SYNTHESIS OF STRAINED SYSTEMS VIA VINYL CARBOCATION INTERMEDIATES

Thesis by
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To my family, whose unwavering support and love have been my foundation throughout this journey.

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to create organic synthesis questions for younger students and helped me practice multiple talks. He exemplifies what it means to be a great mentor as a senior graduate student.

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ABSTRACT

Vinyl carbocations are a class of dicoordinated carbocations. Due to their challenging generation, they have been less studied compared to tricoordinated carbocations. This thesis reports multiple novel reactivities involving vinyl carbocation intermediates.

The first chapter reviews methods for generating vinyl carbocations and past reports of vinyl carbocation C–H insertion. It then introduces a field guide to assist researchers in using vinyl carbocation C–H insertion in their synthesis, providing detailed information and optimal reaction conditions developed in our laboratory.

The second chapter describes a catalytic method for forming medium-sized rings via intramolecular Friedel-Crafts reactions of vinyl carbocation intermediates. These reactive species are catalytically generated through the ionization of vinyl toluenesulfonates by a Lewis acidic lithium cation/weakly coordinating anion salt.

The third chapter details selective [2+2] cycloadditions between vinyl carbocations and terminal alkenes, using a LiHMDS-mediated approach. This method allows for the efficient synthesis of strained cyclobutene-containing bicycles under mild conditions, demonstrating the versatile application of vinyl carbocations in constructing complex strained organic structures.

PUBLISHED CONTENT AND CONTRIBUTIONS

Portions of the work described herein were disclosed in the following publications:

1. Riu, M.-L. Y.; Popov, S.; Wigman, B.; **Zhao, Z.**; Wong, J.; Houk, K. N.; Nelson, H. M. Carbon–Carbon Bond Forming Reactions of Vinyl Cations: A Field Guide. *Under review for Eur. J. Org. Chem.*

Z. Z. participated in execution of experiments and data analysis.

2. **Zhao, Z.**; Popov, S.; Lee, W.; Burch, J. E.; Delgadillo, D. A.; Kim, L.-J.; Shahgholi, M.; Lebrón-Acosta, N.; Houk, K. N.; Nelson, H. M. Accessing Medium-Sized Rings via Vinyl Carbocation Intermediates. *Org. Lett.* **2024**, *26*, 1000-1005.

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Z. Z. participated in project design, execution of experiments, data analysis, and preparation of manuscript.

3. **Zhao, Z.**; Rendel, N. H.; Nelson, H. M. Lithium-mediated Selective [2+2] Cycloadditions via Vinyl Carbocations. *Under preparation.*

Z. Z. participated in project design, execution of experiments, data analysis, and preparation of manuscript.

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LIST OF ABBREVIATIONS

Ac	acetyl
ACN	acetonitrile
An	*para*-anisyl
Ar	generic aryl group
BARF	tetrakis(3,5-bis(trifluoromethyl)phenyl)borate
BINOL	1,1'-Bi-2-naphthol
Bn	benzyl
°C	degree Celsius
Calc'd	calculated
CI	chemical ionization
cm	centimeter(s)
cm^{-1}	wavenumber(s)
conc.	concentrated
CPA	chiral phosphoric acid
Cy	cyclohexyl
D	deuterium
dba	dibenzylideneacetone
DCE	1,2-dichloroethane
DCM	dichloromethane
DEAD	diethyl azodicarboxylate

DFT	density functional theory
DMAP	4-methylaminopyridine
DMEA	dimethylethylamine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
dr	diastereomeric ratio
DTBP	di-*tert*-butyl peroxide
Δ	difference
δ	chemical shift
E	alkene Entgegen isomer
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
ee	enantiomeric excess
EI	electron impact ionization
EIC	extracted ion chromatogram
equiv	equivalent(s)
ESI	electrospray ionization
Et	ethyl
FD	field desorption
FG	functional group
FT	Fourier transform
G	Gibbs free energy
g	gram(s)

GC	gas chromatography
HIV	human immunodeficiency virus
HPLC	high-performance liquid chromatography
HR	high resolution
HTIB	[hydroxy(tosyloxy)iodo]benzene
Hz	hertz(s)
IDPi	imidodiphosphorimidate
in situ	in the reaction mixture
in vacuo	in a vacuum
IPr	1,3-bis(2,6-diisopropylphenyl)imidazole-2-ylidene)
IR	infrared
^{i}Pr	isopropyl
J	coupling constant
K	Kelvin(s)
kcal	kilocalorie(s)
KHMDS	potassium bis(trimethylsilyl)amide
KIE	kinetic isotope effect
L	liter(s)
LC	liquid chromatography

LDA	lithium diisopropylamide
LiF_{20}	lithium tetrakis(pentafluorophenyl)borate
LiHMDS	lithium bis(trimethylsilyl)amide
M	molar (mole(s) per liter); molecular ion
m	meter(s)
mCPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
mg	milligram(s)
MHz	megahertz
MicroED	microcrystal electron diffraction
min	minute(s)
mL	milliliter(s)
mm	millimeter(s)
mmol	millimole(s)
mol	mole(s)
MS	mass spectrometry
MW	molecular weight
m/z	mass to charge ratio

n.d.	not detected
NaHMDS	sodium bis(trimethylsilyl)amide
NBS	*N*-bromosuccinimide
^{n}Bu	butyl
NIS	*N*-iodosuccinimide
NMR	nuclear magnetic resonance spectroscopy
^{n}Pr	propyl
o-DCB/1,2-DCB	1,2-dichlorobenzene
o-DFB/1,2-DFB	1,2-difluorobenzene
Ph	phenyl
ppm	parts per million
R	generic for any atom or functional group
TBS	*tert*-butyldimethylsilyl
^{t}Bu	*tert*-butyl
TES	triethylsilyl
THF	tetrahydrofuran
TIC	total ion chromatogram
TLC	thin layer chromatography
TMS	trimethylsilyl
Tf	trifluoromethanesulfonyl group
Ts	toluenesulfonyl group
UV	ultraviolet

V	volume
w	weight
WCA	weakly coordinating anion
X	heteroatom or functional group
Z	alkene Zusammen isomer

CHAPTER 1

Introduction to Vinyl Carbocations and Their C–H Insertion Reactions

1.1 INTRODUCTION

As a class of highly reactive intermediates, carbocations engage in a broad range of transformations and thus play a crucial role in the synthetic pathways of many complex molecules.[1] Due to the influence of electronic and steric effects as well as hybridization states, the stabilities of different classes of carbocations vary significantly.

Historically, more stabilized carbocations have been more well-studied as they are easy to access. In 1901, the highly π-stabilized triphenylmethyl (trityl) cation was the first carbocation discovered.[2] Since then, other resonance-stabilized tricoordinated sp^2-hybridized

† Portions of this chapter are based on research performed in collaboration with Martin-Louis Y. Riu, Stasik Popov, and Benjamin Wigman. Portions of this chapter have been adapted from the manuscript currently under review for *Eur. J. Org. Chem.*: Riu, M.-L. Y.; Popov, S.; Wigman, B.; Zhao, Z.; Wong, J.; Houk, K. N.; Nelson, H. M. Carbon–Carbon Bond Forming Reactions of Vinyl Cations: A Field Guide.

carbocations, such as iminium cations[3] and oxocarbenium cations[4], have also been widely used in organic synthesis.

In contrast, dicoordinated sp-hybridized vinyl carbocations have been less studied and have had limited applications in synthetic chemistry. It was initially thought that the energy of vinyl carbocations was too high for their generation and existence as intermediates. However, it later became evident that they were necessary to explain certain reactivities. In 1944, Searles and coworkers first proposed an oxygen-stabilized vinyl carbocation intermediate in a hydrolysis reaction of acetylenic ethers to esters under acidic conditions.[5] Twenty years later, Grob and coworkers provided more solid evidence for vinyl carbocation intermediacy while studying the kinetics of hydrolysis reactions of a series of 1-bromostyrenes with functional groups of varying electron richness on the aryl group.[6] Since then, novel vinyl carbocation reactivity has continued to be explored.

In this chapter, we will first review the general approaches used to generate vinyl carbocations. Following that, we will discuss a key reactivity that distinguishes vinyl carbocations from tricoordinated carbocations — the C–H insertion reaction.

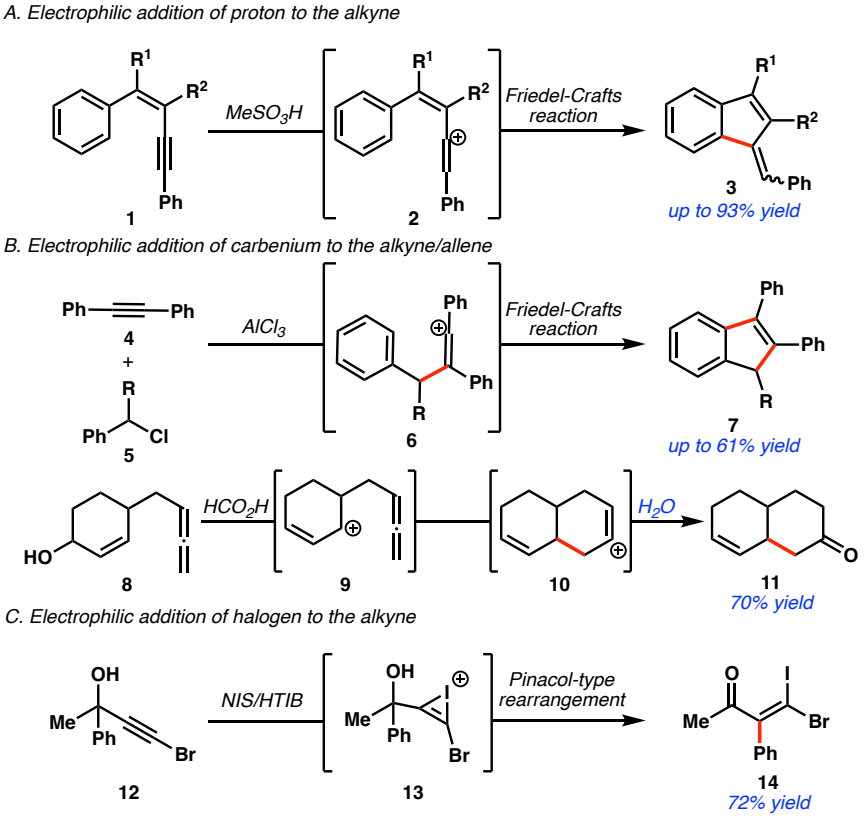
1.2 GENERATION OF VINYL CARBOCATIONS

There are three primary approaches for accessing vinyl carbocation intermediates: (1) electrophilic addition to alkynes/allenes, (2) heterolysis of vinyl (pseudo)halides, and (3) decomposition of β-diazo alcohols.

The first method involves the addition of electrophiles to alkynes and allenes. Protons, as simple electrophiles, can induce this ionization. For instance, Melloni and coworkers demonstrated that a catalytic amount of methanesulfonic acid, a proton source,

was sufficiently acidic to ionize the alkyne precursor **1** into an allylic vinyl carbocation **2** (Scheme 1.1A). This carbocation then underwent a Friedel-Crafts reaction, resulting in Z/E isomers of cyclization product **3**.[7]

Scheme 1.1 *Generation of vinyl carbocations from electrophilic addition to alkynes/allenes.*



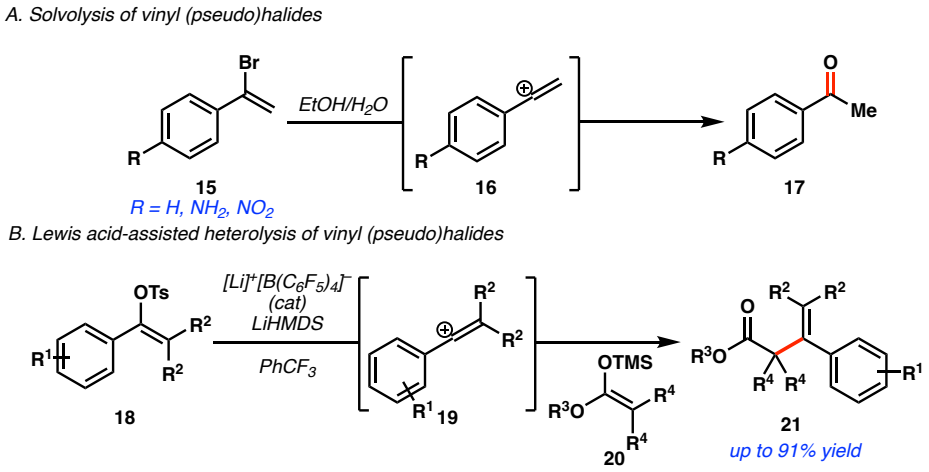
A carbocation can also induce the generation of vinyl carbocation intermediates through addition to alkynes. Modena and coworkers reported that when benzyl chloride **5** was activated by aluminum chloride, an electrophilic attack on alkyne **4** formed vinyl carbocation intermediate **6** (Scheme 1.1B). This intermediate then underwent a Friedel–Crafts reaction, yielding the final product **7**.[8] Furthermore, vinyl cations can be accessed by addition to allenes. For example, Puckett and coworkers reported that when allyl alcohol **8**

was activated, a cyclization occurred to form vinyl carbocation intermediate **10**, which was subsequently quenched by water to yield ketone **11** (Scheme 1.1B).[9]

Other electrophilic heteroatoms such as phosphorus[10], sulfur[11], and halogens can also potentially induce the generation of vinyl carbocations through electrophilic addition to alkynes. For instance, McNeils and coworkers reported that when bromoalkyne **12** was treated with iodine (I_2), an iodonium-stabilized vinyl carbocation **13** was first generated, leading to a Pinacol-type rearrangement on the vicinal alcohol to forge the rearrangement product **14** (Scheme 1.1C).[12]

The second approach for generating vinyl carbocations involves the heterolysis of vinyl (pseudo)halides through solvolysis in polar solvents or activation by Lewis acids. Grob and coworkers reported that benzylic vinyl bromide **15** could undergo solvolysis in aqueous ethanol to yield ketone **17** (Scheme 1.2A). Further Hammett studies supported the intermediacy of vinyl carbocation **16**.[6]

Scheme 1.2 *Generation of vinyl carbocations from heterolysis of vinyl (pseudo)halides.*

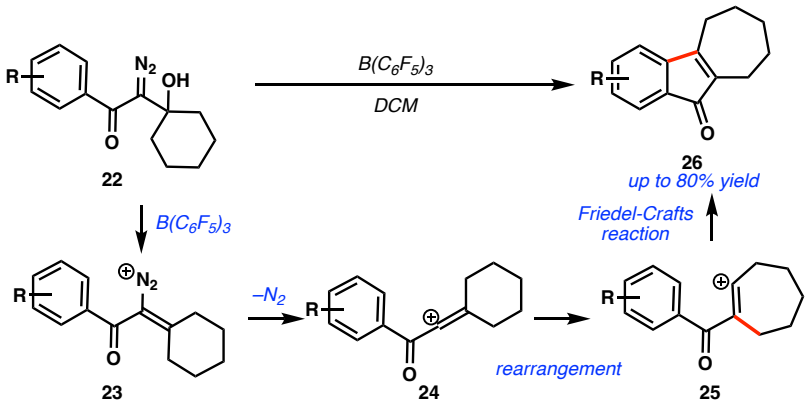


Additionally, Lewis acids can facilitate the heterolysis of vinyl (pseudo)halides in non-polar solvents. Nelson and coworkers reported that vinyl carbocation intermediate **19**

could be generated from vinyl tosylate precursor **18** under the catalysis of the Lewis acid lithium tetrakis(pentafluorophenyl)borate (Li[B(C_6F_5)$_4$]). The cationic intermediate was subsequently trapped by a nucleophilic silyl ketene acetal **20** to yield the coupling product **21** (Scheme 1.2B).[13]

Lastly, vinyl carbocations can be accessed through the decomposition of *β*-diazo alcohols. Brewer and coworkers reported that when *β*-hydroxy-*α*-diazo ketone **22** was treated with the Lewis acidic tris(pentafluorophenyl)borane, loss of the hydroxy group formed vinyl diazonium intermediate **23** (Scheme 1.3). This intermediate then rapidly eliminated N_2 to yield a vinyl carbocation **24**. Due to the destabilizing influence of the adjacent carbonyl group, **24** underwent a Wagner-Meerwein rearrangement to form a new vinyl carbocation **25**, which subsequently underwent a Friedel-Crafts reaction with a nucleophilic aryl group to forge the 5-membered ring in product **26**.[14]

Scheme 1.3 *Generation of vinyl carbocations from decomposition of β-diazo alcohols.*



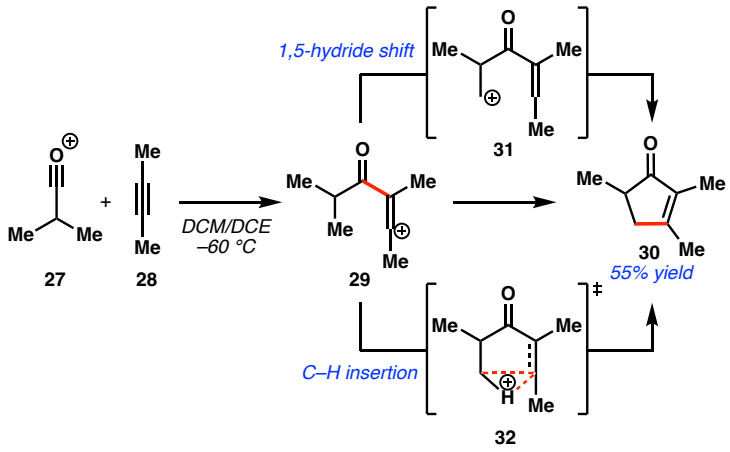
1.3 C–H INSERTION OF VINYL CARBOCATIONS

Similar to most carbocation intermediates, vinyl carbocations can facilitate the cleavage and formation of carbon–carbon (C–C) bonds through reactions, such as cationic

rearrangements[14] and Friedel-Crafts reactions with nucleophilic aromatic compounds[7,8]. Unlike tricoordinated carbocations, vinyl carbocation can induce carbon–hydrogen (C–H) activation at an sp^3 carbon. While C–H functionalization is typically achieved under transition metal catalysis[15], the use of vinyl carbocations offers a potential alternative metal-free approach.

One early example demonstrating the capability of vinyl carbocations to activate C–H bonds was reported by Kucherov and coworkers in 1974 (Scheme 1.4). They observed that when acylium cation **27** reacted with alkyne **28**, 2-cyclopentenone **30** was formed. An initial electrophilic addition from the acylium cation to the alkyne occurred to generate vinyl carbocation intermediate **29**. Subsequently, this intermediate underwent either a 1,5-hydride shift followed by cyclization via cationic intermediate **31** or a concerted C–H activation to furnish product **30**.[16]

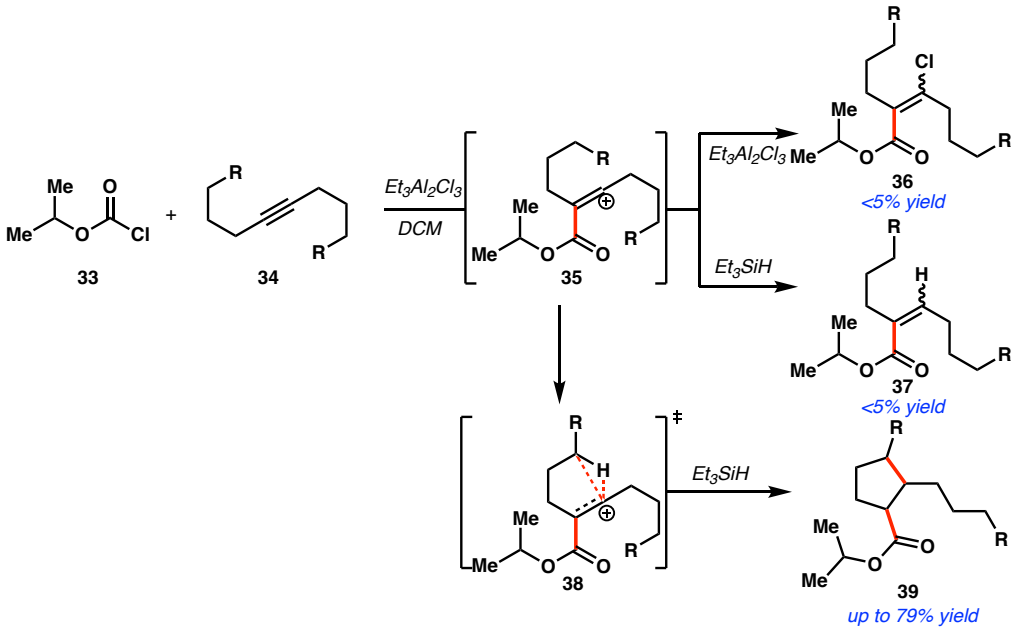
Scheme 1.4 *Kucherov: C–H activation in the acylium-alkyne reaction.*



In 2006, Metzger and coworkers conducted further studies on the C–H insertion reactivity of vinyl carbocation intermediates with a similar system (Scheme 1.5). Initially, it was proposed that the activation of chloroformate **33** by an aluminum-based Lewis acid

induced electrophilic addition to alkyne **34**, leading to the ionization of vinyl carbocation **35**. This intermediate could then undergo trapping either by a chloride anion from ethyl aluminum chloride to form vinyl chloride **36**, or by a hydride transfer from triethylsilane to form alkene **37**. However, **36** and **37** were found to be minor side products (< 5% yield), while the major product was the cyclopentane-containing compound **39**. Building on previous findings, it was suggested that vinyl carbocation **35** participated in a C–H activation reaction with pendant alkyl groups to generate the 5-membered ring observed in product **39**. Quantum-mechanical calculations further supported the proposal of a concerted C–H insertion mechanism for this reaction.[17]

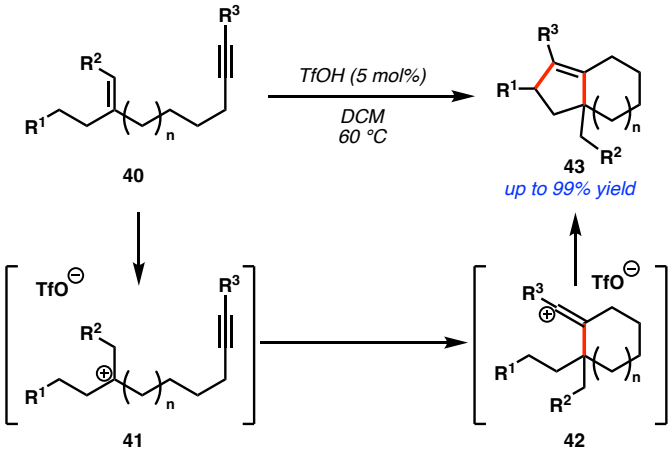
Scheme 1.5 *Metzger: Concerted C–H insertion reactions of vinyl carbocations.*



In 2010, Yamamoto and coworkers reported one of the first examples demonstrating catalytic vinyl carbocation C–H insertion reactivity (Scheme 1.6). Using a catalytic amount of trifluoromethanesulfonic acid, the alkene in precursor **40** was protonated to form tertiary

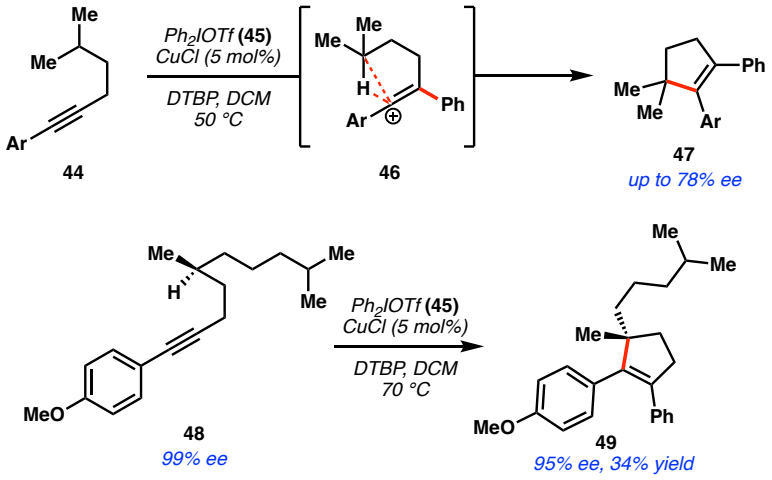
carbocation intermediate **41**. This was followed by an intramolecular electrophilic addition to the alkyne, generating vinyl carbocation intermediate **42**. Subsequently, C–H insertion occurred, resulting in the formation of a 5-membered ring, and product **43** was obtained upon deprotonation.[18]

Scheme 1.6 *Yamamoto: Catalytic vinyl carbocation C–H insertion reaction.*



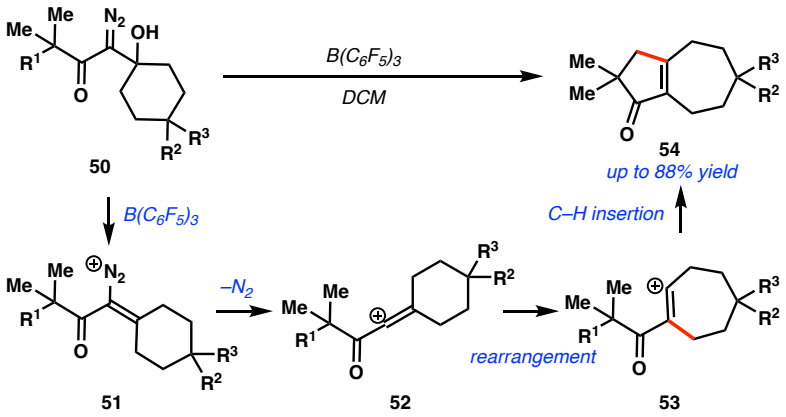
In 2014, Gaunt and coworkers developed a copper-catalyzed system to harness vinyl carbocation C–H insertion reactivity using diaryliodonium salts and an alkyne precursor (Scheme 1.7). It was proposed that the diaryliodonium salt **45** was the source of electrophilic aryl groups to attack alkyne **44**, resulting in the generation of a vinyl carbocation intermediate **46**. This intermediate then underwent a C–H insertion reaction, ultimately forming cyclopentene product **47**.[19] Notably, when enantioenriched alkyne **48** was employed, the stereochemical information from the precursor was largely preserved in the product **49** (95% ee). This finding suggested that this vinyl carbocation C–H insertion followed by a concerted mechanism as opposed to a stepwise 1,5-hydride shift and cyclization process.

Scheme 1.7 *Gaunt: Copper-catalyzed vinyl carbocation generation and C–H insertion.*



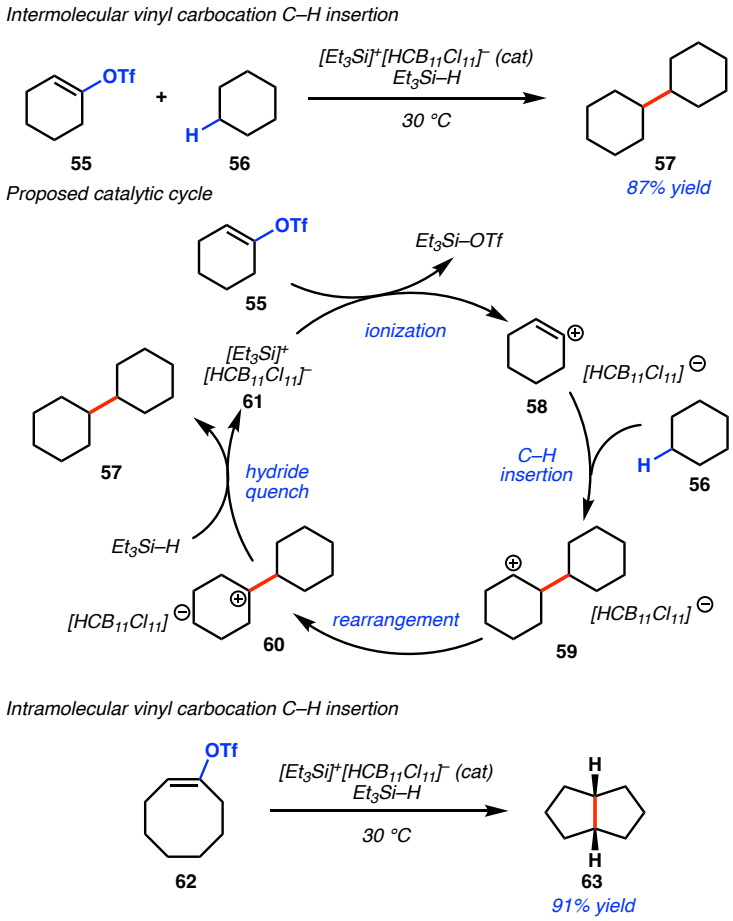
C–H insertion reactivity has also been observed in cases where vinyl carbocation intermediates are generated from *β*-diazo alcohol precursors, as described in the third approach in section ***1.2***. In 2017, Brewer and coworkers reported that when *β*-hydroxy-*α*-diazo ketone **50** was treated with the Lewis acidic tris(pentafluorophenyl)borane, the generation of vinyl carbocation **52** was proposed (Scheme 1.8). This intermediate then rearranged to form new vinyl carbocation **53**, which subsequently underwent C–H insertion to yield the final [5.3.0] bicyclic product **54**.[20]

Scheme 1.8 *Brewer: Vinyl carbocation C–H insertion from β-diazo alcohol.*



In 2018, Nelson and coworkers developed a system for generating vinyl carbocation intermediates and utilizing them in intermolecular C–H insertion reactions through silylium-weakly coordinating anion (WCA) catalysis (Scheme 1.9). In their proposed catalytic cycle, a silylium cation was paired with the WCA in complex **61**. The lack of coordination from the counterion enhanced the Lewis acidity of the silylium cation, facilitating the abstraction of the triflate group from vinyl triflate **55** to generate vinyl carbocation **58**. Subsequently, cation **58** underwent C–H insertion, leading to the formation of a secondary carbocation **59**

Scheme 1.9 *Nelson: Vinyl carbocation C–H insertion through silylium-WCA catalysis.*

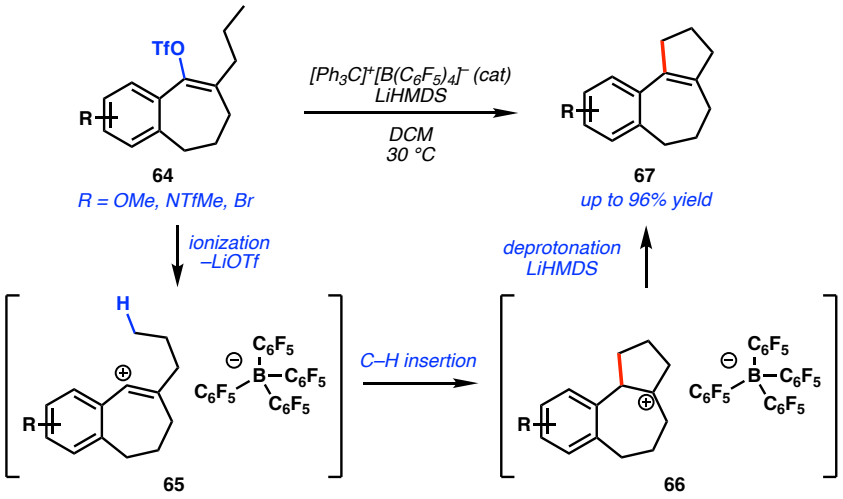


and the concurrent formation of a new C–C bond. A 1,2-hydride shift followed to generate the more stable tertiary carbocation **60**. In the final step, triethylsilane was employed to deliver a hydride to the carbocation, yielding the cross-coupling product **57** and regenerating the silylium carborane complex **61**.[21]

This catalytic system was also applicable to intramolecular C–H insertions. For instance, vinyl triflate **62** could be transformed into the [3.3.0] bicyclic product **63** under these catalytic conditions.

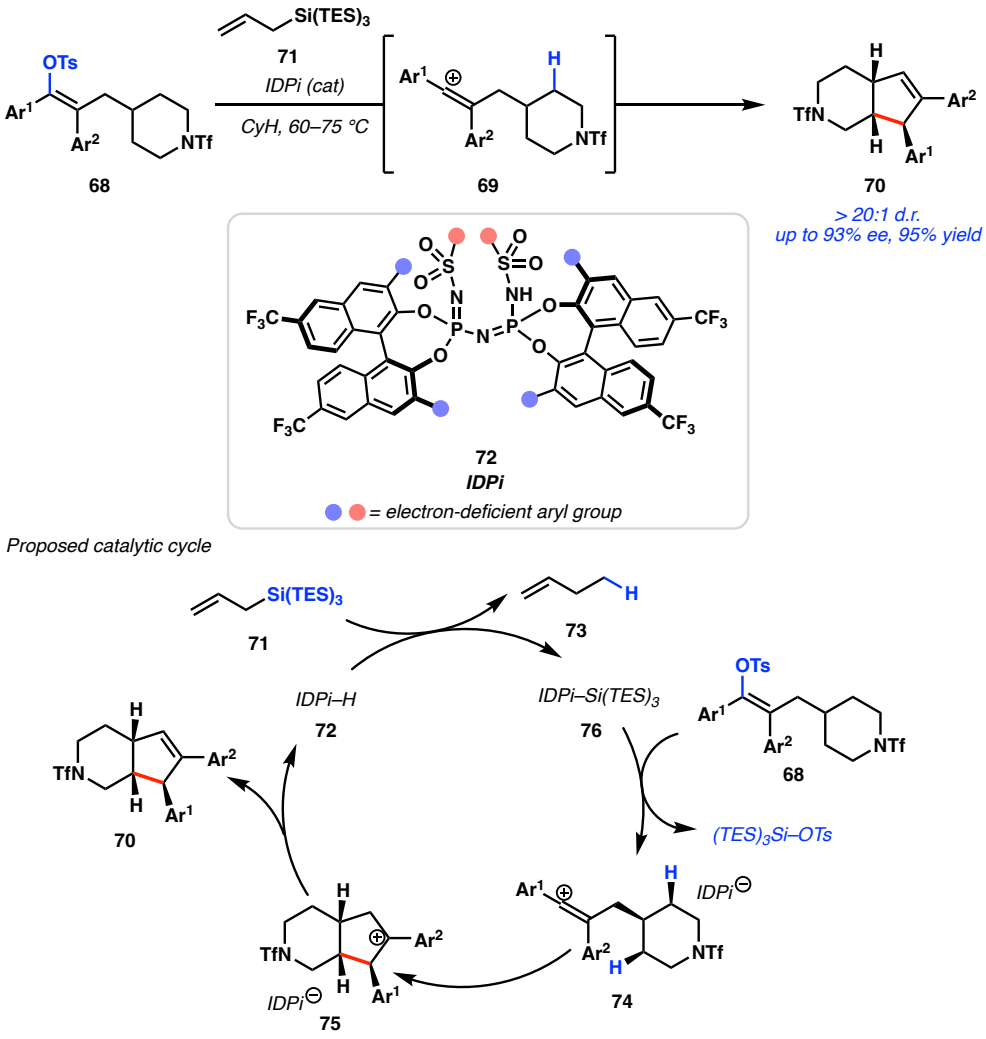
In 2019, Nelson and coworkers developed a milder catalytic system using lithium-WCA to address the limitations of silylium-WCA catalysis, which had poor substrate compatibility due to the high Lewis acidity and reactivity of the silylium species (Scheme 1.10). Commercially available trityl tetrakis(pentafluorophenyl)borate ($[Ph_3C]^+[B(C_6F_5)_4]^-$) was employed as the precatalyst, and upon introduction of LiHMDS, a metathesis reaction was proposed to generate the lithium catalyst $[Li]^+[B(C_6F_5)_4]^-$. The lithium cation in this complex exhibited greater Lewis acidity compared to conventional lithium salts due to the lack of coordination by WCA $[B(C_6F_5)_4]^-$. Upon formation of a catalytically active lithium species, vinyl triflate **64** underwent ionization to forge vinyl carbocation intermediate **65**. Subsequently, an intramolecular C–H insertion occurred, leading to the formation of a 5-membered ring and tertiary carbocation **66**. Finally, LiHMDS facilitated deprotonation to yield product **67** containing a tetrasubstituted olefin.[22] The milder Lewis acidity of the lithium cation allowed the scope of the reaction to be expanded to tolerate a broader range of functional groups, including ethers, sulfonamides, and aryl halides, which were previously incompatible with silylium-WCA catalysis.

Scheme 1.10 *Nelson: Vinyl carbocation C–H insertion through lithium-WCA catalysis.*



In 2022, Nelson and coworkers reported a catalytic asymmetric C–H insertion reaction of vinyl carbocation intermediates utilizing a chiral strong Brønsted acid imidodiphosphorimidate (IDPi) catalyst **72** with a pKa of 2–4 in MeCN,[23] in conjunction with allyl silane **71** (Scheme 1.11). This combination generated a Lewis acidic silylated IDPi **76**, which was found to ionize the vinyl tosylate **68** to form vinyl carbocation intermediate **74**. Subsequently, cation **74** selectively inserted into one of the enantiotopic C–H bonds on the pendant piperidine ring, generating the chiral bicyclic intermediate **75** with high enantioselectivity and diastereoselectivity. In the final step of the catalytic cycle, the IDPi anion reacted as the Brønsted base to induce the β-deprotonation of the tertiary carbocation, resulting in the formation of the nitrogen-containing polycyclic compound **70**. The product contained three contiguous chiral centers with up to 93% ee and >20:1 diastereomeric ratio (dr).[24]

Scheme 1.11 *Nelson: Asymmetric vinyl carbocation C–H insertion.*



1.4 THE FIELD GUIDE OF VINYL CARBOCATION C–H INSERTION

Nelson and coworkers have been at the forefront of developing both silylium- and lithium-WCA systems to access vinyl carbocation intermediates and incorporate them into C–H activation reaction to explore vinyl carbocation reactivity. While the highly Lewis acidic silylium conditions were particularly effective for generating challenging vinyl carbocations, such as strained ones or those lacking π-stabilization.[21] However, the system had poor compatibility with substrates containing heteroatoms. On the other hand, the lithium

conditions showed improved compatibility with heteroatom-containing substrates as lithium is a weaker Lewis acid compared to silylium.[22] However, this approach faced limitations in achieving challenging ionizations that require strong Lewis acidity. The importance and potential of vinyl carbocation C–H insertion have prompted the creation of a field guide aimed at synthetic chemists interested in constructing C−C bonds through Lewis acid-WCA catalytic methods. This guide focuses on silylium- and lithium-initiated reactions that form C−C bonds using vinyl carbocations generated from vinyl triflates. The goal is to provide researchers with valuable context and expedite their selection of optimal reaction conditions and starting materials.

1.4.1 Reaction conditions

Ionization of vinyl triflates was achieved with either silylium-initiated (conditions A) or lithium-initiated (conditions B) condition where the generated Lewis acid is paired with WCA $[HCB_{11}C_{11}]^-$ or $[B(C_6F_5)_4]^-$. Under conditions A, the silylium-carborane initiator is formed *in situ* through a Bartlett-Condon-Schneider silicon-to-carbon hydride transfer[25], where $[Ph_3C]^+$ $[HCB_{11}C_{11}]^-$ is combined with Et_3SiH to form $[Et_3Si]^+$ $[HCB_{11}C_{11}]^-$ and Ph_3CH.[26] Stoichiometric Et_3SiH functions as the terminal reductant, regenerating triethylsilylium that is paired with the catalytic $[HCB_{11}C_{11}]^-$ following hydride transfer. Similarly, under conditions B, $[Ph_3C]^+[B(C_6F_5)_4]^-$ is combined with stoichiometric LiHMDS to form the initiator $[Li]^+[B(C_6F_5)_4]^-$. The remaining equivalents of LiHMDS functions as a base, regenerating the catalytically active Li-WCA species after deprotonation of the carbocation intermediate. While LiHMDS is generally suitable for these reactions, it is susceptible to enamine formation through nucleophilic trapping of the vinyl carbocation. In some cases, LiHMDS may be replaced by LiH to circumvent this issue.

1.4.2 C–H insertion substrate study

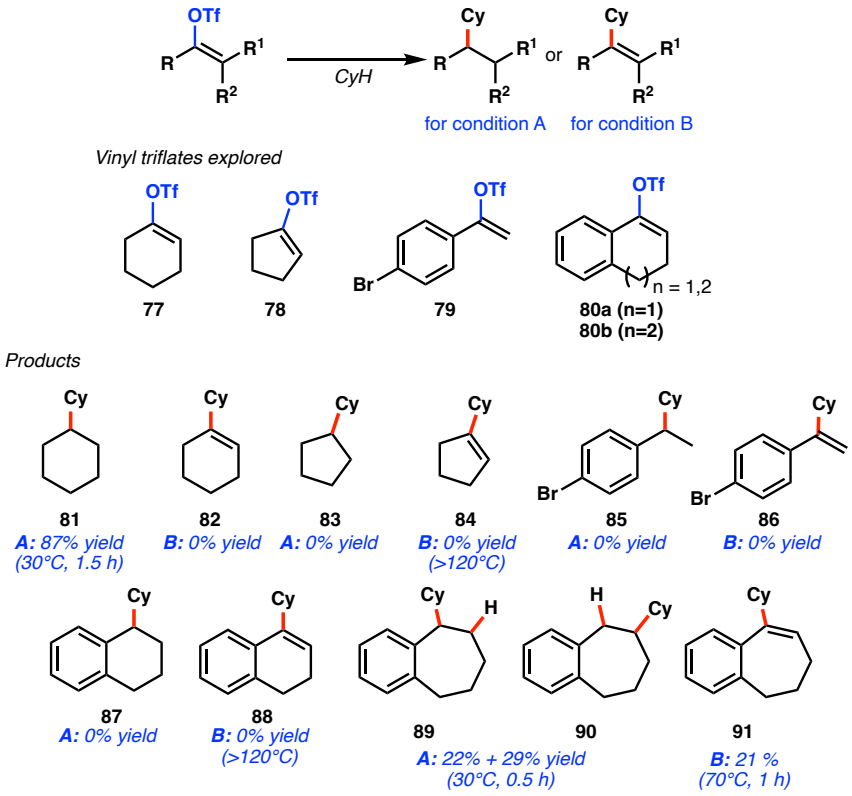
Under silylium conditions A, clean alkylation of cyclohexenyl triflate **77** was achieved, yielding bicyclohexyl **81** in 87% yield after 1.5 hours at 30 °C (Scheme 1.12).[21] However, under lithium-initiated basic conditions B, the desired product **82** was not obtained, indicating some other undesired pathway was outcompeting C–H insertion.

Products derived from cyclopentenyl triflate **78**, specifically cyclohexylation products **83** and **84**, were not observed under either conditions A or B. This is consistent with the significant geometric strain associated with the corresponding 5-membered vinyl carbocation intermediate. Similarly, treatment of tetralone-derived triflate **80a** with cyclohexane did not yield products **87** or **88** under conditions A or B, even after heating the triflates to >120 °C for an extended period of time.

In the case of 4-bromoacetophenone-derived vinyl triflate **79**, no desired products (**85** and **86**) were obtained under either conditions A or B. Conditions B resulted only in the formation of 4-bromoacetylene, while conditions A yielded an intractable mixture of products.

Interestingly, cyclohexylation of benzosuberonyl triflate **80b** under conditions A led to the formation of isomers **89** and **90** in 22% and 29% yield, respectively. Under conditions B, the cyclohexane adduct **91** was obtained as a single isomer but in a lower yield of 21%. The lower yield under conditions B may be attributed to the formation of an enamine via the undesired addition of LiHMDS to the vinyl carbocation.

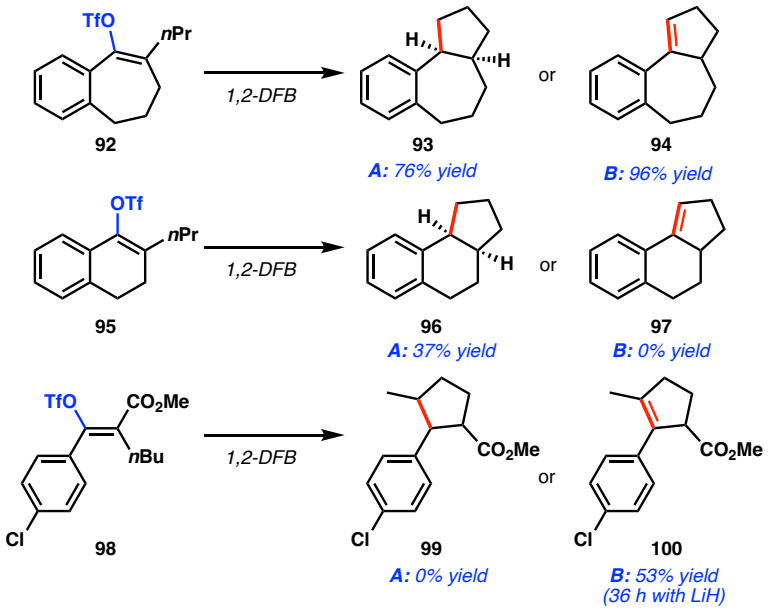
Scheme 1.12 *Investigation of vinyl carbocation intermolecular C–H insertion with cyclohexane.*



Intramolecular C–H insertion followed a similar trend where C–H insertion of propylbenzosuberonyl triflate **92** was observed under both silylium and lithium conditions leading to products **93** and **94** (Scheme 1.13).[22] In contrast, smaller ring-sized tetralonyl triflate **95** only underwent C–H insertion under silylium-initiated conditions, yielding product **96** in 37% yield. Vinyligous acyl triflate **98**, under silylium conditions A, did not produce the desired product **99**. However, under conditions B, which involved the use of LiH instead of LiHMDS at 70°C for 36 hours, cyclopentene product **100** was obtained in 53% yield. This result highlights the enhanced functional group tolerance of conditions B,[27] as LiH prevented ester decomposition that may occur via nucleophilic attack by LiHMDS.

Overall, these examples underscore the distinct reactivity observed between silylium and lithium-initiated conditions in inter- and intramolecular C–H insertion reactions, emphasizing the importance of selecting appropriate reaction conditions based on the substrate's structural and electronic properties.

Scheme 1.13 *Investigation of vinyl carbocation intramolecular C–H insertion.*



1.5 CONCLUSION

Vinyl carbocations, characterized by their highly energetic nature, have historically received less attention compared to the more stable sp^2-hybridized tricoordinated carbocations. Nevertheless, organic chemists have explored various methods to access and utilize these intermediates in selective chemical transformations.

This chapter initially discusses three primary strategies to generate vinyl carbocations: electrophilic addition to alkynes/allenes, heterolysis of vinyl (pseudo)halides, and decomposition of β-diazo alcohols. Next, the evolution of research on the unique C–H

insertion reactivity of vinyl carbocations, beginning with Kucherov's early observations and culminating in recent advancements by Nelson and coworkers is disclosed. These developments include novel catalytic systems designed to induce ionization of challenging vinyl carbocations, expand substrate scope, and enhance stereoselectivity. To promote exploration and broader application of vinyl carbocations as versatile synthetic building blocks in organic chemistry, the final part of the chapter discusses the successes and limitations in silylium and lithium-WCA catalysis pioneered by Nelson and coworkers for synthetic chemists with limited experience in vinyl carbocation generation and reactivity.

Although vinyl carbocations possess significant potential for creating C–C bonds through the activation of otherwise inert C–H bonds, their application in generating complex structures remains somewhat constrained. In intramolecular vinyl carbocation C–H activation reactions, the formation of 5-membered rings is commonly observed, with occasional formation of 6-membered rings.[22] This limitation underscores ongoing challenges in expanding the scope of reactions that utilize vinyl carbocations for synthesizing more intricate molecular architectures.

Utilizing vinyl carbocation intermediates to construct complex and strained structures is a compelling endeavor; thus, my PhD studies have predominantly focused on exploring their reactivity through Li-WCA catalysis and via an IDPi organocatalytic platform. Firstly, I explored the formation of strained medium-sized rings through intramolecular Friedel–Crafts reactions mediated by vinyl carbocation intermediates. Secondly, I expanded the reactivity of vinyl carbocations to produce strained cyclobutene motifs via [2+2] cycloaddition mechanisms. Lastly, I disclose progress towards a catalytic

enantioselective formation of allenes using IDPi catalysis via vinyl carbocation intermediates. The following chapters will delve into detailed discussions of these reactions.

1.6 CONTRIBUTION AND ACKNOWLEDGEMENT

The chemical syntheses in section **1.4** were completed in collaboration with Dr. Martin Riu, Dr. Stasik Popov, and Dr. Ben Wigman.

1.7 EXPERIMENTAL SECTION

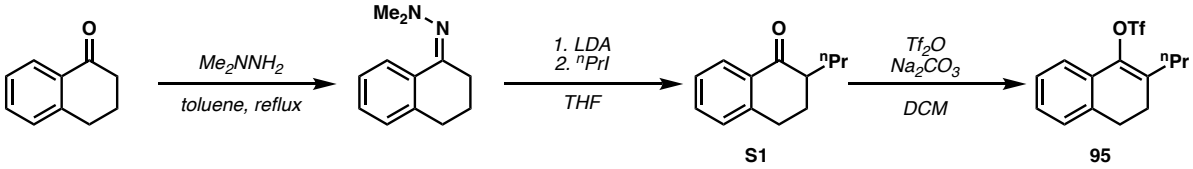
1.7.1 Materials and methods

Unless otherwise stated, all reactions were performed in an MBraun glovebox under nitrogen atmosphere with ≤ 0.5 ppm O_2 levels. All glassware and stir-bars were dried in a 160 °C oven for at least 12 hours and dried under reduced pressure before use. All liquid substrates were either dried over CaH_2 or filtered through dry neutral aluminum oxide. Solid substrates were dried overnight under high vacuum over P_2O_5. All solvents were rigorously dried prior to use. Benzene, trifluorotoluene, dichloromethane, *o*-dichlorobenzene, acetonitrile, and tetrahydrofuran were degassed and dried in a JC Meyer solvent system and stored inside a glovebox. Cyclohexane was distilled over potassium. *o*-Difluorobenzene was distilled over CaH_2. Triethylsilane and triisopropylsilane were dried over sodium and stored inside a glovebox. $[Ph_3C][CHB_{11}Cl_{11}]$ was prepared according to a literature procedure.[31] All other reagents were purchased from commercial suppliers and used as received. Preparatory thin layer chromatography (TLC) was performed using Millipore silica gel 60 F254 pre-coated plates (0.25 mm) and visualized by UV fluorescence quenching. SiliaFlash P60 silica gel (230-400 mesh) was used for flash chromatography. $AgNO_3$-Impregnated silica gel was

prepared by mixing with a solution of $AgNO_3$ (150% v/w of 10% w/v solution in acetonitrile), removing solvent under reduced pressure, and drying at 120 °C. NMR spectra were recorded on a Bruker AV-300 (^1H, ^{19}F), Bruker AV-400 (^1H, ^{13}C, ^{19}F), Bruker DRX-500 (^1H), and Bruker AV-500 (^1H, ^{13}C). ^1H NMR spectra are reported relative to $CDCl_3$ (7.26 ppm) unless noted otherwise. Data for ^1H NMR spectra are as follows: chemical shift (ppm), multiplicity, coupling constant (Hz), integration. Multiplicities are as follows: s = singlet, d = doublet, t = triplet, dd = doublet of doublet, dt = doublet of triplet, ddd = doublet of doublet of doublet, td = triplet of doublet, m = multiplet. ^{13}C NMR spectra are reported relative to $CDCl_3$ (77.0 ppm) unless noted otherwise. GC spectra were recorded on an Agilent 6850 series GC using an Agilent HP-1 (50 m, 0.32 mm ID, 0.25 μm DF) column. GCMS spectra were recorded on a Shimadzu GCMS-QP2010 using a Restek XTI-5 (50 m, 0.25 mm ID, 0.25 μm DF) column interface at room temperature. IR Spectra were record on a Perkin Elmer 100 spectrometer and are reported in terms of frequency absorption (cm^{-1}). High resolution mass spectra (HR-MS) were recorded on a Waters (Micromass) GCT Premier spectrometer, a Waters (Micromass) LCT Premier, or an Agilent GC EI-MS, and are reported as follows: m/z (% relative intensity). Purification by preparative HPLC was done on an Agilent 1200 series instrument with a reverse phase Alltima C18 (5μ, 25 cm length, 1 cm internal diameter) column.

1.7.2 Preparation of vinyl triflate precursors

Triflates **77**,[21] **78**,[21] **79**,[21] **80a**,[21] **80b**,[29] **92**,[22] and **98**[27] were prepared according to literature procedures.



2-propyl-3,4-dihydronaphthalen-1(2H)-one (S1)

In a three-neck flask equipped with a Dean-Stark apparatus was added 3,4-dihydronaphthalen-1(2H)-one (3.00 g, 20.5 mmol, 1 equiv), 1,1-dimethylhydrazine (3.70 g, 61.6 mmol, 3 equiv), toluene (20 mL), and 4-methylbenzenesulfonic acid (0.35 g, 2.1 mmol, 0.1 equiv). The reaction was refluxed at 130 °C overnight. Then it was diluted with diethyl ether and saturated $NaHCO_3$ solution. After the separation of the organic phase and the aqueous phase, the aqueous phase was extracted with diethyl ether two more times. The combined organic phase was washed with brine, dried with mageniusm sulfate, filtered and concentrated *in vacuo* to give the hydrazone intermediate, which was used without further purification.

In a flamed-dried flask was added diisopropylamine (2.53 g, 25.0 mmol, 1.15 equiv) and THF (108 mL). The solution was cooled down to –78 °C and *n*-butyllithium solution (2.53 M, 9.45 mL, 1.1 equiv) was added dropwise. After 1 min, the hydrazone intermediate (4.09 g, 21.7 mmol, 1 equiv) in THF (21 mL) was added dropwise. The reaction was then warmed up to 0 °C and kept for 30 min, then cooled back to –78 °C. *n*-Propyl iodide (4.06 g, 23.9 mmol, 1.1 equiv) was added slowly into the reaction. The reaction was then warmed up to room temperature and stirred overnight. The reaction was quenched by cooling down to 0 °C followed by the addition of 2.5 M HCl (63 mL). This mixture was heated at 50 °C for 1 h. Then the solution was diluted with water and diethyl ether. After the separation of the organic phase and the aqueous phase, the aqueous phase was extracted with diethyl ether two more times. The combined organic phase was washed with saturated $NaHCO_3$ solution

and brine, dried with magnesium sulfate, filtered, and concentrated under reduced pressure to give the crude product. This product was purified by silica flash column chromatography (5% diethyl ether in hexanes) to give ketone **S1** as a yellow solid (2.1 g, 51% yield over 2 steps). The NMR spectra of **S1** matches previously reported data.[30]

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (d, *J* = 7.9 Hz, 1H), 7.49 (t, *J* = 7.5 Hz, 1H), 7.34 (t, *J* = 7.1 Hz, 1H), 7.27 (d, *J* = 7.6 Hz, 1H), 3.04 (dt, *J* = 9.1, 5.0 Hz, 2H), 2.58 – 2.49 (m, 1H), 2.28 (dq, *J* = 13.3, 4.8 Hz, 1H), 1.95 (tddd, *J* = 14.5, 10.7, 7.9, 5.2 Hz, 2H), 1.59 – 1.37 (m, 3H), 1.01 (t, *J* = 7.2 Hz, 3H).

2-propyl-3,4-dihydronaphthalen-1-yl trifluoromethanesulfonates (95)

In a flame dried 100 mL round bottom flask was suspended sodium carbonate (0.84 g, 8.0 mmol, 3 equiv) in anhydrous methylene chloride (27 mL). To this suspension was added ketone **S1** (0.50 g, 2.7 mmol, 1.0 equiv) and the reaction was cooled to 0 °C. Triflic anhydride (0.82 g, 2.9 mmol, 1.1 equiv) was added dropwise at 0 °C and the reaction was allowed to warm up to room temperature. Upon completion of the reaction, as assessed by thin layer chromatography (TLC) analysis, the reaction was quenched with water (15 mL). The layers were separated, and the product was extracted with diethyl ether (3 x 20 mL). The combined organics were dried over magnesium sulfate, filtered, and concentrated to give the crude material as brown oil. The crude product was purified by silica flash column chromatography (25% dichloromethane in hexanes) to give pure vinyl triflate **95** as a colorless oil (0.33 g, 39% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 7.5 Hz, 1H), 7.25 – 7.18 (m, 2H), 7.15 (d, *J* = 7.0 Hz, 1H), 2.83 (t, *J* = 6.9 Hz, 2H), 2.42 (t, *J* = 8.4 Hz, 2H), 2.36 (t, *J* = 7.4 Hz, 2H), 1.55 (h, *J* = 7.6 Hz, 2H), 0.96 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 140.4, 135.5, 133.6, 129.8, 128.1, 127.3, 126.7, 121.2, 118.6 (q, $^{1}J_{C–F}$ = 321.1 Hz), 33.0, 27.5, 27.3, 20.2, 13.9.

^{19}F NMR (376 MHz, $CDCl_3$) δ –73.7.

HR-MS (FD-MS): $C_{14}H_{15}F_3O_3S$ calculated 320.0694; Found 320.0693.

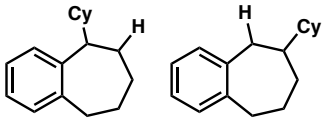
1.7.3 Intermolecular C–H insertion reactions with cyclohexane under Si-mediated conditions A

General Procedure

In a well-kept glovebox, (H_2O, O_2 < 0.5 ppm), a dram vial was charged with $[Ph_3C][HCB_{11}Cl_{11}]$ (0.05 equiv) and this material was suspended in cyclohexane (enough to make a 0.1 M solution of vinyl triflate). Triethylsilane (1.5 equiv) along with a magnetic stirring bar were added to the mixture, and the mixture was shaken until it turned colorless. At this point, vinyl triflate (1.0 equiv) was added to the reaction mixture and was stirred at 30–75 °C (see substrates for specific details). Upon completion, the reaction mixture was passed through a short plug of silica gel inside the glovebox and the plug was washed with hexanes. The combined filtrates were removed from the glovebox and volatile materials were removed under reduced pressure. Some substrates required further purification by silica column chromatography (see below) or preparative high pressure liquid chromatography (HPLC).

Cyclohexane Addition Reactions Previously Reported by our Group

Cyclohexane addition product **81** was prepared from triflate **77**, and the synthesis has been described.[21]



89 **90**

5-cyclohexyl-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene (89) and 6-cyclohexyl-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene (90)

A dram vial was charged with $[Ph_3C][CHB_{11}Cl_{11}]$ (3.8 mg, 0.005 mmol), and this material was dissolved in benzene (0.5 mL). Triethylsilane (17.4 mg, 0.150 mmol) and a magnetic stirring bar were added and the mixture stirred for 10 minutes. Vinyl triflate **80b** (29.2 mg, 0.10 mmol, 1 equiv) was added to the reaction and stirred for 0.5 hours at 30 °C. The reaction mixture was removed from the glovebox and passed through plugged pipette containing a column of silica with ether. Volatile materials were removed under reduced pressure to give products **89** and **90** in 29% and 22% NMR yield, respectively. The crude product was purified by silica flash column chromatography (hexanes) to give a mixture of isomers **89** and **90**. Separation of regioisomers was performed using semi-preparative HPLC (95:5 MeCN:water) to give pure **89** and **90** as colorless oils.

Characterization for **89**

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13 – 6.96 (m, 4H), 3.03 – 2.93 (t, *J* = 13.0 Hz, 1H), 2.66 (dd, *J* = 14.5, 6.4 Hz, 1H), 2.45 (td, *J* = 6.9, 6.5, 3.4 Hz, 1H), 2.07 – 1.96 (m, 2H), 1.96 – 1.86 (m, 2H), 1.83 – 1.70 (m, 3H), 1.66 – 1.52 (m, 3H), 1.48 – 1.36 (m, 1H), 1.25 (ddd, *J* = 29.6, 14.7, 8.1 Hz, 2H), 1.17 – 1.06 (m, 2H), 0.96 – 0.84 (m, 1H), 0.79 (dd, *J* = 12.0, 3.3 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 145.1, 141.9, 130.8, 130.1, 125.7, 125.4, 53.1, 36.5, 32.8, 31.1, 29.1, 28.4, 26.6, 26.5, 26.1.

FTIR (Neat film NaCl): 3059, 3014, 2920, 2850, 2669, 1490, 1447, 1368, 1318, 1266, 1211, 1188, 1159, 1106, 1080, 1033, 977, 939, 756, 746, 549.

HR-MS (ESI-MS) m/z: $[M]^+$ Calc'd for $C_{17}H_{24}$ 228.1878; Found 228.1876.

Characterization for **90**

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16 – 7.12 (m, 4H), 2.91 – 2.75 (m, 3H), 2.70 (d, J = 14.1 Hz, 1H), 2.01 – 1.95 (m, 1H), 1.94 – 1.88 (m, 1H), 1.85 – 1.62 (m, 6H), 1.51 – 1.41 (m, 1H), 1.40 – 1.18 (m, 6H), 1.16 – 1.07 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 143.2, 142.4, 129.1, 128.7, 125.9, 125.8, 43.8, 40.2, 36.4, 35.5, 29.7, 27.4, 26.85, 26.83, 26.80.

FTIR (Neat film NaCl): 3062, 3016, 2919, 2849, 1603, 1493, 1449, 1351, 1050, 927, 909, 894, 749, 734, 726.

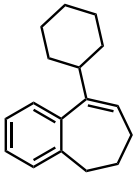
HR-MS (EI-MS) m/z: [M]+ Calc'd for $C_{17}H_{24}$ 228.1878; Found 228.1873.

1.7.4 Intermolecular C–H insertion reactions with cyclohexane under Li-mediated conditions B

General Procedure

In a well-kept glovebox, (H_2O, O_2 < 0.5 ppm), a dram vial was charged with $[Ph_3C][B(C_6F_5)_4]$ (0.05 equiv, 0.0025 mmol). Cyclohexane (0.5 mL) was added followed by LiHMDS (12.5 mg, 0.075 mmol, 1.5 equiv). Vinyl triflate (0.050 mmol, 1.0 equiv) was added and the reaction mixture was stirred at 30–120 °C. The reaction progress was closely monitored by TLC and/or GC. Upon completion of reaction, the mixture was diluted with ether and passed through a plug of silica gel in a pipette. The filtrate was concentrated to give

the crude material. The crude material was purified by silica flash chromatography to give the pure product.



9-cyclohexyl-6,7-dihydro-5*H*-benzo[7]annulene (91)

In a well-kept glovebox, (H_2O, O_2 < 0.5 ppm), a dram vial was charged with $[Ph_3C][B(C_6F_5)_4]$ (2.3 mg, 0.05 equiv, 0.0025 mmol). Cyclohexane (2.0 mL) was added followed by LiHMDS (12.5 mg, 0.075 mmol, 1.5 equiv). Triflate **80b** (14.6 mg, 0.050 mmol, 1.0 equiv) was added and the reaction mixture stirred at 70 °C for 1 hour. At this point, the mixture was diluted with ether and passed through a plug of silica gel in a pipette. The filtrate was concentrated to give the crude material in 21% NMR yield. The crude material was purified by silica flash chromatography (hexanes) to give product **91**.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 – 7.21 (m, 2H), 7.19 – 7.12 (m, 2H), 5.84 (td, *J* = 7.3, 1.4 Hz, 1H), 2.50 (t, *J* = 7.1 Hz, 2H), 2.37 (t, *J* = 11.5 Hz, 1H), 2.02 (p, *J* = 7.1 Hz, 2H), 1.81 – 1.71 (m, 5H), 1.69 (d, *J* = 13.1 Hz, 1H), 1.37 – 1.09 (m, 6H).

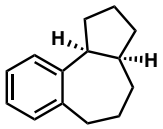
^{13}C NMR (500 MHz, $CDCl_3$) δ 147.1, 141.9, 141.4, 128.4, 126.2, 125.9, 125.8, 122.1, 43.5, 34.5, 33.0, 32.0, 26.9, 26.6, 24.2.

HR-MS (EI-MS) m/z: $[M]^+$ Calc'd for $C_{17}H_{22}$ 226.1721; Found 226.1711.

1.7.5 Intramolecular C–H insertion reactions under Si-mediated conditions A

General Procedure and Comments

In a well-kept glovebox, (H_2O, O_2 < 0.5 ppm), a dram vial was charged with $[Ph_3C]^+[HCB_{11}C_{l1}]^-$ (0.02 equiv) and this material was suspended in cyclohexane to form a 0.033 M solution. Triethylsilane (1.5-4.5 equiv) along with a magnetic stirring bar were added to the mixture, and the mixture was shaken until it turned colorless. At this point, vinyl triflate (1.0 equiv) was added to the reaction mixture and was stirred at 30 °C. Upon completion, the reaction mixture was passed through a short plug of silica gel inside the glovebox and the plug was washed with hexanes. The combined filtrates were removed from the glovebox and volatile materials were removed under reduced pressure. Some substrates required further purification by silica column chromatography (see below). Compound **93** was prepared from vinyl triflate **92**, and the synthesis is described.[22]



2,3,3a,4,5,9b-hexahydro-1*H*-cyclopenta[*a*]naphthalene (93)

In a well-kept glovebox, (H_2O, O_2 < 0.5 ppm), a dram vial was charged with $[Ph_3C]^+[HCB_{11}C_{l1}]^-$ (0.92 mg, 0.0010 mmol, 0.02 equiv.) and this was suspended in cyclohexane (1.5 mL). Triethylsilane (36 µL, 0.225 mmol, 4.5 equiv) was added along with a magnetic stirring bar to the suspension. The suspension was stirred for 5 minutes at 30 °C. Vinyl triflate **92** (16 mg, 0.050 mmol, 1 equiv) was added to the reaction and it was stirred at 30 °C for 15 minutes. The reaction mixture was passed through a plug of silica with hexanes. The resulting solution was brought outside of the glovebox and concentrated to give crude tricyclic compound **93** in 37% NMR yield using nitromethane as an internal standard. Attempts to further purify **93** by column chromatography were unsuccessful. NMR data matches previously reported spectra.[31]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 – 6.98 (m, 4H), 3.36 (td, *J* = 8.0, 2.7 Hz, 1H), 2.86 (ddd, *J* = 15.9, 8.8, 3.8 Hz, 1H), 2.73 (dt, *J* = 16.2, 8.4 Hz, 1H), 2.18 (dtd, *J* = 12.1, 8.0, 3.8 Hz, 1H), 1.67 (dq, *J* = 12.5, 8.7 Hz, 1H), 1.45 – 1.12 (m, 7H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 146.68, 142.94, 124.88, 124.60, 123.27, 122.81, 44.48, 30.83, 30.77, 30.46, 26.10, 21.63, 13.23.

HR-MS (FD-MS): C13H16 calculated 172.1252; Found 172.1266.

1.7.6 Intramolecular C–H insertion reactions under Li-mediated conditions B

General Procedure and Comments

In a well-kept glovebox, (H_2O, O_2 < 0.5 ppm), a dram vial was charged with $[Ph_3C][B(C_6F_5)_4]$ (0.05 equiv). Dichloromethane or 1,2-difluorobenzene was added followed by LiHMDS (1.5 equiv). Vinyl triflate (1.0 equiv) was added, and the mixture stirred with heat (30 °C or 70 °C, depending on the substrate). Upon completion of the reaction, the mixture was removed from the glovebox, where it was diluted with diethyl ether and passed through a short plug of silica. Volatile materials were removed from the filtrate and the resulting crude material was further purified by column chromatography. C−H insertion product **94** was prepared from vinyl triflate **92** in dichloromethane at 30 °C, and the synthesis is described in detail in ref.[22] C−H insertion product **100** was prepared from vinyl triflate **98** in 1,2-difluorobenzene at 70 °C using LiH (3 equiv) in place of LiHMDS, and the synthesis is described in detail in ref.[27]

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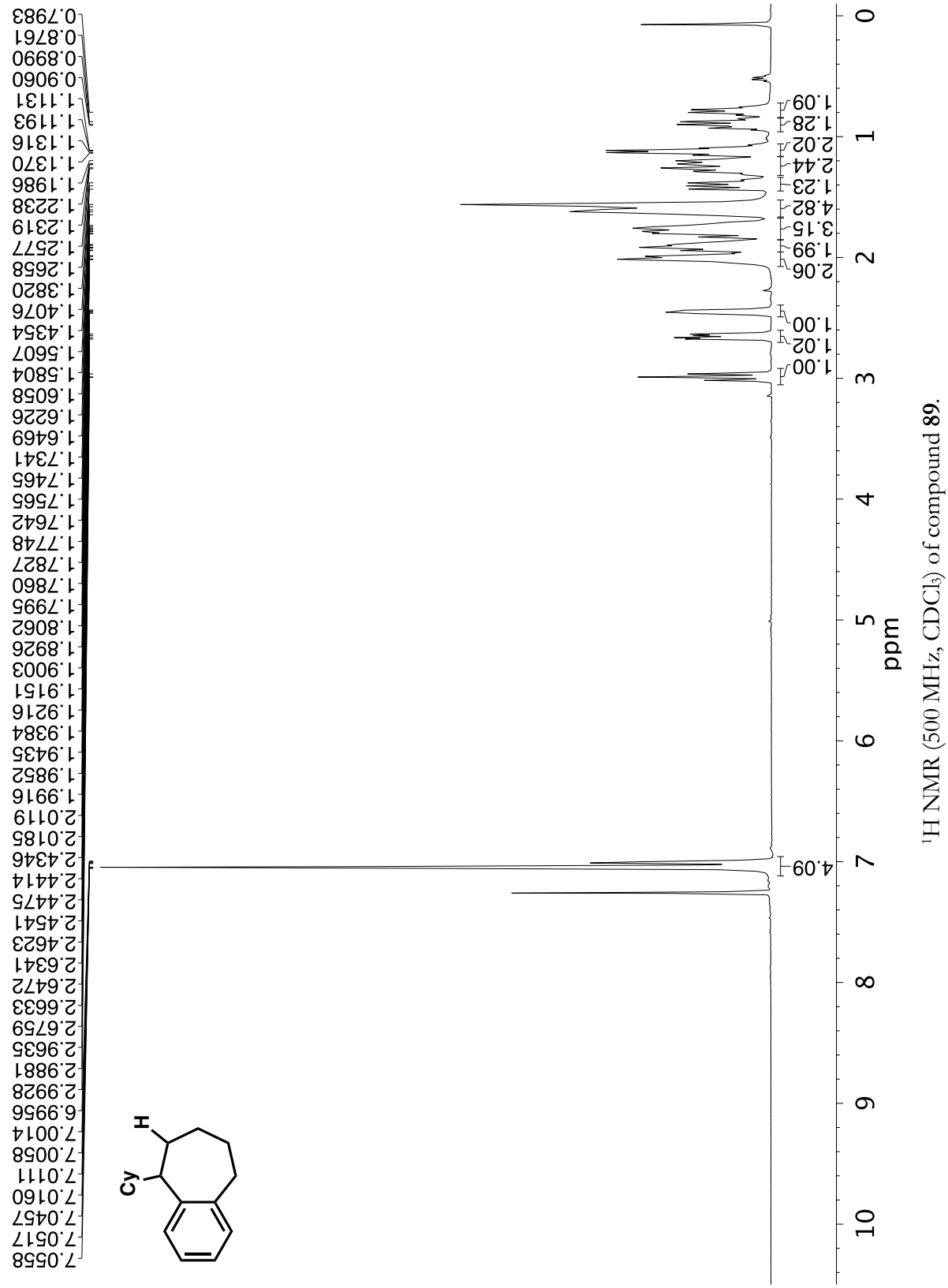
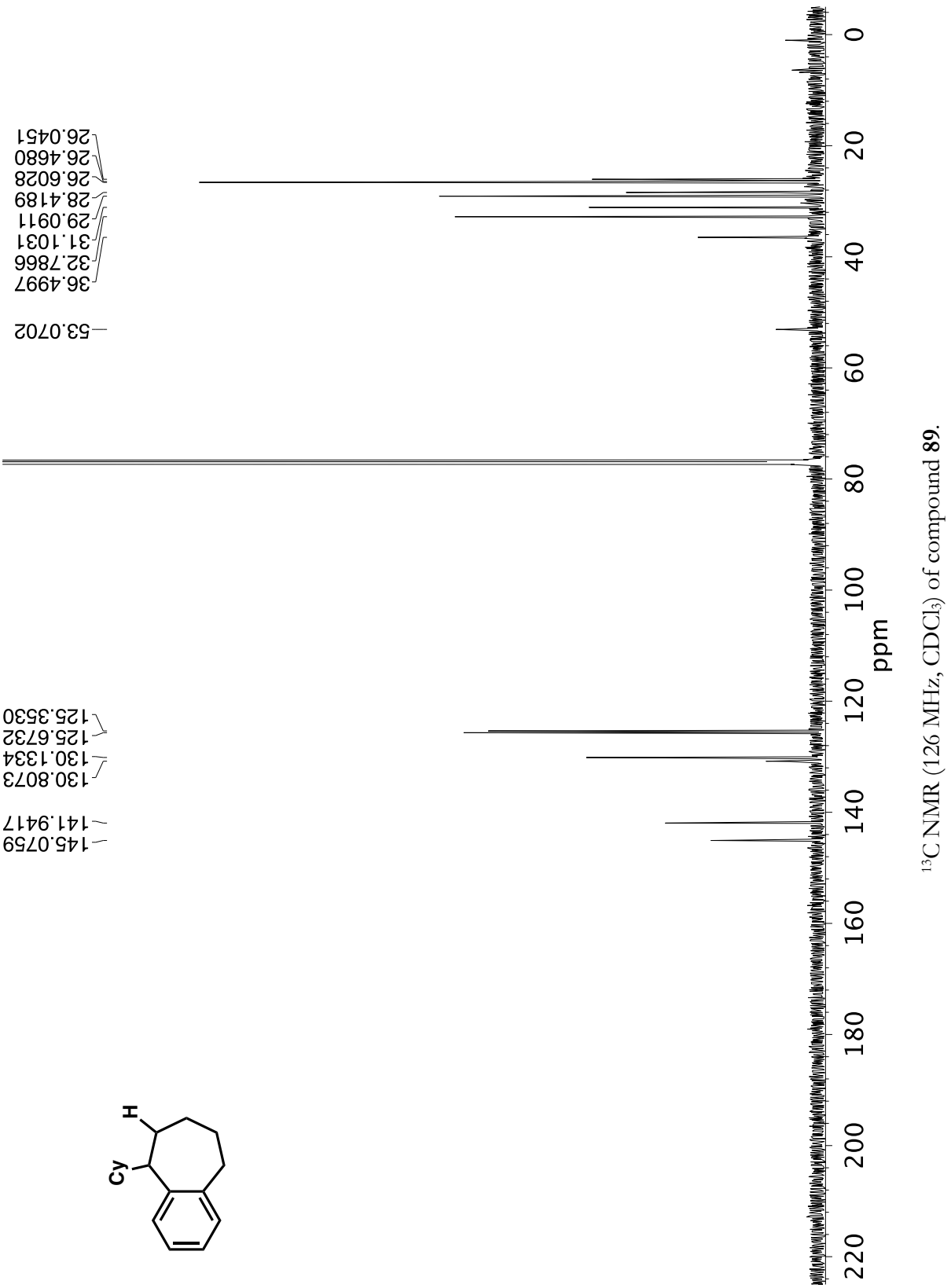
APPENDIX 1

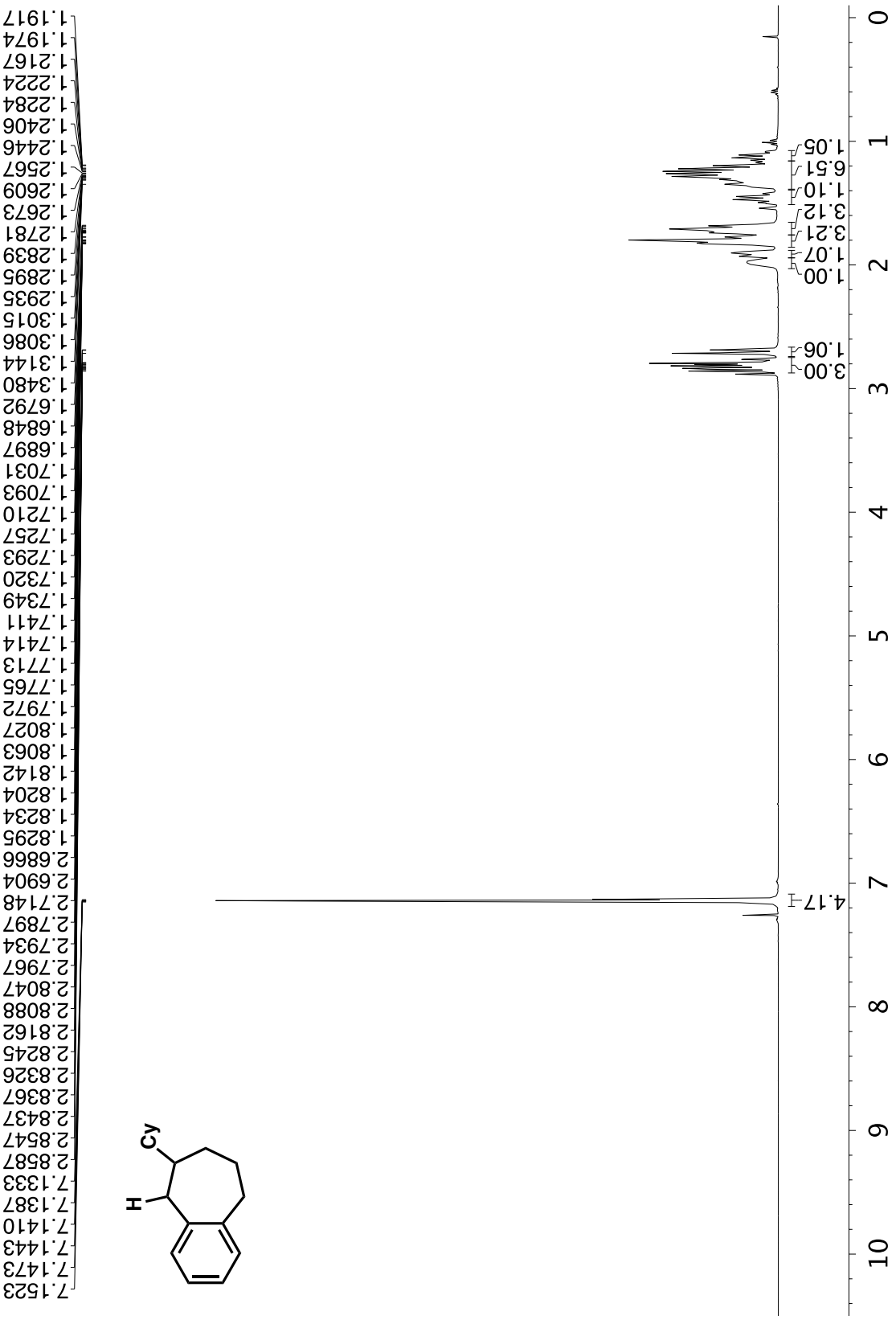
Spectra Relevant to Chapter 1: Introduction to Vinyl Carbocations and Their C–H Insertion Reactions



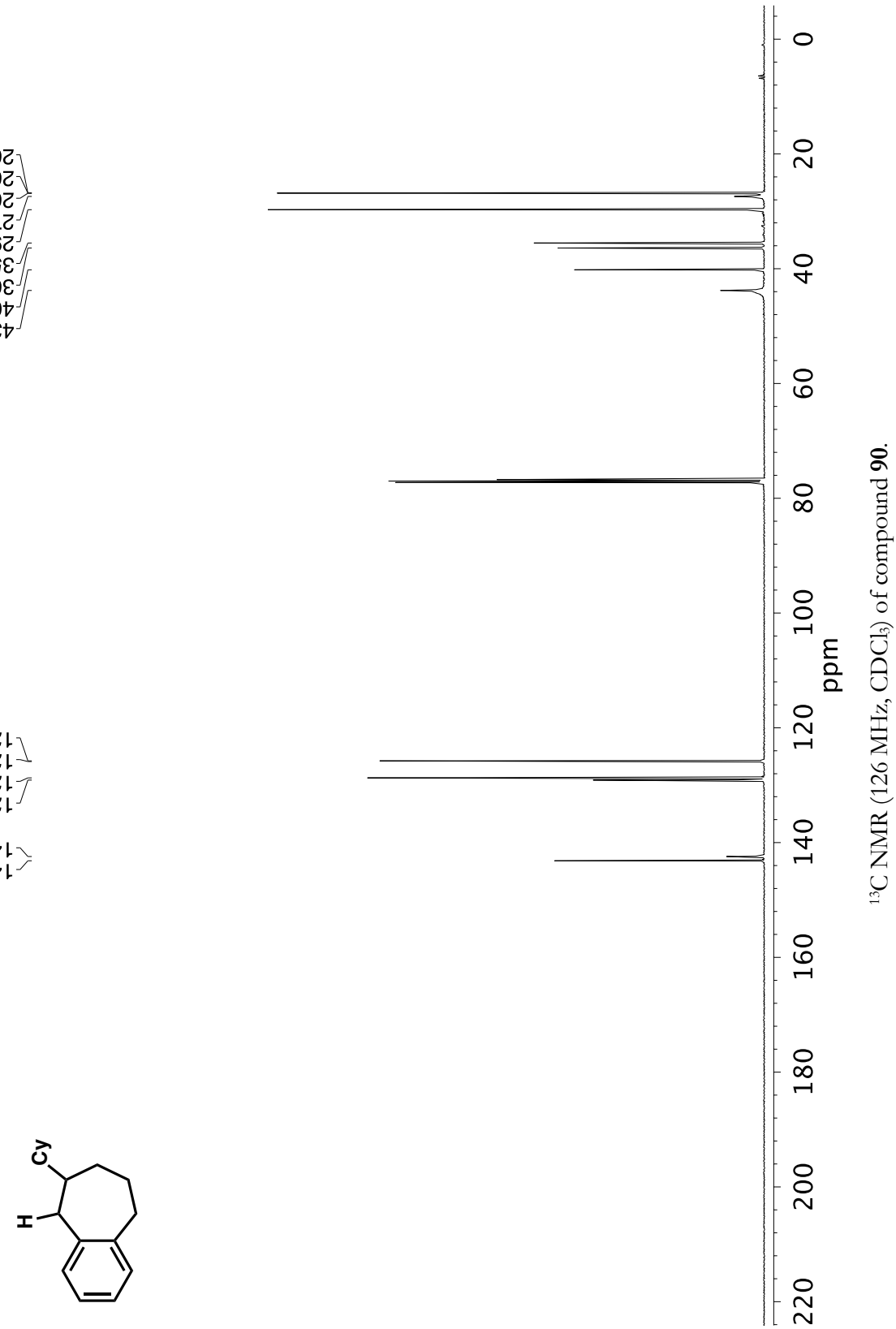
^{1}H NMR (500 MHz, $CDCl_3$) of compound **89**.



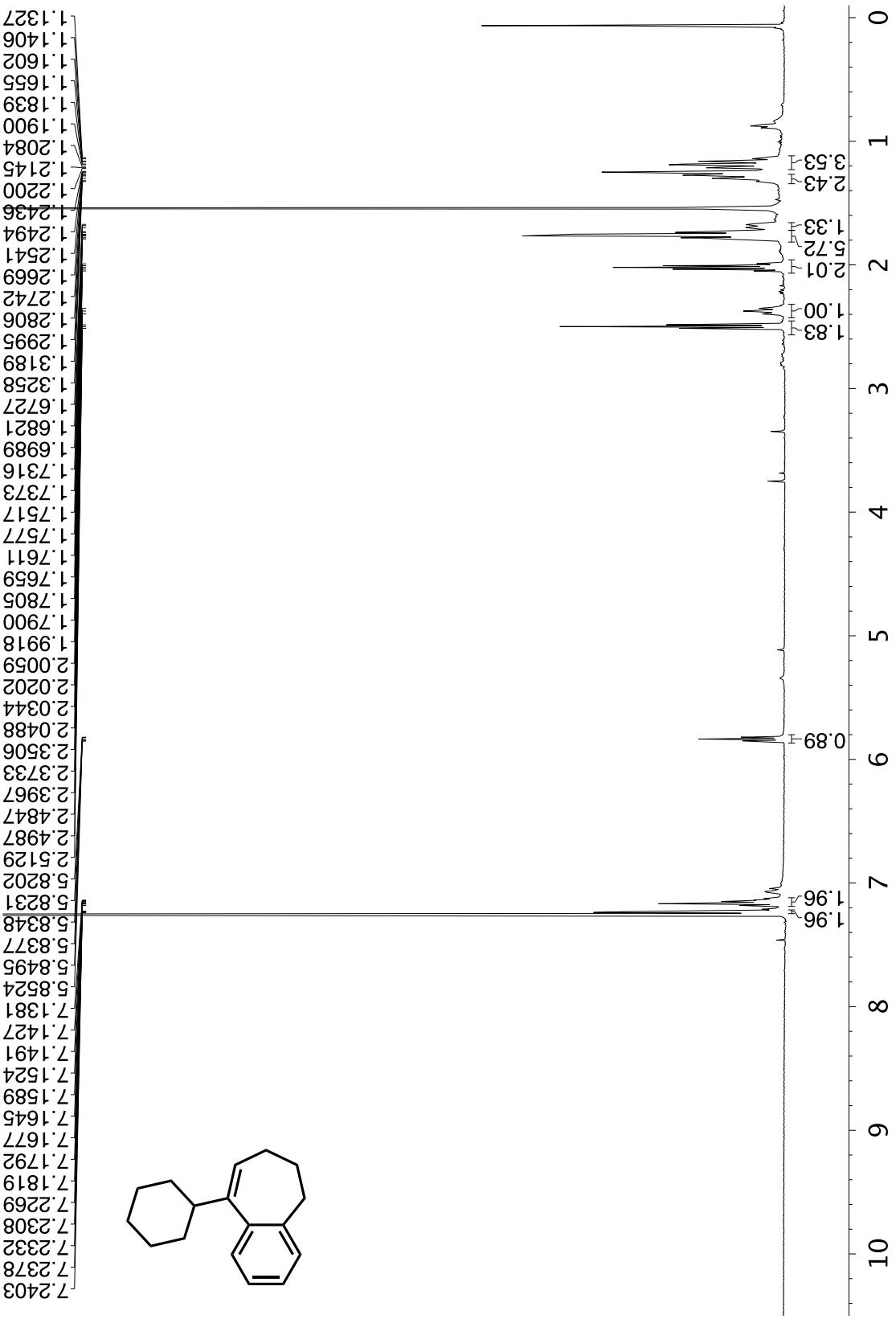
^{13}C NMR (126 MHz, $CDCl_3$) of compound **89**.



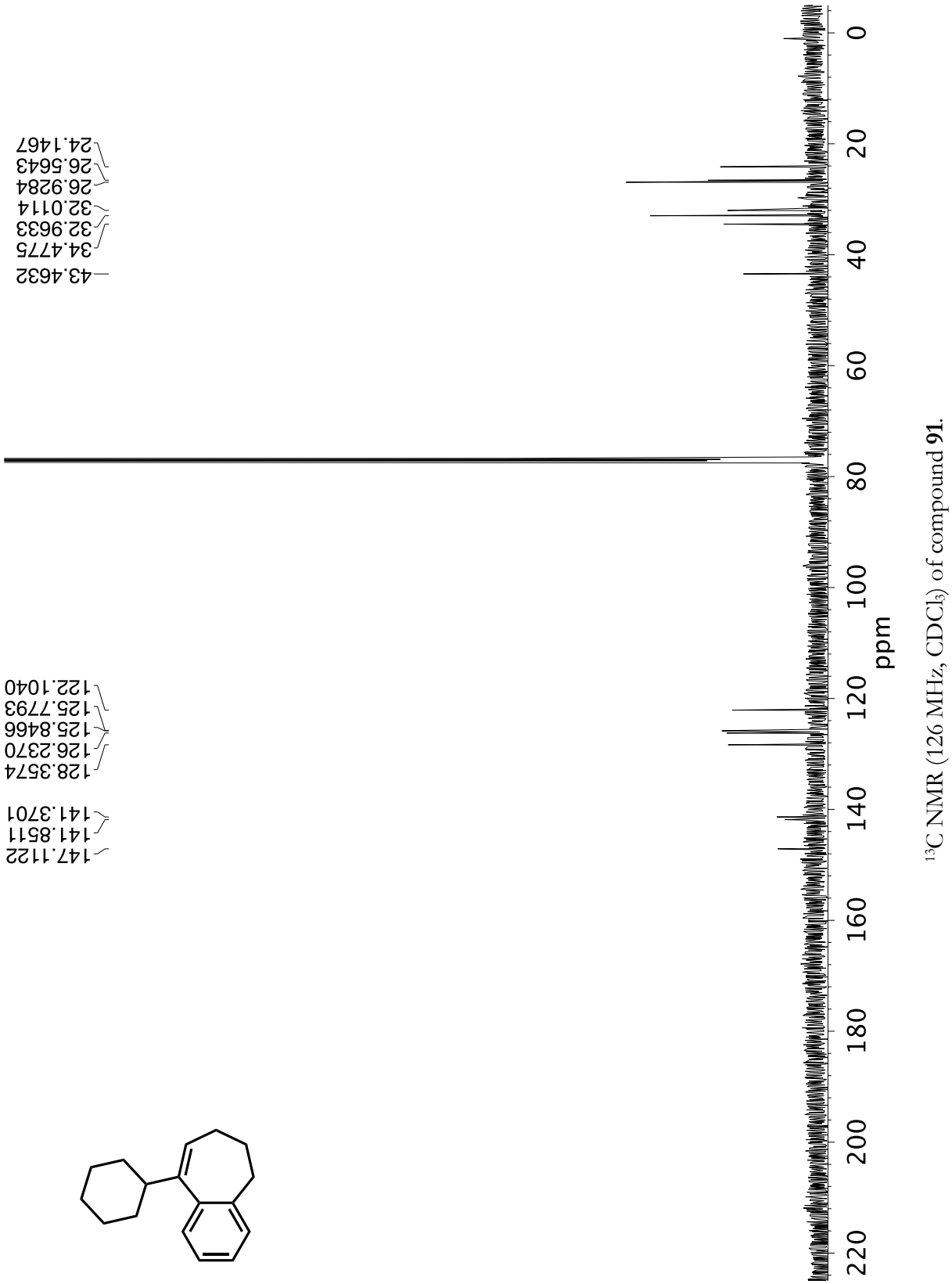
^{1}H NMR (500 MHz, $CDCl_3$) of compound **90**.



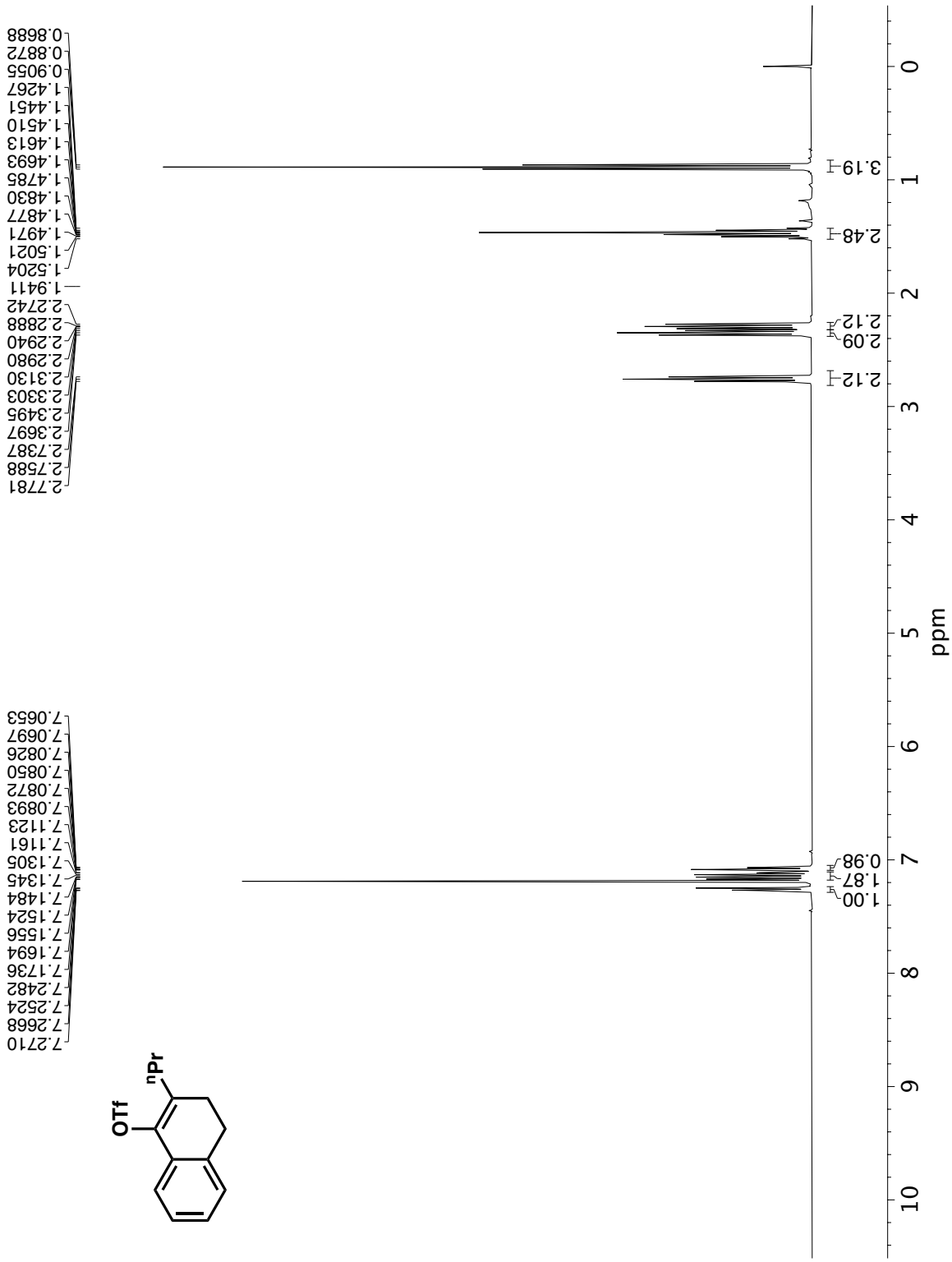
^{13}C NMR (126 MHz, $CDCl_3$) of compound **90**.



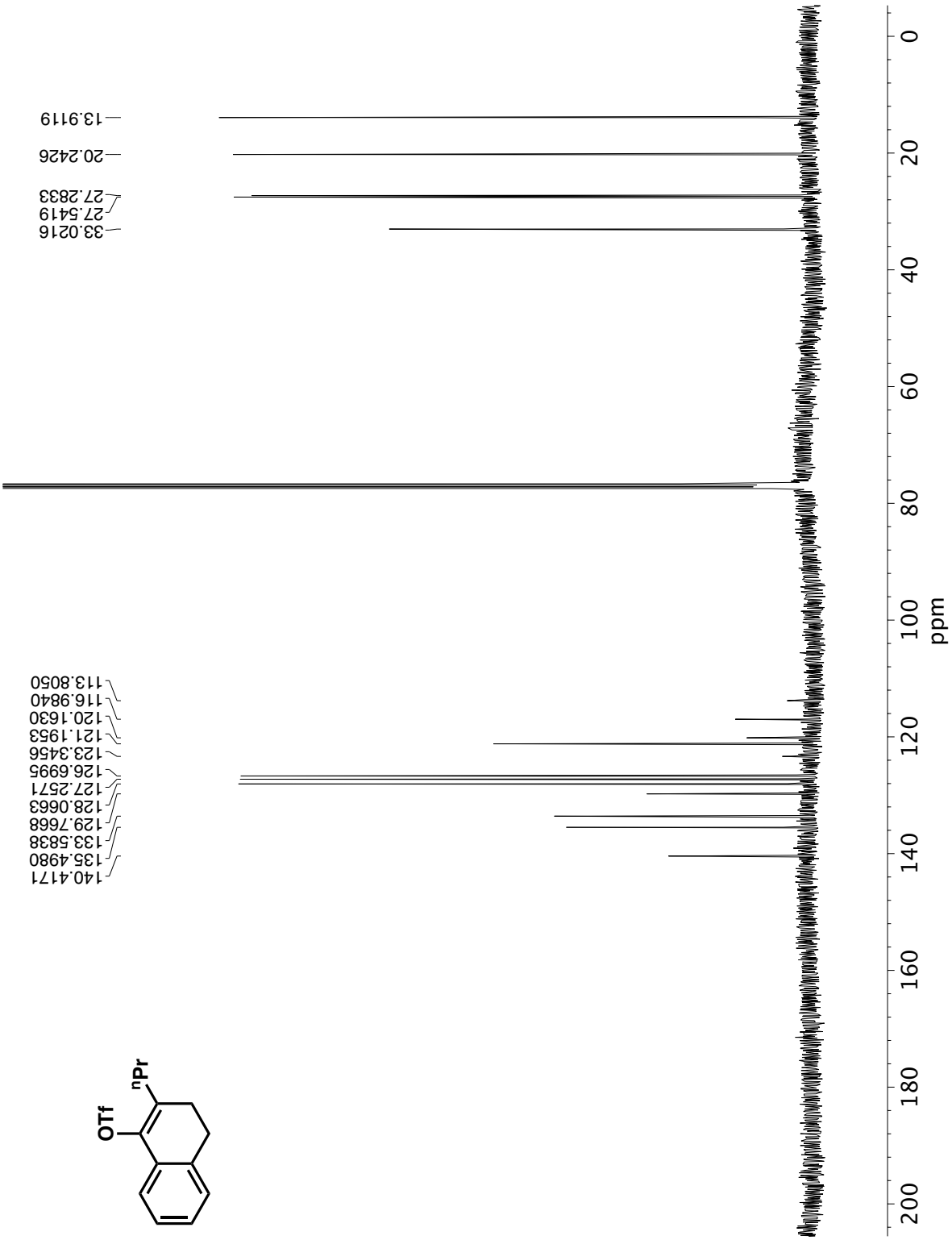
^{1}H NMR (500 MHz, $CDCl_3$) of compound **91**.



^{13}C NMR (126 MHz, $CDCl_3$) of compound **91**.



^{1}H NMR (400 MHz, $CDCl_3$) of compound **95**.



^{13}C NMR (101 MHz, $CDCl_3$) of compound **95**.

^{19}F NMR (376 MHz, $CDCl_3$) of compound **95**.

CHAPTER 2

Accessing Medium-sized Rings via Vinyl Carbocation Intermediates

‡ This chapter is adapted from the published work: Zhao, Z.; Popov, S.; Lee, W.; Burch, J. E.; Delgadillo, D. A.; Kim, L.-J.; Shahgholi, M.; Lebrón-Acosta, N.; Houk, K. N.; Nelson, H. M. Accessing Medium-sized Rings via Vinyl Carbocation Intermediates. *Org. Lett.* **2024**, *26*, 1000-1005.

2.1 INTRODUCTION

Cyclic structural motifs are ubiquitous in natural products, pharmaceuticals, and other industrially relevant compositions of matter.[1,2] Amongst them, 5- and 6-membered rings are the most common cyclic structures due to their ease of preparation.[3,4] In contrast, medium-sized rings (8–11 membered rings) are often more difficult to access, where methods commonly utilized to forge 6- or 5-membered rings fail. Unlike macrocycles (≥12-membered rings), medium-sized rings suffer from torsional and transannular strain; therefore, their annulation reactions can be less favorable and sluggish.[3–7] As a result, medium-sized rings appear less in synthetic molecules, hindering their utility across a broad swath of applications.

Despite their challenging formation, compounds with medium-sized rings are abundant in natural products.[8,9] For some bioactive compounds bearing medium-sized cyclic motifs, it has been proposed that the unique balance of structural rigidity and broad conformational space enables higher binding affinities to biological targets relative to small ring analogs.[10] Despite these facts, the number of methods for medium-sized ring formation remains limited in organic synthesis. Ring expansion from smaller rings is widely used to generate medium-sized rings; however, these reactions need careful design depending on the structure of the medium-sized ring desired and usually require several synthetic steps towards well-poised, smaller ring precursors.[11] For direct annulation methods, catalytic ring-closing metatheses and cross-coupling reactions are the most common, but precious noble metals such as palladium and ruthenium are required as catalysts.[12,13] Medium-sized ring formation through radical intermediates has also been reported, although

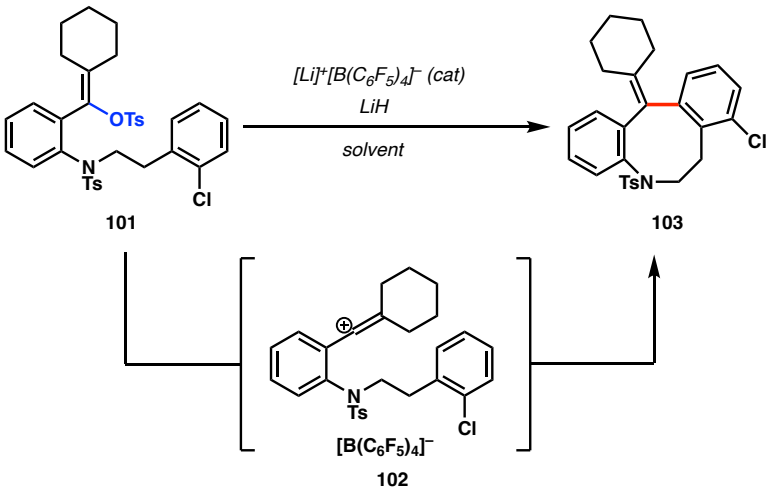
stoichiometric radical sources are commonly used.[12,13] As a result, it is still of great interest to develop catalytic and metal-free annulation reactions to access medium-sized rings.

2.2 MODEL SUBSTRATE STUDY

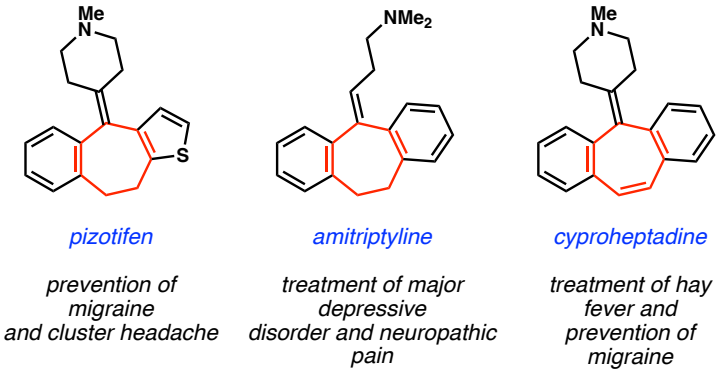
Vinyl tosylate **101** was selected as our model substrate (Scheme 2.1). A sulfonamide was introduced into the aniline-derived scaffold to protect the Lewis basic amine moiety, a common functional group in many bioactive molecules.[14,15] We proposed that vinyl tosylate **101** would transform to tetrahydroazocine **103** under lithium-WCA catalysis. Medium-sized ring **103** features an *exo*-alkene on the 8-membered ring, which is reminiscent of commercial drugs pizotifen,[16] amitriptyline,[17] and cyproheptadine,[18] albeit these comprise more readily prepared 7-membered rings (Scheme 2.2). The established route to these drugs features a key intramolecular Friedel–Crafts acylation of a carboxylic acid to forge their core 7-membered ring. As there are few reports to build larger medium-sized rings via Friedel–Crafts acylation,[19,20] our complementary method provides access to underexplored chemical space via vinyl carbocation intermediates.

Recognizing that electron-deficient arenes are sluggish nucleophiles, we questioned if electrophilic vinyl carbocation species could engage them in Friedel–Crafts reactions. Therefore, we began optimization with vinyl tosylate **101** to study the Friedel–Crafts reactions with electrophilic vinyl cation species (Table 2.1). When vinyl tosylate **101** was subjected to 10 mol% of lithium tetrakis(pentafluorophenyl)borate ($[Li]^+[B(C_6F_5)_4]^-$) (**104**) in 1,2-dichlorobenzene (*o*-DCB) at 140 °C, tetrahydroazocine **103** was formed in 40% yield

Scheme 2.1 *Medium-sized ring formation via vinyl carbocation intermediates.*



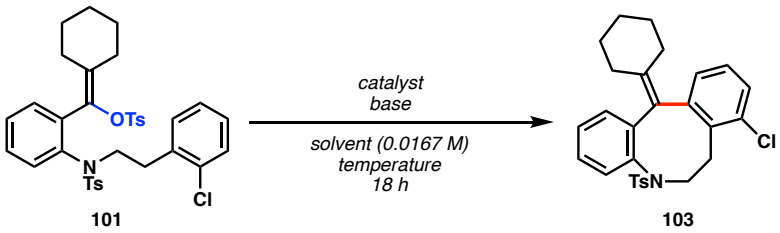
Scheme 2.2 *Commercial drugs with exo-alkene on a 7-membered ring.*



(entry 1). The structure of product **103** was confirmed using microcrystal electron diffraction (microED).[21] Since a significant amount of starting material remained after long reaction times (entry 1), we hypothesized that adding a lithium base could help regenerate the lithium catalyst and improve the reaction yield. Indeed, adding an excess of LiH increased the yield to 74% (entry 2). In contrast, the presence of lithium bis(trimethylsilyl)amide (LiHMDS), which was used in previous reports,[22,23] was detrimental to the reaction, forming the product in 21% yield (entry 3). Performing the reaction without $[Li]^+[B(C_6F_5)_4]^-$ did not provide any tetrahydroazocine **103** (entry 4). Lower loadings of $[Li]^+[B(C_6F_5)_4]^-$ gave lower yields of the

product (entries 5, 6), highlighting the essential role of $[Li]^+[B(C_6F_5)_4]^-$ in this catalytic cyclization. Solvents other than *o*-DCB were also examined but were found inferior (entries 7–9). Hydrogen bonding catalyst **105**, which our group had previously applied in the ionization of vinyl triflates, gave diminished yields (entries 10,11).[23]

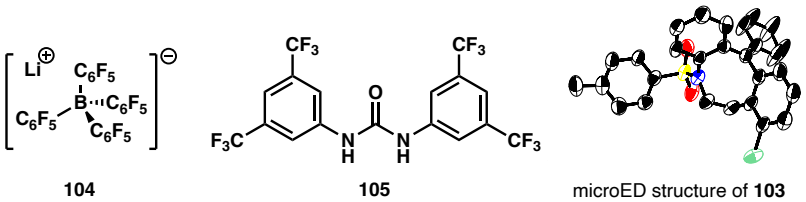
Table 2.1 *Optimization of the reaction conditions to build medium-sized rings.*



101 103

entry	catalyst (mol%)	base (equiv)	solvent	temperature (°C)	yield (%)
1	**104 (10)**	none	*o*-DCB	140	40
2	**104 (10)**	LiH (5)	*o*-DCB	140	74
3	**104 (10)**	LiHMDS (1.5)	*o*-DCB	140	21
4	none	LiH (5)	*o*-DCB	140	n.d.
5	**104 (5)**	LiH (5)	*o*-DCB	140	49
6	**104 (1)**	LiH (5)	*o*-DCB	140	24
7	**104 (10)**	LiH (5)	*o*-DFB	92	n.d.
8	**104 (10)**	LiH (5)	mesitylene	140	50
9	**104 (10)**	LiH (5)	DMF	140	n.d.
10	**105 (10)**	LiH (5)	*o*-DCB	140	19
11	**105 (10)**	LiHMDS (1.5)	*o*-DCB	140	n.d.

* Yields determined by using 1,4-dioxane as an internal standard.

