid BCl_3 revealed the secondary amine in 53% yield with minor desilylation. Unfortunately, the ^1H NMR spectrum and alkenyl region remained unresolved and the *J*-values were difficult to be extrapolated. Using a selective 1D NOESY ^1H NMR decoupling experiment, we found irradiation of the vicinal protons allowed us to elucidate ^3J values of the vicinal peaks. Unfortunately, the major product from both appeared to favor the undesired *trans*-isomer as indicated by the coupling constant J = 16 Hz.



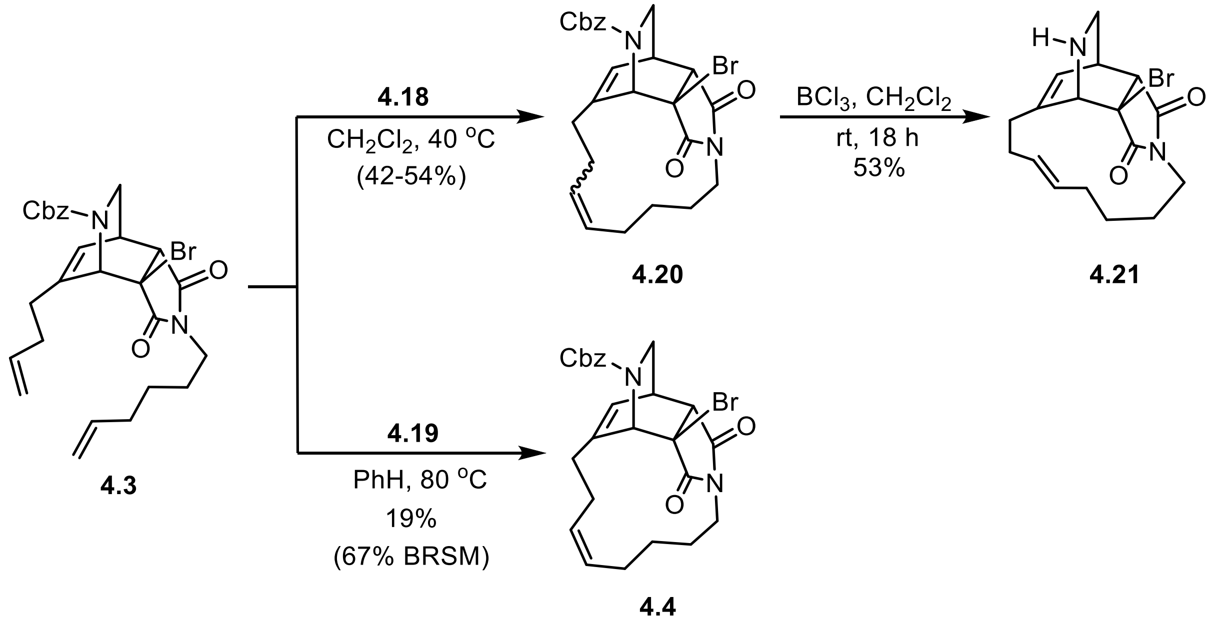
4.17
Grubbs (1st generation)

4.18
Grubbs (2nd generation)

4.19
Grubbs Z-Selective

Figure 4.1 Alkene ring closing metathesis catalysts.

Returning to terminal diolefin **4.3**, we next employed Grubbs Z-Selective catalyst **4.19** (Figure **4.1**) which has been demonstrated to deliver excellent Z-selectivity in RCM and cross metathesis chemistry.[86,87] Gratifyingly, upon reaction with catalyst **4.19**, macrocycle **4.4** was isolated in 19% yield and 67% BRSM. The low yield can be attributed to a lack of optimization, as at the time, our source of catalyst began to provide lower conversion and commercial vendors were out of supply. So rather than wait for suppliers to restock **4.19** we began to purse development of methodology to access the remaining ring systems.

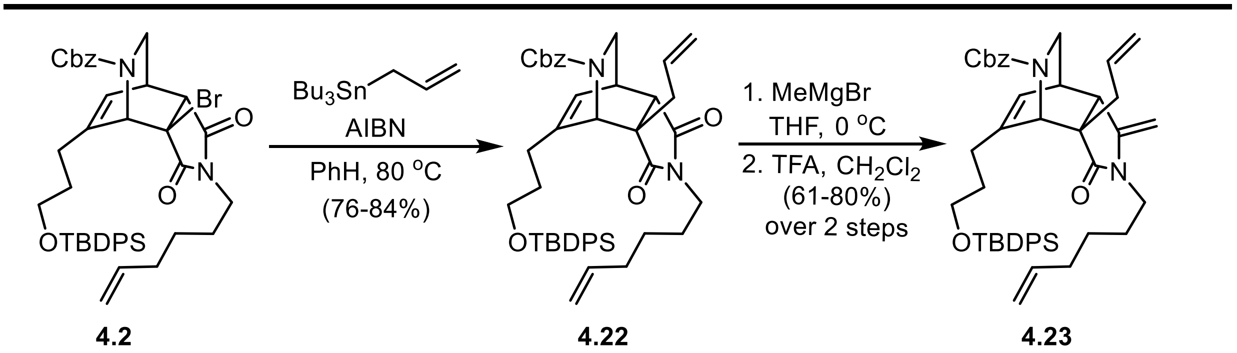


Scheme 4.5 RCM of terminal diolefin with Grubbs II generation and Z-Selective catalysts.

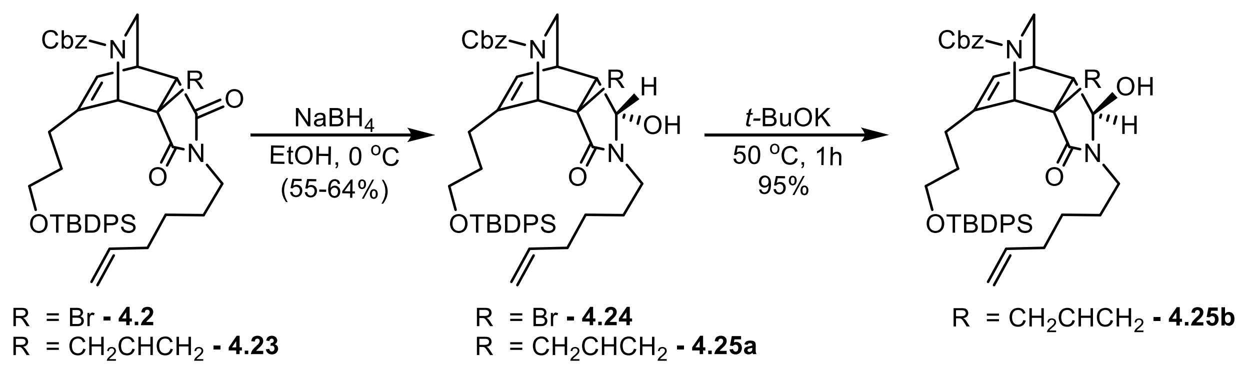
Approach Toward the Ring-Expansion

Shifting our focus again toward the expansion of the maelimide, we next investigated strategies to effect ring expansion and yield the desired 6-membered piperidine ring as seen in xestocyclamine A. To this end, using conditions previously employed by Wenzler and coworkers,[60] allylation of cycloadduct **4.2** occurred cleanly, in high yields, and stereoselectively (Scheme **4.6**). With the quaternary center installed, we next hoped to gain selectivity upon nucleophilic addition and further functionalization. Test experiments were conducted on the reduction of **4.2** and **4.23** with $NaBH_4$ and gave hemiaminals **4.24** and **4.25a** which demonstrated exclusive reactivity at the distal carbonyl. Reduction appeared to occur from the convex face as indicated by ^1H NOESY correlations for both bromide and allyl functional groups. Although inconsequential in the next steps, epimerization of hemiaminal **4.25a** to **4.25b** under basic conditions was necessary for full characterization and assignment.

Synthesis of quaternary center and eneamide

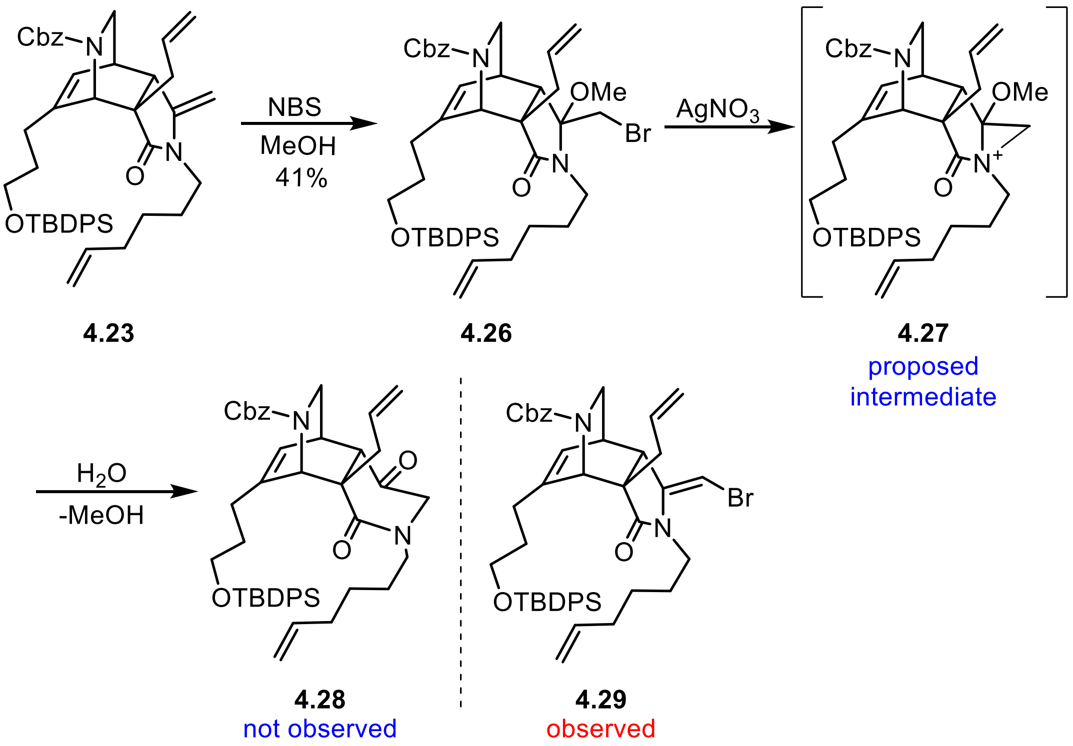


Model system imide reduction



Scheme 4.6 Allylation and **r**eduction of cycloadduct intermediates.

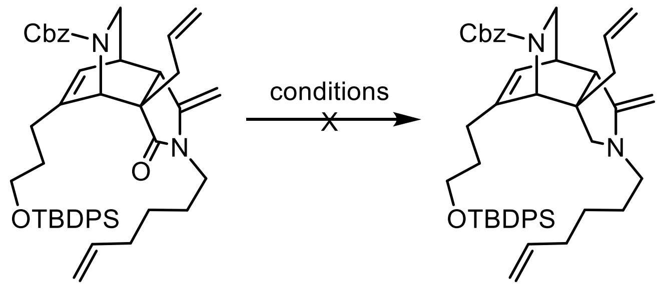
Next from **4.22**, we found upon reaction with MeMgBr, the same selectivity was obtained, and subsequent treatment with TFA furnished eneamide **4.23**. Now with the last remaining carbon installed, our next obstacle became the ring expansion. When treated with NBS in MeOH, the methoxy hemiaminal **4.26** was isolated in modest yields (Scheme **4.7**). From the alkyl bromide, we envisioned treatment with $AgNO_3$ would precipitate AgCl and produce aziridinium **4.27** followed by fragmentation of the central C-N bond upon donation of electrons from the methoxy moiety. However, when treated with $AgNO_3$ or $AgSbF_6$, piperidone **4.28** was not observed and instead vinyl bromide **4.29** was isolated in 47 % yield. It appears both Ag (I) salts function as Lewis acids and facilitate loss of methoxide, from which tautomerization proceeds to the enamine. Attempts to induce aziridinium formation from the alkyl chloride and iodide were also unsuccessful.



Scheme 4.7 Allylation and **r**eduction of cycloadduct intermediates.

Due to the electron poor nature of the amide, formation of the aziridinium appeared to be suppressed. Although an electron withdrawing group would accelerate fragmentation, if aziridinium is never generated it serves no purpose. Therefore, a variety of reductants were reacted with eneamide **4.23** hoping to arrive at the basic tertiary amine (Table **4.2**). Remarkably, the amide proved incredibly resistant to reduction, even upon treatment with strong reducing agents (*e.g.* LAH, Et_3BHLi.). The only reactivity observed was entry 5 where LAH reduced the benzyl carbamate to give the methyl amine. Perhaps reassuringly, in Fürstner and coworkers' total synthesis of xestocyclamine A, reduction was performed in the last step for both approaches

(Schemes **2.9** and **2.10**). Presumably the adjacent quaternary center restricts hydride addition, and we hypothesized that construction of the northern macrocycle may attenuate this observed lack of reactivity.

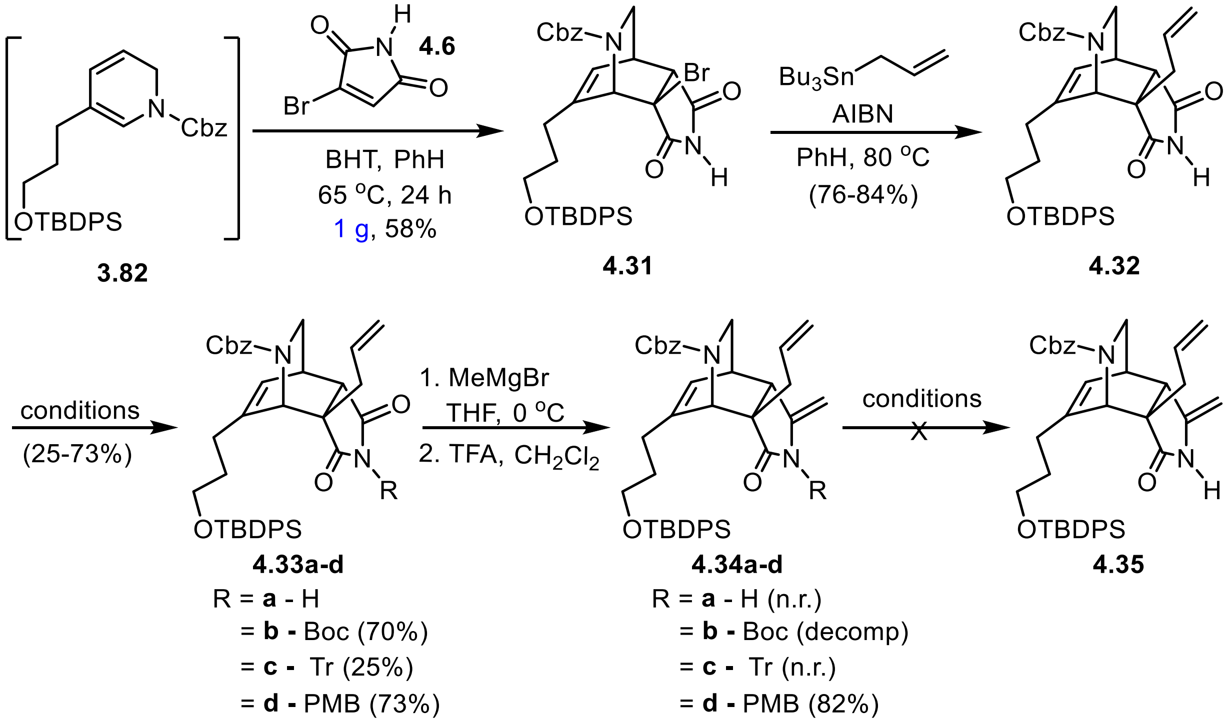


4.23 **4.30**

entry	reductant	equivalents	temperature	solvent	Result
1	DIBAL-H	2	0 °C	2	n.r.
2	Red-Al	2	65 °C	THF	n.r.
3	$LiBH_4$	3	0 °C	THF/MeOH	n.r.
4	Et_3BHLi	10	rt	THF	n.r.
5	LAH	5	0 °C	THF	decomp
6	Et_3OBF_4, $NaBH_4$	1.5	rt	1.5	n.r.

Table 4.2 Screening of reductants against eneamide.

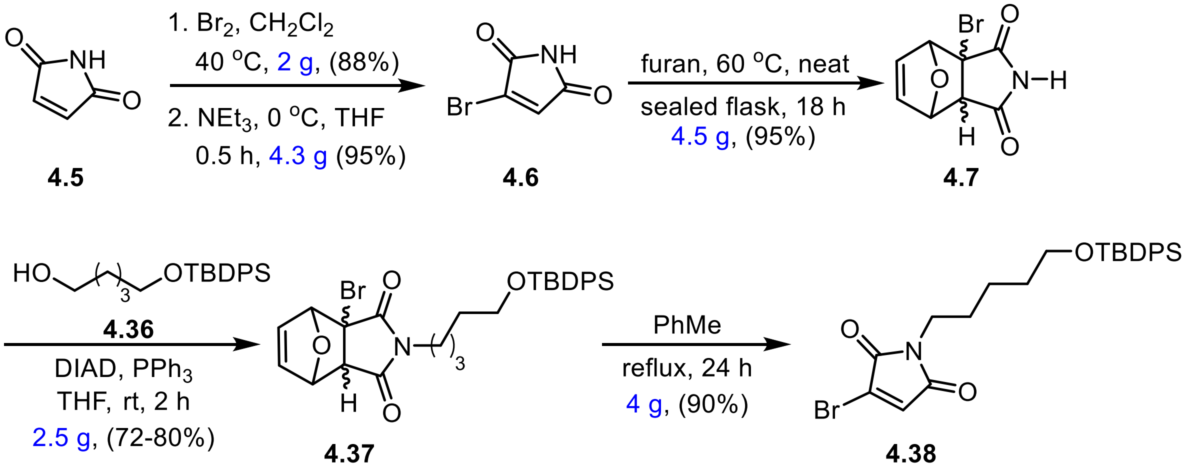
Before abandoning the ring expansion approach, we next investigated the use of a secondary amide prior to the cascade sequence. We hypothesized that perhaps the charged nature of the aziridinium intermediate **4.27**, in addition to its strained structure, may provide an activation barrier too high to overcome while a neutral aziridine may be more accessible. Thus, cycloaddition with bromomaleimide **4.6** and subsequent allylation to cycloadduct **4.32** proceeded in good yields (Scheme **4.8**). However, access to the eneamide was unsuccessful even upon treatment with 6 eq. of MeMgBr. Presumably, the deprotonated amide anion prevents nucleophilic addition at the adjacent carbonyl due to electrostatic repulsion. Therefore, several analogues of protected imides were synthesized **4.33a-c**. The Boc protecting group proved labile in the presence of MeMgBr while the trityl group resulted in no reaction. From the PMB-protected amide, eneamide **4.34c** was accessed in 82% over two steps. Unfortunately, all attempts at deprotection employing reagents such as: DDQ, CAN, $AlCl_3$ and anisole, or neat TFA failed to provide eneamide **4.35**. Again, with lack of success in the modification of the 5-membered ring we planned to focus on the northern macrocycle prior to the ring expansion in hopes of improving reactivity.



Scheme 4.8 Approach toward aziridination from the secondary eneamide.

Installation of the Northern Macrocycle by B-alkyl Suzuki Cross-coupling reaction

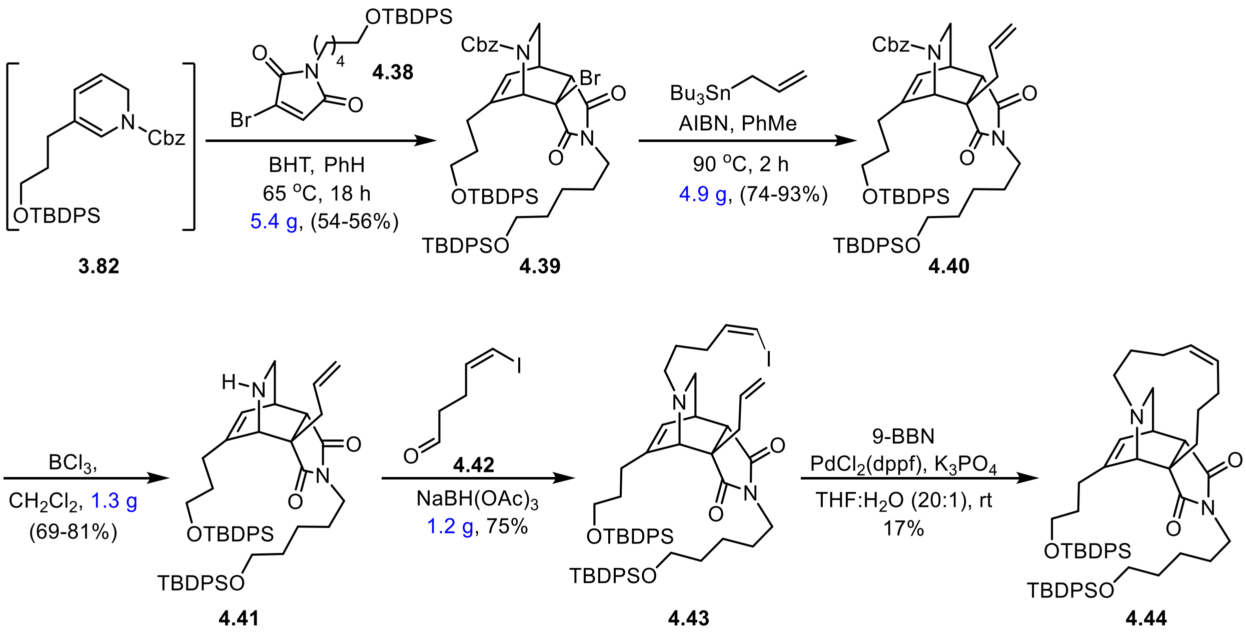
Shifting our attention to away from the ring expansion, we predicted the completed northern macrocyclic ring would induce a conformational change which would facilitate reduction of the amide and thus aziridine formation. Moving forward, we planned on employing a B-alkyl Suzuki cross-coupling reaction as previously mentioned (Scheme **3.1**), similar to both the Danishefsky and Fürstner approaches (Schemes **2.5** and **2.9**), respectively. However, the required hydroboration would likely fail to provide regioselectivity between the desired allylic handle and hexenyl alkyl chain, and thus we proceeded to synthesize a dienophile containing a terminal protected alcohol instead (Scheme **4.9**). The chemistry mirrored (Scheme **4.2**) except we found use of Mitsunobu conditions provided N-alkylated imide **4.38** in more robust yields.



Scheme 4.9 Synthesis of maleimide dienophile with terminal protected alcohol.

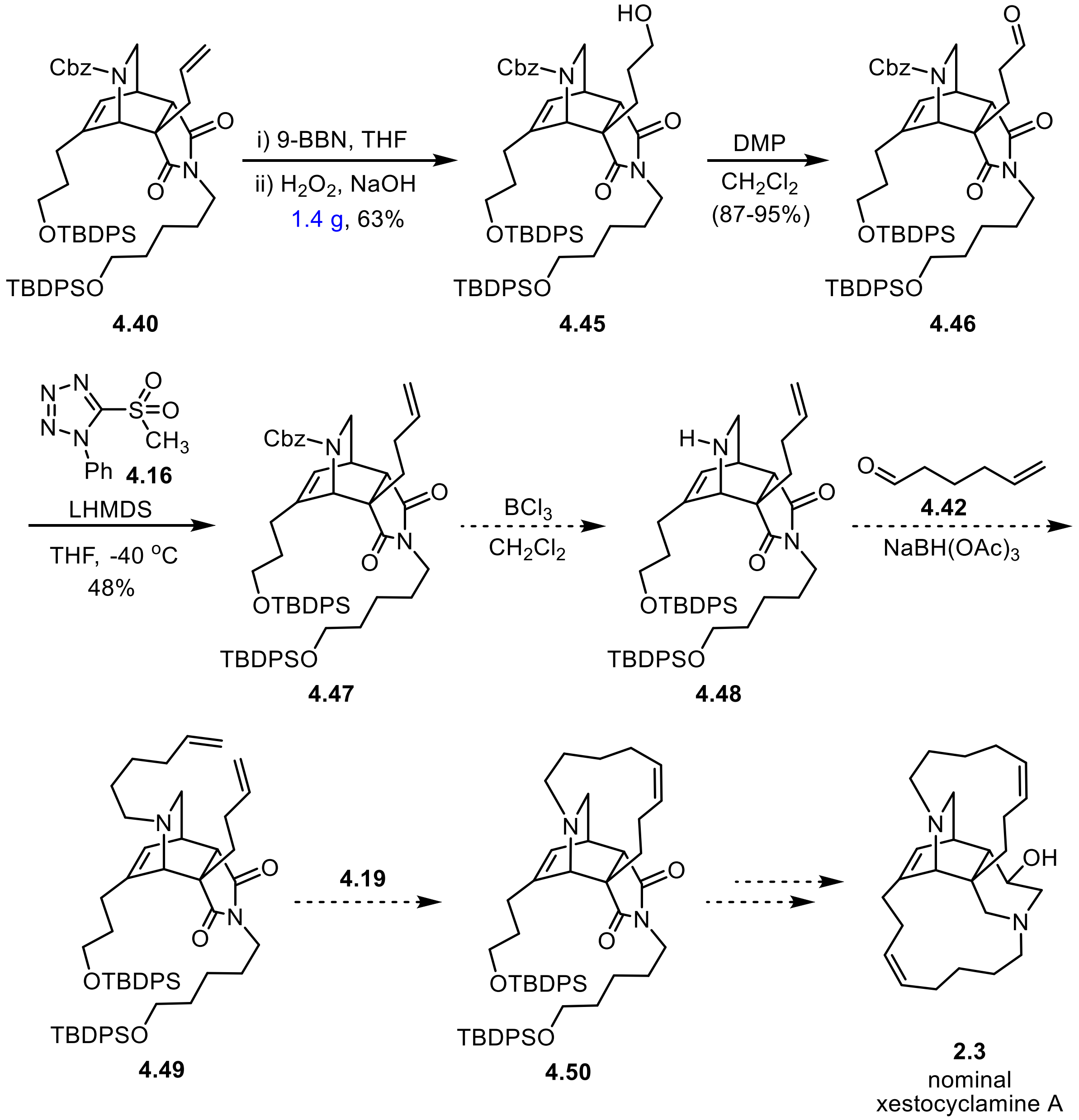
Employing the same methodologies as used previously, access to the secondary amine **4.41** was achieved on gram scale (Scheme **4.10**). Alkylation of the amine was first done by displacement of a tosylate leaving group, but reductive amination employing aldehyde **4.42** and $NaBH(OAc)_3$ was found to give improved yields. Vinyl iodide **4.42** was prepared from commercially available 4-pentyn-1-ol using chemistry reported by the Denmark group.[88] With both the vinyl iodide and allylic alkene installed, substrate **4.43** was now primed to commence the B-alkyl Suzuki cross-coupling. However, both the hydroboration and cross-coupling presented considerable challenges and required extensive optimization. Namely, the borane source proved to be key, as solutions of 9-BBN in hexanes or THF failed to provide full conversion.

Catalytic systems which utilized alkylboranes and Wilkinson's catalyst showed moderate reactivity.[89] Fortunately it was found that 9-BBN dimer, a crystalline solid known for its excellent stability to heat and atmospheric oxygen, gave full conversation.[90,91] Proceeding to the cross-coupling, a variety of bases and solvent systems were investigated, whereas the catalyst, $PdCl_2$(dppf), remained constant due to its bidentate geometry which promotes reductive elimination and prohibits β-hydride elimination.[92] Thallium bases such as Tl_2CO_3 were screened due to their rate enhancement as reported by Kishi and coworkers.[93] Additionally, $AsPh_3$ was investigated due to reports[94] at improving Pd-mediated cross-couplings, but unfortunately both additives failed to provide **4.44**. Lastly, attempts at an intermolecular cross-coupling were briefly studied but were unfruitful.



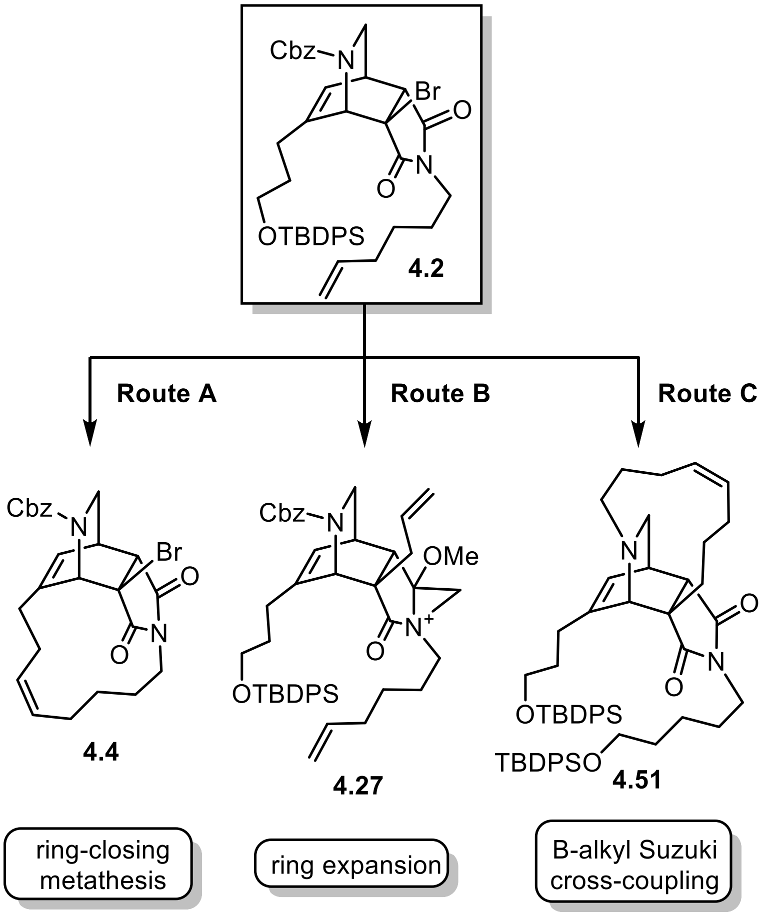
Scheme 4.10 Synthesis of the Northern macrocyclic ring.

We were then pleased to find that K_3PO_4 provided macrocycle **4.44** in 17%, but unfortunately this proved to be irreproducible. Albeit, when repeated, other macrocyclic products were isolated as indicated by HPLC-MS and ^{1}H NMR analysis and suggested the undesired side products may be reduced hemiaminal species or boron adducts. Regardless, due to the incredibly fickle nature of the B-alkyl Suzuki reaction, we next took into consideration the recent report by the Fürstner group and decided to pursue the nominal Δ23 isomer **2.3**.[95]



Scheme 4.11 Synthesis of Δ23 Northern macrocycle.

Our approach toward the Δ23 isomer **4.50**, began with the homologation of the allylic handle to provide the correct substitution pattern. Hydroboration-oxidation with 9-BBN and basic peroxide gave **4.45** in 63%, from which the resulting alcohol was oxidized using Dess-Martin periodinane to give aldehyde **4.46**. Olefination under Julia-Kocienski conditions produced alkene **4.47** in 48%. Moving forward, BCl_3 mediated deprotection and subsequent reductive amination would set the stage for macrocyclization of the Northern ring. Investigations into the ring expansion and closure of the southern macrocycle would then be conducted in due time.

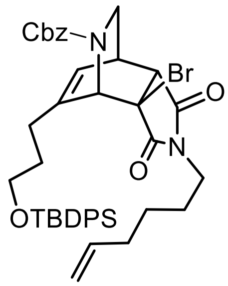


Scheme 4.12 Summary of routes from advanced cycloadduct toward each ring system.

Conclusion to Chapter 4

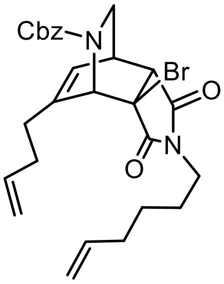
From the advanced cycloadduct intermediate **4.2**, a number of investigations were conducted to develop routes to access the remainder ring systems. Route A successfully accessed macrocycle **4.4** through ring-closing metathesis utilizing Grubbs Z-Selective catalyst. Route B focused on expansion of the 5-membered ring and led to an aziridination strategy and eneamide precursor that awaits further functionalization. Route C provided limited success toward the Northern macrocycle and gave **4.51** in low irreproducible yields.

Experimental Methods

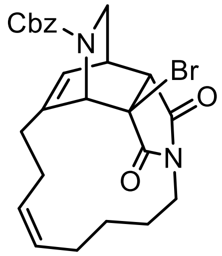


4.2: To a sealed vessel was charged **3.82** (7.68 g, 11.4 mmol) in benzene (57 mL) and DABCO (2.56 g, 22.8 mmol). The vessel was evacuated and heated at 120 °C under static vacuum (ca. 0.01 torr) for 3 h. The reaction mixture was cooled to room temperature, filtered, and the filtrate diluted with water (100 mL), and extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with brine (25 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The crude residual oil was dissolved in benzene (3.8 mL) to which BHT (84 mg, 0.38 mmol) and **4.10** (982 mg, 3.80 mmol) were added. The reaction mixture was placed under static vacuum and maintained at 65 °C for 18 h. The reaction mixture was then cooled to room temperature and concentrated *in vacuo*. The resulting residue was purified via flash chromatography (silica gel, gradient elution, 0-20% EtOAc in hexanes) to yield 1.70 g (58%) of cycloadduct **4.2** as a red oil: R_f 0.3 (8:2 hexanes/EtOAc); ^1H NMR (400 MHz, $CDCl_3$) ∂ 7.65-7.28 (m, 15H), 5.74 (m, 2H), 5.15-4.91 (m, 5H), 3.57-3.38 (m, 5H), 3.22 (m, 1H), 3.12-2.96 (m, 2H), 2.27-1.94 (m, 4H), 1.60-1.20 (m, 8H), 1.04 (s, 9H); ^{13}C NMR (400 MHz,

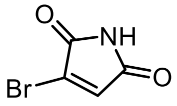
$CDCl_3$) ∂ 174.5 ,174.4, 172.7, 172.6, 155.2, 154.6, 145.5, 145.0, 137.9, 137.8, 136.3, 136.1, 135.5, 135.5, 133.7, 133.6, 129.6, 129.6, 128.4, 128.2, 128.1, 128.0, 127.8, 127.6, 123.9, 123.6, 115.0, 67.5, 67.3, 62.3, 62.2, 57.0, 56.8, 56.3, 55.8, 53.0, 52.9, 45.8, 45.4, 39.2, 34.1, 33.9, 33.0, 29.7, 29.6, 29.1, 29.0, 26.8, 26.6, 25.7, 25.7, 19.1.



