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Synthetic Studies on the Marineosins and Other Related Complex Prodiginines

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Synthetic Studies on the Marineosins and Other Related Complex Prodiginines

A dissertation submitted in partial satisfaction of the

requirements for the degree Doctor of Philosophy

in Chemistry

by

Tyler Keith Allred

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ABSTRACT OF THE DISSERTATION

Synthetic Studies on the Marineosins and Other Related Complex Prodiginines

by

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Doctor of Philosophy in Chemistry

University of California, Los Angeles, 2018

Professor Patrick G. Harran, Chair

Chapter One provides an overview of complex prodiginine alkaloids: streptorubin, roseophilin, and the marineosins. This includes a brief discussion of the prototypical structural features of the prodiginine class of natural products, their isolation, and biochemical properties including the putative biological mechanism of action. Previous research efforts from our laboratory are discussed to highlight our desired strategy for approaching these structural motifs and our goal (this thesis) of developing a unified entry to the C9 ansa linked prodiginines. A brief discussion of the completed efforts and total syntheses of prodiginine alkaloids is provided. The chapter concludes with a detailed discussion of the reported efforts by other research groups en route to targeted total synthesis of the marineosins.

We have developed a unique method of constructing the pyrrolophane core via a late stage phosphoryl-transfer mediated macroaldolization, which was utilized in the production of roseophilin. Chapter Two chronicles our efforts to adapt this approach to the marineosins, which

were precluded by the inability to install an adequate transfer group. Due to these issues, a macrocyclic Heck process was explored as a potential alternative method of ring construction. However, these studies were halted when it was determined that β-substitution on the coupling partner drastically affected the feasibility of the Heck process.

Chapter Three discusses in detail our efforts to capitalize on the electron rich nature of the prodiginine core to engage a reactive functionality on the aliphatic chain and induce macrocyclization. Initial efforts were aimed at photoinduced electron transfer mediated macroannulations. However, low material throughput as a result of a capricious reduction procedure and an inability to obtain pure seco precursors impeded detailed investigations in this area. Further examinations in this manner of approach, attempted to construct the pyrrolophane in a bioinspired radical-engagement. Studies in this area were suspended due to an apparent lack of reactivity of the lipochromophore. Model system studies in this area resulted in the discovery of a novel photoinduced transformation and the development of a new method of constructing C9-substituted prodiginines.

Chapter Four details our efforts to utilize the reactivity discovered in model system studies, which culminated in the synthesis of marineosin A. The photoinduced rearrangement of pyridinophane *N*-oxides proved particularly powerful in the production of the requisite acyl pyrrolophane. After elaboration to a postulated biosynthetic precursor of the marineosins, a cycloisomerization could be effected by treatment with MnO_2. These two key methods allowed for a highly convergent and concise synthesis.

The readily apparent utility of the photoinduced rearrangement methodology caused us to revisit roseophilin. Chapter Five presents how the aforementioned rearrangement allows for facile access to the roseophilin pyrrolophane, which can be readily acylated with isobutyryl chloride. Studies in

this area are ongoing to convert this acylated material into an intermediate that intercepts our previous roseophilin synthesis.

The dissertation of Tyler Keith Allred is approved.

Neil Kamal Garg

Caius Gabriel Radu

Patrick G Harran, Committee Chair

University of California, Los Angeles

2018

This dissertation is dedicated to Cyndi, my rock.

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LIST OF ABBREVIATIONS

MeCN	acetonitrile
PPI	protein protein interactions
MOMP	mitochondrial outer membrane permeability
MBC	4-methoxy-2,2’-bipyrrole-5-carboxaldehyde
2-UP	2-undecylpyrrole
PCP	peptidyl carrier protein
FAD	flavin adenine dependent
OAS	α-oxoamine synthase
HBM	4-hydroxy-2,2’-bipyrrole-5-methanol
FMN	flavin mononucleotide
SAM	S-adenosyl methionine
OMT	O-methyl transferase
ACP	Acyl carrier protein
KR	Ketoreductase
DH	Dehydratase
ER	Enoylreductase
*i*PrOH	isopropanol
DME	1,2-dimethoxyethane
DMF	dimethyl formamide
THF	tetrahydrofuran
NCS	N-chlorosuccinimide
MeCN	acetonitrile

MeOH	methanol
CSA	camphorsulfonic acid
DCE	1,2-dichloroethane
Et_3N	triethylamine
DCM	dichloromethane
KHMDS	potassium hexamethyldisilazide
EtOAc	ethyl acetate
TPAP	tetrapropylammonium perruthenate
NMO	N-methylmorpholine N-oxide
MVK	methyl vinyl ketone
$HCONEt_2$	diethyl formamide
DMS	dimethyl sulfide
NMP	N-methyl pyrorrolidinone
DIPEA	diisopropyl ethyl amine
TBHP	*tert*-butylhydroperoxide
Bu_4NI	tetrabutylammonium iodide
BnBr	benzyl bromide
DDQ	dichlorodicyanoquinone
PivCl	Pivaloyl chloride
DMSO	dimethyl sulfoxide
DMP	Dess Martin periodinane
Boc	*tert*-butyl carbonyl
TMP	2,2,6,6-tetramethylpiperidine

TMSCl	chlorotrimethylsilane
TMSOTf	trimethylsilyl trifluoromethanesulfonate
TESCl	chlorotriethylsilane
DMAP	N,N-dimethyl-4-amino pyridine
SEM	[2-(trimethylsilyl)ethoxy]methyl
*p*TsOH	*para*-toluenesulfonic acid
LiHMDS	lithium hexamethyldisilazide
TBAF	tetrabutylammonium fluoride
TFA	trifluoroacetic acid
TsCl	*p*ara-toluenesulfonyl chloride
PCC	pyridinium chlorochromate
TFAA	trifluoroacetic anhydride
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
LDA	lithium diisopropylamide
TLC	thin liquid chromatography
DABCO	1,4-diazabicyclo[2.2.2]octane
HPLC	high performance liquid chromatography
BODIPY	boron-dipyrromethene
DBA	dibenzylideneacetone
Cy_2NMe	dicyclohexylmethylamine
BRSM	based on recovered starting material
DBU	diazabicyclo[5.4.0]undec-7-ene
PTLC	preparative thin liquid chromatography

FCC	flash column chromatography
NMR	nuclear magnetic resonance
RCM	ring closing metathesis
TBSCl	*tert*-butyldimethylchlorosilane
$MeNO_2$	nitromethane
CDI	carbonyl diimidazole
*m*CPBA	*meta*-chloroperbenzoic acid
FEP	fluorinated ethylene propylene
Et_2O	diethyl ether
FT-IR	Fourier-transform infrared spectroscopy
HMBC	heteronuclear multiple-bond correlation spectroscopy
HMPA	hexamethylphosphoramide
HRMS	high-resolution mass spectrometry
HSQC	heteronuclear single-quantum correlation spectroscopy
MeI	methyl iodide
n-BuLi	*n*-butyl lithium
NOESY	nuclear Overhauser effect spectroscopy
SM	starting material
TIPS	triisopropylsilyl
UV	ultraviolet
UV-Vis	ultraviolet-visible
UV-vis-NIR	ultraviolet-visible-near infrared
XRD	X-ray diffraction

GH	growth hormone
GHS-r	growth hormone secretagogue receptor
SAR	structure-activity relationships
KO	knockout
MBOAT	membrane bound O-acyl transferase
GOAT	ghrelin O-acyl transferase
Boc-Tle-OH	N-Boc *tert*-Leucine
Boc-Gly-OH	*N*-Boc Glycine

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Publications

1. **Tyler K. Allred***, Francesco Manoni, Patrick G. Harran. Exploring the Boundaries of "Practical": De Novo Syntheses of Complex Natural Product-Based Drug Candidates. *Chem. Rev.* **2017**, *117(18)*, 11994-12051

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Public Presentations

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2. **Tyler K. Allred**; Hui Ding; James H. Frederich; Patrick G. Harran. Towards Unified Access to Ansa Bridged Prodiginines: Exploring the Spirocyclic Pyrrolophanes Marineosins A and B. 28th Annual Glenn T. Seaborg Symposium, University of California, Los Angeles, CA. October 2015 (poster presentation)

3. **Tyler K. Allred** & Patrick G. Harran. Progress Towards the Chemical Synthesis of (-)-Marineosin A. Invited Presentation for Chem 190: Orientation to Chemistry and Biochemistry Course, California State University, Fullerton, CA. December 2015. (oral presentation)

4. **Tyler K. Allred**; Zhengao Feng; Robert Craig Clark III, Patrick G. Harran. Towards Unified Access to Ansa Bridged Prodiginines: Exploring the Generation of Marineosins A and B and Roseophilin via Photochemical Rearrangements. 30th Annual Glenn T. Seaborg Symposium, University of California, Los Angeles, CA. November 2017 (poster presentation)

5. **Tyler K. Allred**; Patrick G. Harran. Synthetic Studies Towards the Marineosins and Related Complex Prodiginines. 3rd Annual University of California Chemical Symposium, Lake Arrowhead, CA. March 2018. (oral presentation)

Awards

College of Biological Sciences Dean's List, University of California, Davis. Winter 2009-Winter 2010

College of Letters and Sciences Dean's List, University of California, Davis. Spring 2010-Spring 2012

Graduated with Honors, University of California, Davis, June 2012

Hanson-Dow Teaching Assistant Award, University of California, Los Angeles, November 2014

UCLA Travel Award for 251st ACS National Meeting, San Diego, CA. March 2016

1. Chapter One – Ansa Bridged Prodiginines: An Intriguing Challenge for Synthesis

1.1. Abstract

Polycyclic ansa bridged prodiginine alkaloids isolated from the *Streptomyces* and *Serratia* bacteria are intricate structural motifs. More importantly, the putative interactions with Bcl-2 proteins by members of this class prompted the development of the prodiginine-derived clinical candidate, obatoclax. The bright color associated with these structures has been utilized extensively to explore the biosynthetic production of these structures in detail. Finally, natural isolates of the more complex members are low yielding, indicating synthesis as a necessity for further biochemical investigations.

1.2. Introduction: Ansa Bridged Prodiginine Alkaloids

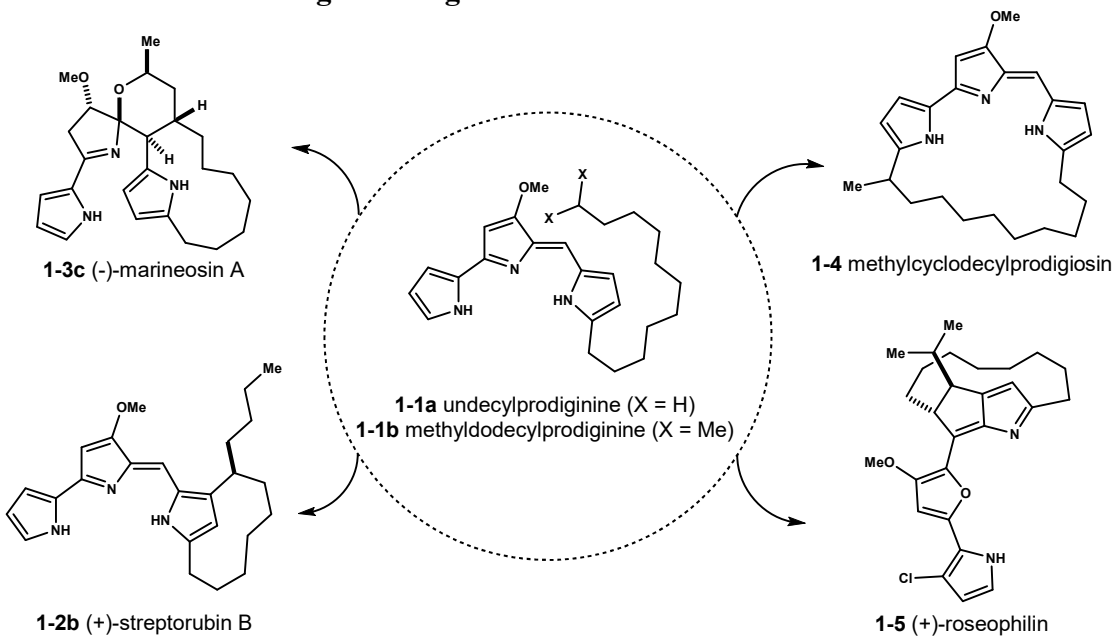


Figure 1.1. Alkylprodiginine Biosynthetic Seco-Precursors to Ansa Bridged Prodiginines

The prodiginine alkaloids hold a unique and privileged position in terms of their chemical and historical significance. These alkaloids are produced by several members of the *Streptomyces* actinomycetes and *Serratia* enterobacteriaceae families.[1,2] The more complex ansa bridged

structures are derived from the simpler aliphatic seco precursors, undecylprodiginine **1-1a** and the branched methyldodecylprodiginine **1-1b** (**Figure 1.1**).[3–6] Biosynthetic construction of the lipochromophore, as well as the ansa bridge have been well studied.[2,7–11] The standard prodiginine core consists of three pyrrole groups, referred to as the A, B, and C rings, joined into a pyrrolylpyrromethene core.[1,12] The A-ring pyrrole and B-ring methoxypyrrole are relatively invariant amongst prodiginine structures, which derives from the manner in which these structures are constructed biosynthetically. The C-ring pyrrole is the primary area of variation, where it is decorated with a wide variety of aliphatic groups depending on the species of origin.[1,2,12] The bright red color commonly associated with these natural products due to their highly conjugated core has attracted interest for over a millennia.[1,2,12]

The name prodiginine derives from "prodigious" due to its speculated responsibility for various instances of bloody or "bleeding bread" throughout history.[1,2,13] In the early 1800's, the Italian pharmacist Bartolomeo Bizio examined whether the alcoholic extracts of *Serratia* could be utilized as dyes for several fabrics, however these extracts, and prodiginines in general, proved to be too light sensitive for this application.[2,14] In more recent years, the interesting array of medically relevant biological activities induced by these structures has warranted further investigations by the scientific community.[2]

1.2.1. Ansa Bridged Prodiginine Alkaloids: Isolation, Structure, and Biochemical Properties

Streptorubin B **1-2b**, the marineosins **1-3a-c**, and roseophilin **1-5** are exemplary members of the intriguing ansa bridged subclass of prodiginine natural products. The marineosins **1-3a-c** and

roseophilin **1-5** are arguably the most complex of known prodiginines. In addition to their intricate structures, the various biochemical activities attributed to these compounds are compelling.

Streptorubin B **1-2b** was isolated in 1975 by Gerber from extracts of *Streptomyces* sp. Y-42 (**Figure 1.2**).[15] The structure exhibited standard prodiginine properties: it was red in acid, yellow in base, and did not diffuse in agar.[15] Gerber noted the similarities between metacycloprodigiosin and the newly isolated pigment.[15] Gerber utilized oxidative degradation studies to identify the butyl side chain and compared the ^{1}H NMR spectra to several synthetic prodiginines that contained substitution at the 2 and 3 positions. Based on these investigations, the new pigment was originally assigned as butylcycloheptylprodigiosin (**1-6, Figure 1.2**).[2,15] Soon afterwards, it was discovered that the data for butylcycloheptylprodigiosin matched an uncharacterized structure named "streptorubrin B" reported by Thirumalachar and coworkers in 1964, which has since been renamed as streptorubin B.[2,16,17] In 1978, Gerber reassigned the structure of streptorubin B to **1-2a** without giving reasons for doing so.[6] This led to confusion as to whether **1-6** was a natural product for several decades. Thomson and coworkers solved this problem by using electron ionization fragmentation comparisons of natural streptorubin B extracts with synthetic **1-6** and synthetic **1-2b**.[18,19] These studies confirmed that **1-6** was a structural misassignment of streptorubin B **1-2b** and not a naturally occurring prodiginine.[19]

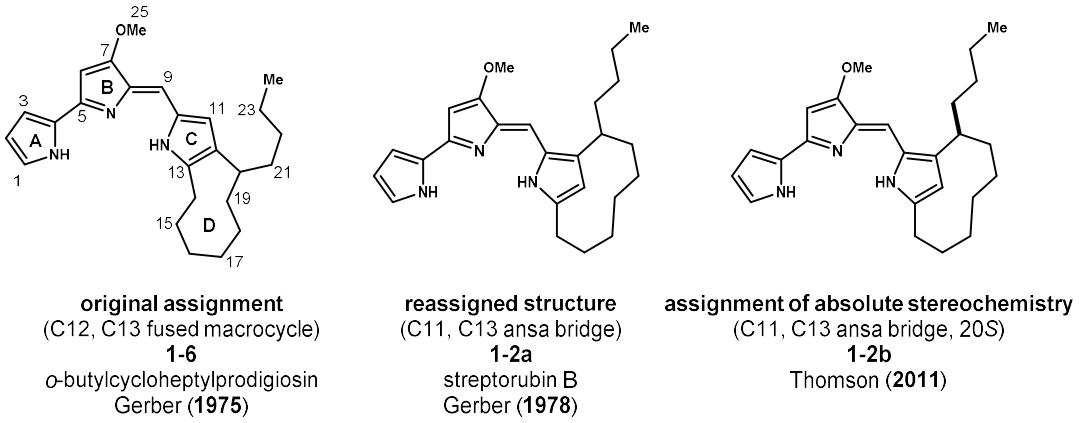


Figure 1.2. Structural and Sterechemical Reassignment of Streptorubin B

The initial reports of detail the antibiotic and antimalarial (*Plasmodium berghei* KBG 173) properties exhibited by streptorubin B.[15,16] More recently, Shore and coworkers examined the cytotoxic activity of **1-2a** with synthetic material.[20,21] It was found to be highly selective towards breast cancer cell lines.[20] Furthermore, it was determined that **1-2a** restores apoptotic signaling, ostensibly via interactions with anti-apoptotic Bcl-2 proteins.[22–24] These discoveries provided the foundation for the development of obatoclax, the first prodiginine-derived clinical candidate (*vide infra*).

Roseophilin **1-5** was isolated in 1992 by Seto and coworkers during an activity guided screen of extracts from a culture broth of *Streptomyces griseoviridis*.[25] Moderate cytotoxicity was exhibited by **1-5** against K562 human erythroid leukemia cells (IC_{50} = 0.34 μM) and KB human epidermoid carcinoma cells (IC_{50} = 0.88 μM).[25] Roseophilin **1-5** was an intriguing discovery since it clearly contained remnants of a traditional prodiginine core, but it has been extensively modified. The aliphatic side chain has been linked to the lipochromophore in two places, one on C-11 and the other at the C-9 bridgehead, creating the ansa bridge and an additional cyclopentene ring. The prodiginine azafulvene B ring has been replaced by a methoxyfuran, which results in the pyrrolophane being in azafulvene form. The last modification is incorporation of a chlorine atom

at the 3-position of the A ring pyrrole. The relative and absolute stereochemistry of roseophilin were confirmed by total synthesis.[26–28] Further investigations into the biological effects of **1-5** reveal that it does not induce DNA strand cleavage *in vitro* when co-administered with Cu^{II} salts, which suggests the biochemical pathways targeted by **1-5** are distinct from other prodiginines.[29] These attributes coupled with its intricate structure have made roseophilin a popular target for synthesis (*vide infra*).

The marineosins were isolated from polar extracts of a marine-derived *Streptomyces*-related actinomycete (strain CNQ-617) by Fenical and coworkers in 2008 (**Figure 1.3**).[30] Fenical and coworkers utilized a series of NMR experiments to assign the relative stereochemistry of these novel spiroiminals as **1-3a** and **1-3b**, named marineosin A and B respectively.[2,30] The absolute stereochemistry was determined during biosynthetic studies by Reynolds and coworkers.[31] The marineosins exhibited very weak antifungal activity against *C. albicans* and moderate cytotoxicity against HCT-116 colon carcinoma cell lines.[30] One interesting result of these studies was that **1-3a** was 10-fold more potent than **1-3b**, which indicated that the configuration of the spiroiminal was directly related to activity.[30] Like roseophilin **1-5**, the marineosins contain aspects of the traditional prodiginine framework, but it has been heavily modified. Most notably, the lipochromophore has been disrupted by the formation of a spiroiminal at C-8. Similar to **1-5**, the marineosin ansa linkage is at the bridgehead C-9 position, instead of the C ring like other ansa bridged prodiginines. Lastly, the B ring has been partially reduced to produce a stereocenter at C7. The biosynthetic implications of these modifications are detailed in the next section.

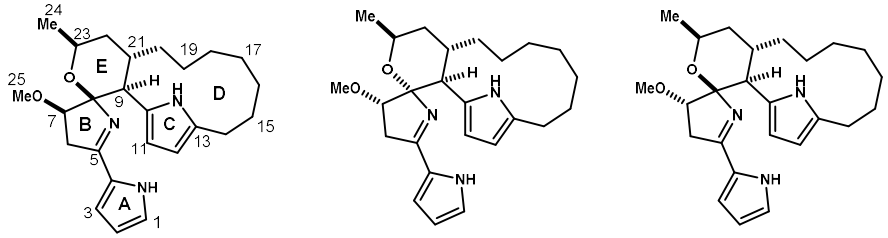


Figure 1.3. Original Structures of Marineosin A and B with the Tentative Stereochemical Reassignment of Marineosin A

Due to its unique structure and biochemical properties, marineosin A has been an appealing target. It has not yet succumbed to synthesis. Shi and coworkers recently reported a synthesis of the original structure of marineosin A, wherein a crystal structure of this synthetic material was obtained.[32] However, the spectral data for synthetic **1-3a** did not match that of the natural material in several areas. The key differences are localized around the B ring. Specifically, the ^{1}H NMR peaks associated with the C6 methylene group in the synthetic material are 2.80 and 2.71 ppm, whereas in the natural material are 2.88 and 1.88 ppm.[32] In addition, the C7 carbon has a shift of 83.7 ppm in the synthetic material and the natural material has a shift of 89.9. The synthetic spiroiminal carbon has a shift of 101.6 ppm, whereas the natural spiroiminal carbon was 106.1 ppm. In addition to these key differences, there are minor shifts of peaks throughout both the ^{13}C NMR and ^{1}H NMR spectra.

Due to the close resemblance of the data for synthetic **1-3a** to that of the natural product, we surmised that the proposed skeletal structure of marineosin A was correct. This led us to believe that the true structure of marineosin A was a diastereomer of **1-3a**. The substantial differences of the data corresponding to the B ring pointed to this region being the source of erroneous assignment allowing us to narrow the number of potential marineosin A structures down to 4 diastereomers,

including **1-3a**. Fenical and coworkers reported NOE correlations between the C7 hydrogen and the C9 bridgehead methine, which they used as a determining factor for their assignment of the C7 stereocenter.[30] Computational modeling revealed that the hydrogen of C7 epimer **1-3c** was calculated to be slightly closer to the C9 hydrogen with a distance of 2.8Å, whereas **1-3a** was calculated to be 2.9Å. The proximity to the spirocenter, as well as twisting of the B ring due to the steric bulk of the pyrrolophane, allows this seemingly contradictory phenomenon to occur. When considering the C8 epimer series (not shown), it appeared unlikely that NOE correlations between the C7 and C9 hydrogens would occur with either of the C7 diastereomers. Furthermore, the spiroiminal model system studies conducted by Snider show that the C7 epimer model has C7 and C8 ^{13}C NMR spectrum shifts of 86.2 and 104.3, respectively, which are close to that of the natural marineosin A.[33] Therefore, we propose that the true structure of marineosin A is the C7 epimer **1-3c** (**Figure 1.3**).

1.2.2. The Intrinsic Pathway of Apoptosis and Its Modulation with the Prodiginine-Derived Clinical Candidate Obatoclax

The biological activities induced by the prodiginine class of natural products are compelling. As described above, streptorubin (**1-2b**) was initially screened for antibiotic and antimalarial properties.[15,16] The clinical potential of **1-2b** as a cancer chemotherapeutic was discovered by Shore and coworkers relatively recently.[20,21] A library of natural products was screened for their ability to interrupt BCL-2 protein-protein interactions, which revealed **1-2b**, as well as several other prodiginines, as viable candidates for this mechanism of inhibition.[20,22] The BCL-2 family of proteins are essential to the apoptotic machinery of the cell, which indicated that prodiginines could potentially be utilized to modulate apoptotic signaling in cancer cells.

Apoptosis is a biochemical process utilized by cell networks to maintain healthy and functional systems by removing damaged or diseased cells. Deregulation of apoptosis is a key physiological alteration required for tumorigenic growth and cancer development.[34] Extensive research into the mechanisms by which cancer sequesters apoptotic signaling has revealed an extensive network of protein-protein interactions (PPI's).[35–38] It is thought that PPI's hold the potential to therapeutically reactivate apoptosis via modulation of these interactions.

Cancer cells can control intrinsic (mitochondrial pathway) apoptotic signals by preventing the release of pro-apoptotic factors from the mitochondria into the cytosol.[39–41] Overexpression of the proteins in the B-cell lymphoma-2 (Bcl-2) family allow these cells to tightly control the integrity of the mitochondrial outer membrane in response to death stimuli.[22] Within the extended Bcl-2 family of proteins, members are either pro-apoptotic or pro-survival and the interactions between these opposing groups govern the mitochondrial pathway to cell death.[22,42] In mammalian cells, there are five pro-survival members (BCL-2, BCL-X_L, BCL-w, MCL1, and A1), which occlude the pro-apoptotic activity of BAK and BAX.[22,43] BAK and BAX reside in the cytosol, however their pro-apoptotic activity localizes on the mitochondrial outer membrane, which becomes permeable in response to intrinsic death signals.[22] It is believed that upon receiving death signals, BAK and BAX undergo conformational shifts and become mitochondrial membrane associated proteins, where they form oligomeric pores.[22,44] These pores allow the release of proteins from the mitochondrial intermembrane space into the cytosol, which activate proteases that lead to the destruction of the cell.[44]

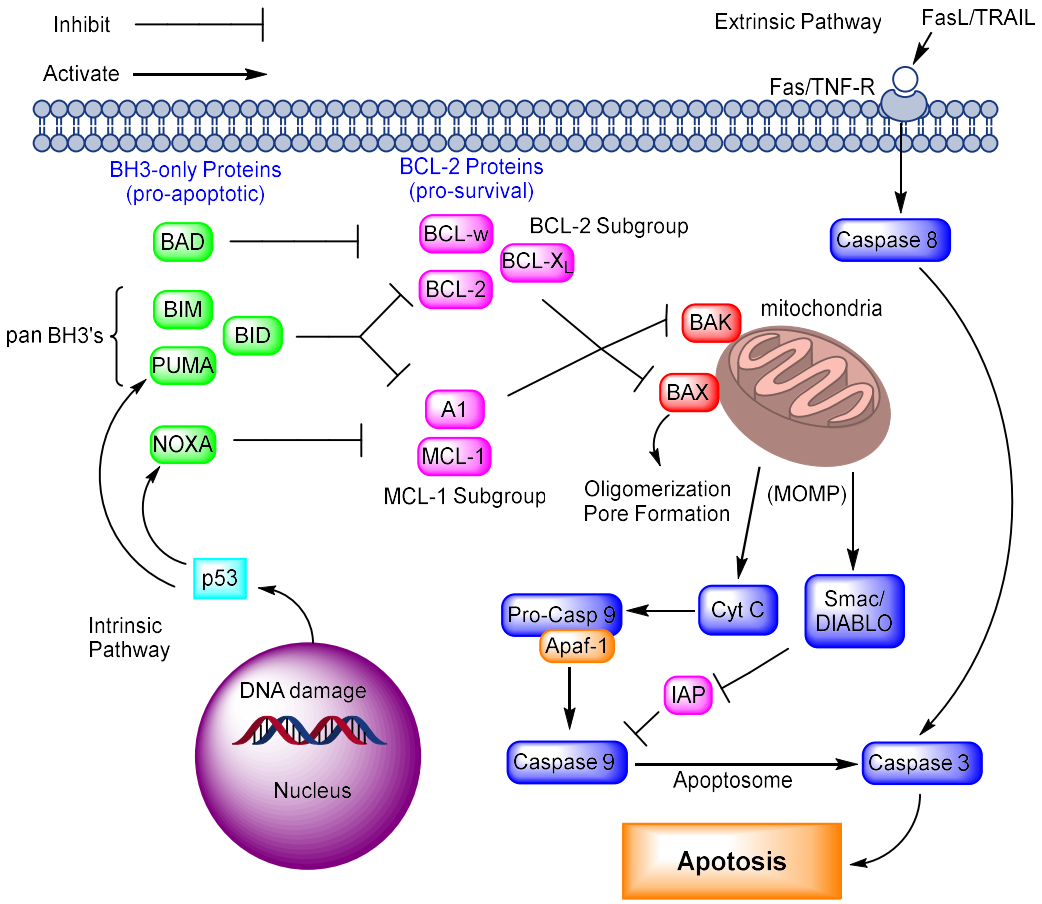


Figure 1.4. Intrinsic (mitochondrial) apoptosis is mediated by the BCL-2 family proteins. The pro-apoptotic and pro-survival members antagonize each other in order to regulate cell death decisions via control of mitochondrial outer-membrane permeability (MOMP).

The interactions between the members of the BCL-2 family are regulated by well-characterized PPI's between four domains of sequence homology known as BCL-2 homology (BH1-4) domains.[22,45,46] BAK and BAX are restrained by the pro-survival members through the formation of heterodimers bound to the BAK/BAX BH3 domain.[22] In response to cellular stress, a second group of pro-apoptotic proteins are upregulated by transcription or post-translational processing, known as the BH3-only proteins (BIM, BAD, t-BID, PUMA, NOXA, BMF, HRF, and BIK) since they lack BH1,2, and 4.[22] These proteins function to directly compete with BAK/BAX by providing an alternative BH3 domain to bind for the well-characterized hydrophobic groove, BH3-receptor site, of the pro-survival members.[22] A crucial portion of the BH3-domain of the pro-

apoptotic BH3-only proteins folds into an amphiphilic α-helix.[47] Structural analyses of the bound BH-3 domain:pro-survival protein complexes indicate that the α-helix contains four conserved hydrophobic residues (denoted as h1-h4) on one side of the helix reside in four hydrophobic pockets (p1-p4) within the groove.[47,48] In addition, there is a conserved aspartate on the BH3 domain serves to create a salt bridge with a conserved arginine on the pro-survival protein.[48] Mutagenesis studies with BIM have indicated that among the conserved hydrophobic residues of the helix, h2 (a leucine residue) is the most important for binding to BCL-X_L, BCL-w, and BCL-2, but less so for MCL-1.[48] This difference in change of binding affinity suggests an altered topology of the BH3 receptor site in MCL-1.[49]

These alterations in the BH3 binding site amongst the Bcl-2 pro-survival proteins bestow selectivity to the BH3-only pro-apoptotic proteins.[22] BIM, t-BID, and PUMA are relatively promiscuous in their binding activity profile, while the others are more selective.[22] This selectivity allows one to divide the pro-survival members into two subgroups: the BCL-2 subgroup (BCL-2, BCL-X_L, BCL-w acted upon by BAD) and the MCL-1 subgroup (MCL-1 and A1 acted upon by NOXA).[22] The increased complexity of this system is utilized in a variety of ways in cells to allow for more precise responses to a variety of stimuli.[22] Studies have shown that the pro-survival proteins work in tandem to regulate BAK and BAX, which means that inhibition of both subgroups would be required to induce apoptosis in cells overexpressing BCL-2 proteins.

Overexpression of the pro-survival BCL-2 proteins is a key feature of many human cancer types.[50,51] Unlike other oncogenes that promote proliferation, BCL-2 overexpression serves to prevent programmed cell death from both internal and external signals.[52] As a result, cancers overexpressing pro-survival BCL-2 proteins have been associated with a general resistance to chemotherapeutics.[52,53] Therefore, the therapeutic manipulation of the BCL-2 pathway could

provide a novel method of addressing cancer. In light of this fact, the discovery of **1-2b**'s putative ability to disrupt BCL-2 PPI's was a major breakthrough and brought with it many questions.

Shore and coworkers modulated the structure of **1-2b** through traditional SAR until they arrived at GX15-070, aka Obatoclax (**1-7**).[24] A key aspect of obatoclax (**1-7**) is that it is reported to engage both the BCL-2 and MCL-1 subgroups of the BCL-2 family *in vitro* and induce cell death.[24] Additional studies indicated that obatoclax had off-target mechanisms of toxicity, which allowed it to induce apoptosis in BAK/BAX knockout cell lines.[54] Obatoclax showed strong synergism when it was administered *in vitro* with other cytotoxins.[54] The capabilities of obatoclax allowed it to be examined in a clinical setting. Obatoclax was investigated in several clinical trials for a variety of cancers.[55–57] Although it had promising results in early *in vitro* and *in vivo* studies, obatoclax had lackluster effects in the clinic, which ultimately resulted in Teva Pharmaceuticals withdrawing the drug from clinical trials.[58]

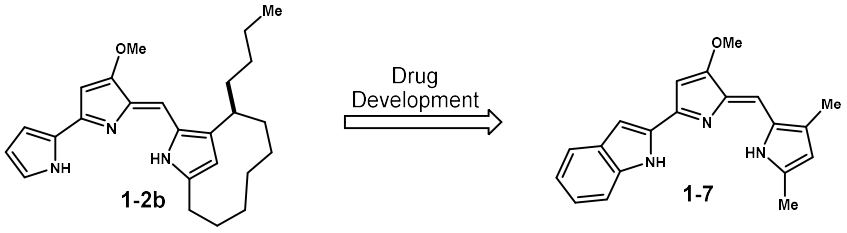


Figure 1.5. The Structure of Obatoclax

The Harran laboratory has a long standing interest in developing small molecules that have the capability to restore apoptotic signaling in cancer cells. We have made several advancements with molecular mimics of Smac, a protein downstream of the Bcl-2 family that is responsible for the freeing of caspases to initiate apoptosis.[59–61] We were intrigued by the above findings and found them compelling enough to initiate a program to further explore ansa bridged prodiginines as potential modulators of BCL-2 PPI's.

We hypothesized that the off-target toxicity observed with **1-7** might be due to the copper nuclease activity and anion transmembrane transport properties induced by other prodiginines, which also bring about apoptosis.[29,62,63] We postulated that the more complex members of the prodiginines **1-3b/c** and **1-5** in which the trispyrrolic core has been modified would have attenuated chelation modes as compared to simpler prodiginines. In order to access these ornate architectures, we first examined the mechanisms by which they are constructed in nature to find inspiration for synthetic production.

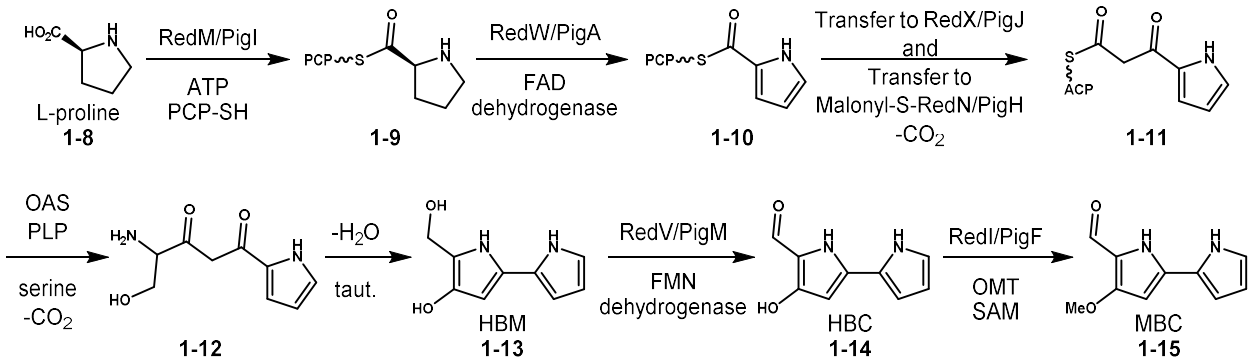
1.2.3. Ansa Bridged Prodiginine Alkaloids: Biosynthetic Pathways

The biosynthetic construction of these alkaloids has intrigued scientists since their discovery and extensive efforts have been put forth to establish the natural mechanisms of their fabrication. The biosynthetic pathways that produce these structures have been reviewed in detail and a brief summary will be given here.[1,2]

The structural similarities between the prodiginines and porphyrins led early investigators to examine whether these motifs harbored a biosynthetic relationship.[64,65] These notions were proven incorrect after potentially common biosynthetic precursors were disqualified and data corresponding to a novel and distinct biosynthetic pathway accumulated.[9,66,67] Wasserman and coworkers utilized feeding studies with radiolabeled building blocks to identify the proline, serine, acetate, and glycine as metabolic precursors to undecylprodigiosin.[10,11] Undecylprodigiosin (**1-1a**) is biosynthesized by the union of two key fragments: 4-methoxy-2,2'-bipyrrole-5-carboxaldehyde (MBC, **1-15**) and 2-undecylpyrrole (2-UP, **1-25**).[11]

The biosynthetic pathway to MBC (**1-15**, **Scheme 1.1**) initiates with the loading of proline onto a peptidyl carrier protein (PCP) via a thioester linkage.[2] This conjugate is then acted upon by a flavin

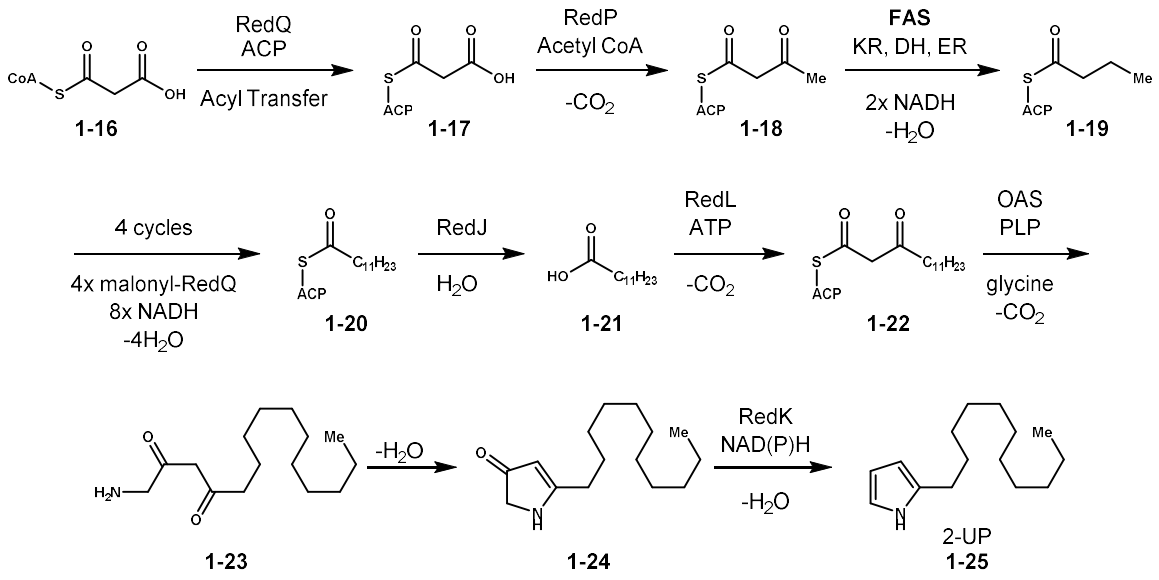
adenine dependent (FAD) dehydrogenase, which oxidizes the pyrrolidine moiety to produce a pyrrole-2-carboxyl thioester (**1-10**).[68,69] This intermediate then undergoes a condensation with a malonyl-CoA derived thioester followed by decarboxylation to produce β-ketothioester **1-11**.[2,69] A subsequent condensation/decarboxyaltion with pyridoxal 5'-phosphate (PLP) bound serine facilitated by a postulated α-oxoamine synthase (OAS), affords aminoalcohol **1-12** upon hydrolysis.[2,69] This short lived intermediate undergoes self-condensation and tautomerization to produce 4-hydroxy-2,2'-bipyrrole-5-methanol (HBM, **1-13**). The primary alcohol is oxidized by a putative flavin mononucleotide (FMN)-bound dehydrogenase and the pyrrole hydroxyl group is methylated via a SAM-dependent O-methyl transferase (OMT) to produce MBC (**1-15**).[2,70]



Scheme 1.1. Biosynthesis of 4-methoxy-2,2'-bipyrrole-5-carboxyaldehyde (**1-15**)

Biosynthetic production of 2-UP (**1-25**, **Scheme 1.2**) commences with malonyl-CoA being loaded onto an acyl carrier protein (ACP) and a condensation/decarboxylation with acetyl-CoA.[3,71,72] The resultant β-ketothioester-ACP conjugate **1-18** is then thought to be acted upon by the ketoreductase (KR), dehydratase (DH), and enoylreductase (ER) modules of the *Streptomyces/Serratia* sp. inherent fatty acid synthase to afford the reduced butanoyl-thioester **1-19**. This process is recapitulated four times to provide the dodecanoyl-thioester.[2,71] Dodecanoic acid (**1-21**) is liberated and then transferred to another ACP, where it undergoes a condensation/decarboxylation with a malonyl-thioester to afford β-ketothioester **1-22**.[2,71] A final condensation is mediated by an

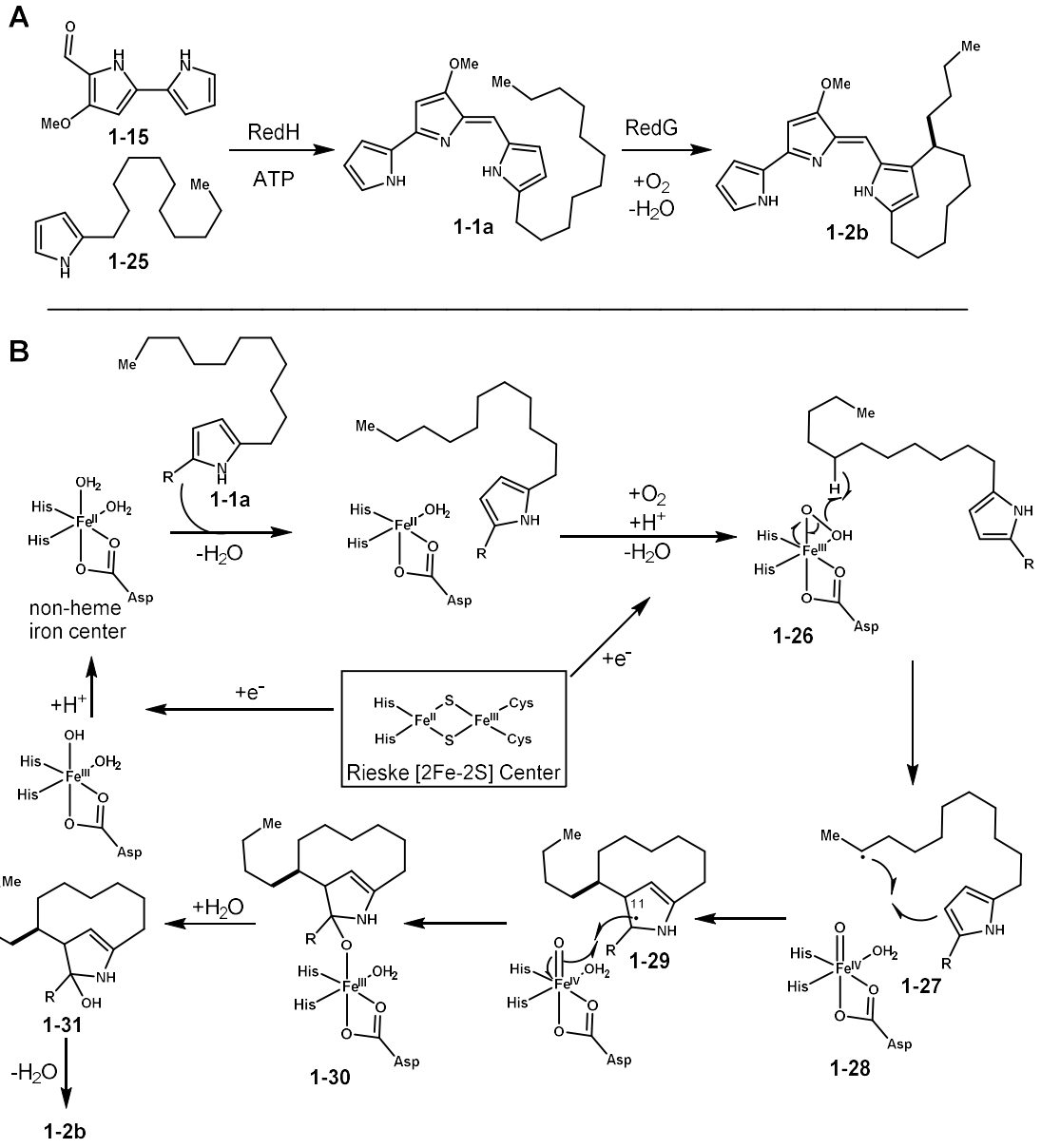
OAS with PLP-bound glycine followed by decarboxylation affords α-aminoketone **1-23**, which undergoes spontaneous cyclization to form 5-undecylpyrrolin-3-one (**1-24**).[71] A reduction of the ketone and dehydration produce 2-UP (**1-25**).[2]



Scheme 1.2. Biosynthesis of 2-undecylpyrrole (**1-25**)

An enzyme mediated condensation reaction combines MBC (**1-15**) and 2-UP (**1-25**) to affords the biosynthetic precursor to several ansa bridged prodiginines, undecylprodigiosin **1-1a** (**Scheme 1.3A**).[73,74] The ansa linkage is constructed by the action of the non-Heme Iron Rieske oxygenase, RedG, which contains an iron-sulfur cluster and iron-binding residues.[7,75] The postulated mechanism for the ansa bridge formation in the case of streptorubin B (**1-2b**) begins by coordination of **1-1a** to the active iron center, which facilitates the loss of water and the binding of molecular oxygen (**Scheme 1.3B**).[75] Electron transfer from the iron-sulfur cluster causes reduction of the non-heme species to an iron-peroxide complex, which abstracts hydrogen from the C20 of **1-1a** to afford carbon-centered radical **1-27** and iron-oxo complex **1-28**.[75] The radical then engages the proximal electron rich lipochromophore to form the ansa bridge via a new carbon-carbon linkage at C11. The resultant radical **1-29** is stabilized by delocalization into the disrupted

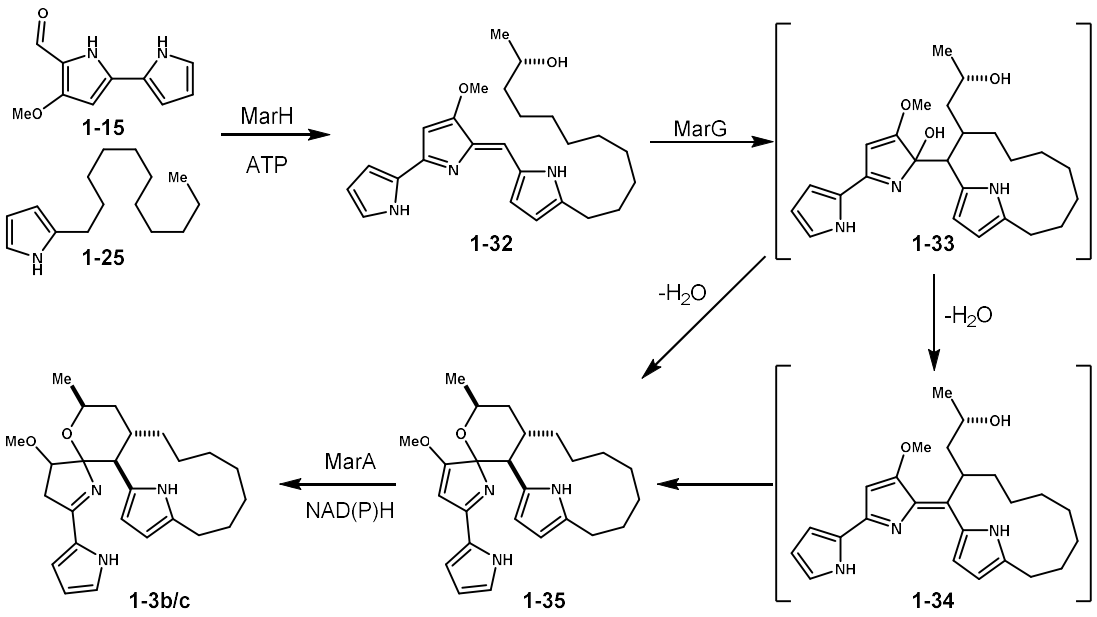
π-system. The oxo ligand of the iron complex then intercepts the carbon-based radical to form a carbon-oxygen-iron linkage, which is hydrolyzed to afford hydroxylated product **1-31** that undergoes dehydration to produce streptorubin B **1-2b**. Alternatively, hydrogen atom abstraction from C11 has been proposed to directly access **1-2b** (Not Shown). However, the hydroxylation mechanism more accurately reflects what occurs with the more complex ansa bridged prodiginines (i.e. the disrupted chromophore of the marineosins and the furan motif of roseophilin).



Scheme 1.3. (A) Biosynthetic Generation of Undecylprodigiosin (**1-1a**) and Streptorubin B (**1-2b**). (B) The Enzymatic Mechanism Underlying the Oxidative Carbocyclization for Ansa Bridge Formation.

In the case of the marineosins, the seco-precursor is 23-hydroxyundecylprodigiosin (**1-31**, **Scheme 1.4**). It was originally thought that an unidentified oxygenase was responsible for the hydroxylation of **1-1a** or its precursor 2-UP (**1-25**).[4,31] However, it was recently discovered that **1-32** originates from MBC and 2-UP like its deoxygenated homologues.[5] A bifunctional enzyme, denominated as MarH, catalyzes the combination of these precursors and hydroxylates C23 to afford **1-32**.[5] Studies

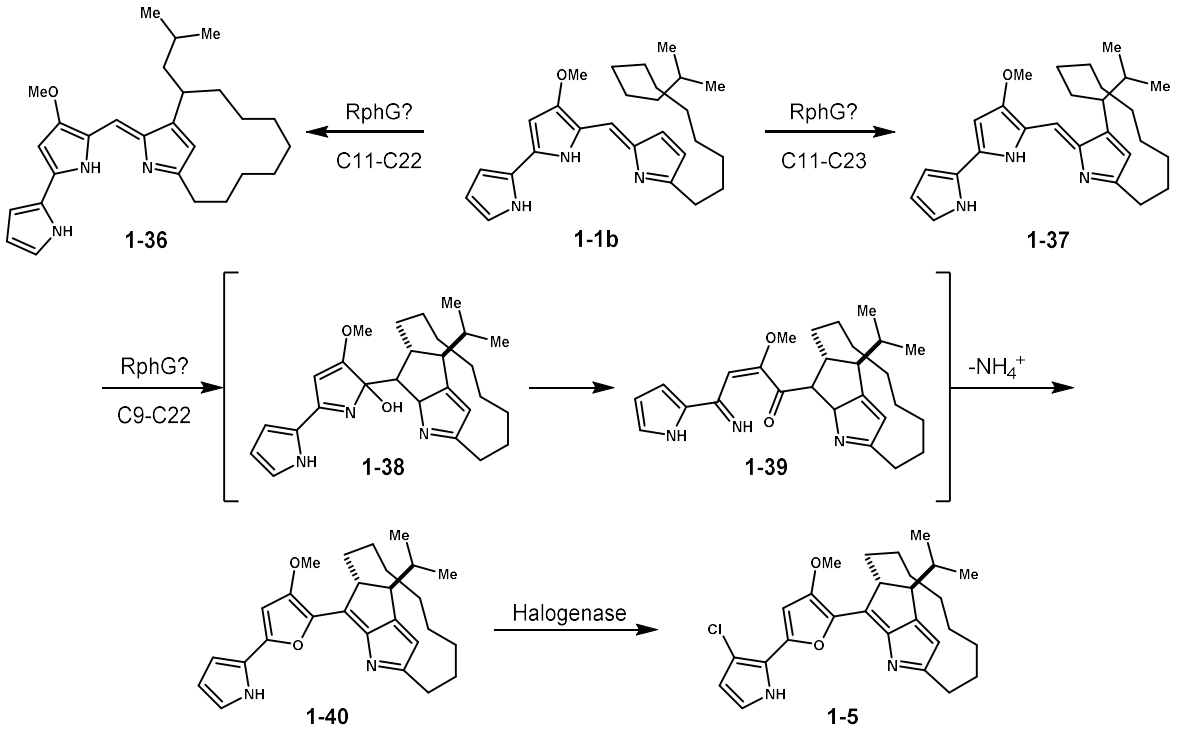
are ongoing to conclusively determine the mechanism by which MarH accomplishes these transformations. **1-32** is acted upon by the non-Heme Rieske iron oxygenase MarG, which facilitates a similar mechanism of ansa bridge formation to that of **1-2b** (*vide supra*), except C9 of the lipochromophore engages the aliphatic carbon radical.[4] When hydroxylated intermediate **1-33** is released from the iron center, it is unclear whether the spiroiminal formation is spontaneous or enzyme-mediated yielding the premarineosins **1-35**. In addition, it is also unclear whether dehydrated intermediate **1-34** is produced at any point. Studies in our laboratory have shown that synthetic **1-34** does not spontaneously cyclize, which strengthens the argument that **1-34** is not produced in nature. The premarineosins are converted to marineosins A and B (**1-3b/c**) by the action of the MarH reductase.[4]



Scheme 1.4. Biosynthetic Origins of Marineosins (**1-3b/c**) and Possible Pathways for Spiroiminal Construction

Although roseophilin has been known in the literature for nearly three decades and has been the subject of several chemical syntheses efforts, its biosynthesis has been largely a mystery until relatively recently. In 2008, Hayakawa and coworkers isolated prodigiosin R1 (**1-36**, **Scheme 1.5**)

from *Streptomyces griseoviridis*, which appeared to be related to roseophilin due to it being derived from the same postulated biosynthetic precursor.[76] Prodigiosin R1 (**1-36**) differs in the regiochemistry of ansa linkage, where a radical is theoretically generated at C22 instead of C23 in the case of rosephilin.[76] A year later, dechlororoseophilin (**1-40**) was isolated by the same group, which indicates that the chlorination is most likely the final step in the biosynthesis.[77] The probable gene cluster for the biosynthesis of **1-5** and **1-36** have been reported, as has circumstantial evidence for the existence of their seco precursor, methyldodecylprodigiosin (**1-1b**).[3,78] The postulated biosynthesis commences with **1-1b**, which can be converted to either **1-36** or **1-37**.[2,75] **1-37** undergoes a second oxidative carbocyclization to afford hemi-iminal **1-38**, which opens the B-ring.[2,75] This ring opening is followed by reclosure and elimination of ammonium to afford dechlororoseophilin (**1-40**), which is subsequently chlorinated by an unidentified halogenase.



Scheme 1.5. Postulated Biosynthetic Production of Prodigiosin R1 (**1-35**) and Roseophilin (**1-5**) from Proposed Metabolic Precursor Methyldodecylprodigiosin (**1-1b**)

Despite the inherent elegance of a bioinspired late-stage ansa bridge formation, most synthetic efforts toward roseophilin and the marineosins focused on building the pyrrolophane early in the synthesis. Our own bioinspired approach to these prodiginines sought to access these pyrrolophanes at later stages in the synthesis via various macrocyclization methodologies. In order to avoid the potential for chaos in utilizing radical intermediates, we developed systems where the lipochromophore and the functionalized aliphatic chain were polarity matched.

1.3. A Bioinspired Approach to Ansa Bridged Prodiginines

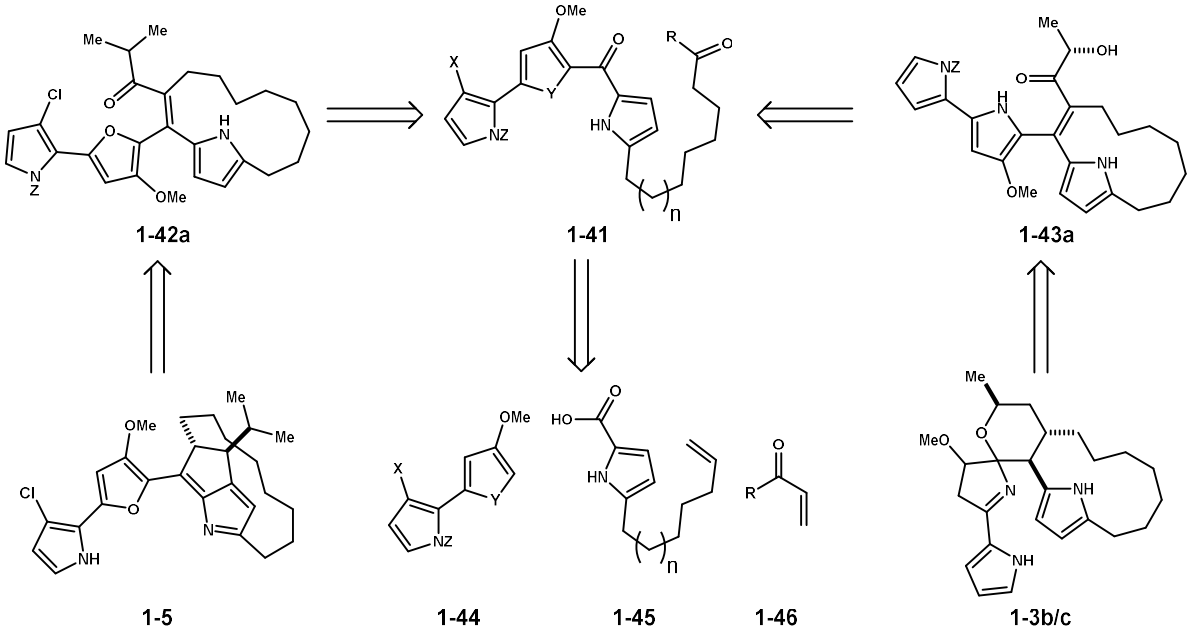


Figure 1.6. Retrosynthetic Analysis: A Bioinspired Synthesis of Roseophilin **1-5** and the Marineosins **1-3b/c**

The simplicity associated with a late stage ansa bridge formation was extremely attractive to us. This allowed us to view roseophilin **1-5** and the marineosins **1-3b/c** as being derived directly from their respective seco precursors. This strategy is radically different from the previous efforts directed at these structures.[2] However, we hypothesized that attempting to utilize a true biomimetic approach via radical generation might prove too chaotic in terms of engaging the lipochromophore

in several positions or the remote aliphatic radical could participate in a variety of alternate processes. Given this hypothesis, we reasoned that if we could introduce polarity on the aliphatic chain and modify the polarity of the lipochromophore, then we could bias the system towards our desired macrocyclization. We leveraged that an aldol condensation could be utilized at a late stage to construct the ansa bridge and the natural products could be accessed after subsequent manipulations of the macrocyclic product. The main issue with this proposal is the macrocyclization would rely on a relatively unfavorable process. We would require an enolate to attack an electron rich bis-aryl ketone generating a hindered aldol salt, which could easily undergo a retroaldol to return starting material. We posited that if an internal trap could be utilized to drive this unfavorable equilibrium forward. This logic had been utilized previously in the reduction of acyl pyrroles to alkyl pyrroles via an N to O tosyl transfer-elimination.[79]

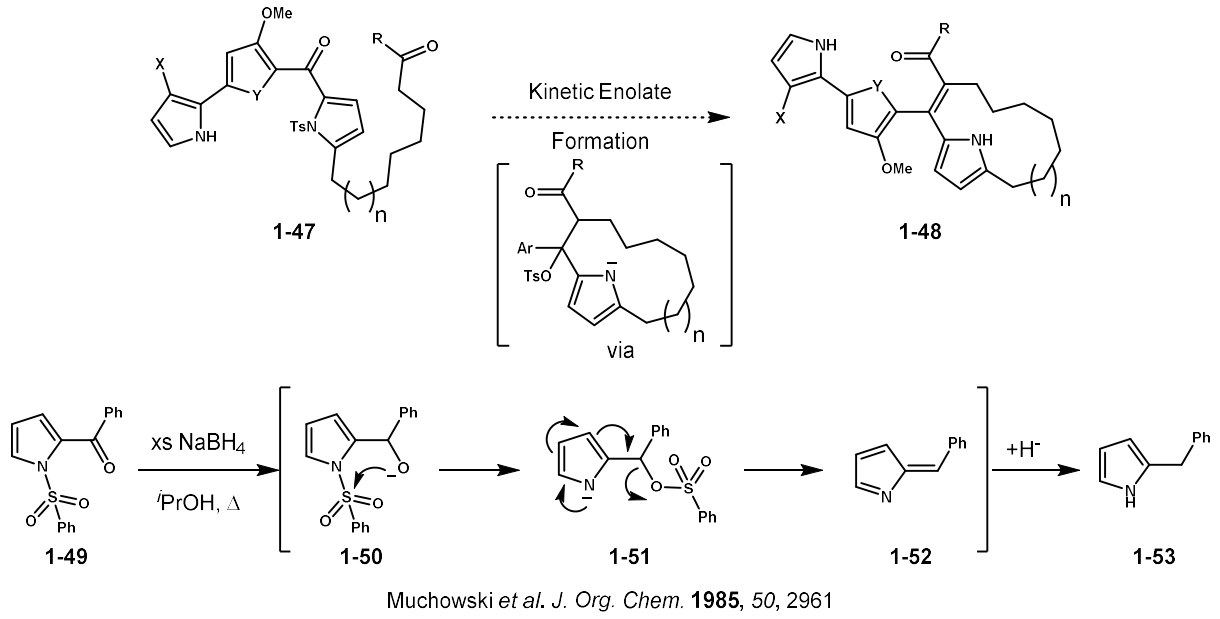


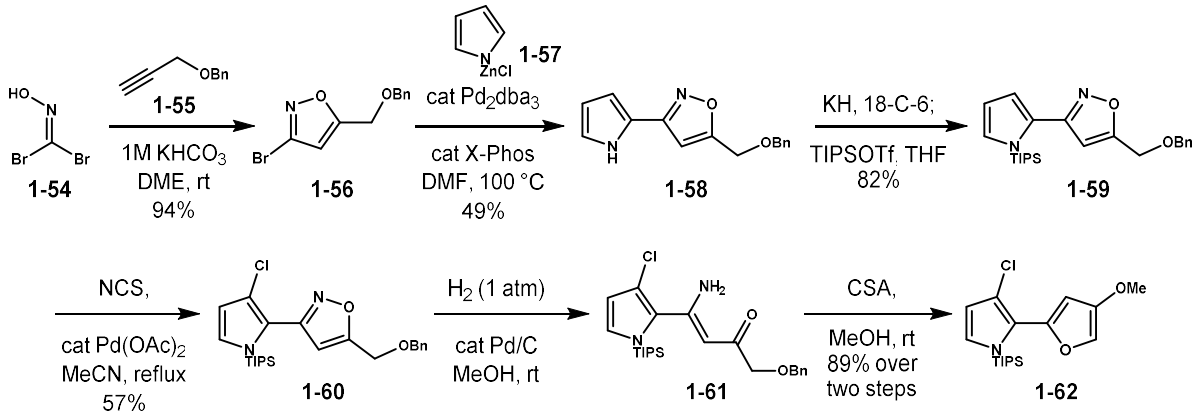
Figure 1.7. Early Proposal for Macroannulation

We hypothesized that our seco precursor could then be derived from the combination of several simpler fragments. We desired a high degree of modularity in these simple fragments to allow for

access to either **1-5** or **1-3b/c** simply by choice of precursors. This modular approach would allow for generation of a library of **1-5** and **1-3b/c** analogs to explore the necessary components for BCL-2 protein interactions.

1.3.1. A Bioinspired Approach to Ansa Bridged Prodiginines: The Total Synthesis of Roseophilin (1-5)

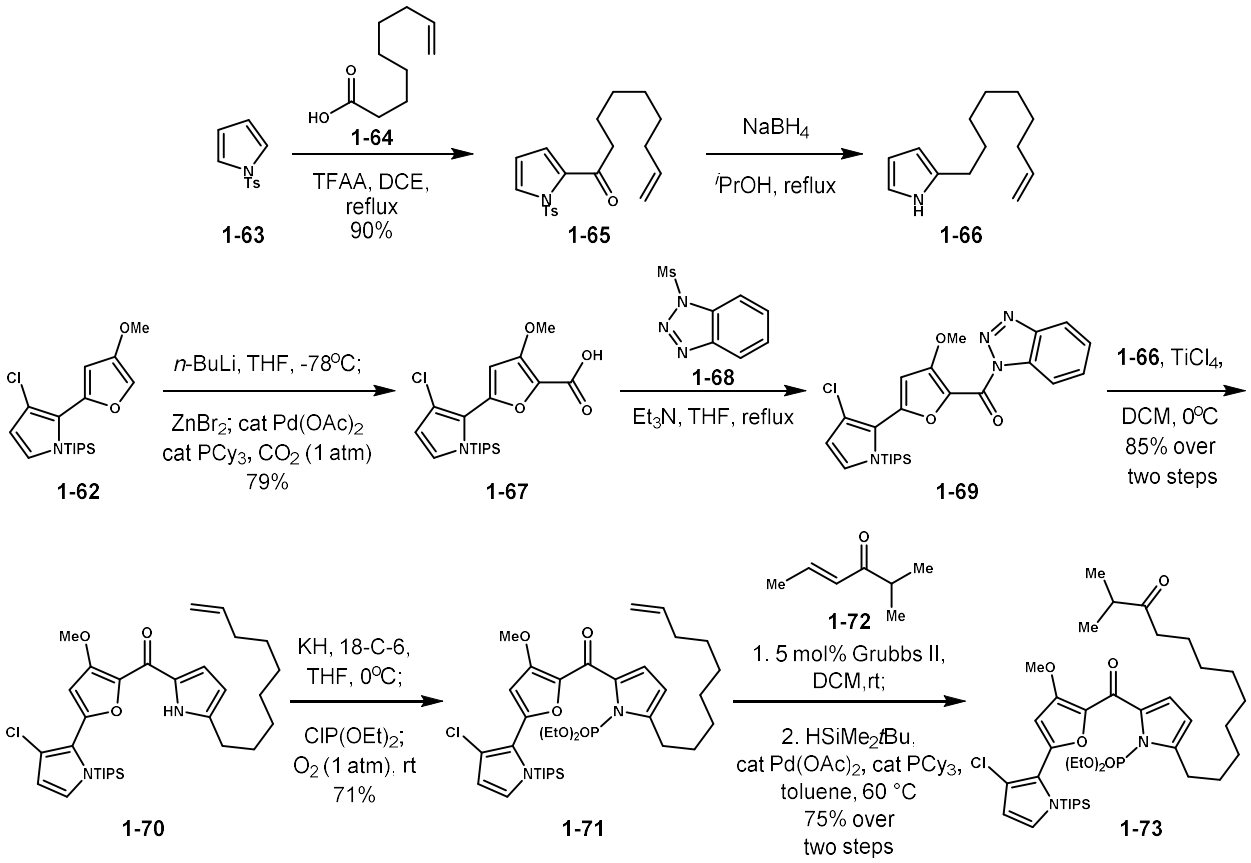
We chose roseophilin **1-5** as our first target to test our proposal of late stage ansa bridge construction. As described above, we desired to use modular building blocks, which could be rapidly assembled into the seco precursor **1-41**. In the case of roseophilin, construction of the pyrrolylfuran component had been reported in the literature.[1,26,80,81] However, these constructions required at least 8 steps and were not generalizable to construct variants of the parent pyrrolofuran **1-62**.



Scheme 1.6. Development of Improved Synthesis of Pyrrolofuran **1-62**

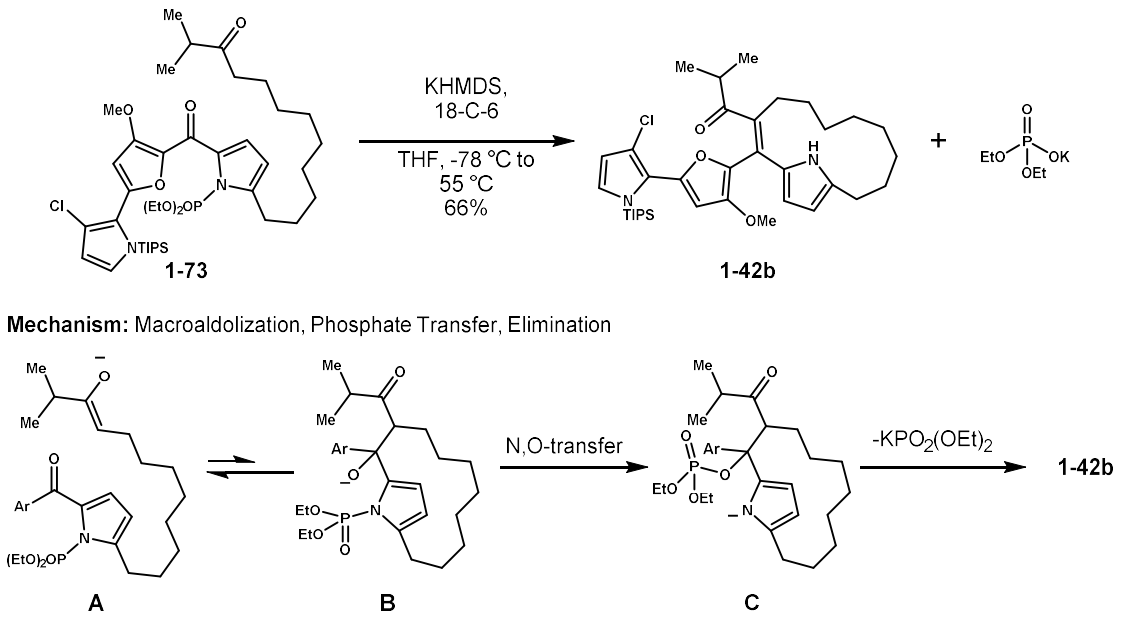
In 2013, our lab reported a more efficient and variable construction of the pyrrolofuran segment, as well as the bipyrrole fragment that would be utilized for the marineosins.[82] Our construction built off of Terashima's work, which considered the ultimate B ring methoxyfuran/pyrrole as a

cyclocondensation product of a derivatized β-diketone.[80,82] Our construction utilized isoxazole **1-60** as a masked β-diketone, which could be unveiled and cyclized in short order to afford several alkoxy pyrrolofuran variants.[82]



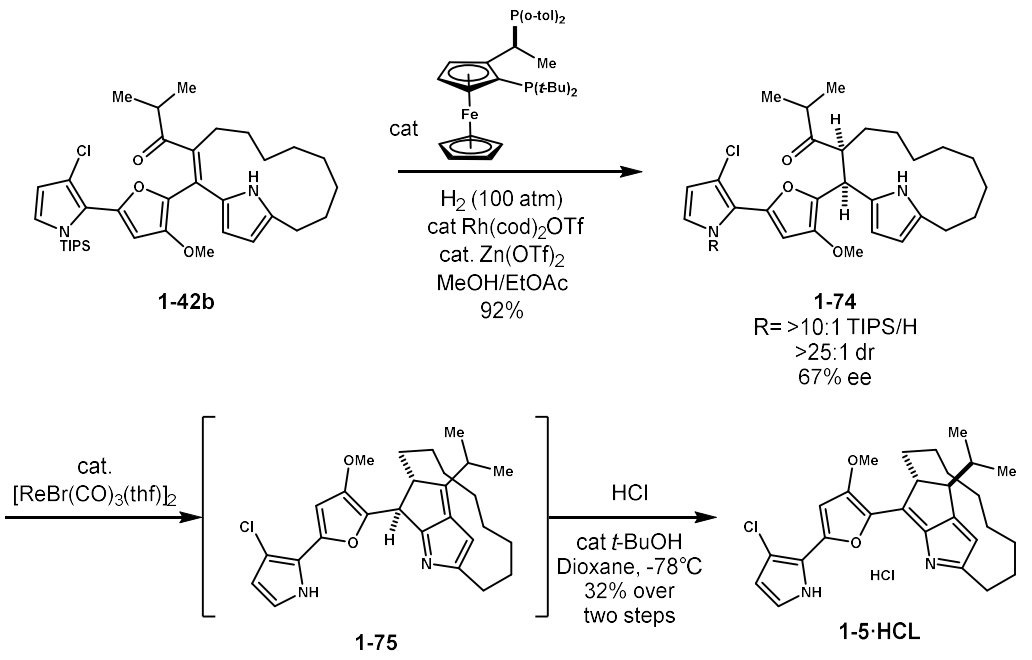
Scheme 1.7. Generation of Macroaldolization Seco Precursor **1-73**

In 2013, our late stage macrocyclization approach was validated by the construction of roseophilin **1-5**, which utilized the internal trap aldolization methodology that we had proposed. Following our studies on optimizing **1-62** synthesis, we were able to quickly access our desired seco precursor **1-73**.[83] Pyrrolofuran segment **1-62** was converted to acylating agent **1-69**, which was then treated with 2-(8-nonenyl)pyrrole (**1-66**) in the presence of the strongly Lewis acidic $TiCl_4$.[84] This biaryl ketone was then elaborated over several steps to seco precursor **1-73**.



Scheme 1.8. Proof of Concept for Late Stage Ansa Bridge Formation – Construction of Macrocycle **1-42b**

With the key seco precursor obtained, Harran and Frederich examined the feasibility of the desired phosphoryl-transfer terminated macroaldolization step. The system had been orchestrated so that the desired kinetic enolate could be generated with confidence. Low temperature deprotonation proved inadequate since only starting **1-73** was obtained on quenching. Similar results were attained when the system was allowed to slowly warm to room temperature or when 18-crown-6 (18-C-6) was added. Gradually increasing the temperature of the reaction to 55 °C proved to be the proper condition to induce the desired annulation process. It is postulated that heating the reaction, as well sequestration of the potassium by 18-crown-6, provide the conditions to establish an unfavorable equilibrium between the stable kinetic enolate and the hindered aldol salt. Once the system has an adequate amount of energy, an irreversible intramolecular N-to-O phosphoryl transfer can occur, which allows the system to slowly syphon intermediate **B** out of the established equilibrium. A subsequent elimination of the phosphate group produces an intermediate aza-fulvene (not shown), which quickly isomerizes to the α,β-unsaturated ketone product **1-42b**.



Scheme 1.9. Completion of Roseophilin **1-5**

After validation of our late stage annulation methodology, we had to consider how to conver macrocyclic enone **1-42b** to the natural product roseophilin **1-5**. Enone **1-42b** differs from the natural product by being two electrons higher in oxidation state and a net hydration. Thus, we utilized an asymmetric conjugate reduction to access ketone **1-74**. A cyclodehydration could be facilitated by treatment with the Lewis acid $[ReBr(CO)_3(thf)]_2$ to afford the unstable prototropisomer of roseophilin **1-5**, which can be converted to the stable hydrochloride salt of **1-5** by treatment with dilute HCl in dioxane.

The construction of **1-5** provided the proof of concept needed for our designed late stage macrocyclization approach. At this stage, our goals became two-fold. One aimed to explore the therapeutic potential of this modified prodiginine scaffold and examine whether the BCL-2 activity could be elicited from these architectures. Secondly, the scope of this line of construction would be further scrutinized in the context of marineosin assembly.

1.4. Thesis Research – Development of Unified Approach to Access Bridgehead Based Ansa Bridged Prodiginines the Marineosins 1-3a-c and Roseophilin 1-5a

Our late stage annulation approach was incumbent upon the development of a generalizable synthetic route to seco precursor **1-41** (**Figure 1.6**). The construction of roseophilin via an end game macroaldolization validated this line of inquiry, however only partially fulfilled our goals.[83] A key end objective was to develop a modular process that could be utilized to construct roseophilin, the marineosins, or hybrids thereof by the simple choice of components used to assemble seco precursor **1-41**. Therefore, our synthetic goals had only been midway accomplished. We posited that the marineosin scaffold would allow us to conduct a more rigorous examination of our strategy.

The marineosins are the most complex members of the ansa bridged prodiginines to have been reported in the literature.[30] Within the marineosin architecture, the prodiginine scaffold has been extensively modified via disruption of the lipochromophore by formation of an unprecedented spirocyclic iminal with the B ring. This interesting structural feature would inherently require us to develop a new dearomative cyclization reaction methodology, which would allow a pendant alcohol to add across an extended π-system.

Unlike the roseophilin framework, which contains a B ring methoxyfuran, the marineosins are derived directly from the tris-pyrrolic core of the traditional prodiginines. The ansa linkage of the marineosins is also truncated by one carbon compared to roseophilin, which introduces an additional amount of ring strain to overcome in the macroannulation. The introduction of the third pyrrole and the smaller ring size bring with them issues in terms of defining an efficient transfer group for the macroaldolization methodology, as well as examining conditions needed to overcome the added ring strain. We anticipated that undertaking a synthesis of the marineosins

would allow us to further refine our late stage annulation strategy and enable reaction discovery for their unique structural elements.

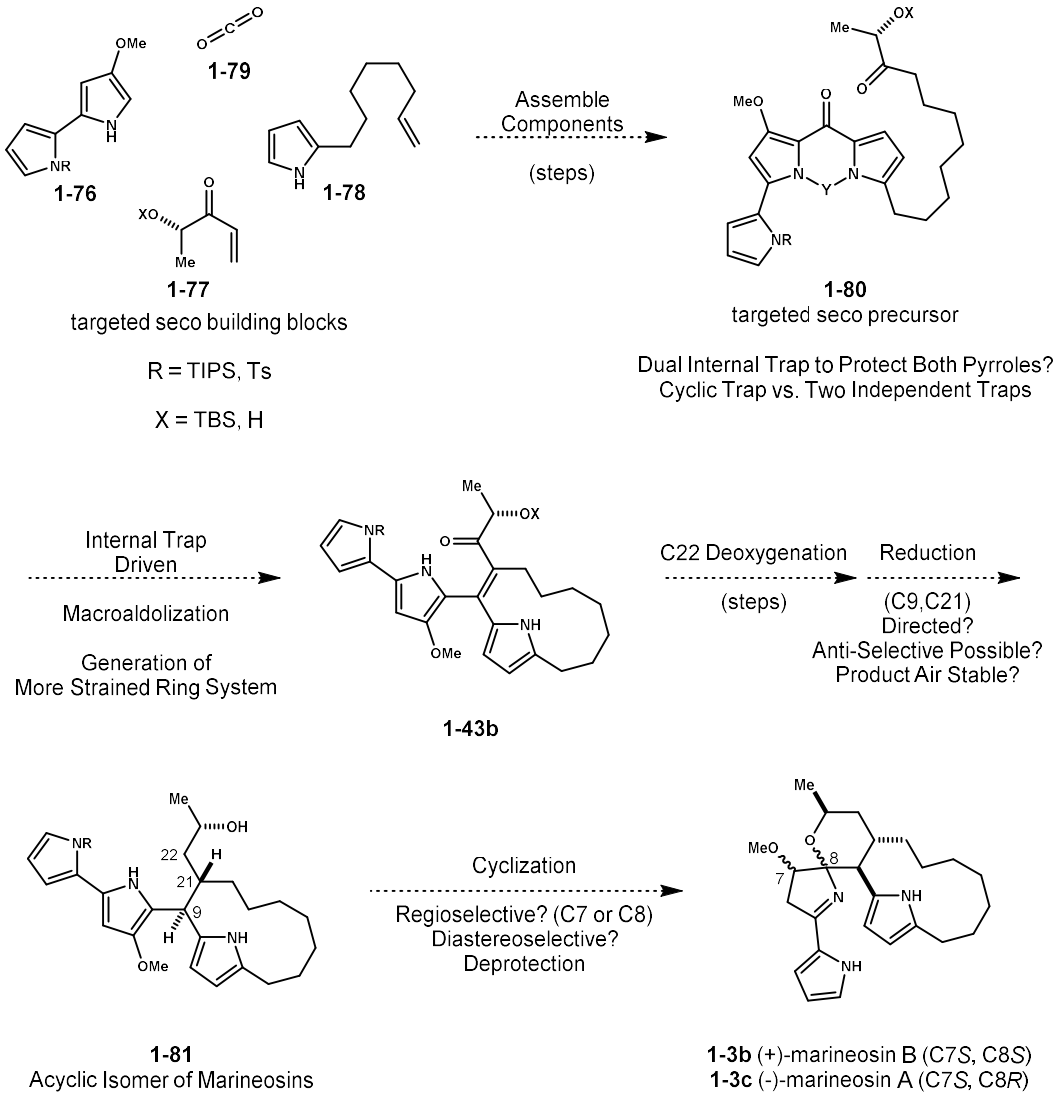


Figure 1.8. Proposed Access to the Marineosins **1-3b/c** and variants thereof from a seco precursor **1-80**

Targeted seco precursor **1-80** could be prepared by analogy to the above described methods for the construction of roseophilin seco precursor **1-73** (**Figure 1.8**). A variety of mono- and dual traps could be examined to control the reactivity of the third pyrrole ring. The key annulation method would be developed for **1-80** to afford **1-43b**. Access to macrocyclic enone **1-43b** would represent

substantial progress due its construction representing the generalizability of our strategy towards the C9-linked ansa bridged prodiginines.

Key intermediate **1-43b** was then envisioned to go through a deoxygenation to eliminate the lingering ketone followed by a reduction that would result in a net anti addition of hydrogen across the C9-C21 tetrasubstituted olefin to afford the acyclic structural isomer of the marineosins **1-81**. It was posited that intermediate **1-81** might be prone to auto-oxidation, which would produce a protected variant of **1**-**34**. However, if **1-81** proved stable or that it could be handled in a manner that prevented auto-oxidation, we believed that methods to induce cyclization of the pendant alcohol on to the B ring methoxypyrrole could be developed. The final step of the approach to the marineosins **1-3b/c** would be a deprotection of the A ring pyrrole. These challenges presented an opportunity to rigorously examine our strategy and develop new methods for the construction and manipulation of ansa bridged prodiginines.

1.5. Completed Efforts and Total Syntheses

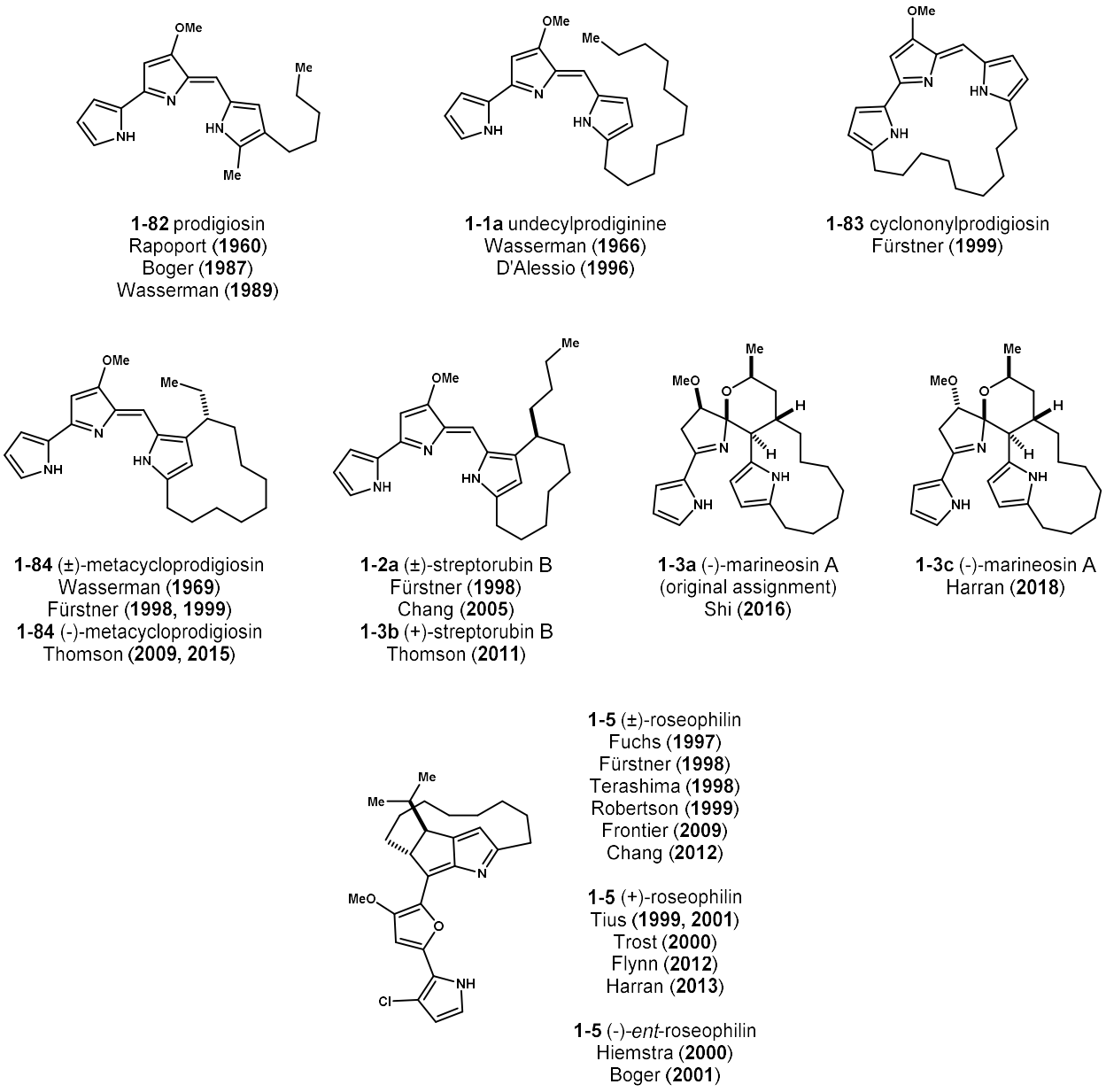


Figure 1.9. Completed Synthetic Efforts. Total and Formal Syntheses of Ansa Bridged Prodiginines.

The prodiginine class of natural products have intrigued the synthetic community for decades, due to both their intriguing structures and compelling biological activities. Rapoport and coworkers developed several synthetic routes to address the structural isomer enigma of prodigiosin **1-82**.[2,85–87] It was during these studies that developed the most common method of accessing the prodiginine

scaffold via a biomimetic condensation reaction between synthetic MBC **1-15** and a functionalized C ring progenitor.[2,86,87] The Boger laboratory were able to produce prodigiosin and a variety of analogues by utilization of their tetrazine Diels-Alder approach to **1-15**.[88,89] An alternative construction of the prodiginine core was reported by D'Alessio and coworkers, which constructs the B-C ring junction via a condensation reaction followed by a palladium catalyzed cross coupling between a pyrroleboronic acid and a triflimidate.[90] This new approach was utilized to construct undecylprodiginine **1-1a**.

In the late 1990's, the Fürstner laboratory made significant strides in the construction of the ansa bridged members of the prodiginine family. They utilized a variety of metal catalyzed processes, such as Tsuji-Trost allylations and ring closing metathesis, to construct the ansa bridged pyrrolophane C ring precursors, which were combined with **1-15** in a Rapoport fashion.[21,91,92] Further synthetic investigations for the development of enantiopure ansa bridged prodiginines by the Thomson laboratory led to the development of an oxidative enolate coupling methodology to construct the requisite 1,4-dicarbonyl structures for Paal-Knorr chemistry.[93] The Thomson laboratory also developed utilized an anionic oxy-Cope rearrangement on a cyclic template for the enantioselective construction of the streptorubin B **1-2b** macrocycle.

Roseophilin **1-5** has been a prime target of many synthetic groups since its discovery. The interesting topology of the system has been viewed as a proving ground for synthesis and its reported biological activities are compelling.[25,29] The Fürstner laboratory was the first to report a completed synthesis of **1-5**.[26] Their route hinged upon the joining of fragments **1-62** and **1-85** in a manner that was analogous to the Rapoport condensation (**Figure 1.10**). Although this acid mediated condensation readily occurs with pyrrole-based nucleophiles, it does not occur

pyrrolofuran **1-62**, which needs to be derivatized as an organocerium agent in order to react with ketone **1-85**.

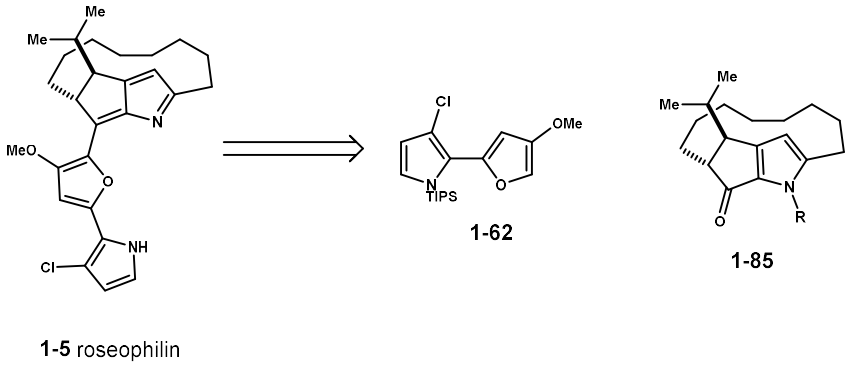


Figure 1.10. Fürstner Retrosynthetic Disconnection of Roseophilin **1-5**

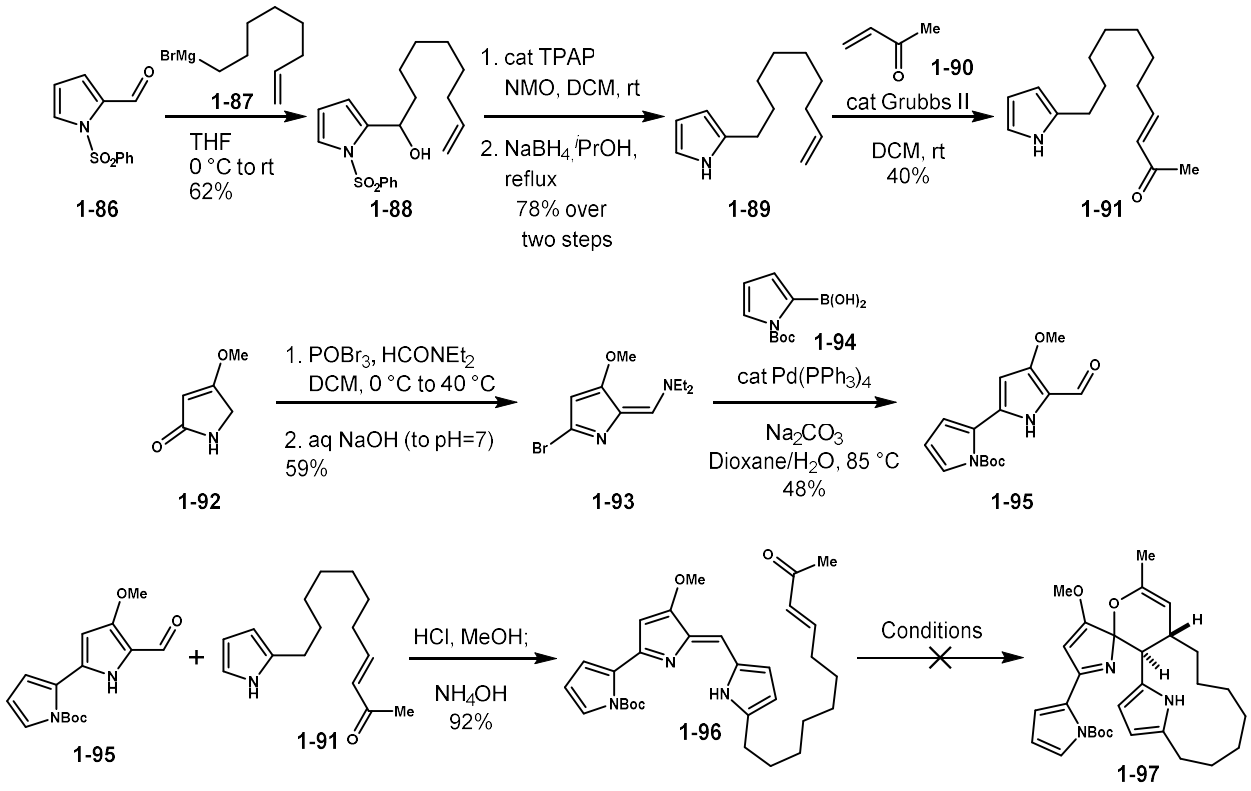
Although there has been significant interest in this modified prodiginine, almost all reported syntheses are formal in nature.[27,28,80,94–104] Our approach (*vide supra*) is the only reported synthesis that does not intercept ketone **1-85**. We sought to utilize our unique approach to roseophilin to access the as yet unconquered marineosins (*vide infra*, Chapter 2).

1.5.1. Ansa Bridged Prodiginine Alkaloid Synthesis: Progress towards the Marineosins

Several groups have reported synthetic efforts toward the marineosins **1-3a/b**, however these structures have yet to succumb to total synthesis. With the exception of Lindsley's hetero-Diels-Alder approach, these synthetic efforts plan to install the A ring pyrrole near the end of the synthesis. These strategies therefore focus mainly on construction of the pyrrolophane and the spiroiminal moieties. This line of retrosynthetic analysis is very different from our own proposal, which proposes to construct the natural product from a seco precursor (*vide supra*).

Lindsley and coworkers reported the first attempts at constructing the marineosins. Their approach relied upon developing seco precursor **1-96** that could undergo an intramolecular inverse-electron-

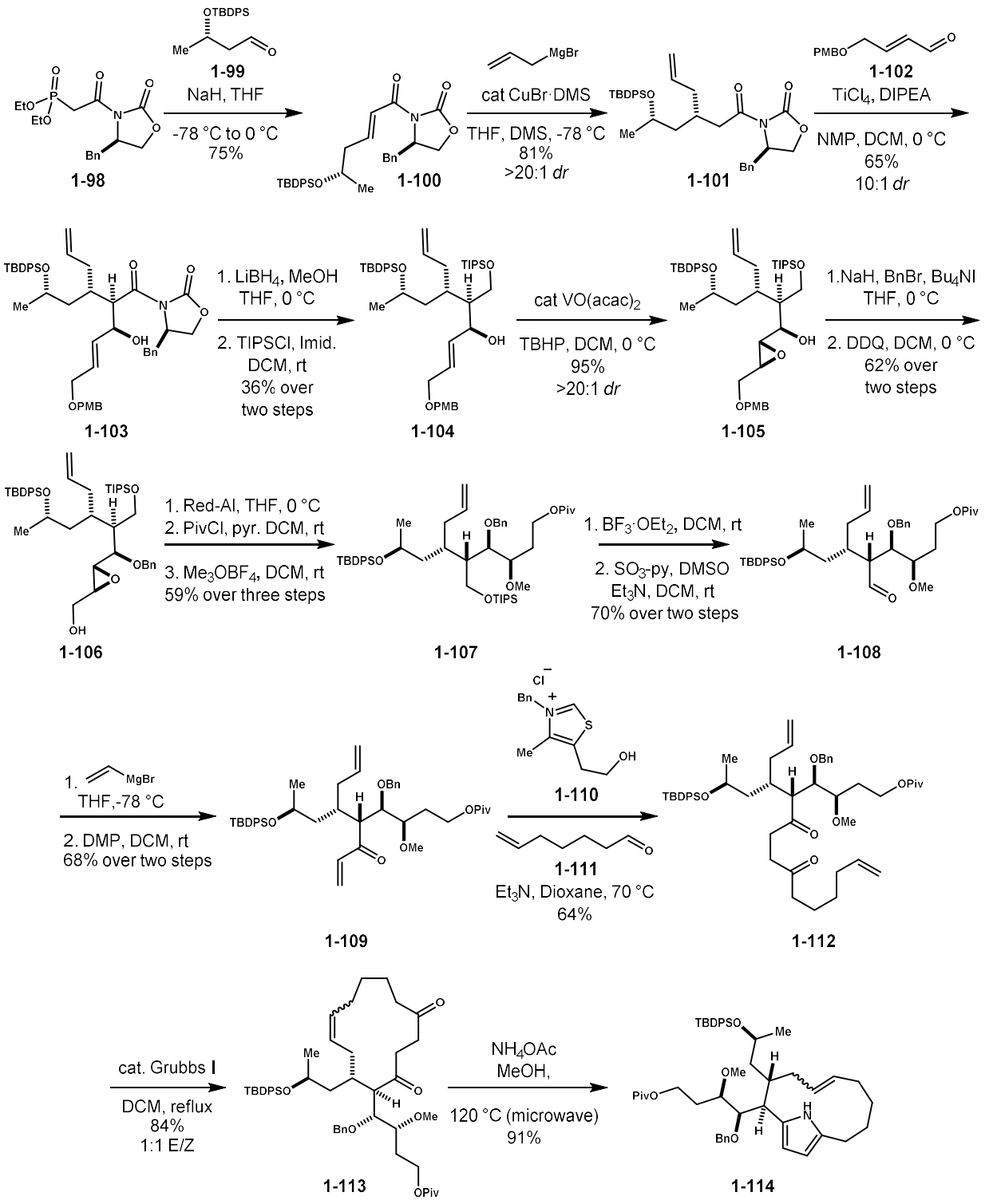
demand-hetero-Diels-Alder reaction to provide **1-97**, which could then be reduced to afford the natural products.[105] This approach was based on a proposed biosynthesis scheme put forth in the isolation report for the marineosins.



Scheme 1.10. Lindsley's Evaluation of Fenical's Proposed Biosynthesis.

The route begins with the construction of 2-(8-nonenyl)pyrrole **1-89** via conditions developed by Muchowski and a cross metathesis with methyl vinyl ketone (MVK, **1-90**) to provide pyrrole **1-91**.[79,105] The MBC variant **1-95** was constructed by a Vilsmeier-Haack reaction with lactam **1-92** followed by a Suzuki coupling with **1-94**. The seco precursor **1-96** was then obtained via a Rapoport condensation. Lindsley and coworkers explored an extensive number of conditions in order to induce the hetero-Diels-Alder reaction to no avail. Computational modeling allowed them

to determine that the desired cycloaddition was energetically unfavorable. Due to these results, this approach was abandoned.



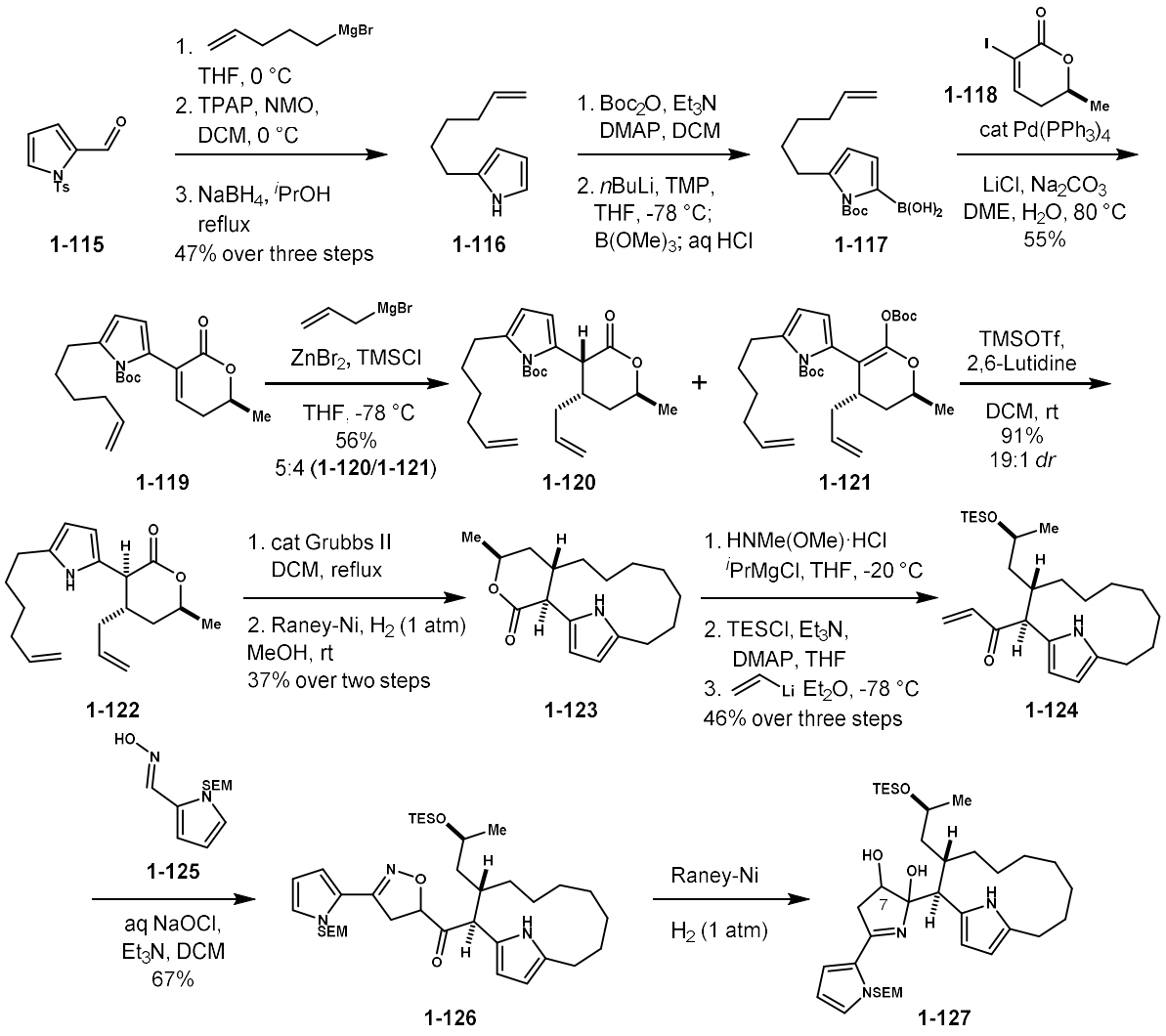
Scheme 1.11. Lindsley's Construction of the Pyrrolophane Moiety of the Marineosins

Following their unsuccessful reports on the intramolecular hetero-Diels-Alder approach, Lindsley and coworkers reported a more conservative route to construct the pyrrolophane moiety of the

marineosins.[106] Their approach focused on establishing the array of stereocenters needed for construction of marineosin A (**Scheme 1.11**). The synthesis commenced with a Horner-Wadsworth Emmons olefination between phosphonate **1-98** and aldehyde **1-99**. Acrylate **1-100** could then be converted to **1-103** via a conjugate addition followed by an aldol, both of which utilized the appended Evan's oxazolidinone to govern diastereoselectivity. This material could then be elaborated to the protected polyalcohol **1-107** over several redox processes. The polyalcohol could be converted over several steps to enone **1-109**, which was subjected to a Stetter reaction with 6-heptenal **1-111**. The dione was then subjected to ring closing metathesis to afford macrocycle followed by pyrrole formation via Paal-Knorr conditions. In addition to reporting an approach to pyrrolophane **1-114**, Lindsley and coworkers also reported elaborating **1-107** to a spiroaminal intermediate (Not shown).[106,107]

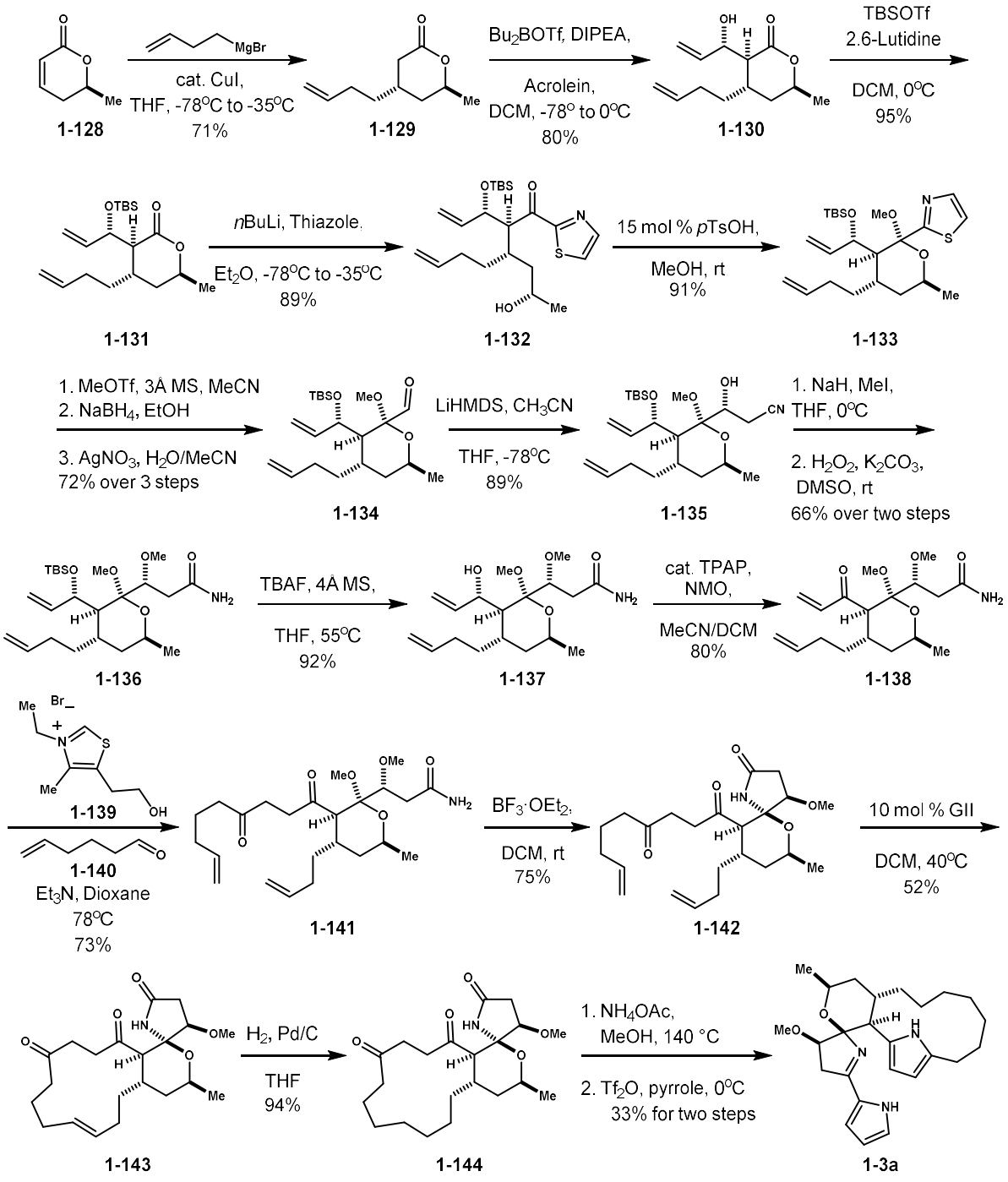
Concurrently with Lindsley's efforts, the Snider laboratory was also exploring the methods to construct the marineosins. Shortly after the report of Lindsley's unsuccessful hetero-Diels Alder attempts, Snider and coworkers reported the construction of marineosin model systems, which could be accessed by dipolar cycloadditions of nitrile oxides to enones followed by hydrogenolysis of the resultant isoxazoline (Not Shown).[33] In a subsequent publication, Snider and coworkers reported a synthesis of an advanced intermediate for the construction of the marineosins.[108] The route utilizes a Suzuki coupling with alkenyl pyrrole boronic acid **1-117** and chiral iodolactone **1-118**. The coupled product **1-119** was then subjected to a diastereoselective conjugate addition and a BOC deprotection to provide diene **1-122**. The pyrrolophane was constructed by ring closing metathesis followed by hydrogenation of the mixture of olefins to provide **1-123**. The lactone was then converted to enone **1-124** through nucleophilic opening of the lactone, alcohol protection, and vinyl Grignard addition to the Weinreb amide. This material was then subjected to the

aforementioned dipolar cycloaddition with to provide isoxazoline **1-126** as a mixture of diastereomers. This material could be hydrogenolyzed to provide what appeared to be a mixture of hemi-iminals. Snider and coworkers attempted to close the spiroiminal system via liberation of the silyl-protected alcohol by treatment with mild acid, but to no avail. Hemi-iminal system **1-127** proved highly sensitive to acidic media, which is exemplified by its fairly rapid decomposition (~10 hrs) in chloroform solvent. Alternatively, Snider and coworkers attempted to methylate the C7 alcohol, however all conditions explored led to decomposition of **1-127**. Given these results, Snider and coworkers abandoned their efforts towards the marineosins.



Scheme 1.12. Snider's Approach to the Marineosins

The most recently reported efforts are those of Shi and coworkers, who reported the synthesis of the nominal structure of marineosin A (**Scheme 1.13**).[32] Surprisingly, the spectral data for the synthetic **1-3a** did not match that of the natural material. Shi provided no hypothesis or rationale as to what the true structure of marineosin could be, however our lab as determined that the natural material is a diastereomer of **1-3a** (i.e. structure **1-3c**, *vide supra*). Shi's approach, like the previously described efforts, utilizes ring closing metathesis to construct the pyrrolophane and utilizes an end game similar to D'Alessio's approach to prodigiosin.



Scheme 1.13. Shi's Construction of the Nominal Marineosin A Structure

Shi's synthesis commences with chiral lactone **1-128**, which is subjected to a diastereoselective conjugate addition followed by an aldol with acrolein to provide β-hydroxy lactone **1-130**. The lactone is then opened by the nucleophilic addition of lithiated thiazole followed by ketal formation

to provide pyran **1-133**. This material is then manipulated over several steps to provide enone **1-138**, which is subjected to a Stetter reaction with 5-hexenal (**1-140**) to afford diketone **1-141**. This material was then treated with the strongly Lewis acidic BF_3 to induce spirocycle formation between the ketal and the primary amide to provide **1-142**. The diene was then annulated using ring closing metathesis followed by hydrogenation to afford the macrocyclic diketone **1-144**. A microwave-assisted Paal-Knorr reaction converted the diketone to the pyrrolophane (Not Shown). This intermediate was then treated with triflic anhydride in pyrrole solvent to form a triflimidate, which undergoes ipso substitution with pyrrole to provide nominal marineosin A **1-3a**.

The synthetic contributions in the area of ansa bridged prodiginine synthesis are expansive and fascinating.[1,2] The above noted strategies to approach the marineosins are accomplishments in their own right. However, the majority of these efforts required extensive sequences to establish the requisite stereochemical relationships of the marineosins, as well as utilized ring closing metathesis to construct the pyrrolophane. Our efforts to establish an efficient construction of the marineosin core from seco precursors followed by adjusting to the oxidation state of the natural product sought to provide an alternative and more modular approach to the marineosins (Chapter 2).

2. Chapter Two – A Late Stage Bioinspired Annulation Approach to the Marineosins

Tyler Allred, Hui Ding, James Frederich, and Patrick Harran

2.1. Introduction

2.1.1. Introduction and General Strategy

Bacteria derived prodiginine alkaloids have drawn considerable attention from synthetic laboratories around the world. A large amount of research on these red pigments has led to elucidation of their biosynthetic origins, analyses of putative biological mechanisms of action, and the development of numerous synthetic constructions.[1,2,22,24] The ansa bridged members of this family of structures are biosynthetically derived from seco precursors via H-atom abstraction/radical generation on the linear aliphatic substituents, engagement of the electron rich lipochromophore, subsequent hydroxylation of the radical, and rearomatization.[7,75] The more complex members of this subgroup are uniquely challenging synthetic targets and have inspired chemists to develop novel methodology to assemble their polycyclic structures. Most synthetic approaches to the ansa bridged prodiginines utilize more or less the same disconnection strategy, which takes advantage of a powerful biomimetic condensation reaction between MBC and the appropriate ansa bridged pyrrolophane (Not Shown).[2,86,87]

An alternative approach inspired by the biosynthetic construction of these compounds was appealing to us.[7,83] The heterocyclic core or a derivative thereof would be constructed with a functionalized aliphatic arm (i.e. a synthetic seco precursor, **2-5**, **Figure 2.1**). This system could be annulated at a late stage to provide advanced macrocyclic intermediates **2-6** that could be converted to these natural products over several manipulations. This concept of ansa bridge formation was validated by our construction of roseophilin **2-7**. We envisioned that this approach could be generalized to construct both roseophilin and the marineosins **2-8a/b**. Although

marineosin and roseophilin contain different aromatic cores, this general approach was intuitive and direct.

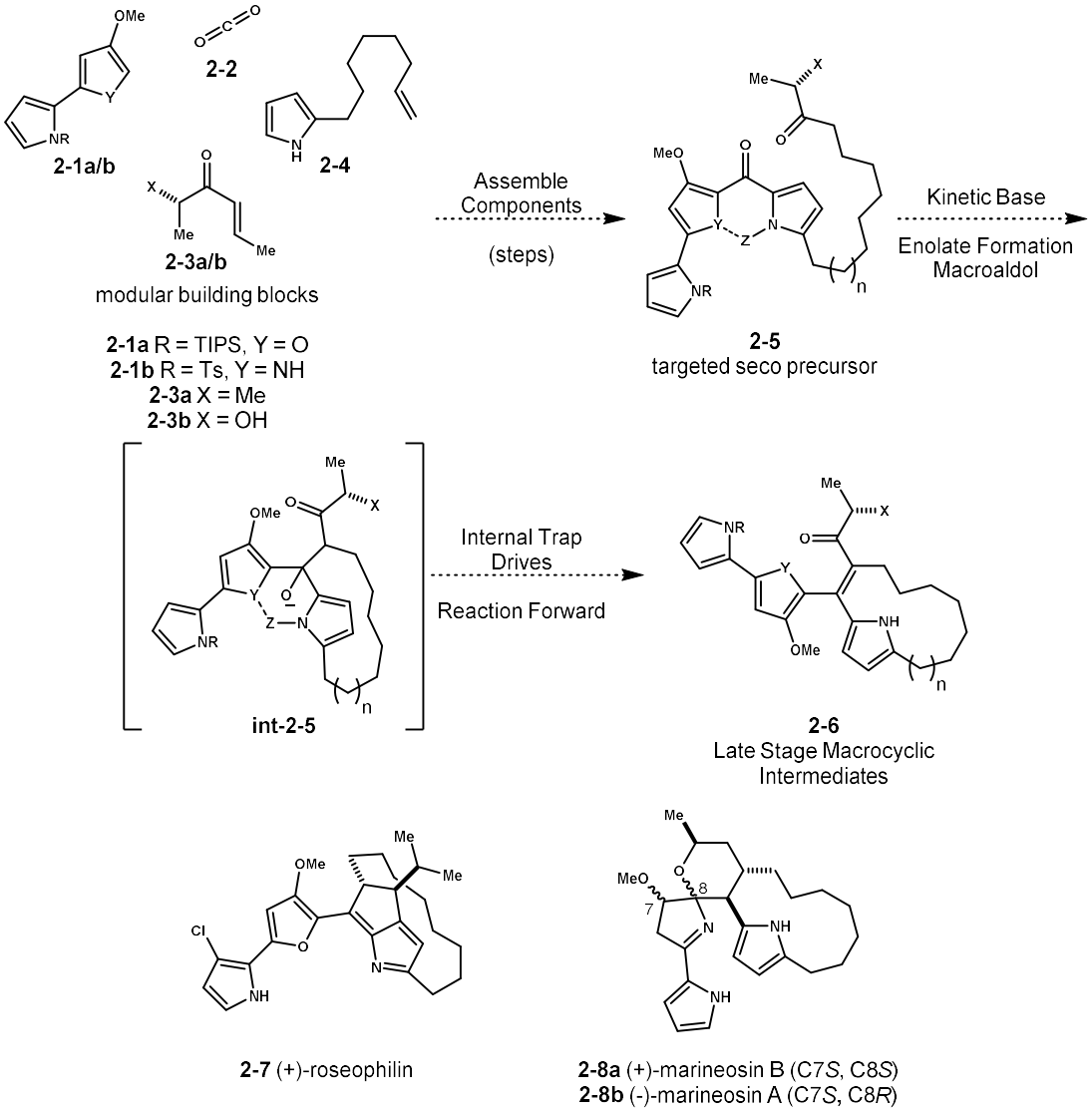


Figure 2.1. Bioinspired Late Stage Macroannulation via Trap Driven Methodology

Our marineosin seco precursor could be assembled in a manner analogous to our roseophilin preparation.[83] The intention was to utilize this modular approach to construct a variety of hybrid molecules upon establishment of a viable route to the marineosins. Here we report our efforts to

construct several seco precursors and the unsuccessful attempts at macroannulation through a variety of methodologies.

2.1.2. Modular Access to Ansa Linked Prodiginines – Proposed Variant for Marineosin Preparation

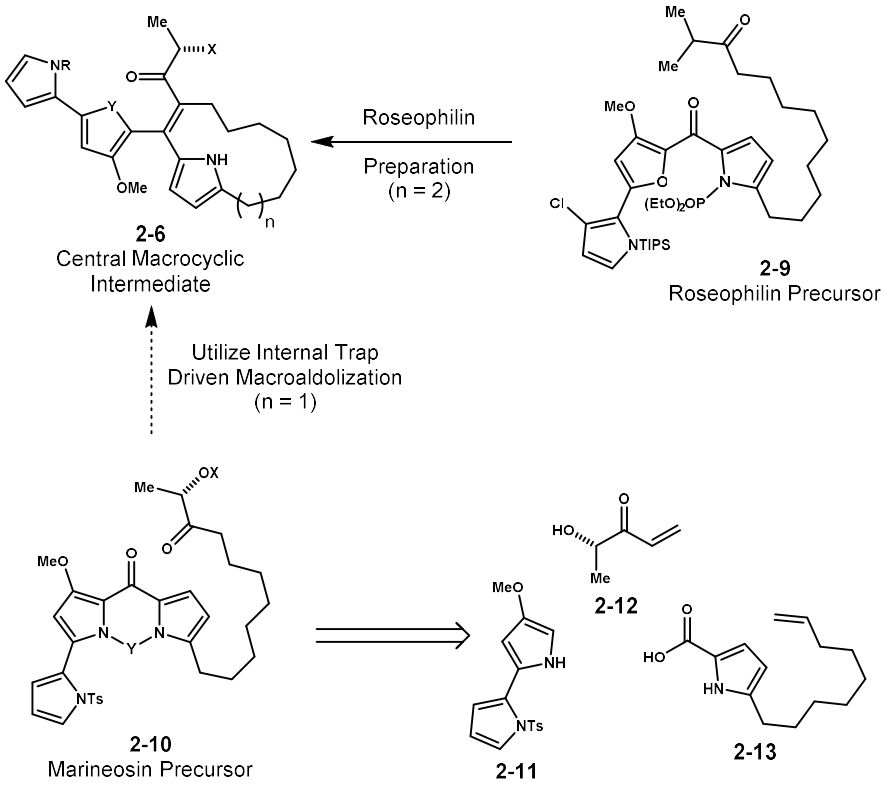


Figure 2.2. Late Stage Macroaldolization Methodology – retrosynthesis parallels roseophilin strategy

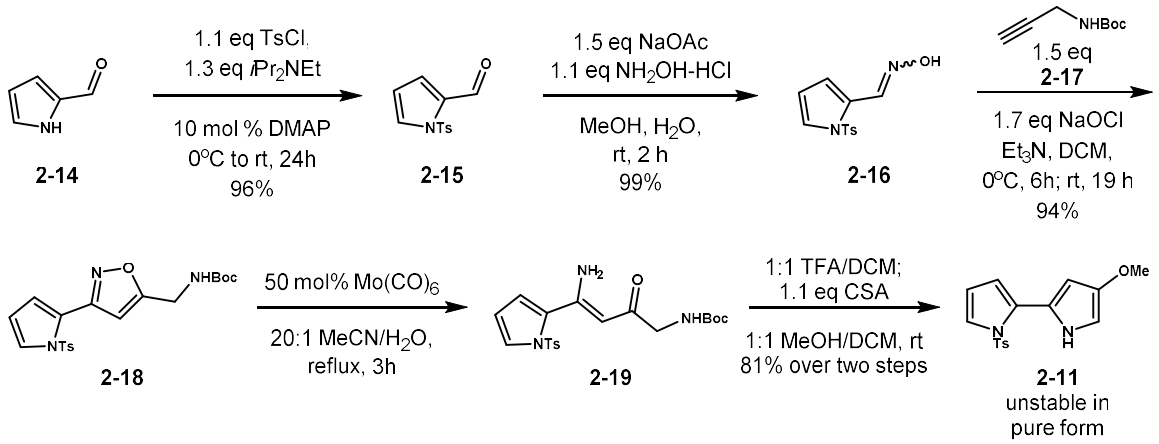
Initially, we targeted seco precursor **2-10** (**Figure 2.2**) and proposed a synthesis that was analogous to our previous efforts to construct roseophilin.[83] This would entail deconstruction seco precursor **2-10** into its constituent building blocks: bipyrrole **2-11**, lactic acid derivative **2-12**, and alkenyl pyrrole acid **2-13**. These materials could be easily combined over several steps to afford the desired seco precursor. Central to this design would be the determination of an efficient protecting/trap group necessary for the key macroaldolization step. The phosphoryl group in the roseophilin

system proved to be efficient in this regard.[109] However, there was concern as to whether this could be effectively translated into the marineosin approach.

A key difference between the marineosin and roseophilin seco precursor is the presence of a trispyrrolic system instead of a pyrrolofuran pyrrole core. The introduction of the third nitrogen brings with it an additional exchangeable proton that, presumably, would need to be protected in order for our aldolization methodology to work. A dual protecting/trap group (i.e. a group that could be attached to both pyrroles) was desired. A group of this nature would allow for several favorable properties to that could be utilized to our advantage. Firstly, a dual group would cyclize the system, which potentially allow for a more reactive conformation of the ketone. Secondly, a group of this nature would be more atom and step economical due it being incorporated in one step and serving as a protective functionality for two pyrroles. The phosphoryl group utilized in the roseophilin preparation contained two ethoxy ligands in addition to the pyrrole. We envisioned that one of these ethoxy groups could be replaced with the B ring pyrrole nitrogen. Therefore, we hypothesized that it might be possible to utilize the phosphoryl as a dual protecting group for the B and C ring pyrrole nitrogens, which would convey the modularity of our approach due to essentially the same protecting/trap group being utilized in the synthesis of either the marineosins or roseophilin.

2.2. Results and Discussion

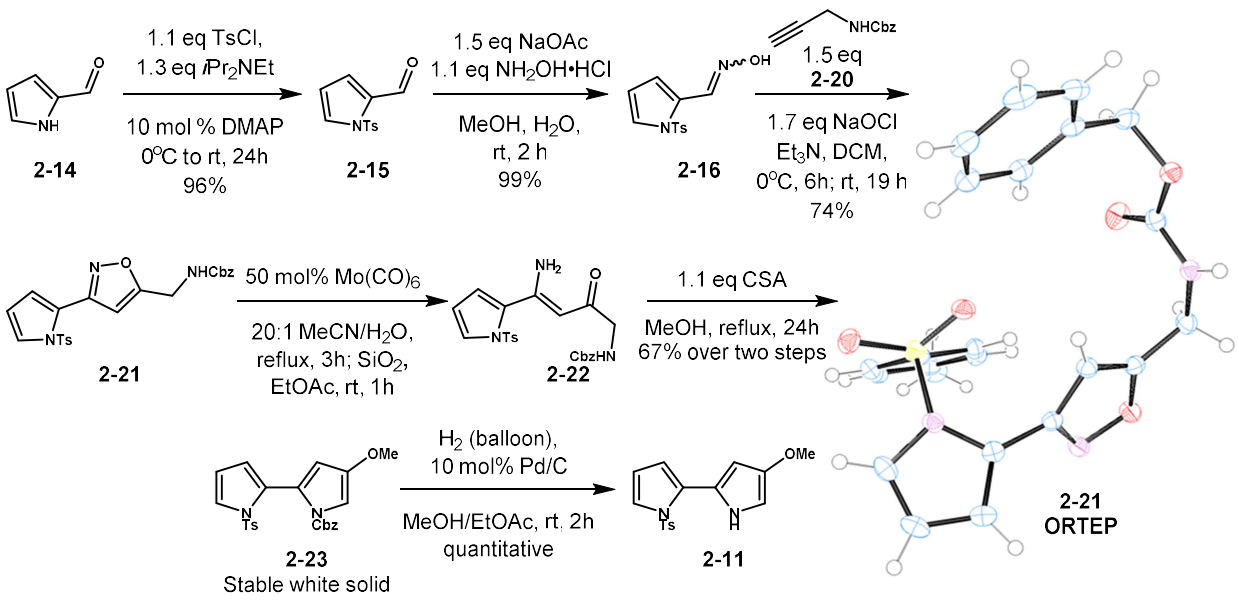
2.2.1. Synthesis of Bipyrrole Fragment



Scheme 2.1. Construction of Bipyrrole **2-11**

In conjunction with our studies on the pyrrolofuran segment of the roseophilin, our lab also examined construction of the bipyrrole fragment **2-11**.[82] Synthesis of the MBC fragment utilized for prodiginine synthesis has been investigated extensively and optimized into a two-step preparation from commercial materials (see section 3.2.1).[110] However, the decarbonylated variant (i.e. **2-11**) has received less attention.[111–113] Our bipyrrole construction mirrored that of the pyrrolofuran, which viewed the B ring methoxypyrrole as the enol ether of a cyclocondensation product of a derivatized β-diketone.[80,82] Isoxazole **2-18** served as a hidden β-diketone, which could be unveiled and cyclized.[82] Commercial pyrrole 2-carboxaldehyde **2-14** was derivatized as the tosyl protected variant **2-15**, followed by condensation with hydroxylamine under mildly acidic conditions to afford oxime **2-16**. The oxime was then dissolved in a DCM/H_2O mixture along with TEA and Boc-protected propargyl amine **2-17**, while aqueous bleach is added dropwise. Oxime **2-16** has poor solubility in DCM, which precludes attempting add this material slowly to the bleach solution. This reaction facilitates the oxidation of the oxime to the nitrile oxide, which undergoes a [3+2] dipolar cycloaddition with **2-17** to afford isoxazole **2-18**. The isoxazole could be partially

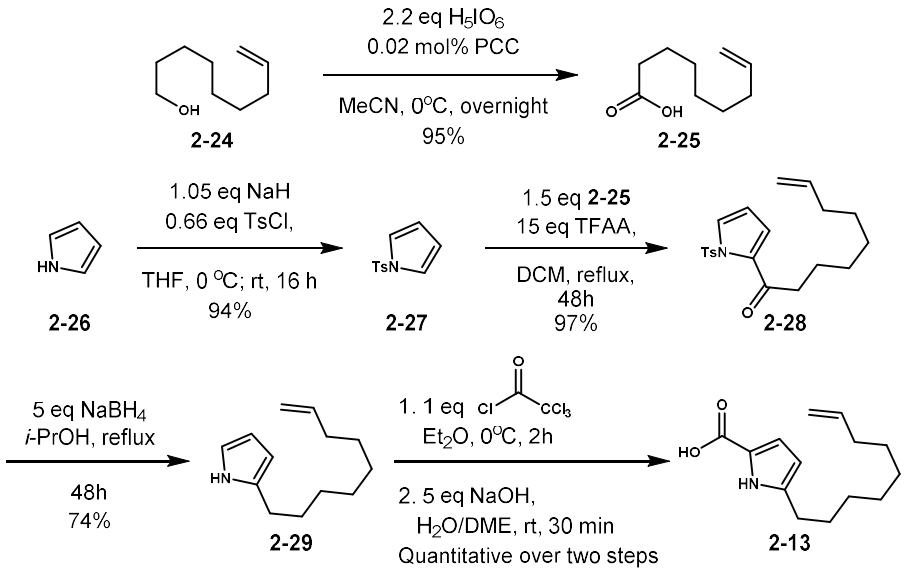
reduced using conditions developed by Nitta, which utilizes $Mo(CO)_6$ in wet acetonitrile.[114] The postulated mechanism involves coordination of the molybdenum by the isoxazole and generation of a molybdenum nitrene, which is hydrolyzed *in situ* to afford a β-aminoenone **2-19**. This material can then be cyclized by treatment with acid to provide **2-11**. The pendant amino group cyclocondenses with the β-diketone to afford a pyrrolinone intermediate, which then ketalizes with methanol followed by elimination of methanol to facilitate aromatization (not shown). Bipyrrole **2-11** is highly unstable and in its pure form progresses at room temperature from a white solid to a purple oily solid, which can be purified to recover a portion of **2-11**. We have been unable to characterize this purple material thoroughly. We hypothesize that the due to the electron rich nature of **2-11**, it readily oxidizes to form reactive species that oligomerize to polypyrrole materials. This property of **2-11** does not interfere with its use as long as it is maintained in dilute solution under inert atmosphere. In addition, the cyclocondensation step is highly variable in yield and difficult to reproduce on scale, which prevents the accumulation of large amounts of **2-11**.



Scheme 2.2. Alternate Access to Bipyrrole **2-23** via Doubly Protected **2-23**

A variant of the above mentioned route that utilizes Cbz-protected propargyl amine allows access to a protected form of bipyrrole, which can be stored for extended periods. The resultant isoxazole **2-21** can then be reduced under the above mentioned conditions to afford the β-aminoenone. This material was more resistant to the room temperature cyclocondensation conditions and required higher temperatures for the reaction to proceed at a reasonable rate. Heating for periods longer than 24 hours resulted in diminished product yields. The resultant doubly protected bipyrrole **2-23** was found to be stable for extended periods as long as it was maintained under an inert atmosphere in a -20 °C freezer. The Cbz group could be cleaved by a relatively facile hydrogenolysis with catalytic Pd/C under a balloon of hydrogen. A short silica plug allows for quantitative production of **2-11**. This alternate route circumvented the issues outlined with direct production of **2-11** and allowed us to produce the bipyrrole precursor **2-23** in decagram quantities that could be easily handled and stored.

2.2.2. Production of the Acyl Pyrrole Fragment



Scheme 2.3. Initial Synthesis of Acyl Pyrrole Fragment **2-13**

Our initial studies utilized the route developed for the roseophilin synthesis to produce the acyl pyrrole fragment.[83] This approach commenced with the oxidation of 8-nonen-1-ol (**2-24**) to acid **2-25** in parallel with the tosylation of pyrrole to provide **2-27**.[115] Utilizing methods developed by Knight and coworkers, tosyl pyrrole can then be acylated with the acid by generation of a mixed anhydride in TFAA to afford acyl pyrrole **2-28**.[116] The acyl pyrrole was then reduced to alkenyl pyrrole **2-29** using the aforementioned conditions developed by Muchowski.[79] **2-29** was then acylated under Friedel-Crafts conditions with trichloroacetyl chloride followed by hydrolysis of the intermediate trichloromethyl ketone to afford acid **2-13**.[117,118] This route was easily scaled to provide decagram quantities of **2-13**, however during the course of the project alcohol **2-24** became prohibitively expensive due to a large price increase. We felt compelled to develop an alternate route to **2-13**.

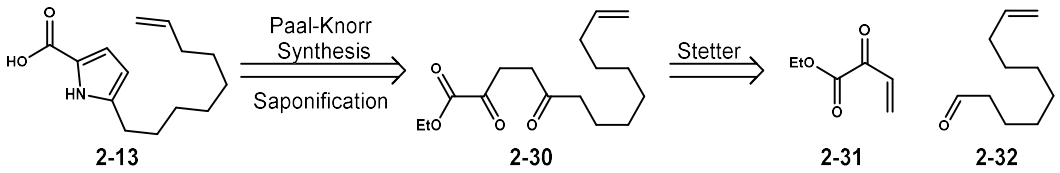


Figure 2.3. Alternative Approach to Pyrrole Acid **2-13**

It was noted that the one carbon homolog of **2-24** (i.e. 9-decen-1-ol, **2-33**) was 10-fold less expensive and we decided to utilize this material as our new starting point. A Paal-Knorr was envisioned to construct the pyrrole at the end of the route, which guided us to 1,4-diketone **2-30** as the synthetic precursor.[119–121] The most obvious disconnection from this material was a Stetter reaction to give Michael acceptor **2-31** and 9-decenal (**2-32**).[122,123]

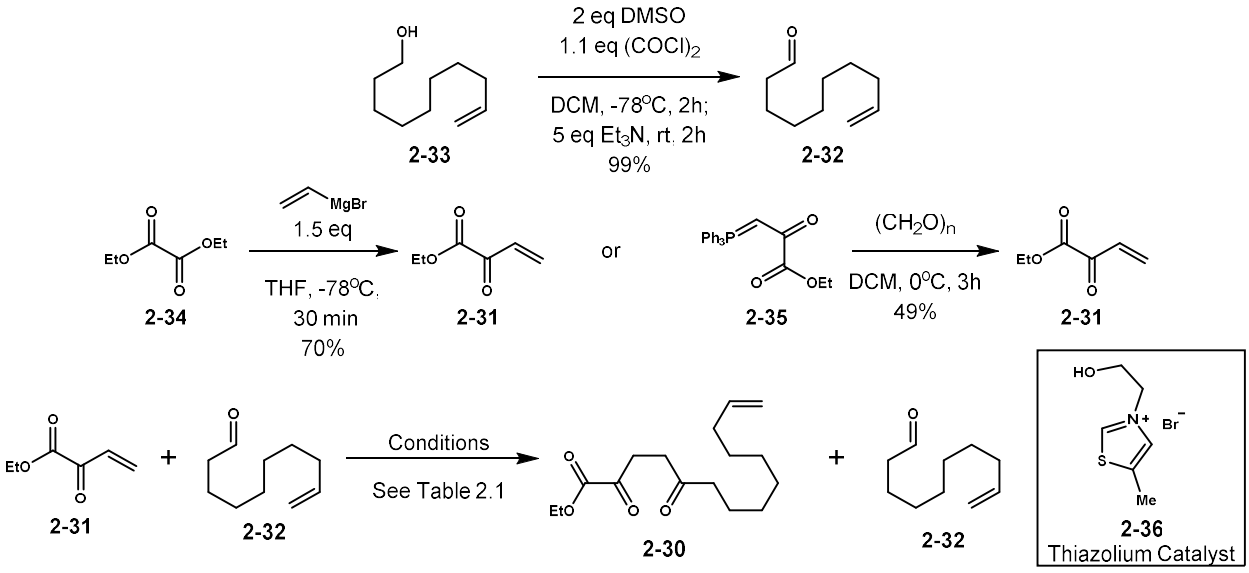


Figure 2.4. Attempts to Access 1,4-diketone **2-30** via a Stetter Reaction

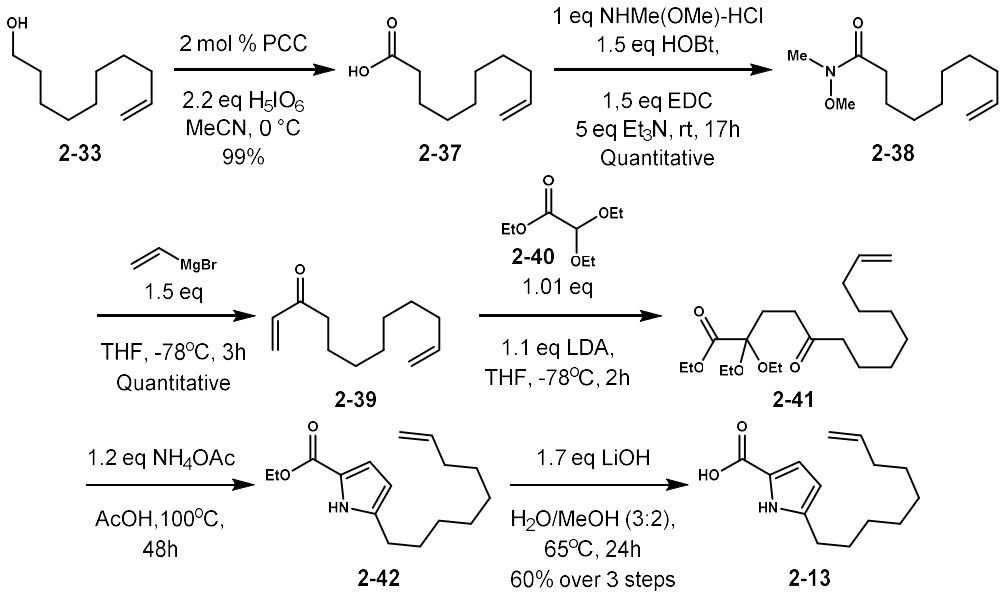
Table 2.1. Screen of Conditions to Generate **2-30** via Stetter Methodology

Entry	Catalyst	Loading	Additive	Temp.	Solvent	Time	Yield of 2-30	Recovered 2-32
1	NaCN	10 mol%	-	35 °C	DMF	1 h	0	0
2	NaCN	13 mol%	-	35 °C	DMF	30 min	0	55
3	**2-36**	10 mol%	20 mol% Et_3N	85 °C	Dioxane	1h	0	57

4	**2-36**	10 mol%	20 mol% Et_3N	Reflux	Dioxane	20 h	0	0
5	**2-36**	10 mol%	20 mol% Et_3N	0 °C	Dioxane	24 h	0	0
6	**2-36**	10 mol%	20 mol% Et_3N	0 °C	DCM	16 h	0	0

Alcohol **2-33** was converted to aldehyde **2-32** via a simple Swern oxidation.[124–126] The Michael acceptor **2-31** proved more difficult to generate and handle, which was accessed via vinyl Grignard addition to diethyl oxalate **2-34**.[127] Initial attempts to isolate and distill **2-31** resulted in the generation of a thick brown oil indicative of lability and a tendency to polymerize. These issues could be circumvented by a careful quench and partial concentration of the crude organic layer to afford **2-31** as a solution in THF that could be stored for several days under Ar at – 20 °C. In addition, polymerization could be further minimized by the addition of trace amounts of galvinoxyl free radical. These methods provided sufficient amounts of material to investigate the generation of 1,4-diketone **2-30**. Alternatively, **2-31** could be generated using the method of Jacobi and coworkers, which utilizes phosphorane **2-35** in a Wittig olefination achieved by bubbling gaseous formaldehyde through the reaction mixture.[128] This procedure provides **2-31** in similar purity to the previously mentioned method.

Several conditions for the generation of **2-30** were examined, which are summarized in **Table 2.1**. Ultimately, these investigations resulted in occasional recovery of starting aldehyde **2-32** and an intractable baseline material, which derives most likely from the polymerization of **2-31**. It became clear after these studies that **2-31** was too unstable under the Stetter conditions to allow the desired process to compete with polymerization. This setback led to the abandonment of this strategy for the preparation of **2-13**.



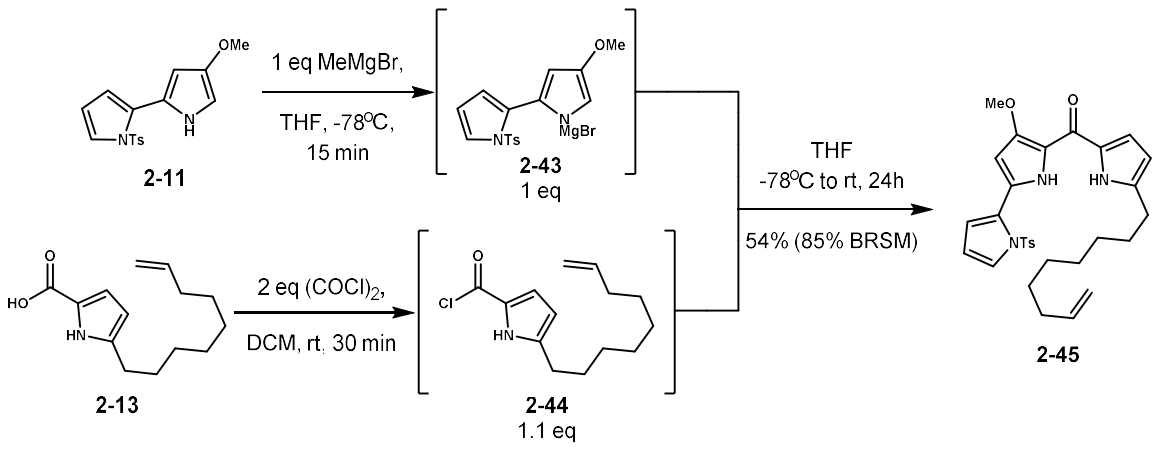
Scheme 2.4. Optimized Scalable and Cost Effective Route to **2-13**

With the Stetter approach proving unusable, an alternative approach was envisioned that would reverse the previously outlined reactivity. Namely, a masked form of ethyl glyoxalate **2-40** could be utilized in a Michael addition to enone **2-39** to access the Paal-Knorr substrate. Alcohol **2-33** was oxidized to acid **2-37** using Hunsen's conditions.[115] This material was then converted to the Weinreb amide followed by treatment with vinyl Grignard at low temperature.[129–131] Cryogenic temperatures proved necessary for this transformation, attempts at 0 °C or -20 °C resulted in the generation of significant amounts of a β-aminoketone impurity (Not shown). At these temperatures, tetrahedral magnesium chelate appears to be unstable for this system, which results in the release of enone **2-39** and the magnesium salt of N,O-dimethylhydroxylamine. These two species then react in a Michael addition to form the β-amino ketone side product. However, at -78 °C this impurity is not observed. Deprotonation of diethoxyethyl acetate (**2-40**) with LDA at low temperature followed by treatment with enone **2-39** provides Paal-Knorr precursor **2-41** via a Michael addition. This material could then be subjected to a Paal-Knorr pyrrole synthesis by treatment with ammonium acetate in refluxing acetic acid.[119–121,132] A final saponification with

lithium hydroxide affords pyrrole acid **2-13** in ~60% for the 6 step process. This route proved to be efficient and scalable providing decagram quantities of **2-13**. In addition, the only purification required for the entire sequence is a short silica plug after the saponification step. With adequate quantities of **2-23** and **2-13** in hand, we were eager to combine these fragments and explore macroannulation conditions.

2.2.3. Acylation of Bipyrrole 2-11 with Acid 2-13 and Incorporation of Protecting/Trap Groups

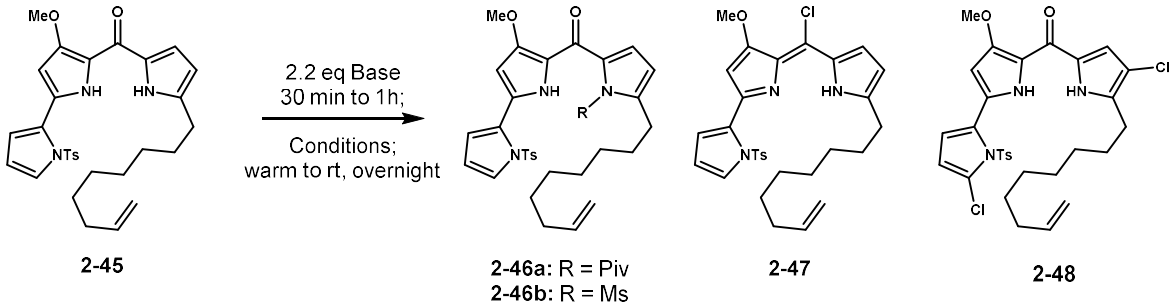
Although a variety of methods exist for the regioselective acylation of pyrroles, we chose to begin with the method developed by Katrizky and coworkers that facilitated our construction of roseophilin.[84,116,133,134] This method involved converting **2-13** into the activated benzotriazole ester followed by treatment with $TiCl_4$ in the presence of the pyrrole. Earlier work in our group determined that this method was not optimal for the production of the marineosin system. This method required the use of excess bipyrrole **2-11**, which could not be recovered from the reaction. A viable alternative method based on the works of Bean and coworkers was developed that capitalized on the inherent nucleophilic activity of bipyrrole **2-11**.[135]



Scheme 2.5. Acylation of Bipyrrole **2-11** to Generate Biarylketone **2-45**

Acid **2-13** was converted to the highly unstable acyl chloride **2-44**, which has a tendency to convert to a black polymeric solid if it is allowed to stand for over an hour. While acyl chloride **2-44** is being generated, bipyrrole is deprotonated by treatment with methylmagnesium bromide to produce the bipyrrolyl magnesium salt at low temperature. Magnesium salt **2-43** is then treated at -78 °C with acyl chloride **2-44** and the mixture is allowed to slowly reach room temperature. This process generates biarylketone **2-45** that is analogous to that generated in our synthesis of roseophilin. This results of this process are variable due to both species being unstable, which requires careful handling of the material when transferring between flasks. The process could reliably generate **2-45** with an average yield of ~45%. At this juncture, we opted to install the

protecting/trap group that would be necessary for our desired aldolization methodology. The results of these investigations are summarized in **Table 2.2**.



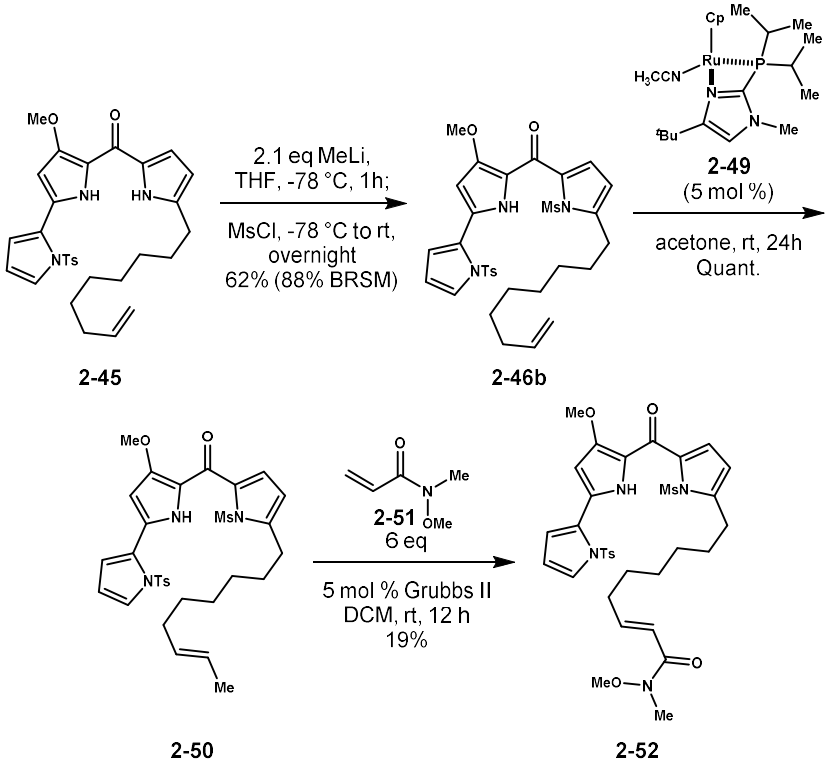
Scheme 2.6. Attempts to Install a Protecting/Trap Group

Table 2.2. Conditions Explored to Install a Protecting/Trap Group

Entry	Base	Reagent	Additive	Temp.	Solvent	Recovered **2-46**	Combined Yield (%)	Ratio (46:47:48)
1	KH	$ClP(OEt)_2$	18-C-6 (4.4eq)	0 °C	THF	75%	0	-
2	KH	$ClP(OEt)_2$	-	0 °C	THF	54%	0	-
3	NaH	PivCl	-	rt	THF	0%	35%	1:0:0
4	NaH	$(COCl)_2$	-	0 °C	THF	32%	11%	0:1:0
5	NaH	TFAA	-	0 °C	THF	98%	0	-
6	NaH	$SOCl_2$	-	0 °C	THF	0	0	-
7	NaH	CDI	Et_3N (2.4 eq)	0 °C	THF	Quant	0	-
8	NaH	$(COCl)_2$	Et_3N (2.4 eq)	0 °C	THF	0	0	-
9	NaH	MsCl	-	-78 °C	THF	56%	23%	0:1:0
10	MeLi	$ClP(OEt)_2$	-	-78 °C	THF	76%	0	-
11	MeLi	MsCl	-	-78 °C	THF	26%	62%	1:0:0
12	MeLi	Ms_2O	-	-78 °C	THF	30%	49%	1:0:0
13	MeLi	$(COCl)_2$	-	-78 °C	THF	0	0	-
14	MeLi	Cl_2POEt	-	-78 °C	THF	11%	0	-
15	MeLi	SO_2Cl_2	-	-78 °C	THF	0	41%	0:0:1
16	MeLi	$ClCH_2SO_2Cl$	-	-78 °C	THF	0	0	-

Considerable effort was made to establish conditions for the efficient installation of the trap group. In all experiments, deprotonation occurred under standard conditions of addition of ketone **2-45** to a solution of base and deprotonation time was maintained between 30 min and 1 hr. Both mono- and bifunctional electrophiles were explored as potential protecting/trap groups. Unfortunately, this system proved to be much more difficult to functionalize than the roseophilin system. Many conditions (Entries 6, 8, 13, 16) resulted in intractable mixtures, which didn't seem to contain any of the desired protected material. The phosphoryl group (Entries 1, 2, 10) that proved so useful for the roseophilin synthesis failed to react with the new system leaving only starting material upon workup. Attempts to incorporate a phosphoryl group that would protect both pyrroles (Entry 14) only provided low recovery of starting ketone. An intriguing albeit ineffectual result was the double chlorination of the heteroaromatic system when the deprotonated form was treated with sulfuryl chloride (Entry 15). Several promising results included the incorporation of pivalate (**2-46a**) and mesylate (**2-46b**) groups into the molecule on the C ring pyrrole (Entries 4, 9, 11, 12). Unfortunately, attempts to resubject the mono-protected material to the reaction resulted only partial recovery of starting material (Not shown). In addition, the mono-mesylated material required laborious chromatography to separate from residual **2-45** due to similar polarity profiles on TLC. In light of these issues, we chose to further explore the mono-mesylated material to see if our desired macroaldolization process could be still be achieved, however we were apprehensive

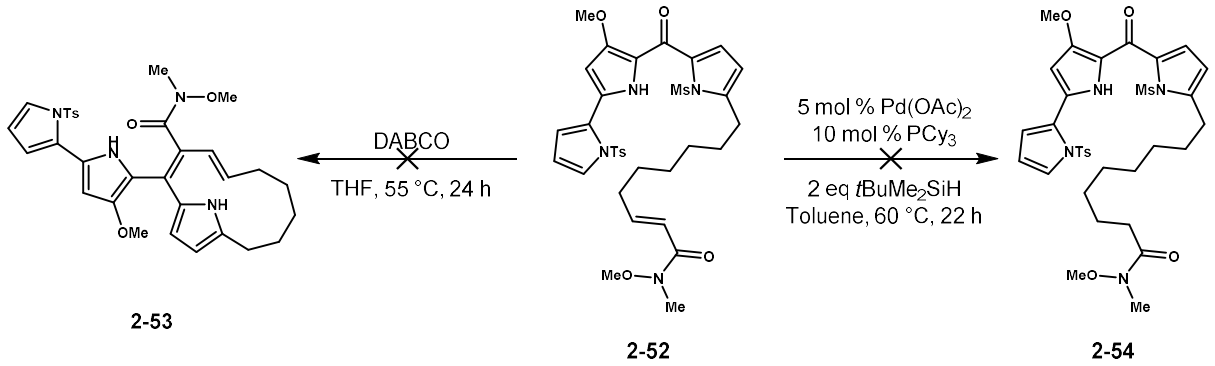
due to the potential complications that could be caused by the presence of the exchangeable proton on the B ring pyrrole.



Scheme 2.7. Elaboration of Biaryl Ketone **2-45** to Macroaldolization Precursor **2-52**

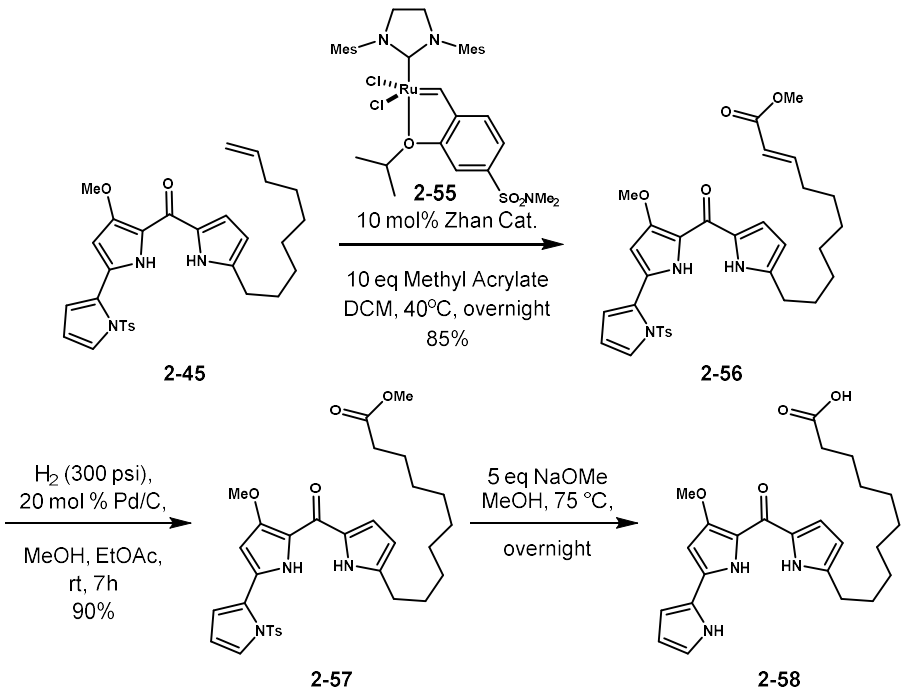
The biaryl ketone **2-45** was mono-mesylated with the optimized conditions to provide **2-46b**. The marineosin ansa bridge system is one carbon truncated as compared to roseophilin. Therefore, in order to utilize similar chemistry for the macrocyclization, the alkenyl chain on the C ring of **2-46b** would need to be shortened via one carbon. It was envisioned that this could be accomplished using contemporary transition metal catalysis. Olefin isomerization is a powerful methodology that has been utilized in a variety of contexts, however a major setback of this field is achieving high positional selectivity.[136–140] However, Grotjahn and coworkers have recently developed an efficient alkene "zipper" catalyst (**2-49**), which depending on the reaction conditions can isomerize an α-olefin stereoselectivity over one position.[138,141] This air sensitive catalyst proved to be

resilient to the functionality present in **2-46b** and provided the isomerized product **2-50** in quantitative yield. This material was then subjected to a cross metathesis with acrylamide **2-51** to afford **2-52** in an unoptimized low yield.[142] We chose acrylamide **2-51** as a partner instead of **2-12** for initial investigations in order to simplify the regiochemistry of deprotonation.



Scheme 2.8. Failed Attempts to Reduce or Cyclize **2-52**

Initially we examined whether acrylamide **2-52** could be reduced using the conditions utilized in the roseophilin synthesis (**Scheme 2.8**).[83,143] The palladium catalyzed hydrosilylation of acrylamide **2-52** proved unsuccessful providing only starting **2-52** on workup. This was the only condition examined for the reduction of **2-52**. Alternatively, we briefly attempted to utilize the acrylamide to our advantage by exploring Morita-Baylis-Hillman methodology.[144,145] Extended heating with DABCO failed to produce any ansa bridged material. Similar to the hydrosilylation reaction, only starting material was recovered from this reaction. In an attempt to gather more information on the system without progressing through the full sequence outlined above, we examined the possibility of annulation with no protecting/trap group.



Scheme 2.9. Examination of Macroaldolization without a Trap Group

To explore the possibility of macroaldolization without a trap group, we decided to examine the one carbon homologated system for ease of preparation. Biaryl ketone **2-45** was subjected to a cross metathesis with the Zhan catalyst 1B and methyl acrylate to afford **2-56**.[146] The acrylate was hydrogenated in a high pressure autoclave to afford ester **2-57**. When this material was treated with anhydrous NaOMe in methanol for several hours at room temperature, the major product that could be observed by HPLC corresponded to the de-tosylated material. The temperature was then increased to reflux and the system was allowed to stir overnight. The reaction which was initially a yellow had turned dark green and HPLC analysis of the reaction indicated the presence of a new compound with a mass of 425 m/z. Unfortunately, this material proved to be saponified product **2-58**. We postulate that this material derives from a leak between the joints of the reflux condenser and the flask, which allowed moisture into the flask.

Admittedly, the inability to efficiently install an effective protecting/trap group was disheartening and hampered further investigations into the macroaldolization. This synthetic approach was not explored thoroughly due to more interest in an alternate approach that wouldn't require the installation of a trap group (*vide infra*).

2.2.4. Exploration of a Heck-Mediated Macrocyclization

With the aldolization chemistry proving ineffective, we explored potential methods of constructing the ansa bridge without the use of a trap group. We established during our protecting group studies that the ketone could be adequately converted into the chlorinated azafulvene **2-47**, which could be utilized as a handle for transition metal catalyzed annulations. In addition, the α-olefin present on the aliphatic chain provided the other component necessary for these types of processes. It was envisioned that the Heck reaction could be a viable means of producing the macrocycle. The Heck-mediated macrocyclization has been utilized in a variety of ways to construct large ring systems. Early work by Ziegler and coworkers established that intramolecular Heck processes were a viable method of constructing macrocyclic rings, which was further supported by the works of Menche in the construction of etnangien and rhizopodin.[147–150] Furthermore, Speicher demonstrated the efficient access to ansa bridged macrocycles via Heck methodology.[151] This precedent in the construction of macrocycles by Pd-catalyzed macroannulation gave us confidence that this could be a feasible approach to the strained pyrrolophane of the marineosin core.

