Regioselective Aziridination of Silyl Allenes and Application for the Synthesis of New Heterocycles

By

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Under the supervision of Professor Jennifer M. Schomaker

At the University of Wisconsin-Madison

Abstract

Rhodium catalyzed aziridination of homoallenic sulfamates has proven to be a successful first step in the synthesis of a diverse array of complex nitrogenated motifs. Previously, however, the resultant methyleneaziridine was limited to the exocyclic isomer. In this work, a reliable direction strategy for the formation of the endocyclic isomer was identified. Placement of a silicon group on the allene so that its C – Si bond is co-planar to the distal pi-bond allowed for stabilization of the developing positive charge during aziridination, and therefore selective activation to form the endocyclic methyleneaziridine. This strategy proved robust, and endocyclic methyleneaziridines were formed in high yields with exclusive formation of the desired isomer regardless of the substitution of the allene. With the endocyclic isomer now readily available, its reactivity could be explored.

First, the endocyclic methyleneaziridine was applied to the synthesis of densely functionalized, nitrogen containing motifs. In comparison with their exocyclic counterparts, the endocyclic methyleneaziridines were found to have differing reactivity. The olefin could be

epoxidized using *meta*-chloroperoxybenzoic acid (*m*CPBA), and the resulting spirocyclic intermediate rapidly rearranged to an azetidin-3-one. This synthesis of the highly substituted four-membered heterocycle represented a novel approach to these motifs, and was found to be both flexible, and to selectively form a single diastereomer. Additional derivatization of these scaffolds gave a diverse array of complex products.

Further use of the endocyclic methyleneaziridine focused not on the complexity of the product motif but rather on its utility. The remaining silyl group could be eliminated upon reaction with a fluoride source, triggering the formation of an alkyne and resultant opening of the aziridine. This strained heterocyclic alkyne and its synthesis represent a new addition to the field of strained alkyne synthesis. Uniquely, the arrangement of heteroatoms activated the alkyne without allowing for detrimental relaxation of ring strain, giving a strained alkyne that balanced reactivity and stability. These alkynes were applied to post-polymerization modification, wherein their unique capability of opening the strain inducing ring after reaction of the alkyne was successfully demonstrated.

Acknowledgements

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Although the work presented herein is my own, I am certain it could not have happened without the Schomaker group and my collaborators in the Raines group. I am thankful for Jen's guidance over the years, but also for her restraint. My goal upon entering graduate school was to become and independent researcher, and although it was not a comfortable experience at all times, she has allowed me to fulfill this. I am also indebted to the group and am appreciative of their conversations and suggestions, which have helped to guide the projects I worked on and to develop the type of scientist I have become. I am especially thankful to Nels, who I met as an undergraduate at MSU, for his patience and general positivity. I am sure I will miss his presence in lab going forward. I am also fortunate to have been able to collaborate with Dr. Brian Gold and Dr. Trish Huang. Brian was hugely influential in shaping the SNO-OCT project, and Trish stepped in at a key moment. I am grateful to both for their contributions.

Beyond simply being quality co-workers, Julie and Steve were mainstays of my life in graduate school. Julie has been a loyal and supportive friend since the first day, and her pep talks helped to keep spirits high in low moments. I can only hope I was as helpful to her as she has been to me. Steve has been both a comfort and a welcome challenge. Our conversations about our work served to inspire me and force me to evolve to a higher standard. I am grateful to both for all of their edits, suggestions, patience, and friendship.

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Dedication

For Grandma and Grandpa, and for Mom and Dad.

Thank you for making my education possible.

Table of Contents

Abbreviations

Å	angstrom(s)
AAC	alkyne-azide cycloaddition
Ac	acetyl
acac	acetylacetone
AcOH	acetic acid
ALO	aryless octyne
aq	aqueous
Ar	aryl
B3LYP	Becke 3-Parameter, Lee-Yang-Parr density functionalization method
BAIB	(diacetoxyiodo)benzene
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
Boc_2O	di-*tert*-butyl dicarbonate
BPS	*tert*-butyldiphenylsilyl
br d	broad doublet
br s	broad singlet
n-BuLi	*normal*-butyllithium

n-butyl	*normal*-butyl
C	Celsius
cat	catalyst
COSY	correlation spectroscopy
Cp	cyclopentadienyl
CSA	camphorsulfonic acid
CSI	chlorosulfonyl isocyanate
CuAAC	copper(I)-catalyzed alkyne-azide cycloaddition
Cy	cyclohexyl
δ	chemical shift in ppm
d	doublet
dd	doublet of doublets
ddd	doublet of doublet of doublets
dddd	doublet of doublet of doublet of doublets
DCE	1,2-dicholroethane
DEAD	diethyl azodicarboxylate
DIAD	di*iso*propyl azodicarboxylate
DMA	*N*,*N*-dimethylacetamide

DMAP	4-dimethylamino pyridine
DMDO	dimethyldioxirane
DMF	*N*,*N*-dimethylformamide
DMAP	4-dimethylaminopyridine
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
dq	doublet of quartets
dt	doublet of triplets
dtt	doublet of triplet of triplets
ee	enantiomeric excess
ESI	electrospray ionization
Et	ethyl
Et_2O	diethyl ether
EtOAc	ethyl acetate
EtOH	ethanol
g	gram
GPC	gel permeation chromatography

h	hour
HPLC	high pressure liquid chromatography
HRMS	high resolution mass spectrometry
Hz	hertz
J	spin-spin coupling constant in hertz
k_2	second-order rate constant
kcal	kilocalorie
KO*t*Bu	potassium *tert*-butoxide
LDA	lithium di*iso*propyl amide
m	multiplet
M	molar
MA	methyleneaziridine
*m*CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
MeOH	methanol
mg	miligrams
MHz	megahertz
min	minute

mmHg	millimeters of mercury
mL	milliliter
mM	millimolar
mmol	millimole(s)
MMPP	magnesium monophthalate
mol	mole(s)
mp	melting point
Ms	methanesulfonyl
MS	molecular sieves
NBS	*N*-bromosuccinimide
nOe	nuclear Overhauser effect
NMR	nuclear magnetic resonance spectroscopy
Nu	nucleophile
OAc	acetate
OCT	cyclooctyne
OMe	methoxy
PDI	polydispersity index
Pg	protecting group

Ph	phenyl
phen	1,10-phenanthroline
PhIO	iodosobenzene
Piv	trimethylacetyl
PPh_3	triphenylphosphine
ppm	parts per million
n-Pr	*normal*-propyl
pyr	pyridine
q	quartet
qd	quartet of doublets
quint	quintet
R_f	retention factor
rt	room temperature
s	singlet
SPAAC	strain-promoted alkyne-azide cycloaddition
TBAF	tetra-*n*-butylammonium fluoride
TBS	*tert*-butyldimethylsilyl
td	triplet of doublets

TEBA	benzyltriethylammonium chloride
TEMPO	2,2,6,6-Tetramethylpiperidine 1-oxyl
TES	triethylsilyl
Tf	trifluoromethanesulfonate
TFA	trifluoroacetic acid
Tf_2O	trifluoroacetic anhydride
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TPA	triphenylacetyl
Tr	triphenylmethyl
Troc	2,2,2-trichloroethoxycarbonyl
Ts	*p*-toluenesulfonyl
tt	triplet of triplets

List of Figures, Schemes and Tables

Chapter 1.

An Introduction to Methyleneaziridines and Their Synthetic Applications

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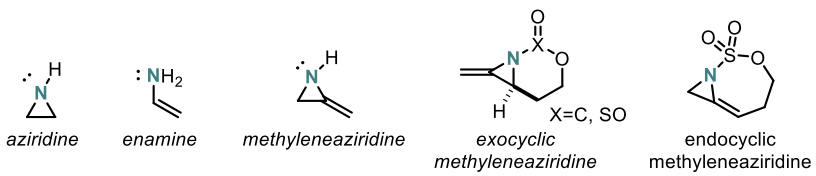
Chapter 1

An Introduction to Methyleneaziridines and their Synthetic Applications

1.1 Introduction

Methyleneaziridines are nitrogenated motifs which have gained interest owing to their high synthetic utility (Figure 1.1). The structure has similarities to aziridines and enamines, but is unique to both. Calculations have predicted 12-13 kcal/mol higher ring strain in methyleneaziridines over that of related aziridines due to the inclusion of the sp^2-hybridized carbon in the ring.[1] Unlike the related enamine, the nitrogen of the methyleneaziridine is computationally predicted to be pyramidal, with little interaction between the nitrogen lone pair and the pi orbitals of the olefin.[1,2] Bicyclic methyleneaziridines, which result from intramolecular nitrene insertion of allenes, give a structure with a defined steric environment of each face of the olefin, an additional advantage in derivatization. Due to their unusual structures, derivatizations of methyleneaziridines and bicyclic methyleneaziridines have been diverse, using different aspects of the structure to impart desired reactivity. This chapter will begin by exploring the synthesis of methyleneaziridines. Then, the exocyclic methyleneaziridines' range as synthetic intermediates will be presented. While there is a large body of work focused on the derivatization of methyleneaziridines, this chapter will focus on bicyclic methyleneaziridines as it is most pertinent

Figure 1.1: *Aziridines and Methyleneazridines*



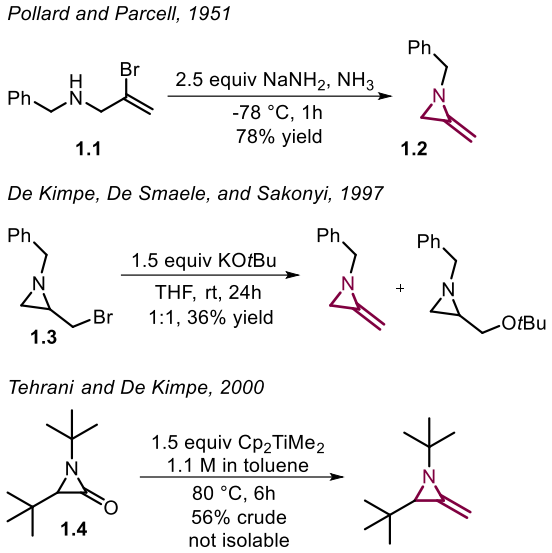
to the research presented.[3] Finally, research into the selective synthesis of unexploited endocyclic methyleneaziridines will be discussed.

1.2 Methyleneaziridine Synthesis

Methyleneaziridines were first synthesized in 1951 by Pollard and Parcell *via* reaction of secondary haloalkenylamines **1.1** with sodium amide in liquid ammonia (Scheme 1.1).[4] Initially the product **1.2** was identified as the corresponding enamine, until its corrected structure was assigned 6 years later in 1957 by Bottini and Roberts.[5] Modifications of the reaction conditions to be milder and to allow for the inclusion of larger substrate scope have been undertaken, but the conditions used today remain largely the same. The method was popularized in the early 2000's by the Shipman group, who used it to access the substrates with which they investigated various aspects of methyleneaziridine reactivity.[3] The method was chosen for its generality; however, drawbacks include the harsh reagents, limited functional group tolerance, and formation of alkyne side products.[3] In addition to the sodium azide induced cyclization of haloalkenylamines, other methodologies for the preparation of methyleneaziridines have been developed. DeKimpe and co-workers reported methyleneaziridine synthesis both by the dehydrobromination of 2-(bromomethyl)aziridines **1.3** and methylation of aziridinones **1.4** (Scheme 1.1).[6,7] Due to limitations of substrate scope and stability of the starting materials, neither have been broadly used.

The synthesis of small rings, such as methyleneaziridines, *via* intramolecular ring closing of linear precursors suffers from an entropic disadvantage. As an alternative to these methods, nitrene insertion of an allene was envisioned as a way to avoid this inherent weakness. An intermolecular version of this desired reaction was first reported in 1975, but low yields and a lack of chemoselectivity hampered the reaction.[8] In part to alleviate these drawbacks, and also to take

Scheme 1.1: *Synthesis of Methyleneaziridines*

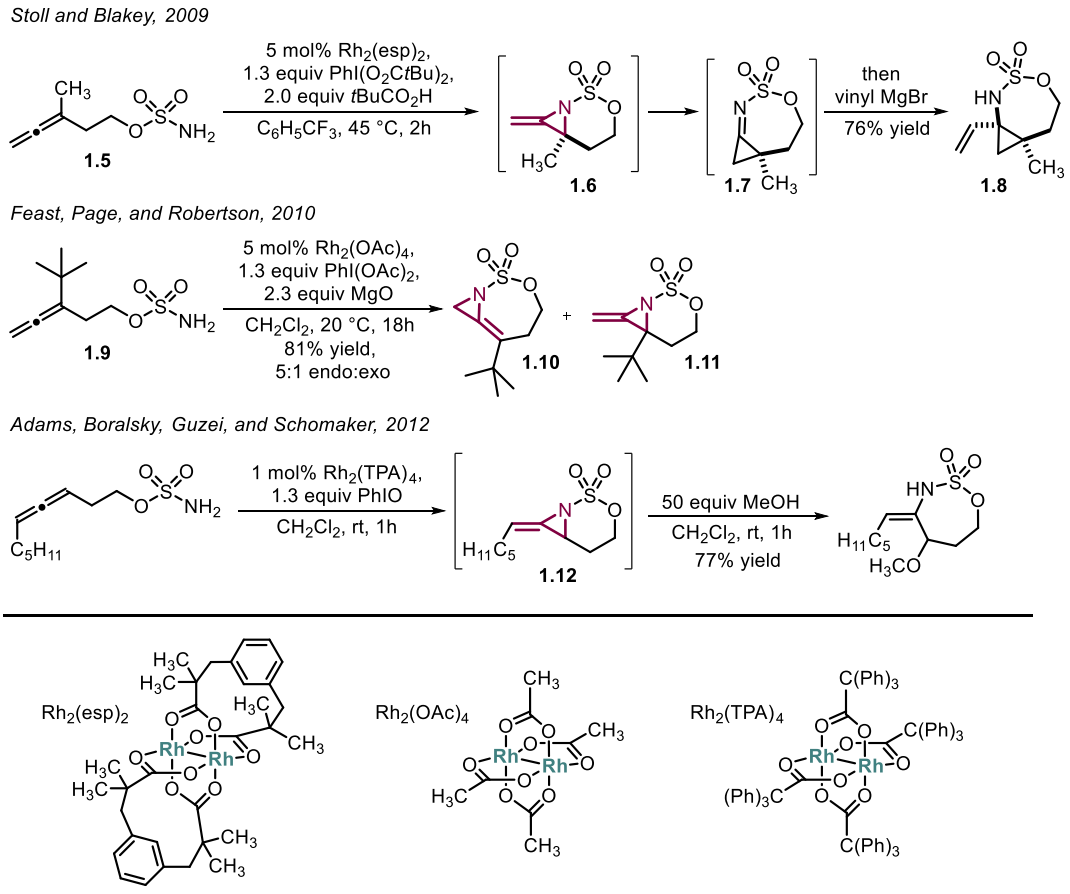


advantage of the unique strain of their bicyclic products, intramolecular nitrene insertion was investigated (Scheme 1.2).

Nitrene precursor, catalyst identity and oxidant were found to be important to the success of intramolecular nitrene insertion. Initial studies examined the use of sulfamate nitrene precursors, rhodium catalysts, and hypervalent iodine oxidants (Scheme 1.2). Blakey and co-workers found these conditions gave highly substituted cyclopropane products **1.8** which were hypothesized to result from the opening of an intermediate cyclopropylimine **1.7**. Though not proposed in the report, this cyclopropylimine **1.7** was potentially formed from the rearrangement of a transient methyleneaziridine **1.6**.[9] Support for this can be found in a later study by the Robertson group.[10] Starting with similar reagents and substrates, a related group of products was reported, including isolated methyleneaziridines. From a *tert*-butyl substituted homoallenic sulfamate **1.9**, both endocyclic and exocyclic methyleneaziridines (**1.10** and **1.11**) were isolated in a 5:1 ratio. However, these aziridinations were limited by their choice of oxidant. Diacetoxyiodobenzene and related hypervalent oxidants generate species such as acetic acid which may act as nuncleophiles,

opening the highly reactive methyleneaziridine, thus precluding other possible reactions. Later work by the Schomaker group found that by replacing these problematic oxidants with iodosobenzene, the transient exocyclic methyleneaziridine **1.12** can be reliably formed and manipulated.[11] Although synthetically useful as intermediates, exocyclic methyleneaziridines formed from intramolecular aziridination of homoallenic sulfamates were too fragile to be isolated.

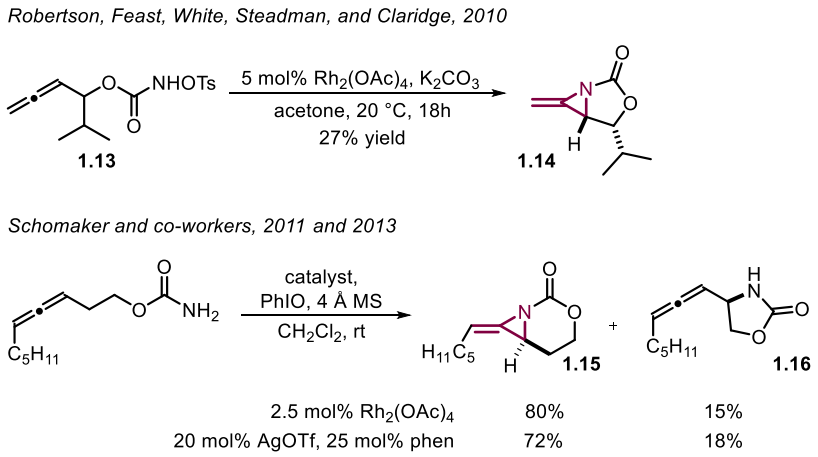
Scheme 1.2: *Bicyclic Methyleneaziridine Synthesis from Homoallenic Sulfamates*



In part due to the instability of methyleneaziridines formed from homoallenic sulfamates, other nitrene precursors were also studied (Scheme 1.3). N-tosyloxycarbamates **1.13** were used with some success by Robertson and co-workers, who found that when reacted with a rhodium catalyst

in the presence of potassium carbonate, small amounts of the exocyclic methyleneaziridines **1.14** could be isolated.[12] Moving to the carbamate precursor in conjunction with a hypervalent iodine oxidant gave Schomaker and co-workers higher yields of the isolable methyleneaziridine **1.15**. The drawback to this approach was the formation of a significant amount of an oxazole side product **1.16**, resulting from competing C-H insertion.[13] A silver catalyst system was developed in which the M:L ratio could be adjusted to give differing ratios of the two products, with some substrates having complete selectivity for one product over the other.[14]

Scheme 1.3: *Bicyclic Methyleneaziridine Synthesis from Allenic and Homoallenic Carbamates*

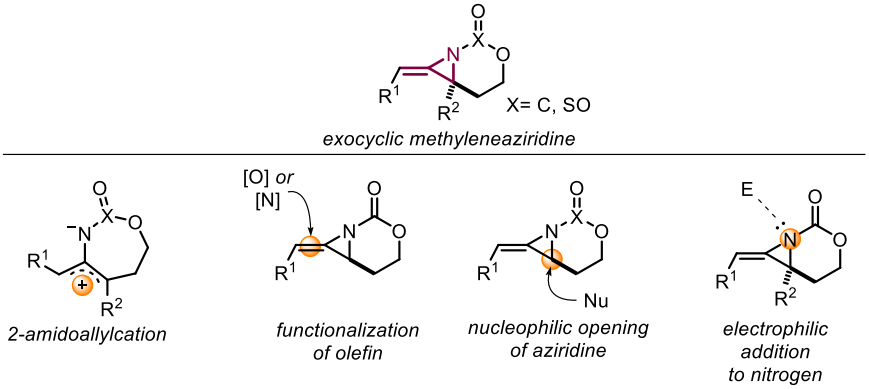


Reliable methods for the synthesis of methyleneaziridines have been developed. Dehydrohalogenation was among the first, and remains among the more popular methods due to its generality and reliable formation of stable methyleneaziridines.[3] However, a body of work has been developed around intramolecular nitrene insertion of allenes and their bicyclic products. Sulfamate precursors were found to give high yielding and clean conversion to exocyclic methyleneaziridines, though they could not be isolated.[9-11] Carbamate precursors gave isolable methyleneaziridines, though with competing C-H amination.[12-14] With reliable methods of synthesis available, the chemistry of these exocyclic methyleneaziridines could be explored.

Derivatization of Exocyclic Methyleneaziridines

Bicyclic methyleneaziridines, which feature activation across three contiguous carbons, have found utility as scaffolds for building complex, densely functionalized and stereodefined products. Newly developed methodologies have accessed a diversity of motifs by exploiting different bonds of the parent methyleneaziridine (Figure 1.2). Opening of the methyleneaziridine to a 2-amidoallylcation was among the first areas to be explored, followed by functionalization of the olefin, nucleophilic aziridine ring opening, and electrophilic addition to the nitrogen. These methods have had some early successes in application towards the synthesis of desired products. The following derivatizations illustrate why bicyclic methyleneaziridines are of interest as synthetic intermediates.

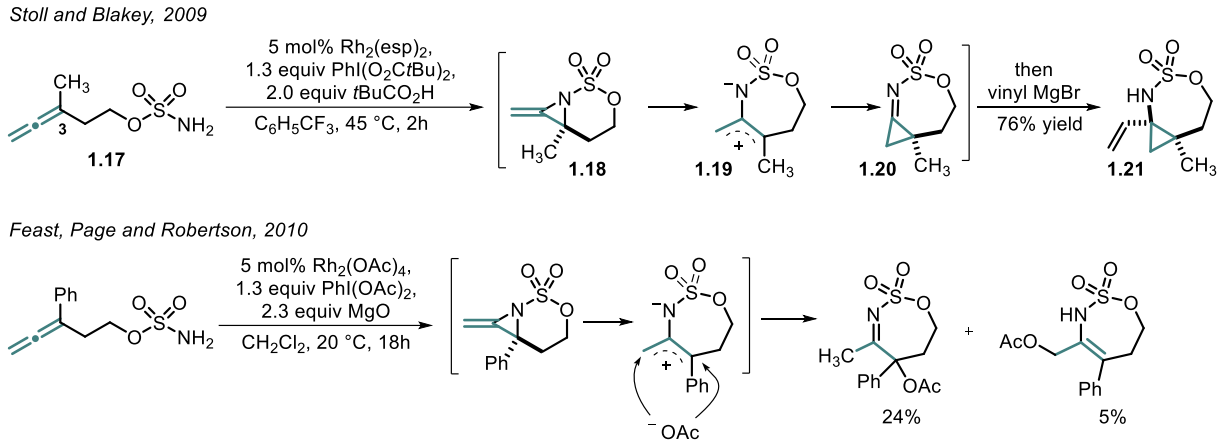
Figure 1.2: *Derivatization of Exocyclic Methyleneaziridines*



With the earliest reports of bicyclic methyleneaziridine synthesis came the earliest reports of their derivatization (Scheme 1.4). In Blakey's 2009 report, an enamine intermediate **1.20**, generated from a homoallenic sulfamate **1.17**, was trapped with a carbon nucleophile to yield highly substituted aminocyclopropanes **1.21**.[15] The enamine likely results from the rearrangement of an initially formed methyleneaziridine **1.18** *via* ring opening to an 2-amidoallylcation **1.19;** evidence for this can be found in the reaction of a chiral allene, in which some racemization was observed over the course of the reaction. The resulting products of the methyleneaziridine opening

reaction were formed diastereoselectively with a range of Grignard reagents, and with substitution of the C-3 position of the allene tolerated (Scheme 1.4). Robertson reported similar products in his investigation of homoallenic sulfamates, resulting from trapping with acetic acid.[16]

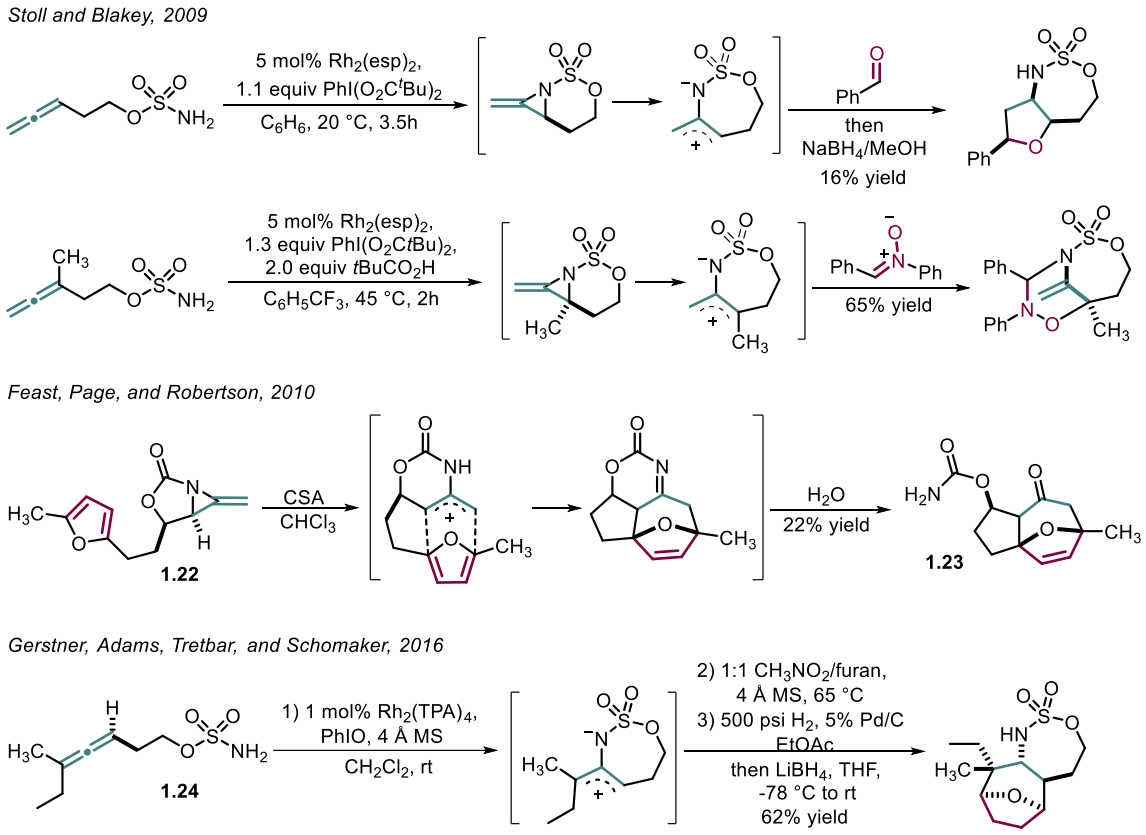
Scheme 1.4: *Nucleophilic Additions to 2-Amidoallylcations*



The 2-amidoallylcation intermediate was also used as a coupling partner in cycloaddition chemistry (Scheme 1.5). Stoll and Blakey reported successful [3+2] cyclization when the 2-amidoallylcation was generated in the presence of benzaldehyde, and [3+3] cyclization when it was generated in the presence of *N*,α-diphenyl nitrone.[9, 17] For each case, the yields were modest and highly substrate dependent. Robertson and co-workers reported a similar transformation when an isolable carbamate-derived bicyclic methyleneaziridine **1.22** was treated with dilute acid.[12] The tethered furan underwent intramolecular [4+3] cyclization to form the polycyclic product **1.23**, albeit in low yield. Expanding on this, Schomaker and co-workers used sulfamate precursors **1.24** in intermolecular [4+3] cyclizations with furan.[18] In a notable expansion of previous studies, the reaction was found to be stereodivergent, with all of the possible *endo*-adducts accessible upon variation of solvents and reducing agents. While the transience of the 2-

amidoallylcation did lead to lower yields, it was shown to be a powerful synthon in the formation of complex products.

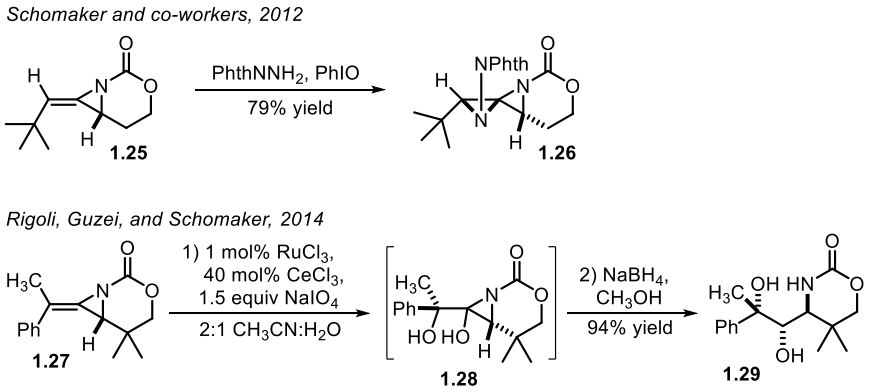
Scheme 1.5: *Cycloadditions of 2-Amidoallylcations*



An alternative mode of bicyclic methyleneaziridine derivatization is the direct functionalization of the olefin (Scheme 1.6). While sulfamate-derived methyleneaziridines are not stable enough to be isolated, and are more easily opened to the 2-amidoallylcation, the carbamate-derived methyleneaziridines are more stable and isolable, making functionalization of the olefin possible. This strategy was employed in the aziridination of carbamate-derived methyleneaziridines **1.25** with N-aminophthalimide by Schomaker and co-workers.[19] The isolable 1,4-diazaspiro[2.2]pentanes **1.26** featured two electronically differentiated aziridines. These were selectively derivatized to give a range of ring-opened products featuring new substitution along

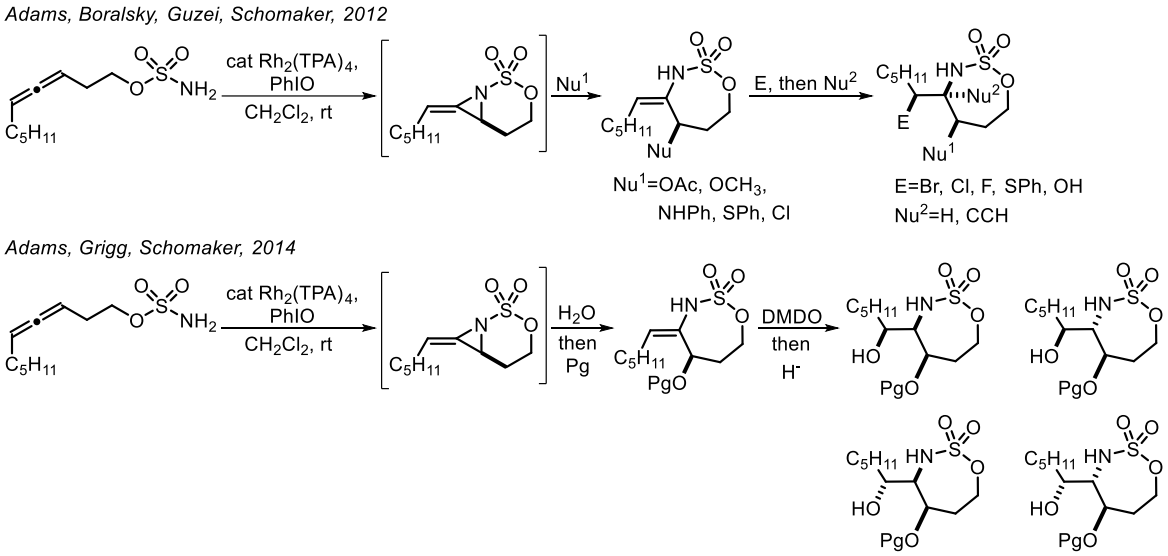
three contiguous carbons in a stereodefined manner. In a similar strategy, Schomaker and co-workers derivatized the methyleneaziridine **1.27** by Ru-catalyzed dihydroxalation of the olefin.[20] This intermediate **1.28** tautomerized with aziridine opening, and reduction of the resulting carbonyl gave 1-amino-2,3-diol products **1.29** in a stereodefined manner. These reactions illustrated the modular derivatization of the exocyclic methyleneaziridine to form densely functionalized, stereodefined products.

Scheme 1.6: *Additions to the Olefin of Methyleneaziridines*

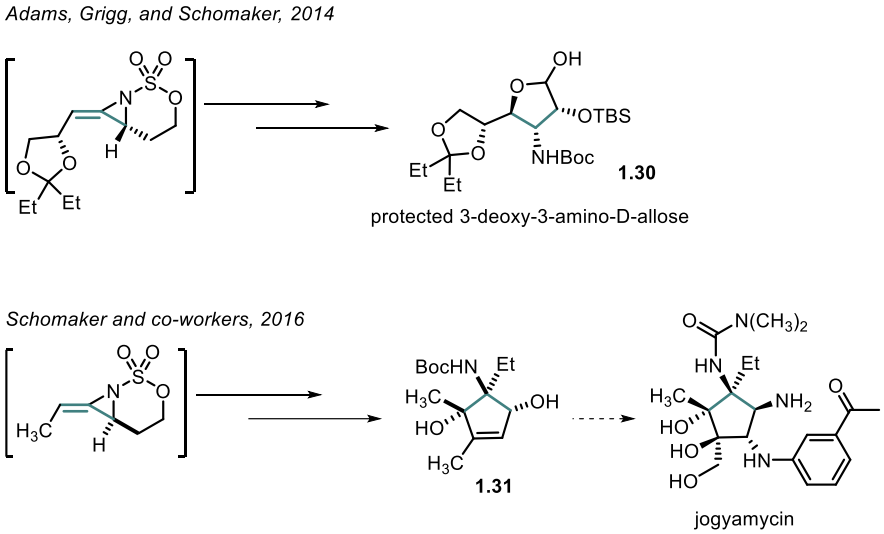


A third strategy for bicyclic methyleneaziridine functionalization was to first target the aziridine bond (Scheme 1.7). Schomaker and co-workers used this strategy to open methyleneaziridines generated *in situ* from homoallenic sulfamates, as they were very sensitive to nucleophilic attack. This strategy was found to be uncommonly versatile and flexible, with investigations of both heteroatom inclusion and stereoisomer formation demonstrating precise control over which products can be accessed.[11] This strategy has been applied to the synthesis of complex products, such as aminosugars **1.30** and the core of jogyamycin **1.31** (Scheme 1.8).[21]

Scheme 1.7: *Nucleophilic Aziridine Opening*



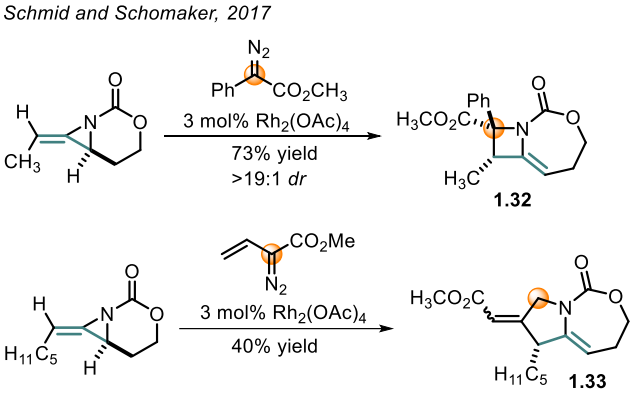
Scheme 1.8: *Complex Products Accessed Using Exocyclic Methyleneaziridines*



In a more recent approach to methyleneaziridine derivatization, the aziridine nitrogen was used as a nucleophile, attacking a Rh-bound carbene and triggering rearrangement to methyleneazetidines (Scheme 1.9).[22] As in those that precede it, this reaction utilizes the constrained geometry of the bicyclic methyleneaziridine to yield a highly diastereoselective

transformation. It was found to give the desired methyleneazetidines **1.32** with a range of carbenes, each time as a single diastereomer. Notably, with a vinylagous carbene, the ring could be expanded to a 2,4-dehydropyrrolidine **1.33**. This novel approach to methyleneaziridine reactivity is anticipated to have additional potential to access new motifs.

Scheme 1.9: *Electrophilic Addition to the Nitrogen of Exocyclic Methyleneaziridines*



The breadth of reactivity used in the derivatization of exocyclic methyleneaziridines demonstrate its utility as a versatile scaffold, especially notable for its flexible and stereocontroled synthesis of densely functionalized aminated motifs. By extension the endocyclic methyleneaziridine, becomes a structure of interest as a possible scaffold. While not previously explored, the differences in strain and steric accessibility imply that this endocyclic isomer would have different reactivity, making it an intriguing target for the development of new methods.

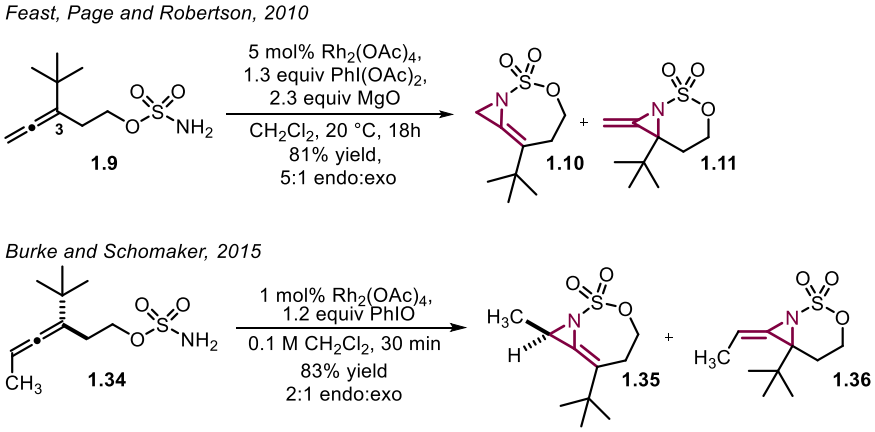
1.3 Synthesis of Endocyclic Methyleneaziridines, Strategy and Scope

The synthesis and resultant chemistry of exocyclic methyleneaziridines has been a fruitful area of discovery. Diverse methods for their derivatization have been developed, establishing the exocyclic methyleneaziridine as a flexible scaffold. However, the exocyclic methyleneaziridine is not the only possible product of intramolecular allene aziridination. The endocyclic

methyleneaziridine, formed from aziridination of the distal position of the allene, serves as a distinct scaffold around which new methods can be developed.

While exocyclic methyleneaziridines have been widely reported, their endocyclic isomers were limited to a single reference prior to the work described herein.[16] Feast and co-workers report the formation of endocyclic methyleneaziridine **1.10** in 68% yield as a mixture with the corresponding exocyclic methyleneaziridine **1.11** in 13% yield (Scheme 1.10). The presence of a bulky *tert*-butyl group at the C-3 position of sulfamate **1.9** is cited as the determining factor in the regioselectivity of this reaction, with the large group impeding formation of the more common exocyclic isomer. In our own studies, a related dialkyl substituted homoallenic sulfamate with a *tert*-butyl group at the C-3 position **1.34** also formed a mixture of regioisomers.[23] The endocyclic methyleneaziridine **1.35** was the major product with 56% yield, and the exocyclic methyleneaziridine **1.36** was formed in 27% yield (Scheme 1.10). While placing a sterically bulky group at the C-3 position does allow for formation of endocyclic methyleneaziridines, alone the strategy is insufficient to cleanly deliver the desired isomer.

Scheme 1.10: *Endocyclic Methyleneaziridines from tert-Butyl Substituted Allenes*



A more effective strategy to obtain the endocyclic methyleneaziridine as a single regioisomer came in combining the steric effects of a bulky group at C-3 with electronic direction

provided by silicon substitution of the allene (Scheme 1.11). When a silyl group was placed at C-3, exclusive formation of the endocyclic isomer was observed in high yields. This was attributed to a contribution from the β-silicon effect, in which a carbocation is stabilized through hyperconjugation with an adjacent C – Si bond. When the Rh-nitrene approaches the allene to form an aziridine at the distal position and give the endoyclic methyleneaziridine, the C – Si bond is co-planar with the p-orbital containing the developing positive charge on C-2. Hyperconjugation stabilizes this charge, lowering the energy of the transition state and increasing favorability of this pathway. However, when the Rh-nitrene approaches the proximal position of the allene, the orientation of the pi orbitals dictate the C – Si bond be perpendicular to the developing charge, and therefore no stabilization is possible. This effect, in addition to the increase in transition state energy dictated by the bulk of the Si containing group, discourages this pathway, delivering the formation of a single regioisomer.

Scheme 1.11: *The Role of Silicon in Allene-Aziridination Regioselectivity*

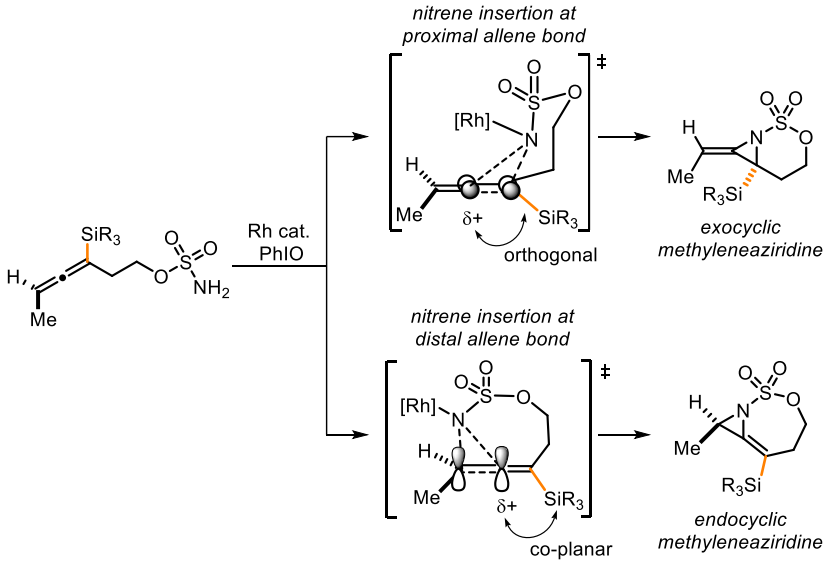
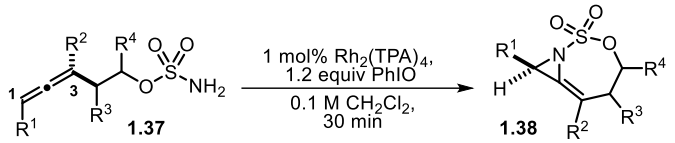
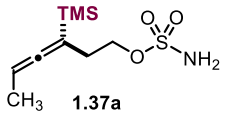
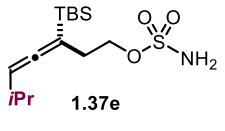
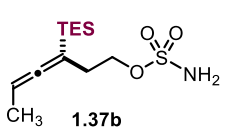
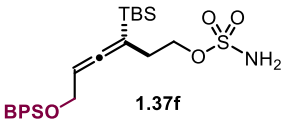
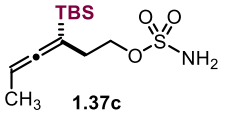
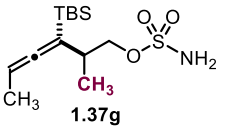
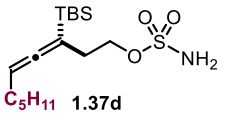
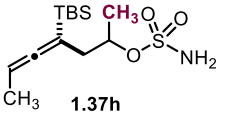


Table 1.1: *Scope of Endocyclic Methyleneaziridines*



entry		yield	entry		yield
1		82%	5		73%
2		96%	6		45%
3		95%	7		42%
4		86%	8		68%

A study of allene substitution was undertaken to better understand the extent of silicon's directing effects, and to determine the tolerance of the reaction to other substituents on the allene. First, the bulk of the silicon group was investigated (Table 1.1). When larger silyl groups such as *tert*-butyldimethylsilane (TBS) and triethylsilane (TES), were placed at C-3, clean reactions and high yields of 95% and 96% respectively were obtained. The smaller group, trimethylsilane (TMS), also gave the endocyclic methyleneaziridine **1.38a** as its sole product in 82% yield, with the slightly diminished yield being attributed to the increased lability of TMS. It is also notable that TMS has a smaller A-value than *t*Bu (2.5 vs 4.9) due to the longer C – Si bond, and so the high yield and regioselectivity of the TMS substituted **1.37a** reaction is further evidence for the electronic effect of silicon driving the regioselectivity of the reaction.[24]

Secondly, the effect of substitution at C-1 was probed (Table 1.1). Larger groups, such as a pentyl chain **1.37d** and an *iso*-propyl group **1.37e**, were placed at this position with no

disturbance to the formation of the endocyclic methyleneaziridine. However, when a tethered alcohol protected with the large *tert*-butyldiphenylsilane (BPS) was included at C-1, diminished yield was reported, along with recovered starting material **1.37f**. However despite this, no exocyclic methyleneaziridine was observed. This substrate also demonstrates that a tethered functionality is tolerated in the reaction. Unfortunately, aromatic groups were not tolerated as substituents of the allene. The starting homoallenic sulfamate was recovered, and its failure to react was attributed to the possible trapping of the catalyst in an intermediate stage of the reaction.

Finally, substitution along the sulfamate tether was investigated. While substitution along the tether could potentially disrupt necessary folding of the substrate, formation of the desired endocyclic methyleneaziridine was observed (**1.38g** and **1.38h**). It was found that placing alkyl groups at either position did not impede the success of the reaction, albeit with some diminishment in yield.

In conclusion, endocyclic methyleneaziridines were successfully synthesized *via* silicon substitution of the homoallenic sulfamate. The exclusive regioselectivity was attributable to a stabilizing β-silicon effect, and it was found that silicon groups of various sizes could direct the aziridination. High yields were obtained for a range of substitutions, although some limitations were identified. Overall, a reliable method for the synthesis of endocyclic methyleneaziridines was developed, enabling investigations of its novel reactivity.

1.5 Conclusions

The chemistry of methyleneazridines and the related bicyclic methyleneaziridines have become a fruitful area of discovery. Their synthesis has been accomplished in a variety of ways, with intramolecular nitrene insertion of allenes proving to be a reliable method of accessing

bicyclic methyleneaziridines. These exocyclic methyleneaziridines have been derivatized through aziridine ring opening, reaction of the 2-amidoallylcation, olefin functionalization, and ring expansion *via* nucleophilic attack of the nitrogen lone pair. With such a diverse range of reactivity demonstrated for the exocyclic isomer, the endocyclic methyleneaziridine became a tempting target. The differences in geometry and strain suggest the possibility of new reactivity which could yield motifs unique to those of the exocyclic isomers. A reliable silicon directing strategy for high yielding endocyclic methyleneaziridine synthesis was developed, and the chemistry of these structures will be the focus of the remaining chapters.

1.6 References

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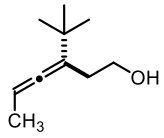
1.7 Experimental Details and Characterization

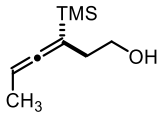
1.7.1 Preparation of homoallenic alcohols

General procedure: In a round bottom flask, lithium aluminum hydride (1 equiv) was suspended in dry THF (0.4 M) under nitrogen atmosphere and cooled to 0 °C. To this was added the corresponding homoallenic ester (1 equiv) dropwise as a solution in THF. The reaction mixture was stirred for 30 min, then quenched at 0 °C with H_2O (2.1 equiv), 1M aqueous NaOH (2.1 equiv), and H_2O (6.3 equiv). The organics were dried over Na_2SO_4, after which the solution was filtered and solvent was removed under reduced pressure. The residual oil was purified via column chromatography.

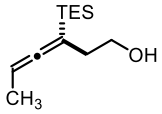


Precursor to compound 1.34. The homoallenic alcohol preceding sulfamate **1.34** was prepared from the corresponding homoallenic ethyl ester (2.13 g, 11 mmol). The crude product was purified

via column chromatography (0% EtOAc/hexanes to 15% EtOAc/hexanes, gradient) to yield the alcohol (360 mg, 2.1 mmol) as a clear oil in a yield of 21%. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 5.18 (qt, *J* = 6.8, 3.3 Hz, 1H), 3.73 (t, *J* = 6.1 Hz, 2H), 2.23 (m, *J* = 6.1, 3.3 Hz, 2H), 1.75 (s, 1H), 1.66 (d, *J* = 6.8 Hz, 3H), 1.05 (s, 9H). ^{13}C-NMR (126 MHz, $CDCl_3$) δ 110.24, 88.57, 61.87, 31.13, 30.55, 29.37, 15.17. HRMS (ESI) *m/z* calculated for $C_{10}H_{19}O$ [$M+H^+$] 155.1231; found 155.1426.

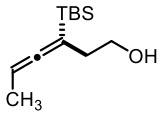


Precursor to compound 1.37a. The homoallenic alcohol preceding sulfamate **1.37a** was prepared from the corresponding homoallenic ethyl ester (3.79 g, 18 mmol). The crude product was purified *via* column chromatography (0% EtOAc/hexanes to 20% EtOAc/hexanes, gradient) to give pure alcohol (2.04 g, 12 mmol) as a clear oil in a yield of 67%. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 4.85 (qt, *J* = 6.9, 3.0 Hz, 1H), 3.74 (q, *J* = 5.7 Hz, 2H), 2.21 (tdd, *J* = 6.4, 3.9, 3.0 Hz, 2H), 1.71 (d, *J* = 5.5 Hz, 1H), 1.63 (d, *J* = 6.9 Hz, 3H), 0.09 (s, 9H). ^{13}C-NMR (126 MHz, $CDCl_3$) δ 206.23, 93.03, 80.76, 62.46, 32.46, 13.98, -1.46. HRMS (ESI) *m/z* calculated for $C_9H_{19}OSi$ [$M+H^+$] 171.1200; found 171.1195.

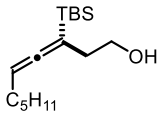


Precursor to compound 1.37b. The homoallenic alcohol preceding sulfamate **1.37b** was prepared from the corresponding homoallenic ester (0.52 g, 2.1 mmol). The crude product was purified *via* column chromatography (0% EtOAc/hexanes to 5% EtOAc/hexanes, gradient) to give pure alcohol (0.44 g, 2.1 mmol) as a clear oil in a yield of 100%. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 4.83 (qt, *J* = 6.8, 3.0 Hz, 1H), 3.75 (q, *J* = 5.1 Hz, 2H), 2.18 (tdd, *J* = 6.1, 3.1, 1.4 Hz, 2H), 1.78 (s, 1H), 1.64 (d, *J* = 6.9 Hz, 3H), 0.94 (t, *J* = 7.9 Hz, 10H), 0.60 (q, *J* = 7.9 Hz, 8H). ^{13}C-NMR (126 MHz,

CDCl3) δ 206.70, 89.72, 80.25, 62.33, 32.59, 13.99, 7.32, 3.07. HRMS (ESI) *m/z* calculated for $C_{12}H_{25}OSi$ [M+H$^+$] 213.1669 found 213.1668.

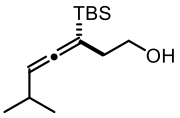


Precursor to compound 1.37c. The homoallenic alcohol preceding sulfamate **1.37c** was prepared from the corresponding homoallenic ester (3.0 g, 12 mmol). The crude product was purified *via* column chromatography (0% EtOAc/hexanes to 10% EtOAc/hexanes, gradient) to yield pure alcohol (2.55 g, 12 mmol) as a clear oil in a yield of 85%. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 4.85 (qt, *J* = 6.8, 3.1 Hz, 1H), 3.76 (q, *J* = 6.0 Hz, 2H), 2.22 (tt, *J* = 6.2, 3.0 Hz, 2H), 1.79 (s, 1H), 1.63 (d, *J* = 6.9 Hz, 3H), 0.91 (s, 9H), 0.05 (d, *J* = 1.9 Hz, 6H). ^{13}C-NMR (126 MHz, $CDCl_3$) δ 207.14, 90.87, 80.84, 62.51, 33.24, 26.80, 17.87, 13.97, -5.95, -5.98. HRMS (ESI) *m/z* calculated for $C_{12}H_{25}OSi$ [M+H$^+$] 213.1670; found 213.1674.

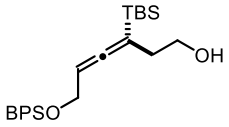


Precursor to compound 1.37d. The homoallenic alcohol preceding sulfamate **1.37d** was prepared from the corresponding homoallenic sulfamate (5.7 g, 18 mmol). The crude product was purified *via* column chromatography (0% EtOAc/hexanes to 5% EtOAc/hexanes, gradient) to give pure alcohol (3.9 g, 15 mmol) as a clear oil in a yield of 81%. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 4.87 (tt, *J* = 6.7, 3.2 Hz, 1H), 3.76 (q, *J* = 5.7 Hz, 2H), 2.22 (td, *J* = 6.0, 3.0 Hz, 2H), 1.98 (q, *J* = 7.2 Hz, 2H), 1.73 (d, *J* = 5.9 Hz, 1H), 1.45 – 1.21 (m, 7H), 0.90 (s, 9H), 0.88 (m, 2H), 0.05 (d, *J* = 1.3 Hz, 6H). ^{13}C-NMR (126 MHz, $CDCl_3$) δ 206.18, 91.29, 86.66, 62.54, 33.33, 31.64, 29.72, 28.89, 26.88,

22.64, 18.01, 14.19, 0.15, -5.82, -5.98. HRMS (ESI) *m/z* calculated for $C_{16}H_{33}NOSi$ [M+H$^+$] 269.2296; found 269.2297.

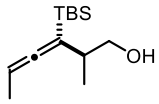


Precursor to compound 1.37e. The homoallenic alcohol preceding homoallenic sulfamate **1.37e** was prepared from the corresponding homoallenic ethyl ester (3.24 g, 11 mmol). The crude product was purified *via* column chromatography (0% EtOAc/hexanes to 5% EtOAc/hexanes, gradient) to give pure alcohol (2.4 g, 10 mmol) as a clear oil in a yield of 91%. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 4.90 (dt, *J* = 6.2, 3.2 Hz, 1H), 3.77 (qd, *J* = 6.0, 3.2 Hz, 2H), 2.29 (s, *J* = 6.6 Hz, 1H), 2.24 (td, *J* = 6.2, 3.2 Hz, 2H), 1.01 (dd, *J* = 6.8, 2.1 Hz, 6H), 0.91 (s, 9H), 0.06 (d, *J* = 0.9 Hz, 6H). ^{13}C-NMR (126 MHz, $CDCl_3$) δ 204.65, 94.22, 92.95, 62.58, 33.39, 28.05, 26.98, 23.16, 23.04, 18.15, -5.63, -6.03. HRMS (ESI) *m/z* calculated for $C_{14}H_{29}OSi$ [M+H$^+$] 241.1983; found 241.1980.

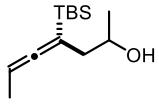


Precursor to compound 1.37f. The homoallenic alcohol preceding sulfamate **1.37f** was prepared from the corresponding homoallenic ethyl ester (1.84 g, 0.35 mmol). The crude product was purified *via* column chromatography (0% EtOAc/hexanes to 20% EtOAc/hexanes, gradient) to give pure alcohol (167 mg, 0.04 mmol) as a white solid in a yield of 10%. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.62 (dq, *J* = 6.5, 1.6 Hz, 4H), 7.39 – 7.28 (m, 6H), 4.97 (tt, *J* = 6.0, 3.2 Hz, 1H), 4.17 – 4.01 (m, 2H), 3.76 (ddd, *J* = 11.0, 6.9, 5.2 Hz, 1H), 3.65 (dt, *J* = 11.1, 5.7 Hz, 1H), 2.25 – 2.12 (m, 2H), 0.98 (s, 9H), 0.83 (s, 9H), 0.00 (s, 6H). ^{13}C-NMR (126 MHz, $CDCl_3$) δ 205.48, 135.77, 135.74, 129.84, 129.81, 127.85, 127.82, 93.79, 86.75, 62.15, 61.83, 33.33, 26.90, 26.85, 19.27,

18.00, -5.82, -6.09. HRMS (ESI) *m/z* calculated for $C_{28}H_{47}N_2O_4SSi_2$ [M+NH_4^+] 563.2795; found 563.2790.



Precursor to compound 1.37g. A racemic mixture of the homoallenic alcohol preceding sulfamate **1.37g** was prepared from the corresponding homoallenic ethyl ester (0.73 g, 2.7 mmol). The crude product was purified *via* column chromatography (0% EtOAc/hexanes to 10% EtOAc/hexanes, gradient) to give pure homoallenic alcohol (0.61 g, 2.7 mmol) as a clear oil in 100% yield as a single diastereomer. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 4.79 (tdd, *J* = 13.8, 6.9, 1.1 Hz, 1H), 3.53 (dq, *J* = 10.6, 6.2 Hz, 1H), 3.37 (dtd, *J* = 10.8, 6.3, 4.5 Hz, 1H), 2.16 (hept, *J* = 6.0, 5.6 Hz, 1H), 1.56 (d, *J* = 6.9 Hz, 3H), 0.99 (dd, *J* = 9.8, 6.8 Hz, 3H), 0.84 (s, 9H), -0.00 (d, *J* = 3.9 Hz, 6H). ^{13}C-NMR (126 MHz, $CDCl_3$) δ 207.62, 207.34, 96.65, 96.35, 81.83, 81.57, 67.90, 67.87, 36.83, 36.73, 26.73, 18.45, 18.06, 13.98, 13.75, -5.65, -5.71, -5.77, -5.80. HRMS (ESI) *m/z* calculated for $C_{13}H_{27}NOSi$ [M+H^+] 226.1826; found 227.1827.

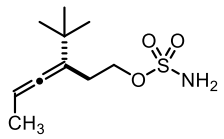


Precursor to compound 1.37h. A racemic mixture of the homoallenic alcohol preceding sulfamate **1.37h** was prepared from the corresponding homoallenic aldehyde (0.24 g, 1.1 mmol). The crude product was purified *via* column chromatography (0% EtOAc/hexanes to 15% EtOAc/hexanes, gradient) to give pure alcohol (0.26 mg, 1.1 mmol) as a clear oil in a yield of 97%. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 4.91 – 4.79 (m, 1H), 4.03 – 3.90 (m, 1H), 2.11 – 2.05 (m, 2H), 1.64 (dd, *J* = 6.9, 3.0 Hz, 3H), 1.21 (dd, *J* = 6.2, 1.1 Hz, 3H), 0.90 (d, *J* = 0.9 Hz, 9H), 0.06 – 0.03 (m, 6H). ^{13}C-NMR (126 MHz, $CDCl_3$) δ 207.26, 207.02, 91.57, 91.33, 80.93, 80.75, 80.75, 67.58, 67.56, 39.98,

39.84, 26.82, 26.71, 22.70, 17.92, 17.89, 13.97, 13.84, 0.15, -5.88, -5.91, -5.94. HRMS (ESI) *m/z* calculated for $C_{13}H_{27}OSi$ [M+H$^+$] 227.1826; found 227.1826.

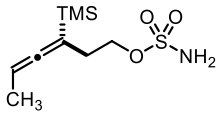
1.7.2 Preparation of homoallenic sulfamates

General procedure: In a 3-neck round bottom flask, chlorosulfonyl isocyanate (2.5 equiv) was cooled to 0℃. To this was added formic acid (2.5 equiv) dropwise. Vigorous gas evolution was observed. The resulting white solid was dissolved in CH_3CN to yield a 0.5 M solution. This solution was stirred at 0℃ for 30 min, and was then warmed to 23℃ and stirred an additional 4-12 h. The reaction was then cooled to 0℃, at which point the homoallenic alcohol (1 equiv) was added as a solution in DMA (0.6 M). The reaction was stirred for 1 h at 23℃, then quenched with the addition of an equal volume of H_2O. The aqueous phase was extracted with EtOAc (x3) and combined organic phases were washed with H_2O (x5). The organic phases were dried over Na_2SO_4, and solvent was removed *via* rotary evaporation. The crude material was purified *via* column chromatography.

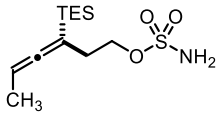


Compound 1.34. The homoallenic sulfamate **1.34** was prepared from the corresponding homoallenic alcohol (370 mg, 1.6 mmol). The crude product was purified *via* column chromatography (0% EtOAc/hexanes to 30% EtOAc/hexanes, gradient) to yield **1.34** (360 mg, 0.06 mmol) as a white solid in a yield of 64%. Mp=78℃. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 5.17 (qt, *J* = 6.8, 3.5 Hz, 1H), 4.64 (d, *J* = 8.5 Hz, 2H), 4.26 (td, *J* = 8.0, 2.3 Hz, 2H), 2.41 (hd, *J* = 8.5, 3.2 Hz, 2H), 1.64 (d, *J* = 6.9 Hz, 3H), 1.04 (s, 9H). ^{13}C-NMR (126 MHz, $CDCl_3$) δ 200.09, 107.99, 89.20, 77.41, 70.68, 33.70, 29.23, 26.46, 15.07, 0.15. IR (neat) 3360, 3274, 2961, 1552, 1343,

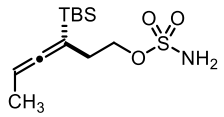
1174, 966, 926, 777. HRMS (ESI) *m/z* calculated for $C_{10}H_{19}NO_3SNa$ [M+Na^+] 256.0983; found 256.0978.



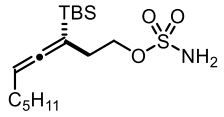
Compound 1.37a. The homoallenic sulfamate was prepared from the corresponding homoallenic alcohol (1.1 g, 6.5 mmol). The crude product was purified *via* column chromatography (0% EtOAc/hexanes to 20% EtOAc/hexanes, gradient) to give pure **1.37a** (1.5 g, 6.0 mmol) as a white solid in a yield of 92%. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 4.92 (s, 2H), 4.80 – 4.72 (m, 1H), 4.18 (t, *J* = 7.4 Hz, 2H), 2.27 (dtt, *J* = 11.4, 7.9, 4.0 Hz, 2H), 1.52 (d, *J* = 7.0 Hz, 3H), 0.00 (s, 9H). ^{13}C-NMR (126 MHz, $CDCl_3$) δ 206.73, 91.08, 81.54, 70.80, 28.19, 13.77, -1.58. HRMS (ESI) *m/z* calculated for $C_9H_{20}NO_3SSi$ [M+H^+] 250.0933; found 250.0928.



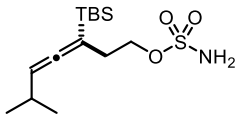
Compound 1.37b. The homoallenic sulfamate was prepared from the corresponding homoallenic alcohol (0.29 g, 1.4 mmol). The crude product was purified *via* column chromatography (0% EtOAc/hexanes to 20% EtOAc/hexanes, gradient) to give pure **1.37b** (0.27 g, 0.83 mmol) as a white solid in a yield of 69%. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 4.83 (dtd, *J* = 10.0, 6.9, 3.1 Hz, 1H), 4.65 (s, 2H), 4.29 (t, *J* = 7.4 Hz, 2H), 2.35 (tdd, *J* = 7.2, 3.0, 1.4 Hz, 2H), 1.62 (d, *J* = 7.0 Hz, 3H), 0.94 (t, *J* = 7.9 Hz, 9H), 0.60 (q, *J* = 7.9 Hz, 6H). ^{13}C-NMR (126 MHz, $CDCl_3$) δ 207.45, 87.87, 81.23, 70.81, 28.48, 13.99, 7.43, 3.15. HRMS (ESI) *m/z* calculated for $C_{12}H_{26}NO_3SSi$ [M+H^+] 252.1358; found 292.1398.



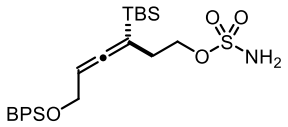
Compound 1.37c. The homoallenic sulfamate **1.37c** was prepared from the corresponding homoallenic alcohol (3.0 g, 14 mmol). The crude product was purified *via* column chromatography (0% EtOAc/hexanes to 20% EtOAc/hexanes, gradient) to yield pure **1.37c** (3.5 g, 12 mmol) as a waxy white solid in a yield of 84%. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 4.85 (dp, *J* = 10.1, 3.4 Hz, 1H), 4.66 (s, 2H), 4.29 (t, *J* = 7.4 Hz, 2H), 2.39 (tt, *J* = 7.2, 3.3 Hz, 2H), 1.62 (d, *J* = 7.0 Hz, 3H), 0.90 (s, 10H), 0.05 (s, 3H), 0.05 (s, 3H). ^{13}C-NMR (126 MHz, $CDCl_3$) δ 207.75, 88.81, 81.66, 70.78, 28.96, 26.74, 17.88, 13.85, -6.04, -6.08. IR (neat) ν = 3362, 3279, 2953, 2857, 1938, 1347, 1181, 804, 768. HRMS (ESI) *m/z* calculated for $C_{12}H_{26}NO_3SSi$ [M+H$^+$] 292.1403; found 292.1398.



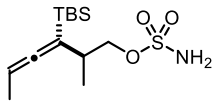
Compound 1.37d. The homoallenic sulfamate was prepared from the corresponding homoallenic alcohol (3.9 g, 15 mmol). The crude product was purified *via* column chromatography (0% EtOAc/hexanes to 10% EtOAc/hexanes, gradient) to give pure **1.37d** (1.3 g, 3.9 mmol) as a white solid in a yield of 26%. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 4.87 (tt, *J* = 6.7, 3.1 Hz, 1H), 4.68 (s, 2H), 4.35 – 4.24 (m, 2H), 2.39 (tt, *J* = 7.1, 3.0 Hz, 2H), 1.96 (q, *J* = 7.0 Hz, 2H), 1.48 – 1.22 (m, 7H), 0.90 (s, 9H), 0.89 (s, 2H), 0.06 (s, 6H). ^{13}C-NMR (126 MHz, $CDCl_3$) δ 206.85, 89.19, 87.40, 70.83, 31.66, 29.61, 29.03, 28.70, 26.82, 22.65, 18.01, 14.21, -5.90, -6.07. HRMS (ESI) *m/z* calculated for $C_{16}H_{33}NNaO_3SSi$ [M+Na$^+$] 370.5788; found 370.1843.



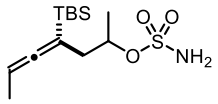
Compound 1.37e. The homoallenic sulfamate was prepared from the corresponding homoallenic alcohol (0.58 g, 2.4 mmol). The crude product was purified *via* column chromatography (0% EtOAc/hexanes to 5% EtOAc/hexanes, gradient) to give pure **1.37e** (0.72 g, 2.2 mmol) as a white solid in a yield of 93%. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 4.91 (dt, *J* = 6.2, 3.2 Hz, 1H), 4.66 (s, 2H), 4.30 (td, *J* = 7.6, 2.1 Hz, 2H), 2.41 (td, *J* = 7.4, 3.2 Hz, 2H), 2.34 – 2.21 (m, *J* = 6.7 Hz, 1H), 1.01 (d, *J* = 2.9 Hz, 3H), 0.99 (d, *J* = 2.9 Hz, 3H), 0.91 (s, 9H), 0.06 (s, 6H). ^{13}C-NMR (126 MHz, $CDCl_3$) δ 205.41, 94.93, 90.80, 70.78, 29.10, 27.87, 26.92, 23.16, 22.90, 18.15, -5.70, - 6.12. HRMS (ESI) *m/z* calculated for $C_{14}H_{30}NO_3SSi$ [M+H$^+$] 320.1716; found 320.1711.



Compound 1.37f. The homoallenic sulfamate was prepared from the corresponding homoallenic alcohol (0.22 g, 0.47 mmol). The crude product was purified *via* column chromatography (0% EtOAc/hexanes to 15% EtOAc/hexanes, gradient) to give pure **1.37f** (131 mg, 0.24 mmol) as a white solid in a yield of 51%. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.71 – 7.65 (m, 4H), 7.47 – 7.36 (m, 6H), 5.02 (tt, *J* = 6.6, 3.3 Hz, 1H), 4.94 (s, 2H), 4.35 – 4.25 (m, 2H), 4.23 (d, *J* = 6.7 Hz, 2H), 2.40 (tt, *J* = 6.3, 3.4 Hz, 2H), 1.05 (s, 9H), 0.87 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H), 0.00 (s, 4H). ^{13}C-NMR (126 MHz, $CDCl_3$) δ 205.76, 135.70, 133.32, 130.01, 127.98, 127.96, 91.64, 87.24, 69.89, 63.01, 28.67, 27.00, 26.75, 19.33, 17.99, 0.15, -5.96, -6.17. HRMS (ESI) *m/z* calculated for $C_{28}H_{47}N_2O_4SSi_2$ [M+NH_4^+] 563.2795; found 563.2790.



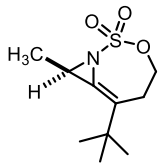
Compound 1.37g. The homoallenic sulfamate was prepared from the corresponding homoallenic alcohol (0.30 g, 1.3 mmol). The crude product was purified *via* column chromatography (0% EtOAc/hexanes to 20% EtOAc/hexanes, gradient) to give pure **1.37g** (0.26 g, 0.84 mmol) as a clear oil in 64% yield as a 1:1 mixture of diastereomers. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 4.88 (overlapping m, 1H), 4.65 (s, 2H), 4.20 (overlapping m, 1H), 3.88 (td, *J* = 9.1, 2.6 Hz, 1H), 2.46 – 2.34 (m, 1H), 1.62 (dd, *J* = 7.0, 3.4 Hz, 3H), 1.13 (dd, *J* = 11.1, 6.7 Hz, 3H), 0.90 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H). ^{13}C-NMR (126 MHz, $CDCl_3$) δ 208.40, 208.10, 95.31, 95.07, 82.82, 82.66, 75.70, 75.66, 33.62, 33.59, 26.78, 26.10, 18.90, 18.51, 17.98, 17.89, 14.35, 13.90, 13.71, -5.66, -5.72, -5.78, -5.79. HRMS (ESI) *m/z* calculated for $C_{13}H_{27}NNaO_3SSi$ [M+Na^+] 328.1379; found 328.1374.



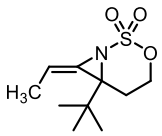
Compound 1.37h. The homoallenic sulfamate was prepared from the corresponding homoallenic alcohol (0.25 g, 1.1 mmol). The crude product was purified *via* column chromatography (0% EtOAc/hexanes to 20% EtOAc/hexanes, gradient) to give pure **1.37h** (65 mg, 0.21 mmol) as a white solid in a yield of 19%. The product was isolated as a 1:1 mixture of diastereomers, as indicated by quantitative ^{13}C-NMR. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 4.81 (overlapping m, 2H), 4.65 (s, 2H), 2.59 – 2.49 (m, 1H), 2.16 (dddd, *J* = 15.1, 8.7, 6.8, 2.7 Hz, 1H), 1.63 (dd, *J* = 7.0, 1.7 Hz, 3H), 1.46 (dd, *J* = 6.2, 2.1 Hz, 3H), 0.90 (d, *J* = 0.8 Hz, 9H), 0.07 – 0.04 (m, 6H). ^{13}C-NMR (126 MHz, $CDCl_3$) δ 208.31, 208.00, 89.41, 89.09, 81.39, 81.33, 81.30, 81.12, 36.99, 36.80, 26.77, 20.53, 20.46, 17.98, 17.91, 13.67, 13.52, -5.88, -6.01. HRMS (ESI) *m/z* calculated for $C_{13}H_{28}NO_3SSi$ [M+H^+] 306.1556; found 306.1554.

1.7.3 Preparation of homoallenic sulfamates

General procedure: The following procedure was adapted from our previously reported syntheses of exocyclic bicyclic methyleneaziridines. The corresponding sulfamate (1 equiv) and $Rh_2(OAc)_4$ (0.05 equiv) were placed in a dry round bottom flask. The solids were dissolved in CH_2Cl_2 (0.2 M), and the resulting solution was stirred for 5 min. PhIO (1.2 equiv) was added in a single portion and the reaction was stirred for 30 min, while monitoring by TLC. When TLC indicated complete consumption of the starting material, the solvent was removed *via* rotary evaporation and the crude reaction mixture was immediately purified *via* column chromatography.

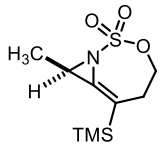


Compound 1.35. The methyleneaziridine was prepared from the corresponding homoallenic sulfamate (50 mg, 0.21 mmol) using the general procedure. The crude product was purified *via* column chromatography (0% EtOAc/hexanes to 15% EtOAc/hexanes, gradient) to give **1.35** (27 mg, 0.12 mmol) as a white solid in a yield of 56%. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 4.51 (m, 2H), 3.74 (qd, *J*=5.85, 1.82, 1H), 2.91 (dddd, *J*=16.6, 2.78 Hz, 1H) 1.56 (d, *J*=5.8, 3H) 1.11 (s, 9H) ^{13}C-NMR (500 MHz, $CDCl_3$) δ 126.85, 121.17, 75.04, 50.33, 35.35, 28.20, 16.68. HRMS (ESI) *m/z* calculated for $C_{10}H_{21}N_2O_3S$ [M+NH_4^+] 249.1273; found 249.1268.

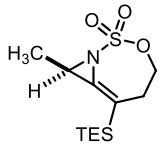


Compound 1.36. The methyleneaziridine was prepared from the corresponding homoallenic sulfamate (50 mg, 0.21 mmol). Purification *via* column chromatography (0% EtOAc/hexanes to

15% EtOAc/hexanes, gradient) gave pure **1.36** (13 mg, 0.06 mmol) as a white solid in a yield of 27%. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 5.75 (q, *J*=7.04, 1H), 4.41 (ddd, *J*=11.73, 5.14, 3.69, 1H), 4.30 (td, *J*=11.66, 11.25, 3.37, 1H), 2.50 (ddd, *J*=15.73, 10.76, 5.17, 1H), 2.12 (m, 1H), 1.80 (d, *J*=7.05, 3H) ^{13}C-NMR (126 MHz, $CDCl_3$) δ 126.94, 102.08, 67.54, 66.98, 35.13, 25.91, 21.48, 14.08. HRMS (ESI) *m/z* calculated for $C_{10}H_{18}NO_3S$ [M+H$^+$] 232.0929; found 232.1002.

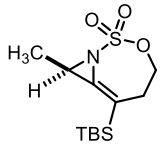


Compound 1.38a. The methyleneaziridine was prepared from the corresponding homoallenic sulfamate (50 mg, 0.20 mmol). Purification *via* column chromatography (0% EtOAc/hexanes to 0% EtOAc/hexanes, gradient) gave pure **1.38a** (32 mg, 0.13 mmol) as a white solid in a yield of 2%. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 4.43 – 4.33 (m, 2H), 3.62 (qd, *J* = 5.9, 1.7 Hz, 1H), 2.85 – 2.71 (m, 1H), 2.17 (dt, *J* = 16.5, 3.1 Hz, 1H), 1.42 (d, *J* = 5.9 Hz, 3H), 0.00 (s, 9H). ^{13}C-NMR (126 MHz, $CDCl_3$) δ 132.06, 113.51, 74.95, 51.03, 28.53, 16.64, -2.01. HRMS (ESI) calculated for $C_9H_{18}NO_3SSi$ [M+H$^+$] 248.0777; found 248.0772.

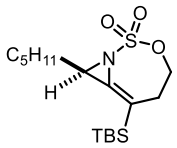


Compound 1.38b. The methyleneaziridine was prepared from the corresponding homoallenic sulfamate (50 mg, 0.21 mmol). Purification *via* column chromatography (0% EtOAc/hexanes to 15% EtOAc/hexanes, gradient) gave pure **12** (38 mg, 0.13 mmol) as a white solid in a yield of 83%. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 4.56 (td, *J* = 11.3, 10.6, 1.5 Hz, 1H), 4.50 (dt, *J* = 11.9, 3.5 Hz, 1H), 3.77 (qd, *J* = 5.9, 1.7 Hz, 1H), 2.94 (dddd, *J* = 16.2, 10.5, 2.8, 1.9 Hz, 1H), 2.31 (ddd, *J* = 16.5, 4.0, 1.4 Hz, 1H), 1.56 (d, *J* = 5.9 Hz, 3H), 0.95 (t, *J* = 7.9 Hz, 9H), 0.64 (qd, *J* = 7.9, 2.1

Hz, 7H). ^{13}C-NMR (126 MHz, $CDCl_3$) δ 133.04, 110.94, 74.71, 51.05, 28.98, 16.66, 7.33, 2.67. HRMS (ESI) calculated for $C_{12}H_{24}NO_3SSi$ [M+H$^+$] 290.1246; found 290.1241.

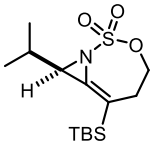


Compound 1.38c. The methyleneaziridine was prepared from the corresponding homoallenic sulfamate (1.2 g, 4.0 mmol). Purification *via* column chromatography (0% EtOAc/hexanes to 10% EtOAc/hexanes, gradient) gave pure **1.38c** (1.1 g, 3.8 mmol) as a white solid in a yield of 95%. Mp=88℃. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 4.58 (td, *J* = 11.5, 11.0, 1.3 Hz, 1H), 4.49 (ddd, *J* = 11.9, 3.9, 2.8 Hz, 1H), 3.76 (qd, *J* = 5.9, 1.8 Hz, 1H), 2.97 (ddt, *J* = 15.6, 10.9, 2.3 Hz, 1H), 2.36 (ddd, *J* = 16.5, 4.0, 1.3 Hz, 1H), 1.56 (d, *J* = 5.9 Hz, 3H), 0.90 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H). ^{13}C-NMR (126 MHz, $CDCl_3$) δ 133.44, 111.72, 74.78, 51.15, 29.73, 26.65, 17.69, 16.67. IR (neat) ν = 2958, 2930, 2886, 2858, 1754, 1275, 834. HRMS (ESI) calculated for $C_{12}H_{24}NO_3SSi$ [M+H$^+$] 290.1246 found 290.1241.

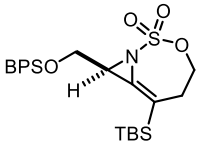


Compound 1.38d. The methylene aziridine was prepared from the corresponding homoallenic sulfamate (1.5 g, 4.3 mmol). Purification *via* column chromatography (0% EtOAc/hexanes to 10% EtOAc/hexanes, gradient) gave pure **1.38d** (1.3 g, 3.7 mmol) as a white solid in a yield of 86%. Mp=50℃. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 4.57 (t, *J* = 10.9 Hz, 1H), 4.48 (ddd, *J* = 11.9, 3.8, 2.8 Hz, 1H), 3.74 – 3.69 (m, 1H), 2.97 (ddt, *J* = 16.1, 11.0, 2.4 Hz, 1H), 2.36 (ddd, *J* = 16.4, 3.9, 1.2 Hz, 1H), 2.01 – 1.90 (m, 1H), 1.59 – 1.48 (m, 6H), 1.40 – 1.28 (m, 4H), 0.90 (s, 9H), 0.11 (d, *J* = 6.7 Hz, 6H). ^{13}C-NMR (126 MHz, $CDCl_3$) δ 132.98, 111.64, 74.72, 55.73, 31.24, 30.32, 29.82,

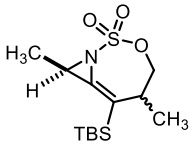
26.69, 26.16, 22.56, 17.76, 14.10, -6.23, -6.34. IR (neat) ν = 3357, 3271, 2961, 1343, 1174, 927, 551. HRMS (ESI) calculated for $C_{16}H_{25}NO_3SSi$ [M+H$^+$] 346.1872; found 346.1867.



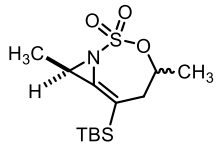
Compound 1.38e. The methylene aziridine was prepared from the corresponding homoallenic sulfamate (50 mg, 0.16 mmol). Purification *via* column chromatography (0% EtOAc/hexanes to 5% EtOAc/hexanes, gradient) gave pure **1.38e** (38 mg, 0.12 mmol) as a white solid in a yield of 77%. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 4.45 (t, *J* = 10.9 Hz, 1H), 4.37 (ddd, *J* = 11.9, 3.7, 2.9 Hz, 1H), 3.56 (dd, *J* = 4.5, 1.8 Hz, 1H), 2.88 (ddt, *J* = 16.0, 11.0, 2.5 Hz, 1H), 2.26 (ddd, *J* = 16.4, 3.8, 1.1 Hz, 1H), 2.01 (pd, *J* = 6.8, 4.6 Hz, 1H), 1.04 (d, *J* = 6.8 Hz, 3H), 0.83 (d, *J* = 6.8 Hz, 3H), 0.80 (s, 9H), 0.02 (s, 3H), 0.00 (s, 3H). ^{13}C-NMR (126 MHz, $CDCl_3$) δ 132.71, 112.11, 74.60, 60.93, 30.05, 28.49, 26.79, 19.77, 17.98, 17.81, -6.11, -6.26. HRMS (ESI) calculated for $C_{14}H_{30}N_2O_3SSi$ [M+NH_4^+] 335.1825; found 335.1820.



Compound 1.38f. The methyleneaziridine was prepared from the corresponding homoallenic sulfamate (30 mg, 0.05 mmol). Purification *via* column chromatography (0% EtOAc/Hex to 15% EtOAc/Hex, gradient) gave pure **1.38f** as a white solid (13 mg, 0.02 mmol) in 44% yield. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.69 (m, 4H), 7.42 (m, 6H), 4.60 (t, *J* = 10.9 Hz, 1H), 4.54 – 4.46 (m, 1H), 4.02 – 3.93 (m, 1H), 3.88 – 3.79 (m, 2H), 3.03 – 2.89 (m, 1H), 2.42 – 2.31 (m, 1H), 1.05 (s, 9H), 0.88 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H). ^{13}C-NMR (126 MHz, $CDCl_3$) δ 135.80, 135.75, 132.83, 130.05, 130.04, 127.99, 112.65, 74.79, 62.39, 55.26, 29.81, 26.80, 26.68, 19.36, 17.75, - 6.28, -6.46. HRMS (ESI) *m/z* calculated for $C_{28}H_{45}N_2O_4SSi$ [M + NH_4^+] 561.2639; found 561.2634.



Compound 1.38g. The methyleneaziridine was prepared from the corresponding homoallenic sulfamate (50 mg, 0.21 mmol). Purification *via* column chromatography (0% EtOAc/ Hex to 10% EtOAc/Hex, gradient) gave pure **1.38g** as a white solid (27 mg, 0.09 mol) in a yield of 42%. Mp=116℃. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 4.70 (d, *J* = 11.8 Hz, 1H), 4.25 (dd, *J* = 11.9, 2.9 Hz, 1H), 3.68 (q, *J* = 5.9 Hz, 1H), 2.59 (qd, *J* = 7.1, 1.8 Hz, 1H), 1.54 (d, *J* = 5.9 Hz, 3H), 1.38 (d, *J* = 7.1 Hz, 3H), 0.92 (s, 10H), 0.13 (s, 3H), 0.09 (s, 3H). ^{13}C-NMR (126 MHz, $CDCl_3$) δ 131.99, 117.59, 78.94, 49.81, 35.10, 26.63, 17.81, 16.54, 16.12, -5.96, -6.81. IR (neat) ν = 3355, 3270, 2960, 1732, 1227, 1077, 835, 764. HRMS (ESI) *m/z* calculated for $C_{13}H_{29}N_2O_3SSi$ [M + NH_4^+] 321.1668; found 321.1663.



Compound 1.38h. The methyleneaziridine was prepared from the corresponding homoallenic sulfamate (50 mg, 0.17 mmol). Purification *via* column chromatography (0% EtOAc/ Hex to 10% EtOAc/Hex, gradient) gave pure **1.38h** white solid in a 1:1 mixture of diastereomers (35 mg, 0.12 m mol). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 5.43 (dtt, *J* = 12.6, 6.3, 3.1 Hz, 1H), 4.86 (dq, *J* = 10.2, 6.5 Hz, 1H), 3.73 – 3.58 (m, 2H), 2.87 (ddd, *J* = 16.1, 10.2, 1.8 Hz, 1H), 2.64 (ddd, *J* = 17.8, 2.8, 1.4 Hz, 1H), 2.51 (ddd, *J* = 17.8, 11.0, 1.1 Hz, 1H), 2.27 (d, *J* = 16.0 Hz, 1H), 1.56 (d, *J* = 5.9 Hz, 2H), 1.54 (d, *J* = 5.9 Hz, 3H), 1.48 (d, *J* = 6.3 Hz, 2H), 1.43 (d, *J* = 6.5 Hz, 3H), 0.90 (s, 5H), 0.89 (s, 8H), 0.10 (s, 6H), 0.09 (s, 3H). ^{13}C-NMR (126 MHz, $CDCl_3$) δ 133.59, 132.72, 110.59, 107.62, 85.18, 80.58, 49.78, 38.42, 36.15, 29.83, 26.76, 26.62, 22.01, 21.25, 17.71, 16.55, -6.19, -6.23, -

6.34, -6.43. HRMS (ESI) *m/z* calculated for $C_{13}H_{29}N_2O_3SSi$ [M + NH_4^+] 321.1668; found 321.1663.

Chapter 2.

Synthesis of Azetidin-3-ones from Endocyclic Methyleneaziridines and their Derivatization

This chapter is adapted from sections published in:

Burke, E. G.; Schomaker, J. M.

Angew. Chem. Int. Ed., **2015**, *54*, 12097-12101.

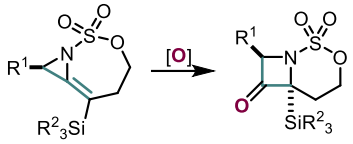
Chapter 2

Synthesis of Azetidin-3-ones from Endocyclic Methyleneaziridines and their Derivatization

2.1 Introduction

Exocyclic methyleneaziridines have had success in being applied to a range of synthetic challenges. Their endocyclic isomers, however, had not previously been explored because of the difficulty associated with synthesizing them selectively. Once a reliable method of directing nitrene insertion to the distal position *via* silyl substitution of the allene was developed, the utility of endocyclic methyleneaziridines as scaffolds upon which to build complex motifs could be explored. This chapter describes how the unique strain and steric environment of endocyclic methylene aziridines was leveraged in the ring expansion to azeitidin-3-ones, and describes the elaboration of these small rings to their azetidine derivatives (Scheme 2.1).

Scheme 2.1: *Synthesis of Azetidin-3-ones from Endocyclic Methyleneaziridines*

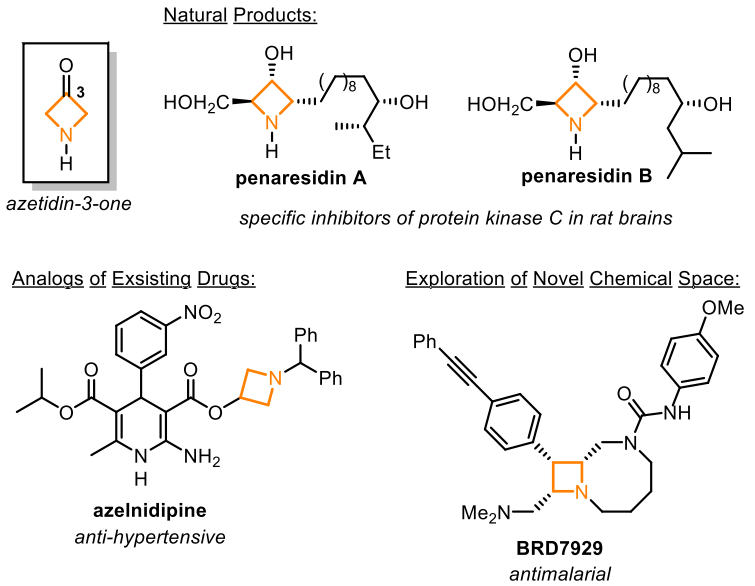


2.2 Background

Azetidin-3-ones and their azetidine-3-ol derivatives are less well known than the azetidin-2-one isomers (β-lactams), widely known for their use as antibiotics.[1] Despite their relative obscurity, they are a class of molecules which have been recognized as having biological relevance (Figure 2.1).[2] Natural products such as penaresidin A and B have been identified as specific

inhibitors of actomyosin ATPase, an enzyme which plays a key role in muscle contraction.[3] Outside of naturally occurring molecules, azetidin-3-ols have also been integrated into useful drug analogs, as is the case with azelnidipine.[4] The class of drugs to which it belongs has been used to treat hypertension, and inclusion of the azetidine led to mitigation of undesired side effects such as increased heart rate.[5] Additionally, azetidines have been the subject of growing interest as an area of underexplored chemical space, and as a result of these investigations compounds such as BRD7929 have been identified as having value, in this case, as an antimalarial lead.[6] However, despite an established case for interest in this motif, their continued study is hampered by challenging synthesis of the strained and sterically encumbered ring.

Figure 2.1: *Bioactive Azetidines*

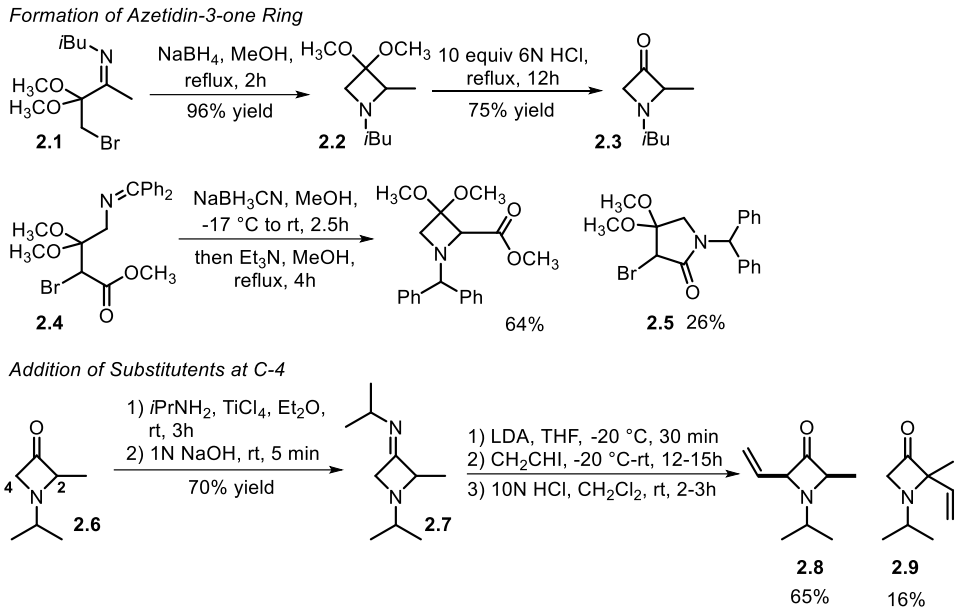


While many strategies such as oxidative ring contraction and expansion of azabicyclo[1.1.0]butanes have been found to be effective methods for the synthesis of azetidin-3-ones, syntheses which allow for the inclusion of varied substitution or control of diastereoselectivity are more rare.[7] One such example comes from De Kimpe and co-workers, and

uses the ring closing of a β-bromoketimine **2.1** to give singly substituted azetidin-3-ones **2.3** which can be further elaborated in subsequent steps (Scheme 2.2).[8] The β-bromoketimines **2.1**, synthesized from corresponding diones, are closed to 3,3-dimethoxyazetidines **2.2** and then hydrolyzed under acidic conditions to yield the desired azetidin-3-ones **2.3**. This route was used to target the core of penaresidin (Figure 2.1), though it proved problematic. While the 4-membered ring was formed as the sole product for alkyl-substituted β-bromoketimines **2.1**, competing formation of the 4,4-dimethoxypyrrolidin-2-one **2.5** was reported in the case of ester-substituted β-bromoketimine **2.4** analogs. Additionally, the inclusion of substitution at C-4 was achieved by conversion of the singly substituted azetidine-3-one **2.6** to an imine **2.7**, followed by deprotonation with a bulky base at the less sterically hindered C-4 position at low temperatures. While this approach did favor substitution at C-4 resulting in azetidinone **2.8**, C-2 substitution resulting in azetidinone **2.9** was also reported. The separation of isomers was challenging, and in some cases, impossible. Additionally, the undesired stereoisomer of the penaresidin azetidine was formed upon substitution, and a method to address this was not reported. While this strategy did successfully yield asymmetric azetidin-3-ones, it also proved a showcase for the challenges of adding substituents to small rings selectively.

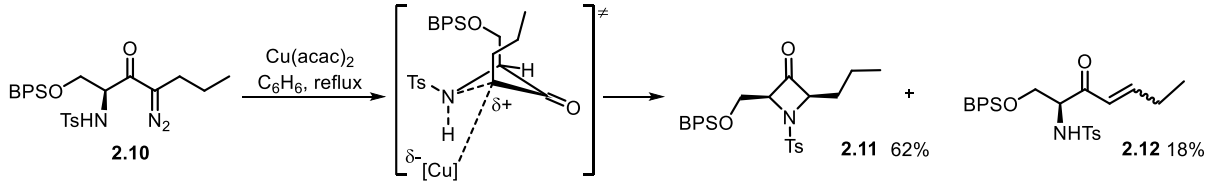
As an alternative to adding substituents after ring formation, another strategy is to build substitution into linear starting materials which is retained after cyclization. This was the strategy employed by Burtoloso and Correia in their copper catalyzed carbenoid N-H insertion of α,α'-dialkyl-α-diazoketones (Scheme 2.3).[9] The starting diazoketone **2.10** was prepared from L-serine, with this as the source of initial stereochemical information. Upon ring formation, only the cis-isomer **2.11** was observed. This stereochemical outcome was rationalized to be the result of minimization of steric interference with the approaching metal during the transition state. A

Scheme 2.2: *De Kimpe and Co-Workers Synthesis of Azetidin-3-ones*



limited substrate scope was explored, with each substrate giving only the cis-stereoisomer in modest yields. While this method does successfully give single isomers of substituted azetidin-3-ones **2.11**, it does suffer from substantial competing β-hydride elimination **2.12** which can be minimized but not eliminated through manipulation of reaction conditions.

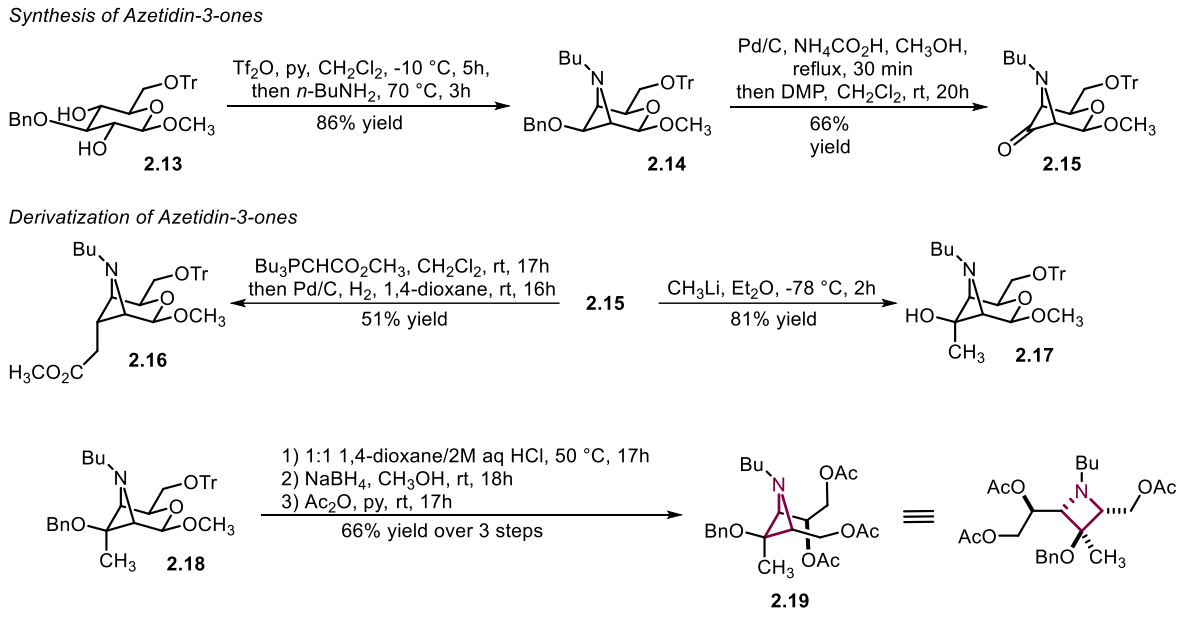
Scheme 2.3: *Burtoloso and Correia Synthesis of Azetidin-3-ones*



A third strategy for the synthesis of highly substituted azetidin-3-ones which was presented by Martinez and Fleet, and uses sugars as initial sources of stereochemistry (Scheme 2.4).[10] In this report, a double amine displacement of a protected sugar **2.13** would yield single enantiomers of bicyclic azetidines **2.14** in high yields. Oxidation with Dess Martin periodinane (DMP) gave

the desired azetidin-3-one **2.15**. These azetidin-3-ones **2.15** were further elaborated, with Witting olefination **2.16** or the stereospecific reduction of the carbonyl **2.17**. The acetal could be opened upon hydrolysis under acidic conditions **2.19**, though this was only demonstrated from azetidin-3-ol derivatives **2.18**, and not from the corresponding azetidine-3-ones **2.15**. This method is appealing for its high yields, and stereo- and regiochemical control of substituents. However, its use of carbohydrate starting materials and limited potential for derivatization are drawbacks.

Scheme 2.4: *Martinez and Fleet's Synthesis and Derivatization of Azetidin-3-ones*

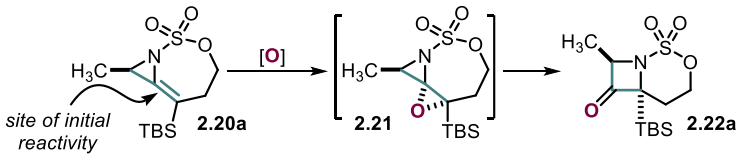


In order to fully exploit the potential of new biologically relevant azetidin-3-one and azetidine products, a synthesis is needed which can incorporate a range of functionality in a stereodefined manner into the highly substituted small rings. This is a challenging prospect, and several methods have been developed in effort to fill this need. While these previously reported methods do give the desired products, there are remaining drawbacks in scope and selectivity. Herein is presented an alternative synthesis which uses the rearrangement of endocyclic methyleneaziridines as a unique route to azetidin-3-ones and their azetidine derivatives.

2.3 Synthesis of Azetidin-3-ones

While the majority of azeitin-3-one forming methods focus on converting linear substrates to cyclic products, this approach has inherent drawbacks. High substitution of linear precursors may necessitate unwieldy syntheses or promote the formation of unwanted side products, while additions to less substituted azetidin-3-ones suffer from poor regio- or stereocontrol. An alternative to these approaches would be to form the azetidin-3-one *via* a ring expansion, and the endocyclic methyleneaziridine makes an ideal starting point for this strategy (Scheme 2.5).[11] Owing to its unique strain, the olefin of the endocyclic isomer **2.20a** is higher in energy than its exocyclic counterpart. This allowed for epoxidation **2.21**, which was followed by rapid rearrangement of the spirocyclic intermediate to form the azetidin-3-one **2.22b**. Additionally, the high substitution found in the endocyclic methyleneaziridine would be transferred in a stereodefined manner to the product rings. This synthesis yielded a trisubstituted ring diastereoselectively **2.22b** with high potential for further derivatization.

Scheme 2.5: *Conversion of Endocyclic Methyleneaziridines to Azetidin-3-ones*



The success of this ring expansion method hinged on the clean epoxidation of the olefin. With other functional groups present in the molecule, and a bulky silyl group potentially blocking the approach to the olefin, the selection of the appropriate oxidizing agent was challenging. The first reagent which was attempted was dimethyldioxirane (DMDO) (Table 2.1). Because of its small size, it was hypothesized that it would be able to approach the olefin with minimal negative interactions with the bulky silyl group. Upon reaction of 2 equivalents of DMDO with methyleneaziridine **2.12a**, the desired azetidin-3-one was observed in 27% yield, with the

remainder of the mass being converted to a number of unisolable products. While this was a promising starting point, the consistency of DMDO concentration from batch to batch was a concern, and so commercially available reagents were explored. Magnesium monoperoxyphthalate (MMPP) was tried without success, and *meta*-chloroperoxybenzoic acid (*m*CPBA) returned only 5% of the desired product, with the remaining starting material being lost to decomposition. However, when diluted from 0.3M to 0.05M the reaction with *m*CPBA was found to dramatically improve, giving 84% of the azetidin-3-one as a single diastereomer. The relative stereochemistry of this diastereomer was determined by nOe studies, which showed interaction between the substituents of the silyl group and the proton on C-1, but no interaction with the protons of the methyl group also at C-1.[11] With the conditions of the reaction thus optimized, further exploration of this method could be undertaken.

Table 2.1: *Optimization of Oxidation Conditions*

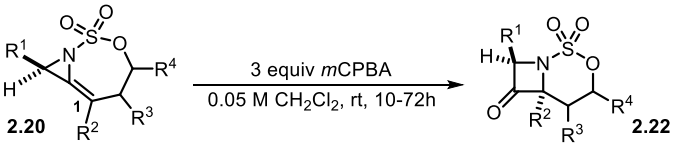
entry	conditions	yield	d.r.
1	2 equiv DMDO, 0.1 M CH_2Cl_2	27%	--
2	1 equiv MMPP in 4:1 H_2O:MeOH, 0.1 M	0%	--
3	3 equiv *m*CPBA, 0.3 M CH_2Cl_2	5%	--
4	3 equiv *m*CPBA, 0.1 M CH_2Cl_2	75%	>19:1
5	3 equiv *m*CPBA, 0.05 M CH_2Cl_2	84%	>19:1

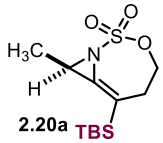
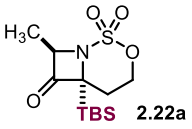
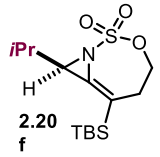
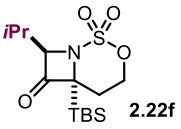
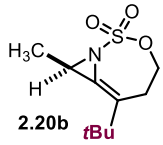
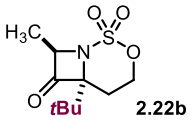
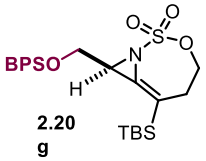
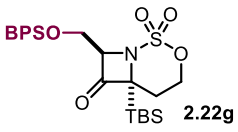
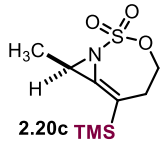
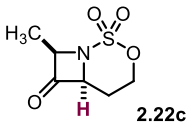
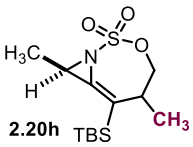
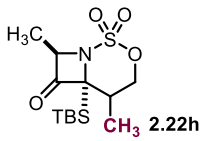
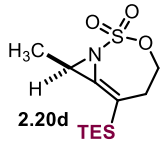
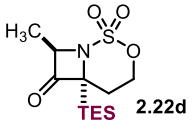
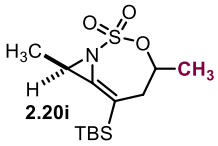
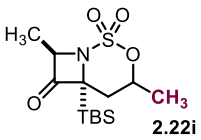
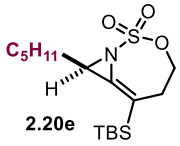
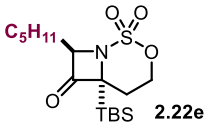
>19:1 d.r. indicated only one isomer observed at the detection limit of ^{1}H-NMR

A range of endocyclic methyleneaziridines were then subjected to the chosen reaction conditions to assess the generality of the reaction (Table 2.2). First, the *tert*-butyl substituted methyleneaziridine **2.20b** performed similarly to those which were silyl-substituted at C-1. This indicated that the silicon, which had been crucial in the formation of the endocyclic methyleneaziridine, was not playing a role in directing this reaction. Also of interest was the reaction of the TMS substituted methyleneaziridine **2.20c**. Analysis of the crude product showed

the expected azetidinone product with the TMS group still present in the structure. Yet after purification with silica gel, desilyation occurred with retention of diastereomeric purity to yield azetidinone **2.22c**. This unexpected result offered ease in removal of the silyl group used to direct the formation of the endocyclic methylene aziridine, facilitating access to 2,4-disubstituted azetidinones such as **2.22c**. Other substituents such as *iso*-propyl (**2.20f**), or the tethered alcohol (**2.20g**) were tolerated in modest yields, as was substitution of along the sulfamate ring (**2.20h** and **2.20i**). Altogether, the epoxidation and rearrangement was found to be reasonably general, with

Table 2.2: *Scope of Azetidin-3-one Synthesis*



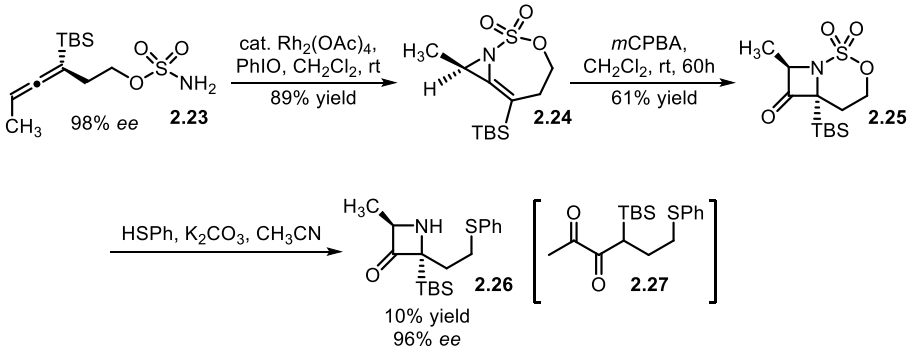
entry		yield	d.r.	entry		yield	d.r.
1	 2.20a TBS	 TBS 2.22a	84%	>19:1	6	 2.20 f TBS	 TBS 2.22f	66%	>19:1
2	 2.20b *t*Bu	 *t*Bu 2.22b	72%	>19:1	7	 2.20 g TBS	 TBS 2.22g	45%	>19:1
3	 2.20c TMS	 H 2.22c	63%	>19:1	8	 2.20h TBS	 TBS CH3 2.22h	77%[a]	>19:1[b]
4	 2.20d TES	 TES 2.22d	63%	>19:1	9	 2.20i TBS	 TBS CH3 2.22i	68%	>19:1[b]
5	 2.20e TBS	 TBS 2.22e	83%	>19:1					

[a]Yield based on recovered starting material. [b]>19:1 for each isomer
>19:1 d.r. indicated only one isomer observed at the detection limit of ^{1}H-NMR

the desired azetidinone formed for all endocyclic methyleneaziridines upon which it was attempted.