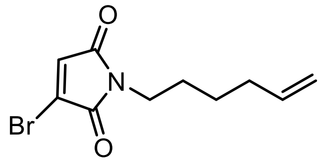
4.3: To a solution of sulfone **4.16** (149 mg, 0.663 mmol) in THF (2.6 mL) at -78 °C was added LHMDS (1 M in THF, 0.73 mL, 0.730 mmol) and maintained at -78 °C for 1 h. A solution of **4.2** (351 mg, 0.663 mmol) in THF (4 mL) was then added dropwise via cannula and the reaction mixture maintained for 0.5 h and then warmed to -40 °C for 2 h. Reaction mixture was diluted with brine (10 mL), and extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The resulting residue was purified via flash chromatography (silica gel, gradient elution, 5-15% EtOAc in hexanes) to yield 173 mg (53%) of alkene **4.3** as a clear yellow oil: R_f 0.3 (8:2 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) ∂ 7.40 (m, 5H), 5.85 (t, *J* = 7.0 Hz, 1H), 5.74 (m, 1H), 5.61 (m, 1H), 5.21-4.89 (m, 7H) 3.52 (td, *J* = 8.5, 1.6 Hz, 1H), 3.45 (m, 2H), 3.31 (m, 1H), 3.14 (m, 1H), 3.09 (t, *J* = 2.8 Hz, 1H), 2.24-2.04 (m, 6H), 1.50 (m, 2H), 1.33 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 174.5, 174.4, 172.8, 172.6, 155.3, 154.7, 145.2, 144.6, 137.8, 136.7, 136.5, 136.3, 136.1, 128.5, 128.4, 128.2, 128.1, 128.0, 127.8, 124.2, 123.8, 115.6, 115.5, 115.0, 67.5, 67.4, 56.9, 56.8, 56.3, 55.8, 53.0, 52.9, 45.9, 45.6, 39.2, 34.1, 33.9, 33.0, 32.7, 30.4, 30.3, 26.6, 25.7, 25.6; LRMS $[M+H]^+$ calc. for $C_{27}H_{31}BrN_2O_4$ (m/z): 527.5, found 527.6



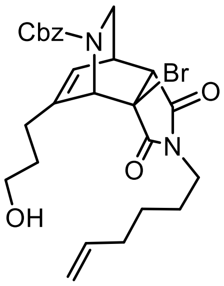
4.4: To a solution of **4.3** (38 mg, 0.072 mmol) in PhH (36 mL) at 80 °C was added a solution of Grubbs Z-Selective catalyst (5 mg, 0.007 mmol) in PhH (1 mL) via syringe pump over 3 h. The reaction mixture was maintained at 80 °C for 18 h. The reaction vessel was opened to the atmosphere and stirred for 5 min, concentrated *in vacuo*, and purified via flash chromatography (silica gel, gradient elution, 0-30% EtOAc in hexanes) to yield 6 mg (17%) of **4.4** as a yellow oil: R$_f$ 0.3 (7:3 hexanes/EtOAc); ^{1}H NMR (400 MHz, CDCl$_3$) ∂ 7.36 (m, 5H), 5.98 (m, 1H), 5.57 (m, 2H), 5.20 (m, 2H), 5.10-4.94 (d, *J* = 64.8 Hz, 1H), 3.55 (m, 3H), 3.38 (m, 1H), 3.20 (dt, *J* = 10.7, 2.7 Hz, 1H), 3.11 (m, 1H), 2.51 (m, 1H), 2.13-1.82 (m, 6H), 1.68-1.47 (m, 3H); ^{13}C NMR (400 MHz, CDCl$_3$) δ 174.8, 173.1, 155.5, 154.8, 145.7, 145.0, 136.3, 130.9, 130.8, 129.4, 129.3, 128.5, 128.1, 128.0, 127.8, 123.1, 122.8, 67.5, 67.4, 57.6, 57.1, 57.0, 53.3, 53.1, 45.5, 45.2, 39.8, 33.8, 33.6, 33.5, 27.7, 27.5, 26.3, 22.0; LRMS [M+H]$^+$ calc. for C$_{25}$H$_{28}$BrN$_2$O$_4$ (m/z): 499.12, found 499.4



4.6: To a solution of maleimide (2.0 g, 20.6 mmol) in CH$_2$Cl$_2$ (20 mL) was added bromine (1.2 mL, 22.6 mmol). The reaction mixture was maintained at reflux for 3 h and then allowed to cool to 0 °C. The resulting precipitate was filtered and rinsed thoroughly with cold CHCl$_3$ to provide 4.39 g (83%) of dibromomaleimide as a white solid. To a cooled solution of crude dibromomaleimide (4.39 g, 17.1 mmol) in THF (70 mL) at 0 °C was added NEt$_3$ (2.0 mL, 14.6 mmol) over 10 min and maintained at 0 °C for 30 min. The reaction mixture was diluted in water (50 mL) and the extracted with EtOAc (3 x 25 mL). The combined organic extracts were washed with brine (25 mL), dried (MgSO$_4$), and concentrated *in vacuo* to afford 2.70 g (90%) of **4.6** as a white solid that was used without further purification. Spectral data matched reported literature values.[96]

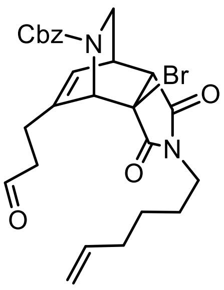


4.10: To a sealed flask was charged a suspension **4.6** (2.70 g, 15.4 mmol) in furan (20 mL) and heated at 60 °C for 24 h. The reaction mixture was cooled to room temperature and concentrated *in vacuo* to yield a white solid that was used without further purification. The resulting solid was dissolved in acetone (57 mL), to which K_2CO_3 (12.0 g, 86.9 mmol) and 6-bromohex-1-ene (4.7 mL, 34.8 mmol) were added. The resulting mixture was heated at 70 °C in a sealed tube for 2 h. The reaction mixture was allowed to cool to room temperature, filtered, diluted with water (100 mL), and extracted with EtOAc (3 x 30 mL). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The resulting residue was purified via flash chromatography (silica gel, gradient elution, 0-10% EtOAc in hexanes) to give 2.55 g (47%) of a mixture of diastereomers as a yellow oil. The resulting mixture was dissolved in toluene (20 mL) and heated in an open flask at 110 °C for 48 h. The reaction mixture was allowed to cool to room temperature and concentrated *in vacuo* to yield 2.64 g (52% over 3 steps) of **4.10** as a pure red oil: ^{1}H NMR (400 MHz, $CDCl_3$) ∂ 6.79 (s, 1H), 4.73 (ddt, *J* = 17.0, 10.2 , 6.8 Hz, 1H), 4.91 (m, 2H), 3.49 (t, *J* = 7.2 Hz, 2H), 2.01 (q, *J* = 7.1 Hz, 2H), 1.54 (p, *J* = 7.6 Hz, 2H), 1.31 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) ∂168.5, 165.3, 138.0, 131.7, 131.2, 114.9, 38.6, 33.0, 27.8, 25.8.

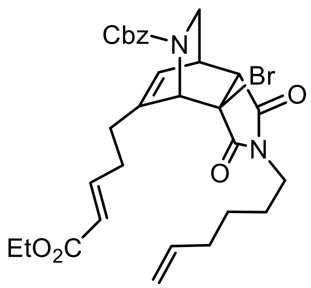


4.13: To a solution of **4.2** (339 mg, 0.440 mmol) in MeCN (1.8 mL) was added 70% HF-pyridine (0.32 mL, 17.6 mmol) in one portion. Reaction mixture was maintained at room temperature for 2 h, quenched with saturated aq. $NaHCO_3$ (30 mL) and extracted with EtOAc (3 x 5 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The resulting residue was purified via flash chromatography (silica gel, gradient elution, 0-10% EtOAc in hexanes) to yield 225 mg (95%)

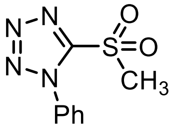
of **4.13** as a clear yellow oil: R_f 0.3 (1:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) ∂ 7.35 (m, 5H), 5.88, (m, 1H), 5.75 (m, 1H), 5.22-4.97 (m, 5H), 3.53 (m, 5H), 3.31 (m, 1H), 3.15 (app. dt, *J* = 10.5, 2.7 Hz, 1H), 3.10 (t, *J* = 2.5 Hz, 1H), 2.15 (dt, *J* = 29.9, 6.2 Hz, 2H), 2.05 (m, 2H), 1.73-1.46 (m, 4H), 1.33 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 174.4, 174.3, 172.8, 155.4, 154.6, 145.6, 144.9, 137.9, 136.2, 128.5, 128.3, 128.2, 128.1, 127.8, 124.1, 123.7, 115.0, 67.5, 67.4, 61.6, 56.9, 56.7, 56.3, 55.8, 53.0, 52.9, 45.9, 45.6, 39.2, 34.1, 33.9, 33.0, 29.7, 29.6, 29.5, 29.3, 26.6, 25.7, 14.0; LRMS $[M+H]^+$ calc. for $C_{26}H_{31}BrN_2O_5$ (m/z): 531.45, found 531.4



4.14: To a solution of **4.13** (322 mg, 0.606 mmol) in CH_2Cl_2 (2.4 mL) was added DMP (282 mg, 0.666 mmol) in one portion. Reaction mixture was maintained at room temperature for 3 h, then quenched with a 1:1 solution of $NaHCO_3$:$Na_2S_2O_3$ (10 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The resulting residue was purified via flash chromatography (silica gel, gradient elution, 0-30% EtOAc in hexanes) to yield 284 mg (89%) of **4.14** as a clear yellow oil: R_f 0.3 (7:3 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) ∂ 9.54 (d, *J* = 36 Hz, 1H), 7.31 (m, 5H), 5.83 (d, *J* = 6.3 Hz, 1H), 5.71 (m, 1H), 5.17-4.19 (m, 5H), 3.48 (m, 3H), 3.27 (m, 1H), 3.10 (m, 2H), 2.54 (m, 4H), 2.02 (m, 2H), 1.47 (br s, 2H), 1.3 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 200.0, 199.6, 174.2, 174.1, 172.7, 172.6, 155.3, 154.5, 144.0, 143.4, 137.8, 136.2, 136.1, 128.4, 128.3, 128.2, 128.0, 127.7, 124.7, 124.6, 115.0, 67.5, 67.4, 56.7, 56.5, 56.1, 55.4, 45.6, 45.1, 40.1, 39.1, 34.0, 33.8, 32.9, 26.5, 25.7, 25.7, 25.6; LRMS $[M+H]^+$ calc. for $C_{26}H_{29}BrN_2O_5$ (m/z): 531.13, found 531.4

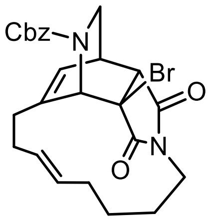


4.15: To a solution of **4.14** (50 mg, 0.094 mmol) in THF (0.9 mL) was added carboxyethyl methylene triphenylphosphine (39 mg, 0.113 mmol) in one portion and stirred at room temperature for 3 h. Reaction mixture was quenched with water (10 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The resulting residue was purified via flash chromatography (silca gel, gradient elution, 0-20% EtOAc in hexanes) to yield 41 mg (75%) of **4.15** as a clear yellow oil: R_f 0.3 (7:3 hexanes/EtOAc); ^1H NMR (400 MHz, $CDCl_3$) ∂ 7.29 (m, 5H), 6.69 (m, 1H), 5.81 (m, 1H), 5.66 (m, 2H), 5.17-4.87 (m, 5H), 4.08 (m, 2H), 3.38 (m, 3H), 3.23 (m, 1H), 3.03 (m, 2H), 2.16 (m, 4H), 1.99 (m, 2H), 1.43 (m, 2H), 1.21 (m, 6H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 174.5, 174.4, 173.0, 172.8, 166.3, 155.5, 154.7, 146.8, 146.4, 144.7, 144.1, 138.0, 136.4, 136.2, 128.7, 128.6, 128.5, 128.2, 127.9, 124.8, 124.7, 122.5, 115.2, 67.8, 67.7, 60.5, 60.4, 60.3, 56.9, 56.8, 56.3, 55.6, 53.1, 53.0, 46.0, 45.7, 39.4, 34.3, 34.1, 33.2, 32.0, 31.9, 28.9, 26.8, 25.9, 14.4, 14.3.

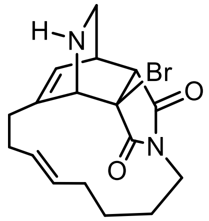


4.16: To a solution of 1-phenyl-1H-tetrazole-5-thiol (1.5 g, 8.42 mmol) in THF (33 mL) was added (NEt_3, 8.83 mmol) and MeI (0.6 mL, 9.26 mmol) sequentially. Reaction mixture was stirred for 2 h at room temperature, diluted with water (50 mL) and extracted (3 x 20 mL) EtOAc. The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The resulting residue was purified via recrystallization (1:1:1) Hexane/Et_2O/CH_2Cl_2 to yield 1.41 g (87%) of methyl thioether as a light-yellow solid: R_f 0.5 (95:5 MeOH/ CH_2Cl_2). Spectral data matched reported literature values. [97]

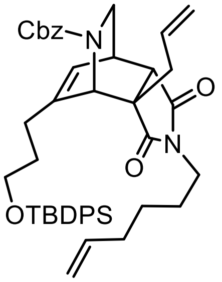
To methyl thioether (1.41 g, 7.34 mmol) in EtOH (29 mL) was added ammonium molybdate tetrahydrate (3.63 g, 2.94 mmol) and H_2O_2 (30% wt/wt, 1.3 mL, 44.0 mmol), sequentially. Reaction mixture was stirred overnight at room temperature, diluted with water, and extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The resulting residue was purified via recrystallization (1:1:1) Hexane/Et_2O/CH_2Cl_2 to yield 1.04 g (63%) of sulfone **4.16** as a white solid: R_f 0.3 (7:3 hexanes/EtOAc). Spectral data matched reported literature values.[97]



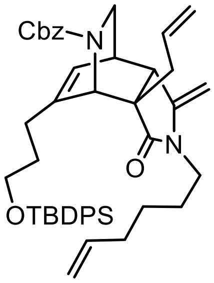
4.20: To degassed solution of Grubbs-II catalyst (6 mg, 0.007 mmol) in CH_2Cl_2 (5 mL) was added a solution of **4.3** (39 mg, 0.074 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was heated at 40 °C for 2 h under static vacuum (ca. 0.01 torr). The reaction vessel was then opened to the atmosphere and stirred for 5 min, concentrated *in vacuo*, and purified via flash chromatography (silica gel, gradient elution, 0-10% EtOAc in hexanes) to yield 20 mg (54%) of macrocycle **4.20** as a yellow oil: R_f 0.3 (9:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) ∂ 7.36 (m, 5H), 5.92 (m, 1H), 5.38-5.16 (m, 4H), 5.09-4.92 (d, *J* = 64.5 Hz, 1H), 3.51 (m, 2H), 3.41-3.33 (m, 2H), 3.13 (dt, *J* = 10.6, 2.6 Hz, 1H), 3.08 (m, 1H), 2.49-2.00 (m, 5H), 1.75-1.44 (m, 4H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 175.1, 175.0, 173.1, 155.5, 154.9, 143.9, 143.2, 136.3, 131.9, 131.8, 129.1, 129.0, 128.4, 128.1, 128.0, 127.8, 122.6, 122.2, 67.4, 57.3, 57.0, 56.7, 53.2, 53.0, 46.3, 46.0, 40.1, 34.0, 33.8, 32.3, 32.2, 29.7, 26.3,26.2, 25.1; LRMS $[M+H]^+$ calc. for $C_{25}H_{28}BrN_2O_4$ (m/z): 499.12, found 499.4



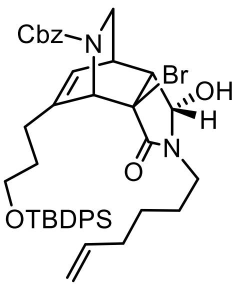
4.21: To a solution of **4.20** (25 mg, 0.032 mmol) in CH_2Cl_2 (0.3 mL) was added BCl_3 (1 M in CH_2Cl_2, 0.1 mL, 0.97 mmol). The reaction mixture was allowed to stir at room temperature overnight, quenched with saturated aq. $NaHCO_3$ to pH = 9 and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The resulting residue was purified via flash chromatography (silica gel, gradient elution, 0-5% methanol in CH_2Cl_2) to yield 7 mg (58%) of amine **4.21** as a yellow oil: R_f 0.2 (95:5 CH_2Cl_2:MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) ∂ 5.90 (m, 1H), 5.41-5.20 (m, 2H), 3.78 (s, 1H), 3.51-3.41 (m, 2H), 3.20 (m, 1H), 3.12 (m, 1H), 3.05 (d, *J* = 2.9 Hz, 1H), 2.66 (dd, *J* = 10.2, 2.4 Hz, 1H), 2.50 (m, 1H), 2.22-2.06 (m, 5H), 1.70-1.54 (m, 4H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 175.5, 173.6, 143.2, 131.7, 129.3, 122.2, 58.4, 53.2, 44.2, 40.0, 33.2, 32.2, 29.8, 29.6, 26.3, 26.2, 25.1



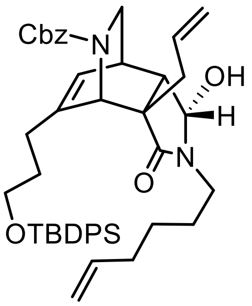
4.22: To a solution of **4.2** (1.53 mg, 1.99 mmol) and AIBN (33 mg, 0.20 mmol) in PhMe (6.6 mL) was added tributylallyl stannane (1.2 mL, 3.97 mmol). The reaction mixture was maintained at 90 °C for 2 h, allowed to cool to room temperature and concentrated *in vacuo.* The resulting residue was purified via flash chromatography (silica gel:K_2CO_3 (10:1), gradient elution, 0-10% EtOAc in hexanes) to yield 1.17 g (80%) of **4.22** as a yellow oil: R_f 0.3 (9:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) ∂ 7.63-7.30 (m, 15H), 5.69 (m, 2H), 5.53 (m, 2H), 5.20-4.89 (m, 6H), 4.77-4.63 (d, *J* = 57.9 Hz, 1H), 3.64-3.47 (m, 2H), 3.34-3.16 (m, 4H), 2.98 (ddd, *J* = 32.9, 10.7, 2.5 Hz, 1H), 2.73 (ddd, *J* = 39.9, 13.4, 6.8, 1H), 2.51 (app t, *J* = 3.5 Hz, 1H), 2.24-2.01 (m, 5H), 1.78- 1.59 (m, 2H), 1.44-1.29 (m, 5H), 1.04 (s, 9H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 178.3, 178.2, 177.2, 177.0, 155.4, 154.9, 146.3, 145.7, 138.0, 136.4, 136.1, 135.5, 133.7, 131.3, 131.2, 129.5, 129.5, 128.5, 128.4, 128.2, 128.0, 127.8, 127.6, 126.9, 123.3, 123.0, 120.2, 114.8, 67.4, 67.1, 62.5, 62.4, 54.7, 54.2, 53.4, 53.3, 46.3, 46.2, 45.9, 38.5, 38.4, 33.9, 33.7, 33.1, 29.9, 29.3, 29.2, 26.9, 26.8, 25.8, 25.8, 23.4



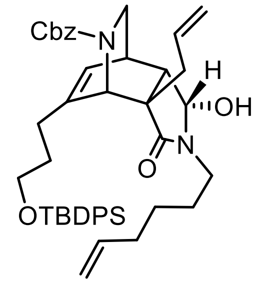
4.23: To a solution of **4.22** (100 mg, 0.137 mmol) in THF (0.6 mL) at 0 °C, was added MeMgBr (1 M in Et_2O, 0.41 mL, 0.41 mmol) and stirred for 1 h. Reaction mixture was quenched with saturated aq. NH_4Cl and extracted with EtOAc (3 x 5 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The resulting oil was dissolved in CH_2Cl_2 (0.85 mL) and cooled to 0 °C to which TFA (0.02 mL, 0.27 mmol) was added and allowed to stir for 1 h. Reaction mixture was neutralized to pH = 8 with saturated aq. $NaHCO_3$ and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried ($MgSO_4$), concentrated *in vacuo*. The resulting residue was purified via flash chromatography (silica gel, gradient elution, 0-30% EtOAc in hexanes) to yield 72 mg (72% Over 2 Steps) of **4.23** as a yellow oil: R_f 0.3 (7:3 hexanes/EtOAc); ^1H NMR (400 MHz, $CDCl_3$) ∂ 7.63-7.30 (m, 15H), 5.70 (m, 2H), 5.55 (m, 2H), 5.10-4.91 (m, 6H), 4.66-4.53 (d, *J* = 50.8 Hz, 1H), 4.14 (m, 2H), 3.57-3.47 (m, 2H), 3.32-3.23 (m, 3H), 2.90-2.83 (m, 3H), 2.59 (m, 2H), 2.17-2.02 (m, 5H), 1.78- 1.48 (m, 2H), 1.42-1.29 (m, 6H), 1.04 (s, 9H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 175.3, 155.4, 155.1, 148.8, 148.6, 145.8, 145.1, 138.2, 138.1, 136.8, 136.4, 135.5, 133.9, 133.8, 132.6, 132.5, 129.5, 128.4, 128.3, 128.1, 128.0, 127.9, 127.7, 127.5, 123.6, 123.3, 118.8, 118.7, 114.7, 83.8, 83.5, 67.1, 66.8, 62.7, 62.6, 54.5, 54.0, 53.6, 46.3, 46.1, 43.2, 39.5, 37.7, 37.4, 33.2, 33.2, 29.9, 29.4, 29.3, 26.8, 26.0, 25.9, 25.6, 25.6, 19.1



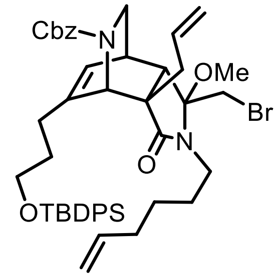
4.24: To a solution of **4.2** (65 mg, 0.084 mmol) in EtOH (0.5 mL) at 0 °C, was added $NaBH_4$ (13 mg, 0.338 mmol). The reaction mixture was warmed to room temperature and stirred overnight. Reaction mixture was quenched with water (10 mL) and extracted with EtOAc (3 x 5 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The resulting oil was purified via flash chromatography (silica gel, gradient elution, 10-30% EtOAc in hexanes) to yield 36 mg (55%) of **4.24** as a yellow oil: R_f 0.3 (7:3 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) ∂ 7.63-7.27 (m, 15H), 5.83-5.74 (m, 2H), 5.38 (m, 1H), 5.15-4.90 (m, 5H), 3.59-3.47 (m, 2H), 3.41 (app d, *J* = 10.8 Hz, 1H), 3.31 (m, 1H), 3.10-2.89 (m, 5H), 2.23 (m, 2H), 2.05 (q, *J* = 7.1 Hz, 2H), 1.63-1.30 (m, 6H), 1.03 (s, 9H); ^{13}C NMR (400 MHz, $CDCl_3$) 168.9, 155.6, 155.3, 138.4, 136.7, 136.5, 135.7, 134.0, 129.7, 128.6, 128.2, 128.1, 127.9, 127.8, 125.0, 115.0, 81.5, 67.4, 67.2, 63.7, 62.7, 62.6, 57.8, 57.3, 50.7, 50.6, 47.0, 46.6, 40.1, 33.3, 32.4, 32.2, 29.9, 29.6, 29.4, 27.0, 26.5, 26.0, 19.3, 39.4, 34.3, 34.1, 33.2, 32.0, 31.9, 28.9, 26.8, 25.9, 14.4, 14.3



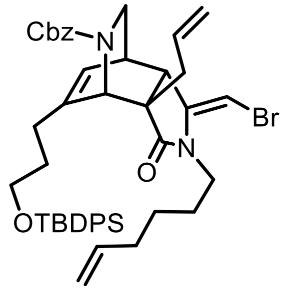
4.25a: To a solution of **4.22** (427 mg, 0.584 mmol) in EtOH (5.8 mL) at 0 °C, was added $NaBH_4$ (88 mg, 2.34 mmol). The reaction mixture was maintained at 0 °C for 0.5 h and then stirred at room temperature for 18 h. Reaction mixture was quenched with water (10 mL) and extracted with EtOAc (3 x 5 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The resulting oil was purified via flash chromatography (silica gel, gradient elution, 10-30% EtOAc in hexanes) to yield 232 mg (54%) of **4.25a** as a yellow oil: R_f 0.3 (7:3 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) ∂ 7.63-7.30 (m, 15H), 5.70 (m, 2H), 5.55 (m, 2H), 5.10-4.91 (m, 6H), 4.66-4.53 (d, *J* = 50.8 Hz, 1H), 4.14 (m, 2H), 3.57-3.47 (m, 2H), 3.32-3.23 (m, 3H), 2.90-2.83 (m, 3H), 2.59 (m, 2H), 2.17-2.02 (m, 5H), 1.78- 1.48 (m, 2H), 1.42-1.29 (m, 6H), 1.04 (s, 9H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 175.3, 155.4, 155.1, 148.8, 148.6, 145.8, 145.1, 138.2, 138.1, 136.8, 136.4, 135.5, 133.9, 133.8, 132.6, 132.5, 129.5, 128.4, 128.3, 128.1, 128.0, 127.9, 127.7, 127.5, 123.6, 123.3, 118.8, 118.7, 114.7, 83.8, 83.5, 67.1, 66.8, 62.7, 62.6, 54.5, 54.0, 53.6, 53.6, 46.3, 46.1, 43.2, 39.5, 37.7, 37.4, 33.2, 33.2, 29.9, 29.4, 29.3, 26.8, 26.0, 25.9, 25.6, 25.6, 19.1; LRMS [M+H]$^+$ LRMS [M+H]$^+$ calc. for $C_{46}H_{73}N_2O_4Si$ 732.40 (m/z): found 716.8



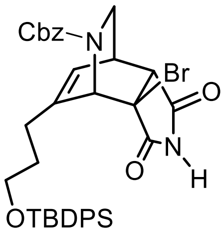
4.25b: To a solution of **4.25a** (30 mg, 0.041 mmol) in THF (1 mL) was added KO*t*-Bu (23 mg, 0.205 mmol) and stirred 50 ^{O}C for 1 h. Reaction mixture quenched with water (5 mL) and extracted with EtOAc (3 x 5 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The resulting oil was purified via flash chromatography (silica gel, gradient elution, 10-30% EtOAc in hexanes) to yield 16 mg (53%) of **4.25b** as a yellow oil: R_f 0.3 (7:3 hexanes/EtOAc); ^{1}H NMR (400 MHz, CDCl3) ∂ 7.63-7.27 (m, 15H), 5.70 (m, 3H), 5.21-4.91 (m, 6H), 4.62 (d, *J* = 51.1 Hz, 1H), 4.40 (d, *J* = 11.7 Hz, 1H), 3.65-3.48 (m, 2H), 3.32 (m, 1H), 3.18 (app d, *J* = 9.5 Hz, 1H), 3.01-2.81 (m, 3H), 2.72 (ddd, *J* = 43.3, 13.1, 5.4 Hz, 1H), 2.16 (m, 4H), 1.93 (d, *J* = 11. 7Hz, 1H), 1.79 (bs, 1H), 1.44 (m, 6H), 1.03 (s, 9H); ^{13}C NMR (400 MHz, CDCl3) δ 173.5, 155.2, 147.0, 138.3, 135.7, 135.2, 135.0, 134.0, 129.6, 128.6, 128.5, 128.3, 128.2, 128.1, 127.8, 127.7, 122.2, 121.9, 119.9, 115.0, 85.6, 77.3, 67.3, 67.0, 62.9, 55.9, 55.7, 48.3, 46.7, 39.8, 39.8, 39.3, 34.7, 34.4, 33.4, 30.1, 29.6, 29.5, 26.9, 26.8, 26.7, 26.1, 19.3, 33.2, 32.0, 31.9, 28.9, 26.8, 25.9, 14.4, 14.3; LRMS [M+H]$^+$ calc. for $C_{46}H_{73}N_2O_4Si$ 732.40 (m/z): found 716.8



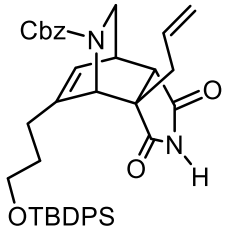
4.26: To a cooled solution of **4.23** (373 mg, 0.512 mmol) in MeOH (2.6 mL) at 0 ^{o}C was added NBS (91 mg, 0.512 mmol) as as single portion. Reaction mixture was maintained at 0 ^{o}C for 1.5 h and concentrated *in vacuo*. The resulting residue was purified via flash chromatography (silica gel, gradient elution, 0-10% EtOAc in hexanes) to yield 175 mg (41%) of **4.26** as a yellow oil: R$_f$ 0.3 (8:2 hexanes/EtOAc); ^{1}H NMR ∂ 7.63-7.28 (m, 15H), 5.88 (m, 1H), 5.72 (m, 1H), 5.58 (m, 1H), 5.16-4.92 (m, 6H), 4.66 (d, *J* = 45.9 Hz, 1H), 3.74-3.36 (m, 5H), 3.27 (m, 1H), 3.18 (s, 3H), 2.93 (m, 2H), 2.48 (m, 1H), 2.4-1.89 (m, 5H), 1.57 (m, 4H), 1.30 (m, 2H), 1.03 (s, 9H); ^{13}C NMR (400 MHz, CDCl$_3$) δ 176.0, 155.2, 146.5, 138.2, 136.4, 135.7, 134.0, 133.3, 129.7, 128.5, 128.2, 128.0, 127.8, 127.7, 122.1, 118.0, 115.0, 92.6, 67.3, 66.9, 62.9, 55.0, 54.7, 54.1, 53.9, 50.4, 49.0, 48.8, 47.4, 47.1, 41.4, 39.8, 33.3, 32.1, 31.4, 30.1, 29.8, 29.5, 28.7, 27.0, 26.3, 19.3



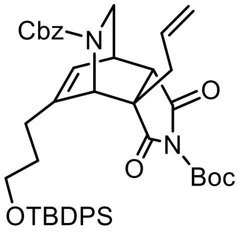
4.29: To a solution of **4.26** (80 mg, 0.095 mmol) in MeOH (0.5 mL) was added AgNO$_3$ (16 mg, 0.095 mmol) and stirred at room temperature for 6 h. Reaction mixture was diluted with water (10 mL) and extracted with EtOAc (3 x 5 mL). The combined organic extracts were washed with brine (10 mL), dried (MgSO$_4$) and concentrated *in vacuo*. The resulting residue was purified via flash chromatography (silica gel, gradient elution, 0-10% EtOAc in hexanes) to yield 36 mg (47%) of **4.29** as a yellow oil: R$_f$ 0.3 (9:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, CDCl$_3$) ∂ 7.64-7.29 (m, 15H), 5.72 (m, 1H), 5.65 (m, 1H), 5.54 (m, 1H), 5.30 (dd, *J* = 4.9, 1.3 Hz, 1H), 5.12-4.96 (m, 6H), 4.64 (dd, *J* = 52.5, 1.2 Hz, 1H), 3.58-3.46 (m, 3H), 3.30 (m, 2H), 3.15 (m, 1H), 2.95 (ddd, *J* = 26.7, 10.5, 2.6 Hz, 1H), 2.25 (m, 3H), 2.04 (m, 2H), 1.66 (m, 2H), 1.39 (m, 4H), 1.09 (s, 9H); ^{13}C NMR (400 MHz, CDCl$_3$) ∂ 175.4, 155.6, 155.3, 146.4, 145.8, 145.1, 144.9, 138.2, 138.1, 136.8, 136.5, 135.7, 134.1, 134.0, 132.3, 132.2, 129.7, 129.6, 128.6, 128.4, 128.3, 128.1, 127.8, 123.4, 123.1, 119.4, 119.3, 115.2, 79.5, 79.2, 67.4, 67.1, 62.9, 62.8, 54.9, 54.5, 54.4, 54.3, 46.8, 46.6, 44.2, 39.9, 39.4, 33.3, 33.1, 32.9, 30.1, 29.5, 29.4, 27.0, 26.0, 25.7, 19.3; LRMS $[M+H]^+$ calc. for $C_{46}H_{55}BrN_2O_4Si$ 806.31 (m/z): found 809.6



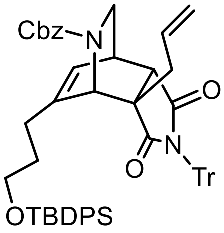
4.31: To a sealed vessel was charged **3.82** (4.27 g, 6.34 mmol) in benzene (32 mL) and DABCO (1.42 g, 12.7 mmol). The vessel was evacuated and heated at 120 °C under static vacuum (ca. 0.01 torr) for 3 h. The reaction mixture was cooled to room temperature, filtered, and the filtrate diluted with water (100 mL), and extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with brine (25 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The crude residual oil was transferred to a sealed flask containing BHT (70 mg, 0.32 mmol) and bromomaleimide (558 mg, 3.17 mmol) in benzene (3.2 mL). The vessel was placed under static vacuum (ca. 0.01 torr) and maintained at 65 °C for 18 h. Reaction mixture was cooled to room temperature concentrated *in vacuo*. The resulting residue was purified via flash chromatography (silica gel, gradient elution, 0-50% EtOAc in hexanes) to yield 840 mg (39%) of **4.31** as a white foam: R_f 0.3 (1:1 hexanes/EtOAc); ^1H NMR (400 MHz, $CDCl_3$) ∂ 8.21 (bs, 1H), 7.61-7.27 (m, 11H), 5.83 (dd, *J* = 11.1, 6.0 Hz, 1H), 5.15 (m, 2H), 5.05 (dd, *J* = 64.3, 1.2 Hz, 1H), 3.57-3.46 (m, 3H), 3.22 (m, 1H), 3.12 (dd, *J* = 6.3, 3.0 Hz, 1H), 3.01 (app. ddd, *J* = 34.4, 10.6, 2.6 Hz, 1H), 2.22 (m, 2H), 1.62 (m, 2H), 1.04 (s, 9H); ^{13}C NMR (400 MHz, $CDCl_3$) ∂ 174.5, 174.4, 172.5, 172.3, 155.4, 154.8, 145.7, 145.1, 136.4, 136.2, 135.7, 133.8, 129.8, 129.7, 128.6, 128.4, 128.3, 128.0, 127.8, 124.3, 124.0, 67.8, 67.6, 62.5, 62.4, 58.0, 57.9, 56.3, 55.8, 54.5, 54.4, 45.8, 45.5, 34.1, 33.8, 29.9, 29.3, 29.2, 27.0, 19.3.



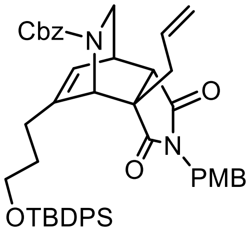
4.32: To a solution **4.31** (2.26 g, 3.29 mmol) and AIBN (54 mg, 0.329 mmol) in toluene (11 mL) was added tributylallyl stannane (2.0 mL, 6.58 mmol). The reaction mixture was maintained at 90 °C for 2 h, allowed to cool to room temperature and concentrated *in vacuo.* The resulting residue was purified via flash chromatography (silica gel:K_2CO_3 (10:1), gradient elution, 0-10% EtOAc in hexanes) to yield 1.79 g (84%) of **4.32** as a yellow oil: R_f 0.3 (7:3 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) ∂ 7.63-7.30 (m, 15H), 5.78 (m, 1H), 5.63 (m, 1H), 5.12 (m, 4H), 4.68 (d, *J* = 58.4 Hz, 1H), 3.57-47 (m, 2H), 3.22 (m, 2H), 2.92 (ddd, *J* = 33.1, 10.4, 2.3 Hz, 1H), 2.66 (ddd, *J* = 39.8, 13.8, 6.7 Hz, 1H), 2.55 (m, 1H), 2.22 (m, 3H), 1.59 (m, 4H), 1.03 (s, 9H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 155.6, 147.1, 146.4, 135.7, 131.1, 129.7, 128.7, 128.6, 128.4, 128.0, 127.8, 123.8, 123.5, 121.0, 67.6, 67.4, 62.9, 54.3, 47.0, 46.3, 39.1, 34.3, 30.2, 29.6, 29.5, 27.8, 27.0, 19.3.



4.33b: To a solution of **4.32** (300 mg, 0.462 mmol), DIPEA (0.16 mL, 0.926 mmol), and DMAP (3 mg, 0.023 mmol) in CH_2Cl_2 (1.1 mL) was added a solution of Boc_2O (121 mg, 0.554 mmol) in CH_2Cl_2 (1.1 mL). Reaction mixture was stirred at room temperature overnight, quenched with water (5 mL), and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The resulting residue was purified via flash chromatography (silica gel, gradient elution, 0-20% EtOAc in hexanes) to yield 36 mg (47%) of **4.29** as a yellow oi: R_f 0.3 (8:2 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) ∂ 7.63- 7.30 (m, 15H), 5.81 (m, 1H), 5.63 (m, 1H), 5.12 (m, 4H), 4.72 (d, *J* = 59.8 Hz, 1H), 3.54 (m, 2H), 3.26 (m, 2H), 2.98 (ddd, *J* = 32.2, 10.4, 2.1 Hz, 1H), 4.72 (ddd, *J* = 38.5, 13.7, 6.2 Hz, 1H), 2.57 (m, 1H), 2.24 (m, 3H), 1.62 (m, 2H), 1.51 (s, 9H), 1.03 (s, 9H).

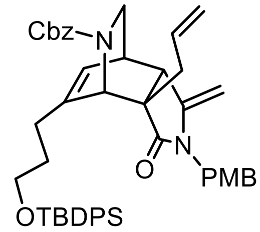


4.33c: To a solution of **4.32** (100 mg, 0.458 mmol) and TrCl (153 mg, 0.550 mmol) in CH_2Cl_2 (2.3 mL) was added a solution of NEt_3 (0.11 ml, 0.824 mmol) dropwise. Reaction mixture was stirred at room temperature overnight, quenched with water (5 mL), and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The resulting residue was purified via flash chromatography (silica gel, gradient elution, 0-20% EtOAc in hexanes) to yield 101 mg (25%) of **4.33c** as a yellow oi: R_f 0.3 (8:2 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) ∂ 7.62- 7.20 (m, 30H), 5.75 (m, 1H), 5.24-5.12 (m, 5H), 4.58 (d, *J* = 50.0 Hz, 1H), 3.50-3.32 (m, 2H), 3.19 (m, 1H), 3.03 (m, 1H), 2.87-2.64 (m, 2H), 2.56 (dd, *J* = 8.5, 2.5 Hz, 1H), 2.35 (m, 1H), 1.89 (m, 2H), 1.65-1.39 (m, 2H), 1.05 (s, 9H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 177.5, 177.3, 176.3, 176.1, 155.4, 154.9, 146.7, 146.1, 142.0, 141.9, 136.6, 136.2, 135.9, 135.7, 134.0, 133.9, 131.9, 131.7, 129.7, 128.6, 128.5, 128.3, 128.2, 128.0, 127.9, 127.8, 127.7, 127.5, 126.7, 124.0, 123.7, 120.6, 74.3, 67.5, 67.2, 62.6, 62.4, 54.5, 53.9, 53.4, 53.3, 46.7, 46.5, 46.3, 39.7, 34.2, 33.9, 30.5, 30.3, 29.6, 29.4, 27.0, 19.4.