It was postulated that ketone **2-45** could be converted into seco precursor **2-59**, which would contain either allylic alcohol or enone functionalities (**Figure 2.5**). Macrocyclization of the allylic alcohol could theoretically generate the C21 stereocenter in an enantioselective manner if β-hydride elimination could be biased towards the alcohol to generate enol **2-60**, which would

tautomerize to ketone **2-61**. The redox-relay strategy for enantioselective Heck arylations developed by Sigman and coworkers seemed to be a viable method of achieving this result.[152] Alternatively if the enone system is utilized in the annulation, strained conjugated enone **2-62** would be generated. We postulated that if this material could be generated, it would undergo a facile 6π-electrocyclization to relieve the steric interaction between the B ring methoxy group and the ketone. This process would generate marineosin core in one operation and controlled reductions of **2-63** could be investigated to access the premarineosins and the marineosins **2-8a/b**.

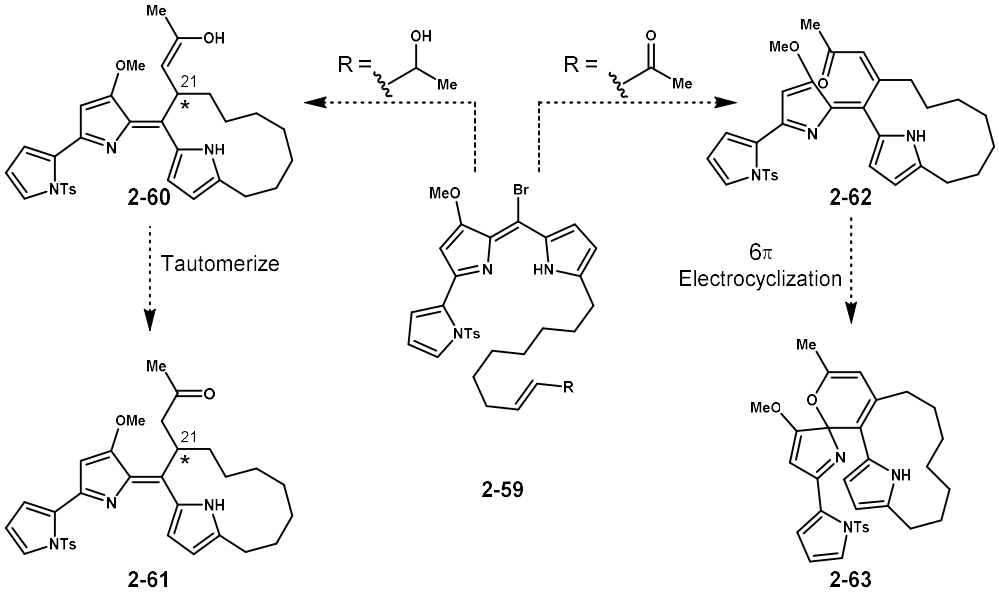
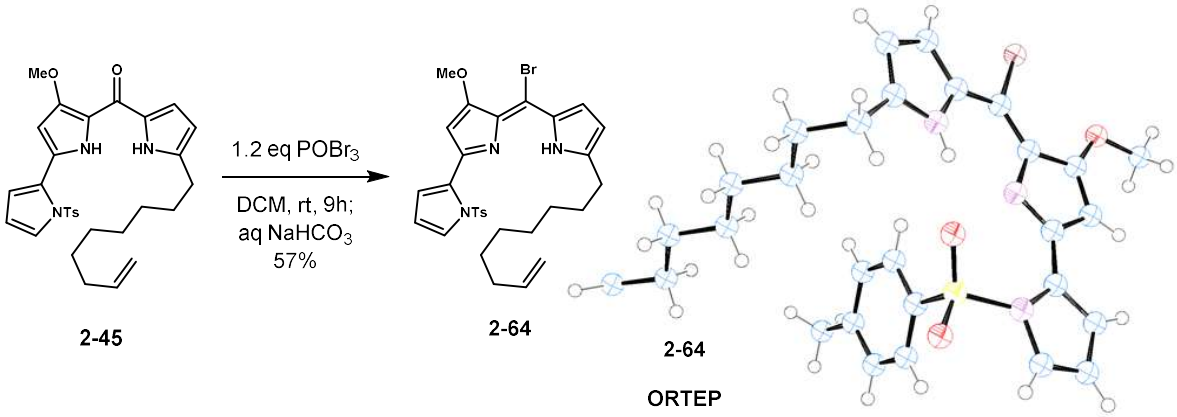


Figure 2.5. Projected Access to Pyrrolophanes via a Heck-Mediated Annulation

It was determined that ketone **2-45** could be converted to either aryl chloride **2-47** or aryl bromide **2-64** treatment with the corresponding phosphorous oxyhalide in DCM (**Scheme 2.10**). This process proved to be considerably capricious. Yields were variable and highly dependent on the purity of the phosphorous oxybromide, with freshly sublimed reagent providing consistently higher yields. In addition if not handled carefully, **2-64** could easily hydrolyze back to **2-45**. However after developing an efficient workup and purification procedure, the production of **2-64** became routine. An X-ray structure of **2-64** clearly displays the prodiginine core adopts a cis

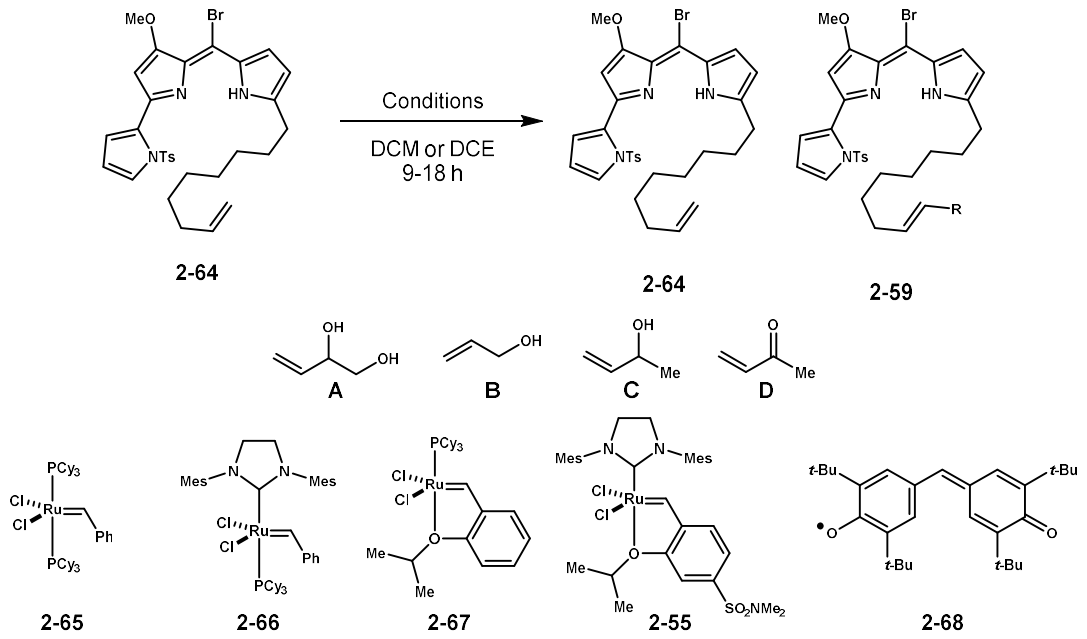
conformation (i.e. the azafulvene nitrogen and the C ring N-H are facing each other). The olefin at the end of the aliphatic chain could not be observed due to uncertainties in the crystal structure.



Scheme 2.10. Conversion of Ketone **2-46** to Aryl Bromide **2-64**

With an established method to produce **2-64**, our next objective was to establish an efficient cross metathesis method to append the desired functionalities to the α-olefin. We initially explored diol **A** as a cross metathesis partner with the hope that the diol would further bias the β-hydride elimination towards the alcohol due to a chelation effect (Entries 1-4). Unfortunately, all attempts to merge this partner with **2-64** resulted in either recovery of starting material or hydrolysis back to **2-45**. Most likely the hydroscopic nature of **A**, which was not stored over molecular sieves, introduced water into the reaction and the extended periods of heating provided sufficient energy for the hydrolysis to occur. The yields of these reactions were not determined. The electron rich nature of **2-64** was a concern and it was postulated that this moiety might easily oxidize in the presence of oxygen. In order to circumvent this potential issue, galvinoxyl radical was explored as an inhibitor of radical generation by oxidative degradation of **2-64** (Entries 5 and 6). However, this additive did not seem to have an effect on the reaction. In addition to the electron rich nature of the brominated prodiginine core, the azafulvene nitrogen was a concern due to its Lewis basicity,

which could disrupt the catalytic cycle by forming a stable complex with the ruthenium catalyst. There are several commonly used Lewis acid additives that compete more efficiently for complexation.[153,154] The addition of $Ti(O\textit{i}Pr)_4$ to the reaction allowed for the clean cross metathesis of **2-64** with partner **B** in high yield (Entry 7). Alternatively, the use of a more stable catalyst allowed for cross metathesis to occur without the need for an additive (Entry 8). These optimized conditions allowed for the routine access to various versions of **2-59**.



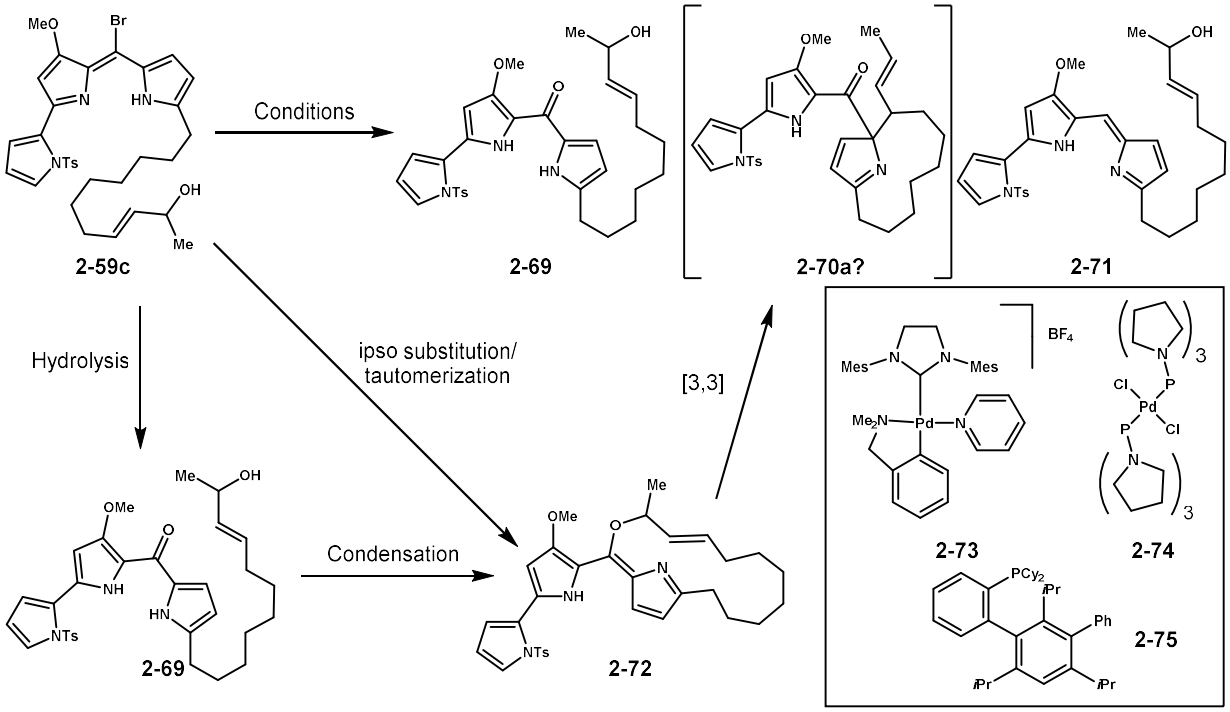
Scheme 2.11. Examination of Cross Metathesis Partners and Catalysts to Generate **2-59**

Table 2.3. Optimization of Cross Metathesis Conditions

Entry	Catalyst (10 mol %)	Partner	Temp.	Additive	Recovered **2-64**	Yield
1	2-66	A	35 °C	-	100%	0%
2	2-66	A	75 °C	-	0%	ND
3	2-65	A	75 °C	-	0%	ND
4	2-55	A	35 °C	-	85%	0%
5	2-66	B	35 °C	0.5 mol % **2-68**	51%	0%
6	2-67	B	35 °C	0.5 mol % **2-68**	20%	0%
7	2-66	B	35 °C	30 mol % Ti(O*i*Pr)$_4$	0%	82%
8	2-55	C	35 °C	-	22%	67%
9	2-66	D	35 °C	-	43%	57%
10	2-66	D	35 °C	30 mol % Ti(O*i*Pr)$_4$	0%	47%

With the cross metathesis issue resolved, we examined our desired Heck-mediated macrocyclization, which are summarized in **Table 2.4** and **Scheme 2.12**. There are no examples

of prodiginine derived aryl halides being utilized in Heck or cross coupling processes in the literature. However, there are several cases of BODIPY and porphyrin frameworks being constructed in the literature, which are further functionalized by Heck or cross coupling processes.[155,156] Our studies commenced with examination of Fu's conditions with P(*t*Bu)$_3$ as a ligand due to its ability to engage electron rich aryl halides in Heck and cross coupling reactions (Entries 1, 2, 9–12, 15).[157,158]



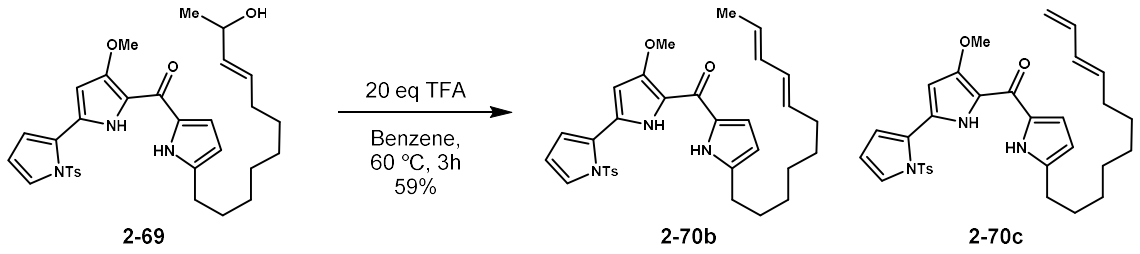
Scheme 2.12. Examination of Heck Macroannulation with Alcohol **2-59c** and Mechanistic Hypothesis for Generation of Ansa Linked **2-70**

Table 2.4. Screen of Conditions for Heck-Mediated Macrocyclization

Entry	Catalyst	Ligand	Base	Additive	Solvent/ Temp/Time	**2-59c**	Comb. Yield	Ratio 69:70:71
1	Pd_2DBA_3 (5 mol %)	$[HP(tBu_3)_3]BF_4$ (20 mol %)	Cy_2NMe (3 eq)	AgOAc (1 eq)	Dioxane 65 °C, 18h	Quant.	-	-
2	Pd_2DBA_3 (5 mol %)	$[HP(tBu_3)_3]BF_4$ (25 mol %)	Cy_2NMe (3 eq)	-	Dioxane 85 °C, 24 h	56%	20%	1:0:0

3	Pd_2DBA_3 (5 mol %)	Dppe (20 mol %)	iPr_2NEt	-	MeCN 85 °C, 18 h	0%	0%	0%
4	Pd_2DBA_3 (5 mol %)	Dppe (20 mol %)	iPr_2NEt	NaI (2 eq)	MeCN 85 °C, 18h	0%	0%	0%
5	**2-73** (5 mol %)	-	K_2CO_3 (2.5 eq)	-	Dioxane 85 °C, 16h	Quant.	-	-
6	**2-73** (5 mol)	-	K_2CO_3 (1.2 eq)	-	Dioxane 100 °C, 19 h	62%	18%	0:1:0
7	**2-74** (2 mol %)	-	K_2CO_3 (2 eq)	Bu_4NBr (0.45 eq)	DMF 100 °C, 16 h	0%	8.5%	0:1:0
8	**2-74** (2 mol %)	-	K_2CO_3 (2 eq)	Bu_4NBr (0.45 eq)	DMF 70 °C, 16 h	0%	58%	2:1:0
9	Pd_2DBA_2/ $Pd[P(tBu)_3]_2$ (5 mol % each)	-	Cy_2NMe (3 eq)	-	Dioxane 85 °C, 34 h	75%	25%	1:0:0
10	$Pd[P(tBu)_3]_2$ (10 mol %)	-	Cy_2NMe (3 eq)	Ag_2CO_3 (0.5 eq)	Dioxane 85 °C, 12 h	0%	88%	3:5:2
11	$Pd[P(tBu)_3]_2$ (10 mol %)	-	Cy_2NMe (3 eq)	**2-68** (2 mol %)	Dioxane 85 °C, 12 h	8.5%	51%	2.5:2:1
12	$Pd[P(tBu)_3]_2$ (10 mol %)	-	Cy_2NMe (3 eq)	$Ti(OiPr)_4$ (3 mol %)	Dioxane 85 °C, 12 h	10%	47%	3:1:3
13	$Pd(OAc)_2$ (10 mol %)	**2-75** (20 mol %)	$NaHCO_3$ (2.5 eq)	-	DMF 100 °C, 19 h	ND	-	-
14	$Pd(OAc)_2$ (10 mol %)	**2-75** (20 mol %)	Cy_2NMe (2.4 eq)	-	Dioxane 100 °C, 17 h	0%	9%	0:2:1
15	Pd_2DBA_3 (10 mol %)	$[HP(tBu)_3]BF_4$ (24 mol %)	Cy_2NMe (3 eq)	**2-68** (3 mol %) $Ti(iOPr)_4$ (0.5 eq)	Dioxane 85 °C, 19 h	0%	5%	0:1:0

However, the desired pyrrolophane **2-61** was never observed. Instead, the hydrolysis of **2-59c**, which regenerates the ketone at C9 to give a net cross metathesis product of ketone **2-46** with partner **C**, was consistently isolated. It is unclear whether **2-69** was produced during the course of the reaction or if it arises during the workup of the reaction. Several conditions provided small amounts of reduction product **2-71**, which indicated that oxidative addition was occurring but the olefinic partner was not engaging the palladium species in a productive manner. In addition to **2-69**, a nonpolar mixture of diastereomers was isolated, which were originally thought to be indicative of an interesting new type of ansa linkage (Entries 6, 7, 8, 10, 11, 12, 14, 15). It was postulated that this structure arose from addition of the allylic alcohol to the azafulvene followed by rearomatization via loss of HBr. This intermediate material could interconvert between two tautomeric forms by exchange of the pyrrole proton between the B and C rings (only **2-72** is shown). Intermediate **2-72** could then undergo a Claisen rearrangement to produce the ansa bridge. However upon more rigorous investigation, it was found that simple acid mediated dehydration of **2-69** provided an inseparable mixture of olefin regioisomers **2-70b/c** that corresponded to the data originally assigned for **2-70a** (**Scheme 2.13**). When considering the conditions of the desired macrocyclic Heck reaction, it is believed that **2-70b/c** arise from intermediate **2-72**, where the high temperature and excess base facilitate elimination of the proposed macrocyclic ether. This process would be driven by the release of ring strain, as well as the generation of the carbonyl moiety.

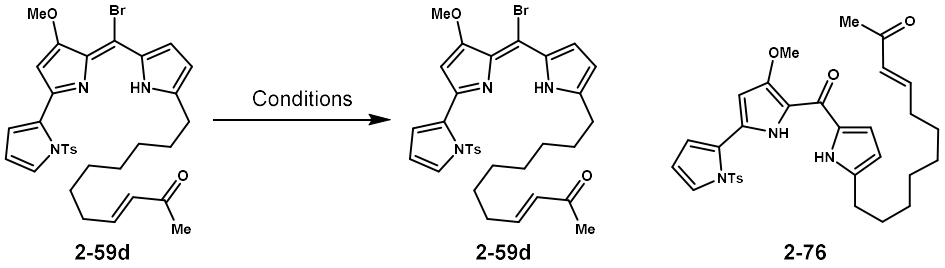


2-69 **2-70b** **2-70c**

Scheme 2.13. Acid Mediated Dehydration of **2-69**

Alternatively, the ligand Cy*Phine, developed by Johannes and coworkers, was also examined, due to its ability to facilitate Mizoroki-Heck reactions with electron rich heteroaryl bromides (Entries 13 and 14).[159] However, these conditions also proved inadequate for the production of **2-61**. The side products isolated suggested that the catalyst may be unstable to the reaction conditions, since there was very little indication of oxidative addition occurring. Cationic Palladacycle **2-73** was investigated in order to alleviate this perceived instability, as well as examine a more active catalytic system (Entries 5–8).[160] Unfortunately, this system provided similar results to the other conditions attempted.

At this stage, we decided to explore cyclization conditions on **2-59d**, which are summarized in **Scheme 2.14** and **Table 2.5**. Unfortunately, the issues observed with allylic alcohol **2-59c** were also present in enone **2-59d**. In many cases, starting material was recovered with the hydrolysis product **2-76** being the only other tractable and isolable product. These setbacks were disheartening and caused us to reexamine our strategy.



Scheme 2.14. Exploration of Proposed Heck Annulation/6π Electrocyclization

Table 2.5. Screened Conditions for Heck/6π Process

Entry	Catalyst	Ligand	Base	Additive	Solvent Temp/Time	Rec. **2-59d**	% **2-76**
1	$Pd[P(tBu)_3]_2$ (10 mol %)	-	*i*PrNEt (3 eq)	Ag_2CO_3 (1 eq)	MeCN 85 °C, 18 h	0%	0%

2	$Pd[P(tBu)_3]_2$ (10 mol %)	-	Cy_2NMe (3 eq)	Ag_2CO_3 (0.5 eq)	Dioxane 85 °C, 12 h	15%	19%
3	**2-73** (15 mol %)	-	Cy_2NMe (2 eq)	-	Dioxane 100 °C, 50 h	3.5%	
4	$Pd(OAc)_2$ (15 mol %)	**2-75** (30 mol %)	Cy_2NMe (2.5 eq)	-	Dioxane 100 °C, 42 h	ND	ND
5	$Pd(OAc)_2$ (20 mol %)	$[HP(tBu)_3]BF_4$ (25 mol %)	Cy_2NMe (5 eq)	AgOTf (1 eq)	Dioxane 85 °C, 13 h	0%	0%
6	Pd_2DBA_3 (5 mol %)	$[HP(tBu)_3]BF_4$ (20 mol %)	Cy_2NMe (3 eq)	$Ti(OiPr)_4$ (30 mol %) **2-68** (1 mol %)	Dioxane 85 °C, 24 h	0%	Major (ND)
7	$PdCl_2(PPh_3)_2$ (10 mol %)	X-Phos (20 mol %) $[HP(tBu)_3]BF_4$ (40 mol %)	Na_2CO_3 (3 eq)	-	DMSO 90 °C, 15 h	0%	43%
8	$PdCl_2(PPh_3)_2$ (10 mol %)	X-Phos (20 mol %) $[HP(tBu)_3]BF_4$ (40 mol %)	*i*PrNEt (3 eq)	-	DMSO 90 °C, 16 h	0%	0%
9	$PdCl_2(PPh_3)_2$ (10 mol %)	X-Phos (20 mol %) $[HP(tBu)_3]BF_4$ (40 mol %)	*i*PrNEt (3 eq)	Ag_2CO_3 (1.5 eq)	DMSO 90 °C, 16 h	0%	0%
10	$PdCl_2(PPh_3)_2$ (10 mol %)	X-Phos (20 mol %) $[HP(tBu)_3]BF_4$ (40 mol %)	*i*PrNEt (3 eq)	-	DMF 90 °C, 16 h	ND	ND

2.2.5. Examination of the Hiyama-Denmark Coupling to Access Synthetic Precursors to the Marineosins

Our inability to construct a pyrrolophane via the Heck annulation was frustrating. It was clear that oxidative addition to C-Br bond of **2-59** was occurring, due to isolation of the reduced product **2-71**. However, it appeared that the olefin partner was not engaging the intermediate Pd^{II} species. It was postulated that if a more active coupling partner was utilized that this lack of reactivity could be overcome. It was determined that if the olefin was functionalized with one of the metalloid

groups utilized in the various types of cross coupling methodologies perhaps the process would be competent enough to construct the ansa bridge.[161] The Hiyama coupling methodology emerged as an attractive approach to constructing the ansa-linkage.[162–166] The C-Si bond is fairly robust and would allow for ease of handling intermediates up to the intramolecular coupling. In addition, the recent advances in the hydrosilylation of alkynes would allow for rapid construction and incorporation into the seco precursor.[167] We planned to construct a truncated variant of **2-64** (i.e. **2-77**), which could be combined via cross metathesis with vinyl oxasilole **2-78** to provide the seco precursor **2-79** (**Figure 2.6**). The ansa bridge would then be constructed with the intramolecular Hiyama coupling to produce **2-80**. This material could then be converted to hexadehydromarineosin via an oxidation and subsequent 6π electrocyclization.

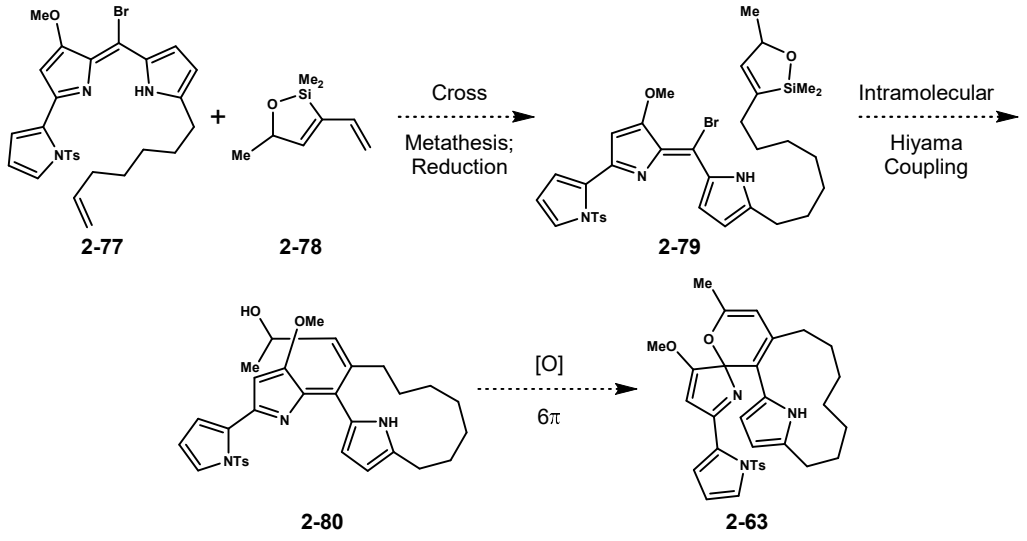
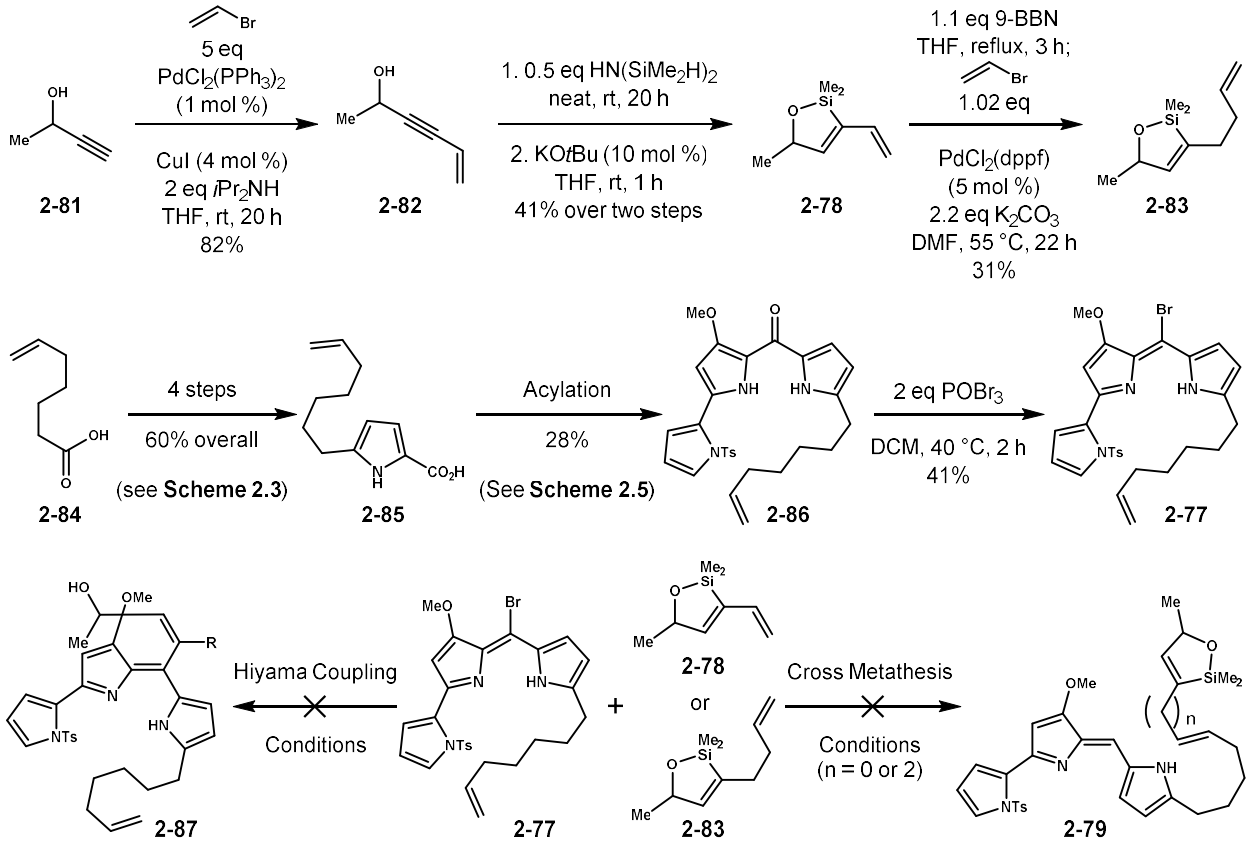


Figure 2.6. Projected Construction of Ansa Bridge via Hiyama Coupling

The construction of vinyl oxasilole **2-78** commenced with (±)-3-butyn-2-ol (**2-81**) and vinyl bromide, which are coupled via palladium catalysis to provide enynol **2-82** (**Scheme 2.15**).[168] This alcohol was silylated and then treated with base to induce an intramolecular hydrosilylation of the

alkyne to provide oxasilole **2-78**.[169] The truncated vinyl bromide **2-77** was constructed in a manner that was analogous to **2-64** (*vide supra*).



Scheme 2.15. Construction of Oxasilole **2-78** and Truncated Vinyl Bromide **2-77** for Examination in Cross Metathesis and Hiyama Coupling Studies

Utilizing our optimized conditions for cross metathesis with oxasilole **2-78** and vinyl bromide **2-77** failed to produce any of the desired composite **2-79**. Recovered **2-77** was the only tractable material obtained from these preliminary experiments. It was postulated that the steric bulk of oxasilole **2-78** was interfering with efficient cross metathesis, as well as the potentially problematic diene motif embedded in the structure. To examine if these areas were the source of the inactivity in cross metathesis reactions, a 2 carbon linker was installed between the vinyl group and the oxasilole (i.e **2-83**). This material also proved problematic in the cross metathesis with the reaction failing to proceed and isolation of only starting **2-77**. With the change in linker length proving

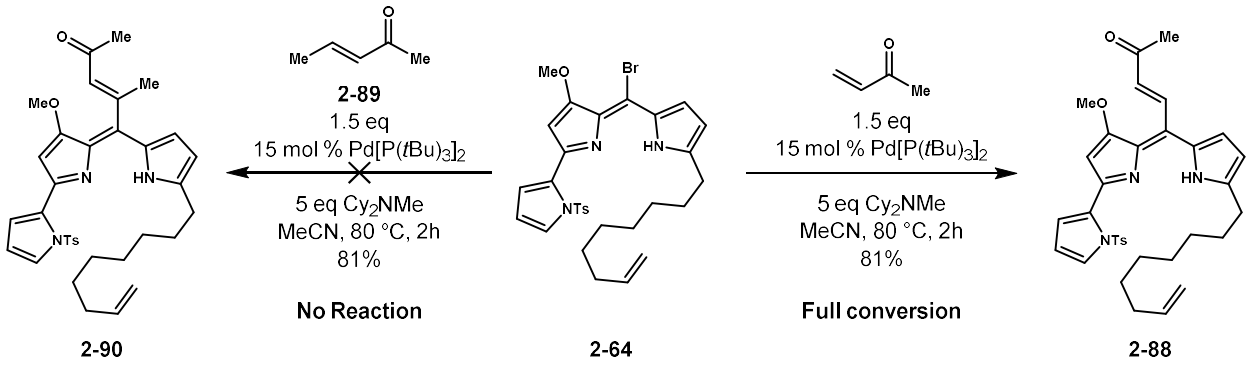
ineffectual on the progression of the reaction, it was posited that the vinyl silane might be the culprit for the inactivity observed. A potential side process occurring in the reaction might be the transmetallation of the vinyl silane to form a vinyl ruthenium species, which subsequently decomposes and destroys the catalyst in the process.

The difficulties in the cross metathesis route caused us to consider a rearrangement of steps. If a successful Hiyama coupling could be established, then the resultant material could be annulated using ring closing metathesis to access the desired pyrrolophane. Several experiments were performed with either **2-78** or **2-83** to establish entry to coupled product **2-87**. However, after a small screen of Pd catalysts, no coupled product could be observed. Once again, recovered **2-77** was often the result of these experiments.

2.2.6. Development of an Efficient Bimolecular Heck for the Generation of a Marineosin Model System

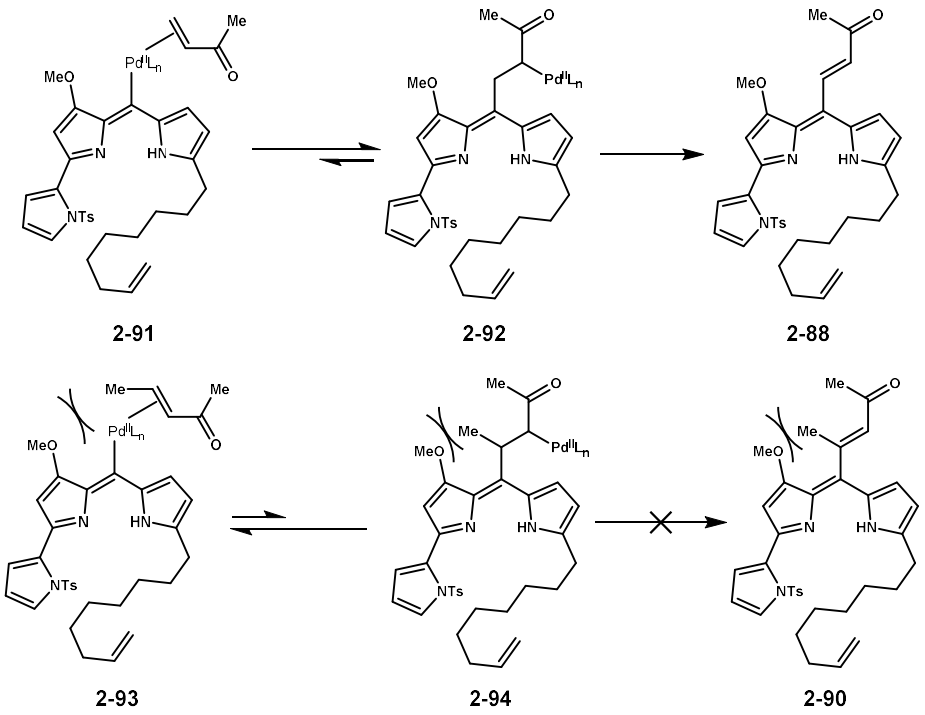
With our Heck macrocyclization and Hiyama coupling approaches proving ineffective, we were concerned that aryl bromide **2-59** was the source of the issue. Specifically, the identification of **2-71** as a side products indicated that oxidative addition to the C9-Br bond was occurring, however the olefin partner was not engaging properly (**Scheme 2.12**). This lack of reactivity led other side processes to dominate the reaction. In addition, the hydrolysis product **2-69** indicated that oxidative addition was possibly not occurring at a fast enough rate before catalyst decomposition. In order to further investigate the source of this hindered activity, we sought to develop a bimolecular Heck variant to examine these bromo-prodiginine derivatives in detail.

Aryl bromide **2-64** was chosen as our model system to explore the bimolecular Heck reaction, which was prepared by the route outlined in **Sections 2.2.3** and **2.2.4**. We chose MVK (**D**) as our coupling partner and initially examined Fu's catalytic system to govern the coupling.[157,158] In nonpolar solvent, the desired coupling product was observed in low yield. However, this was the first instance of C-C bond formation at the desired C9 position, which boded well for our approach. It was determined that increasing the solvent polarity corresponded with a faster and more efficient reaction. The optimized conditions for the bimolecular Heck reaction with aryl bromide **2-64** are treatment with Fu's catalyst, an excess of MVK, a large excess of Cy_2NMe in acetonitrile at 80 °C for 2 hours (**Scheme 2.16**). This process reliably produced coupled product **2-77** in 60-80% yield.



Scheme 2.16. Bimolecular Heck Model Studies

Unfortunately, when the coupling partner was changed to enone **2-89**, the reaction failed to proceed. This simple incorporation of a β-substituent shut down the coupling process and the only isolable material was starting aryl bromide **2-64**. This interesting result was informative on the issues discussed with the intramolecular variant (*vide supra*). It was postulated that this lack of reactivity towards the more substituted **2-89** was due to sterics (**Scheme 2.17**).



Scheme 2.17. Mechanistic Hypothesis for Reactivity Differences in Bimolecular Heck Reaction

In the case of **2-88**, the olefin ligand on Pd^{II} intermediate **2-91** could orient itself so the ketone substituent is distal to the B ring methoxy group. This orientation allows migratory insertion to occur with ease followed by β-hydride elimination to provide **2-88**. However, once the coupling partner has a β-substituent, there is significant steric clashing between that group and the B-ring methoxy group. It is postulated that this interaction provides a high enough energy barrier to prevent the Heck process from proceeding to **2-90**. This type of interaction leads to interesting structural configurations in more advanced intermediates towards the marineosins (see Chapter 4). The lack of reactivity with β-substituted enones provided insight into the failed intramolecular annulations examined (*vide supra*). However, the ability to couple aryl bromide **2-64** was an accomplishment, which we intended to exploit to examine potential endgame strategies towards the marineosins (See Chapter 3).

2.3. Conclusion

In order to establish a unified approach to C9-linked ansa bridged prodiginines, an adjustment of the methods used to construct roseophilin was needed to examine the feasibility of the approach to access the marineosins. Efficient and scalable processes were developed to produce the building blocks **2-11** and **2-13**, which were combined to construct the desired seco precursor. Unfortunately, the inability to install a protecting/trap group precluded the ability to construct the marineosin pyrrolophane in a manner analogous to roseophilin. In an attempt to bypass the protecting/trap group issue, Heck and cross coupling methodologies were explored as potential ways to construct the pyrrolophane. Notably, we were able to access C9 brominated or chlorinated prodiginines, novel motifs not reported before in the literature. Although our desired annulation chemistry could not be realized, we were able to establish conditions for the functionalization of these structures using palladium catalysis. Due to the issues encountered with this synthetic approach, alternative methods became more attractive and shifted our attention towards methods that more closely rivaled the biosynthetic construction of the marineosins.

2.4. Experimental

2.4.1. Materials and Methods

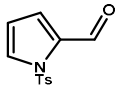
All reactions were carried out using oven- or flame-dried glass and a magnetic stir bar under an atmosphere of argon (Ar) unless otherwise indicated. Tetrahydrofuran (THF), diethyl ether (Et_2O), methylene chloride (DCM), toluene, acetonitrile (MeCN), and methanol were dried by passage through activated alumina using a GlassContour® solvent drying system. Dioxane, triethylamine, and *N,N*-dicyclohexylmethylamine (Cy_2NMe) were distilled from CaH_2 under inert atmosphere prior to use. Phosphorous oxybromide ($POBr_3$) was purchased from Oakwood Scientific and sublimed prior to use by vacuum distillation. Methyl vinyl ketone was distilled from anhydrous K_2CO_3 prior to use. Commercial Pd_2dba_3 was recrystallized from $CHCl_3$ to afford purified $Pd_2dba_3 \cdot CHCl_3$ prior to use. All other commercial reagents and catalysts were used as received unless otherwise indicated.

NMR spectra were recorded on Bruker Advance spectrometers (400 MHz, 500 MHz) and are reported as δ values in ppm relative to $CDCl_3$ (calibrated to 7.27 ppm in ^1H NMR and 77.16 ppm in ^{13}C NMR, unless otherwise indicated) and were conducted at room temperature (unless otherwise indicated). ^1H NMR coupling constants are reported in Hz. Splitting patterns are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), septet (sept), multiplet (m), broad (br), apparent (app), and combinations thereof. Column chromatography was conducted on silica gel 60 (240-400 mesh) purchased from Silicycle or neutral aluminum oxide (activated, Brockmann I) purchased from Sigma Aldrich. Thin layer chromatography (TLC) was performed using pre-coated, glass-backed plates (SiO_2, 60 PF254, 0.25 mm or neutral Al_2O_3, 0.25 mm) and visualized using a combination of UV, anisaldehyde, and potassium permanganate staining.

All late-materials harbouring an azafulvene were stored for prolonged periods of time (>5 h) protected from light at -20 °C. Under these conditions, compounds could be stored for several weeks without decomposition. Solutions of azafulvenes undergo a color change from bright orange to red to dark purple over several hours when exposed to visible light. In most cases involving these motifs, it was necessary to protect reaction mixtures from light to prevent unwanted decomposition.

2.4.2. Experimental Procedures and Characterization Data

1-Tosyl-1*H*-pyrrole-2-carbaldehyde (2-14)

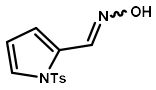


2-15

A 500 mL flask was charged with 2-pyrrole carbaldehyde **2-14** (20.03 g, 210.68 mmol) and Hünigs base (47 mL, 269.81 mmol, 1.3 eq) in DCM (70 mL, 3M) was treated with tosyl chloride (44.18 g, 231.7 mmol, 1.1 eq) portionwise and DMAP (2.57 g, 21.07 mmol, 10 mol %) at 0 °C. After 30 min, the reaction was warmed to room temperature. After 24 h, the solution was diluted with DCM (200 mL) and water (200 mL). The aqueous layer was extracted with DCM (2 x 100 mL). The combined organic extracts were washed successively with 1M HCl (3 x 300 mL), sat. aqueous $NaHCO_3$ (3 x 300 mL), and brine (300 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated to afford **2-15** (50.5 g, 96%) in >95% purity as a brown solid that darkens on standing. This material was used without further purification.

1-Tosyl-1*H*-pyrrole-2-carbaldehyde (2-15):
^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 9.96 (s, 1H), 7.79 (d, *J* = 8.2 Hz, 2H), 7.63-7.6 (m, 1H), 7.31 (d, *J* = 8.2 Hz, 2H), 7.17-7.12 (m, 1H), 6.39 (t, *J* = 3.3 Hz), 2.41 (s, 3H)

1-tosyl-1*H*-pyrrole-2-carbaldehyde oxime (2-16)

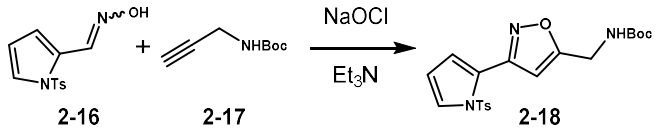


2-16

A 500 mL flask was charged with aldehyde **2-15** (35.2 g, 141.2 mmol), $NH_2OH{\cdot}HCl$ (10.9 g, 156.9 mmol, 1.1 eq), and $NaOAc{\cdot}3H_2O$ (28.83 g, 211.87 mmol, 1.5 eq). The solids were then taken up in a 10:1 $MeOH/H_2O$. The suspension was rapidly stirred at room temperature for 2 h, when TLC indicated starting material was fully consumed. The reaction was concentrated under reduced pressure. The tan solids were taken up in $CHCl_3$ (300 mL) and washed with sat. aqueous $NaHCO_3$ (2 x 300 mL). The organic extracts were dried over $MgSO_4$, filtered and concentrated to afford oxime **2-16** (36.5 g, 97%) as a ~4:1 mixture of oxime stereoisomers.

1-tosyl-1*H*-pyrrole-2-carbaldehyde oxime (2-16):
^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) (major isomer) 8.58 (s, 1H), 7.68 (d, *J* = 8.75 Hz, 2H), 7.38 (dd, *J* = 1.5, 3.1 Hz, 1H), 7.29 (d, *J* = 8.45 Hz, 2H), 6.72-6.7 (m, 1H), 6.29 (t, *J* = 3.4 Hz, 1H), 2.39 (s, 3H)

***Tert*-Butyl ((3-(1-tosyl-1*H*-pyrrol-2-yl)isoxazole-5-yl)methyl)carbamate (2-18)**



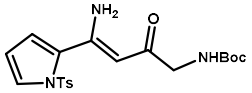
2-16 **2-17** **2-18**

To a solution of NaOCl (87 mL, 66.61 mmol, 1.8 eq) and Et_3N (0.52 mL, 3.73 mmol, 10 mol%) in DCM (95 mL) at 0 °C, alkyne **2-17** (6.9 g, 44.49 mmol, 1.2 eq) was added and the mixture was stirred for 5 minutes. Then oxime **2-16** (9.8 g, 37.07 mmol) in DCM (95 mL) was added dropwise over two hours. The mixture was then allowed to warm to room temperature overnight (~16h). The reaction was then diluted with H_2O and extracted with DCM. The organics were dried over $MgSO_4$, filtered, and concentrated to an orange oil. The residue was purified by flash column chromatography (SiO_2, 5:1→4:1 Hexanes/EtOAc) to afford **2-18** (12.7 g, 82%).

***Tert*-Butyl ((3-(1-tosyl-1*H*-pyrrol-2-yl)isoxazole-5-yl)methyl)carbamate (2-18):**
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.52 (d, *J* = 8.4 Hz, 2H), 7.45 (dd, *J* = 1.7, 3.3 Hz, 1H), 7.20 (d, *J* = 7.9 Hz, 2H), 6.53 (dd, *J* = 1.7, 3.4 Hz, 1H), 6.50-6.48 (m, 1H), 6.31 (t, *J* = 3.4 Hz, 1H), 5.11 (bs, 1H), 4.5-4.4 (m, 2H), 2.34 (s, 3H), 1.46 (9H)

^{13}C NMR (100 MHz, $CDCl_3$): 169.1, 155.5, 145.3, 135.2, 129.8, 127.2, 125.8, 122.8, 118.7, 112.4, 104.5, 80.33, 36.7, 28.3, 21.6, 14.2

Benzyl (Z)-(4-hydroxy-2-oxo-4-(1-tosyl-1H-pyrrol-2-yl)but-3-en-1-yl)carbamate (2-19)

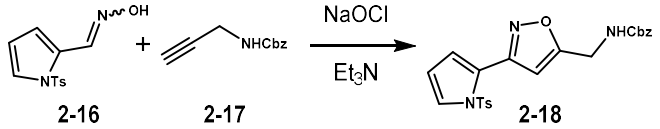


2-19

To a solution of degassed MeCN/H_2O (20:1, 126 mL, 0.1M), $Mo(CO)_6$ (1.6069 g, 6.08 mmol, 50 mol%) was added. The mixture was heated to 90 °C until the solids dissolved. The mixture was then cooled to 50 °C and isoxazole **2-18** (5.08 g, 12.17 mmol) in a solution of MeCN (20 mL) was added to the mixture. The reaction was then heated to 90 °C for 4h when TLC indicated starting material had been consumed. The reaction mixture was then concentrated to a dark brown oil, which was then diluted with EtOAc and SiO (~10 g) was added. The mixture was vigorously stirred at room temperature for 1h. The mixture was then flushed through a SiO_2 plug with EtOAc. The mixture was then concentrated to a black/brown solid.

Benzyl (Z)-(4-hydroxy-2-oxo-4-(1-tosyl-1H-pyrrol-2-yl)but-3-en-1-yl)carbamate (2-19):
^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 9.71 (bs, 1H), 7.62 (d, *J* = 8.1 Hz, 2H), 7.51-7.45 (m, 1H), 6.55-6.49 (m, 1H), 6.29 (t, *J* = 3.25 Hz, 1H), 5.37 (s, 1H), 4.93 (s, 1H), 3.86 (s, 2H), 2.40 (s, 3H), 1.45 (s, 9H)

Benzyl ((3-(1-tosyl-1*H*-pyrrol-2-yl)isoxazole-5-yl)methyl)carbamate (2-21)



A 2-L flask equipped with a mechanical stirrer was charged with a solution of benzyl prop-2-ynylcarbamate **2-20** (20.93 g, 110.66 mmol, 1.25 eq), Et_3N (1.55 mL, 11.12 mmol, 12.5 mol %), and NaOCl (6% aqueous solution, 232 mL, 177.64 mmol, 2 eq) in DCM (200 mL) at 0 °C. Oxime **2-16** (23.4 g, 88.53 mmol) suspended in DCM (~400 mL) was added dropwise over 6 hours. The reaction mixture was then allowed to warm to room temperature overnight (~16 h). The reaction was diluted with water (300 mL) and extracted with DCM (3 x 200 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting orange oil was purified by flash chromatography (SiO_2, 4:1→2:1 hexanes/EtOAc) to afford a viscous yellow oil.

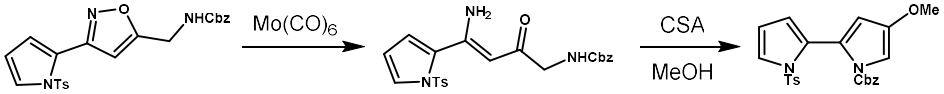
Crystallizes in MeCN at low temperature

Benzyl ((3-(1-tosyl-1*H*-pyrrol-2-yl)isoxazole-5-yl)methyl)carbamate (2-21):
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.53 (d, *J* = 8.6 Hz, 2H), 7.46 (dd, *J* = 1.7, 3.3 Hz, 1H), 7.38-7.28 (m, 5H), 7.20 (d, *J* = 8.2 Hz, 2H), 6.54 (dd, *J* = 1.7, 3.3 Hz, 2H), 6.51 (bs, 1H), 6.33 (t, *J* = 3.3 Hz, 1H), 5.25 (bs, 1H), 5.16 (bs, 2H), 4.55 (d, *J* = 6 Hz, 2H), 2.35 (s, 3H)

^{13}C NMR (125 MHz, $CDCl_3$): 168.3, 156.1, 155.6, 145.3, 136.0, 135.2, 129.8, 128.6, 128.3, 128.2, 127.1, 125.9, 122.7, 118.8, 112.5, 104.8, 67.3, 37.0, 21.6

HRMS (ESI) m/z, 452.1275 (452.1280 calcd. For $C_{23}H_{22}N_3O_5S$, $(M+H)^+$)

Benzyl 4-methoxy-1'-tosyl-1*H*,1'*H*-[2,2'-bipyrrole]-1-carboxylate (2-23)



In a 250 mL flask, molybdenum hexacarbonyl (2.348 g, 8.89 mmol, 50 mol %) was suspended in MeCN/H_2O (20:1, 180 mL, 0.1M). The suspension was heated to 90 °C with vigorous stirring until the solids dissolved (~15 minutes). The resulting colorless solution was removed from the oil bath and allowed to cool for 5 minutes. A solution of isoxazole **2-21** (8.03 g, 17.79 mmol) in MeCN (30 mL) was added dropwise. The resulting yellow/orange solution was warmed to 90 °C for 4 h and turned dark brown. The reaction was then cooled to room temperature and concentrated to a black oil. The reaction was taken up in EtOAc (100 mL) and SiO_2 (20 g) was added. The mixture was stirred vigorously while air was bubbled through the solution for an hour. The mixture was then filtered over a SiO_2 plug and washed with copious amounts of EtOAc (~1.5 L). The brown solution was then concentrated to give brown solids (8.2 g). This material was taken on to the next step.

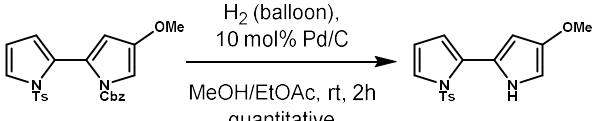
The brown solids were dissolved in MeOH (120 mL) and treated with CSA (4.54 g, 19.54 mmol, 1.1 eq). The reaction was then heated to reflux for 23 h. The reaction was then cooled and concentrated to a black paste. The paste was taken up in EtOAc (200 mL) and washed with sat. aqueous $NaHCO_3$ (3 x 200 mL) (***NOTE:** Vigorous bubbling occurs during the quench) and brine (200 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated to a black/brown oil. Purification by flash chromatography (SiO_2, 9:1→4:1 Hexanes/EtOAc) afforded **2-23** (5.4 g, 11.98 mmol, 67% over two steps) as a white/off-white solid.

benzyl (*Z*)-(4-hydroxy-2-oxo-4-(1-tosyl-1H-pyrrol-2-yl)but-3-en-1-yl)carbamate (2-22)
^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 9.70 (bs, 1H), 7.61 (d, *J* = 8.3 Hz, 2H), 7.50-7.46 (m, 1H), 7.42-7.21 (m, 8H), 6.54-6.48 (m, 1H), 6.28 (t, *J* = 2.9 Hz, 1H), 5.68-5.61 (m, 1H), 5.12 (s, 2H), 4.92 (s, 1H), 3.91 (d, *J* = 4.3 Hz, 2H), 2.38 (s, 3H)
Benzyl 4-methoxy-1'-tosyl-1*H*,1'*H*-[2,2'-bipyrrole]-1-carboxylate (2-23):
^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.42 (d, *J* = 8.2 Hz, 2H), 7.34-7.31 (m, 3H), 7.28-7.23 (m, 3H), 7.18 (d, *J* = 8.1 Hz, 2H), 6.94 (d, *J* = 2.0 Hz, 1H), 6.18-6.16 (m, 2H), 5.68 (d, *J* = 2.1 Hz, 1H), 5.16 (bs, 2H), 3.74 (s, 3H), 2.36 (s, 3H)

^{13}C NMR (125 MHz, $CDCl_3$) 150.0, 148.9, 144.7, 135.8, 134.7, 129.5, 128.5, 128.46, 128.4, 127.2, 125.5, 123.3, 121.5, 116.8, 111.3, 110.2, 102.4, 68.8, 57.5, 21.6

HRMS (ESI) m/z 451.1324 (451.1328 calcd. For $C_{24}H_{23}N_2O_5S$, $(M+H)^+$)

4'-methoxy-1-tosyl-1*H*,1'*H*-2,2'-bipyrrole (2-11) from 2-23



2-23
Stable white solid
2-11

A 2-necked 100 mL flask was charged with **2-23** (1.04 g, 2.3 mmol) and palladium on carbon (10% w/w, 0.202 g, 0.19 mmol, ~10 mol %) under an inert atmosphere. The solids were then taken up in EtOAc/MeOH (1:1, 20 mL). The resulting suspension was then partially evacuated and backfilled with H_2, thrice. The reaction was then vigorously stirred under a H_2 balloon for 3 hours. The reaction was then filtered over a SiO_2 plug with EtOAc (100 mL). The filtrate was concentrated to afford a glassy yellow/white solid that darkens on exposure to atmosphere. This material was used immediately.

4'-methoxy-1-tosyl-1*H*,1'*H*-2,2'-bipyrrole (2-11):
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.58 (s, 1H), 7.35 (dd, *J* = 1.9, 3.2 Hz, 1H), 7.32 (d, *J* = 8.2 Hz, 2H), 7.14 (d, *J* = 8.2 Hz, 2H), 6.45 (dd, *J* = 1.8, 2.7 Hz, 1H), 6.27-6.18 (m, 2H), 5.78 (dd, *J* = 1.9, 2.8 Hz, 1H), 3.72 (s, 3H), 2.34 (s, 3H)

HRMS (ESI) m/z, 317.0969 (317.0954 calculated for $C_{16}H_{17}N_2O_3S^+$, $(M+H)^+$)

1-Tosyl-1*H*-pyrrole (2-27)

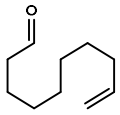
2-27

In a 250 mL flask, a suspension of NaH (60% in mineral oil, 1.81 g, 75.66 mmol, 1.05 eq) in THF (20 mL) at 0 °C was treated with a solution of pyrrole (5 mL, 72.06 mmol) in THF (20 mL). The mixture was stirred for 45 minutes. *p*-Toluenesulfonyl chloride (9.16 g, 48.05 mmol, 0.66 eq) in THF (20 mL) was then added dropwise. The reaction was then allowed to warm to room temperature overnight (~16 h). The mixture was then diluted with H_2O (200 mL) and washed with Et_2O (200 mL). The aqueous layer was then washed with Et_2O (2 x 100 mL). The combined organics were then dried over $MgSO_4$, filtered and concentrated to light brown solids, which were recrystallized in hexanes to afford tan crystals (10 g, 94%).

1-Tosyl-1*H*-pyrrole (2-27):

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.73 (d, *J* =8.1 Hz, 2H), 7.28 (d, *J* = 8 Hz, 2H), 7.16-7.13 (m, 2H), 6.29-6.26 (m, 2H), 2.39 (s, 3H)

8-decenal (2-32)



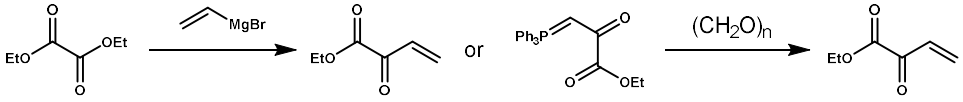
2-32

In a 50 mL flask, a solution oxalyl chloride (1.2 mL, 13.99 mmol, 1.1 eq) in DCM (8 mL) was added dropwise to a mixture of DMSO (2 mL, 28.15 mmol, 2.2 eq) in DCM (8 mL) at -78 °C. The reaction was stirred for 30 minutes at -78 °C. Alcohol **2-33** (2.28 mL, 12.78 mmol) in DCM (8 mL) was added dropwise to the reaction. The mixture was then stirred for 2 hours at -78 °C followed by treatment with Et_3N (9 mL, 65.99 mmol, 5.1 eq). The mixture was then allowed to warm to room temperature over 1.5 h. The reaction was then diluted with Et_2O (50 mL) and 1M aqueous HCl (100 mL). The organic layer was then washed with sat. aqueous $NaHCO_3$ (100 mL) followed by brine (100 mL). The aqueous layers were re-extracted with Et_2O (100 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated to a clear oil (1.944 g, 99%)

8-decenal (2-32):

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 9.71 (s, 1H), 5.75 (ddt, *J* = 3.3, 6.8, 16.9 Hz, 1H), 4.97-4.85 (m, 2H), 2.37 (dt, *J* = 1.4, 7.3 Hz, 2H), 1.99 (q, *J* = 7.0 Hz, 2H), 1.58 (p, 7.3 Hz, 2H), 1.38-1.22 (m, 8H)

Ethyl 2-Oxobut-3-enoate (2-31)



2-34 2-31 2-35 2-31

Method A:

In a 250 mL flask, a solution of vinylmagnesium bromide (1.03 M, 20 mL, 20.71 mmol, 1.5 eq) was added dropwise over 10 minutes to a -78 °C solution of diethyl oxalate (1.86 mL, 13.74 mmol) in THF (60 mL). The reaction was stirred for 20 minutes at -78 °C and then quenched with 1M H_2SO_4 (10 mL). The reaction was allowed to warm to room temperature over 10 minutes and then diluted with Et_2O (50 mL). The organic layer was then washed with sat. aqueous $NaHCO_3$ (50 mL) followed by brine (50 mL). The organics were dried over $NaSO_4$, filtered and carefully concentrated to remove the Et_2O and some THF. Galvinoxyl radical (6 mg, 0.013 mmol, 0.1 mol %) was added to the solution to inhibit polymerization of **2-31**. The yield of the reaction was calculated from NMR by comparison of the residual THF peaks with those of **2-31** (1.23 g, 70%, 1.23 M in THF).

Method B:

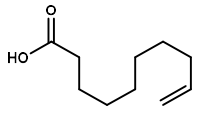
Following the literature procedure (Jacobi, P.A. & Cai, G. *Heterocycles*, **1993**, *35(2)*, 1103-1120), a 250 mL flask was charged with phosphorane **2-35** (2.67 g, 7.11 mmol) dissolved in DCM (50 mL) at 0 °C. A 100 mL flask was charged with paraformaldehyde (25.9 g, 862 mmol, 120 eq) and heated to 120 °C under a stream of argon. An outlet from this cracking process was placed into the flask with **2-35**, which allowed CH_2O/Ar to bubble through the solution. The reaction flask contained a pressure outlet that flowed into a 10% NaOH solution (200 mL) to sequester unreacted CH_2O. TLC indicated consumption of starting material after 3 hours. The reaction was diluted with pentane (30 mL), filtered and concentrated. The brown/yellow oil was then passed through a SiO_2 plug with 5% Et_2O in pentane. The filtrate was concentrated to a pale yellow oil (0.445 g, 49%).

Crude Ethyl 2-Oxobut-3-enoate (2-31) obtained from Method A:

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 6.70 (dd, *J* =10.6, 17.7 Hz, 1H), 6.33 (d, *J* = 17.7 Hz, 1H), 5.92 (d, *J* = 10.6 Hz, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 1.17 (t, *J* = 7.0 Hz, 3H)

^{13}C NMR (125 Hz, $CDCl_3$) 183.3, 161.4, 133.7, 130.9, 62.0, 17.8

9-decenoic acid (2-37)



2-37

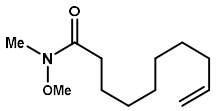
Periodic acid (16.69 g, 73.25 mmol, 2.2 eq) was dissolved in MeCN (340 mL, 0.1 M) over the course of 15 minutes at room temperature. The reaction was then cooled to 0 °C and alcohol **2-33** (5.2 g, 33.2 mmol) was added in one portion followed by PCC (0.143 g, 0.67 mmol, 2 mol %). The pale yellow/orange solution was then allowed to warm to room temperature overnight (~16 h). The yellow/orange reaction mixture contained green solids, which clung to the walls of the

flask. The reaction mixture was then filtered over celite and the green solids were washed with EtOAc. The filtrate was then partitioned between brine (300 mL) and EtOAc (200 mL). The organics were then dried over $MgSO_4$, filtered and concentrated to give **2-37** an orange oil (5.6 g, 99%). This material was used without further purification. (***NOTE:** The reaction can scale effectively on 120 mmol scale the yield was 95%).

9-decenoic acid (2-37):
^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 11.62 (br s, 1H), 5.8 (ddt, *J* = 3.2, 6.7, 16.8 Hz, 1H), 5.01-4.9 (m, 2H), 2.34 (t, *J* = 7.4 Hz, 2H), 2.03 (q, *J* = 7.4 Hz, 2H), 1.62 (p, *J* = 7.2 Hz, 2H), 1.41-1.25 (m, 8H)

^{13}C NMR (125 Hz, $CDCl_3$) 180.3, 138.9, 114.0, 33.9, 33.6, 28.9, 28.8, 28.76, 28.71, 24.5

***N*-Methoxy-*N*-methyldec-9-enamide (2-38)**

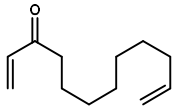


2-38

A 250 mL flask was charged with acid (1.73 g, 10.17 mmol), HNMe(OMe)·HCl (0.99 g, 10.17 mmol, 1 eq), HOBt (2.33 g, 15.26 mmol, 1.5 eq), and EDC·HCl (2.92 g, 15.26 mmol, 1.5 eq). The mixture was dissolved in DCM (50 mL, 0.2 M) and Et_3N (7.1 mL, 50.93 mmol, 5 eq) was added dropwise. The mixture was stirred at room temperature overnight (17 h). The reaction was then concentrated to yellow paste, which was taken up in Et_2O (100 mL). The organic layer was then washed with 1M HCl (100 mL), sat. aqueous $NaHCO_3$ (100 mL), and brine (100 mL). The organics were dried over $MgSO_4$, filtered and concentrated to give **2-38** an orange oil (2.29 g, quantitative). (***NOTE:** When scaled to 100 mmol the yield remains >90%).

***N*-Methoxy-*N*-methyldec-9-enamide (2-38):**
^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 5.78 (ddt, *J* = 6.7, 10.0, 17.0 Hz, 1H), 5.01-4.87 (m, 2H), 3.66 (s, 3H), 3.16 (s, 3H), 2.39 (t, *J* =7.4 Hz, 2H), 2.01 (q, *J* = 6.99 Hz, 2H), 1.61 (p, *J* = 7.3 Hz, 2H), 1.42-1.20 (m, 8H)

Dodeca-1,11-dien-3-one (2-39)



2-39

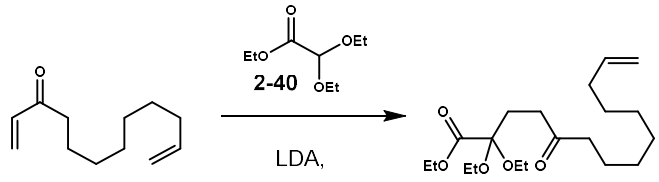
To a solution of vinylmagnesium bromide (1.03 M, 82 mL, 79.18 mmol, 1.4 eq) in THF (60 mL) at -78 °C, amide **2-38** (12 g, 56.3 mmol) in THF (80 mL) was added dropwise. The reaction was stirred at -78 °C for 3 hours. The reaction was quenched with 1M aqueous HCl (80 mL) at -78 °C and then allowed to warm to room temperature over 10 minutes. The mixture was extracted with Et_2O (200 mL) followed by washing the organics with brine (200 mL). The organics were dried over $MgSO_4$, filtered and concentrated to afford **2-39** as a light orange oil (10.1 g, quantitative).

Dodeca-1,11-dien-3-one (2-39):

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 6.32 (dd, *J* = 10.7, 17.7 Hz, 1H), 6.18 (d, *J* = 17.7 Hz, 1H), 5.83-5.71 (m, 1H), 5.78 (d, *J* = 10.3 Hz, 1H), 4.99-4.86 (m, 2H), 2.55 (t, *J* = 7.4 Hz, 2H), 2.00 (q, *J* = 6.8 Hz, 2H)1.64-1.54 (m, 2H), 1.38-1.21 (m, 8H)

^{13}C NMR (125 MHz, $CDCl_3$): 201.0, 138.9, 136.4, 127.8, 114.0, 39.4, 33.6, 29.1, 29.0, 28.79, 28.70, 23.8

Ethyl 2,2-Diethoxy-5-oxotetradec-13-enoate (2-41)



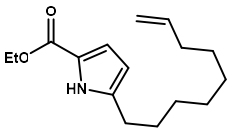
2-39 2-41

To a solution of diisopropylamine (8.3 mL, 59.22 mmol, 1.1 eq) in THF (90 mL), *n*BuLi (2.4 M in Hexanes, 24.1 mL, 57.93 mmol, 1.08 eq) was added at 0 °C. The mixture was stirred for 20 minutes and then cooled to -78 °C. Ethyl diethoxyacetate (**2-40**, 9.72 mL, 54.33 mmol, 1.01 eq) in THF (60 mL) was added dropwise and the mixture was stirred for an additional 20 minutes after the addition was complete. Enone **2-39** (9.7 g, 53.8 mmol) in THF (75 mL) was then added dropwise. The reaction was stirred at -78 °C for 2 hours, when TLC indicated consumption of starting material. The reaction was quenched with 1 M HCl (70 mL) and allowed to warm to room temperature over 30 minutes. The mixture was then extracted with Et_2O (2 x 100 mL) and the organics were washed with brine (300 mL). The organics were then dried over $MgSO_4$, filtered and concentrated to afford **2-41** as a light orange oil, which was used in the next step without isolation.

Ethyl 2,2-Diethoxy-5-oxotetradec-13-enoate (2-41) crude material:

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 5.81 (ddt, *J* = 3.4, 6.7, 16.9 Hz, 1H), 5.06-4.85 (m, 2H), 4.25 (q, *J* = 7.0 Hz, 2H), 3.79-3.62 (m, 2H), 3.63-3.35 (m, 4H), 2.46-2.3 (m, 4H), 2.18 (t, *J* = 7.7 Hz, 2H), 2.04 (q, *J* = 6.7 Hz, 2H), 1.65-1.49 (m, 2H), 1.44-1.15 (m, 15H)

Ethyl 5-(non-8-en-1-yl)-1*H*-pyrrole-2-carboxylate (2-42)



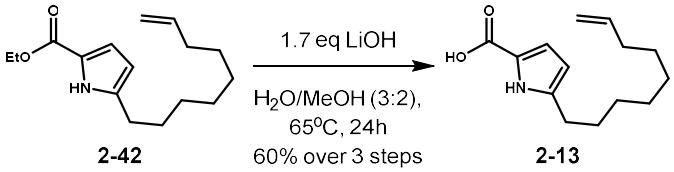
2-42

Crude acetal **2-41** from the above reaction was dissolved in acetic acid (270 mL, 0.2 M) with NH_4OAc (4.97 g, 64.51 mmol, 1.2 eq). The reaction was heated to 100 °C for 42 h, when TLC indicated starting material consumed. The reaction was concentrated and then diluted with Et_2O (300 mL) followed by washing with H_2O (200 mL), 1 M HCl (200 mL), and sat. aqueous $NaHCO_3$

(200 mL). The organics were dried over $MgSO_4$, filtered and concentrated to provide **2-42** as a dark brown oil. This material was used in the next step without isolation.

Ethyl 5-(non-8-en-1-yl)-1*H*-pyrrole-2-carboxylate (2-42) crude material:
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.94 (bs, 1H), 6.81 (dd, *J* = 2.6, 3.5 Hz, 1H), 5.95 (dd, *J* = 2.5, 3.4 Hz, 1H), 5.79 (ddt, *J* = 3.5, 6.7, 16.9 Hz, 1H), 5.02-4.89 (m, 2H), 4.29 (q, *J* = 7.1 Hz, 2H), 2.6 (t, *J* = 7.7 Hz, 2H), 2.03 (q, *J* = 7.2 Hz, 2H), 1.62 (p, *J* = 7.3 Hz, 2H), 1.43-1.12 (m, 11)

5-(non-8-en-1-yl)-1*H*-pyrrole-2-carboxylic acid (2-13)



2-42 **2-13**

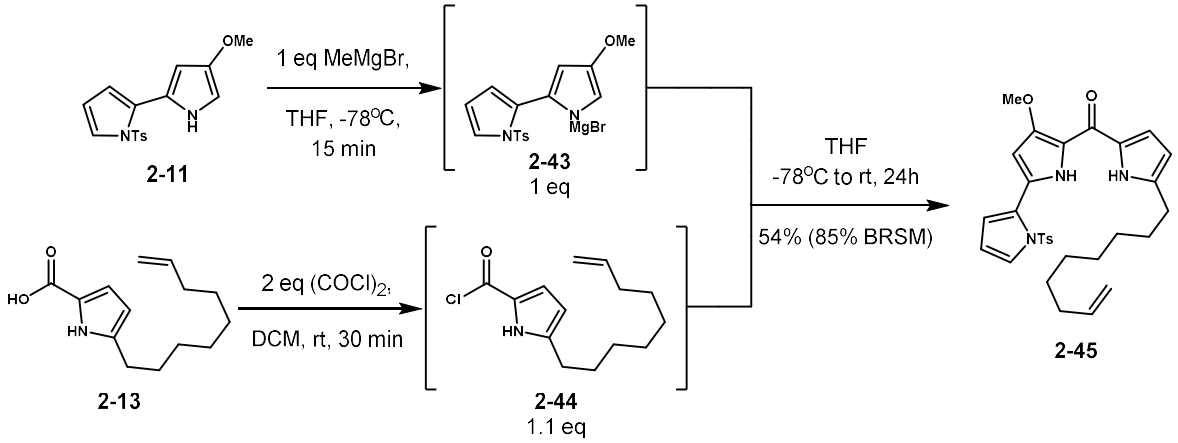
The crude ester **2-42** was dissolved in 3:2 Methanol/H_2O (36.5 mL, 1.5 M). Anhydrous LiOH (2.19 g, 91.64 mmol, 1.7 eq) was added in one portion. The mixture was then warmed to 65 °C and stirred at this temperature for 20 h. The reaction was then cooled and diluted with H_2O (100 mL) and was washed with Et_2O (100 mL). The aqueous layer was then acidified with 2 M HCl (60 mL) and were extracted with Et_2O (3 x 200 mL). The organics were then dried over $MgSO_4$, filtered and concentrated to a black/red oil. This material was purified by flash column chromatography (SiO_2, 4:1 Hexanes/EtOAc) to afford **2-13** as a dark brown oil (7.99 g, 63%). (NOTE: Acid **2-13** is unstable to extended storage and slowly decomposes)

5-(non-8-en-1-yl)-1*H*-pyrrole-2-carboxylic acid (2-13):
^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 9.02 (bs, 1H), 6.97 (dd, *J* = 3.7, 2.4 Hz, 1H), 6.01 (dd, *J* = 3.7, 2.4 Hz, 1H), 5.8 (ddt, *J* = 16.9, 6.7, 3.5 Hz, 1H), 5.03-4.9 (m, 2H), 2.62 (t, *J* = 7.6 Hz, 2H), 2.07-2.01 (m, 2H), 1.68-1.61 (m, 2H), 1.38-1.3 (m, 8H)

^{13}C NMR (100 MHz, $CDCl_3$): 165.7, 139.1, 120.0, 118.3, 114.2, 108.7, 102.9, 33.7, 29.2, 29.16, 29.1, 29.0, 28.9, 27.8

HRMS (ESI) 236.1655 (236.1651 calcd for $C_{14}H_{22}NO_2$, $(M+H)^+$)

Acylation of Bipyrrole 2-11 with Alkenyl Pyrrole Acid 2-13



(**NOTE:** Intermediates **2-43** and **2-44** are unstable and the yields of the process roughly correlate with how long it takes to transfer **2-44**).

To a solution of acid **2-13** (2.90 g, 12.33 mmol, 1.1 eq to **2-11**) in DCM (36 mL) at room temperature, freshly distilled oxalyl chloride (2.12 mL, 24.71 mmol, 2 eq) was added dropwise (**NOTE*:** vigorous gas evolution). The reaction was stirred at room temperature for 30 minutes. The reaction was then concentrated to a brown oil and digested in 15 mL of THF. This process was repeated three times to afford **2-44** as a solution in THF used immediately.

As **2-44** is forming, a 250 mL flask is charged with freshly prepared **2-11** (3.54 g, 11.19 mmol) and dissolved in THF (60 mL). The reaction was then cooled to -78 °C and methylmagnesium bromide (3 M in Et_2O, 3.81 mL, 11.43 mmol, 1.02 eq) was added dropwise. The reaction was then stirred for 30 minutes. The THF solution of acid chloride **2-44** prepared above was then added dropwise over 10 minutes. The reaction was allowed to slowly warm to room temperature over 24 hours. The reaction was then quenched by the addition of MeOH (25 mL) and concentrated to a paste. The crude paste was dissolved in EtOAc (200 mL) and washed with sat. aqueous NH_4Cl (200 mL). The organics were dried with $MgSO_4$, filtered and concentrated to a black oil. This first batch was combined with a second batch (2.81 g, 11.94 mmol of **2-13** and 3.157 g, 9.98 mmol of **2-11**) both produced on the same day for purification by flash column chromatography (SiO_2, 7:1→5:1 Hexanes/EtOAc) to afford **2-45** as a brown foam (6.1 g, 54%) and recovered **2-11** as an unstable yellow oil (2.1 g, 31% recovered).

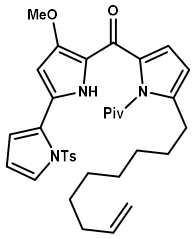
(4-methoxy-1'-tosyl-1*H*,1'*H*-[2,2'-bipyrrol]-5-yl)(5-(non-8-en-1-yl)-1*H*-pyrrol-2-yl) methanone (2-45):

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 10.08 (s, 1H), 9.75 (s, 1H), 7.47 (dd, *J* = 1.7, 3.3 Hz, 1H), 7.43 (d, *J* = 8.4 Hz, 2H), 7.39 (dd, *J* = 2.5, 3.6 Hz, 1H), 7.12 (d, *J* = 8.4 Hz, 2H), 6.42 (dd, *J* = 1.8, 3.4 Hz, 1H), 6.30 (t, *J* = 3.4 Hz, 1H), 6.09-6.03 (m 2H), 5.8 (ddt, *J* = 3.6, 6.7, 16.9 Hz, 1H), 5.02-4.89 (m, 2H), 3.94 (s, 3H), 2.67 (t, *J* = 7.6 Hz, 2H), 2.31 (s, 3H), 2.04 (q, *J* = 7.02 Hz, 2H), 1.68 (p, *J* = 7.4 Hz, 2H), 1.43-1.21 (m, 8H)

^{13}C NMR (100 MHz, $CDCl_3$): 169.6, 145.3, 139.2, 139.1, 134.7, 129.9, 129.8, 129.6, 127.1, 126.8, 126.0, 125.1, 117.5, 117.4, 116.7, 114.2, 114.0, 111.9, 108.6, 97.9, 58.2, 33.7, 29.2, 29.1, 29.0, 28.9, 28.0, 21.6

HRMS (ESI) m/z, 534.2420 (534.2426 calculated for $C_{30}H_{36}N_3O_4S^+$, $(M+H)^+$)

1-(2-(4-methoxy-1'-tosyl-1*H*,1'*H*-[2,2'-bipyrrole]-5-carbonyl)-5-(non-8-en-1-yl)-1*H*-pyrrol-1-yl)-2,2-dimethylpropan-1-one (2-46a)



2-46a

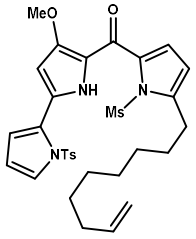
To a stirred suspension of NaH (60% in mineral oil, 10.4 mg, 0.26 mmol, 1.4 eq) in THF (3 mL), a solution of ketone **2-45** (96.7 mg, 0.18 mmol) in THF (0.5 mL) was added dropwise. The solution was stirred at room temperature for 30 minutes. Pivaloyl chloride (22 µL, 0.18 mmol, 1 eq) was added dropwise to the solution. The reaction was stirred at room temperature for 24 h. The reaction was then quenched with AcOH (1 mL). The reaction was concentrated to a brown oil that was purified by flash column chromatography (SiO_2, 9:1→85:15→4:1 Hexanes/EtOAc) to afford **2-45** as a brown foam (41.5 mg, 43% recovered) and **2-46a** as a brown oil (39.4 mg, 35%).

1-(2-(4-methoxy-1'-tosyl-1*H*,1'*H*-[2,2'-bipyrrole]-5-carbonyl)-5-(non-8-en-1-yl)-1*H*-pyrrol-1-yl)-2,2-dimethylpropan-1-one (2-46a) mixture of rotamers:

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 9.56 (s, 1H), 7.50 (d, *J* = 3.9 Hz, 1H), 7.47 (dd, *J* = 1.7, 3.3 Hz, 1H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.12 (d, *J* = 8.3 Hz, 2H), 6.41 (dd, *J* = 1.5, 3.4 Hz, 1H), 6.31 (t, *J* = 3.4 Hz, 1H), 6.13 (d, *J* = 3.9 Hz, 1H), 6.03 (d, *J* = 3.1 Hz), 5.81 (ddt, *J* = 3.6, 6.9, 16.9 Hz, 1H), 5.03-4.89 (m, 2H), 3.88 (s, 3H), 2.62-2.47 (m, 2H), 2.32 (s, 3H), 2.04 (q, *J* = 7.1 Hz, 2H), 1.76-1.62 (m, 2H), 1.45-1.18 (m, 17H)

^{13}C NMR (125 MHz, $CDCl_3$): 185.4, 170.3, 150.5, 145.1, 140.8, 139.0, 134.6, 132.5, 129.6, 127.0, 125.8, 125.1, 124.9, 117.4, 116.5, 116.2, 114.0, 111.7, 108.4, 97.9, 57.8, 45.0, 33.6, 29.2, 29.1, 28.95, 28.90, 28.7, 28.1, 26.9, 26.5, 21.5

(4-methoxy-1'-tosyl-1*H*,1'*H*-[2,2'-bipyrrol]-5-yl)(1-(methylsulfonyl)-5-(non-8-en-1-yl)-1*H*-pyrrol-2-yl)methanone (2-46b)



2-46b

To a solution of methyllithium (1.6 M in Et_2O, 0.24 mL, 0.38 mmol, 2.1 eq) in THF (5 mL) at -78 °C, a solution of ketone **2-45** (96.7 mg, 0.18 mmol) in THF (0.5 mL) was added dropwise. The reaction was stirred at -78 °C for 1 h then methanesulfonyl chloride (0.07 mL, 0.90 mmol, 5 eq) was added dropwise. The mixture was then allowed to slowly warm to room temperature overnight (~16 h). The reaction was then concentrated to a brown oil. Purification by flash column chromatography (Si_2O, 9:1→4:1 Hexanes/EtOAc) afforded **2-46b** as brown oil (68.3 mg, 62%) and **2-45** as a brown oil (25 mg, 26% recovered).

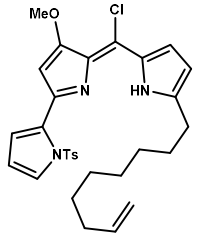
(4-methoxy-1'-tosyl-1*H*,1'*H*-[2,2'-bipyrrol]-5-yl)(1-(methylsulfonyl)-5-(non-8-en-1-yl)-1*H*-pyrrol-2-yl)methanone (2-46b):

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 9.65 (s, 1H), 7.47 (dd, *J* = 1.7, 3.3 Hz, 1H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.18 (d, *J* = 8.4 Hz, 2H), 6.78 (d, *J* = 3.5 Hz, 1H), 6.44 (dd, *J* = 1.7, 3.4 Hz, 1H), 6.30 (t, *J* = 3.4 Hz, 1H), 6.04 (d, *J* = 3.5 Hz, 1H), 5.87 (d, *J* = 3.0 Hz, 1H), 5.81 (ddt, *J* = 3.5, 6.7, 16.9 Hz, 1H), 5.03-4.89 (m, 2H), 3.76 (s, 3H), 3.74 (s, 3H), 2.90 (t, *J* = 7.7 Hz, 2H), 2.32 (s, 3H), 2.08-2.00 (m, 2H), 1.70 (p, *J* = 7.5 Hz, 2H), 1.46-1.20 (m, 8H)

^{13}C NMR (100 MHz, $CDCl_3$) 172.8, 153.6, 145.5, 143.2, 139.1, 134.2, 134.0, 130.0, 127.3, 126.1, 125.5, 125.2, 119.3, 117.5, 116.9, 114.2, 111.8, 109.9, 97.8, 58.1, 44.3, 33.7, 29.4, 29.3, 29.0, 28.9, 28.8, 28.6, 21.6

HRMS (ESI) m/z, 612.2168 (612.2197 calculated for $C_{31}H_{38}N_3O_6S_2^+$, $(M+H)^+$)

(*E*)-5'-(chloro(5-(non-8-en-1yl)-1*H*-pyrrol-2yl)methylene)-4'-methoxy-1-tosyl-1*H*,5'*H*-2,2'-bipyrrole (2-47)



2-47

Method A:

To a suspension of NaH (60% in mineral oil, 17.4 mg, 0.435 mmol, 2.1 eq) in THF (4 mL), a solution of ketone **2-45** (109.5 mg, 0.205 mmol) in THF (0.5 mL) was added dropwise. The solution was stirred at 0 °C for 1.5 h and then oxalyl chloride (27 µL, 0.315 mmol, 1.5 eq) was added dropwise. The reaction was allowed to slowly warm to room temperature overnight (~16 h). The red/brown mixture was then concentrated and purified by flash column chromatography (SiO_2, 9:1→4:1 Hexanes/EtOAc) to afford **2-45** as a brown oil (31.1 mg, 32% recovery) and **2-47** as a light sensitive red oil (12.7 mg, 11%).

Method B:

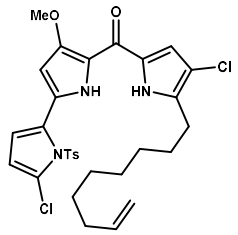
To a solution of ketone **2-45** (0.3017 g, 0.56 mmol) in DCE (3 mL, 0.2 M), freshly distilled $POCl_3$ (0.16 mL, 1.71 mmol, 3 eq) was added dropwise. The mixture immediately turned dark red after the first drop of $POCl_3$. The reaction was then heated to 70 °C for 2.5 h. The reaction was then cooled to room temperature and diluted with DCM (20 mL). The mixture was washed with sat. aqueous $NaHCO_3$ (50 mL). The organics were dried over K_2CO_3, filtered and concentrated to a dark red/black oil. The oil was purified by flash column chromatography (neutral Al_2O_3, 10:1 Hexanes/EtOAc) to afford **2-47** as a dark red oil (0.1462 g, 47%). This material was protected from light with aluminum foil and stored in the freezer at -20 °C.

(*E*)-5'-(chloro(5-(non-8-en-1yl)-1*H*-pyrrol-2yl)methylene)-4'-methoxy-1-tosyl-1*H*,5'*H*-2,2'-bipyrrole (2-47):

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 12.55 (s, 1H), 7.67 (dd, *J* = 1.7, 3.1 Hz, 1H), 7.58 (d, *J* = 8.3 Hz, 2H), 7.09 (d, *J* = 8.2 Hz, 2H), 7.00 (d, *J* = 3.7 Hz, 1H), 6.71 (dd, *J* = 1.6, 3.4 Hz, 1H), 6.35 (t, *J* = 3.4 Hz, 1H), 6.10 (d, *J* = 3.7 Hz, 1H), 5.79 (ddt, *J* = 3.5, 6.7, 16.9 Hz, 1H), 5.76 (s, 1H), 5.00-4.88 (m, 2H), 3.81 (s, 3H), 2.79 (t, *J* = 7.6 Hz, 2H), 2.29 (s, 3H), 2.00 (q, *J* = 7.1 Hz, 2H), 1.68 (p, *J* = 7.5 Hz, 2H), 1.40-1.20 (m, 8H)

HRMS (ESI) m/z, 552.2058 (552.2082 calculated for $C_{30}H_{35}ClN_3O_3S^+$, $(M+H)^+$)

(5'-chloro-4-methoxy-1'-tosyl-1*H*,1'*H*-[2,2'-bipyrrol]-5-yl)(4-chloro-5-(non-8-en-1-yl)-1*H*-pyrrol-2-yl)methanone (2-48)



2-48

To a solution of methyllithium (1.6 M in Et_2O, 0.24 mL, 0.38 mmol, 2.1 eq) in THF (5 mL) at -78 °C, a solution of ketone **2-45** (96.7 mg, 0.18 mmol) in THF (0.5 mL) was added dropwise. The reaction was stirred at -78 °C for 1 h then sulfuryl chloride (20 µL, 0.25 mmol, 1.4 eq) was added dropwise. The reaction was allowed to slowly warm to room temperature overnight (~16 h). The reaction was then concentrated and purified by flash column chromatography (SiO_2, 9:1 Hexanes/EtOAc) to afford **2-48** as a brown oil (44.6 mg, 41%).

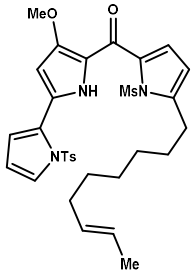
(5'-chloro-4-methoxy-1'-tosyl-1*H*,1'*H*-[2,2'-bipyrrol]-5-yl)(4-chloro-5-(non-8-en-1-yl)-1*H*-pyrrol-2-yl)methanone (2-48):

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 10.38 (s, 1H), 10.30 (s, 1H), 7.55 (d, *J* = 8.3 Hz, 2H), 7.28 (d, *J* = 2.3 Hz, 1H), 7.13 (d, *J* = 8.2 Hz, 2H), 6.33 (d, *J* = 3.5 Hz, 1H), 6.16 (d, *J* = 3.5 Hz, 1H), 6.13 (d, *J* = 2.9 Hz, 1H), 5.86-5.73 (m, 1H), 5.03-4.88 (m, 2H), 4.00 (s, 3H), 2.62 (t, *J* = 7.5 Hz, 2H), 2.30 (s, 3H), 2.03 (q, *J* = 6.9 Hz, 2H), 1.69-1.54 (m, 2H), 1.42-1.18 (m, 8H)

^{13}C NMR (100 MHz, $CDCl_3$): 169.2, 149.8, 145.7, 139.1, 135.1, 134.7, 129.76, 129.70, 128.6, 127.6, 127.4, 127.2, 121.2, 117.4, 116.7, 116.5, 114.2, 111.8, 99.0, 58.3, 33.7, 29.2, 29.1, 29.0, 28.8, 28.6, 25.5, 21.6

HRMS (ESI) m/z, 602.1637 (602.1642 calculated for $C_{30}H_{34}Cl_2N_3O_4S^+$, $(M+H)^+$)

(*E*)-(4-methoxy-1'-tosyl-1*H*,1'*H*-[2,2'-bipyrrol]-5-yl)(1-(methylsulfonyl)-5-(non-7-en-1-yl)-1*H*-pyrrol-2-yl)methanonone (2-50)



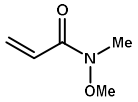
2-50

A 10 mL flask was charged with alkene **2-46b** (0.1912 g, 0.312 mmol) dissolved in dry, deoxygenated acetone (1.5 mL). The flask was then transported into a glove bag, where catalyst **2-49** (3.6 mg, 0.005 mmol, 2 mol %) was added. The reaction was sealed, removed from the glovebag, and stirred under inert atmosphere for 24 h. The reaction was then filtered through a SiO_2 plug with EtOAc. The filtrate was concentrated to afford **2-50** as a brown oil (0.1912 g, quantitative).

(*E*)-(4-methoxy-1'-tosyl-1*H*,1'*H*-[2,2'-bipyrrol]-5-yl)(1-(methylsulfonyl)-5-(non-7-en-1-yl)-1*H*-pyrrol-2-yl)methanonone (2-50):

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 9.64 (s, 1H), 7.48 (dd, *J* = 1.7, 3.2 Hz, 1H), 7.42 (d, *J* = 8.3 Hz, 2H), 7.19 (d, *J* = 8.3 Hz, 2H), 6.78 (d, *J* = 3.6 Hz, 1H), 6.44 (dd, *J* = 1.8, 3.3 Hz, 1H), 6.31 (t, *J* = 3.4 Hz, 1H), 6.04 (d, *J* = 3.7 Hz, 1H), 5.87 (d, *J* = 2.9 Hz, 1H), 5.46-5.36 (m, 2H), 3.77 (s, 3H), 3.75 (s, 3H), 2.90 (t, *J* = 7.7 Hz, 2H), 2.33 (s, 3H), 2.03-1.92 (m, 2H), 1.70 (p, *J* = 7.5 Hz, 2H), 1.66-1.61 (m, 2H), 1.46-1.29 (m, 5H)

***N*-methoxy-*N*-methylacrylamide (2-51)**



2-51

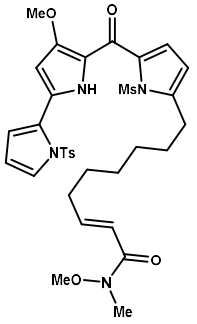
To a solution of NHMe(OMe)·HCl (9.7536 g, 100.01 mmol) in DCM (300 mL, 0.33M) at 0 °C, $NaHCO_3$ (16.8152 g, 200.16 mmol, 2 eq) was added followed by acryloyl chloride (3.57 mL, 50.03 mmol, 1 eq). The reaction was then stirred for 3h at 0 °C. The reaction was then dried over $MgSO_4$, filtered, and concentrated to afford **2-51** (9.8568 g, 86%) as a clear oil.

N-methoxy-N-methylacrylamide (2-51):

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.66 (dd, *J* = 10.4, 17.1 Hz, 1H), 6.34 (dd, *J* = 2.0, 17.1 Hz, 1H), 5.68 (dd, *J* = 2.0, 10.4 Hz, 1H), 3.64 (s, 3H), 3.18 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 166.3, 128.8, 125.9, 61.7, 32.2

(*E*)-*N*-methoxy-9-(5-(4-methoxy-1'-tosyl-1*H*,1'*H*-[2,2'-bipyrrole]-5-carbonyl)-1-(methylsulfonyl)-1*H*-pyrrol-2-yl)-*N*-methylnon-2-enamide (2-52)



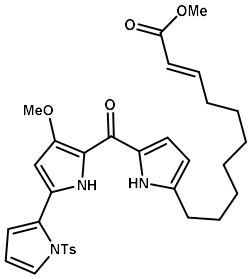
2-52

To a mixture of alkene **2-50** (0.1912 g, 0.312 mmol) and amide **2-50** (0.2265 g, 1.96 mmol, 6 eq) in DCM (10 mL) at room temperature, Grubbs 2nd generation catalyst **2-66** (6.7 mg, 0.007 mmol, 2.5 mol %) was added. The reaction was stirred at room temperature for 12 h. Another portion of **2-66** (6.6 mg, 0.007 mmol, 2.5 mol % was added and the mixture was stirred for an additional 12 hours. The reaction was concentrated and then diluted with Et_2O (20 mL). The mixture was then flushed through a SiO_2 plug with Et_2O (200 mL). The filtrate was concentrated to afford **2-52** as a brown oil (40.5 mg, 19%) that is contaminated with the dimer of **2-51**.

(*E*)-*N*-methoxy-9-(5-(4-methoxy-1'-tosyl-1*H*,1'*H*-[2,2'-bipyrrole]-5-carbonyl)-1-(methylsulfonyl)-1*H*-pyrrol-2-yl)-*N*-methylnon-2-enamide (2-52):

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 9.65 (s, 1H), 7.43-7.39 (m, 1H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.12 (d, *J* = 8.4 Hz, 2H), 6.98-6.85 (m, 1H), 6.75-6.69 (m, 1H), 6.40-6.37 (m, 1H), 6.28-6.22 (m, 2H), 6.01-5.96 (m, 1H), 5.84-5.79 (m, 1H), 5.41-5.29 (m, 1H), 3.70 (s, 3H), 3.67 (s, 3H), 2.84 (q, *J* = 7.4 Hz, 2H), 2.26 (s, 3H), 2.03-1.89 (m, 2H), 1.68-1.60 (m, 2H), 1.40-1.26 (m, 8H)

Methyl (*E*)-10-(5-(4-methoxy-1'-tosyl-1*H*,1'*H*-[2,2'-bipyrrole]-5-carbonyl)-1*H*-pyrrol-2-yl)dec-2-enoate (2-56)



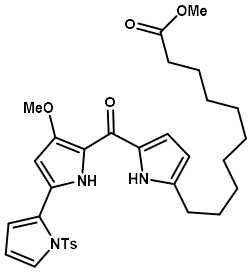
2-56

To a solution of **2-45** (0.1000 g, 0.187 mmol) and methyl acrylate (0.17 mL, 1.87 mmol, 10 eq) in DCM (1.2 mL, 0.15 M), Zhan catalyst **2-55** (13.2 mg, 0.018 mmol, 10 mol %) was added. The mixture was then heated to reflux for 16 hrs. The mixture was then cooled to room temperature and concentrated. The crude oil was purified by flash column chromatography (SiO_2, 1:1 Hexanes/EtOAc) to afford **2-56** (94 mg, 85%) as a brown oil.

Methyl (*E*)-10-(5-(4-methoxy-1'-tosyl-1*H*,1'*H*-[2,2'-bipyrrole]-5-carbonyl)-1*H*-pyrrol-2-yl)dec-2-enoate (2-56):

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 10.05 (bs, 1H), 9.74 (bs, 1H), 7.49-7.45 (m, 1H), 7.43 (d, *J* = 8.2 Hz, 2H), 7.41-7.37 (m, 1H), 7.13 (d, *J* = 8.2 Hz, 2H), 7.02-6.91 (m, 2H), 6.44-6.40 (m, 1H), 6.31 (t, *J* = 3.4 Hz, 2H), 6.09-6.02 (m, 2H), 5.81 (d, *J* = 15.6 Hz, 1H), 3.94 (s, 3H), 3.71 (s, 3H), 2.67 (t, *J* = 7.5 Hz, 2H), 2.22-2.14 (m, 2H), 1.72-1.63 (m, 2H) 1.49-1.25 (m, 8H)

Methyl 10-(5-(4-methoxy-1'-tosyl-1*H*,1'*H*-[2,2'-bipyrrole]-5-carbonyl)-1*H*-pyrrol-2-yl)decanoate (2-57)



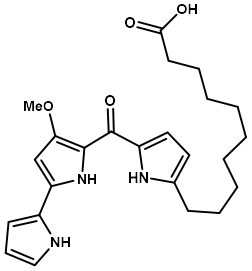
2-57

An autoclave was charged with ester **2-56** (40 mg, 0.067 mmol) and Pd/C (10 wt% on C, 10 mg, 0.0093 mmol, 15 mol %). The mixture was taken up in a 6:1 mixture of MeOH/EtOAc (15 mL, 0.005 M) and pressurized with H_2 (300 psi). The mixture was stirred at room temperature for 7 hrs, when TLC indicated acrylate **2-56** had been consumed. The reaction was then passed through a plug of Celite, which was subsequently rinsed with $CHCl_3$ (2 x 10 mL) and 1:1 MeOH/$CHCl_3$ (2 x 5 mL). The filtrate was concentrated to afford **2-57** (36 mg, 90%).

Methyl 10-(5-(4-methoxy-1'-tosyl-1*H*,1'*H*-[2,2'-bipyrrole]-5-carbonyl)-1*H*-pyrrol-2-yl)decanoate (2-57):

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 10.08 (bs, 1H), 9.76 (bs, 1H), 7.48-7.45 (m, 1H), 7.43 (d, *J* = 8.2 Hz, 2H), 7.41-7.38 (m, 1H), 7.12 (d, *J* = 8.2 Hz, 2H), 6.43-6.41 (m, 1H), 6.30 (t, *J* = 3.4 Hz, 1H), 6.08-6.04 (m, 2H), 3.94 (s, 3H), 3.66 (s, 3H), 2.67 (t, *J* = 7.6 Hz, 2H), 2.31 (s, 3H), 1.73-1.56 (m, 4H), 1.40-1.22 (m, 8H)

Attempted Macroaldolization with Ester 2-57



2-58

To a solution of ester **2-57** (15 mg, 0.0253 mmol) in MeOH (3.6 mL, ~0.01 M), a freshly prepared solution of NaOMe (0.27M in MeOH, 0.2 mL, 0.054 mmol, 2 eq) was added. The mixture was stirred at room temperature for 90 min then equipped with a condenser and warmed to 75 °C for

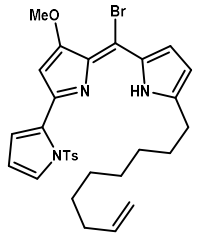
2h. HPLC analysis indicated only partial cleavage of the tosyl group. Another portion of NaOMe (0.3 mL, 0.081 mmol, 3 eq) was added and the mixture was stirred overnight (~17h) at 75 °C. The mixture was then cooled to room temperature, diluted with $CHCl_3$, and quenched with sat. aqueous NH_4Cl. The organics were then dried over $MgSO_4$, filtered, and concentrated. The residue was purified by preparative TLC (SiO_2, 20:1 $CHCl_3$/MeOH) to afford **2-58** as a yellow-green solid.

10-(5-(4-methoxy-1'-tosyl-1*H*,1'*H*-[2,2'-bipyrrole]-5-carbonyl)-1*H*-pyrrol-2-yl)decanoic acid (2-58):

^{1}H NMR (500 MHz, $(CD_3)_2SO$): δ 11.93 (bs, 1H), 11.27 (s, 1H), 11.21 (s, 1H), 10.89 (d, *J* = 2.7 Hz, 1H), 7.12 (dd, *J* = 2.5, 3.5 Hz, 1H), 6.84-6.80 (m, 1H), 6.61-6.57 (m, 1H), 6.27 (d, *J* = 3.0 Hz, 1H), 6.07 (dt, *J* = 2.5, 3.3 Hz, 1H), 5.88 (dd, *J* = 2.5, 3.5 Hz, 1H), 3.82 (s, 3H), 2.56 (t, *J* = 7.6 Hz, 2H), 2.16 (t, *J* = 7.4 Hz, 2H), 1.55 (p, *J* = 7.0 Hz, 2H), 1.46 (p, *J* = 7.1 Hz, 2H), 1.30-1.18 (m, 10H)

^{13}C NMR (125 MHz, $(CD_3)_2SO$): 174.9, 169.9, 151.3, 139.2, 130.1, 130.0, 124.4, 119.6, 116.3, 116.1, 109.4, 107.4, 92.0, 58.1, 34.1, 29.6, 29.3, 29.2, 29.0, 27.4, 24.9

(*E*)-5'-(bromo(5-non-8-en-1-yl)-1*H*-pyrrol-2-yl)methylene)-4'-methoxy-1-tosyl-1*H*,5'*H*-2,2'-bipyrrole (2-64)



2-64

To a solution of ketone **2-45** (0.1984 g, 0.37 mmol) in DCM (3 mL) at room temperature, a solution of freshly sublimed $POBr_3$ (0.1287 g, 0.44 mmol, 1.2 eq) in DCM (1 mL) was added dropwise. The reaction turns dark red after the first drop of $POBr_3$ solution. The mixture was stirred for 9 h. The reaction was diluted with DCM (50 mL) and washed with sat. aqueous $NaHCO_3$ (2 x 50 mL). The organics were dried over K_2CO_3, filtered and concentrated to a dark red oil. The oil was purified by flash column chromatography (neutral Al_2O_3, 15:1 Hexanes/EtOAc) to afford **2-64** as red oil (0.1253 g, 57%). This material was protected from light with aluminum foil and stored at -20 °C.

Recrystallized with MeCN

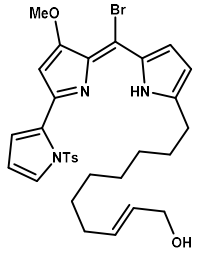
(*E*)-5'-(bromo(5-non-8-en-1-yl)-1*H*-pyrrol-2-yl)methylene)-4'-methoxy-1-tosyl-1*H*,5'*H*-2,2'-bipyrrole (2-64):

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 12.66 (s, 1H), 7.67 (dd, *J* = 1.7, 3.2 Hz, 1H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.10 (d, *J* = 8.2 Hz, 2H), 7.02 (d, *J* = 2.9 Hz, 1H), 6.72 (dd, *J* = 1.8, 3.5 Hz, 1H), 6.35 (t, *J* = 3.3 Hz, 1H), 6.11-6.06 (m, 1H), 5.78 (ddt, *J* = 3.7, 6.7, 16.9 Hz, 1H), 5.77 (s, 1H), 5.00-4.88 (m, 2H), 3.81 (s, 3H), 2.76 (t, *J* = 7.6 Hz, 2H), 2.30 (s, 3H), 1.99 (q, *J* = 7.1 Hz, 2H), 1.67 (p, *J* = 7.4 Hz, 2H), 1.40-1.20 (m, 8H)

^{13}C NMR (125 MHz, $CDCl_3$): 166.9, 153.4, 145.9, 144.8, 139.1, 138.3, 135.0, 130.5, 130.3, 129.4, 128.0, 127.4, 122.9, 119.9, 119.7, 113.9, 111.4, 109.5, 99.1, 58.3, 33.6, 29.2, 29.1, 29.1, 28.9, 28.7, 28.0, 21.4

HRMS (ESI) m/z, 596.1589 (596.1583 calculated for $C_{30}H_{35}BrN_3O_3S^+$, $(M+H)^+$)

(*E*)-10-(5-((*E*)-bromo(4'-methoxy-1-tosyl-1*H*,5'*H*-2,2'-[bipyrrol]-5-ylidene)methyl)-1*H*-pyrrol-2-yl)dec-2-en-1-ol (2-59b)



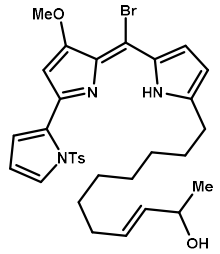
2-59b

To a solution of alkene **2-64** (75.2 mg, 0.12 mmol) in DCM (2 mL), a solution of Grubbs 2nd generation catalyst (5.3 mg, 0.006 mmol, 5 mol %) in DCM (1 mL) was added followed by Ti(O*i*Pr)$_4$ (11 µL, 0.037 mmol, 30 mol %) and allyl alcohol **B** (0.09 mL, 1.32 mmol, 11 eq). The reaction was protected from light with aluminum foil and heated to 35 °C. After 2 h, another portion of Grubbs 2nd generation catalyst was added (2.6 mg, 0.003 mmol, 2.5 mol %). After an additional 2 h, another portion of Grubbs 2nd generation catalyst was added (2.7 mg, 0.003 mmol, 2.5 mol %, 10 mol % overall from the three additions). The reaction was stirred at 35 °C for 24 h total. The reaction was concentrated to a red oil and purified by flash column chromatography (neutral Al_2O_3, 4:1→0:1 Hexanes/EtOAc) to afford **2-59b** as a red oil (64.9 mg, 82%). This material was protected from light with aluminum foil and stored at -20 °C. The product appears as a ~2:1 mixture of prototropisomers by the ^{1}H NMR spectrum.

(*E*)-10-(5-((*E*)-bromo(4'-methoxy-1-tosyl-1*H*,5'*H*-2,2'-[bipyrrol]-5-ylidene)methyl)-1*H*-pyrrol-2-yl)dec-2-en-1-ol (2-59b):

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 12.64 (s, 1H), 7.69-7.63 (m, 1H), 7.56 (d, *J* = 8.2 Hz, 2H), 7.09 (d, *J* = 8.1 Hz, 2H), 7.02-6.97 (m, 1H), 6.74-6.69 (m, 1H), 6.37-6.32 (m, 1H), 6.10-6.05 (m, 1H), 5.76 (s, 1H), 5.69-5.53 (m, 2H), 4.05 (d, *J* = 5.2 Hz, 2H), 3.81 (s, 3H), 2.76 (q, *J* = 7.7 Hz, 2H), 2.30 (s, 3H), 1.98 (q, *J* = 6.8 Hz, 2H), 1.76-1.58 (m, 2H), 1.43-1.28 (m, 8H)

(*E*)-11-(5-((*E*)-bromo(4'-methoxy-1-tosyl-1*H*,5'*H*-2,2'-[bipyrrol]-5-ylidene)methyl)-1*H*-pyrrol-2-yl)undec-3-en-2-ol (2-59c)



2-59c

To a solution of alkene **2-64** (0.1092 g, 0.183 mmol) in DCM (1 mL), Zhan catalyst **2-55** (6.3 mg, 0.009 mmol, 5 mol %) was added followed by 3-buten-2-ol **C** (0.15 mL, 1.74 mmol, ~10 eq). The mixture was then protected from light and warmed to 35 °C. A second portion of **2-55** (5.9 mg, 0.008 mmol, ~5 mol %) dissolved in DCM (1 mL) was added dropwise over 6 h via a syringe pump. The reaction was stirred for 24 h total. The reaction was then concentrated and purified by flash column chromatography (neutral Al_2O_3, 4:1→1:1 Hexanes/EtOAc) to afford **2-59c** as a dark red oil (73.5 mg, 67%) and **2-64** as a red oil (24.2 mg, 22% recovered). This material was protected from light with aluminum foil and stored at -20 °C. The product appears as a ~3:2 mixture of prototropisomers by the ^{1}H NMR spectrum.

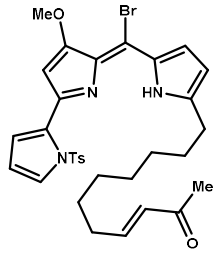
(*E*)-11-(5-((*E*)-bromo(4'-methoxy-1-tosyl-1*H*,5'*H*-2,2'-[bipyrrol]-5-ylidene)methyl)-1*H*-pyrrol-2-yl)undec-3-en-2-ol (2-59c):

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 12.63 (s, 0.6 H), 12.53* (s, 0.4H), 7.67-7.66 (m, 1H), 7.56 (d, *J* = 7.7 Hz, 2H), 7.10 (d, *J* = 7.7 Hz, 2H), 7.01 (d, *J* = 3.8 Hz, 0.6H), 7.00* (d, *J* = 3.8 Hz, 0.4H), 6.72-6.70 (m, 1H), 6.35 (t, *J* = 3.4 Hz, 1H), 6.09-6.07 (m, 1H), 5.77 (s, 0.6H), 5.75* (s, 0.4H), 5.60 (dt, *J* = 15.5, 6.7 Hz, 1H), 5.47 (dd, *J* = 15.5, 6.5 Hz, 1H), 4.25-4.22 (m, 1H), 3.82 (s, 3H), 2.79-2.74 (m, 2H), 2.31 (s, 3H), 1.98-1.93 (m, 2H), 1.68-1.64 (m, 2H), 1.41-1.21 (m, 6H), 1.24 (d, *J* = 6.4 Hz, 3H), 0.89-0.83 (m, 2H)

^{13}C NMR (125 MHz, $CDCl_3$): 167.0, 166.8*, 153.6, 153.4*, 146.0, 145.7*, 144.8, 138.4, 135.2, 134.0, 131.1, 130.8*, 130.6, 130.6, 129.4, 129.3*, 128.0, 127.4, 123.0, 120.4, 119.9, 119.8, 119.6*, 111.4, 11.3*, 109.5, 109.4*, 98.1, 98.0*, 68.6, 58.4, 58.3*, 31.9, 29.3, 29.2*, 29.1, 29.05, 28.99*, 28.9, 28.0, 27.9, 23.3, 21.5

HRMS (ESI) m/z 662.1660 (662.1664 calculated for $C_{32}H_{38}BrN_3O_4SNa$, $(M+Na)^+$).

(*E*)-11-(5-((*E*)-bromo(4'-methoxy-1-tosyl-1*H*,5'*H*-2,2'-[bipyrrol]-5-ylidene)methyl)-1*H*-pyrrol-2-yl)undec-3-en-2-one (2-59d)



2-59d

To a solution of alkene **2-64** (0.3054 g, 0.51 mmol) in DCM (10 mL), Grubbs 2nd generation catalyst **2-66** (21.8 mg, 0.025 mmol, 5 mol %) was added followed by methyl vinyl ketone **D** (0.22 mL, 2.63 mmol, ~5 eq). The reaction was heated to 35 °C for 10 h. Another portion of **2-66** (21.8 mg, 0.025 mmol, 5 mol %) was added and the reaction was stirred for an additional 14 h at 35 °C. The reaction was then concentrated to afford a dark red oil. The crude oil was purified by flash column chromatography (neutral Al_2O_3, 10:1→6:1 Hexanes/EtOAc) to afford **2-59d** (0.1911 g, 59%) as a dark red oil and **2-64** (0.1210 g, 40% recovered) as a red oil. This material was protected from light with aluminum foil and stored at -20 °C. The product appears as a ~7:3 mixture of prototropisomers by the ^{1}H NMR spectrum.

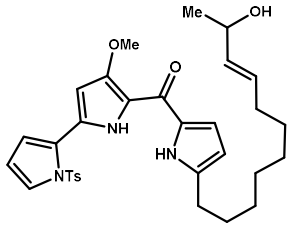
(*E*)-11-(5-((*E*)-bromo(4'-methoxy-1-tosyl-1*H*,5'*H*-2,2'-[bipyrrol]-5-ylidene)methyl)-1*H*-pyrrol-2-yl)undec-3-en-2-one (2-59d):

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 12.65 (bs, 0.7H), 12.54* (bs, 0.3H), 7.67-7.64 (m, 1H), 7.55 (d, *J* = 8.3 Hz, 2H), 7.08 (d, *J* = 8.3 Hz, 2H), 7.00 (d, *J* = 3.9 Hz, 0.7H), 6.98* (d, *J* = 4.0 Hz, 0.3H), 6.76 (dt, *J* = 6.9, 15.9 Hz, 1H), 6.71 (dd, *J* = 1.7, 3.5 Hz, 1H), 6.34 (t, *J* = 3.4 Hz, 1H), 6.09-6.06 (m, 1H), 6.02 (d, *J* = 15.9 Hz, 1H), 5.79 (s, 0.7H), 5.74* (s, 0.3H), 3.80 (s, 3H), 2.75 (t, *J* = 7.5 Hz, 2H), 2.29 (s, 3H), 2.21 (s, 3H), 2.15 (q, *J* = 6.9 Hz, 2H), 1.66 (p, *J* = 7.3 Hz, 2H), 1.46-1.22 (m, 8H)

^{13}C NMR (125 MHz, $CDCl_3$): 198.8, 167.0, 166.9*, 153.7, 153.5*, 148.7, 145.9, 145.7*, 145.0, 138.5, 136.9, 135.2, 135.1, 131.2, 130.7, 130.6*, 129.5, 129.3, 128.1, 127.5, 123.0, 120.4, 120.0, 119.9*, 111.6, 111.5*, 109.6, 109.4*, 99.2, 98.9*, 58.5, 58.4*, 32.4, 29.7, 29.3, 29.1, 29.05, 29.03, 28.0, 27.9, 26.8, 21.6

HRMS (ESI) 638.1684 (638.1688 calculated for $C_{32}H_{37}BrN_3O_4S$, $(M+H)^+$).

(*E*)-(5-(10-hydroxyundec-8-en-1-yl)-1*H*-pyrrol-2-yl)(4-methoxy-1'-tosyl-1*H*,1'*H*-[2,2'-bipyrrol]-5-yl)methanone (2-69)



2-69

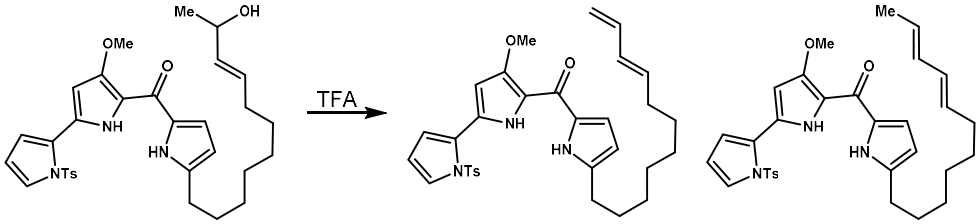
To a refluxing (40 °C) solution of alkene **2-45** (0.1024 g, 0.19 mmol) and 3-buten-2-ol **C** (0.16 mL, 1.85 mmol, ~10 eq) in DCM (3 mL, 0.05 M overall), Grubbs 2nd generation catalyst **2-66** (12.2 mg, 0.014 mmol, 7.5 mol %) in DCM was added dropwise over 3 hrs. The reaction was stirred at reflux for 19 hrs overall. The mixture was concentrated to a brown oil, which was purified by flash column chromatography (SiO_2, 4:1→2:1→1:1 Hexanes/EtOAc) to afford **2-69** (0.0831 g, 75%) as a brown oil and **2-45** (0.0257 g, 25% recovered) as a brown oil. The spectral data for alcohol **2-69** prepared by this method matched the material isolated from intramolecular Heck attempts.

(*E*)-(5-(10-hydroxyundec-8-en-1-yl)-1*H*-pyrrol-2-yl)(4-methoxy-1'-tosyl-1*H*,1'*H*-[2,2'-bipyrrol]-5-yl)methanone (2-69):

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 10.10 (bs, 1H), 9.76 (bs, 1H), 7.48-7.44 (m, 1H), 7.42 (d, *J* =8.2 Hz, 2H), 7.40-7.38 (m, 1H), 7.12 (d, *J* = 8.2 Hz, 2H), 6.42 (dd, *J* =1.7, 3.3 Hz, 1H), 6.30 (t, *J* = 3.3 Hz, 1H), 6.07-6.03 (m, 2H), 5.61 (dt, *J* = 6.6, 15.4 Hz, 1H), 5.50 (dd, *J* = 6.5, 15.4 Hz, 1H), 4.25 (p, *J* = 6.5 Hz, 1H), 3.93 (s, 3H), 2.66 (t, *J* = 7.6 Hz, 2H), 2.30 (s, 3H), 2.00 (q, *J* = 6.9 Hz, 2H), 1.67 (p, *J* = 7.2 Hz, 2H), 1.40-1.27 (m, 8H), 1.24 (d, *J* = 6.5 Hz, 3H)

^{13}C NMR (125 MHz, $CDCl_3$): 169.7, 149.2, 145.3, 139.4, 134.7, 134.1, 131.0, 129.8, 129.7, 128.8, 128.4, 127.1, 126.1, 125.0, 124.9, 117.4, 116.6, 111.9, 108.5, 97.9, 68.9, 58.2, 32.0, 29.1, 29.08, 29.04, 28.9, 27.9, 23.4, 21.6

Dehydration of Hydrolysis Product to Produce Acyclic Dienes



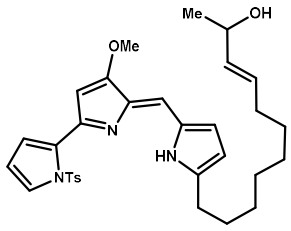
2-69 2-70b 2-70c

To a solution of alcohol (20.7 mg, 0.035 mmol) in benzene (4 mL, 0.01M), TFA (0.06 mL, 0.78 mmol, ~20 eq) was added dropwise. The mixture was heated to 60 °C for 3 hrs. The reaction was then cooled to room temperature and diluted with EtOAc (10 mL). The mixture was washed with saturated $NaHCO_3$ (10 mL) and brine (10 mL). The organics were dried with $MgSO_4$, filtered, and concentrated to a yellow-brown oil. The inseparable mixture of olefin isomers decomposed with

extended exposure to SiO_2. The crude ^1H NMR spectrum is provided below, which corresponds to the material isolated from the intramolecular Heck attempts.

(E)-(4-methoxy-1'-tosyl-1H,1'H-[2,2'-bipyrrol]-5-yl)(5-(undeca-8,10-dien-1-yl)-1H-pyrrol-2-yl)methanone (2-70b) & (4-methoxy-1'-tosyl-1H,1'H-[2,2'-bipyrrol]-5-yl)(5-((7E,9E)-undeca-7,9-dien-1-yl)-1H-pyrrol-2-yl)methanone (2-70c):
Crude ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 10.08 (bs, 1H), 9.75 (bs, 1H), 7.48-7.45 (m, 1H), 7.43 (d, *J* = 8.2 Hz, 2H), 7.41-7.37 (m, 1H), 7.12 (d, *J* = 8.2 Hz, 2H), 6.44-6.39 (m, 1H), 6.33-6.28 (m, 2H), 6.09-6.04 (m, 2H), 6.03-4.89 (m, 4H), 3.93 (s, 3H), 2.67 (t, *J* = 7.5 Hz, 2H), 2.31 (s, 3H), 2.09-1.97 (m, 2H), 1.70-1.60 (m, 2H), 1.43-1.20 (m, 8H)

(*E*)-11-(5-((*Z*)-(4'-methoxy-1-tosyl-1*H*,5'*H*-[2,2'-bipyrrol]-5-ylidene)methyl)-1*H*-pyrrol-2-yl)undec-3-en-2-ol (2-71)

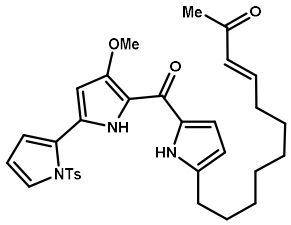


2-71

A Schlenk tube was charged with Pd cat **2-74** (1.5 mg, 0.002 mmol, 5 mol%), K_2CO_3 (28 mg, 0.202 mmol, 2 eq), and NBu_4Br (14 mg, 0.043 mmol, ~45 mol%). The system was evacuated and refilled with Argon thrice. A solution of **2-59c** (64 mg, 0.099 mmol) in DMF (20 mL, 0.005M) was sparged with Argon for 10 minutes, then added to the Schlenk tube. The reaction was wrapped with aluminum foil and kept in the dark. The mixture was heated to 100 °C and stirred overnight (~16h). The reaction was diluted with EtOAc and washed with saturated aqueous $NaHCO_3$. The organics were then washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was then purified by flash column chromatography (SiO_2, 2:1→1:1 Hexanes/EtOAc) to afford **2-71** (6.5 mg, 10%) and **2-70b/c** (4.5 mg, 8%).

(*E*)-11-(5-((*Z*)-(4'-methoxy-1-tosyl-1*H*,5'*H*-[2,2'-bipyrrol]-5-ylidene)methyl)-1*H*-pyrrol-2-yl)undec-3-en-2-ol (2-71):
^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.66 (dd, *J* = 1.6, 3.2 Hz, 1H), 7.60 (d, *J* = 8.4 Hz, 2H), 7.08 (d, *J* = 8.4 Hz, 2H), 6.82 (s, 1H), 6.68 (dd, *J* = 1.8, 3.6 Hz, 1H), 6.59 (d, *J* = 3.6 Hz, 1H), 6.34 (t, *J* = 3.4 Hz, 1H), 6.04 (d, *J* = 3.6 Hz, 1H), 5.65 (s, 1H), 5.59 (dt, *J* = 6.7, 15.2 Hz, 1H), 5.50-5.43 (m, 1H), 4.29-4.18 (m, 1H), 3.77 (s, 3H), 2.76 (t, *J* = 7.6 Hz, 2H), 2.29 (s, 3H), 1.95 (q, *J* = 6.9 Hz, 2H), 1.68 (p, *J* = 7.5 Hz, 2H), 1.44-1.18 (m, 8H), 1.23 (d, *J* = 6.4 Hz, 3H)

(E)-11-(5-(4-methoxy-1'-tosyl-1H,1'H-[2,2'-bipyrrole]-5-carbonyl)-1H-pyrrol-2-yl)undec-3-en-2-one (2-76)

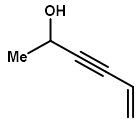


2-76

(Note: This material was never purified and fully characterized. The reappearance of two pyrrolic protons and the crude residue's yellow brown color led to the assumption that this was the product.)

Crude ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 12.53 (s, 0.3H), 10.00 (s, 1H), 9.73 (s, 1H), 7.73 (d, *J* = 15.8 Hz, 4H), 7.64-7.59 (m, 4H), 7.48-7.37 (m, 12H), 7.18-7.03 (m, 4H), 7.08 (d, *J* = 15.8 Hz, 4H), 6.88-6.69 (m, 4H), 6.46-6.26 (m, 4H), 6.13-5.96 (m, 4H), 3.93 (s, 3H), 2.83-2.59 (m, 2H), 2.89-2.60 (m, 8H), 2.45-2.0 (m, 31 H), 2.02-0.70 (m, 120H)

Hex-5-en-3-yn-2-ol (2-82)

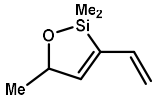


2-82

To a solution of vinyl bromide (1M in THF, 225 mL, 225 mmol, 5 eq) in THF (180 mL), $PdCl_2(COD)_2$ (0.129 g, 0.45 mmol, 1 mol %), PPh_3 (0.236 g, 0.9 mmol, 2 mol %), and CuI (0.3 g, 1.58 mmol, 3.5 mol %) were added followed by diisopropylamine (12.7 mL, 90 mmol, 2 eq). The reaction mixture turned dark yellow. 3-butyn-2-ol (3.64 mL, 45 mmol) was added and the mixture was stirred at room temperature for 20 h. The mixture was then filtered through a layer of Celite and carefully concentrated (220 mbar with a 40 °C water bath). The crude oil was purified by flash column chromatography (SiO_2, 5:1 Hexanes/EtOAc) to afford **2-82** (7.2 g, 60 wt % in hexanes, quant.) as a clear oil.

Hex-5-en-3-yn-2-ol (2-82):
^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 5.81 (ddd, *J* = 1.8, 11.0, 17.4 Hz, 1H), 5.64 (dd, *J* = 2.1, 17.4 Hz, 1H), 5.48 (dd, *J* = 2.1, 11.0 Hz, 1H), 4.64 (dq, *J* = 1.8, 6.4 Hz, 1H), 1.47 (d, *J* = 6.4 Hz, 3H)

2,2,5-trimethyl-3-vinyl-2,5-dihydro-1,2-oxasilole (2-78)



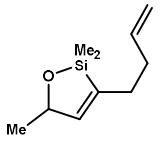
2-78

To a solution of alcohol **2-82** (3.2 g, 60 wt % in hexanes, ~20 mmol) in THF (60 mL, 0.3 M), tetramethyldisilazane (1.8 mL, 10 mmol, 0.5 eq) was added. The mixture was stirred at room

temperature for 16 hrs. The reaction mixture was then carefully concentrated (40 mbar with a 40 °C water bath).
The crude oil was then treated with KO^{t}Bu (0.2 M in THF, 10 mL, 2 mmol, 10 mol %). The mixture was allowed to stir for 1 hr. The reaction was then diluted with Et_2O (50 mL) and saturated NH_4Cl (50 mL). The organic layer was then washed with brine (50 mL) and dried over $MgSO_4$ and filtered. The organics were carefully concentrated to afford a crude orange oil. The oil was purified by flash column chromatography (SiO_2 pretreated with 0.5% Et_3N in Hexanes, 80:1→60:1→40:1 Hexanes/EtOAc) to afford **2-78** (1.26 g, ~41% over two steps) as a yellow oil.

2,2,5-trimethyl-3-vinyl-2,5-dihydro-1,2-oxasilole (2-78):
^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 6.60 (dd, *J* = 10.1, 17.4 Hz, 1H), 6.56-6.54 (m, 1H), 5.14-5.05 (m, 2H), 4.85-4.80 (m, 1H), 1.27 (d, *J* = 6.6 Hz, 3H), 0.35 (s, 3H), 0.32 (s, 3H)

3-(but-3-en-1yl)-2,2,5-trimethyl-2,5-dihydro-1,2-oxasilole (2-83)

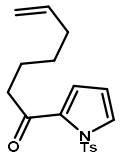


2-83

To neat **2-78** (1.25 g, 8.1 mmol), a solution of 9-BBN in THF (0.5M in THF, 17.5 mL, 8.75 mmol, 1.08 eq) was added. The mixture was then refluxed for 2 hrs. The reaction was then cooled to room temperature and diluted with DMF (35 mL). $PdCl_2$(dppf)·DCM (0.33 g, 0.4 mmol, 5 mol %), K_2CO_3 (2.3 g, 16.5 mmol, 2.05 eq), and vinyl bromide (1M in THF, 10 mL, 1.25 eq) were added and the mixture was heated to 55 °C for 22 hrs. The mixture was cooled to room temperature and diluted with EtOAc (50 mL) and H_2O (100 mL). The organic layer was then washed with H_2O (100 mL x 2) and brine (50 mL), dried over $MgSO_4$, filtered and concentrated. The crude was then purified by flash column chromatography (SiO_2 pretreated with 0.5% Et_3N in Hexanes, 80:1→60:1→40:1 Hexanes/EtOAc) to afford **2-83** (0.497 g, 31%) as a yellow green oil contaminated with ~9% **2-78**.

3-(but-3-en-1yl)-2,2,5-trimethyl-2,5-dihydro-1,2-oxasilole (2-83):
^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 6.35-6.32 (m, 1H), 5.82 (ddt, *J* = 6.4, 10.2, 16.8 Hz, 1H), 5.07-4.95 (m, 2H), 4.77-4.70 (m, 1H), 2.34-2.29 (m, 2H), 2.22-2.14 (m, 2H), 1.23 (d, *J* = 6.5 Hz, 3H), 0.25 (s, 3H), 0.23 (s, 3H)

1-(1-tosyl-1*H*-pyrrol-2-yl)hept-6-en-1-one



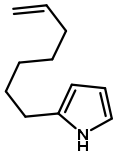
To a solution of tosyl pyrrole **2-27** (5 g, 22.59 mmole) and hept-6-enoic acid **2-84** (4.3 g, 33.54 mmol, 1.5 eq – prepared according to Kadyrov, R. *Chem. Eur. J.* **2013**, *19(3)*, 1002-1012) in DCE (48 mL, 0.5 M), trifluoroacetic anhydride (48 mL, 339.83 mmol, 15 eq) at 0 °C. The mixture was then warmed to reflux for 27 h. The reaction was concentrated and then dissolved in DCM (100

mL). The mixture was washed with sat. aqueous $NaHCO_3$ (2 x 100 mL). The organics were dried over $MgSO_4$, filtered and concentrated to a dark orange oil. The crude was purified by flash column chromatography (SiO_2, 19:1 Hexanes/EtOAc) to afford an orange oil (6.2 g, 83%).

1-(1-tosyl-1*H*-pyrrol-2-yl)hept-6-en-1-one:
^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.88 (d, *J* = 8.2 Hz, 2H), 7.80-7.76 (m, 1H), 7.30 (d, *J* = 8.2 Hz, 2H), 7.01 (d, *J* = 3.3 Hz, 1H), 6.31 (t, *J* = 3.3 Hz, 1H), 5.75 (ddt, *J* = 6.7, 10.3, 17.1 Hz, 1H), 5.01-4.89 (m, 2H), 2.67 (t, *J* = 7.4 Hz, 2H), 2.41 (s, 3H), 2.02 (q, *J* = 7.1 Hz, 2H), 1.61 (p, *J* = 7.6 Hz, 2H), 1.35 (p, *J* = 7.6 Hz, 2H)

^{13}C NMR (125 MHz, $CDCl_3$): 188.7, 144.5, 138.3, 135.8, 133.2, 129.9, 129.7, 129.2, 128.1, 123.0, 114.4, 110.0, 39.1, 33.3, 28.2, 24.2, 21.5

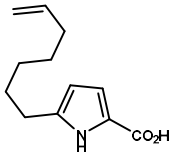
2-(hept-6-en-1-yl)-1*H*-pyrrole



To a stirred suspension of sodium borohydride (3.537 g, 93.5 mmol, 5 eq) in isopropanol (55 mL), the above obtained orange oil (6.2 g, 18.7 mmol) in isopropanol (20 mL) was added dropwise. The reaction was then heated to reflux for 48 h. The reaction was then cooled to 0 °C and H_2O (100 mL) was slowly added to the mixture. The mixture was then extracted with DCM (3 x 100). The organics were then dried over $MgSO_4$, filtered and concentrated to an orange oil (3.0 g, 98%). This material was used in the next step without purification.

2-(hept-6-en-1-yl)-1*H*-pyrrole:
^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.90 (s, 1H), 6.66 (dd, *J* = 2.4, 3.8 Hz, 1H), 6.13 (dd, *J* = 2.8, 5.5 Hz, 1H), 5.94-5.89 (m, 1H), 5.81 (ddt, *J* = 6.6, 10.2, 16.9 Hz, 1H), 5.05-4.90 (m, 2H), 2.60 (t, *J* = 7.6 Hz, 2H), 2.05 (q, *J* = 6.9 Hz, 2H), 1.63 (p, *J* = 7.5 Hz, 2H), 1.47-1.34 (m, 2H)

5-(hept-6-en-1-yl)-1*H*-pyrrole-2-carboxylic acid (2-85)



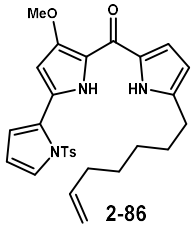
2-85

To a solution of alkenyl pyrrole obtained above (3.0 g, 18.7 mmol) in Et_2O (60 mL) at 0 °C, trichloroacetyl chloride (2.1 mL, 18.7 mmol, 1 eq) was added. The mixture was stirred at 0 °C for 1.5 h. The reaction was then concentrated to a red oil and redissolved in DME (23 mL). A 2 M aqueous sodium hydroxide solution (47 mL, 94 mmol, 5 eq) was then added to the mixture. The reaction was stirred at room temperature for 45 minutes. The reaction was then acidified with aqueous 2M HCl (50 mL) and extracted with DCM (3 x 50 mL). The organics were then dried over $MgSO_4$, filtered and concentrated to a black/brown oil. The oil was purified by flash column

chromatography (SiO_2, 3:1 Hexanes/EtOAc) to afford **2-85** as a brown oil (2.8 g, 74%, 60% from **2-84**).

5-(hept-6-en-1-yl)-1*H*-pyrrole-2-carboxylic acid (2-85):
^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 9.00 (s, 1H), 6.98-6.92 (m, 1H), 6.09-6.00 (m, 1H), 5.80 (ddt, *J* = 6.6, 10.1, 16.9 Hz, 1H), 5.03-4.90 (m, 2H), 2.65 (t, *J* = 7.5 Hz, 2H), 2.05 (q, *J* = 6.9 Hz, 2H), 1.65 (p, *J* =7.5 Hz, 2H), 1.47-1.30 (m, 2H)

Acylation of Bipyrrole 2-11 with Alkenyl Pyrrole Acid 2-85

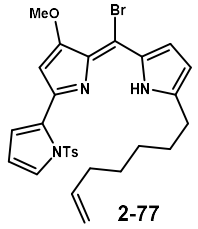


2-86

To a solution of acid **2-85** (0.63 g, 3.03 mmol, 1.5 eq to **2-11**) in DCM (12 mL) at room temperature, freshly distilled oxalyl chloride (0.24 mL, 2.74 mmol, 2 eq) was added dropwise (**NOTE*:** vigorous gas evolution). The reaction was stirred at room temperature for 1 hr. The reaction was then concentrated to a brown oil and digested in 8 mL of THF. This process was repeated three times to afford the acyl chloride as a solution in THF used immediately.
As the acyl chloride is forming, a 50 mL flask is charged with freshly prepared **2-11** (0.667 g, 2.1 mmol) and dissolved in THF (6 mL). The reaction was then cooled to -78 °C and methylmagnesium bromide (3 M in Et_2O, 0.95 mL, 2.86 mmol, 1.3 eq) was added dropwise. The reaction was then stirred for 30 minutes. The THF solution of acid chloride prepared above was then added dropwise over 10 minutes. The reaction was allowed to slowly warm to room temperature over 18 hours. The reaction was then quenched by the addition of MeOH (5 mL) and concentrated to a paste. The crude paste was dissolved in EtOAc (100 mL) and washed with sat. aqueous NH_4Cl (100 mL). The organics were dried with $MgSO_4$, filtered and concentrated to a black oil. This material was purified by flash column chromatography (SiO_2, 6:1→5:1→4:1→3:1→2.5:1 Hexanes/EtOAc) to afford **2-86** as a brown foam (302 mg, 28%) and recovered **2-11** as an unstable yellow oil (245 mg, 37% recovered).

(5-(hept-6-en-1-yl)-1*H*-pyrrol-2-yl)(4-methoxy-1'-tosyl-1*H*,1'*H*-[2,2'-bipyrrol]-5-yl)methanone (2-86):
^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 10.04 (bs, 1H), 9.72 (bs, 1H), 7.47 (dd, *J* = 1.8, 3.4 Hz, 1H), 7.44 (d, *J* = 8.2 Hz, 2H), 7.40-7.37 (m, 1H), 7.13 (d, *J* = 8.2 Hz, 2H), 6.42 (dd, *J* = 1.8, 3.4 Hz, 1H), 6.31 (t, *J* = 3.4 Hz, 1H), 6.09-6.04 (m, 2H), 5.81 (ddt, *J* = 6.7, 10.1, 16.9 Hz, 1H), 5.03-4.92 (m, 2H), 3.94 (s, 3H), 2.68 (t, *J* = 7.6 Hz, 2H), 2.06 (q, *J* = 7.2 Hz, 2H), 1.69 (p, *J* = 7.4 Hz, 2H), 1.48-1.25 (m, 4H)

(*E*)-5'-(bromo(5-(hept-6-en-1-yl)-1*H*-pyrrol-2-yl)methylene)-4'-methoxy-1-tosyl-1*H*,5'*H*-2,2'-bipyrrole (2-77)



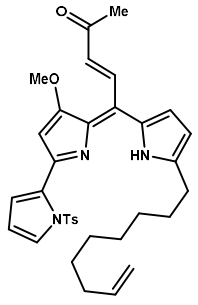
2-77

To a solution of ketone **2-86** (0.6519 g, 1.29 mmol) in DCM (5.5 mL), a solution of freshly sublimed $POBr_3$ (0.5596 g, 1.95 mmol, 1.5 eq) in DCM (1 mL) was added dropwise. The reaction turned dark red after the first few drops of $POBr_3$. The reaction was then heated to 35 °C for 2 h. The reaction was then cooled to room temperature, diluted with DCM (50 mL), and quenched with sat. aqueous $NaHCO_3$ (100 mL). The aqueous layer was extracted with DCM (2 x 25 mL). The combined organics were then dried over K_2CO_3, filtered and concentrated to a dark red oil. The oil was purified by flash column chromatography (neutral Al_2O_3, 15:1 Hexanes/EtOAc) to afford **2-77** as a red oil (0.2985 g, 41%). This material was protected from light with aluminum foil and stored at -20 °C.

(*E*)-5'-(bromo(5-(hept-6-en-1-yl)-1*H*-pyrrol-2-yl)methylene)-4'-methoxy-1-tosyl-1*H*,5'*H*-2,2'-bipyrrole (2-77):

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 12.64 (bs, 1H), 7.69-7.64 (m, 1H), 7.57 (d, J = 8.2 Hz, 2H), 7.10 (d, J = 8.2 Hz, 2H), 7.01 (d, J = 3.6 Hz, 1H), 6.74-6.70 (m, 1H), 6.35 (t, J = 3.4 Hz, 1H), 6.07 (d, J = 3.6 Hz, 1H), 5.82-5.72 (m, 2H), 5.00-4.87 (m, 2H), 3.82 (s, 3H), 2.81-2.70 (m, 2H), 2.31 (s, 3H), 2.05-1.95 (m, 2H), 1.73-1.66 (m, 2H), 1.43-1.33 (m, 4H)

(3*E*, 5*Z*)-5-(4'-methoxy-1-tosyl-1*H*,5'*H*-[2,2'-bipyrrol]-5'-ylidene)-5-(5-(non-8-en-1-yl)-1*H*-pyrrol-2-yl)pent-3-en-2-one (2-88)



2-88

A flame dried 25 mL Schlenk tube was charged with bromide **2-64** (22.5 mg, 0.037 mmol) in MeCN (0.4 mL, 0.1 M). The mixture was then degassed via three freeze-pump-thaw cycles. Methyl vinyl ketone (5 µL, 0.059 mmol, ~1.5 eq) was then added and the flask was placed in a glove bag under an Ar atmosphere, where $Pd(P\textit{t}Bu_3)_2$ (3.0 mg, 5.87 µmol, 15 mol %) was added. The flask was then removed from the glove bag and Cy_2NMe (0.04 mL, 0.186 mmol, 5 eq) was then added. The reaction mixture was then heated to 80 °C until TLC indicated starting material consumed (~2.5 hours). The reaction was cooled to room temperature and concentrated. The crude

red residue was purified by pTLC (neutral Al_2O_3, 2:1 Hexanes/EtOAc) to afford **2-88** (20.4 mg, 81%, 2:1 mixture of **2-88**/Cy_2NMe) as a purple/black oil.