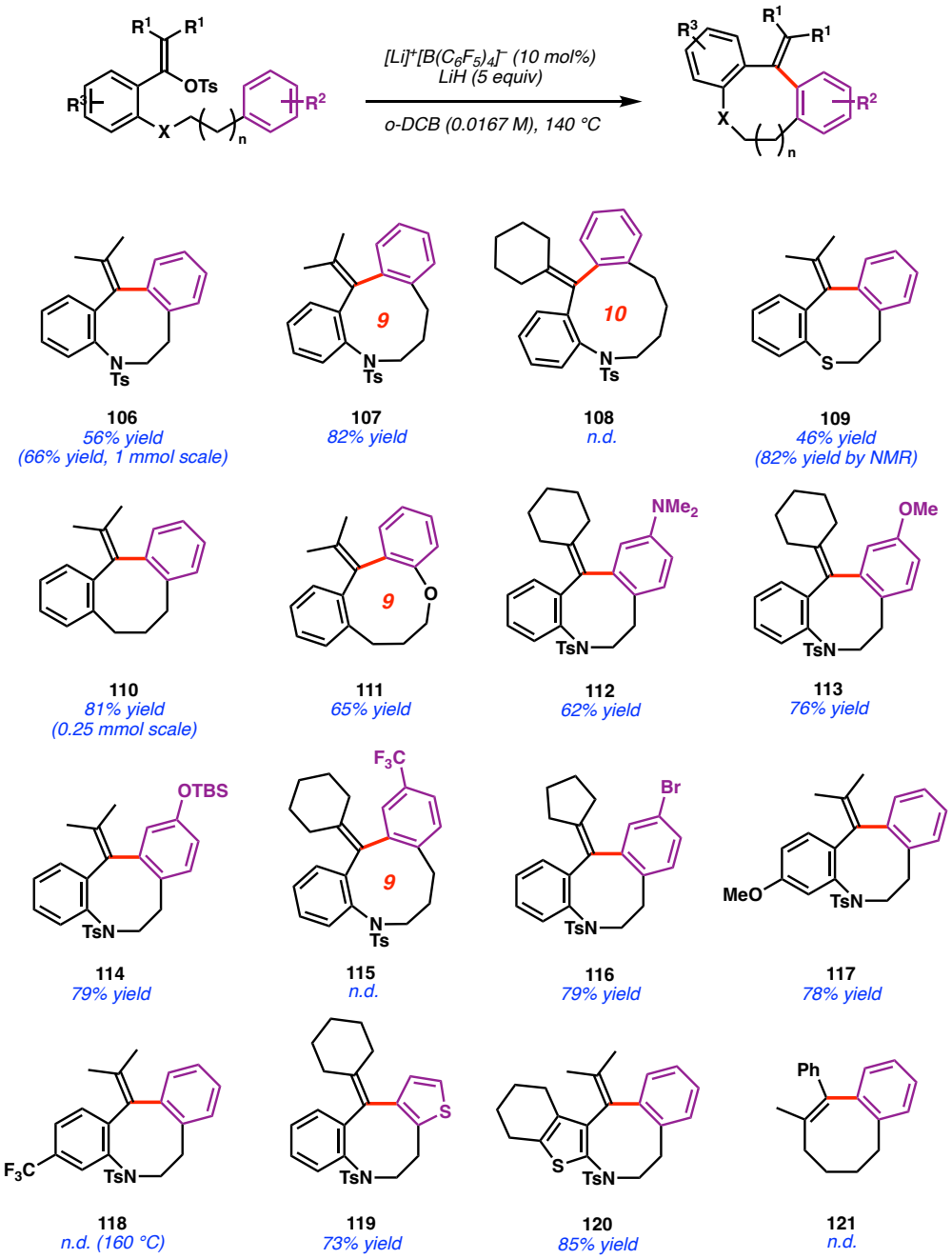


104 105 microED structure of **103**

2.3 SUBSTRATE STUDY

With the optimized conditions, we set out to explore the substrate scope. First, we tested various ring sizes. Similar to vinyl tosylate **101**, the substrate with a non-substituted aryl nucleophile also gave the 8-membered ring product **106** in moderate yield (Scheme 2.3). A 9-membered ring was also formed under this system giving tetrahydroazonine **107** with a yield of 82%. However, 10-membered ring formation proved difficult, as hexahydroazecine **108** was not observed under the reaction conditions. We also found that the sulfonamide could be replaced with other functional groups. For example, thioether **109** was obtained with a moderate yield of 46%, and medium-sized carbocycle **110** could be synthesized in 81% yield. The 9-membered ring ether **111** could be produced in 65% yield with an electron-rich arene as the nucleophile. Substitution effects on the aryl nucleophile were also studied. Phenyl groups with the dimethylamino and methoxy groups could give the 8-membered ring products with good yields (**112** and **113**). Notably, *tert*-butyldimethylsilyl (TBS) protected phenol was also tolerated under the reaction conditions as 79% yield of **114** was obtained. Unfortunately, when the strong electron-withdrawing group trifluoromethyl was present on the aryl group, product **115** was not formed. With a weak electron-withdrawing group, such as bromine, the medium-sized ring product **116** could be obtained smoothly in 79% yield. The electronic effect of the aryl ring vicinal to the vinyl tosylate in the starting material was also examined. With an electron-donating methoxy group, product **117** was formed with 78% yield. Conversely, product **118** was not obtained because the respective vinyl tosylate with an electron-withdrawing trifluoromethyl group had no reactivity, which could be due to the challenging ionization to the vinyl cation intermediate. Furthermore, heterocycles could also

Scheme 2.3 *Scope of Li-WCA catalyzed medium-sized ring formation.*

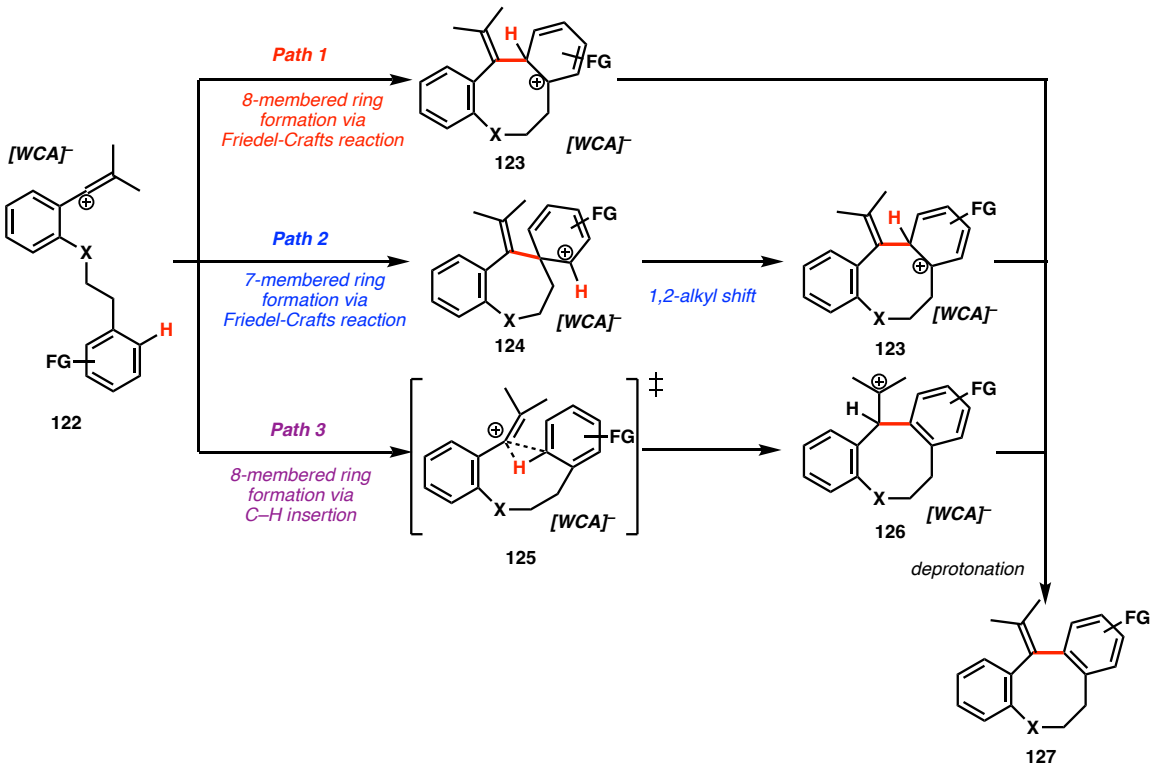


be used in the reaction. Thiophene was tolerated, yielding the 8-membered ring product **119** and **120** in 73% and 85% yield, respectively. The two aryl groups fused with the medium-sized ring in the product were important to this cyclization. Product **121** could not be formed

when only one fused aryl ring was on the 8-membered ring. Reducing sp^2 carbon in the medium-sized ring in **121** (4 sp^2 carbon atoms instead of 5) might introduce more transannular strain and make the cyclization more challenging.[7] To show the reaction is scalable, tetrahydroazocine **106** was synthesized with 66% yield on the scale of 1 mmol (0.4 g).

2.4 MECHANISTIC STUDY

Scheme 2.4 *Possible mechanistic pathways of the medium-sized ring formation.*

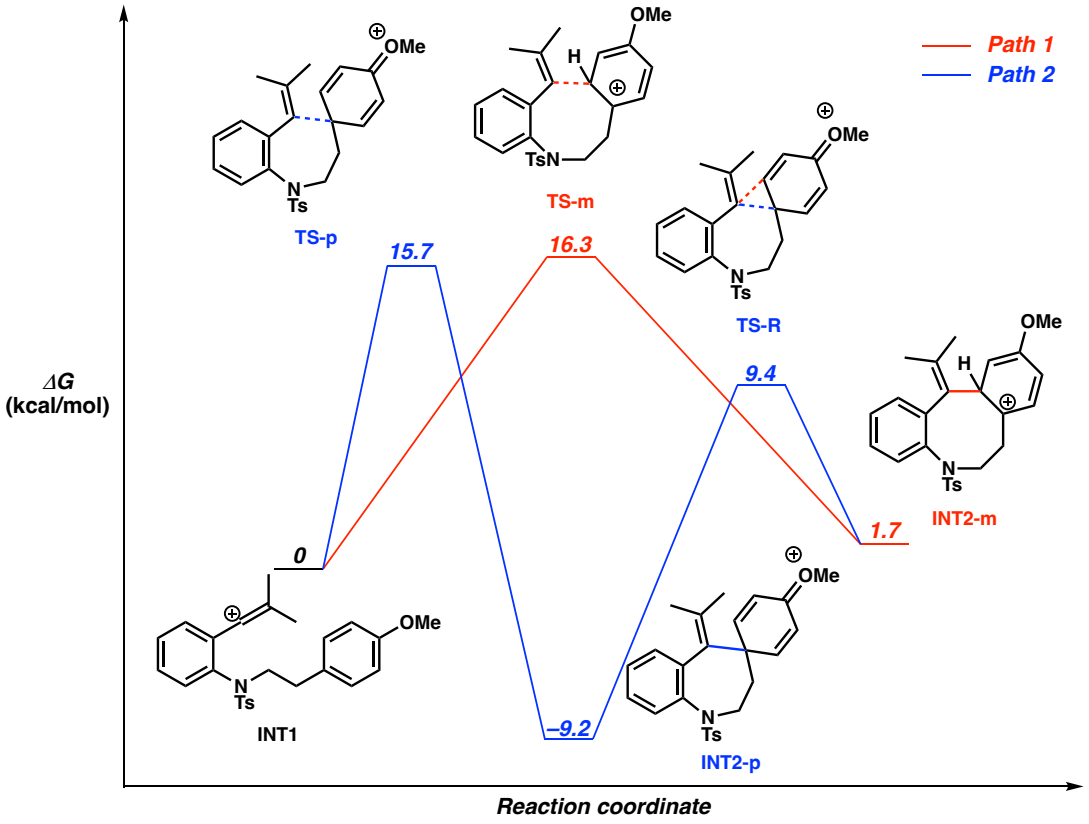


Because forming medium-sized rings through direct cyclization is challenging, we decided to study the reaction mechanism further. Lithium-WCA catalysis systems employing $[Li]^+[B(C_6F_5)_4]^-$ have been demonstrated to ionize vinyl sulfonates to vinyl carbocations.[22] Here, we proposed three possible pathways in forming 8-membered ring **127** from the vinyl carbocation **122** (Scheme 2.4). **Path 1** is a conventional Friedel–Crafts reaction of the vinyl carbocation where the medium-sized ring intermediate **123** is formed in one step. In **Path 2**, the vinyl carbocation reacts with the aromatic π-system at the *ipso* carbon to form a 7-membered ring in **124**, which often harbors less ring strain than the corresponding 8-membered ring. A 1,2-shift of the alkyl group then occurs to expand the ring to give intermediate **123**. Alternatively, in **Path 3**, a concerted insertion of the vinyl carbocation into an aryl C–H bond is operative, mechanistically analogous to the insertion of vinyl carbocations into alkyl C–H bonds.[22–24]

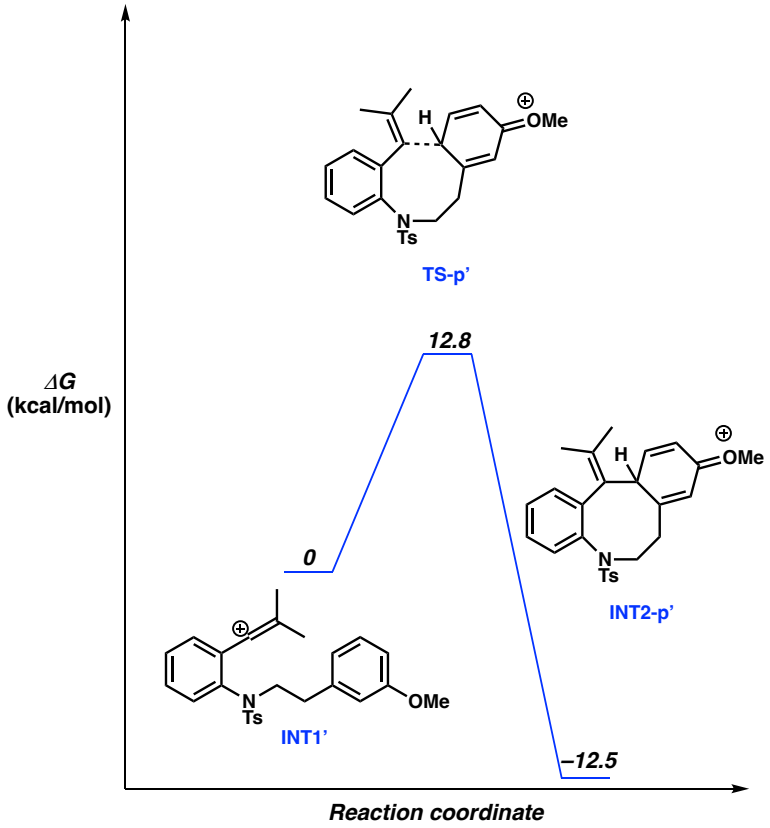
In order to differentiate the potential mechanisms of **Path 1** and **Path 2**, these proposed pathways were evaluated by density functional theory (DFT) calculations (Scheme 2.5). **INT1** can undergo the hypothetical Friedel–Crafts reaction via **TS-m** (16.3 kcal/mol) to form 8-membered ring **INT2-m** (**Path 1**). For the other putative mechanism shown in **Path 2**, **INT1** goes through 7-membered ring formation via **TS-p** (15.7 kcal/mol) and subsequent 1,2-alkyl shift **TS-R** (9.4 kcal/mol). Potentially owing to ring strain and stabilization from oxonium resonance, arenium **INT2-p** is thermodynamically more stable than **INT2-m**. The alkyl shift of **INT2-p** is energetically feasible, given that the deprotonation step is not attainable from **INT2-p**. These calculations support the anisyl substituent (**113**, Scheme 2.3) proceeding through either **Path 1** or **Path 2** since $\Delta\Delta G^{\ddagger}$ is only 0.6 kcal/mol. Because of the small energy difference between **Path 1** and **Path 2**, we carried

out further computations to probe the influence of electronic effects (Scheme 2.6). Here, we found that the formation of 8-membered ring **INT2-p'** originating from the electron-rich carbon *para* to methoxy group was considerably favorable relative to both **Path 1** and **Path 2** from **INT1**, suggesting a strong electronic bias in **INT1**.

Scheme 2.5 *Computational investigation of the medium-sized ring formation via vinyl carbocations.*

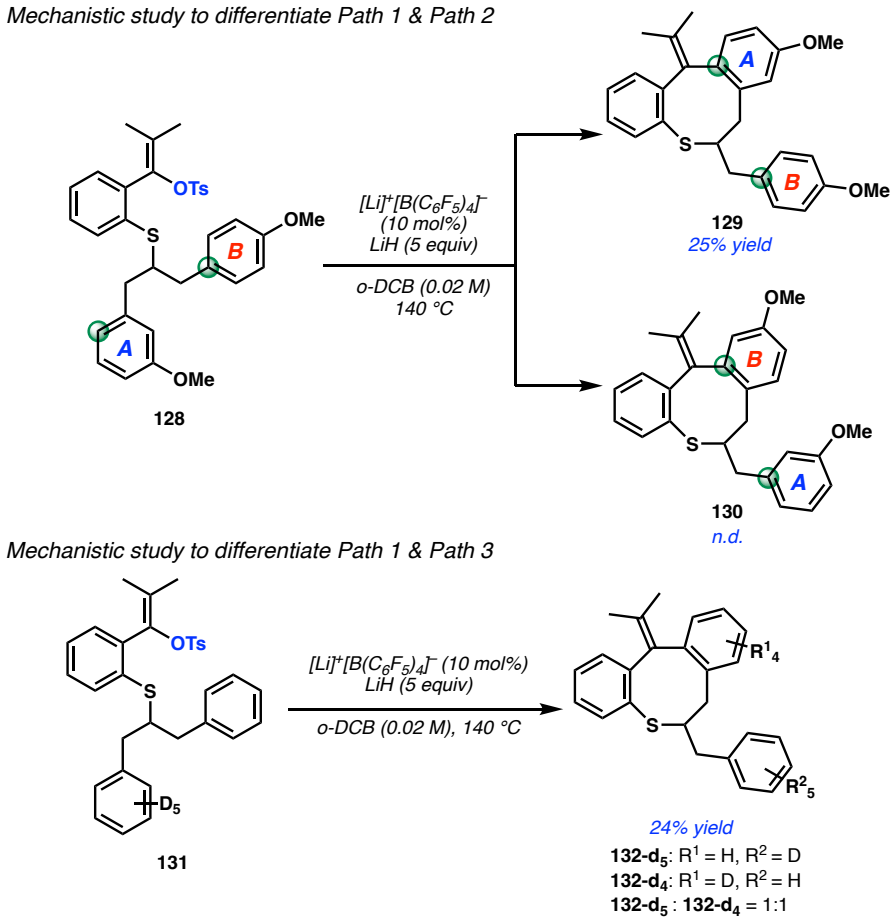


Scheme 2.6 *Computational investigation of methoxy group position influence on the medium-sized ring formation.*



Therefore, vinyl tosylate **128** was designed to experimentally probe the influence of electronic effects on mechanism. Tosylate **128** has two aromatic nucleophiles (green balls highlight the most nucleophilic positions). If **Path 1** were operative, ring A would incorporate into the product (**129**, Scheme 2.7). Conversely, if 7-membered ring formation occurred first, as in **Path 2,** ring B would incorporate into the cyclic scaffold (**130**). Interestingly, tosylate **128** favored the formation of **129** in 25% yield, although the reaction led to a complex mixture. Various analytical techniques including NMR and LC-MS suggested this was the major cyclization product.

Scheme 2.7 *Experimental mechanistic study with branched vinyl tosylate precursors.*



From these calculations and experiments, direct C–H insertion (**Path 3**) could not be excluded. Thus, we prepared vinyl tosylate **131** to probe the feasibility of **Path 3**. Under the standard reaction condition, a mixture of **132-d$_5$** and **132-d$_4$** was obtained with a distribution of roughly 1:1. This result was inconsistent with **Path 3**, where a primary KIE in the putative product-determining step would provide a larger ratio between **132-d$_5$** and **132-d$_4$**. Overall, the reactions of vinyl tosylates **128** and **131** both support **Path 1** as a potential reaction mechanism, consistent with canonical Friedel–Crafts reactivity.

2.5 CONCLUSION

In conclusion, we have discovered a method to access medium-sized rings via vinyl carbocation intermediates. Vinyl tosylates are used as the precursor and ionized into vinyl carbocations under the Li-WCA catalysis system. It is followed by an intramolecular Friedel–Crafts reaction with aryl nucleophiles to form medium-sized rings. These discoveries further demonstrate the application of vinyl cations in chemical synthesis.

2.6 CONTRIBUTION AND ACKNOWLEDGEMENT

The MicroED structure analyses in sections **2.2** and **2.3** were completed in collaboration with Dr. Jessica E. Burch, Dr. David A. Delgadillo, and Dr. Lee-Joon Kim. The substrate study in section **2.3** was completed in collaboration with Dr. Stasik Popov. The computational analysis (DFT) in section **2.4** was completed in collaboration with Dr. Woojin Lee.

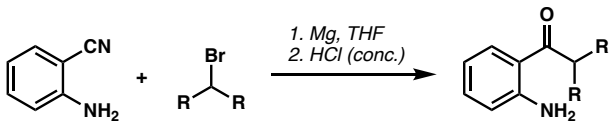
2.7 EXPERIMENTAL SECTION

2.7.1 Materials and methods

Unless otherwise stated, all reactions were performed in a VAC glovebox under nitrogen atmosphere with ≤ 3.0 ppm O_2 levels. All glassware and stir-bars were dried in a 160 °C oven for at least 12 hours and dried *in vacuo* before use. All liquid substrates were rigorously dried (over CaH_2 or filtered through dry neutral aluminum oxide) before use. Ethyl

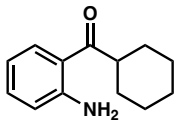
ether, tetrahydrofuran, dichloromethane, dimethylformamide, toluene, and hexanes were degassed and dried in a JC Meyer solvent system. Acetonitrile, triethylamine, and pyridine were distilled over CaH_2. 1,2-dichlorobenzene was degassed and dried in a JC Meyer solvent system and stored inside the glovebox for benchtop Friedel-Crafts reactions. Solid substrates were dried over P_2O_5. $[Li]^+[B(C_6F_5)_4]^-$ salts were synthesized according to literature procedure.[45] Thin layer chromatography (TLC) was performed using Millipore silica gel 60 F_{254} pre-coated plates (0.25 mm) and visualized by UV fluorescence quenching. SiliaFlash P60 silica gel (230-400 mesh) was used for flash chromatography. NMR spectra were recorded on a Bruker AV-400 (^1H, ^{13}C), Bruker DRX-500 (^1H, ^{13}C), and Bruker AV-500 (^1H, ^{13}C). ^1H NMR spectra are reported relative to $CDCl_3$ (7.26 ppm) unless noted otherwise. Data for ^1H NMR spectra are as follows: chemical shift (ppm), multiplicity, coupling constant (Hz), and integration. Multiplicities are as follows: s = singlet, d = doublet, t = triplet, dd = doublet of doublet, dt = doublet of triplet, ddd = doublet of doublet of doublet, td = triplet of doublet, tt = triplet of triplet, quint = quintet, sept = septet, and m = multiplet. ^{13}C NMR spectra are reported relative to $CDCl_3$ (77.0 ppm) unless noted otherwise. IR Spectra were record on a Perkin Elmer 100 spectrometer and are reported in terms of frequency absorption (cm^{-1}). High resolution mass spectra (HR-MS) were recorded on a Waters (Micromass) GCT Premier spectrometer, a Waters (Micromass) LCT Premier, an Agilent GC EI-MS, and are reported as follows: m/z (% relative intensity). Purification by preparative HPLC was done on an Agilent 1200 series instrument with a reverse phase Alltima C_{18} (5m, 25 cm length, 1 cm internal diameter) column. Unless noted otherwise, aluminum dry bath heating blocks were used as the heating source for the reactions that require heating.

2.7.2 Preparation of vinyl tosylate substrates



Representative scheme for the reaction between Grignard reagent and aryl nitrile.

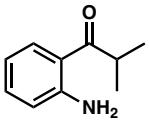
General procedure 1: Magnesium (3.0 equiv) was put into a flame-dried three-neck flask equipped with a condenser. THF (12.3 equiv) was then added into the flask. Alkyl bromide (1.0 equiv) was added slowly into the flask to keep the solution under gentle reflux. After the formation of the Grignard reagent, cooled the solution down to 0 °C and 2-aminobenzonitrile (3.0 equiv) in THF (36.9 equiv) was added dropwise. The reaction was run overnight. After this the reaction was quenched with water and concentrated hydrochloric acid to make the pH down to 1. Then it was extracted with ethyl ether three times. The combined organic phase was washed with saturated sodium bicarbonate solution and brine. It was dried with magnesium sulfate, filtered, and concentrated to give the crude product. The crude product was purified via flash column chromatography to give the product.



(2-aminophenyl)(cyclohexyl)methanone (S2).

Synthesized according to general procedure 1 starting from 2-aminobenzonitrile (3.00 g, 0.0254 mol). Crude product was purified *via* flash column chromatography using 20% ethyl ether in hexanes to give the product as a yellow solid (2.51 g, 48.6% yield).

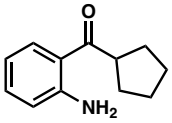
^{1}H NMR data matches previous report.[25]



1-(2-aminophenyl)-2-methylpropan-1-one (S3).

Synthesized according to general procedure 1 starting from 2-aminobenzonitrile (4.00 g, 0.0423 mol). Crude product was purified *via* flash column chromatography using 10% ethyl ether in hexanes to give the product as a yellow solid (5.45 g, 78.9% yield).

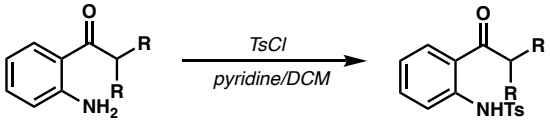
^{1}H NMR data matches previous report.[26]



(2-aminophenyl)(cyclopentyl)methanone (S4).

Synthesized according to general procedure 1 starting from 2-aminobenzonitrile (9.24 g, 0.0783 mol). Crude product was purified *via* flash column chromatography using 10% ethyl ether in hexanes to give the product as a white solid (13.32 g, 88.8% yield).

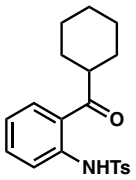
^{1}H NMR data matches previous report.[27]



Representative scheme for N-tosylation of anilines.

General Procedure 2: To a round bottom flask was added aniline (1.0 equiv) followed by DCM (13.0 equiv) and pyridine (7.0 equiv). This was cooled to 0 °C and then tosyl chloride (1.42 equiv) was added. The reaction was warmed up to room temperature and stirred for 12 hours. The reaction was diluted with additional DCM (15 equiv) and water. The layers were separated and the aqueous later was extracted twice more with DCM. The combined organics were washed 1M aqueous HCl, water, and brine in that order and the dried over magnesium

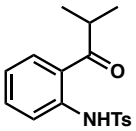
sulfate, filtered, and concentrated. The crude product was purified by flash column chromatography to give pure material as a white solid.



***N*-(2-(cyclohexanecarbonyl)phenyl)-4-methylbenzenesulfonamide (S5).**

Synthesized according to general procedure 2 starting from the corresponding aniline **S2** (14.9 g, 0.0733 mol). Crude product was purified *via* flash column chromatography using 20% ethyl acetate in hexanes to give sulfonamide **S5** as a white solid (26.2 g, 80% yield).

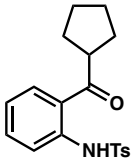
^{1}H NMR data matches previous report.[28]



***N*-(2-isobutyrylphenyl)-4-methylbenzenesulfonamide (S6).**

Synthesized according to general procedure 2 starting from the corresponding aniline **S3** (4.00 g, 0.0245 mol). Crude product was purified *via* flash column chromatography using 30% ethyl acetate in hexanes to give sulfonamide **S6** as a white solid (5.15 g, 66% yield).

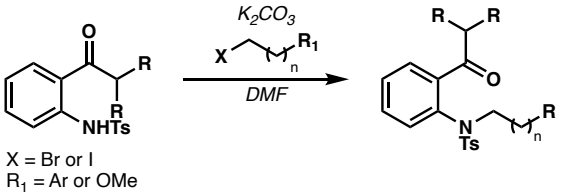
^{1}H NMR data matches previous report.[28]



***N*-(2-(cyclopentanecarbonyl)phenyl)-4-methylbenzenesulfonamide (S7).**

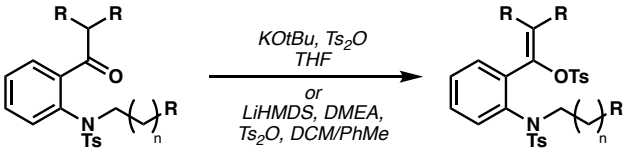
Synthesized according to general procedure 2 starting from the corresponding aniline **S4** (11.8 g, 0.0625 mol). Crude product was purified *via* flash column chromatography using 20% ethyl acetate in hexanes to give sulfonamide **S7** as a white solid (10.43 g, 48.59% yield).

^{1}H NMR data matches previous report.[29]



Representative scheme for N-alkylation of sulfonamides.

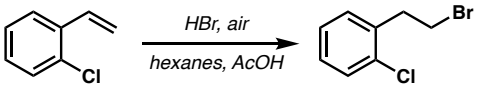
General Procedure 3: To an oven dried 20 mL scintillation vial was added sulfonamide (1.0 equiv) followed by DMF (13.0 equiv). To the solution was added and potassium carbonate (2.0 equiv) and alkyl iodide/bromide (2.0 equiv unless noted) under a stream of N_2. The vial was sealed and heated to 100 °C for 24 h. The reaction mixture was cooled to rt, diluted with water and ether. The layers were separated, and the aqueous layer was extracted with ether (3x). The combined organics were washed with water (3x) and brine (1x) then dried over $MgSO_4$, filtered, and concentrated to give crude product. The crude product was purified by flash column chromatography.



Representative scheme for N-alkylation of sulfonamides.

General Procedure 4 (KO*t*Bu): The corresponding ketone (1 equiv) was dissolved in THF (36.9 equiv) and cooled to 0 °C. To this was added a solution of potassium *tert*-butoxide (1.5 equiv) in THF (18.4 equiv). This was stirred 1.5 hours and then tosic anhydride (1.5 equiv) was added and the reaction was warmed up to rt. After 4 hours, the reaction mixture (generally a thick slurry) was diluted with ethyl acetate. This was washed with water (x1) and brine (x1) then dried over $MgSO_4$, filtered, and concentrated to give crude vinyl tosylate. This was purified by flash column chromatography to give pure vinyl tosylate.

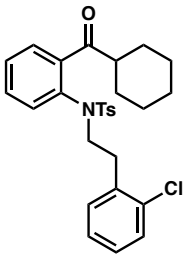
General Procedure 5 (LiHMDS/DMEA): Followed established literature procedure[16]. Inside a glovebox, LiHMDS (2.0 equiv) was dissolved in dry toluene (20.8 equiv) inside a round bottom flask which was then removed from the glovebox. To this was added distilled *N,N*-dimethylethylamine (DMEA, 2.0 equiv) and ketone (1.0 equiv) in dry toluene (9.4 equiv). After stirring for 20 minutes, tosic anhydride (2.0 equiv) in DCM (39.0 equiv) was added and this was stirred for one hour at room temperature. The reaction was then diluted with diethyl ether and 0.25 M aqueous NaOH. The layers were separated and the aqueous was extracted with diethyl ether (x3). The combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated to give crude vinyl tosylate. This was purified by flash column chromatography to give pure vinyl tosylate.



1-(2-bromoethyl)-2-chlorobenzene (S8).

1-chloro-2-vinylbenzene (3.45 g, 3.15 mL, 25.0 mmol) in hexanes (112.5 mL) was stirred at 0 °C and the air was bubbled through the solution for 1h. Hydrobromic acid in acetic acid (9.19 mL, 52.5 mmol, 33% w/V) was then added, and the reaction went in the closed flask for 20 min. The reaction solution was washed with saturated sodium bicarbonate solution and brine. Then it was dried with sodium sulfate and concentrated to give the crude product. The product was purified via flash column chromatography using hexanes to give the product as a colorless liquid (3.85 g, 70.2% yield).

^{1}H NMR data matches previous report.[30]



***N*-(2-chlorophenethyl)-*N*-(2-(cyclohexanecarbonyl)phenyl)-4-methylbenzenesulfonamide (S9).**

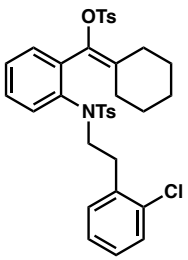
Synthesized according to general procedure 3 starting from the corresponding sulfonamide **S5** (0.54 g, 0.0015 mol) and 1-(2-bromoethyl)-2-chlorobenzene **S8** (1.31 g, 0.00600 mol). Crude product was purified via flash column chromatography using 25% ethyl ether in hexanes to give sulfonamide **S9** as a white powder (0.50 g, 67% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.48 (d, *J* = 8.3 Hz, 2H), 7.39 (ddd, *J* = 7.5, 7.5, 1.3 Hz, 1H), 7.33 (ddd, *J* = 7.8, 7.8, 1.8 Hz, 1H), 7.29 (m, 1H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.17 (m, 3H), 6.78 (dd, *J* = 7.9, 1.2 Hz, 1H), 3.95 (m, 1H), 3.49 (m, 1H), 3.42 (tt, *J* = 10.8, 3.4 Hz, 1H), 3.10 (m, 1H), 2.94 (m, 1H), 2.41 (s, 3H), 2.11 (m, 1H), 1.94-1.56 (m, 5H), 1.46-1.22 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 206.8, 143.6, 141.8, 136.8, 136.0, 135.5, 134.2, 131.0, 130.6, 129.5, 129.4, 129.3, 128.2, 128.1, 128.0, 127.0, 51.3, 49.3, 32.8, 29.2, 26.0, 25.9, 21.4.

FTIR (Neat film NaCl): 3065, 2928, 2853, 1690, 1596, 1444, 1351, 1159, 1092, 580

HR-MS (ESI-MS) m/z: [M+Na]+ Calc'd for $C_{28}H_{30}ClNO_3SNa$ 518.1533; Found 518.1528.



(2-((*N*-(2-chlorophenethyl)-4-methylphenyl)sulfonamido)phenyl)(cyclohexylidene)methyl-4-methylbenzenesulfonate (101).

Synthesized according to general procedure 4 starting from the corresponding ketone **S9** (1.47 g, 2.96 mmol). Crude product was purified via flash column chromatography using benzene to give vinyl tosylate **101** as a white solid (0.66 g, 34% yield).

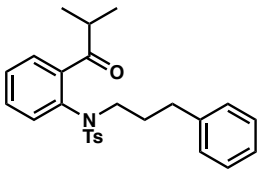
*^{1}H NMR had poor resolution at room temperature, so ^{1}H NMRs are reported below at 70 °C.

^{1}H NMR (500 MHz, $CDCl_3$, 70 °C) δ 7.71 (d, *J* = 7.8 Hz, 2H), 7.57 (d, *J* = 7.8 Hz, 2H), 7.44 (br s, 1H), 7.31 (m, 2H), 7.25 (m, 3H), 7.09 (m, 2H), 7.04 (d, *J* = 7.8 Hz, 3H), 6.97 (m, 1H), 3.60 (m, 1H), 3.44 (m, 1H), 2.79 (m, 1H), 2.59 (m, 1H), 2.49 (m, 1H), 2.43 (s, 3H), 2.32 (m, 1H), 2.26 (s, 3H), 2.10 (m, 2H), 1.68 (br s, 2H), 1.59 (br s, 2H), 1.51 (br s, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 144.4, 143.4, 139.0, 136.8, 136.39, 136.36, 135.6, 134.5, 134.1, 133.6, 130.9, 129.4, 129.3, 128.4, 128.0, 127.79, 127.76, 126.8, 50.8, 32.3, 30.6, 28.7, 27.0, 26.7, 26.2, 21.4, 21.3.

FTIR (Neat film NaCl): 3066, 2973, 2928, 2855, 1597, 1475, 1444, 1356, 1176, 1160, 656, 571, 552.

HR-MS (ESI-MS) m/z: [M+Na]+ Calc'd for $C_{35}H_{36}ClNO_5S_2Na$ 672.1621; Found 672.1607.



***N*-(2-isobutyrylphenyl)-4-methyl-*N*-(3-phenylpropyl)benzenesulfonamide (S10).**

Synthesized according to general procedure 3 starting from the corresponding sulfonamide **S6** (2.00 g, 0.00630 mol) and (3-iodopropyl)benzene (2.32 g ,0.00945 mol). Crude product

was purified *via* flash column chromatography using 30% ether in hexanes to give sulfonamide **S10** as a white solid (2.60 g, 95% yield).

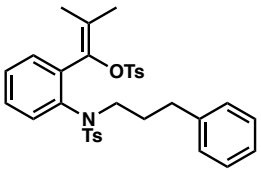
*NMR had poor resolution at room temperature, so NMRs are reported below at 70 °C.

^{1}H NMR (500 MHz, $CDCl_3$, 70 °C) δ 7.55 (d, *J* = 7.5 Hz, 1H), 7.49 (s, 2H), 7.35 (t, *J* = 7.5 Hz, 1H), 7.30 (t, *J* = 7.6 Hz, 1H), 7.23 (d, *J* = 7.6 Hz, 4H), 7.15 (t, *J* = 7.4 Hz, 1H), 7.09 (d, *J* = 7.3 Hz, 2H), 6.79 (s, 1H), 3.64 – 3.55 (m, 3H), 2.59 (t, *J* = 7.5 Hz, 2H), 2.41 (s, 3H), 1.98 – 1.85 (m, 2H), 1.24 (s, 3H), 1.23 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$, 70 °C) δ 207.4, 143.5, 141.7, 141.0, 137.2, 135.8, 130.5, 129.3, 129.2, 128.3, 128.2, 128.0, 127.9, 125.9, 51.6, 39.3, 33.1, 29.5, 21.3, 18.8.

FTIR (Neat film NaCl): 3063, 3027, 2971, 2932, 2871, 1694, 1596, 1348, 1161, 980, 700, 658, 576.

HR-MS (CI-MS) m/z: [M+H]+ Calc'd for $C_{26}H_{30}NO_3S$ 436.1946; Found 436.1946.



2-methyl-1-(2-((4-methyl-*N*-(3-phenylpropyl)phenyl)sulfonamido)phenyl)prop-1-en-1-yl-4-methylbenzenesulfonate (S11).

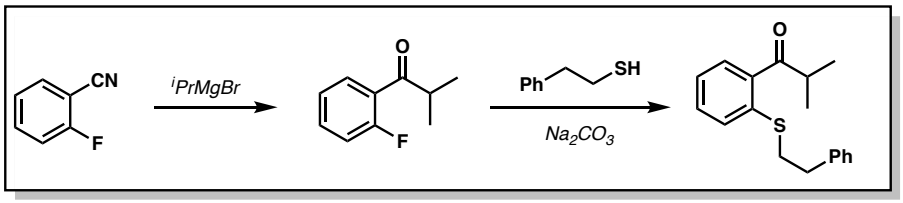
Synthesized according to general procedure 4 starting from the corresponding ketone **S10** (2.60 g, 0.00597 mol). Crude product was purified *via* flash column chromatography using 25% diethyl ether in hexanes to give vinyl tosylate **S11** as a yellow solid (1.10 g, 31% yield).

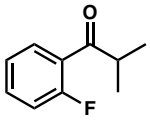
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (app d, *J* = 8.2 Hz, 4H), 7.40 (s, 1H), 7.31 – 7.21 (m, 6H), 7.20 – 7.15 (m, 1H), 7.12 (d, *J* = 8.1 Hz, 2H), 7.03 (d, *J* = 6.9 Hz, 2H), 6.92 (s, 1H), 3.41 – 3.18 (m, 2H), 2.42 (s, 3H), 2.36 (t, *J* = 7.6 Hz, 2H), 2.33 (s, 3H), 1.80 (s, 3H), 1.76 – 1.65 (m, 2H), 1.60 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 144. 5, 143.3, 140.9, 138.9, 138.0, 136.4, 134.1, 133.6, 129.9, 129.6, 129.3, 129.28, 129.26, 128.23, 128.21, 127.96, 127.91, 127.7, 125.8, 51.0, 32.9, 29.1, 21.5, 21.4, 20.3, 18.6.

FTIR (Neat film NaCl): 3063, 3027, 2971, 2932, 2871, 1694, 1596, 1495, 1348, 1161, 980, 700, 658, 576.

HR-MS (ESI-MS) m/z: [M+H]+ Calc'd for $C_{33}H_{36}NO_5S_2$ 590.2035; Found 590.2061.

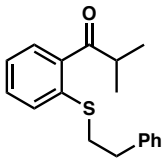




1-(2-fluorophenyl)-2-methylpropan-1-one (S12).

Magnesium (0.602 g, 24.8 mmol) was put into a flame-dried three-neck flask equipped with a condenser. THF (24 mL) was then added into the flask. 2-bromopropane (3.02 g, 2.33 mL, 24.8 mmol) was added slowly into the flask to keep the solution under gentle reflux. After the formation of the Grignard reagent, cooled the solution down to 0 °C and 2-fluorobenzonitrile (2.21 g, 20.6 mmol) in THF (20 mL) was added dropwise. The reaction was run overnight. After this the reaction was quenched with water and concentrated hydrochloric acid to make the pH down to 1. Then it was extracted with ethyl ether three times. The combined organic phase was washed with saturated sodium bicarbonate solution and brine. It was dried with magnesium sulfate, filtered, and concentrated to give the crude product. The crude product was purified via flash column chromatography using 2% ethyl acetate in hexanes to give the product as an oil (1.35 g, 39.3% yield).

^{1}H NMR data matches previous report.[31]



2-methyl-1-(2-(phenethylthio)phenyl)propan-1-one (S13).

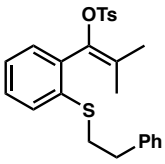
2-phenylethane-1-thiol (1.96 g, 1.91 mL, 14.2 mmol), 1-(2-fluorophenyl)-2-methylpropan-1-one (**S12**) (1.18 g, 7.10 mmol), sodium carbonate (3.01 g, 28.4 mmol), and DMF (7 mL) was added to a flask. The solution was heated at 100 °C in the silicone oil bath overnight. After this, ethyl acetate and water was added into the solution. After the separation, the organic phase was washed with water three times and then washed with brine. The organic phase was dried with sodium sulfate and concentrated to give the crude product. The crude product was purified with flash column chromatography with 2% ethyl acetate in hexanes to give the product **S13** as a pale-yellow oil (0.53 g, 26% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J = 7.7 Hz, 1H), 7.41 (m, 2H), 7.30 (m, 2H), 7.22 (m, 4H), 3.44 (sept, J = 6.8 Hz, 1H), 3.15 (m, 2H), 2.94 (m, 2H), 1.20 (d, J = 6.9 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 207.3, 140.3, 138.3, 137.9, 131.2, 128.9, 128.6, 128.5, 128.1, 126.5, 124.8, 38.2, 35.0, 34.9, 18.8.

FTIR (Neat film NaCl): 3061, 3027, 2969, 2930, 2870, 1691, 1585, 1454, 1431, 1214, 1075, 974, 738, 697.

HR-MS (CI-MS) m/z: [M+H]+ Calc'd for $C_{18}H_{21}OS$ 285.1313; Found 285.1323.



2-methyl-1-(2-(phenethylthio)phenyl)prop-1-en-1-yl 4-methylbenzenesulfonate (S14).

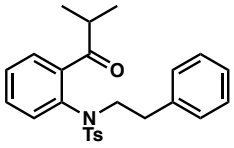
Synthesized according to general procedure 5 starting from the corresponding ketone **S13** (0.34 g, 0.0012 mol). Crude product was purified via flash column chromatography using 40% ether in hexanes to give vinyl tosylate **S14** as a pale yellow oil (0.29 g, 55% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.4 Hz, 2H), 7.29 (m, 2H), 7.23 (m, 2H), 7.16 (m, 3H), 7.07 (m, 2H), 7.02 (d, *J* = 7.7 Hz, 2H), 2.97 (m, 2H), 2.79 (m, 2H), 2.29 (s, 3H), 1.92 (s, 3H), 1.60 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 143.9, 140.3, 139.6, 137.7, 134.4, 133.5, 132.6, 129.1, 129.0, 128.6, 128.4, 128.2, 127.8, 127.3, 126.5, 124.8, 35.4, 34.2, 21.5, 19.9, 18.4.

FTIR (Neat film NaCl): 3062, 3032, 2918, 2856, 1598, 1496, 1454, 1364, 1176, 1086, 1071, 990, 823, 809, 792.

HR-MS (ESI-MS) m/z: [M+Na]+ Calc'd for $C_{25}H_{26}O_3S_2Na$ 461.1221; Found 461.1209.



***N*-(2-isobutyrylphenyl)-4-methyl-*N*-phenethylbenzenesulfonamide (S15).**

Synthesized according to general procedure 3 starting from the corresponding sulfonamide **S6** (2.00 g, 0.0063 mol) and (2-iodoethyl)benzene (2.19 g. 0.00945 mol). Crude product was purified via flash column chromatography using 30% ether in hexanes to give sulfonamide **S15** as a white solid (1.70 g, 64% yield).

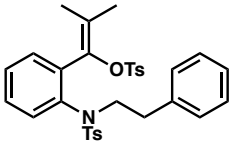
*NMR had poor resolution at room temperature, so NMRs are reported below at 70 °C.

^{1}H NMR (500 MHz, $CDCl_3$, 70 °C) δ 7.58 (d, *J* = 7.6 Hz, 1H), 7.53 (d, *J* = 7.8 Hz, 2H), 7.37 (t, *J* = 7.5 Hz, 1H), 7.33 (t, *J* = 7.7 Hz, 1H), 7.23 (d, *J* = 7.3 Hz, 4H), 7.17 (d, *J* = 7.3 Hz, 1H), 7.09 (d, *J* = 7.4 Hz, 2H), 6.85 (d, *J* = 7.7 Hz, 1H), 3.82 (s, 2H), 3.58 (sept, *J* = 6.9 Hz, 1H), 2.90 (s, 2H), 2.40 (s, 3H), 1.24 (s, 3H), 1.23 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$, 70 °C) δ 207.2, 143.6, 141.6, 138.2, 137.0, 135.7, 130.6, 129.3, 129.2, 128.5, 128.4, 128.0, 127.9, 126.4, 53.3, 39.2, 34.8, 31.4, 18.8.

FTIR (Neat film NaCl): 2924, 1693, 1596, 1455, 1349, 1163, 1093, 1056, 1033, 1017, 815, 688, 579.

HR-MS (CI-MS) m/z: [M+H]+ Calc'd for $C_{25}H_{28}NO_3S$ 422.1790; Found 422.1790.



2-methyl-1-(2-((4-methyl-*N*-phenethylphenyl)sulfonamido)phenyl)prop-1-en-1-yl-4-methylbenzenesulfonate (S16).

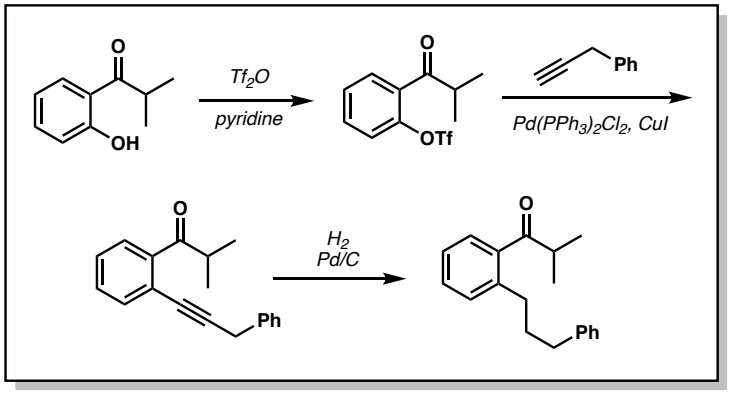
Synthesized according to general procedure 4 starting from the corresponding ketone **S15** (1.70 g, 0.00403 mol). Crude product was purified *via* flash column chromatography using 25% diethyl ether in hexanes to give vinyl tosylate **S16** as a yellow solid (0.76 g, 33% yield).

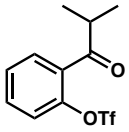
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 – 7.59 (m, 2H), 7.56 (d, *J* = 8.0 Hz, 2H), 7.51 – 7.44 (m, 1H), 7.38 – 7.29 (m, 2H), 7.29 – 7.23 (m, 2H), 7.23 – 7.14 (m, 3H), 7.07 (d, *J* = 8.1 Hz, 2H), 6.93 (d, *J* = 6.5 Hz, 3H), 3.60 (d, *J* = 10.9 Hz, 1H), 3.36 (td, *J* = 13.0, 4.9 Hz, 1H), 2.73 (td, *J* = 12.7, 5.3 Hz, 1H), 2.48 (td, *J* = 12.7, 4.8 Hz, 1H), 2.42 (s, 3H), 2.29 (s, 3H), 1.81 (s, 3H), 1.65 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.5, 143.5, 139.0, 138.5, 137.9, 136.1, 134.1, 133.8, 130.2, 129.5, 129.4, 129.1, 128.6, 128.3, 128.2, 127.9, 126.3, 53.1, 34.5, 21.6, 21.5, 20.4, 18.69.

FTIR (Neat film NaCl): 3064, 3028, 2921, 1598, 1487, 1446, 1352, 1305, 1190, 1177, 1161, 1093, 1083, 814.

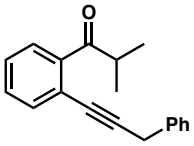
HR-MS (ESI-MS) m/z: [M+Na]+ Calc'd for $C_{32}H_{33}NO_5S_2Na$ 598.1698; Found 598.1689.





2-isobutyrylphenyl trifluoromethanesulfonate (S17).

1-(2-Hydroxyphenyl)-2-methylpropan-1-one (9.60 g, 58.5 mmol, 1.0 equiv) was dissolved in pyridine (56.9 g, 58.0 mL, 720 mmol, 12.0 equiv) and cooled to 0 °C. Triflic anhydride (19.8 g, 70.2 mmol, 1.2 equiv) was added dropwise. The reaction was warmed up to rt and stirred for 12h. Ethyl acetate (150 mL) was added to the reaction it was washed with aqueous 1M $CuSO_4$ (50 mL x 4) and brine (100 mL x 1). The organic layer was dried over $MgSO_4$, filtered and concentrated to give crude aryl triflate. Crude material was purified by silica flash column chromatography using 5% ethyl acetate in hexanes to give pure aryl triflate as yellow oil **S17** (12.9 g, 75% yield). Spectral data match those reported in the literature.[32]



2-methyl-1-(2-(3-phenylprop-1-yn-1-yl)phenyl)propan-1-one (S18).

$Ph(PPh_3)_2Cl_2$ (237 mg, 0.337 mmol) and CuI (64.2 mg, 0.337 mmol) were added into a flame-dried Schlenk flask. Triethylamine (46 mL) and 2-isobutyrylphenyl trifluoromethanesulfonates (**S17**) (2.00 g, 6.74 mmol) were then added under nitrogen

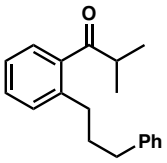
atmosphere. And at last prop-2-yn-1-ylbenzene (2.34 g, 2.52 mL, 20.2 mmol) was added and the reaction was heated at 70 °C in the silicone oil bath overnight. The reaction was cooled down to room temperature and quenched with saturated ammonium chloride solution. The mixture was extracted with ethyl acetate three times, and the combined organic phase was washed with water two times and brine. It was dried with magnesium sulfate, filtered, and concentrated to give the crude product. The crude product was purified via flash column chromatography using 10% ethyl ether in hexanes to give the product **S18** as an oil (0.62 g, 35% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (dd, *J* = 7.5, 1.4 Hz, 1H), 7.46 (dd, *J* = 7.5, 1.4 Hz, 1H), 7.37 (m, 6H), 7.26 (tt, *J* = 7.8, 1.6 Hz, 1H), 3.85 (s, 2H), 3.62 (sept, *J* = 6.9 Hz, 1H), 1.12 (d, *J* = 6.8 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 208.9, 142.2, 136.3, 133.5, 130.2, 128.6, 128.0, 127.8, 127.6, 126.8, 121.2, 92.7, 81.0, 39.1, 26.0, 18.5.

FTIR (Neat film NaCl): 3386, 3063, 3030, 2972, 2932, 2873, 2199, 1768, 1690, 1593, 1454, 1214, 980, 757, 698.

HR-MS (ESI-MS) m/z: [M+Na]+ Calc'd for $C_{19}H_{18}ONa$ 285.1255; Found 285.1243.



2-methyl-1-(2-(3-phenylpropyl)phenyl)propan-1-one (S19).

Alkyne **S18** (0.750 g, 2.86 mmol) was dissolved in ethanol (50 mL). Pd/C (0.103 g, 0.0972 mmol, 10% Pd) was then added. Hydrogen gas was blown into the solution for a while and the reaction was run under hydrogen atmosphere (1 atm) overnight. The reaction solution was filtered through celite and concentrated to give the crude product. The crude product

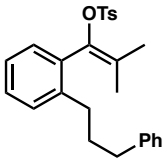
was purified by flash chromatography with 4% ether in hexanes to give the product **S19** (0.63 g, 83% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 7.8 Hz, 1H), 7.36 (t, *J* = 7.0 Hz, 1H), 7.31-7.21 (m, 4H), 7.21-7.14 (m, 3H), 3.30 (sept, *J* = 6.9 Hz, 1H), 2.76 (m, 2H), 2.68 (t, *J* = 7.8 Hz, 2H), 1.93 (m, 2H), 1.16 (d, *J* = 6.9 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 209.6, 142.3, 141.7, 138.8, 130.7, 130.5, 128.5, 128.3, 127.4, 125.8, 125.7, 39.1, 35.9, 33.5, 33.4, 18.7.

FTIR (Neat film NaCl): 3062, 3026, 2969, 2931, 2869, 1686, 1454, 1221, 976, 745, 633.

HR-MS (ESI-MS) m/z: [M+H]+ Calc'd for $C_{19}H_{23}O$ 267.1749; Found 267.1750.



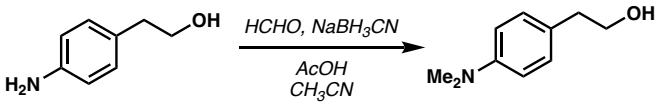
2-methyl-1-(2-(3-phenylpropyl)phenyl)prop-1-en-1-yl 4-methylbenzenesulfonate (S20). Synthesized according to general procedure 5 starting from the corresponding ketone **S19** (0.64 g, 0.0024 mol). Crude product was purified via flash column chromatography using 20% ethyl acetate in hexanes to give vinyl tosylate **S20** as a white solid (0.32 g, 32% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 8.4 Hz, 2H), 7.27 (t, *J* = 7.4 Hz, 2H), 7.19 (m, 2H), 7.15 (m, 1H), 7.11 (d, *J* = 6.8 Hz, 2H), 7.07 (t, *J* = 7.4 Hz, 1H), 6.98 (d, *J* = 8.2 Hz, 2H), 6.97 (t, *J* = 6.2 Hz, 1H), 2.57 (m, 1H), 2.53 (t, *J* = 7.7 Hz, 2H), 2.34 (m, 1H), 2.29 (s, 3H), 1.93 (s, 3H), 1.68 (quint, *J* = 8.0 Hz, 2H), 1.57 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 143.9, 142.3, 142.0, 140.9, 134.5, 132.6, 132.3, 129.1, 128.8, 128.4, 128.3, 127.6, 127.0, 125.7, 125.2, 35.7, 32.6, 32.0, 21.5, 19.9, 18.4.

FTIR (Neat film NaCl): 3065, 3026, 2922, 2859, 1599, 1496, 1453, 1367, 1081, 990, 823, 810.

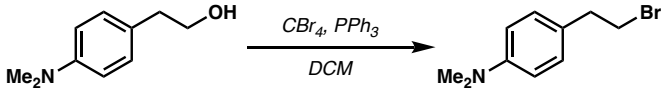
HR-MS (ESI-MS) m/z: [M+Na]+ Calc'd for $C_{26}H_{28}O_3SNa$ 443.1657; Found 443.1649.



2-(4-(dimethylamino)phenyl)ethan-1-ol (S21).

2-(4-aminophenyl)ethan-1-ol (2.06 g, 15.0 mmol) in acetonitrile (150 mL) was added formaldehyde (37% in water, 11.2 mL, 150 mmol), sodium cyanoborohydride (2.83 g, 45.0 mmol), and acetic acid (0.987 mL, 17.2 mmol). After 3 h, the reaction was basified to pH 7-8 with saturated sodium bicarbonate solution. The mixture was extracted with ethyl acetate three times. The combined organic phase was washed with brine, dried with magnesium sulfate, and concentrated to give the crude product. The crude product was purified *via* flash column chromatography using 20% methanol in ethyl ether with 5% triethylamine to give the product **S21** as yellow oil (2.43 g, 98.0% yield).

^{1}H NMR data matches previous report.[33]

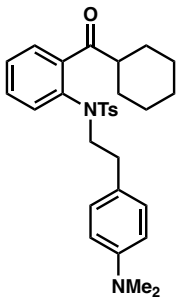


4-(2-bromoethyl)-*N*,*N*-dimethylaniline (S22).

2-(4-(dimethylamino)phenyl)ethan-1-ol **S21** (1.65 g, 10.0 mmol) and carbon tetrabromide (4.97 g, 15.0 mmmol) were dissolved in DCM (30 mL). It was cooled to 0 °C, and a solution of triphenylphosphine (2.62 g, 10.0 mmol) in DCM (20 mL) was added into it. The reaction was warmed to room temperature and run overnight. It was washed with water, and after separation the aqueous phase was extracted with DCM two times. The combined organic phase was dried with magnesium sulfate and then filtered. It was concentrated to give the crude product. The crude product was purified *via* flash column chromatography using 11%

ethyl ether in hexanes with 5% triethylamine to give bromide **S22** as white solid (1.10 g, 48.2% yield).

^{1}H NMR data matches previous report.[34]



N-(2-(cyclohexanecarbonyl)phenyl)-N-(4-(dimethylamino)phenethyl)-4-methylbenzene sulfonamide (S23).

Synthesized according to general procedure 3 starting from the corresponding sulfonamide **S5** (0.86 g, 0.0024 mol) and 4-(2-bromoethyl)-N,N-dimethylaniline **S22** (1.09 g, 0.00482 mol). Crude product was purified via flash column chromatography using 20% ethyl acetate in hexanes to give sulfonamide **S23** as a white powder (0.50 g, 41% yield).

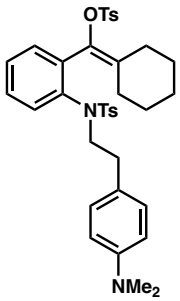
*NMR had poor resolution at room temperature, so ^{1}H NMR is reported below at 60 °C.

^{1}H NMR (500 MHz, $CDCl_3$, 60 °C) δ 7.56 (d, *J* = 7.6 Hz, 1H), 7.52 (d, *J* = 8.0 Hz, 2H), 7.36 (dd, *J* = 7.4, 7.4 Hz, 1H), 7.32 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.23 (d, *J* = 8.0 Hz, 2H), 6.96 (d, *J* = 8.2 Hz, 2H), 6.80 (d, *J* = 7.9 Hz, 1H), 6.66 (d, *J* = 8.1 Hz, 2H), 3.73 (br s, 2H), 3.40 (tt, *J* = 11.2, 3.4 Hz, 1H), 2.90 (s, 6H), 2.77 (m, 2H), 2.41 (s, 3H), 2.01 (br s, 2H), 1.83 (d, *J* = 12.6 Hz, 2H), 1.70 (d, *J* = 12.5 Hz, 1H), 1.46 (br s, 2H), 1.37 (m, 2H), 1.28 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 207.4, 149.4, 143.7, 141.9, 136.8, 134.7, 130.7, 129.7, 129.4, 129.4, 128.5, 128.1, 128.1, 127.1, 113.0, 53.4, 49.2, 40.8, 33.8, 29.7, 28.6, 26.0, 21.6.

FTIR (Neat film NaCl): 2925, 2854, 1691, 1522, 1350, 1163, 1033, 577.

HR-MS (ESI-MS) m/z: [M+Na]+ Calc'd for $C_{30}H_{36}N_2O_3SNa$ 527.2344; Found 527.2333.



cyclohexylidene(2-((*N*-(4-(dimethylamino)phenethyl)-4-methylphenyl)sulfonamido)phenyl) methyl 4-methylbenzenesulfonate (S24).

Synthesized according to general procedure 5 starting from the corresponding ketone **S23** (0.34 g, 0.00067 mol). Crude product was purified via flash column chromatography using 50% ether in hexanes with 5% triethylamine to give vinyl tosylate **S24** as a white solid (0.18 g, 41% yield).

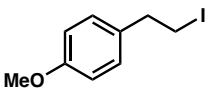
*NMR had poor resolution at room temperature, so ^{1}H NMR is reported below at 70 °C.

^{1}H NMR (500 MHz, $CDCl_3$, 70 °C) δ 7.69 (d, *J* = 7.7 Hz, 2H), 7.57 (d, *J* = 7.8 Hz, 2H), 7.43 (br s, 1H), 7.29 (m, 2H), 7.26 (d, *J* = 7.6 Hz, 2H), 7.08 (d, *J* = 7.9 Hz, 2H), 6.98 (d, *J* = 6.6 Hz, 1H), 6.79 (d, *J* = 8.0 Hz, 2H), 6.62 (d, *J* = 8.0 Hz, 2H), 3.56 (m, 1H), 3.39 (m, 1H), 2.90 (s, 6H), 2.61 (m, 1H), 2.49 (m, 1H), 2.43 (s, 3H), 2.40 (m, 1H), 2.31 (s, 3H), 2.28 (m, 1H), 2.11 (m, 1H), 2.04 (m, 1H), 1.69 (br s, 2H), 1.59 (br s, 2H), 1.50 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 149.3, 144.2, 143.4, 139.2, 136.7, 136.2, 135.5, 134.2, 133.6, 129.4, 129.4, 129.4, 129.3, 128.7, 128.3, 128.1, 127.8, 126.4, 125.5, 112.8, 53.2, 40.8, 33.4, 30.6, 28.7, 27.0, 26.7, 26.2, 21.6, 21.6.

FTIR (Neat film NaCl): 3032, 2929, 2857, 1616, 1597, 1522, 1445, 1352, 1188, 1176, 1161, 1093, 807, 789, 572, 555.

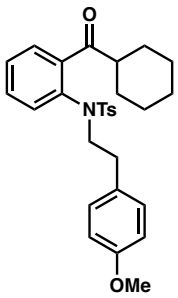
HR-MS (ESI-MS) m/z: [M+H]+ Calc'd for $C_{37}H_{43}N_2O_5S_2$ 659.2614; Found 659.2619.



1-(2-iodoethyl)-4-methoxybenzene (S25).

Iodine (3.96 g, 15.6 mmol) and triphenylphosphine (4.09g, 15.6 mmol) was added to DCM (24 mL). To the solution was added imidazole (1.15 g, 16.9 mmol) in DCM (10 mL) and stirred together for 15 min. Then the alcohol (1.98 g, 13.0 mmol) in DCM (5 mL) was added and it was stirred overnight. The reaction was washed with sodium thiosulfate solution, and the organic phase was dried with magnesium sulfate and filtered. The solution was then concentrated to give the crude product. The crude product was purified by flash column chromatography using 5% ethyl ether in hexanes to give the product as a white solid (3.15 g, 92.5% yield).

^{1}H NMR data matches previous report.[35]



***N*-(2-(cyclohexanecarbonyl)phenyl)-*N*-(4-methoxyphenethyl)-4-methylbenzenesulfonamide (S26).**

Synthesized according to general procedure 3 starting from the corresponding sulfonamide **S5** (1.02 g, 0.00286 mol) and 1-(2-iodoethyl)-4-methoxybenzene **S25** (1.50 g, 0.00572 mol). Crude product was purified via flash column chromatography using 40% ether in hexanes to give sulfonamide **S26** as a white powder (1.22 g, 86.7% yield).

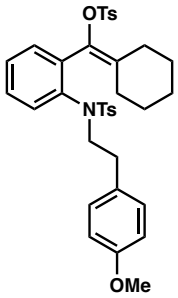
*NMR had poor resolution at room temperature, so NMRs are reported below at 70 °C.

^{1}H NMR (500 MHz, $CDCl_3$, 70 °C) δ 7.54 (m, 3H), 7.37 (t, *J* = 7.4 Hz, 1H), 7.32 (t, *J* = 7.8 Hz, 1H), 7.24 (d, *J* = 7.8 Hz, 2H), 6.99 (d, *J* = 7.4 Hz, 2H), 6.82 (d, *J* = 8.1 Hz, 1H), 6.78 (d, *J* = 6.9 Hz, 2H), 3.76 (s, 3H), 3.75 (br s, 2H), 3.36 (m, 1H), 2.81 (br s, 2H), 2.41 (s, 3H), 2.01 (br s, 2H), 1.83 (m, 2H), 1.69 (m, 1H), 1.36 (m, 5H).

^{13}C NMR (126 MHz, $CDCl_3$, 70 °C) δ 206.6, 158.4, 143.4, 141.9, 136.9, 136.0, 130.3, 129.4, 129.2, 129.1, 128.3, 127.9, 127.8, 114.1, 55.1, 53.6, 49.2, 33.9, 29.0, 25.9, 25.7, 21.2.

FTIR (Neat film NaCl): 3032, 2930, 2853, 1691, 1513, 1350, 1248, 1162, 578

HR-MS (ESI-MS) m/z: [M+H]+ Calc'd for $C_{29}H_{34}NO_4S$ 492.2209; Found 492.2229.



cyclohexylidene(2-((*N*-(4-methoxyphenethyl)-4-methylphenyl)sulfonamido)phenyl)methyl 4-methylbenzenesulfonate (S27).

Synthesized according to general procedure 5 starting from the corresponding ketone **S26** (0.58 g, 0.0012 mol). Crude product was purified via flash column chromatography using 40% ether in hexanes to give vinyl tosylate **S27** as a white solid (0.43 g, 56% yield).

*NMR had poor resolution at room temperature, so NMRs are reported below at 50 °C.

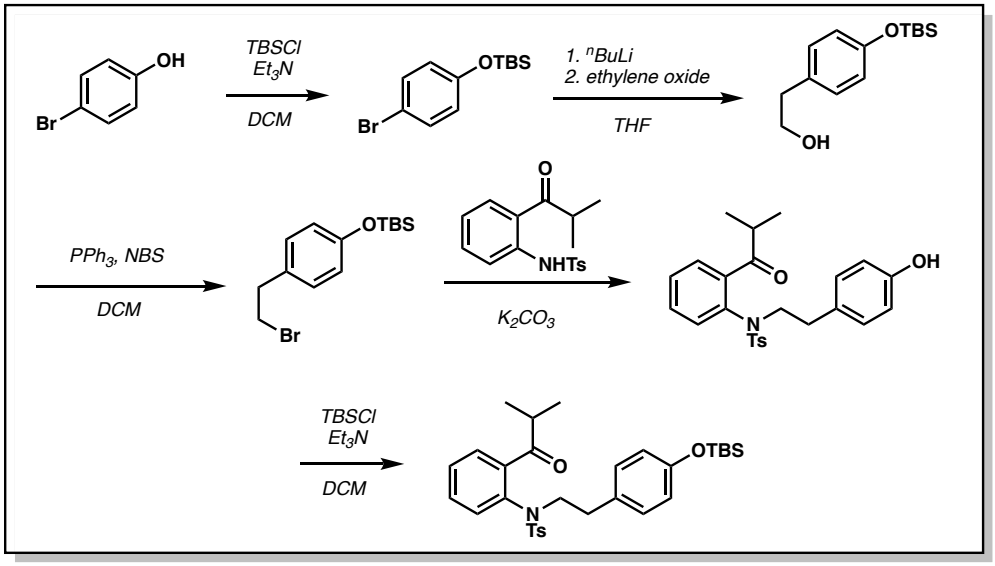
^{1}H NMR (500 MHz, $CDCl_3$, 50 °C) δ 7.67 (d, *J* = 7.9 Hz, 2H), 7.57 (d, *J* = 8.2 Hz, 2H), 7.43 (br s, 1H), 7.31 (m, 2H), 7.26 (d, *J* = 6.6 Hz, 2H), 7.09 (d, *J* = 8.0 Hz, 2H), 6.96 (br s, 1H), 6.83 (d, *J* = 8.6 Hz, 2H), 6.74 (d, *J* = 8.6 Hz, 2H), 3.76 (s, 3H), 3.59 (ddd, *J* = 13.2, 5.5, 5.5 Hz, 1H), 3.38 (ddd, *J* = 12.2, 5.0, 5.0 Hz, 1H), 2.66 (ddd, *J* = 12.8, 5.4, 5.4 Hz, 1H), 2.44 (m,

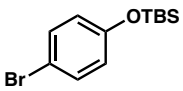
2H), 2.43 (s, 3H), 2.31 (s, 3H), 2.29 (m, 1H), 2.12 (m, 1H), 2.03 (m, 1H), 1.67 (m, 2H), 1.54 (m, 4H).

^{13}C NMR (126 MHz, $CDCl_3$, 50 °C) δ 158.1, 144.2, 143.2, 139.2, 136.6, 136.5, 135.5, 134.4, 133.5, 130.5, 129.4, 129.3, 129.2, 129.1, 128.1, 127.9, 127.6, 113.8, 55.1, 53.0, 33.5, 30.4, 28.5, 26.8, 26.6, 26.1, 21.3, 21.2.

FTIR (Neat film NaCl): 3029, 2971, 2928, 2855, 1611, 1597, 1512, 1364, 1175, 1157, 788, 656, 570, 552.

HR-MS (ESI-MS) m/z: [M+Na]+ Calc'd for $C_{36}H_{39}NO_6S_2Na$ 668.2117; Found 668.2093.



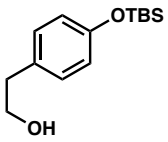


(4-bromophenoxy)(*tert*-butyl)dimethylsilane (S28).

In the DCM (50mL) solution of the 4-bromophenol (9.94 g, 57.8 mmol) and triethylamine (7.26 g, 71.7 mmol) was added the DCM (50mL) solution of *tert*-butyldimethylsilyl chloride (13.0 g, 86.7 mmol). After a day, the reaction was done. It was then diluted and washed with water 2 times until the aqueous phase was strongly acidic. The organic phase was then

washed with sat. $NaHCO_3$, dried with $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by column chromatography with 2.4% diethyl ether in hexanes as a colorless liquid (15.95g, 96.1% yield).

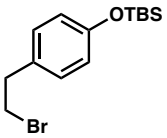
^{1}H NMR matches previous report.[36]



2-(4-((tert-butyldimethylsilyl)oxy)phenyl)ethan-1-ol (S29).

In a 3-neck flask equipped with a condenser was added **S28** (5.40 g, 18.8 mmol) and THF (38 mL). The solution was cooled down to –78°C. n-BuLi (2.06 M in hexanes, 10.0 mL, 20.7 mmol) was added dropwise, and the reaction was left at –78°C for 30 min after the addition. Then ethylene oxide (2.5 M in THF, 15.0 mL, 37.6 mmol) was added dropwise at –78°C. The reaction was warmed to 0°C for 30 min, and then it was heated at 40°C for 30 min, which was followed by reflux for 1 h. After the reaction was complete, the solution was concentrated in vacuo and then diluted with DCM and washed with 1M HCl (40 mL). The aqueous phase was extracted with DCM 2 times. The combined organic phase was washed with sat. $NaHCO_3$ and brine, dried with $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by column chromatography with 50% hexanes and 50% diethyl ether to give the product **S29** as a pale-yellow oil (1.72 g, 36.2% yield).

^{1}H NMR matches previous report.[36]



(4-(2-bromoethyl)phenoxy)(tert-butyl)dimethylsilane (S30).

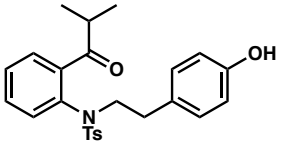
S29 (1.72 g, 6.81 mmol) was dissolved in DCM (17 mL) and the solution was cooled down to 0°C. After 10 min, triphenylphosphine (2.14 g, 8.18 mmol) and *N*-bromosuccinimide (1.46 g, 8.18 mmol) was added into the solution. After 4 hours, the reaction was complete and quenched by sat. $NaHCO_3$. The solution was extracted with DCM 3 times. The combined organic phase was washed with brine, dried with $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by column chromatography with 2.4% diethyl ether in hexanes to give the product **S30** as a colorless liquid (1.67 g, 77.7% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (d, *J* = 8.6 Hz, 2H), 6.78 (d, *J* = 8.5 Hz, 2H), 3.52 (t, *J* = 7.8 Hz, 2H), 3.09 (t, *J* = 7.8 Hz, 2H), 0.98 (s, 9H), 0.19 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 153.5, 130.6, 128.6, 119.1, 37.7, 32.3, 24.6, 17.2, –5.5.

FTIR (Neat film NaCl): 2956, 2929, 2857, 1608, 1508, 1471, 1463, 1252, 911, 837, 779.

HR-MS (CI-MS) m/z: [M]+ Calc'd for $C_{14}H_{23}OSiBr$ 314.0701; Found 314.0708.



N-(4-hydroxyphenethyl)-N-(2-isobutyrylphenyl)-4-methylbenzenesulfonamide (S31).

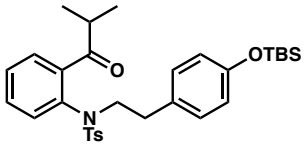
Synthesized according to general procedure 3 starting from the corresponding sulfonamide **S6** (1.26 g, 0.00396 mol) and (4-(2-bromoethyl)phenoxy)(tert-butyl)dimethylsilane **S30** (1.49 g, 0.00476 mol). Crude product was purified via flash column chromatography using 25% acetone in hexanes to give sulfonamide **S31** as a white powder (0.63 g, 36% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.46 (d, *J* = 8.1 Hz, 2H), 7.40 (td, *J* = 7.5, 1.3 Hz, 1H), 7.34 (td, *J* = 7.6, 1.8 Hz, 1H), 7.23 (d, *J* = 8.0 Hz, 2H), 6.96 (d, *J* = 8.1Hz, 2H), 6.77 – 6.70 (m, 3H), 3.95 (br, 1H), 3.66 (hepta, *J* = 6.9 Hz, 1H), 3.46 (br, 1H), 2.88 (br, 1H), 2.62 (br, 1H), 2.41 (s, 3H), 1.36 – 1.06 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 207.3, 153.3, 142.8, 140.5, 135.7, 133.7, 129.8, 129.0, 128.8, 128.7, 128.5, 127.2, 127.0, 126.4, 114.4, 52.2, 38.2, 32.8, 20.5, 18.2 (br), 17.6 (br)

FTIR (Neat film NaCl): 3377, 2973, 2931, 2871, 1690, 1614, 1595, 1516, 1444, 1347, 1214, 1159, 1090, 981, 815, 657, 577.

HR-MS (ESI-MS) m/z: [M+Na]+ Calc'd for $C_{25}H_{27}NO_4SNa$ 460.1535; Found 460.1558.



***N*-(4-((*tert*-butyldimethylsilyl)oxy)phenethyl)-*N*-(2-isobutyrylphenyl)-4-methylbenzenesulfonamide (S32).**

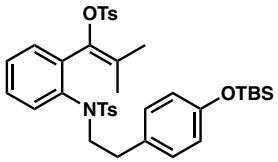
S31 (0.51 g, 1.2 mmol) and triethylamine (0.16 mL, 1.2 mmol) were added in DCM (6 mL). *Tert*-butyldimethylsilyl chloride (0.18 g, 1.2 mmol) was also dissolved in DCM (6 mL) and the solution was added into the first solution slowly. Reaction was monitored by TLC and additional *tert*-butyldimethylsilyl chloride (0.09 g, 0.6 mmol) and triethylamine (0.08 mL, 0.6 mmol) were added each time until **S31** was completely consumed. The reaction was then diluted with DCM, washed with 1M HCl, saturated $NaHCO_3$ solution, and brine in order. The organic phase was dried with $MgSO_4$, filtered, and concentrated in vacuo. Crude product was purified via column chromatography using 20% diethyl ether in hexanes to give sulfonamide **S32** as a yellow oil (0.53 g, 82% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.46 (m, 2H), 7.39 (td, *J* = 7.5, 1.3 Hz, 1H), 7.33 (td, *J* = 7.6, 1.8 Hz, 1H), 7.23 (d, *J* = 8.4 Hz, 2H), 6.94 (d, *J* = 8.6 Hz, 2H), 6.75 (dd, *J* = 7.9, 1.3 Hz, 1H), 6.71 (d, *J* = 8.6 Hz, 2H), 3.99 (br, 1H), 3.67 (hepta, *J* = 6.9 Hz, 1H), 3.48 (br, 1H), 2.88 (br, 1H), 2.62 (br, 1H), 2.41 (s, 3H), 1.33 – 1.09 (m, 6H), 0.96 (s, 9H), 0.17 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 207.1, 153.3, 142.7, 140.5, 135.7, 133.8, 129.8, 129.6, 128.7, 128.6, 128.4, 127.2, 127.0, 126.4, 119.1, 52.1, 38.2, 32.9, 24.7, 20.5, 17.2, –5.5.

FTIR (Neat film NaCl): 2957, 2929, 2858, 1694, 1596, 1510, 1471, 1350, 1260, 1163, 914.

HR-MS (ESI-MS) m/z: [M+Na]+ Calc'd for $C_{31}H_{41}NO_4SSiNa$ 574.2423; Found 574.2432.



1-(2-((N-(4-((tert-butyldimethylsilyl)oxy)phenethyl)-4-methylphenyl)sulfonamido)phenyl)-2-methylprop-1-en-1-yl 4-methylbenzenesulfonate (S33).

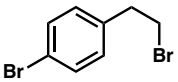
Synthesized according to general procedure 6 starting from the corresponding ketone **S32** (0.43 g, 0.00078 mol). Crude product was purified via flash column chromatography using 14% acetone in hexanes to give vinyl tosylate **S33** as a white solid (0.49 g, 89% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (s, 2H), 7.55 (d, *J* = 8.0 Hz, 2H), 7.47 (s, 1H), 7.39 – 7.29 (m, 2H), 7.27 (s, 2H), 7.08 (d, *J* = 8.1 Hz, 2H), 6.91 (s, 1H), 6.78 – 6.73 (m, 2H), 6.69 – 6.65 (m, 2H), 3.56 (br s, 1H), 3.34 (td, *J* = 12.9, 4.8 Hz, 1H), 2.62 (td, *J* = 12.8, 5.4 Hz, 1H), 2.45–2.33 (m, 1H), 2.42 (s, 3H), 2.31 (s, 3H), 1.81 (s, 3H), 1.64 (s, 3H), 0.97 (s, 9H), 0.17 (d, *J* = 0.7 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 153.0, 143.5, 142.4, 138.0, 136.9, 135.2, 133.1, 132.8, 130.1, 129.2, 128.5, 128.43. 128.40, 127.2, 127.0, 118.8, 52.2, 32.6, 24.7, 20.53, 20.52 19.4, 17.7, 17.2, –5.4.

FTIR (Neat film NaCl): 2955, 2927, 2856, 1598, 1509, 1353, 1258, 1189, 1177, 1159, 1083, 912, 804, 573.

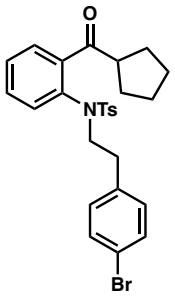
HR-MS (ESI-MS) m/z: [M+Na]+ Calc'd for $C_{38}H_{47}NO_6S_2SiNa$ 728.2512; Found 728.2511.



1-bromo-4-(2-bromoethyl)benzene (S34)

2-(4-bromophenyl)ethan-1-ol (2.01 g, 10.0 mmol) in DCM (25 mL) was cooled down to 0 °C. Triphenylphosphine (3.15 g, 12.0 mmol) and *N*-bromosuccinimide (2.14 g, 12.0 mmol) was then added into the solution and it was stirred overnight to room temperature. The reaction was quenched by saturated sodium bicarbonate solution. It was then separated, and the aqueous phase was extracted with DCM three times. The combined organic phase was dried with magnesium sulfate and concentrated to give the crude product. The crude product was purified via flash chromatography to give the product **S34** as a cloudy oil (2.45 g, 92.8% yield).

^{1}H NMR data matches previous report.[37]



***N*-(4-bromophenethyl)-*N*-(2-(cyclopentanecarbonyl)phenyl)-4-methylbenzenesulfonamide (S35).**

Synthesized according to general procedure 3 starting from 2.91 mmol of the corresponding sulfonamide **S7** (1.00 g, 0.00291 mol) and 1-bromo-4-(2-bromoethyl)benzene **S34** (1.52 g, 0.00582 mol). Crude product was purified via flash column chromatography using 40% ether in hexanes to give sulfonamide **S35** as a white powder (1.06g, 69% yield).

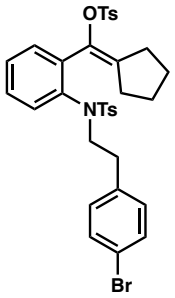
*NMR had poor resolution at room temperature, so NMRs are reported below at 70 °C.

^{1}H NMR (500 MHz, $CDCl_3$, 70 °C) δ 7.59 (d, *J* = 7.6 Hz, 1H), 7.51 (d, *J* = 8.4 Hz, 2H), 7.38 (t, *J* = 7.5 Hz, 1H), 7.35 (d, *J* = 6.4 Hz, 2H), 7.33 (t, *J* = 7.6 Hz, 1H), 7.23 (d, *J* = 7.9 Hz, 2H), 6.96 (d, *J* = 7.8 Hz, 2H), 6.84 (d, *J* = 7.9 Hz, 1H), 3.77 (br s, 2H), 3.63 (quint, *J* = 8.0 Hz, 1H), 2.86 (br s, 2H), 2.42 (s, 3H), 1.93 (br s, 4H), 1.76 (m, 2H), 1.62 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$, 70 °C) δ 206.2, 143.3, 142.3, 137.4, 136.7, 136.1, 131.4, 130.4, 130.2, 129.2, 129.0, 128.7, 127.9, 127.8, 120.2, 53.1, 50.3, 34.3, 30.3, 26.1, 21.2.

FTIR (Neat film NaCl): 3064, 3028, 2952, 2867, 1690, 1595, 1488, 1440, 1348, 1159, 572.

HR-MS (EI-MS) m/z: [M+Na]+ Calc'd for $C_{27}H_{28}BrNO_3SNa$ 548.0871; Found 548.0877.



(2-((*N*-(4-bromophenethyl)-4-methylphenyl)sulfonamido)phenyl)(cyclopentylidene)methyl 4-methylbenzenesulfonate (S36).

Synthesized according to general procedure 5 starting from the corresponding ketone **S35** (0.92 g, 0.00175 mol). Crude product was purified via flash column chromatography using 40% ether in hexanes to give vinyl tosylate **S36** as a white solid (0.72 g, 61% yield).

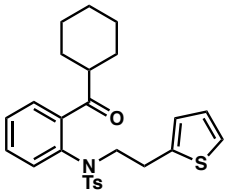
*NMR had poor resolution at room temperature, so NMRs are reported below at 70 °C.

^{1}H NMR (500 MHz, $CDCl_3$, 70 °C) δ 7.63 (m, 4H), 7.48 (d, *J* = 7.4 Hz, 1H), 7.31 (m, 4H), 7.26 (d, *J* = 8.0 Hz, 2H), 7.13 (d, *J* = 7.8 Hz, 2H), 6.94 (d, *J* = 7.6 Hz, 1H), 6.83 (d, *J* = 7.8 Hz, 2H), 3.54 (m, 2H), 2.63 (m, 3H), 2.43 (s, 3H), 2.35 (s, 3H), 2.26 (m, 3H), 1.65 (br s, 4H).

^{13}C NMR (126 MHz, $CDCl_3$, 70 °C) δ 144.3, 143.3, 141.9, 138.5, 137.6, 136.6, 135.2, 133.2, 131.3, 130.3, 130.2, 130.1, 129.3, 129.2, 129.1, 129.0, 128.0, 128.0, 127.9, 120.0, 52.7, 33.9, 30.8, 30.1, 26.2, 25.8, 21.2, 21.2.

FTIR (Neat film NaCl): 3070, 3032, 2957, 2869, 1597, 1488, 1352, 1189, 1176, 1160, 806, 788, 659, 572, 553.

HR-MS (EI-MS) m/z: [M+Na]+ Calc'd for $C_{34}H_{34}BrNO_5S_2Na$ 702.0959; Found 702.0975.



_N_-(2-(cyclohexanecarbonyl)phenyl)-4-methyl-_N_-(2-(thiophen-2-yl)ethyl)benzenesulfonamide (S37).

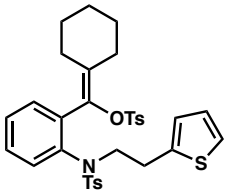
Synthesized according to general procedure 3 starting from the corresponding sulfonamide **S5** (1.50 g, 0.00420 mol) and 2-(2-iodoethyl)thiophene (1.50 g, 0.00630 mol). Crude product was purified *via* flash column chromatography using 15% ether in hexanes to give sulfonamide **S37** as a white solid (0.80 g, 40% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.48 (d, *J* = 8.3 Hz, 2H), 7.39 (td, *J* = 7.5, 1.2 Hz, 1H), 7.34 (td, *J* = 7.7, 1.7 Hz, 1H), 7.24 (d, *J* = 8.3 Hz, 2H), 7.10 (dd, *J* = 5.1, 1.2 Hz, 1H), 6.88 (dd, *J* = 5.1, 3.4 Hz, 1H), 6.76 – 6.73 (m, 2H), 4.04 (br s, 1H), 3.60 (br s, 1H), 3.35 (tt, *J* = 11.4, 3.4 Hz 1H), 3.25 (br s, 1H), 3.00 (br s, 1H), 2.41 (s, 3H), 2.10 (br s, 1H), 1.92 (br s, 1H), 1.87 – 1.77 (m, 2H), 1.69 (d, *J* = 12.5 Hz, 1H), 1.63 – 1.53 (m, 1H), 1.41 – 1.18 (m, 4H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 206.8, 143.7, 141.4, 140.0, 136.5, 134.6, 130.8, 129.4, 129.3, 128.2, 127.8, 127.7, 126.8, 125.2, 123.7, 53.1, 49.0, 28.8, 25.8, 21.4.

FTIR (Neat film NaCl): 3068, 2929, 1854, 1690, 1596, 1444, 1350, 1162, 1092, 907, 728.

HR-MS (ESI-MS) m/z: [M+Na]+ Calc'd for $C_{26}H_{29}NO_3S_2Na$ 490.1487; Found 490.1496.



cyclohexylidene(2-((4-methyl-*N*-(2-(thiophen-2-yl)ethyl)phenyl)sulfonamido)phenyl)methyl 4-methylbenzenesulfonate (S38).

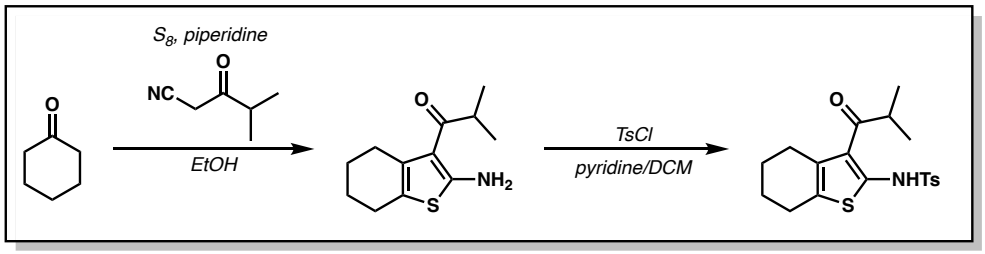
Synthesized according to general procedure 3 starting from the corresponding ketone **S37** (0.55 g, 0.0012 mol). Crude product was purified *via* flash column chromatography using 30% diethyl ether in hexanes to give vinyl tosylate **S38** as a yellow solid (0.49 g, 67% yield).

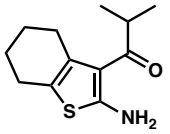
^{1}H NMR (500 MHz, $CDCl_3$, 55 °C) δ 7.67 (d, *J* = 7.9 Hz, 2H), 7.56 (d, *J* = 8.4 Hz, 2H), 7.55 (br s, 1H), 7.44 – 7.26 (m, 5H), 7.15 – 7.04 (m, 2H), 6.93 (br s, 1H), 6.87 – 6.85 (m, 1H), 6.60 (s, 1H), 3.65 (ddd, *J* = 13.7, 12.0, 5.3 Hz, 1H), 3.46 (ddd, *J* = 13.8, 12.0, 5.0 Hz, 1H), 2.95 (ddd, *J* = 14.5, 12.2, 5.3 Hz, 1H), 2.75 (ddd, *J* = 14.5, 11.9, 4.9 Hz, 1H), 2.51 – 2.40 (m, 1H), 2.43 (s, 3H), 2.32 – 2.25 (m, 1H), 2.31 (s, 3H), 2.20 – 2.00 (m, 2H), 1.80 – 1.66 (m, 2H), 1.66 – 1.50 (m, 4H).

^{13}C NMR (126 MHz, $CDCl_3$, 55 °C) δ 144.4, 143.6, 140.8, 139.3, 136.8, 136.5, 135.6, 134.5, 133.7, 129.5, 129.4, 129.2, 128.3, 128.0, 127.9, 126.8, 125.0, 123.5, 52.9, 30.6, 28.7, 27.0, 26.8, 26.3, 21.5.

FTIR (Neat film NaCl): 2930, 2925, 2856, 1492, 1356, 1175, 1093, 802, 573.

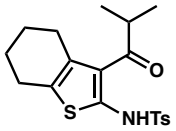
HR-MS (ESI-MS) m/z: [M+NH_4]+ Calc'd for $C_{33}H_{39}N_2O_5S_3$ 639.2021; Found 639.2044.





1-(2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophen-3-yl)-2-methylpropan-1-one (S39).

Cyclohexanone (1.25 g, 12.7 mmol, 1.0 equiv) was added to a 100 mL schlenk followed by α-cyano isopropyl ketone (1.70 g, 15.3 mmol, 1.2 equiv) and this was dissolved in ethanol (20 mL). To this solution was added S_8 (3.92 g, 15.3 mmol, 1.2 equiv) and piperidine (1.30 g, 15.3 mmol, 1.2 equiv). The reaction vessel was sealed and heated to 65 °C in the silicone oil bath for 48 hours. Upon completion, the reaction was cooled to r.t. and poured onto ice. After the ice melted, the resultant suspension was filtered and washed with water followed by pentane. The light yellow solid (2.54 g, ca. 89%) was dried under vacuum and carried forward to the next step without further purification.

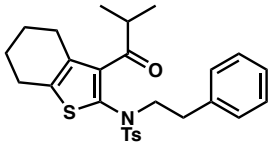


***N*-(3-isobutyryl-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-yl)-4-methylbenzenesulfonamide (S40).**

Synthesized from the crude material **S39** (2.54 g, ca. 11.3 mmol) from the previous step according to a slightly modified general procedure 2 using 26 equiv of DCM (18 mL) instead of 13 equiv. The crude product was purified by flash column chromatography using 30% ether/hexanes to give roughly a 7:1 mixture of desired sulfonamide **S40** to ditosylated

sulfonamide (2.80 g, ca. 60% yield desired). This was carried forward without additional purification. Representative ^{1}H NMR shifts of desired product shown below.

^{1}H NMR (300 MHz, $CDCl_3$) δ 11.60 (s, 1H), 7.75 (d, *J* = 8.3 Hz, 2H), 7.24 (d, *J* = 8.3 Hz, 2H), 3.12 (sept, *J* = 6.7 Hz, 1H), 2.74 – 2.59 (m, 4H), 2.38 (s, 3H), 1.82 – 1.72 (m, 4H), 0.99 (d, *J* = 6.7 Hz, 6H).



***N*-(3-isobutyryl-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-yl)-4-methyl-*N*-phenethylbenzenesulfonamide (S41).**

Synthesized according to general procedure 3 starting from the corresponding sulfonamide **S40** (2.80 g, 0.00742 mol) (7:1 mixture) and (2-iodoethyl)benzene (2.57 g, 0.0111 mol). Crude product was purified *via* flash column chromatography using 20% ether in hexanes and then recrystallization from boiling DCM/hexanes (1:1) to give sulfonamide **S41** as yellow crystalline solid (1.35 g, 38% yield).

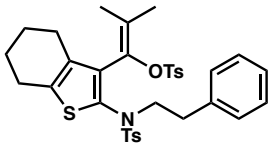
*NMR had poor resolution at room temperature, so NMRs are reported below at 70 °C.

^{1}H NMR (500 MHz, $CDCl_3$, 70 °C) δ 7.55 (d, *J* = 8.3 Hz, 2H), 7.30 – 7.21 (m, 5H), 7.20 – 7.15 (d, *J* = 8.3 Hz, 2H), 4.15 – 3.21 (br s, 2H), 3.55 (quint, *J* = 6.9 Hz, 1H), 2.92 (t, *J* = 8.5 Hz, 2H), 2.71 – 2.51 (br s, 2H), 2.64 (t, *J* = 6.1 Hz, 2H), 2.42 (s, 3H), 1.94 – 1.68 (m, 4H), 1.13 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$, 70 °C) δ 204.4, 144.3, 140.0, 137.9, 137.5, 134.4 (d, *J* = 2.9 Hz), 133.1, 129.5, 128.7, 128.6, 128.4, 126.7, 54.6, 39.4, 34.9, 25.2, 25.1, 22.9, 22.4, 21.6.

FTIR (Neat film NaCl): 3206, 3029, 2931, 2868, 1685, 1597, 1560, 1454, 1356, 1167, 1091, 1059, 662, 575.

HR-MS (ESI-MS) m/z: [M+Na]+ Calc'd for $C_{27}H_{31}NO_3S_2Na$ 504.1643; Found 504.1660.



2-methyl-1-(2-((4-methyl-*N*-phenethylphenyl)sulfonamido)-4,5,6,7-tetrahydrobenzo[*b*]thiophen-3-yl)prop-1-en-1-yl 4-methylbenzenesulfonate (S42).

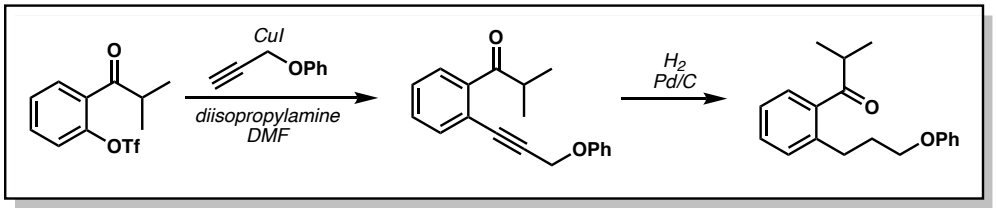
Synthesized according to a slightly modified general procedure 5 starting from the corresponding ketone **S41** (1.35 g, 0.00280 mol). Followed procedure with exception that 10 mL of PhMe was used for ketone solution and 14 mL DCM used for tosic anhydride due to poor solubility of ketone. Crude product was purified *via* flash column chromatography using 20% diethyl ether in hexanes to give vinyl tosylate **S42** as a white solid (0.39 g, 22% yield).

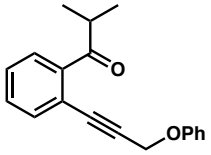
^{1}H NMR (500 MHz, $CDCl_3$, 70 °C) δ 7.69 (d, *J* = 7.9 Hz, 2H), 7.63 (d, *J* = 8.0 Hz, 2H), 7.26 – 7.19 (m, 7.7 Hz, 4H), 7.17 (app q, *J* = 7.0 Hz, 1H), 7.12 (d, *J* = 8.0 Hz, 2H), 7.00 (d, *J* = 7.4 Hz, 2H), 3.65 (td, *J* = 12.8, 12.4, 5.4 Hz, 1H), 3.50 (td, *J* = 12.7, 5.0 Hz, 1H), 2.86 (dd, *J* = 16.4, 5.5 Hz, 1H), 2.80 – 2.61 (m, 4H), 2.45 – 2.35 (m, 1H), 2.41 (s, 3H), 2.33 (s, 3H), 1.98 – 1.81 (m, 4H), 1.79 (s, 3H), 1.61 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$, 70 °C) δ 144.3, 143.5, 138.6, 136.8, 136.7, 135.2, 134.7, 134.6, 133.1, 131.1, 129.5, 129.5, 129.4, 128.7, 128.4, 128.3, 127.8, 127.4, 126.3, 54.2, 34.8, 25.4, 25.0, 23.5, 22.8, 21.4, 21.3, 20.0, 18.5.

FTIR (Neat film NaCl): 3199, 3063, 3028, 2932, 2858, 1598, 1453, 1351, 1176, 1162, 1092, 1059, 813, 661, 580, 547.

HR-MS (ESI-MS) m/z: [M+Na]+ Calc'd for $C_{34}H_{37}NO_5S_3Na$ 658.1732; Found 658.1712.





2-methyl-1-(2-(3-phenoxyprop-1-yn-1-yl)phenyl)propan-1-one (S43).

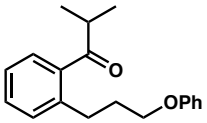
Copper iodide (6.43 mg, 0.034 mmol, 0.01 equiv) and $Pd(PPh_3)_4$ (39.0 mg, 0.034 mmol, 0.01 equiv) were added to a Schlenk flask and vacuum/backfilled three times. This was dissolved in DMF (12 mL) and added diisopropylamine (1.02 g, 10.1 mmol, 3 equiv) aryl triflate **S17** (1.00 g, 3.38 mmol, 1.0 equiv) and (prop-2-yn-1-yloxy)benzene (1.34 g, 10.1 mmol, 3.0 equiv). The resulting solution was heated to 80 °C in the silicone oil bath for 16 hours. The reaction was cooled to r.t and diluted with 30 mL of H_2O. This was then extracted with diethyl ether (3 x 40 mL). The combined organics were washed with 1M aqueous HCl (50 mL), water (50 mL), and brine (50 mL). Afterwards, the organic layer was dried over $MgSO_4$, filtered, and concentrated to give crude alkyne. This was purified by silica flash column chromatography using 3% ether in hexanes to give desired product **S43** as an orange oil (540 mg, 58% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.53 – 7.46 (m, 2H), 7.42 – 7.35 (m, 2H), 7.34 – 7.30 (m, 2H), 7.01 (ddd, J = 9.1, 7.0, 0.9 Hz, 3H), 4.94 (s, 2H), 3.53 (sept, J = 6.9 Hz, 1H), 1.09 (d, J = 6.9, 6H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 208.0, 157.6, 141.9, 133.8, 130.3, 129.5, 128.6, 127.7, 121.5, 119.9, 114.9, 88.7, 85.4, 56.4, 38.9, 18.4.

FTIR (Neat film NaCl): 3063, 2971, 2932, 2871, 1691, 1598, 1589, 1494, 1211, 1033, 752, 590.

HR-MS (CI-MS) m/z: [M]+ Calc'd for $C_{19}H_{18}O_2$ 278.1307; Found 278.1307.



2-methyl-1-(2-(3-phenoxypropyl)phenyl)propan-1-one (S44).

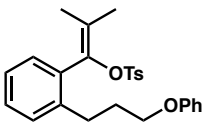
To a 25 mL roundbottom flask was added 10% Pd/C (70.4 mg, 0.066 mmol, 0.034 equiv) and suspended in 8 mL of ethanol. To this was added alkyne **S43** (0.540 g, 1.94 mmol, 1.0 equiv) and the reaction was sparged with hydrogen gas for 10 minutes. After the sparging, a new hydrogen balloon was attached and reaction stirred for 18 hours. At this point, the reaction was filtered through celite and concentrated. The crude material was purified by a short silica plug with 5% ether in hexanes to give pure ketone **S44** as a light yellow oil (0.230 g, 1.94 mmol, 42% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.53 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.38 (td, *J* = 7.5, 1.3 Hz, 1H), 7.33 – 7.19 (m, 4H), 6.94 (td, *J* = 7.3, 1.1 Hz, 1H), 6.91 (d, *J* = 8.8 Hz, 2H), 4.00 (t, *J* = 6.2 Hz, 2H), 3.36 (sept, *J* = 6.9 Hz, 1H), 2.96 – 2.79 (m, 2H), 2.26 – 1.97 (m, 2H), 1.18 (d, *J* = 6.9 Hz, 6H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 209.3, 158.9, 141.1, 138.6, 130.9, 130.7, 129.4, 127.6, 125.8, 120.5, 114.5, 67.0, 38.9, 31.3, 30.2, 18.7.

FTIR (Neat film NaCl): 3067, 2930, 2869, 1686, 1599, 1497, 1469, 1243, 1037, 976, 751, 591.

HR-MS (CI-MS) m/z: [M+H]+ Calc'd for $C_{19}H_{23}O_2$ 283.1698; Found 283.1700.



2-methyl-1-(2-(3-phenoxypropyl)phenyl)prop-1-en-1-yl 4-methylbenzenesulfonate (S45).

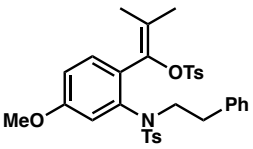
Synthesized according to general procedure 5 starting from the corresponding ketone **S44** (0.23 g, 0.00082 mol). Crude product was purified *via* flash column chromatography using 30% ether in hexanes to give vinyl tosylate **S45** as a white solid (90 mg, 25% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (d, *J* = 8.4 Hz, 2H), 7.31 – 7.24 (m, 1H), 7.26 – 7.25 (m, 1H), 7.23 – 7.19 (m, 1H), 7.16 (td, *J* = 7.5, 1.6 Hz, 1H), 7.09 (td, *J* = 7.5, 1.4 Hz, 1H), 7.01 (t, *J* = 8.0 Hz, 3H), 6.93 (t, *J* = 7.4 Hz, 1H), 6.84 (d, *J* = 7.7 Hz, 2H), 3.87 – 3.79 (m, 2H), 2.77 – 2.65 (m, 1H), 2.51 – 2.40 (m, 1H), 2.31 (s, 3H), 1.91 (s, 3H), 1.90 – 1.83 (m, 2H), 1.55 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 158.9, 143.9, 141.1, 140.7, 134.5, 132.7, 132.3, 129.4, 129.1, 128.9, 128.8, 127.5, 127.2, 125.4, 120.5, 114.4, 66.8, 29.7, 29.1, 21.5, 19.8, 18.3.

FTIR (Neat film NaCl): 3065, 2923, 2870, 1600, 1497, 1367, 1245, 1177, 1080, 1037, 990.

HR-MS (ESI-MS) m/z: [M+Na]+ Calc'd for $C_{26}H_{28}O_4SNa$ 459.1606; Found 459.1619.



1-(4-methoxy-2-((4-methyl-N-phenethylphenyl)sulfonamido)phenyl)-2-methylprop-1-en-1-yl 4-methylbenzenesulfonate (S46).

Synthesized according to general procedure 5 starting from the cooresponding ketone N-(2-isobutyryl-5-methoxyphenyl)-4-methyl-N-phenethylbenzenesulfonamide (0.548 g, 0.00158 mol). Crude product was purified *via* flash column chromatography using 1:1 hexanes:diethyl ether to give vinyl tosylate **S46** as a yellow solid (0.31 g, 32% yield).

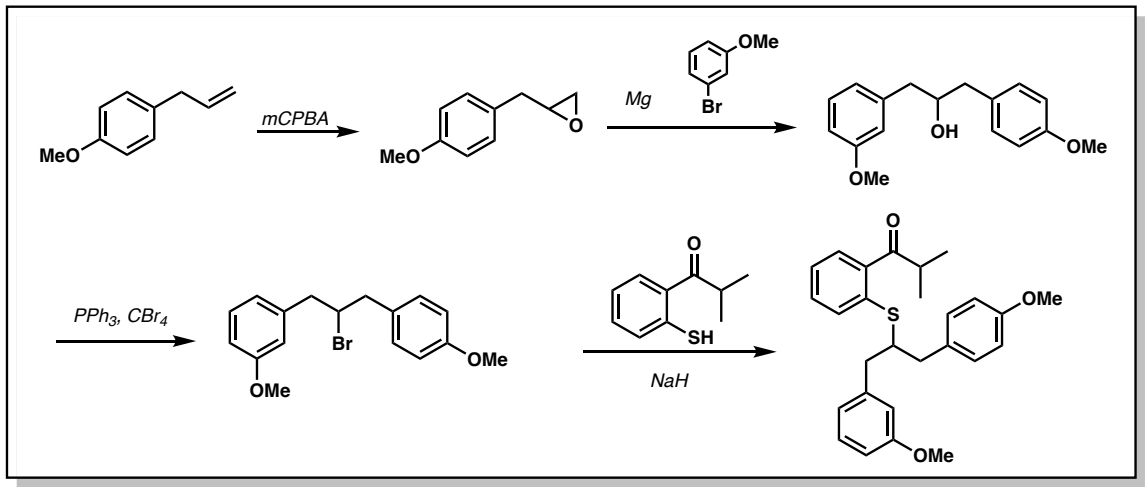
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 7.9 Hz, 2H), 7.51 (d, *J* = 8.2 Hz, 2H), 7.31 (br s, 1H), 7.21–7.18 (m, 2H), 7.17 – 7.07 (m, 3H), 7.03 (d, *J* = 8.1 Hz, 2H), 6.86 (d, *J* = 7.6 Hz, 2H,), 6.85 – 6.77 (m, 1H), 6.39 (br s, 1H), 3.66 (s, 3H), 3.53 (ddd, *J* = 12.2, 12.2, 6.0 Hz,

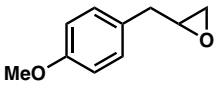
1H), 3.29 (ddd, *J* = 13.6, 12.2, 4.9 Hz, 1H), 2.66 (ddd, *J* = 12.6, 12.6, 5.3 Hz, 1H), 2.50 – 2.38 (m, 1H), 2.35 (s, 3H), 2.24 (s, 3H), 1.71 (s, 3H), 1.56 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.0, 143.5, 142.5, 139.1, 137.5, 136.8, 135.12 133.4, 133.2, 128.4, 128.4, 127.7, 127.3, 127.2, 126.9, 125.3, 114.0, 112.2, 54.4, 52.1, 33.5, 20.5, 20.5, 19.5, 17.7.

FTIR (Neat film NaCl): 3028, 2924, 1686, 1603, 1569, 1496, 1456, 1352, 1305, 1291, 1189, 1176, 1162, 1093, 1034, 985, 948, 830, 814, 786, 756, 695, 658, 567.

HR-MS (ESI-MS) m/z: $[M+Na]^+$ Calc'd for $C_{33}H_{35}NO_6S_2Na$ 628.1804; Found 628.1814.

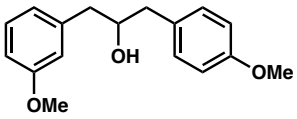




2-(4-methoxybenzyl)oxirane (S47).

1-allyl-4-methoxybenzene (5.00 g, 33.7 mmol) was dissolved in DCM (68 mL) and the solution was cooled down to 0 °C. m-chloroperoxybenzoic acid (9.98 g, 40.5 mmol, 70%) was added portion wise over 10 min. The reaction was stirred under room temperature overnight. It was then quenched with saturated $NaHSO_3$ solution. After the separation, the organic phase was washed with saturated $NaHCO_3$ solution and brine. It was then dried with $MgSO_4$, filtered, and concentrated in vacuo to get the product as an orange liquid **S47** (4.42

g, 79.8% yield). The product **S47** was used in the next step without further purification. Spectral data match those reported in the literature.[38]



1-(3-methoxyphenyl)-3-(4-methoxyphenyl)propan-2-ol (S48).