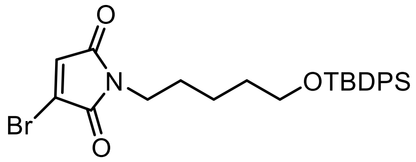
4.33d: To a cooled solution of **4.32** (988 mg, 1.52 mmol), PPh_3 (438 mg, 1.67 mmol), and 4-methoxybenzyl alcohol (0.2 mL, 1.67 mmol) in THF (5 mL) at 0 ^{o}C was added DIAD (0.33 mL, 1.67 mmol) dropwise. Reaction mixture was allowed to warm to room temperature and stir overnight, then quenched with water (5 mL) and extracted with EtOAc (3 x 5 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The resulting residue was purified via flash chromatography (silica gel, gradient elution, 0-15% EtOAc in hexanes) to yield 864 mg (73%) of **4.33d** as a yellow oi: R_f 0.3 (8:2 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) ∂

7.62- 7.26 (m, 15H), 7.19 (dd, *J* = 8.3, 5.6 Hz, 2H), 6.74 (dd, *J* = 8.3, 5.6 Hz, 2H), 5.50 (m, 2H), 5.10-4.97 (m, 4H), 4.66 (d, *J* = 58.2 Hz, 1H), 4.42 (m, 2H), 3.67 (d, *J* = 5.7 Hz, 2H), 3.50-3.36 (m, 2H), 3.23 (d, *J* = 10.6 Hz, 1H), 3.14 (m, 1H), 2.94 (ddd, *J* = 34.6, 10.5, 2.5 Hz, 1H), 2.66 (ddd, *J* = 39.3, 13.7, 6.5 Hz, 1H), 2.50 (dd, *J* = 5.7, 2.9 Hz, 1H), 2.20 (m, 1H), 1.97 (m, 2H), 1.43 (m, 2H), 1.03 (s, 9H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 178.2, 178.1, 177.1, 176.9, 159.4, 155.6, 155.1, 146.4, 145.8, 136.6, 136.3, 135.7, 133.9, 131.4, 131.3, 130.3, 129.7, 128.7, 128.6, 128.4, 128.2, 128.0, 127.8, 123.2, 123.0, 120.4, 120.3, 113.8, 67.6, 67.3, 62.7, 62.6, 55.3, 54.9, 54.4, 53.6, 53.5, 46.7, 46.4, 46.1, 41.9, 38.8, 34.2, 33.9, 30.0, 29.1, 27.0, 19.3.

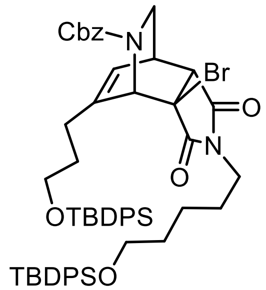


4.34d: To a cooled solution of **4.33d** (1.53 g, 1.99 mmol) in THF (8 mL) at 0 °C, was added MeMgBr (3 M in Et_2O, 3.3 mL, 9.93 mmol) dropwise. Reaction mixture was maintained at 0 ^{o}C for 1 h then warmed to room temperature and stirred for 2 h. Reaction mixture was quenched with saturated aq. NH_4Cl and extracted with EtOAc (3 x 5 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The resulting oil was dissolved in CH_2Cl_2 (8 mL) and cooled to 0 °C to which TFA (0.15 mL, 1.99 mmol) was added and allowed to stir for 1 h. Reaction mixture was neutralized to pH = 8 with saturated aq. $NaHCO_3$ and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried ($MgSO_4$), concentrated *in vacuo*. The resulting residue was purified via flash chromatography (silica gel, gradient elution, 0-20% EtOAc in hexanes) to yield 1.25 g (72% Over 2 Steps) of **4.34d** as a yellow oil: R_f 0.3 (8:2 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) ∂ 7.64- 7.26 (m, 15H), 7.06 (m, 2H), 6.79 (dd, *J* = 8.3, 4.2 Hz, 2H), 5.65 (m, 2H), 5.12-4.99 (m, 4H), 4.72-4.55 (m, 2H), 4.30 (m, 1H), 4.13 (m, 2H), 3.73 (m, 3H), 3.58-3.40 (m, 2H), 3.24 (d, *J* = 10.5 Hz, 1H), 2.98-2.62 (m, 4H), 2.22 (m, 3H), 1.62 (m, 2H), 1.04 (s, 9H); ^{13}C

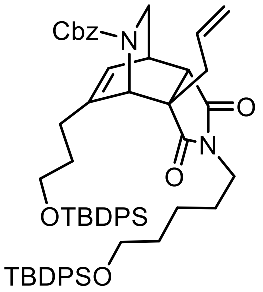
NMR (400 MHz, $CDCl_3$) δ 175.8, 159.0, 155.6, 155.3, 148.5, 148.3, 145.8, 145.2, 136.9, 136.5, 135.7, 134.0, 132.8, 132.7, 129.7,128.8, 128.6, 128.4, 128.3, 128.1, 128.0, 127.9, 127.8, 127.7, 127.1, 124.2, 123.9, 119.2, 119.1, 113.8, 85.6, 85.3, 67.4, 67.0, 62.9, 62.8, 55.3, 54.7, 54.2, 54.0, 46.5, 46.3, 43.5, 43.2, 39.9, 37.9, 37.6, 30.2, 29.5, 29.4, 27.0, 19.3.



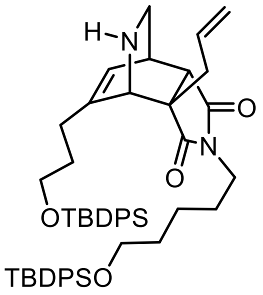
4.38: To a solution of **4.7** (1.30 g, 5.31 mmol), 5-(tert-butyldimethylsilyloxy)-1-pentanol (2.0 g, 5.84 mmol), and PPh_3 (1.53 g, 5.84 mmol) in THF (21 mL) at 0 °C was added DIAD (1.1 mL, 5.84 mmol) dropwise. The reaction mixture was maintained at 0 °C for 30 min, and then allowed to warm to room temperature for 2 h. The reaction mixture was quenched with saturated aq. NH_4Cl (10 mL), poured into brine (20 mL), and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo.* The resulting residue was purified by flash chromatography (silica gel, gradient elution 0-10% EtOAc in hexanes) to afford a mixture of diastereomers as a yellow oil. The resulting mixture was dissolved in toluene (30 mL) and heated in an open flask at 110 °C for 48 h. The reaction mixture was allowed to cool to room temperature and concentrated *in vacuo* to yield 2.98 g (79% over 2 steps) as a red oil that was used without further purification. ^1H NMR (400 MHz, $CDCl_3$) ∂ 6.79 (s, 1H), 4.73 (ddt, *J* = 17.0, 10.2 , 6.8 Hz 1H), 4.91 (m, 2H), 3.49 (t, *J* = 7.2 Hz, 2H), 2.01 (q, *J* = 7.1 Hz, 2H), 1.54 (p, *J* = 7.6 Hz, 2H), 1.31 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) ∂ 168.5, 165.3, 138.0, 131.7, 131.2, 114.9, 38.6, 33.0, 27.8, 25.8



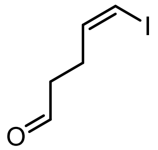
4.39: To a sealed vessel was charged **3.82** (4.04 g, 5.99 mmol) in benzene (30 mL) and DABCO (1.35 g, 12.0 mmol). The vessel was evacuated and heated at 120 °C under static vacuum (ca. 0.01 torr) for 3 h. The reaction mixture was cooled to room temperature, filtered, and the filtrate diluted with water (100 mL), and extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with brine (25 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The crude residual oil was dissolved in benzene (2 mL) to which BHT (44 mg, 0.20 mmol) and **4.38** (1.00 g, 2.00 mmol) were added. The reaction mixture was placed under static vacuum (ca. 0.01 torr) and maintained at 65 °C for 18 h. Reaction mixture was then cooled to room temperature and concentrated *in vacuo*. The resulting residue was purified via flash chromatography (silica gel, gradient elution, 0-20% EtOAc in hexanes) to yield 1.21 g (60%) of **4.39** as a red oil: R_f 0.3 (8:2 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) ∂ 7.63-7.27 (m, 15H), 5.71 (m, 1H), 5.15-4.95 (m, 3H), 3.57-3.33 (m, 7H), 3.20 (m, 1H), 3.07-2.93 (m, 2H), 2.27-1.99 (m, 2H), 1.75-1.35 (m, 6H), 1.24 (m, 2H), 1.00 (s, 9H); ^{13}C NMR (400 MHz, $CDCl_3$) ∂ 174.5, 174.4, 172.7, 172.6, 155.2, 154.7, 145.6, 145.0, 136.4, 136.2, 135.5, 133.9, 133.7, 133.6, 129.6, 129.5, 128.5, 128.3, 128.2, 128.1, 127.8, 127.7, 127.6, 126.9, 123.9, 123.7, 67.5, 67.3, 63.5, 62.3, 62.2, 57.1, 56.9, 56.3, 55.8, 53.1, 53.0, 45.8, 45.5, 39.3, 34.1, 33.9, 31.9, 29.7, 29.2, 29.1, 27.1, 26.9, 23.1, 19.2; LRMS $[M+H]^+$ calc. for $C_{57}H_{67}BrN_2O_6Si_2$ 1010.4 (m/z): found 1090.4



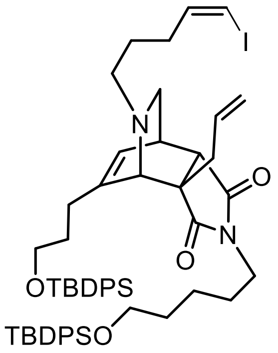
4.40: To a solution of **4.39** (2.61 g, 2.64 mmol) and AIBN (43 mg, 0.26 mmol) in toluene (8.8 mL) was added tributylallyl stannane (1.6 mL, 5.29 mmol). Reaction mixture was heated at 90 °C for 2 h, cooled to room temperature and concentrated *in vacuo.* The resulting residue was purified via flash chromatography (silica gel:K_2CO_3 (10:1), gradient elution, 0-20% EtOAc in hexanes) to yield 2.29 g (89%) of **4.40** as a red oil: R_f 0.3 (8:2 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) ∂ 7.69-7.27 (m, 25H), 5.66 (t, *J* = 6.8 Hz, 1H), 5.53 (m, 1H), 5.15-5.02 (m, 4H), 4.77-4.62 (dd, *J* = 58.1, 1.1 Hz, 1H), 3.64-3.42 (m, 4H), 3.36-3.13 (m, 4H), 3.07-2.91 (ddd, *J* = 29.6, 10.7, 2.6 Hz, 1H), 2.76-2.58 (m, 1H), 2.49 (t, *J* = 3.2 Hz, 1H), 2.25-2.01 (m, 3H), 1.75-1.24 (m, 8H), 1.02 (m, 18H); ^{13}C NMR (400 MHz, $CDCl_3$) ∂ 178.2, 178.1, 177.1, 177.0, 155.4, 154.9, 146.3, 145.7, 136.4, 136.1, 135.5, 133.9, 133.7, 131.3, 131.2, 129.5, 129.4, 128.5, 128.4, 128.2, 128.0, 127.8, 127.6, 127.5, 123.2, 122.9, 120.2, 120.1, 67.3, 67.1, 63.6, 62.5, 62.4, 54.7, 54.2, 53.4, 53.3, 46.3, 46.2, 45.9, 38.5, 33.9, 33.7, 31.9, 29.9, 29.3, 29.2, 27.4, 26.8, 23.1, 19.1.



4.41: To a solution of **4.40** (200 mg, 0.205 mmol) in CH_2Cl_2 (0.82 mL) was added BCl_3 (1 M in toluene, 0.41 mL, 0.410 mmol) dropwise. The reaction mixture was maintained at room temperature and stirred overnight. Reaction mixture was quenched by dropwise addition of saturated aq. $NaHCO_3$ to pH = 8 and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The resulting residue was purified via flash chromatography (silica gel, gradient elution, 0-5% methanol in CH_2Cl_2) to yield 140 mg (81%) of **4.41** as a red oil: R_f 0.3 (95:5 CH_2Cl_2/MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) ∂ 7.69-7.34 (m, 20H), 5.63 (m, 2H), 5.08 (m, 2H), 3.59 (m, 4H), 3.44 (m, 1H), 3.28 (m, 1H), 3.06 (br s, 1H), 2.85 (d, *J* = 9.6 Hz, 1H), 2.64 (d, *J* = 7.3 Hz, 2H), 2.42 (m, 2 H), 2.18-2.04 (m, 2H), 1.75-1.24 (m, 10H), 1.02 (s, 18H); ^{13}C NMR (400 MHz, $CDCl_3$) ∂ 179.5, 178.0, 147.3, 135.5, 133.9, 133.8, 132.4, 129.5, 129.4, 128.5, 128.4, 127.6, 127.5, 121.3, 119.6, 63.6, 63.1, 55.8, 52.3, 47.0, 44.4, 38.4, 38.3, 33.7, 32.0, 29.9, 29.6, 27.4, 26.8, 23.1, 19.1.



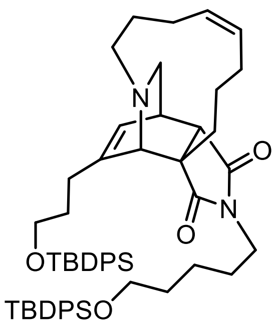
4.42: To a solution of DMSO (0.23 mL, 3.17 mmol) in CH_2Cl_2 (4.3 mL) at -78 °C was added oxalyl chloride (0.12 mL, 1.45 mmol) dropwise. Reaction mixture was maintained at -78 °C for 15 min, then (Z)-5-iodopent-4-en-1-ol (280 mg, 1.32 mmol) was added dropwise and maintained at-78 °C for 20 min. NEt_3 (0.92 mL, 6.6 mmol) was added and continued to stir at-78 °C for 20 min. Reaction mixture was removed from ice bath and continued to stir at room temperature for 15 min. Mixture was quenched with brine (15 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The resulting residue was purified via flash chromatography (silica gel, gradient elution, 0-20% EtOAc in hexanes) to yield 147 mg (53%) of **4.42** as a red oil: R_f 0.3 (8:2 hexanes/EtOAc). Spectral data matched reported literature values.[98]



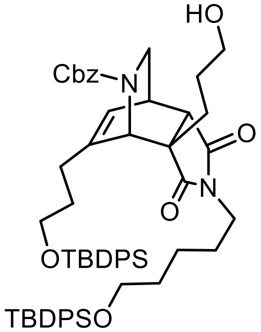
4.43: To a solution of **4.41** (210 mg, 0.250 mmol) and **4.42** (53 mg, 0.250 mmol) in DCE (0.86 mL) was added $NaBH(OAc)_3$ (74 mg, 0.350 mmol) in one portion. Reaction mixture was stirred at room temperature for 2 h, quenched with saturated aq. $NaHCO_3$ to pH = 9 and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The resulting residue was purified via flash chromatography (silica gel, gradient elution, 0-10% EtOAc in hexanes) to yield 195 mg, (75%) of **4.43** as a red oil: R_f 0.3 (9:1

hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) ∂ 7.69-7.34 (m, 10H), 6.18 (m, 1H), 5.66 (m, 1H), 5.08 (dd, *J* = 34.2, 17.1 Hz, 2H), 3.59 (m, 4H), 3.26 (m, 2H), 3.06-2.95 (m, 1H), 2.80-2.63 (m, 1H), 2.40 (m, 1H), 2.28-2.03 (m, 3H), 1.8 (m, 1H), 1.69-1.24 (m, 7H), 1.03 (s, 9H); ^{13}C NMR (400 MHz, $CDCl_3$) ∂ 179.8, 178.3, 144.3, 140.8, 135.5, 133.9, 133.8, 132.8, 129.5, 129.4, 127.6, 127.5, 121.3, 119.3, 82.7, 63.6, 63.1, 62.2, 56.7, 53.9, 53.2, 46.3, 38.5, 38.3, 34.4, 32.3, 32.0, 31.2, 29.4, 27.4, 26.8, 26.7, 23.2, 19.1.

4.43: To a solution of **4.41** (67 mg, 0.080 mmol) and K_2CO_3 (55 mg, 0.40 mmol) in 1:1 MeCN/DCM (0.8 mL) was added (Z)-5-iodopent-4-en-1-yl 4-methylbenzenesulfonate (32 mg, 0.090 mmol). Reaction mixture was heated at reflux overnight, allowed to cool to room temperature, diluted with water (5 mL) and extracted with EtOAc (3 x 5 mL). The combined organic extracts were washed with brine (5 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The resulting residue was purified via flash chromatography (silica gel, gradient elution, 0-10% EtOAc in hexanes) to yield 48 mg (58%) of **4.43** as a red oil: R_f 0.3 (9:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) ∂ 7.69-7.34 (m, 10H), 6.18 (m, 1H), 5.66 (m, 1H), 5.08 (m, 2H), 3.59 (m, 4H), 3.26 (m, 2H), 3.06-2.95 (m, 1H), 2.80-2.63 (m, 1H), 2.40 (m, 1H), 2.28-2.03 (m, 3H), 1.8 (m, 1H), 1.69-1.24 (m, 7H), 1.03 (s, 9H); ^{13}C NMR (400 MHz, $CDCl_3$) ∂ 179.8, 178.3, 144.3, 140.8, 135.5, 133.9, 133.8, 132.8, 129.5, 129.4, 127.6, 127.5, 121.3, 119.3, 82.7, 63.6, 63.1, 62.2, 56.7, 53.9, 53.2, 46.3, 38.5, 38.3, 34.4, 32.3, 32.0, 31.2, 29.4, 27.4, 26.8, 26.7, 23.2, 19.1.

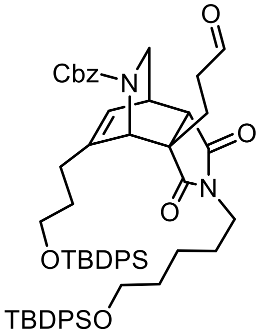


4.44: A solution of **4.43** (24 mg, 0.023 mmol) in THF (0.3 mL) was charged to a vessel containing 9-BBN (11 mg, 0.046 mmol) and stirred at room temperature for 2 h. To the reaction mixture was added THF (0.75 mL) and water (0.25 mL), sequentially. The resulting mixture was added via syringe pump over 3 h to a solution of $PdCl_2dppf$ (2 mg, 0.002 mmol), and K_3PO_4 (10 mg, 0.046 mmol) in THF (4 mL). The reaction mixture was allowed to stir at room temperature for 18 h, and then concentrated *in vacuo*. The resulting residue was purified via flash chromatography (silica gel, gradient elution, 0-20% EtOAc in hexanes) to yield (4 mg, 17%) as a yellow oil: R_f 0.3 (8:2 hexanes/EtOAc); 7.63-7.35 (m, 25H), 5.69 (dd, *J* = 6.4, 1.2 Hz, 1H), 5.56 (m, 1H), 5.46 (m, 1H), 4.81 (s, 1H), 4.57 (td, *J* = 10.9, 1.9 Hz, 1H), 3.80 (m, 1H), 3.69 (t, *J* = 6.0 Hz, 1H), 3.60 (t, *J* = 6.4 Hz, 2H), 3.55 (m, 2H), 3.31 (m, 3H), 3.18 (m, 1H), 2.98 (dd, *J* = 10.6, 2.6 Hz, 1H), 2.74 (t, *J* = 15.5 Hz, 1H), 2.31 (d, *J* = 2.9 Hz, 1H), 2.13 (m, 4H), 1.92 (m, 6H), 1.65 (m, 22H), 1.29 (m, 4H), 1.03 (s, 18H).

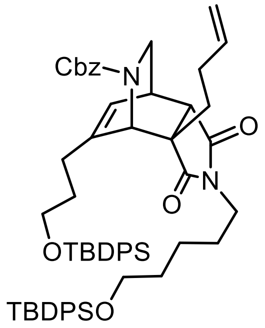


4.45: To a solution of 9-BBN Dimer (249 mg, 1.02 mmol) in THF (2.9 mL) was added a solution of **4.40** (1.42 g, 1.46 mmol) in THF (2.9 mL). Reaction mixture was stirred at room temperature for 1.5 h and then cooled to 0 °C. NaOH (10% wt/vol, 1.8 mL, 4.38 mmol) and H_2O_2 (50% wt/vol, 0.55 mL, 9.64 mmol) were added sequentially. Reaction mixture was maintained at 0 °C for 1 h, quenched with water (20 mL) and extracted with EtOAc (3 x 15 mL). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The resulting residue was purified via flash chromatography (silica gel, gradient elution, 0-20% EtOAc in hexanes) to yield 893 mg (62%) of **4.45** as a yellow oil: R_f 0.3 (8:2 hexanes/EtOAc); ^{1}H NMR

(400 MHz, CDCl$_3$) ∂ 7.63-7.26 (m, 25H), 5.67 (m, 1H), 5.20-5.03 (m, 2H), 4.71 (d, *J* = 33.9 Hz, 1H), 3.61-3.43 (m, 6H), 3.32 (m, 3H), 3.19 (m, 1H), 2.97 (ddd, *J* = 31.4, 10.5, 2.5 Hz, 1H), 2.44 (dd, *J* = 6.9, 2.8 Hz, 1H), 2.12 (m, 2H), 1.84 (m, 2H), 1.52 (m, 16H), 1.03 (s, 18H); ^{13}C NMR (400 MHz, CDCl$_3$) ∂ 178.8, 178.6, 177.3, 177.2, 155.8, 155.1, 146.4, 145.9, 136.6, 136.5, 135.7, 134.1, 133.9, 129.7, 128.7, 128.6, 128.5, 128.2, 128.0, 127.8, 127.7, 123.2, 123.0, 67.4, 63.8, 62.7, 62.6, 62.4, 54.8, 54.0, 53.1, 48.1, 47.6, 46.3, 46.1, 38.8, 34.2, 34.0, 32.1, 31.0, 30.1, 29.5, 29.4, 27.8, 27.6, 27.0, 23.4, 19.3.



4.46: To a solution of **4.45** (200 mg, 0.202 mmol) in CH$_2$Cl$_2$ (0.8 mL) was added DMP (129 mg, 0.303 mmol) in one portion. Reaction mixture was maintained at room temperature for 3 h, then quenched with a 1:1 solution of NaHCO$_3$:Na$_2$S$_2$O$_3$ (10 mL) and extracted with CH$_2$Cl$_2$ (3 x 5 mL). The combined organic extracts were dried (Na$_2$SO$_4$) and concentrated *in vacuo*. The resulting residue was purified via flash chromatography (silica gel, gradient elution, 0-20% EtOAc in hexanes) to yield 174 mg (87%) of **4.46** as a light-yellow oil: R$_f$ 0.3 (8:2 hexanes/EtOAc); ^{1}H NMR (400 MHz, CDCl$_3$) ∂ 9.61 (d, *J* = 81.4 Hz, 1H), 7.63-7.27 (m, 25H), 5.68 (m, 1H), 5.21-5.02 (m, 2H), 4.73 (d, *J* = 75.2 Hz, 1H), 3.61-3.45 (m, 4H), 3.31-3.14 (m, 4H), 2.97 (ddd, *J* = 39.6, 10.5, 2.4 Hz, 1H), 2.80 (m, 1H), 2.57 (m, 1H), 2.38 (m, 2H), 2.07 (m, 4H), 1.69-1.40 (m, 8H), 1.03 (s, 18H); ^{13}C NMR (400 MHz, CDCl$_3$) δ 200.7, 199.9, 178.3, 176.9, 176.8, 155.6, 154.9, 146.2, 145.6, 136.5, 136.3, 135.7, 134.1, 133.9, 129.8, 129.7, 128.8, 128.6, 128.3, 128.0, 127.8, 123.5, 123.3, 67.7, 67.4, 63.8, 62.7, 62.6, 53.6, 52.7, 52.0, 51.8, 49.1, 48.6, 46.3, 45.9, 42.4, 39.1, 38.8, 34.1, 33.9, 32.1, 31.1, 30.1, 29.5, 29.4, 27.5, 27.0, 26.7, 26.5, 25.8, 23.4, 19.3.



4.47: To a solution of **4.16** (25 mg, 0.111 mmol) in THF (0.25 mL) at -78 °C was added LHMDS (1 M in THF, 0.11 mL, 0.11 mmol) dropwise and maintained at -78 °C for 1 h. A solution of **4.46** (100 mg, 0.101 mmol) in THF (0.25 mL) was added dropwise and the reaction mixture maintained at – 78 °C for 45 min and then warmed to -50 °C for 2 h. Reaction mixture was removed from ice bath and stirred at room temperature for 15 min, quenched with brine (10 mL) and extracted with EtOAc (3 x 5 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The resulting residue was purified via flash chromatography (silica gel, gradient elution, 0-15% EtOAc in hexanes) to yield 48 mg (48%) of **4.47** as a colorless oil: R_f 0.3 (8:2 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) ∂ 7.63-7.27 (m, 25H), 5.66 (m, 2H), 5.11 (m, 2H), 4.93 (m, 2H), 4.70 (d, *J* = 58.8 Hz, 1H), 3.64-3.47 (m, 4H), 3.32-3.15 (m, 4H), 2.97 (ddd. *J* = 31.6, 10.5, 2.3 Hz, 1H), 2.48 (dd, *J* = 5.2, 3.0 Hz, 1H), 2.03 (m, 5H), 1.59 (m, 8H), 1.03 (s, 18H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$) δ 178.7, 178.6, 177.4, 177.3, 155.6, 155.1, 146.5, 145.8, 137.2, 136.9, 136.7, 136.4, 135.7, 134.1, 133.9, 131.7, 130.0, 129.7, 128.7, 128.6, 128.4, 128.2, 128.0, 127.8, 127.7, 125.1, 123.1, 122.8, 115.8, 115.7, 67.5, 67.3, 63.8, 62.7, 62.6, 55.1, 54.5, 53.3, 47.4, 47.3, 46.4, 46.0, 38.8, 34.3, 34.0, 33.8, 32.1, 30.1, 29.8, 29.5, 29.4, 29.2, 29.1, 27.6

References

(79) Takenaka, N.; Huang, Y.; Rawal, V. H. *Tetrahedron* **2002**, *58* (41), 8299–8305.

(80) Huang, Y.; Iwama, T.; Rawal, V. H. *J. Am. Chem. Soc*. **2000**, 7843–7844.

(81) Huang, Y.; Iwama, T.; Rawal, V. H. *Org. Lett.* **2002**, *4* (7), 1163–1164.

(82) Lombardo, L. *Tetrahedron Lett.* **1982**, *23* (41), 4293–4296.

(83) Julia, M.; Paris, J.-M. *Tetrahedron Lett.* **1973**, *14* (49), 4833–4836.

(84) Baudin, J. B.; Hareau, G.; Julia, S. A.; Ruel, O. A. *Tetrahedron Lett.* **1991**, *32* (9), 1175–1178.

(85) Blakemore, P. R.; Cole, W. J.; Kocieński, P. J.; Morley, A. *Synlett* **1998**, (1), 26–28.

(86) Marx, V. M.; Herbert, M. B.; Keitz, B. K.; Grubbs, R. H. *J. Am. Chem. Soc.* **2013**, *135* (1), 94–97.

(87) Keitz, B. K.; Endo, K.; Patel, P. R.; Herbert, M. B.; Grubbs, R. H. *J. Am. Chem. Soc.* **2012**, *134* (1), 693–699.

(88) Denmark, S. E.; Yang, S. M. *J. Am. Chem. Soc.* **2002**, *124* (10), 2102–2103.

(89) Burgess, K.; van der Donk, W. A.; Westcott, S. A.; Marder, T. B.; Baker, R. T.; Calabrese, J. C. *J. Am. Chem. Soc.* **1992**, *114* (24), 9350–9359.

(90) Soderquist, J. A.; Brown, H. C. *J. Org. Chem.* **1981**, *46* (22), 4599–4600.

(91) Knights, E. F.; Brown, H. C. *J. Am. Chem. Soc.* **1968**, *90* (19), 5281–5283.

(92) Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chemie - Int. Ed.* **2001**, *40* (24), 4544–4568.

(93) Uenishi, J.; Beau, J. M.; Armstrong, R. W.; Kishi, Y. *J. Am. Chem. Soc.* **1987**, *109* (15), 4756–4758.

(94) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113* (25), 9585–9595.

(95) Meng, Z.; Fürstner, A. *J. Am. Chem. Soc.* **2020**, *142* (27), 11703–11708.

(96) Baker, J.; Caddick, S.; Smith, M. WO 2011/018613 A l, February 17, **2011**.

(97) Lebrun, M.-E.; Le Marquand, P.; Berthelette, C. *J. Org. Chem.* **2006**, *71* (5), 2009–2013.

(98) Cooke, M. P.; Widener, R. K. *J. Org. Chem.* **1987**, *52* (8), 1381–1396.

Appendix A.4: Spectra Relevant to Chapter 4

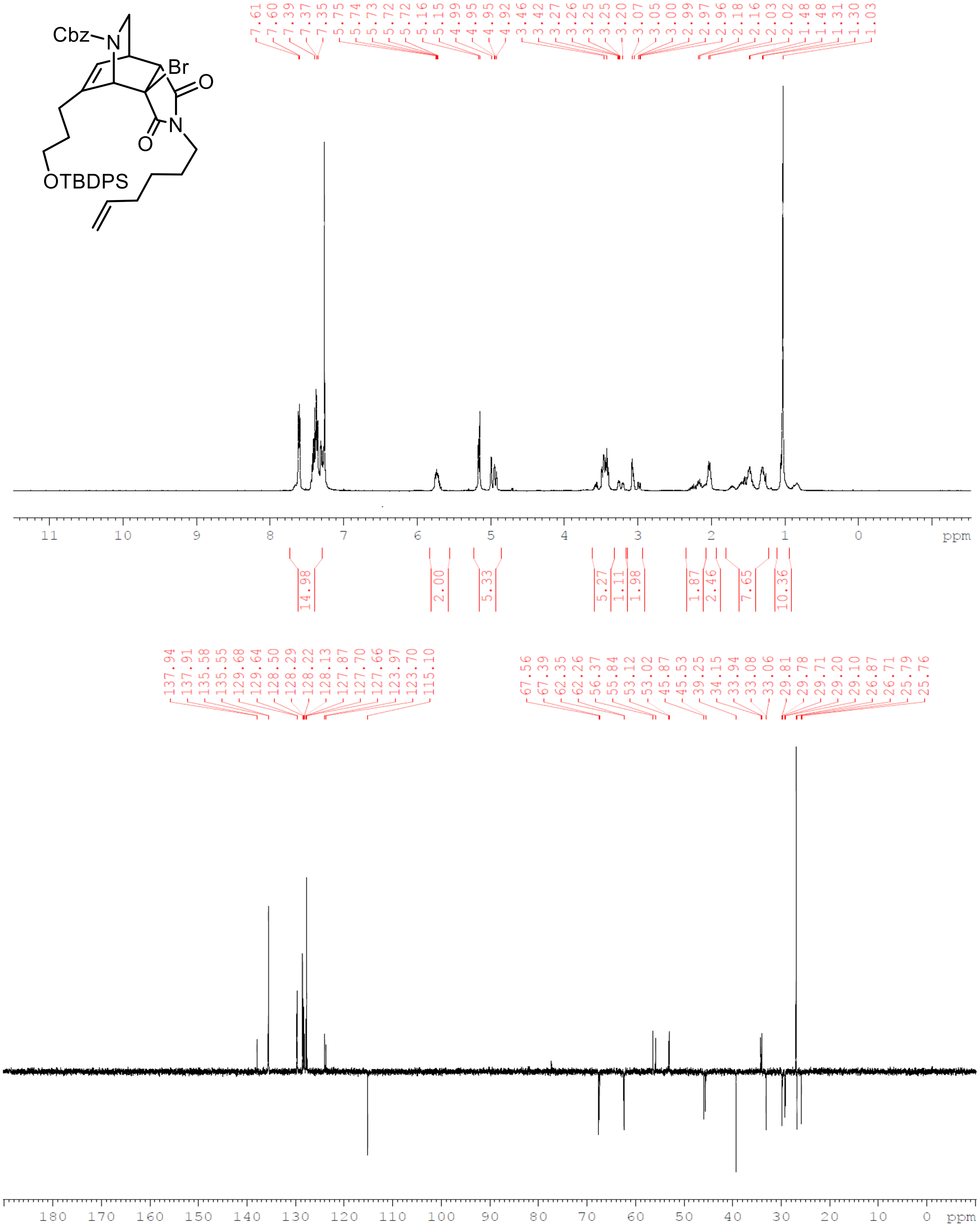


Figure A.4.1 ^{1}H NMR (400 MHz, CDCl$_3$) and DEPT-135 NMR (400 MHz, CDCl$_3$) of **4.2**