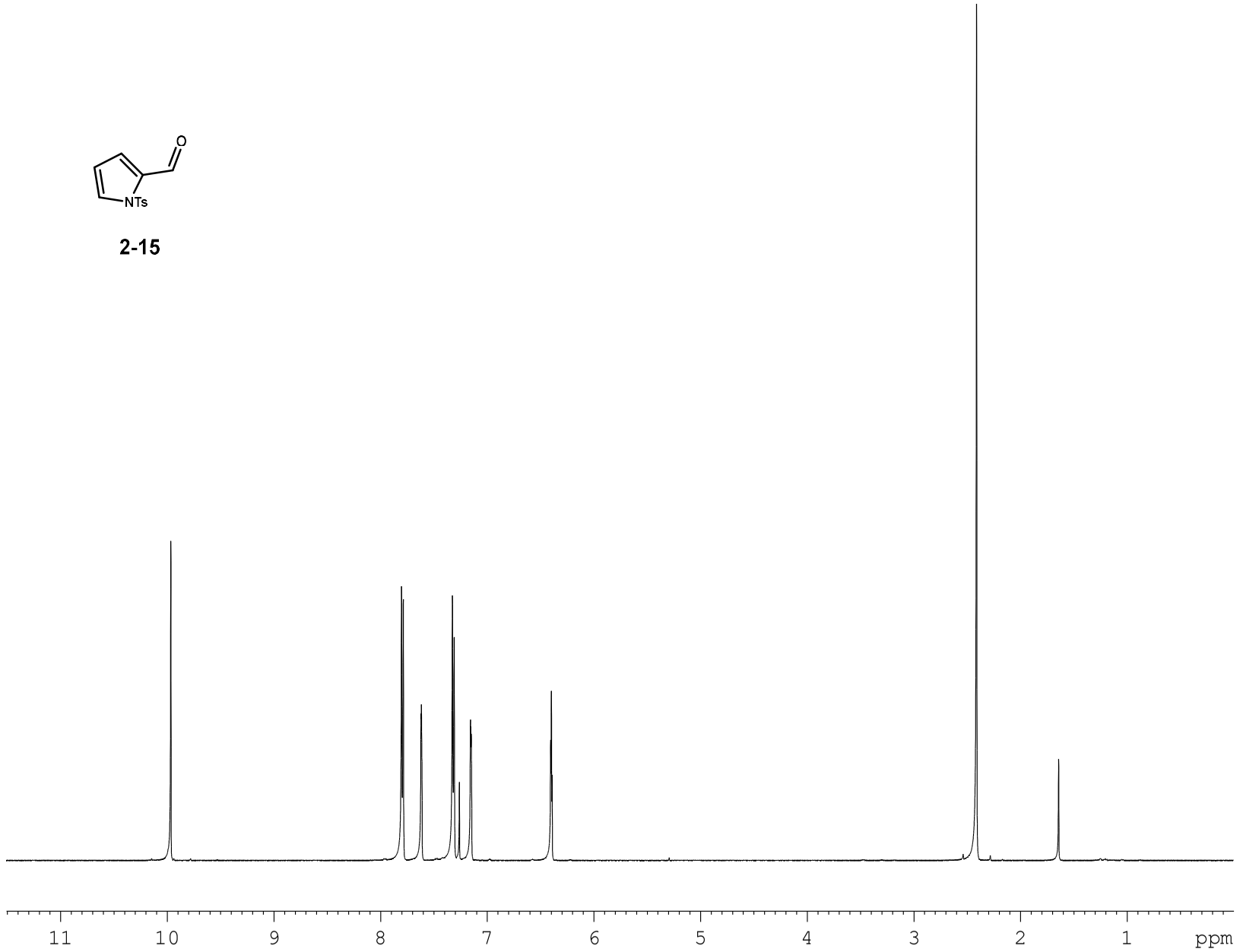
(3*E*, 5*Z*)-5-(4'-methoxy-1-tosyl-1*H*,5'*H*-[2,2'-bipyrrol]-5'-ylidene)-5-(5-(non-8-en-1-yl)-1*H*-pyrrol-2-yl)pent-3-en-2-one (2-88):

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 12.68 (bs, 1H), 8.11 (d, *J* = 16.2 Hz, 1H), 7.67-7.63 (m, 1H), 7.58 (d, *J* = 8.2 Hz, 2H), 7.09 (d, *J* = 8.2 Hz, 2H), 6.73-6.71 (m, 1H), 6.69 (d, *J* = 16.2 Hz, 1H), 6.35 (t, *J* = 3.2 Hz, 1H), 6.07 (d, *J* = 3.2 Hz, 1H), 5.83-5.72 (m, 2H), 4.99-4.86 (m, 2H), 3.81 (s, 3H), 2.78 (t, *J* = 7.6 Hz, 2H), 2.40 (s, 3H), 2.30 (s, 3H), 1.99 (q, *J* = 7.0 Hz, 2H), 1.71-1.64 (m,2H)1.39-1.17 (m, 8H)

^{13}C NMR (125 MHz, $CDCl_3$ as a 1:1 mixture with Cy_2NMe): 198.8, 167.1, 155.2, 145.8, 144.9, 141.1, 139.2, 138.1, 135.3, 135.0, 131.6, 131.1, 130.9, 129.4, 128.6, 128.2, 127.5, 124.5, 120.7, 119.9, 114.0, 111.6, 109.4, 98.6, 59.3, 58.8, 53.4, 33.7, 32.8, 30.5, 29.4, 29.35, 29.27, 29.25, 29.0, 28.9, 28.9, 28.1, 27.2, 26.3, 26.2, 21.6

LRMS (ESI) m/z, 586.3 (586.3 calculated for $C_{34}H_{40}N_3O_4S^+$, $(M+H)^+$)

2.4.3. NMR Spectra Relevant to Chapter 2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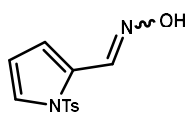

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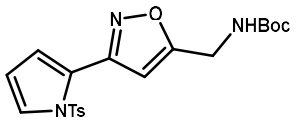

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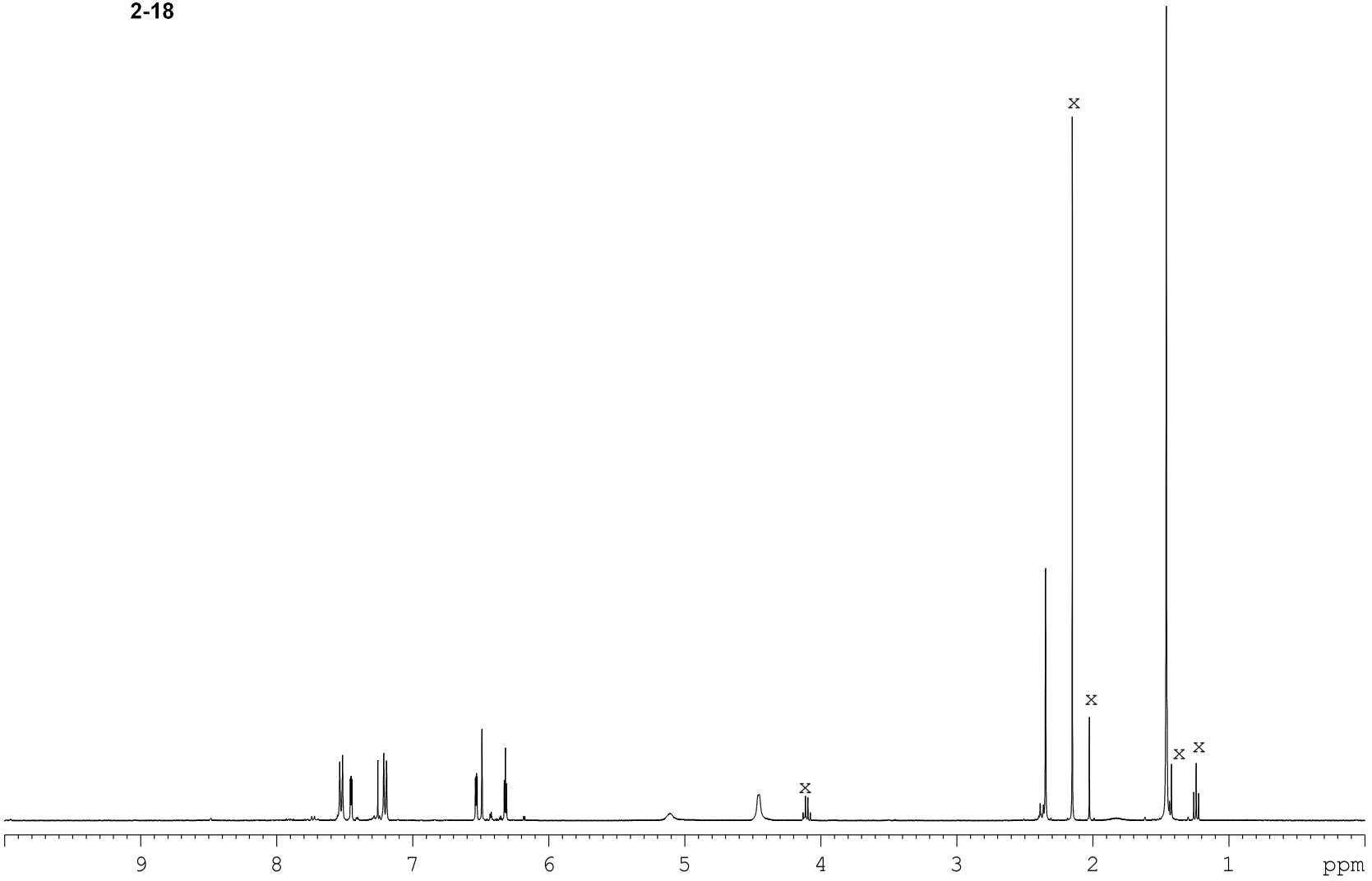

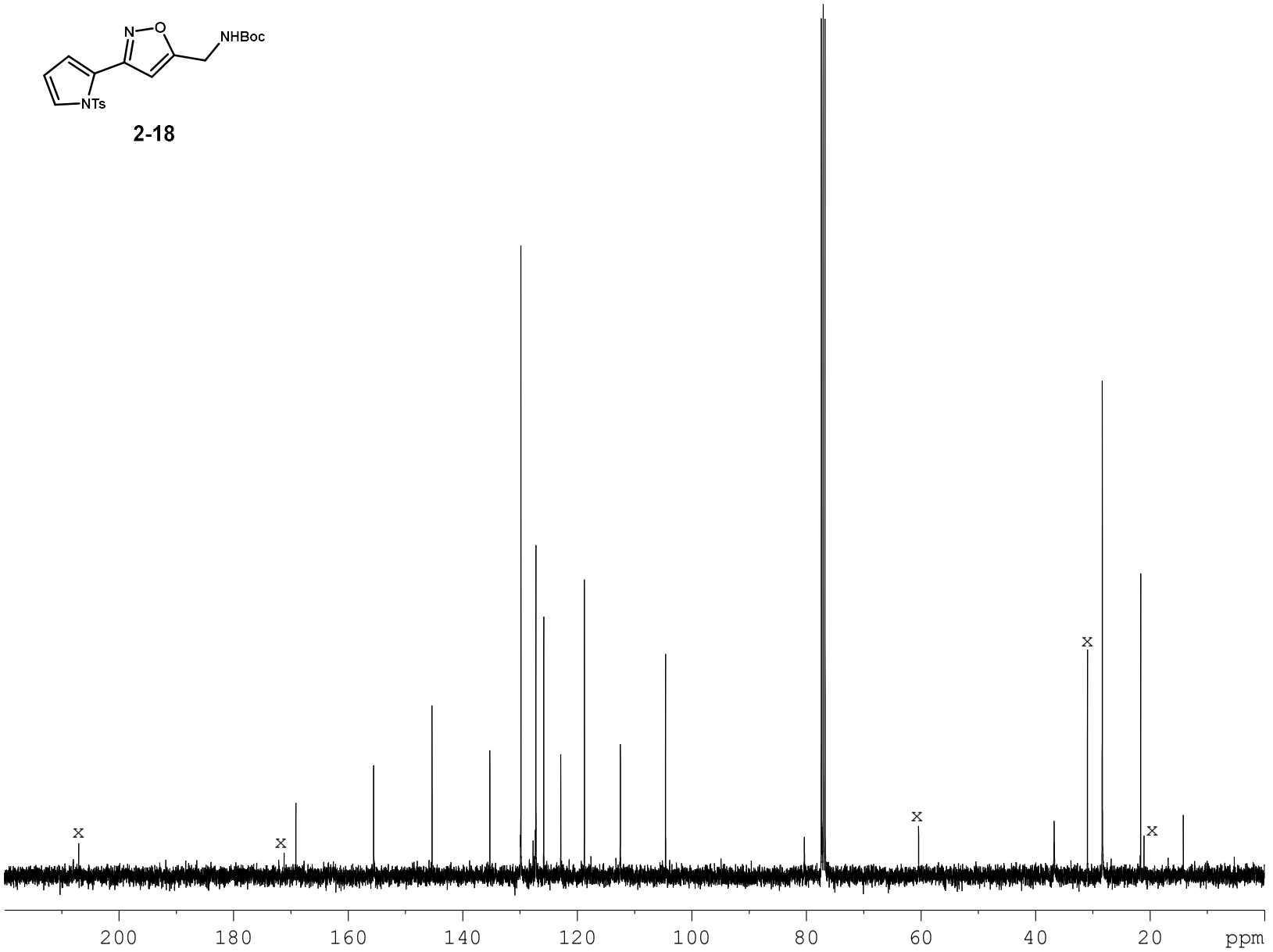
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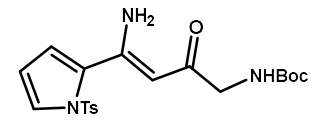

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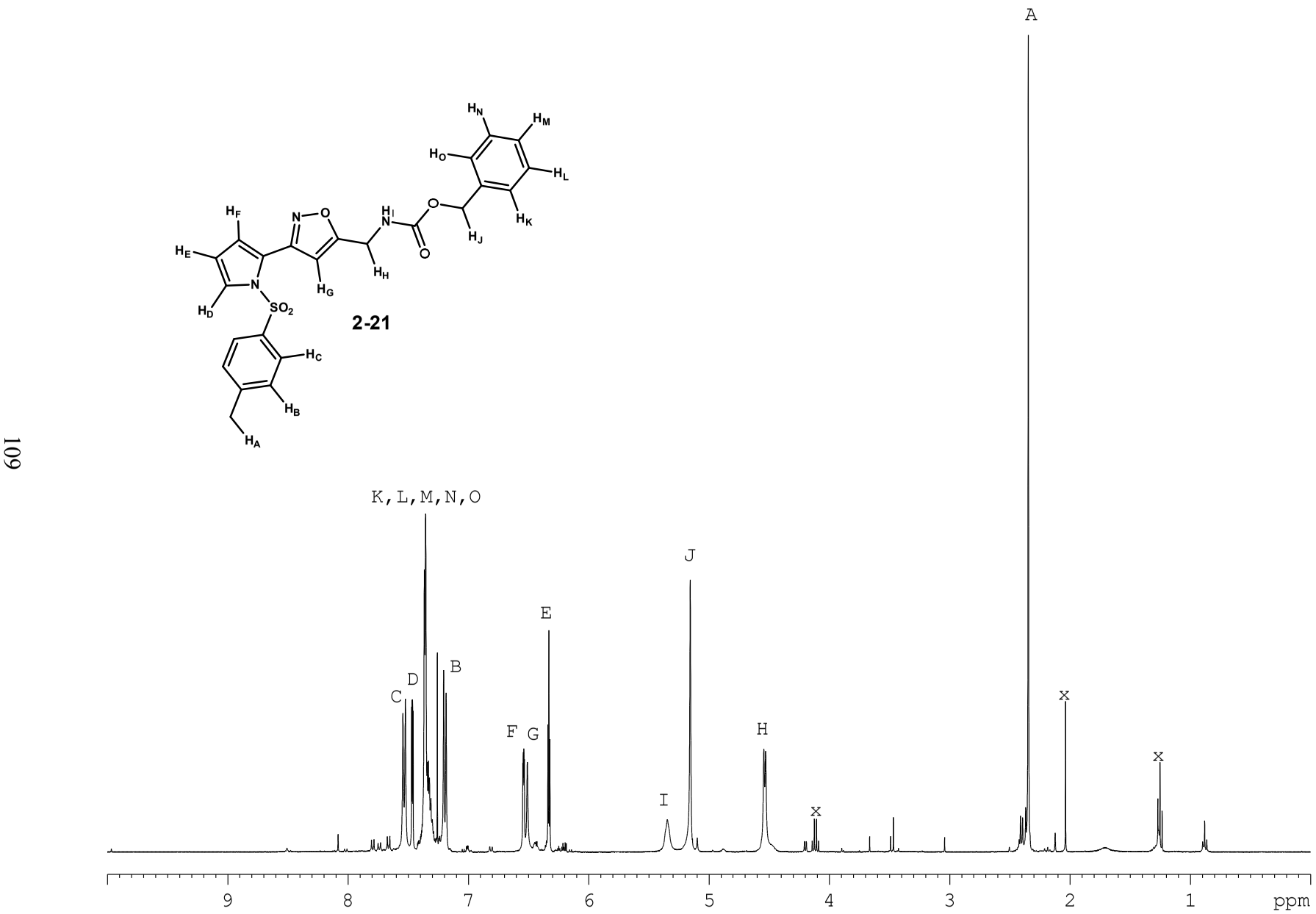
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K,L,M,N,O
J
E
B
D
C
F G
I
H
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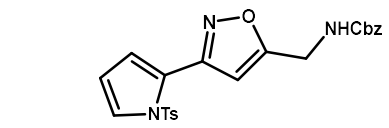

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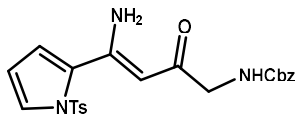

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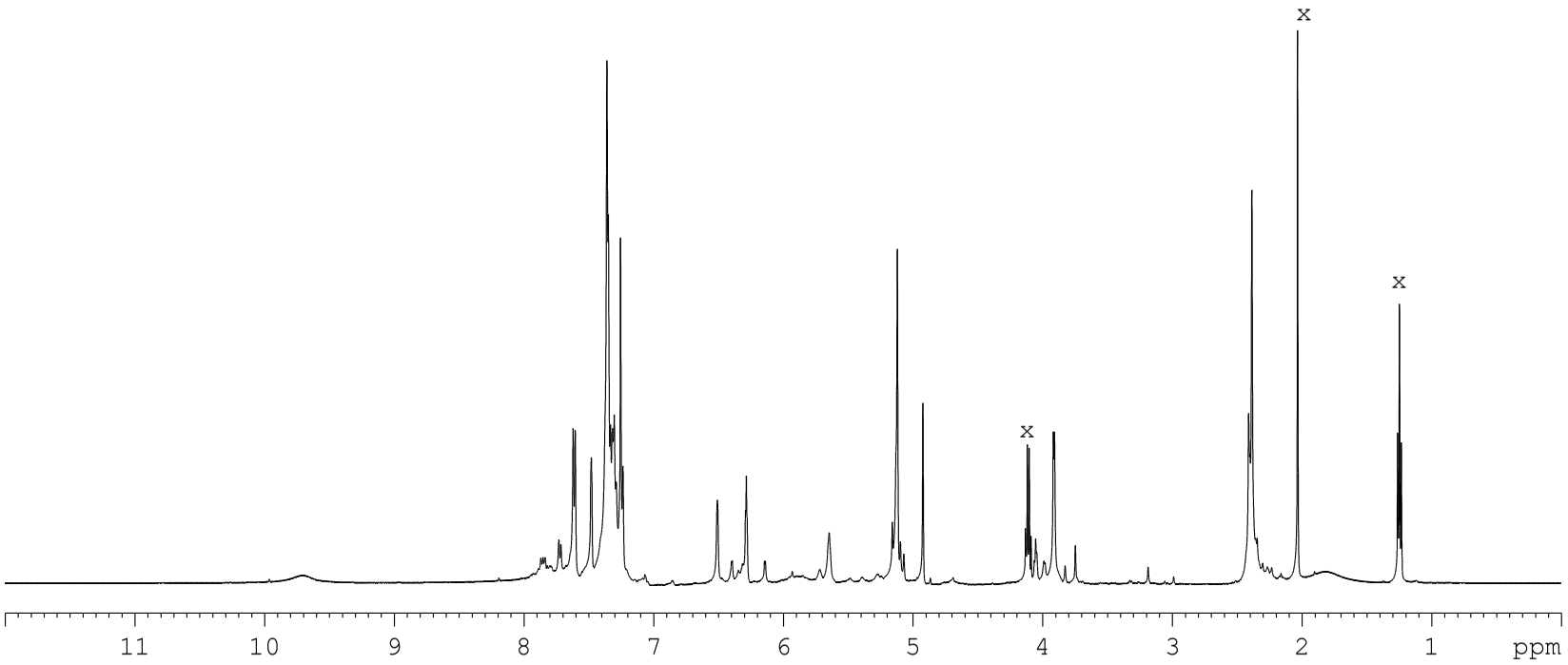

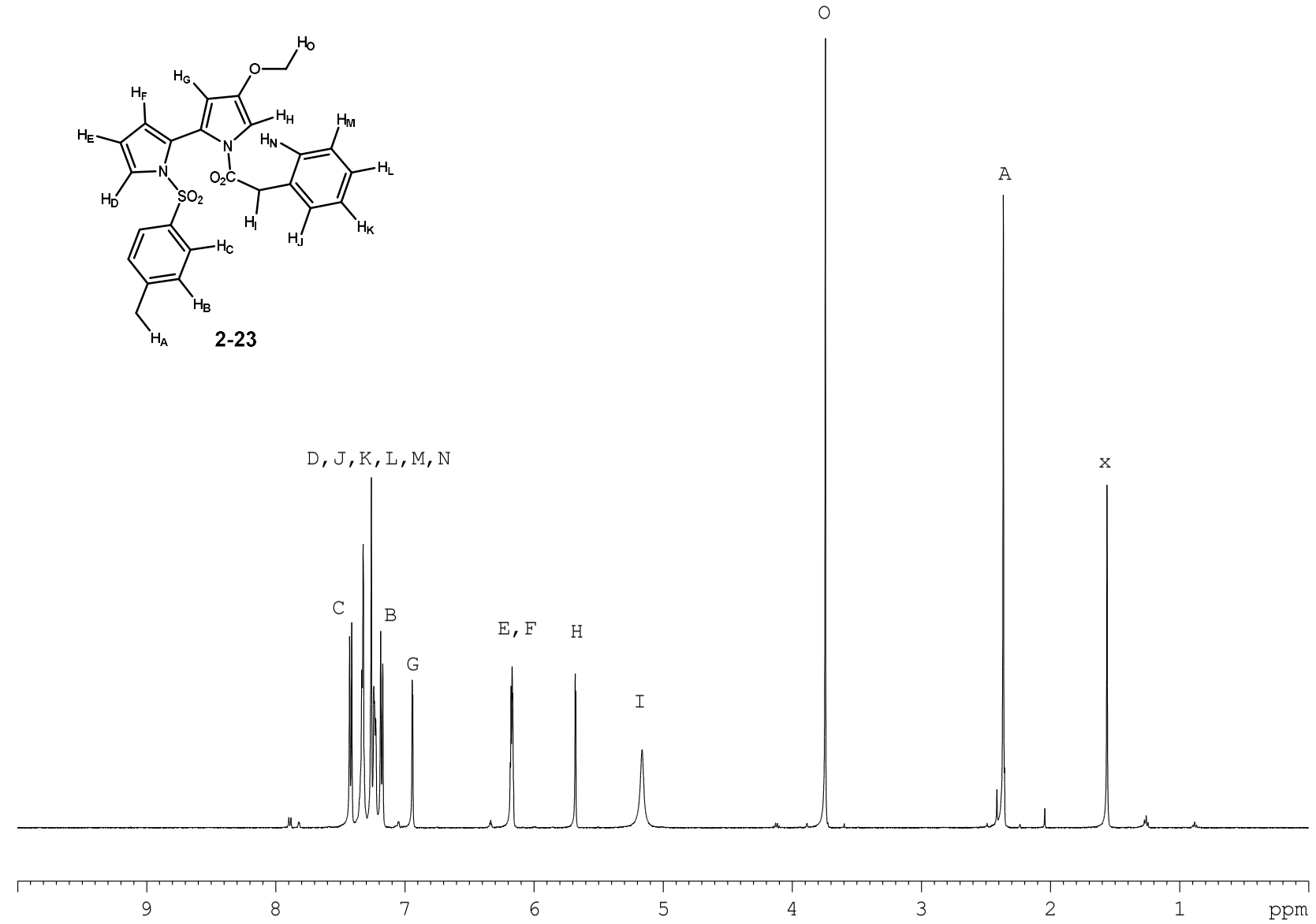
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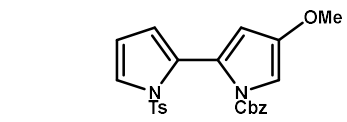
ppm
2-23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Ts
N
Cbz

2-23

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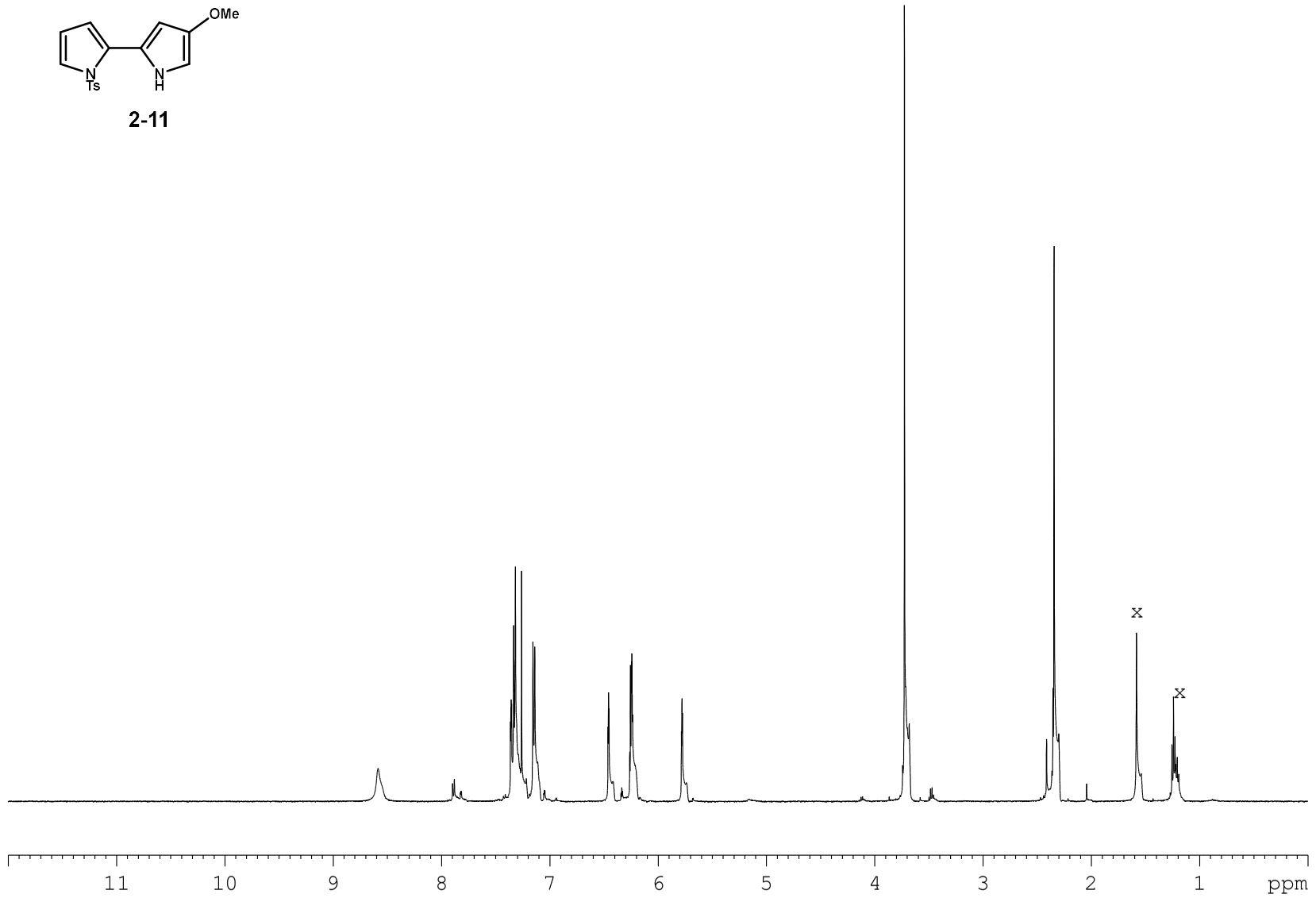
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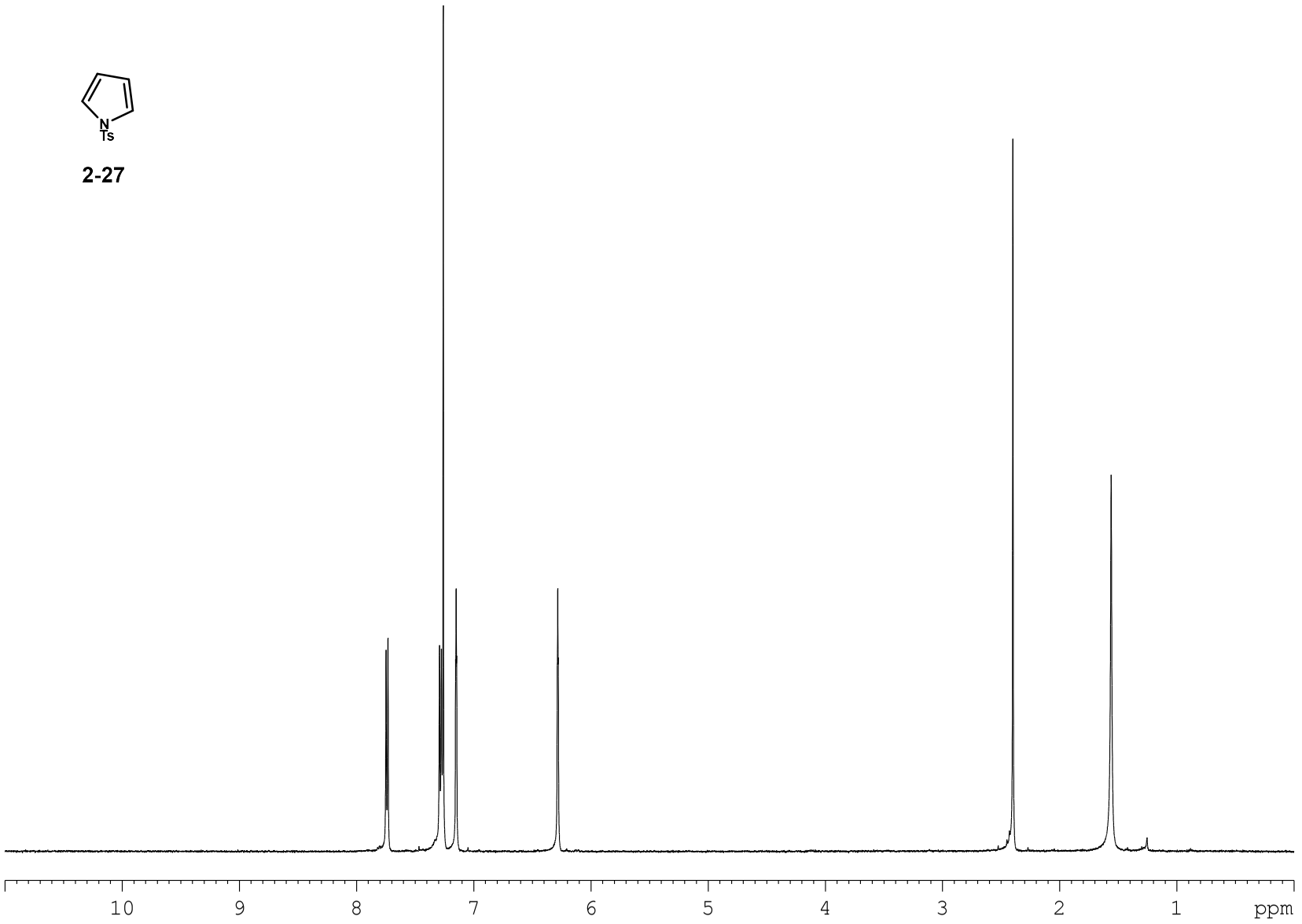
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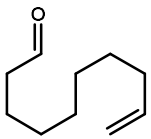

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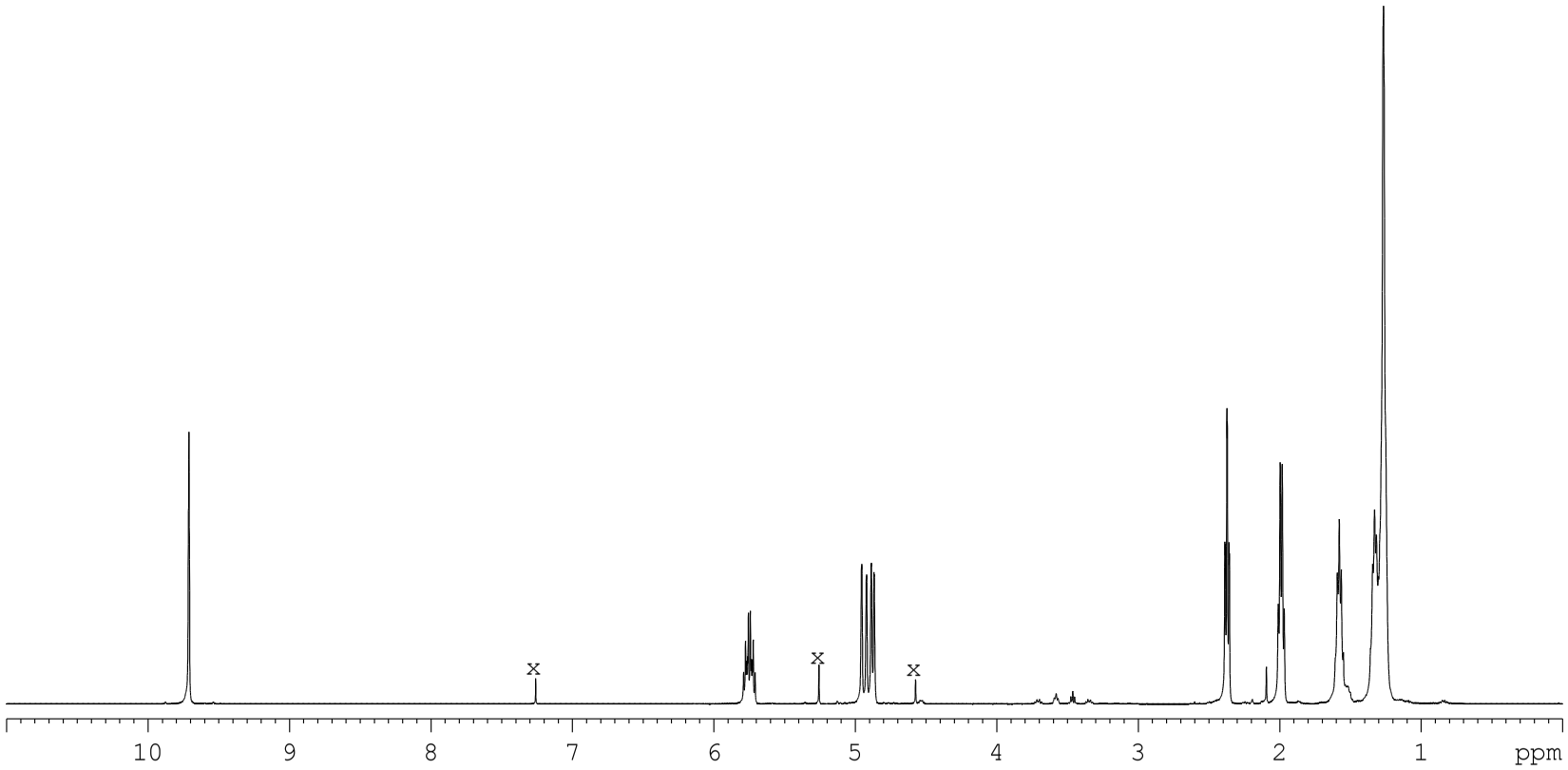

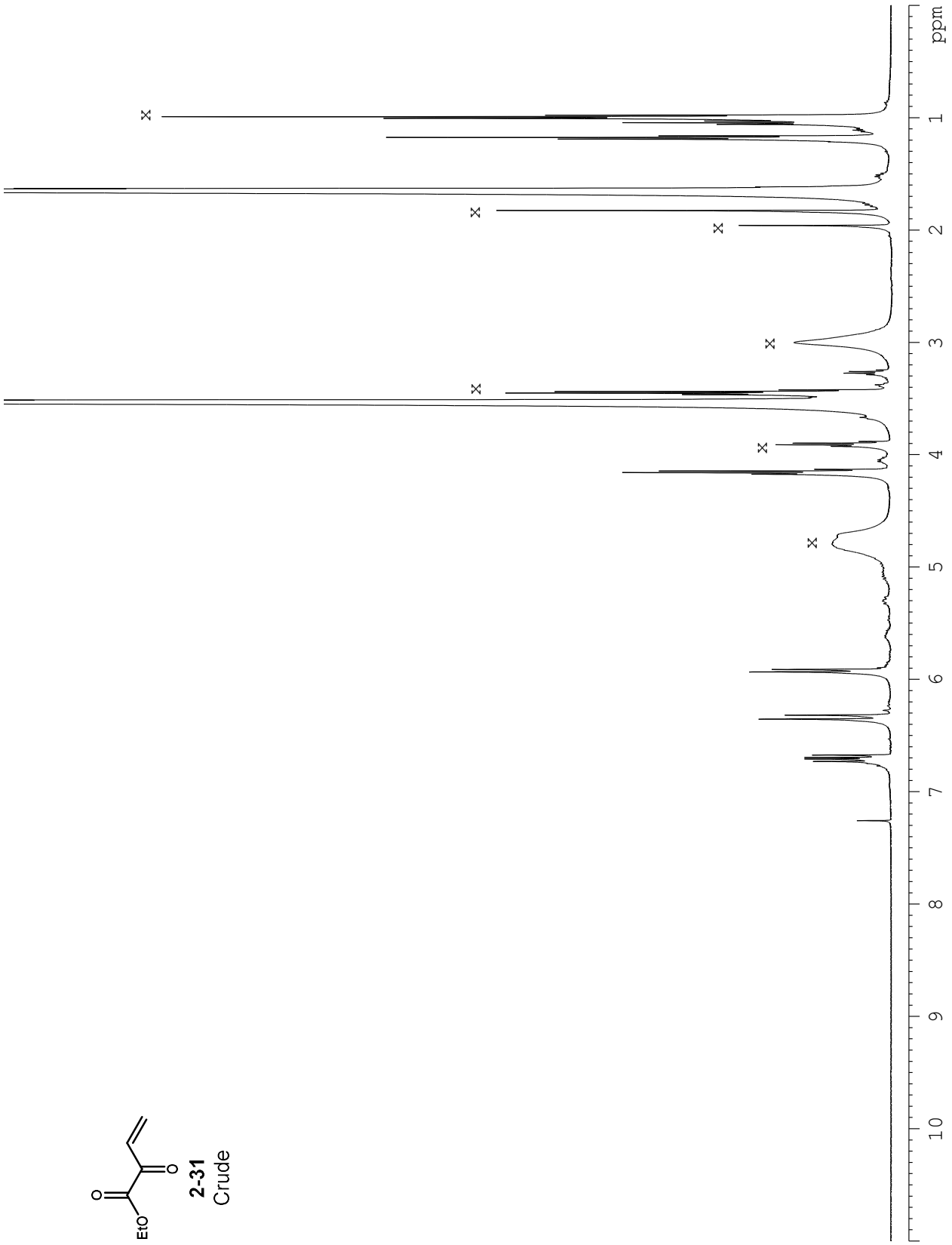
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9
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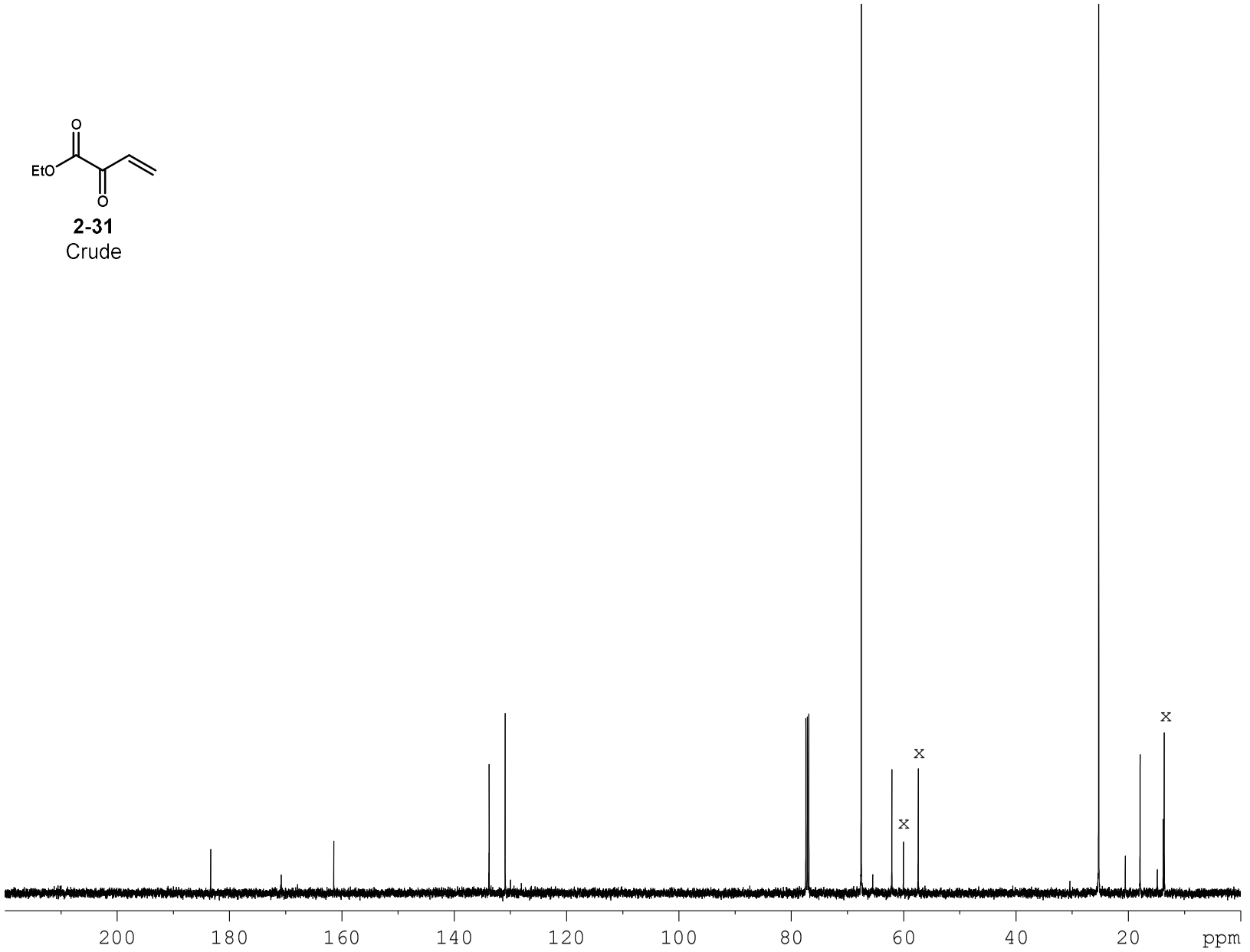
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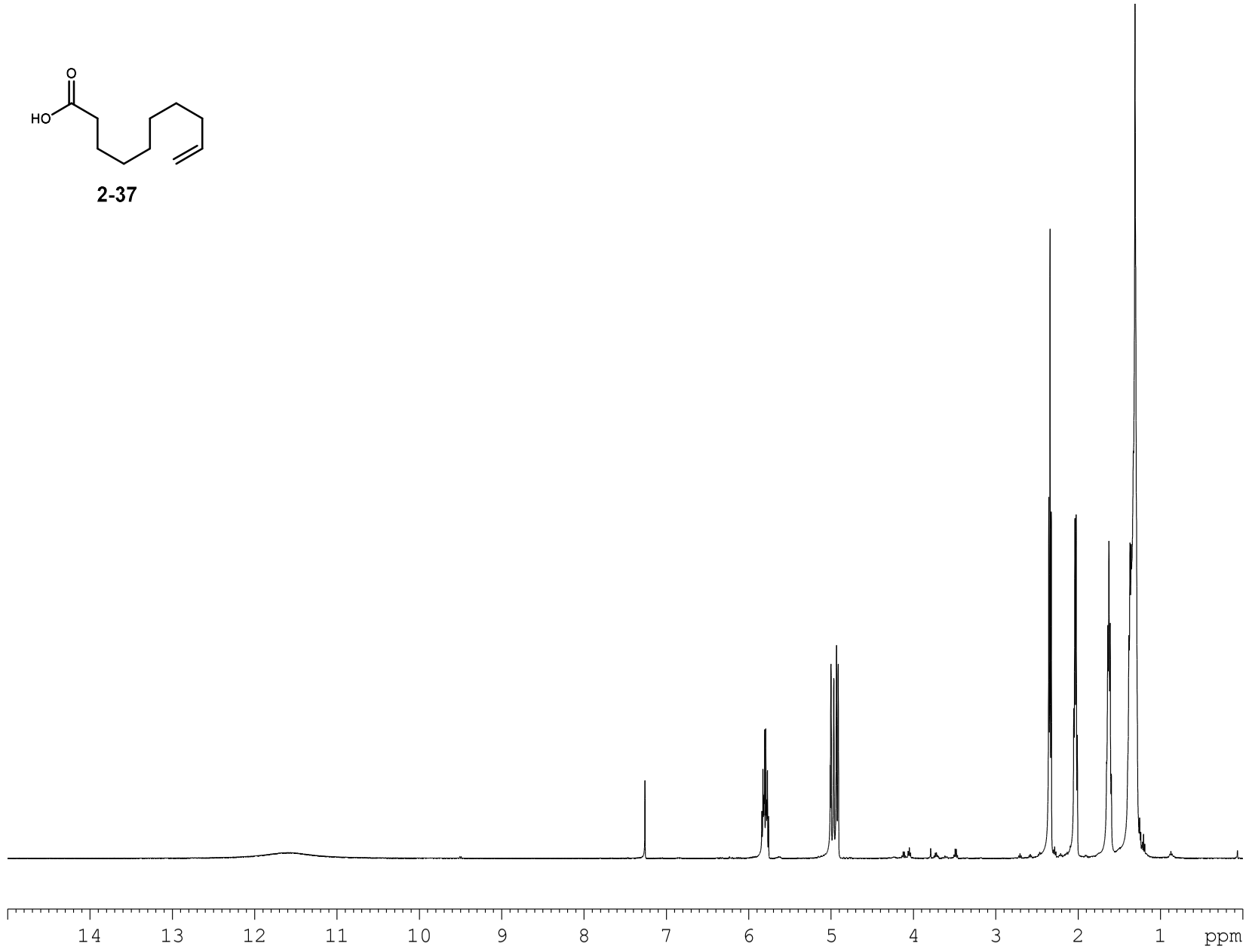
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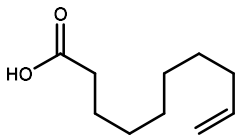

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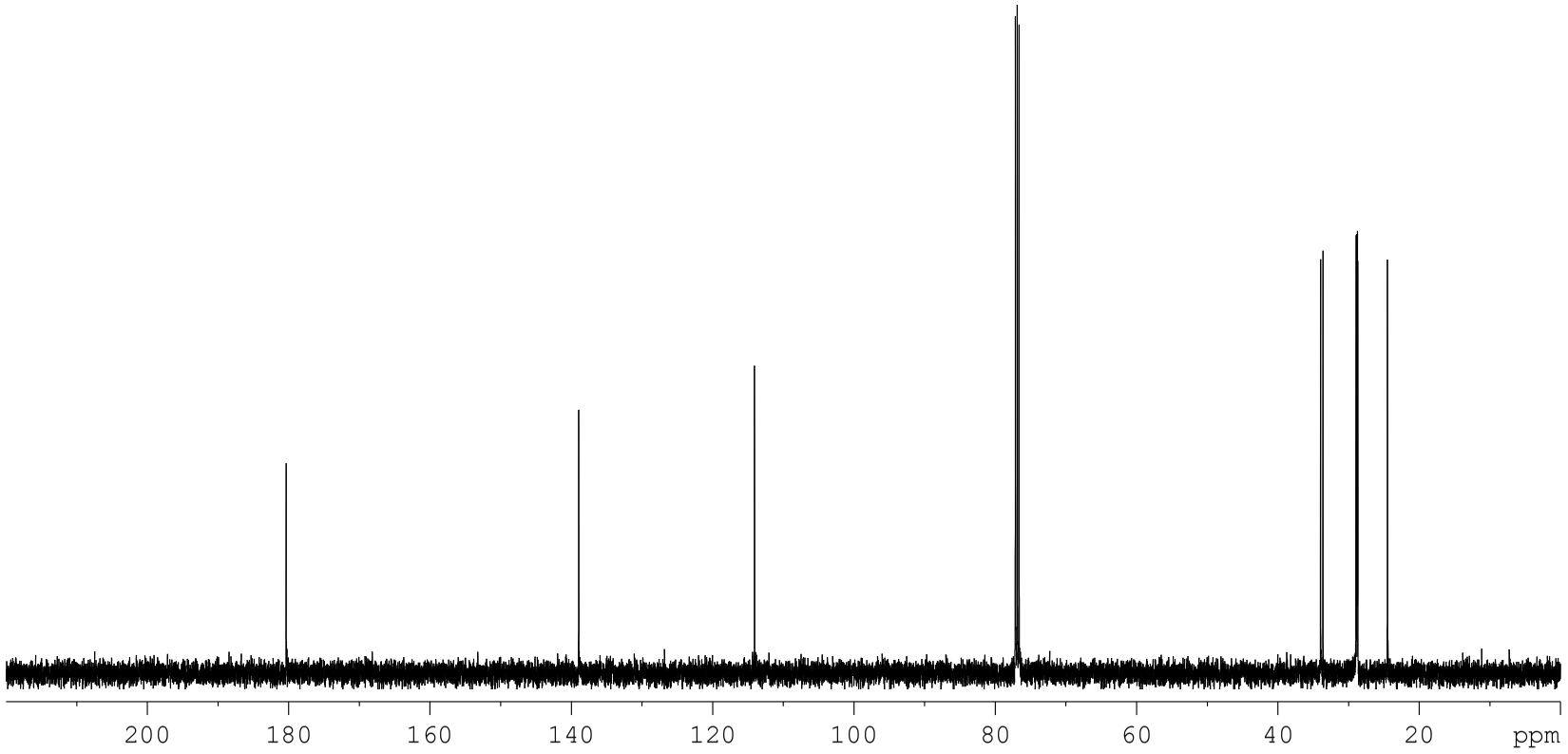

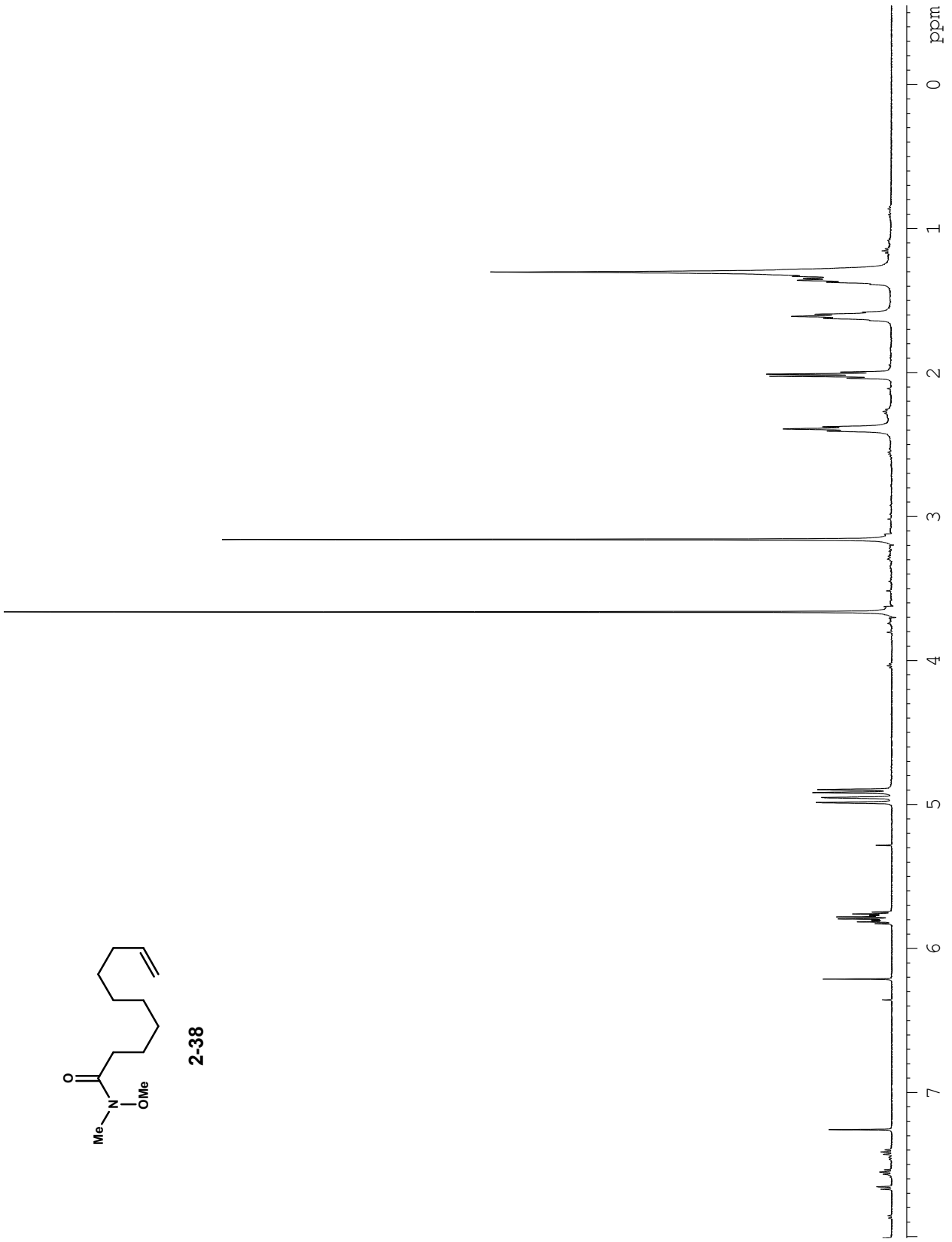
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5
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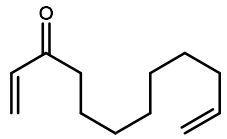

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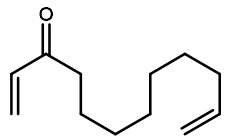

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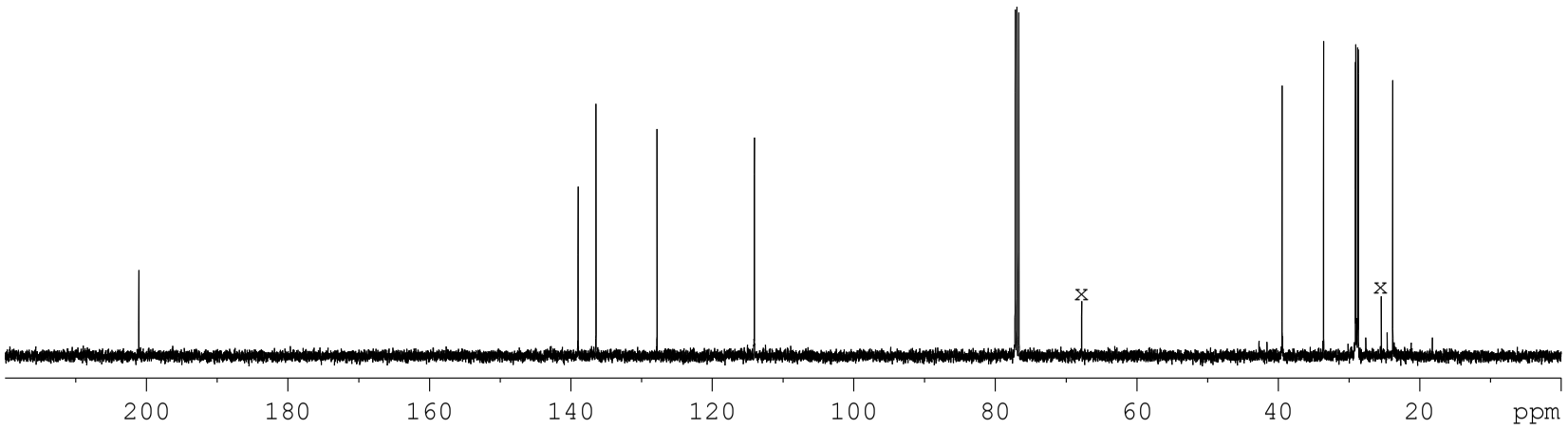

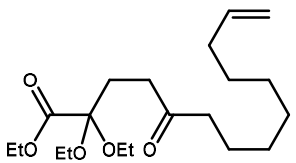

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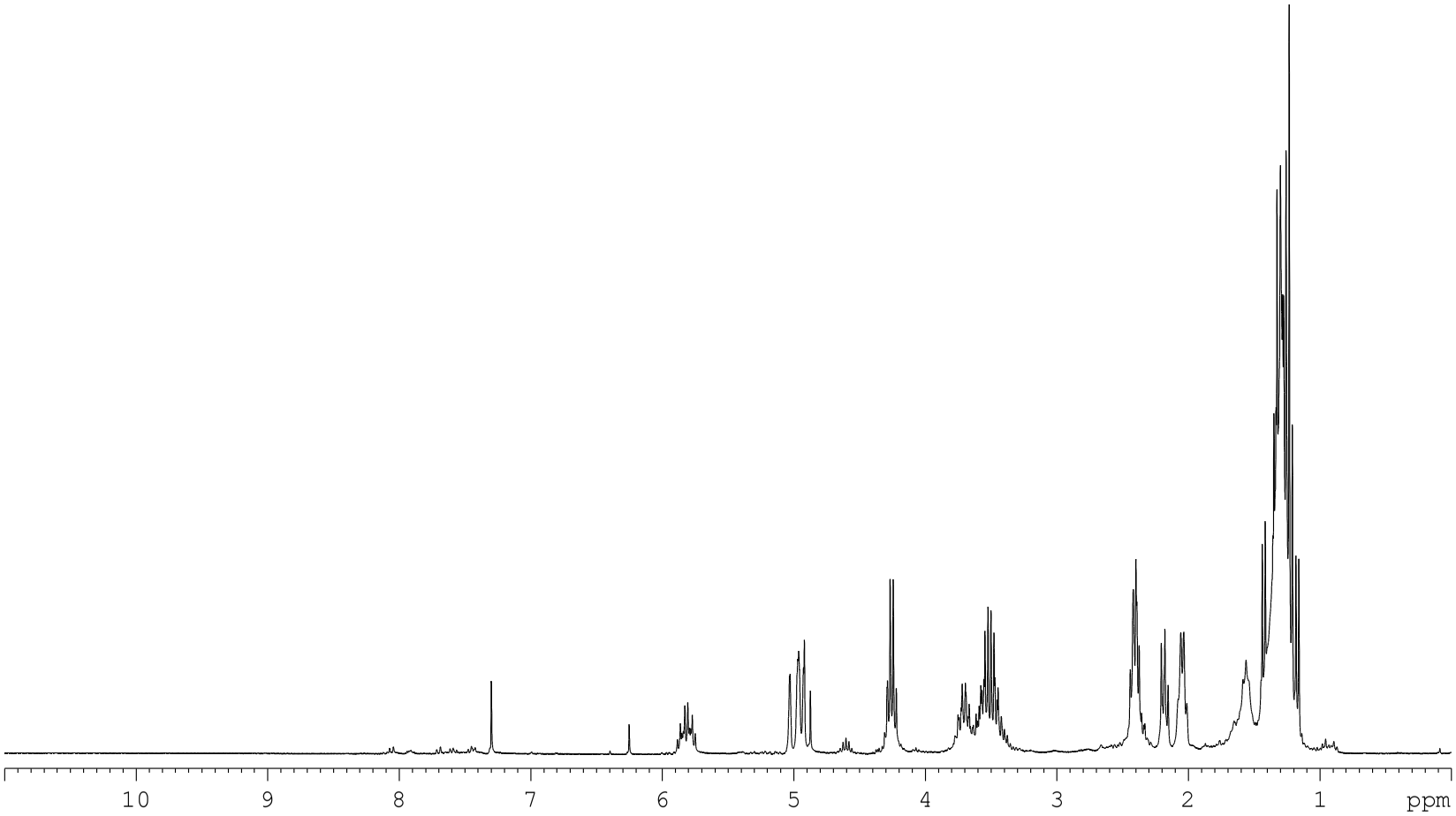

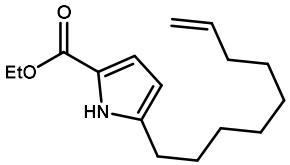

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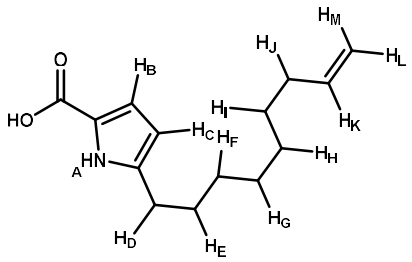
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H_C
H_F
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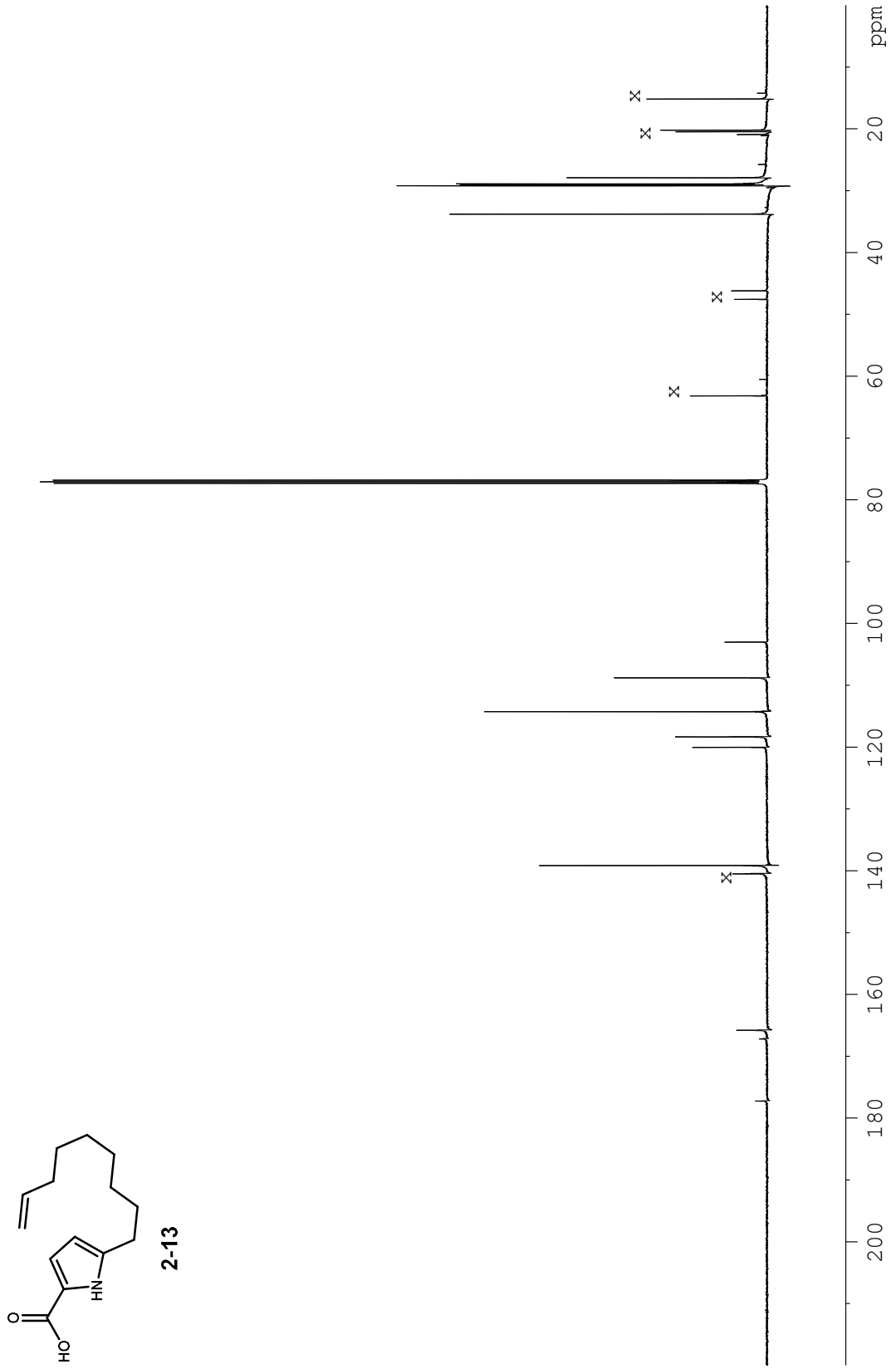
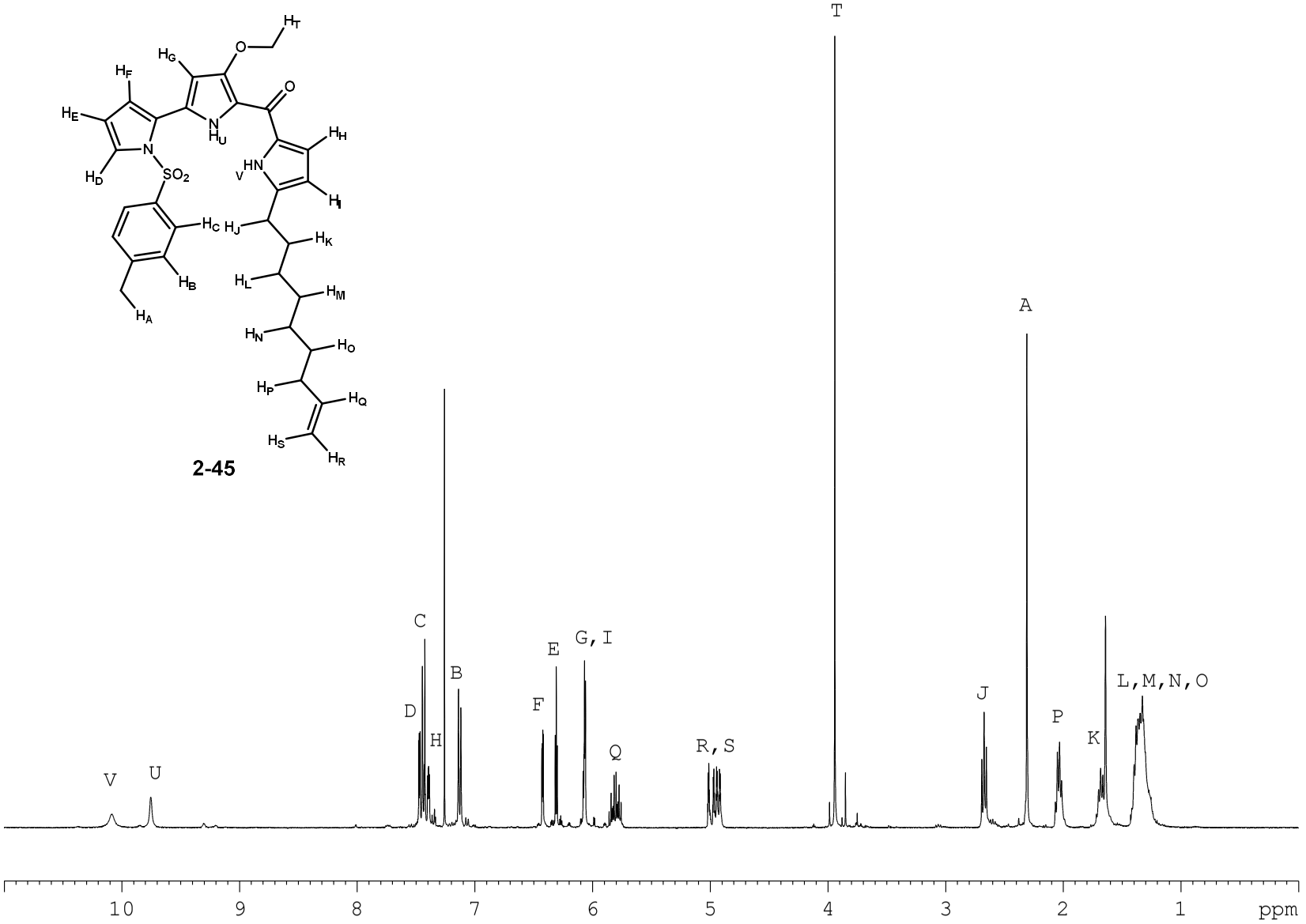
H_D
H_E
H_G
H_H
H_I
H_J
H_M
H_L
H_K

2-13

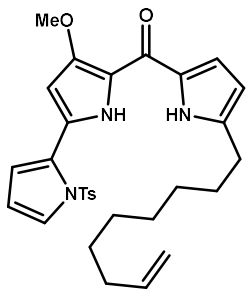
A
B
C
K
L,M
D
x
J
E
F,G,H,I
12
11
10
9
8
7
6
5
4
3
2
1
ppm



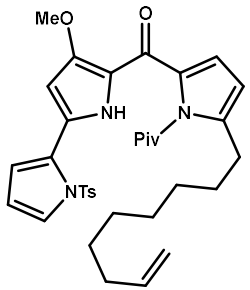
2-13


T
A
C
B
D
H
E
G,I
F
Q
R,S
J
P
K
L,M,N,O
V
U
10
9
8
7
6
5
4
3
2
1
ppm

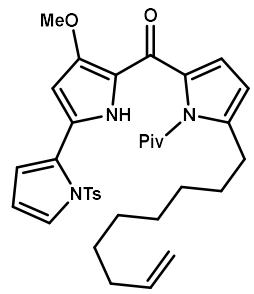
2-45



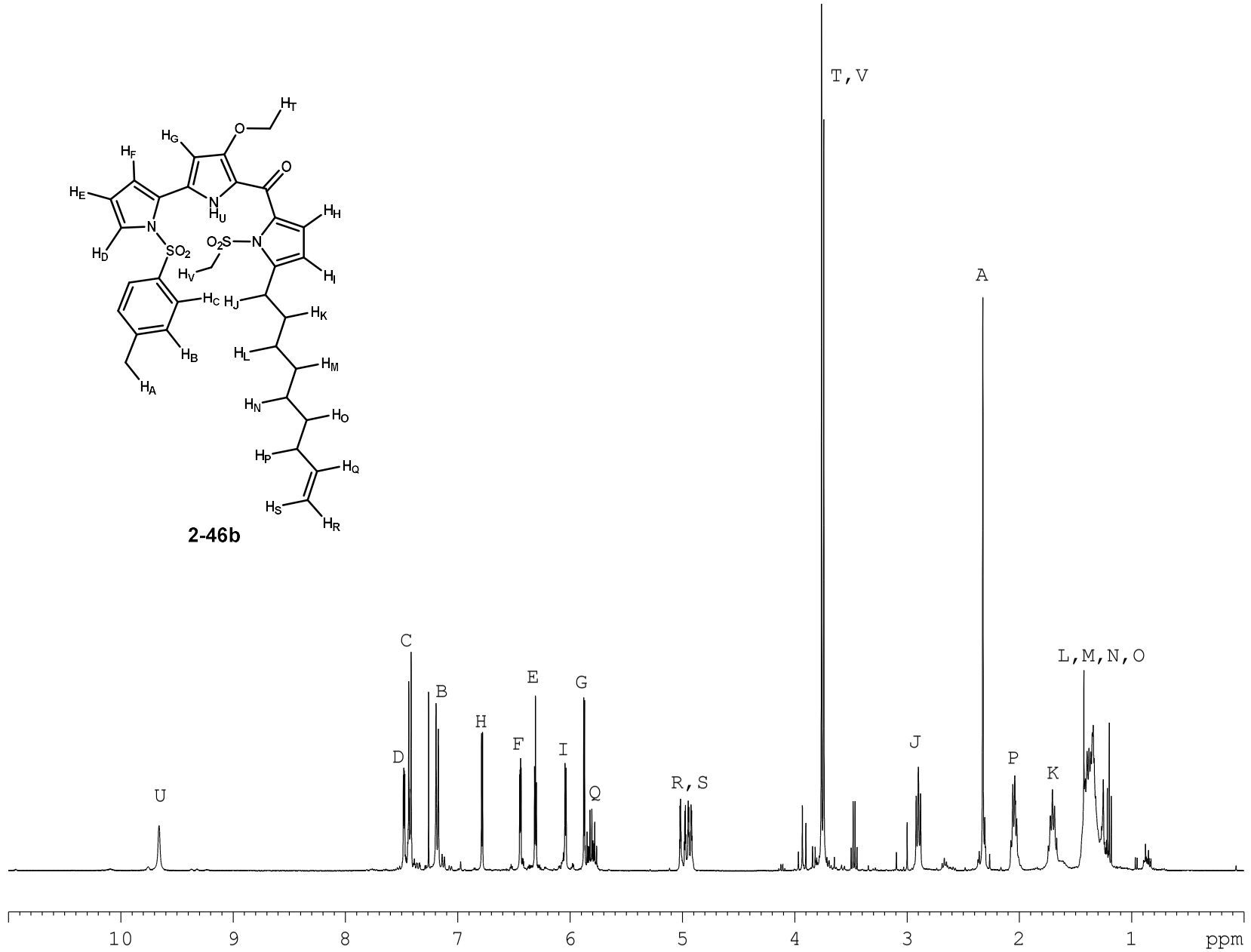
2-45



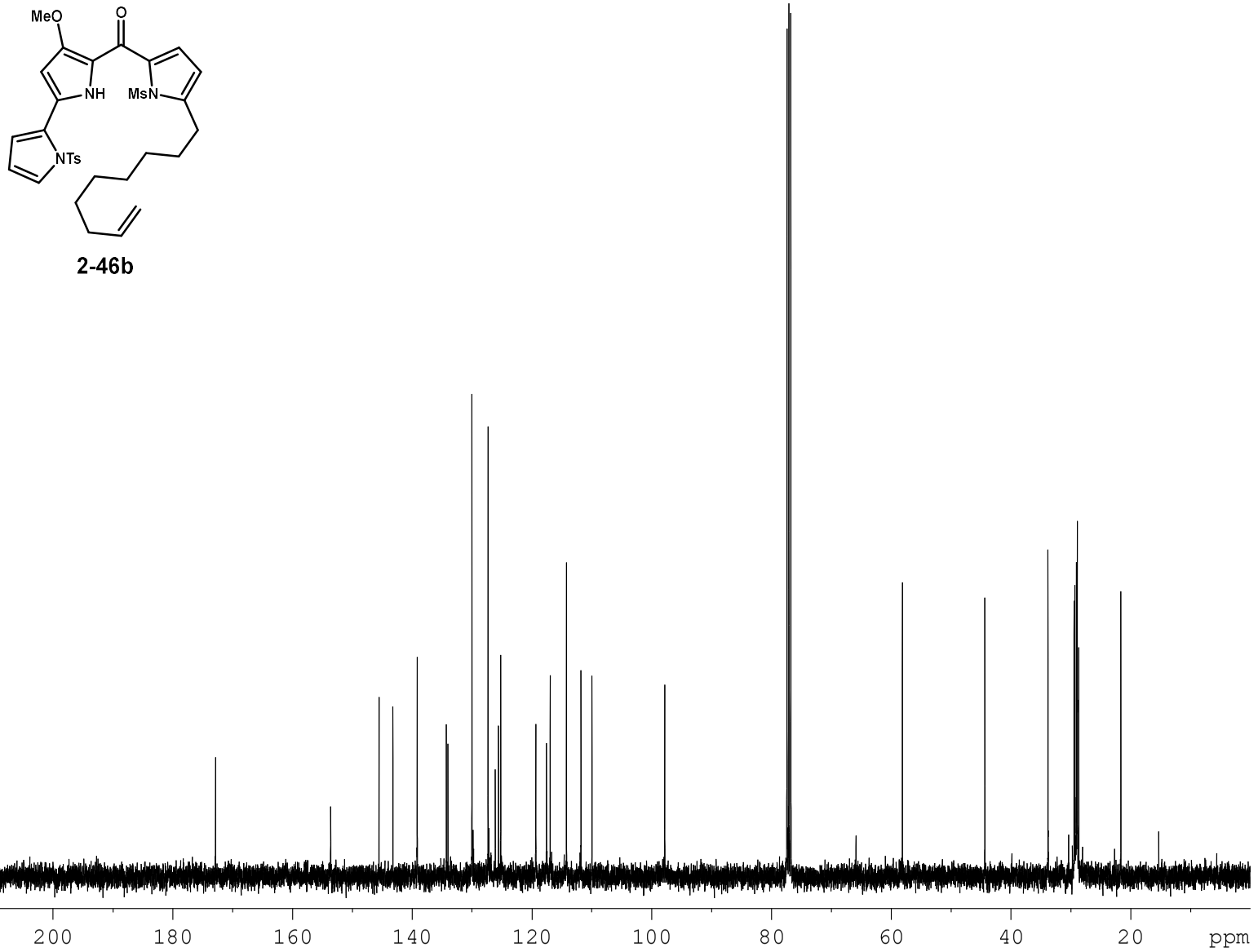
2-46a

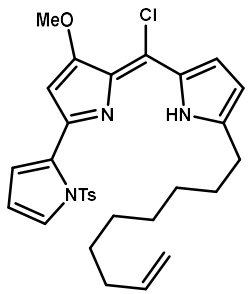


2-46a

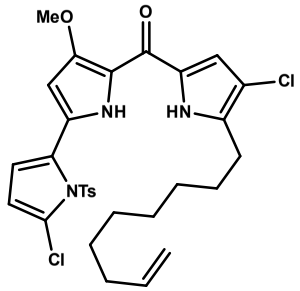

T,V
A
L,M,N,O
C
B
E
G
H
F
I
D
Q
R,S
J
P
K
U
10
9
8
7
6
5
4
3
2
1
ppm

2-46b

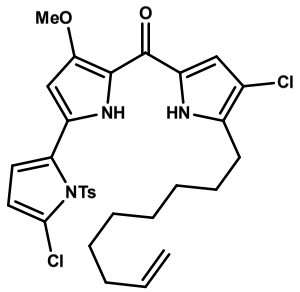

MeO
O
NH
MsN
NTs
2-46b
200
180
160
140
120
100
80
60
40
20
ppm



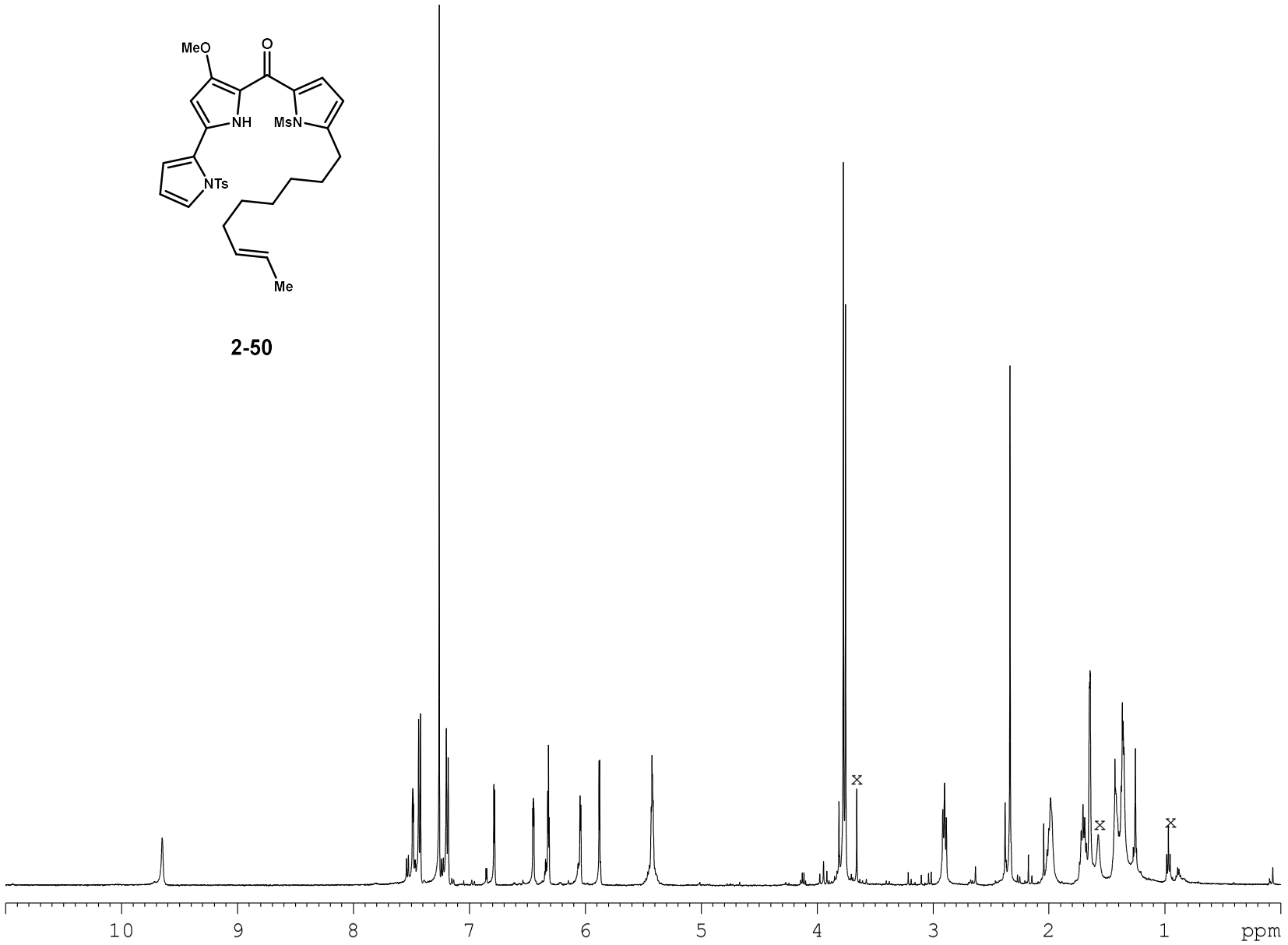
2-47

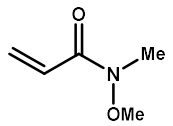


2-48

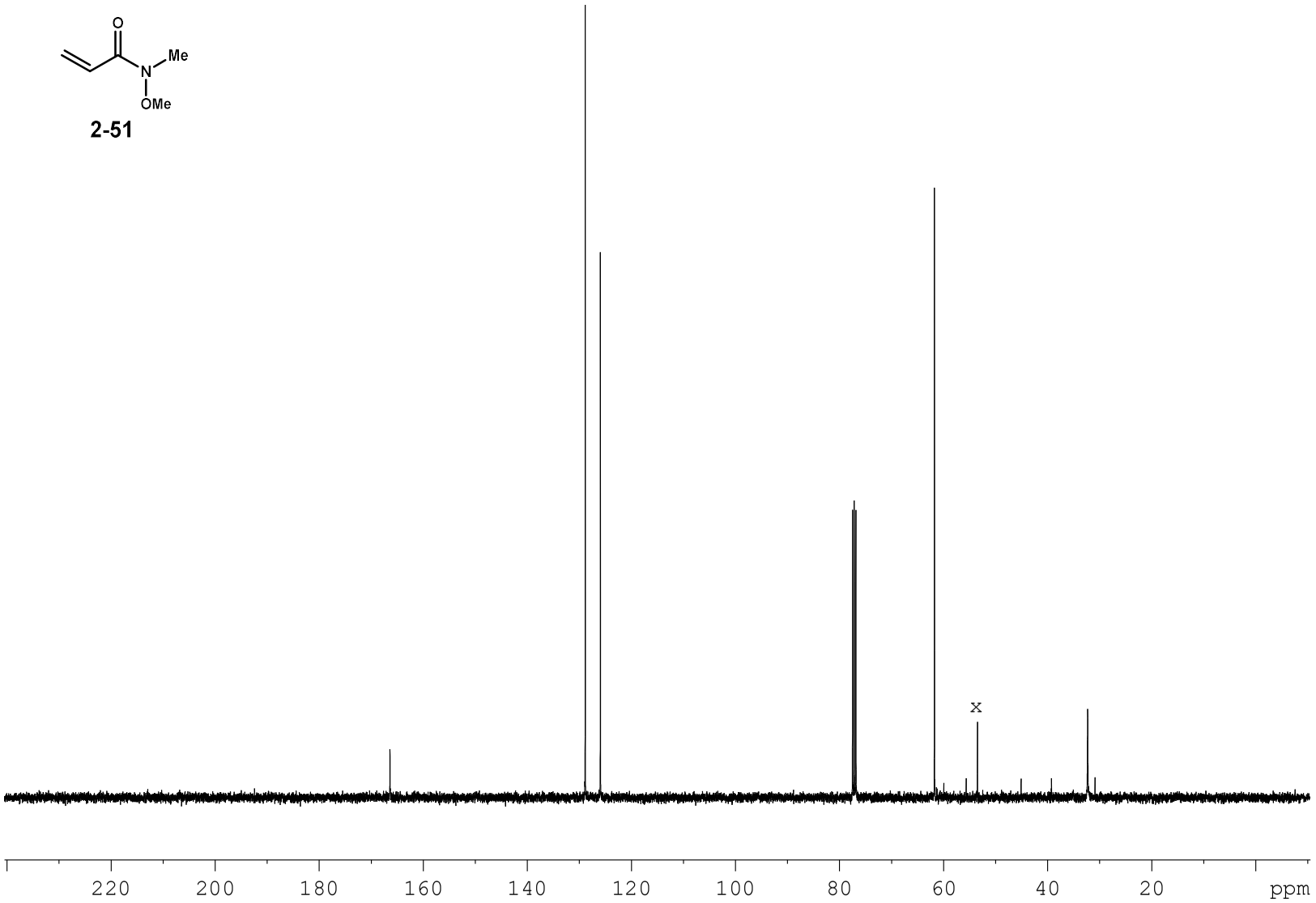


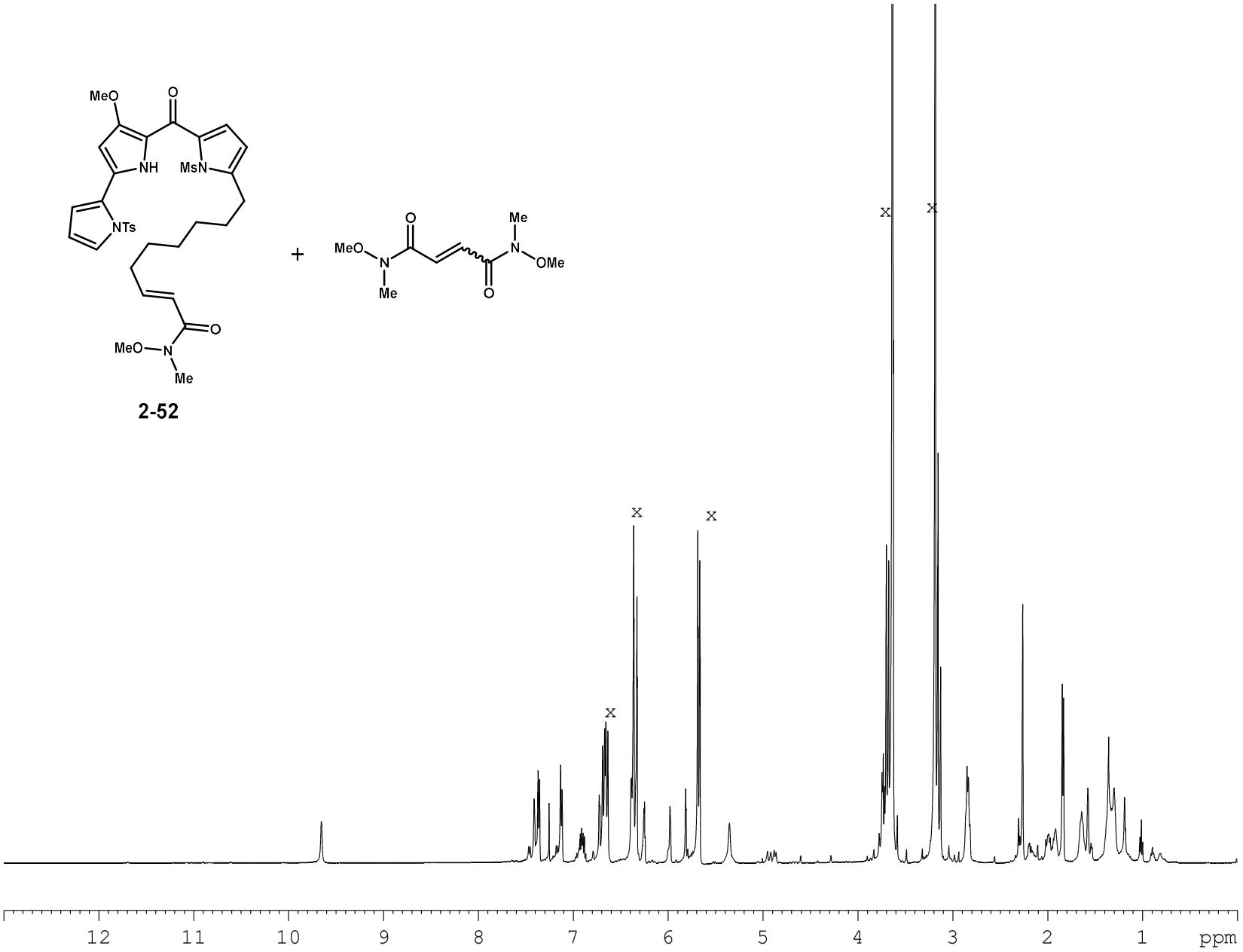
2-48


MeO
O
NH
MsN
NTs
Me
2-50
x
x
x
10
9
8
7
6
5
4
3
2
1
ppm

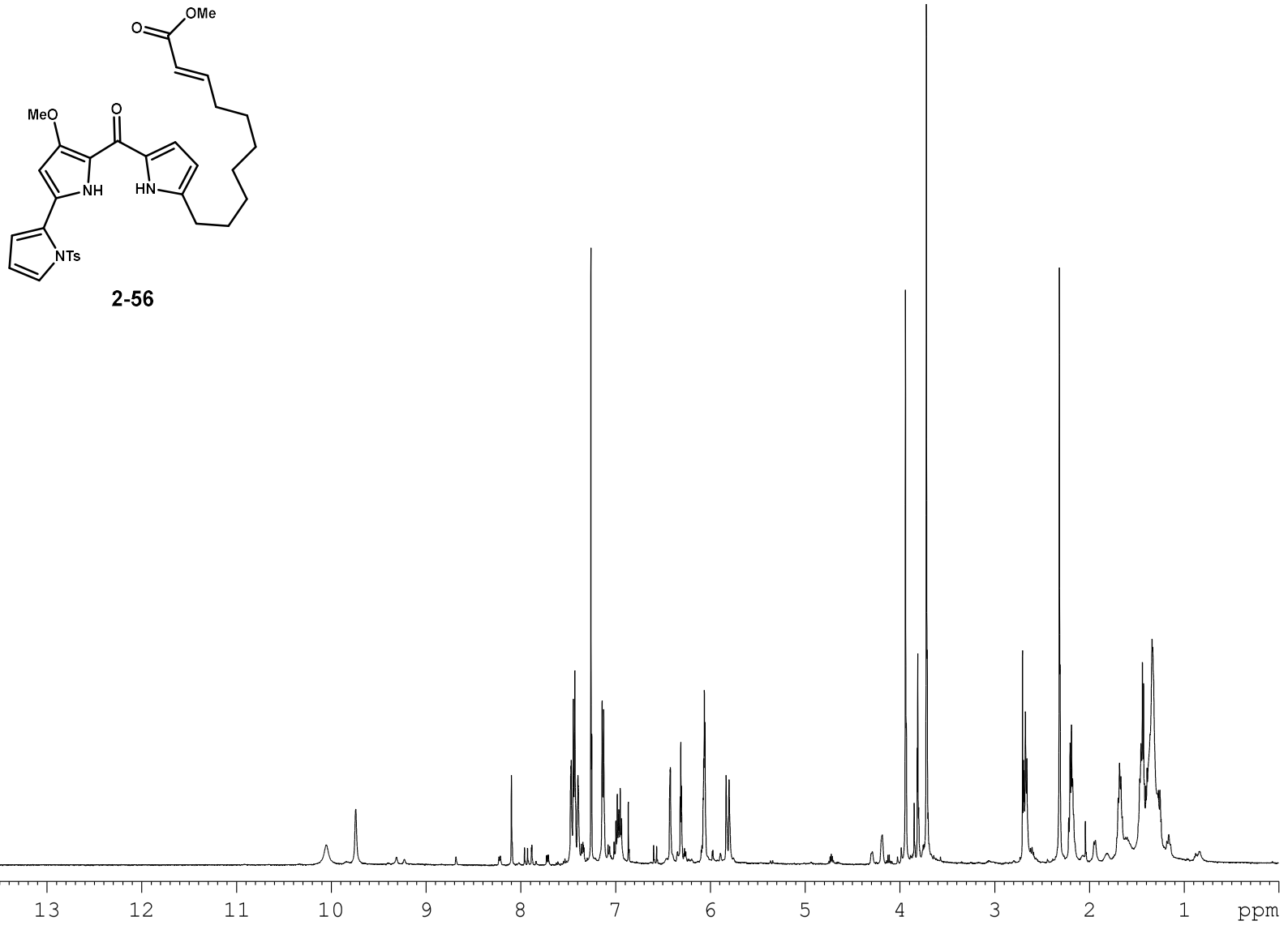


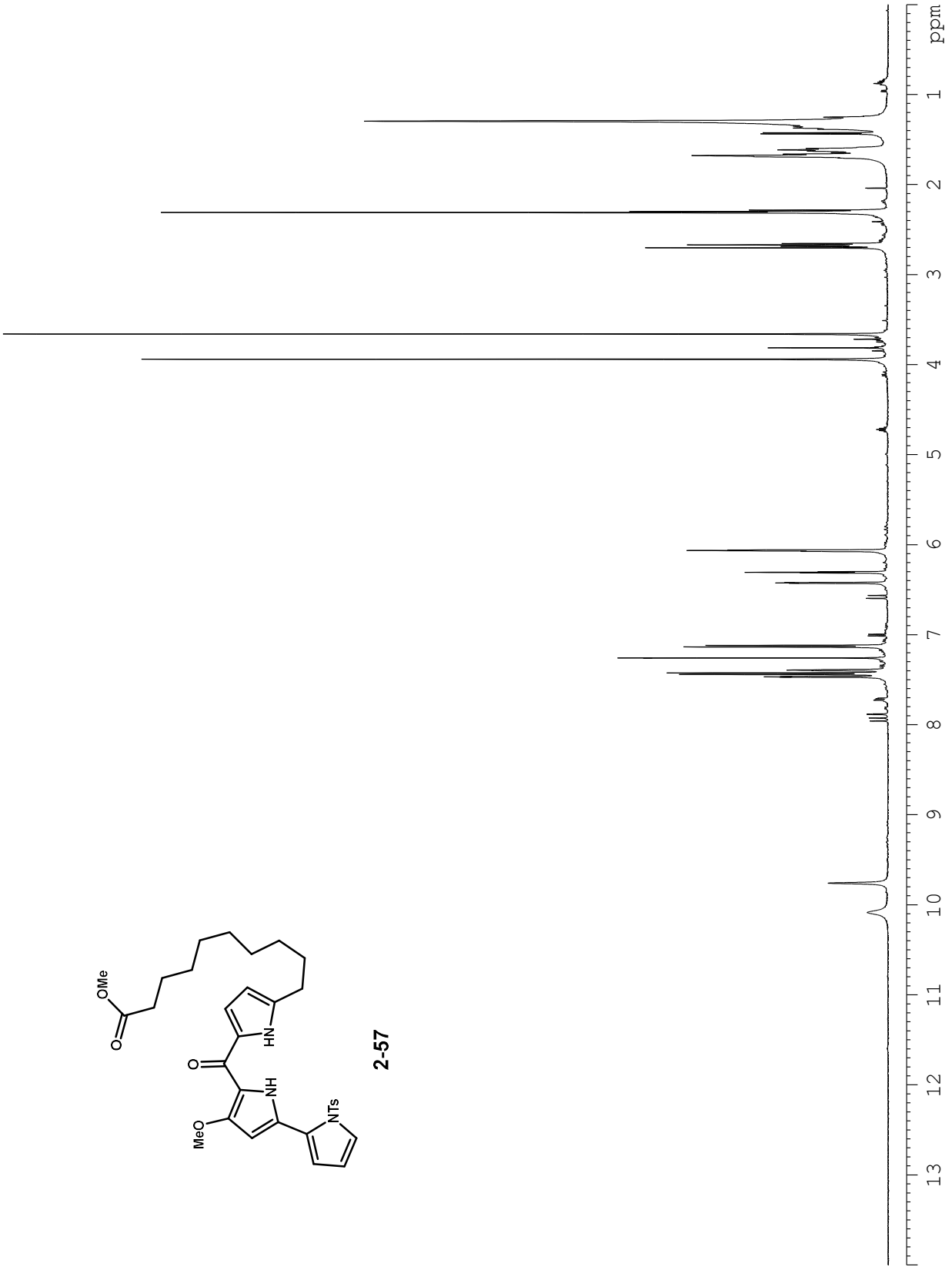
2-51


O
N
Me
OMe
2-51
x
220
200
180
160
140
120
100
80
60
40
20
ppm

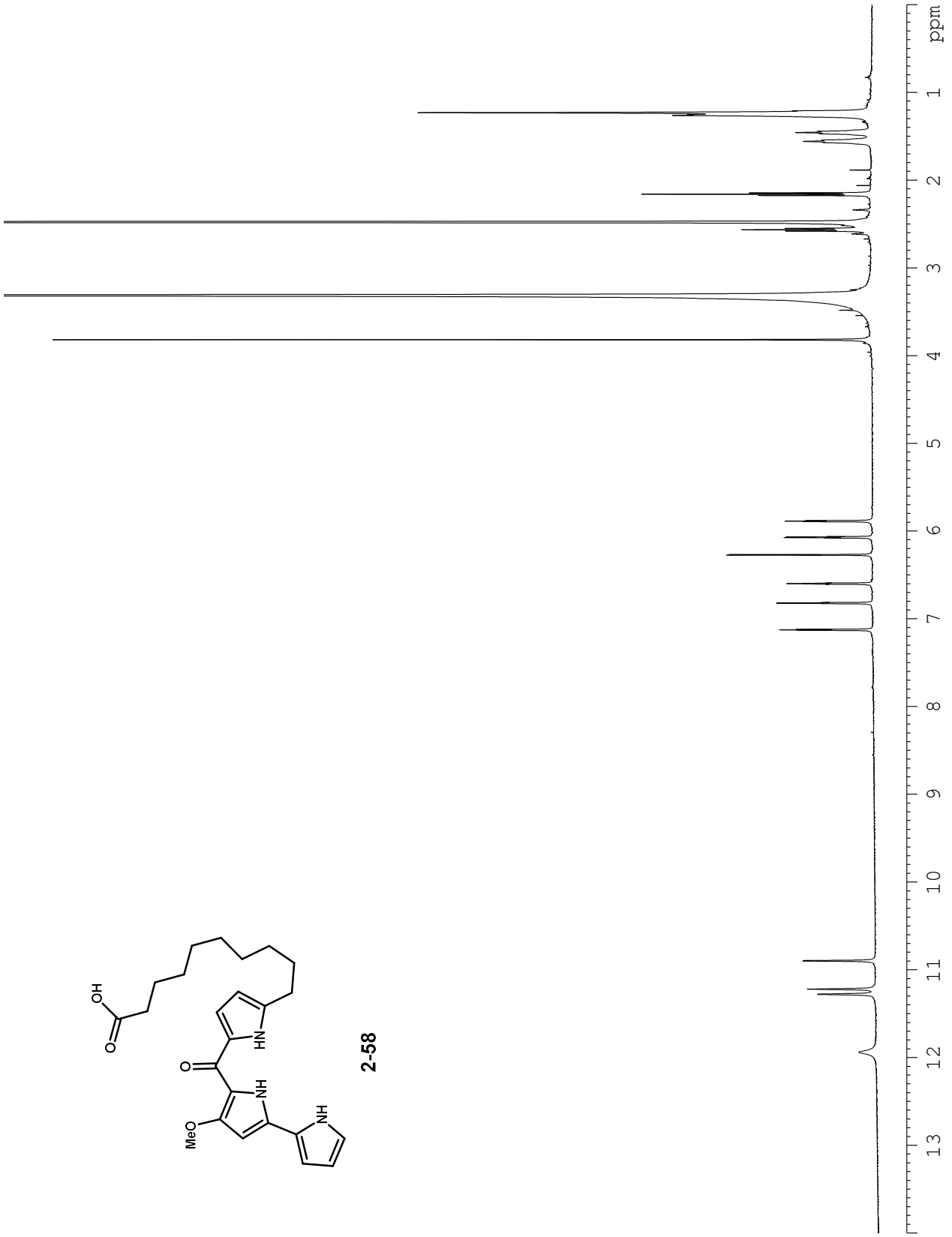

MeO
O
NH
MsN
NTs
MeO
N
Me
O
+
MeO
N
Me
O
O
Me
N
OMe
x
x
x
x
12
11
10
9
8
7
6
5
4
3
2
1
ppm

2-52

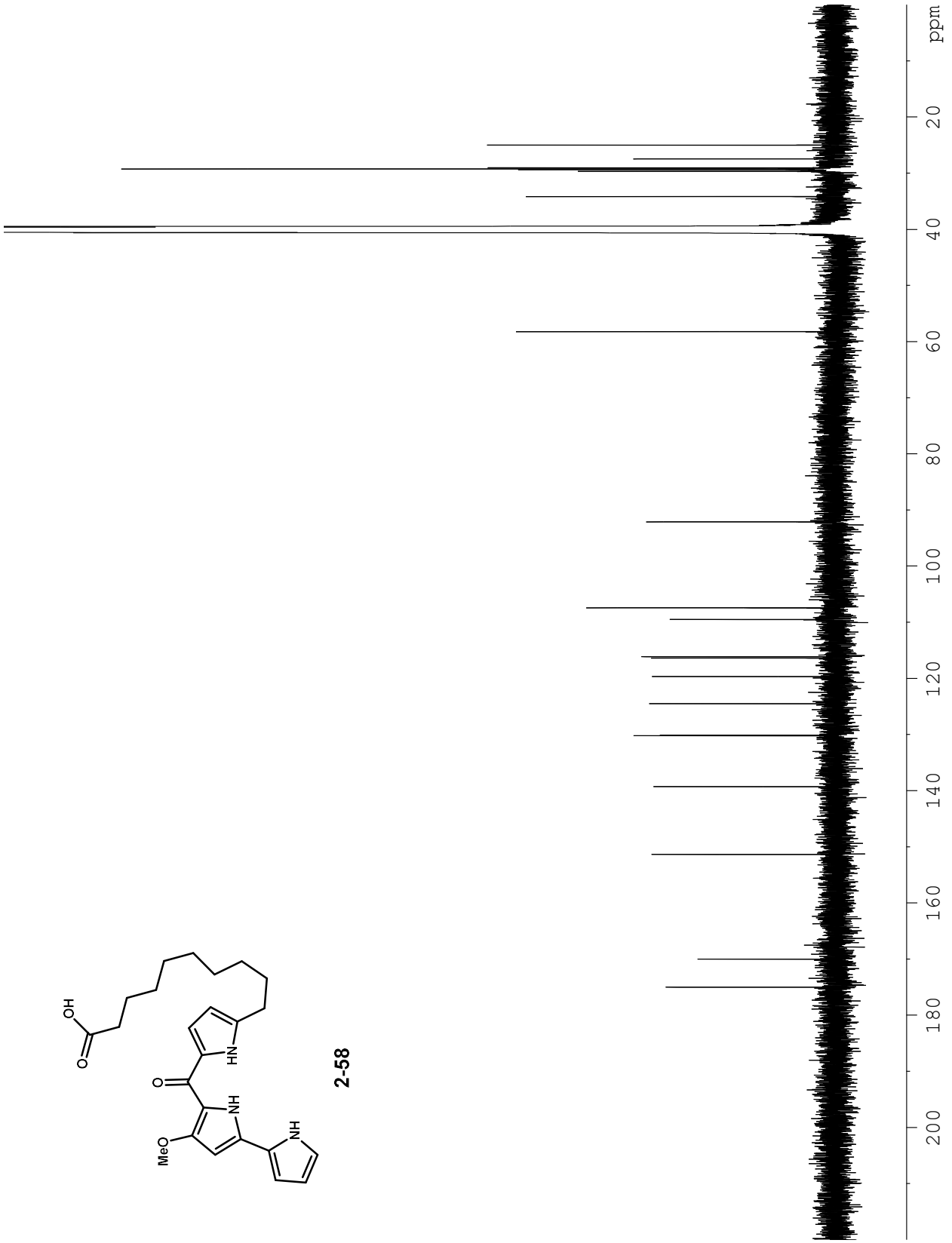

OMe
O
MeO
O
NH
HN
NTs
2-56
13
12
11
10
9
8
7
6
5
4
3
2
1
ppm



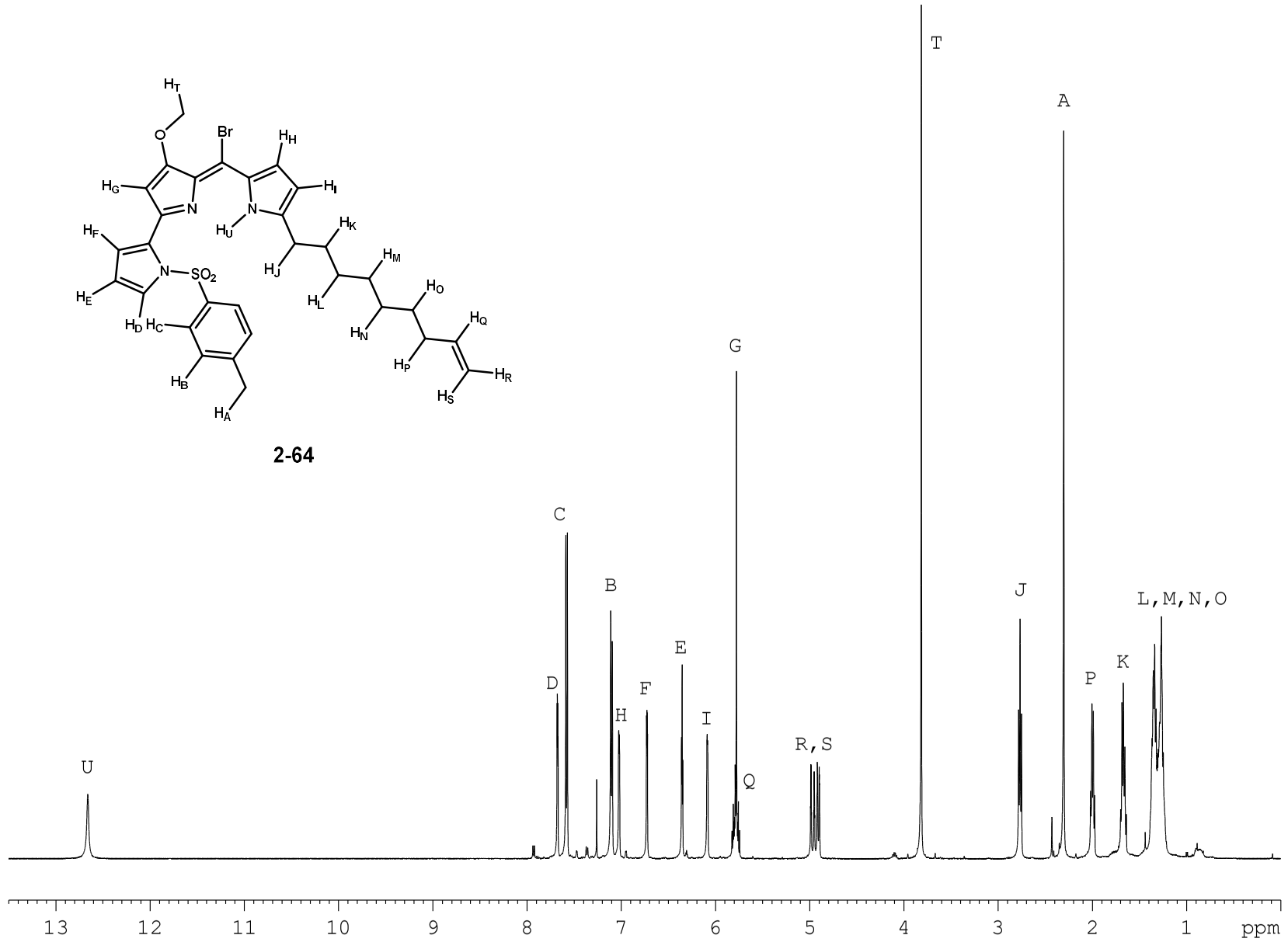
2-57

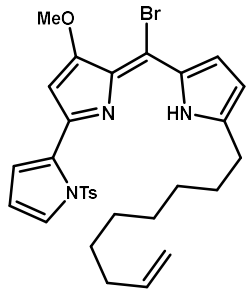


2-58

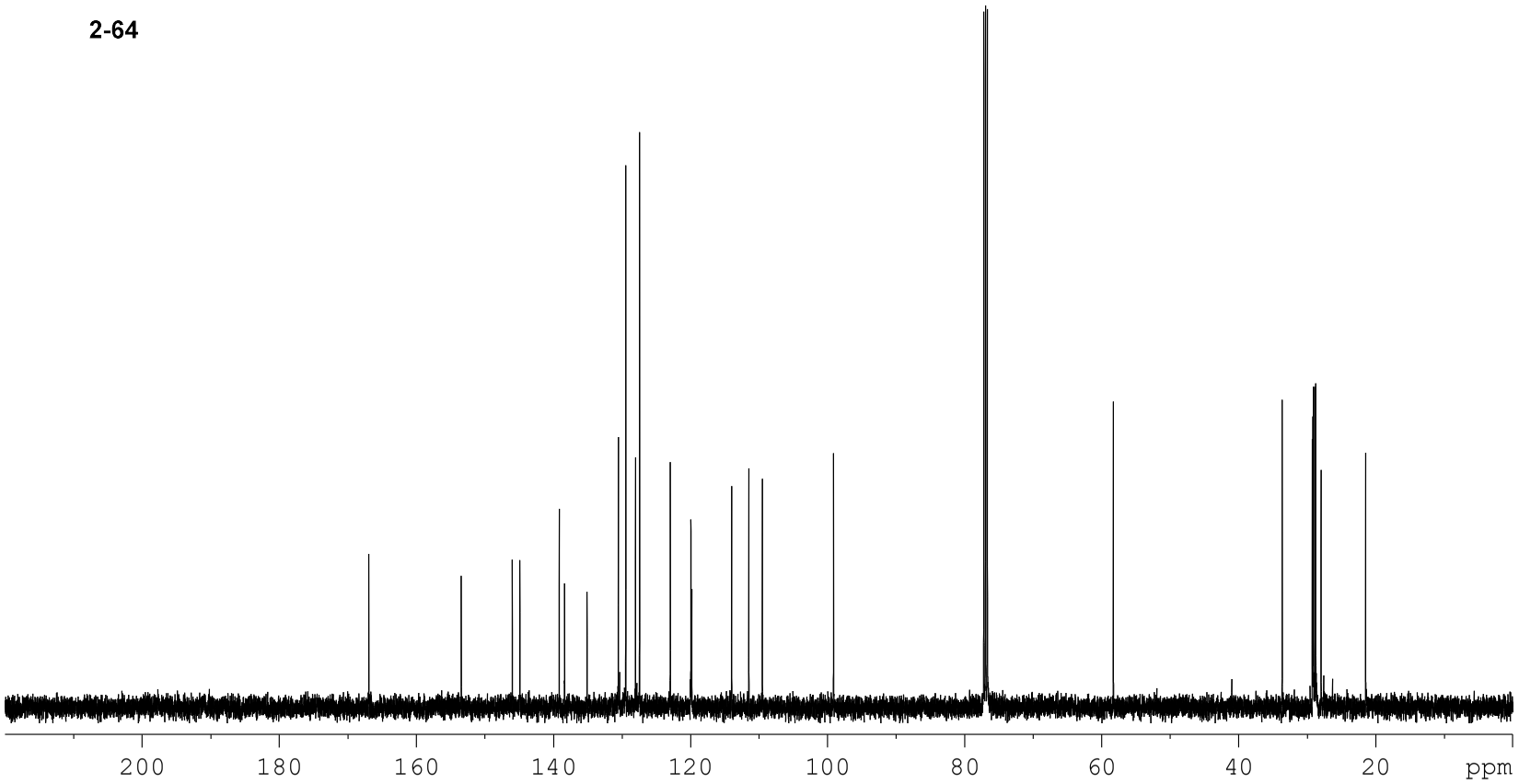


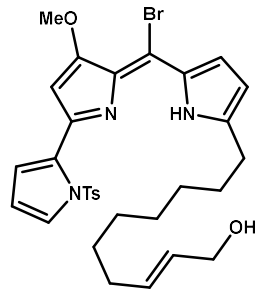
2-58


H_T
O
Br
H_H
H_G
H_I
N
N
H_U
H_K
H_F
H_J
H_M
N
SO2
H_L
H_O
H_E
H_D H_C
H_N
H_Q
H_P
H_R
H_B
H_S
H_A
2-64
T
A
G
C
B
J
L,M,N,O
E
K
D
F
P
H
I
R,S
Q
U
13
12
11
10
9
8
7
6
5
4
3
2
1
ppm

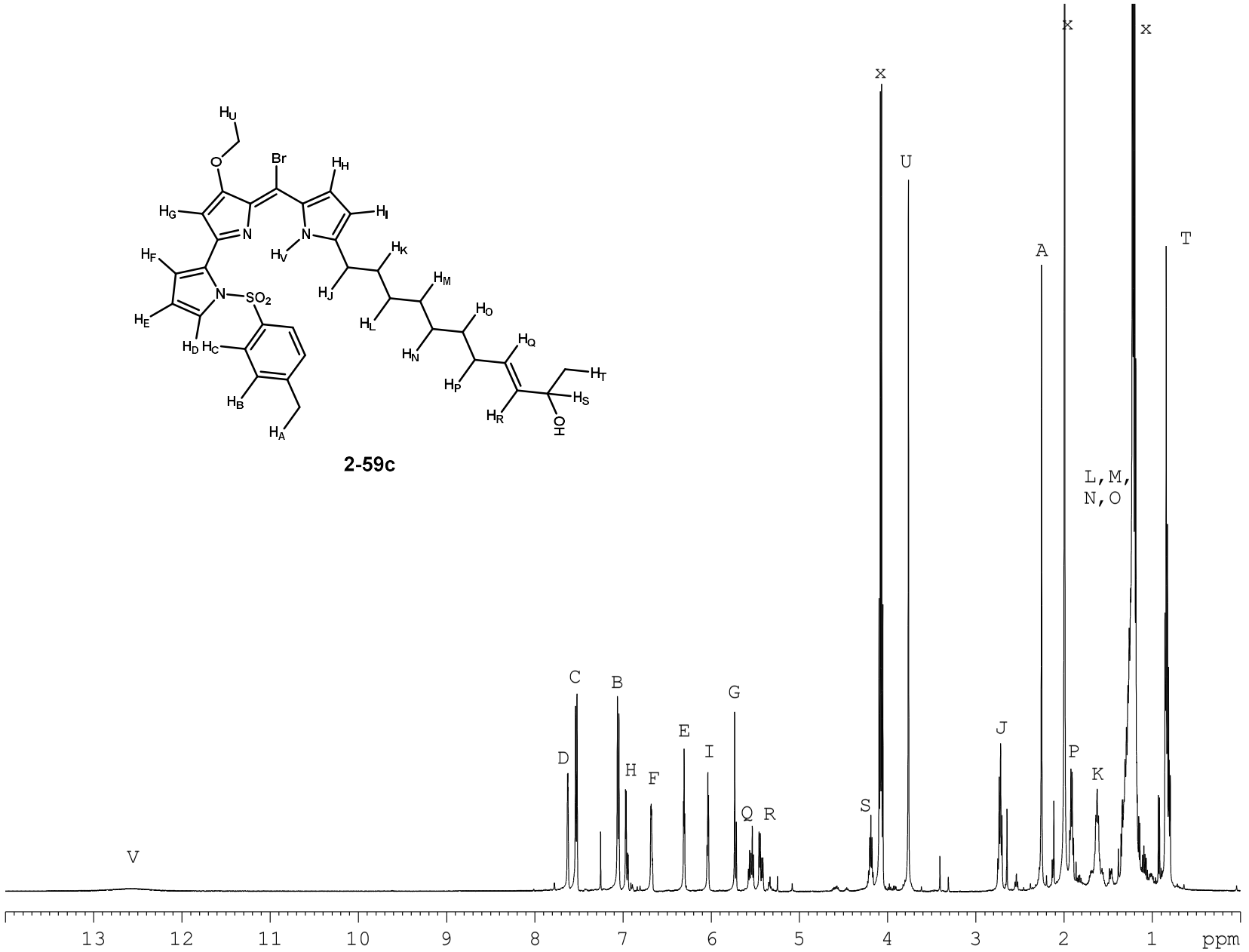


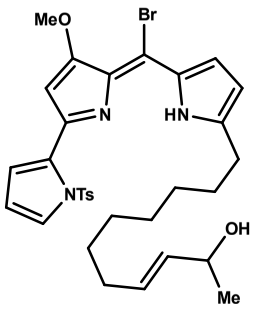
2-64





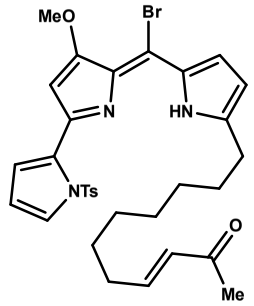
2-59b


2-59c
V
D
C
B
H
F
E
I
G
Q
R
S
x
U
J
A
x
P
K
L, M,
N, O
x
T
13
12
11
10
9
8
7
6
5
4
3
2
1
ppm

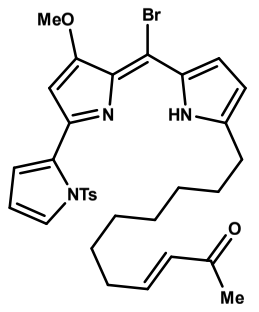

MeO
Br
N
HN
NTs
OH
Me

2-59c

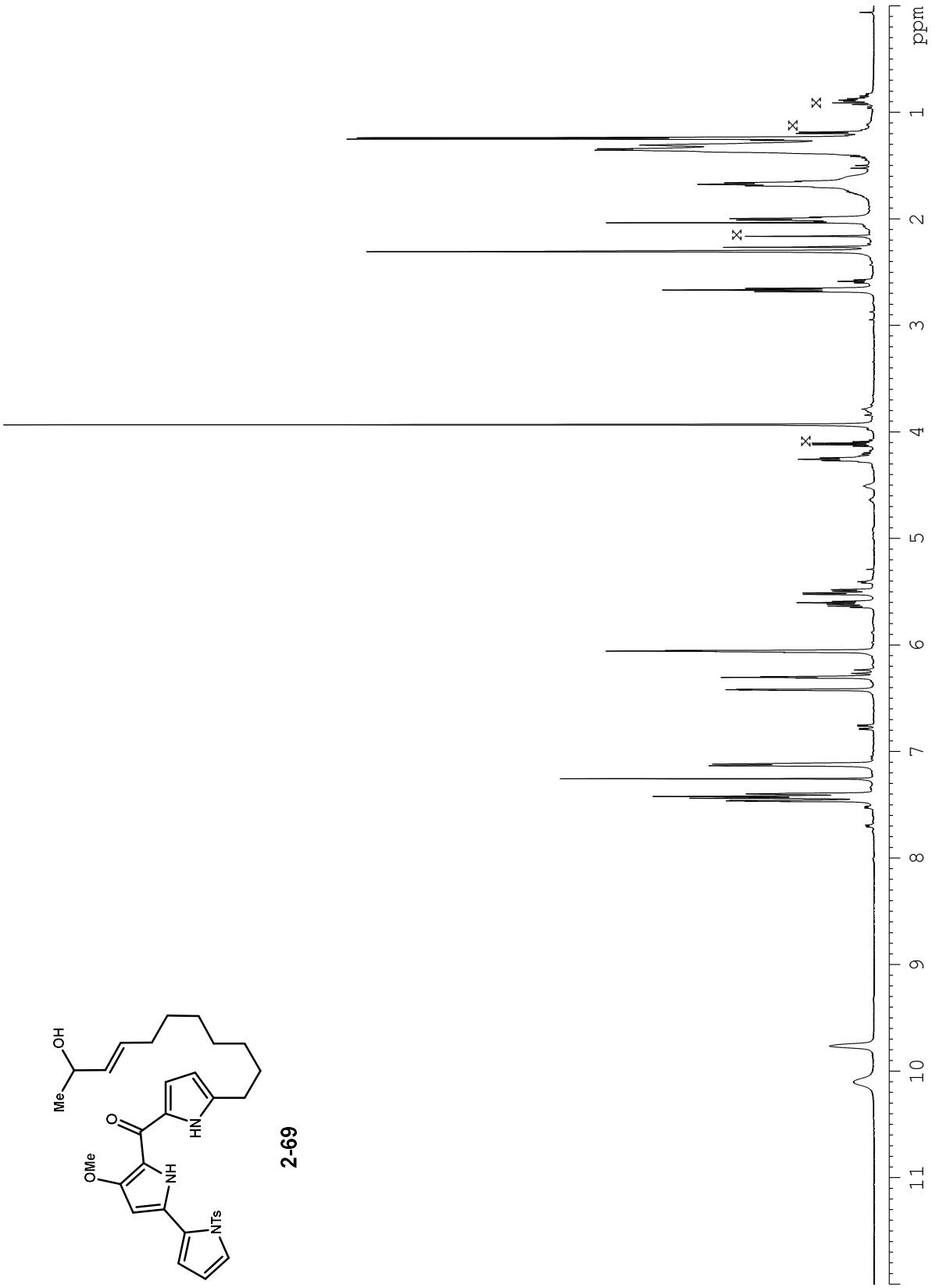
x
x
x
220
200
180
160
140
120
100
80
60
40
20
ppm

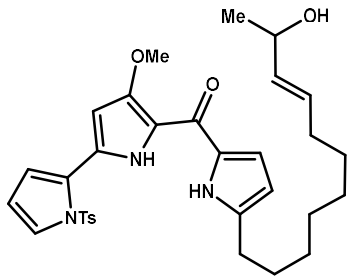


2-59d

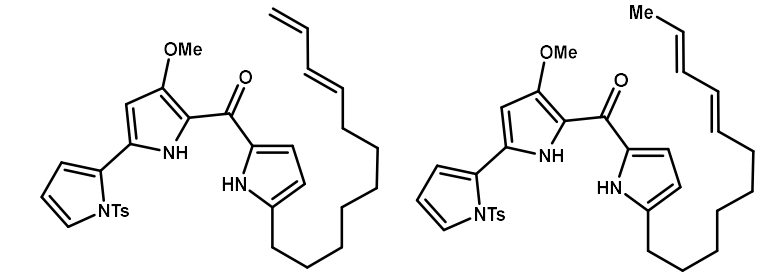


2-59d


Me
OH
O
HN
OMe
NH
NTs
2-69
x
x
x
x
ppm
1
2
3
4
5
6
7
8
9
10
11

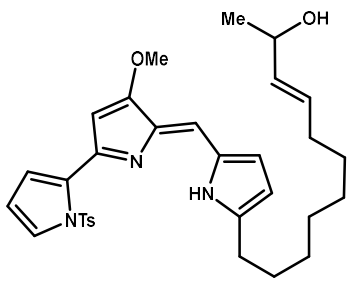


2-69

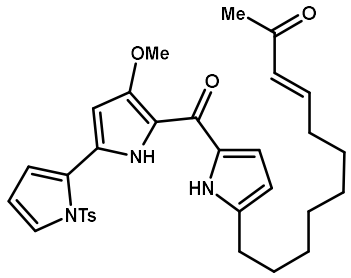


2-70b

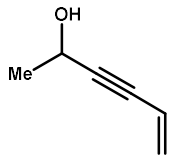
2-70c



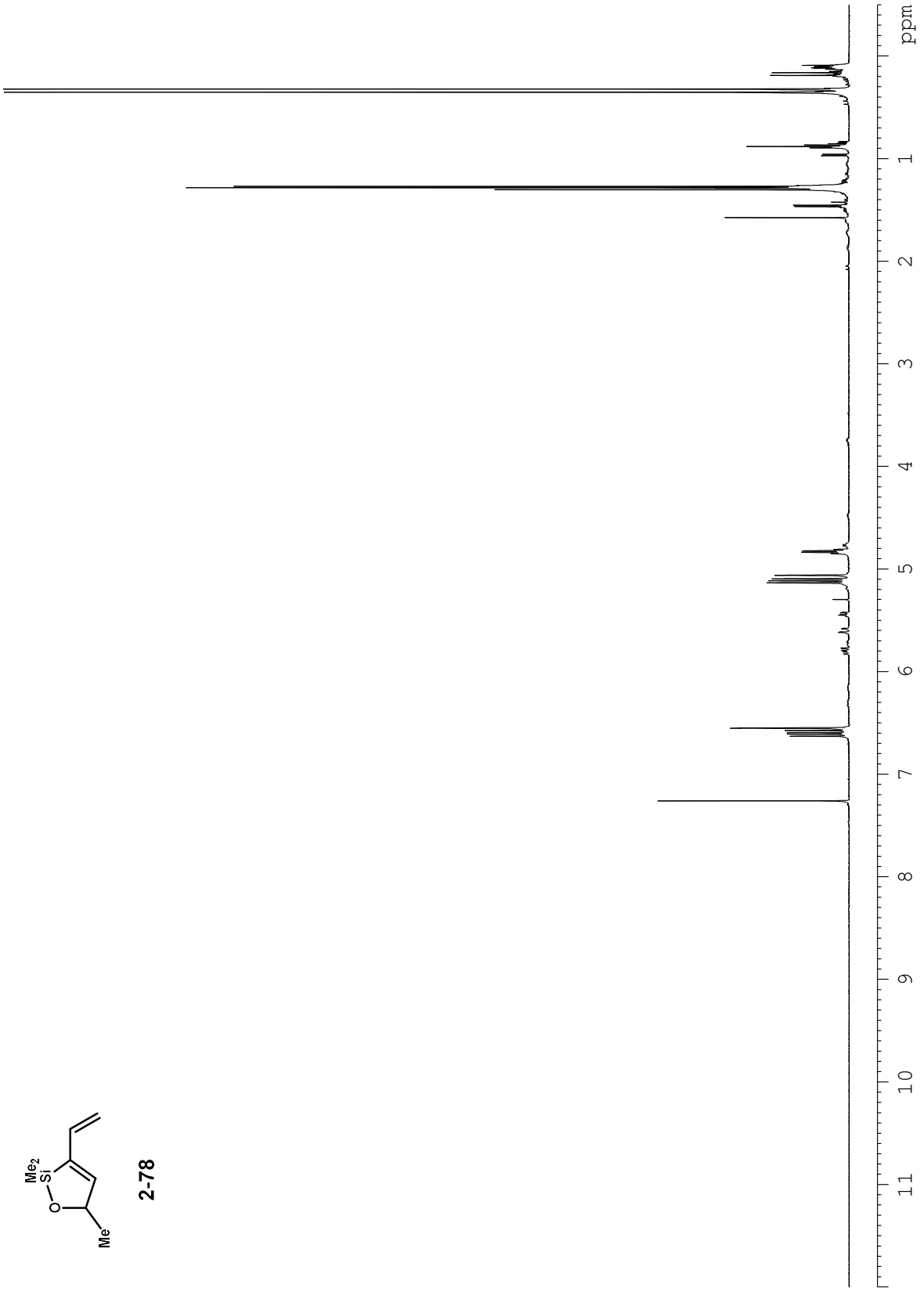
2-71



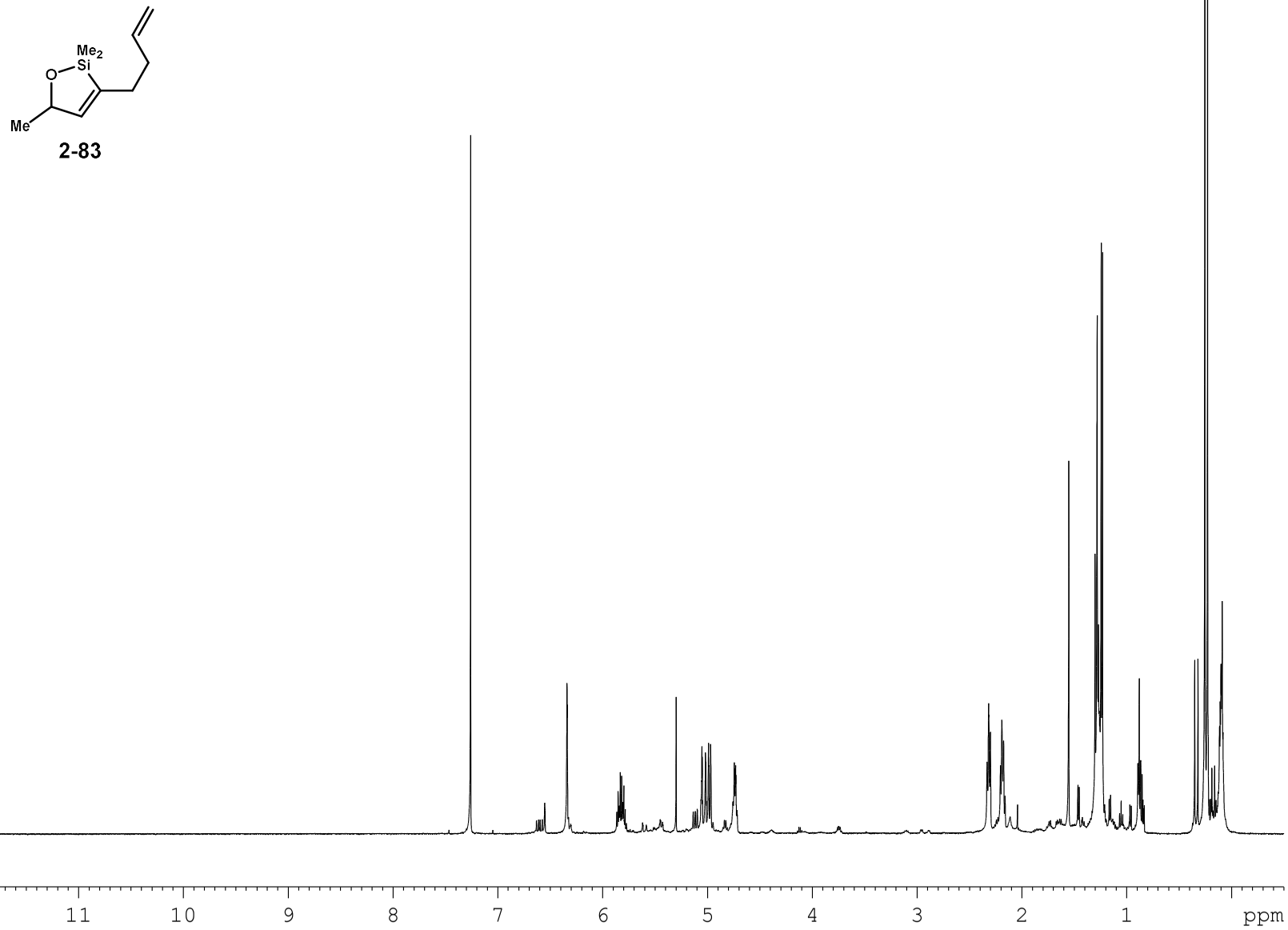
2-76

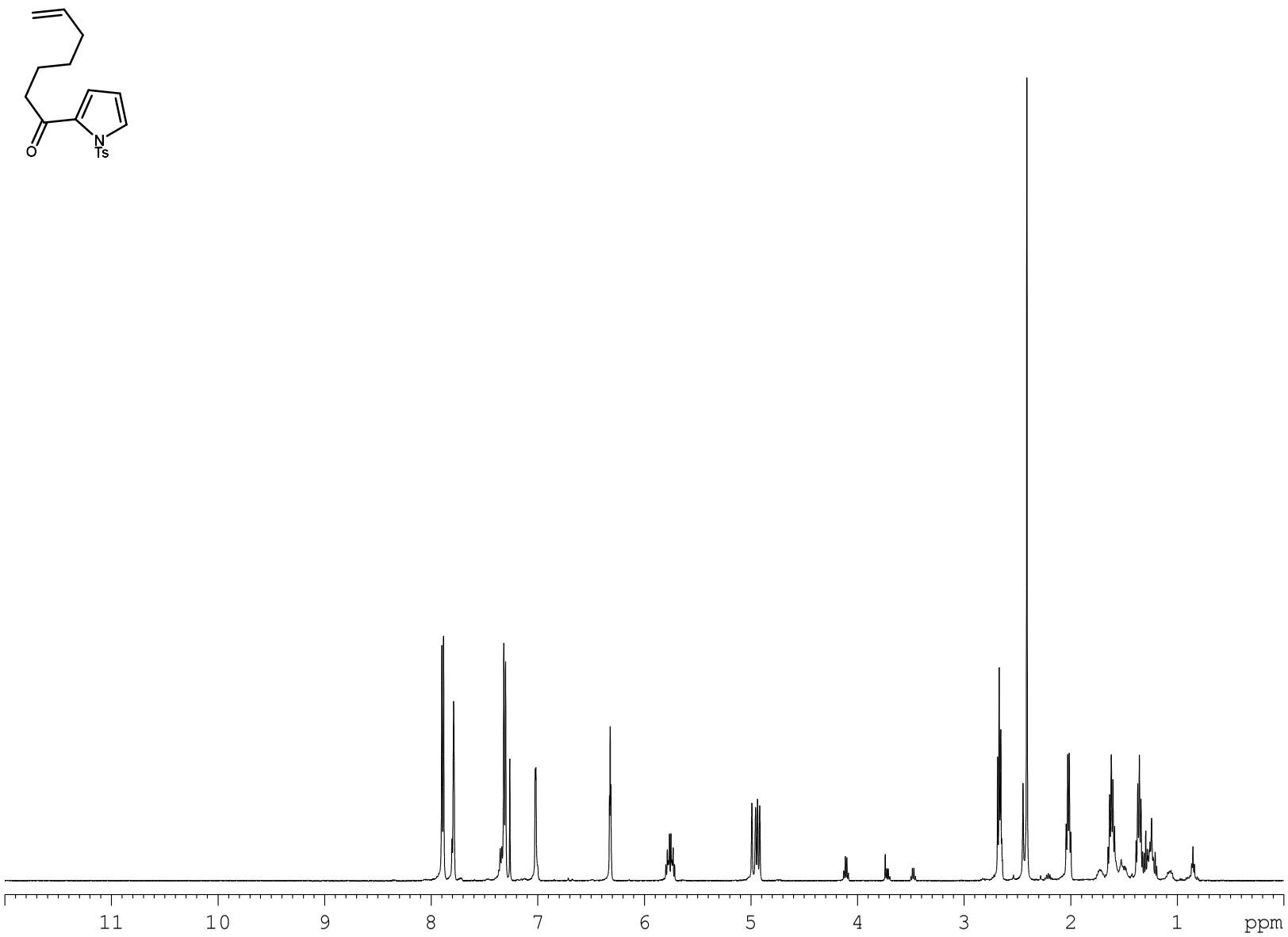


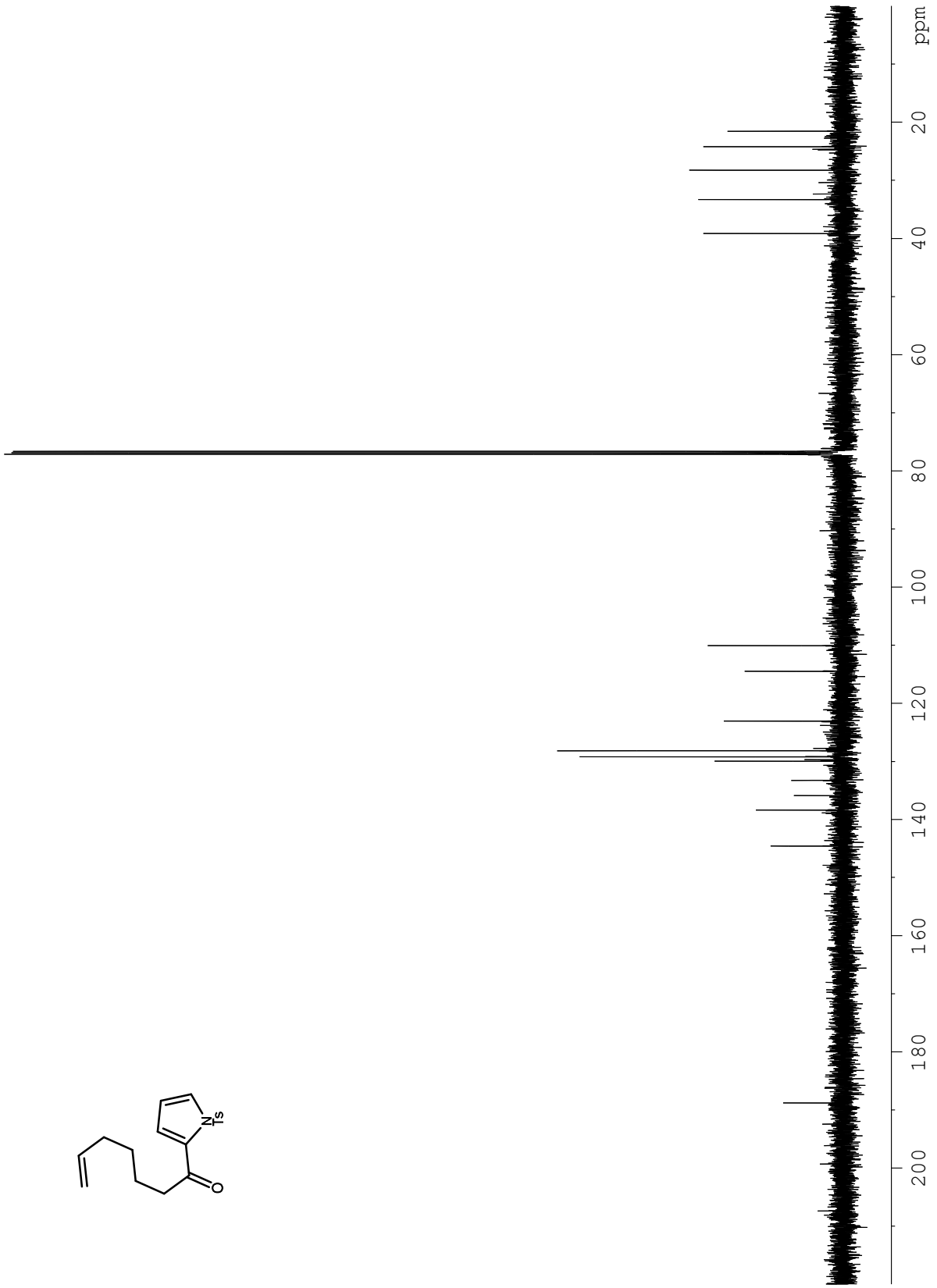
2-82

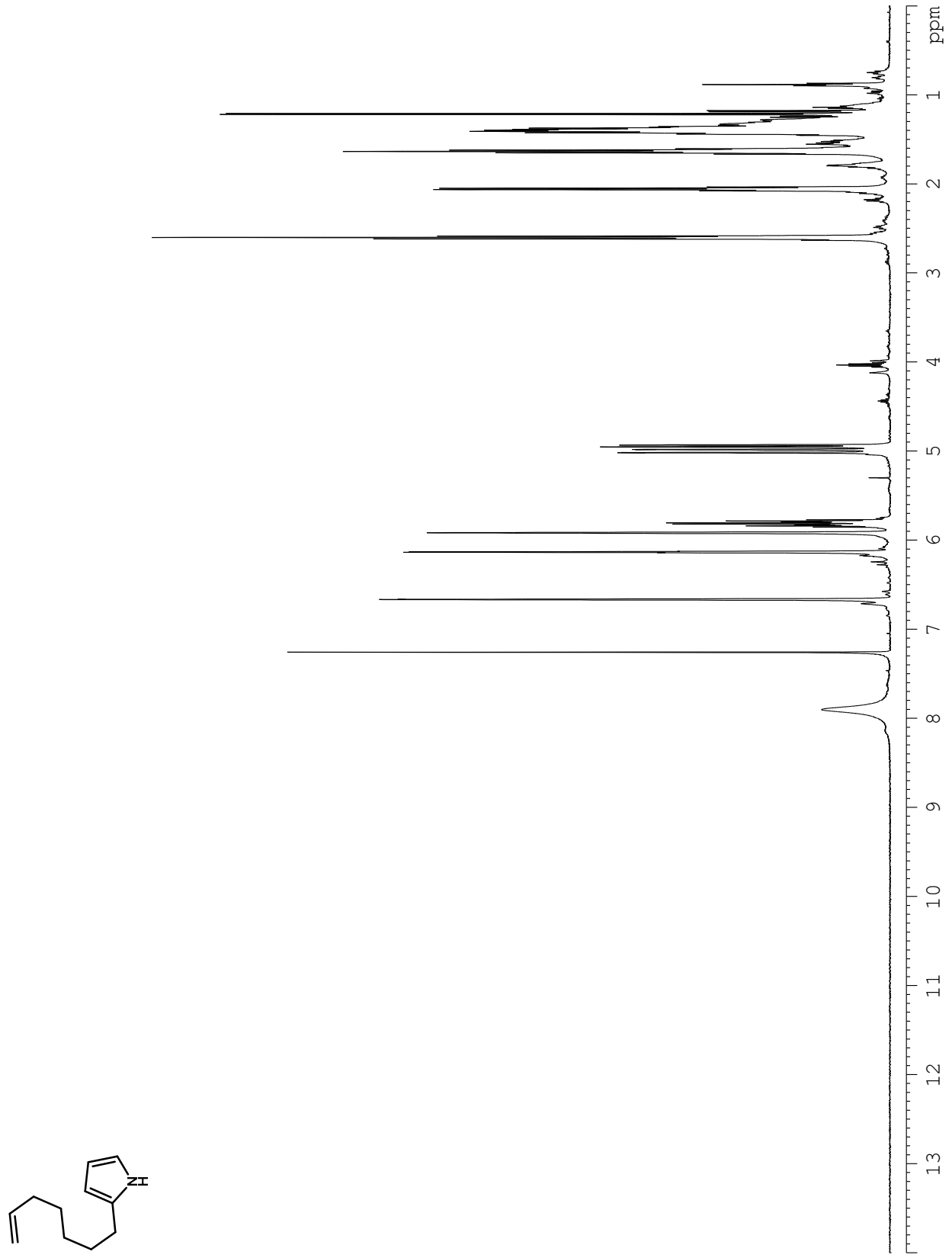


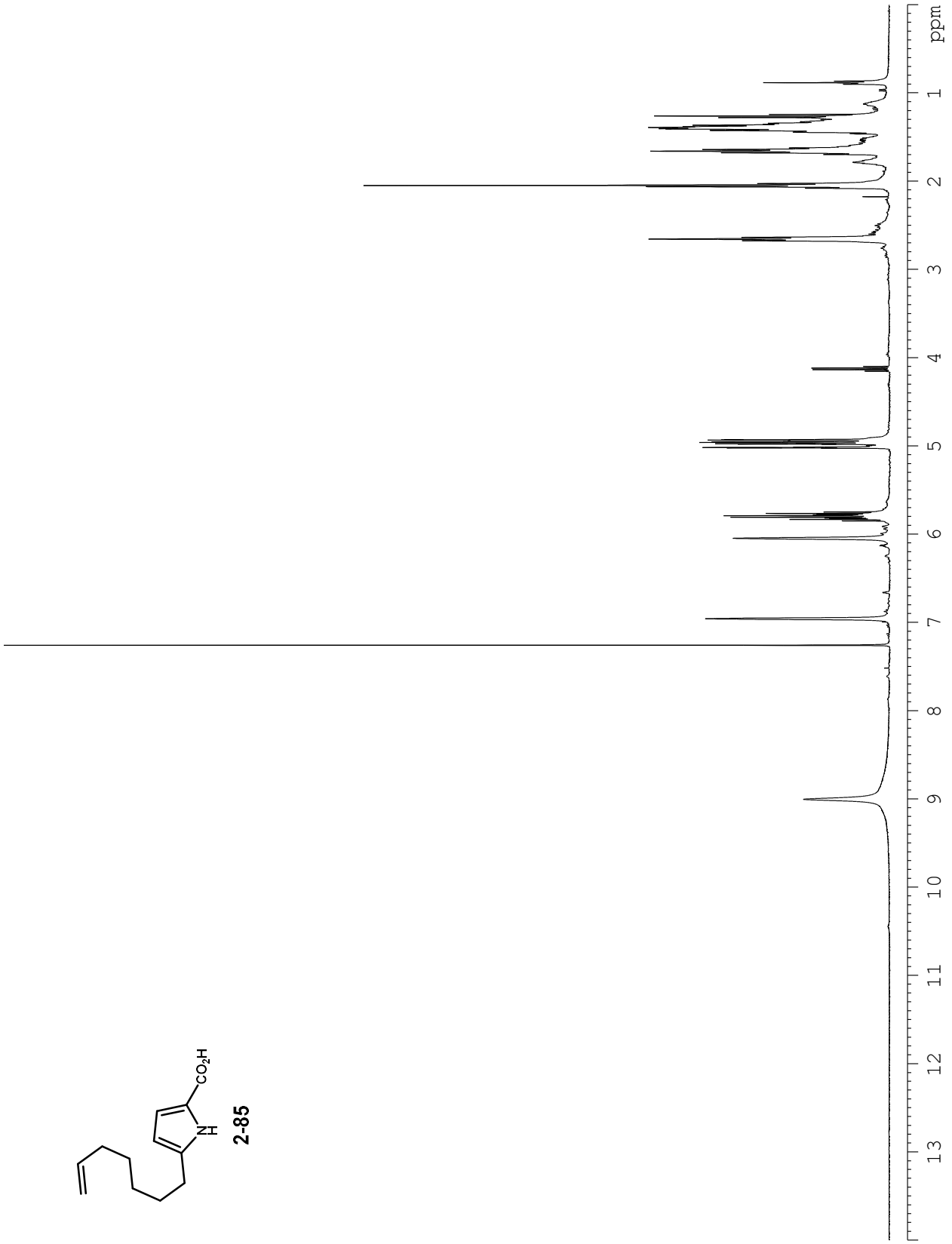
2-78


Me2
Si
O
Me
2-83
11
10
9
8
7
6
5
4
3
2
1
ppm

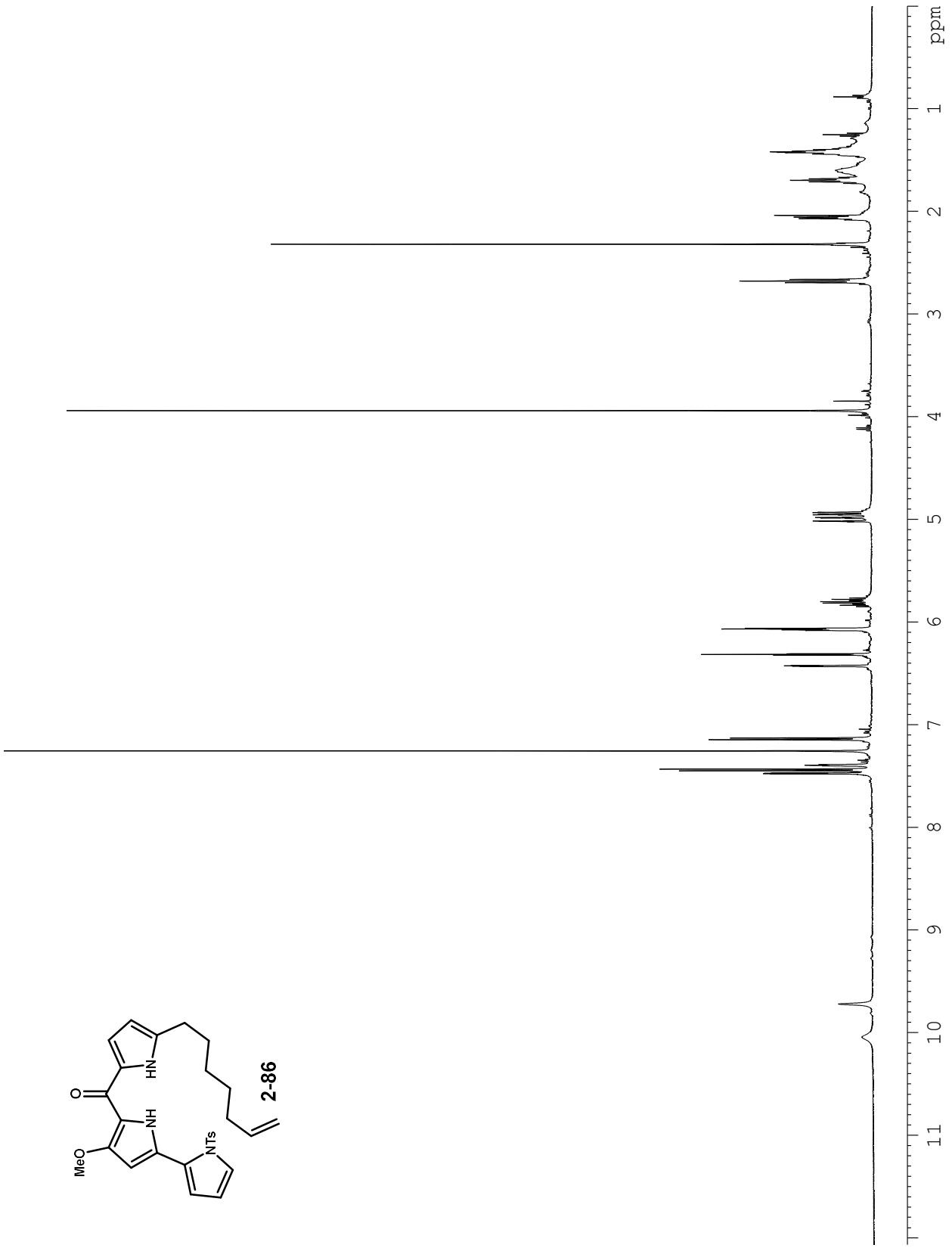

O
N
Ts
11
10
9
8
7
6
5
4
3
2
1
ppm

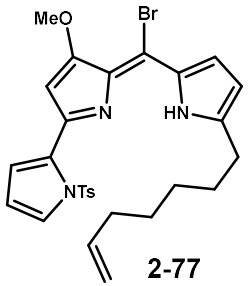

N
Ts
O
ppm
20
40
60
80
100
120
140
160
180
200


ppm
1
2
3
4
5
6
7
8
9
10
11
12
13

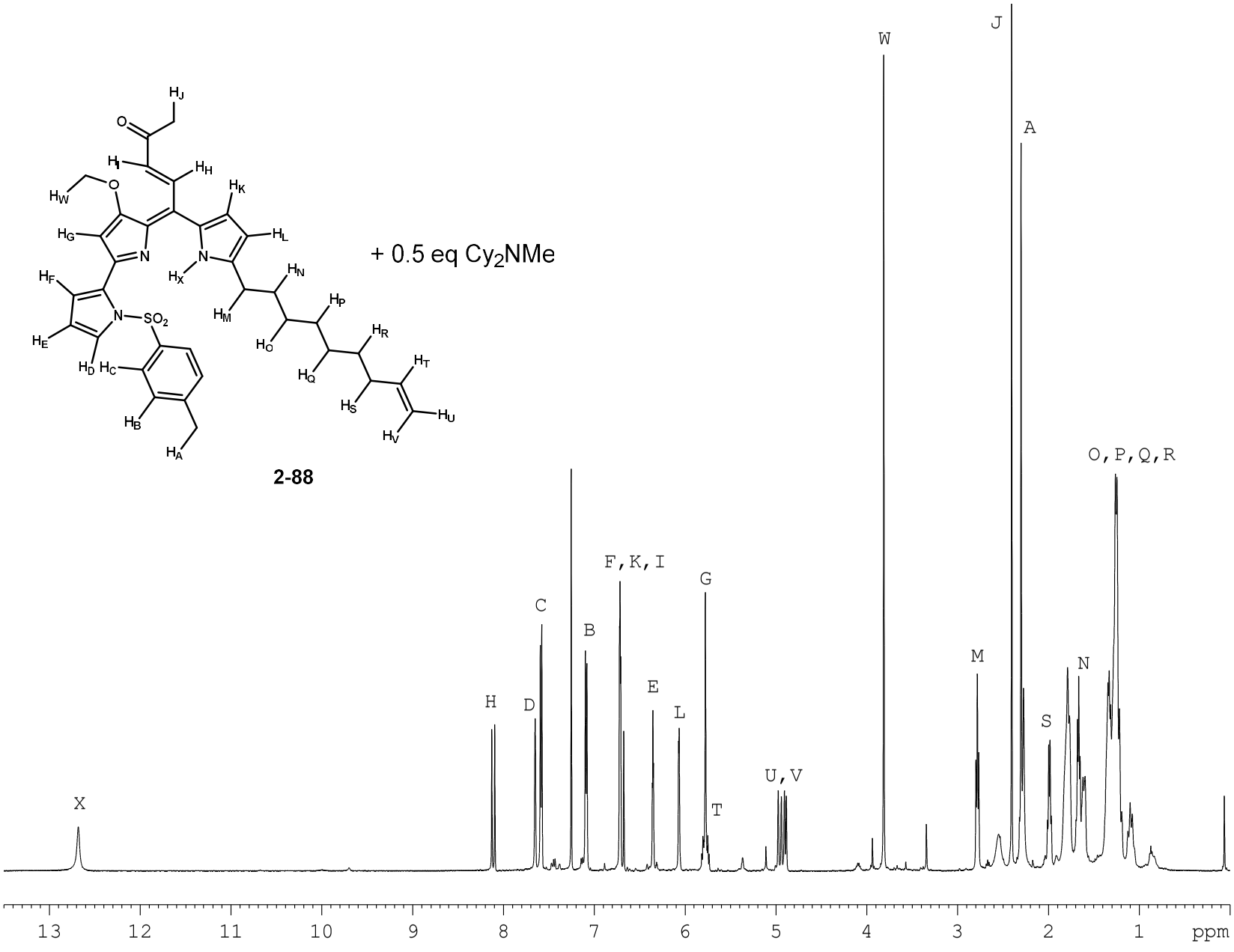


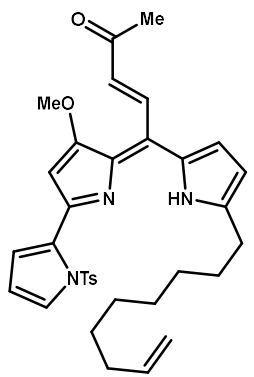
2-85


ppm
1
2
3
4
5
6
7
8
9
10
11
HN
NH
NTs
MeO
O
2-86



2-77


+ 0.5 eq Cy2NMe
2-88
X
H
D
C
B
F,K,I
E
L
G
T
U,V
W
M
J
A
S
N
O,P,Q,R
13
12
11
10
9
8
7
6
5
4
3
2
1
ppm



2-88

+ 0.5 eq Cy_2NMe

3. Chapter Three – Direct Engagement and Functionalization of Lipochromophore to Access the Pyrrolophane Core of the Marineosins

Tyler Allred, Zhengao Feng, and Patrick Harran

3.1. Introduction

3.1.1. Introduction and General Strategy

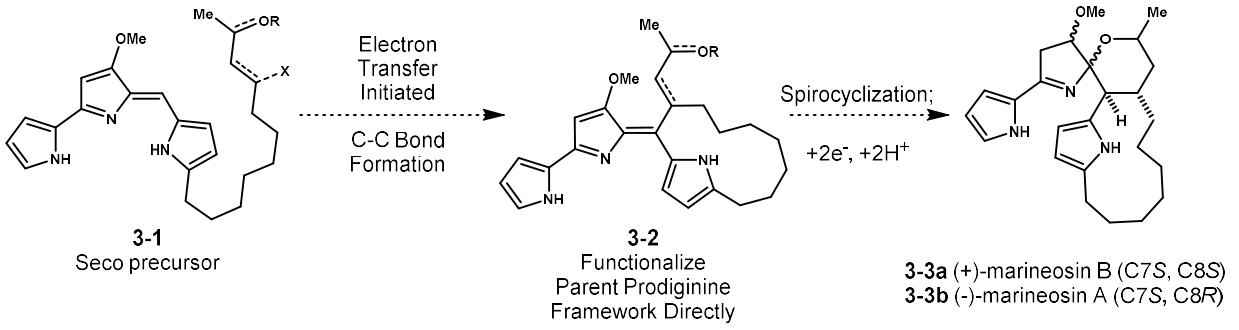


Figure 3.1. Proposed Access to Pyrrolophane **3-2** via Activation/Engagement of Prodiginine Core

With our initial studies on generating the marineosin pyrrolophane moiety proving more challenging than initially anticipated, we considered a more intrepid approach that would capitalize on the inherently high electron density of the prodiginine scaffold. Namely, we postulated that if a functionalized aliphatic chain could be appended to the prodiginine and then activated in some manner to reveal a reactive, electrophilic site that would induce attack by the lipochromophore directly in a manner analogous to the biosynthetic construction of these structures (**Figure 3.1**). Such a transformation, although powerful and elegant, contains the possibility of producing an array of ansa bridged compounds depending on what position the prodiginine chooses to utilize in the capture of the electrophile. Although wary of this possibility, we desired to explore this approach to determine if it could be effectively accomplished in the laboratory. If this approach to pyrrolophane construction is successful, then new chemistry would need to be developed for the generation of the spirocyclic iminal.

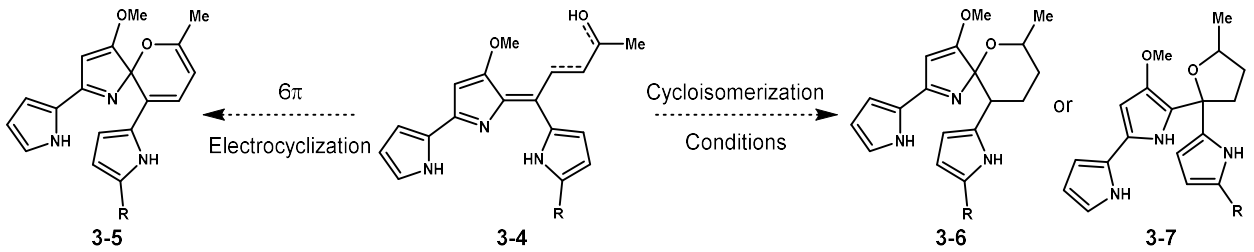


Figure 3.2. Proposed Study to Understand Conditions Required to Induce Cyclization to Construct Spiroiminal Model Compounds (**3-5** or **3-6**)

In planning our approach, we realized that model system **3-4** would be an ideal system to study a variety of cyclization conditions (**Figure 3.2**). It would be advantageous if our route to **3-4** could access both an enone derivative to study the potential of the previously mentioned 6π electrocyclization and the saturated derivative to examine direct hydration of the C8-C9 olefin. In the latter case, regioselectivity of the hydration would be an issue that would need to be addressed. Structural isomer **3-7** could arise from addition to the azafulvene and might prove to be the dominant pathway of hydration. However with this model system, it would be possible to examine a wide variety of hydration conditions and potentially gain insight into how to construct either **3-6** or **3-7** selectively via modulation of reaction conditions. The lessons learned during the studies with **3-4** would ideally translate into use on **3-2** for the completion of the marineosin natural products.

3.2. Results and Discussion

3.2.1. Synthesis of Photoinduced Electron Transfer (PET) Mediated Annulation Seco Precursor

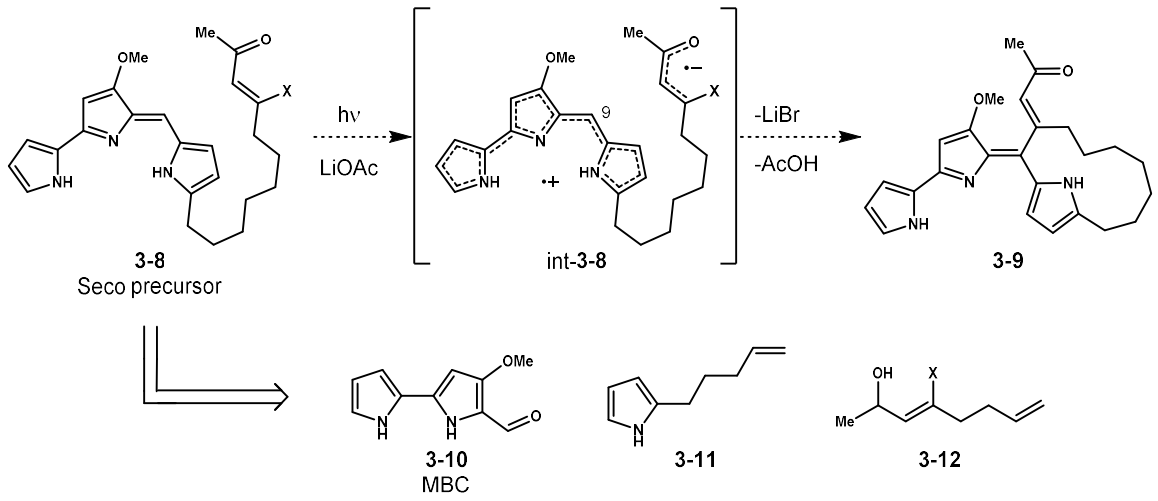
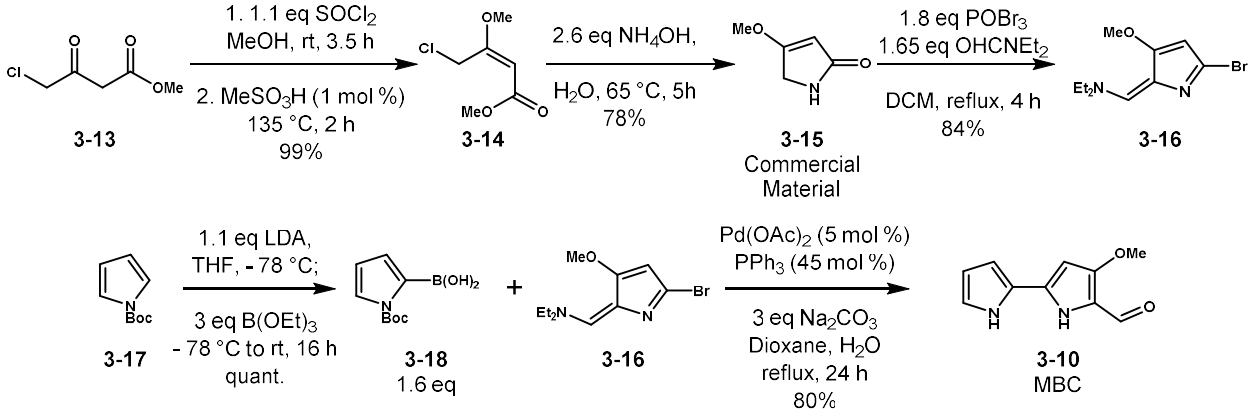


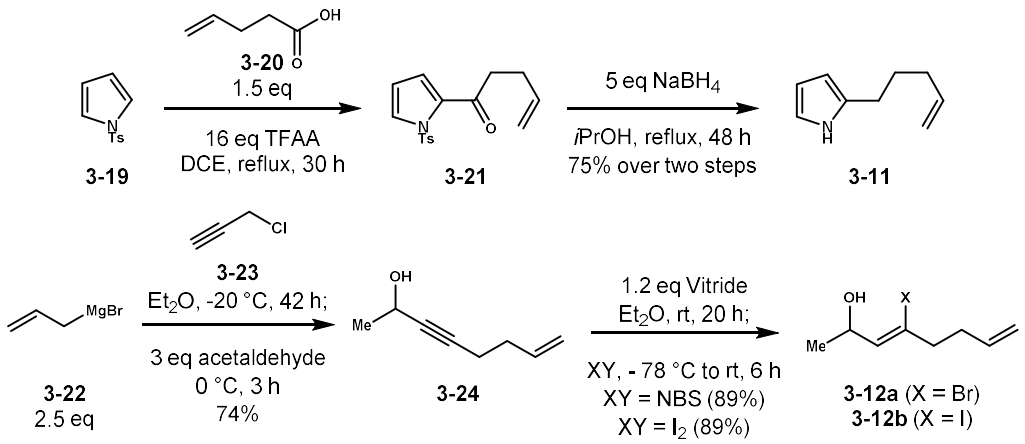
Figure 3.3. Proposed Construction of Pyrrolophane via PET-Mediated Annulation and Targeted Building Blocks for Seco Precursor **3-8**

We were initially inspired by photoinduced-electron transfer chemistry, a process that is typically associated with the Witkop cyclization.[170–173] Our lab has successfully utilized this type of reactivity in the construction of diazonamide A to produce a strained ansa bridge comprising the eastern macrocycle.[174] We postulated that this strategy would take advantage of the innately high electron density of the prodiginine scaffold, which could upon activation by light transfer an electron into an electrophilic β-halo enone on the pendant aliphatic chain (**Figure 3.3**). The resultant radical ion pair could then undergo a mesolytic elimination of HBr to produce a biradical, which would collapse to produce the pyrrolophane. We found this bold approach intriguing and set out to examine it in detail, however we were wary that the regiochemistry of the biradical combination might prove difficult to control. It was determined that seco precursor **3-8** could be constructed in a fairly rapid manner from the combination of building blocks **3-10**, **3-11**, and **3-12**.



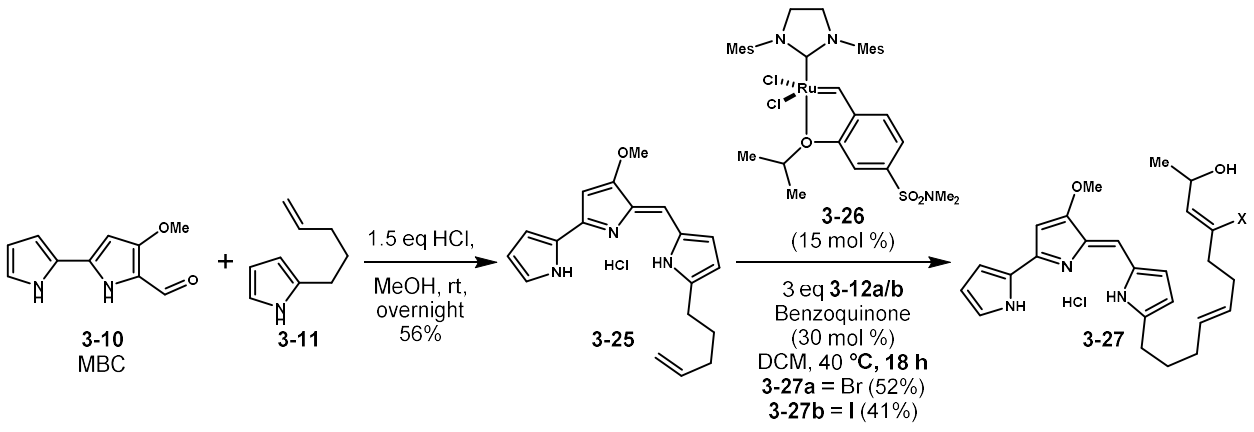
Scheme 3.1. Synthetic Production of 4-methoxy-2,2'-bipyrrole-5-carboxaldehyde (MBC, **3-10**)

4-methoxy-2,2'-bipyrrole-5-carboxaldehyde (MBC, **3-10**) is a common building block utilized in the construction of prodiginine natural products and analogs thereof.[1,2] Due to its utility in this regard, there has been an extensive amount of effort in order to produce **3-10** in an efficient manner.[86,87,89,110,175,176] We chose to replicate the concise route developed by Lavallée and coworkers, which was utilized for industrial production of obatoclax and is the most efficient procedure reported to date (**Scheme 3.1**).[110,177] This procedure commences with pyrroline-2-one **3-15**, which is a commercial material albeit expensive. **3-15** can be accessed fairly easily with a three step process. Methyl 4-chloroacetoacetate (**3-13**) was treated with thionyl chloride in methanol to produce an intermediate dimethoxy ketal, which then dissolved in neat methanesulfonic acid to induce elimination of methanol to form acrylate derivative **3-14**. This material was then subjected to ammonium hydroxide to provide 4-methoxy-3-pyrrolin-2-one **3-15**. Bromoimidate **3-16** was accessed by subjection to Vilsmeier-Haack conditions.[110,178] This intermediate was then combined with boronic acid **3-18**, produced from a lithiation/borylation of **3-17**, via a Suzuki coupling/Boc thermolysis to provide MBC (**3-10**).



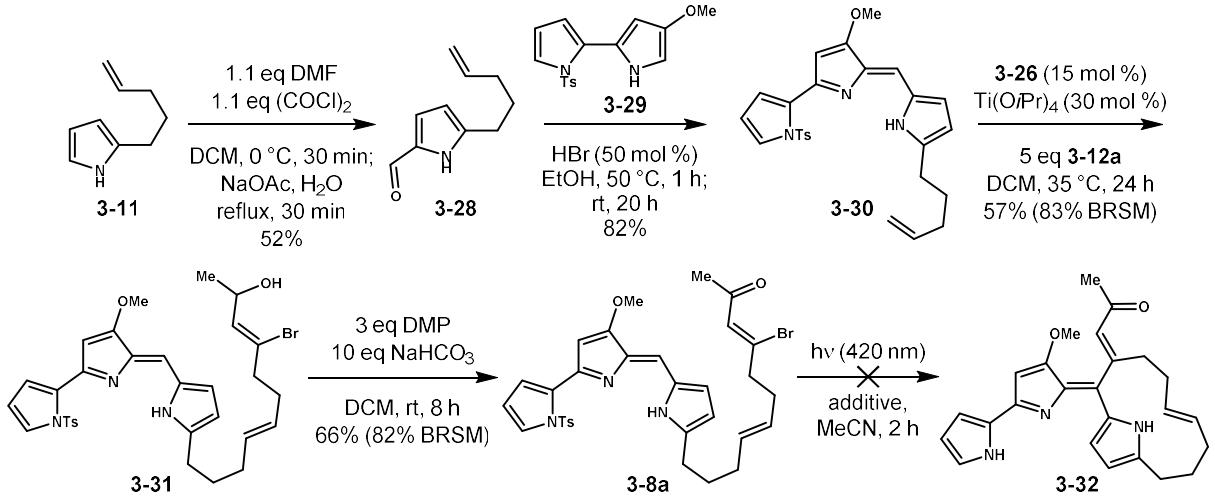
Scheme 3.2. Synthesis of Alkenyl Pyrrole **3-11** and Vinyl Halide **3-12**

The alkenyl pyrrole fragment **3-11** could be accessed utilizing the chemistry discussed in Chapter Two. Tosyl pyrrole could be acylated with 4-pentenoic acid followed by reduction to obtain **3-11** (**Scheme 3.2**). The alcohol segment was constructed using the procedure developed by Hopf and Priebe.[179,180] In the optimized procedure, propargyl chloride was treated with excess allyl Grignard at a low temperature to form an intermediate magnesiated alkyne, which was treated with acetaldehyde to provide alcohol **3-24** after distillation. Hydroalumination of **3-24** was accomplished with Vitride® (Sodium bis[2-methoxyethoxy]aluminium hydride) followed by addition of an electrophilic source of halide (i.e, NBS for Br and I_2 of I) to provide **3-12**.



Scheme 3.3. Combination of Building Blocks to Generate Prodiginine **3-27**

MBC (**3-10**) and alkenyl pyrrole **3-11** were combined in acid mediated Rapoport condensation to produce the dark red prodiginine core (**Scheme 3.3**).[177] This material could be isolated as either the free base or its hydrochloric salt depending on the workup procedure utilized. Our prior studies on cross metatheses with these prodiginine scaffolds (see Chapter Two) suggested that higher yields could be obtained if the substrate remained as the salt form or if the Lewis basic site was sequestered in some manner. Prodiginine salt **3-25** underwent a cross metathesis with alcohol **3-12** facilitated by the Zhan catalyst **3-26**.



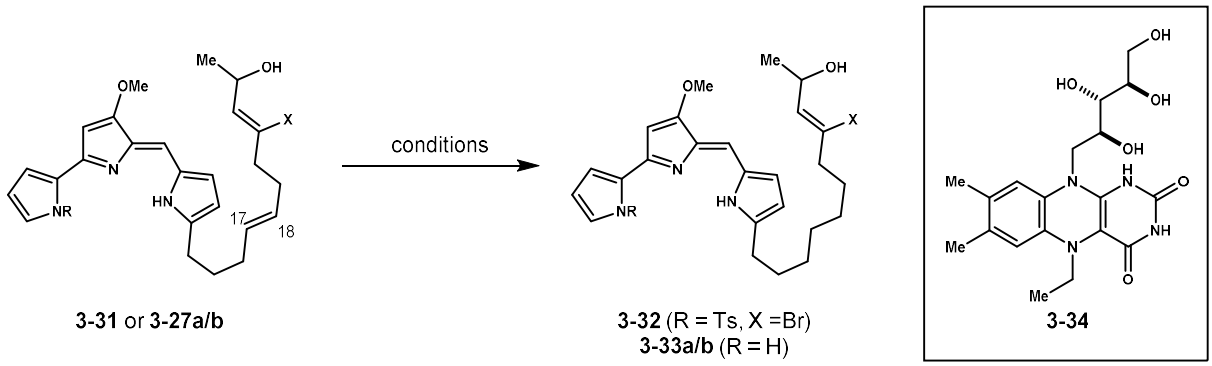
Scheme 3.4. Alternative Access to Protected Seco Precursor **3-8** and Early PET Attempts

Alternatively, a protected variant of **3-26** (i.e. **3-31**) could be constructed utilizing similar chemistry. The alkenyl pyrrole could be formylated using a mild modification Vilsmeier-Haack.[181] During the course of our studies, we determined that alkenyl pyrroles like **3-11** are sensitive to acidic media, decomposing readily via polymerization. However, elongating the alkenyl chain appears to increase the stability of these structures towards acidic environments. Formyl pyrrole **3-28** could then be combined with bipyrrole **3-29** via a Rapoport condensation, where the electronics are reverse as compared to the traditional system.[113] A cross metathesis was then performed to combine the prodiginine with alcohol **3-12a** to afford **3-31**. The allylic alcohol could

then be oxidized with Dess-Martin periodinane to obtain an unsaturated form our desired PET substrate **3-32**.[182] Several irradiation conditions were explored with **3-32** in an attempt to induce PET and ring closure; however, all cases resulted in intractable mixtures. After these failed attempts to close the pyrrolophane, it was postulated that the presence of the additional olefin on the aliphatic chain might prevent the prodiginine core from accessing the electrophilic β-halo enone. This hypothesis led us to examine how to selectively reduce this olefin.