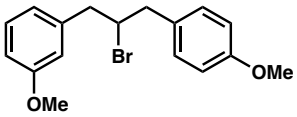
In a flamed-dried 3-neck flask was added magnesium (0.51 g, 21.1 mmol) and THF (22 mL). A small amount of iodine was added to assist the initiation of Grignard reagent formation. 1-bromo-3-methoxybenzene (3.78 g, 20.2 mmol) was added into the reaction slowly to keep a gentle reflux of the reaction. Upon completion of the addition, the reaction was left stirred for 1 hour. Then copper iodide (0.38 g, 2.02 mmol) was added into the reaction and it was cooled down to 0 °C. **S47** (2.21 g, 13.5 mmol) in THF (22 mL) was added slowly into the reaction, and it was then warmed up to room temperature overnight. The reaction was quenched with saturated NH_4Cl solution at 0 °C and then diluted with diethyl ether. After the separation, the aqueous phase was extracted with diethyl ether two more times. The combined organic phase was washed with brine, dried with $MgSO_4$, filtered, and concentrated in vacuo to give the crude product. The crude product was purified *via* flash column chromatography using 1:1 diethyl ether and hexanes to give the product **S48** as a yellowish oil (2.64 g, 72% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.20 (m, 1H), 7.15 (d, J = 8.7 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 6.84 – 6.80 (m, 1H), 6.80 – 6.76 (m, 2H), 4.02 (tt, J = 8.1, 4.7 Hz, 1H), 3.80 (s, 3H), 3.80 (s, 3H), 2.82 (ddd, J = 12.7, 7.8, 4.6 Hz, 2H), 2.71 (ddd, J = 13.6, 8.1, 5.0 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 160.1, 158.6, 140.4, 130.70, 130.67, 129.9, 122.1, 115.4, 114.3, 112.2, 73.9, 55.6, 55.5, 43.7, 42.8.

FTIR (Neat film NaCl): 3436, 2995, 2936, 2835, 1610, 1583, 1511, 1488, 1245, 1035, 806, 781, 696.

HR-MS (FD-MS) m/z: [M]+ Calc'd for $C_{17}H_{20}O_3$ 272.1412; Found 272.1410.



1-(2-bromo-3-(4-methoxyphenyl)propyl)-3-methoxybenzene (S49).

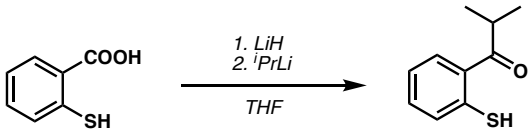
In a flask was added **S48** (1.32 g, 4.85 mmol), DCM (15 mL) and carbon tetrabromide (2.41 g, 7.27 mmol). The solution was cooled down to 0 °C. Triphenylphosphine (1.27 g, 4.85 mmol) was dissolved in DCM (10 mL) in another flask and slowly added to the reaction. The reaction was warmed up to room temperature overnight. It was then quenched with DCM and water. After the separation, the aqueous phase was extracted with DCM two more times. The combined organic phase was washed with brine, dried with $MgSO_4$, filtered, and concentrated in vacuo to give the crude product. The crude product was purified *via* flash column chromatography using 2% diethyl ether in hexanes to give the product **S49** as a colorless liquid (0.56 g, 34% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (t, J = 8.1 Hz, 1H), 7.12 (d, J = 8.2 Hz, 2H), 6.85 (d, J = 8.7 Hz, 2H), 6.82 – 6.77 (m, 2H), 6.76 – 6.74 (m, 1H), 4.33 (tt, J = 8.1, 5.8 Hz, 1H), 3.80 (s, 3H), 3.80 (s, 3H), 3.22 – 3.04 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.9, 158.8, 140.4, 130.8, 130.6, 129.8, 121.9, 115.4, 114.2, 112.3, 57.8, 55.6, 55.5, 45.2, 44.4.

FTIR (Neat film NaCl): 2989, 2870, 1393, 1143.

HR-MS (FD-MS) m/z: [M]+ Calc'd for $C_{17}H_{19}O_2Br$ 334.0568; Found 334.0563.



1-(2-mercaptophenyl)-2-methylpropan-1-one (S50).

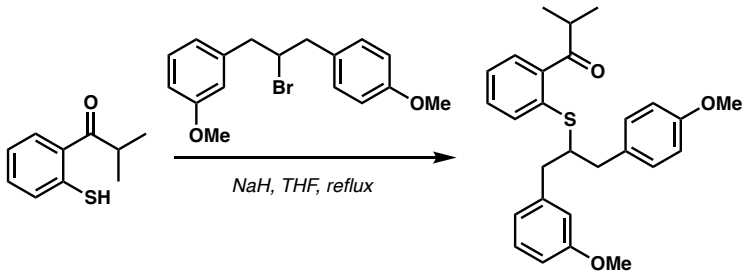
In a flamed dried 3-neck flask was added 2-mercaptobenzoic acid (2.00 g, 13.0 mmol) and THF (26 mL). Lithium hydride (0.31 g, 39 mmol) was added slowly, and the reaction was refluxed for 45 min. Then the solution was cooled down to 0 °C. Isopropyllithium (0.7 M in pentane, 18.5 mL, 13.0 mmol) was added slowly to the solution. After 12 hours, the reaction was quenched with saturated NH_4Cl solution. The solution was then acidified with 3 M HCl until the aqueous phase did not crash out solid anymore. It was then diluted with water and diethyl ether. After the separation, the aqueous phase was extracted with diethyl ether two more times. The combined organic phase was washed with brine, dried with $MgSO_4$, filtered, and concentrated in vacuo to give the crude product. The crude product was purified via flash column chromatography using 12.5% diethyl ether in hexanes to give the product **S50** as a yellow liquid (1.73 g, 74% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.9 Hz, 1H), 7.32 – 7.09 (m, 3H), 4.17 (s, 1H), 3.47 (hept, *J* = 6.8 Hz, 1H), 1.16 (d, J = 6.9 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 205.4, 137.3, 132.7, 132.0, 131.9, 130.3, 124.7, 36.3, 19.1.

FTIR (Neat film NaCl): 2971, 2931, 2871, 2537, 1665, 1587, 1558, 1468, 1220, 1083, 988, 739.

HR-MS (FD-MS) m/z: [M]+ Calc'd for $C_{10}H_{12}OS$ 180.0609; Found 180.0603.



1-(2-((1-(3-methoxyphenyl)-3-(4-methoxyphenyl)propan-2-yl)thio)phenyl)-2-methylpropan-1-one (S51).

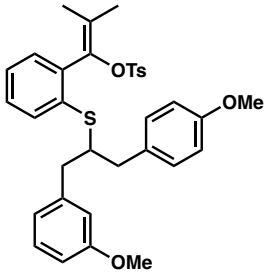
In a flamed Schlenk flask was charged with NaH (89 mg, 2.2 mmol, 60% dispersion in mineral oil) and THF (11 mL). The reaction was cooled down to 0 degree and **S50** (0.40 g, 2.2 mmol) was added dropwise. The reaction was then warmed to room temperature and left for 15 minutes. After, **S49** (1.1 g, 3.3 mmol) was added and the reaction was refluxed at 66 °C in the silicone oil bath overnight. After the reaction was complete, the reaction was diluted with diethyl ether and water. After the separation of the two phases, the aqueous phase was extracted with diethyl ether two more times. The combined organic phase was washed with 1M NaOH, saturated NH_4Cl, and brine. It was then dried with $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by column chromatography to get the product **S51** as a pale-yellow oil (0.57 g, 59% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (td, *J* = 7.6, 1.4 Hz, 2H), 7.24 (td, *J* = 7.6, 1.6 Hz, 1H), 7.15 (td, *J* = 7.4, 1.3 Hz, 1H), 7.11 (t, *J* = 7.9 Hz, 1H), 6.99 (d, *J* = 8.5 Hz, 2H), 6.73 (d, *J* = 8.0 Hz, 2H), 6.66 (dd, J = 7.9, 2.1 Hz, 2H), 6.60 (t, J = 2.0 Hz, 1H), 3.71 (s, 6H), 3.49 (pent, J = 7.0 Hz, 1H), 3.21 (hept, J = 6.8 Hz, 1H), 2.79 – 2.63 (m, 4H), 1.04 (d, J = 6.9 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 209.1, 159.6, 158.2, 142.6, 140.7, 134.5, 132.0, 131.0, 130.24, 130.21, 129.3, 127.9, 126.2, 121.6, 115.0, 113.7, 111.7, 55.3, 55.2, 52.1, 40.6, 39.7, 39.6, 18.45, 18.43.

FTIR (Neat film NaCl): 2962, 2929, 1691, 1611, 1602, 1584, 1512, 1465, 1438, 1261, 1248, 1037, 978.

HR-MS (ESI-MS) m/z: [M+Na]+ Calc'd for $C_{27}H_{30}O_3SNa$ 457.1813; Found 457.1820.



1-(2-((1-(3-methoxyphenyl)-3-(4-methoxyphenyl)propan-2-yl)thio)phenyl)-2-methylprop-1-en-1-yl 4-methylbenzenesulfonate (128).

Synthesized according to a slightly modified general procedure 5 starting from the corresponding ketone **S51** (0.56 g, 0.0013 mol). Crude product was purified *via* flash column chromatography using 33% diethyl ether in hexanes to give vinyl tosylate **128** as a yellowish oil (0.42 g, 54% yield).

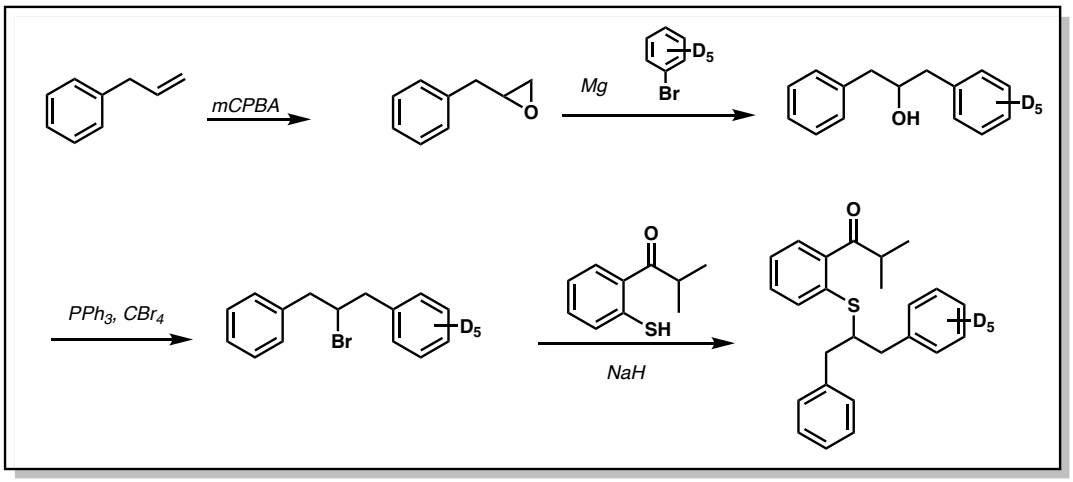
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (dd, *J* = 8.4, 2.8 Hz, 2H), 7.25 – 7.09 (m, 3H), 7.07 (d, *J* = 7.2 Hz, 2H), 7.01 (dd, *J* = 8.5, 1.9 Hz, 2H), 6.91 (dd, *J* = 8.3, 3.5 Hz, 2H), 6.83 – 6.75 (m, 2H), 6.75 – 6.70 (m, 1H), 6.68 (d, *J* = 7.6 Hz, 1H), 6.64 (s, 1H), 3.79 (m, 3H), 3.77 (m, 3H), 3.44 (tt, *J* = 7.4, 3.7 Hz, 1H), 2.80 – 2.51 (m, 4H), 2.20 (m, 3H), 1.93 (m, 3H), 1.57 (s, 3H). (Some singlet peaks split likely due to the existence of rotamers.)

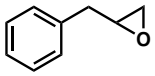
^{13}C NMR (101 MHz, $CDCl_3$) δ 158.5, 157.1, 142.8, 140.0, 139.7, 138.8, 136.1, 133.3, 131.8, 130.3, 130.0, 129.2, 128.9, 128.2, 127.9, 127.0, 126.6, 124.4, 120.6, 114.1, 112.6, 110.4,

54.2, 54.1, 50.1, 39.5, 38.6, 20.4, 18.9, 17.5. (Some peaks split likely due to the existence of rotamers.)

FTIR (Neat film NaCl): 2915, 1600, 1584, 1512, 1463, 1455, 1436, 1364, 1248, 1189, 1176, 1085, 1036, 990, 823, 809, 793, 740.

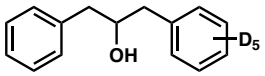
HR-MS (ESI-MS) m/z: $[M+NH_4]+$ Calc'd for $C_{34}H_{40}NO_5S_2$ 606.2348; Found 606.2336.





2-benzyloxirane (S52).

Allylbenzene (5.00 g, 42.3 mmol) was dissolved in DCM (84 mL) and the solution was cooled down to 0 °C. m-chloroperoxybenzoic acid (12.5 g, 50.8 mmol, 70%) was added portion wise over 10 min. The reaction was stirred under room temperature overnight. It was then quenched with saturated $NaHSO_3$ solution. After the separation, the organic phase was washed with saturated $NaHCO_3$ solution and brine. It was then dried with $MgSO_4$, filtered, and concentrated in vacuo to get the product as a pale yellow liquid **S52** (3.05 g, 53.7% yield). The product **S52** was used in the next step without further purification. Spectral data match those reported in the literature.[38]



1-phenyl-3-(phenyl-*d*$_5$)propan-2-ol (S53).

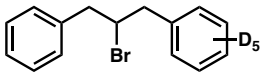
In a flamed-dried 3-neck flask was added magnesium (0.87 g, 35.7 mmol) and THF (36 mL). A small amount of iodine was added to assist the initiation of Grignard reagent formation. 1-bromobenzene-2,3,4,5,6-d$_5$ (5.52 g, 34.1 mmol) was added into the reaction slowly to keep a gentle reflux of the reaction. Upon completion of the addition, the reaction was left stirred for 1 hour. Then copper iodide (0.65 g, 3.4 mmol) was added into the reaction and it was cooled down to 0 °C. **S52** (3.05 g, 22.7 mmol) in THF (36 mL) was added slowly into the reaction, and it was then warmed up to room temperature overnight. The reaction was quenched with saturated NH_4Cl solution at 0 °C and then diluted with diethyl ether. After the separation, the aqueous phase was extracted with diethyl ether two more times. The combined organic phase was washed with brine, dried with $MgSO_4$, filtered, and concentrated in vacuo to give the crude product. The crude product was purified *via* flash column chromatography using 33% diethyl ether in hexanes to give the product **S53** as a colorless liquid (4.37 g, 88.5% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.28 (m, 2H), 7.25–7.21 (ddd, J = 7.0, 3.4, 1.6 Hz, 3H), 4.08 (tt, J = 8.2, 4.7 Hz, 1H), 2.88 (ddd, J = 13.7, 4.8, 1.1 Hz, 2H), 2.77 (ddd, J = 13.7, 8.2, 0.8 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 138.5, 138.3, 129.4, 129.0 (t, J = 24 Hz), 128.6, 128.1 (t, J = 24 Hz), 126.5, 126.0 (t, J = 24 Hz), 73.6, 43.4, 43.3.

FTIR (Neat film NaCl): 3407, 3027, 2916, 2273, 1600, 1569, 1496, 1454, 1384, 1355, 1189, 1176, 1068, 1030, 988, 821, 747, 699, 545.

HR-MS (FD-MS) m/z: [M]+ Calc'd for $C_{15}H_{11}OD_5$ 217.1515; Found 217.1523.

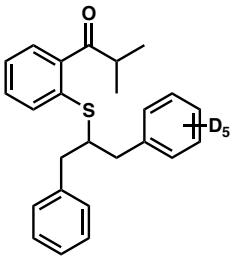


1-(2-bromo-3-phenylpropyl)benzene-2,3,4,5,6-d_5 (S54).

In a flask was added **S53** (3.36 g, 15.5 mmol), DCM (20 mL) and carbon tetrabromide (7.69 g, 23.2 mmol). The solution was cooled down to 0 °C. Triphenylphosphine (6.08 g, 23.2 mmol) was dissolved in DCM (13 mL) in another flask and slowly added to the reaction. The reaction was warmed up to room temperature overnight. It was then quenched with DCM and water. After the separation, the aqueous phase was extracted with DCM two more times. The combined organic phase was washed with brine, dried with $MgSO_4$, filtered, and concentrated in vacuo to give the crude product. The crude product was purified *via* flash column chromatography using 2% diethyl ether in hexanes to give the product **S54** as a colorless liquid (3.00 g, 63.0% yield, 91% purity).

*The product had 9% of alkene side product from elimination, but was used directly in the next synthetic step.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.16 (m, 5H), 4.37 (tt, J = 8.2, 5.7 Hz, 1H), 3.22 (ddd, J = 14.3, 5.8, 1.3 Hz, 2H), 3.14 (ddd, J = 14.3, 8.2, 1.8 Hz, 2H).



2-methyl-1-(2-((1-phenyl-3-(phenyl-d_5)propan-2-yl)thio)phenyl)propan-1-one (S55).

In a flamed Schlenk flask was charged with NaH (0.27 g, 6.7 mmol, 60% dispersion in mineral oil) and THF (22 mL). **S50** (0.80 g, 4.4 mmol) was added dropwise. The reaction was stirred for 15 minutes under room temperature. After, **S54** (1.9 g, 6.7 mmol) was added

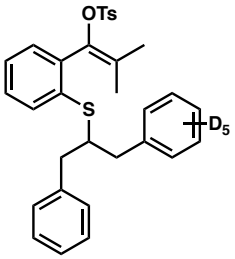
and the reaction was refluxed at 66 °C in the silicone oil bath overnight. After the reaction was complete, the reaction was diluted with diethyl ether and water. After the separation of the two phases, the aqueous phase was extracted with diethyl ether two more times. The combined organic phase was washed with 1M NaOH, saturated NH_4Cl and brine. It was then dried with $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by column chromatography to get the product **S55** as a pale yellow oil (0.75 g, 45% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.35 (m, 2H), 7.31 (t, *J* = 7.6 Hz, 1H), 7.29–7.27 (m, 1H), 7.25 – 7.16 (m, 3H), 7.14 (d, *J* = 6.9 Hz, 2H), 3.60 (penta, *J* = 7.0 Hz, 1H), 3.27 (hepta, *J* = 6.9 Hz, 1H), 2.90 – 2.76 (m, 4H), 1.10 (d, *J* = 6.9 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 208.0, 141.6, 138.0, 137.8, 133.3, 131.0, 129.2, 128.2, 127.3, 126.9, 125.4, 125.2, 50.9, 39.6, 39.5, 38.6, 17.4.

FTIR (Neat film NaCl): 2967, 2925, 2850, 2273, 1692, 1585, 1496, 1454, 1435, 1382, 1342, 1261, 1215, 1077, 1029, 977, 747, 700, 544.

HR-MS (FD-MS) m/z: [M]+ Calc'd for $C_{25}H_{21}OSD_5$ 379.2018; Found 379.2011.



2-methyl-1-(2-((1-phenyl-3-(phenyl-d_5)propan-2-yl)thio)phenyl)prop-1-en-1-yl-4-methylbenzenesulfonate (131).

Synthesized according to a slightly modified general procedure 5 starting from the corresponding ketone **S55** (0.76 g, 0.0020 mol). Crude product was purified *via* flash column

chromatography using 33% diethyl ether in hexanes to give vinyl tosylate **131** as a yellowish oil (0.50 g, 47% yield).

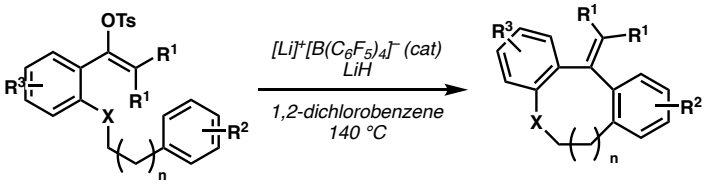
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.8 Hz, 2H), 7.23–7.20 (m, 1H), 7.19 – 6.95 (m, 9H), 6.82 (d, *J* = 8.0 Hz, 2H), 3.42 (p, *J* = 7.0 Hz, 1H), 2.77 – 2.49 (m, 4H), 2.12 (s, 3H), 1.86 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.8, 138.7, 138.3, 138.0, 136.1, 134.0, 133.3, 131.8, 128.9, 128.2, 128.1, 127.93, 127.91, 127.3, 127.2, 127.0, 126.6, 125.4, 125.3, 124.4, 49.9, (39.47, 39.42, 39.37, 39.32), 20.4, 18.9, 17.5. (The secondary alkyl carbon split to 4 peaks likely due to the existence of rotamers.)

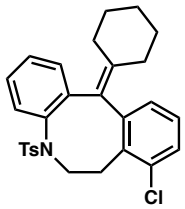
FTIR (Neat film NaCl): 2920, 2853, 2362, 2273, 1634, 1598, 1496, 1454, 1436, 1364, 1189, 1176, 1085, 1069, 990, 821, 807, 792, 740, 701, 669, 590, 561, 546.

HR-MS (FD-MS) m/z: [M]+ Calc'd for $C_{32}H_{27}O_3S_2D_5$ 533.2107; Found 533.2099.

2.7.3 Friedel-Crafts reactions



General Procedure 6: In the glovebox, lithium tetrakis(pentafluorophenyl)borate (0.1 equiv), lithium hydride (5.0 equiv), and vinyl tosylate (1.0 equiv) were dissolved into 1,2-dichlorobenzene (618 equiv) to generate a 0.0143 M solution for the vinyl tosylate. The reaction was heated under 140 °C overnight. The reaction solution was directly purified *via* flash column chromatography using hexanes and then ethyl acetate to get rid of 1,2-dichlorobenzene. Then the crude product was purified *via* flash column chromatography again to get the pure product.



8-chloro-12-cyclohexylidene-5-tosyl-5,6,7,12-tetrahydrodibenzo[*b*,*e*]azocine (103).

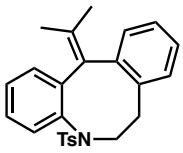
Synthesized according to general procedure 6 starting from the corresponding vinyl tosylate **101** (0.150 g, 0.000231 mol). Crude product was purified via flash column chromatography using 10% ethyl ether in hexanes to give the product **103** as a white powder (0.080 g, 73% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 7.8 Hz, 2H), 7.36 (d, *J* = 7.9 Hz, 2H), 7.25 (m, 2H), 7.18 (m, 1H), 7.08 (m, 3H), 6.90 (d, *J* = 8.0 Hz, 1H), 4.31 (dd, *J* = 15.3, 6.9 Hz, 1H), 3.56 (dd, *J* = 14.9, 6.9 Hz, 1H), 3.36 (dd, *J* = 15.1, 9.4 Hz, 1H), 2.80 (dd, *J* = 15.3, 9.4 Hz, 1H), 2.46 (s, 3H), 2.21 (m, 2H), 2.06 (m, 2H), 1.87 (m, 1H), 1.57 (m, 5H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 146.1, 145.4, 143.2, 140.5, 139.4, 139.2, 136.7, 133.9, 130.1, 130.0, 129.8, 128.7, 128.1, 127.8, 127.7, 127.6, 127.4, 127.3, 50.3, 33.7, 31.8, 31.5, 28.1, 27.8, 26.5, 21.6.

FTIR (Neat film NaCl): 3062, 2925, 2852, 1560, 1482, 1446, 1349, 1158, 1092, 569.

HR-MS (ESI-MS) m/z: [M+Na]+ Calc'd for $C_{28}H_{28}ClNO_2SNa$ 500.1427; Found 500.1436.



12-(propan-2-ylidene)-5-tosyl-5,6,7,12-tetrahydrodibenzo[*b*,*e*]azocine (106).

Synthesized according to general procedure 6 at 140 °C for 36 hours starting from the corresponding vinyl tosylate **S16** (28.6 mg, 0.0500 mmol). Crude product was purified *via*

flash column chromatography using a gradient of 1-15% diethyl ether in hexanes to give arene **106** as white solid (11.3 mg, 56% yield).

Performing the reaction with **S16** (572 mg, 1.00 mmol) in a Schlenk heating at 140 °C in the silicone oil bath outside the glovebox gave the product **106** as a white solid (265 mg, 66% yield).

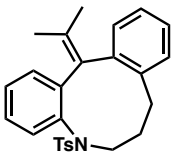
*NMR had poor resolution at room temperature, so NMR spectra are reported below at 75 °C.

^{1}H NMR (500 MHz, DMSO-d_6, 75 °C) δ 7.70 (d, J = 7.8 Hz, 2H), 7.38 (d, J = 7.9 Hz, 2H), 7.30 – 7.16 (m, 2H), 7.15 – 7.00 (m, 6H), 3.60 (br s, 2H), 2.97 (br s, 2H), 2.39 (s, 3H), 1.68 (s, 3H), 1.56 (s, 3H).

^{13}C NMR (126 MHz, DMSO-d_6, 75 °C) δ 143.7, 143.5, 139.7, 138.9, 138.7, 134.5, 131.6, 130.5, 130.3, 128.9, 128.4, 127.8, 127.7, 127.3, 127.2, 51.5 (br s), 37.5 (br s), 21.9, 21.4, 21.1.

FTIR (Neat film NaCl): 3065, 2955, 2923, 2854, 1738, 1599, 1484, 1447, 1348, 1325, 1159, 1092, 1020, 813, 717, 568, 549.

HR-MS (CI-MS) m/z: [M]+ Calc'd for $C_{25}H_{25}NO_2S$ 403.1606; Found 403.1620.



13-(propan-2-ylidene)-5-tosyl-6,7,8,13-tetrahydro-5*H*-dibenzo[*b*,*e*]azonine (107).

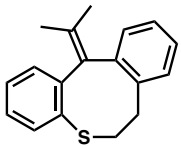
Synthesized according to general procedure 6 at 140 °C for 36 hours starting from the corresponding vinyl tosylate **S11** (29.5 mg, 0.0500 mmol). Crude product was purified *via* flash column chromatography using a gradient of 1-15% diethyl ether in hexanes to give the product **107** as white solid (17.1 mg, 82% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 – 7.72 (m, 2H), 7.40 (d, *J* = 7.6 Hz, 1H), 7.34 (d, *J*= 8.1 Hz, 2H), 7.28 (t, *J* = 7.5 Hz, 1H), 7.17 (d, *J* = 7.2 Hz, 1H), 7.15 – 6.96 (m, 4H), 6.72 (d, *J* = 8.0 Hz, 1H), 3.64 – 3.43 (m, 2H), 2.71 – 2.48 (m, 2H), 2.46 (s, 3H), 1.79 (s, 3H), 1.60 (s, 3H), 1.57 – 1.47 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 158.0, 142.4, 139.6, 137.5, 132.8, 131.7, 131.0, 129.1, 128.8, 127.9, 126.8, 125.9, 123.9, 122.3, 73.7, 31.6, 29.6, 21.4, 21.1.

FTIR (Neat film NaCl): 3062, 2973, 2920, 2859, 1597, 1483, 1445, 1350, 1161, 1083, 814, 754, 697.

HR-MS (CI-MS) m/z: [M+H]+ Calc'd for $C_{26}H_{28}NO_2S$ 418.1841; Found 418.1840.



12-(propan-2-ylidene)-7,12-dihydro-6H-dibenzo[b,e]thiocine (109).

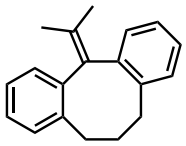
Synthesized according to general procedure 6 starting from the corresponding vinyl tosylate **S14** (21.9 mg, 0.0500 mmol). Crude product was purified via flash column chromatography using 5% ethyl ether in hexanes to give the product **109** as an oil (6.1 mg, 46% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 7.5 Hz, 1H), 7.23 (d, *J* = 7.6 Hz, 1H), 7.17 (t, *J* = 7.5 Hz, 2H), 7.12 (t, *J* = 7.2 Hz, 1H), 7.10 – 7.03 (m, 3H), 3.50 – 3.25 (m, 2H), 3.09 – 2.85 (m, 2H), 1.71 (s, 3H), 1.61 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 140.1, 136.1, 136.0, 132.0, 131.8, 130.9, 130.2, 129.7, 127.1, 127.0, 126.9, 126.8, 37.8, 33.1, 21.6, 21.1.

FTIR (Neat film NaCl): 2917, 2850, 1664, 1484, 1463, 1444, 1260, 1018, 798, 749.

HR-MS (FD-MS) m/z: [2M]+ Calc'd for $C_{36}H_{36}S_2$ 532.2258; Found 532.2257.



12-(propan-2-ylidene)-5,6,7,12-tetrahydrodibenzo[*a*,*d*][8]annulene (110).

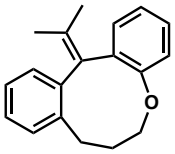
Synthesized according to general procedure 6 starting from the corresponding vinyl tosylate **S20** (105 mg, 0.250 mmol). Crude product was purified via flash column chromatography using 5% ethyl ether in hexanes to give the product **110** as a white powder (50 mg, 81% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 – 7.01 (m, 8H), 2.87 (app d, J = 55.2 Hz, 4H), 2.26 (br s, 1H), 1.65 (s, 6H), 1.55 – 1.39 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.3, 140.7, 136.9, 129.7, 128.8, 127.9, 126.5, 126.4, 37.9 (br), 29.1 (br), 20.7.

FTIR (Neat film NaCl): 3058, 3012, 2978, 2922, 2847, 1483, 1444, 1371, 1062, 1041, 769, 747.

HR-MS (CI-MS) m/z: [M]+ Calc'd for $C_{19}H_{20}$ 248.1565; Found 248.1562.



13-(propan-2-ylidene)-6,7,8,13-tetrahydrodibenzo[*b*,*e*]oxonine (111).

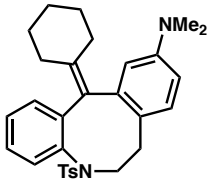
Synthesized according to general procedure 6 at 140 °C for 48 hours starting from the corresponding vinyl tosylate **S45** (21.8 mg, 0.0500 mmol). Crude product was purified *via* flash column chromatography using a gradient of 0-4% diethyl ether in hexanes to give the product **111** as colorless oil (8.6 mg, 65% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (d, *J* = 5.7 Hz, 1H), 7.20 – 7.05 (m, 5H), 6.98 (dd, *J* = 14.7, 7.6 Hz, 2H), 4.05 – 3.98 (m, 1H), 3.45 – 3.31 (m, 2H), 2.66 (d, *J* = 12.9 Hz, 1H), 2.14 (tt, *J* = 9.8, 4.1 Hz, 1H), 1.73 (s, 3H), 1.72 – 1.65 (m, 1H), 1.60 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 157.9, 142.3, 139.6, 137.5, 132.7, 131.7, 131.0, 129.1, 128.8, 127.9, 126.7, 125.9, 123.9, 122.3, 73.6, 31.6, 29.5, 21.4, 21.0.

FTIR (Neat film NaCl): 3062, 3017, 2923, 2857, 1598, 1570, 1483, 1445, 1380, 1238, 1061, 754, 741, 630.

HR-MS (CI-MS) m/z: [M]+ Calc'd for $C_{19}H_{20}O$ 264.1514; Found 264.1512.



12-cyclohexylidene-N,N-dimethyl-5-tosyl-5,6,7,12-tetrahydrodibenzo[*b*,*e*]azocin-10-amine (112).

Synthesized according to general procedure 6 starting from the corresponding vinyl tosylate **S24** (32.9 mg, 0.0500 mmol). Crude product was purified via flash column chromatography using 10% ethyl ether in hexanes to give the product **112** as a white powder (0.015 g, 62% yield).

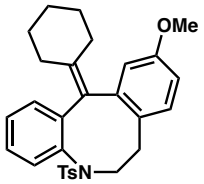
*NMR had poor resolution at room temperature, so NMRs are reported below at 75 °C in DMSO-d_6.

^{1}H NMR (500 MHz, DMSO-d_6, 75 °C) δ 7.75 (d, *J* = 7.8 Hz, 2H), 7.43 (d, *J* = 7.8 Hz, 2H), 7.33 (d, *J* = 7.6 Hz, 1H), 7.24 (t, *J* = 7.6 Hz, 1H), 7.13 (t, *J* = 7.9 Hz, 1H), 6.95 (d, *J* = 8.0 Hz, 1H), 6.88 (dd, *J* = 8.3, 2.5 Hz, 1H), 6.56 – 6.35 (m, 2H), 4.19 – 4.09 (m, 1H), 3.20 (d, *J* = 12.0 Hz, 1H), 2.83 (d, *J* = 2.7 Hz, 7H), 2.74 – 2.64 (m, 1H), 2.42 (d, *J* = 2.8 Hz, 3H), 2.18 – 1.92 (m, 4H), 1.59 – 1.45 (m, 6H).

^{13}C NMR (126 MHz, DMSO-d_6, 75 °C) δ 149.2, 142.7, 139.0, 138.3, 137.5, 131.13, 130.1, 129.5, 129.4, 127.5, 126.7, 125.9, 112.2, 110.5, 51.5 (br), 36.0 (br), 30.9, 30.5, 27.2, 26.8, 25.7, 20.5.

FTIR (Neat film NaCl): 2922, 2850, 1604, 1505, 1483, 1445, 1341, 1156, 1091, 869, 716, 651, 569, 548.

HR-MS (ESI-MS) m/z: [M+H]+ Calc'd for $C_{30}H_{35}N_2O_2S$ 487.2419; Found 487.2413.



12-cyclohexylidene-10-methoxy-5-tosyl-5,6,7,12-tetrahydrodibenzo[*b,e*]azocine (113).

Synthesized according to general procedure 6 starting from the corresponding vinyl tosylate **S27** (32.3 mg, 0.0500 mmol). Crude product was purified via flash column chromatography using 10% ethyl ether in hexanes to give the product **113** as a white powder (0.018 g, 76% yield).

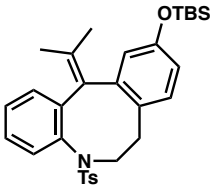
*NMR had poor resolution at room temperature, so NMRs are reported below at 75 °C in DMSO-d_6.

^{1}H NMR (500 MHz, DMSO-d_6, 75 °C) δ 7.73 (d, J = 7.6 Hz, 2H), 7.41 (d, J = 7.8 Hz, 2H), 7.32 (d, J = 7.6 Hz, 1H), 7.23 (dd, J = 7.5, 7.5 Hz, 1H), 7.12 (ddd, J = 7.6, 7.6, 1.6 Hz, 1H), 6.98 (d, J = 8.2 Hz, 1H), 6.93 (d, J = 8.0 Hz, 1H), 6.68 (s, 1H), 6.65 (d, J = 8.2 Hz, 1H), 4.41 (br s, 1H), 3.68 (s, 3H), 3.21 (br s, 1H), 2.75 (br s, 1H), 2.48 (m, 1H), 2.41 (s, 3H), 2.16-2.02 (m, 2H), 2.02-1.90 (m, 2H), 1.74 (br s, 1H), 1.58-1.44 (m, 5H).

^{13}C NMR (126 MHz, DMSO-d_6, 75°C) δ 158.6, 143.6, 139.9, 139.0, 138.9, 131.4, 131.2, 131.1, 130.4, 130.2, 128.4, 127.8, 127.6, 114.8, 112.3, 55.6, 52.0, 36.9, 31.7, 31.3, 27.9, 27.6, 26.5, 21.4.

FTIR (Neat film NaCl): 2922, 2851, 1602, 1572, 1484, 1446, 1343, 1157, 1093, 1039, 874, 813, 737, 717, 651, 569, 549.

HR-MS (ESI-MS) m/z: [M+Na]+ Calc'd for $C_{29}H_{31}NO_3SNa$ 496.1922; Found 496.1930.



10-((*tert*-butyldimethylsilyl)oxy)-12-(propan-2-ylidene)-5-tosyl-5,6,7,12-tetrahydrodibenzo[b,e]azocine (114).

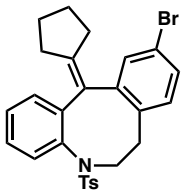
Synthesized according to general procedure 6 starting from the corresponding vinyl tosylate **S33** (35.3 mg, 0.0500 mmol). Crude product was purified via flash column chromatography using 10% ethyl ether in hexanes to give the product **114** as a white powder (0.021 g, 79% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (br s, 2H), 7.39 – 7.17 (m, 4H), 7.09 (t, *J* = 7.5 Hz, 1H), 6.99 – 6.81 (m, 2H), 6.64 – 6.48 (m, 2H), 4.21 (br s, 1H), 3.33 (br s, 1H), 2.83 (br s, 1H), 2.68 (br s, 1H), 2.44 (s, 3H), 1.77 (s, 3H), 1.65 (s, 3H), 0.96 (s, 9H), 0.16 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 154.7, 143.5, 139.9, 139.2, 134.0, 132.8, 132.1, 131.2, 130.4, 130.0, 129.0, 128.0, 127.7, 125.9, 120.8, 118.4, 52.4, 38.1, 26.1, 22.1, 21.9, 21.3, 18.6, –4.1.

FTIR (Neat film NaCl): 2955, 2928, 2856, 1600, 1489, 1347, 1258, 1159, 1093, 877.

HR-MS (ESI-MS) m/z: [M+NH_4]+ Calc'd for $C_{31}H_{43}N_2O_3SSi$ 551.2764; Found 551.2759.



10-bromo-12-cyclopentylidene-5-tosyl-5,6,7,12-tetrahydrodibenzo[b,e]azocine (116).

Synthesized according to general procedure 6 starting from the corresponding vinyl tosylate **S36** (34.0 mg, 0.0500 mmol). Crude product was purified via flash column chromatography using 10% ethyl ether in hexanes to give the product **116** as a white powder (0.020 g, 79% yield).

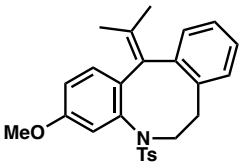
*NMR had poor resolution at room temperature, so NMRs are reported below at 75 °C in DMSO-d_6.

^{1}H NMR (500 MHz, DMSO-d_6, 75 °C) δ 7.73 – 7.59 (m, 2H), 7.38 (dd, J = 7.6, 1.7 Hz, 3H), 7.33 (s, 1H), 7.28 (dd, J = 8.1, 2.2 Hz, 1H), 7.25 (t, J = 7.5 Hz, 1H), 7.15 (td, J = 7.7, 1.6 Hz, 1H), 7.06 (d, J = 8.1 Hz, 2H), 3.82 (br s, 2H), 2.99 (br s, 2H), 2.39 (s, 3H), 2.23 (br s, 2H), 2.00 (br s, 2H), 1.64 (app s, 4H). **CH_2 next to nitrogen is very broad and hard to see/integrate.

^{13}C NMR (126 MHz, DMSO-d_6, 75 °C) δ 142.9, 138.9, 132.1, 130.5, 129.68, 129.4, 129.2, 128.9, 127.2, 126.8, 119.3, 50.5 (br), 35.9 (br), 30.8, 30.6, 29.6, 25.6, 25.5, 20.6.

FTIR (Neat film NaCl): 2952, 2924, 2857, 1454, 1347, 1158, 1091, 1077, 717, 568.

HR-MS (ESI-MS) m/z: $[M+Na]^+$ Calc'd for $C_{27}H_{26}BrNO_2SNa$ 530.0765; Found 530.0781.



3-methoxy-12-(propan-2-ylidene)-5-tosyl-5,6,7,12-tetrahydrodibenzo[*b*,*e*]azocine (117)

Synthesized according to general procedure 6 at 140 °C for 24 hours starting from the corresponding vinyl tosylate **S46** (30.3 mg, 0.0500 mmol). Crude product was purified *via*

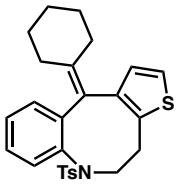
flash column chromatography using 3:1 hexanes:diethyl ether to give the product **117** as white solid (0.017 g, 78% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (br s, 2H), 7.35 (br s, 2H), 7.21–6.92 (m, 5H), 6.79 (br s, 1H), 6.44 (br s, 1H), 4.27 (br s, 1H), 3.64 (s, 3H), 3.46 (br s, 1H), 2.89–2.69 (m, 2H), 2.50–2.22 (m, 3H), 1.80 (s, 3H), 1.62 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 157.4, 142.2, 131.9, 129.5, 128.6, 127.7, 126.7, 126.6, 126.0, 125.6, 113.4, 112.3, 54.2, 50.7, 37.7, 20.7, 20.5, 20.0.

FTIR (Neat film NaCl): 2989, 2870, 1605, 1495, 1443, 1381, 1347, 1287, 1157, 1143, 1091, 813, 688, 584.

HR-MS (ESI-MS) m/z: $[M]^+$ Calc'd for $C_{26}H_{27}NO_3SNa$ 456.1609; Found 456.1596.



11-cyclohexylidene-6-tosyl-4,5,6,11-tetrahydrobenzo[*b*]thieno[3,2-*e*]azocine (119).

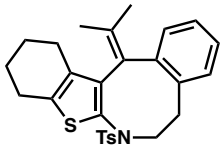
Synthesized according to general procedure 6 at 140 °C for 20 hours starting from the corresponding vinyl tosylate **S38** (31.1 mg, 0.0500 mmol). Crude product was purified *via* flash column chromatography using a gradient of 0-30% diethyl ether in hexanes to give the product **119** as white solid (16.5 mg, 73% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, J = 8.3 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 7.26 – 7.20 (m, 2H), 7.14 – 7.04 (m, 1H), 6.92 (d, J = 5.1 Hz, 1H), 6.88 – 6.82 (m, 1H), 6.77 (d, J = 5.1 Hz, 1H), 4.15 (ddd, J = 14.5, 5.5, 2.1 Hz, 1H), 3.48 (ddd, J = 15.8, 10.5, 2.1 Hz, 1H), 2.98 (dd, J = 14.4, 10.3 Hz, 1H), 2.81 (dd, J = 15.7, 5.3 Hz, 1H), 2.46 (s, 3H), 2.27 – 2.14 (m, 3H), 2.12 (dd, J = 8.4, 4.4 Hz, 1H), 1.87 – 1.79 (m, 1H), 1.73 – 1.65 (m, 1H), 1.63 – 1.48 (m, 4H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 145.9, 143.2, 142.0, 141.0, 139.3, 138.4, 135.0, 130.3, 130.2, 129.6, 128.6, 128.1, 127.6, 127.4, 125.5, 120.8, 51.4, 32.0, 31.6, 31.1, 28.4, 27.9, 26.6, 21.5.

FTIR (Neat film NaCl): 3062, 2921, 2851, 1598, 1483, 1343, 1157, 1094, 864, 737, 726, 661.

HR-MS (ESI-MS) m/z: [M+H]+ Calc'd for $C_{26}H_{28}NO_2S_2$ 450.1561; Found 450.1562.



13-(propan-2-ylidene)-7-tosyl-5,6,7,9,10,11,12,13-octahydrobenzo[*e*]benzo[4,5]thieno[2,3-*b*]azocine (120).

Synthesized according to general procedure 6 at 120 °C for 20 hours starting from the corresponding vinyl tosylate **S42** (31.8 mg, 0.0500 mmol). Crude product was purified *via* flash column chromatography using a gradient of 1-20% diethyl ether in hexanes to give the product **120** as white solid (19.6 mg, 85% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (d, J = 7.8 Hz, 2H), 7.32 (d, J = 7.9 Hz, 2H), 7.21 – 7.04 (m, 4H), 4.26 (dd, J = 15.1, 7.1 Hz, 1H), 3.41 (dd, J = 15.0, 9.7 Hz, 1H), 3.00 – 2.71 (m, 2H), 2.71 – 2.47 (m, 4H), 2.44 (s, 3H), 1.86 – 1.79 (m, 2H), 1.75 (s, 3H), 1.75 – 1.67 (m, 2H), 1.60 (s, 3H).

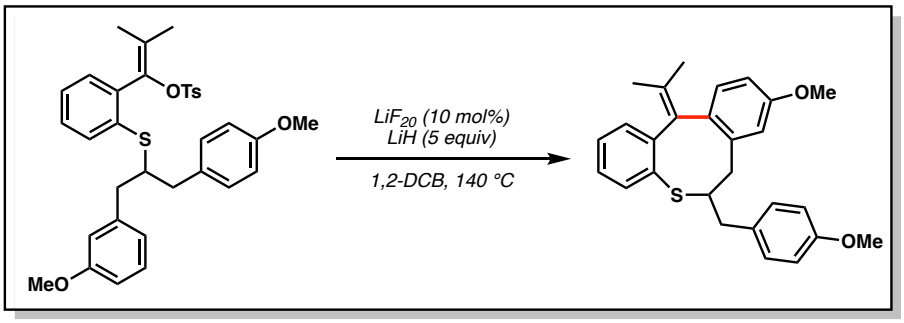
^{13}C NMR (126 MHz, $CDCl_3$) δ 143.6, 143.4, 143.1, 139.1, 137.8, 134.8, 133.7, 132.9, 132.7, 130.4, 129.6, 128.9, 128.39, 127.6, 126.8, 126.7, 51.7, 38.9, 25.1, 25.0, 23.3, 22.7, 21.6, 21.3, 21.0.

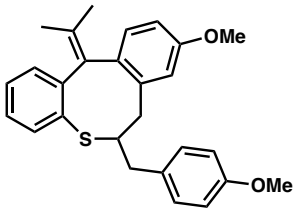
FTIR (Neat film NaCl): 3059, 2986, 2929, 2857, 2843, 1484, 1441, 1341, 1159, 1091, 731, 659, 545.

HR-MS (ESI-MS) m/z: [M+Na]+ Calc'd for $C_{27}H_{29}NO_2S_2Na$ 486.1537; Found 486.1538.

2.7.4 Mechanism studies

2.7.4.1 8-membered ring formation vs 7-membered ring formation





9-methoxy-6-(4-methoxybenzyl)-12-(propan-2-ylidene)-7,12-dihydro-6*H*-dibenzo[*b*,*e*]thiocine (129)

In the glovebox, lithium tetrakis(pentafluorophenyl)borate (3.4 mg, 0.0050 mmol, 0.1 equiv), lithium hydride (2.0 mg, 0.25 mmol, 5.0 equiv), and vinyl tosylate **128** (29.4 mg, 0.0500 mmol, 1.0 equiv) were dissolved into 1,2-dichlorobenzene (2.5 mL) to generate a 0.02 M solution for the vinyl tosylate. The reaction was heated under 140 °C overnight. The reaction solution was directly purified *via* flash column chromatography using hexanes and then ethyl acetate to get rid of 1,2-dichlorobenzene. Then the crude product was purified *via* preparative TLC to get the product. The yield was determined by NMR with nitromethane as the internal standard from the crude reaction.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 – 7.13 (m, 2H), 7.09 – 7.01 (m, 3H), 6.99 – 6.89 (m, 1H), 6.83 (d, J = 8.4 Hz, 2H), 6.78 – 6.58 (m, 2H), 6.56 – 6.37 (m, 1H), 4.05–3.90 (m, 1H), 3.79 (s, 3H), 3.76 – 3.66 (m, 3H), 3.36 – 3.17 (m, 1H), 2.91 – 2.64 (m, 3H), 1.70 (br, 3H), 1.60 – 1.56 (m, 3H).

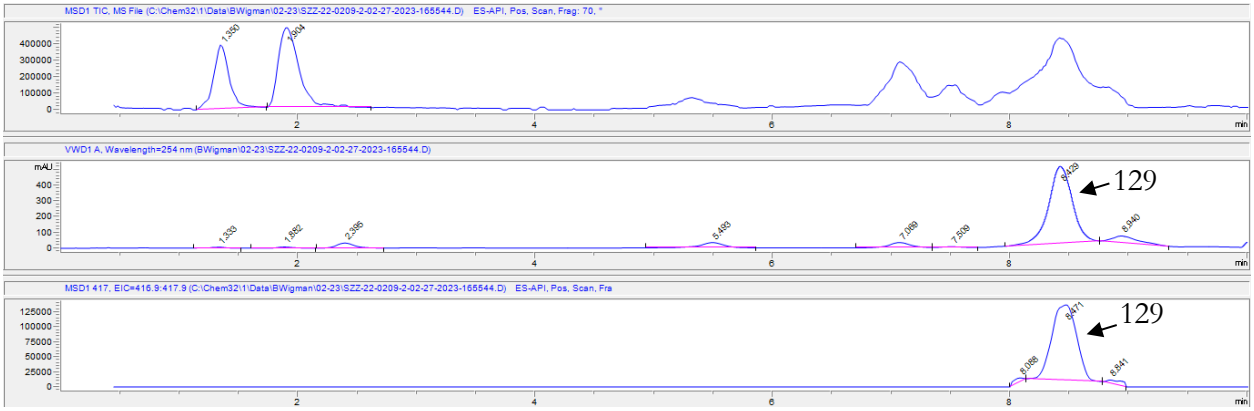
IR (Neat film NaCl): 2907, 2851, 2834, 1603, 1583, 1511, 1496, 1463, 1440, 1245, 1177, 1155, 1114, 1035, 807, 752.

HR-MS (FD-MS) m/z: $[M]^+$ Calc'd for $C_{27}H_{28}O_2S$ 416.1810; Found 416.1804.

***** ^{13}C NMR was complicated due to the existence of rotamers.

Despite the reaction forming **129/130** is complicated with multiple products, LC-MS shows the isolated **129** is the major Friedel-Crafts product (MW = 417) based on the UV (second row, Figure 2.1) and EIC chromatogram (third row**,** Figure 2.1).

Figure 2.1 *The LC-MS trace of the reaction forming* ***129****. (first row: TIC chromatogram; second row: UV (254 nm) chromatogram; third row: EIC (MW = 417) chromatogram; method: 75%:25% water:ACN (0.01 min) to 26%:74% water:ACN (9.80 min) to 100% ACN (9.81 min))*



The ^{1}H NMR of **129** is also complicated (Figure 2.2). A zoom-in into the aromatic region of the ^{1}H NMR shows there are two characteristic doublets each with 2 protons (one is overlapped with one other proton signal) which is corresponding to a *para*-substituted aromatic ring (Figure 2.3). This pattern is only seen if **129** is formed, instead of **130** which has no *para*-substituted aromatic rings.

Figure 2.2 *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***129***.

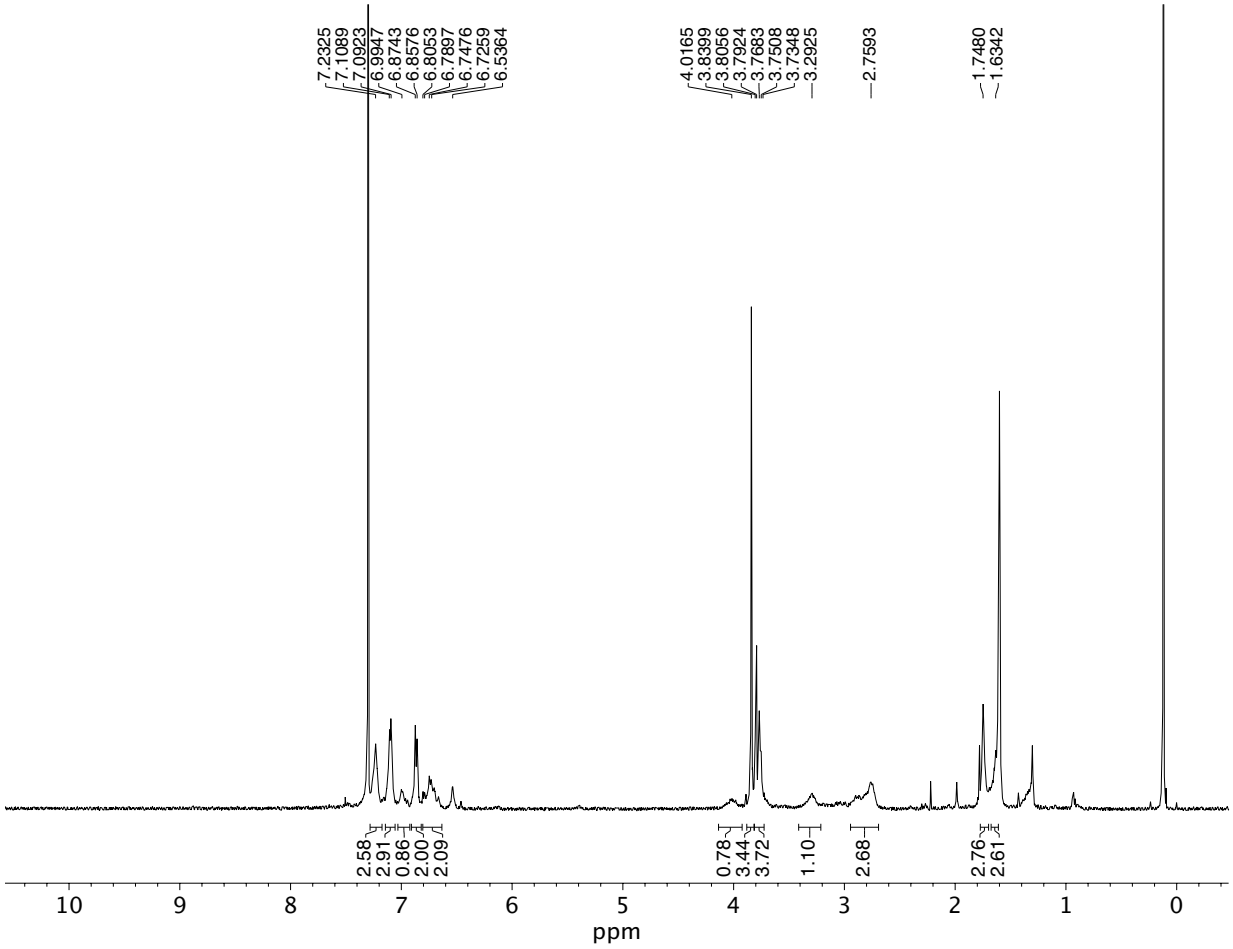
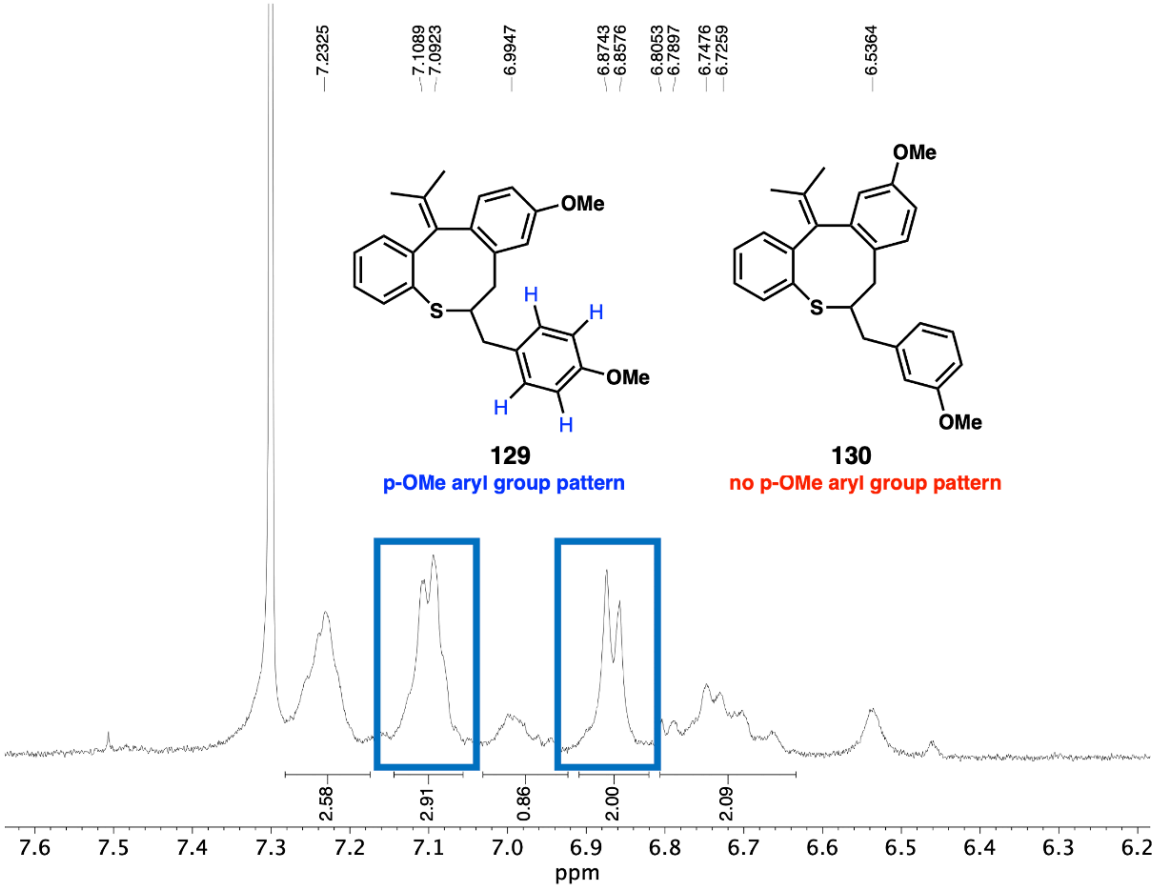
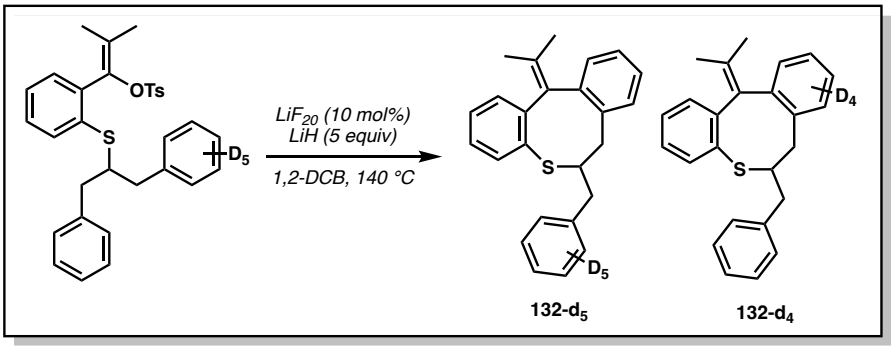


Figure 2.3 *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***129*** *(zoom-in of 7.7–6.1 ppm).*



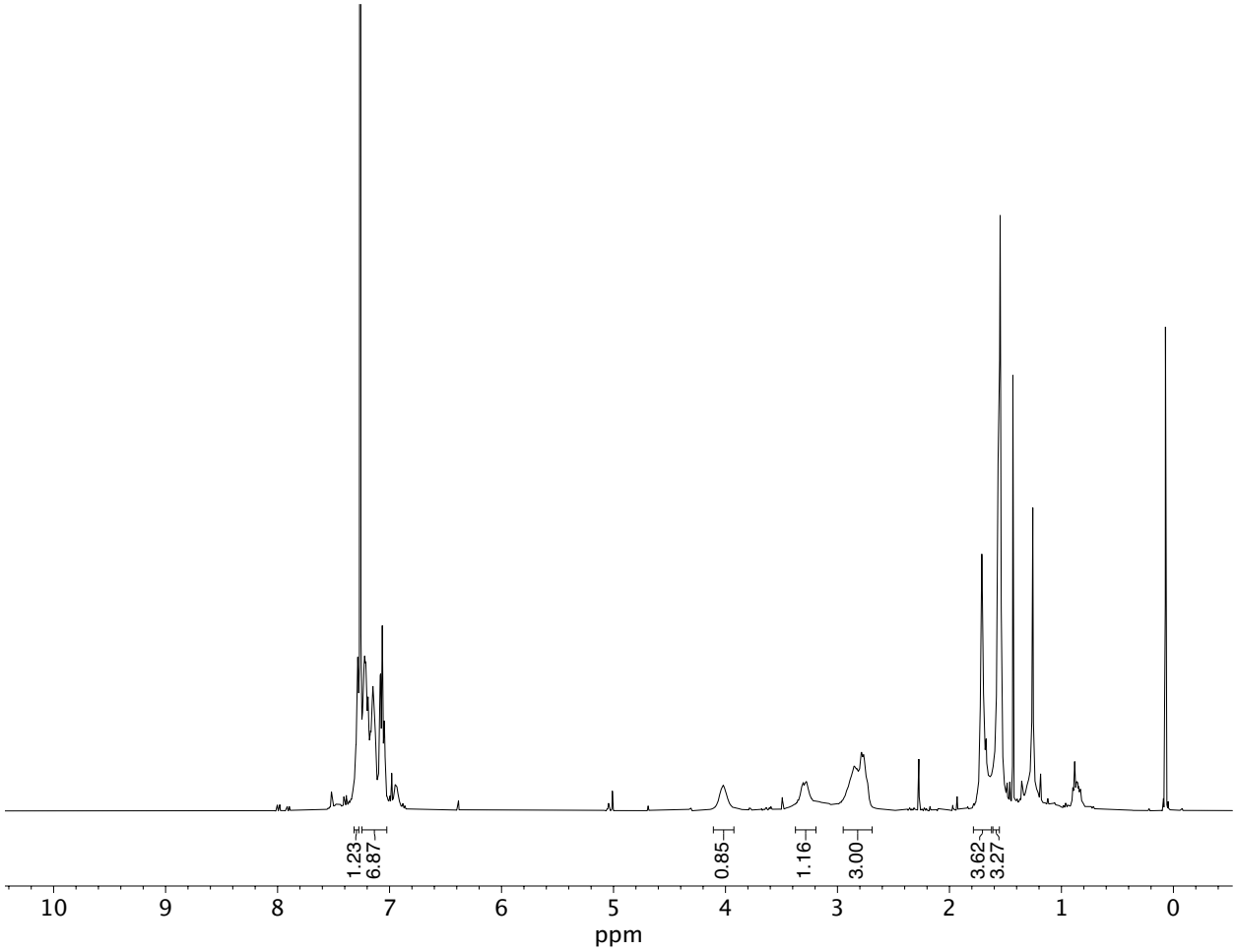
2.7.4.2 Friedel-Crafts reactions vs C–H insertions



In the glovebox, lithium tetrakis(pentafluorophenyl)borate (3.4 mg, 0.0050 mmol, 0.1 equiv), lithium hydride (2.0 mg, 0.25 mmol, 5.0 equiv), and vinyl tosylate **131** (26.7 mg, 0.0500 mmol, 1.0 equiv) were dissolved into 1,2-dichlorobenzene (2.5 mL) to generate a 0.02 M solution for the vinyl tosylate. The reaction was heated under 140 °C overnight. The reaction solution was directly purified *via* flash column chromatography using hexanes and then ethyl acetate to get rid of 1,2-dichlorobenzene. Then the crude product was purified *via* preparative TLC to get the product.

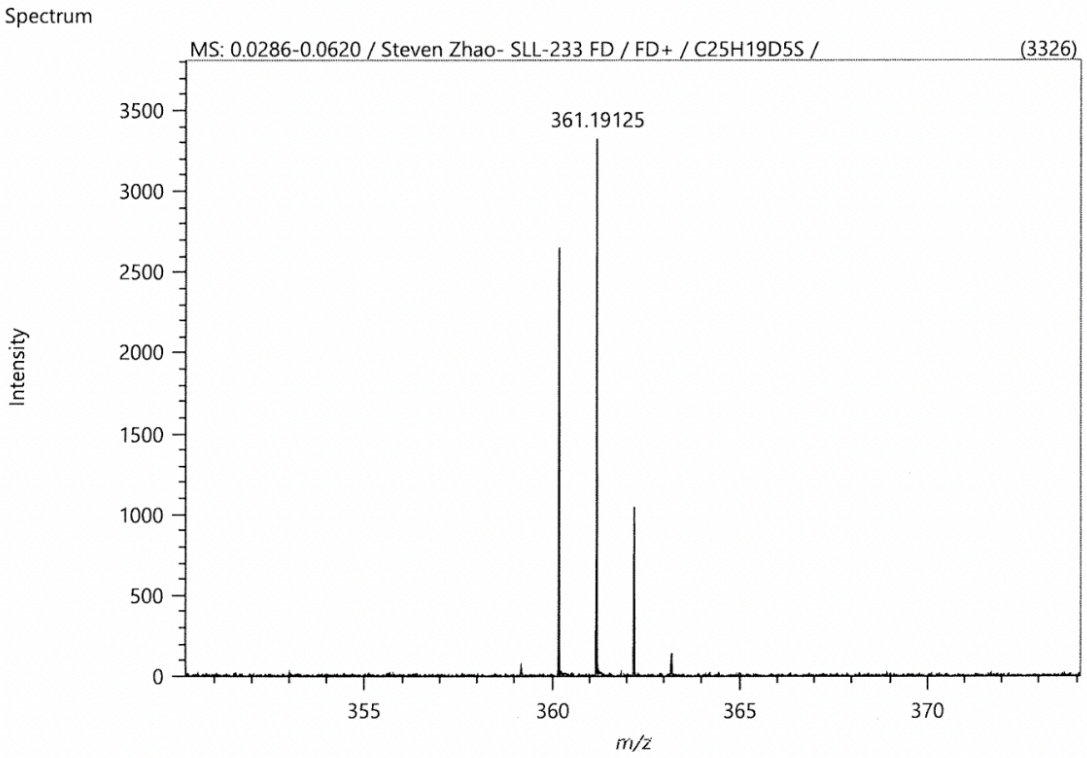
^{1}H NMR shows the product is the desired 8-membered ring product from the Friedel-Crafts reaction (Figure 2.4).

Figure 2.4 *^{1}H NMR (400 MHz, $CDCl_3$) of the mixture product* ***132-d$_5$*** *and* ***132-d$_4$****.*



The HR-MS of this **132-d$_5$** and **132-d$_4$** mixture showed their ratio is around 1:1 (Figure 2.5).

Figure 2.5 *HR-MS report of products* ***132***.



Elemental Composition

Parameters	
Tolerance:	±3.00 ppm
Electron:	Odd/Even
Charge:	0
DBE:	-1.5 - 100.0

Elements Set 1:

Symbol	C	H	O	Hx	S
Min	0	0	0	0	1
Max	100	50	2	5	1

Results

Mass	Intensity	Formula	Calculated Mass	Mass Difference [mDa]	Mass Difference [ppm]	DBE
360.18528	2654.29	C25 H20 S Hx4	360.18498	0.30	0.83	14.0
361.19125	3325.59	C25 H19 S Hx5	361.19126	0.00	-0.01	14.0

2.7.5 Computational studies

2.7.5.1 Computational methods

Density functional theory (DFT) computations were performed with Gaussian 16.[39] The *ω*B97X-D functional was used to optimize molecular geometries.[40] Geometry optimizations were completed with the def2-SVP basis set[41] and the SMD solvation model accounting for the effect of *o*-dichlorobenzene.[42] Frequency calculations were conducted at the same level of theory used for the geometry optimizations in order to obtain thermal Gibbs free energies and characterize the stationary points on the potential energy surface. Single point energies were obtained using the def2-TZVPP basis set.[41] Intrinsic reaction coordinate (IRC) calculations were performed to verify that a transition state (TS) connects the reactant and the product on the potential energy surface.

Conformation searches were executed by Grimme's Conformer-Rotamer Ensemble Sampling Tool (CREST) to find the lowest energy conformers.[43] CYLview was employed to visualize molecular structures.[44]

2.7.5.2 Energies and Cartesian coordinates of calculated structures

Table 2.2 *Energies of the optimized structures (ωB97X-D/def2-SVP/SMD=o-dichlorobenzene).*

Structure	E	ZPE	H	T.S	G(T)
INT1	-1684.511784	0.488122	-1683.967990	0.159247	-1684.127237
INT2-m	-1684.517623	0.488675	-1683.974546	0.154411	-1684.128957
INT2-p	-1684.540119	0.491438	-1683.994980	0.151622	-1684.146602
TS-R	-1684.510634	0.489840	-1683.967969	0.148111	-1684.116080
TS-m	-1684.487656	0.487587	-1683.945750	0.154876	-1684.100626
TS-p	-1684.487267	0.487612	-1683.945149	0.155956	-1684.101105
INT1'	-1684.514887	0.488449	-1683.971117	0.157303	-1684.128420
INT2-p'	-1684.543812	0.491621	-1683.998548	0.151343	-1684.149891

TS-p'	-1684.493320	0.488175	-1683.950954	0.15397	-1684.104924

Table 2.3 *Single point energies (ωB97X-D/def2-TZVPP/SMD=o-dichlorobenzene)*

Structure	E
INT1	-1686.093476
INT2-m	-1686.094830
INT2-p	-1686.117135
TS-R	-1686.088536
TS-m	-1686.069921
TS-p	-1686.070019
INT1'	-1686.094658
INT2-p'	-1686.122058
TS-p'	-1686.076146

2.7.5.3 Cartesian coordinates for structures of Table 2.2 and Table 2.3.

INT1

Charge: 1

C	1.010925	2.218217	-1.610785
C	0.888011	3.600868	-1.684825
C	0.210187	4.350815	-0.706262
C	-0.374103	3.697303	0.351702
C	-0.316478	2.271450	0.429751
C	0.444571	1.523471	-0.537879
N	0.574344	0.151369	-0.403093
S	1.240534	-0.519113	1.029589

O	1.194203	0.518883	2.049986
O	0.585558	-1.794229	1.246058
C	2.929708	-0.785623	0.579620
C	3.371549	-2.078045	0.312049
C	4.701369	-2.267857	-0.057593
C	5.584951	-1.187605	-0.163886
C	5.105490	0.103562	0.114899
C	3.786097	0.315549	0.489808
H	3.430847	1.322746	0.716836
H	5.784797	0.956458	0.043497
C	7.021660	-1.390179	-0.553025
H	7.223482	-2.434283	-0.827385
H	7.687923	-1.119712	0.281271
H	7.291539	-0.746886	-1.404319
H	5.057500	-3.279536	-0.265035
H	2.688551	-2.924943	0.395747
C	0.712378	-0.702418	-1.594856
H	0.790888	-1.735254	-1.232421
C	-0.477762	-0.578117	-2.540632
C	-1.098495	1.623801	1.343579
C	-1.973173	1.084349	2.132742
C	-3.414738	1.027430	1.680255
C	-1.629881	0.505254	3.478936

H	-0.583323	0.672749	3.751446
H	-1.824503	-0.577544	3.443986
H	-4.016044	1.643889	2.365127
H	-3.552030	1.384320	0.652382
H	-0.462577	0.401803	-3.040463
H	-0.312790	-1.321454	-3.338441
H	1.652051	-0.484128	-2.127471
H	-0.917341	4.238263	1.128153
H	0.152969	5.436495	-0.790447
H	1.361960	4.121703	-2.519950
H	1.580810	1.686461	-2.372265
C	-1.834140	-0.787041	-1.905689
C	-2.066767	-1.776631	-0.947512
C	-2.922183	0.008100	-2.293961
C	-3.332292	-1.981330	-0.394548
H	-1.246763	-2.406969	-0.596763
C	-4.189605	-0.182453	-1.757917
H	-2.772852	0.796478	-3.037410
C	-4.406662	-1.179930	-0.797314
H	-3.461738	-2.762167	0.355452
H	-5.030543	0.443607	-2.063332
H	-2.294354	0.948427	4.235009
H	-3.764044	-0.012269	1.751470

O	-5.656905	-1.278375	-0.304044
C	-5.934805	-2.265893	0.658738
H	-5.336706	-2.126185	1.575709
H	-6.997576	-2.166593	0.912768
H	-5.756794	-3.281764	0.266712

There are no imaginary frequencies

INT2-m

Charge: 1

C	1.321834	2.259574	-1.336273
C	0.919234	3.493721	-1.840293
C	-0.383603	3.942277	-1.622329
C	-1.280294	3.157272	-0.899534
C	-0.882914	1.927444	-0.365420
C	0.431861	1.482840	-0.592325
N	0.807780	0.204790	-0.085104
S	1.832928	0.088172	1.220559
O	2.066516	1.442537	1.698495
O	1.293378	-0.926627	2.118241
C	3.361183	-0.547587	0.569836

C	4.306478	0.345254	0.061170
C	5.490189	-0.153149	-0.469991
C	5.749505	-1.532447	-0.499073
C	4.786237	-2.403191	0.024924
C	3.595103	-1.920984	0.563489
H	2.857753	-2.606563	0.984278
H	4.972415	-3.479923	0.018009
C	7.046987	-2.051496	-1.052754
H	7.319974	-1.530139	-1.982038
H	6.996131	-3.129771	-1.257334
H	7.864903	-1.884023	-0.333277
H	6.234095	0.542863	-0.865829
H	4.119562	1.420377	0.091749
C	0.461962	-1.046179	-0.765712
H	0.258235	-1.812196	-0.003403
C	-0.721099	-0.961125	-1.735958
C	-1.830311	1.042812	0.375746
C	-1.842634	0.938545	1.718293
C	-2.649723	-0.076187	2.479912
C	-1.016081	1.837009	2.592490
H	-1.660407	2.284902	3.366766
H	-0.515464	2.640218	2.039340
H	-2.028512	-0.496153	3.285925

H	-3.523601	0.391197	2.962269
H	-0.620805	-0.067107	-2.370902
H	-0.618921	-1.824746	-2.405347
H	1.323971	-1.391586	-1.362799
H	-2.302953	3.505553	-0.733977
H	-0.704492	4.907628	-2.019762
H	1.622093	4.102388	-2.413040
H	2.332351	1.889121	-1.517057
C	-2.112916	-0.999418	-1.170088
C	-2.913650	-2.102460	-1.391330
C	-2.721524	0.173879	-0.507001
C	-4.256432	-2.138932	-0.995420
H	-2.503070	-2.974017	-1.904754
C	-4.113275	0.055796	-0.075242
H	-2.915441	0.786787	-1.440008
C	-4.887211	-1.051922	-0.356033
H	-4.823826	-3.045681	-1.214977
H	-4.561144	0.907250	0.441873
H	-0.245481	1.249584	3.113838
H	-2.997748	-0.917891	1.865022
O	-6.165977	-1.031629	0.024720
C	-6.985995	-2.159648	-0.220877
H	-7.977400	-1.908388	0.172891

H -6.608341 -3.053719 0.301288

H -7.070168 -2.367452 -1.299929

There are no imaginary frequencies

INT2-p

Charge: 1

C 1.740215 2.398813 -0.817479

C 1.593455 3.784488 -0.865930

C 0.378507 4.365953 -0.503788

C -0.685113 3.569459 -0.079027

C -0.546053 2.180434 0.001746

C 0.677889 1.610361 -0.381259

N 0.753531 0.188630 -0.385799

S 1.433502 -0.621936 0.890869

O 1.468681 0.302999 2.012076

O 0.735735 -1.901098 1.006589

C 3.104931 -0.969233 0.403403

C 3.384893 -2.126565 -0.322042

C 4.689759 -2.356906 -0.748160

C 5.719354 -1.451584 -0.456651

C	5.407118	-0.299892	0.280229
C	4.108813	-0.051901	0.714306
H	3.875767	0.842935	1.293905
H	6.197442	0.415094	0.522067
C	7.132451	-1.723699	-0.891432
H	7.663793	-0.791986	-1.133023
H	7.163564	-2.384512	-1.769085
H	7.692144	-2.220259	-0.081856
H	4.914382	-3.262922	-1.316423
H	2.593815	-2.844668	-0.545002
C	0.084916	-0.509261	-1.475693
H	0.014097	-1.571624	-1.211463
C	-1.297917	0.074414	-1.765617
C	-1.637562	1.296460	0.503406
C	-2.080542	1.405312	1.774162
C	-3.235943	0.621862	2.338892
C	-1.416779	2.300540	2.785746
H	-0.438003	2.673189	2.464629
H	-1.278981	1.738794	3.723645
H	-4.017446	0.397899	1.602782
H	-2.888091	-0.326268	2.781781
H	-1.204684	1.052630	-2.256887
H	-1.809549	-0.591931	-2.475189

H	0.680574	-0.436284	-2.400872
H	-1.633376	4.029406	0.208412
H	0.256122	5.450195	-0.552600
H	2.424969	4.409126	-1.198974
H	2.675512	1.920050	-1.115198
C	-2.233637	0.271849	-0.501148
C	-2.370673	-1.094165	0.071677
C	-3.505870	0.791349	-1.075730
C	-3.461960	-1.877319	-0.108491
H	-1.503390	-1.492271	0.607945
C	-4.615706	0.033352	-1.219405
H	-3.496216	1.822576	-1.438801
C	-4.601709	-1.330210	-0.776110
H	-3.482680	-2.894660	0.279577
H	-5.529355	0.416239	-1.675409
H	-2.063233	3.161076	3.025829
H	-3.709372	1.193410	3.151022
O	-5.680055	-2.001275	-1.007329
C	-5.815838	-3.378799	-0.625683
H	-5.744299	-3.476844	0.465711
H	-6.811983	-3.678933	-0.964784
H	-5.049550	-3.987394	-1.124410

There are no imaginary frequencies

TS-R

Charge: 1

C	1.507565	2.369705	-0.722466
C	1.198449	3.692647	-1.028379
C	-0.126734	4.125529	-0.990087
C	-1.138759	3.235715	-0.637921
C	-0.839778	1.914270	-0.291680
C	0.498517	1.484863	-0.340837
N	0.763106	0.111704	-0.073120
S	1.708963	-0.359213	1.215005
O	1.827685	0.795488	2.091786
O	1.148583	-1.609977	1.707728
C	3.314130	-0.722075	0.543230
C	3.565241	-1.981026	-0.000195
C	4.812952	-2.238935	-0.563152
C	5.816355	-1.261980	-0.581046
C	5.539653	-0.009518	-0.011797
C	4.298843	0.267605	0.550338
H	4.096575	1.240789	1.001089

H	6.314336	0.761462	-0.004783
C	7.170002	-1.547003	-1.169002
H	7.168743	-2.477669	-1.752745
H	7.922488	-1.649200	-0.370530
H	7.499394	-0.724729	-1.821549
H	5.012093	-3.223855	-0.992348
H	2.798626	-2.757557	0.024630
C	0.498969	-0.867920	-1.125653
H	0.385620	-1.854877	-0.655473
C	-0.755530	-0.524582	-1.923746
C	-1.939316	0.998874	0.150476
C	-2.125759	0.736781	1.479759
C	-3.173098	-0.151384	2.056446
C	-1.267374	1.400463	2.513933
H	-0.541847	2.116320	2.118050
H	-0.717780	0.623719	3.069268
H	-3.139214	-0.124211	3.152408
H	-4.178918	0.157068	1.730701
H	-0.645307	0.438533	-2.437350
H	-0.849586	-1.285128	-2.715382
H	1.346146	-0.919194	-1.831726
H	-2.178095	3.572658	-0.611256
H	-0.374267	5.159738	-1.237842

H	1.994892	4.383055	-1.313416
H	2.537896	2.015621	-0.783890
C	-2.049635	-0.570949	-1.164012
C	-2.552210	-1.832626	-0.751164
C	-2.927117	0.587043	-1.045857
C	-3.889182	-2.006270	-0.511871
H	-1.883990	-2.695844	-0.741924
C	-4.345698	0.349699	-0.772401
H	-2.775762	1.363623	-1.805335
C	-4.821835	-0.908587	-0.550259
H	-4.248424	-3.013243	-0.294170
H	-5.030421	1.199261	-0.773826
H	-1.921553	1.907089	3.241578
H	-3.041428	-1.198778	1.739346
O	-6.133683	-1.067342	-0.340050
C	-6.676337	-2.360667	-0.151888
H	-6.280080	-2.840618	0.757507
H	-7.757788	-2.222889	-0.035791
H	-6.492064	-3.009032	-1.023823

1 imaginary frequency: –140.91 cm^{-1}

TS-m

Charge: 1

C	1.659123	2.141509	-0.929783
C	1.492579	3.515355	-1.118783
C	0.274249	4.136655	-0.834452
C	-0.789750	3.387624	-0.348538
C	-0.622506	2.010765	-0.116431
C	0.607649	1.383636	-0.429280
N	0.672182	-0.030959	-0.328444
S	1.427139	-0.745150	0.973115
O	1.316441	0.204485	2.070364
O	0.872842	-2.084971	1.083774
C	3.140799	-0.887355	0.534458
C	4.030514	0.113010	0.922302
C	5.362779	0.023056	0.526399
C	5.818130	-1.050994	-0.248925
C	4.900139	-2.047088	-0.616535
C	3.567136	-1.976537	-0.228669
H	2.866465	-2.765639	-0.507387
H	5.239516	-2.897643	-1.213092
C	7.259173	-1.157000	-0.663275
H	7.809437	-0.229646	-0.453367

H	7.346213	-1.379646	-1.737335
H	7.756488	-1.976946	-0.120805
H	6.063991	0.803666	0.831028
H	3.685471	0.950362	1.531098
C	0.426572	-0.798207	-1.548687
H	0.300490	-1.850637	-1.261705
C	-0.819894	-0.296388	-2.276190
C	-1.630891	1.246456	0.538851
C	-2.037764	0.835670	1.716367
C	-3.043306	-0.204859	2.091750
C	-1.365796	1.551216	2.878337
H	-2.158806	1.975975	3.513074
H	-0.679272	2.346821	2.569758
H	-2.931361	-0.450106	3.155370
H	-4.065252	0.169694	1.934330
H	-0.685108	0.749396	-2.588288
H	-0.901659	-0.876838	-3.208604
H	1.291282	-0.728880	-2.231564
H	-1.749140	3.856515	-0.122222
H	0.155883	5.209092	-0.998095
H	2.322721	4.106135	-1.511555
H	2.602151	1.654566	-1.185183
C	-2.114563	-0.446282	-1.520394

C	-2.609605	-1.723512	-1.213762
C	-2.957723	0.663060	-1.252688
C	-3.903320	-1.908333	-0.752258
H	-1.984479	-2.600278	-1.398507
C	-4.272120	0.477047	-0.785060
H	-2.694346	1.643975	-1.651176
C	-4.752829	-0.801160	-0.531645
H	-4.253918	-2.922783	-0.559331
H	-4.925845	1.335295	-0.621523
H	-0.804876	0.803959	3.456987
H	-2.906330	-1.118242	1.502651
O	-6.004689	-0.899974	-0.064022
C	-6.548566	-2.174208	0.209694
H	-7.569201	-2.003181	0.572537
H	-5.975693	-2.700547	0.990940
H	-6.592316	-2.800454	-0.696515

1 imaginary frequency: –297.45 cm^{-1}

TS-p

Charge: 1

C	1.678658	2.167778	-0.878696
C	1.460934	3.535673	-1.061209
C	0.212652	4.107971	-0.801815
C	-0.830398	3.317741	-0.337453
C	-0.611780	1.946318	-0.107902
C	0.645416	1.368167	-0.408245
N	0.745471	-0.041377	-0.317029
S	1.520341	-0.756225	0.969275
O	1.419449	0.187070	2.072924
O	0.976448	-2.100556	1.079509
C	3.228201	-0.886726	0.503705
C	3.643360	-1.960507	-0.286954
C	4.969359	-2.020590	-0.699420
C	5.891781	-1.029409	-0.329318
C	5.448231	0.027988	0.474976
C	4.122656	0.107420	0.895547
H	3.786338	0.932439	1.525714
H	6.153184	0.804166	0.782298
C	7.324920	-1.123438	-0.773017
H	7.391738	-1.324599	-1.852759
H	7.834453	-1.952632	-0.256565
H	7.876988	-0.198933	-0.555403
H	5.299718	-2.858545	-1.318482

H	2.939616	-2.745729	-0.568944
C	0.383245	-0.810078	-1.506172
H	0.250590	-1.856335	-1.201834
C	-0.888631	-0.268527	-2.153872
C	-1.578337	1.150325	0.559731
C	-2.062531	0.834814	1.736809
C	-3.144488	-0.117499	2.135096
C	-1.376840	1.564767	2.884272
H	-0.596843	2.262241	2.561736
H	-0.924960	0.807052	3.540867
H	-4.113491	0.191047	1.720204
H	-2.921174	-1.130962	1.778625
H	-0.738911	0.769685	-2.484866
H	-1.045964	-0.845666	-3.079306
H	1.198295	-0.772663	-2.249389
H	-1.809769	3.748392	-0.121447
H	0.057096	5.175854	-0.963992
H	2.275302	4.161449	-1.432389
H	2.644759	1.720123	-1.118262
C	-2.161503	-0.367896	-1.344747
C	-2.595990	-1.635724	-0.890011
C	-3.122003	0.675427	-1.361258
C	-3.911093	-1.871945	-0.545850

H	-1.890667	-2.469212	-0.867780
C	-4.446986	0.452757	-0.990773
H	-2.845305	1.648222	-1.773601
C	-4.858378	-0.822418	-0.599472
H	-4.206883	-2.872270	-0.229468
H	-5.179313	1.260917	-1.019815
H	-2.148948	2.108316	3.450173
H	-3.228315	-0.140695	3.228219
O	-6.143702	-0.965998	-0.271783
C	-6.632534	-2.231315	0.129344
H	-6.132213	-2.584942	1.045078
H	-7.700800	-2.096695	0.336187
H	-6.513348	-2.981363	-0.668965

1 imaginary frequency: –232.18 cm^{-1}

INT1'

Charge: 1

C	0.873986	2.381439	-1.254939
C	0.757846	3.761624	-1.120733
C	0.044298	4.355027	-0.065401

C	-0.578524	3.549501	0.859243
C	-0.526130	2.128935	0.719890
C	0.260601	1.536289	-0.328918
N	0.371573	0.153860	-0.411073
S	1.077271	-0.712051	0.886440
O	0.934737	0.110607	2.078963
O	0.519903	-2.052248	0.843173
C	2.787384	-0.769319	0.446111
C	3.572353	0.368579	0.646703
C	4.908586	0.331638	0.268380
C	5.471401	-0.821162	-0.301821
C	4.657093	-1.947429	-0.479426
C	3.314692	-1.931997	-0.111875
H	2.688568	-2.815396	-0.247060
H	5.081518	-2.857688	-0.909200
C	6.910646	-0.836368	-0.731865
H	7.529618	-0.202188	-0.081625
H	7.004459	-0.445722	-1.758491
H	7.320447	-1.855855	-0.727081
H	5.532906	1.213922	0.427821
H	3.150472	1.266129	1.103230
C	0.494985	-0.501060	-1.726299
H	0.517523	-1.581446	-1.535058

C	-0.658929	-0.167138	-2.663097
C	-1.332124	1.359686	1.513899
C	-2.234481	0.770473	2.232913
C	-3.670646	0.807738	1.758341
C	-1.933058	0.062866	3.527022
H	-2.466323	0.579498	4.339182
H	-0.860680	0.033628	3.744517
H	-4.044473	-0.224083	1.694316
H	-4.265609	1.347959	2.510116
H	-0.590936	0.880844	-2.991217
H	-0.493505	-0.768342	-3.572587
H	1.453018	-0.242832	-2.206586
H	-1.146382	3.970348	1.690404
H	-0.009390	5.440946	0.017845
H	1.264154	4.401325	-1.847225
H	1.472604	1.965139	-2.064654
C	-2.058179	-0.425454	-2.145747
C	-2.303874	-1.300683	-1.079467
C	-3.136656	0.208834	-2.769646
C	-3.612332	-1.534503	-0.643015
H	-1.472865	-1.785391	-0.569574
C	-4.442793	-0.045078	-2.345215
H	-2.954932	0.900597	-3.596174

C	-4.689281	-0.911822	-1.287977
H	-5.281248	0.447815	-2.843265
H	-2.324948	-0.963000	3.463531
H	-3.783176	1.296823	0.783091
H	-5.703359	-1.108679	-0.934688
O	-3.916587	-2.320602	0.411373
C	-2.869123	-2.948140	1.115194
H	-3.331506	-3.478344	1.957095
H	-2.335369	-3.678106	0.483531
H	-2.138826	-2.219041	1.502671

There are no imaginary frequencies

INT2-p'

Charge: 1

C	1.494789	2.042645	-1.376370
C	1.318957	3.290026	-1.970197
C	0.100729	3.956456	-1.837627
C	-0.939426	3.373928	-1.115433
C	-0.771418	2.132158	-0.494081
C	0.463535	1.471708	-0.628093

N	0.603000	0.183063	-0.028017
S	1.610140	-0.020008	1.284452
O	1.868246	1.303543	1.830318
O	1.019284	-1.062140	2.113244
C	3.141514	-0.657429	0.641142
C	4.169829	0.231383	0.323940
C	5.352844	-0.265566	-0.212292
C	5.528852	-1.639380	-0.434977
C	4.482990	-2.508817	-0.098344
C	3.292856	-2.029446	0.442973
H	2.492204	-2.718442	0.717449
H	4.603704	-3.583269	-0.257040
C	6.824602	-2.164067	-0.987612
H	7.241474	-1.483000	-1.743607
H	6.697276	-3.157218	-1.440395
H	7.572937	-2.257453	-0.183597
H	6.161088	0.427582	-0.458652
H	4.045715	1.300534	0.504636
C	0.218884	-1.025106	-0.757630
H	0.031867	-1.819095	-0.021629
C	-1.006386	-0.866756	-1.660970
C	-1.879876	1.452351	0.241985
C	-1.963366	1.453216	1.585964

C	-2.929443	0.606506	2.373305
C	-1.070909	2.310956	2.436484
H	-1.690329	2.888010	3.143220
H	-0.452403	3.006170	1.856917
H	-2.498458	0.384531	3.360634
H	-3.881114	1.133029	2.553000
H	-0.845825	-0.030394	-2.357802
H	-1.039746	-1.781581	-2.268336
H	1.045714	-1.356865	-1.411409
H	-1.896913	3.892113	-1.021154
H	-0.042439	4.933685	-2.303995
H	2.132252	3.738507	-2.544569
H	2.437782	1.504270	-1.489888
C	-2.355673	-0.701595	-1.013508
C	-3.165934	-1.788862	-0.855848
C	-2.846193	0.666005	-0.665089
C	-4.520730	-1.630318	-0.443553
H	-2.793254	-2.780539	-1.112593
C	-4.267224	0.742812	-0.251854
H	-2.834550	1.212291	-1.634172
C	-5.076477	-0.334803	-0.190064
H	-4.654812	1.735960	-0.012479
H	-0.397493	1.679688	3.035387

H	-3.146996	-0.353837	1.888421
H	-6.127921	-0.265832	0.090552
O	-5.337935	-2.622994	-0.303816
C	-4.929175	-3.983059	-0.504773
H	-5.815047	-4.588929	-0.290798
H	-4.614021	-4.134916	-1.546293
H	-4.119596	-4.243264	0.190227

There are no imaginary frequencies

TS-p'

Charge: 1

C	1.564688	2.053575	-1.241333
C	1.494838	3.405227	-1.591358
C	0.376917	4.177533	-1.266903
C	-0.686977	3.603318	-0.584291
C	-0.613430	2.252583	-0.193428
C	0.518274	1.470157	-0.540796
N	0.477171	0.079918	-0.252231
S	1.255552	-0.496894	1.107824
O	1.269861	0.607392	2.055794

O	0.618666	-1.761007	1.440474
C	2.926042	-0.827497	0.611062
C	3.892873	0.165167	0.763143
C	5.189514	-0.081172	0.318310
C	5.532962	-1.303236	-0.273875
C	4.539901	-2.286569	-0.403716
C	3.240750	-2.060385	0.035468
H	2.480093	-2.837671	-0.057148
H	4.792992	-3.250584	-0.852138
C	6.930376	-1.571099	-0.758453
H	7.597650	-0.721787	-0.558669
H	6.935840	-1.766438	-1.842229
H	7.349515	-2.462748	-0.267192
H	5.952077	0.691832	0.440041
H	3.635663	1.116795	1.231211
C	0.192596	-0.835397	-1.358696
H	0.009166	-1.827564	-0.924947
C	-1.021287	-0.382002	-2.167848
C	-1.609482	1.662829	0.617660
C	-2.019148	1.306231	1.804839
C	-3.035049	0.286743	2.207822
C	-1.330220	2.059779	2.933383
H	-2.114438	2.516767	3.556202

H	-0.640930	2.837724	2.586518
H	-2.834496	-0.026839	3.240497
H	-4.046060	0.717458	2.170839
H	-0.830506	0.607273	-2.608825
H	-1.115229	-1.079235	-3.014412
H	1.062843	-0.911593	-2.034256
H	-1.572653	4.186988	-0.327473
H	0.336072	5.228933	-1.555744
H	2.323112	3.858283	-2.140101
H	2.429734	1.450556	-1.523257
C	-2.333152	-0.363926	-1.420822
C	-2.918793	-1.570351	-1.024345
C	-3.029941	0.845445	-1.205440
C	-4.222190	-1.588817	-0.512760
H	-2.369042	-2.500043	-1.175403
C	-4.353268	0.810846	-0.705189
H	-2.671801	1.762183	-1.671990
C	-4.948445	-0.383431	-0.374195
H	-4.907511	1.745397	-0.595873
H	-0.770366	1.328697	3.533053
H	-2.995340	-0.590625	1.554334
H	-5.967390	-0.430116	0.013383
O	-4.860361	-2.695837	-0.135437

C -4.206094 -3.946445 -0.221148

H -4.913008 -4.691265 0.162802

H -3.951024 -4.196544 -1.263633

H -3.292853 -3.963990 0.395636

1 imaginary frequency: –281.76 cm^{-1}

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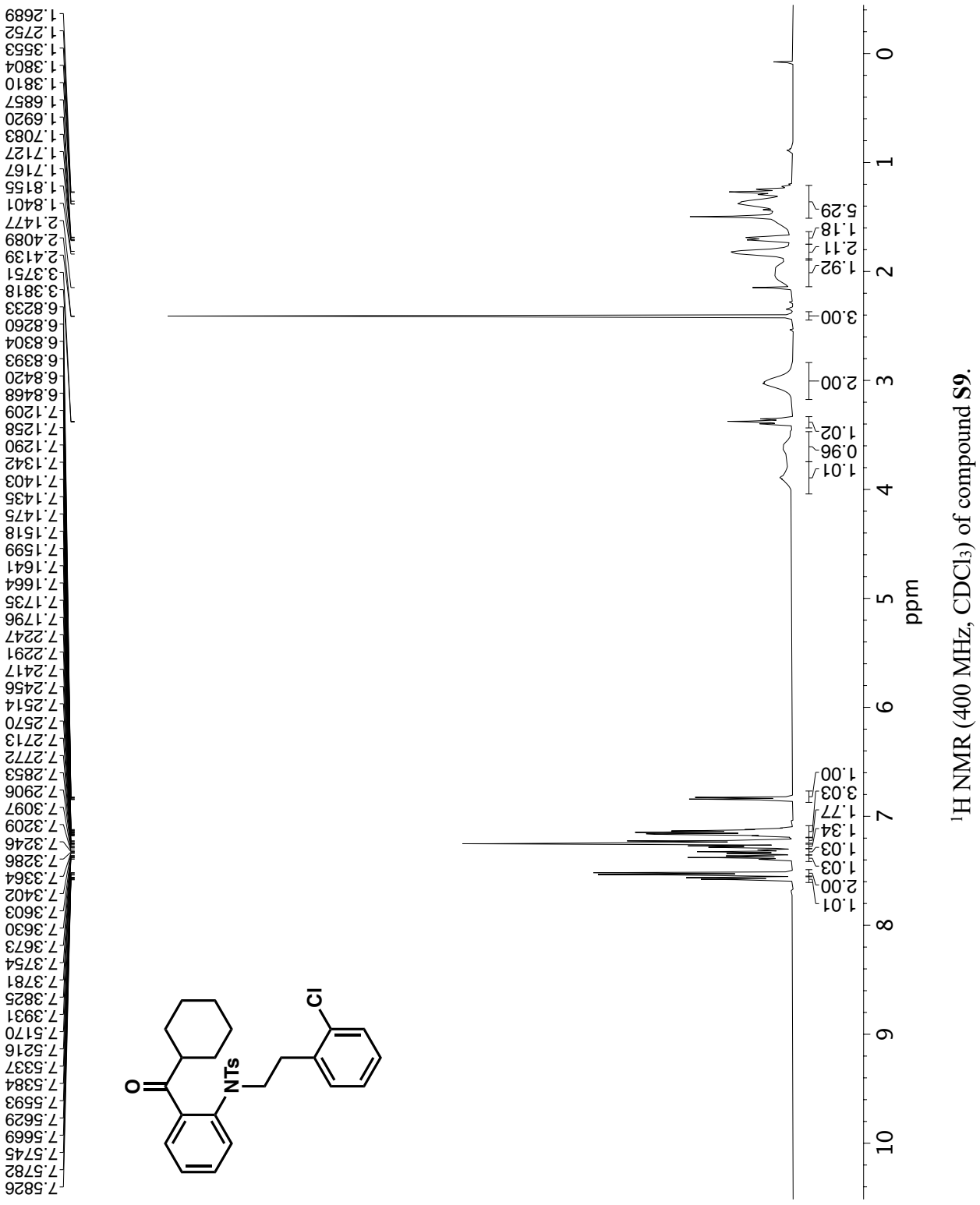
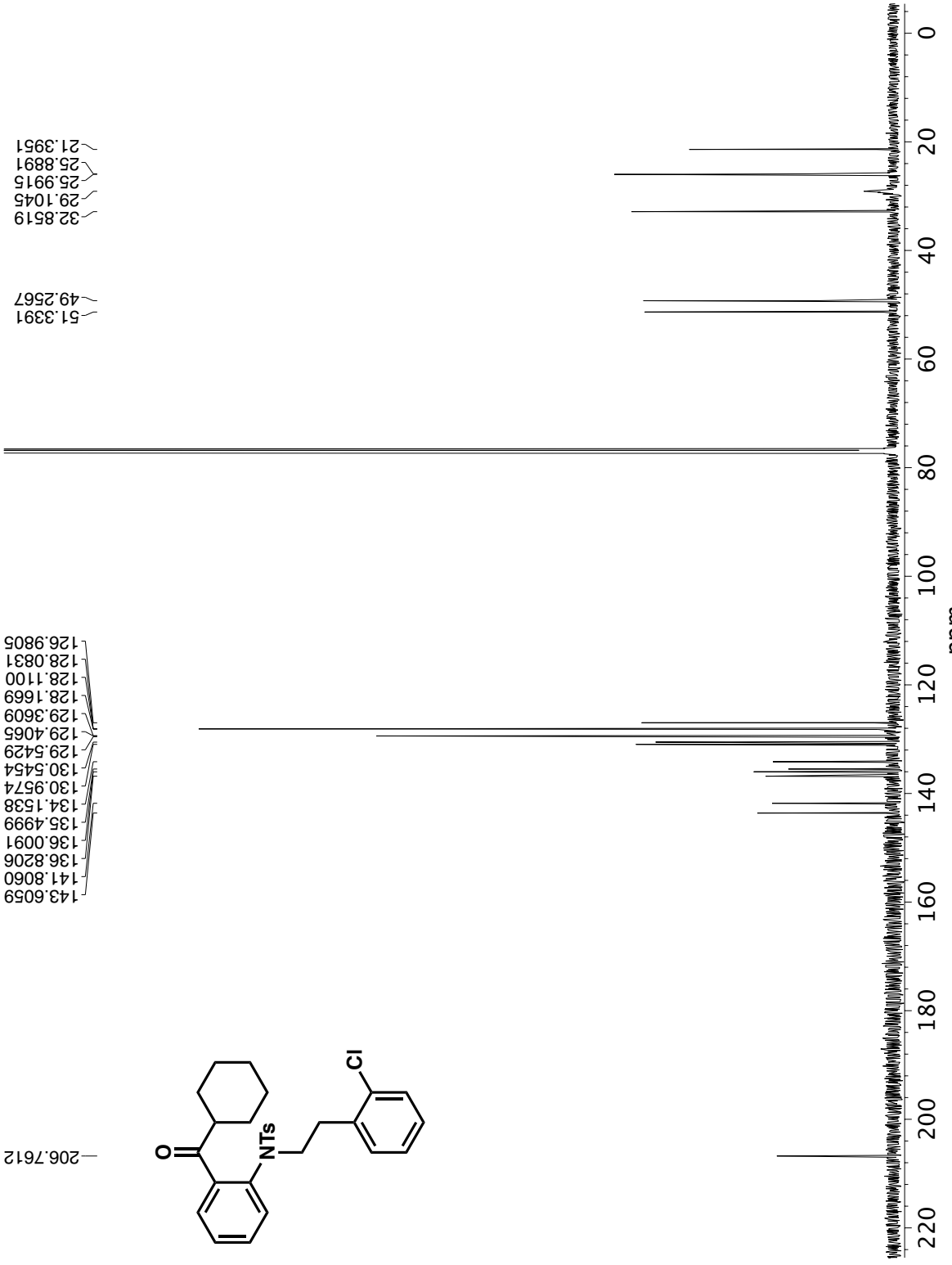
APPENDIX 2

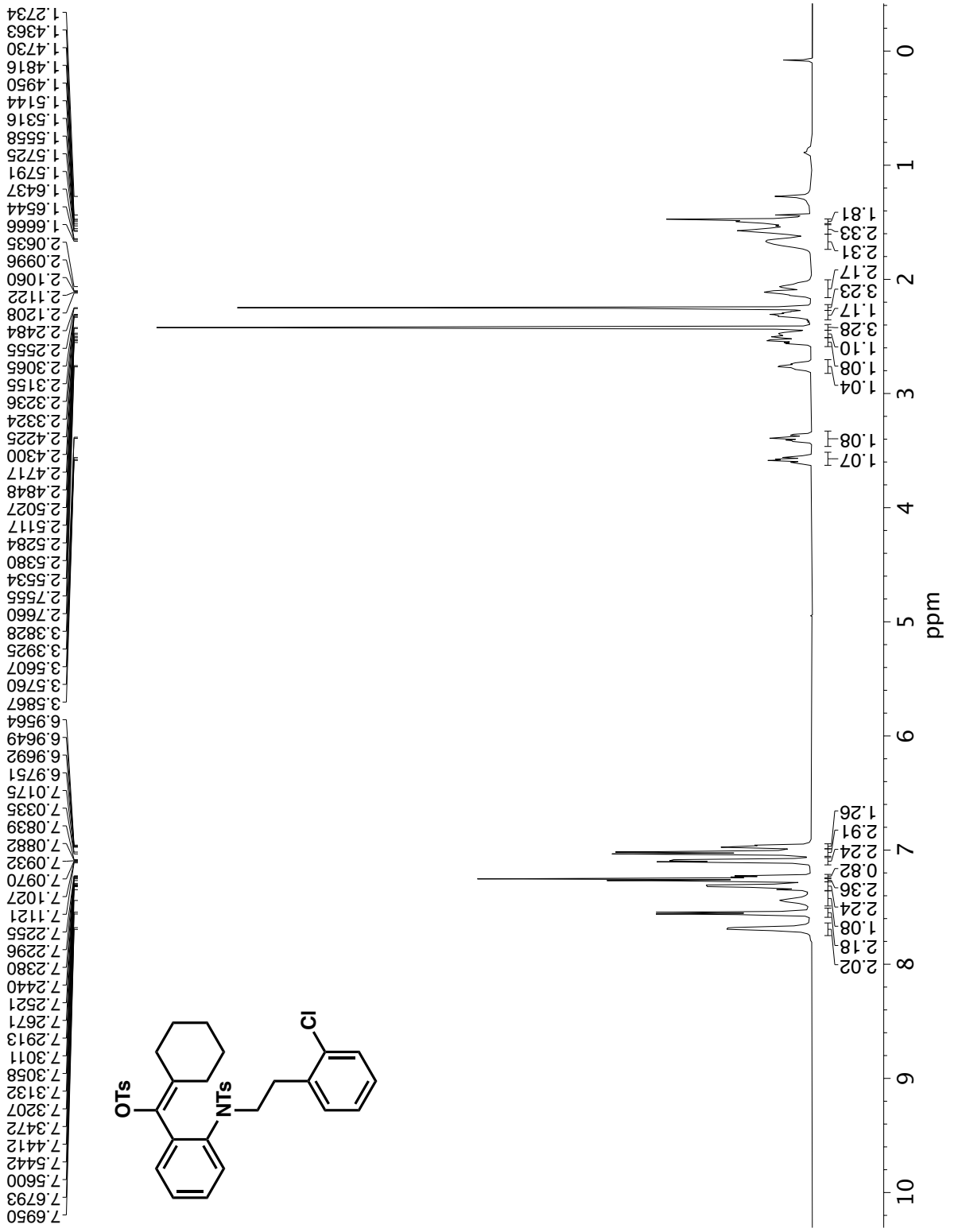
Spectra Relevant to Chapter 2: Accessing Medium-sized Rings via Vinyl Carbocation Intermediates



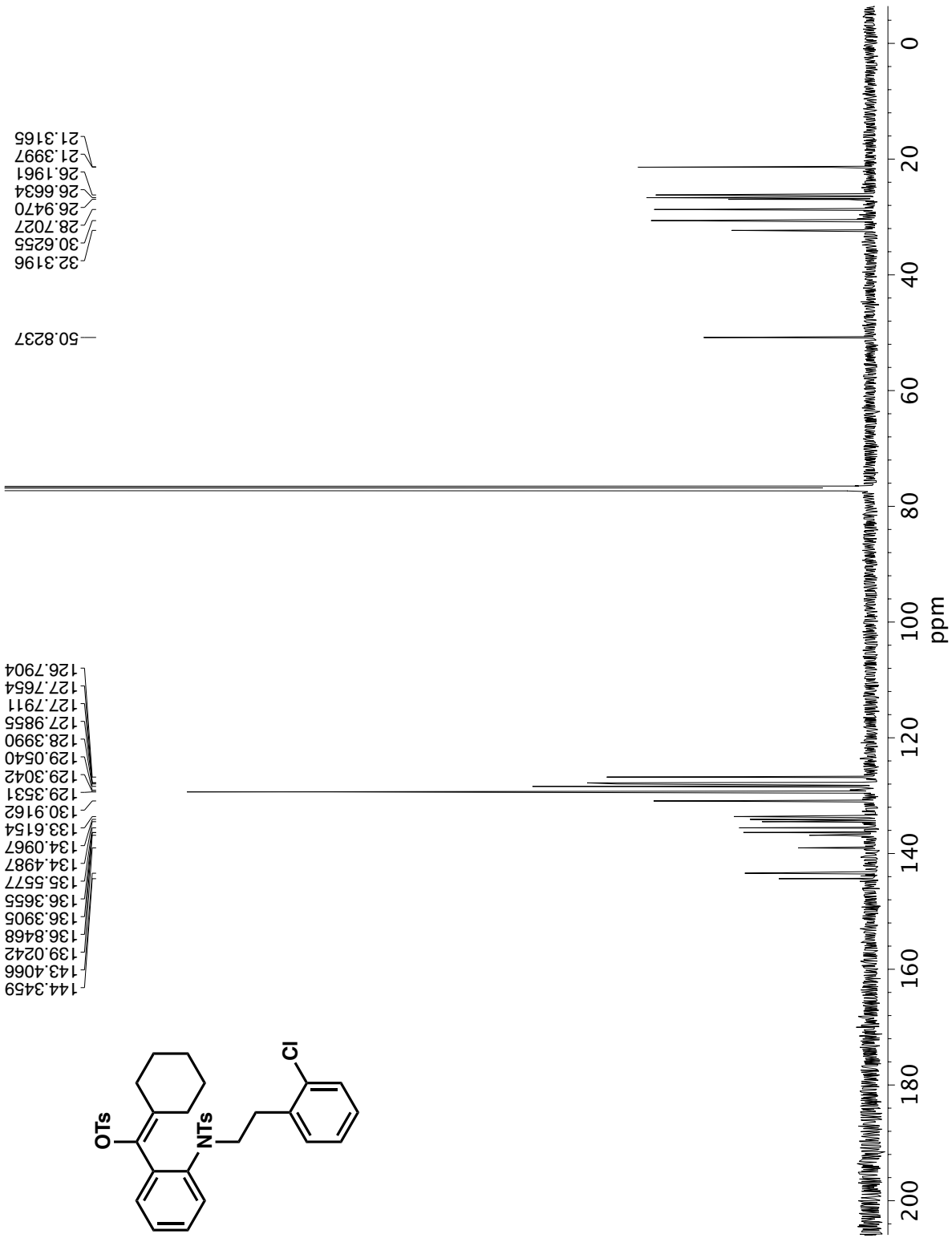
^{1}H NMR (400 MHz, $CDCl_3$) of compound **S9**.