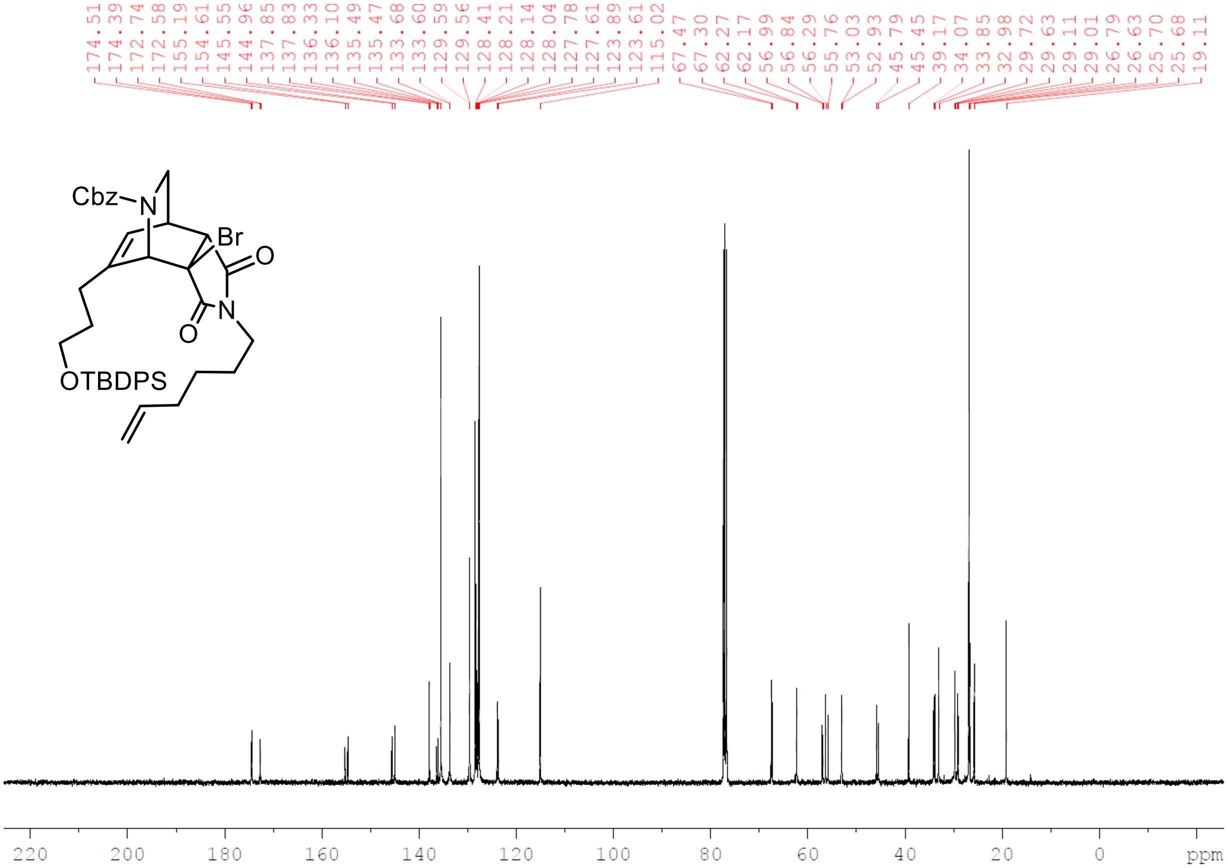


Figure A.4.2 ^{13}C NMR (400 MHz, CDCl$_3$) of **4.2**

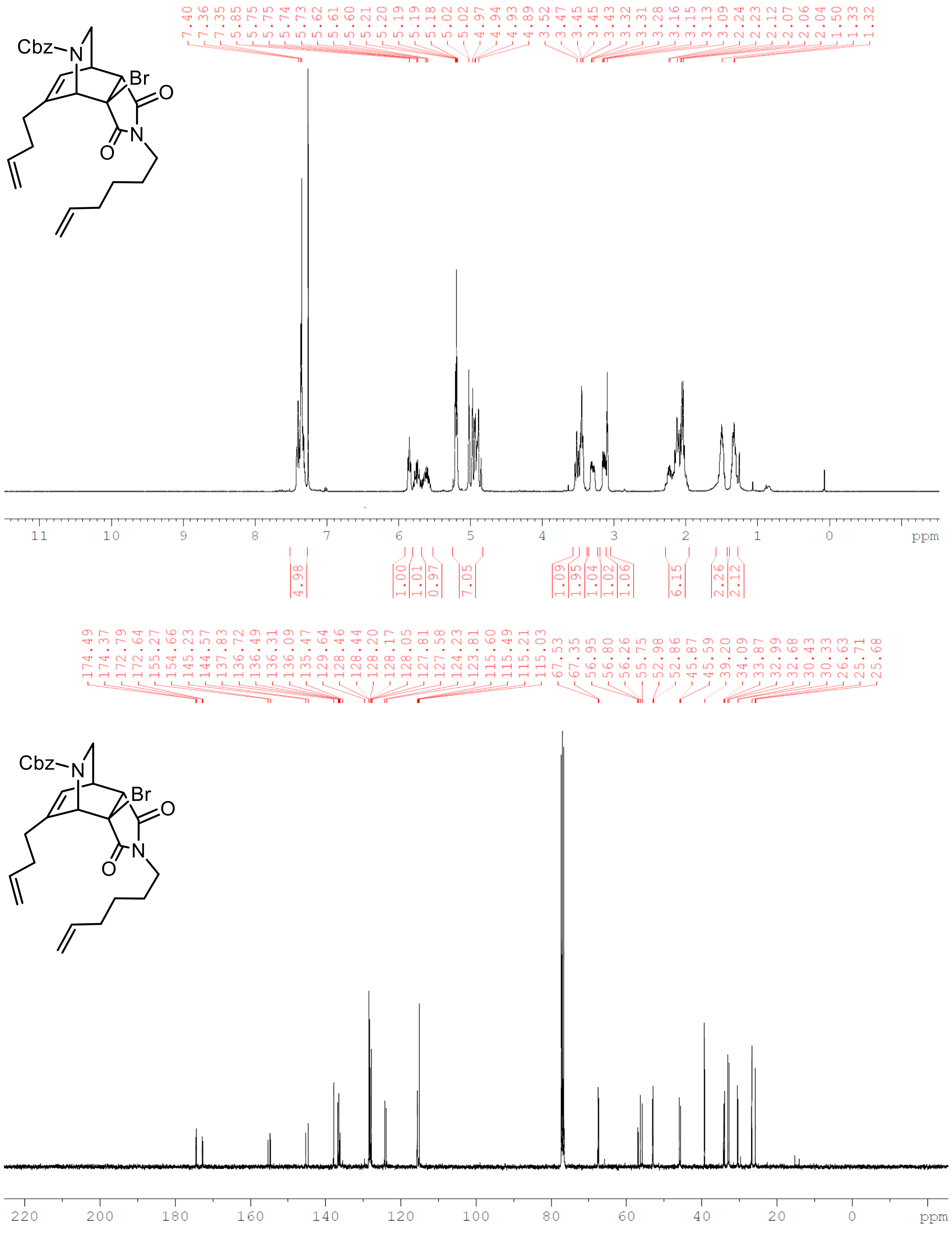


Figure A.4.3 ^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (400 MHz, CDCl$_3$) of **4.3**

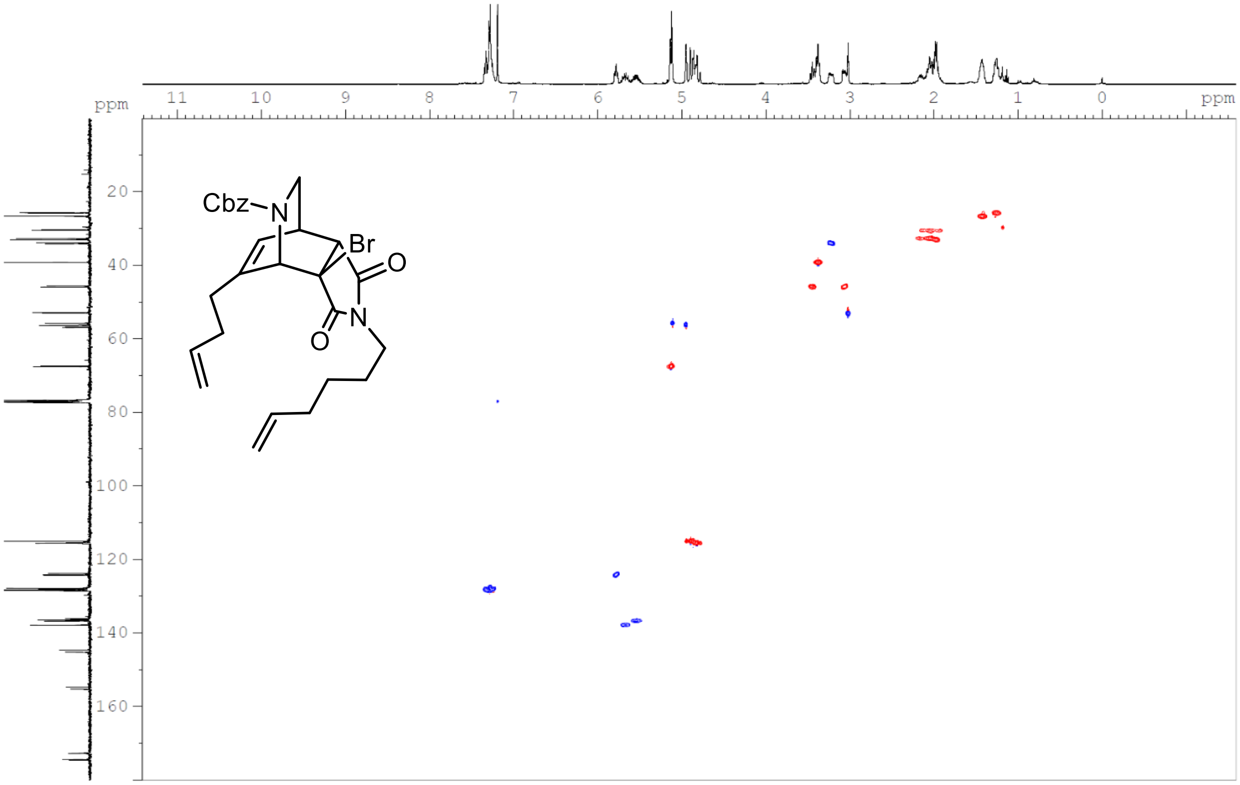


Figure A.4.4 HSQC NMR (400 MHz, $CDCl_3$) of **4.3**

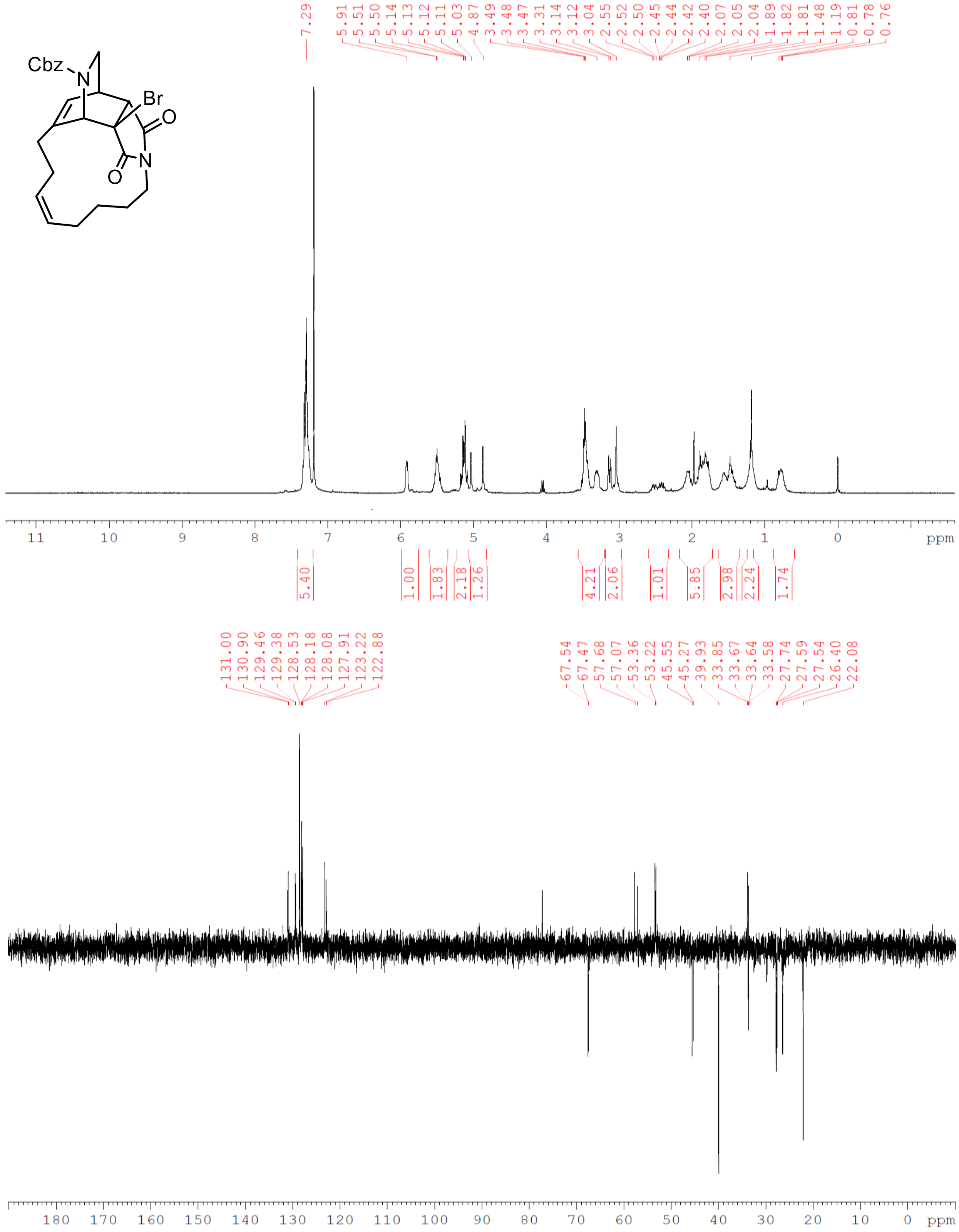


Figure A.4.5 ^{1}H NMR (400 MHz, $CDCl_3$) and DEPT-135 NMR (400 MHz, $CDCl_3$) of **4.4**

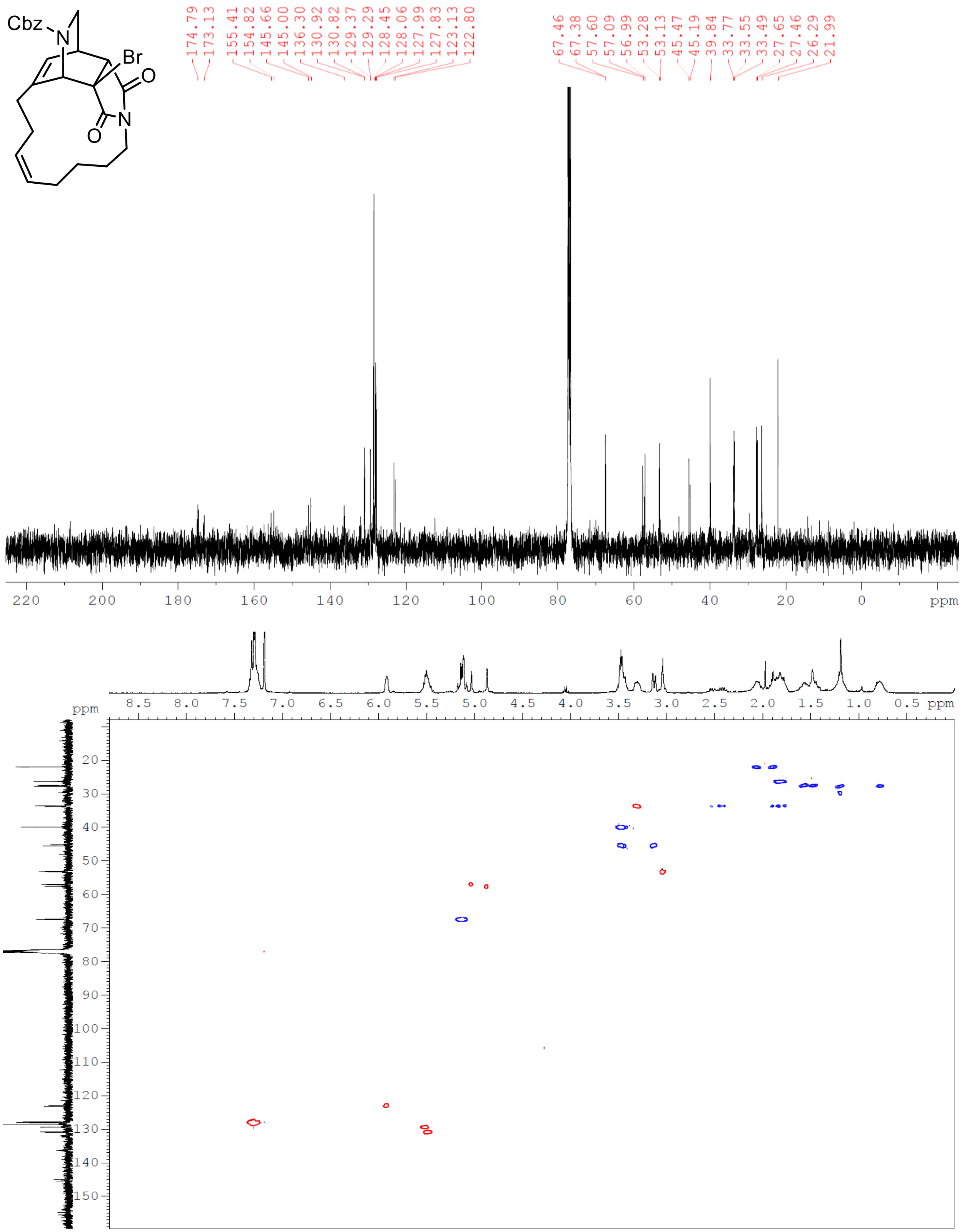


Figure A.4.6 ^{13}C NMR (400 MHz, CDCl$_3$) and HSQC NMR (400 MHz, CDCl$_3$) of **4.4**

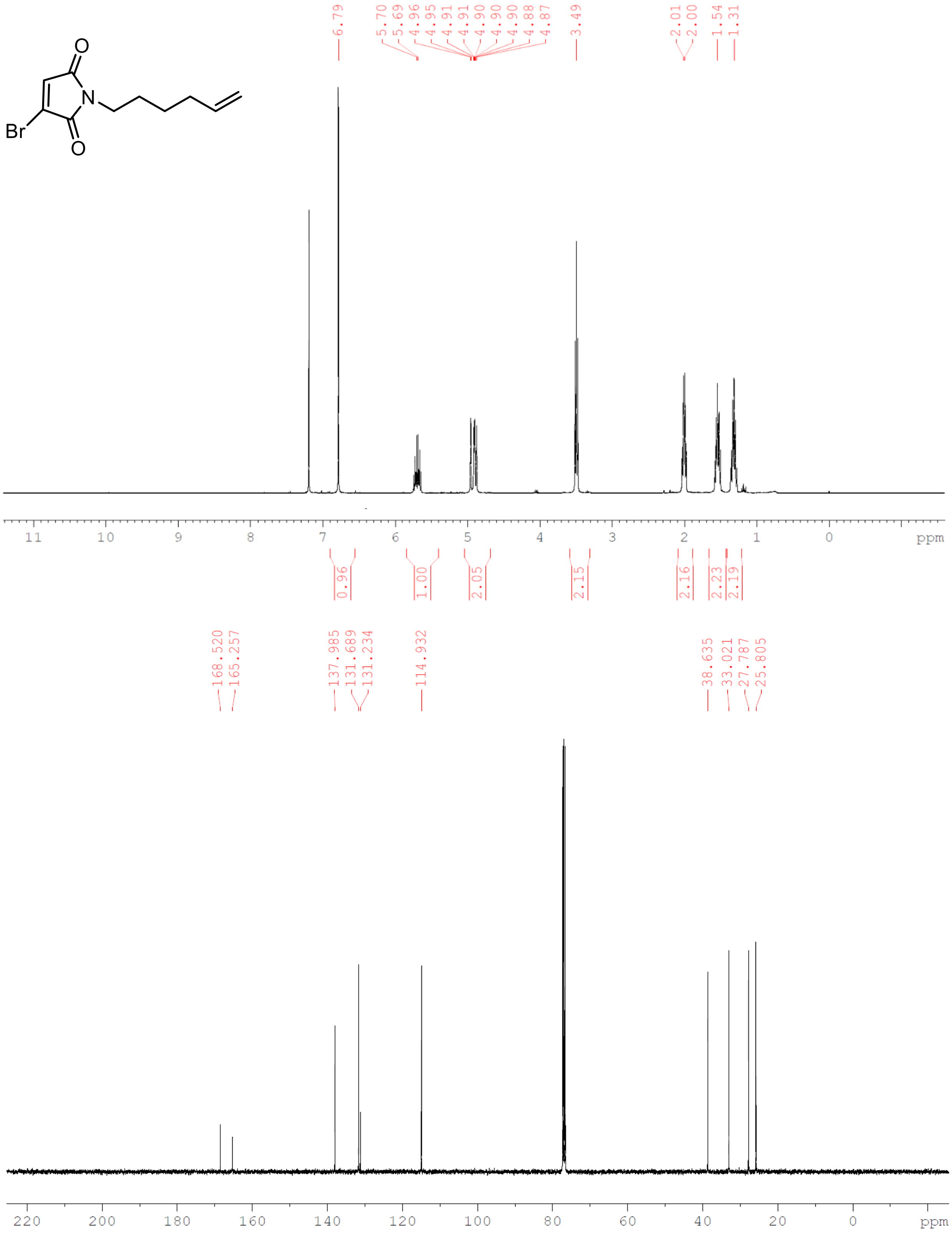


Figure A.4.7 ^{1}H NMR (400 MHz, $CDCl_3$) and DEPT-135 NMR (400 MHz, $CDCl_3$) of **4.10**

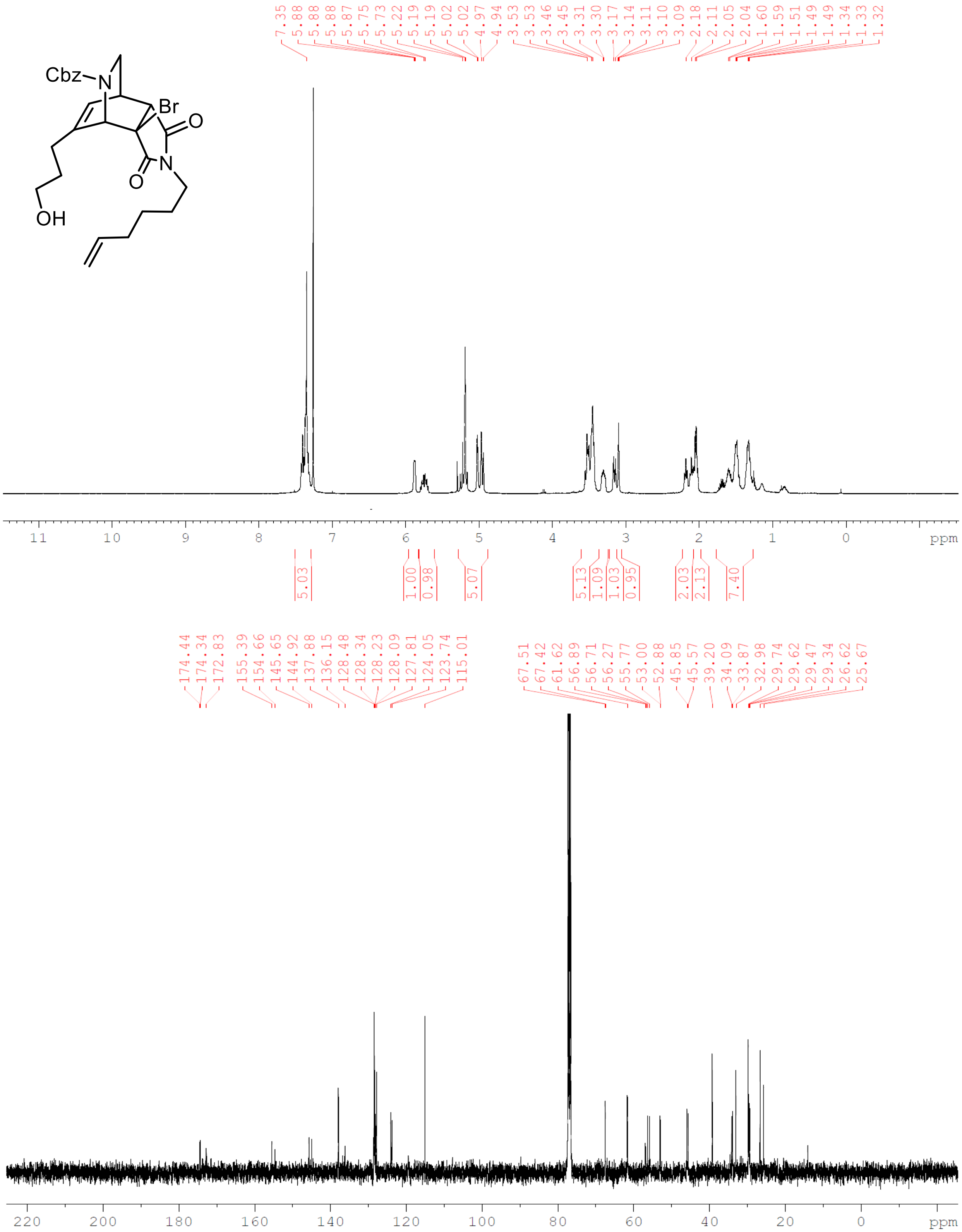


Figure A.4.8 ^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (400 MHz, CDCl$_3$) of **4.13**

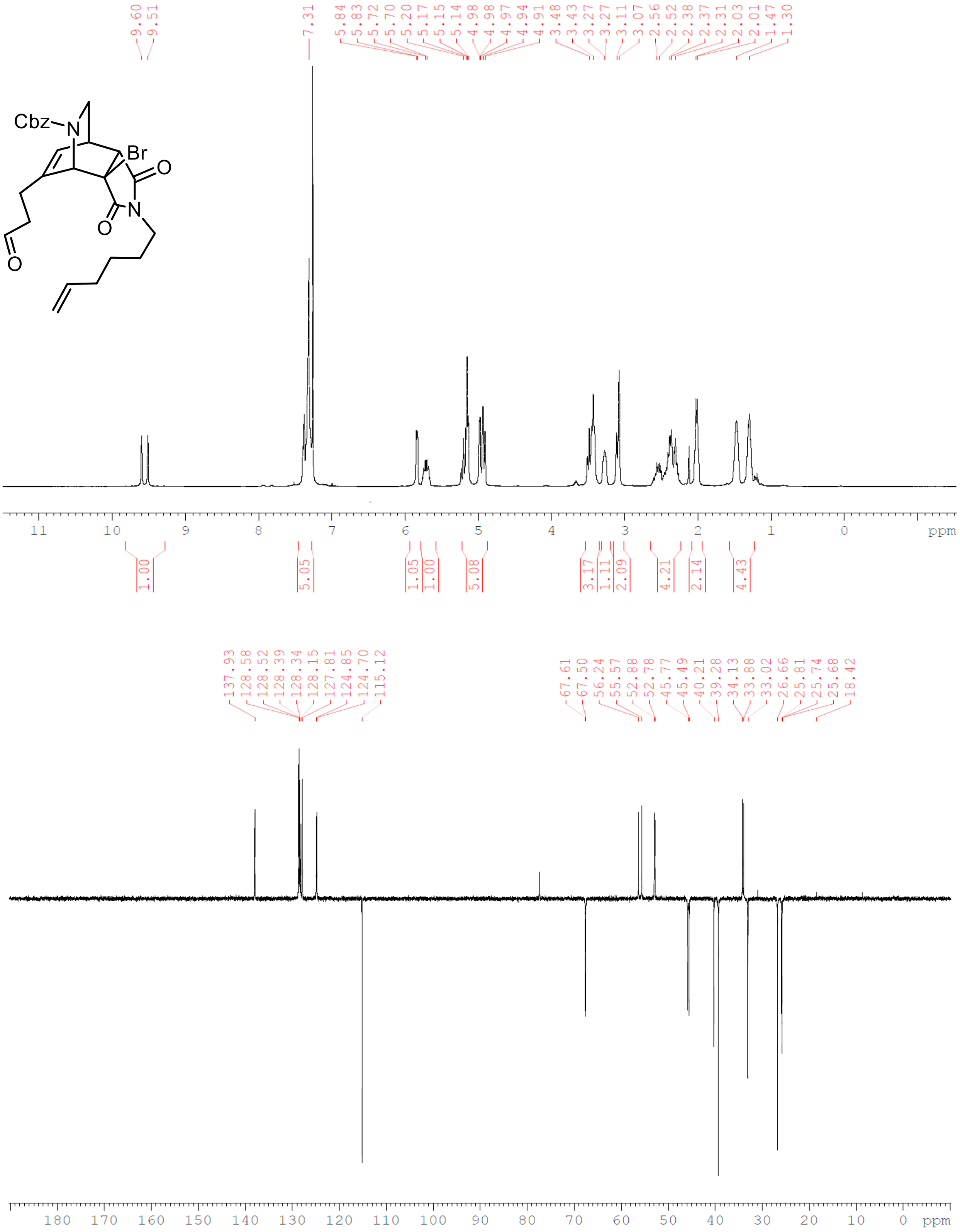


Figure A.4.9 ^{1}H NMR (400 MHz, $CDCl_3$) and DEPT-135 NMR (400 MHz, $CDCl_3$) of **4.14**

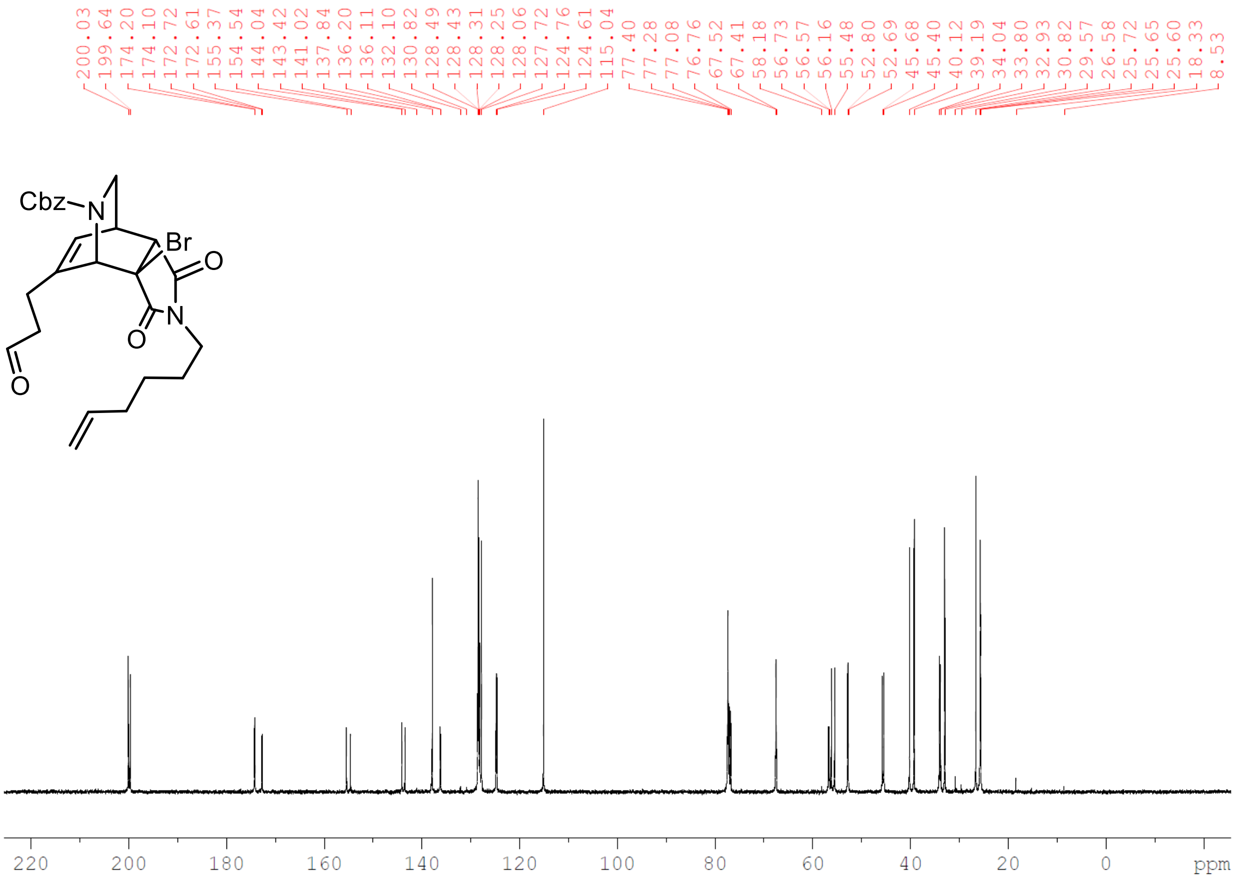
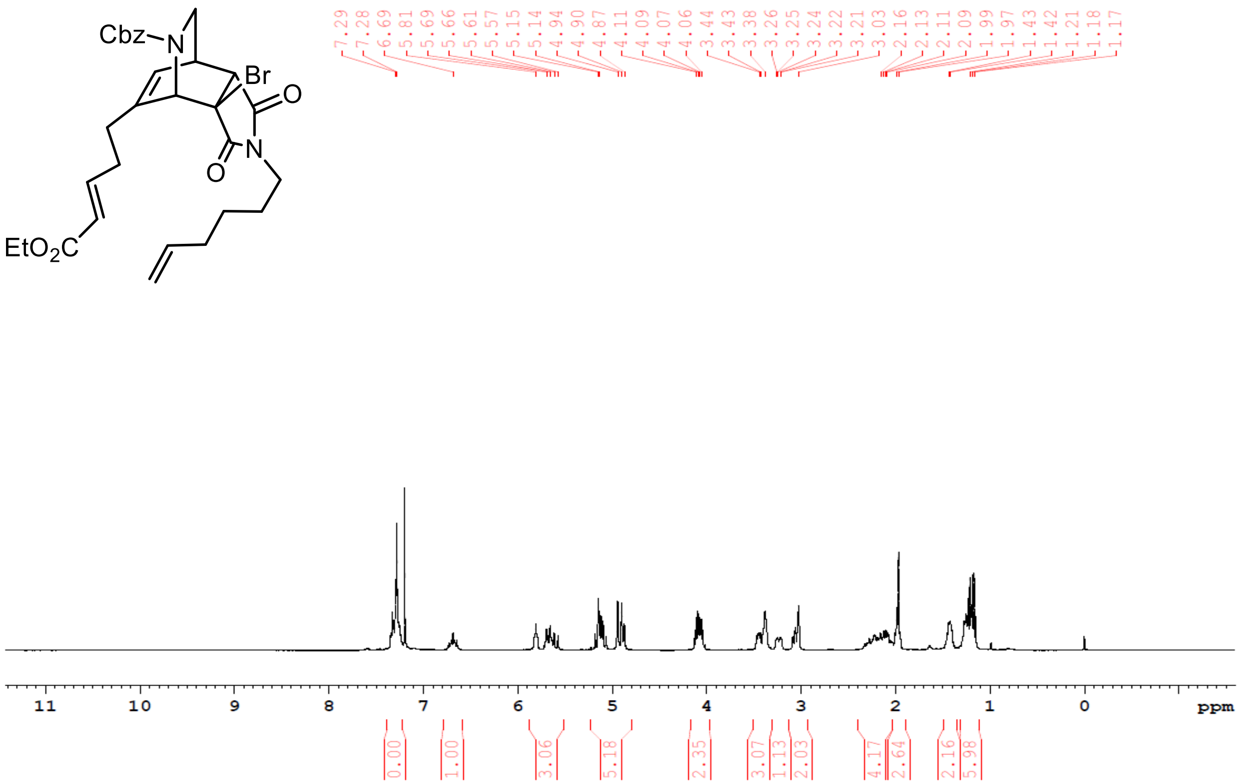


Figure A.4.10 ^{13}C NMR (400 MHz, CDCl$_3$) of **4.14**



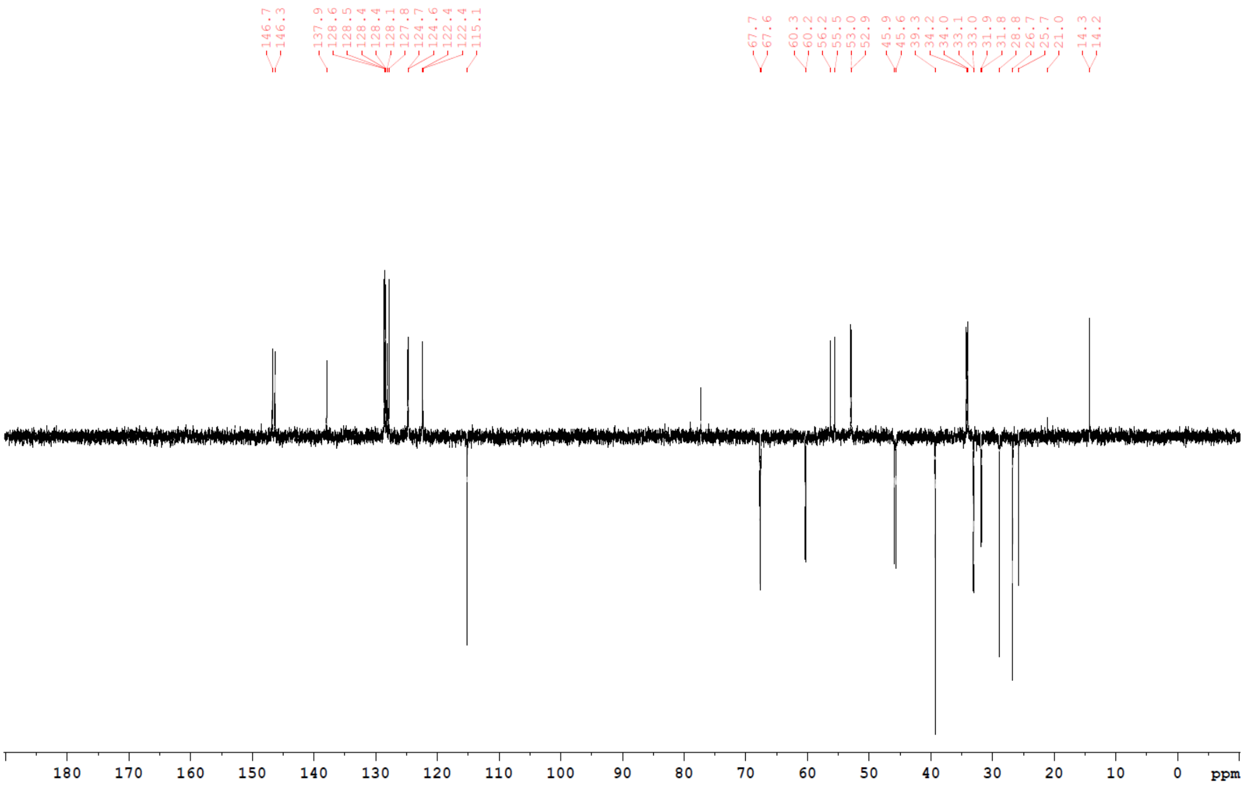


Figure A.4.11 ^{1}H NMR (400 MHz, CDCl$_3$) and DEPT-135 NMR (400 MHz, CDCl$_3$) of **4.15**