The methods available to reduce the C17-C18 olefin were considerably constricted due to the presence of the vinyl halide moiety. The conditions screened for this reduction are summarized in **Scheme 3.5** and **Table 3.1**. Diimide was identified as a potential reagent for this transformation due to its relatively mild production and selectivity for more sterically accessible olefins. Potassium azodicarboxylate was initially examined as a diimide precursor and showed poor conversion to the desired saturated system, which required multiple resubjections in order to push the reaction to completion (Entry 1).[183,184] A small solvent screen indicated that DCM was the most effective solvent for the reduction using PADA (Entries 4, 5, 6, and 7). The iron catalyzed reduction procedure developed by Baran and coworkers proved ineffective and ultimately led to substrate decomposition (Entry 2).[185] Due to the partial success of diimide, several other methods for diimide generation were investigated. Treatment of vitamin B_2 derivative **3-34** with hydrazine, which in the presence of oxygen generates diimide, proceeded slowly and substantial amounts of overreduction (as determined by HPLC trace) were observed before starting material was consumed.[186] The generation of diimide from the base-mediated decomposition of $TsNHNH_2$ showed some promise, however it proved difficult to remove the tosyl impurities from the desired (Entries 8, 9, 10, and 11).[187,188] The most successful procedure developed utilized *o*-nitrobenzenesulfonylhydrazide (NBSH), which is generated *in situ* by treatment of NBSCl with

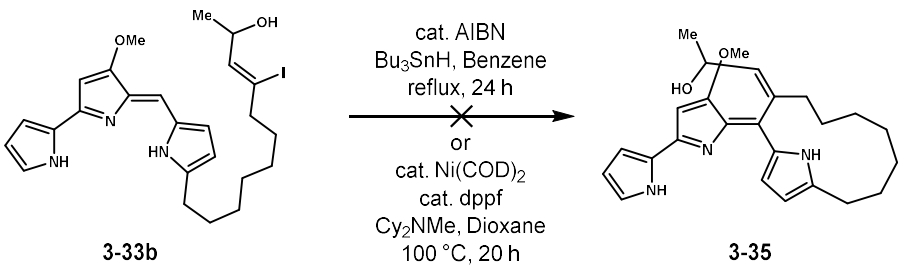
hydrazine at low temperature and then warming to room temperature.[189–191] Unfortunately, this process proved capricious and difficult to reproduce reliably. In addition, attempts on larger scales than 30 mg led to the formation of impurities that were difficult to remove. In light of these issues, a small amount of the reduced material was obtained to further explore the ring closing processes.



Scheme 3.5. Reduction of C17-C18 Olefin

Table 3.1. Conditions Examined for Olefin Reduction

Entry	Substrate	Reagent	Solvent	Temp.	Time	Yield
1	**3-27b**	PADA (100 eq) AcOH (200 eq)	DCM	rt	36 h	25%
2	**3-27b**	$Fe(acac)_3$ (30 mol %) $PhSiH_3$ (1.5 eq)	EtOH/ Ethylene Glycol	60 °C	16 h	0%
3	**3-27a**	**3-34** (25 mol %) N_2H_4 (34 eq), O_2 (atm)	EtOH	rt	5 h	ND (overreduction observed by HPLC)
4	**3-27b**	PADA (36 eq) AcOH (72 eq)	Dioxane	rt	24 h	ND (low conversion)
5	**3-27b**	PADA (5 eq) AcOH (10 eq)	Pyridine	rt	16 h	NR
6	**3-27b**	PADA (10 eq) AcOH (20 eq)	Pyridine	90 °C	12 h	0%
7	**3-27a**	PADA (6 eq) AcOH (12 eq)	MeOH	rt	12 h	NR
8	**3-27a**	$TsNHNH_2$ (5 eq) NaOAc (3 eq)	EtOH	80 °C	16 h	ND (Substantial Ts derived impurity)
9	**3-27b**	$TsNHNH_2$ (2 eq) NaOAc (2 eq)	EtOH	80 °C	16 h	31% (47% BRSM)
10	**3-27b**	$TsNHNH_2$ (4 eq) NaOAc (8 eq)	EtOH	80 °C	5 h	36% (impure)
11	**3-27b**	$TsNHNH_2$ (5 eq) Et_3N (10 eq)	EtOH	80 °C	13 h	ND (Substantial Ts derived impurity)
12	**3-27b**	NBSCl (5 eq) N_2H_4 (10 eq)	MeCN	rt	17 h	57%
13	**3-31**	PADA (20 eq) AcOH (40 eq)	DCM	rt	48 h	69%



Scheme 3.6. Attempts at Annulation from Iodoalkene **3-33b**

Although it was challenging to obtain pure samples of the reduced iodoalkene **3-33b**, a small amount was utilized to probe a bioinspired approach to the ansa bridge via radical generation from the vinyl iodide. The starting material was consumed after heating for an extensive period of time giving rise to several new products on the HPLC trace. However, the masses observed for these new products did not correspond to the desired product and more closely resembled the radical reacting in different processes.[192,193] A nickel-mediated Heck process was briefly examined with this system, but the reaction provided an intractable mixture upon isolation. We briefly explored an alternate order of synthetic steps to access **3-33a/b**, which would circumvent this reduction issue by performing a cross metathesis between **3-11** and **3-12a/b** followed by the reduction of the isolated olefin. This alternate route would allow for easier purification of the reduction product due to the problematic prodiginine core not being present. Unfortunately, these attempts resulted mainly in the recovery of starting material or decomposition under more forcing conditions.

Currently, poor access to the reduced vinyl bromide/iodide **3-33a/b** hinders further useful experiments for the preparation of the PET seco precursor **3-8**. A more efficient and reliable reduction of the C17-C18 olefin would allow for a more in depth examination of this approach.

3.2.2. Perketal Fragmentation as a Means to Generate an Aliphatic Radical for a Biomimetic Lipochromophore Engagement

(NOTE: With the exception of producing **3-45** and **3-47**, the experiments discussed in this section (3.2.2) were performed exclusively by Zhengao Feng and are discussed only to show the progression of the project.)

Taking a step back and considering the biosynthetic origin of the *ansa*-bridge (see Section 1.2.3), we postulated that chemical generation of a radical on the aliphatic chain could produce the pyrrolophane in a bioinspired manner. We hypothesized that the chelating nature of the prodiginine framework could pre-organize the system around a metal center that was capable of generating a radical on the aliphatic chain. The carbon radical would then engage the nearby electron-rich lipochromophore to construct the *ansa*-bridge. Although we were confident the system could be effectively templated, we were wary of potential regioisomeric issues that could arise from radical addition to undesired positions on the prodiginine framework.

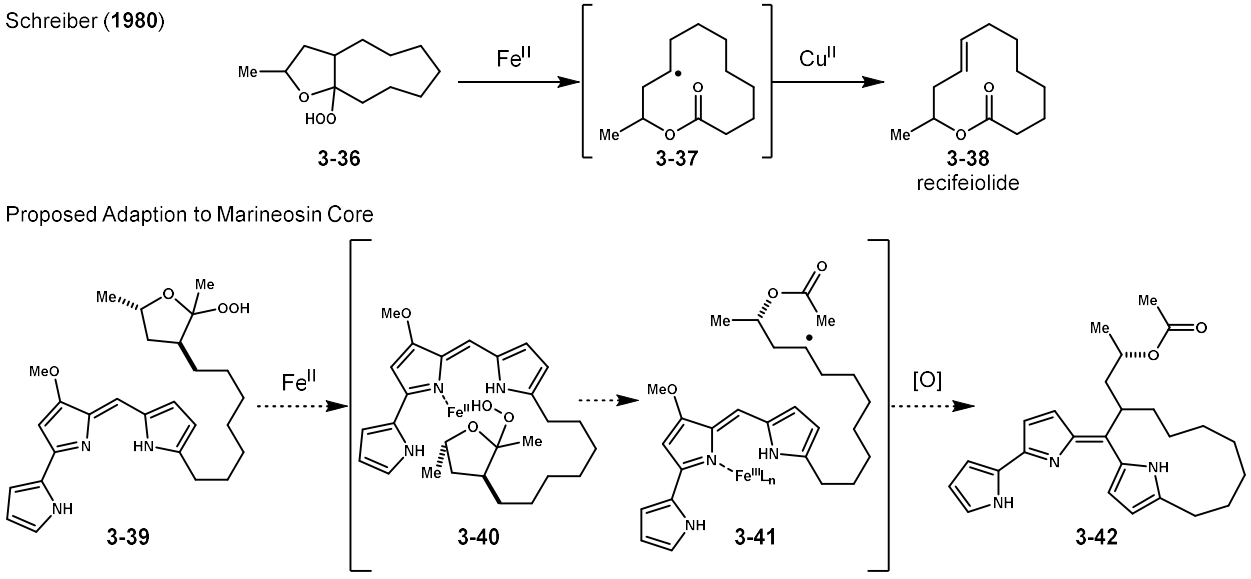
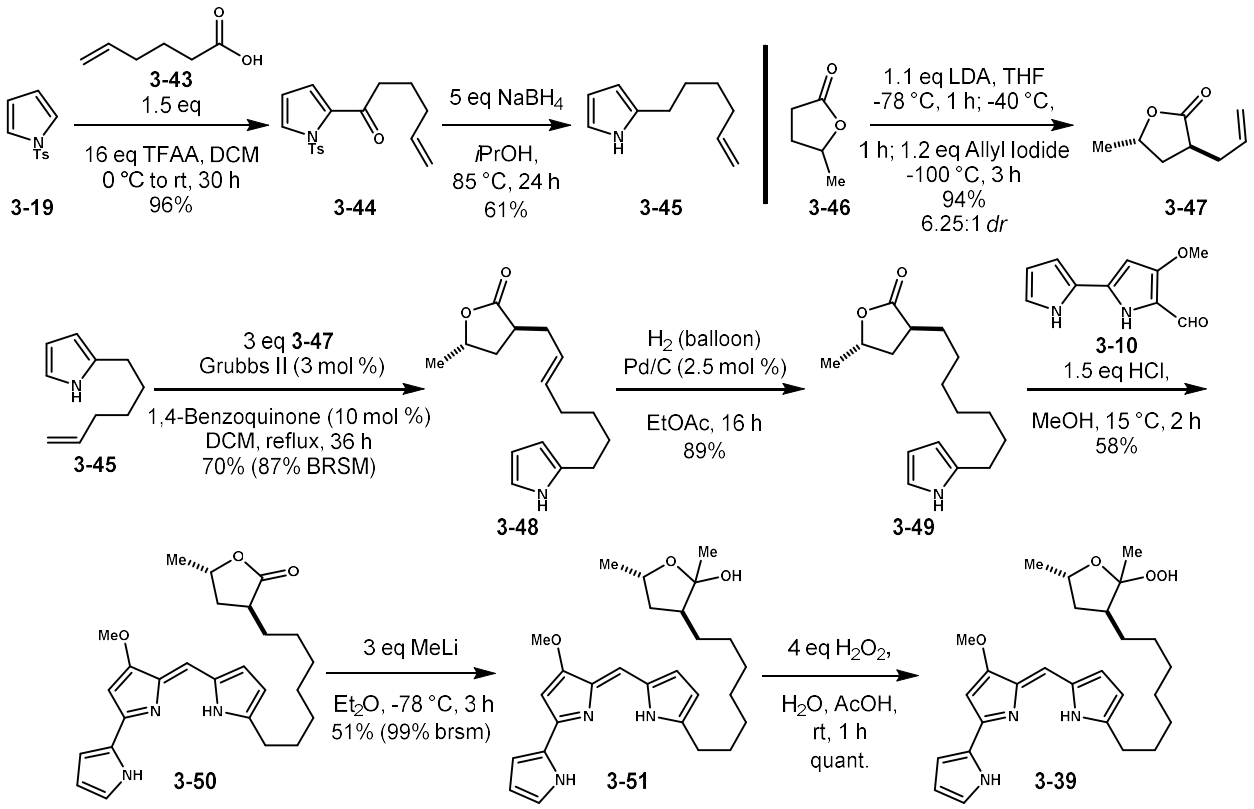


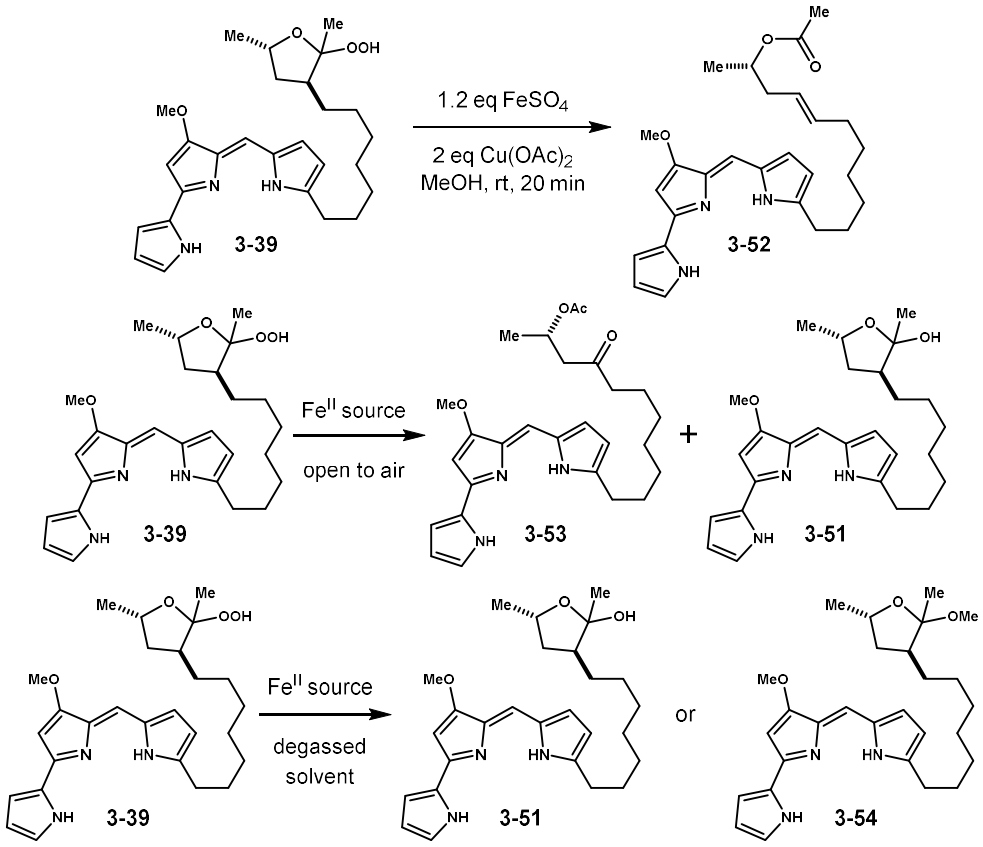
Figure 3.4. Schreiber Approach to Recifeiolide (**3-38**) and Proposed Adaption to Construct Marineosin Pyrrolophane

There are a variety of methods to generate aliphatic radicals and we were intrigued by the works of Kochi, which examined the reduction of alkyl hydroperoxides with Fe^{II} salts.[194–200] These processes reductively cleaved the weak O-O bond to produce an alkoxy radical that underwent a 1,5-hydrogen atom abstraction to generate an aliphatic radical, which could be treated with Cu^{II} salts to generate aliphatic halides or olefins depending on the copper counter ion. These processes were expanded upon by Schreiber and Cekovic.[201–207] Schreiber's modification, which involves the fragmentation of cyclic α-alkoxy hydroperoxides to afford carbon-based radicals, was already being utilized in our laboratory for the synthesis of callyspongiolide and we chose to adapt this strategy to the marineosin system (**Figure 3.4**).[208] Importantly, it was postulated that the Lewis acidic reducing metal would first be coordinated by the prodiginine core, which would bring the radical in closer proximity to the core. After reduction of the hydroperoxide, the radical would be aptly positioned to directly engage the lipochromophore, which would produce pyrrolophane **3-42** after oxidation of the resultant stabilized radical.



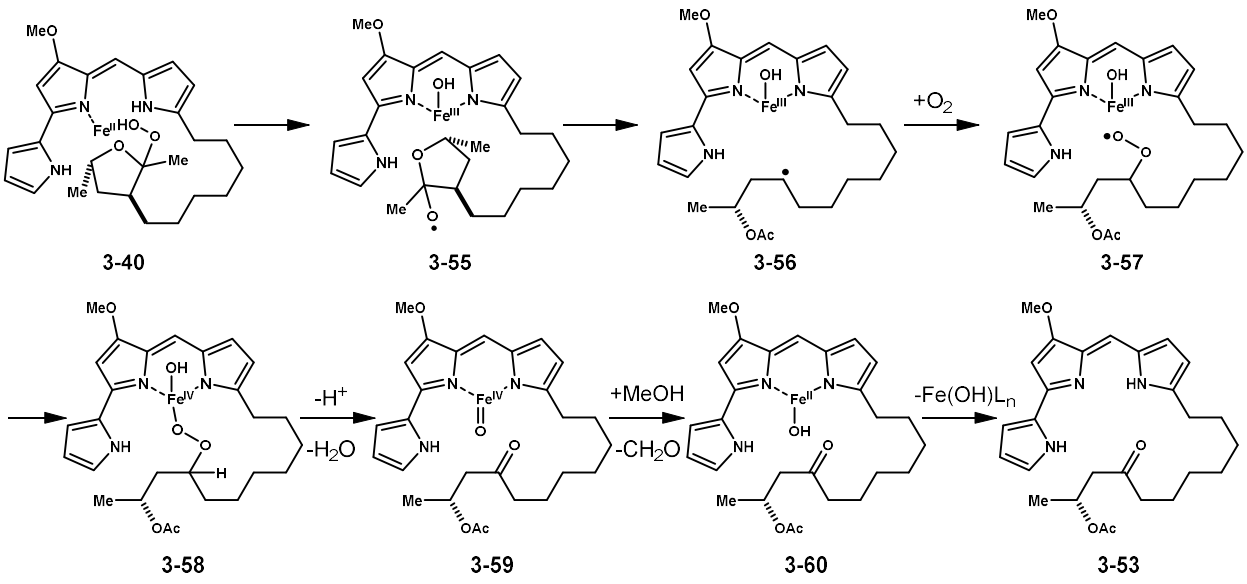
Scheme 3.7. Construction of Radical Precursor **3-39**

The α-alkoxy hydroperoxide **3-39** was prepared in 8 steps from tosyl pyrrole **3-19** (**Scheme 3.7**). 2-(5-hexenyl)-pyrrole (**3-45**) was constructed in a manner discussed previously (*vide supra*). The lactone cross metathesis partner **3-47** was produced by allylation of racemic γ-valerolactone (**3-46**) in a modest diastereomeric ratio. There are a variety of methods to enantioselectively access to (*S*)-γ-valerolactone, which would be utilized if an efficient ansa bridge construction could be developed.[209–211] A cross metathesis of **3-45** and **3-47** followed by hydrogenation afforded the tethered system **3-49**. This material was then combined with MBC (**3-10**) via a Rapoport condensation to afford prodiginine **3-50**. The nucleophilic addition of the methyllithium to the lactone afforded lactol **3-51**, which could be converted to the requisite α-alkoxy hydroperoxide by treatment with H_2O_2 in acidic media.



Scheme 3.8. Examination of Radical-Mediated Pyrrolophane Formation

With general access to **3-49**, a variety of reductive radical generation methods were examined (**Scheme 3.8**). The conditions originally reported by Schreiber were efficient at achieving the desired ring fragmentation, but the only observable product was the olefinated prodiginine **3-52**. It was postulated that the added copper salt reacted too quickly to allow for lipochromophore engagement of the radical and a somewhat slower oxidant would be required for this process. It was determined that atmospheric oxygen could be a viable option as the terminal oxidant. With the reaction flask open to the atmosphere, several Fe^{II} sources were examined for their potential to perform the desired transformation. Unfortunately, the desired pyrrolophane **3-42** was not observed during the course of these studies. However, an intriguing product frequently isolated was ketone **3-53** (*vide infra*).

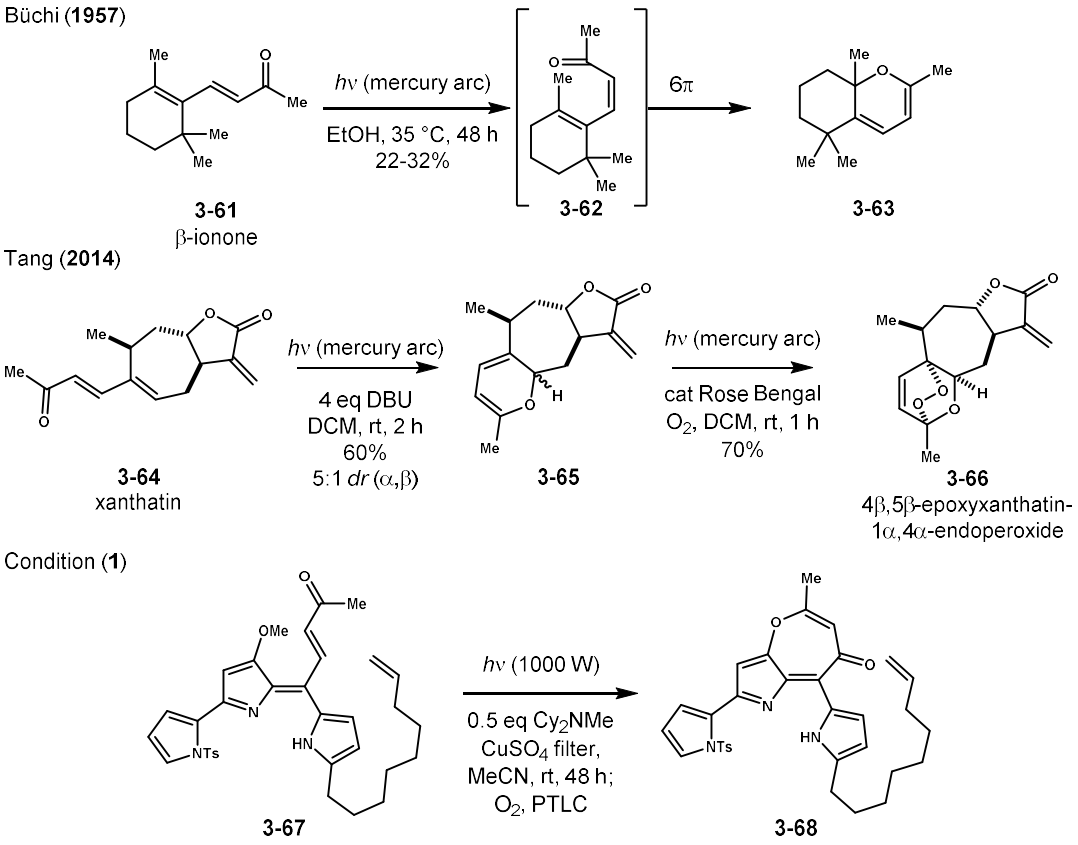


Scheme 3.9. Postulated Mechanism for Formation of Ketone **3-53**

The postulated mechanism for the production of **3-53** is shown in **Scheme 3.9**. It is postulated that the Lewis basic azafulvene nitrogen would coordinate to the Lewis acidic iron (II) sulfate. The metal center then reduces the weak peroxide bond to produce hydroxide and an alkoxy radical, which fragments the tetrahydrofuran ring to produce aliphatic radical **3-56**. This radical would then be intercepted by molecular oxygen resulting in the formation of peroxy radical **3-57**. This radical oxidizes the pendant iron center to generate an iron (IV) peroxy-complex. This mechanism is reminiscent of those utilized by nature to generate the iron (IV) complexes present in enzyme cofactors.[212–214] In this case the chelating nature of the prodiginine framework stabilizes the reactive iron (IV) species in a manner similar to porphyrins. The cleavage of the peroxide linkage occurs via elimination to produce a ketone tethered to the iron (IV) oxo-complex (i.e. **3-59**). It is assumed that complex **3-59** is highly oxidizing and can convert the reaction solvent to formaldehyde via ligand exchange. This process reduces the system to an iron (II) hydroxy-complex, which is hydrolyzed on workup to provide **3-53**.

The other common product isolated from these atmospheric reductions was lactol **3-51**, which is most likely generated by exchange with water facilitated by the Lewis acidic iron species. Interestingly, the fragmentation process is not observed when the system is rigorously deoxygenated and only trans-ketalization is observed. The inability to elicit any observable activity from the prodiginine core was troubling. It is possible that complexing the system with a Lewis acid results in a net deactivation of the lipochromophore, which inhibits reactivity toward the aliphatic radical. With regards to the biosynthesis of the ansa bridge, the reactive iron center is sequestered by enzymatic histidine residues leading to the notion that the prodiginine core is not chelated to the metal. Certainly, this hypothesis could be examined in detail using iron (II) salts complexed with ligands more efficient at chelation than the prodiginine in continued efforts to construct the pyrrolophane as proposed.

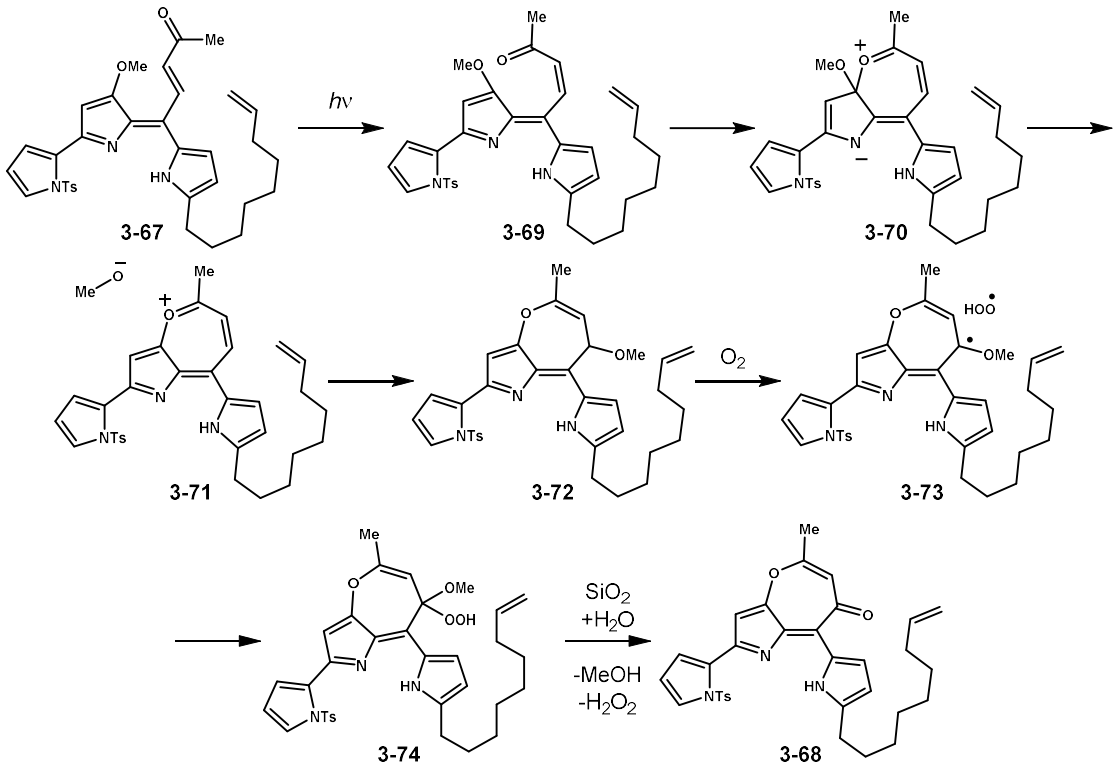
3.2.3. Examination of the 6π Electrocyclization End Game on Model Systems



Scheme 3.10. Literature Precedent for Hetero-6π-electrocyclization and Attempts in Model System **3-67**

Initially we conducted experiments to explore the feasibility of the hetero-6π-electrocyclization in a model system. There are only a few instances of this process being accomplished with dieneones in the literature.[215–219] The works of Büchi and White on photo-induced hetero-electrocyclization β-ionone or derivatives thereof are seminal. White and coworkers determined that the addition of trialkylamine bases increased the overall efficiency and rate of this process.[216] Interestingly, Tang and coworkers utilized this process for the biomimetic construction of 4β,5β-epoxyxanthatin-1α,4α-endoperoxide.[219] Enone **3-67** was chosen as our initial model system due to access having been established previously (See Section 2.2.6). The literature conditions utilize a mercury arc lamp to induce the olefin isomerization/electrocyclization process, which was postulated to be

unnecessary for **3-67**. The highly conjugated system is dark red in color with an absorption wavelength of ~460 nm. It was determined that a powerful halogen lamp when coupled with a filter solution could be utilized to narrow the irradiation range to prevent side processes from occurring. A 0.4M aqueous $CuSO_4$ has a transmission range of ~340 to 540 nm, which was an adequate range for the desired irradiation.[220] When subjected to the 1000W halogen lamp for 2 days with the $CuSO_4$ filter, a new compound was observed by crude ^1H NMR spectrum, as well as some remaining **3-67**. However, the reaction mixture had become noticeably darker changing from dark red to dark purple, which was counter to what was expected if the chromophore had been photo-bleached by electrocyclization. Interestingly, this new material was purple in color and the product band darkened considerably as the PTLC was developing. Extensive spectroscopic analysis indicated that the most likely structure was **3-68**.



Scheme 3.11. Postulated Mechanism for Production of Ketone **3-68**

A mechanistic hypothesis for the formation of **3-68** is provided in **Scheme 3.11**. First, irradiation of the system facilitates the isomerization of the enone from the *E* isomer to the *Z* isomer **2-69**. This isomer has a considerable steric strain due to the ketone and methoxy groups occupying the same space. However, the ketone can relieve this steric interaction via a conjugate addition to the B ring. This process appears to occur much faster than the desired hetero-6π-electrocyclization. The resultant Michael adduct **3-70** eliminates methoxide, which can then add via another Michael to the α,β-unsaturated oxonium species to produce **3-72**. This electron rich allylic ether is two electrons higher in oxidation state than a highly conjugated aromatic system, which makes it prone to facile oxidation. When the crude reaction is loaded onto a PTLC plate, one can observe a significant darkening in color as the product band climbs the plate. It is hypothesized that this darkening is the result of oxidation by atmospheric oxygen to generate α-alkoxy peroxide **3-74**, which on the mildly acidic PTLC plate can hydrolyze to afford **3-68**. This result was fascinating, however it effectively eliminated the hetero-6π-electrocyclization as an option to construct the spiroiminal core of the marineosins. Our aim now shifted to developing an alternate method of constructing this unique structural feature.

3.2.4. Direct Anti-Markovnikov Hydration of the Prodiginine Azafulvene

The intriguing result of the *ipso* substitution of the methoxy group by ketone in **3-67** led us to explore an alternate approach where the spiroiminal would be accessed by direct cycloisomerization of a pendant alcohol onto the azafulvene, which could also be viewed as an intramolecular anti-Markovnikov hydration. The most common method of achieving a net anti-Markovnikov is through the hydroboration/oxidation sequence developed by Brown.[221,222] The area of anti-Markovnikov hydration has recently seen a surge in interest with several novel

methods reported by the Grubbs, Herzon, and Nicewicz laboratories.[223–226] Unfortunately, these methods were postulated to be incongruous with the prodiginine system. The Lewis basic nature of the azafulzene could coordinate the metal catalysts and modulate the activity in an unproductive manner (see Section 3.22). Alternatively, the Nicewicz method requires the use of a photoredox catalyst, which is excited in the same range as the prodiginine chromophore. In addition, the inherently reactive site of the prodiginine core's azafulvene would be position C9, which could lead to tetrahydrofuran type products instead of the desired pyran (**Figure 3.5**). In spite of these potential issues, it was posited that anti-Markovnikov selectivity could be achieved via other means. It was determined that if the prodiginine core could be partially reduced to **3-75** and then treated with acid or a transition metal complex, which would facilitate cyclization to provide a product at the same oxidation state as the natural product (i.e. **3-76**). Intermediate **3-75** would most likely need to be handled under inert atmosphere to prevent auto-oxidation back to **3-4**. It was postulated that the spirocyclization could have modest diastereoselectivity based on the results of other reported marineosin models.[33,107,227] In addition, we were confident that an enantioselective reduction of **3-4** could be achieved to allow access to optically active derivatives.

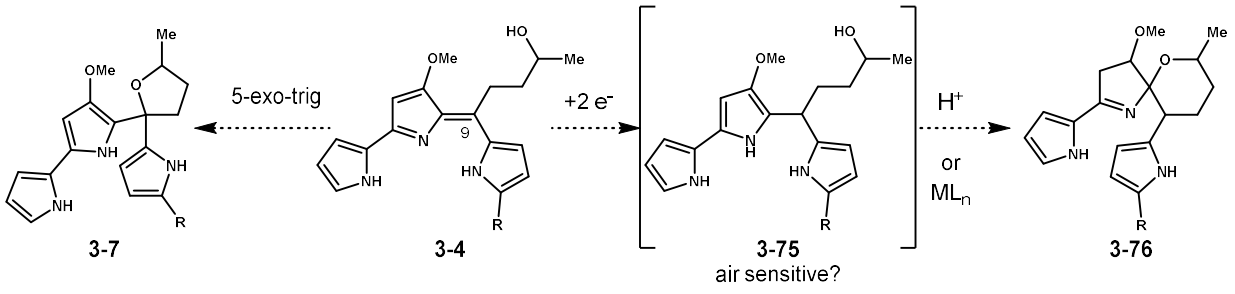
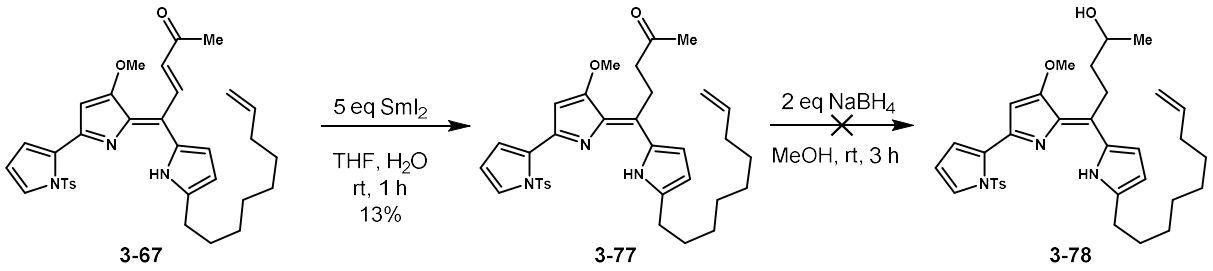


Figure 3.5. Proposed Intramolecular Net Anti-Markovnikov Hydration to Construct Spiroiminal Model

With the route to **3-67** established, we explored conditions to reduce the system. A variety of reduction conditions were examined to reduce the α,β-unsaturated ketone.[228] Hydrogenations with supported metal catalysts resulted in low recovery of starting material or decomposition, it is

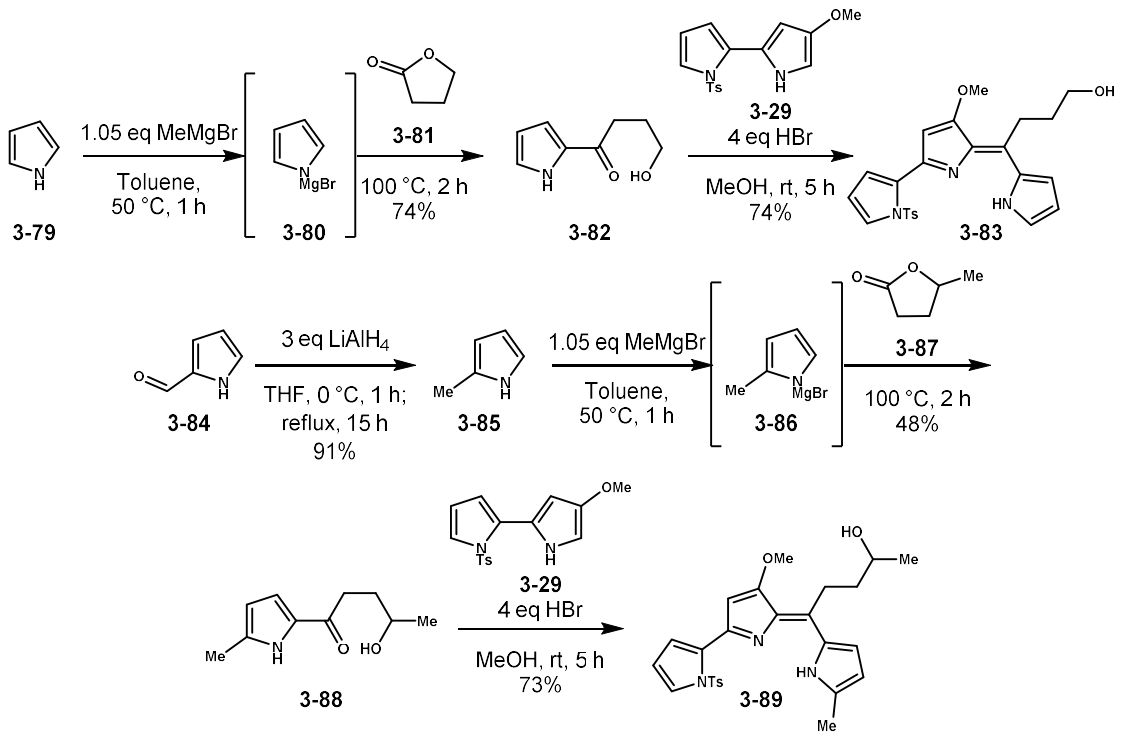
postulated that the aromatic prodiginine core adheres tightly to the catalyst carbon surface. Unfortunately, the only successful, albeit low yielding, conditions were hydrogenation with Raney Nickel or reduction using Kagan's reagent.[229] Ketone **3-77** proved to be unstable and difficult to purify, with preparative TLC being the most efficient option for purification. With the desire to obtain alcohol **3-78** in one operation from **3-67**, attempts were made to push the reduction further with larger equivalents of samarium (II) iodide. These experiments resulted in cleavage of the tosyl protecting group and decomposition into a myriad of products when monitored by HPLC. A stepwise reduction procedure was attempted via isolation of the ketone and reduction using sodium borohydride. However, this procedure proved disastrous with the isolation of an intractable mixture.



Scheme 3.12. Attempts to Reduce Model System **3-67**

The long sequence required to access **3-67** and the low yielding reduction conditions caused us to reconsider our model system studies. The ease of the Rapoport procedure was enticing as a strategy to construct the **3-4** prodiginine model system, which would allow rapid access due to its convergent nature. This approach would require the combination of bipyrrole **3-29** with a pyrrolylketone partner, a tactic seldom seen in the literature. Hao and coworkers reported that $POCl_3$, a fairly harsh reagent, was required to mediate the condensation.[230] Alternatively, Smith and coworkers reported that *ipso* substitution of a C9 chloride with Grignard reagents could install aliphatic groups at that position.[231] However, neither of these methods would tolerate the presence

of a free alcohol in the system. Not satisfied with either of the literature conditions, we proceeded to examine the condensation of **3-29** with ketones via traditional Rapoport conditions.



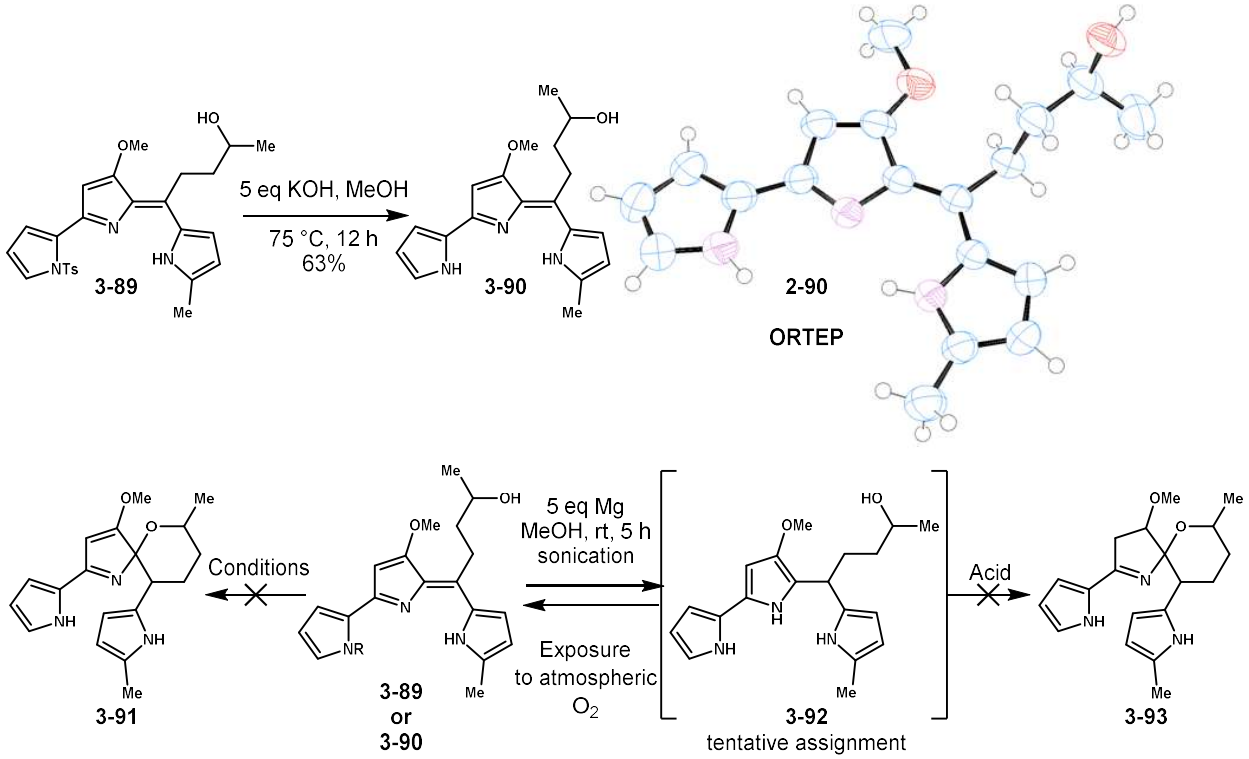
Scheme 3.13. Access to Marineosin Model Systems for Spirocyclization Studies

We initially targeted **3-83** as our desired model system, which could be assembled from **3-82** and **3-29** via a condensation. Fortunately, a one-step preparation of **3-82** had been reported by Nicolaou and coworkers during their efforts on X-14547A.[232] When the magnesium salt of pyrrole was treated with a lactone at high temperature, C-acylation occurs almost exclusively. This method was utilized to construct gram quantities of **3-82**. To our delight, the first attempt to combine **3-29** and **3-82** via acid-mediated condensation was both informative and successful. After the addition of several drops of HBr, the reaction became dark red in color (a characteristic of the prodiginine core) and after several hours the HPLC trace indicated complete conversion to a compound of the desired mass. However after neutralization and isolation, the spectroscopic data for this product was surprisingly complex. Both the ^{1}H and ^{13}C NMR spectra contained a multitude of peaks, which

indicated that **3-83** might exist in a variety of similar energy conformations. There have been few studies on the conformational dynamics of the prodiginine scaffold.[19,233] Thomson and coworkers posit that the ansa linkage of certain prodiginines serves to enforce the more biologically useful conformation (i.e. the conformation where an intramolecular hydrogen bond forms between the azafulvene nitrogen and C-ring nitrogen).[19] A fact that further enforces this notion is that there is a substituent at C13 in all known natural prodiginines. Therefore, since model system **3-83** lacks any substituents, other conformations of the prodiginine core become available.

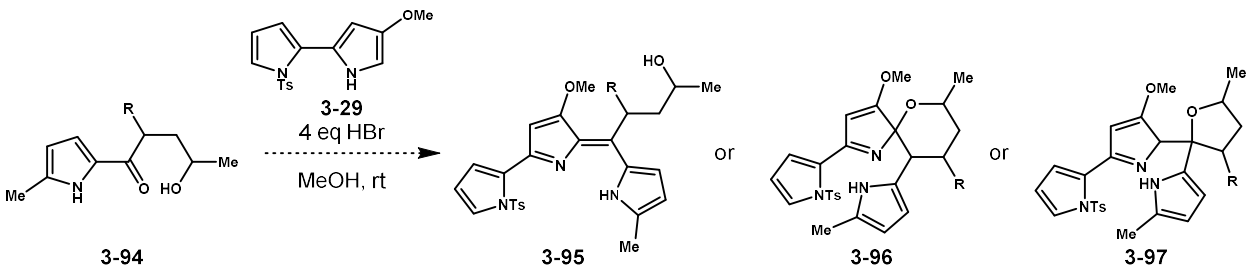
The complexity associated with analysis of **3-83** resulted in it being ineligible for use as a model system. It was postulated that the slightly more complicated model **3-89** might provide more tractable spectra allowing for in depth exploration of our desired cycloisomerization. Pyrrole 2-carboxaldehyde (**3-84**) was reduced to 2-methylpyrrole (**3-85**) by the use of lithium aluminum hydride and was then converted to its magnesium salt, which was subjected to γ-valerolactone (**3-87**) at high temperature. The requisite ketopyrrole **3-88** could be precipitated from toluene in relatively high purity. Again, the first attempt of the acid-mediated condensation was successful. Fortunately, the spectroscopic data for **3-89** was much easier to interpret, containing one clearly major conformer and others in less than 15% total based on the ^{1}H NMR spectrum. Further confirmation of the structure was obtained via X-ray crystallographic analysis of the de-tosylated material (**Scheme 3.14**). This result partially confirms the hypothesis that the C13 substituent is crucial for the prodiginine preference of one conformer.

With **3-89** in hand, a variety of conditions were explored for direct cyclization onto the prodiginine scaffold (**Scheme 3.14**). Our initial attempts looked at acid/transition metal catalyzed direct hydration of the azafulvene. Unfortunately, the major isolated material in most cases was starting **3-89**, otherwise intractable mixtures were obtained.



Scheme 3.14. Preliminary Attempts to Induce Spirocyclization

One auspicious process that was discovered during the course of these studies was the ability to reduce the prodiginine core. Sonication of magnesium metal in methanol for several hours provides a yellow/brown material that turns red rather quickly when exposed to atmospheric oxygen. This reddening is accelerated when the material comes into contact with neutral alumina. Considerable difficulty was encountered when attempting to characterize this yellow material due to handling issues. This material was tentatively assigned as the partially reduced structure **3-92**, due to the isolation of **3-90** after exposure to atmospheric oxygen. We sought to use this process to our advantage and try to access spirocycle **3-93**, a structure at the oxidation state of the marineosin natural products, directly from intermediate **3-92**. Several attempts were made to induce cyclization with strong acids. However, these resulted only in recovery of **3-90**. Extended heating with acids resulted in a myriad of products by TLC.



Scheme 3.15. Proposed Synthesis of Branched Spirocyclization Model System

We found it unusual that in most cases **3-90** was isolated, even in cases where it seemed that the red color of the prodiginine core seemed to diminish. The difficulty encountered in inducing spirocyclization in model **3-90** suggested that the branching/ansa bridge provided a steric interaction with the B ring methoxy that facilitates the spirocyclization. Based on this hypothesis, another model system could be proposed where a branch is installed on the C9 substituent to examine if cyclization is easier to achieve with more steric hindrance in the system. A branched pyrroloketone **3-94** could be utilized in a condensation reaction with **3-29** to provide the model system. However, it is unclear whether the installation of this branch will be sufficient to alter the system so that **3-96** or **3-97** are preferred over **3-95**. Further studies in this area are ongoing in our laboratory.

3.3. Conclusion

In an attempt to construct the ansa bridge at a late stage in the synthesis of the marineosins, direct functionalization of the prodiginine core was explored. The utility of the Rapoport condensation was utilized to construct several seco precursors to the pyrrolophane. However, the inability to efficiently and cleanly reduce the isolated olefin in **3-27a/b** or **3-31** hindered progress with the photo-induced electron transfer approach. The radical-based approach to construct the ansa bridge in a manner similar to the biosynthesis led to the isolation of oxygenated seco precursor **3-53**. Following these efforts, we examined end game spirocyclization methods, which led to the discovery of several novel transformations. Filtered irradiation of enone **3-67** generated the unique polyheterocycle **3-68**, which is postulated to arise from an *ipso* substitution of the B-ring methoxy group by the enone and autooxidation. It was determined that C9 substituted prodiginines could be accessed via a condensation of the requisite pyrroloketone with bipyrrole **3-29**. This modification of the Rapoport condensation allowed for the generation of marineosin model systems, which could be utilized for spirocyclization studies. The difficulty associated with accessing the marineosin pyrrolophane at a late stage led to a revision of strategy (Chapter 4), which would utilize knowledge gained from the model systems.

3.4. Experimental

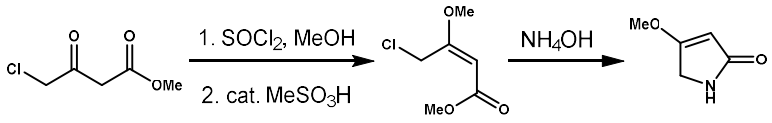
3.4.1. Materials and Methods

All reactions were carried out using oven- or flame-dried glass and a magnetic stir bar under an atmosphere of argon (Ar) unless otherwise indicated. Tetrahydrofuran (THF), diethyl ether (Et_2O), methylene chloride (DCM), toluene, acetonitrile (MeCN), and methanol were dried by passage through activated alumina using a GlassContour® solvent drying system. Triethylamine, and diisopropylamine were distilled from CaH_2 under inert atmosphere prior to use. All other commercial reagents and catalysts were used as received unless otherwise indicated.

NMR spectra were recorded on Bruker Advance spectrometers (400 MHz, 500 MHz) and are reported as δ values in ppm relative to $CDCl_3$ (calibrated to 7.27 ppm in ^1H NMR and 77.16 ppm in ^{13}C NMR, unless otherwise indicated) and were conducted at room temperature (unless otherwise indicated). ^1H NMR coupling constants are reported in Hz. Splitting patterns are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), septet (sept), multiplet (m), broad (br), apparent (app), and combinations thereof. Column chromatography was conducted on silica gel 60 (240-400 mesh) purchased from Silicycle or neutral aluminum oxide (activated, Brockmann I) purchased from Sigma Aldrich. Thin layer chromatography (TLC) was performed using pre-coated, glass-backed plates (SiO_2, 60 PF254, 0.25 mm or neutral Al_2O_3, 0.25 mm) and visualized using a combination of UV, anisaldehyde, and potassium permanganate staining.

3.4.2. Experimental Procedures and Characterization

4-methoxy-1,5-dihydro-2*H*-pyrrol-2-one (3-15)



$SOCl_2$ (24 mL, 220.5 mmol, 1.05 eq) was added dropwise to anhydrous MeOH (24 mL, 594.0 mmol, 2.85 eq) at -15 °C under an inert atmosphere. After addition was complete β-ketoester **3-13** (24 mL, 208.0 mmol) was added dropwise over 15 minutes. The mixture was then allowed to warm to room temperature and stirred for 3.5h. The reaction was then concentrated to afford an oil. $MeSO_3H$ (0.14 mL, 2.16 mmol, ~1 mol%) was added to the oil and the mixture was heated to 135 °C under reduced pressure (120-140 mbar) with a Dean-Stark trap and condenser attached. After 1.5h, no vapor was observed above the trap. The resultant dark mixture was then distilled (84-85 °C, 9-10 mbar) to afford **3-14** (33.2 g, 97%) as a colorless liquid that was used directly in the next step.

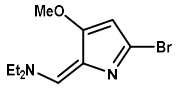
To an aqueous solution of NH_4OH (10 wt% in H_2O, 184 mL, 527.7 mmol, 2.6 eq) at 65 °C, ester **3-14** (33.2 g, 201.7 mmol) was added via syringe pump over 3.5h. After addition, the mixture was stirred at 65 °C for an additional 1.5h. The mixture was then cooled to room temperature and solid NaCl was added. The mixture was then extracted with DCM several times and the combined organics were washed with brine. The organics were then dried over Na_2SO_4, filtered, and concentrated to afford **3-15** (12.3 g, 54%) as a pale yellow solid. The aqueous layer was then continuously extracted with DCM for 60h to afford another batch of **3-15** (5.5 g, 78% overall yield).

4-methoxy-1,5-dihydro-2*H*-pyrrol-2-one (3-15):

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 6.91 (s, 1H), 5.03-5.00 (m, 1H), 3.88 (s, 2H), 3.76 (s, 3H)

^{13}C NMR (125 MHz, $CDCl_3$): 176.0, 175.8, 94.2, 58.3, 46.7

(*E*)-*N*-((5-bromo-3-methoxy-2*H*-pyrrol-2-ylidene)methyl)-*N*-ethylethanamine (3-16)



3-16

To a solution of $POBr_3$ (30.3 g, 105.9 mmol, 1.8 eq) in DCM (100 mL) at 0 °C, a solution of $CHONEt_2$ (10.68 mL, 95.87 mmol, 1.65 eq) in DCM (20 mL) was added slowly. The reaction was then stirred for 30 minutes at 0 °C. Pyrrolinone **3-15** (6.61 g, 58.52 mmol) was added in two portions over 10 minutes. The mixture was then allowed to warm to room temperature over 10 minutes. The mixture was then heated to reflux (40 °C) for 4 hours, then cooled to room temperature. The reaction mixture was then slowly poured over ice water, followed by treatment with aqueous 2M NaOH until the mixture's pH was 8-9. The mixture was extracted with DCM (200 mL x 3). The organic extracts were dried over $MgSO_4$, filtered, and concentrated to afford a black oil. The crude was then passed through a SiO_2 plug with a solution of 9:1 Hexanes/EtOAc.

The filtrate was concentrated to afford crude **3-16** (12.71 g, 60%, 1:1 mixture of product/$CHONEt_2$) an orange-brown oil. This material was used directly in the next step.

(*E*)-*N*-((5-bromo-3-methoxy-2*H*-pyrrol-2-ylidene)methyl)-*N*-ethylethanamine (3-16):
^{1}HNMR (500 MHz, $CDCl_3$, 1:1 mix of product/$CHONEt_2$): δ (ppm) 6.99 (s, 1H), 5.59 (s, 1H), 4.11 (q, *J* = 7.0 Hz, 2H), 3.75 (s, 3H), 3.27 (q, *J* = 7.1 Hz, 2H), 1.32-1.25 (m, 6H)

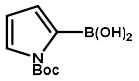
***Tert*-Butyl-1*H*-pyrrole-1-carboxylate (3-17)**

3-17

To a solution of pyrrole (3 mL, 43.2 mmol) in MeCN (43 mL, 1M), DMAP (0.5289 g, 4.32 mmol, 10 mol %) and Boc_2O (11.9 mL, 51.8 mmol, 1.2 eq) were added. The mixture was stirred at room temperature for 24 hours. The reaction was then diluted with Et_2O and washed with 1M aqueous $KHSO_4$. The organics were then washed with saturated aqueous $NaHCO_3$ and brine, then dried over $MgSO_4$, filtered, and concentrated to an orange oil. The crude was distilled under vacuum (10 torr, Bath temp: 90 °C, thermometer temp: 65 °C) to afford **3-17** (7.1795 g, quant.) as a clear oil.

***Tert*-Butyl-1*H*-pyrrole-1-carboxylate (3-17):**
^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.23 (dd, *J* = 2.0, 2.6 Hz, 2H), 6.21 (dd, *J* = 2.0, 2.6 Hz, 2H), 1.59 (s, 9H)

(1-(*tert*-butylcarbonyl)-1*H*-pyrrol-2-yl)boronic acid (3-18)

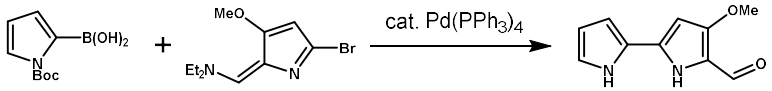


3-18

To a solution of diisopropylamine (13.86 mL, 98.89 mmol, 1.1 eq) in THF (515 mL, 0.175M) at 0 °C, *n*BuLi (2.5 M in Hexanes, 39.8 mL, 99.6 mmol, 1.1 eq) was added slowly. The mixture was stirred at 0 °C for 20 minutes and then cooled to -78 °C where **3-17** (15.04 g, 90 mmol) was added dropwise. The reaction was stirred at -78 °C for 1 hour, then $B(OEt)_3$ (30.6 mL, 179.8 mmol, 2 eq) was added dropwise to the mixture. The reaction was then allowed to slowly warm to room temperature overnight (~16 hours). The reaction was then quenched with aqueous 1M $KHSO_4$ (200 mL) and allowed to stir at room temperature for 1 hour. The reaction was then extracted with Et_2O (200 x 3). The organics were dried over $MgSO_4$ and filtered through a SiO_2 plug. The filtrate was concentrated to afford **3-18** (20 g, quant.) as an unstable white/light brown solid, which was used directly in the next step.

(1-(*tert*-butylcarbonyl)-1*H*-pyrrol-2-yl)boronic acid (3-18):
^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.47-7.43 (m, 1H), 7.11-7.08 (m, 1H), 7.04 (bs, 2H), 6.28-6.23 (m, 1H), 1.62 (s, 9H)

4-methoxy-1*H*,1*H*'-[2,2'-bipyrrole]-5-carbaldehyde (MBC, 3-10)

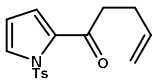


3-18 3-16 3-10

A flask was charged with $Pd(OAc)_2$ (1.2665 g, 5.64 mmol, 10 mol %) and PPh_3 (6.6805 g, 25.46 mmol, 45 mol %). The solids were then taken up in toluene (30 mL) and heated to 70 °C for 30 min to afford a yellow solution, which was cooled to room temperature and Na_2CO_3 (17.9 g, 168.9 mmol, 3 eq) was added in one portion. In a separate flask a mixture of **3-16** (14.6 g, 56.3 mmol) and **3-18** (~20 g, 90.0 mmol, 1.6 eq) were taken up in a degassed 10:1 mixture of dioxane/H_2O (220 mL, 0.25 M). This mixture was then transferred into the flask containing the Pd catalyst. The mixture was then heated to reflux for 24 hours. The reaction was then cooled to room temperature and poured into 1.25 L of H_2O, where it was slowly acidified with a 2M aqueous HCl solution to a pH of 7. The precipitated solids were filtered and washed with H_2O, acetone, a small amount of $CHCl_3$, and finally a small amount of Et_2O to afford **3-10** (8.578 g, 80%) as a pale yellow solid.

4-methoxy-1*H*,1*H*'-[2,2'-bipyrrole]-5-carbaldehyde (MBC, 3-10):
^{1}H NMR (500 MHz, $(CD_3)_2SO$): δ (ppm) 11.40 (bs, 1H), 11.23 (bs, 1H), 9.29 (s, 1H), 6.92-6.89 (m, 1H), 6.76-6.71 (m, 1H), 6.26 (s, 1H), 6.11 (t, *J* = 2.8 Hz, 1H), 3.83 (s, 3H)

1-(1-tosyl-1*H*-pyrrol-2-yl)pent-4-3en-1-one (3-21)

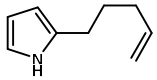


3-21

To a solution of 1-tosyl-1*H*-pyrrole (**3-19**) (15.19 g, 68.65 mmol) and 4-pentenoic acid (10.5 mL, 102.88 mmol, 1.5 eq) in DCE (230 mL, 0.3M) at 0 °C, TFAA (145 mL, 1.02 mol, 15 eq) was added dropwise. The reaction was then warmed to room temperature and then heated to reflux (65 °C) for 30 hours. The reaction mixture was then concentrated to a black/brown oil. The crude was dissolved in DCM (200 mL) and washed with saturated aqueous $NaHCO_3$ (200 mL x 2). The organics were then dried over $MgSO_4$, filtered, and concentrated to afford **3-21** as a black brown oil. This material was used in the next step without purification.

1-(1-tosyl-1*H*-pyrrol-2-yl)pent-4-3en-1-one (3-21):
^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.89 (d, *J* = 8.2 Hz, 2H), 7.79 (dd, *J* = 1.5, 3.5 Hz, 1H), 7.31 (d, *J* = 8.2 Hz, 2H), 7.03 (dd, *J* = 1.5, 3.3.6 Hz, 1H), 6.32 (t, *J* = 3.5 Hz, 1H), 5.76 (ddt, *J* = 6.7, 10.3, 16.7 Hz, 1H), 5.03-4.89 (m, 2H), 2.77 (t, *J* = 7.6 Hz, 2H), 2.41 (s, 3H), 2.34 (q, *J* = 7.1 Hz, 2H)

2-(pent-4-en-1-yl)-1*H*-pyrrole (3-11)



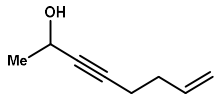
3-11

To a stirred suspension of $NaBH_4$ (12.984 g, 343.23 mmol, 5 eq) in isopropanol (210 mL), a solution of **3-21** (Assumed 100%, 68.65 mmol) in isopropanol (70 mL) was added slowly. The mixture was then heated to reflux for 48 hours. The reaction was then cooled to room temperature and carefully quenched by the slow addition of ice water. The isopropanol was then removed from the mixture, which was then washed with DCM (200 mL x 2). The organics were then washed with brine (100 mL) and then dried over $MgSO_4$ followed by filtration. The filtrate was concentrated to afford a black/brown oil, which was purified by flash column chromatography (SiO_2, 9:1 Hexanes/EtOAc) to afford **3-11** (6.746 g, 73% over two steps) as a yellow oil that darkens on standing.

2-(pent-4-en-1-yl)-1*H*-pyrrole (3-11):

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.95 (bs, 1H), 6.73-6.68 (m, 1H), 6.20-6.15 (m, 1H), 5.99-5.94 (m, 1H), 5.87 (ddt, *J* = 6.6, 10.2, 16.8 Hz, 1H), 5.13-4.98 (m, 2H), 2.66 (t, *J* = 7.6 Hz, 2H), 2.16 (q, *J* = 7.1 Hz, 2H), 1.77 (p, *J* = 7.5 Hz, 2H)

Oct-7-en-3-yn-2-ol (3-24)



3-24

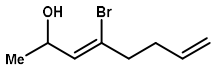
To a suspension of Mg (10.07 g, 414.25 mmol, 5 eq) in Et_2O (250 mL, 0.33 M), allyl bromide (17.9 mL, 207.12 mmol, 2.5 eq) was added at a rate to maintain a gentle reflux. After addition, the mixture was refluxed for 1.5 hours and then cooled to room temperature. The solution was transferred into a flame dried 500 mL flask. The mixture was cooled to 0 °C and propargyl chloride (6 mL, 82.94 mmol) was added dropwise. The reaction was then cooled to -20 °C and maintained at this temperature for 42 hours. The reaction was then warmed to 0 °C and freshly distilled acetaldehyde (14 ml, 250.44 mmol, 3 eq) was added dropwise. The mixture was then stirred at 0 °C for 3 hours. The mixture was then quenched by the careful addition to saturated aqueous NH_4Cl (500 mL). The mixture was then extracted with Et_2O (200 mL x 2) and the organics were dried over $MgSO_4$, filtered, and concentrated to a yellow oil. The crude oil was distilled (10-15 torr, thermometer temp: 108 °C) to afford **3-24** (7.5979 g, 74%) as a clear oil.

Oct-7-en-3-yn-2-ol (3-24):

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 5.84 (ddt, *J* = 6.3, 10.2, 16.6 Hz, 1H), 5.10-4.99 (m, 2H), 4.54-4.46 (m, 1H), 2.32-2.19 (m, 4H), 1.78 (bs, 1H), 1.41 (d, *J* = 6.5 Hz, 3H)

^{13}C NMR (125 MHz, $CDCl_3$): 136.8, 115.6, 83.8, 82.7, 58.5, 32.8, 24.7, 18.4

(*Z*)-4-bromoocta-3,7-dien-2-ol (3-12a)



3-12a

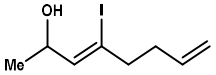
To a solution of Red-Al (sodium bis(2-methoxyethoxy)aluminum hydride, 60 wt % in toluene, 2.86 M in toluene, 7.78 mL, 22.26 mmol, 1.3 eq) in Et_2O (51 mL) at 0 °C, **3-24** (2.1276 g, 17.13 mmol) in Et_2O (17 mL) was added dropwise (*CAUTION*: vigorous gas evolution). The mixture was then allowed to warm to room temperature overnight. The excess Red-Al was then destroyed by the addition of EtOAc (2 mL) and stirring for 30 minutes. The mixture was then cooled to -78 °C and NBS (3.0466 g, 17.12 mmol, ~1 eq) was added in two portions over 10 minutes. The reaction was then allowed to slowly warm to 0 °C over 2 hours. The reaction was then quenched by the addition of saturated aqueous $Na_2S_2O_3$ and the mixture was extracted with Et_2O (100 mL x 2). The organics were then dried over $MgSO_4$, filtered and concentrated to afford an orange oil. The crude was then purified by flash column chromatography (SiO_2, 10:1 Hexanes/EtOAc) to afford **3-12a** (3.1377 g, 89%) as a pale yellow oil.

(*Z*)-4-bromoocta-3,7-dien-2-ol (3-12a):

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 5.82-5.69 (m, 2H), 5.09-4.97 (m, 2H), 4.65 (dt, *J* = 6.4, 13.7 Hz, 1H), 2.54-2.48 (m, 2H), 2.35-2.27 (m, 2H), 1.67 (bs, 1H), 1.28 (d, *J* = 6.4 Hz, 3H)

^{13}C NMR (125 MHz, $CDCl_3$): 136.4, 133.0, 127.7, 115.7, 68.0, 40.8, 32.1, 22.2

(*Z*)-4-iodooocta-3,7-dien-2-ol (3-12b)



3-12b

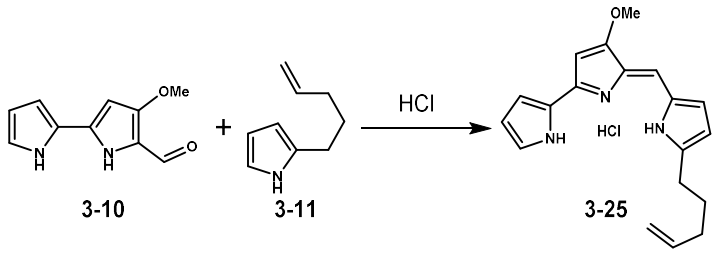
To a solution of Red-Al (sodium bis(2-methoxyethoxy)aluminum hydride, 60 wt % in toluene, 2.86 M in toluene, 7.04 mL, 20.14 mmol, 1.2 eq) in Et_2O (51 mL) at 0 °C, **3-24** (2.0861 g, 16.79 mmol) in Et_2O (17 mL) was added dropwise (*CAUTION*: vigorous gas evolution). The mixture was then allowed to warm to room temperature overnight. The excess Red-Al was then destroyed by the addition of EtOAc (2 mL) and stirring for 30 minutes. The mixture was then cooled to -78 °C and I_2 (4.3415 g, 17.1 mmol, ~1 eq) was added (*NOTE*: The I_2 has a tendency to clump at this temperature and prevent the stir bar from stirring effectively). The reaction was then allowed to slowly warm to 0 °C over 6 hours. The reaction was then quenched by the addition of saturated aqueous $Na_2S_2O_3$ and the mixture was extracted with Et_2O (100 mL x 2). The organics were then dried over $MgSO_4$, filtered and concentrated to afford an orange oil. The crude was then purified by flash column chromatography (SiO_2, 10:1 Hexanes/EtOAc) to afford **3-12a** (3.7562 g, 89%) as an orange oil.

(*Z*)-4-iodooocta-3,7-dien-2-ol (3-12b):

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 5.79 (ddt, *J* = 6.6, 10.1, 16.9 Hz, 1H), 5.66 (dt, *J* = 1.1, 7.3 Hz, 1H), 5.15-4.97 (m, 2H), 4.50 (p, *J* = 6.5 Hz, 1H), 2.65-2.55 (m, 2H), 2.37-2.27 (m, 2H), 1.72 (bs, 1H), 1.31 (d, *J* = 6.3 Hz, 3H)

^{13}C NMR (125 MHz, $CDCl_3$): 138.7, 136.3, 115.8, 107.8, 72.8, 44.48, 33.3, 22.0

Condensation of MBC 3-10 with Alkenylpyrrole 3-11



To a suspension of **3-10**(2.0147 g, 10.59 mmol) and **3-11** (2.1399 g, 15.82 mmol, 1.5 eq) in MeOH (50 mL, 0.2M), anhydrous HCl (1M in MeOH, 15.9 mL, 15.9 mmol, 1.5 eq) was added. The mixture was stirred at room temperature for 5 hours. An additional portion of **3-11** (0.4028 g, 2.97 mmol, 0.3 eq) was added. The mixture was then allowed to stir overnight (~16 hours). HPLC indicated that **3-10** was consumed. The reaction was concentrated to a black purple solid. The crude oily solid was dissolved in 1:1 Hexanes/EtOAc and flushed through a neutral Al_2O_3 plug. The filtrate was concentrated to afford hydrochloride salt **3-25** (2.0506 g, 56%) as a viscous red-purple oil.

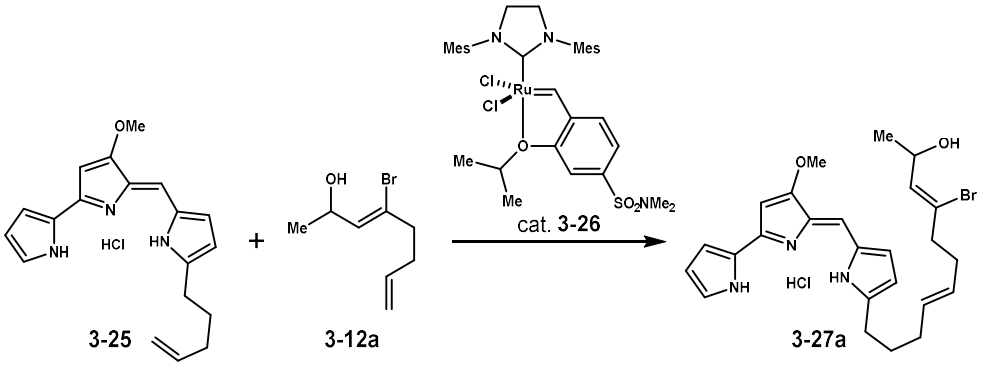
(*Z*)-4'-methoxy-5'-((5-(pent-4-en-1-yl)-1*H*-pyrrol-2yl)methylene)-1*H*,5'*H*-2,2'-bipyrrole hydrochloride (3-25):

^{1}H NMR (400 MHz, CD_3CO_2D): δ (ppm) 7.29 (dd, *J* = 1.3, 2.3 Hz, 1H), 7.08 (dd, *J* = 1.2, 3.8 Hz, 1H), 7.00 (s, 1H), 6.93 (d, *J* = 3.3 Hz, 1H), 6.34 (dd, *J* = 2.4, 3.8 Hz, 1H), 6.28 (s, 1H), 6.22 (d, *J* = 3.9 Hz, 1H), 5.84 (ddt, *J* = 6.6, 10.2, 16.9 Hz, 1H), 5.08-4.91 (m, 2H), 3.97 (s, 3H), 2.82 (t, *J* = 7.7 Hz, 2H), 2.13 (q, *J* = 7.1 Hz, 2H), 1.81 (p, *J* = 7.6 Hz, 2H)

^{13}C NMR (100 MHz, CD_3CO_3D): 166.9, 149.7, 137.9, 127.9, 126.1, 122.1, 121.6, 118.7, 115.9, 115.4, 114.8, 114.5, 112.3, 112.0, 93.6, 58.6, 33.0, 28.1, 27.3

LRMS (ESI) m/z, 308.2 (308.2 calculated for $C_{19}H_{22}N_3O^+$, $(M+H)^+$)

Cross Metathesis of Pentenyl Prodiginine 3-25 with Bromoalcohol 3-12a



To a solution of **3-25** (0.3206, 0.93 mmol), **3-12a** (0.7668 g, 3.73 mmol, 4 eq), and benzoquinone (31.6 mg, 0.33 mmol, 36 mol %) in DCM (4 mL), **3-26** (67.9 mg, 0.092 mmol, 10 mol %) was added. The reaction was then heated to reflux (40 °C). An additional portion of **3-26** (33.4 mg, 0.045 mmol, 5 mol %) in DCM (2 mL) was added via syringe pump over 8 hours. The reaction was stirred for an additional 12 hours. The reaction was then concentrated and purified by flash column chromatography (SiO_2, 10:1→4:1→2:1→1:1→2:3 Hexanes/EtOAc) to afford **3-27a** (0.2538 g, 52%) as a dark purple foam.

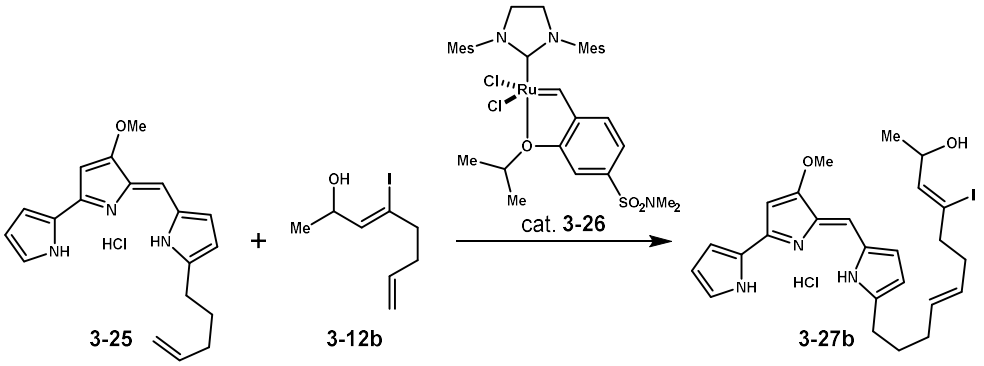
(3*Z*,7*E*)-4-bromo-11-(5-((*Z*)-(4'-methoxy-1*H*,5'*H*-[2,2'-bipyrrol]-5'-ylidene)methyl)-1*H*-pyrrol-2-yl)undeca-3,7-dien-2-ol (3-27a):

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 12.85(s, 1H), 12.67 (s, 1H), 12.63 (s, 1H), 7.28-7.24 (m, 1H), 7.00 (s, 1H), 6.97-6.93 (m, 1H), 6.85-6.80 (m, 1H), 6.39-6.34 (m, 1H), 6.22-6.17 (m, 1H), 6.08 (s, 1H), 5.77 (d, *J* = 7.3 Hz, 1H), 5.63-5.27 (m, 2H), 4.62 (p, *J* = 6.5 Hz, 1H), 4.02 (s, 3H), 2.92 (t, *J* = 7.2 Hz, 2H), 2.46 (t, *J* = 7.3 Hz, 2H), 2.30-2.19 (m, 2H), 2.10 (q, *J* = 6.9 Hz, 2H), 1.84 (p, *J* = 7.2 Hz, 2H), 1.25 (d, *J* = 6.6 Hz, 3H)

^{13}C NMR (125 MHz, $CDCl_3$): 166.3, 149.0, 133.3, 133.0, 131.0, 129.1, 128.6, 127.8, 126.2, 126.0, 122.1, 121.5, 118.0, 116.3, 112.6, 112.0, 93.1, 68.0, 58.8, 41.3, 32.1, 30.9, 28.8, 27.8, 22.2

LRMS (ESI) m/z, 484.1 and 486.2 (484.2 and 486.2 calculated for $C_{25}H_{31}BrN_3O_2^+$, $(M+H)^+$)

Cross Metathesis of Pentenyl Prodiginine 3-25 with Iodoalcohol 3-12b



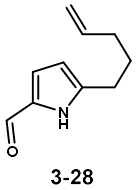
To a solution of **3-25** (1.4636 g, 4.25 mmol), **3-12b** (3.6071 g, 14.30 mmol, 3.4 eq), and benzoquinone (0.1378 g, 1.27 mmol, 30 mol %) in DCM (20 mL), **3-26** (0.3124 g, 0.425 mmol, 10 mol %) was added. The mixture was then heated to reflux (40 °C). An additional portion of of **3-26** (0.1549 g, 0.211 mmol, 5 mol %) in DCM (5 mL) was added via syringe pump over 8 hours. The reaction was stirred at 40 °C for an additional 10 hours. The reaction was then concentrated and then purified by flash column chromatography (SiO_2, 4:1→2:1→1:1 Hexanes/EtOAc) to afford **3-27b** (0.9835 g, 41%) as a dark purple foam.

(3*Z*,7*E*)-4-iodo-11-(5-((*Z*)-(4'-methoxy-1*H*,5'*H*-[2,2'-bipyrrol]-5'-ylidene)methyl)-1*H*-pyrrol-2-yl)undeca-3,7-dien-2-ol (3-27b):

^{1}H NMR (500 MHz, CD_3CO_2D): δ (ppm) 7.35-7.31 (m, 1H), 7.12 (d, *J* = 3.6 Hz, 1H), 7.07 (s, 1H), 6.97-6.91 (m, 1H), 6.38 (dd, *J* = 2.5, 3.6 Hz, 1H), 6.35 (s, 1H), 6.27-6.22 (m, 1H), 5.74-5.61 (m, 1H), 5.61-5.31 (m, 2H), 4.51-4.42 (m, 1H), 4.03 (s, 3H), 2.95-2.85 (m, 2H), 2.57-2.46 (m, 2H), 2.28-2.16 (m, 2H), 2.15-2.05 (m, 2H), 1.90-1.77 (m, 2H), 1.22 (d, *J* = 6.3 Hz, 3H)

LRMS (ESI) m/z, 532.0 (532.1 calculated for $C_{25}H_{31}IN_3O_2^+$, $(M+H)^+$)

5-(pent-4-3n-1-yl)-1*H*-pyrrole-2-carbaldehyde (3-28)



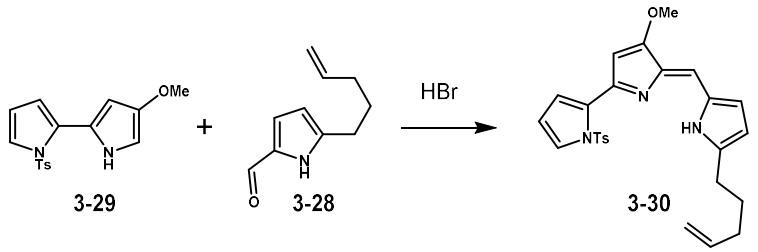
3-28

To a solution of DMF (0.13 mL, 1.67 mmol, 1.1 eq) in DCM (1 mL) at 0 °C, freshly distilled oxalyl chloride (0.14 mL, 1.63 mmol, 1.1 eq) was added dropwise. The reaction was stirred for 30 minutes at 0 °C. Then **3-11** (0.2016 g, 1.49 mmol) in DCM (1 mL) was added dropwise. The reaction was stirred until TLC indicated the starting material was consumed. Then $NaOAc{\cdot}3H_2O$ (1.0244 g, 7.52 mmol, 5 eq) in H_2O (6 mL) was added. The reaction was refluxed for 30 minutes. The mixture was then cooled to room temperature and extracted with DCM (20 mL x 3). The organics were washed with saturated aqueous $NaHCO_3$ and brine. The organics were dried over $MgSO_4$, filtered through a SiO_2 plug and concentrated to afford **3-28** (0.1279 g, 52%) as a brown oil.

5-(pent-4-3n-1-yl)-1*H*-pyrrole-2-carbaldehyde (3-28):

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 9.68 (bs, 1H), 9.36 (s, 1H), 6.89 (dd, *J*= 2.5, 3.6 Hz, 1H), 6.08 (dd, *J* = 3.0, 3.6 Hz, 1H), 5.80 (ddt, *J* = 6.6, 10.2, 16.9 Hz, 1H), 5.06-4.96 (m, 2H), 2.68 (t, *J*= 7.68 Hz, 2H), 2.14-2.07 (m, 2H), 1.80-1.72 (m, 2H)

(*Z*)-4'-methoxy-5'-((5-(pent-4-en-1-yl)-1*H*-pyrrol-2-yl)methylene)-1-tosyl-1*H*,5'*H*-2,2'-bipyrrole (3-30)

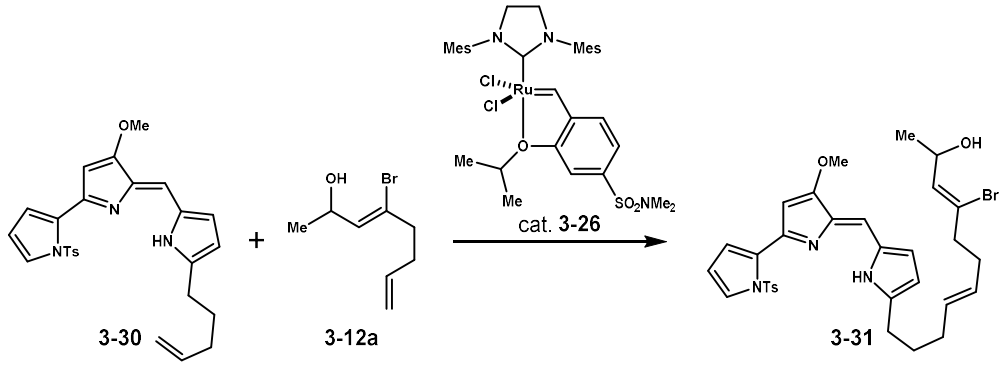


A solution of **3-29** (prepared according procedures described in Chapter 2, 0.3195 g, 1.01 mmol) and **3-28** (0.1687 g, 1.03 mmol, 1.02 eq) in EtOH (20 mL, 0.05 M) was warmed to 50 °C. HBr (48% in H_2O, 8.89 M, 0.06 mL, 0.53 mmol, 50 mol %) was added and the mixture was stirred at 50 °C for 1 hour. The mixture was then cooled to room temperature and stirred for 20 hours. The reaction was then concentrated to afford a red paste, which was taken up in DCM (50 mL) and washed with saturated aqueous $NaHCO_3$. The organic layer was dried over $MgSO_4$, filtered, and concentrated to a black red oil, which was purified by flash column chromatography (neutral Al_2O_3, 15:1 Hexanes/EtOAc) to afford **3-30** (0.3843 g, 82%) as a red oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.69-7.65 (m, 1H), 7.60 (d, *J*= 8.2 Hz, 2H), 7.09 (d, *J* = 8.2 Hz, 2H), 6.83 (s, 1H), 6.72-6.67 (m, 1H), 6.60 (d, *J* = 3.6 Hz, 1H), 6.35 (t, *J* = 3.6 Hz, 1H), 6.05 (d, *J* = 3.6 Hz, 1H), 5.80 (ddt, *J*= 6.7, 10.2, 16.9 Hz, 1H), 5.66 (s, 1H), 5.02-4.90 (m, 2H), 3.78 (s, 3H), 2.79 (t, *J* = 7.6 Hz, 2H), 2.29 (s, 3H), 2.12 (q, *J* = 7.1 Hz, 2H), 1.79 (p, *J* = 7.5 Hz, 2H)

^{13}C NMR (125 MHz, $CDCl_3$): 166.9, 155.6, 144.8, 144.2, 140.2, 138.4, 135.5, 131.4, 129.6, 129.4, 128.1, 127.5, 120.3, 119.2, 118.2, 114.7, 111.3, 109.3, 96.7, 58.2, 33.3, 28.6, 27.6, 21.5

Cross Metathesis of Protected Pentenyl Prodiginine 3-30 and Bromoalcohol 3-12a



To a solution of **3-30** (53.3 mg, 0.11 mmol) in DCM (1.5 mL), **3-26** (4.1 mg, 0.0055 mmol, 5 mol %) was added followed by **3-12a** (0.1157 g, 0.56 mmol, 5 eq) and Ti(O*i*Pr)$_4$ (0.01 mL, 0.034 mmol, ~30 mol %). The reaction was then heated to reflux (40 °C). Two additional portions of **3-26** (2.1 mg each, 2.8 µmol each, 2.5 mol % each) were added after 2 and 4 hours had passed, respectively. The reaction was stirred at 40 °C for an additional 20 hours. The reaction was then concentrated and purified by flash column chromatography (neutral Al_2O_3, 10:1→6:1→2:1 Hexanes/EtOAc) to afford **3-31** (41.7 mg, 57%) as a dark red oil and recovered **3-30** (13.9 mg, 26%).

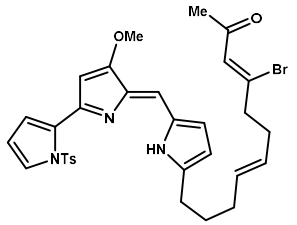
(3*Z*,7*E*)-4-bromo-11-(5-((*Z*)-(4'-methoxy-1-tosyl-1*H*,5'*H*-[2,2'-bipyrrol]-5'-ylidene)methyl)-1*H*-pyrrol-2-yl)undeca-3,7-dien-2-ol (3-31):

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.69-7.65 (m, 1H), 7.59 (d, *J* = 8.2 Hz, 2H), 7.08 (d, *J* = 8.2 Hz, 2H), 6.82 (s, 1), 6.71-6.67 (m, 1H), 6.59 (d, *J* = 3.6 Hz, 1H), 6.37-6.31 (m, 1H), 6.08-6.00 (m, 1H), 5.77-5.62 (m, 2H), 5.54-5.25 (m, 2H), 4.66-4.56 (m, 1H), 3.77 (s, 3H), 2.82-2.71 (m, 2H), 2.45-2.37 (m, 2H), 2.29 (s, 3H), 2.27-2.15 (m, 2H), 2.14-1.98 (m, 2H), 1.81-1.66 (m, 2H), 1.21 (d, *J* = 6.3 Hz, 3H)

^{13}C NMR (125 MHz, $CDCl_3$): 166.9, 155.6, 144.7, 144.4, 140.1, 135.5, 132.8, 131.4, 131.2, 129.5, 129.4, 128.4, 128.1, 128.0, 127.7, 127.6, 120.5, 119.2, 118.3, 111.3, 109.2, 68.0, 58.2, 41.4, 32.0, 30.9, 29.0, 27.5, 22.2, 21.6

LRMS (ESI) m/z, 638.2 and 640.2 (638.2 and 640.2 calculated for $C_{32}H_{37}BrN_3O_4S^+$, $(M+H)^+$)

(3*Z*,7*E*)-4-bromo-11-(5-((*Z*)-(4'-methoxy-1-tosyl-1*H*,5'*H*-[2,2'-bipyrrol]-5'-ylidene)methyl)-1*H*-pyrrol-2-yl)undeca-3,7-dien-2-one (3-8a)



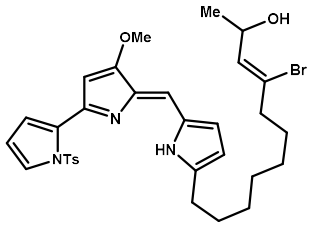
3-8a

To a solution of **3-31** (20.5 mg, 0.032 mmol) in DCM (0.32 mL, 0.1 M) at room temperature, Dess Martin Periodinane (21.4 mg, 0.050 mmol, 1.5 eq) was added followed by $NaHCO_3$ (27.1 mg, 0.32 mmol, 10 eq). The reaction was stirred for 4 hours at room temperature. Another portion of DMP (13.3 mg, 0.031 mmol, 1 eq) was added and the mixture was stirred for an additional 4 hours. The reaction was then quenched by the addition of 10 wt% $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$. The mixture was then washed with DCM (10 mL x 3) and the organics were dried over $MgSO_4$, filtered, and concentrated to a red oil. The crude was purified by preparative TLC (neutral Al_2O_3, 4:1 Hexanes/EtOAc) to afford **3-8a** (8.6 mg, 42%) as a dark red oil and recovered **3-31** (9.5 mg, 46%).

(3*Z*,7*E*)-4-bromo-11-(5-((*Z*)-(4'-methoxy-1-tosyl-1*H*,5'*H*-[2,2'-bipyrrol]-5'-ylidene)methyl)-1*H*-pyrrol-2-yl)undeca-3,7-dien-2-one (3-8a):

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.69-7.65 (m, 1H), 7.59 (d, *J* = 8.2 Hz, 2H), 7.08 (d, *J* = 8.2 Hz, 2H), 6.82 (s, 1H), 6.71-6.67 (m, 1H), 6.62-6.56 (m, 1H), 6.52 (s, 1H), 6.37-6.32 (m, 2H), 6.06-6.01 (m, 1H), 5.64 (s, 1H), 5.43-5.26 (m, 2H), 3.77 (s, 3H), 2.82-2.73 (m, 2H), 2.63-5.51 (m, 2H), 2.37-2.30 (m, 2H), 2.29 (s, 3H), 2.28 (s, 3H), 2.15-2.02 (m, 2H), 1.84-1.70 (m, 2H)

(*Z*)-4-bromo-11-(5-((*Z*)-(4'-methoxy-1-tosyl-1*H*,5'*H*-[2,2'-bipyrrol]-5'-ylidene)methyl)-1*H*-pyrrol-2-yl)undec-3-en-2ol (3-32)



3-32

To a solution of **3-31** (20.1 mg, 0.031 mmol) in DCM (3.1 mL, 0.01M), potassium azodicarboxylate (PADC, 30.5 mg, 0.15 mmol, 5 eq) was added followed by dropwise addition of AcOH (1M in DCM, 0.31 mL, 0.31 mmol, 10 eq). The mixture was stirred for 16 hours at room temperature. HPLC indicated that the reaction was incomplete. Another portion of PADC (30.4 mg, 0.15 mmol, 5 eq) was added followed by another portion of AcOH (1M in DCM, 0.31 mL, 0.31 mmol, 10 eq) and the mixture was stirred for 8 hours. TLC indicated reaction not complete. The reaction was then diluted with water and extracted with DCM. The organics were then dried over $MgSO_4$, filtered, and concentrated to a red oil. The crude oil was then resubjected to the reaction conditions (10 eq of PADC and 20 eq AcOH) for 16 hours. HPLC indicated that the

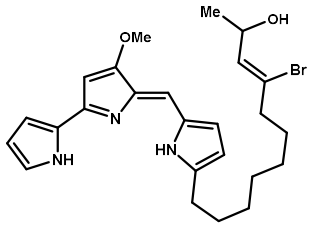
reaction was complete.The reaction was then diluted with water and extracted with DCM. The organic extracts were dried over $MgSO_4$, filtered and concentrated to provide a red oil. The crude oil was then purified by preparative TLC (neutral Al_2O_3, 2:1 Hexanes/EtOAc) to afford **3-32** (13.8 mg, 69%) as a red oil.

(*Z*)-4-bromo-11-(5-((*Z*)-(4'-methoxy-1-tosyl-1*H*,5'*H*-[2,2'-bipyrrol]-5'-ylidene)methyl)-1*H*-pyrrol-2-yl)undec-3-en-2ol (3-32):

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.69-7.65 (m, 1H), 7.60 (d, *J*= 8.1 Hz, 2H), 7.09 (d, *J* = 8.1 Hz, 2H), 6.83 (s, 1H), 6.71-6.66 (m, 1H), 6.60 (d, *J* = 3.4 Hz, 1H), 6.35 (t, *J* = 3.4 Hz, 1H), 6.04 (d, *J* = 3.4 Hz, 1H), 5.70 (d, *J* = 7.3 Hz, 1H), 5.65 (s, 1H), 4.63 (dt, *J* = 6.5, 7.3 Hz, 1H), 3.78 (s, 3H), 2.77 (t, *J* = 7.5 Hz, 2H), 2.35 (t, *J* = 7.4 Hz, 2H), 2.30 (s, 3H), 1.69 (p, *J* = 7.3 Hz, 2H), 1.49 (p, *J* = 7.3 Hz, 2H), 1.40-1.32 (m, 2H), 1.31-1.16 (m, 4H), 1.26 (d, *J* = 6.5 Hz, 3H)

LRMS (ESI) m/z, 640.2 and 642.2 (640.2 and 642.2 calculated for $C_{32}H_{39}BrN_3O_4S^+$, $(M+H)^+$)

(*Z*)-4-bromo-11-(5-((*Z*)-(4'-methoxy-1*H*,5'*H*-[2,2'-bipyrrol]-5'-ylidene)methyl)-1*H*-pyrrol-2-yl)undec-3-en-2ol (3-33a)



3-33a

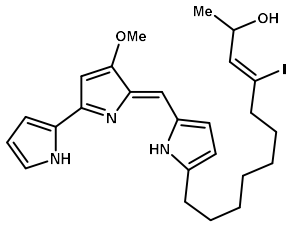
To a solution of **3-27a** (49.8 mg, 0.095 mmol) and $NaOAc{\cdot}3H_2O$ (39.5 mg, 0.29 mmol, 3 eq) in EtOH (2 mL, 0.05 M), $TsNHNH_2$ (88.9 mg, 0.47 mmol, 5 eq) was added. The mixture was then heated to 80 °C overnight (~16 hours). The reaction was then cooled and concentrated. The crude red paste was dissolved in EtOAc and washed with saturated aqueous $NaHCO_3$. The organics were then dried over $MgSO_4$, filtered through a SiO_2 plug with EtOAc, and concentrated to a black/purple oil. The oil was then purified via flash column chromatography (SiO_2, 4:1→1:1 Hexanes/EtOAc) to afford **3-33a** as a black/red oil that appears to consist of two prototropisomers (1:1 ratio) contaminated with 1.5 eq of $TsNHNH_2$.

(*Z*)-4-bromo-11-(5-((*Z*)-(4'-methoxy-1*H*,5'*H*-[2,2'-bipyrrol]-5'-ylidene)methyl)-1*H*-pyrrol-2-yl)undec-3-en-2ol (3-33a):

^{1}H NMR (500 MHz, CD_3CO_2D): δ (ppm) 7.36-7.33 (m, 1H), 7.16-7.12 (m, 1H), 7.09 (s, 0.5 H), 7.08* (s, 0.5H), 7.00-6.93 (m, 1H), 6.41-6.38 (m, 1H), 6.37 (s, 0.5H), 6.36* (s, 0.5H), 6.29-6.24 (m, 1H), 5.86-5.80 (m, 1H), 7.74-4.64 (m, 1H), 4.06 (s, 1.5H), (s, 1.5H), 2.94-2.84 (m, 2H), 2.47-2.35 (m, 2H), 1.83-1.72 (m, 2H), 1.62-1.50 (m, 2H), 1.46-1.29 (m, 6H), 1.29-1.23 (m, 3H)

LRMS (ESI) m/z, 486.1 and 488.1 (486.2 and 488.2 calculated for $C_{25}H_{33}BrN_3O_2^+$, $(M+H)^+$)

(*Z*)-4-iodo-11-(5-((*Z*)-(4'-methoxy-1*H*,5'*H*-[2,2'-bipyrrol]-5'-ylidene)methyl)-1*H*-pyrrol-2-yl)undec-3-en-2ol (3-33a)



3-33b

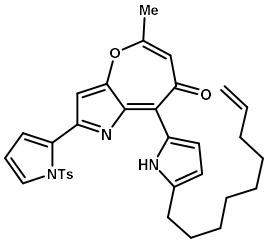
To a solution of **3-27b** (50 mg, 0.088 mmol) in MeCN (1 mL, 0.1M) at 0 °C, *o*-nitrobenzenesulfonyl chloride (NBSCl, 98 mg, 0.44 mmol, 5 eq) was added followed by hydrazine (0.03 mL, 0.95 mmol, ~10 eq). The reaction was then allowed to warm to room temperature overnight (~17 hours). The reaction was then diluted with EtOAc and washed with saturated aqueous $NaHCO_3$. The organics were then dried over $MgSO_4$, filtered through a SiO_2 plug with EtOAc, and concentrated to a black/red solid. The crude solid was then purified via flash column chromatography (SiO_2, 4:1→2:1 Hexanes/EtOAc) to afford **3-33b** (26.7 mg, 57%) as a black/red oil.

(*Z*)-4-iodo-11-(5-((*Z*)-(4'-methoxy-1*H*,5'*H*-[2,2'-bipyrrol]-5'-ylidene)methyl)-1*H*-pyrrol-2-yl)undec-3-en-2ol (3-33a):

^{1}H NMR (500 MHz, CD_3CO_2D): δ (ppm) 7.35-7.31 (m, 1H), 7.13 (d, *J* = 3.7 Hz, 1H), 7.09 (s, 1H), 6.99-6.95 (m, 1H), 6.38 (dd, *J* = 2.6, 3.7 Hz, 1H), 6.36 (s, 1H), 6.26 (d, *J* = 3.7 Hz, 1H), 5.68-5.62 (m, 1H), 4.52-4.43 (m, 1H), 4.04 (s, 3H), 2.84 (t, *J* = 7.5 Hz, 2H), 2.45 (t, *J* = 6.9 Hz, 2H), 1.78-1.69 (m, 2H), 1.56-1.47 (m, 2H), 1.44-1.26 (m, 6H), 1.23 (d, *J* = 6.2 Hz, 3H)

LRMS (ESI) m/z, 534.1 (534.2 calculated for $C_{25}H_{33}IN_3O_2^+$, $(M+H)^+$)

Irradiation of Enone Model System 3-67



3-68

The filter solution was prepared by dissolving 100 g $CuSO_4$ in 1 L of H_2O to afford a blue solution. Enone **3-67** (prepared according to procedures reported in Chapter 2, 21.1 mg, 0.036 mmol) was dissolved in MeCN (1 mL). The mixture was degassed via three freeze-pump-thaw cycles. A beaker was filled with the $CuSO_4$ filter solution and the reaction was submerged in the filter. A 1000 W halogen bulb was used to irradiate the reaction for 24 hrs. The reaction became noticeably darker. The reaction was then concentrated and purified by pTLC (SiO_2, 2:1 Hexanes/EtOAc) to afford **3-68** as a purple/black oil.

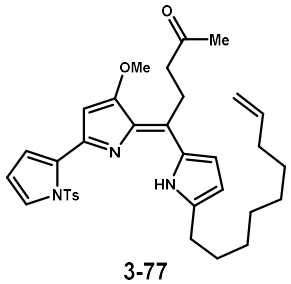
5-methyl-8-(5-(non-8-en-1yl)-1*H*-pyrrol-2-yl)-2-(1-tosyl-1*H*-pyrrol-2-yl)-7*H*-oxepino[3,2-*b*]pyrrol-7-one (3-68):

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 11.35 (s, 1H), 7.60 (d, *J* = 8.3 Hz, 2H), 7.45 (dd, *J* = 1.6, 3.2 Hz, 1H), 7.22 (d, *J* = 8.3 Hz, 2H), 6.84 (s, 1H), 6.63 (dd, *J* = 2.4, 3.3 Hz, 1H), 6.45 (dd, *J* = 1.6, 3.3 Hz, 1H), 6.40 (t, *J* = 3.3 Hz, 1H), 6.13-6.08 (m, 1H), 5.81 (ddt, *J* = 6.6, 10.2, 16.9 Hz, 1H), 5.4 (s, 1H), 5.02-4.89 (m, 2H), 2.73 (t, *J* = 7.7 Hz, 2H), 2.40 (s, 3H), 2.38 (s, 3H), 2.08-2.00 (m, 2H), 1.79-1.70 (m, 2H), 1.46-1.28 (m, 8H)

^{13}C NMR (125 MHz, $CDCl_3$): 188.7, 147.2, 145.5, 139.2, 138.2, 137.2, 135.4, 133.9, 131.6, 129.8, 127.2, 125.5, 125.0, 124.6, 123.8, 118.0, 117.3, 116.7, 114.2, 112.8, 111.6, 109.3, 33.8, 29.7, 29.3, 29.2, 29.1, 28.9, 28.2, 27.6, 21.6

HRMS (ESI) m/z, 570.2394 (570.2421 calculated for $C_{33}H_{36}N_3O_4S^+$, $(M+H)^+$)

Reduction of Enone Model System 3-67



3-77

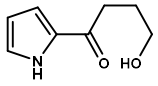
To a solution of **3-67** (32 mg, 0.055 mmol) in degassed MeOH (1.1 mL, 0.05M) at 0 °C, a solution of SmI_2 in THF (~0.2M, 1.5 mL, 0.3 eq, ~5 eq) was added dropwise. The reaction was stirred for one hour, during which the reaction progressed from dark red to dark purple to yellow to blue and finally pink. The reaction was quenched by the addition of water and diluted with EtOAc. The aqueous layer was washed with EtOAc. The organics were then dried over $MgSO_4$, filtered through a neutral Al_2O_3 plug with EtOAc, and concentrated to a red oil. The residue was purified by preparative TLC (neutral Al_2O_3, 2:1 Hexanes/EtOAc) to afford **3-77** (10.5 mg, 32%) as a red oil.

(*Z*)-5-(4'-methoxy-1-tosyl-1*H*,5'*H*-[2,2'-bipyrrol]-5'-ylidene)-5-(5-(non-8-en-1-yl)-1*H*-pyrrol-2-yl)pentan-2-one (3-77):

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 12.67 (bs, 1H), 7.60 (d, *J* = 8.2 Hz, 2H), 7.40-7.31 (m, 1H), 7.09 (d, *J* = 8.0 Hz, 2H), 6.77 (d, *J* = 3.6 Hz, 1H), 6.65 (dd, *J* = 1.7, 3.2 Hz, 1H), 6.33 (t, *J* = 3.3 Hz, 1H), 6.05 (d, *J* = 3.6 Hz, 1H), 5.85-5.72 (m, 1H), 5.75 (s, 1H), 5.04-4.84 (m, 2H), 3.77 (s, 3H), 3.21 (dd, *J* =6.9, 9.7 Hz, 2H), 2.79-2.71 (m, 4H), 2.30 (s, 3H), 2.17 (s, 3H), 1.99 (q, *J* = 6.9 Hz, 2H), 1.71-1.48 (m, 4H), 1.40-1.28 (m, 6H)

^{13}C NMR (125 MHz, $CDCl_3$): 208.0, 166.9, 153.0, 145.2, 144.7, 139.2, 138.7, 137.2, 135.4, 131.4, 131.1, 129.4, 128.6, 127.9, 127.6, 127.3, 118.7, 118.0, 114.0, 111.4, 109.0, 98.4, 58.4, 45.6, 33.7, 29.8, 29.4, 29.3, 29.2, 29.0, 28.9, 28.0, 23.6, 21.6

4-hydroxy-1-(1*H*-pyrrol-2-yl)butan-1-one (3-82)



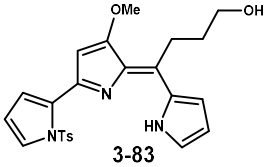
3-82

To a solution of MeMgBr (3.0 M in Et_2O, 6.8 mL, 20.42 mmol, 2.05 eq) in toluene (30 mL), pyrrole (**3-79**) (1.67 mL, 24.07 mmol, 2.2 eq) was added dropwise. The mixture was heated to 50 °C for 1 hour. (*CAUTION*: VENT NEEDLE REQUIRED to allow Et_2O to escape the reaction mixture). Lactone **3-81** (0.76 mL, 9.97 mmol) in toluene (10 mL) was then added dropwise. The reaction mixture was then heated to 100 °C for 2 hours. The reaction mixture was then cooled to room temperature and quenched with saturated NH_4Cl. The mixture was then extracted with EtOAc and the organics were dried over $MgSO_4$, filtered, and concentrated to a black/brown oil. The crude was purified by flash column chromatography (SiO_2, 4:1→2:1 Hexanes/EtOAc) to afford **3-82** (1.1268 g, 74%) as a yellow solid that turns brown on standing.

4-hydroxy-1-(1*H*-pyrrol-2-yl)butan-1-one (3-82)

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.38 (bs, 1H), 7.03 (ddd, *J* = 1.2, 2.7, 3.9 Hz, 1H), 6.95 (ddd, *J* = 1.5, 2.4, 3.4 Hz, 1H), 6.28 (dt, *J* = 2.5, 3.8 Hz, 1H), 3.72 (t, *J* = 6.0 Hz, 2H), 2.94 (t, *J* = 7.0 Hz, 2H), 2.11 (s, 1H), 1.98 (p, *J* = 6.4 Hz, 2H)

(*Z*)-4-(4'-methoxy-1-tosyl-1*H*,5'*H*-[2,2'-bipyrrol]-5'-ylidene)-4-(1*H*-pyrrol-2-yl)butan-1-ol (3-83)



3-83

To a solution of **3-82** (0.1774 g, 1.15 mmol) and **3-29** (0.3606 g, 1.14 mmol, 1 eq) in MeOH (10 mL, 0.1 M) at room temperature, HBr (48% in H_2O, 8.89 M, 0.5 mL, 4.44 mmol, 4 eq) was added. The reaction was stirred for 5 hours at room temperature. The mixture was then diluted with EtOAc and the mixture was washed with 1M aqueous K_2CO_3. The organics were then dried over $MgSO_4$, filtered, and concentrated to a dark red orange foam. The crude material was then purified by flash column chromatography (neutral Al_2O_3, 10:1→6:1→2:1→1:1→1:2→1:4 Hexanes/EtOAc) to afford **3-82** (0.3923 g, 75%) as an orange foam.

^{1}H NMR spectrum of **3-83** is complex in d_6-DMSO, $CDCl_3$, C_6D_6, and CD_3CN indicating the formation of aggregates and other higher order structures in solution. The ^{1}H NMR spectrum of **3-83** in CD_3CO_2D is the most simple, however extended exposure (~1 week) to acetic acid results in decomposition.

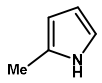
(*Z*)-4-(4'-methoxy-1-tosyl-1*H*,5'*H*-[2,2'-bipyrrol]-5'-ylidene)-4-(1*H*-pyrrol-2-yl)butan-1-ol (3-83):

^{1}H NMR (500 MHz, CD_3CO_2D): δ 7.81-7.69 (m, 1H), 7.69-7.63 (m, 0.6H)*, 7.62-7.51 (m, 2H), 7.47-7.38 (m, 0.4H), 7.37-7.25 (m, 2H), 6.72-6.62 (m, 2H), 6.61-6.51 (m, 1H), 4.21 (s, 1H)*, 4.13 (s, 2H), 3.79 (t, *J* = 5.9 Hz, 2H), 3.44-3.23 (m, 1H), 2.35 (s, 3H), 2.11-2.04 (m, 2H), 1.96-1.86 (m, 1H)

^{1}H NMR (500 MHz, $CDCl_3$): δ 13.13 (bs, 0.23 H), 9.77 (bs, 0.09H), 8.91 (bs, 0.16H), 8.69 (bs, 0.26H), 8.50 (bs, 0.16H), 8.41 (bs, 0.11H), 7.65 (dd, *J* =1.7, 3.2 Hz, 0.27H), 7.53 (d, *J* = 8.4 Hz, 0.55H), 7.41-7.32 (m, 1H), 7.26-7.22 (m, 0.34H), 7.21 (d, *J* = 8.4 Hz, 0.30H), 7.18-7.12 (m, 0.54H), 7.08 (d, *J* = 8.2 Hz, 0.56H), 6.98 (d, *J* = 7.9 Hz, 0.26H), 6.85 (d, *J* = 3.3 Hz, 0.23H), 6.82 (dd, *J* =1.5, 2.6 Hz, 0.14H), 6.74 (dd, *J* = 1.6, 2.6 Hz, 0.13H), 6.72 (dd, *J* = 1.6, 2.6 Hz, 0.14H), 6.71-6.67 (m, 0.27), 6.35 (t, *J* = 3.3 Hz, 0.25H), 6.32-6.14 (m, 2H), 6.13-6.10 (m, 0.13H), 5.97 (t, *J* = 8.0 Hz, 0.14H), 5.95 (d, *J* = 3.0 Hz, 0.10H), 5.92 (d, *J* = 3.0 Hz, 0.18H), 5.83-5.76 (m, 0.38H), 4.05 (t, *J* = 7.0 Hz, 0.25H), 3.87 (t, *J* = 5.7 Hz, 0.27H), 3.83 (s, 0.61H), 3.82-3.80 (m, 0.41H), 3.79 (s, 0.44H), 3.72 (s, 0.46H), 3.71-3.67 (m, 1H), 3.11 (t, *J* = 7.5 Hz, 0.54H), 2.81-2.73 (m, 0.14), 2.60-2.46 (m, 0.58H), 2.43 (t, *J* = 7.5 Hz, 0.11H), 2.40 (t, *J* = 7.5 Hz, 0.11H) 2.36 (s, 0.84H), 2.31 (s, 0.43H), 2.30 (s, 0.83H), 2.10-2.00 (m, 0.66H), 1.95 (p, *J* = 6.8 Hz, 0.67H), 1.56 (bs, 1H)

HRMS (ESI) m/z, 452.1633 (452.1639 calculated for $C_{24}H_{26}N_3O_4S^+$, $(M+H)^+$)

2-methyl-1*H*-pyrrole (3-85)

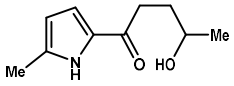


3-85

To a solution of **3-84** (9.5272 g, 100.18 mmol) in THF (125 mL, 0.8 M) at 0 °C, LAH (11.4362 g, 301.34 mmol, 3 eq) was carefully added in small portions (*CAUTION*: Vigorous reaction, very exothermic). The reaction was then heated to reflux for 16 hours and then cooled to room temperature. The reaction was then slowly poured into ice water and the mixture was washed with Et_2O (200 mL x 3). The organics were washed with brine and then dried over $MgSO_4$, filtered, and carefully concentrated to afford **3-85** (7.384 g, 91%) as an orange oil contaminated with THF.

2-methyl-1*H*-pyrrole (3-85):
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.93 (bs, 1H), 6.71-6.61 (m, 1H), 6.17-6.04 (m, 1H), 5.93-5.84 (m, 1H), 2.28 (s, 3H)

4-hydroxy-1-(5-methyl-1*H*-pyrrol-2-yl)pentan-1-one (3-88)



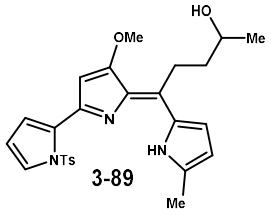
3-88

To a solution of MeMgBr (3.0 M in Et_2O, 5.99 mL, 17.98 mmol, 2.0 eq) in toluene (30 mL), pyrrole (**3-79**) (1.7492 g, 21.56 mmol, 2.4 eq) was added dropwise. The mixture was heated to 50 °C for 1 hour. (*CAUTION*: VENT NEEDLE REQUIRED to allow Et_2O to escape the reaction mixture). Lactone **3-87** (0.86 mL, 8.98 mmol) in toluene (6 mL) was then added dropwise. The reaction mixture was then heated to 100 °C for 2 hours. The reaction mixture was then cooled to room temperature and quenched with saturated NH_4Cl. The mixture was then extracted with EtOAc and the organics were dried over $MgSO_4$, filtered, and concentrated to a black/brown oil. The crude was purified by flash column chromatography (SiO_2, 4:1→2:1→1:1 Hexanes/EtOAc) to afford **3-88** (0.7867 g, 48%) as a yellow solid that turns brown on standing.

4-hydroxy-1-(5-methyl-1*H*-pyrrol-2-yl)pentan-1-one (3-88):
^{1}H NMR (500 MHz, $CDCl_3$): δ 9.11 (bs, 1H), 6.85 (dd, *J* = 2.4, 3.6 Hz, 1H), 5.97 (dd, *J* = 2.4, 3.6 Hz, 1H), 3.91-3.80 (m, 1H), 2.95-2.81 (m, 2H), 2.33 (bs, 1H), 2.30 (s, 3H), 1.88 (ddt, *J* = 7.0, 10.9, 14.1 Hz, 1H), 1.78 (p, *J* = 7.2 Hz, 1H), 1.22 (d, *J* = 6.2 Hz, 3H)

^{13}C NMR (125 MHz, $CDCl_3$): 190.1, 136.1, 130.7, 117.7, 109.6, 67.6, 34.0, 33.9, 23.6, 13.2

(*Z*)-5-(4'-methoxy-1-tosyl-1*H*,5'*H*-[2,2'-bipyrrol]-5'-ylidene)-5-(5-methyl-1*H*-pyrrol-2-yl)pentan-2-ol (3-89)



3-89

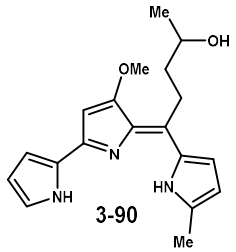
To a solution of **3-88** (0.3620 g, 1.99 mmol) and **3-29** (0.6327 g, 2.00 mmol, 1 eq) in MeOH (20 mL, 0.1M) at room temperature, HBr (48% in H_2O, 8.89 M, 0.9 mL, 8.00 mmol, 4 eq) was added. The reaction was stirred at room temperature for 5 hours. The reaction was the diluted with DCM and washed with saturated aqueous $NaHCO_3$. The organics were then dried over $MgSO_4$, filtered, and concentrated to a dark red foam. The crude was purified by flash column chromatography (neutral Al_2O_3, 4:1→3:1→2:1→1:1 Hexanes/EtOAc) to afford **3-89** (0.6945 g, 73%) as a red foam. Prodiginine **3-89** exists as mainly one conformer, but several smaller conformers are observed in the ^{1}H NMR spectrum.

(*Z*)-5-(4'-methoxy-1-tosyl-1*H*,5'*H*-[2,2'-bipyrrol]-5'-ylidene)-5-(5-methyl-1*H*-pyrrol-2-yl)pentan-2-ol (3-89):
^{1}H NMR (500 MHz, $CDCl_3$): δ 12.91 (bs, 1H), 7.62 (dd, *J* = 1.7, 3.0 Hz, 1H), 7.55 (d, *J* = 8.3 Hz, 2H), 7.06 (d, *J* = 8.3 Hz, 2H), 6.82 (d, *J* = 3.7 Hz, 1H), 6.63 (dd, *J* = 1.6, 3.3 Hz, 1H), 6.33 (t, *J* = 3.4 Hz, 1H), 6.04 (d, *J* = 3.6 Hz, 1H), 5.73 (s, 1H), 3.92-3.83 (m, 1H), 3.80 (s, 3H), 3.14-2.98 (m, 2H), 2.43 (s, 3H), 2.29 (s, 3H), 1.92 (bs, 1H), 1.89-1.73 (m, 2H), 1.22 (d, *J* = 6.2 Hz, 3H)

^{13}C NMR (125 MHz, $CDCl_3$): 166.8, 152.6, 144.7, 140.1, 139.8, 137.1, 135.3, 131.7, 131.3, 129.3, 127.6, 127.2, 118.5, 118.3, 111.3, 110.0, 98.6, 67.5, 58.4, 41.7, 25.3, 23.1, 21.6, 13.6

LRMS (ESI) m/z, 480.1949 (480.1952 calculated for $C_{26}H_{30}N_3O_4S^+$, $(M+H)^+$)

(*Z*)-5-(4'-methoxy-1*H*,5'*H*-[2,2'-bipyrrol]-5'-ylidene)-5-(5-methyl-1*H*-pyrrol-2-yl)pentan-2-ol (3-90)



3-90

To a solution of **3-88** (0.3611 g, 1.99 mmol) and **3-29** (0.7276 g, 2.3 mmol, 1.15 eq) in MeOH (20 mL, 0.1M), HBr (48% in H_2O, 8.89 M, 0.9 mL, 8.00 mmol, 4 eq) was added and the mixture was stirred at room temperature overnight (~16 hours). The reaction was then concentrated to give a viscous black purple oil, which was used directly in the next step.
Crude **3-89** was dissolved in MeOH (20 mL, 0.1 M) and KOH (0.5885 g, 10.4 mmol, 5 eq) was added. The mixture was then refluxed overnight (~16 hours) and then cooled to room temperature. The reaction was then concentrated to a black residue, which was taken up in EtOAc and flushed through a neutral Al_2O_3 plug. The filtrate was concentrated to afford **3-90** (0.57 g, 88% over two steps) as a red black solid.

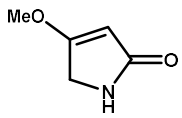
Crystals suitable for X-ray diffraction analysis were obtained by dissolving in hot THF and slow cooling to room temperature.

(*Z*)-5-(4'-methoxy-1*H*,5'*H*-[2,2'-bipyrrol]-5'-ylidene)-5-(5-methyl-1*H*-pyrrol-2-yl)pentan-2-ol (3-90):
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.99-6.94 (m, 1H), 6.71 (d, *J* = 3.5 Hz, 1H), 6.67-6.63 (m, 1H), 6.31 (t, *J* = 2.9 Hz, 1H), 6.01 (s, 1H), 5.99 (d, *J* = 3.5 Hz, 1H), 3.92 (s, 3H), 3.92-3.84 (m, 1H), 3.12-2.99 (m, 2H), 2.39 (s, 3H), 1.91-1.71 (m, 2H), 1.21 (d, *J* = 6.1 Hz, 3H)

^{13}C NMR (125 MHz, $CDCl_3$): 168.3, 155.5, 138.2, 136.8, 136.2, 132.2, 128.7, 120.9, 117.0, 111.2, 110.5, 109.5, 96.5, 67.7, 58.5, 41.5, 25.1, 23.1, 14.0

LRMS (ESI) m/z, 326.2 (326.2 calculated for $C_{19}H_{24}N_3O_2^+$, $(M+H)^+$)

3.4.3. NMR Spectra Relevant to Chapter 3



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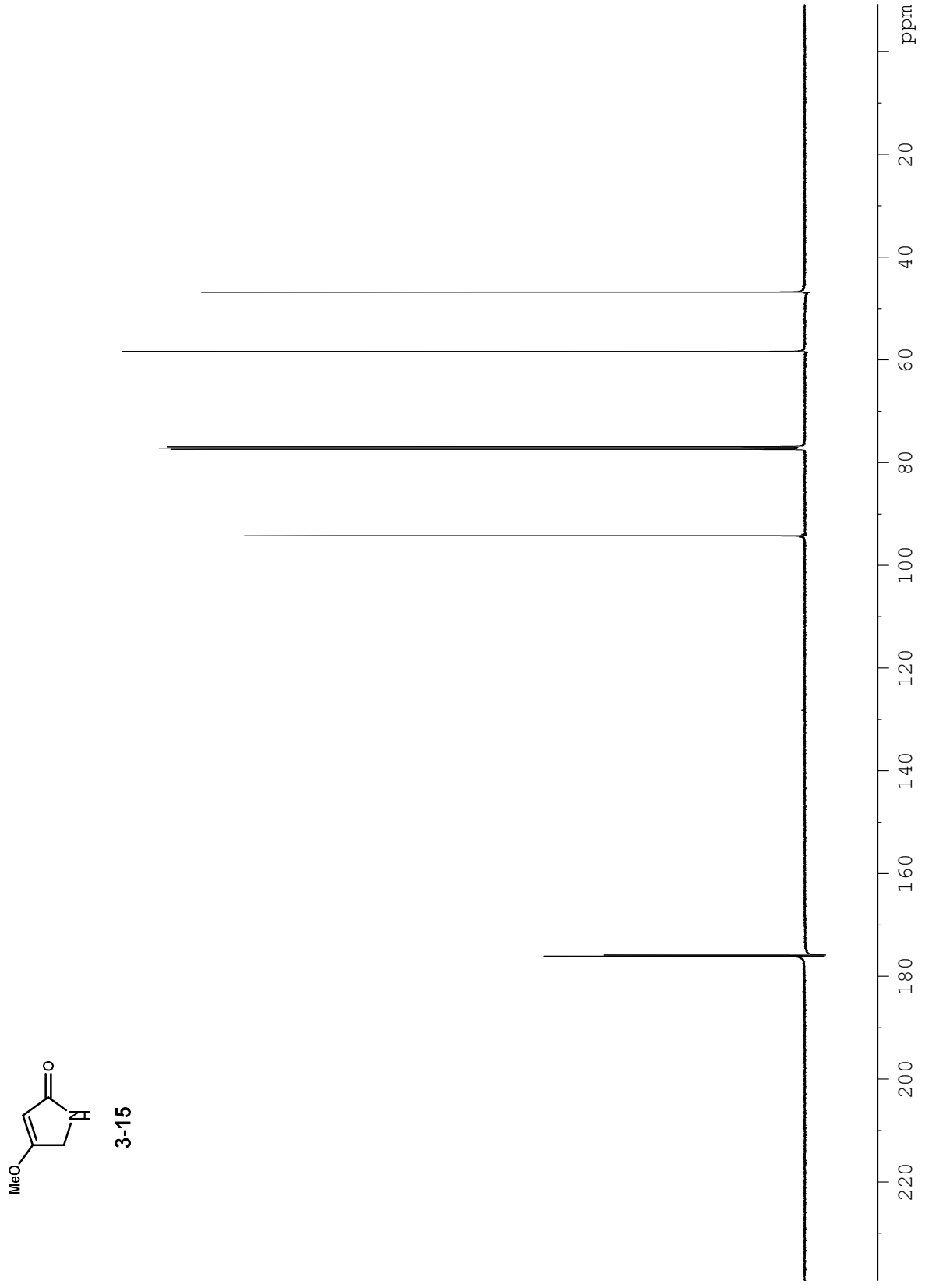
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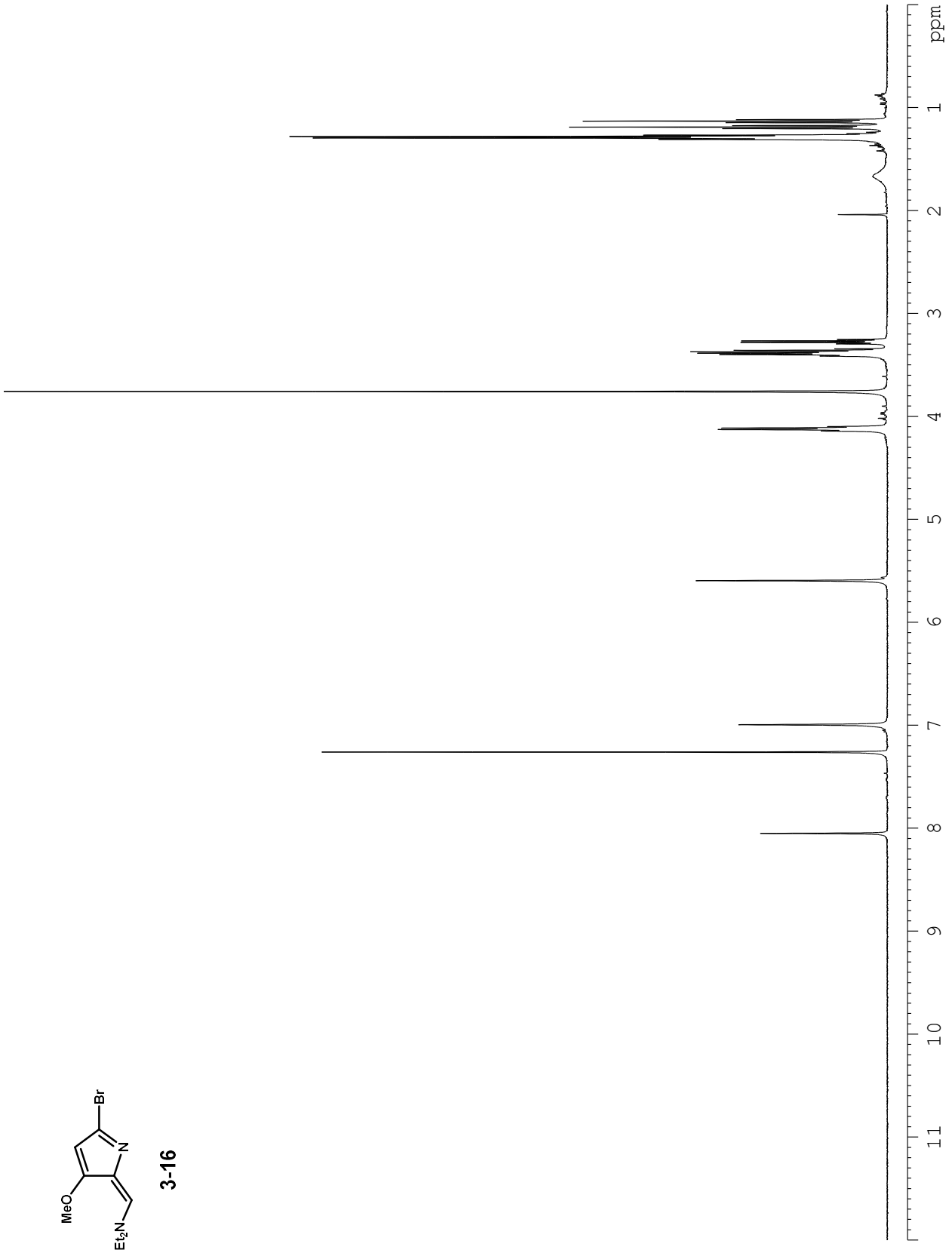
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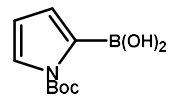
11

3-17



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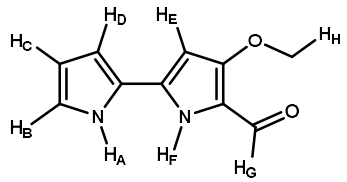

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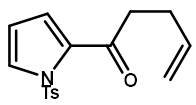

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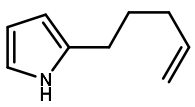

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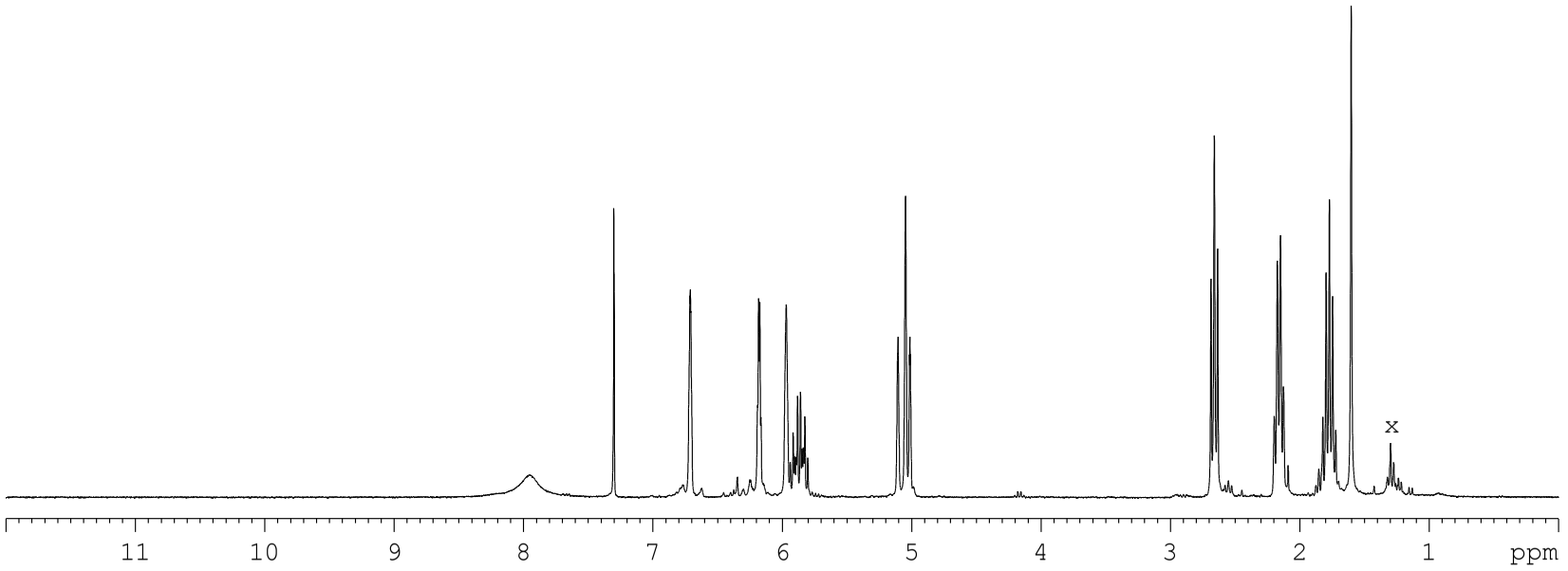

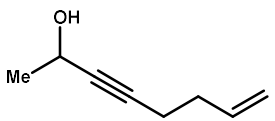

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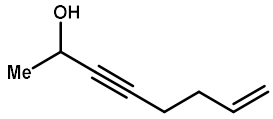

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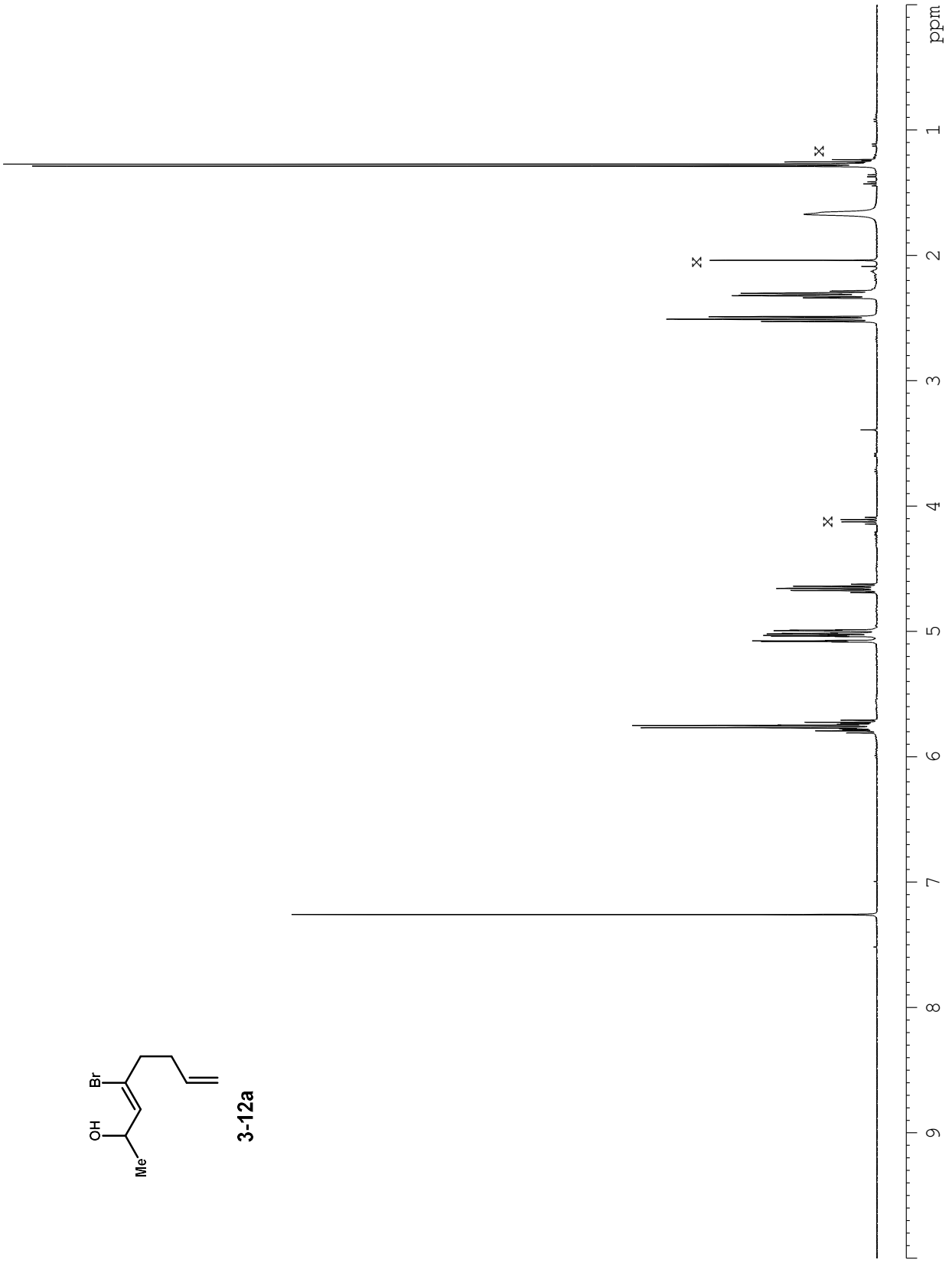

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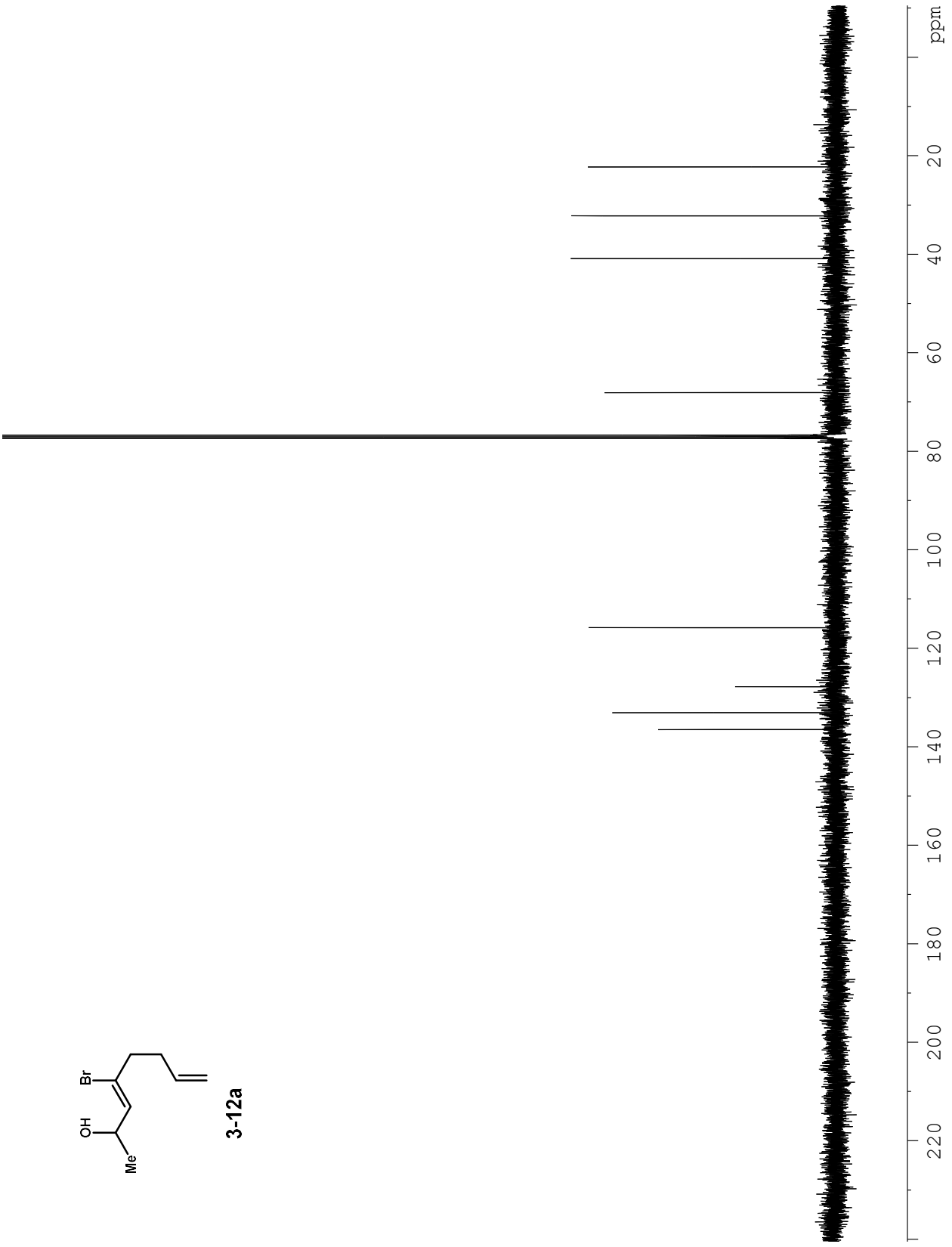
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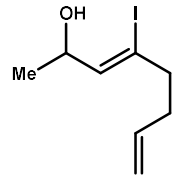

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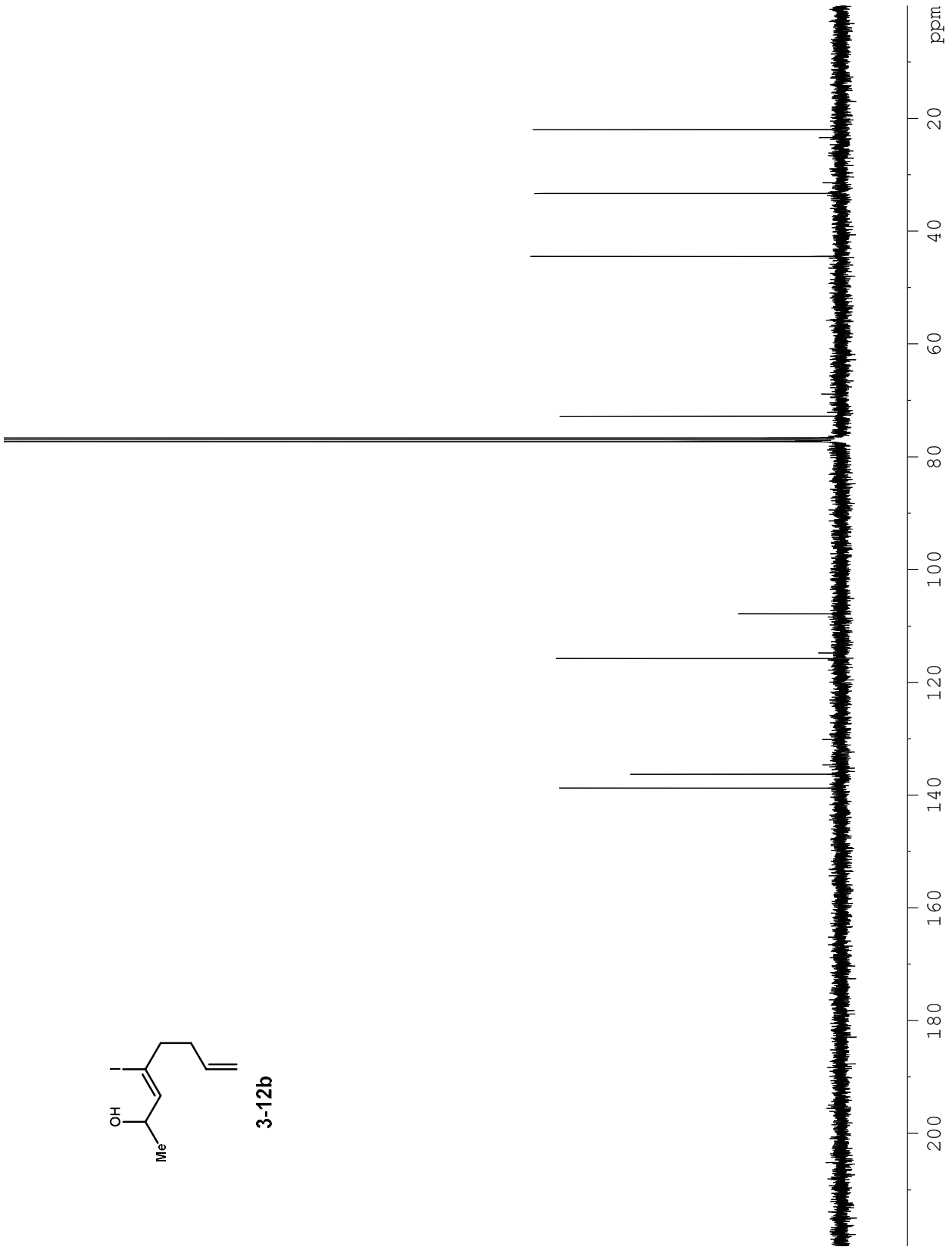
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60
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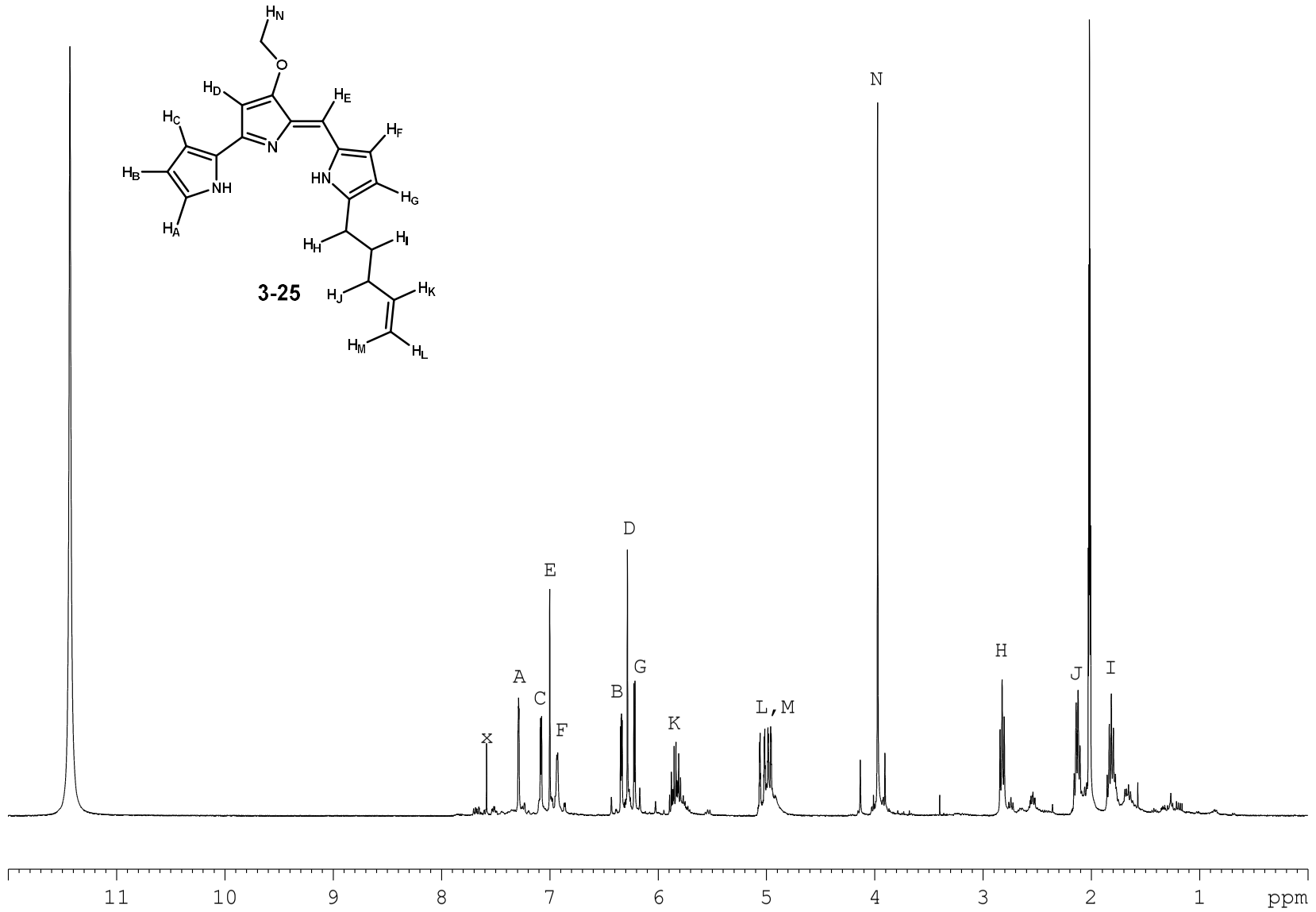
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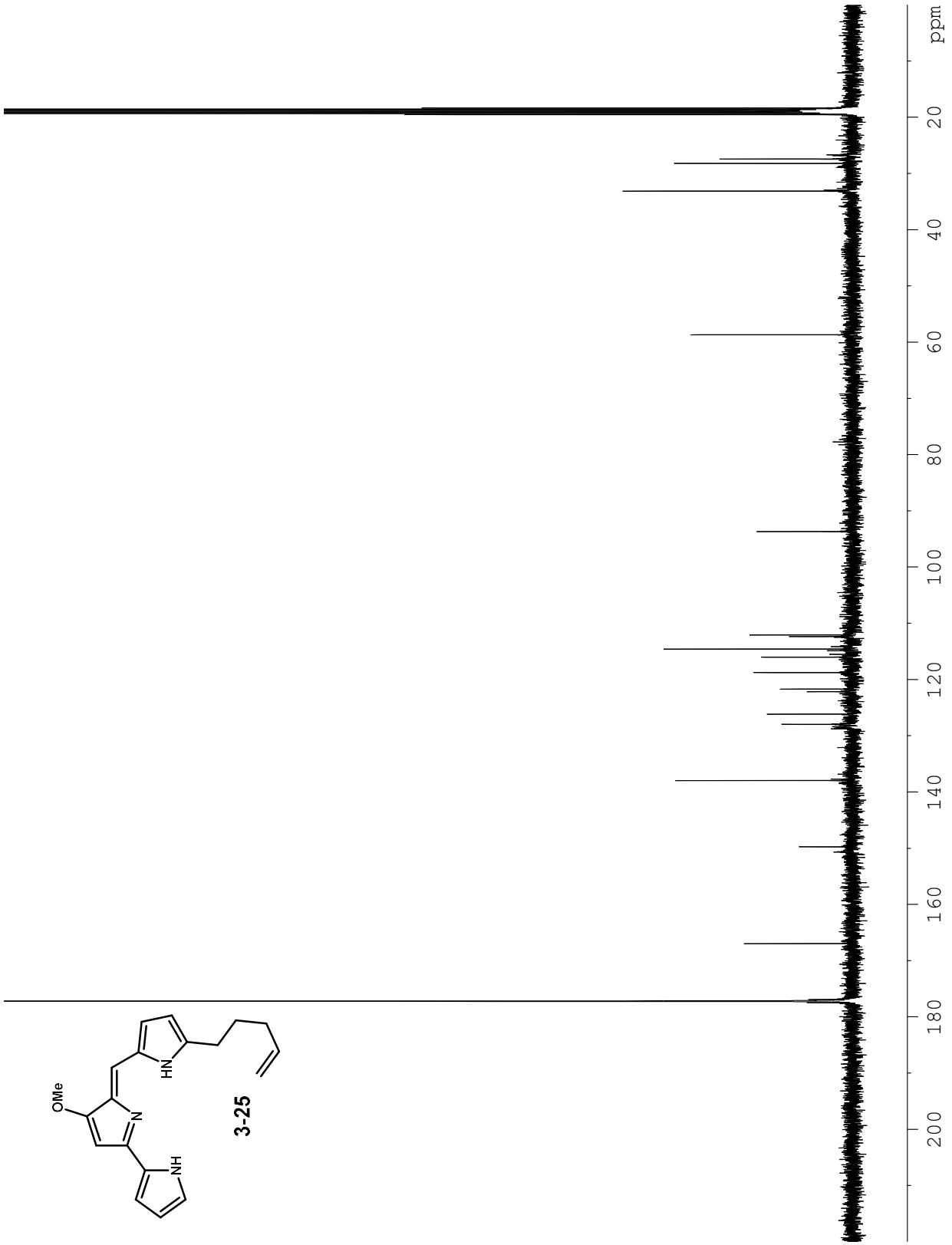
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NH
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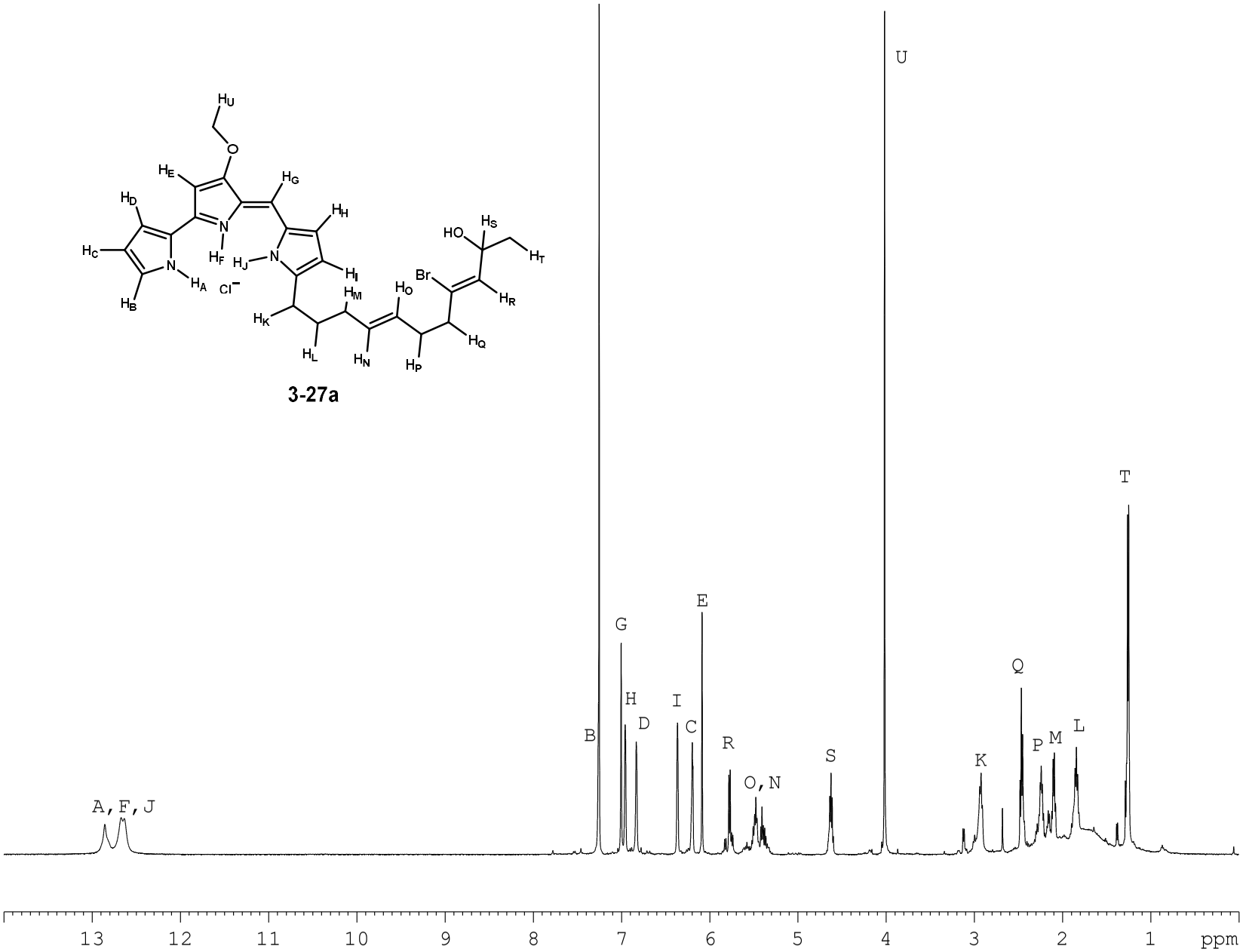
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HP
HQ
Br
HR
HO
HS
HT
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U
T
E
G
Q
H
I
D
C
B
R
S
O,N
K
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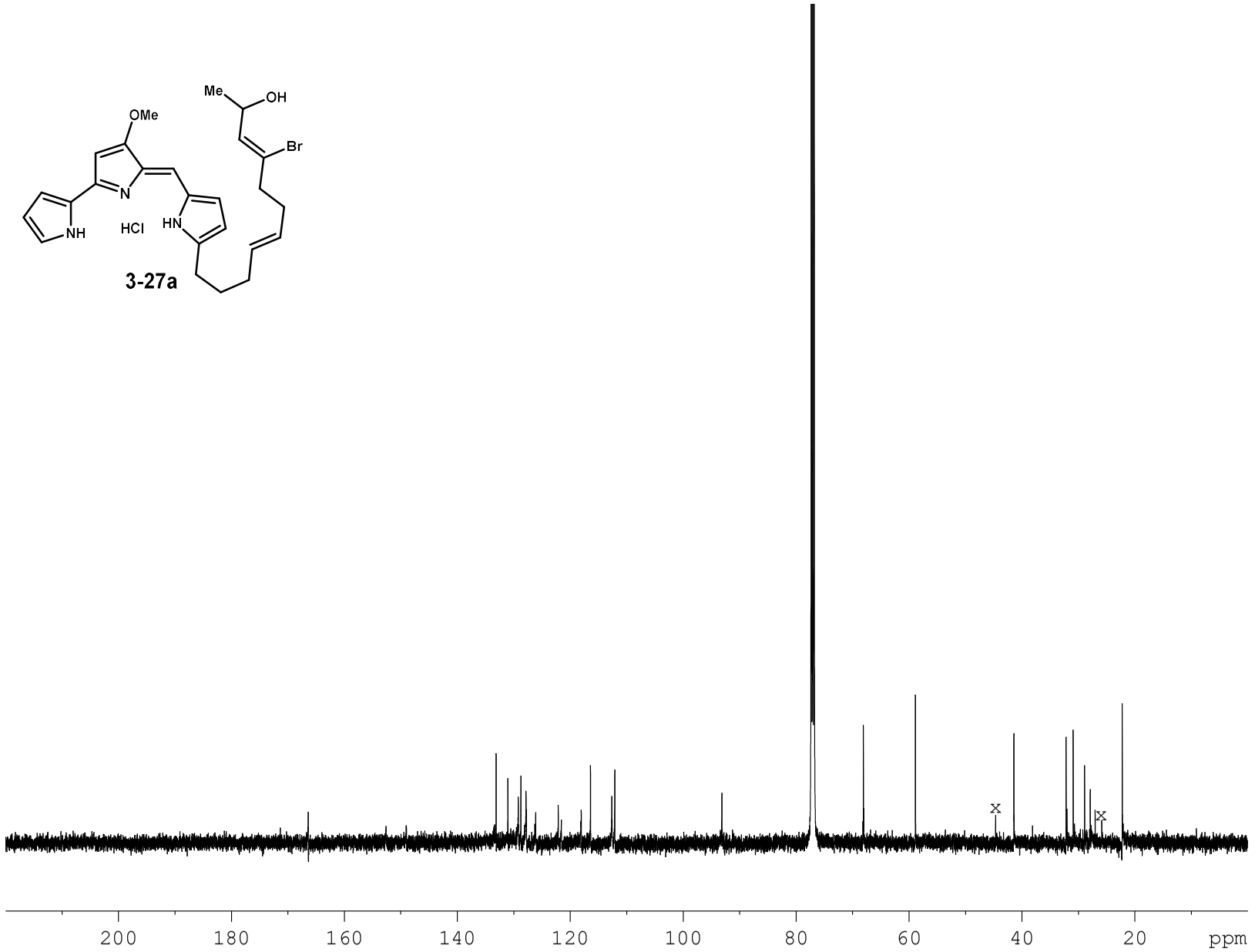
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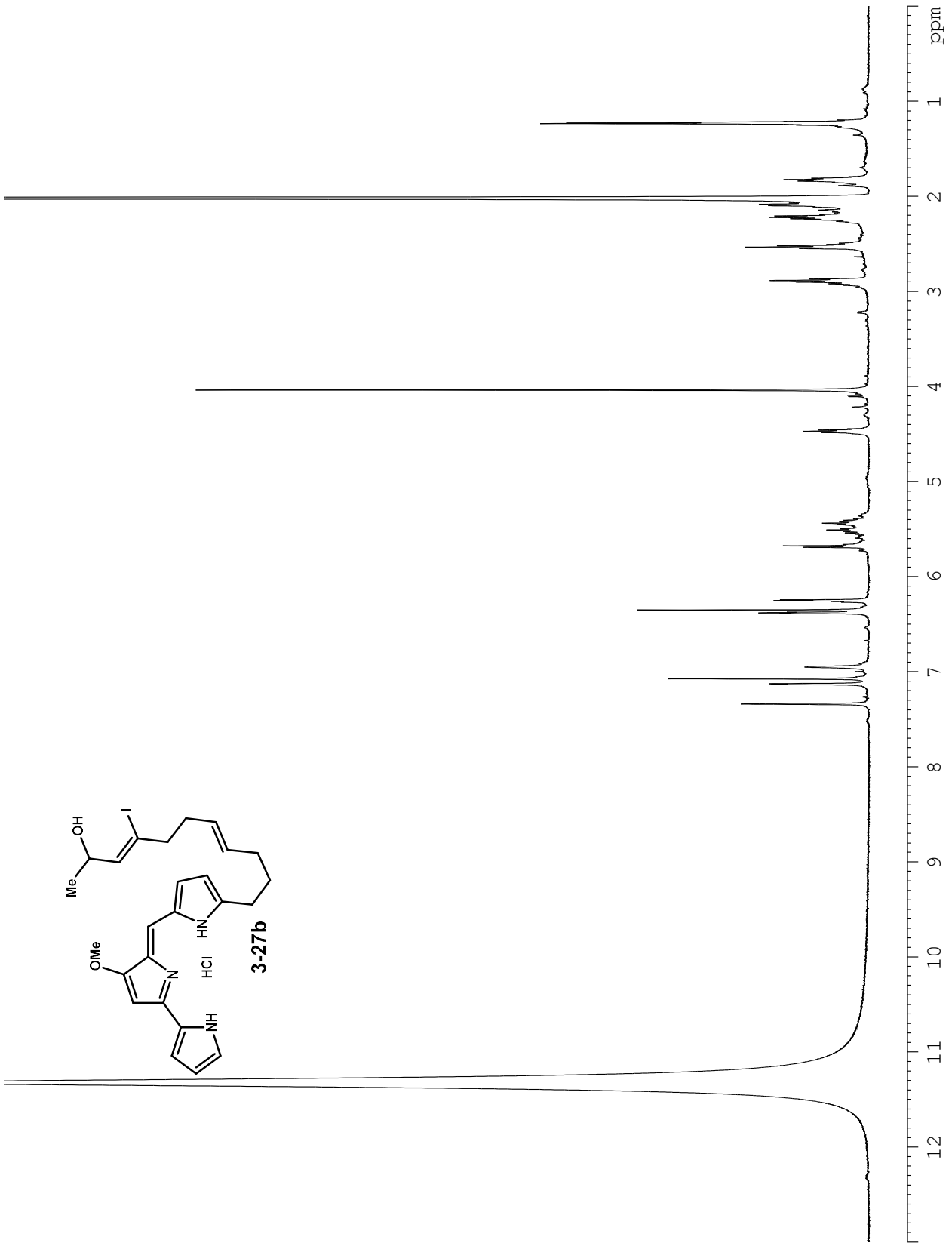
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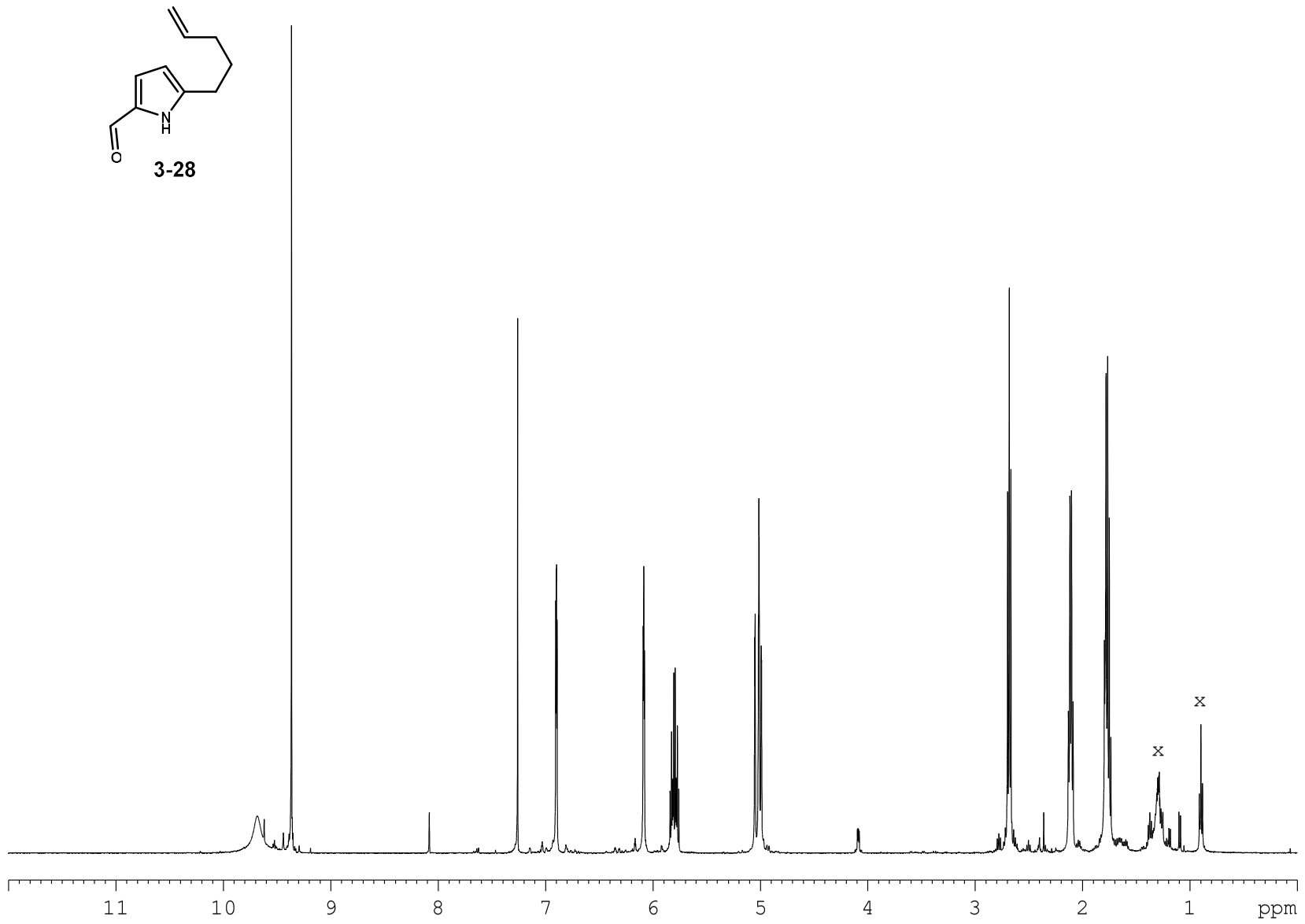
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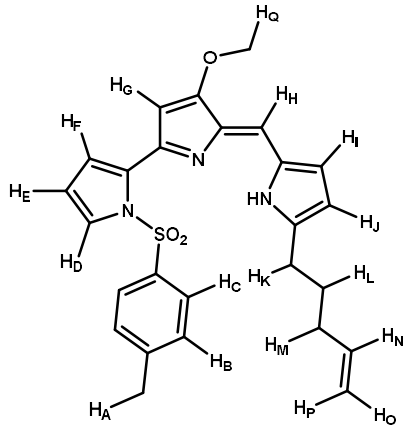
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HK
HL
HM
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HB
HA
HP
HO