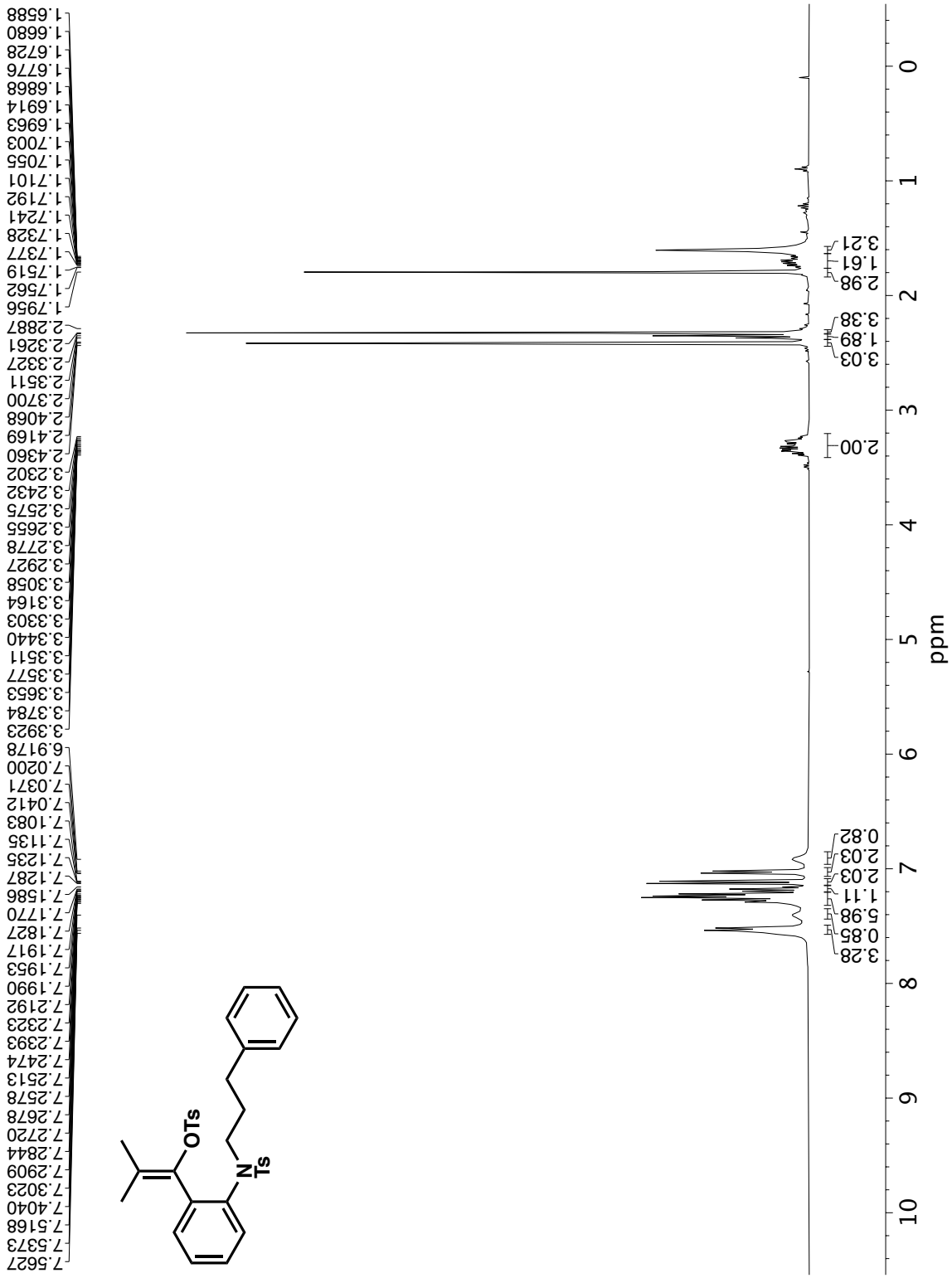
^{13}C NMR (101 MHz, $CDCl_3$) of compound **S9**.



^{1}H NMR (500 MHz, $CDCl_3$, 70 °C) of compound **101**.

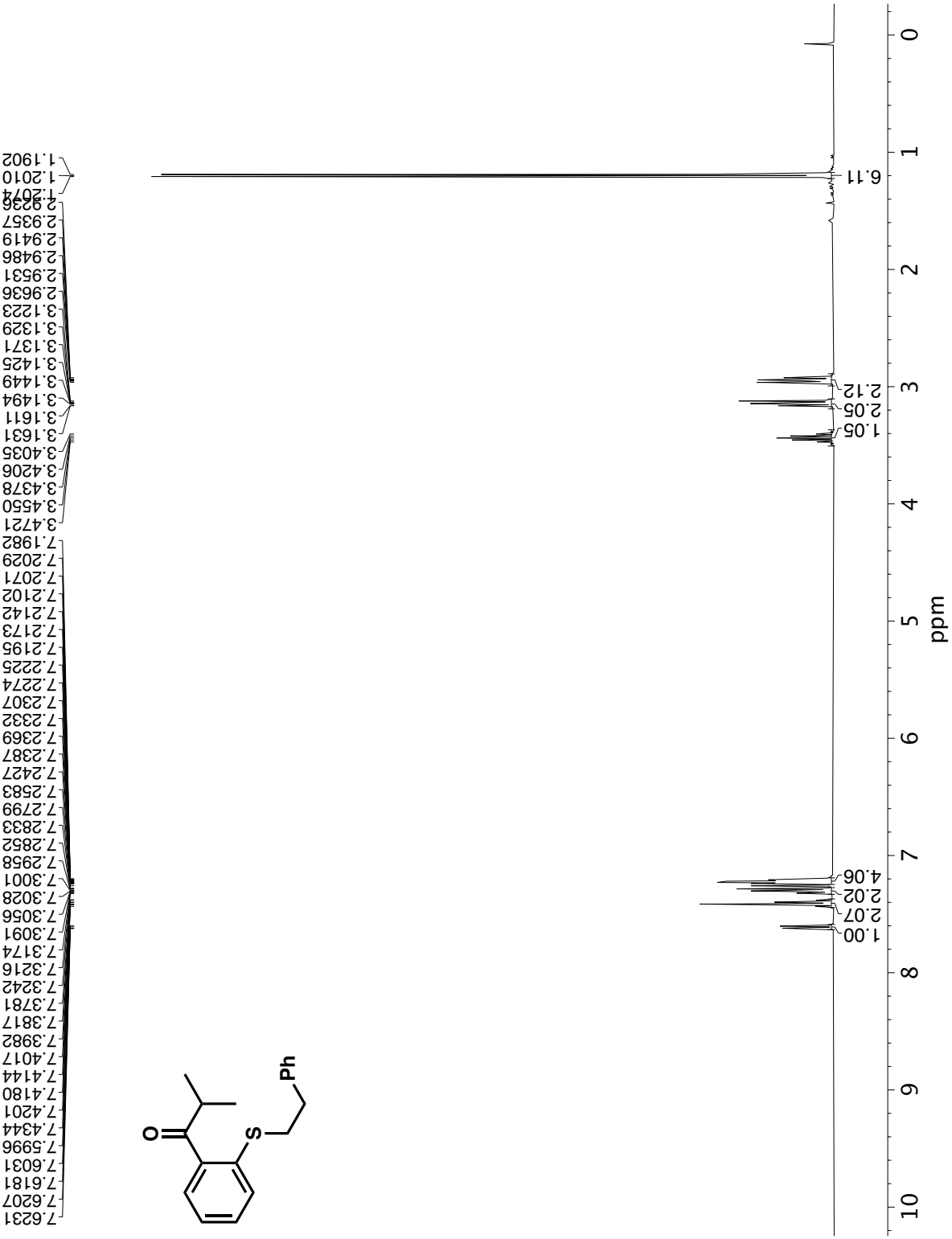


^{13}C NMR (126 MHz, $CDCl_3$) of compound **101**.

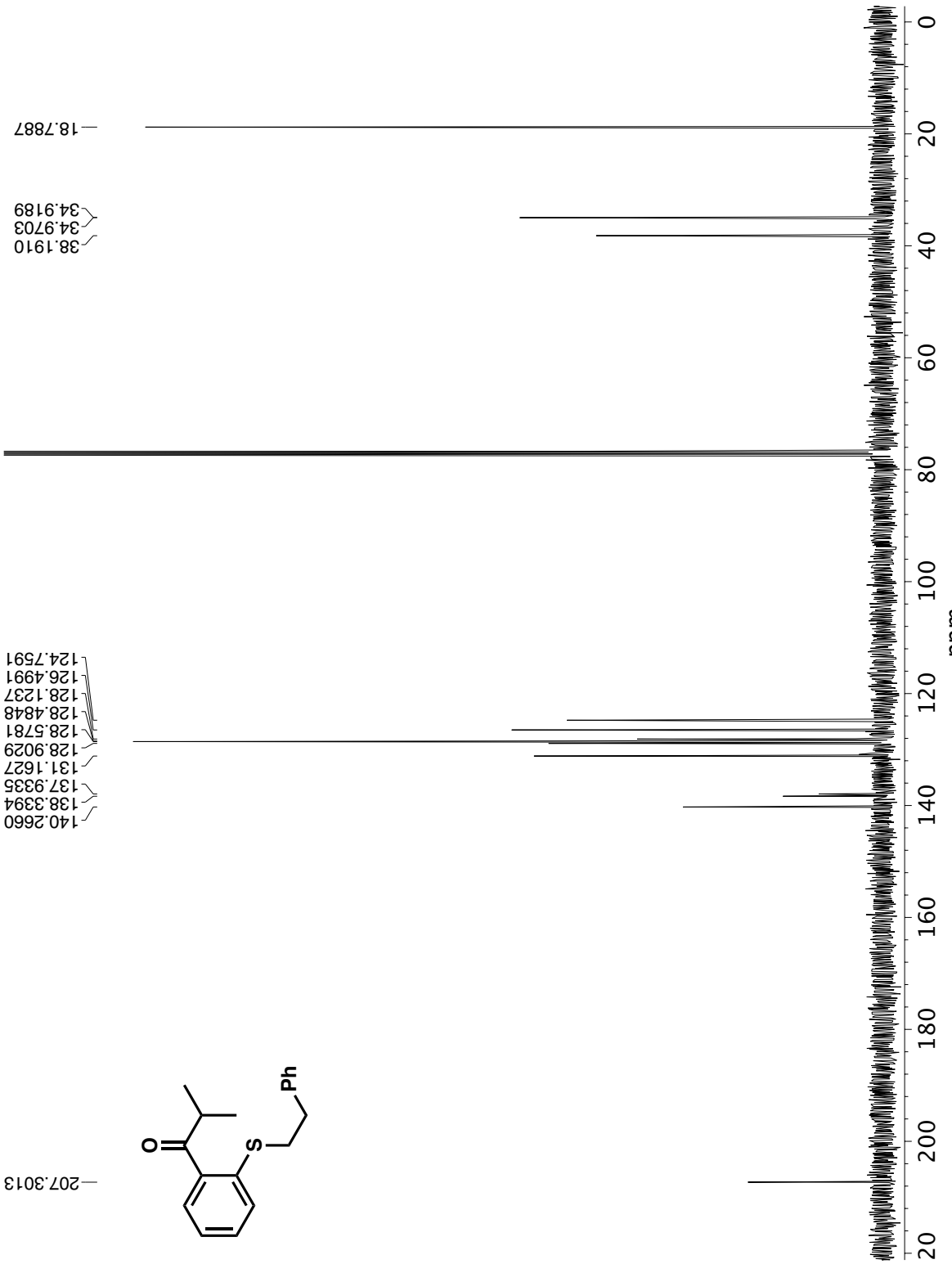


^{1}H NMR (400 MHz, $CDCl_3$) of compound **S11**.

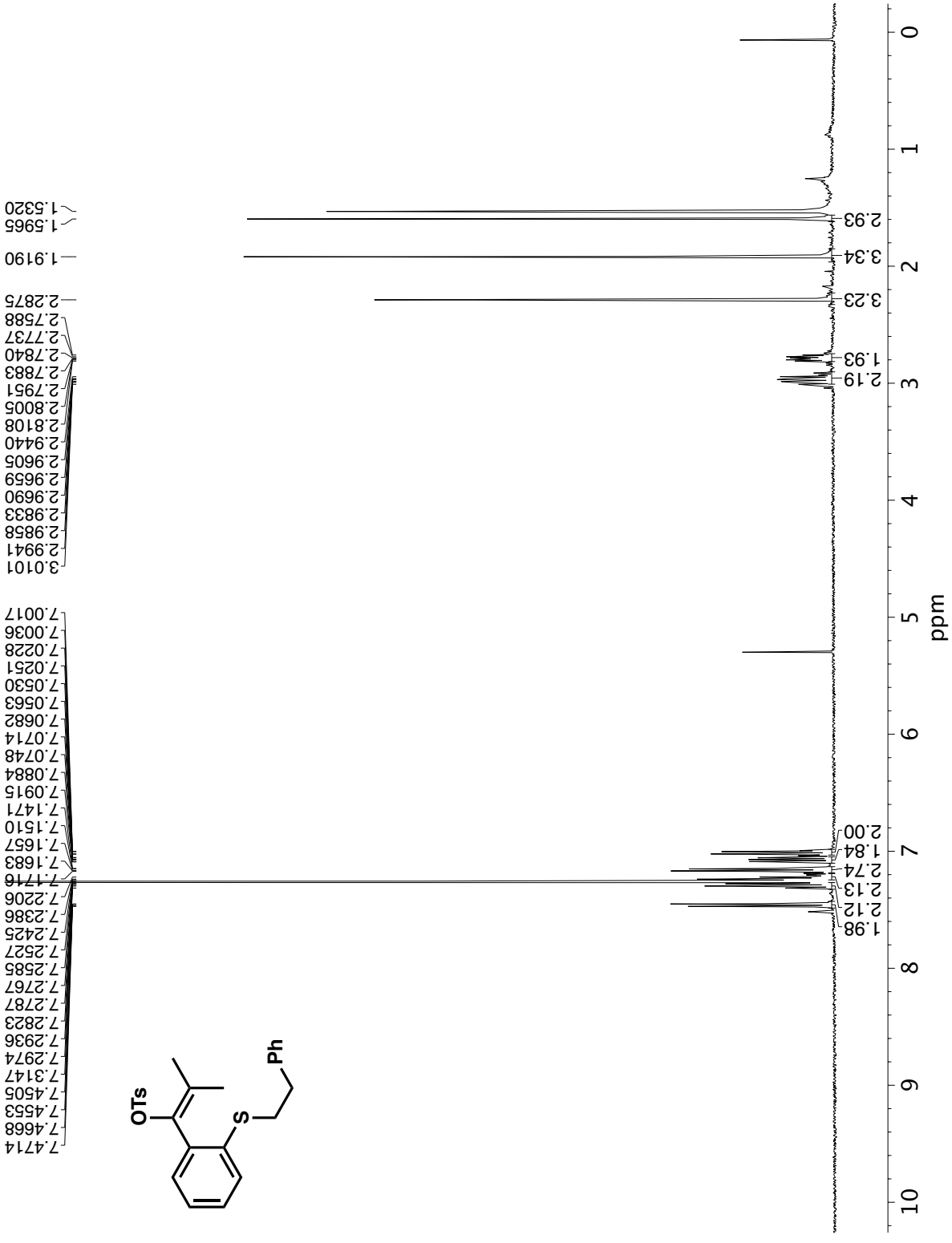
^{13}C NMR (101 MHz, $CDCl_3$) of compound **S11**.



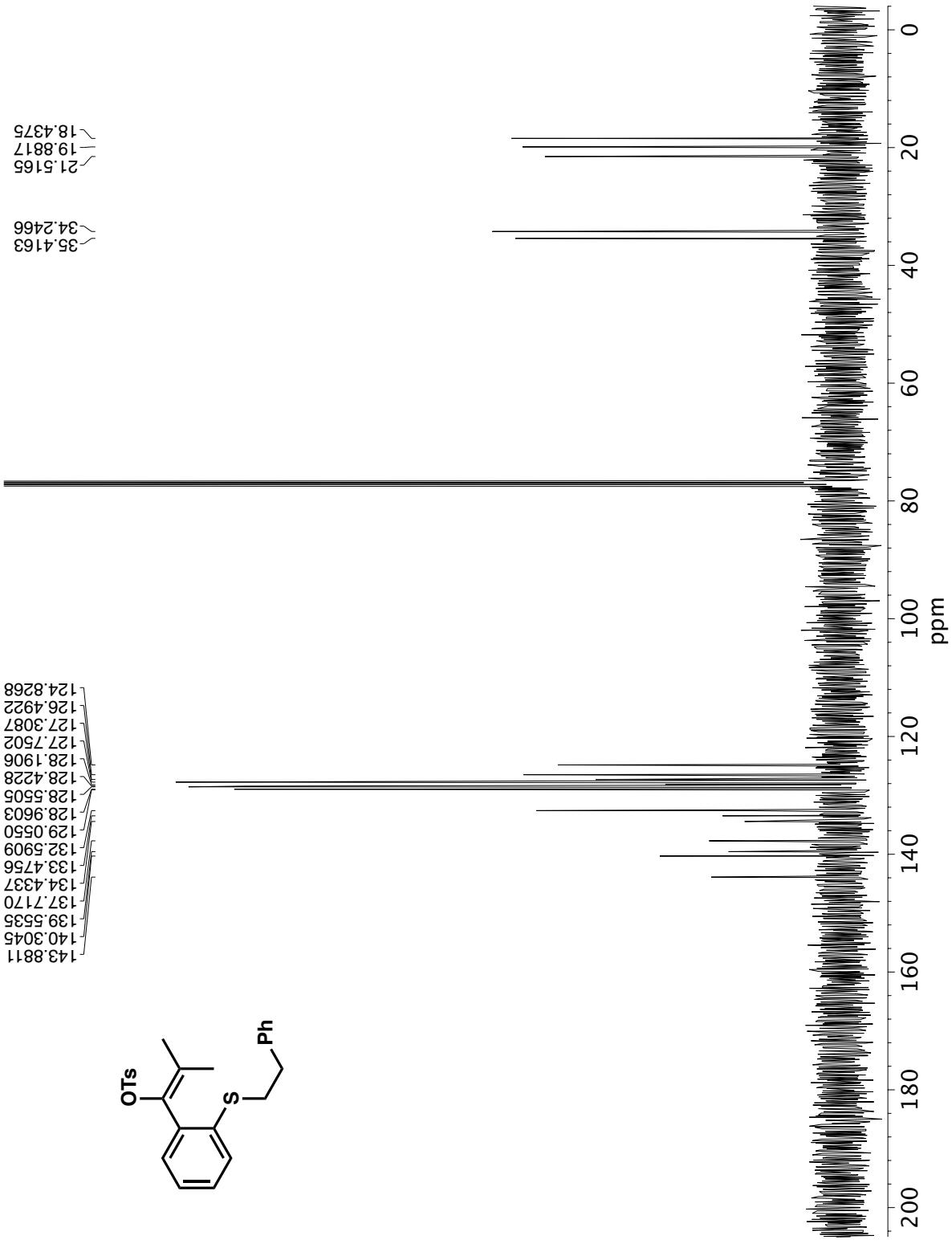
^{1}H NMR (400 MHz, $CDCl_3$) of compound **S13**.



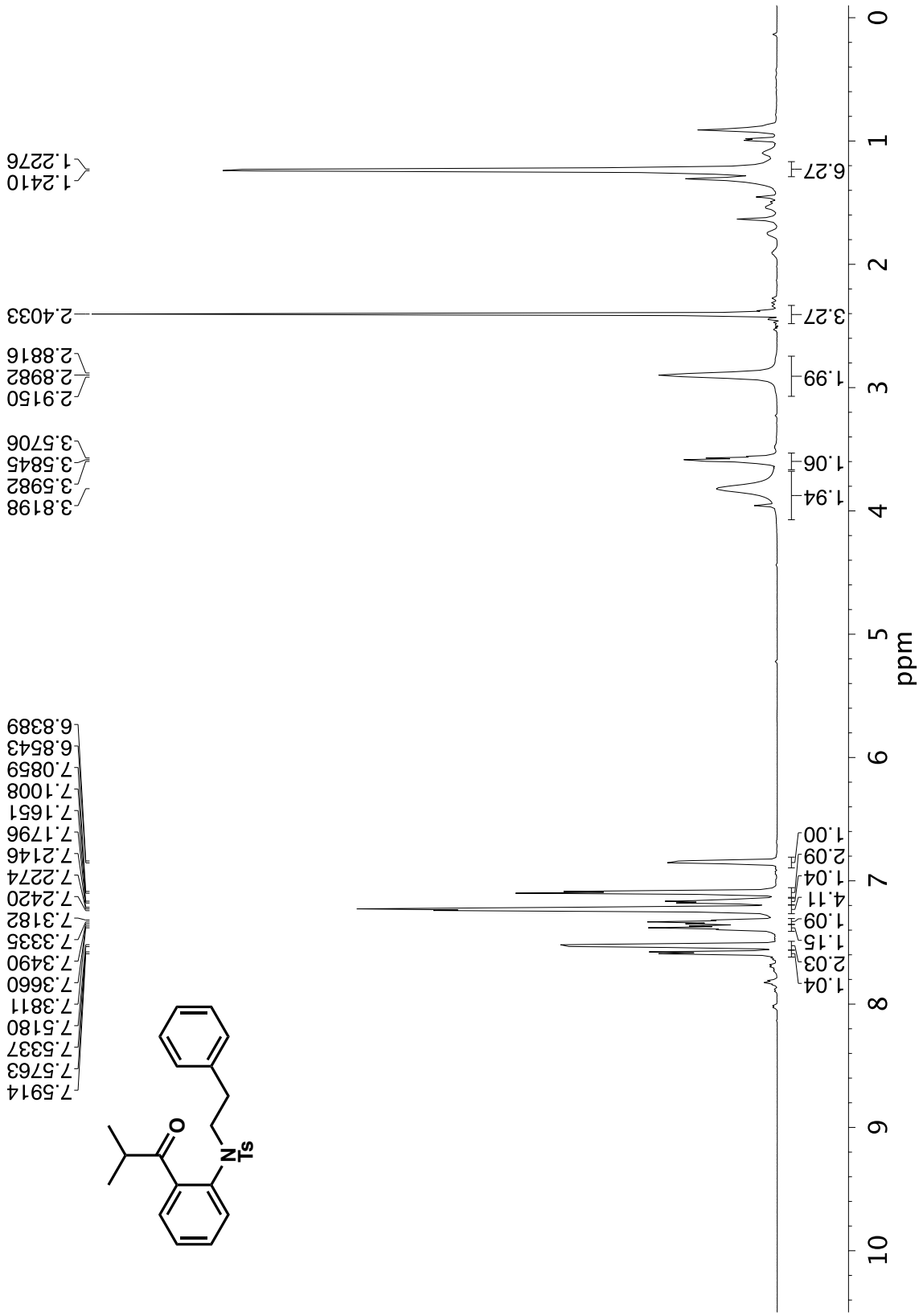
^{13}C NMR (101 MHz, $CDCl_3$) of compound **S13**.



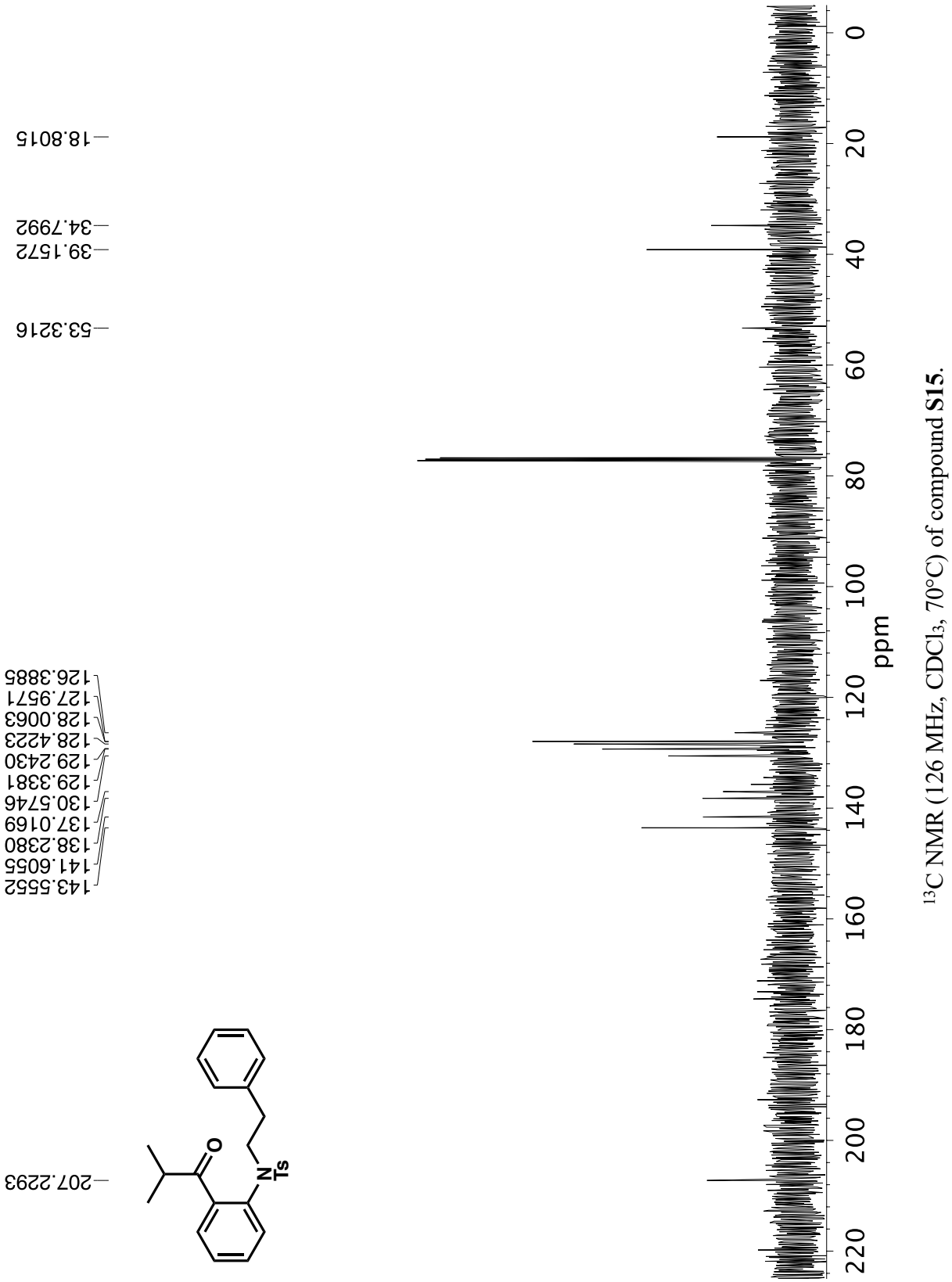
^{1}H NMR (400 MHz, $CDCl_3$) of compound **S14**.



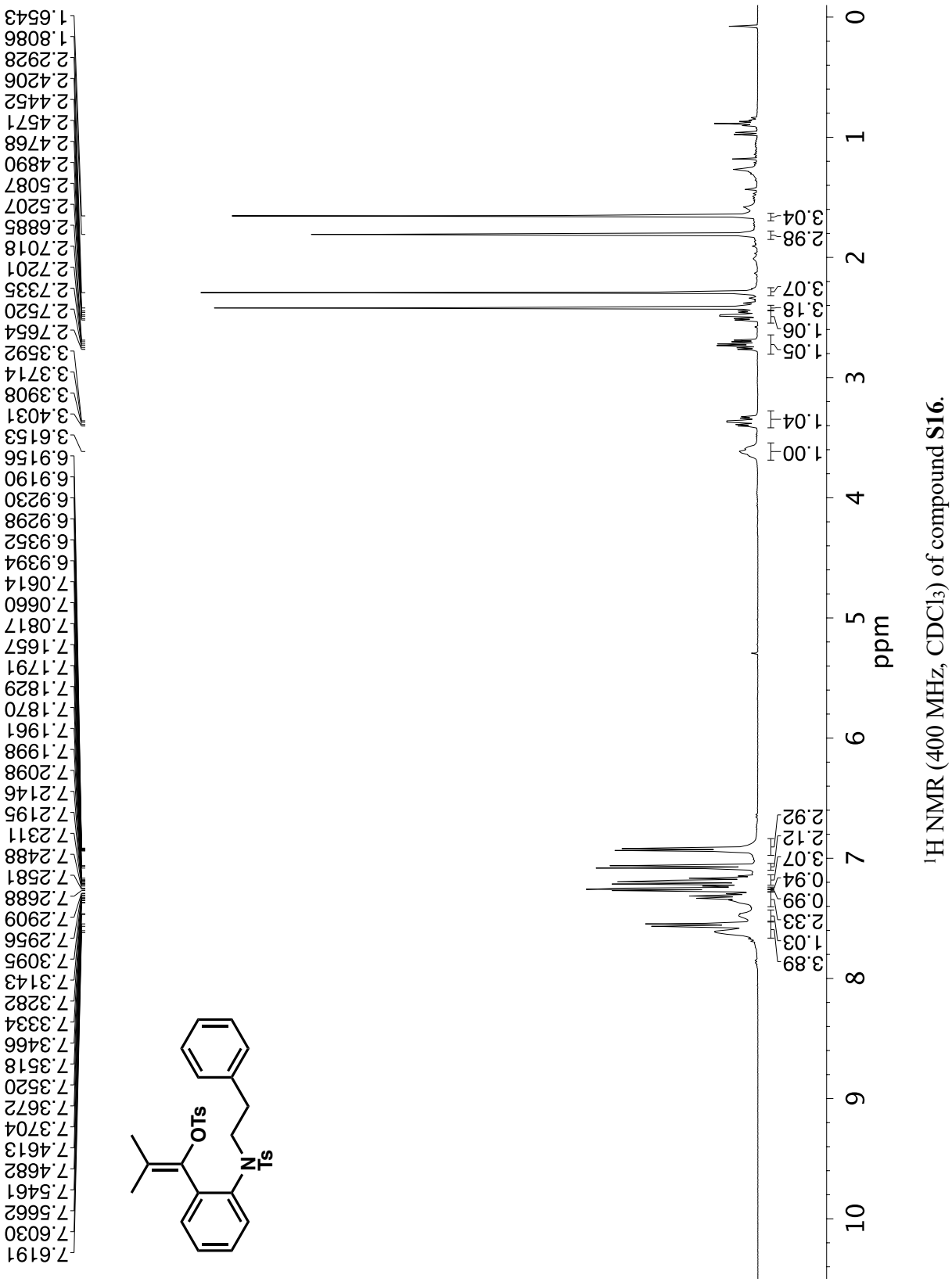
^{13}C NMR (101 MHz, $CDCl_3$) of compound **S14**.



^{1}H NMR (500 MHz, $CDCl_3$, 70°C) of compound **S15**.



^{13}C NMR (126 MHz, $CDCl_3$, 70°C) of compound **S15**.



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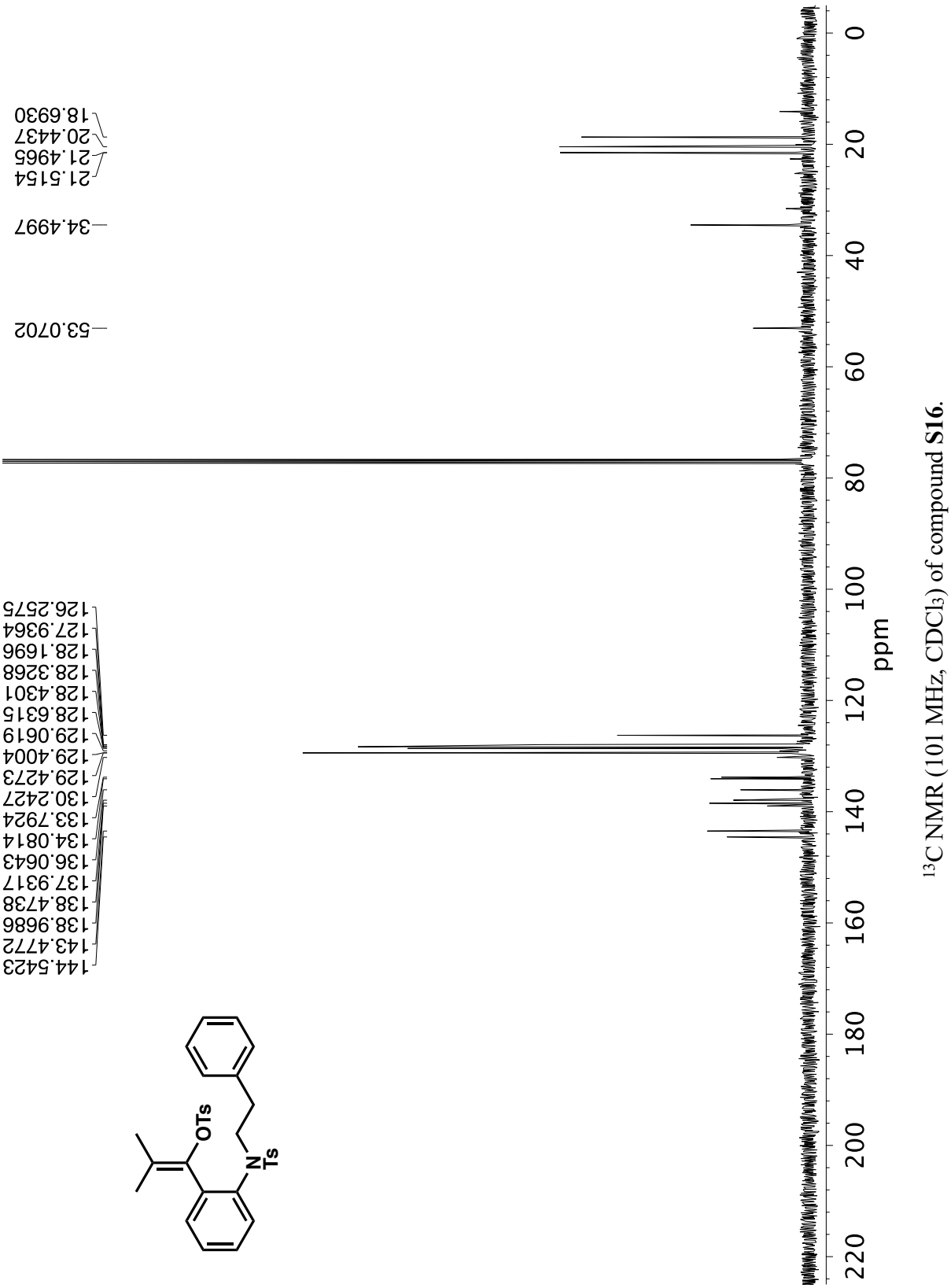

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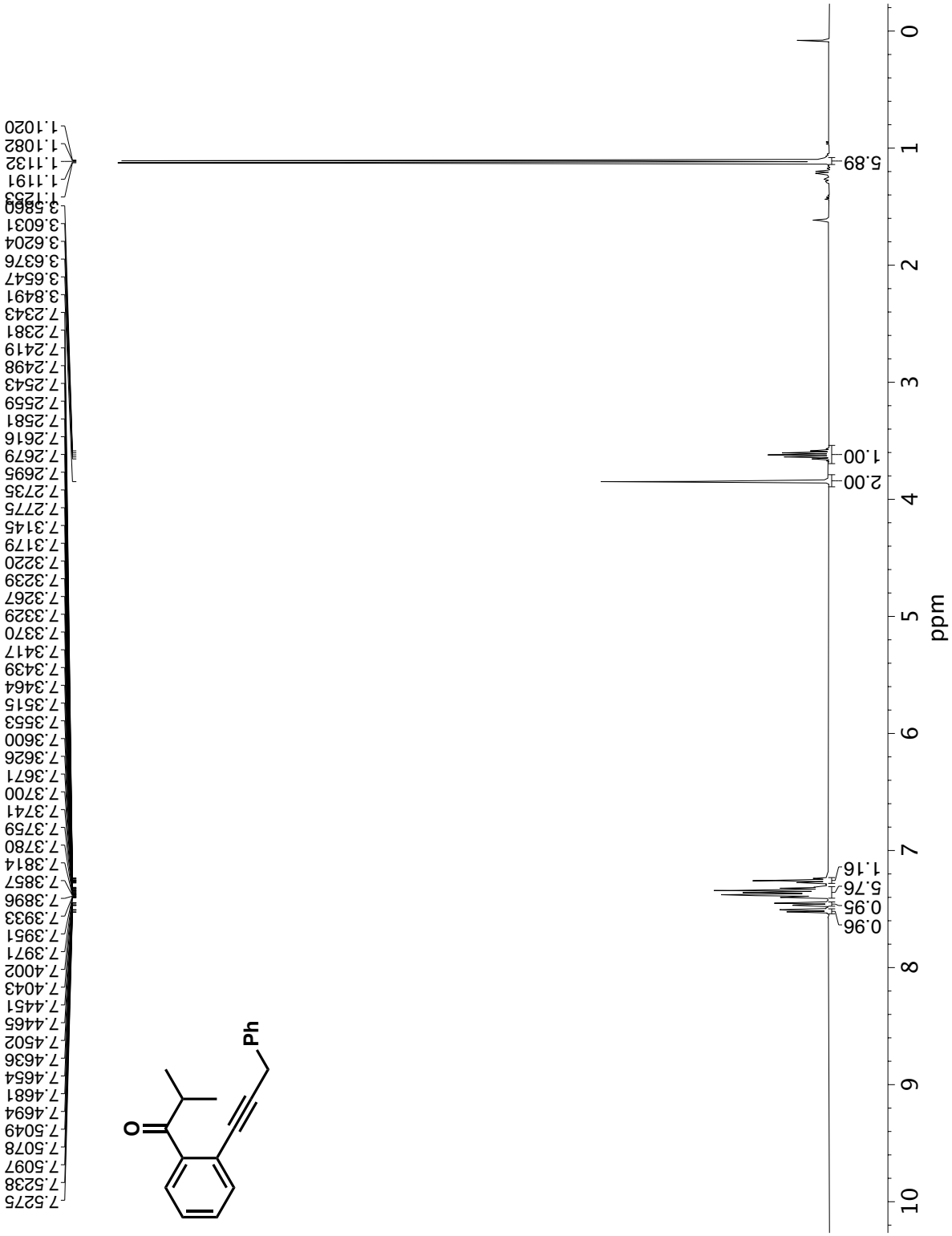

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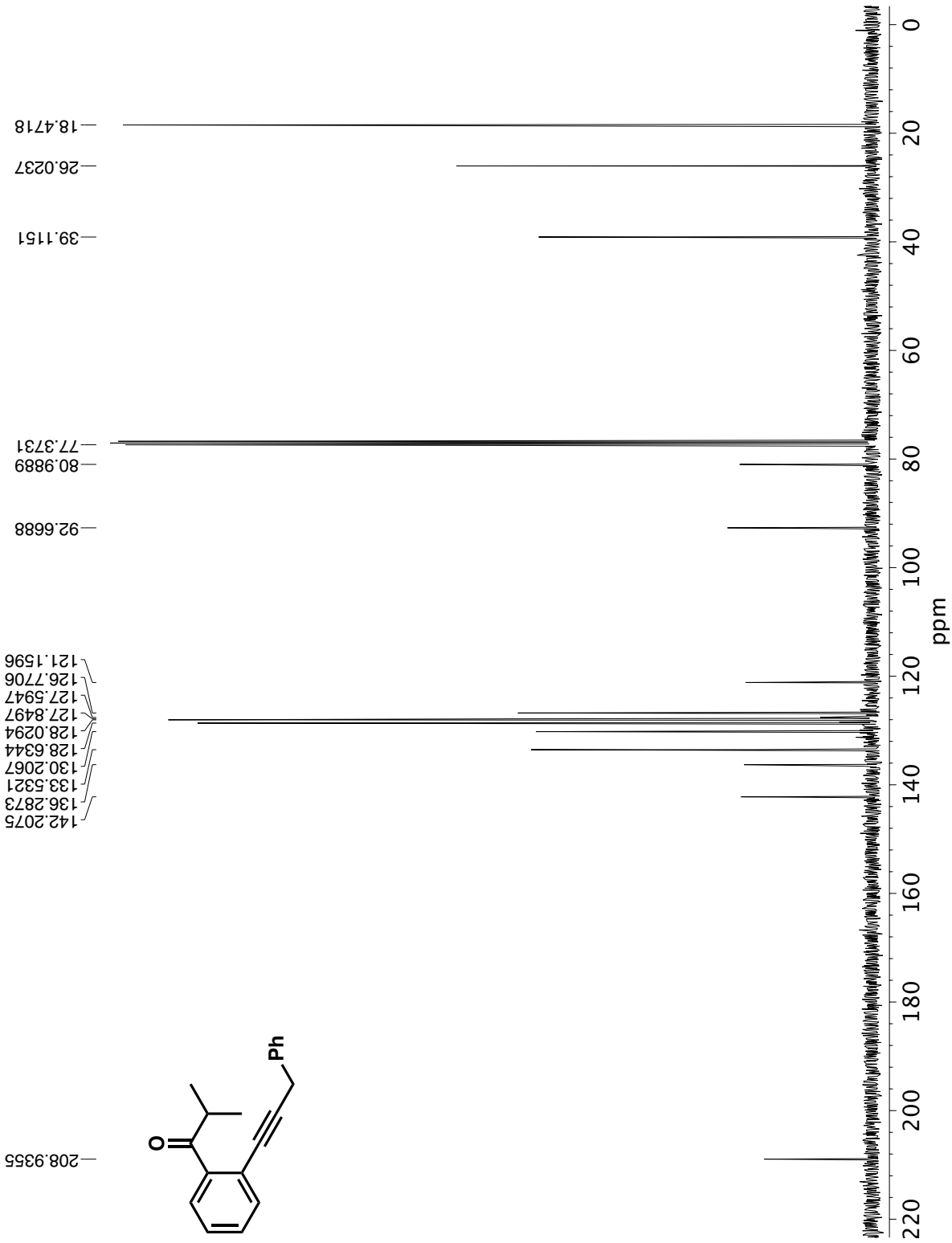
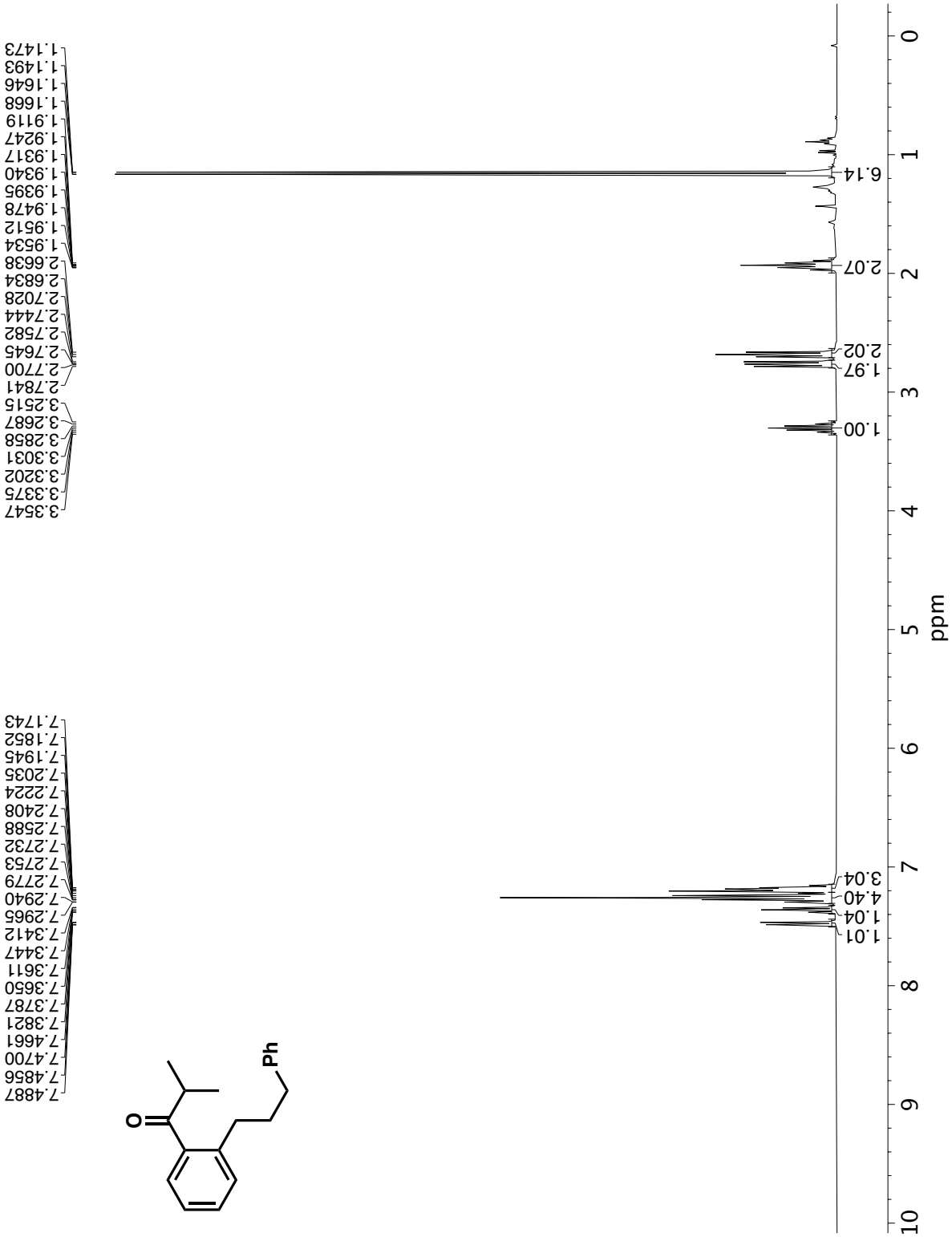
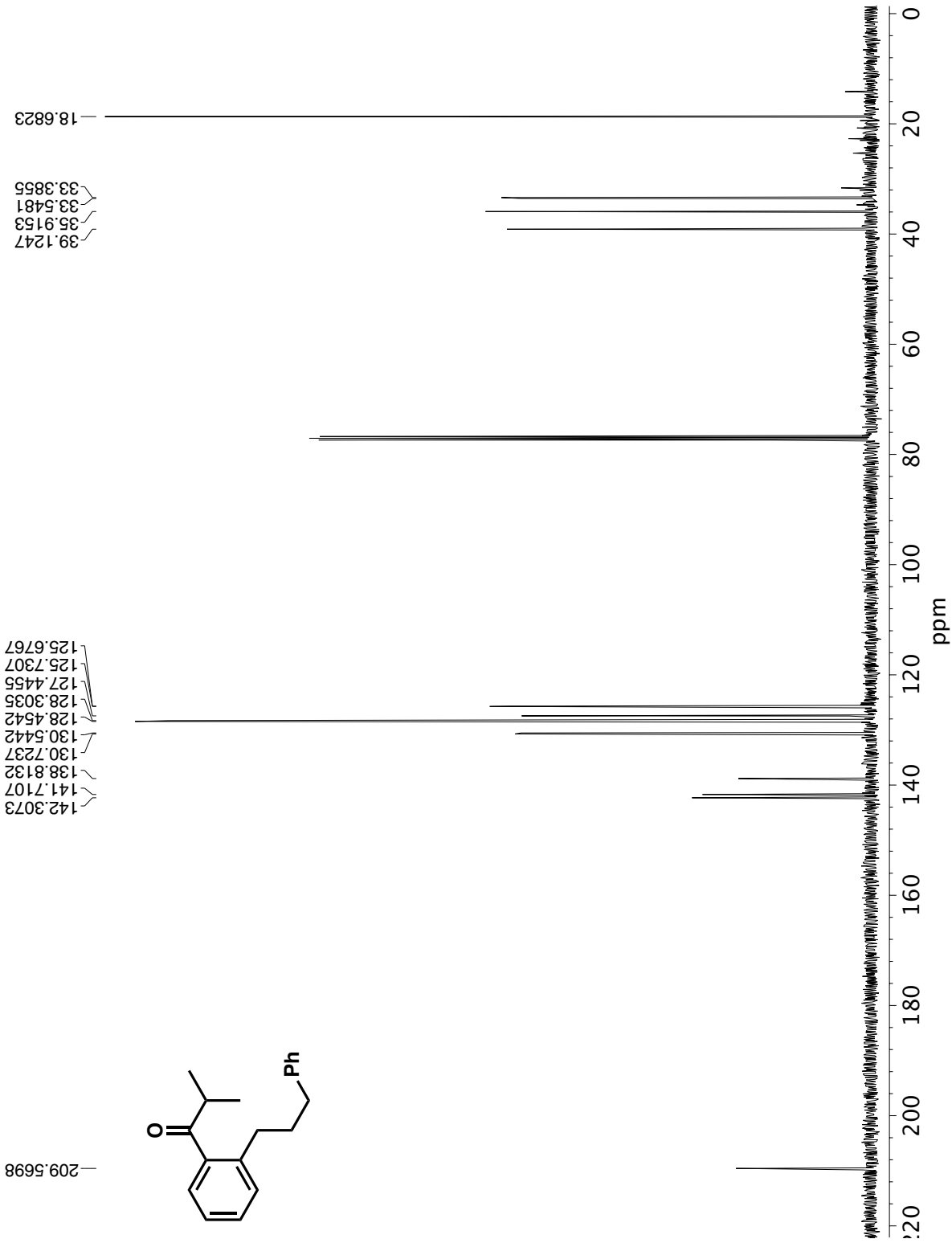


^{13}C NMR (101 MHz, $CDCl_3$) of compound **S18**.



^{1}H NMR (400 MHz, $CDCl_3$) of compound **S19**.



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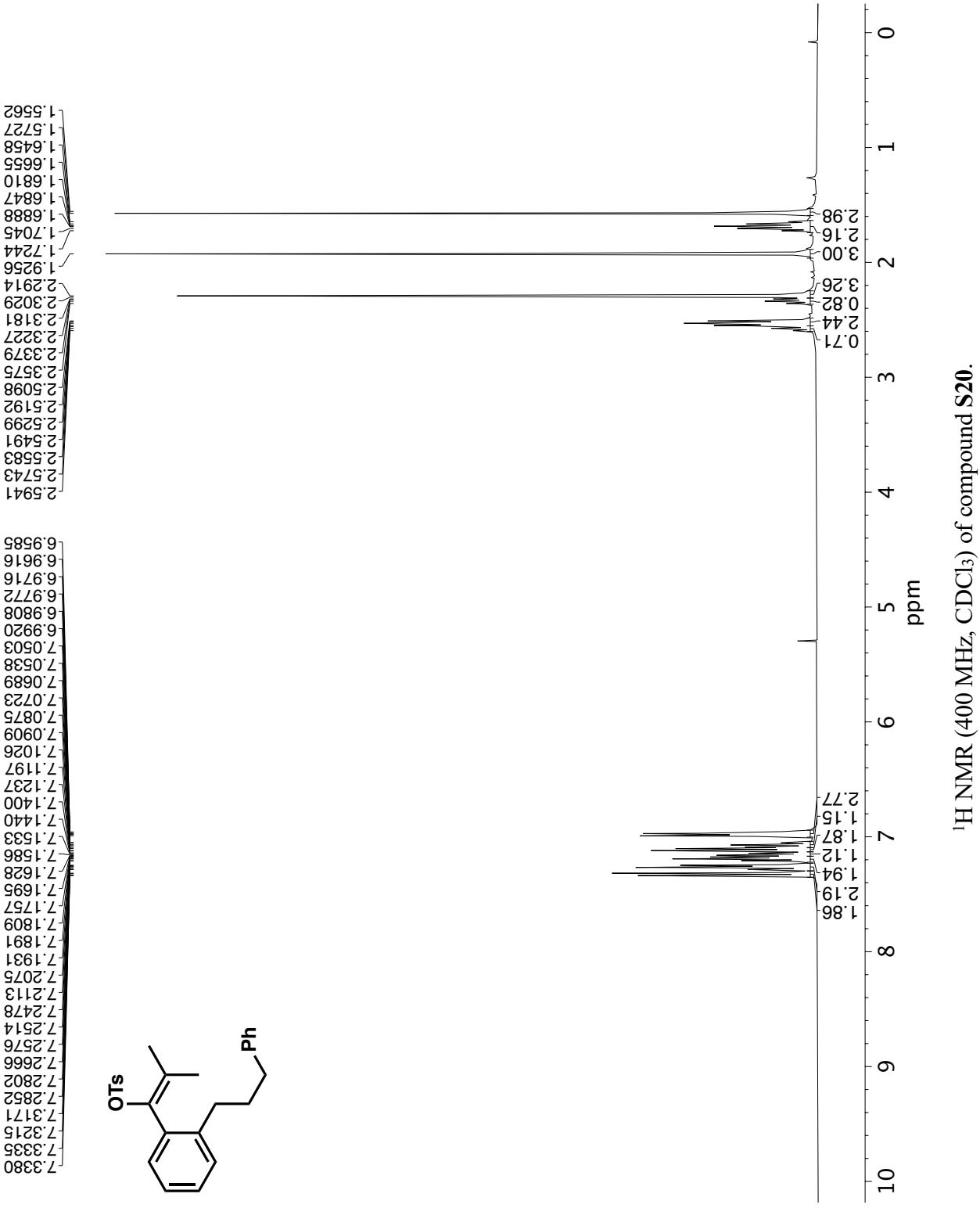

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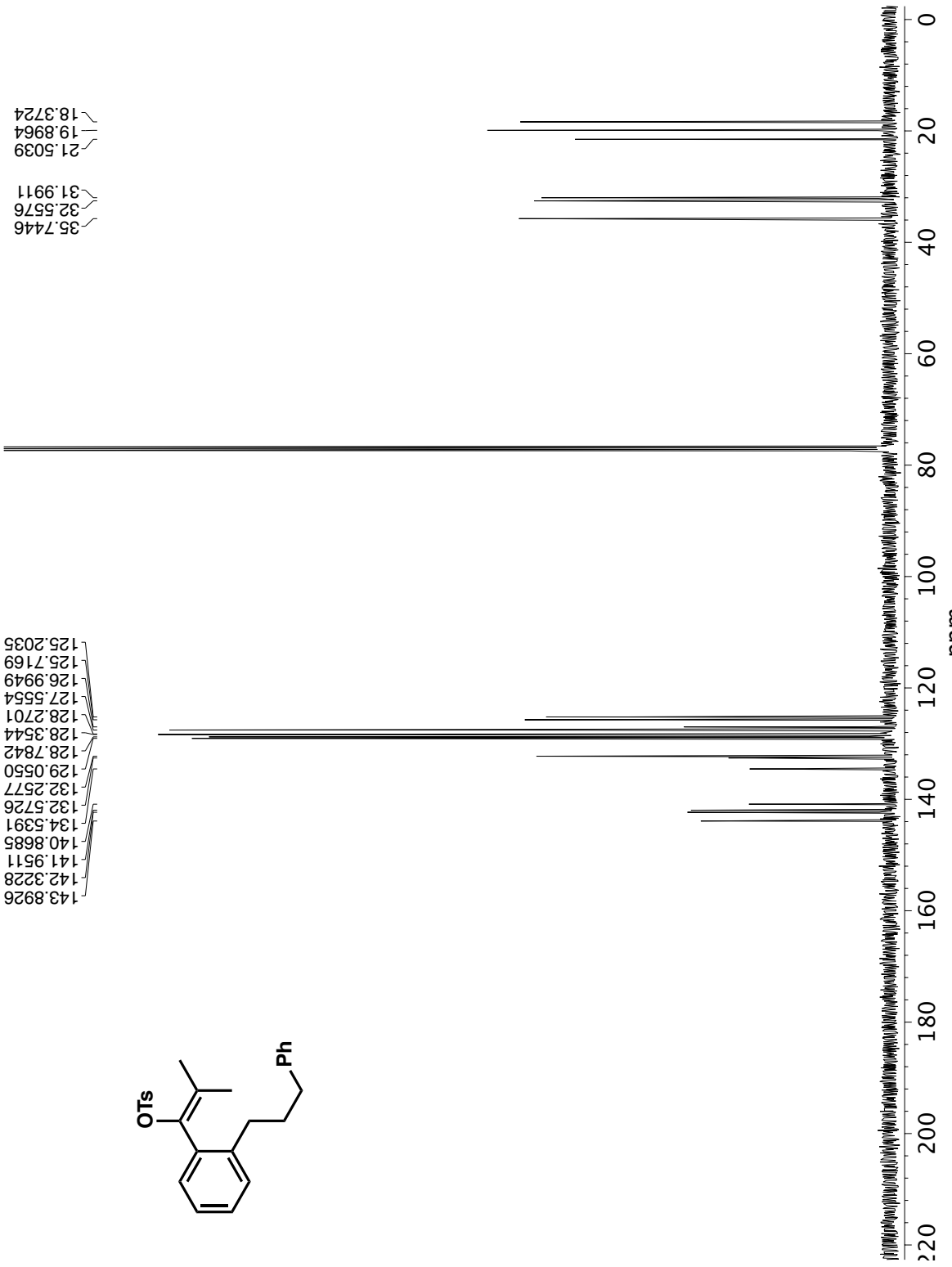
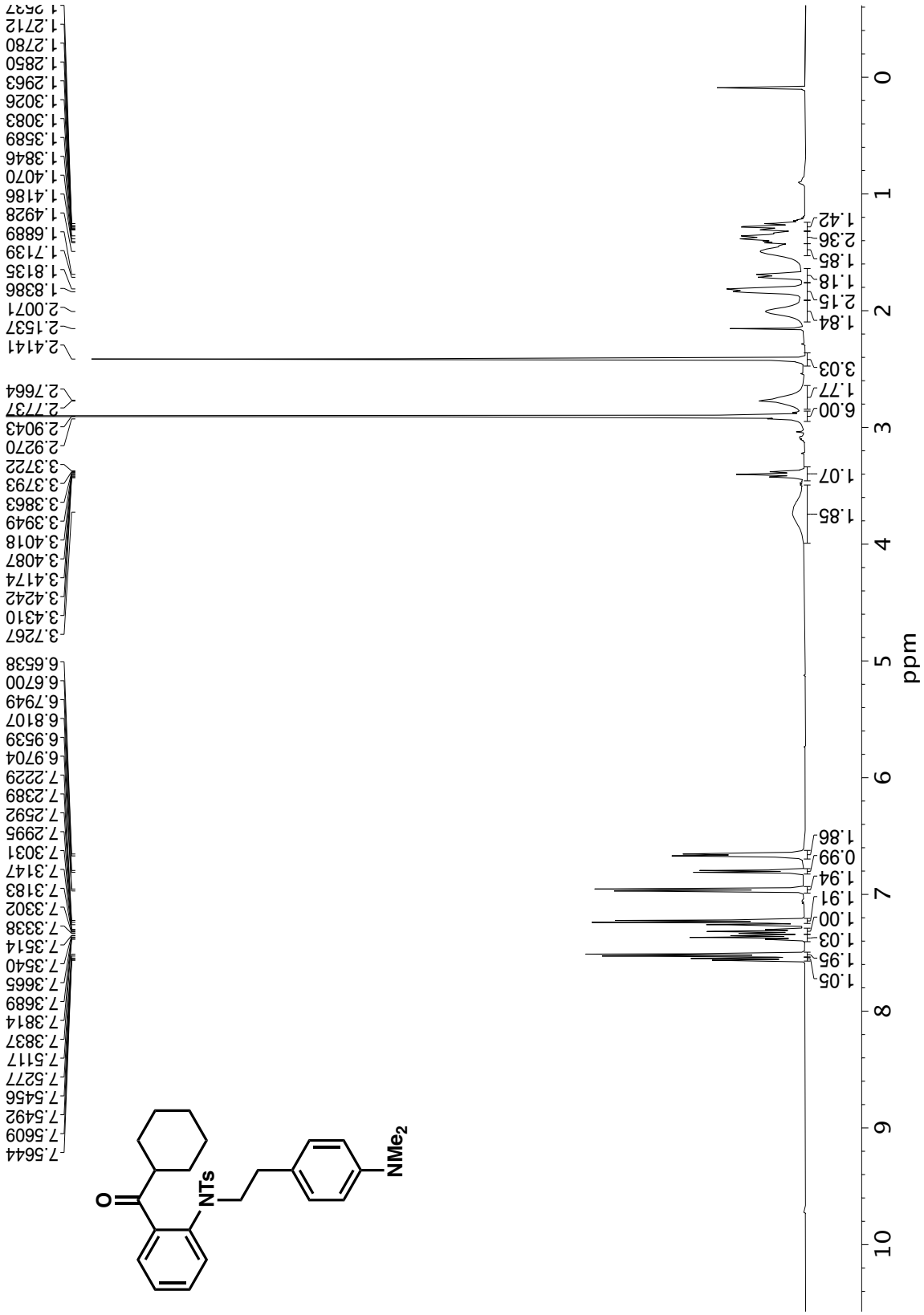
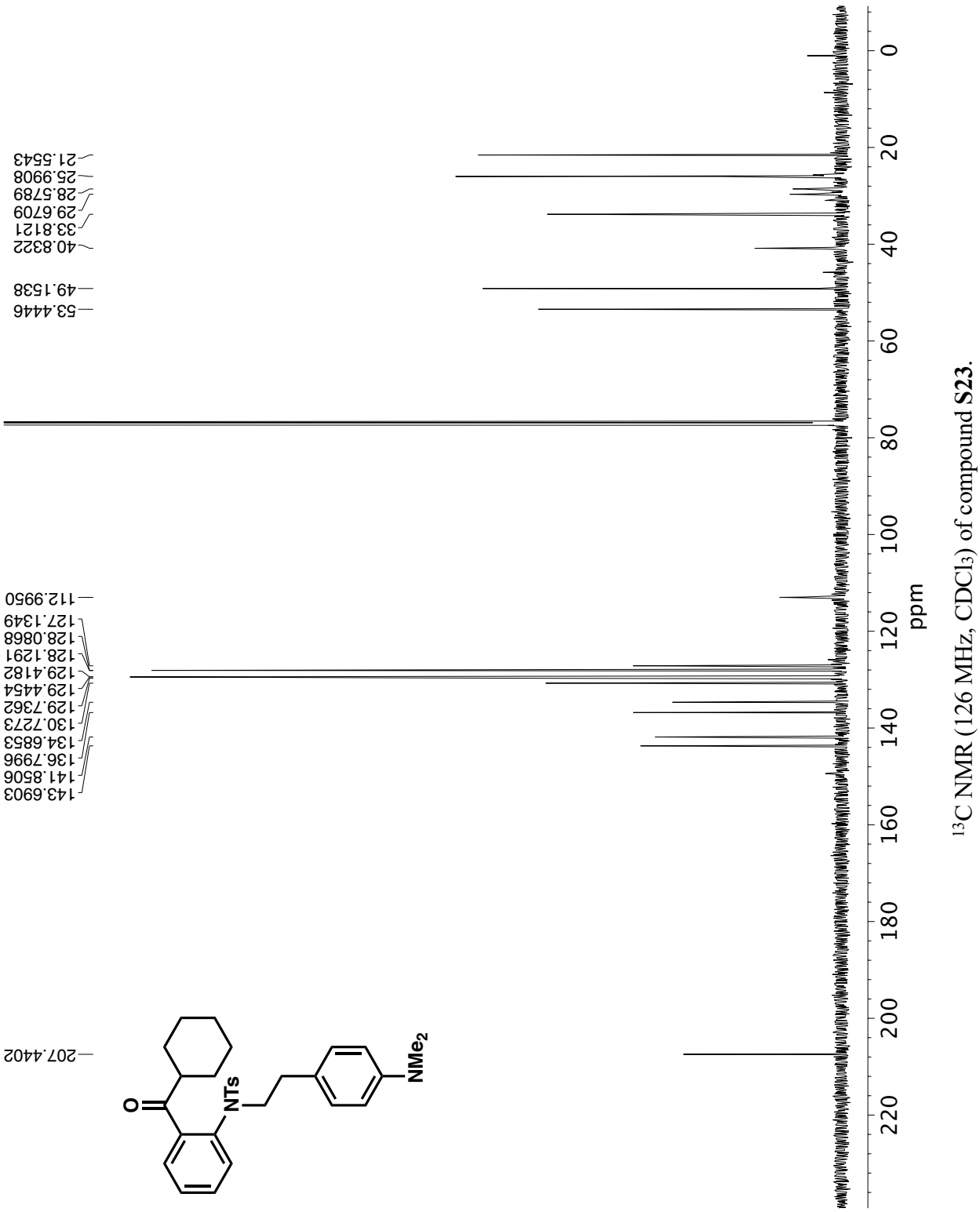


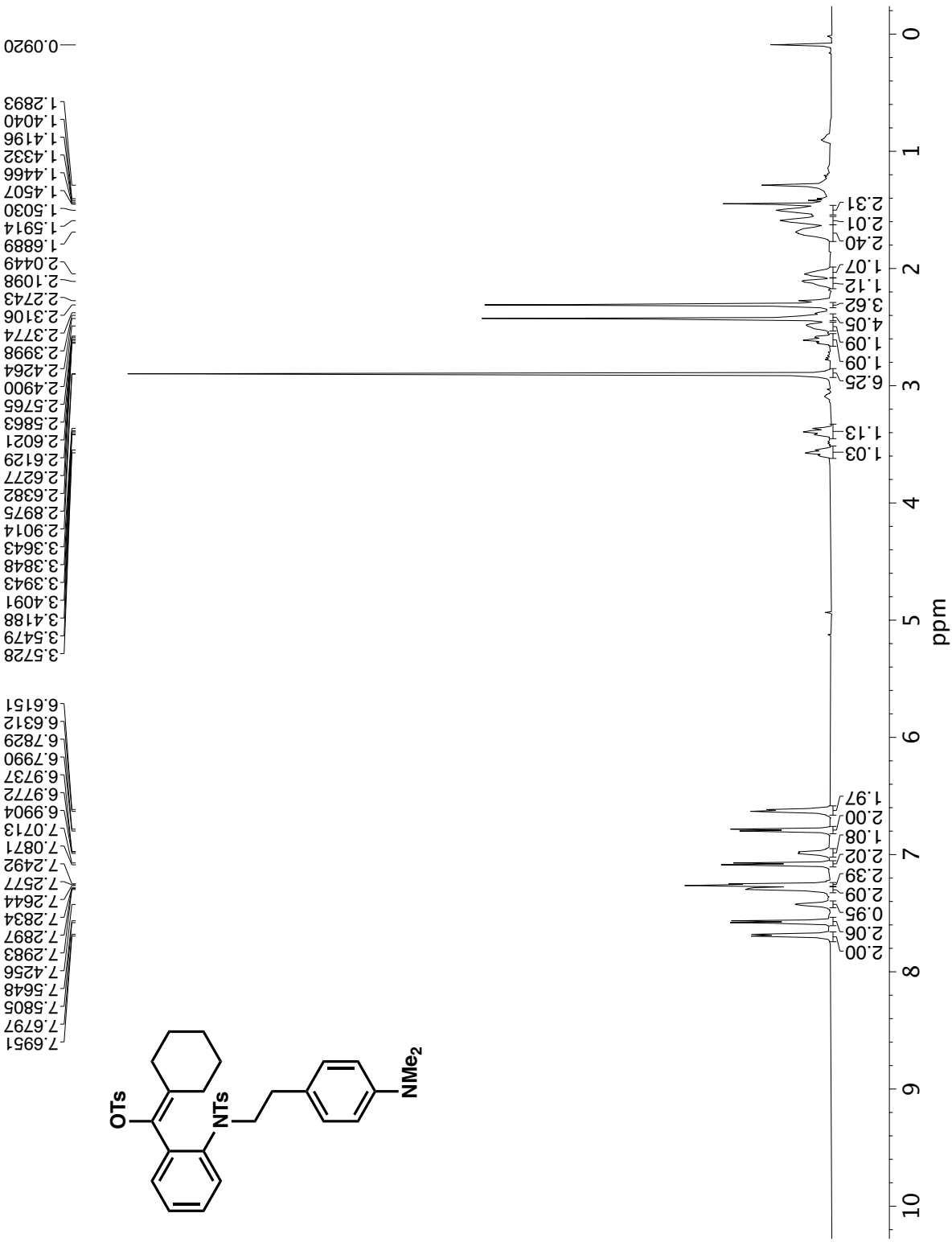
^{13}C NMR (101 MHz, $CDCl_3$) of compound **S20**.



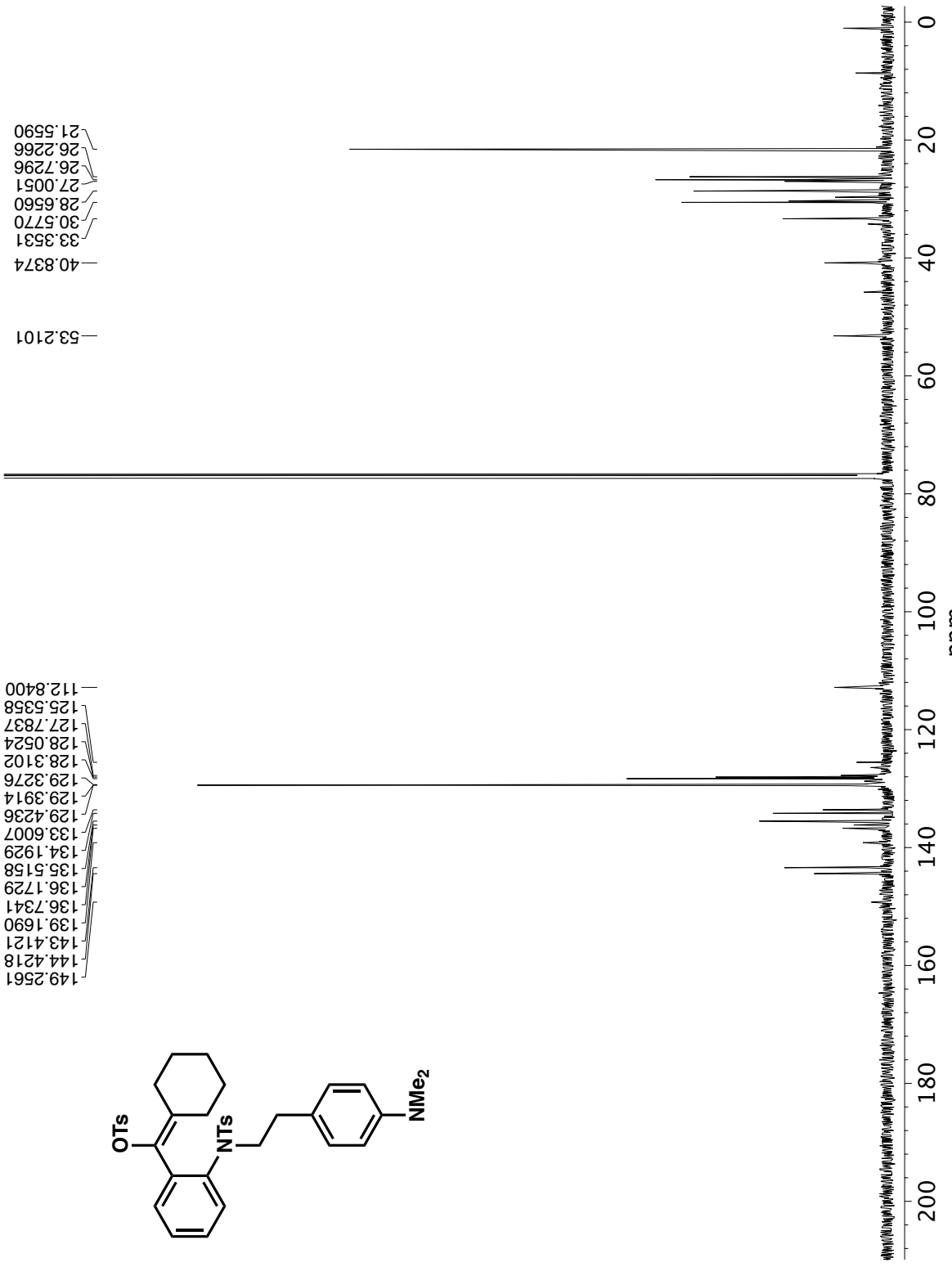
^{1}H NMR (500 MHz, $CDCl_3$, 60°C) of compound **S23**.



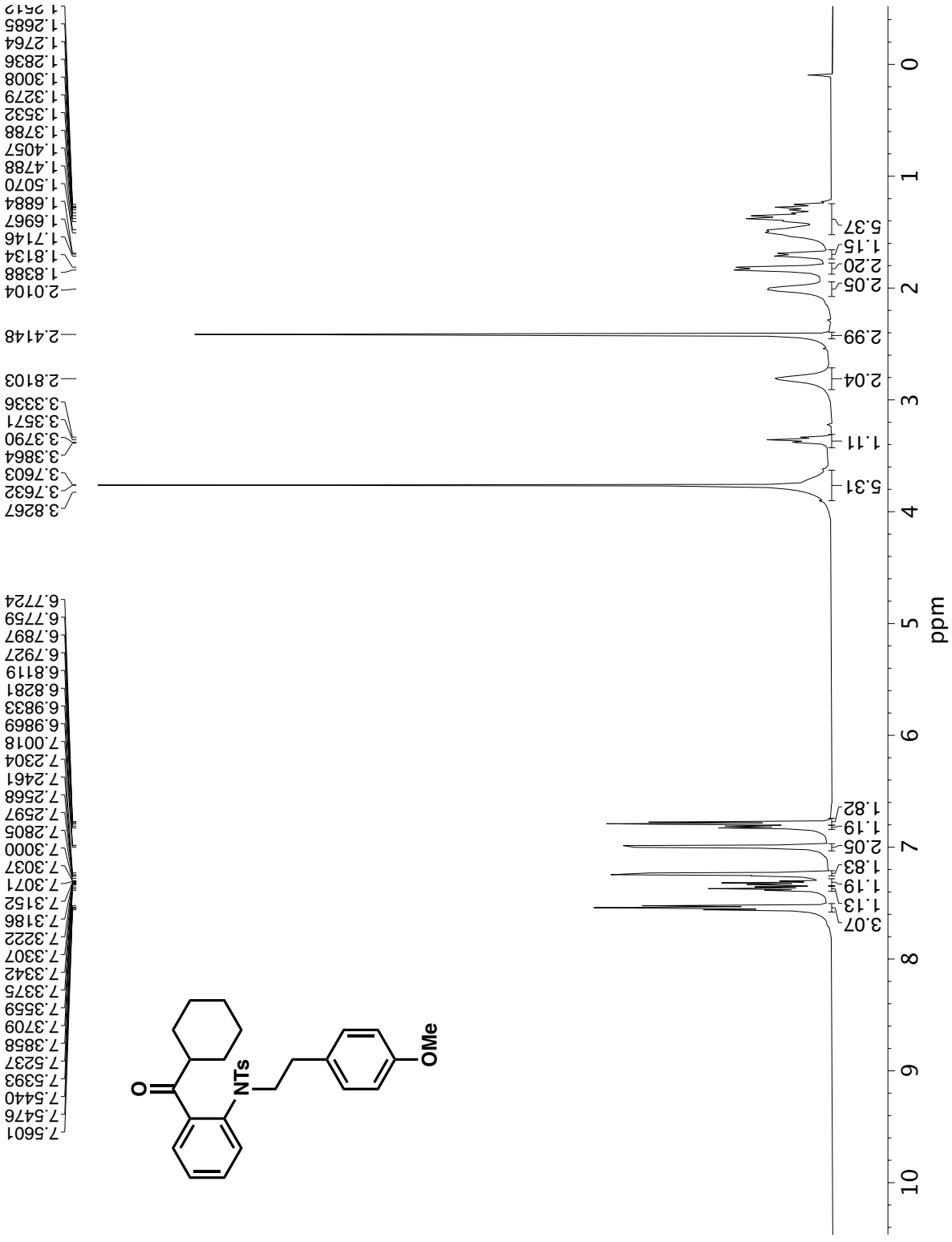
^{13}C NMR (126 MHz, $CDCl_3$) of compound **S23**.



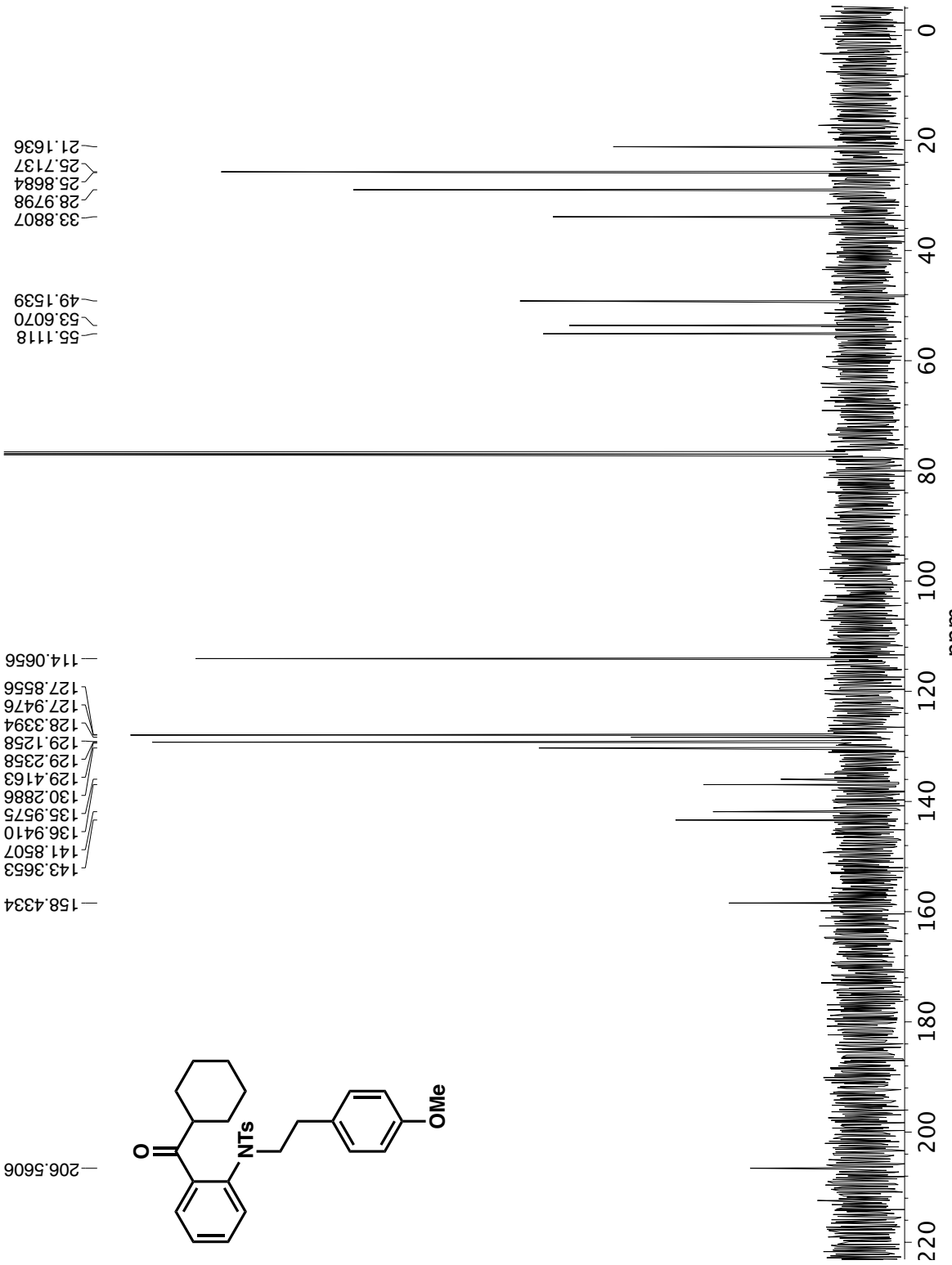
^{1}H NMR (500 MHz, $CDCl_3$, 70°C) of compound **S24**.



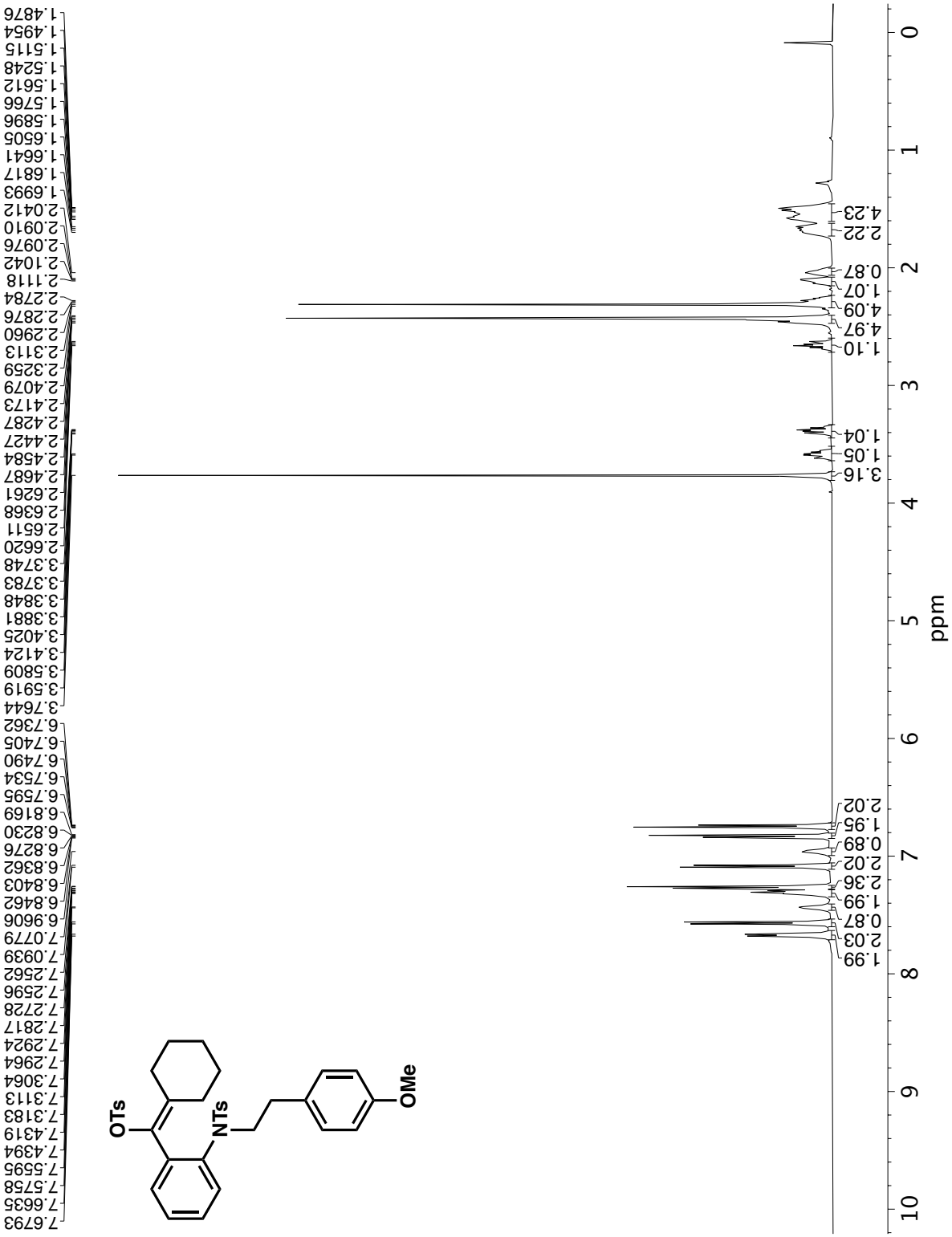
^{13}C NMR (126 MHz, $CDCl_3$) of compound **S24**.



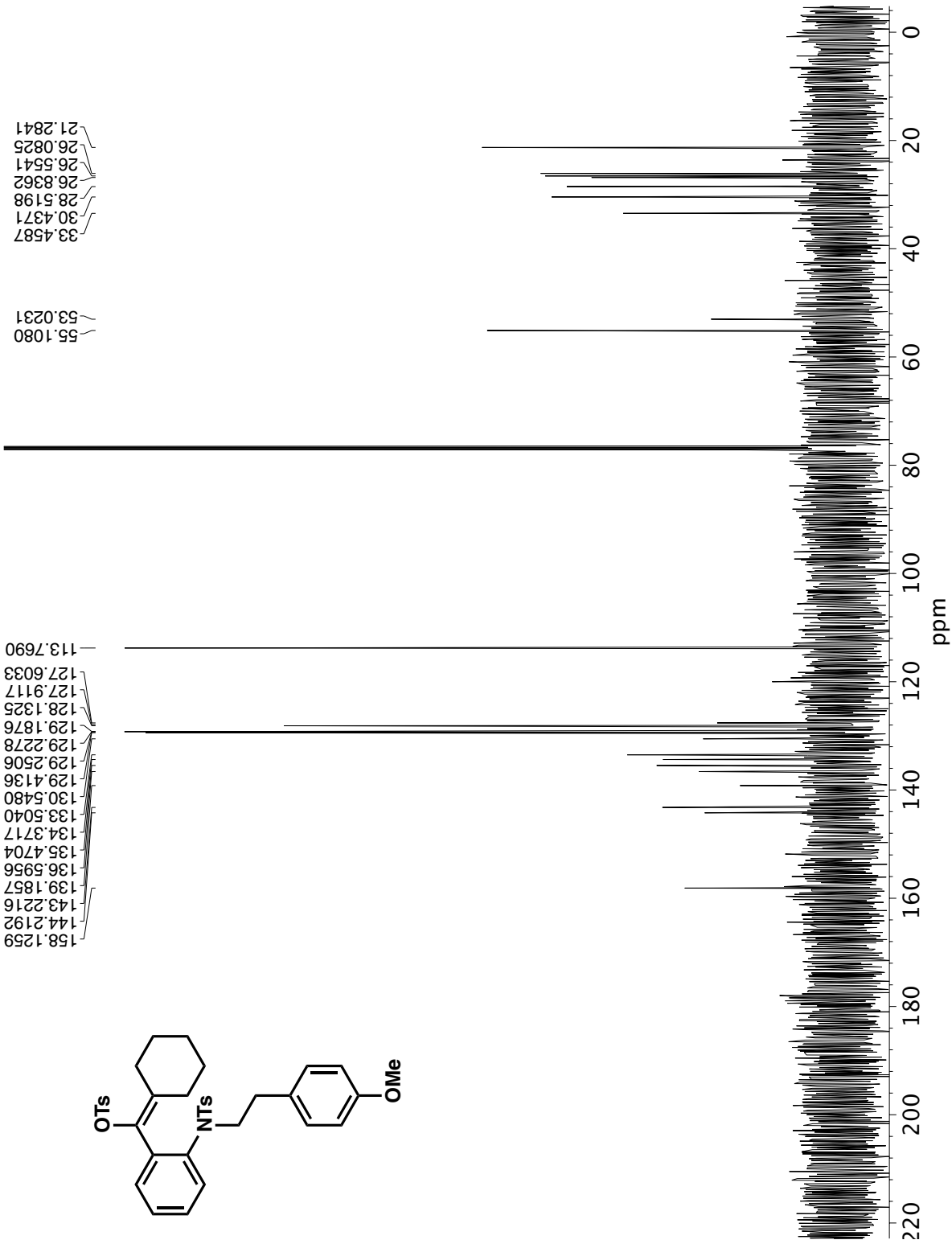
^{1}H NMR (500 MHz, $CDCl_3$, 70°C) of compound **S26**.



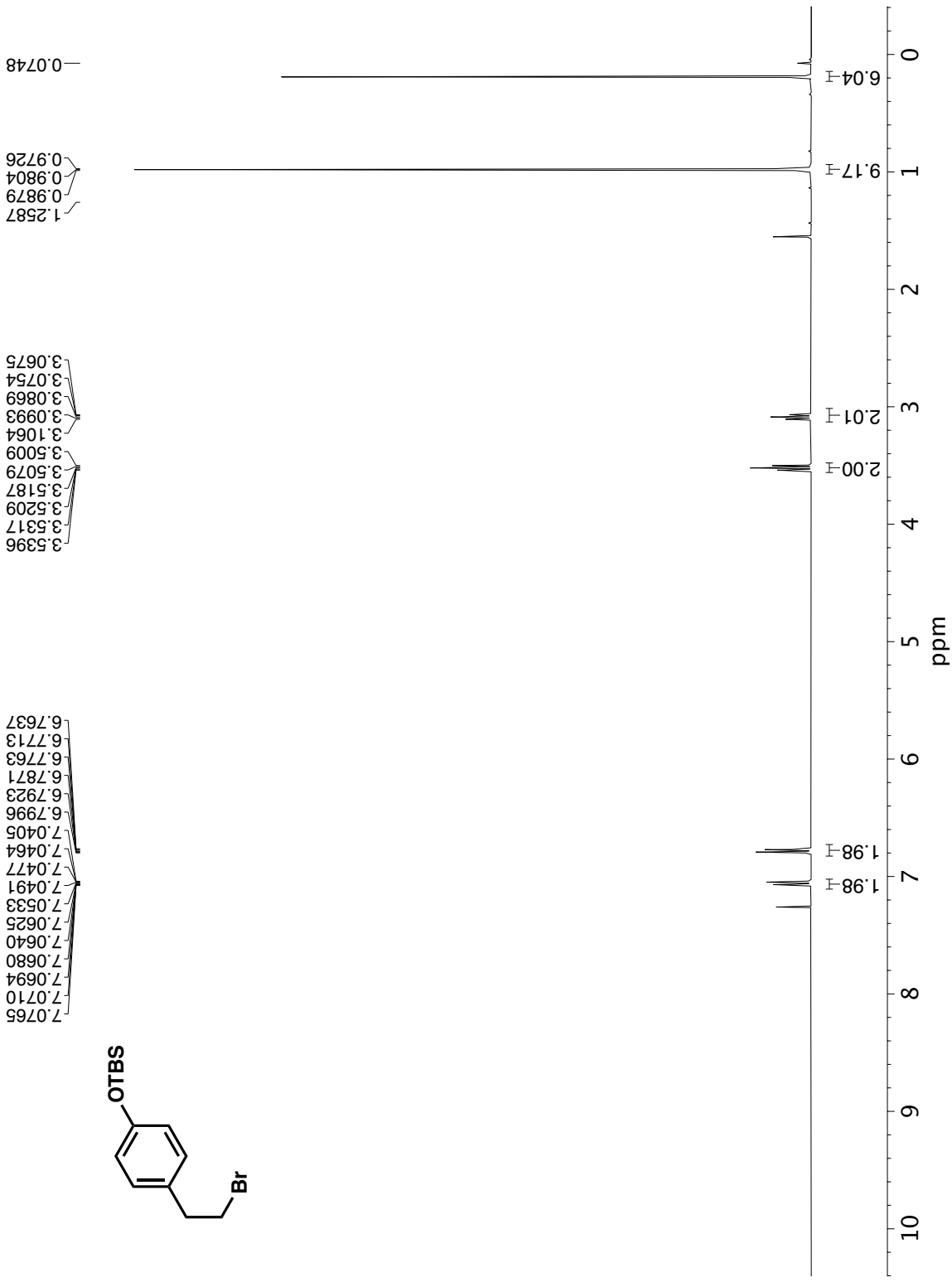
^{13}C NMR (126 MHz, $CDCl_3$, 70°C) of compound **S26**.



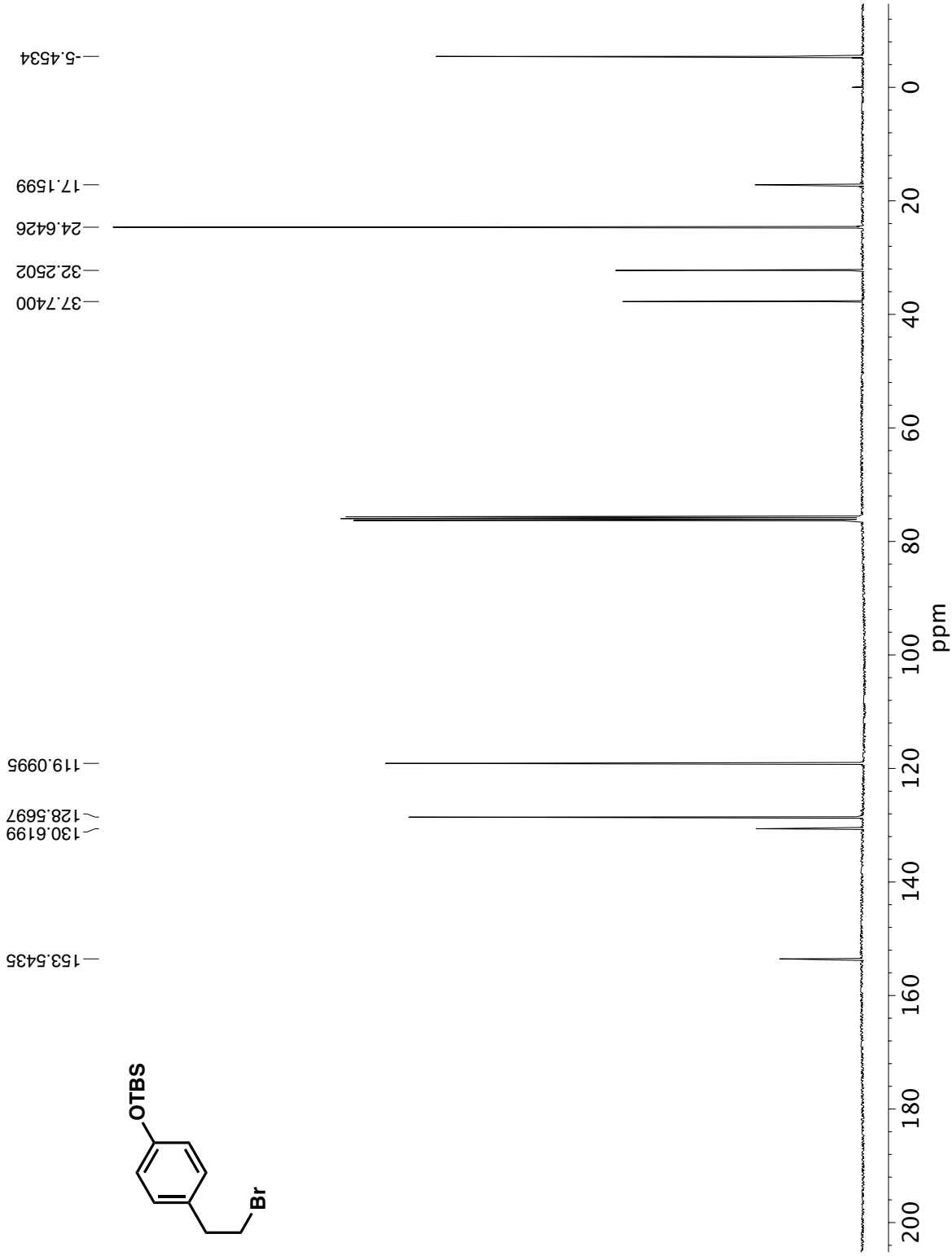
^{1}H NMR (500 MHz, $CDCl_3$, 50°C) of compound **S27**.



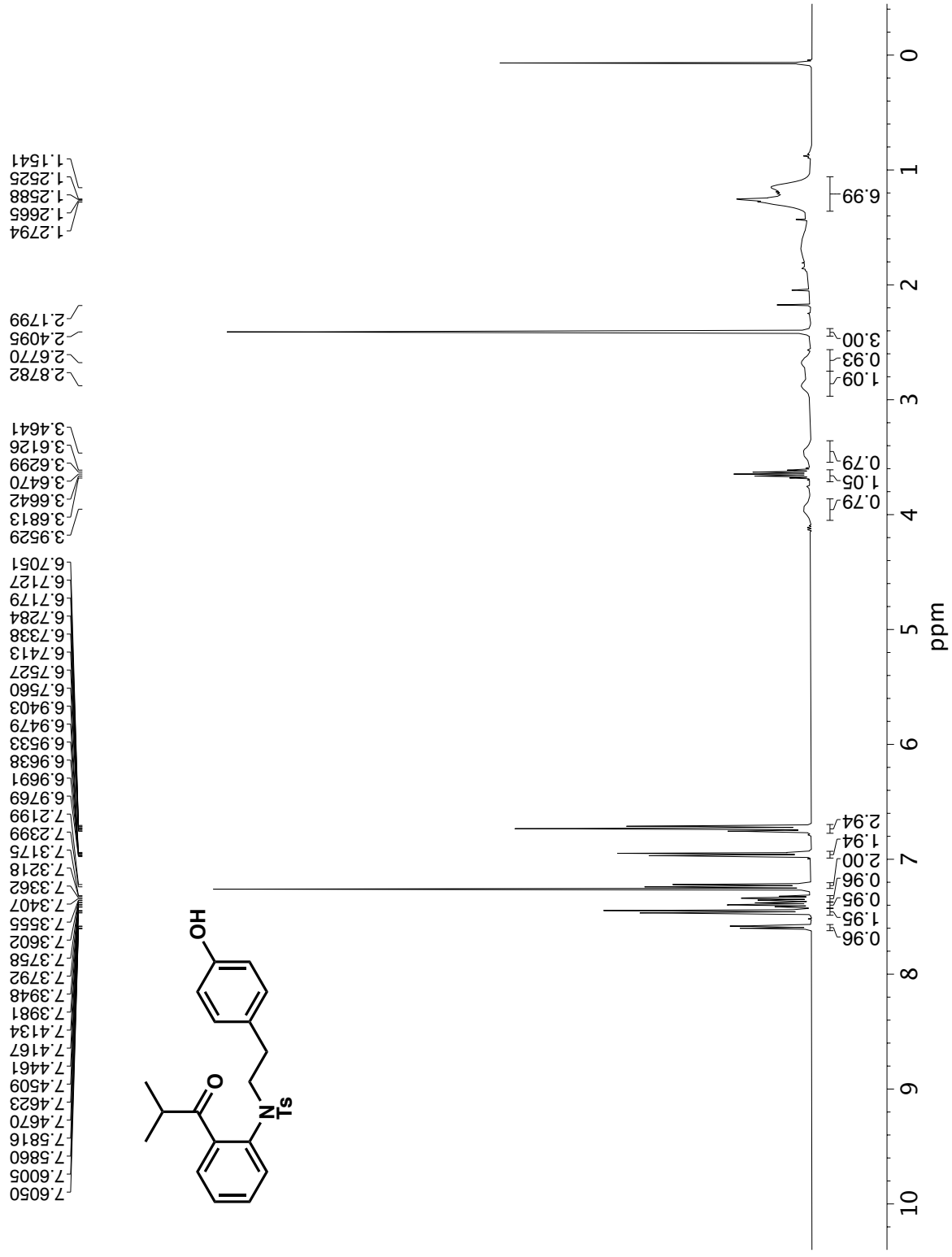
^{13}C NMR (126 MHz, $CDCl_3$, 50°C) of compound **S27**.



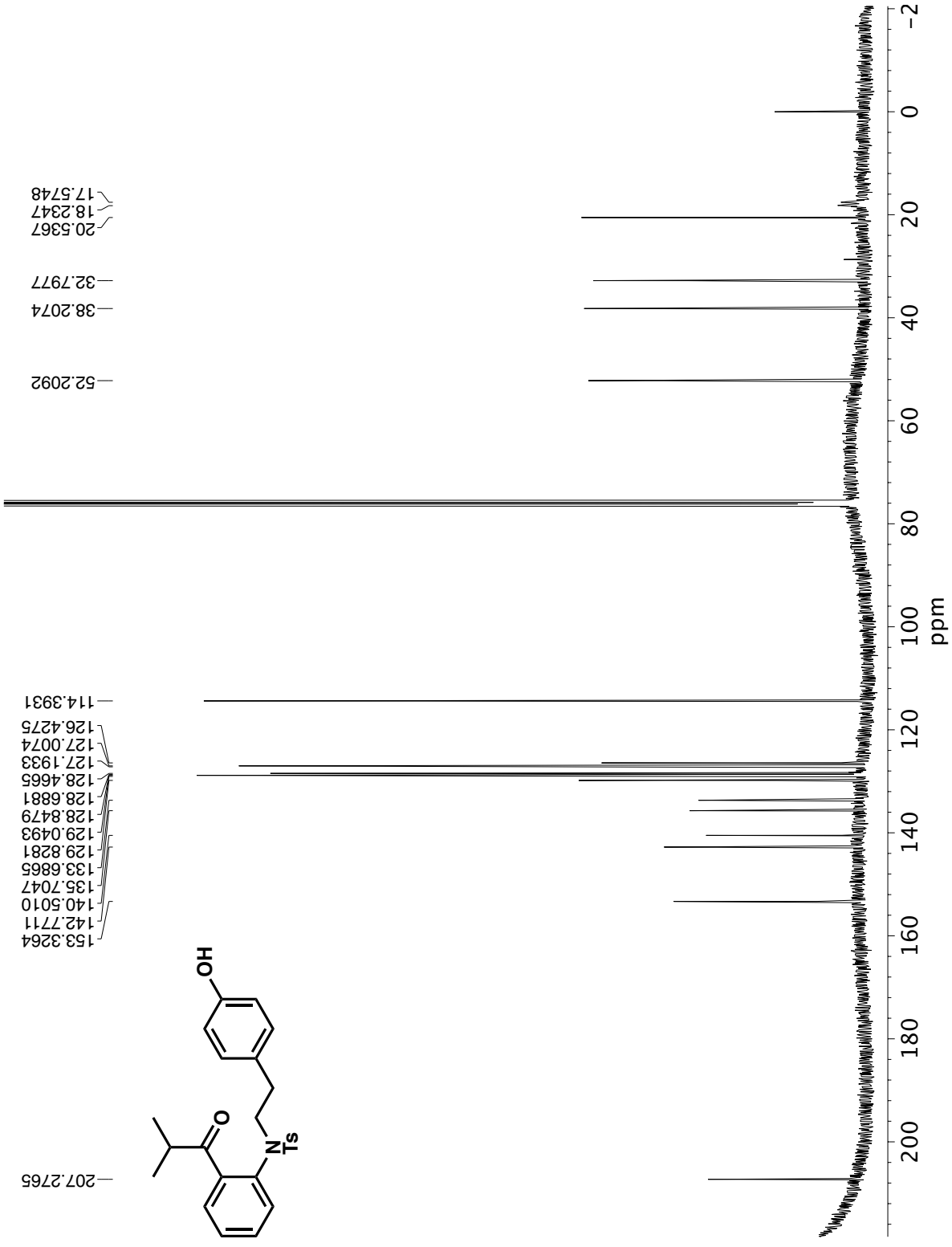
^{1}H NMR (400 MHz, $CDCl_3$) of compound **S30**.



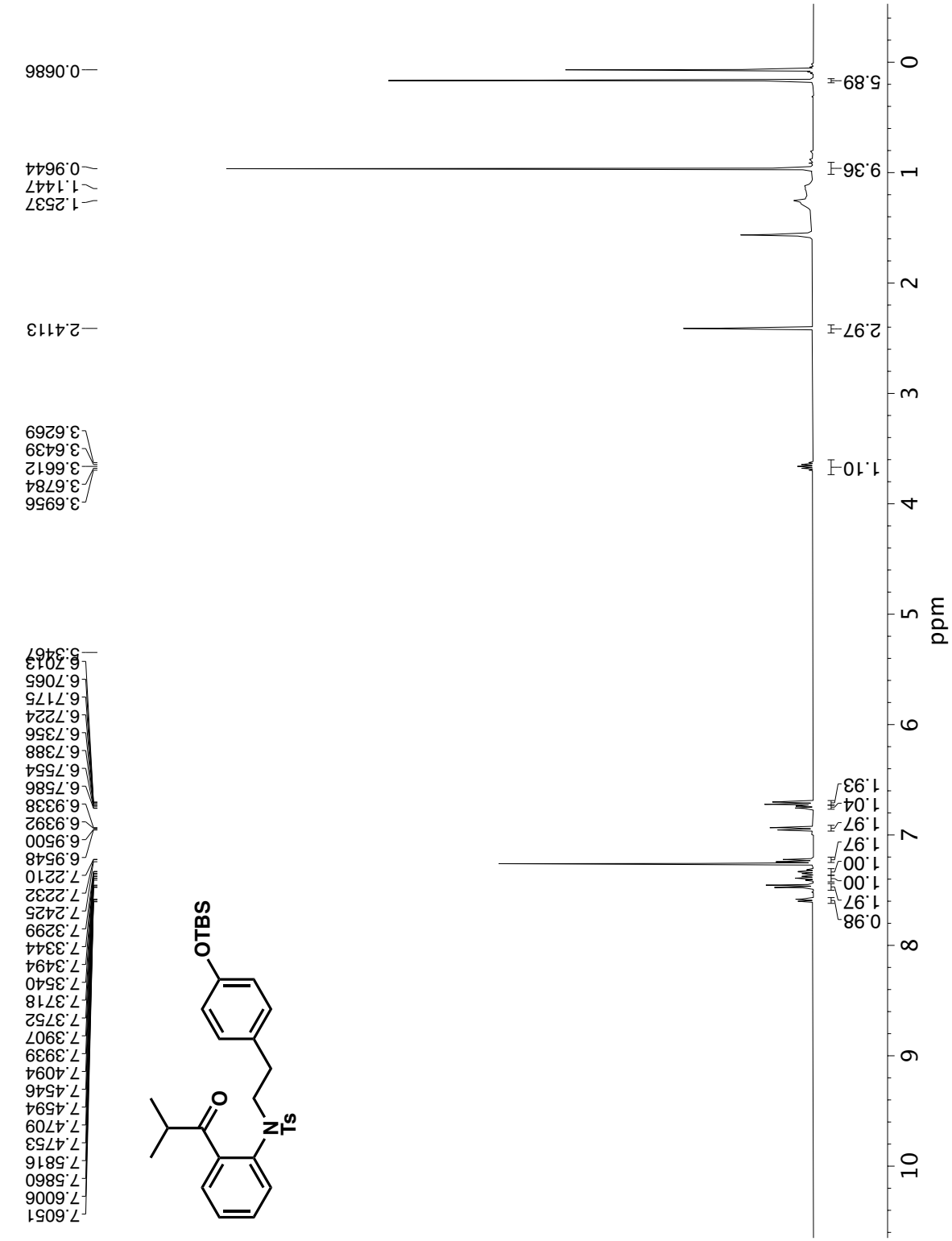
^{13}C NMR (101 MHz, $CDCl_3$) of compound **S30**.