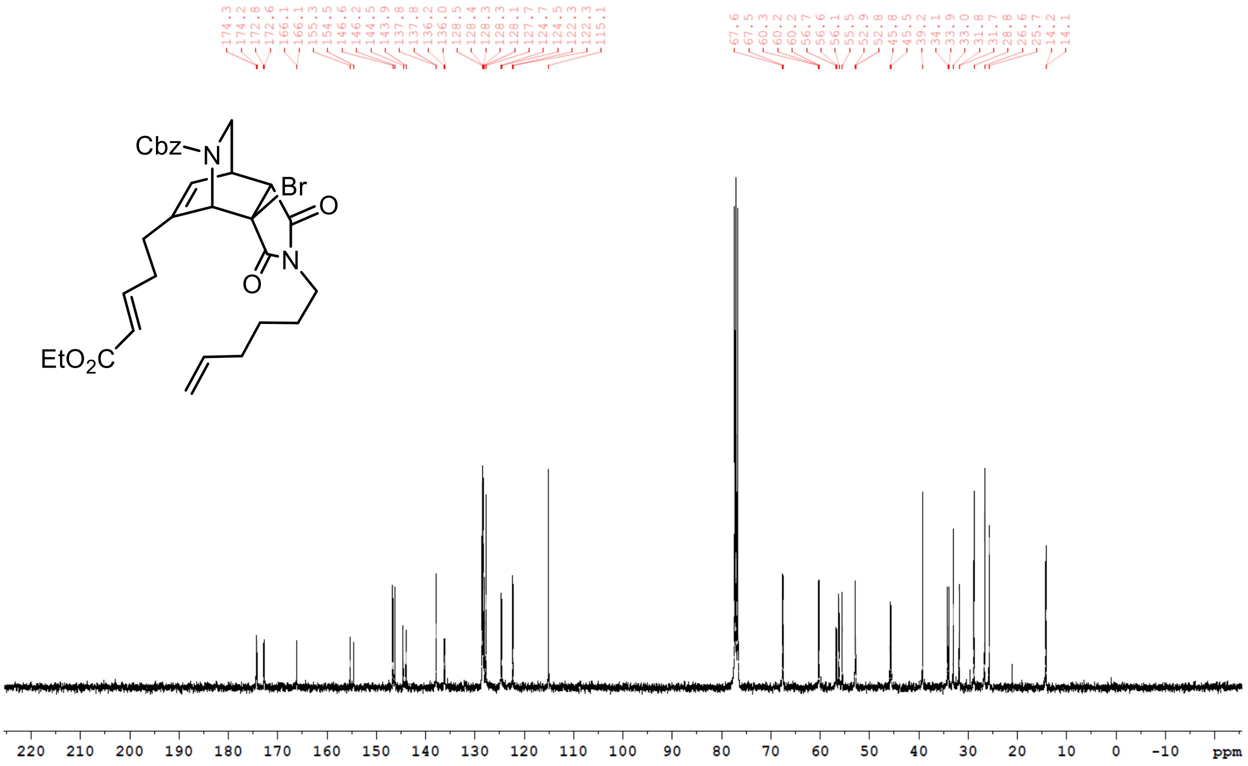


Figure A.4.12 ^{13}C NMR (400 MHz, CDCl$_3$) of **4.15**

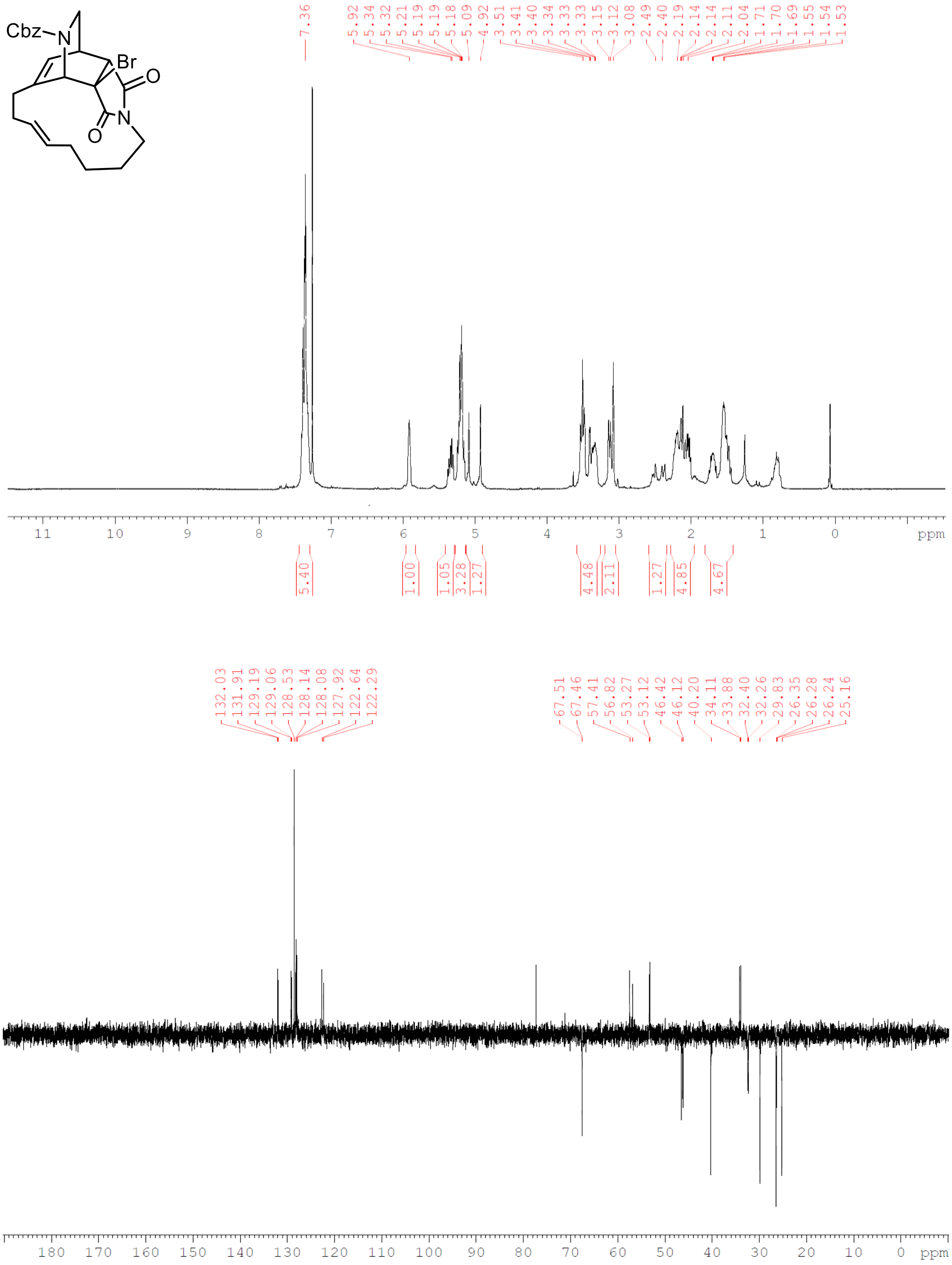


Figure A.4.13 ^{1}H NMR (400 MHz, $CDCl_3$) and DEPT-135 NMR (400 MHz, $CDCl_3$) of **4.20**

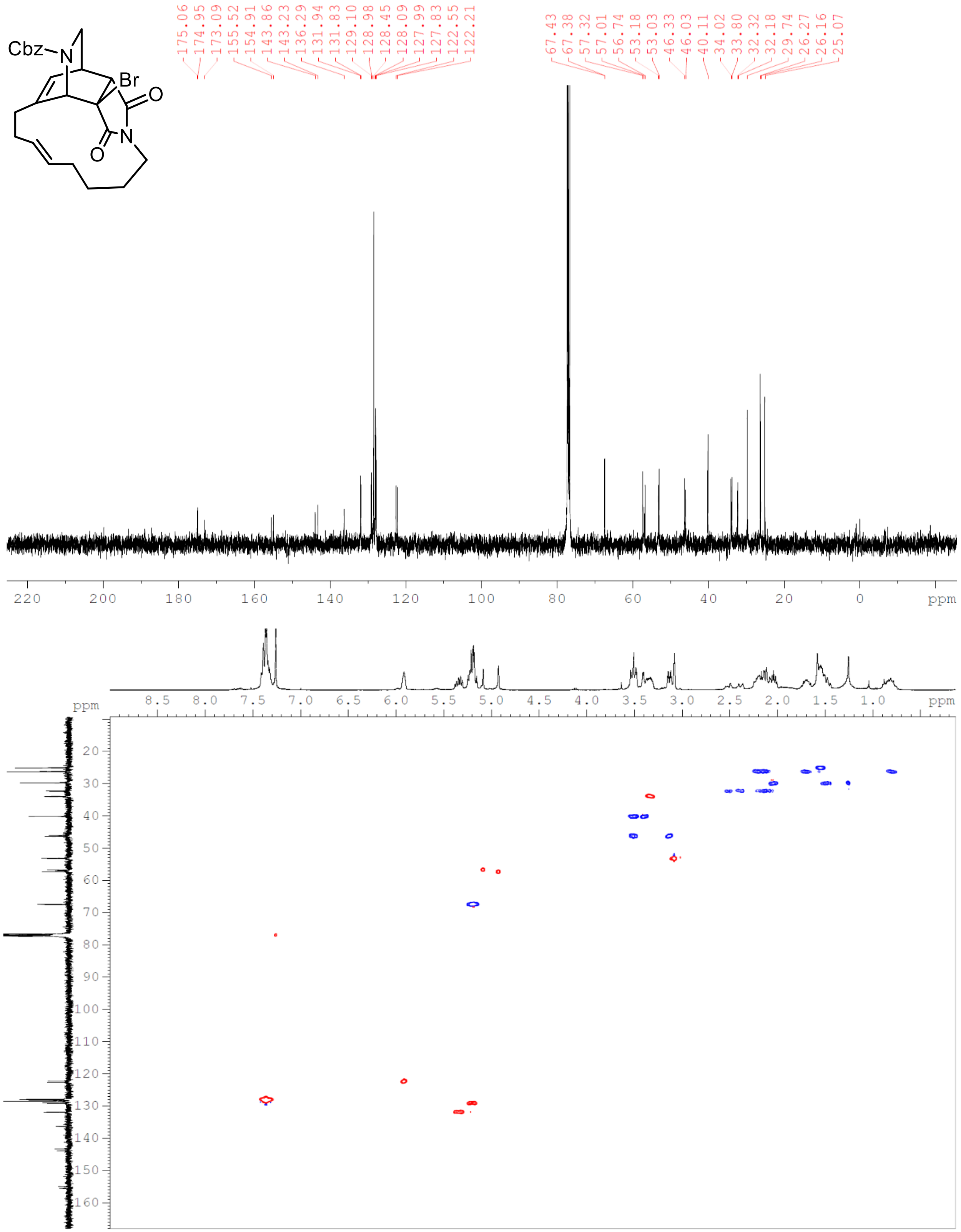


Figure A.4.14 ^{13}C NMR (400 MHz, CDCl$_3$) and HSQC NMR (400 MHz, CDCl$_3$) of **4.20**

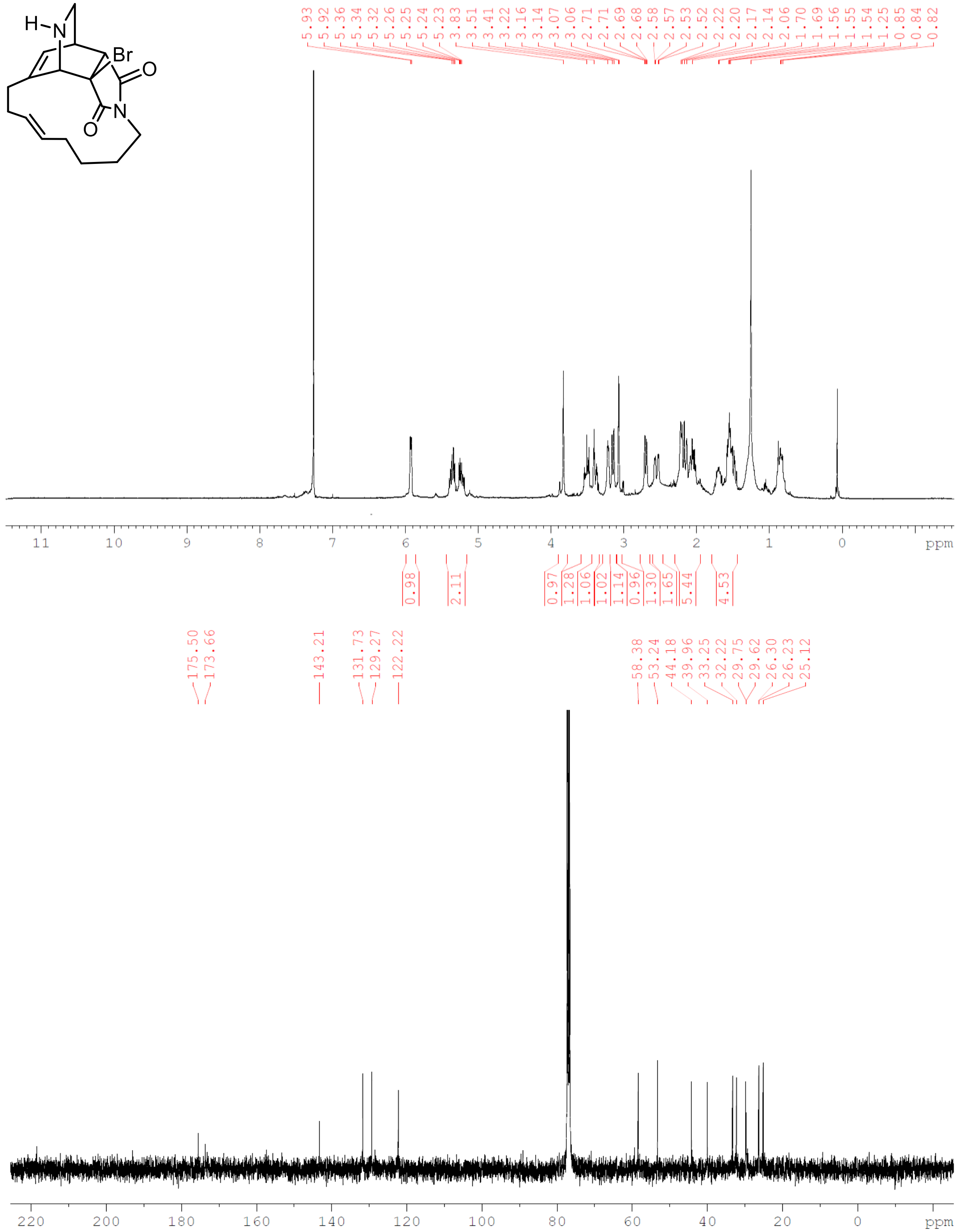


Figure A.4.15 ^{1}H NMR (400 MHz, $CDCl_3$) and DEPT-135 NMR (400 MHz, $CDCl_3$) of **4.21**

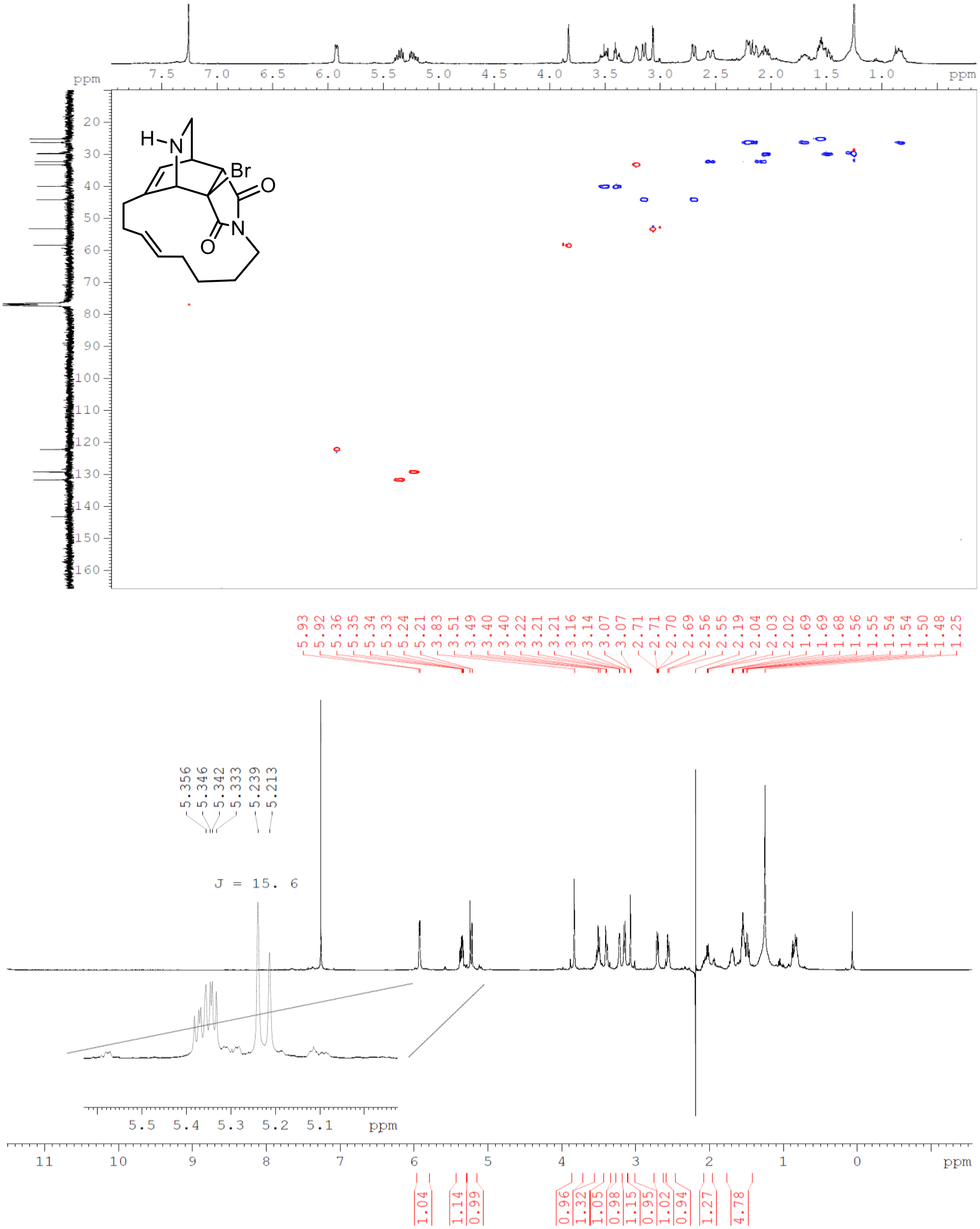


Figure A.4.16 HSQC NMR (400 MHz, $CDCl_3$) and 1D ^1H Homodecoupling NOE NMR at 2.22 ppm (400 MHz, $CDCl_3$) of **4.21**

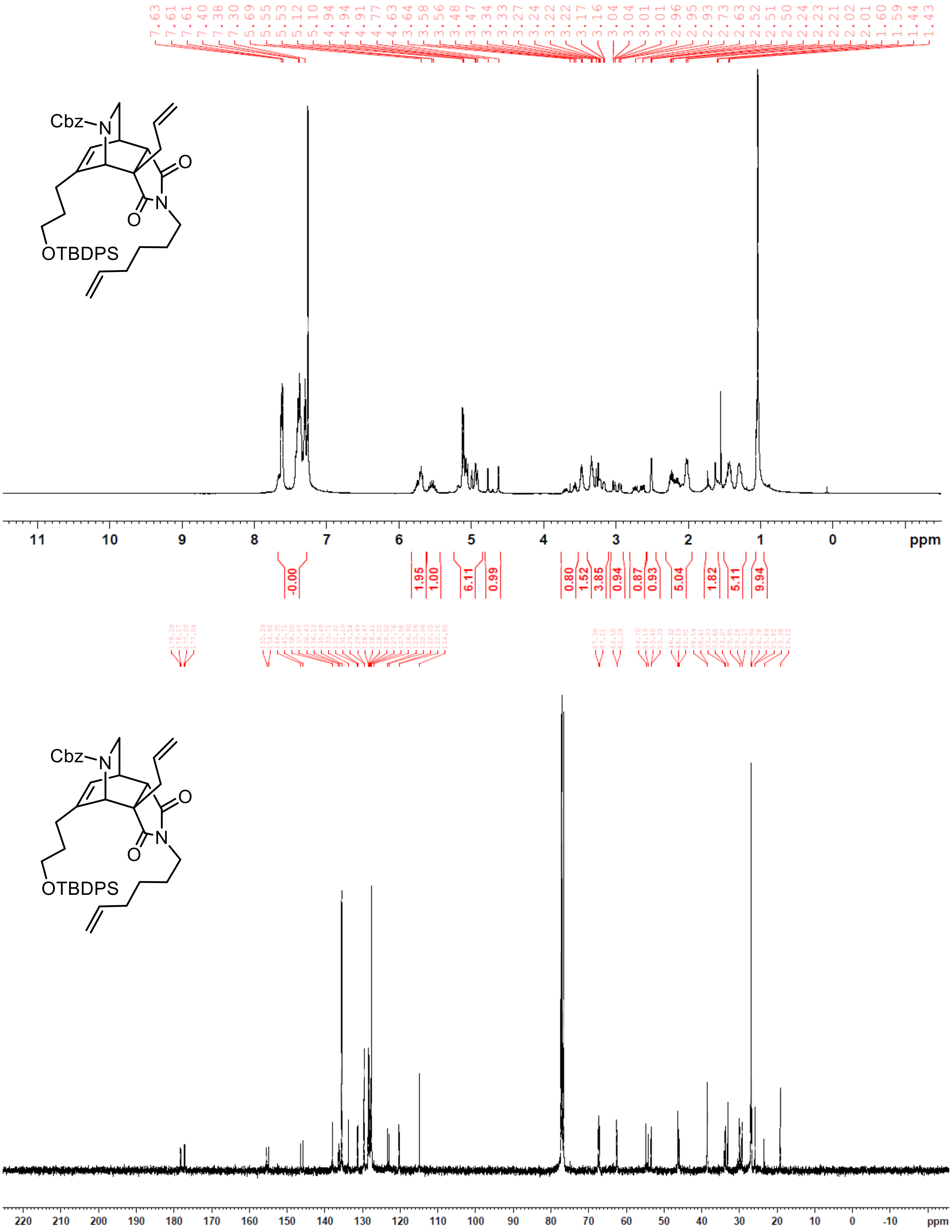


Figure A.4.17 ^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (400 MHz, CDCl$_3$) of **4.22**

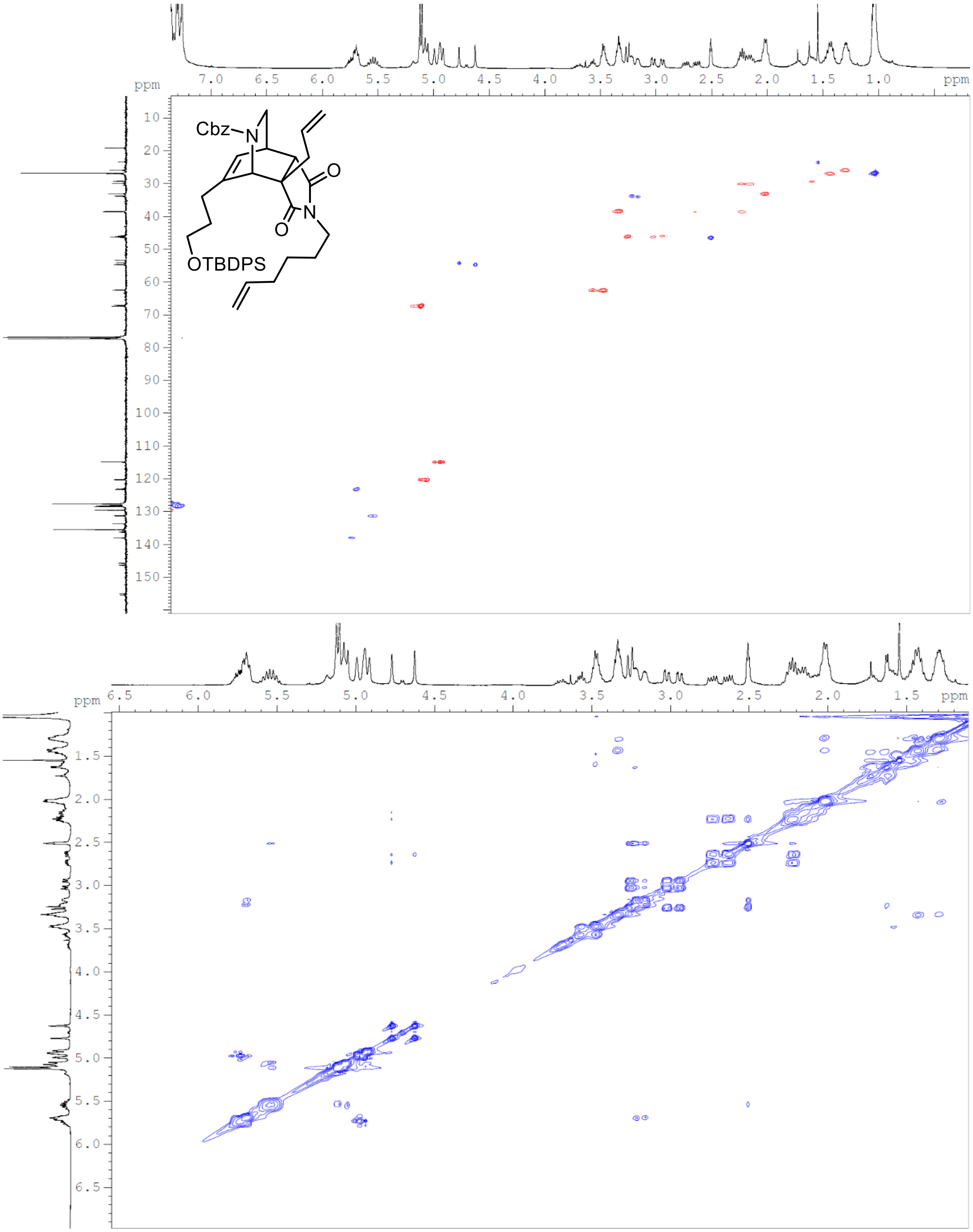


Figure A.4.18 HSQC NMR (400 MHz, $CDCl_3$) and NOESY NMR (400 MHz, $CDCl_3$) of **4.22**

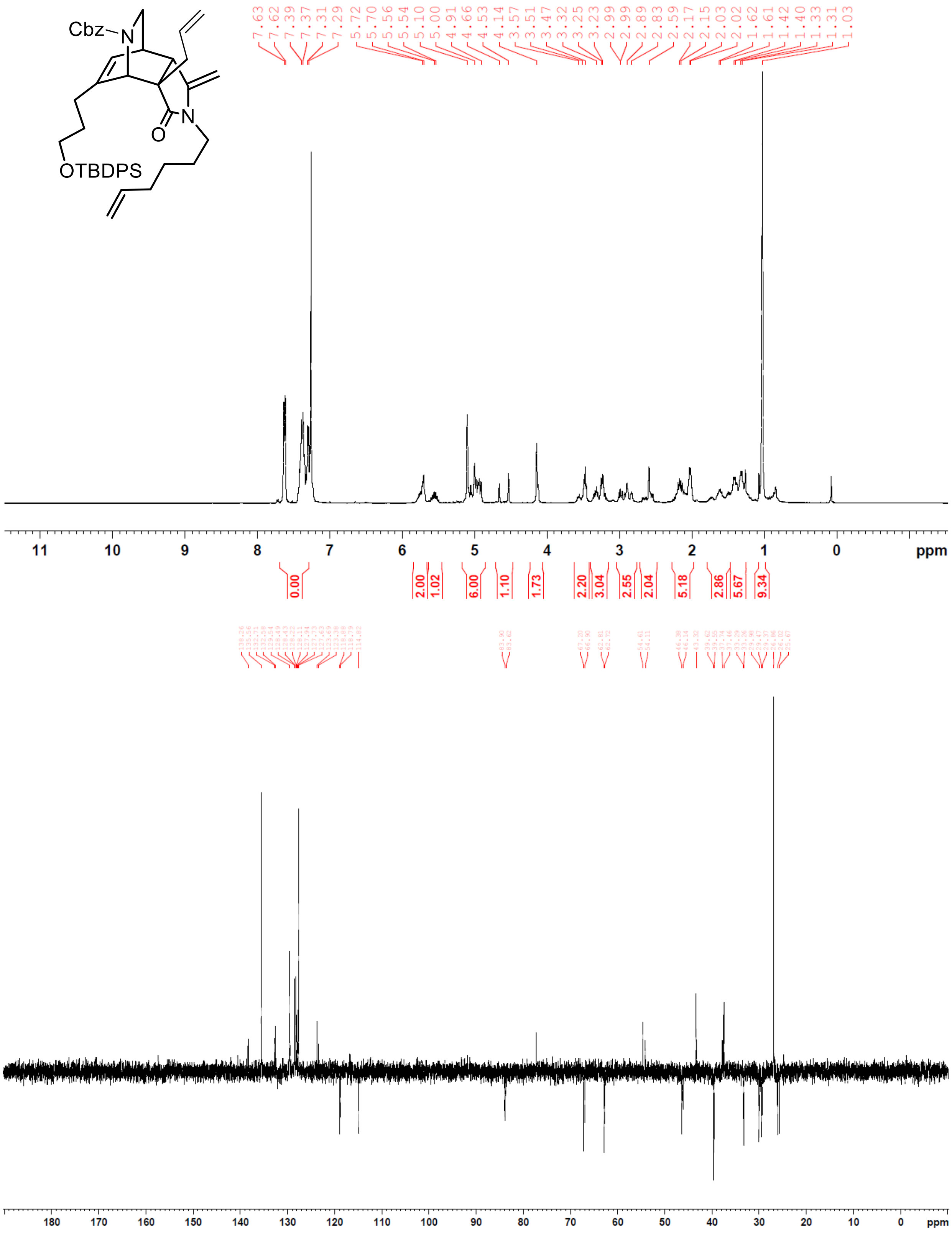


Figure A.4.19 ^1H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (400 MHz, CDCl$_3$) of **4.23**

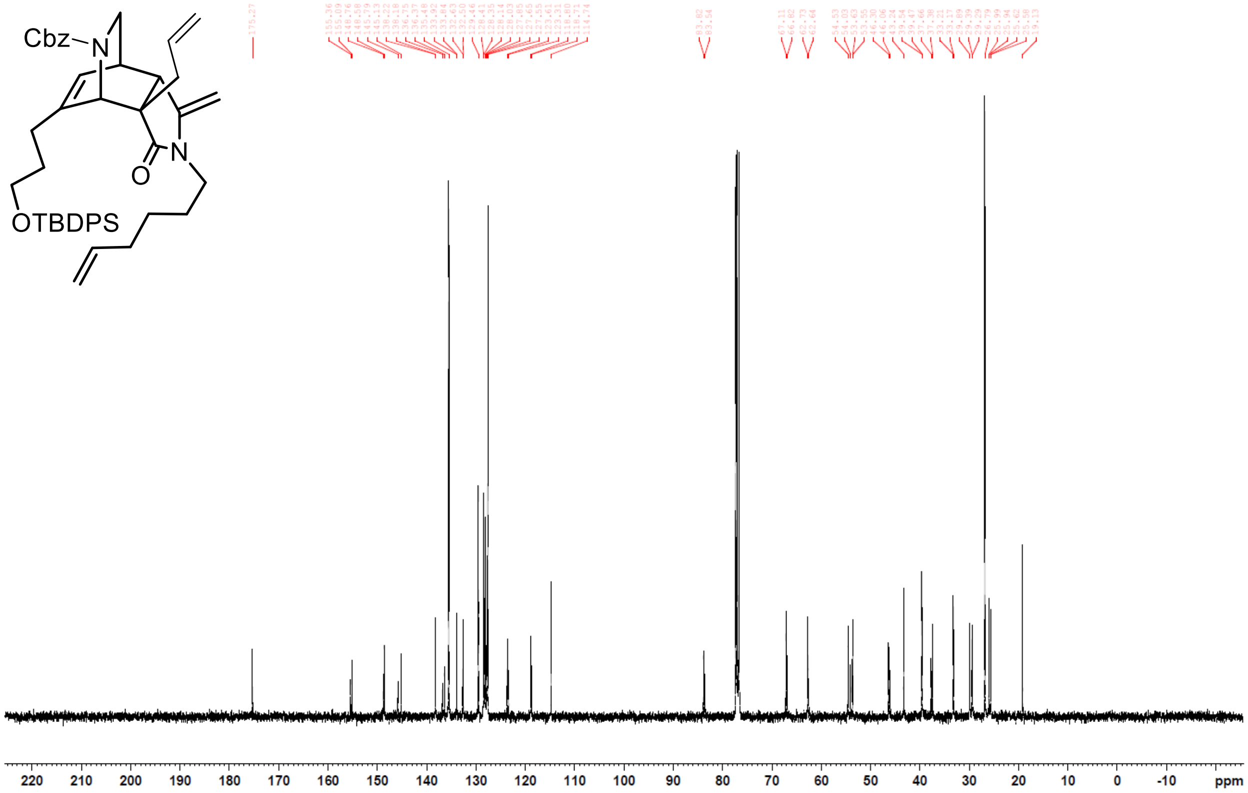


Figure A.4.20 ^{13}C NMR (400 MHz, CDCl$_3$) of **4.23**

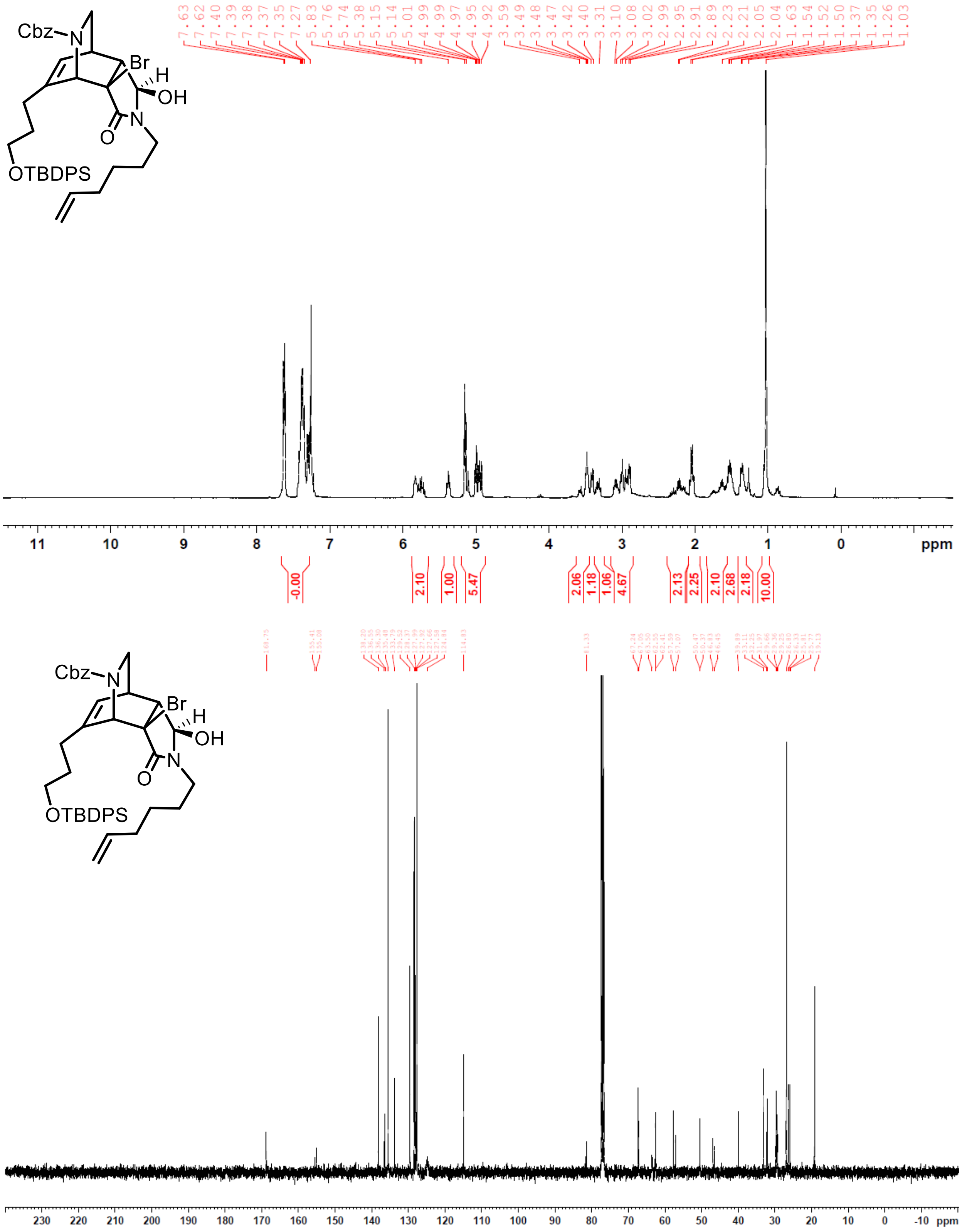


Figure A.4.21 ^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (400 MHz, CDCl$_3$) of **4.24**