One of the more interesting features of using allenes as starting materials is that they possess axial chirality which can potentially be transferred to point chirality in the products of their reaction.[12] To see if this could be possible for the transformation of homoallenic sulfamates to the endocyclic methyleneaziridine and on to the azetidin-3-one, an enantiopure homoallenic sulfamate **2.23** was prepared. The sulfamate was then converted to the methyleneaziridine **2.24** *via* Rh-catalyzed nitrene insertion, and the resulting endocyclic methyleneaziridine **2.24** was subjected to the epoxidation and rearrangement conditions (Scheme 2.6). The product azetidin-3-one **2.25** was formed as expected, then derivatized to include a chromophore for chiral HPLC analysis, **2.26**. This was done by opening of the sulfamate ring with thiophenol and subsequent hydrolysis. The low yield was attributed to the opening of the azetidin-3-one to the di-one side product **2.27**. As anticipated, transfer of chirality was observed; the product azetidin-3-one **2.26** measured to have 96% *ee*. This transfer of chirality would be of interest to those looking to access enantiopure azetidin-3-ones or their azetidine derivatives.

Scheme 2.6: *Transfer of Chirality in Azetidin-3-one Synthesis*



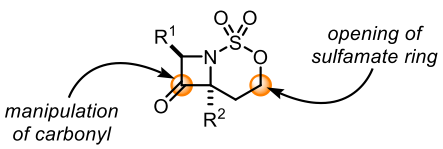
In conclusion, a new approach to azetidin-3-one synthesis was presented in which an endocyclic methyleneaziridine underwent ring expansion *via* epoxidation of the olefin and

subsequent rearrangement. The reaction was optimized for the use of a commercial oxidant (*m*CPBA), and the conditions were successfully applied to the synthesis of a range of azetidin-3-ones. Additionally, it was found that axial chirality originating in the homoallenic sulfamate could be converted to point chirality in the synthesis of the endocyclic methyleneaziridine, and then preserved in the conversion to the azetidin-3-one. Altogether this unique synthesis is an alternative to previously described syntheses and provides a variety of azetidin-3-ones whose further elaboration was then studied.

2.4 Derivatization

While azetidin-3-ones have been a structure of interest in and of themselves, their derivatives are often considered a target of higher interest. Because of this, the derivatization of the azetidin-3-ones derived from endocyclic methyleneaziridines was explored. Interestingly, these azetidin-3-ones have multiple sites of reactivity, the carbonyl of the azetidin-3-one, and the sulfamate ring (Figure 2.2). Differentiating between these two sites of reactivity would allow for elaboration to a wide range of products of potential biological relevance, and the inclusion of functional groups which would not have been compatible for inclusion in the starting homoallenic sulfamates. With these goals in mind, the reactivity of the bicyclic azetidin-3-ones was undertaken.

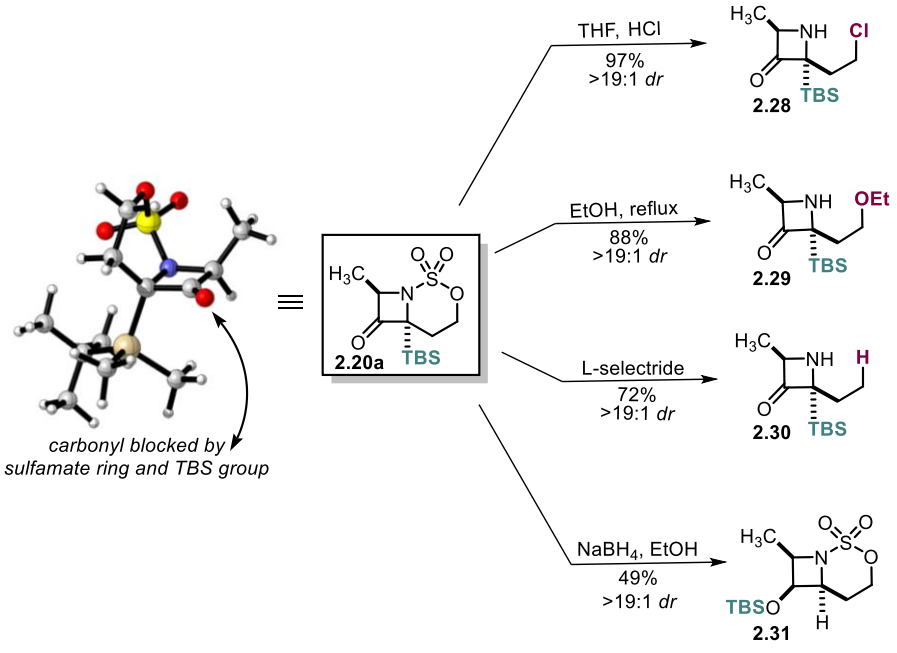
Figure 2.2: *Points of Derivatization of Azetidin-3-ones*



Initial studies of the derivatization of the bicyclic azetidin-3-ones focused on the opening of the sulfamate ring (Scheme 2.7). It was found that when a bulky silicon group such as TBS was

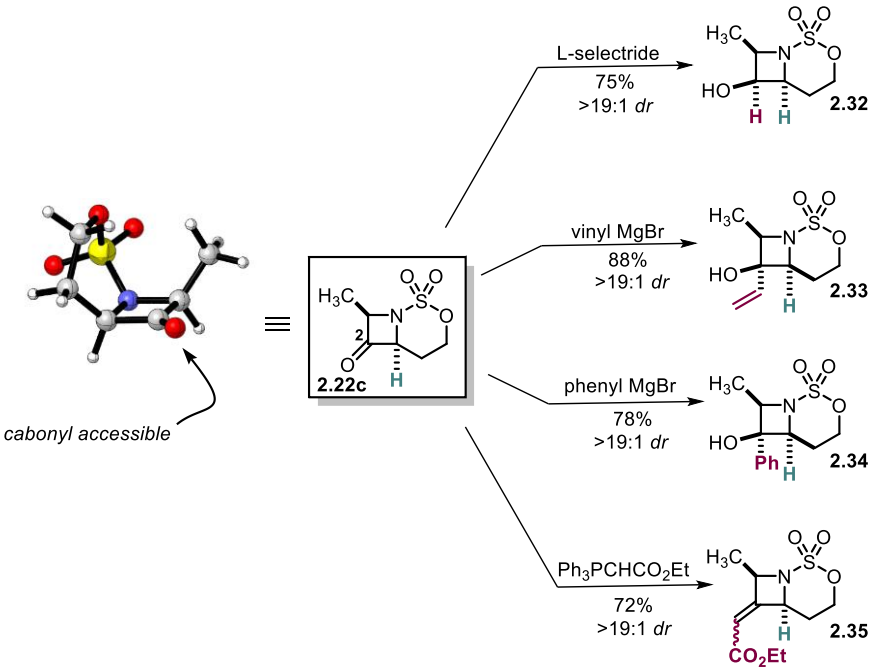
at the C-1 position **2.22a**, this group would shield the bottom face of the carbonyl, while the sulfamate ring would curve across the top face, thus effectively blocking the carbonyl from nucleophilic attack. This blocking left the sulfamate ring as the most reactive moiety in the structure, and thus was the only functional group to react when exposed to nucleophilic conditions (Scheme 2.7). Using these TBS-substituted azetidinones, the sulfamate ring was opened with hydrochloric acid **2.28** and with ethanol **2.29**, installing a chlorine and an ethoxy-substituent, respectively. Additionally, when a larger reducing agent such as L-selectride was used, selective opening of the sulfamate ring was observed, leaving the carbonyl undisturbed **2.30**. The exception to this behavior was found with sodium borohydride. Given the small size of this reducing agent, it was able to reduce the carbonyl without first reacting with the sulfamate ring. Interestingly, the resulting azetidin-3-ol underwent silyl migration, with preservation of the relative stereochemistry **2.31**. Generally, it was found the sulfamate ring could be manipulated to introduce new functionality and to remove it from the structure without interfering with the carbonyl.

Scheme 2.7: *Derivatization of the Sulfamate Ring of Azetidin-3-ones*



Alternatively, it was found that the carbonyl could be targeted if instead the TMS derived H-substituted bicyclic azetidin-3-one **2.22c** was used (Scheme 2.8). In this case, the top face of the carbonyl remains sheltered by the sulfamate ring, while the bottom face of the ring is then exposed to nucleophilic attack. With this substitution not only is the carbonyl the most reactive, but nucleophilic approach is biased towards the convex face (Scheme 2.8). Thus, the products formed by nucleophilic attack of the carbonyl are formed with high diastereoselectivity. In contrast to the reaction of TBS-substituted azetidin-3-one **2.22a**, when H-substituted azetidin-3-one **2.22b** was treated with L-selectride reduction of the carbonyl was isolated **2.32**, with none of the ring opened product analogous to **2.30** was observed. Additionally, vinyl **2.33** and aryl groups **2.34** could be similarly added to the carbonyl *via* Gringard reagents. This offered a simple approach to forming a new C-C bond at C-2 with high diastereoselectivity. Another approach to forming a new C-C bond at C-2 was demonstrated by the use of a Wittig olefination **2.35**. In total,

Scheme 2.8: *Derivatization of the Carbonyl of Azetidin-3-ones*



these reactions demonstrate the synthetic utility this scaffold as the carbonyl could be transformed into a diverse array of products that could potentially be of interest.

Overall, the successful integration of new functionality and manipulation of existing groups found in the bicyclic azetidin-3-one was achieved. Substitution at the C-3 position once again proved pivotal, in this instance directing reactivity to either the sulfamate ring or the carbonyl. When substituted with a large group such as TBS, the carbonyl was effectively blocked, and the sulfamate ring could be opened with a variety of nucleophiles. When the bulky silyl group is replaced with a proton, the carbonyl becomes the most reactive group and can be easily manipulated. These reactions help to further broaden the scope of accessible azetidin-3-one and azetidine derivatives, showing the utility of this approach in the exploration of unchartered chemical space in the search for new biologically relevant structures.

2.5 Conclusion

Azetidin-3-ones and their azetidine derivatives have been gaining interest as biologically relevant structures. However, their synthesis is made challenging by their small, highly strained ring size, a challenge which becomes more difficult when the targets are highly substituted. While some approaches have been previously outlined, they often suffer from low yields and low selectivity. Here, trisubstituted azetidin-3-ones were synthesized using the endocyclic methyleneaziridine. The strained olefin was able to be epoxidized using commercially available *m*CPBA, then the spirocyclic intermediate rearranged to form the azetidin-3-one product as a single diastereomer. These products could be further derivatized, with the identity of the silicon directing group dictating whether the sulfamate ring or the carbonyl would be the site of reactivity. With this method finding such success starting from the endocyclic methylene aziridine, other synthetic possibilities stemming from this scaffold were explored.

2.6 References

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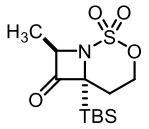
2.7 Experimental

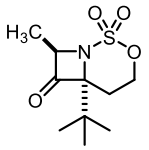
2.7.1 Preparation of Azetidin-3-ones

General Procedure: The corresponding methyleneaziridine (1 equiv) was added to a round bottom flask, then dissolved in CH_2Cl_2 (0.05 M). The resulting solution was cooled to 0℃, at which point 77% *meta*-chloroperoxybenzoic acid (3 equiv.) was added in a single portion. The reaction was stirred for 10-70 h. When the methyleneaziridine had been completely consumed as judged by TLC (CAM stain), the reaction was quenched with saturated aqueous $NaHCO_3$.

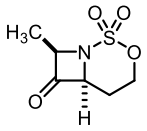
The organic layer was washed with one portion of saturated aqueous $NaHCO_3$ and saturated aqueous Na_2SO_3 (x1), then dried over Na_2SO_4. The solution was concentrated *via* rotary evaporation and the crude material purified *via* column chromatography.



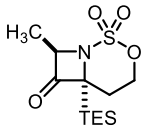
Compound 2.22a. The azetidin-3-one was prepared from the corresponding methyleneaziridine (30 mg, 0.10 mmol). The crude product was purified *via* column chromatography (0% EtOAc/hexanes to 10% EtOAc/hexanes, gradient) to give the product as a white solid (27 mg, 0.09 mmols) in 84% yield. Mp=82℃. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 4.49 (td, *J* = 12.8, 12.4, 2.7 Hz, 1H), 4.41 (ddd, *J* = 11.9, 5.3, 1.0 Hz, 1H), 4.37 (q, *J* = 6.5 Hz, 1H), 2.56 (ddd, *J* = 14.6, 12.9, 5.4 Hz, 1H), 2.09 (ddd, *J* = 14.6, 2.6, 1.0 Hz, 1H), 1.37 (d, *J* = 6.5 Hz, 3H), 0.98 (s, 9H), 0.23 (s, 3H), 0.16 (s, 3H). ^{13}C-NMR (126 MHz, $CDCl_3$) δ 208.33, 98.09, 70.74, 60.53, 29.74, 27.40, 18.53, 16.01. IR (neat) ν = 2963, 2935, 1710, 1468, 1414, 782. HRMS (ESI) calculated for $C_{12}H_{24}NO_4SSi$ [M+H$^+$] 306.1195; found 306.1190.



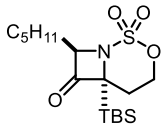
Compound 2.22b. The azetidin-3-one was prepared from the corresponding methyleneaziridine (60 mg, 0.25 mmol). The crude product was purified *via* column chromatography (0% EtOAc/Hex to 15% EtOAc/Hex, gradient) to give the product as a white solid (41 mg, 0.17 mmols) in 67% yield. Mp=95℃. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 4.45 (ddd, *J* = 12.1, 5.6, 1.2 Hz, 1H), 4.34 (dd, *J* = 13.1, 2.8 Hz, 1H), 4.30 (q, *J* = 6.5 Hz, 2H), 2.33 (ddd, *J* = 14.2, 13.2, 5.6 Hz, 1H), 2.09 (ddd, *J* = 14.3, 2.7, 1.3 Hz, 1H), 1.35 (d, *J* = 6.5 Hz, 3H), 1.08 (s, 9H) ^{13}C-NMR (126 MHz, $CDCl_3$) δ 205.42, 100.75, 68.93, 60.52, 38.83, 26.87, 24.75, 15.87 IR (neat) ν = 3358, 3272, 2960, 1730,1343, 836, 514. HRMS (ESI) *m/z* calculated for $C_{10}H_{18}NO_4S$ [M+H$^+$] 248.0912; found 248.0952.



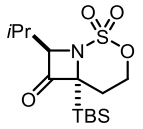
Compound 2.22c. The corresponding methyleneaziridine (0.54 g, 2.2 mmol) was dissolved in 44 mL CH_2Cl_2 in a 250 mL round bottom flask. The product was purified *via* silica gel chromatography (0% EtOAc/hexanes to 30% EtOAc/hexanes, gradient) to yield 285 mg (1.5 mmol) of the product (68% yield). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 5.09 (dt, *J* = 5.7, 1.5 Hz, 1H), 4.54 (dt, *J* = 12.4, 2.4 Hz, 1H), 4.48 (ddt, *J* = 11.8, 6.3, 1.1 Hz, 2H), 4.39 (q, *J* = 6.6 Hz, 1H), 2.58 (ddt, *J* = 14.9, 13.1, 6.0 Hz, 1H), 2.10 (ddt, *J* = 14.9, 2.8, 1.5 Hz, 1H), 1.41 (d, *J* = 6.6 Hz, 3H). ^{13}C-NMR (126 MHz, $CDCl_3$) δ 204.99, 86.55, 69.70, 60.07, 26.13, 16.27. HRMS (ESI) calculated for $C_6H_{10}NO_4S$ [M+H$^+$] 192.0331; found 192.0326.



Compound 2.22d. The azetidin-3-one was prepared from the corresponding methyleneaziridine (38 mg, 0.13 mmol). The crude product was purified *via* column chromatography (0% EtOAc/hexanes to 20% EtOAc/hexanes, gradient) to give the product as a white solid (38 mg, 0.12 mmols) in 96% yield. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 4.48 (m, 1H), 4.41 (ddd, *J* = 11.9, 5.3, 1.0 Hz, 1H), 4.27 (q, *J* = 6.5 Hz, 1H), 2.50 (ddd, *J* = 14.6, 12.9, 5.3 Hz, 1H), 2.08 (ddd, *J* = 14.6, 2.6, 1.0 Hz, 1H), 1.37 (d, *J* = 6.5 Hz, 3H), 1.02 (t, *J* = 7.9 Hz, 10H), 0.78 (qd, *J* = 7.9, 4.5 Hz, 6H). ^{13}C-NMR (126 MHz, $CDCl_3$) δ 208.43, 97.98, 70.81, 60.56, 29.42, 16.05, 7.34, 1.41. HRMS (ESI) calculated for $C_{12}H_{24}NO_4SSi$ [M+H$^+$] 306.1195; found 306.1190.

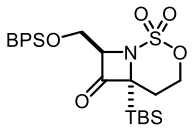


Compound 2.22e. The azetidin-3-one was prepared from the corresponding methyleneaziridine (29 mg, 0.09 mmol). The crude product was purified *via* column chromatography (0% EtOAc/hexanes to 10% EtOAc/hexanes, gradient) to give the product as a waxy white solid (25 mg, 0.07 mmol) in 83% yield. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 4.47 (td, *J* = 12.8, 12.4, 2.7 Hz, 1H), 4.38 (ddd, *J* = 11.8, 5.2, 0.8 Hz, 1H), 4.18 (dd, *J* = 7.6, 5.3 Hz, 1H), 2.54 (ddd, *J* = 14.5, 13.0, 5.3 Hz, 1H), 2.13 – 2.05 (m, 1H), 1.84 (ddt, *J* = 13.7, 10.7, 5.5 Hz, 1H), 1.61 (dddd, *J* = 13.6, 10.5, 7.6, 4.9 Hz, 1H), 1.46 (dddt, *J* = 21.6, 11.1, 5.7, 2.5 Hz, 2H), 1.39 – 1.27 (m, 4H), 0.97 (s, 9H), 0.93 – 0.85 (m, 3H), 0.22 (s, 3H), 0.15 (s, 3H). ^{13}C-NMR (126 MHz, $CDCl_3$) δ 208.00, 97.93, 70.69, 64.64, 31.85, 30.23, 29.71, 27.39, 25.36, 22.67, 18.53, 14.19, -7.40, -7.61. IR (neat) ν = 3352, 3267, 2964, 2931, 1359, 1175, 927, 837, 551. HRMS (ESI) calculated for $C_{16}H_{32}NO_4SSi$ [M+H$^+$] 362.1821; found 362.1816.

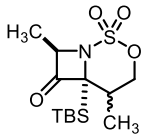


Compound 2.22f. The azetidin-3-one was prepared from the corresponding methyleneaziridine (50 mg, 0.16 mmol). The crude product was purified *via* column chromatography (0% EtOAc/hexanes to 10% EtOAc/hexanes, gradient) to give the product as a white solid (35 mg, 0.10 mmols) in 66% yield. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 4.48 (td, *J* = 13.0, 12.4, 2.7 Hz, 2H), 4.40 – 4.33 (m, 1H), 3.98 (d, *J* = 5.5 Hz, 1H), 2.54 (ddd, *J* = 14.5, 13.0, 5.3 Hz, 1H), 2.21 (dq, *J* = 13.3, 6.7 Hz, 1H), 2.10 (d, *J* = 13.0 Hz, 1H), 1.06 (d, *J* = 6.7 Hz, 3H), 1.02 (d, *J* = 6.6 Hz, 4H), 0.99 (s, 9H), 0.22 (s, 3H), 0.15 (s, 3H). ^{13}C-NMR (126 MHz, $CDCl_3$) δ 132.65, 112.10, 74.59, 60.88, 30.00,

28.43, 26.75, 19.73, 17.94, 17.76, -6.15, -6.30. HRMS (ESI) calculated for $C_{14}H_{27}NO_4SSi$ [M+H$^+$] 334.1464; found 334.1503.

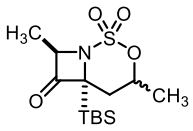


Compound 2.22g. The azetidin-3-one was prepared from the corresponding methyleneaziridine (32 mg, 0.06 mmol). The crude product was purified *via* column chromatography (0% EtOAc/hexanes to 6% EtOAc/hexanes, gradient) to give the product as a white solid (14 mg, 0.03 mmols) in 45% yield. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.81 – 7.68 (m, 4H), 7.46 – 7.34 (m, 6H), 4.63 (td, *J* = 13.0, 2.7 Hz, 1H), 4.40 – 4.29 (m, 2H), 4.00 (m, 1H), 3.92 (m, 1H), 2.56 (ddd, *J* = 14.5, 13.1, 5.2 Hz, 1H), 2.11 (dd, *J* = 14.6, 1.6 Hz, 1H), 1.03 (s, 9H), 0.99 (s, 10H), 0.24 (s, 3H), 0.20 (s, 3H). ^{13}C-NMR (126 MHz, $CDCl_3$) δ 206.42, 135.88, 135.80, 133.30, 129.85, 129.82, 127.85, 127.82, 98.02, 70.67, 65.67, 62.65, 29.92, 27.47, 26.84, 19.33, 18.52, -7.27, -7.54. HRMS (ESI) calculated for $C_{28}H_{41}NO_4SSi_2$ [M+H$^+$] 560.2322; found 560.2317.



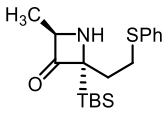
Compound 2.22h. The azetidin-3-one was prepared from the corresponding methyleneaziridine (29 mg, 0.09 mmol). The crude product was purified *via* column chromatography (0% EtOAc/hexanes to 10% EtOAc/hexanes, gradient) to give the product as a white solid (25 mg, 0.07 mmols) in 37% yield. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 4.68 (d, *J* = 11.8 Hz, 1H), 4.27 – 4.21 (m, 1H), 3.66 (q, *J* = 5.9 Hz, 1H), 2.58 (qd, *J* = 7.1, 2.1 Hz, 1H), 1.52 (d, *J* = 5.9 Hz, 3H), 1.35 (d, *J* = 7.1 Hz, 4H), 0.90 (s, 10H), 0.11 (s, 3H), 0.07 (s, 4H). ^{13}C-NMR (126 MHz, $CDCl_3$) δ 208.78, 207.40, 101.51, 101.26, 77.26, 75.55, 60.89, 60.17, 35.64, 31.10, 29.85, 27.72, 27.62, 18.98, 18.94,

16.52, 16.19, 15.61, 10.88, 1.18, 0.15, -5.70, -5.92, -6.19, -6.22. HRMS (ESI) calculated for $C_{13}H_{26}NO_4SSi$ [M+H$^+$] 320.1352; found 320.1347.



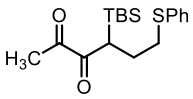
Compound 2.22i. The azetidin-3-one was prepared from the corresponding methyleneaziridine (35 mg, 0.12 mmol). The crude product was purified *via* column chromatography (0% EtOAc/hexanes to 6% EtOAc/hexanes, gradient) to give the product as a clear oil (15 mg, 0.05 mmols) in 41% yield and a 1:1.4 mixture of diastereomers. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 4.74 dp, *J* = 9.1, 6.3 Hz, 1H, major), 4.67 – 4.57 (m, 1H, minor), 4.35 (q, *J* = 6.5 Hz, 1H, minor), 4.25 (q, *J* = 6.7 Hz, 1H, major), 2.56 (dd, *J* = 13.6, 5.6 Hz, 1H, major), 2.38 (dd, *J* = 13.6, 9.1 Hz, 1H, major), 2.21 – 2.14 (m, 2H, minor), 1.45 (d, *J* = 6.4 Hz, 3H, major), 1.39 (d, *J* = 6.3 Hz, 3H, major), 1.36 (d, *J* = 6.4 Hz, 3H, minor), 1.34 (d, *J*= 6.4 Hz, 3H, minor), 1.01 (s, 9H, major), 0.98 (s, 9H, minor), 0.23 (s, 3H, major), 0.21 (s, 3H, major), 0.17 (s, 3H, minor), 0.16 (s, 3H, minor). ^{13}C-NMR (126 MHz, $CDCl_3$) δ 211.00, 208.40, 96.79, 96.17, 79.93, 78.73, 63.69, 60.34, 40.88, 36.93, 27.40, 27.31, 20.30, 20.15, 18.95, 18.84, 18.53, 16.02, -7.32, -7.39, -7.63, -7.67. HRMS (ESI) calculated for $C_{13}H_{26}NO_4SSi$ [M+H$^+$] 320.1352; found 320.1347.

2.7.2 Opening of Sulfamate Ring



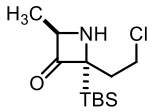
Compound 2.26. The azetidin-3-one **2.25** (which was prepared according to the same procedures as **2.22a**) (50 mg, 0.16 mmol) was placed in a 6 mL dram vial and dissolved in 0.8 mL CH_3CN. To this was added thiophenol (0.04 mL, 0.39 mmol), then K_2CO_3 (55 mg, 0.39 mmol). The reaction

was stirred for 3 h, then was quenched with 0.1 M HCl (2 mL) and diluted with EtOAc (2 mL). After stirring for 30 min, the pH of the solution was adjusted to 11 using 1 M NaOH. The aqueous phase was extracted with CH_2Cl_2 (5x5mL) and the combined organic phases were dried over Na_2SO_4. The solvent was removed *via* rotary evaporation and the crude product purified *via* column chromatography (0% EtOAc/Hex to 10% EtOAc/Hex, gradient) to give a white solid in 34% yield (18 mg, 0.054 mmol). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.32 (d, *J* = 4.3 Hz, 4H), 7.29 – 7.21 (m, 1H), 5.41 (d, *J* = 11.3 Hz, 1H), 4.29 (dq, *J* = 11.5, 6.9 Hz, 1H), 3.35 – 3.13 (m, 2H), 2.66 (ddd, *J* = 15.8, 8.8, 7.1 Hz, 1H), 2.60 – 2.47 (m, 1H), 1.47 (d, *J* = 6.9 Hz, 3H), 1.00 (s, 9H), 0.17 (s, 3H), 0.16 (s, 3H). ^{13}C-NMR (126 MHz, $CDCl_3$) δ 203.96, 134.37, 130.05, 129.66, 127.39, 100.59, 58.43, 36.26, 30.10, 28.09, 19.82, 15.81, -6.19, -6.51. HRMS (ESI) calculated for $C_{18}H_{30}NOSSi$ [M+H$^+$] 336.1851; found 336.1812.

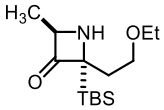


Compound 2.27. The azetidin-3-one **2.25** (30 mg, 0.10 mmol) was dissolved in 0.50 mL CH_3CN. To this solution was added thiophenol (24 μL, 0.24 mmol) and K_2CO_3 (14 mg, 0.10 mmol). The resulting solution was stirred for 1 h. The reaction was diluted with 2 mL EtOAc, then quenched with an equal volume of 1 M HCl. The resulting biphasic solution was stirred for 30 min, then brought to pH 10 with 1 M NaOH. The aqueous phase was extracted with CH_2Cl_2 (3x10 mL). The combined organic phases were dried over Na_2SO_4 and the solvent removed *via* rotary evaporation. The crude product was purified *via* column chromatography (0% EtOAc/Hex to 10% EtOAc/Hex, gradient) to give a yellow oil in 64% yield (21 mg, 0.06 mmol). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.27 (m, 4H), 7.17 (dq, *J* = 8.5, 4.8, 4.1 Hz, 1H), 3.64 (dd, *J* = 11.9, 2.0 Hz, 1H), 2.84 (ddd, *J* = 13.7, 7.9, 6.0 Hz, 1H), 2.79 – 2.70 (m, 1H), 2.48 – 2.35 (m, 1H), 2.33 (s, 3H), 1.85 (dddd, *J* = 14.3, 8.3, 6.7, 2.0 Hz, 1H), 0.89 (s, 10H), -0.02 (s, 3H), -0.16 (s, 3H). ^{13}C-NMR (126 MHz, $CDCl_3$)

δ 200.23, 197.99, 136.07, 129.08, 129.06, 126.14, 35.85, 34.40, 27.24, 26.76, 23.80, 18.31, -5.60, -7.03. HRMS (ESI) calculated for $C_{18}H_{29}O_2SSi$ [M+H$^+$] 337.1658; found 337.1653.

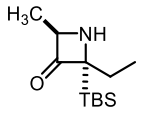


Compound 2.28. The azetidin-3-one **2.22a** (30 mg, 0.098 mmol) was placed in a dry 6 mL dram vial and dissolved in 0.5 mL THF. To this was added 1 drop of concentrated HCl. The reaction was stirred for 1.5 h, then quenched with saturated aqueous $NaHCO_3$ (5mL). The aqueous phase was extracted with EtOAc (3x5 mL). The combined organic layers were dried over Na_2SO_4 and the solvent removed *via* rotary evaporation. The crude product was purified *via* column chromatography (0% EtOAc/Hex to 10% EtOAc/Hex, gradient) to give clear oil (25 mg, 0.95 mmol) in 97% yield. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 4.98 (d, *J* = 11.3 Hz, 1H), 4.08 (dq, *J* = 11.3, 6.9 Hz, 1H), 3.76 (ddd, *J* = 11.2, 10.5, 4.7 Hz, 1H), 3.57 (ddd, *J* = 11.4, 5.8, 3.7 Hz, 1H), 2.62 (ddd, *J* = 16.1, 10.4, 5.9 Hz, 1H), 2.45 (dt, *J* = 15.3, 4.2 Hz, 1H), 1.25 (d, *J* = 6.9 Hz, 3H), 0.82 (s, 9H), 0.00 (s, 6H). ^{13}C-NMR (126 MHz, $CDCl_3$) δ 203.64, 98.87, 58.73, 40.89, 39.69, 27.85, 19.66, 15.83, -6.40, -6.89. HRMS (ESI) calculated for $C_{12}H_{25}ClNOSi$ [M+H$^+$] 262.1394; found 262.1389.

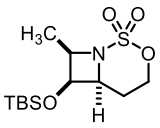


Compound 2.29. The azetidin-3-one **2.22a** (50 mg, 0.16 mmol) was placed in a 10 mL round bottom flask and dissolved in 1.64 mL EtOH. The solution was heated to 70 °C for 2 h, at which point starting material was completely consumed. The solvent was removed *via* rotary evaporation and the crude product was purified *via* column chromatography (0% EtOAc/Hex to 4% EtOAc/Hex, gradient) to give product (38 mg, 0.14 mmol) in 88% yield as a colorless oil. ^{1}H-NMR (500 MHz, CDCl3) δ 5.84 (d, *J* = 12.3 Hz, 1H), 4.05 (dq, *J* = 13.6, 6.9 Hz, 1H), 3.88 (td, *J*

= 11.1, 2.6 Hz, 1H), 3.34 – 3.17 (m, 3H), 2.48 (ddd, *J* = 15.2, 10.9, 4.5 Hz, 1H), 2.12 (dt, *J* = 15.2, 3.2 Hz, 1H), 1.16 (d, *J* = 6.8 Hz, 3H), 0.98 (t, *J* = 7.0 Hz, 3H), 0.81 (s, 9H), 0.00 (s, 3H), -0.04 (s, 3H). ^{13}C-NMR (126 MHz, $CDCl_3$) δ 205.23, 98.90, 66.61, 65.60, 57.32, 37.12, 27.73, 19.27, 15.21, 14.63, -6.98, -7.08.



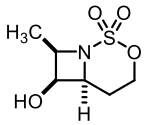
Compound 2.30. Azetidinone **2.22a** (50 mg, 0.164 mmol) was dissolved in THF, then cooled to 0℃. 1M L-selectride in THF (0.33 mL, 0.33 mmol) was added dropwise. The resulting solution was stirred at 0℃ for 30 min. Reaction was quenched with saturated aqueous NH_4Cl (5 mL), then the aq phase was extracted with EtOAc (3x5 mL). Combined org phases were dried over Na_2SO_4. Solution was concentrated under rotary evaporation. Crude product was purified *via* silica gel chromatography (0% EtOAc/Hex -10% EtOAc/Hex, gradient) to give product (24 mg, 0.10 mmol) as a white solid in 62% yield. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 4.85 (d, *J* = 10.5 Hz, 1H), 4.26 (dq, *J* = 10.6, 6.9 Hz, 1H), 2.33 (dq, *J* = 14.8, 7.4 Hz, 1H), 2.20 (dq, *J* = 14.6, 7.2 Hz, 1H), 1.38 (d, *J* = 6.9 Hz, 3H), 1.09 (t, *J* = 7.3 Hz, 3H), 0.99 (s, 9H), 0.19 (s, 3H), 0.18 (s, 3H). ^{13}C-NMR (126 MHz, $CDCl_3$) δ 205.14, 103.06, 57.38, 30.77, 27.73, 19.18, 14.26, 10.22, -6.16, -6.43. HRMS (ESI) calculated for $C_{12}H_{25}NOSi$ [M+H$^+$] 228.1779 found 228.1784.



Compound 2.31. In a 5 mL round bottom flask, azetidinone **2.22a** (50 mg, 0.16 mmol) was dissolved in 1.5 mL CH_3CH_2OH, then cooled to 0℃. To this was added $NaBH_4$ (22 mg, 0.59 mmol), and the resulting solution was stirred at room temperature for 0.5 h. The solvent was then removed under reduced pressure, and the remaining oil dissolved in 5 mL EtOAc. The solution

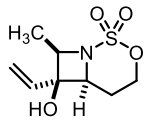
was washed with H_2O (3x5 mL), then saturated aqueous NaCl (1x5 mL). The combined organic phases were dried over Na_2SO_4, and solvent was removed *via* rotary evaporation. The product was isolated in 49% yield (24 mg, 0.08 mmol) as a white solid after column chromatography (0% EtOAc/Hex to 50% EtOAc/Hex, gradient). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 4.90 – 4.80 (m, 1H), 4.73 (ddd, *J* = 13.9, 12.0, 2.6 Hz, 1H), 4.41 (dd, *J* = 11.7, 5.6 Hz, 1H), 3.55 (dd, *J* = 8.6, 1.5 Hz, 1H), 3.46 (dq, *J* = 8.5, 6.3 Hz, 1H), 2.62 – 2.46 (m, 1H), 1.73 – 1.60 (m, 1H), 1.34 (d, *J* = 6.3 Hz, 3H), 0.90 (s, 10H), 0.10 (s, 3H), 0.05 (s, 3H). ^{13}C-NMR (126 MHz, $CDCl_3$) δ 91.50, 77.68, 68.63, 56.71, 28.15, 25.72, 21.02, 17.91, -3.89, -4.51. HRMS (ESI) calculated for $C_{12}H_{26}NO_4SSi$ [$M+H^+$] 308.1352; found 308.1347.

2.7.3 Manipulation of Carbonyl

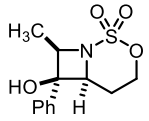


Compound 2.32. The azetidin-3-one **2.22c** (50 mg, 0.26 mmol) was dissolved in 1.5 mL THF in a dry 5 mL round bottom flask. This solution was cooled to 0℃, at which point 1 M L-selectride in THF (0.26 mL, 0.26 mmol) was added dropwise. The reaction was stirred for 30 min at 0℃, then warmed to rt and quenched with saturated aqueous NH_4Cl (5mL). The aqueous phase was extracted with EtOAc (3x5mL) and the combined organic phases were dried over Na_2SO_4. The solvent was removed under rotary evaporation and the crude product was purified by silica gel chromatography (0% EtOAc/Hex to 50%, gradient) to give product as a clear oil (40 mg, 0.21 mmol) in 78% yield. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 4.60 (d, *J* = 9.0 Hz, 1H), 4.51 (ddd, *J* = 12.3, 5.2, 2.4 Hz, 1H), 4.21 (ddd, *J* = 13.7, 12.3, 3.6 Hz, 1H), 4.01 (dqd, *J* = 9.1, 7.0, 2.1 Hz, 1H), 3.23 (ddd, *J* = 8.7, 6.1, 4.2 Hz, 1H), 3.04 (dd, *J* = 4.2, 2.1 Hz, 1H), 2.58 (dddd, *J* = 15.7, 13.8, 8.6, 5.3

Hz, 1H), 2.36 (dddd, *J* = 15.7, 6.1, 3.5, 2.5 Hz, 1H), 1.40 (d, *J* = 7.0 Hz, 3H). ^{13}C-NMR (126 MHz, $CDCl_3$) δ 66.98, 59.20, 54.43, 47.38, 27.35, 18.89. HRMS (ESI) calculated for $C_6H_{11}NO_4S$ [M+H$^+$] 194.0487; found 194.0482.

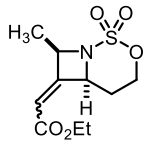


Compound 2.33. The azetidin-3-one **2.22c** (50 mg, 0.26 mmol) was placed in a dry 6 mL dram vial. The solid was dissolved in 1.3 mL of THF, then cooled to 0℃. To the solution was added 1 M vinyl magnesium bromide (0.26 mL, 0.26 mmol). The reaction was stirred for 15 min, then quenched with saturated aqueous NH_4Cl. The aqueous phase was extracted with EtOAc (3x5 mL) and the combined organics dried over Na_2SO_4. The solvent was removed *via* rotary evaporation and the crude product was purified *via* column chromatography (0% EtOAc/hexanes to 30% EtOAc/hexanes, gradient) to give a white solid (28 mg, 0.13 mmol) in 46% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.94 (dd, *J* = 17.1, 10.8 Hz, 1H), 5.27 (dd, *J* = 17.1, 1.4 Hz, 1H), 5.18 (dd, *J* = 10.8, 1.4 Hz, 1H), 4.33 (dd, *J* = 12.1, 5.3 Hz, 1H), 4.26 (ddd, *J* = 14.3, 12.2, 3.8 Hz, 1H), 3.90 (dd, *J* = 9.0, 7.0 Hz, 1H), 2.99 (dd, *J* = 9.3, 6.3 Hz, 1H), 2.70 (tdd, *J* = 15.2, 9.3, 6.2 Hz, 1H), 2.51 (p, *J* = 1.7 Hz, 1H), 2.22 (ddd, *J* = 14.9, 5.5, 3.5 Hz, 1H), 1.14 (d, *J* = 6.9 Hz, 3H). ^{13}C-NMR (126 MHz, $CDCl_3$) δ 136.59, 117.07, 67.10, 65.04, 64.45, 49.52, 28.20, 17.39. HRMS (ESI) calculated for $C_8H_{13}NO_4S$ [M+NH$^+$] 237.0909; found 237.0904.



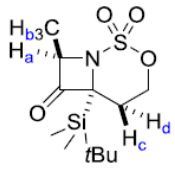
Compound 2.34. The azetidin-3-one **2.22c** (50 mg, 0.26 mmol) was dissolved in 1 mL of THF. The resulting solution was cooled to 0 °C, at which point 1.0 M phenylmagnesium bromide in THF (0.26 mL, 0.26 mmol) was added dropwise. The reaction was stirred at 0 °C for 30 min, and

was then quenched with saturated aqueous NH_4Cl. The aqueous phase was extracted with EtOAc (3x5 mL) and the combined organic phases were dried with Na_2SO_4 and filtered. The solvent was removed *via* rotary evaporation and the crude product was purified *via* column chromatography (0% EtOAc/Hex to 30% EtOAc/Hex, gradient) to give a white solid in 78% yield. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.47 – 7.40 (m, 2H), 7.40 – 7.34 (m, 2H), 7.34 – 7.28 (m, 1H), 4.68 (d, *J* = 8.7 Hz, 1H), 4.63 (ddd, *J* = 12.2, 5.8, 1.3 Hz, 1H), 4.39 – 4.33 (m, 1H), 4.29 (ddd, *J* = 14.6, 12.2, 3.8 Hz, 1H), 3.00 (dd, *J* = 9.1, 6.5 Hz, 1H), 2.83 (tdd, *J* = 14.9, 9.1, 5.8 Hz, 1H), 2.37 (dddd, *J* = 15.2, 6.5, 3.8, 1.3 Hz, 1H), 1.24 (d, *J* = 6.9 Hz, 3H). ^{13}C-NMR (126 MHz, $CDCl_3$) δ 139.77, 128.75, 128.18, 125.59, 67.20, 66.76, 64.04, 51.28, 27.94, 16.81. HRMS (ESI) calculated for $C_{12}H_{16}NO_4S$ [M+H$^+$] 270.0795; found 270.0793.



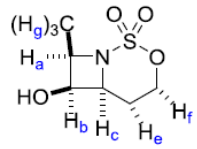
Compound 2.35. Azetidinone **2.22c** (50 mg, 0.26 mmol) was placed in a dry 6 mL dram vial, then dissolved in 0.9 mL CH_3OH. The solution was cooled to 0℃, then Ph_3PCHCO_2Et was added. After 15 min reaction was warmed to room temperature and stirred an additional 2h. Solvent was removed *via* rotary evaporation. Crude product was purified *via* column chromatography (0% EtOAc/hexanes to 30% EtOAc/hexanes, gradient) to give a white solid (49 mg, 0.19 mmol) in 72% yield. 1H NMR (500 MHz, CDCl3) δ 4.62 (d, *J* = 8.5 Hz, 1H), 4.55 (p, *J* = 6.9 Hz, 1H), 4.38 (ddd, *J* = 11.3, 6.2, 5.0 Hz, 1H), 4.31 (ddd, *J* = 11.6, 8.1, 4.9 Hz, 1H), 4.05 (q, *J* = 7.1 Hz, 2H), 3.26 (ddd, *J* = 16.4, 8.1, 5.0 Hz, 1H), 3.08 (ddd, *J* = 16.4, 6.2, 5.0 Hz, 1H), 1.48 (d, *J* = 6.8 Hz, 3H), 1.40 (t, *J* = 7.1 Hz, 3H). 13C NMR (126 MHz, CDCl3) δ 171.34, 159.26, 135.45, 125.01, 80.31, 69.71, 67.03, 60.55, 46.82, 26.43, 21.36, 21.19, 14.69, 14.33. HRMS (ESI) calculated for $C_{10}H_{16}NO_5S$ [M+H$^+$] 262.0743 found 262.0744.

2.7.4 nOe Data



(Si)CH_3	H_a	0.18%	(Si)*t*Bu	H_a	0.26%
	H_b	0.00%		H_b	0.00%
	H_c	0.28%		H_c	0.05%
	H_d	1.5%		H_d	0.15%

An nOe correlation of 0.18% was observed between the $Si(CH_3)_2$ groups and H_a, while no correlation was observed between the $Si(CH_3)_2$ groups and H_b. This indicated that the TBS group and H_a are on the same face of the azetidinone ring. Similarly, an nOe correlation of 0.26% was observed between the Si(*t*Bu) group and Ha, while no correlation was observed between the Si(*t*Bu) group and H_b, further indicating that the TBS group and H_a are on the same side of the ring.



H_a	H_c	4.3%	H_b	H_a	3.8%
	H_g	1.48%		H_c	2.9%
				H_g	0.6%
H_c	H_b	2.9%	H_g	H_a	1.3%
	H_e	2.7%		H_b	0.7%
	H_f	1.1%			

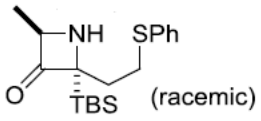
An nOe correlation of 4.3% was observed between H_a and H_c suggesting that both H's are on the same face of the azetidinone ring. Further supporting this assignment is the absence of an nOe correlation between H_g and H_c. An nOe correlation of 3.8% between H_b and H_a and an nOe correlation of 2.9% between H_b and H_c suggest that all three of the H's are on the same face of the azetidine ring. Further supporting this assignment is the relatively small nOe correlation of 0.6% between H_b and H_g. Also, an nOe correlation of 4.3% was observed between H_a and H_c.

2.7.5 HPLC Traces

10/29/2014 10:09:03 1 / 1

C:\LabSolutions\Data\Eileen\EB2233B 215 235_882014_1.lcd

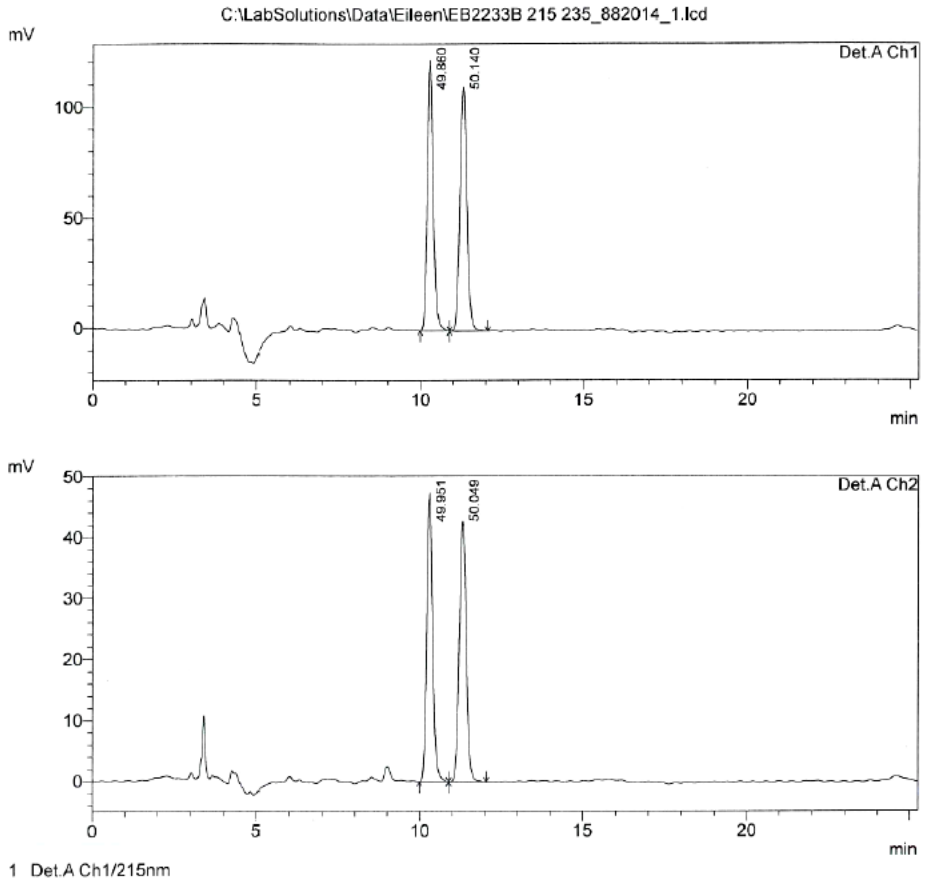
Acquired by	: Admin
Sample Name	: EB2233B
Sample ID	:
Tray#	: 1
Vail #	: 11
Injection Volume	: 1 uL
Data File Name	: EB2233B 215 235_882014_1.lcd
Method File Name	: EB2233B.lcm
Batch File Name	: EB2233B 215 235.lcb
Report File Name	: Default.lcr
Data Acquired	: 8/8/2014 1:30:58 PM
Data Processed	: 8/9/2014 11:37:26 AM



(racemic)

Compound 2.27

<Chromatogram>

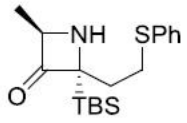


1 Det.A Ch1/215nm
2 Det.A Ch2/235nm

10/29/2014 09:58:05 1

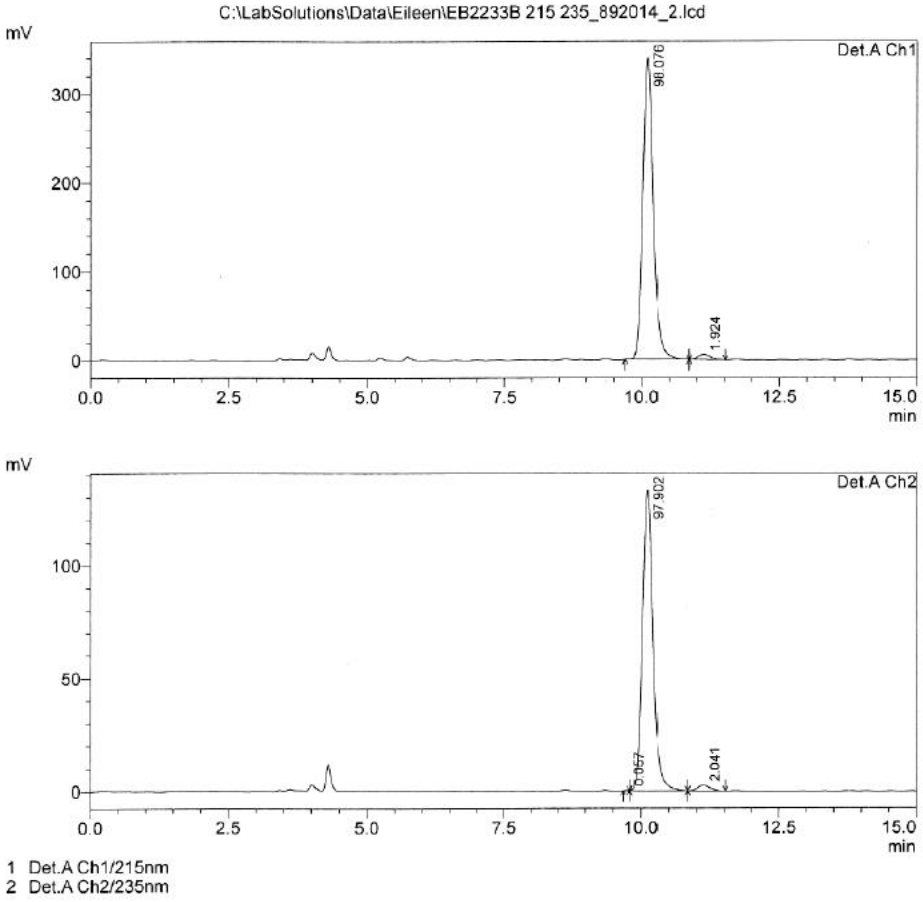
C:\LabSolutions\Data\Eileen\EB2233B 215 235_892014_2.lcd

Acquired by	: Admin
Sample Name	: EB2298B
Sample ID	:
Tray#	: 1
Vail #	: 22
Injection Volume	: 1 uL
Data File Name	: EB2233B 215 235_892014_2.lcd
Method File Name	: EB2233B.lcm
Batch File Name	: EB2233B 215 235.lcb
Report File Name	: Default.lcr
Data Acquired	: 8/9/2014 11:02:49 AM
Data Processed	: 8/9/2014 11:33:27 AM



Compound 2.27

<Chromatogram>



1 Det.A Ch1/215nm
2 Det.A Ch2/235nm

Chapter 3.

Manipulation of Strain and Electronic Effects in the Synthesis of Heterocyclic Alkynes and Evaluation of Their Improved Efficiency

This chapter is adapted from sections published in:

Burke, E. G.; Gold. B.; Hoang, T. T.; Raines, R. T.; Schomaker, J. M.

J. Am. Chem. Soc., **2017**, *139*, 8029-8037.

The work described in this chapter was done as part of a joint project with members of the Raines research group, Dr. Brian Gold (computational analysis of strained alkynes) and Dr. Trish Huang (bioconjugation studies). While the research presented in this chapter represents my contributions to the project, a more complete account of our research can be found in the journal article cited on page 69.

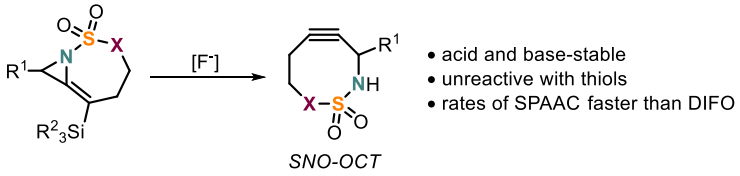
Chapter 3

Manipulation of Strain and Electronic Effects in the Synthesis of Heterocyclic Alkynes and Evaluation of Their Improved Efficiency

3.1 Introduction

As with the exocyclic methyleneaziridines which preceded them, endocyclic methyleneaziridines are scaffolds which can be modified along more than one mode of reactivity. While oxidation of the olefin and subsequent rearrangement yielded the highly substituted small rings of the azetidin-3-ones, it was found that elimination of the silyl group would yield a strained heterocyclic alkyne. These strained alkynes (SNO-OCT) were found to be remarkably stable towards common reaction conditions, while maintaining high reactivity towards 1,3-dipoles. In this chapter, the synthesis, derivatization and relative reactivity of SNO-OCTs will be explored.

Scheme 3.1: *Synthesis of Heterocyclic Alkynes from Endocyclic Methyleneazrirdines*



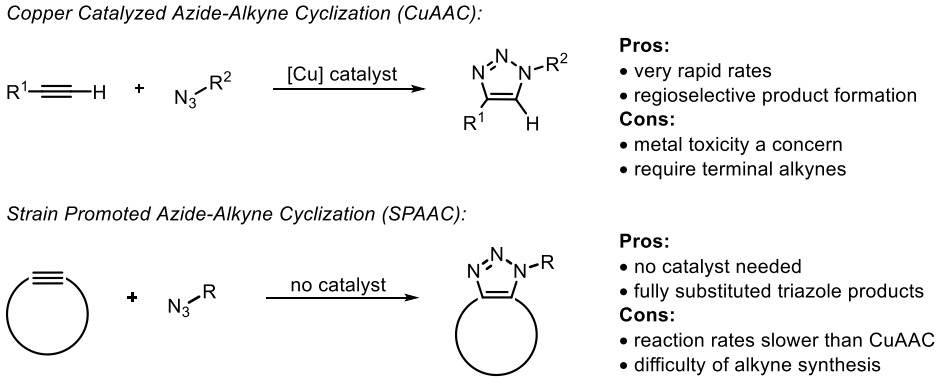
3.2 Background

The development of bioorthogonal reactions have enabled the study of a range of bio-molecules, and has become a ubiquitous tool which has enabled a diversity of studies which were not previously possible. Features key to a useful biorthogonal reaction are selectivity between endogenous functional groups, lack of reactivity or toxicity towards the native biological system, fast reaction kinetics and ease of preparation. A class of reactions has been developed which fulfill

these requirements, beginning with the Staudinger ligation,[1] and then expanding to include 1,3-dipolar reactions of azides,[2] diazos,[3] nitrones,[4] and nitrile imines,[5] oxime,[6] and esterifications,[7] and more recently, tetrazine ligantions.[8]

One of the most widely used reactions of this class is the azide-alkyne cycloaddition (AAC) (Scheme 3.2). Originally, a copper catalyst was used to increase the rate of reaction (CuAAC),[9] and following that, additional metal catalysts featuring ruthenium,[10] or silver[11] were also utilized to accomplish this. However, despite their utility, these metal catalysts came paired with inherent disadvantages, primarily the toxicity of the metals to the biological systems they were employed to study.[12] As an alternative, a series of metal free AACs and related reactions were developed which relied on strained alkynes to increase the rates of reaction (strain promoted alkyne-azide cyclizations, SPAAC).[2] Like their metal-catalyzed predecessors, these reactions became popular outside of biorthogonal labeling and have found utility in the manipulation of proteins,[13] materials chemistry,[14] and as synthetic building blocks.[15] Despite their many successes, challenges remain, especially as the desired applications have become more diverse. Lengthy or inflexible syntheses, functional group incompatibility, poor stability, and solubility all placed limitations on the applications of strained alkynes. An additional problem which has chronically plagued strained

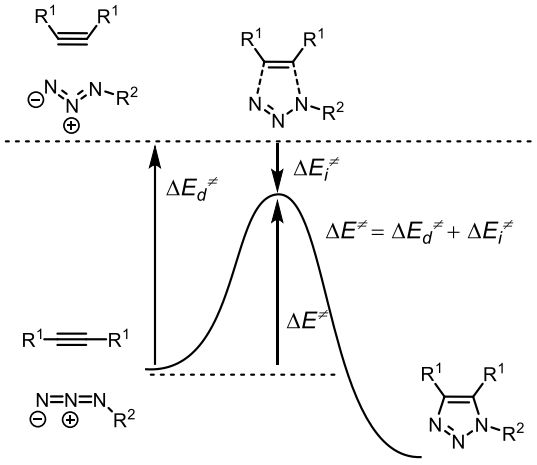
Scheme 3.2: *Azide-Alkyne Cyclization Overview*



alkynes has been their instability and reactivity with sulfur nucleophiles, limiting their practicality in the biological settings they were initially designed for use in. Below, the strategies to improve these reactions will be examined, alongside the synthesis and reactivity of selected strained alkynes.

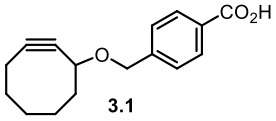
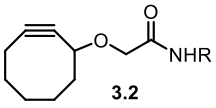
The two main methods of increasing alkyne reactivity can be conceptualized by the distortion/interaction model as outlined by Schoenebeck, Ess, Jones and Houk (Figure 3.1).[16] According to this model, the energy of the transition state ($\Delta E^{\ddagger}$) is the sum of the energy required to distort the azide and alkyne into their transition state geometry ($\Delta E_d^{\ddagger}$) and the energy of the interaction of the two distorted components in the transition state ($\Delta E_i^{\ddagger}$). Based on this, one way to lower the $\Delta E^{\ddagger}$, and therefore increase the rate of the reaction, is to start with an alkyne whose geometry more closely resembles the geometry of the alkyne in the transition state. The second way to lower $\Delta E^{\ddagger}$ is to increase the interaction of the alkyne with the azide in the transition state through electronic manipulation of the alkyne. Both approaches have been taken, and the results of their application are discussed below.

Figure 3.1: *Distortion/Interaction Model of Azide-Alkyne Cyclization*

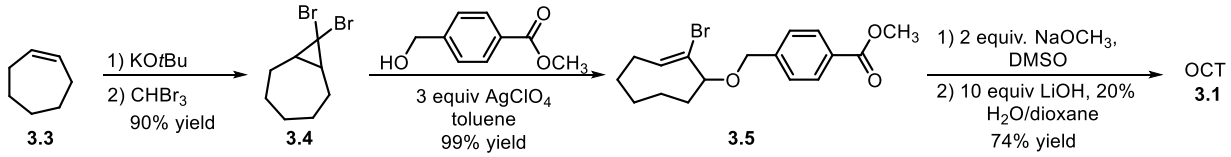


The first cyclooctyne to be reported for use in biological labeling was the carbocycle **3.1** (OCT).[2a] The alkyne **3.1** was developed based on the idea that increased rate could be obtained by increasing strain across the alkyne, and therefore decreasing $\Delta E_d^{\ddagger}$. This was an important conceptual step forward for the field, as it allowed for the valuable AAC reaction to take place without the need for an accompanying metal catalyst. Unfortunately, OCT's rate of reaction (0.0024 $M^{-1}s^{-1}$ with benzyl azide in CD_3CN) was considerably slower than that of its metal-catalyzed counterparts, and its hydrophobicity was problematic for use in biological settings (Table 3.1). The synthesis of OCT is relatively short, proceeding in 3 steps from the expensive, though commercially available cycloheptene **3.3** (Scheme 3.3). The cycloalkene **3.3** first undergoes cyclopropanation **3.4**, followed by opening of the small ring and installation of the ester which

Table 3.1: *Comparison of OCT and Derivative*

Structure	 **3.1**	 **3.2**
Name	OCT	ALO
Second-order Rate Constant	0.0024 $M^{-1}s^{-1}$ in CH_3CN	(not reported)
Stability and Related Properties	• Hydrophobilc • Slow reaction rate	• Increased solubility in water • Lower yields
Yield	66% in 3 steps	12% in 4 steps

Scheme 3.3: *OCT Synthesis*

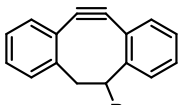
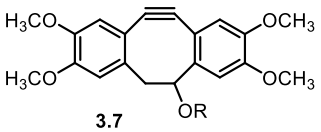
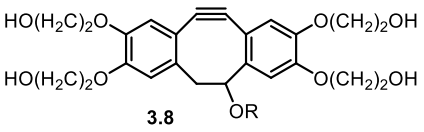
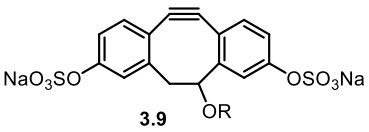


serves as a handle to which the desired tag or biomolecule can be added to the molecule **3.5**. In the last step the vinyl-bromide is eliminated to form the target strained alkyne **3.1**. However, this synthetic route offered few points of derivatization. While the analog (aryless octyne, ALO) **3.2**, made in effort to reduce the hydrophobicity of the original OCT **3.1**, was made using this synthesis, the route was ultimately abandoned in the search for cycloalkynes with faster rates and improved solubility in polar media.[17]

Potentially the most widely investigated mode of increasing reaction rates is to further increase strain on the alkyne by shrinking the size of the strain-inducing ring. In dibenzocyclooctyne (DIBO) **3.6**, the inclusion of sp^2-hybridized carbons through fused aryl rings was shown to dramatically increase reaction rates (Table 3.2).[2b] The cycloalkyne **3.6** was synthesized by the dimerization of phenylacetaldehyde **3.10**, followed by opening of the oxo-bridge **3.11** and dibromination of the olefin **3.12**. The alkyne **3.6** is then formed in a subsequent elimination of the bromines **3.13** (Scheme 3.4). Unfortunately, the significant increase in rate came with several notable drawbacks. The increased strain made the ring more sensitive, and decomposition upon storage was observed, as well as undesired background reactivity with thiols.[18] Additionally, the aryl rings increased the lipophilicity of the system, causing sequestration by membranes or non-specific serum binding.[19]

In an effort to minimize these less desirable properties, several analogs were designed using the same synthesis (Scheme 3.4, Method A). Tetramethoxydibenzocyclooctyne (TMDIBO) **3.7**, which included methoxy groups on the aryl rings, was found to have improved stability towards air and moderately basic conditions, while stability towards thiols and acidic conditions remained somewhat problematic.[20] Additionally, an increase in rate was observed, though the significance of this increase should be approached with caution, as reported rates can differ. To improve upon

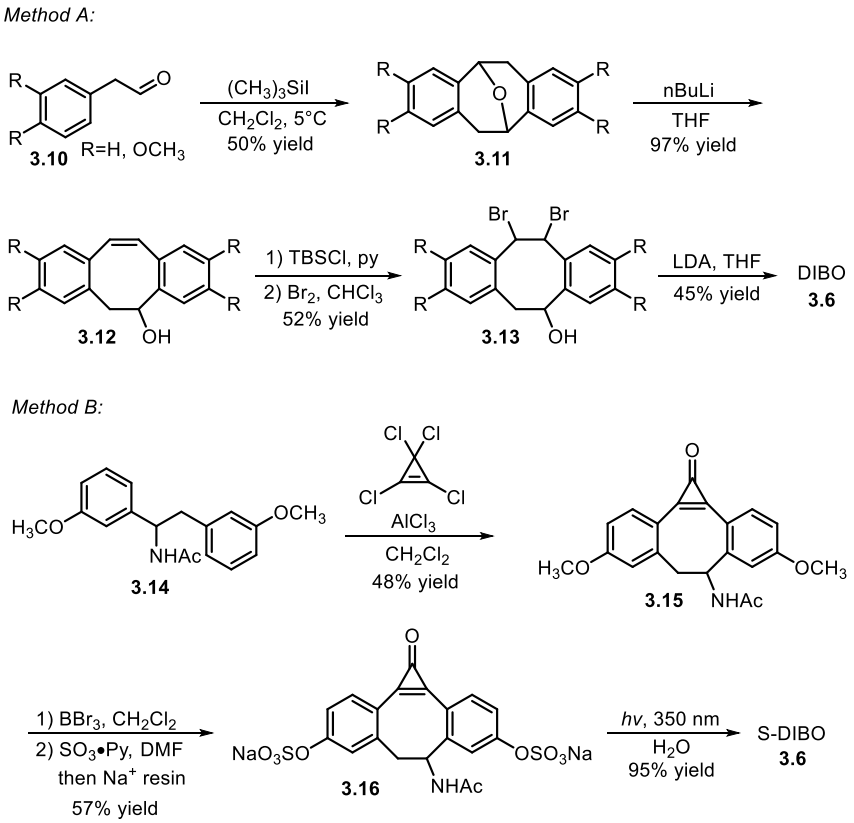
Table 3.2: *Comparison of DIBO and Derivatives*

Structure	 **3.6** R=H, OH	 **3.7**
Name	DIBO	TMDIBO
Second-order Rate Constant	0.057 $M^{-1}s^{-1}$ in CH_3OH	0.094 $M^{-1}s^{-1}$ in CH_3OH
Stability and Related Properties	• Decomposition at rt within ~3d (R=H) • Reactive with thiols • Lipophilic	• Stable to air, basic conditions • Sensitive to acids and thiols • Displays serum binding
Yield	10% in ~6 steps (R=OH)	57% in 6 steps
Structure	 **3.8**  **3.9**	
Name	THE-DIBO	S-DIBO
Second-order Rate Constant	0.17 $M^{-1}s^{-1}$ in CH_3OH	0.12 $M^{-1}s^{-1}$ in CH_3OH
Stability and Related Properties	• Less prone to decomposition or reaction with thiols • Product triazole observed to have some decompositon	• cannot pass through cell membranes • stable to thiols, moderately acidic or basic conditions
Yield	24% in 7 steps	17% in 8 steps

this, the methoxy groups of TMDIBO **3.7** were further elaborated in the 2,3,8,9-tetrakis(2-hydroxyethoxy)-5,6-dihydro-11,12-didehydrodibenzo[a,e][8]annulene (THE-DIBO) **3.8** derivative.[21] This strained alkyne was designed with the intention of yielding an alkyne which is both more stable towards thiols, and more hydrophilic. These aims were achieved, and a modest increase in rate was again observed. As an unanticipated result of the increased activation of the new substituents, decomposition of the product triazoles was observed.

A third derivative, S-DIBO **3.9**, aimed to increase hydrophilicity by including charged substituents on the aryl rings.[19] Its synthesis was achieved using an alternate synthetic route (Scheme 3.4, Method B) in which Friedel-Crafts acylation of **3.14** with 1,2,3,3-tetrachlorocyclopropene gave cyclopropenone **3.15** after hydrolysis.[2c] Methoxy substituents were converted to the desired sulfate salts **3.16**, and the desired cycloalkyne **3.9** was unmasked following the treatment of cyclopropenone **3.16** with 350 nm light. The product alkyne **3.9** was more water-soluble than its parent DIBO **3.6**. Additionally, S-DIBO **3.9** was reported to have an increased reaction rate with benzyl azide. However, in an unanticipated result, the charged S-DIBO **3.9** was found to be unable to pass through cell membranes, limiting its applications. While DIBO **3.6** has enabled a breadth of work, it has remained limited by its hydrophobicity, fragility,

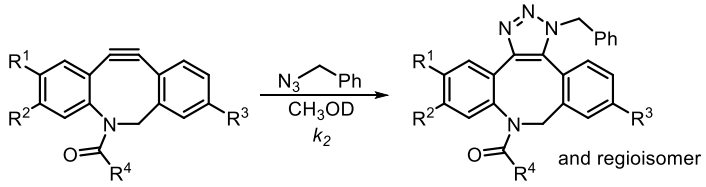
Scheme 3.4: *DIBO Synthesis*



and non-selective reactivity. Attempts to mitigate these drawbacks through derivatization have been made, but are ultimately limited by the constraints of the synthetic routes.

The structurally related dibenzoazacyclooctyne (DIBAC, Table 3.3 entry 1, **3.16**) similarly features two aryl rings which increase strain and therefore reactivity.[2k] In addition, the inclusion of N within the octyne ring improves solubility in polar solvents and provides a convenient handle for functionalization. While drawbacks associated with highly strained rings such as background reactivity persist, DIBAC **3.16** has one of the fastest reported rates, and studies of its substitution have been undertaken to more systematically than for previous cyclic alkynes (Table 3.3). It was found that the inclusion of polar groups such as Br, F, or OCH_3 lead to increased activation of the alkyne and therefore gave faster rates.

Table 3.3: *Comparison of DIBAC Derivatives and Their Second Order Rate Constants*

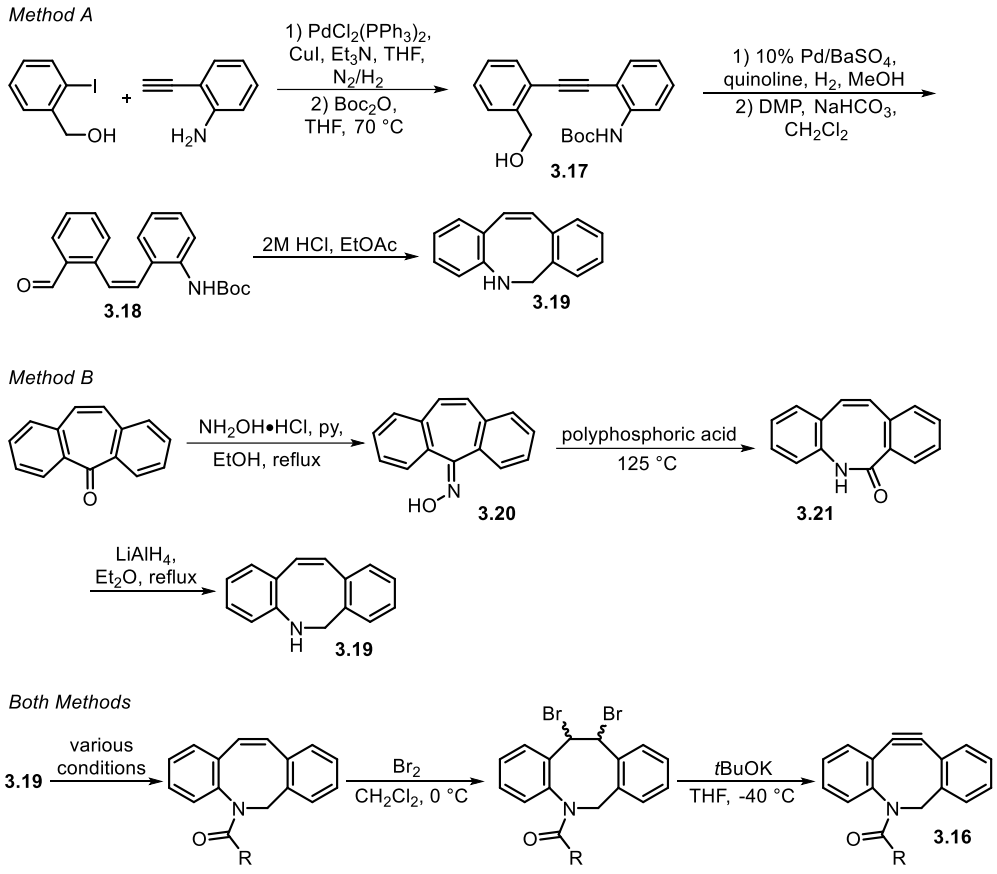


entry	R^1	R^2	R^3	R^4	k_2
1	H	H	H	$(CH_2)_3CO_2CH_3$	0.31
2	Cl	H	H	$(CH_2)_3CO_2CH_3$	0.9
3	Cl	Br	H	$(CH_2)_3CO_2CH_3$	0.8
4	OCH_3	H	H	$(CH_2)_3CO_2CH_3$	0.45
5	H	OCH_3	OCH_3	$(CH_2)_3CO_2CH_3$	0.62
6	H	F	F	$C_{15}H_{31}$	0.51

[a] k_2 measured in CD_3CN

Two main syntheses have been developed to access these derivatives, each using the same final three steps (Scheme 3.). The key step of Method A uses a Sonogashira cross coupling **3.17** followed by reduction of the triple bond and oxidation of the alcohol **3.18**, to reach the common intermediate **3.19** after ring closure. In contrast, the key step of Method B relies on the Beckmann rearrangement of **3.20** to **3.21**, and reduction of the amide to reach **3.19**. In the synthesis of

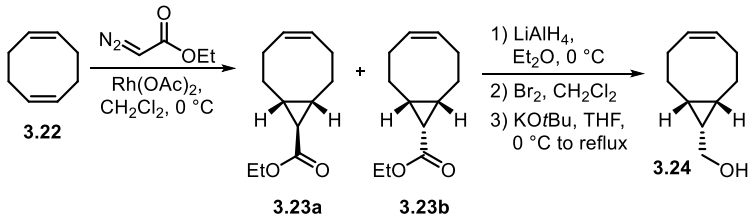
Scheme 3.5: *Synthesis of DIBAC*



analogs, both methods have been used, although Method A has proven more flexible (Scheme 3.6).[22] Outside of creating analogs to increase rates for biological studies, derivatization can allow for optimization for other applications. For example, modification of DIBAC **3.9** to include Br at R^2 and R^3 gave a derivative which found use as a monomer in the synthesis of conjugated polymers.[23] This modified DIBAC unit could be reacted with different azides to include a range of aromatic groups into the product polymer, and therefore quickly test their impact on the polymer's electronic properties.

Beyond the addition of aryl rings, other ways of increasing strain on the alkyne have been explored, including the addition of small rings to the octyne. Bicyclo[6.1.0]nonyne (BCN) **3.24** was developed as an alternative to the lengthy synthesis and lipophilicity of the aryl strain induced cyclooctynes.[2e] The synthesis, noted for its brevity, began with Rh-carbene insertion of 1,5-cyclooctadiene **3.22**, separation of the endo and exo isomers **3.23a** and **3.23b**, then reduction of the ester, bromination of the remaining olefin and then elimination to the alkyne to give BCN **3.24** in 46% overall yield (Scheme 3.6). With a second order rate constant of 0.29 $M^{-1}s^{-1}$, BCN **3.24** was competitive with the aryl substituted strained alkynes. The drawback of this synthesis, however, was that the simplicity of the synthesis offers essentially no points of derivatization, and to date, no analogs have been reported.

Scheme 3.6: *Synthesis of BCN*

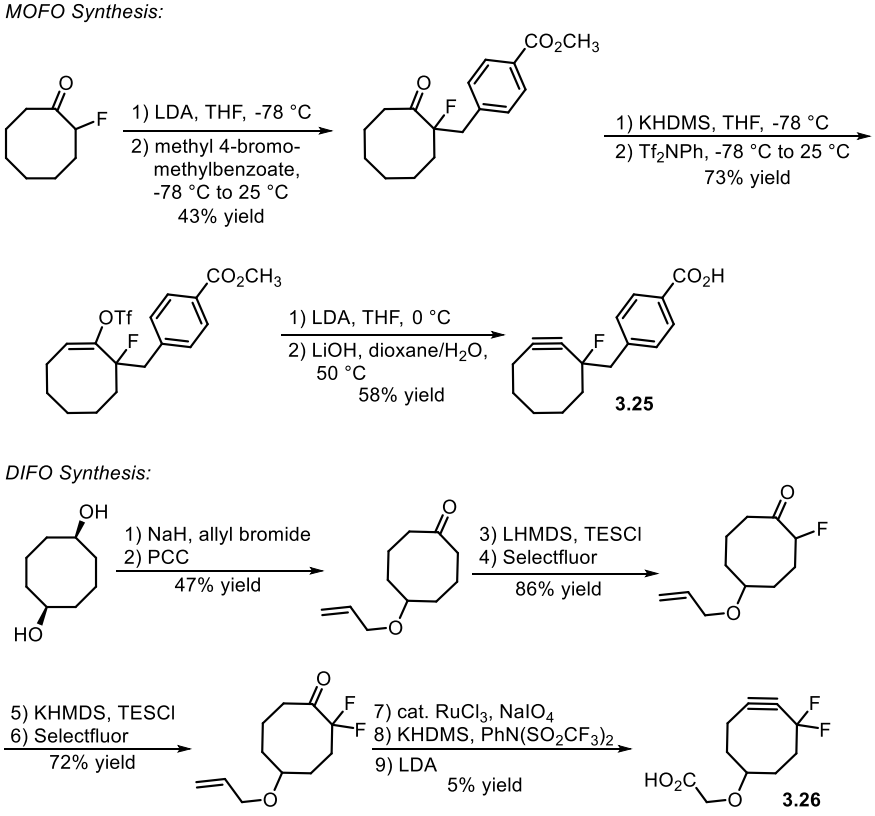


3.22 **3.23a** **3.23b** **3.24**

While very effective, using strain to decrease $\Delta E_d^{\ddagger}$ and increase reaction rates will always come paired with problematic instability and lack of selectivity. However, activation of alkynes by increasing the $\Delta E_i^{\ddagger}$ is an alternative approach which can sidestep some of these issues. This method has been employed by the installation of electron-withdrawing groups with the intent of activating the alkyne. One of the most prominent examples of this is the installation of fluorine at the propargyl position of the cycloalkyne. Both mono- (MOFO, **3.25**) and difluorinated (DIFO, **3.26**) analogs were synthesized using different routes, both starting with carbocyclic octanes to which fluorines were added (Scheme 3.7).[17, 2h] The syntheses are a limitation, as the DIFO **3.26** synthesis was lengthy and low yielding and neither of the syntheses were flexible enough to

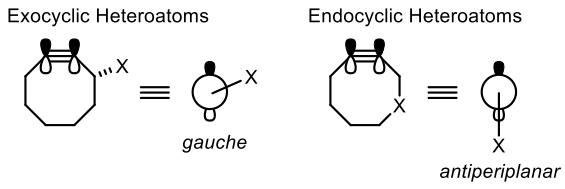
accommodate further derivatization. However, MOFO **3.25** and DIFO **3.26** did successfully illustrate the effectiveness of electronic activation of the alkyne. MOFO **3.25** showed a doubling of rate to 0.0043 $M^{-1}s^{-1}$ when compared to the analogs which lacked fluorine, while the rate of DIFO **3.26** was an order of magnitude faster, with a rate of 0.076 $M^{-1}s^{-1}$. These rates have enabled the productive use of fluorinated alkynes in biological labeling, with DIFO **3.26** being noted as particularly useful in living systems.[24] However, despite the successful demonstration of electronic activation, the synthetic limitations remain problematic.

Scheme 3.7: *Synthesis of Fluorinated Cycloalkynes*



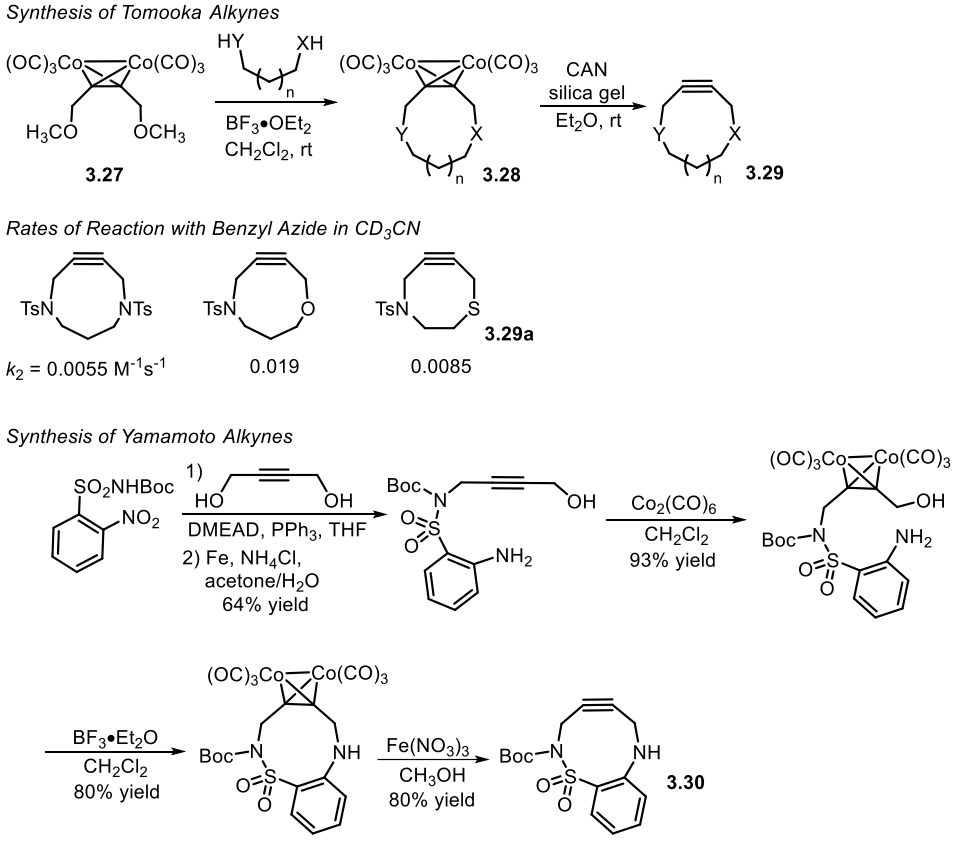
While the electronic activation of alkynes with exocyclic heteroatoms was shown to be successful in MOFO **3.25** and DIFO **3.26**, the geometry of the ring precludes optimal overlap between the C-X and alkyne pi orbitals.[25] By contrast, if the heteroatoms are included in the ring, optimal antiperiplanar orientation is enforced by the ring. Thus, a strained alkyne with endocyclic heteroatoms at the propargyl positions in the ring is predicted to offer high alkyne activation (Figure 3.2). These motifs have been difficult to synthesize, and only two reports of strained alkynes which fit this description have been made. The first was from Tomooka and co-workers, in which a double Nicholas reaction of a cobalt-protected alkyne **3.27** was used to form the strained rings **3.28**, with the alkyne being revealed after deprotection **3.29**.[2m] This synthesis allowed for the formation of a range of heterocycles, with variation in both ring size and heteroatom substitution (Scheme 3.8). When their rates were tested with benzyl azide, it was found that contrary to prediction these heterocycles were slower to react than DIFO **3.26**, and on the same order of magnitude as MOFO **3.25**. The relative decrease in rate was attributed to the relaxation of the ring strain caused by the inclusion of heteroatoms into the ring. A second strained heterocycle with propargylic nitrogens **3.30** was reported by Kaneda, Naruse and Yamamoto.[26] The second order rate constants (k_2) were not directly measured for this heterocycle, which were synthesized *via* a similar route to the Tomooka alkynes (Scheme 3.8). Nevertheless, comparative rate studies found that Yamamoto's cyclononynes reacted at rates similar to the Tomooka alkynes. Given how recent these reports are, little is known about the application and stability of heterocyclic strained alkynes in the systems in which they might be employed. However, the

Figure 3.2: *Comparison of Exocyclic and Endocyclic Heteroatoms*



flexibility of their syntheses offer an advantage over those of other strained alkynes, and further study will doubtless be undertaken.

Scheme 3.8: *Synthesis of Cyclic Alkynes with Endocyclic Heteroatoms*



Since their introduction, the use of strained alkynes in AAC chemistry has been an active area of study. A diverse range of strained alkynes and their syntheses have been reported, and they have been useful in areas where CuAAC and other biorthogonal reactions have been limited. Despite their successes, disadvantages associated with solubility, selectivity, fragility and limited adaptability of the syntheses have continued to drive the search for new alternatives. Herein, a set of strained heterocyclic alkynes will be discussed which aim to address some of the remaining shortcomings of the field.

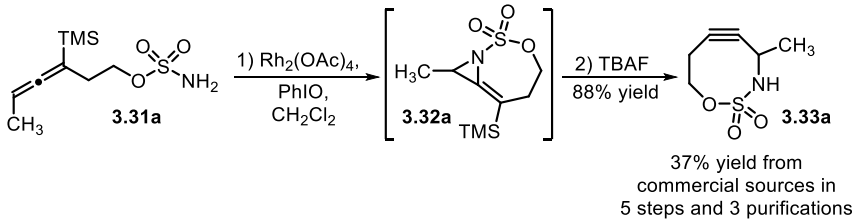
3.3 Synthesis of SNO-OCTs

While many examples of strained alkynes have been reported since their introduction as an alternative to CuAAC and other metal-catalyzed AAC reactions, limitations surrounding their solubility in aqueous media, stability towards common reaction conditions, and flexibility in synthesis have been identified. To address these concerns, cycloalkynes which incorporate electronic activation, specifically by the inclusion of endocyclic heteroatoms, have become attractive targets. While existing syntheses of these desired targets do exist and give greater flexibility in comparison to those of their more strain-activated counterparts, examples of 8-membered heterocyclic alkynes are rare. Herein, a different approach to the synthesis of these heterocycles is presented, along with an analysis of their stability.

The endocyclic methyleneaziridine, which has proven to be a valuable intermediate in the synthesis of azetidine-3-ones and their azetidine derivatives (Chapter 2), was found to also be useful in the construction of strained alkynes. In this method, the silyl substituent was key not only to direct the regiochemistry of the aziridination, but also in the formation of the SNO-OCT rings (Scheme 3.9). Treatment of the endocyclic methyleneaziridine **3.31a** with a fluoride source such as tetrabutylammonium fluoride (TBAF) led to activation and subsequent elimination of the silyl group. This triggered the formation of the alkyne and opening of the aziridine ring. Unlike previous syntheses of cycloalkynes with endocyclic heteroatoms which formed the strained ring from the addition of two linear precursors, the ring expansion in this synthesis was highly favorable, with the driving force of strain release leading to a high yielding, rapid reaction. Additionally, the formation of the endocyclic methyleneaziridine and subsequent ring opening could be done in a single reaction flask. Upon noting the consumption of the initial homoallenic sulfamate **3.31a**, the TBAF solution was added directly to the aziridination reaction. In

comparison to other reported syntheses, the SNO-OCT derivatives are competitive, with SNO-OCT **3.33a** being made from commercial sources in 5 steps with 3 purifications and 37% total yield.

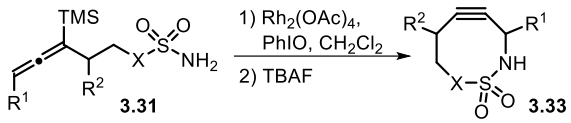
Scheme 3.9: *Synthesis of SNO-OCT*

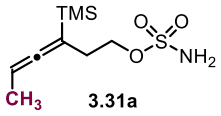
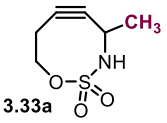
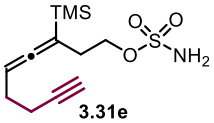
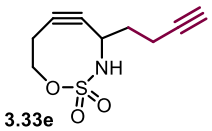
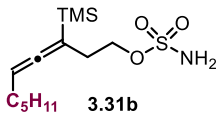
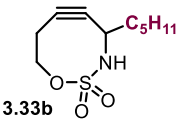
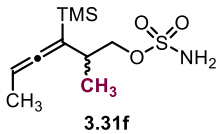
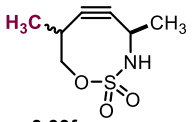
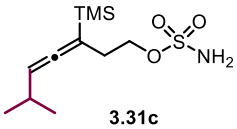
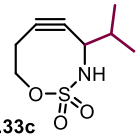
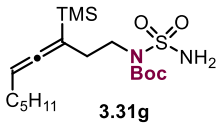
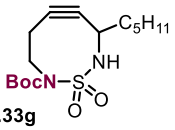
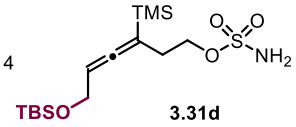
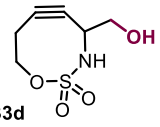


Many of the issues which have plagued strained alkynes are linked to the activation of the alkyne *via* increased ring strain. While this does lead to faster rates of reaction with azides and other alkyne coupling partners, the decrease in $\Delta E_d^{\ddagger}$ activates the alkyne indiscriminately which leads to undesired reactivity and decomposition. To limit this, an alternative is to deemphasize alkyne activation by strain induction and instead electronically activate the alkyne, increasing $\Delta E_i^{\ddagger}$. With the SNO-OCT derivatives, this was found to be successful. Upon heating at 50 °C for 18h, SNO-OCT **3.33b** showed no significant decomposition. Additionally, SNO-OCT **3.33b** was unaffected by exposure to trifluoroacetic acid (TFA) or aqueous NaOH for 18h. Similarly, it was inert to reaction in a pH 7 solution of 150 nM reduced glutathione over 24h. These are favorable indications of SNO-OCT's biocompatibility, as well as its utility in other synthetic settings.

As the demand for cyclic alkynes grows outside of biological labeling, new alkynes will need to be developed to cater to these areas. However, one of the most challenging points for previously reported syntheses has been the derivatization of the cyclic alkynes which they produce. In contrast to this, the synthesis of SNO-OCT has been found to be more flexible (Table 3.4). First, the substitution of the starting homoallenic sulfamate could be easily altered, allowing for further derivatization. Alkyl groups of varying sizes could easily be incorporated, varying from

Table 3.4: *Derivatization of SNO-OCT*

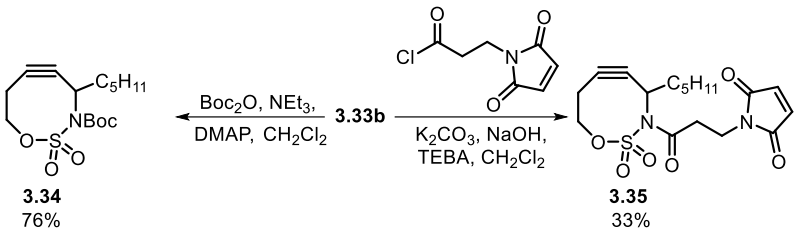


entry			yield	entry			yield
1			88%	5			>99%[a]
2			89%	6			47%
3			71%[a]	7			65%
4			66%				

[a]Yield from isolated methyleneaziridine

methyl to *iso*-propyl (entries 1, 2, and 3). Additionally, functional handles such as alcohols and alkynes could be incorporated at this position (entries 4 and 5). Substitution along the tether was also found to be tolerated in the formation of **3.33f** (entry 6), which adds a new site of functionalization in the ring. Secondly, the heteroatoms contained within the ring could be altered by changing the nitrene precursor. With a sulfamide **3.31g** in place of the sulfamate, nitrene insertion occured with the same regiochemical preference, and the resulting endocyclic methylene aziridine could then be opened to form **3.33g** (entry 7). Also, after formation of the alkyne, the propargyl nitrogen can be manipulated (Scheme 3.11). Protection of the nitrogen with a Boc group proceeded smoothly, and incorporation of the valuable maleimide demonstrated the inclusion of functional handles at a second position on the ring. In total, the diversity of alkynes synthesized showcases the previously unmatched flexibility of this synthetic route.

Scheme 3.10: *Inclusion of Groups at the Propargylic Nitrogen*



3.34
76%

3.35
33%

Endocyclic methyleneaziridines have provided a scaffold upon which a distinct cycloalkyne synthesis was developed. The ring expansion approach enabled the synthesis of strained rings with endocyclic heteroatoms which had been a daunting challenge with previous methods. The heterocycles which arose from this synthesis were found to be more stable than their solely strain activated peers, in line with prediction. Additionally, this synthetic approach enabled the formation of a range of heterocycles, with diversification of heteroatoms and substitution position, as well as functional group inclusion. With these derivatives in hand, an analysis of the impact of these modifications on reactivity could be evaluated.

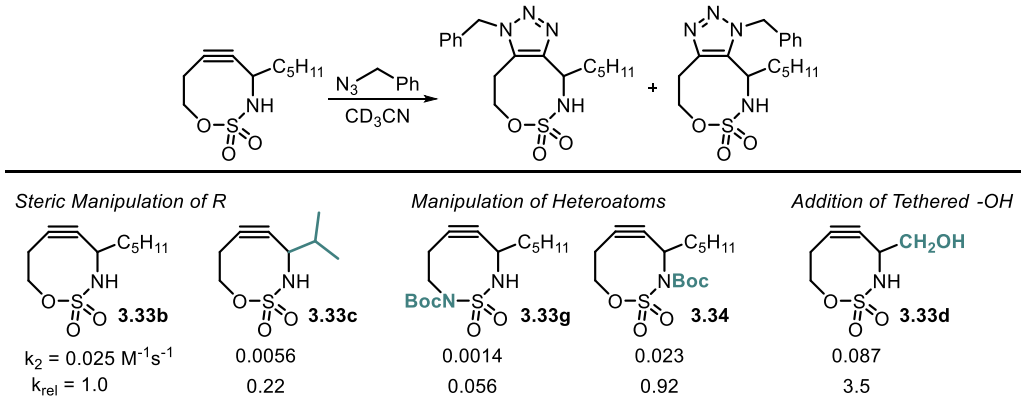
3.4 Impact of Structural Changes on the Rates of SNO-OCT

Without rapid rates of reactivity, the SPAAC reaction would not be useful in the biological labeling for which it was developed. Because of this, second order rate constants (k_2) remain one of the most important features upon which cyclic alkynes are evaluated. In order to better understand the relevance of SNO-OCT derivatives, as well as the impact of individual features on the rate of the reaction, the k_2 of the 1,3-dipolar cycloaddition of SNO-OCT derivatives with benzyl azide in CD_3CN were measured and compared to standard alkyne **3.16b** (krel).

The synthesis of SNO-OCT allowed for the synthesis of a range of cycloalkynes, and these structural differences were predicted to have impacts on the rates of reaction (Table 3.5). One feature which was manipulated was the steric bulk of the substituent at the propargylic position.

It was predicted that a larger group at this position would cause negative steric interactions with the incoming azide, and thus lead to a slower rate of reaction. This was confirmed in the measured k_2, which showed the *iso*-propyl substituted **3.33c** proceeded with a rate constant five times slower than the standard alkyne **3.33b**. Another feature that was evaluated was the manipulation of heteroatoms within the strain-inducing ring. Two competing effects were at play. Inclusion of a more electron poor heteroatom would inductively activate the alkyne and therefore increase the rate. Conversely, the bond lengths of an electron poor heteroatom would be longer, thus increasing bond lengths, decreasing ring strain and leading to a decreased rate. In the comparison of sulfamide-derived **3.33g** to sulfamate-derived **3.33b**, the inclusion of a homopropargylic N in place of O leads to a significantly slower rate, as would be expected for longer bond lengths and decreased ring strain. When the propargyl N is made more electron poor by the addition of an election-withdrawing Boc group as in SNO-OCT **3.34** very little impact on the rate was observed. In this case, computations identified that a negative steric interaction between the Boc group and the alkyl substituent may shoulder some of the responsibility for the lack of predicted rate increase.[27] Finally, it was found that increasing the electrophilicity of the propargyl substituent led to dramatic increases in rate, as was seen in the alcohol substituted **3.33d**. These observations

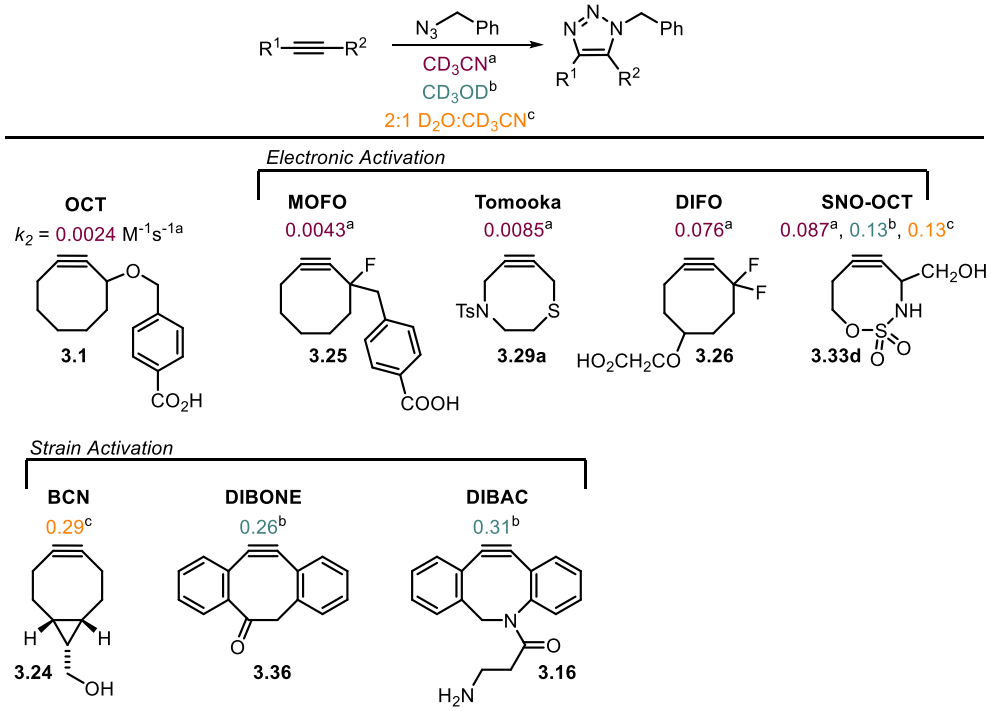
Table 3.5: *Rate Comparison of SNO-OCT Derivatives*



help to better understand the impact of the different structural features of the ring on reactivity and could aid in the design of faster derivatives in the future.

Finally, the rates of the SNO-OCT derivatives were compared to previously reported strained alkynes (Table 3.6). When compared to OCT **3.1**, heterocyclic SNO-OCT **3.33d** was an order of magnitude faster. For electronically activated alkynes, SNO-OCT was found to be faster than the Tomooka alkynes **3.29a**, which also feature endocyclic heteroatoms, as well as being faster than MOFO **3.25** and DIFO **3.26**, which are activated by exocyclic heteroatoms. While alkynes which rely solely on activation by high ring strain still have the fastest reported rates, measurement in the same solvent systems for direct comparison revealed that SNO-OCT **3.33d** had a k_2 on the same order of magnitude. Overall, the measured rates of the SNO-OCTs are comparable to those of some of the most widely used strained alkynes.

Table 3.6: *Rate Comparison of SNO-OCT Derivatives*



Gratifyingly, the measured k_2 of various SNO-OCT derivatives were found to be rapid. Structural changes were found to influence the relative k_2 values, with smaller, electrophilic substituents leading to faster rates. Additionally, the SNO-OCT **3.16e** was found to be competitive, being faster than other electronically activated cycloalkynes and on the same order of magnitude as faster strain activated cycloalkynes.

3.5 Conclusions

The introduction of strain as a method to increase the reactivity of alkynes in AAC reactions was an innovative step forward in the field of biorthogonal reactions. Because of this, much research has been done to improve these reactions, for which significant drawbacks remain. Among the common issues which have plagued SPAAC reactions are a lack of selectivity, and synthetic inflexibility of the strained alkynes. By comparison, SNO-OCT derivatives, which employ endocyclic methyleneaziridines as synthetic intermediates, have been shown to be uncommonly stable without sacrificing reactivity. The fastest SNO-OCT derivative measured (**3.33d**) was found to outpace DIFO and other electronically activated alkynes, while having a k_2 on the same order as solely strain activated alkynes. The unique structure and synthetic flexibility of SNO-OCT are favorable for biorthogonal labeling, and also to applications beyond.

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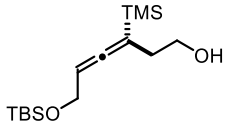
3.7 Experimental

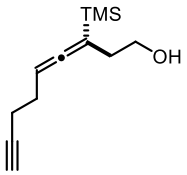
3.7.1 Preparation of homoallenic alcohols

General procedure: In a round bottom flask, lithium aluminum hydride (1 equiv) was suspended in dry THF (0.4 M) under nitrogen atmosphere and cooled to 0 °C. To this was added the corresponding homoallenic ester (1 equiv) dropwise as a solution in THF. The reaction mixture was stirred for 30 min, then quenched at 0 °C with H_2O (2.1 equiv), 1M aqueous NaOH (2.1 equiv), and H_2O (6.3 equiv). The organics were dried over Na_2SO_4, after which the solution was filtered and solvent was removed under reduced pressure. The residual oil was purified via column chromatography.

Information for the precursors to **3.31a-c, 3.31f** and **3.31g** can be found in Chapter 1.



Precursor to compound 3.31d. The homoallenic alcohol was prepared from the corresponding homoallenic ester (2.22 g, 6.4 mmol). The crude product was purified via column chromatography (0% EtOAc/hexanes to 10% EtOAc/hexanes, gradient) to yield the alcohol (1.92 g, 6.4 mmol) as a clear oil in a yield of 99%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.04 (tt, *J* = 4.8, 2.9 Hz, 1H), 4.19 (dd, *J* = 12.4, 4.8 Hz, 1H), 4.13 (dd, *J* = 12.4, 5.0 Hz, 1H), 3.83 (m, 1H), 3.71 – 3.62 (m, 1H), 2.83 (s, 1H), 2.29 – 2.15 (m, 2H), 0.91 (s, 9H), 0.11 (s, 9H), 0.08 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$ HRMS δ 204.20, 96.48, 87.22, 61.37, 60.65, 32.44, 26.08, 25.80, 18.62, -1.53, -5.18, -5.24. (ESI) *m/z* calculated for $C_{15}H_{32}O_2Si_2Na$ $[M+Na]^+$ 323.1833; found, 323.1830.

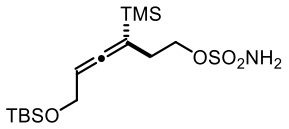


Precursor to compound 3.31e. The homoallenic alcohol was prepared from the corresponding homoallenic ester (2.0 g, 8.3 mmol). The crude product was purified via column chromatography (0% EtOAc/hexanes to 10% EtOAc/hexanes, gradient) to yield the alcohol (1.2 g, 5.7 mmol) as a clear oil in a yield of 69%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.95 (tt, *J* = 6.2, 3.0 Hz, 1H), 3.76 (tt, *J* = 6.3, 3.6 Hz, 2H), 2.36 – 2.12 (m, 6H), 1.98 (t, *J* = 2.5 Hz, 1H), 1.68 (s, 1H), 0.10 (d, *J* = 0.8 Hz, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 204.91, 94.74, 84.89, 84.25, 68.90, 62.37, 32.51, 27.85, 18.89, -1.47. HRMS (ESI) *m/z* calculated for $C_{12}H_{20}OSi$ $[M + H]^+$ 209.1356, found 209.1355.

3.7.2 Preparation of homoallenic sulfamates

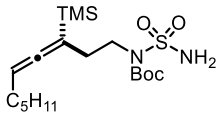
General procedure: In a 3-neck round bottom flask, chlorosulfonyl isocyanate (2.5 equiv) was cooled to 0℃. To this was added formic acid (2.5 equiv) dropwise. Vigorous gas evolution was observed. The resulting white solid was dissolved in CH_3CN to yield a 0.5 M solution. This solution was stirred at 0℃ for 30 min, and was then warmed to 23℃ and stirred an additional 4-12 h. The reaction was then cooled to 0℃, at which point the homoallenic alcohol (1 equiv) was added as a solution in DMA (0.6 M). The reaction was stirred for 1 h at 23℃, then quenched with the addition of an equal volume of H_2O. The aqueous phase was extracted with EtOAc (x3) and combined organic phases were washed with H_2O (x5). The organic phases were dried over Na_2SO_4, and solvent was removed *via* rotary evaporation. The crude material was purified *via* column chromatography.

Information for compounds to **3.31a-c** and **3.14f** can be found in Chapter 1.



Compound 3.31d. The homoallenic sulfamate was prepared from the corresponding homoallenic alcohol (4.5 g, 15 mmol). The crude product was purified via column chromatography (0% EtOAc/hexanes to 20% EtOAc/hexanes, gradient) to yield the product (75 mg, 0.20 mmol) as a waxy white solid in 1% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.38 (s, 2H), 5.01 (ddt, *J* = 8.9, 5.0, 3.4 Hz, 1H), 4.34 (ddd, *J* = 9.2, 8.2, 4.5 Hz, 1H), 4.32 (ddd, *J*= 8.2, 3.6, 3.1 Hz, 1H), 4.29 (dd, *J* = 11.5, 5.3 Hz, 1H), 4.14 (dd, *J* = 11.5, 9.1 Hz, 1H), 2.43 (ddd, *J* = 16.7, 4.5, 3.1 Hz, 1H), 2.36 (ddd, *J* = 16.8, 9.2, 3.6 Hz, 1H), 0.91 (s, 9H), 0.11 (s, 3H), 0.11 (s, 3H), 0.10 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 204.63, 94.11, 87.26, 69.42, 62.57, 27.55, 26.11, 18.64, -1.67, -5.10. HRMS (ESI) *m/z* calculated for $C_{15}H_{33}NO_4SSi_2$ [M+H$^+$] 380.1742; found, 380.1739.

Preparation of homoallenic sulfamide:

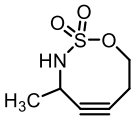


Compound 3.31g. A dry, 50 mL round bottom flask was placed under a nitrogen atmosphere and charged with the desired alcohol (500 mg, 2.2 mmol, 1 equiv), triphenylphosphine (754 mg, 2.9 mmol, 1.3 equiv), and *tert*-butyl aminosulfonylcarbamate (563 mg, 2.9 mmol, 1.3 equiv) were combined in dry THF (8.5 mL, 0.3 M) and cooled to 0 °C. Diisopropyldicarboxylate (0.57 mL, 2.9 mmol. 1.3 equiv) was added in a dropwise fashion to the resulting solution. The reaction mixture was warmed to room temperature and stirred for 4 h before the solvent was removed under reduced pressure. The resulting oil was diluted with hexanes and the solvent again removed under reduced pressure. The crude product was purified *via* column chromatography (0% EtOAc/hexanes to 25% EtOAc/hexanes, gradient) to yield pure homoallenic sulfamide (677 mg,

1.7 mmol) as a white solid in a yield of 76%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.25 (s, 2H), 4.85 (tt, *J* = 6.7, 2.8 Hz, 1H), 3.74 (ddd, *J* = 8.7, 7.3, 1.3 Hz, 2H), 2.34 – 2.19 (m, 2H), 1.97 – 1.89 (m, 2H), 1.53 (s, 9H), 1.43 – 1.28 (m, 6H), 0.94 – 0.86 (m, 3H), 0.09 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 206.13, 152.45, 93.14, 86.58, 84.35, 47.60, 31.62, 29.51, 29.10, 28.45, 28.27, 22.66, 14.20, -1.42. HRMS (ESI) *m/z* calculated for $C_{18}H_{40}N_3O_4SSi$ [$M+NH_4^+$] 427.2057; found, 427.2055.

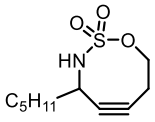
3.7.3 Preparation of SNO-OCT alkynes

General procedure. The following procedure was adapted from our previously reported syntheses of endocyclic bicyclic methyleneaziridines.[3] The homoallenic sulfamate (1 equiv) and $Rh_2(OAc)_4$ (0.05 equiv) were placed in a dry round bottom flask. The solids were dissolved in CH_2Cl_2 to prepare a 0.2 M solution and stirred for 5 min at rt. PhIO (1.2 equiv) was added in a single portion and the reaction mixture was stirred for 30 min while monitoring by TLC. When TLC indicated complete consumption of the starting material, 1 M TBAF in THF (2 equiv) was added. After 5 min at rt, the reaction was checked for completion by TLC. The reaction was then quenched by the addition of an equal volume of water and extracted with 3 portions of EtOAc. The combined organics were dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure and the crude product purified by column chromatography.