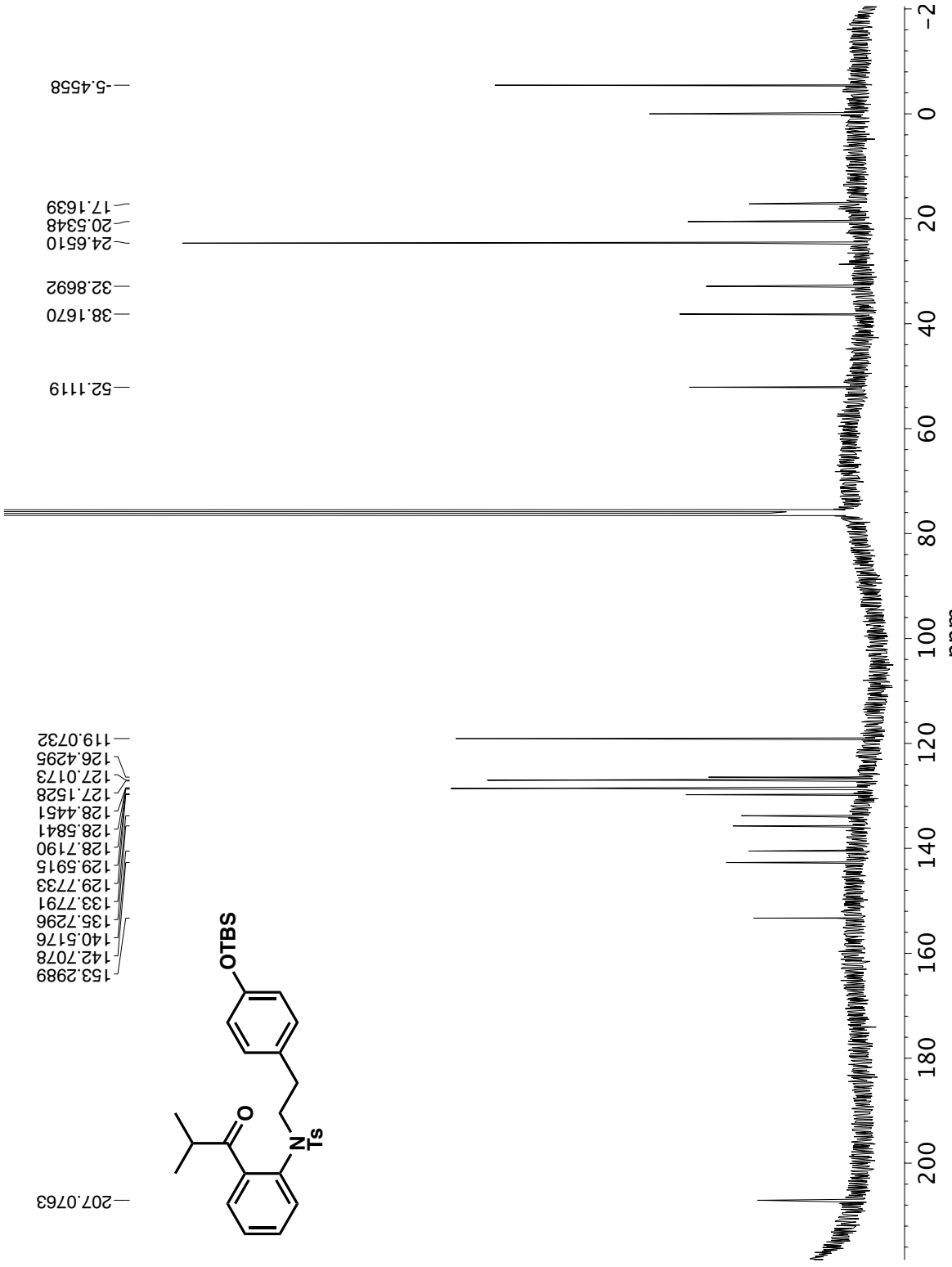
^{1}H NMR (400 MHz, $CDCl_3$) of compound **S31**.



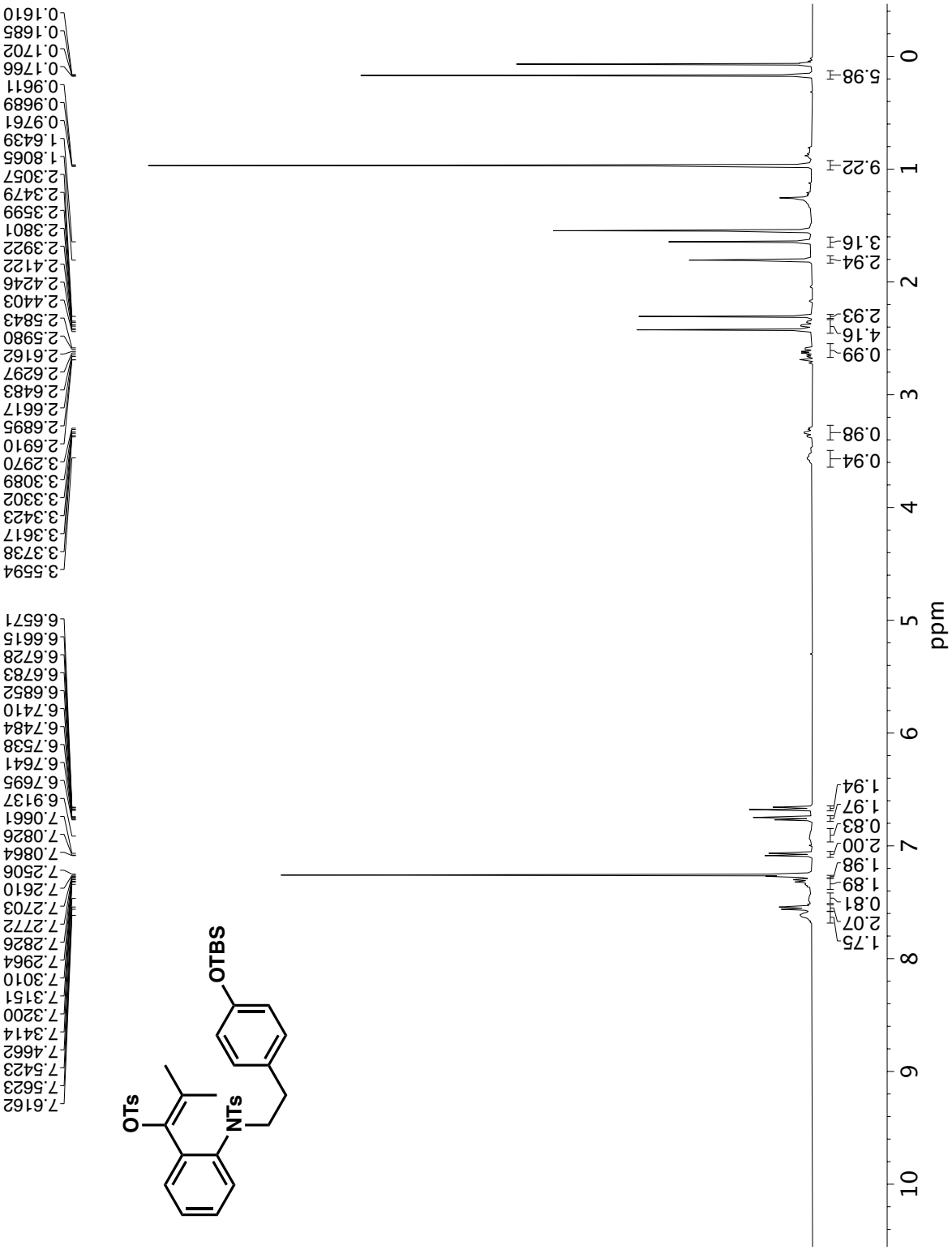
^{13}C NMR (101 MHz, $CDCl_3$) of compound **S31**.



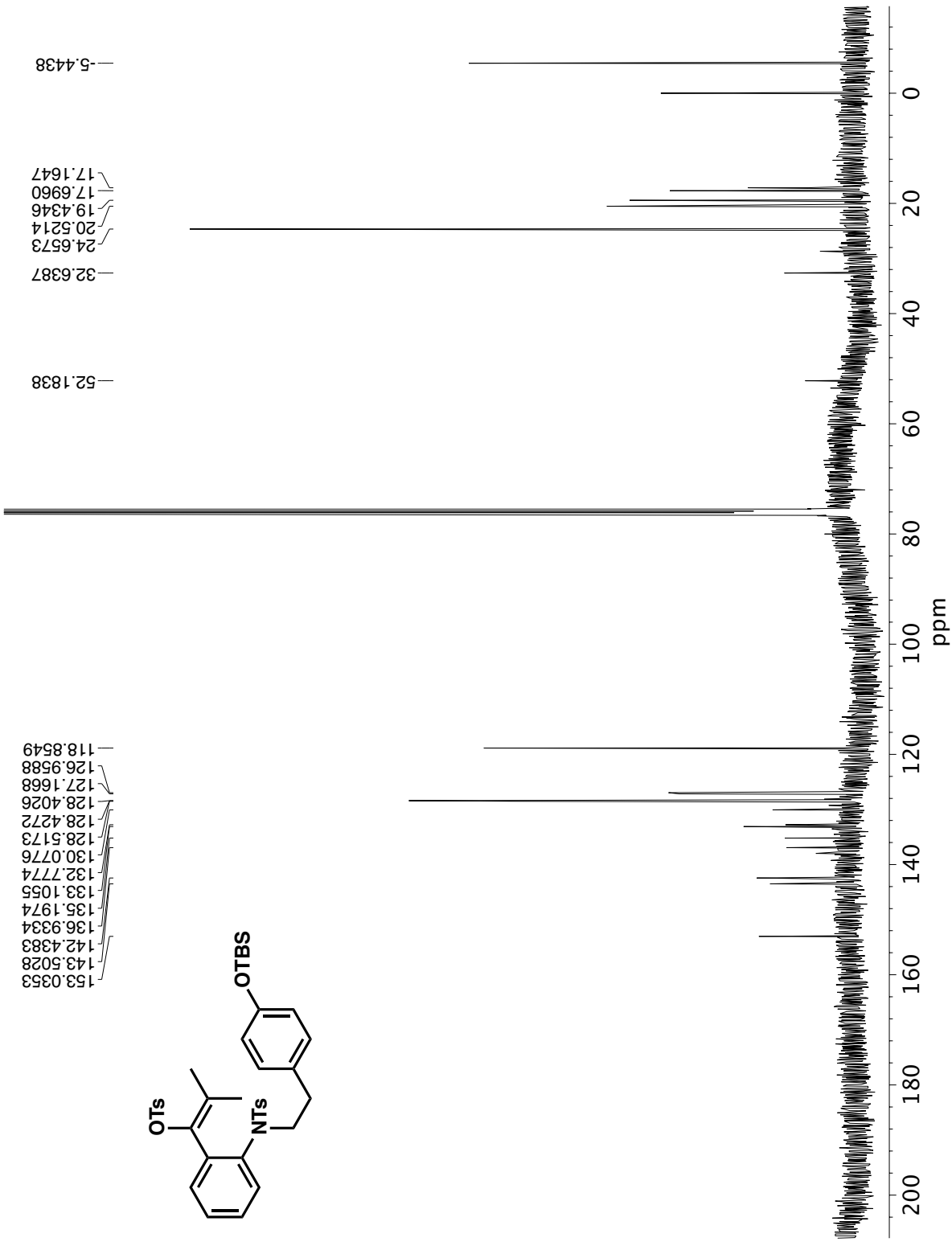
^{1}H NMR (400 MHz, $CDCl_3$) of compound **S32**.



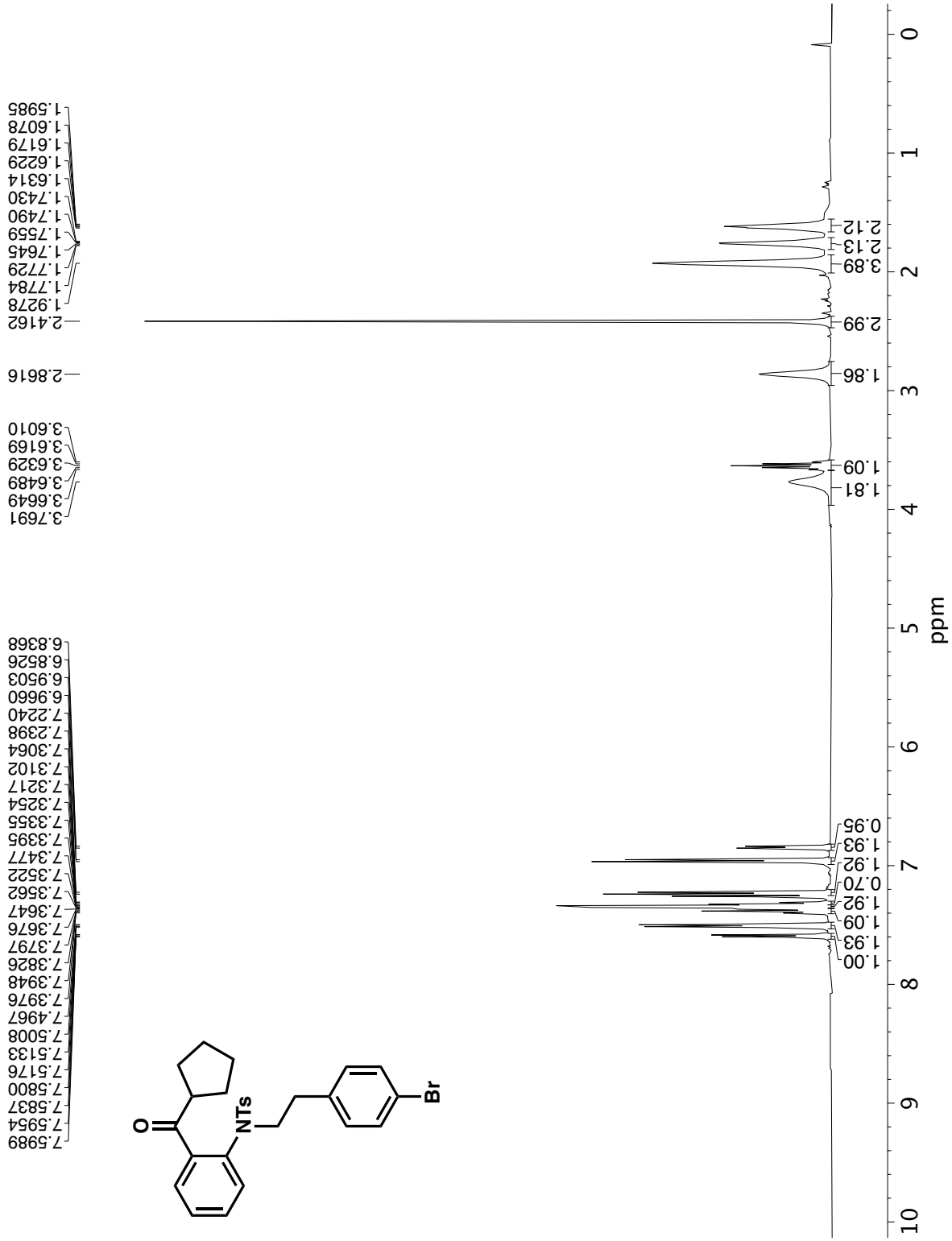
^{13}C NMR (101 MHz, $CDCl_3$) of compound **S32**.



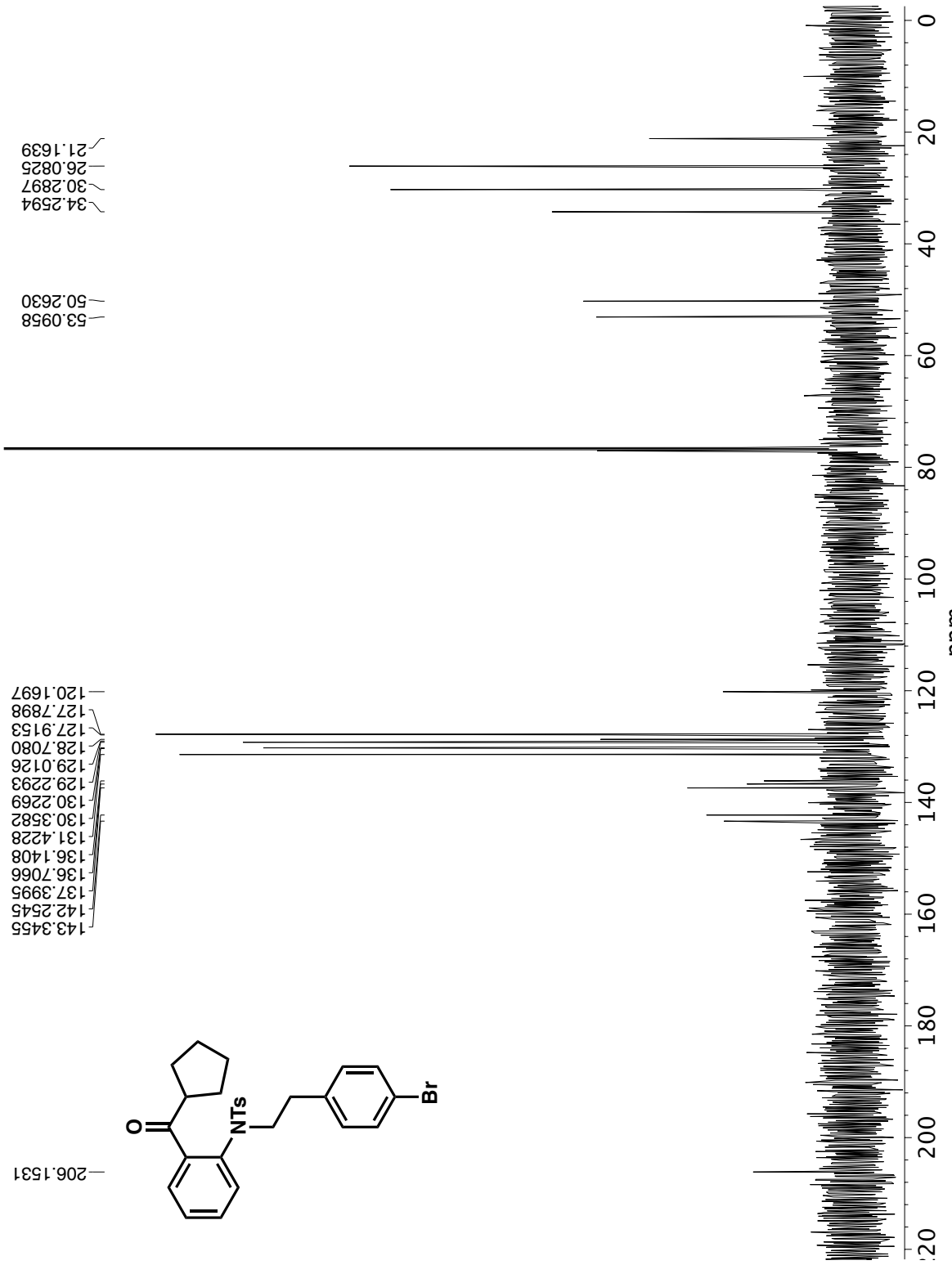
^{1}H NMR (400 MHz, $CDCl_3$) of compound **S33**.



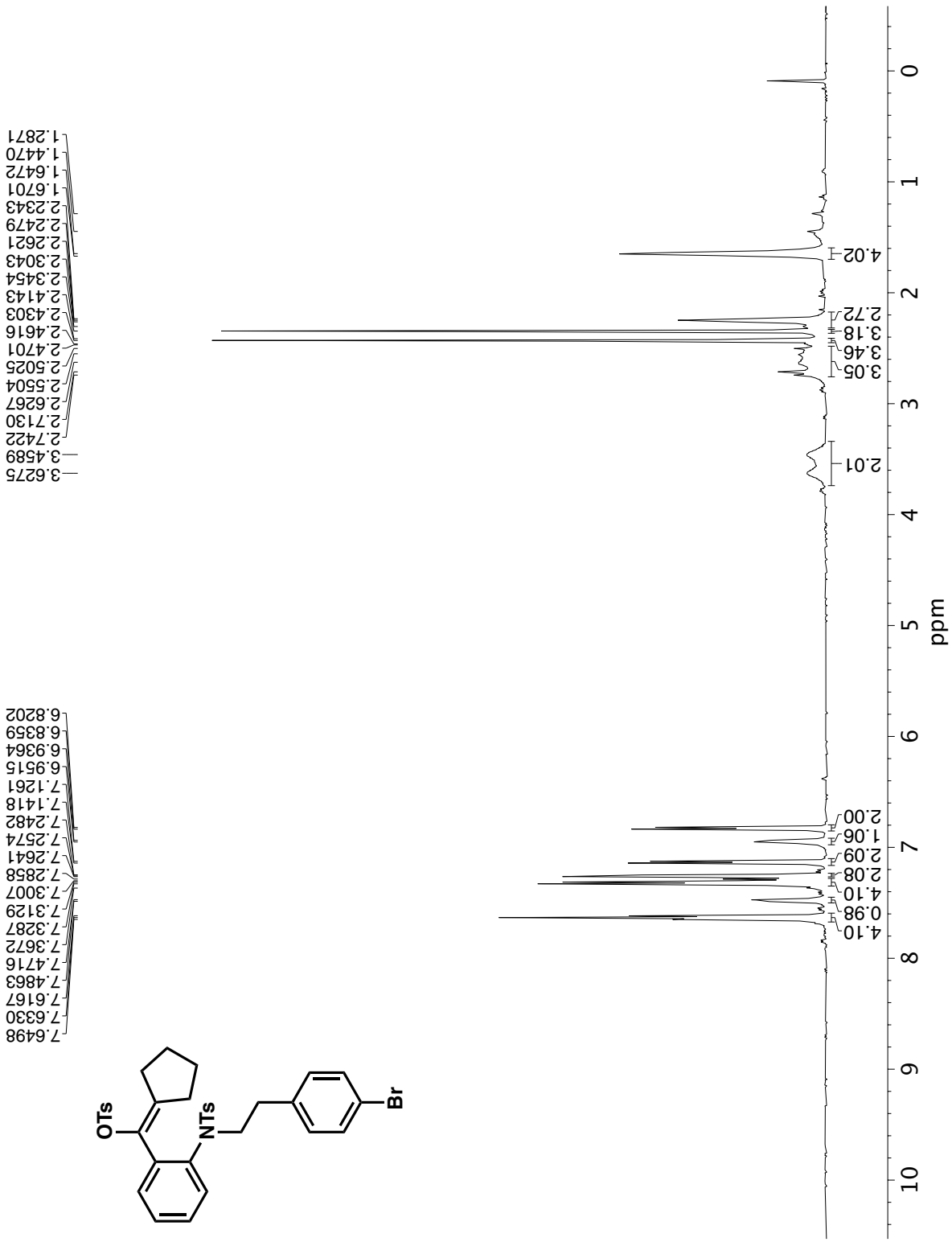
^{13}C NMR (101 MHz, $CDCl_3$) of compound **S33**.



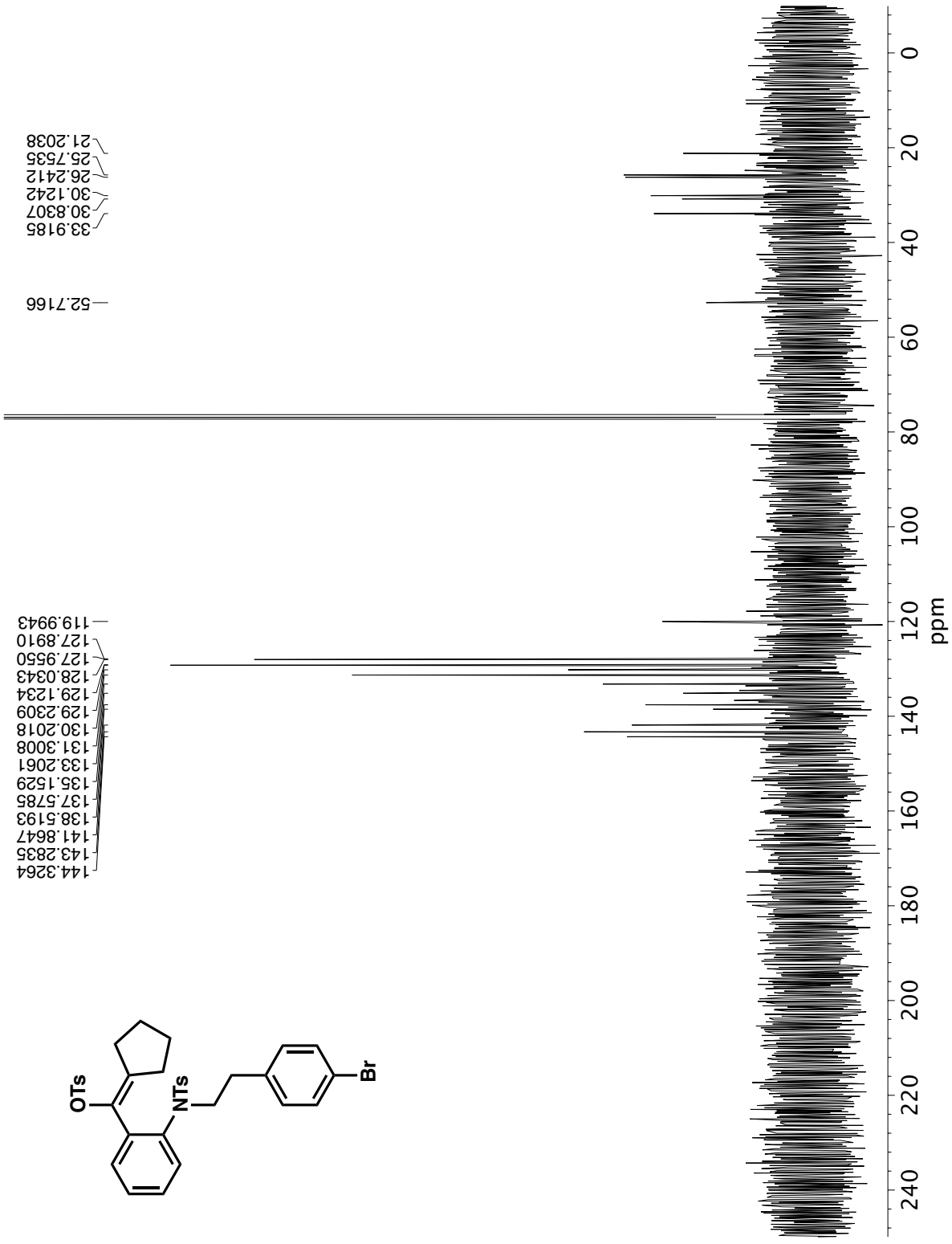
^{1}H NMR (500 MHz, $CDCl_3$, 70°C) of compound **S35**.



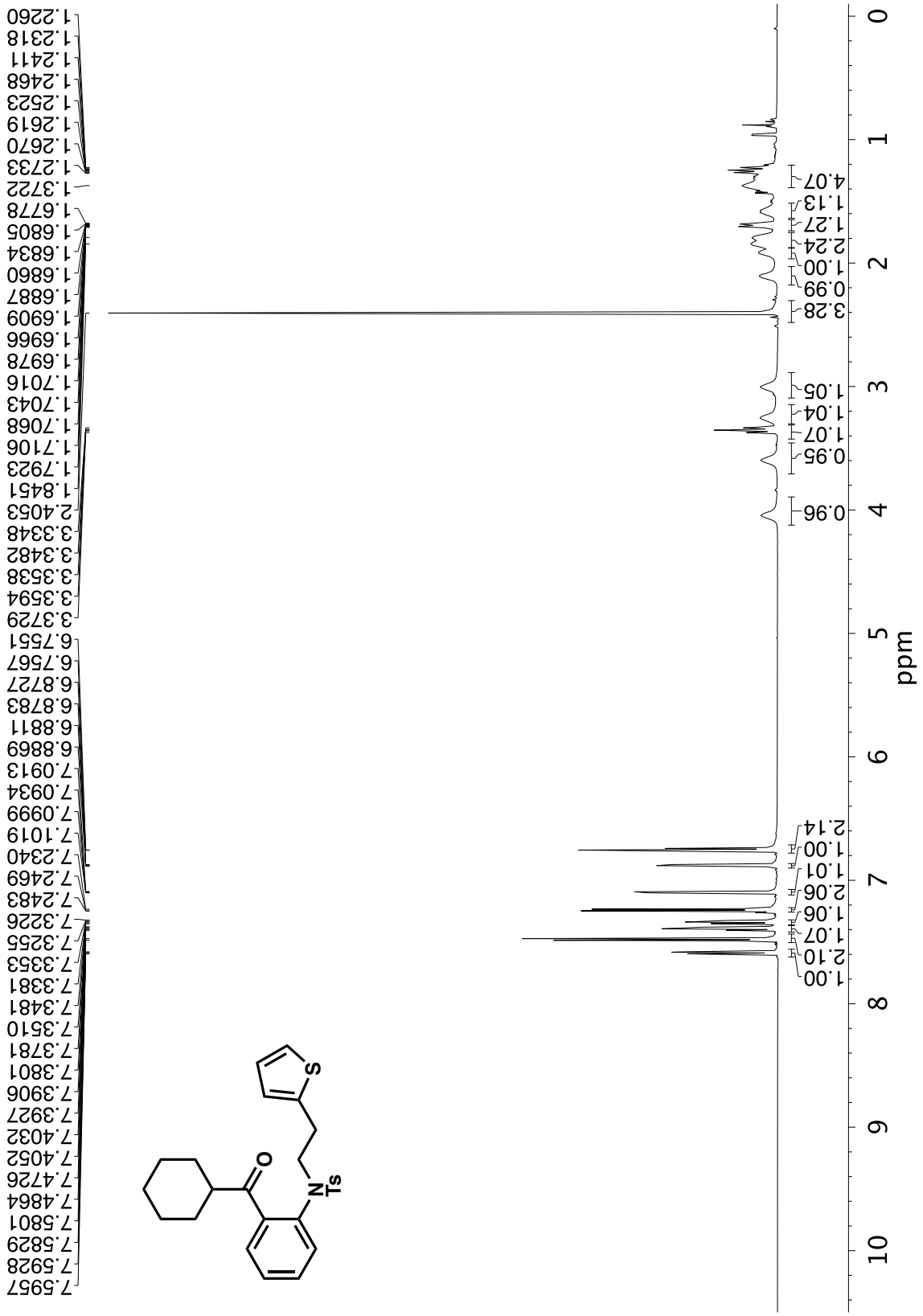
^{13}C NMR (126 MHz, $CDCl_3$, 70°C) of compound **S35**.



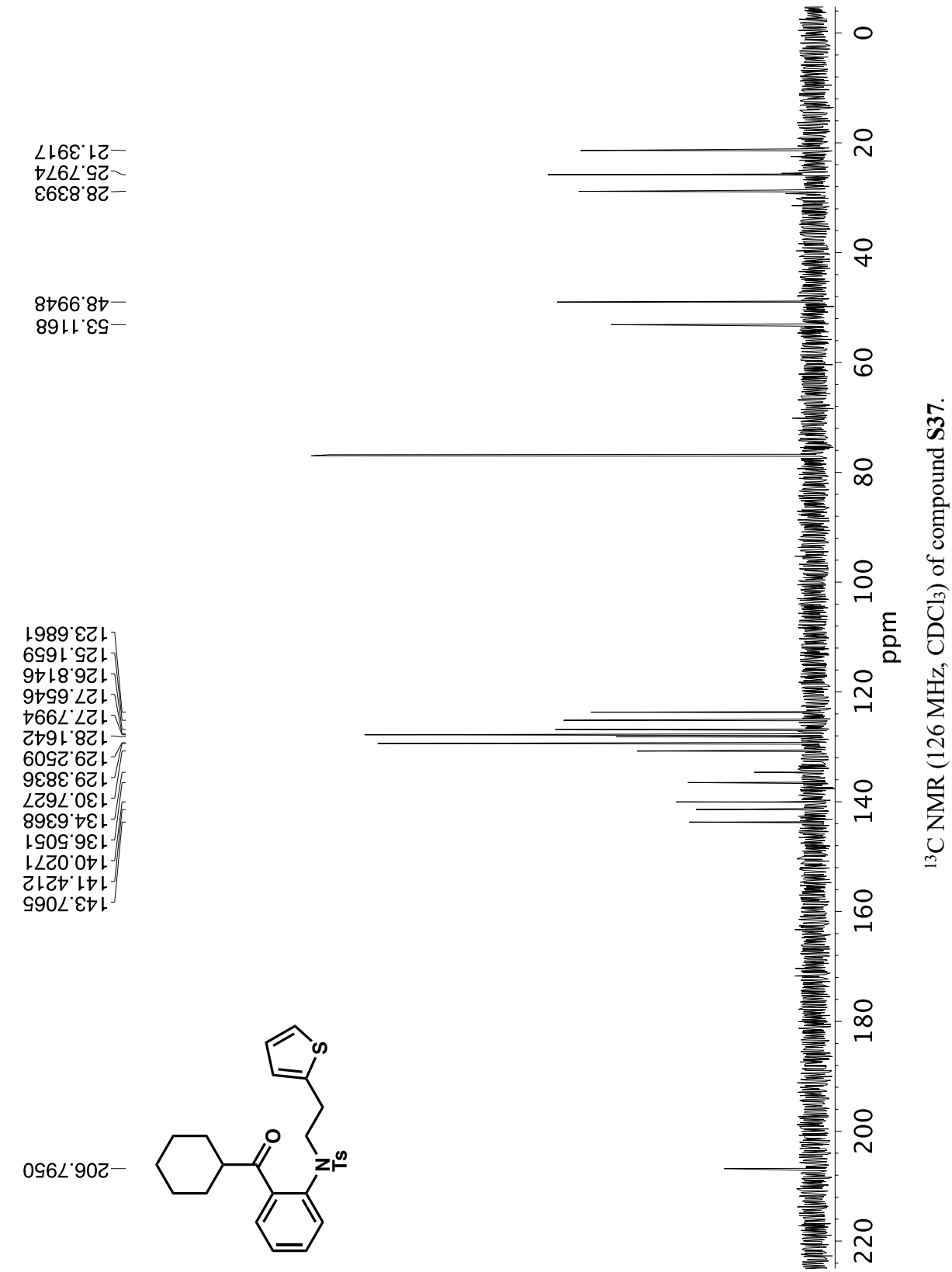
^{1}H NMR (500 MHz, $CDCl_3$, 70°C) of compound **S36**.



^{13}C NMR (126 MHz, $CDCl_3$, 70°C) of compound **S36**.

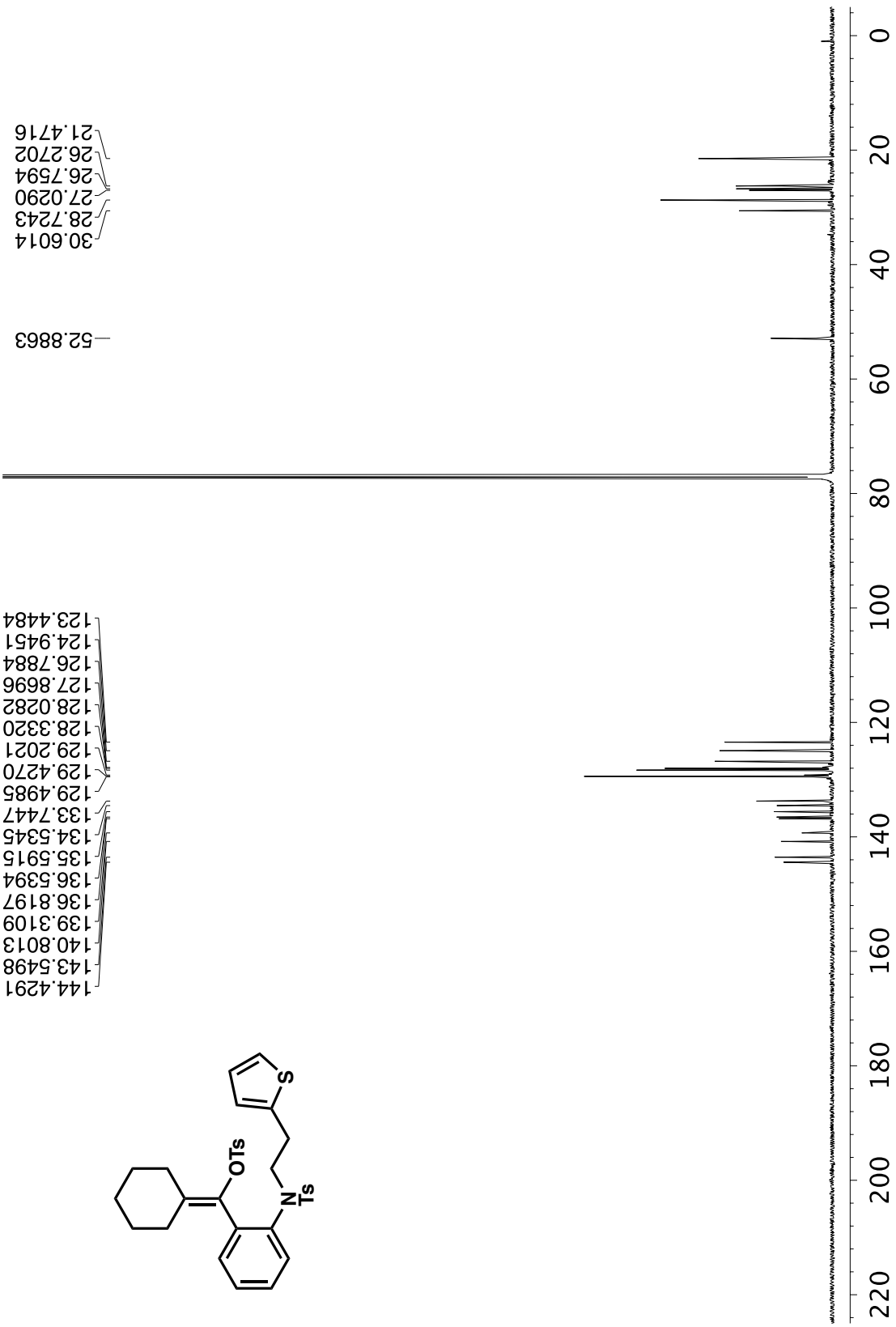


^{1}H NMR (500 MHz, $CDCl_3$) of compound **S37**.

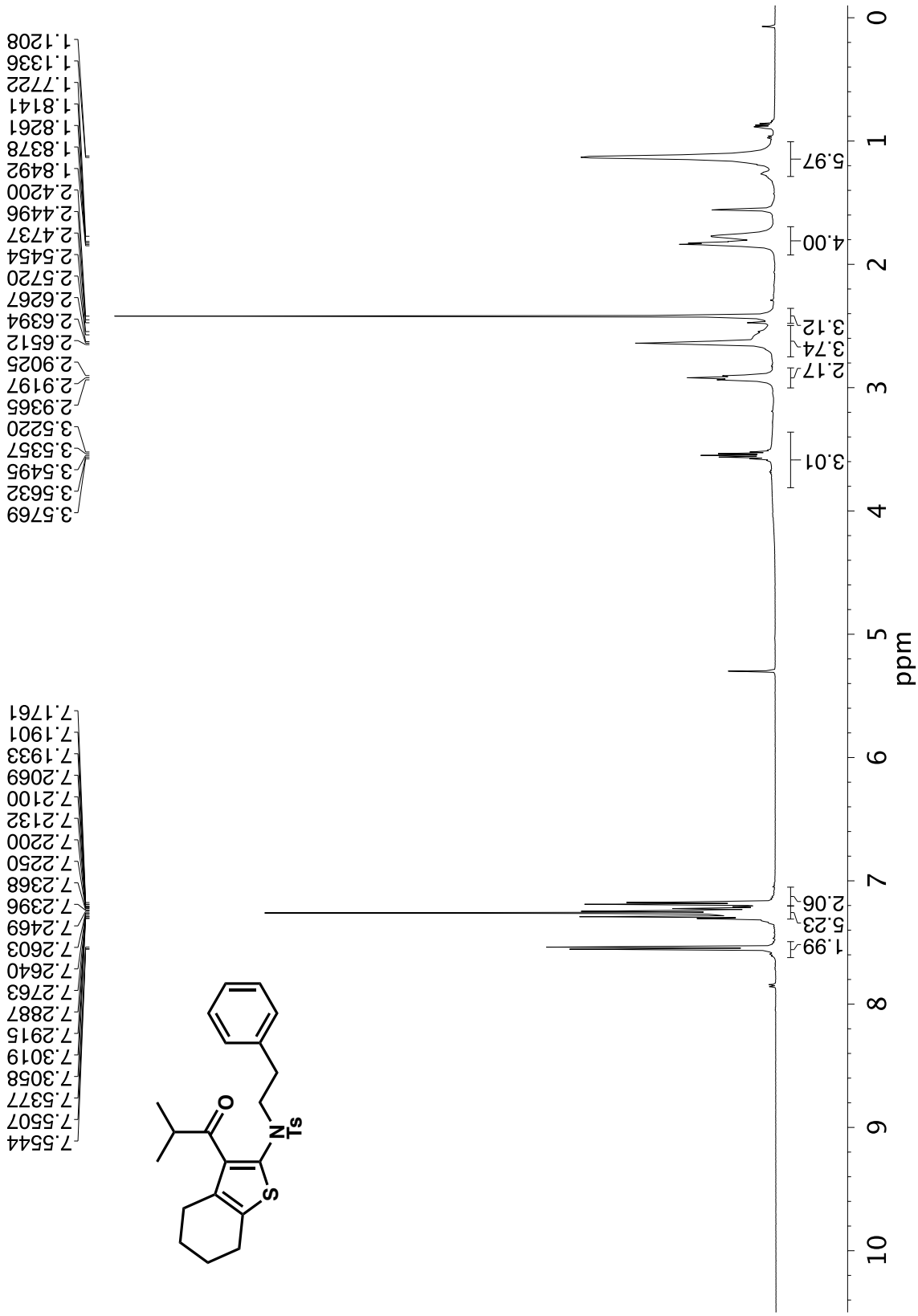


^{13}C NMR (126 MHz, $CDCl_3$) of compound **S37**.

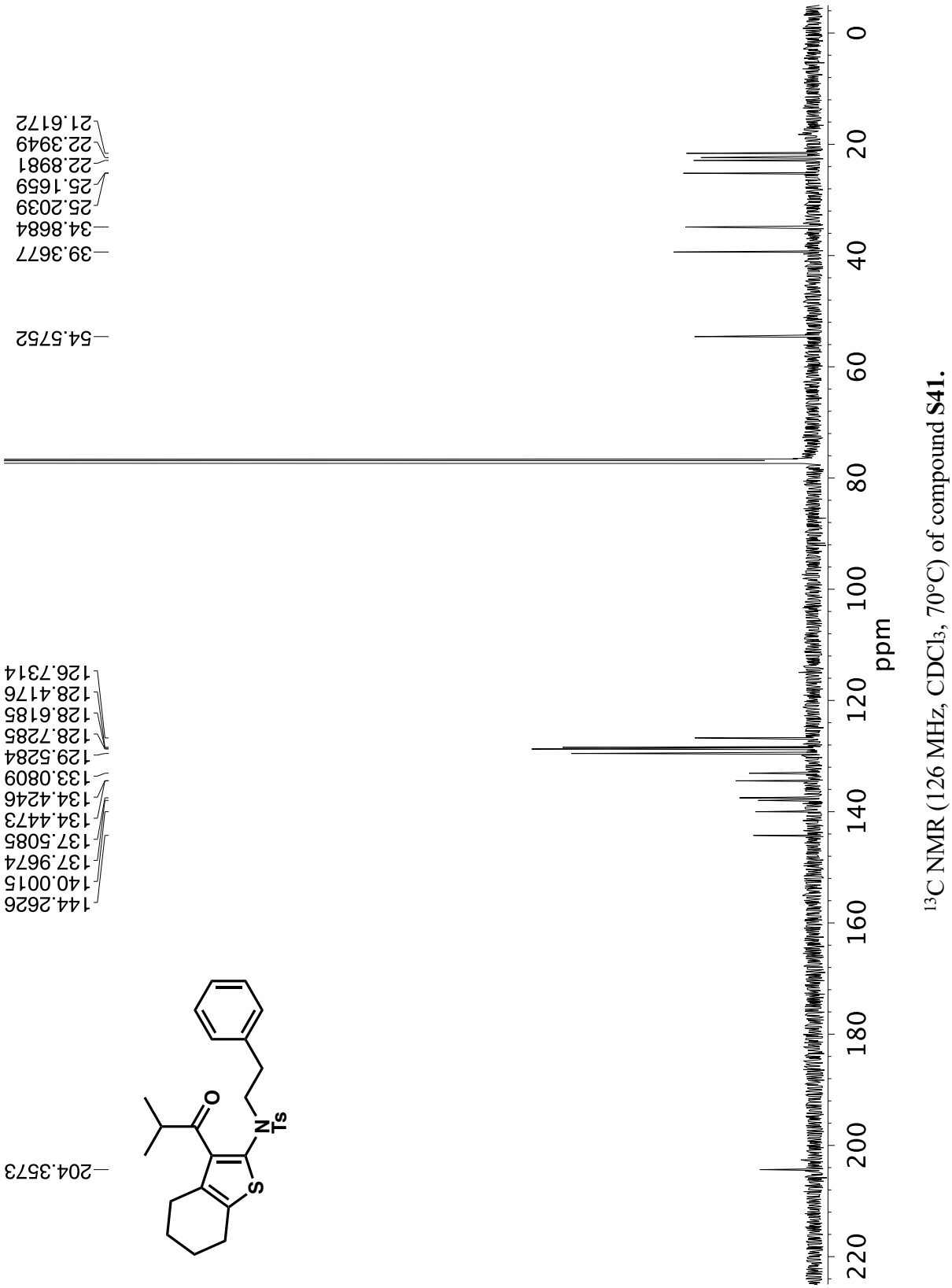
^{1}H NMR (500 MHz, $CDCl_3$, 55°C) of compound **S38**.



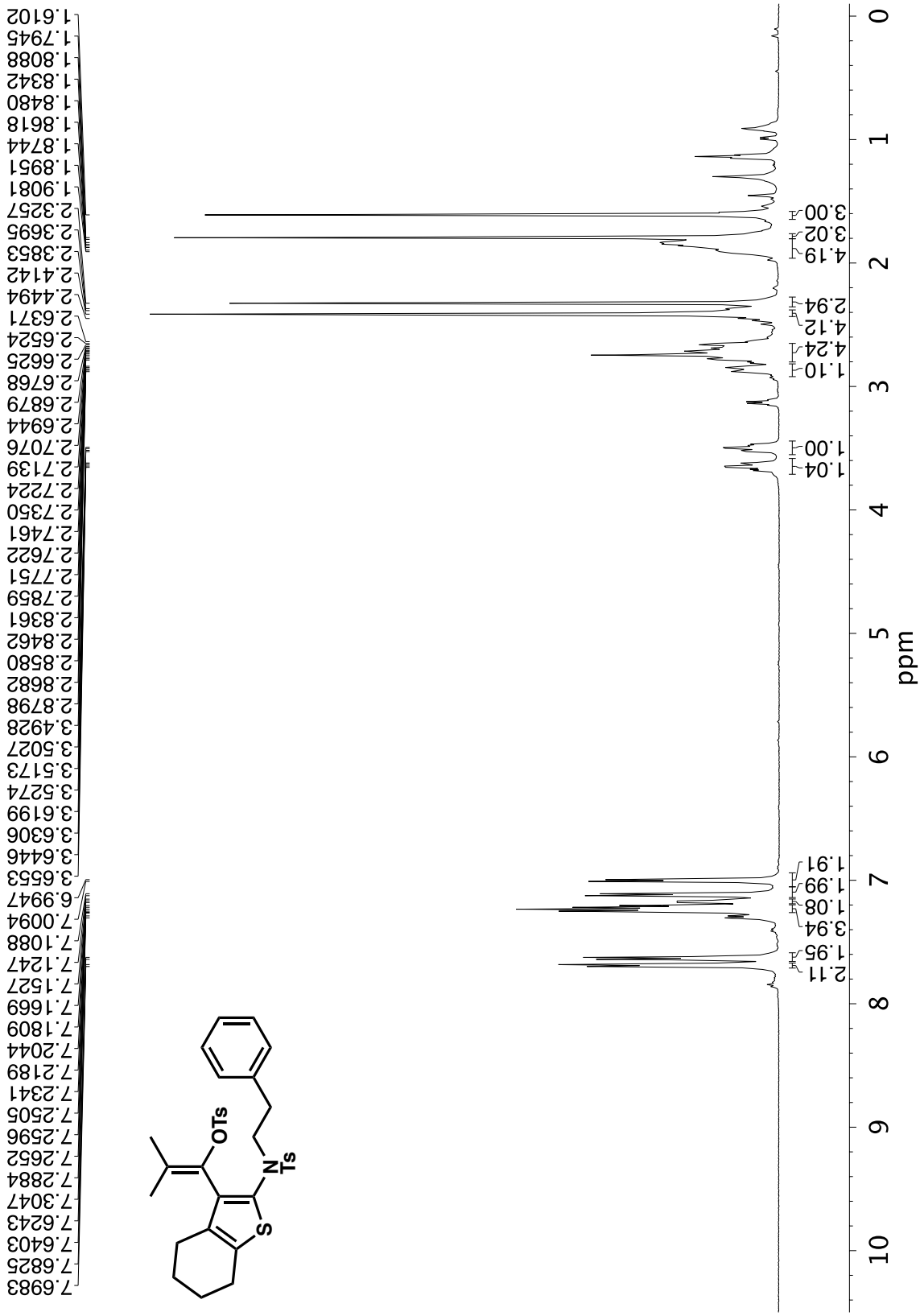
^{13}C NMR (126 MHz, $CDCl_3$, 55°C) of compound **S38**.



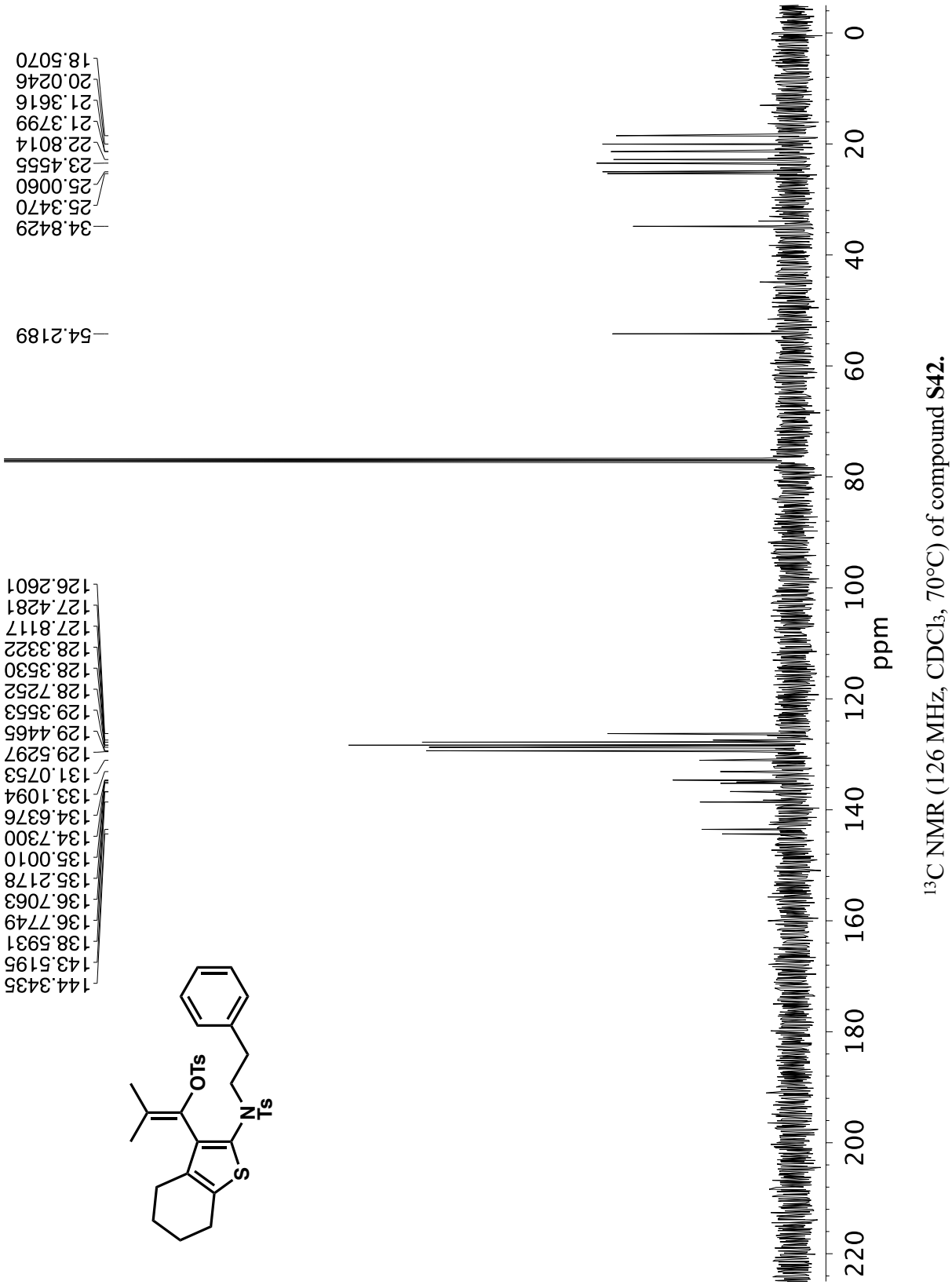
^{1}H NMR (500 MHz, $CDCl_3$, 70°C) of compound **S41.**



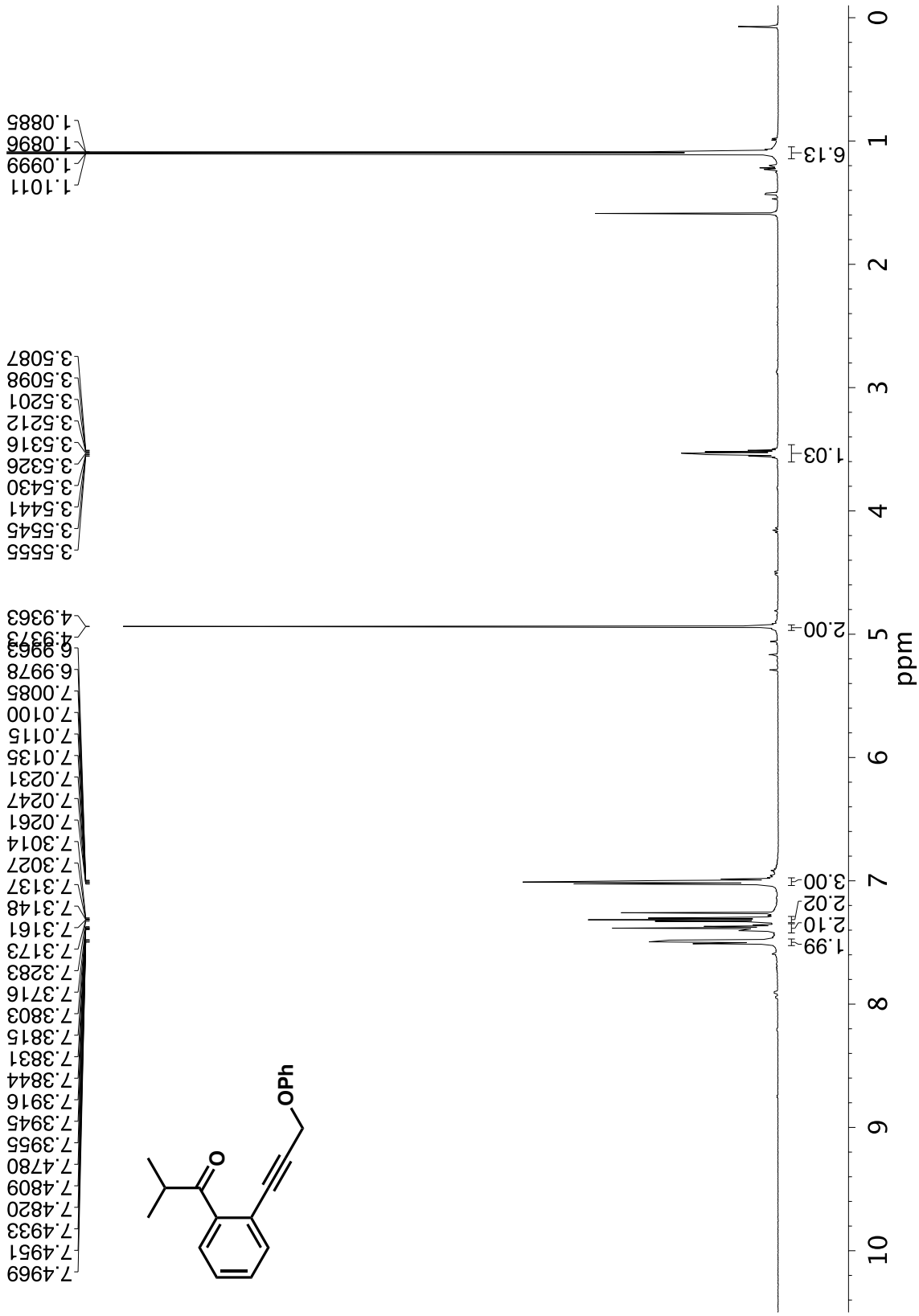
^{13}C NMR (126 MHz, $CDCl_3$, 70°C) of compound **S41.**



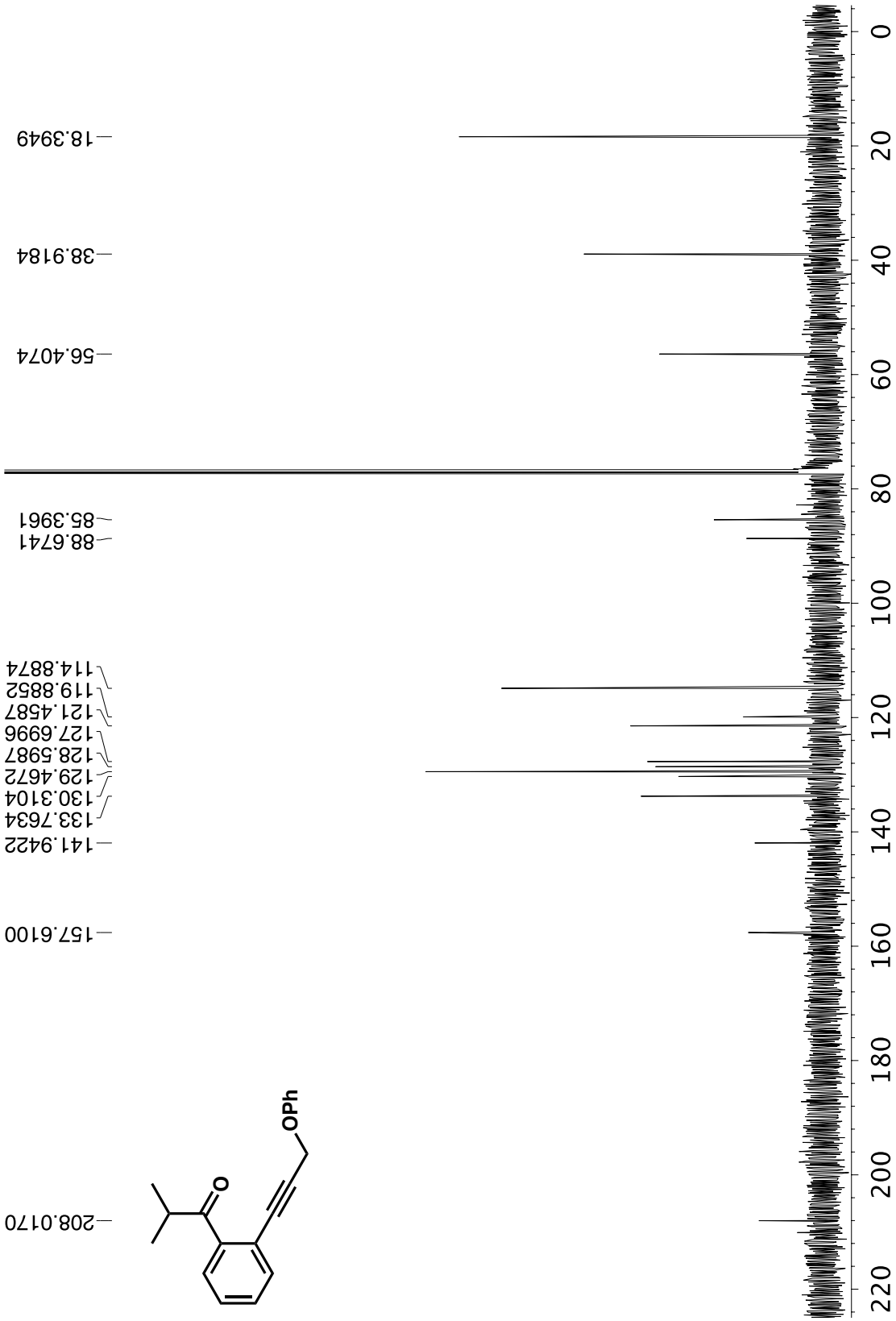
^{1}H NMR (500 MHz, $CDCl_3$, 70°C) of compound **S42.**



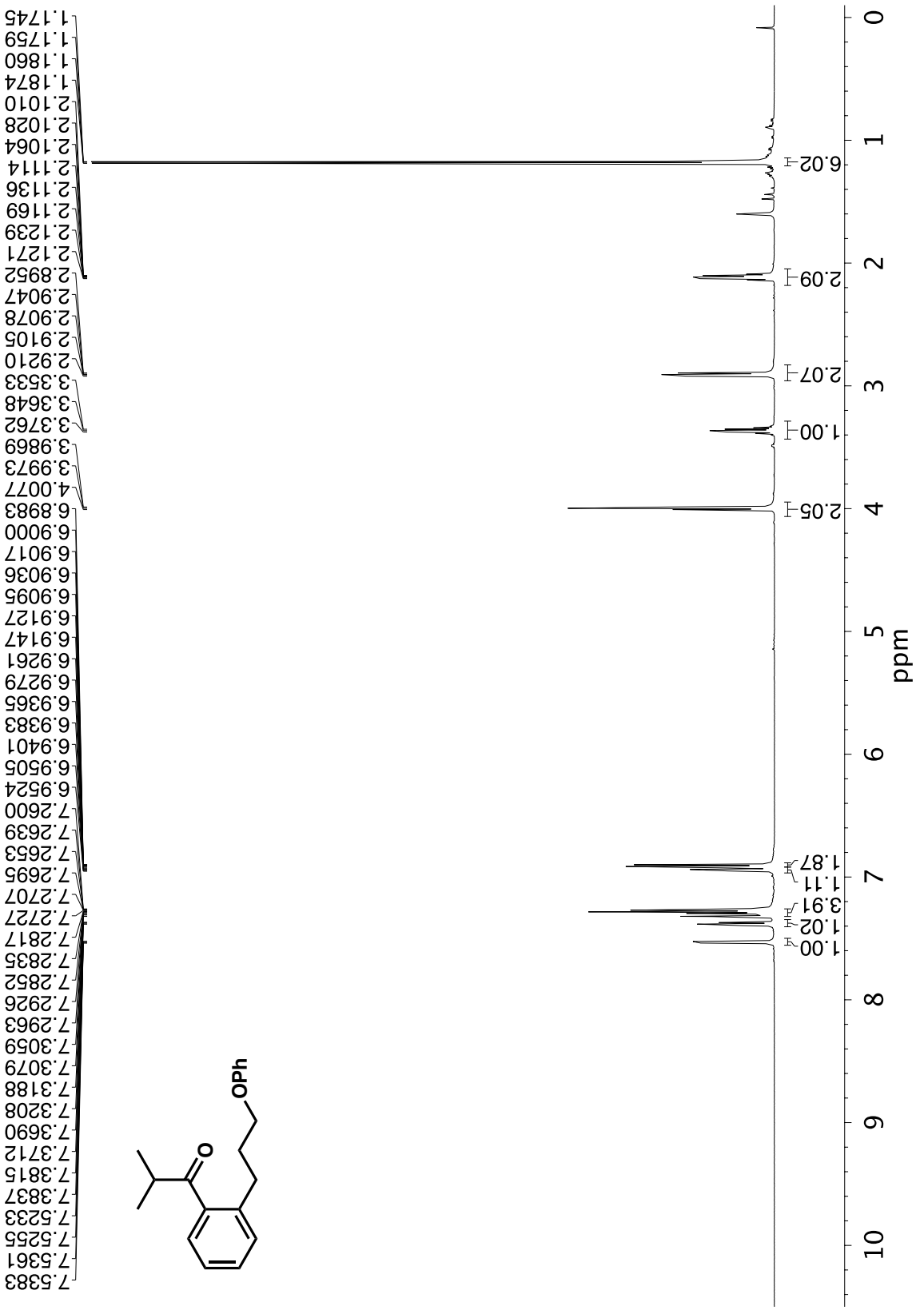
^{13}C NMR (126 MHz, $CDCl_3$, 70°C) of compound **S42.**



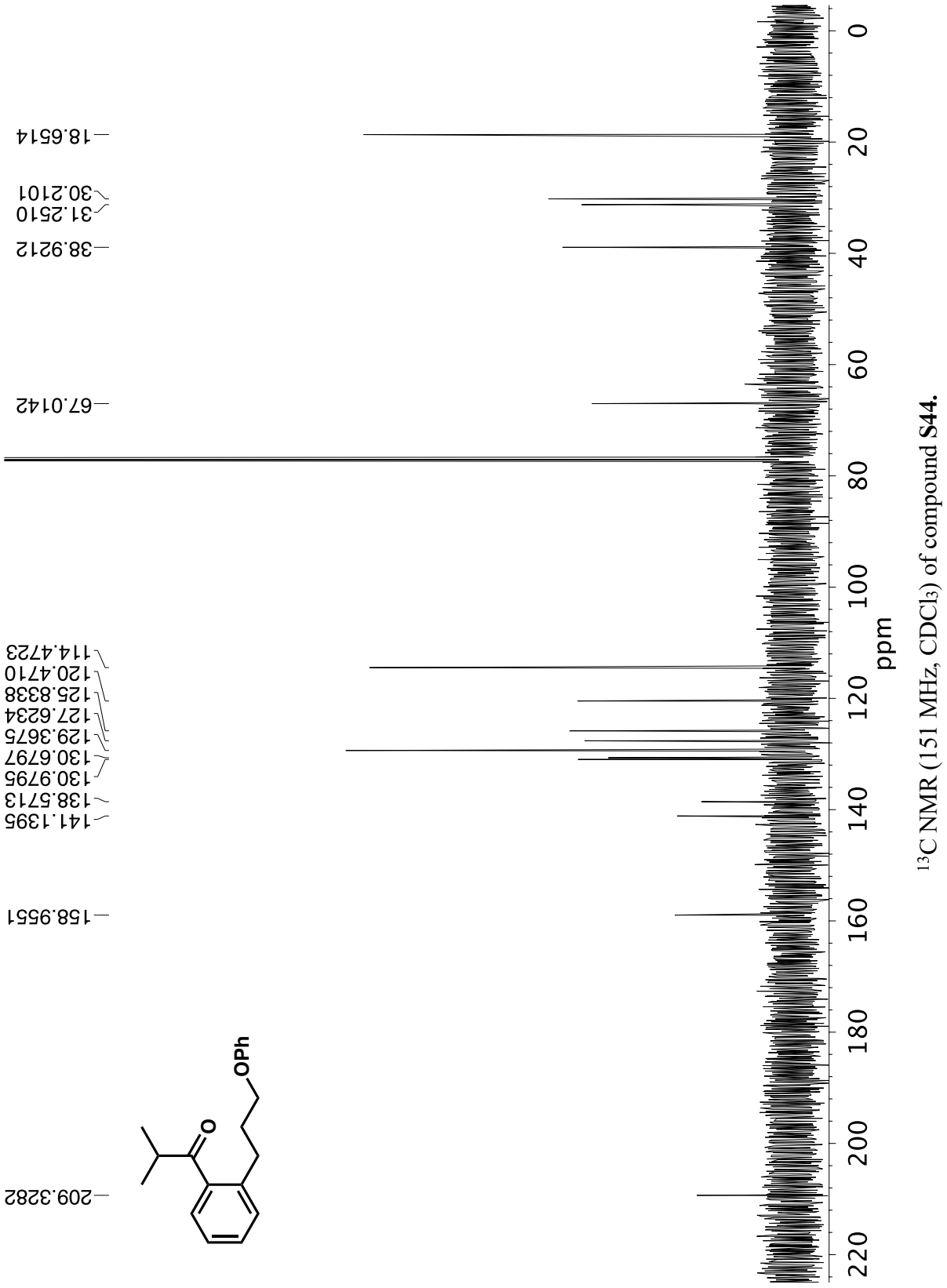
^{1}H NMR (600 MHz, $CDCl_3$) of compound **S43.**



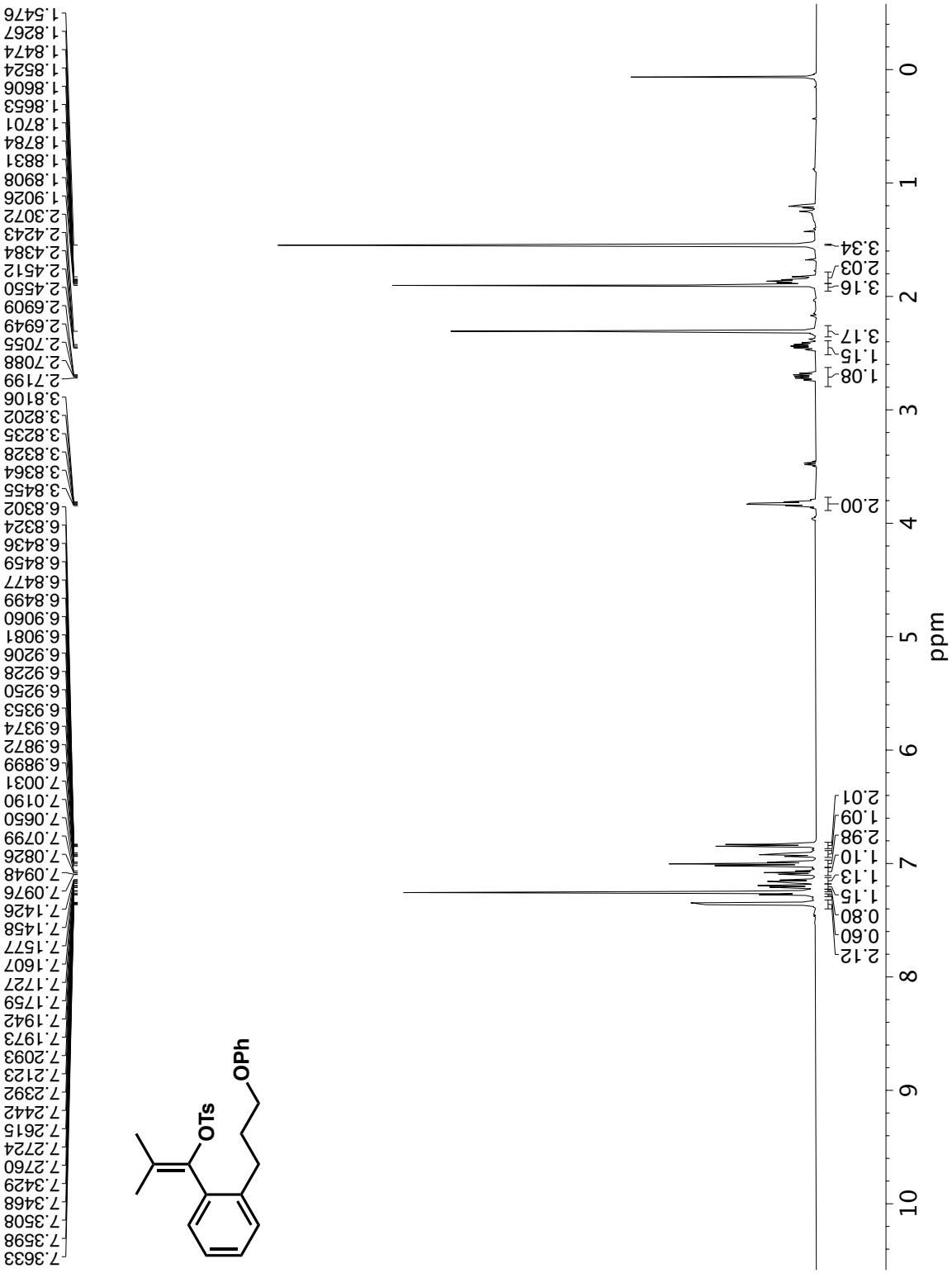
^{13}C NMR (151 MHz, $CDCl_3$) of compound **S43.**



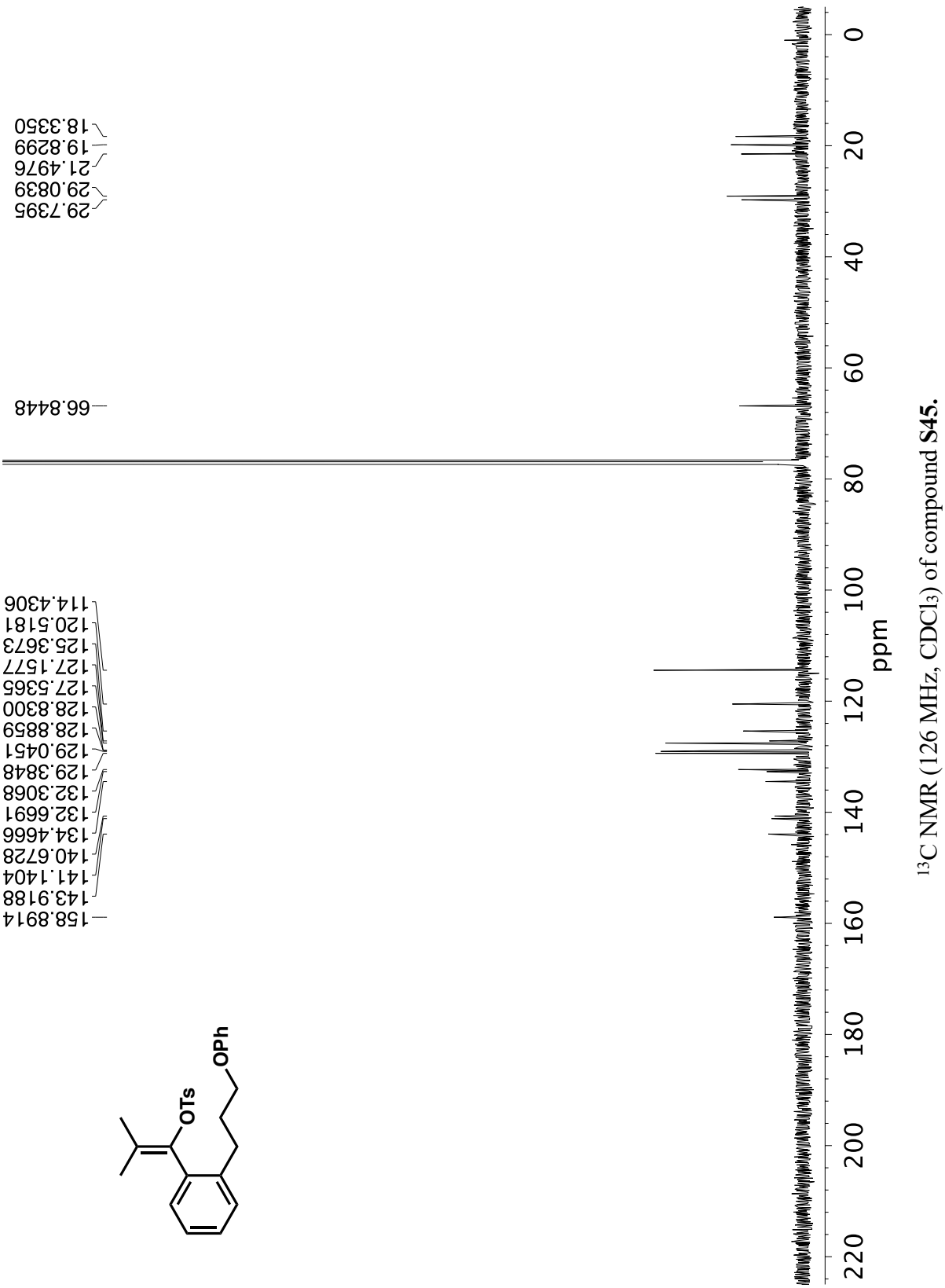
^{1}H NMR (600 MHz, $CDCl_3$) of compound **S44.**



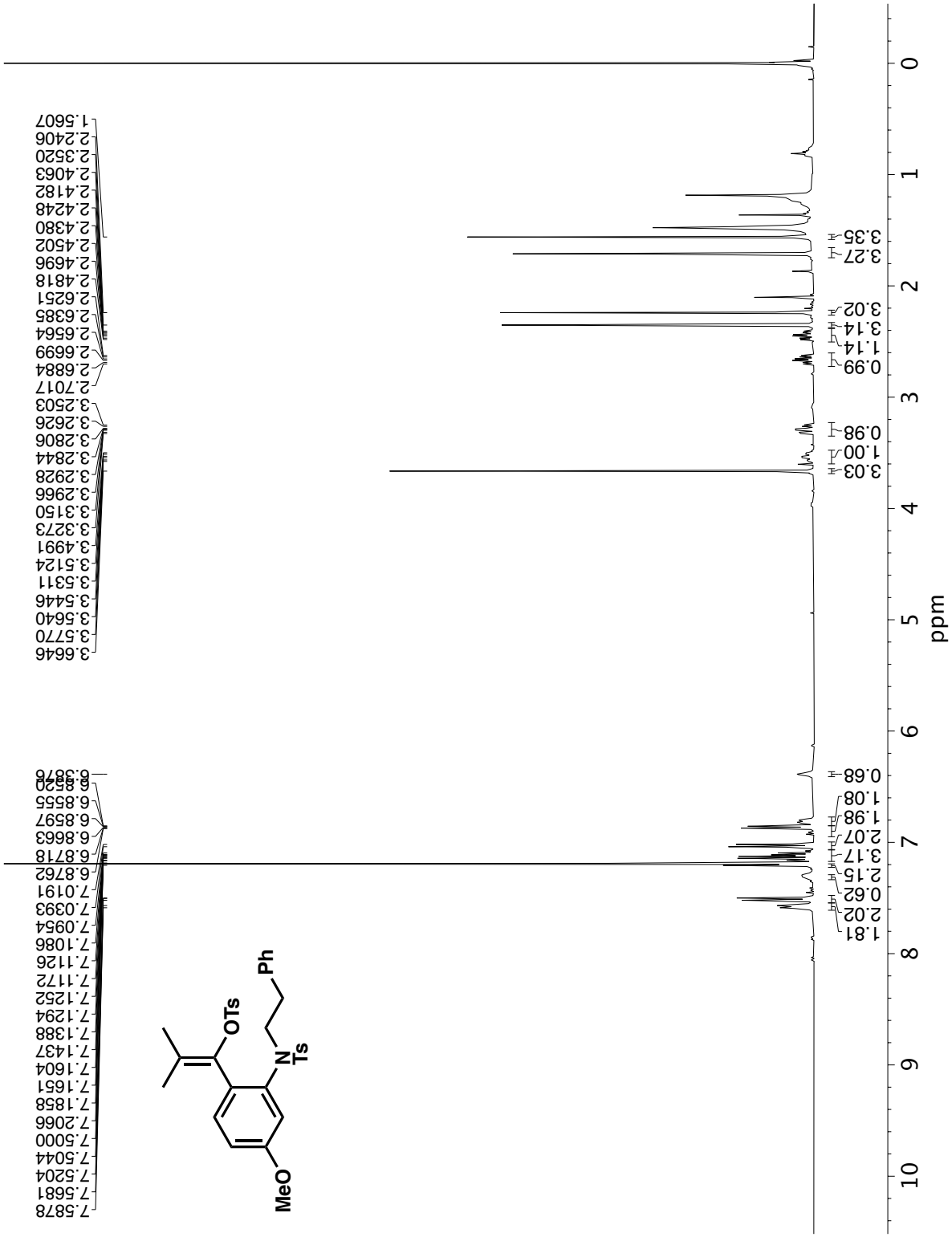
^{13}C NMR (151 MHz, $CDCl_3$) of compound **S44.**



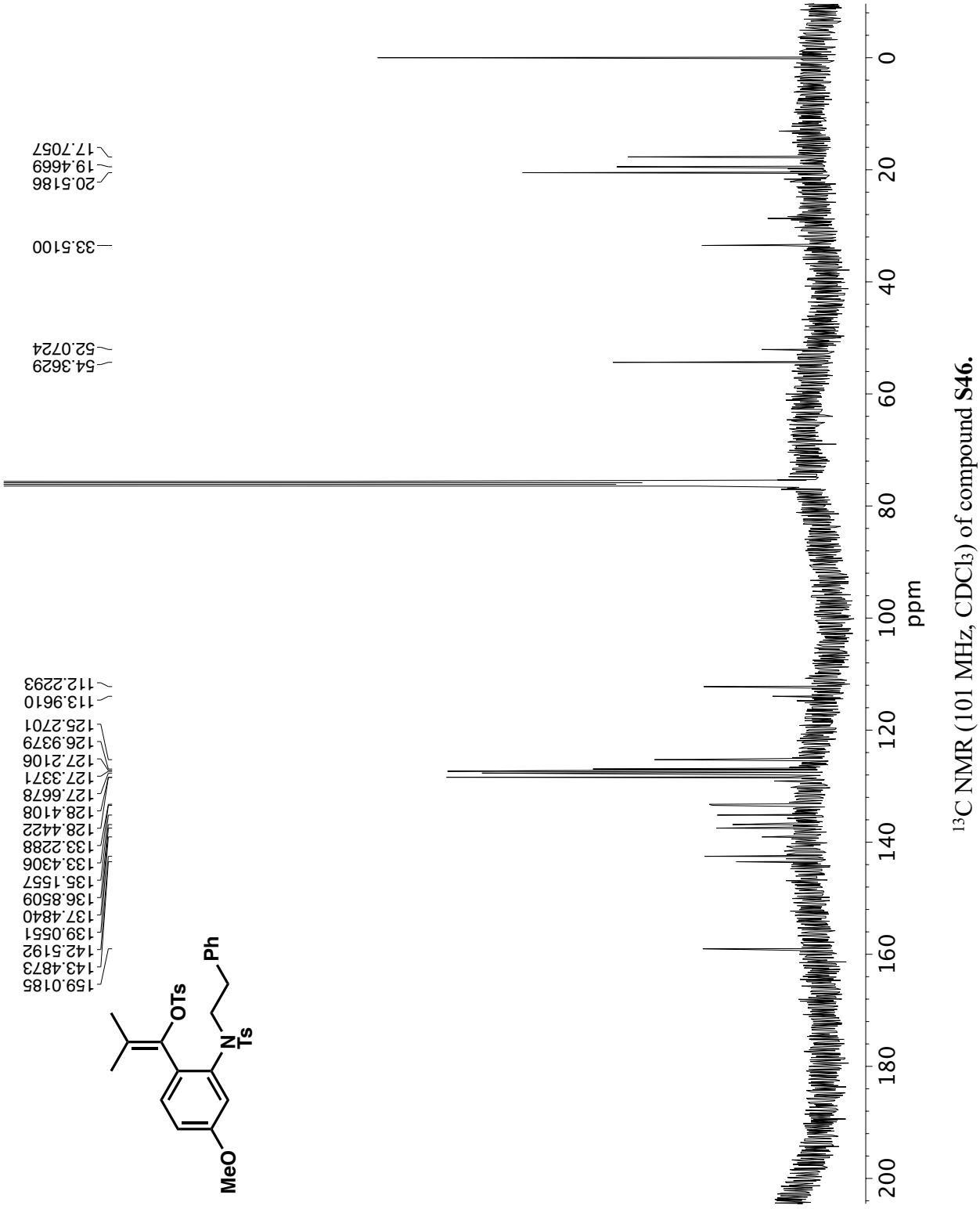
^{1}H NMR (500 MHz, $CDCl_3$) of compound **S45.**



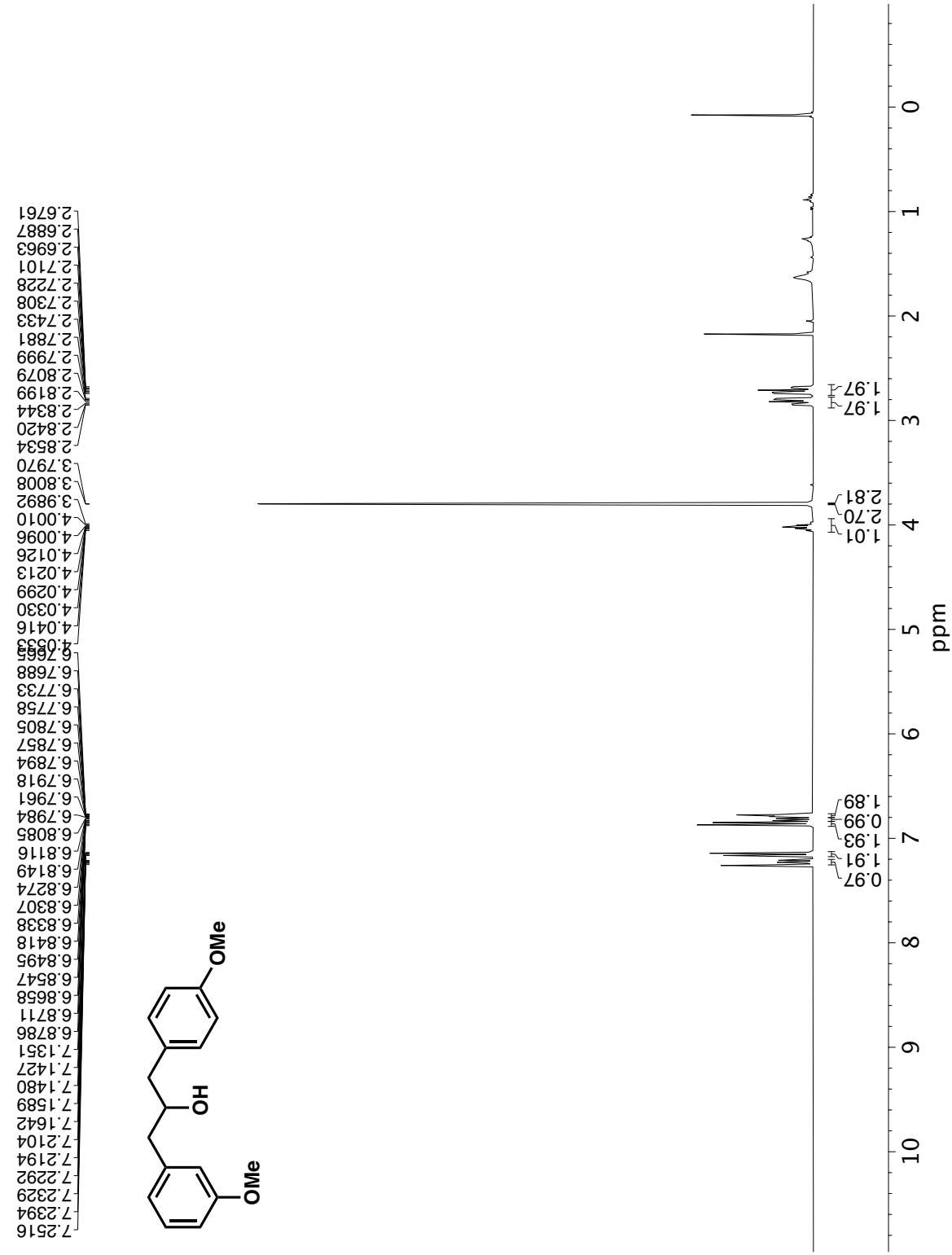
^{13}C NMR (126 MHz, $CDCl_3$) of compound **S45.**



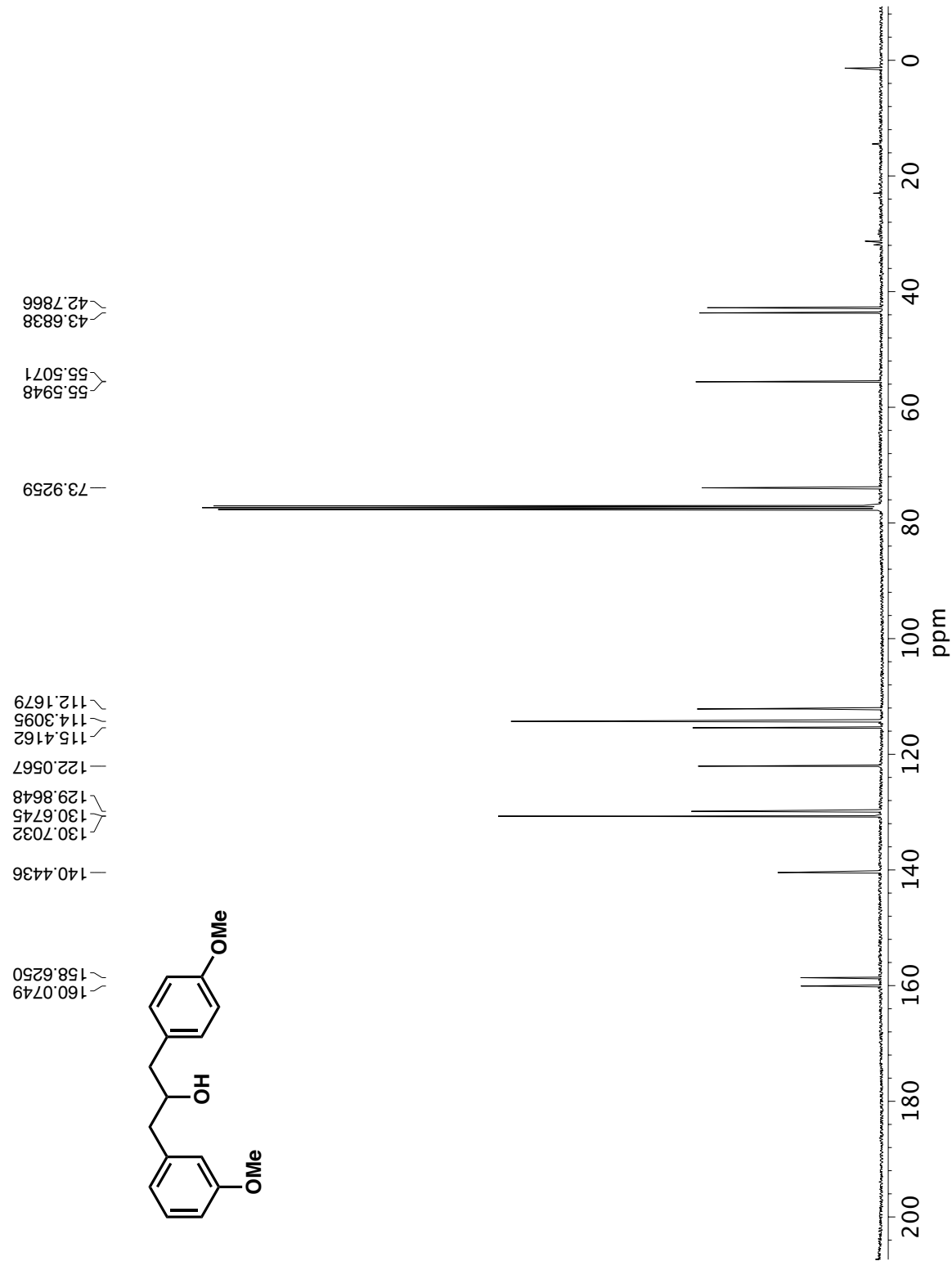
^{1}H NMR (400 MHz, $CDCl_3$) of compound **S46.**



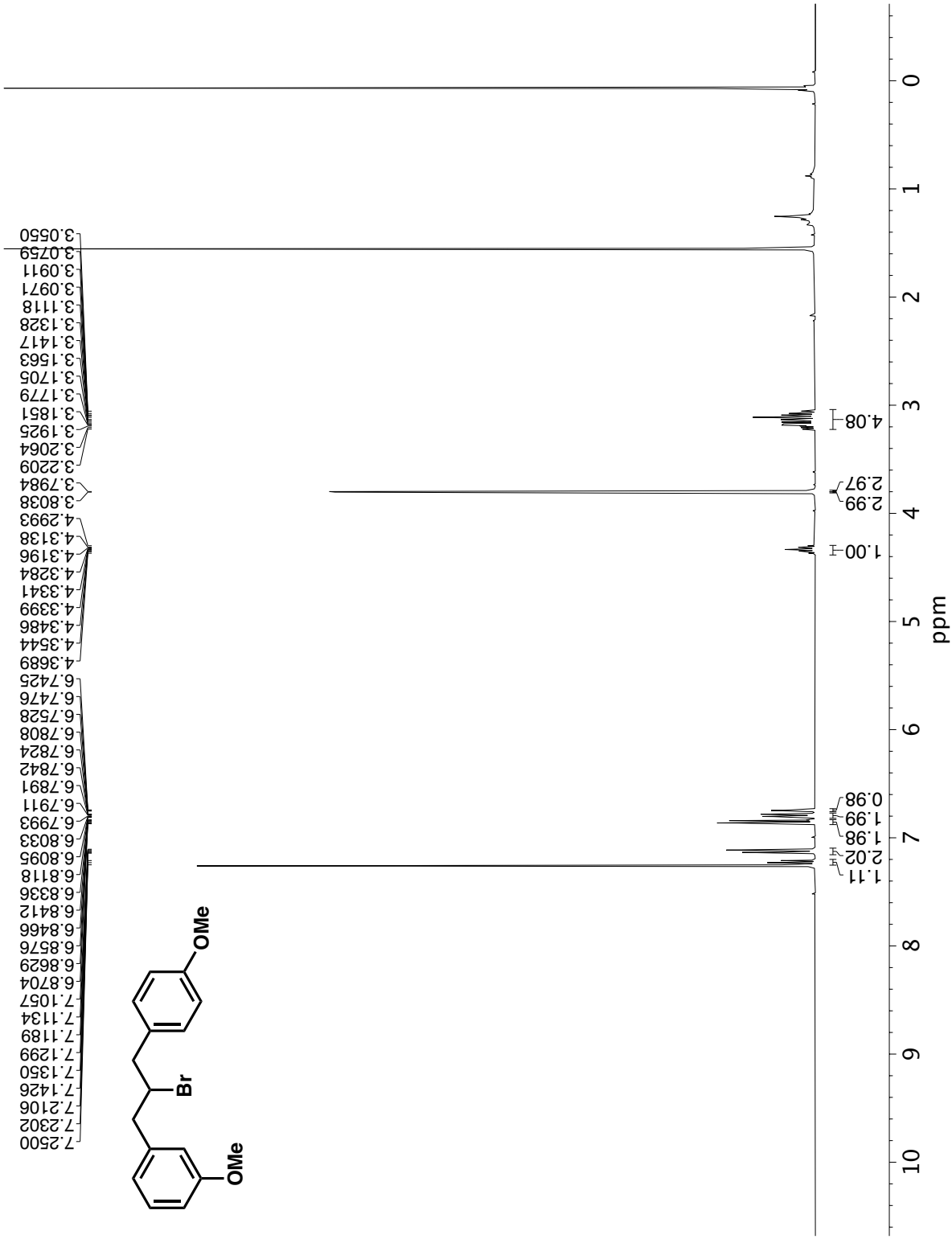
^{13}C NMR (101 MHz, $CDCl_3$) of compound **S46.**



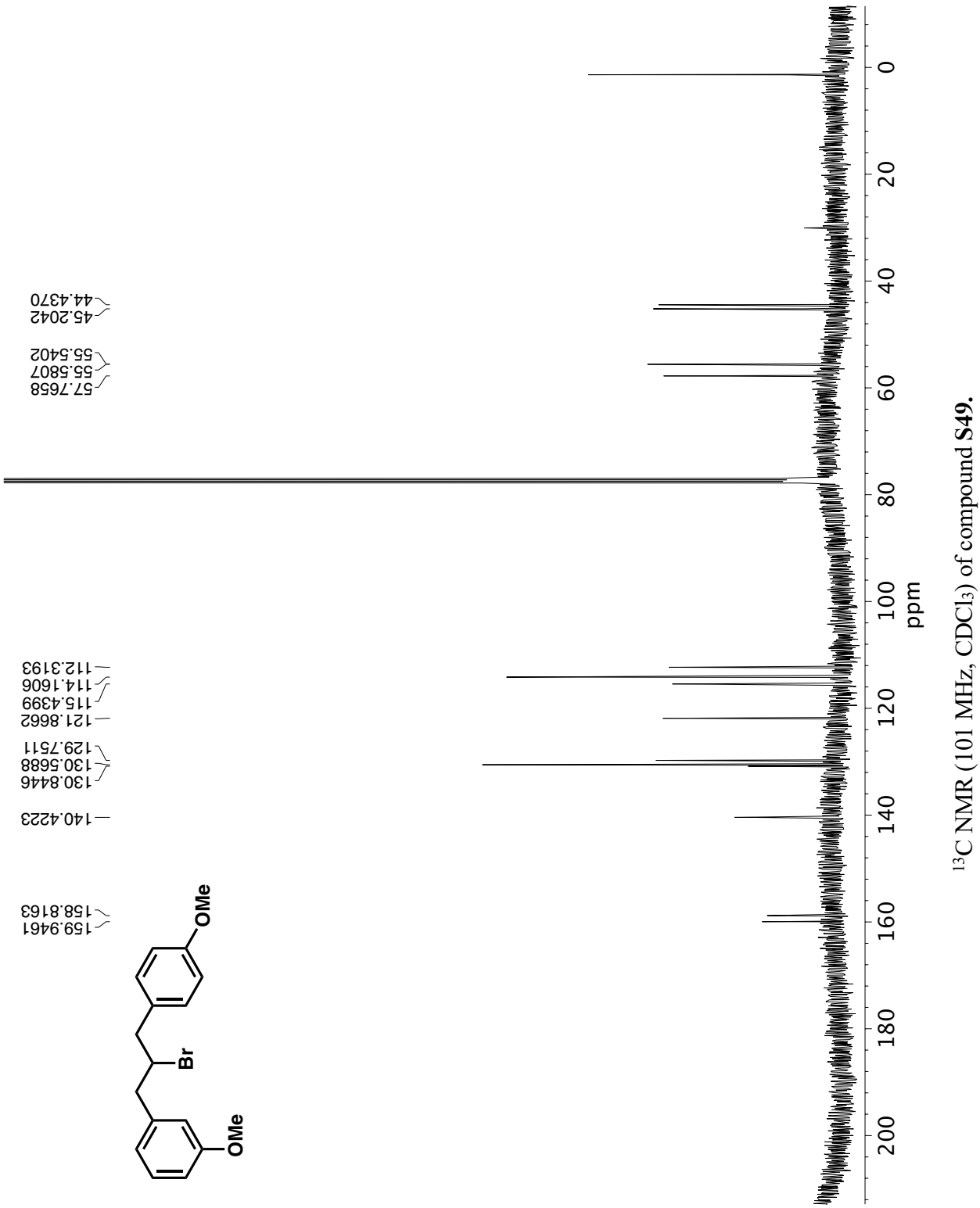
^{1}H NMR (400 MHz, $CDCl_3$) of compound **S48.**



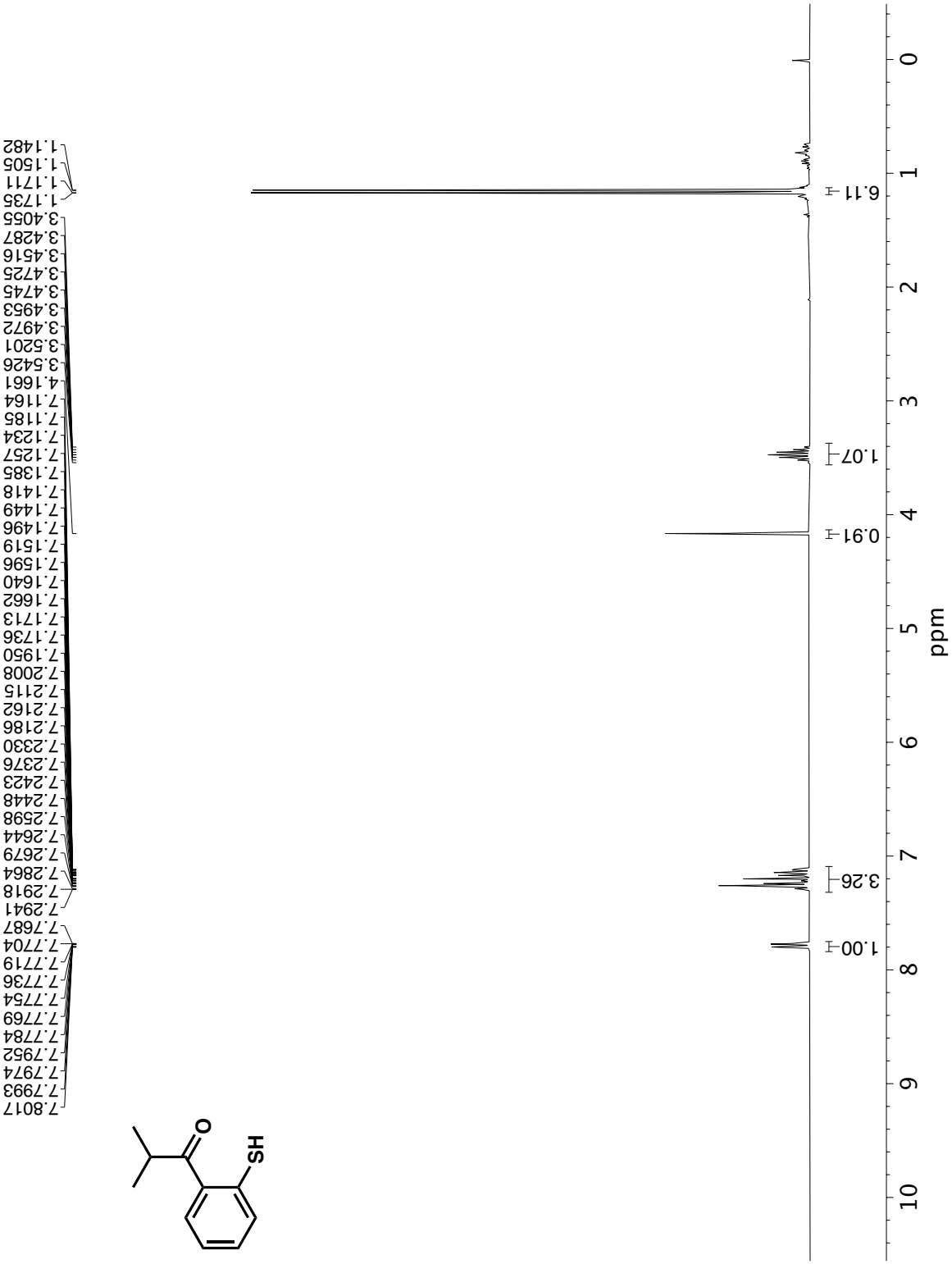
^{13}C NMR (101 MHz, $CDCl_3$) of compound **S48.**



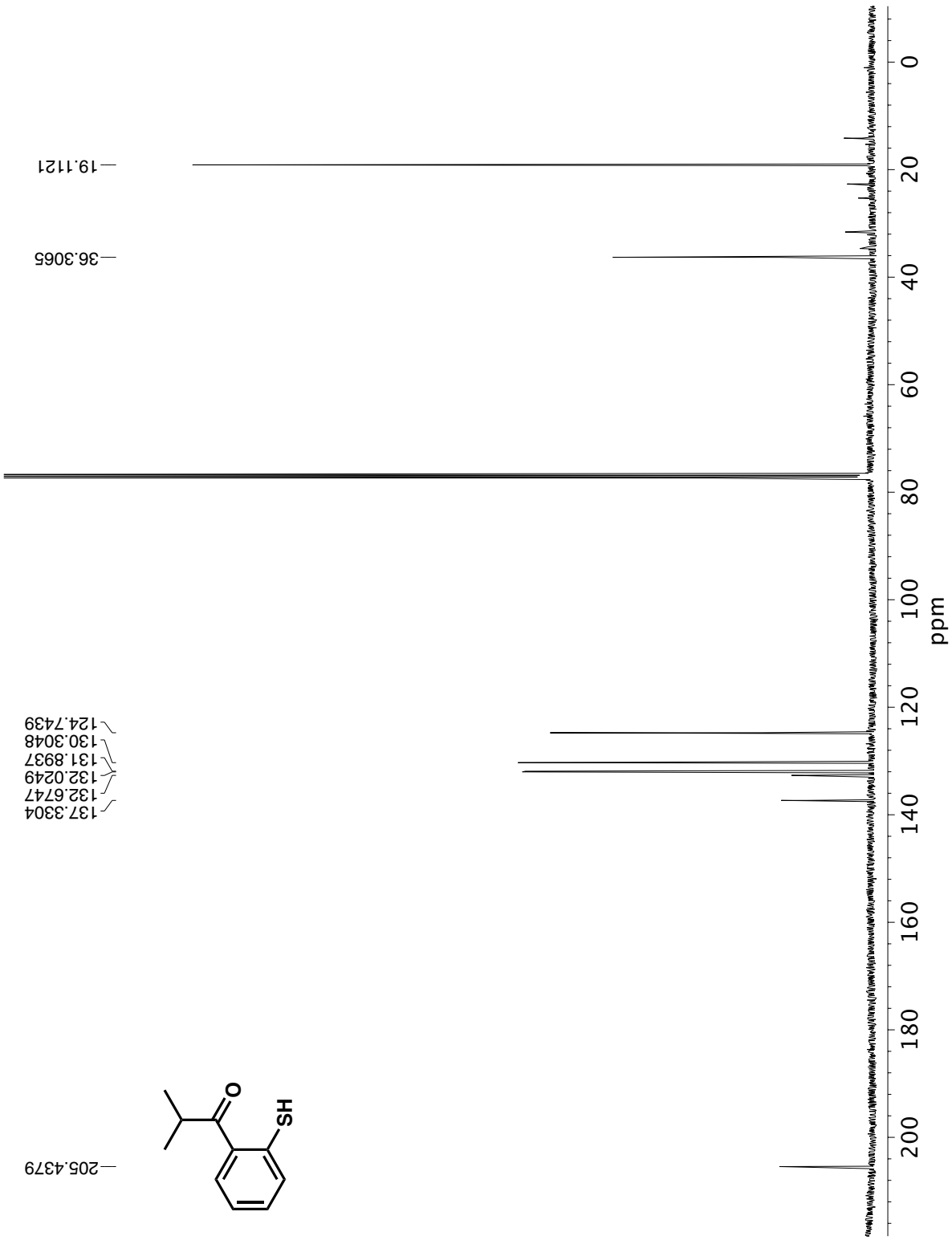
^{1}H NMR (400 MHz, $CDCl_3$) of compound **S49.**



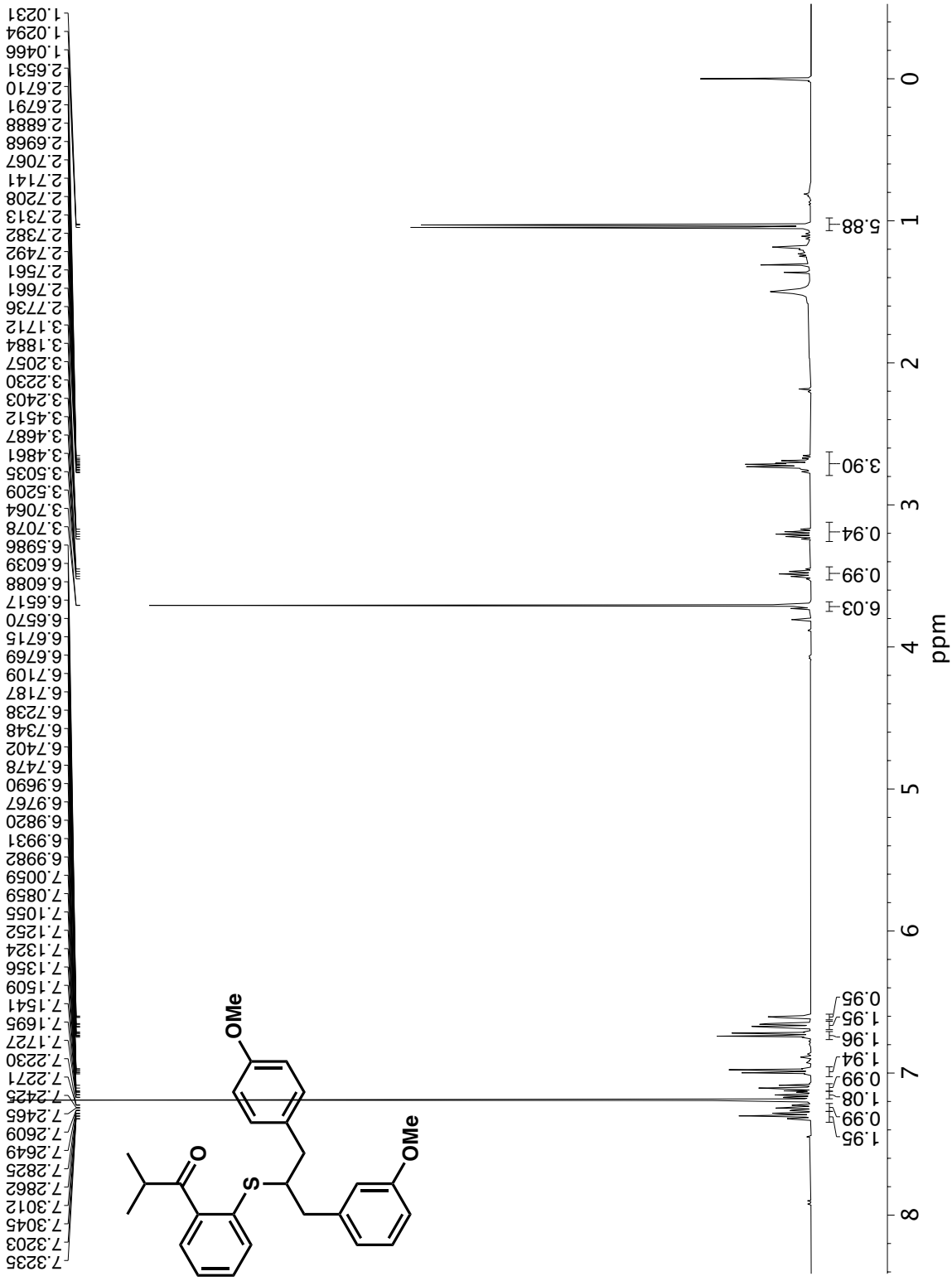
^{13}C NMR (101 MHz, $CDCl_3$) of compound **S49.**



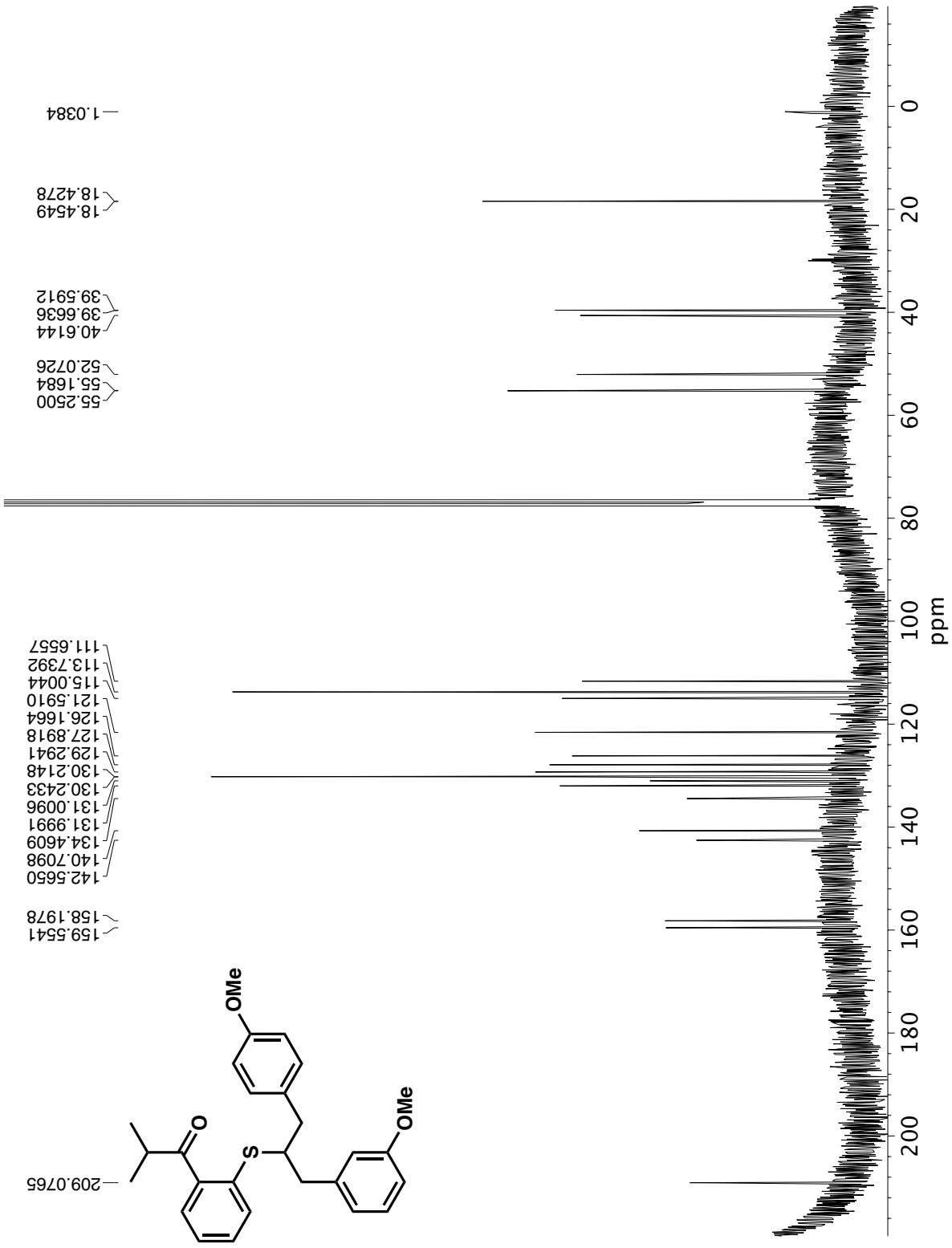
^{1}H NMR (300 MHz, $CDCl_3$) of compound **S50.**



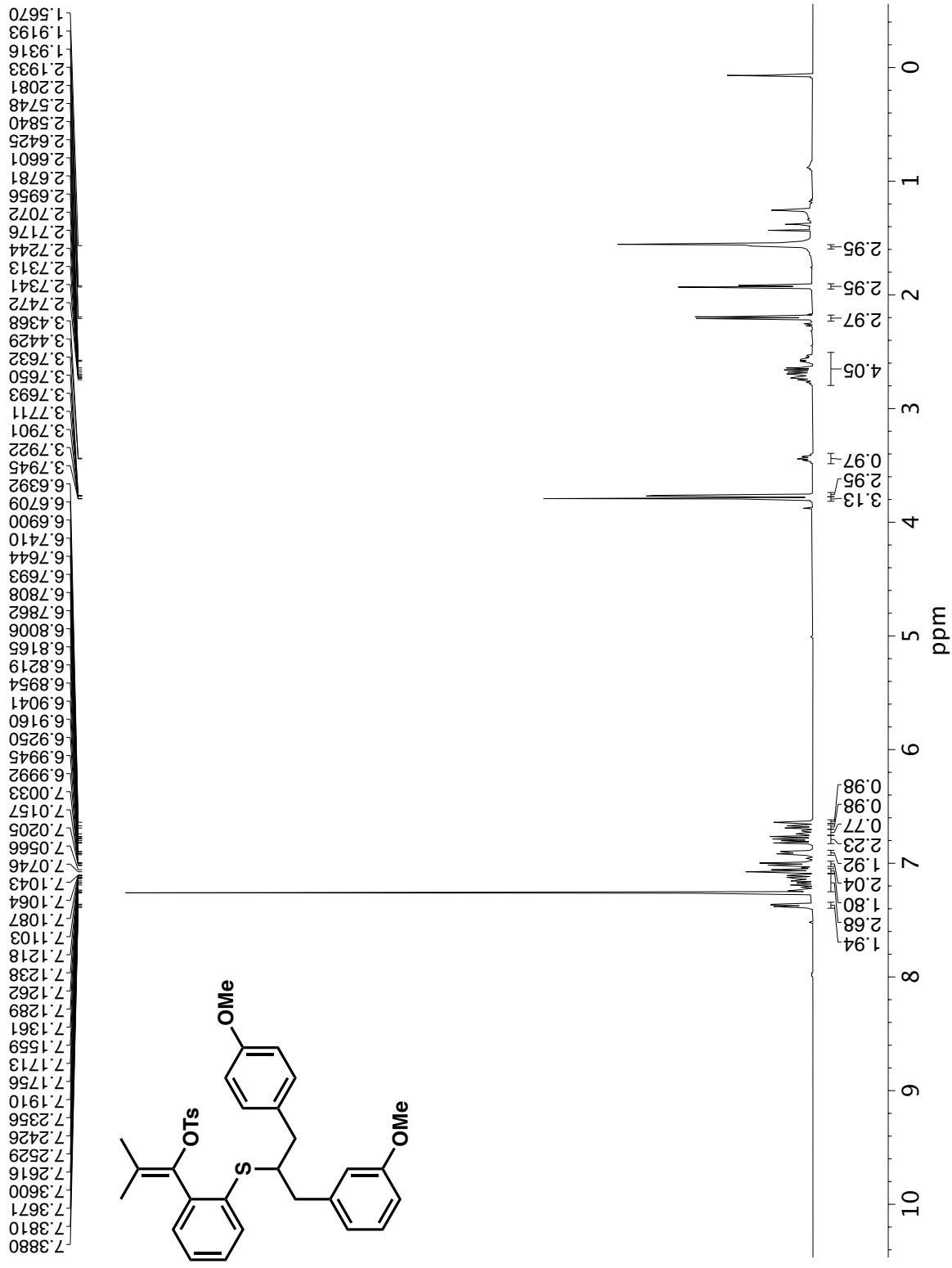
^{13}C NMR (101 MHz, $CDCl_3$) of compound **S50.**



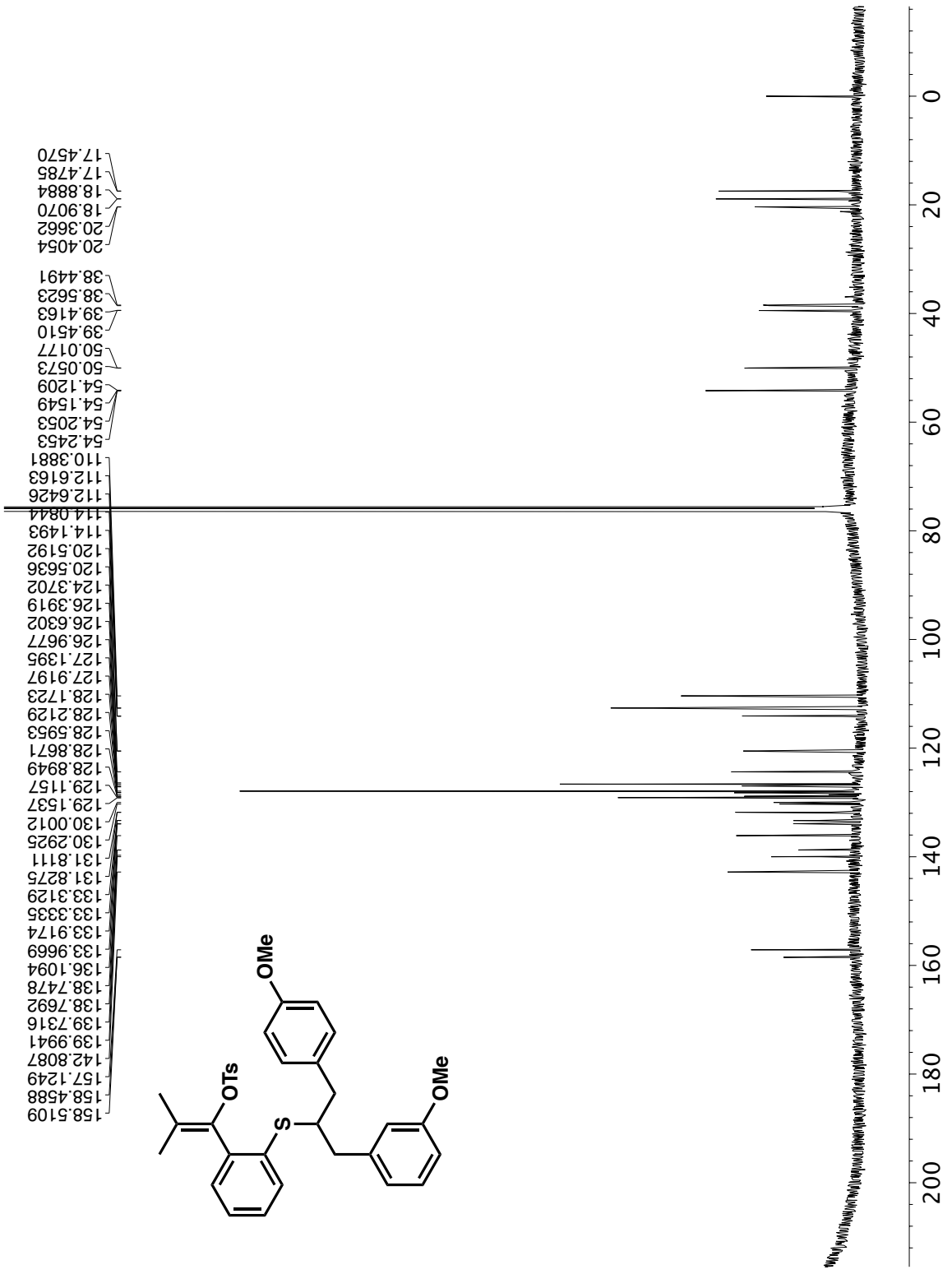
^{1}H NMR (400 MHz, $CDCl_3$) of compound **S51.**



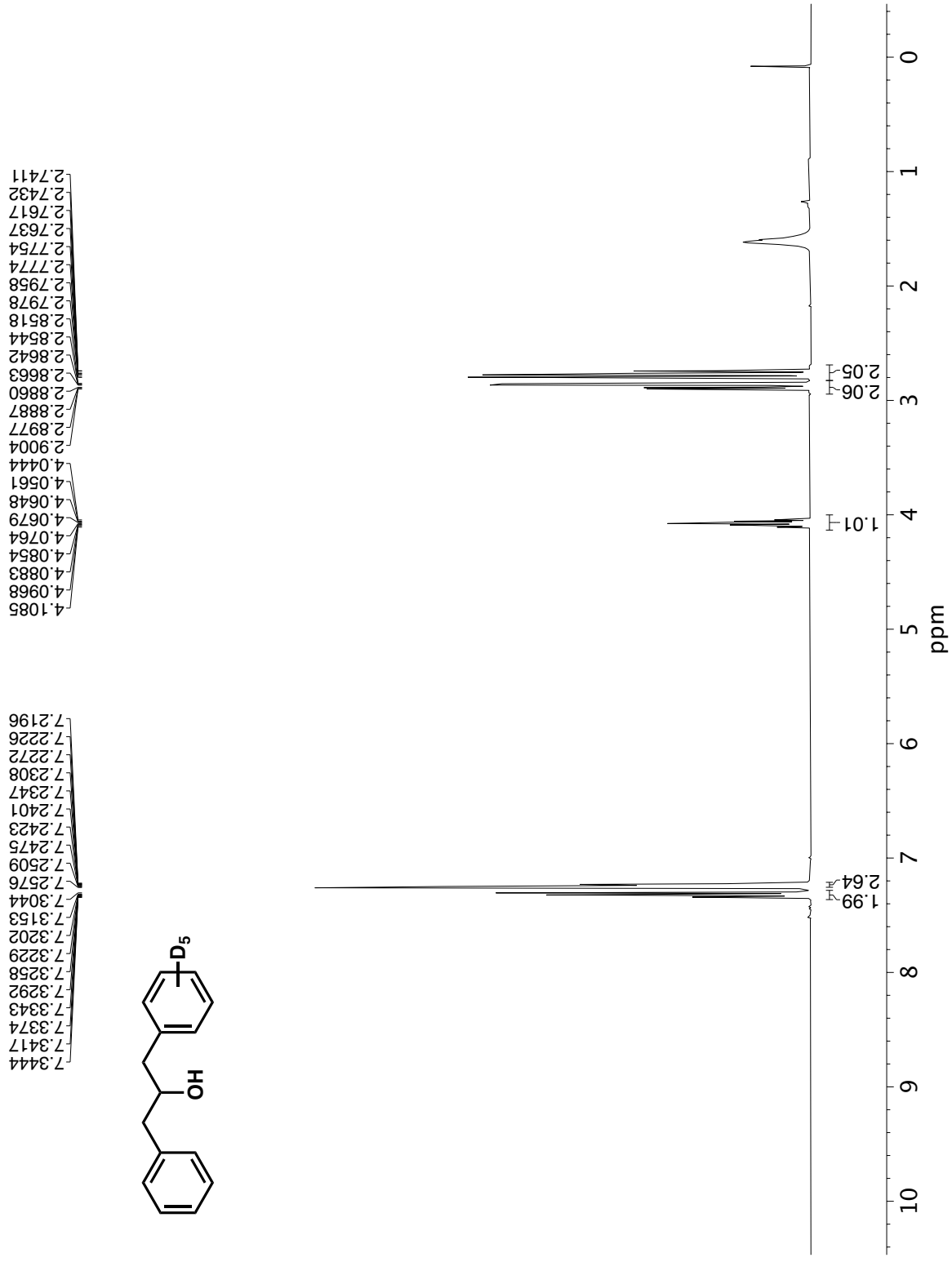
^{13}C NMR (101 MHz, $CDCl_3$) of compound **S51.**



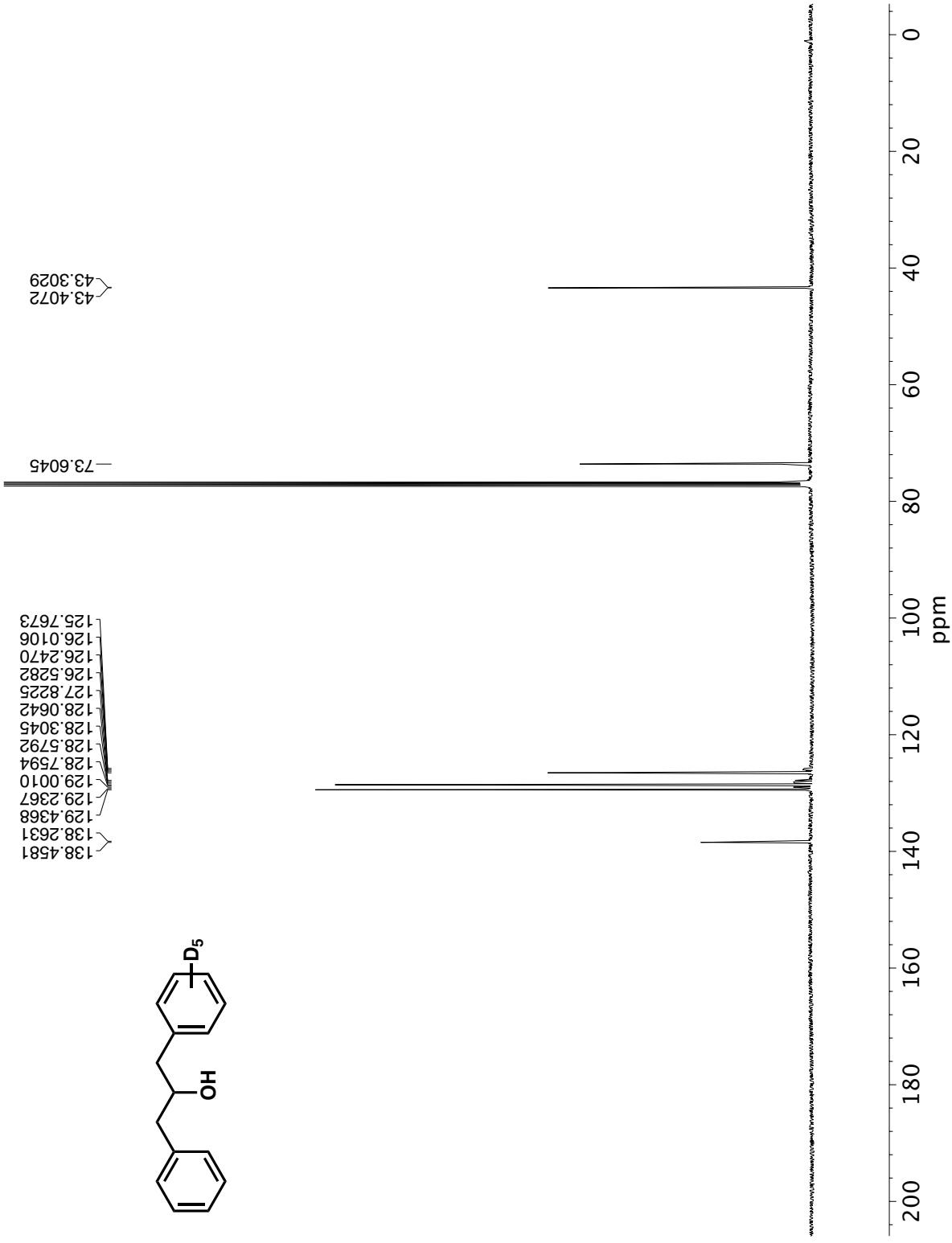
^{1}H NMR (400 MHz, $CDCl_3$) of compound **128**.



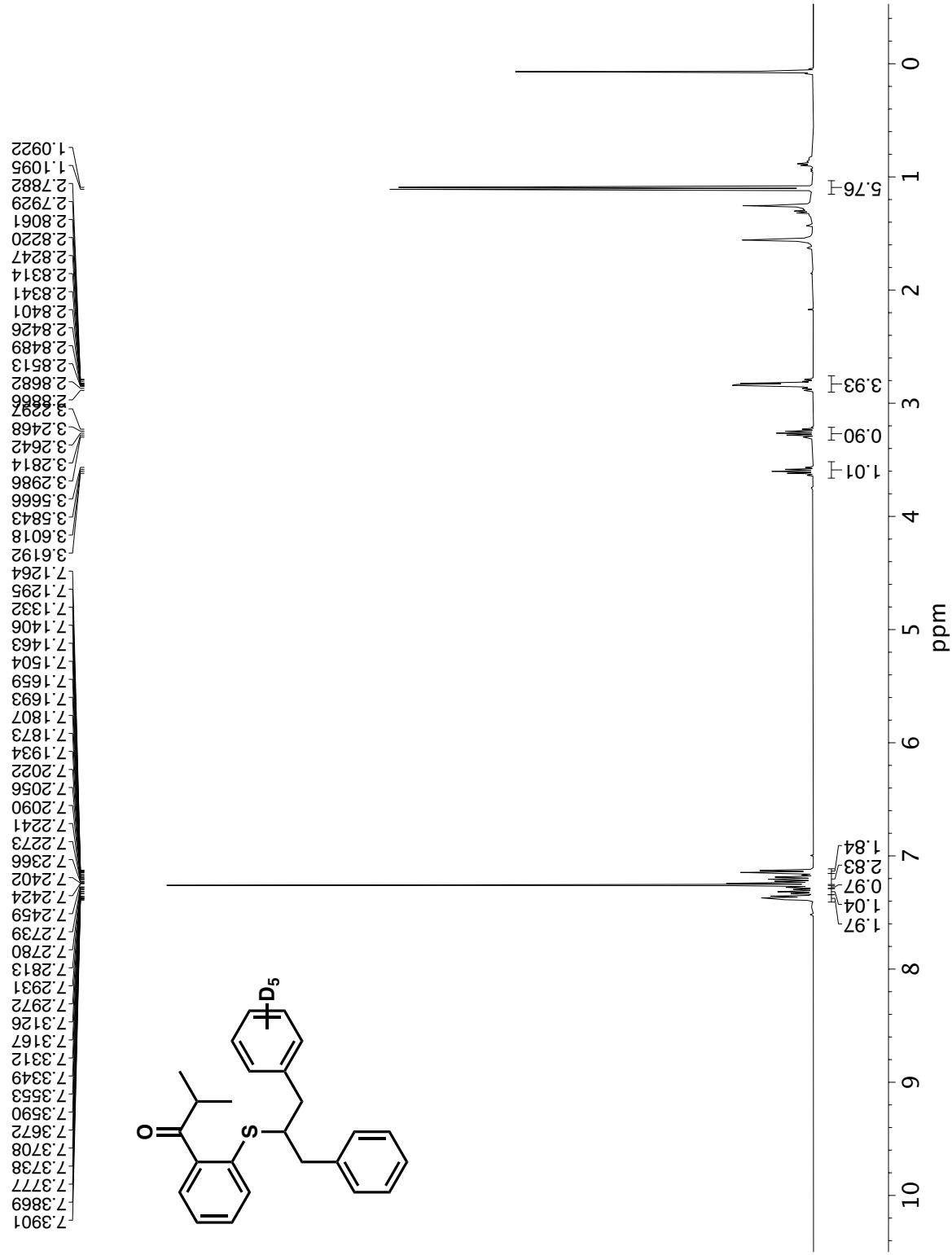
^{13}C NMR (101 MHz, $CDCl_3$) of compound **128**.



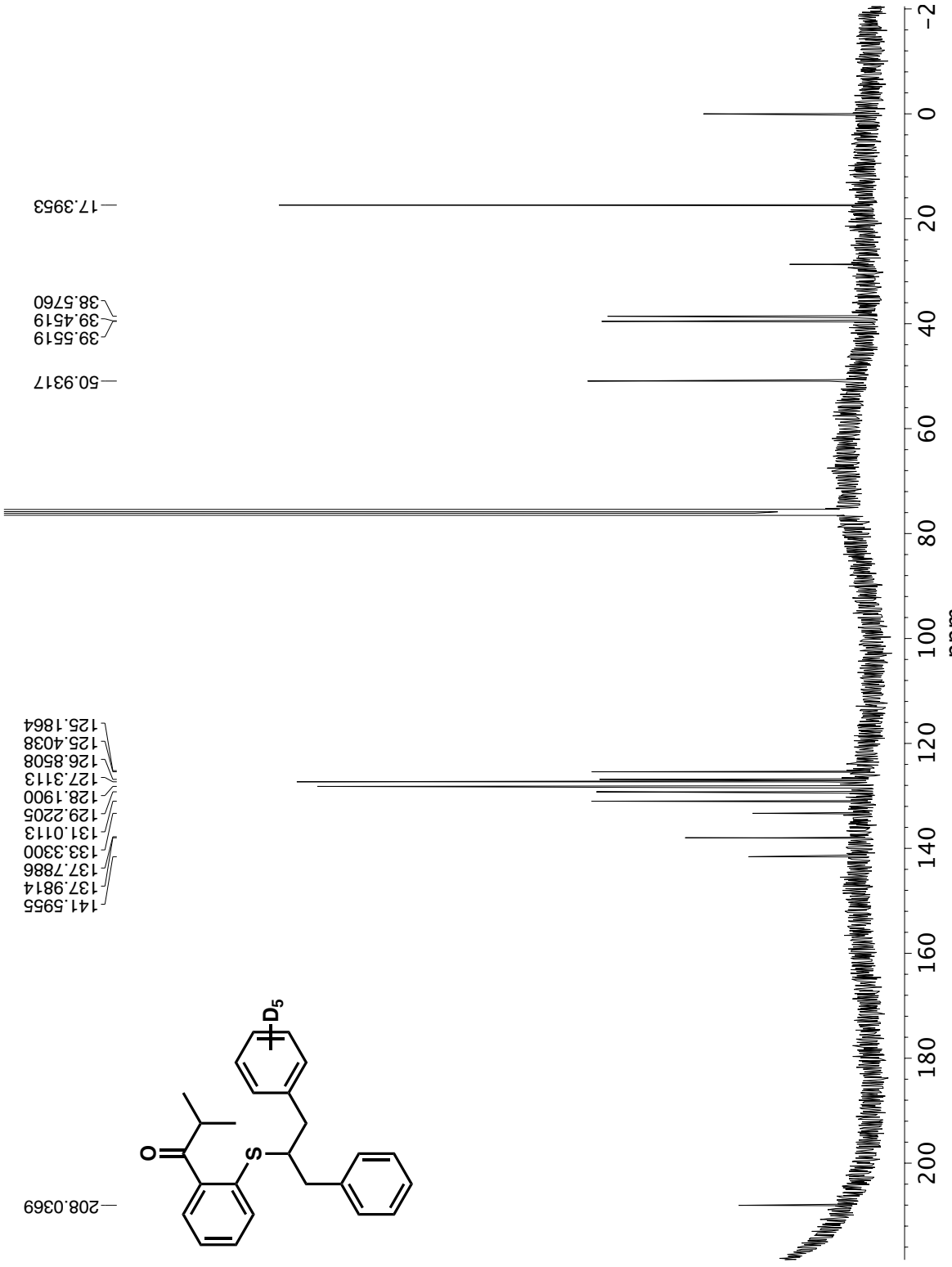
^{1}H NMR (400 MHz, $CDCl_3$) of compound **S53**.



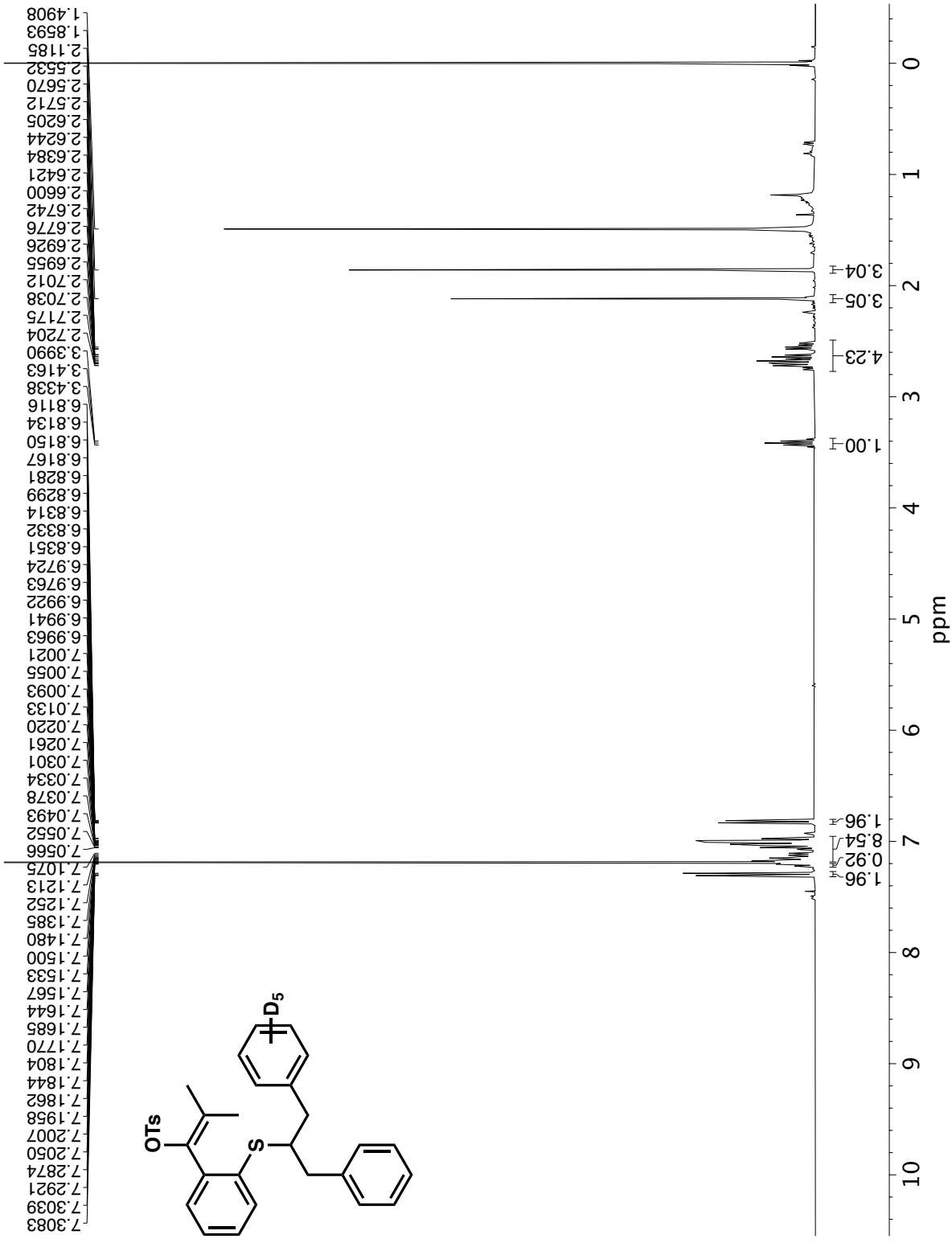
^{13}C NMR (101 MHz, $CDCl_3$) of compound **S53**.



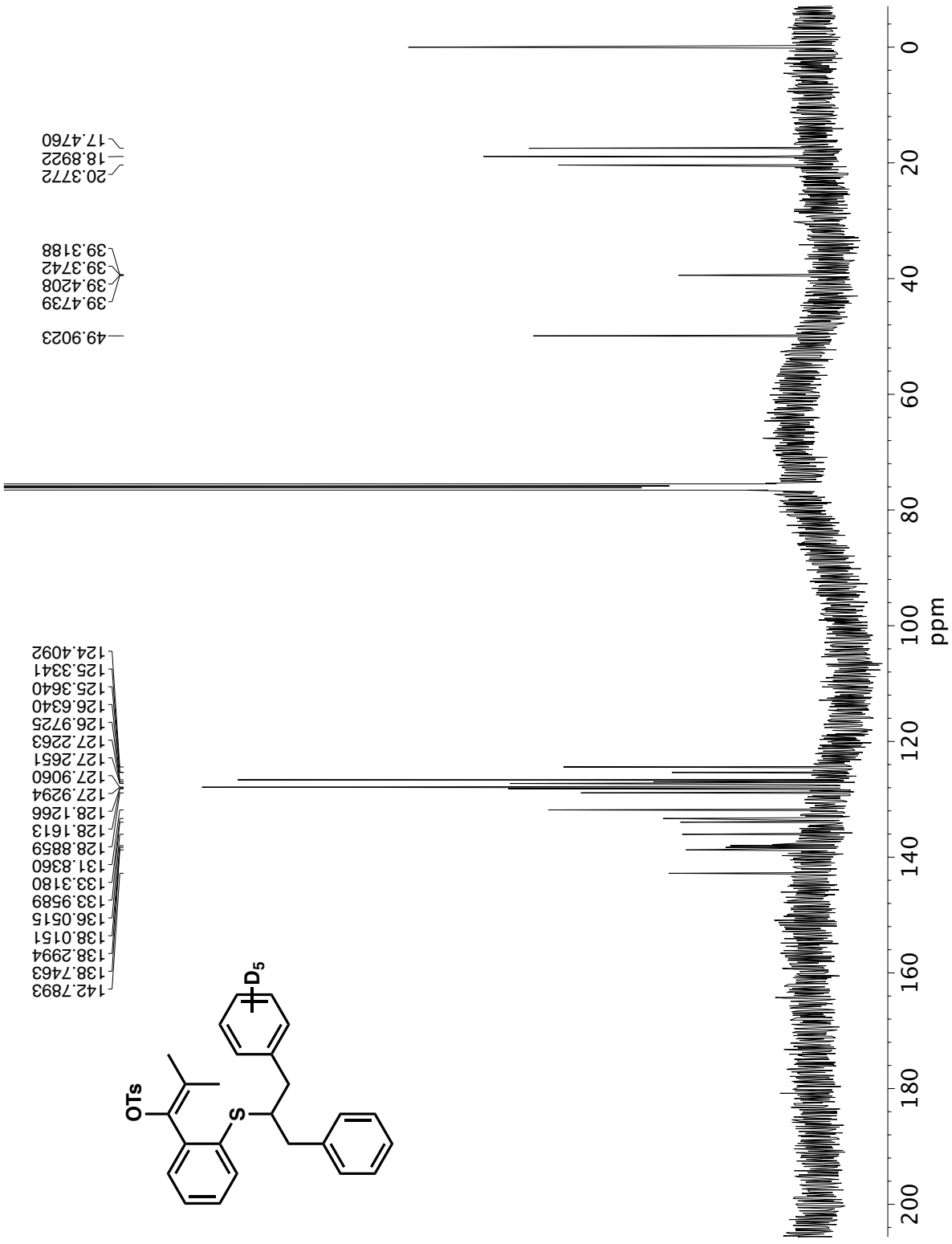
^{1}H NMR (400 MHz, $CDCl_3$) of compound **S5**.



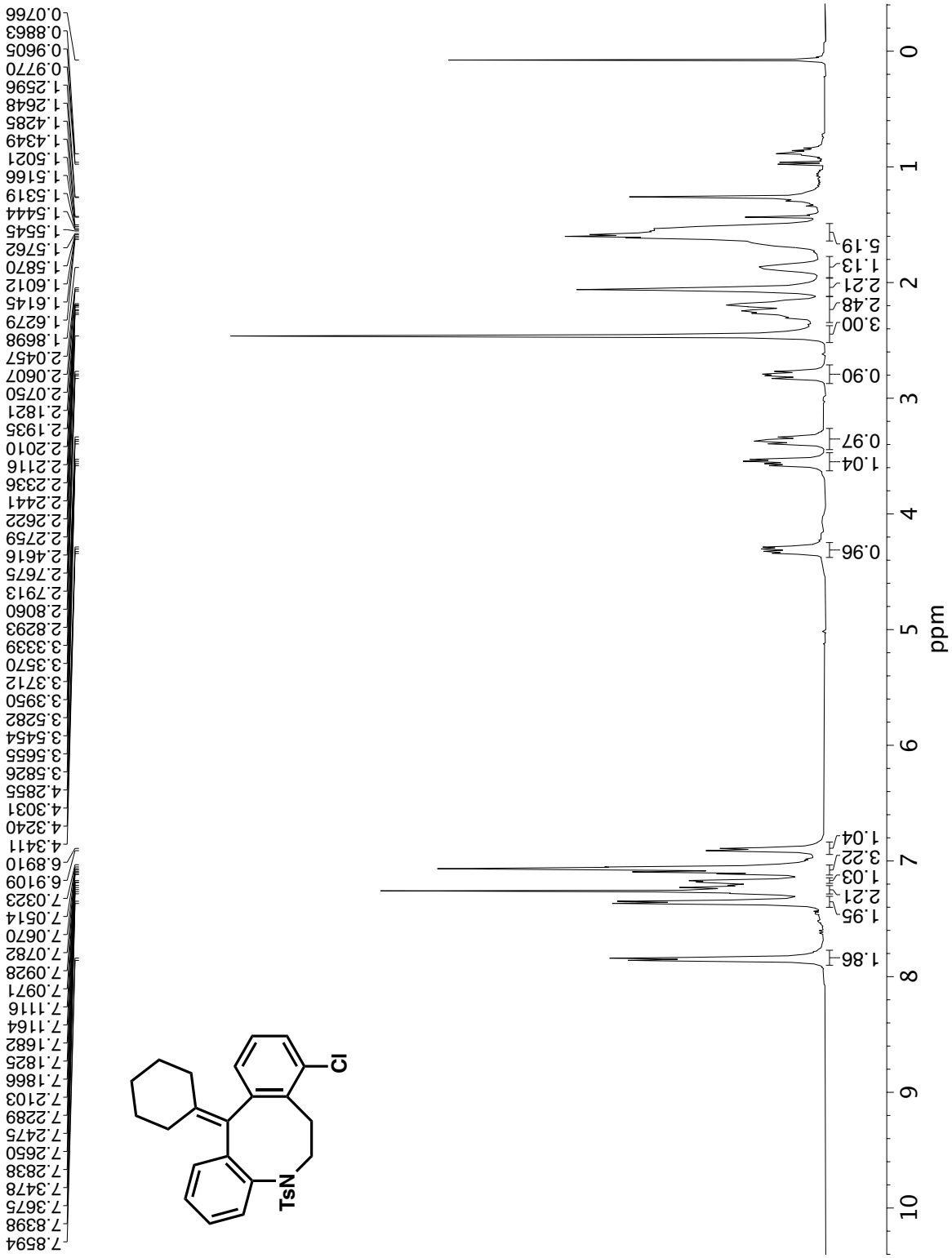
^{13}C NMR (101 MHz, $CDCl_3$) of compound **S55**.



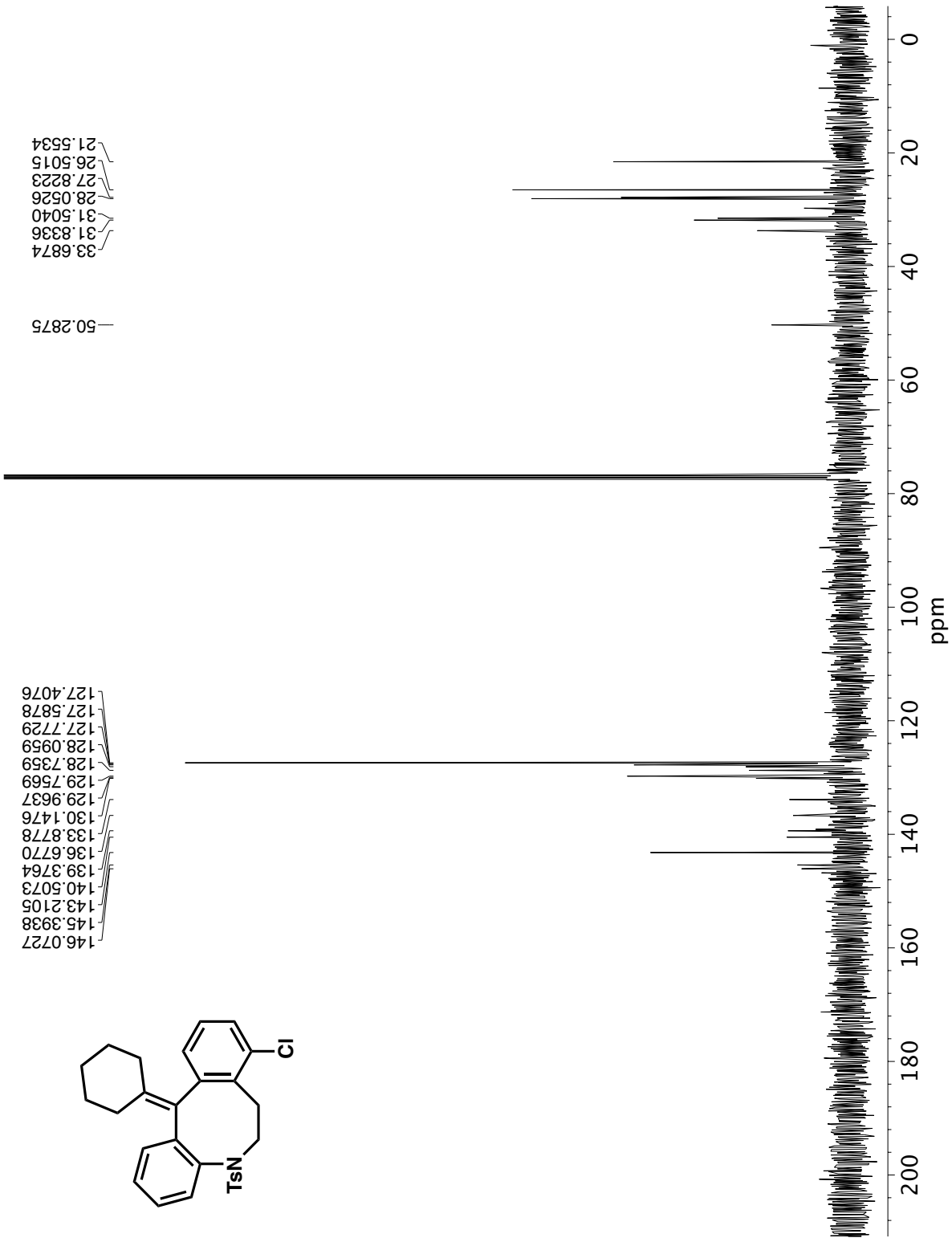
^{1}H NMR (400 MHz, $CDCl_3$) of compound **131**.



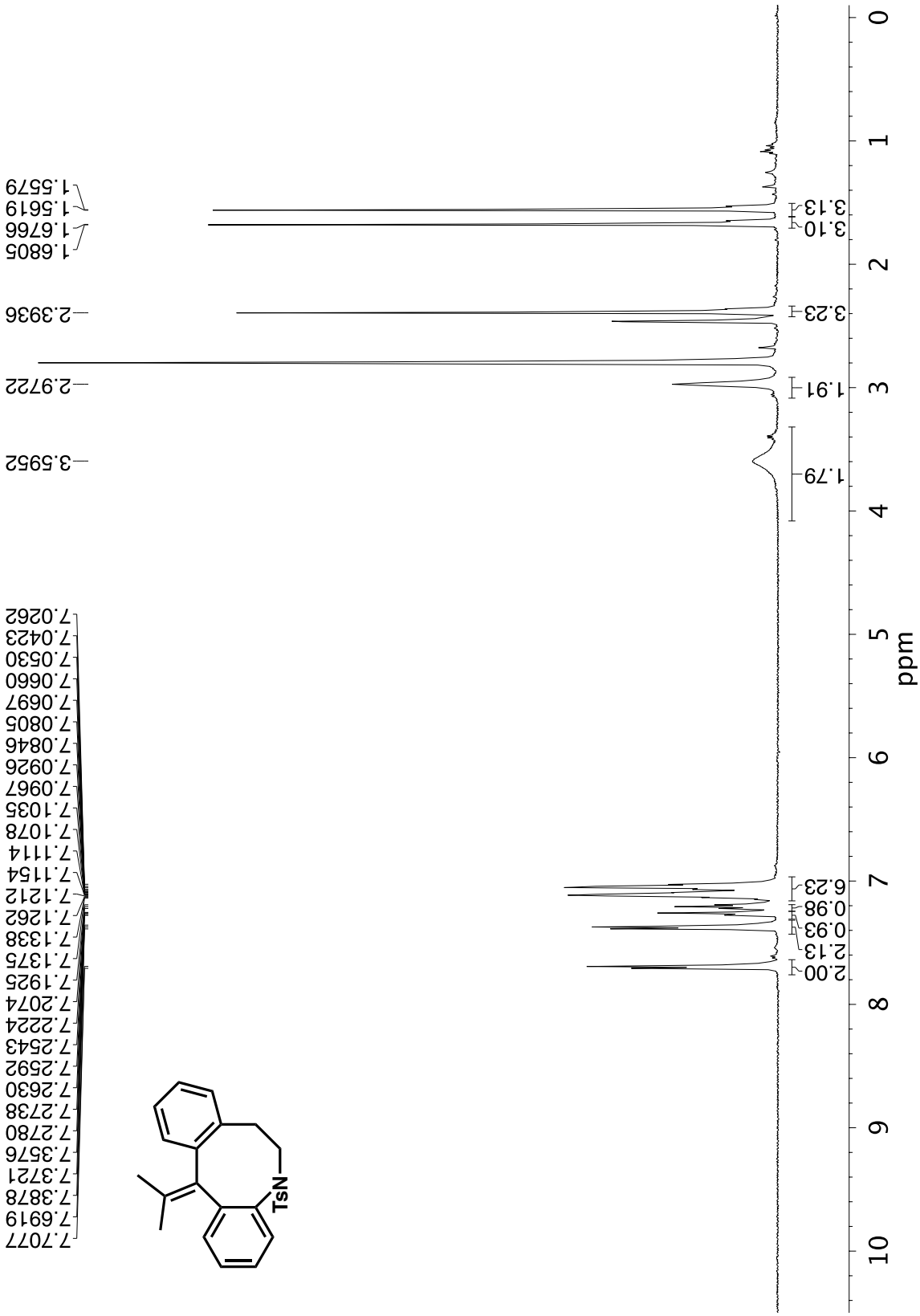
^{13}C NMR (101 MHz, $CDCl_3$) of compound **131**.



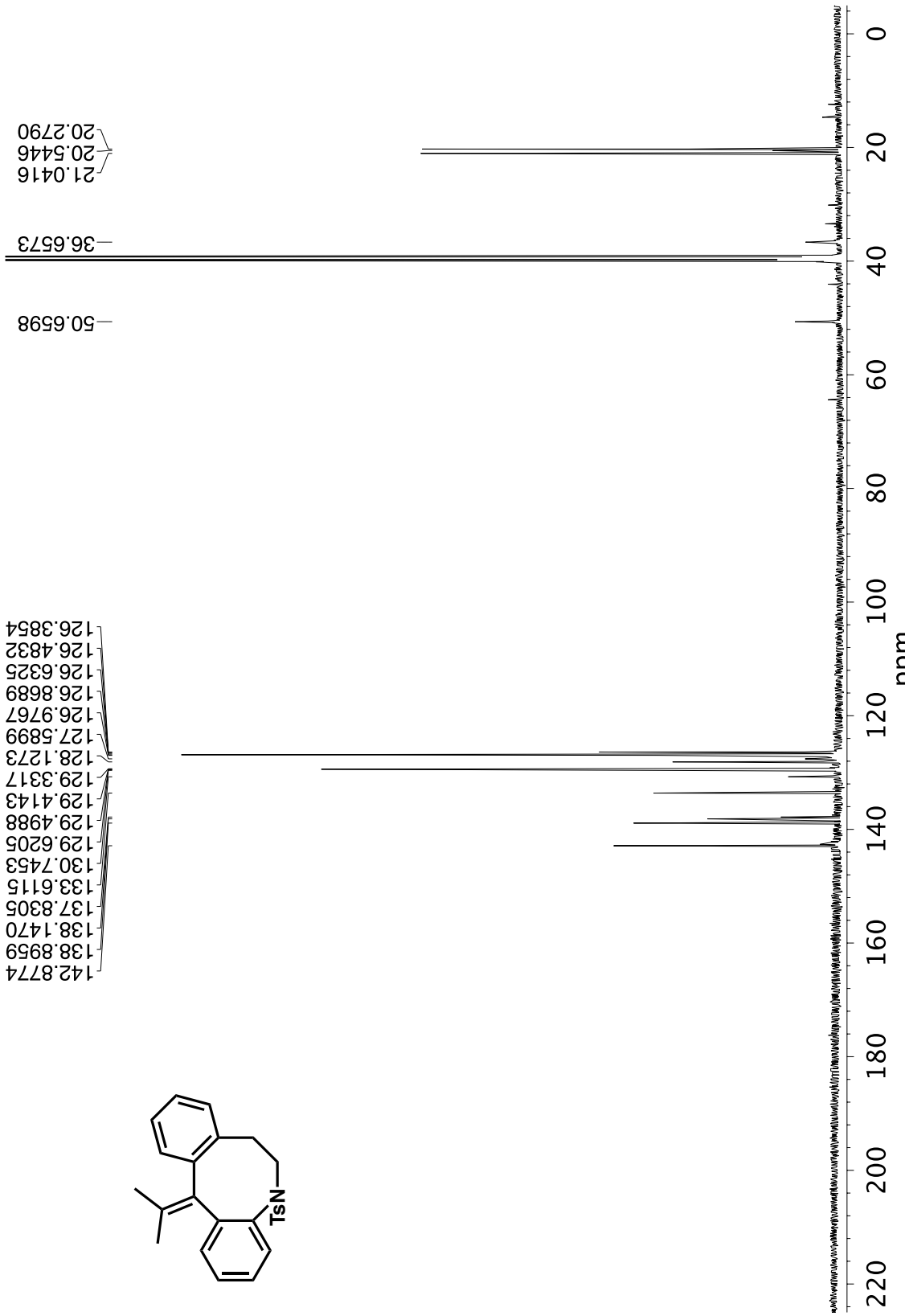
^{1}H NMR (400 MHz, $CDCl_3$) of compound **103**.



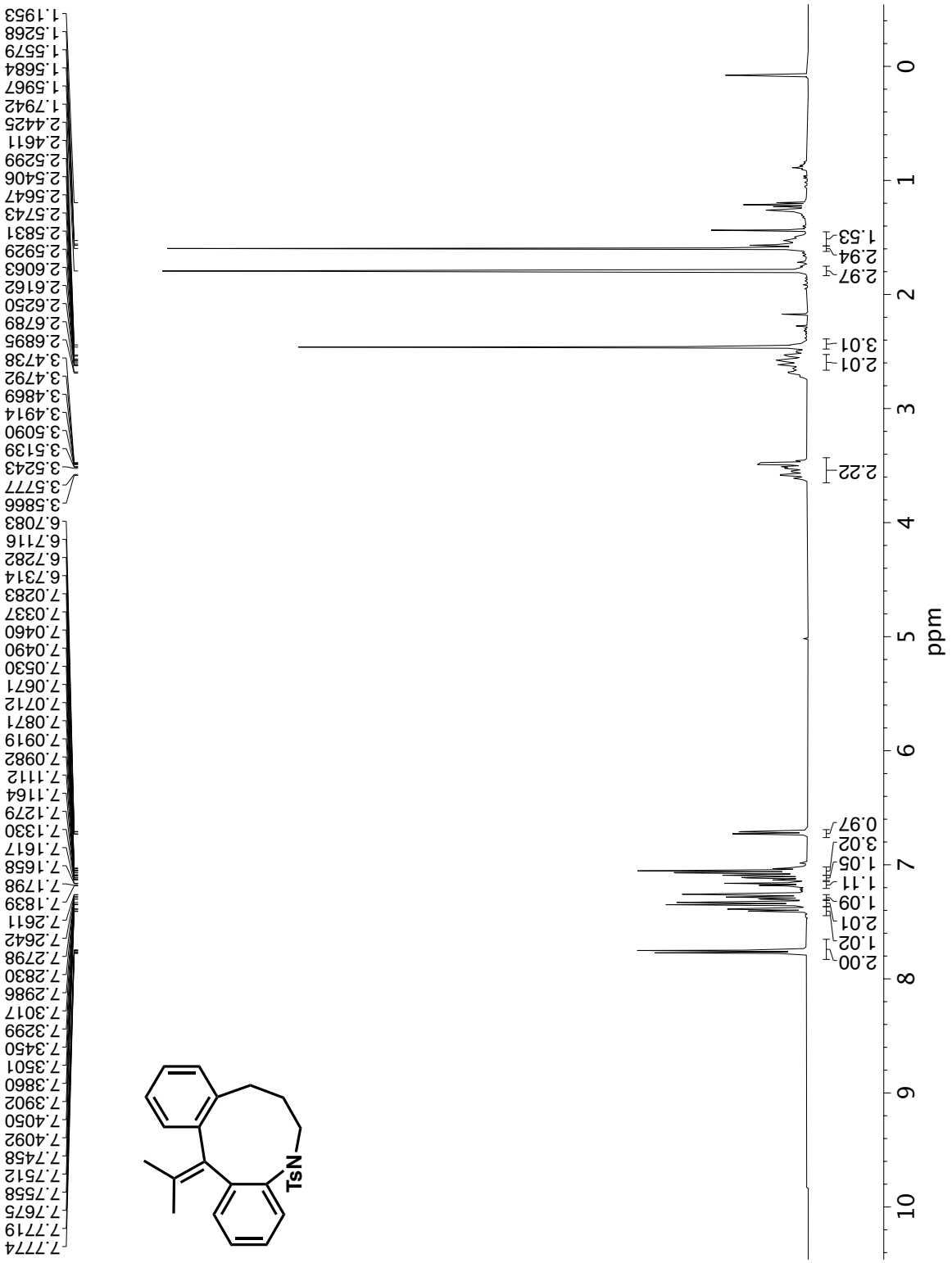
^{13}C NMR (101 MHz, $CDCl_3$) of compound **103**.



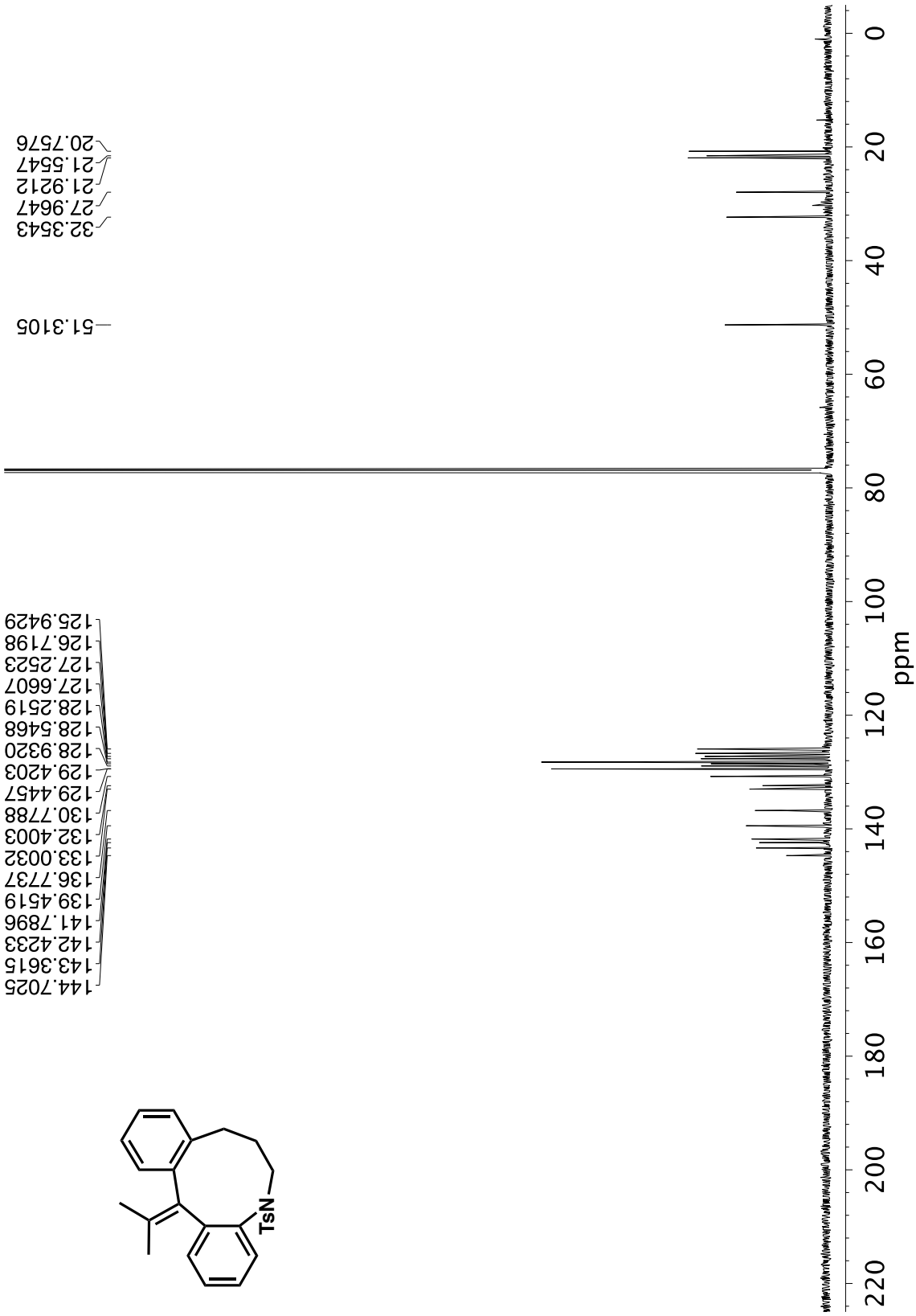
^{1}H NMR (500 MHz, DMSO-d_6, 125°C) of compound **106**.



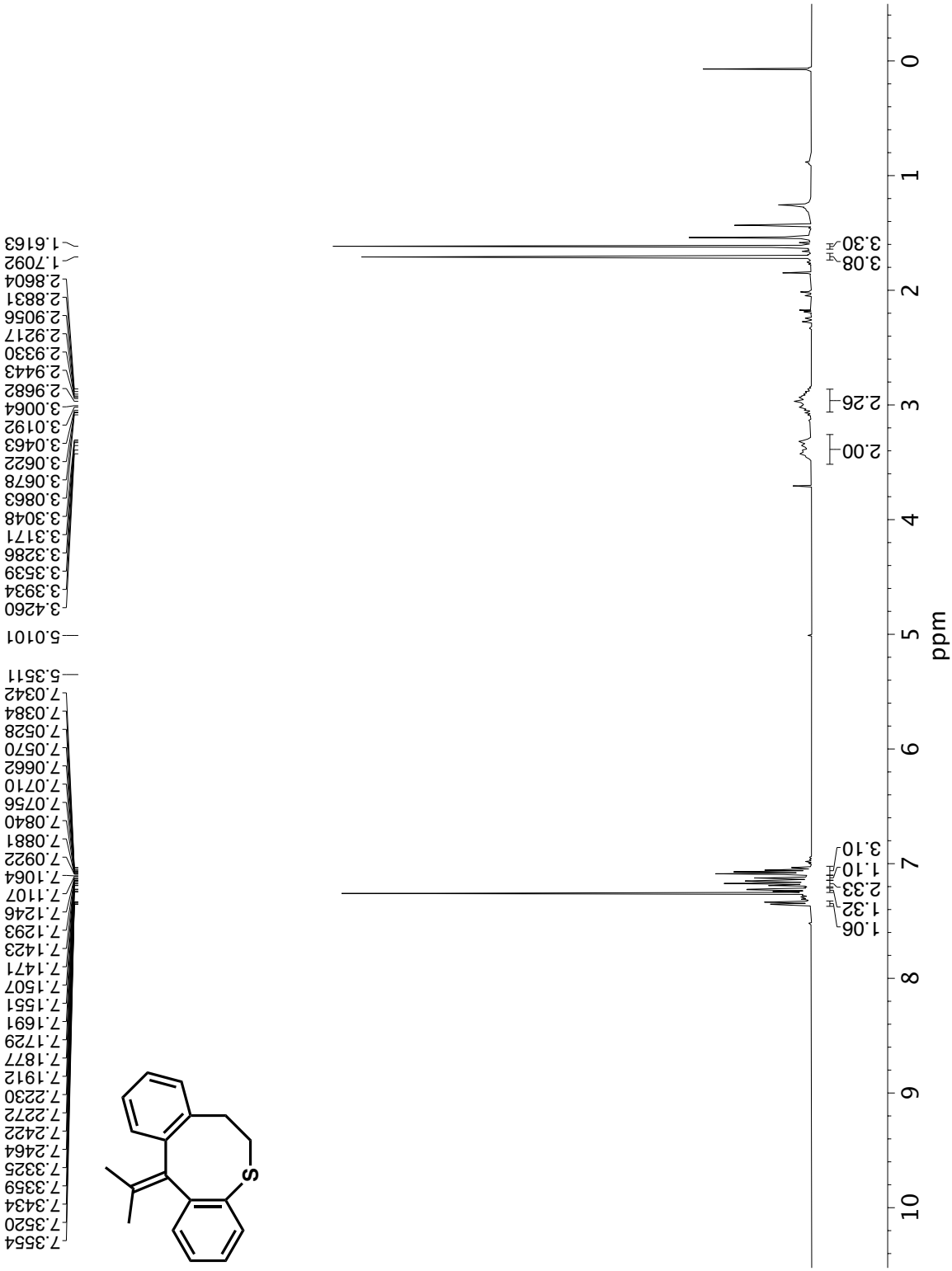
^{13}C NMR (126 MHz, DMSO-d_6, 75°C) of compound **106**.



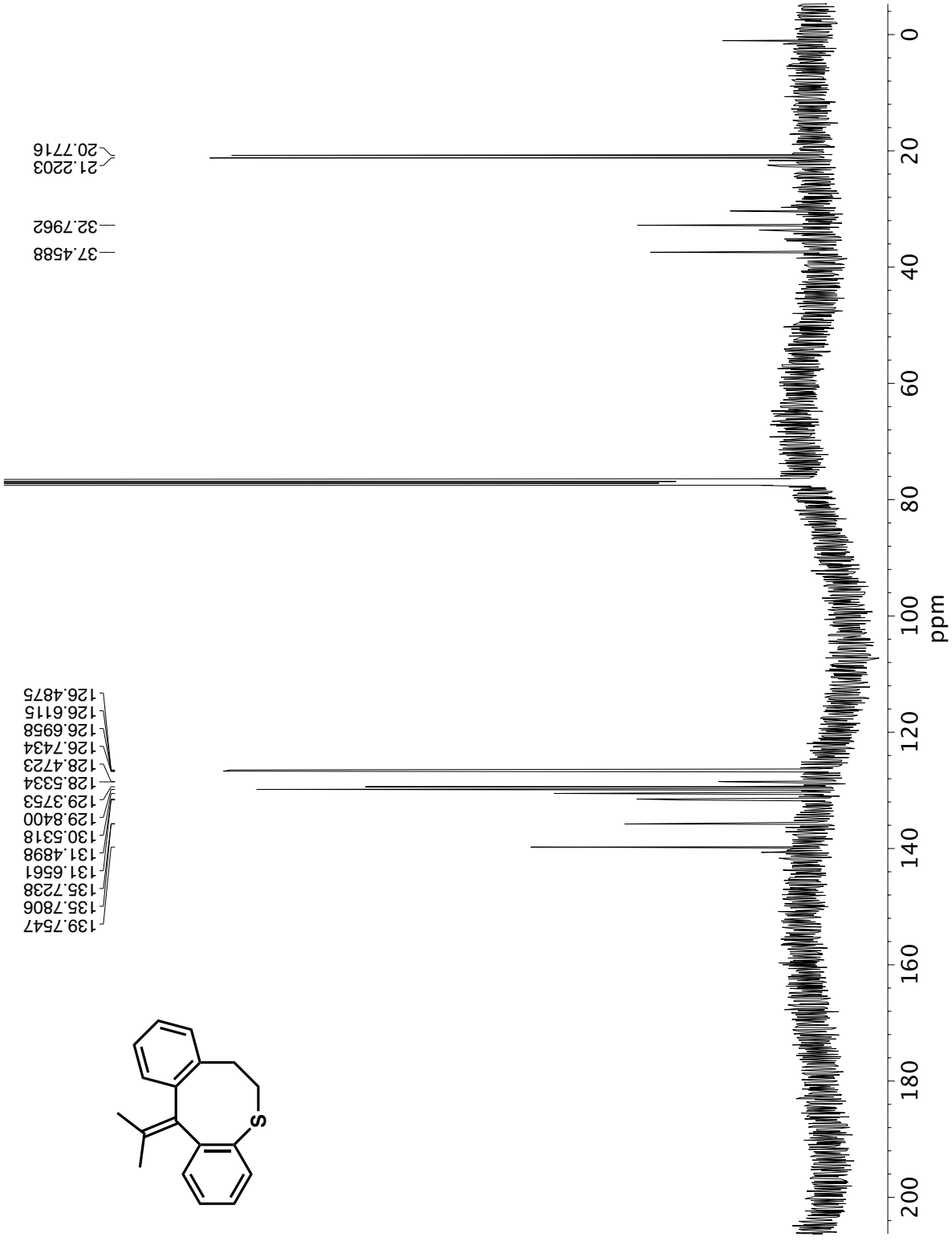
^{1}H NMR (500 MHz, $CDCl_3$) of compound **107**.



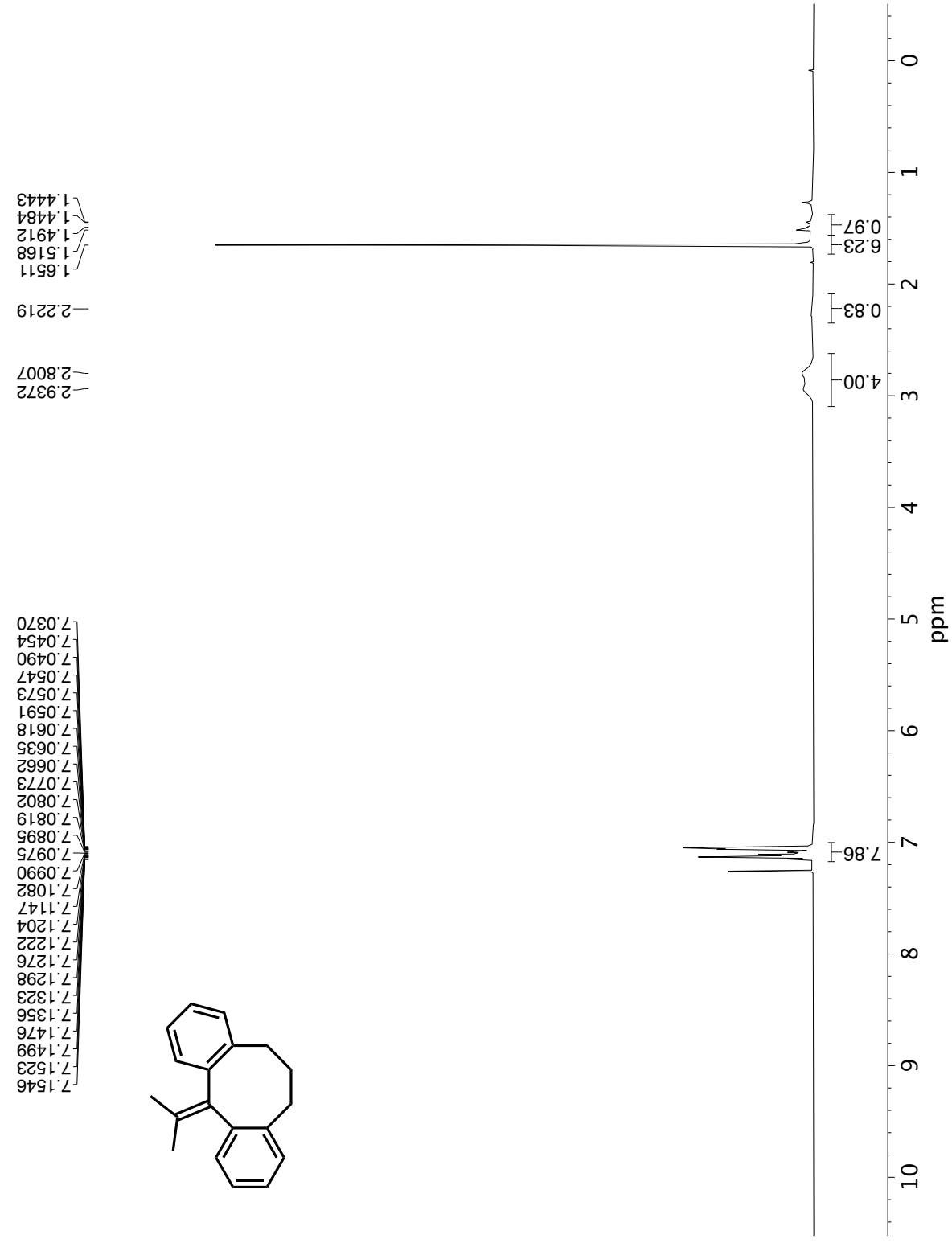
^{13}C NMR (126 MHz, $CDCl_3$) of compound **107**.



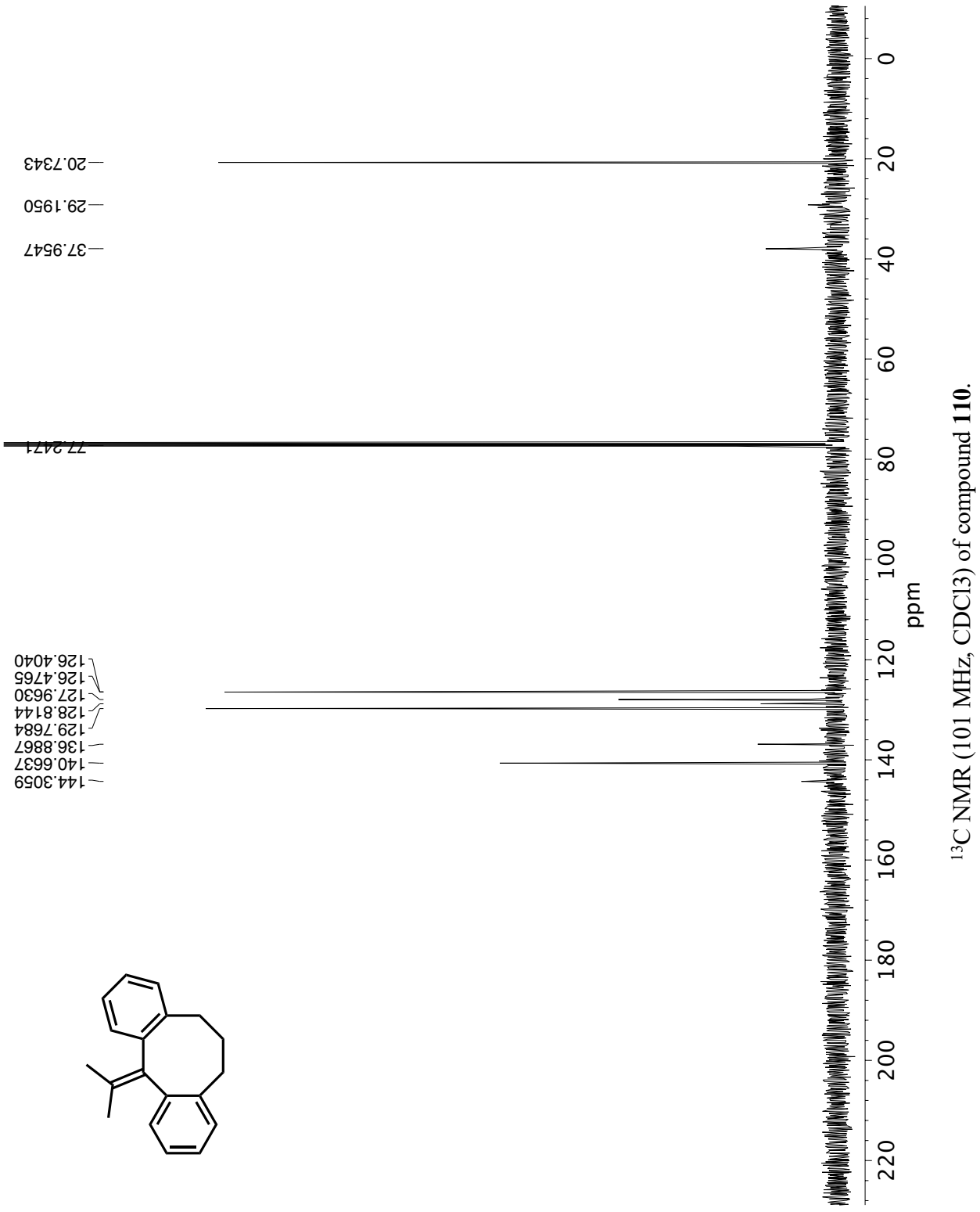
^{1}H NMR (400 MHz, $CDCl_3$) of compound **109**.



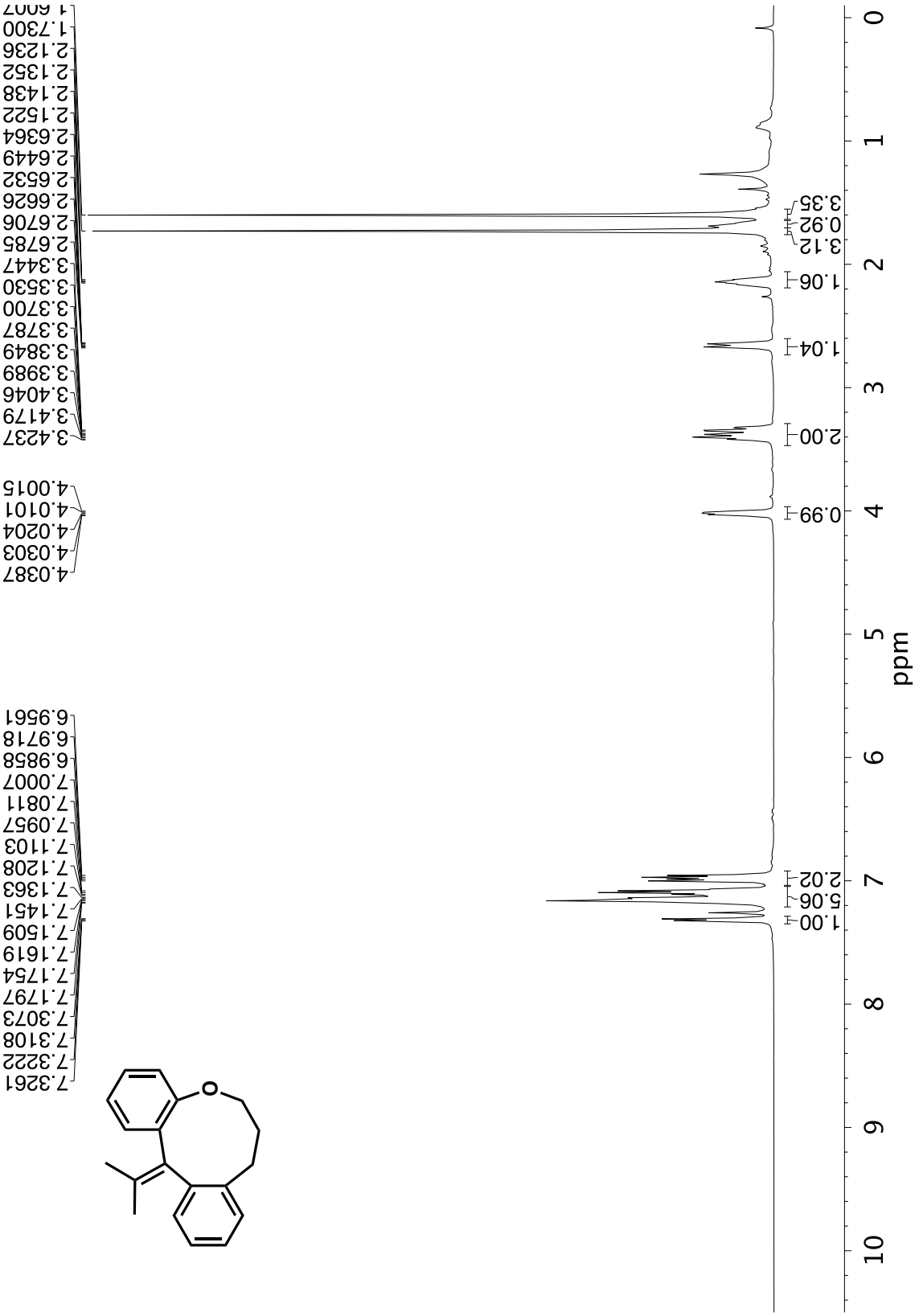
^{13}C NMR (101 MHz, $CDCl_3$) of compound **109**.



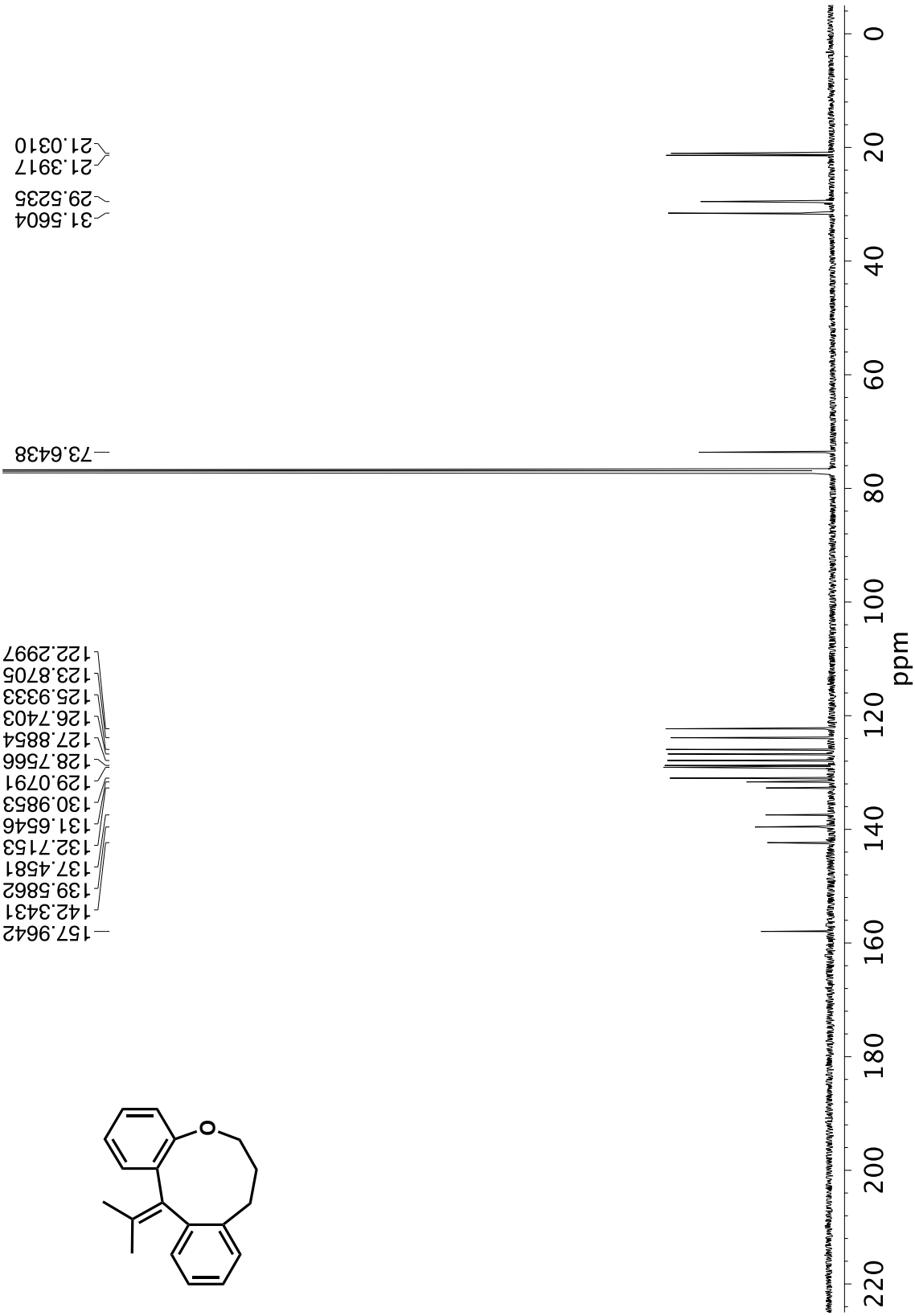
^{1}H NMR (400 MHz, $CDCl_3$) of compound **110**.



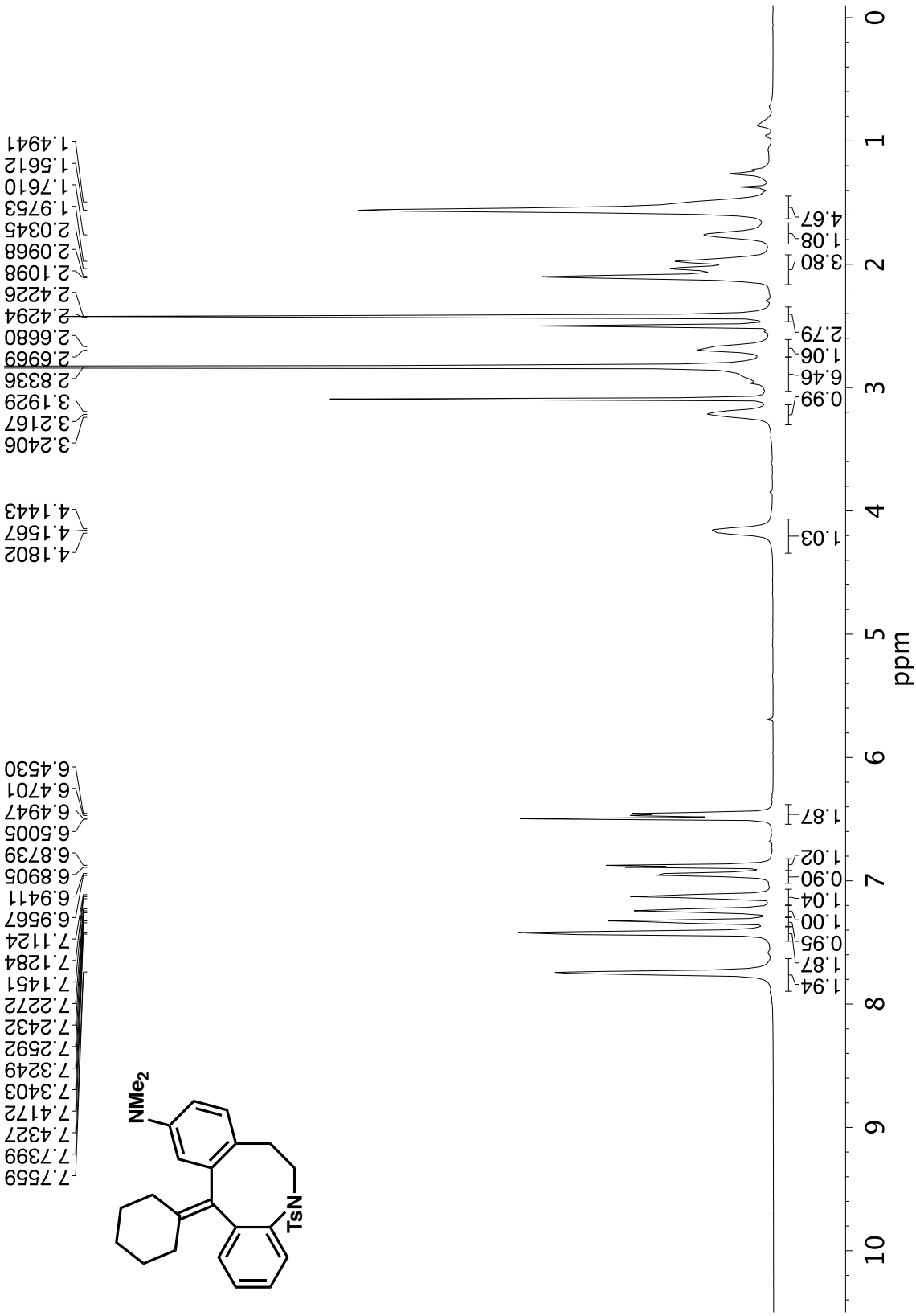
^{13}C NMR (101 MHz, CDCl3) of compound **110**.



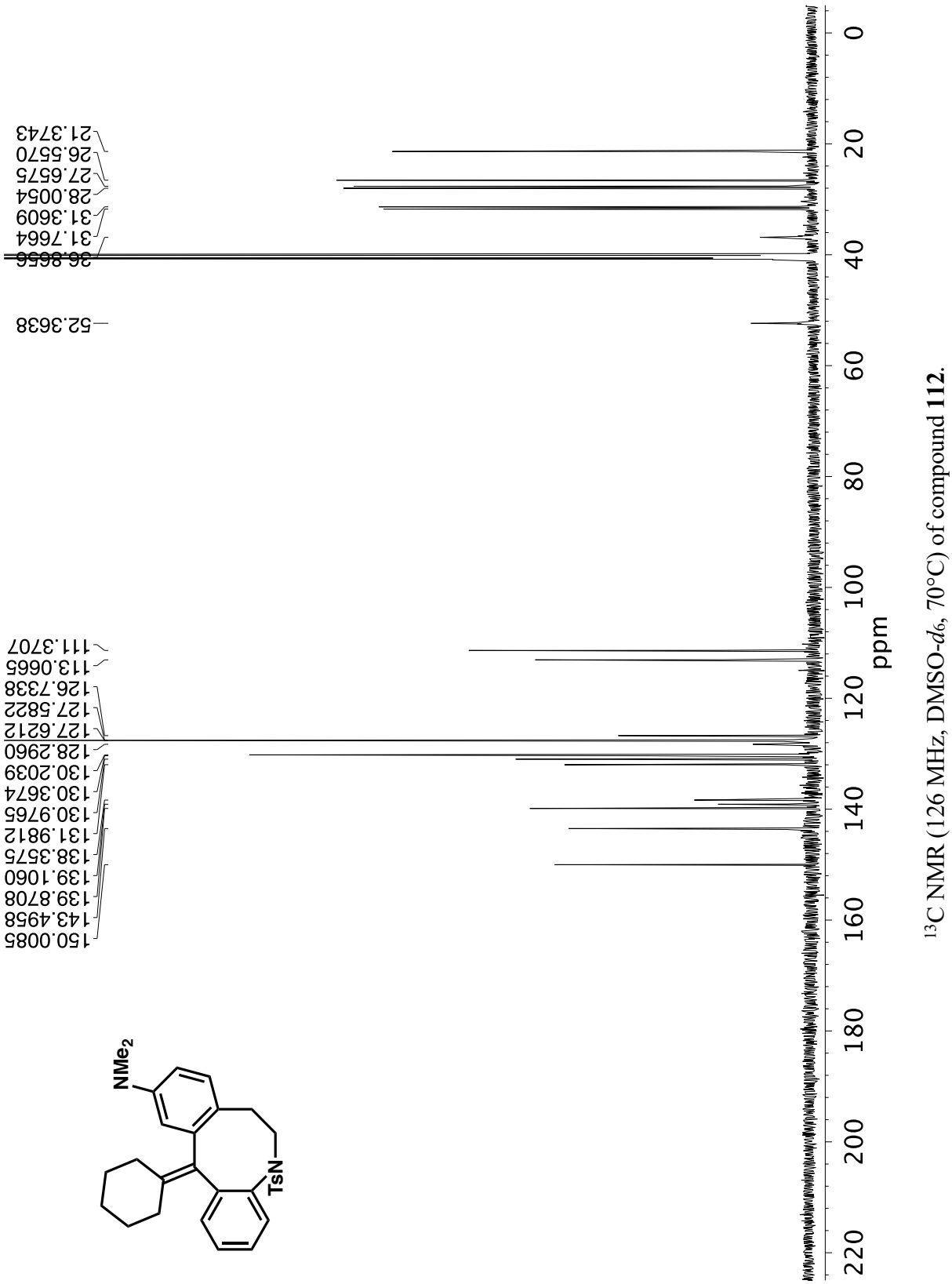
^{1}H NMR (500 MHz, $CDCl_3$) of compound **111.**



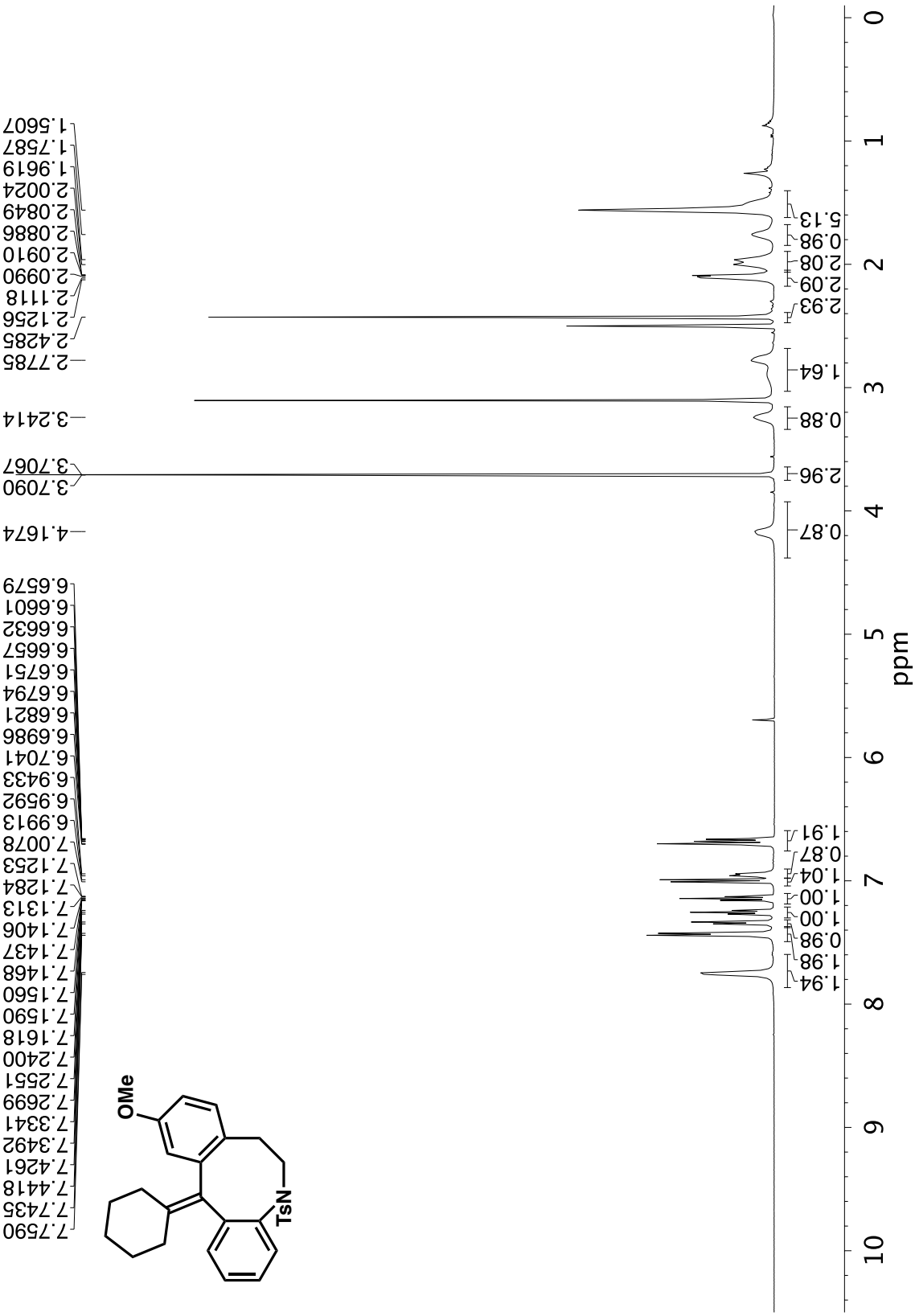
^{13}C NMR (126 MHz, $CDCl_3$) of compound **111.**



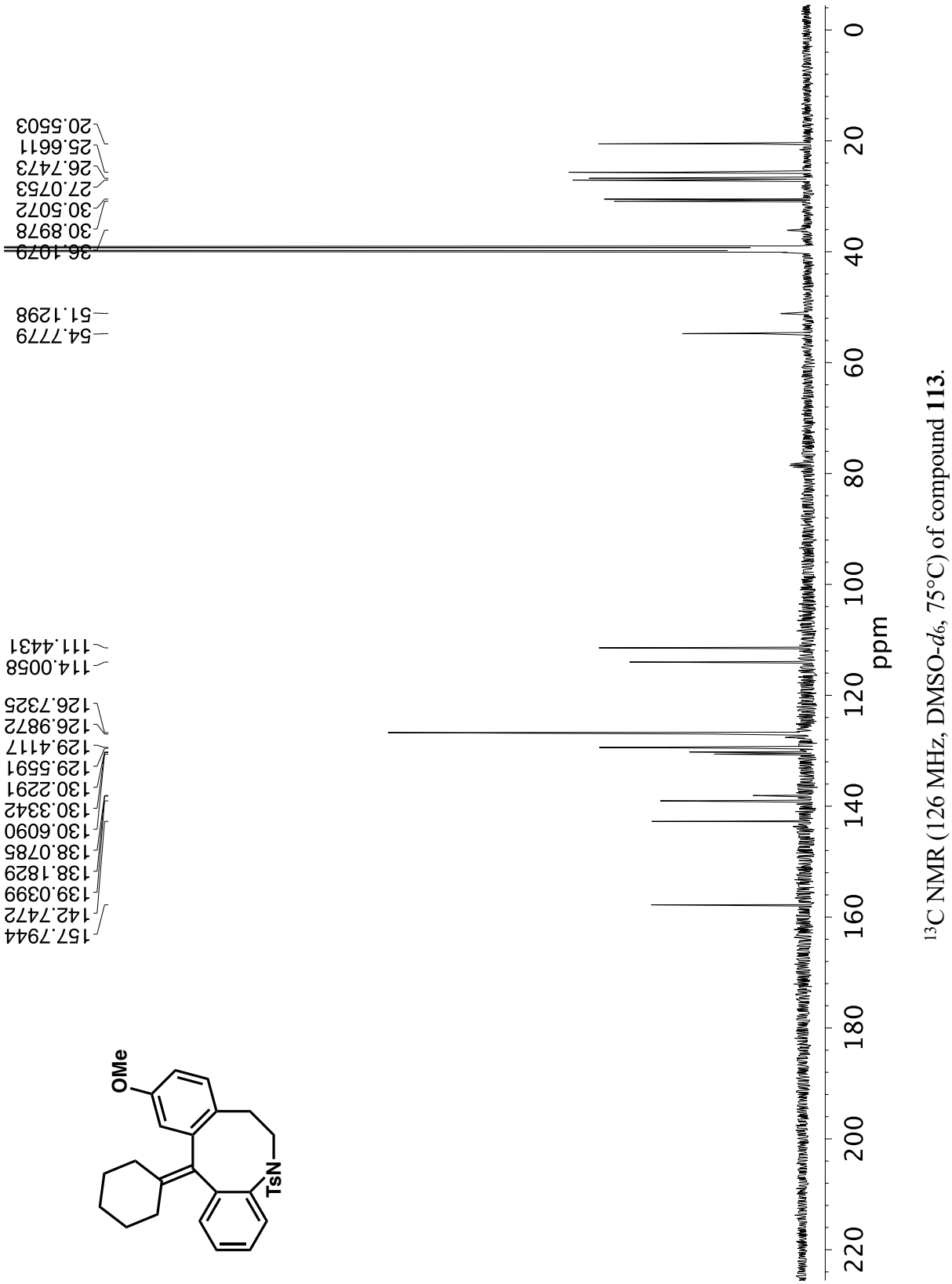
^{1}H NMR (500 MHz, DMSO-d_6, 75°C) of compound **112**.



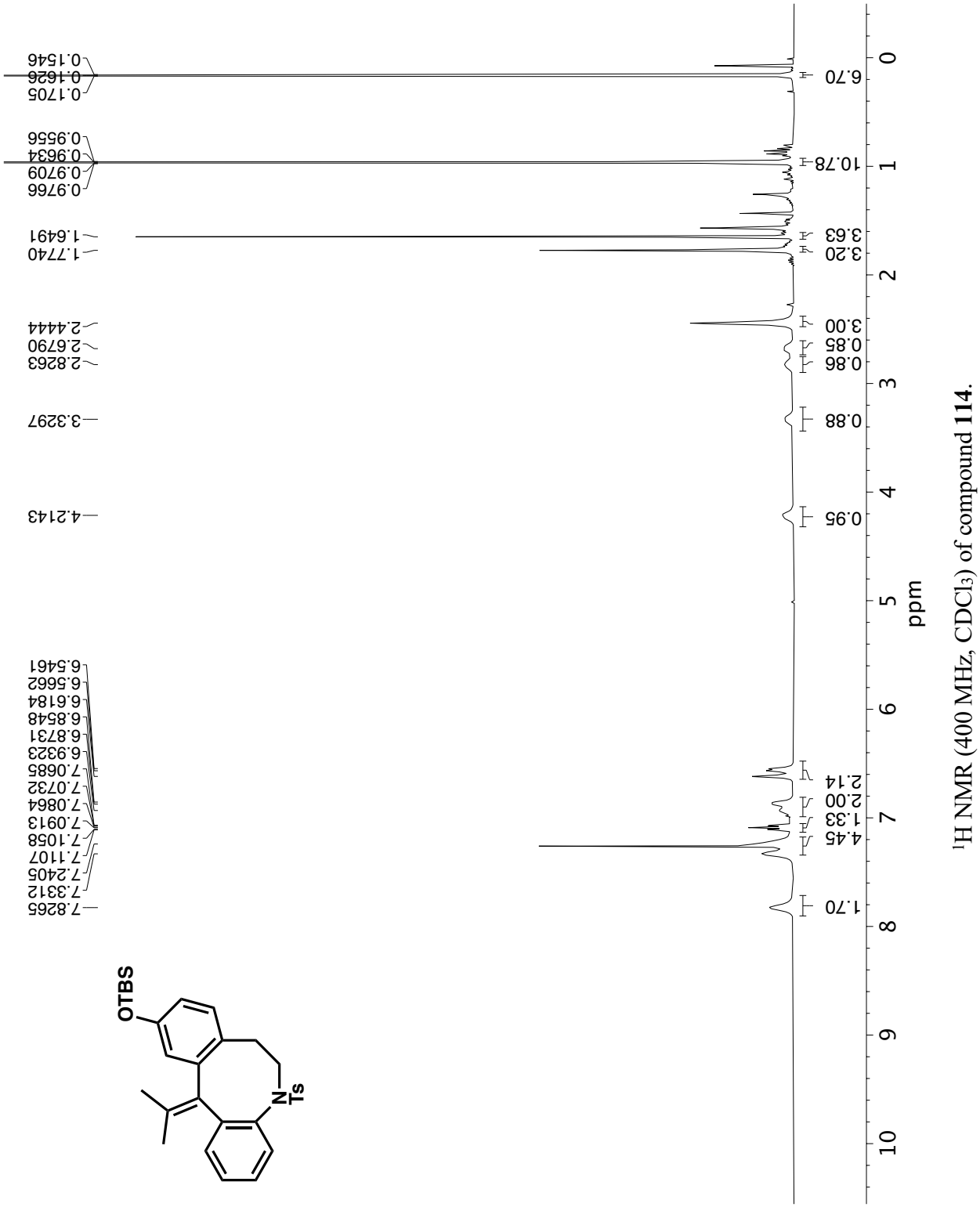
^{13}C NMR (126 MHz, DMSO-d_6, 70°C) of compound **112**.



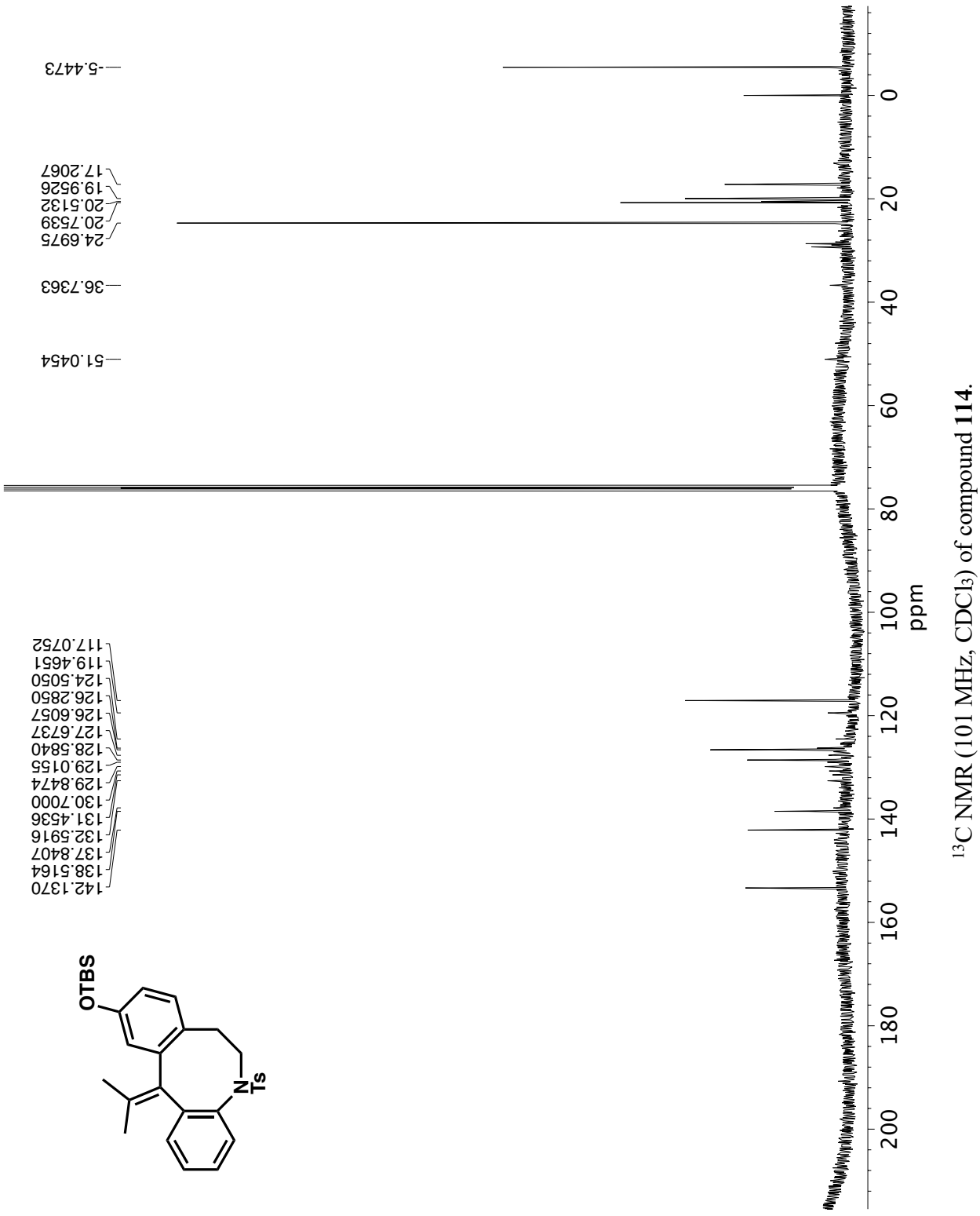
^{1}H NMR (500 MHz, DMSO-d_6, 75°C) of compound **113**.



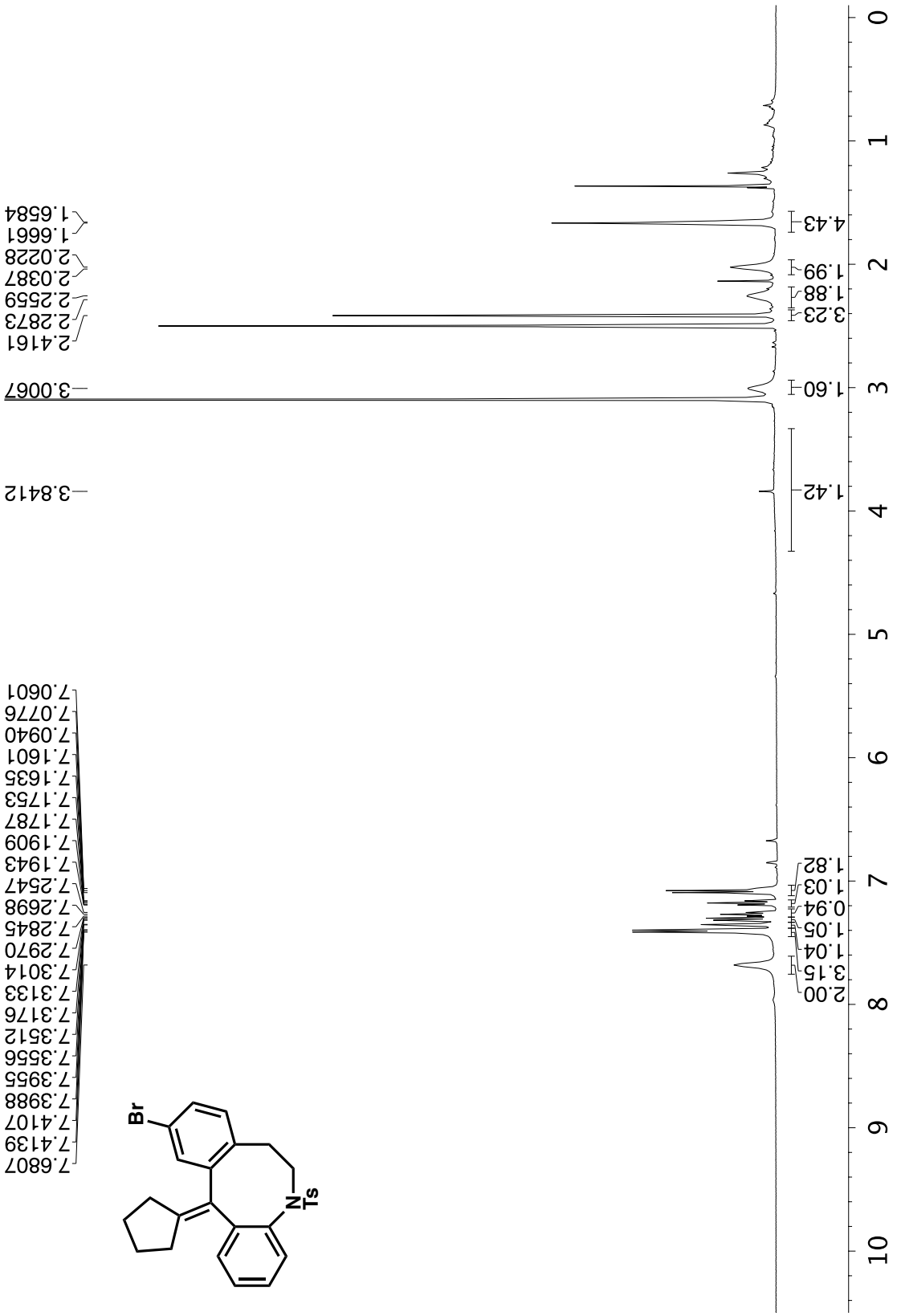
^{13}C NMR (126 MHz, DMSO-*d*$_6$, 75°C) of compound **113**.



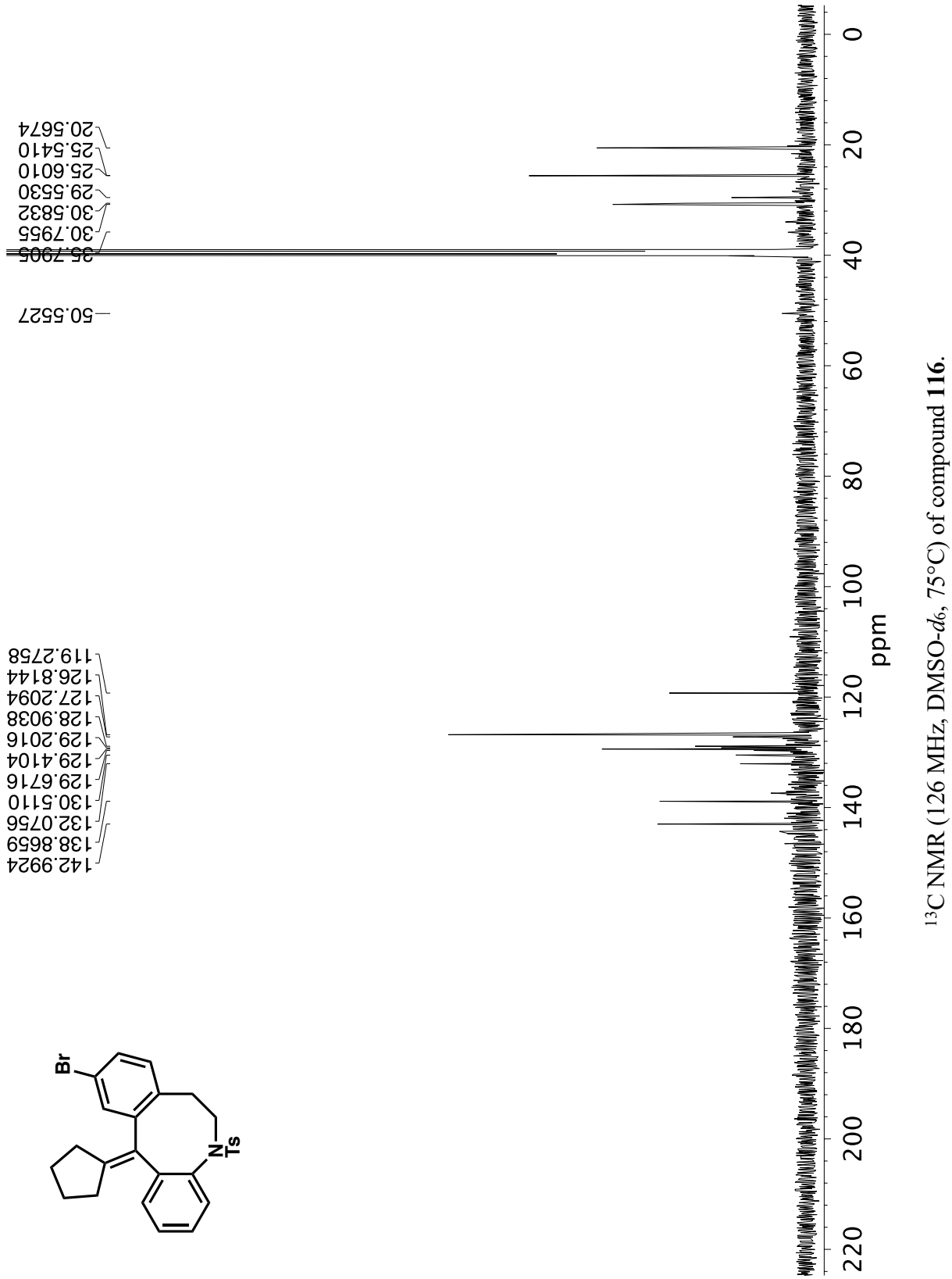
^{1}H NMR (400 MHz, $CDCl_3$) of compound **114**.



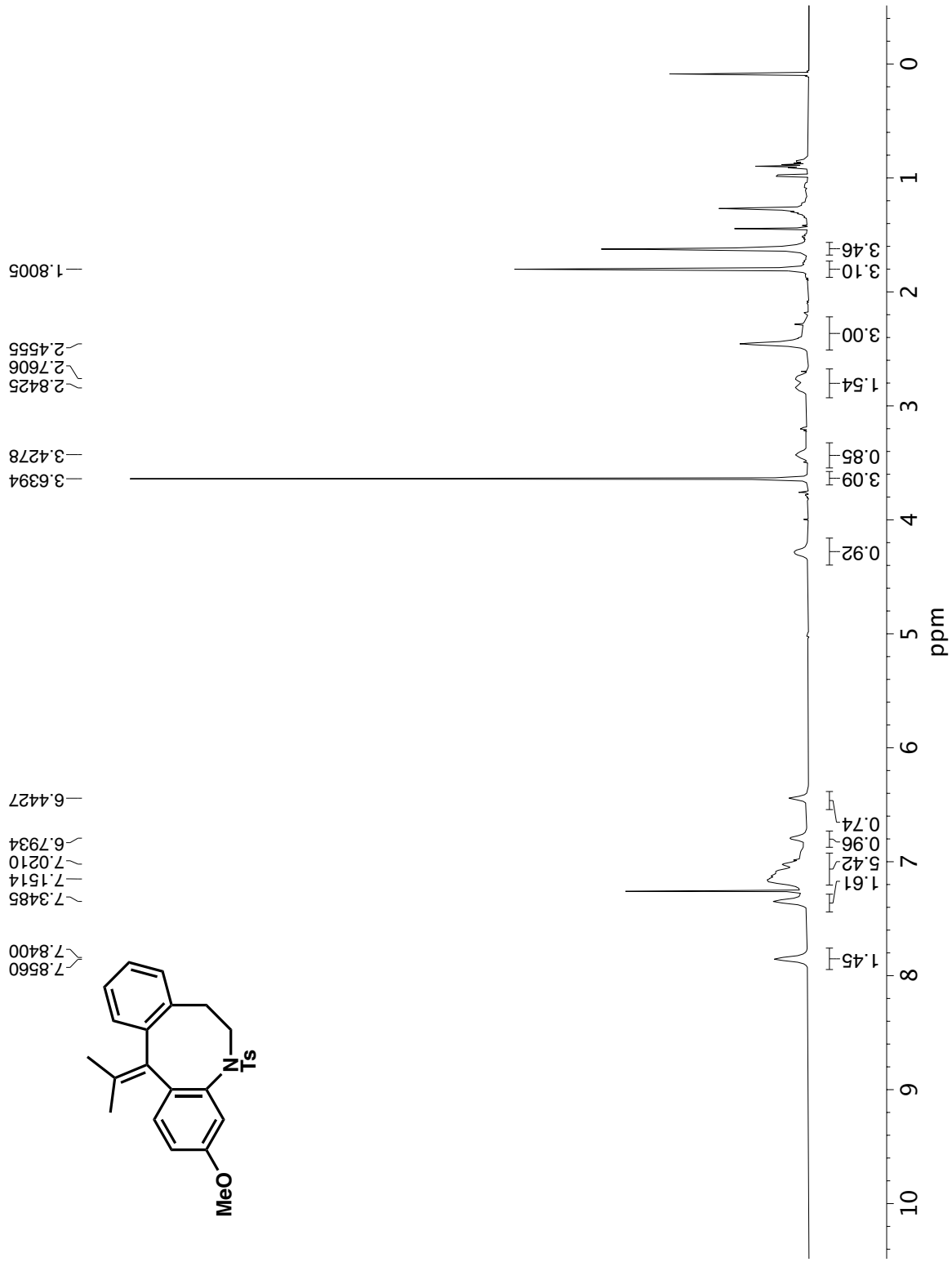
^{13}C NMR (101 MHz, $CDCl_3$) of compound **114**.



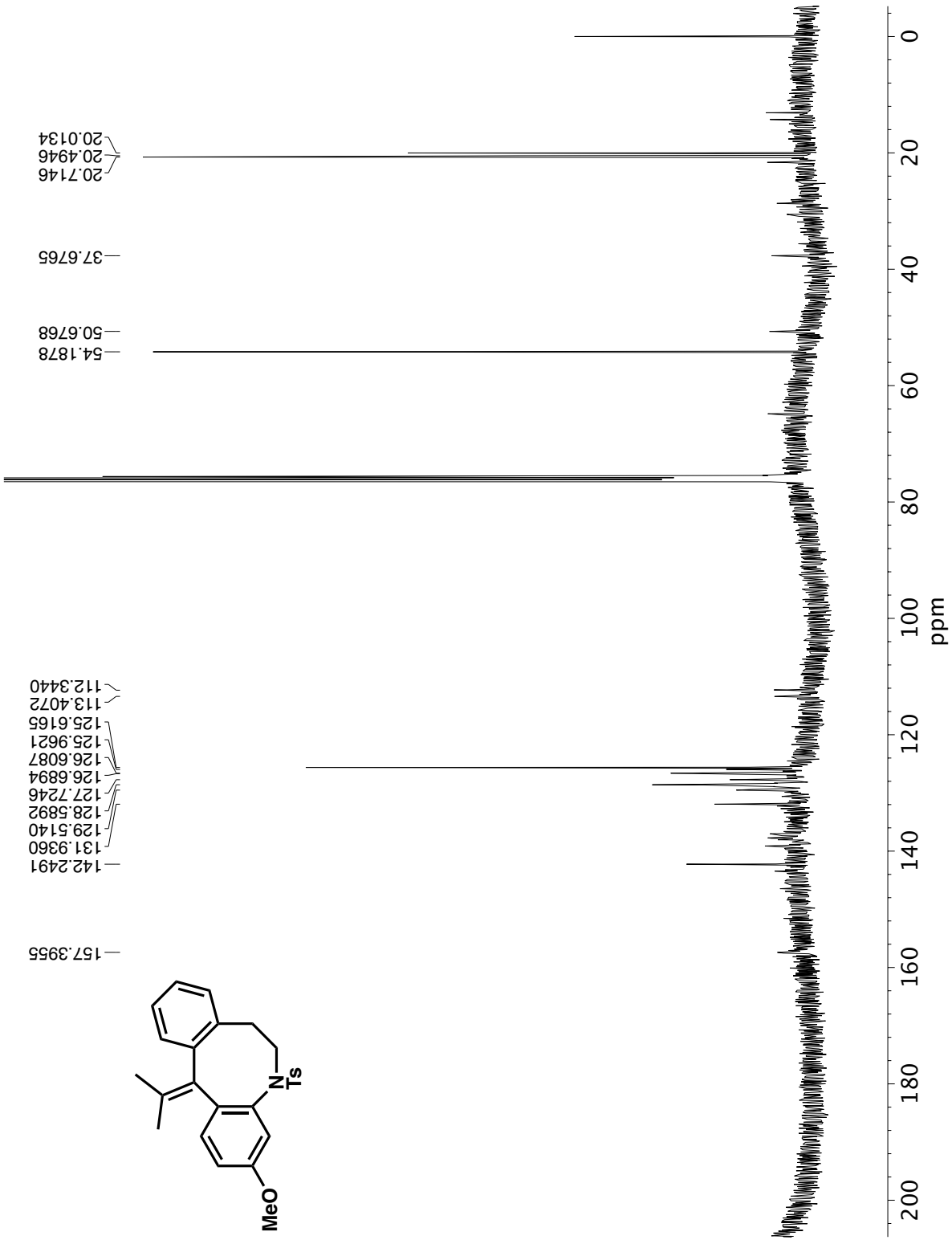
^{1}H NMR (500 MHz, DMSO-d_6, 75°C) of compound **116**.



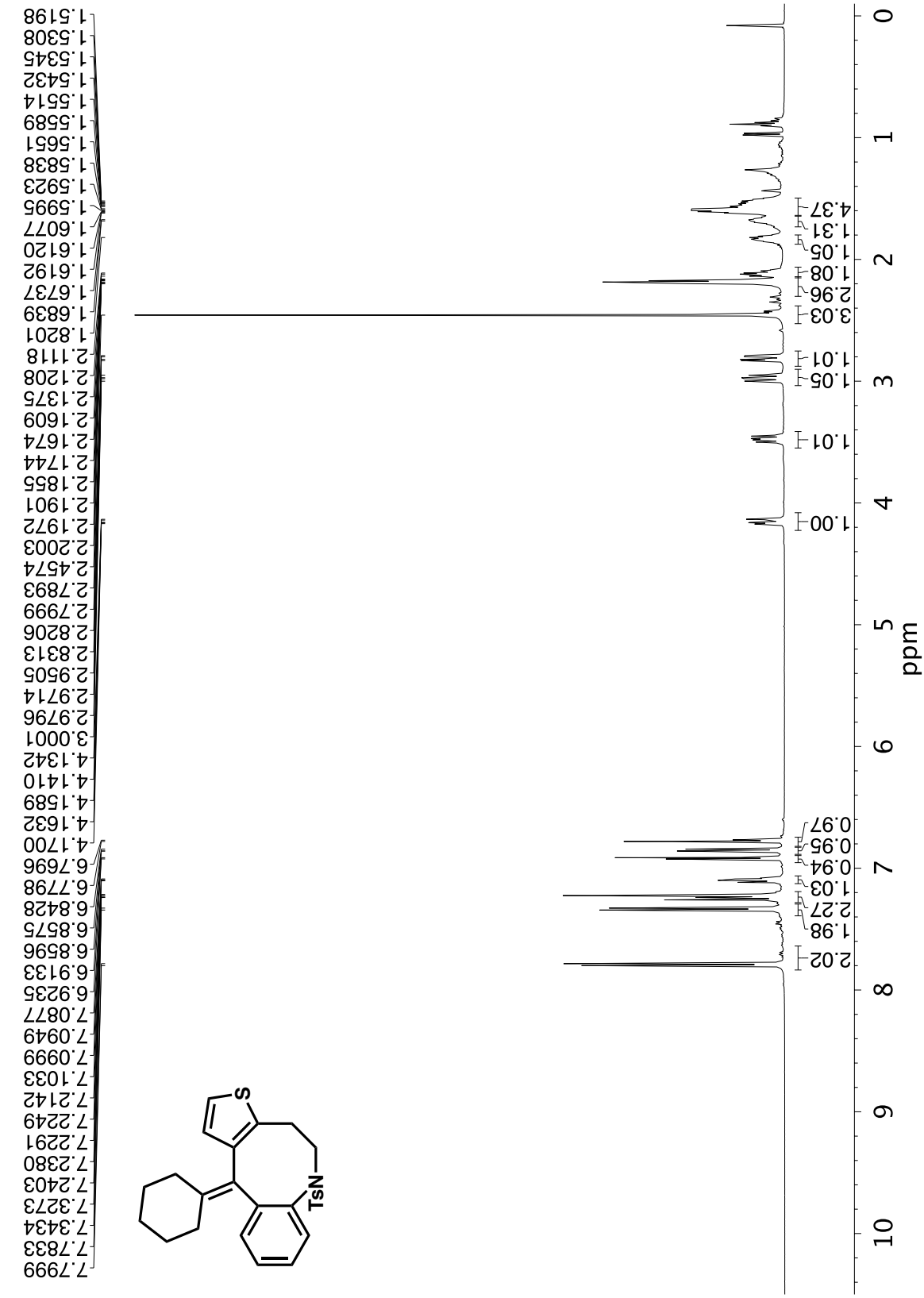
^{13}C NMR (126 MHz, DMSO-*d*$_6$, 75°C) of compound **116**.



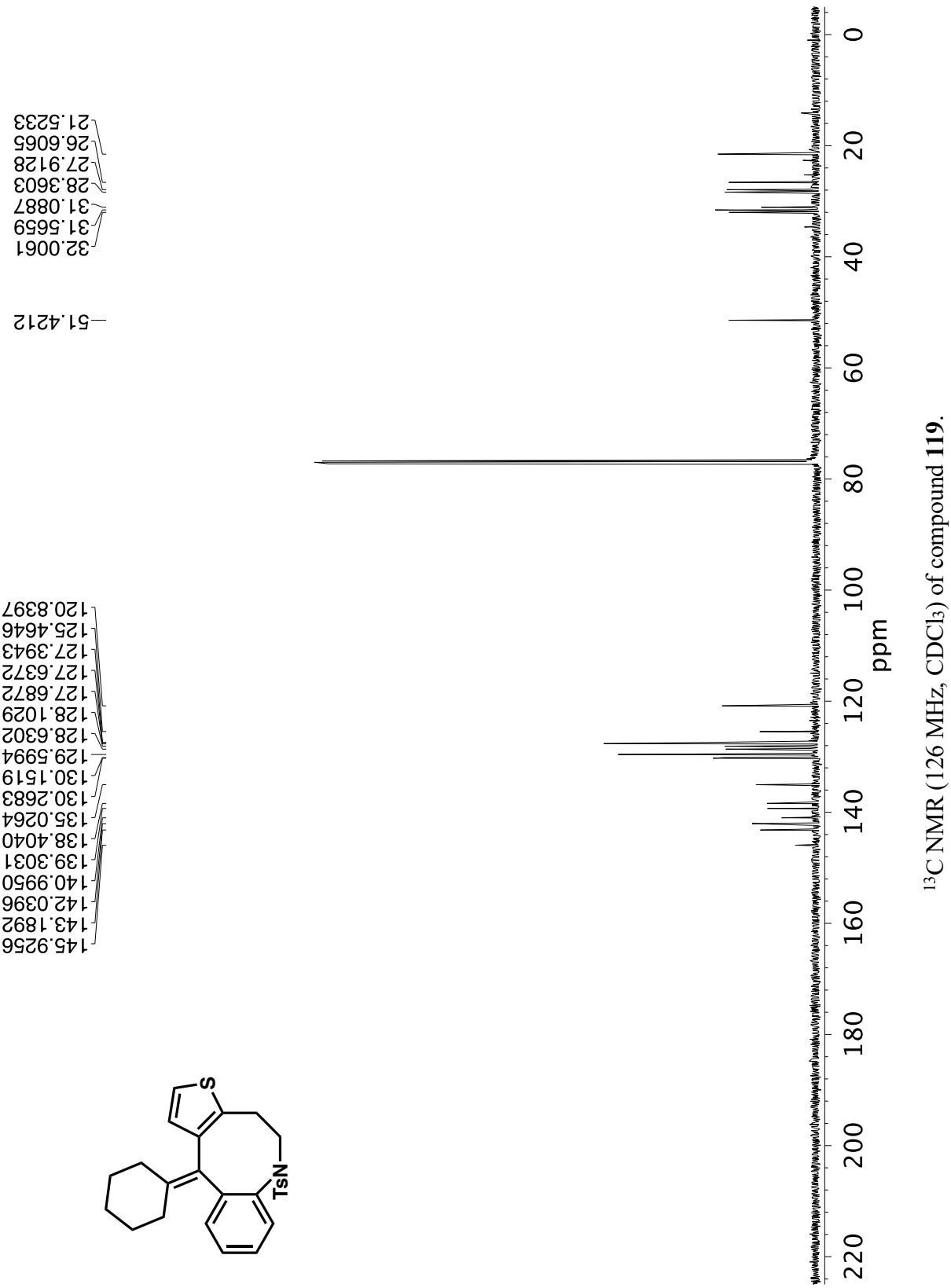
^{1}H NMR (500 MHz, $CDCl_3$) of compound **117.**



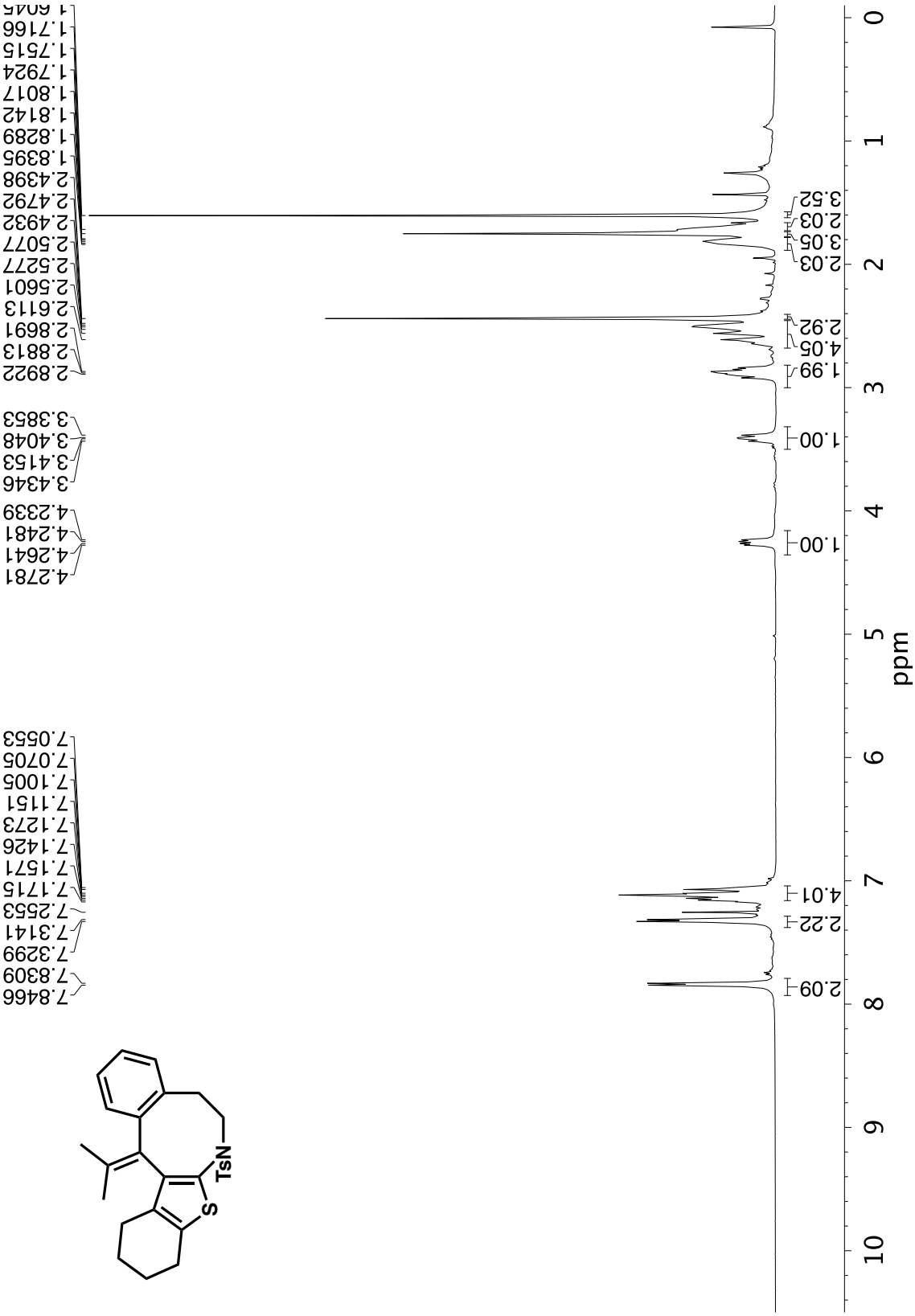
^{13}C NMR (101 MHz, $CDCl_3$) of compound **117.**



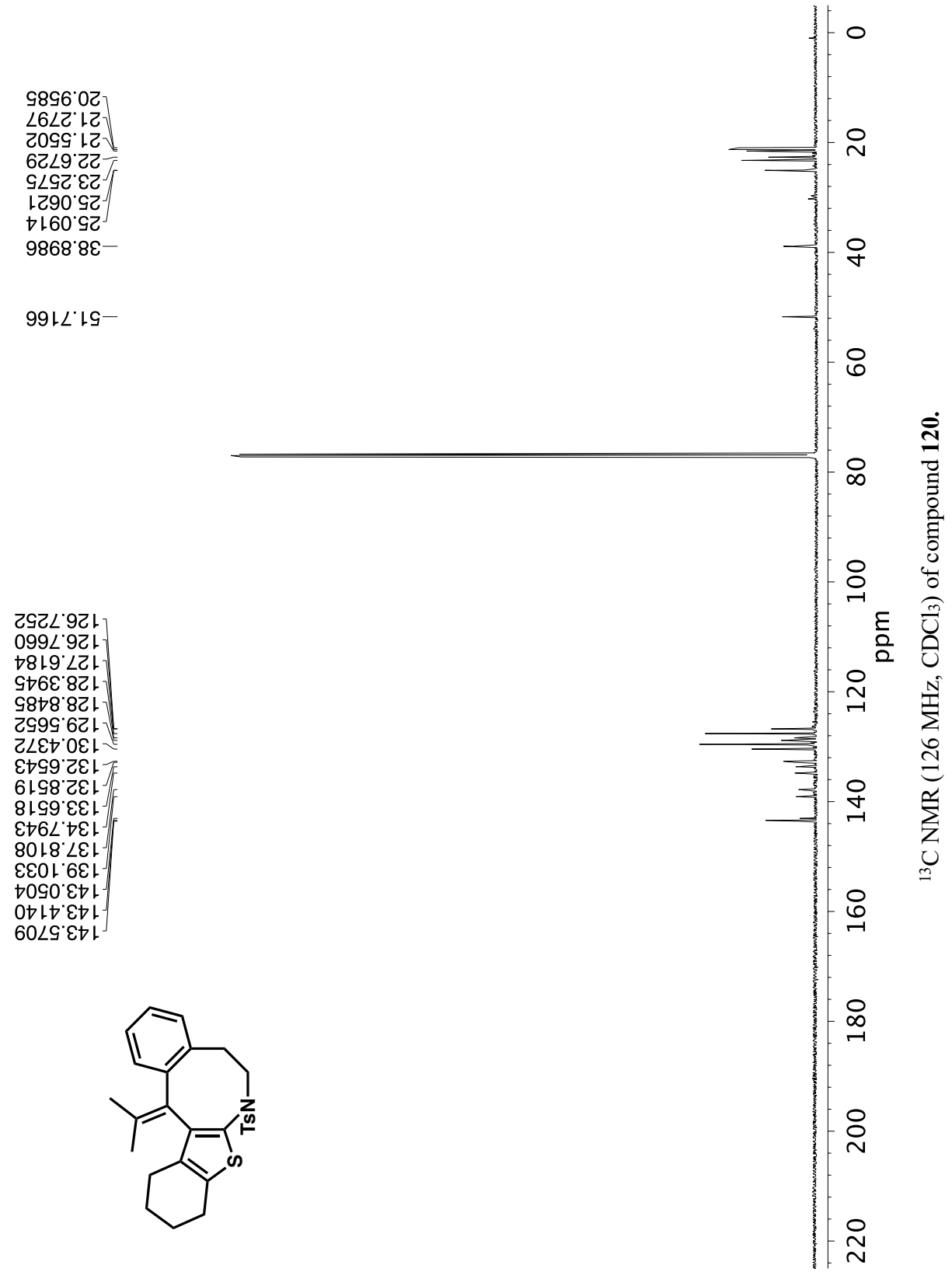
^{1}H NMR (500 MHz, $CDCl_3$) of compound **119**.



^{13}C NMR (126 MHz, $CDCl_3$) of compound **119**.



^{1}H NMR (500 MHz, $CDCl_3$) of compound **120.**



^{13}C NMR (126 MHz, $CDCl_3$) of compound **120.**

CHAPTER 3

Lithium-mediated Selective [2+2] Cycloadditions via Vinyl Carbocations

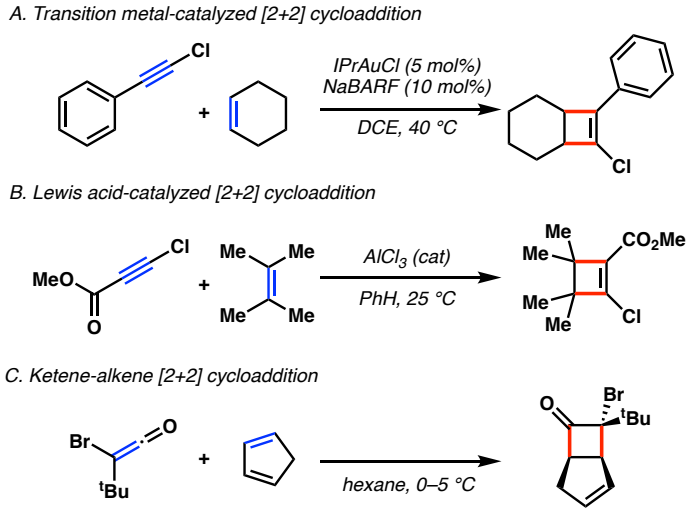
3.1 INTRODUCTION

Cyclobutene motifs with strained 4-membered carbocycles[1] are versatile blocks in organic synthesis and are critical structures in various natural products.[2,3] The [2+2] cycloaddition reaction offers a straightforward and efficient method for synthesizing these strained structures, allowing the formation of two bonds in a single step.[4] Alkenes and alkynes are the most common precursors for [2+2] cycloadditions. However, due to orbital symmetry restrictions described by the Woodward-Hoffmann rules,[5] most [2+2] cycloadditions require photochemical conditions.[6]

Transition metals such as gold[7], palladium[8], and cobalt[9] can activate alkyne species and facilitate [2+2] cycloadditions with alkene partners under thermal conditions (Scheme 3.1A). Lewis acids can also promote some thermal [2+2] cycloadditions, although polarized alkynes, such as ynones[10,11] and terminal alkynes[12], are often required for these reactions

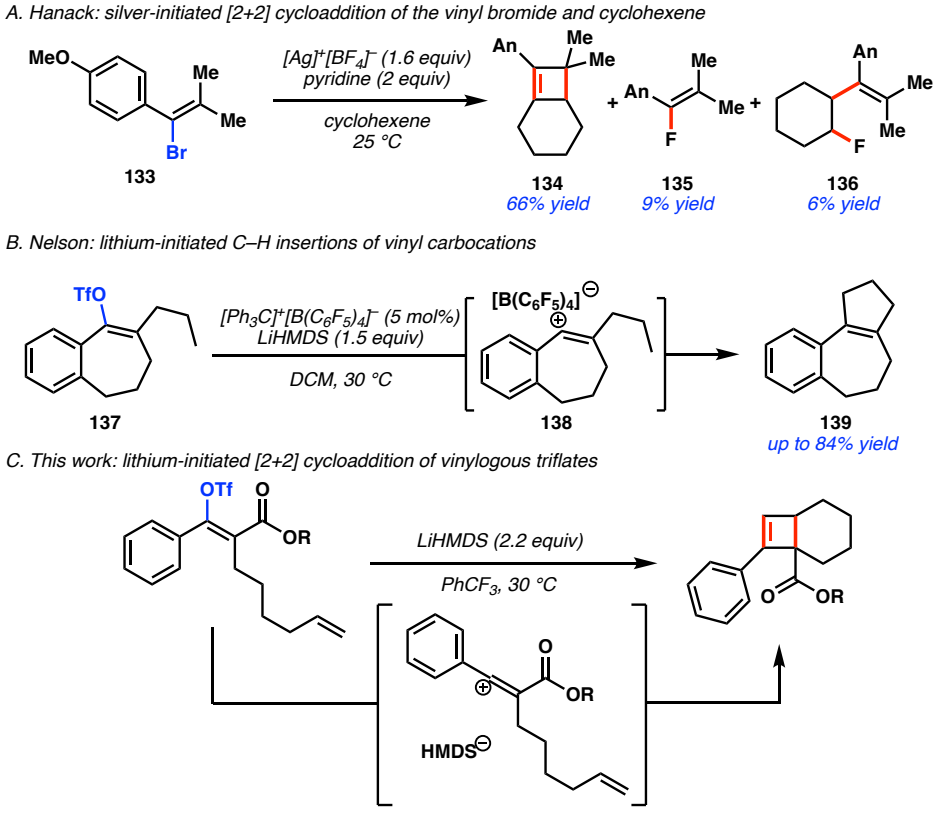
(Scheme 3.1B). A concerted thermal [2+2] cycloaddition can also be achieved when ketenes react with other ketenes or alkenes (Scheme 3.1C).[13]

Scheme 3.1 *Thermal [2+2] cycloadditions with alkenes and alkynes. Me, methyl; ^{t}Bu, tert-butyl.*



As highly electron-deficient species, vinyl carbocations are also reactive towards alkenes, potentially yielding [2+2] cycloaddition products. This type of reactivity was previously reported by Griesbaum[14], Olah[15], and Hanack[16]. However, these reactions typically require strong Brønsted acids, such as hydrogen chloride and fluorosulfuric acid, or stoichiometric noble metal Lewis acids and often present selectivity issues. For example, in the presence of silver tetrafluoroborate ($AgBF_4$), a vinyl carbocation generated from the readily ionizable vinyl bromide **133**, which reacted with cyclohexene to yield the cyclobutene product **134.** However, side products such as vinyl fluoride **135** and ring-opening product **136**, induced by the nucleophilic trapping of fluorides, were also observed (Scheme 3.2A).[16a] Developing a system with better selectivity towards [2+2] cycloaddition products following vinyl cation generation is thus of great interest.

Scheme 3.2 *[2+2] cycloadditions via vinyl carbocations. (A) Silver-initiated [2+2] cycloaddition of the vinyl bromide and cyclohexene (B) Lithium-initiated C–H insertions of vinyl carbocations (C) This work: Lithium-initiated [2+2] cycloaddition of vinylogous triflates. An, para-anisyl.*



Our laboratory has developed a Lewis acid-weakly coordinating anion (WCA) approach to induce challenging ionizations from vinyl sulfonates to access vinyl carbocation intermediates.[17–21] When the precatalyst trityl tetrakis(pentafluorophenyl)borate ($[Ph_3C]^+[B(C_6F_5)_4]^-$) and lithium additive lithium bis(trimethylsilyl)amide (LiHMDS) are added together, a metathesis reaction is proposed to occur, forming the lithium-WCA pair ($[Li]^+[B(C_6F_5)_4]^-$). The lithium in this highly Lewis acidic pair abstracts the trifluoromethanesulfonate (triflate) group from the vinyl triflate precursor **137** (Scheme

3.2B).[18] In this catalytic system, the nucleophilicities of both the WCA species $[B(C_6F_5)_4]^-$ and the sterically hindered LiHMDS are weak. Therefore, the high-energy vinyl cation intermediate **138** is not prone to nucleophilic quenching, and the C–H functionalization product **139** is furnished.

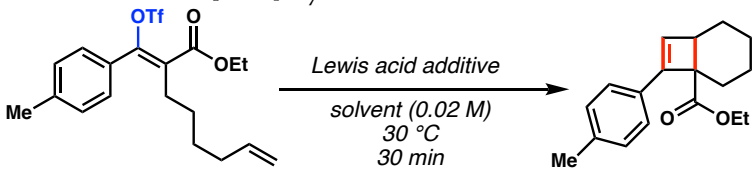
3.2 MODEL SUBSTRATE STUDY

Utilizing the Li-WCA system, we extended this system to vinyl cation [2+2] cycloadditions (Scheme 3.2C). After initial experiments, we identified that vinyl triflate **140** could undergo cycloaddition to yield [4.2.0] bicycle **141**. Therefore, we used vinyl triflate **140** as a model substrate to optimize the reaction conditions (Table 3.1).

Inspired by the previously reported lithium-WCA catalytic conditions from our laboratory[18], we found that using 10 mol% $[Li]^+[B(C_6F_5)_4]^-$ and 1.2 equivalents of LiHMDS in cyclohexane (CyH) produced compound **141** in 40% yield (entry 1) after 30 minutes at 30 °C. Increasing the equivalents of LiHMDS to 2.2 improved the yield to 54% (entry 2). The $[Li]^+[B(C_6F_5)_4]^-$ catalyst was necessary to initiate the reaction, as no reaction occurred with only LiHMDS in CyH (entry 3). The reaction yield was further enhanced to 72% when using the aromatic, electron-deficient trifluorotoluene ($PhCF_3$) solvent (entry 4). Surprisingly, in the absence of the expensive $[Li]^+[B(C_6F_5)_4]^-$ catalyst, LiHMDS initiated the reaction in $PhCF_3$ with an 84% yield (entry 5). Other common lithium bases, such as lithium *tert*-butoxide (LiO^tBu) (entry 6), lithium diisopropylamide (LDA) (entry 7), and lithium hydride (LiH) (see experimental section) were evaluated, but they either failed to induce the ionization of the vinyl triflate precursor or resulted in complex mixtures. Subsequently, trimethylsilylamide bases were evaluated. Sodium bis(trimethylsilyl)amide (NaHMDS)

dropped the yield to 47% (entry 8), while no reaction was observed with potassium (KHMDS) (entry 9) or protic bis(trimethylsilyl)amide (H-HMDS) (see experimental section). Lastly, a solvent screen was undertaken. Most halogenated solvents, including dichloromethane and 1,2-dichloroethane, or nucleophilic solvents, such as tetrahydrofuran (THF) (entry 10), acetonitrile and diethyl ether, resulted in low or no yield of product **141** (see experimental section). In the end, we decided to use entry 5 as the optimized conditions for further studies.

Table 3.1 *Optimization of the [2+2] cycloaddition reaction.*



140 141

entry	Lewis acid additive	solvent	yield (%)
1	$[Li]^+[B(C_6F_5)_4]^-$ (10 mol%) + LiHMDS (1.2 equiv)	CyH	40
2	$[Li]^+[B(C_6F_5)_4]^-$ (10 mol%) + LiHMDS (2.2 equiv)	CyH	54
3	LiHMDS (2.2 equiv)	CyH	no reaction
4	$[Li]^+[B(C_6F_5)_4]^-$ (10 mol%) + LiHMDS (2.2 equiv)	$PhCF_3$	72
5	**LiHMDS (2.2 equiv)**	**$PhCF_3$**	**84**
6	LiO^tBu (2.2 equiv)	$PhCF_3$	no reaction
7	LDA (2.2 equiv)	$PhCF_3$	n.d.
8	NaHMDS (2.2 equiv)	$PhCF_3$	47
9	KHMDS (2.2 equiv)	$PhCF_3$	n.d.
10	LiHMDS (2.2 equiv)	THF	n.d.

* Yield determined by ^1H NMR using nitromethane as an internal standard. TfO, trifluoromethanesulfonate; Et, ethyl; Cy, cyclohexyl; Ph, phenyl; LiHMDS, lithium bis(trimethylsilyl)amide; LDA, lithium diisopropylamide; NaHMDS, sodium

bis(trimethylsilyl)amide; KHMDS, potassium bis(trimethylsilyl)amide; THF, tetrahydrofuran.

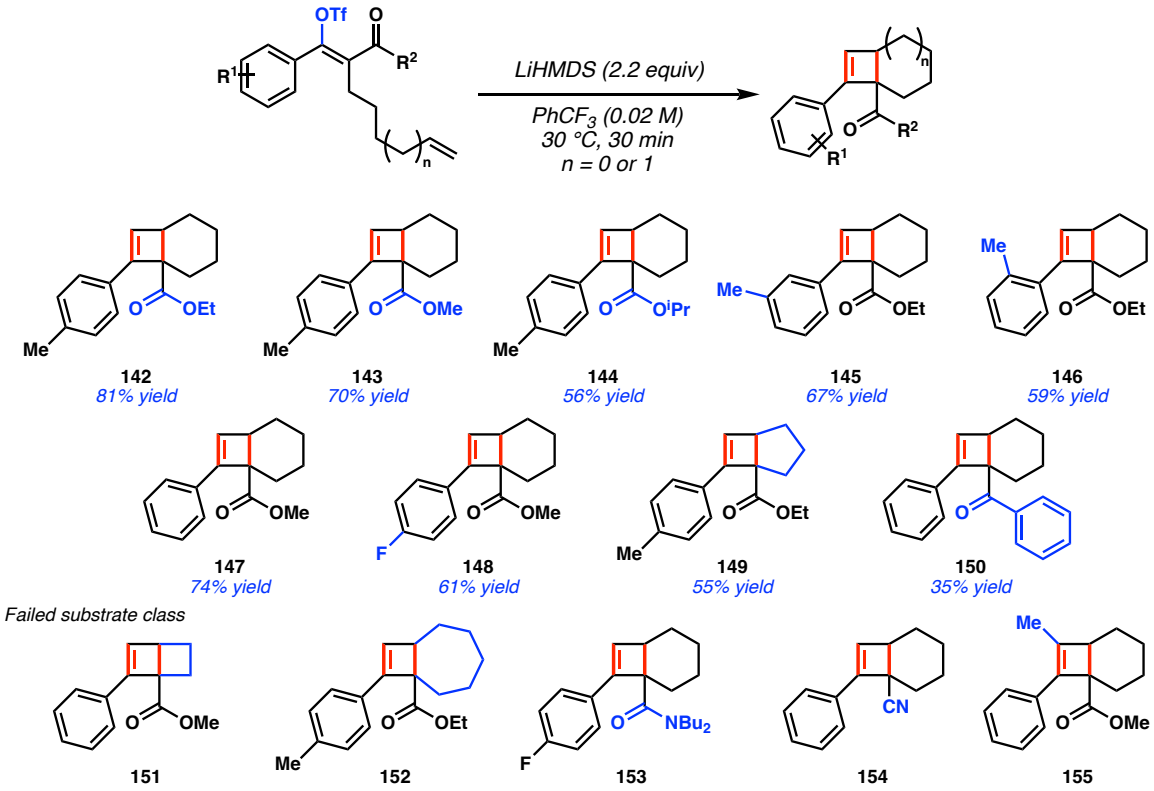
3.3 SUBSTRATE STUDY

With the optimized conditions (entry 5, Table 3.1), we set out to explore the substrate scope (Scheme 3.3). Starting from model substrate **140**, we achieved an isolated yield of 81% for product **141**. We also examined the influence of different ester substitutions on the reaction, obtaining methyl ester **143** and isopropyl ester **144** in 70% and 56% yield, respectively. Additionally, we studied the steric effect of the vicinal aryl group on the vinyl triflate. Vinyl triflate precursors with *meta*- and *ortho*-methylated aryl groups generated their corresponding products **145** and **146** in 67% and 59% yield, respectively. Regarding the electronic effects of the aryl group, besides moderately electron-rich tolyl groups, an electron-neutral phenyl group, and a moderately electron-poor *para*-fluorophenyl group were well tolerated, forming products **147** and **148** in 74% and 61% yield, respectively. Product **149**, containing a [3.2.0] bicycle, was generated with a slightly decreased yield of 55%. Unfortunately, attempts to synthesize the more strained [2.2.0] or [5.2.0] derivatives **151** and **152** were unsuccessful.

Moreover, substrates with different carbonyl-based functional groups other than an ester could also undergo this type of [2+2] cycloaddition reaction. Product **150**, bearing a ketone, was furnished in 35% yield. Vinyl triflate derivatives with amide or nitrile groups were evaluated, but products **153** and **154** were not observed.

In closing, the high selectivity of this [2+2] cycloaddition was limited to terminal alkenes. When the influence of alkene substitution on reactivity was studied with a vinyl triflate with 1,2-disubstituted alkene, a complex mixture was formed and compound **155** was not observed.

Scheme 3.3 *Scope of the [2+2] cycloaddition reaction from vinylogous triflate precursors under LiHMDS. The reaction was performed on 0.05 mmol scale unless otherwise specified. All yield were isolated yield unless specified. All structures were characterized by NMR. ^{i}Pr, isopropyl; Bu, n-butyl.*



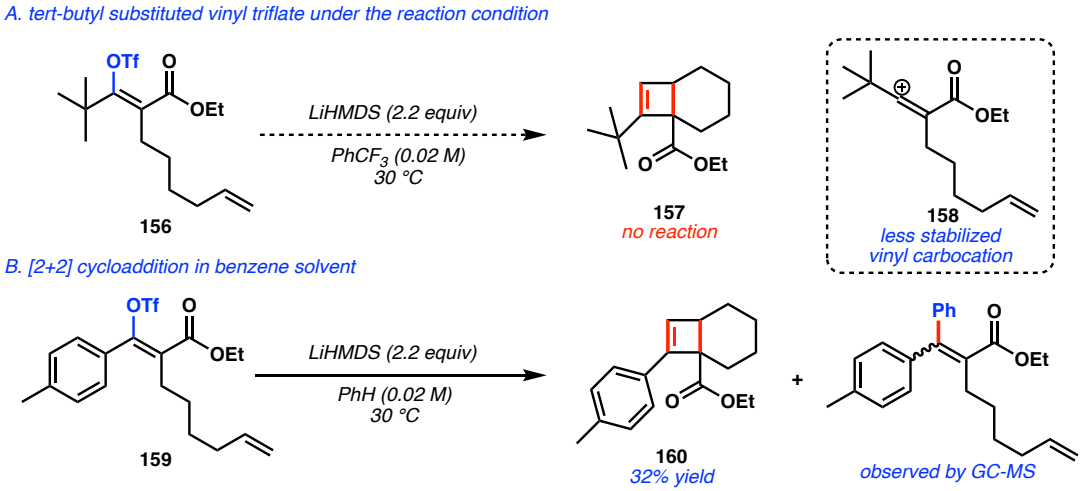
3.4 MECHANISTIC STUDY

Following the substrate scope studies, additional experiments were conducted to gain a deeper understanding of the reaction mechanism. To probe the intermediacy of the vinyl carbocation, *tert*-butyl substituted vinyl triflate **156** was subjected to the standard reaction conditions (Scheme 3.4A). At 30 °C, no reactivity was observed and the vinyl triflate was recovered. The stability of the vinyl triflate could be attributed to the higher energy of the hypothetical vinyl carbocation intermediate **158**, which lacks π-stabilization from vicinal

aryl groups compared to the vinyl triflates utilized in this reaction. Consequently, the activation energy required for the abstraction of triflate to generate the vinyl carbocation was very high, and precursor **156** remained stable and did not undergo ionization.

Further evidence of the cationic intermediate was obtained when vinyl triflate **159** was subjected to LiHMDS in benzene solvent (Scheme 3.4B). Product **160** was observed in 32% yield along with a mixture of side products. Gas chromatography-mass spectrometry (GC-MS) analysis identified these minor products as the Friedel-Crafts adducts of benzene onto the vinyl carbocation intermediate. This result further supports the intermediacy of the vinyl carbocation in the cycloaddition mechanism.

Scheme 3.4 *Scope of the [2+2] cycloaddition from vinylogous triflate precursors under LiHMDS. The reaction was performed on 0.05 mmol scale unless otherwise specified. All yield were isolated yield unless specified. All structures were characterized by NMR.*



3.5 CONCLUSION

In conclusion, we have discovered a LiHMDS-mediated selective [2+2] cycloaddition between a vinyl carbocation and a terminal alkene. This method provides

synthetic chemists with mild conditions and quick access to strained cyclobutene-containing [4.2.0] and [3.2.0] bicycles from vinylogous triflate precursors, further demonstrating the versatile application of vinyl carbocations in constructing strained systems.

3.6 CONTRIBUTION AND ACKNOWLEDGEMENT

The substrate study in section **3.3** was completed in collaboration with Nils H. Rendel.

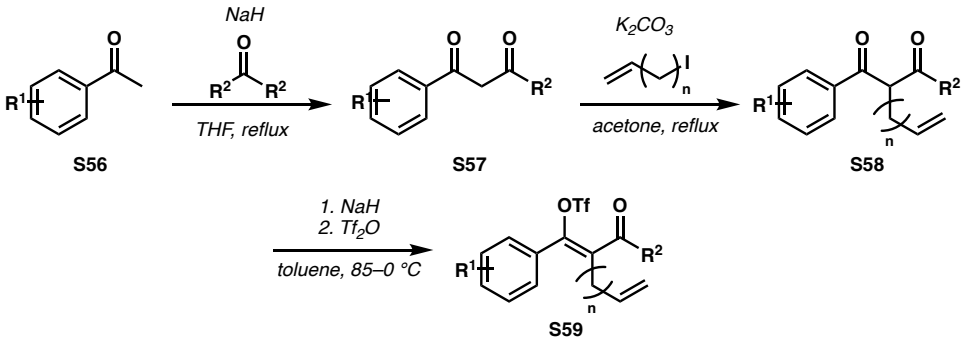
3.7 EXPERIMENTAL SECTION

3.7.1 Materials and methods

Unless otherwise stated, all reactions were performed in a MBraun glovebox under nitrogen atmosphere with ≤ 3.0 ppm O_2 levels. All glassware and stir-bars were dried in a 160 °C oven for at least 12 hours and dried *in vacuo* before use. All liquid substrates were rigorously dried (over CaH_2 or filtered through dry neutral aluminum oxide) before use. Ethyl ether, tetrahydrofuran, dichloromethane, 1,2-dichloroethane, acetonitrile, benzene, and toluene were dried in a JC Meyer solvent system. Trifluorotoluene were distilled over CaH_2 and degassed. $[Li]^+[B(C_6F_5)_4]^-$ salts were synthesized according to literature procedure.[22] Thin layer chromatography (TLC) was performed using Millipore silica gel 60 F_{254} pre-coated plates (0.25 mm) and visualized by UV fluorescence quenching. SiliaFlash P60 silica gel (230-400 mesh) was used for flash chromatography. NMR spectra were recorded on a Varian 500, a Bruker Ascend 400 with Prodigy cryoprobe, or a Varian Oxford 300. Data for ^1H NMR spectra are as follows: chemical shift (ppm), multiplicity, coupling constant (Hz),

and integration. Multiplicities are as follows: s = singlet, d = doublet, t = triplet, dt = doublet of triplet, ddd = doublet of doublet of doublet, ddt = doublet of doublet of triplet, td = triplet of doublet, tt = triplet of triplet, tdt = triplet of doublet of triplet, q = quartet, qd = quartet of doublet, qt = quartet of triplet, p = pentet, hept = septet, and m = multiplet. IR Spectra were record on a Thermo Scientific Nicolet iS50 FT-IR and are reported in terms of frequency absorption (cm^{-1}). Unless noted otherwise, silicone oil bath was used as the heating source for the reactions that require heating.

3.7.2 Preparation of vinyl triflate substrates

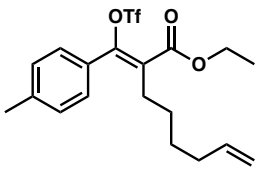


Representative scheme for vinyl triflate substrates synthesis.

General Procedure 7: A three-neck flask was charged with sodium hydride (4 equiv). THF (to make a 0.33 M solution of ketone **S56**) and dialkyl carbonate (4 equiv) were added into the flask through a syringe. Ketone **S56** (1 equiv) was then added slowly into the reaction solution, and the solution was heated to reflux. After 18 hours, the reaction was cooled down to 0 °C and quenched with conc. hydrochloric acid slowly until pH = 1. The mixture was extracted with diethyl ether 3 times. The combined organic phase was washed with brine, dried with magnesium sulfate, filtered, and then concentrated in vacuo. The crude product was purified via flash column chromatography with hexanes and diethyl ether as eluents to get the pure product **S57**.

General Procedure 8: A 3-neck flask was charged with acetone (to make a 0.33 M solution of ester **S57**), ester **S57** (1 equiv), potassium carbonate (1.5 equiv), and alkyl iodide (2 equiv). The solution was refluxed for 18 hours. Then, acetone was removed in vacuo, and water and diethyl ether were added to dilute the mixture. After the separation, the aqueous phase was extracted with diethyl ether 2 more times. The combined organic phase was washed with brine, dried with magnesium sulfate, filtered, and concentrated in vacuo. The crude product was purified via flash column chromatography with hexanes and diethyl ether as eluents to get the pure product **S58**.

General Procedure 9: In a flame-dried Schlenk flask, sodium hydride (1.8 equiv) was mixed with toluene (9 equiv). β-keto ester **S58** was dissolved in toluene (9 equiv) and the solution was added to sodium hydride slurry via syringe. The reaction was heated at 85 °C for 1.5 hours. After it was cooled down to 0 °C, triflic anhydride (1.5 equiv) was added dropwise via syringe. After 1 hour, the reaction was quenched with water and diluted with dichloromethane. After the separation, the aqueous phase was extracted 2 more times with dichloromethane. The combined organic phase was washed with brine, dried with sodium sulfate, decanted, and concentrated in vacuo. The crude product was purified via flash column chromatography with 5% triethylamine in hexanes and diethyl ether as eluents to get the pure product **S59**.



ethyl 2-(p-tolyl(((trifluoromethyl)sulfonyl)oxy)methylene)oct-7-enoate (140).

Synthesized according to General Procedure 7, 8, and 9.

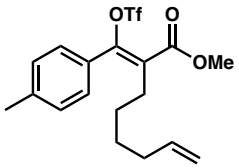
^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.29 (d, *J* = 8.3 Hz, 2H), 7.25 (d, *J* = 7.9 Hz, 2H), 5.72 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 4.97 – 4.86 (m, 2H), 4.30 (q, *J* = 7.1 Hz, 2H), 2.38 (s, 3H), 2.33 – 2.22 (m, 2H), 1.98 – 1.90 (m, 2H), 1.48 – 1.38 (m, 2H), 1.37 – 1.26 (m, 5H).

^{13}C NMR (101 MHz, CD_2Cl_2) δ 165.5, 147.3, 141.3, 138.5, 129.3, 129.2, 128.6, 128.2, 118.2 (q, J = 322 Hz), 114.4, 61.9, 33.2, 29.8, 28.2, 27.8, 21.3, 13.9.

^{19}F NMR (282 MHz, CD_2Cl_2) δ -75.00.

FTIR (Neat film NaCl): 2980, 2936, 2864, 1727, 1642, 1611, 1511, 1421, 1368, 1298, 1209, 1140, 1023, 973, 914, 846, 639.

HR-MS (FD-MS) m/z: [M]+ Calc'd for $C_{19}H_{23}O_5F_3S$ 420.1218; Found 420.1223.



methyl 2-(p-tolyl(((trifluoromethyl)sulfonyl)oxy)methylene)oct-7-enoate (S61).

Synthesized according to General Procedure 7, 8, and 9.

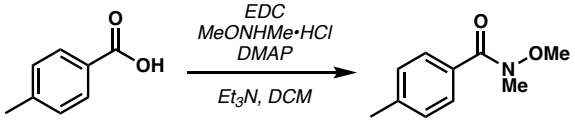
^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.28 (d, *J* = 7.9 Hz, 2H), 7.25 (d, *J* = 7.8 Hz, 2H), 5.84 – 5.52 (m, 1H), 4.99 – 4.85 (m, 2H), 3.83 (s, 3H), 2.38 (s, 3H), 2.29 (t, *J* = 7.8 Hz, 2H), 1.95 (q, *J* = 7.2 Hz, 2H), 1.43 (p, *J* = 7.7 Hz, 2H), 1.31 (p, *J* = 7.6 Hz, 2H).

^{13}C NMR (101 MHz, CD_2Cl_2) δ 165.9, 147.6, 141.3, 138.4, 129.3, 129.1, 128.4, 128.1, 118.1 (*J* = 321.2 Hz), 114.3, 52.2, 33.1, 29.8, 28.2, 27.8, 21.2.

^{19}F NMR (376 MHz, CD_2Cl_2) δ -75.01.

FTIR (Neat film NaCl): 3077, 2929, 2860, 1730, 1642, 1610, 1510, 1419, 1301, 1208, 1138, 1024, 978, 912, 840, 761, 727, 641, 606.

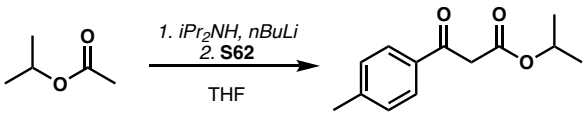
HR-MS (FD-MS) m/z: [M]+ Calc'd for $C_{18}H_{21}O_5F_3S$ 406.1062; Found 406.1059.



S62

***N*-methoxy-*N*,4-dimethylbenzamide (S62).**

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimidium chloride (EDC, 14.1 g, 73.4 mmol, 2 equiv), 4-dimethylaminopyridine (DMAP, 0.45 g, 3.7 mmol, 0.1 equiv), *O*,*N*-dimethylhydroxylaminium chloride (3.94 g, 40.4 mmol, 1.1 equiv), DCM (74 mL, to make a 0.5 M solution of the carboxylic acid), and 4-methylbenzoic acid (5.00 g, 36.7 mmol, 1 equiv) were added to a flask. Triethylamine (10.2 mL, 2 equiv) was then added slowly. After 18 hours, the reaction was quenched with water. After the separation, the organic phase was washed with 1 M HCl solution 2 times, saturated sodium bicarbonate solution, and brine. It was then dried with magnesium sulfate and concentrated in vacuo. The crude product **S62** was used in the next step without further purification.

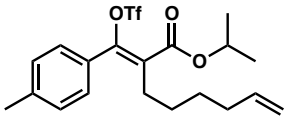


S63

isopropyl 3-oxo-3-(*p*-tolyl)propanoate (S63).

Tetrahydrofuran (THF, 60 mL) and diisopropylamine (2.54 mL, 18.0 mmol, 3 equiv) were added into a Schlenk flask. The solution was cooled down to –78 °C and n-butyllithium solution (2.38 M, 7.82 mL, 18.6 mmol, 3.1 equiv) was added dropwise. After 1 minute, isopropyl acetate (2.1 mL, 18 mmol, 3 equiv) was added into the solution at –78 °C. The solution was stirred under this temperature for another 15 minutes. Then, **S62** (1.08 g, 6.00 mmol, 1 equiv) in THF (12 mL) was added at –78 °C and the solution was stirred for another 15 minutes. Then it was warmed up to 0 °C and stirred for 18 hours

warming up to 25 °C. The reaction was quenched with saturated sodium bicarbonate solution and diluted with diethyl ether and water. After the separation, the aqueous phase was extracted with diethyl ether 2 more times. The combined organic phase was washed with brine, dried with magnesium sulfate, filtered, and concentrated in vacuo. The crude product was purified via flash column chromatography with hexanes:diethyl ether = 5:1 as eluents to get the pure product **S63** (0.77 g, 58% yield).



isopropyl 2-(p-tolyl(((trifluoromethyl)sulfonyl)oxy)methylene)oct-7-enoate (S64).

Synthesized according to General Procedure 8 and 9 from **S63**.

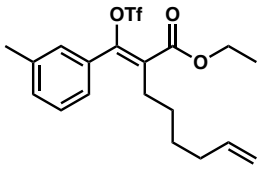
^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.28 (d, *J* = 8.3 Hz, 2H), 7.24 (d, *J* = 8.1 Hz, 2H), 5.72 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 5.15 (p, *J* = 6.3 Hz, 1H), 4.96 – 4.84 (m, 2H), 2.38 (s, 3H), 2.32 – 2.21 (m, 2H), 2.01 – 1.88 (m, 2H), 1.47 – 1.38 (m, 2H), 1.32 (d, *J* = 6.6 Hz, 6H), 1.34 – 1.24 (m, 2H).

^{13}C NMR (101 MHz, CD_2Cl_2) δ 165.0, 146.9, 141.2, 138.5, 129.3, 129.2, 128.9, 128.2, 118.2 (q, J = 321 Hz), 114.4, 70.0, 33.2, 29.9, 28.3, 27.7, 21.5, 21.3.

^{19}F NMR (376 MHz, CD_2Cl_2) δ -74.86.

FTIR (Neat film NaCl): 3078, 2981, 2931, 2862, 1723, 1661, 1642, 1611, 1511, 1453, 1421, 1389, 1375, 1354, 1295, 1276, 1247, 1205, 1182, 1138, 1103, 1024, 970, 844, 606.

HR-MS (FD-MS) m/z: [M]+ Calc'd for $C_{20}H_{25}O_5F_3S$ 434.1375; Found 434.1379.



ethyl 2-(m-tolyl(((trifluoromethyl)sulfonyl)oxy)methylene)oct-7-enoate (S65).

Synthesized according to General Procedure 7, 8, and 9.

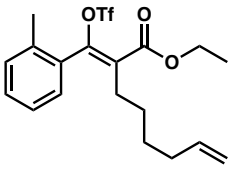
^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.29 – 7.19 (m, 2H), 7.18 – 7.11 (m, 2H), 5.66 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 4.90 – 4.80 (m, 2H), 4.24 (q, *J* = 7.1 Hz, 2H), 2.30 (d, *J* = 0.8 Hz, 3H), 2.27 – 2.16 (m, 2H), 1.95 – 1.81 (m, 2H), 1.46 – 1.34 (m, 2H), 1.30 – 1.22 (m, 5H).

^{13}C NMR (101 MHz, CD_2Cl_2) δ 165.4, 147.2, 138.6, 138.4, 131.3, 131.0, 129.7, 128.7, 128.4, 126.3, 122.8, 118.1 (q, $^{1}J_{C–F}$ = 322 Hz), 114.3, 113.3, 61.8, 53.6, 33.1, 29.7, 28.2, 27.6, 21.0, 13.8.

^{19}F NMR (282 MHz, CD_2Cl_2) δ -75.02.

FTIR (Neat film NaCl): 2930, 1727, 1421, 1368, 1301, 1243, 1207, 1139, 1017, 981, 913, 852, 823, 761, 710, 606.

HR-MS (FD-MS) m/z: [M]+ Calc'd for $C_{19}H_{23}O_5F_3S$ 420.1218; Found 420.1227.



ethyl 2-(o-tolyl(((trifluoromethyl)sulfonyl)oxy)methylene)oct-7-enoate (S66).

Synthesized according to General Procedure 7, 8, and 9.

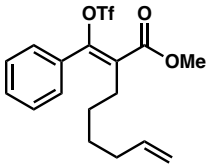
^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.37 (td, *J* = 7.4, 1.7 Hz, 1H), 7.32 – 7.19 (m, 3H), 5.69 (ddt, *J* = 17.1, 10.4, 6.7 Hz, 1H), 4.94 – 4.82 (m, 2H), 4.32 (qd, *J* = 7.1, 1.5 Hz, 2H), 2.31 (s, 3H), 2.28 – 2.22 (m, 1H), 2.03 (dt, *J* = 13.7, 7.7 Hz, 1H), 1.90 (qt, *J* = 7.0, 1.4 Hz, 2H), 1.46 – 1.37 (m, 2H), 1.36 (t, *J* = 7.2 Hz, 3H), 1.30 – 1.23 (m, 2H).

^{13}C NMR (101 MHz, CD_2Cl_2) δ 165.4, 147.0, 138.5, 137.9, 130.9, 130.8, 130.6, 130.2, 129.9, 125.8, 118.1 (q, *J* = 322 Hz), 114.4, 62.0, 33.2, 29.7, 28.3, 27.3, 19.1, 13.9.

^{19}F NMR (376 MHz, CD_2Cl_2) δ -75.56.

FTIR (Neat film NaCl): 3075, 2931, 2860, 1728, 1641, 1602, 1421, 1369, 1300, 1248, 1209, 1180, 1140, 1018, 969, 912, 843, 769, 730, 606.

HR-MS (FD-MS) m/z: [M]+ Calc'd for $C_{19}H_{23}O_5F_3S$ 420.1218; Found 461.1231.



methyl 2-(phenyl(((trifluoromethyl)sulfonyl)oxy)methylene)oct-7-enoate (S67).

Synthesized according to General Procedure 7, 8, and 9.

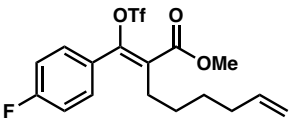
^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.53 – 7.33 (m, 5H), 5.71 (ddt, *J* = 17.0, 10.3, 6.7 Hz, 1H), 4.97 – 4.81 (m, 2H), 3.84 (s, 3H), 2.36 – 2.23 (m, 2H), 1.94 (tdt, *J* = 8.2, 6.7, 1.4 Hz, 2H), 1.48 – 1.37 (m, 2H), 1.34 – 1.25 (m, 2H).

^{13}C NMR (101 MHz, CD_2Cl_2) δ 165.9, 147.4, 138.5, 131.1, 130.8, 129.3, 128.7, 128.7, 118.2 (*J* = 321 Hz), 114.5, 52.4, 33.2, 29.8, 28.3, 27.8.

^{19}F NMR (376 MHz, CD_2Cl_2) δ -75.07.

FTIR (Neat film NaCl): 3076, 2931, 2860, 1732, 1642, 1491, 1421, 1302, 1280, 1249, 1209, 1139, 979, 913, 838, 700, 627, 616.

HR-MS (FD-MS) m/z: [M]+ Calc'd for $C_{17}H_{19}O_5F_3S$ 392.0905; Found 392.0901.



methyl 2-((4-fluorophenyl)(((trifluoromethyl)sulfonyl)oxy)methylene)oct-7-enoate (S68).

Synthesized according to General Procedure 7, 8, and 9.

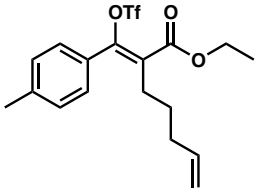
^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.47 – 7.38 (m, 2H), 7.22 – 7.12 (m, 2H), 5.72 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 4.97 – 4.84 (m, 2H), 3.84 (s, 3H), 2.35 – 2.21 (m, 2H), 1.99 – 1.90 (m, 2H), 1.50 – 1.40 (m, 2H), 1.37 – 1.27 (m, 2H).

^{13}C NMR (101 MHz, CD_2Cl_2) δ 165.62, 163.85 (*J* = 252.3 Hz), 146.24, 138.34, 131.58 (*J* = 8.9 Hz), 129.14, 127.24 (*J* = 3.6 Hz), 118.0 (*J* = 321.7 Hz), 115.9 (*J* = 22.2 Hz), 114.41, 52.33, 33.09, 29.73, 28.19, 27.63.

^{19}F NMR (376 MHz, CD_2Cl_2) δ -75.03, -109.16.

FTIR (Neat film NaCl): 3079, 2932, 2861, 1731, 1642, 1604, 1508, 1420, 1290, 1280, 1207, 1159, 1137, 1100, 1017, 979, 964, 912, 849, 829, 814, 762, 734, 605.

HR-MS (FD-MS) m/z: [M]+ Calc'd for $C_{17}H_{18}O_5F_4S$ 410.0811; Found 410.0807.



ethyl 2-(p-tolyl(((trifluoromethyl)sulfonyl)oxy)methylene)hept-6-enoate (S69).

Synthesized according to General Procedure 7, 8, and 9.

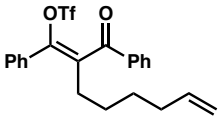
^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.29 (d, *J* = 8.4 Hz, 2H), 7.24 (d, *J* = 8.2 Hz, 2H), 5.68 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 4.97 – 4.76 (m, 2H), 4.30 (q, *J* = 7.1 Hz, 2H), 2.38 (s, 3H), 2.33 – 2.24 (m, 2H), 2.01 – 1.90 (m, 2H), 1.56 – 1.49 (m, *J* = 7.6 Hz, 2H), 1.34 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, CD_2Cl_2) δ 165.5, 147.5, 141.3, 137.8, 129.3, 129.2, 128.4, 128.2, 118.2 (q, *J* = 322 Hz), 114.9, 61.9, 33.1, 29.5, 27.6, 21.3, 13.9.

^{19}F NMR (376 MHz, CD_2Cl_2) δ -74.95.

FTIR (Neat film NaCl): 3079, 2980, 2933, 1728, 1661, 1643, 1611, 1511, 1421, 1369, 1300, 1209, 1140, 1023, 973, 840, 609.

HR-MS (FD-MS) m/z: [M]+ Calc'd for $C_{18}H_{21}O_5F_3S$ 406.1062; Found 406.1070.



2-benzoyl-1-phenylocta-1,7-dien-1-yl trifluoromethanesulfonate (S70).

Synthesized according to General Procedure 8 and 9.

^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.06 – 7.93 (m, 2H), 7.65 (td, *J* = 7.3, 1.5 Hz, 1H), 7.59 – 7.42 (m, 7H), 5.65 (ddt, *J* = 17.1, 10.7, 6.7 Hz, 1H), 4.89 – 4.79 (m, 2H), 2.44 – 2.33 (m, 2H), 1.88 (q, *J* = 7.1 Hz, 2H), 1.39 (tt, *J* = 8.0, 6.2 Hz, 2H), 1.28 (dt, *J* = 15.2, 7.6 Hz, 2H).

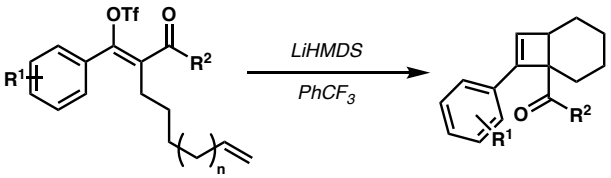
^{13}C NMR (101 MHz, CD_2Cl_2) δ 194.4, 143.6, 138.4, 135.6, 134.8, 134.4, 130.9, 130.7, 129.6, 129.5, 129.0, 128.9, 118.0 (*J* = 322.2 Hz), 114.5, 33.2, 30.6, 28.4, 27.3.

^{19}F NMR (376 MHz, CD_2Cl_2) δ -74.92.

FTIR (Neat film NaCl): 3065, 2931, 2859, 1670, 1597, 1449, 1417, 1317, 1274, 1208, 1136, 954, 922, 840, 695, 606.

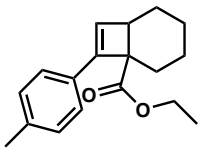
HR-MS (FD-MS) m/z: [M]+ Calc'd for $C_{22}H_{21}O_4F_3S$ 438.1113; Found 438.1092.

3.7.3 [2+2] cycloaddition



General Procedure 10: In the glovebox, LiHMDS (2.2 equiv) was added in a dram vial. Trifluorotoluene (to make a 0.02 M solution of the vinyl triflate) was then added to dissolve LiHMDS. Finally, the vinyl triflate (1 equiv) was added. The reaction was stirred for 30

minutes in a heating block at 30 °C. It was then brought outside of the glovebox. The reaction solution was directly loaded onto the silica gel to purify the cycloaddition product via flash column chromatography with hexanes and diethyl ether as eluents.



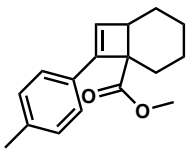
ethyl 8-(p-tolyl)bicyclo[4.2.0]oct-7-ene-1-carboxylate (142).

Prepared from 0.050 mmol vinyl triflate **140** according to General Procedure 10. The crude reaction was purified via flash column chromatography (hexanes:diethyl ether = 10:1) to afford product **142** as a pale yellow oil (11 mg, 81% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, *J* = 7.7 Hz, 2H), 7.11 (d, *J* = 7.7 Hz, 2H), 6.47 (d, *J* = 1.2 Hz, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.06 (t, *J* = 4.5 Hz, 1H), 2.33 (s, 3H), 2.30 – 2.17 (m, 1H), 2.07 – 1.93 (m, 2H), 1.90 – 1.75 (m, 1H), 1.69 – 1.58 (m, 3H), 1.50 – 1.48 (m, 1H), 1.19 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 175.9, 148.3, 138.0, 131.4, 130.9, 129.4, 125.3, 60.8, 52.6, 43.3, 26.6, 24.3, 21.7, 18.0, 17.8, 14.6.

FTIR (Neat film NaCl): 3026, 2935, 2865, 1719, 1508, 1446, 1365, 1269, 1235, 1160, 1110, 1095, 1064, 1050, 807.



methyl 8-(*p*-tolyl)bicyclo[4.2.0]oct-7-ene-1-carboxylate (143).

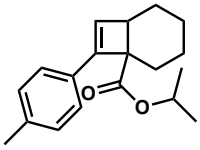
Prepared from 0.050 mmol vinyl triflate **S61** according to General Procedure 10. The crude reaction was purified via flash column chromatography (hexanes:diethyl ether = 10:1) to afford product **143** as a pale yellow oil (9 mg, 70% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.0 Hz, 2H), 7.12 (d, *J* = 7.9 Hz, 2H), 6.49 (d, *J* = 1.3 Hz, 1H), 3.68 (s, 3H), 3.07 (t, *J* = 4.7 Hz, 1H), 2.36 – 2.27 (m, 1H), 2.34 (s, 3H), 2.00 (dt, *J* = 14.1, 5.3 Hz, 1H), 1.84 (ddt, *J* = 15.4, 10.3, 5.2 Hz, 1H), 1.70 – 1.59 (m, 2H), 1.54 – 1.44 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 176.4, 148.2, 138.1, 131.5, 130.8, 129.5, 125.3, 52.5, 52.2, 43.4, 26.5, 24.3, 21.7, 18.0, 17.7.

FTIR (Neat film NaCl): 3025, 2942, 2864, 1723, 1508, 1456, 1433, 1270, 1256, 1239, 1182, 1161, 1065, 1051, 808.

HR-MS (FD-MS) m/z: [M]+ Calc'd for $C_{17}H_{20}O_2$ 256.1458; Found 256.1465.



isopropyl 8-(p-tolyl)bicyclo[4.2.0]oct-7-ene-1-carboxylate (144).

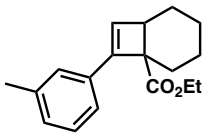
Prepared from 0.050 mmol vinyl triflate **S64** according to General Procedure 10. The crude reaction was purified via flash column chromatography (hexanes:diethyl ether = 10:1) to afford product **144** as a pale yellow oil (8 mg, 56% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, *J* = 7.0 Hz, 2H), 7.11 (d, *J* = 7.8 Hz, 2H), 6.46 (d, *J* = 1.2 Hz, 1H), 5.03 (hept, *J* = 6.3 Hz, 1H), 3.05 (t, *J* = 4.7 Hz, 1H), 2.33 (s, 3H), 2.27 (ddd, *J* = 13.8, 8.7, 6.6 Hz, 1H), 1.98 (dt, *J* = 14.1, 5.5 Hz, 1H), 1.84 (ddd, *J* = 13.5, 10.1, 5.2 Hz, 1H), 1.67 – 1.59 (m, 2H), 1.55-1.47 (m, 3H), 1.20 (d, *J* = 6.3 Hz, 3H), 1.15 (d, *J* = 6.2 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 175.0, 148.1, 137.5, 131.0, 130.6, 129.0, 125.1, 67.5, 52.5, 42.9, 26.2, 24.0, 21.7, 21.4, 17.8, 17.5.

FTIR (Neat film NaCl): 2979, 2935, 2865, 1716, 1271, 1241, 1108, 809.

HR-MS (FD-MS) m/z: [M]+ Calc'd for $C_{19}H_{24}O_2$ 284.1771; Found 284.1775.



ethyl 8-(m-tolyl)bicyclo[4.2.0]oct-7-ene-1-carboxylate (145).

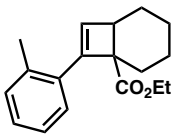
Prepared from 0.050 mmol vinyl triflate **S65** according to General Procedure 10. The crude reaction was purified via flash column chromatography (hexanes:diethyl ether = 10:1) to afford product **145** as a pale yellow oil (9 mg, 67% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 – 7.12 (m, 3H), 7.05 (d, *J* = 7.4 Hz, 1H), 6.53 (d, *J* = 1.3 Hz, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.06 (t, *J* = 4.7 Hz, 1H), 2.38 – 2.25 (m, 4H), 2.00 (dt, *J* = 14.0, 5.4 Hz, 1H), 1.88 – 1.77 (m, 1H), 1.69 – 1.58 (m, 2H), 1.53 – 1.44 (m, 2H), 1.34 – 1.26 (m, 1H), 1.19 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 175.83, 148.48, 138.24, 133.49, 132.42, 128.93, 128.62, 125.97, 122.54, 60.75, 52.68, 43.39, 26.56, 24.34, 21.79, 18.07, 17.77, 14.57.

FTIR (Neat film NaCl): 2930, 2861, 1719, 1456, 1234, 1158, 1051, 783.

HR-MS (FD-MS) m/z: [M]+ Calc'd for $C_{18}H_{22}O_2$ 270.1614; Found 270.1620.



ethyl 8-(o-tolyl)bicyclo[4.2.0]oct-7-ene-1-carboxylate (146).

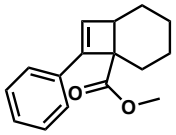
Prepared from 0.050 mmol vinyl triflate **S66** according to General Procedure 10. The crude reaction was purified via flash column chromatography (hexanes:diethyl ether = 10:1) to afford product **146** as a pale yellow oil (8 mg, 59% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 – 7.10 (m, 3H), 7.08 – 7.05 (m, 1H), 6.42 (d, *J* = 1.3 Hz, 1H), 4.16 (qd, *J* = 7.1, 0.8 Hz, 2H), 3.05 (t, *J* = 4.4 Hz, 1H), 2.44 (s, 3H), 2.41 – 2.25 (m, 1H), 2.01 – 1.93 (m, 1H), 1.92 – 1.75 (m, 1H), 1.71 – 1.58 (m, 2H), 1.53 – 1.46 (m, 2H), 1.29 – 1.23 (m, 1H), 1.19 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 176.1, 148.4, 137.9, 137.4, 132.1, 131.2, 127.6, 126.9, 126.0, 60.8, 53.6, 43.9, 26.4, 24.5, 22.6, 18.2, 17.9, 14.6.

FTIR (Neat film NaCl): 3065, 2935, 2864, 1719, 1489, 1460, 1365, 1250, 1235, 1161, 1116, 1095, 1065, 1049, 760, 722.

HR-MS (FD-MS) m/z: [M]+ Calc'd for $C_{18}H_{22}O_2$ 270.1614; Found 270.1614.



methyl 8-phenylbicyclo[4.2.0]oct-7-ene-1-carboxylate (147).

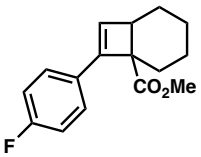
Prepared from 0.050 mmol vinyl triflate **S67** according to General Procedure 10. The crude reaction was purified via flash column chromatography (hexanes:diethyl ether = 10:1) to afford product **147** as a pale yellow oil (9 mg, 74% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.22 (m, 4H), 7.18 – 7.14 (m, 1H), 6.49 (d, *J* = 1.3 Hz, 1H), 3.61 (s, 3H), 3.06 – 2.95 (m, 1H), 2.24 (ddd, *J* = 15.4, 8.9, 5.5 Hz, 1H), 1.94 (dt, *J* = 14.1, 5.5 Hz, 1H), 1.86 – 1.72 (m, 1H), 1.64 – 1.51 (m, 2H), 1.44 (ddd, *J* = 8.1, 5.7, 3.7 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 176.3, 148.3, 133.5, 132.7, 128.8, 128.2, 125.3, 52.6, 52.3, 43.5, 26.6, 24.3, 18.0, 17.7.

FTIR (Neat film NaCl): 2981, 2945, 2865, 1723, 1447, 1433, 1270, 1237, 1162, 1064, 1052, 761, 695.

HR-MS (FD-MS) m/z: [M]+ Calc'd for $C_{16}H_{18}O_2$ 242.1301; Found 242.1303.



methyl 8-(4-fluorophenyl)bicyclo[4.2.0]oct-7-ene-1-carboxylate (148).

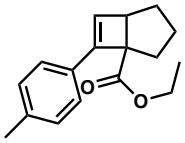
Prepared from 0.050 mmol vinyl triflate **S68** according to General Procedure 10. The crude reaction was purified via flash column chromatography (hexanes:diethyl ether = 10:1) to afford product **148** as a pale yellow oil (8 mg, 61% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.29 (m, 2H), 7.04 – 6.96 (m, 2H), 6.48 (d, J = 1.2 Hz, 1H), 3.69 (s, 3H), 3.08 (t, J = 4.7 Hz, 1H), 2.29 (ddd, J = 14.9, 10.2, 5.2 Hz, 1H), 1.98 (dt, J = 13.8, 5.1 Hz, 1H), 1.85 (ddt, J = 15.7, 10.6, 5.2 Hz, 1H), 1.71 – 1.60 (m, 2H), 1.54 – 1.45 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 176.18, 162.71 (d, $^{1}J_{C–F}$ = 262.1 Hz), 147.24, 132.08 (d, J = 2.6 Hz), 129.83 (d, J = 3.4 Hz), 127.17 (d, J = 8.1 Hz), 115.80 (d, $^{2}J_{C–F}$ = 21.5 Hz), 52.64, 52.31, 43.43, 26.58, 24.22, 17.96, 17.66.

FTIR (Neat film NaCl): 2944, 2906, 2866, 1723, 1681, 1661, 1506, 1271, 1232, 1158, 831, 818.

HR-MS (FD-MS) m/z: [M]+ Calc'd for $C_{16}H_{17}O_2F$ 260.1207; Found 260.1214.



ethyl 7-(p-tolyl)bicyclo[3.2.0]hept-6-ene-1-carboxylate (149).

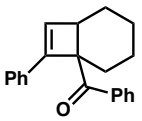
Prepared from 0.050 mmol vinyl triflate **S69** according to General Procedure 10. The crude reaction was purified via flash column chromatography (hexanes:diethyl ether = 10:1) to afford product **149** as a pale yellow oil (7 mg, 55% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.0 Hz, 2H), 7.12 (d, *J* = 7.9 Hz, 2H), 6.25 (d, *J* = 1.0 Hz, 1H), 4.27 – 4.11 (m, 2H), 3.29 (d, *J* = 7.0 Hz, 1H), 2.34 (s, 3H), 1.93 (ddd, *J* = 16.1, 12.4, 6.5 Hz, 2H), 1.81 (dt, *J* = 12.2, 6.2 Hz, 1H), 1.70 (ddt, *J* = 18.0, 12.0, 6.0 Hz, 1H), 1.58 (d, *J* = 6.0 Hz, 1H), 1.52 – 1.38 (m, 1H), 1.21 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 175.0, 144.3, 137.8, 129.6, 129.1, 127.8, 125.0, 60.5, 60.2, 50.3, 27.8, 26.3, 24.3, 21.4, 14.3.

FTIR (Neat film NaCl): 2935, 2855, 1720, 1508, 1445, 1366, 1300, 1259, 1145, 1083, 1034, 824, 804.

HR-MS (ESI-MS) m/z: [M]+ Calc'd for $C_{17}H_{20}O_2$ 256.1458; Found 256.1460.



phenyl(8-phenylbicyclo[4.2.0]oct-7-en-1-yl)methanone (150).

Prepared from 0.050 mmol vinyl triflate **S70** according to General Procedure 10. The crude reaction was purified via flash column chromatography (hexanes:diethyl ether = 10:1) to afford product **150** as a pale yellow oil (5 mg, 35% yield).

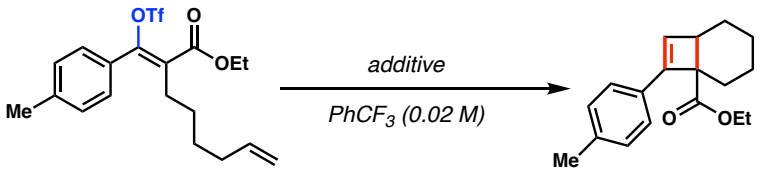
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 – 7.83 (m, 2H), 7.53 – 7.47 (m, 1H), 7.46 – 7.33 (m, 6H), 7.32 (d, *J* = 1.4 Hz, 1H), 6.64 (d, *J* = 1.2 Hz, 1H), 3.17 (t, *J* = 4.5 Hz, 1H), 2.48 (dt, *J*

= 14.7, 7.5 Hz, 1H), 2.11 (dt, *J* = 14.4, 5.6 Hz, 1H), 2.01 (ddt, *J* = 13.9, 10.8, 5.3 Hz, 1H), 1.91 – 1.82 (m, 1H), 1.72 (ddd, *J* = 17.5, 11.5, 5.6 Hz, 1H), 1.64 (dt, *J* = 12.0, 6.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 205.0, 150.2, 138.1, 133.8, 132.0, 132.0, 128.9, 128.5, 128.4, 128.3, 125.8, 59.0, 43.8, 26.7, 24.7, 18.3, 18.1.

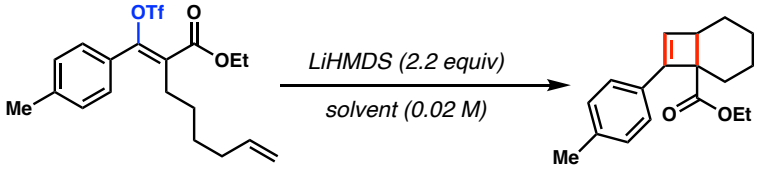
FTIR (Neat film NaCl): 3057, 2933, 2862, 1667, 1597, 1577, 1507, 1490, 1446, 1423, 1238, 1219, 1028, 758, 695.

HR-MS (FD-MS) m/z: [M]+ Calc'd for $C_{21}H_{20}O$ 288.1509; Found 288.1507.

3.7.4 Reaction optimization



Lewis acid screen	yield (%)
2.2 equiv LiH	no reaction
2.2 equiv LiO^{t}Bu	no reaction
2.2 equiv LDA	n.d.
2.2 equiv NaHMDS	47
2.2 equiv KHMDS	n.d.
2.2 equiv H-HMDS	no reaction



solvent	yield (%)

benzene	32 + Friedel-Crafts product
chloroform	n.d.
1,2-dichloroethane	60
tetrahydrofuran	n.d.
acetonitrile	n.d.
diethyl ether	36
dichloromethane	39

3.8 REFERENCES

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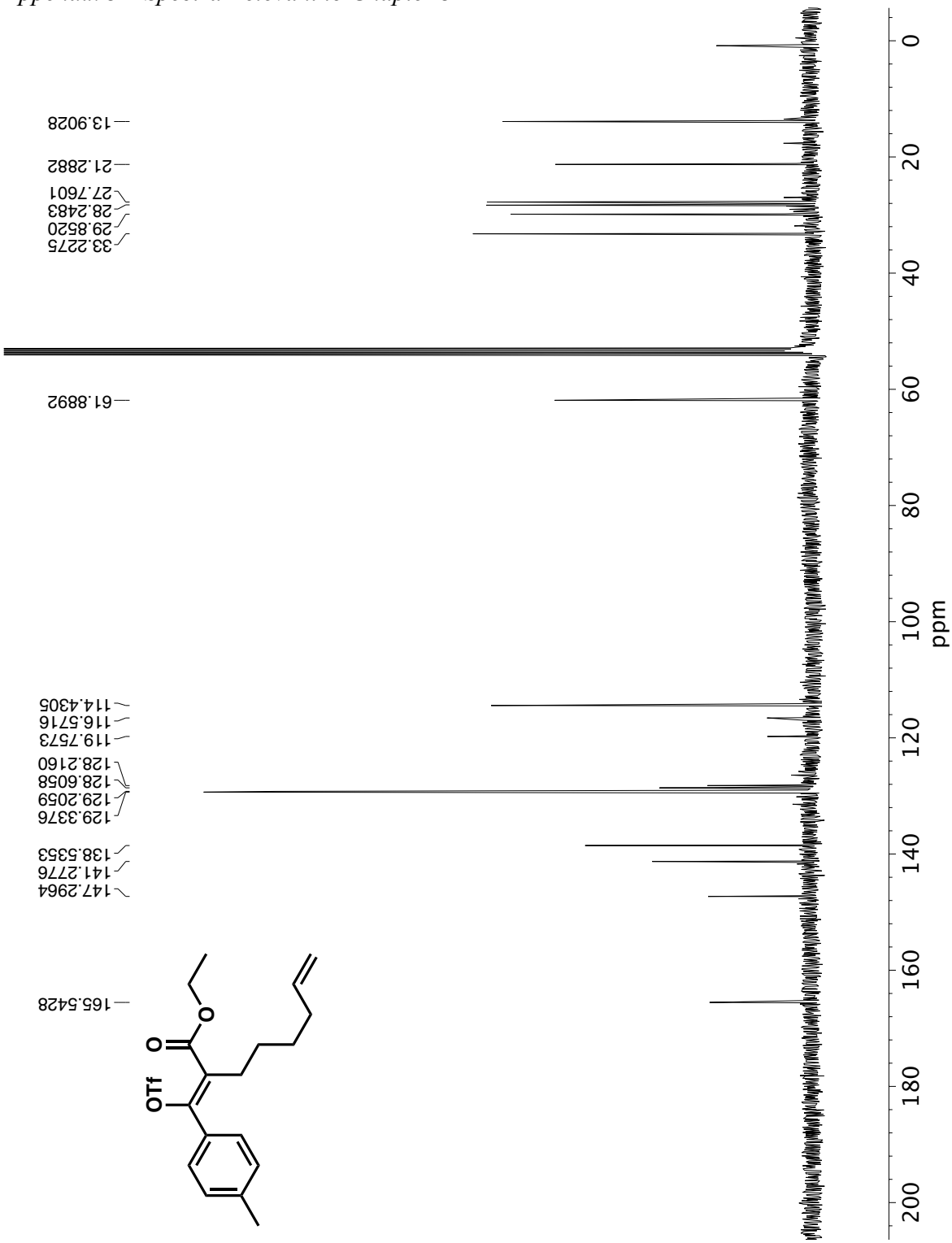
APPENDIX 3

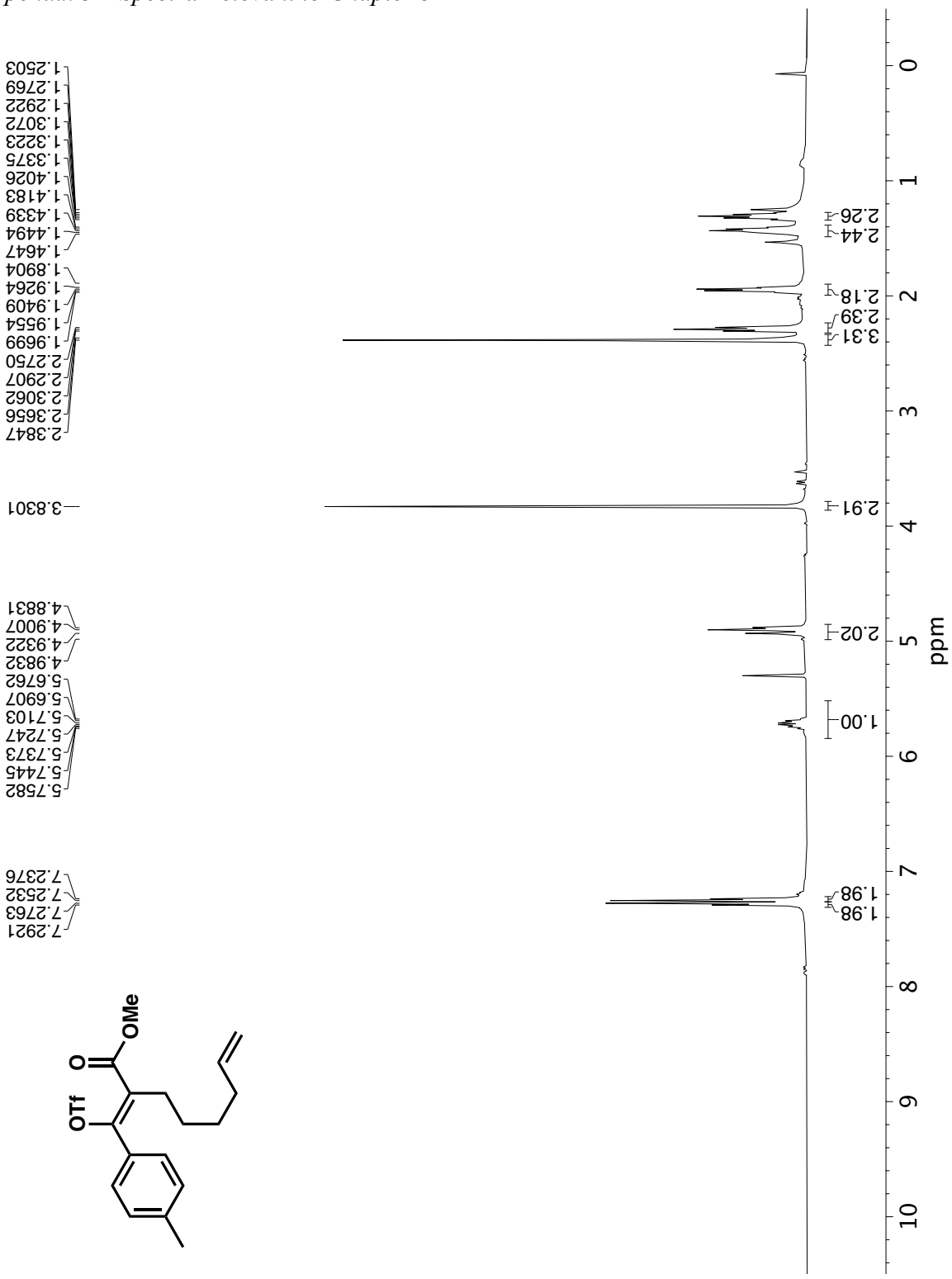
Spectra Relevant to Chapter 3: Lithium-mediated Selective [2+2] Cycloadditions via Vinyl Carbocations

^{1}H NMR (400 MHz, CD_2Cl_2) of compound **140**.

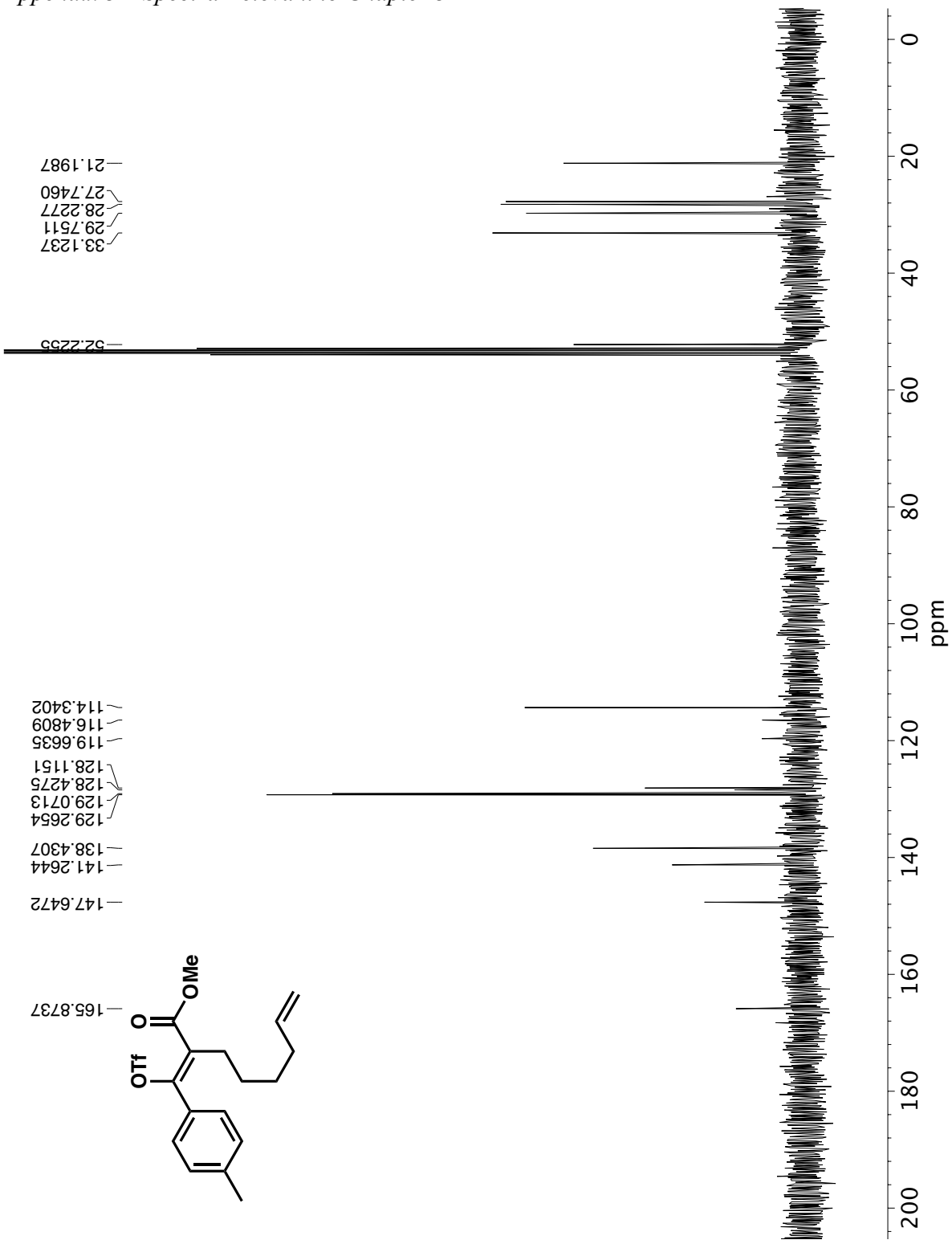


^{13}C NMR (101 MHz, CD_2Cl_2) of compound **140**.

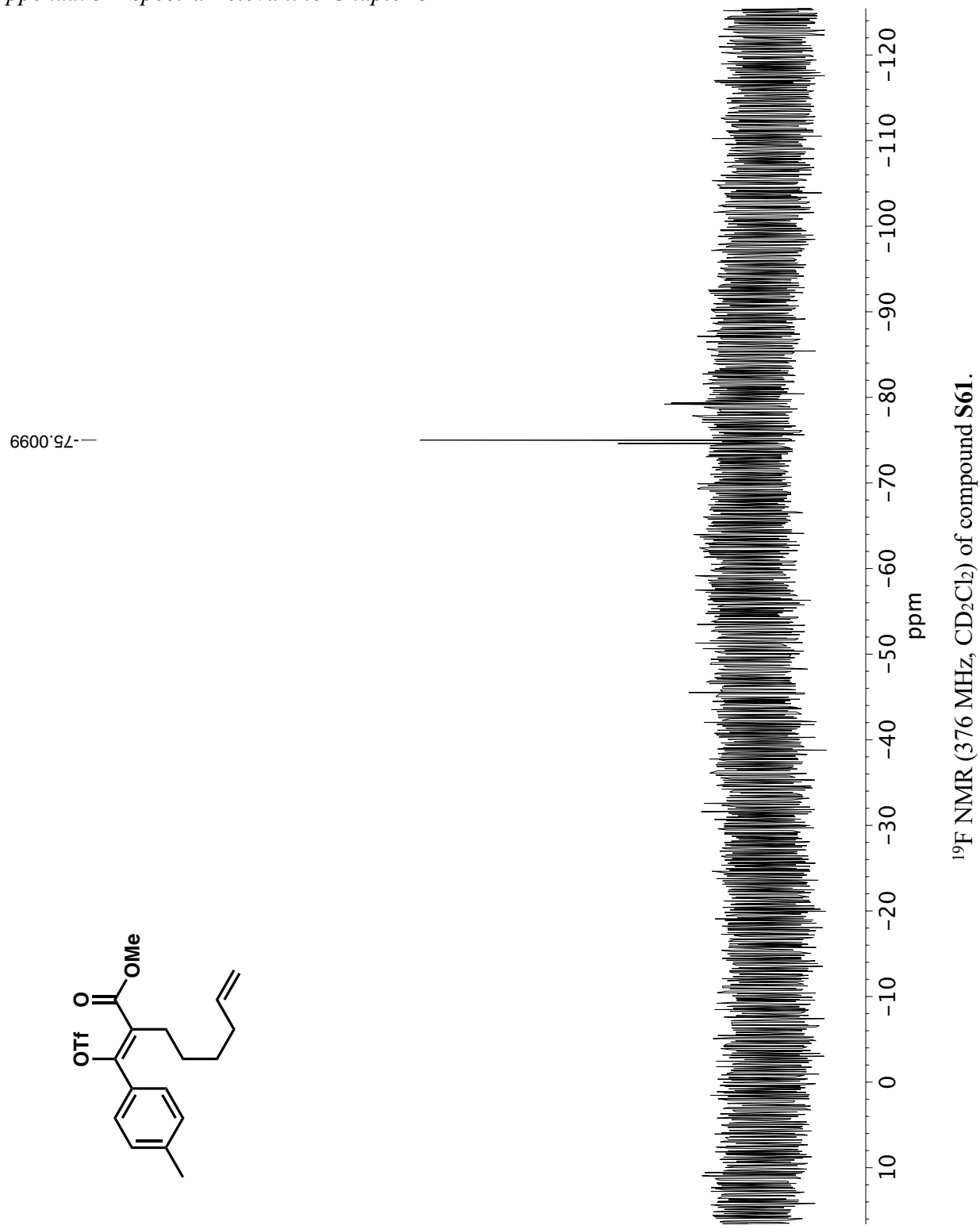
^{19}F NMR (376 MHz, CD_2Cl_2) of compound **140**.



^{1}H NMR (500 MHz, CD_2Cl_2) of compound **S61**.

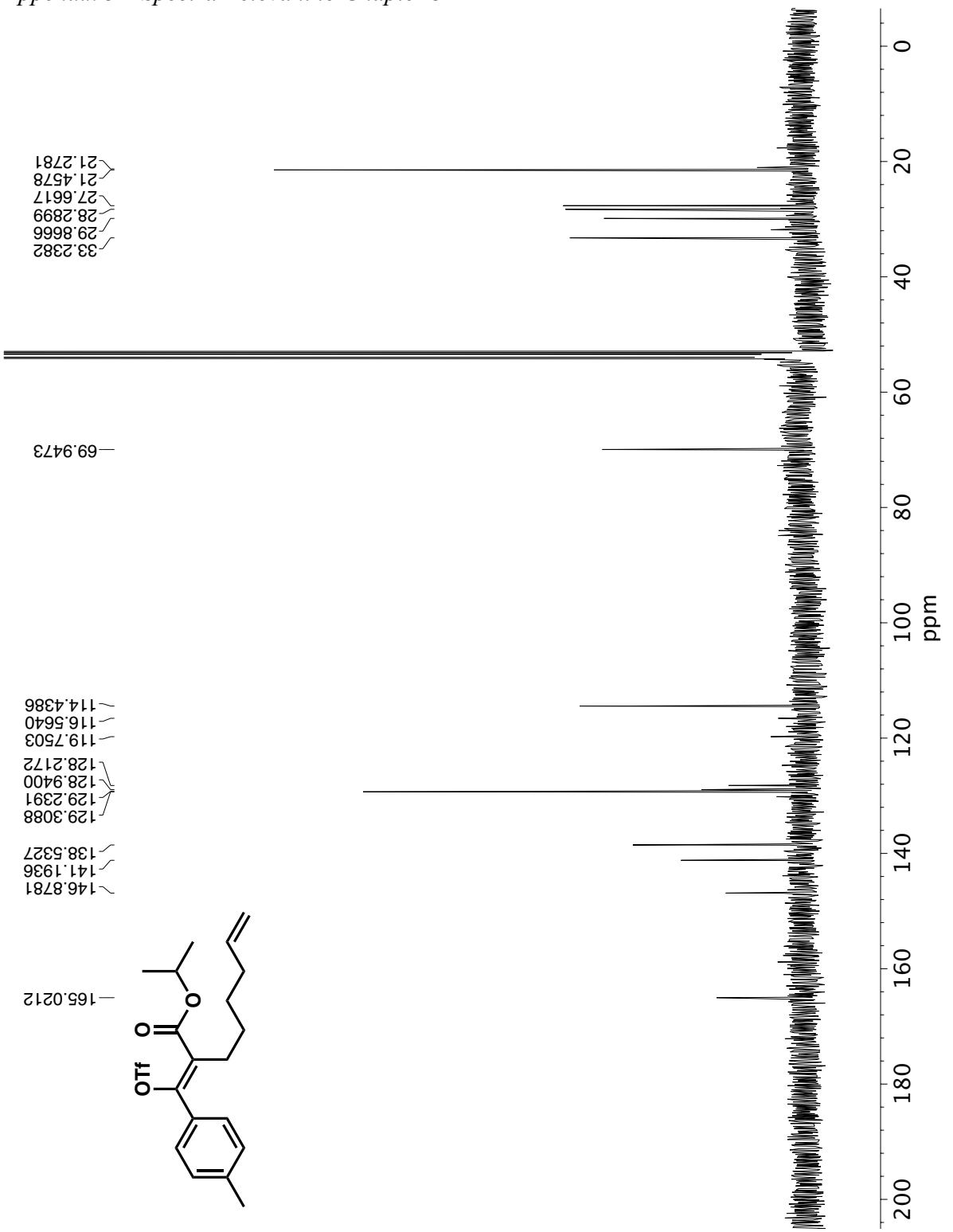


^{13}C NMR (101 MHz, CD_2Cl_2) of compound **S61.**

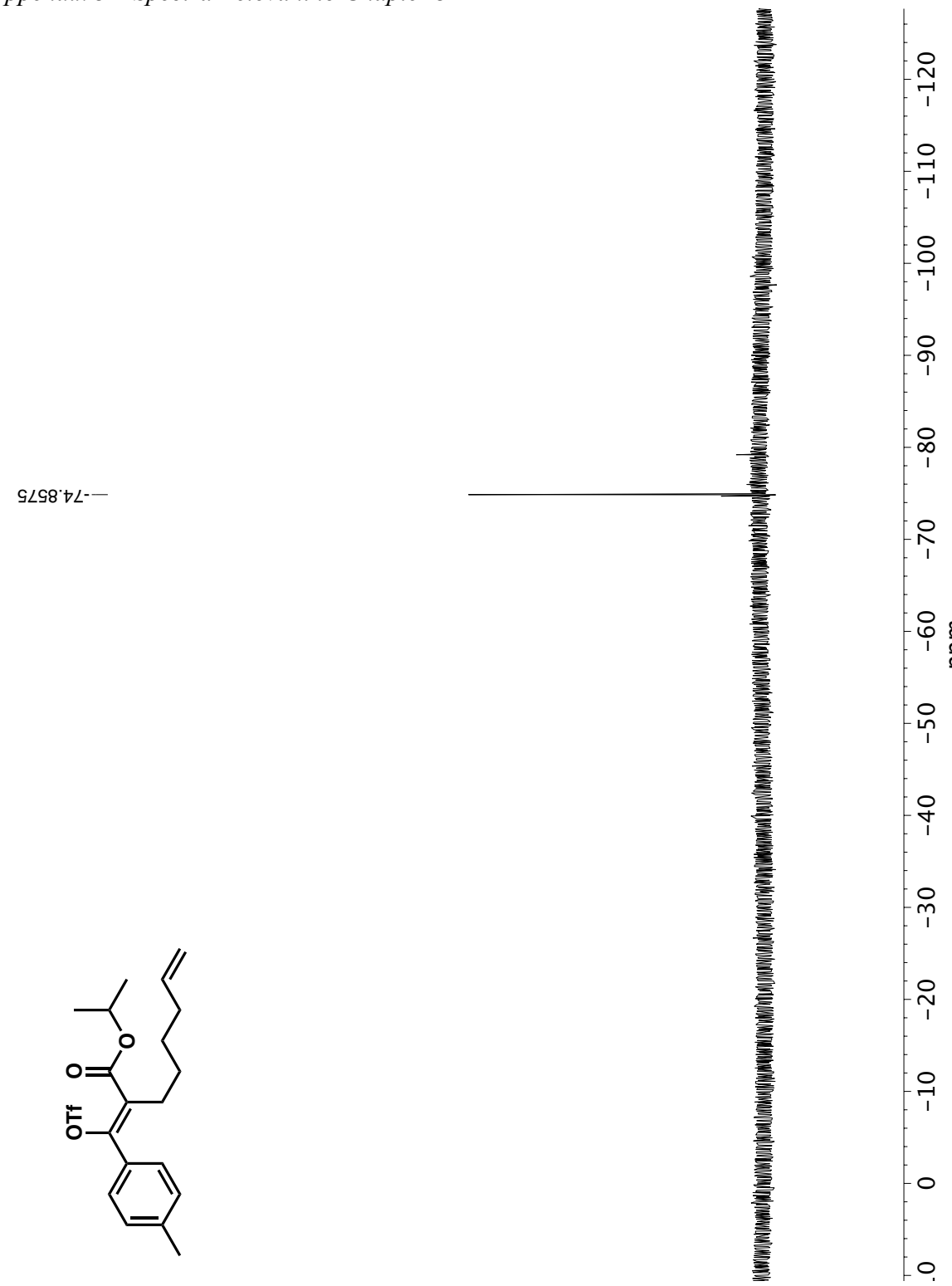


^{19}F NMR (376 MHz, CD_2Cl_2) of compound **S61**.

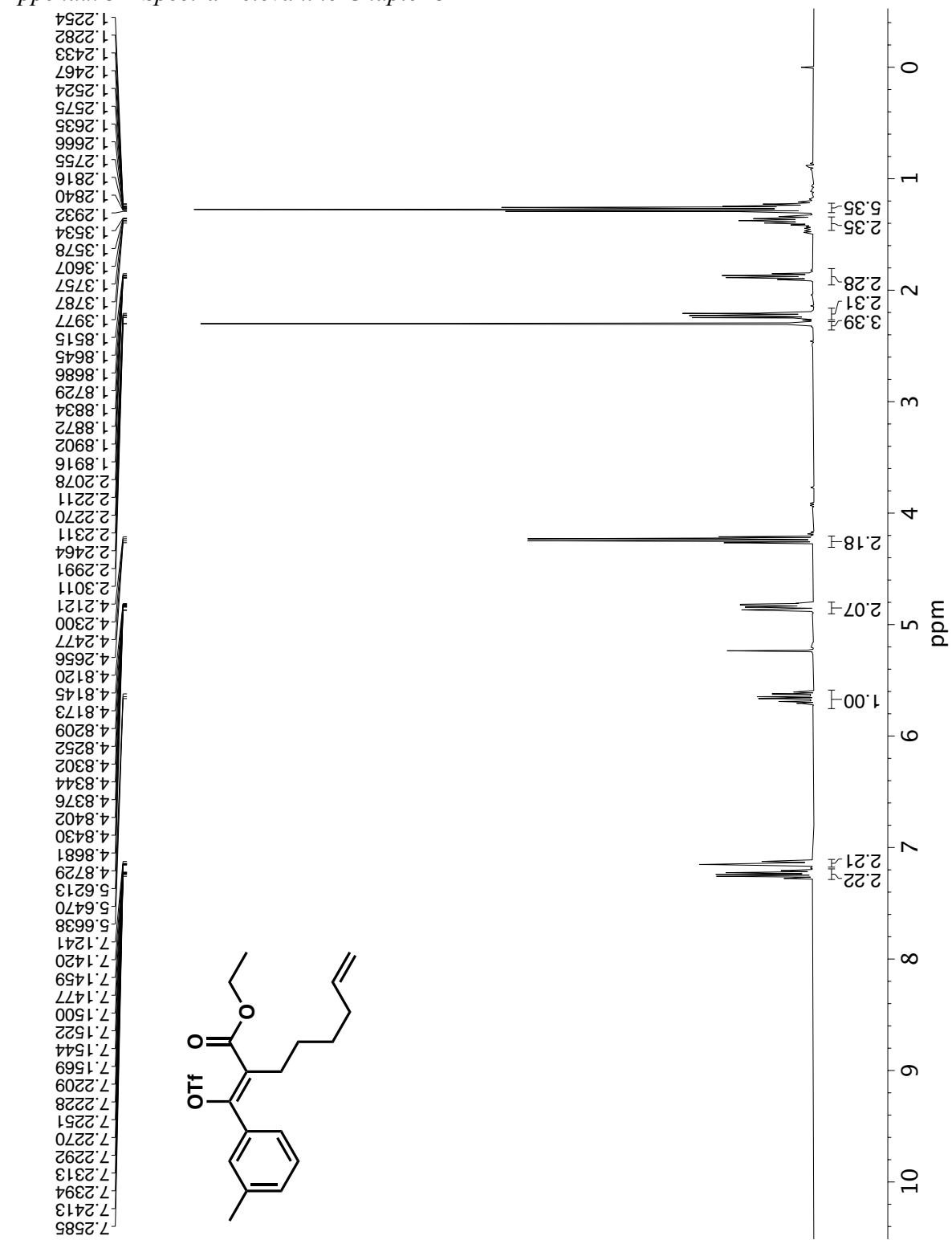
^{1}H NMR (400 MHz, CD_2Cl_2) of compound **S64**.



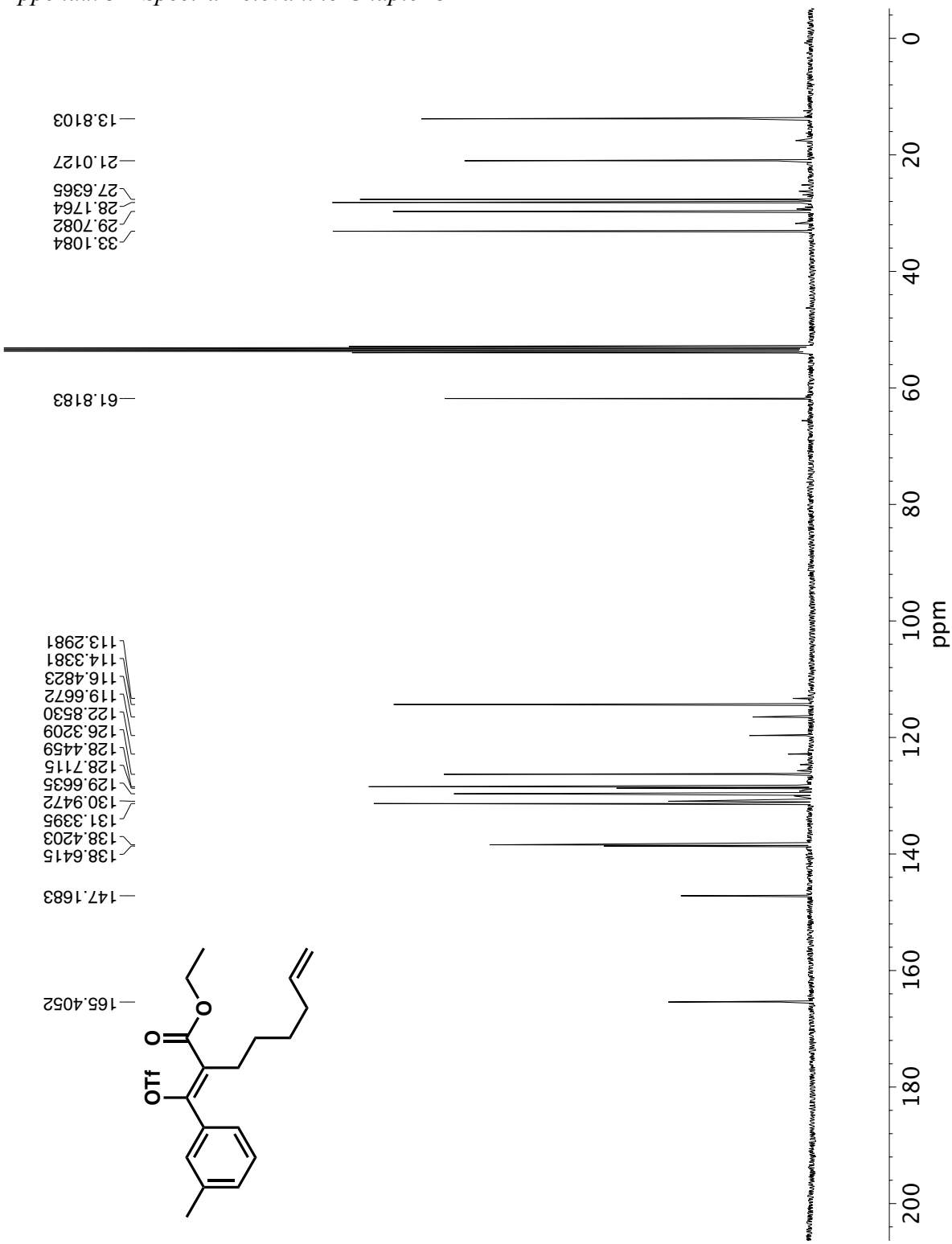
^{13}C NMR (101 MHz, CD_2Cl_2) of compound **S64**.



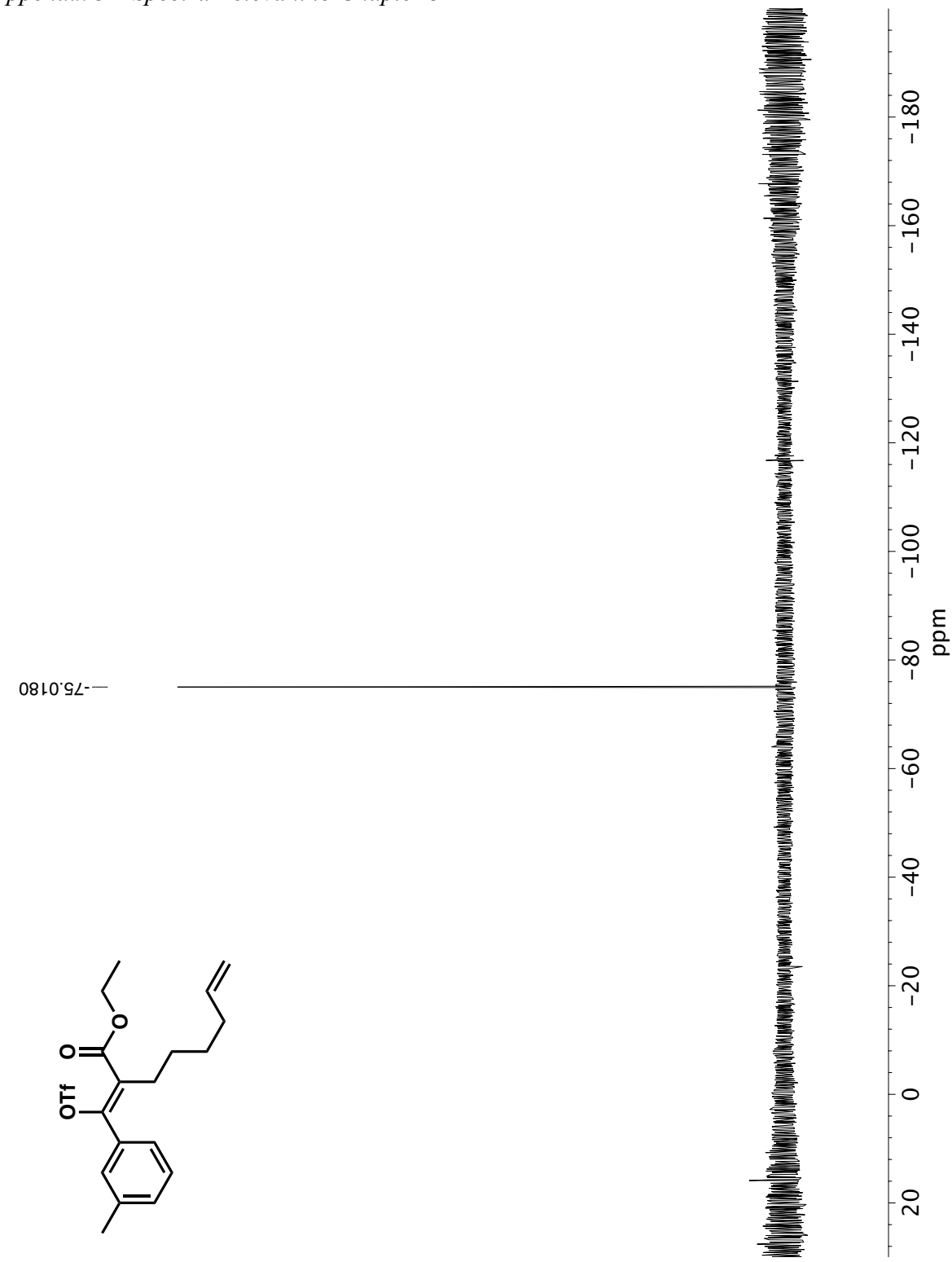
^{19}F NMR (376 MHz, CD_2Cl_2) of compound **S64**.



^{1}H NMR (400 MHz, CD_2Cl_2) of compound **S65**.

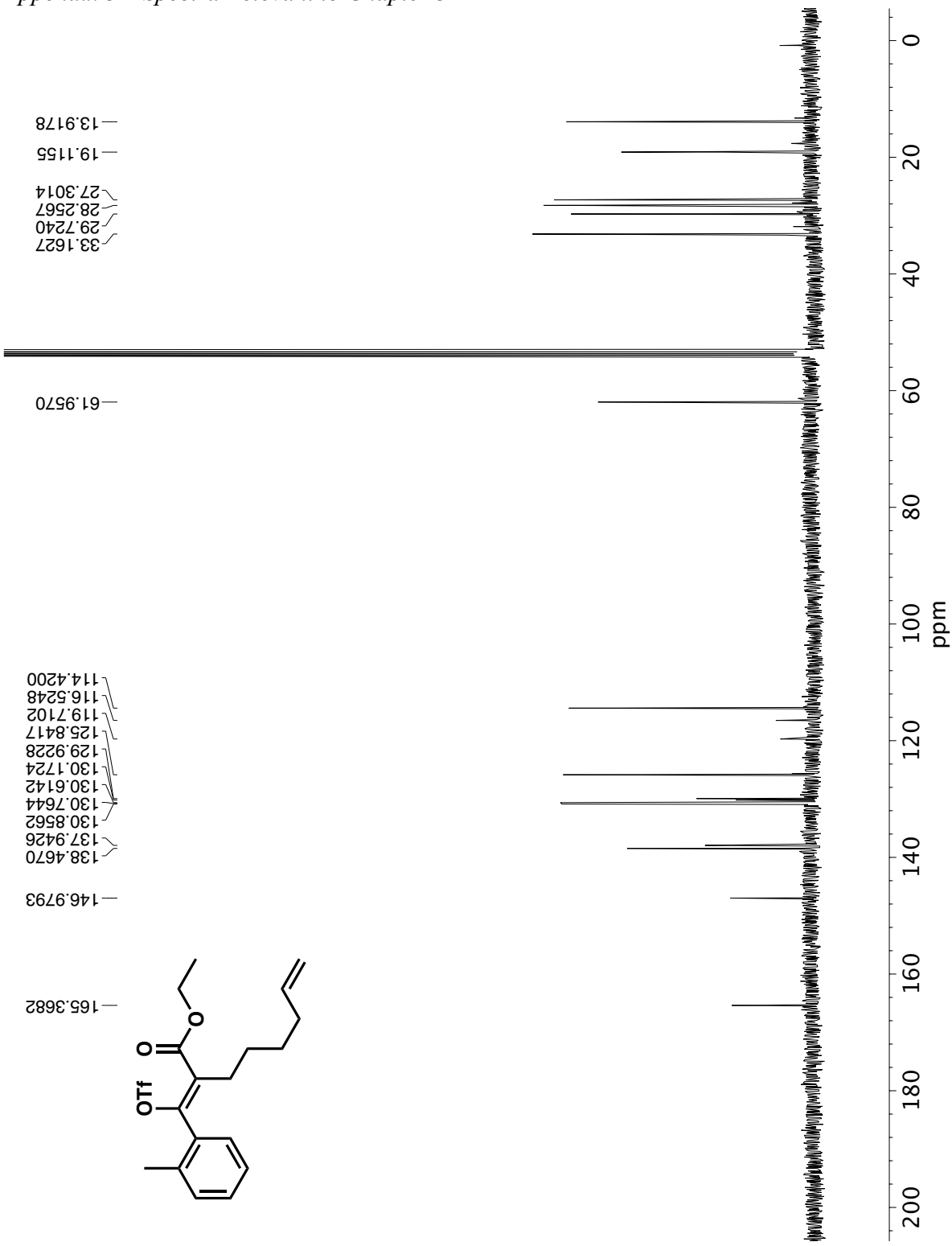


^{13}C NMR (101 MHz, CD_2Cl_2) of compound **S65**.



^{19}F NMR (282 MHz, CD_2Cl_2) of compound **S65**.

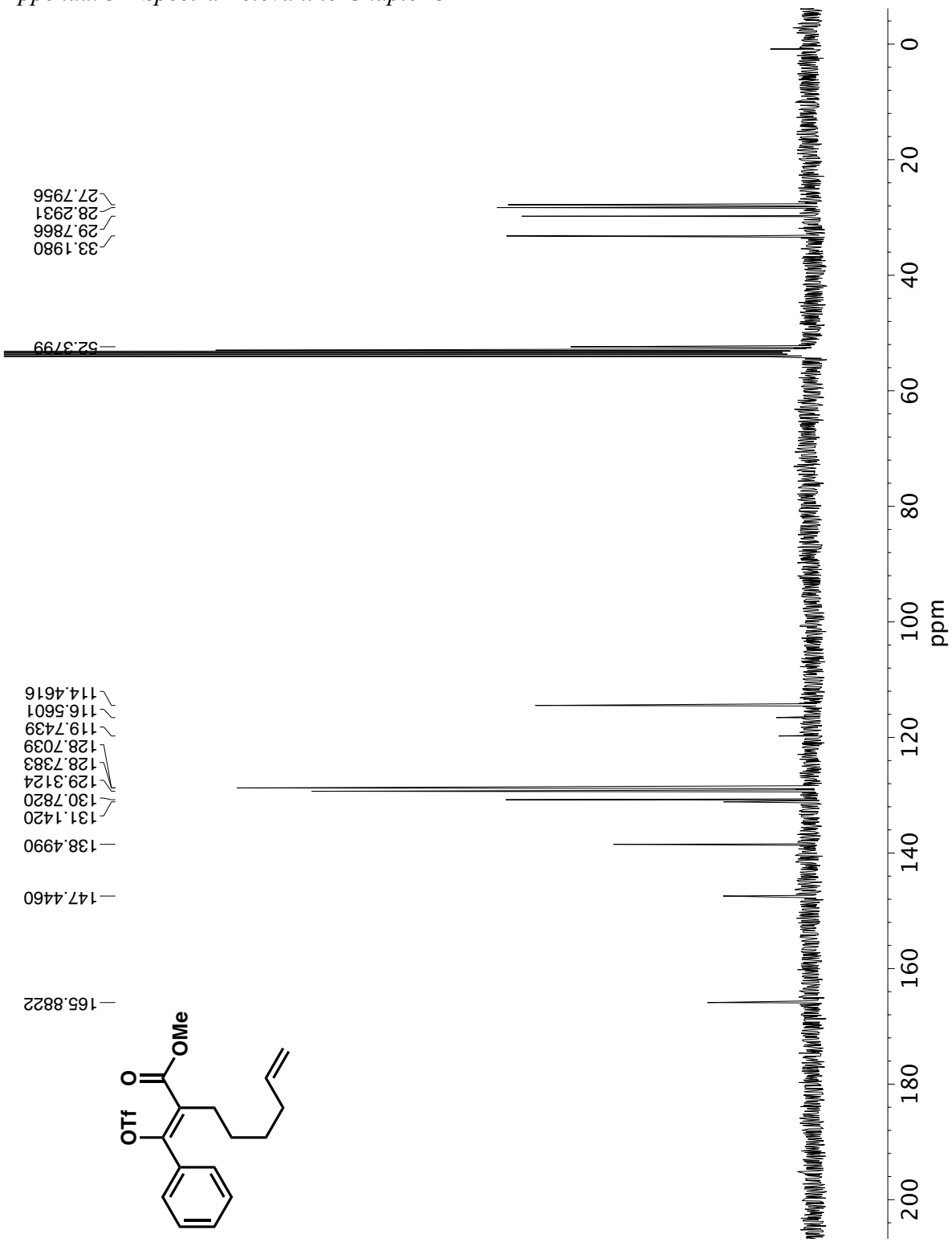
^{1}H NMR (400 MHz, CD_2Cl_2) of compound **S66**.



^{13}C NMR (101 MHz, CD_2Cl_2) of compound **S66**.

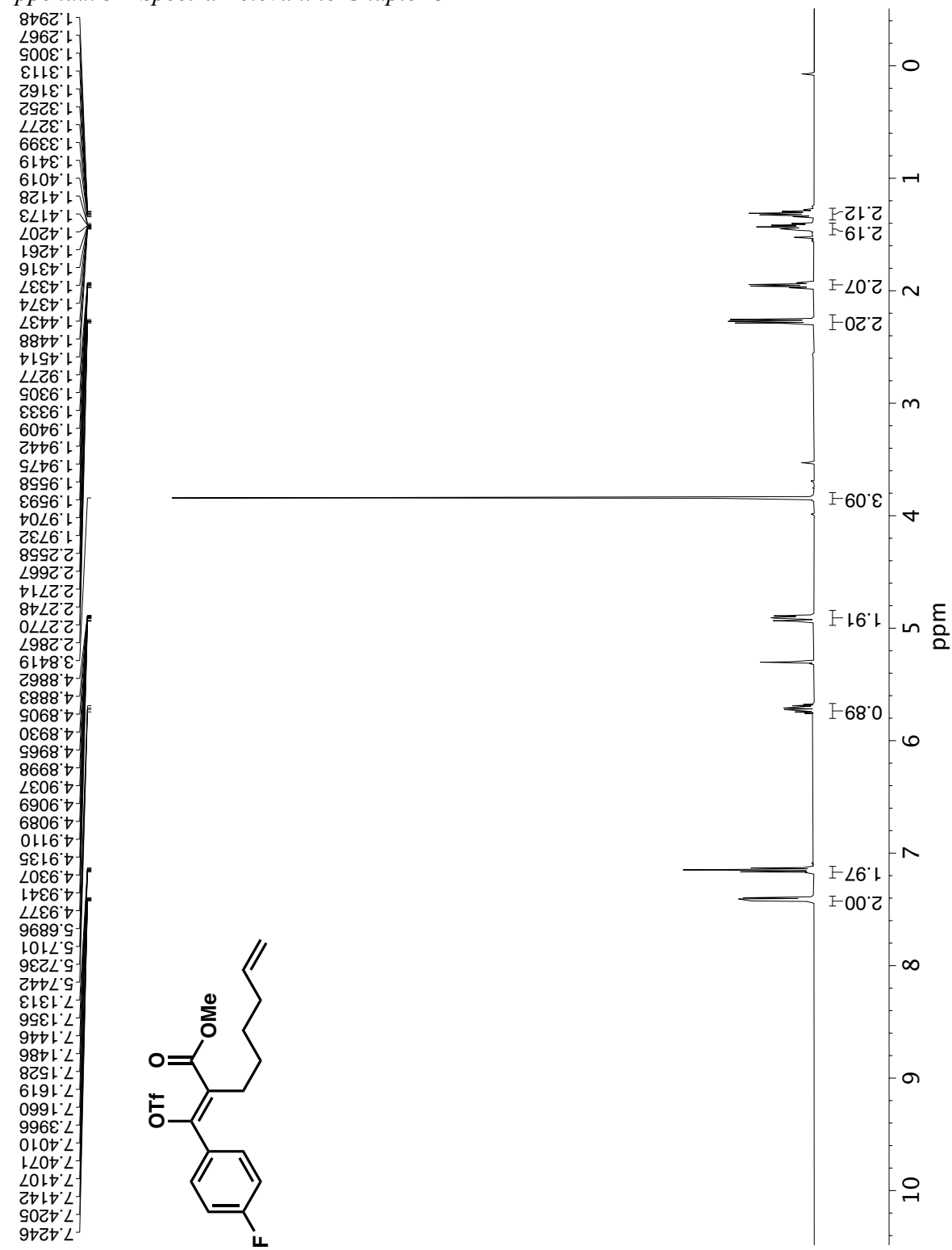
^{19}F NMR (376 MHz, CD_2Cl_2) of compound **S66**.

^{1}H NMR (400 MHz, CD_2Cl_2) of compound **S67**.

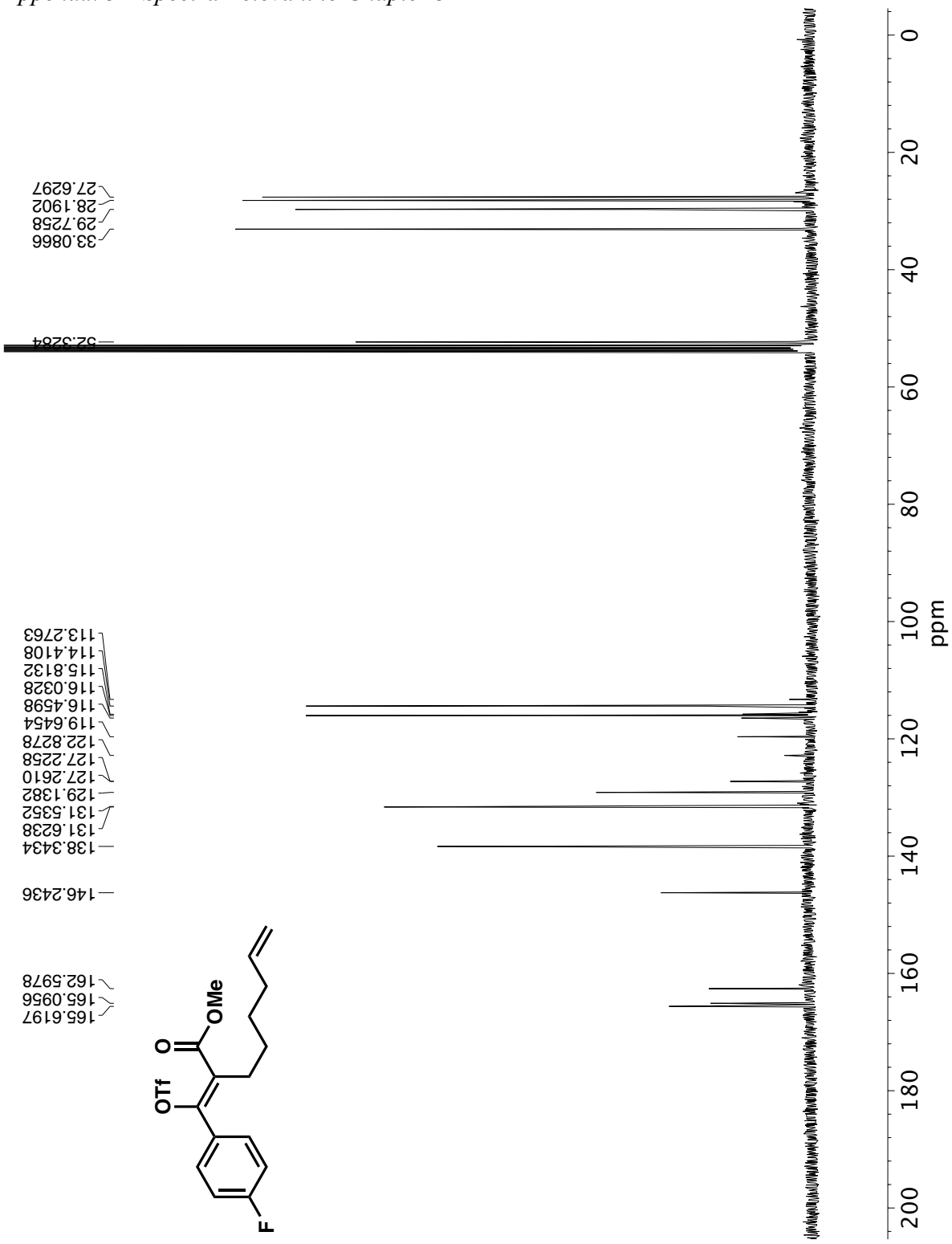


^{13}C NMR (101 MHz, CD_2Cl_2) of compound **S67**.

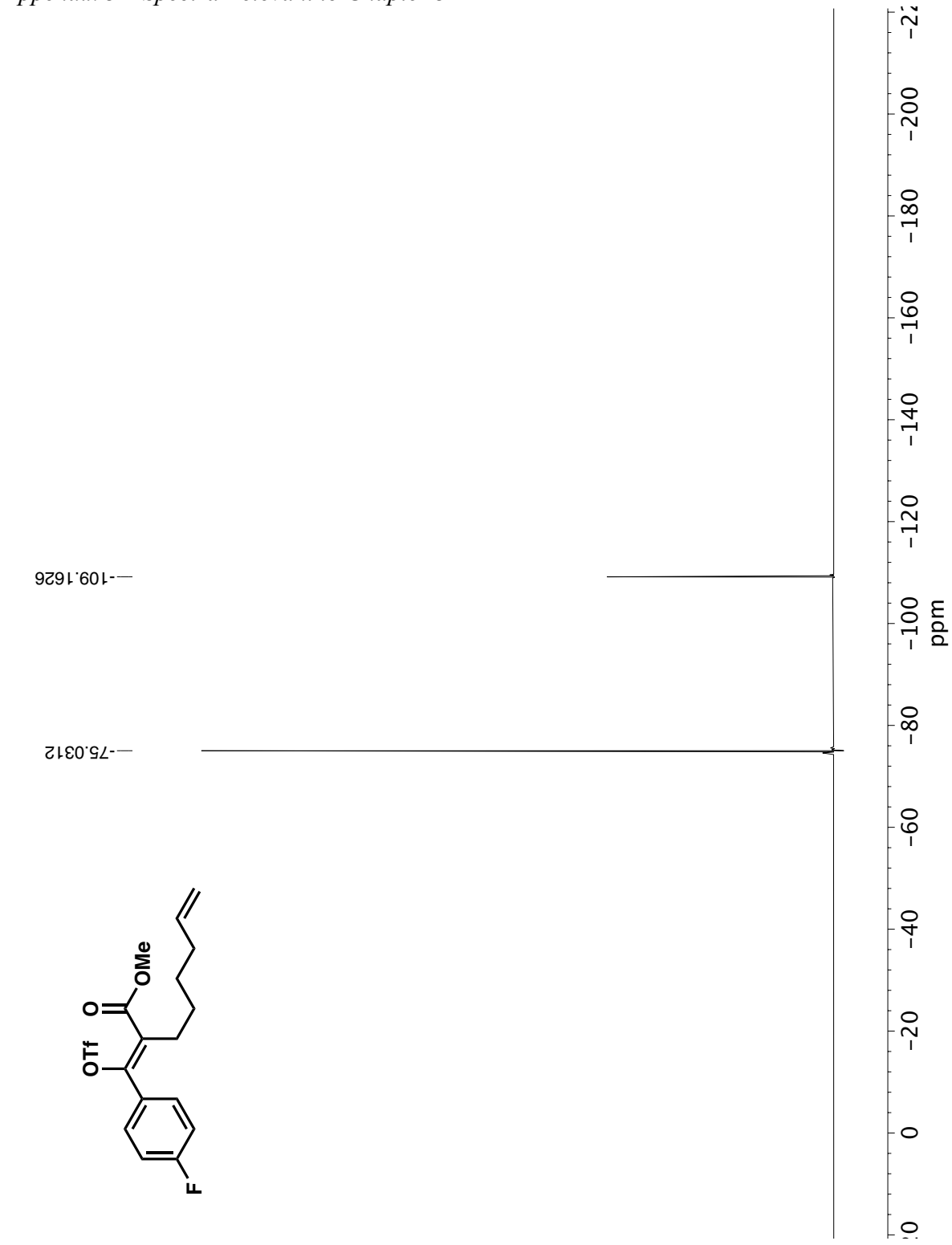
^{19}F NMR (376 MHz, CD_2Cl_2) of compound **S67**.



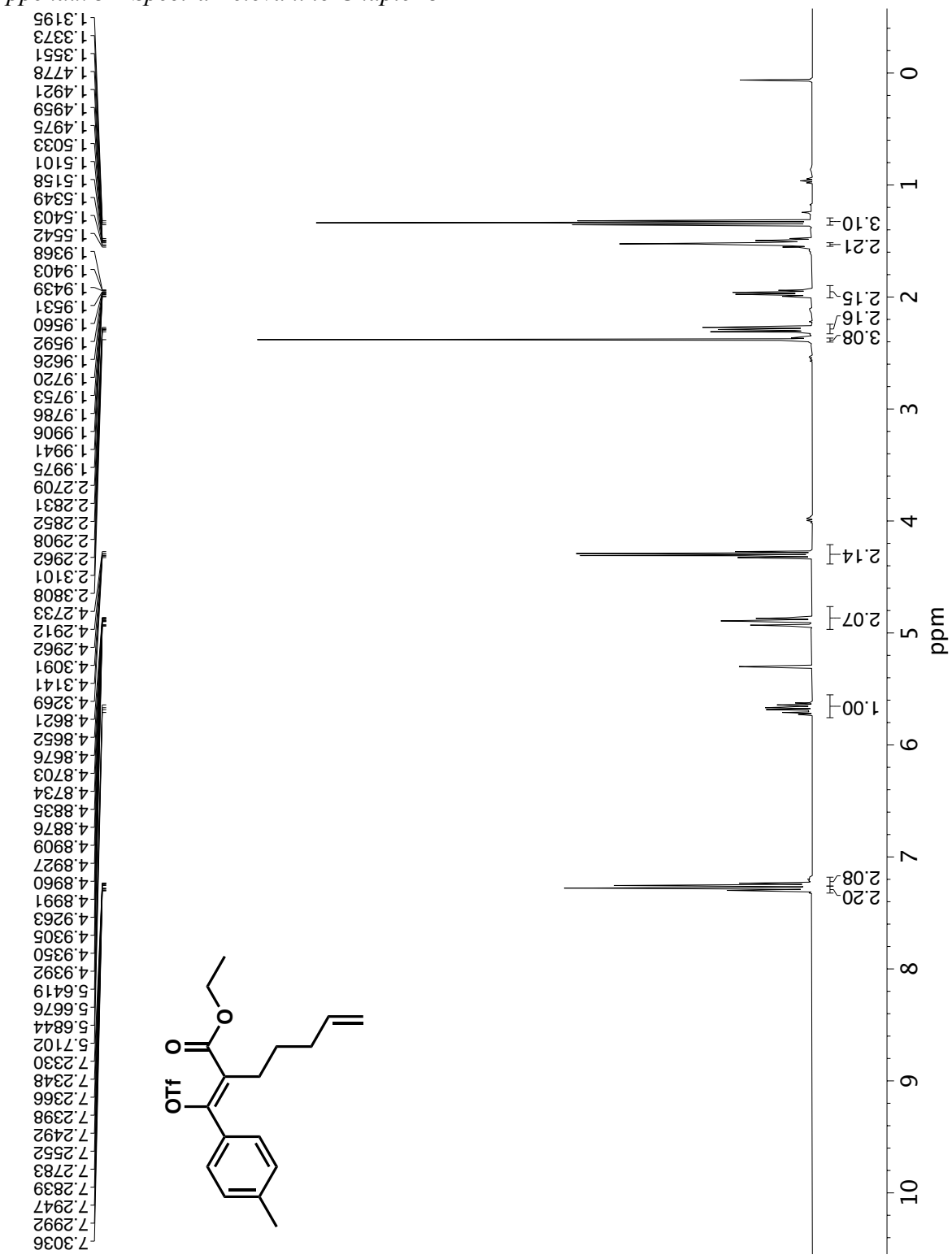
^{1}H NMR (500 MHz, CD_2Cl_2) of compound **S68**.



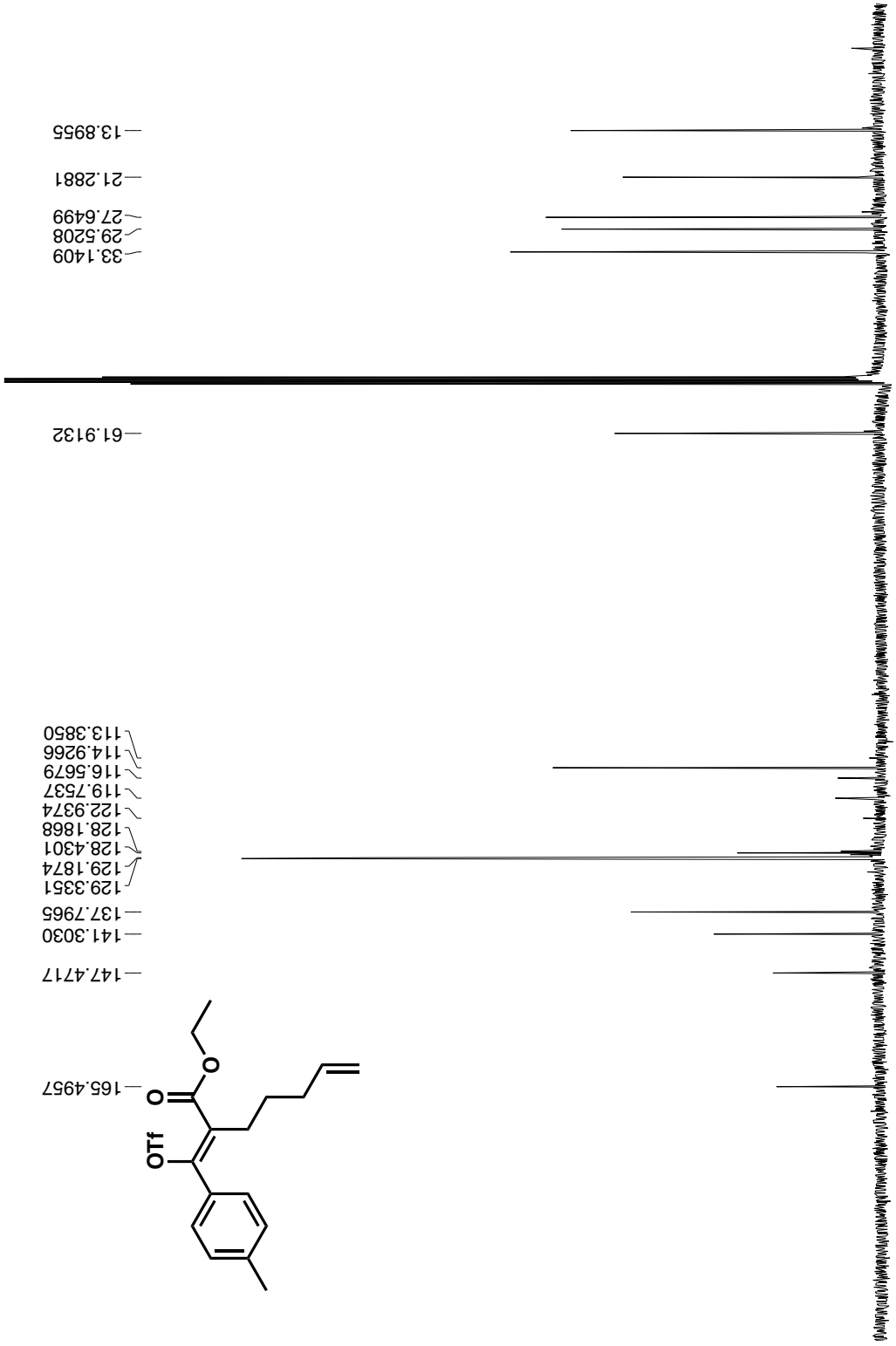
^{13}C NMR (101 MHz, CD_2Cl_2) of compound **S68**.



^{19}F NMR (376 MHz, CD_2Cl_2) of compound **S68**.



^{1}H NMR (400 MHz, CD_2Cl_2) of compound **S69**.

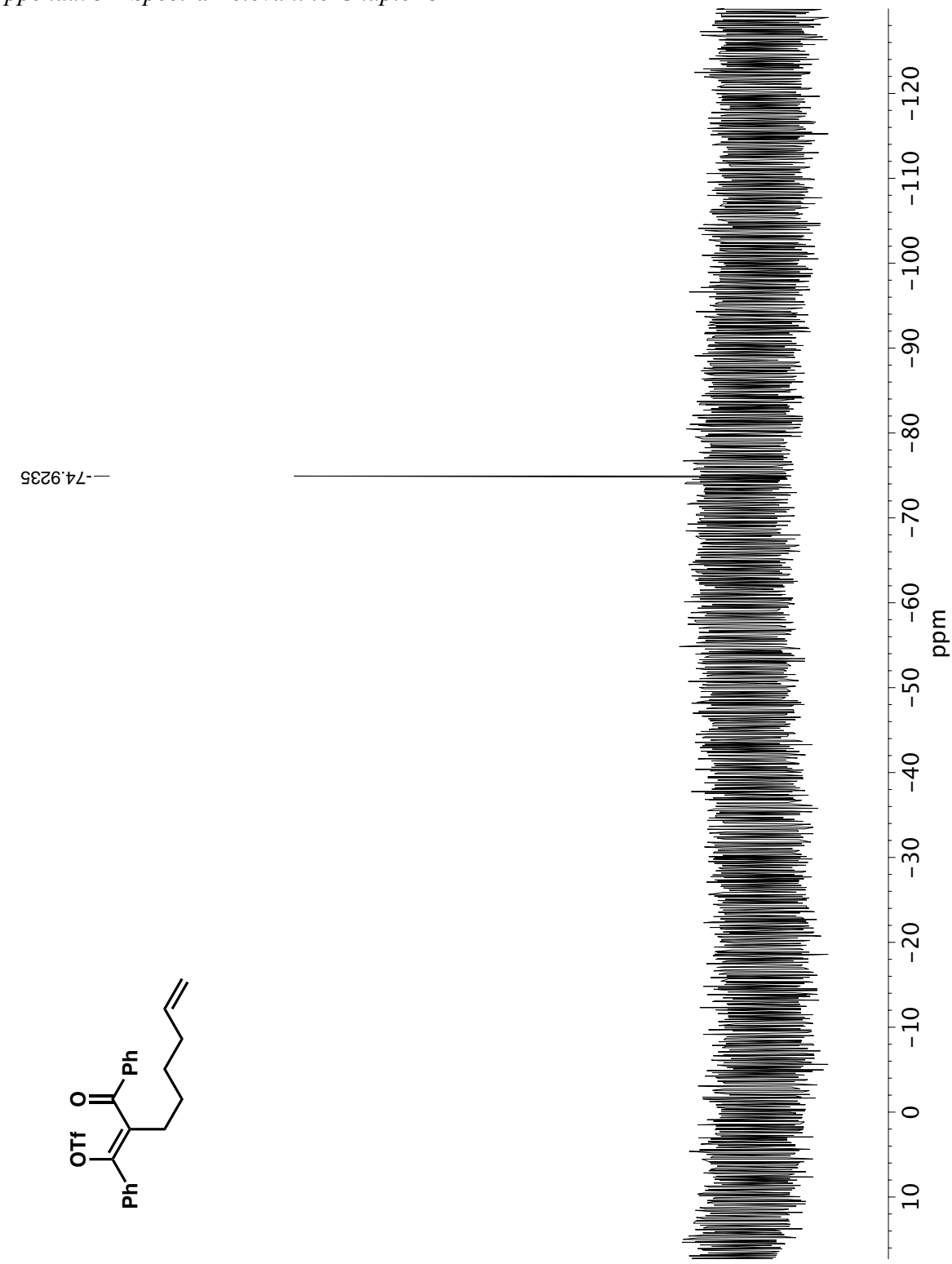


^{13}C NMR (101 MHz, CD_2Cl_2) of compound **S69**.

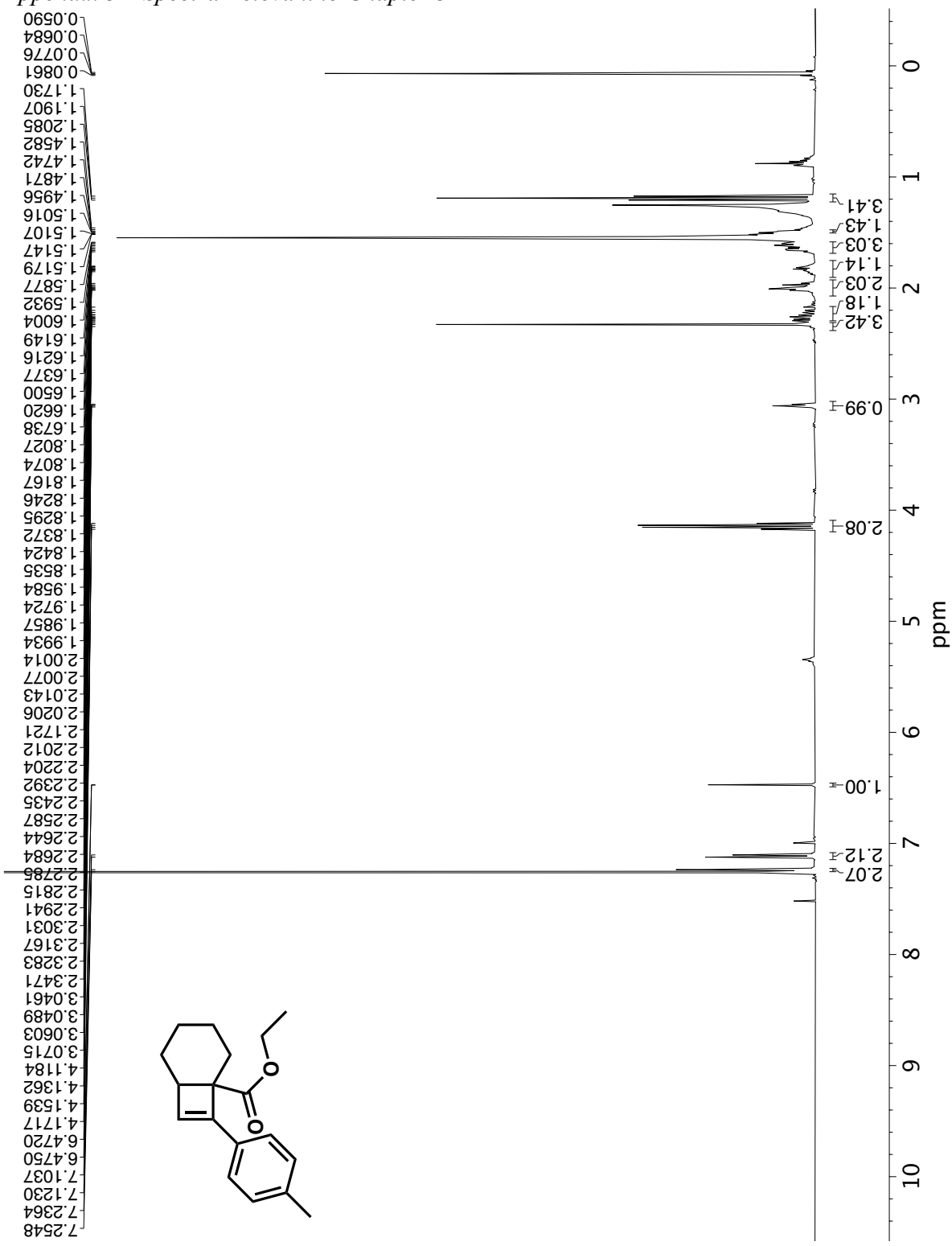
^{19}F NMR (376 MHz, CD_2Cl_2) of compound **S69**.

^{1}H NMR (500 MHz, CD_2Cl_2) of compound **S70**.

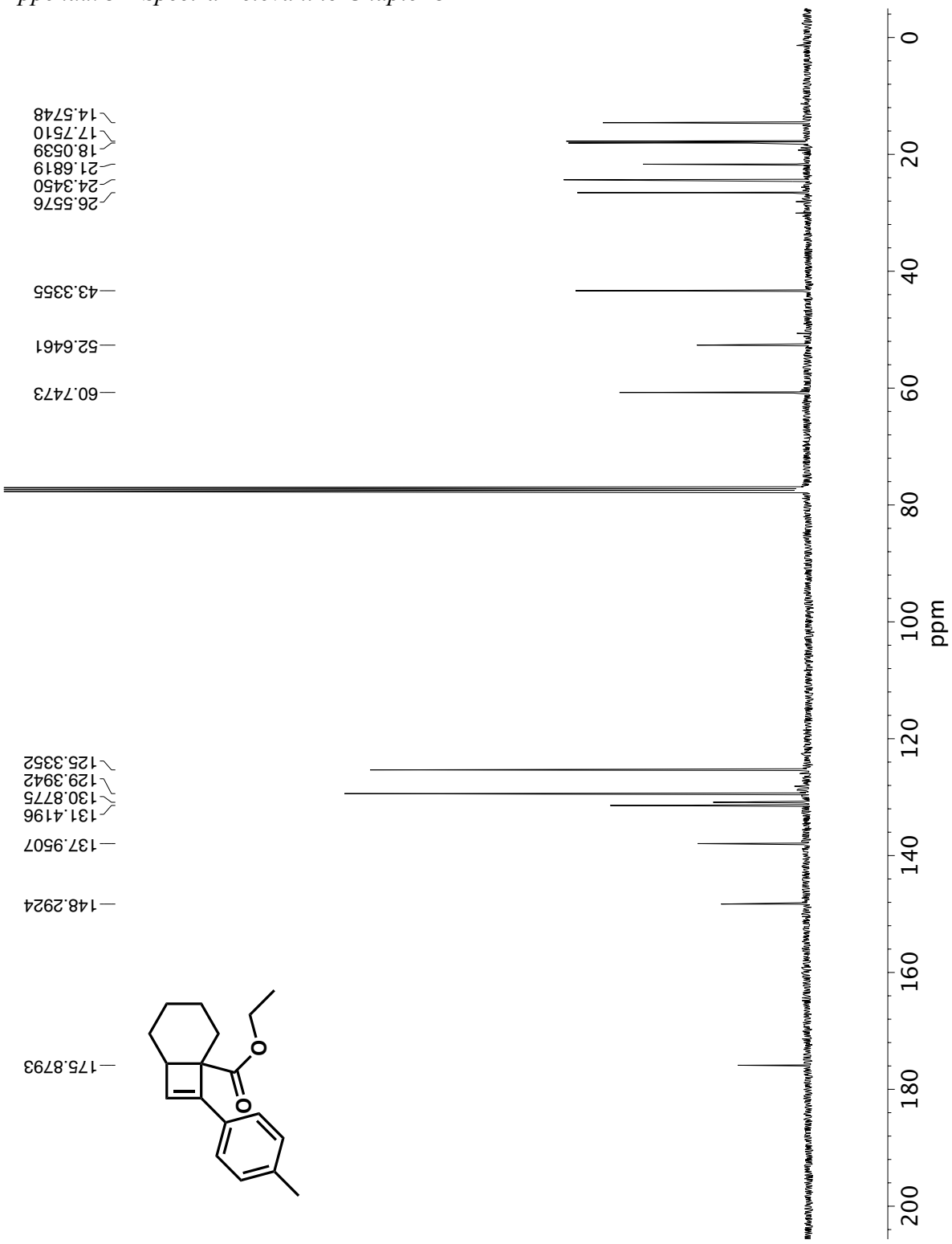
^{13}C NMR (101 MHz, CD_2Cl_2) of compound **S70**.



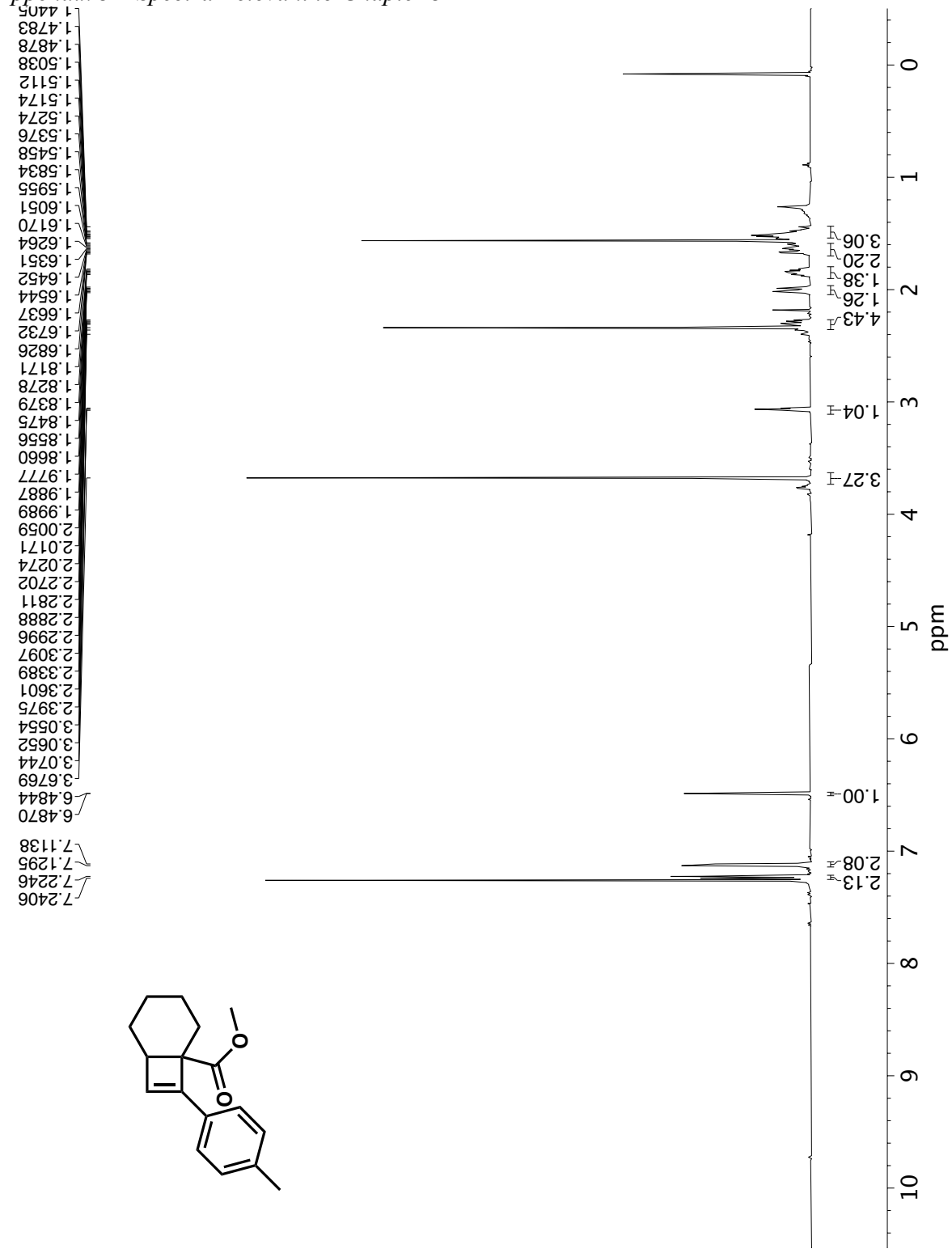
^{19}F NMR (376 MHz, CD_2Cl_2) of compound **S70**.



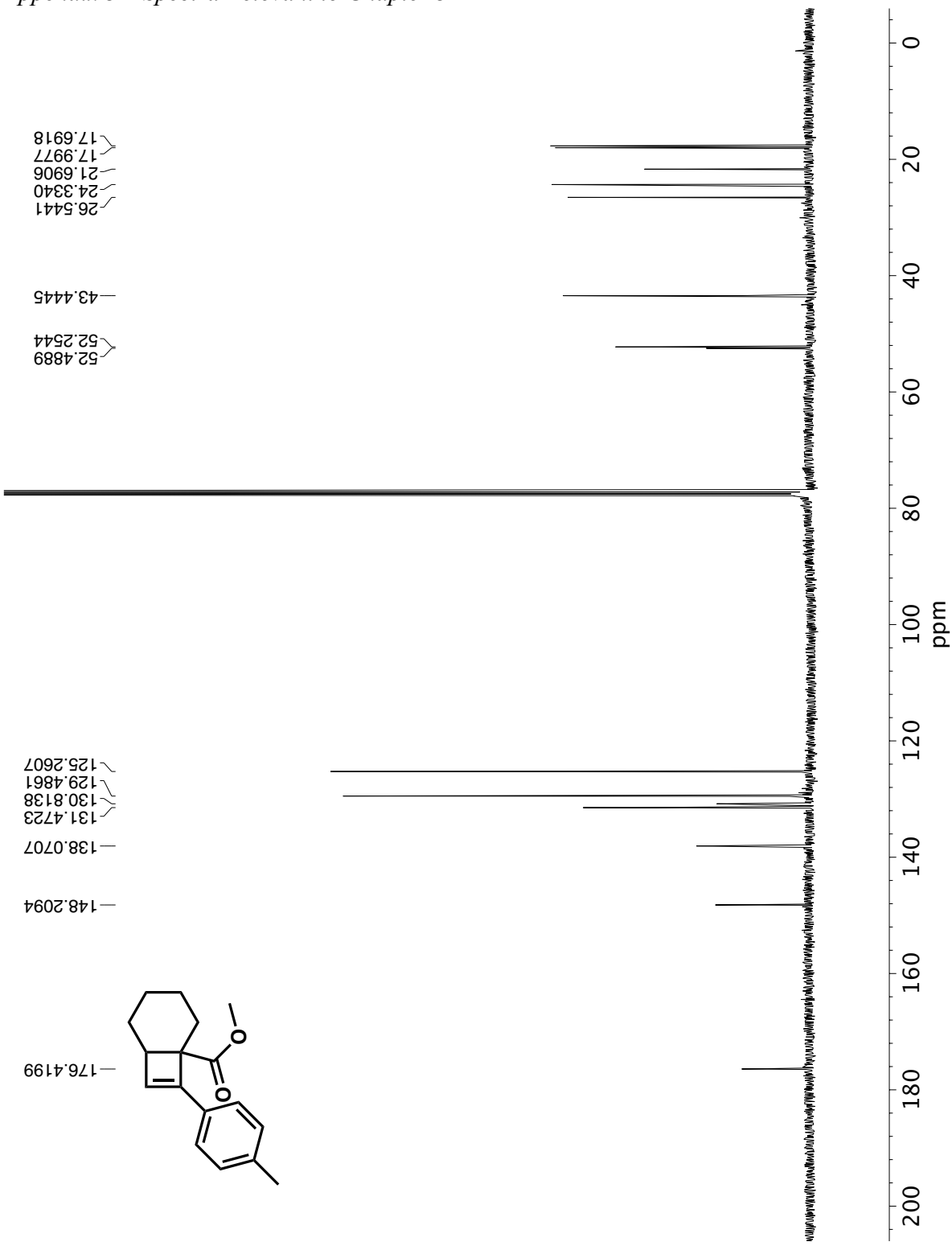
^{1}H NMR (400 MHz, $CDCl_3$) of compound **142**.



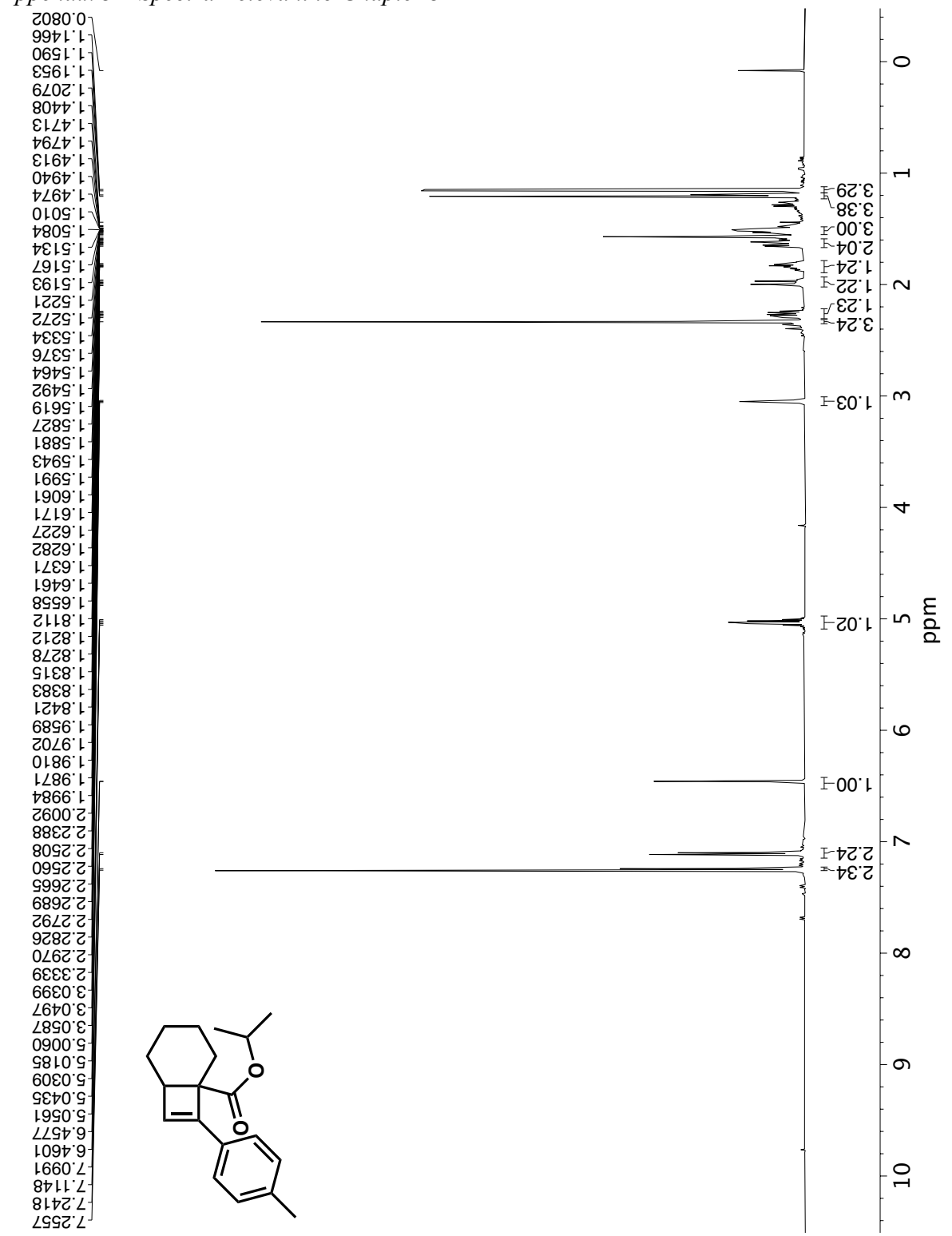
^{13}C NMR (101 MHz, $CDCl_3$) of compound **142**.



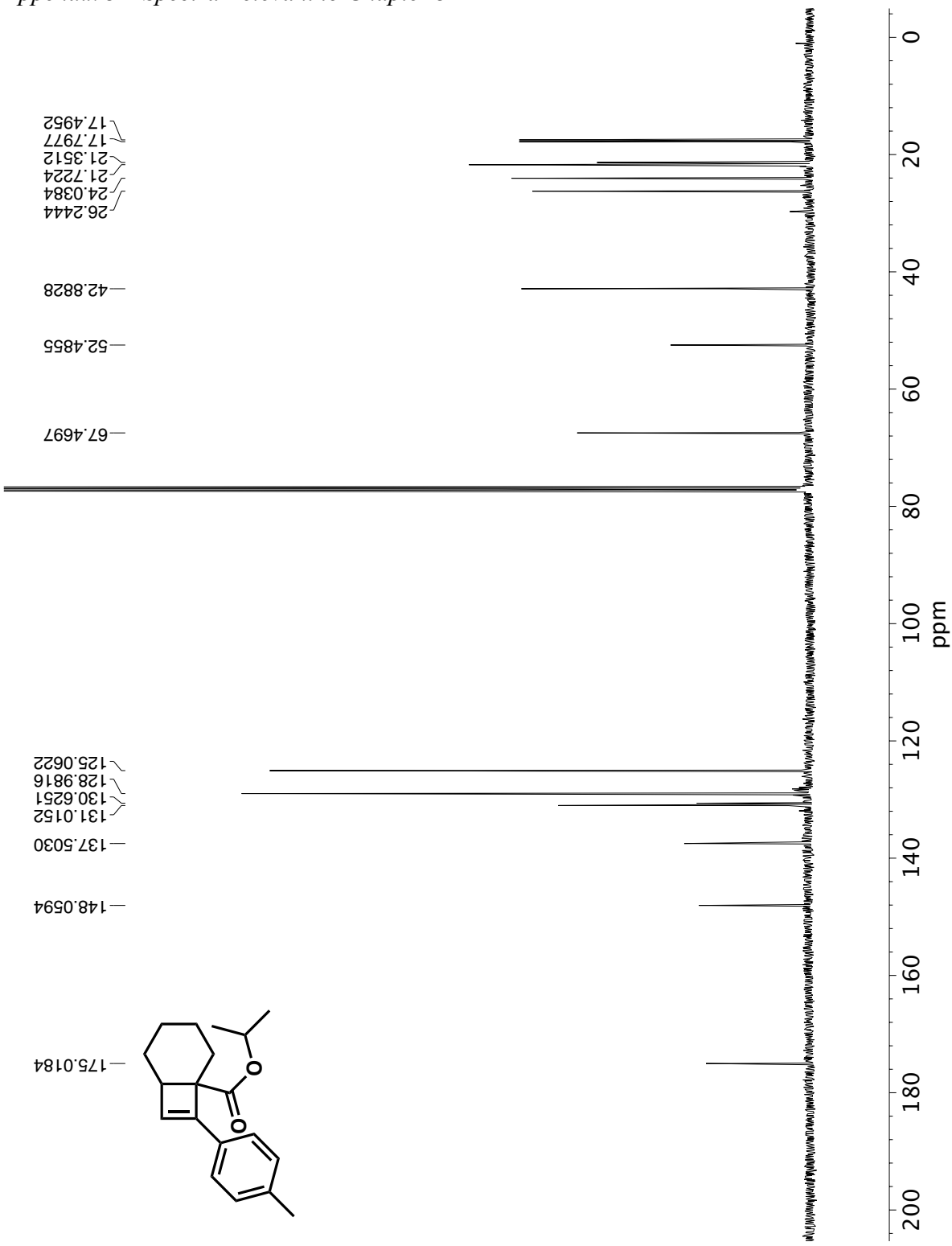
^{1}H NMR (500 MHz, $CDCl_3$) of compound **143**.



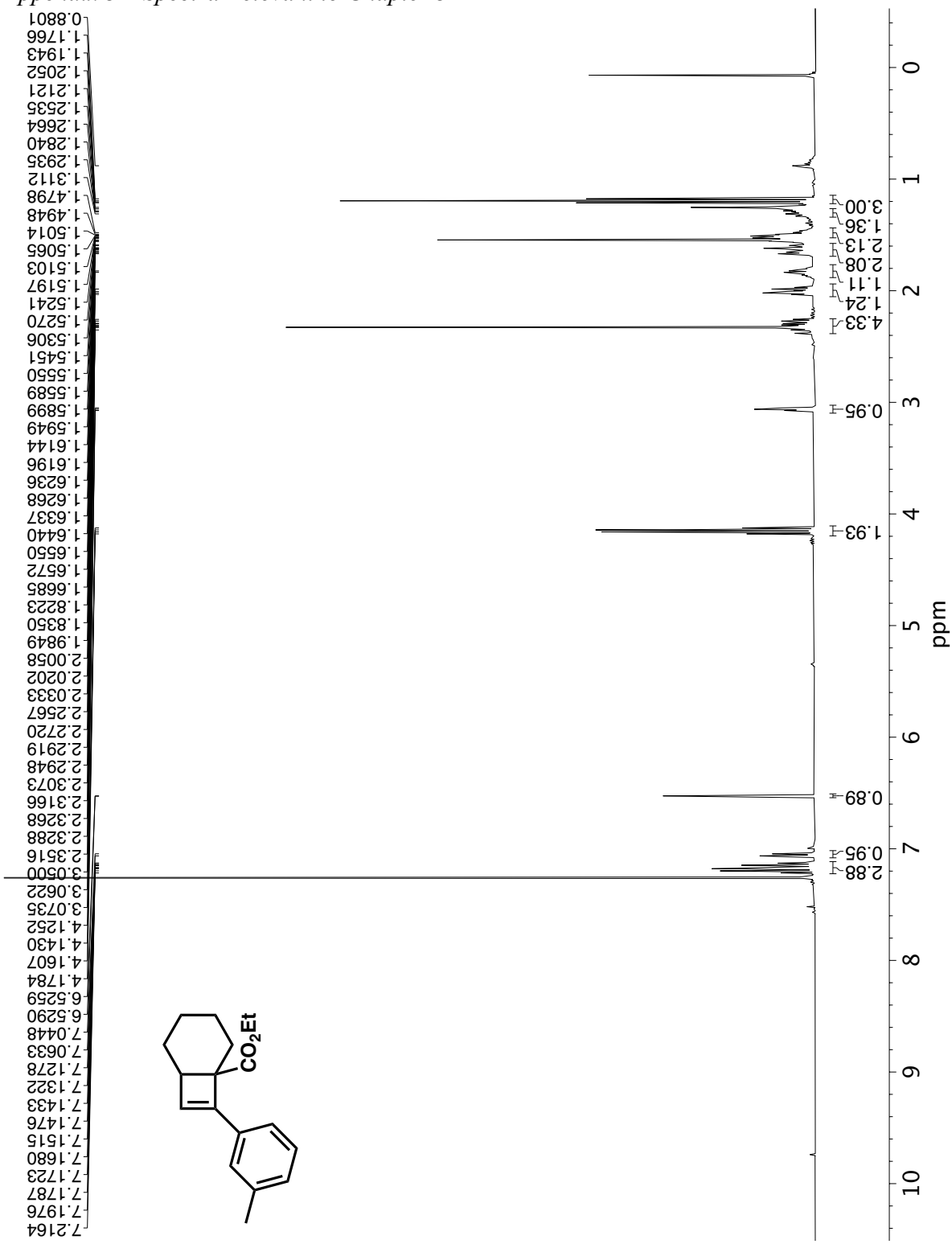
^{13}C NMR (101 MHz, $CDCl_3$) of compound **143**.



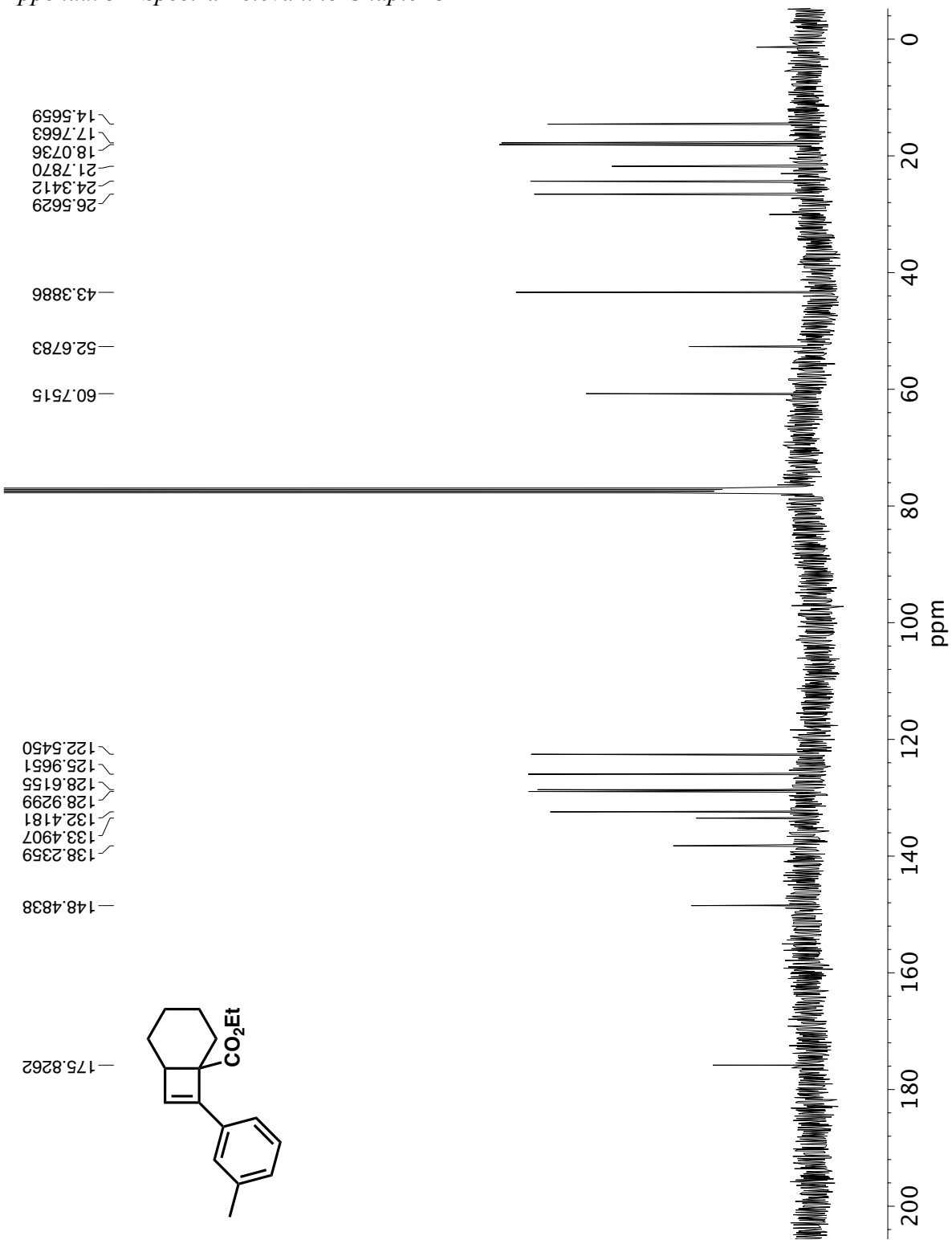
^{1}H NMR (500 MHz, $CDCl_3$) of compound **144**.



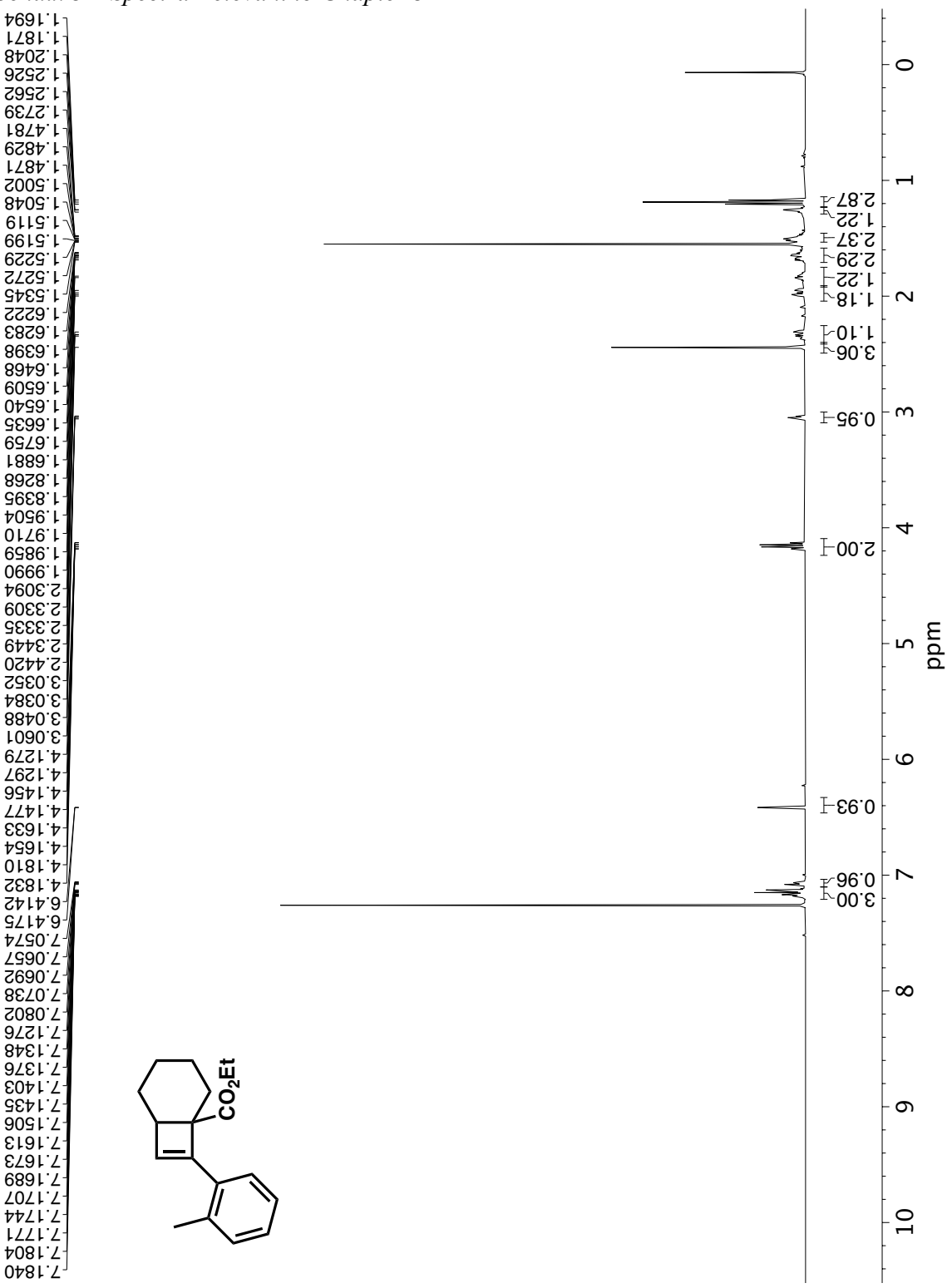
^{13}C NMR (101 MHz, $CDCl_3$) of compound **144**.



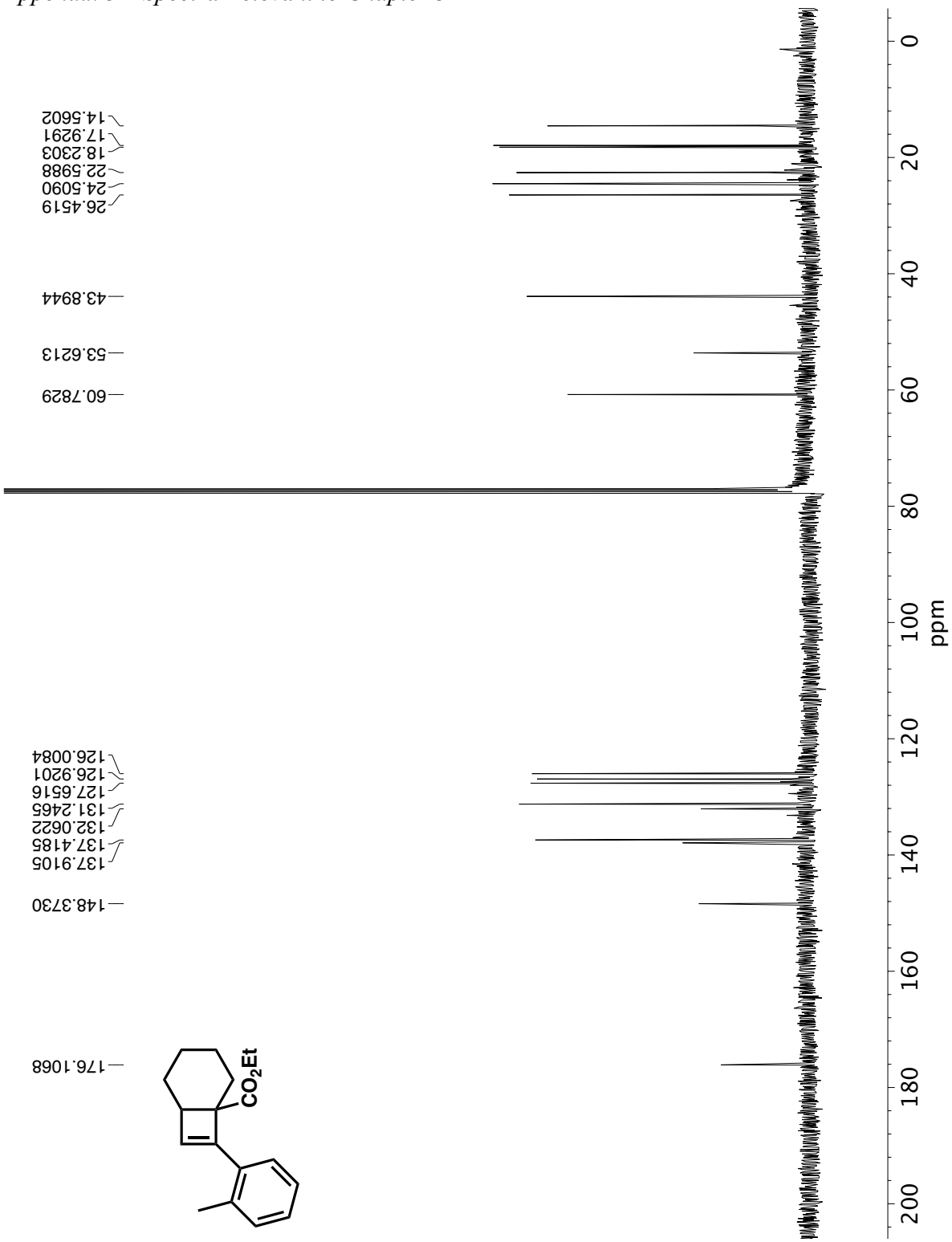
^{1}H NMR (400 MHz, $CDCl_3$) of compound **145**.



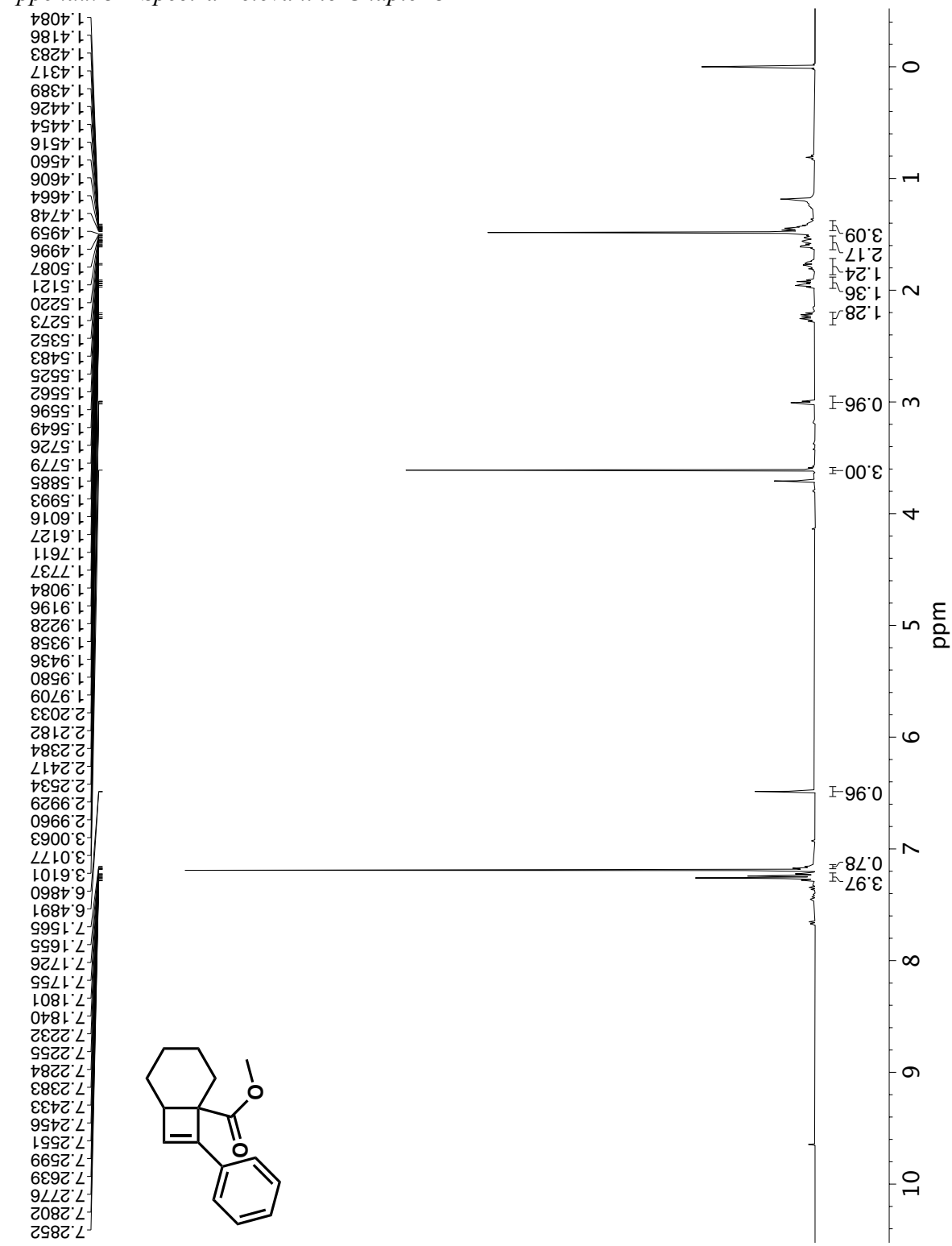
^{13}C NMR (101 MHz, $CDCl_3$) of compound **145**.



^{1}H NMR (400 MHz, $CDCl_3$) of compound **146**.



^{13}C NMR (101 MHz, $CDCl_3$) of compound **146**.



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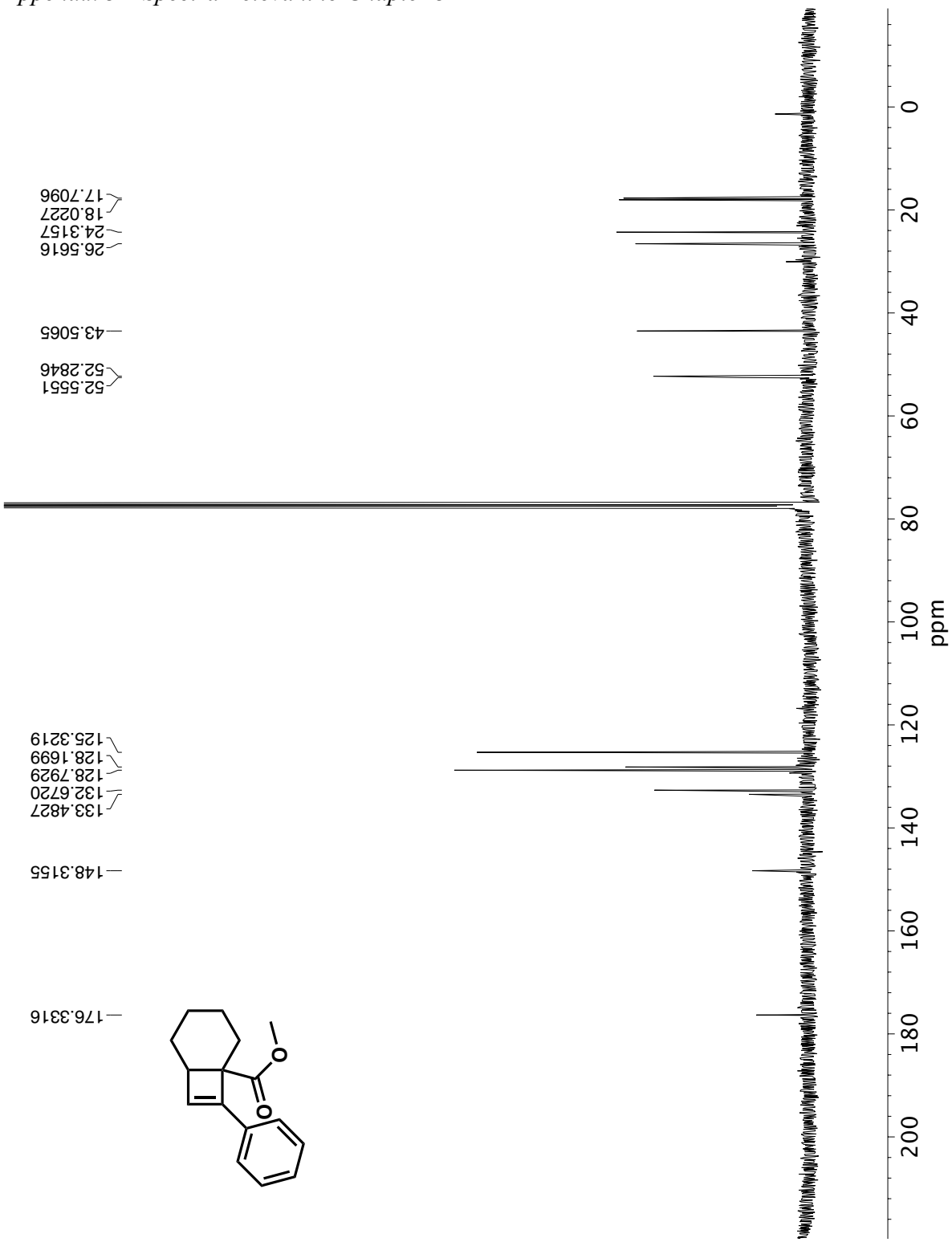
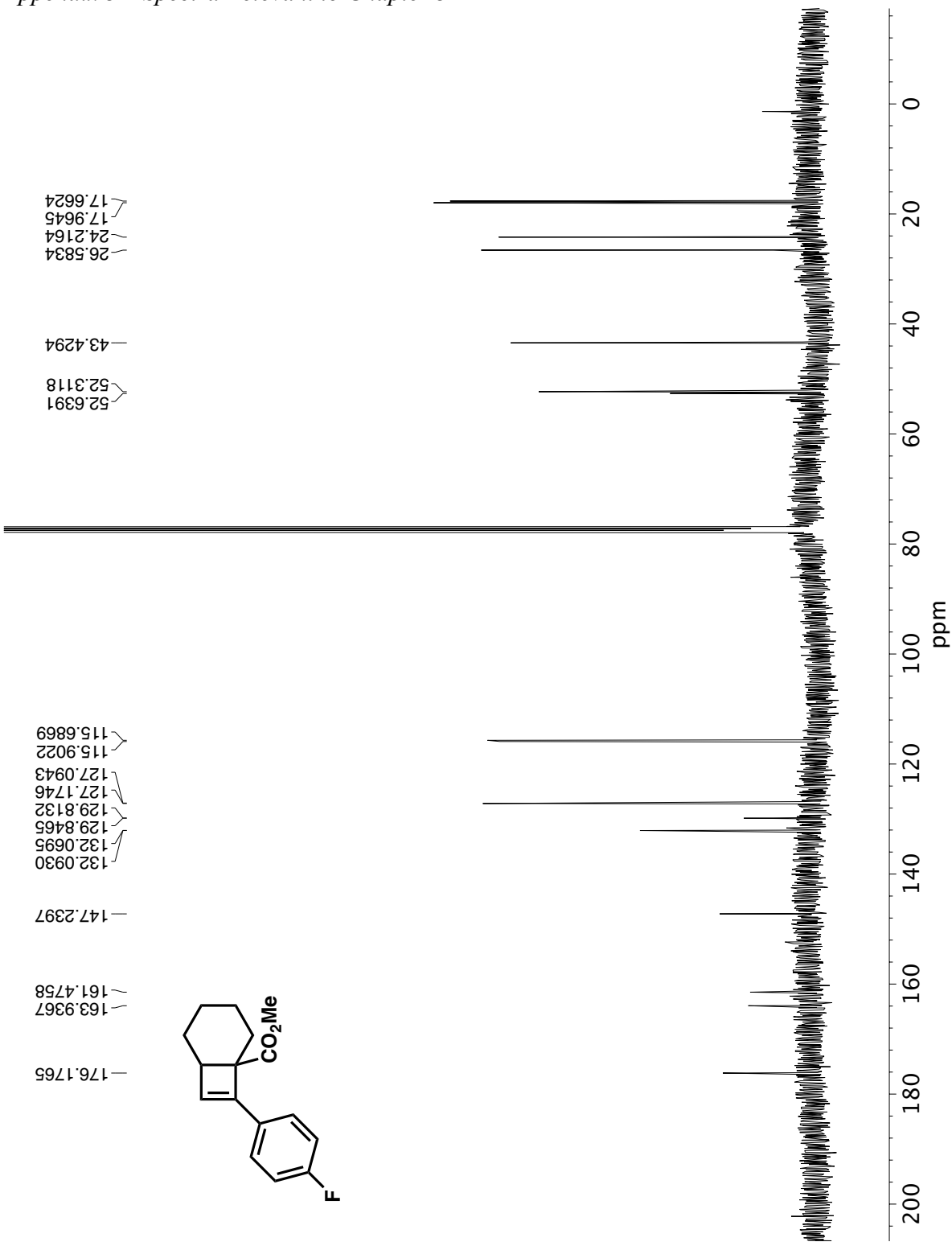


^{13}C NMR (101 MHz, $CDCl_3$) of compound **147**.

^{1}H NMR (500 MHz, $CDCl_3$) of compound **148**.



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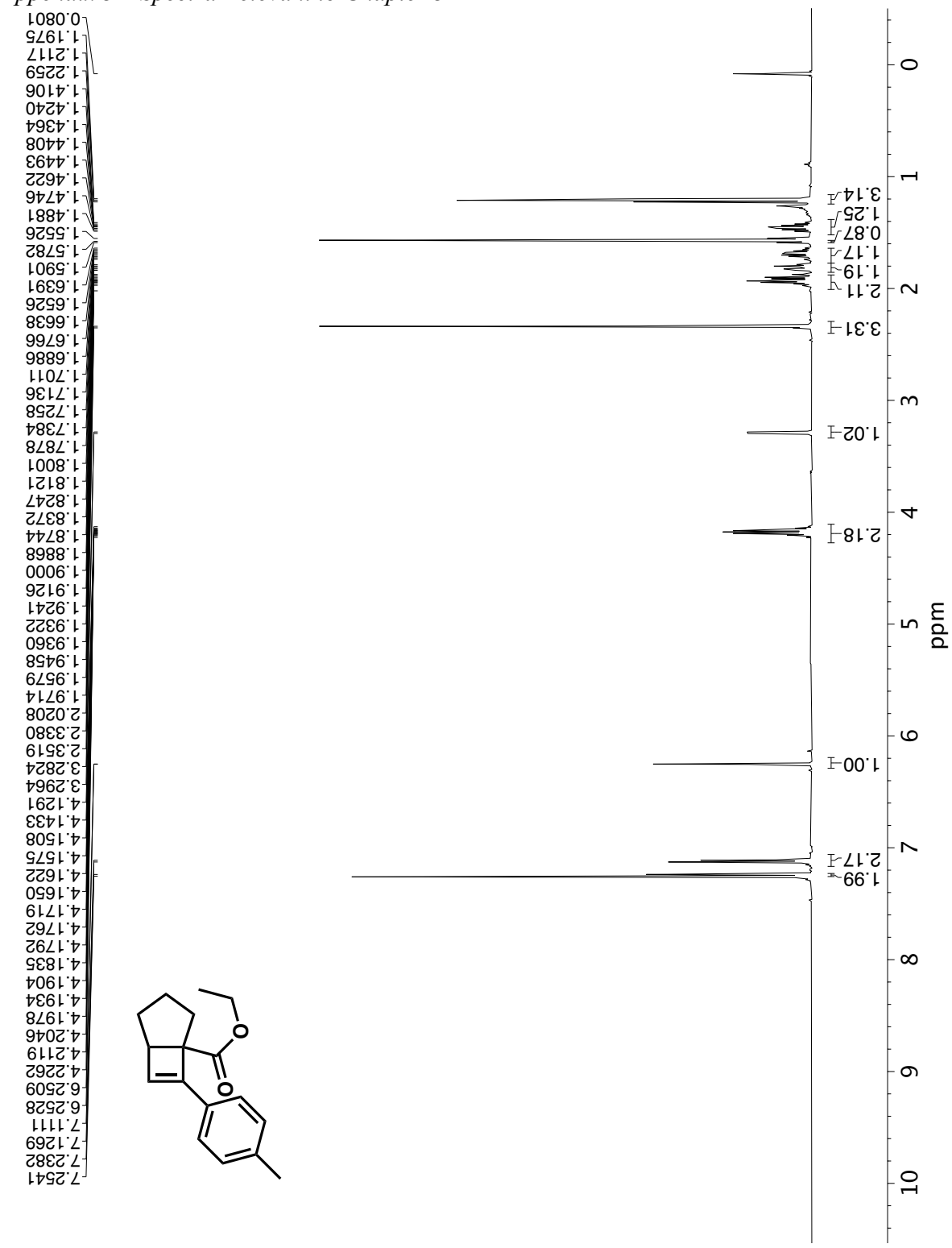
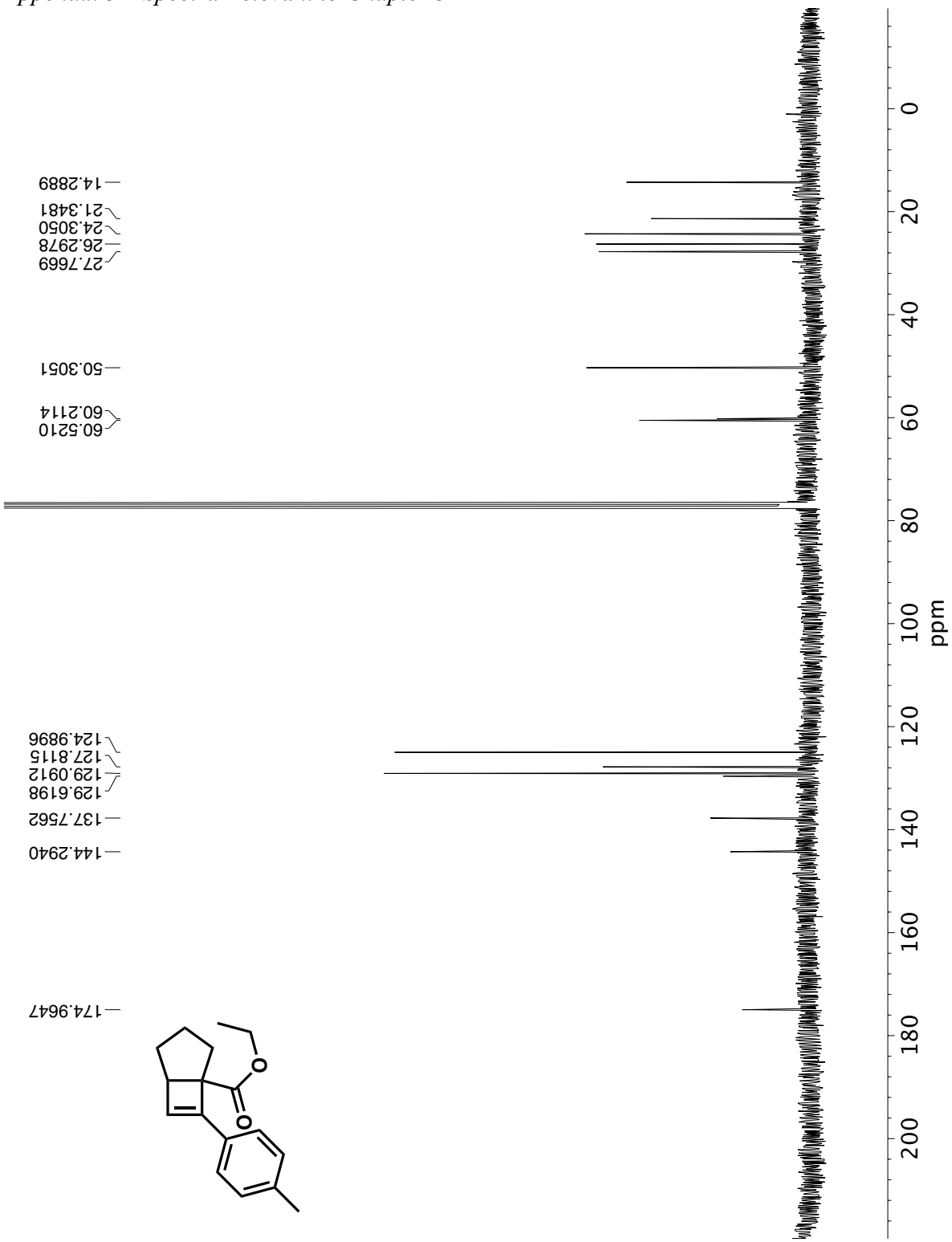


^{1}H NMR (500 MHz, $CDCl_3$) of compound **149**.



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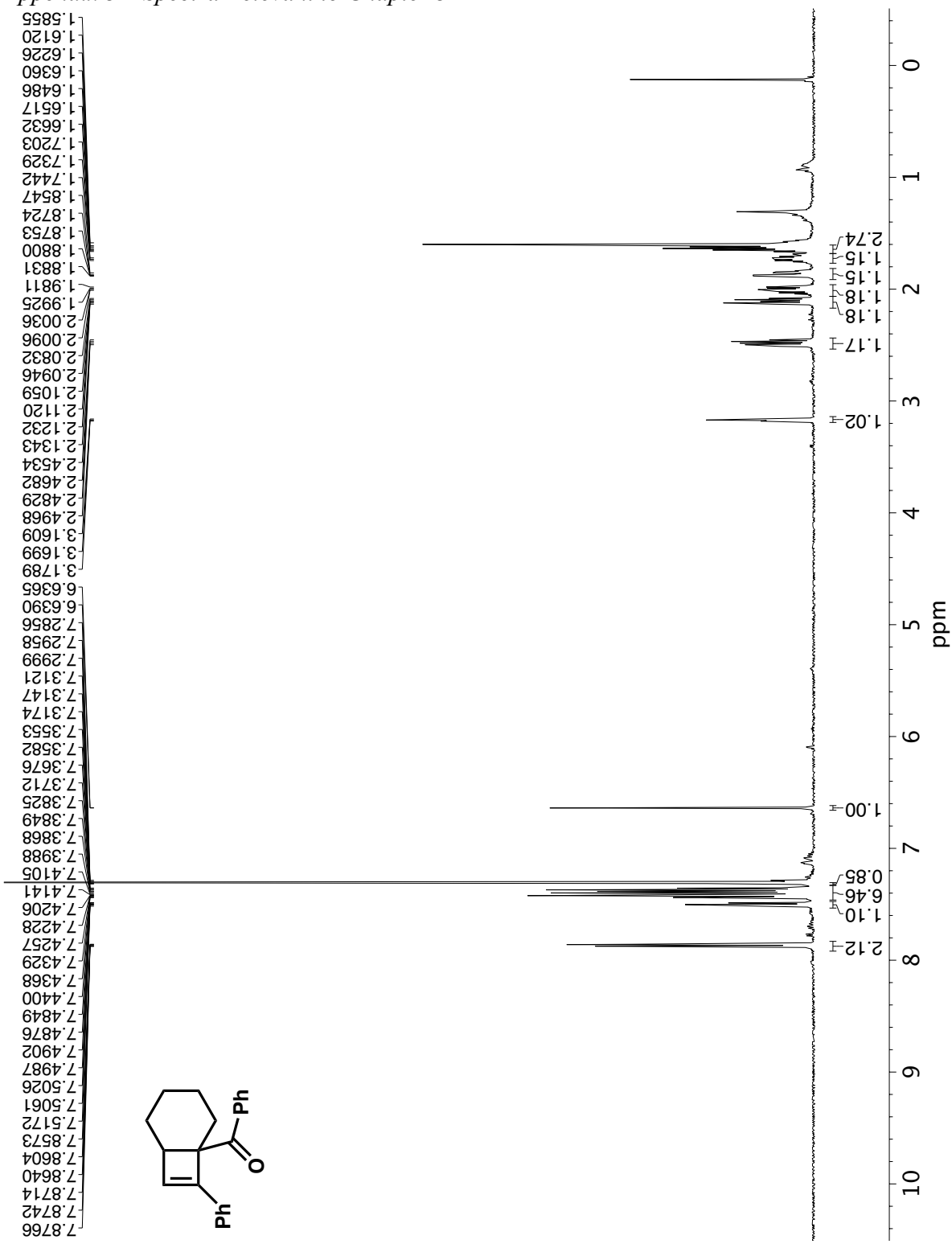

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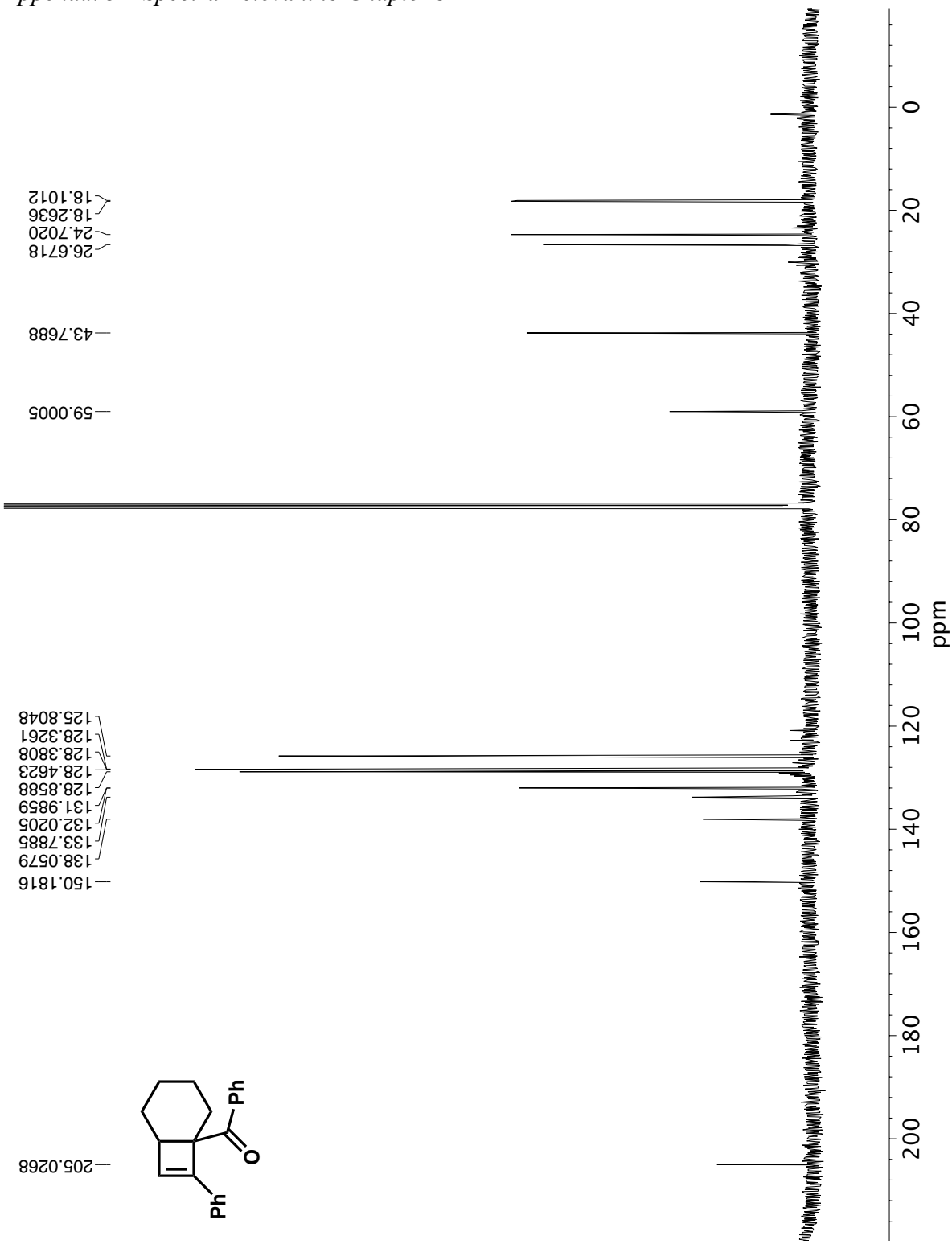

^{13}C NMR (101 MHz, $CDCl_3$) of compound **150**.

ABOUT THE AUTHOR

Zhenqi (Steven) Zhao（赵振起）was born on March 24, 1996, in Changchun, Jilin Province, China, to parents Zhongwei Zhao（赵忠伟） and Ying Lu（陆颖）. He attended the High School Attached to Jilin University. In his high school years, he participated in the Chemistry Olympiad and won a gold medal in the 2014 Chinese Chemistry Olympiad.

After high school, Steven moved to Beijing to begin his undergraduate studies at Peking University, where he earned a Bachelor of Science in Chemical Biology in 2019. During his time at Peking University, he conducted research in Professor Xing Chen's lab, focusing on unnatural sugar metabolic labeling in plants and the mechanism study of protein cysteine residue artificial *S*-glycosylation with peracetylated sugar probes. These research experiences inspired him to pursue a PhD in organic chemistry.

In 2019, Steven moved to Los Angeles, California, to pursue his PhD at the University of California, Los Angeles (UCLA), where he joined Professor Hosea Nelson's lab. In 2021, Steven transferred to the California Institute of Technology (Caltech) in Pasadena, California, following Professor Nelson's relocation to continue his PhD studies. In the Nelson group, Steven worked on projects involving the development of new synthetic methodologies using vinyl carbocation intermediates and asymmetric catalysis.

Steven currently resides in the Hollywood neighborhood of Los Angeles, California. His hobbies include camping, hiking, skiing, running, playing tennis, and enjoying his Nintendo Switch.