3-30

X
Q
A
C
H
G
K
D
B
F
I
E
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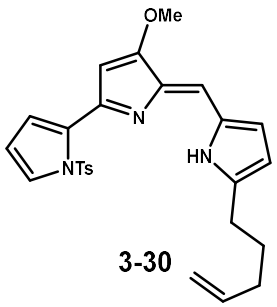

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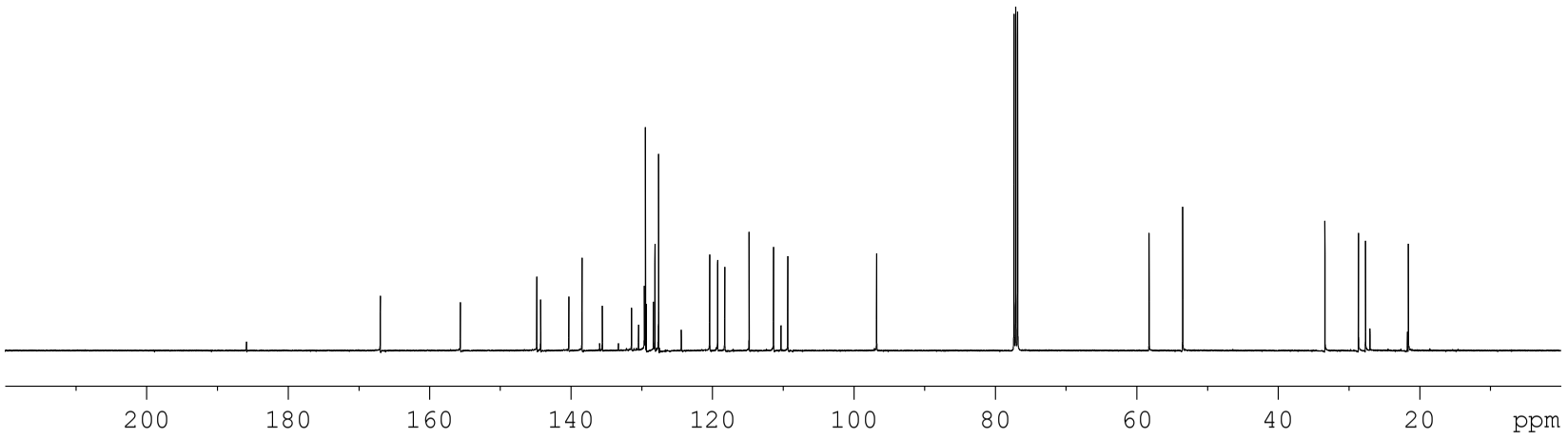

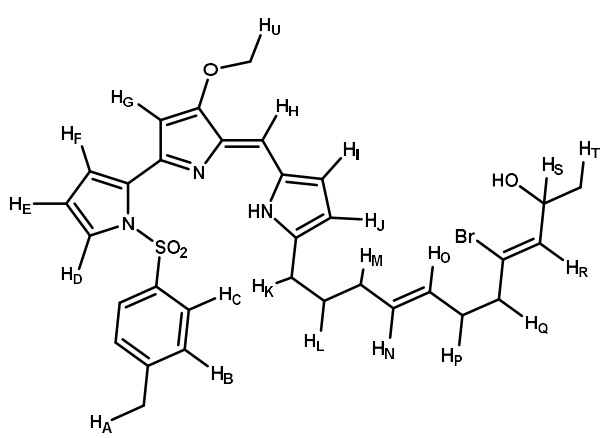
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HL
HN
HP
HB
HA

3-31

U
A
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C
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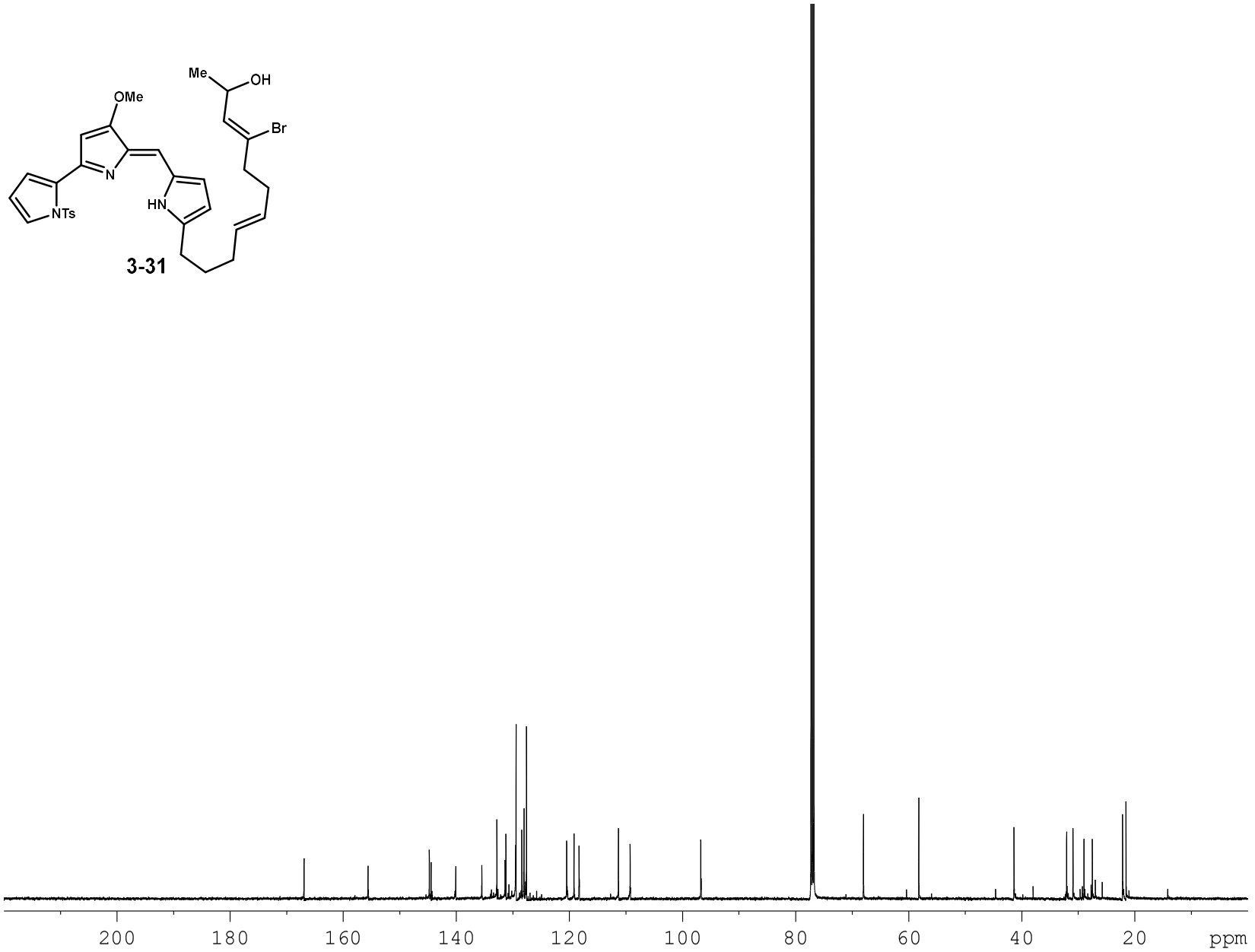
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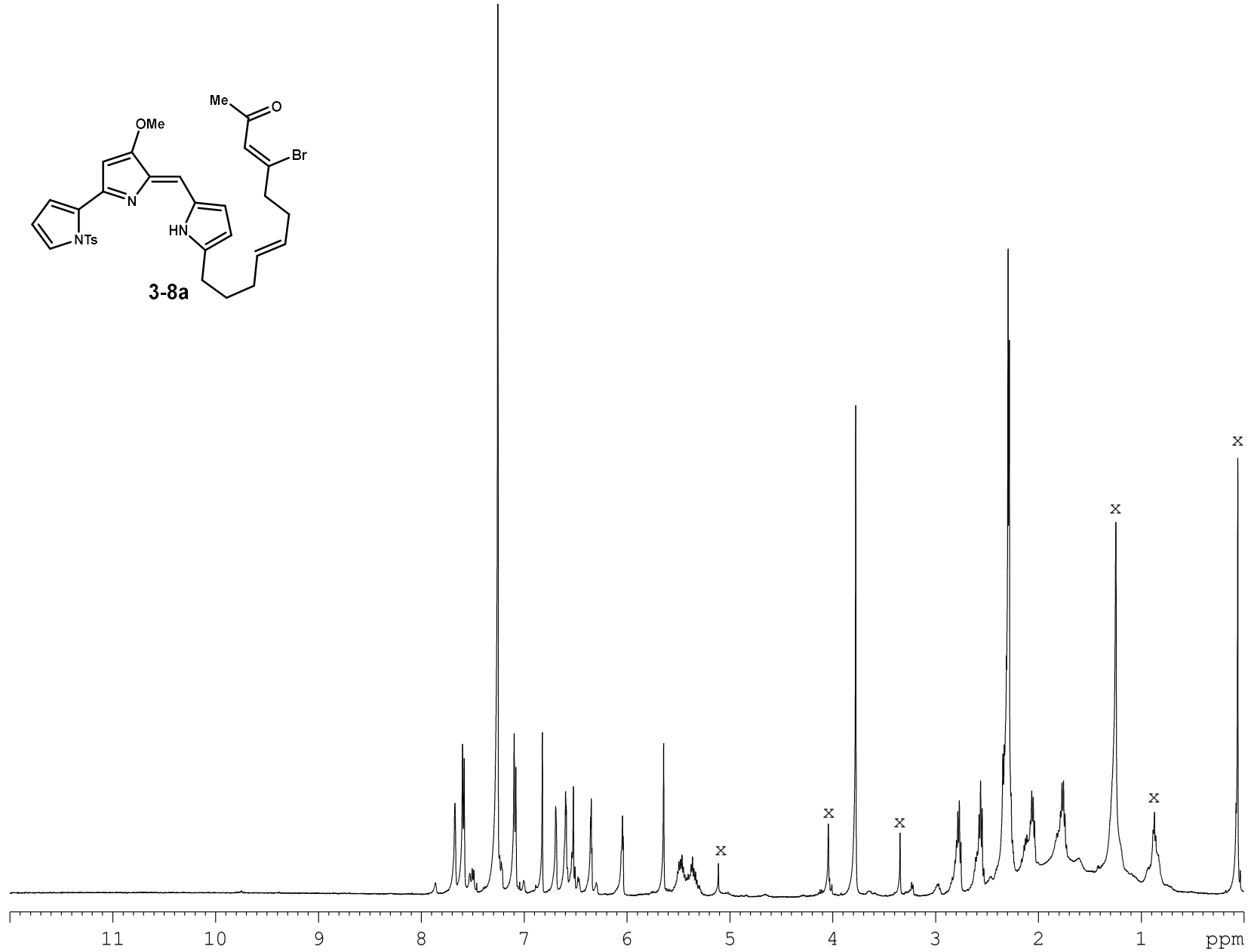
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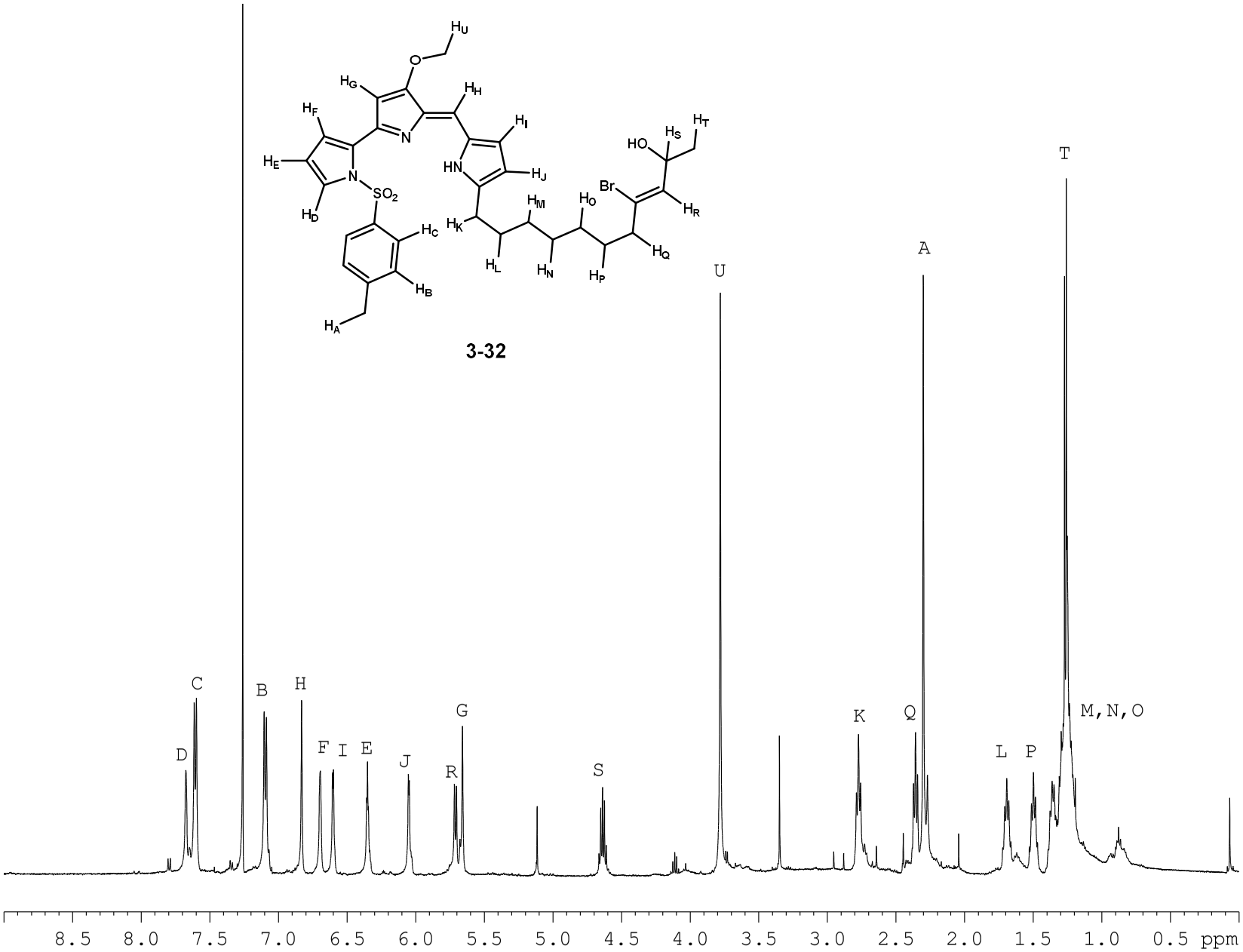
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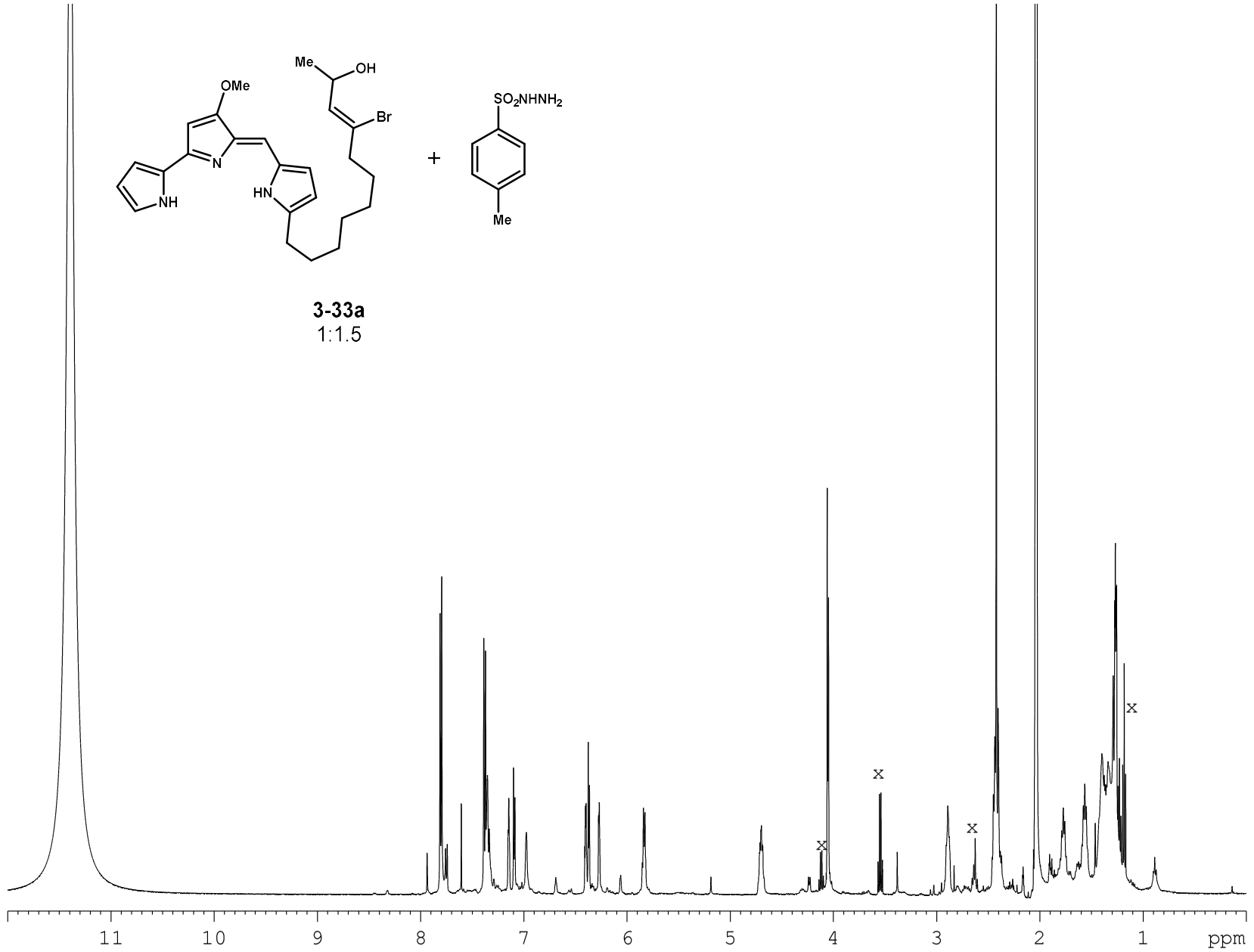
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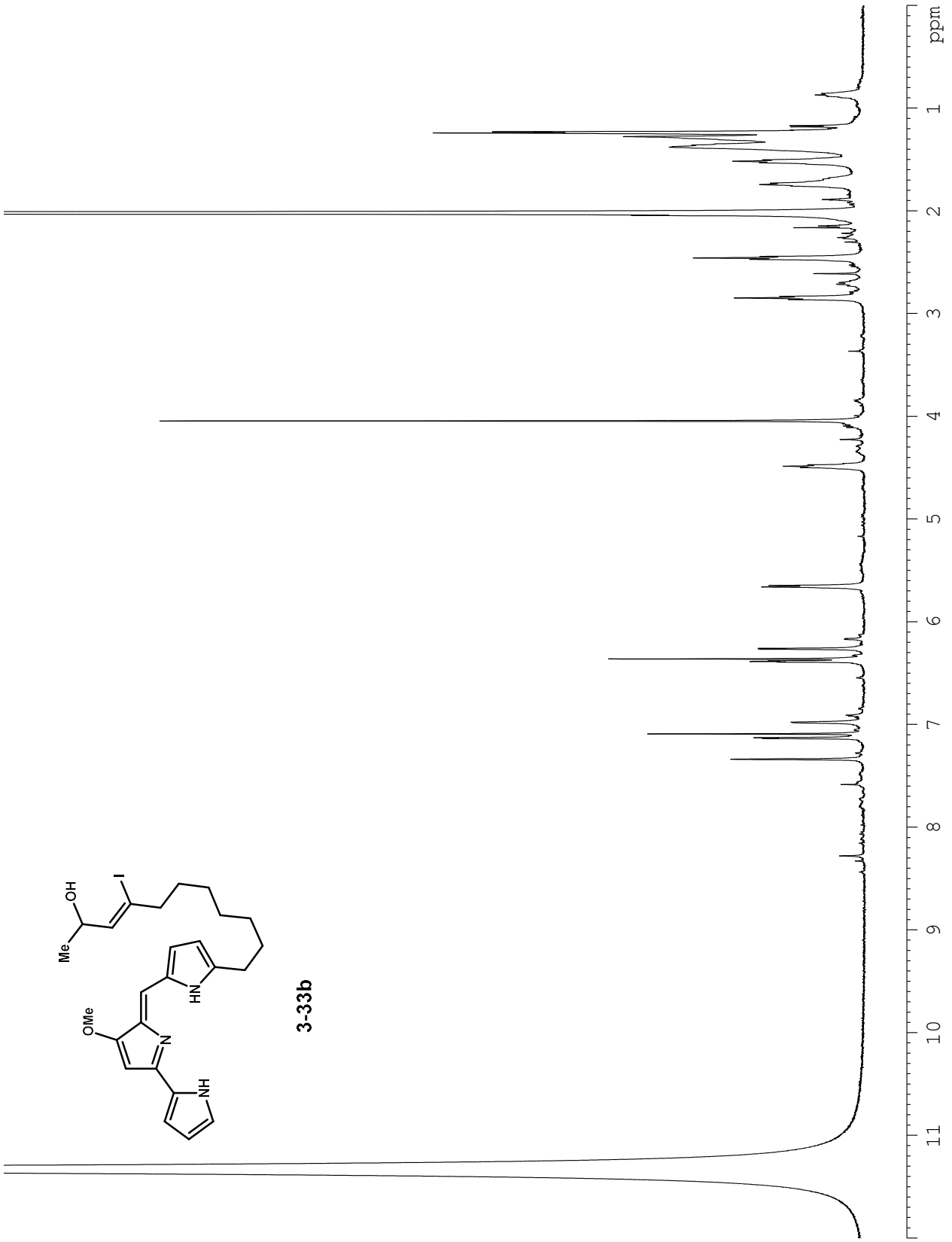
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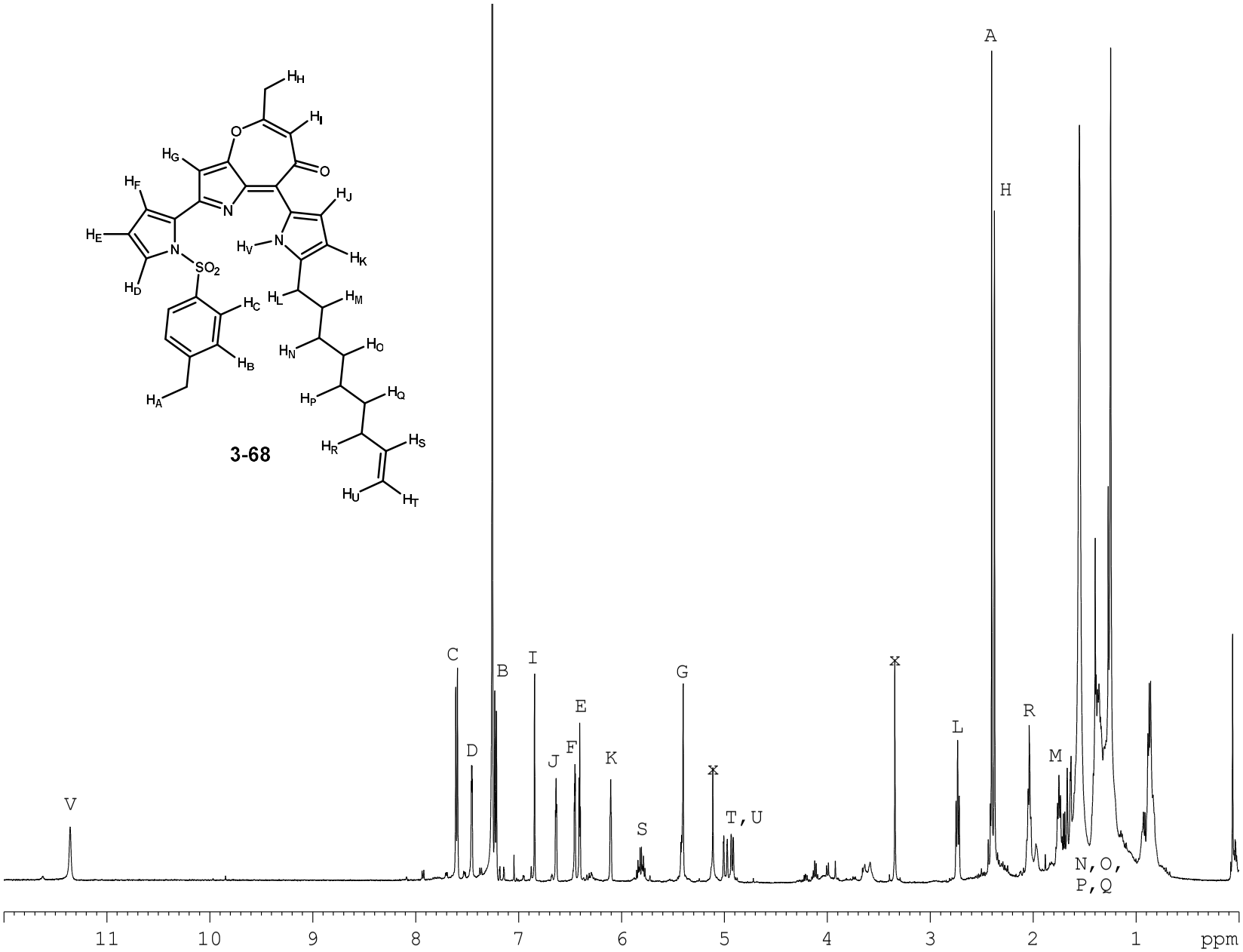
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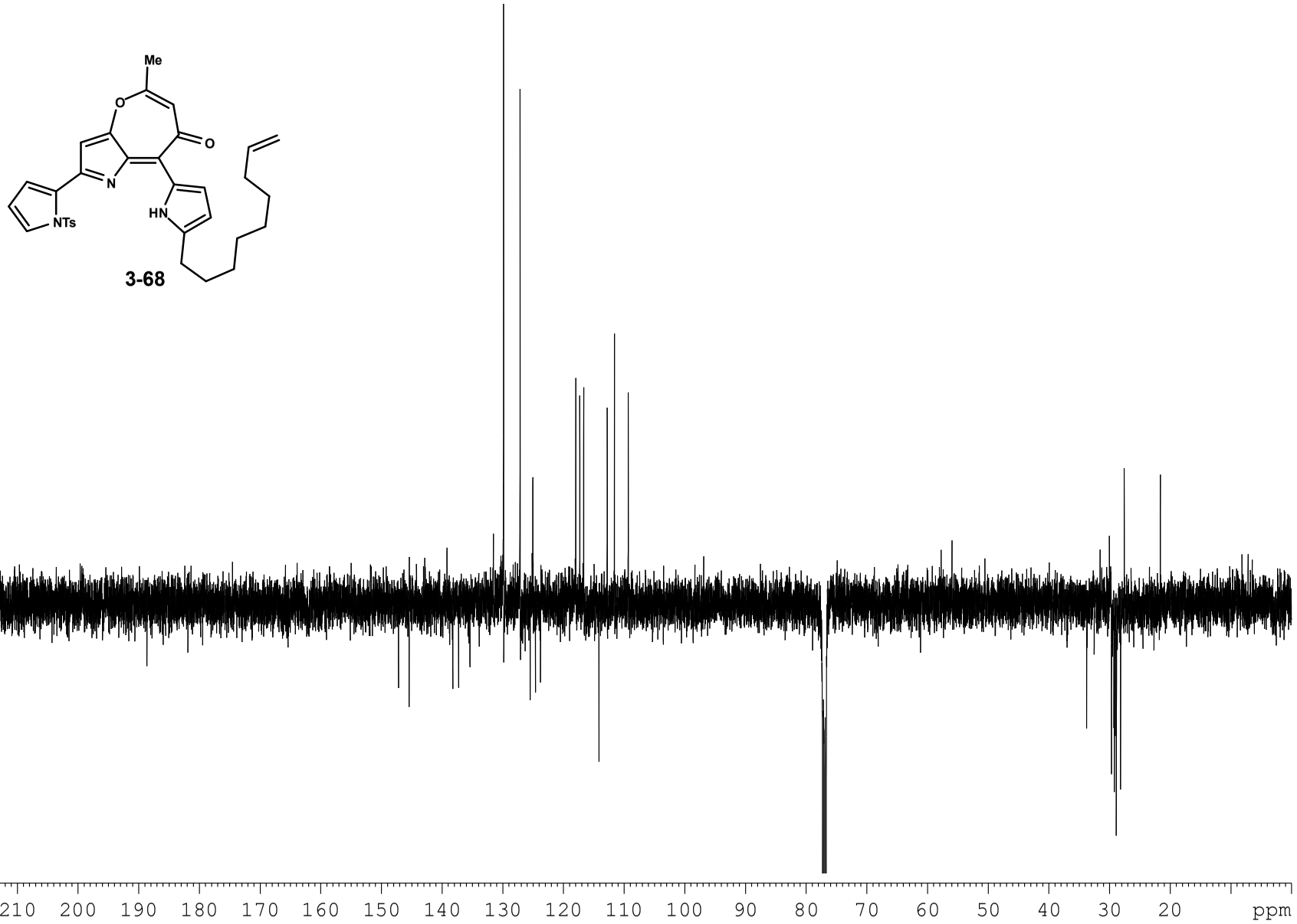
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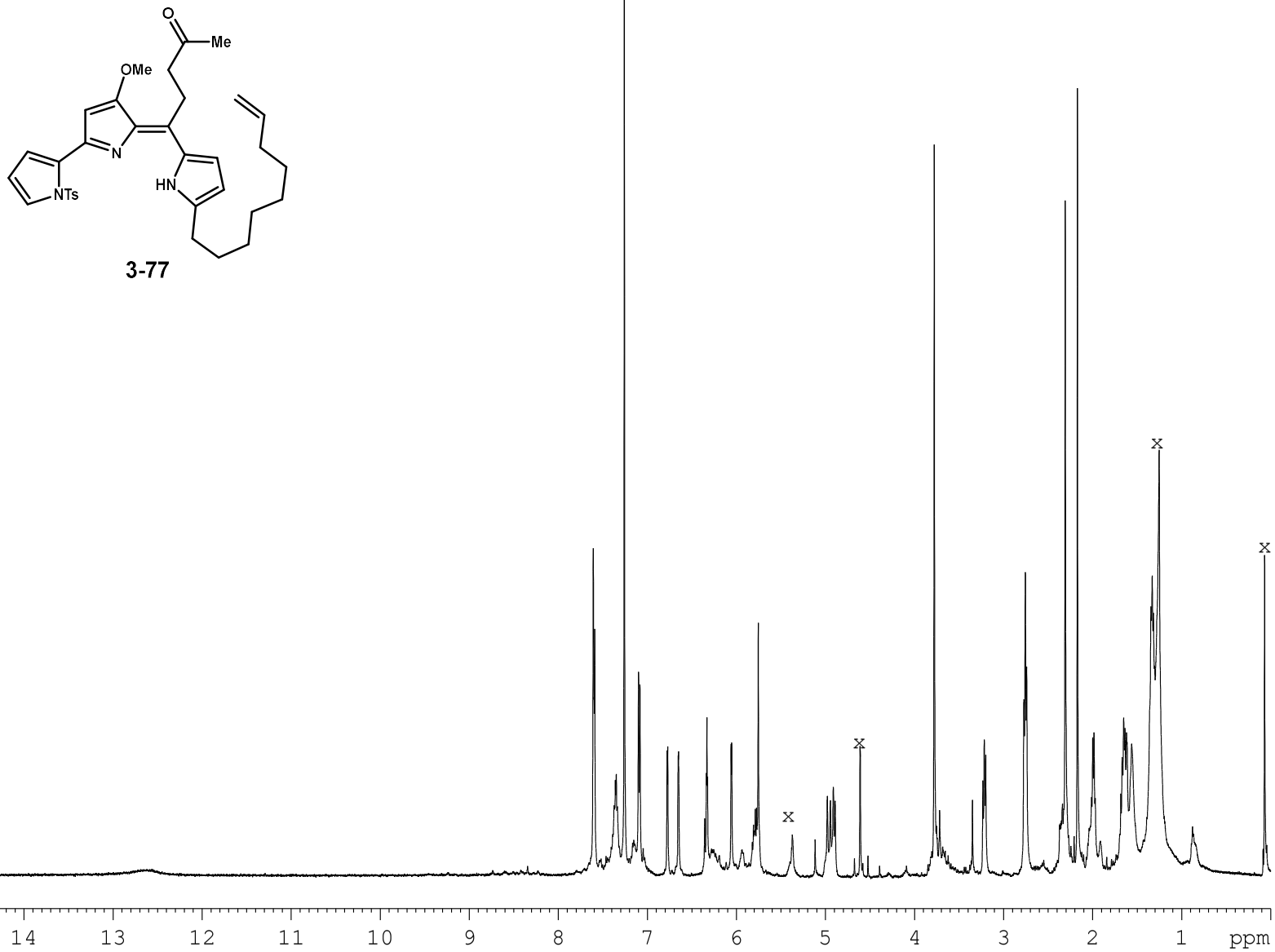
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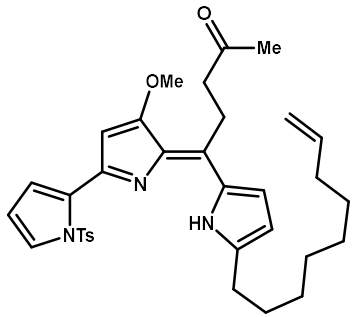

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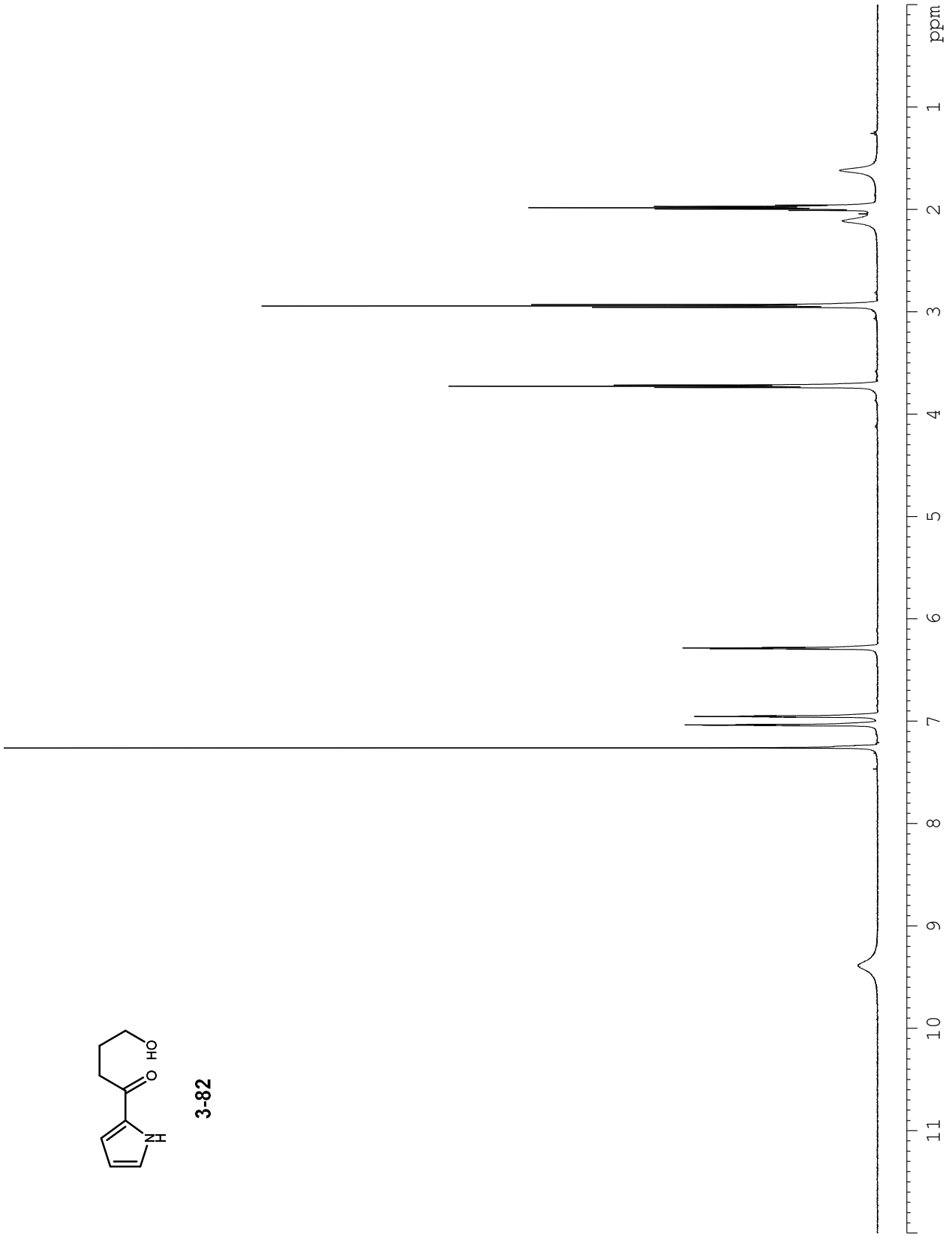

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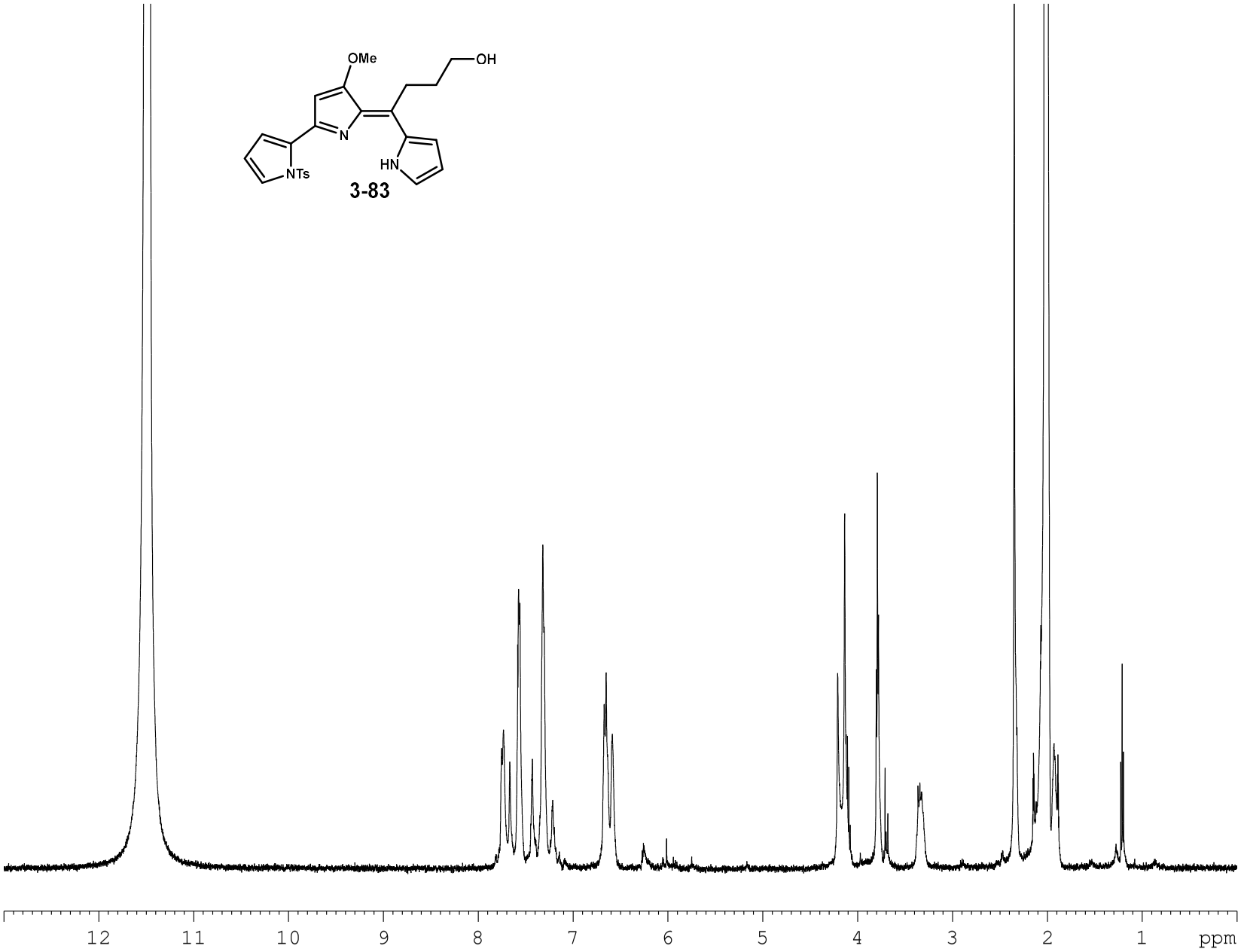
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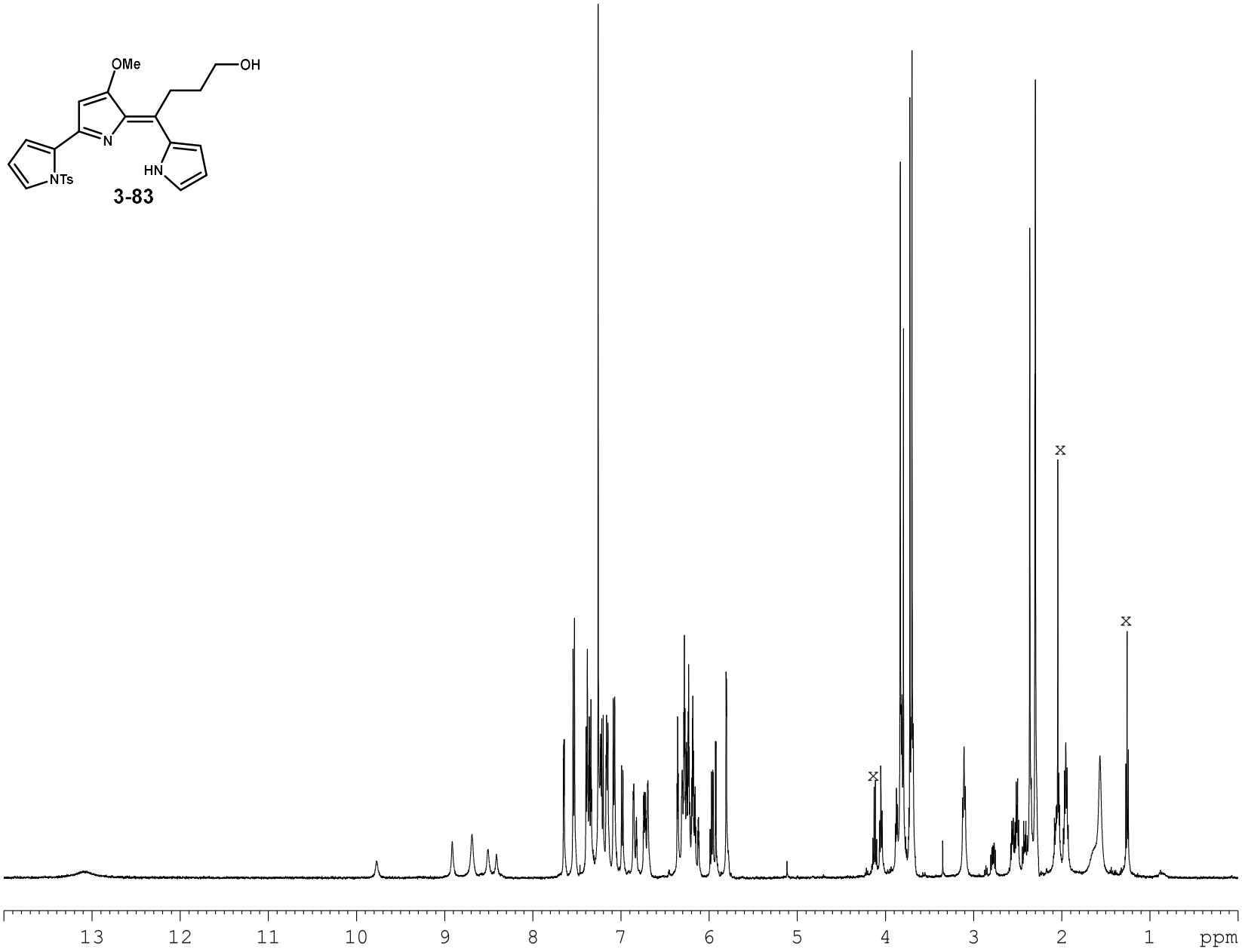
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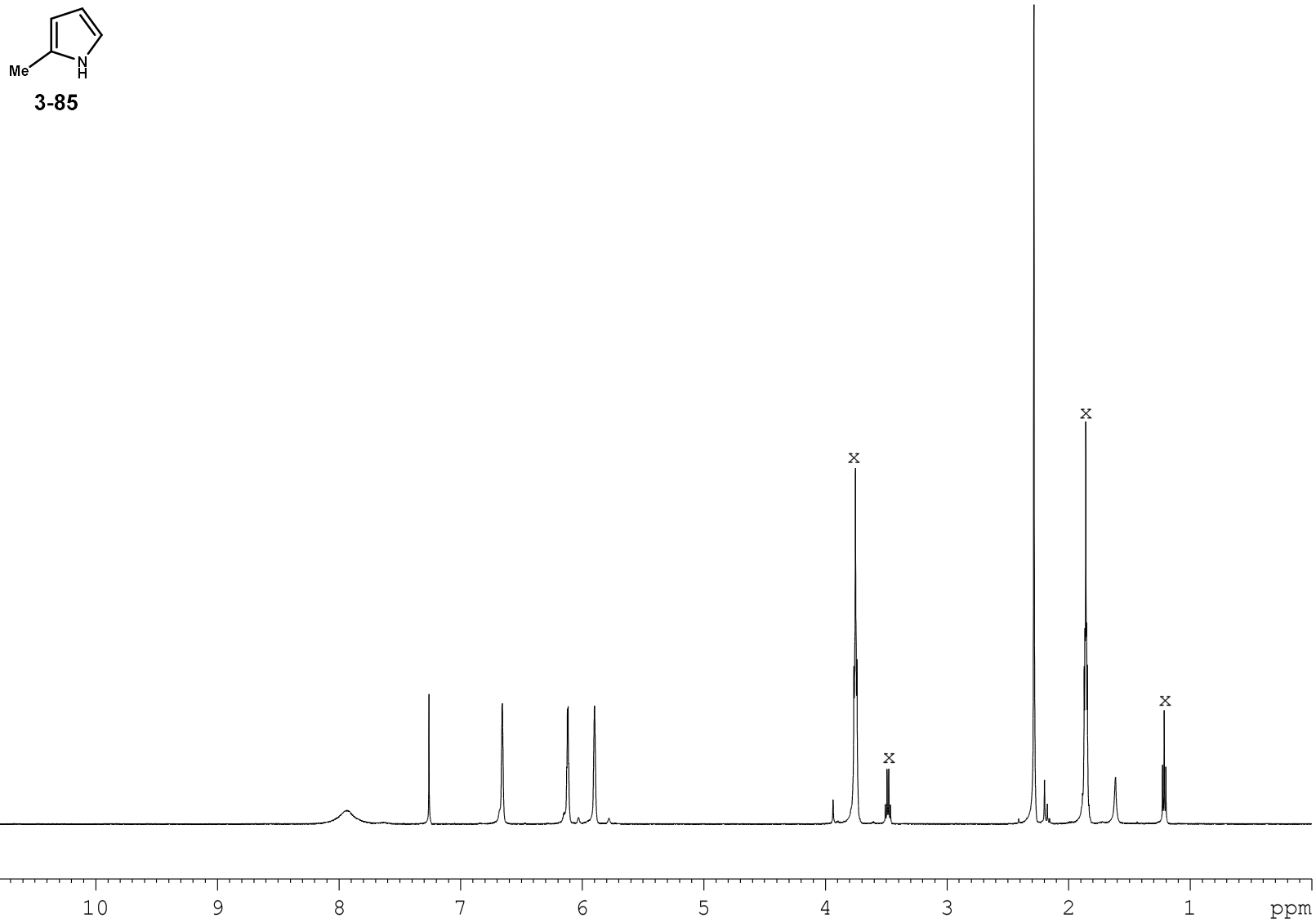
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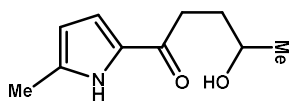

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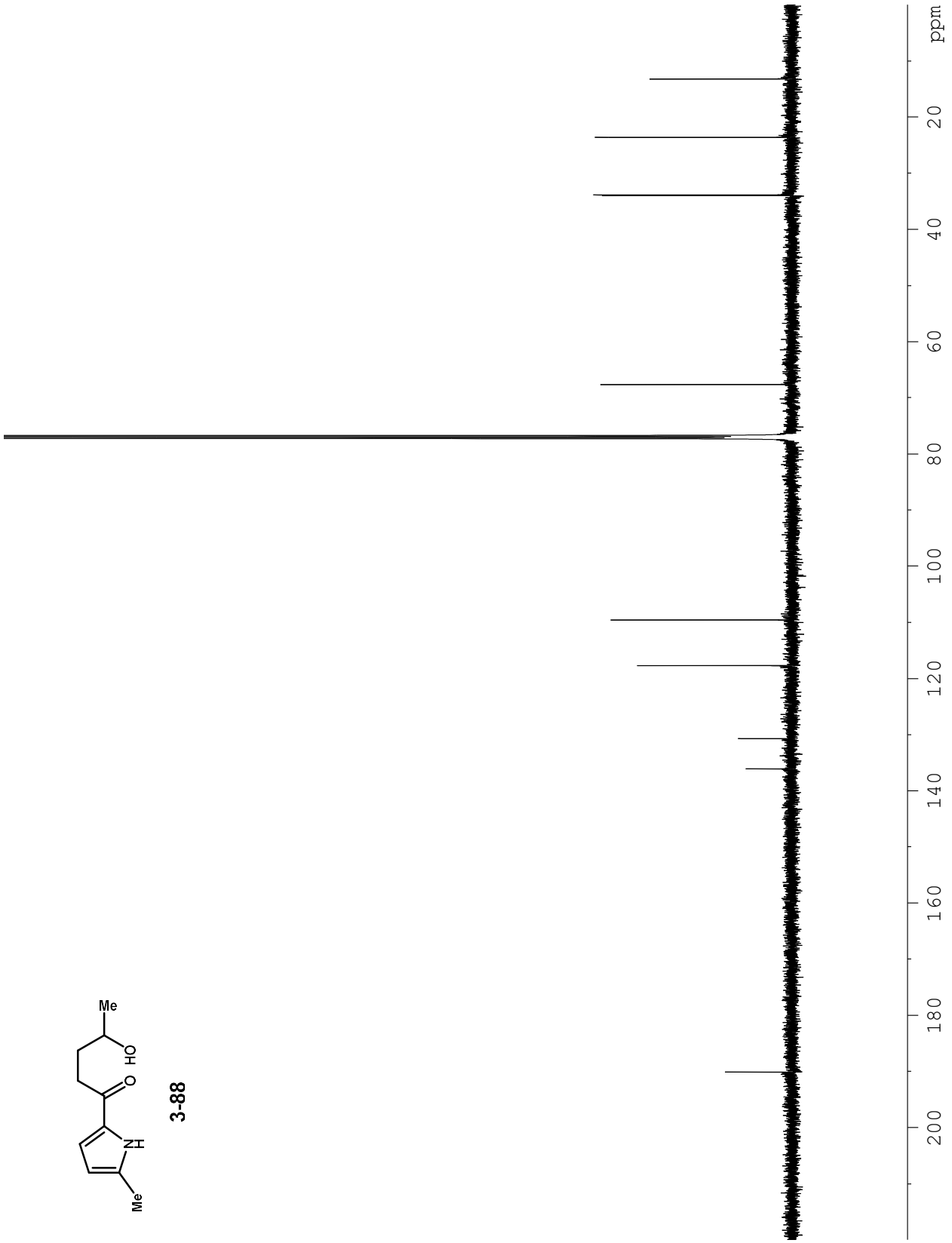
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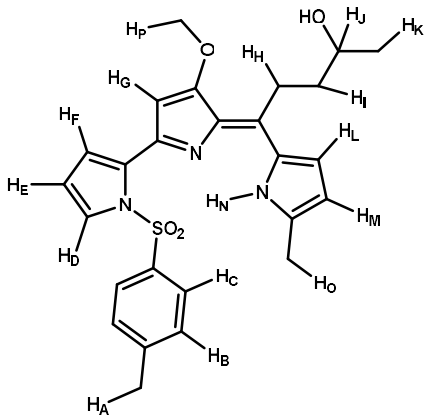
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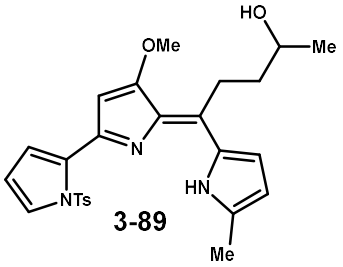

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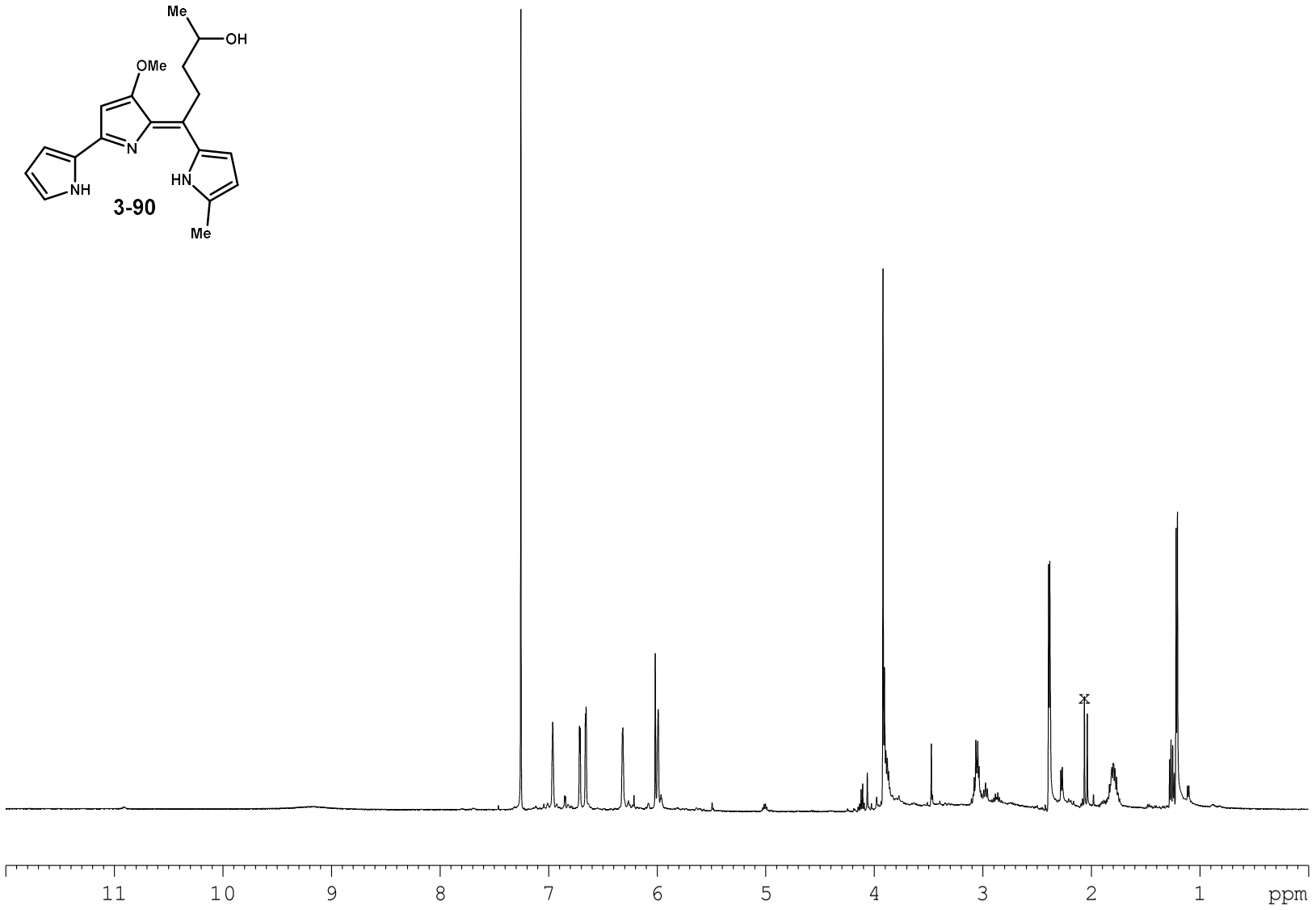
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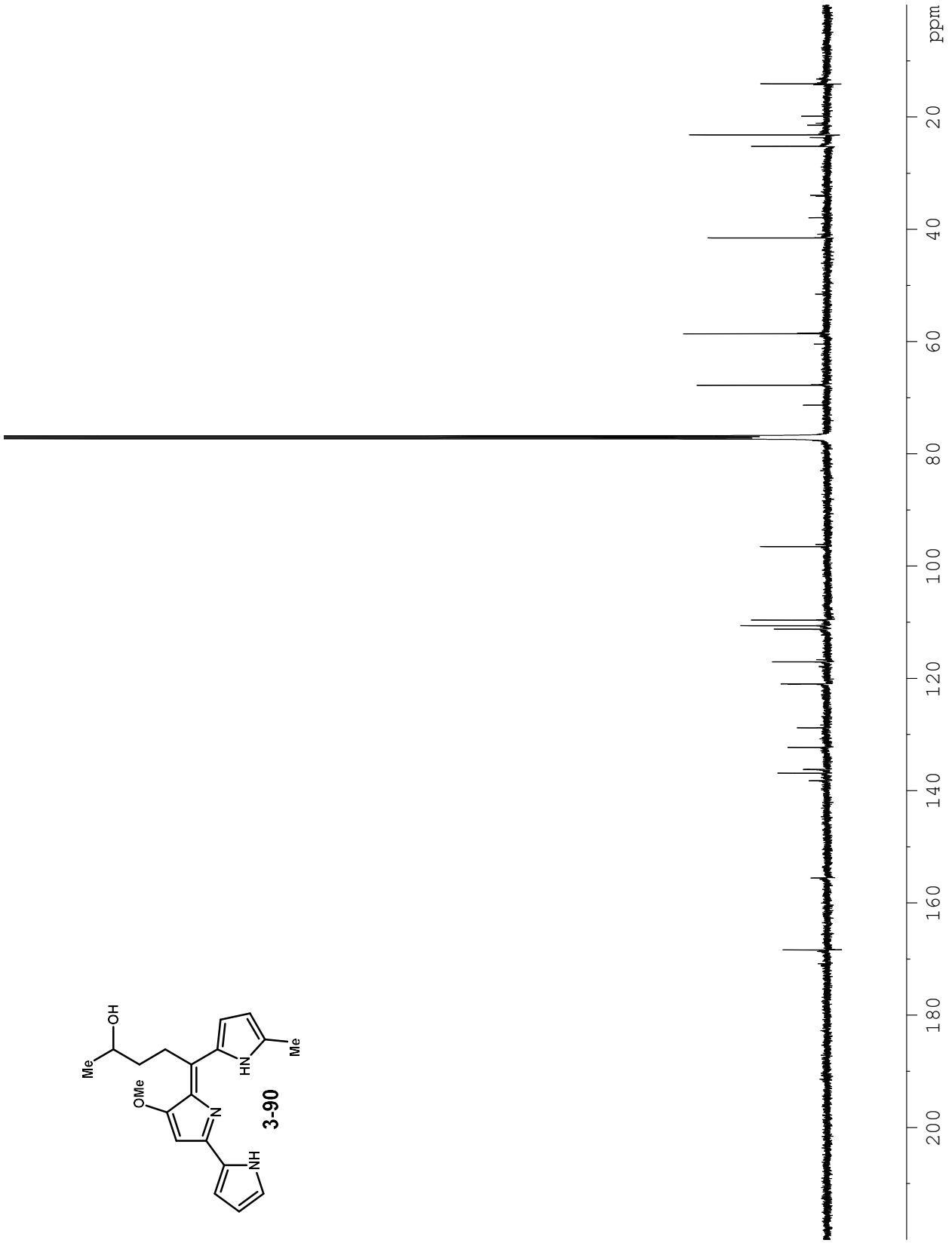
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4. Chapter Four – A Modular Nine Step Synthesis of Marineosin A

Tyler Allred, Zhengao Feng, Evan Hurlow, and Patrick Harran

4.1. Introduction

4.1.1. Introduction and General Strategy

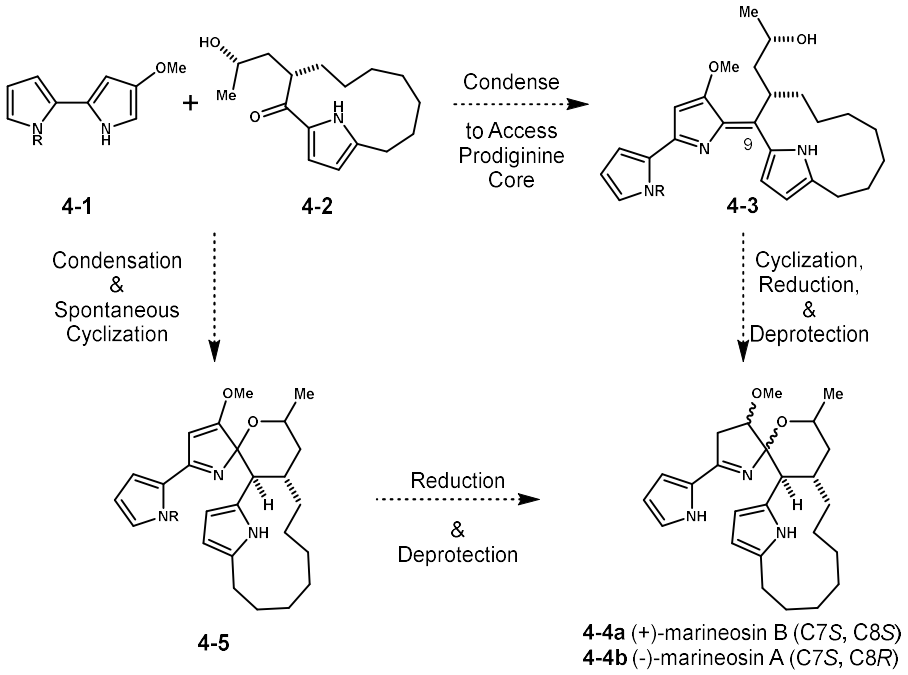


Figure 4.1. Proposed Synthesis of Marineosins through Modified Rapoport Condensation

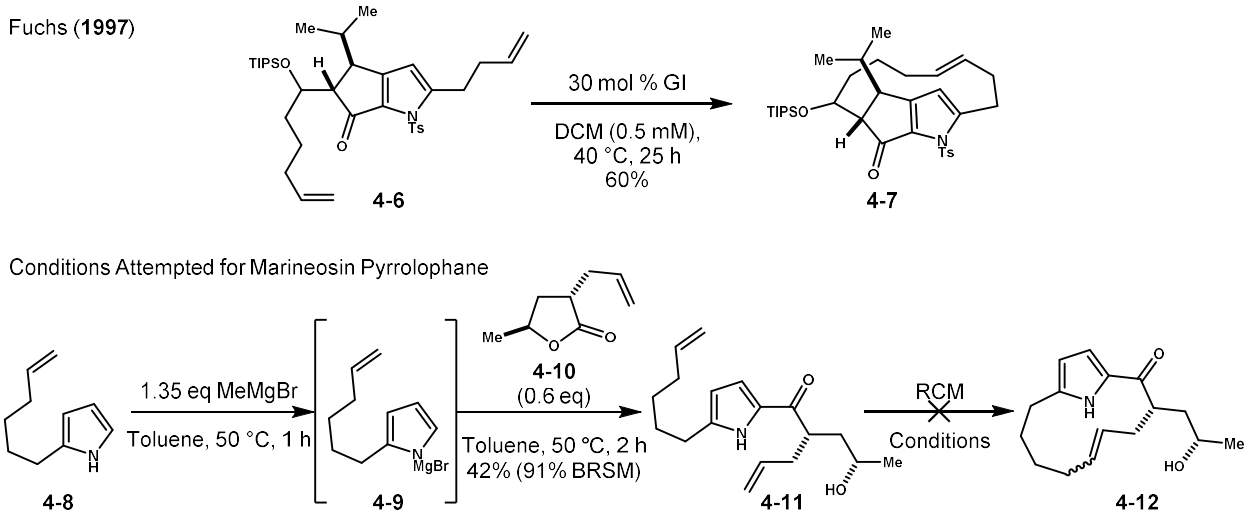
When considering the challenges encountered with the late stage ansa bridge formation strategies (Chapters 2 and 3), we considered alternative approaches to the marineosins. The newfound utility of pyrroloketones as partners in modified Rapoport condensations (Chapter 3) presented us with a modular method of constructing prodiginines functionalized at C9. It was postulated that this approach could be utilized in the production of the marineosins if the ansa bridge was already present in the condensation partner (**Figure 4.1**). This approach is analogous to other syntheses of ansa bridged prodiginine natural products; however, this particular condensation would employ a pyrroloketone partner instead of the traditional formyl pyrrole derivative.[1,2] This process would

produce prodiginine **4-3**, which could then be subjected to a cycloisomerization followed by reduction and deprotection to afford the marineosins (**4-4a/b**). However, it was unclear whether prodiginine **4-3** would be isolable or if spontaneous cyclization would occur producing the premarineosins **4-5**. Although structure **4-3** is a postulated intermediate in the marineosin biosynthesis, it has never been observed or isolated. Only the premarineosins **4-5** are obtained after Rieske oxygenase mediated ansa bridge construction (Chapter 1).[4] If our proposed condensation reaction was successful and we were able to isolate **4-3**, then it would be possible to address the unresolved issues in the marineosin biosynthesis. Herein, we reported a convergent and modular approach to the marineosins through intermediate acyl pyrrolophane **4-2**.

4.2. Results and Discussion

4.2.1. Direct Pyrrolophane Construction by Ring Closing Metathesis

Our initial approach to pyrrolophane **4-2** relied on ring closing metathesis to construct the ansa bridge. This approach has been utilized several times to construct a variety of ansa linked systems.[99,234–236] The formal synthesis of roseophilin developed by Fuchs and coworkers utilized ring closing metathesis on bicyclic substrate **4-6**.[99] During their studies it was determined that the –OTIPS substituent oriented the hexenyl side chain in a manner that facilitated the ring closure. Molecular mechanics of **4-11** indicated that the alcohol side chain induced a similar effect. It was postulated that the RCM precursor **4-11** could be accessed by the Nicolaou pyrrole acylation method that proved useful in the model system studies (Chapter 3).[232]



Scheme 4.1. Attempts to Construct Pyrrolophane through Direct Ring Closing Metathesis

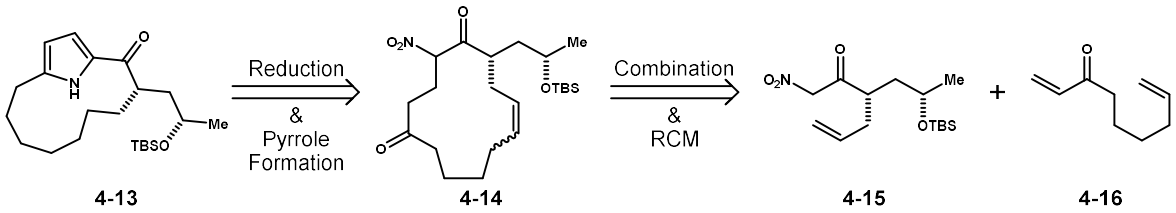
The construction of **4-8** was described previously (see Chapter 3). This material was then converted to the magnesium salt and treated with **4-10**. To our delight, this procedure afforded **4-11** in modest yield on the first attempt, which provided ample material to examine the desired ring closing metathesis process. Several metathesis catalysts, additives, and concentrations were screened in an attempt to produce **4-12**. Unfortunately, the only consistently observed tractable

mass on the HPLC trace was starting **4-11** otherwise peaks corresponding to oligomers were observed. It was postulated that the smaller ansa linkage of the marineosin pyrrolophane as compared to the roseophilin pyrrolophane causes an increase in the strain of the ring system, which in turn requires more energy to force the system into the reactive conformation for ring closure. This situation is similar to our previous attempts to the construct the ansa bridge at a late stage. However, Snider's efforts towards marineosin A utilize RCM and are able to construct the pyrrolophane in moderate yield.[108] With this in mind, it was postulated that the additional unsaturation in the diene starting material **4-11** (i.e. the ketone) increases the strain, which precludes the ability of the system to efficiently undergo RCM. This hypothesis was confirmed shortly after our initial attempts at RCM, when Perez and Nelson reported their unsuccessful RCM attempts to construct the marineosin pyrrolophane with additional unsaturation in the ansa linkage.[237] The inability of our desired system to efficiently proceed through RCM caused us to reconsider our strategy.

4.2.2. Pyrrolophane Construction via 13-Membered Carbocycle Generation and Attempted Pyrrole Formation

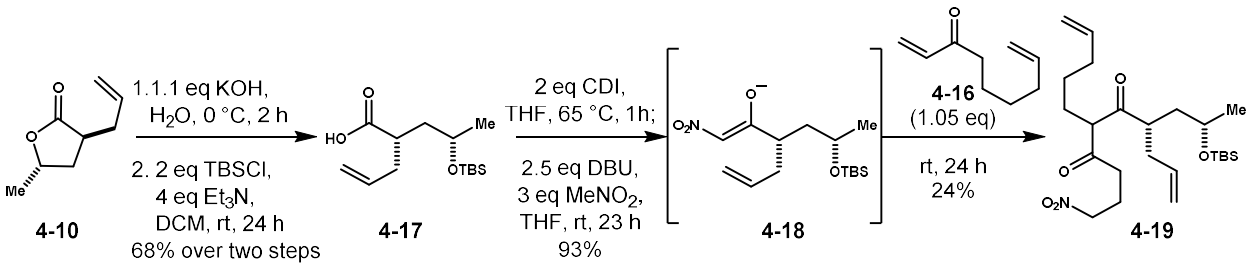
With the RCM approach on a pyrrole containing substrate proving unfeasible, it was postulated that metathesis could be utilized to construct a carbocycle that contains the necessary functionality to construct a pyrrole in a subsequent step. This approach is analogous to the efforts of Lindsley and Shi towards the marineosin scaffold.[32,106] However, those approaches required lengthy sequences to establish the stereochemistry of what would become the B ring of marineosin A (see Chapter 1), which would not be required for our construction of **4-2**. It was posited that the pyrrolophane could be derived from an internal condensation/aromatization sequence from **4-14**

with the nitro group acting as a masked amine. This carbocycle could be accessed from RCM and a combination of **4-15** and **4-16** via a conjugate addition.

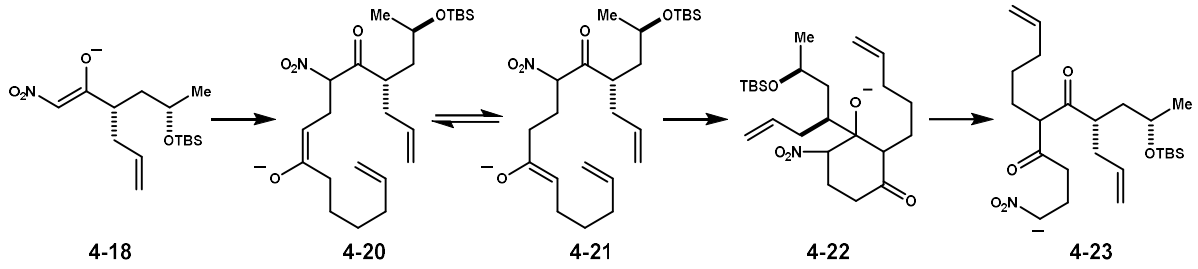


Scheme 4.2. Proposed Construction of Acyl Pyrrolophane **4-13**

The sequence commenced with lactone **4-10**, which is saponified and protected as the TBS derivative (**Scheme 4.3**). This processed proved more difficult than initially anticipated. Under most standard saponification conditions, the lactone/acid α-stereocenter readily epimerizes to a 1:1 mixture of diastereomers.[238,239] This epimerization can be minimized by cooling the reaction and careful monitoring of the reaction through ^{1}H NMR spectrum analysis of aliquots. In addition to the facile epimerization, the seco acid intermediate has a tendency to lactonize if the workup procedure is too acidic. However, a workable procedure was developed that utilized an aqueous saponification followed by treatment with TBSCl and triethylamine to afford acid **4-17**. This material was then converted to α-nitroketone intermediate **4-18**, which was then subjected to enone **4-16** (produced via a route described in Chapter 2) in an attempt to achieve α-nitroketone formation and conjugate addition in one flask.[240]

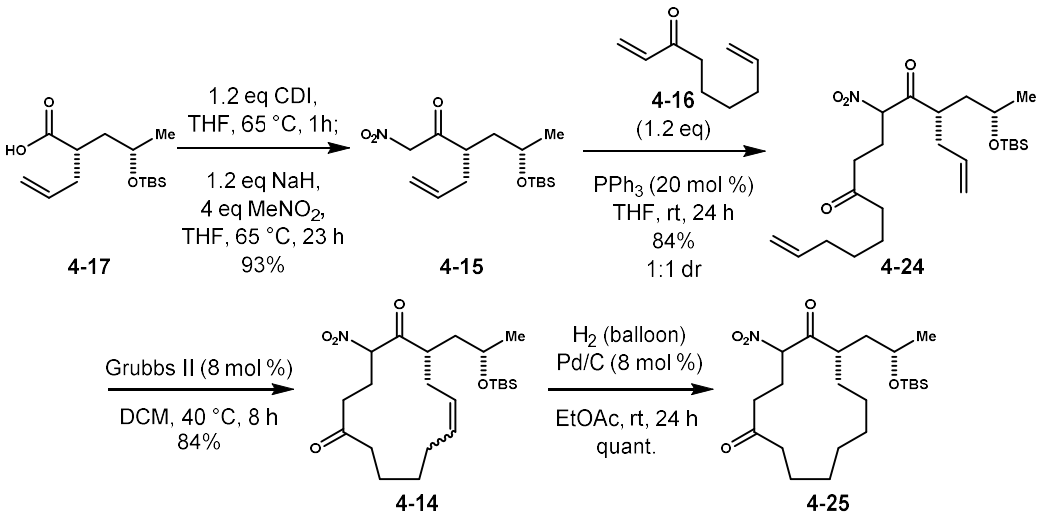


Scheme 4.3. Production of Rearranged β-diketone **4-19**



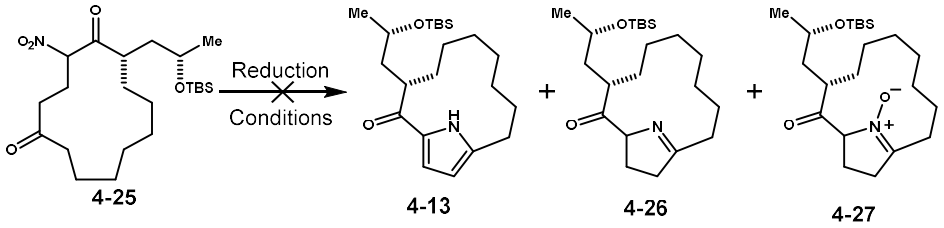
Scheme 4.4. Mechanism of Chain Extension Rearrangement

However the desired conjugate addition product was not observed, instead rearranged β-diketone product **4-19** was isolated. This type of rearrangement was studied in detail by Hesse and coworkers, who utilized it in the construction of several natural products (**Scheme 4.4**).[241–243] Under the basic reaction conditions, the conjugate addition occurs to give intermediate adduct enolate **4-20**, which can equilibrate to **4-21**. After equilibration, a Dieckmann-like process can occur followed by elimination of the nitronate to give rearranged **4-23**. This process takes advantage of the inherent ability of α-nitroketones to behave like pseudo esters.[244] This reactivity is exemplified by the fact that lactone **4-10** is isolated if the TBS protecting group is removed from **4-15**. These results indicated that a more mild procedure was required for the conjugate addition to enone **4-16**.



Scheme 4.5. Construction of Carbocycle **4-25**

Acid **4-17** was activated by carbonyl diimidazole and then treated with the sodium salt of nitromethane to provide α-nitroketone **4-15** (**Scheme 4.5**).[245] A mild procedure for the conjugate addition of α-nitroketones to enones was developed by Ono and coworkers, which utilized catalytic triphenylphosphine to afford adduct **4-24** as an inconsequential 1:1 mixture of two diastereomers.[246] This material was subjected to ring closing metathesis to followed by hydrogenation to produce carbocycle **4-25**.

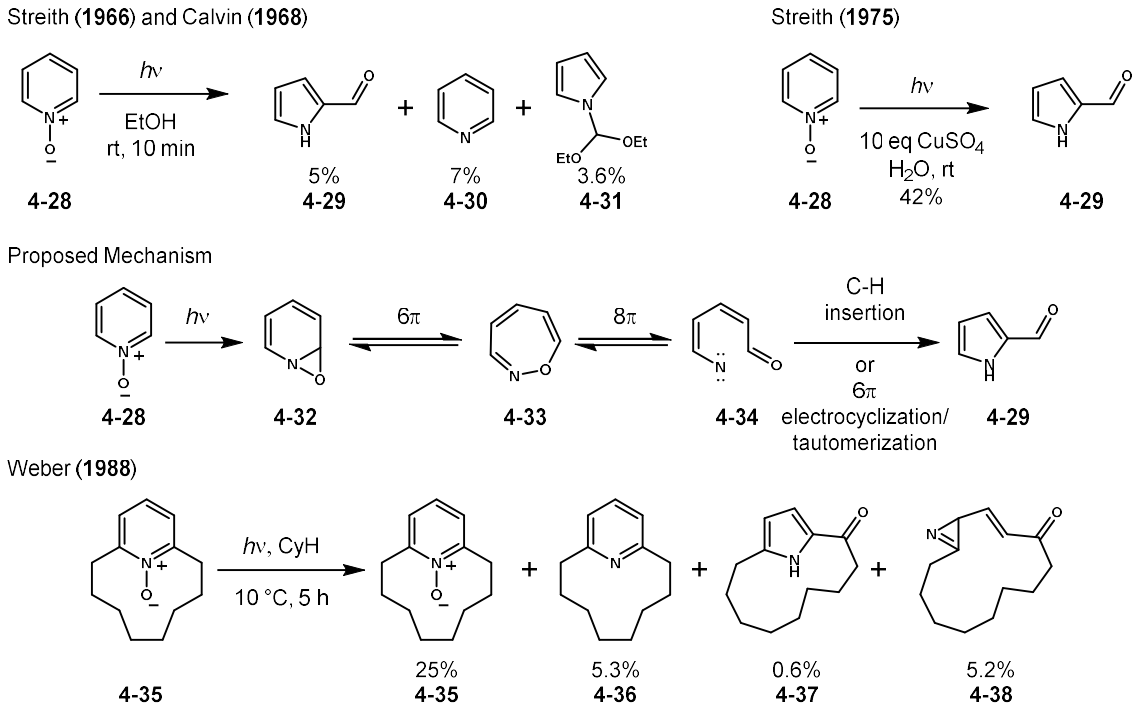


Scheme 4.6. Attempted Reduction of Nitro Group

The reduction of the nitro group present in **4-25** proved to be more difficult than originally anticipated. It was postulated that pyrrole **4-13** could be accessed directly from **4-25** due to there being several known methods that convert γ-nitroketones into pyrroles.[247–249] However, these conditions afforded intractable mixtures of products, with only trace amounts of **4-13** observed by

HPLC. With the direct route proving ineffective, we posited that **4-13** could be produced by first reducing the nitro group to an amine followed by an oxidation of **4-26**, which is derived from an intramolecular condensation. An extensive array of conditions were examined to effect this reduction.[250–255] The nitro group of **4-25** proved fairly resilient to hydrogenations with most conditions providing starting material after isolation. Reductions with zinc dust in acidic media afforded intractable mixtures with only trace amounts of the desired mass being observed by HPLC. Studies in this area were halted due to the development of a more concise and unique construction of the pyrrolophane (*vide infra*).

4.2.3. Photoinduced Rearrangements of Pyridinophane N-Oxides to Access Acyl Pyrrolophanes



Scheme 4.7. Photoinduced Rearrangement of Pyridine N-Oxides

An intriguing transformation that caught our attention was the photo-induced rearrangement of pyridine N-oxides into acyl pyrroles (**Scheme 4.7**).[256–258] This transformation was originally

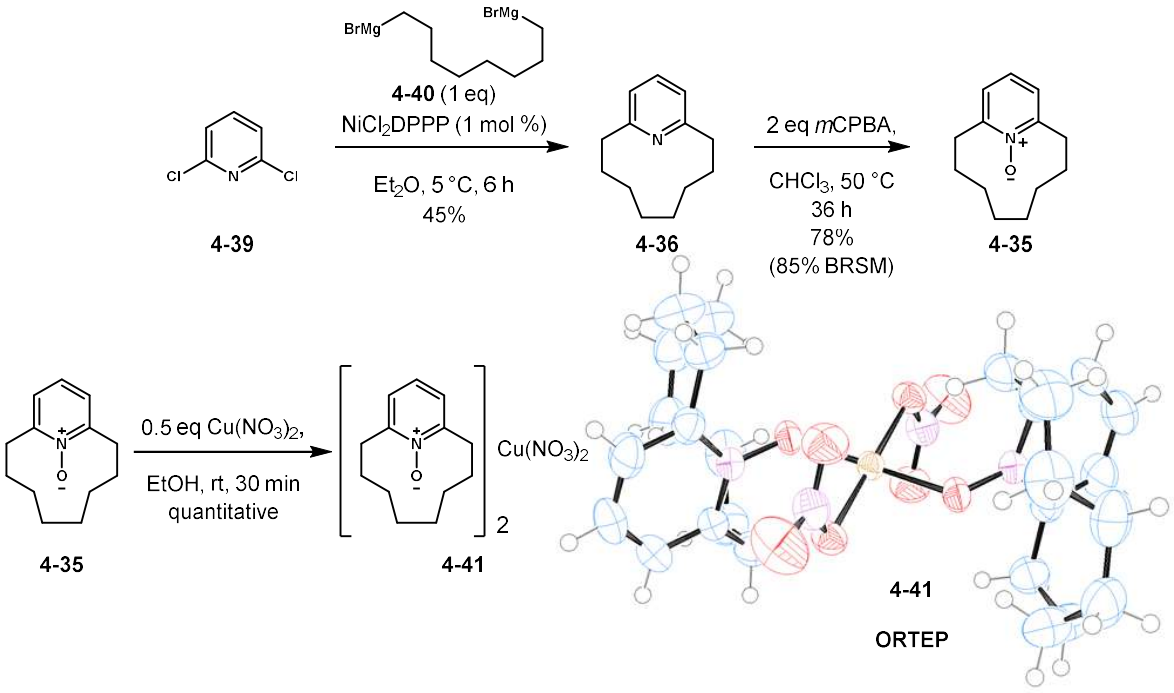
discovered by Streith and coworkers who reported the isolation of 2-formylpyrrole (**4-29**) after irradiating an aqueous solution of **4-28**. Further examination of the process by Calvin and Alkaitis revealed that when pyridine N-oxide was irradiated in alcoholic solvents, a deoxygenated product (i.e. pyridine, **4-30**) could also be isolated as well as acetal **4-31**.[257]

The proposed mechanism for the process commences with the photoinduced cycloisomerization of the N-oxide to oxaziridine **4-32**. This material is a strong oxidant that can oxidize the reaction solvent to produce pyridine (**4-30**) and an oxygenated solvent product. The oxaziridine can then undergo a 6π electrocyclic ring opening followed by an 8π electrocyclic ring opening to reveal nitrene **4-34**. The nitrene can then undergo an insertion process into the aldehyde α C-H bond to provide **4-29**. Alternatively, a 6π electrocyclization could occur to produce the 2H-pyrrole (not shown), which would rapidly tautomerize to **4-29**. Further investigations into this process by Streith and coworkers found that the addition of copper (II) salts to the reaction dramatically increased the yield.[258] It is postulated that the copper ion stabilizes nitrene intermediate **4-34**, which impedes polymerization and allows for a more productive conversion to **4-29**. Overman and coworkers utilized this modification to produce 3-methoxy-2-formylpyrrole (not shown), which was utilized as the starting material in their construction of didehydrostemofoline and isodidehydrostemofoline.[259]

Weber and Rohn examined this transformation in the context of pyridinophane N-oxides, which could be constructed in two steps, resulting in the construction of several acyl pyrrolophanes.[260] Interestingly, azirine **4-38** was isolated during these studies and arises from an internal cyclization of the intermediate vinyl nitrene. Among the ring systems produced, pyrrolophane **4-37** caught our attention due to it corresponding to the size of the marineosin macrocycle. Unfortunately, the reported yield of pyrrolophane **4-47** was 0.6%, which made this process seem untenable for use in

a total synthesis. Nevertheless, we were fascinated by this transformation, as well as the conciseness of the approach, and commenced studies to determine whether the photochemical production of **4-37** could be optimized.

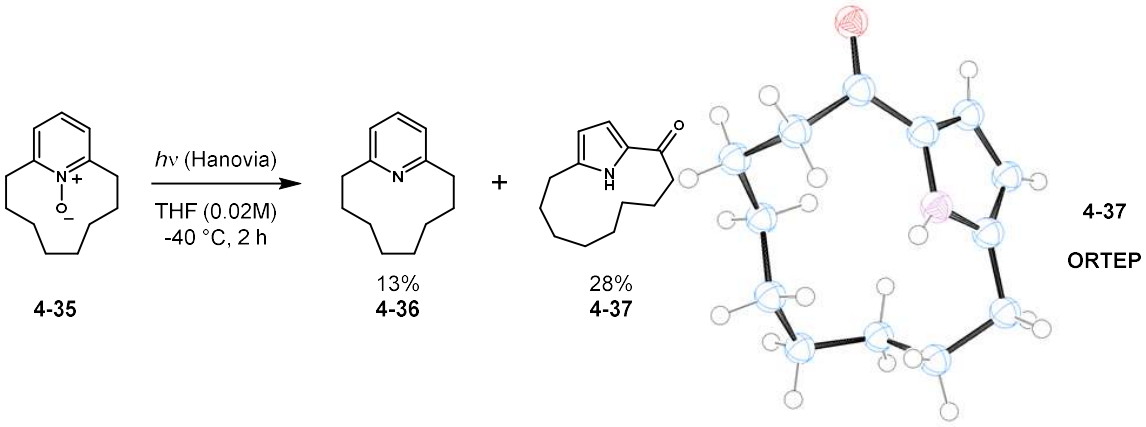
One pleasing aspect of this approach is the ansa bridge is constructed in the first step via successive nickel-catalyzed Kumada couplings of di-Grignard **4-40** to 2,6-dichloropyridine (**4-39**, **Scheme 4.8**).[261,262] This process provides pyridinophane **4-36** in moderate yield, which can be converted to the N-oxide **4-35** by treatment with *m*CPBA.[260] A small screen of oxidation conditions was explored, however *m*CPBA proved superior to other conditions both in terms of rate and yield. Due to the findings of Streith and coworkers on the beneficial nature of adding copper (II) salts to the photochemical reaction, copper (II) complex **4-41** was prepared in order to examine its effects on the transformation.[258,263] Complex **4-41** was unambiguously characterized by X-ray crystallography (**Scheme 4.8**).



Scheme 4.8. Preparation of Pyridinophane N-Oxide **4-35** and Complexation with Cu^{II}

With a scalable route to **4-35** established, the key photochemical rearrangement was explored in detail (**Scheme 4.9** and **Table 4.1**). The literature conditions were reproduced to obtain **4-35** in adequate quantities for use in TLC analysis of altered conditions. In addition, X-ray crystallography data for **4-37** was obtained. Our investigations initially focused on the use of copper (II) salt additives due to the reports of Streith.[258] The optimized conditions reported by Streith showed a five-fold increase in yield as compared to the literature preparation of **4-37** on the first attempt (Entry 2). However, there was significant difficulty associated with this procedure due to insolubility of **4-35** in water. In order to rectify this issue, we examined the use of the slightly organic soluble $Cu(acac)_2$ in acetonitrile. However, this condition proved incompetent for the desired transformation. It was discovered that preformation of the transition metal complex with copper (II) nitrate provided organic soluble crystals (*vide supra*). To our delight, irradiation of the complex in ethanol provided **4-37** in 7.3% (Entry 5). Intriguingly, a control experiment with pure **4-35** provided the desired pyrrolophane in higher yield than complex **4-41** (Entry 7). A solvent screen of the irradiation on **4-35** allowed for the identification of ethyl acetate as equally effective as ethanol and DCM as moderately effective (Entry 9 and 10). Irradiation of **4-35** in aprotic solvents provides a cleaner reaction profile as determined by crude ^{1}H NMR spectrum analysis, which is postulated to arise from a decreased ability of the unstable oxaziridine intermediate to oxidize the solvent. Studies by Weber and Rohn showed that the photochemical rearrangement of sterically hindered 2,6-substituted pyridines, which behave poorly in the aqueous copper (II) conditions, could be improved by irradiation at low temperature.[264] Our first attempt at a low temperature irradiation was very informative and performed in DCM, which was the solvent of choice for Weber and Rohn. This process provided pyrrolophane **4-37** in 13.7% yield (Entry 11). However, this transformation in DCM was capricious giving a range of yields upon further

investigations. Examining the low temperature transformation in other solvents led to higher and more consistent isolated yields of **4-37**. It was determined that the optimal conditions for this transformation were irradiation in THF at -40 °C, which provides **4-37** in 28% yield, a ~45 fold increase as compared to the reported conditions (Entry 15). This process also proceeded well in ethanol at the same temperature, however the THF condition provides a cleaner reaction profile. In an effort to increase throughput, an alternative condition that utilizes a lower intensity Rayonet reactor was developed, which is somewhat variable in yield of **4-37** ranging from 10-18% (Entry 17). This alternative condition and the optimized condition could be performed at the same time to allow for increased production of **4-37**.



Scheme 4.9. Optimized Conditions for Photochemical Rearrangement of **4-35**

Table 4.1. Optimization of Conditions to Generate **4-37** from **4-35**

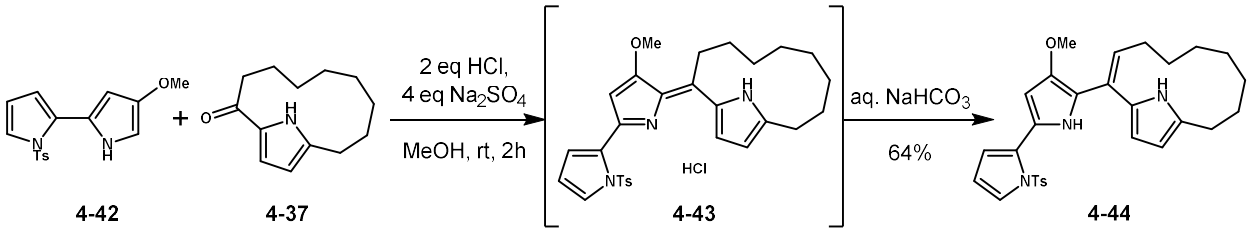
Entry	Solvent	Temp.	Time	Additive	Lamp	Rec. **4-35**	% of **4-36**	% of **4-37**
1	Cyclohexane	rt	5 h	-	Hanovia	25%	5.3%	0.6%
2	H_2O	rt	5 h	$CuSO_4$ (10 eq)	Hanovia	18%	ND	4%
3	MeCN	rt	2 h	$Cu(acac)_2$ (10 eq)	Hanovia	0%	0%	0%
4	MeCN	rt	2 h	$Cu(NO_3)_2$ (0.5 eq)	Hanovia	0%	0%	0%
5	EtOH	rt	2 h	$Cu(NO_3)_2$ (0.5 eq)	Hanovia	0%	0%	7.3%
6	DME	rt	4 h	$Cu(NO_3)_2$ (0.5 eq)	Rayonet	100%	NR	NR
7	EtOH	rt	1.5 h	-	Hanovia	0%	ND	9.2%

8	Dioxane	rt	2 h	-	Hanovia	0%	0%	0%
9	EtOAc	rt	1.5 h	-	Hanovia	0%	ND	9.4%
10	DCM	rt	2 h	-	Hanovia	0%	ND	6.5%
11	DCM	-40 °C	30 min	-	Hanovia	28.5%	5%	13.7%
12	EtOAc	-40 °C	1.5 h	-	Hanovia	0%	11%	11%
13	Et_2O	-40 °C	1.5 h	-	Hanovia	0%	16%	12%
14	EtOH	-40 °C	1.5 h	-	Hanovia	0%	16%	26%
15	THF	-40 °C	1.5 h	-	Hanovia	0%	13%	28%
16	DME	-40 °C	1.5 h	-	Hanovia			
17	DME	rt	10-12 h	-	Rayonet	0%	8%	18%

In an attempt to further optimize this process, we briefly explored conducting the irradiation under continuous flow conditions. It was anticipated that this approach was inherently scalable and had the potential to reduce reaction times. The efforts Afonso and coworkers demonstrated that the irradiation of pyridinium salts could be successfully adapted from batch to continuous flow conditions with a large overall increase in productivity.[265] The variables examined were temperature, concentration, and flow rate for continuous flow through 4 mm diameter fluorinated ethylene propylene (FEP) tubing wrapped around a photoreactor immersion well. It was determined that irradiation of a 5 mM solution at -78 °C with a 34 minute residence time resulted in a TLC that was comparable to the batch condition. Although this finding represented a marked improvement in terms of production speed, the yield of the optimized continuous flow conditions was 9.5%. This reduction in yield when compared to the batch conditions effectively nullified the benefits gained from a shorter experiment time.

To examine the feasibility of the condensation between an acyl pyrrolophane and **4-1**, a test reaction was performed with between **4-37** and **4-42**. To our delight, the dark red color associated with prodiginine formation was observed. Interestingly, the red product that was isolated did not contain the traditional prodiginine core. Instead of containing an azafulvene core (i.e. **4-43**),

condensation product **4-44** was determined to exist in a tautomeric form, where the pi bond has been placed within the ansa ring system. It is postulated that this novel form of the prodiginine core stems from a relief of steric strain between the B ring and the ansa bridge. An analogous version of this tautomeric form was observed by Terashima and coworkers during their work on roseophilin. Condensation of the pyrrolofuran segment with Boc-protected acetyl pyrrole resulted in a similar structure, however the structure tautomerized into the azafulvene structure upon cleavage of the Boc group (not shown). This result gave us confidence that our planned disconnection was indeed viable and suggested that increased steric strain due to the α-branching in **4-2** would prove useful in cycloisomerization of a pendant alcohol onto the lipochromophore.

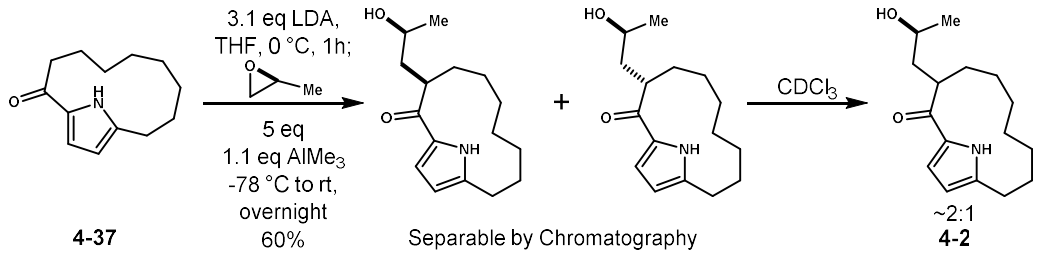


4-42 4-37 4-43 4-44

Scheme 4.10. Condensation with ansa bridged acyl pyrrole **4-37** to construct a novel prodiginine tautomer

All that remained for the production of **4-2** was the installment of the (2*S*)-2-hydroxypropyl substituent. The most direct method to introduce this moiety was treatment of the enolate derived from **4-37** with (*S*)-propylene oxide (**4-42**), a readily available enantiopure commodity chemical. Surprisingly, there are only a few known methods to alkylate ketone-derived enolates with epoxides. The works of Crotti and Posner have established that the most efficient methods of opening epoxides with lithium enolates is through activation of the epoxide with a Lewis acid additive.[266–269] After a short screen of Lewis acids, we were able to determine that the optimal conditions for the generation of **4-2** were deprotonation of **4-37** in a large excess of LDA followed

by treatment with **4-42** and $AlMe_3$. The use of excess base allows this route to circumvent the need to protect the pyrrole nitrogen by producing the putative dianion, which reacts preferentially at the α-position. The alkylation proceeds with a low diastereomeric ratio of ~2:1 at the α-position and the 2 diasteromers are separable by chromatography. Interestingly, the α-stereocenter completely epimerizes over the course of several hours in chloroform solvent. It is believed that the trace amounts of acid in solution facilitate the loss of stereochemical fidelity. Despite the epimerization issue, gram quantities of **4-2** could be obtained from this approach, which allowed for the examination of the modified Rapoport condensation to construct the C13 ansa bridged prodiginine core of the marineosins (NOTE: All successful alkylation reactions thus far have been performed by Zhengao Feng).

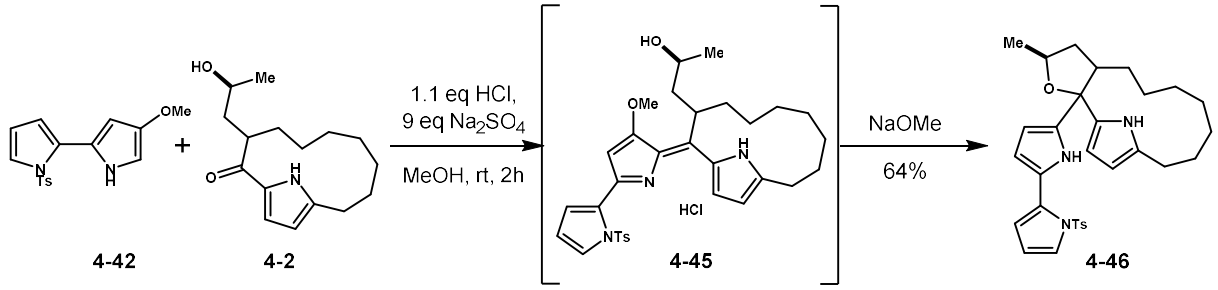


Scheme 4.11. Alkylation of Acyl Pyrrolophane **4-37**

4.2.4. Completion of Marineosin A

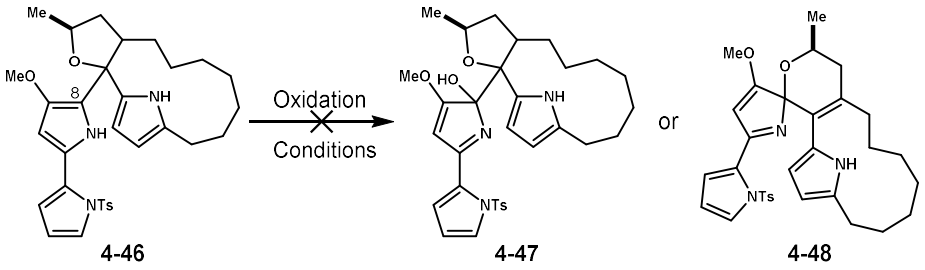
With sufficient quantities of **4-1** and **4-2** in hand, we were eager to explore the feasibility of an acid mediated coupling of these fragments to construct the ring opened isomer of the marineosins (i.e. **4-3**). As anticipated treatment of a solution with HCl resulted in a dark red mixture, however the organic layer quickly turned a pale yellow/orange on aqueous basic workup indicating that the lipochromophore is disrupted in basic media, an exciting observation. In the first few experiments, the condensation product was isolated in a disappointingly low yield (10-20%), but more

interestingly it was determined to exist in ring closed isomer **4-46**, isolated as ~1:1 mixture of the two *cis* diastereomers. It is postulated that under acidic conditions the open form **4-45** is more favorable, as indicated by the dark red color of the reaction, but on neutralization/basification of the mixture, the pendant alcohol can acts as a nucleophile on the electrophilic azafulvene to relieve the strain between the B ring and the ansa bridge link at C9. This structure represents another novel form of the prodiginine core unique to the C9 ansa bridged series of prodiginines. More thorough investigation of the condensation process revealed that low recovery was due to the reversibility of the condensation (i.e. intermediate **4-45** is susceptible to hydrolysis), which could be remedied with the inclusion of a desiccant and performing a non-aqueous neutralization. These modifications greatly enhanced production of **4-46**.

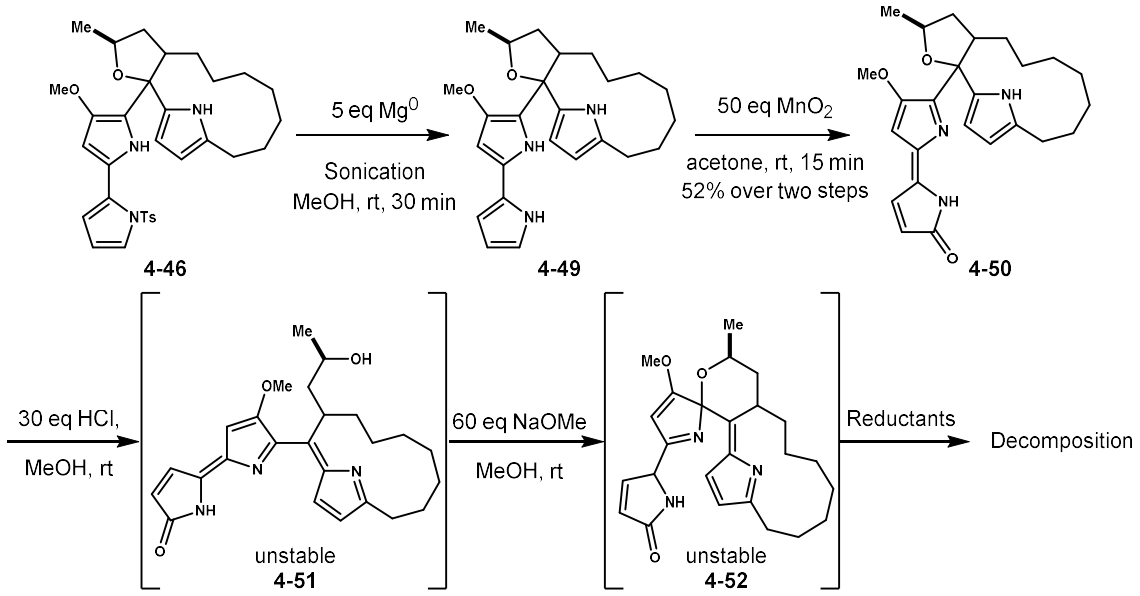


Scheme 4.12. Construction of *iso*-Premarineosin **4-46**

We were excited about the prospects of **4-46**, which is a tosyl-protected structural isomer of the biosynthetic precursors to the marineosins (i.e. **4-5**). Given this consideration, it was postulated that the most direct method of accessing the marineosins would require ring opening of the tetrahydrofuran followed by a cycloisomerization of the revealed alcohol onto C8. The electronics of the electron rich bipyrrole system would need to be inverted to allow for the umpolung addition of the alcohol to the desired position instead of re-addition to C9. Initially, exposure of **4-46** to a variety of oxidants was explored to see if the ring opening step could be circumvented. However, most of these experiments resulted in decomposition into intractable mixtures.



Scheme 4.13. Attempts to Induce Ring Expansion from **4-46** to **4-48**

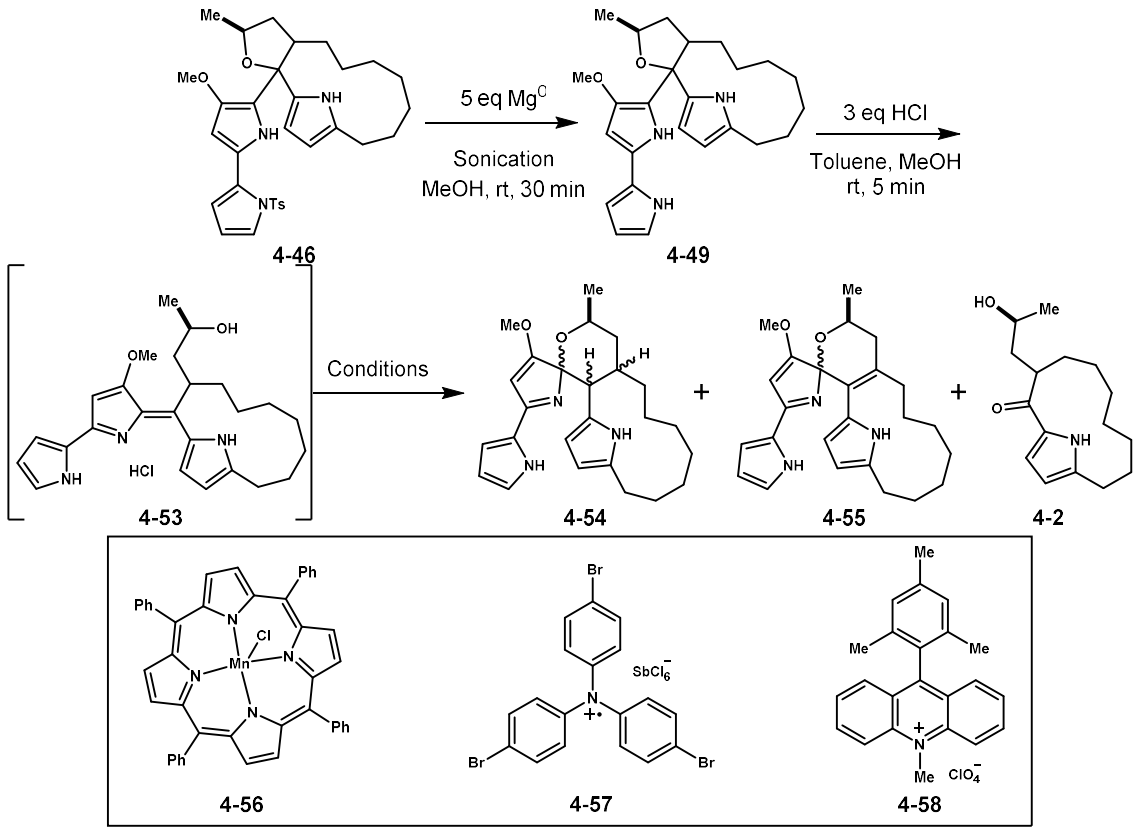


Scheme 4.14. Oxidation of iso-Premarineosin **4-49** and Attempts to Induce Spirocyclization

It was postulated that the presence of the tosyl group dampened the electron rich nature of the bipyrrole and its removal would make the system more susceptible to oxidation or electronic modulation. The tosyl group could be cleaved utilizing conditions developed for the model system (see Chapter 3) by sonication of magnesium metal in methanol.[270] Treatment of **4-49** with MnO_2 resulted in a clean conversion to a new polar yellow spot, which was determined to be oxygenated **4-50**. It was postulated that this material could be opened by treatment with acid and subsequent treatment with base would induce cyclization at the desired C8 position. Unfortunately, the tentative ring opened form and closed isomers were highly unstable, which made them difficult to characterize by any means other than qualitative color changes and TLC analysis. Treatment of **4-**

50 in with excess HCl resulted in a dark red solution, which was then transferred dropwise into a solution of NaOMe in methanol providing an orange solution. TLC indicated the complete conversion of **4-50** into a more polar orange spot, which was presumed to be **4-52**. Treatment of the reaction mixture with a variety of reductants in an attempt to obtain a stable product resulted in decomposition into a myriad of products by TLC, none of which corresponded to the desired mass (NOTE: The above mentioned studies with **4-50** were conducted primarily by Zhengao Feng).

Due to the instability issues associated with handling the derivatives of oxygenated **4-50**, we decided to alter our strategy to a more ambitious and direct approach. It was proposed that ring opening of **4-49** would regenerate the lipochromophore, which could then undergo an anti-Markovnikov hydration of the azafulvene. It was posited that modulation of the aromatic system's electronics, possibly by complexation with a metal, could allow for the umpolung addition of the alcohol onto C8. This transformation is somewhat analogous to the hydration of nitriles, where the nitrile is complexed with a metal that facilitates the addition of water or some other nucleophile, the prototypical method utilizing the platinum-based Parkins' catalyst.[271–274]



Scheme 4.15. Exploration of Direct Hydration of Azafulvene **4-53**

Table 4.2. Optimization of Spirocyclization Conditions

Entry	Reagent/Catalyst	Additives	Solvent	Yield of **4-54**	Yield of **4-55**	Yield of **4-2**
1	MnO_2 (20 eq)	-	Acetone	6.2%	ND	ND
2	$Mn(OAc)_3$ (5 eq)	-	MeCN	Detected	Detected	Detected
3	K_3FeCN_6 (5 eq)	-	MeCN	Detected	Detected	Detected
4	$Mn(dpm)_3$ (2 eq)	-	Toluene/MeOH	Detected	Detected	Detected
5	$Co(acac)_3$ (2 eq)	-	Toluene/MeOH	0%	0%	Major
6	$Co(dpm)_3$ (2 eq)	-	Toluene/MeOH	0%	0%	Major
7	$Fe(acac)_3$ (6 eq)	-	MeCN	0%	0%	Major
8	$Fe(acac)_3$ (6 eq)	$PhSiH_3$ (12 eq)	*i*PrOH	0%	0%	Major
9	**4-56** (2 eq)	O_2 (balloon)	MeCN	Detected	Major	Detected
10	TfOH (5 eq)	-	MeCN	0%	0%	Major
11	$MeSO_3H$ (5 eq)	-	MeCN	0%	0%	Major

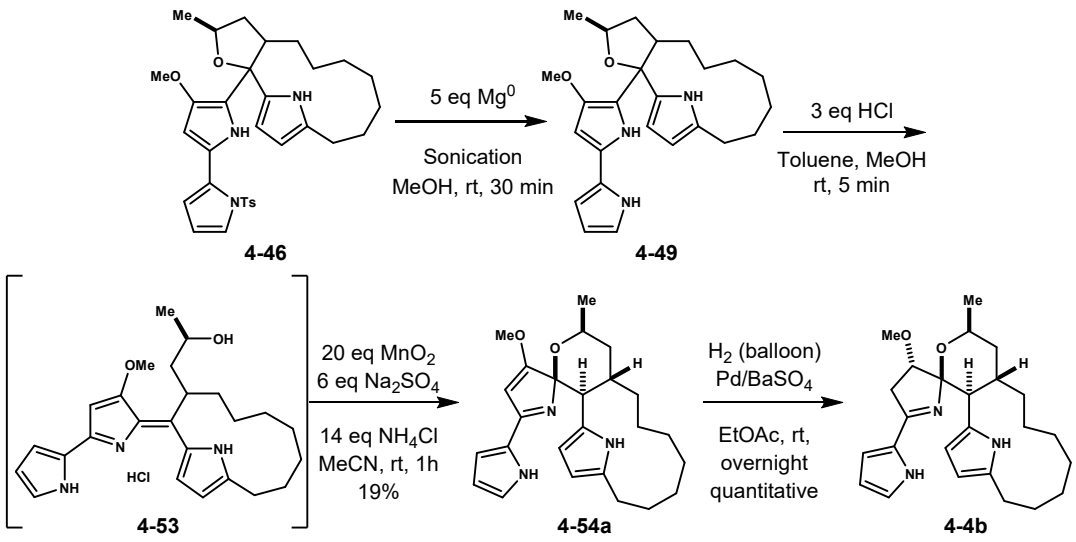
12	PTSA (5 eq)	-	MeCN	0%	0%	Major
13	CSA (5 eq)	-	MeCN	0%	0%	Major
14	Ph_3PAuCl (20 mol%)	-	MeCN	0%	0%	Major
15	**4-57** (20 mol %)	-	DCM	0%	0%	Major
16	**4-58** (10 mol%)	$PhCH(CN)_2$ (0.5 eq)	MeCN	0%	0%	Major
17	$NiCl_2$ (10 eq)	PhCHNOH (10 eq) 4Å MS	MeCN	0%	0%	Major
18	$ZnCl_2$ (100 eq)	PhCHNOH (10 eq) 4Å MS	MeCN	Trace	0%	Major
19	$ClRu(Ph_3P)_3$ (10 eq)	PhCHNOH (10 eq) 4Å MS	MeCN	0%	0%	Major
20	$Pd(OAc)_2$ (5 eq)	2,2'-Bipyridine (5 eq) 4Å MS	Dioxane	0%	0%	Major
21	$Pd(OAc)_2$ (5 eq)	$Sc(OTf)_3$ (5 eq) 4Å MS	AcOH	0%	0%	Major
22	Mn(dpm) (5 eq)	$PhSiH_3$ (10 eq)	*i*PrOH	Detected	Detected	Detected
23	$Mn(OAc)_3$ (5 eq)	-	AcOH	Minor	Detected	Major
24	MnO_2 (20 eq)	-	MeCN	15%	ND	ND
25	MnO_2 (20 eq)	Na_2SO_4 (6 eq) NH_4Cl (14 eq)	MeCN	19%	19%	ND
26	MnO_2/SiO_2 (20 eq)	4Å MS NH_4Cl (6 eq)	MeCN			
27	MnO_2/SiO_2 (20 eq)	C_6F_5OH (20 eq) 4Å MS	MeCN	0%	0%	Major

Deprotected tetrahydrofuran **4-49** was treated with HCl to afford a dark red/purple solution, presumed to be **4-53**, which was unstable for extended periods of time. Neutralization of this intermediate did not lead to spirocycles **4-54**, which suggests that this intermediate is not formed during the biosynthesis of the marineosins. At this stage, we examined a variety of methods in order to induce the anti-Markovnikov spirocycle-forming etherification of the azafulvene. Our initial experiment utilized MnO_2, which has been shown to be an effective mediator of nitrile hydration (**Table 4.2**, Entry 1).[273–275] HPLC analysis of the mixture indicated the formation of several compounds with the desired mass of 408 m/z, as well as an oxidation product (presumably

4-55) and a retro-condensation product (i.e. **4-2**). Preparative HPLC purification of the mixture provided a mixture of **4-54** isomers in low yield, with the major isomer containing to the marineosin A stereochemistry. This was an exciting result, however the low yield of the process encouraged us to examine other possible methods.

A variety of metal catalysts were examined to see if stepwise oxidation of the putative prodiginine intermediate could be achieved via single electron transfer or by direct oxidation (Entries 2-9). In several of these conditions, the 2 electron oxidation product (i.e. m/z 406) was the major product observed by HPLC. However, we were more interested in achieving a direct hydration of the system and did not pursue these conditions further. Acid mediated hydration was examined (Entries 10-13), unfortunately the only observable signal by HPLC was the retro-condensation product. Reversible single electron transfer catalysis was investigated using triarylaminium salt **4-57** and acridinium salt **4-58** (Entries 15 and 16).[226,276,277] Once again, the retro-condensation product was the only observable product. Due to **4-2** being consistently observed, it was obvious that intermediate **4-53** was sensitive to adventitious H_2O. This issue could be mitigated to some degree by the inclusion of desiccants.

We then examined several nitrile hydration methods to no avail (Entries 17-21).[272,278–280] At this stage, since MnO_2 was the only method that had shown the desired reactivity, it was explored further. The inclusion of Na_2SO_4 or molecular sieves in the reaction substantially improved the yield of the MnO_2-facilitated cycloisomerization process. In addition, ammonium chloride was utilized as an additive to ensure that the system remained mildly acidic to prevent generation of the free base of **4-53**, which is thought to rapidly reclose to **4-49**.



Scheme 4.16. Completion of Marineosin A (**4-4b**)

With our optimized conditions for identified for cycloisomerization, a simple 2 electron reduction of the correct stereoisomer of **4-54** would provide either marineosin A or B. This process could be accomplished by using conditions reported by Snider laboratory during their studies on marineosin model systems.[108] Spiroiminal **4-54a** was subjected to a hydrogen atmosphere in the presence of Pd on $BaSO_4$ to afford marineosin A (**4-4b**) (NOTE: The final step in the synthesis has only been conducted by Zhengao Feng). Efforts to determine the true structure of marineosin B are ongoing in our laboratory.

4.3. Conclusion

The total synthesis of (-)-marineosin A **4-4b** occurs in 9 operations. The route is concise and features several unique and unusual transformations. The photochemical rearrangement of pyridinophane N-oxide **4-35** into pyrrolophane **4-37** represents a powerful yet hitherto unutilized method of constructing ansa bridged pyrroles. Our optimization of this process allows for facile production of pyrrolophanes of different ring sizes. Condensations of acyl pyrrolophanes, such as **4-2** and **4-37**, result in novel tautomeric forms of the prodiginine motif. The work also answers lingering questions on the biosynthesis of the marineosins considering that acyclic precursor **4-53** is inherently unstable, prone to hydrolysis, and does not spontaneously cyclize into the premarineosins. A novel cycloisomerization process on a manganese dioxide surface was discovered to allow for production of premarineosin **4-54a**, which could be elaborated to marineosin A in one step. Further work is underway in our laboratory to understand the mechanism of the cycloisomerization and to exploit the potential of the photochemical rearrangement of pyridinophane N-oxides for use in the construction roseophilin (Chapter 5).

4.4. Experimental

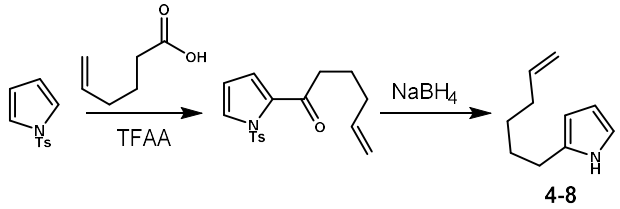
4.4.1. Materials and Methods

All reactions were carried out using oven- or flame-dried glass and a magnetic stir bar under an atmosphere of argon (Ar) unless otherwise indicated. Tetrahydrofuran (THF), diethyl ether (Et_2O), methylene chloride (DCM), toluene, acetonitrile (MeCN), and methanol were dried by passage through activated alumina using a GlassContour® solvent drying system. Triethylamine, and diisopropylamine were distilled from CaH_2 under inert atmosphere prior to use. Acidic MnO_2 was produced by reacting $KMnO_4$ with an excess of $MnSO_4$ according to the procedures put forth in the Encyclopedia of Reagents for Organic Synthesis. All other commercial reagents and catalysts were used as received unless otherwise indicated. Photoreactions were carried out in either a standard Ace Chem Glass immerision well photoreactor or the low temperature immersion well photoreactor with a Hanovia 450W mercury arc lamp. Also, photoreactions were examined in a Rayonet photoreactor with a 254 and 300 nm bulb set.

NMR spectra were recorded on Bruker Advance spectrometers (400 MHz, 500 MHz) and are reported as δ values in ppm relative to $CDCl_3$ (calibrated to 7.27 ppm in ^1H NMR and 77.16 ppm in ^{13}C NMR, unless otherwise indicated) and were conducted at room temperature (unless otherwise indicated). ^1H NMR coupling constants are reported in Hz. Splitting patterns are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), septet (sept), multiplet (m), broad (br), apparent (app), and combinations thereof. Column chromatography was conducted on silica gel 60 (240-400 mesh) purchased from Silicycle or neutral aluminum oxide (activated, Brockmann I) purchased from Sigma Aldrich. Thin layer chromatography (TLC) was performed using pre-coated, glass-backed plates (SiO_2, 60 PF254, 0.25 mm or neutral Al_2O_3, 0.25 mm) and visualized using a combination of UV, anisaldehyde, and potassium permanganate staining.

4.4.2. Experimental Procedures and Characterization

2-(hex-5-en-yl)-1*H*-pyrrole (4-8)



4-8

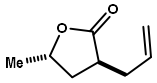
To a solution of Ts pyrrole (7.0011 g, 31.63 mmol) and 5-hexenoic acid (5.4089 g, 47.38 mmol, 1.5 eq) in DCE (95 mL, 0.3M) at 0 °C, TFAA (67 mL, 474.58 mmol, 15 eq) was added slowly. The mixture was then warmed to room temperature and then heated to reflux for 30h. The mixture was then cooled and concentrated. The crude residue was dissolved in DCM and washed with sat. aqueous $NaHCO_3$. The organics were then dried over $MgSO_4$, filtered, and concentrated to a black oil, which was used directly in the next step.

To a stirred suspension of $NaBH_4$ (5.9861 g, 158.23 mmol, 5 eq) in *i*PrOH (100 mL), a solution of crude acyl pyrrole (assume 100% from previous step, 31.63 mmol) in *i*PrOH was added slowly. The mixture was then heated to reflux for 48h. The reaction was then cooled to 0 °C and carefully quenched by the addition of ice water. The *i*PrOH was removed under reduced pressure and the mixture was extracted with DCM. The organics were then washed with brine, dried over $MgSO_4$, filtered and concentrated to a black/brown oil. The residue was then purified by flash column chromatography to afford **4-8** (1.5211 g, 32%) as a yellow oil that darkens on standing.

2-(hex-5-en-yl)-1*H*-pyrrole (4-8):

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.93 (bs, 1H), 6.71 (dd, *J* =2.4, 3.8 Hz, 1H), 6.17 (dd, *J* = 2.8, 5.5 Hz, 1H), 6.00-5.93 (m, 1H), 5.85 (ddt, *J* =6.6, 10.3, 16.9 Hz, 1H), 5.14-4.94 (m, 2H), 2.65 (t, *J* =7.5 Hz, 2H), 2.13 (q, *J* = 7.1 Hz, 2H), 1.69 (p, *J* = 7.5 Hz, 2H), 1.50 (p, *J* = 7.4 Hz, 2H)

***Trans*-3-allyl-5-methyldihydrofuran-2-(3*H*)-one (4-10)**



3-47

To a solution of diisopropylamine (4.84 mL, 34.53 mmol, 1.15 eq) in THF (300 mL) at 0 °C, *n*BuLi (2.5 M in Hexanes, 13.2 mL, 33.00 mmol, 1.1eq) was added. The mixture was stirred for 20 minutes and then cooled to -78 °C. Racemic **3-46** (2.89 mL, 30.19 mmol) in a solution of THF (10 mL) was added dropwise over 10 minutes. The mixture was stirred for an hour at -78 °C and then an hour at -40 °C. The reaction was recooled to -78 °C and allyl iodide (3.29 mL, 35.98 mmol, 1.2 eq). The reaction was then allowed to warm to -40 °C and stirred at this temperature for 4 hours. The reaction was then quenched by addition to saturated aqueous NH_4Cl (600 mL). the mixture was then extracted with Et_2O several times. The organics were dried over $MgSO_4$, filtered, and concentrated to an orange oil. The crude was purified by flash column chromatography (SiO_2, 10:1→6:1 Hexanes/EtOAc) to afford **3-47** (4.26 g, quant.) as a pale yellow oil with a *dr* of ~5:1 (*trans:cis*) as determined by the ^{1}H NMR spectrum.

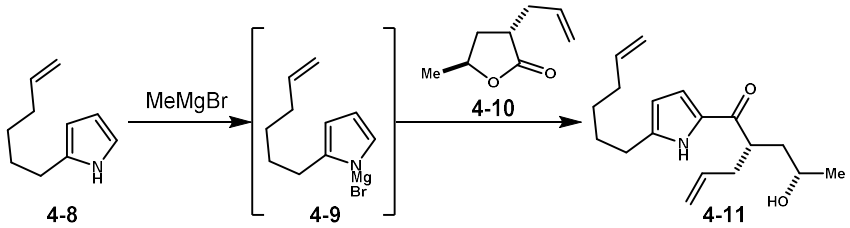
(*NOTE*: The *dr* of this process can be improved up to 7.5:1 by cooling the enolate to -100 °C instead of -78 °C before addition of allyl iodide.)

***Trans*-3-allyl-5-methyldihydrofuran-2-(3*H*)-one (4-10):**

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 5.72 (ddt, *J* = 7.0, 10.0, 17.0 Hz, 1H), 5.19-5.04 (m, 2H), 4.65 (sextet, *J* = 6.3 Hz, 0.84H), 4.54-4.45 (m, 0.16H)*, 2.81-2.68 (m, 1H), 2.67-2.61 (m, 0.16H)*, 2.60-2.51 (m, 0.84H), 2.48-2.39 (m, 0.16H)*, 2.33-2.19 (m, 1H), 2.18-2.08 (m, 0.84H)*, 2.03-1.92 (m, 0.84 H), 1.41 (d, *J* = 6.1 Hz, 0.48 H)*, 1.37 (d, *J* = 6.1 Hz, 2.52H)

^{13}C NMR (125 MHz, $CDCl_3$): 178.5, 134.3, 117.7, 74.9, 38.9, 34.6, 34.1, 21.1

Acylation of Pyrrole 4-8 with Lactone 4-10



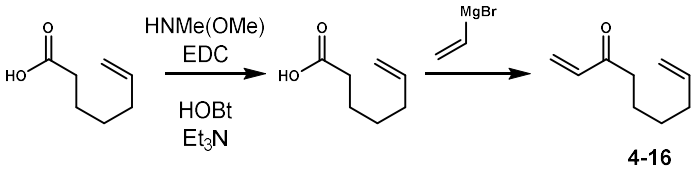
To a solution of MeMgBr (3.0 M in Et_2O, 0.45 mL, 1.35 mmol, 1.35 eq) in toluene (3 mL), **4-8** (prepared according to procedures described in Chapter 3, 0.2234 g, 1.49 mmol, 1.5 eq) was added dropwise. The mixture was heated to 50 °C for 1 hour. (*CAUTION*: VENT NEEDLE REQUIRED to allow Et_2O to escape the reaction mixture). Lactone **4-10** (prepared according to procedures described in Chapter 3, 0.1402 g, 1.0 mmol) in toluene (1 mL) was then added dropwise. The reaction mixture was then stirred at 50 °C for 2 hours. The reaction mixture was then cooled to room temperature and quenched with saturated NH_4Cl. The mixture was then extracted with EtOAc and the organics were dried over $MgSO_4$, filtered, and concentrated to a black/brown oil. The crude was purified by flash column chromatography (SiO_2, 6:1→4:1→2:1 Hexanes/EtOAc) to afford **4-11** (0.1202 g, 42%) as an oil along with recovered **4-10** (0.070 g, 49%) and **4-8** (0.1529 g, 68%).

1-(5-(hex-5-en-1-yl)-1*H*—pyrrol-2-yl)-2-(2-hydroxypropyl)pent-4-en-1-one (4-11):

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 10.18 (bs, 1H), 6.97 (dd, *J* = 2.5, 3.6 Hz, 1H), 5.99 (dd, *J* = 2.6, 3.5 Hz, 1H), 5.75 (ddt, *J* = 6.7, 10.2, 16.9 Hz, 1H), 5.02-4.87 (m, 2H), 3.78-3.69 (m, 1H), 3.46 (ddt, *J* = 3.4, 7.1, 10.4 Hz, 1H), 2.65 (t, *J* = 7.7 Hz, 2H), 2.47 (p, *J* = 6.9 Hz, 1H), 2.23 (p, *J* = 7.1 Hz, 1H), 2.06 (q, *J* = 7.1 Hz, 2H), 1.89 (ddd, *J* = 2.6, 10.3, 14.2 Hz, 1H), 1.67 (p, *J* = 7.7 Hz, 2H), 1.57 (ddd, *J* = 3.3, 9.8, 14.2 Hz, 1H), 1.44 (p, *J* = 7.5 Hz, 2H), 1.13 (d, *J* = 6.1 Hz, 3H)

^{13}C NMR (125 MHz, $CDCl_3$): 193.0, 142.3, 138.4, 135.9, 131.3, 118.6, 116.6, 114.7, 108.8, 65.5, 42.6, 41.2, 37.8, 33.4, 28.6, 28.5, 27.7, 24.3

Generation of Enone Partner 4-16

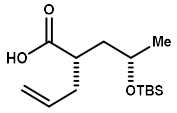


4-16

To a solution of 6-heptenoic acid (4.6842 g, 36.54 mmol) in DCM (180 mL, 0.2 M), EDC·HCl (10.5096 g, 54.82 mmol, 1.5 eq), HOBt·H_2O (8.4021 g, 54.86 mmol, 1.5 eq), and HNMe(OMe)·HCl (3.5798 g, 36.71 mmol, 1 eq) were added followed by Et_3N (25.5 mL, 182.95 mmol, 5 eq). The reaction was stirred overnight (~16 hours) at room temperature. The reaction was then concentrated and to yellow solids. The solids were taken up in Et_2O (300 mL) and the mixture was washed with 1M aqueous HCl (100 mL x 3), saturated aqueous $NaHCO_3$ (100 mL x 2), and brine (200 mL). The organics were then dried with $MgSO_4$, filtered through a SiO_2 plug, and concentrated to afford the intermediate Weinreb amide (5.4 g, 86%) as a clear oil.
To a solution of vinylmagnesium bromide (0.9M in THF, 32 mL, 28.80 mmol, 1.5 eq) in THF (40 mL) at -40 °C, intermediate Weinreb amide (3.35 g, 19.56 mmol) in THF (10 mL) was added dropwise. The reaction was stirred at -40 °C for 3 hours. The reaction was then quenched with 1M aqueous HCl and extracted with Et_2O. The organics were then dried over $MgSO_4$, filtered, and carefully concentrated to an orange oil. The crude oil was purified by flash column chromatography (SiO_2, 40:1→20:1 Hexanes/EtOAc) to afford **4-16** (6.244 g, 3.6:1 mixture of Hexanes:**4-16**, 1.92 g of **4-16**, 71%) as a clear oil.

Nona-1,8-dien-3-one (4-16):
^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 6.34 (dd, *J* = 10.6, 17.7, 1H), 6.20 (dd, *J* = 1.0, 17.7 Hz, 1H), 5.80 (dd, *J* = 1.0, 10.6 Hz, 1H), 5.79 (ddt, *J* = 6.5, 10.0, 16.9 Hz, 1H), 5.03-4.90 (m, 2H), 2.58 (t, *J* = 7.4 Hz, 2H), 2.10-2.01 (m, 2H), 1.63 (p, *J* = 7.5 Hz, 2H), 1.46-1.36 (m, 2H)

2-(2-((*tert*-butyldimethylsilyl)oxy)propyl)pent-4-enoic acid (4-17)



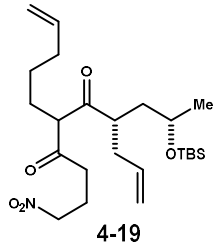
4-17

To neat **4-10** (2.0318 g, 14.49 mmol) at 0 °C, 1M aqueous KOH (15.8 mL, 1.1 eq) was added and the mixture was warmed to room temperature. The reaction was stirred for 2 hours before it was neutralized with 1M $KHSO_4$ (15.7 mL, 1.08 eq). The reaction was extracted with EtOAc and the organics were dried over $MgSO_4$, filtered, and concentrated to a clear oil. This material is used immediately in the next step.
The crude acid was dissolved in DCM (48 mL, 0.3M) and Et_3N (6.46 mL, 46.36 mmol, 3.2 eq) followed by the portion wise addition of TBSCl (5.4615 g, 36.23 mmol, 2.5 eq). The mixture was then allowed to stir at room temperature for 48 hours. MeOH (6 mL) was then added and the mixture was stirred at room temperature for 1 hour. The reaction was then diluted with EtOAc and washed with 0.5M aqueous citric acid. The organics were then washed with brine and dried over $MgSO_4$, filtered, and concentrated to afford a clear yellow oil. The crude oil was purified by flash

column chromatography (SiO_2, 20:1→10:1 Hexanes/EtOAc) to afford **4-17** (2.6729 g, 68% over two steps) as a clear oil.

2-(2-((*tert*-butyldimethylsilyl)oxy)propyl)pent-4-enoic acid (4-17):
^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 5.75 (ddt, *J* = 6.8, 10.0, 17.0 Hz, 1H), 5.11-5.01 (m, 2H), 3.90 (ddt, *J* = 6.1, 9.3, 14.5 Hz, 1H), 2.74-2.66 (m, 1H), 2.40 (p, *J* = 7.0 Hz, 1H), 2.25 (p, *J* = 7.0 Hz, 1H), 1.79 (ddd, *J* = 3.3, 10.3, 14.3 Hz, 1H), 1.53 (ddd, *J* = 3.2, 8.3, 14.0 Hz, 1H), 1.14 (d, *J* = 6.0 Hz, 1H), 0.87 (s, 9H), 0.04 (s, 6H)

One Pot α-Nitroketone Formation, Michael Addition, and Chain Extension Rearrangement

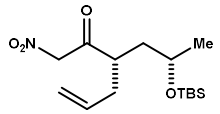


4-19

To a solution of CDI (0.3266 g, 2.01 mmol, 2 eq) in THF (3 mL), **4-17** (0.2717 g, 0.997 mmol) was added dropwise followed by DBU (0.03 mL, 0.2 mmol, 20 mol %). The reaction was stirred at room temperature for 1.5 hours, then $MeNO_2$ (0.16 mL, 2.98 mmol, 3 eq) and DBU (0.35 mL, 2.34 mmol, 2.3 eq). The reaction was stirred at room temperature for 36 hours. Then **4-16** (0.1454 g, 1.05 mmol, 1.05 eq) in THF (2 mL) was added. The mixture was stirred for 24 hours at room temperature and then at 40 °C for 3 hours. The reaction was quenched with saturated aqueous citric acid and the mixture was extracted with Et_2O. The organics were dried over $MgSO_4$, filtered, and concentrated to an orange oil. The crude was purified by flash column chromatography (SiO_2, 10:1→4:1→2:1 Hexanes/EtOAc) to afford **4-19** (0.1098 g, 24%) as a pale yellow oil. (Note: These conditions epimerize the α-position that contains the allyl substituent.)

7-(2-((*tert*-butyldimethylsilyl)oxy)propyl)-1-nitro-5-(pent-4-en-1-yl)dec-9-ene-4,6-dione (4-19):
^{1}H NMR (500 MHz, $CDCl_3$): δ 5.88-5.63 (m, 2H), 5.16-4.87 (m, 4H), 4.47-4.37 (m, 2H), 3.98-3.82 (m, 1H), 2.60-2.52 (m, 2H), 2.49-2.32 (m, 4H), 2.31-2.22 (m, 2H), 2.14-2.01 (m, 3H), 1.91-1.71 (m, 1H), 1.65-1.50 (m, 4H), 1.44-1.32 (m, 2H), 1.18-1.11 (m, 3H), 0.91-0.86 (m, 9H), 0.09-0.03 (m, 6H)

3-(2-((*tert*-butyldimethylsilyl)oxy)propyl)-1-nitrohex-5-en-2-one (4-15)

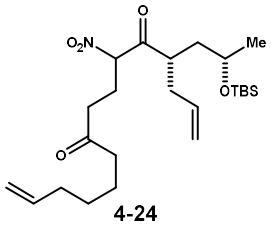


4-15

To a solution of CDI (1.4297 g, 8.81 mmol, 1.2 eq) in THF (14 mL), **4-17** (1.9978 g, 7.33 mmol) in THF (14 mL) was added slowly. The mixture was then refluxed (70 °C) for 1 hour (*CAUTION*: Gas evolution, make sure there is a vent needle).
In a separate flame dried flask, a suspension of NaH (0.3520 g, 8.8 mmol, 1.2 eq) in THF (8 mL) at 0 ° C is treated with $MeNO_2$ (1.57 mL, 29.32 mmol, 4 eq). The mixture was then stirred at room temperature for 30 minutes. The mixture of acyl imidazole was then transferred into the nitronate solution and the mixture was refluxed for 20 hours. The reaction was then cooled to room temperature and diluted with EtOAc. The mixture was then washed with 1M aqueous $KHSO_4$ and the organics were dried over $MgSO_4$, filtered, and concentrated to afford an orange oil. The crude oil was purified by flash column chromatography (SiO_2, 10:1→4:1 Hexanes/EtOAc) to afford **4-15** (2.1385 g, 92%) as a pale yellow oil. α-nitroketone **4-15** exists as ~10:1 mixture of ketone/enol tautomers.

3-(2-((*tert*-butyldimethylsilyl)oxy)propyl)-1-nitrohex-5-en-2-one (4-15):
^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 13.25 (s, 0.1H)*, 6.75 (s, 0.1H)*, 5.70 (ddt, *J* = 7.1, 10.2, 17.3 Hz, 1H), 5.34 (s, 2H), 5.14-5.01 (m, 2H), 3.92 (ddt, *J* = 6.2, 10.1, 12.5 Hz, 1H), 3.82-3.74 (m, 0.1H)*, 2.90-2.74 (m, 1H), 2.51-2.45 (m, 0.1H)*, 2.41 (p, *J* = 7.1 Hz, 0.9H), 2.32-2.24 (m, 0.1H), 2.20 (p, *J* = 7.0 Hz, 1H), 2.01 (ddd, *J* = 4.2, 10.2, 14.3 Hz, 0.9H), 1.84-1.70 (m, 0.1H)*, 1.64-1.49 (m, 1H), 1.15 (d, *J* = 6.1 Hz, 2.7H), 1.14-1.11 (m, 0.3H)*, 0.88 (s, 1H)*, 0.87 (s, 8H), 0.07 (s, 0.6H)*, 0.06 (s, 2.7H), 0.03 (s, 2.7H)

4-(2-((*tert*-butyldimethylsilyl)oxy)propyl)-6-nitropentadeca-1,14-diene-5,9-dione (4-24)



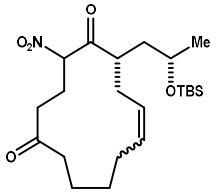
4-24

To a solution of **4-15** (0.5955 g, 1.88 mmol) and **4-16** (0.3142 g, 2.27 mmol, 1.2 eq) in THF (2 mL, 1M) at room temperature, PPh_3 (0.0491 g, 0.187 mmol, 10 mol %) was added. The reaction was stirred at room temperature for 24 hours. An additional portion of PPh_3 (0.0484 g, 0.184 mmol, 10 mol %) was added and the reaction was stirred for an additional 29 hours. The reaction was then concentrated and purified by flash column chromatography (SiO_2, 30:1→20:1→10:1 Hexanes/EtOAc) to afford **4-24** (0.7175 g, 84%) as a pale yellow oil. α-Nitroketone **4-24** is a 1:1 mixture of diastereomers at the α-nitro position and exists as ~10:1 mixture of the ketone/enol tautomers.

4-(2-((*tert*-butyldimethylsilyl)oxy)propyl)-6-nitropentadeca-1,14-diene-5,9-dione (4-24):
^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 5.76 (ddt, *J* = 6.7, 10.0, 16.9 Hz, 1H), 5.72-5.62 (m, 1H), 5.50 (dd, *J* = 3.3, 10.6 Hz, 0.5H), 5.45 (dd, *J* = 3.6, 10.2 Hz, 0.5H), 5.14-4.89 (m, 4H), 3.89-3.79 (m, 1H), 3.07-2.96 (m, 1H), 2.63-2.52 (m, 1H), 2.52-2.20 (m, 5H), 2.39 (t, *J* = 7.4 Hz, 2H), 2.04 (q, *J* = 7.1 Hz, 2H), 1.98-1.85 (m, 1H), 1.62-1.51 (m, 2H), 1.37 (p, *J* = 7.5 Hz, 2H), 1.15 (d, *J* = 6.0 Hz, 1.35H), 1.15 (d, *J* = 6.1 Hz, 1.35H), 1.14-1.11 (m, 0.3H)*, 0.89 (s, 0.5H)*, 0.88 (s, 0.5H)*, 0.86 (s, 4H), 0.85 (s, 4H), 0.08-0.00 (m, 6H)

^{13}C NMR (125 MHz, $CDCl_3$): 208.7, 208.6, 201.2, 201.1, 138.3, 138.2, 134.3, 134.1, 118.2, 118.1, 114.8, 114.8, 92.5, 92.1, 67.0, 66.9, 45.8, 44.7, 42.6, 40.6, 40.1, 37.6, 36.5, 36.2, 33.4, 28.3, 25.93, 25.92, 25.84, 25.82, 23.8, 23.4, 23.3, 23.2, 23.18, 23.1, 18.2, 18.1, -4.1, -4.2, -4.7, -4.8

6-(2-((*tert*-butyldimethylsilyl)oxy)propyl)-4-nitrocyclotridec-8-ene-1,5-dione (4-14)



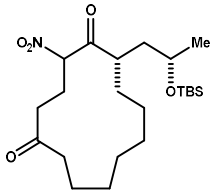
4-14

To a solution of **4-24** (1.0084 g, 2.22 mmol) in DCM (230 mL, 0.01M), GII (75.9 mg, 0.089 mmol, 4 mol %) was added. The reaction was then heated to reflux (40 °C). Additional portions of GII (37.9 mg + 37.2 mg, 0.044 mmol + 0.044 mmol, 4 mol % total) were added after 2 and 4 hours, respectively. The mixture was refluxed for 7.5 hours total. The reaction was then concentrated and purified by flash column chromatography (SiO_2, 40:1→30:1→20:1→10:1→4:1 Hexanes/EtOAc) to afford **4-14** (0.7933 g, 84%) as a brown oil. Macrocycle **4-14** is an undetermined mixture of Z:E isomers, a 1:1 diasteromeric mixture at the α-nitro position, and a mixture of conformers at room temperature.

6-(2-((*tert*-butyldimethylsilyl)oxy)propyl)-4-nitrocyclotridec-8-ene-1,5-dione (4-14):
^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 5.59-5.19 (m, 3H), 3.93-3.73 (m, 1H), 3.12-2.90 (m, 1H), 2.68-2.12 (m, 8H), 2.02-1.84 (m, 2H), 1.55-1.45 (m, 2H), 1.39-1.29 (m, 2H), 1.19-1.10 (m, 3H), 0.92-0.77 (m, 9H), 0.10-0.00 (m, 6H)

HRMS (ESI) m/z, 426.2658 (426.2670 calculated for $C_{22}H_{40}NO_5Si^+$, $(M+H)^+$)

13-(2-((*tert*-butyldimethylsilyl)oxy)propyl)-2-nitrocyclotridecane-1,5-dione (4-25)



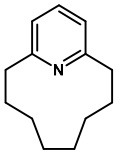
4-25

To a solution of **4-14** (0.1492 g, 0.35 mmol) in EtOAc (3.5 mL, 0.1 M), Pd/C (35.4 mg, 0.033 mmol, 10 mol %) was added. The system was then pressurized with H_2 (40 bar) and stirred for 24 hours at room temperature. The reaction was then filtered through a SiO_2 plug with EtOAc and concentrated to afford **4-25** (0.1499 g, quant.) as a purple oil. Macrocycle **4-25** is a 1:1 diasteromeric mixture at the α-nitro position and a mixture of conformers at room temperature.

13-(2-((*tert*-butyldimethylsilyl)oxy)propyl)-2-nitrocyclotridecane-1,5-dione (4-25):
^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 5.57-5.39 (m, 1H), 3.86-3.77 (m, 0.3H)*, 3.76-3.63 (m, 0.7H), 3.04-2.86 (m, 1H), 2.71-2.27 (m, 6H), 2.22 (ddd, *J* = 3.3, 7.6, 11.4 Hz, 1H), 1.92 (ddd, *J* = 3.6, 7.9, 13.7 Hz, 1H), 1.86-1.35 (m, 6H), 1.34-1.26 (m, 4H), 1.20-1.12 (m, 2H), 1.11-1.06 (m, 3H), 0.91-0.81 (m, 9H), 0.09-0.00 (m, 6H)

HRMS (ESI) m/z, 428.2814 (428.2827 calculated for $C_{22}H_{42}NO_5Si^+$, $(M+H)^+$)

[8](2,6)-pyridinophane (4-36)



4-36

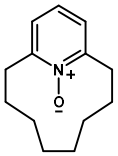
To a suspension of freshly activated Mg (4.8641 g, 200.16 mmol, 2 eq) in Et_2O (250 mL), a small crystal of I_2 was added and the mixture was stirred for 5 minutes at room temperature. 1,8-dibromooctane (18.7 mL, 101.53 mmol, 1.01 eq) was added dropwise over 1h, while allowing the mixture to gently reflux. After the addition was complete, the mixture was refluxed for 2h and then allowed to cool to room temperature. The stirring is shut off and the mixture settles into a biphasic mixture with a clear to slightly cloudy top layer and a dark gray viscous bottom layer.
Another flask is charged with 2,6-dichloropyridine **4-39** (14.8062 g, 100.04 mmol) and $NiCl_2$DPPP (2.722 g, 5.02 mmol, 5 mol%). The solids were then dissolved in Et_2O (1 L, 0.1M) and cooled to 5 °C. The di-Grignard was then added dropwise over 6h while the reaction was maintained between 5-10 °C. After the addition was complete, the reaction was allowed to warm to room temperature overnight (~16h). The reaction was then quenched by pouring into ice water. The mixture was then filtered over Celite® and the filtrate was extracted with Et_2O several times. The combined organics were then washed with brine, dried over $MgSO_4$, filtered, and concentrated to afford an orange oil. The residue was purified by flash column chromatography (SiO_2, 50:1→40:1→30:1 Hexanes/EtOAc) to afford **4-36** (8.9583 g, 47%) as a clear oil.

[8](2,6)-pyridinophane (4-36):
^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.45 (t, *J* = 7.6 Hz, 1H), 6.88 (d, *J* = 7.6 Hz, 2H), 2.83 (dd, *J* = 5.8, 7.1 Hz, 4H), 1.78 (p, *J* = 6.3 Hz, 4H), 1.42-1.33 (m, 4H), 1.06-0.95 (m, 4H)

^{13}C NMR (125 MHz, $CDCl_3$): 160.4, 136.5, 119.9, 35.6, 26.1, 24.9, 23.0

HRMS (ESI) m/z 190.1583 (190.1590 calculated for $C_{13}H_{20}N^+$, $(M+H)^+$)

[8](2,6)-pyridinophane *N*-oxide (4-35)



4-35

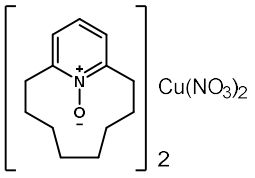
To a solution of pyridinophane **4-36** (16.05 g, 84.78 mmol) in $CHCl_3$ (115 mL, 0.75 M), *m*-CPBA (75%, 39.038 g, 169.66 mmol, 2 eq) was added. The mixture was then heated to 50 °C for 36 hours and then cooled to room temperature. The mixture was diluted with $CHCl_3$ (200 mL) and K_2CO_3 (23.435 g, 169.56 mmol, 2 eq) was added. The mixture was stirred at room temperature for 2h and then filtered to remove the solids, which were washed with $CHCl_3$. The filtrate was then washed with aqueous 1M K_2CO_3. The organics were then dried over $MgSO_4$, filtered and concentrated. A second batch (16.05 g of **4-36**) using the exact same conditions was combined with the first, which was then purified by flash column chromatography (10:1→4:1→3:2→0:1 Hexanes/EtOAc) to afford **4-35** (27.2 g, 78%) as a slight yellow oil that crystallized on standing. In addition, **4-36** (2.345 g, 7%) was recovered from the reaction.

[8](2,6)-pyridinophane *N*-oxide (4-35):
^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.00 (s, 3H), 3.74 (ddd, *J* = 5.3, 8.3, 13.4 Hz, 2H), 2.46 (ddd, *J* = 5.6, 6.7, 12.6 Hz, 2H), 2.36-2.26 (m, 2H), 1.72-1.58 (m, 2H), 1.50-1.38 (m, 2H), 1.34-1.22 (m, 2H), 0.86-0.70 (m, 2H), 0.49-0.36 (m, 2H)

^{13}C NMR (125 MHz, $CDCl_3$): 154.0, 124.5, 124.0, 30.2, 26.9, 23.8

HRMS (ESI) m/z 206.1534 (206.1539 calculated for $C_{13}H_{20}NO^+$, $(M+H)^+$)

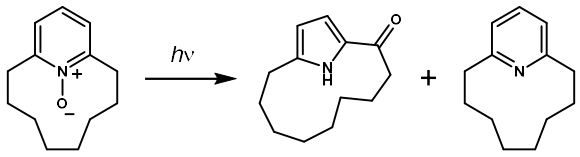
Bis{[8](2,6)-pyridinophane N-oxide}Copper (II) Nitrate (4-41)



4-41

To a solution of $Cu(NO_2)_2$ (0.4641 g, 1.99 mmol, 50 mol%) in EtOH (20 mL) at room temperature, N-oxide **4-35** (0.8207 g, 3.99 mmol) was added in one portion. The reaction progresses from blue to green and completes as a blue-green with solids. The mixture was stirred for 40 minutes total. The reaction was then diluted with EtOH (10-15 mL) and heated until the solids dissolved. The mixture was then allowed to cool to room temperature and followed by cooling to -20 °C for several hours. The blue-green crystals were then filtered, washed with cold EtOH, and dried under vacuum to afford **4-41** (1.189, quant.) as blue-green crystals that were of sufficient quality for X-ray diffraction analysis.

Irradiation of Pyridinophane *N*-oxide 4-35



4-35 **4-37** **4-36**

Condition 1:

A 1 L immersion well photoreactor was charged with a solution of pyridinophane N-oxide **4-35** (3.9 g, 19.18 mmol) in THF (1 L, 0.02M). The solution was cooled to -40 °C and then irradiated with a 450 W Hanovia Mercury Arc lamp for 3h. The mixture was monitored by the ^1H NMR spectrum analysis of aliquots. The lamp was removed and the mixture was warmed to room temperature and concentrated. The residue was then purified by flash column chromatography (SiO_2, 70:15:15 Hexanes/EtOAc/DCM) to afford **4-37** (1.08 g, 28%) as a white crystalline solid and **4-36** (0.472 g, 13%) as a clear oil. Alternatively, the crude reaction can be flushed through a SiO_2 plug with EtOAc to remove the polymer. The filtrate can be partially concentrated and then diluted with hexanes to induce precipitation and the solids can be filtered to afford pure **4-37**. The mother liquor can be purified by flash column chromatography to afford additional **4-37**.

Condition 2:

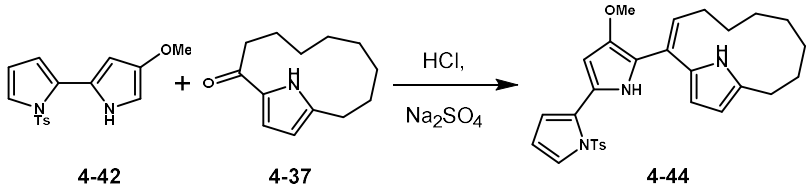
A solution of pyridinophane N-oxide **4-35** (0.02M in THF, 19.18 mmol) in quartz test tubes (10 x 100 mL) can be irradiated in a Rayonet photoreactor (254 nm bulb set) for 15 hours at room temperature. The reaction are then concentrated and purified as indicated above to afford **4-37** (0.701 g, 18%) and **4-36** (0.290 g, 8%).

1[1]*H*-1(2,5)-pyrrolacyclodecaphan-2-one (4-37):

[1]H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.79 (bs, 1H), 6.97 (dd, *J* = 2.7, 3.8 Hz, 1H) ,6.08 (dd, *J* = 2.7, 3.8 Hz, 1H), 2.74 (dd, *J* = 5.4, 7.3 Hz, 2H), 2.68 (dd, *J* = 5.03 6.5 Hz, 2H), 1.83-1.73 (m, 4H), 1.58-1.50 (m, 2H), 1.36 (p, *J* = 5.7 Hz, 2H), 1.25-1.15 (m, 2H), 1.11-1.01 (m, 2H)

[13]C NMR (125 MHz, $CDCl_3$): 190.3, 137.9, 132.3, 115.9, 111.5, 36.1, 27.0, 26.7, 26.2, 23.5, 23.4, 23.3, 21.7

Condensation Reaction between Bipyrrole 4-42 and Acyl Pyrrolophane 4-37



4-42 4-37 4-44

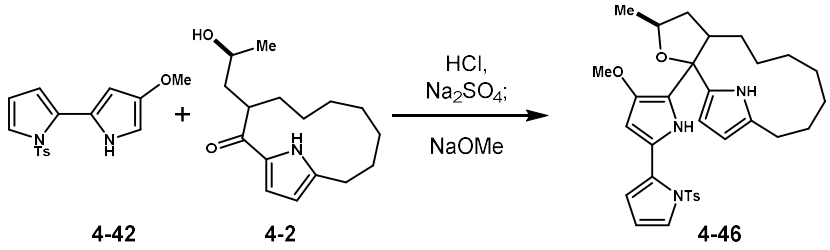
To a solution of Na_2SO_4 (0.2129 g, 1.78 mmol, 4 eq), bipyrrole **4-42** (0.218 g, 0.69 mmol, 1.5 eq), and pyrrolophane **4-37** (0.0916 g, 0.44 mmol) in MeOH (8 mL, 0.05M), HCl (1M in MeOH, 0.9 mL, 0.9 mmol, 2 eq) was added. The reaction turns dark red and was stirred for 2h. The reaction was quenched with saturated aqueous $NaHCO_3$ and extracted with EtOAc. The organics were then dried over Na_2SO_4, filtered through an Al_2O_3 plug with EtOAc, and concentrated to a red oil. The residue was purified by flash column chromatography (SiO_2 neutralized with 1% Et_3N in Hexanes, 30:1→15:1→10:1→0:1 Hexanes/EtOAc) to afford **4-44** (0.1420 g, 64%) as a red oil.

(*E*)-2-(4-methoxy-1'-tosyl-1*H*,1'*H*-[2,2'-bipyrrol]-5-yl)-1[1]*H*-1(2,5)-pyrrolacyclodecaphan-2-ene (4-44):

[1]H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.45 (bs, 1H), 8.00 (bs, 1H), 7.33-7.29 (m, 3H), 7.14 (d, *J* = 8.0 Hz, 2H), 6.53 (t, *J* = 8.4 Hz, 1H), 6.21 (t, *J* = 3.3 Hz, 1H), 6.17 (dd, *J* = 1.8, 3.4 Hz, 1H), 6.07 (t, *J* = 2.9 Hz, 1H), 5.95 (t, *J* = 2.9 Hz, 1H), 5.93 (d, *J* = 3.0 Hz, 1H), 3.79 (s, 3H), 2.65 (t, *J* = 6.1 Hz, 2H), 2.35 (s, 3H), 2.04 (q, *J* = 7.7 Hz, 2H), 1.58 (p, *J* = 5.4 Hz, 2H), 1.48-1.40 (m, 2H), 1.40-1.32 (m, 2H), 1.30-1.15 (m, 4H), 0.88-0.76 (m, 2H)

[13]C NMR (125 MHz, $CDCl_3$): 145.2, 144.7, 135.0, 132.4, 129.5, 128.4, 127.6, 127.2, 126.6, 125.3, 123.4, 116.9, 116.3, 114.7, 111.79, 108.5, 105.5, 99.2, 58.0, 28.7, 28.0, 27.9, 27.8, 27.3, 26.9, 25.3, 21.6

Condensation of Bipyrrole 4-42 and Branched Acyl Pyrrolophane 4-2



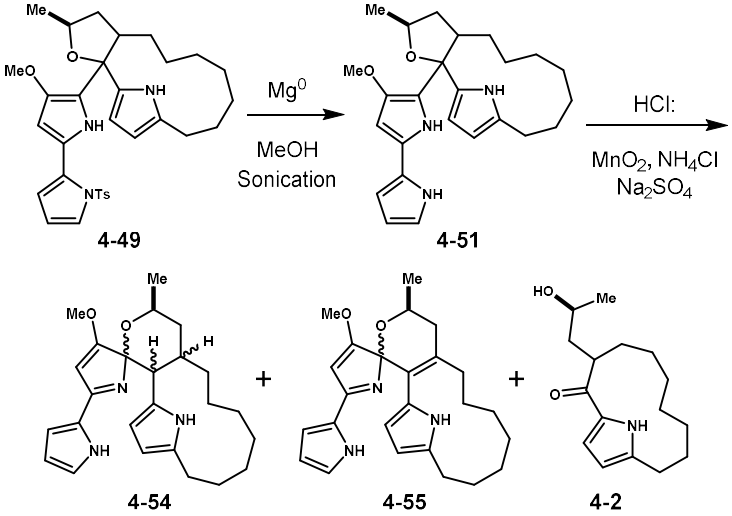
4-42 4-2 4-46

To a solution of **4-2** (0.278 g, 1.05 mmol) and **4-42** (0.358 g, 1.13 mmol, ~1.1 eq) were mixed in MeOH (20 mL, 0.05M) with Na_2SO_4 (1.100 g, 9.23 mmol, ~9 eq) at 0 °C. HCl (1M in MeOH, 1.1 mL, 1.1 mmol, ~1.05 eq) was added dropwise to the mixture over 15 minutes resulting in a dark red/black reaction. The reaction was stirred at 0 °C for an additional 1.5 hours. The reaction was then added dropwise into another flask containing NaOMe (1M in MeOH, 3.0 mL, 3.0 mmol, 3 eq) at 0 °C with vigorous stirring, resulting in an orange solution. The mixture was then concentrated and purified by flash column chromatography (SiO_2 neutralized with 1% Et_3N in Hexanes, 20:1→15:1→10:1 Hexanes/EtOAc) to afford **4-44** (0.386 g, 65%) as a yellow oil that reddens over time. **4-44** is best stored as a stock solution in toluene at -20 °C.

(2^5S)-2^2-(4-methoxy-1'-tosyl-1*H*,1'*H*-[2,2'-bipyrrol]-5-yl)-2^5-methyl-2^2,2^3,2^4,2^5-tetrahydro-1^1*H*-1(2,5)-pyrrola-2(2,3)-furanacyclononaphane (4-44):

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 9.42 (bs, 0.5H), 9.34 (bs, 0.5H), 9.21 (bs, 1H), 7.39-7.30 (m, 3H), 7.14 (d, *J* = 8.3 Hz, 1H), 7.06 (d, *J* = 8.3 Hz, 1H), 6.28 (t, *J* = 3.3 Hz, 1H), 6.26-6.23 (m, 1H), 5.99 (d, *J* = 3.2 Hz, 1H), 5.83-5.80 (m, 1H), 5.73 (q, *J* = 3.1 Hz, 1H), 4.44-4.35 (m, 0.5H), 4.13-4.06 (m, 0.5H), 3.80 (s, 1.5H), 3.77 (s, 1.5H), 2.99 (q, *J* = 7.4 Hz, 0.5H), 2.90 (t, *J* = 7.2 Hz, 0.5H), 2.73-2.52 (m, 2H), 2.47-2.37 (m, 0.5H), 2.31 (s, 1.5H), 2.28 (s, 1.5H), 2.28-2.21 (m, 0.5H), 1.92-1.84 (m, 1H), 1.83-1.43 (m, 4.5H), 1.43-1.32 (m, 1.5H),1.31 (d, *J* = 6.1 Hz, 1.5H), 1.25 (d, *J* = 5.9 Hz, 1.5H), 1.30-1.26 (m, 1.5H), 1.16-1.05 (m, 2H), 1.03-0.78 (m, 4.5H)

(2R,3'S,4'S,6'S)-3-methoxy-6'-methyl-5-(1*H*-pyrrol-2-yl)spiro[pyrrole-2,2'-1(2,5)-pyrrola-2(3,4)-pyranacyclononaphane] or Premarineosin A (4-52)



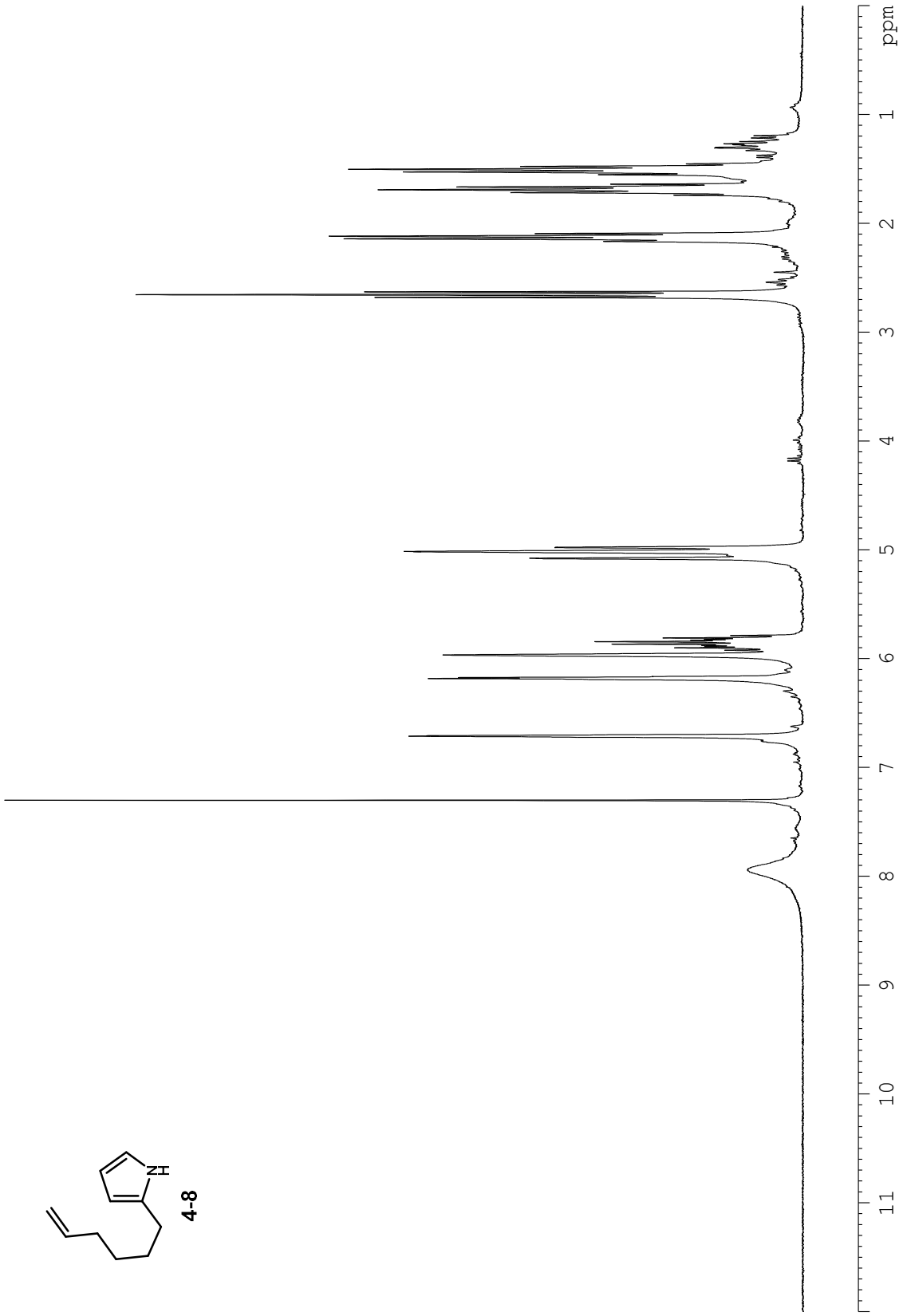
In a one dram vial, tetrahydrofuran (20 mg, 0.035 mmol) was azeotroped with toluene thrice to remove any moisture. Then material was then taken up in MeOH (0.35 mL, 0.1M) and Mg (4.6 mg, 0.19 mmol, ~5 eq) was added. The mixture was then sealed under inert atmosphere and sonicated for 30 minutes. When TLC indicated that SM was consumed, reaction was diluted with toluene (1 mL) and the solution was removed from the solids by transfer into another dram vial. The mixture was concentrated, diluted with toluene (1-2 mL) and reconcentrated twice. The materials was then taken up in toluene and flushed through a Celite® plug with toluene to afford the detosylated material as a yellow solution.

HCl (1M in MeOH, 0.11 mL, 0.11 mmol, 3 eq) was then added, which causes the solution to turn dark red/purple. The HCl and MeOH are removed under reduced pressure with no heating. The solution of prodiginine salt is then added slowly to a dram vial containing MnO_2 (60 mg, 0.69 mmol, 20 eq), NH_4Cl (30 mg, 0.56 mmol, 16 eq), and Na_2SO_4 (30 mg). When the dark red/purple color does not disappear upon addition, the solution is added to another vial containing the cycloisomerization mixture. This process repeats until the solution is depleted. The reaction mixtures are then filtered and the solids are washed with MeOH. The filtrate is concentrated and dissolved in MeCN and refiltered. The filtrate is then concentrated and purified by preparative HPLC. The desired premarineosin A isomer elutes at 6.8 min.

HPLC Conditions

Waters Sunfire C18 column (19 x 250 mm) with UV detection at 280 nm; Solution A is 0.1% formic acid in H_2O and Solution B is 0.1% formic acid in MeCN; increase gradient of solution B from 40% to 47% 0-8 min, 47% to 100% 8-9 minutes, flow rate: 12 mL/min

4.4.3. NMR Spectra Relevant to Chapter 4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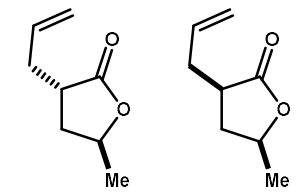

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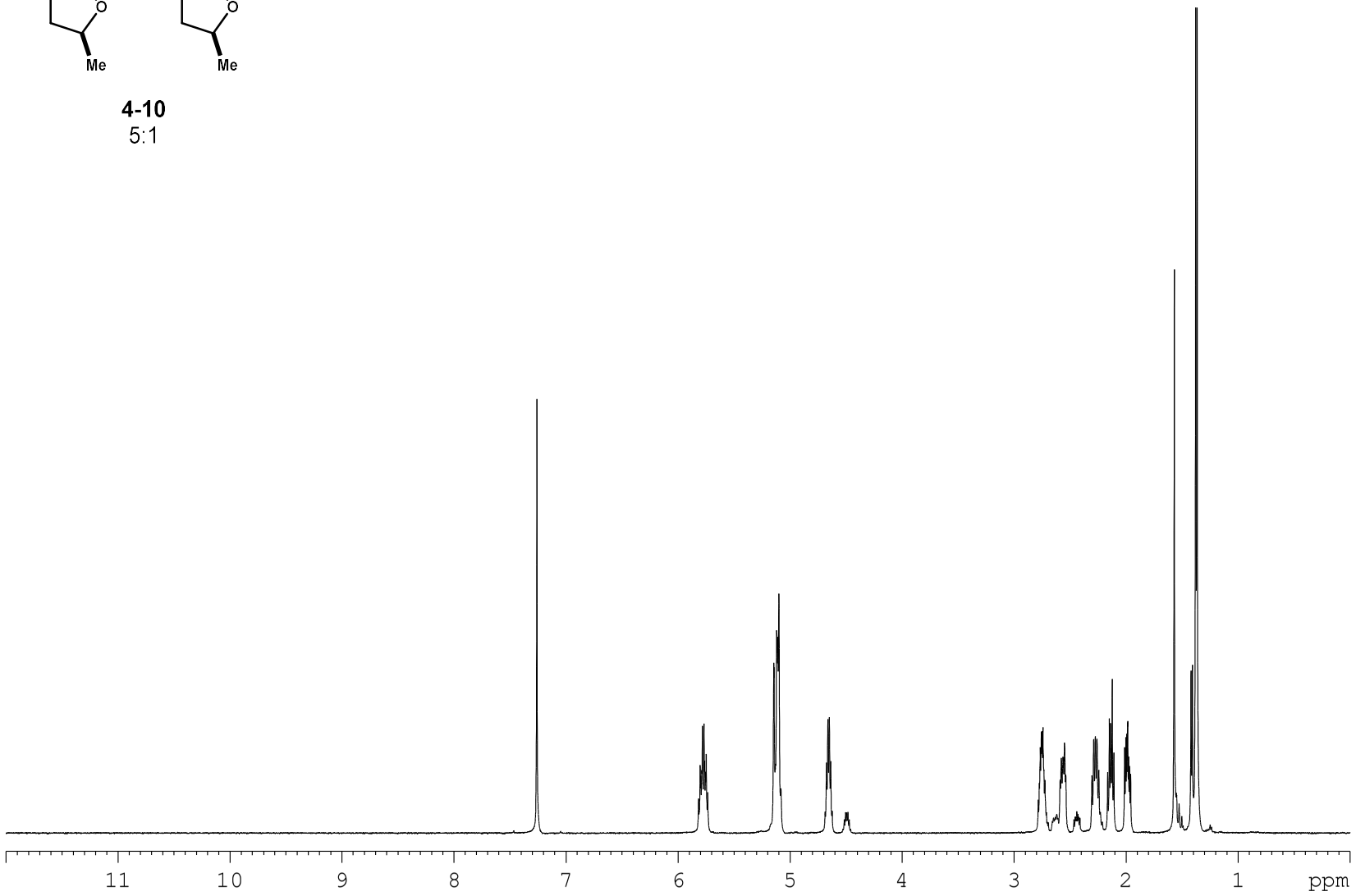

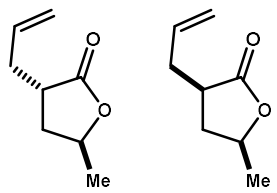

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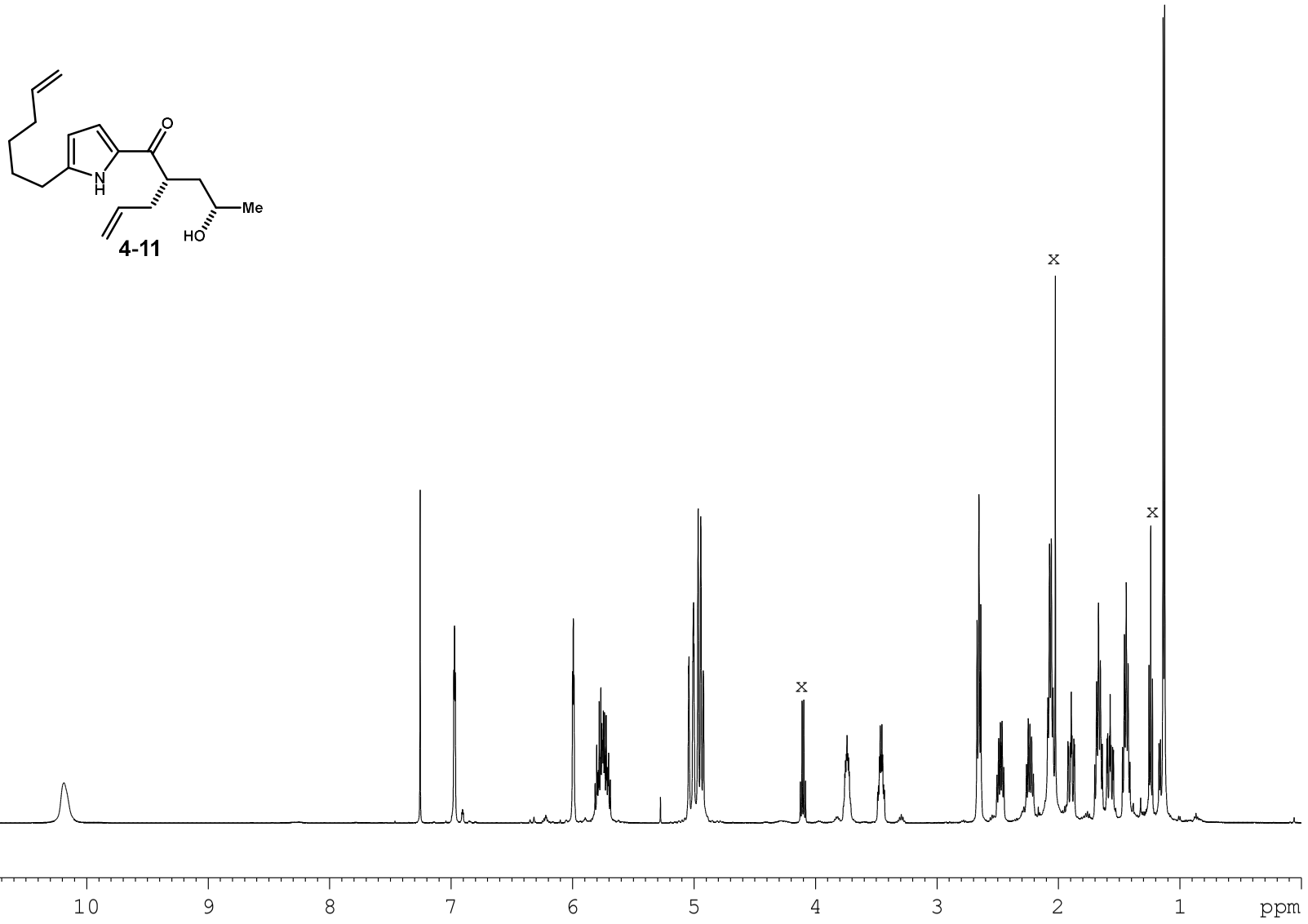
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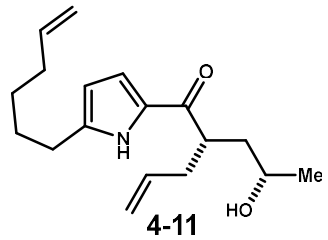

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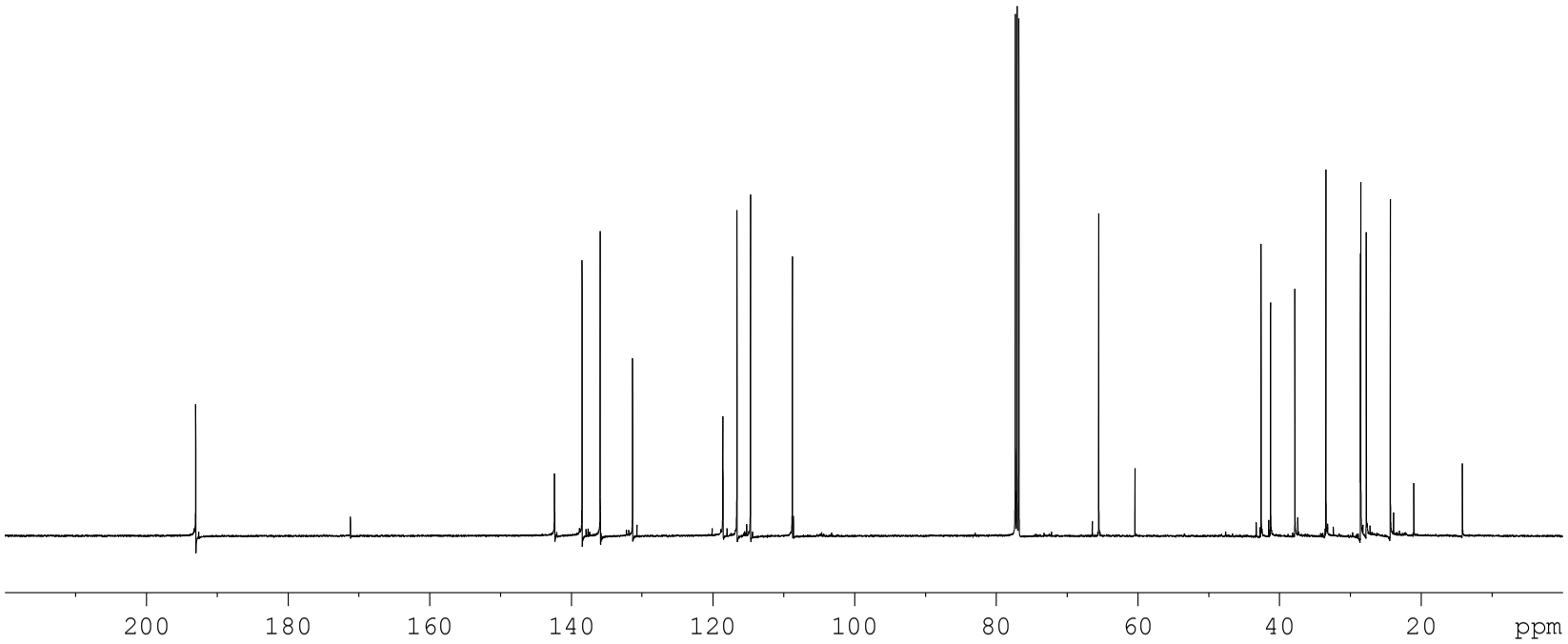

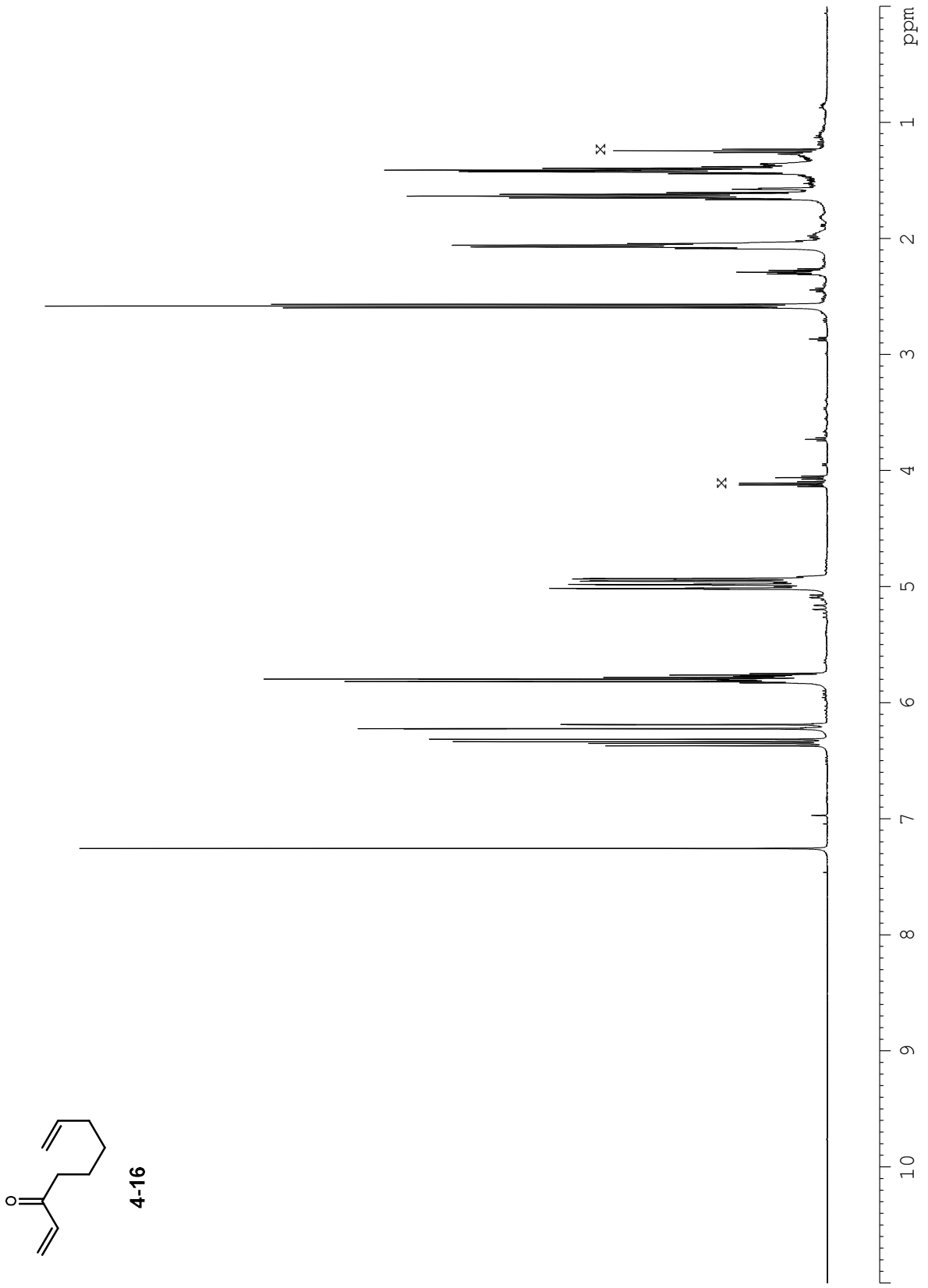

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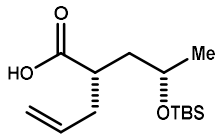

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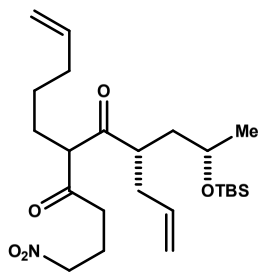

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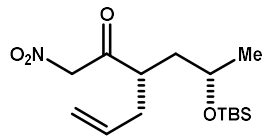

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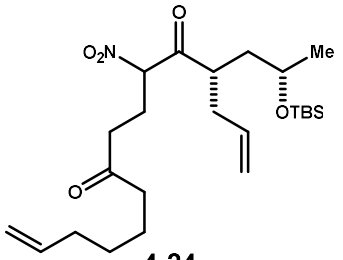

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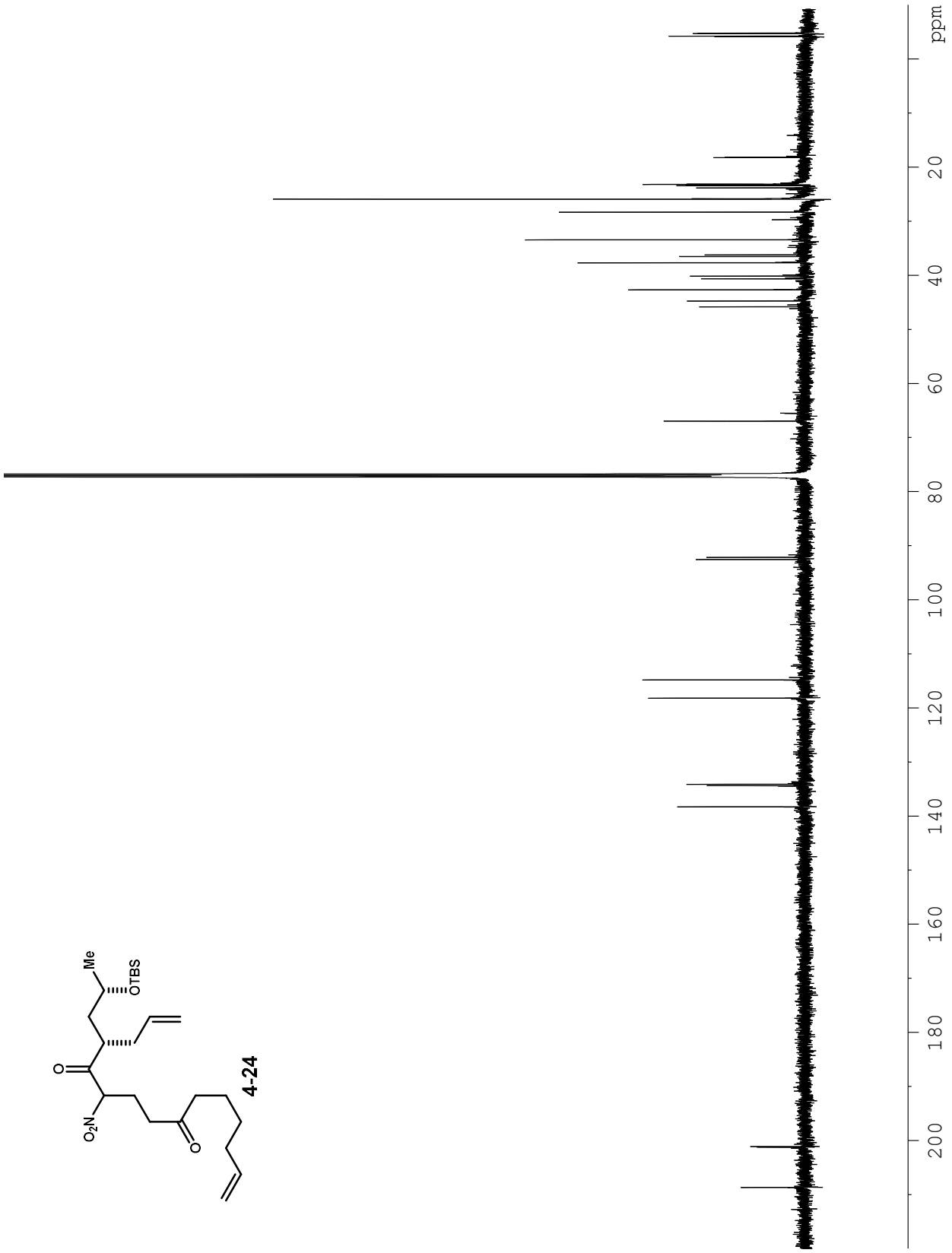
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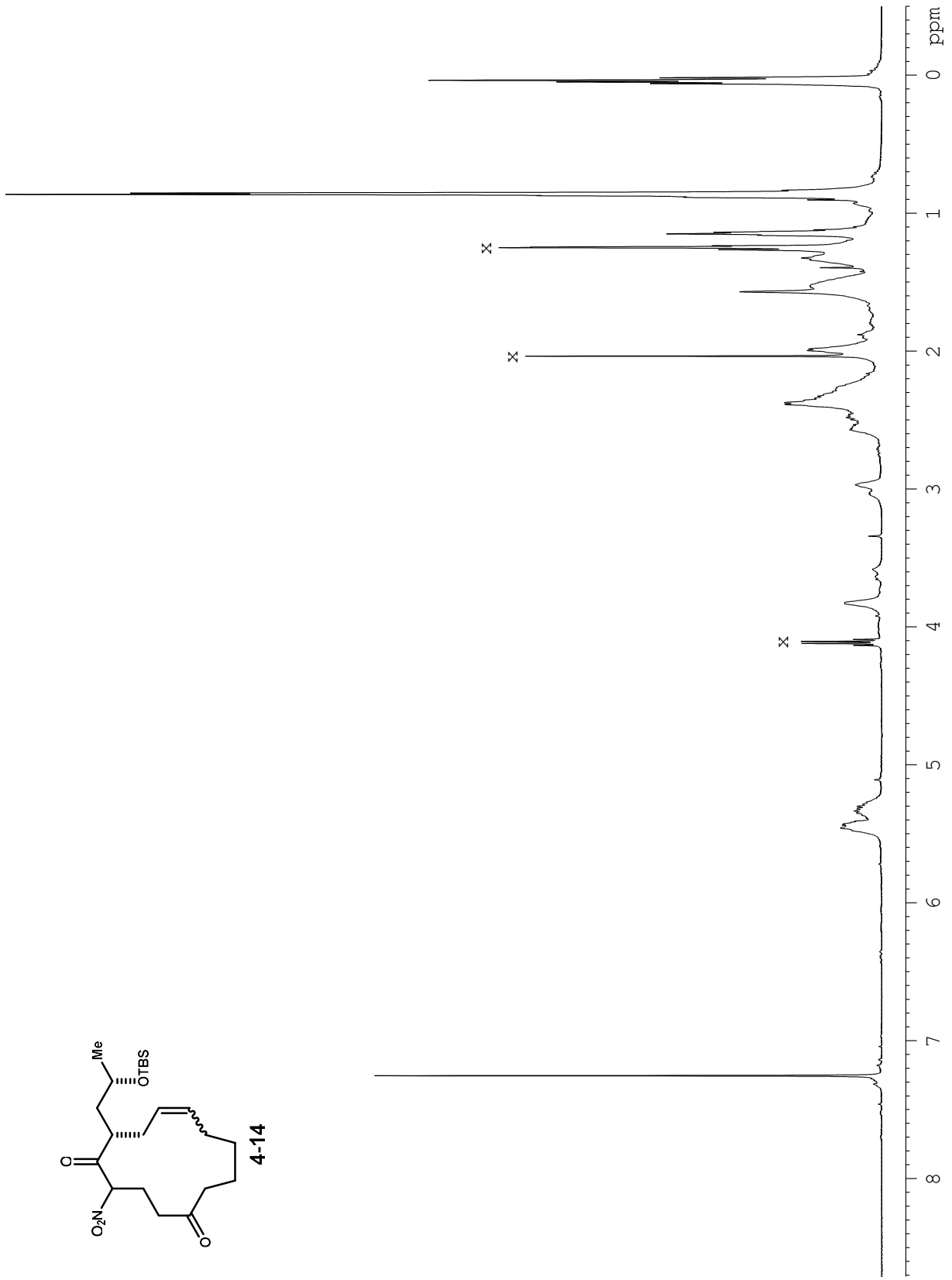
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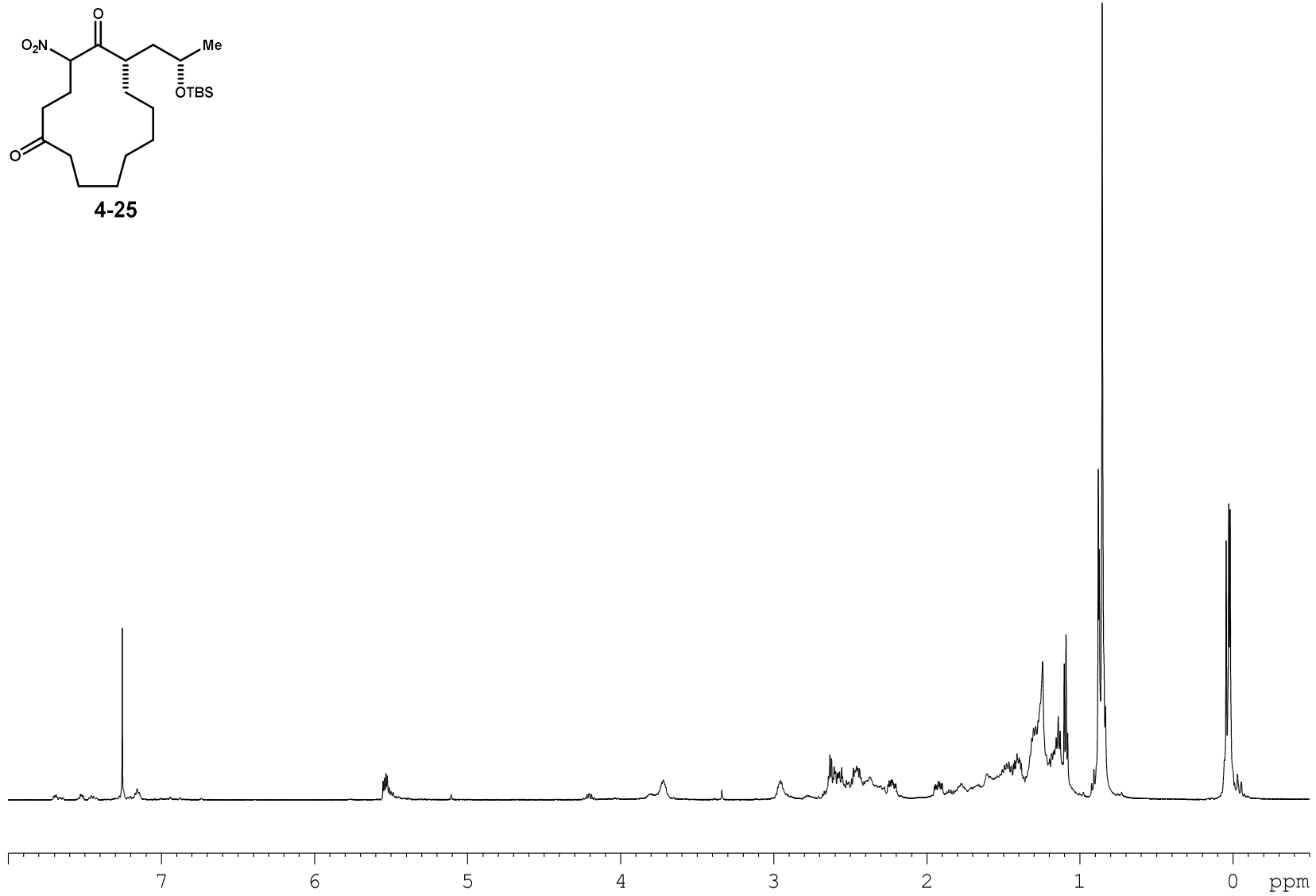

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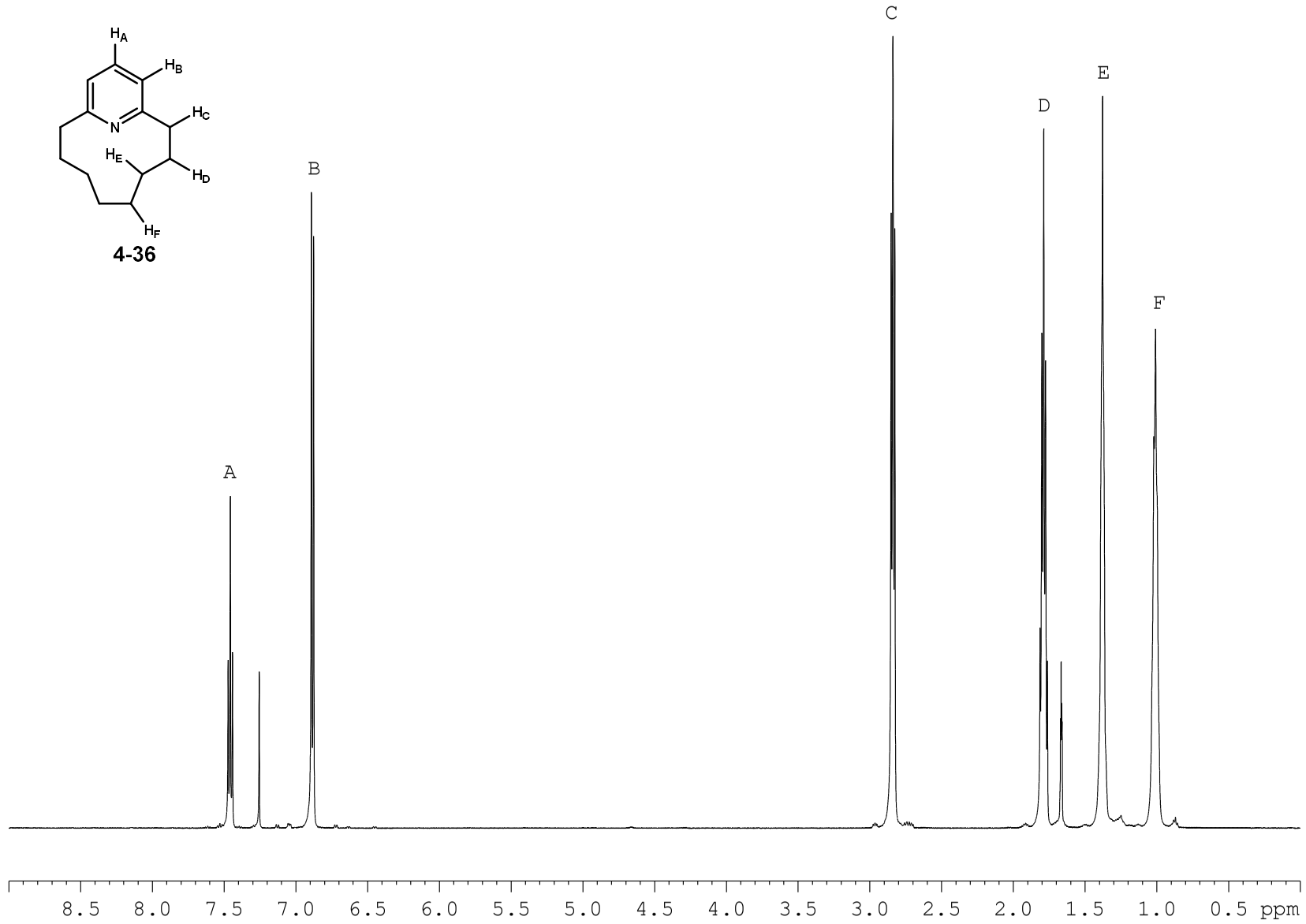
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H_E
H_D
H_F
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B
C
D
E
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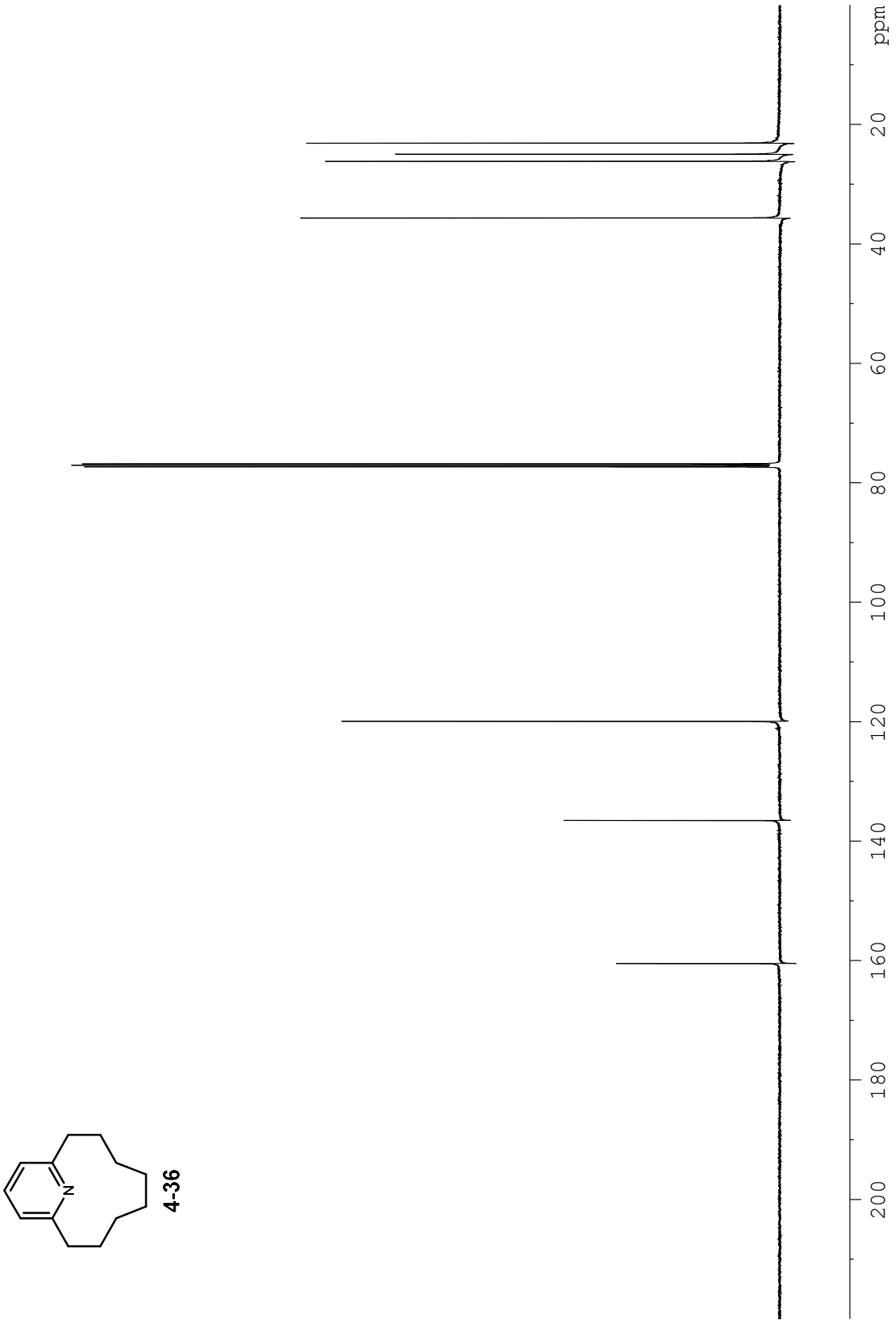

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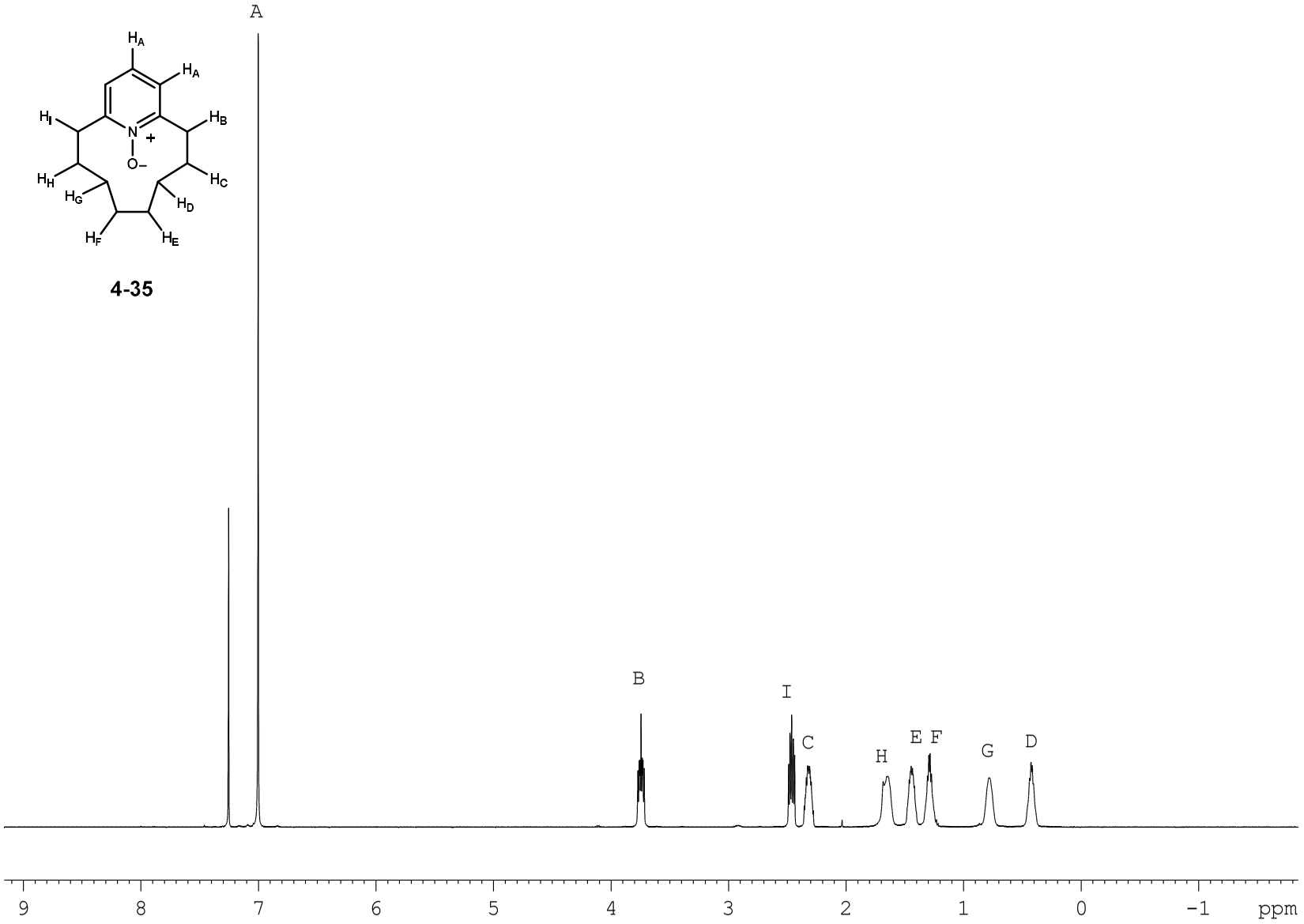

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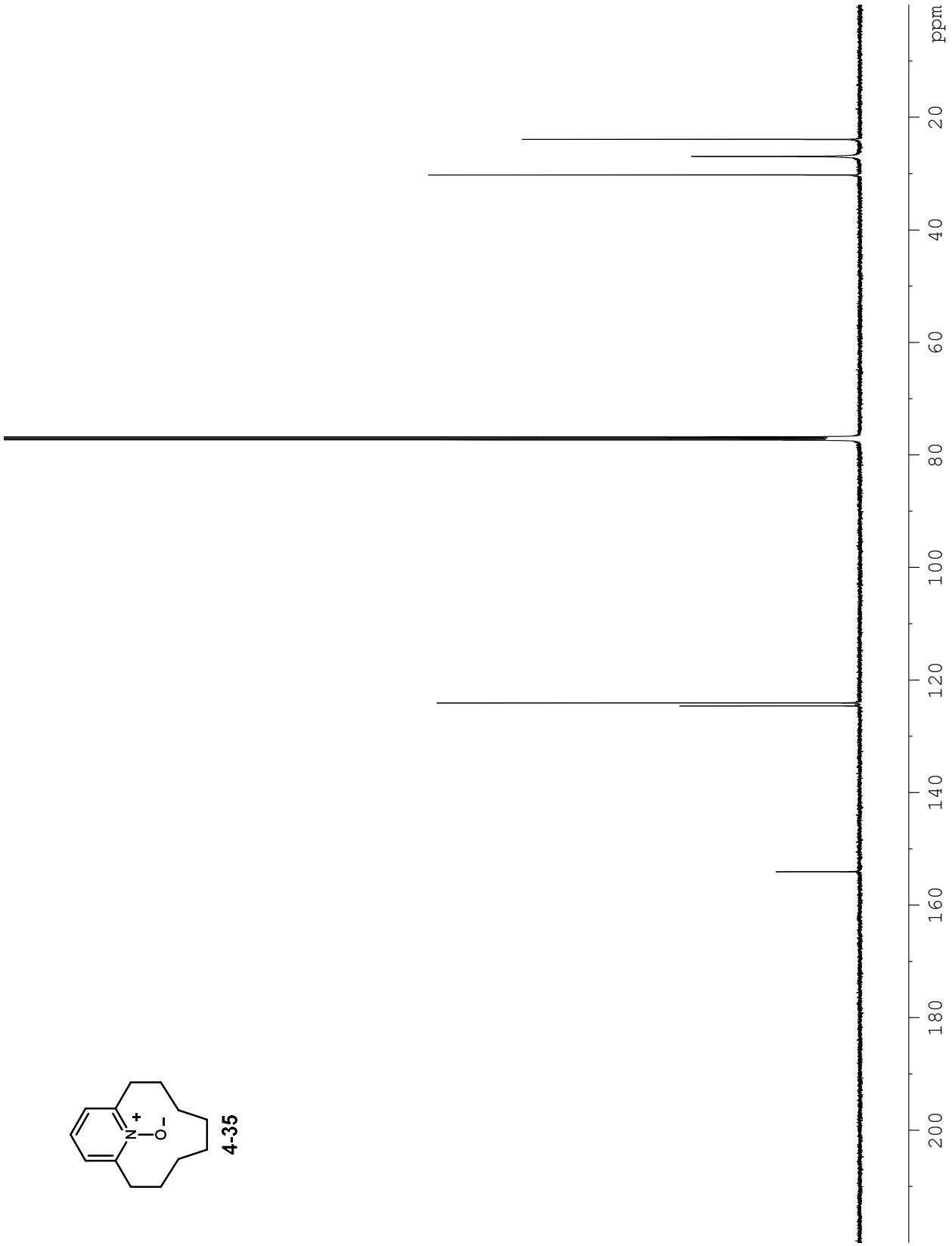

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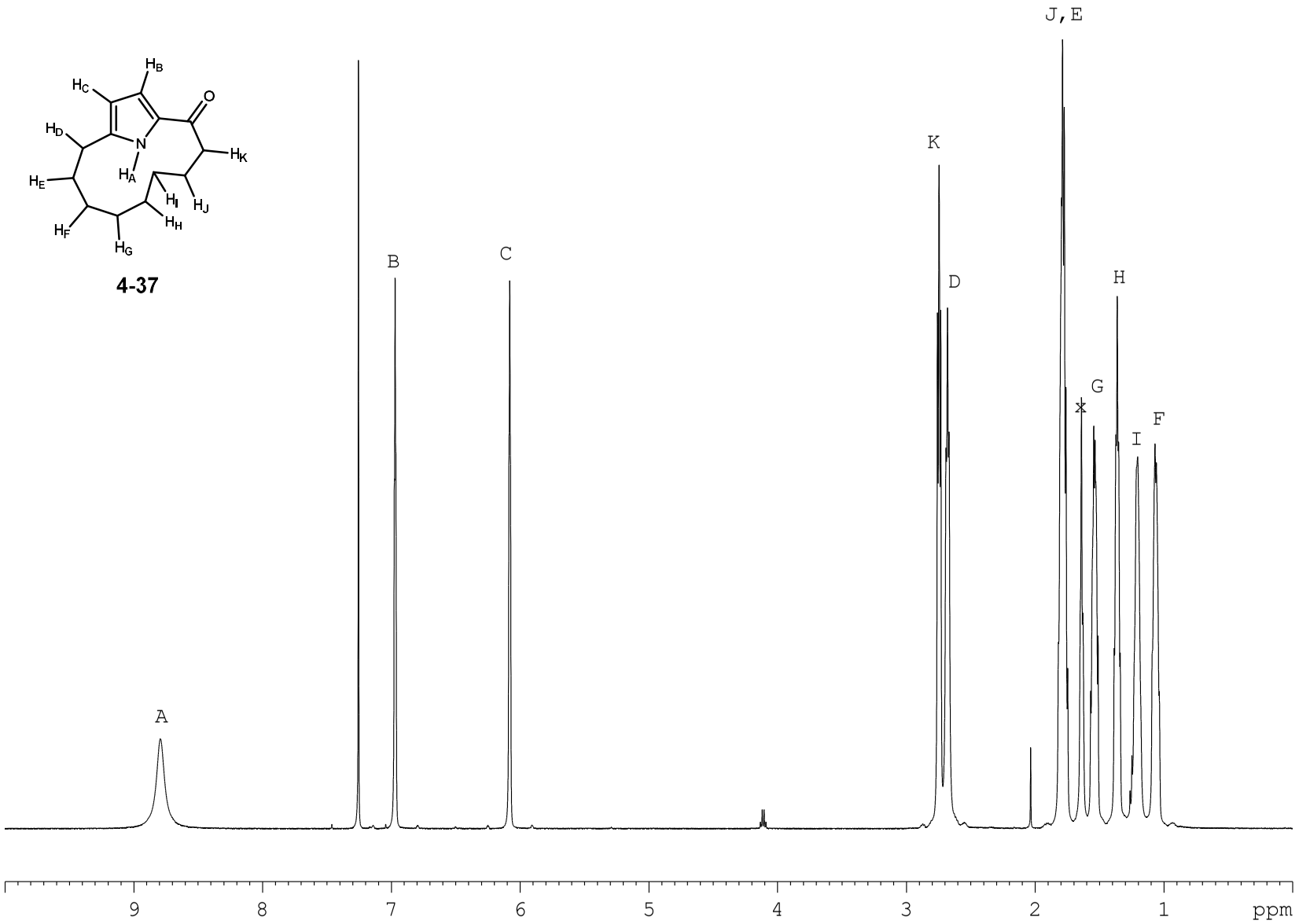
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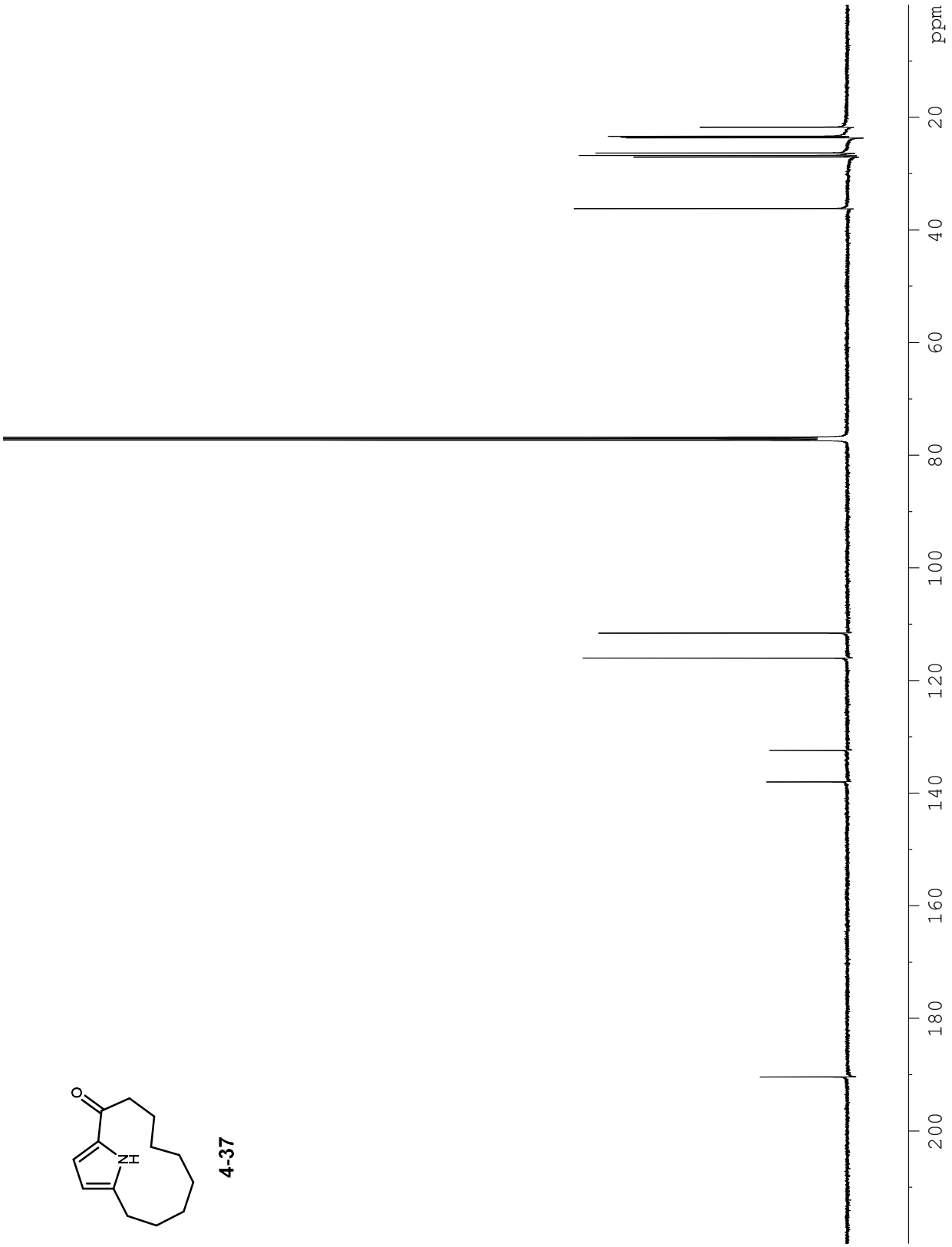

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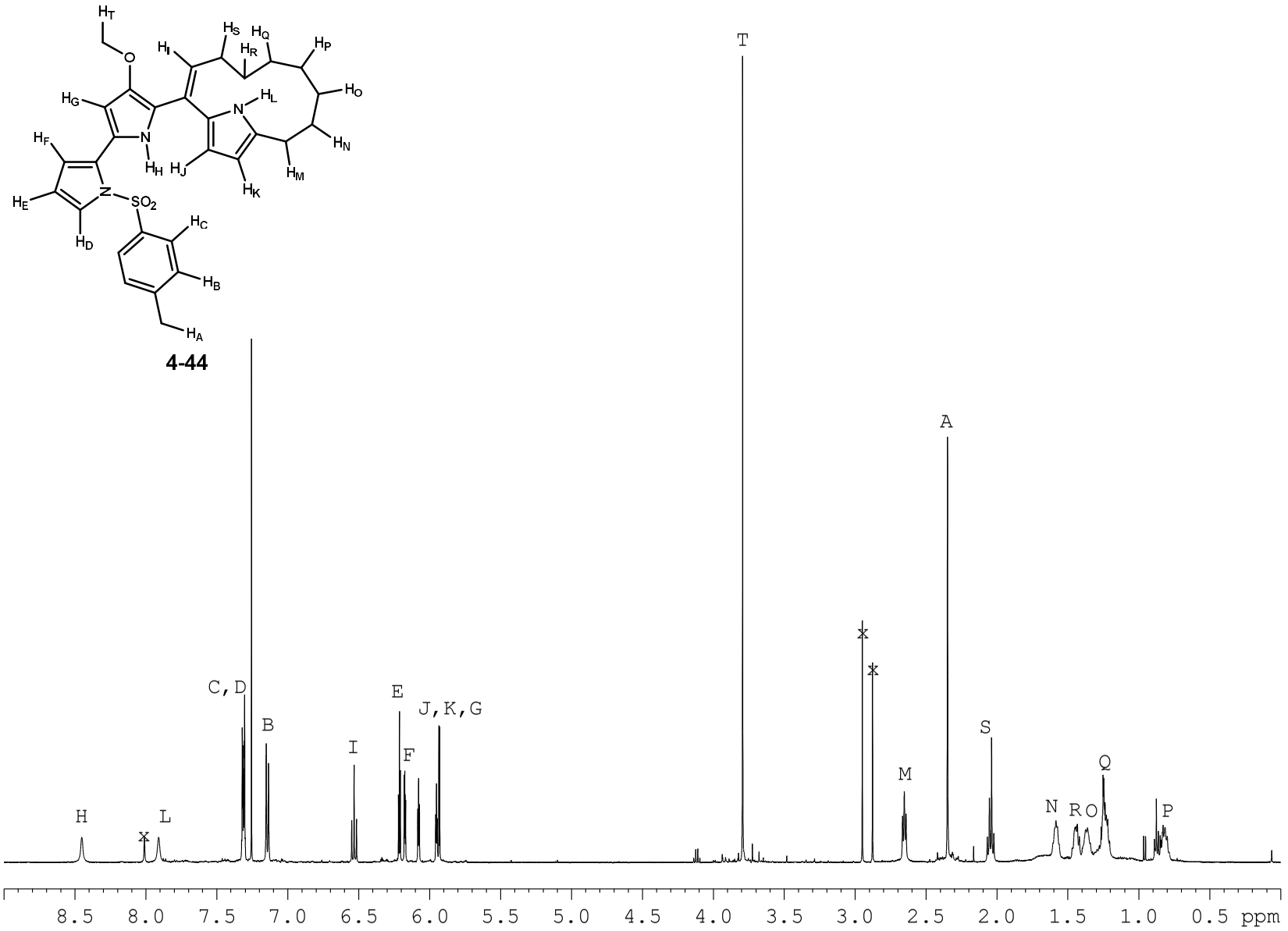
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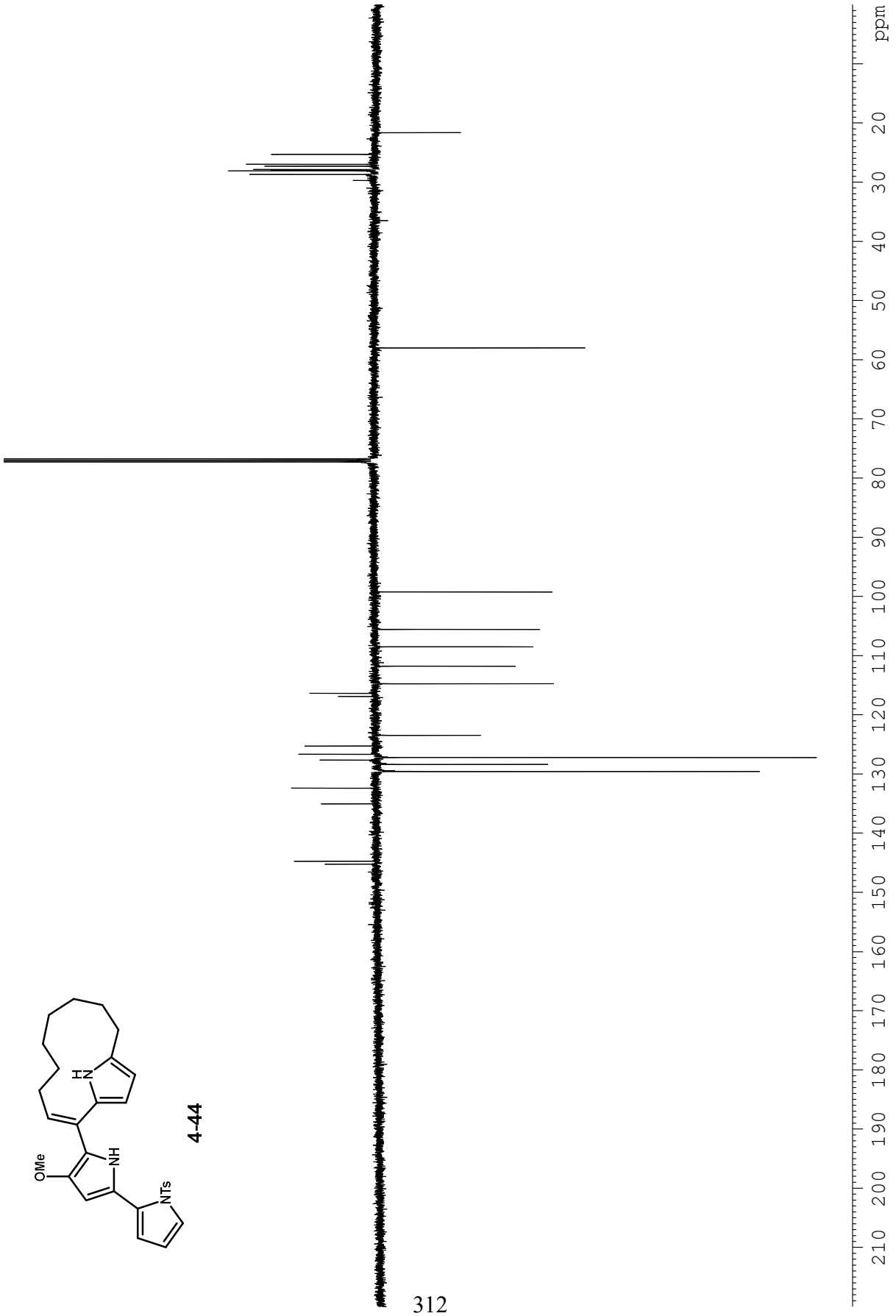
4-44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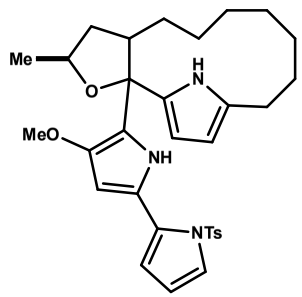
4-44



4-46

5. Chapter Five – A Formal Approach to Roseophilin

Tyler Allred, Robert Craig Clark III, and Patrick Harran

5.1. Introduction

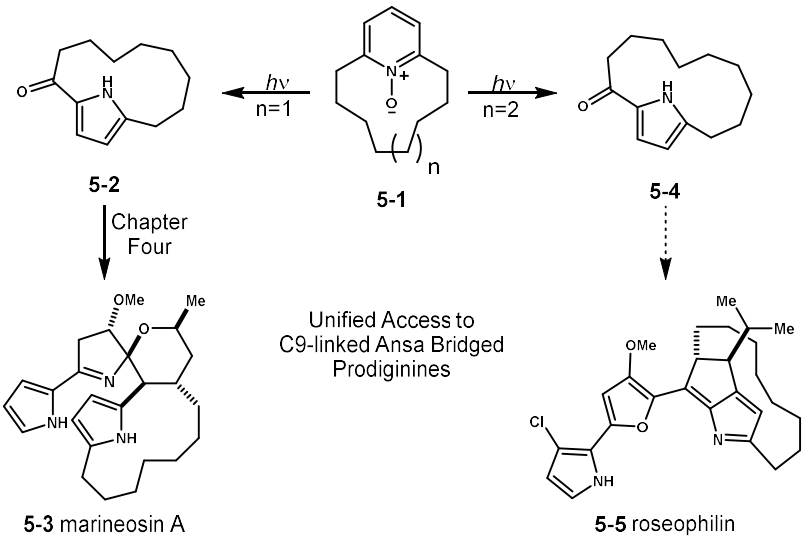


Figure 5.1. Proposed Access to Roseophilin via the Photochemical Rearrangement of Pyridinophane N-Oxides

Roseophilin (**5-5**, **Figure 5.1**) is a modified prodiginine alkaloid discovered in the extracts of *Streptomyces griseoviridis*.[25] Interestingly, this molecule contains the remnants of the prodiginine core, however it has been heavily modified to produce a chlorinated pyrrolofuran attached to a tricyclic ansa bridged pyrrolophane. Biosynthetic studies and the isolation of related structures have shown that **5-5** derives from a traditional prodiginine framework and the modifications occur after ansa bridge construction (see Chapter 1).[2] The intricate structure of **5-5** when coupled with its reported biological activity have made it an attractive target for chemical synthesis. With the exception of our approach reported in 2013, all other constructions of **5-5** were formal in nature focusing on the construction of Fürstner's tricyclic acyl pyrrolophane (**5-7**).[26–28,83,94–98,102,104] This approach requires formation of organocerium **5-6**, a substance that requires highly specialized conditions for adequate formation and efficient addition to **5-7**. Our 2013 synthesis circumvented

this issue by delaying the macrocyclic ring closure until late in the construction, akin to the biosynthetic production of the ansa bridge. This key ring closure was facilitated by an N-O phosphoryl group transfer and subsequent elimination to render the macroaldolization irreversible affording **5-9**. Macrocyclic enone was elaborated to roseophilin over several steps.

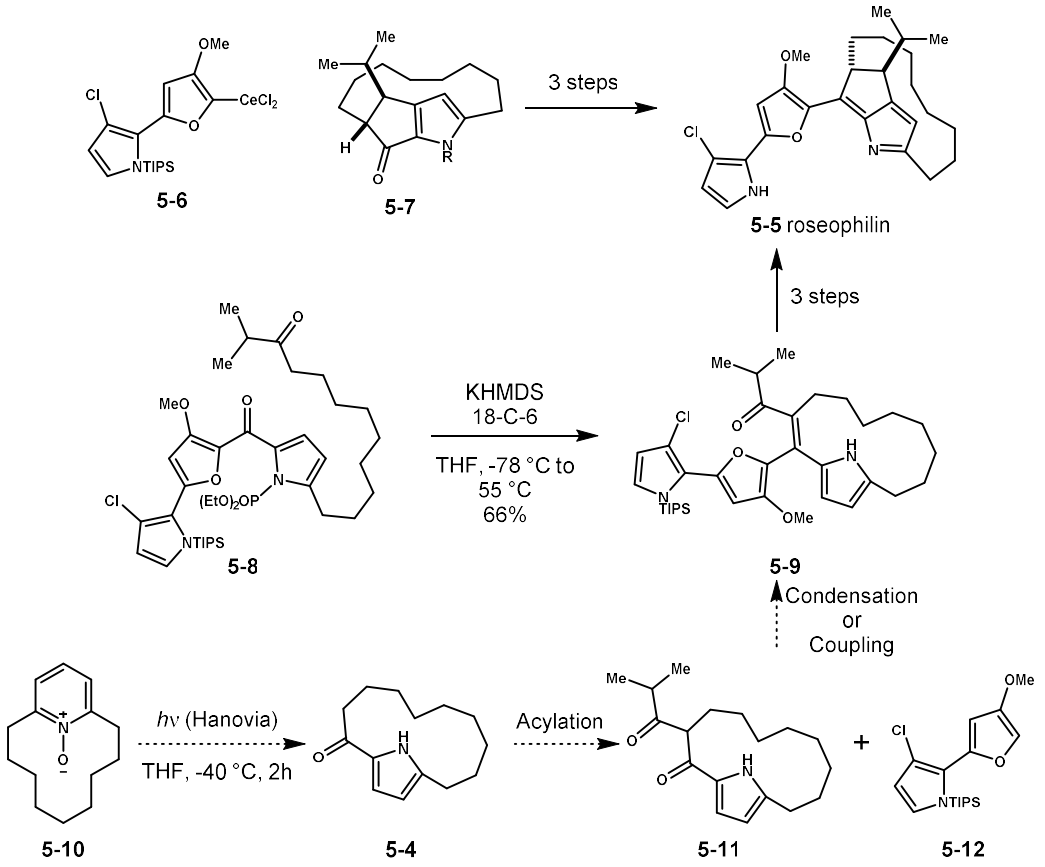


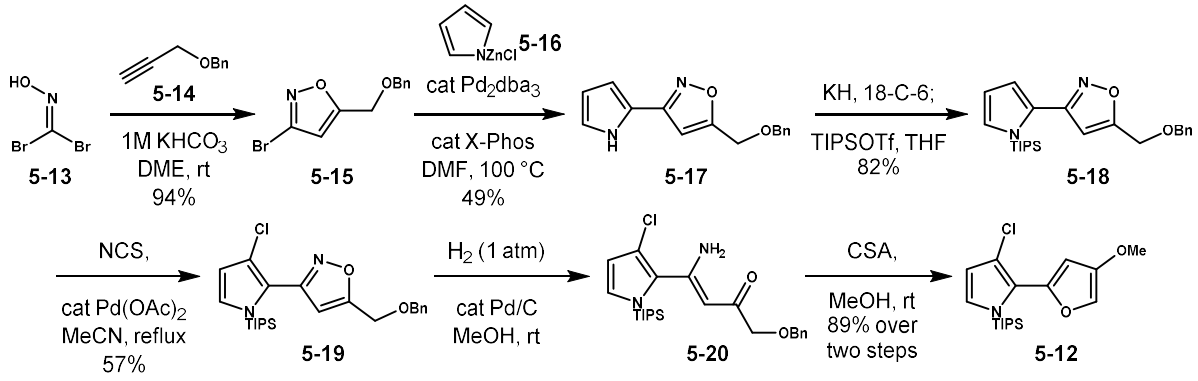
Figure 5.2. Fürstner's End Game to Roseophilin (**5-5**), Harran's 2013 Construction, and the Proposed Formal Approach Based on the Photoinduced Rearrangement of Pyridinophane N-Oxides

Our original goal was to develop a modular approach to the C-9 linked ansa bridged prodiginines that could be utilized for the construction of **5-5** and **5-3**. However after experiencing considerable difficulty in application of our late stage macrocyclization strategy developed for roseophilin (**5-5**) to the marineosin pyrrolophane ring system (**5-3**, see Chapters 2 and 3), it was found that acyl pyrrolophane **5-2** could be constructed via a photochemical rearrangement of pyridinophane N-

oxide prototype **5-1** (Chapter 4). The production of pyrrolophane **5-2** allowed for facile access to the marineosin scaffold. It was postulated that this powerful method could be utilized as a platform to access a variety of pyrrolophane ring sizes, including the transformation of **5-10** to **5-4**, which would correspond to the roseophilin pyrrolophane ring system. When considering our 2013 approach, we postulated that macrocyclic enone **5-9** could be intercepted via an alternate route which starting from pyridinophane N-oxide **5-10**. The optimized irradiation conditions would convert this material to pyrrolophane **5-4** and a simple acylation would afford coupling precursor **5-11**. This approach was anticipated to be shorter than our previously reported synthesis and, more importantly, establish a unified approach to the C9-linked ansa bridged prodiginines. Herein, we demonstrate a concise and convergent synthetic preparation of the natural product roseophilin **5-5**.

5.2. Results and Discussion

5.2.1. Construction of the Pyrrolofuran Segment

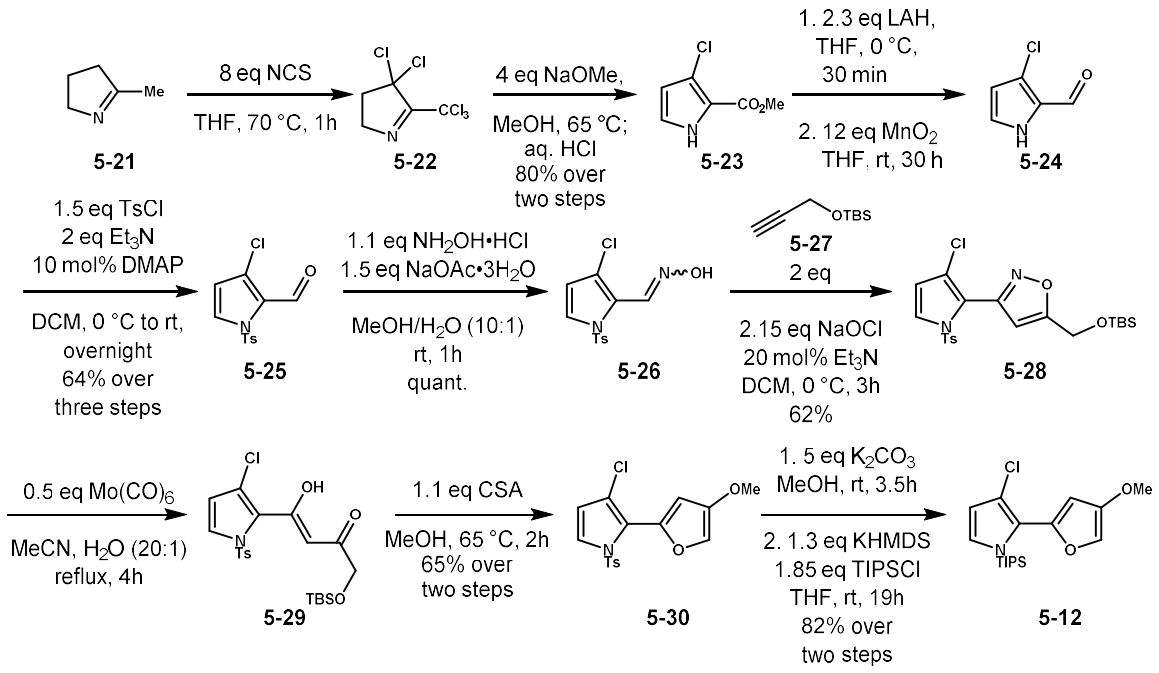


Scheme 5.1. Original Approach to Pyrrolofuran **5-15**

During our initial studies aimed at roseophilin, we developed a novel approach to the pyrrolofuran segment, which relied on a directed C-H chlorination and internal cyclocondensation (**Scheme 5.1**, see Chapter 1).[82,83] While this route was concise and high yielding, there were issues with reproducibility and scalability, especially at the chlorination step. Therefore, we sought to develop an alternate route that avoided these issues.

When considering the bipyrrole construction utilized in the synthesis of marineosin A (see Chapter 2), it was determined that a pyrrolofuran variant could be achieved if a method for the reliable generation of **5-24** was available. A scalable procedure for the synthesis of **5-23** had been reported (**Scheme 5.2**).[281] Exhaustive allylic chlorination of 2-pyrroline (**5-21**) afforded intermediate **5-22**, which when treated with sodium methoxide provided **5-23**. This route could be effectively scaled to produce **5-23** in decagram quantities. The ester was then reduced with excess LAH followed by immediate oxidation of the unstable primary carbinol with MnO_2 to afford aldehyde **5-24**, which was then protected as the tosyl derivative. The aldehyde was then converted to oxime **5-26** under mildly acidic conditions, which was then subjected to the aforementioned oxidation/dipolar cycloaddition conditions with **5-27** as the dipolarophile partner. This process afforded isoxazole

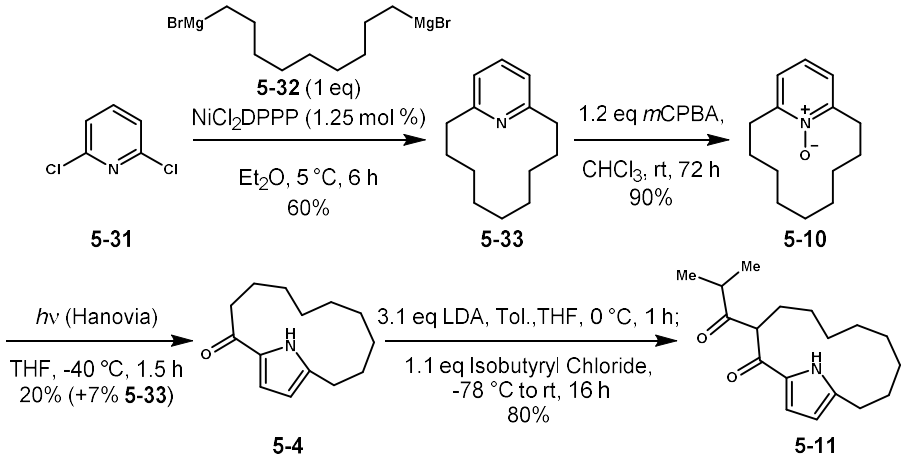
5-28 in good yield, which can then be elaborated to **5-30** via a $Mo(CO)_6$-mediated reduction and the acid-catalyzed cyclocondensation.[82,114] A simple protecting group swap could be achieved by detosylation with K_2CO_3 in MeOH and silylation with TIPSCl to provide **5-12**.



Scheme 5.2. Alternate Access to Pyrrolofuran **5-15**

Although this approach is longer than our previous approach, it is more reliable and scalable. The troublesome directed C-H chlorination step has been circumvented by installment of the chlorine in the first step. This route allowed for the production of multigram quantities of **5-12**, which could be stored as a stock solution in THF or benzene at -20 °C for extended periods.

5.2.2. Synthesis and Acylation of Ketopyrrolophane 5-4

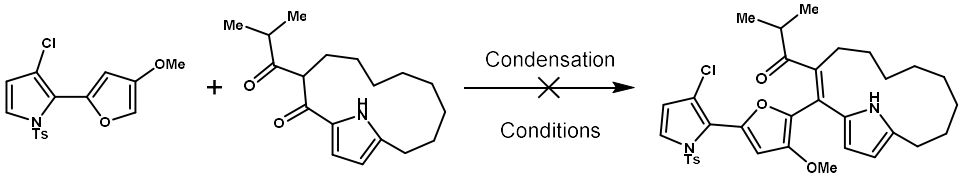


Scheme 5.3. Construction of β-diketone **5-30**

The construction of acyl pyrrolophane **5-4** was analogous to that described for the marineosin ring system (see Chapter 4). A nickel-catalyzed Kumada cyclocoupling of di-Grignard **5-32**, the one carbon homolog of the di-Grignard required for the marineosin pyrrolophane, to 2,6-dichloropyridine constructs pyridinophane **5-33**.[261,264] Not surprising, the average yield for this approach is better than that of the marineosin system, due to less strain in the formation of a larger pyridinophane. The pyridinophane was converted to pyridinophane N-oxide **5-10** without issue by treatment with *m*CPBA. This material was then subjected to our optimized irradiation conditions to induce the rearrangement to acyl pyrrolophane **5-4** in 20% yield on the first attempt. Initially, we utilized ethyl isobutyrate (not shown) as an acylating agent, which provided clean full conversion to **5-11** on the first attempt. However, reattempting this procedure revealed the capricious nature of the reaction, which seemed to only progress to 50% conversion at best in later attempts. Fortunately, after a small screen of acylating agents (i.e. isobutyryl anhydride, isobutyryl chloride, and isobutyryl cyanide), it was determined that isobutyryl chloride could be utilized to reliably generate **5-11** with full conversion and high yield. Interestingly, **5-11** exists exclusively in the ketone tautomer, which is unusual for a β-diketone. All that remained at this stage for the

formal synthesis of roseophilin (**5-5**) was identifying conditions that could facilitate the net condensation between **5-11** and **5-12**.

5.2.3. Attempts to Complete the Roseophilin Formal Synthesis by Combination of β-Diketone 5-11 and Pyrrolofuran 5-12

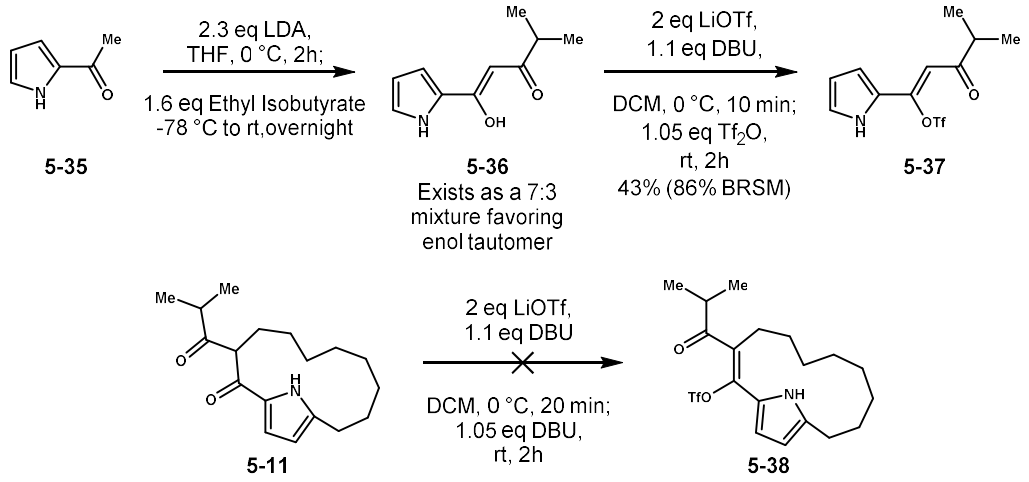


5-30 5-11 5-34

Scheme 5.4. Attempts at Direct Condensation

A net condensation reaction is the last transformation required to complete the formal approach to roseophilin and achieve our initial goal of developing a modular route that can access all known C9 linked ansa bridged prodiginines. Early studies by Terashima and Fürstner showed that the direct condensation of the pyrrolofuran segment and the tricyclic pyrrolophane ketone (see Chapter 1) was not a feasible process.[26,80,100] However, it was postulated that condensation might be possible in the case of **5-30**, due to the pyrroloketone being activated by the α-isobutyryl group. Surprisingly, there was only one reported method of the direct condensation of furan derivatives with β-diketones, which utilized catalytic amounts of AgOTF.[282] However, Marinelli and coworkers also reported that a variety of other Lewis and protic acids work with varying degrees of success.[282] Several attempts with AgOTf and other acids resulted either in recovery of starting **5-11** or decomposition into intractable mixtures. At this stage, it was decided that the β-diketone moiety would need to be activated in some manner to allow for efficient coupling. It was postulated that metalation α to the furan oxygen of **5-12**, a process which we were familiar with and utilized

in our 2013 synthesis, and transition metal mediated cross coupling with an enol derivative of **5-11** would be a viable method of combining the fragments to produce **5-9**.



Scheme 5.5. Construction of Triflation Model and Attempts to Convert **5-11** to **5-38**

A model system was produced in order to determine what conditions could efficiently activate the β-diketone with the correct regiochemistry. 2-Acetylpyrrole (**5-35**) was deprotonated with LDA and then acetylated with ethyl isobutyrate to afford β-diketone **5-36**. Several conditions were screened for the production of an activated enone.[283–286] Most conditions resulted in complex mixtures or recovery of starting material. Fortunately, the method developed by Pale and coworkers allowed for the production of enol triflate **5-37** albeit with only 50% conversion.[284] *These conditions were not optimized for this substrate.* These conditions were then examined with **5-11** and only resulted in recovery of the starting material. Upon further consideration, this lack of reactivity is not surprising. The model **5-36** exists as a tautomeric mixture preferring the enol form, which allows for facile generation of the enolate under the reaction conditions. On the other hand, diketone **11** exists solely in the ketone tautomer, which indicates that energy gained from producing a conjugated system is not sufficient to overcome the strain of the ansa bridge. *Efforts to identify sufficient conditions for activating **5-11** are ongoing.*

5.2.4. Future Research: End Game Strategy for the Formal Completion of Roseophilin and the Exploration of Novel C9-Linked Ansa Bridged Prodiginines as BH3 Mimetics

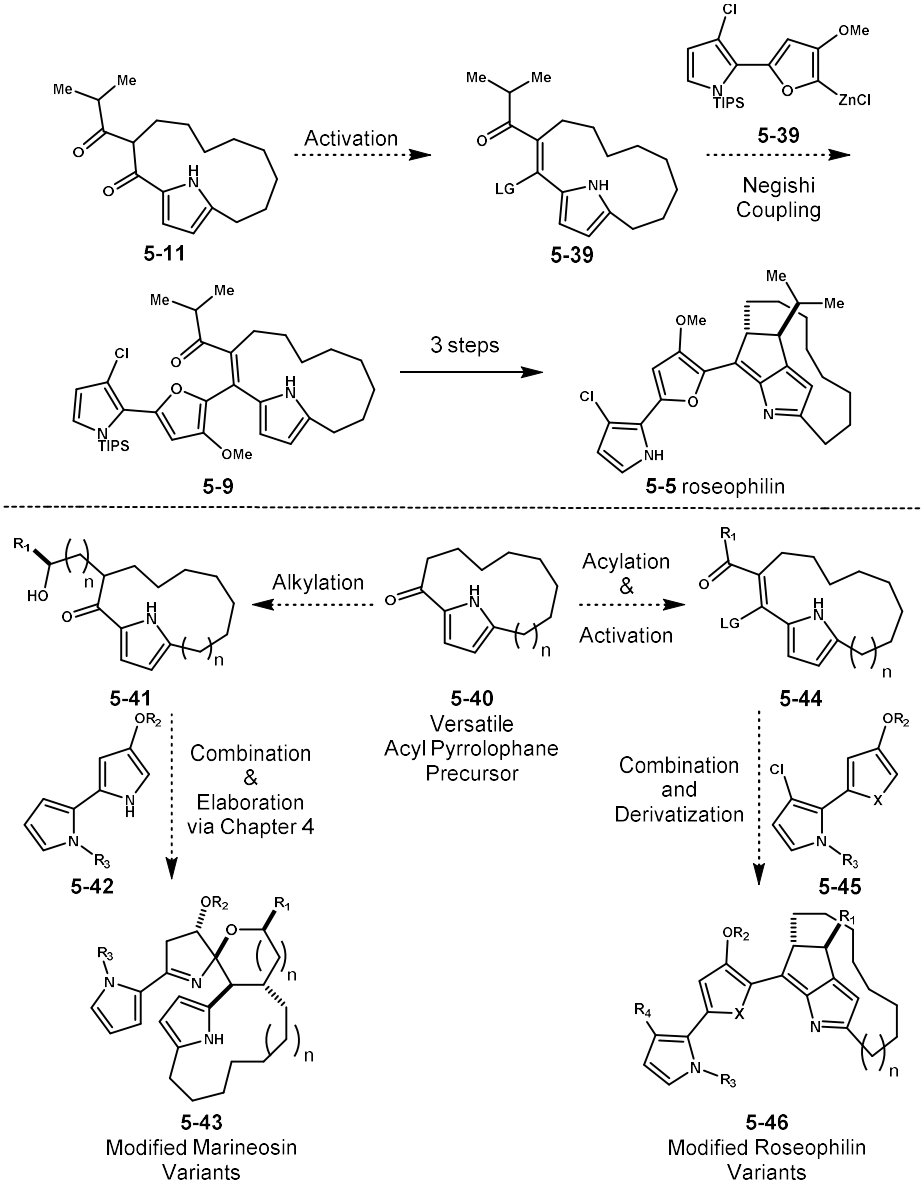


Figure 5.3. Future Research for the Completion of Roseophilin and Development of Novel C9 Linked Analogs

Efforts to complete the formal synthesis of roseophilin (**5-5**) are ongoing. This approach would hinge on identifying an appropriate method for activating the β-diketone to produce enone **5-39**. This material could then be subjected to a transition metal catalyzed Negishi coupling, which we are confident will provide access to macrocyclic enone **5-9**. This material could then be elaborated

to roseophilin via our published procedures. Upon completion of the formal approach to roseophilin, we will have established our initial goal of developing a modular unified approach to the C9-linked ansa bridged prodiginines. This achievement will enable the facile development of marineosin and roseophilin analogs at key positions in the structure. Namely, the pyrrolophane ring size (i.e. **5-40**) could be modified to alter conformation and the prodiginine cores could be decorated with a variety of substituents. The modular nature of the bipyrrole/pyrrolofuran synthesis allows for the incorporation of new groups at the B ring ether and the A ring nitrogen (i.e. **5-42** and **5-45**). Choice of pyrrolophane alkylation agent would allow for the examination of different sized spiroiminals in marineosin analogs (**5-43**). In the case of roseophilin, either the pyrrolofuran or bipyrrole coupling partner could be utilized to produce the traditional prodiginine core or the roseophilin heterocyclic system (**5-46**). The goal of these modification would be to explore the potential of these structures to mimic the BH3 helical motif, which would impart them with activity against BCL-2 proteins.

5.3. Conclusion

We have demonstrated that the photoinduced rearrangement of pyridinophane N-oxides into acyl pyrrolophanes is a versatile method that can be utilized in the construction of C9-linked ansa bridged prodiginines. We originally examined this process in the context of a synthetic route to marineosin A (**5-3**, see Chapter 4). The success of the method caused us to consider its utility in the context of roseophilin (**5-5**), a compound that we had already constructed via a macroaldolization approach (see Chapters 1 and 2). Irradiation of pyridinophane N-oxide **5-10** resulted in the isolation roseophilin pyrrolophane **5-4**, which provided support that this method could help achieve our initial goal of a unified approach to C9-linked ansa bridged prodiginines. Acyl pyrrolophane could be readily acylated to afford diketone **5-11**, which is separated from **5-9** by a net condensation. While a direct condensation seems unfeasible, a two step approach in which the system is activated and then coupled to pyrrolofuran **5-12** is promising. Efforts to complete the formal synthesis of roseophilin through generation of intermediate **5-9** are ongoing in our laboratory, which we are confident will be accessed soon.

5.4. Experimental

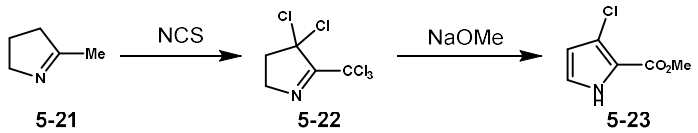
5.4.1. Materials and Methods

All reactions were carried out using oven- or flame-dried glass and a magnetic stir bar under an atmosphere of argon (Ar) unless otherwise indicated. Tetrahydrofuran (THF), diethyl ether (Et_2O), methylene chloride (DCM), toluene, acetonitrile (MeCN), and methanol were dried by passage through activated alumina using a GlassContour® solvent drying system. Triethylamine, and diisopropylamine were distilled from CaH_2 under inert atmosphere prior to use. All other commercial reagents and catalysts were used as received unless otherwise indicated. Photoreactions were carried out in either a standard Ace Chem Glass immerision well photoreactor or the low temperature immersion well photoreactor with a Hanovia 450W mercury arc lamp. Also, photoreactions were examined in a Rayonet photoreactor with a 254 and 300 nm bulb set.

NMR spectra were recorded on Bruker Advance spectrometerrs (400 MHz, 500 MHz) and are reported as δ values in ppm relative to $CDCl_3$ (calibrated to 7.27 ppm in ^1H NMR and 77.16 ppm in ^{13}C NMR, unless otherwise indicated) and were conducted at room temperature (unless otherwise indicated). ^1H NMR coupling constants are reported in Hz. Splitting patterns are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), septet (sept), multiplet (m), broad (br), apparent (app), and combinations thereof. Column chromatography was conducted on silica gel 60 (240-400 mesh) purchased from Silicycle or neutral aluminum oxide (activated, Brockmann I) purchased from Sigma Aldrich. Thin layer chromatography (TLC) was performed using pre-coated, glass-backed plates (SiO_2, 60 PF254, 0.25 mm or neutral Al_2O_3, 0.25 mm) and visualized using a combination of UV, anisaldehyde, and potassium permanganate staining.

5.4.2. Experimental Procedures and Characterization

methyl 3-chloro-1*H*-pyrrole-2-carboxylate (5-23)



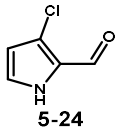
A 1 L flask was equipped with a reflux condenser and charged with NCS (80 g, 599.11 mmol, 8 eq), which was then suspended in THF (190 mL). 2-methylpyrroline **5-21** (7.1 mL, 74.98 mmol) was then added dropwise (*CAUTION*: Large Exotherm). After addition was complete, the reaction was refluxed for 2h and then allowed to cool to room temperature. The mixture was diluted with H_2O (120 mL) and then extracted with hexanes. The combined organics were then washed with brine, dried over Na_2SO_4, filtered, and concentrated to a red oil, which was used directly in the next step.

A freshly prepared solution of NaOMe (6.9 g of Na in 110 mL of MeOH, 300 mmol, 4 eq) was cooled to 0 °C and crude **5-22** was added slowly to the mixture. The reaction warms during the addition. After the addition was complete, the reaction was stirred for 2h at room temperature. The reaction was then diluted with H_2O (30 mL) and then slowly acidified by the addition 12M HCl. The reaction was then concentrated and extracted with EtOAc several times. The combined organics were then washed with sat. aqueous $NaHCO_3$ and brine. The organics were then dried over $MgSO_4$, filtered, and concentrated to afford a crystalline solids and a red oil. The mixture was recrystallized with hexanes/Et_2O (2:1, 30 mL) to give **5-23** (5.2 g, 43%) as light brown crystals. The mother liquor could be purified by flash column chromatography (SiO_2, 5:1→3:1 Hexanes/EtOAc) to provide additional **5-23** (4.4 g, 80% combined overall yield).

methyl 3-chloro-1*H*-pyrrole-2-carboxylate (5-23):

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 9.07 (bs, 1H), 6.86 (t, J = 3.0 Hz, 1H), 6.25 (t, J = 3.0 Hz, 1H), 3.89 (s, 3H)

3-chloro-1*H*-pyrrole-2-carbaldehyde (5-24)



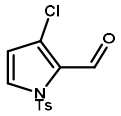
To a suspension of LAH (4.358 g, 114.85 mmol, 2.37 eq) in THF (200 mL) at 0 °C, **5-23** (7.70 g, 48.26 mmol) as a solution in THF (50 mL) was added dropwise over 1h. The reaction was then allowed to warm to room temperature over 30 min. After starting material was consumed as determined by TLC, H_2O (5 mL) was added dropwise followed by aqueous NaOH (4M, 5 mL) and finally an additional portion of H_2O (15 mL) was added. The mixture was then stirred for 20 min. The reaction was then filtered over Celite® and the solids were washed with THF to provide a yellow filtrate solution.

To the filtrate solution, MnO_2 (25.37 g, 268 mmol, 5.5 eq) was added in one portion and the mixture was stirred at room temperature overnight (~16 h). An additional portion of MnO_2 (25.0 g, 287.5 mmol, 6 eq) was added and the mixture was stirred for 6 h. A final portion of MnO_2 (10.0

g, 115 mmol, 2.4 eq) was added and the mixture was stirred overnight (~16h). The mixture was then filtered over Celite® and the solids were washed with Et_2O. The filtrate was concentrated to an unstable brown oil that was used immediately.

3-chloro-1*H*-pyrrole-2-carbaldehyde (5-24):
^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 9.71 (s, 1H), 9.50 (bs, 1H), 7.11-7.04 (m, 1H), 6.33 (t, *J* = 2.6 Hz, 1H)

3-chloro-1-tosyl-1*H*-pyrrole-2-carbaldehyde (5-25)



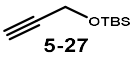
5-25

To a solution of crude **5-24** (Assume 100% from previous step, 48.26 mmol) in DCM (50 mL, 1M) at 0 °C, DMAP (0.58 g, 4.76 mmol, 10 mol%) and Et_3N (13.8 mL, 98.46 mmol, 2 eq) were added followed by TsCl (14.243 g, 74.70 mmol, ~1.5 eq) added in several portions. The reaction was then allowed to warm to room temperature overnight (~16 h). The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (100 mL) and the mixture was vigorously stirred for 20 minutes. The reaction was then filtered through Celite® and the solids were washed with DCM. The organics were separated and washed with aqueous 1M HCl and brine. The organics were dried over $MgSO_4$, filtered, and concentrated to afford **5-25** (8.8 g, 64% over three steps) as a brown solid.

3-chloro-1-tosyl-1*H*-pyrrole-2-carbaldehyde (5-25):
^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 9.88 (s, 1H), 7.85 (d, *J* = 8.4 Hz, 2H), 7.67 (d, *J* = 3.4 Hz, 1H), 7.33 (d, *J* = 8.4 Hz, 2H), 6.38 (d, *J* = 3.4 Hz, 1H), 2.42 (s, 3H)

^{13}C NMR (125 MHz, $CDCl_3$): 176.8, 146.1, 134.4, 130.3, 129.9, 128.5, 128.2, 127.1, 113.0, 21.7

***tert*-butyldimethyl(prop-2-yn-1-yloxy)silane (5-27)**

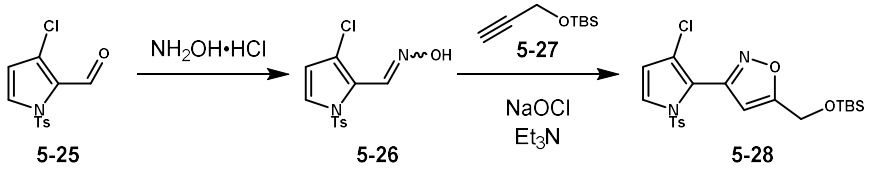


5-27

To a mix of propargyl alcohol (21 mL, 363.7 mmol) and imidazole (36 g, 528.9 mmol, 1.45 eq) in DCM (600 mL, 0.6M) at 0 °C, TBSCl (64 g, 424.6 mmol, 1.17 eq) was added. The resulting suspension was stirred at 0 °C for 2h. The reaction was then quenched by the addition of sat. aqueous NH_4Cl. The aqueous layer was then extracted with Et_2O several times. The combined organics were washed with brine, dried over $MgSO_4$, filtered and carefully concentrated. The crude mixture was then distilled (95-100°C, 195 mbar) to afford **5-27** (59.7 g, 96%) as a clear oil.

***tert*-butyldimethyl(prop-2-yn-yloxy)silane (5-27):**
^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 4.31 (d, *J* = 2.4 Hz, 2H), 2.38 (t, *J* = 2.4 Hz, 1H), 0.91 (s, 9H), 0.12 (s, 6H)

Oxime Formation and Dipolar Cycloaddition to Produce Isoxazole (5-28)



5-25 5-26 5-28

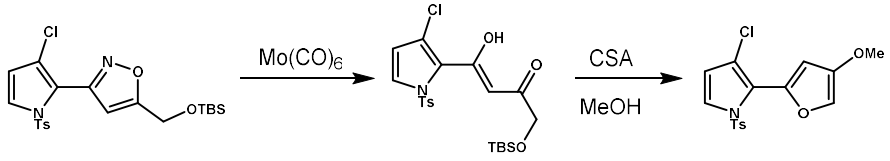
To a solution of **5-25** (8.8 g, 31.01 mmol) and NaOAc·3H_2O (6.338 g, 46.57 mmol, 1.5 eq) in MeOH/H_2O (154 mL, 10:1, 0.2 M), NH_2OH·HCl (2.379 g, 34.23 mmol, 1.1 eq) was added. The reaction was stirred for 1h. The reaction mixture was then concentrated to brown solids. The solids were then taken up in $CHCl_3$ and washed with sat. aqueous $NaHCO_3$. The organics were then dried over $MgSO_4$, filtered, and concentrated to afford crude **5-26**, which was used directly in the next step.

To a solution of crude **5-26** (assume 100% from previous step, 31.01 mmol) in DCM/H_2O (154 mL, 10:1, 0.2M), Et_3N (0.87 mL, 6.24 mmol, 20 mol %) and **5-27** (12.6 mL, 66.42 mmol, 2.15 eq) were added. The mixture was then cooled to 0 °C. With vigorous stirring, aqueous NaClO (8.25%, 63 mL, 66.33 mmol, 2.15 eq) was added dropwise to mixture over 30 minutes. The mixture was then warmed to room temperature and stirred for 3h. The reaction was then diluted with H_2O (100 mL). The aqueous layer was then washed with DCM (100 mL x 3) and the combined organics were washed with brine. The organics were then dried over $MgSO_4$, filtered, and concentrated to afford a red oil. The crude was purified by flash column chromatography (SiO_2, 50:1→30:1→20:1→10:1 Hexanes/EtOAc) to afford **5-28** (9.0 g, 62% over two steps) as an orange oil.

5-(((tert-butyldimethylsilyl)oxy)methyl)-3-(3-chloro-1-tosyl-1*H*-pyrrol-2-yl)isoxazole (5-28):
^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.58 (d, *J* = 8.5 Hz, 2H), 7.42 (d, *J* = 3.3 Hz, 1H), 7.25 (d, *J* = 8.5 Hz, 2H), 6.43 (t, *J* = 0.8 Hz, 1H), 6.35 (d, *J* = 3.3 Hz, 1H), 4.85 (d, *J* = 0.8 Hz, 2H), 2.39 (s, 3H), 0.94 (s, 9H), 0.14 (s, 6H)

^{13}C NMR (125 MHz, $CDCl_3$): 171.7, 152.9, 145.7, 134.8, 129.9, 129.9, 127.7, 127.6, 123.9, 121.1, 118.4, 113.2, 105.0, 57.3, 25.7, 21.7, 18.3, -5.3

Reduction of Isoxazole 5-28 and Cyclocondensation to Form Pyrrolofuran 5-30



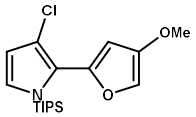
5-28 5-29 5-30

To a degassed mixture of MeCN:H_2O (10:1, 32 mL, 0.1M), $Mo(CO)_6$ (0.4542 g, 1.72 mmol, ~50 mol%) was added. The mixture was then heated to 90 °C for 20 minutes until the solids dissolved. The mixture was then cooled to 50 °C and **5-28** (1.50 g, 3.21 mmol) in MeCN (5 mL) was added. The mixture was then heated to 90 °C for 4h. TLC indicated that the starting material was consumed. The reaction was then cooled to room temperature and concentrated to a black oil. The crude was taken up EtOAc and SiO_2 (~2 g) was added. The mixture was stirred for 2h at room temperature and then filtered over Celite®. The solids were washed with copious amounts of EtOAc and the filtrate was concentrated to a brown solid, which was used directly in the next step.

To a solution of crude **5-29** (assume 100% from previous step, 3.21 mmol) in MeOH (20 mL, 0.15M), CSA (0.8205 g, 3.53 mmol, 1.1 eq) was added. The mixture was then heated to 65 °C for 1.5h. The reaction was then concentrated to a black paste and then taken up in EtOAc. The mixture was washed with sat. aqueous $NaHCO_3$. The organics were dried over $MgSO_2$, filtered and concentrated to a red oil. The crude oil was purified by flash column chromatography (SiO_2, 10:1→4:1→3:2→2:3 Hexanes/EtOAc) to afford **5-30** (0.7388 g, 65% over two steps) as a yellow oil that darkens over time. This material is best stored as a stock solution in THF or Toluene at -20 °C.

3-chloro-2-(4-methoxyfuran-2-yl)-1-tosyl-1*H*-pyrrole (5-30):
^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.55 (d, *J* = 8.5 Hz, 2H), 7.40 (d, *J* = 3.3 Hz, 1H), 7.25 (d, *J* = 8.5 Hz, 2H), 7.14 (d, *J* = 0.9 Hz, 1H), 6.34 (d, *J* = 0.9 Hz, 1H), 6.30 (d, *J* = 3.4 Hz, 1H), 3.76 (s, 3H), 2.41 (s, 3H)

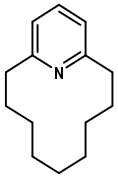
3-chloro-2-(4-methoxyfuran-2-yl)-1-(triisopropylsilyl)-1*H*-pyrrole (5-15)



To a solution of **5-25** (0.890 g, 2.53 mmol) in MeOH (16 mL, 0.2 M), K_2CO_3 (1.8 g, 13.0 mmol, 5 eq) was added in one portion. The reaction was then stirred at room temperature for 3.5 hours. The mixture was then diluted with EtOAc and H_2O. The aqueous layer was washed with EtOAc and the combined organics were washed with sat. aqueous NH_4Cl and dried over $MgSO_4$. The organics were filtered and concentrated to afford crude pyrrolofuran.
This material was immediately dissolved in THF (3 mL, 0.8M) and cooled to 0 °C. KHMDS (0.7M in toluene, 4.7 mL, 3.3 mmol, 1.3 eq) was added dropwise. The reaction mixture turned red. After 30 minutes at 0 °C, TIPSCl (1.0 mL, 4.67 mmol, 1.85 eq) was added dropwise. The reaction was then warmed to room temperature and stirred for 19 hours. The reaction was then quenched with sat. NH_4Cl and extracted with EtOAc. Organics were dried over $MgSO_4$, filtered and concentrated. The crude oil was purified by flash column chromatography (SiO_2, 50:1→30:1→20:1 Hexanes/EtOAc) to afford **5-15** (0.740 g, 82%) as a yellow oil.

3-chloro-2-(4-methoxyfuran-2-yl)-1-(triisopropylsilyl)-1*H*-pyrrole (5-15):
^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.12-7.10 (m, 1H), 6.82 (d, *J* = 3.0 Hz, 1H), 6.36-6.34 (m, 1H), 6.27 (d, *J* = 3.0 Hz, 1H), 3.75 (s, 3H), 1.26 (heptet, *J* = 7.3 Hz, 3H), 1.06 (d, *J* = 7.3 Hz, 18 H)

[9](2,6)-pyridinophane (5-33)



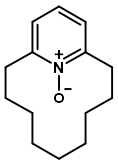
5-33

To a suspension of freshly activated Mg (5.86 g, 244.16 mmol, 2.2 eq) in Et_2O (250 mL), a small crystal of I_2 was added and the mixture was stirred for 5 minutes at room temperature. 1,9-dibromononane (24.8 mL, 121.9 mmol, 1.2 eq) was added dropwise over 1h, while allowing the mixture to gently reflux. After the addition was complete, the mixture was refluxed for 2h and then allowed to cool to room temperature. The stirring is shut off and the mixture settles into a biphasic mixture with a clear to slightly cloudy top layer and a dark gray viscous bottom layer.
Another flask is charged with 2,6-dichloropyridine **4-39** (14.86 g, 100.41 mmol) and $NiCl_2$DPPP (0.718 g, 1.32 mmol, 1.25 mol%). The solids were then dissolved in Et_2O (1 L, 0.1M) and cooled to 5 °C. The di-Grignard was then added dropwise over 6h while the reaction was maintained between 5-10 °C. After the addition was complete, the reaction was allowed to warm to room temperature overnight (~16h). The reaction was then quenched by pouring into ice water. The mixture was then filtered over Celite® and the filtrate was extracted with Et_2O several times. The combined organics were then washed with brine, dried over $MgSO_4$, filtered, and concentrated to afford an orange oil. The residue was purified by flash column chromatography (SiO_2, 50:1→40:1→30:1 Hexanes/EtOAc) to afford **4-36** (9.4555 g, 47%) as a clear oil.

[9](2,6)-pyridinophane (5-33):
^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.44 (t, *J* = 7.7 Hz, 1H), 6.90 (d, *J* = 7.7 Hz, 2H), 2.83 (dd, *J* = 5.5, 7.6 Hz, 4H), 1.85 (p, *J* = 6.1 Hz, 4H), 1.34-1.16 (m, 6H), 0.87 (p, *J* = 6.7 Hz, 4H)

^{13}C NMR (125 MHz, $CDCl_3$): 161.2, 136.5, 120.7, 37.1, 25.6, 25.1, 25.0, 24.7

[9](2,6)-pyridinophane *N*-oxide (5-10)



5-10

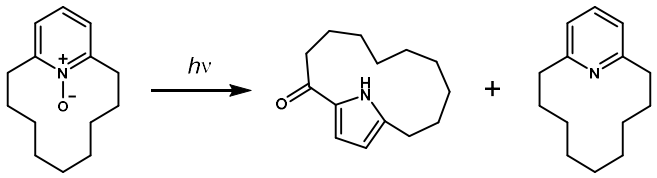
To a solution of pyridinophane **5-33** (17.8 g, 87.54 mmol) in $CHCl_3$ (120 mL, 0.7M) at room temperature, *m*-CPBA (24.3 g, 105.60 mmol, 1.2 eq) was added in three portions over 30 minutes. The mixture was then stirred at room temperature for 3 days. The mixture was diluted with $CHCl_3$ (120 mL) and K_2CO_3 (36.5 g, 264.10 mmol, 4 eq) was added in one portion. The mixture was then stirred for 2h at room temperature. The solids were then filtered and washed with $CHCl_3$. The filtrate was then washed with 1M aqueous K_2CO_3. The organics were then dried over $MgSO_4$, filtered, and concentrated. A second batch of the same size (17.8 g, 87.54 mmol) was run in parallel and combined at this stage. The combined residue was then purified by flash column

chromatography (10:1→4:1→3:2→0:1 Hexanes/EtOAc) to afford **5-10** (34.75 g, 90%) as a slight yellow oil that crystallized to an off white solid on standing or seeding.

[9](2,6)-pyridinophane *N*-oxide (5-10):
^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.09-6.96 (m, 3H), 3.55 (dt, *J* = 4.5, 13.1 Hz, 2H), 2.67-2.53 (m, 2H), 2.39 (ddd, *J* = 4.7, 10.9, 15.5 Hz, 2H), 1.60 (sextet, *J* = 7.1 Hz, 1H), 1.55-1.46 (m, 2H), 1.46-1.37 (m, 2H), 1.04-0.93 (m, 4H), 0.93-0.83 (m, 1H), 0.43-0.29 (m, 2H)

^{13}C NMR (125 MHz, $CDCl_3$): 152.9, 125.1, 123.9, 32.3, 25.5, 24.7, 23.3, 19.8

Irradiation of Pyridinophane *N*-oxide 5-10



5-10 5-4 5-33

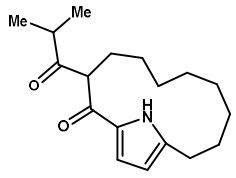
Condition 1:
A 1 L immersion well photoreactor was charged with a solution of pyridinophane N-oxide **5-10** (3.9 g, 17.78 mmol) in THF (1 L, 0.02M). The solution was cooled to -40 °C and then irradiated with a 450 W Hanovia Mercury Arc lamp for 3h. The mixture was monitored by the ^{1}H NMR spectrum analysis of aliquots. The lamp was removed and the mixture was warmed to room temperature and concentrated. The residue was then purified by flash column chromatography (SiO_2, 70:15:15 Hexanes/EtOAc/DCM) to afford **5-4** (0.8 g, 20%) as a white crystalline solid and **5-33** (0.253 g, 7%) as a clear oil. Alternatively, the crude reaction can be flushed through a SiO_2 plug with EtOAc to remove the polymer. The filtrate can be partially concentrated and then diluted with hexanes to induce precipitation and the solids can be filtered to afford pure **5-4**. The mother liquor can be purified by flash column chromatography to afford additional **5-4**.

Condition 2:
A solution of pyridinophane N-oxide **5-10** (0.02M in THF, 17.78 mmol) in quartz test tubes (10 x 100 mL) can be irradiated in a Rayonet photoreactor (254 nm bulb set) for 15 hours at room temperature. The reaction are then concentrated and purified as indicated above to afford **5-4** (0.390 g, 10%) and **5-33** (0.34 g, 9%).

1^1*H*-1(2,5)-pyrrolacycloundecaphan-2-one (5-4):
^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.83 (s, 1H), 6.99-6.93 (m, 1H), 6.07-6.01 (m, 1H), 2.72-2.58 (m, 4H), 1.81-1.73 (m, 2H), 1.64-1.57 (m, 2H), 1.43-1.34 (m, 2H), 1.31-1.18 (m, 4H), 1.18-1.10 (m, 2H), 0.81-0.71 (m, 2H),

^{13}C NMR (125 MHz, $CDCl_3$): 191.5, 139.9, 132.6, 116.9, 109.9, 37.0, 28.1, 27.9, 26.9, 26.5, 26.4, 26.3, 26.2

3-isobutyryl-1[1]*H*-1(2,5)-pyrrolacycloundecaphan-2-one (5-11)



5-11

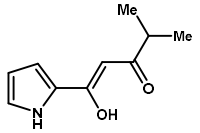
To a solution of DIPA (0.15 mL, 1.07 mmol, 3.2 eq) in toluene (7 mL), *n*BuLi (2.5M in Hexanes, 0.40 mL, 1.00 mmol, 3.1 eq) was added. The mixture was stirred for 20 min at room temperature and then cooled to 0 °C. **5-4** (71.6 mg, 0.32 mmol) was stripped with toluene (2 mL x 3) and then dissolved in THF (3.5 mL). The THF solution was then added dropwise by syringe pump over 45 minutes to the solution of LDA. The yellow solution was stirred at 0 °C for 1h and then cooled to -78 °C. Isobutyryl chloride (0.04 mL, 0.38 mmol, 1.2 eq) in toluene (0.5 mL) was then added dropwise over 5 minutes to the reaction. The mixture was stirred at -78 °C for two hours until TLC indicated that reaction was complete. The reaction was then quenched with sat. aqueous NH_4Cl and the mixture was extracted with EtOAc. The organics were dried over $MgSO_4$, filtered, and concentrated to an orange oil. The crude was purified by flash column chromatography (SiO_2, 40:1→20:1→10:1→4:1 Hexanes/EtOAc) to afford **5-11** (79.3 mg, 84%) as a white solid.

3-isobutyryl-1[1]*H*-1(2,5)-pyrrolacycloundecaphan-2-one (5-11):

[1]H NMR (500 MHz, $CDCl_3$): δ 9.89 (s, 1H), 6.96 (dd, *J* = 2.1, 3.4 Hz, 1H), 6.03 (dd, *J* = 2.1, 3.4 Hz, 1H), 4.13 (dd, *J* = 5.3, 12.4 Hz, 1H), 2.83 (heptet, *J* = 6.8 Hz, 1H), 2.78-2.61 (m, 2H), 2.34-2.20 (m, 1H), 1.71-1.41 (m, 4H), 1.37-1.20 (m, 4H), 1.18-1.06 (m, 2H), 1.15 (d, *J* = 6.9 Hz, 3H), 1.11 (d, *J* = 6.8 Hz, 3H), 0.76-0.63 (m, 1H), 0.27-0.14 (m, 1H)

[13]C NMR (125 MHz, $CDCl_3$): 213.5, 184.3, 141.5, 130.9, 118.9, 110.0, 64.7, 42.2, 29.1, 29.0, 28.9, 26.4, 25.8, 24.5, 23.6, 21.9, 18.0, 17.4

(*Z*)-1-hydroxy-4-methyl-1-(1*H*-pyrrol-2-yl)pent-1-en-3-one (5-36)



5-36

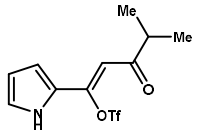
To a solution of DIPA (6.42 mL, 45.8 mmol, 2.5 eq) in THF (85 mL), *n*BuLi (2.5M in Hexanes, 16.8 mL, 42.00 mmol, 2.3 eq) was added. The mixture was stirred for 20 min at room temperature and then cooled to 0 °C. **5-35** (2.002 g, 18.34 mmol) was stripped with toluene (10 mL x 3) and then dissolved in THF (10 mL). The THF solution was then added dropwise by syringe pump over 20 minutes to the solution of LDA. The solution was stirred at 0 °C for 1h and then cooled to -78 °C. Ethyl Isobutyrate (4.0 mL, 29.7 mmol, 1.6 eq) in THF (5 mL) was then added dropwise over 15 minutes to the reaction. The mixture was allowed to warm slowly to room temperature overnight (~16h). The reaction was then quenched with aqueous 1M $KHSO_4$ and the mixture was extracted with Et_2O. The organics were dried over $MgSO_4$, filtered, and concentrated to a red oil. The crude was purified by flash column chromatography (SiO_2, 10:1→4:1 Hexanes/EtOAc) to

afford **5-36** (2.732 g, 83%) as a red oil. **5-36** exists as a 7:3 mixture of the enol:ketone tautomeric forms.

(*Z*)-1-hydroxy-4-methyl-1-(1*H*-pyrrol-2-yl)pent-1-en-3-one (5-36):
^{1}H NMR (500 MHz, $CDCl_3$): δ 15.51 (s, 0.7H), 9.44 (bs, 1H), 7.06 (ddd, *J* = 1.3, 2.7, 3.9 Hz, 0.3H)*, 7.02 (ddd, *J* = 1.3, 2.6, 3.8 Hz, 0.7H), 6.92 (ddd, *J* = 1.2, 2.4, 3.6 Hz, 0.3H)*, 6.86 (ddd, *J* = 1.2, 2.4, 3.6 Hz, 0.7H), 6.32-6.26 (m, 1H), 5.89 (s, 0.7H), 3.93 (s, 0.6H)*, 2.81 (heptet, *J* = 6.8 Hz, 0.3H)*, 2.50 (heptet, *J* = 6.8 Hz, 0.7H), 1.20 (d, *J* = 6.9 Hz, 5.4H), 1.13 (d, *J* =6.9 Hz, 0.6H)

^{13}C NMR (125 MHz, $CDCl_3$): 207.9*, 190.0, 183.0*, 181.9, 131.7*, 130.3*, 125.5*, 123.9, 117.8, 114.2, 111.2*, 111.0, 92.8, 51.2*, 41.2*, 34.9, 19.7, 18.0*

(*Z*)-4-methyl-3-oxo-1-(1*H*-pyrrol-2-yl)pent-1-en-1-yl trifluoromethanesulfonate (5-37)



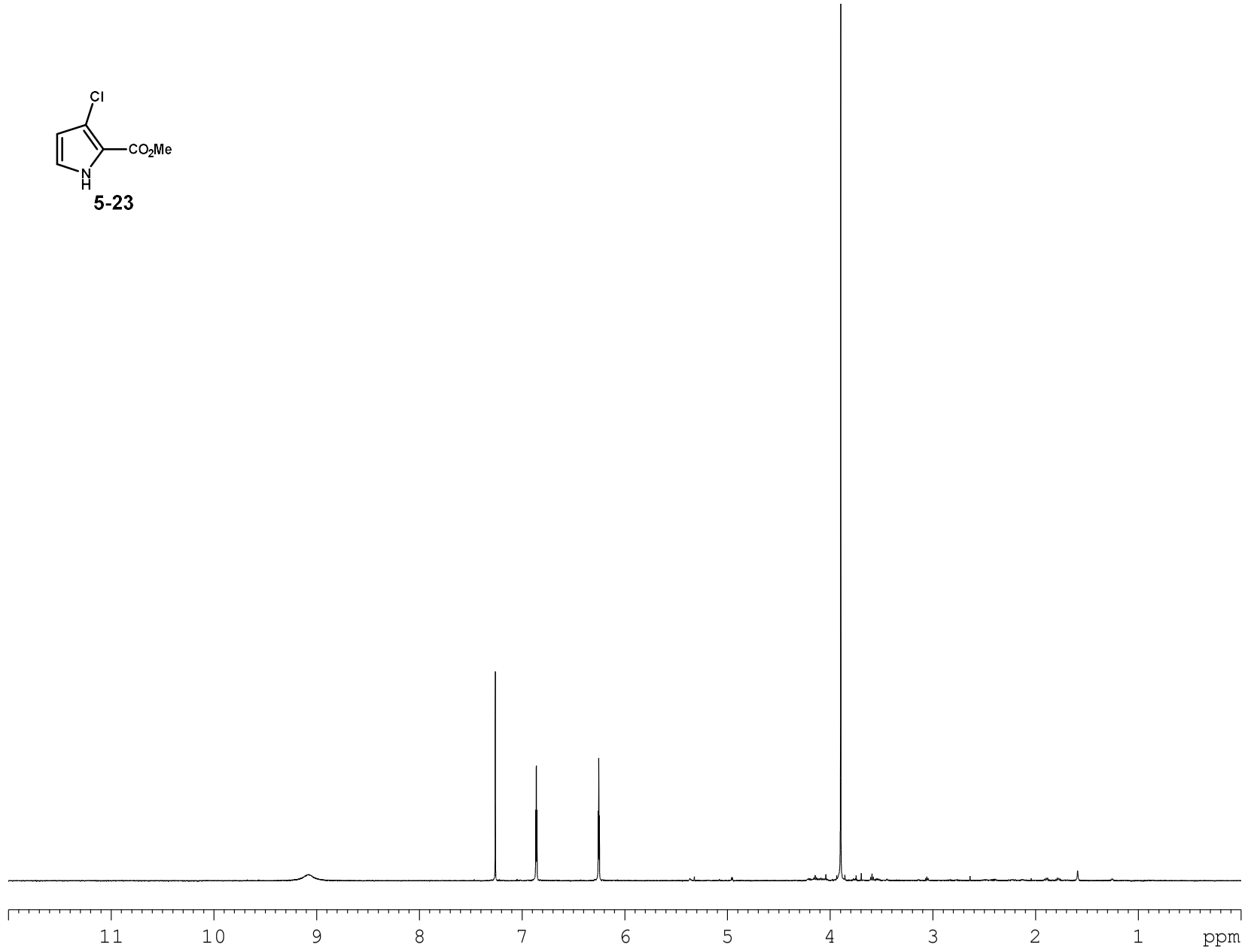
5-37

To a solution of **5-36** (0.1825 g, 1.01 mmol) in DCM (20 mL, 0.05M) at 0 °C, LiOTf (stripped with toluene 2 mL x 3, 0.3172 g, 2.03 mmol, 2 eq) was added. Then DBU (0.17 mL, 1.13 mmol, 1.1 eq) was added and the mixture was stirred for 20 min at 0 °C. Tf_2O (0.18 mL, 1.07 mmol, 1.05 eq) was then added dropwise to the reaction. The reaction was then allowed to warm to room temperature overnight (~16h). The reaction was then diluted with DCM and sat. aqueous NH_4Cl. The aqueous layer was washed several times with DCM. The combined organics were then dried over $MgSO_4$, filtered, and concentrated to afford a red/black oil. The crude was then purified by flash column chromatography (SiO_2, 30:1→10:1→4:1 Hexanes/EtOAc) to afford **5-37** (0.1346 g, 43%) as a yellow oil and recovered **5-36** (0.078 g, 43%). Triflate **5-37** is contaminated with starting material due to having very similar R_f values.

(*Z*)-4-methyl-3-oxo-1-(1*H*-pyrrol-2-yl)pent-1-en-1-yl trifluoromethanesulfonate (5-37):
^{1}H NMR (500 MHz, $CDCl_3$): δ 9.68 (s, 1H), 7.13 (ddd, *J* = 1.2, 2.8, 3.6 Hz, 1H), 6.91 (ddd, *J* = 1.2, 2.2, 3.6 Hz, 1H), 6.51 (d, *J* = 1.0 Hz, 1H), 6.31 (dt, *J* = 2.4, 3.7 Hz, 1H), 2.65 (heptet, *J* = 6.6 Hz, 1H), 1.26 (d, *J* = 6.8 Hz, 6H)

^{13}C NMR (125 MHz, $CDCl_3$): 175.4, 162.5, 132.5, 126.4, 116.8, 112.1, 111.2, 111.0, 33.5, 19.8

5.4.3. NMR Spectra Relevant to Chapter 5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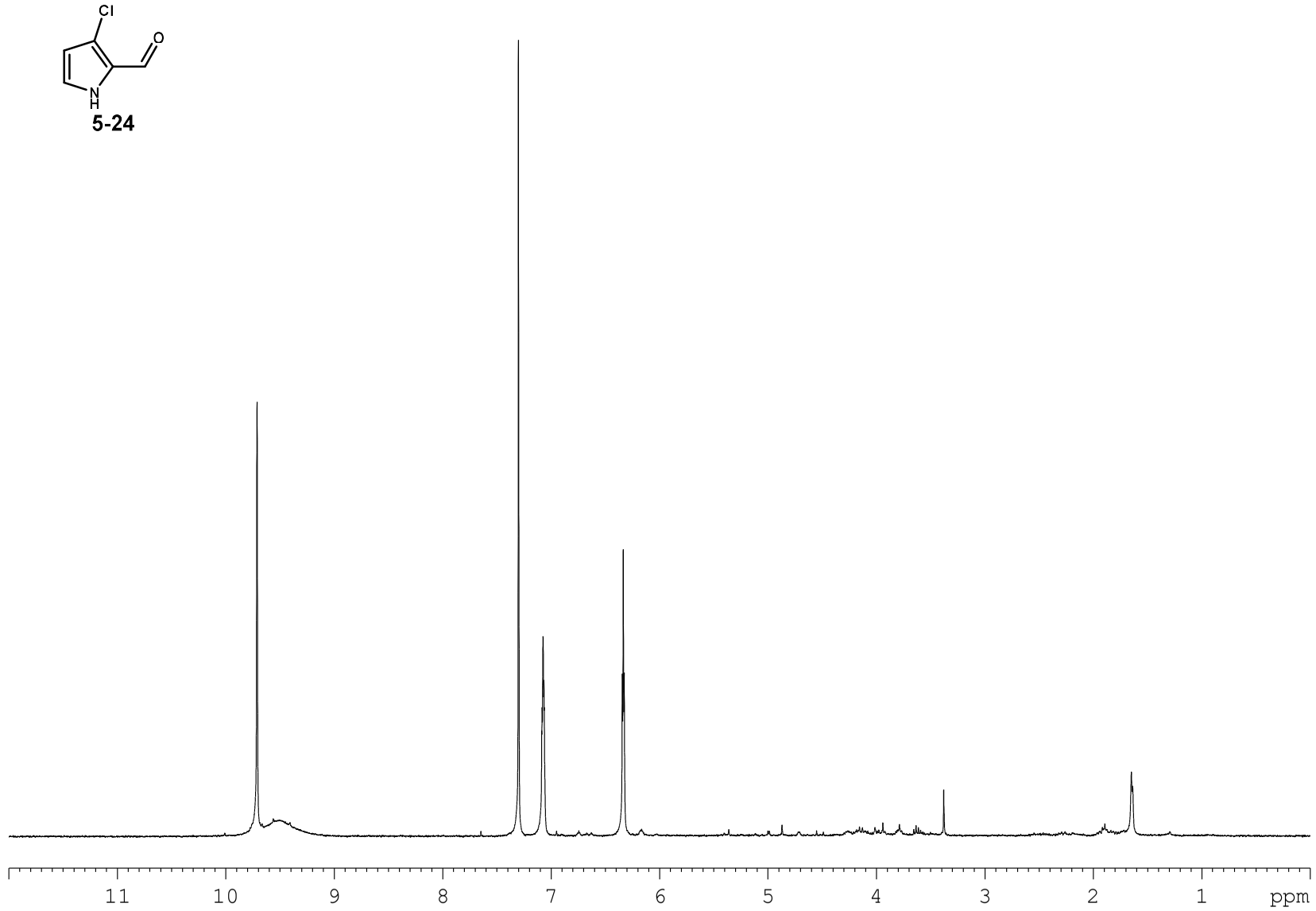
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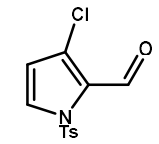

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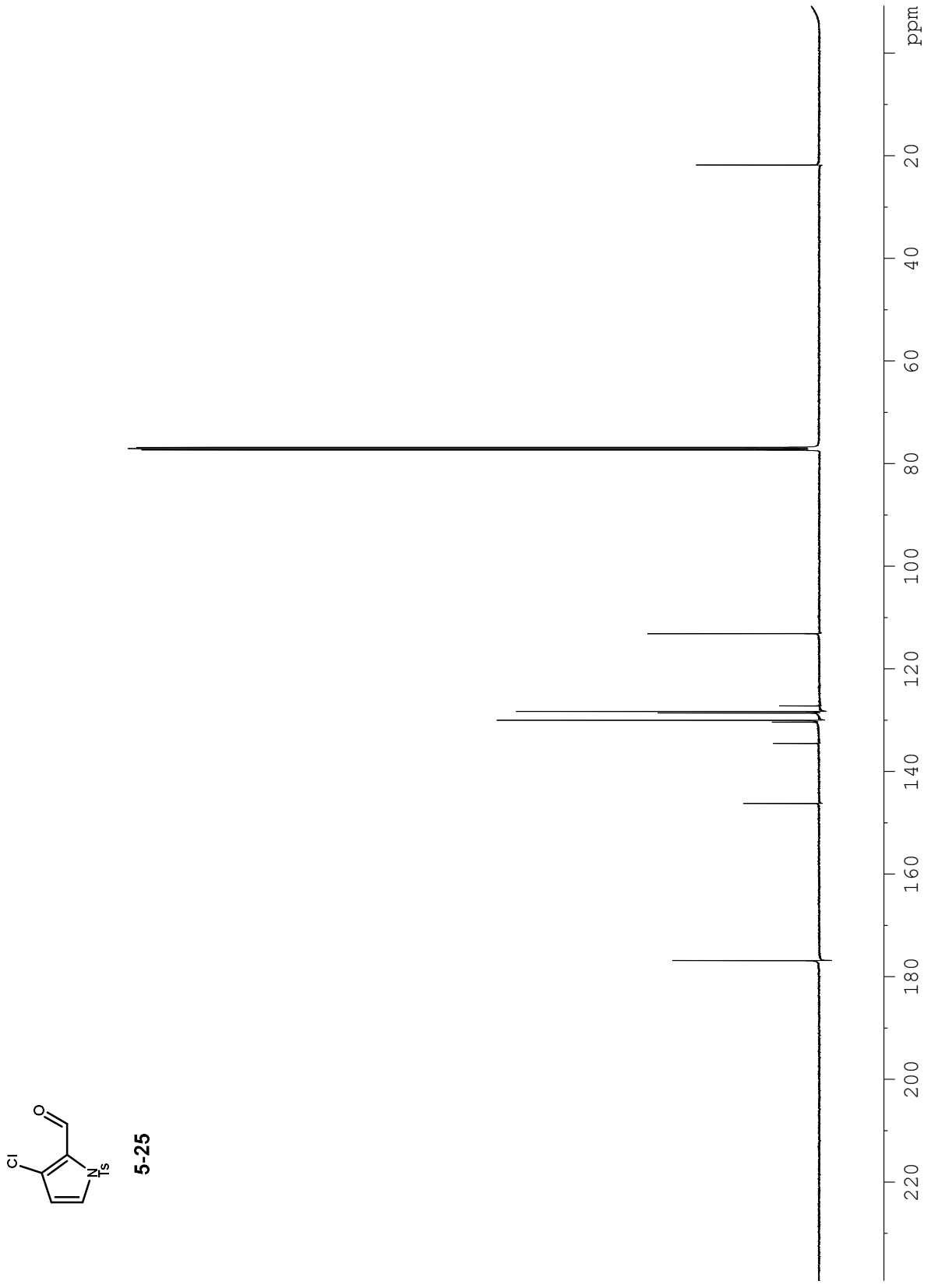

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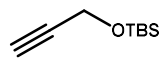

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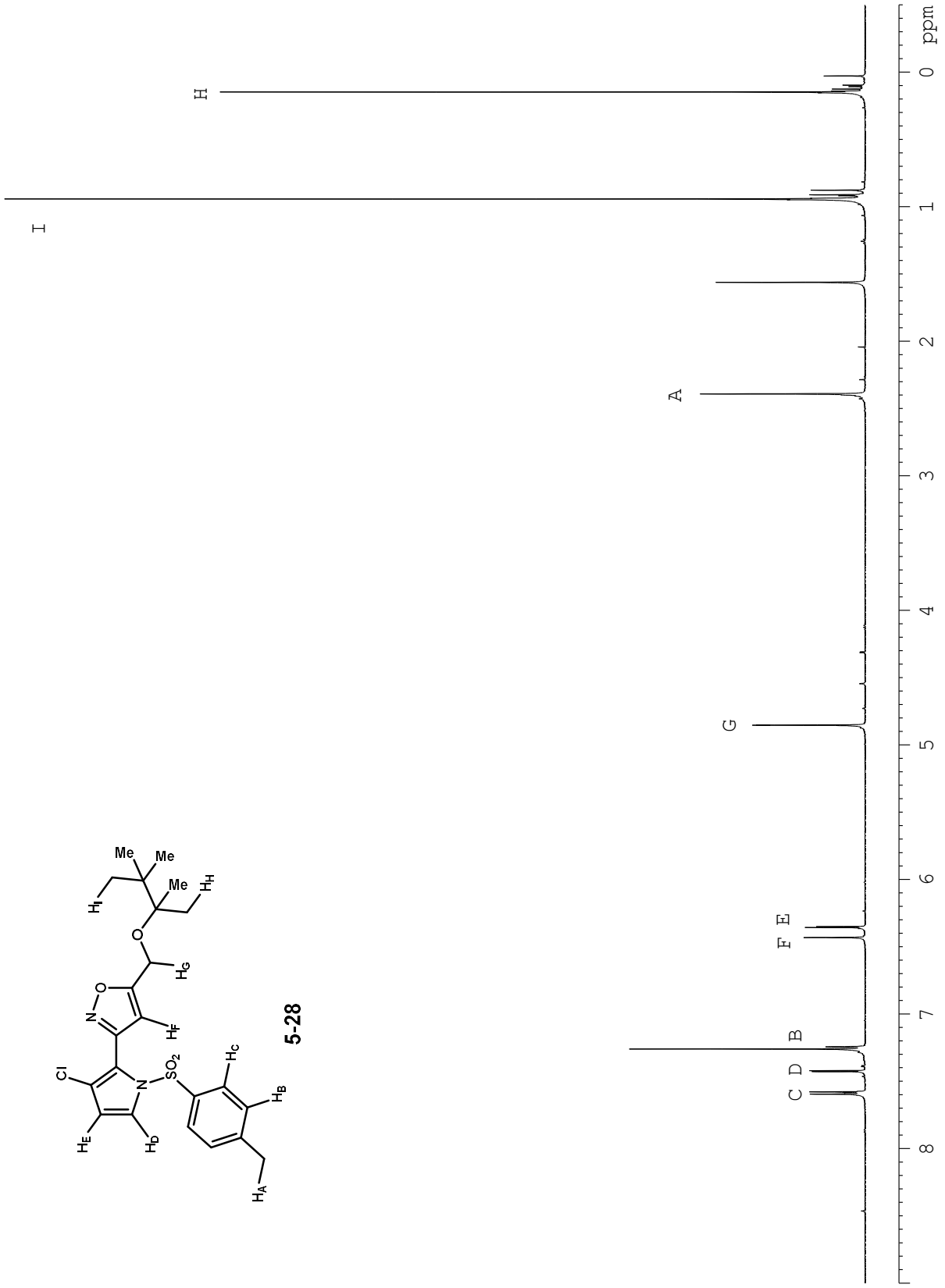
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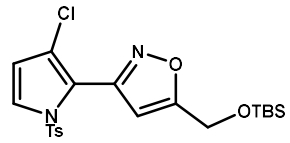

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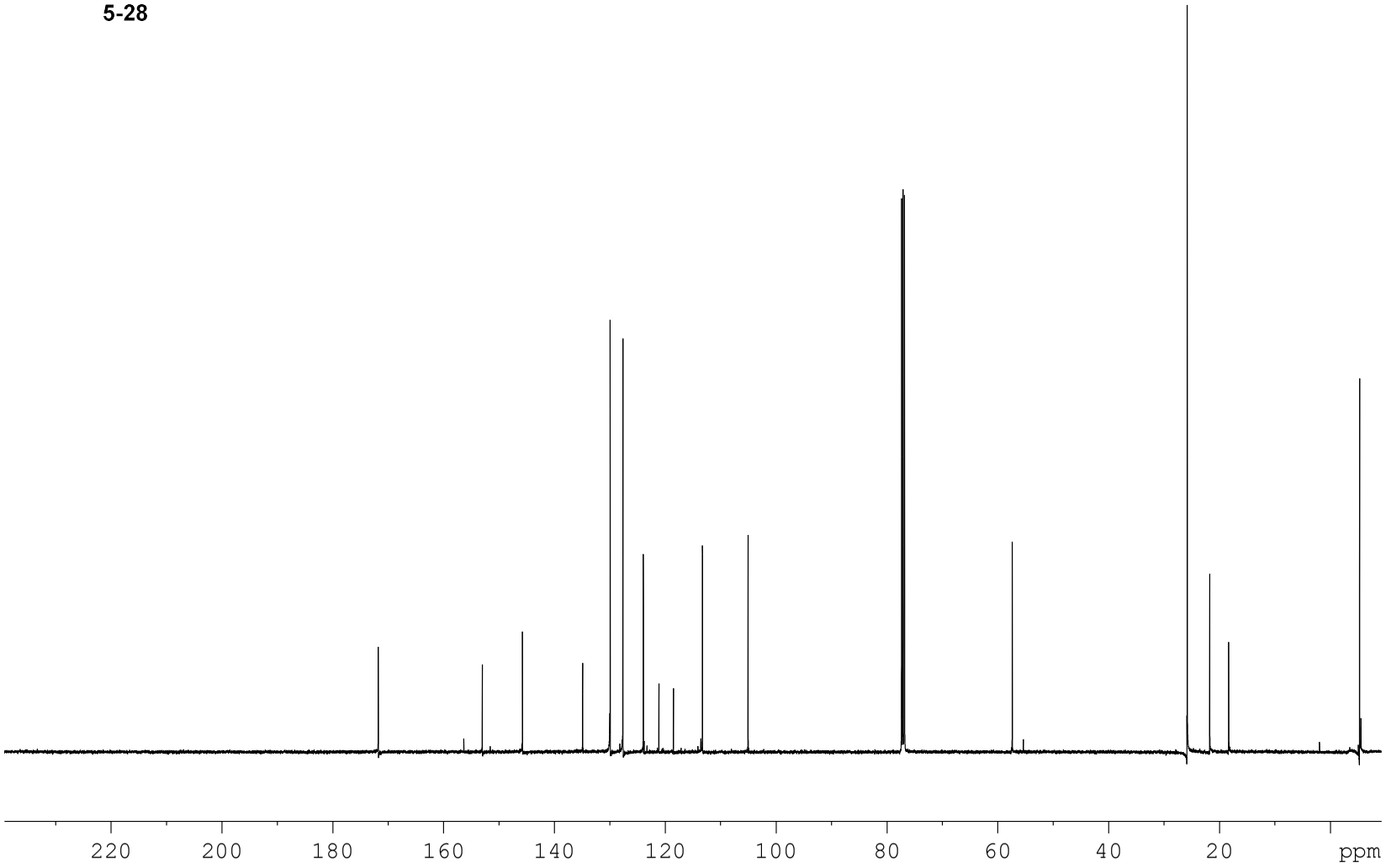

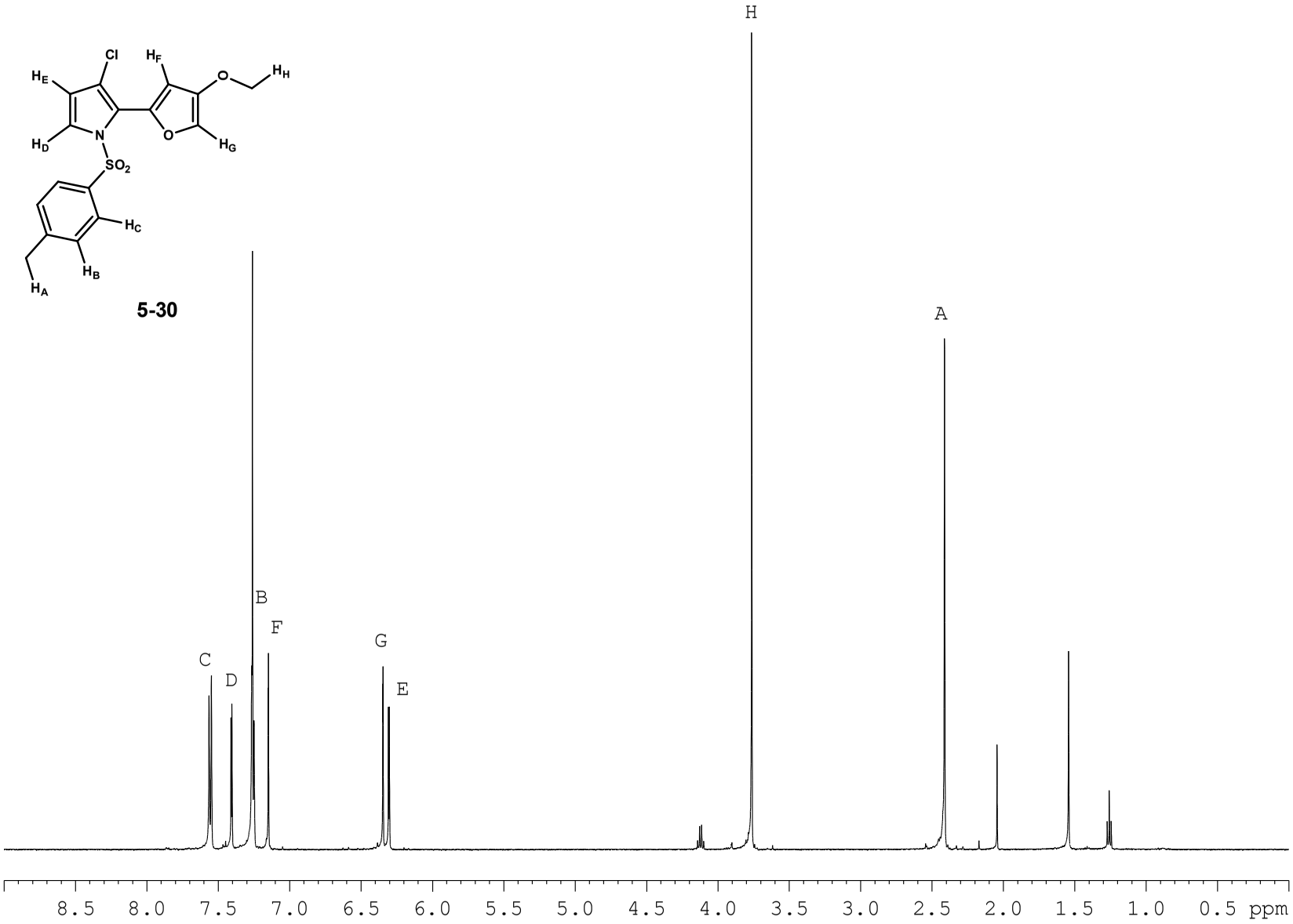
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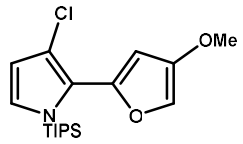

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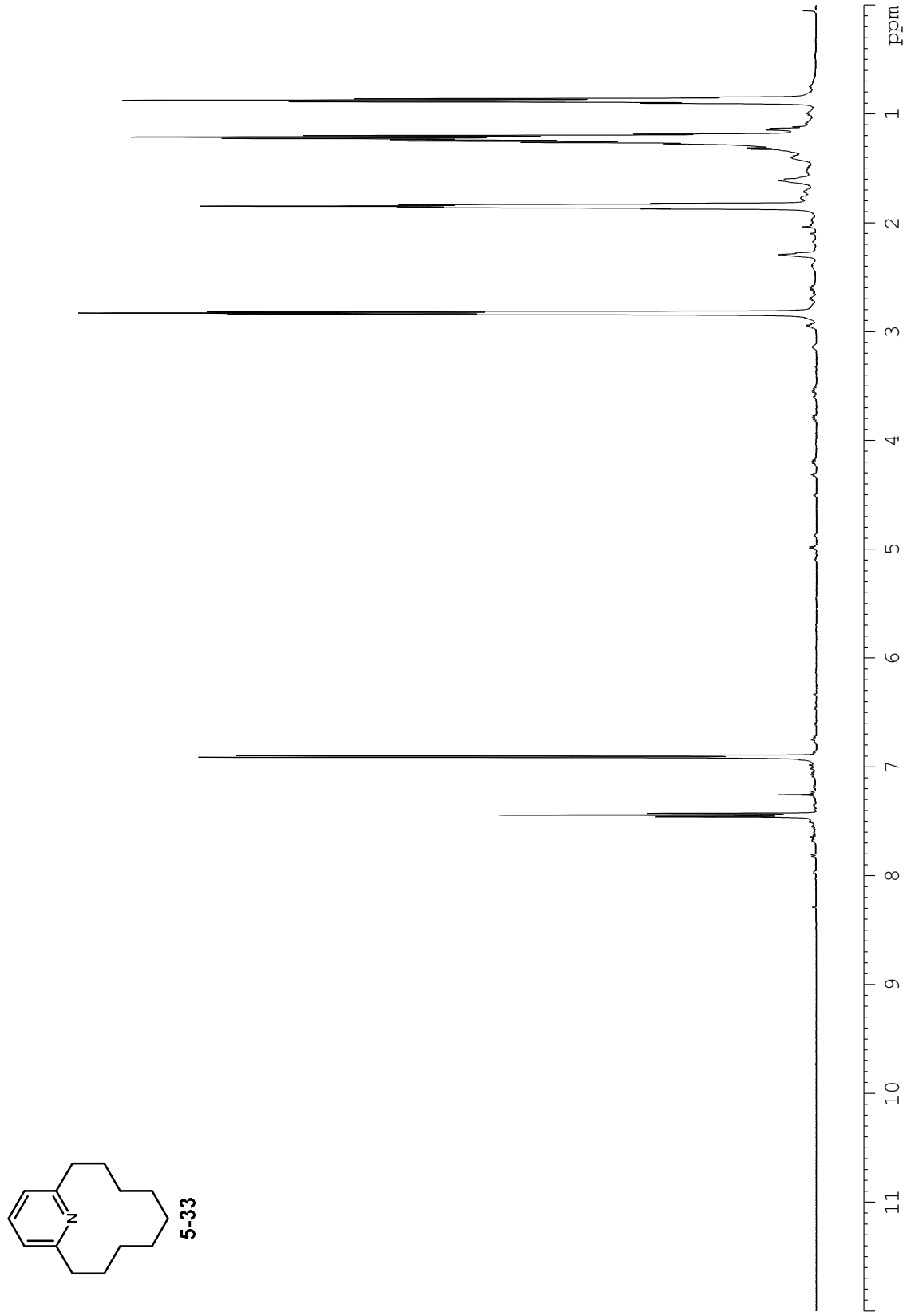
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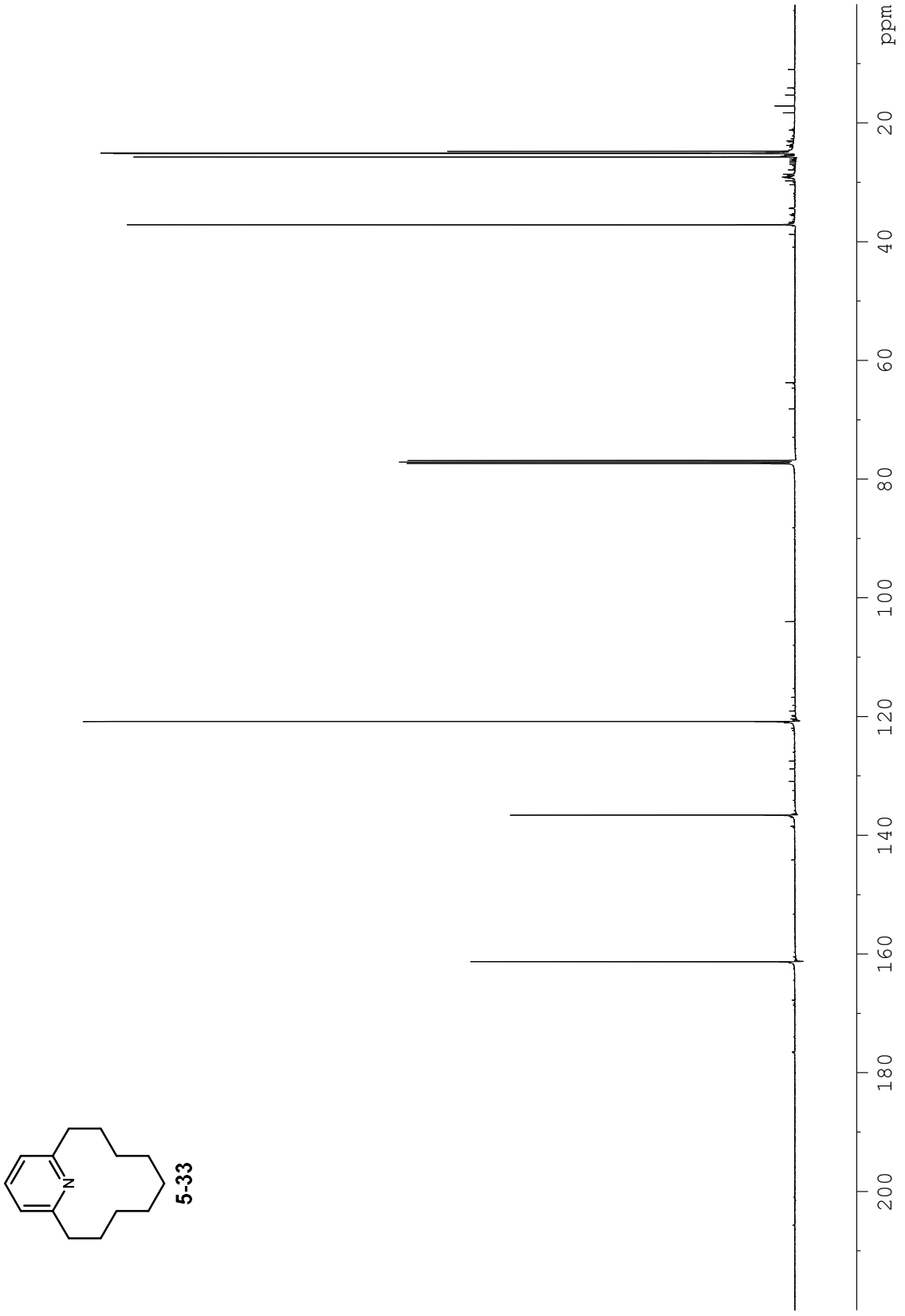
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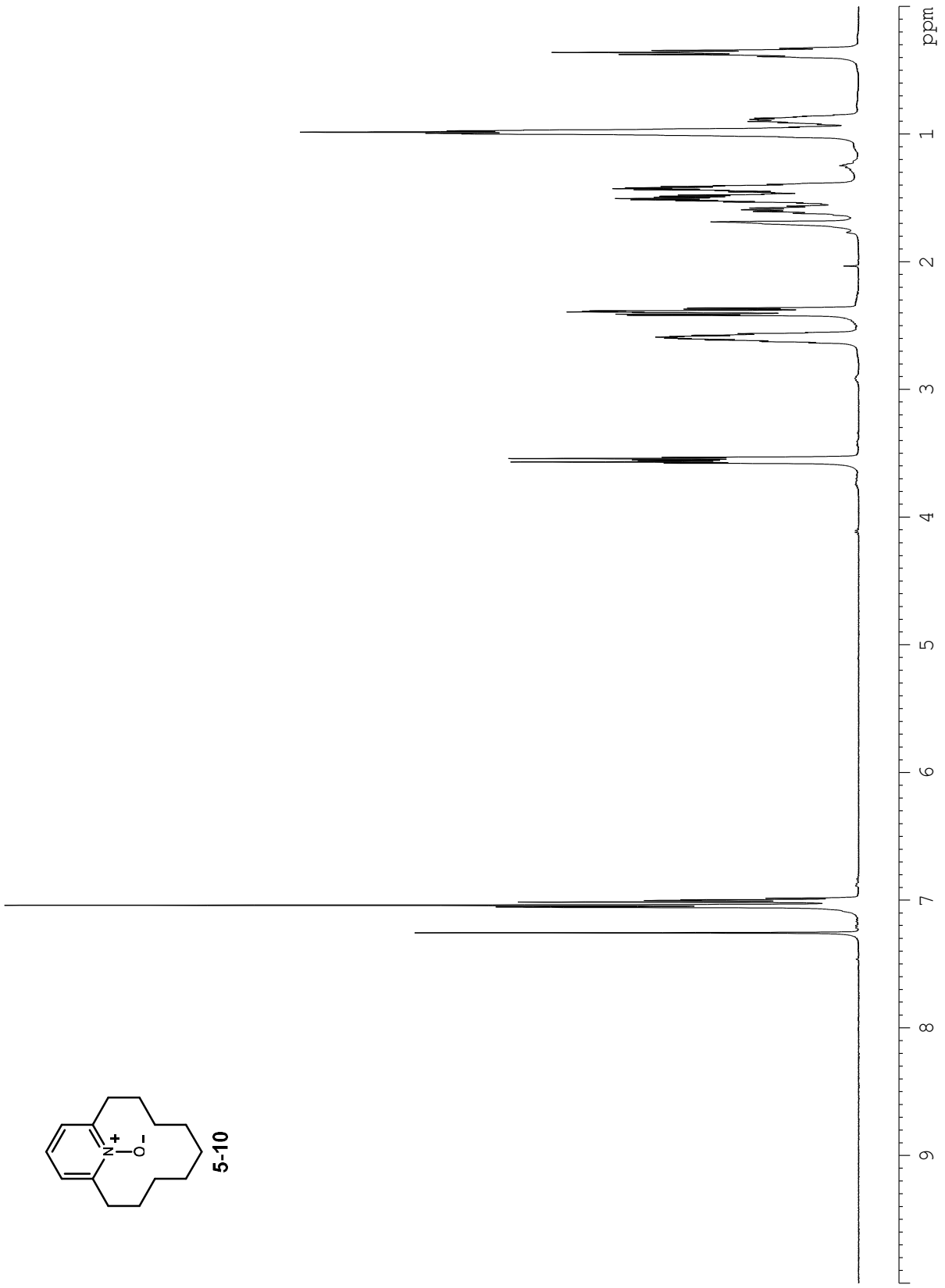

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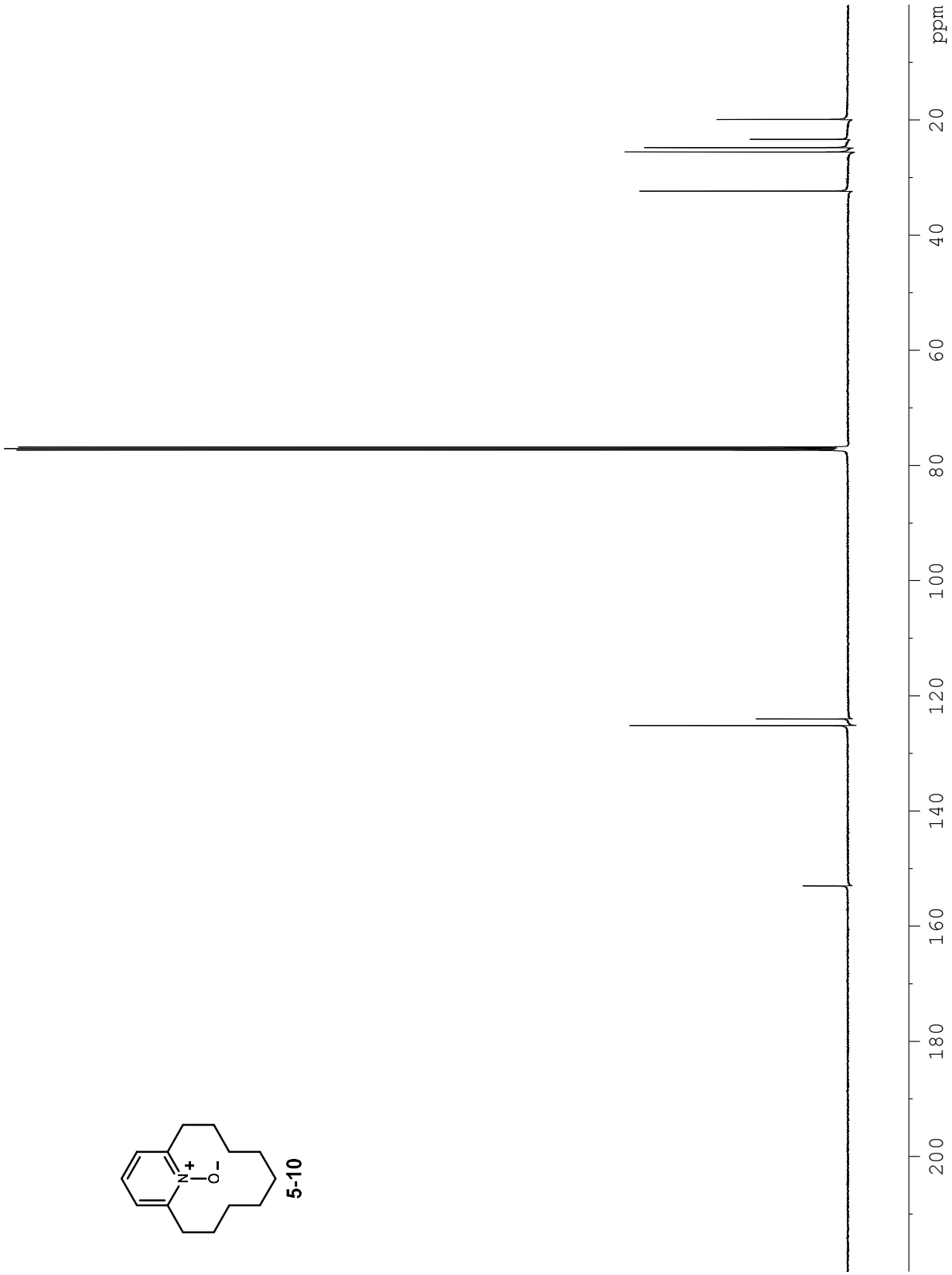

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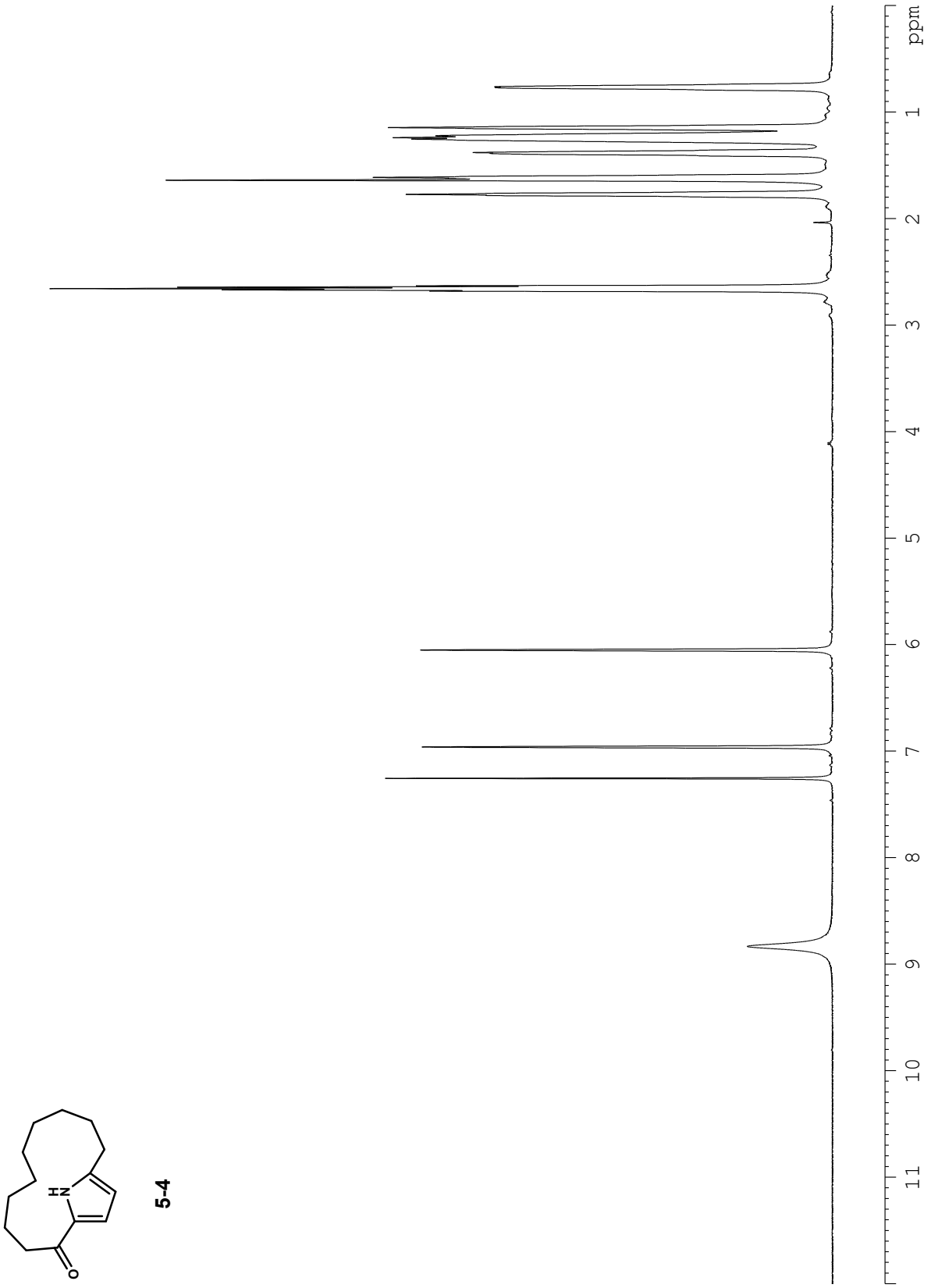

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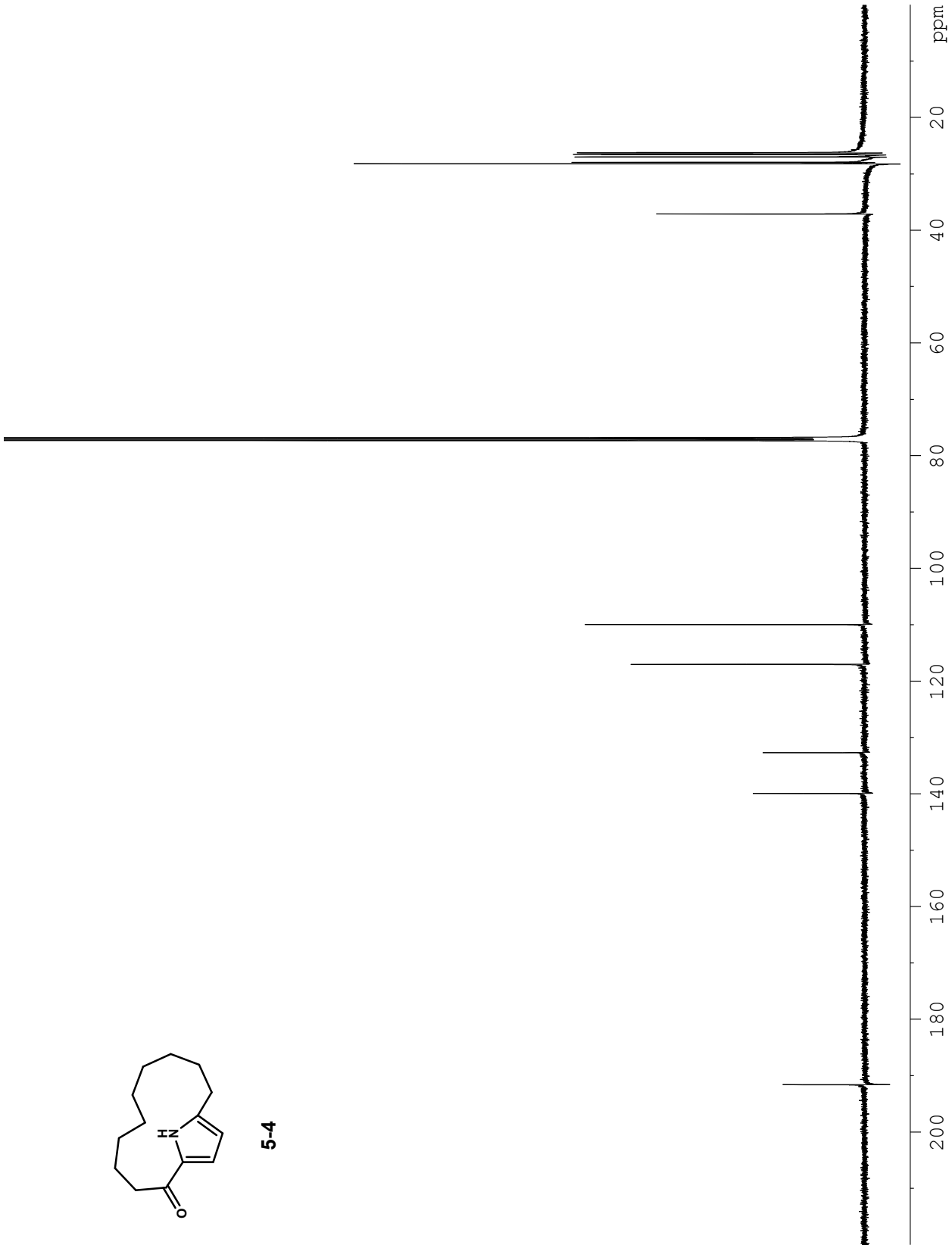

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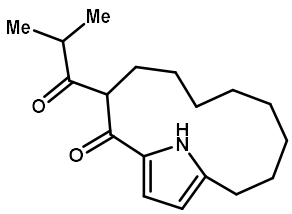

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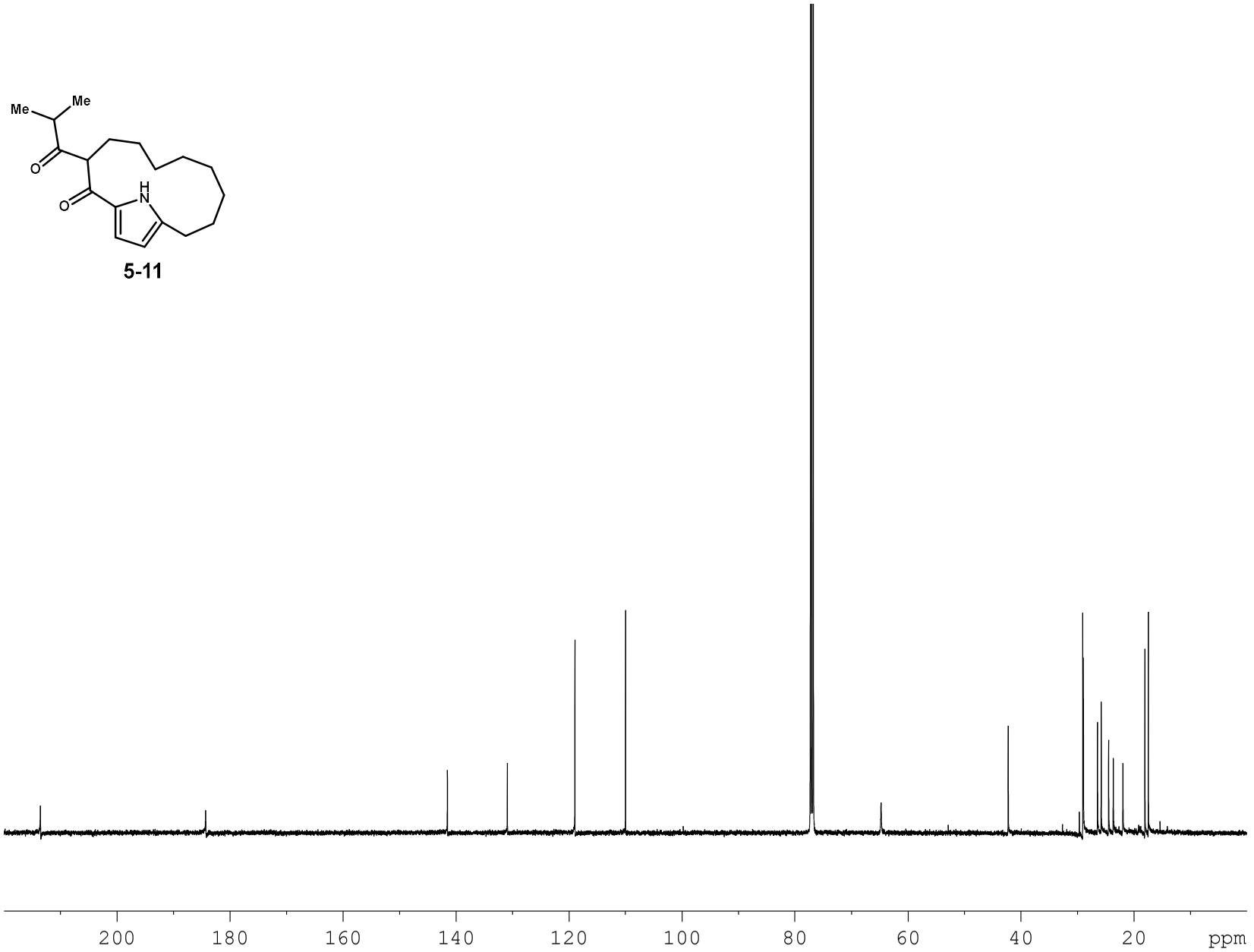
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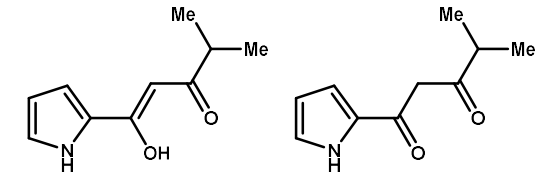

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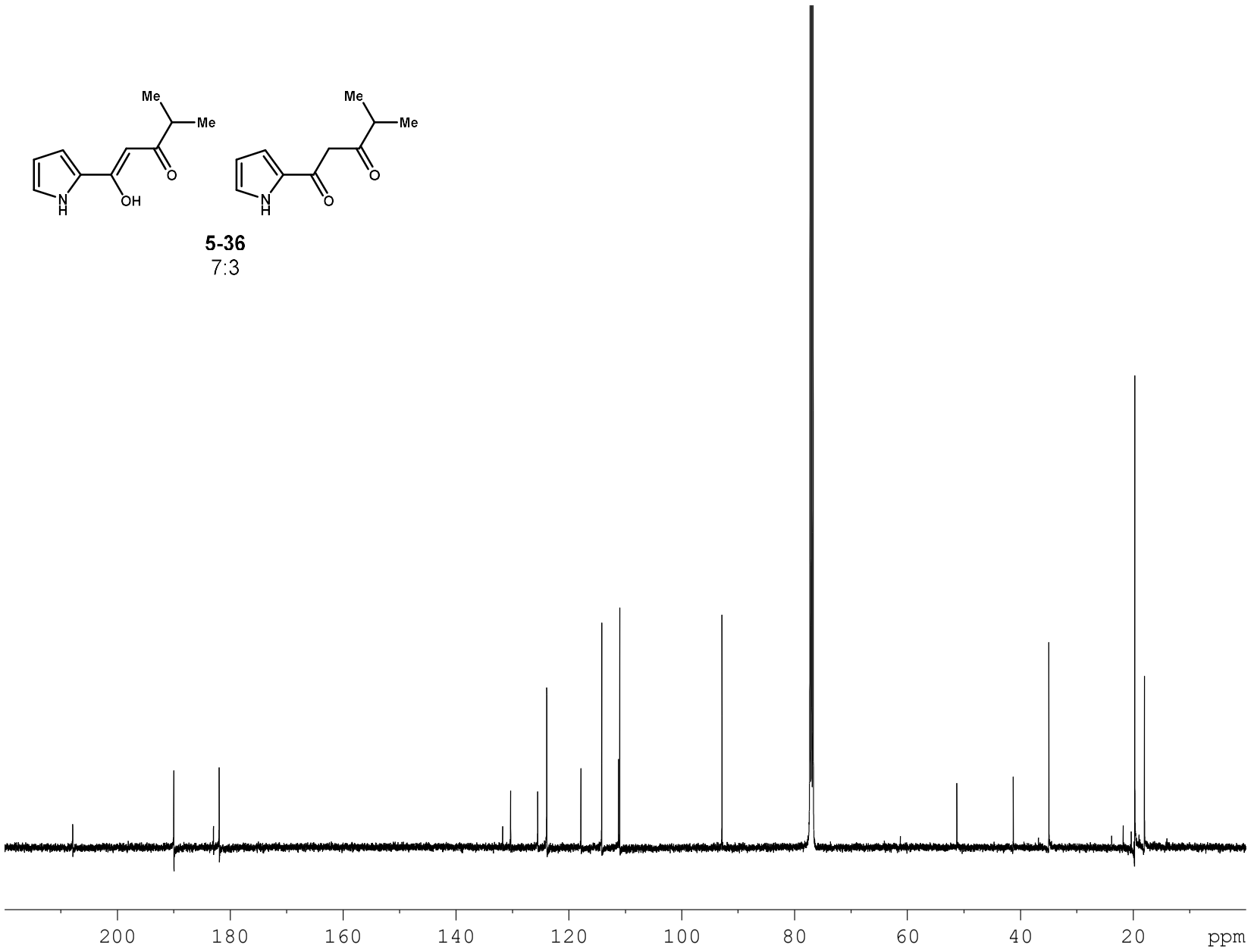

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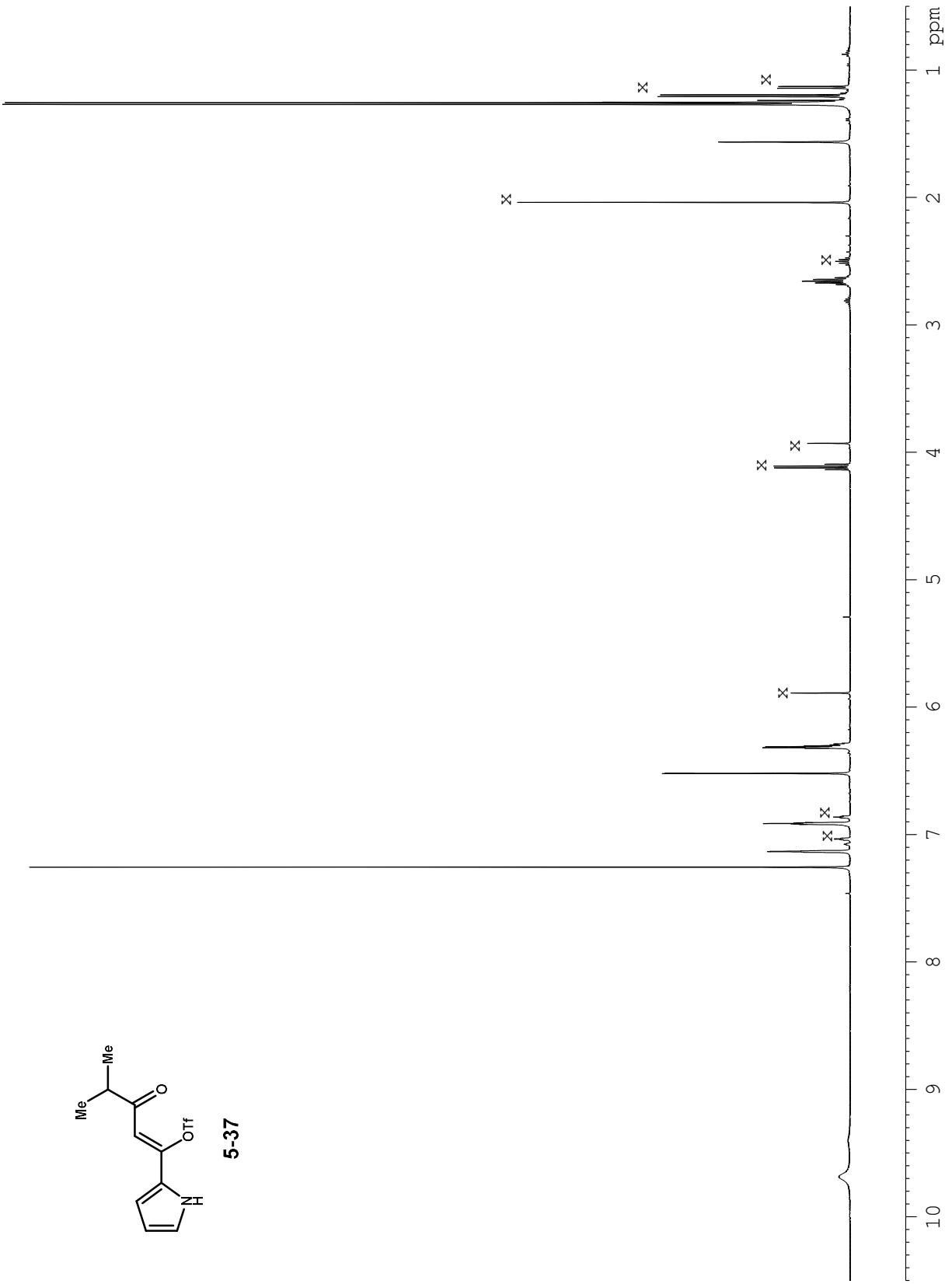
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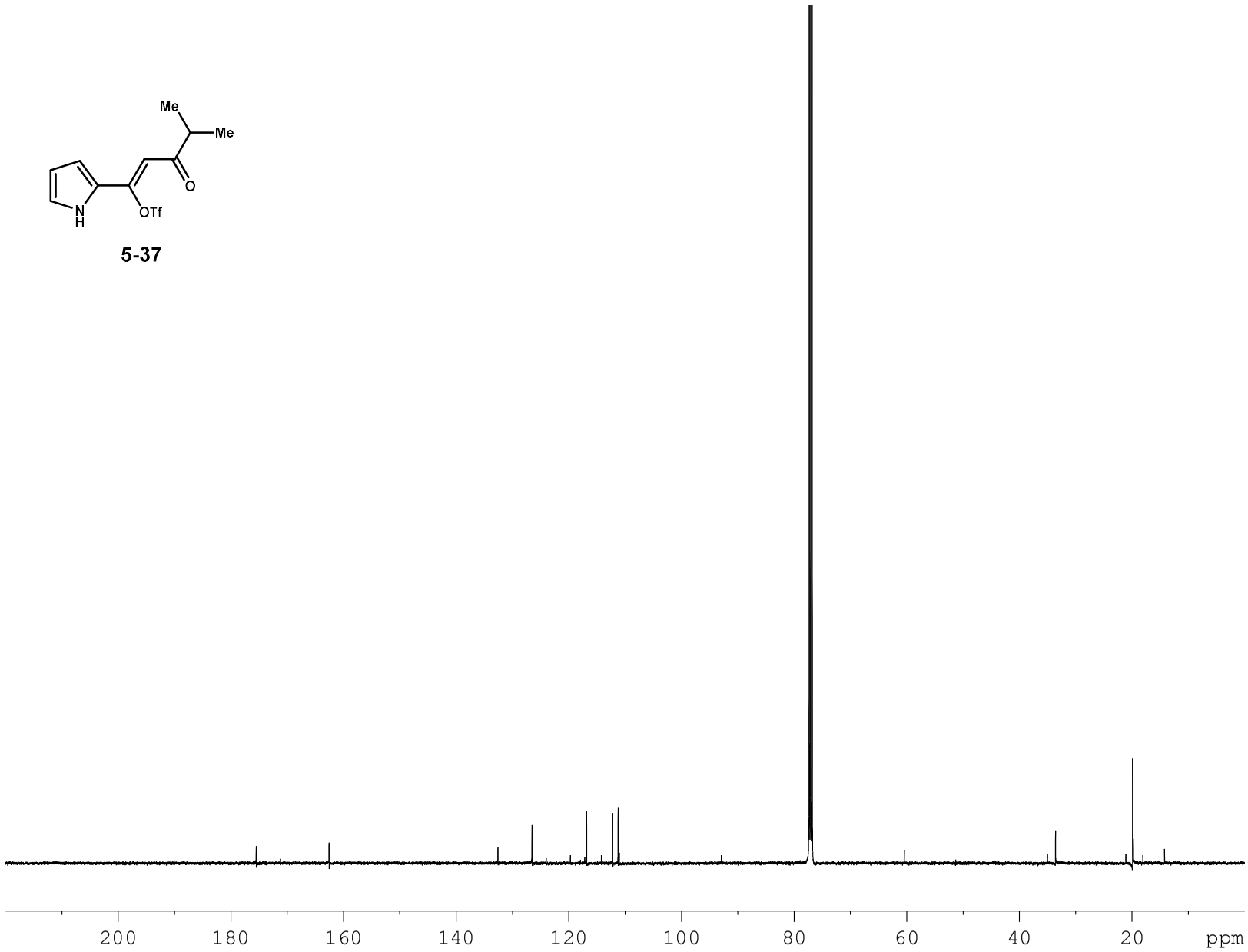


5-37

6. Appendix One: Developing an Effective Inhibitor of Ghrelin O-Acyl Transferase

Tyler Allred, Ryan Hollibaugh, and Patrick Harran

6.1. Introduction

This appendix is a standalone section that describes my first research project undertaken in the Harran laboratory, which was to assist in the efforts to develop a small molecule inhibitor of ghrelin Oacyltransferase (GOAT). Ghrelin is a small peptide hormone with an atypical octanoylate linkage and has implications in energy and glucose homeostasis. Ghrelin is the only known octanoylated hormone and is the only identified substrate of GOAT. Therefore, the ghrelin signaling could be selectively modulated by inhibition of GOAT with few anticipated off target effects. Chapter Six describes several SAR investigations on a previous lead compound. Namely, the deletion of a hydrogen bond donor via incorporation of an alkyne and attempts to improve proteolytic stability/restrict conformational freedom by macrocyclization. Unfortunately, these modifications resulted in loss of potency and were not pursued further.

6.1.1. The Interplay of Ghrelin, GOAT, and GHS-r as Modulators of Growth Hormone and Energy Homeostasis

Ghrelin (**6-1**) is a 28-amino acid peptidic hormone that has been shown to be intimately involved in growth hormone (GH) regulation, orexigenic signaling, and both energy and glucose homeostasis.[287,288] Studies conducted at Merck identified the endogenous receptor for ghrelin prior to ghrelin's discovery, which was designated as growth hormone secretagogue receptor (GHS-r).[289,290] These studies resulted in the generation of several GHS-r agonists with MK-0677 (**6-2**) being the prototype member.[288–290] Treatment with **6-2** induces both growth hormone release from the pituitary gland and growth hormone releasing hormone (GHRH) from the hypothalamus.[288–

[290] Motifs of this type were highly sought after and were examined as therapeutics for the treatment of a variety of GH associated diseases.[288,290]

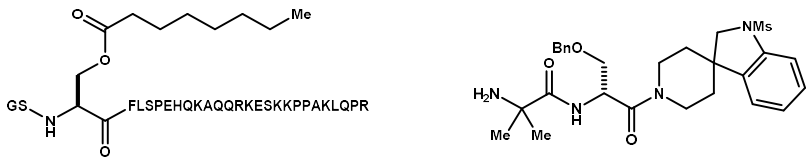


Figure 6.1. The Structures of Octanoyl Ghrelin (**6-1**) and GHS-r agonist ibutamoren (MK-0677, **6-2**)

Despite the success and extensive examination of these GHS-r agonists and their receptor, the native ligand remained a mystery until ghrelin was reported by Kojima and coworkers.[287] Through activity guided assays of extracts, an acylated peptide hormone was identified as the endogenous ligand for GHS-r and was denominated as ghrelin (**6-2**).[287] Further investigations noted that the most biologically active form of ghrelin contains an atypical octanoylation of its serine-3 residue.[287] Ghrelin was the first, and is currently the only known, hormone identified to have an octanoyl modification.[288,291]

The enzyme responsible for this unique feature of ghrelin remained unknown until 2008, when the laboratories of Brown and Goldstein conducted an activity guided screen of the sixteen membrane bound O-acyl transferases (MBOATs) encoded in the mouse genome.[292] It was determined that MBOAT4 was the only member that was able to produce octanoylated ghrelin.[292] Concurrently with this study, Gutierrez and coworkers identified a cell line that could produce acyl ghrelin upon addition of octanoic acid and utilized siRNA targeting to identify MBOAT4 as the acyl transferase responsible for octanoyl ghrelin formation.[293] After these studies, MBOAT4 was denominated as ghrelin O-acyl transferase (GOAT) and the acyl donor was subsequently identified as octanoyl CoA.[294] Since its discovery, no native ligand other than ghrelin has been identified for GOAT and no other enzyme capable of ghrelin octanoylation has been reported. Both GOAT and ghrelin are

primarily expressed in the digestive tract with a large percentage being from the oxyntic portion of the stomach.[288,295]

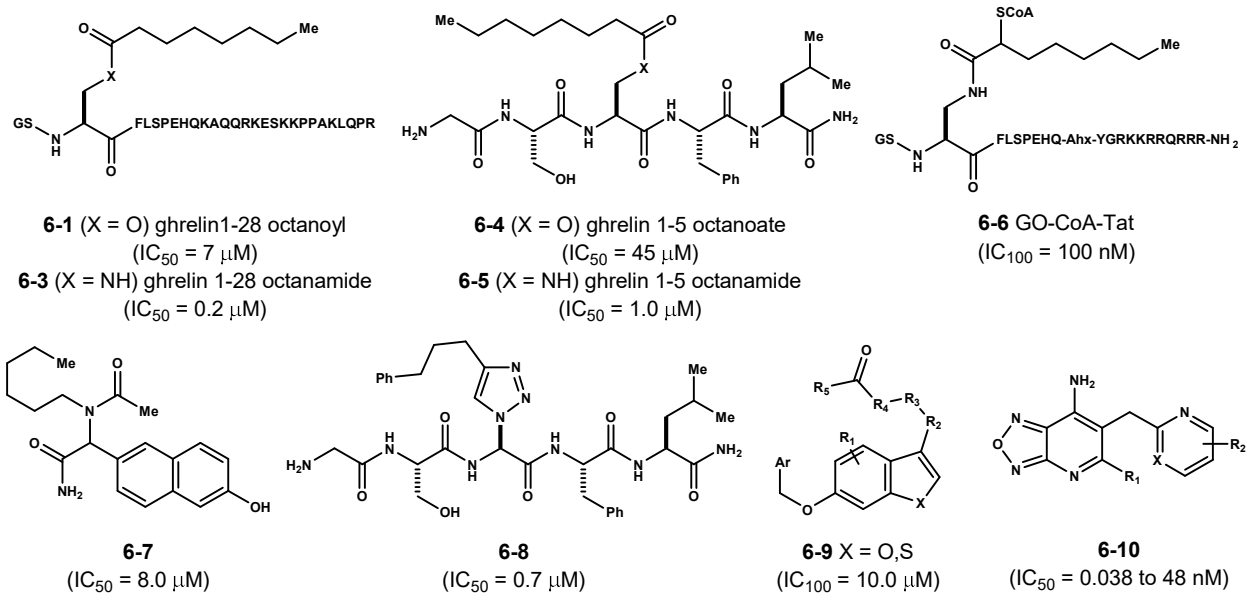
After its initial disclosure, it was noted that ghrelin levels appeared to rise prior to meal consumption and would fall afterwards, which led to the thought that ghrelin served as an orexigenic signal that complemented the satiety inducing hormone leptin.[296–299] However, recent studies have shown that the levels of ghrelin required to induce changes in feeding behavior far exceed those that exist under physiological conditions, even when subjected to starvation conditions, which has caused apprehension on its function as an orexigenic signal.[300] While the effect of raising ghrelin levels seems to promote feeding behavior, the ablation of ghrelin does not affect feeding or weight gain with a standard diet.[288,301,302] Ghrelin knockout (KO) mice display an indistinguishable phenotype from the wild type controls under standard feeding conditions, while more rigorous examination under alternative feeding conditions has been somewhat inconclusive.[288] It has been shown that ghrelin KO mice have modest resistance to weight gain when provided a high-fat diet, which suggests that ghrelin is involved in regulating energy balance and influences metabolism in several ways, besides as a potential hunger signal.[303]

Despite ghrelin's complicated relationship with feeding and metabolism, its function in glucose homeostasis has been more clearly elucidated.[288,304–306] Ghrelin interacts with its receptor in islet β-cells in the pancreas to prevent the buildup of intracellular calcium ions, which causes a suppression of insulin export in response to glucose.[304,305] This interaction has clear consequences on glucose homeostasis through the modulation of insulin levels. Furthermore, it has been shown that ghrelin KO or its islet β-cell receptor animals are better able to clear oral or intraperitoneally administered glucose.[288,306] These studies have suggested that ghrelin signaling pathways have an adverse effect on metabolism and glucose homeostasis.

When considering the physiological implications of GOAT, the generation of GOAT knockout mice have shown minimal to no phenotype, similar to what has been observed with ghrelin and GHS-r KO mice, under standard or high fat feeding conditions.[307] A recent study showed that GOAT KO mice were better able to resist obesity when fed a medium chain triglyceride or high fat diet supplemented with sucrose as compared to the wild type control or the GOAT KO fed an un-supplemented diet.[308] While a very mild phenotype is observed under normal feeding conditions, a strong phenotype presents itself under severe caloric restriction. Studies have shown that GOAT KO are much more susceptible to hypoglycemia induced mortality than the wild type.[307] However, it was determined that this phenotype stems from ghrelin modulation or lack thereof by on growth hormone levels and it was shown that administration of GH to these GOAT KO mice was sufficient to rescue them.[307]

Due to the adverse effects that the ghrelin pathway has on homeostasis and the relatively mild phenotype observed in KO mice, therapeutic modulation of ghrelin has been a subject of considerable interest to the pharmaceutical industry.[309] A variety of structural motifs that interact with GHS-r have been reported.[290,310,311] However, passage through the blood-brain barrier is required for these potential drugs to be efficacious, which leads to a high potential for neurotoxicity with off-target interactions.[288] A more direct regulation of physiological ghrelin levels by adjustment of ghrelin production would be more desirable due to ghrelin being produced in the digestive tract.[287,312]

6.1.2. The Development of Ghrelin O-Acyltransferase (GOAT) Inhibitors



6-1 (X = O) ghrelin1-28 octanoyl (IC_{50} = 7 μM)
6-3 (X = NH) ghrelin 1-28 octanamide (IC_{50} = 0.2 μM)

6-4 (X = O) ghrelin 1-5 octanoate (IC_{50} = 45 μM)
6-5 (X = NH) ghrelin 1-5 octanamide (IC_{50} = 1.0 μM)

6-6 GO-CoA-Tat (IC_{100} = 100 nM)

6-7 (IC_{50} = 8.0 μM)

6-8 (IC_{50} = 0.7 μM)

6-9 X = O,S (IC_{100} = 10.0 μM)

6-10 (IC_{50} = 0.038 to 48 nM)

Figure 6.2. Reported Inhibitors of Ghrelin O-Acyltransferase

A unique opportunity for medicinal chemistry arises from the mutual specificity between ghrelin, octanoate, and GOAT. An inhibitor of GOAT should have very few, if any, mechanism-based toxic effects due to the almost undetectable phenotype in GOAT KO mice. In addition, the high selectivity associated with GOAT and ghrelin indicates that interactions with other acyltransferases should be minimized.[288] Moreover, the localization of GOAT in the digestive tract precludes the need for an inhibitor to pass through the blood-brain barrier, which is a major drawback for the inhibitors of GHS-r. When considered in conjunction with the therapeutic potential of mitigating ghrelin production, these properties necessitate the development of small molecule inhibitors of GOAT.[293,294,296]

Several groups have explored the generation of GOAT inhibitors due to their attractive therapeutic potential. Shortly after their initial disclosure of GOAT, the laboratories of Brown and Goldstein reported that acyl ghrelin unsurprisingly acts as a GOAT inhibitor and inhibition capability could be substantially increased by converting the octanoate ester linkage to an octanamide (i.e. **6-3**).[294]

In addition, it was determined that small pentapeptides (**6-4** and **6-5**) derived from the first 5 residues from the N-terminus of ghrelin are readily acylated by GOAT and may also serve as inhibitors with reduced potency.[294] Following this report, Barnett and coworkers reasoned that since GOAT must bind both octanoyl CoA and ghrelin for the acylation, a bisubstrate mimetic could be an effective inhibitor.[313] They developed an inhibitor named GO-CoA-Tat (**6-6**) that incorporates the first 10 amino acids of octanamide ghrelin 1-28, an intact CoA unit attached the octanoyl chain, and a TAT sequence (to promote endocytosis) is attached to the C-terminus of the truncated ghrelin via a aminohexanoate linker.[313] This inhibitor retains activity in cell-based assays and was shown to reduce circulating ghrelin levels *in vivo*.[313] Mice fed a high fat diet were more resistant to weight gain when treated with a regimen of GO-CoA-Tat.[313] More importantly, GO-CoA-Tat administration improved performance in glucose tolerance tests indicating that energy homeostasis is better controlled with ghrelin suppression.[313] These results serve as indicators for the therapeutic potential of GOAT inhibition, however it has not been determined if GO-CoA-Tat will be viable in the clinic due to its high molecular weight, highly peptidal character, and required intraperitoneal dosing. These drawbacks could be remedied by the development of a potent small molecule inhibitor.

A major hurdle for the development of a small molecule GOAT inhibitor is the lack of structural data regarding the enzyme and its active site. Human GOAT is a 435-residue membrane-bound enzyme and no functional structure of GOAT, or any MBOAT, has been elucidated to date. It has been postulated that GOAT contains 11 transmembrane helices and certain tolerances of the active site have been reported.[314,315] Benzamide **6-7** was the first reported small molecule inhibitor of GOAT, which was reported by Janda and Garner.[316] This structure was identified during a screen using their reported fluorescence-based assay for GOAT activity. However, no further exploration

of this compound or analogs thereof have been reported. Hougland and coworkers probed the tolerance of the active site by examining the activity of substituted triazoles as bioisosteres for the octanoate ester of ghrelin, which resulted in the discovery of triazole **6-8** as a lead compound.[317] Takeda Pharmaceutical has patented a class of heterocyclic compounds with the general structure of **6-9**, several of which fully inhibit GOAT at 10 μM *in vitro*.[318] Finally, Boehringer Ingelheim has patented a class of substituted amino oxadiazolopyridines with the general structure of **6-10**, several of which are claimed to have subnanomolar potency.[319]

6.1.3. Hypothesis Driven Design of In Vivo Inhibitors of Ghrelin O-Acyl Transferase

At the onset of this project, our laboratory chose to utilize the octanoylated pentapeptide sequence reported by Brown and Goldstein as a launching point to develop a peptidomimetic small molecule inhibitor of GOAT. Peptidomimetics are small molecules that retain the binding or recognition properties of the parent peptide on which they are based, but have improved pharmacokinetic properties.[320,321] This approach would require the identification of key recognition components for binding to GOAT, while modifying the overall structure and removing unnecessary polar functionality. This is a classic approach in medicinal chemistry, which has been utilized in the development of several successful drugs.[288] Our laboratory's systematic modification of the octanoylated pentapeptide and SAR analysis resulted in lead compound **6-11**. The studies that show the evolution of **6-5** to **6-11** have been documented.[288] Briefly, the octanoate has been converted to a *trans*-substituted cyclobutane, the three C- terminal amino acids have been replaced by one D-proline derivative, and serine-2 has been replaced by *tert*-leucine. One of the amide carbonyls have been converted to a thioamide to increase resistance to protease activity. However,

6-11 still greatly resembles a peptide with several amide linkages, which are susceptible to exo-peptidase enzymes.

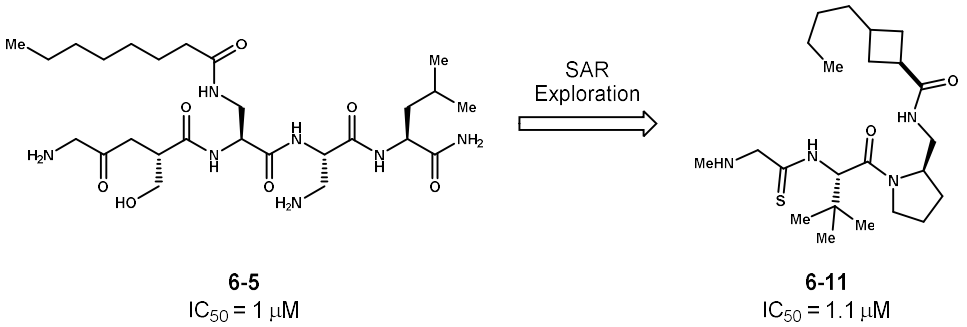


Figure 6.3. SAR Exploration of Pentapeptide **6-5** to Produce Peptidomimetic **6-11**

Several options were examined to either eliminate or mask the polar nature of the lead. The cyclobutanoyl amide portion of the molecule was identified as one area where lipophilicity could be increased; in addition the necessity of a hydrogen bond acceptor at this position could be probed. It was hypothesized that conversion of the cyclobutanoyl amide to an alkyne could address these issues, as well as providing a functional handle to explore a variety of groups in this portion of the molecule. In addition, the dramatic change in geometry in converting an amide to an alkyne would allow for the probing of active site flexibility in "octanoyl" portion of the lead.

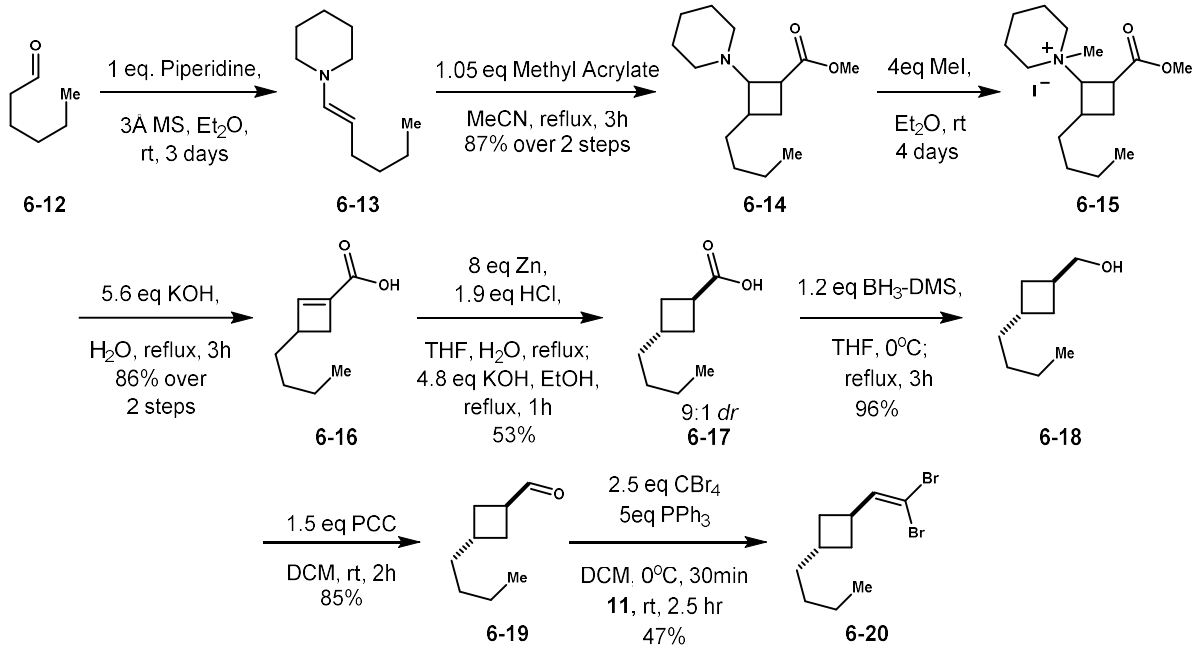
Alternatively, another viable method of reducing the peptidal-nature of the lead is incorporation of the system into a macrocyclic framework. Generally, constraining peptide systems into macrocycles imparts increased stability towards proteases.[322–324] In addition, this alteration would greatly reduce the conformational degrees of freedom for the system leading to a more defined conformation, which might improve binding capability. *In vitro* pharmacokinetic studies revealed that the modified terminal sarcosine residue was readily cleaved. It was hypothesized that introduction of a macrocycle in the southern portion of **6-11** could lead to more metabolically

stable inhibitors of GOAT. With these modifications in mind, we set out to identify synthetic routes to access the alkyne and macrocyclic derivatives.

6.2. Results and Discussion

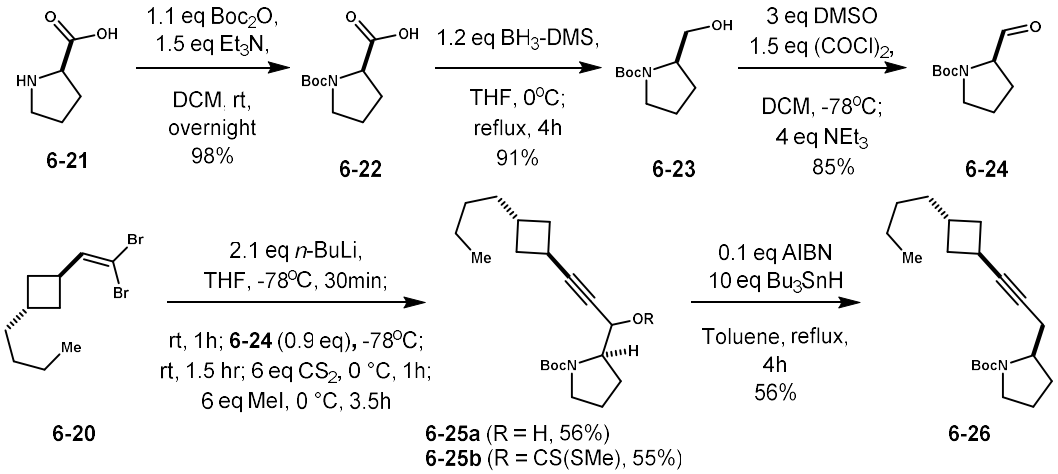
6.2.1. Construction of the Alkyne Based Inhibitors

Our approach to the cyclobutyl portion of the lead is based on the cyclobutane construction developed by Dehmlow.[325] The synthesis commences with a condensation reaction between hexanal (**6-12**) and piperidine to afford enamine **6-13**, which was then treated with methyl acrylate at high temperature to effect a Michael-Mannich cascade to construct the cyclobutane core as an inconsequential mixture of diastereomers. This is a reliable approach that has been utilized to produce a variety of cyclobutanes.[326,327] The piperidine is then quaternized by treatment with excess methyl iodide to afford **6-15**, which then undergoes a Hofmann elimination/saponification when refluxed in aqueous KOH to afford acid **6-16**. This material can then be undergo a conjugate reduction by treatment with activated zinc in aqueous HCl to afford predominately the *trans* isomer.[325] It was determined that a basic workup can further enrich the mixture with the desired diastereomer. This approach was easily scaled to afford decagram quantities of **6-17**.



Scheme 6.1. Construction of Alkyne Precursor **6-20**

The acid could then be converted to aldehyde **6-17** by a simple two step procedure. We originally considered converting the aldehyde to the alkyne via Ohira-Bestmann homologation.[328–330] However, the process proved capricious for this system. In addition, the alkyne product proved difficult to isolate cleanly when produced from this method. The Corey-Fuchs method was then explored and cleanly provided dibromoalkene **6-20**, albeit in modest yield.[331] This approach proved superior because the second portion of the Corey-Fuchs method generates a lithium acetylide *in situ*, which could be used for direct functionalization.

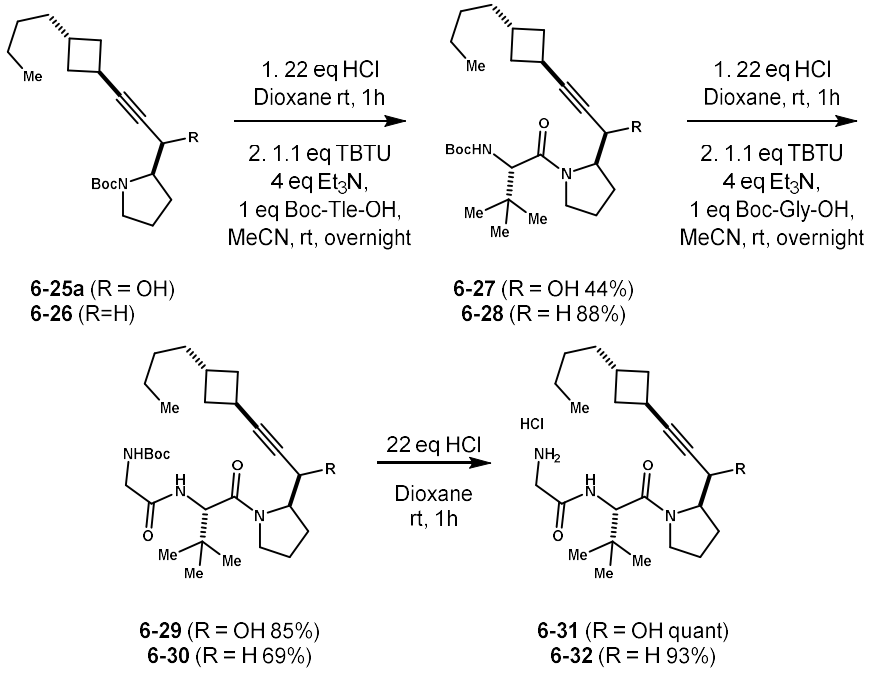


Scheme 6.2. Generation and Functionalization of Alkyne

It was envisioned that the lower portion of the lead would be combined with the acetylide via nucleophilic addition to Boc-D-prolinal (**6-24**). **6-24** was produced in three steps as shown in **Scheme 6.2**. The acetylide generation and nucleophilic addition go smoothly and on aqueous quench at this stage affords propargylic alcohol **6-25**, a versatile functionality that could be used for further derivatization. The acetylide addition is a highly diastereoselective process with only one diastereomer observed in the crude mixture. Unfortunately, the configuration of this newly generated stereocenter was not assigned. Alternatively, the intermediate alkoxide could be trapped

with CS_2 and methyl iodide to afford xanthate **6-25b** in good yield, which could then be deoxygenated with Barton-McCombie conditions to afford **6-26**.[332–334]

Propargylic alcohol **6-25a** and deoxygenated **6-26** were then deprotected to afford the free intermediate secondary amines, which were acylated under standard coupling conditions with Boc-Tle-OH. Another deprotection and acylation with protected glycine followed by a final deprotection afforded the desired alkyne GOAT inhibitors. These compounds were then examined *in vitro* for their ability to suppress the formation of acyl ghrelin.[288] Unfortunately, the conversion of the amide to the alkyne resulted in inactive compounds.

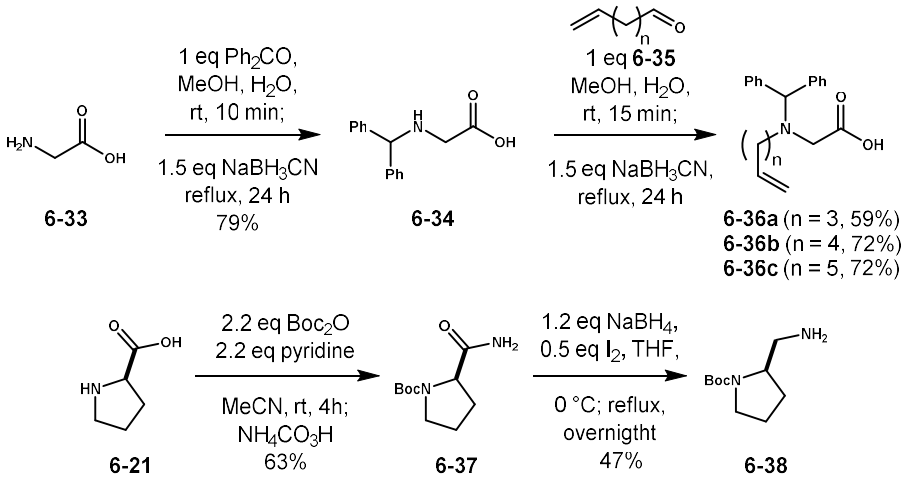


Scheme 6.3. Completion of Alkyne GOAT Inhibitors **6-31** and **6-32**

6.2.2. Production of Macrocyclic GOAT Inhibitors

With the conversion of the cyclobutanamide group to an alkyne proving unsuccessful, we turned our attention to the generation of macrocyclic inhibitors. We chose to link the terminal glycine

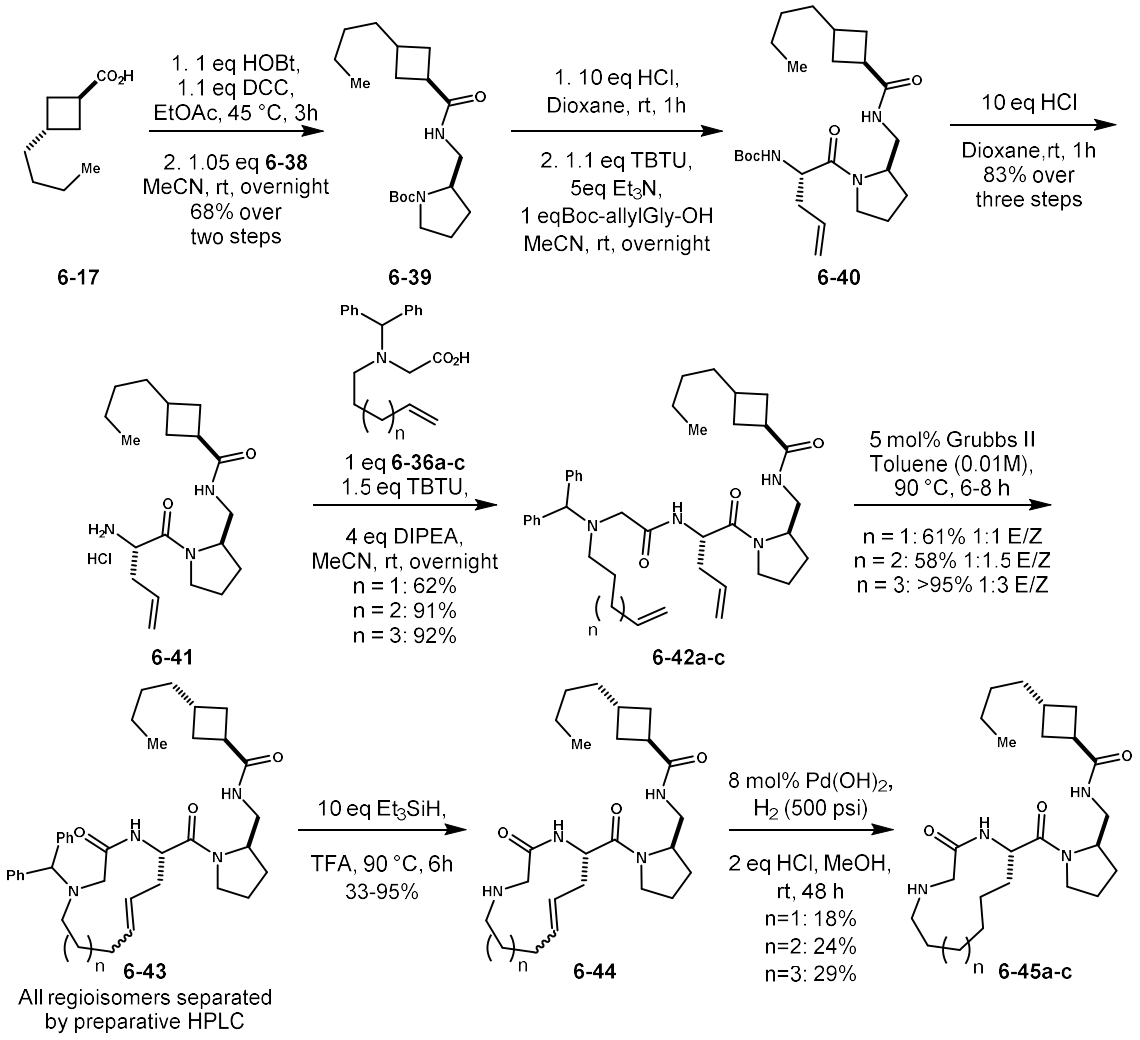
residue to the P2 *tert*-leucine group. Prior studies had indicated that increased lipophilicity at P2 was well tolerated. Ring closing metathesis was the chosen method for macrocyclization due to the relative ease in constructing different ring sizes by choice of olefinic group appended to the P1 glycine. Glycine (**6-33**) was protected as the benzhydryl derivative and then a reductive amination was used to install different olefin linker chain lengths (**6-36a-c**).[335]



Scheme 6.4. Generation of Macrocycle Building Blocks **6-36** and **6-38**

Access to aminomethylpyrrolodine **6-38** was accessed via two steps from D-proline (**6-21**).[336] This material was then coupled to **6-17** with a standard DCC coupling. The secondary amine was then liberated by treatment with acid and then acylated with Boc-allylGly-OH to afford **6-40**. This material was then deprotected to afford **6-41**. This key intermediate could be coupled to modified glycine residues **6-36a-c** to afford the seco precursors **6-42a-c**. These structures were then subjected to RCM with catalytic amounts of Grubbs 2nd generation catalyst to afford E/Z mixtures of macrocycles. These regioisomers were inseparable by flash column chromatography. Fortunately, they could be separated by preparative HPLC to afford each pure regioisomer. The initial attempts to cleave the benzhydryl group via hydrogenolysis resulted only in reduction of the ring olefin, but reductive cleavage could be effected by treatment with excess Et_3SiH in refluxing

TFA.[337,338] Alternatively, the saturated variants could be accessed by telescoping the deprotection into a hydrogenation to afford **6-45a-c**. This modular route allowed for the production of a small library of nine macrocycles. However, the *in vitro* activities of all the macrocycles produced and tested were either inactive or less potent than **6-11**.



Scheme 6.5. Construction of a Small Macrocycle Library

6.3. Conclusion

The therapeutic manipulation of ghrelin levels carries with it the potential to treat several human diseases. The selective inhibition of GOAT would be the ideal approach to control ghrelin levels and to study the ghrelin signaling pathway in more detail. A hypothesis driven approach was utilized to convert octanoylated pentapepted **6-5** into the more drug-like small molecule lead **6-11**. However, this structure is still remains peptidal in nature, which means that it is still highly polar and susceptible to exo-peptidases. We explored two modifications of this lead, the first being conversion of the cyclobutanoyl amide into an alkyne. This modification probed the necessity of a hydrogen bond acceptor at this position of the lead, as well as probed the flexibility of the enzyme active through a change in geometry. This change proved ineffective and activity was completely lost. Incorporation of the peptidal framework into a macrocyclic motif was the second modification that was explored. It was anticipated that this change would increase the lead's proteolytic stability, however, all the macrocycles constructed displayed reduced activity in *in vitro* assays. This project is ever evolving and new structural motifs with improved pharmacokinetic properties are currently being developed.

6.4. Experimental

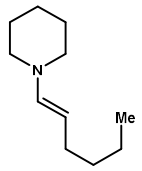
6.4.1. Materials and Methods

All reactions were carried out using oven- or flame-dried glass and a magnetic stir bar under an atmosphere of argon (Ar) unless otherwise indicated. Tetrahydrofuran (THF), diethyl ether (Et_2O), methylene chloride (DCM), toluene, acetonitrile (MeCN), and methanol were dried by passage through activated alumina using a GlassContour® solvent drying system. Triethylamine, and diisopropylamine were distilled from CaH_2 under inert atmosphere prior to use. All other commercial reagents and catalysts were used as received unless otherwise indicated.

NMR spectra were recorded on Bruker Advance spectrometerrs (400 MHz, 500 MHz) and are reported as δ values in ppm relative to $CDCl_3$ (calibrated to 7.27 ppm in ^1H NMR and 77.16 ppm in ^{13}C NMR, unless otherwise indicated) and were conducted at room temperature (unless otherwise indicated). ^1H NMR coupling constants are reported in Hz. Splitting patterns are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), septet (sept), multiplet (m), broad (br), apparent (app), and combinations thereof. Column chromatography was conducted on silica gel 60 (240-400 mesh) purchased from Silicycle or neutral aluminum oxide (activated, Brockmann I) purchased from Sigma Aldrich. Thin layer chromatography (TLC) was performed using pre-coated, glass-backed plates (SiO_2, 60 PF254, 0.25 mm or neutral Al_2O_3, 0.25 mm) and visualized using a combination of UV, anisaldehyde, and potassium permanganate staining.

6.4.2. Experimental Procedures and Characterization

1-(hex-1-en-1-yl)piperidine (6-13)

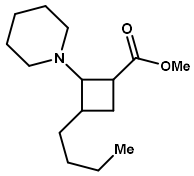


6-13

To a flask with 120 g of activated 3Å molecular sieves, Et_2O (180 mL, 2.7 M) was added followed by hexanal **6-12** (60 mL, 488.26 mmol). Piperidine (48.1 mL, 486.93 mmol, 0.99 eq) was added dropwise to the solution over 30 minutes. The solution was allowed to sit for three days at room temperature with occasional swirling. The reaction mixture was then filtered over Celite and concentrated to a light yellow oil, which was carried on to the next step without purification.

1-(hex-1-en-1-yl)piperidine (6-13):
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.80 (d, *J* = 12.0 Hz, 1H), 4.36 (dt, *J* = 6.9, 13.9 Hz, 1H), 2.78-2.69 (m, 4H), 1.95-1.93 (m, 2H), 1.57-1.27 (m, 10H), 0.88 (m, 3H)

Methyl 3-butyl-2-(piperidin-1-yl)cyclobutane-1-carboxylate (6-14)

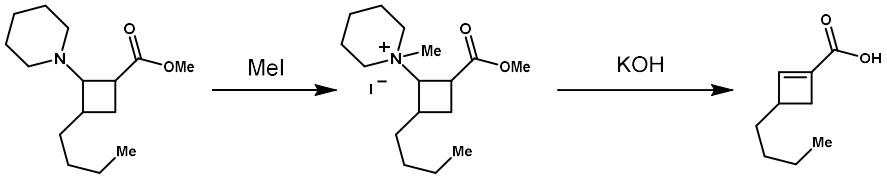


6-14

Enamine **6-13** (assume 100% from the previous step, 487 mmol) was dissolved in MeCN (180 mL, 2.7M) followed by the addition of methyl acrylate (47 mL, 518.64 mmol, 1.05 eq). The solution was then heated to reflux for 3 hours and then cooled to room temperature. The solution was concentrated to afford **6-14** (107.4 g, 87%) as an orange oil, which was used in the next step without purification. **6-14** is a mixture of all 8 diastereomers

Methyl 3-butyl-2-(piperidin-1-yl)cyclobutane-1-carboxylate (6-14):
^{1}H NMR (400 MHz, $CDCl_3$): δ 3.73 (m, 1H), 2.85-2.70 (m, 1H), 2.65-2.6 (m, 2H), 2.4-2.35 (m, 2H), 2.35-2.2 (m, 2H), 2.1-2.0 (m, 1H), 1.98 (s,3H) 1.56-1.23 (m, 12H), 0.86-0.83 (m, 3H)

3-butylcyclobut-1-ene-1-carboxylic acid (6-16)



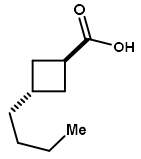
6-14 6-15 6-16

Tertiary amine **6-14** (107.4 g, 423.85 mmol) was dissolved in Et_2O (200 mL, ~2M) and MeI (106 mL, 1.702 mol, 4 eq) was added. The reaction mixture was allowed to sit for 4 days at room temperature with occasional swirling. The reaction mixture proceeded from an orange solution to a biphasic mixture with a yellow top layer and viscous orange bottom layer. The top layer was decanted and the viscous bottom layer was carefully concentrated to afford crude **6-15** as red viscous oil, which was used in the next step without purification.

Ammonium salt **6-15** (assume 100% from previous step, 423.85 mmol) was then treated with aqueous KOH (4M, 300 mL, 1.20 mol, ~3 eq). The reaction mixture was mechanically shaken until the viscous orange layer dissolved (about 30 min). The reaction mixture was then refluxed for 3 hours, then cooled to room temperature. The reaction was diluted with another portion of aqueous KOH (4M, 300 mL, 1.20 mol, ~3 eq) and the mixture was then washed with Et_2O several times. The aqueous layer was then acidified with aqueous 6M HCl (500 mL, 3.0 mol, 7.5 eq) and extracted with Et_2O several times. The organics were then dried over Na_2SO_4 and concentrated to afford **6-16** (56.1 g, 86% over two steps) as a dark red oil, which was taken on to the next step without purification.

3-butylcyclobut-1-ene-1-carboxylic acid (6-16):
^{1}H NMR (300 MHz, $CDCl_3$): δ 6.97 (d, *J* = 1.1 Hz, 1H), 2.82 (dd, *J* = 4.2, 13.2 Hz, 1H), 2.75-2.64 (m, 1H), 2.24 (dd, *J* = 1.5, 13.2 Hz, 1H), 1.56-1.40 (m, 2H), 1.38-1.26 (m, 4H), 0.88 (t, *J* = 7.1 Hz, 3H)

***trans*-3-butylcyclobutane-1-carboxylic acid (6-17)**



6-17

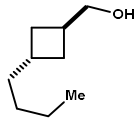
Acid **6-16** (10.1 g, 65.49 mmol) was dissolved in THF (400 mL) and aqueous HCl (0.3 M, 410 mL, 122.5 mmol, 1.88 eq). Freshly activated Zn (38.9 g, 594.98 mmol, 8 eq) was added portionwise to the reaction over the course of 1h. The mixture was then refluxed for 2 hours and then allowed to cool to room temperature. The reaction mixture was then extracted with Et_2O several times. The organics were then concentrated to afford an oil. The crude was taken up in H_2O/EtOH (5:1, 300 mL) and KOH (17.63 g, 314.35 mmol, 4.8 eq) was added. The mixture was refluxed for 1 hour and then cooled to room temperature. The reaction was extracted with ether several times. The reaction was then acidified with aqueous HCl (6M, 100 mL) and extracted with Et_2O several times. The organics were then dried over $MgSO_4$, filtered and concentrated to a dark

brown oil. The residue was purified by flash column chromatography (SiO_2, 4:1 Hexanes/EtOAc) to provide **6-17** (6.0 g, 59%) as a yellow oil.

***trans*-3-butylcyclobutane-1-carboxylic acid (6-17):**
^{1}H NMR (300 MHz, $CDCl_3$): δ 12.17 (s, 1H), 3.16-3.01 (m, 1H), 2.47-2.31 (m, 2H), 1.96-1.80 (m, 2H), 1.42 (q, J=7.35 Hz, 2H), 1.26 (p, J=6.69 Hz, 2H), 1.82 (m, 2H), 0.86 (t, *J* = 7.1 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$):182.9, 35.9, 34.8, 32.0, 30.2, 29.1, 22.5, 13.9

***trans*-3-butylcyclobutylmethanol** (**6-18**)



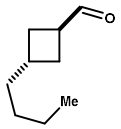
6-18

Acid **6-17** (2.0089 g, 12.86 mmol) was dissolved in THF (15 mL, 0.85M) and cooled to 0 °C. BH_3·DMS (2M in THF, 7.7 mL, 15.40 mmol, 1.2 eq) was added dropwise to the mixture, which was stirred at 0 °C for 30 minutes and then warmed to room temperature. The reaction mixture was then heated to reflux for 3 hours and then cooled to room temperature. The reaction was carefully quenched by the addition of ice water. The THF was removed under reduced pressure and the mixture was then extracted with EtOAc. The organics were dried over Na_2SO_4, filtered, and then concentrated to afford **6-18** (1.7613 g, 96%) as a light brown oil.

***trans*-3-butylcyclobutylmethanol (6-18):**
^{1}H NMR (300 MHz, $CDCl_3$): δ 3.57 (d, *J* = 7.3Hz, 2H), 2.52 (s, 1H), 2.39-2.30 (m, 1H), 2.17 (heptet, *J* = 7.45Hz, 1H), 1.85-1.74 (m, 2H), 1.70-1.60 (m, 2H), 1.38 (q, *J* = 7.6 Hz, 2H), 1.24 (sextet, *J* = 7.4 Hz, 2H), 1.13 (p, *J* =7.5 Hz, 2H), 0.83 (t, *J* =7.4 Hz, 3H)

^{13}C NMR (75 MHz, $CDCl_3$): δ 66.9, 36.5, 33.1, 31.8, 31.0, 29.4, 29.3, 22.6, 22.5, 13.9

***trans*-3-butylcyclobutane-1-carbaldehyde (6-19)**



6-19

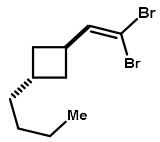
To a solution of alcohol **6-18** (1.20 g, 8.43 mmol) in DCM (17 mL, 0.5M), Celite® (1.0 g) was added followed by PCC (2.7381 g, 12.70 mmol, 1.5 eq). The reaction was stirred for 2h at room temperature when TLC indicated that the starting material was consumed. SiO_2 (2 g) was then added to the reaction mixture and the mixture was stirred for 10 minutes at room temperature. The mixture was flushed through a silica plug with DCM. The filtrate was concentrated to afford **6-19** (1.0 g, 85%) as a pale yellow oil. The isolated material is a roughly 10:1 mixture of the *trans/cis* isomers.

***trans*-3-butylcyclobutane-1-carbaldehyde (6-19):**

^{1}H NMR (300 MHz, $CDCl_3$): δ 9.75 (d, *J* =2.0 Hz, 1H), 9.6 (d, J=2.1 Hz, 0.1H)*, 3.08-2.96 (m, 1H), 2.38-2.27 (m, 2H), 2.21 (h, *J* = 7.6 Hz, 1H), 1.85-1.72 (m, 2H), 1.4 (q, *J* =7.6 Hz, 2H), 1.24 (sextet, *J* = 7.1 Hz, 2H), 1.14 (p, *J* = 7.2 Hz, 2H), 0.83 (t, *J* = 7.2 Hz, 3H)

^{13}C NMR (75 MHz, $CDCl_3$): δ 202.9, 53.2, 42.4, 36.2, 32.1, 28.9, 27.4, 22.4, 13.8

trans-1-butyl-3-(2,2-dibromovinyl)cyclobutane (6-20)



6-20

To a solution of CBr_4 (5.9532 g, 17.95 mmol, 2.5 eq) in of DCM (25 mL) at 0 °C, PPh_3 (9.4452 g, 36.01 mmol, 5 eq) was added. The solution was stirred for 30 minutes at 0 °C and progressed from clear to cloudy red. A solution of aldehyde **6-19** (1.0 g, 7.13 mmol) in DCM (8 mL) was added dropwise to the red mixture. The solution was then warmed to room temperature and stirred for 2.5 hours. The reaction changed color from cloudy red to cloudy brown during this period. The reaction was quenched by the careful addition of sat. aqueous $NaHCO_3$ (CAUTION*: vigorous bubbling occurs during the quench). The reaction mixture was then diluted with hexanes and filtered through a Celite® plug with hexanes. The filtrate was then washed with sat. aqueous $NaHCO_3$ and the organics were dried over Na_2SO_4. The organics were then filtered and concentrated to afford white crystals, which were filtered and washed with hexanes. The filtrate was then flushed through a SiO_2 plug with hexanes and the filtrate was concentrated to afford **6-20** (1.0 g, 47%) as a clear colorless oil. The isolated material is a roughly 10:1 mixture of *trans/cis* isomers.

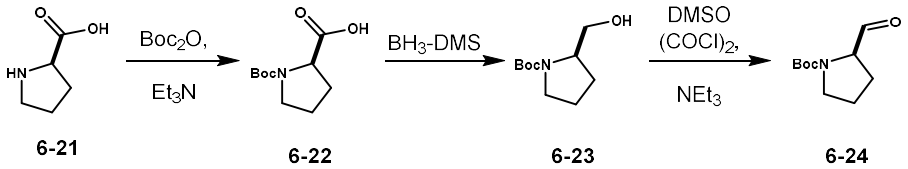
trans-1-butyl-3-(2,2-dibromovinyl)cyclobutane (6-20):

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.63 (d, *J* = 8.6 Hz, 1H), 6.41 (d, *J* =8.2 Hz, 0.1H)*, 3.16-3.01 (m, 1H), 2.23 (h, *J* = 7.2 Hz, 1H), 2.06-1.86 (m, 4H), 1.44 (q, *J* = 7.6 Hz, 2H), 1.29 (sextet, *J* = 7.3 Hz, 2H), 1.18 (pentet, J= 7.6 Hz, 2H), 0.88 (t, J=7.3 Hz, 3H)

^{13}C NMR (125 MHz, $CDCl_3$): δ 143.8, 87.0, 35.7, 35.2, 32.9, 31.9, 29.3, 22.5, 14.0

IR: 2956, 2924, 2853, 1611, 1456, 802, 773, 675

Conversion of *D*-proline (6-22) into Boc-*D*-Prolinal (6-24)



6-21 6-22 6-23 6-24

To a solution of **6-21** (3.095 g, 26.8 mmol) in DCM (25 mL, ~1M), Boc_2O (6.8 mL, 29.59 mmol, 1.1 eq) was added followed by Et_3N (8.4 mL, 60.26 mmol, 2.2 eq). The mixture was stirred for 6h at room temperature. The reaction was then quenched with aqueous 1M $KHSO_4$ and extracted with DCM. The organic layer was then washed with brine. The organics were then dried over Na_2SO_4, filtered, and then concentrated to afford **6-22** (5.65 g, 98%) as a white solid, which was used without further purification.

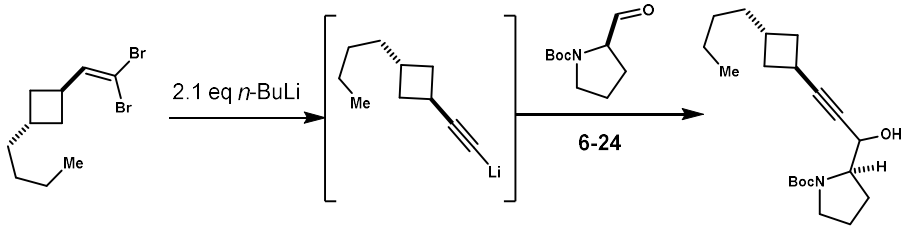
To a solution of acid **6-22** (8.4 g, 39.02 mmol) dissolved in THF (50 mL, 0.8M) at 0 °C, BH_3·DMS (2M in THF, 23 mL, 46.0 mmol, 1.2 eq) was added dropwise. The reaction was stirred at 0 °C for 30 minutes and then warmed to room temperature. The reaction was then refluxed for 4 hours and then cooled to room temperature. The reaction was then cooled to 0 °C and quenched with ice water. The THF was removed from the reaction and the mixture was extracted with EtOAc several times. The organic layer was then dried with Na_2SO_4, filtered, and concentrated. The crude oil was then purified by flushing through a SiO_2 plug with 1:1 Hexanes/EtOAc to afford **6-23** (7.17 g, 91%), which was used without further purification.

To a solution of $(COCl)_2$ (0.65 mL, 7.58 mmol, 1.5 eq) in DCM (15 mL) -78°C, a solution of DMSO (1.1 mL, 15.5 mmol, 3 eq) in DCM (1 mL) was added. The solution was stirred for 30 minutes at -78 °C. A solution of alcohol **6-23** (1.0169 g, 5.05 mmol) in DCM (5 mL) was added dropwise to the reaction. The solution was stirred for 1.5 hours at -78 °C. The solution was then warmed to 0 °C and Et_3N (3.6 mL, 25.7 mmol, 5 eq) was added dropwise to the stirred solution. The solution became cloudy/foamy and slightly orange. The solution was stirred for 3 hours as it warmed from 0 °C to room temperature. The reaction was then quenched with sat. aqueous $NaHCO_3$ and extracted with Et_2O several times. The organics were then dried over $MgSO_4$ and concentrated to a yellow oil. The crude oil was then purified with flash column chromatography (SiO_2, 5:1→2:1 Hexanes/EtOAc) to provide **6-24** (0.8589 g, 85%). Aldehyde **6-24** exists as a mixture of rotamers.

Boc-*D*-Prolinal (6-24):

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.46 (bs, 0.4H), 9.38 (bs, 0.6H)*, 4.15-4.04 (m, 0.4H), 4.01-3.93 (m, 0.6H)*, 3.53-3.12 (m, 2H), 2.16-1.70 (m, 4H), 1.39 (bs, 5H), 1.34 (bs, 3H)*

Combining Alkyne Precursor 6-20 with Aldehyde 6-24



6-20 6-25a

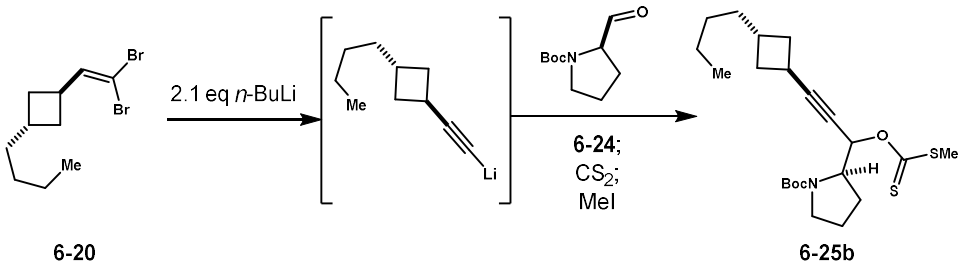
To a solution of dibromide **6-20** (0.5069 g, 1.71 mmol) in THF (6 mL) at -78 °C, *n*BuLi (2.5M in Hexanes, 1.42 mL, 3.57 mmol, 2.1 eq) was added dropwise. The solution was stirred at -78 °C for 30 minutes and at room temperature for 1h. The solution went from clear to orange. The solution was then cooled to -78°C and a solution of aldehyde **6-24** (0.3098 g, 1.56 mmol, 0.9 eq) in THF (3 mL) was added dropwise. The solution was then allowed to warm to room temperature and stirred for 1.5 hours. The reaction was quenched by the addition of water and the mixture was extracted with Et_2O. The organics were dried over Na_2SO_4, filtered, and concentrated to a yellow oil. The crude was purified with flash column chromatography (SiO_2, 2:1 Hexanes/ EtOAc) to afford **6-25a** (0.2954 g, 57%) and recovered **6-24** (60.5 mg, 20%). Propargyl alcohol **6-25a** exists as a mixture of rotamers.

***tert*-butyl (*R*)-2-((*R*)-3-(*trans*-3-butylcyclobutyl)-1-hydroxyprop-2-yn-1-yl)pyrrolidine-1-carboxylate (6-25a):**

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.95-5.75 (m, 1H), 4.45-4.3(m, 1H), 4.0-3.8 (m, 1H), 3.61-3.41 (m, 1H), 3.38-3.26 (m, 1H), 3.0-2.88 (m, 1H), 2.31 (sextet, *J* =7.2 Hz, 1H), 2.14-2.01 (m, 2H), 2.00-1.94 (m, 1H), 1.94-1.85 (m, 2H), 1.82-1.67 (m, 2H), 1.41 (s, 9H), 1.32 (q, *J* = 7.6 Hz, 2H), 1.20 (p, J=7.3 Hz, 2H), 1.10 (sextet, J=6.7 Hz, 2H), 0.81 (t, J= 7.25 Hz, 3H)

^{13}C NMR (125 MHz, $CDCl_3$): 156.8, 90.0, 80.2, 80.0*, 78.8, 67.1, 67.0*, 63.3, 62.8*, 48.1, 47.4*, 36.5, 36.4, 35.9, 35.5, 35.5, 34.5, 34.4, 34.3, 32.7, 32.5, 32.4, 29.2, 29.0, 28.5, 28.2, 23.8, 23.6, 22.4, 22.4, 20.9, 20.8, 13.9 (mixture of Boc rotamers)

Combining Alkyne Precursor 6-20 with Aldehyde 6-24 followed by Carbon Disulfide/Methyl Iodide Quench



6-20 6-25b

To a solution of dibromoalkene **6-20** (0.4009 g, 1.35 mmol) in THF (6 mL) -78 °C, *n*BuLi (2.5M in Hexanes, 1.14 mL, 2.875 mmol, 2.1 eq) was added dropwise. The solution changed color from light yellow to orange. The solution was stirred at -78 °C for 30 minutes, then warmed to room temperature and stirred for 1h. The solution was then cooled to -78 °C and a solution of aldehyde **6-24** (0.2339 g, 1.17 mmol, 0.85 eq) in THF (4 mL) was added dropwise. The mixture was then warmed to room temperature and stirred for 1h. The reaction was then cooled to 0 °C and CS_2 (0.49 mL, 8.1 mmol, 6 eq) was added dropwise. The solution was then stirred for an hour at 0 °C and then MeI (0.50 mL, 8.1 mmol, 6 eq) was added dropwise. The reaction was stirred for 3.5 hours at 0 °C. The reaction was then quenched by the addition of water and the mixture was extracted with Et_2O. The organics were dried over Na_2SO_4 and concentrated to an orange oil. The crude was purified by flash column chromatography (SiO_2, 4:1 Hexanes/EtOAc) to afford **6-25b** (0.3159 g, 55%). Xanthate **6-25b** exists as a mixture of Boc rotamers.

***tert*-butyl (*R*)-2-((*R*)-3-(*trans*-3-butylcyclobutyl)-1-(((methylthio)carbonothioyl)oxy)prop-2-yn-1-yl)pyrrolidine-1-carboxylate (6-25b):**

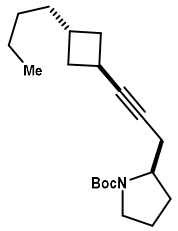
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.78-6.66 (m, 0.3H), 6.6-6.52 (m, 0.7H)*, 4.2-3.96 (m, 1H), 3.60-3.20 (m, 2H), 3.03-2.93 (m, 1H), 2.54 (s, 3H), 2.42-2.3 (m, 1H), 2.28-2.2 (m, 1H), 2.18-1.94 (m, 4H), 1.93-1.84 (m, 2H), 1.83-1.72 (m, 1H), 1.45 (s, 6H), 1.40 (s, 3H)*, 1.39-1.30 (m, 2H), 1.26 (sextet, J = 7.2 Hz, 2H), 1.16 (m, 2H), 0.85 (t, J = 7.1 Hz, 3H)

^{13}C NMR (125 MHz, $CDCl_3$): 214.9, 213.3*, 154.2, 153.8*, 93.2, 80.0, 79.9*, 79.3, 75.2, 74.6, 74.1, 74.0, 73.6, 60.7, 60.5*, 58.1, 55.2, 46.9, 36.4, 35.8, 35.7, 35.5, 34.2, 34.1, 32.8, 32.5, 32.4, 29.2, 28.4, 28.3, 27.4, 26.2, 24.1, 23.4, 23.3, 23.0, 22.5, 22.4, 21.5, 21.01, 19.2, 14.0, 13.9 (mixture of rotamers)

IR: 2959, 2927, 2240, 1694, 1389, 1210, 1167, 1116, 1051

HRMS: Mass Expected for $C_{22}H_{36}NO_3S_2^+$: 426.2136 *m*/*z* Mass Observed: 426.2121 *m*/*z*

***tert*-butyl (*R*)-2-(3-(*trans*-3-butylcyclobutyl)prop-2-yn-1-yl)pyrrolidine-1-carboxylate (6-26)**



6-26

To a solution of xanthate **6-25b** (0.2366 g, 0.556 mmol) and AIBN (12.8 mg, 0.078 mmol, 15 mol%) in toluene (10 mL, 0.05M), Bu_3SnH (1.50 mL, 5.57mmol, 10 eq) was added. The reaction was then heated to reflux for 4 hours. The solution changed from yellow to black to clear. The solution was quenched with the addition of aqueous 1M NaOH and extracted with EtOAc. The organic layer was partially concentrated and then flushed through a SiO_2 plug with hexanes followed by ethyl acetate. The ethyl acetate filtrate was concentrated to a yellow oil. The crude was purified by flash column chromatography (15:1→10:1→5:1 Hexanes/EtOAc) to afford **6-26** (98.8 mg, 56%) as a yellow oil. Alkyne **6-26** exists as a mixture of Boc rotamers.

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.93-3.73 (m, 1H), 3.46-3.26 (m, 2H), 2.96-2.86 (m, 1H), 2.62-2.45 (m, 1H), 2.41-2.26 (m, 2H), 2.16-2.03 (m, 2H), 2.02-1.82 (m, 3H), 1.82-1.71 (m, 2H), 1.62 (m, 1H), 1.44 (s, 9H), 1.36 (q, *J* = 7.4 Hz, 2H), 1.25 (heptet, *J* = 7.0 Hz, 2H), 1.14 (pentet, *J* =7.4 Hz, 2H), 0.85 (t, *J* = 6.7 Hz, 3H)

^{13}C NMR (125 MHz, $CDCl_3$): 154.3, 86.5, 86.2*, 79.2, 78.9*, 77.9, 77.6*, 56.4, 47.0, 46.7*, 36.6, 36.4, 35.7, 34.8, 32.7, 32.5, 30.5, 29.7, 29.4, 29.2, 28.5, 24.3, 23.6, 22.9, 22.6, 22.5, 21.7, 21.3, 20.7, 14.0

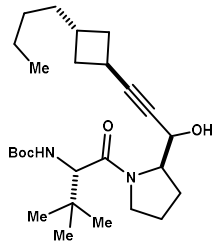
IR: 2961, 2928, 2249, 1694, 1391, 1240, 1169, 1117

HRMS (ESI) m/z, 320.2577 (320.2589 calculated for $C_{20}H_{34}NO_2^+$, $(M+H)^+$)

General Boc Deprotection Method- The carbamate is dissolved in a designated amount of 4M HCl in Dioxane. The reaction is stirred until TLC indicates that starting material is consumed, normally 1h. The reaction mixture is then concentrated to afford the crude HCl salt, which is used without purification.

General Amide Coupling Method- To a MeCN solution (0.2M) of amine and acid (1 eq), TBTU (1.1 eq) and triethylamine/diisopropylethylamine (5 eq) are added. The solution was then stirred until TLC indicates that starting material is consumed, usually overnight. The reaction is the quenched with the addition of aqueous 1M HCl and extracted with ethyl acetate. The organic layer is washed with saturated $NaHCO_3$ and brine. The organics are then dried over $MgSO_4$, filtered, and concentrated. The crude residue is either carried on to the next step or purified by flash column chromatography.

***tert*-butyl ((*S*)-1-((R)-2-((R)-3-((1s,3R)-3-butylcyclobutyl)-1-hydroxyprop-2-yn-1-yl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)carbamate (6-27)**



6-27

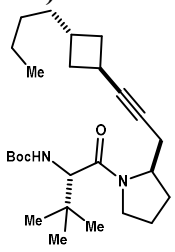
Starting with **6-25a** (0.2954 g, 0.881 mmol) both the general deprotection (22eq HCl) and general amide coupling (Boc-t-leucine) procedures were utilized. The crude was purified by flash column chromatography (SiO_2, 4:1 Hexanes/EtOAc) to afford **6-27** (0.1735 g, 44% over two steps). Amide **6-27** exists as a mixture of rotamers.

***tert*-butyl ((*S*)-1-((R)-2-((R)-3-((1s,3R)-3-butylcyclobutyl)-1-hydroxyprop-2-yn-1-yl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)carbamate (6-27):**

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.81 (bs, 0.6H), 5.69 (bs, 0.4H)*, 5.32-5.11 (m, 1H), 4.61-4.49 (m, 1H), 4.36-4.26 (m, 1H), 4.23-4.14 (m, 1H), 3.79-3.70 (m, 1H), 3.70-3.61 (m, 1H), 3.00-2.89 (m, 0.6H), 2.80-2.69 (m, 0.4H)*, 2.36-2.21 (m, 1H), 2.15 (m, 3H), 1.97-1.80 (m, 2H), 1.79-1.67 (m, 1H), 1.65-1.54 (m, 1H), 1.43 (s, 9H), 1.36 (q, *J* = 7.9 Hz, 2H), 1.28-1.16 (m, 4H), 1.14 (p, *J* = 7.1 Hz, 2H), 0.97 (s, 9H), 0.87 (m, 3H)

^{13}C NMR (125 MHz, $CDCl_3$): 172.2, 170.9*, 155.7, 90.4, 89.6*, 79.5, 78.5, 77.9*, 65.7, 65.5*, 64.0, 63.9*, 60.2, 58.7*, 49.5, 36.4, 36.0, 35.9, 35.4, 35.1, 34.3, 34.3, 32.7, 32.3, 31.4, 29.2, 29.1, 28.2, 28.1, 26.4, 26.2, 24.0, 22.5, 22.4, 21.4, 20.9, 20.8, 14.0

***tert*-butyl ((*S*)-1-((*R*)-2-(3-((1*S*,3*R*)-3-butylcyclobutyl)prop-2-yn-1-yl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)carbamate (6-28)**



6-28

Starting with **6-26** (98.8 mg, 0.309 mmol) both the general deprotection (22 eq) and general amide coupling (Boc-*t*-leucine) procedures were utilized. The crude (0.1174 g, 88% over two steps) was carried on to the next step without purification. Amide **6-28** exists as a mixture of rotamers.

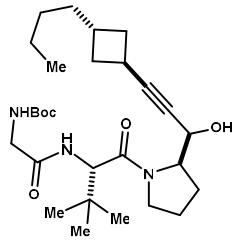
***tert*-butyl ((*S*)-1-((*R*)-2-(3-((1*S*,3*R*)-3-butylcyclobutyl)prop-2-yn-1-yl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)carbamate (6-28):**

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.29 (d, *J* = 9.7 Hz, 1H), 4.25 (d, *J* = 9.9 Hz, 1H), 4.17-4.04 (m, 1H), 3.81-3.70 (m, 1H), 3.60-3.49 (m, 1H), 2.96-2.86 (m, 1H), 2.75-2.62 (m, 1H), 2.32-2.26 (m,

2H), 2.14-2.0 (m, 3H), 1.98-1.91 (m, 1H), 1.91-1.81 (m, 2H), 1.66-1.55 (m, 1H), 1.46-1.39 (m, 11H), 1.24 (sextet, *J* = 7.0 Hz, 2H), 1.14 (p, *J* =7.2 Hz, 2H), 0.97 (s, 9H), 0.85 (t, *J* =7.3 Hz, 3H)

^{13}C NMR (125 MHz, $CDCl_3$): 170.3, 155.7, 86.4, 79.2, 77.4, 66.5, 58.3, 56.6*, 47.9, 36.5, 36.2, 35.6, 35.1, 34.9, 34.6, 32.7, 32.4, 29.3, 29.1, 28.2, 27.7, 26.7, 26.4, 26.2, 25.2, 23.5, 22.5, 22.2, 21.6, 21.1, 13.9, 13.4

***tert*-butyl (2-(((*S*)-1-((*R*)-2-((*R*)-3-((1*S*,3*R*)-3-butylcyclobutyl)-1-hydroxyprop-2-yn-1-yl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-2-oxoethyl)carbamate (6-29)**

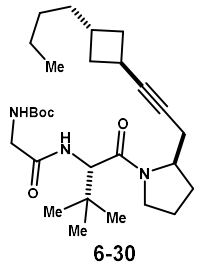


6-29

Starting with **6-27** (0.1116 g, 0.248 mmol) both the general deprotection (22 eq) and general amide coupling (Boc-glycine) procedures were utilized. The crude orange-yellow oil was then purified using flash column chromatography (SiO_2, 25:1 DCM/MeOH) to afford **6-29** (0.1068 g, 85% over two steps) as a yellow-orange oil.

***tert*-butyl (2-(((*S*)-1-((*R*)-2-((*R*)-3-((1*S*,3*R*)-3-butylcyclobutyl)-1-hydroxyprop-2-yn-1-yl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-2-oxoethyl)carbamate (6-29):**
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.74 (d, *J* = 7.6 Hz, 1H), 5.12 (bs, 1H), 4.74 (dd, *J* = 2.6, 9.1 Hz, 1H), 4.60-4.53 (m, 1H), 4.25-4.17 (m, 1H), 3.92-3.83 (m, 1H), 3.83-3.76 (m, 1H), 3.75-3.65 (m, 2H), 2.99-2.90 (m, 1H), 2.38-2.26 (m, 1H), 2.20-1.99 (m, 3H), 1.98-1.83 (m, 2H), 1.82-1.73 (m, 1H), 1.61-1.55 (m, 1H), 1.45(s, 9H), 1.41-1.31 (m, 2H), 1.25 (sextet, *J* = 7.2 Hz, 2H), 1.19-1.09 (m, 2H), 1.00 (s, 9H), 0.86 (t, *J* =7.5 Hz, 3H)

***tert*-butyl (2-(((*S*)-1-((*R*)-2-(3-((1*S*,3*R*)-3-butylcyclobutyl)prop-2-yn-1-yl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-2-oxoethyl)carbamate (6-30)**



6-30

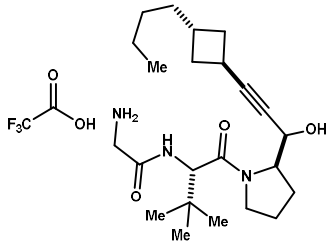
Starting with **6-28** (0.1174 g, 0.271 mmol) both the general deprotection (22 eq) and general amide coupling (Boc-glycine) procedures were utilized. The crude was purified by flash column chromatography (SiO_2, 30:1 DCM/MeOH) to afford **6-30** (91.5 mg, 69% over two steps). Amide **6-30** exists as a mixture of rotamers.

***tert*-butyl (2-(((*S*)-1-((*R*)-2-(3-((1*S*,3*R*)-3-butylcyclobutyl)prop-2-yn-1-yl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-2-oxoethyl)carbamate (6-30):**

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.90-6.71 (m, 1H), 5.45-5.25 (m, 1H), 4.62 (d, *J* = 8.7 Hz, 1H), 4.11-4.03 (m, 1H), 3.92-3.79 (m, 1H), 3.75-3.64 (m, 2H), 3.59-3.48 (m, 1H), 2.92-2.84 (m, 1H), 2.71-2.58 (m, 1H), 2.35-2.2 (m, 2H), 2.1-1.95 (m, 4H), 1.95-1.89 (m, 1H), 1.88-1.77 (m, 2H), 1.64-1.50 (m, 1H), 1.40 (s, 9H), 1.36-1.28 (m, 2H), 1.27-1.17 (m, 2H), 1.16-1.05 (m, 2H), 1.00 (s, 2H)*, 0.94 (s, 7H), 0.86-0.79 (m, 3H)

^{13}C NMR (125 MHz, $CDCl_3$): 169.4, 168.8, 155.7, 86.4, 85.7, 79.9, 56.7, 56.5, 48.0, 36.5, 36.2, 35.6, 35.5, 34.5, 32.6, 32.4, 29.2, 29.1, 29.0, 28.2, 28.1, 27.6, 26.6, 26.5, 26.3, 26.2, 23.4, 22.4, 22.4, 22.2, 21.6, 21.1, 17.3, 13.9, , 13.4

2-(((*S*)-1-((*R*)-2-((*R*)-3-((1*S*,3*R*)-3-butylcyclobutyl)-1-hydroxyprop-2-yn-1-yl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-2-oxoethan-1-aminium 2,2,2-trifluoroacetate(6-31)



6-31

Starting with **6-29** (0.1068 g, 0.211 mmol) the general deprotection method (22 eq) was utilized to afford the hydrochloride salt of **6-31** (93.1 mg, quant.) as a light orange foam. A small portion of the foam was then purified using Reverse Phase HPLC (elutes at 10 min) to give a clear oil of the trifluoroacetate salt. Amine **6-31** exists as a mixture of rotamers.

HPLC Conditions: Waters Sunfire C18 column (19 x 250 mm) with UV detection at 280 nm; Solution A: H_2O w/0.1% trifluoroacetic acid and Solution B: MeCN w/0.1% trifluoroacetic acid;

increase gradient of solution B from 65% to 95%, 0-10 min, 95-100%, 10-11 min, 100%, 11-15 min, flow rate 30 mL/min

2-(((*S*)-1-((*R*)-2-((*R*)-3-((1*S*,3*R*)-3-butylcyclobutyl)-1-hydroxyprop-2-yn-1-yl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-2-oxoethan-1-aminium 2,2,2-trifluoroacetate (6-31):

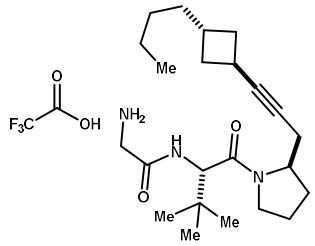
^{1}H NMR (500 MHz, CD_3OD): δ 4.89 (dd, *J* = 2.0, 8.0 Hz, 1H), 4.71-4.68 (m, 1H), 4.13-4.06 (m, 1H), 3.76 (d, *J* = 16.1 Hz, 1H), 3.70 (d, *J* =16.1 Hz, 1H), 3.83-3.66 (m, 2H), 3.05-2.95 (m, 0.6H), 2.89-2.79 (m, 0.4H)*, 2.42-2.32 (m, 1H), 2.24-2.08 (m, 3H), 2.08-1.99 (m, 1H), 1.98-1.90 (m, 2H), 1.89-1.79 (m, 1H), 1.69-1.57 (m, 1H), 1.46-1.34 (m, 2H), 1.29 (sextet, *J* = 7.4 Hz, 2H), 1.19 (p, *J* = 7.7 Hz, 2H), 1.04 (s, 2H)*, 1.03 (s, 7H), 0.89 (t, *J* = 7.2 Hz, 2H), 0.88 (t, *J* = 7.2 Hz, 1H)*

^{13}C NMR (125 MHz, CD_3OD): 170.2, 165.8, 90.3, 89.5*, 79.1, 78.6*, 62.7, 62.7, 61.9, 61.8, 58.0, 48.9, 40.0, 36.5, 35.7, 35.4, 34.7, 34.6, 34.1, 32.7, 32.6, 29.1, 28.9, 25.4, 25.4, 25.3, 24.0, 22.3, 22.2, 21.3, 20.7, 13.0

IR: 3300, 2957, 2927, 2232, 1678, 1367, 1330, 1243, 1098, 1032

HRMS (ESI) m/z, 406.3055 (406.3069 calculated for $C_{23}H_{40}N_3O_3^+$, $(M+H)^+$)

2-(((*S*)-1-((*R*)-2-(3-((1*S*,3*R*)-3-butylcyclobutyl)prop-2-yn-1-yl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-2-oxoethan-1-aminium 2,2,2-trifluoroacetate (6-32)



6-32

Starting with **6-30** (91.5 mg, 0.187 mmol) the general deprotection method (22 eq) was utilized to afford the hydrochloride salt of **6-32** (74.2 mg, 93%) as a brown yellow foam. A small portion of the foam was then purified using Reverse Phase HPLC (elutes at 12.5 min) to give a clear oil of the trifluoroacetate salt. Amine **6-32** exists as a mixture of rotamers.

HPLC Conditions: Waters Sunfire C18 column (19 x 250 mm) with UV detection at 280 nm; Solution A: H_2O w/0.1% trifluoroacetic acid and Solution B: MeCN w/0.1% trifluoroacetic acid; increase gradient of solution B from 65% to 95%, 0-10 min, 95-100%, 10-11 min, 100%, 11-15 min, flow rate 30 mL/min

2-(((*S*)-1-((*R*)-2-(3-((1*S*,3*R*)-3-butylcyclobutyl)prop-2-yn-1-yl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-2-oxoethan-1-aminium 2,2,2-trifluoroacetate (6-32):

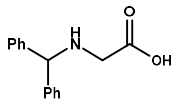
^{1}H NMR (500 MHz, CD_3OD) δ 4.61-4.51 (m, 1H), 4.11-4.01 (m, 1H), 3.81-3.71 (m, 1H), 3.76 (d, *J* = 16.1 Hz, 1H), 3.71 (d, *J* = 16.1 Hz, 1H), 3.67-3.59 (m, 1H), 2.98-2.88 (m, 1H), 2.81-2.86 (m, 0.3H)*, 2.67-2.48 (m, 1.7H), 2.41-2.30 (m, 1H), 2.23 (ddd, *J* = 2.1, 9.3, 16.3 Hz, 1H), 2.14-2.0

(m, 4H), 2.00-1.80 (m, 4H), 1.60-1.49 (m, 1H), 1.40 (q, *J* = 7.6 Hz, 2H), 1.29 (sextet, *J* = 7.3 Hz, 2H), 1.18 (p, *J* = 7.8 Hz, 2H), 1.05 (s, 2H)*, 1.01 (s, 7H), 0.87 (t, *J* = 7.3 Hz, 2.2H), 0.86 (t, *J* = 7.3Hz, 0.8H)

^{13}C NMR (125 MHz, CD_3OD): 169.7, 165.8, 86.1, 85.4*, 77.0, 76.4*, 58.0, 57.1, 39.9, 36.5, 36.1, 36.0, 35.5, 34.55, 34.54, 34.43, 34.42, 34.3, 34.2, 32.6, 32.5, 29.2, 29.0, 28.5, 28.6, 25.8, 25.4, 23.0, 22.9, 22.3, 22.2, 21.5, 21.4, 21.3, 21.0, 13.0

LRMS (ESI) m/z, 390.2 (390.3 calculated for $C_{23}H_{40}N_3O_2^+$, $(M+H)^+$)

Benzhydrylglycine (6-34)



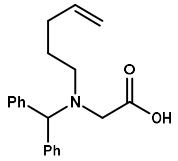
6-34

To a solution of glycine **6-33** (7.523 g, 100.22 mmol) in a mixture of MeOH/H_2O (10:1, 220 mL, ~0.5M), benzophenone (18.295 g, 100.40 mmol, 1 eq) was added. The solution was stirred for 15 minutes at room temperature. Then $NaBH_3CN$ (9.590 g, 152.62 mmol, 1.5 eq) was added to the mixture and the reaction was heated to reflux for 24 hours. The reaction was then cooled to room temperature and concentrated to a white oil. The residue was taken up in aqueous NaOH (0.85M, 116 mL, 100.86 mmol, 1 eq) and the mixture was washed with Et_2O several times. The aqueous layer was then acidified with aqueous HCl to pH 4. The solution was then cooled to 0 °C and allowed to crystallize. The crystals were filtered and washed with water. The crystals were then dried to afford **6-34** (18.996 g, 79%) as a white crystals.

Benzhydrylglycine (6-34):
^{1}H NMR (500 MHz, CD_3OD): δ 7.49-7.33 (m, 10H), 5.57 (*s*, 1H), 3.36 (*s*, 2H)

^{13}C NMR (125 MHz, CD_3OD) δ 169.1, 135.9, 128.8, 128.6, 127.3, 64.9

***N*-benzhydryl-*N*-(pent-4-en-1-yl)glycine (6-36a)**

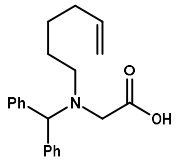


6-36a

A solution of amine **6-34** (2.497 g, 10.35 mmol) and 4-pentenal (0.8688 g, 10.33 mmol, 1 eq) in a mixture of MeOH/H_2O (10:1, 22 mL, 0.5M) was stirred for 15 minutes. Then $NaBH_3CN$ (0.9828 g, 15.63 mmol, 1.5 eq) was added and the mixture was heated to reflux for 20 hours. The mixture was then cooled and concentrated. The residue was then purified by flash column chromatography (SiO_2, 20:1→10:1 $CHCl_3$/MeOH) to afford **6-36a** (1.9 g, 59%) as a white solid.

***N*-benzhydryl-*N*-(pent-4-en-1-yl)glycine (6-36a):**
^{1}H NMR (500 MHz, CD_3OD): δ 7.55-7.47 (m, 4H), 7.40-7.30 (m, 4H), 7.32-7.24 (m, 2H), 5.65 (ddt, *J* = 6.7, 10.3, 17.1 Hz, 1H), 5.46 (s, 1H), 4.95-4.85 (m, 2H), 3.46 (s, 2H), 3.01-2.85 (m, 2H), 1.96 (q, *J* = 6.9 Hz, 2H), 1.68 (p, *J* = 7.6 Hz, 2H)

***N*-benzhydryl-*N*-(hex-5-en-1-yl)glycine (6-36b)**



6-36b

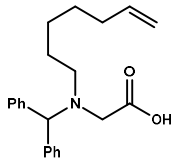
A solution of amine **6-34** (7.3058 g, 30.27 mmol) and 5-hexenal (2.9714 g, 30.27 mmol, 1 eq) in a mixture of MeOH/H_2O (10:1, 66 mL, 0.5M) was stirred for 15 minutes. Then $NaBH_3CN$ (2.8645 g, 45.58 mmol, 1.5 eq) was added and the mixture was heated to reflux for 20 hours. The mixture was then cooled and concentrated to a light purple oil. The residue was then purified by flash column chromatography (SiO_2, 20:1→10:1 $CHCl_3$/MeOH) to afford **6-36b** (7.1 g, 72%) as a white solid.

***N*-benzhydryl-*N*-(hex-5-en-1-yl)glycine (6-36b):**
^{1}H NMR (500 MHz, CD_3OD): δ 7.51 (d, 4H, J= 7.50), 7.36 (t, 4H, J= 7.53), 7.31-7.28 (m, 2H), 5.70 (ddt, *J* = 6.7, 10.2, 16.9 Hz, 1H), 5.51 (s, 1H), 4.95-4.87 (m, 2H), 3.47 (s, 2H), 2.98-2.92 (m, 2H), 1.95 (q, *J* = 7.1 Hz, 2H), 1.61 (p, *J* = 7.7 Hz, 2H), 1.29 (p, *J* = 7.4 Hz, 2H)

^{13}C NMR (125 MHz, CD_3OD) δ 170.59, 137.7, 137.6, 128.66, 128.16, 127.95, 113.94, 72.58, 53.27, 52.67, 32.64, 25.52, 24.24

LRMS (ESI) m/z, 324.1 (324.2 calculated for $C_{21}H_{26}NO_2^+$, $(M+H)^+$)

***N*-benzhydryl-*N*-(hept-6-en-1-yl)glycine (6-36c)**

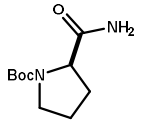


6-36c

A solution of amine **6-34** (0.6544 g, 2.71 mmol) and 6-heptenal (0.303 g, 2.70 mmol, 1 eq) in a mixture of MeOH/H_2O (10:1, 6.6 mL, 0.5M) was stirred for 15 minutes. Then $NaBH_3CN$ (0.2623 g, 4.10 mmol, 1.5 eq) was added and the mixture was heated to reflux for 18 hours. The mixture was then cooled and concentrated to a white oil. The residue was then purified by flash column chromatography (SiO_2, 20:1→10:1 $CHCl_3$/MeOH) to afford **6-36b** (0.607 g, 72%) as a white solid.

***N*-benzhydryl-*N*-(hept-6-en-1-yl)glycine (6-36c):**
^{1}H NMR (500 MHz, CD_3OD) δ 7.53 (d, *J* = 7.3 Hz, 4H), 7.41-7.35 (m, 4H), 7.34-7.29 (m, 2H), 5.77 (ddt, *J* = 6.75, 10.12, 17.09 Hz, 1H), 5.54 (s, 1H), 5.01-4.87 (m, 2H), 3.50 (s, 2H), 3.00-2.91 (m, 2H), 1.98 (q, 2H, J=7.05 Hz), 1.67-1.54 (m, 4H), 1.34-1.25 (m, 2H)

***tert*-butyl (*R*)-2-carbamoylpyrrolidine-1-carboxylate (6-37)**

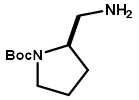


6-37

To a solution of *D*-proline **6-21** (40.1557 g, 348.78 mmol) in MeCN (640 mL), a mixture of Boc_2O (180 mL, 783.50 mmol, 2.25 eq) and pyridine (65 mL, 806.87 mmol, 2.3 eq) in MeCN (280 mL) was added dropwise. The solution was stirred at room temperature for 4h whern the mixture became an orange translucent color. NH_4HCO_3 (63.809 g, 807.10 mmol, 2.3 eq) was added in portions and the mixture was stirred at room temperature for 36h. The reaction progressed to a dark orange color. The reaction was then filtered and the solids were washed with MeCN. The filtrate was then concentrated to an orange oil. The residue was then recrystallized with EtOAc/pentanes. The crystals were then washed with hexanes and Et_2O and then dried to afford **6-37** (47.0 g, 63%) as orange crystals. Amide **6-37** exists as a mixture of rotamers.

***tert*-butyl (*R*)-2-carbamoylpyrrolidine-1-carboxylate (6-37):**
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.85 (bs, 0.5H), 6.01 (bs, 0.5H)*, 5.66-5.28 (m, 1H), 4.41-4.15 (m, 1H), 3.63-3.23 (m, 2.5H), 2.43-2.27 (m, 0.5H)*, 2.28-2.08 (m, 1H), 1.96-1.76 (m, 2H), 1.46 (bs, 9H)

***tert*-butyl (*R*)-2-(aminomethyl)pyrrolidine-1-carboxylate (6-38)**



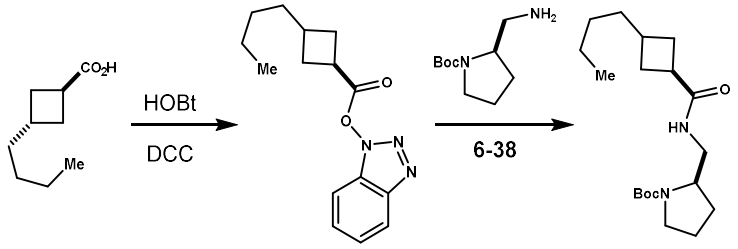
6-38

To a slurry of $NaBH_4$ (8.4954 g, 224.56 mmol, 1.2 eq) in THF (450 mL) at 0 °C, a solution of I_2 (23.8785 g, 94.08 mmol, 50 mol%) in THF (225 mL) was added dropwise. The reaction was then warmed to room temperature and a solution of amide **6-37** (39.8 g, 185.75 mmol) in THF (100 mL) was added dropwise. The reaction was then heated to reflux overnight (~16h). The reaction was then cooled to room temperature and acidified with aqueous HCl. The THF was then removed under reduced pressure and the mixture was extracted with EtOAc several times. The aqueous layer was then basified to pH 11 with aqueous 2M NaOH and then washed with EtOAc. The organics were then dried over $MgSO_4$, filtered, and concentrated to afford **6-38** (14.5 g, 39%) as a yellow oil. Carbamate **6-38** exists as a mixture of rotamers.

***tert*-butyl (*R*)-2-(aminomethyl)pyrrolidine-1-carboxylate (6-38):**
^{1}H NMR (400 MHz, $CDCl_3$): δ 3.77-3.50 (*m*, 1H), 3.45-3.11 (*m*, 2H), 2.82-2.63 (*m*, 1H), 2.62-2.48 (m, 1H), 1.83 (bs, 1H), 1.77-1.60 (m, 3H), 1.39-1.31 (m, 9H), 1.26 (bs, 2H)

^{13}C NMR (100 MHz, $CDCl_3$): 154.6, 78.9, 59.5, 57.7, 46.7, 45.2, 28.8, 28.3, 23.5, 22.9

***tert*-butyl (*R*)-2-(((1*S*,3*R*)-3-butylcyclobutane-1-carboxamido)methyl)pyrrolidine-1-carboxylate (6-39)**



6-17 **6-17a** **6-39**

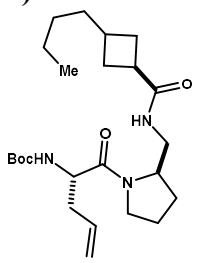
To a solution of acid **6-17** (4.3 g, 27.5 mmol) and HOBt·H_2O (4.2231 g, 27.5 mmol) in EtOAc (40 mL), a solution of DCC (5.997 g, 29.06 mmol, 1.05 eq) was added dropwise over 20 minutes. The solution was then warmed to 45 °C and stirred for 3h. The reaction mixture was then filtered and the filtrate was concentrated to a light orange solid. The solid was then taken up in boiling hexanes and the solution was hot filtered. The filtrate was then cooled to -20 °C and allowed to crystallize overnight. The crystals were filtered and washed with hexanes. The crystals were then dried to provide the intermediate activated ester (5.6 g, 20.48 mmol). The ester was then dissolved in MeCN (90 mL) and amine **6-38** (4.306 g, 21.5 mmol, 1.05 eq) in MeCN (20 mL) was added to the mixture. The reaction was then stirred overnight (~16h) at room temperature. The reaction was then quenched with aqueous 1M HCl and extracted with EtOAc. The organic layer was then washed with sat. aqueous $NaHCO_3$ and brine. The organics were dried over $MgSO_4$, filtered, and concentrated to afford crude **6-39** (6.4 g, 68% over two steps) as an orange oil, which was used without further purification. Amide **6-39** exists as a mixture of rotamers.

***tert*-butyl (*R*)-2-(((1*S*,3*R*)-3-butylcyclobutane-1-carboxamido)methyl)pyrrolidine-1-carboxylate (6-39):**

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.07-3.97 (m, 1H), 3.51-3.26 (m, 3H), 3.25-3.14 (m, 1H), 2.98-2.87 (m, 1H), 2.43-2.19 (m, 3H), 2.02-1.92 (m, 2H), 1.90-1.76 (m, 3H), 1.72-1.61 (m, 1H), 1.57-1.37 (m, 11H), 1.34-1.21 (m, 2H), 1.21-1.12 (m, 2H), 0.86 (t, J = 7.3 Hz, 3H)

LRMS (ESI) m/z 339.2 (339.3 calculated for $C_{19}H_{35}N_2O_3^+$, $(M+H)^+$)

***tert*-butyl ((*S*)-1-((*R*)-2-(((1*S*,3*R*)-3-butylcyclobutane-1-carboxamido)methyl)pyrrolidin-1-yl)-1-oxopent-4-en-2-yl)carbamate (6-40)**



6-40

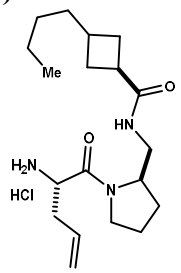
Starting with **6-39** (1.3574 g, 4.01 mmol) both the standard deprotection (22 eq) and coupling procedures (Boc-allylGly-OH) were utilized. The crude material was purified by flash column chromatography (SiO_2, 50:1→20:1 $CHCl_3$/MeOH) to afford **6-40** (1.455 g, 83% over two steps) as a brown oil. Amide **6-40** exists as a mixture of rotamers.

***tert*-butyl ((*S*)-1-((*R*)-2-(((1*S*,3*R*)-3-butylcyclobutane-1-carboxamido)methyl)pyrrolidin-1-yl)-1-oxopent-4-en-2-yl)carbamate (6-40):**

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.98 (bs, 1H), 5.72 (ddt, J = 7.3, 10.0, 17.3 Hz, 1H), 5.23-4.98 (m, 3H), 4.41-4.26 (m, 1H), 4.22-4.12 (m, 1H), 3.67-3.57 (m, 1H), 3.55-3.44 (m, 2H), 3.40-3.26 (m, 1H), 3.00-2.87 (m, 1H), 2.46-2.35 (m, 1H), 2.35-2.18 (m, 4H), 1.99-1.92 (m, 2H), 1.90-1.73 (m, 4H), 1.47-1.35 (m, 11H), 1.28-1.19 (m, 3H), 1.19-1.11 (m, 2H), 0.84 (t, J = 7.1 Hz, 3H)

^{13}C NMR (125 MHz, $CDCl_3$): 176.1, 171.5, 155.5, 132.4, 118.8, 79.7, 57.5, 51.9, 47.2, 42.7, 38.4, 36.5, 36.1, 35.8, 31.6, 30.2, 29.2, 28.7, 28.1, 24.0, 22.5, 13.9

(*S*)-1-((*R*)-2-(((1*S*,3*R*)-3-butylcyclobutane-1-carboxamido)methyl)pyrrolidin-1-yl)-1-oxopent-4-en-2-aminium chloride (6-41)



6-41

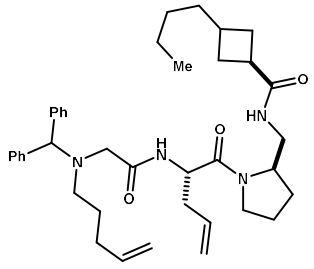
Starting with **6-40** (1.455 g, 3.34 mmol) the standard deprotection (22) procedure was utilized, which afforded crude **6-41** (1.0384 g, 83%) that was used directly in the next step without purification.

(*S*)-1-((*R*)-2-(((1*S*,3*R*)-3-butylcyclobutane-1-carboxamido)methyl)pyrrolidin-1-yl)-1-oxopent-4-en-2-aminium chloride (6-41):
^{1}H NMR (500 MHz, CD_3OD): δ 5.81 (ddt, *J* = 7.3, 9.9, 17.0 Hz, 1H), 5.36-5.22 (m, 2H), 4.22-4.16 (m, 1H), 4.15-4.09 (m, 1H), 3.62-3.34 (m, 3H), 3.11-3.00 (m, 1H), 2.69-2.58 (m, 1H), 2.56-2.46 (m, 2H), 2.37-2.20 (m, 3H), 2.10-2.01 (m, 1H), 1.99-1.90 (m, 2H), 1.90-1.79 (m, 2H), 1.47 (q, *J* = 7.2 Hz, 2H), 1.36-1.26 (m, 3H), 1.26-1.17 (m, 2H), 0.89 (t, *J* = 7.2 Hz, 3H)

^{13}C NMR (500 MHz, CD_3OD): 177.6, 166.8, 130.4, 120.1, 58.0, 51.4, 46.6, 40.0, 37.6, 36.0, 35.8, 34.1, 31.7, 29.8, 29.8, 29.1, 27.1, 23.3, 22.3, 13.0

LRMS (ESI) m/z, 336.2 (336.3 calculated for $C_{19}H_{34}N_3O_2^+$, $(M+H)^+$)

(1*S*,3*R*)-*N*-(((*R*)-1-((*S*)-2-(2-(benzhydryl(pent-4-en-1-yl)amino)acetamido)pent-4-enoyl)pyrrolidin-2-yl)methyl)-3-butylcyclobutane-1-carboxamide (6-42a)



6-42a

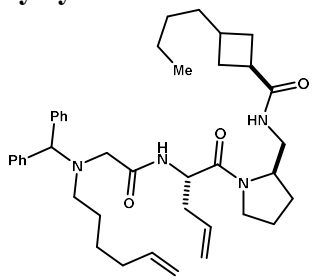
Hydrochloride salt **6-41** (0.4926 g, 1.32 mmol) and acid **6-36a** (0.4128 g, 1.33 mmol) were combined under standard coupling conditions. The crude was purified by flash column chromatography (SiO_2, 50:1 $CHCl_3$/MeOH) to afford **6-42b** (0.5503 g, 66%) as an orange oil.

(1*S*,3*R*)-*N*-(((*R*)-1-((*S*)-2-(2-(benzhydryl(pent-4-en-1-yl)amino)acetamido)pent-4-enoyl)pyrrolidin-2-yl)methyl)-3-butylcyclobutane-1-carboxamide (6-42a):
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.06 (d, *J* = 7.9 Hz, 1H), 7.39-7.31 (m, 4H), 7.31-7.16 (m, 6H), 7.16-7.10 (m, 1H), 5.76 (ddt, *J* = 7.3, 10.0, 17.0 Hz, 1H), 5.66 (ddt, *J* = 6.4, 10.0, 16.7 Hz, 1H), 5.21-5.07 (m, 2H), 4.95-4.85 (m, 3H), 4.74-4.66 (m, 1H), 4.22-4.11 (m, 1H), 3.68-3.58 (m, 2H), 3.57-3.51 (m, 1H), 3.24 (ddd, *J* = 4.2, 7.3, 11.6 Hz, 1H), 3.16 (d, *J* = 17.1 Hz, 1H), 3.11 (d, *J* =

17.1 Hz, 1H), 2.59-2.48 (m, 3H), 2.45-2.37 (m, 1H), 2.35-2.26 (m, 1H), 2.26-2.18 (m, 2H), 2.11-1.72 (m, 6H), 1.67-1.53 (m, 3H), 1.47-1.38 (m, 2H), 1.34-1.27 (m, 2H), 1.24-1.16 (m, 2H), 1.14-1.04 (m, 2H), 0.81 (t, *J* = 7.3 Hz, 3H)

^{13}C NMR (125 MHz, $CDCl_3$): 176.1, 171.2, 170.9, 141.1, 141.0, 137.7, 132.5, 128.4, 128.4, 128.2, 128.1, 127.2, 127.2, 118.8, 114.7, 71.5, 58.1, 55.3, 52.8, 50.2, 47.3, 43.5, 38.4, 36.6, 36.5, 35.9, 31.6, 31.2, 30.3, 30.2, 29.2, 29.1, 25.5, 24.0, 22.5, 13.9

(1*S*,3*R*)-*N*-(((*R*)-1-((S)-2-(2-(benzhydryl(hex-5-en-1-yl)amino)acetamido)pent-4-enoyl)pyrrolidin-2-yl)methyl)-3-butylcyclobutane-1-carboxamide (6-42b)



6-42b

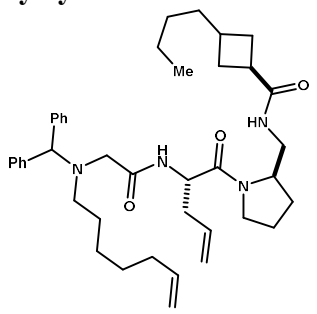
Hydrochloride salt **6-41** (1.878 g, 5.05 mmol) and acid **6-36b** (1.6863 g, 5.21 mmol) were combined under standard coupling conditions. The crude was purified by flash column chromatography (SiO_2, 50:1→20:1→10:1 $CHCl_3$/MeOH) to afford **6-42b** (2.9527 g, 91%).

(1*S*,3*R*)-*N*-(((*R*)-1-((S)-2-(2-(benzhydryl(hex-5-en-1-yl)amino)acetamido)pent-4-enoyl)pyrrolidin-2-yl)methyl)-3-butylcyclobutane-1-carboxamide (6-42b):
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.07 (d, *J* = 7.9 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 7.6 Hz, 2H), 7.31-7.26 (m, 2H), 7.25-7.16 (m, 4H), 7.13 (t, *J* = 4.8 Hz, 1H), 5.77 (ddt, *J* = 7.1, 9.8, 17.1 Hz, 1H), 5.70 (ddt, *J* = 6.6, 10.2, 16.8 Hz, 1H), 5.21-5.09 (m, 2H), 4.96-4.86 (m, 2H), 4.85 (s, 1H), 4.73-4.65 (m, 1H), 4.22-4.09 (m, 1H), 3.68-3.58 (m, 2H), 3.57-3.51 (m, 1H), 3.51-3.41 (m, 1H), 3.25 (ddd, *J* = 4.2, 7.05, 13.7 Hz, 1H), 3.16 (d, *J* = 17.3 Hz, 1H), 3.11 (d, *J* = 17.3 Hz, 1H), 2.90-2.81 (m, 1H), 2.59-2.49 (m, 3H), 2.47-2.37 (m, 1H), 2.35-2.26 (m, 1H), 2.27-2.18 (m, 2H), 2.05-1.98 (m, 2H), 1.95 (q, *J* = 6.7 Hz, 2H), 1.91-1.82 (m, 1H), 1.83-1.71 (m, 2H), 1.68-1.61 (m, 1H), 1.49 (p, *J* = 7.65 Hz, 2H), 1.45-1.38 (m, 1H), 1.34-1.14 (m, 6H), 1.08 (p, *J* = 6.7 Hz, 2H), 0.82 (t, *J* = 7.3 Hz, 3H)

^{13}C NMR (125 MHz, $CDCl_3$): 176.2, 171.4, 171.0, 141.3, 141.2, 138.3,132.7, 128.8, 128.6, 128.5, 128.4, 128.3, 128.2, 127.4, 127.3, 127.2, 119.0, 114.7, 71.5, 58.2, 56.5, 55.4, 53.1, 50.3, 48.3, 47.4, 45.7, 43.7, 38.6, 36.7, 36.7, 36.6, 36.2, 36.0, 35.9, 33.4, 31.8, 31.7, 31.5, 30.4, 30.4, 30.3, 30.3, 29.4, 29.3, 29.2, 29.1, 26.5, 25.7, 24.1, 22.8, 22.6, 22.6, 22.5, 14.1, 14.1

LRMS (ESI) m/z, 641.4 (641.4 calculated for $C_{40}H_{57}N_4O_3^+$, $(M+H)^+$)

(1*S*,3*R*)-*N*-(((*R*)-1-((*S*)-2-(2-(benzhydryl(hept-6-en-1-yl)amino)acetamido)pent-4-enoyl)pyrrolidin-2-yl)methyl)-3-butylcyclobutane-1-carboxamide (6-42c)



6-42c

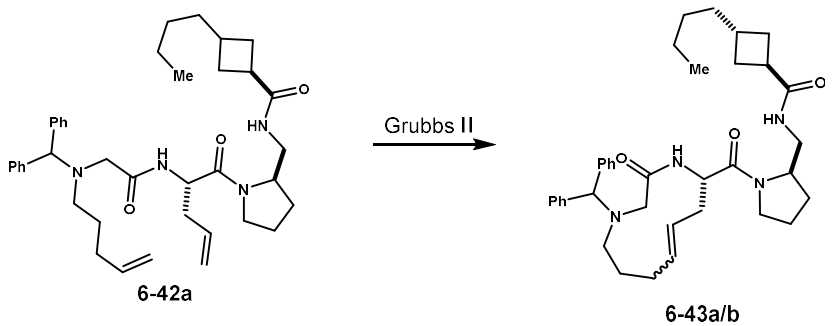
Hydrochloride salt **6-41** (0.9001 g, 2.42 mmol) and acid **6-36b** (0.8477 g, 2.51 mmol) were combined under standard coupling conditions. The crude was purified by flash column chromatography (SiO_2, 50:1→20:1→10:1 $CHCl_3$/MeOH) to afford **6-42b** (1.4552 g, 92%).

(1*S*,3*R*)-*N*-(((*R*)-1-((*S*)-2-(2-(benzhydryl(hept-6-en-1-yl)amino)acetamido)pent-4-enoyl)pyrrolidin-2-yl)methyl)-3-butylcyclobutane-1-carboxamide (6-42c):
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.07 (d, *J* = 7.7 Hz, 1H), 7.51-7.28 (m, 6H), 7.24-7.08 (m, 4H), 5.87-5.64 (m, 2H), 5.22-5.03 (m, 2H), 5.00-4.85 (m, 2H), 4.83 (s, 1H), 4.73-4.65 (m, 1H), 4.38-4.23 (m, 1H), 4.21-4.10 (m, 1H), 3.69-3.58 (m, 2H), 3.57-3.51 (m, 1H), 3.49-3.35 (m, 2H), 3.29-3.20 (m, 1H), 3.14 (d, *J* = 17.3 Hz, 1H), 3.10 (d, *J* = 17.3 Hz, 1H), 2.90-2.81 (m, 1H), 2.60-2.46 (m, 2H), 2.45-2.37 (m, 1H), 2.34-2.26 (m, 1H), 2.25-2.18 (m, 1H), 2.10-1.90 (m, 4H), 1.91-1.71 (m, 2H), 1.70-1.58 (m, 2H), 1.53-1.01 (m, 10H), 0.81 (t, *J* = 7.3 Hz, 3H)

^{13}C NMR (125 MHz, $CDCl_3$): 176.2, 171.5, 171.0, 141.3, 141.2, 138.9, 138.7, 132.6, 128.6, 128.5, 128.3, 128.2, 127.3, 127.3, 119.0, 114.4, 114.3, 71.5, 58.2, 55.4, 53.2, 50.3, 47.4, 43.6, 38.6, 36.7, 36.6, 36.0, 33.6, 33.6, 31.8, 30.4, 30.3, 29.3, 29.2, 28.9, 28.6, 26.8, 26.4, 26.1, 24.1, 22.6

General Ring Closing Metathesis Procedure- To a solution of diene in toluene (0.01 M), Grubbs 2nd generation catalyst (2.5 mol%) was added. The mixture was then heated to 90 °C. Additional portions of catalyst (2.5 mol% x 2) were added at 2 and 4h, respectively. The reaction was stirred at 90 °C for 6-7h total when HPLC analysis indicated that reaction was complete. The reaction was cooled to room temperature and concentrated to a black oil. The crude was then purified as indicated.

RCM of Diene 6-42a

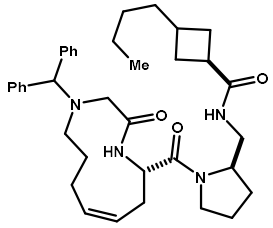


6-42a 6-43a/b

Starting with **6-42a** (0.48525 g, 0.77 mmol) the standard RCM procedure was utilized. The crude reaction mixture was purified by flash column chromatography (SiO_2, 50:1 $CHCl_3$/MeOH) to afford a mixture of **6-43a/b** (0.2807 g, 61%) as a 1:1 Z/E mixture as determined by HPLC trace. A small portion of the mixture could be further purified by preparative HPLC to provide pure **6-43a** and **6-43b**.

HPLC Conditions: Waters Sunfire C18 column (19 x 250 mm) with UV detection at 280 nm; Solution A: H_2O w/0.1% trifluoroacetic acid and Solution B: MeCN w/0.1% trifluoroacetic acid; increase gradient of solution B from 45% to 65%, 0-15 min, 65% to 100%, 15-20 min, flow rate 15 mL/min

(1*S*,3*R*)-*N*-(((*R*)-1-((*S*,*Z*)-1-benzhydryl-3-oxo-1,4-diazacycloundec-7-ene-5-carbonyl)pyrrolidin-2-yl)methyl)-3-butylcyclobutane-1-carboxamide (6-43a)



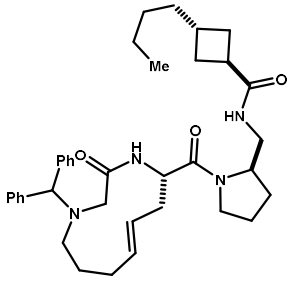
6-43a

Under the above mentioned HPLC conditions, **6-43a** elutes at 7 minutes. Macrocycle **6-43a** exists as a mixture of conformers at room temperature.

(1*S*,3*R*)-*N*-(((*R*)-1-((*S*,*Z*)-1-benzhydryl-3-oxo-1,4-diazacycloundec-7-ene-5-carbonyl)pyrrolidin-2-yl)methyl)-3-butylcyclobutane-1-carboxamide (6-43a):
^{1}H NMR (500 MHz, CD_3OD): δ 7.68-7.48 (m, 4H), 7.41 (t, *J* = 7.3 Hz, 4H), 7.38-7.28 (m, 2H), 5.67-5.50 (m, 1H), 5.39 (dt, *J* = 3.8, 10.6 Hz, 0.3H)*, 5.32 (dt, *J* = 4.3, 9.9 Hz, 0.7H), 4.82-4.75 (m, 0.7H), 4.57 (q, *J* = 5.5 Hz, 0.3H)*, 4.41-4.30 (m, 0.3H)*, 4.22-4.09 (m, 0.7H), 3.78-3.53 (m, 2H), 3.51-3.33 (m, 4H), 3.27-3.16 (m, 1H), 3.12-3.00 (m, 1H), 3.00-2.91 (m, 1H), 2.91-2.78 (m, 1H), 2.61-2.50 (m, 1H), 2.37-2.12 (m, 4H), 1.97-1.86 (m, 2H), 1.84-1.70 (m, 3H), 1.69-1.57 (m, 2H), 1.47 (q, *J* = 7.2 Hz, 1H), 1.39 (q, *J* = 7.4 Hz, 2H), 1.34-1.22 (m, 3H), 1.16 (p, *J* = 7.4 Hz, 2H), 0.88 (t, *J* = 7.2 Hz, 3H)

LRMS (ESI) m/z, 599.4 (599.4 calculated for $C_{37}H_{51}N_4O_3^+$, $(M+H)^+$)

(1*S*,3*R*)-*N*-(((*R*)-1-((*S*,*E*)-1-benzhydryl-3-oxo-1,4-diazacycloundec-7-ene-5-carbonyl)pyrrolidin-2-yl)methyl)-3-butylcyclobutane-1-carboxamide (6-43b)



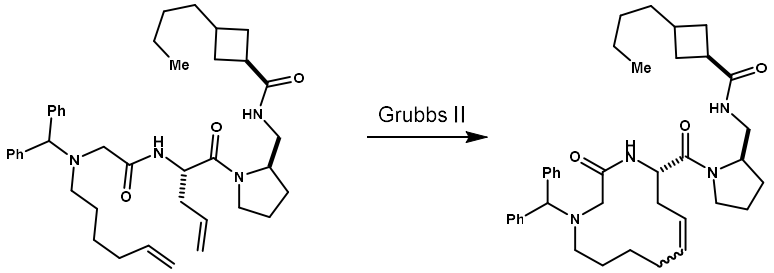
6-43b

Under the above mentioned HPLC conditions, **6-43b** elutes at 16.5 minutes. Macrocycle **6-43b** exists as a mixture of conformers at room temperature.

(1*S*,3*R*)-*N*-(((*R*)-1-((*S*,*E*)-1-benzhydryl-3-oxo-1,4-diazacycloundec-7-ene-5-carbonyl)pyrrolidin-2-yl)methyl)-3-butylcyclobutane-1-carboxamide (6-43b):
^{1}H NMR (500 MHz, CD_3OD): δ 7.69-7.14 (m, 10H), 5.62 (dt, *J* = 7.0, 17.0 Hz, 0.7H), 5.52 (dt, *J* = 7.0, 16.3 Hz, 0.7H), 5.47-5.40 (m, 0.6H)*, 4.74 (d, *J* = 11.4 Hz, 0.3H)*, 4.58 (d, *J* = 11.2 Hz, 0.7H), 4.50-4.41 (m, 0.3H)*, 4.31-4.18 (m, 0.7H), 3.80-3.69 (m, 1H), 3.65-3.54 (m, 1H), 3.53-3.43 (m, 1H), 3.42-3.36 (m, 1H),3.36-3.31 (m, 2H), 3.27-3.18 (m, 0.3H)*, 3.13-3.00 (m, 0.7H), 2.99-2.90 (m, 1H), 2.83-2.53 (m, 3H), 2.47-2.26 (m, 3H), 2.22-2.14 (m, 1H), 2.11-1.62 (m, 8H), 1.46 (q, *J* = 7.3 Hz, 1H),1.42-1.33 (m, 2H), 1.28 (sextet, *J* = 7.5H, 2H), 1.24-1.18 (m, 1H), 1.18-1.09 (m, 2), 0.94-0.79 (m, 3H)

LRMS (ESI) m/z, 599.4 (599.4 calculated for $C_{37}H_{51}N_4O_3^+$, $(M+H)^+$)

RCM of Diene 6-42b

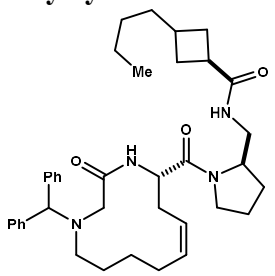


6-42b 6-43c/d

Starting with **6-42b** (0.2189 g, 0.34 mmol) the standard RCM procedure was utilized. The crude reaction mixture was purified by flash column chromatography (SiO_2, 50:1 $CHCl_3$/MeOH) to afford a mixture of **6-43a/b** (0.1822 g, 87%) as a 1.5:1 Z/E mixture as determined by HPLC trace. A small portion of the mixture could be further purified by preparative HPLC to provide pure **6-43c** and **6-43d**.

HPLC Conditions: Waters Sunfire C18 column (19 x 250 mm) with UV detection at 280 nm; Solution A: H_2O w/0.1% trifluoroacetic acid and Solution B: MeCN w/0.1% trifluoroacetic acid; increase gradient of solution B from 45% to 65%, 0-15 min, 65% to 100%, 15-20 min, flow rate 15 mL/min

(1*S*,3*R*)-*N*-(((*R*)-1-((*S*,*Z*)-1-benzhydryl-3-oxo-1,4-diazacyclododec-7-ene-5-carbonyl)pyrrolidin-2-yl)methyl)-3-butylcyclobutane-1-carboxamide (6-43c)



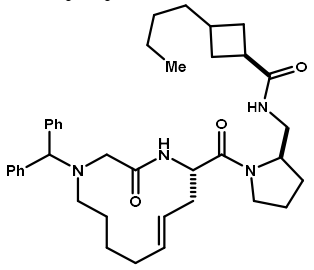
6-43c

Under the above mentioned HPLC conditions, **6-43c** elutes at 11.5 minutes. Macrocycle **6-43c** exists as a mixture of conformers at room temperature.

^{1}H NMR (500 MHz, CD_3OD): δ 8.80-8.58 (m, 0.5H)*, 7.81-7.63 (m, 4H), 7.53-7.32 (m, 6H), 6.50-6.30 (m, 0.5H), 5.83-5.59 (m, 0.5H)*, 5.53-5.27 (m, 2H), 5.27-5.12 (m, 0.5H), 4.29-3.95 (m, 2H), 3.89-3.74 (m, 0.5H)*, 3.75-3.63 (m, 0.5H), 3.62-3.46 (m, 2H), 3.46-3.30 (m, 2H), 3.25-3.13 (m, 1H), 3.13-2.75 (m, 2H), 2.69-2.49 (m, 1H), 2.49-2.28 (m, 1H), 2.28-2.10 (m, 4H), 2.07-1.69 (m, 9H), 1.69-1.55 (m, 1H), 1.53-1.44 (m, 1H), 1.40 (q, *J* = 7.3 Hz, 2H), 1.29 (sextet, *J* = 7.3 Hz, 2H), 1.35-1.22 (m, 2H), 1.17 (p, *J* = 7.3 Hz, 2H), 0.88 (t, *J* = 7.4 Hz, 3H)

LRMS (ESI) m/z, 613.2 (613.4 calculated for $C_{38}H_{53}N_4O_3^+$, $(M+H)^+$)

(1*S*,3*R*)-*N*-(((*R*)-1-((*S*,*E*)-1-benzhydryl-3-oxo-1,4-diazacyclododec-7-ene-5-carbonyl)pyrrolidin-2-yl)methyl)-3-butylcyclobutane-1-carboxamide (6-43d)



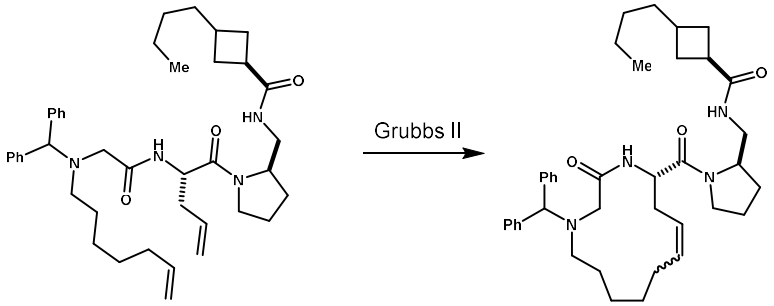
6-43d

Under the above mentioned HPLC conditions, **6-43d** elutes at 13.9 minutes. Macrocycle **6-43d** exists as a mixture of conformers at room temperature.

^{1}H NMR (500 MHz, CD_3OD): δ 7.84-7.60 (m, 4H), 7.46 (q, *J* = 7.6 Hz, 4H), 7.41 (m, 2H), 5.48 (dt, *J* = 7.3, 16.7 Hz, 1H), 5.44-5.35 (m, 1H), 4.26-3.90 (m, 2H), 3.79-3.63 (m, 1H), 3.59-3.45 (m, 2H), 3.44-3.35 (m, 2H), 3.26-3.14 (m, 1H), 3.11-2.90 (m, 2H), 2.84-2.37 (m, 2H), 2.37-2.07 (m, 5H), 2.05-1.72 (m, 9H), 1.71-1.57 (m, 1H), 1.41 (q, *J* = 7.2 Hz, 2H), 1.29 (sextet, *J* = 7.2 Hz, 2H), 1.17 (p, *J* = 7.4 Hz, 2H), 1.35-1.12 (m, 2H), 0.88 (t, *J* = 7.3 Hz, 3H)

LRMS (ESI) m/z, 613.2 (613.4 calculated for $C_{38}H_{53}N_4O_3^+$, $(M+H)^+$)

RCM of Diene 6-42c

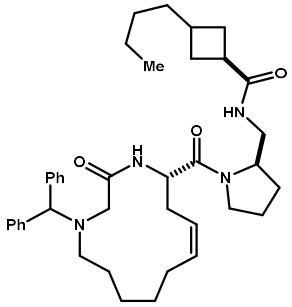


6-42c 6-43e/f

Starting with **6-42b** (0.2476 g, 0.38 mmol) the standard RCM procedure was utilized. The crude reaction mixture was purified by flash column chromatography (SiO_2, 50:1 $CHCl_3$/MeOH) to afford a mixture of **6-43a/b** (0.2365 g, quant.) as a 3:1 Z/E mixture as determined by HPLC trace. A small portion of the mixture could be further purified by preparative HPLC to provide pure **6-43e** and **6-43f**.

HPLC Conditions: Waters Sunfire C18 column (19 x 250 mm) with UV detection at 280 nm; Solution A: H_2O w/0.1% trifluoroacetic acid and Solution B: MeCN w/0.1% trifluoroacetic acid; increase gradient of solution B from 45% to 65%, 0-15 min, 65% to 100%, 15-20 min, flow rate 15 mL/min

(1*S*,3*R*)-*N*-(((*R*)-1-((*S*,*Z*)-1-benzhydryl-3-oxo-1,4-diazacyclotridec-7-ene-5-carbonyl)pyrrolidin-2-yl)methyl)-3-butylcyclobutane-1-carboxamide (6-43e)



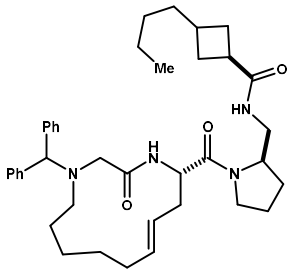
6-43e

Under the above mentioned HPLC conditions, **6-43e** elutes at 12.5 minutes. Macrocycle **6-43e** exists as a mixture of conformers at room temperature.

^{1}H NMR (500 MHz, CD_3OD): δ 7.73-7.54 (m, 4H), 7.50-7.35 (m, 6H), 5.61 (dt, *J* = 8.6, 14.6 Hz, 0.6H)*, 5.54 (dt, *J* =7.9, 14.2 Hz, 0.7H), 5.48-5.37 (m, 0.7), 5.15-5.06 (m, 0.7H), 4.47-4.33 (m, 0.3H)*, 4.26-4.13 (m, 0.3)*, 4.16-4.07 (m, 0.7H), 4.05-3.69 (m, 2H), 3.68-3.51 (m, 2H), 3.50-3.33 (m, 3), 3.22-3.04 (m, 1H), 3.03-2.84 (m, 1H), 2.67-2.44 (m, 2), 2.41-2.14 (m, 5H), 2.12-1.66 (m, 9H), 1.64-1.53 (m, 2H), 1.53-1.35 (m, 3H), 1.35-1.24 (m, 3H), 1.18 (p, *J* = 7.6 Hz, 2H), 0.90 (t, *J* = 7.0 Hz, 1H)*, 0.89 (t, *J* = 7.2 Hz, 2H)

LRMS (ESI) m/z, 627.4 (627.4 calculated for $C_{39}H_{55}N_4O_3^+$, $(M+H)^+$)

(1*S*,3*R*)-*N*-(((*R*)-1-((*S*,*E*)-1-benzhydryl-3-oxo-1,4-diazacyclotridec-7-ene-5-carbonyl)pyrrolidin-2-yl)methyl)-3-butylcyclobutane-1-carboxamide (6-43f)



6-43f

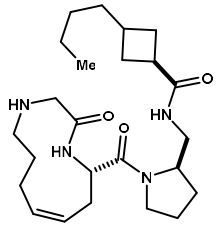
Under the above mentioned HPLC conditions, **6-43f** elutes at 18.5 minutes. Macrocycle **6-43f** exists as a mixture of conformers at room temperature.

^{1}H NMR (500 MHz, CD_3OD): δ 7.57 (d, *J* = 7.6 Hz, 2H), 7.54-7.47 (m, 2H), 7.47-7.34 (m, 3H), 7.33-7.18 (m, 3H), 5.68-5.56 (m, 0.6H)*, 5.45 (dt, *J* = 7.3, 17.5 Hz, 1.4H), 4.83-4.73 (m, 1H), 4.35-4.13 (m, 1H), 3.74-3.54 (m, 2H), 3.55-3.35 (m, 3H), 3.08-2.89 (m, 1H), 2.88-2.75 (m, 1H), 2.64-2.47 (m, 2H), 2.41-2.09 (m, 5H), 2.08-1.88 (m, 4H), 1.88-1.79 (m, 2H), 1.79-1.70 (m, 1H), 1.70-1.51 (m, 4), 1.50-1.39 (m, 3H), 1.39-1.18 (m, 5H), 1.18-1.08 (m, 2), 0.89 (t, *J* = 7.0 Hz, 1H)*, 0.86 (t, *J* = 7.3 Hz, 2H)

LRMS (ESI) m/z, 627.4 (627.4 calculated for $C_{39}H_{55}N_4O_3^+$, $(M+H)^+$)

Standard Diphenylmethane Deprotection- Macrocycle **6-43** was dissolved in TFA (0.05M) and Et_3SiH (10 eq) was added. The mixture was heated to reflux until TLC indicated that SM was consumed (normally 6 hours). The reaction was then cooled to and basified with 1M NaOH. The mixture was extracted with Et_2O. The organics were then dried over $MgSO_4$ and filtered. The filtrate was concentrated to afford a crude residue, which was purified as indicated.

(1*S*,3*R*)-3-butyl-*N*-(((*R*)-1-((*S*,*Z*)-3-oxo-1,4-diazacycloundec-7-ene-5-carbonyl)pyrrolidin-2-yl)methyl)cyclobutane-1-carboxamide (6-44a)



6-44a

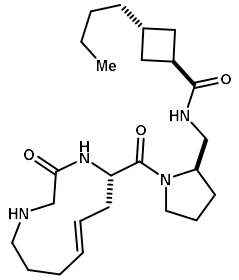
Starting with amine **6-43a** (22.4 mg, 0.033 mmol) the standard DPM deprotection method was utilized. The crude material was then purified by a pipette column (SiO_2, 50:1→25:1→10:1 $CHCl_3$/MeOH) to afford **6-44a** (13.6 mg, 95%). Macrocycle **6-44a** exists as a mixture of conformers at room temperature.

^{1}H NMR (500 MHz, CD_3OD): δ 5.63 (dt, *J* = 6.5, 10.3 Hz, 0.3H)*, 5.51 (dt, *J* = 6.5, 10.2 Hz, 0.7H), 5.46-5.35 (m, 1H), 4.69-4.55 (m, 1H), 4.44 (d, *J* = 11.5 Hz, 1H), 4.16 (d, *J* = 4.7 Hz, 1H), 3.88-3.76 (m, 1H), 3.61 (q, *J* = 8.4 Hz, 1H), 3.45-3.32 (m, 3H), 3.08-2.96 (m, 1H), 2.95-2.64 (m, 4H), 2.57 (q, *J* = 12.0 Hz, 1H), 2.39-2.14 (m, 4H), 2.14-1.87 (m, 5H), 1.87-1.70 (m, 3H), 1.70-1.59 (m, 1H), 1.54-1.42 (m, 2H), 1.40-1.26 (m, 4H), 1.25-1.20 (m, 2H), 0.89 (t, *J* = 6.7 Hz, 3H)

^{13}C NMR (125 MHz, CD_3OD): 177.5, 177.4, 173.7, 173.5, 171.4, 171.1, 134.2, 134.0, 124.6, 124.4, 57.7, 57.4, 52.0, 51.8, 51.2, 50.1, 46.7, 45.7, 45.40, 45.3, 41.9, 40.5, 36.2, 36.1, 36.0, 35.8, 31.7, 31.6, 31.4, 31.1, 29.8, 29.1, 28.9, 28.7, 28.2, 28.1, 28.0, 27.2, 26.4, 25.8, 23.3, 23.0, 22.9, 22.4, 22.3, 20.9, 14.0, 13.0

LRMS (ESI) m/z, 433.4 (433.3 calculated for $C_{24}H_{41}N_4O_3^+$, $(M+H)^+$)

(1*S*,3*R*)-3-butyl-*N*-(((*R*)-1-((*S*,*E*)-3-oxo-1,4-diazacycloundec-7-ene-5-carbonyl)pyrrolidin-2-yl)methyl)cyclobutane-1-carboxamide (6-44b)



6-44b

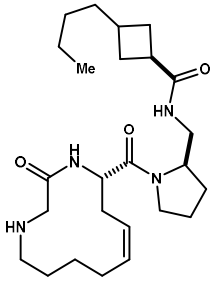
Starting with amine **6-43b** (89.6 mg, 0.149 mmol) the standard DPM deprotection method was utilized. The crude material was then purified by a preparative HPLC (elutes at 6 min) to afford **6-44b** (12.8 mg, 34%) as the TFA salt. Macrocycle **6-44b** exists as a mixture of conformers at room temperature.

HPLC Conditions: Waters Sunfire C18 column (19 x 250 mm) with UV detection at 280 nm; Solution A: H_2O w/0.1% trifluoroacetic acid and Solution B: MeCN w/0.1% trifluoroacetic acid; increase gradient of solution B from 45% to 65%, 0-15 min, 65% to 100%, 15-20 min, flow rate 15 mL/min

^{1}H NMR (500 MHz, CD_3OD): δ 5.74-5.59 (m, 0.3H)*, 5.52 (dt, J = 7.4, 10.0 Hz, 0.7H), 5.47-5.35 (m, 1H), 4.73-4.43 (m, 1H), 4.28 (t, J = 6.5 Hz, 0.3H)*, 4.24-4.11 (m, 0.3H), 4.06 (d, J = 6.5 Hz, 0.3H), 3.84-3.71 (m, 1H), 3.69-3.55 (m, 2H), 3.11-2.89 (m, 2H), 2.78-2.50 (m, 1H), 2.46-2.19 (m, 4H), 2.13-1.99 (m, 2H), 1.99-1.87 (m, 2H), 1.88-1.77 (m, 2H), 1.77-1.65 (m, 2H), 1.63-1.51 (m, 1H), 1.51-1.42 (m, 2H), 1.42-1.26 (m, 7H), 1.25-1.19 (m, 2H), 1.09-0.93 (m, 3H), 0.89 (t, J = 6.9 Hz, 3H)

LRMS (ESI) m/z, 433.4 (433.3 calculated for $C_{24}H_{41}N_4O_3^+$, $(M+H)^+$)

(1*S*,3*R*)-3-butyl-*N*-(((*R*)-1-((*S*,*Z*)-3-oxo-1,4-diazacyclododec-7-ene-5-carbonyl)pyrrolidin-2-yl)methyl)cyclobutane-1-carboxamide (6-44c)



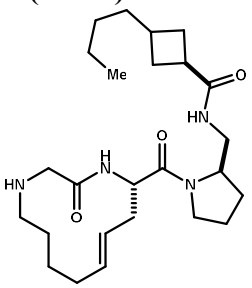
6-44c

Starting with amine **6-43c** (55.2 mg, 0.09 mmol) the standard DPM deprotection method was utilized. The crude material was then purified by a preparative HPLC to afford **6-44c** (35.2 mg, 70%) as the TFA salt. Macrocycle **6-44c** exists as a mixture of conformers at room temperature.

^{1}H NMR (500 MHz, $(CD_3)_2SO$): δ 9.08 (bs, 1H), 9.02 (bs, 1H), 8.79 (d, *J* = 9.7 Hz, 1H), 7.94 (t, *J* = 6.1 Hz, 0.3H)*, 7.68 (t, *J* = 5.8 Hz, 0.7H), 5.32-5.14 (m, 2H), 4.99-4.88 (m, 0.3H)*, 4.82-4.71 (m, 0.7H), 4.03-3.88 (m, 1H), 3.72 (bs, 1.4H), 3.66 (bs, 0.7H)*, 3.55-3.28 (m, 3H), 3.28-3.16 (m, 1H), 3.15-3.02 (m, 2H), 2.96-2.82 (m, 1H), 2.80-2.57 (m, 2H), 2.44-2.37 (m, 1H), 2.34-1.99 (m, 5H), 1.93-1.58 (m, 8H), 1.58-1.45 (m, 1H), 1.44-1.28 (m, 5H), 1.21 (sextet, *J* = 6.9 Hz, 2H), 1.15-1.05 (m, 2H), 0.81 (t, *J* = 7.3 Hz, 3H)

HRMS: Mass expected for $C_{25}H_{43}N_4O_3^+$: 447.3335 *m/z*, Mass observed: 447.3321 *m/z*

(1*S*,3*R*)-3-butyl-*N*-(((*R*)-1-((*S*,*E*)-3-oxo-1,4-diazacyclododec-7-ene-5-carbonyl)pyrrolidin-2-yl)methyl)cyclobutane-1-carboxamide (6-44d)



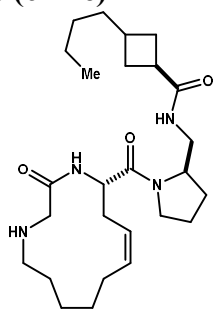
6-44d

Starting with amine **6-43d** (31.2 mg, 0.05 mmol) the standard DPM deprotection method was utilized. The crude material was then purified by a pipette column (SiO_2, 100:1→50:1→20:1→10:1 $CHCl_3$/MeOH) to afford **6-44d** (19.1 mg, 85%). Macrocycle **6-44d** exists as a mixture of conformers at room temperature.

^{1}H NMR (500 MHz, CD_3OD): δ 5.69-5.48 (m, 1H), 5.38 (dt, *J* = 9.9, 18.1 Hz, 1H), 4.22-4.10 (m, 1H), 3.67-3.57 (m, 2H), 3.44-3.32 (m, 3H), 3.12 (d, *J* = 16.4 Hz, 1H), 3.08-2.95 (m, 1H), 2.81-2.62 (m, 2H), 2.55-2.45 (m, 2H), 2.37-2.22 (m, 3H), 2.23-1.99 (m, 3H), 1.99-1.89 (m, 3H), 1.88-1.71 (m, 4H), 1.61-1.51 (m, 2H), 1.47 (p, *J* = 7.2 Hz, 2H), 1.38-1.26 (m, 3H), 1.26-1.19 (m, 2H), 0.97 (q, *J* = 7.3 Hz, 1H), 0.89 (t, *J* = 7.2 Hz, 3H)

HRMS: Mass expected for $C_{25}H_{43}N_4O_3^+$: 447.3335 *m/z*, Mass observed: 447.3354 *m/z*

(1*S*,3*R*)-3-butyl-*N*-(((*R*)-1-((*S*,*Z*)-3-oxo-1,4-diazacyclotridec-7-ene-5-carbonyl)pyrrolidin-2-yl)methyl)cyclobutane-1-carboxamide (6-44e)

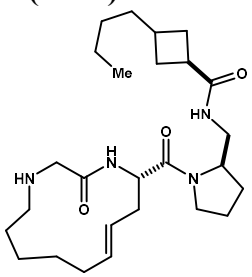


6-44e

Starting with amine **6-43e** (77.9 mg, 0.12 mmol) the standard DPM deprotection method was utilized. The crude material was then purified by a pipette column (SiO_2, 100:1→50:1→20:1→10:1 $CHCl_3$/MeOH) to afford **6-44e** (43.6 mg, 79%). Macrocycle **6-44e** exists as a mixture of conformers at room temperature.

^{1}H NMR (500 MHz, CD_3OD): δ 5.60 (dt, *J* = 8.6, 14.1 Hz, 0.3H)*, 5.51 (dt, *J* = 9.7, 13.5 Hz, 0.7H), 5.46-5.30 (m, 1H), 4.45-4.32 (m, 0.3H)*, 4.22-4.09 (m, 0.7H), 3.94-3.62 (m, 3H), 3.61-3.53 (m, 1H), 3.44-3.35 (m, 3H), 3.24-3.08 (m, 1H), 3.08-2.93 (m, 2H), 2.59-2.43 (m, 1H),2.39-2.13 (m, 4H), 2.08-1.98 (m, 2H), 1.97-1.88 (m, 2H), 1.87-1.76 (m, 3H), 1.77-1.66 (m, 1H), 1.66-1.55 (m, 2H), 1.54-1.42 (m, 3H), 1.42-1.34 (m, 1H), 1.35-1.25 (m, 4H), 1.25-1.20 (m, 2H), 0.89 (t, *J* = 7.2 Hz, 3H)

(1*S*,3*R*)-3-butyl-*N*-(((*R*)-1-((*S*,*E*)-3-oxo-1,4-diazacyclotridec-7-ene-5-carbonyl)pyrrolidin-2-yl)methyl)cyclobutane-1-carboxamide (6-44f)

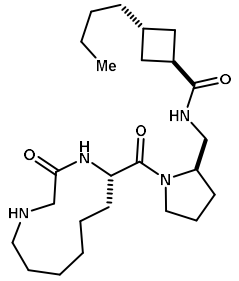


6-44f

Starting with amine **6-43f** (29.9 mg, 0.047 mmol) the standard DPM deprotection method was utilized. The crude material was then purified by a pipette column (SiO_2, 100:1→50:1→20:1→10:1 $CHCl_3$/MeOH) to afford **6-44e** (21.0 mg, 97%). Macrocycle **6-44e** exists as a mixture of conformers at room temperature.

^{1}H NMR (500 MHz, $(CD_3)_2SO$): δ 7.97-7.86 (m, 1H), 7.76 (d, *J* = 7.9 Hz, 0.3H)*, 7.53 (t, *J* = 5.6 Hz, 0.7H), 5.60-5.47 (m, 0.6H)*, 5.43 (dt, *J* = 8.2, 18.0 Hz, 0.7H), 5.27 (dt, *J* = 7.6, 17.7 Hz, 0.7H), 4.76-4.67 (m, 0.3H)*, 4.64-4.54 (m, 0.7H), 4.28-4.20 (m, 0.3H)*, 4.00-3.88 (m, 0.7H), 3.57-3.43 (m, 2H), 3.25-3.04 (m, 3H), 3.00-2.84 (m, 1H), 2.71 (dd, *J* = 3.3, 17.3 Hz, 1H), 1.66-1.56 (m, 1H), 2.44-2.38 (m, 1H), 2.38-2.28 (m, 2H), 2.20-2.09 (m, 3H), 2.09-1.93 (m, 2H), 1.91-1.82 (m, 1H), 1.81-1.71 (m, 2H), 1.71-1.59 (m, 3H), 1.55-1.41 (m, 2H), 1.41-1.33 (m, 4H), 1.29-1.17 (m, 5H), 1.17-1.09 (m, 2H), 0.81 (t, *J* = 7.0 Hz, 3H)

(1*S*,3*R*)-3-butyl-*N*-(((*R*)-1-((*S*)-3-oxo-1,4-diazacycloundecane-5-carbonyl)pyrrolidin-2-yl)methyl)cyclobutane-1-carboxamide (6-45a)



6-45a

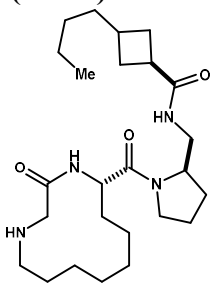
Starting with a mixture of **6-43a/b** (55.0 mg, 0.092 mmol) the standard DPM deprotection method was utilized. The crude material was then dissolved in MeOH (3 mL, 0.03M) and HCl (1M in MeOH, 0.18 mL, 0.18 mmol, 2 eq) was added. The mixture was then loaded into an autoclave with $Pd(OH)_2$ (5.2 mg, 0.0074 mmol, 8 mol %). The system was pressurized with H_2 (500 psi) and stirred at room temperature for 48h. The reaction mixture was then filtered over Celite® and washed with MeOH. The filtrate was concentrated and purified by preparative HPLC (elutes at 3.75 min) to afford **6-45a** (9.4 mg, 18% over two steps). Macrocycle **6-45a** exists as a mixture of conformers at room temperature.

^{1}H NMR (500 MHz, CD_3OD): δ 5.07 (dd, *J* = 4.1, 10.0 Hz, 0.3H)*, 4.79 (dd, *J* = 3.8, 7.9 Hz, 0.7H), 4.41-4.33 (m, 0.3H), 4.19-4.08 (m, 0.7H), 3.80 (d, *J* = 14.0 Hz, 1H), 3.76 (d, *J* = 14.4 Hz, 1H), 3.67-3.59 (m, 1H), 3.59-3.51 (m, 1H), 3.44-3.32 (m, 4H), 3.28-3.14 (m, 1H), 3.12-2.97 (m, 2H), 2.37-2.20 (m, 3H), 2.11-1.98 (m, 2H), 1.98-1.89 (m, 2H), 1.88-1.77 (m, 3H), 1.76-1.56 (m, 3H), 1.53-1.43 (m, 3), 1.43-1.34 (m, 3H), 1.31 (sextet, *J* = 6.8 Hz, 2H), 1.26-1.19 (m, 2H), 0.89 (t, *J* = 7.1 Hz, 3H)

^{13}C NMR (125 MHz, CD_3OD): 177.4, 169.9, 164.8, 57.6, 51.7, 46.6, 46.5, 40.3, 36.0, 35.8, 31.6, 29.9, 29.8, 29.1, 27.7, 27.1, 25.2, 23.3, 22.7, 22.3, 21.1, 20.6, 20.1, 13.0

LRMS (ESI) m/z, 435.3 (435.3 calculated for $C_{24}H_{43}N_4O_3^+$, $(M+H)^+$)

(1*S*,3*R*)-3-butyl-*N*-(((*R*)-1-((*S*)-3-oxo-1,4-diazacyclododecane-5-carbonyl)pyrrolidin-2-yl)methyl)cyclobutane-1-carboxamide (6-45b)



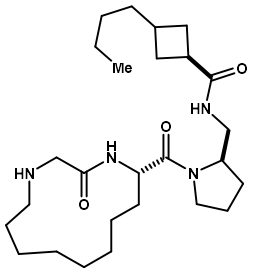
6-45b

Starting with a mixture of **6-43c/d** (94.7 mg, 0.154 mmol) the standard DPM deprotection method was utilized. The crude material was then dissolved in MeOH (3 mL, 0.05M) and HCl (1M in MeOH, 0.30 mL, 0.30 mmol, 2 eq) was added. The mixture was then loaded into an autoclave with $Pd(OH)_2$ (5.2 mg, 0.0074 mmol, 8 mol %). The system was pressurized with H_2 (500 psi) and stirred at room temperature for 48h. The reaction mixture was then filtered over Celite® and washed with MeOH. The filtrate was concentrated and purified by preparative HPLC (elutes at 4 min) to afford **6-45b** (9.4 mg, 18% over two steps). Macrocycle **6-45b** exists as a mixture of conformers at room temperature.

^{1}H NMR (500 MHz, CD_3OD): δ 5.12 (dd, *J* = 4.5, 9.9 Hz, 0.2H)*, 4.96-4.88 (m, 0.8H), 4.38-4.28 (m, 0.2H)*, 4.19-4.06 (m, 0.8H), 3.87 (d, *J* = 15.1 Hz, 1H), 3.81 (d, *J* = 15.2 Hz, 1H), 3.68-3.60 (m, 1H), 3.59-3.49 (m, 1H), 3.49-3.33 (m, 3H), 3.26-3.16 (m, 1H), 3.12-2.96 (m, 2H), 2.40-2.21 (m, 3H), 2.09-2.02 (m, 1H), 2.00-1.88 (m, 3H), 1.87-1.75 (m, 4H), 1.70-1.55 (m, 3H), 1.53-1.34 (m, 8H), 1.33-1.26 (m, 2H), 1.26-1.17 (m, 2H), 0.89 (t, *J* = 7.2 Hz, 3H)
^{13}C NMR (125 MHz, CD_3OD): 177.3, 170.2, 164.7, 57.5, 57.4, 51.7, 50.8, 46.6, 46.3, 45.9, 41.8, 40.4, 36.0, 35.8, 31.6, 31.1, 29.9, 29.8, 29.1, 28.9, 28.2, 27.1, 25.4, 24.9, 24.8, 24.6, 23.3, 23.2, 22.9, 22.8, 22.3, 21.1, 20.8, 13.0

LRMS (ESI) m/z, 449.3 (449.3 calculated for $C_{25}H_{45}N_4O_3^+$, $(M+H)^+$)

(1*S*,3*R*)-3-butyl-*N*-(((*R*)-1-((*S*)-3-oxo-1,4-diazacyclotridecane-5-carbonyl)pyrrolidin-2-yl)methyl)cyclobutane-1-carboxamide (6-45c)



6-45c

Starting with a mixture of **6-43e/f** (0.2399 g, 0.38 mmol) the standard DPM deprotection method was utilized. The crude material was then dissolved in MeOH (12 mL, 0.03M) and HCl (1M in MeOH, 0.76 mL, 0.76 mmol, 2 eq) was added. The mixture was then loaded into an autoclave with $Pd(OH)_2$ (28.7 mg, 0.04 mmol, 10 mol %). The system was pressurized with H_2 (500 psi) and

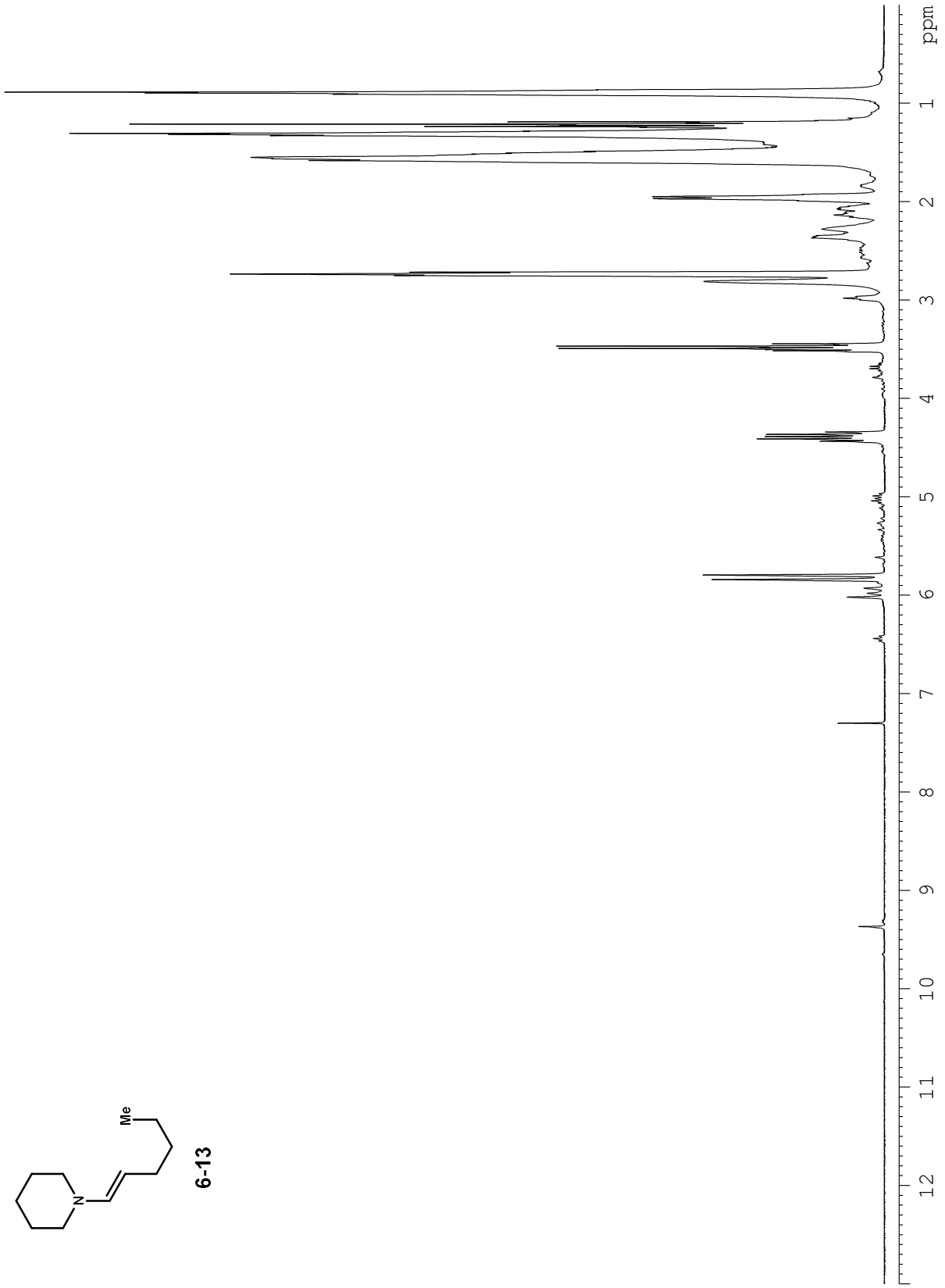
stirred at room temperature for 48h. The reaction mixture was then filtered over Celite® and washed with MeOH. The filtrate was concentrated and purified by flash column chromatography (SiO_2, 100:1→50:1→20:1→10:1 $CHCl_3$/MeOH) to afford **6-45c** (51.5 mg, 29% over two steps). Macrocycle **6-45c** exists as a mixture of conformers at room temperature.

^{1}H NMR (500 MHz, CD_3OD): δ 4.74 (dd, *J* = 2.2, 10.9 Hz, 0.2H)* 4.66-4.55 (m, 0.8H), 4.28-4.06 (m, 1H), 3.80-3.66 (m, 1H), 3.63-3.50 (m, 1H), 3.50-3.32 (m, 3H), 3.23-2.94 (m, 2H), 2.83-2.66 (m, 1H), 2.65-2.47 (m, 1H), 2.45-2.20 (m, 4H), 2.09-2.00 (m, 1H), 1.99-1.89 (m, 2H), 1.88-1.77 (m, 3H), 1.76-1.67 (m, 1H), 1.67-1.52 (m, 3H), 1.53-1.26 (m, 12H), 1.26-1.16 (m, 3H), 0.89 (t, *J* = 7.0 Hz, 3H)

^{13}C NMR (125 MHz, CD_3OD): 177.4, 172.2, 171.3, 57.6, 57.4, 51.6, 51.5, 50.8, 46.7, 45.7, 41.8, 40.4, 36.0, 36.0, 35.8, 31.6, 30.4, 29.8, 29.2, 29.1, 28.9, 28.7, 28.1, 27.3, 27.2, 26.3, 26.1, 24.6, 24.5, 24.1, 23.6, 23.3, 22.3, 22.2, 21.7, 20.9, 13.0

LRMS (ESI) m/z, 463.3 (463.3 calculated for $C_{26}H_{47}N_4O_3^+$, $(M+H)^+$)

6.4.3. NMR Spectra Relevant to Appendix One



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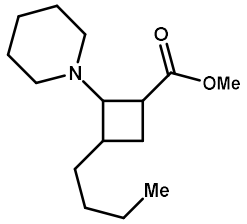
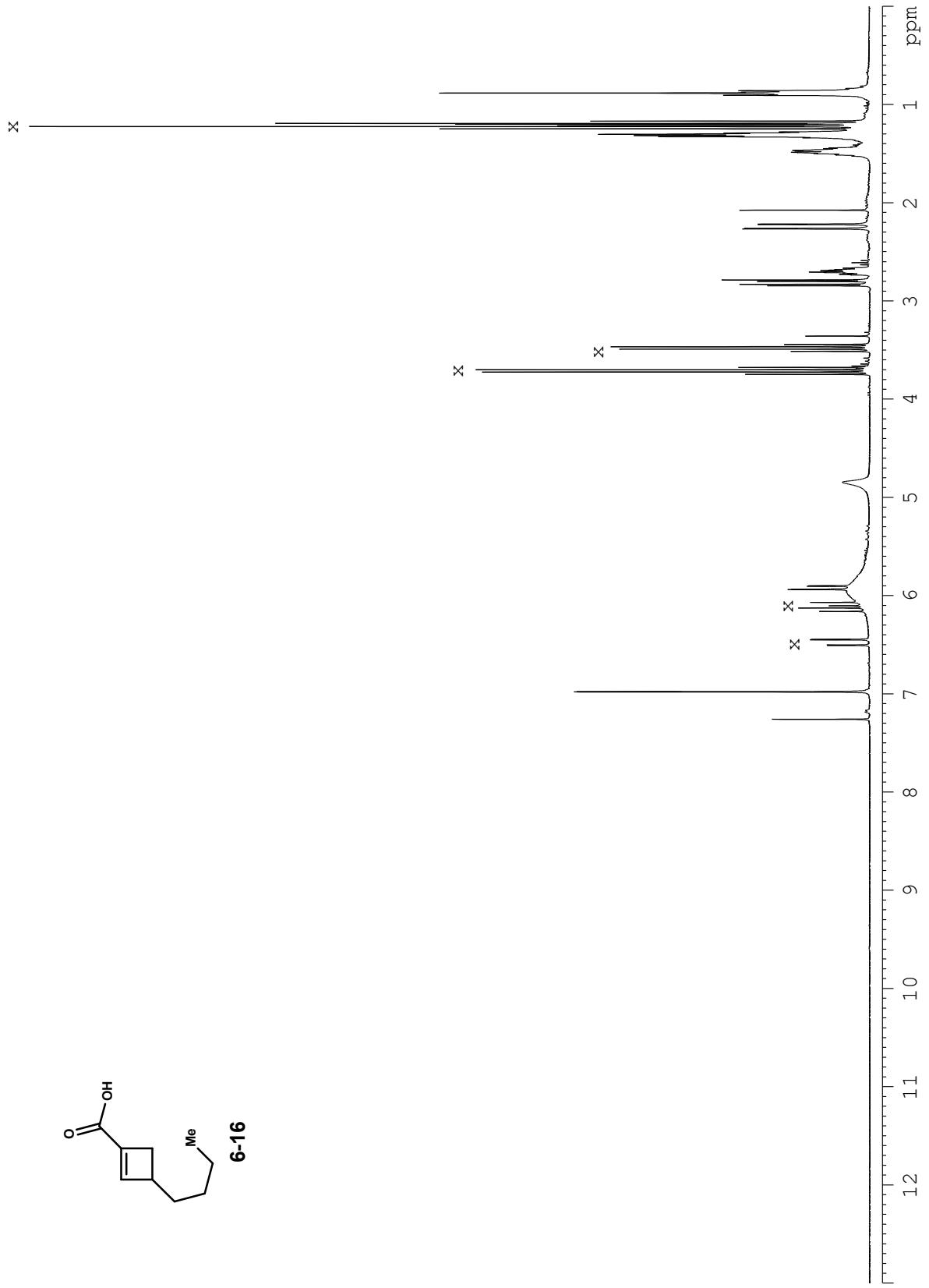


6-14
All 8 diastereomers



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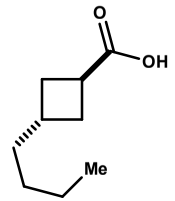

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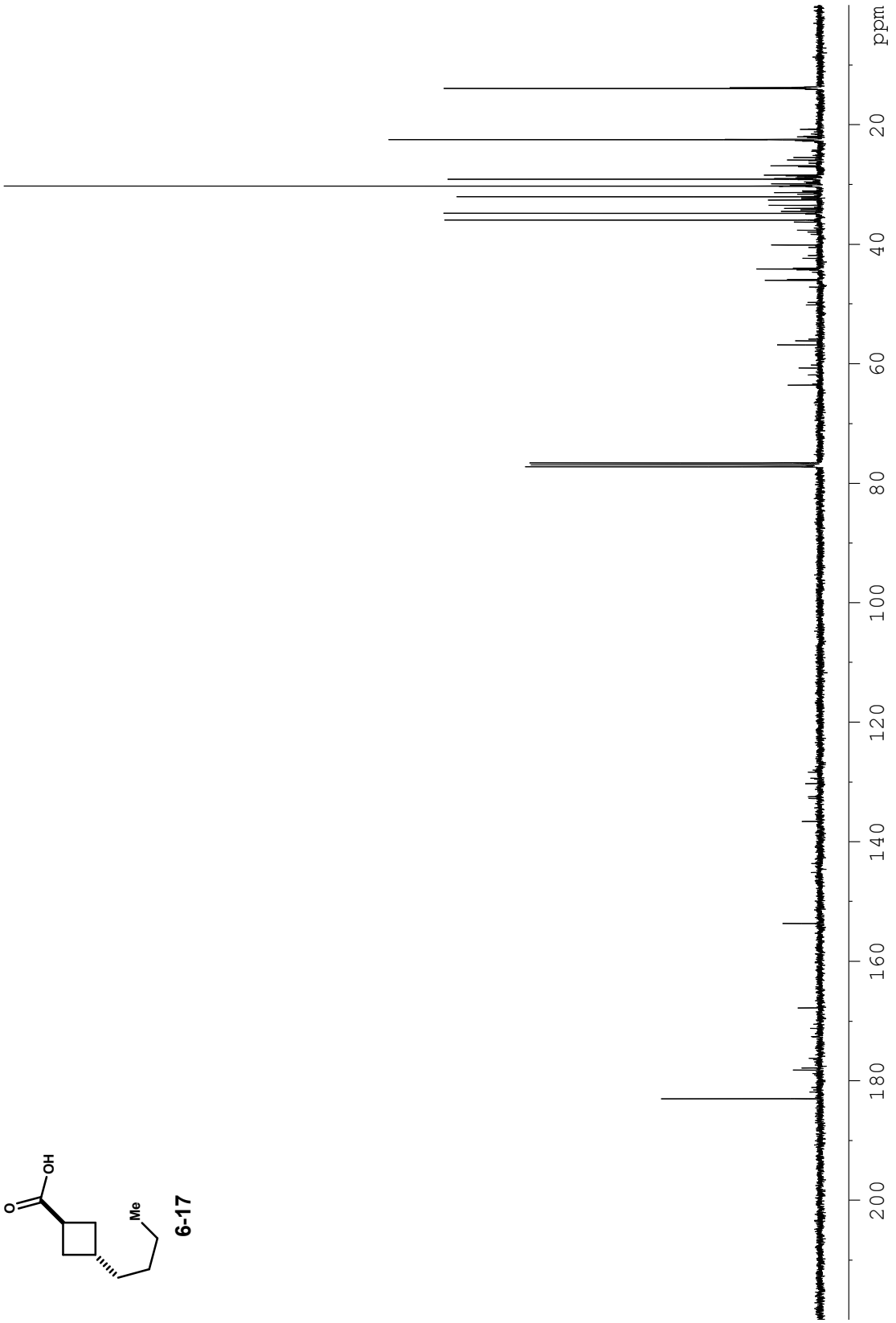
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80
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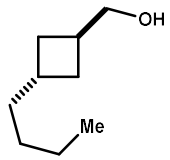
200



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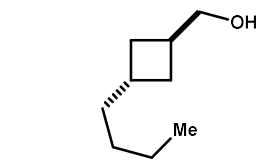

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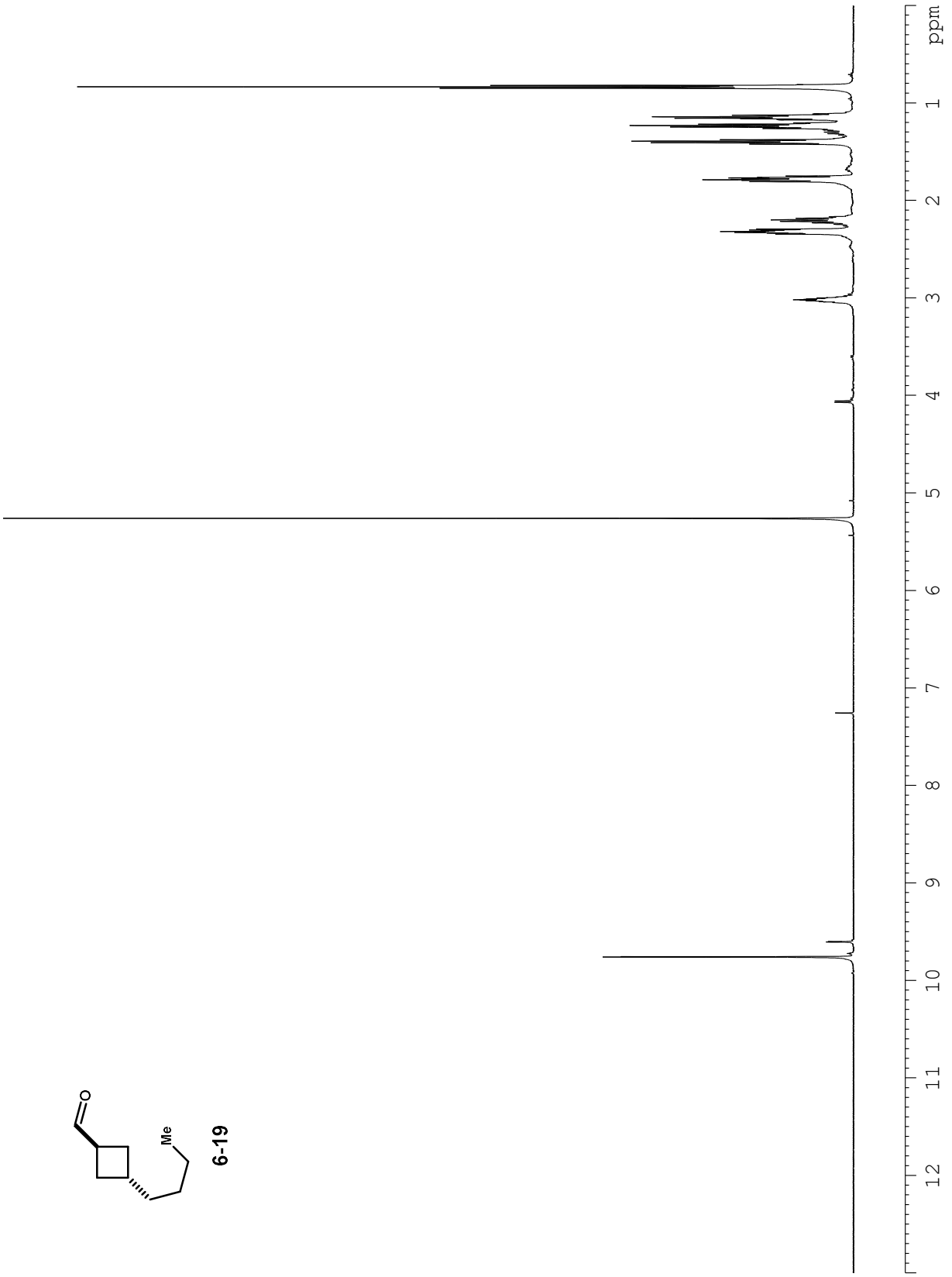
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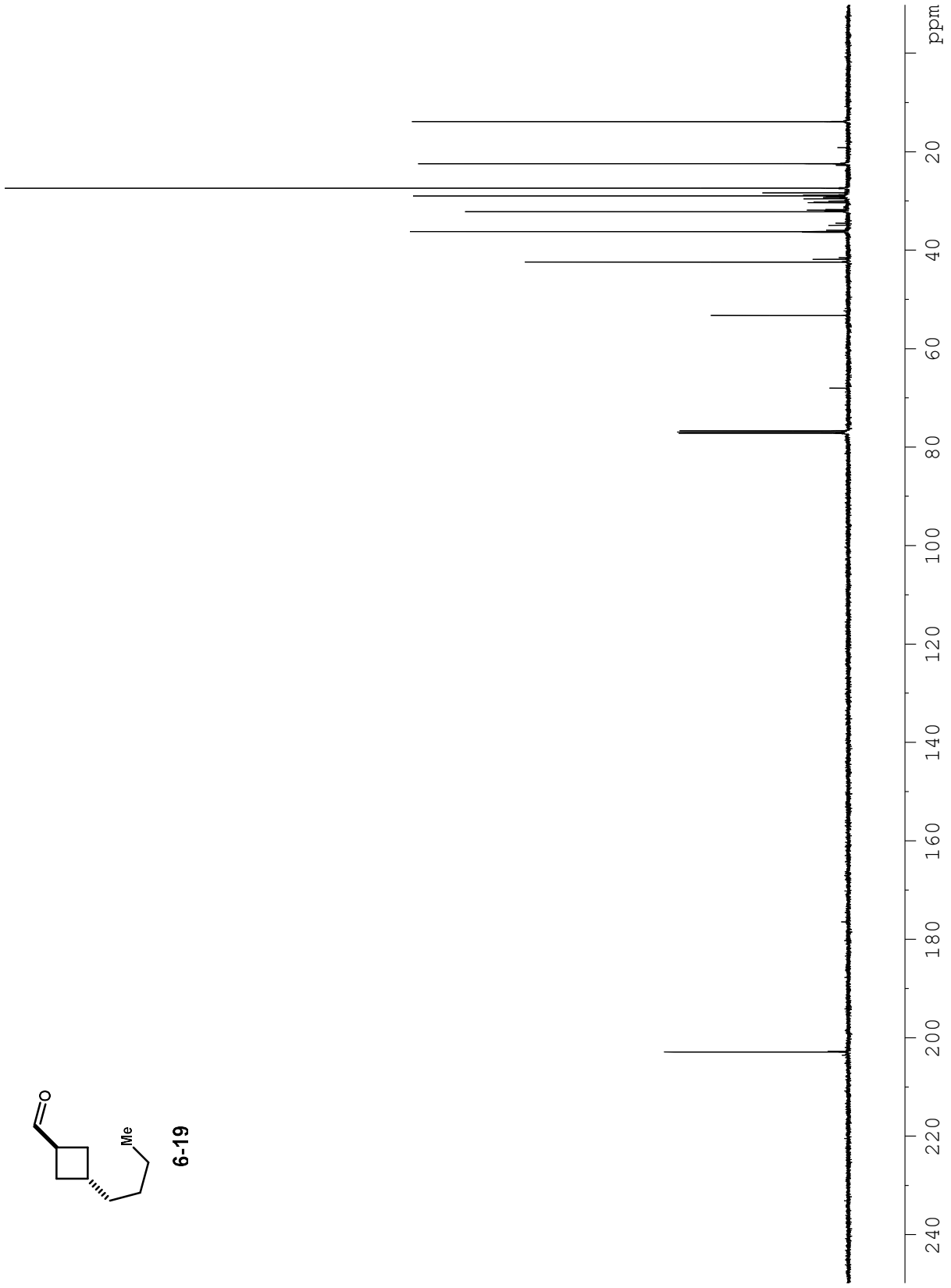
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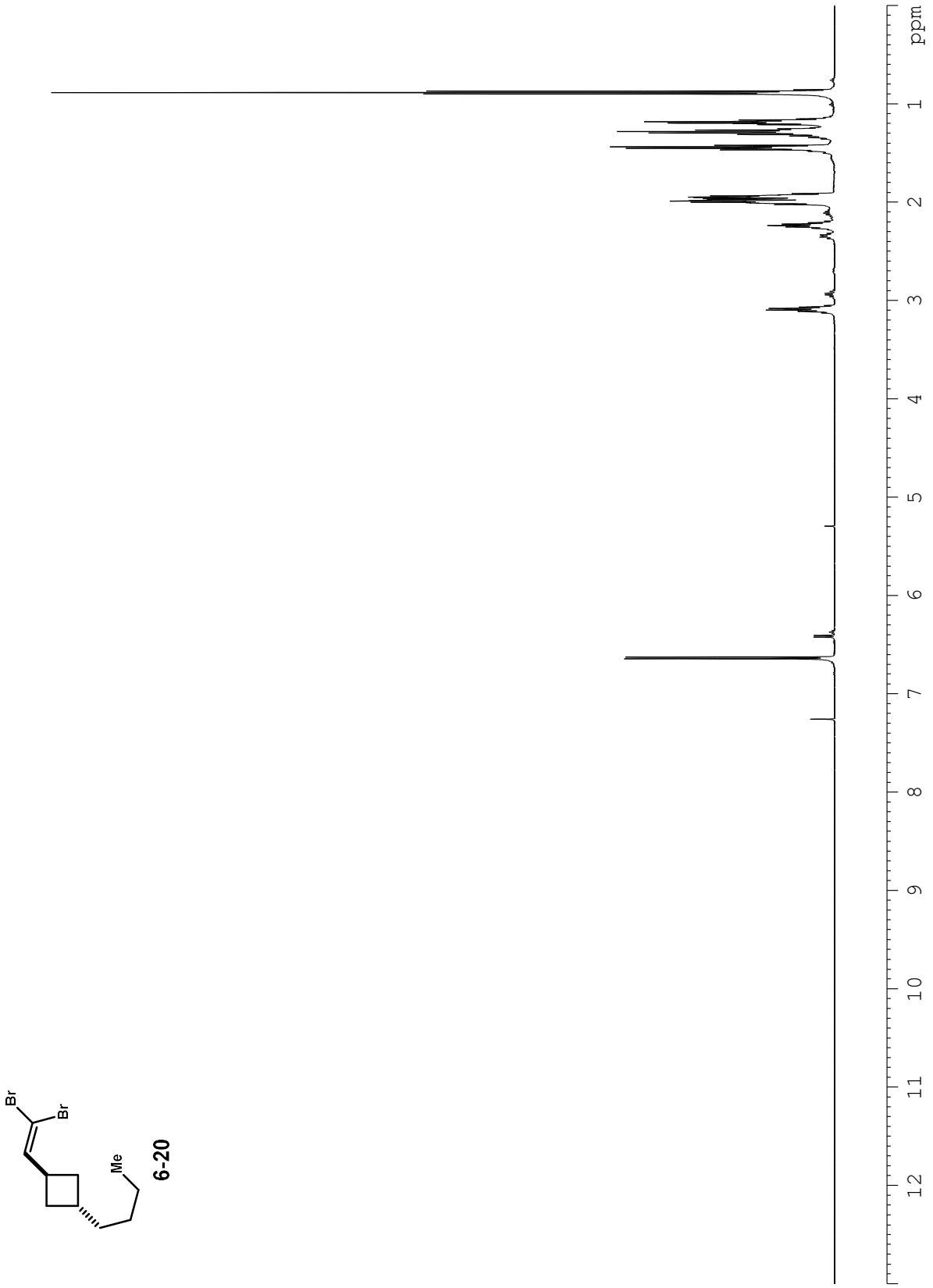
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ppm
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11
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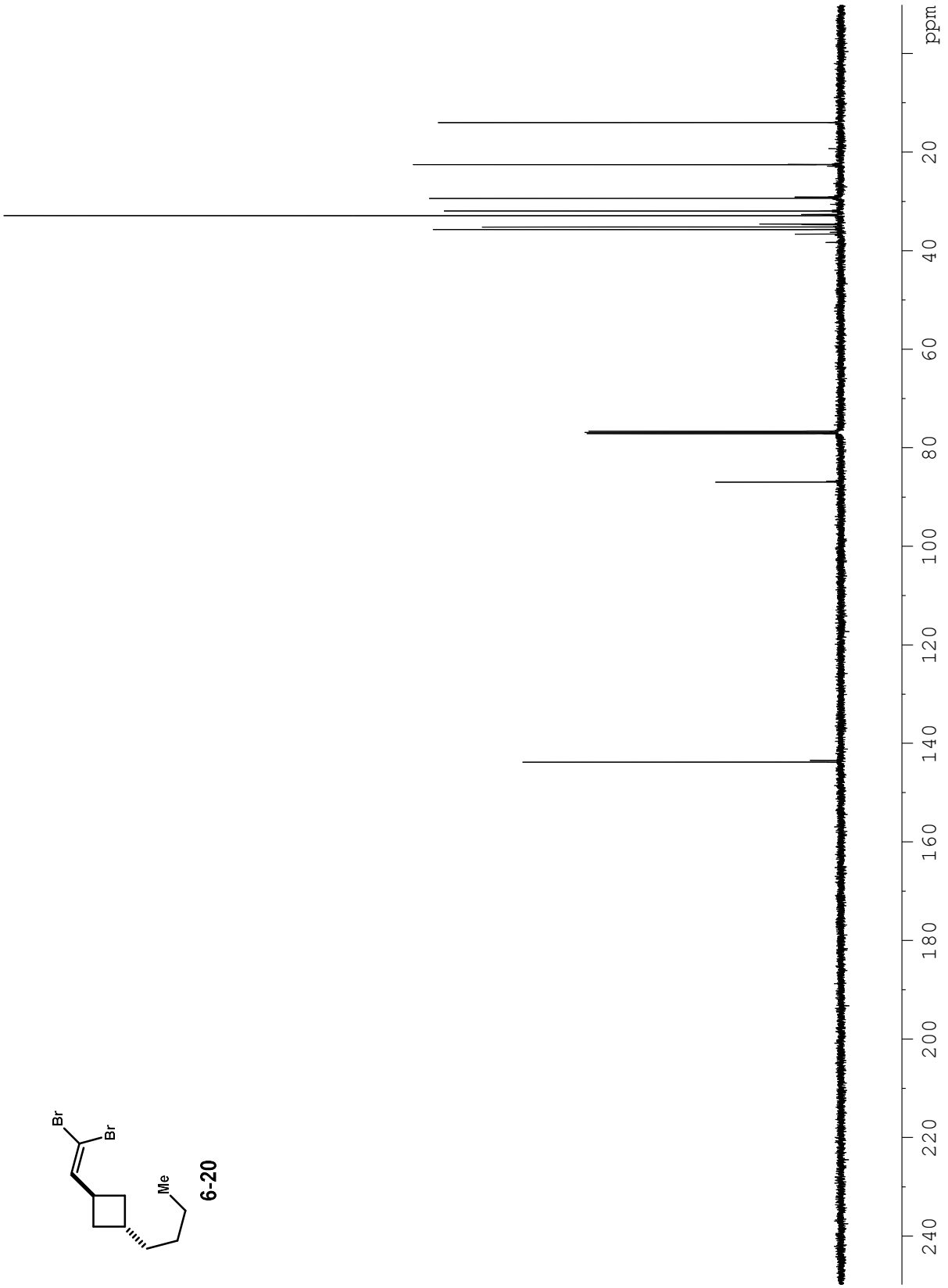
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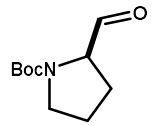

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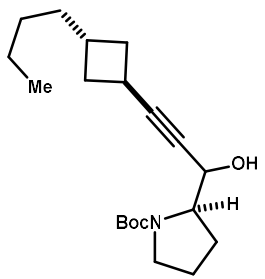

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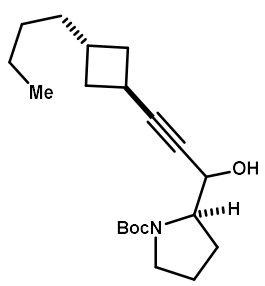

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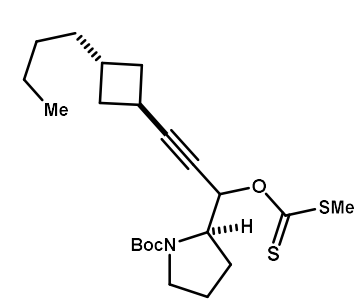

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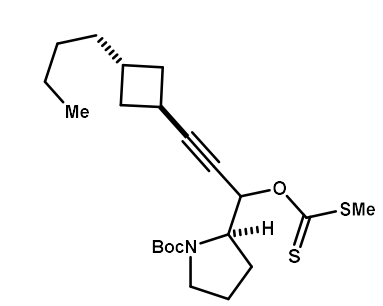

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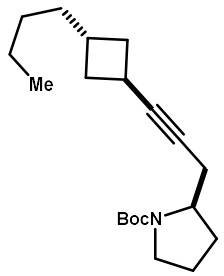

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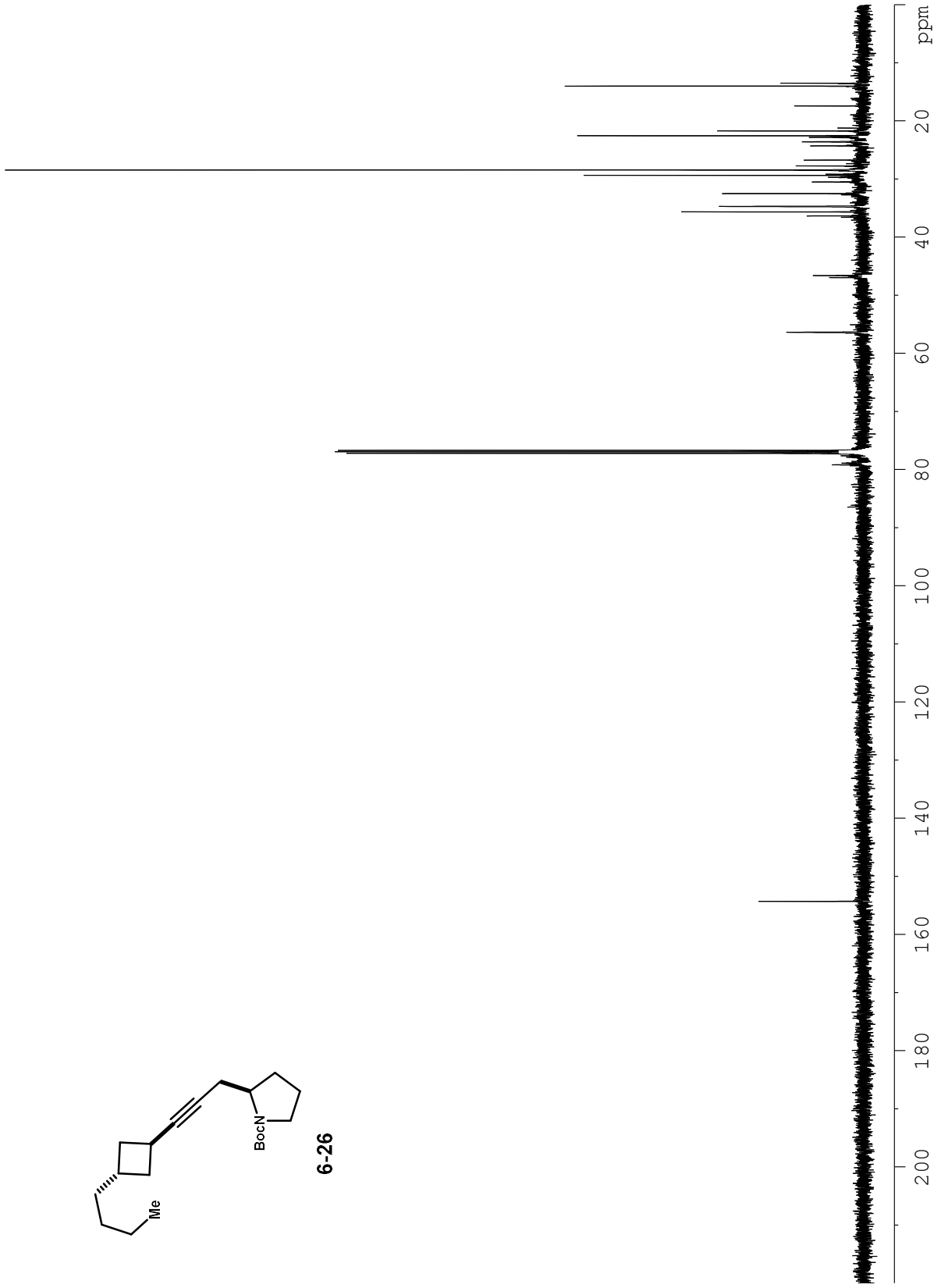

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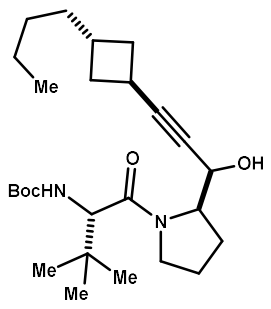

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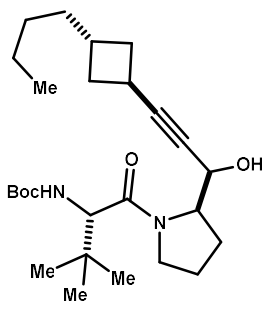

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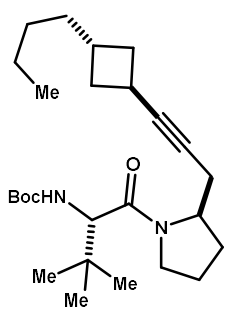

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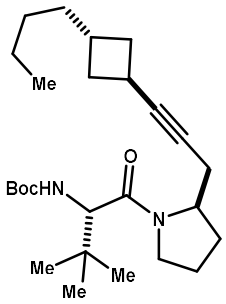

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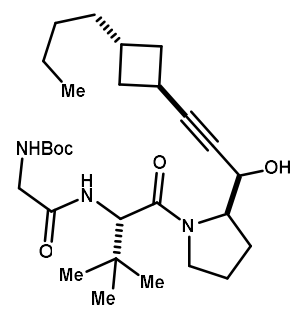

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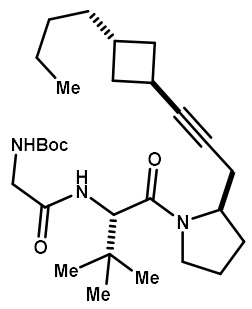

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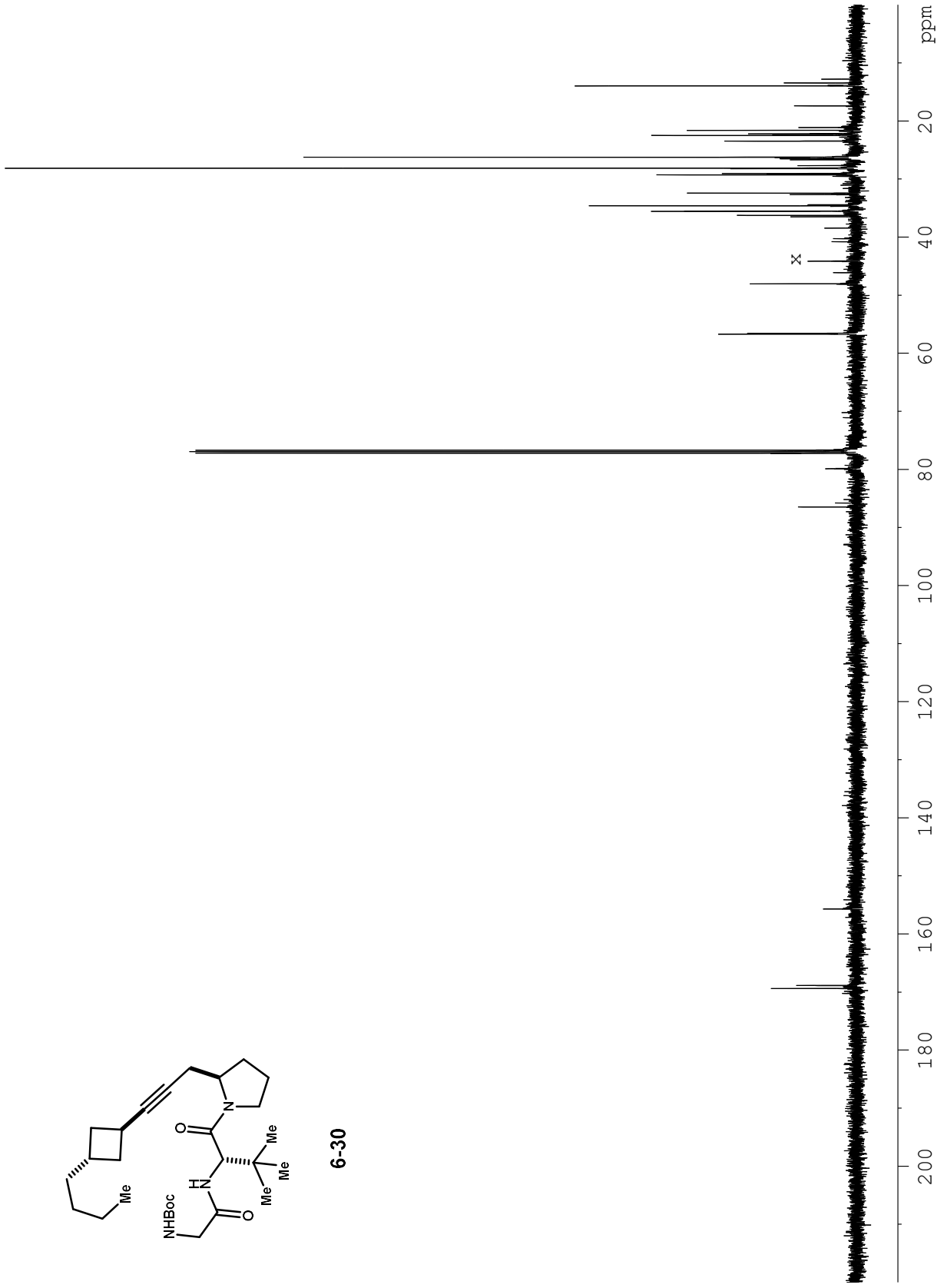

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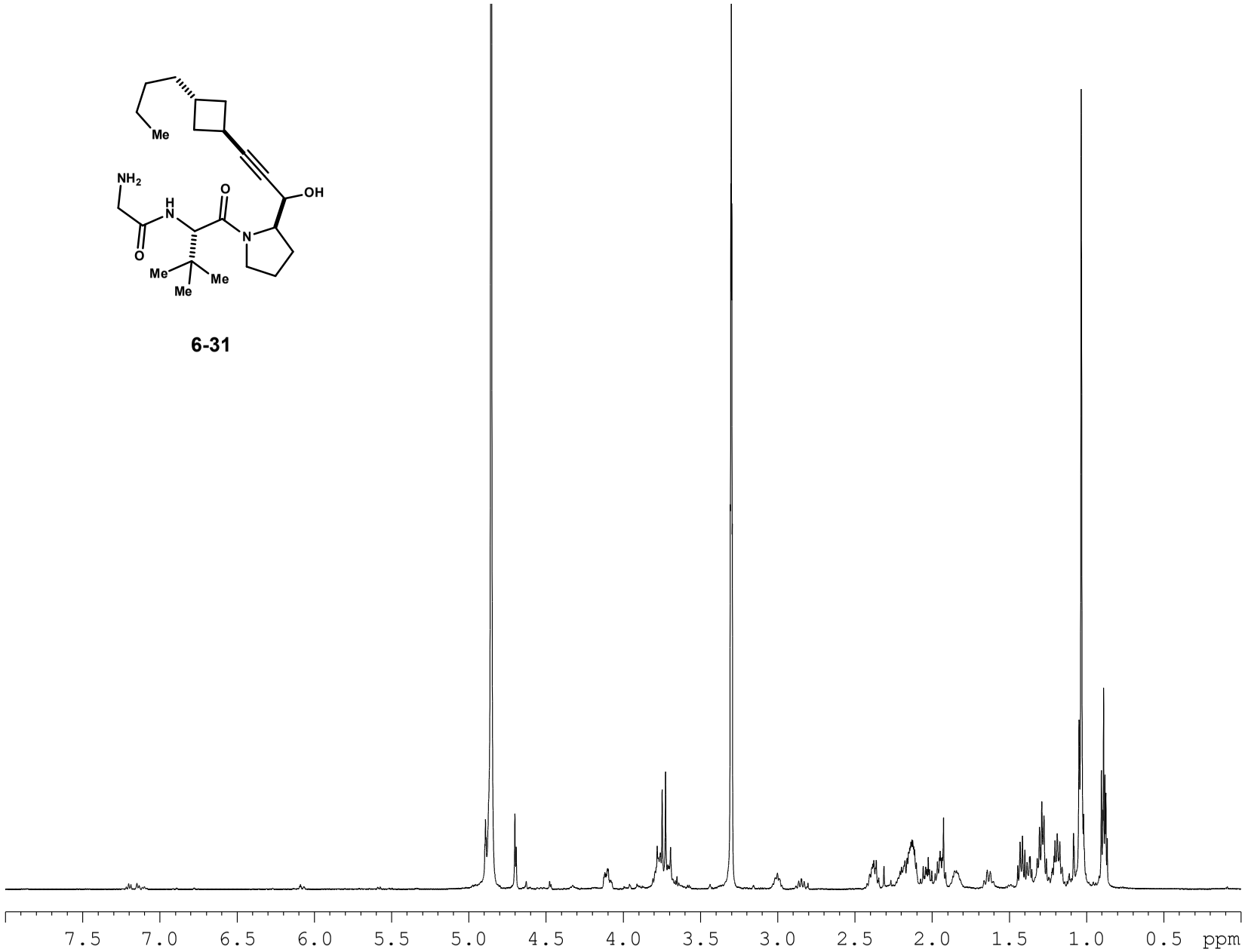
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ppm

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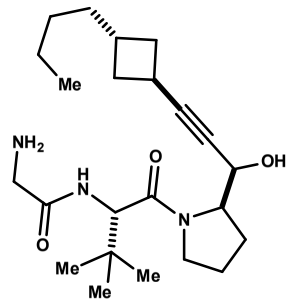

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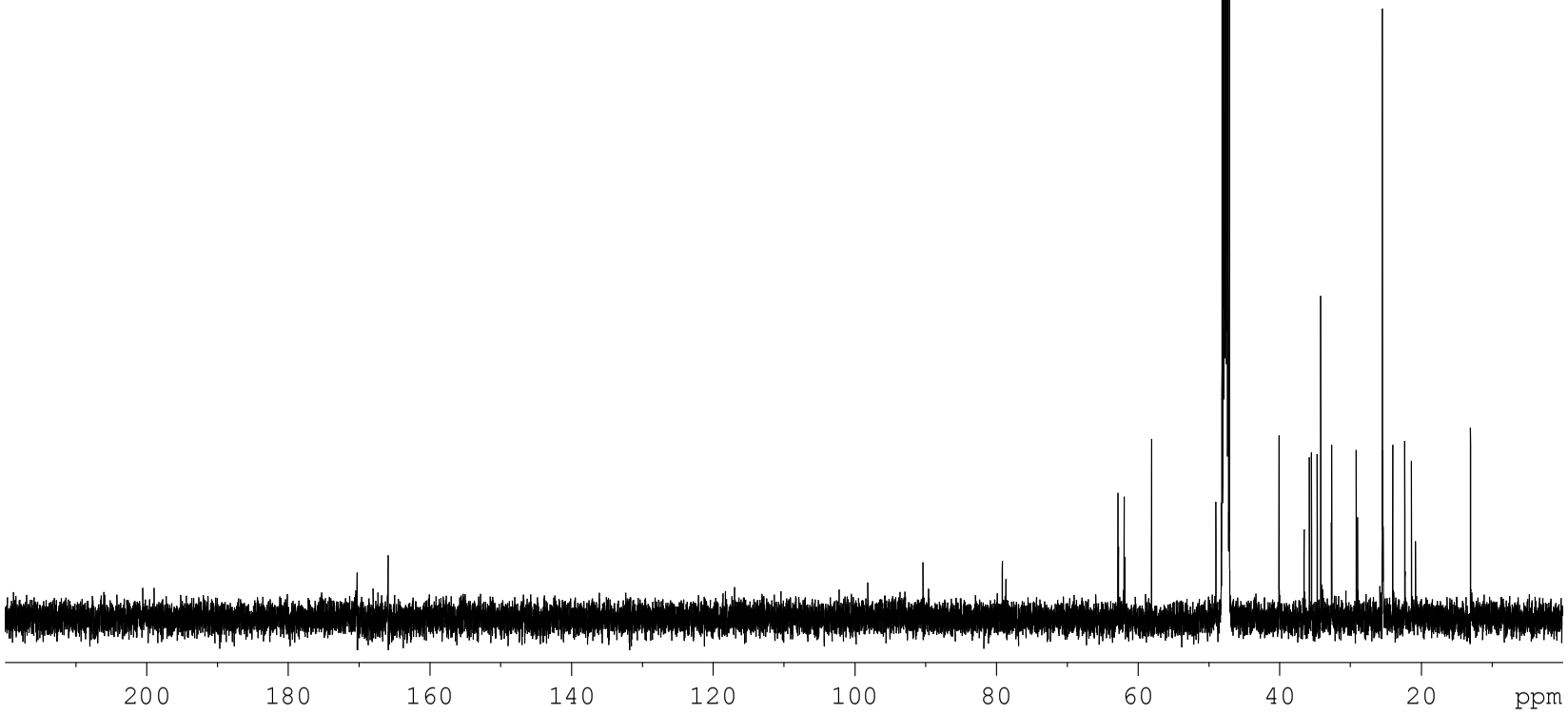

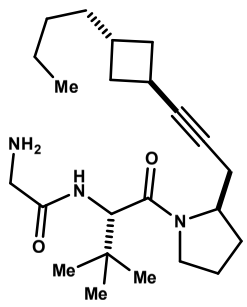

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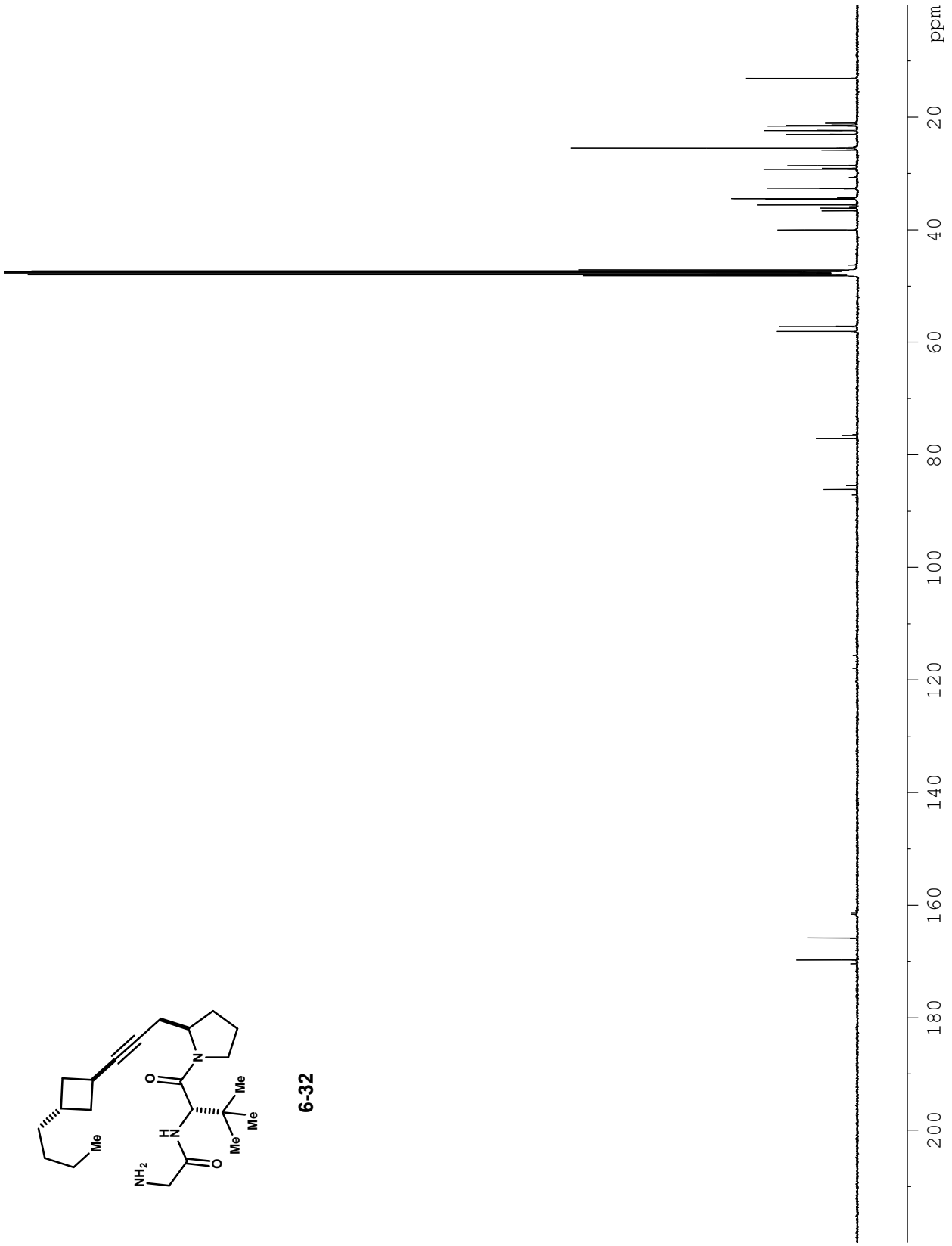

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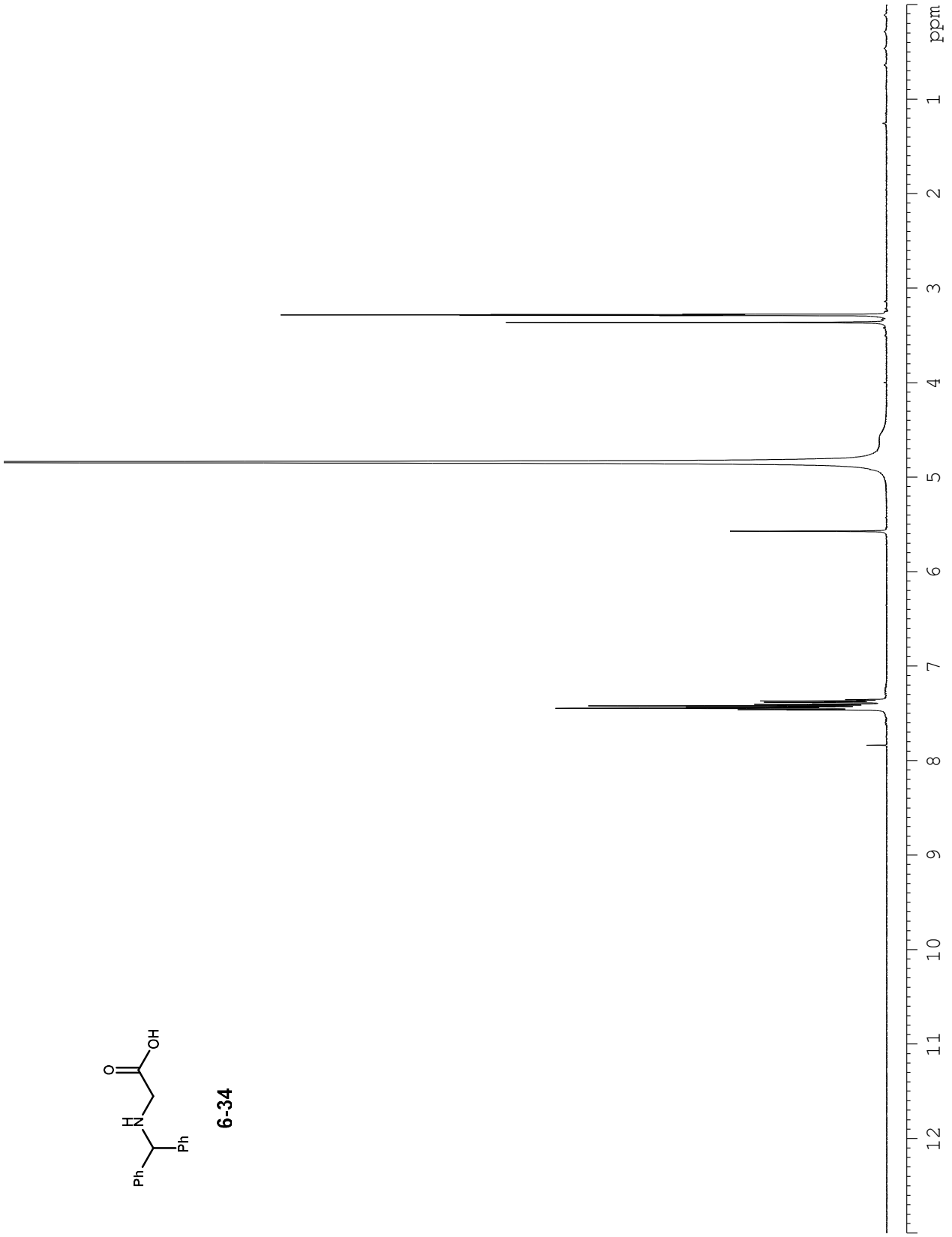

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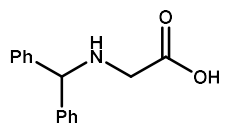

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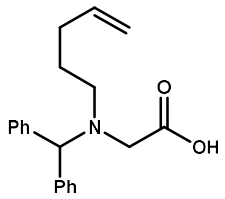

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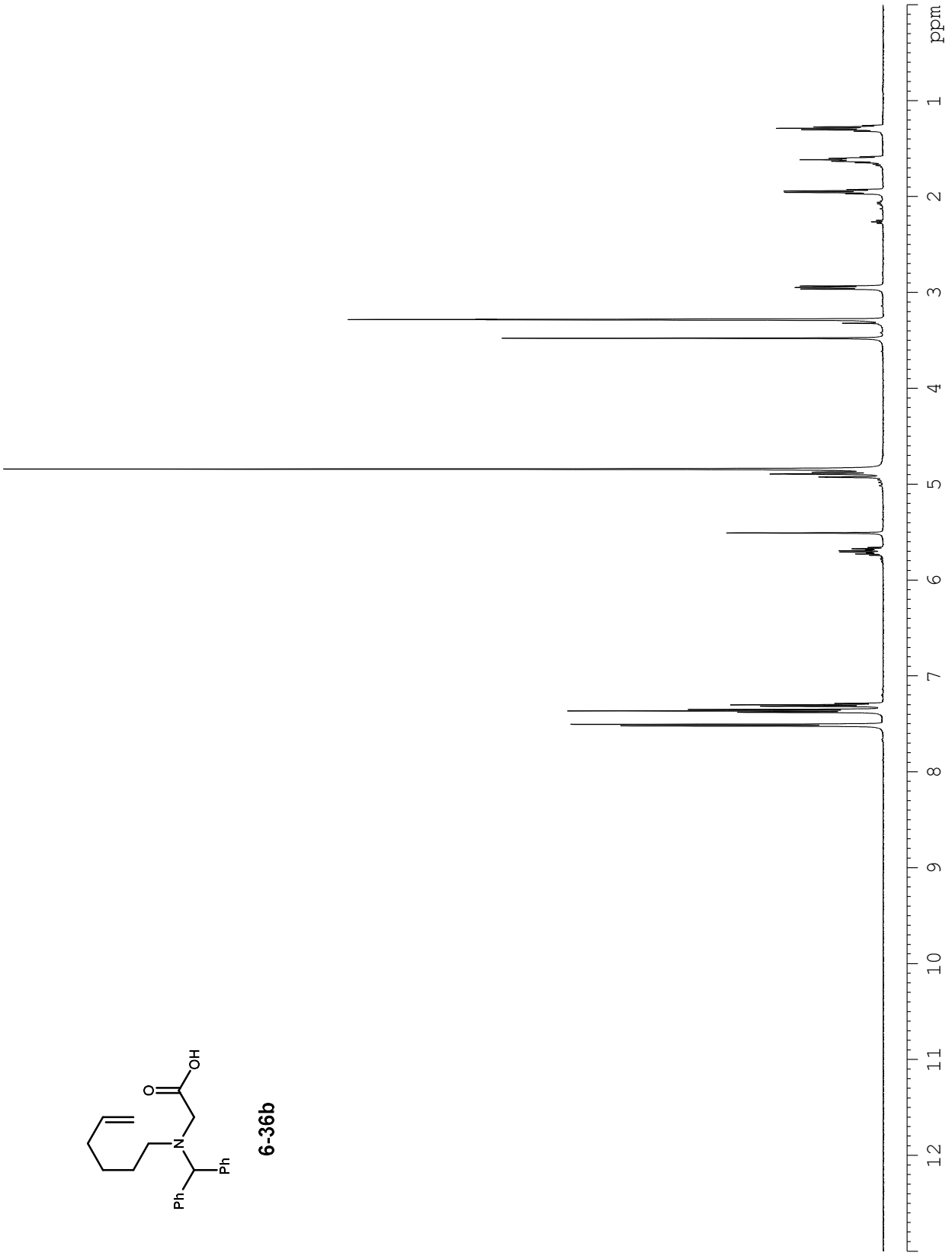

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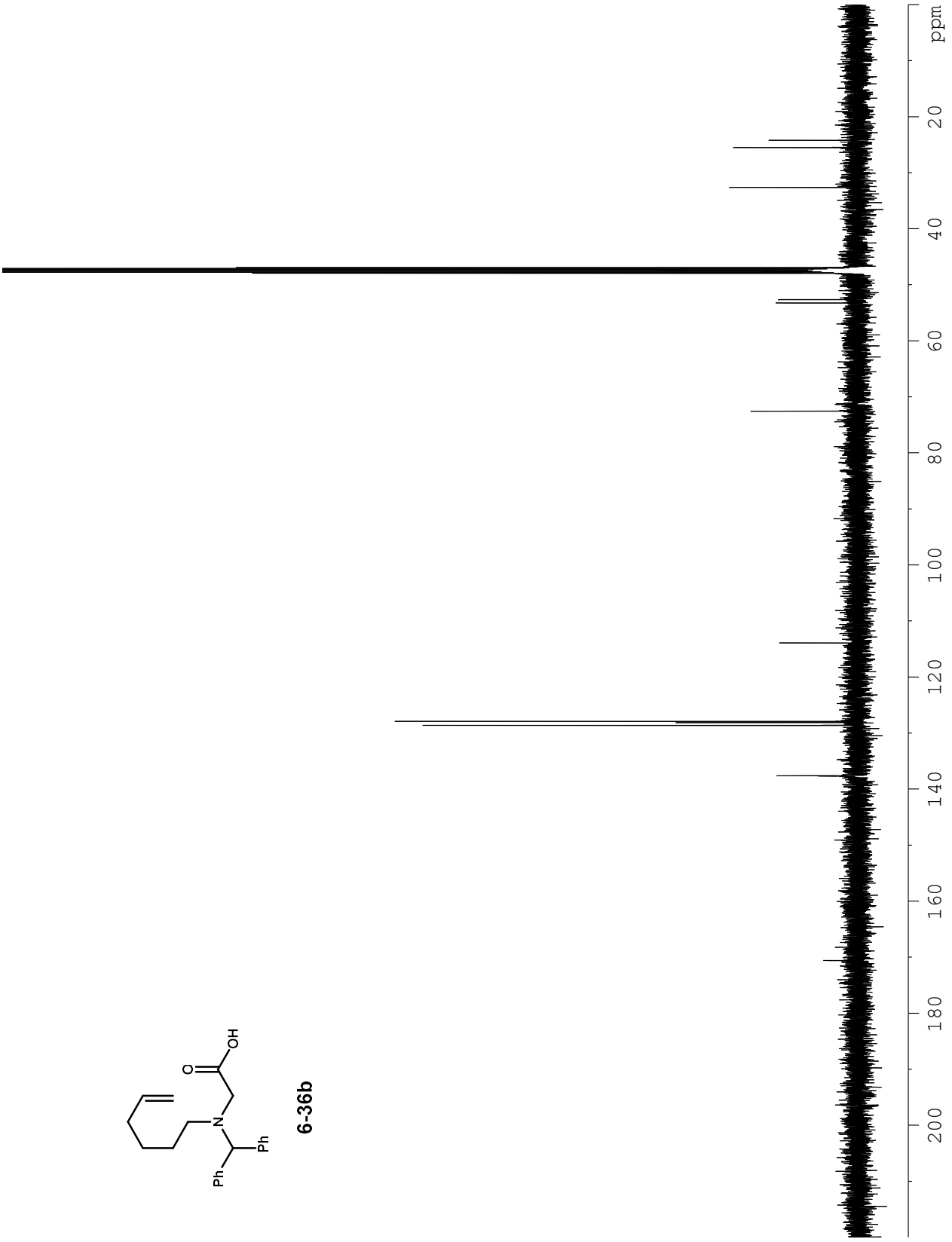

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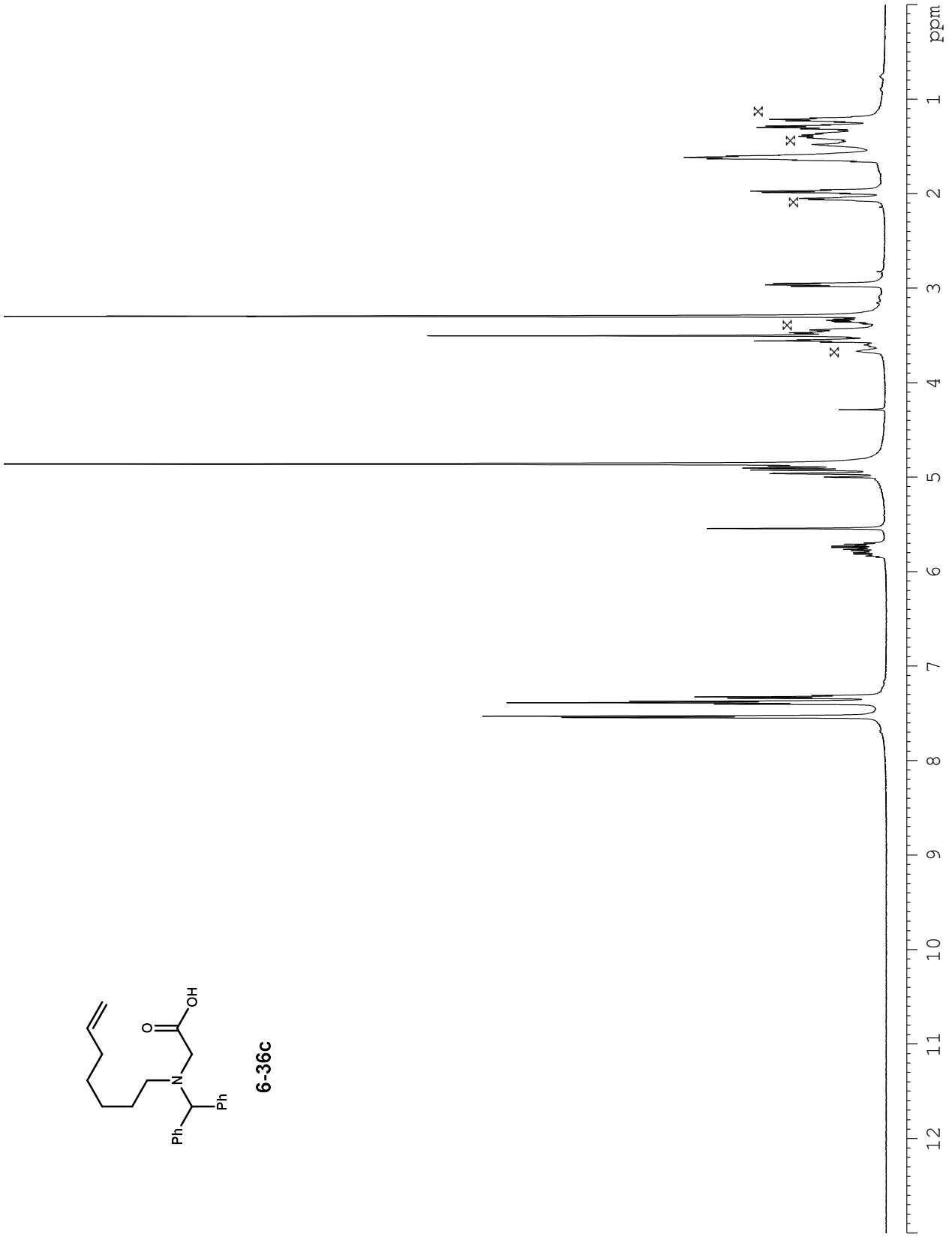

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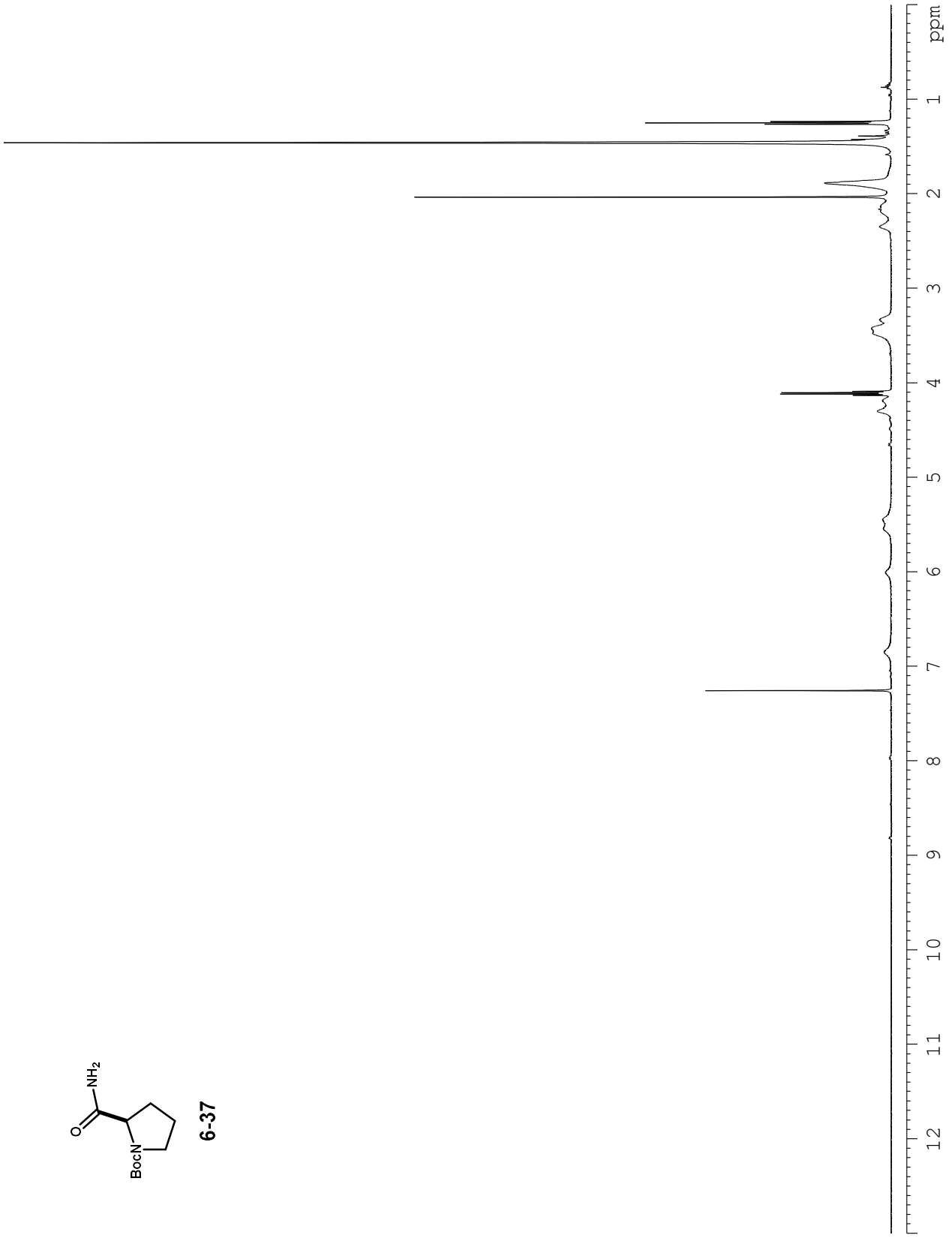

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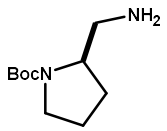

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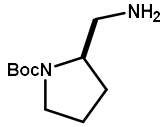

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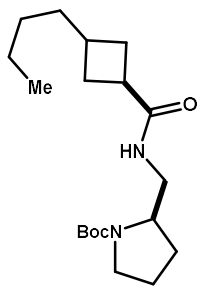

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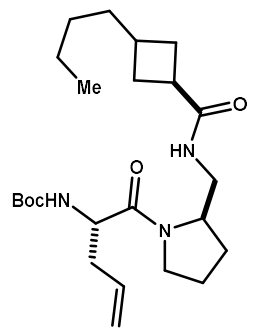

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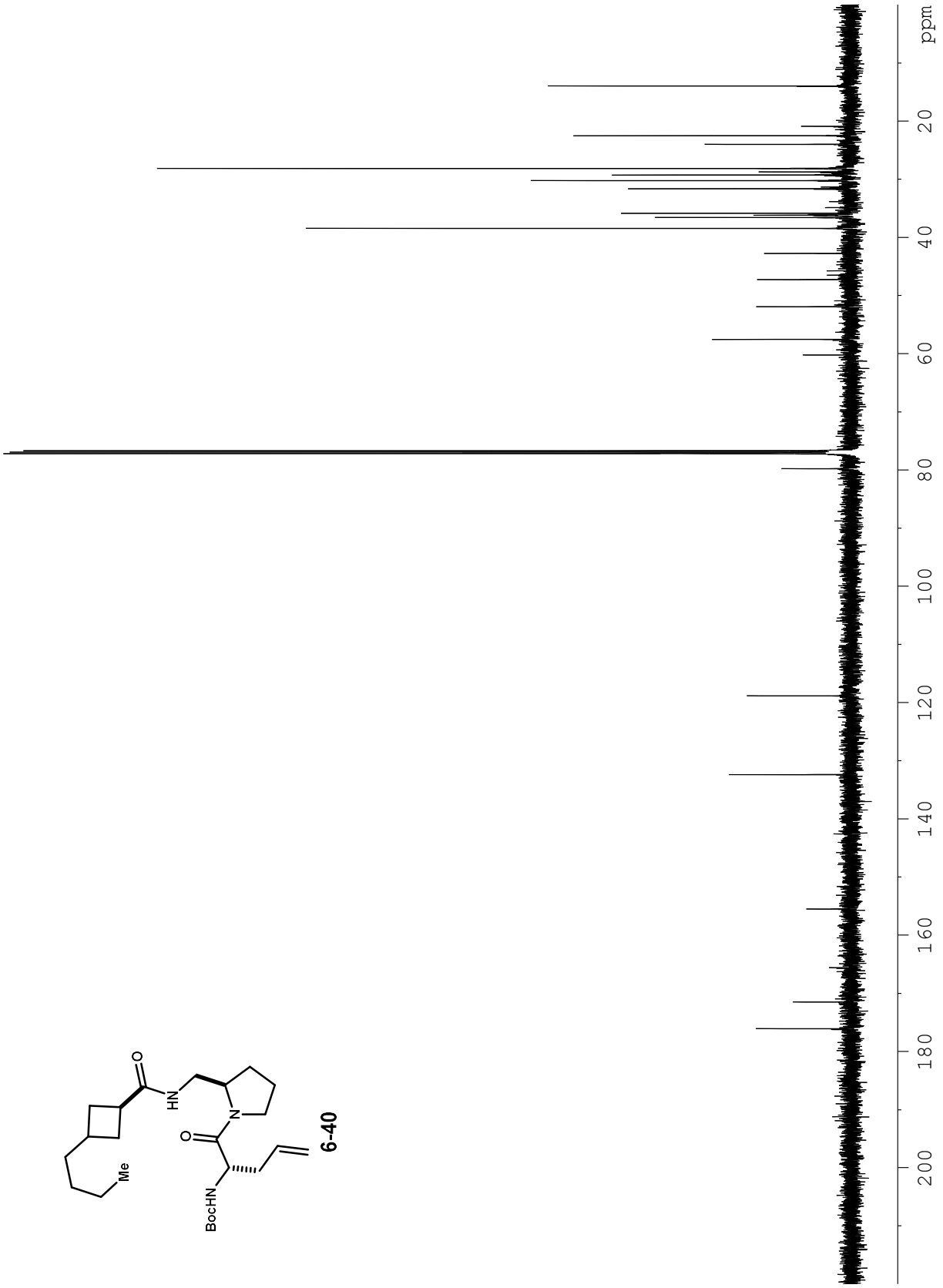

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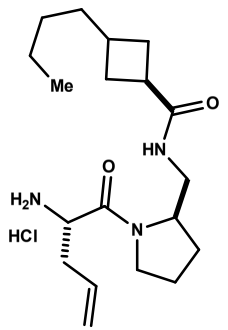

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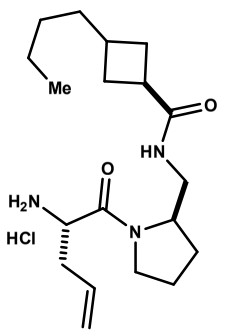

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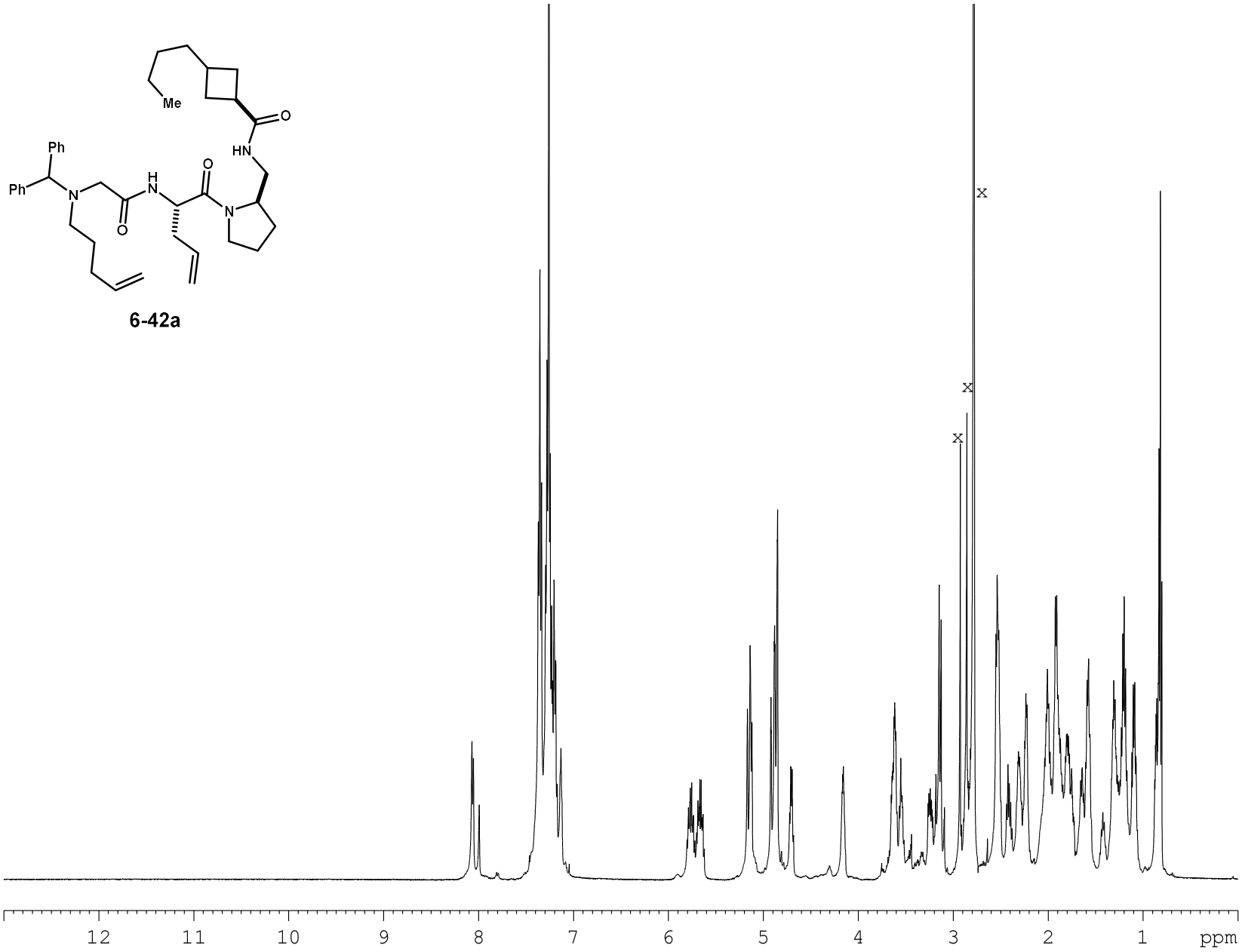
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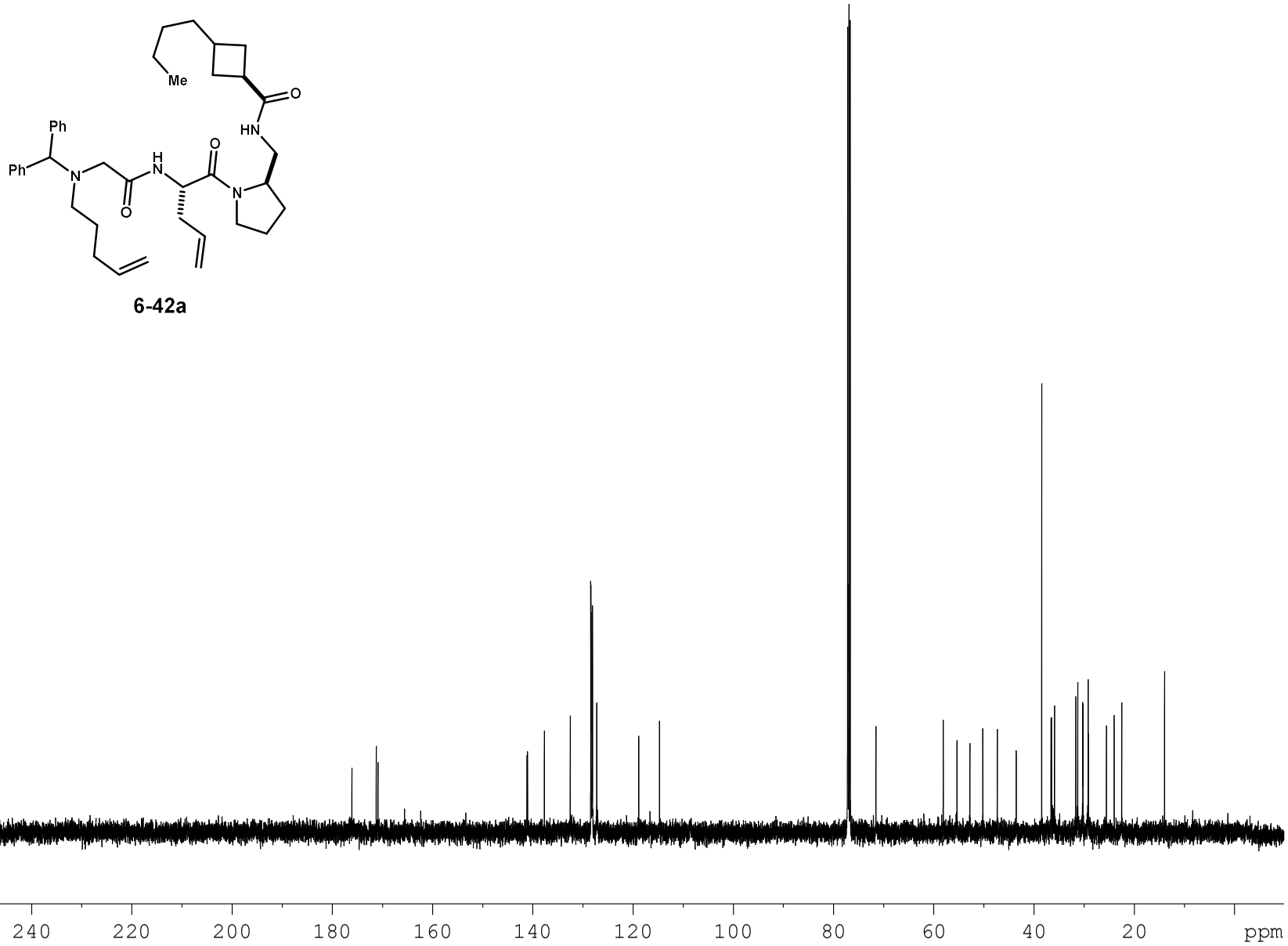
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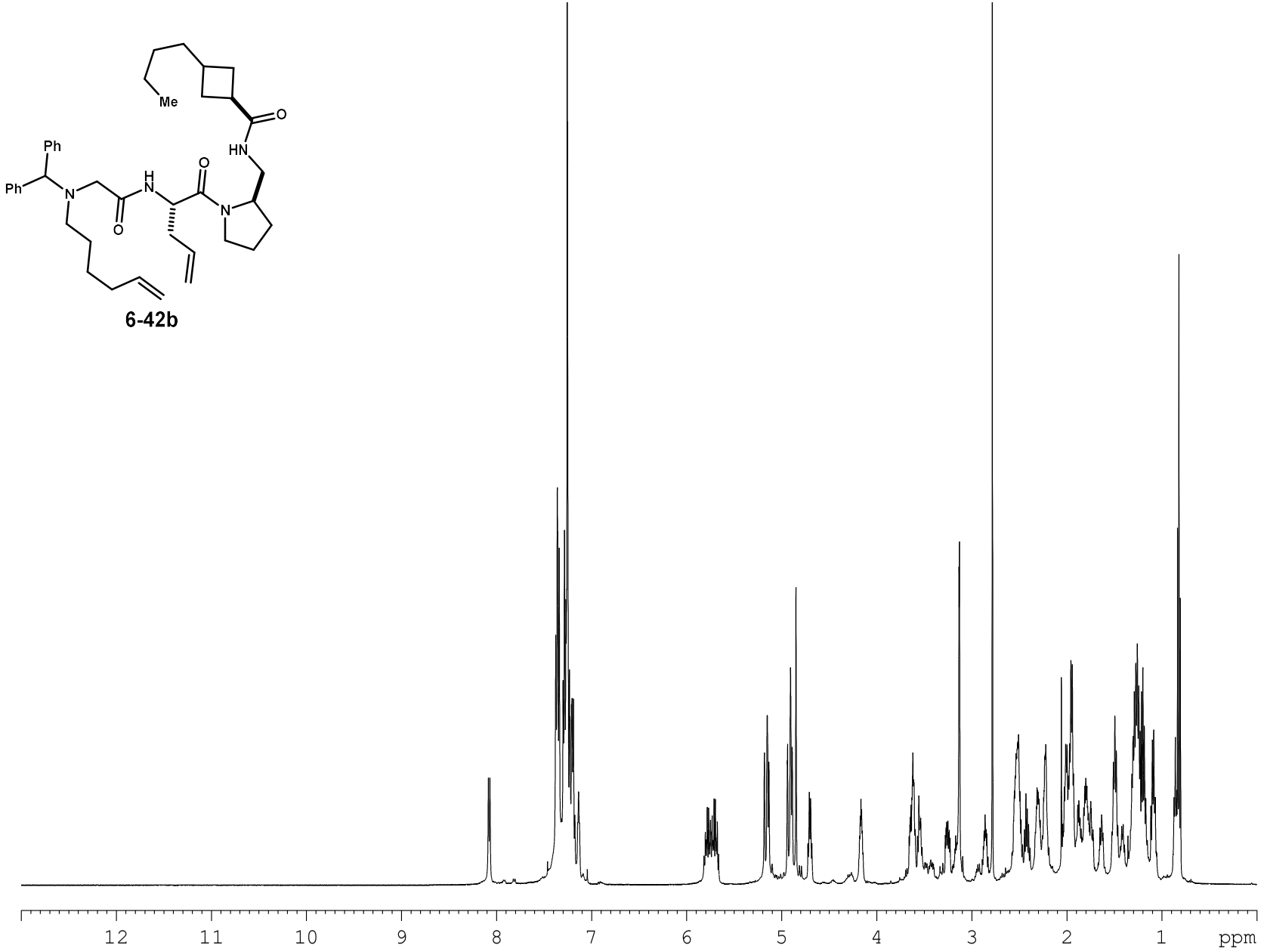

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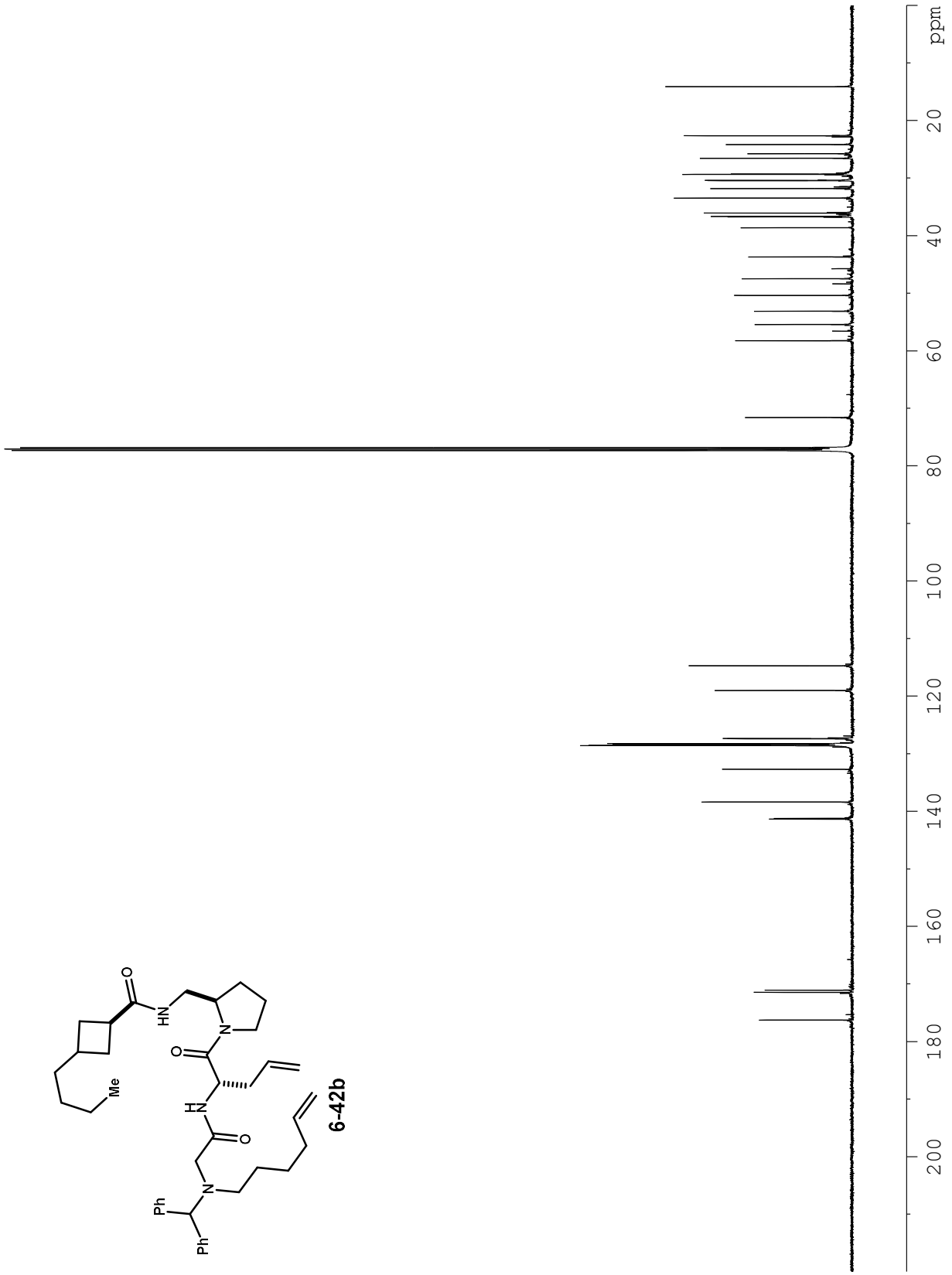

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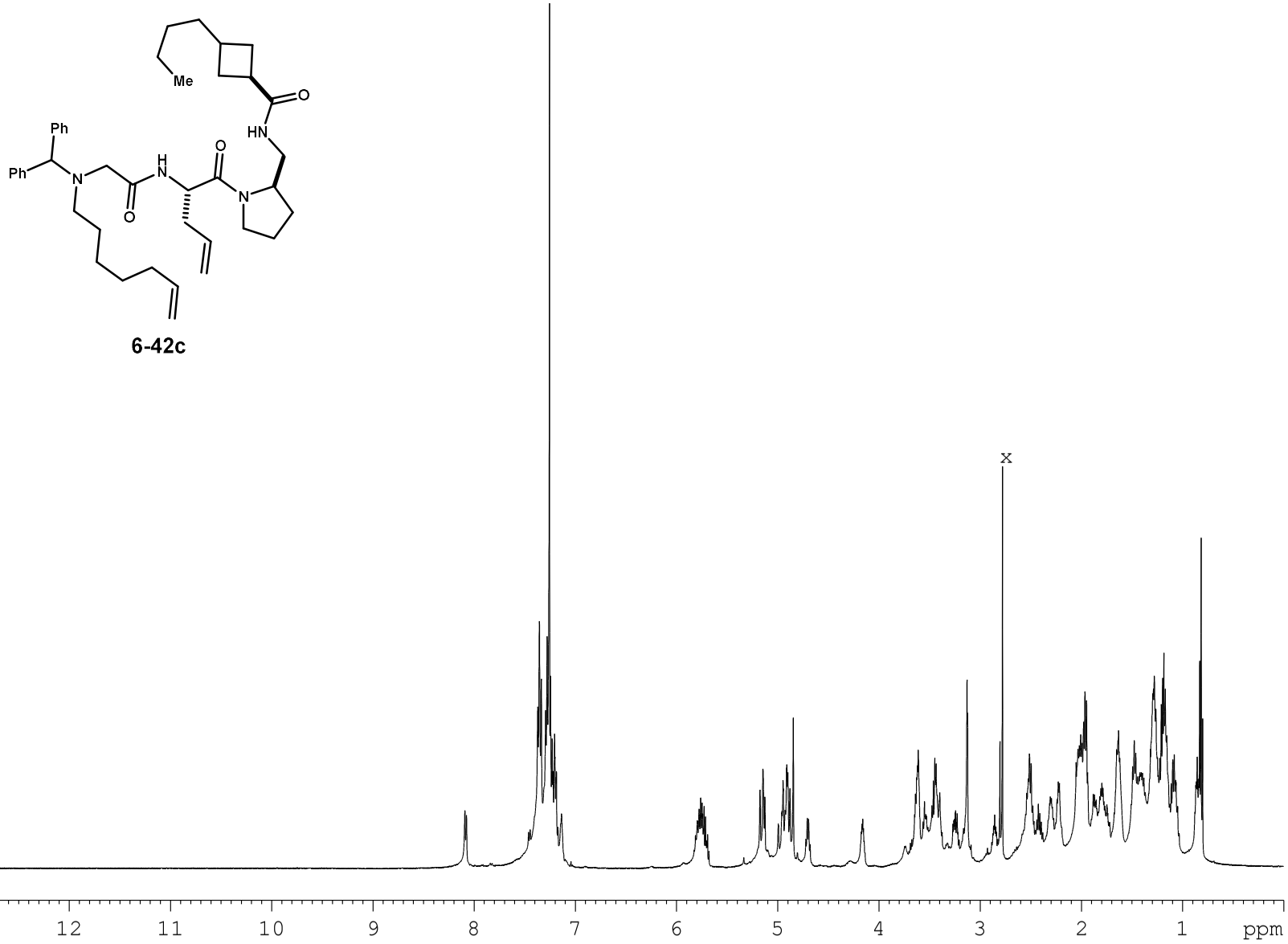

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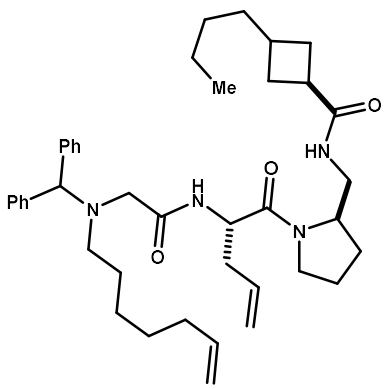

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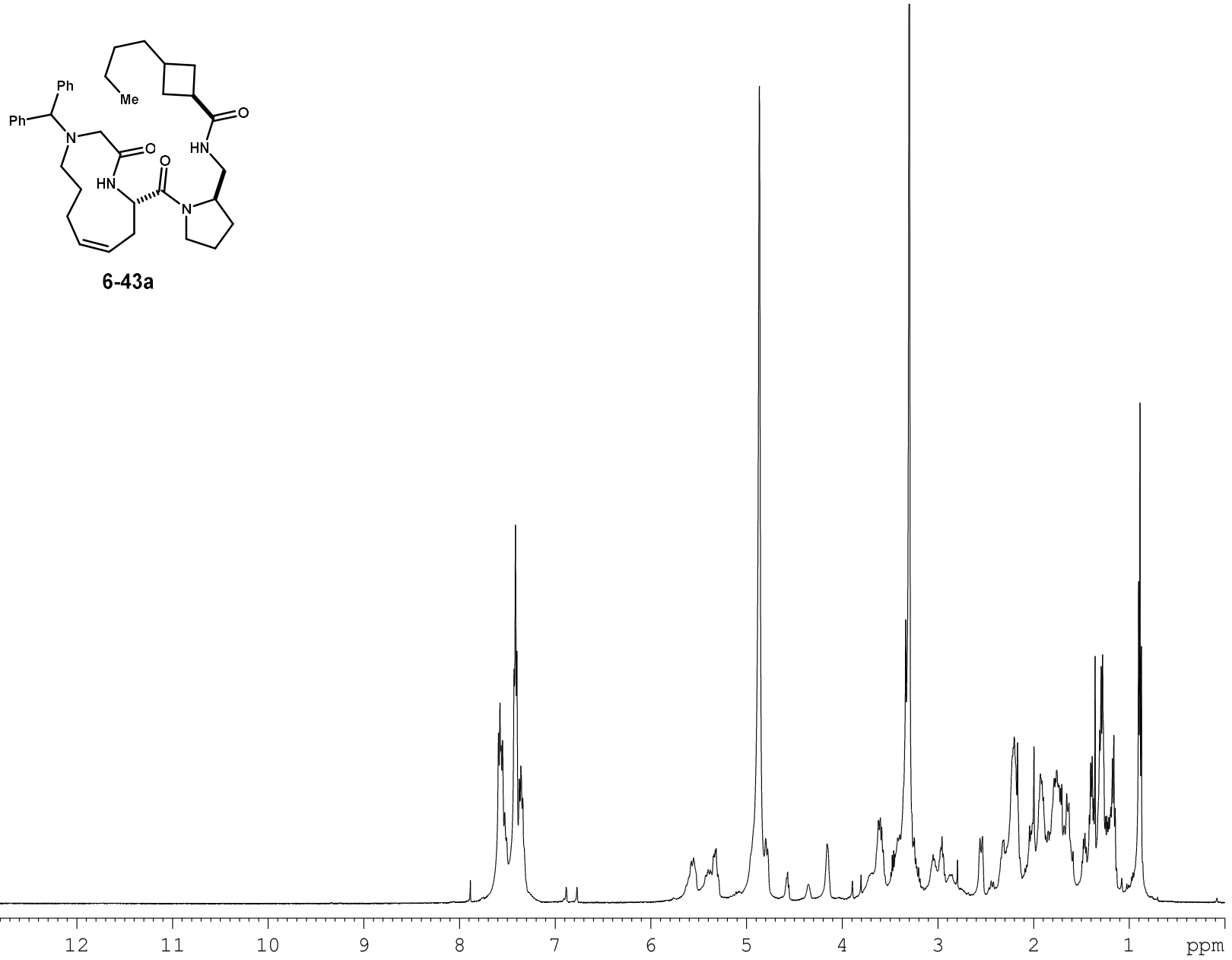

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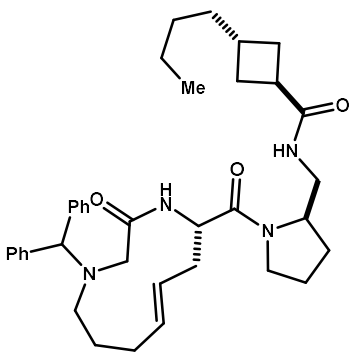

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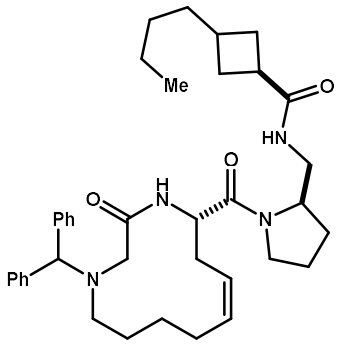

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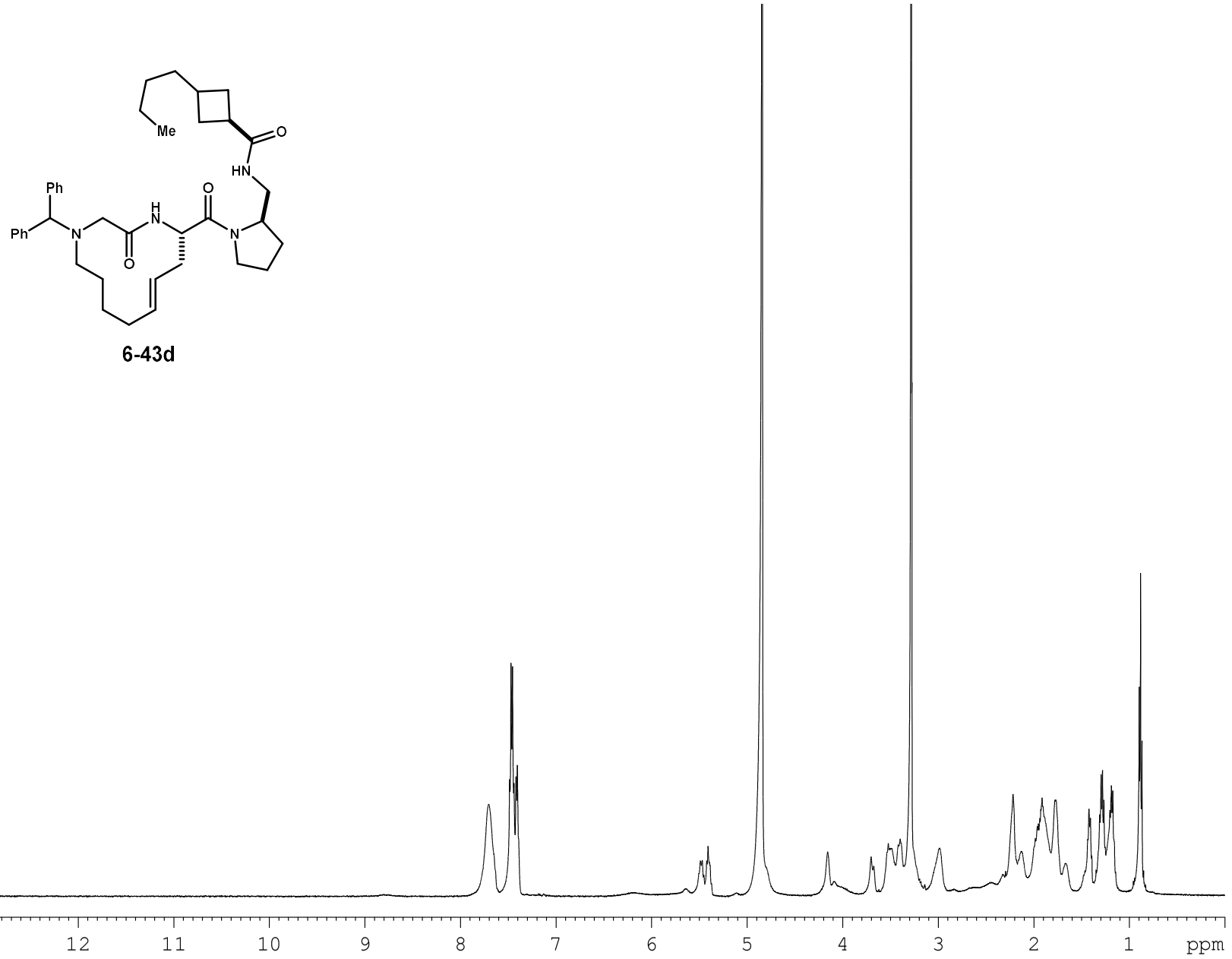

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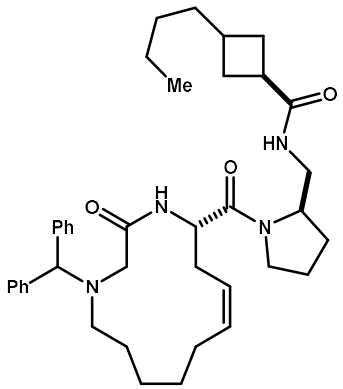

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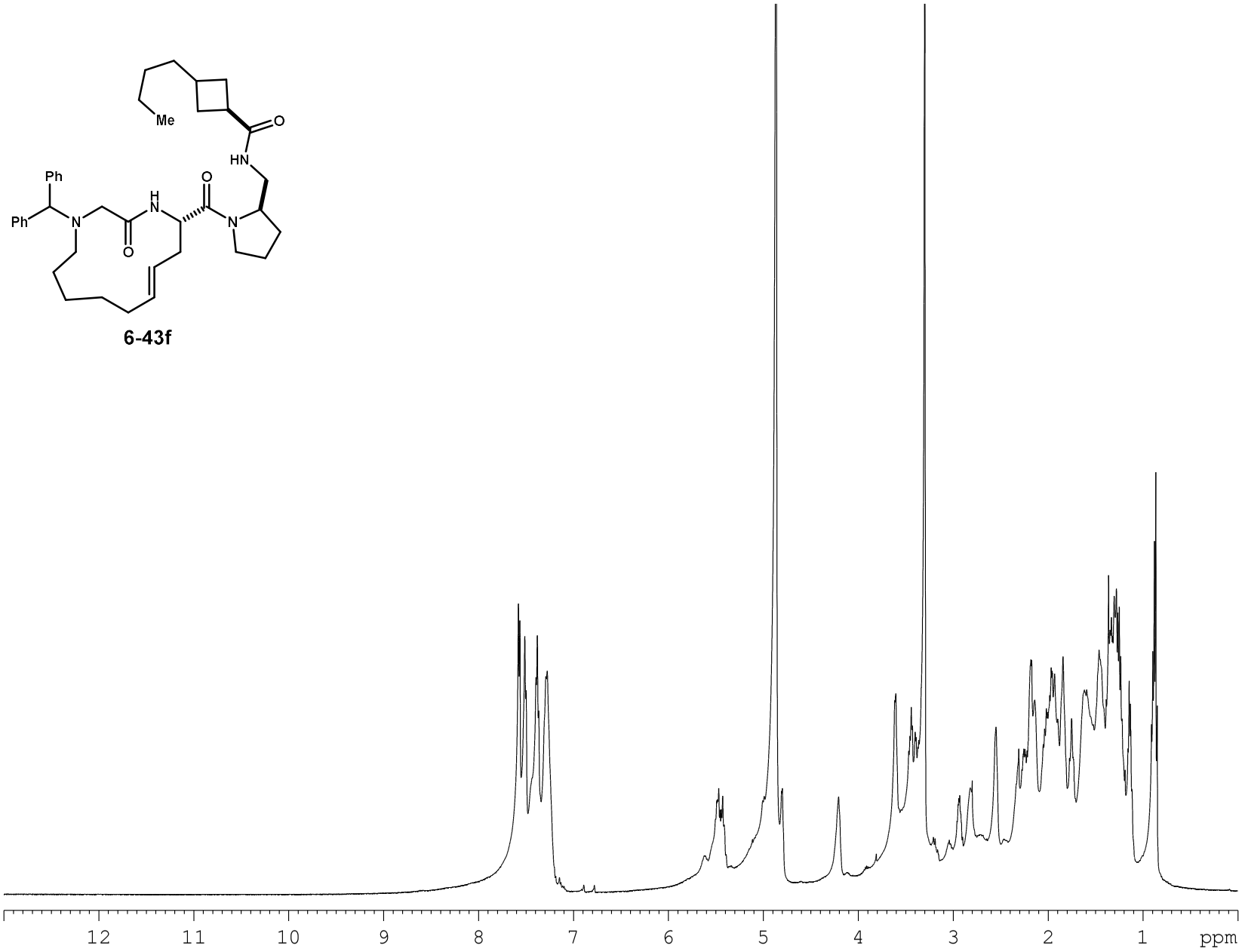

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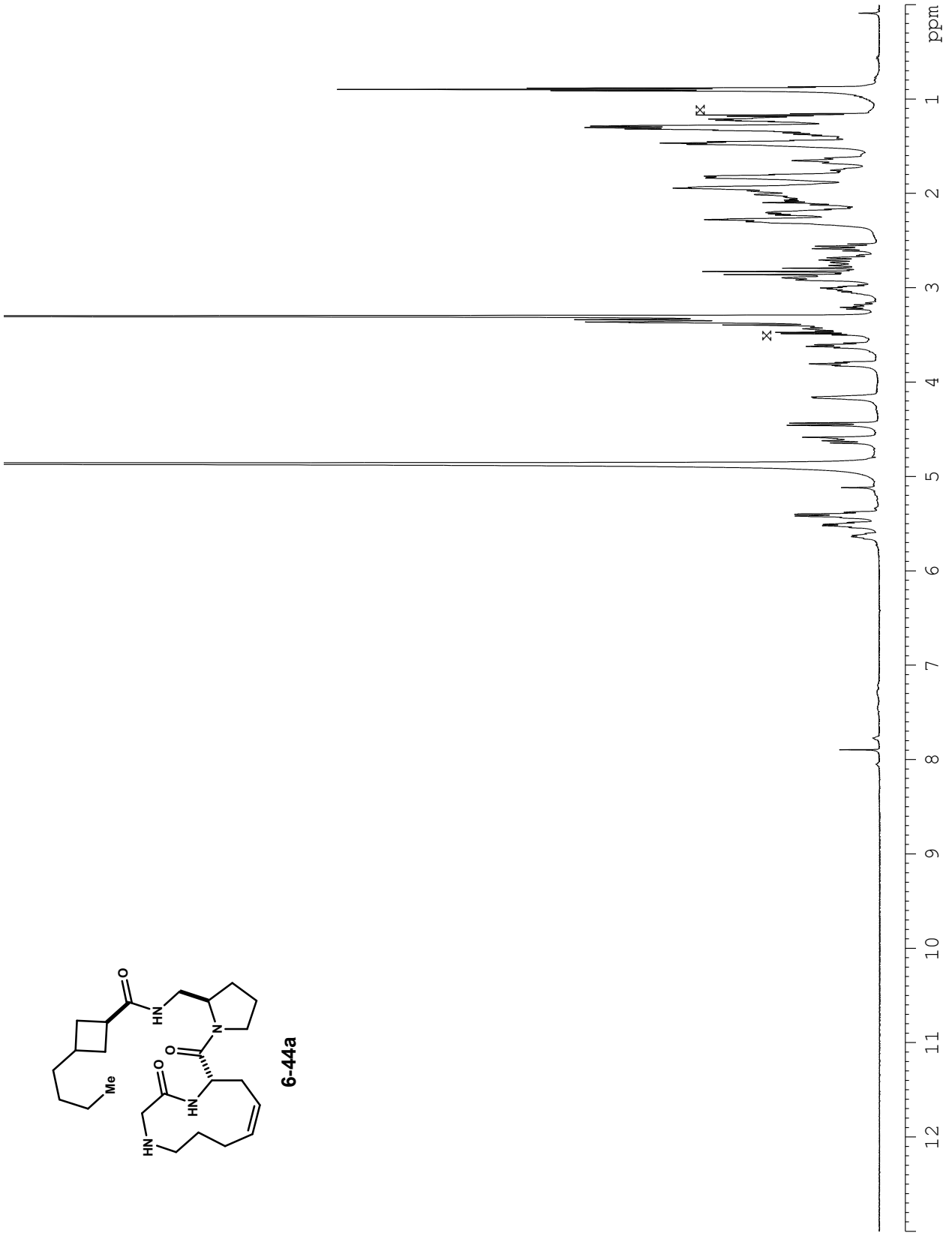

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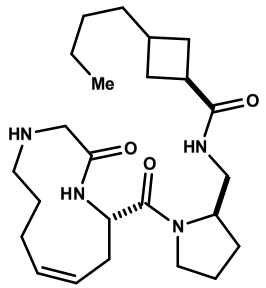

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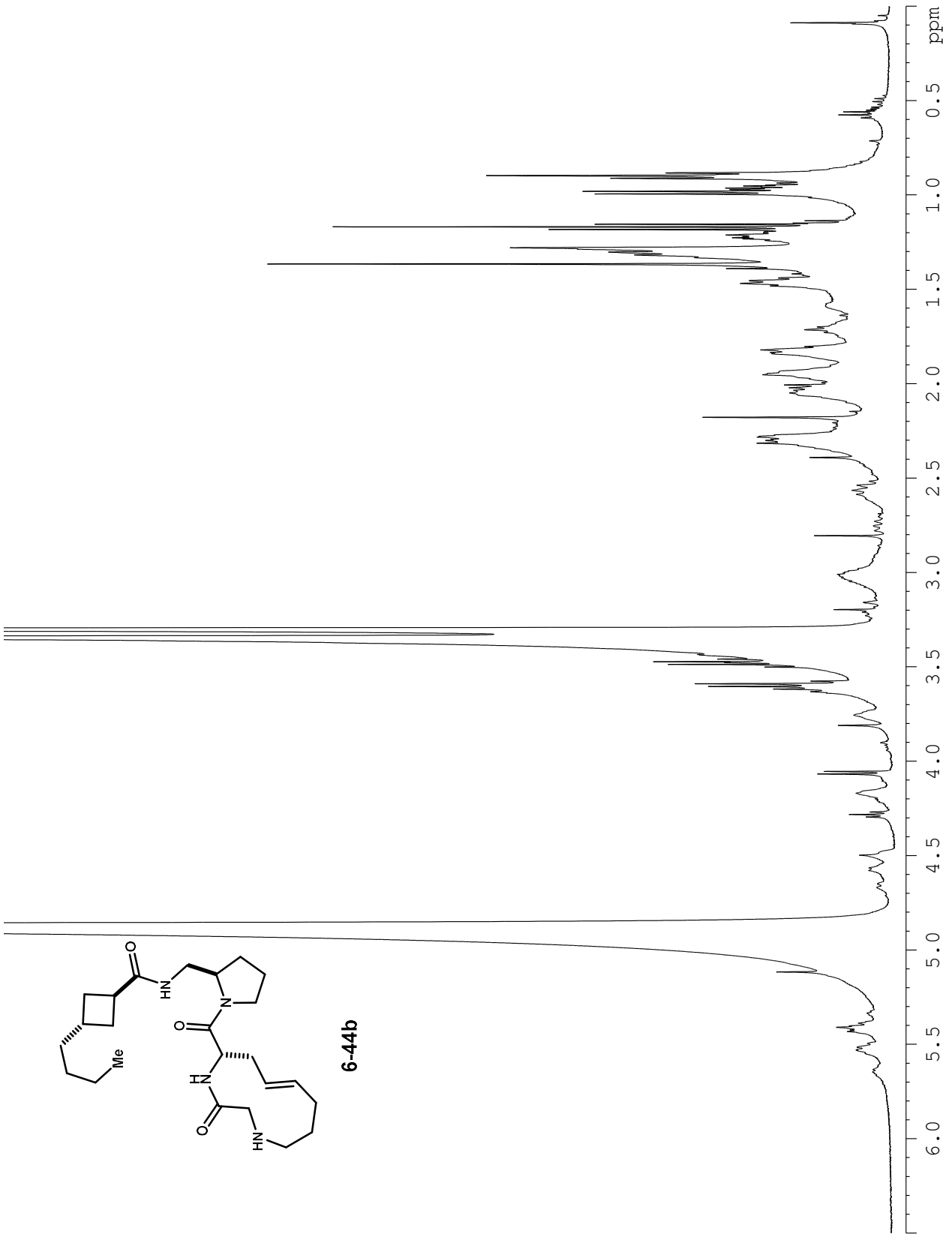

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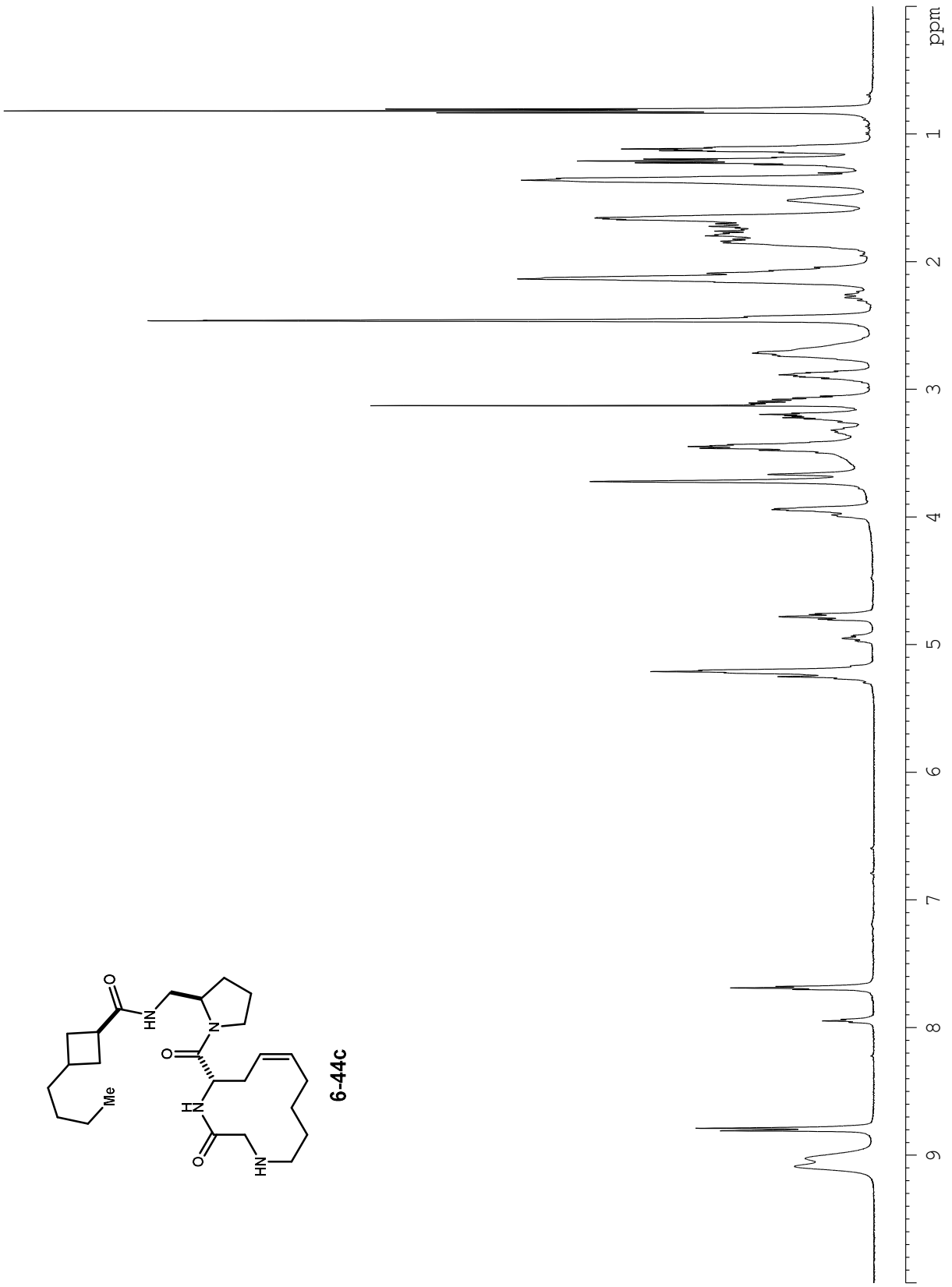

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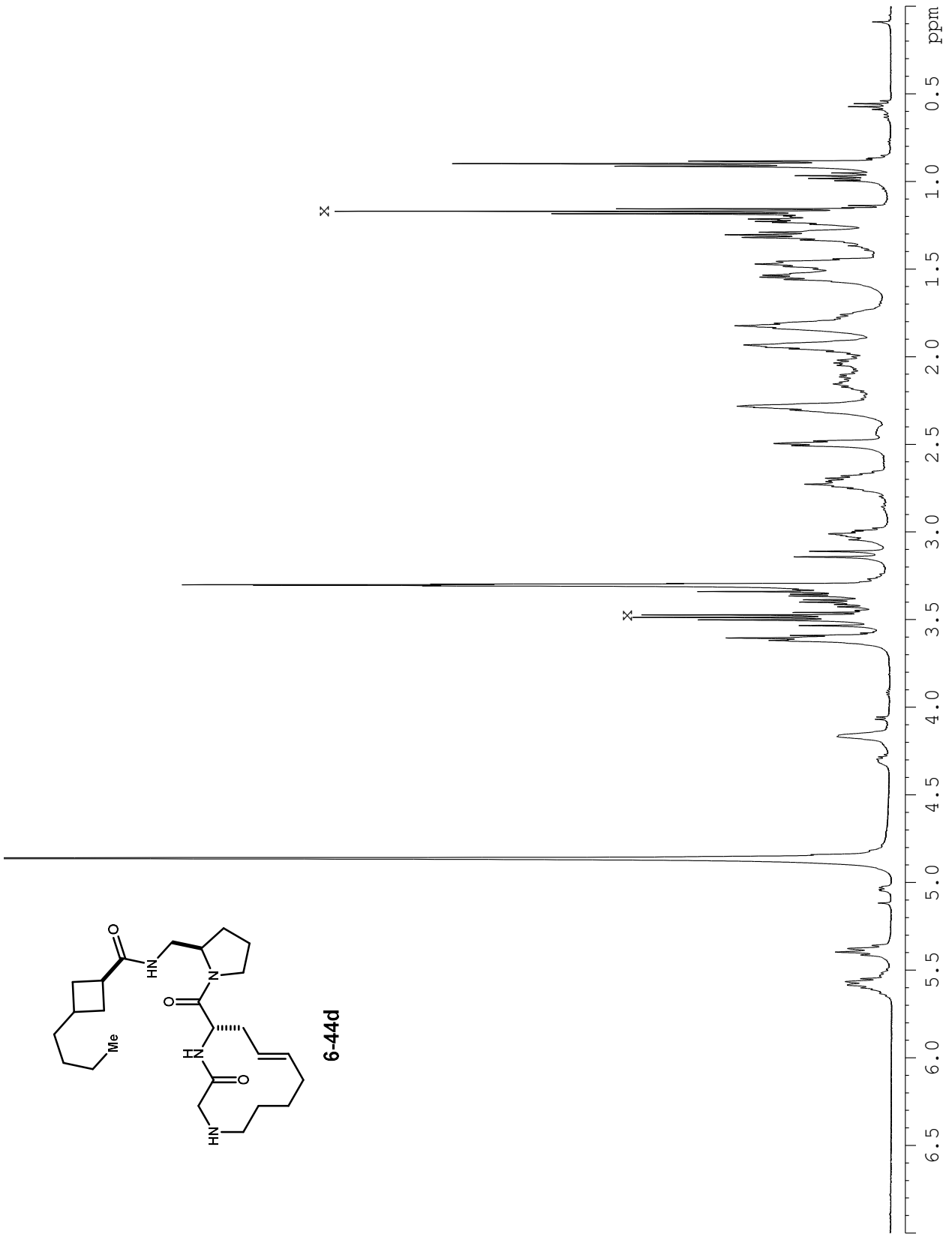

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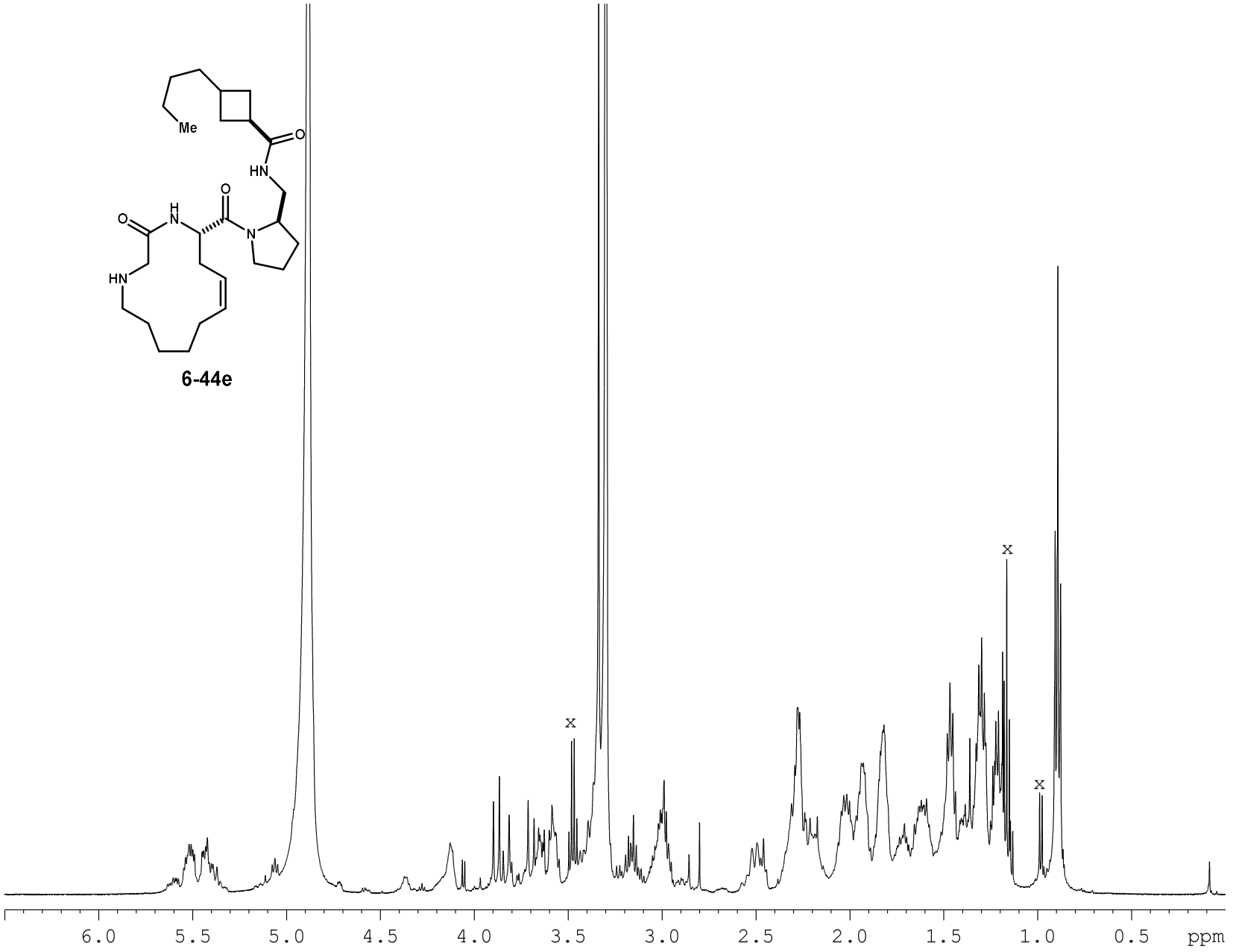
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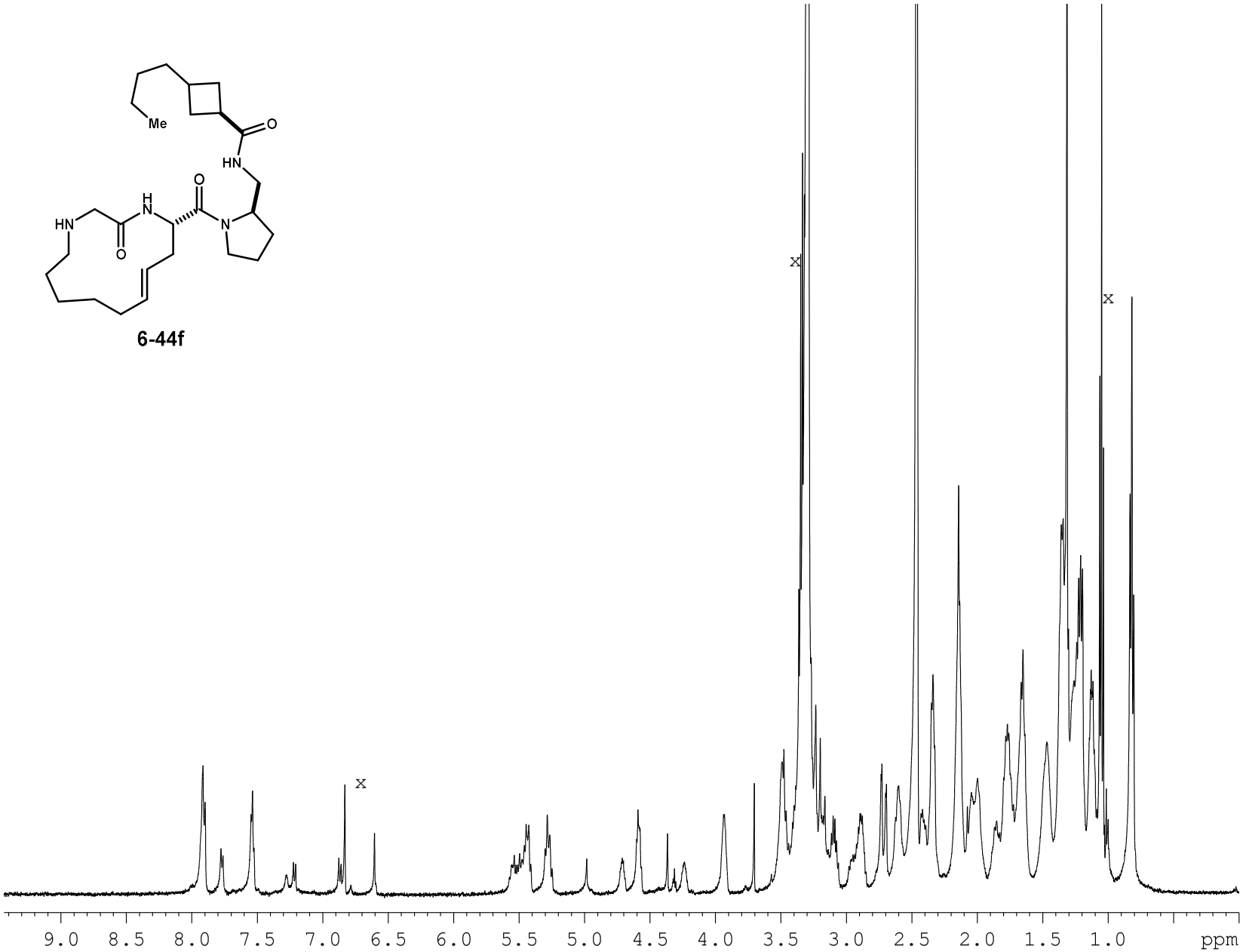
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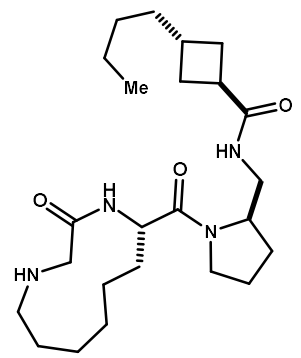

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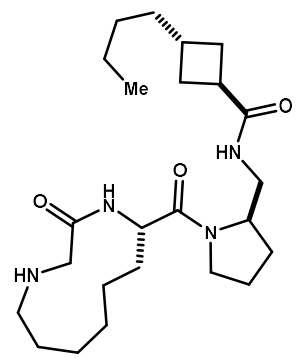

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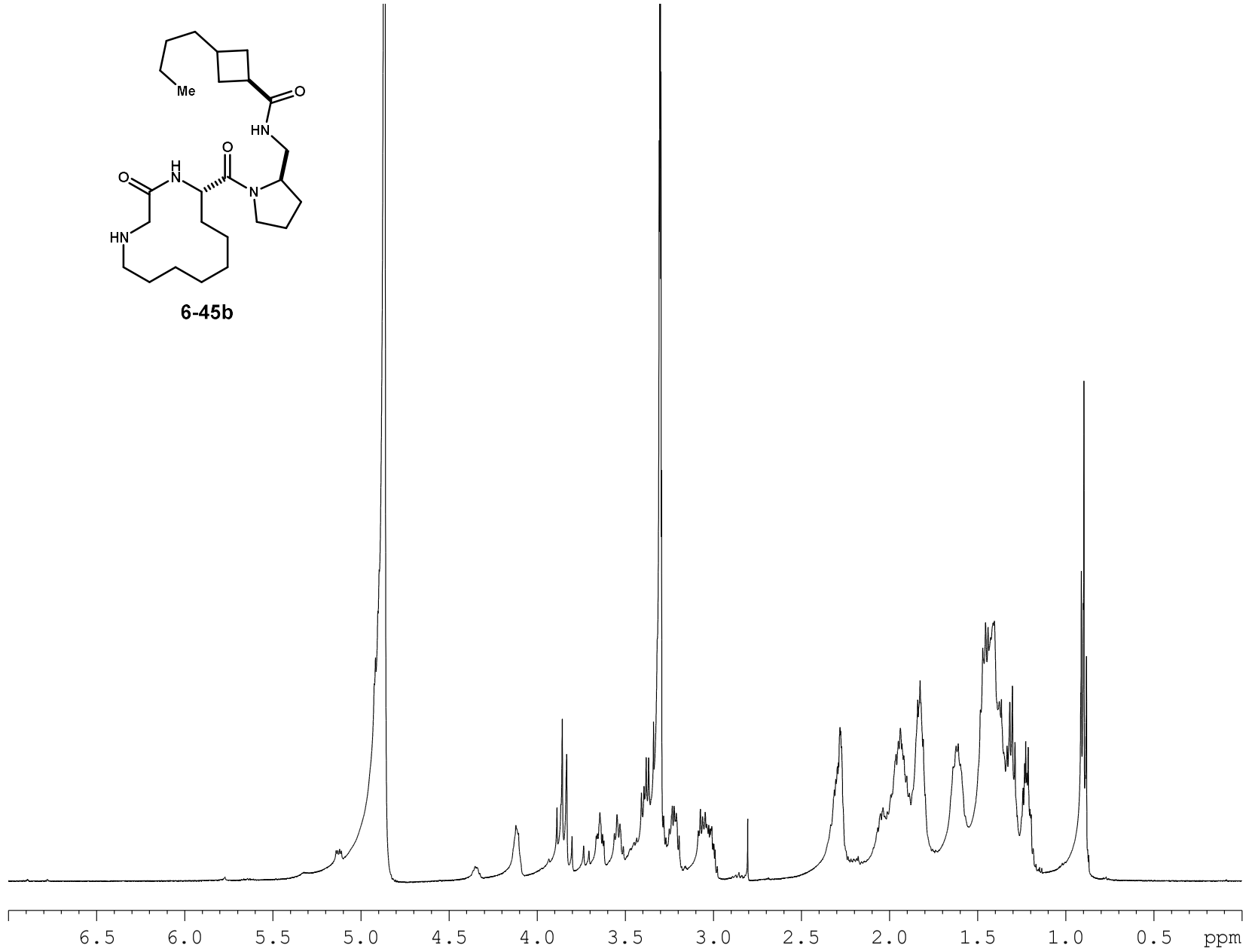
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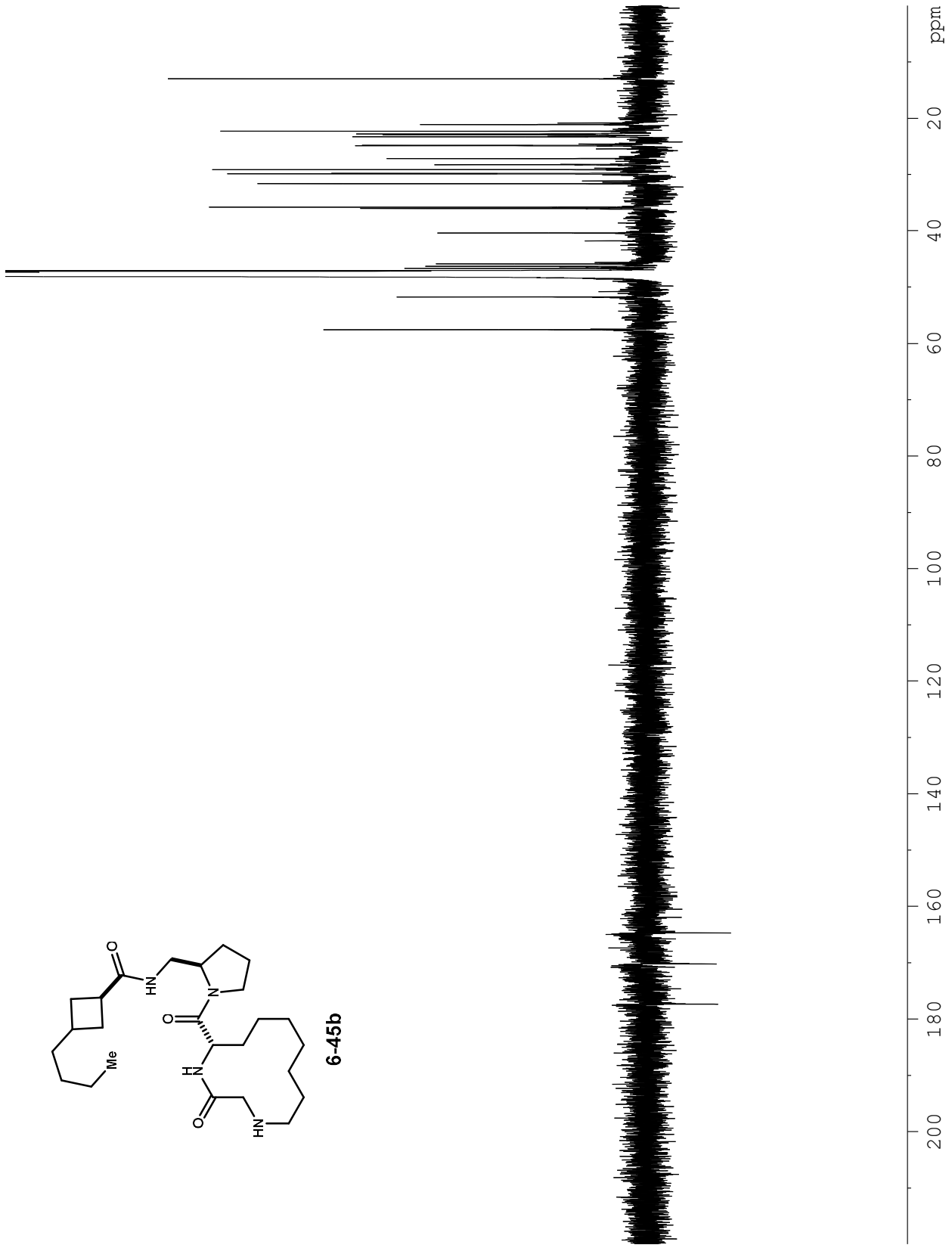
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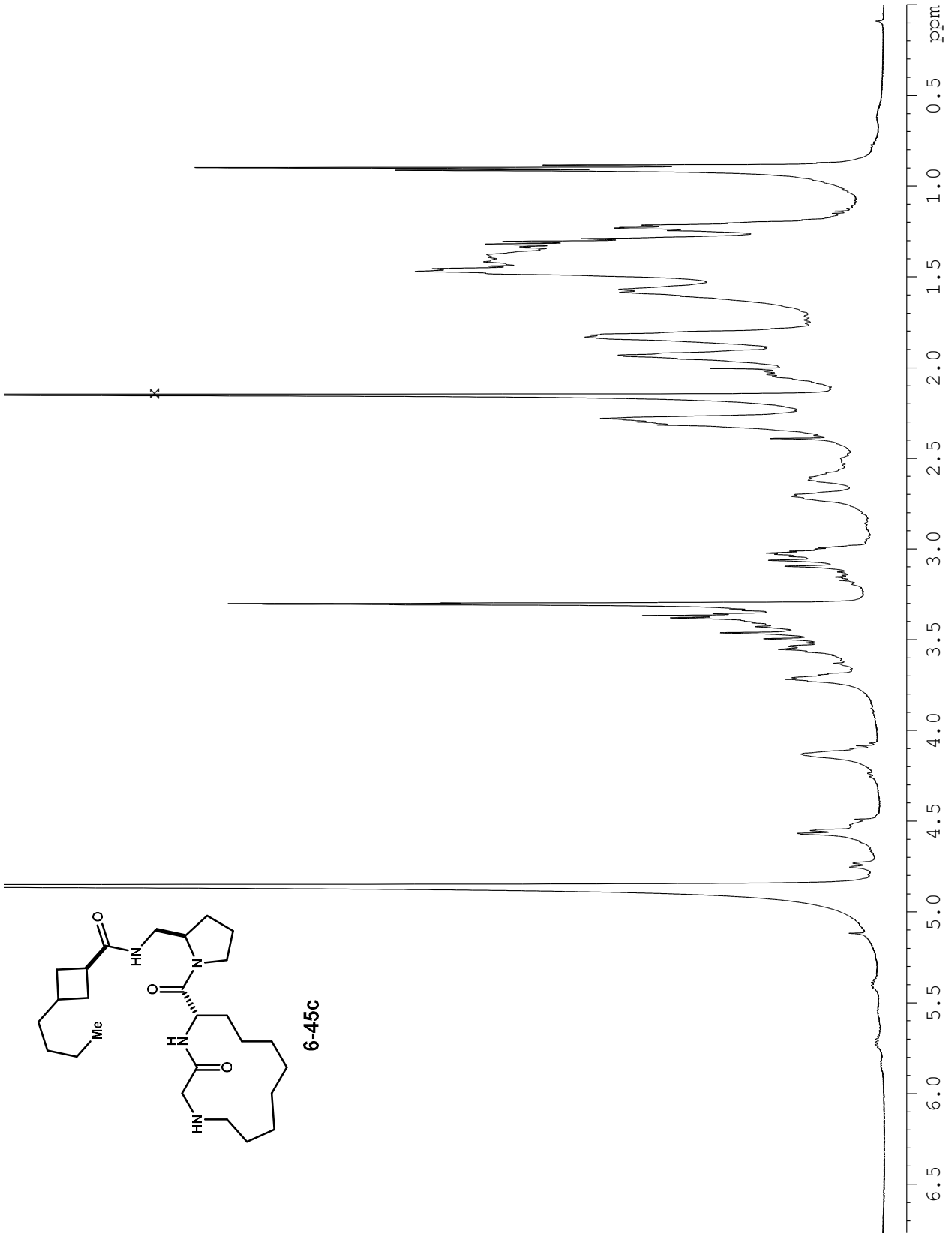
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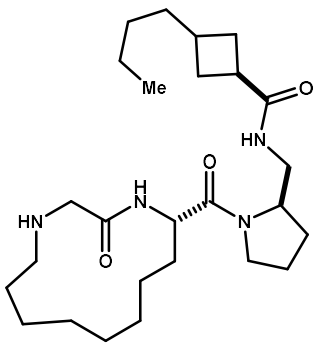

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