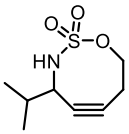


Compound 3.33a. The cyclic alkyne was prepared from the corresponding homoallenic sulfamate (250 mg, 1.0 mmol). Purification by column chromatography (0% EtOAc/hexanes to 6% EtOAc/hexanes, gradient) furnished pure **3.16a** (154 mg, 0.88 mmol) as a white solid in a yield of

88%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.21 (d, *J* = 7.1 Hz, 1H), 4.92 (ddd, *J* = 11.0, 9.9, 4.2 Hz, 1H), 4.67 (ddd, *J* = 11.0, 5.3, 3.1 Hz, 1H), 4.35 (pt, *J* = 7.0, 2.3 Hz, 1H), 2.75 (dddd, *J* = 17.0, 10.0, 5.3, 2.6 Hz, 1H), 2.41 (dddd, *J* = 17.0, 4.2, 3.1, 2.1 Hz, 1H), 1.38 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 97.23, 96.59, 76.43, 44.66, 21.65, 19.04. HRMS (ESI) *m/z* calculated for $C_6H_9NNaO_3S$ [M+Na^+] 198.0195 found 198.0195.

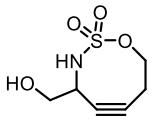


Compound 3.33b. The cyclic alkyne was prepared from the corresponding homoallenic sulfamate (1.3 g, 4.3 mmol). Purification by column chromatography (0% EtOAc/hexanes to 15% EtOAc/hexanes, gradient) furnished pure **3.16b** (0.90 g, 3.9 mmol) as a white solid in a yield of 89%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.10 (d, *J* = 7.2 Hz, 1H), 4.92 (ddd, *J* = 10.6, 10.5, 4.2 Hz, 1H), 4.66 (ddd, *J* = 11.0, 5.3, 3.0 Hz, 1H), 4.23 (dtd, *J* = 8.8, 6.8, 3.5 Hz, 1H), 2.75 (dddd, *J* = 17.7, 10.1, 5.3, 2.6 Hz, 1H), 2.41 (ddt, *J* = 17.0, 4.6, 2.5 Hz, 1H), 1.77 – 1.59 (m, 2H), 1.44 – 1.26 (m, 6H), 0.89 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 97.38, 96.84, 76.47, 49.62, 32.80, 31.23, 25.63, 22.55, 21.87, 14.06. HRMS (ESI) *m/z* calculated for $C_{10}H_{21}N_2O_3S$ [M+NH_4^+] 249.1267; found, 249.1265.

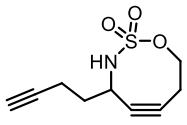


Compound 3.33c. Due to inseparable impurities arising in the synthesis of the homoallenic alcohol, the unpurified material was carried through the synthesis of the homoallenic sulfamate and to the methyleneaziridine, at which point the material was purified. The cyclic alkyne was prepared from the methyleneaziridine (0.28 g, 1.0 mmol) by treatment with 2.0 equiv of 1M TBAF in THF (2.0 mL. 2.0 mmol). Purification by column chromatography (0% EtOAc/hexanes to 20%

EtOAc/hexanes, gradient) furnished pure **3.33c** (157 mg, 0.71 mmol) as a white solid in a yield of 71%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.35 (d, *J* = 7.2 Hz, 1H), 4.92 (td, *J* = 10.6, 4.2 Hz, 1H), 4.65 (ddd, *J* = 11.0, 5.3, 2.8 Hz, 1H), 4.02 (tt, *J* = 7.2, 2.4 Hz, 1H), 2.76 (dddd, *J* = 17.0, 10.3, 5.3, 2.7 Hz, 1H), 2.40 (ddt, *J* = 17.0, 4.4, 2.5 Hz, 1H), 1.99 – 1.83 (m, *J* = 6.8 Hz, 1H), 1.00 (dd, *J* = 6.7, 1.8 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 98.43, 95.81, 76.54, 55.97, 30.78, 21.89, 19.31, 18.79. HRMS (ESI) *m/z* calculated for $C_8H_{17}N_2O_3S$ [M+NH_4^+] 221.0954 found 221.0951.

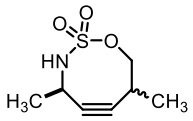


Compound 3.33d. The cyclic alkyne **3.33d** was prepared from the corresponding homoallenic sulfamate (28 mg, 0.074 mmol). The crude product was purified via column chromatography (0% EtOAc/hexanes to 50% EtOAc/hexanes, gradient) to yield pure **3.33d** (9 mg, 0.047 mmol) as a white solid in 66% yield. The general procedure was adapted to use 5 equiv of 1 M TBAF in THF to allow for complete deprotection of the tethered alcohol in addition to the desilylation and ring expansion process. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.78 (d, *J* = 7.2 Hz, 1H), 4.93 (ddd, *J* = 11.0, 9.2, 4.4 Hz, 1H), 4.73 (ddd, *J* = 11.1, 5.2, 4.0 Hz, 1H), 4.32 (qd, *J* = 7.2, 6.0, 2.6 Hz, 1H), 3.83 (dt, *J* = 11.4, 3.9 Hz, 1H), 3.71 (ddd, *J* = 11.4, 7.7, 3.7 Hz, 1H), 2.77 (dddd, *J* = 16.9, 9.1, 5.1, 2.4 Hz, 1H), 2.50 (dtd, *J* = 17.0, 4.1, 2.1 Hz, 1H), 2.05 (d, *J* = 9.7 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 101.10, 93.13, 76.33, 62.03, 50.89, 21.76. HRMS (ESI) *m/z* calculated for $C_6H_{10}NO_4S$ [M+H^+] 192.0325; found, 192.0324.



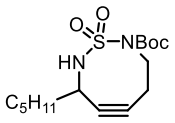
Compound 3.33e. Due to inseparable impurities arising in the synthesis of the homoallenic sulfamate, the unpurified material was carried through the Rh-catalyzed aziridination of the

homoallenic sulfamate to the methyleneaziridine, at which point the material was purified. The cyclic alkyne was prepared from the methyleneaziridine (14 mg, 0.05 mmol) by treatment with 1.1 equiv of 1M TBAF in THF (55 µL, 0.055 mmol). Purification by column chromatography (0% EtOAc/hexanes to 10% EtOAc/hexanes, gradient) furnished pure **3e** (11 mg, 0.05 mmol) as a white solid in a quantitative yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.57 (d, *J* = 7.0 Hz, 1H), 5.86 (ddd, *J* = 11.0, 7.8, 4.7 Hz, 1H), 5.74 (dt, *J* = 10.7, 5.1 Hz, 1H), 5.38 (qt, *J* = 7.2, 2.3 Hz, 1H), 3.67 (dddd, *J* = 17.0, 7.5, 5.0, 2.1 Hz, 1H), 3.53 (dtd, *J* = 17.0, 4.8, 2.2 Hz, 1H), 3.42 (dddd, *J* = 16.7, 7.8, 6.1, 2.7 Hz, 1H), 3.32 (dddd, *J* = 17.1, 7.0, 6.1, 2.7 Hz, 1H), 3.04 (t, *J* = 2.7 Hz, 1H), 3.03 – 2.96 (m, 1H), 2.91 – 2.83 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 98.37, 95.57, 82.34, 76.40, 70.42, 48.57, 31.40, 21.83, 15.25. HRMS (ESI) *m/z* calculated for $C_9H_{10}NO_3S$ [M-H^+] 212.0387 found 212.0388.



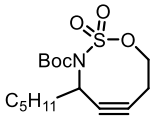
Compound 3.33f. The cyclic alkyne **3.33f** was prepared from the corresponding homoallenic sulfamate (200 mg, 0.76 mmol). The crude product was purified via column chromatography (0% EtOAc/hexanes to 10% EtOAc/hexanes, gradient) to yield pure **3.33f** (67 mg, 0.35 mmol) as a white solid in 47% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.54 (major, d, *J* = 6.8 Hz, 2H), 5.50 (minor, d, *J* = 7.0 Hz, 1H), 4.88 (major, dd, *J* = 10.9, 4.2 Hz, 2H), 4.57 (minor, dd, *J* = 10.8, 9.5 Hz, 1H), 4.52 (minor, dd, *J* = 10.8, 5.2 Hz, 1H), 4.37 (major, dd, *J* = 11.0, 3.7 Hz, 2H), 4.32 (minor, qd, *J* = 7.0, 2.5 Hz, 1H), 4.26 (major, pd, *J* = 6.9, 2.0 Hz, 2H), 3.03 (minor, dqdd, *J* = 9.5, 7.1, 5.2, 2.5 Hz, 1H), 2.77 (major, dtdd, *J* = 11.0, 7.1, 3.9, 1.9 Hz, 2H), 1.36 (major, d, *J* = 7.0 Hz, 6H), 1.33 (minor, d, *J* = 7.0 Hz, 3H), 1.22 (major, d, *J* = 7.1 Hz, 6H), 1.06 (minor, d, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 100.78, 100.74, 95.80, 95.53, 82.35, 81.93, 44.58, 44.54, 28.89,

28.65, 19.30, 18.91, 16.58, 14.08. HRMS (ESI) *m/z* calculated for $C_7H_{15}N_2O_3S$ [M+NH_4^+] 207.0798 found 207.0798.



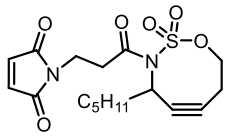
Compound 3.33g. The cyclic alkyne **3.33g** was prepared from the corresponding homoallenic sulfamide (1.7 g, 4.1 mmol). The general procedure was employed, with the exception that $Rh_2(TPA)_4$ was substituted for $Rh_2(OAc)_4$ to improve the selectivity between endocyclic and exocyclic methyleneaziridines. The crude product was purified via column chromatography (0% EtOAc/hexanes to 20% EtOAc/hexanes, gradient) to yield pure **3.16c** (0.90 g, 3.9 mmol) as a white solid in 65% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.90 (s, 1H), δ 4.37 (dtt, *J* = 11.7, 8.6, 5.7 Hz, 2H), 4.03 (ddd, *J* = 14.1, 6.2, 2.3 Hz, 1H), 2.74 (dddd, *J* = 17.1, 11.5, 6.0, 3.2 Hz, 1H), 2.30 – 2.18 (m, 1H), 1.56 (s, 9H), 1.54 – 1.22 (m, 8H), 0.89 (td, *J* = 7.0, 4.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.29, 96.98, 92.81, 84.45, 51.59, 49.31, 35.95, 32.40, 31.31, 28.25, 25.86, 25.23, 22.58, 14.04.HRMS (ESI) *m/z* calculated for $C_{15}H_{30}N_3O_4S$ [M+NH_4^+] 348.1952; found, 348.1947.

3.7.4 Procedures for Addition to the Propargyl Nitrogen



Compound 3.34. Compound **3.33b** (0.25 g, 1.1 mmol) was dissolved in CH_2Cl_2 (0.2 M). To this solution was added di-*tert*-butyl dicarbonate (0.35 g, 1.6 mmol) and triethylamine (0.23 mL, 1.6 mmol), followed by 4-dimethylaminopyridine (13 mg, 0.11 mmol). The reaction was stirred at ambient temperature under a N_2 atmosphere until TLC indicated complete consumption of **3.33b**.

The reaction mixture was quenched by the addition of an equal volume of saturated aqueous NH_4Cl. The aqueous phase was extracted with 3 x 10 mL portions of CH_2Cl_2 and the combined organic phases dried over Na_2SO_4. The solution was filtered and the volatiles removed under reduced pressure. The crude product was purified *via* column chromatography (0% EtOAc/hexanes to 25% EtOAc/hexanes, gradient) to yield pure cyclic alkyne **6** (0.28 g, 0.84 mmol) as a white solid in 76% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.06 (ddd, *J* = 12.4, 11.1, 4.0 Hz, 1H), 4.97 (td, *J* = 8.0, 2.8 Hz, 1H), 4.62 (dd, *J* = 11.1, 6.0 Hz, 1H), 2.92 (dddd, *J* = 17.1, 12.4, 6.1, 2.9 Hz, 1H), 2.30 (dd, *J* = 17.1, 3.9 Hz, 1H), 2.04 – 1.89 (m, 2H), 1.54 (s, 9H), 1.40 – 1.28 (m, 6H), 0.89 (td, *J* = 6.8, 5.7, 3.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.01, 96.15, 94.46, 85.29, 75.03, 55.61, 33.48, 31.15, 28.51, 26.00, 22.61, 21.72, 14.09. HRMS (ESI) *m/z* calculated for $C_{15}H_{26}NO_5S$ [M+H$^+$] 332.1526; found, 332.1515.

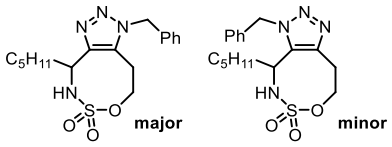


Compound 3.35. A solution of potassium carbonate (50 mg, 0.36 mmol), sodium hydroxide (6.4 mg, 0.16 mmol), **3.33b** (23 mg, 0.1 mmol) and benzyltriethylammonium chloride (2.2 mg, 0.01 mmol) in CH_2Cl_2 (0.3M) was cooled to 0 °C. To this was added 3-maleimidopropropionyl chloride (21 mg, 0.11 mmol) in CH_2Cl_2 (0.6 M), and resulting solution was stirred at 0 °C for 1h. Reaction was then diluted with an equal volume of hexanes, then filtered through celite and solvent was removed *via* rotary evaporation. The crude product was purified by column chromatography (0% EtOAc/hexanes to 20% EtOAc/hexanes, gradient) to yield pure cyclic alkyne **3.35** (12 mg, 0.033 mmol) as a pale yellow solid in 33% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.71 (s, 2H), 5.46 (ddd, *J* = 9.0, 7.1, 2.9 Hz, 1H), 5.04 (ddd, *J* = 12.4, 11.1, 4.0 Hz, 1H), 4.65 (dd, *J* = 11.1, 6.1 Hz, 1H), 3.92 (ddd, *J* = 14.5, 8.8, 5.8 Hz, 1H), 3.83 (ddd, *J* = 14.3, 8.7, 5.9 Hz, 1H), 3.31 (ddd, *J* = 17.5,

8.7, 5.8 Hz, 1H), 3.04 (ddd, *J* = 17.5, 8.8, 5.9 Hz, 1H), 2.93 (dddd, *J* = 17.1, 12.5, 6.2, 3.0 Hz, 1H), 2.33 (dd, *J* = 17.1, 4.0 Hz, 1H), 1.97 (tt, *J* = 10.2, 4.4 Hz, 1H), 1.92 – 1.79 (m, 1H), 1.38 – 1.25 (m, 6H), 0.93 – 0.81 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.30, 170.52, 134.39, 96.12, 93.15, 75.62, 52.29, 36.24, 33.97, 33.07, 31.23, 25.95, 22.60, 21.79, 14.10. HRMS (ESI) *m/z* calculated for $C_{17}H_{26}N_3O_6S$ [M+NH_4^+] 400.1537 found 400.1537.

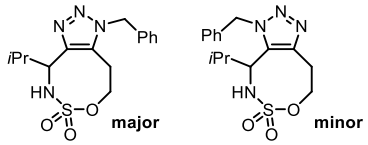
3.7.5 General procedure for reactions with benzyl azide

General Procedure. The cyclic alkyne (1 equiv) was dissolved in CH_3CN (0.1 M). Benzyl azide (1.1 equiv) was added to the resulting solution and the reaction mixture stirred for 1 h to ensure full conversion. The solvent was then removed under reduced pressure and the resulting oil dissolved in a minimum volume of CH_2Cl_2. The solvent was again removed under reduced pressure and the triazole products characterized without further purification.

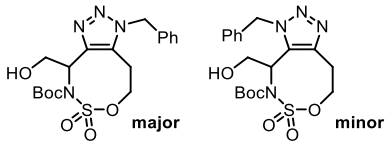


Triazoles from 3.33b. The triazole was prepared from alkyne **3.33b** (15 mg, 0.065 mmol). The resulting triazoles were obtained as a clear oil (24 mg, 0.065 mmol) in quantitative yield as a mixture of regioisomers (2.2:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.30 (m, 4.45H), 7.17 – 7.08 (m, 2.8H), 5.65 – 5.42 (m, 4.35H), 4.59 (major, dd, *J* = 9.1, 4.9 Hz, 1H), 4.56 (minor, m, 0.45H), 4.15 (minor, td, *J* = 11.8, 5.5 Hz, 0.45H), 3.88 (major, ddd, *J* = 11.7, 6.4, 5.3 Hz, 1H), 3.80 (major, ddd, *J* = 11.9, 7.8, 5.2 Hz, 1H), 3.74 – 3.63 (minor, m, 0.45H), 3.34 – 3.15 (m, 1.9H), 3.01 (major, ddd, *J* = 16.1, 6.5, 5.2 Hz, 1H), 2.35 – 2.22 (major, m, 1H), 1.96 (major, ddd, *J* = 14.2, 9.6, 5.0 Hz, 1H), 1.75 – 1.59 (m, 0.45H), 1.59 – 1.43 (m, 2.2H), 1.43 – 1.19 (m, 6.9H), 0.89 (major, td, *J* = 6.9, 4.8 Hz, 3H), 0.80 (minor, t, *J* = 7.2 Hz, 1.4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 134.79,

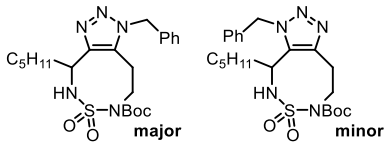
134.36, 129.41, 128.86, 127.07, 126.87, 69.25 (minor), 67.46 (major), 52.70, 52.50, 51.14 (major), 50.22(minor), 34.11, 33.39 (major), 31.40, 31.05, 26.41, 25.58, 24.86, 24.79, 22.59, 22.36, 14.12 (major), 13.99 (minor). HRMS (ESI) *m/z* calculated for $C_{17}H_{25}N_4O_3S$ [M+H$^+$] 365.1642; found, 365.1638.



Triazoles from 3.33c. The triazole was prepared from alkyne **3.33c** (10 mg, 0.05 mmol). The resulting triazoles were obtained as a pale yellow oil (17 mg, 0.05 mmol) in quantitative yield as a mixture of regioisomers (3.4:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 – 7.30 (m, 4H), 7.12 (td, J = 7.5, 1.7 Hz, 2.5H), 5.65 (major, d, J = 15.7, 1 H), 5.58 (minor, d, J = 16.0 Hz, 0.3 H), 5.49 (d, J = 15.7 Hz, 1.3 H), 4.80 (m, 1.3H), 4.59 (minor, ddd, J = 11.7, 6.6, 1.8 Hz, 0.3H), 4.49 (major, dd, J = 9.0, 5.3 Hz, 1H), 4.37 (minor, dd, J = 6.3, 3.9 Hz, 0.3H), 4.18 (minor, td, J = 11.8, 5.5 Hz, 0.3H), 3.96 (major, dt, J = 11.2, 5.3 Hz, 1H), 3.69 – 3.60 (major, m, 1H), 3.59 – 3.49 (minor, m, 0.3 H), 3.34 – 3.23 (m, 1.3 H), 2.96 (major, dt, J = 16.0, 5.2 Hz, 1H), 2.73 (major, pd, J = 6.8, 5.3 Hz, 1H), 1.12 (major, d, J = 6.8 Hz, 3H), 1.00 (minor, dd, J = 6.7, 1.7 Hz, 0.9H), 0.98 (major, d, J = 6.9 Hz, 3H), 0.73 (minor, d, J = 6.9 Hz, 0.9H).^{13}C NMR (126 MHz, $CDCl_3$) δ 146.72 (major), 140.76 (minor), 134.87 (major), 134.18 (minor), 129.66, 129.52, 129.39, 128.98, 128.92, 127.07, 126.89, 69.51(minor), 67.44(major), 56.74 (major), 55.30 (minor), 53.57 (minor), 52.61 (major), 31.39 (minor), 30.97 (major), 25.32 (minor), 22.71 (major), 19.84 (major), 19.55 (minor), 17.33 (major), 15.36 (minor). HRMS (ESI) *m/z* calculated for $C_{15}H_{19}N_4O_3S$ [M-H$^+$] 335.1183; found, 335.1185.

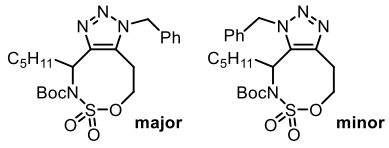


Triazoles from 3.33d. The triazoles were prepared from alkyne **3.33d** (12 mg, 0.063 mmol). The resulting compounds were obtained as a clear oil (20 mg, 0.061 mmol) as a mixture of regioisomers (3.3:1) in quantitative yield. ^{1}H NMR (500 MHz, CD_3CN) δ 7.45 – 7.29 (m, 4.5H), 7.23 – 7.16 (m, 2H), 6.36 (minor, d, J = 6.6 Hz, 0.30H), 6.27 (major, d, J = 9.1 Hz, 1H), 5.64 – 5.47 (m, 2.6H), 4.62 (ddd, J = 9.5, 5.8, 4.1 Hz, 1.3H), 4.53 (minor, ddd, J = 11.9, 7.2, 1.5 Hz, 0.3H), 4.22 (major, dt, J = 12.2, 5.1 Hz, 1H), 4.13 – 4.01 (m, 1.3H), 3.97 (major, dd, *J* = 11.5, 5.9 Hz, 1H), 3.92 (major, ddd, *J* = 12.1, 9.5, 4.7 Hz, 1H),3.75 – 3.58 (m, 1H), 3.40 (major, ddd, J = 16.5, 9.5, 5.3 Hz, 1H), 3.16 – 3.06 (m, 1H), 3.03 (major, dt, J = 16.5, 4.8 Hz, 1H). ^{13}C NMR (126 MHz, CD_3CN) δ 145.29, 136.64, 136.36 131.62, 129.95, 129.85, 129.72, 129.36, 129.24, 129.13, 128.13, 128.04, 69.53 (minor), 68.33 (major), 64.27 (major), 63.41, 55.28, 53.79, 52.79, 52.41, 24.94 (minor), 23.05 (major). HRMS (ESI) *m/z* calculated for $C_{13}H_{17}N_4O_4S$ [$M+H^+$] 325.0965; found, 325.0959.



Triazoles from 3.33g. The triazoles were prepared from alkyne **3.33g** (17 mg, 0.052 mmol) and obtained as a clear oil (22 mg, 0.048 mmol) as a mixture of regioisomers (3.2:1) in a quantitative yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 – 7.29 (m, 3.5H), 7.25 – 7.13 (m, 3H), 5.81 (major, d, *J* = 15.6 Hz, 1H), 5.71 (minor, d, *J* = 16.1 Hz, 0.31H), 5.54 (minor, d, *J* = 15.9 Hz, 0.32H), 5.23 (major, d, *J* = 15.6 Hz, 1H), 5.09 (major, s, 1H), 4.36 (p, *J* = 6.7, 5.5 Hz, 2H), 4.16 (major, s, 1H), 4.11 – 3.88 (m, 0.6H), 3.79 (major, dd, *J* = 14.4, 7.9 Hz, 1H), 3.34 – 3.20 (m, 1H), 3.15 (minor, dt, *J* = 14.6, 5.8 Hz, 0.3H), 2.67 (major, dd, *J* = 15.2, 6.3 Hz, 1H), 2.31 – 2.10 (m, 2H), 1.68 (p, *J*

= 8.0, 7.5 Hz, 1H), 1.63 – 1.52 (m, 2H), 1.47 (ddq, *J* = 9.4, 5.9, 2.8, 2.3 Hz, 1H), 1.36 (s, 3H), 1.35 (s, 9H), 1.28 (ddd, *J* = 35.1, 17.1, 9.8 Hz, 4H), 1.17 – 1.08 (m, 0.3H), 1.03 (dp, *J* = 7.2, 4.6, 2.7 Hz, 0.3H), 0.93 – 0.85 (major, m, 3H), 0.79 (minor, t, *J* = 7.2 Hz, 0.9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ151.82, 151.09, 145.88, 134.95, 134.68, 132.31, 129.33, 129.24, 128.94, 128.78, 128.70, 128.32, 127.29, 127.02, 85.28 (major), 84.49 (minor), 52.37, 52.37, 50.09, 48.95, 47.30(minor), 44.49 (major), 31.66, 31.43 (major), 31.04, 28.01, 27.87, 26.21 (minor), 22.59, 21.33 (major), 14.12 (major), 13.99 (minor). HRMS (ESI) *m/z* calculated for $C_{22}H_{34}N_5O_4S$ [M+H$^+$] 464.2333; found, 464.2323.

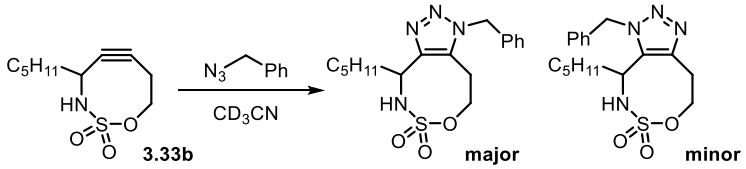


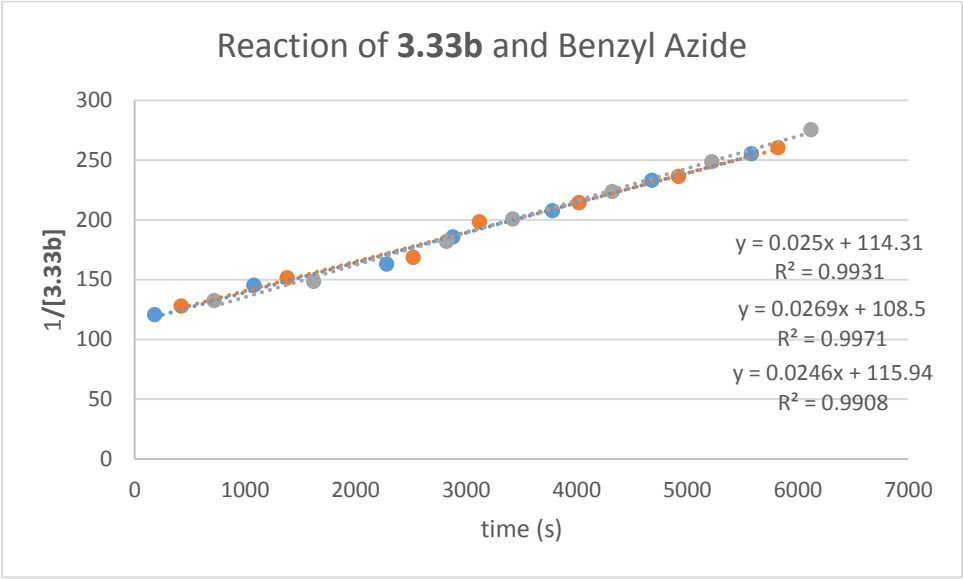
Triazoles from 3.34. The triazoles were prepared from alkyne **3.34** (10 mg, 0.031 mmol). The product was obtained (14 mg, 0.030 mmol) as a clear oil as a mixture of regioisomers (2.0:1) in a quantitative yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.29 (m, 5H), 7.26 – 7.21 (m, 0.5H), 7.14 – 7.05 (m, 2H), 5.80 (minor, d, J = 15.6 Hz, 0.5H), 5.69 – 5.59 (m, 2H), 5.51 (major, dd, J = 10.4, 4.9 Hz, 1H), 5.43 (major, d, J = 15.8 Hz, 1H), 4.76 (minor, td, J = 10.6, 3.0 Hz, 0.5H), 4.68 (minor, dt, J = 11.0, 3.8 Hz, 0.5H), 4.18 (major, ddd, J = 12.2, 6.2, 3.2 Hz, 1H), 3.90 (major, ddd, J = 11.2, 6.9, 2.9 Hz, 1H), 3.30 (minor, tdt, J = 17.1, 9.6, 3.1 Hz, 1H), 3.04 – 2.90 (major, m, 2H), 2.61 – 2.49 (major, m, 1H), 2.43 – 2.29 (major, m, 1H), 2.19 (minor, dddd, J = 13.5, 10.5, 8.4, 4.8 Hz, 0.5H), 1.68 (minor, dddd, J = 13.7, 10.3, 7.2, 5.7 Hz, 1H), 1.54 (minor, s, 6H), 1.45 (major, s, 9H), 1.38 (tt, J = 9.8, 6.1 Hz, 3H), 1.32 – 1.19 (m, 2H), 1.10 – 0.94 (m, 2H), 0.90 (major, dt, J = 14.4, 7.0 Hz, 3H), 0.74 (minor, t, J = 7.2 Hz, 1.5H). ^{13}C NMR (126 MHz, $CDCl_3$) 152.04, 150.76,

135.14, 134.81, 129.44, 128.90, 127.47, 127.03, 86.20, 85.37, 74.78 (minor), 69.47 (major), 57.35 (major), 52.78 (minor), 52.66 (minor), 52.50 (major), 32.15 (major), 31.78, 31.50 (major), 31.09, 27.99 (minor), 27.93, 27.18, 25.83, 25.60, 23.31 (major), 22.62, 22.33, 14.15 (major), 13.96 (minor). HRMS (ESI) *m/z* calculated for $C_{22}H_{33}N_4O_5S$ [M+H$^+$] 465.2166; found, 465.2163.

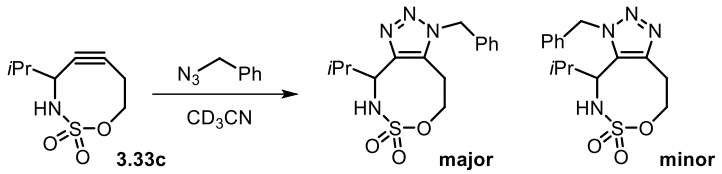
3.7.6 Kinetic data for the reactions with benzyl azide

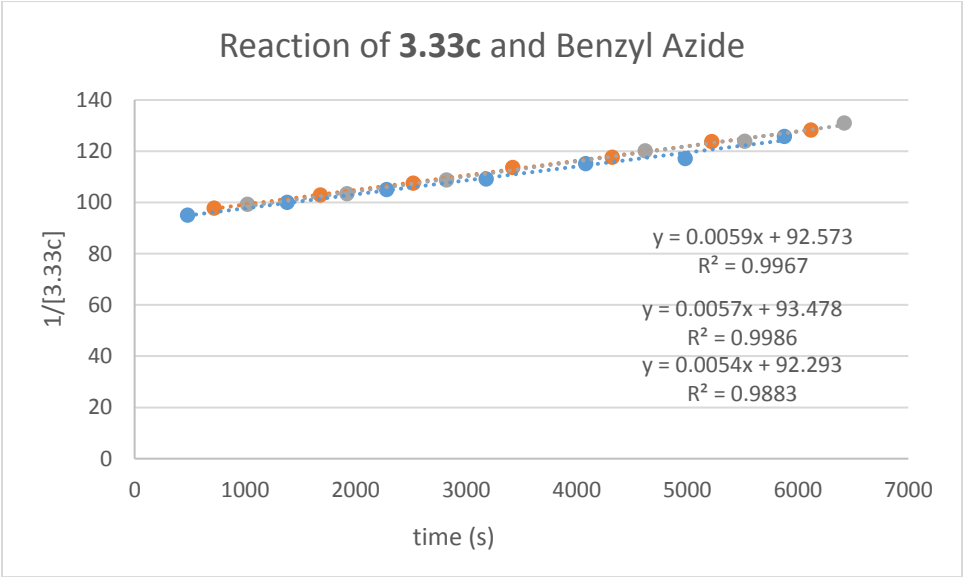
General Procedure. A stock solution of cycloalkyne (0.02 M) and a stock solution of benzyl azide and mesitylene (0.02 M with respect to both solutes) were combined in equal volumes in a small cuvette, then rapidly mixed. The resulting solution was transferred to an NMR tube and the reaction progress was monitored by ^{1}H-NMR at 25 °C, with spectra taken once every 15 min over the course of several hours. The k_2 values were determined by measuring the decrease in cycloalkyne signal integrations which were standardized relative to the mesitylene standard. Inverse concentration of cycloalkyne was plotted against time, and the points were fitted by linear regression. The slope of the resulting line corresponded to the k_2 value. Each experiment was run in triplicate and the k_2 values for each trial were averaged.



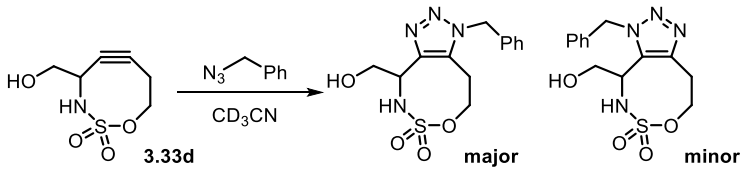


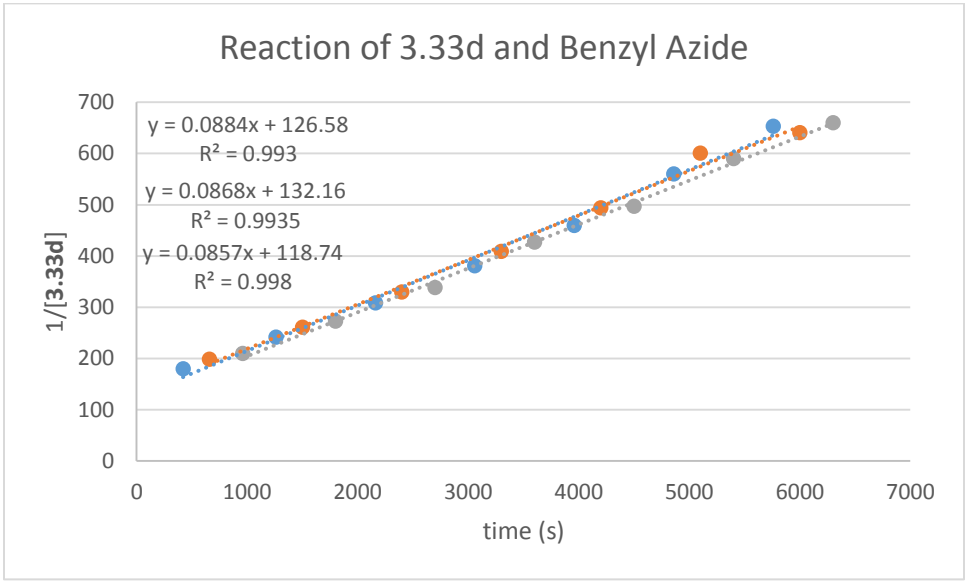
k_2=0.026±0.001$M^{-1}s^{-1}$



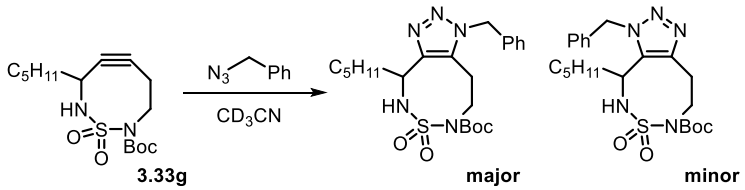


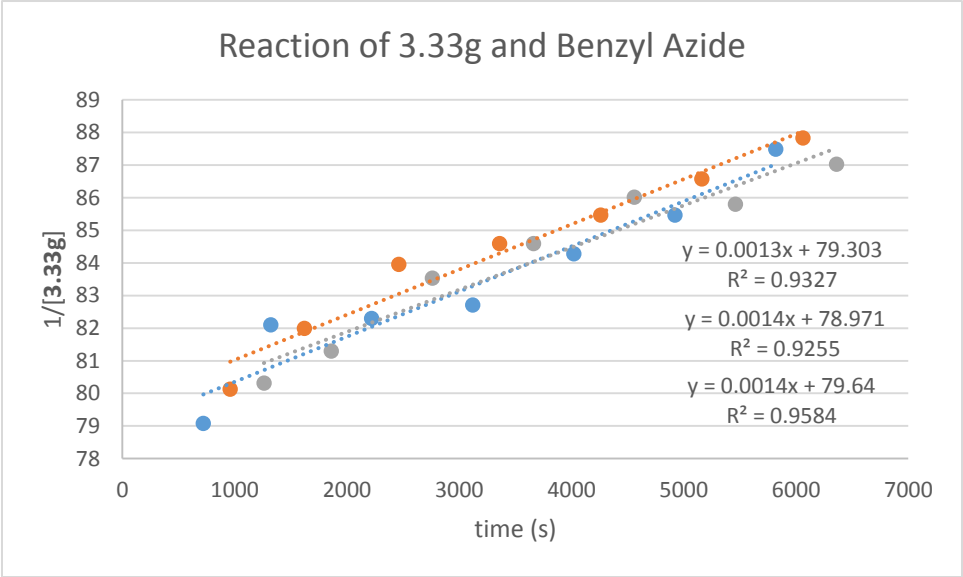
k_2=0.0057±0.0002$M^{-1}s^{-1}$



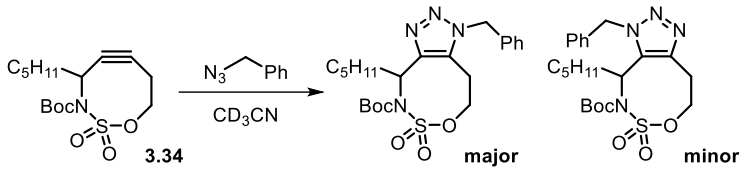


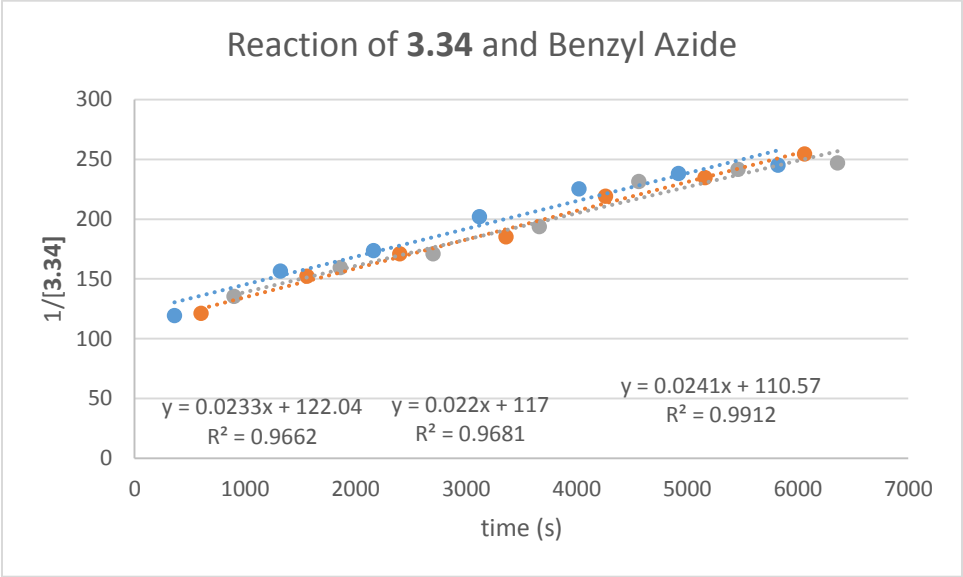
k_2=0.087±0.001 $M^{-1}s^{-1}$





k_2=0.0014±0.00005 $M^{-1}s^{-1}$





k_2=0.023±0.0009 $M^{-1}s^{-1}$

Chapter 4.

Explorations of SNO-OCT Reactivity and Application Towards Post-Polymerization Modification

This chapter is adapted from sections published in:

Burke, E. G.; Gold. B.; Hoang, T. T.; Raines, R. T.; Schomaker, J. M.

J. Am. Chem. Soc., **2017**, *139*, 8029-8037.

and

Burke, E. G.; Schomaker, J. M.

J. Org. Chem., **2017**, (submitted).

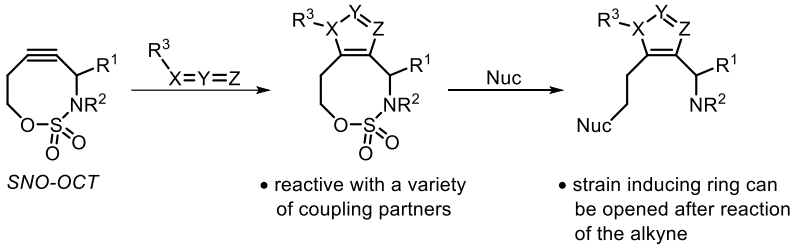
Chapter 4

Explorations of SNO-OCT Reactivity and Application Towards Post-Polymerization Modification

4.1 Introduction

For strain-promoted alkyne azide cycloaddition (SPAAC), the endocyclic methyleneaziridine derived SNO-OCTs have been found to be among the fastest reacting strained alkynes currently reported, and the flexibility of their synthesis is unmatched. However, strained alkynes are being applied to a series of reactions which expand beyond the alkyne-azide cycloadditions for which they were first developed, and alongside this their applications have also grown. While SNO-OCT was found to be well equipped for established SPAAC applications, it possesses uncommon properties which hold promise for broader utility. In this chapter, these unique features which make SNO-OCT attractive in less traditional areas of cycloalkyne use are explored.

Scheme 4.1: *Expansion of SNO-OCT Reactivity*



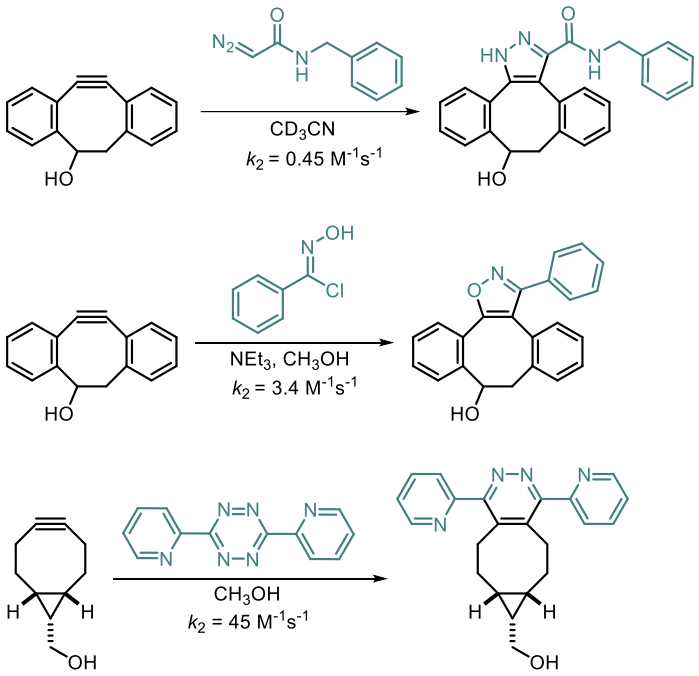
4.2 Background

The need for reliable bioorthogonal reactivity has driven the introduction and development of SPAAC.[1] However, more recently these highly efficient reactions have found increased application in areas outside of this, including as synthetic intermediates,[2] and for materials

applications such as surface modification.[3] In order to better serve these areas, features beyond reaction rate needed to be considered, prompting the expansion of investigations of strained alkynes. Questions of the broadness of reactivity, control of regioselectivity, and suitability toward application have begun to be explored, though much work remains to be done.

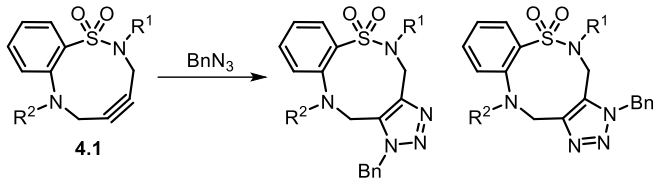
While SPAAC has found wide utility, growing interest has pushed the expansion of coupling partners for the strained alkynes. One fruitful area has been the coupling of strained alkynes with other 1,3-dipoles (Scheme 4.2). Diazo compounds have been found to be attractive coupling partners due to their small size and stability in biological conditions.[4] Their reaction rates often outpace those of azides, and are also accelerated by polar protic solvents. Similarly, nitrile oxides have become popular for their reactivity with strained alkynes (strain-promoted alkyne nitrile oxide cycloaddition, SPANOC).[5] Attractive for the relative stability and lack of toxicity in comparison to azides, nitrile oxides are also easily generated, and like diazo-compounds, are often faster to react than their azide counterparts. A potential drawback is the requirement of an oxidant such as bisacetoxyiodobenzene (BAIB) to generate the active species. Nevertheless, this too can be advantageous. Ledin, Kelishetti, and Boons were able to leverage this need for an oxidant into a chemoselective method of post-polymerization modification.[6] A polymer which contained both azide and nitrile oxide functionalities was synthesized, then a DIBAC derivative was introduced in the absence of BAIB, reacting only with the azides. Next, a second DIBAC derivative was introduced in the presence of BAIB, which reacted cleanly with the nitrile oxides. Moving away from 1,3-dipoles, tetrazine ligations have become increasingly popular, owing to their rapid reactivity which has found to be orders of magnitude faster than that of azides.[7] The introduction of these new functional groups has broadened the utility of strained alkynes, and enabled more creative studies.

Scheme 4.2: *Reactivity of Strained Alkynes with Various Coupling Partners*



While the regiochemistry of 1,3-dipolar cycloadditions to alkynes can be controlled with metal catalysts, this factor is less easily manipulated in reactions of strained alkynes.[8] Often, the product triazoles are reported as 1:1 mixtures of regioisomers.[9] This may not be of consequence when used for biological labeling, but when applying these reactions to synthetic endeavors, this aspect becomes more important. Kaneda, Naruse and Yamamoto found that in reactions of the asymmetrical cyclononyne **4.1** the identity of the groups on the nitrogen impacted the regioselectivity of the reaction with benzyl azide (Scheme 4.3). The regioisomeric ratios ranged from 2.5:1 to 1.3:1, with the highest ratio belonging to the H-substituted isomer. Though relatively unexplored, this example of tunable regioselectivity may mark the beginning of increased interest as the applications of these reactions shift.

Scheme 4.3: *Regioselectivity of 2-Aminobenzenesulfonamide-Containing Cyclononynes*



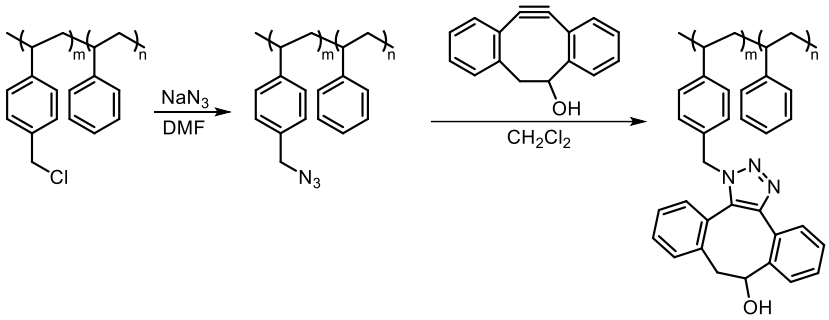
R^1	R^2	yield	*r.r.*
H	H	97%	2.5:1
Boc	H	99%	1.7:1
Boc	Ac	99%	1.3:1

Beyond their initial applications, reactions of strained alkynes have expanded to add value to other fields, with post-polymerization modification being especially well served. The functional groups present in polymers are a key factor in determining the physical properties, with polar groups identified as having the potential to influence surface, barrier, dying, and rheological behaviors.[10] In addition, the solubility, adhesion, toughness, and miscibility of bulk polymers are also known to be influenced by the presence of polar groups.[11] However, polymerization of monomers which include these desired functional groups can be challenging. The direct co-polymerization of monomers containing polar groups is limited by several factors including: catalyst poisoning when early transition metal catalysts are employed, low turn-over frequencies in the presence of late transition metal catalysts and mismatched rates of polymerization between polar and non-polar monomers. These challenges have led to the need to utilize either specialized catalysts or monomers with protected or distant functional groups to successfully install polar groups into polymers.[12]

Alternatively, functional groups can be added into a polymer after it has been synthesized (Scheme 4.4). This strategy has been successfully employed with "click" reactions, attractive in this setting for the same features which brought them prominence in other fields: high reaction rates, clean reactivity, and broad functional group tolerance.[13] The use of strained alkynes has

been especially notable, in many cases being more useful than its metal catalyzed counterpart. Strained alkynes avoid common pitfalls of CuAAC in post-polymerization modification, including degradation of the polymer backbone by the copper catalyst, or morphology changes imposed by chelation of the remaining metal by product triazoles.[14] Furthermore, the exclusion of metals is important to polymers intended for use in biological settings, wherein trace metals may lead to toxicity.[15] Finally, strained alkynes have been cited as operationally simpler to conduct, with fewer reagents needed to perform the desired coupling.[16]

Scheme 4.4: *Post-Polymerization Modification with DIBO*



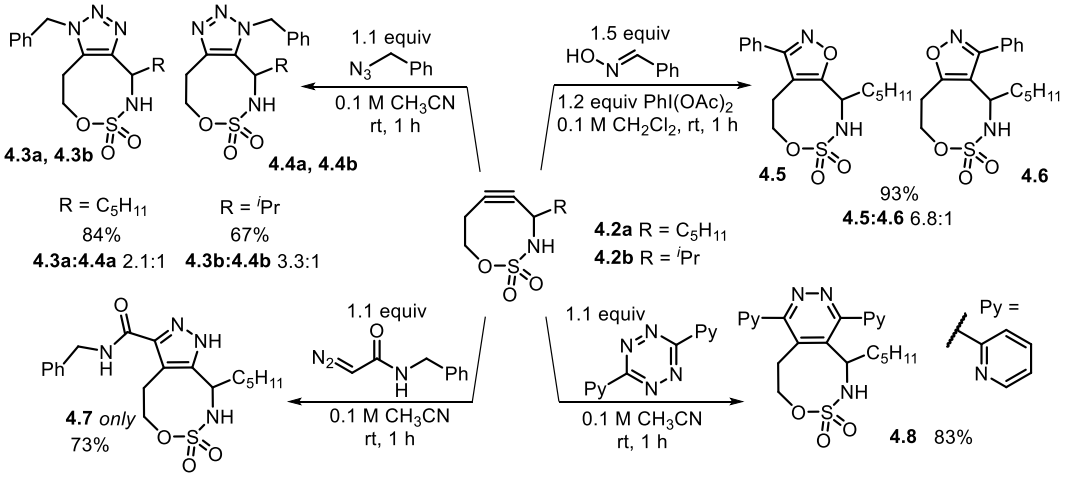
As the popularity of strained alkynes has grown, so have the creative applications of these rings. Interest in their use in the materials field and the potential for rapid library building of varied heterocycles has broadened their utility, but also highlighted areas where new development is needed. The flexible SNO-OCT is poised to meet some of these growing needs, due to its clean reactivity between a range of coupling partners, and its unmatched potential for modification after reaction of the alkyne.

4.3 Reactivity with Alkyne Coupling Partners

Applications of strained alkynes have focused on their reactions with 1,3-dipoles, and primarily with azides. These reactions gained this attention because they have been found to be rapid, high yielding reactions which form few if any byproducts. Similarly, SNO-OCT **4.2** was

found to react with azides to form product triazoles **4.3** and **4.4** cleanly (Scheme 4.5). However, growing interest has been forming around the reaction of strained alkynes with other coupling partners.[4, 5, 7] SNO-OCT was found to rapidly form a range of heterocycles such as oxazoles **4.5** and **4.6**, diazoles **4.7**, and pyrazines **4.8**. This diversity strengthens its utility in synthetic settings, as well as enabling greater flexibility in design of systems in which SNO-OCT may be used as a linker.

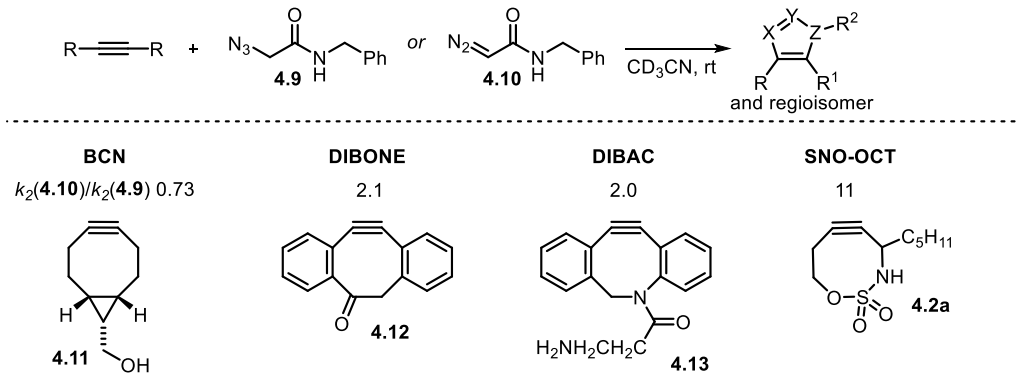
Scheme 4.5: *Reaction of SNO-OCT with Various Coupling Partners*



Interestingly, the inclusion of heteroatoms in SNO-OCT results in electronic differentiation of the alkyne. This may be a factor influencing the regioselectivity observed in the products of coupling reactions. While reactions of previously reported strained alkynes result in equal mixtures of regioisomers, SNO-OCT **4.2a** furnished a 2:1 mixture of **4.3a**:**4.4a** in reaction with benzyl azide (Scheme 4.6).[17] There is an effect of steric hindrance on the regioselectivity; as the size of the R group is increased from pentyl in **4.2a** to an *iso*-propyl group in **4.2b**, the resulting ratio of regioisomers **4.3a**:**4.4b** improves to 3:1. However, there is also an electronic component to the regioselectivity, as switching to more polarized 1,3-dipoles such as benzaldehyde oxime or diazoacetate, even higher ratios are observed. In the crude reaction mixture oxazoles **4.5** and **4.6** were formed in a 7:1 ratio, while in the reaction of diazoacetate, only diazole **4.7** was observed.

While not pivotal for the bioorthogonal applications for which strained alkynes were initially developed, this feature may be of interest to those who intend to use this chemistry for more synthetic applications.

Scheme 4.6: *Comparative Rates of Azide and Diazo Reactions with Strained Alkynes*



In addition to the versatility offered by SNO-OCT's reactivity with a range of coupling partners, the difference in the rates between these reactions may offer opportunities for the development of orthogonal reactions. When the rate of 1,3-dipolar cycloadditions of diazoacetamide **4.10** was compared to that of azidoacetamide **4.9**, little difference in rate was noted with several commonly used strained alkynes. At most, a doubling of the rate for DIBONE **4.12** and DIBAC **4.13** was observed. When the more polarized SNO-OCT **4.2a** was reacted with these 1,3-dipoles, it was found to have a much larger difference in rates. SNO-OCT **4.2a** reacted at a rate eleven times faster with diazoacetamide **4.10** than with azidoacetamide **4.9**. While this rate difference is still too small for selective reaction with diazoacetamide **4.10** in the presence of azidoacetamide **4.9**, it represents a starting point, and suggests it may be possible that SNO-OCT derivatives could be designed which would increase the differences in these rates.

In total, the unique structure of SNO-OCT has been shown to have an interesting impact on reactivity with a variety of coupling partners. Beyond simply displaying high rates and clean reactions, more nuanced differences were found. Regioselectivity was found to be impacted by the electronic differentiation and steric environment of the alkyne. Additionally, the relative rates between the coupling partners were found to be amplified with SNO-OCT, as illustrated in the comparison of diazo **4.10** to azide **4.9**. These differences which may be of little note when applied to traditional labeling may have larger impact on the use of SNO-OCT derivatives in other fields.

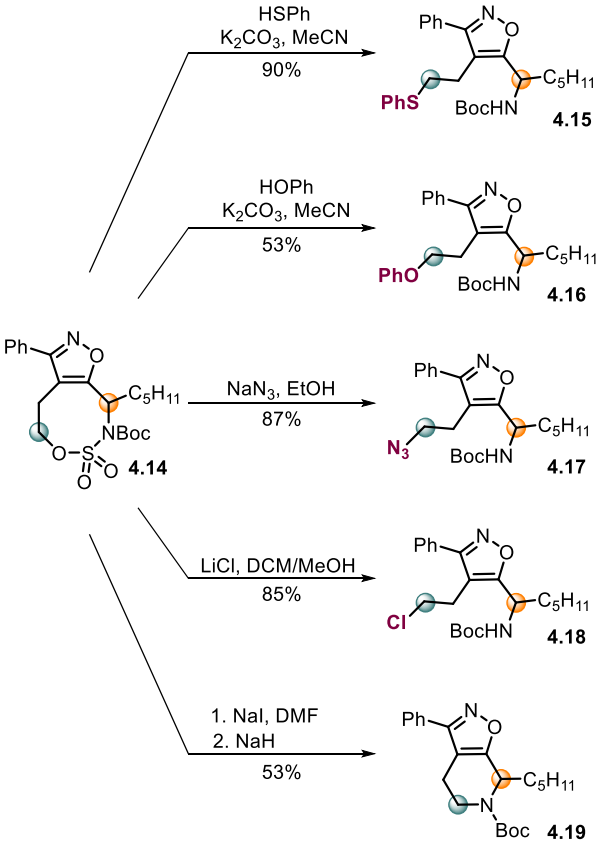
4.4 Opening of Strain-Inducing Ring

Much attention has been paid to the design of unique ring structures which can better activate alkynes and increase the rate of 1,3-dipolar cycloadditions (Chapter 3). However, minimal attention has been paid to these ring structures after the reaction of the alkyne. With hydrophobicity being a concern for biological applications, and the limitation of steric bulk an interest of post-polymerization modification, manipulation of the strain-inducing ring after reaction of the alkyne could be a potential solution to some of these shortcomings.[18] To date, no attempts to open or otherwise amend these rings has been reported. However, SNO-OCT is unique to other strained alkynes and can easily be manipulated. Its opening marks the first report of the manipulation of a strain inducing ring after reaction of the alkyne.

Among the features that make SNO-OCT distinctive is its stability towards common reaction conditions, including nucleophiles.[17] However, it was found that when the nitrogen was activated by addition of a sufficiently electron-withdrawing group, the sulfamate ring was sensitive to nucleophilic attack. Oxazole **4.14**, arising from the addition of Boc protected SNO-OCT and benzaldehyde oxime, was successfully opened by a range of nucleophiles, including thiophenol, phenol, sodium azide and lithium chloride (Scheme 4.7). This range of nucleophiles not only

demonstrated the incorporation of several heteroatoms, but also the incorporation of polar groups which have traditionally been challenging functionalities to include in polymers. Also, the inclusion of an azide to yield **4.17** represents the incorporation of functional handles for further manipulation. Additionally, it was found that the ring could undergo contraction to form piperidine **4.19**, first being opened with sodium iodide, followed by treatment with sodium hydride. These reactions represent a new functionality of strained alkynes.

Scheme 4.7: *Manipulations of Strain-Inducing Ring*



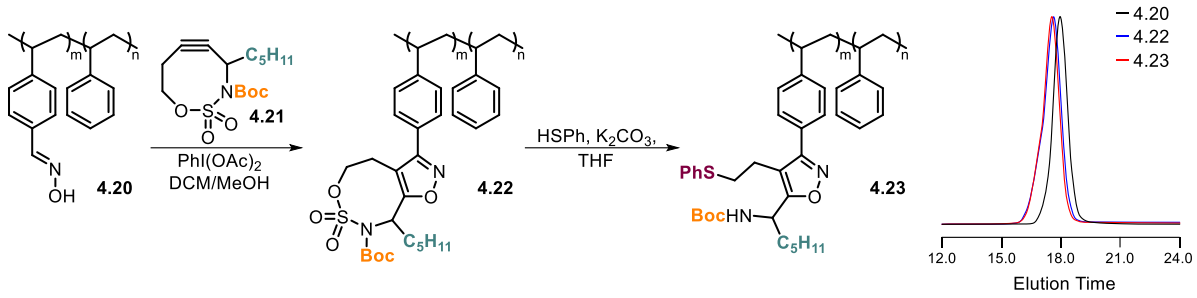
4.5 Post-Polymerization Modification

One area which may most benefit from SNO-OCT's unique set of properties is post-polymerization modification. However, properties which have hampered strained alkynes in other settings remain, including their sensitivity to common reaction conditions, hydrophobicity and

steric bulk.[18] SNO-OCT, which has been found to be uncommonly stable and soluble in aqueous conditions has the additional advantage of being able to be manipulated after reaction, thus allowing for further tuning of bulk properties or inclusion of additional functionality.

In order to assess the utility of SNO-OCT in post-polymerization modification, SNO-OCT **4.21** was appended to a polystyrene backbone and then opened (Scheme 4.8). The polymer **4.20** was prepared from known procedures to include nitrile oxide-substituted monomers. This functionalized polystyrene **4.20** was then reacted with SNO-OCT **4.21** in the presence of bisacetoxyiodobenzene. Full conversion was observed after several hours, with ^{1}H-NMR analysis indicating complete consumption of the nitrile oxide and inclusion of the sulfamate. Comparison of polydispersity indices (PDI's) showed the conversion to be clean, with little variation between individual polymers. Furthermore, the resultant polymer **4.22** was then reacted with thiophenol in the presence of potassium carbonate to determine whether the sulfamate ring could be cleanly opened once incorporated into a polymer. It was found that after stirring with only 3 equivalents per sulfamate ring for 18h, the ring was opened as indicated by ^{1}H-NMR. Additionally, the narrow PDI was maintained through this reaction, indicating clean reactivity. The gel permeation chromatography (GPC) traces also showed the expected shifts corresponding to changes in the overall polymer mass. In summary, SNO-OCT **4.21** was shown to not only be cleanly incorporated into the polymer, but was also able to be opened, successfully demonstrating the potential of opening SNO-OCT's sulfamate ring.

Scheme 4.8: *Addition and Opening of SNO-OCT to a Polystyrene Backbone*



4.6 Conclusion

SNO-OCT alkynes have been found to possess features which make them unique from other strained alkynes. Their versatility in coupling partners and enhanced regiochemistry make them more attractive for synthetic applications. Additionally, the ability to open the strain inducing ring after reaction of the alkyne is the only example of its kind, and also has important synthetic implications. It has been shown that this system can be employed in post-polymerization modification with clean reactions of both the addition of the alkyne and its subsequent opening. The utility of this system has just begun to be explored, and will likely prove beneficial in additional applications.

4.7 References

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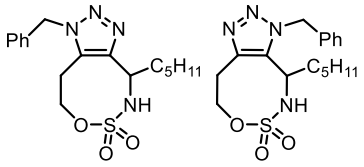
4.8 Experimental

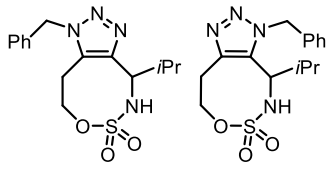
4.8.1 Reaction of SNO-OCT with benzyl azide

General procedure for the formation of triazoles. The cyclic alkyne **4.2** (1 equiv) was dissolved in CH_3CN (0.1 M). Benzyl azide (1.1 equiv) was added to the resulting solution and the reaction mixture stirred for 1 h to ensure full conversion. The solvent was then removed under reduced pressure and the resulting oil dissolved in a minimum volume of CH_2Cl_2. The solvent was again removed under reduced pressure and the triazole products characterized without further purification.



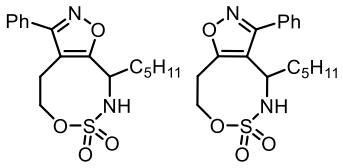
Compounds 4.3a and 4.4a. The reigoisomer triazoles **4.3a** and **4.4a** were prepared from alkyne **4.2a** (15 mg, 0.065 mmol). The resulting triazoles **4.3a** and **4.4a** were obtained as a clear oil (24 mg, 0.065 mmol) in quantitative yield as a mixture of regioisomers (2.2:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.30 (m, 4.45H), 7.17 – 7.08 (m, 2.8H), 5.65 – 5.42 (m, 4.35H), 4.59 (major, dd, *J* = 9.1, 4.9 Hz, 1H), 4.56 (minor, m, 0.45H), 4.15 (minor, td, *J* = 11.8, 5.5 Hz, 0.45H), 3.88 (major, ddd, *J* = 11.7, 6.4, 5.3 Hz, 1H), 3.80 (major, ddd, *J* = 11.9, 7.8, 5.2 Hz, 1H), 3.74 – 3.63 (minor, m, 0.45H), 3.34 – 3.15 (m, 1.9H), 3.01 (major, ddd, *J* = 16.1, 6.5, 5.2 Hz, 1H), 2.35 – 2.22 (major, m, 1H), 1.96 (major, ddd, *J* = 14.2, 9.6, 5.0 Hz, 1H), 1.75 – 1.59 (m, 0.45H), 1.59 – 1.43 (m, 2.2H), 1.43 – 1.19 (m, 6.9H), 0.89 (major, td, *J* = 6.9, 4.8 Hz, 3H), 0.80 (minor, t, *J* = 7.2 Hz, 1.4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 134.79, 134.36, 129.41, 128.86, 127.07, 126.87, 69.25 (minor), 67.46 (major), 52.70, 52.50, 51.14 (major), 50.22(minor), 34.11, 33.39 (major), 31.40, 31.05, 26.41,

25.58, 24.86, 24.79, 22.59, 22.36, 14.12 (major), 13.99 (minor). HRMS (ESI) *m/z* calculated for $C_{17}H_{25}N_4O_3S$ [M+H$^+$] 365.1642; found, 365.1638.

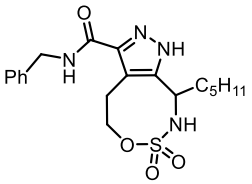


Compounds 4.3b and 4.4b. The two reigoisomer triazoles of **4.3b** and **4.4b** were prepared from alkyne **4.2b** (10 mg, 0.05 mmol). The resulting triazoles **4.3b** and **4.4b** were obtained as a pale yellow oil (17 mg, 0.05 mmol) in quantitative yield as a mixture of regioisomers (3.4:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 – 7.30 (m, 4H), 7.12 (td, J = 7.5, 1.7 Hz, 2.5H), 5.65 (major, d, J = 15.7, 1 H), 5.58 (minor, d, J = 16.0 Hz, 0.3 H), 5.49 (d, J = 15.7 Hz, 1.3 H), 4.80 (m, 1.3H), 4.59 (minor, ddd, J = 11.7, 6.6, 1.8 Hz, 0.3H), 4.49 (major, dd, J = 9.0, 5.3 Hz, 1H), 4.37 (minor, dd, J = 6.3, 3.9 Hz, 0.3H), 4.18 (minor, td, J = 11.8, 5.5 Hz, 0.3H), 3.96 (major, dt, J = 11.2, 5.3 Hz, 1H), 3.69 – 3.60 (major, m, 1H), 3.59 – 3.49 (minor, m, 0.3 H), 3.34 – 3.23 (m, 1.3 H), 2.96 (major, dt, J = 16.0, 5.2 Hz, 1H), 2.73 (major, pd, J = 6.8, 5.3 Hz, 1H), 1.12 (major, d, J = 6.8 Hz, 3H), 1.00 (minor, dd, J = 6.7, 1.7 Hz, 0.9H), 0.98 (major, d, J = 6.9 Hz, 3H), 0.73 (minor, d, J = 6.9 Hz, 0.9H).^{13}C NMR (126 MHz, $CDCl_3$) δ 146.72 (major), 140.76 (minor), 134.87 (major), 134.18 (minor), 129.66, 129.52, 129.39, 128.98, 128.92, 127.07, 126.89, 69.51(minor), 67.44(major), 56.74 (major), 55.30 (minor), 53.57 (minor), 52.61 (major), 31.39 (minor), 30.97 (major), 25.32 (minor), 22.71 (major), 19.84 (major), 19.55 (minor), 17.33 (major), 15.36 (minor). HRMS (ESI) *m/z* calculated for $C_{15}H_{19}N_4O_3S$ [M-H$^+$] 335.1183; found, 335.1185.

4.8.2 Reactions of SNO-OCT with Various Coupling Partners

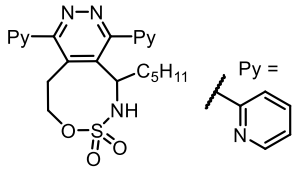


Compound 4.5. The cyclic alkyne **4.2a** (0.56 g, 2.4 mmol) was dissolved in acetoniltrile (0.1M). To this was added benzaldehyde oxime (0.44 g, 3.6 mmol), and diacetoxyiodobenzene (0.94 g, 2.9 mmol). Reaction was stirred at room temperature for 1h to ensure complete consumption of starting alkyne. Solvent was removed under reduced pressure. The crude product was purified by column chromatography (0% EtOAc/hexanes to 20% EtOAc/hexanes, gradient) to yield pure oxazole **4.5** as a single regioisomer (0.78 g, 2.2 mmol) as a white crystalline solid in 93% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 – 7.44 (m, 5H), 4.77 (q, J = 3.3, 2.4 Hz, 2H), 4.50 (ddd, J = 11.7, 5.5, 4.5 Hz, 1H), 4.24 (ddd, J = 11.7, 9.9, 5.0 Hz, 1H), 3.30 (ddd, J = 15.7, 9.9, 5.5 Hz, 1H), 2.93 (dt, J = 16.0, 4.8 Hz, 1H), 2.21 (tdd, J = 13.8, 6.5, 3.1 Hz, 1H), 1.96 – 1.83 (m, 1H), 1.54 – 1.45 (m, 2H), 1.45 – 1.30 (m, 4H), 0.95 – 0.87 (m, 3H).^{13}C NMR (126 MHz, $CDCl_3$) δ 169.47, 163.13, 130.10, 129.22, 128.64, 128.52, 109.16, 70.26, 52.05, 32.70, 31.28, 25.03, 22.54, 21.53, 14.11. HRMS (ESI) *m/z* calculated for $C_{17}H_{23}N_2O_4S$ [M+H$^+$] 351.1373 found 351.1371.



Compound 4.7. The cyclic alkyne **4.2a** (10 mg, 0.044 mmol) was dissolved in CH_3CN (0.1 M). To the resulting solution was added *N*-benzyl-2-diazoacetamide (8.5 mg, 0.048 mmol). The

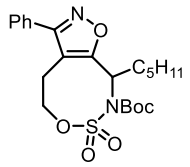
reaction was stirred for 1 h to ensure full conversion, then the volatiles removed under reduced pressure. The resulting oil was dissolved in a minimum volume of CH_2Cl_2, then solvent was again removed under reduced pressure and the diazole products characterized without further purification. The product **4.7** was obtained (14 mg, 0.033 mmol) as a clear oil as a single regioisomer in 73% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.88 (s, 1H), 7.40 – 7.21 (m, 5H), 5.38 (d, J = 9.0 Hz, 1H), 4.63 – 4.45 (m, 2H), 4.43 – 4.29 (m, 2H), 3.50 (t, J = 6.4 Hz, 2H), 1.82 (ddtt, J = 23.3, 14.1, 9.4, 5.4 Hz, 2H), 1.55 – 1.17 (m, 6H), 0.94 – 0.79 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) 162.77, 138.11, 137.86, 128.85, 127.79, 127.68, 127.03, 115.62, 72.34, 49.53, 43.15, 33.06, 31.28, 25.45, 22.55, 21.33, 14.08. HRMS (ESI) *m/z* calculated for $C_{19}H_{27}N_4O_4S$ [M+H$^+$] 407.1748; found, 407.1739.



Compound 4.8. The cyclic alkyne **4.2a** (23 mg, 0.05 mmol) was dissolved in CH_3CN (0.1M). To this was added 3,6-di-2-pyridyl-1,2,4,5-tetrazine (26 mg, 0.055 mmol), and the resulting solution was stirred for 4h. Solvent was removed *via* rotary evaporation. The crude product was purified by column chromatography (0% EtOAc/hexanes to 30% EtOAc/hexanes, gradient) to yield pure pyridazine **4.8** (18 mg, 0.04 mmol) as a white solid in 83% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.71 (dt, *J* = 4.1, 2.0 Hz, 2H), 8.33 (d, *J* = 7.9 Hz, 1H), 8.20 (dd, *J* = 18.5, 9.4 Hz, 2H), 8.02 (td, *J* = 7.7, 1.8 Hz, 1H), 7.94 (td, *J* = 7.8, 1.8 Hz, 1H), 7.55 – 7.47 (m, 1H), 7.44 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H), 4.85 – 4.72 (m, 2H), 4.54 (td, *J* = 11.1, 6.4 Hz, 1H), 3.74 (td, *J* = 9.4, 6.3 Hz, 2H), 1.35 (qd, *J* = 11.3, 9.3, 4.8 Hz, 1H), 1.30 – 1.16 (m, 1H), 1.16 – 0.91 (m, 4H), 0.76 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.97, 157.51, 157.00, 155.74, 148.63, 148.36,

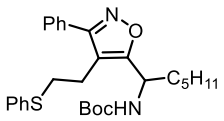
140.87, 138.16, 137.24, 136.58, 125.41, 124.99, 124.67, 123.94, 71.83, 51.14, 32.36, 31.09, 28.51, 26.52, 22.18, 13.86. HRMS (ESI) *m/z* calculated for $C_{22}H_{24}N_5O_3S$ [M-H^+] 438.1605 found 438.1609.

4.8.3 Synthesis of Oxazole 4.14

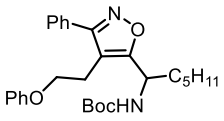


Compound 4.14. Oxazole **4.5** (50 mg, 0.14 mmol) was dissolved in CH_2Cl_2 (0.2 M). To this solution was added di-*tert*-butyl dicarbonate (47 mg, 0.21 mmol) and triethylamine (30 µL, 0.21 mmol), followed by 4-dimethylaminopyridine (1.7 mg, 0.14 mmol). The reaction was stirred at ambient temperature under a N_2 atmosphere until TLC indicated complete consumption of **4.5**. The reaction mixture was quenched by the addition of an equal volume of saturated aqueous NH_4Cl. The aqueous phase was extracted with 3 x 10 mL portions of CH_2Cl_2 and the combined organic phases dried over Na_2SO_4. The solution was filtered and the volatiles removed under reduced pressure. The crude product was purified *via* column chromatography (0% EtOAc/hexanes to 25% EtOAc/hexanes, gradient) to yield pure oxazole **4.14** (24 mg, 0.05 mmol) as a white solid in 39% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 – 7.47 (m, 3H), 7.45 – 7.39 (m, 2H), 5.62 (dd, *J* = 8.9, 6.4 Hz, 1H), 4.55 (ddd, *J* = 11.7, 6.3, 2.6 Hz, 1H), 4.41 (ddd, *J* = 11.6, 9.1, 2.3 Hz, 1H), 2.97 (ddd, *J* = 17.0, 9.1, 2.6 Hz, 1H), 2.89 (ddd, *J* = 17.0, 6.2, 2.3 Hz, 1H), 2.42 – 2.33 (m, 2H), 1.69 – 1.57 (m, 2H), 1.54 (s, 9H), 1.48 – 1.32 (m, 4H), 0.97 – 0.88 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.95, 163.40, 150.75, 129.95, 129.14, 128.93, 128.57, 109.05, 86.01, 72.89, 57.20, 31.33, 28.01, 25.44, 22.58, 22.02, 14.14. HRMS (ESI) *m/z* calculated for $C_{22}H_{31}N_2O_6S$ [M+H^+] 451.1897 found 451.1895.

4.8.4 Manipulations of Oxazole 4.14

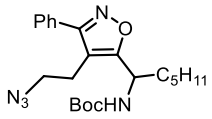


Compound 4.15. Oxazole **4.14** (38 mg, 0.08 mmol) was dissolved in CH_3CN (0.2M). To this was added thiophenol (17 µL, 0.17 mmol) and potassium carbonate (24 mg, 0.17 mmol). The heterogeneous solution was stirred overnight, then partitioned between water and CH_2Cl_2. Aqueous layer was extracted (3x2mL CH_2Cl_2) then dried over Na_2SO_4. Solution was filtered, and solvent was removed *via* rotary evaporation. Crude product was purified *via* column chromatography (0% EtOAc/hexanes to 30% EtOAc/hexanes, gradient) to yield pure oxazole **4.15** (35 mg, 0.072 mmol) as a yellow oil in 90% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 – 7.48 (m, 2H), 7.48 – 7.37 (m, 3H), 7.25 – 7.12 (m, 5H), 4.97 (d, *J* = 9.1 Hz, 1H), 4.89 (q, *J* = 8.0 Hz, 1H), 3.01 (dt, *J* = 12.9, 7.0 Hz, 1H), 2.95 – 2.76 (m, 3H), 1.85 (q, *J* = 7.3 Hz, 2H), 1.43 (s, 9H), 1.39 – 1.16 (m, 6H), 0.87 (q, *J* = 6.3, 4.7 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.84, 162.52, 155.01, 135.63, 129.69, 129.66, 129.41, 129.08, 128.99, 128.20, 126.30, 112.21, 80.13, 46.56, 34.17, 33.47, 31.46, 28.47, 25.73, 22.84, 22.59, 14.11. HRMS (ESI) *m/z* calculated for $C_{28}H_{38}N_2O_3S$ [M+H$^+$] 481.2519 found 481.2512.

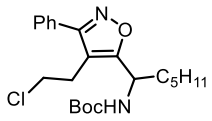


Compound 4.16. Oxazole **4.14** (23 mg, 0.05 mmol) was dissolved in MeCN (0.1M). To this was added phenol (9.4 mg, 0.10 mmol) and potassium carbonate (14 mg, 0.10 mmol). Reaction was stirred at 45 °C for several hours until complete consumption of starting material was indicated by thin layer chromatography. Solvent was removed under reduced pressure. Crude

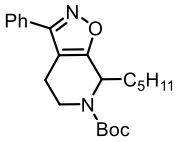
product was purified *via* column chromatography (0% EtOAc/hexanes to 25% EtOAc/hexanes, gradient) to yield pure oxazole **4.16** (12 mg, 0.027 mmol) as a colorless oil in 53% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (dt, *J* = 6.8, 3.9 Hz, 2H), 7.55 – 7.42 (m, 3H), 7.25 – 7.17 (m, 2H), 6.91 (t, *J* = 7.3 Hz, 1H), 6.80 – 6.71 (m, 2H), 5.09 (d, *J* = 9.3 Hz, 1H), 5.03 (q, *J* = 8.3, 7.9 Hz, 1H), 4.04 (dd, *J* = 10.5, 4.8 Hz, 1H), 3.94 (dt, *J* = 9.1, 6.8 Hz, 1H), 3.13 (dt, *J* = 14.1, 6.9 Hz, 1H), 3.02 (dt, *J* = 14.9, 6.3 Hz, 1H), 1.91 (q, *J* = 7.3 Hz, 2H), 1.43 (s, 9H), 1.30 (t, *J* = 5.3 Hz, 6H), 0.92 – 0.83 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.28, 162.92, 158.39, 155.00, 129.55, 129.46, 129.37, 128.82, 128.38, 120.84, 114.37, 110.33, 79.98, 66.92, 46.62, 34.13, 31.41, 28.35, 25.65, 22.47, 13.98. HRMS (ESI) *m/z* calculated for $C_{28}H_{37}N_2O_4$ [M+H$^+$] 465.2748 found 465.2749.



Compound 4.17. The oxazole **4.14** (23 mg, 0.05 mmol) was dissolved in EtOH (0.1M) and sodium azide (9.8 mg, 0.15 mmol) was added. The resulting solution was stirred at room temperature for 24h. Solvent was then removed *via* rotary evaporation, and resulting oil was purified by column chromatography (0% EtOAc/hexanes to 20% EtOAc/hexanes, gradient) to yield pure **4.17** (18 mg, 0.043 mmol) as a colorless oil in 87% yield ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (dt, *J* = 5.9, 3.6 Hz, 2H), 7.54 – 7.39 (m, 3H), 5.01 (d, *J* = 9.3 Hz, 1H), 4.94 (q, *J* = 8.0 Hz, 1H), 3.43 – 3.34 (m, 1H), 3.27 (dt, *J* = 12.2, 7.4 Hz, 1H), 2.97 – 2.71 (m, 2H), 1.90 (qd, *J* = 9.5, 4.8 Hz, 2H), 1.44 (s, 9H), 1.32 (m, 6H), 0.95 – 0.82 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.46, 162.70, 155.11, 129.85, 129.32, 129.07, 128.26, 110.27, 80.22, 51.01, 46.46, 33.94, 31.48, 28.46, 25.74, 22.59, 22.39, 14.10. HRMS (ESI) *m/z* calculated for $C_{22}H_{32}N_5O_3$ [M+H$^+$] 414.2500 found 414.2495.



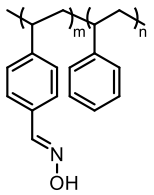
Compound 4.18. Oxazole **4.14** (23 mg, 0.05 mmol) was dissolved in 1:1 CH_3OH:CH_2Cl_2 (0.1M). To this was added lithium chloride (13 mg, 0.31 mmol). Reaction was stirred at room temperature for several hours until complete consumption of starting material was indicated by thin layer chromatography. Solvent was removed under reduced pressure. Crude product was purified *via* column chromatography (0% EtOAc/hexanes to 15% EtOAc/hexanes, gradient) to yield pure oxazole **4.18** (17 mg, 0.042 mmol) as a colorless oil in 85% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (dt, *J* = 5.7, 3.4 Hz, 2H), 7.48 (h, *J* = 3.9, 3.3 Hz, 4H), 4.95 (q, *J* = 8.5, 7.7 Hz, 2H), 3.61 – 3.50 (m, 1H), 3.47 – 3.34 (m, 1H), 3.07 (tdd, *J* = 14.7, 11.6, 6.8 Hz, 2H), 1.89 (hept, *J* = 6.2, 5.1 Hz, 3H), 1.44 (s, 9H), 1.36 – 1.28 (m, *J* = 3.8, 3.3 Hz, 6H), 0.88 (q, *J* = 4.7, 2.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.65, 162.59, 155.11, 129.87, 129.29, 129.09, 128.21, 110.38, 80.23, 46.45, 43.21, 33.92, 31.47, 28.47, 25.86, 25.74, 22.59, 14.11. HRMS (ESI) *m/z* calculated for $C_{17}H_{24}ClN_2O$ [M+H$^+$] 406.2086 found 406.2091.



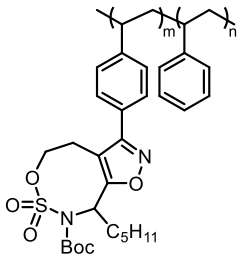
Compound 4.19. Oxazole **4.14** (24 mg, 0.05 mmol) was dissolved in *N*,*N*-dimethylformamide (0.1M). To this was added sodium chloride (11 mg, 0.08 mmol) and heated to 45 °C. After 30 min sodium hydroxide (60% in mineral oil, 7.6 mg, 0.19 mmol) was added and solution was heated further to 60 °C. Reaction was stirred overnight, then cooled to room temperature. Reaction quenched with 0.1M HCl aq. Aqueous layer extracted 3 x 2 mL portions of CH_2Cl_2 and the combined organic phases dried over Na_2SO_4. The solution was filtered and the volatiles

removed under reduced pressure. The crude product was purified *via* column chromatography (0% EtOAc/hexanes to 25% EtOAc/hexanes, gradient) to yield pure oxazole **4.19** (11 mg, 0.03 mmol) as a white solid in 53% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (dq, *J* = 8.0, 3.2, 2.6 Hz, 2H), 7.39 (tdd, *J* = 4.7, 3.5, 1.5 Hz, 3H), 5.19 (d, *J* = 79.4 Hz, 1H), 4.31 (d, *J* = 92.0 Hz, 1H), 2.88 (s, 1H), 2.75 (s, 1H), 2.50 (dd, *J* = 15.5, 2.9 Hz, 1H), 1.83 (ddt, *J* = 13.9, 10.9, 5.7 Hz, 1H), 1.67 (dtd, *J* = 14.2, 9.1, 5.6 Hz, 1H), 1.51 – 1.44 (m, 2H), 1.43 (s, 9H), 1.36 – 1.22 (m, 4H), 0.83 (q, *J* = 8.0, 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.90, 160.00, 154.76, 129.89, 129.42, 129.04, 127.49, 110.12, 80.79, 52.09, 51.33, 37.17, 33.46, 31.68, 28.55, 25.78, 22.73, 14.16. HRMS (ESI) *m/z* calculated for $C_{22}H_{31}N_2O_3$ [M+H$^+$] 371.2329 found 371.2323.

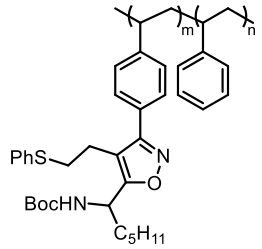
4.8.5 Post-Polymerization Modification



Poly(4-vinylbenzaldoxime-co-styrene) 4.20. Poly(4-vinylbenzaldehyde-co-styrene) (320 mg, 0.1 mmol) was dissolved in CH_2Cl_2 (0.03M). To this was added hydroxylamine hydrochloride (195 mg, 0.36 mmol) and trimethylamine (510 µL, 0.73 mmol). Reaction was stirred for 18h, then diluted with CH_2Cl_2 (25 mL), washed with water 3 × 10 mL, dried over Na_2SO_4, filtered, then concentrated under reduced pressure. Polymer was purified *via* precipitation into cold hexanes to give **4.20** in 79% yield as a white powder (254 mg, 0.08mmol). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (s, 1H), 6.83 (d, *J* = 237.9 Hz, 25H), 3.06 (d, *J* = 7.7 Hz, 1H), 2.36 – 1.03 (m, 9H). M_n (g/mol) = 3835 (GPC, $Đ_M$= 1.199).



Polymer 4.22. Poly(4-vinylbenzaldoxime-co-styrene) **4.20** (89 mg, 0.029 mmol) and SNO-OCT **4.21** (106 mg, 0.32 mmol) were dissolved in CH_2Cl_2 (0.2M). To this was added a solution of diacetoxyiodobenzene (103 mg, 0.32 mmol) in CH_3OH (0.2M). Reaction was stirred for 18h, then solvent was removed under reduced pressure. Crude polymer was purified by precipitation into cold CH_3OH to give **4.22** in 62% yield as a white powder (103 mg, 0.018 mmol). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 – 6.22 (m, 38H), 5.61 (s, 1H), 4.41 (d, *J* = 69.7 Hz, 2H), 3.01 – 2.62 (m, 1H), 2.47 – 2.24 (m, 2H), 2.20 – 1.21 (m, 27H), 0.91 (d, *J* = 23.7 Hz, 4H). M_n (g/mol) = 5698 (GPC, $Đ_M$= 1.298).

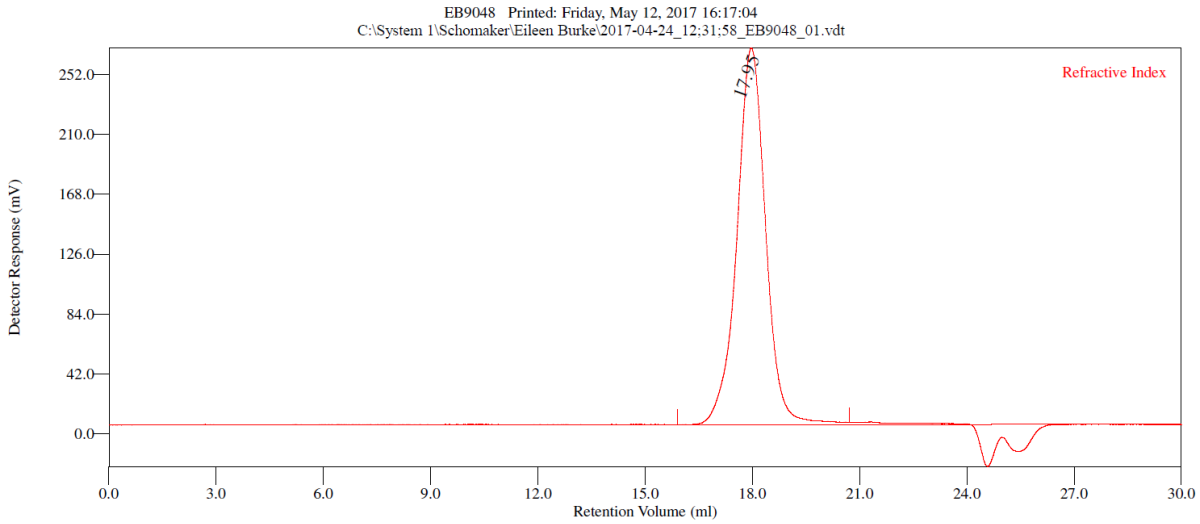


Polymer 4.23. Polymer **4.22** (40 mg, 0.01 mmol) was dissolved in CH_2Cl_2 (0.002M). To this was added thiophenol (19 µL, 0.17 mmol) and potassium carbonate (24 mg, 0.17 mmol). Reaction was stirred overnight, then quenched with sat. aq. NH_4Cl, extracted 3 x 1 mL CH_2Cl_2, washed with sat. aq. $NaHCO_3$, and dried over Na_2SO_4. Solution was filtered, then solvent removed *via* rotary evaporation. Polymer was purified *via* precipitation into cold CH_3OH to give **4.23** in 75% yield as a white powder (30 mg, 0.006 mmol). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.82

(d, J = 264.5 Hz, 51H), 4.96 (s, 1H), 4.87 (s, 1H), 3.22 – 2.58 (m, 4H), 2.22 – 1.66 (m, 6H), 1.54 (s, 12H), 1.49 – 0.65 (m, 24H). M_n (g/mol) = 6333 (GPC, $Đ_M$= 1.249).

4.8.6 GPC Traces

Compound 4.20



Conventional Calibration - Homopolymers : Results

Peak RV - (ml)	17.953
Mn - (Daltons)	3,835
Mw - (Daltons)	4,597
Mz - (Daltons)	5,393
Mp - (Daltons)	4,310
Mw / Mn	1.199
Percent Above Mw: 0	0.000
Percent Below Mw: 0	0.002
Mw 10.0% Low	2,043
Mw 10.0% High	8,683
RI Area - (mvml)	245.57
UV Area - (mvml)	0.00

Annotation	
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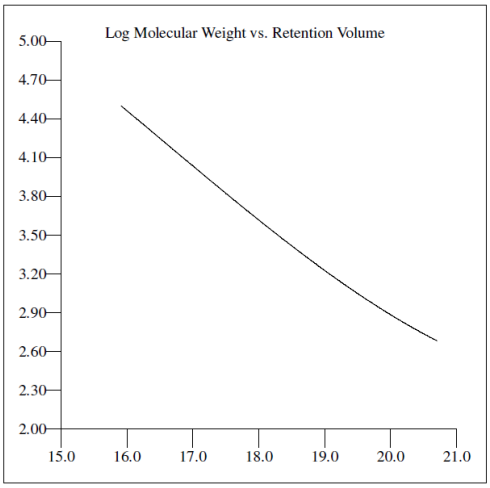
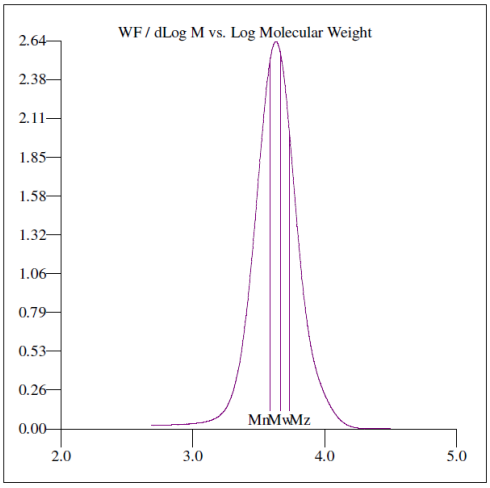
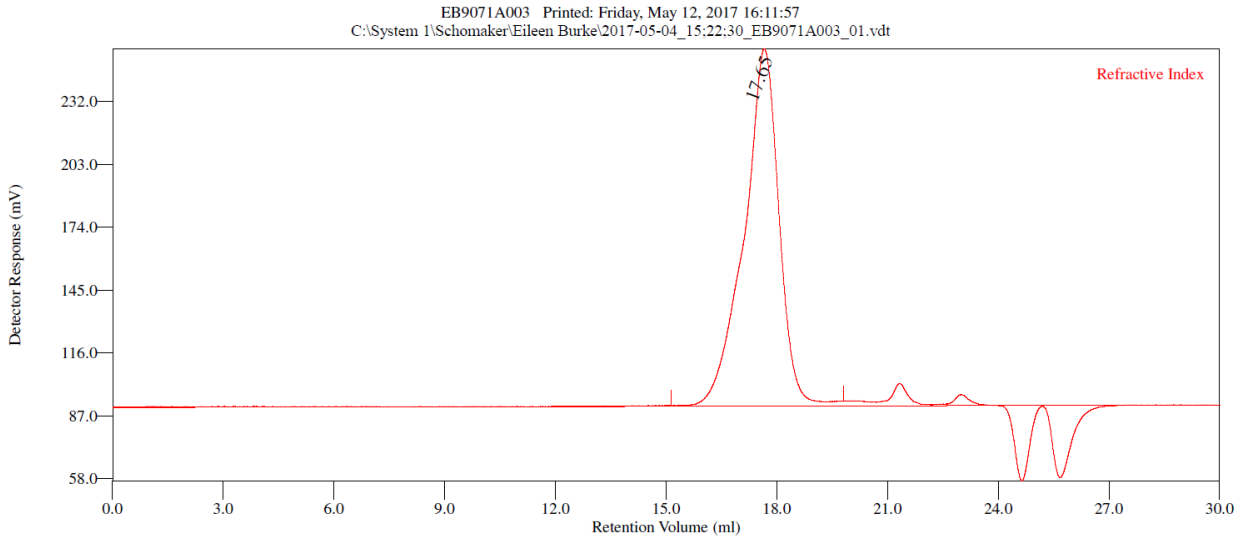
Date Acquired	Apr 24, 2017 - 12:31:58
Solvent	THF
Acquisition Operator	admin : Administrator
Calculation Operator	admin : Administrator
Column Set	GMHx1
System	System 1
Flow Rate - (ml/min)	1.000
Inj Volume - (ul)	100.0
Volume Increment - (ml)	0.00333
Detector Temp. - (deg C)	40.0
Column Temp. - (deg C)	40.0
OmniSEC Build Number	257





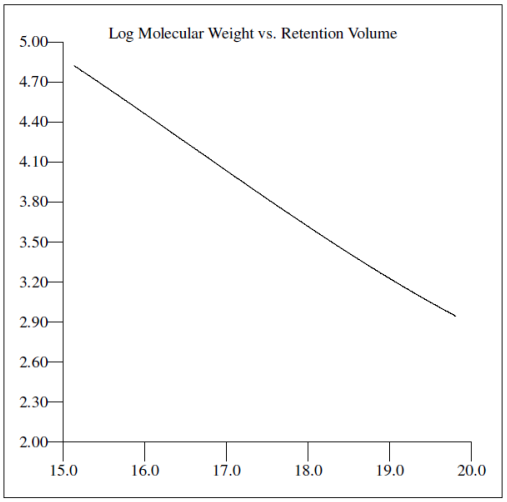
Compound 4.22

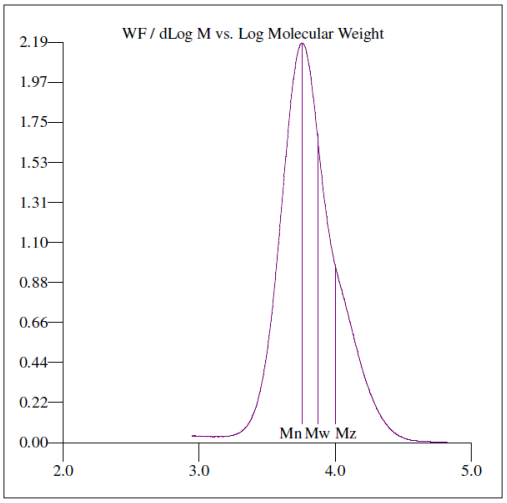


Conventional Calibration - Homopolymers : Results

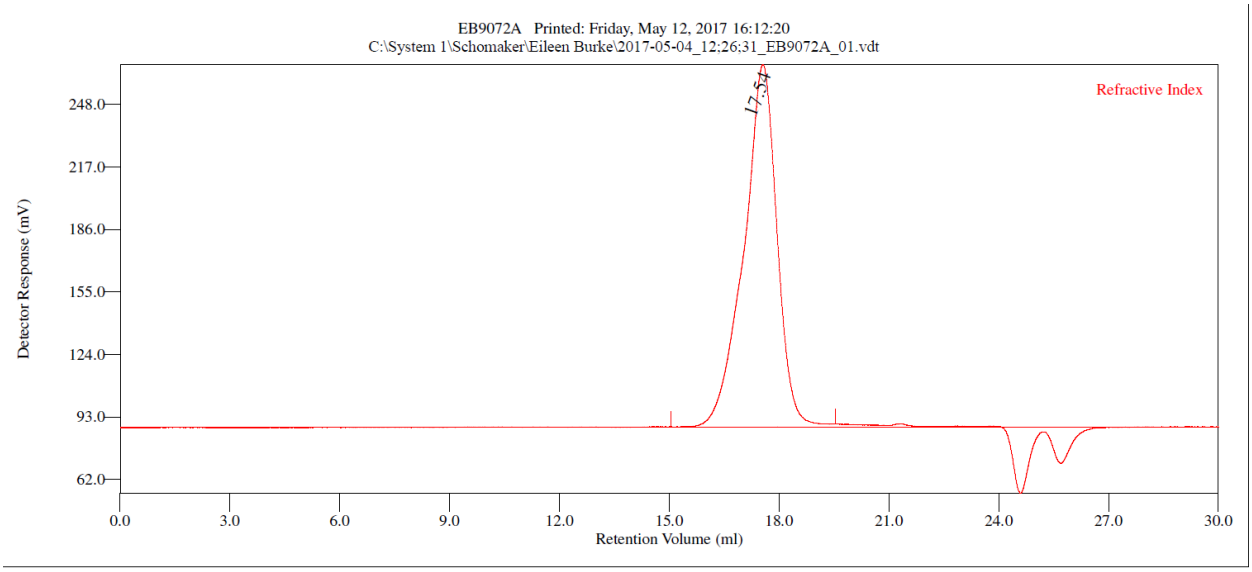
Peak RV - (ml)	17.647
Mn - (Daltons)	5,698
Mw - (Daltons)	7,397
Mz - (Daltons)	9,975
Mp - (Daltons)	5,762
Mw / Mn	1.298
Percent Above Mw: 0	0.000
Percent Below Mw: 0	0.004
Mw 10.0% Low	2,901
Mw 10.0% High	17,417
RI Area - (mvml)	181.45
UV Area - (mvml)	0.00

Annotation	
Method File	PSCAL02_27_17-0002.vcm
Limits File	;30_EB9071A003_01-PSCAL02_27_17-0002-0000.lim
Date Acquired	May 04, 2017 - 15:22:30
Solvent	THF
Acquisition Operator	admin : Administrator
Calculation Operator	admin : Administrator
Column Set	GMHx1
System	System 1
Flow Rate - (ml/min)	1.000
Inj Volume - (ul)	100.0
Volume Increment - (ml)	0.00333
Detector Temp. - (deg C)	40.0
Column Temp. - (deg C)	40.0
OmniSEC Build Number	257





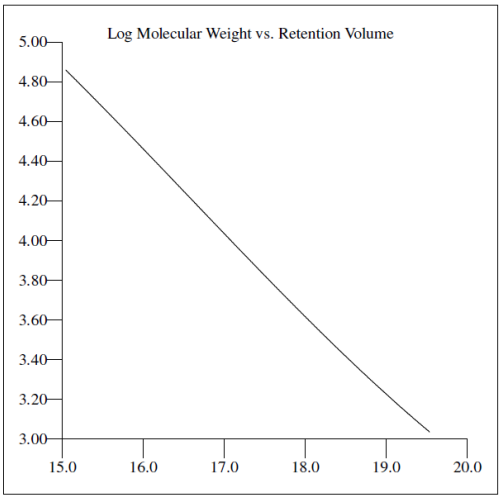
Compound 4.23

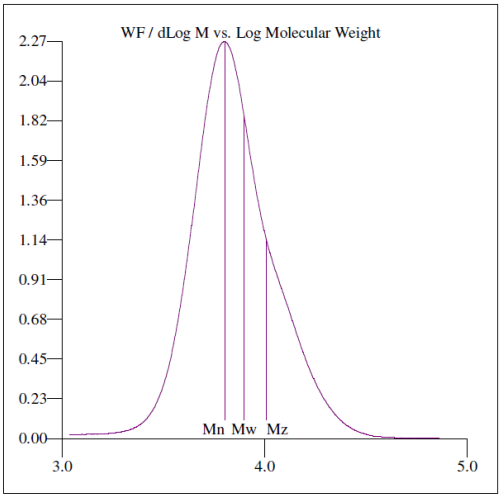


Conventional Calibration - Homopolymers : Results

Peak RV - (ml)	17.540
Mn - (Daltons)	6,333
Mw - (Daltons)	7,911
Mz - (Daltons)	10,172
Mp - (Daltons)	6,382
Mw / Mn	1.249
Percent Above Mw: 0	0.000
Percent Below Mw: 0	0.002
Mw 10.0% Low	3,325
Mw 10.0% High	17,579
RI Area - (mvml)	189.32
UV Area - (mvml)	0.00

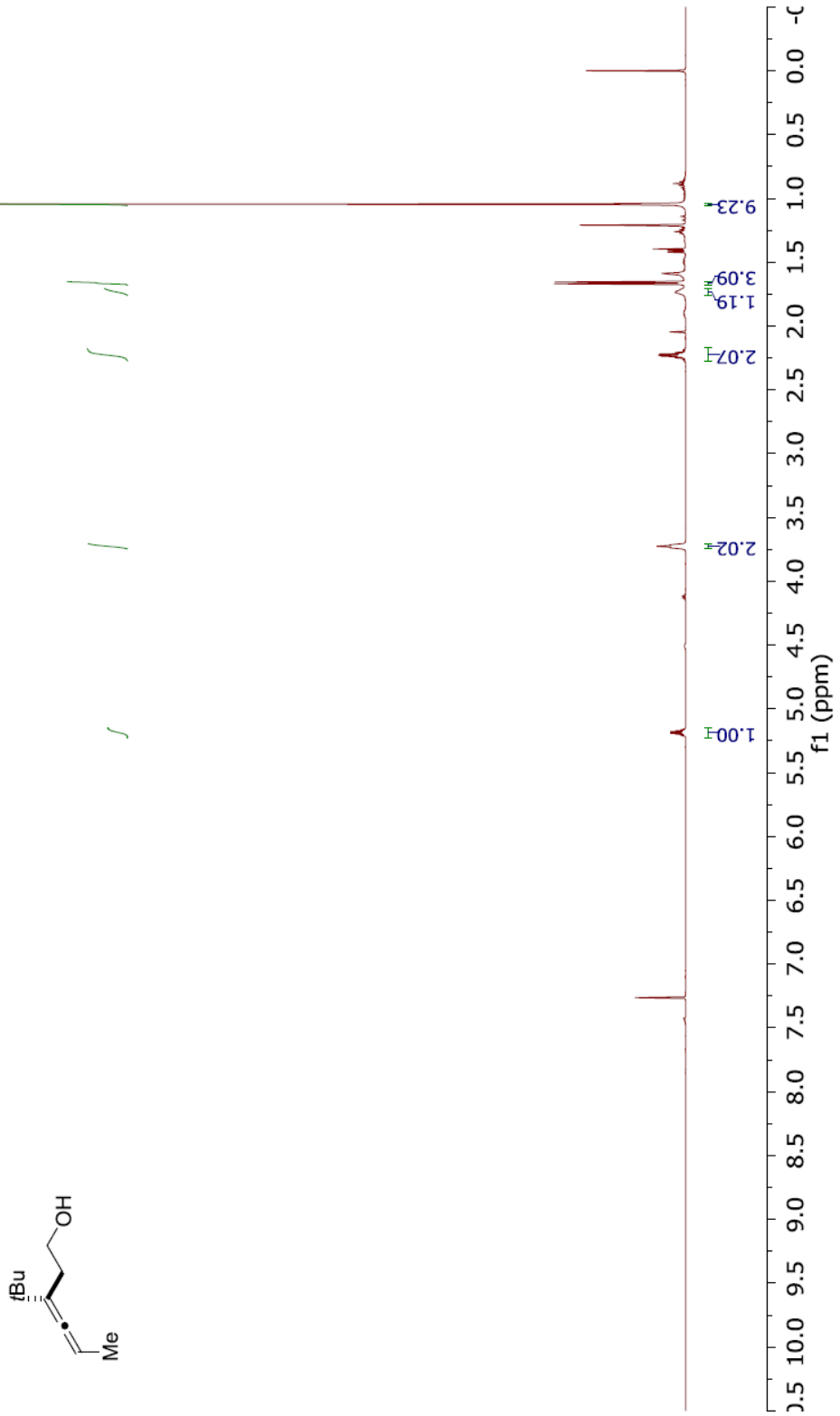
Annotation	
Method File	PSCAL02_27_17-0002.vcm
Limits File	2:26:31_EB9072A_01-PSCAL02_27_17-0002-0000.lim
Date Acquired	May 04, 2017 - 12:26:31
Solvent	THF
Acquisition Operator	admin : Administrator
Calculation Operator	admin : Administrator
Column Set	GMHx1
System	System 1
Flow Rate - (ml/min)	1.000
Inj Volume - (ul)	100.0
Volume Increment - (ml)	0.00333
Detector Temp. - (deg C)	40.0
Column Temp. - (deg C)	40.0
OmniSEC Build Number	257