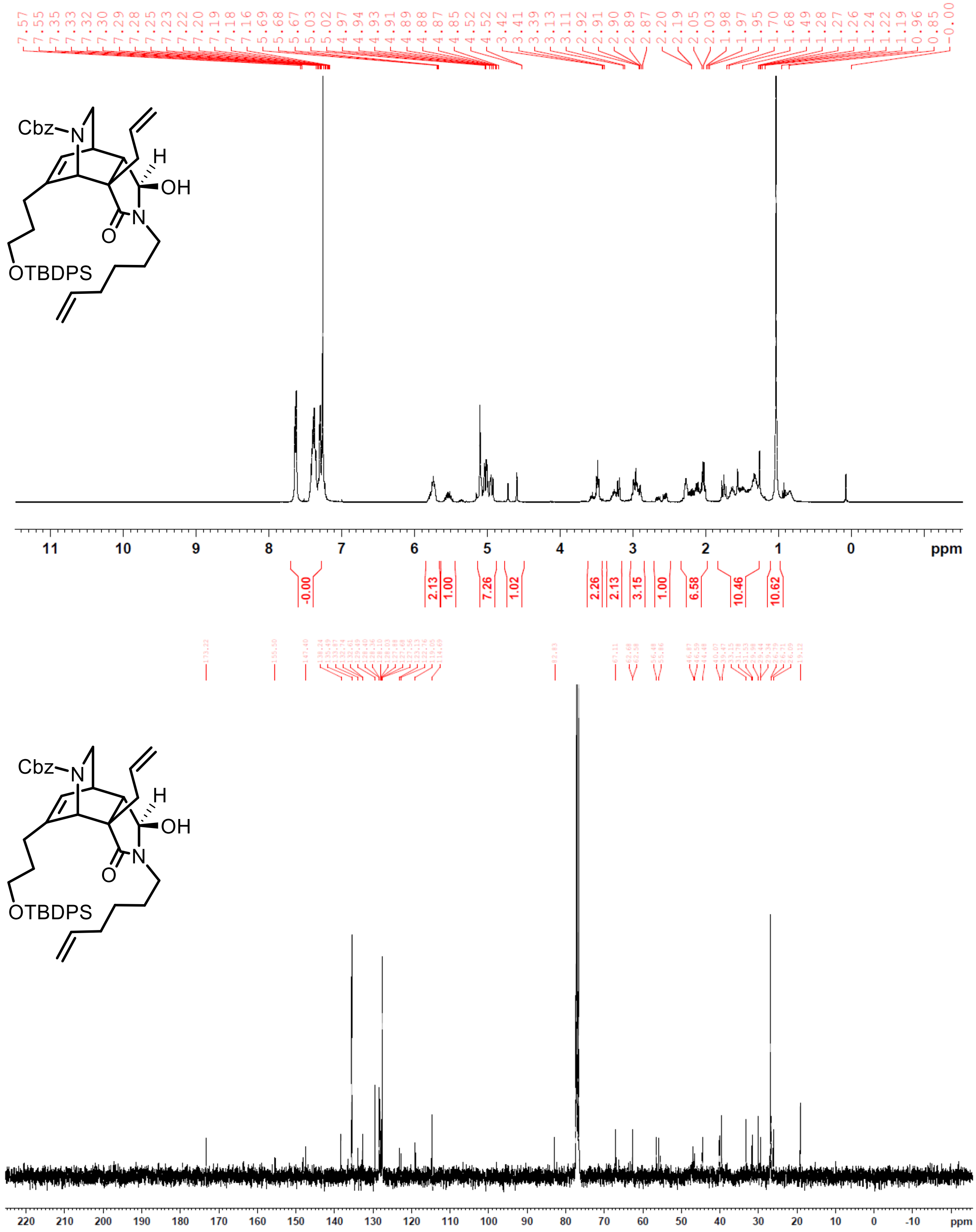


Figure A.4.22 ^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (400 MHz, CDCl$_3$) of **4.25a**

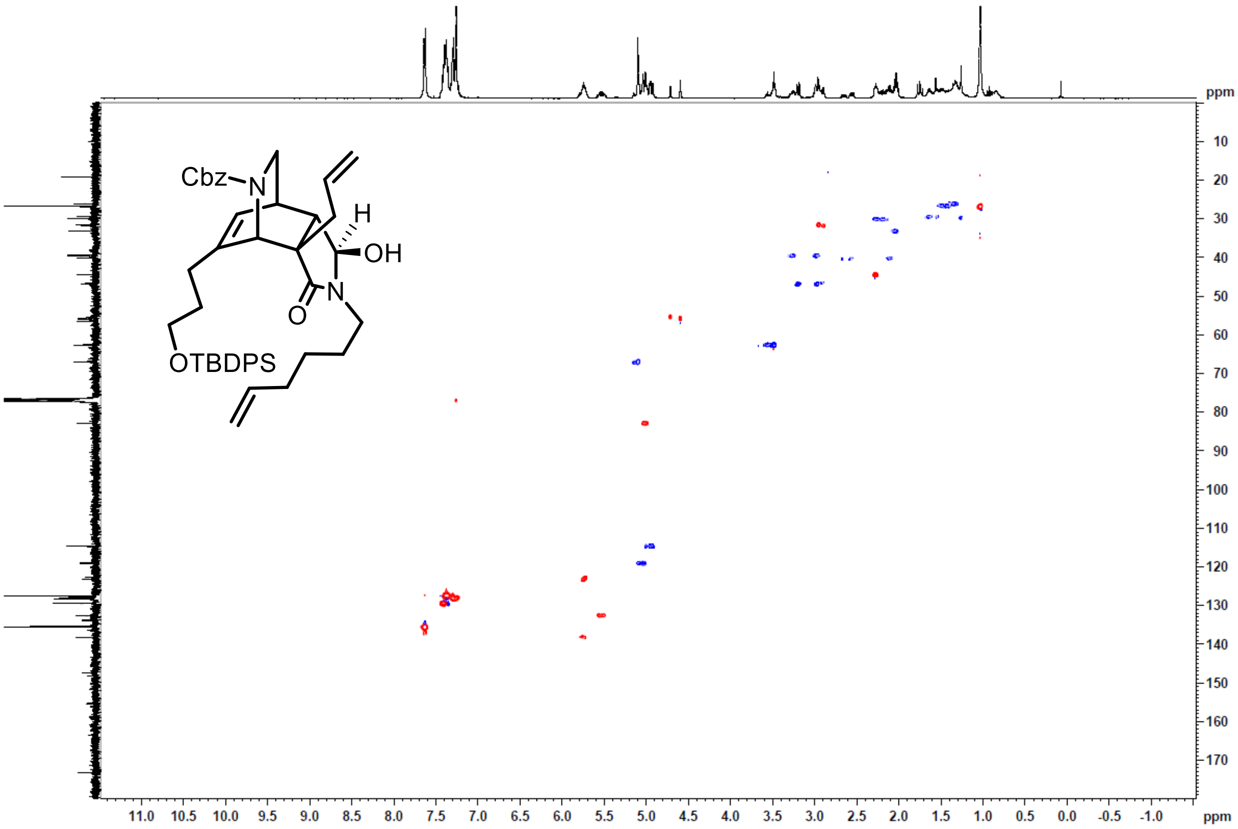


Figure A.4.23 HSQC NMR (400 MHz, CDCl$_3$) of **4.25a**

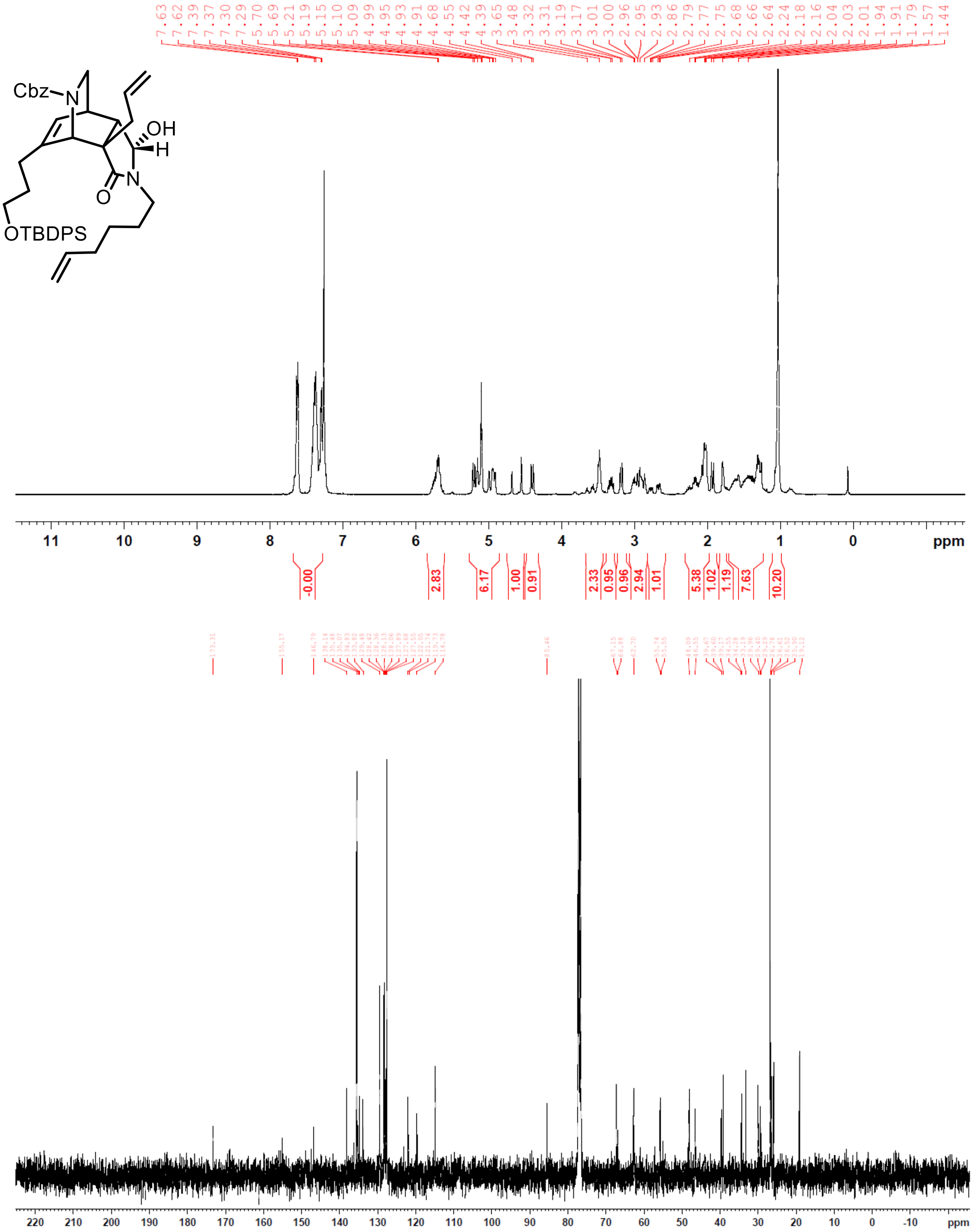


Figure A.4.24 ^1H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (400 MHz, $CDCl_3$) of **4.25b**

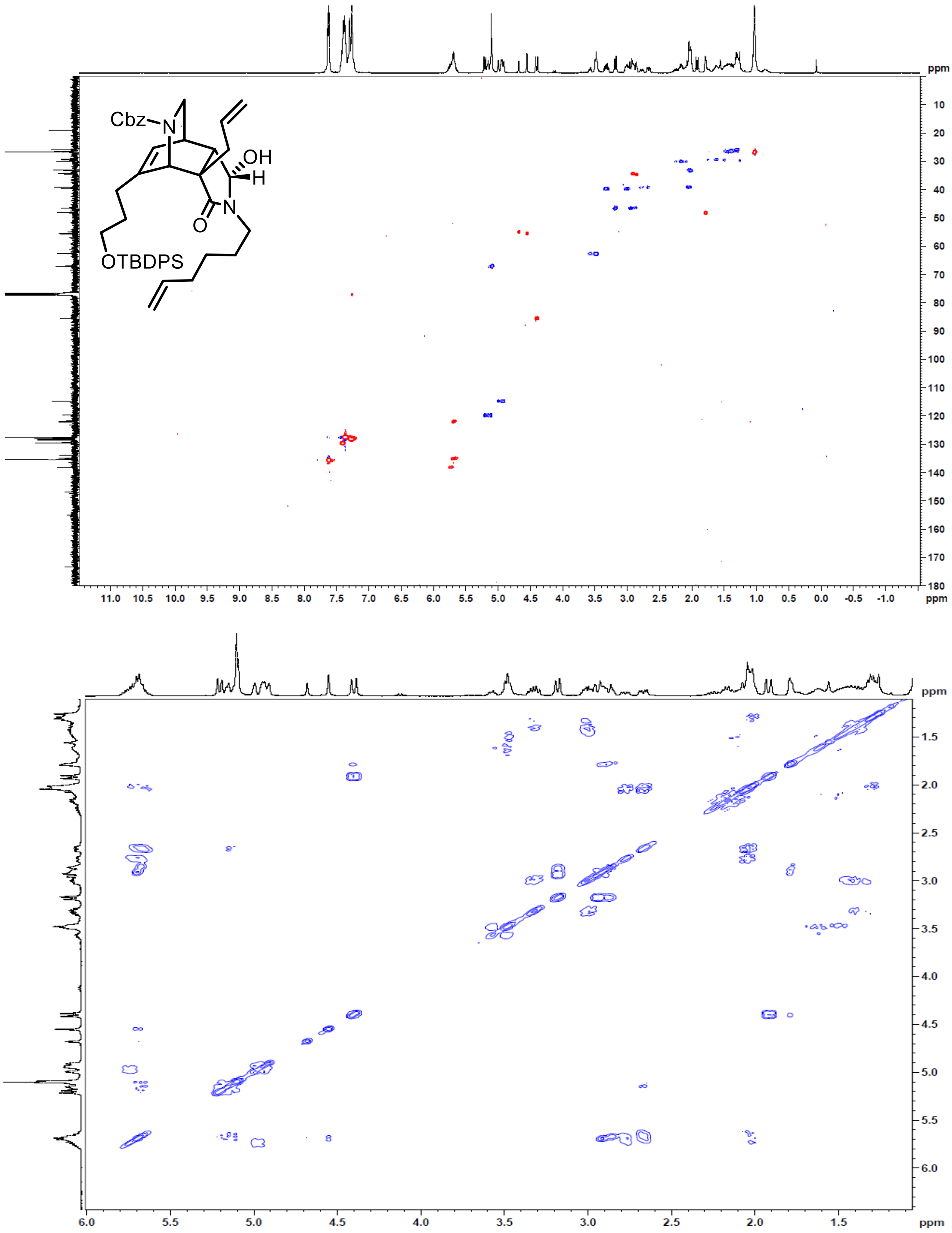


Figure A.4.25 HSQC NMR (400 MHz, $CDCl_3$) and COSY NMR (400 MHz, $CDCl_3$) of **4.25b**

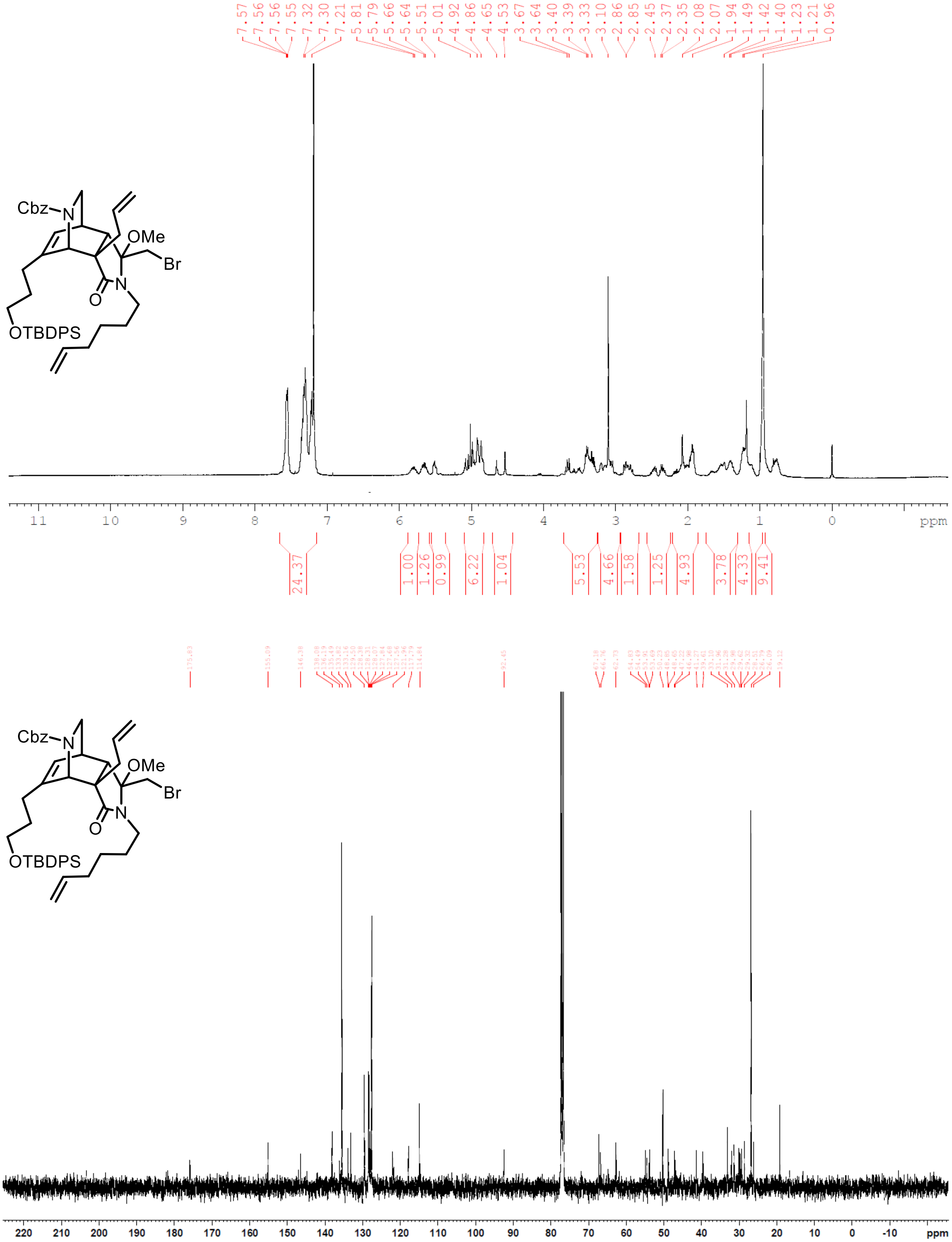


Figure A.4.26 ^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (400 MHz, CDCl$_3$) of **4.26**

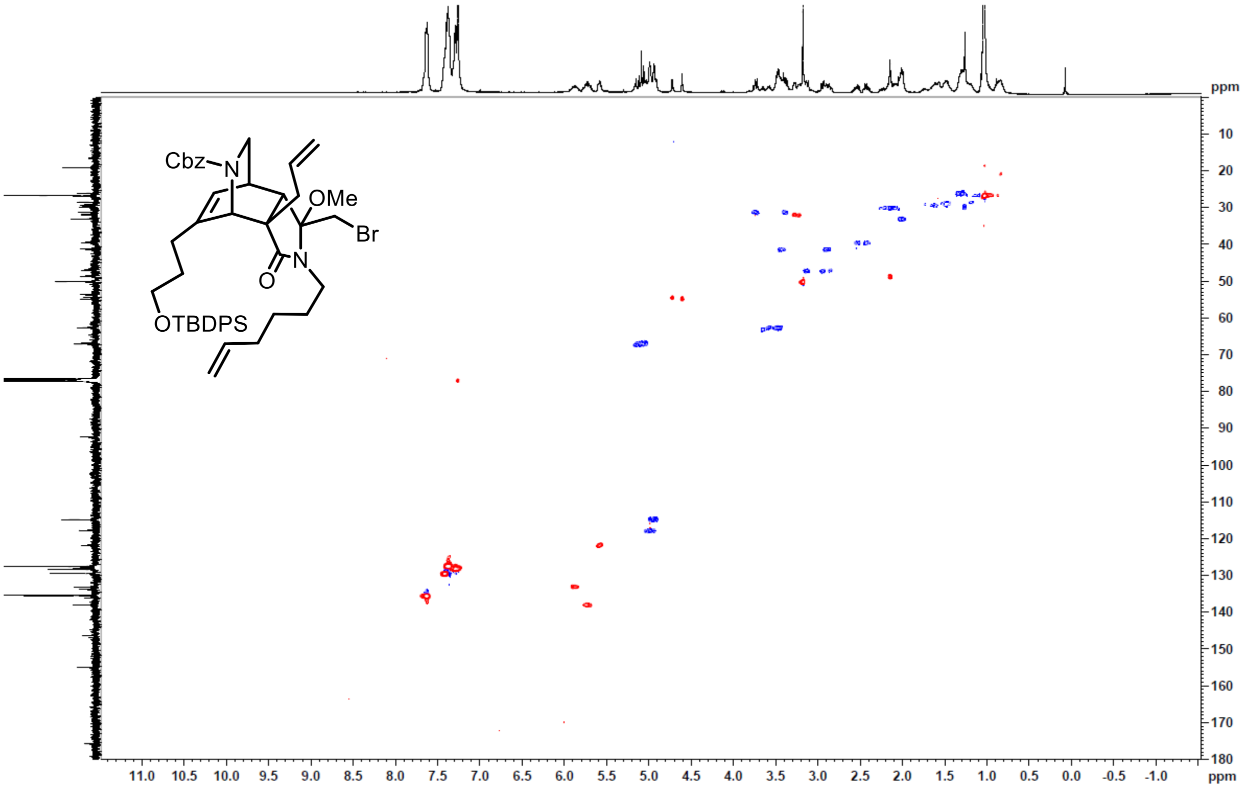


Figure A.4.27 HSQC NMR (400 MHz, $CDCl_3$) of **4.26**

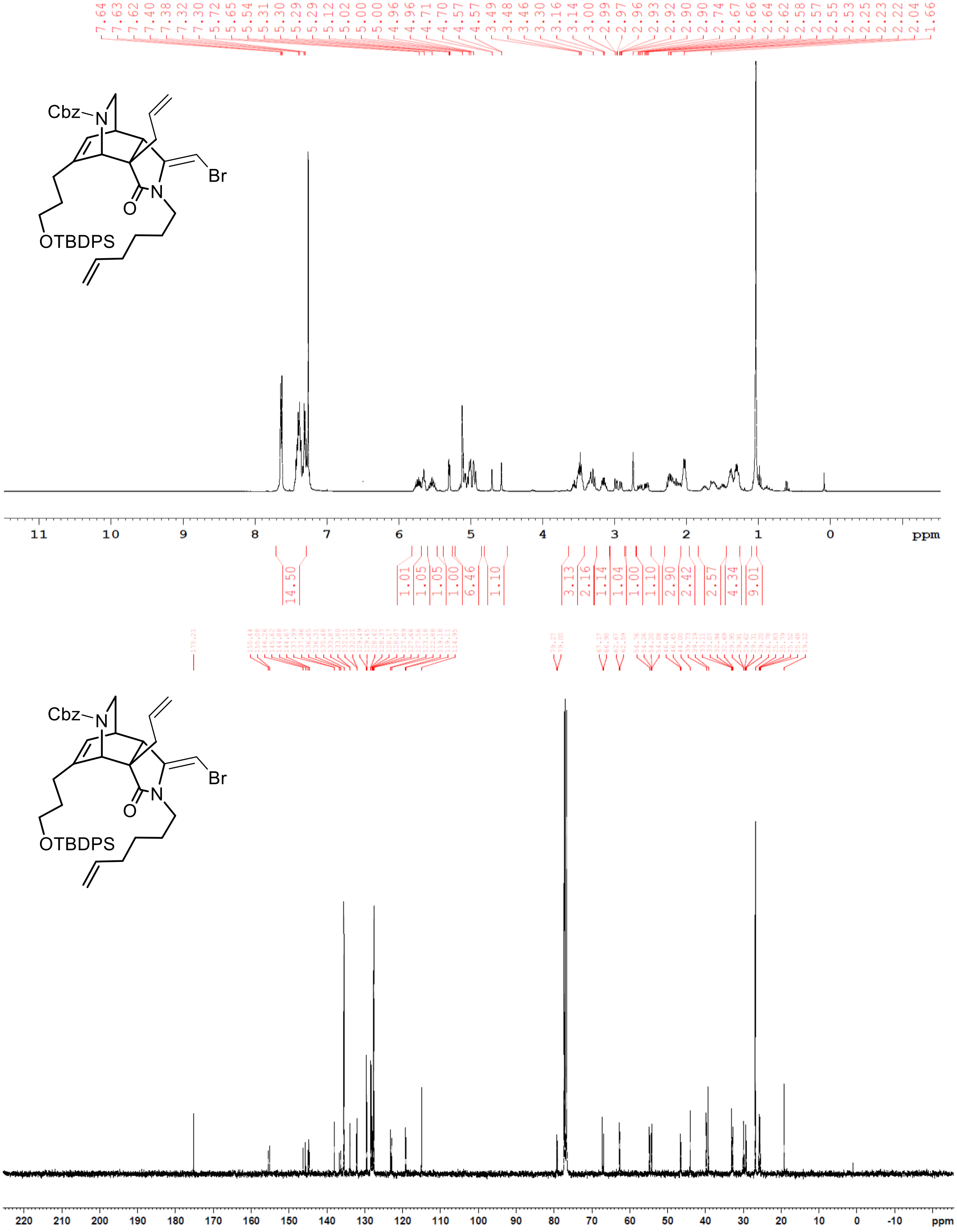


Figure A.4.28 ^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (400 MHz, CDCl$_3$) of **4.29**

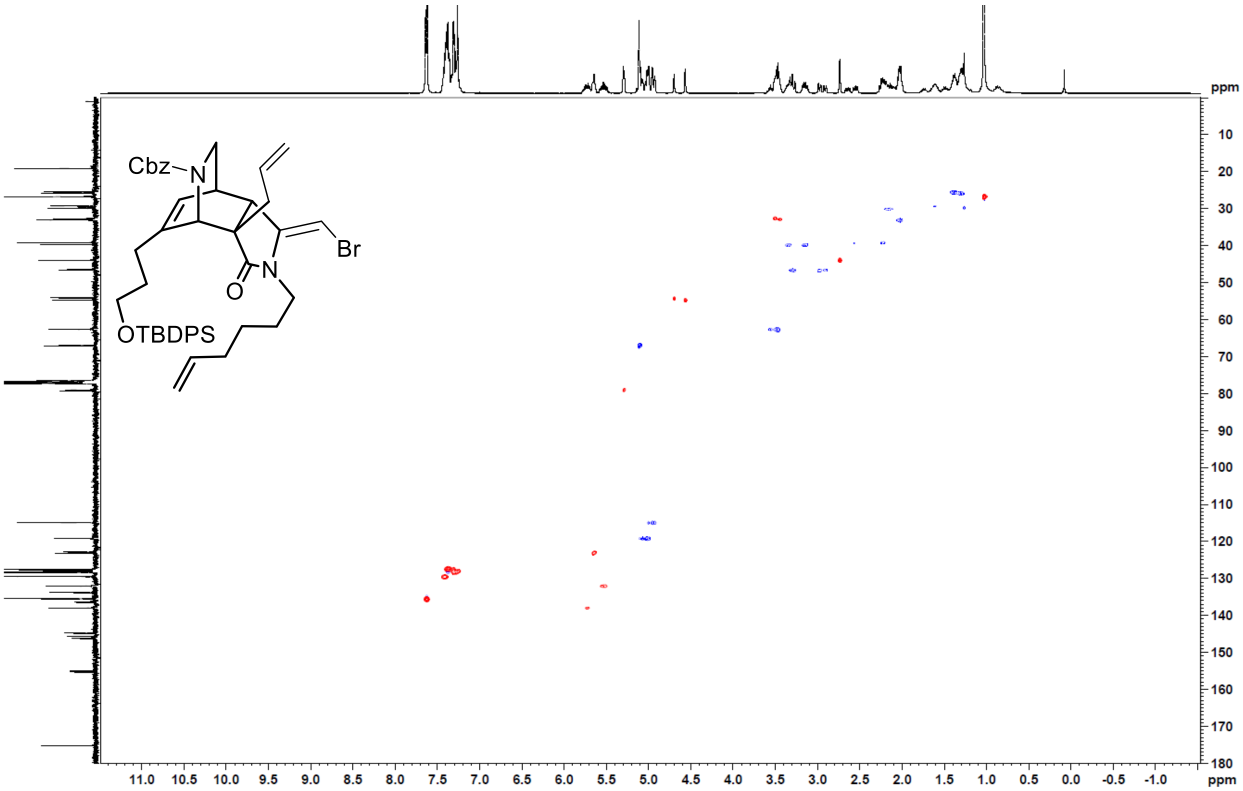


Figure A.4.29 HSQC NMR (400 MHz, CDCl$_3$) and ^{1}H NMR (400 MHz, CDCl$_3$) of **4.29**

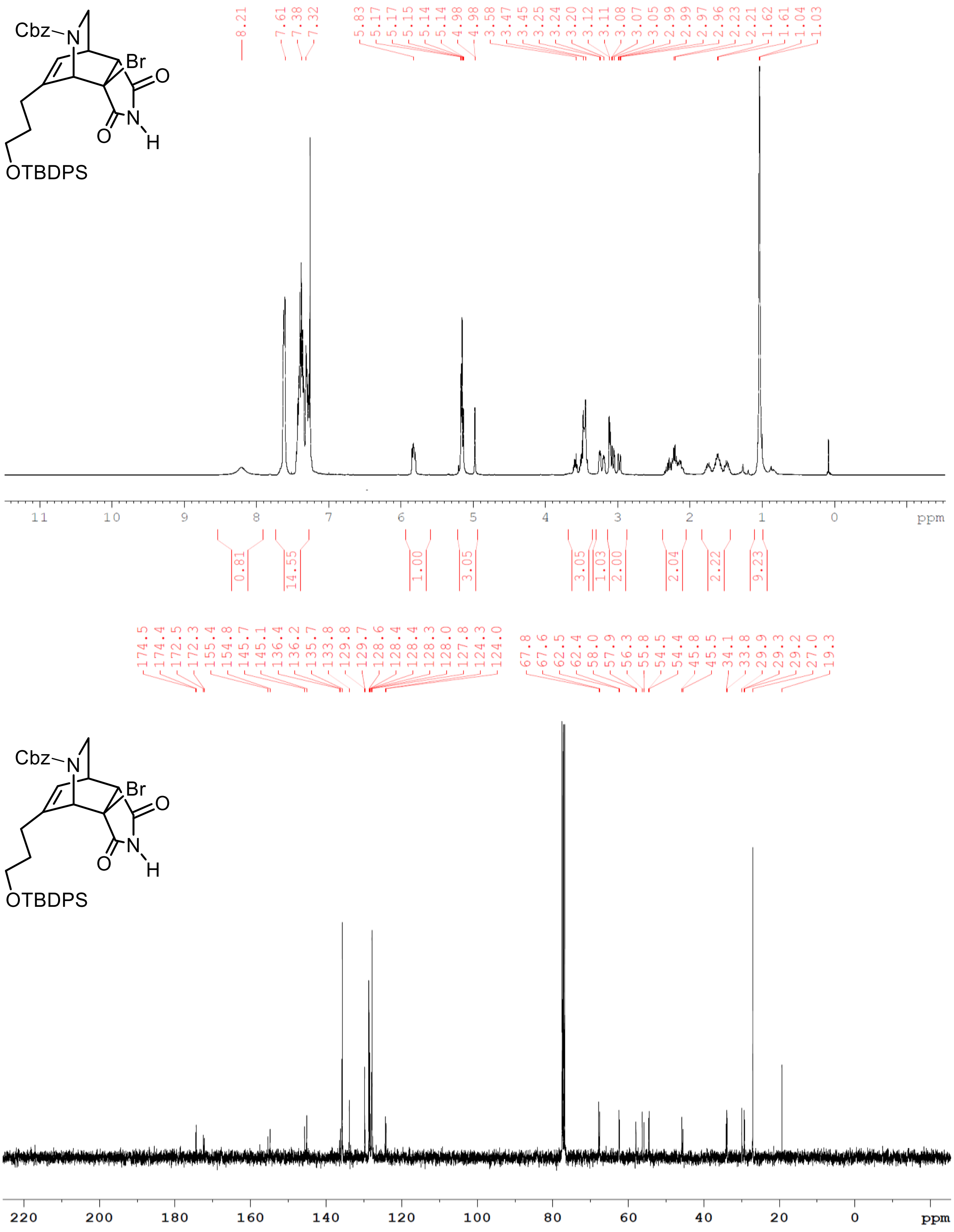


Figure A.4.30 ^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (400 MHz, CDCl$_3$) of **4.31**

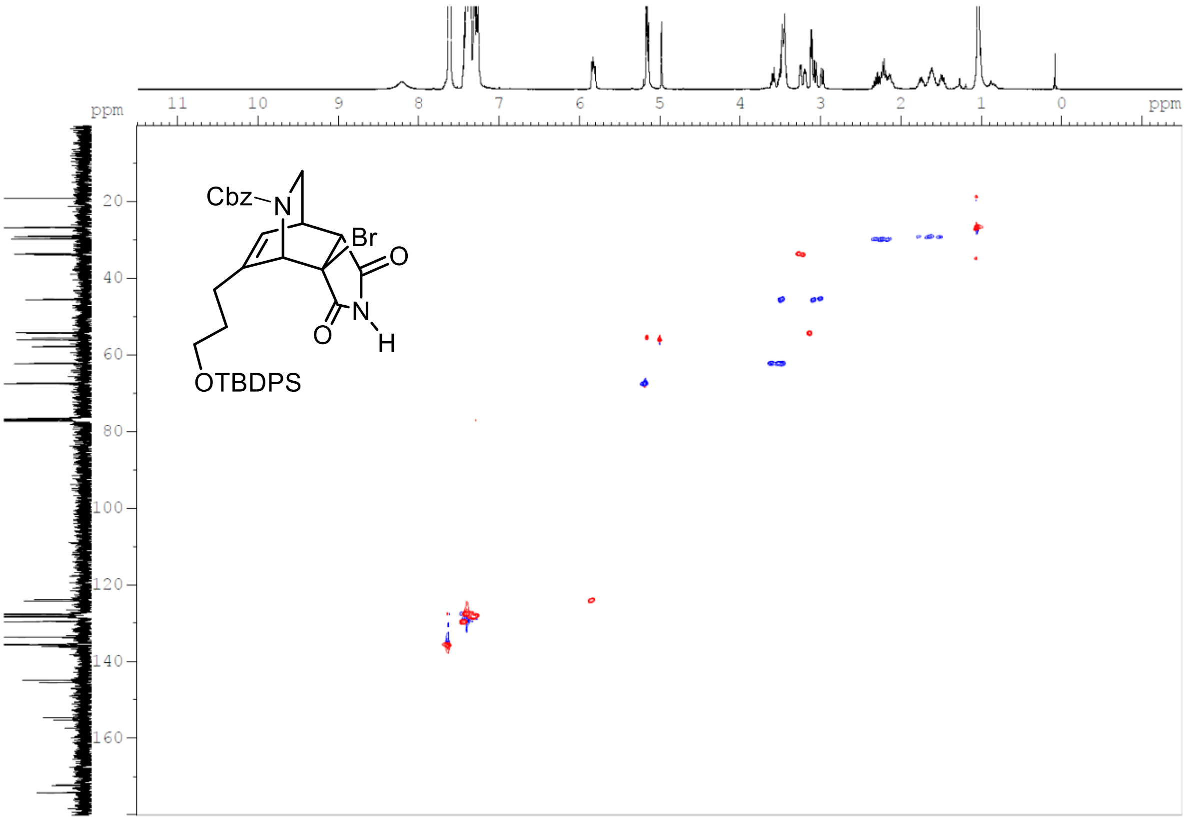


Figure A.4.31 HSQC NMR (400 MHz, CDCl$_3$) of **4.31**

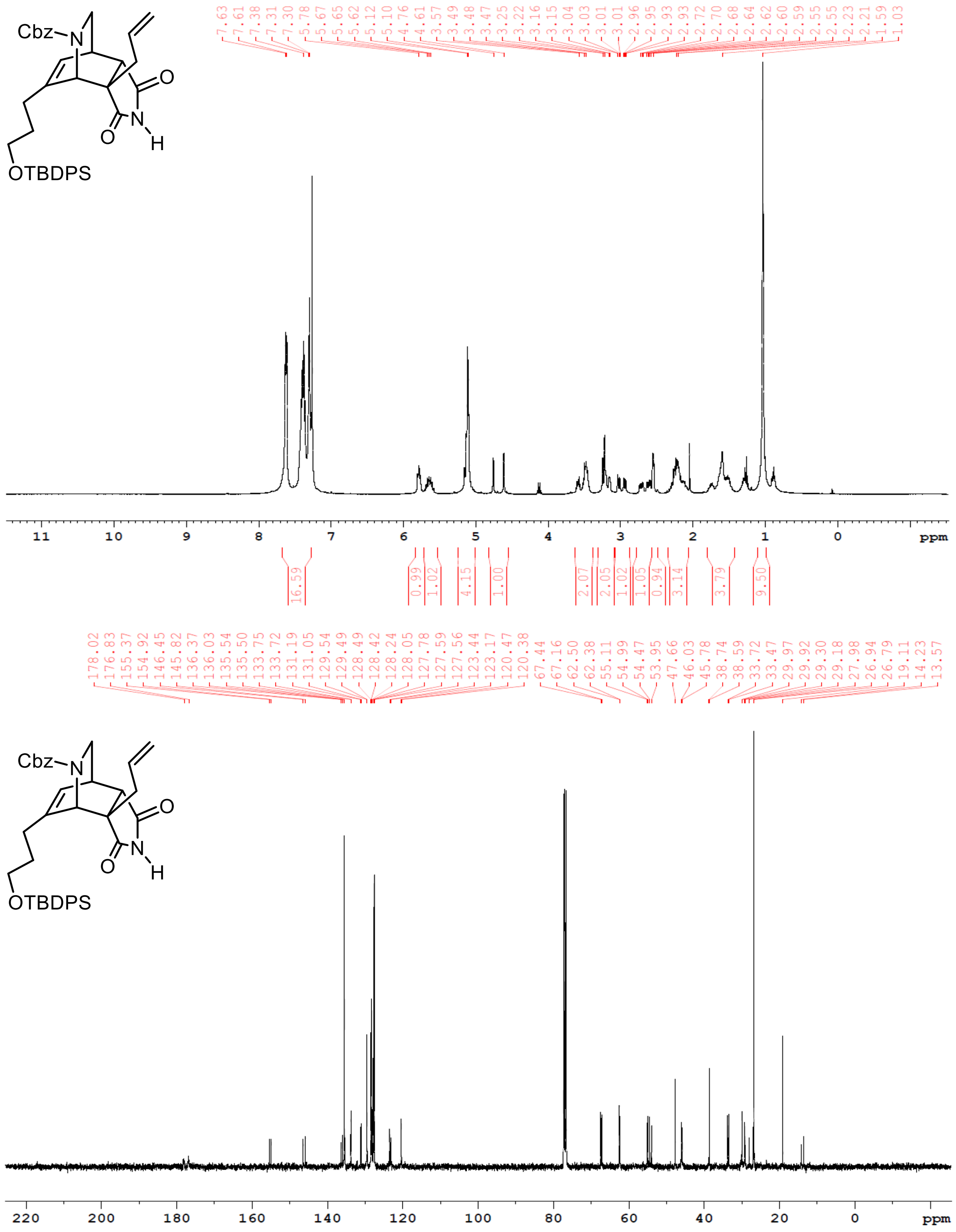


Figure A.4.32 ^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (400 MHz, CDCl$_3$) of **4.32**

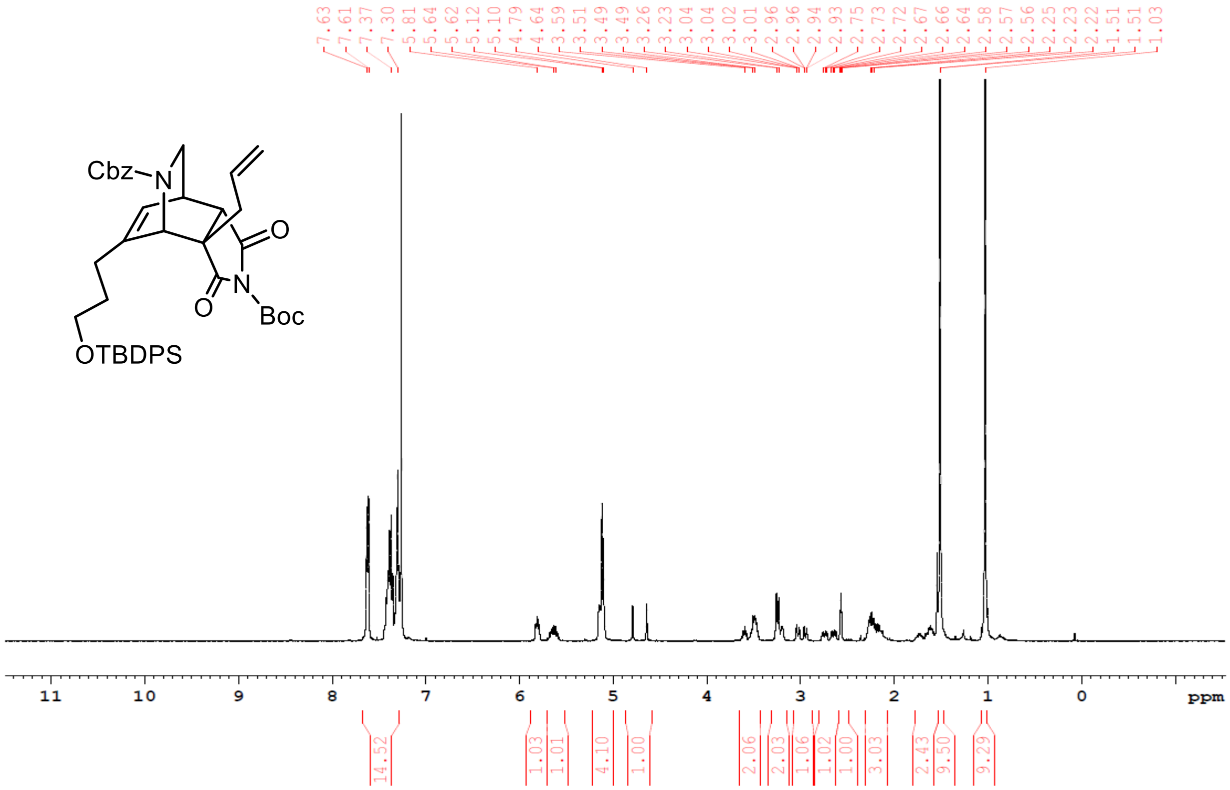


Figure A.4.33 ^{1}H NMR (400 MHz, CDCl$_3$) of **4.33b**

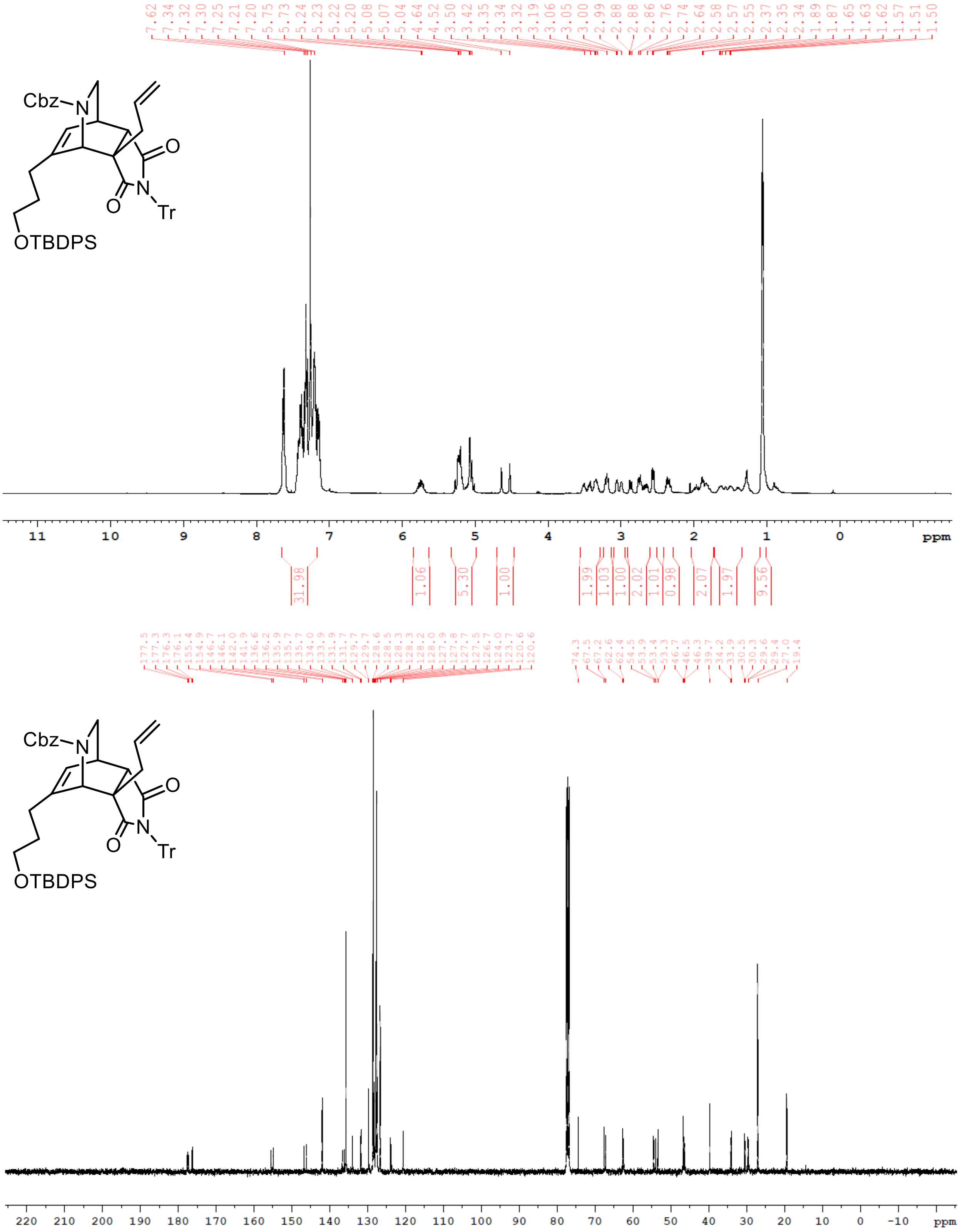


Figure A.4.34 ^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (400 MHz, CDCl$_3$) of **4.33c**

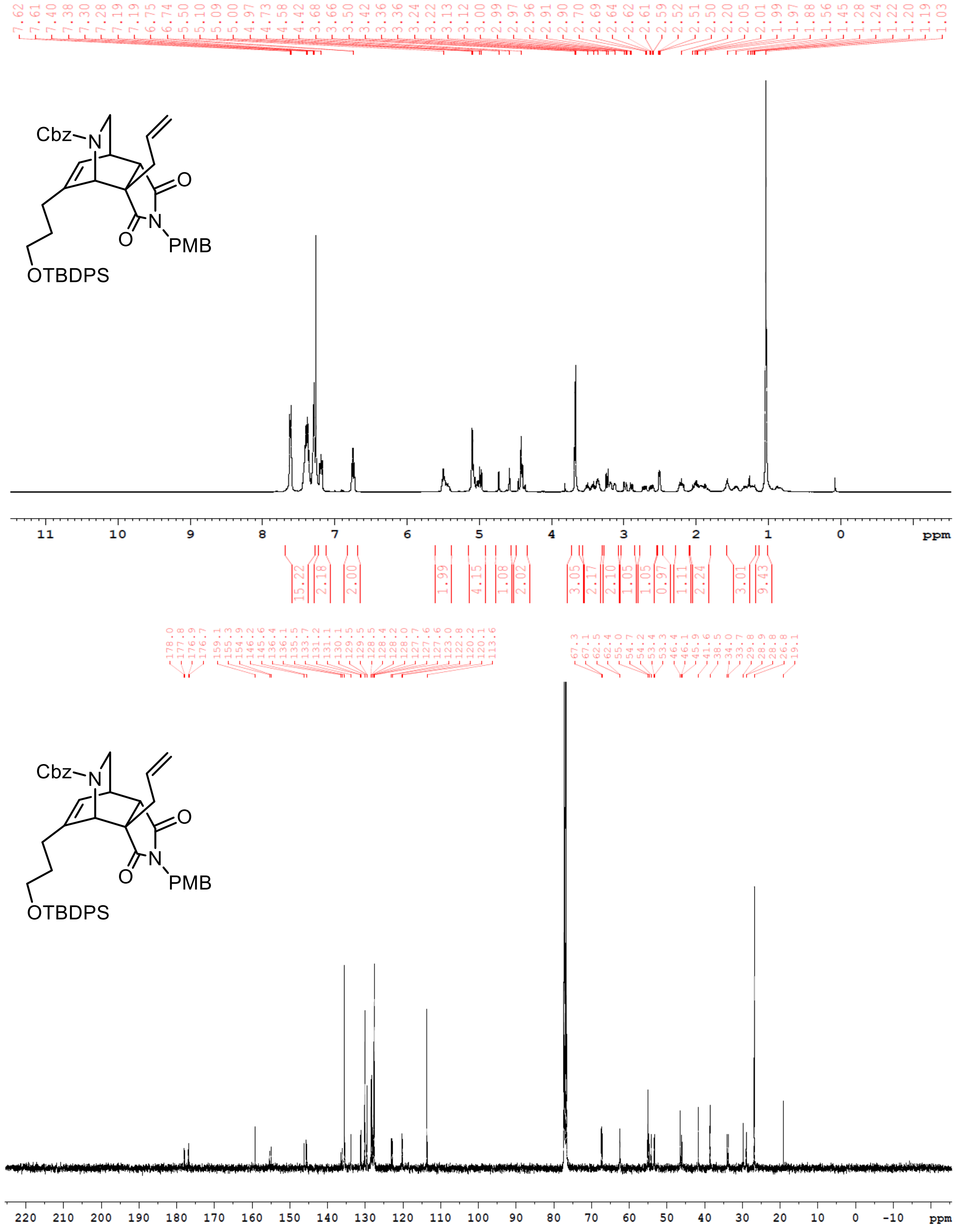


Figure A.4.35 ^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (400 MHz, CDCl$_3$) of **4.33d**

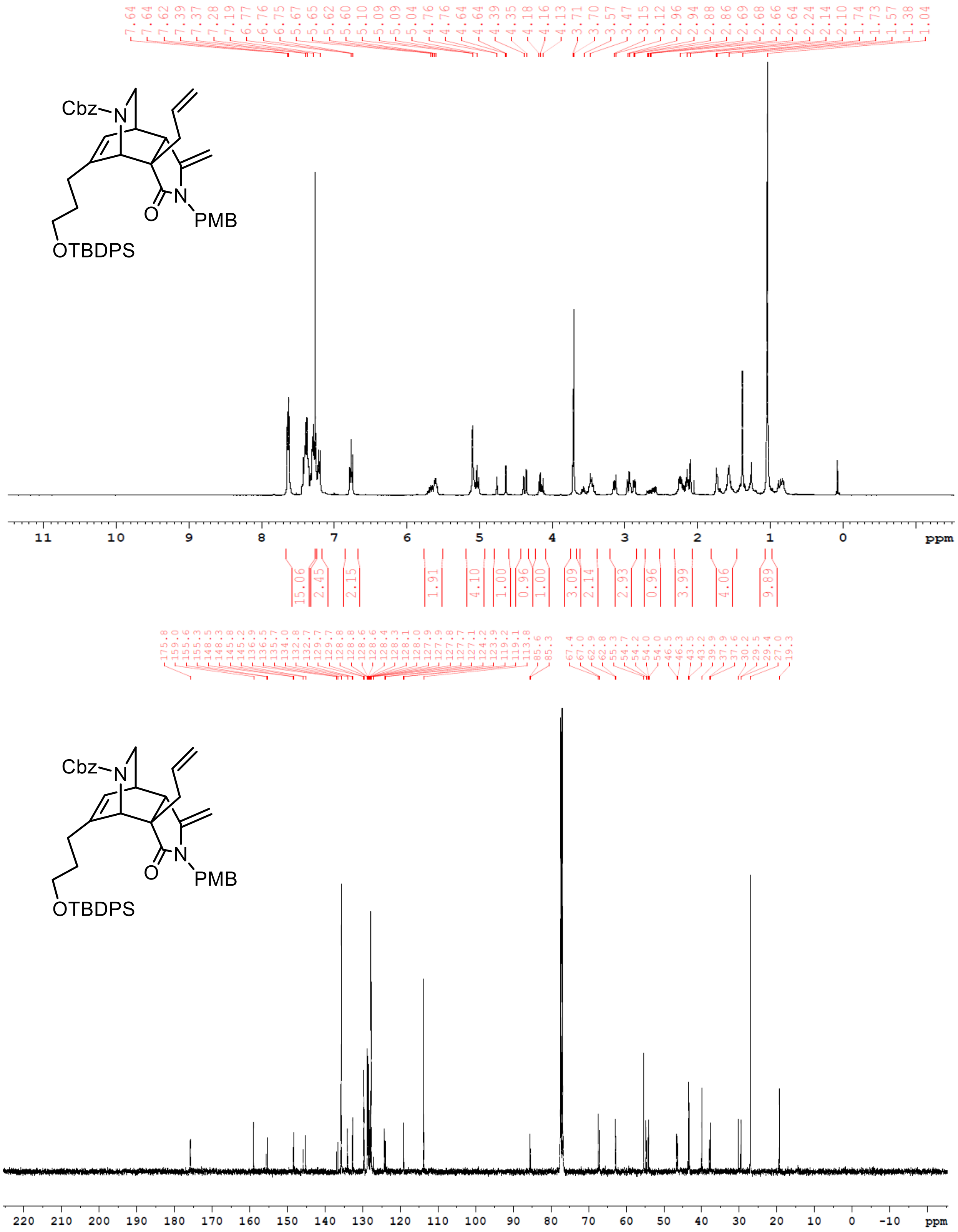


Figure A.4.36 ^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (400 MHz, CDCl$_3$) of **4.34d**

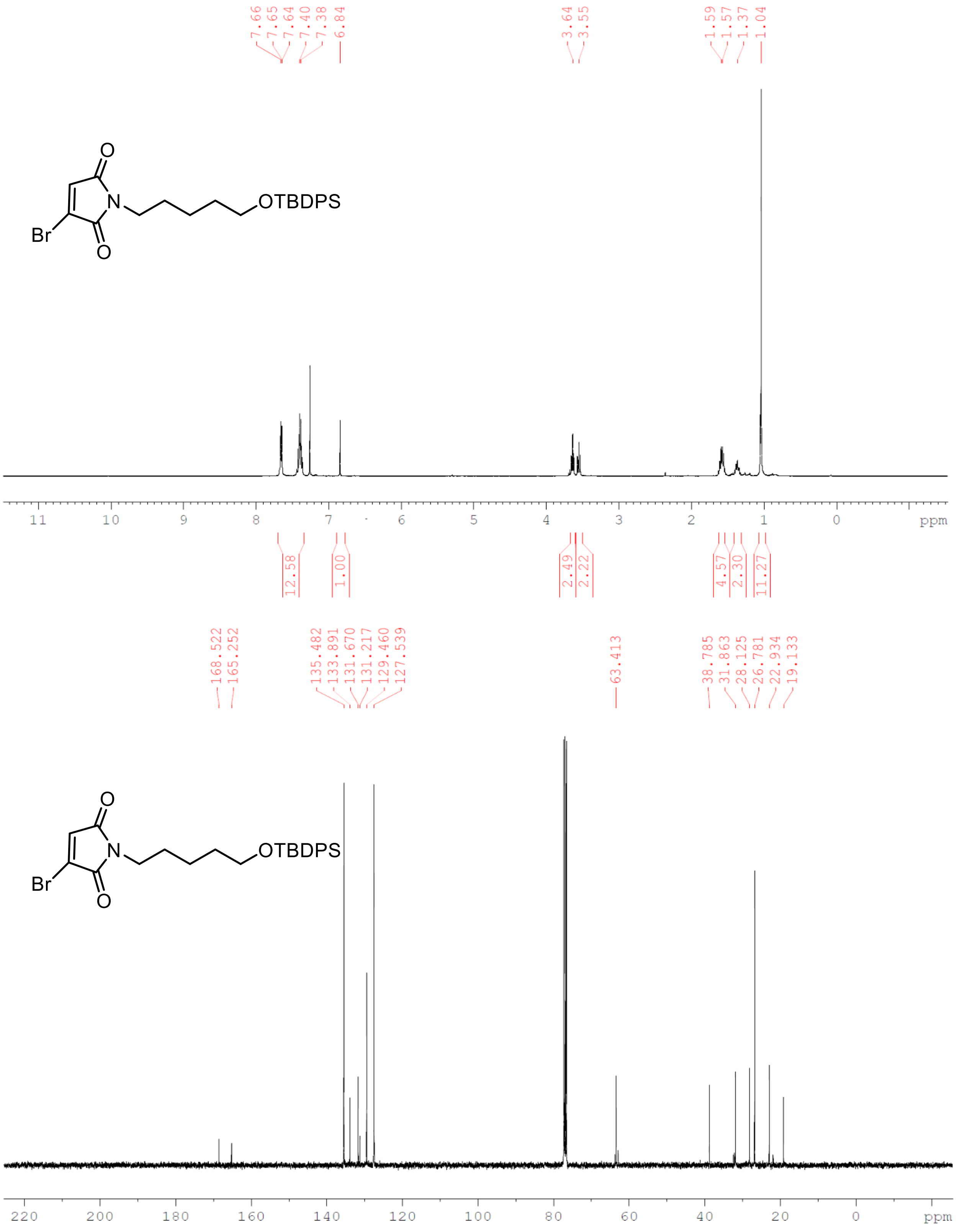


Figure A.4.37 ^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (400 MHz, CDCl$_3$) of **4.38**

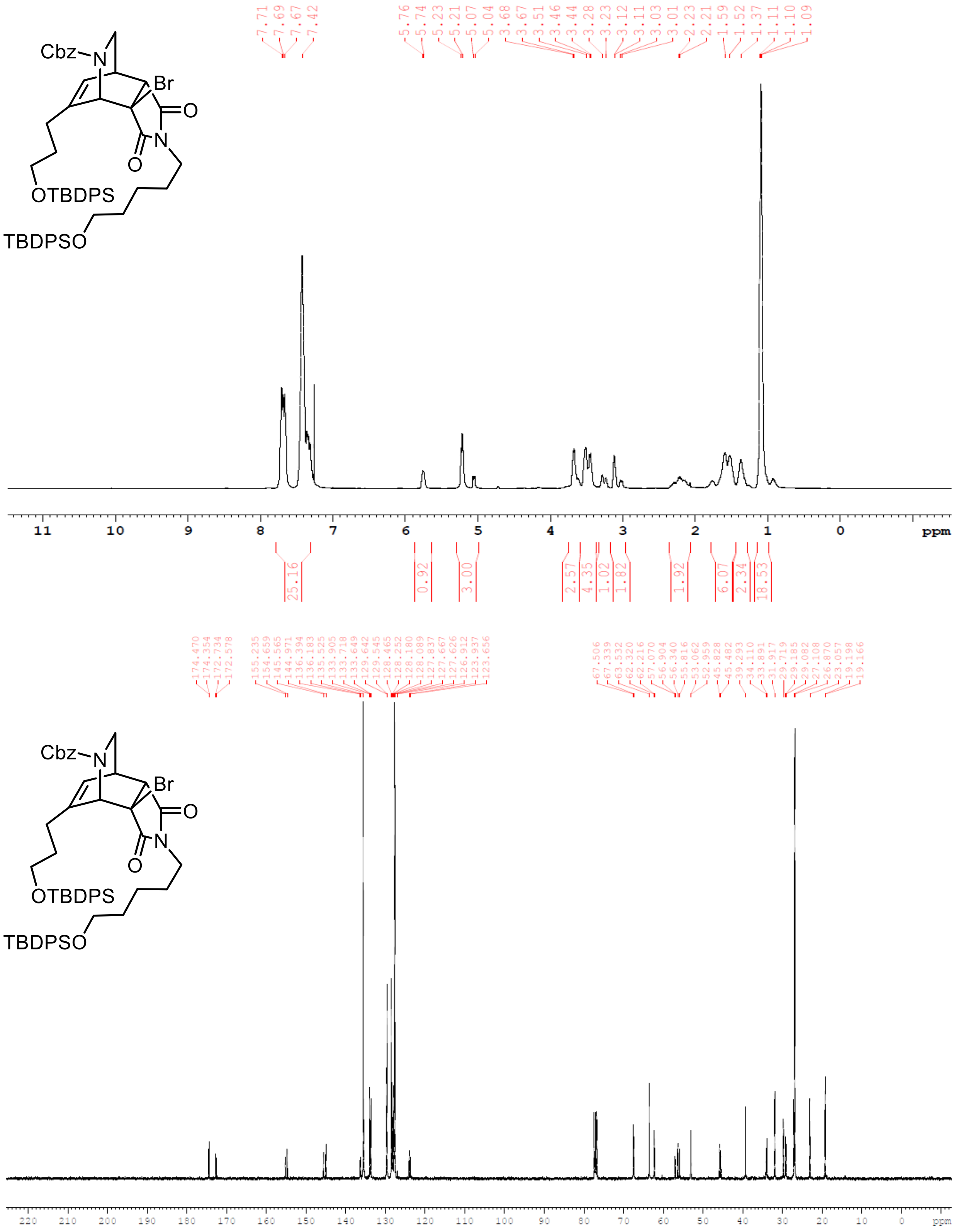


Figure A.4.38 ^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (400 MHz, CDCl$_3$) of **4.39**

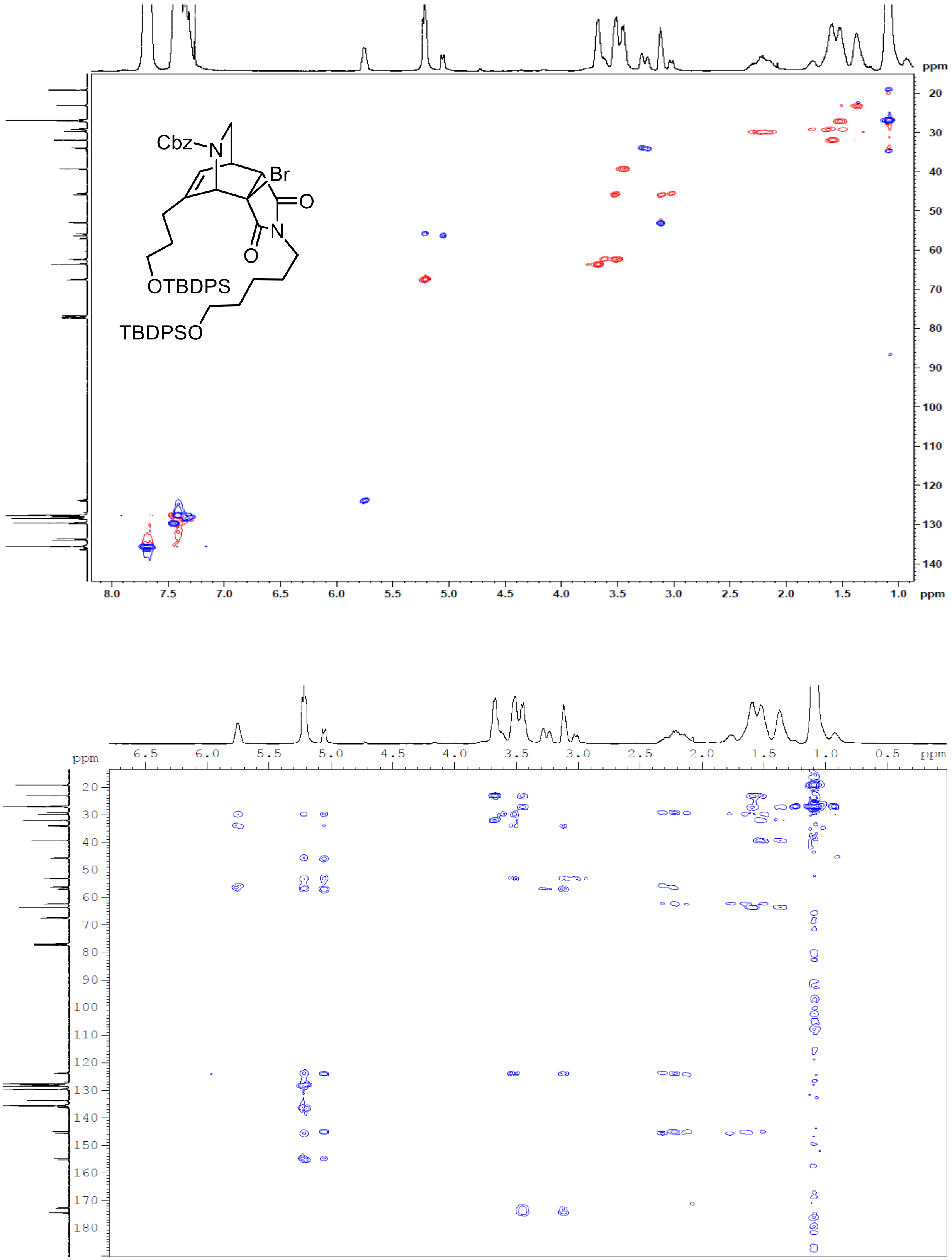


Figure A.4.39 HSQC NMR (400 MHz, CDCl$_3$) and HMBC NMR (400 MHz, CDCl$_3$) of **4.39**

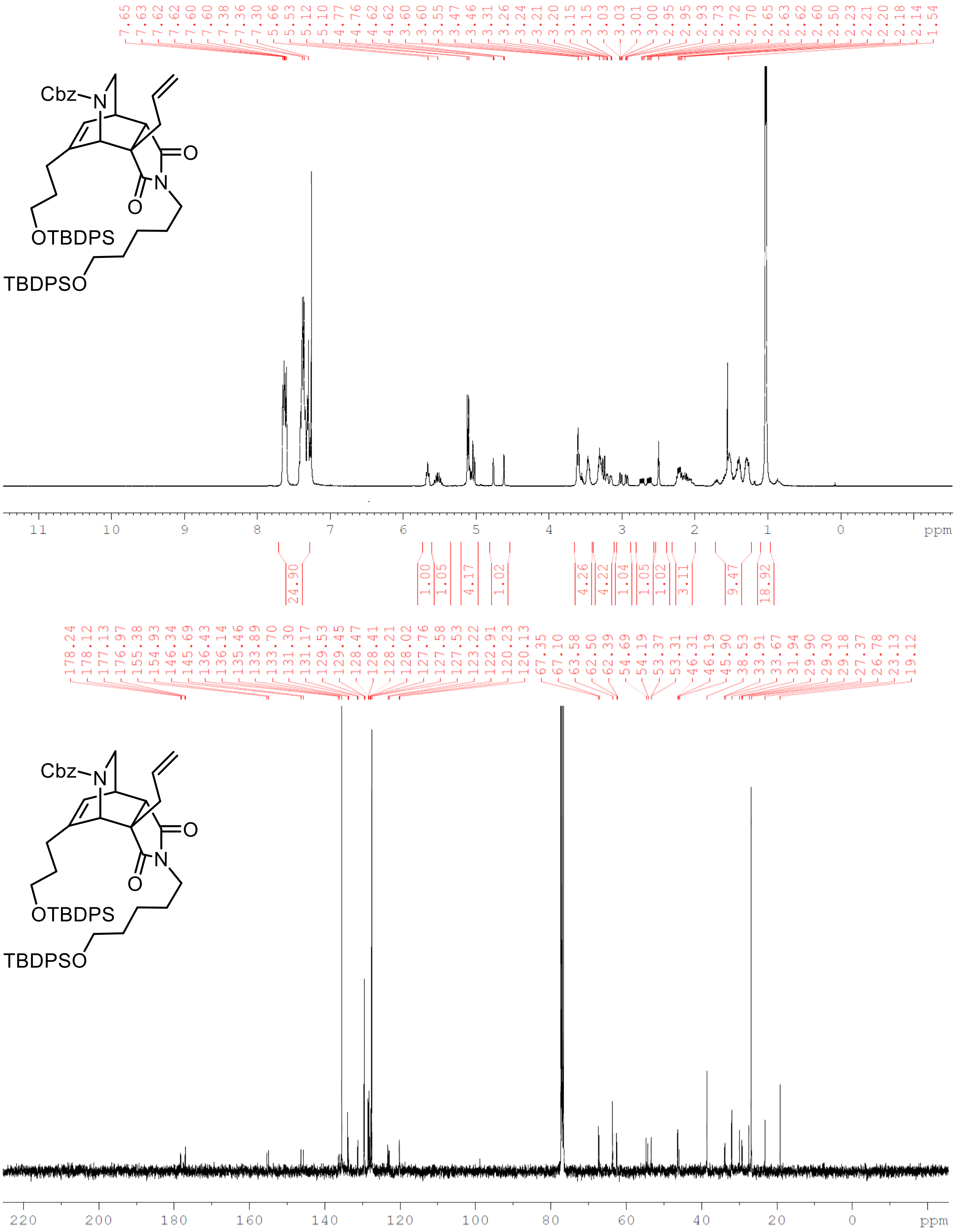


Figure A.4.40 ^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (400 MHz, CDCl$_3$) of **4.40**

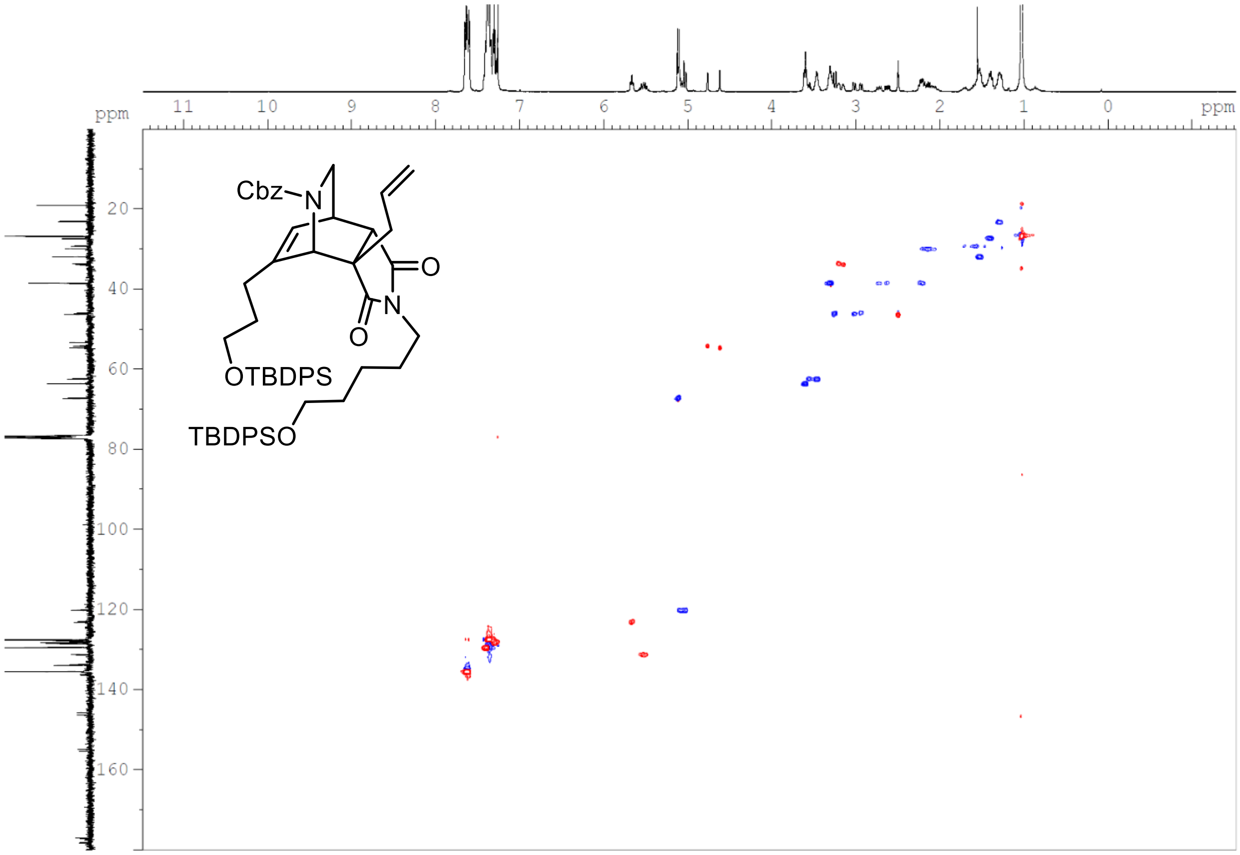


Figure A.4.41 HSQC NMR (400 MHz, CDCl$_3$) of **4.40**

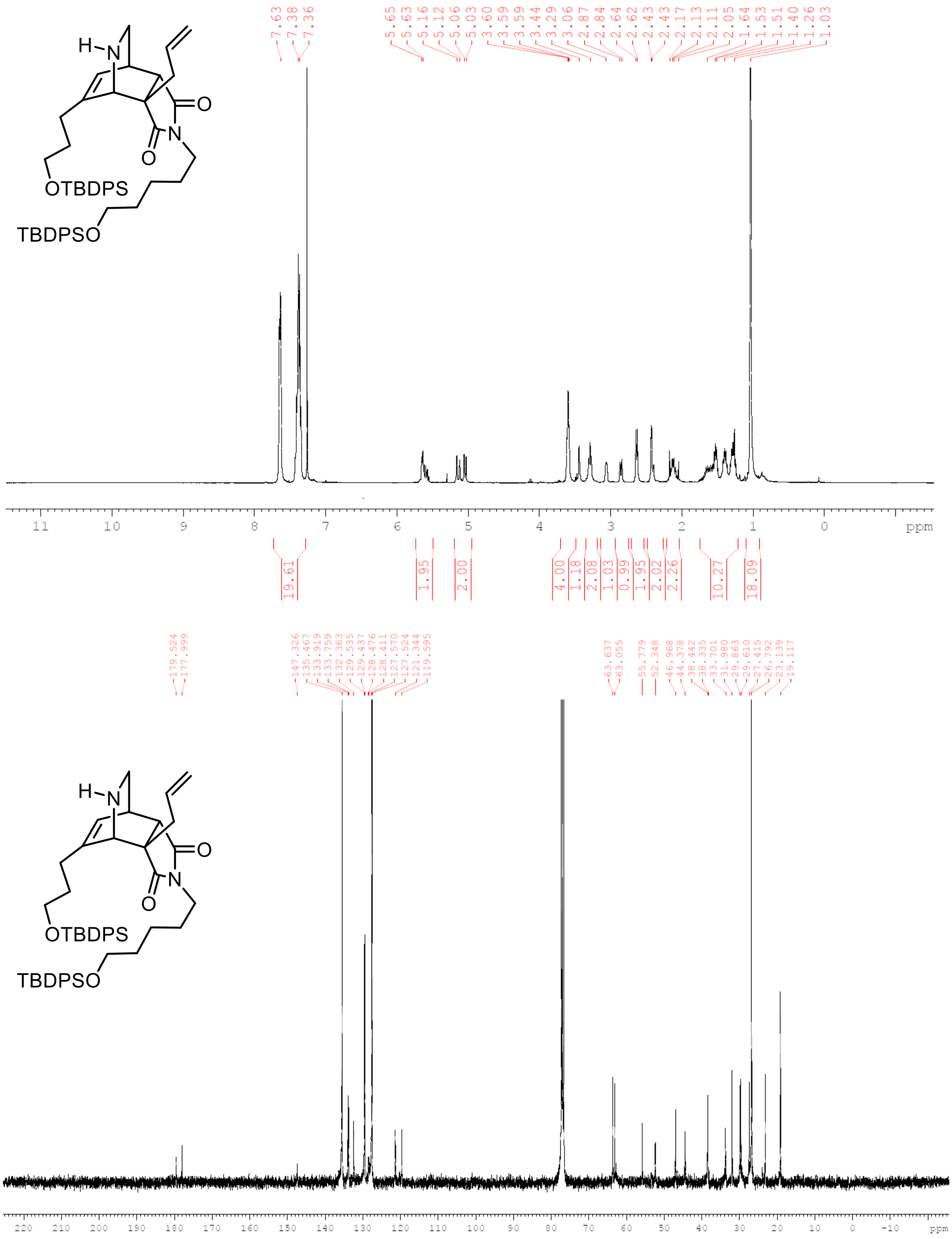


Figure A.4.42 ^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (400 MHz, CDCl$_3$) of **4.41**

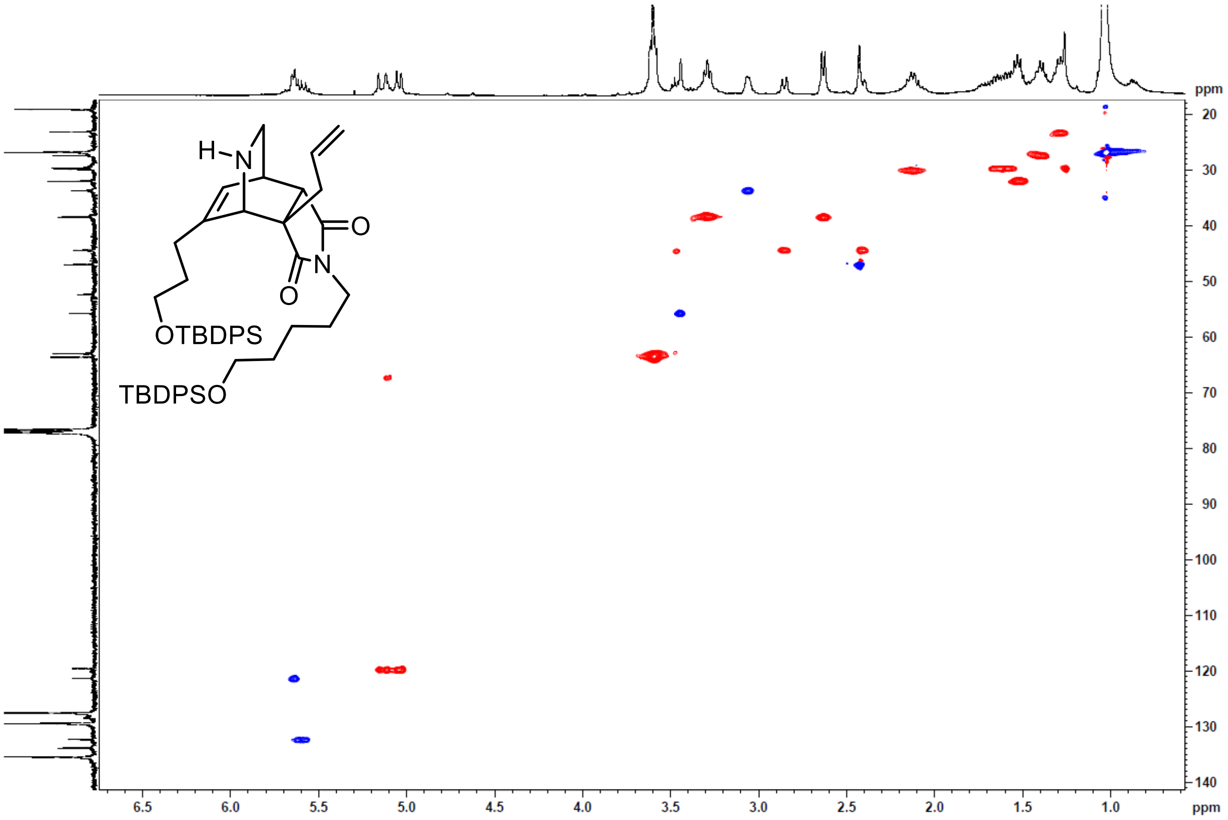


Figure A.4.43 HSQC NMR (400 MHz, CDCl$_3$) of **4.41**

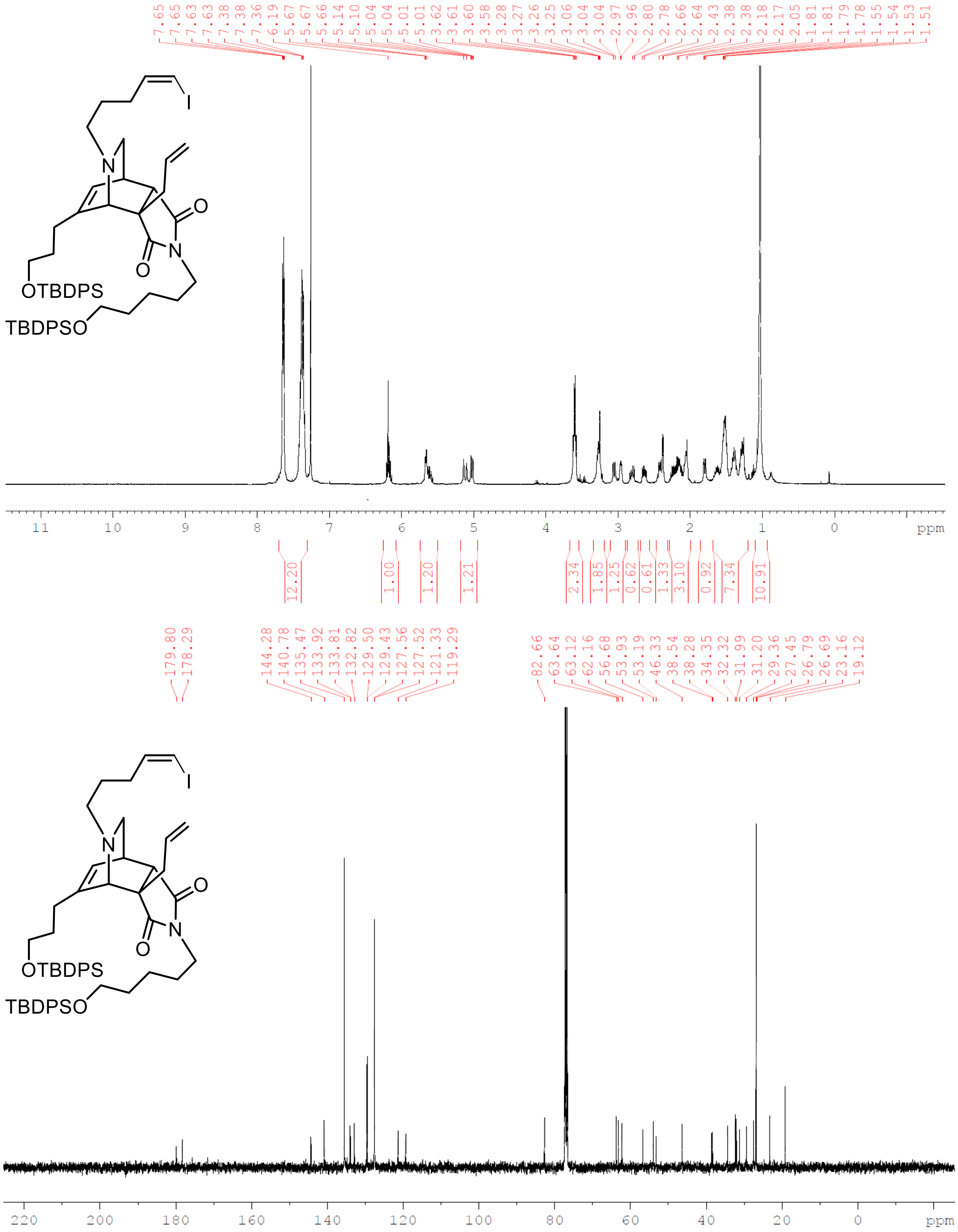


Figure A.4.44 ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (400 MHz, $CDCl_3$) of **4.43**

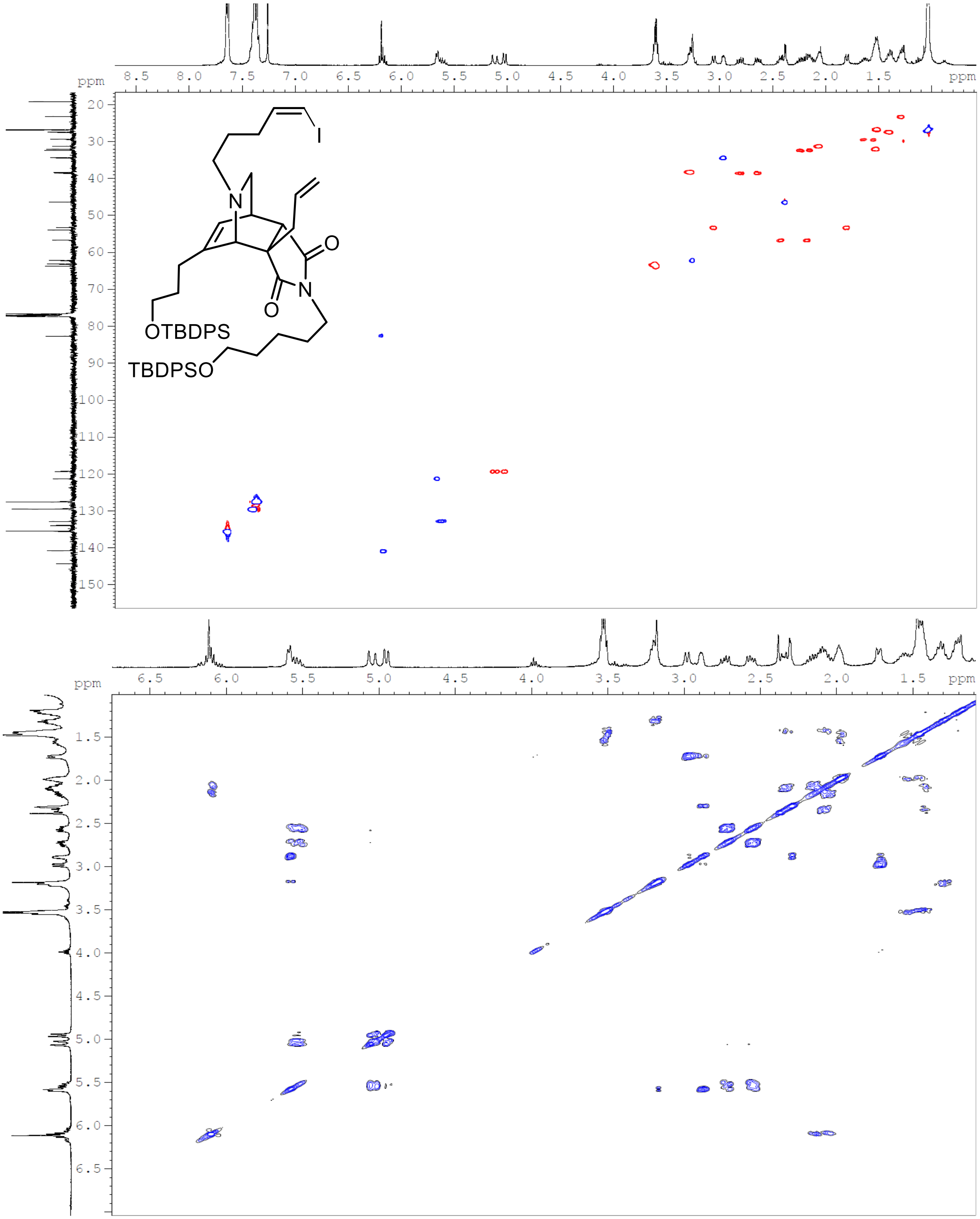


Figure A.4.45 HSQC NMR (400 MHz, $CDCl_3$) and COSY NMR (400 MHz, $CDCl_3$) of **4.43**

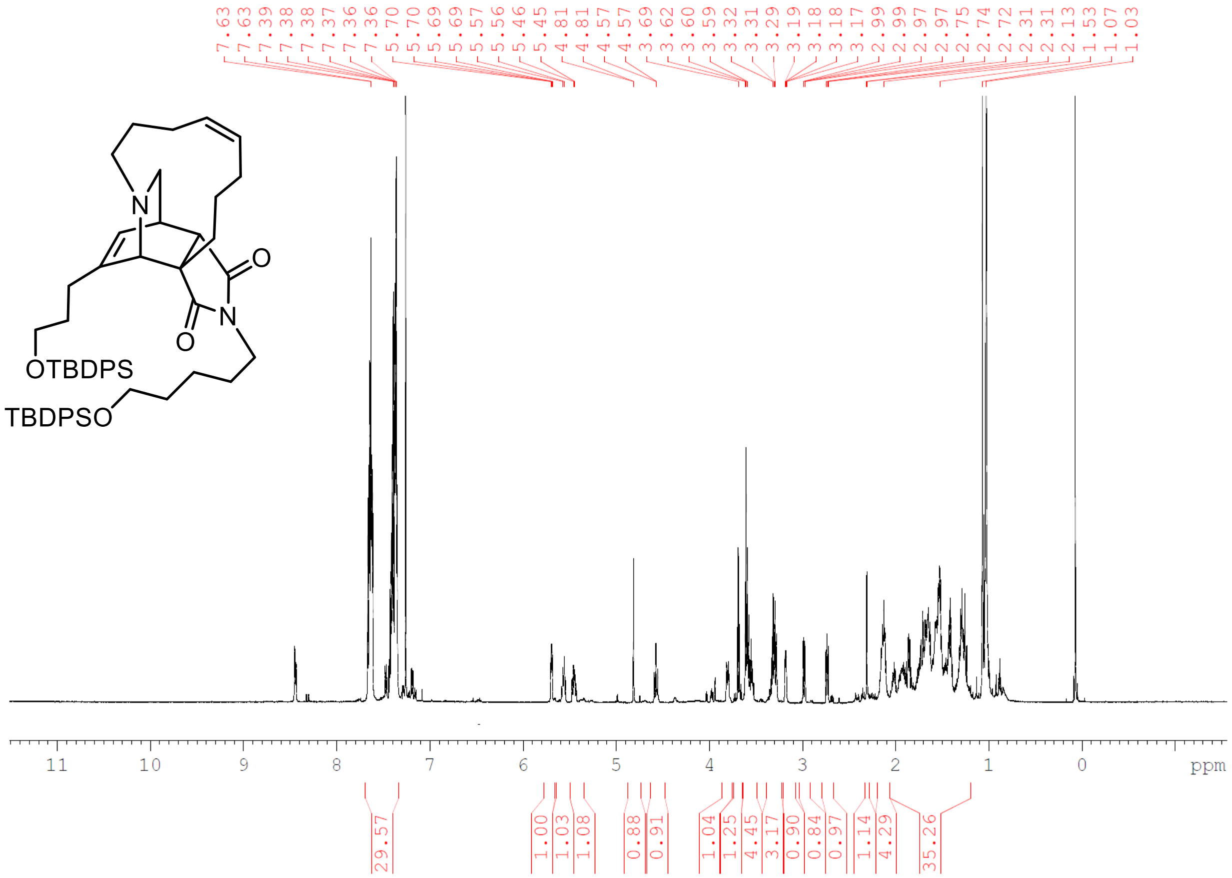


Figure A.4.46 ^{1}H NMR (400 MHz, CDCl$_3$) of **4.44**

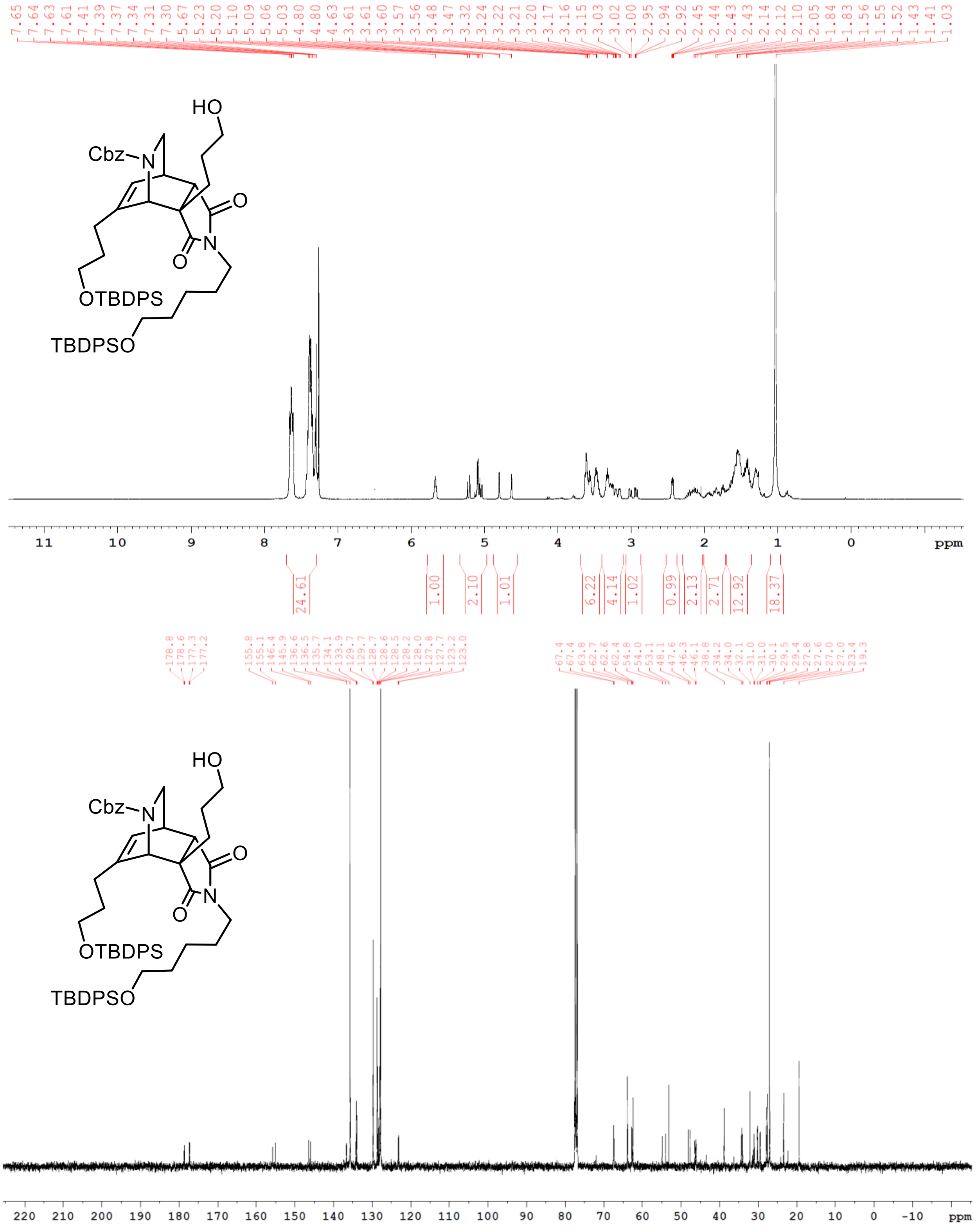


Figure A.4.47 ^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (400 MHz, CDCl$_3$) of **4.45**

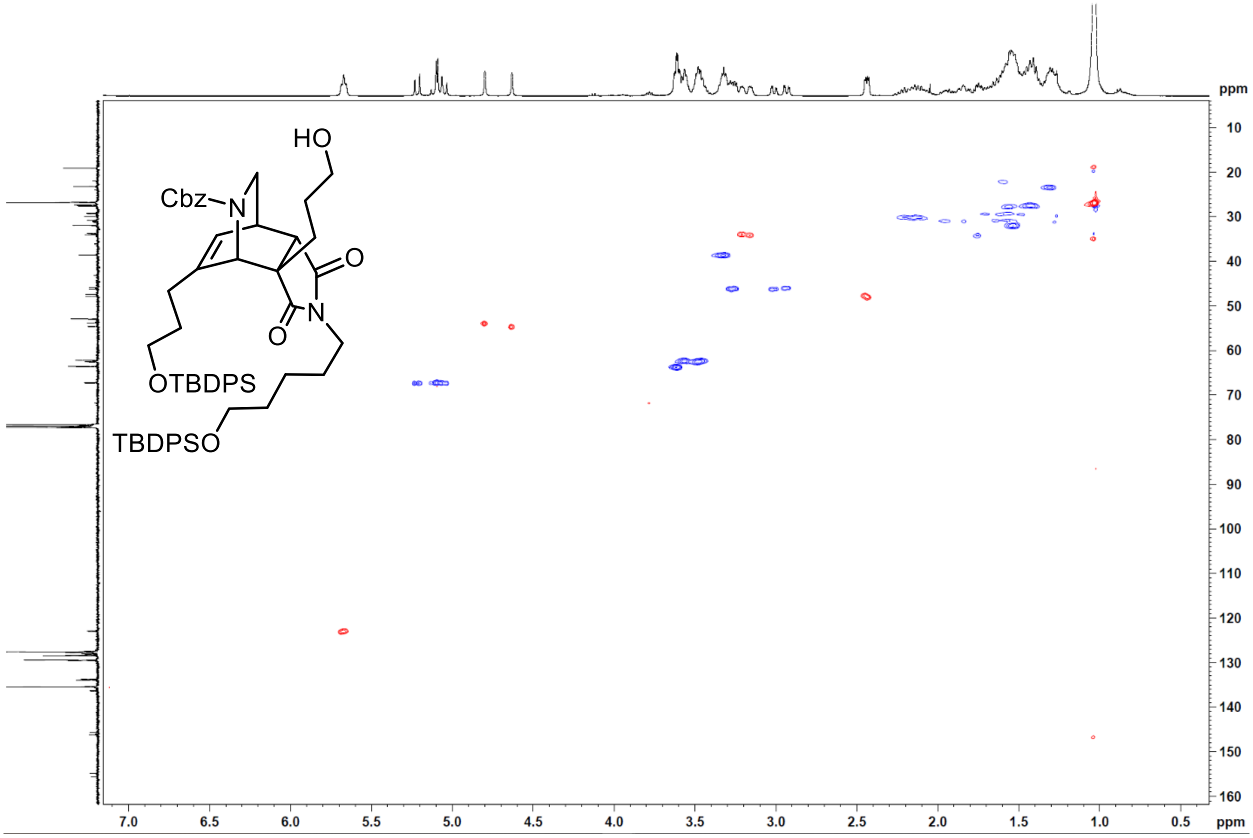


Figure A.4.48 HSQC NMR (400 MHz, $CDCl_3$) of **4.45**

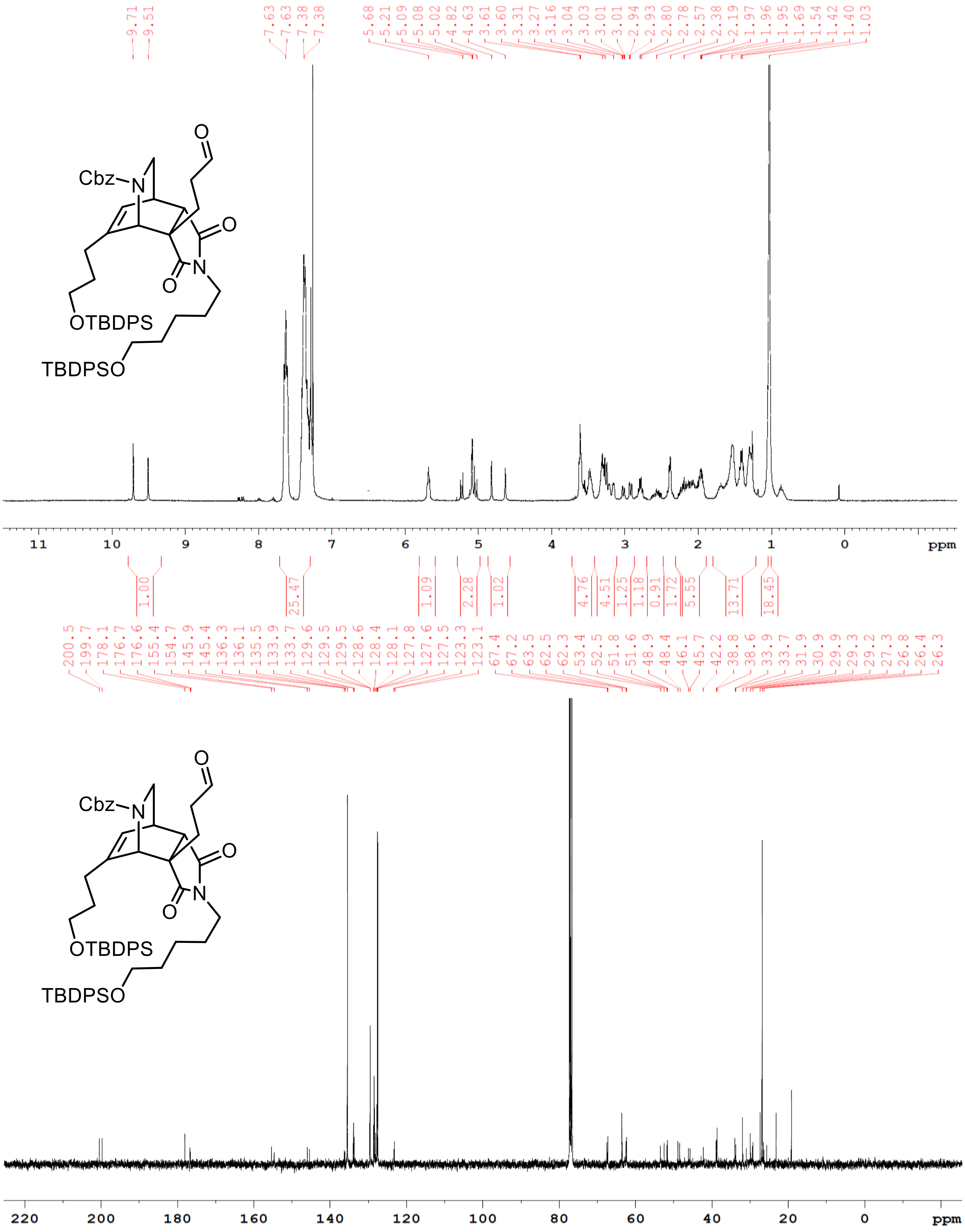


Figure A.4.49 ^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (400 MHz, CDCl$_3$) of **4.46**

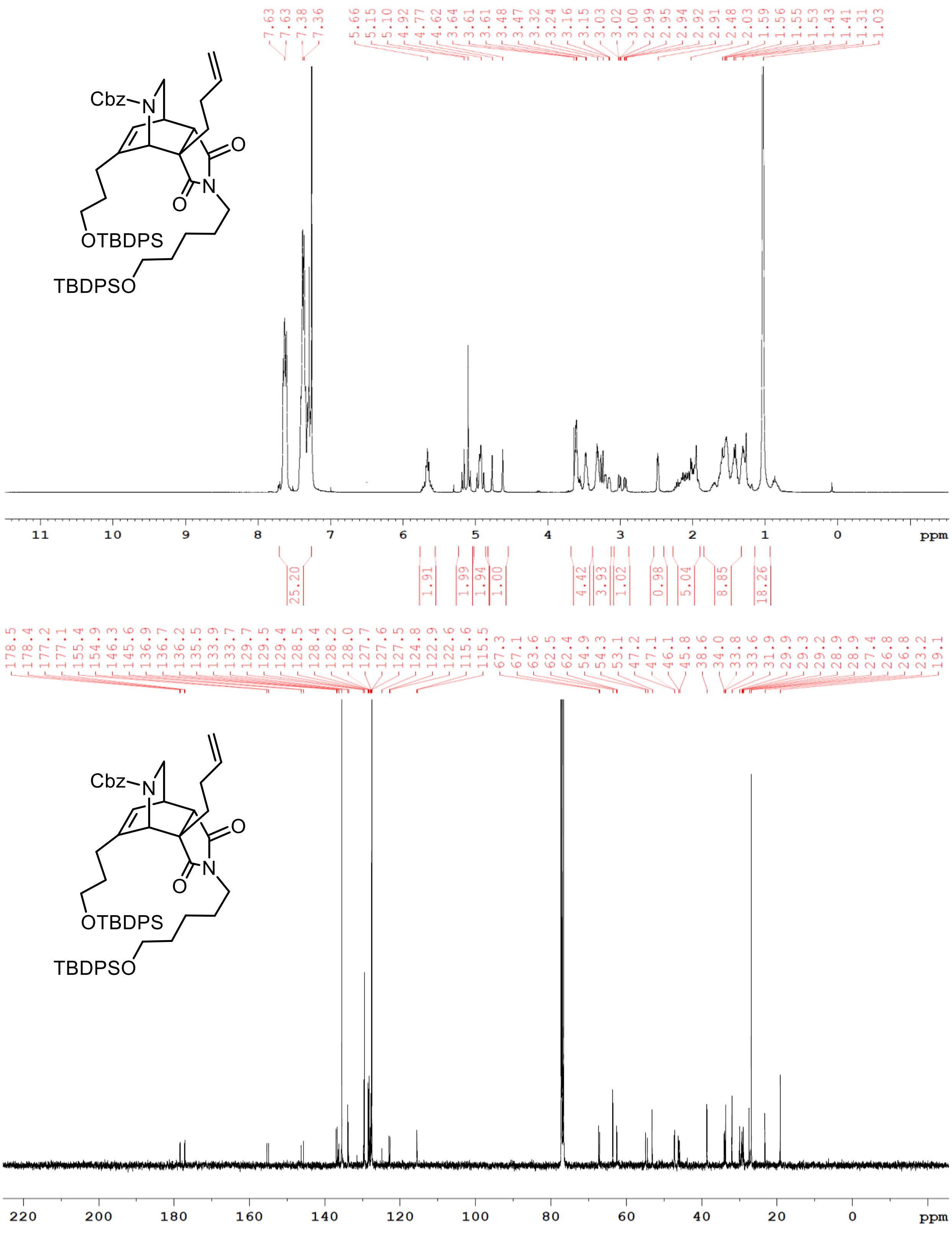


Figure A.4.50 ^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (400 MHz, CDCl$_3$) of **4.47**

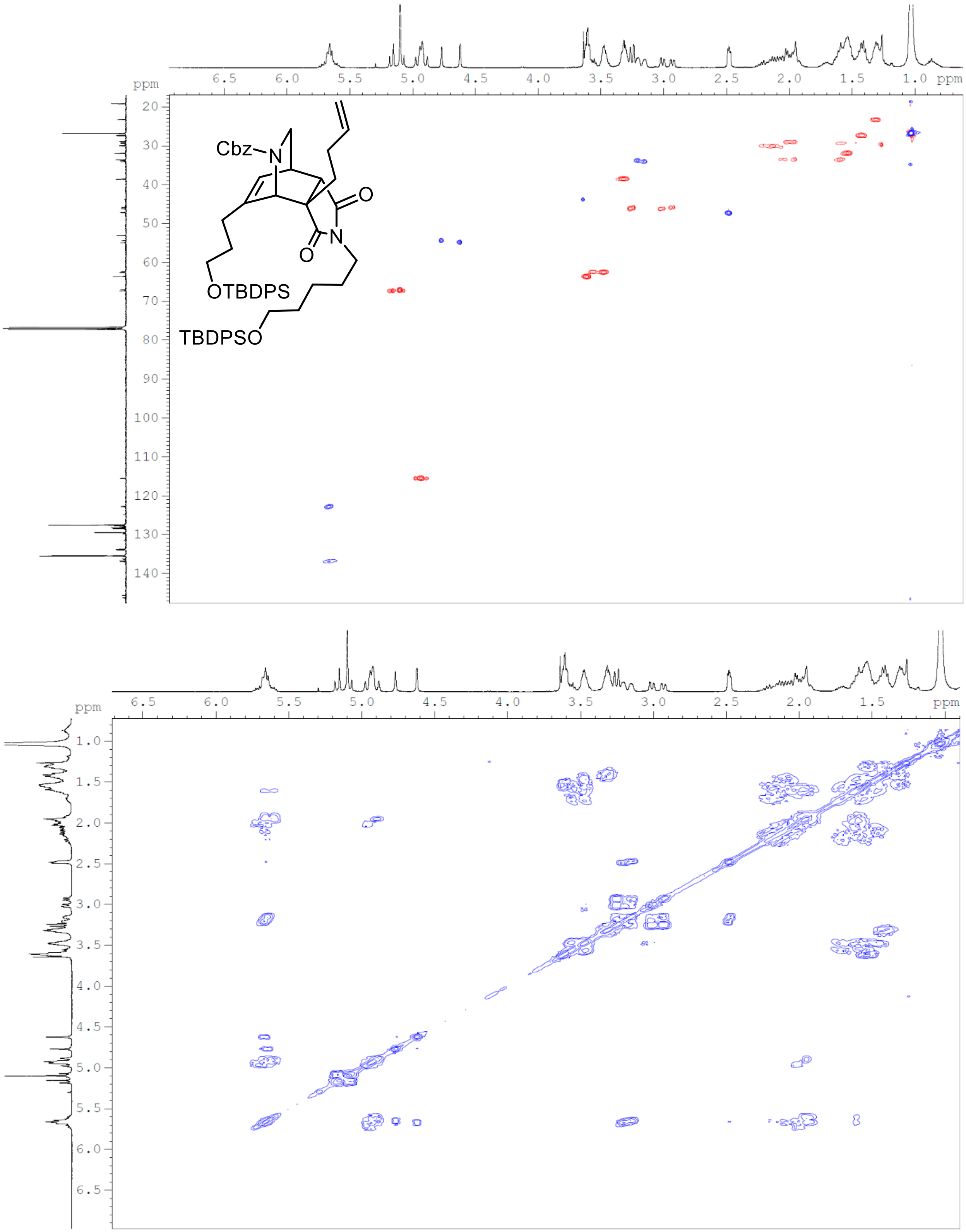


Figure A.4.51 HSQC NMR (400 MHz, $CDCl_3$) and COSY NMR (400 MHz, $CDCl_3$) of **4.47**