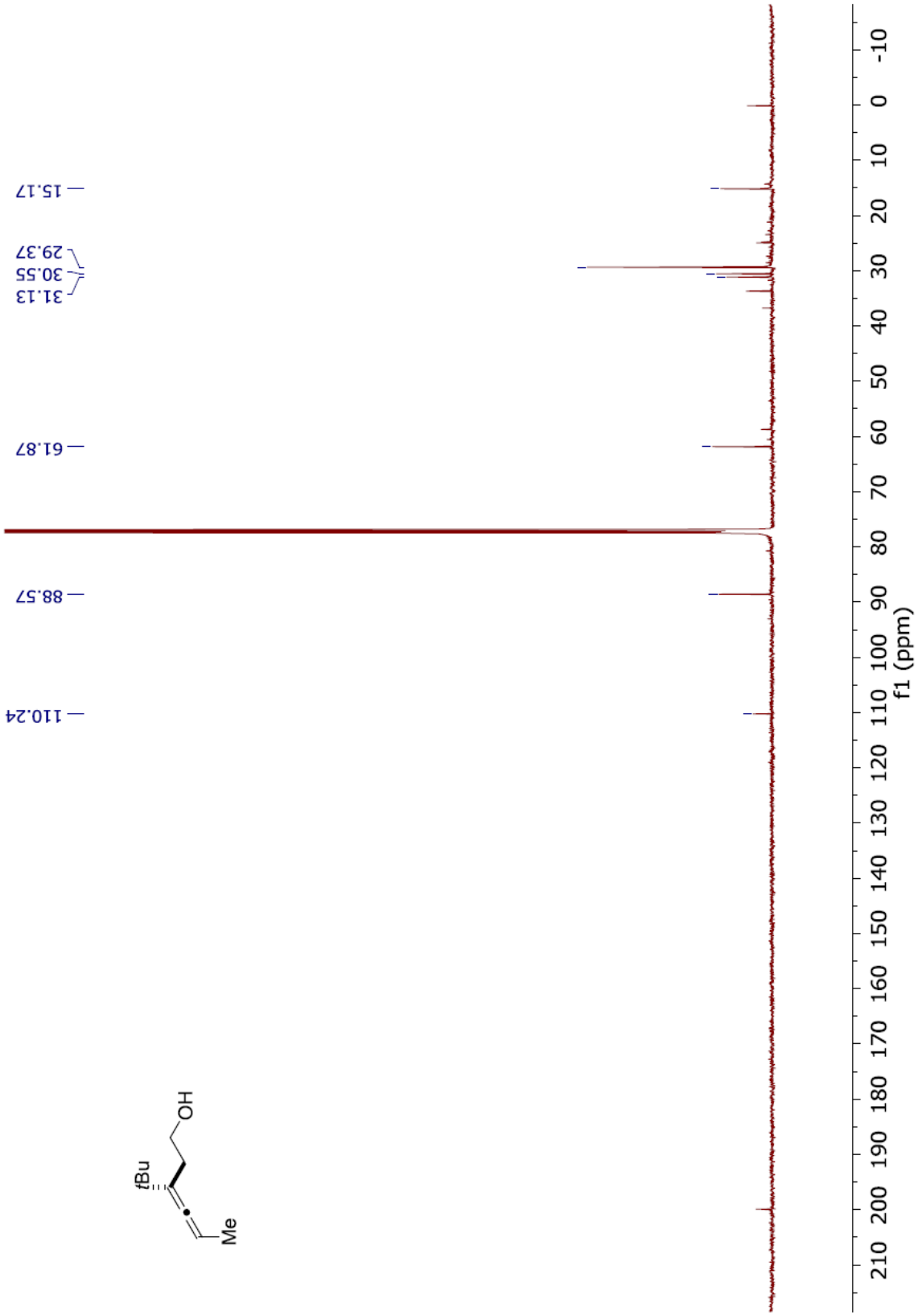


Appendix. Selected ^{1}H- and ^{13}C-NMR Spectra

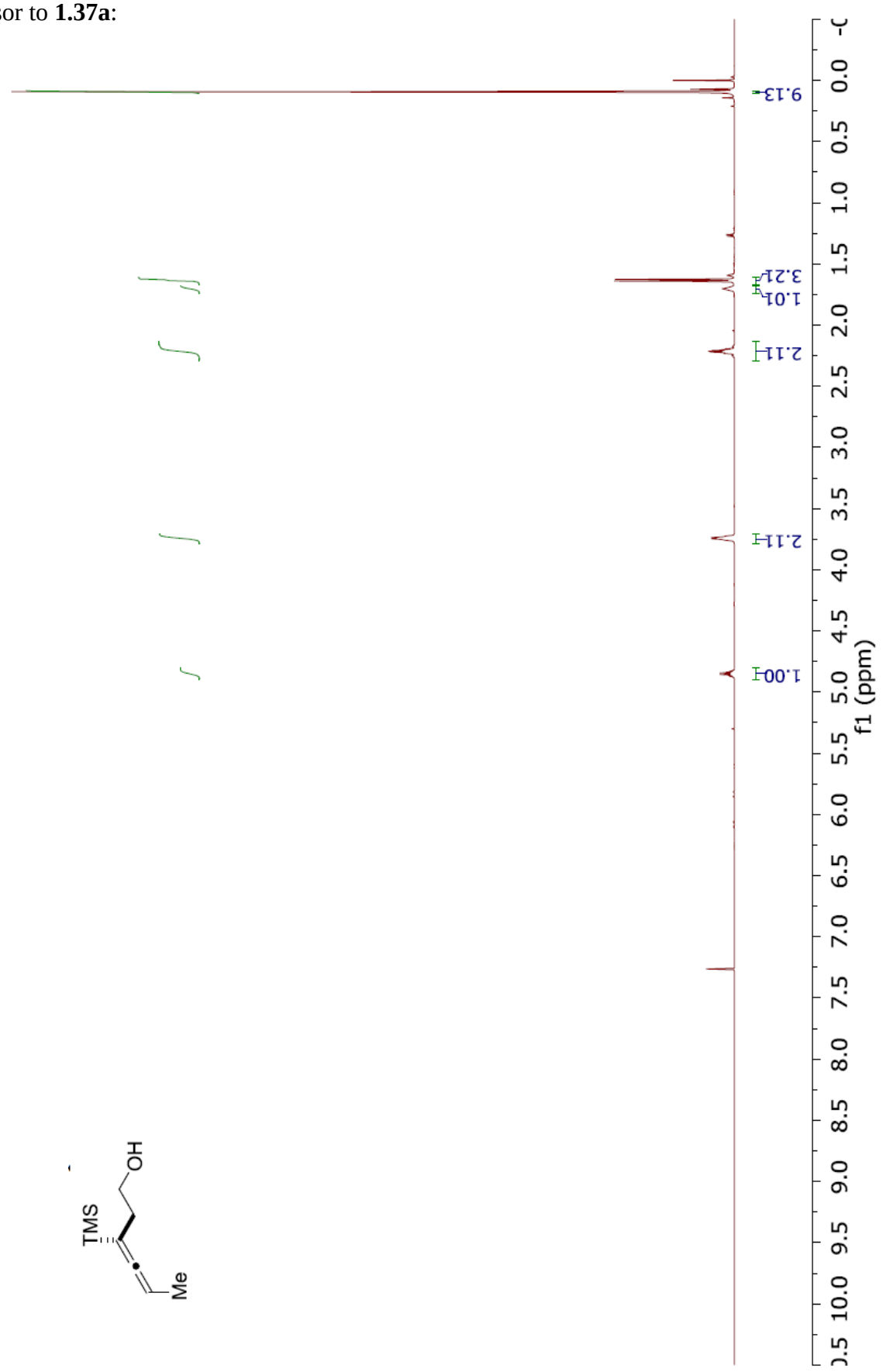
Precursor to **1.34**:



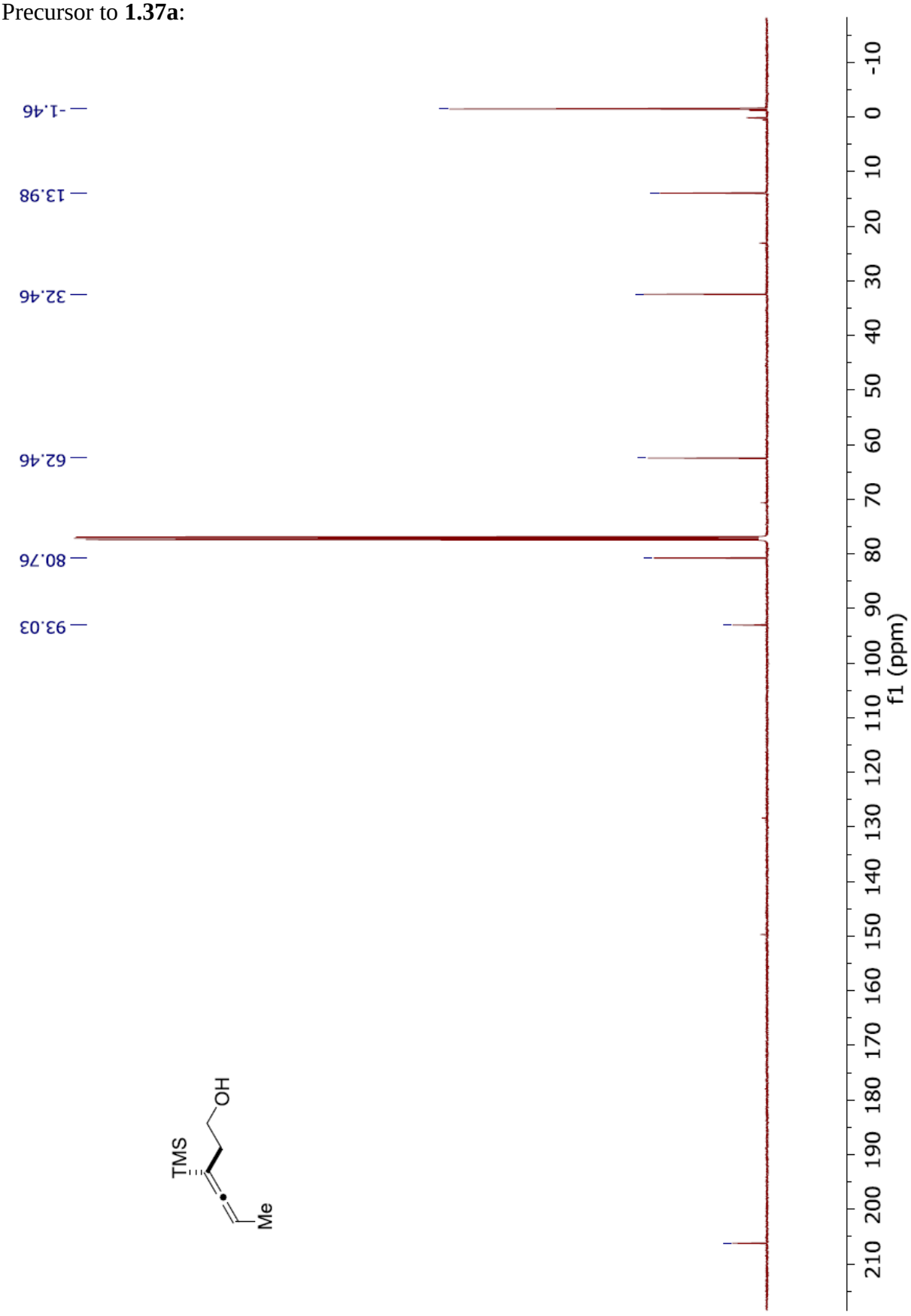
Precursor to **1.34**:



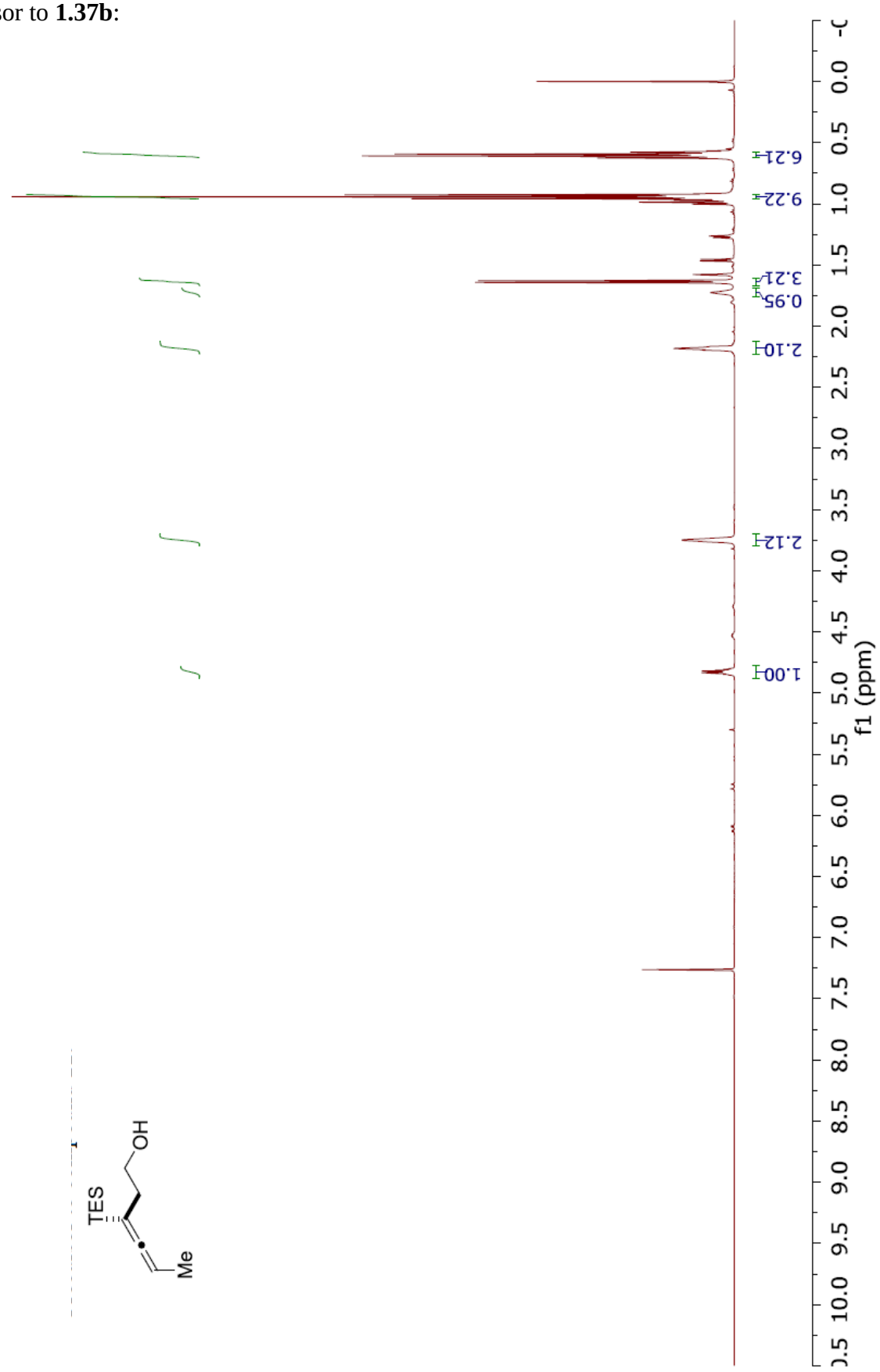
Precursor to **1.37a**:



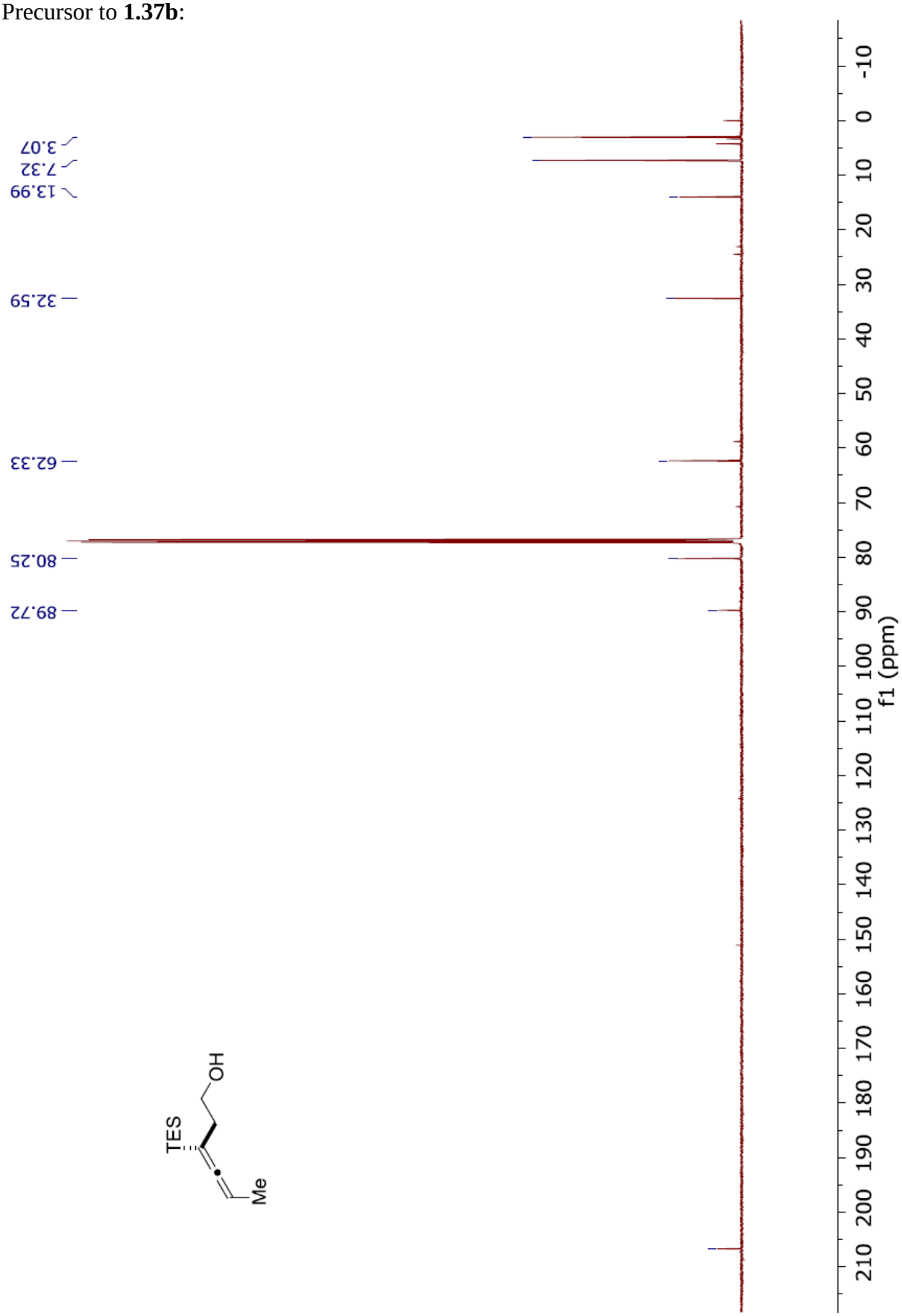
Precursor to **1.37a**:



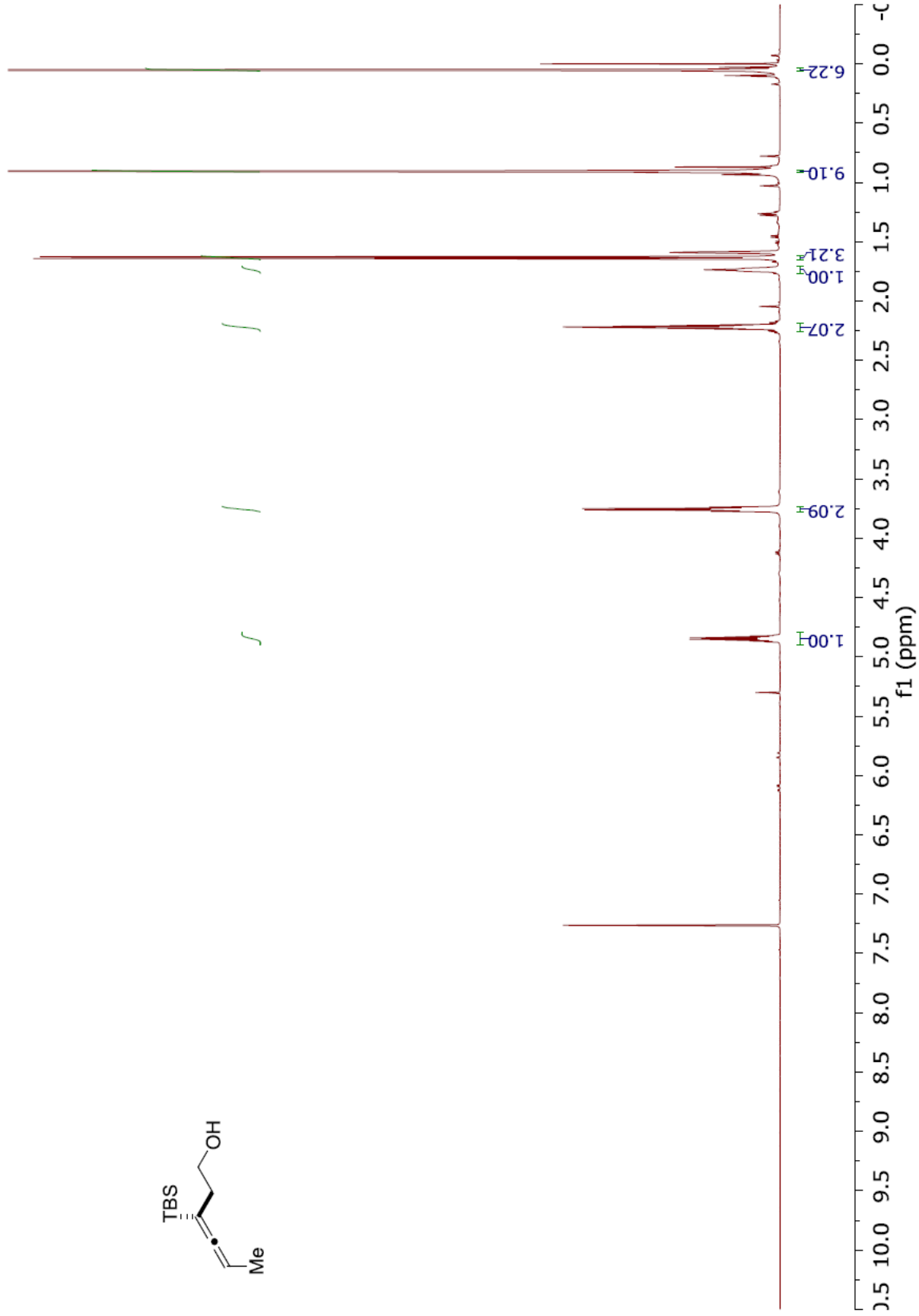
Precursor to **1.37b**:



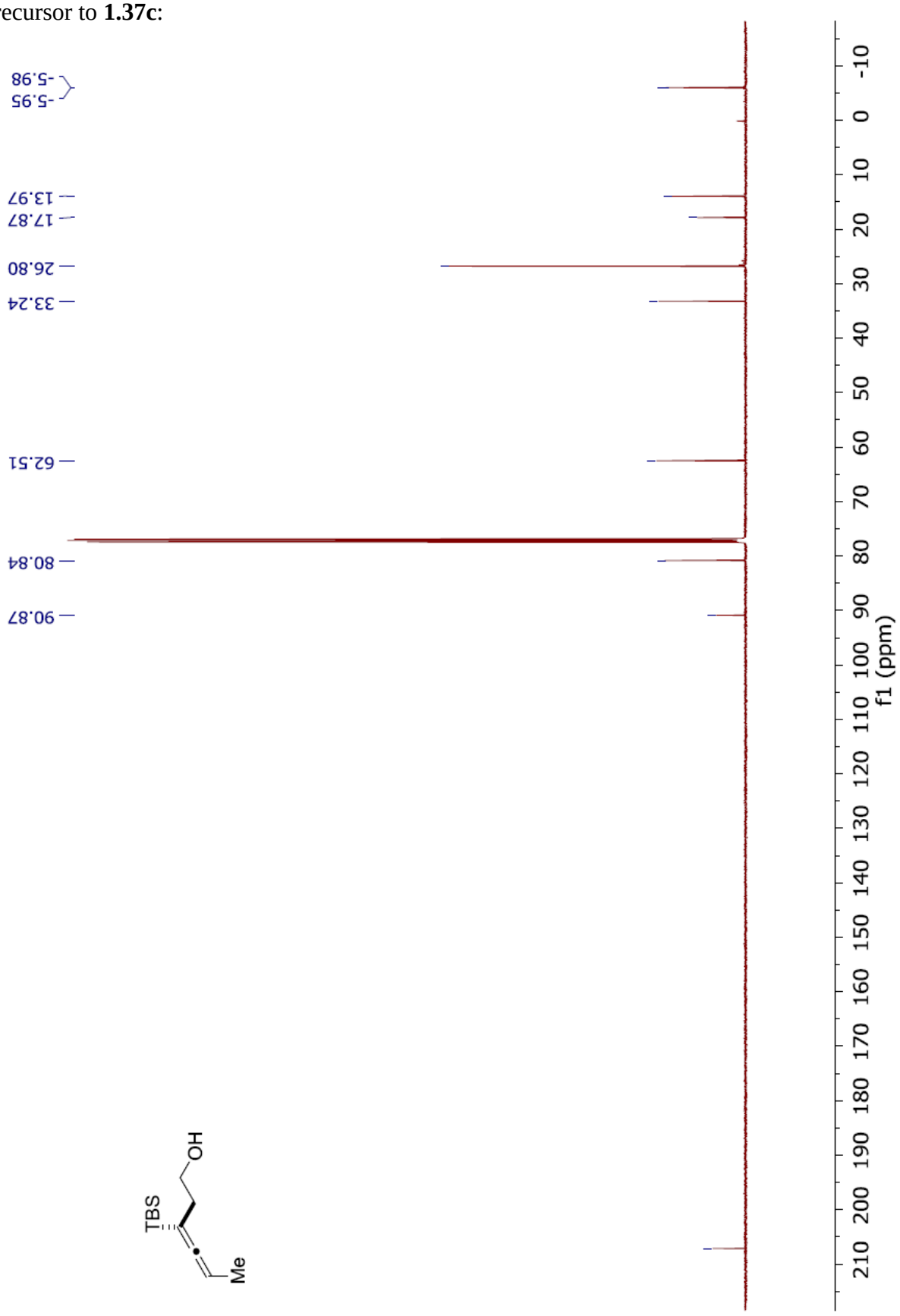
Precursor to **1.37b**:



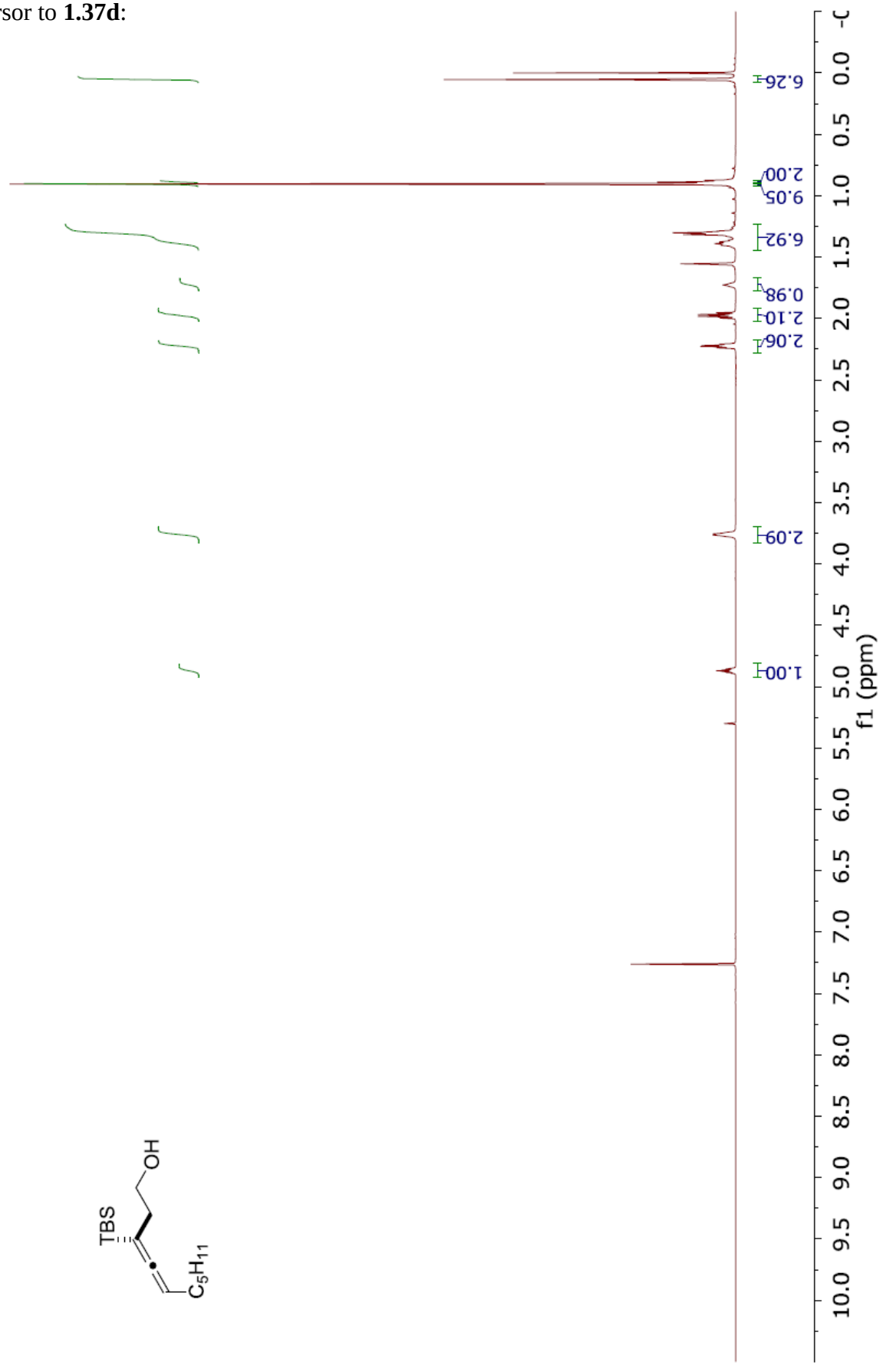
Precursor to **1.37c**:



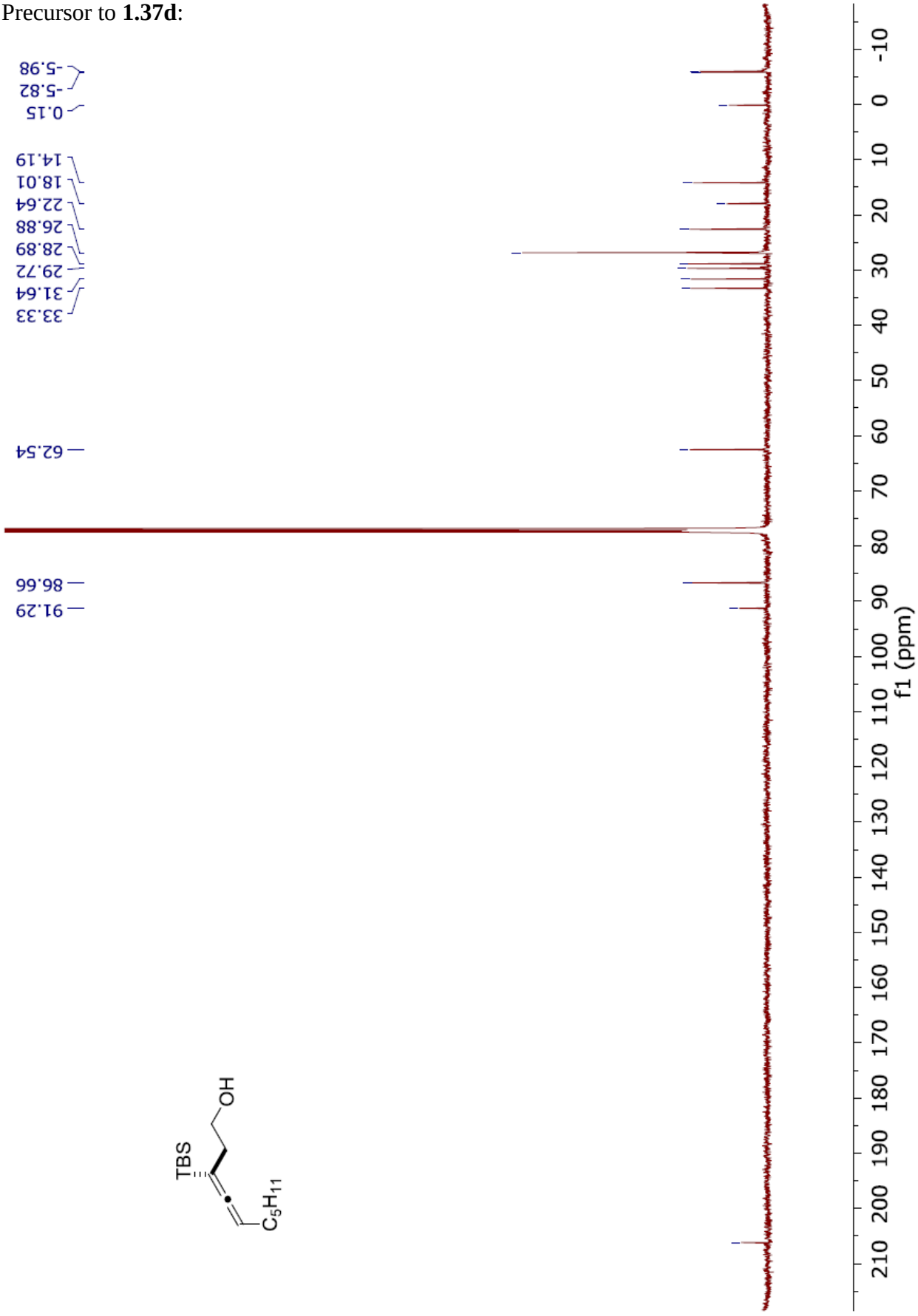
Precursor to **1.37c**:



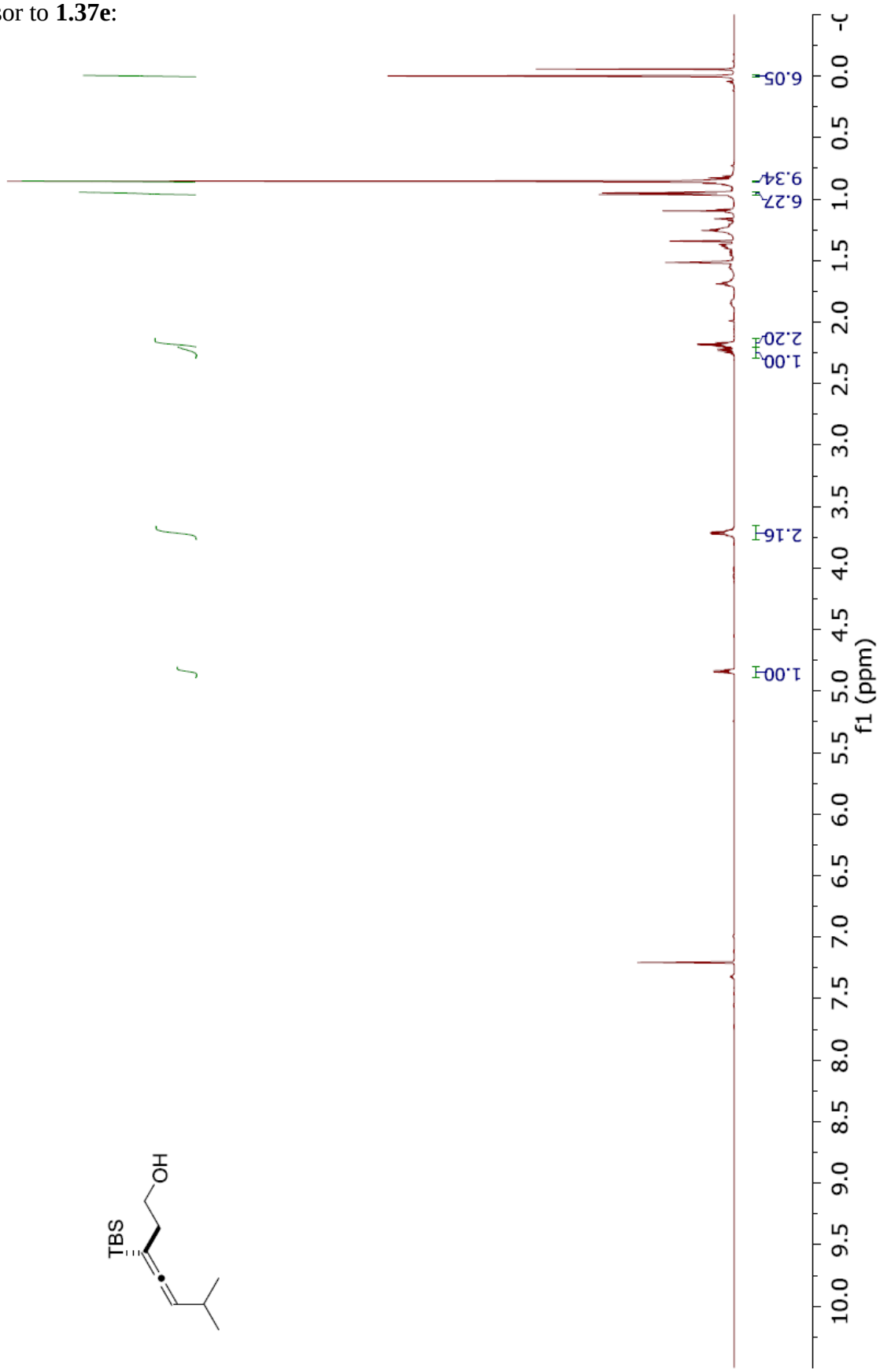
Precursor to **1.37d**:



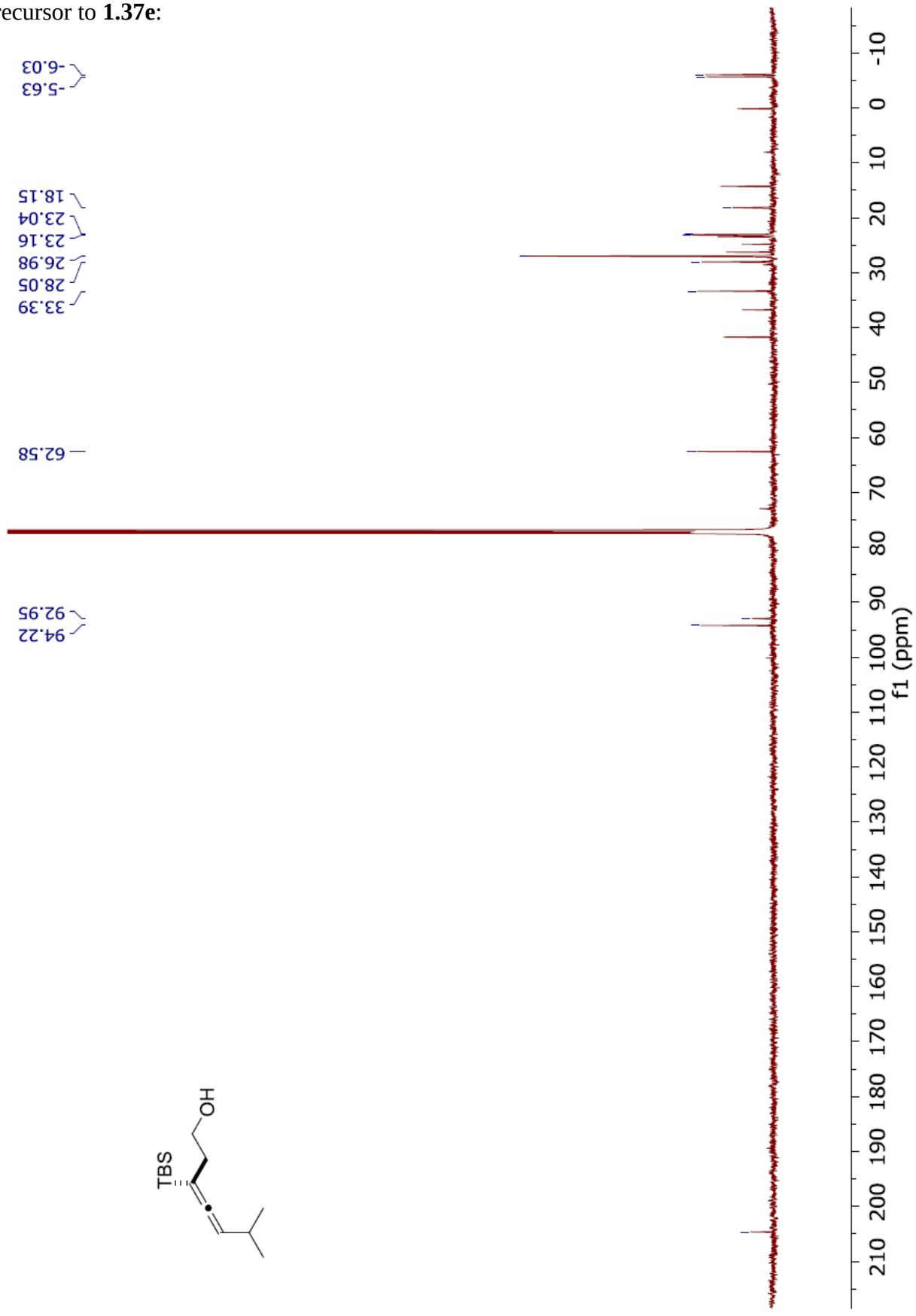
Precursor to **1.37d**:



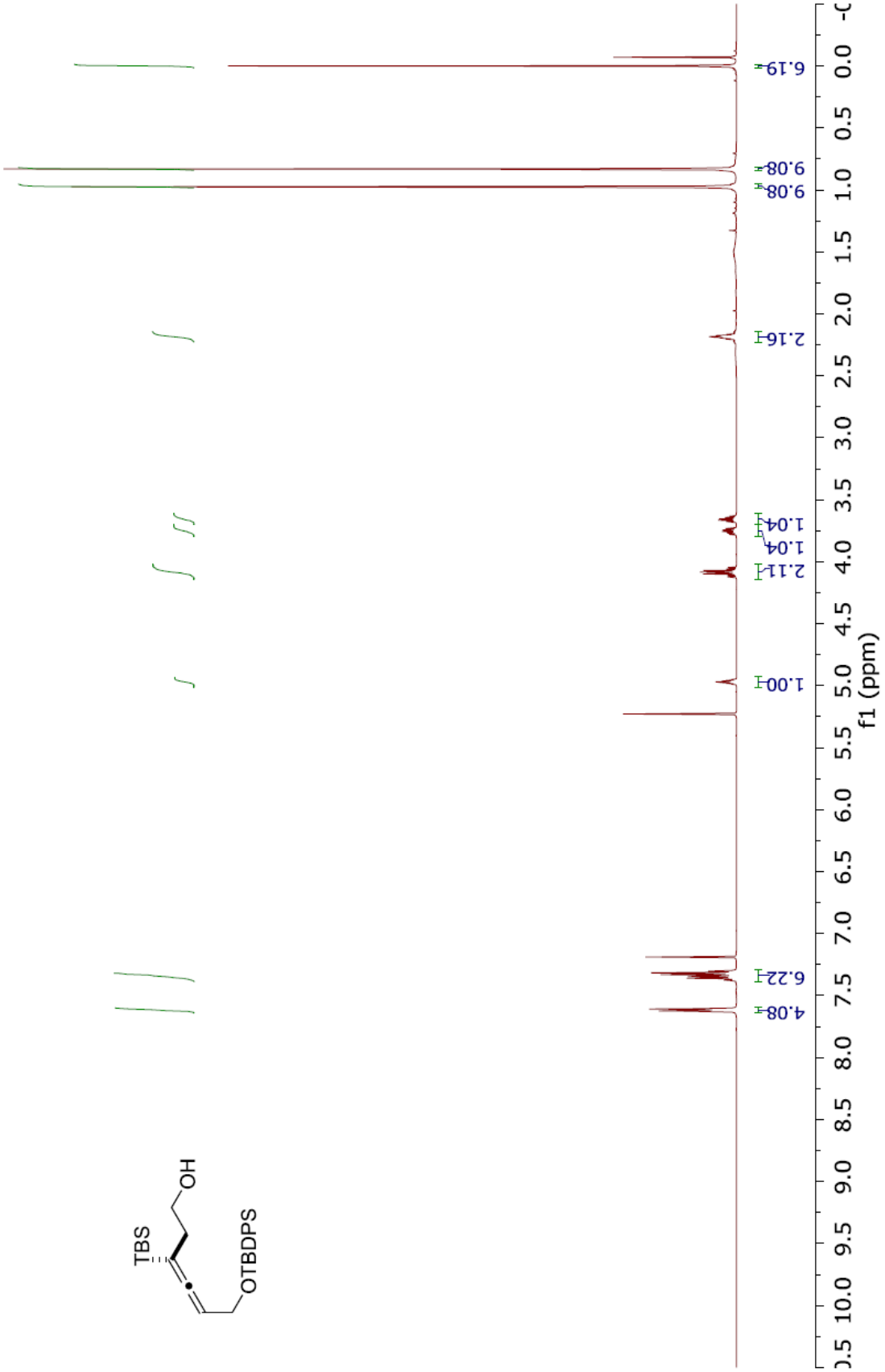
Precursor to **1.37e**:



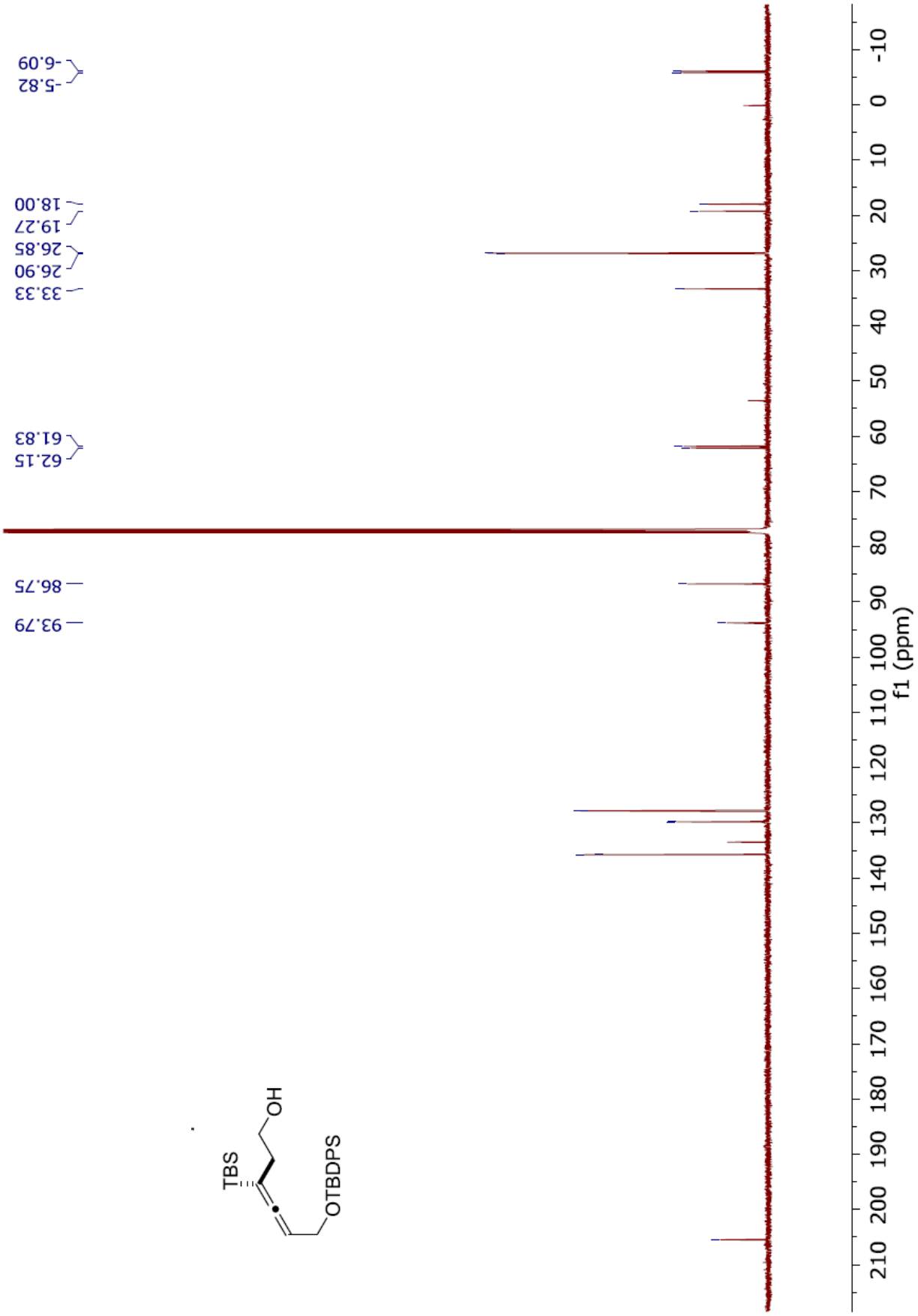
Precursor to **1.37e**:



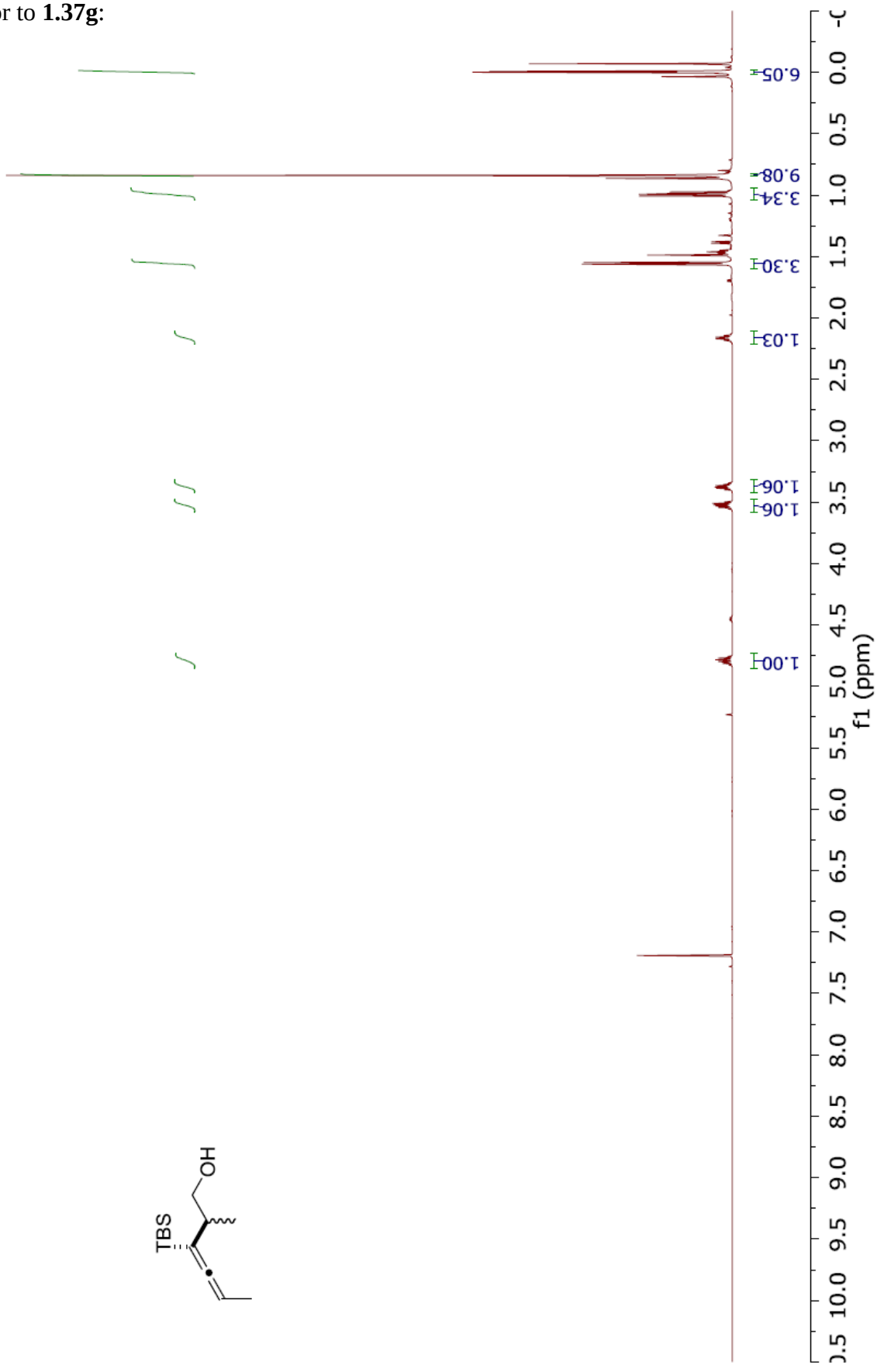
Precursor to **1.37f**:



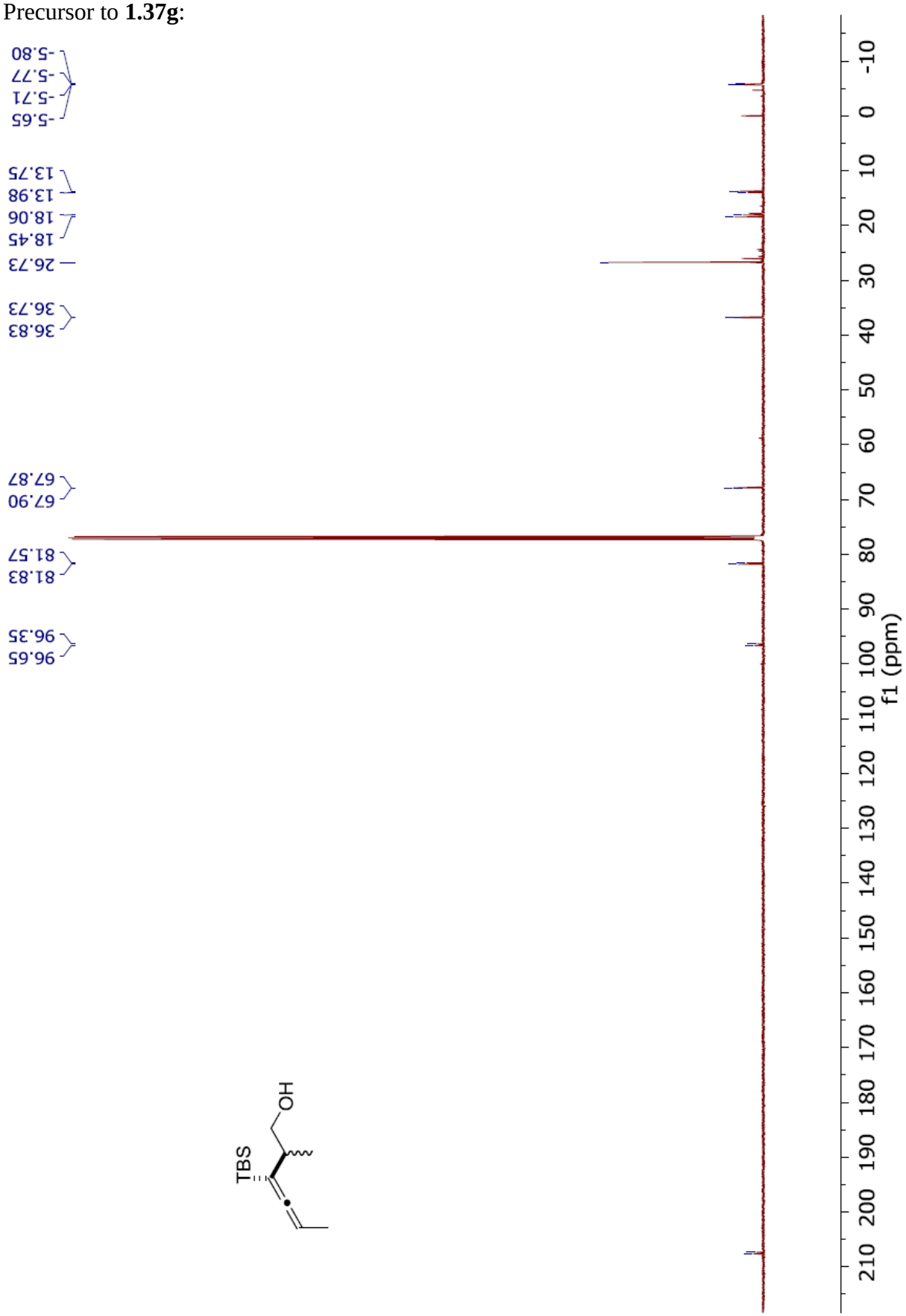
Precursor to **1.37f**:



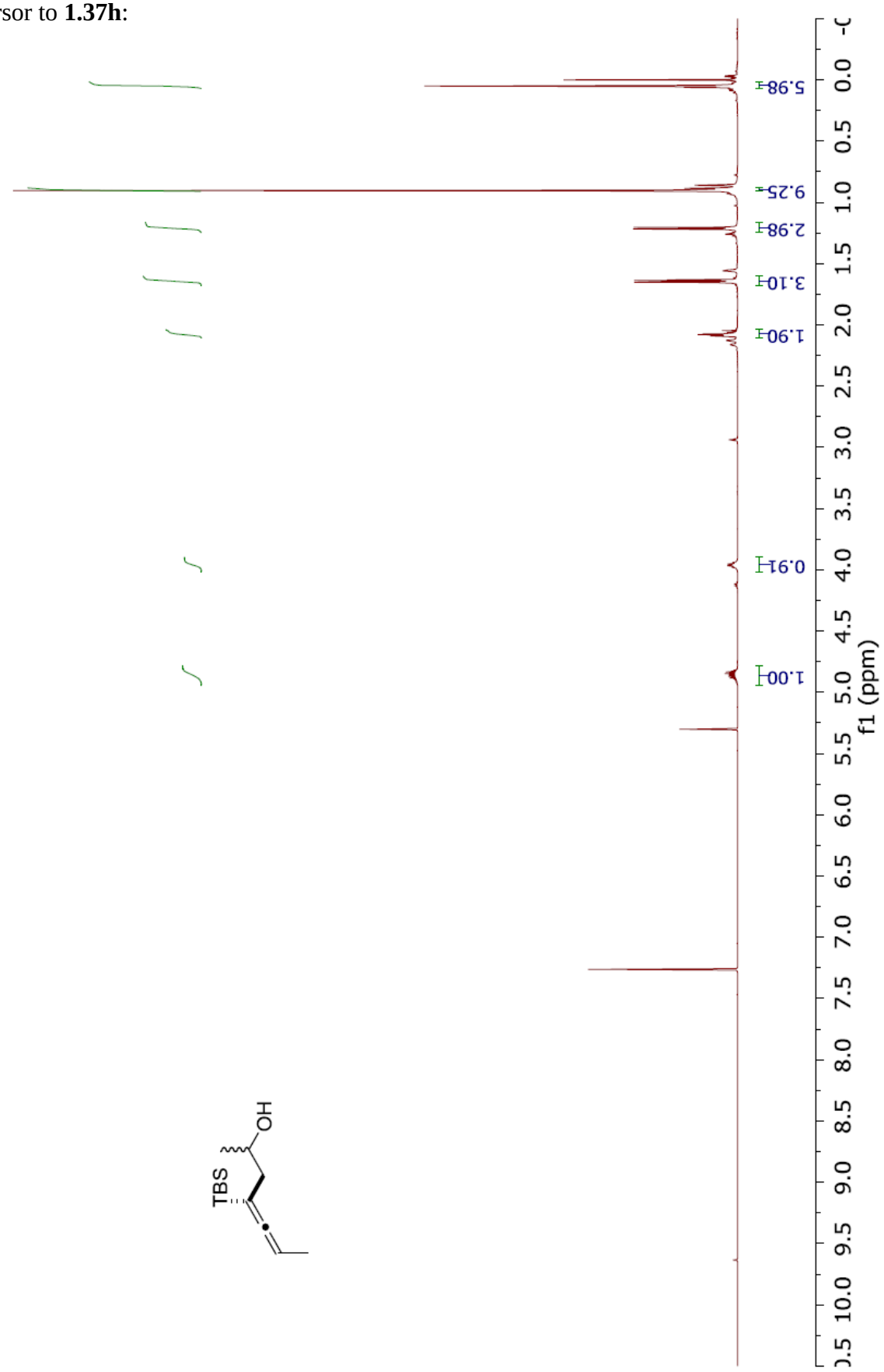
Precursor to **1.37g**:



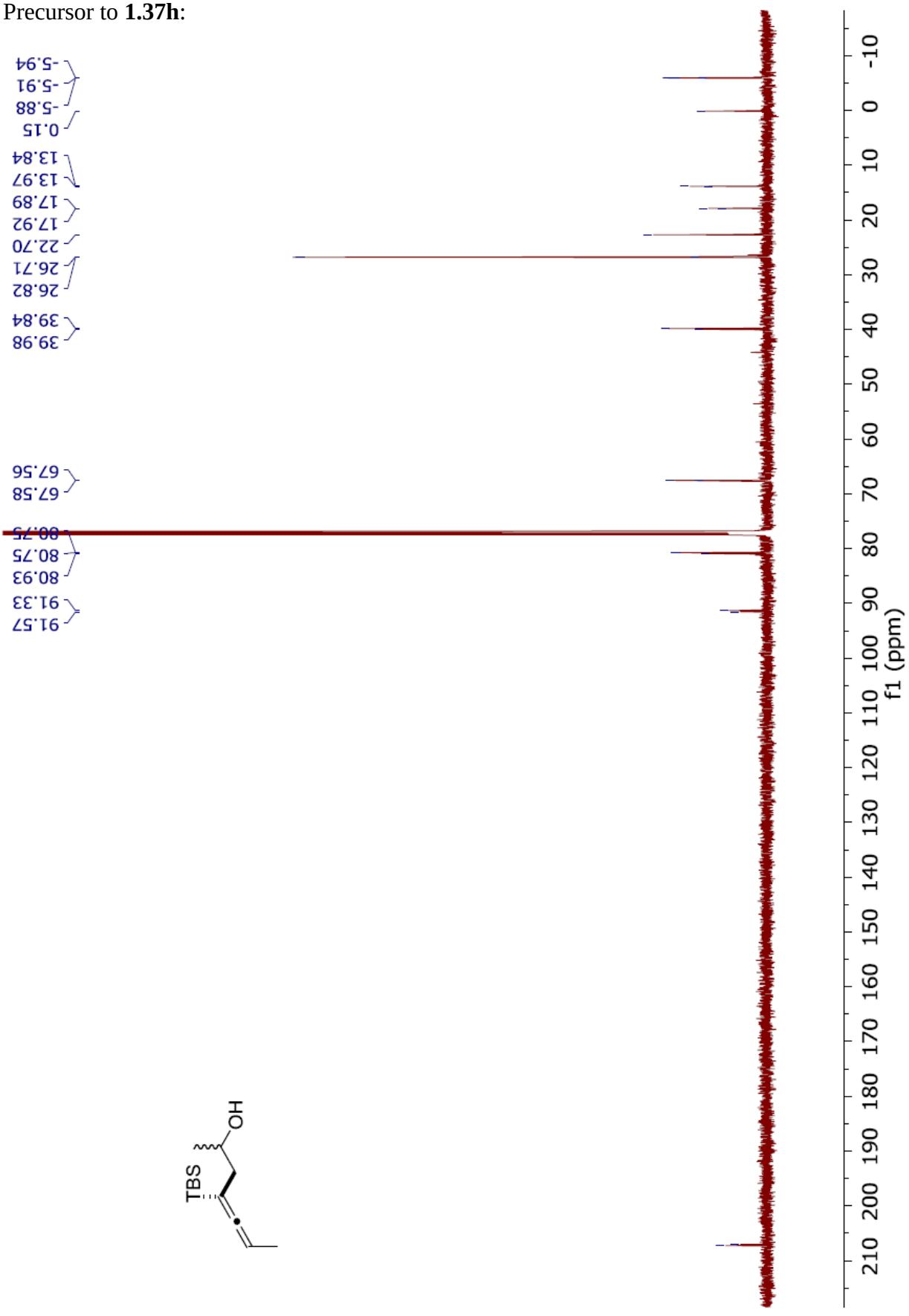
Precursor to **1.37g**:



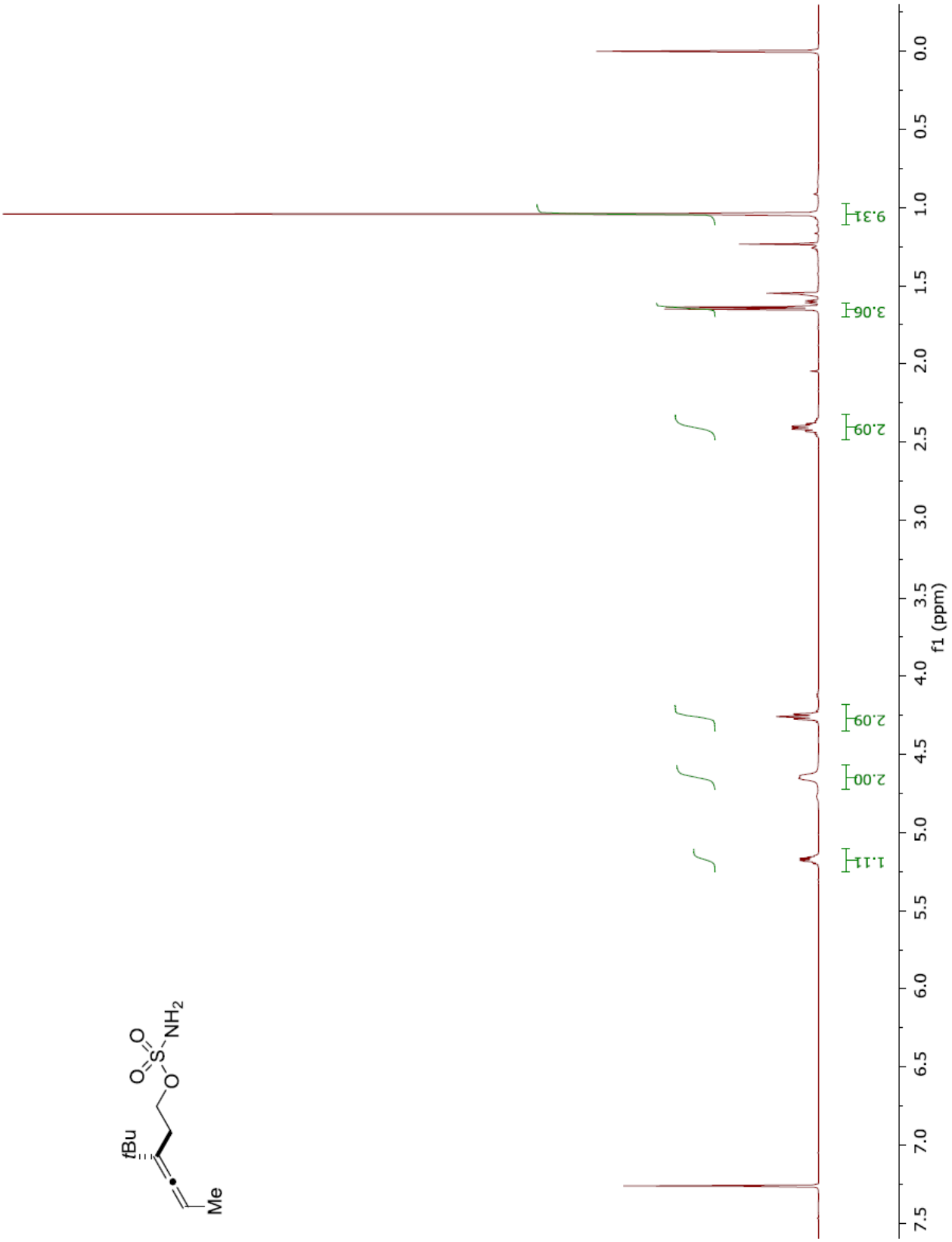
Precursor to **1.37h**:



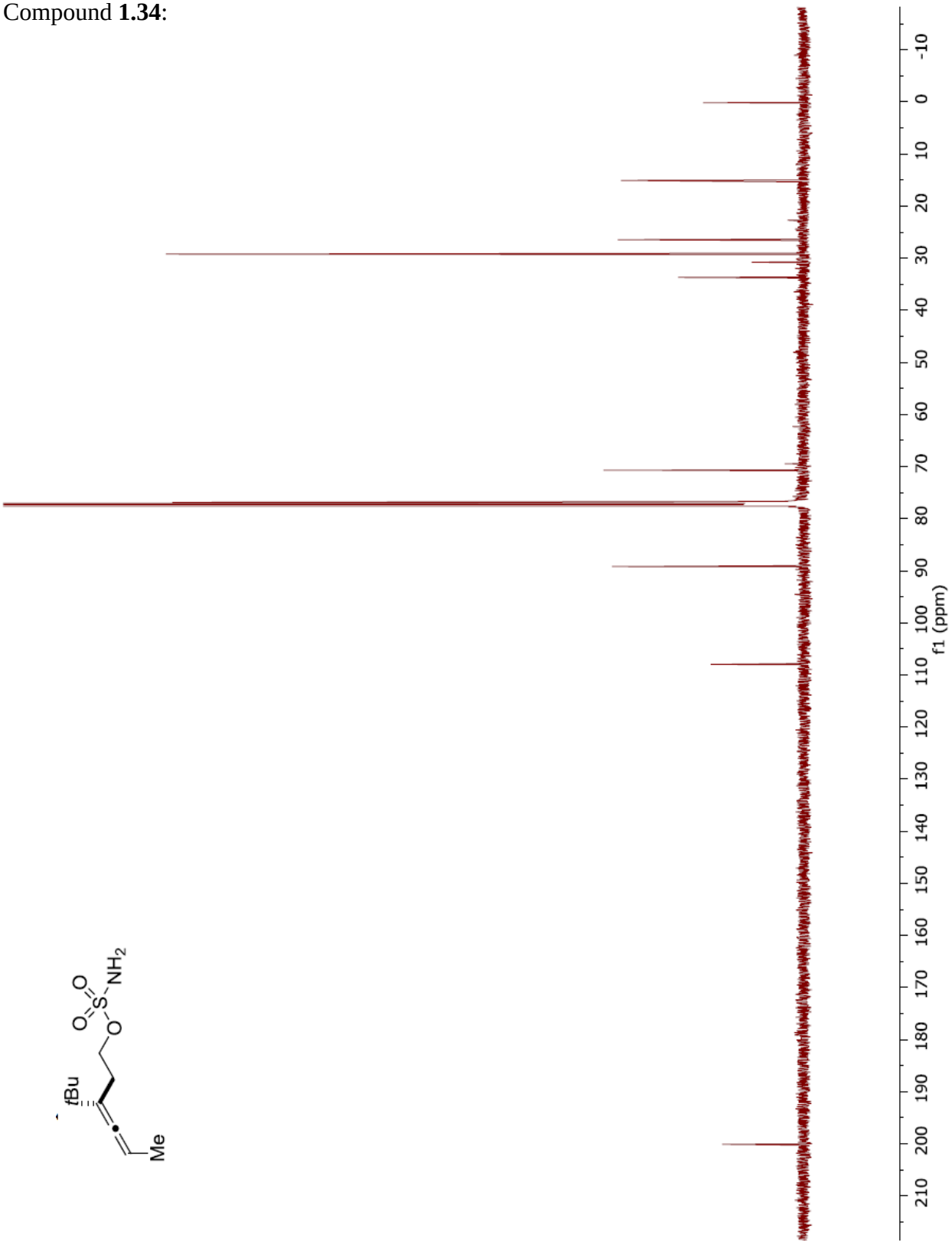
Precursor to **1.37h**:



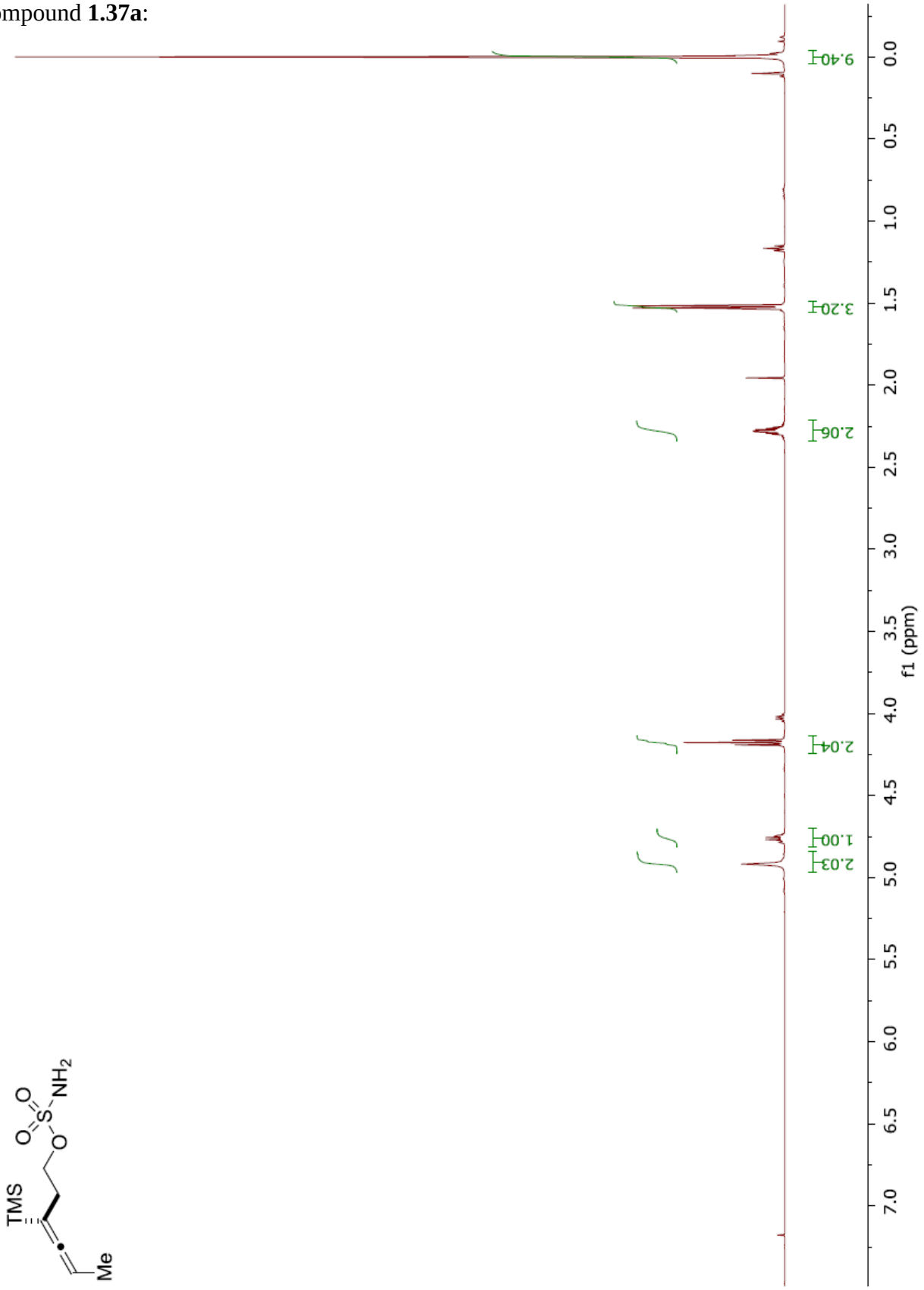
Compound **1.34**:



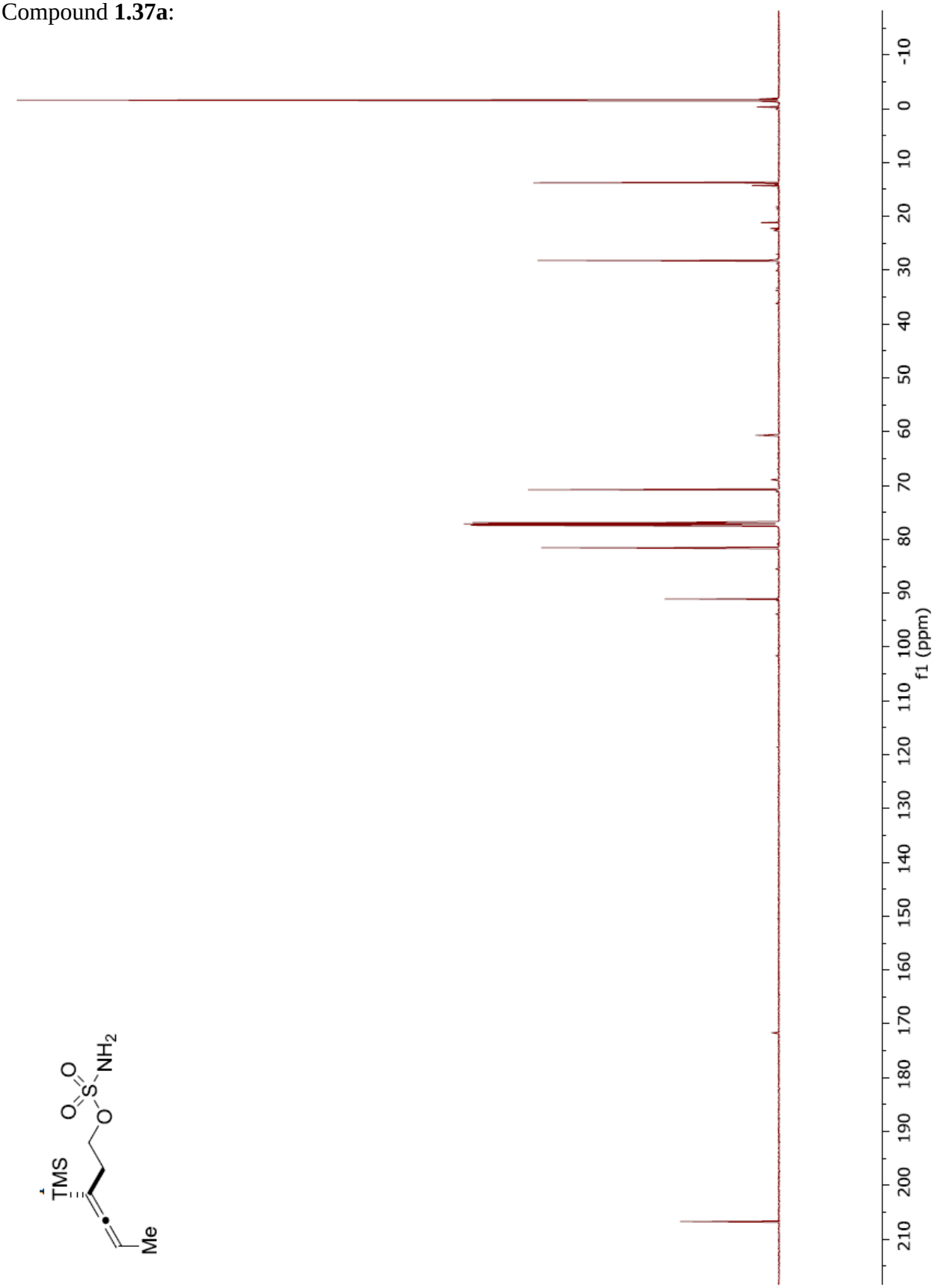
Compound **1.34**:



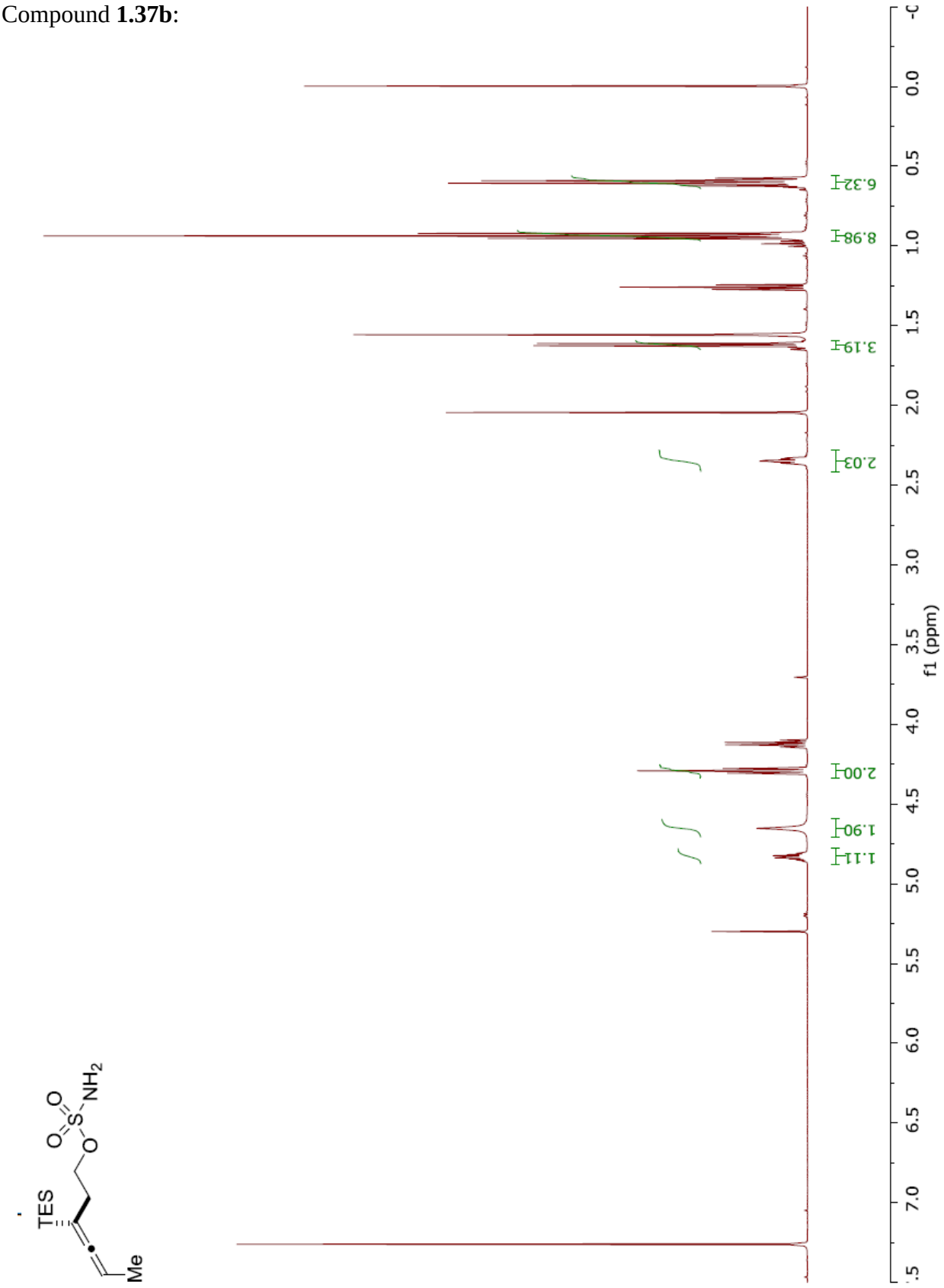
Compound **1.37a**:



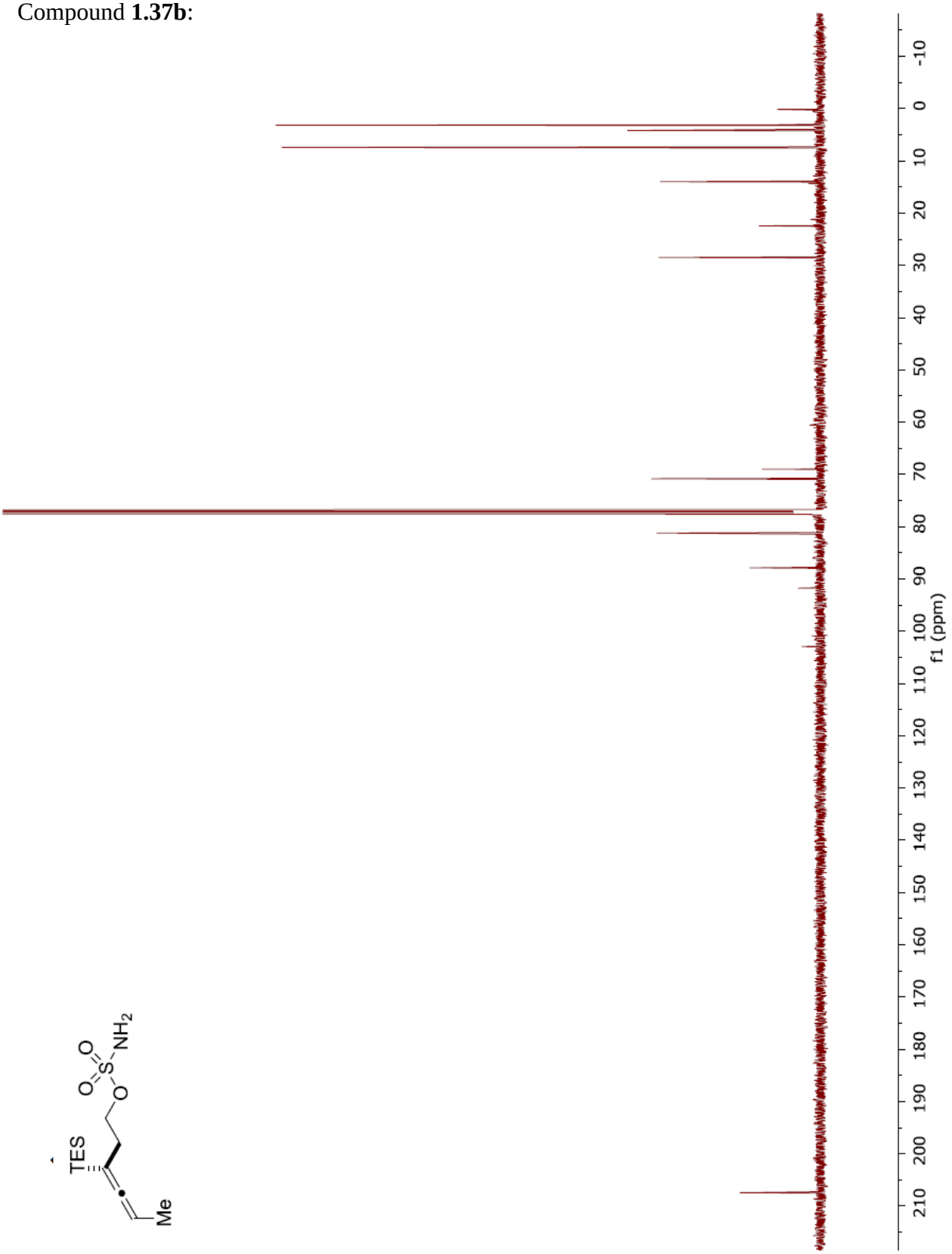
Compound **1.37a**:



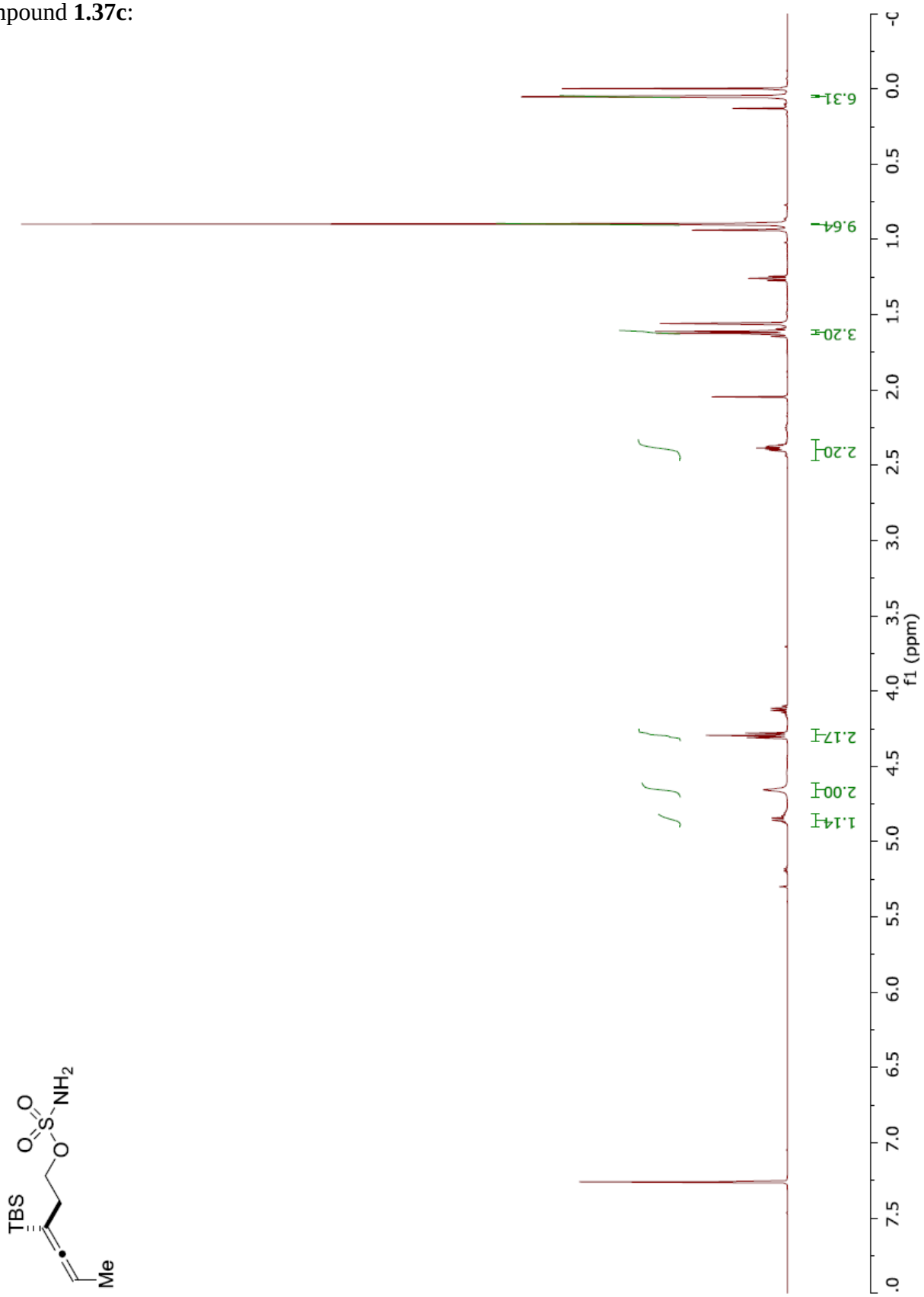
Compound **1.37b**:



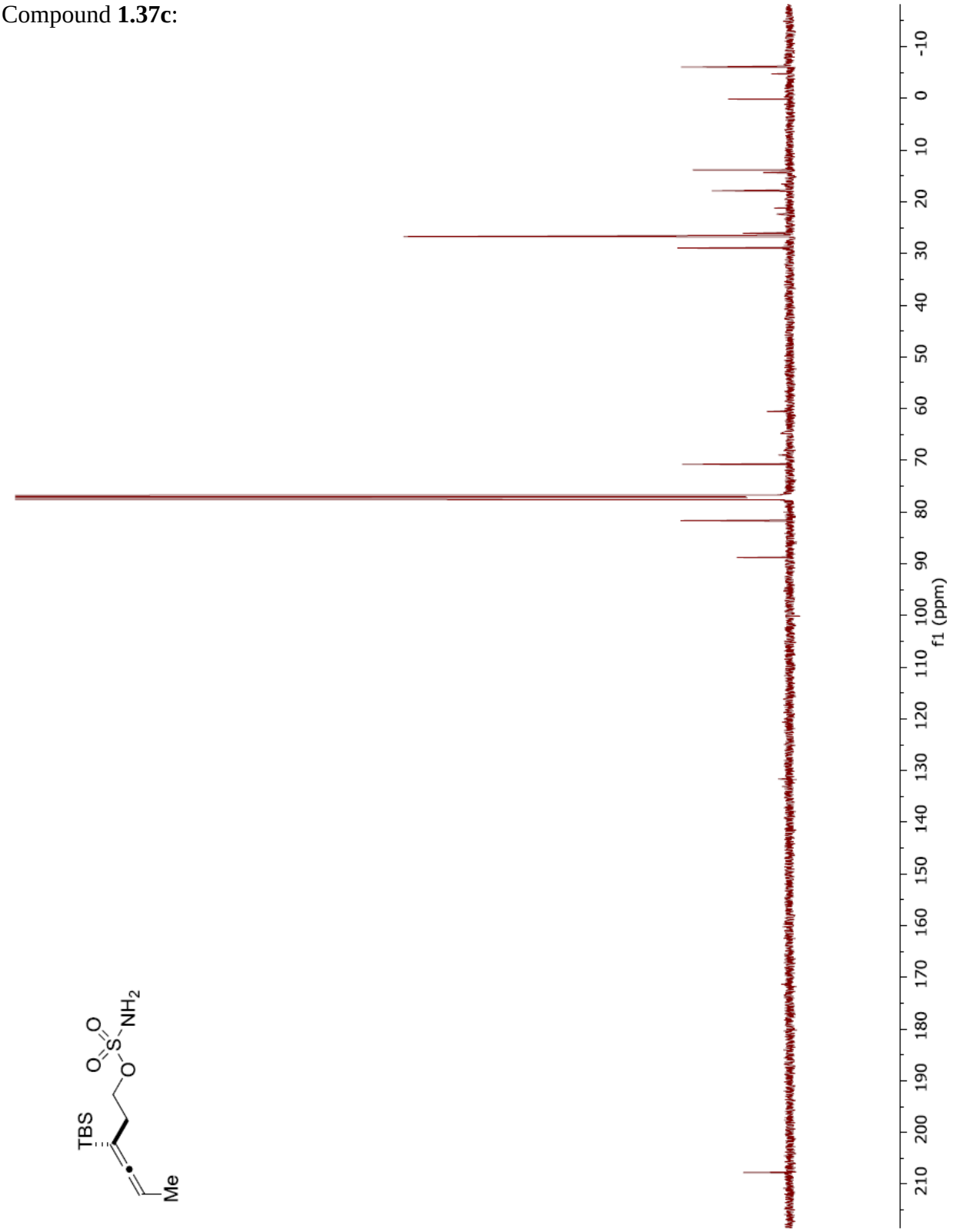
Compound **1.37b**:



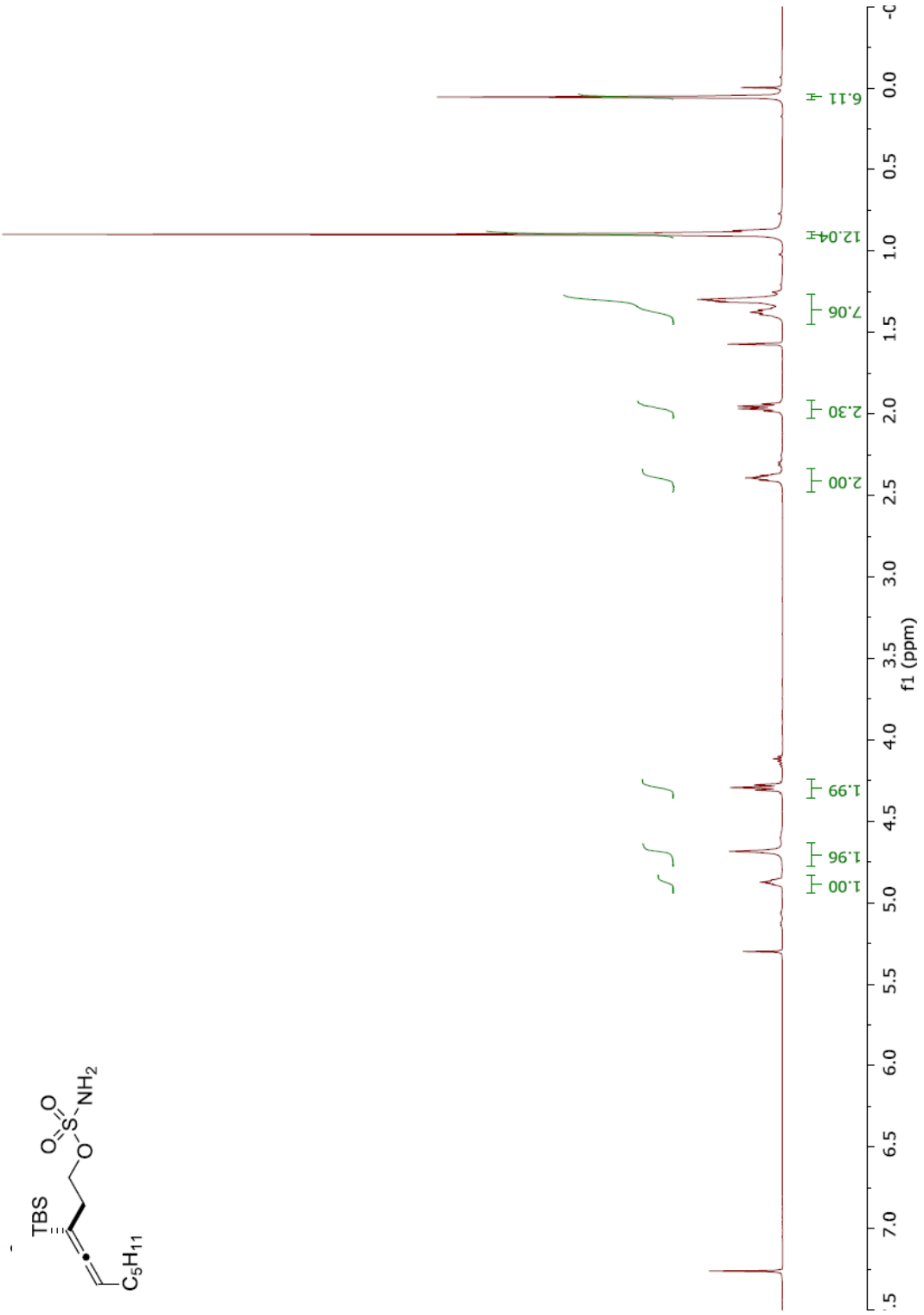
Compound **1.37c**:



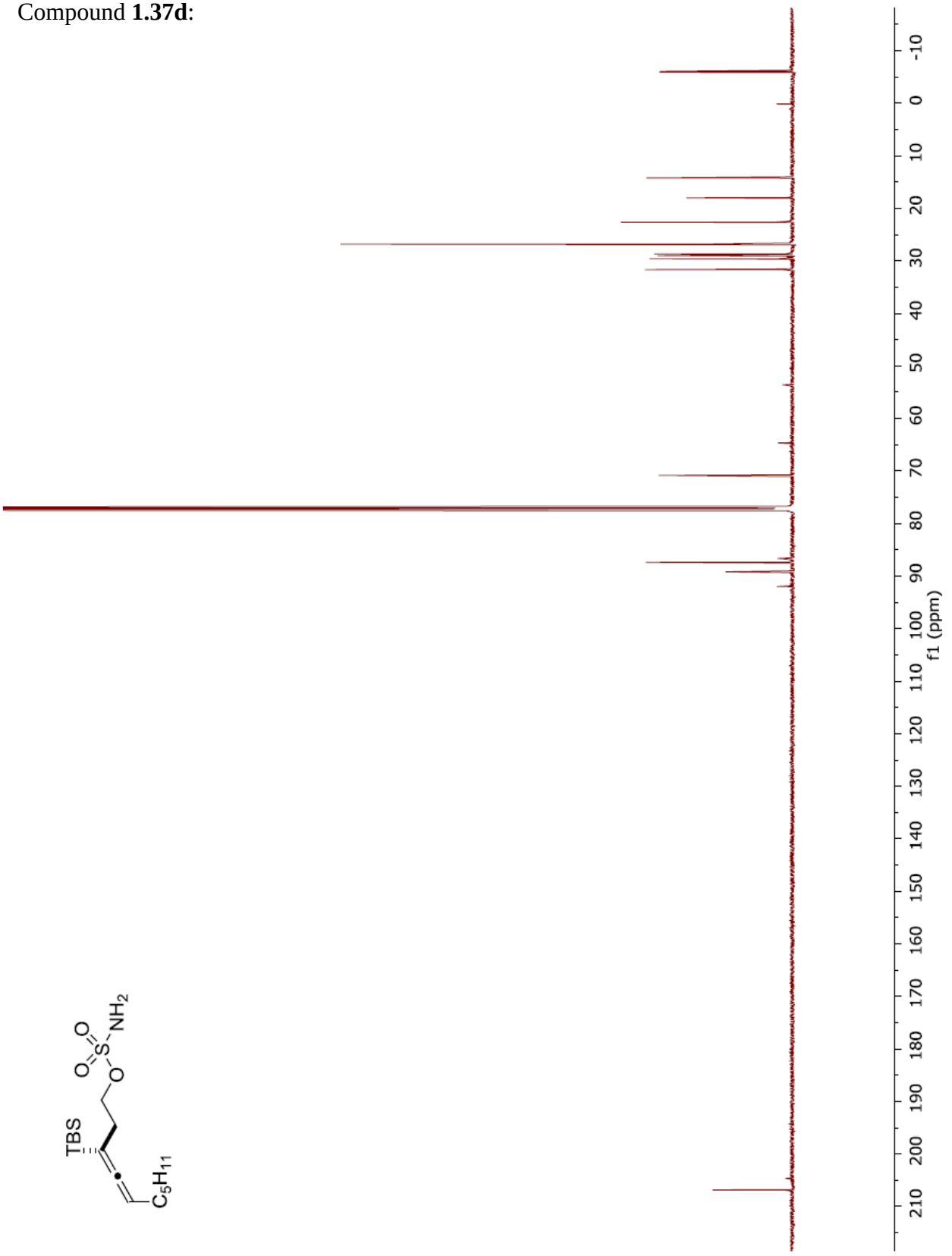
Compound **1.37c**:



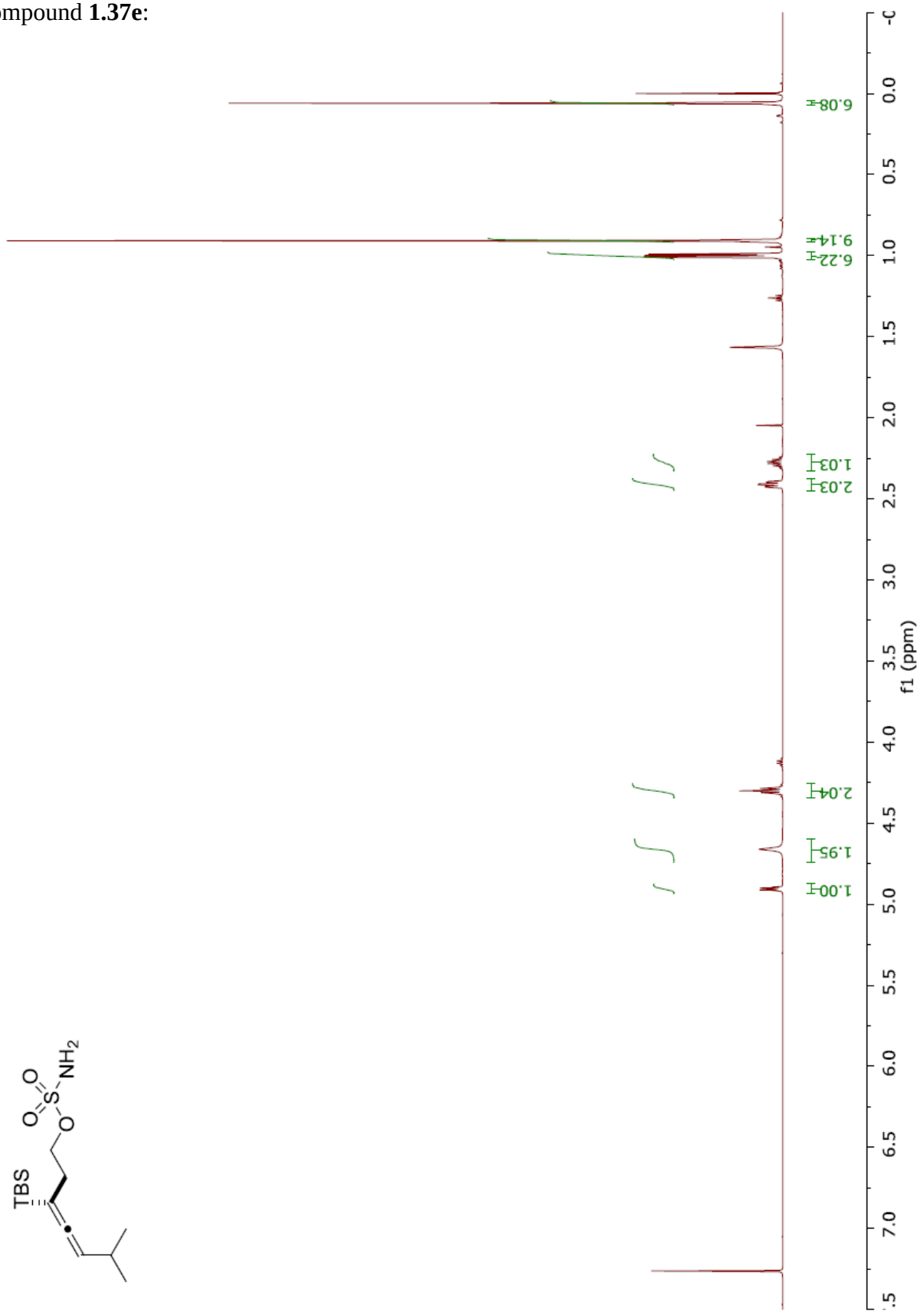
Compound **1.37d**:



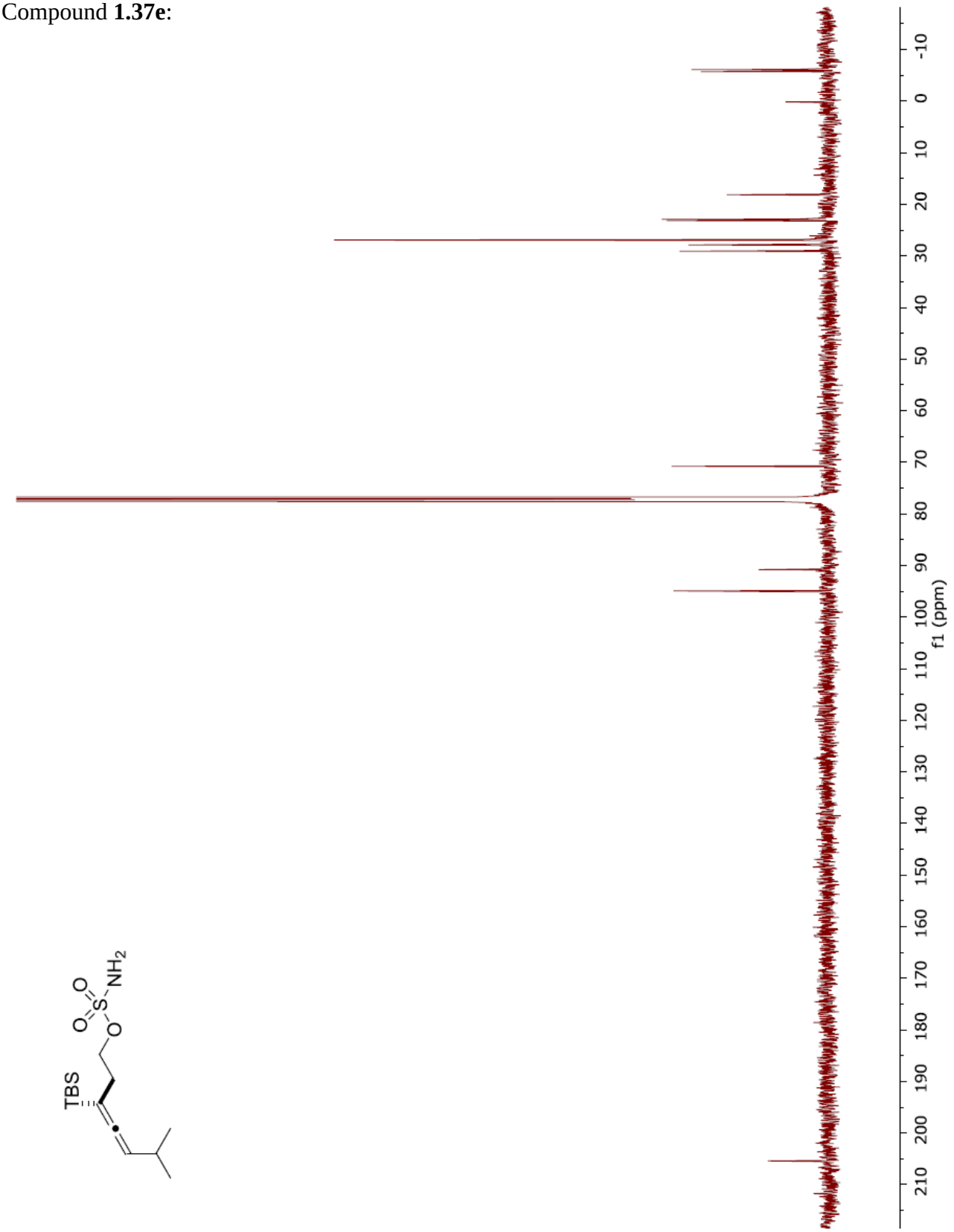
Compound **1.37d**:



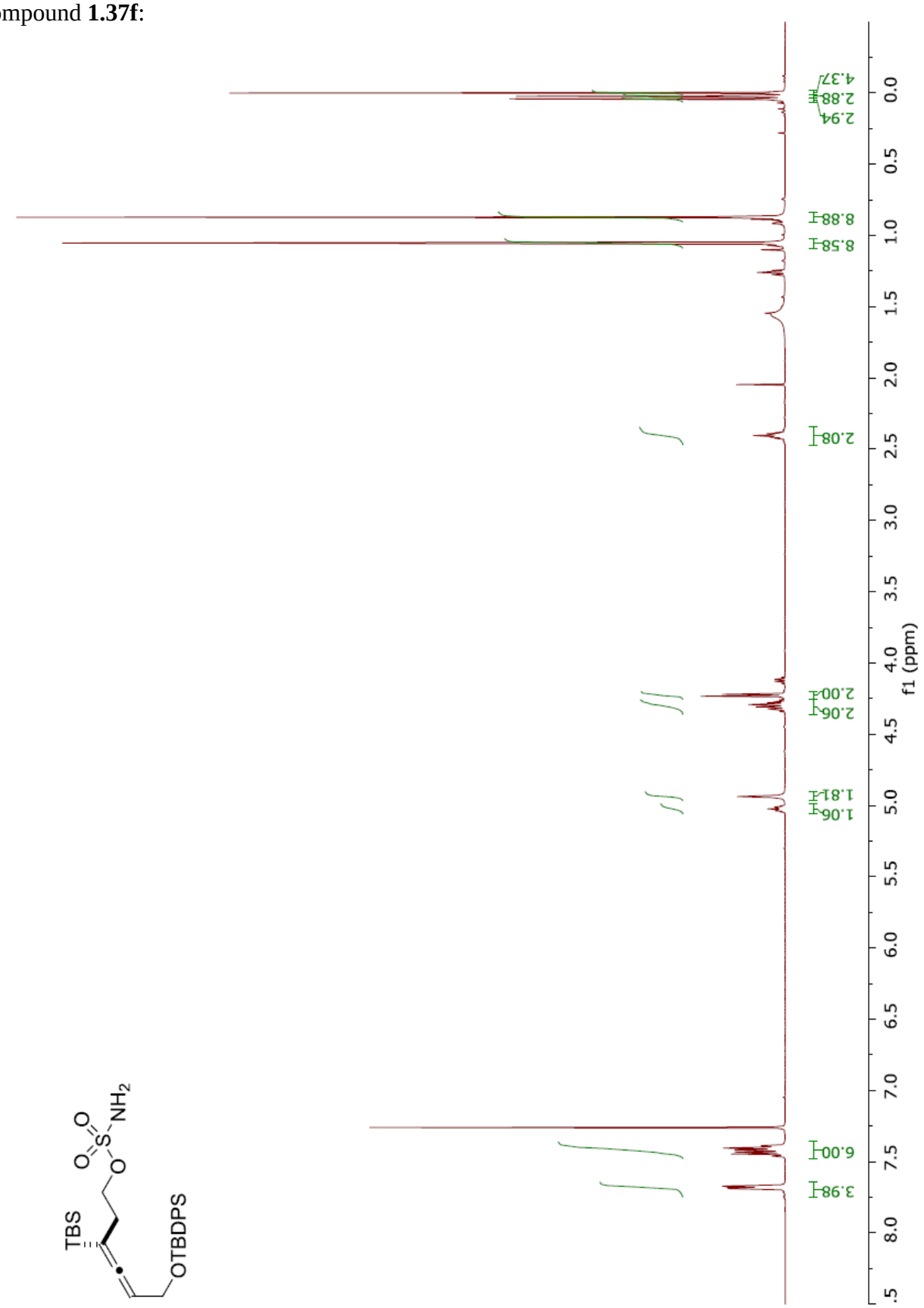
Compound **1.37e**:



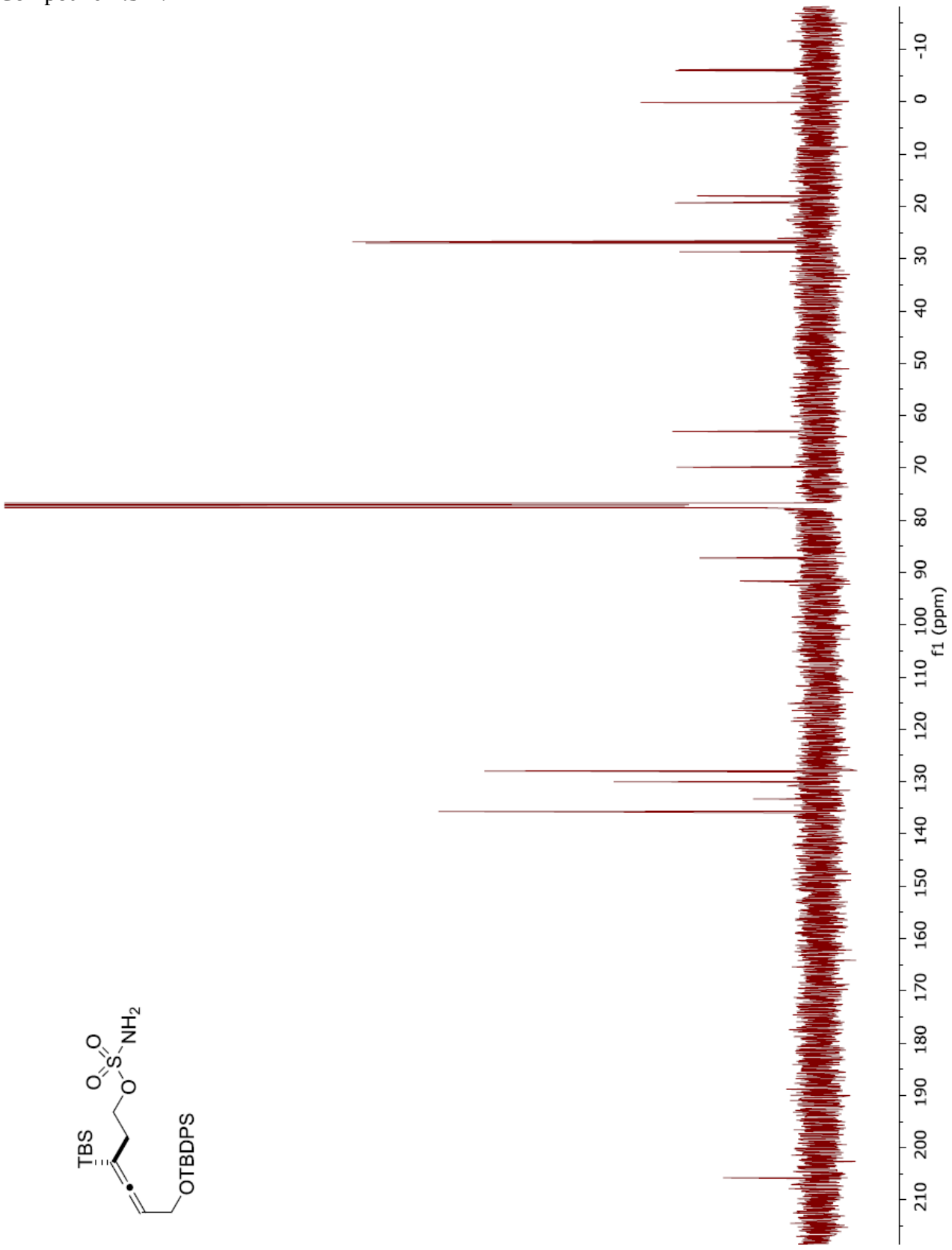
Compound **1.37e**:



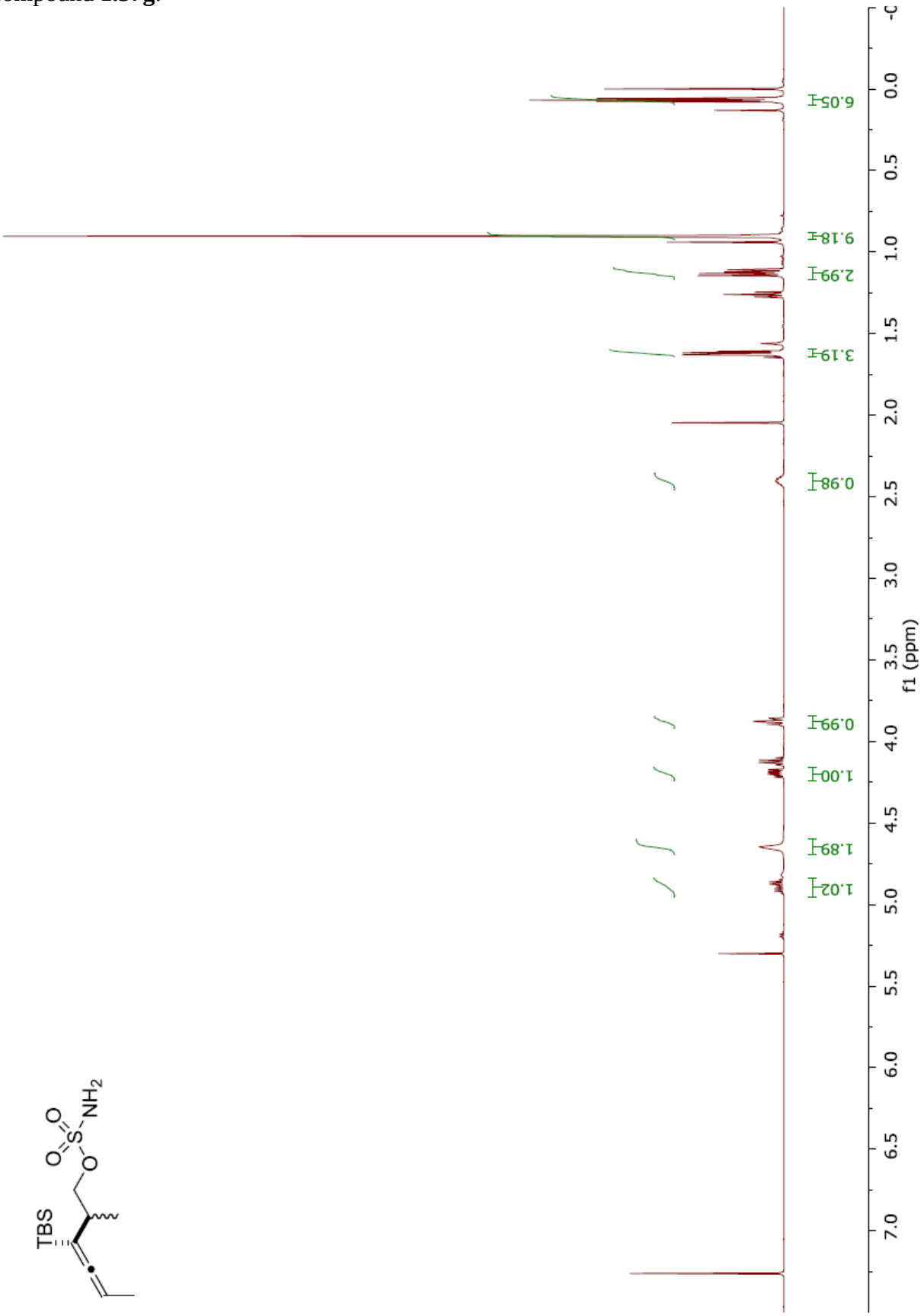
Compound **1.37f**:



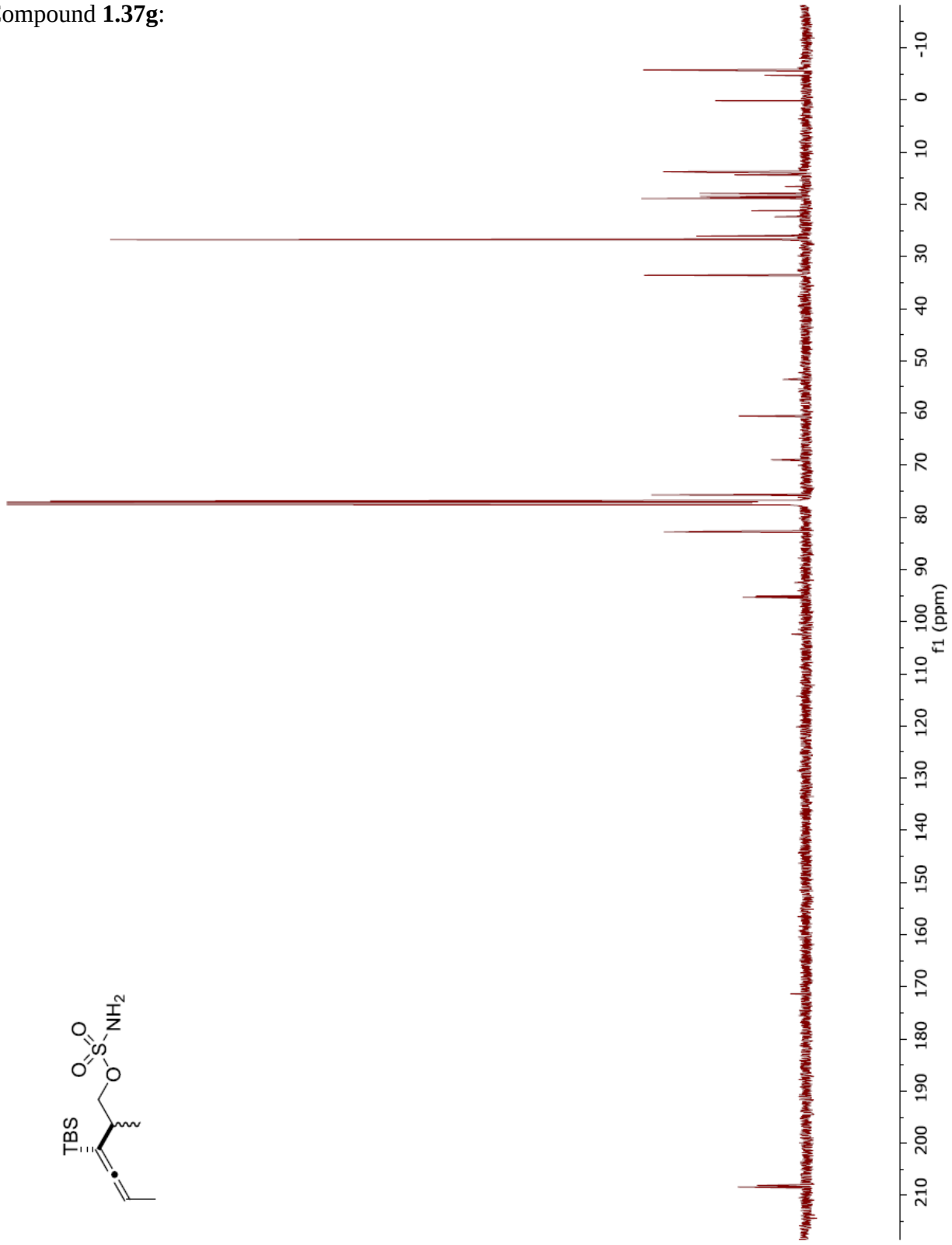
Compound **1.37f**:



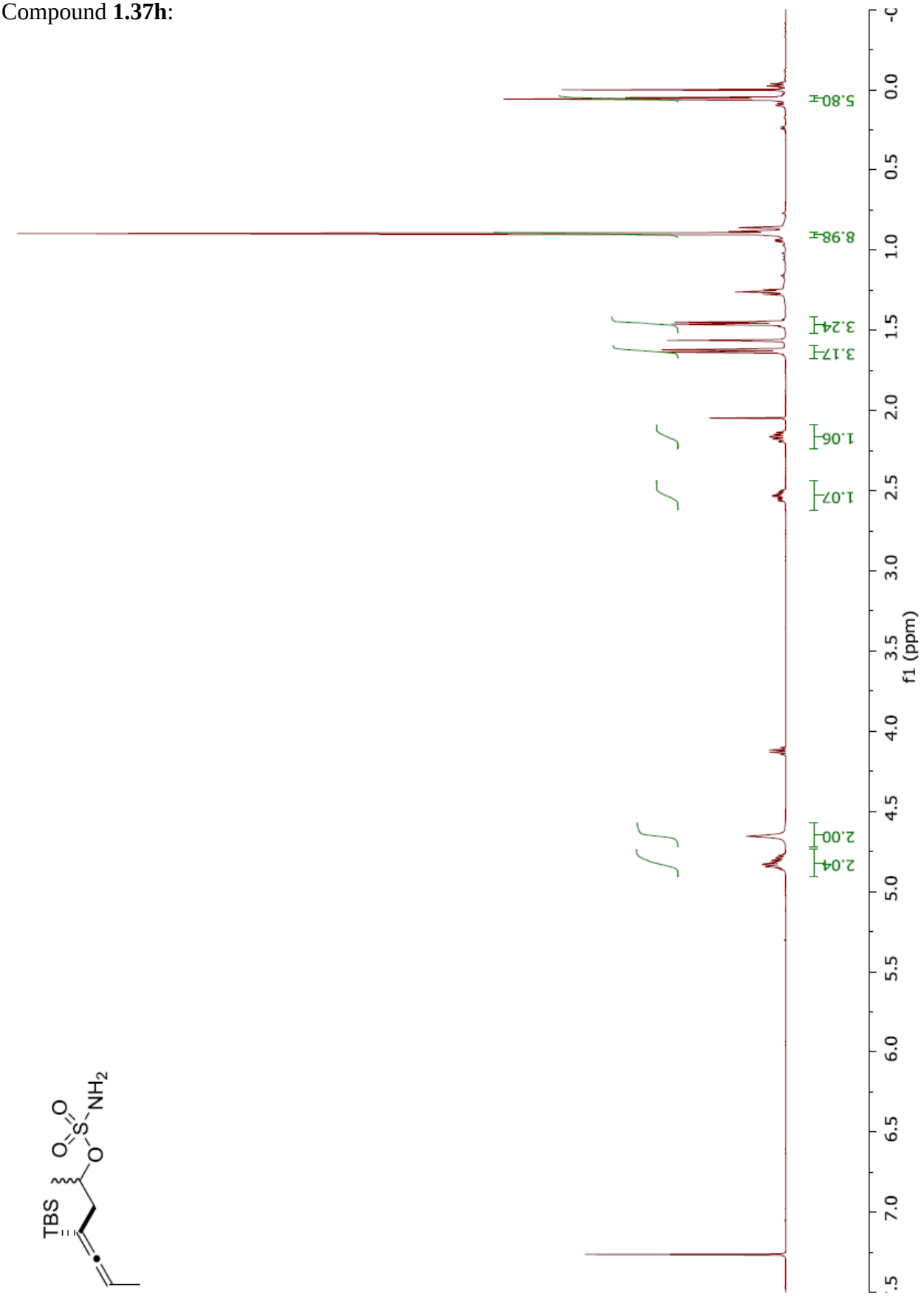
Compound **1.37g**:



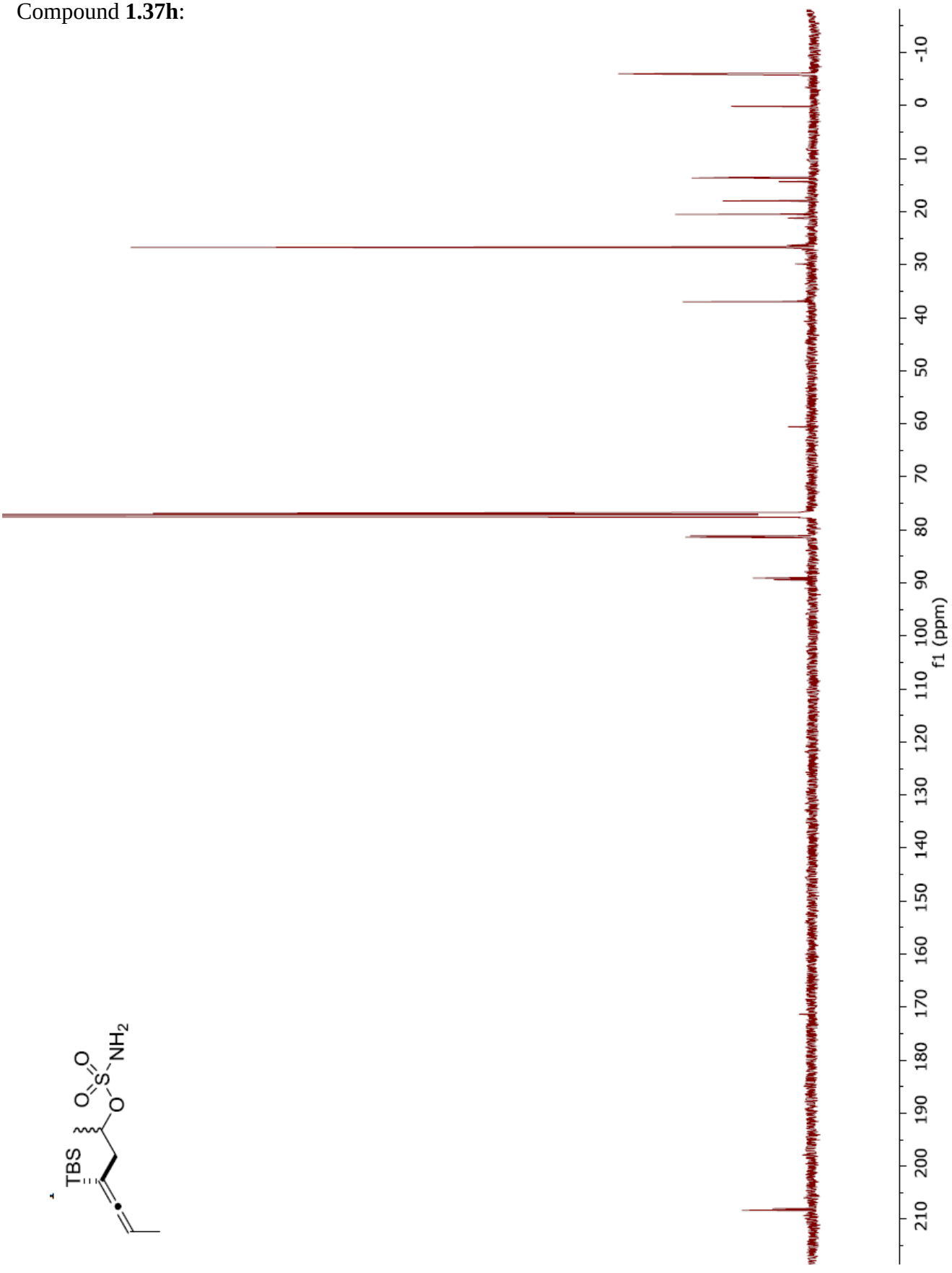
Compound **1.37g**:



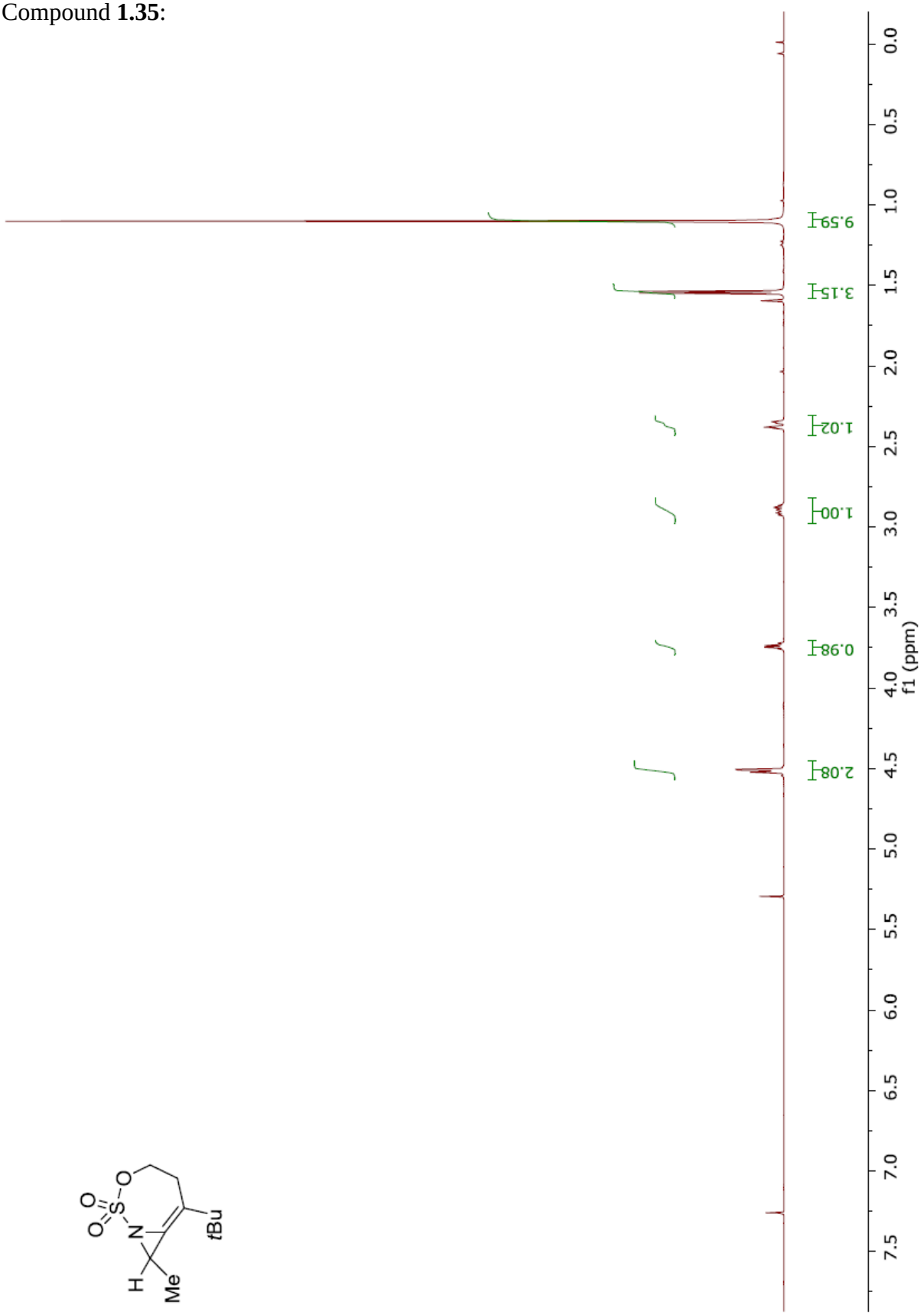
Compound **1.37h**:



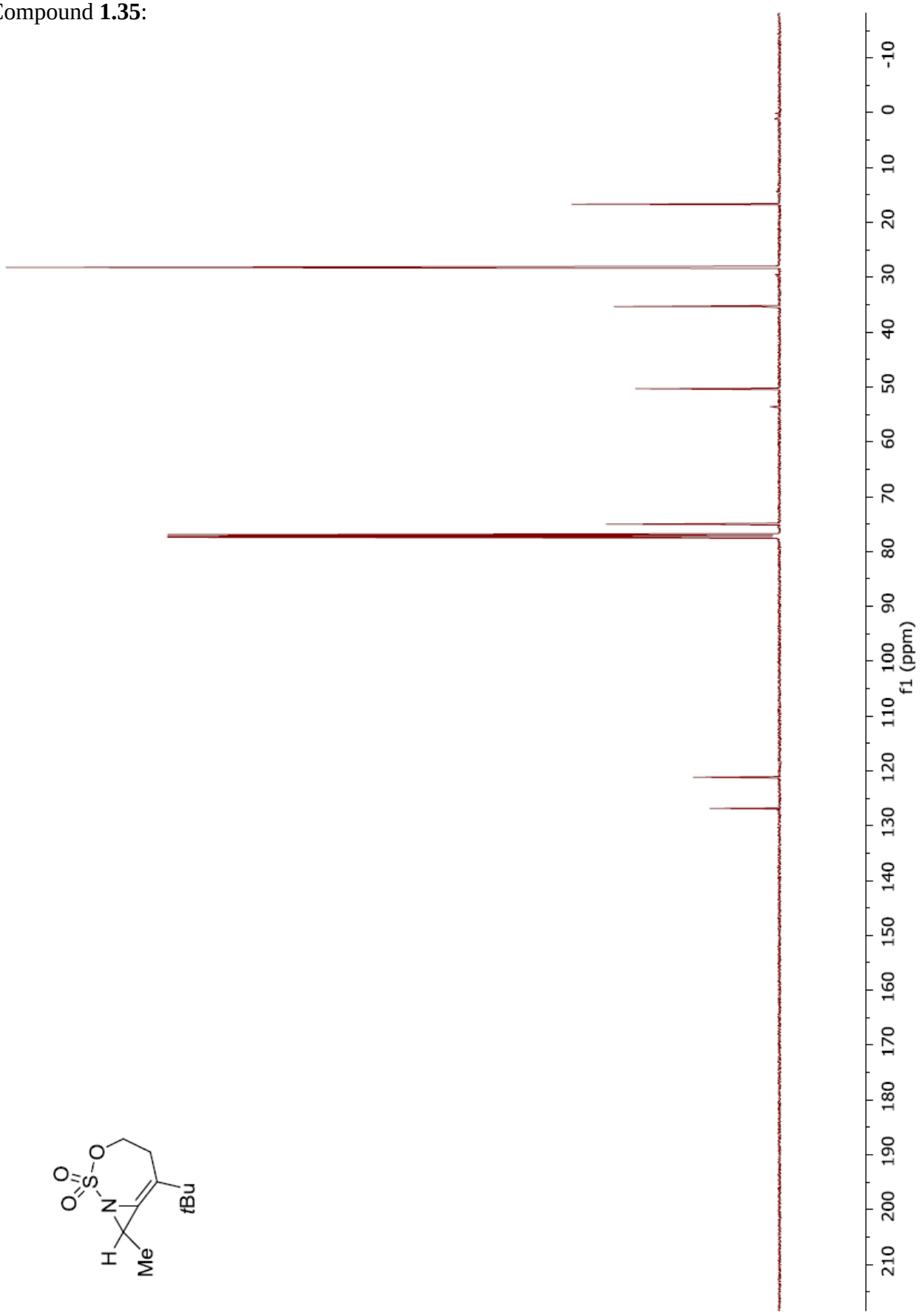
Compound **1.37h**:



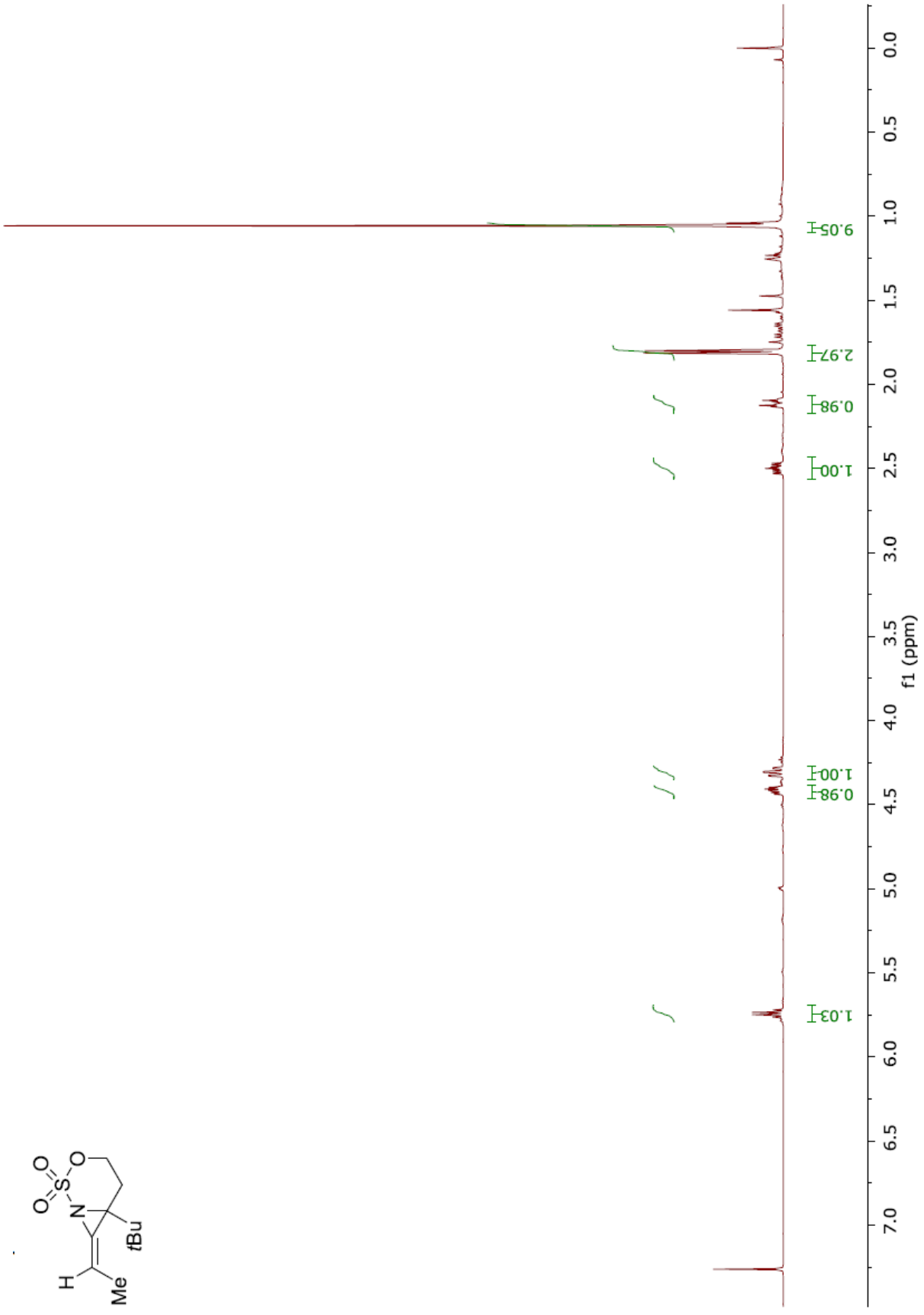
Compound **1.35**:



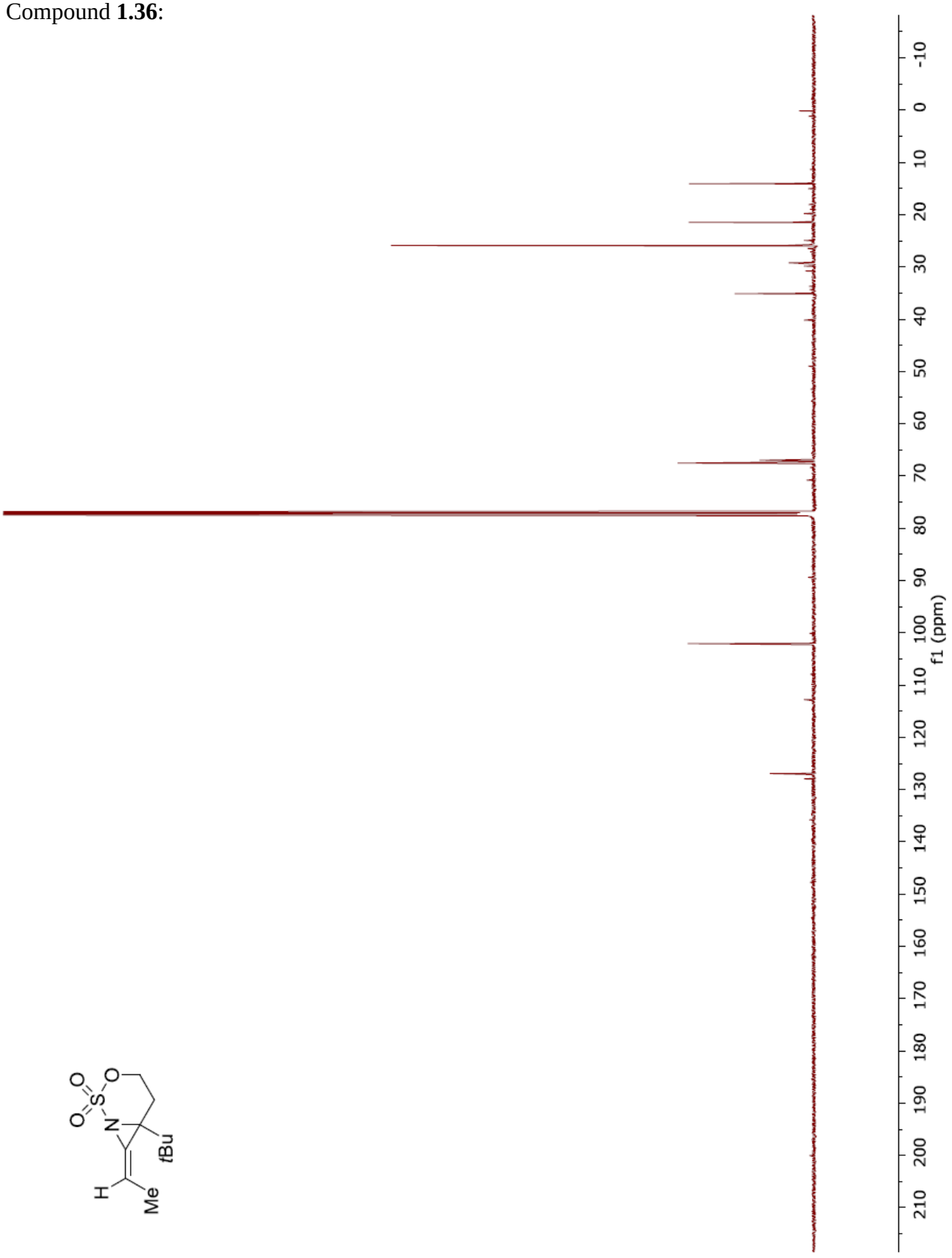
Compound **1.35**:



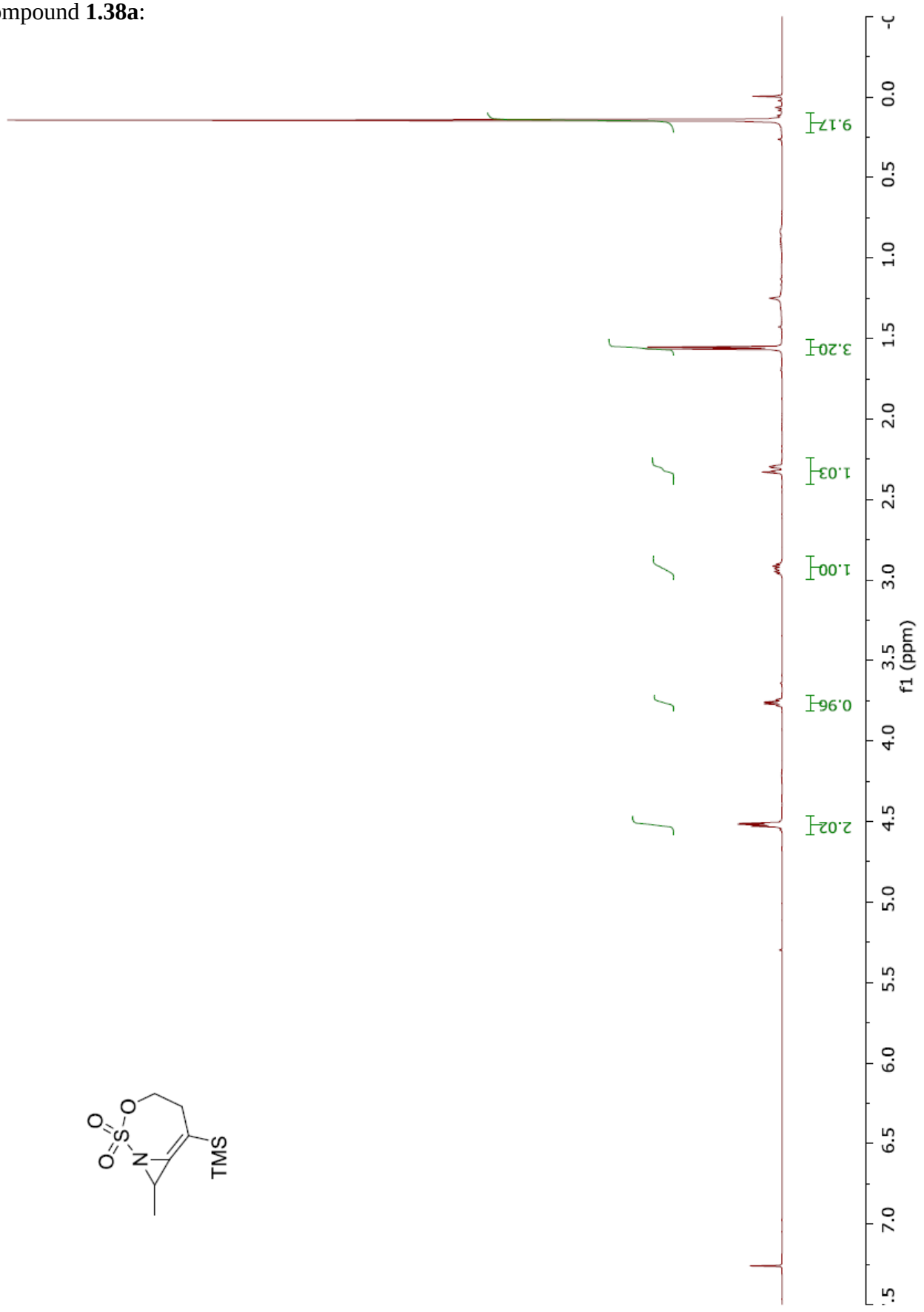
Compound **1.36**:



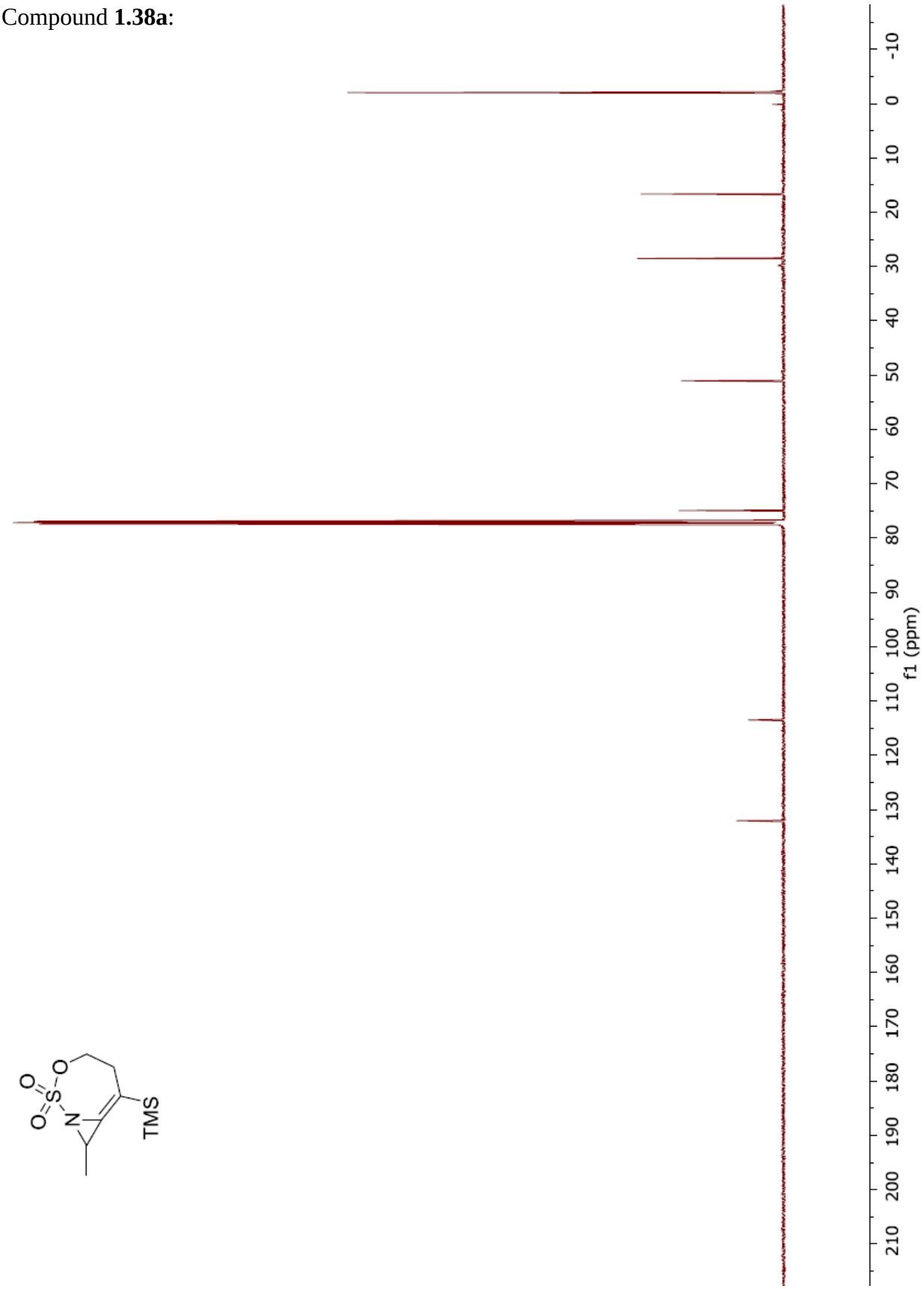
Compound **1.36**:



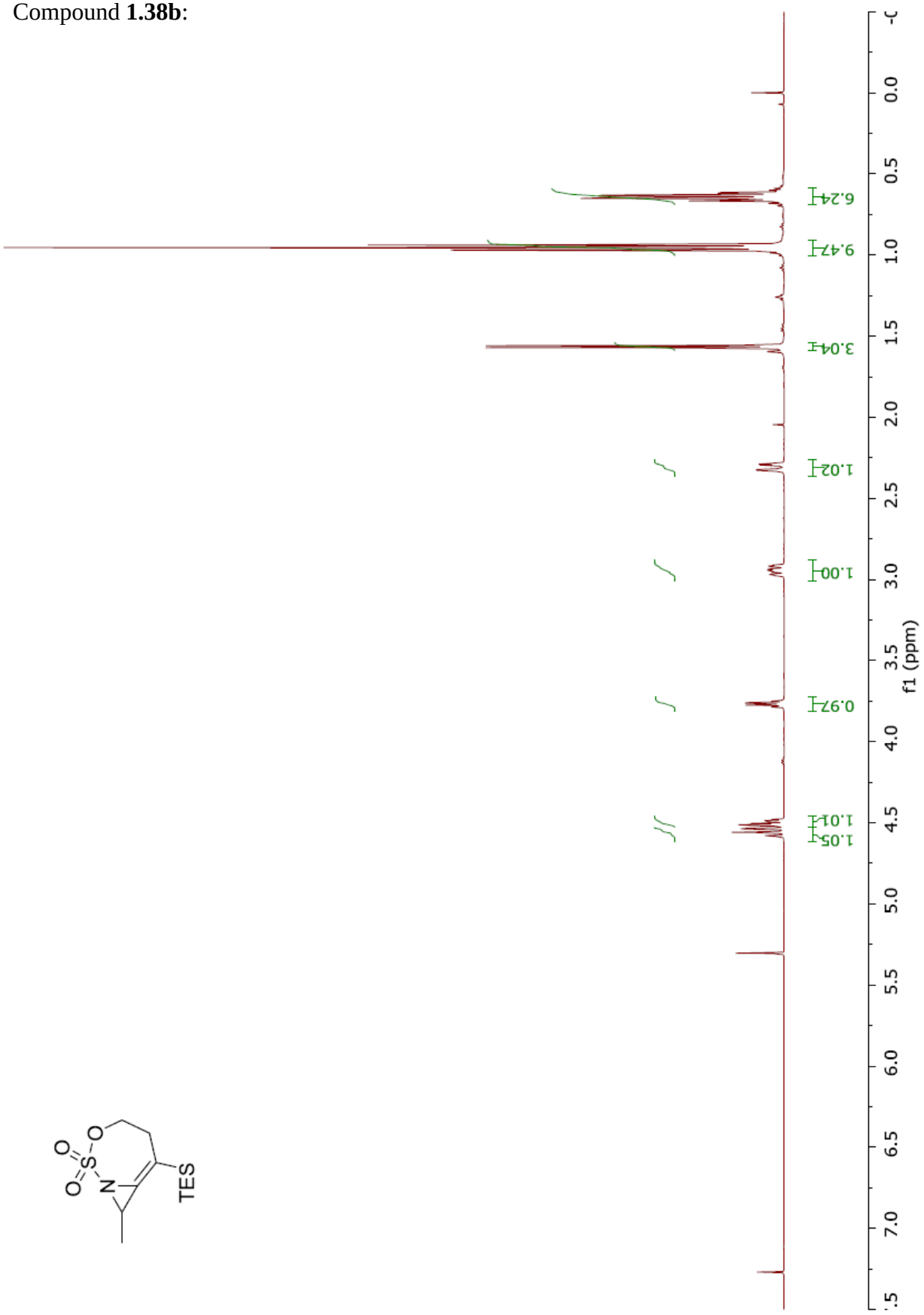
Compound **1.38a**:



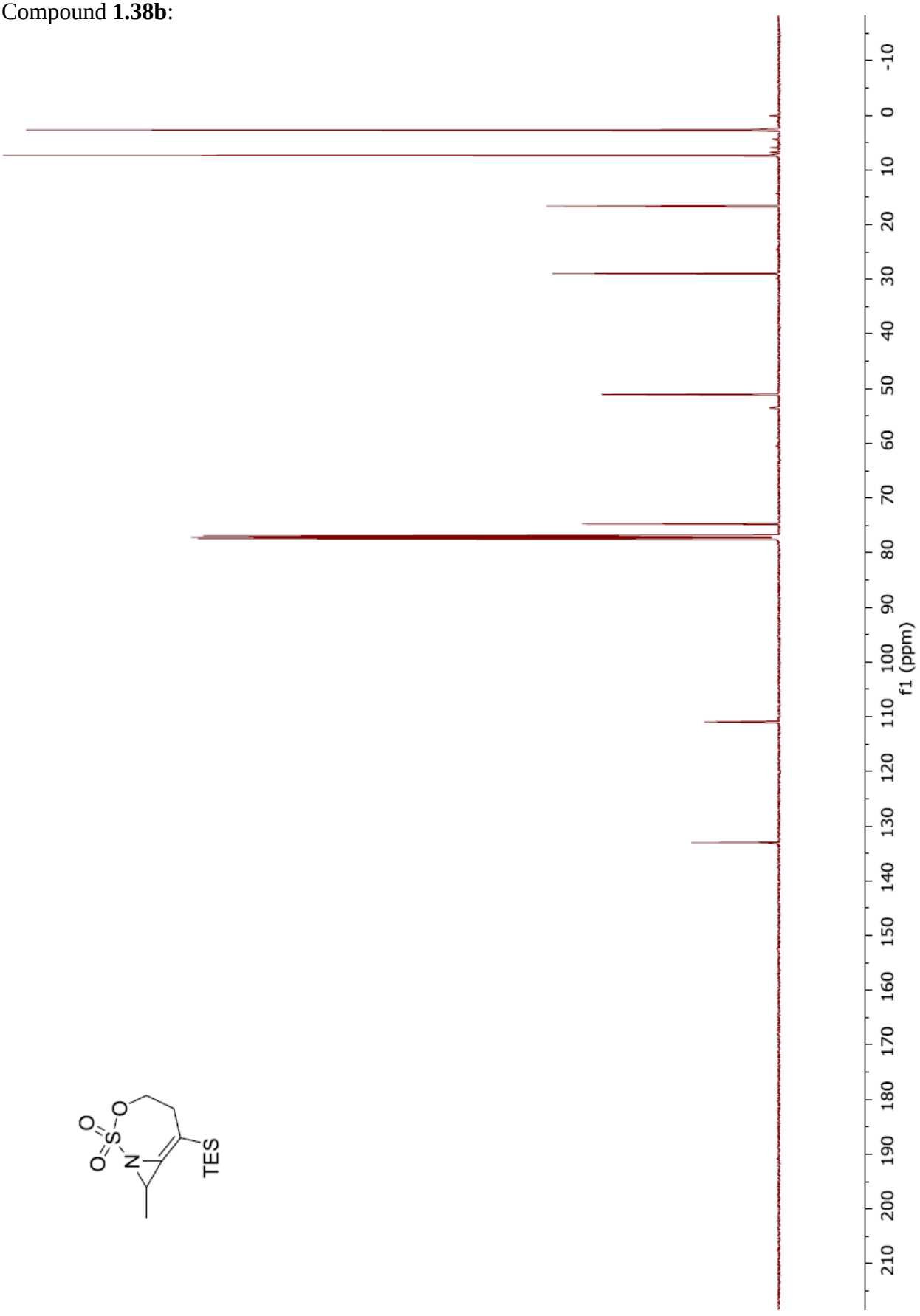
Compound **1.38a**:



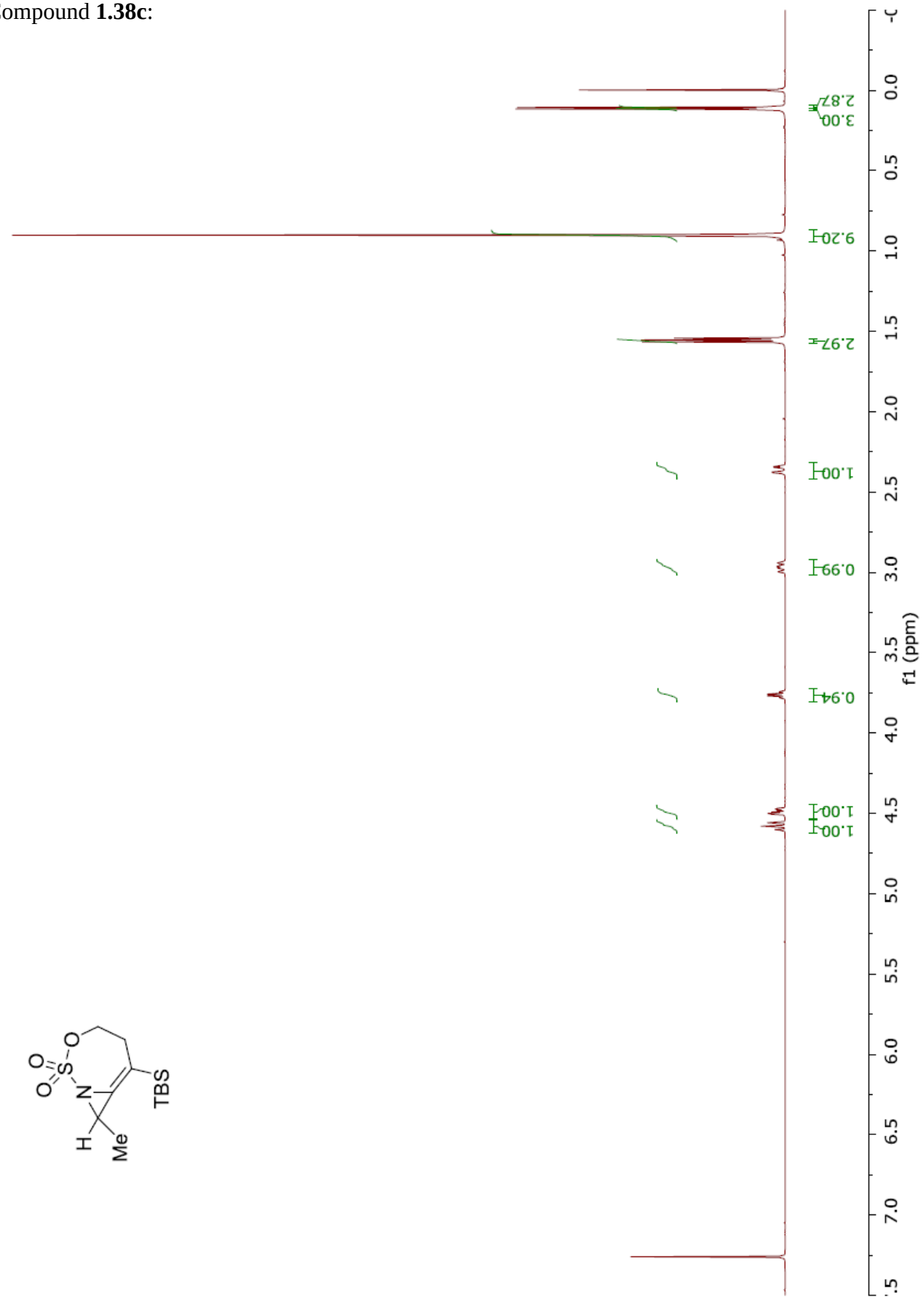
Compound **1.38b**:



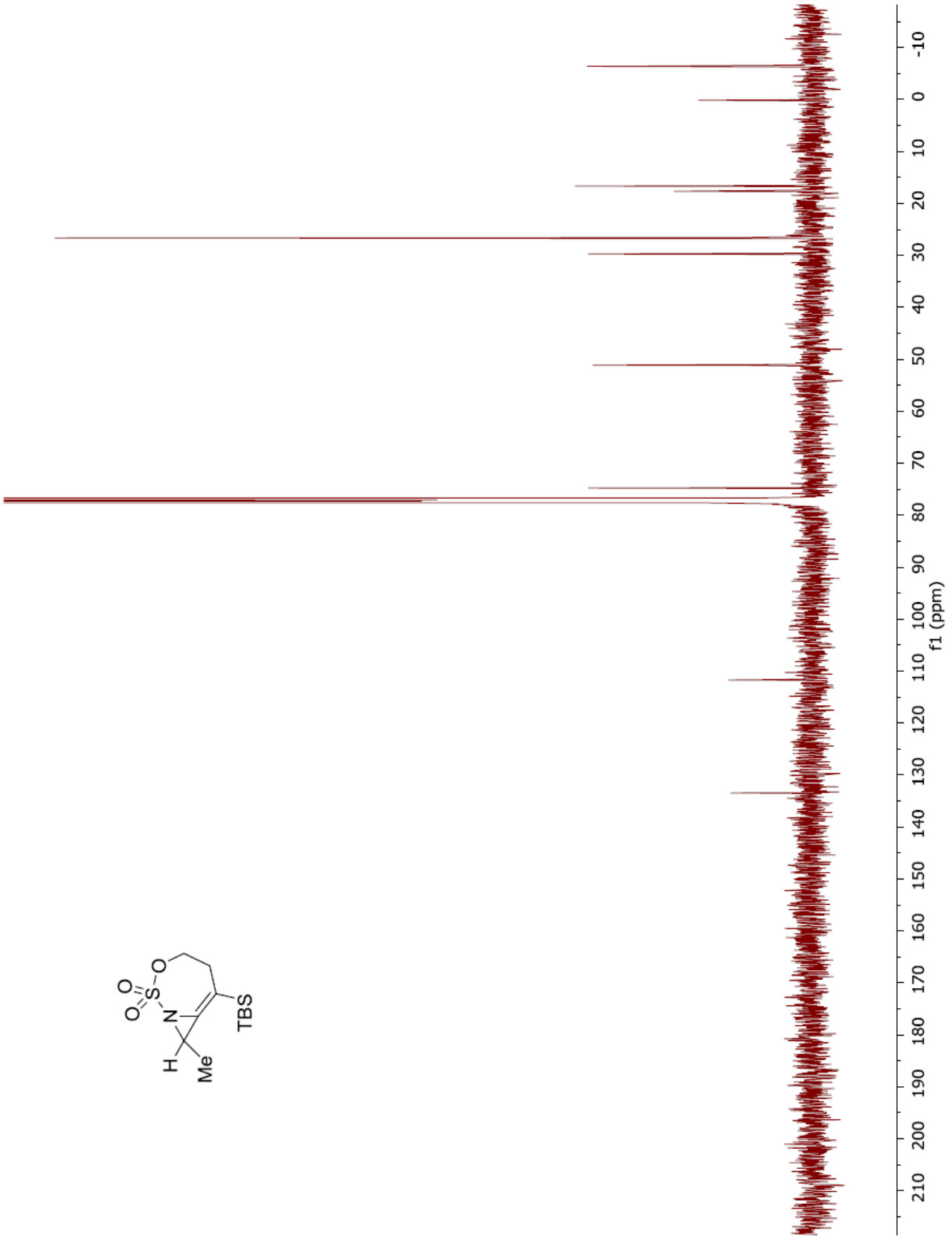
Compound **1.38b**:



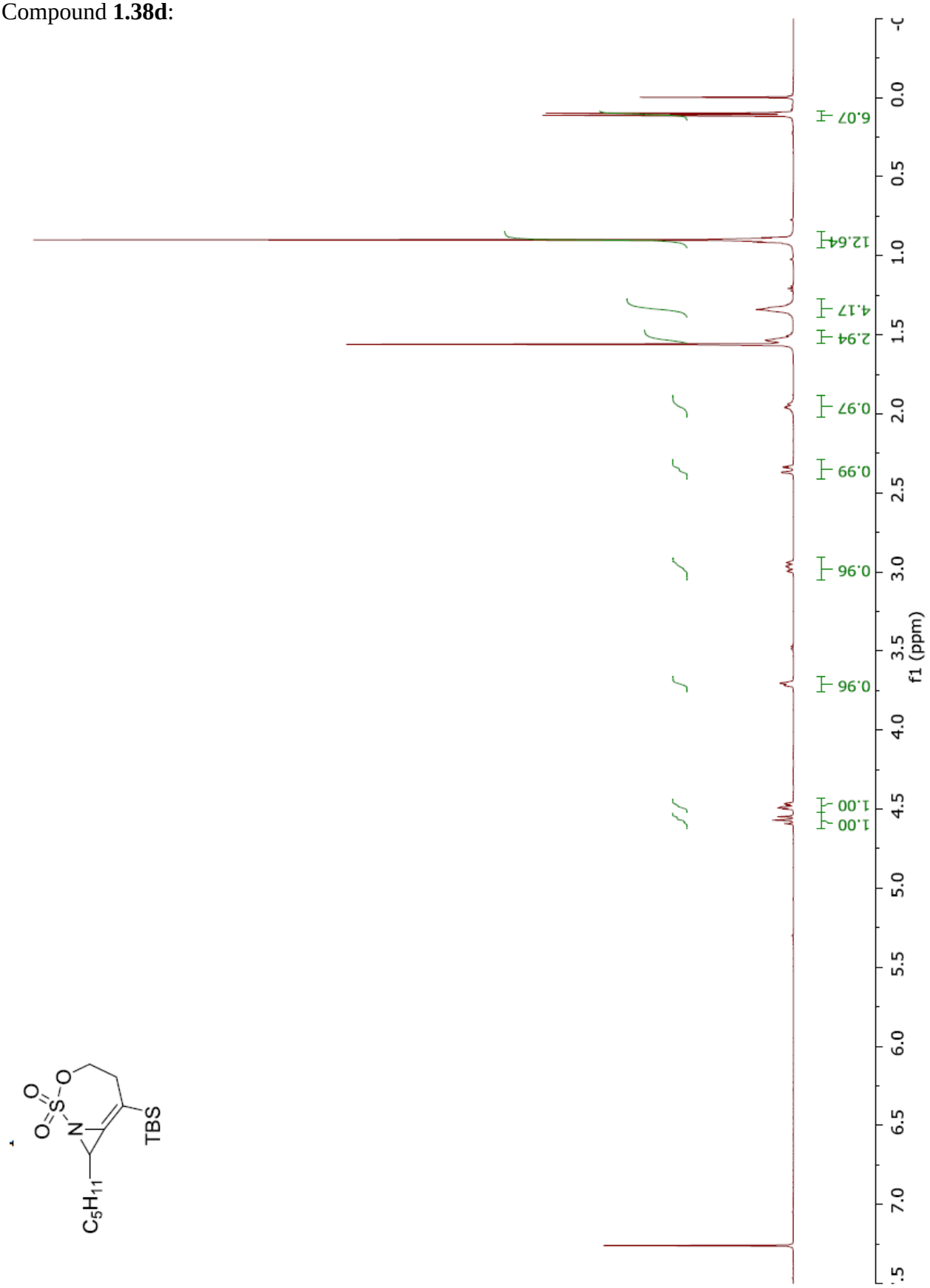
Compound **1.38c**:



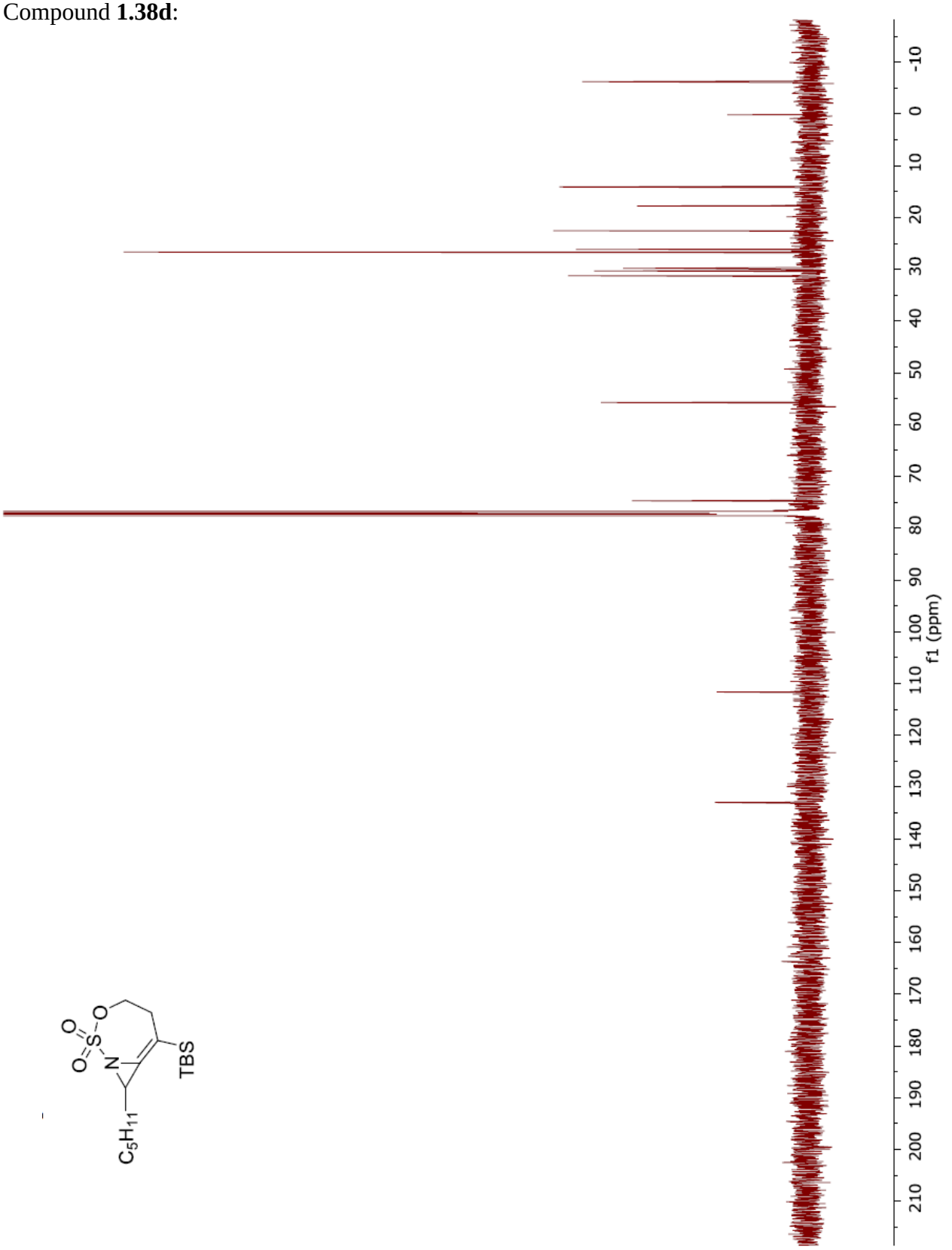
Compound **1.38c**:



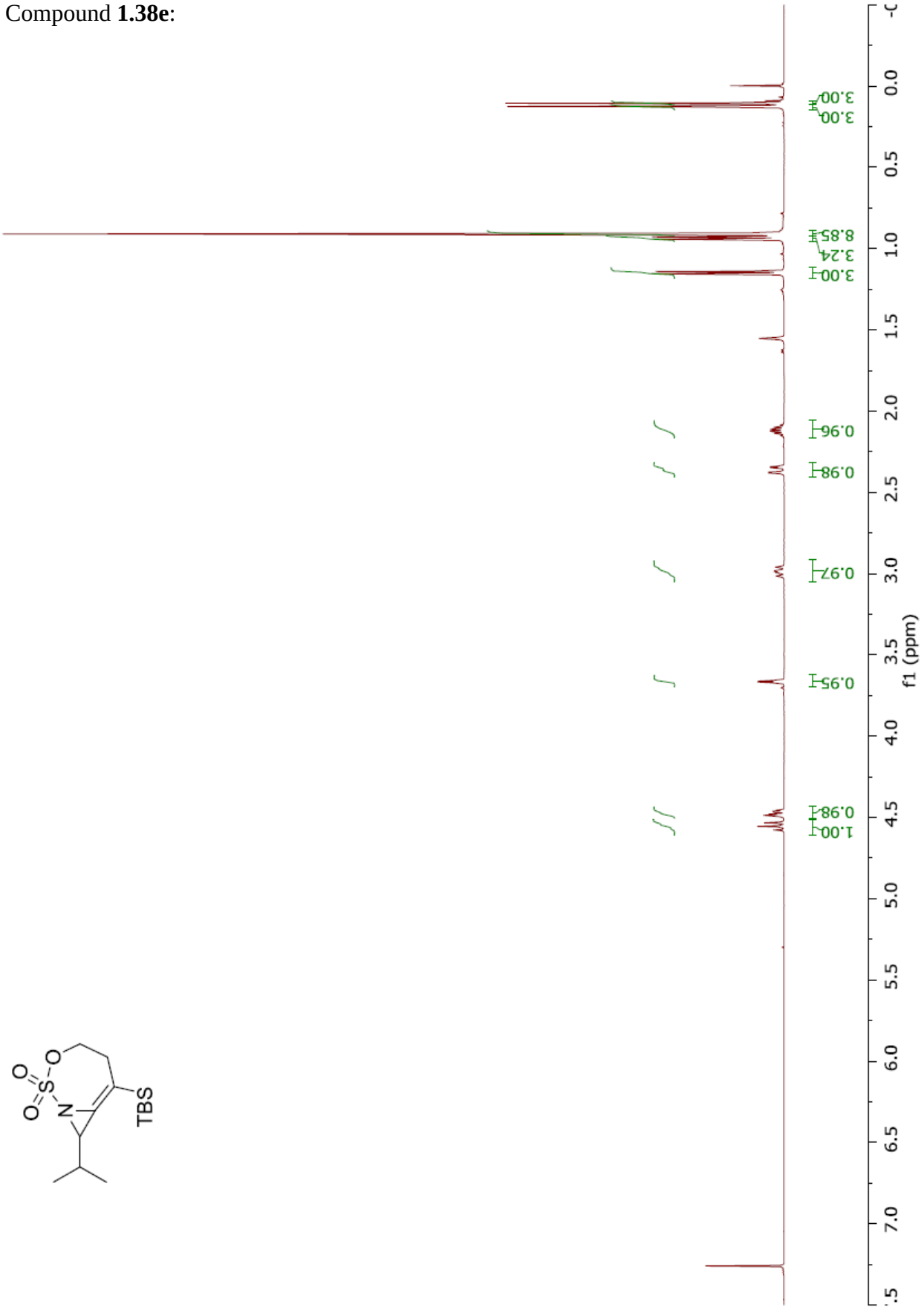
Compound **1.38d**:



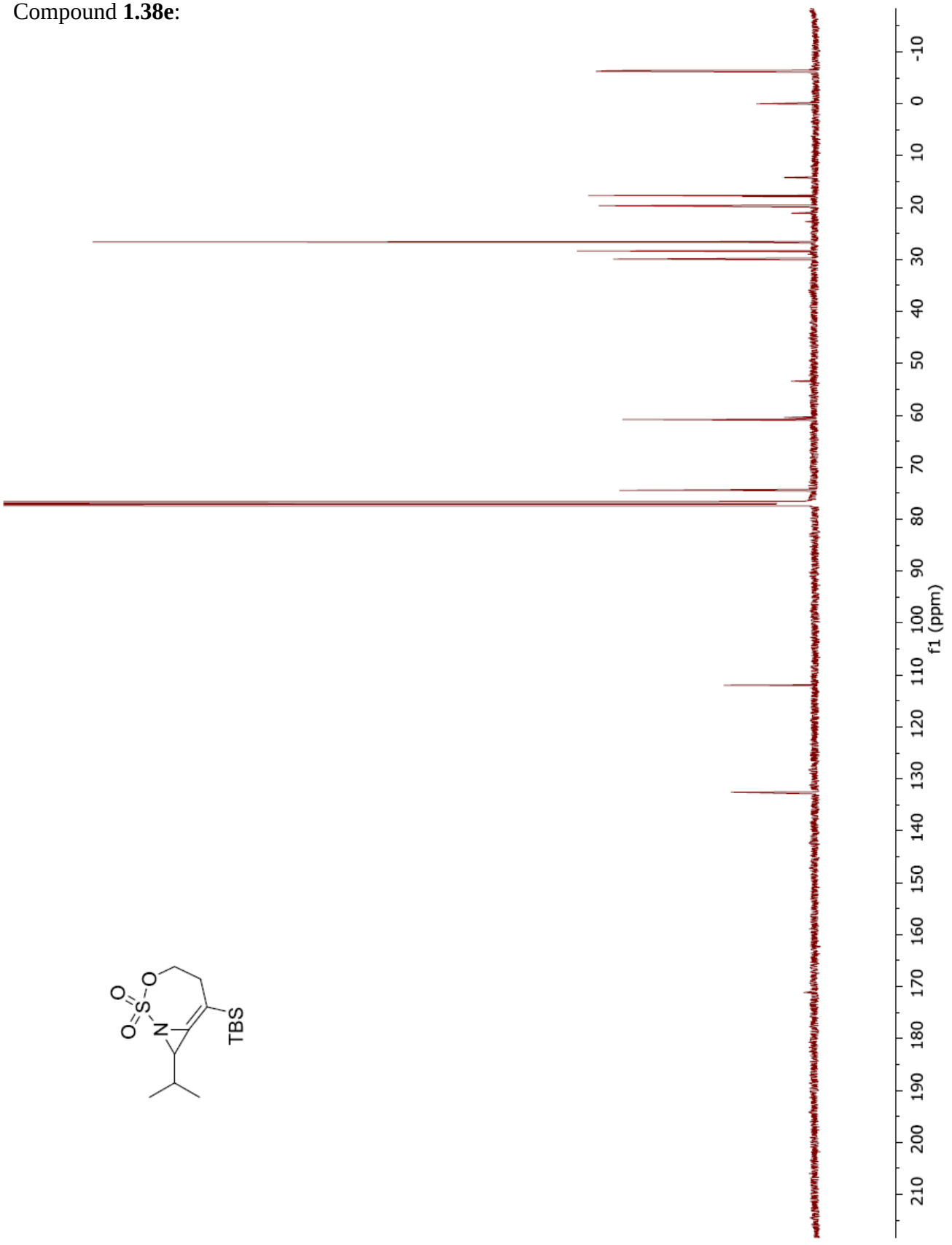
Compound **1.38d**:



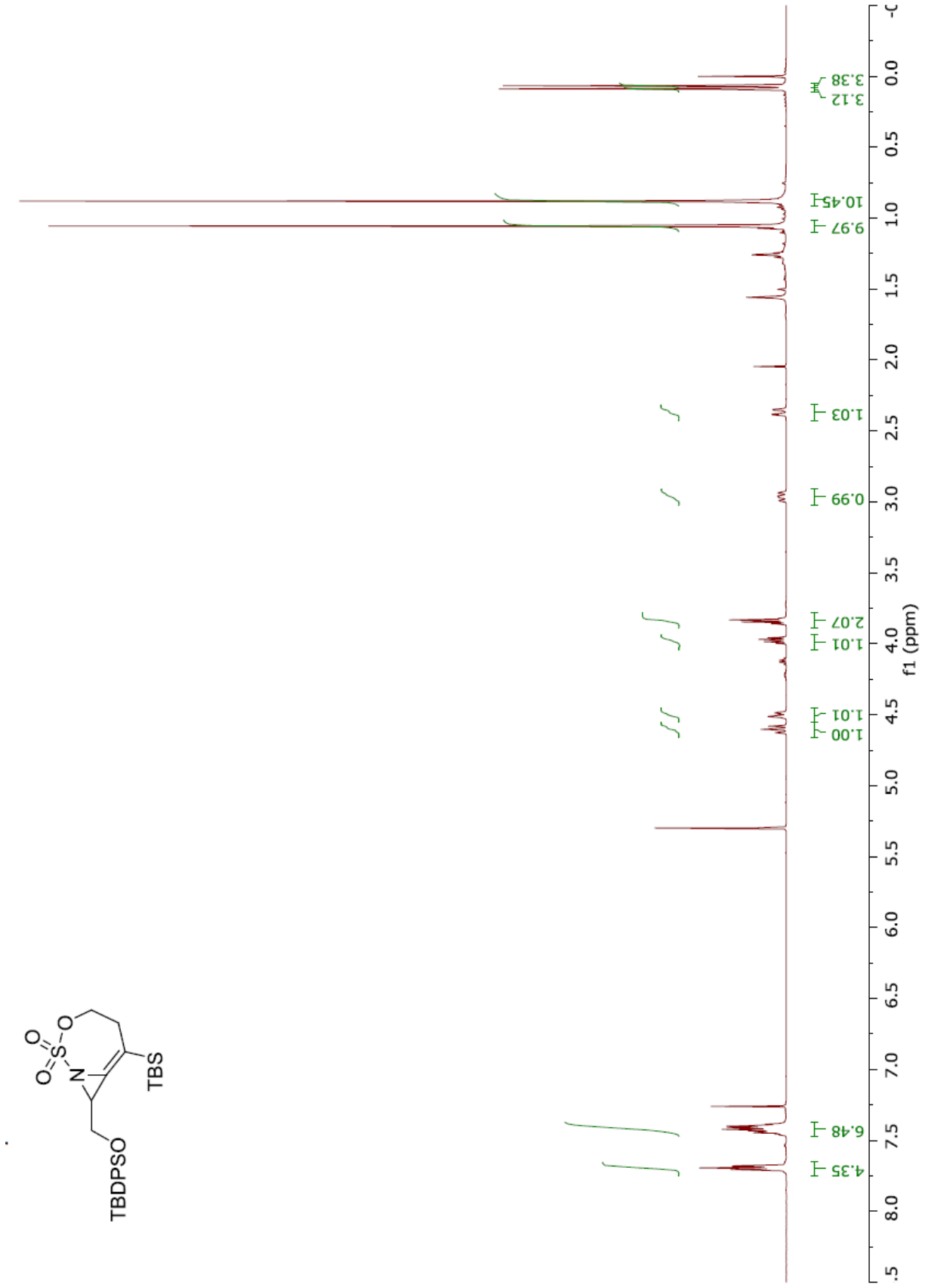
Compound **1.38e**:



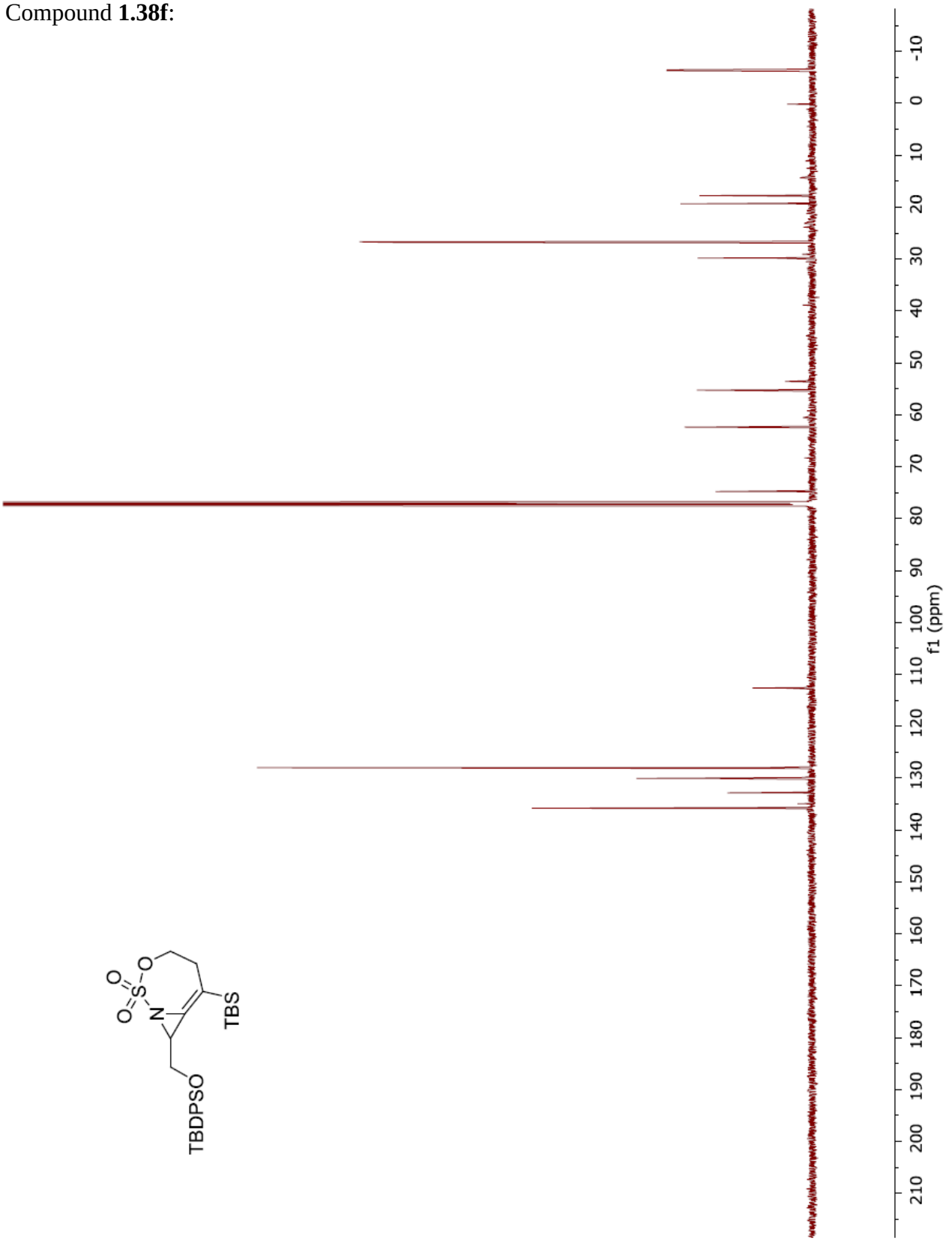
Compound **1.38e**:



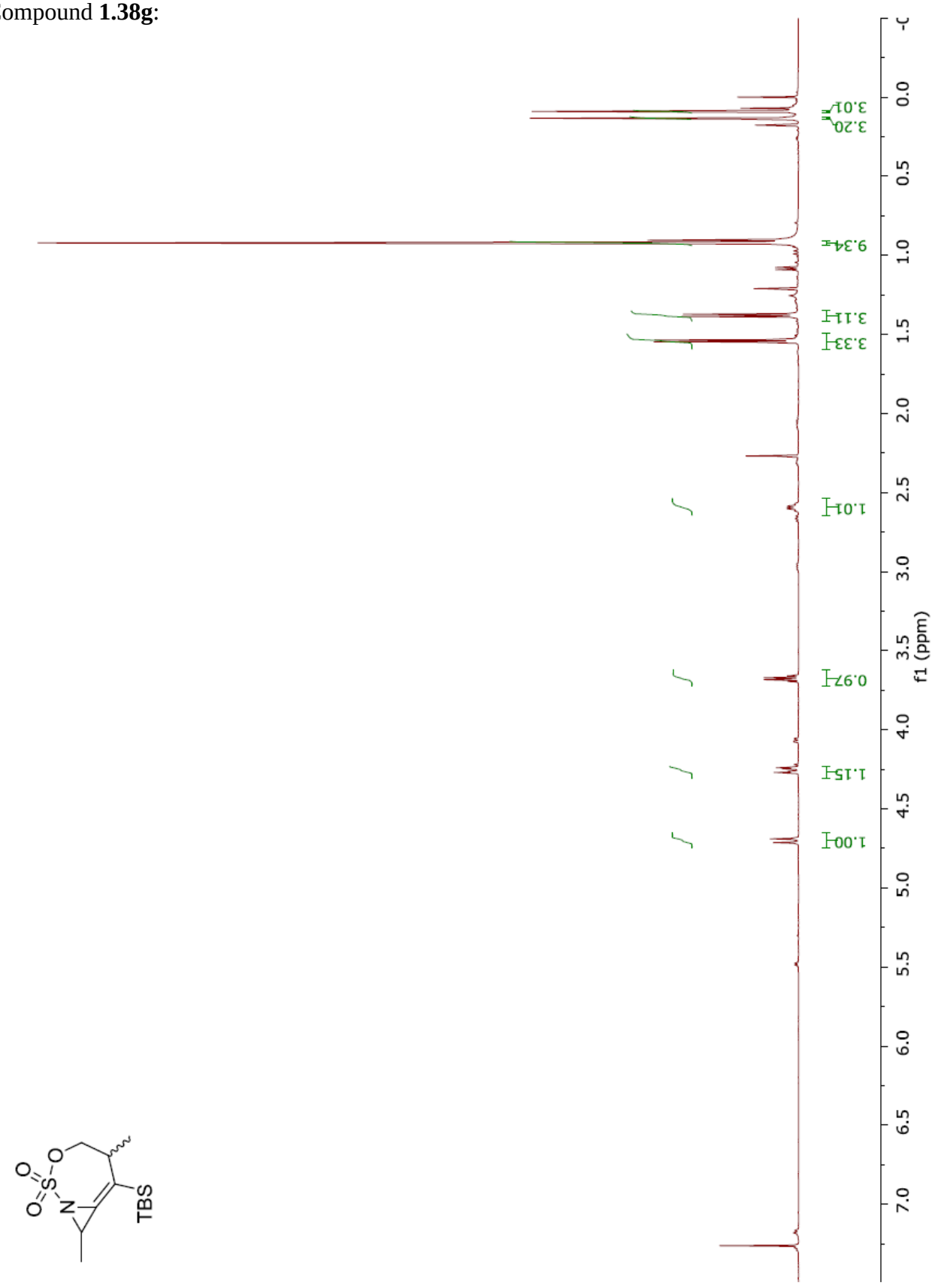
Compound **1.38f**:



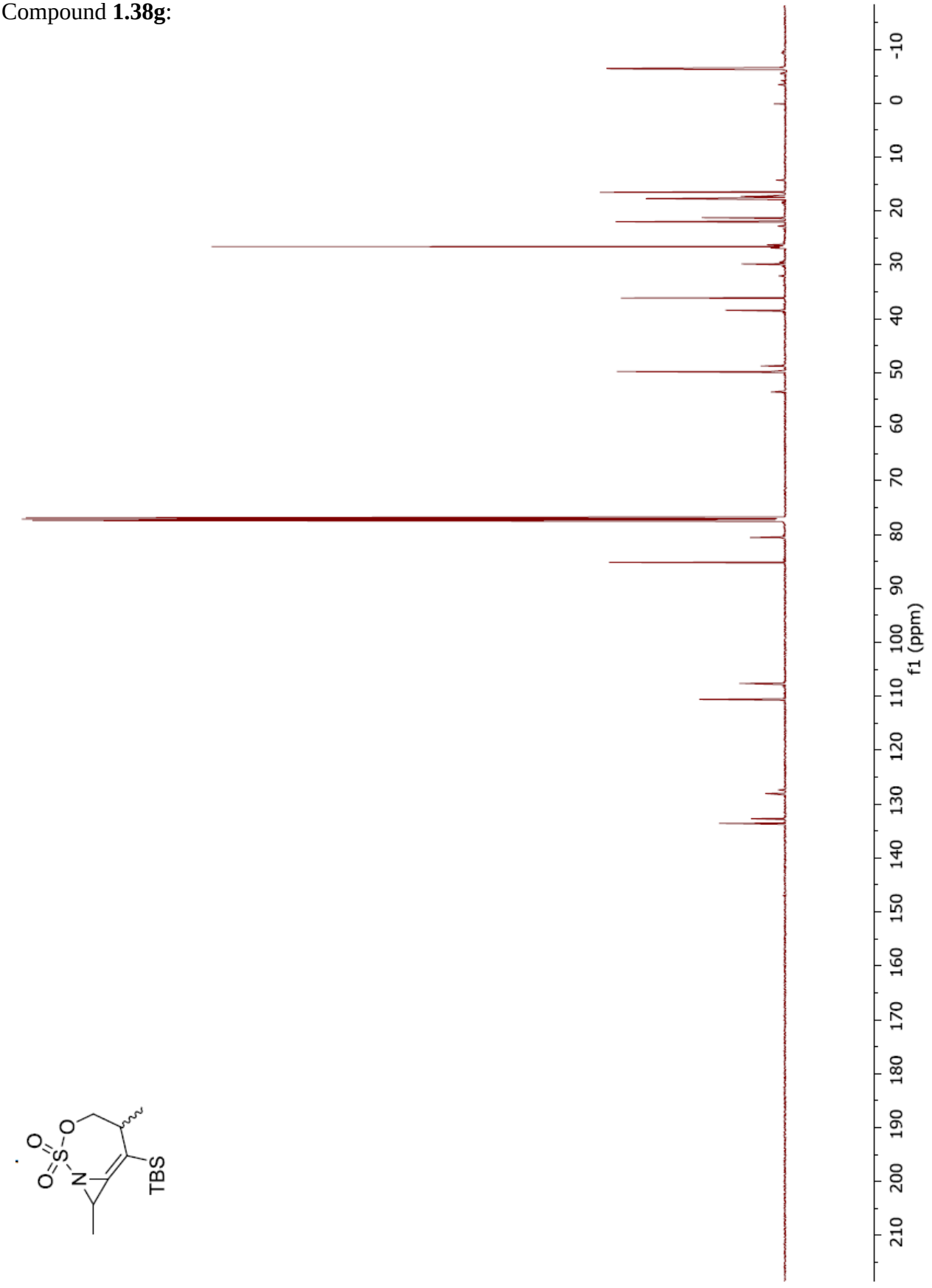
Compound **1.38f**:



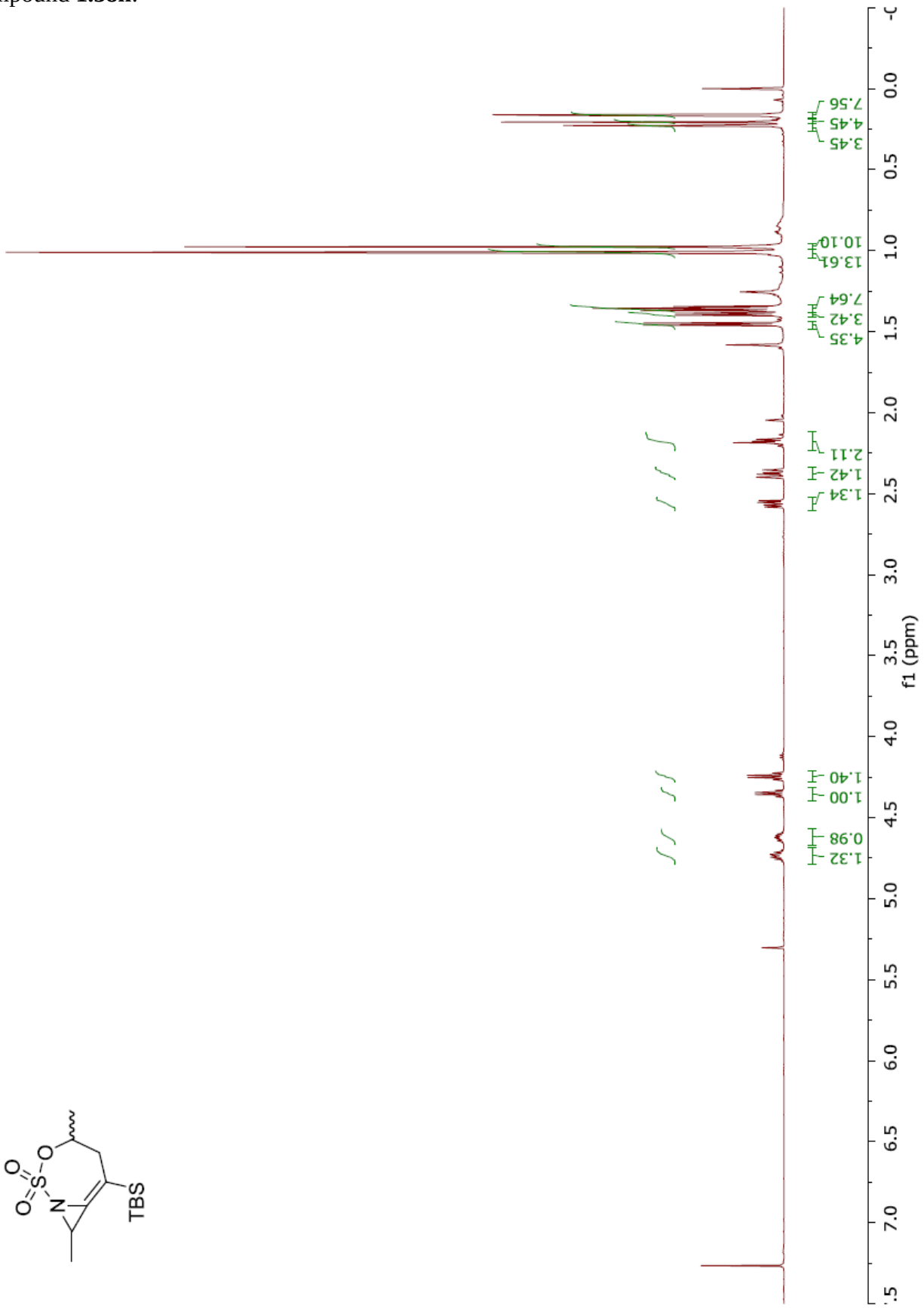
Compound **1.38g**:



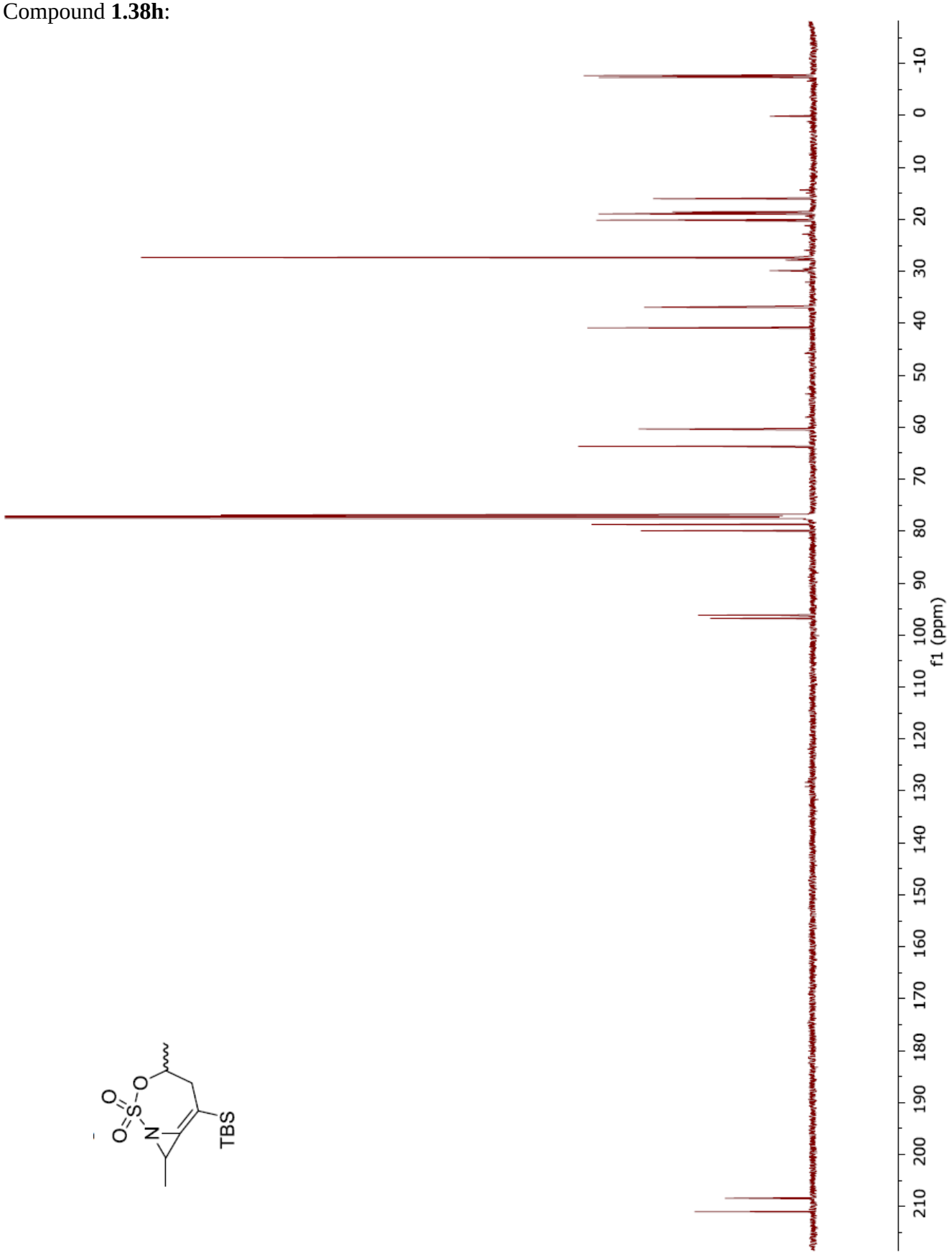
Compound **1.38g**:



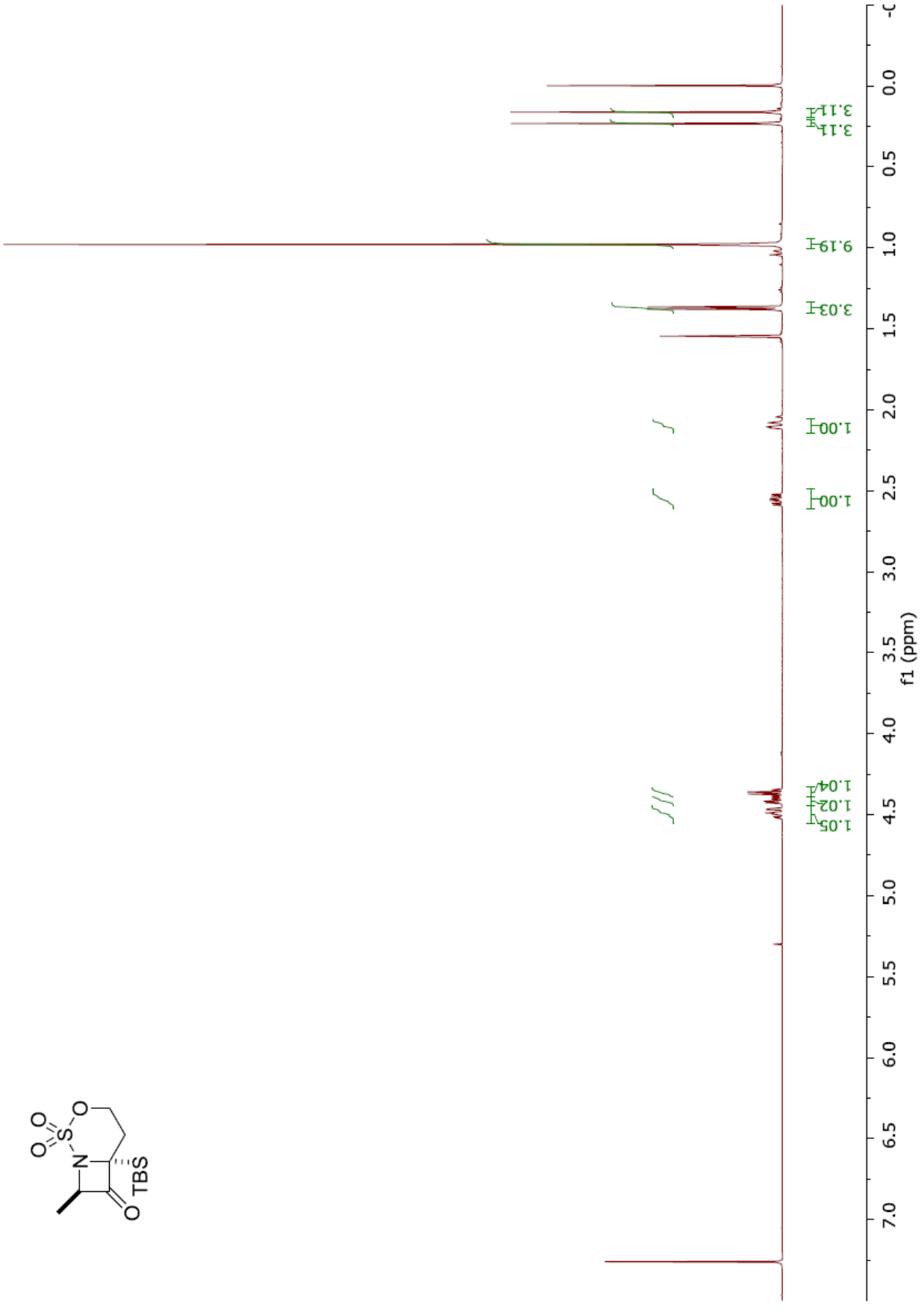
Compound **1.38h**:



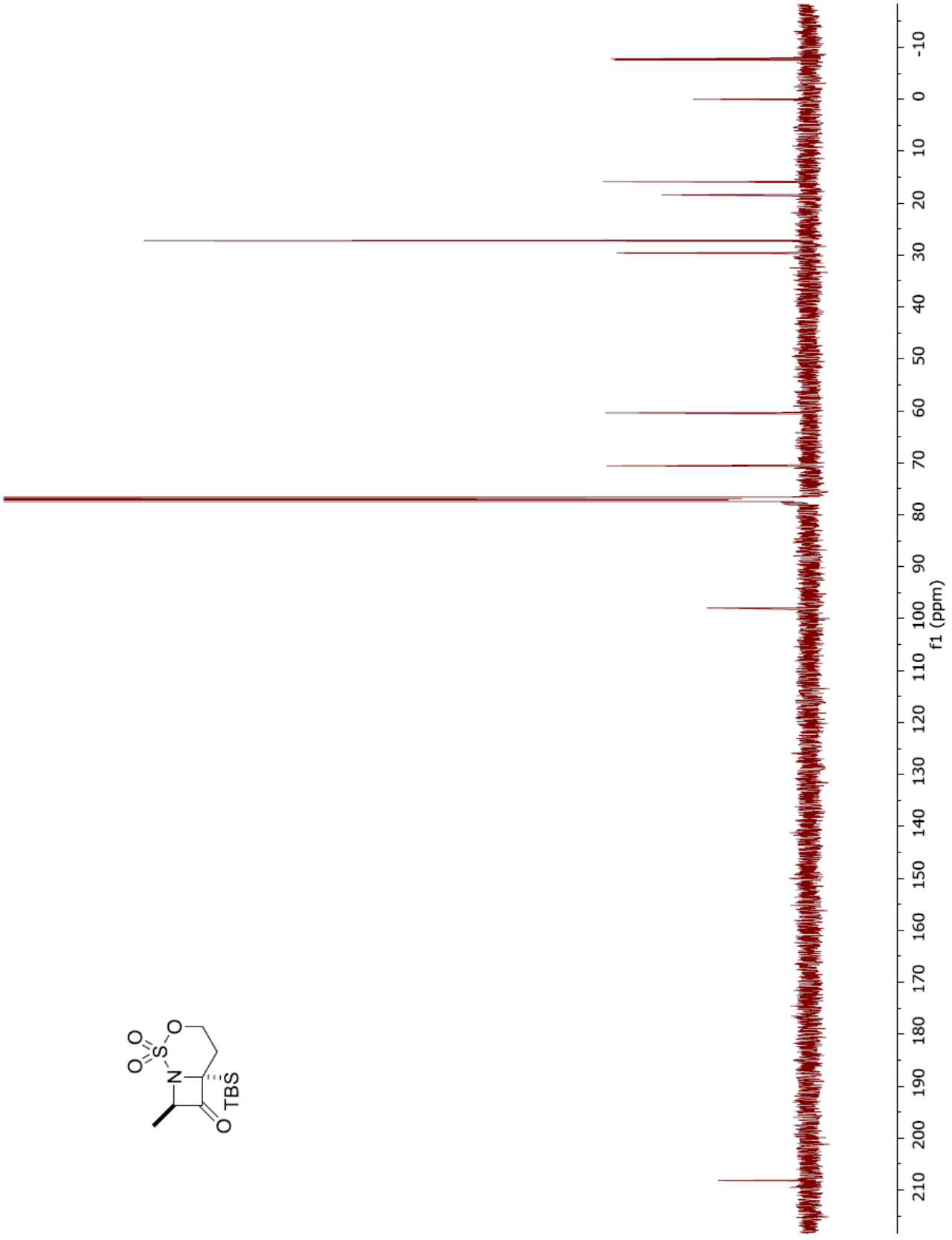
Compound **1.38h**:



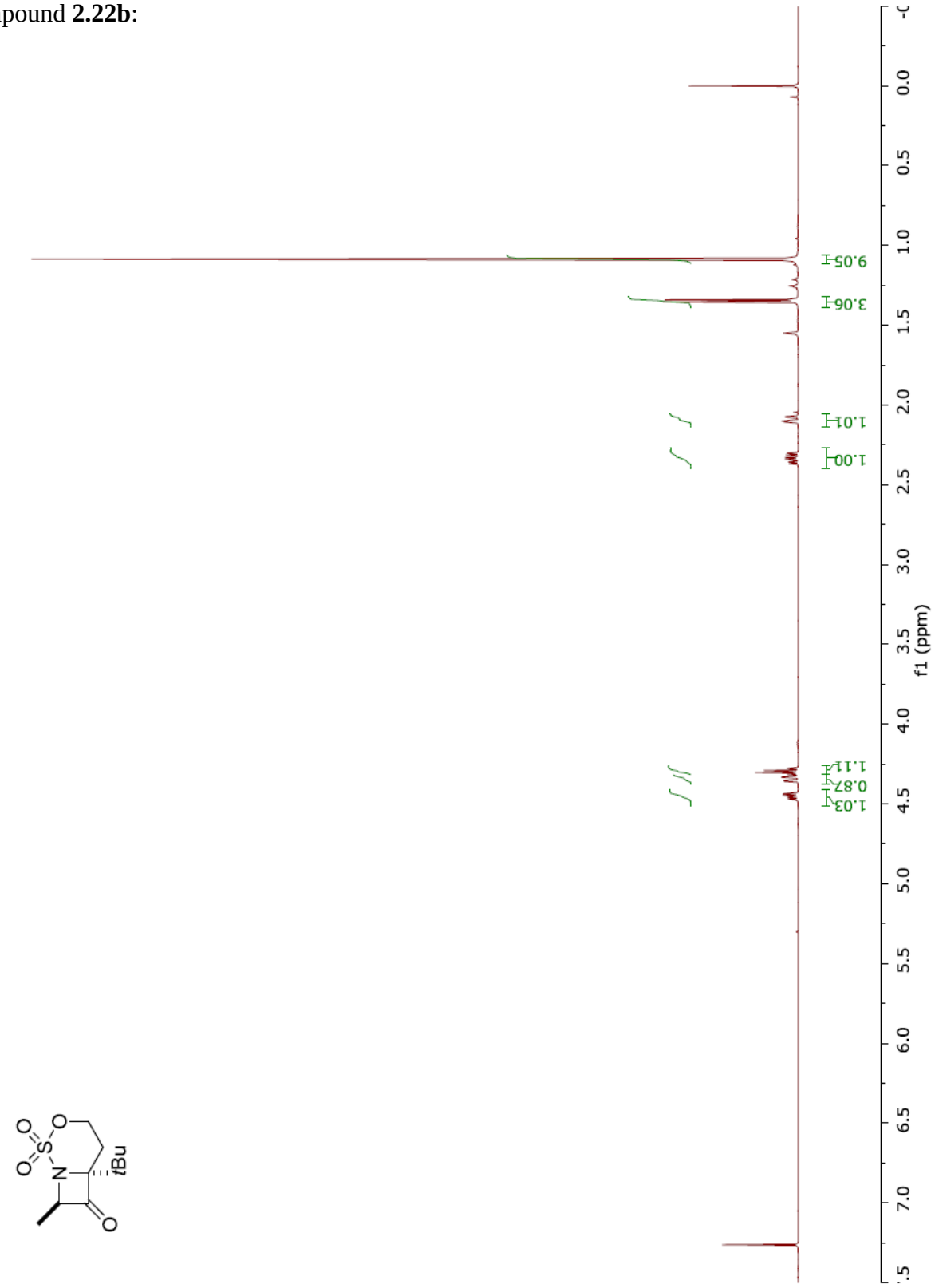
Compound **2.22a**:



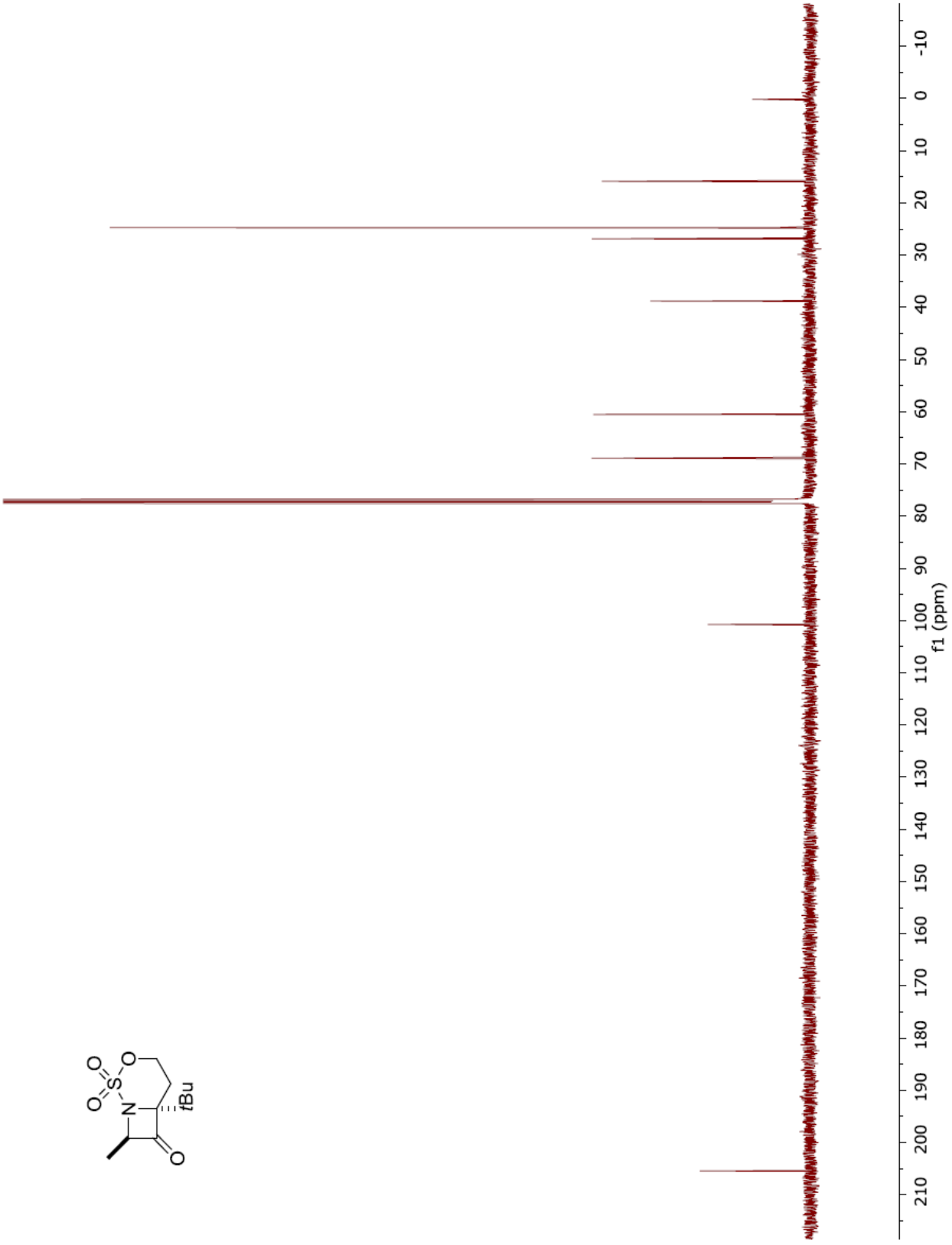
Compound **2.22a**:



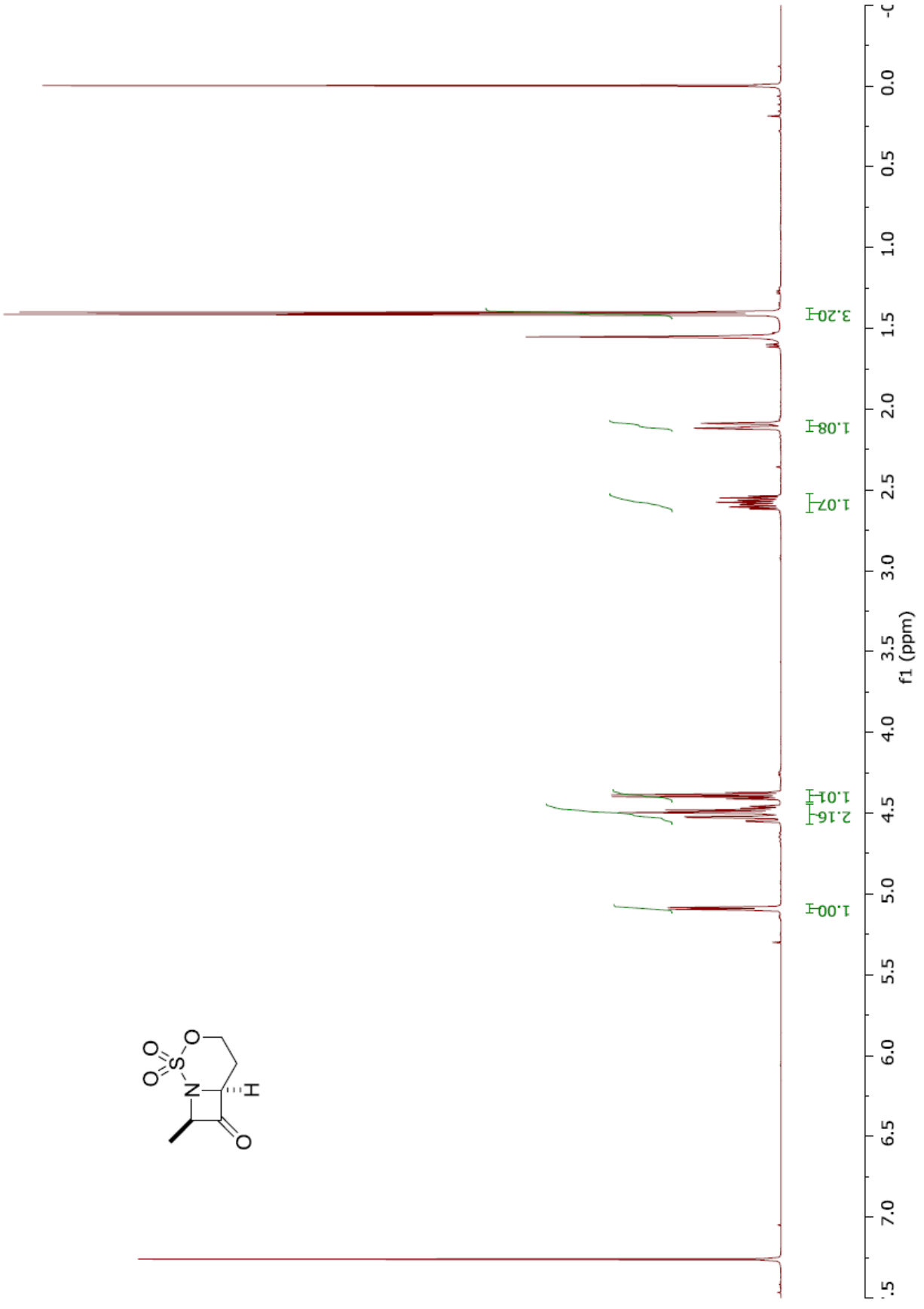
Compound **2.22b**:



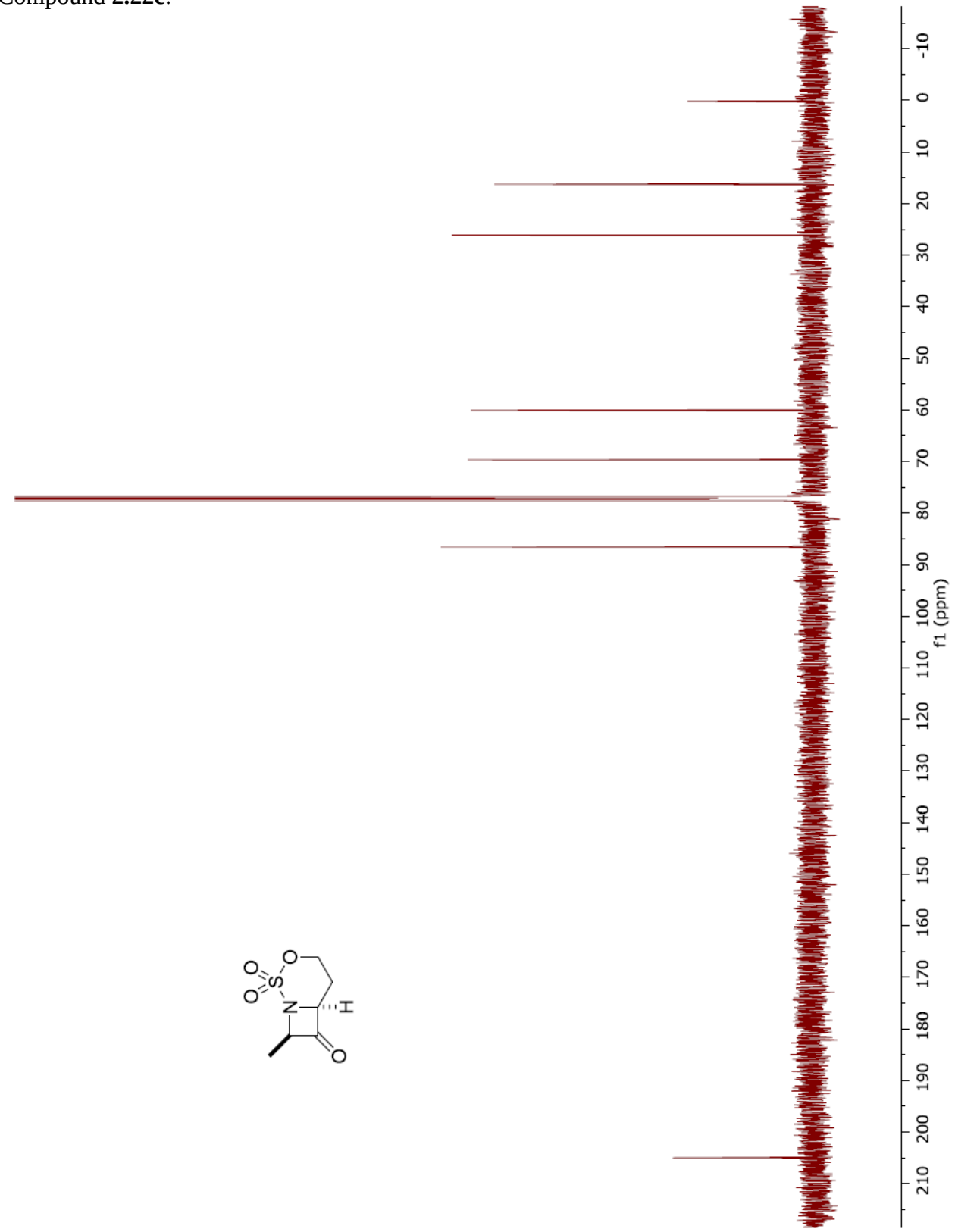
Compound **2.22b**:



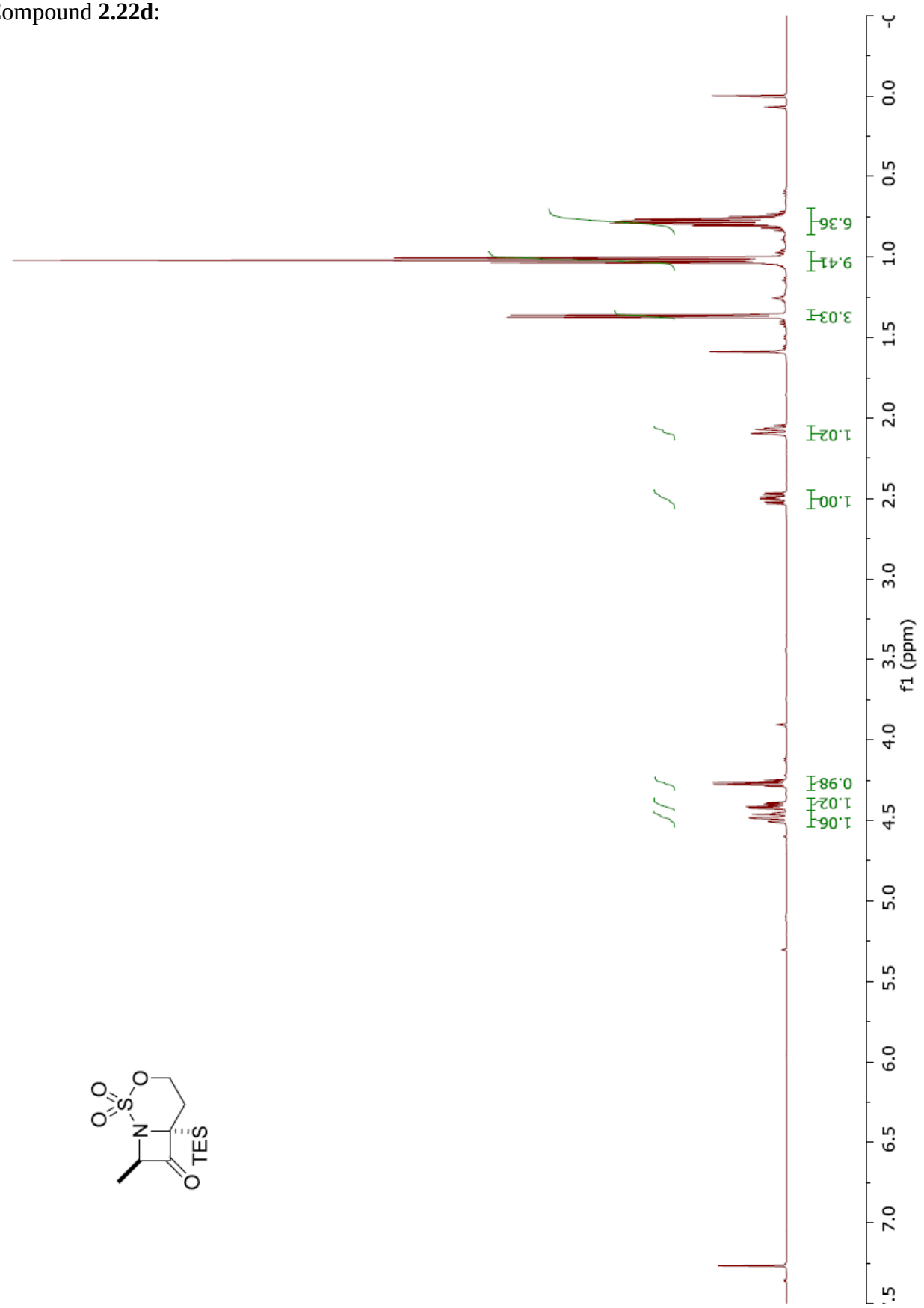
Compound **2.22c**:



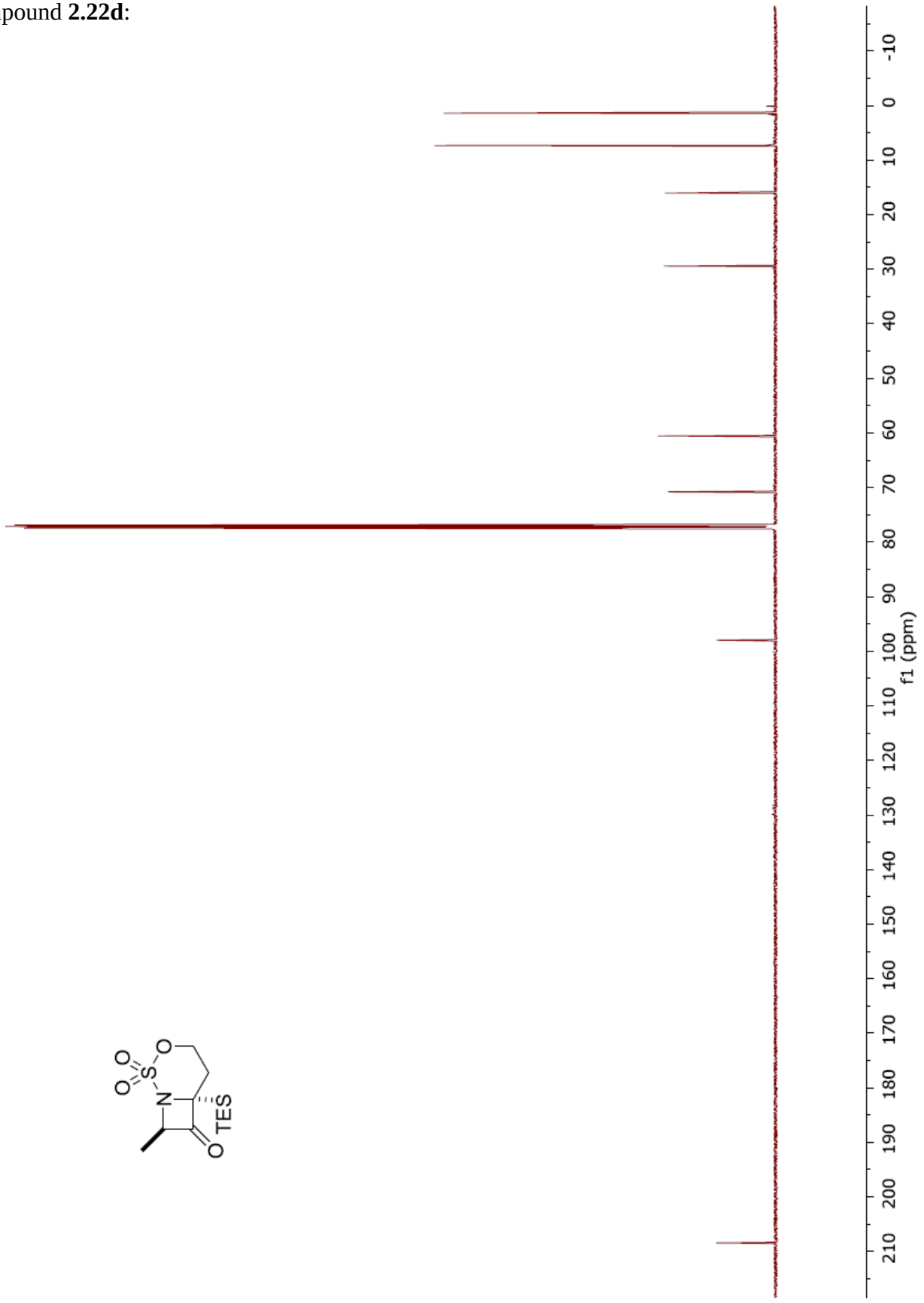
Compound **2.22c**:



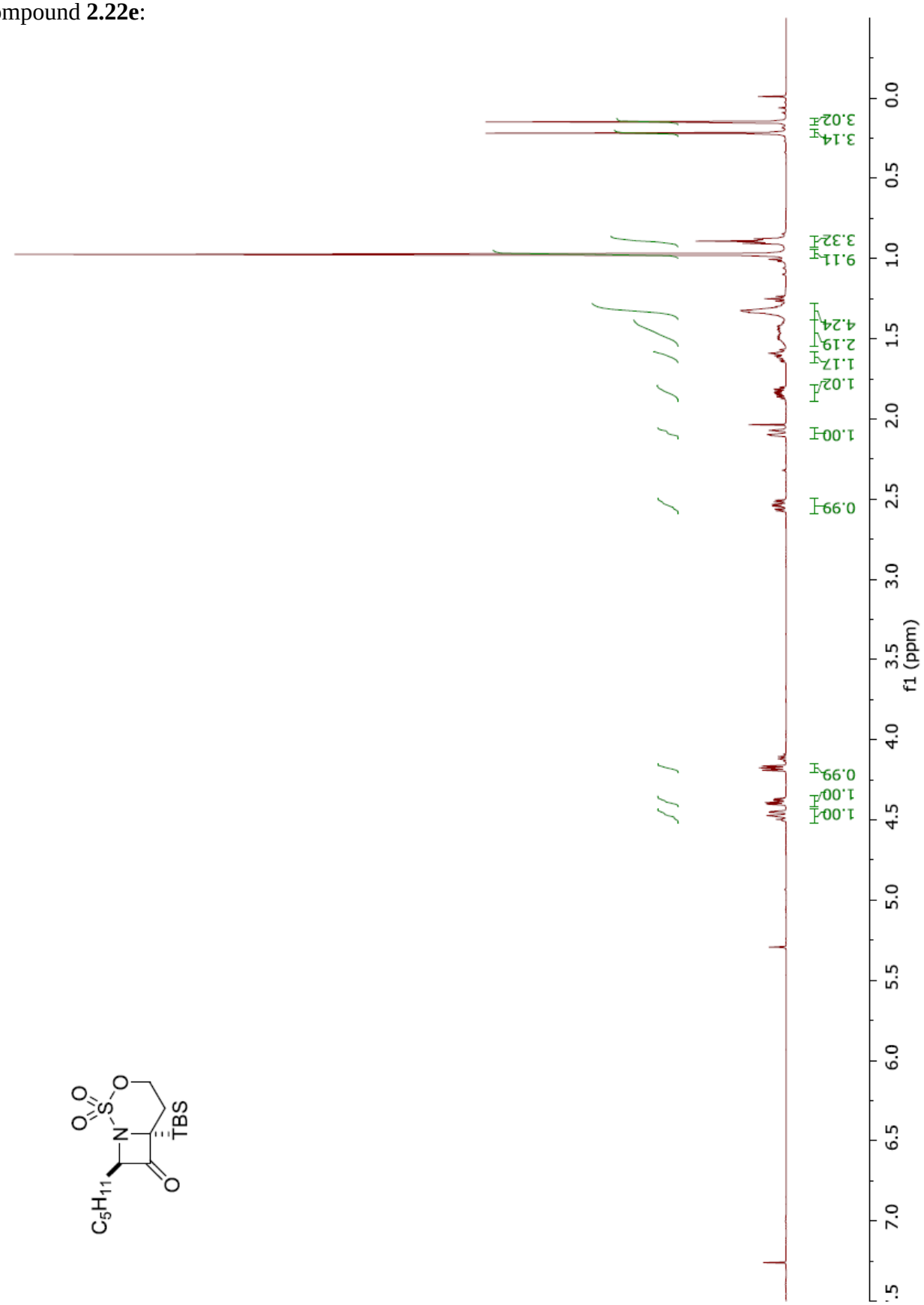
Compound **2.22d**:



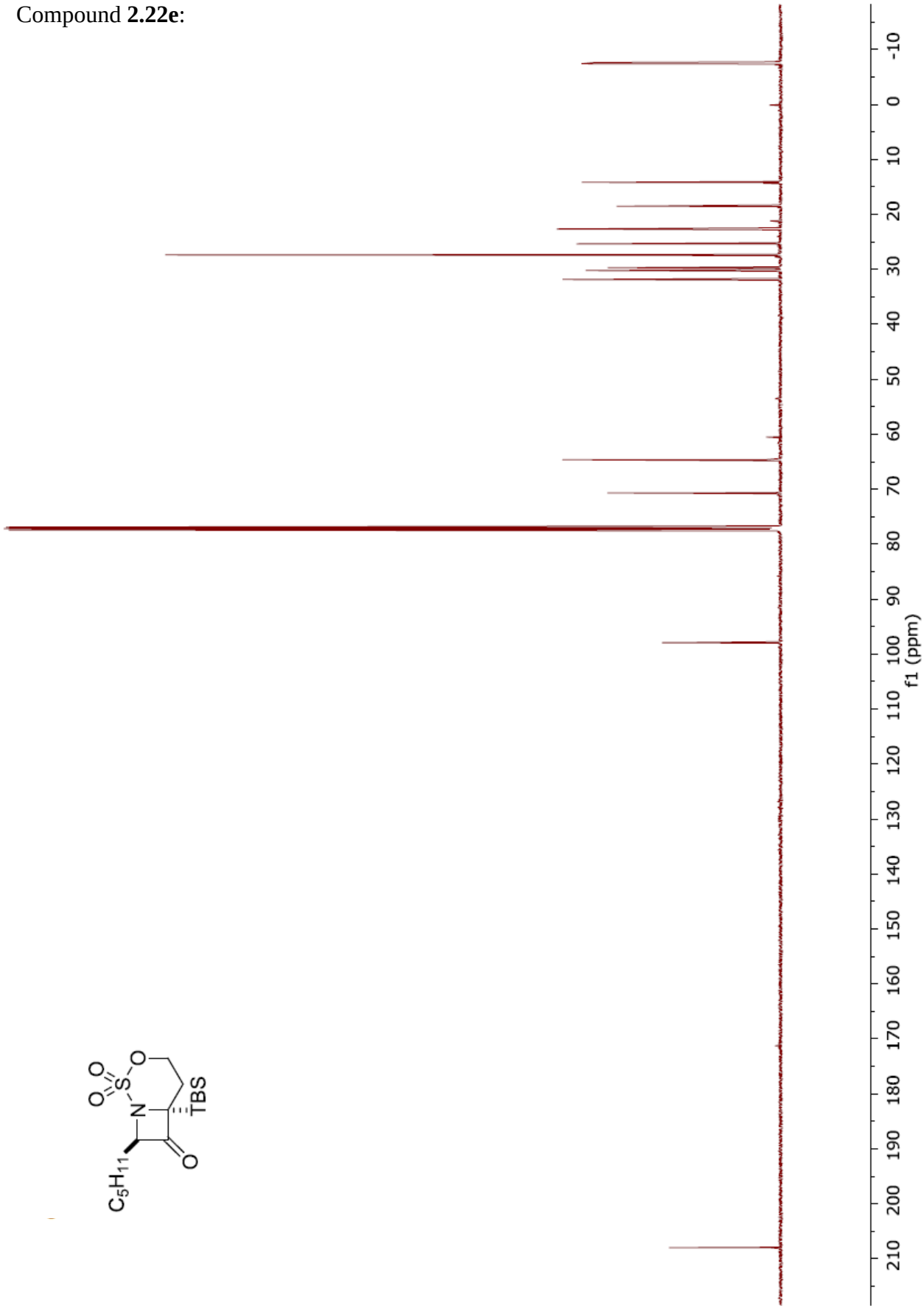
Compound **2.22d**:



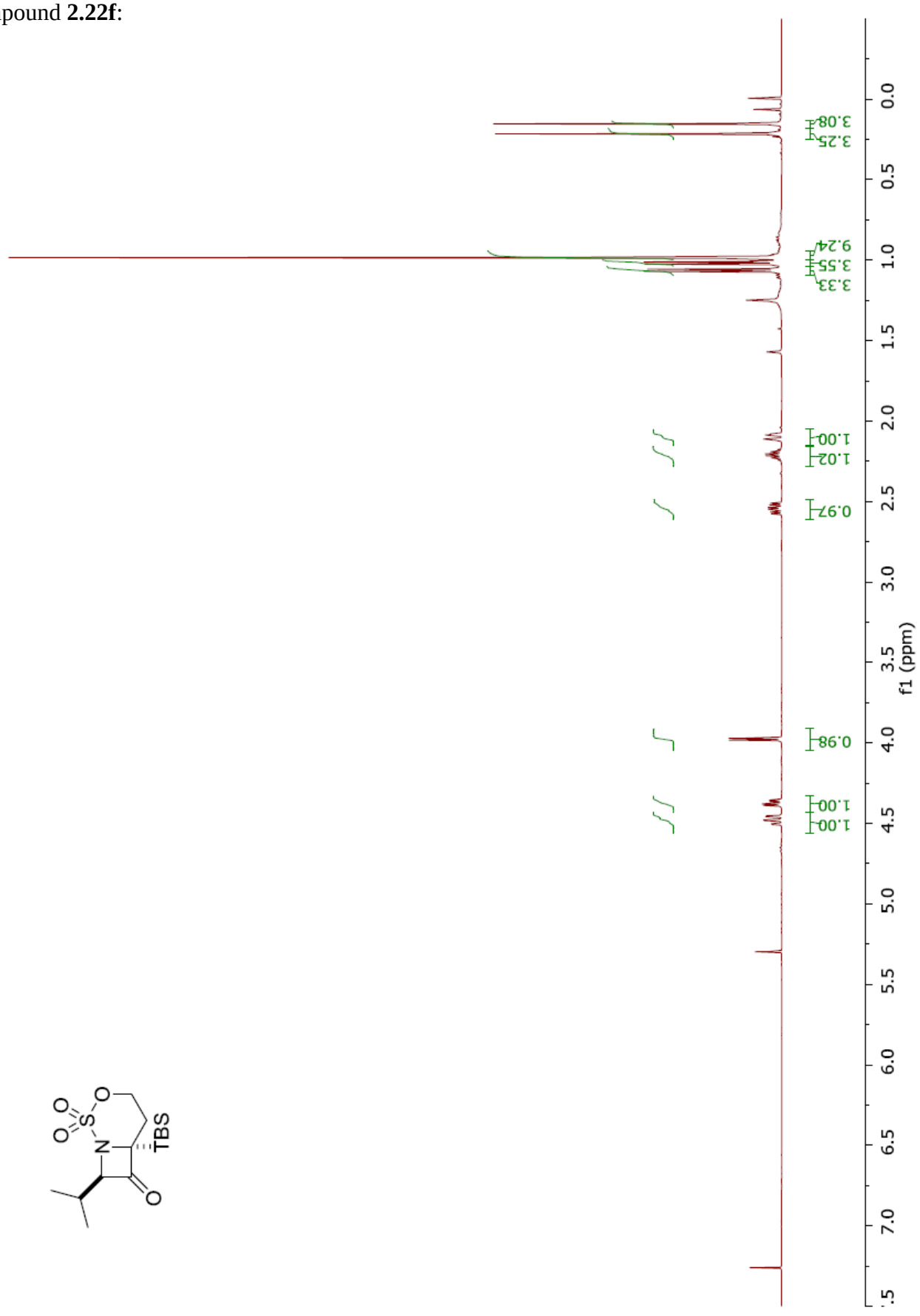
Compound **2.22e**:



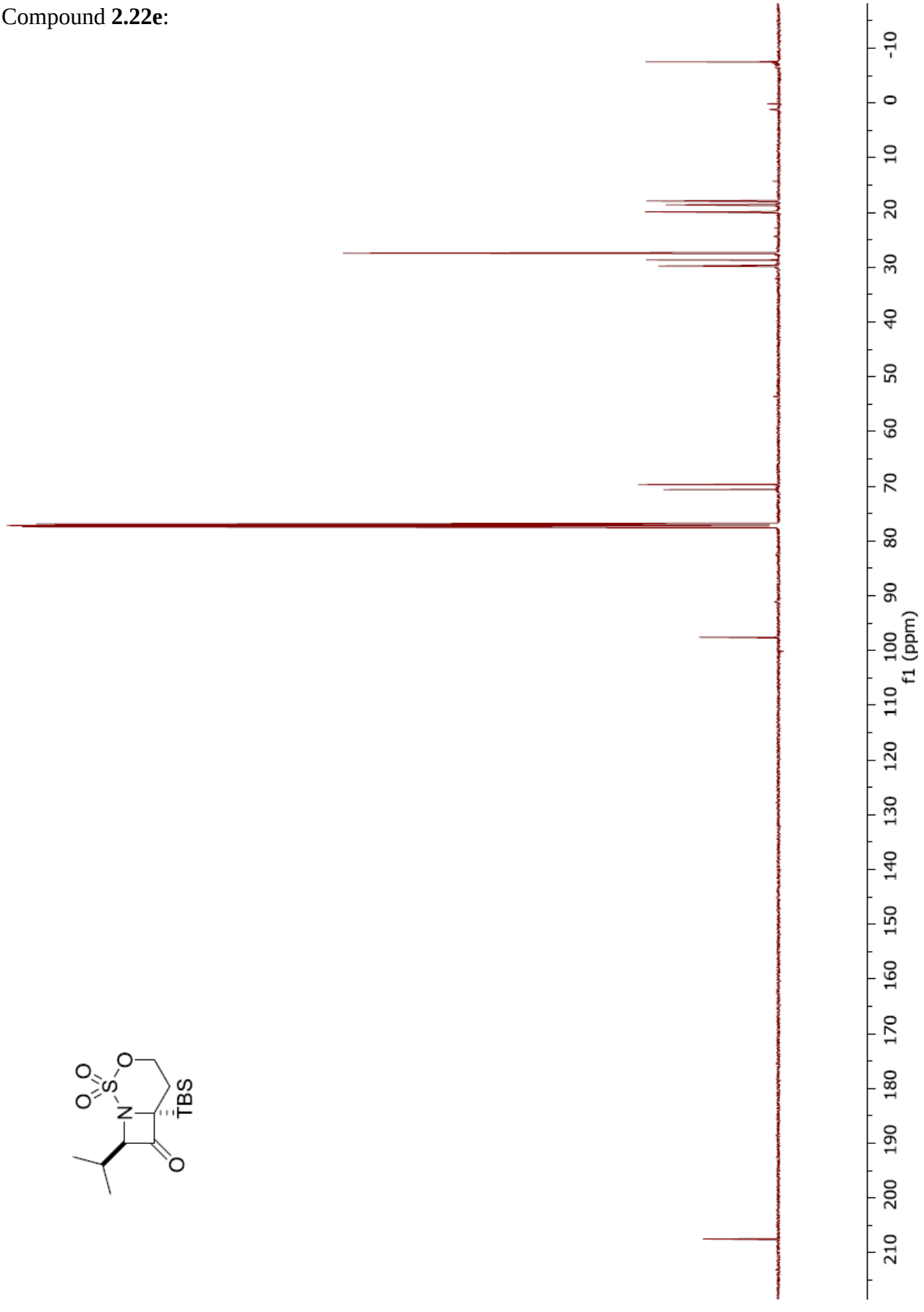
Compound **2.22e**:



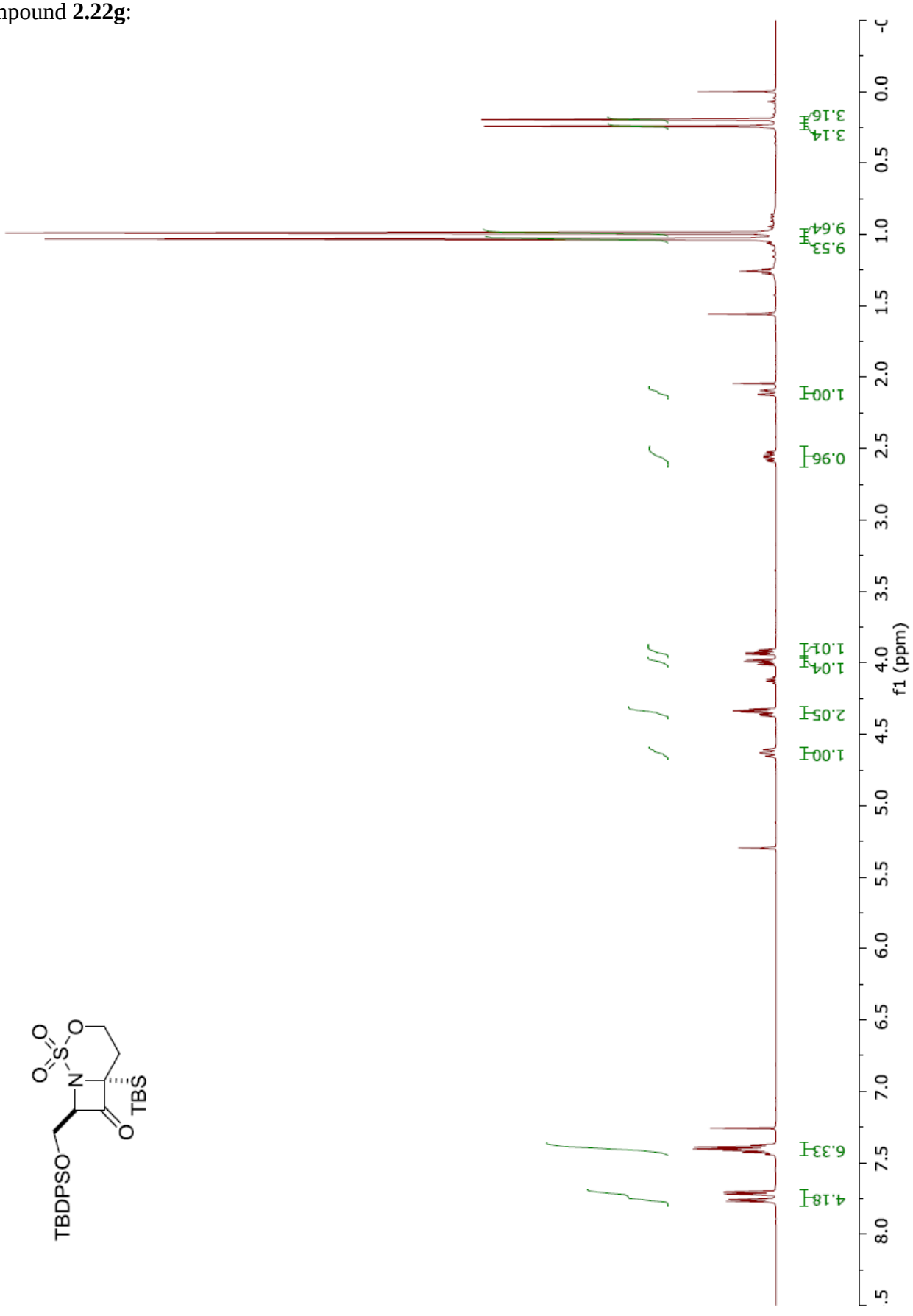
Compound **2.22f**:



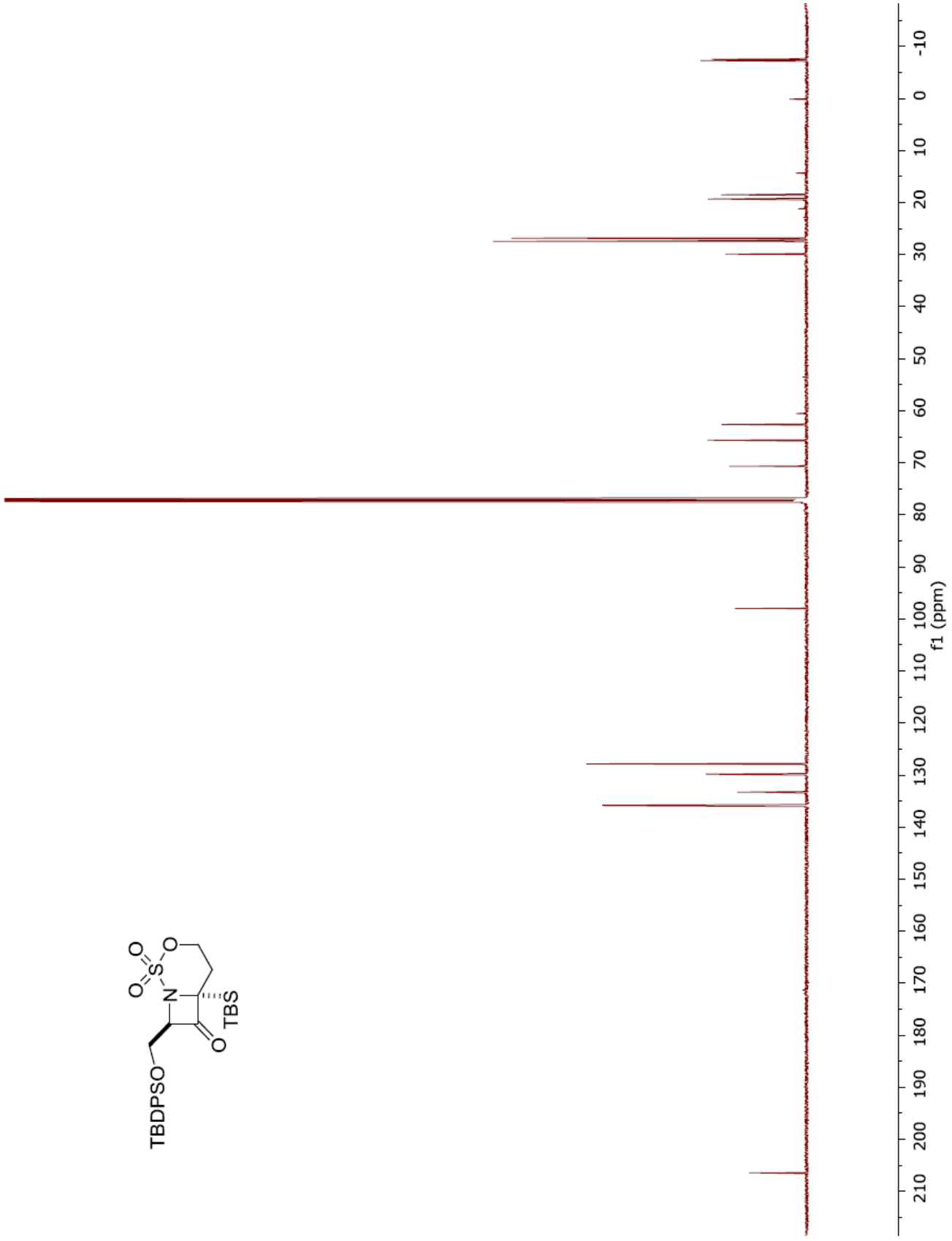
Compound **2.22e**:



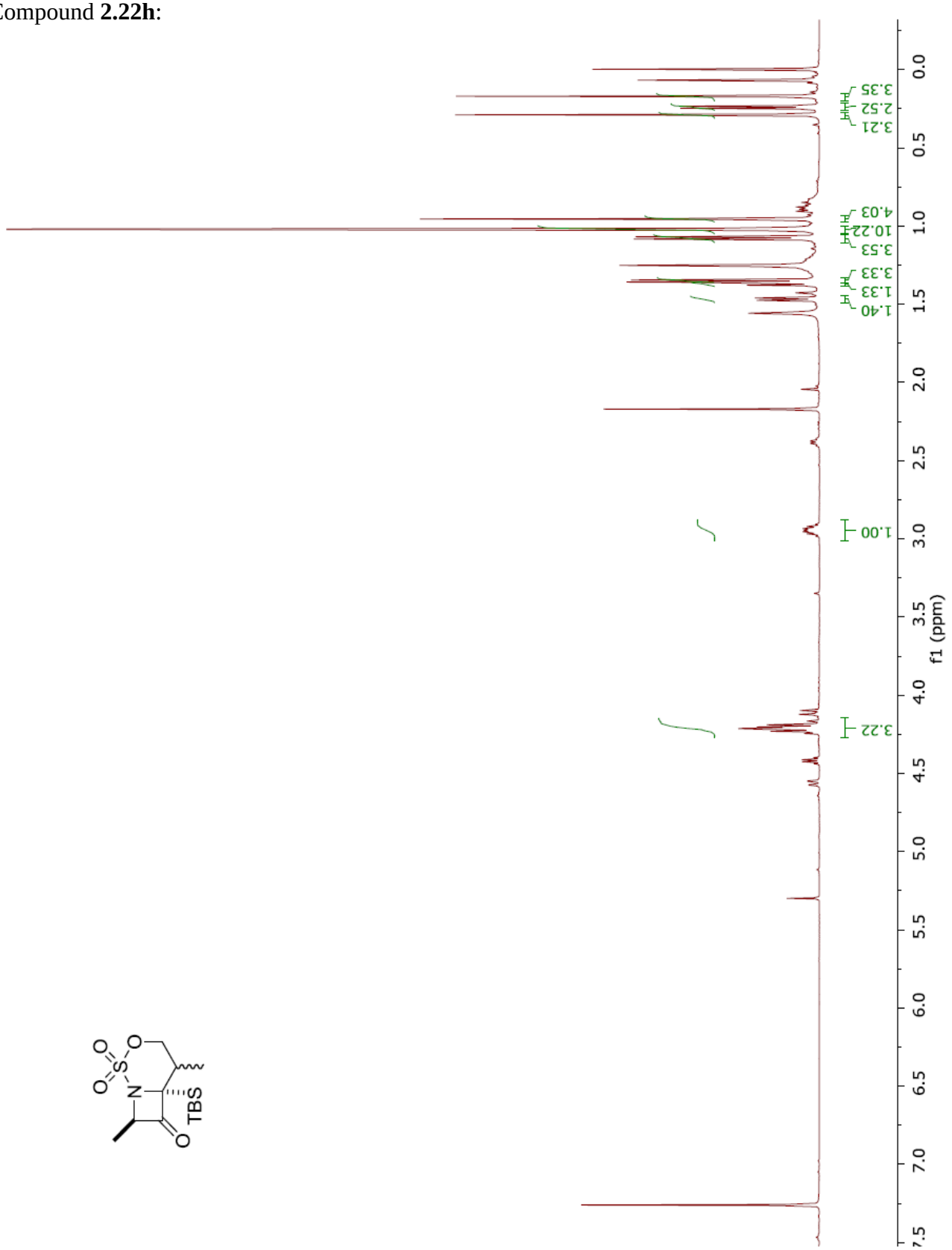
Compound **2.22g**:



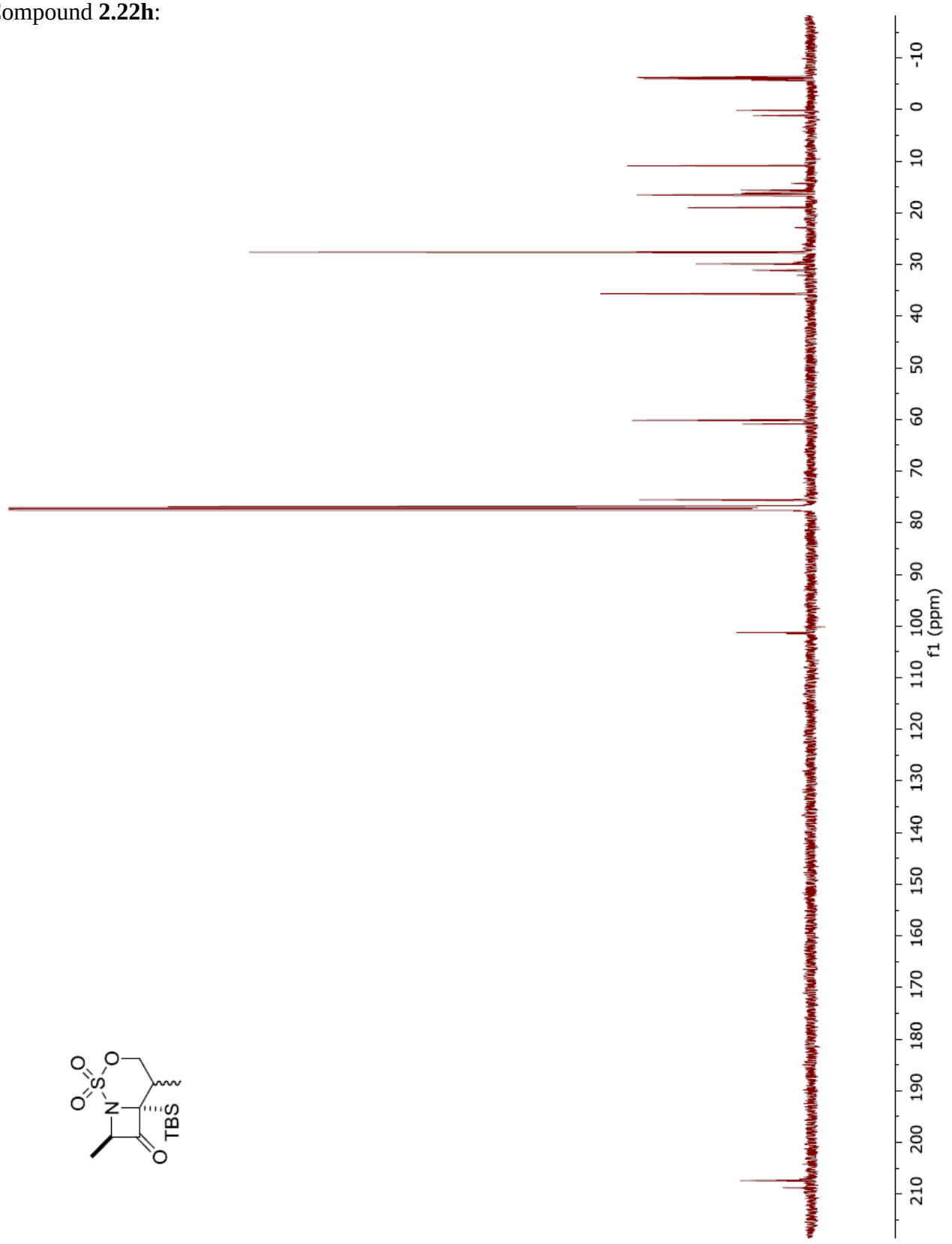
Compound **2.22g**:



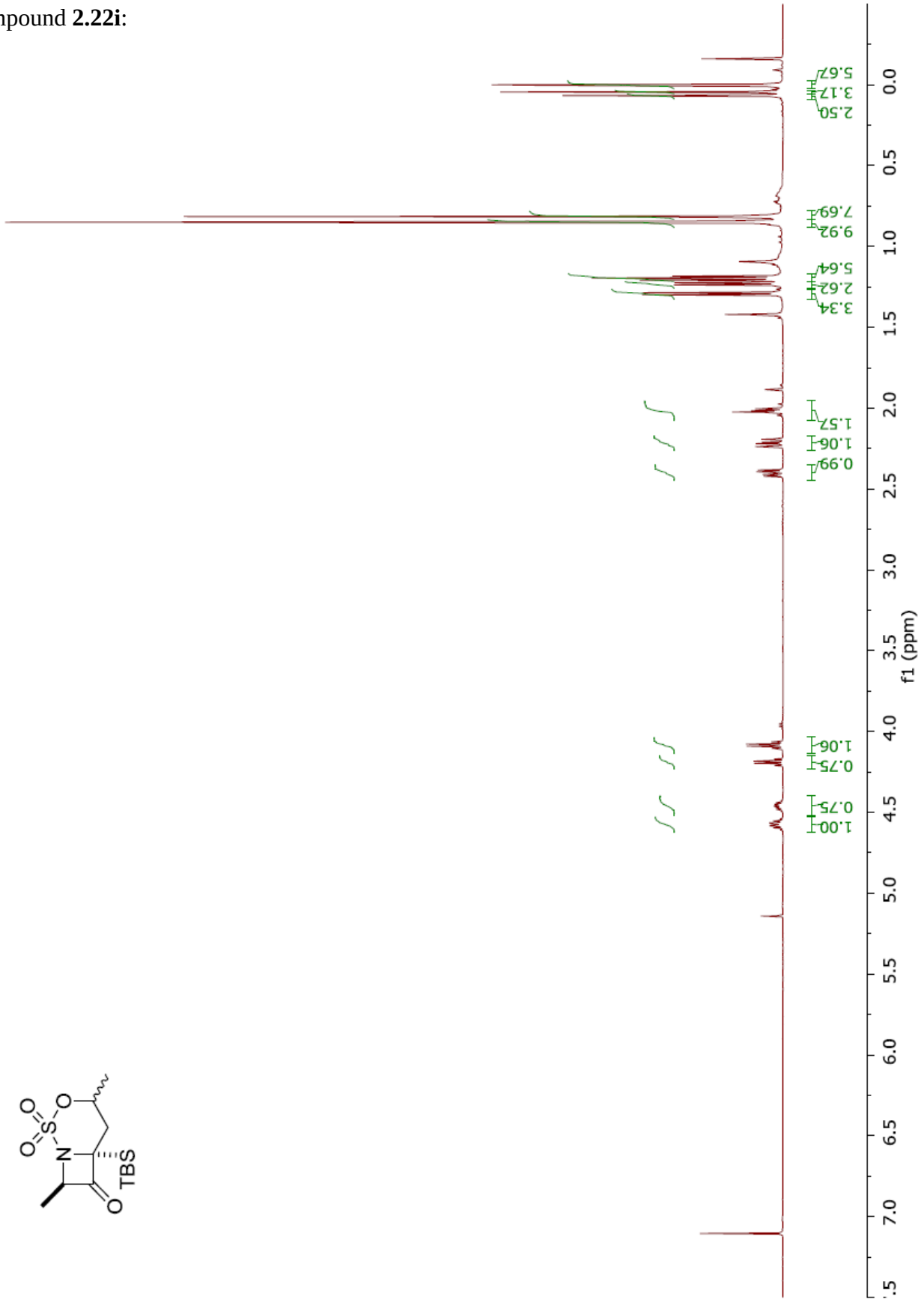
Compound **2.22h**:



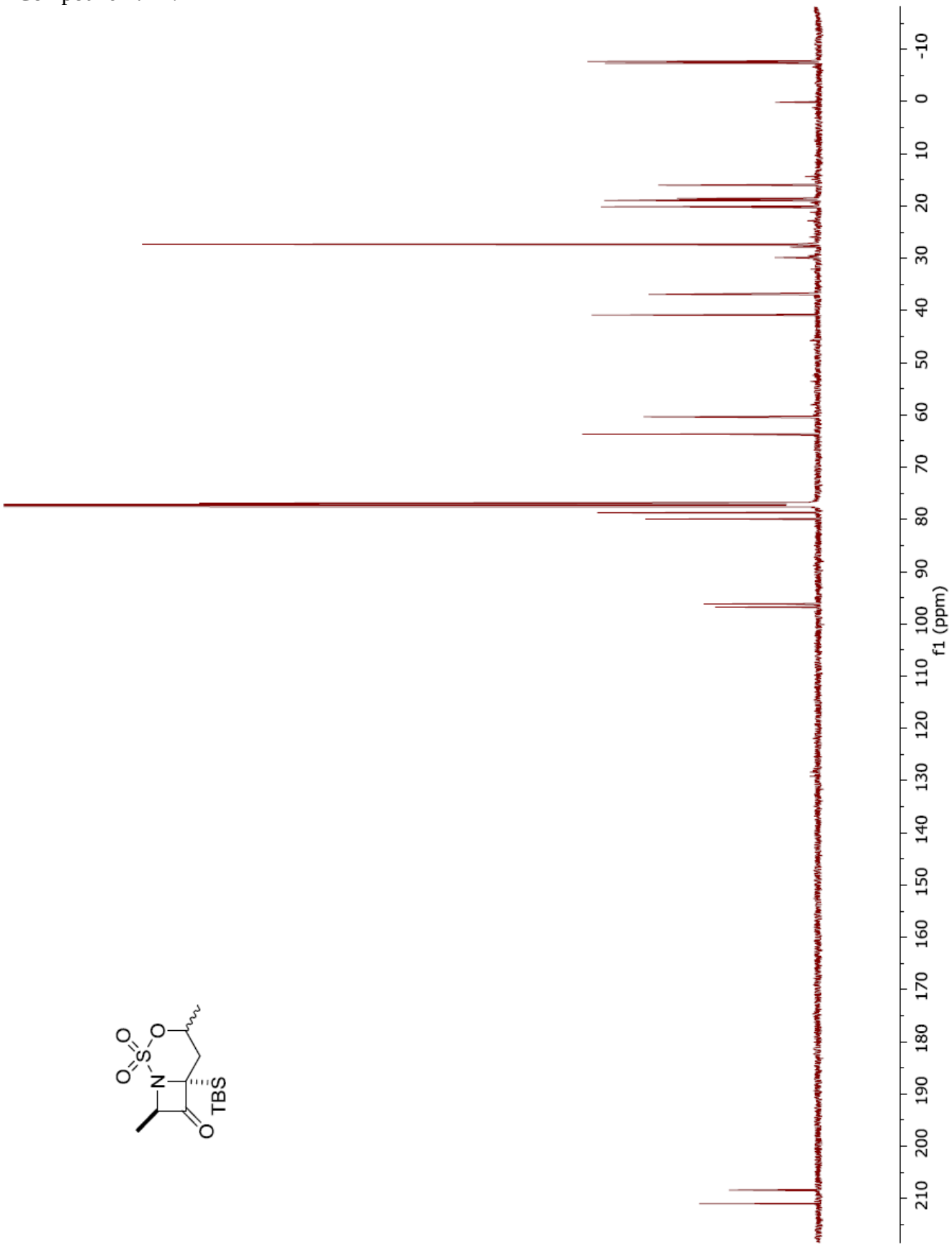
Compound **2.22h**:



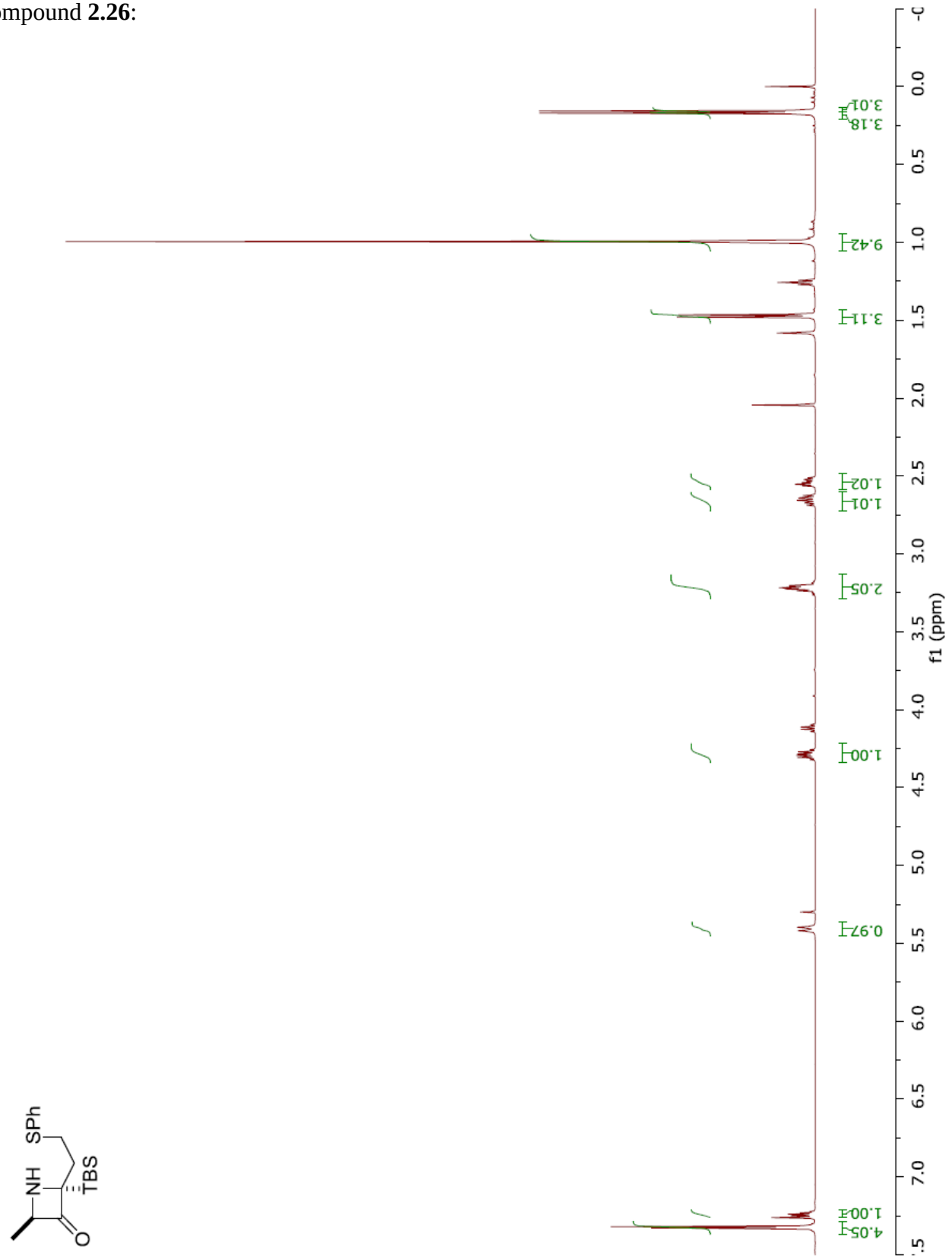
Compound **2.22i**:



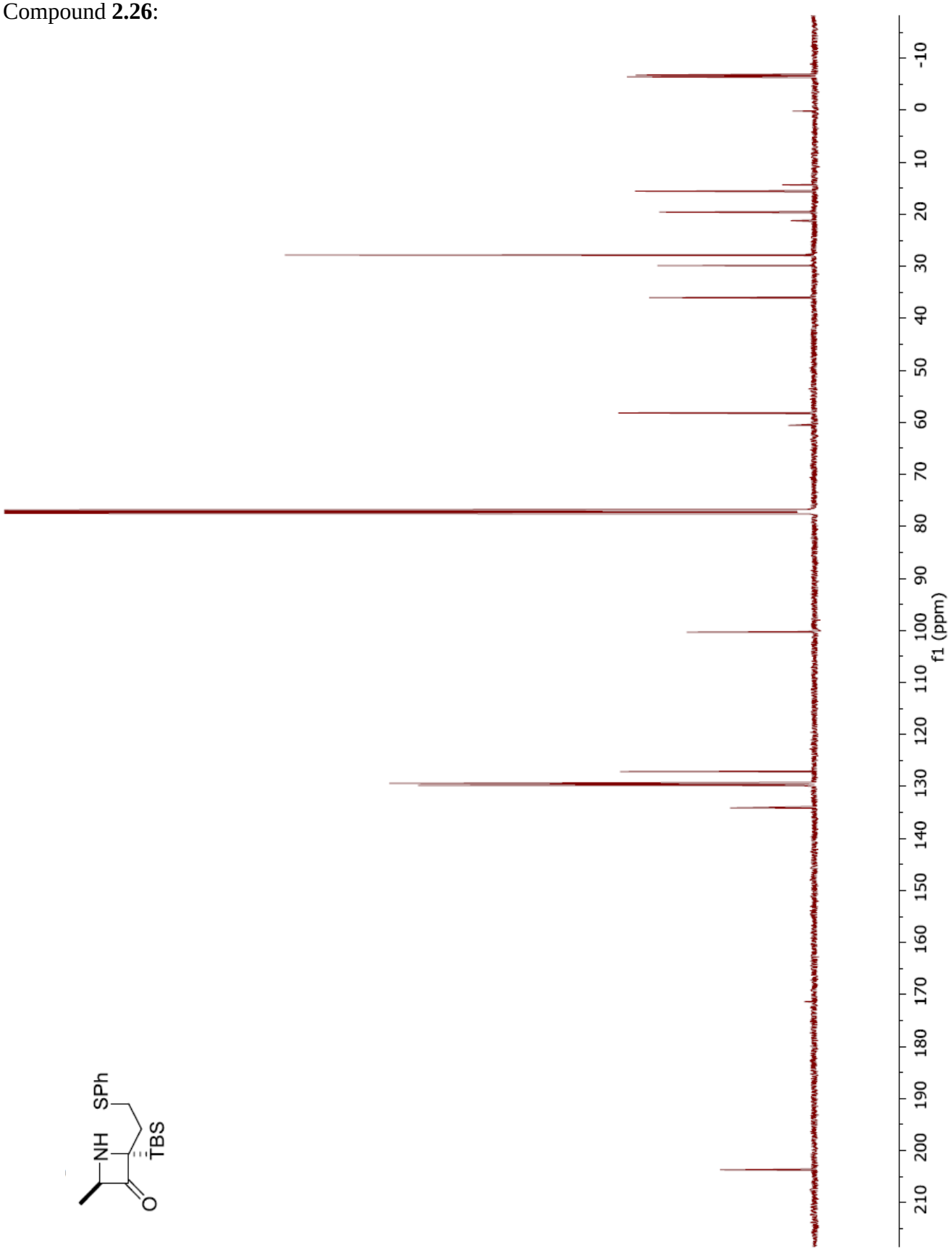
Compound **2.22i**:



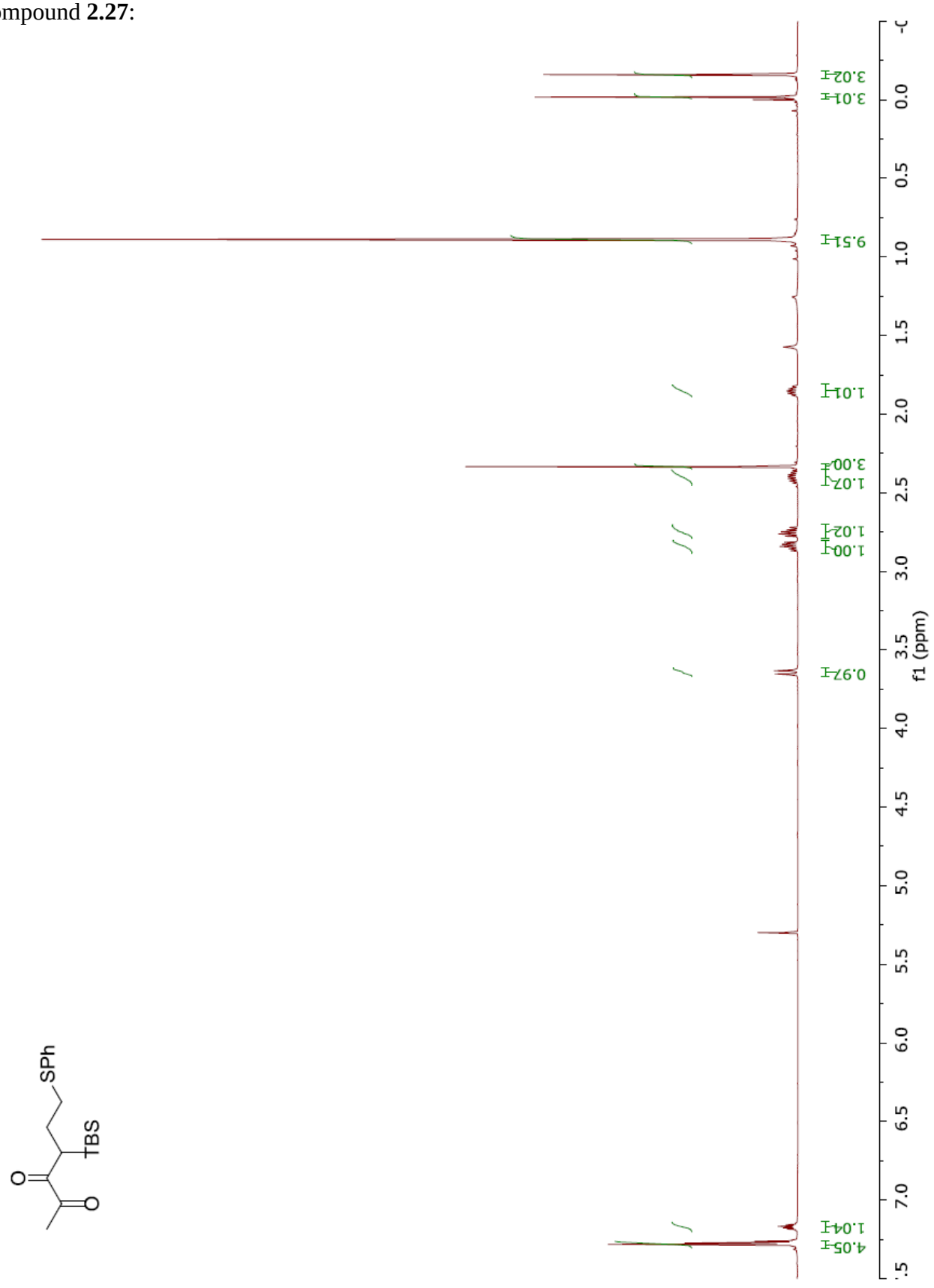
Compound **2.26**:



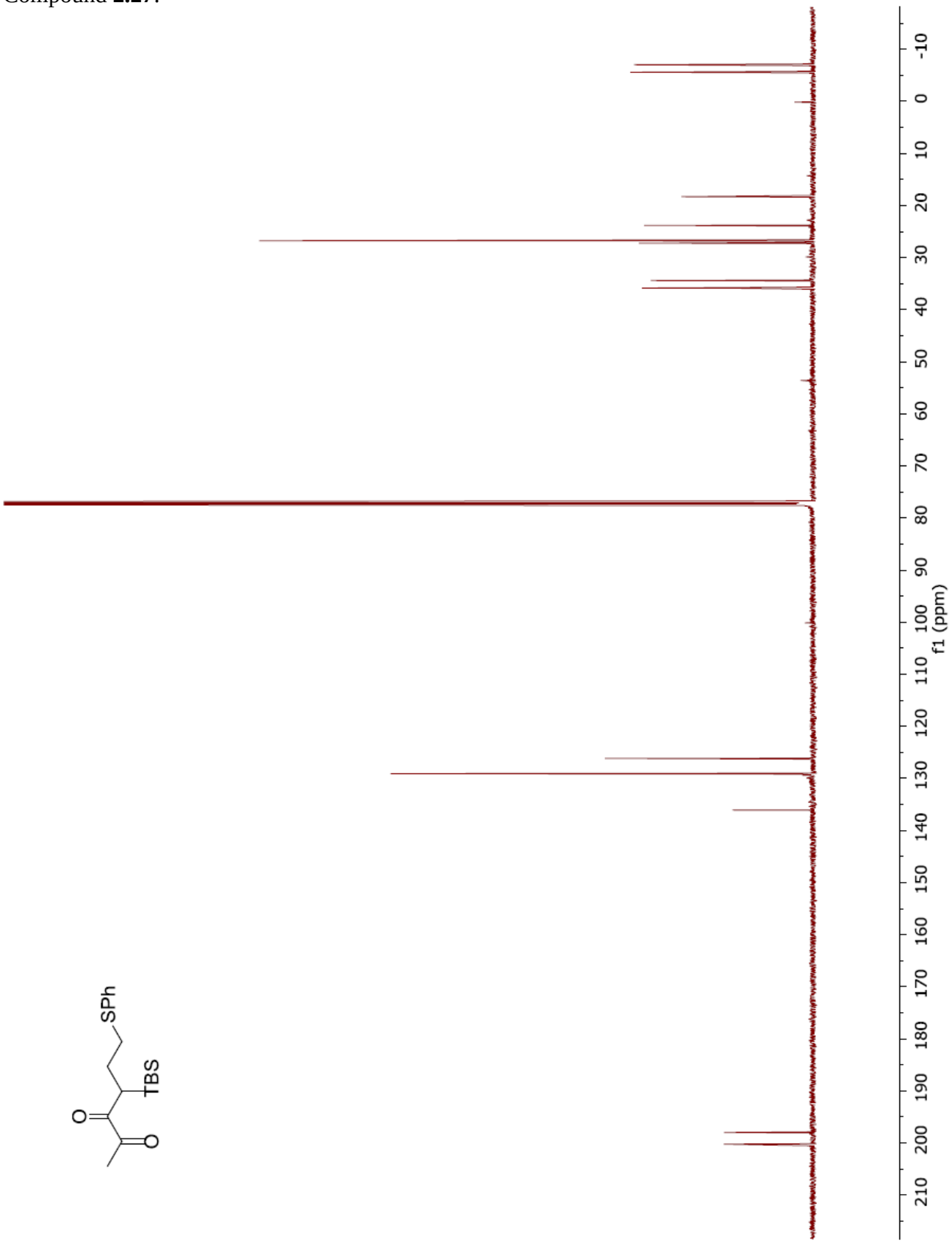
Compound **2.26**:



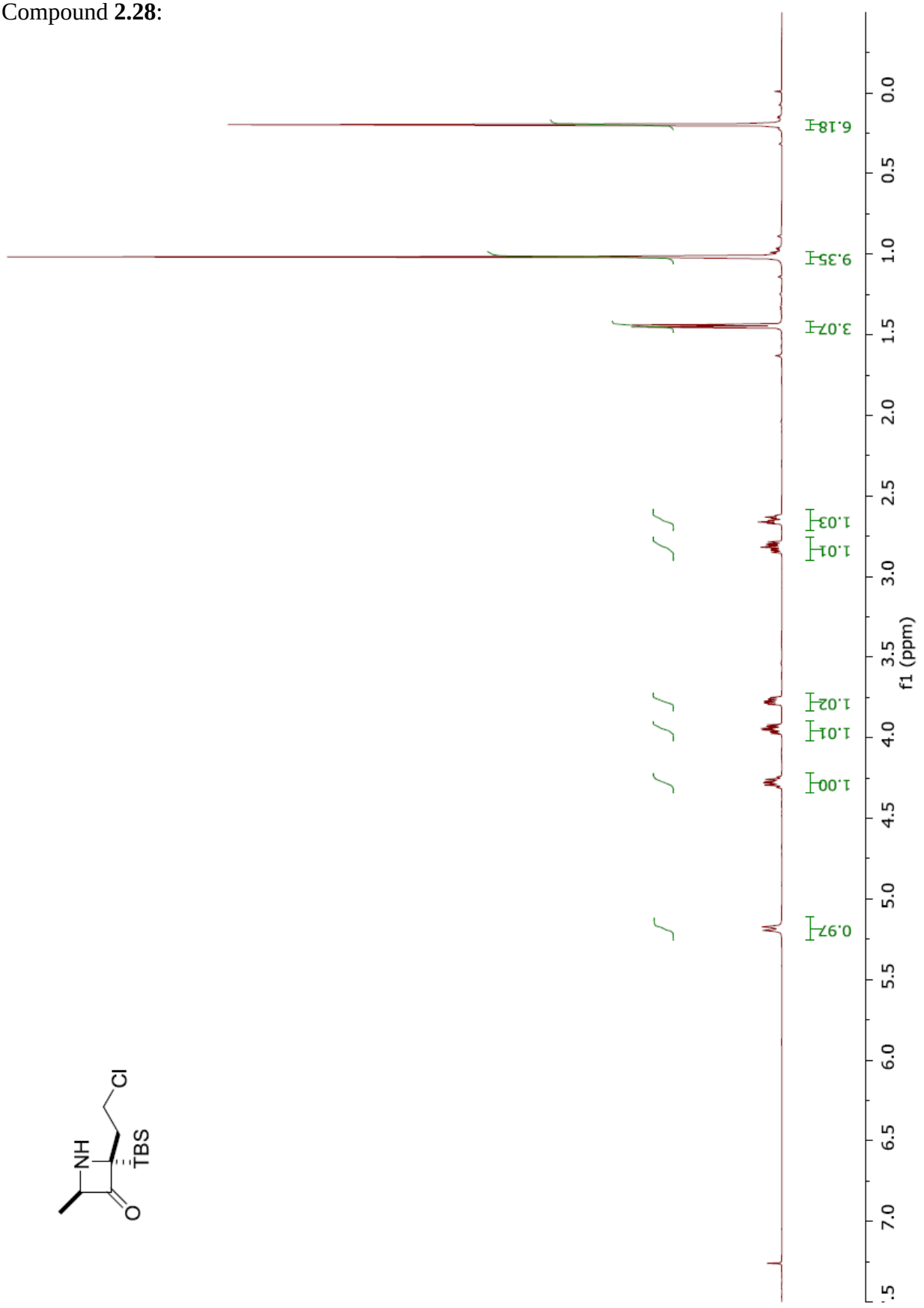
Compound **2.27**:



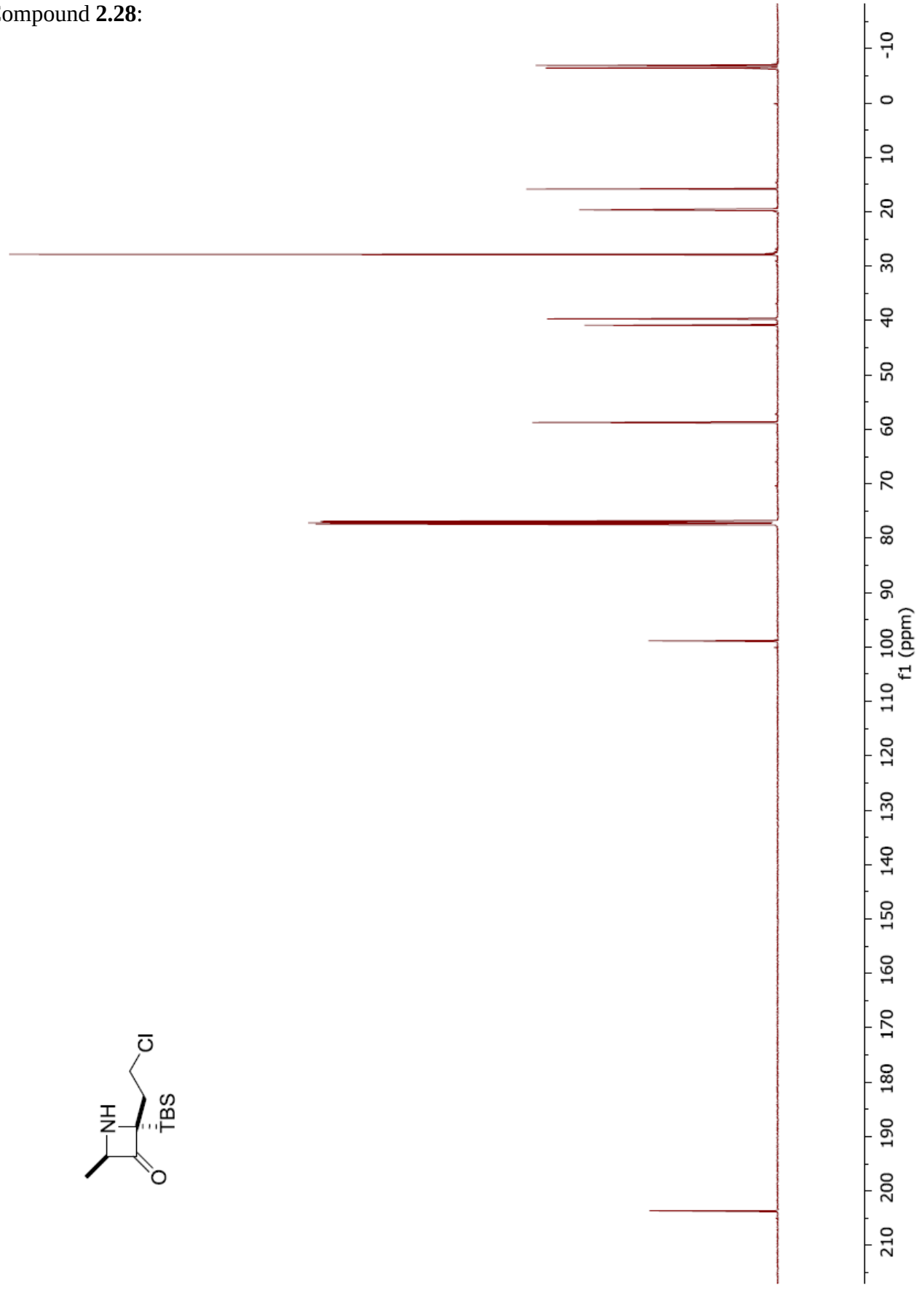
Compound **2.27**:



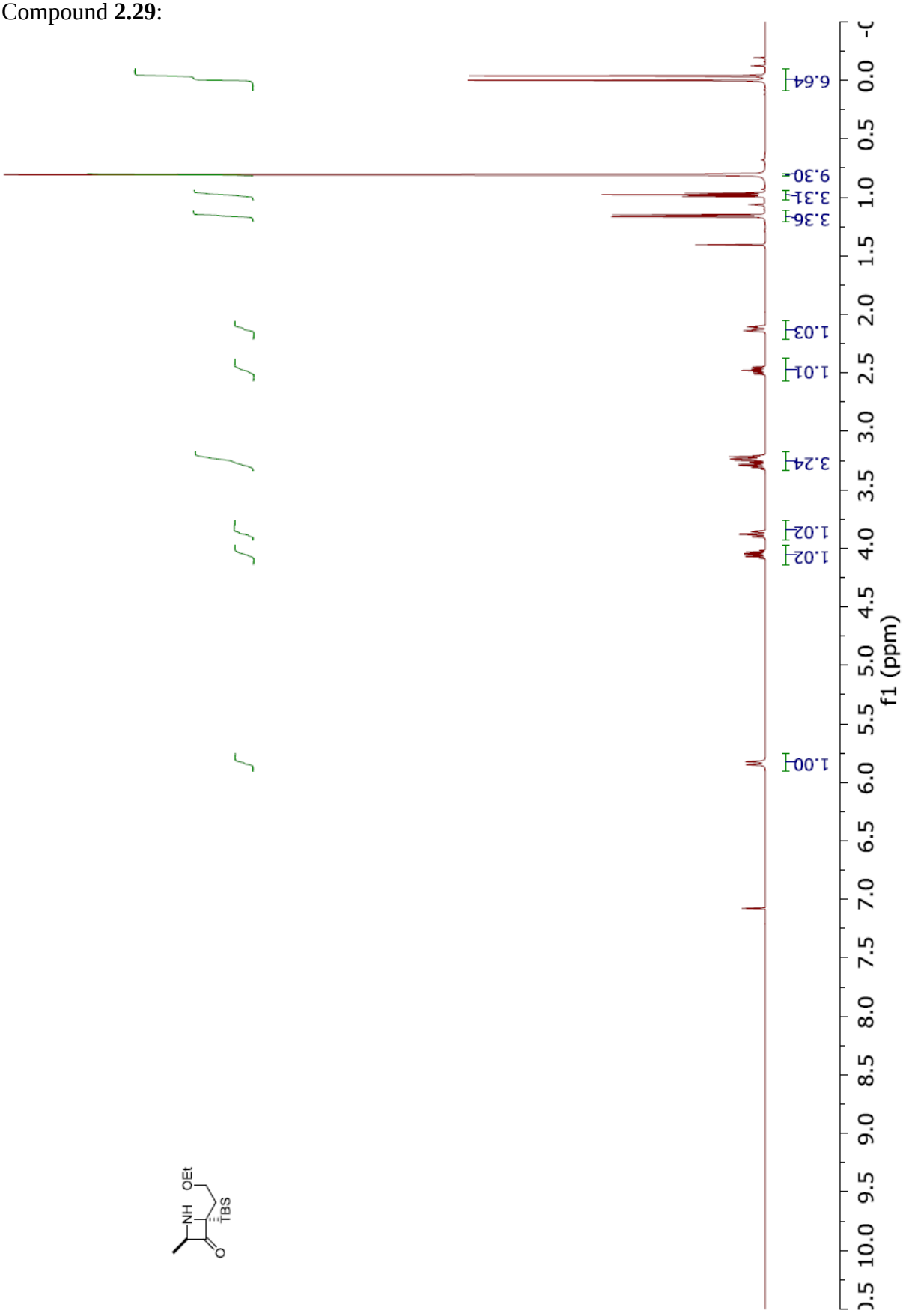
Compound **2.28**:



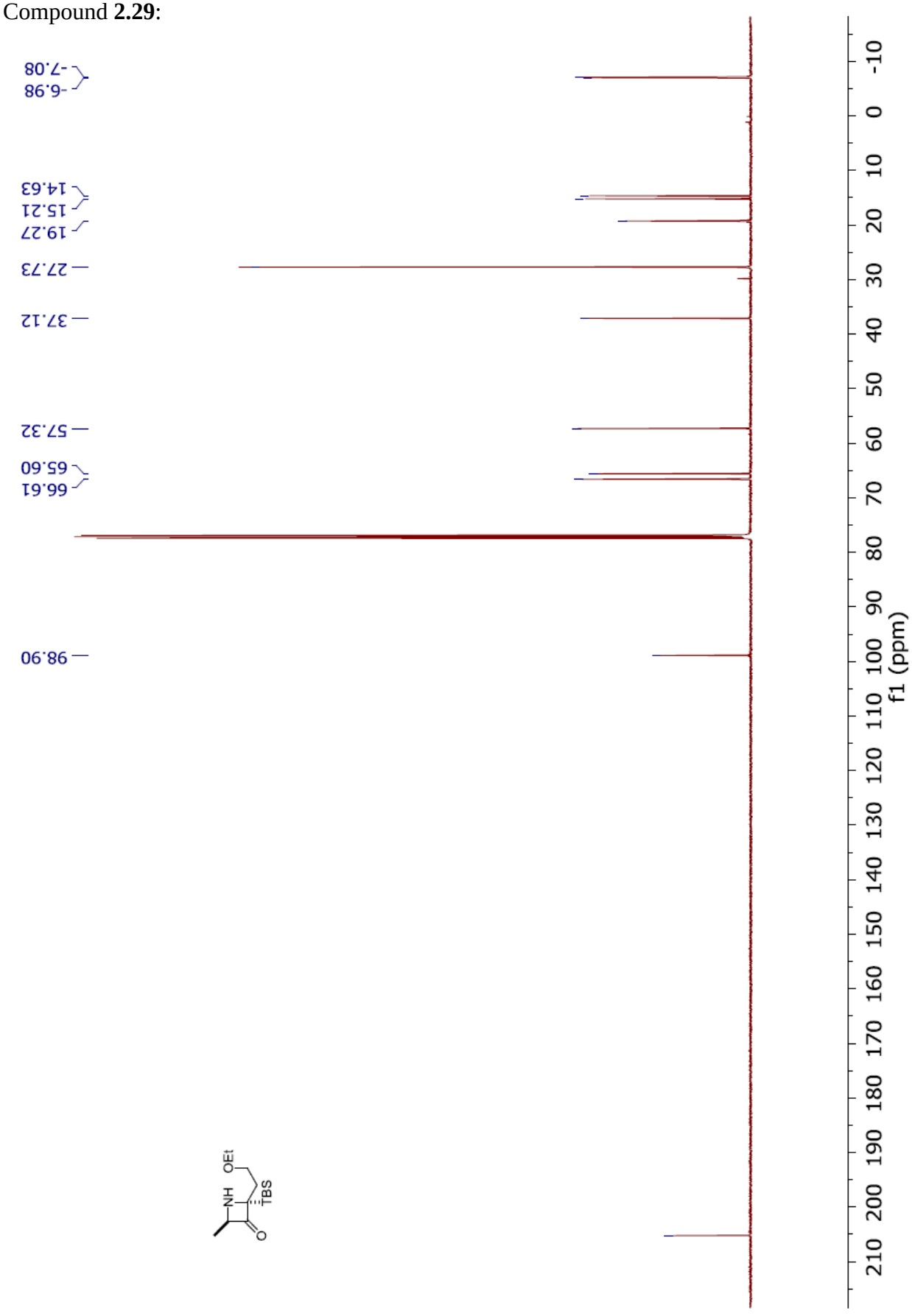
Compound **2.28**:



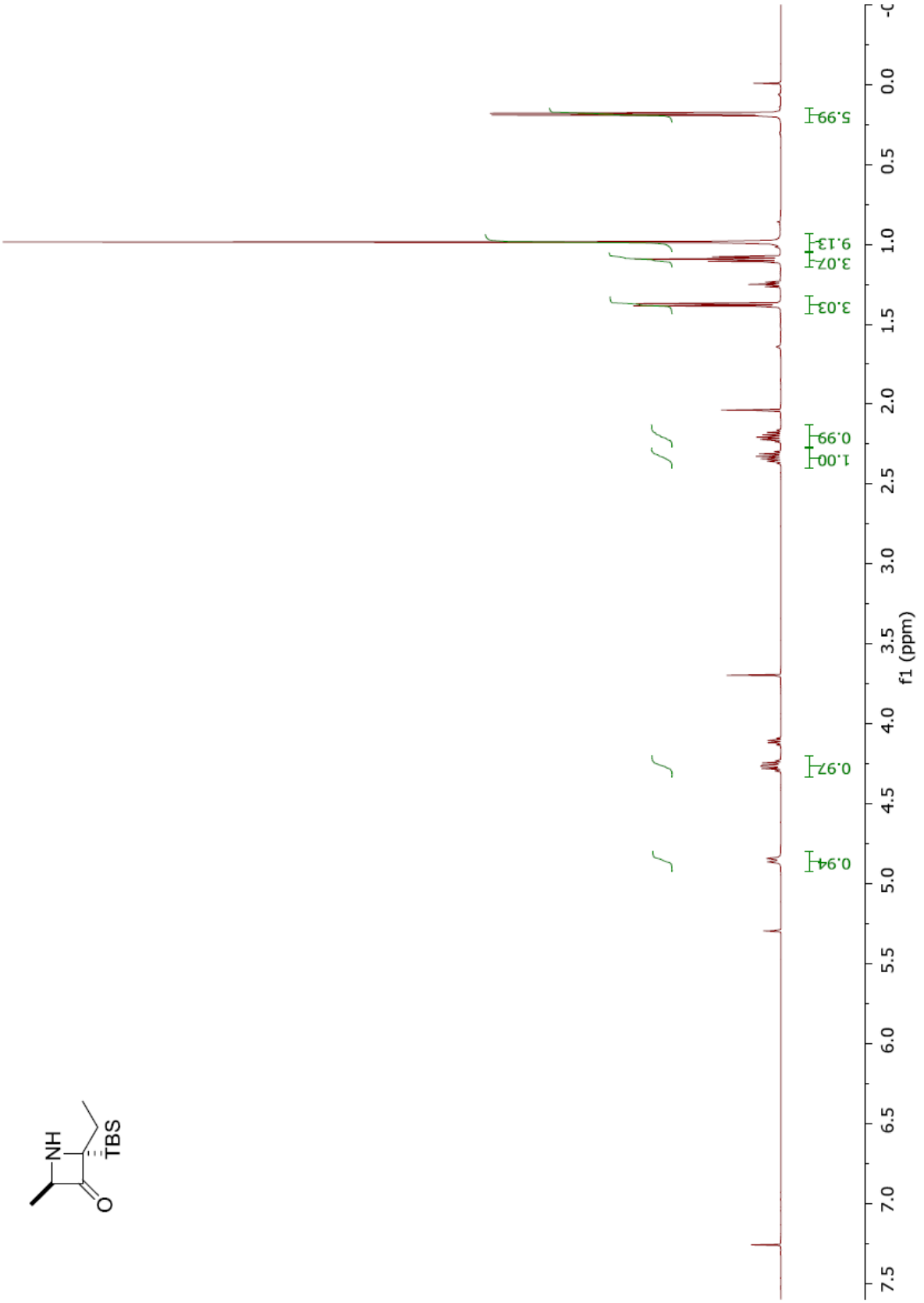
Compound **2.29**:



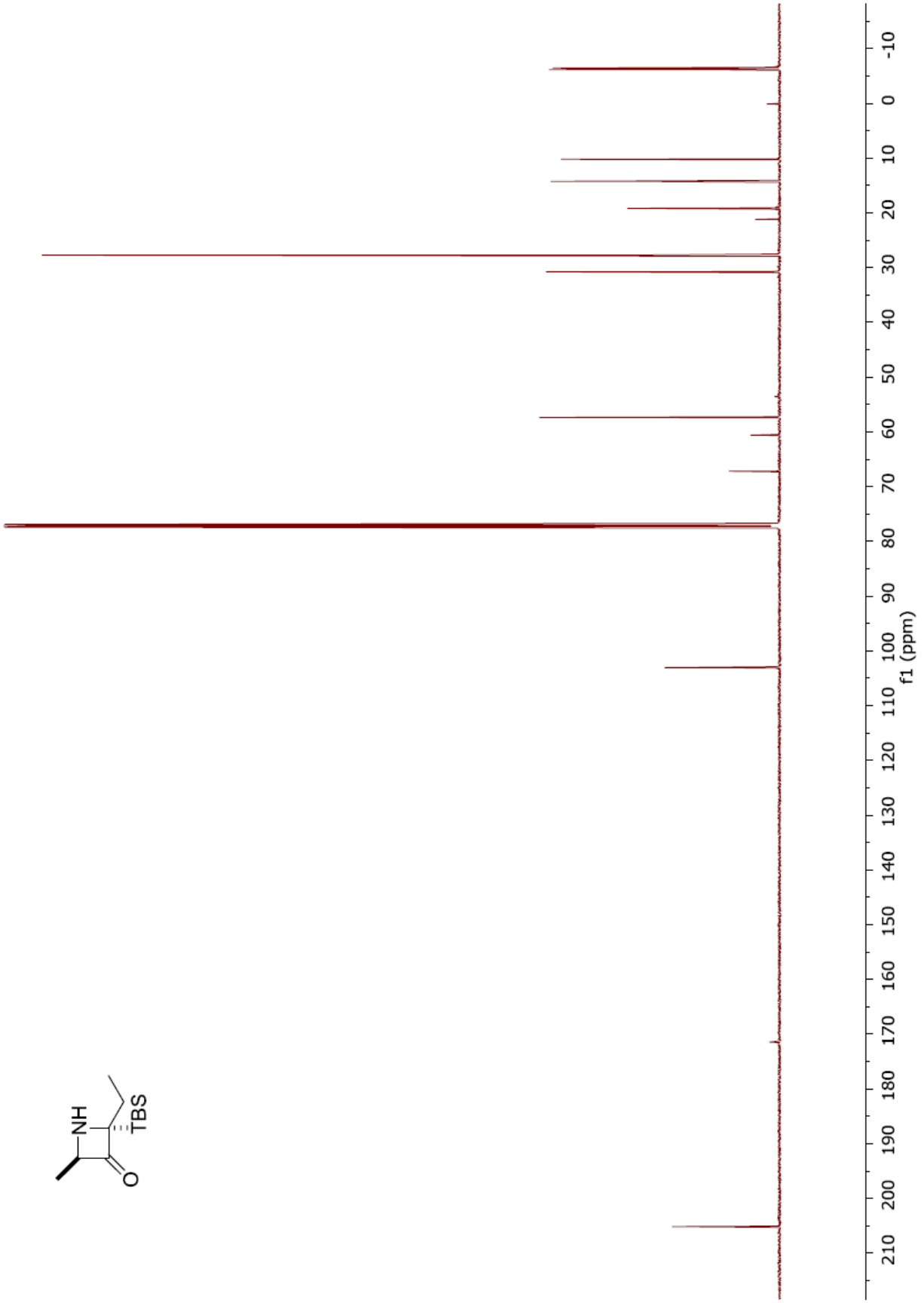
Compound **2.29**:



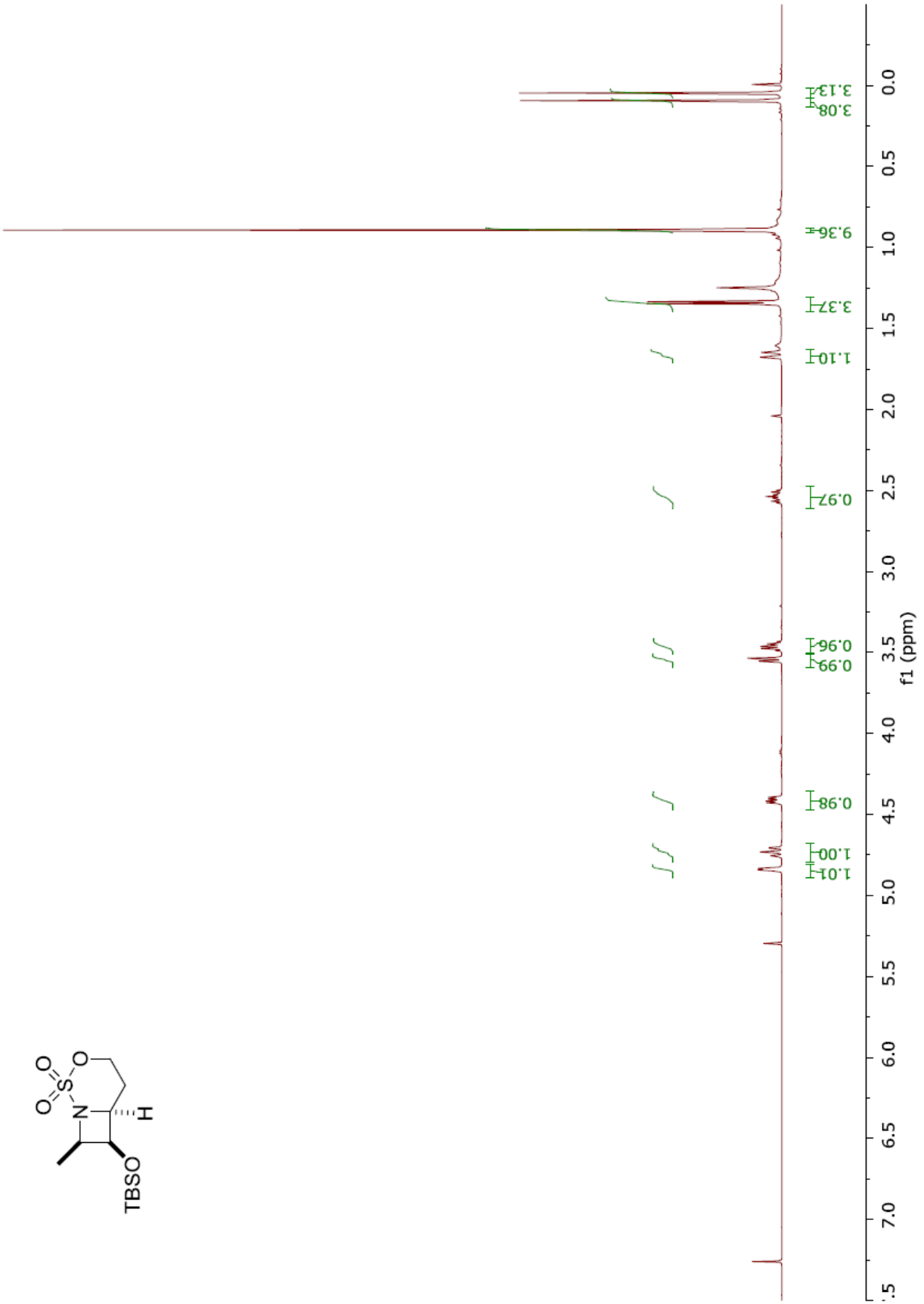
Compound **2.30**:



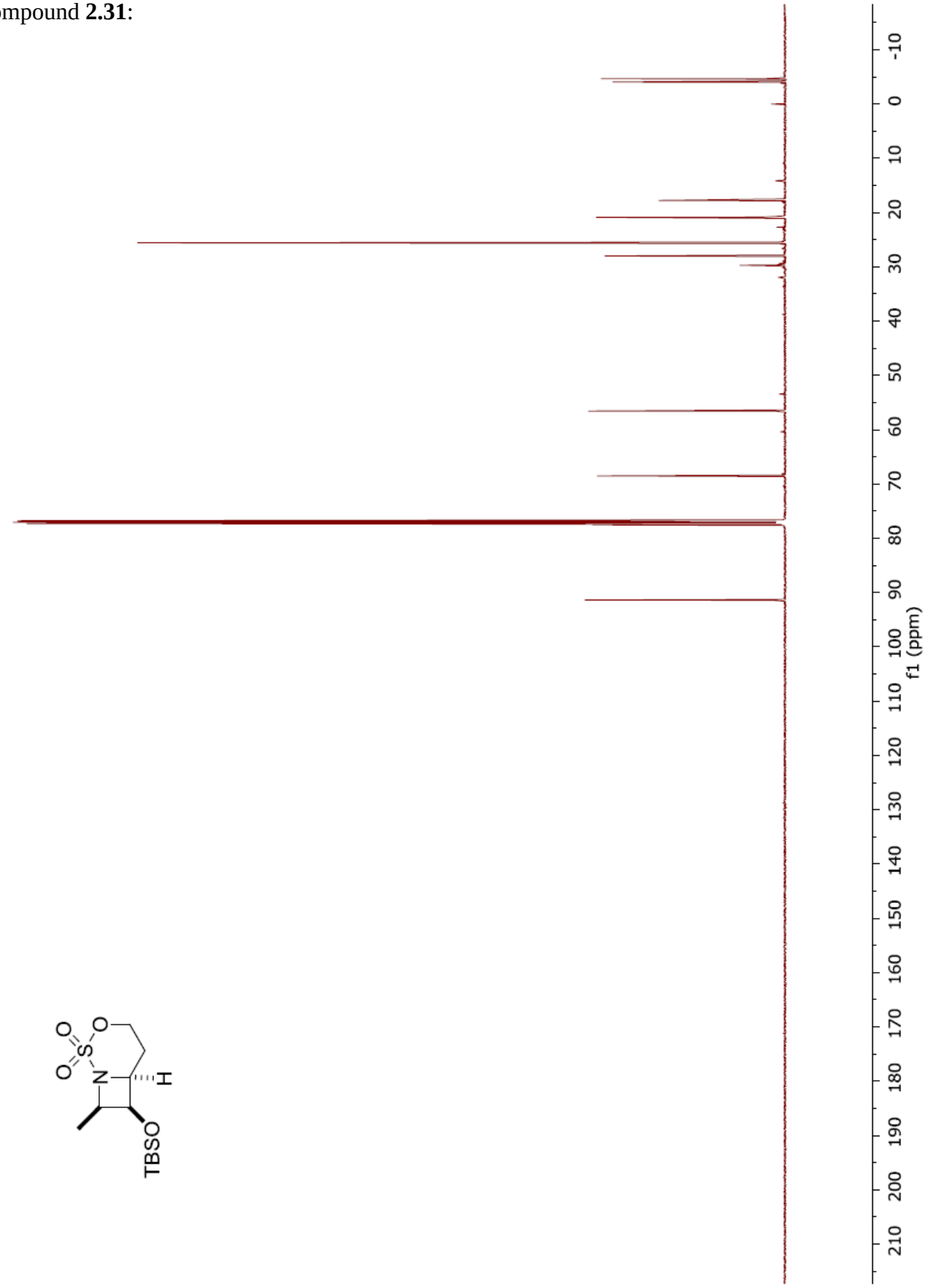
Compound **2.30**:



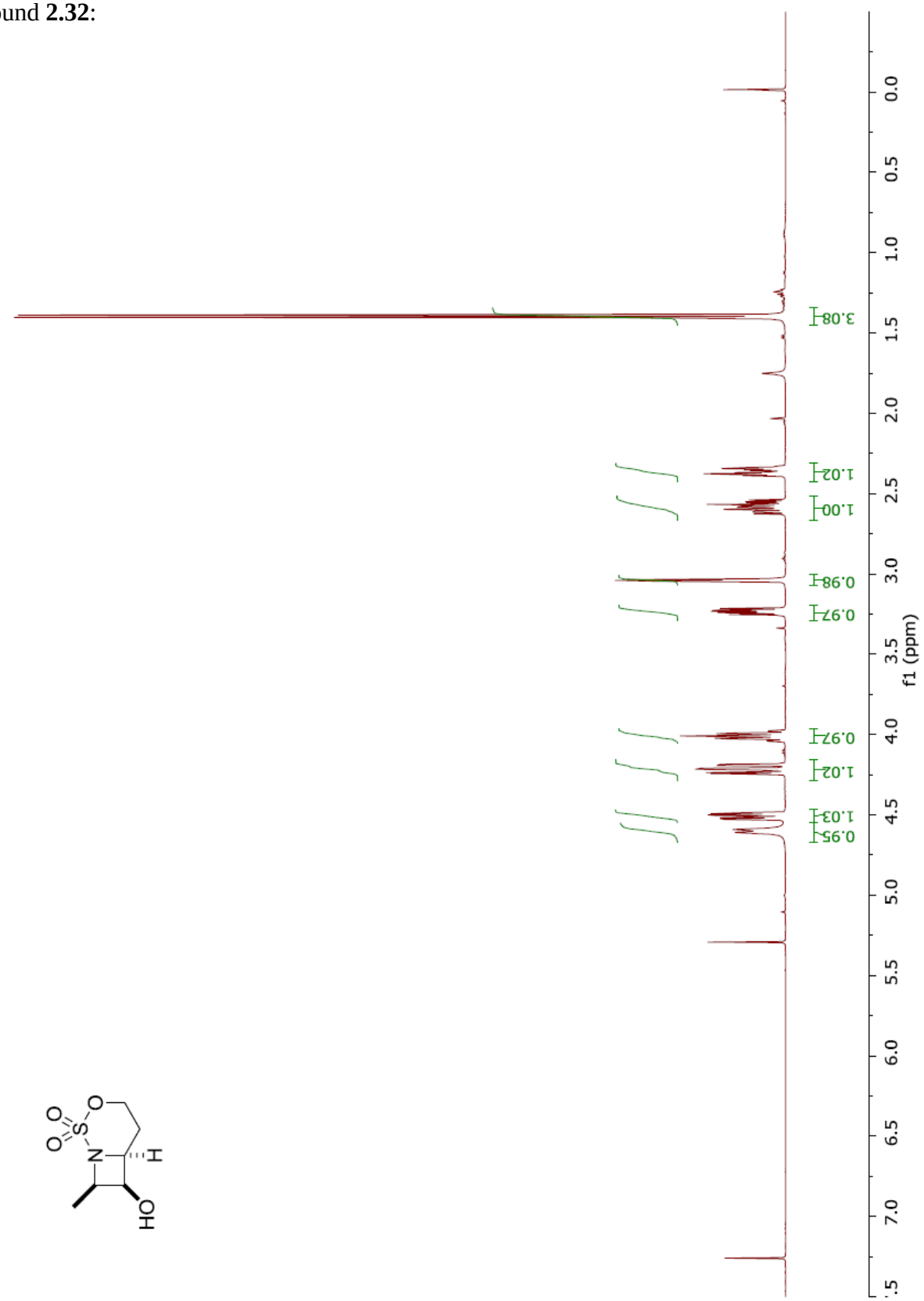
Compound **2.31**:



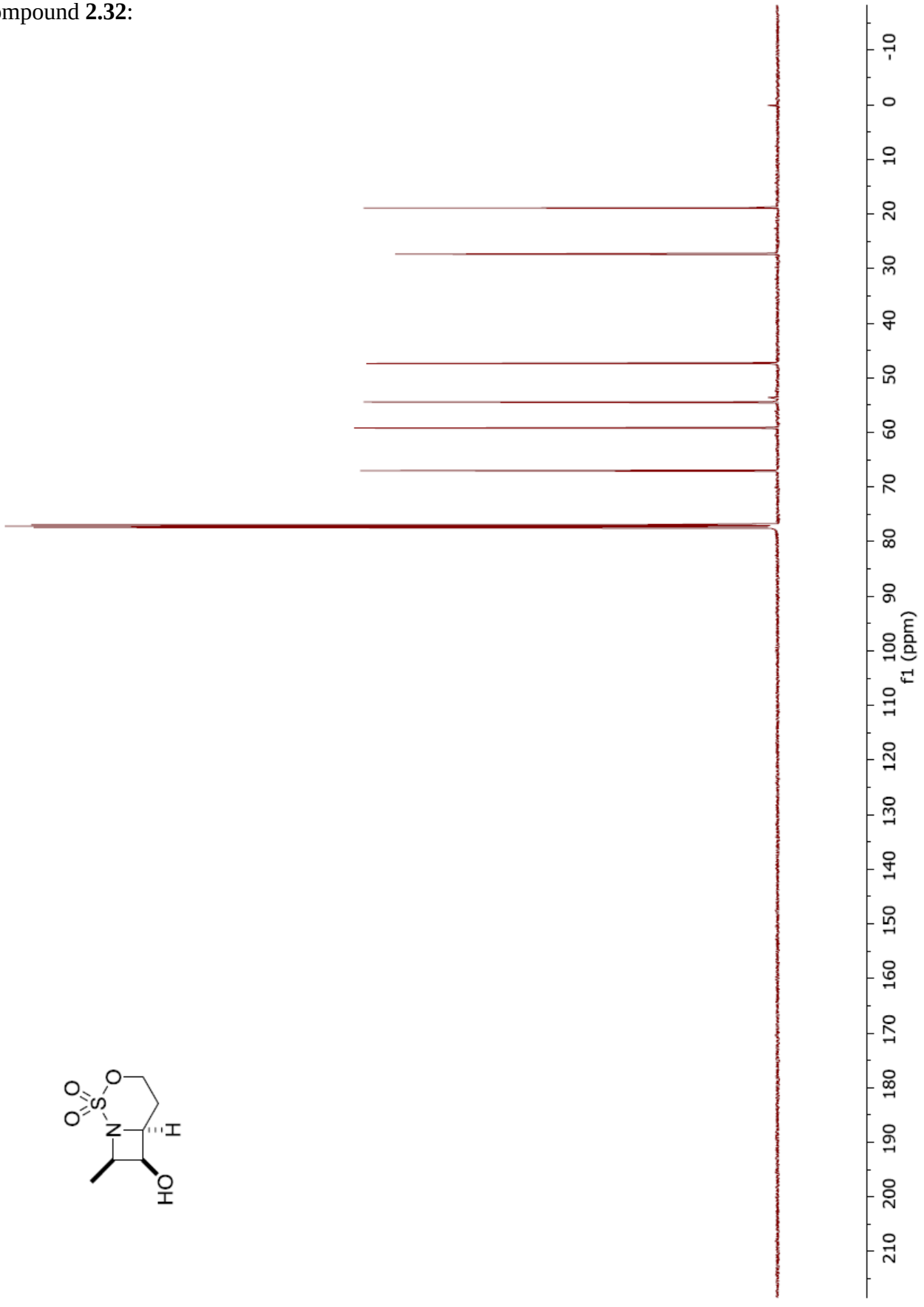
Compound **2.31**:



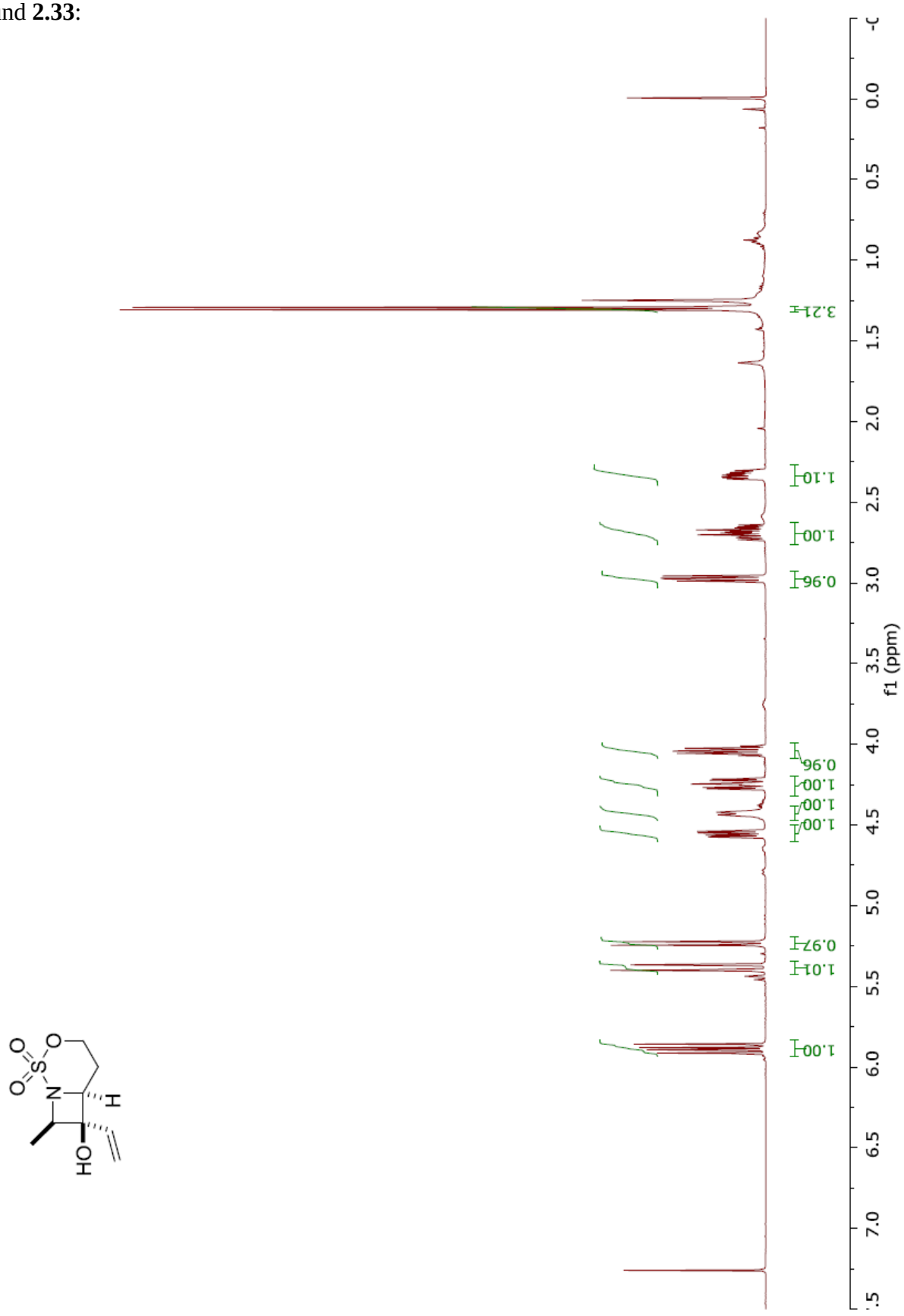
Compound **2.32**:



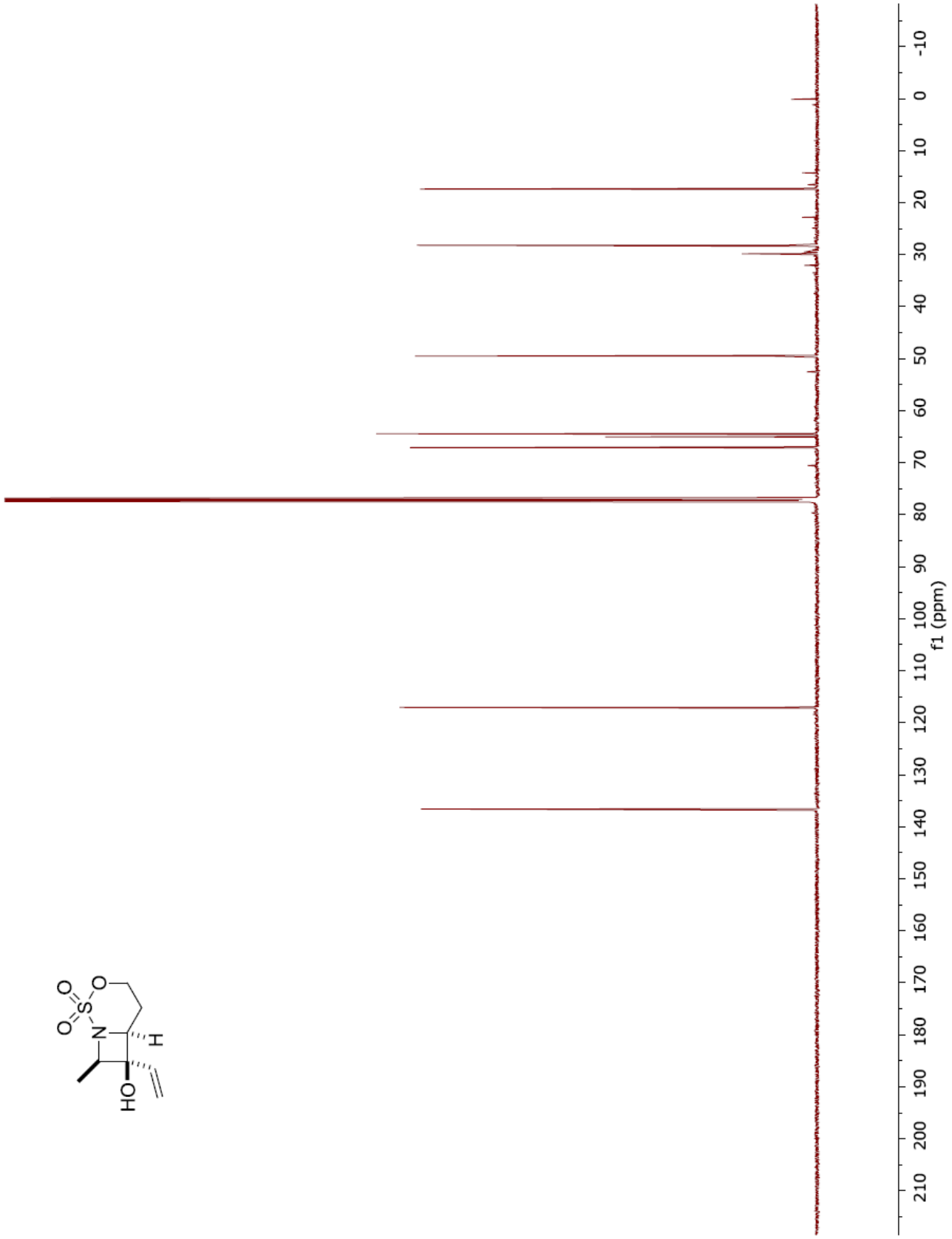
Compound **2.32**:



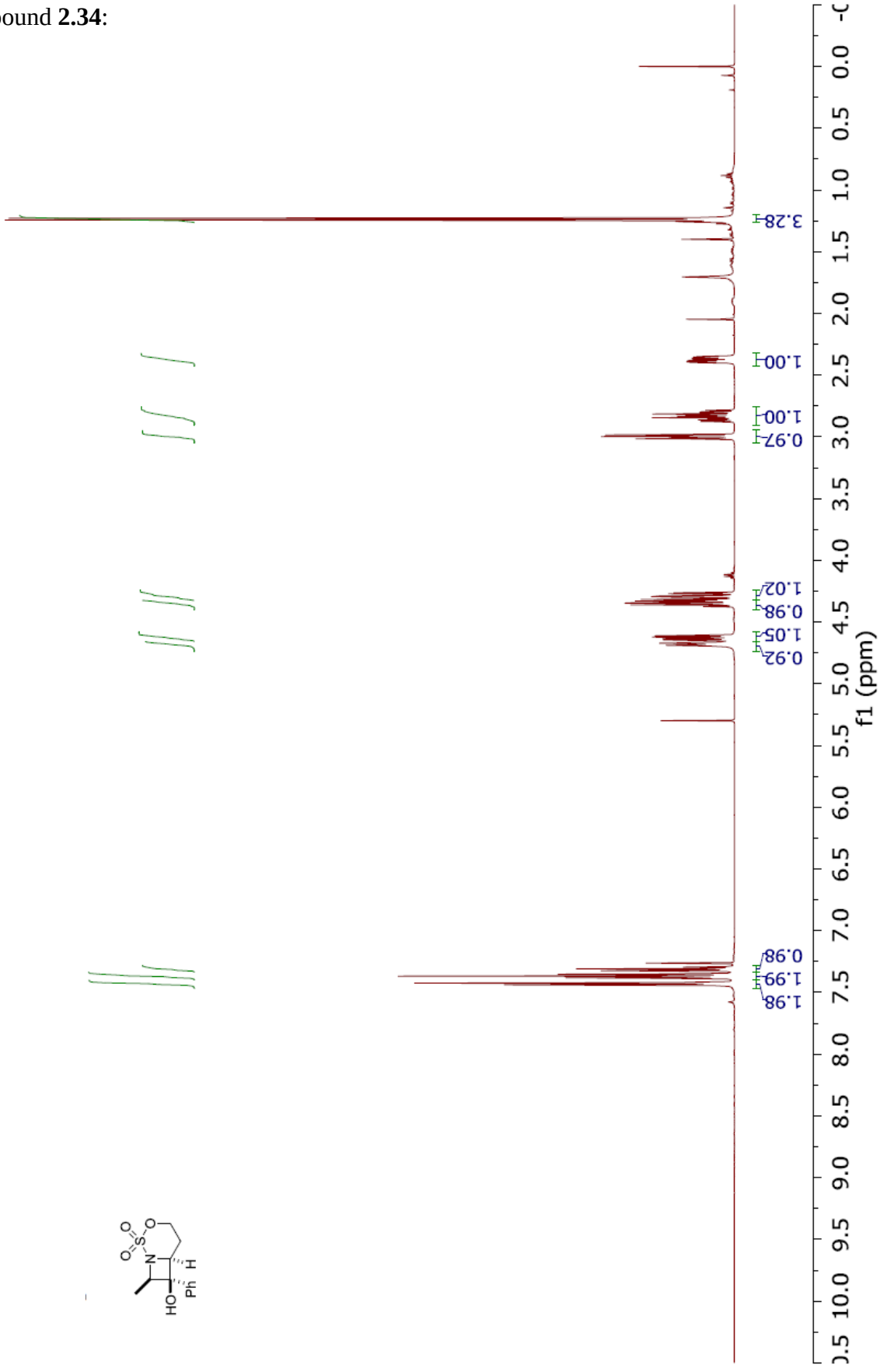
Compound **2.33**:



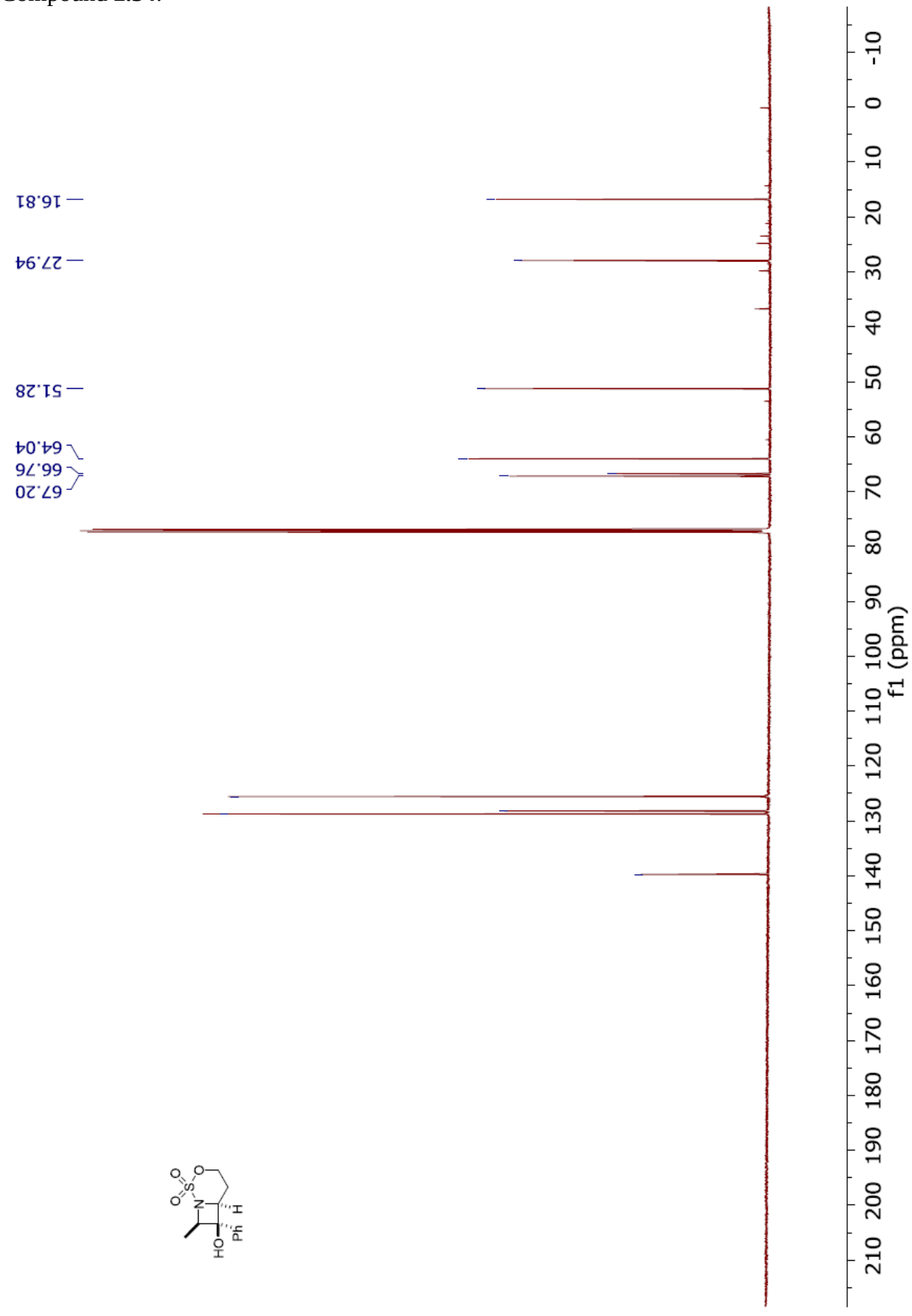
Compound **2.33**:



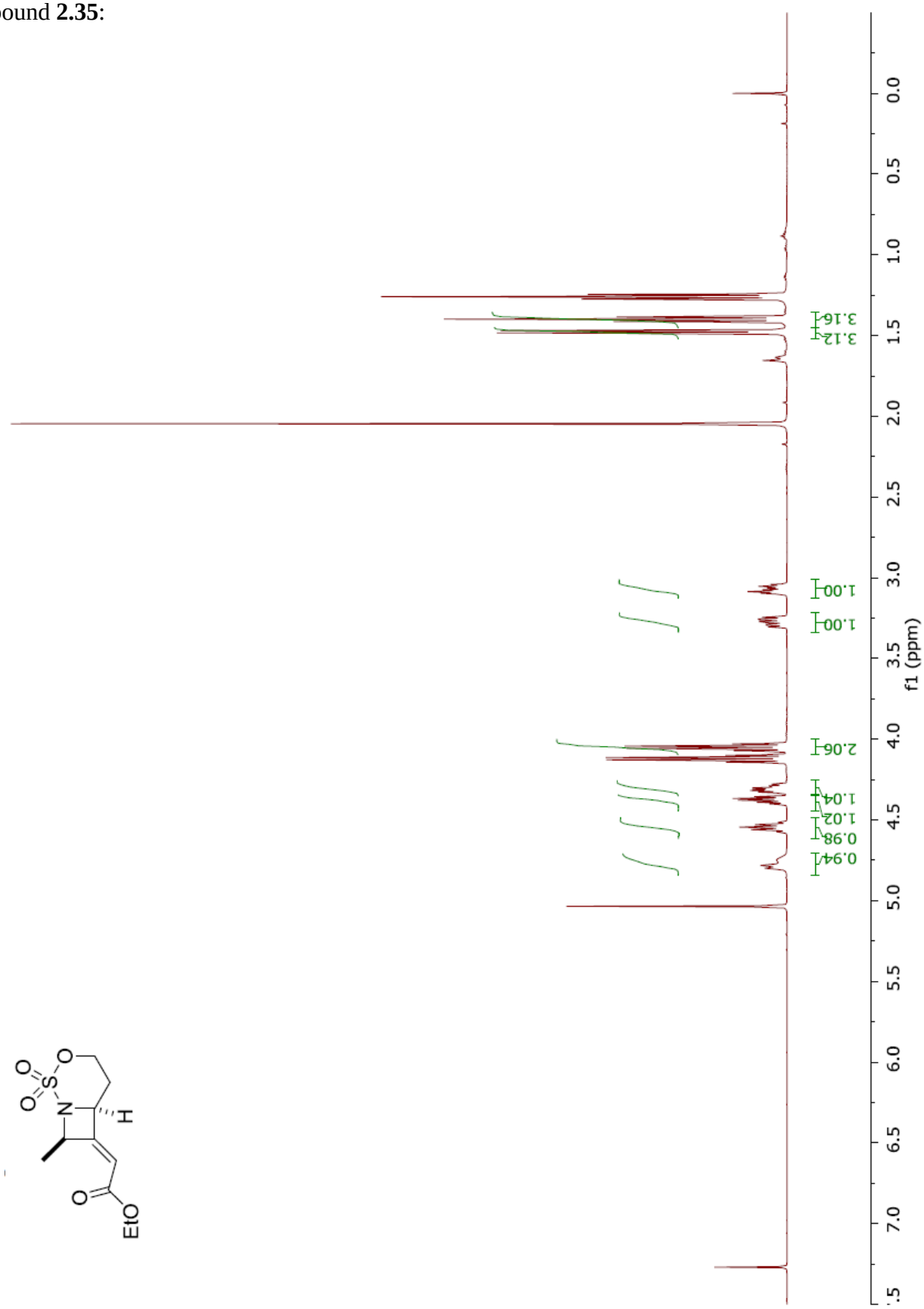
Compound **2.34**:



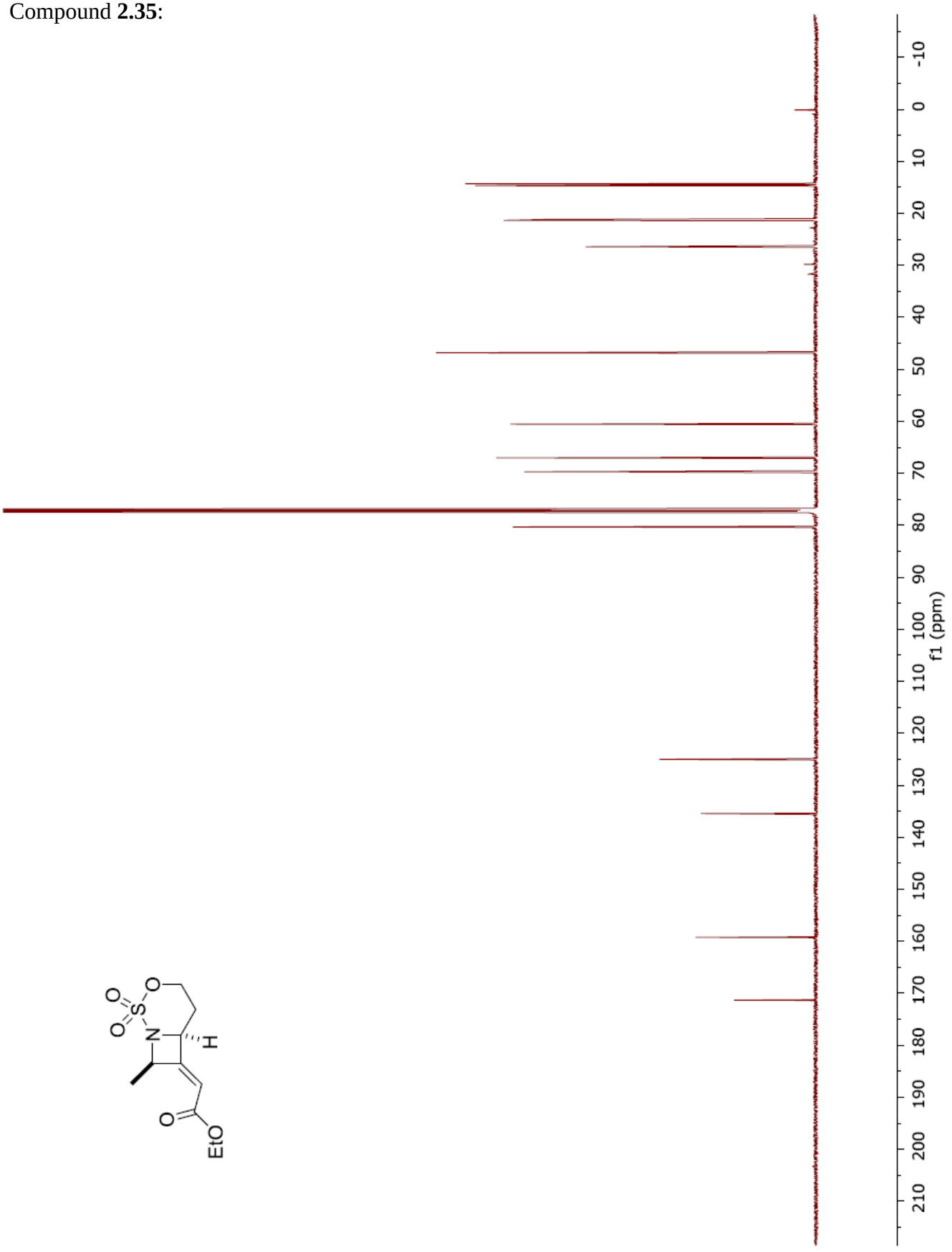
Compound **2.34**:



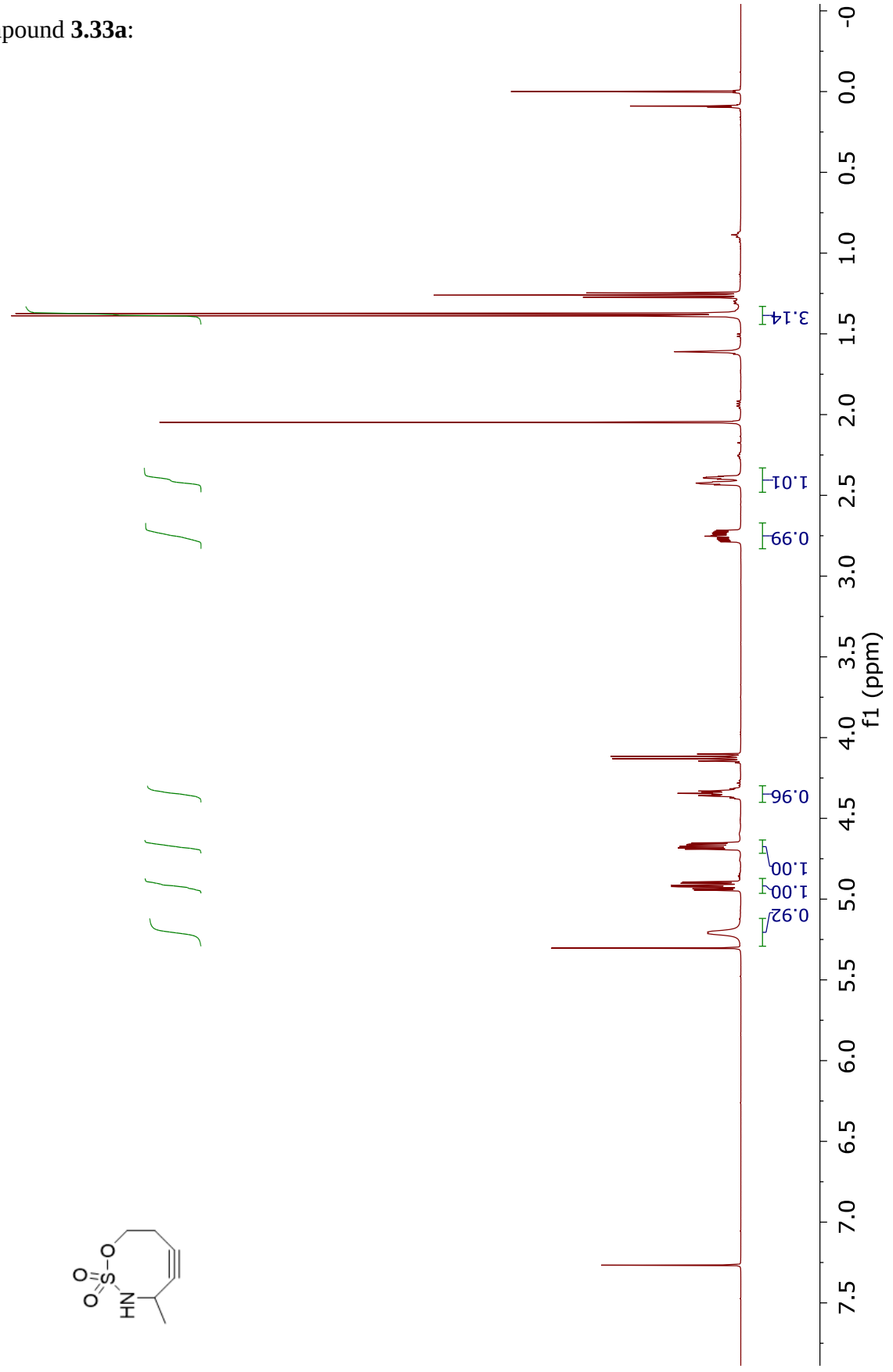
Compound **2.35**:



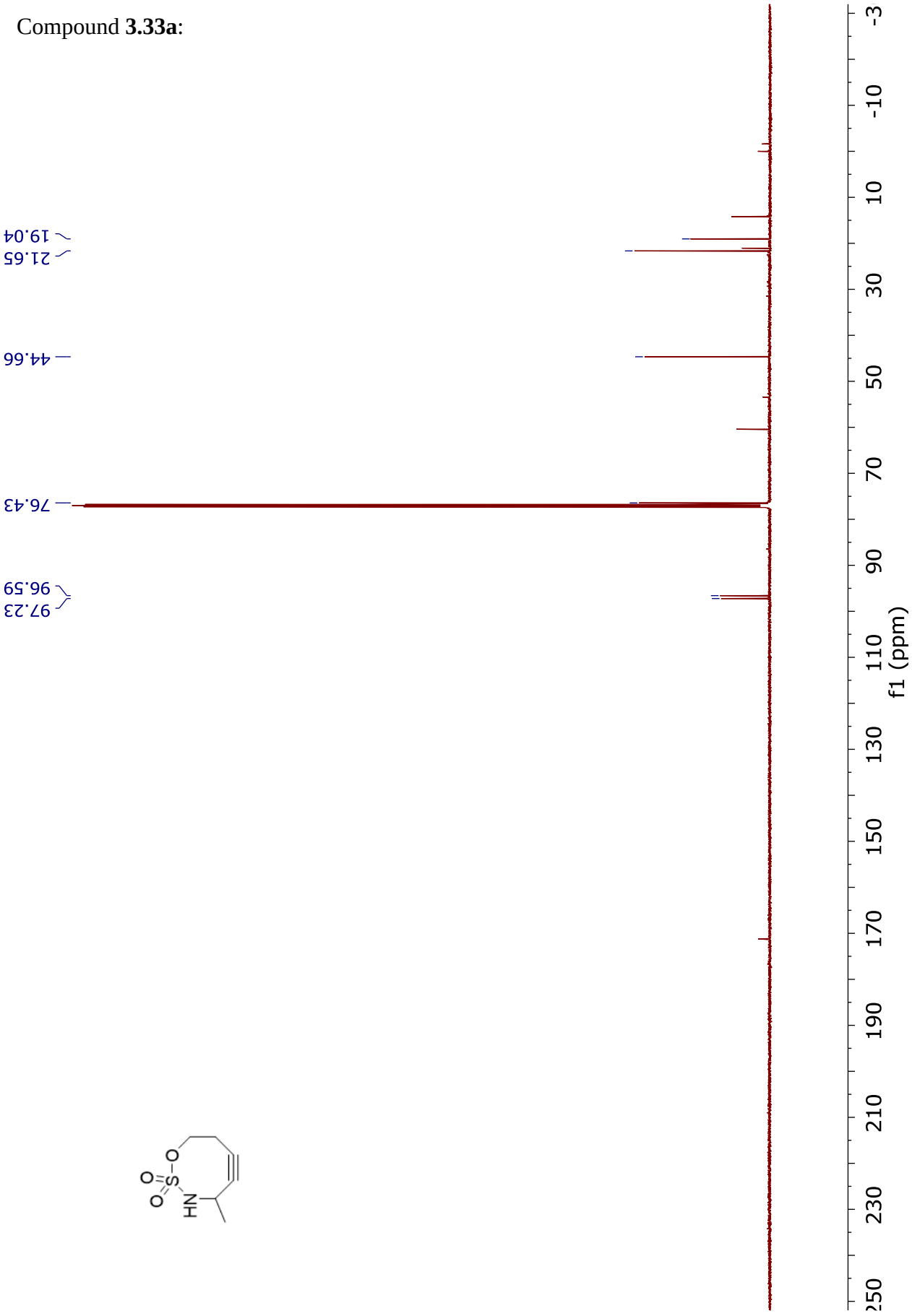
Compound **2.35**:



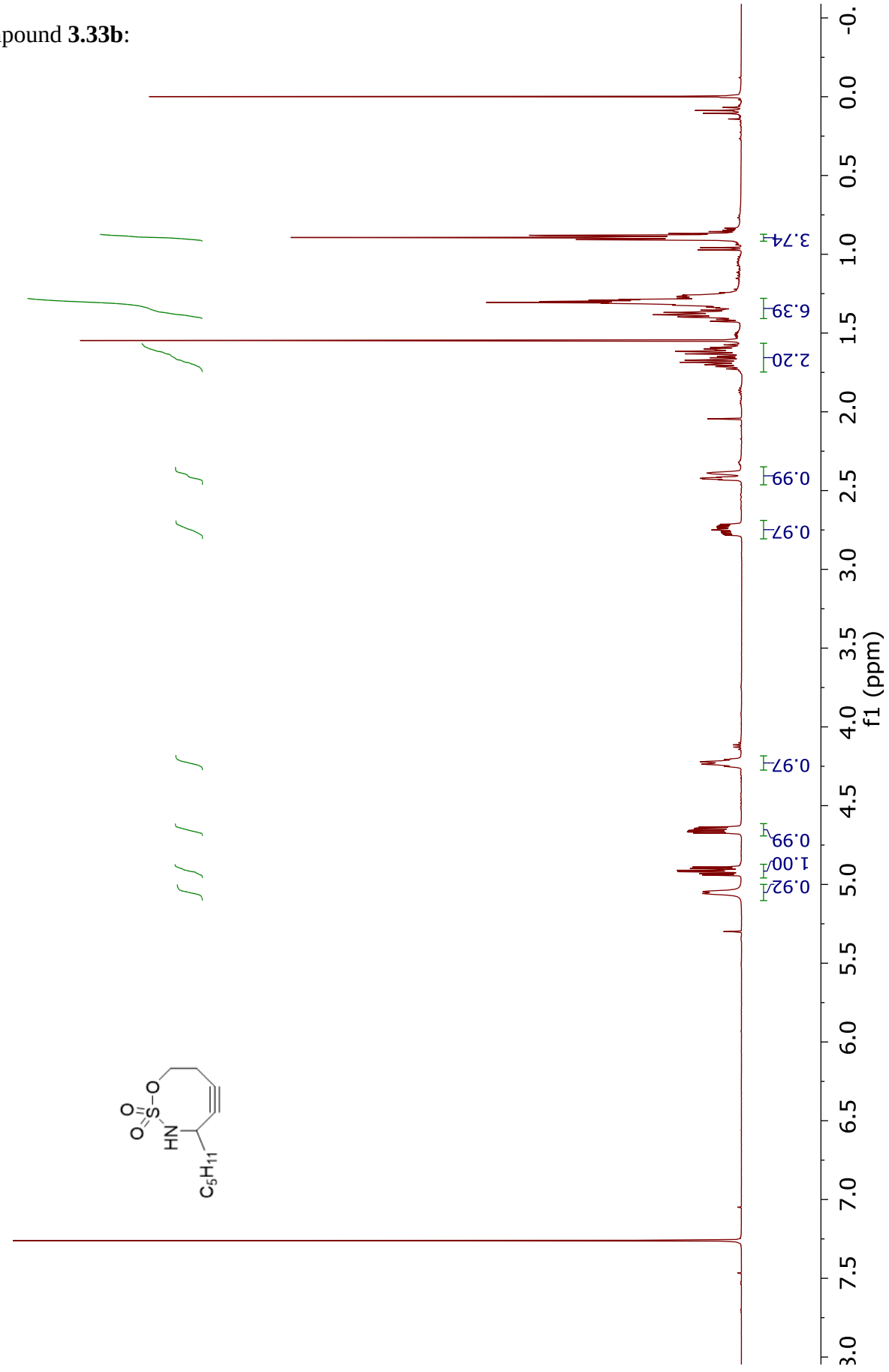
Compound **3.33a**:



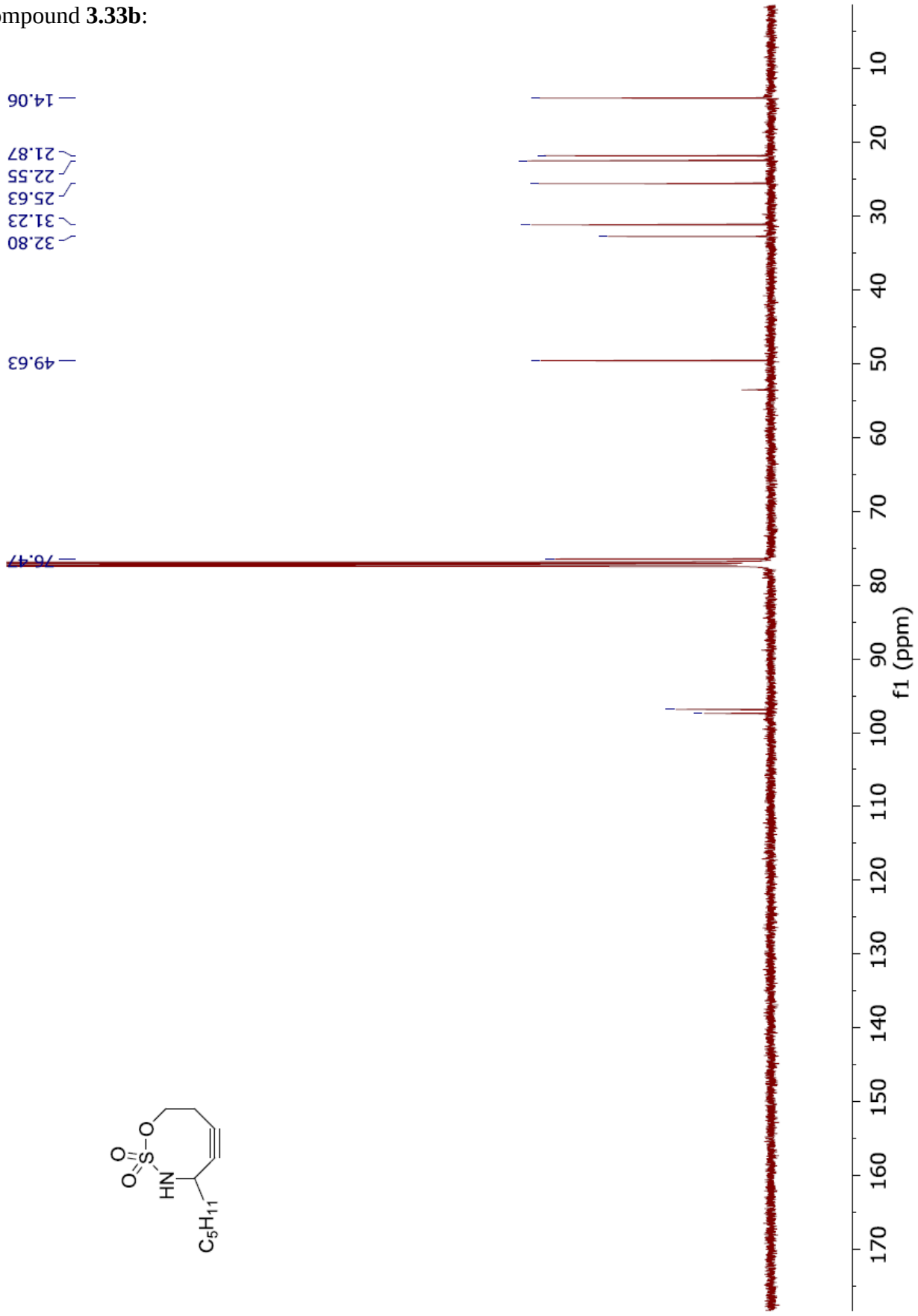
Compound **3.33a**:



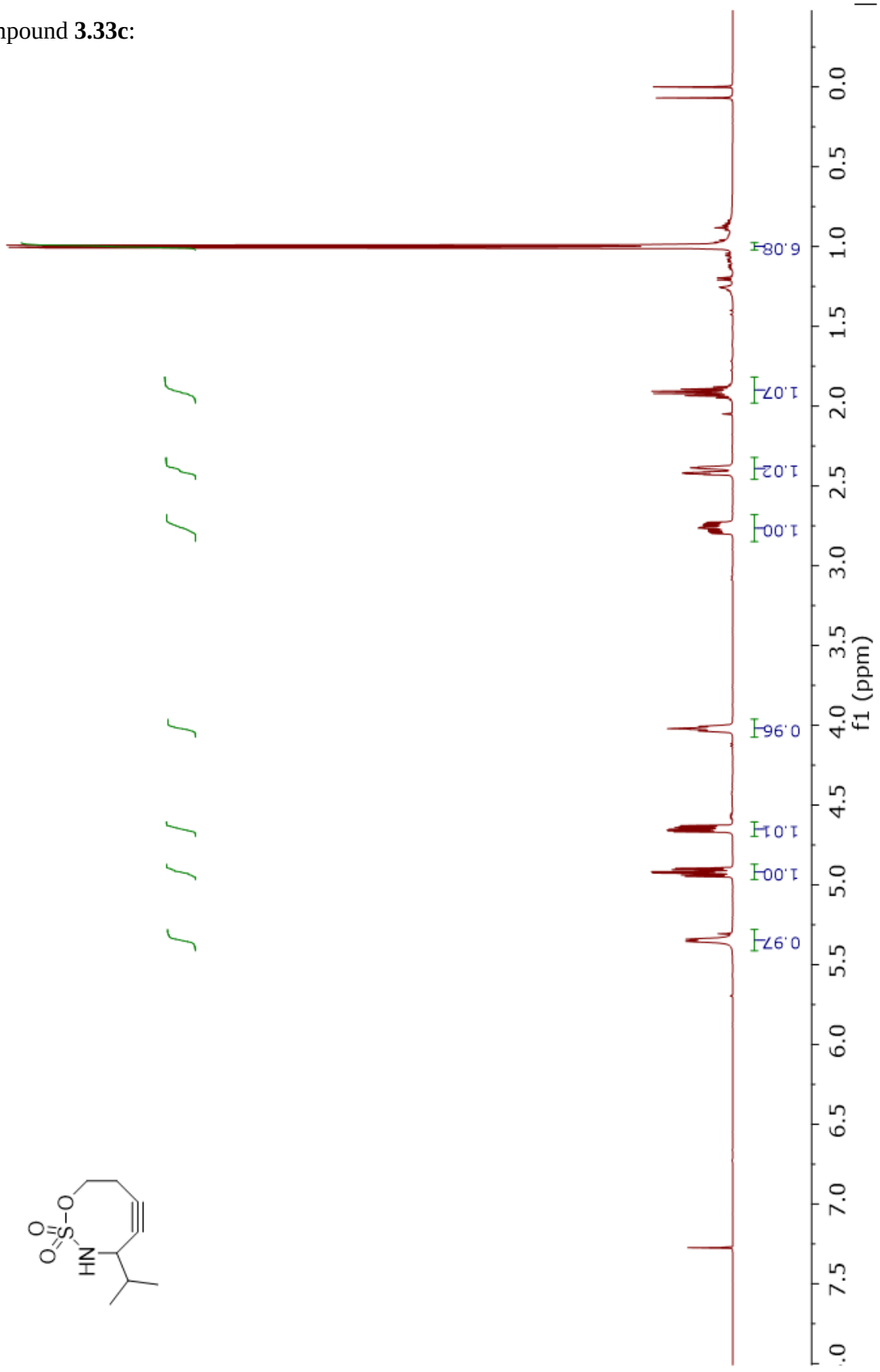
Compound **3.33b**:



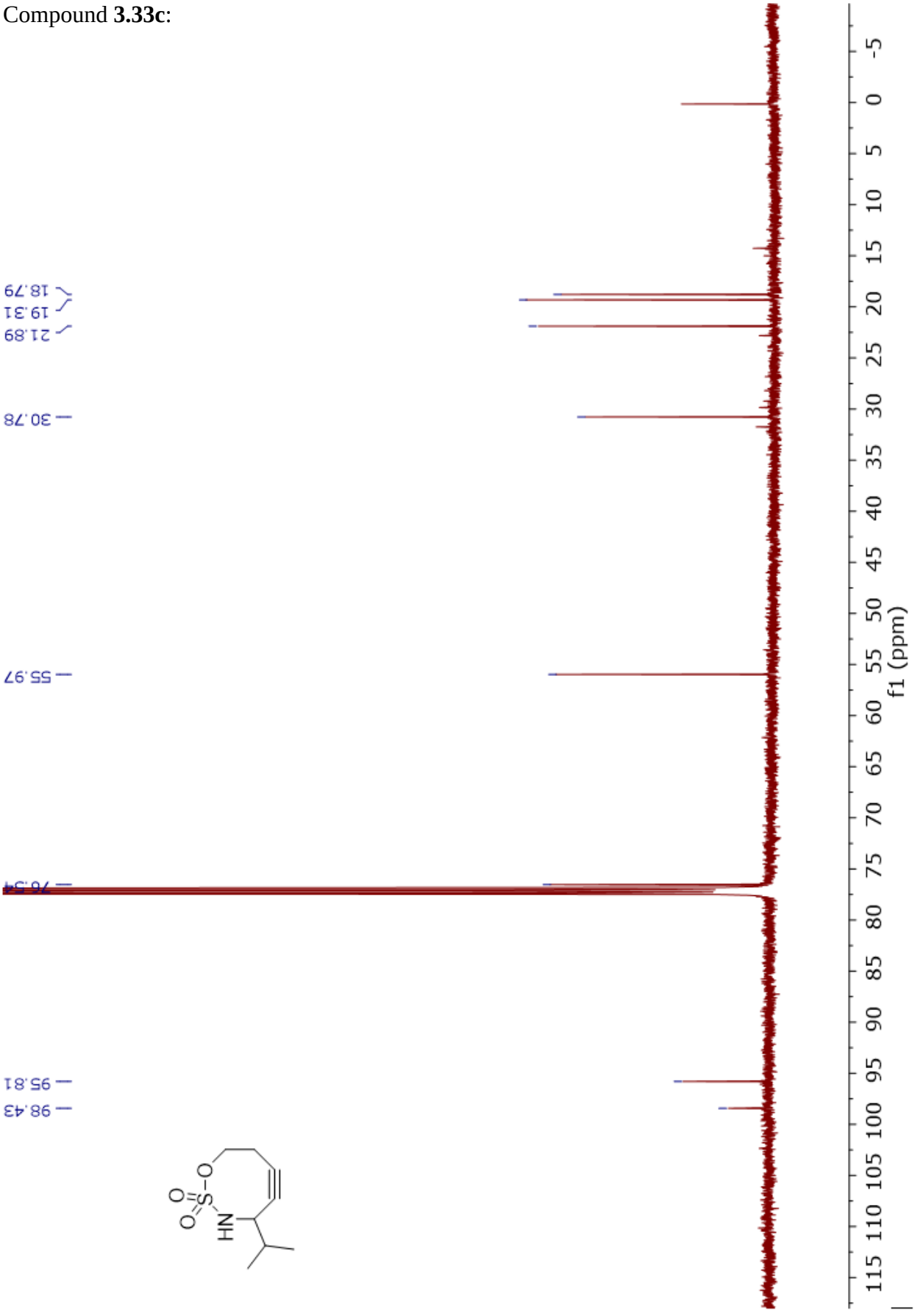
Compound **3.33b**:



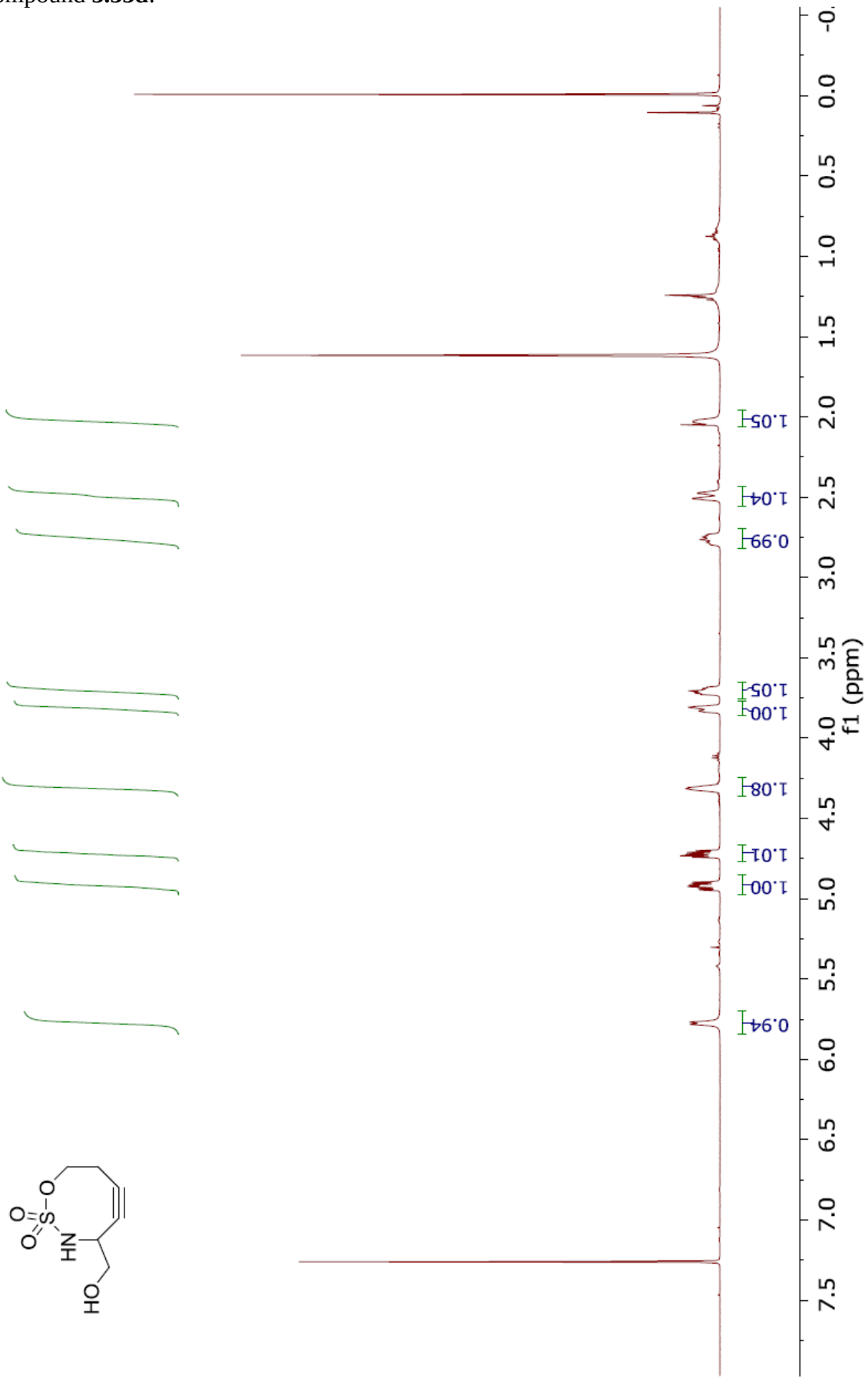
Compound **3.33c**:



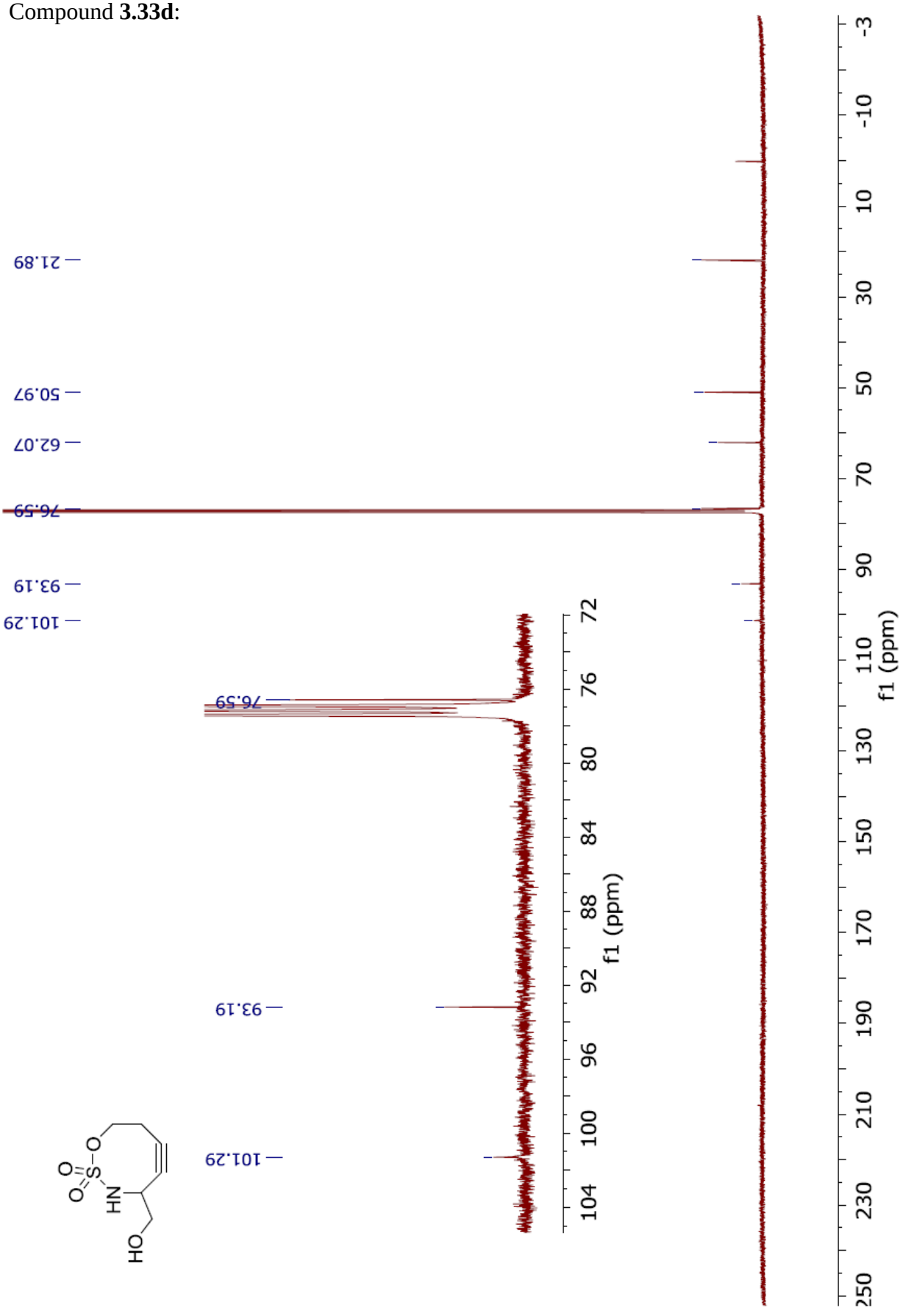
Compound **3.33c**:



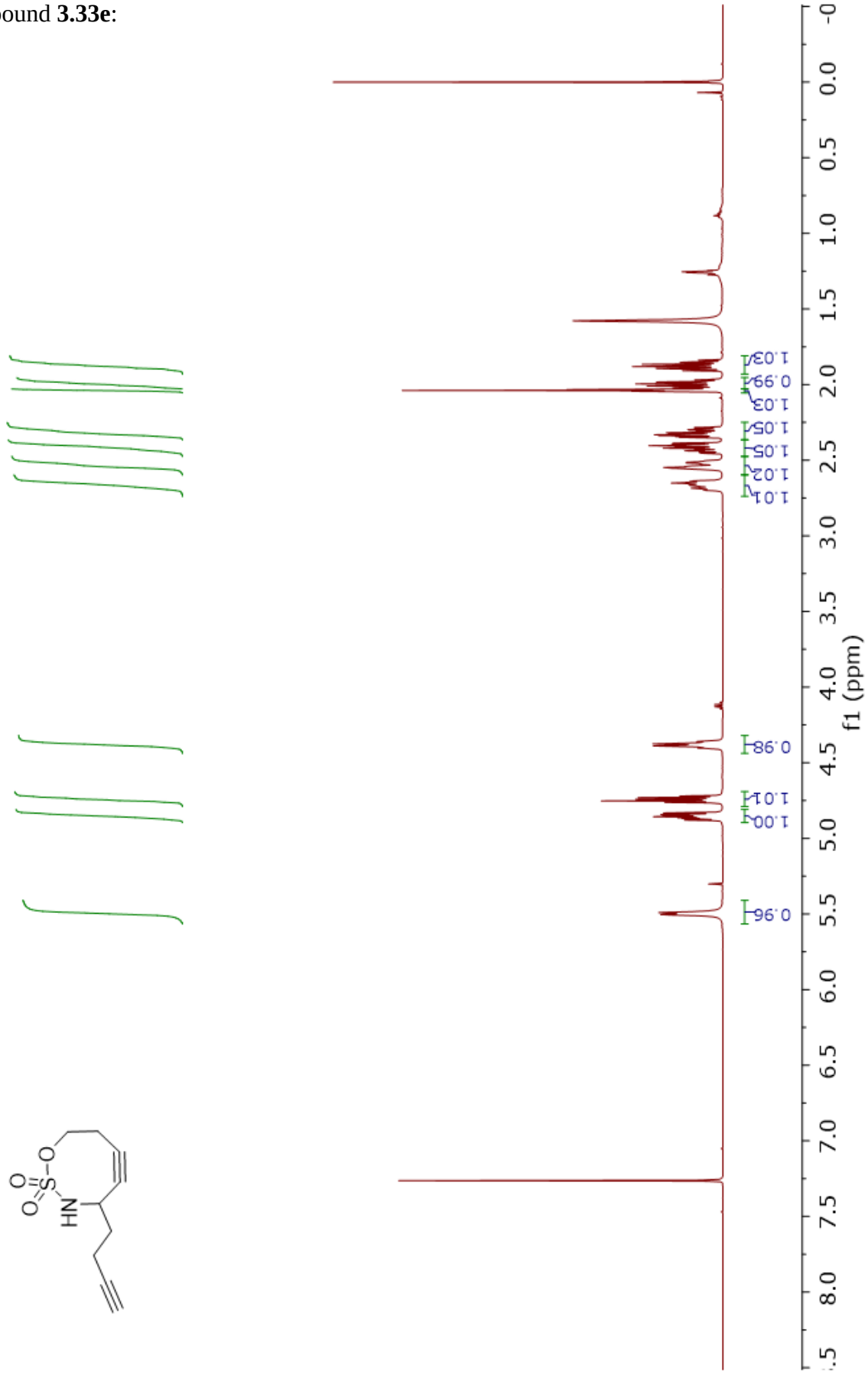
Compound **3.33d**:



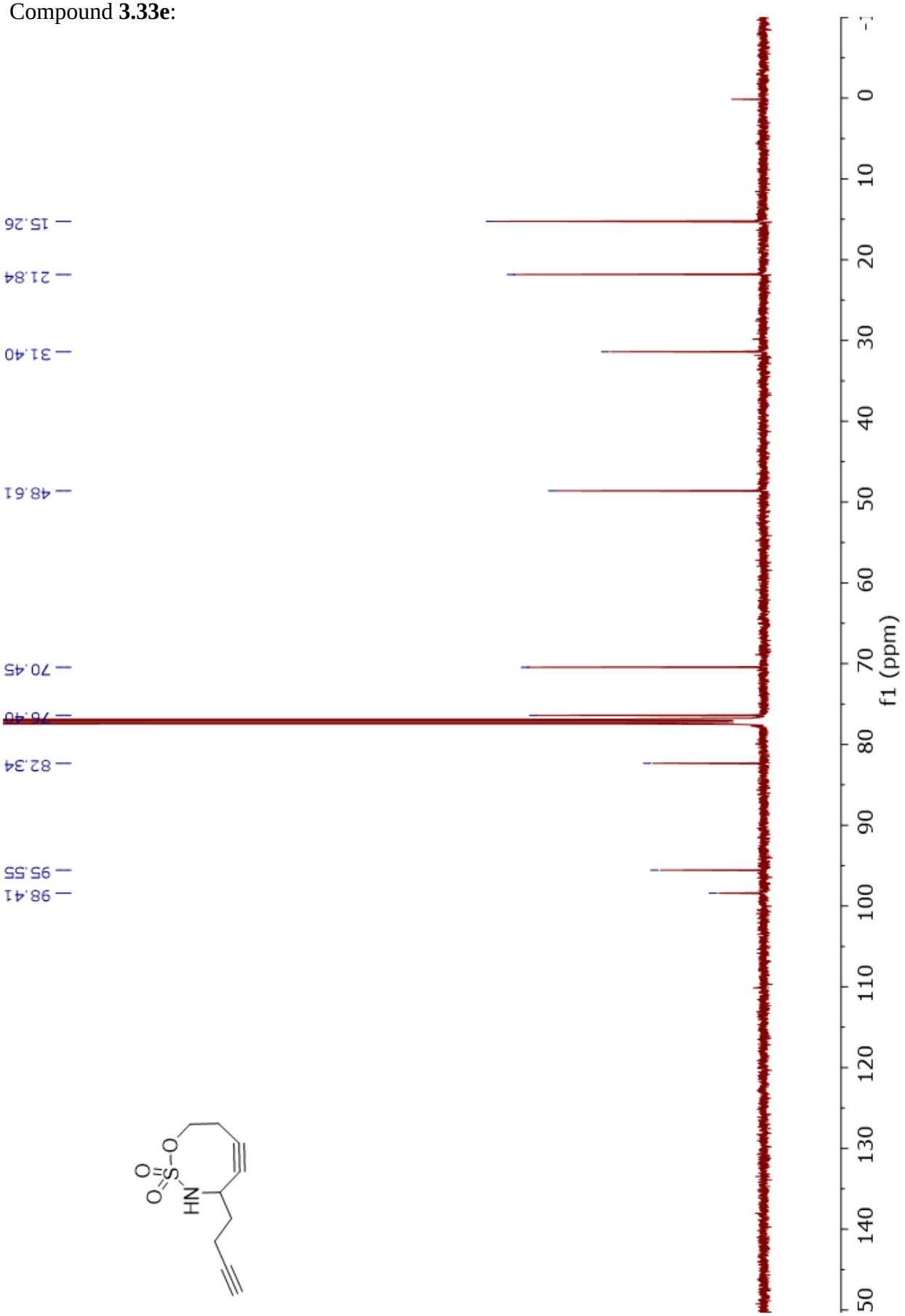
Compound **3.33d**:



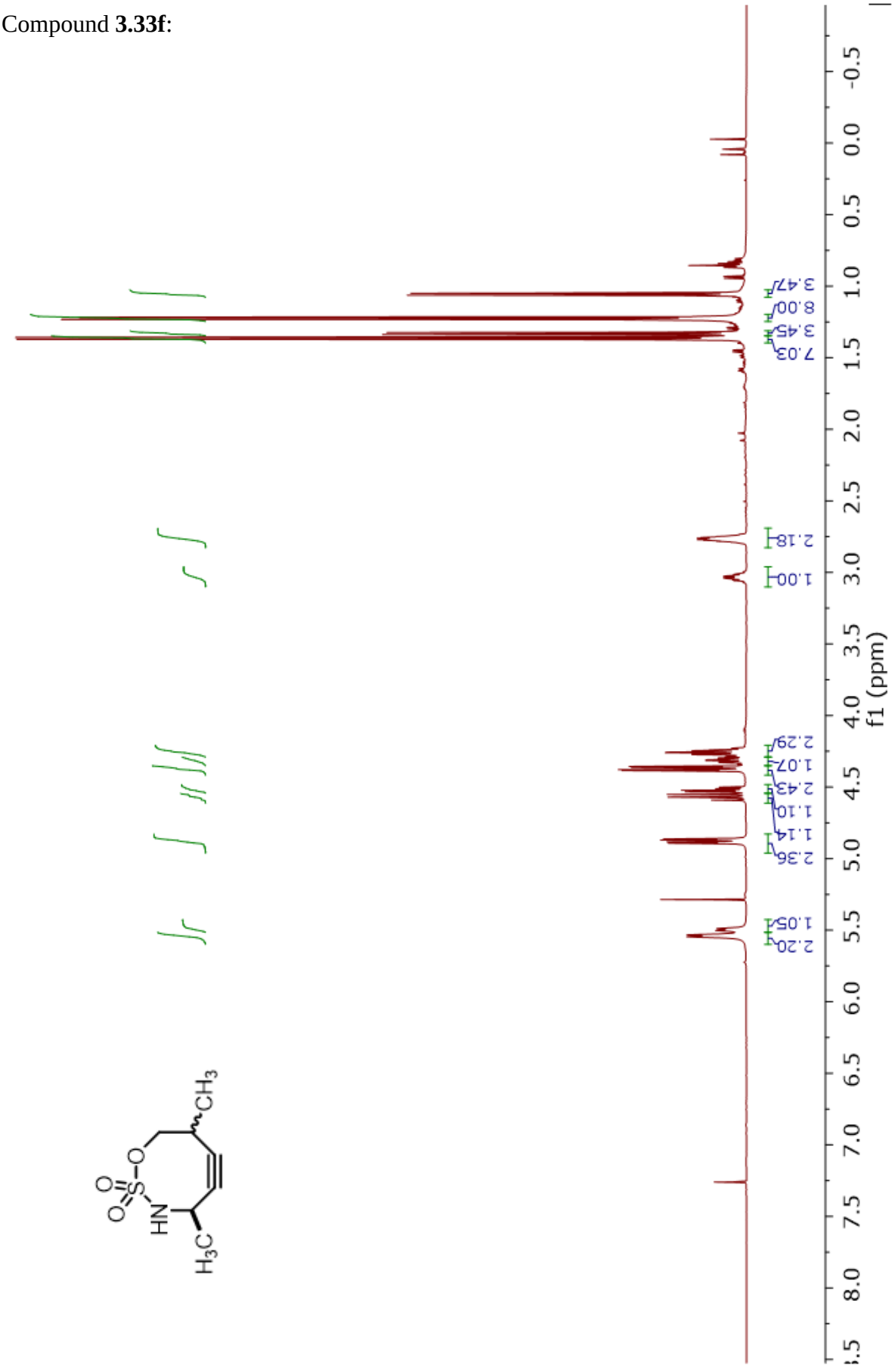
Compound **3.33e**:



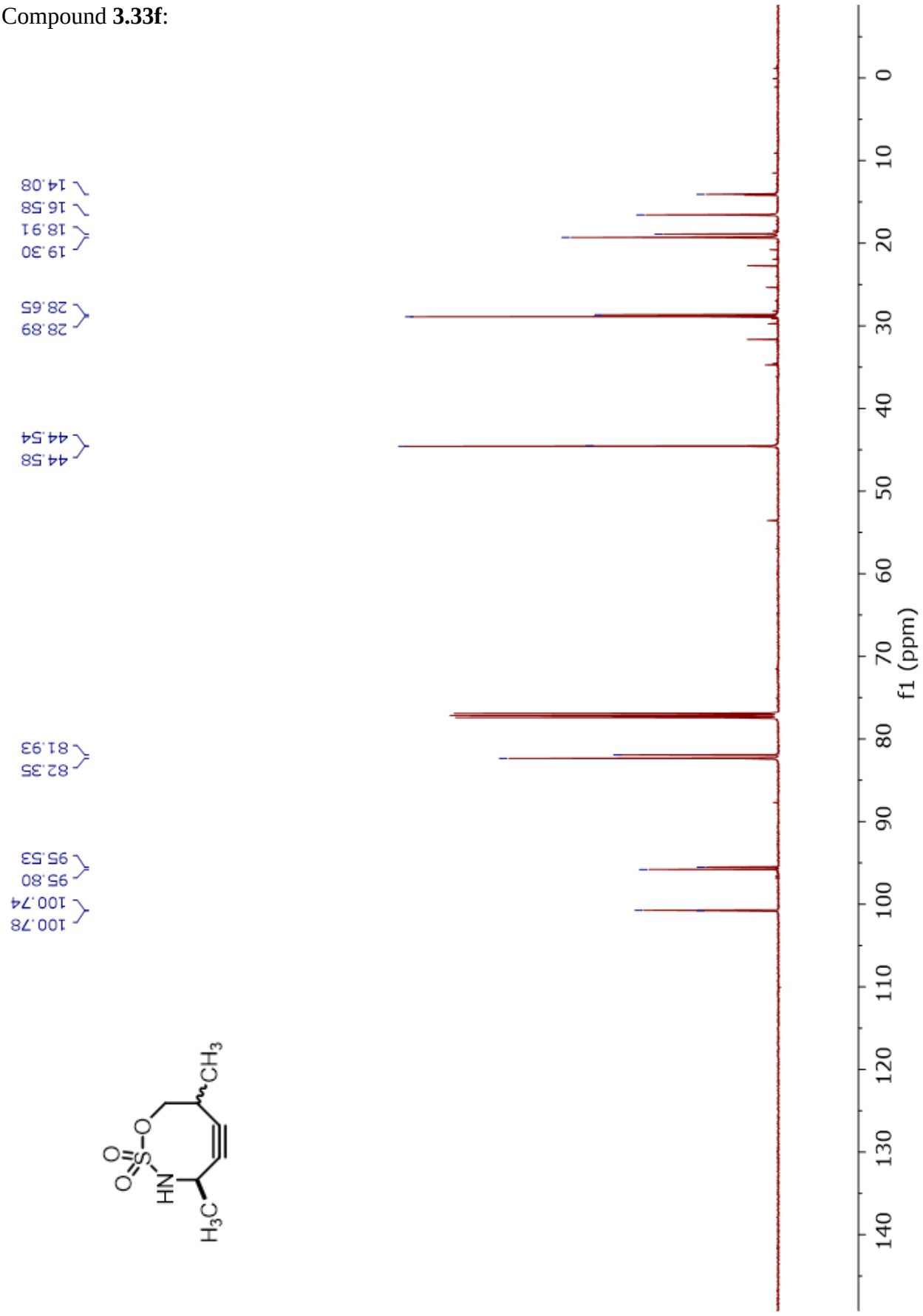
Compound **3.33e**:



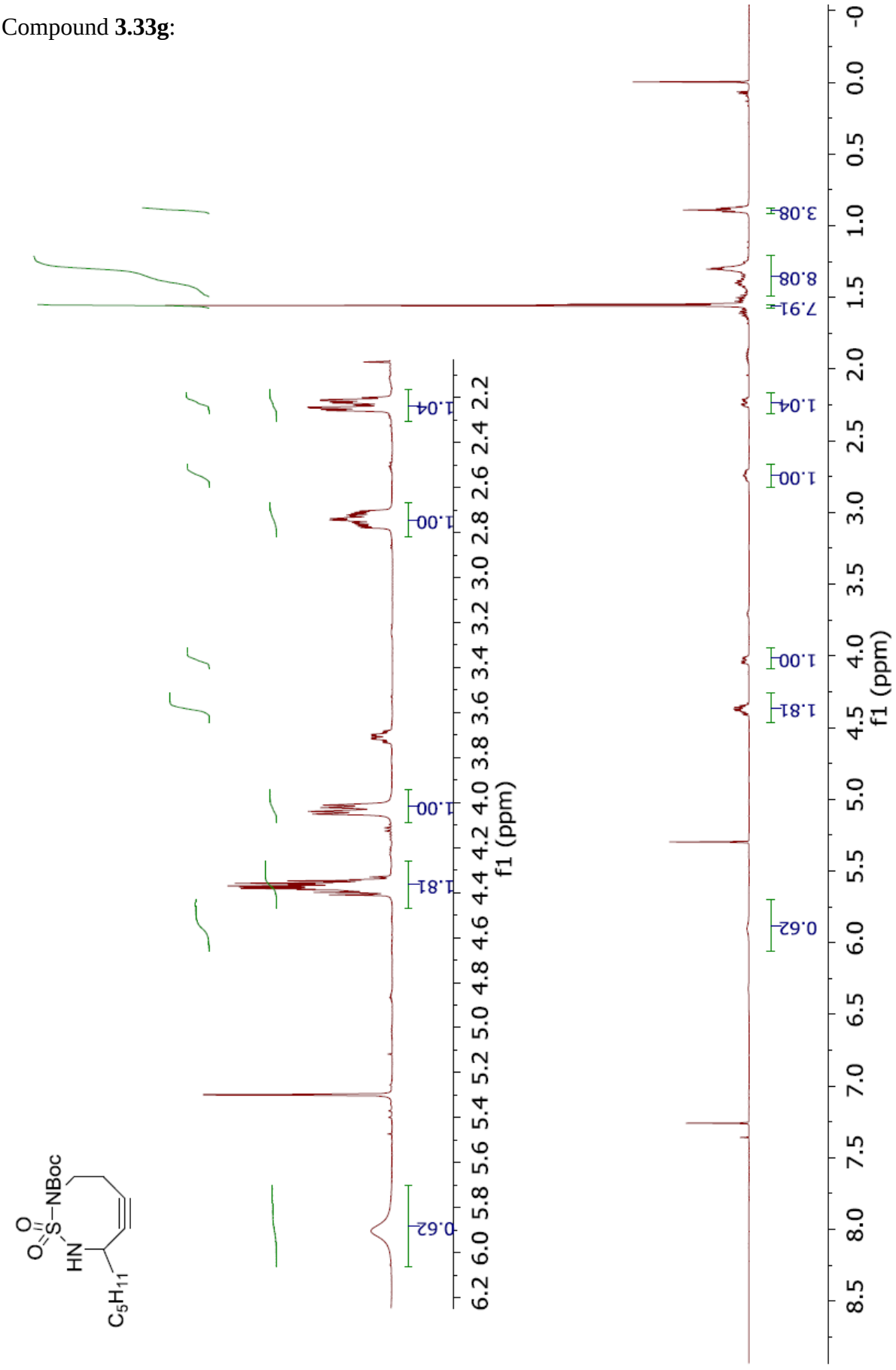
Compound **3.33f**:



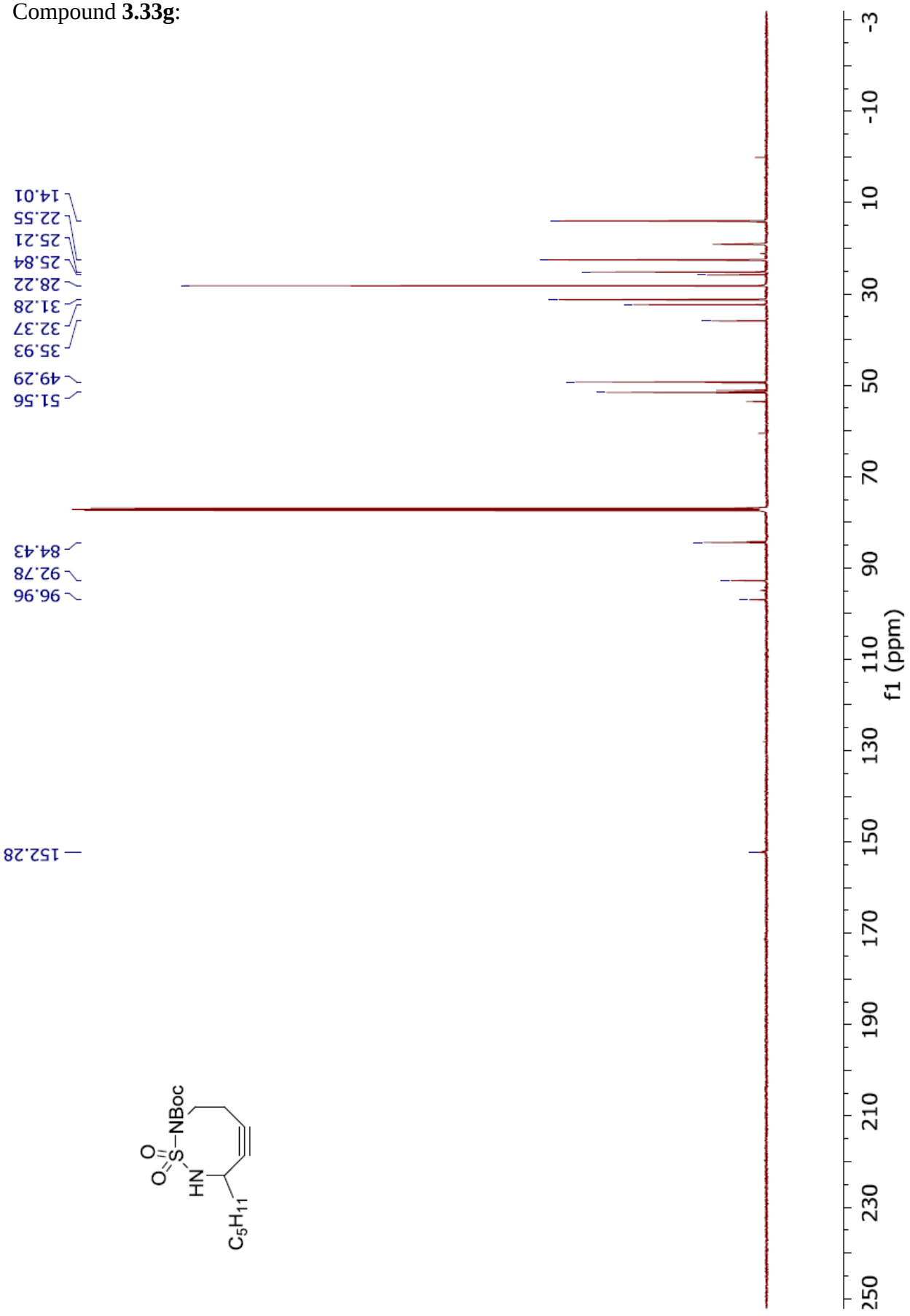
Compound **3.33f**:



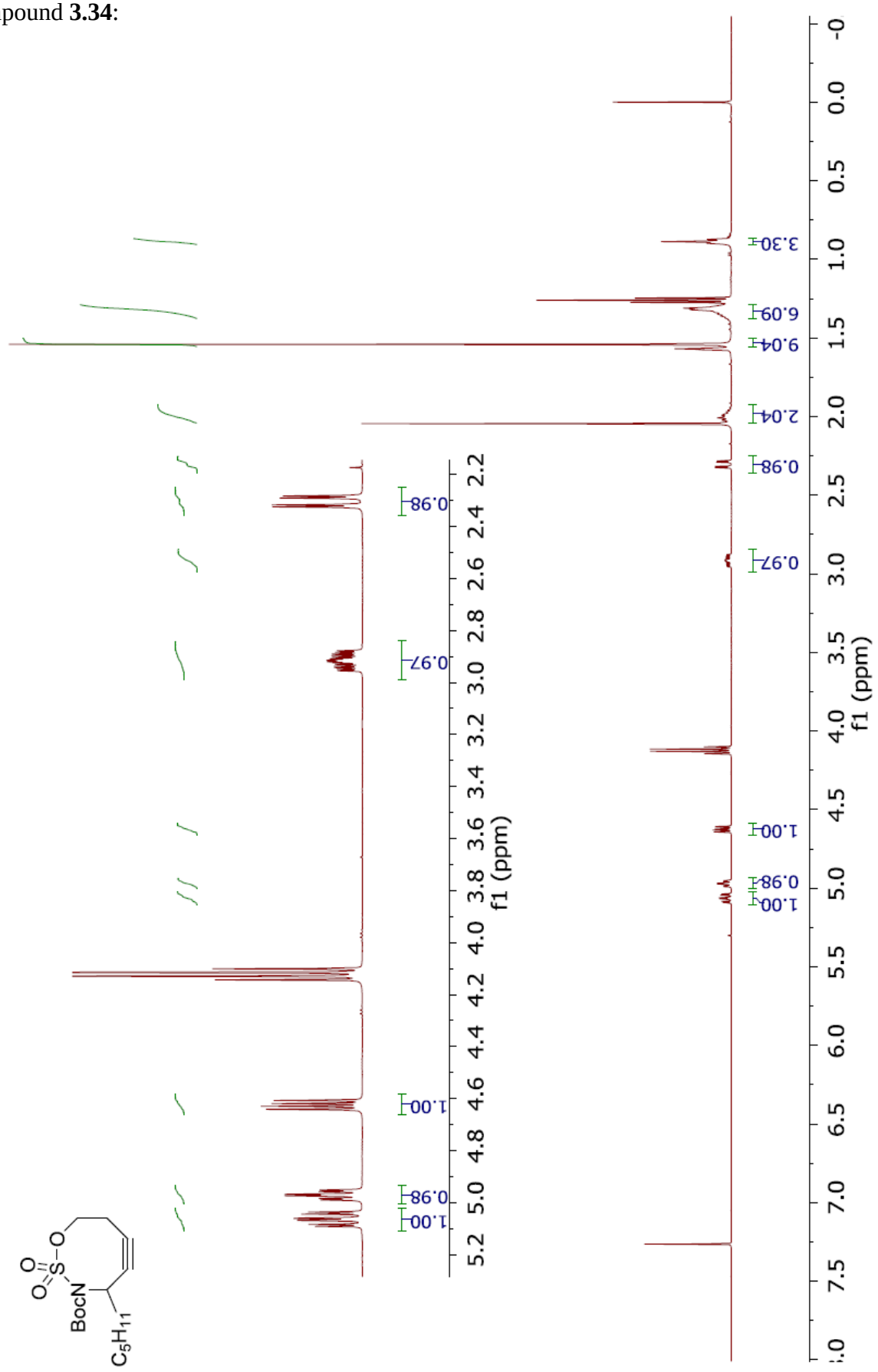
Compound **3.33g**:



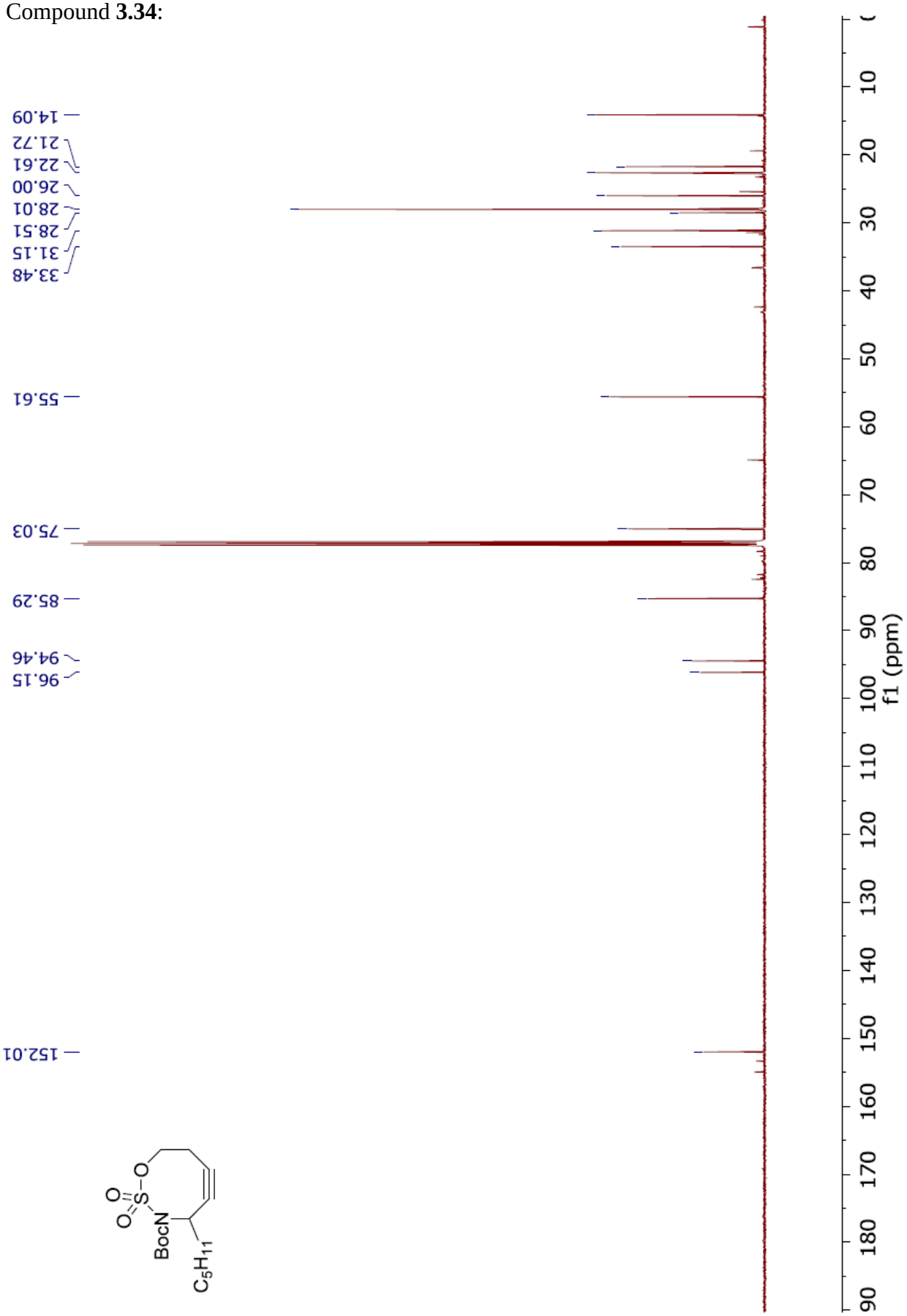
Compound **3.33g**:



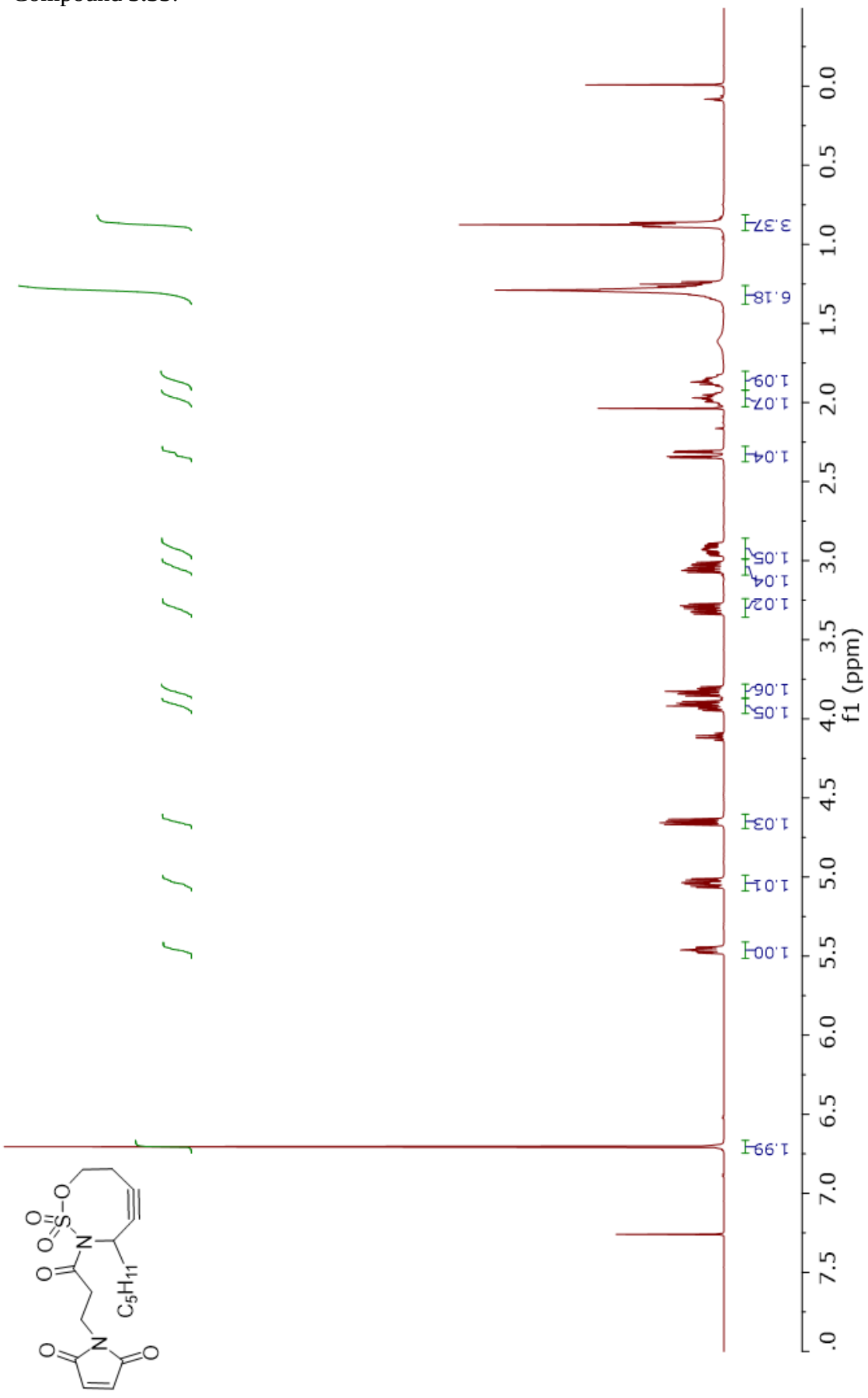
Compound **3.34**:



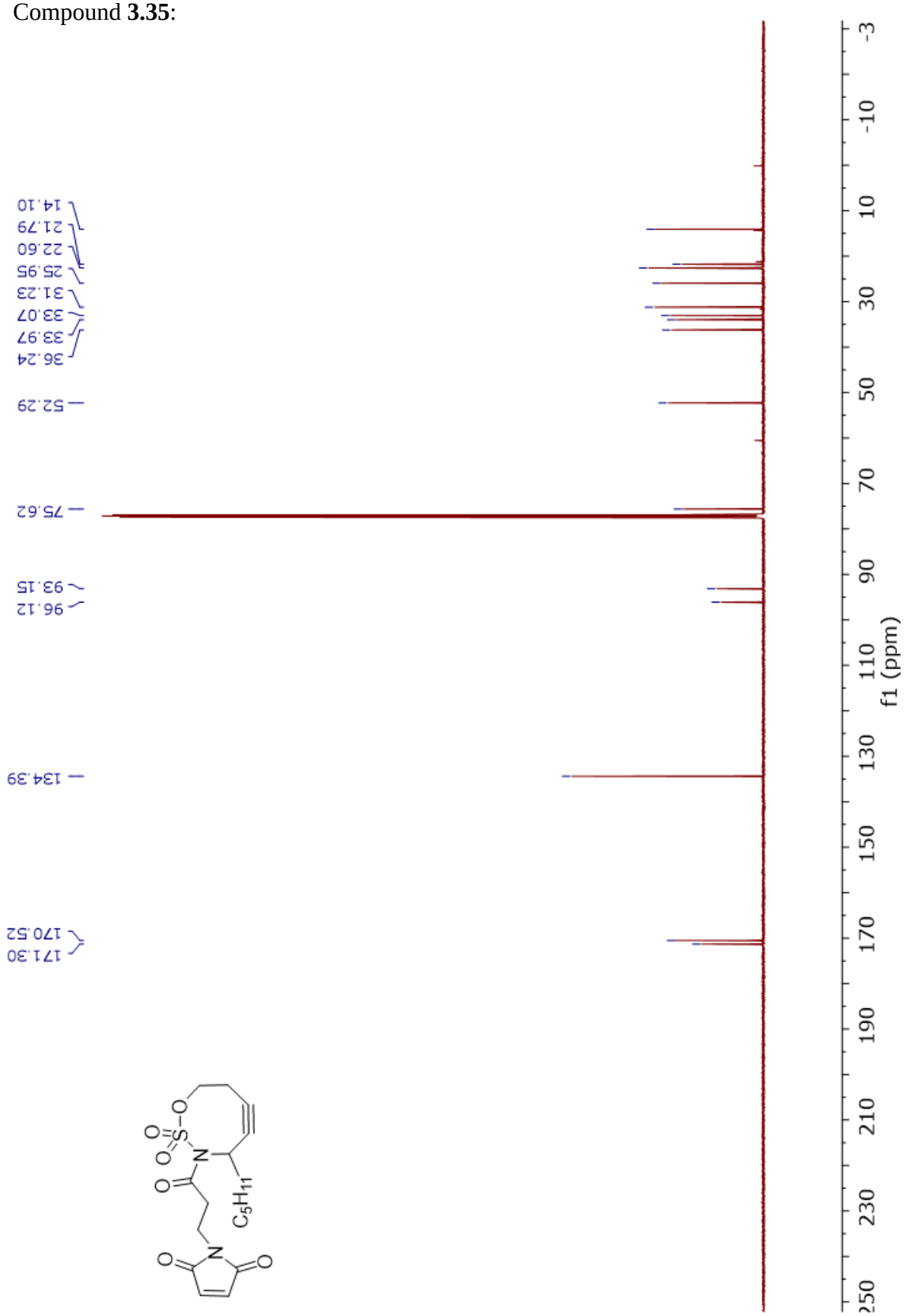
Compound **3.34**:



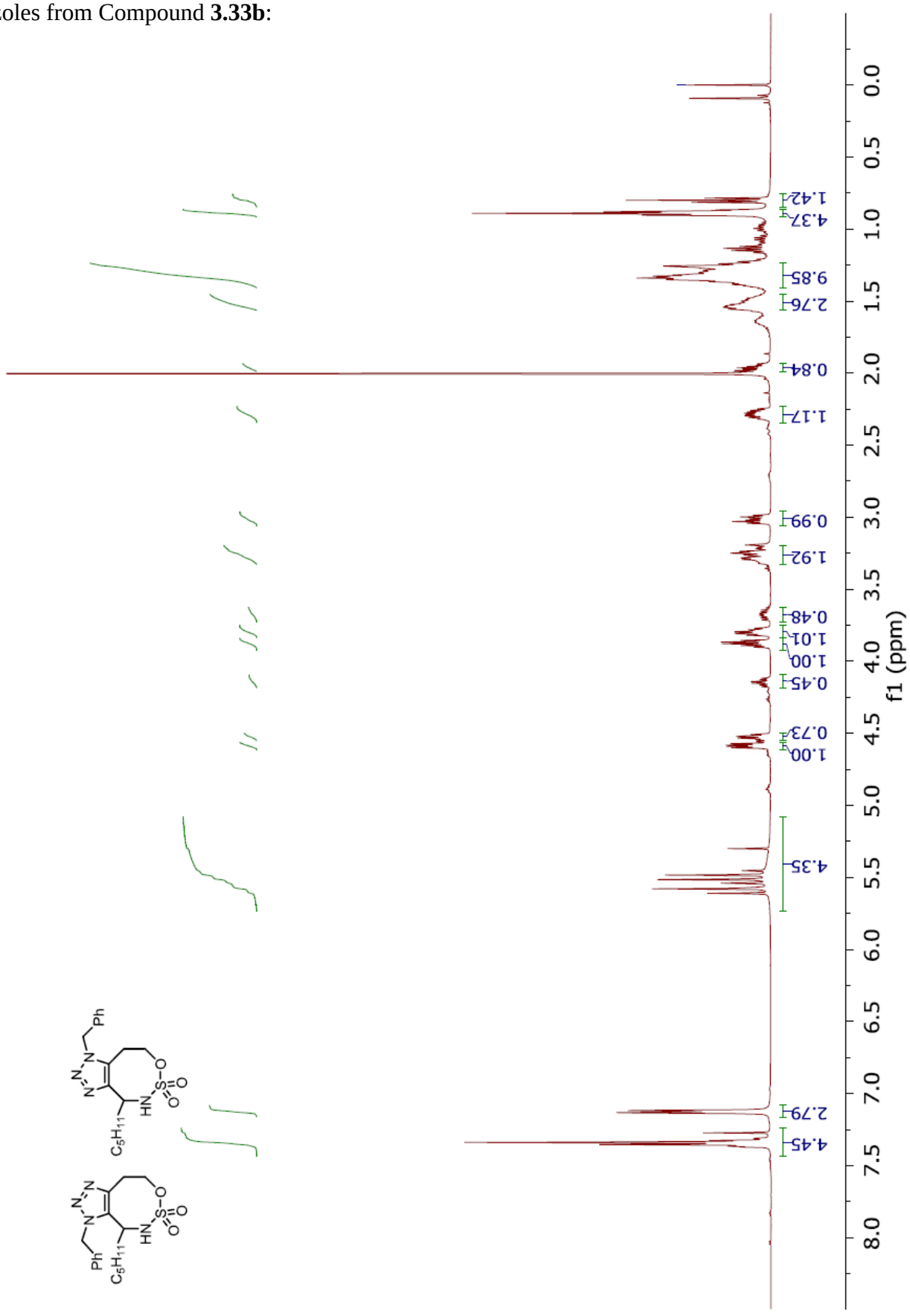
Compound **3.35**:



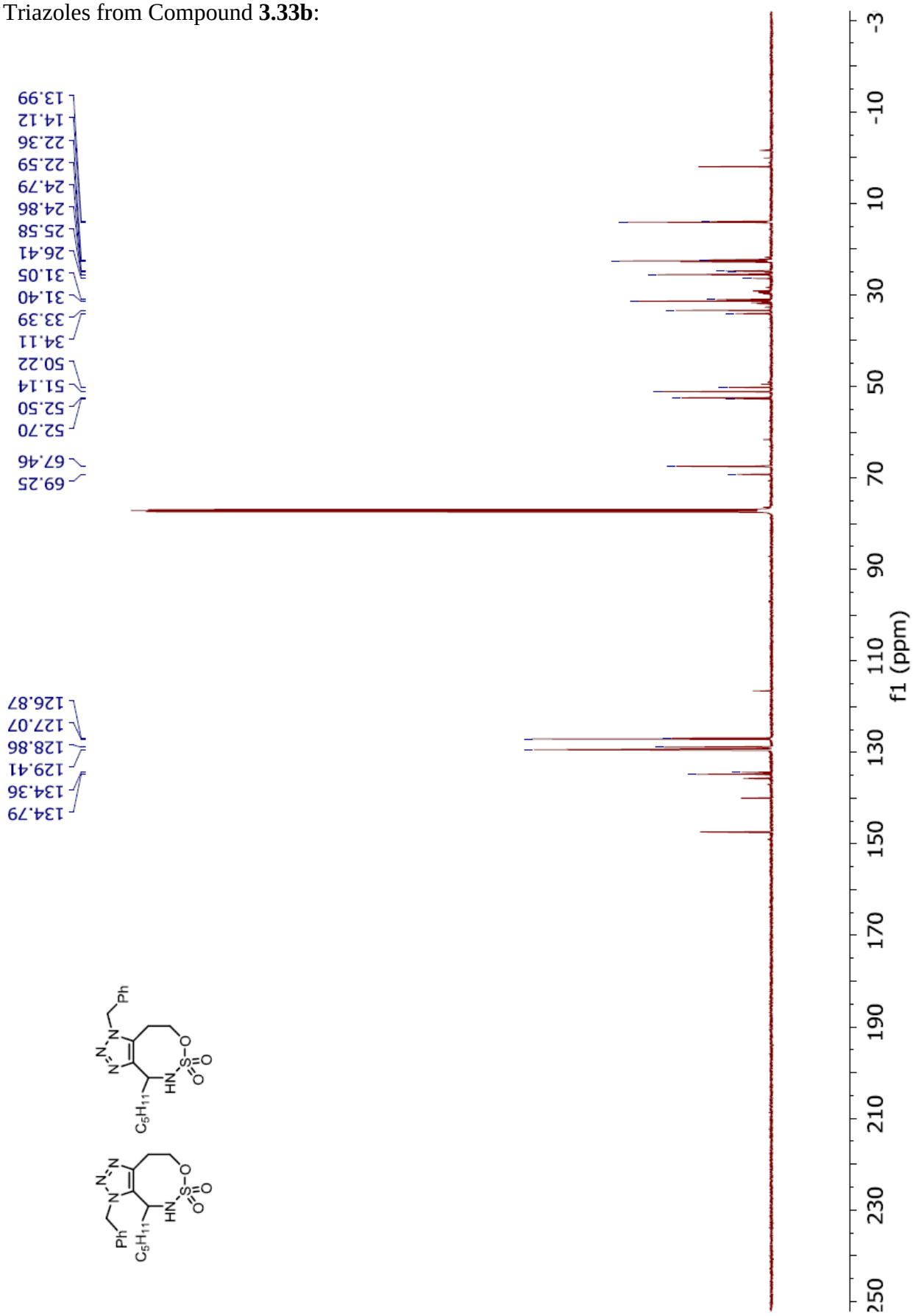
Compound **3.35**:



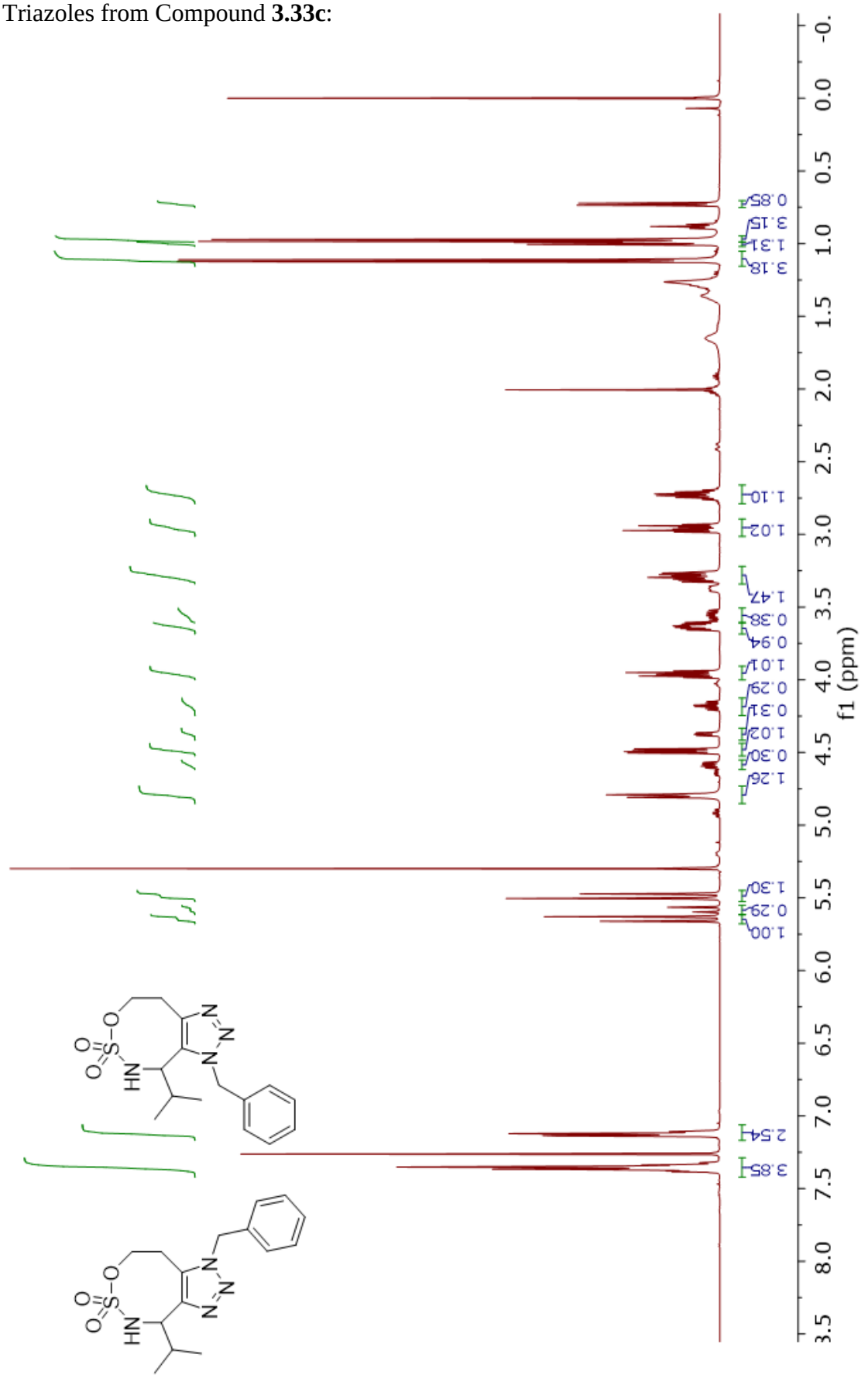
Triazoles from Compound **3.33b**:



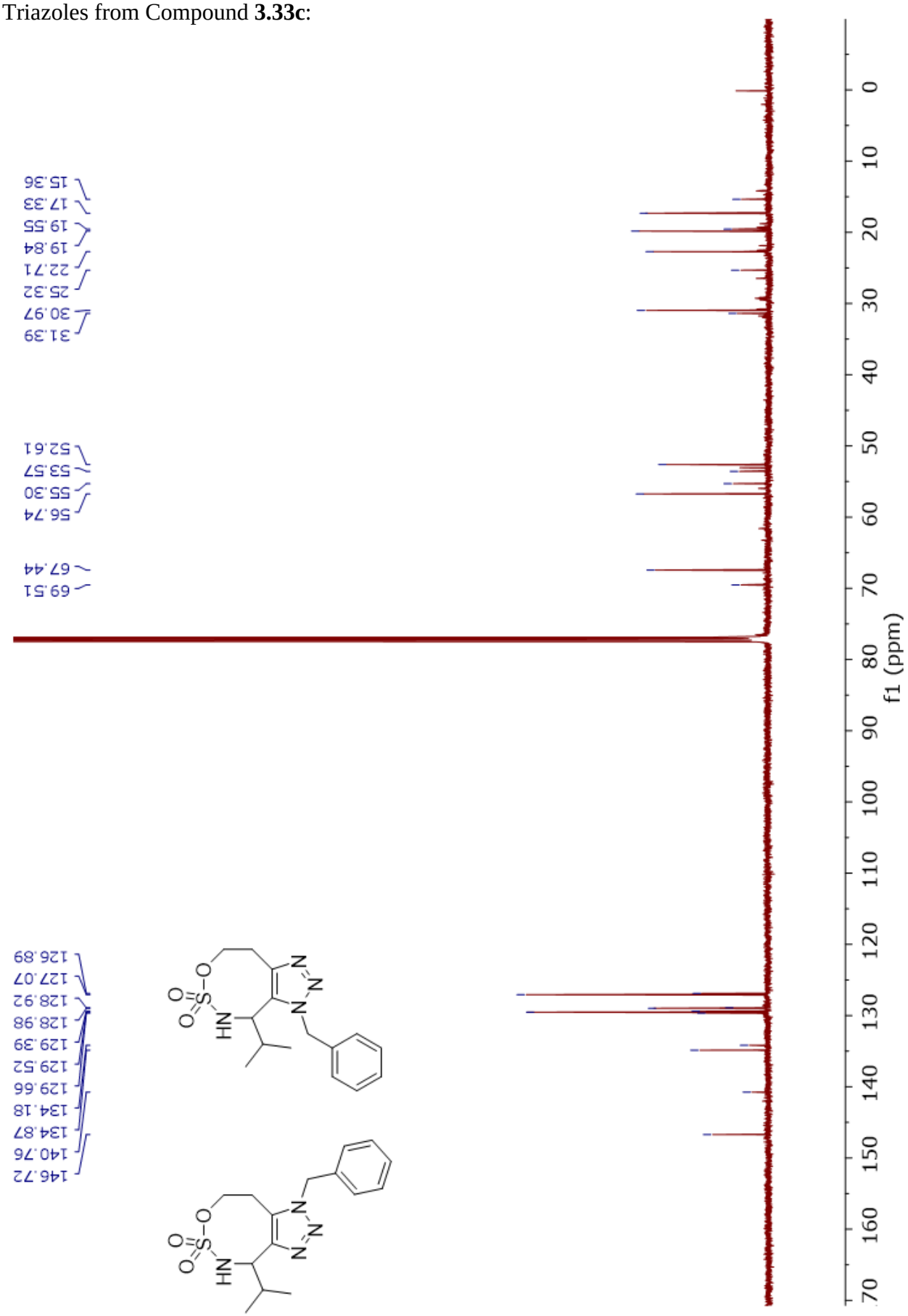
Triazoles from Compound **3.33b**:



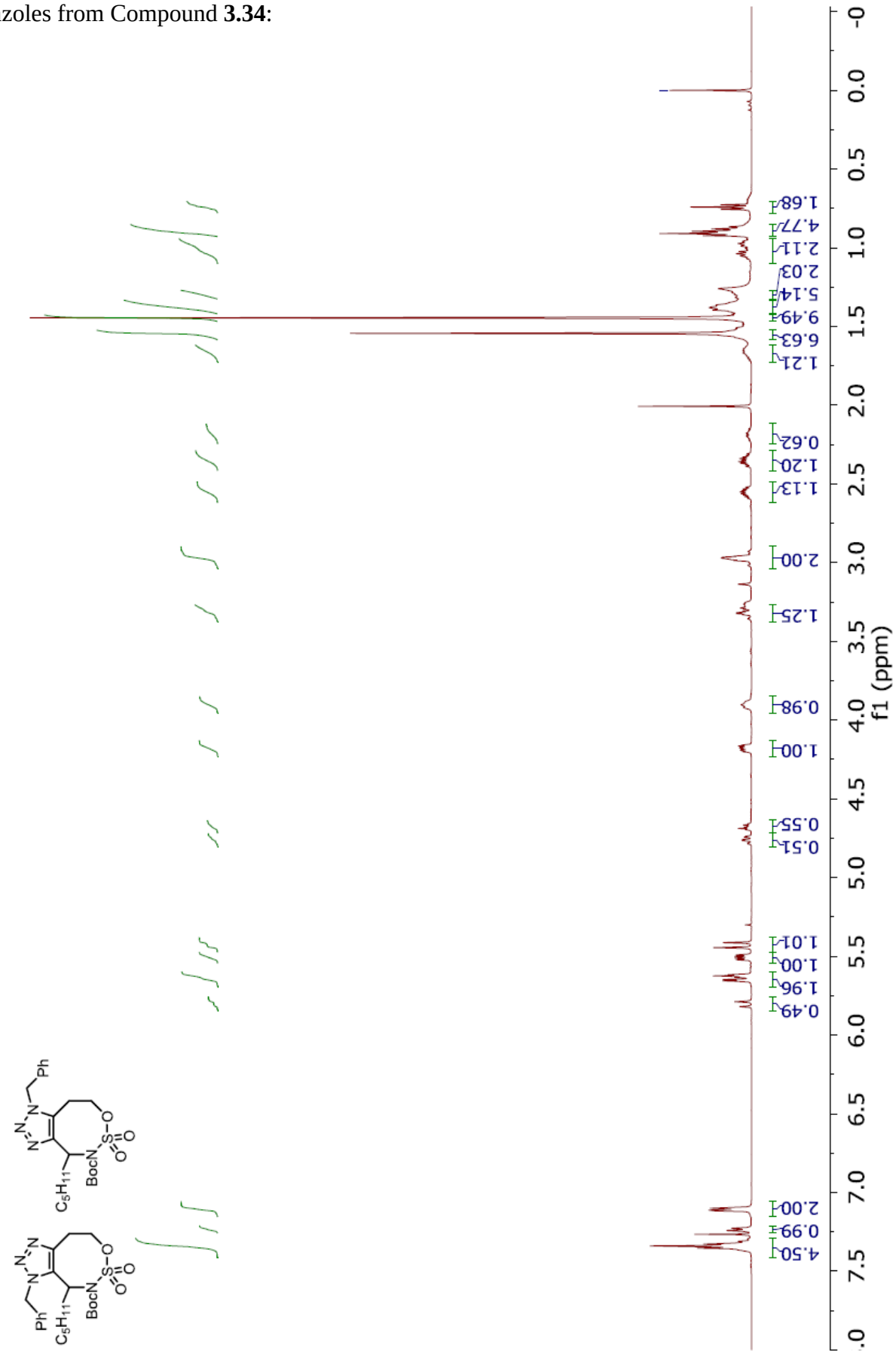
Triazoles from Compound **3.33c**:



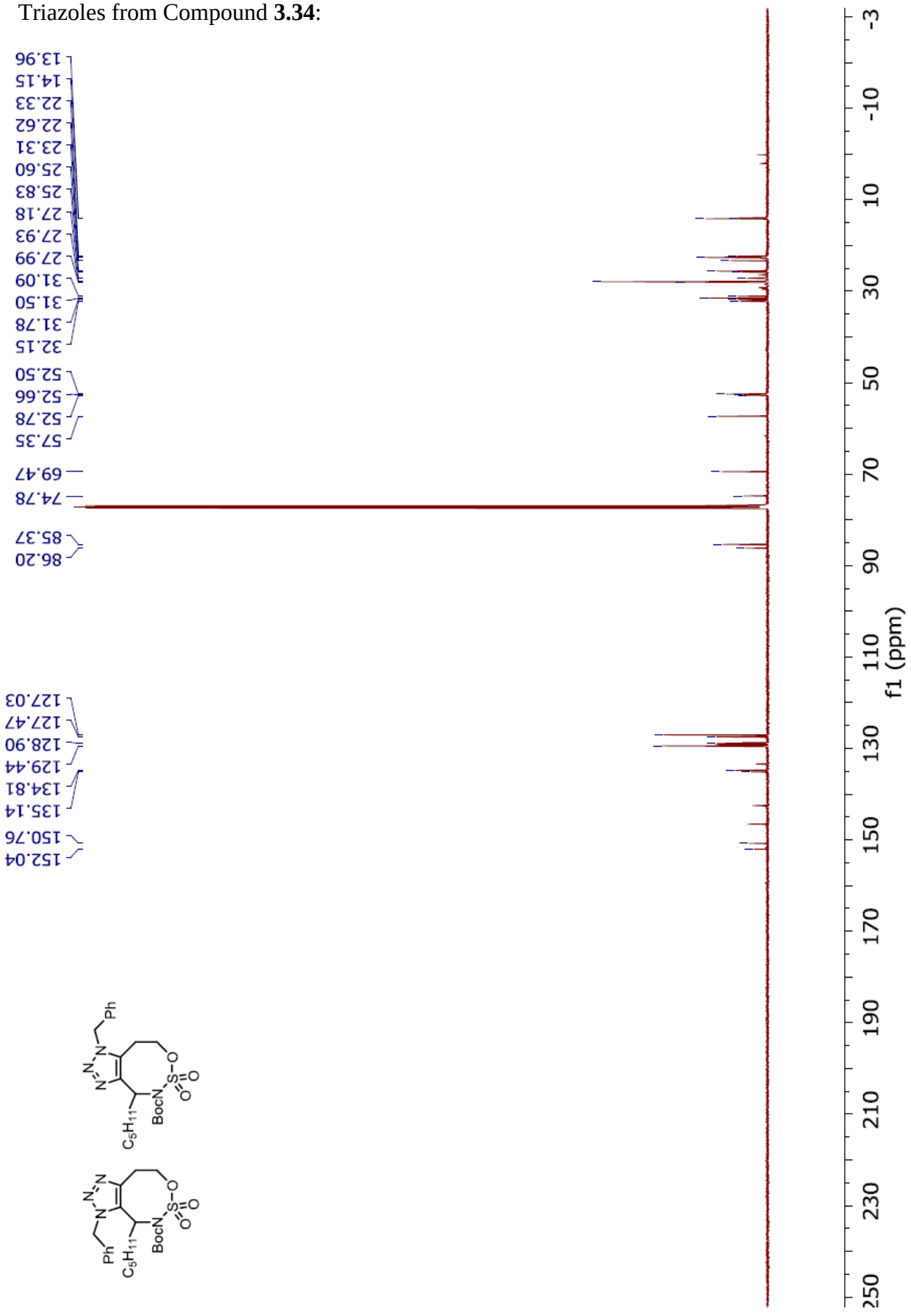
Triazoles from Compound **3.33c**:



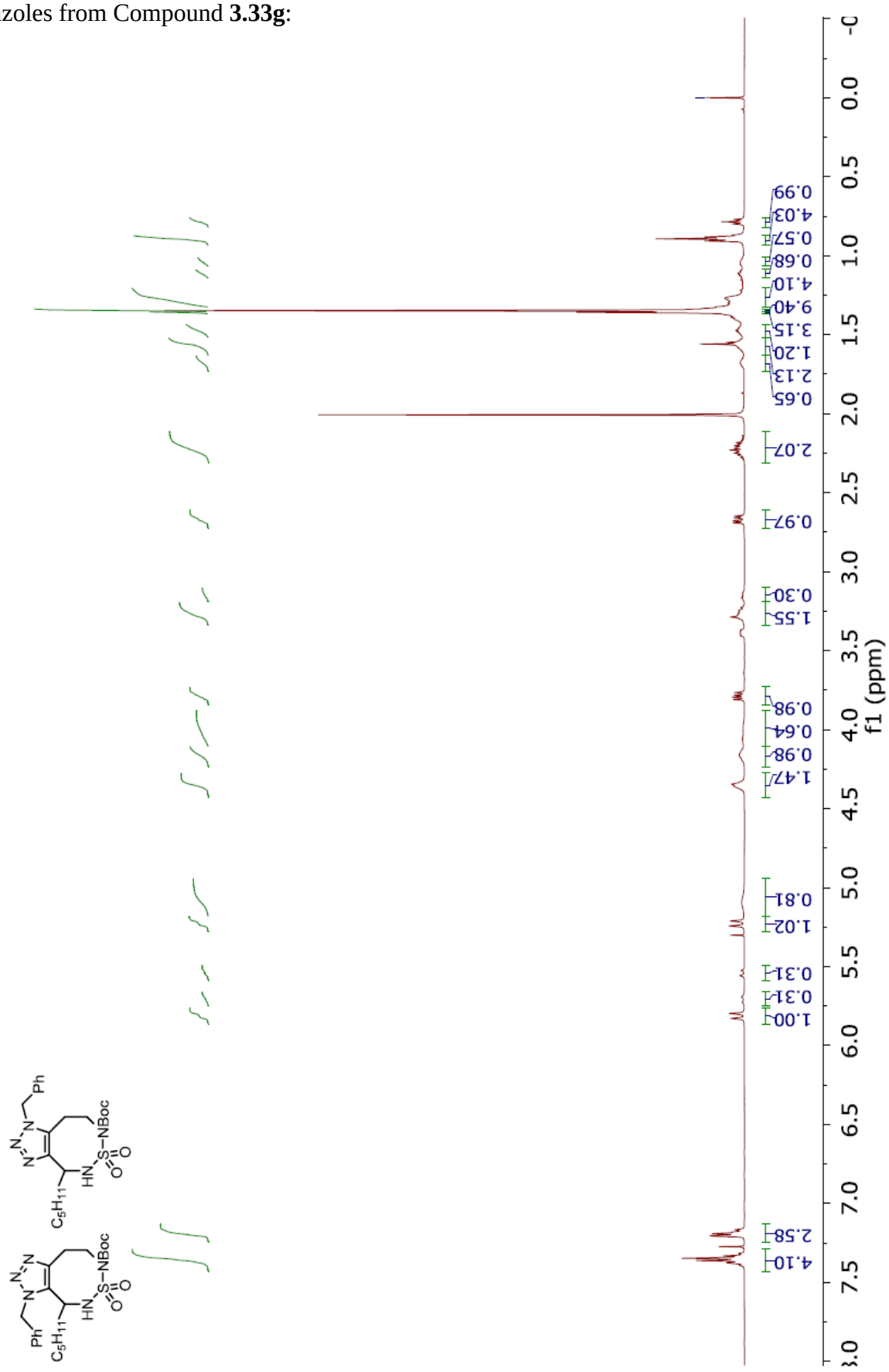
Triazoles from Compound **3.34**:



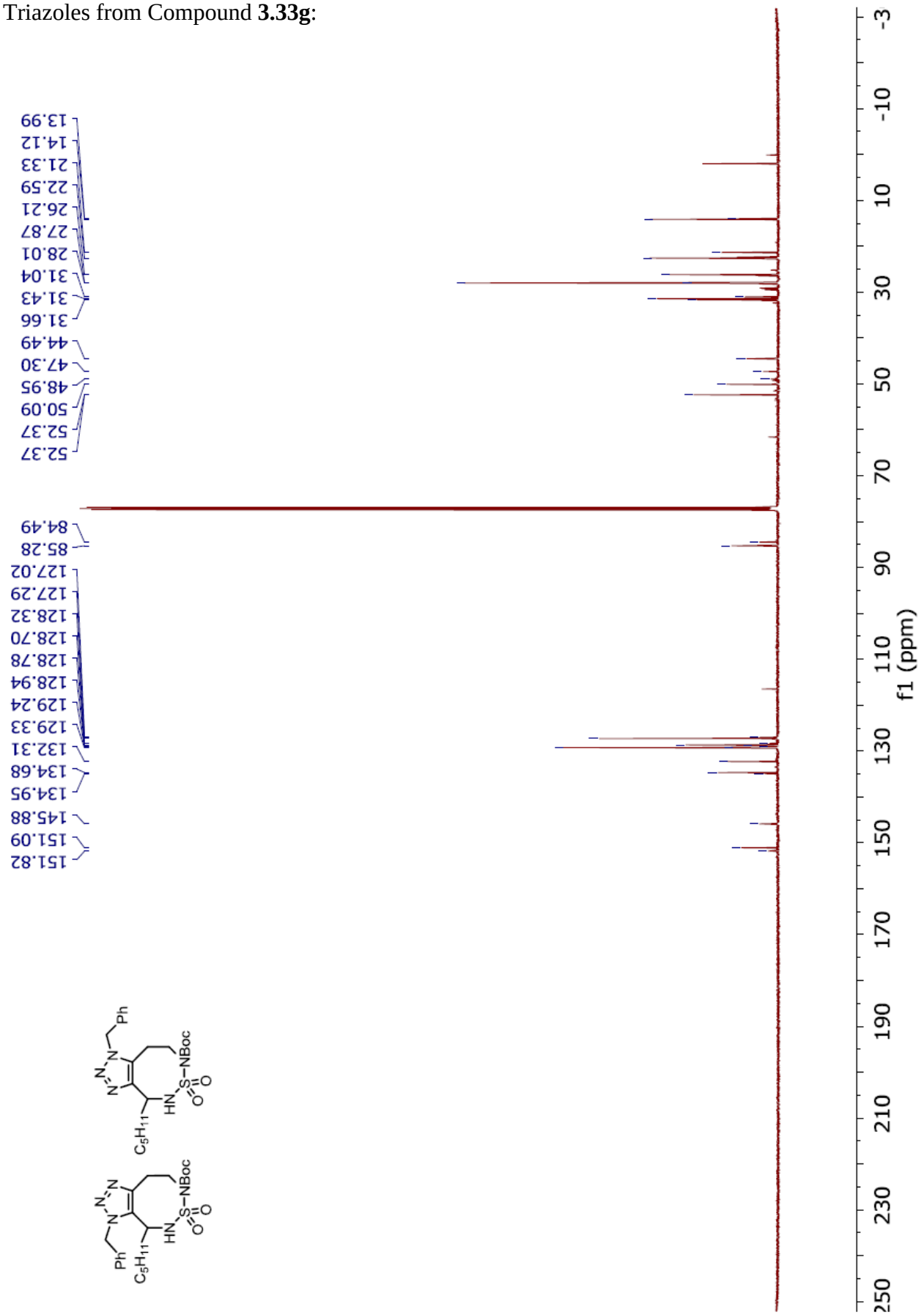
Triazoles from Compound **3.34**:



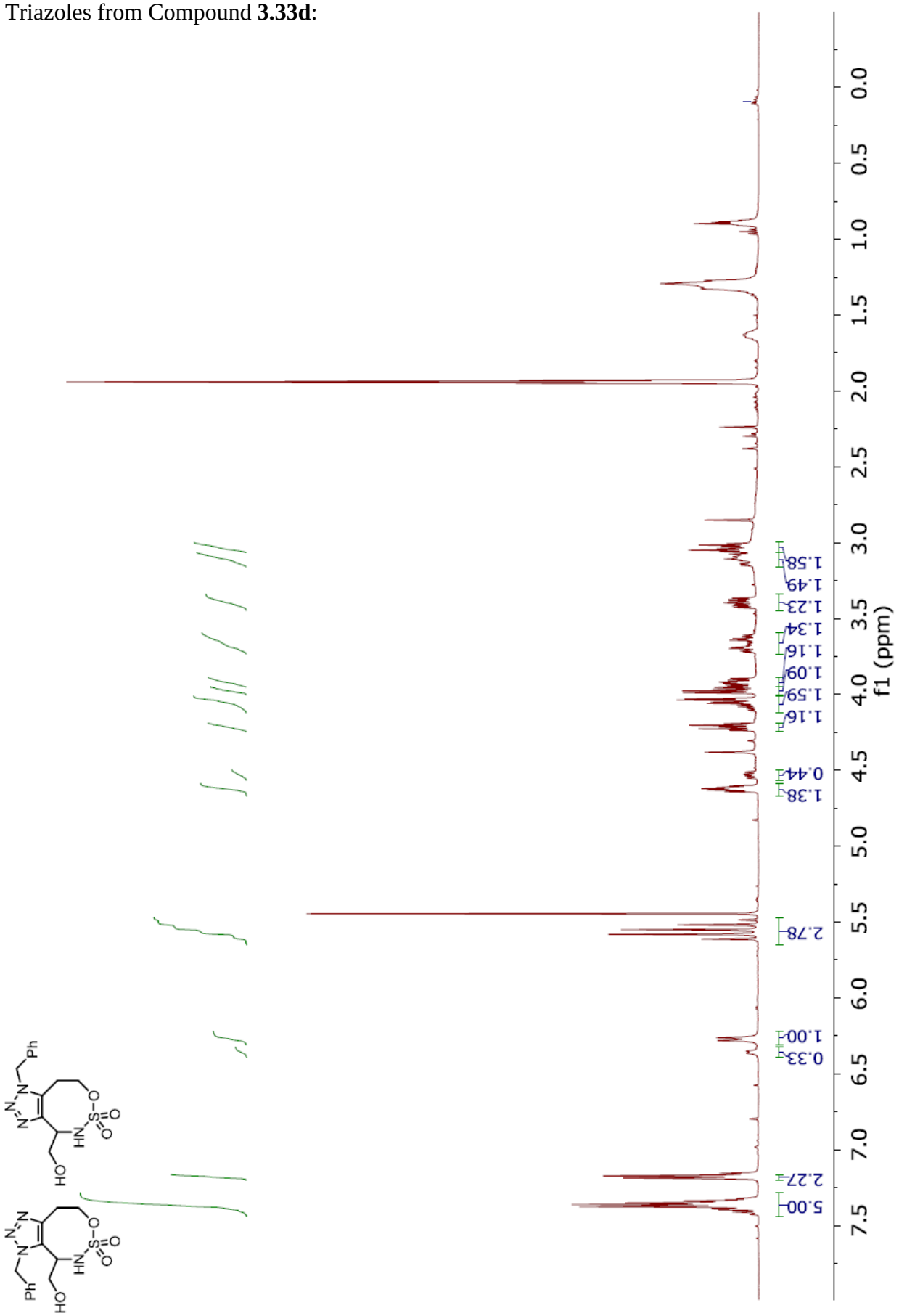
Triazoles from Compound **3.33g**:



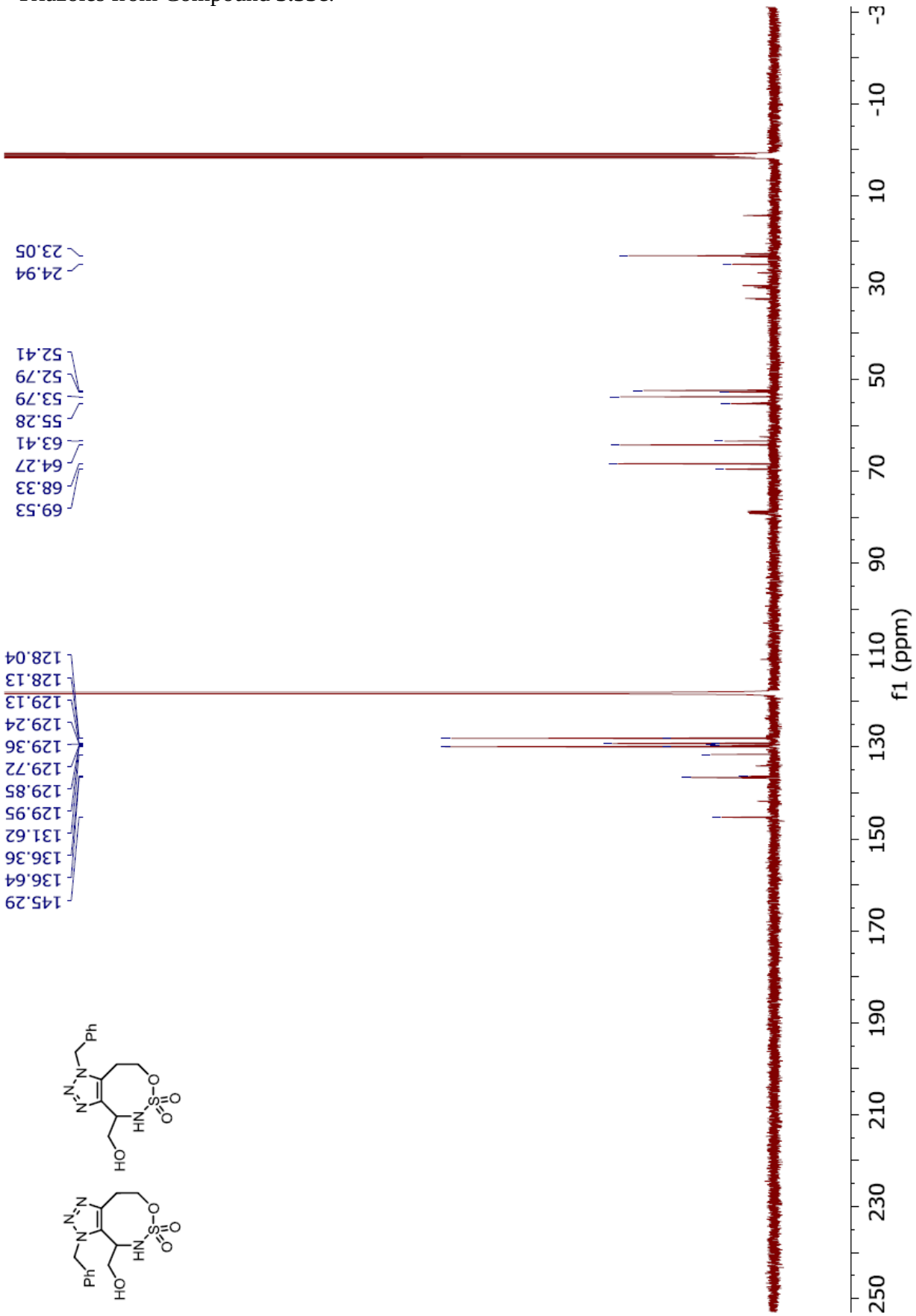
Triazoles from Compound **3.33g**:



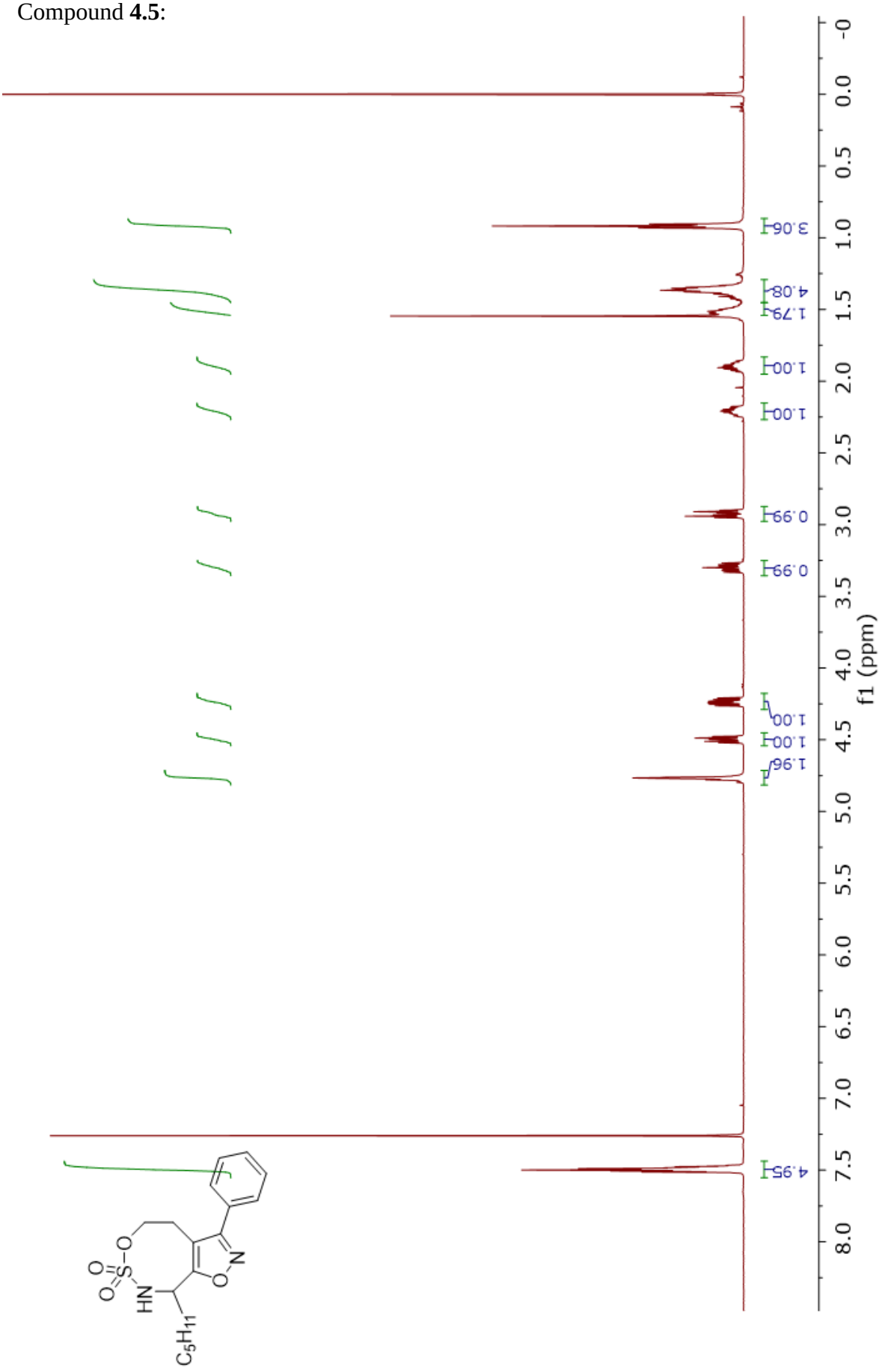
Triazoles from Compound **3.33d**:



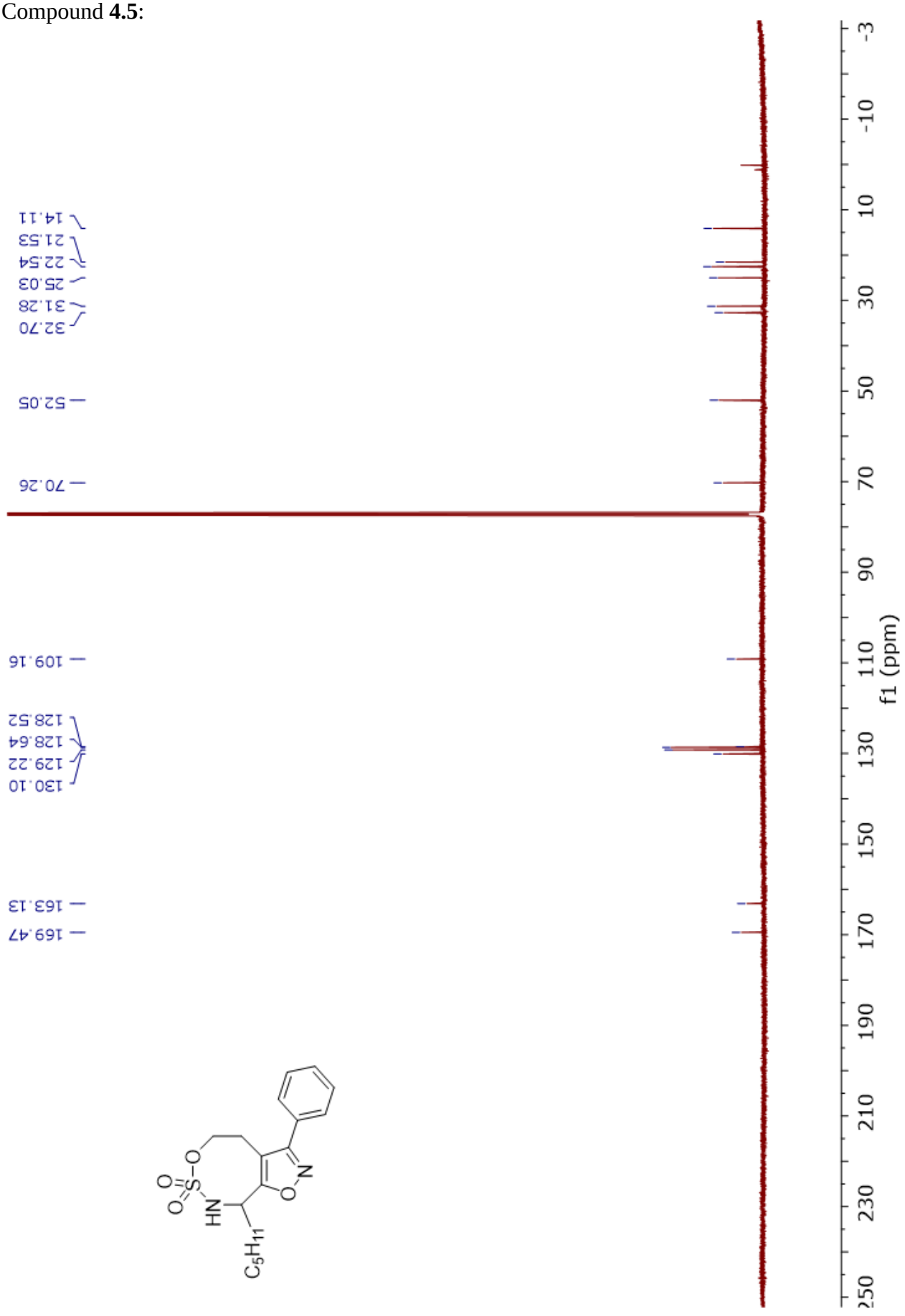
Triazoles from Compound **3.33e**:



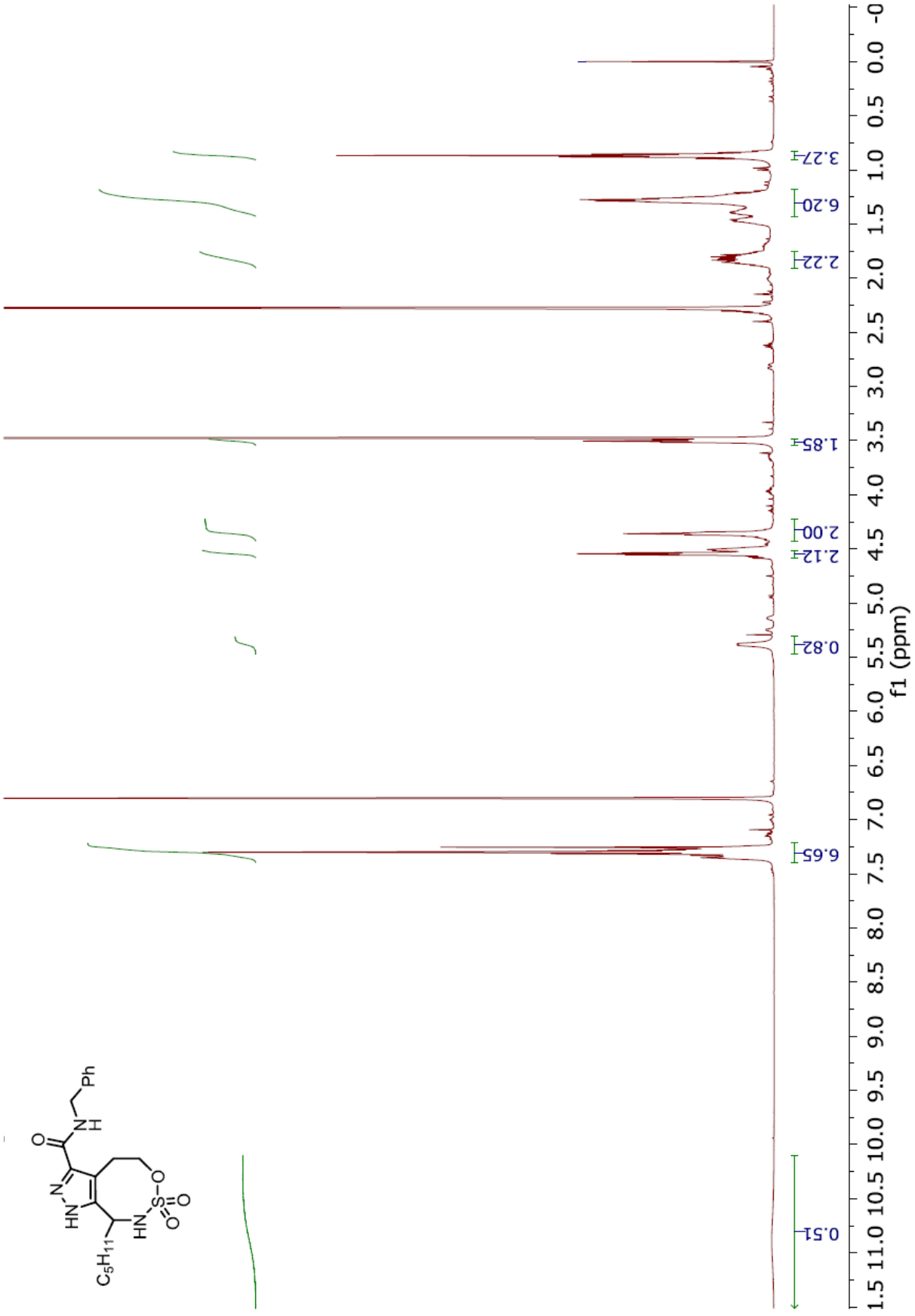
Compound **4.5**:


3.06
4.08
1.79
1.00
1.00
0.99
0.99
1.00
1.00
1.96
4.95
f1 (ppm)
HN
O
S
O
O
N
O
C5H11

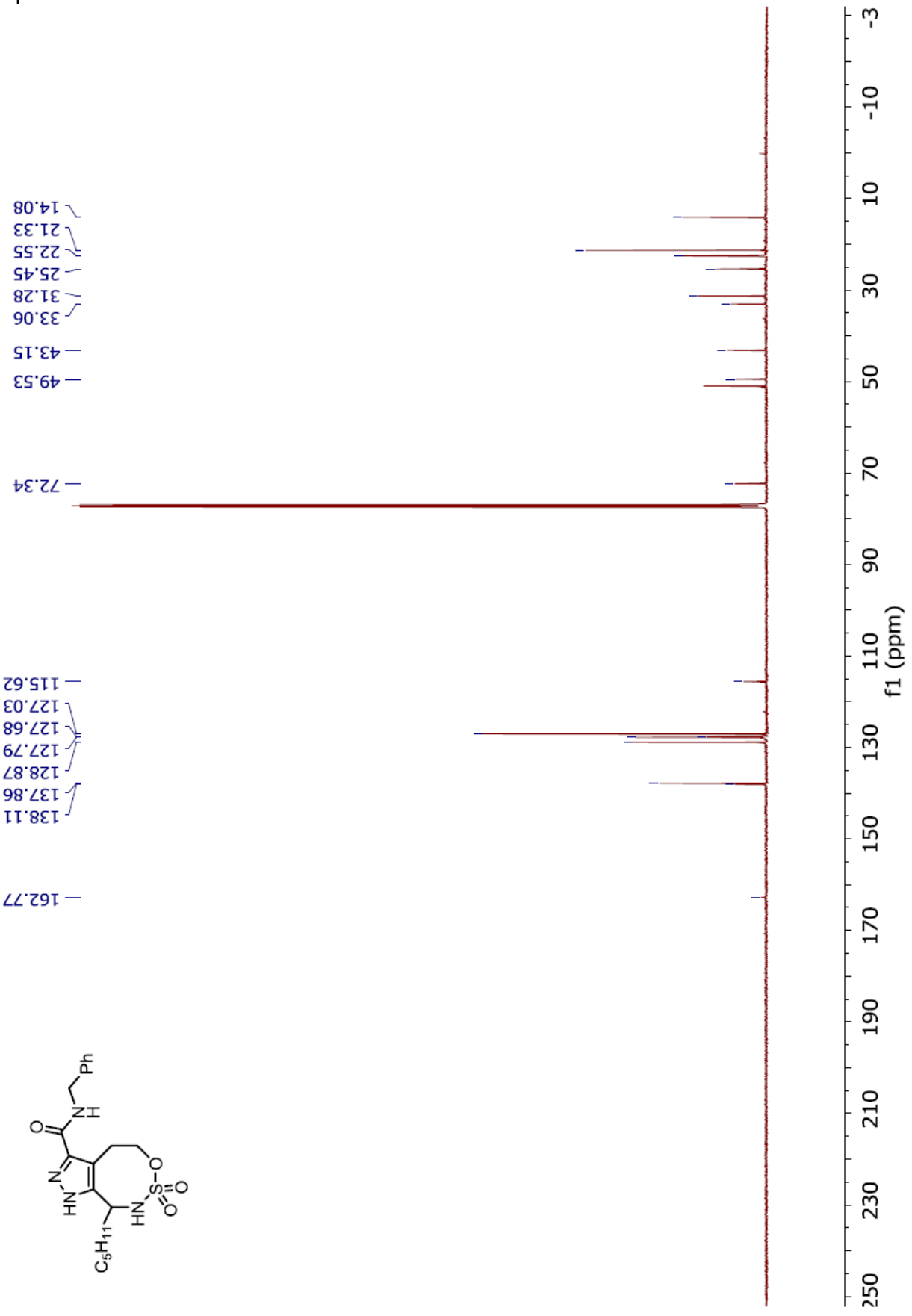
Compound **4.5**:


14.11
21.53
22.54
25.03
31.28
32.70
52.05
70.26
109.16
128.52
128.64
129.22
130.10
163.13
169.47
f1 (ppm)
-3
-10
10
30
50
70
90
110
130
150
170
190
210
230
250
O
S
O
O
HN
N
O
C5H11

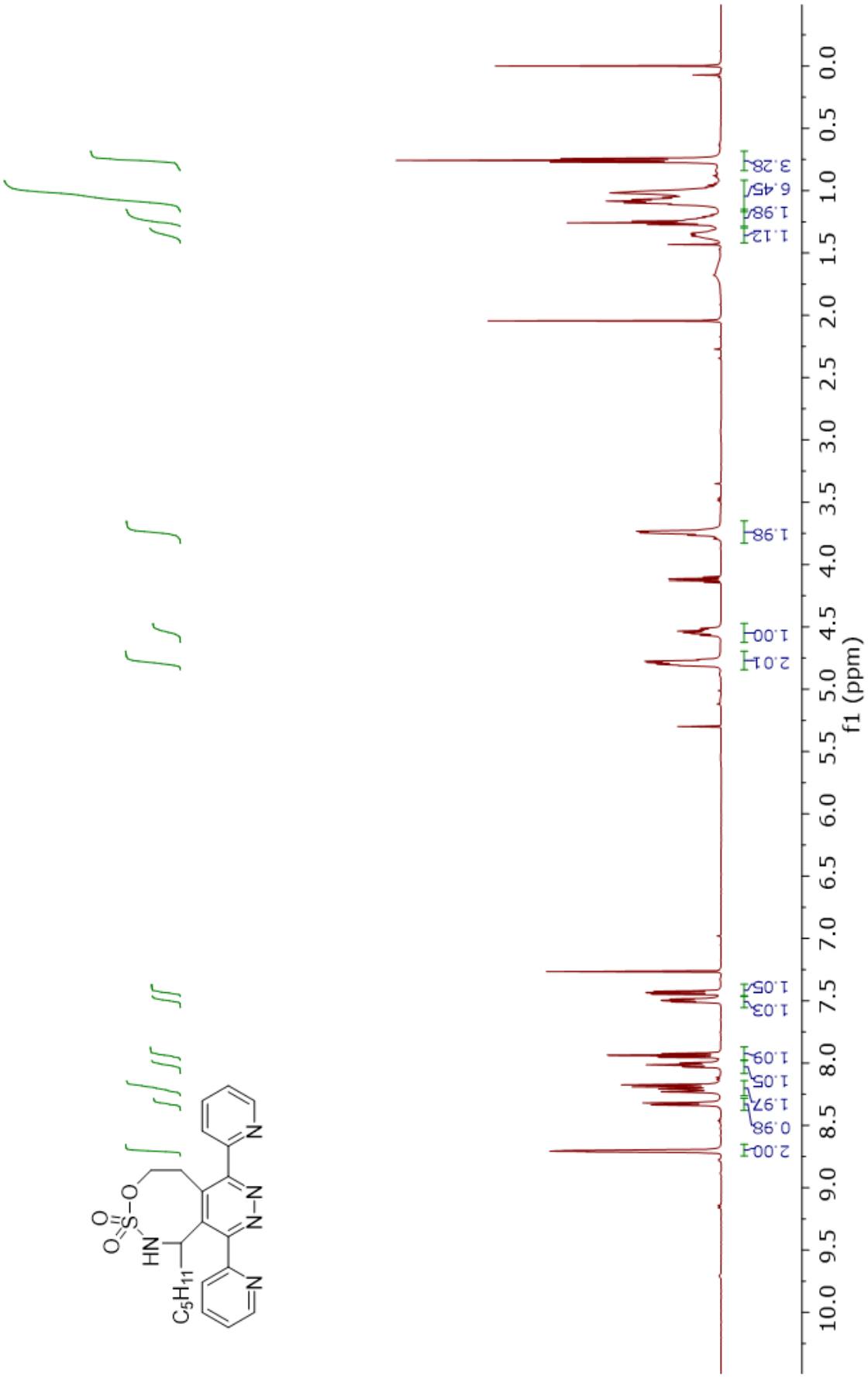
Compound **4.7**:


3.27
6.20
2.22
1.85
2.00
2.12
0.82
6.65
0.51
f1 (ppm)
Ph
N
H
O
N
HN
O
S
O
O
HN
C_5H_{11}

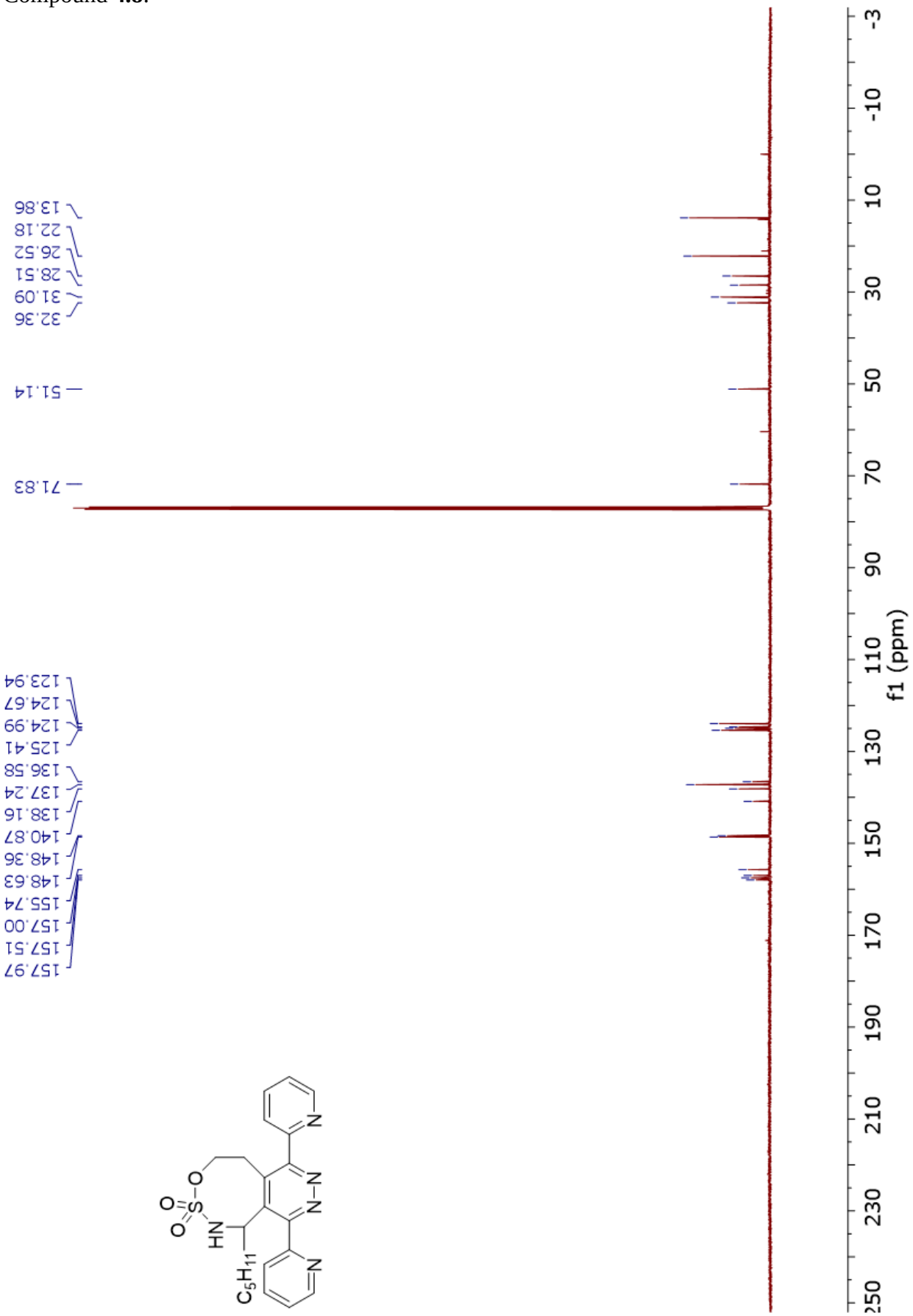
Compound **4.7**:


14.08
21.33
22.55
25.45
31.28
33.06
43.15
49.53
72.34
115.62
127.03
127.68
127.79
128.87
137.86
138.11
162.77
f1 (ppm)

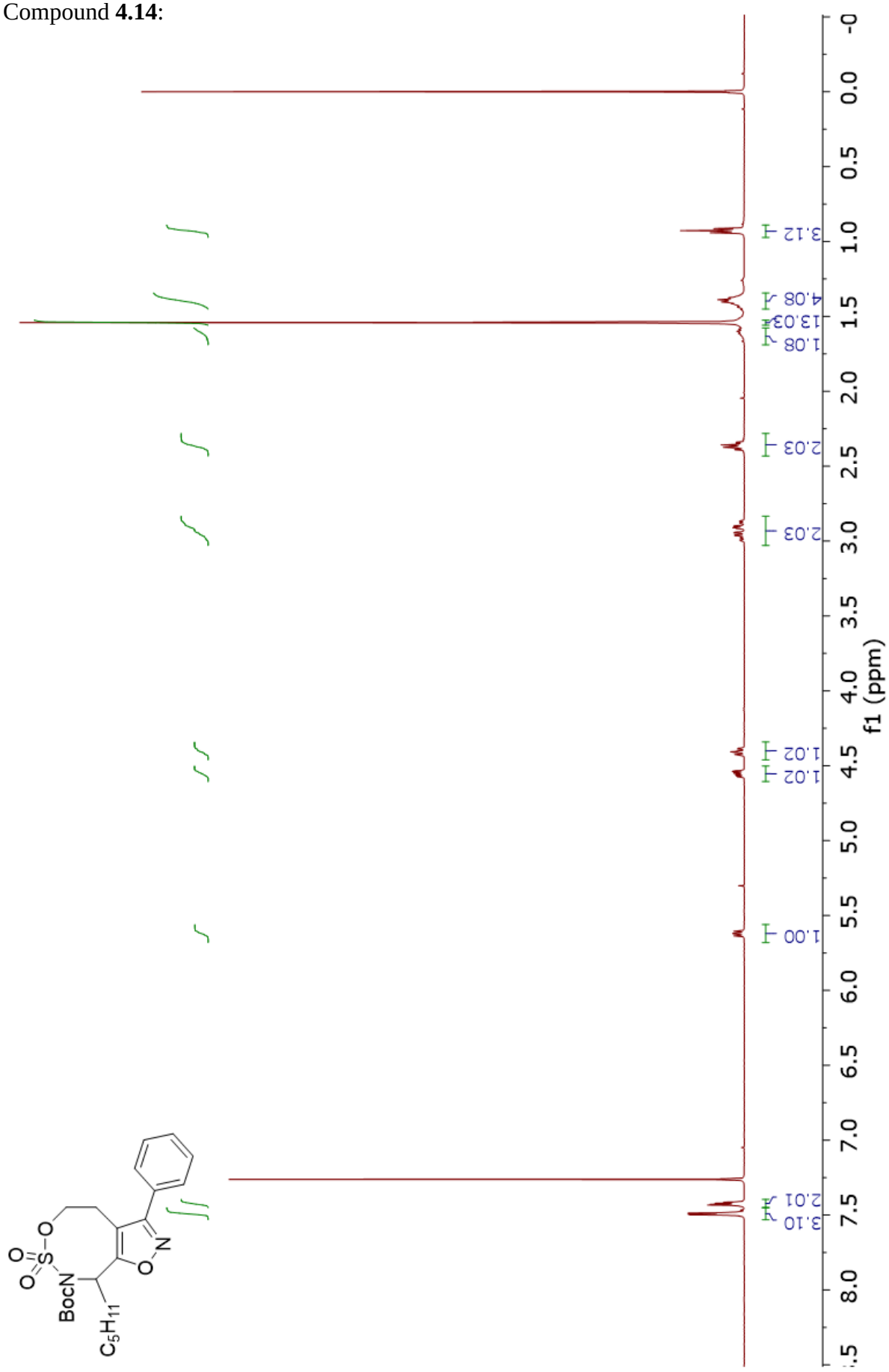
Compound **4.8**:



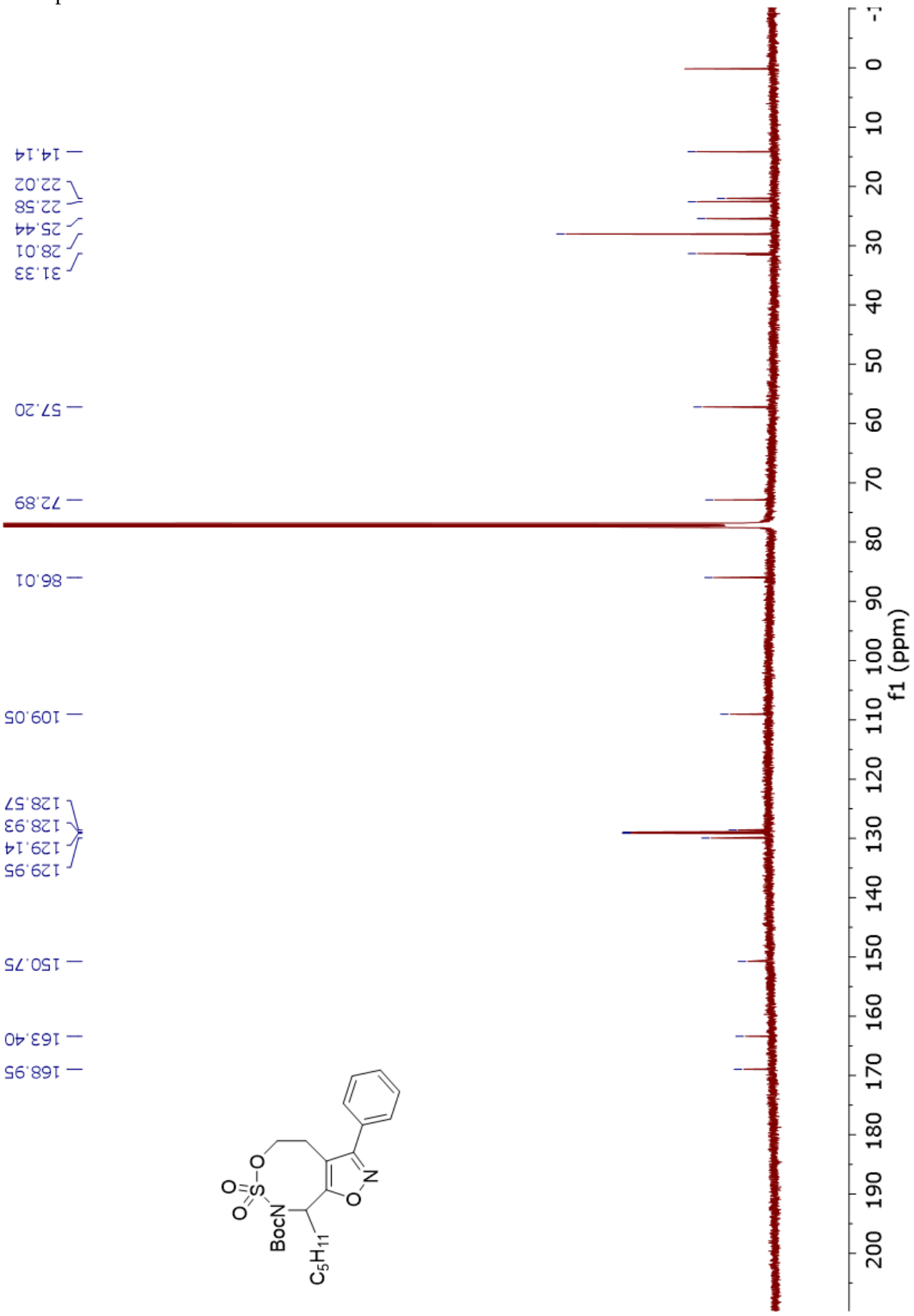
Compound **4.8**:


13.86
22.18
26.52
28.51
31.09
32.36
51.14
71.83
123.94
124.67
124.99
125.41
136.58
137.24
138.16
140.87
148.36
148.63
155.74
157.00
157.51
157.97
f1 (ppm)

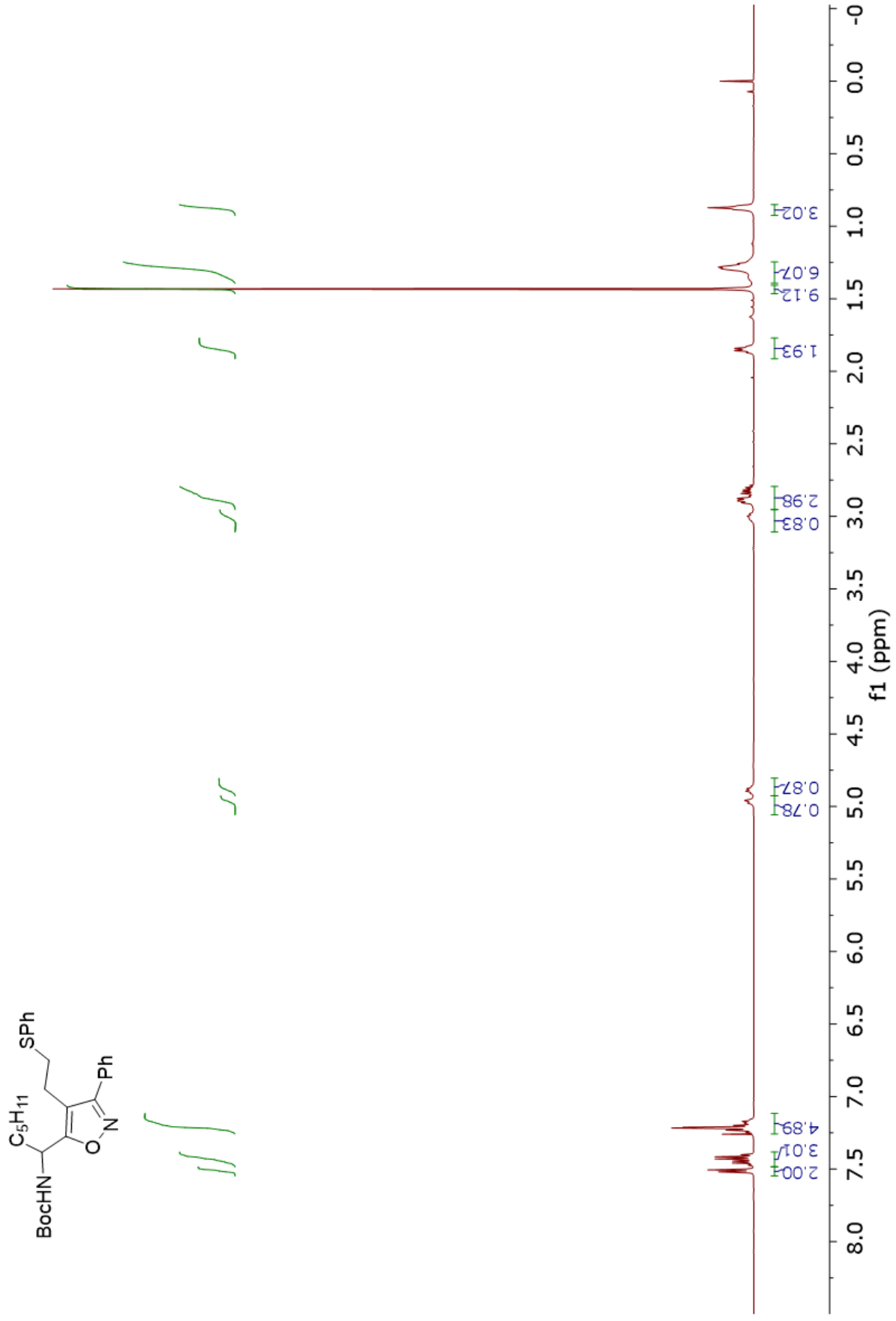
Compound **4.14**:



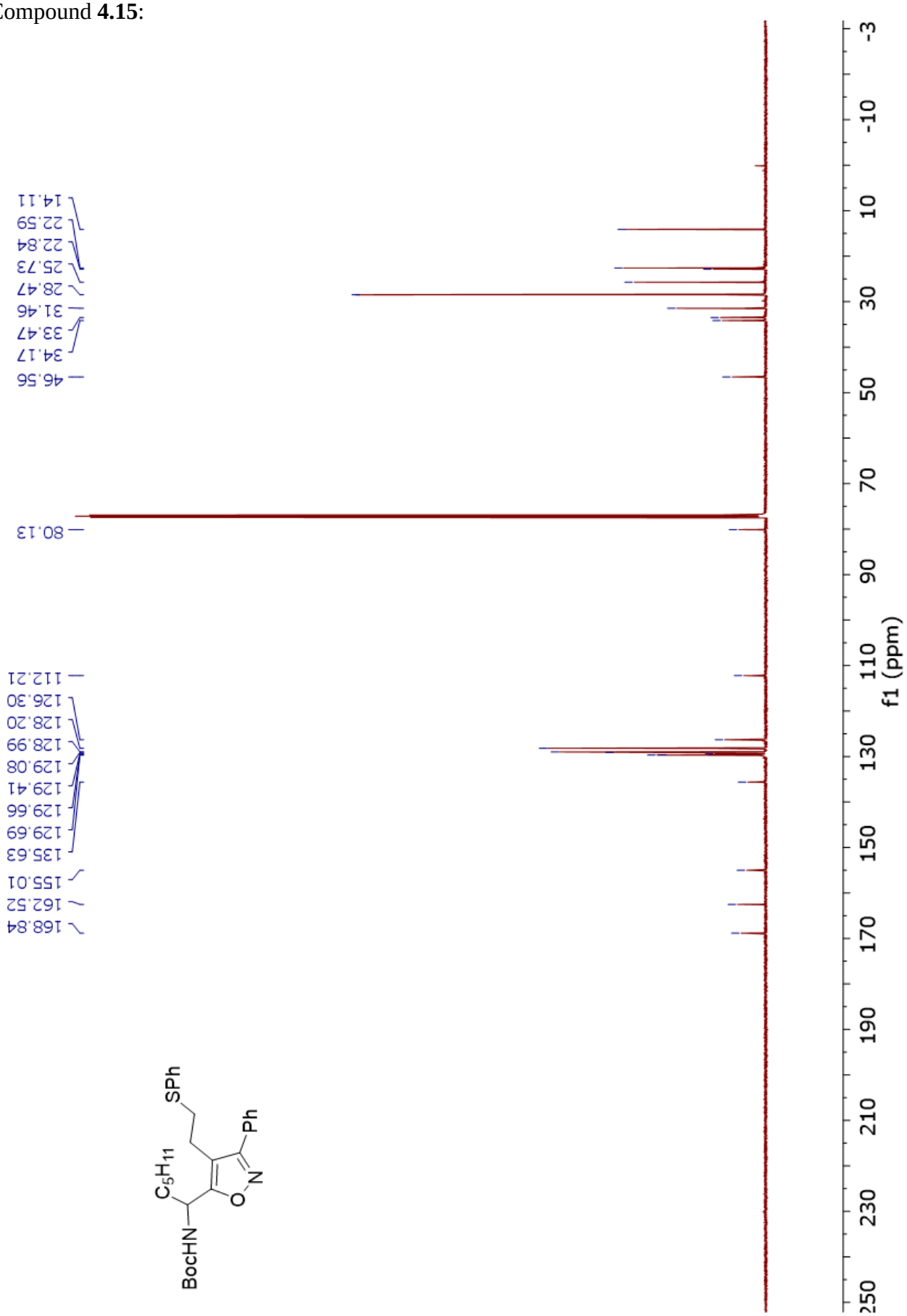
Compound **4.14**:



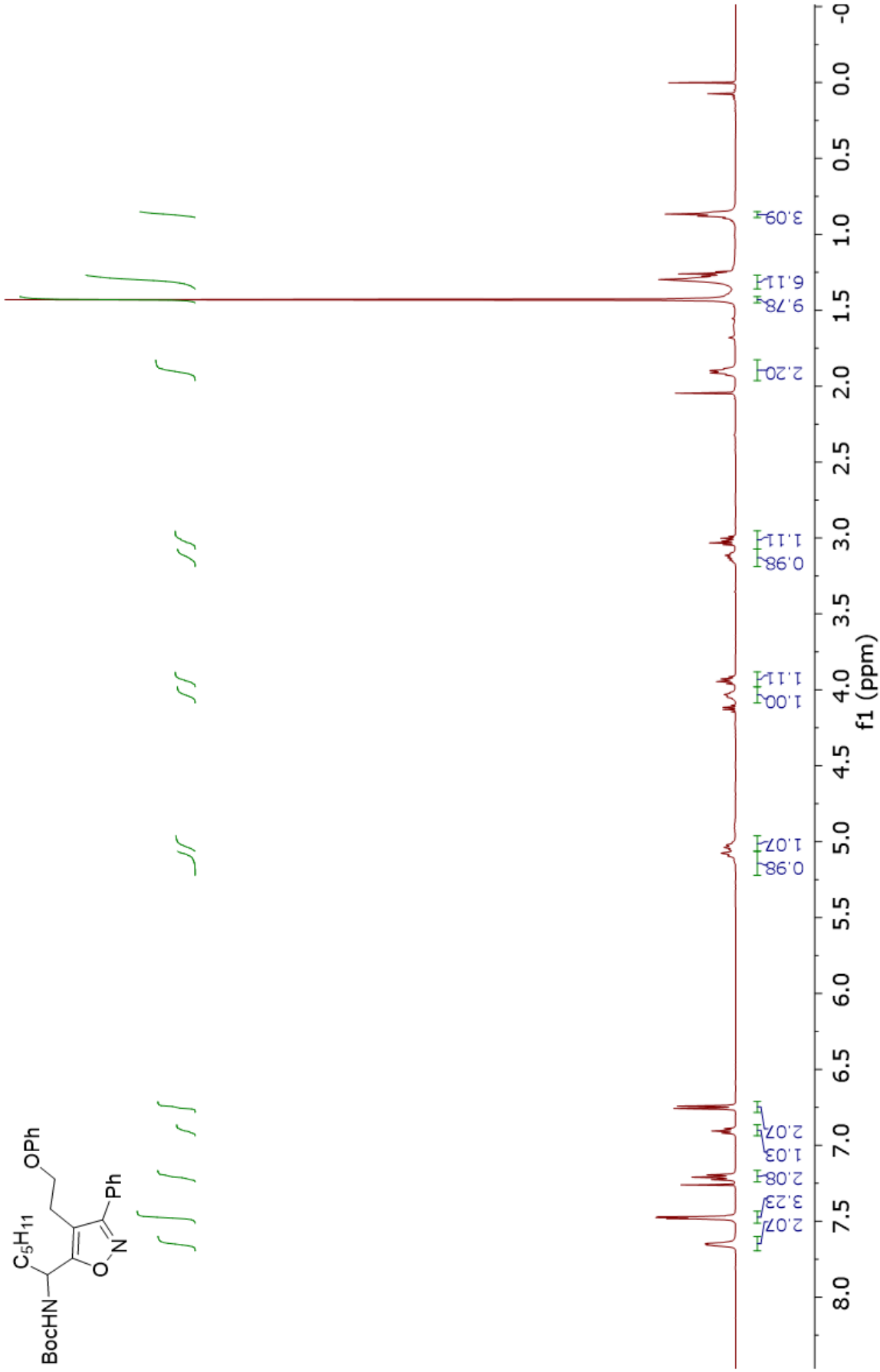
Compound **4.15**:



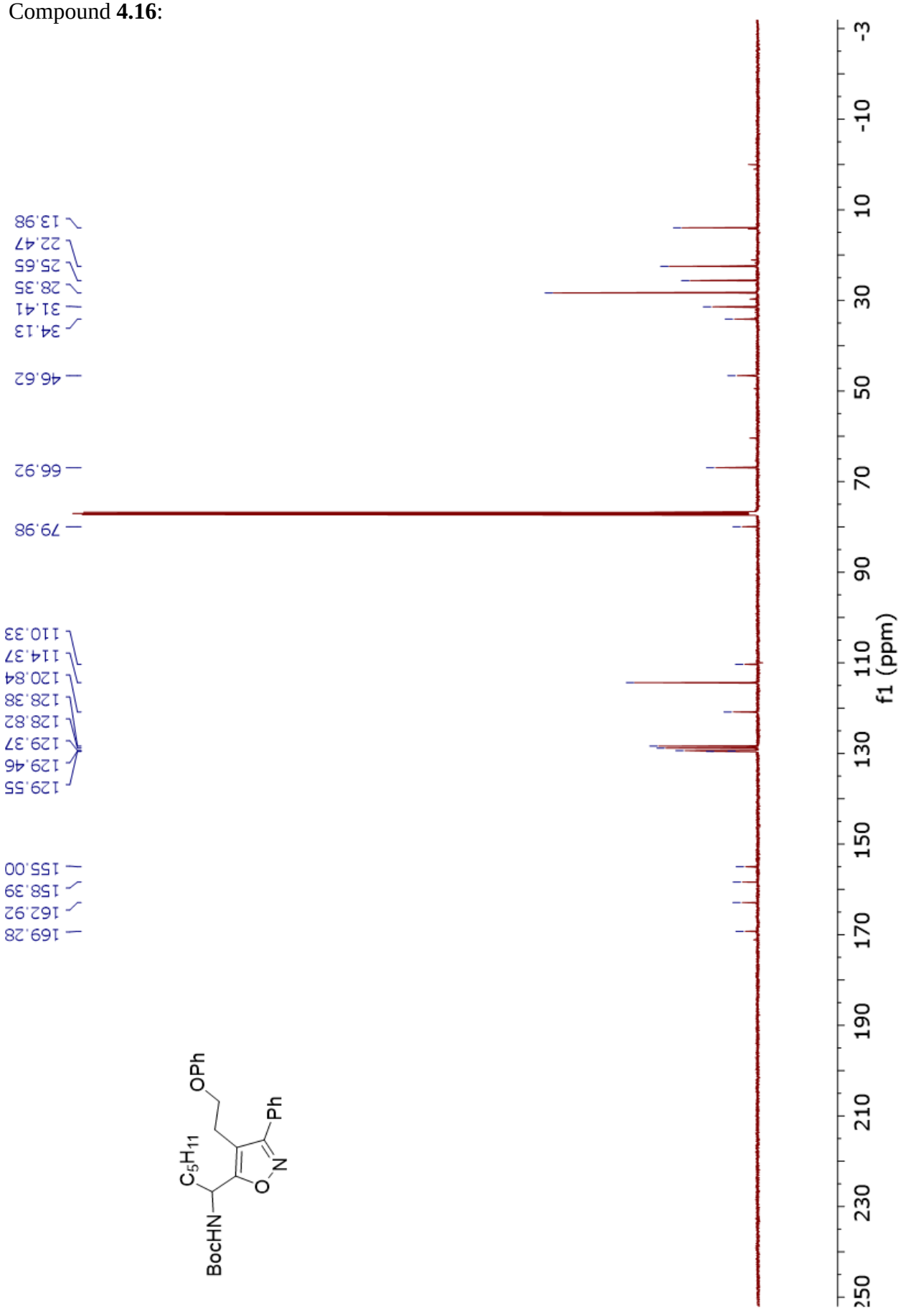
Compound **4.15**:



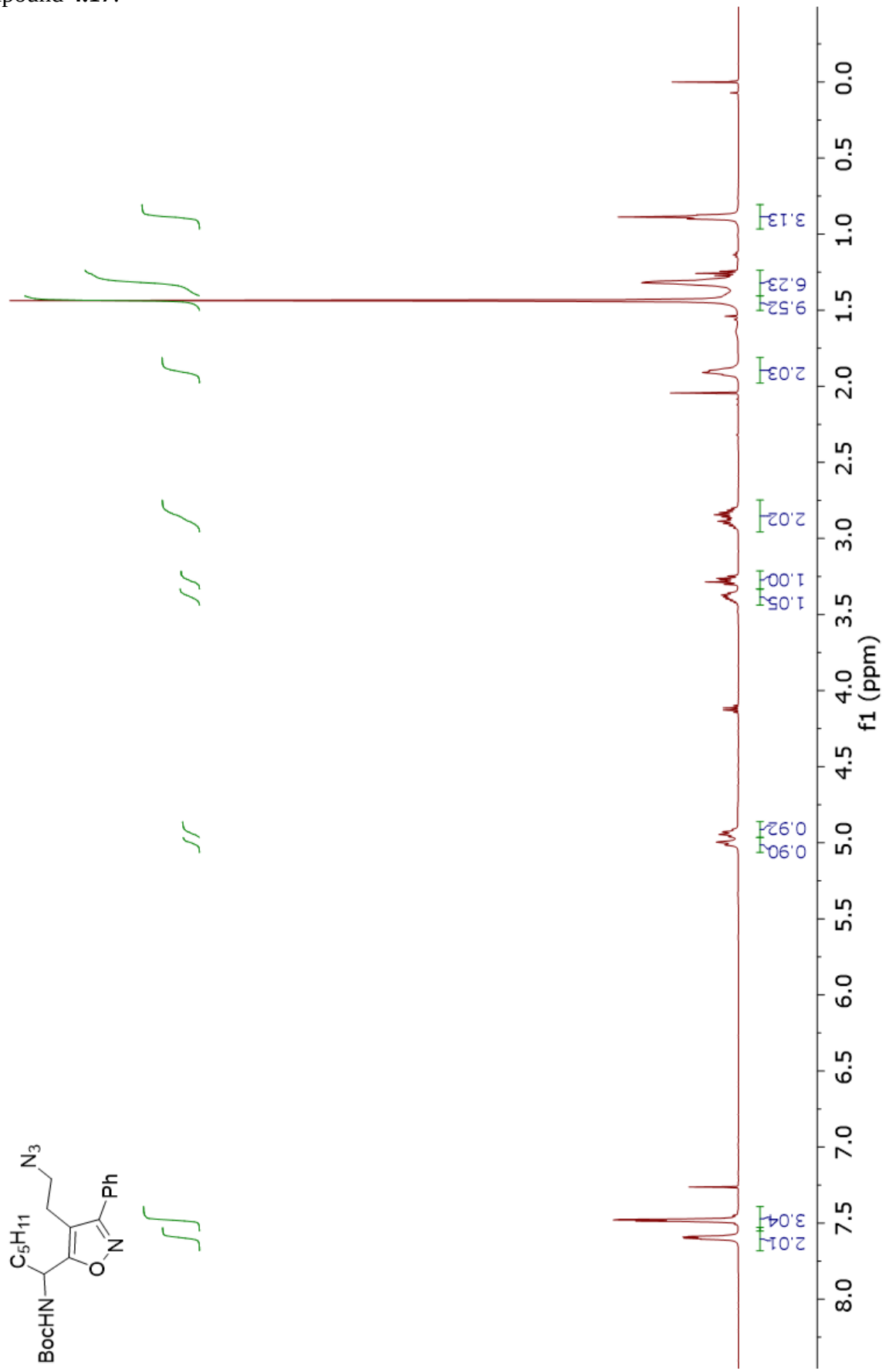
Compound **4.16**:



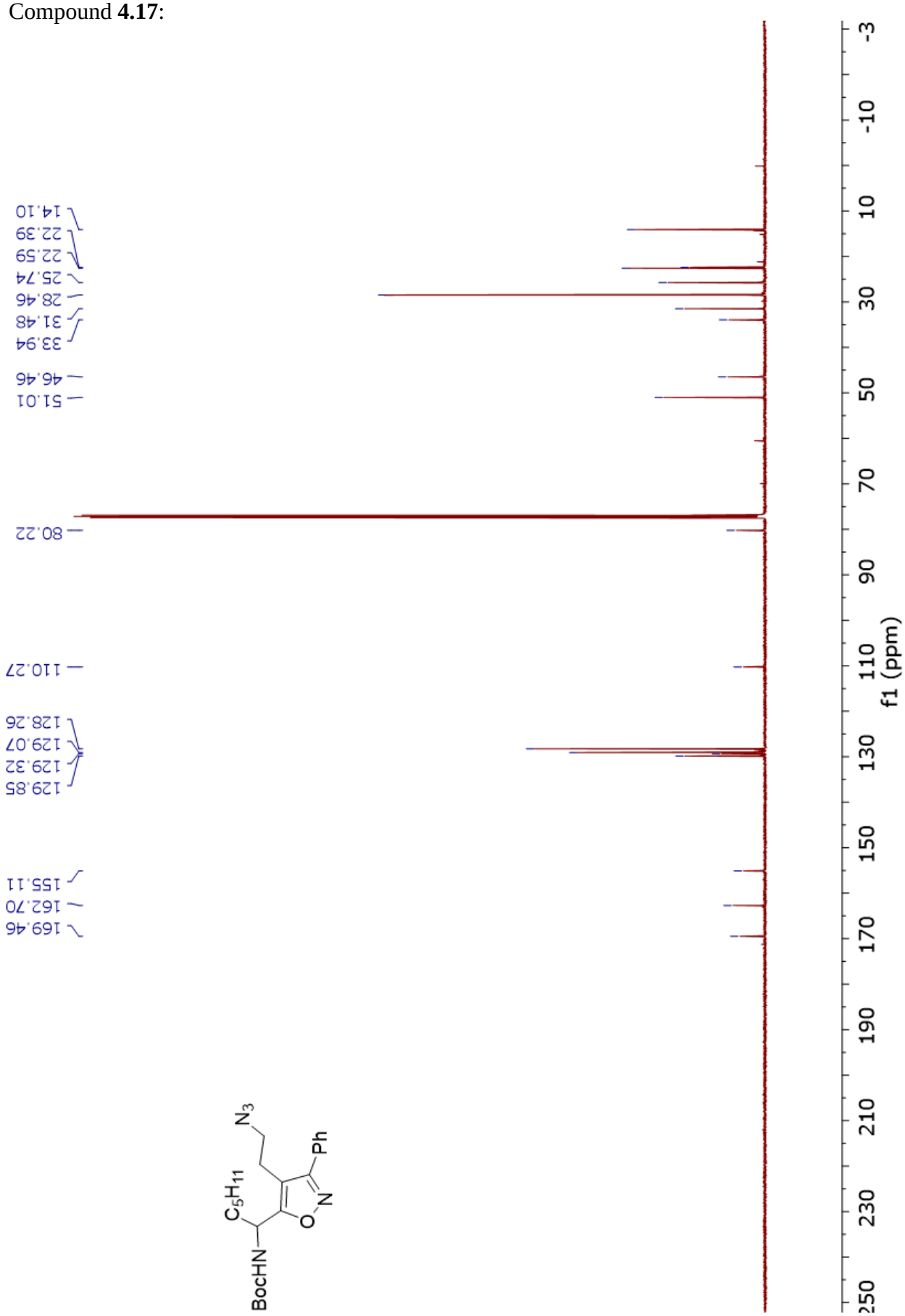
Compound **4.16**:



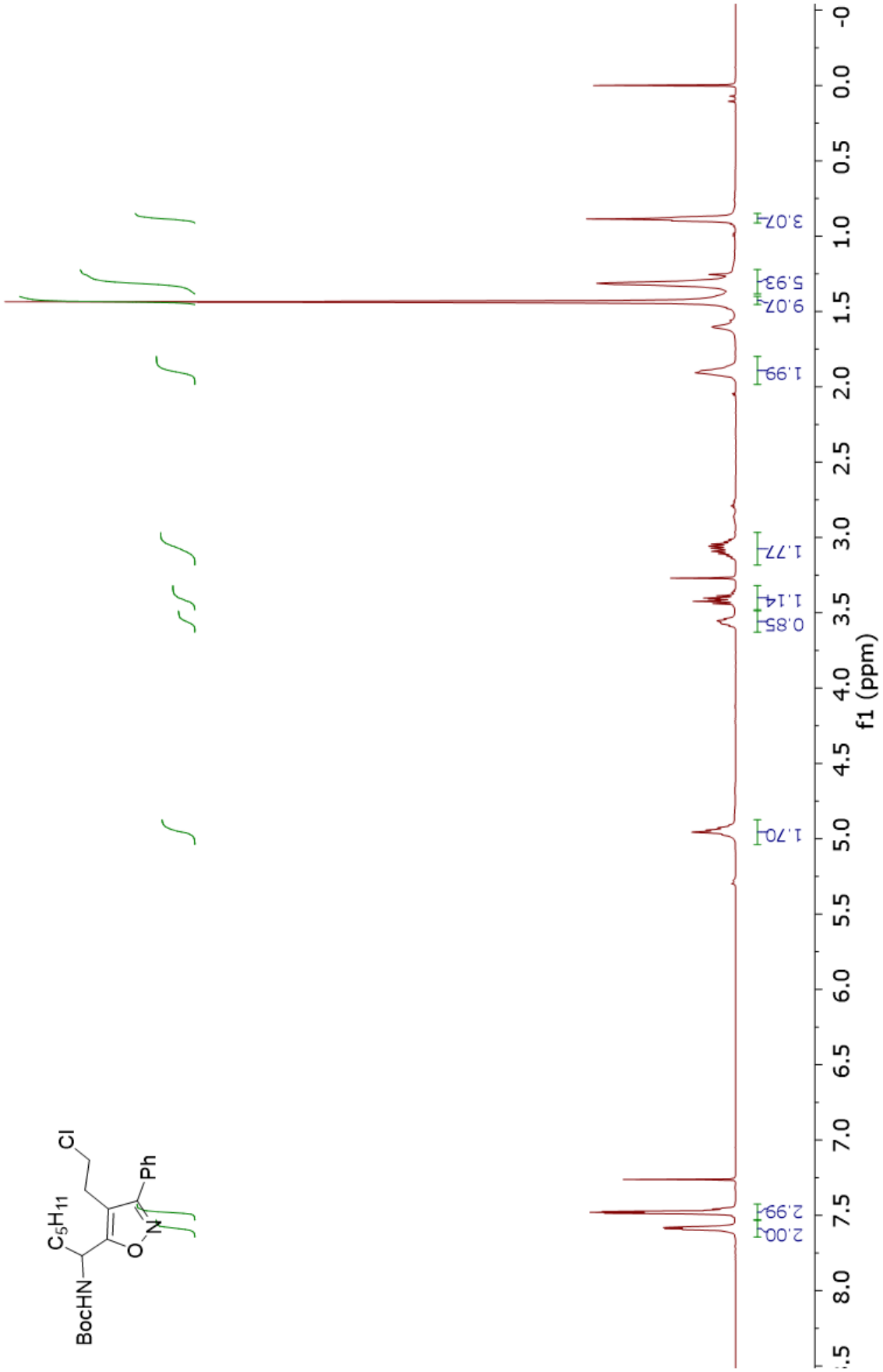
Compound **4.17**:



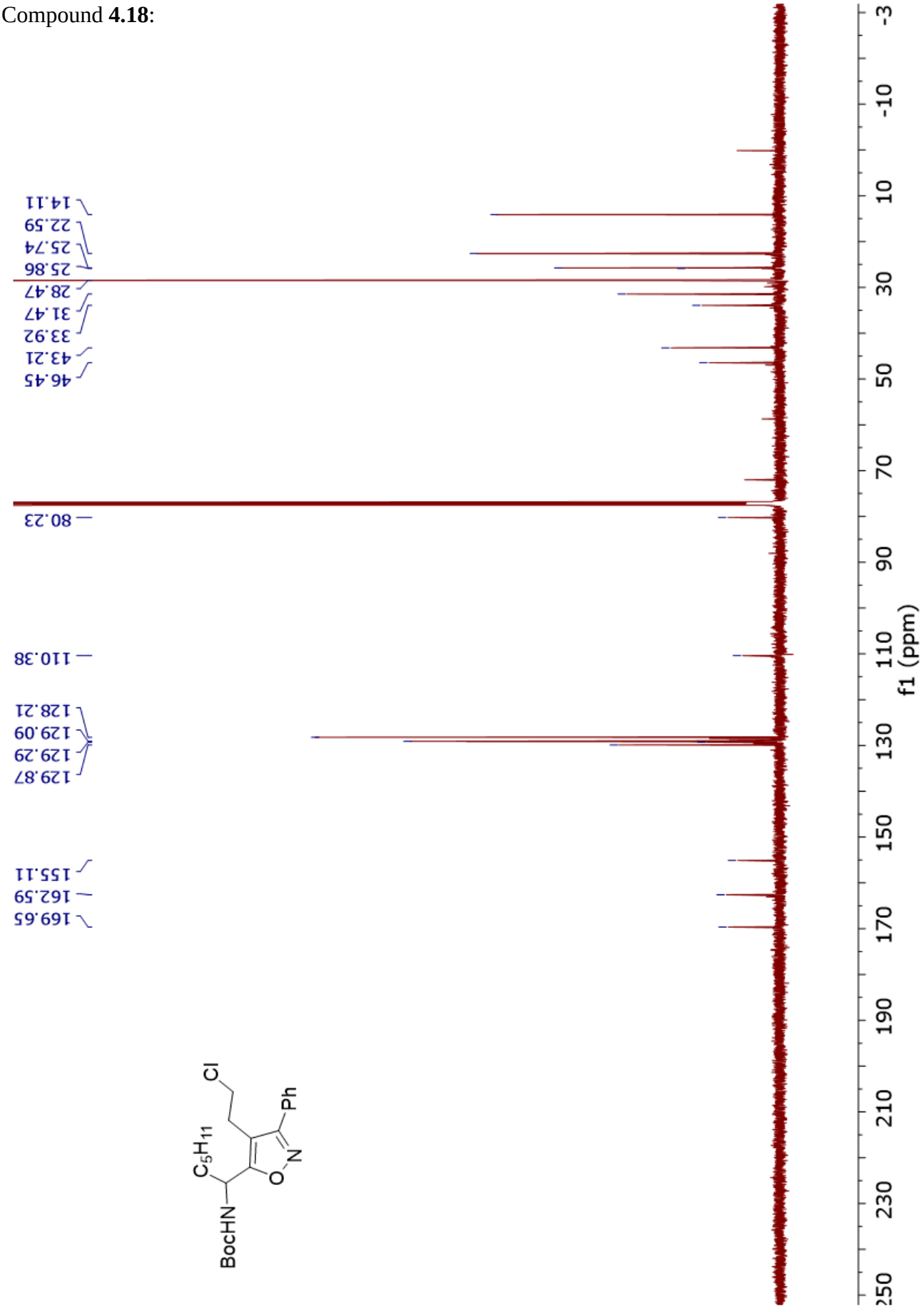
Compound **4.17**:



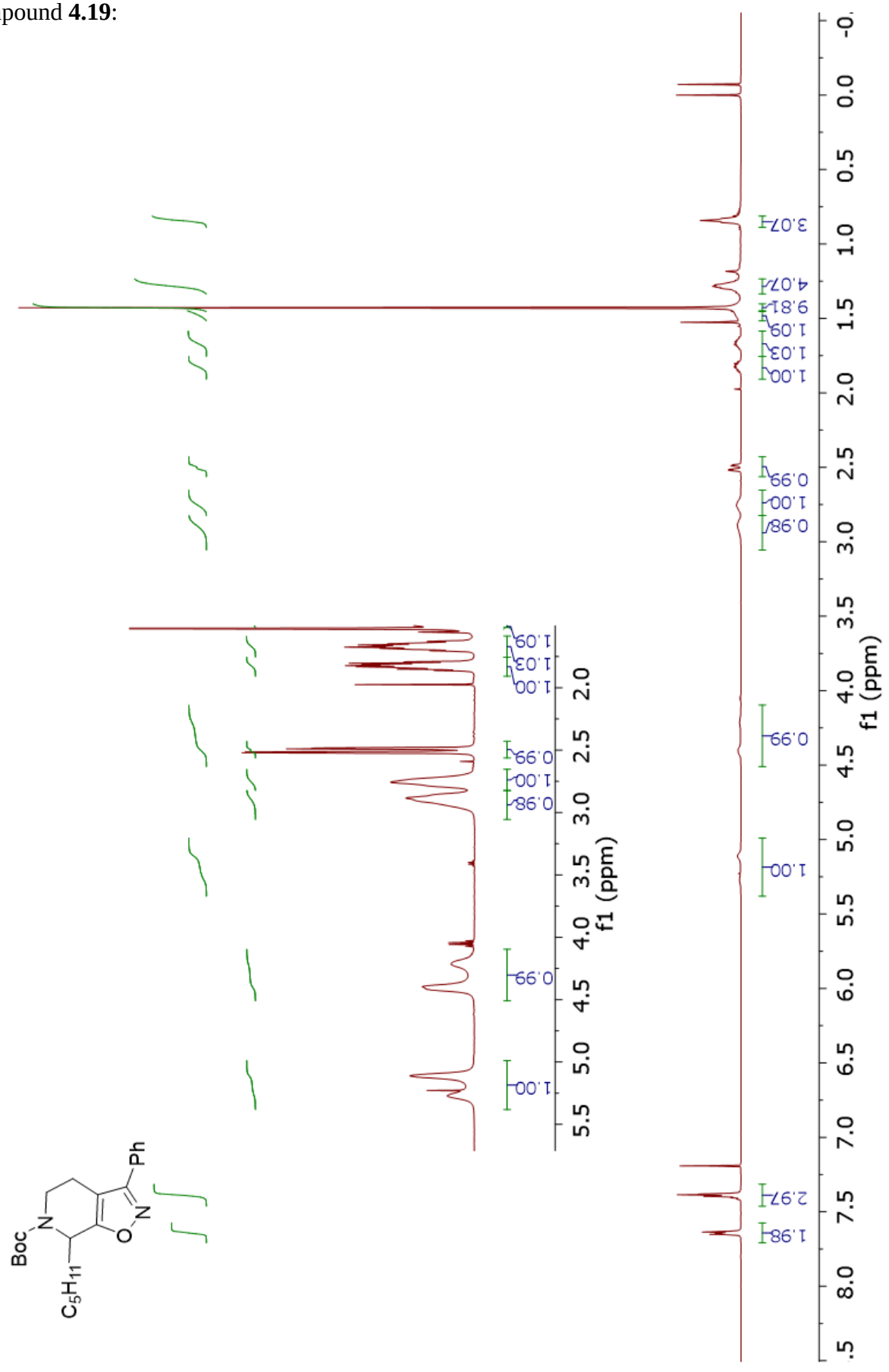
Compound **4.18**:



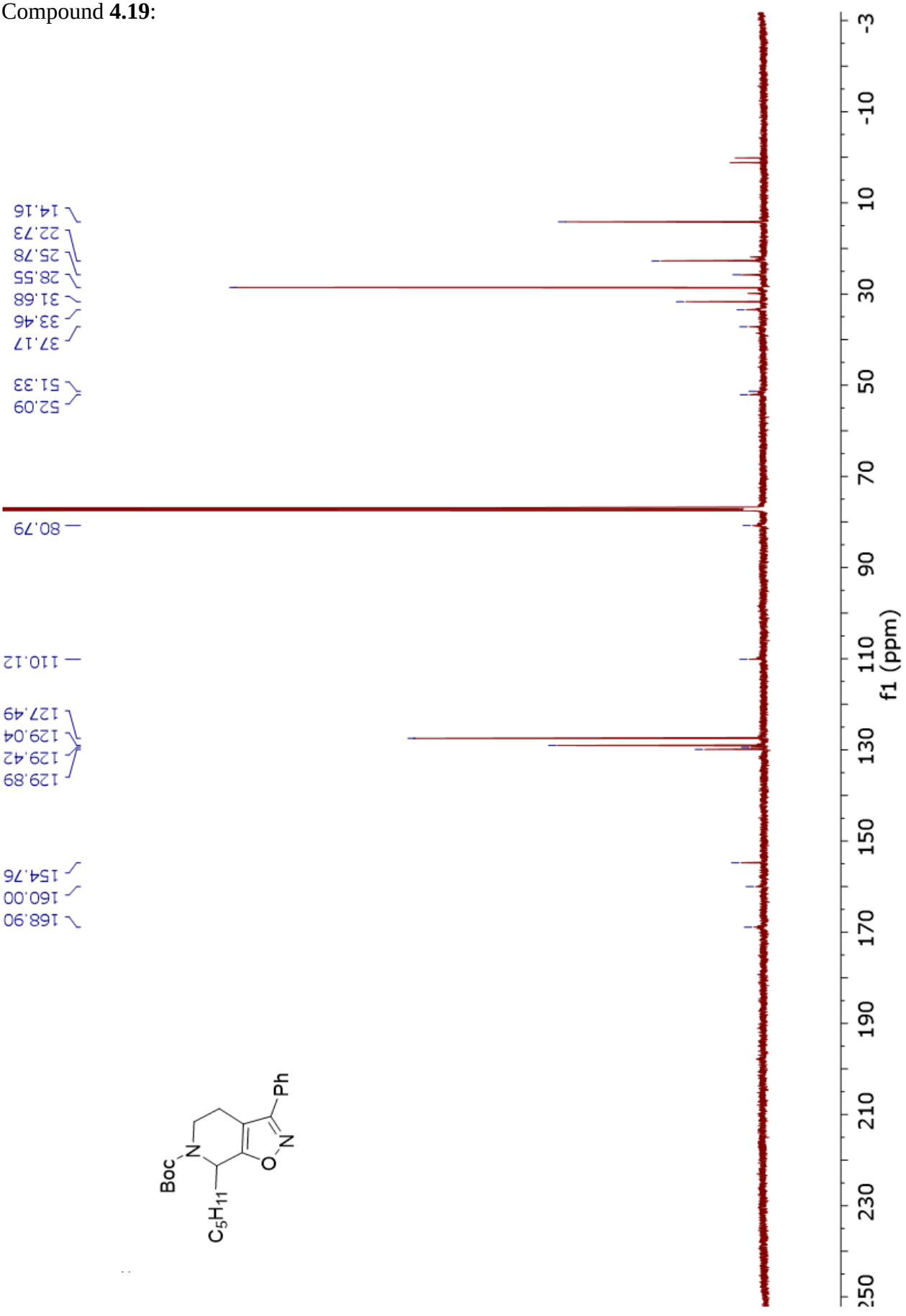
Compound **4.18**:



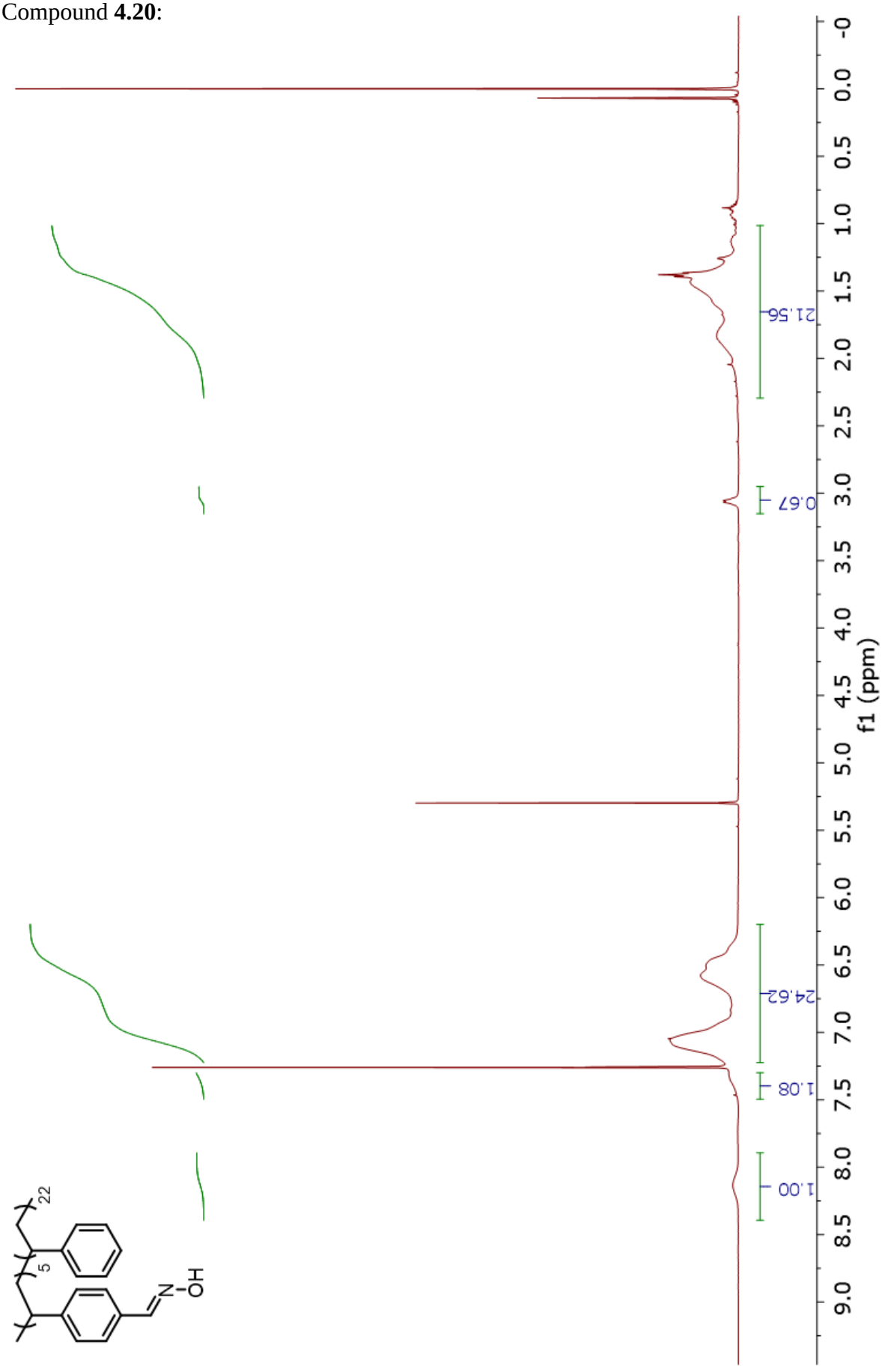
Compound **4.19**:



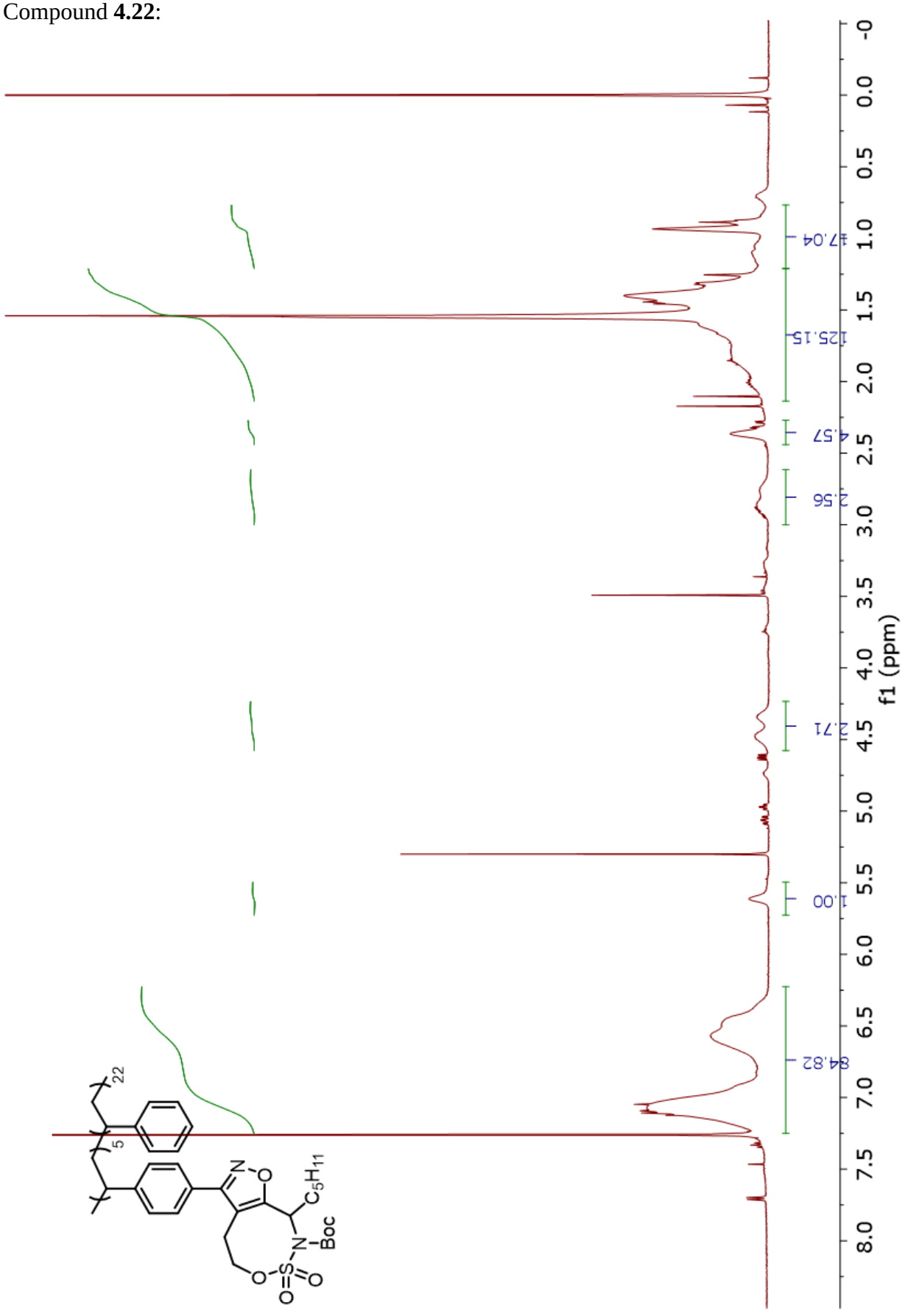
Compound **4.19**:



Compound **4.20**:



Compound **4.22**:



Compound **4.23**: