Modular and Stereocontrolled Synthesis of Aminated Stereotriads *via* Allene Aziridination: Development and Application to Complex Molecule Synthesis

By

Christopher S. Adams

A dissertation submitted in partial fulfillment of

the requirements for the degree of

Doctor of Philosophy

(Chemistry)

at the

UNIVERSITY OF WISCONSIN-MADISON

2015

Date of final oral examination: 7/07/2015

The dissertation is approved by the following members of the Final Oral committee:

Jennifer M. Schomaker, Associate Professor, Chemistry
John F. Berry, Associate Professor, Chemistry
Steven D. Burke, Professor, Chemistry
Samuel H. Gellman, Professor, Chemistry
Laura L. Kiessling, Professor, Chemistry

Abstract

The allene motif is a valuable but underexplored scaffold for oxidative functionalization. In analogy to the diverse oxidation chemistry of alkenes, there exists the potential to form three adjacent heteroatom-bearing stereocenters ("stereotriads") from the allene motif. The ability to form stereotriads from allenes in a modular manner, with variability in the substituents that can be installed, would have powerful applications for the diversity-oriented synthesis of biologically relevant molecules. Simultaneously, it is necessary to develop selective methods for the synthesis of single regioisomers and stereoisomers of product, in order to avoid obtaining complex product mixtures. The work described herein addresses these goals in the context of allene aziridination.

In initial work, homoallenic sulfamates were demonstrated to undergo intramolecular aziridination with high chemo-, regio-, and stereoselectivity to afford bicyclic methylene aziridines. A multi-component, one-pot reaction for the elaboration of these compounds to diverse aminated stereotriads was developed. The stereochemical principles of this process were studied in order to achieve selective access to any desired stereotriad stereoisomer. This methodology was then applied towards the diversity-oriented synthesis of aminocyclopentitol scaffolds. In addition, the reactivity of bicyclic methylene aziridines towards other chemical processes was explored in intermolecular [4 + 3] cycloadditions. Taken together, the work described in this thesis demonstrates the feasibility of achieving both tunable and selective oxidations of allenes for the synthesis of complex amine stereotriads.

Acknowledgements

To begin, I would like to acknowledge my collaborators in the work described herein. Luke Boralsky's research paved the way for my first project in the group, and he provided significant help along the way in his usual jovial manner. I then teamed up with R. David Grigg for my next project; he was an excellent colleague and friend and taught me a lot about how to carry out research in a thorough and logical manner. Mentoring and collaborating with Nels Gerstner was a task made easy due to his impressive work ethic, breadth of organic chemistry knowledge, and easy-going nature. Jared Rigoli was particularly helpful in initiating the Jogyamycin work and for also being a constant source of new ideas and (just as importantly) jokes. Maik Tretbar's assistance in obtaining X-ray crystal data was also crucial and his professional demeanor was much appreciated.

I'd also like to thank everyone else in my office and the "allene subgroup" who gave excellent feedback and suggestions over the years: Jared Rigoli, Dagmara Marston, John Hershberger, Nate Connell, Cale Weatherly, Alicia Phelps, Ryan van Hoveln (yeah it was only like two weeks but who cares), Eileen Burke, Ryan Reeves, Lu Liu, and Minsoo Ju.

Charlie Fry, Martha Vestling, and Ilia Guzei are thanked for providing high quality facilities for collecting the vast amount of characterization data that went into this work.

My greatest thanks have to go to my adviser, Jen Schomaker. Her tireless effort and determination over the years have been an excellent example to follow. Jen has always made sure her students have every opportunity to succeed, while also being willing to let us learn and grow at our own pace. I've enjoyed our many interactions over the years, whether it was joking about something, going back and forth over a manuscript, or just commiserating over something annoying. I have Jen to thank more than anyone else for helping me to succeed as a chemist.

Of course, I wouldn't have decided to pursue a PhD in organic chemistry without the guidance of my numerous teachers throughout my education. My two high school chemistry teachers, Tony Manly and Dennis Lin, were very inspirational in their excitement for the field they taught, and made learning chemistry the highlight of my highschool studies. In college, Keith Woerpel and David Van Vranken stood out as professors who viewed teaching as an endeavor that is just as important, if not more so, than research itself. In particular, working in Dave's lab (and working through the endless mechanism sessions during group meeting) was a fun and rewarding way to develop my lab skills starting out as a novice. And at UW-Madison, in addition to my work in the Schomaker group, I really valued being able to TA for some excellent instructors: Sam Gellman, Helen Blackwell, Christian Hackenberger, Tehshik Yoon, and Nick Hill. In addition, I'd like to thank Steve Burke and Hans Reich for helpful discussions over the years.

I also need to thank all my Madison friends (you know who you are) for making the past five years a fun and unforgettable process. Finally, I'd like to thank my family, and especially my fiancée Caroline English, for supporting me when I was discouraged and having confidence in my ability to succeed in my graduate studies. The past five years have been challenging in a multitude of ways, and I couldn't have made it to this point without their (and everyone else's) help.

Table of Contents

List of Figures

List of Schemes

List of Tables

Abbreviations

Å	angstrom(s)
Ac	acetyl
Ac_2O	acetic anhydride
AcOH	acetic acid
aq	aqueous
Ar	aryl
B3LYP	Becke 3-Parameter, Lee-Yang-Parr density functional method
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
Boc_2O	di-*tert*-butyl dicarbonate
bs	broad singlet
^{n}Bu	*normal*-butyl
^{n}BuLi	*normal*-butyllithium
C	Celsius
COSY	correlation spectroscopy
CSI	chlorosulfonyl isocyanate
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

DASP	1,4-diazaspiro[2.2]pentane
DCE	1,2-dichoroethane
DEAD	diethylazodicarboxylate
DIAD	di*iso*propyl azodicarboxylate
DMAP	4-dimethylamino pyridine
DMDO	dimethyldioxirane
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethylsulfoxide
dr	diastereomeric ratio
ddt	doublet of doublet of triplets
dq	doublet of quartets
dt	doublet of triplets
ee	enantiomeric excess
EI	electron ionization
ESI	electrospray ionization
equiv	equivalents
esp	α,α,α',α'-tetramethyl-1,3-benzenedipropionic acid
Et	ethyl
Et_2O	diethyl ether
EtOAc	ethyl acetate
EtOH	ethanol
g	grams

h	hours
HRMS	high resolution mass spectrometry
Hz	hertz
IC_{50}	half maximal inhibitory concentration
imid	imidazole
IR	infrared spectroscopy
J	spin-spin coupling constant in hertz
kcal	kilocalories
KO^tBu	potassium *tert*-butoxide
LDA	lithium di*iso*propyl amide
m	multiplet
M	molar
MA	methylene aziridine
*m*CPBA	3-chloroperbenzoic acid
MCR	multi-component reaction
Me	methyl
MeCN	acetonitrile
MeOH	methanol
mg	miligrams
MHz	megahertz
mmHg	millimeters of mercury
min	minutes
mL	milliliters

mM	milimolar
mmol	milimoles
mol	moles
mp	melting point
Ms	methanesulfonyl
MS	molecular sieves
NaH	sodium hydride
NBS	N-bromosuccinimide
NCS	N-chlorosuccinimide
NBSH	2-nitrobenzenesulfonylhydrazine
NIS	N-iodosuccinimide
NMR	nuclear magnetic resonance spectroscopy
Nu	nucleophile
OAc	acetate
OMe	methoxy
OTf	trifluoromethanesulfonate
p	pentet
Ph	phenyl
PhIO	iodosylbenzene
$PhI(OAc)_2$	(diacteoxyiodo)benzene
$PhNH_2$	aniline
PhSH	thiophenol
Piv	trimethylacetyl

PMB	*p*-methoxybenzyl
PMP	*p*-methoxyphenyl
PPh_3	triphenylphosphine
ppm	parts per million
^{n}Pr	*normal*-propyl
pyr	pyridine
q	quartet
qd	quartet of doublets
RCM	ring-closing metathesis
R_f	retention factor
RedAl	sodium bis(2-methoxyethoxy)aluminum hydride
rt	room temperature
s	singlet
SDE	spirodiepoxide
SM	starting material
STABH	sodium triacetoxyborohydride
t	triplet
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TCICA	trichloro*iso*cyanuric acid
td	triplet of doublets
TFA	trifluoroacetic acid

THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TMSCN	trimethylsilyl cyanide
TPA	triphenylacetate
Ts	*p*-toluenesulfonyl
$ZnEt_2$	diethylzinc

Chapter 1

The Conversion of Allenes to Strained Heterocycles as a Route to Complex Stereotriads

This chapter is adapted with permissions from sections published in:

Adams, C. S.; Weatherly, C. D.; Burke, E. G.; Schomaker, J. M.

Chem. Soc. Rev. **2014**, *43*, 3136-3163

1.1. Introduction

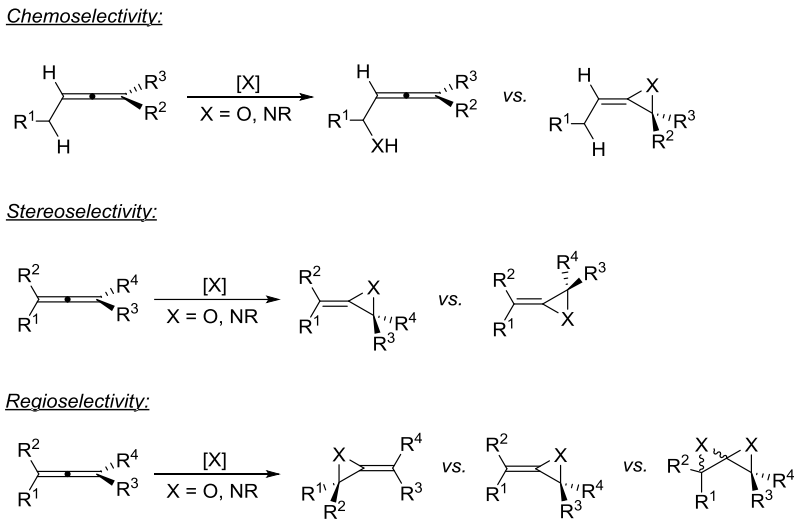
The oxidative functionalization of alkenes is one of the most explored and effective methods for forming two contiguous carbon-heteroatom bonds in a stereo- and regiocontrolled manner. Well-known examples of this method include alkene dihydroxylation, aminohydroxylation, epoxidation, and aziridination.[1] The functionalization of alkenes bearing allylic heteroatom substituents for the formation of three adjacent carbon-heteroatom bonds (i.e. "stereotriads") is more challenging. Depending on the desired stereochemical outcome, access would be needed to either the (*E*) and (*Z*) isomer of the necessary alkene, and the absolute stereochemistry of the allylic substituent would have to be controlled. Furthermore, depending on the nature of the allylic substituent, stereochemical mismatch[2] or chemical incompatibility issues could occur.

An alternate approach for the formation of stereotriad motifs is the application of alkene oxidation methods to a 1,2-diene, or allene. Allenes are intriguing substrates for this process for a variety of reasons. For one, the two unsaturations present in an allene permit the installation of four functional groups into this three-carbon unit. Additionally, the use of enantioenriched, axially chiral allene substrates can allow for the transfer of axial chirality to point chirality in the sp^3-hybridized products.[3] Finally, the wealth of straightforward methods for allene synthesis[4] allows for access to a variety of differentially substituted allenes for functionalization.

This chapter will focus on the epoxidation and aziridination of allenes to form strained, three-membered heterocycles as shown in Scheme 1.1.[5] The high ring strain of these compounds (often 12-13 kcal greater than the corresponding saturated heterocycle,)[6] as well as the presence of an additional alkene for further functionalization, makes these compounds versatile building blocks for the synthesis of stereotriad products. However, the chemo-, regio-, and stereoselective

functionalization of allenes by this method is often challenging, as highlighted in Scheme 1.1. Appropriate oxidants must be used to avoid competing allylic oxidation, and the principles governing stereocontrol and regiocontrol in the addition of oxidants to allene substrates must be understood to avoid obtaining complex product mixtures. Herein, the strategies employed to obtain selective allene oxidation products will be reviewed, with a focus on methods that provide access to complex stereotriad products. Additionally, a short survey of common methods for allene synthesis will be provided, in order to demonstrate their relative ease of preparation.

Scheme 1.1. Possible chemo-, stereo-, and regioselectivity issues in allene functionalization.



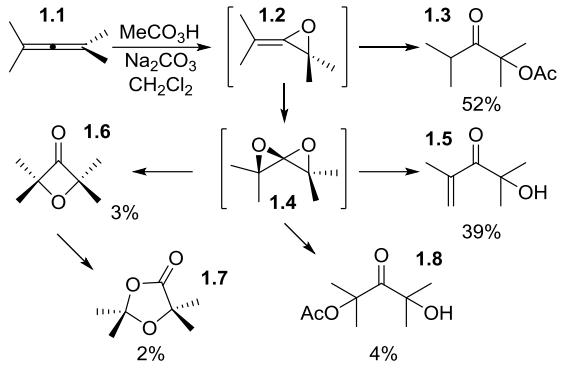
1.2. Allene epoxidation

1.2.1. Early work with peracid reagents

The earliest reports of allene epoxidation were carried out by the group of Crandall in 1966.[7] The peracetic acid oxidation of tetramethylallene was investigated with the goal of isolating epoxide products (Scheme 1.2). Neither the allene oxide **1.2** or spirodiepoxide **1.4** were observed; instead, the α-oxygenated ketones **1.3**, **1.5**, and **1.8** were isolated, as well as oxetan-3-one **1.6** and its Baeyer-Villiger oxidation product **1.7**. This result highlights the high sensitivity of

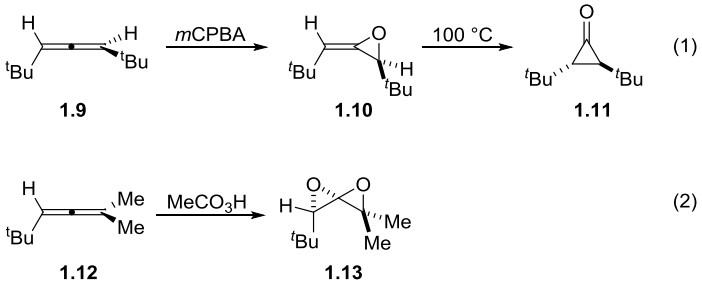
intermediates **1.2** and **1.4**, as well as the challenges of achieving regioselective oxidation of even simple, symmetrically substituted allenes under these conditions.

Scheme 1.2. Products obtained from the peracetic acid oxidation of tetramethylallene.



Two years later, the groups of Greene and Crandall reported the isolation of an allene oxide, its cyclopropanone tautomer, and a spirodiepoxide (SDE). The use of bulky, *tert*-butyl-substituted allenes proved crucial to obtaining allene oxides that would not rapidly undergo a second epoxidation and were stable enough to be isolated and characterized. Greene reported the allene oxide resulting from oxidation of 1,3-di-*tert*-butylallene **1.9** and demonstrated its thermal isomerization to cyclopropanone **1.11** (Scheme 1.3, eq 1).[8] Concurrently with Greene, Crandall reported the isolation of the first stable spirodiepoxide derived from the trisubstituted allene **1.12** (Scheme 1.3, eq 2).[9] However, due to the structural limitations necessary to isolate these products, no further transformations of these initial products were reported.

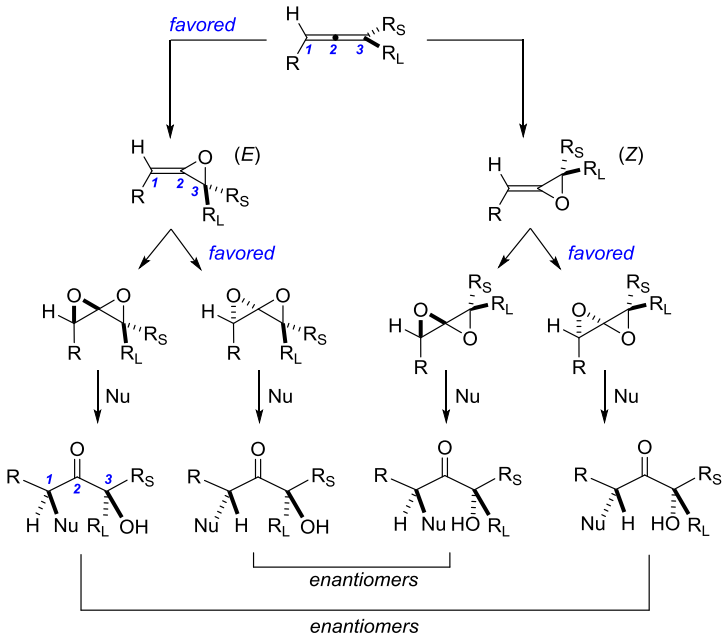
Scheme 1.3. Isolation of allene oxides and spirodiepoxides**.**



1.2.2. Spirodiepoxide formation with DMDO and ring-opening.

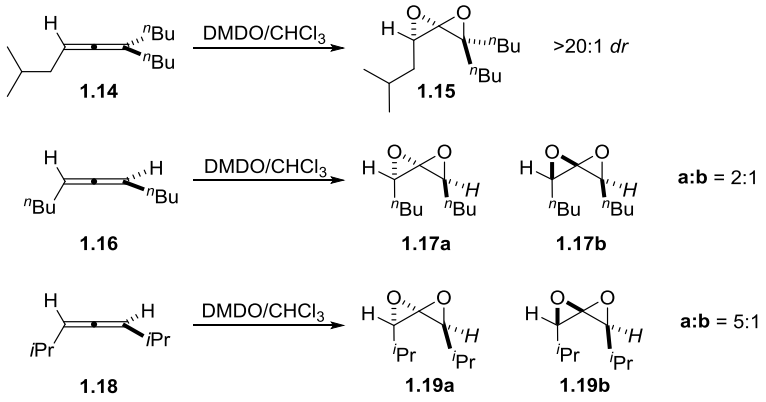
As seen in Scheme 1.2, the use of peracid epoxidizing agents generally led to complex mixtures of product resulting from unselective decomposition of both the allene oxide and spirodiepoxide (SDE). The development of dimethyldioxirane (DMDO) as a powerful but operationally mild oxidant provided access to SDEs in higher yields. In 1988 Crandall and co-workers described the DMDO oxidation of aliphatic allenes to spirodiepoxides in high yields and diastereoselectivities.[10] They proposed a model based on the known reactivity of DMDO with alkenes to rationalize the diastereomeric mixtures obtained (Scheme 1.4).[11] The first epoxidation event is predicted to occur at the more substituted (i.e., electron-rich) double bond of the allene, with the oxidant approaching from the π-face opposite the bulkier substituent on the adjacent olefin. This results in favored formation of the (*E*)-allene oxide. Epoxidation of the allene oxides is also predicted to occur at the π-face opposite the bulkiest group of the newly formed epoxide. Addition of nucleophiles to the less-hindered epoxide results in the formation of stereodefined α-hydroxy ketones *via* a ring-opening cascade. Importantly, if the first epoxidation event is unselective, degradation of the *ee* of an enantiopure allene can be expected, as the (*E*) and (*Z)* allene oxides lead to enantiomeric products upon ring-opening (due to destruction of the C2 stereocenter).

Scheme 1.4. Stereochemical model for diastereoselectivity in allene epoxidation.



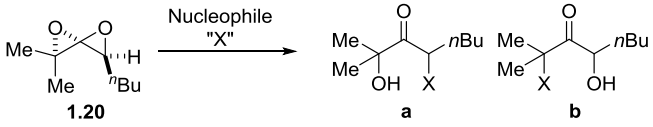
Scheme 1.5 demonstrates the diastereoselectivity of the bisepoxidation of several racemic allenes.[12] The facial selectivity of the initial epoxidation is observed to be high in each case; for the symmetrical allene **1.14**, this results in high overall *dr* as the subsequent epoxidation only forms enantiomeric products. For the 1,3-disubtituted allenes **1.16** and **1.18**, the *dr*'s reflect the selectivity of the second epoxidation event. The higher diastereoselectivity for epoxidation of **1.18** is rationalized by the greater steric difference of ^{i}Pr vs. H as compared to ^{n}Bu vs. H for **1.16**.

Scheme 1.5. DMDO epoxidation of allenes to form spirodiepoxides.



Intermolecular ring-opening of SDEs could be achieved readily with a variety of nucleophiles to provide valuable α,α'-disubstituted ketone products that are potential precursors to stereotriads.[11] As shown in Table 1.1, the regioselectivity of ring-opening was generally high in favor of attack at the less hindered epoxide.

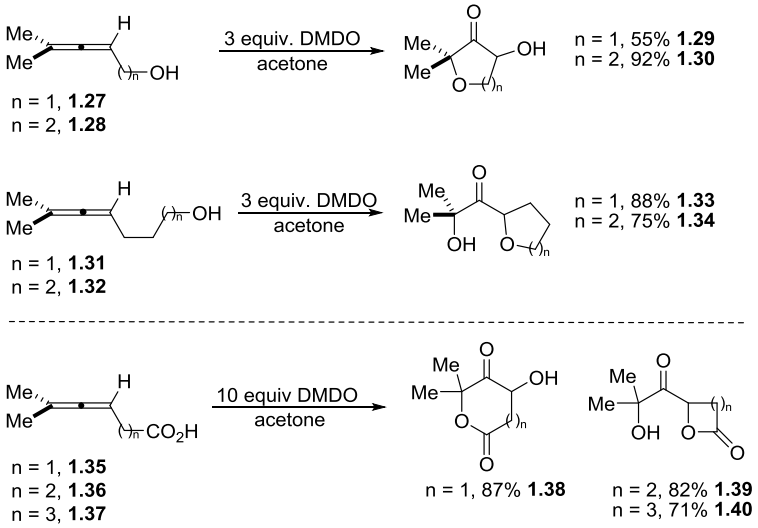
Table 1.1. Intermolecular ring-opening of spirodiepoxide **1.20**.



entry	reagent	X	yield	a:b	product
1	H_2O/THF	OH	80%	NA	**1.21**
2	Bu_4NOAc/AcOH	OAc	quant.	100:0	**1.22**
3	$^nPrOH/K_2CO_3$	OPr	95%	83:17	**1.23**
5	$BnNH_2$	BnNH	61%	100:0	**1.24**
6	PhSH	SPh	55%	100:0	**1.25**
7	Bu_4NF	F	35%	100:0	**1.26**

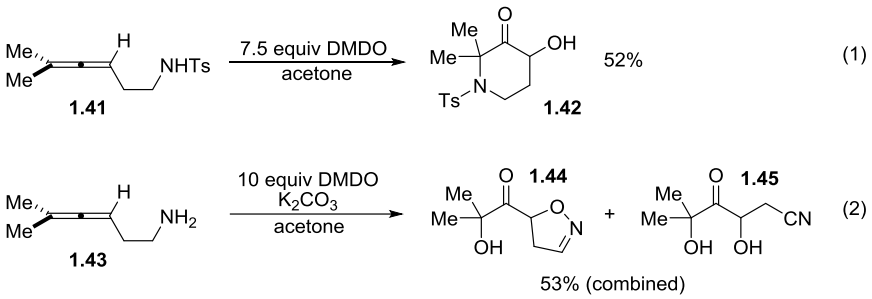
Regioselective intramolecular ring-opening could also be achieved with allenes containing tethered nucleophilic functional groups (Scheme 1.6). Bis-epoxidation/ring-opening tandems could be achieved with tethered alcohol and acid functionalities, with the regioselectivity of ring-opening controlled by the tether length between the allene and nucleophile.[13]

Scheme 1.6. Epoxidation and intramolecular ring opening of alcohol/acid-tethered allenes.



Similar results were obtained with tethered amine functionality (Scheme 1.7).[14] For the unprotected amine **1.43**, mixtures of products resulting from both amine and allene oxidation were obtained, as would be expected.

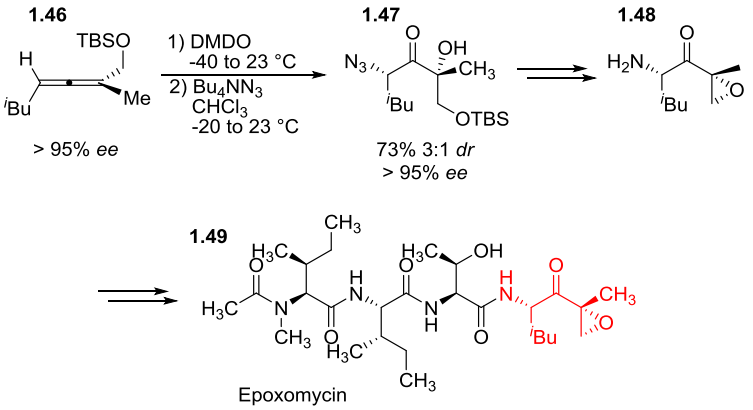
Scheme 1.7. Epoxidation and intramolecular ring opening of amine-tethered allenes.



1.2.3. Application of spirodiepoxide opening to complex molecule synthesis

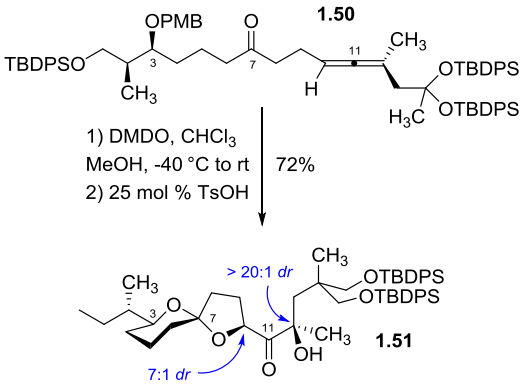
The group of Lawrence Williams has utilized allene epoxidation to install complex heteroatom-containing motifs in the context of many total syntheses. In their first example (Scheme 1.8), epoxidation/ring-opening of allene **1.46** was used to generate a complex α,β-epoxy-α'-aminoketone segment of the proteasome inhibitor epoxomycin.[15] The reaction successfully set the two chiral centers adjacent to the ketone, with moderate *dr* and excellent transfer of axial to central chirality. The use of a trisubstituted allene, with all substituents being sterically differentiated, was likely crucial to obtaining a stereoselective outcome to this oxidation (recall Scheme 1.4).

Scheme 1.8. Demonstration of allene epoxidation in epoxomycin synthesis.



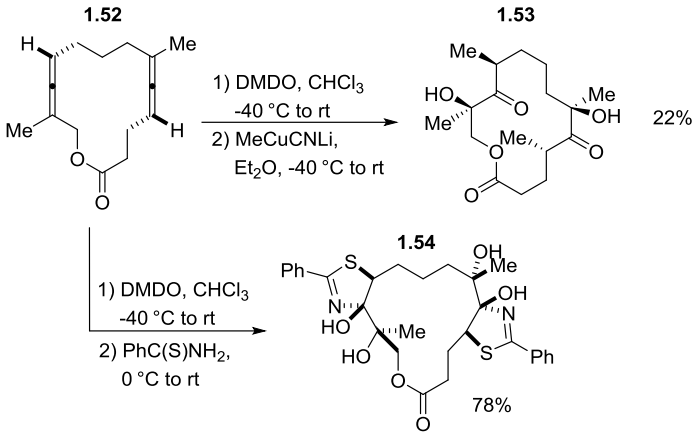
In the partial synthesis of pectenotoxin 4, the Williams group utilized a highly regio- and diastereoselective allene epoxidation cascade to form both a spiroketal and α-hydroxy ketone moiety (Scheme 1.9).[16] Spiroketal formation likely occurred by ring-opening of the SDE (not shown) by the C7 ketone, followed by capture of the resulting oxocarbenium by the oxidatively deprotected C3 PMB-alcohol. This reaction highlights the ability of allene oxidations to access impressively complex chemical motifs with good stereoselectivity in a single transformation.

Scheme 1.9. Spiroketal formation *via* allene epoxidation and ring-opening.



A recent, inventive demonstration of the potential of spirodiepoxides in complex molecule synthesis is the use of macrocyclic bis-allenes to prepare analogues of the important macrolide antibiotic erythromycin.[17] As shown in Scheme 1.10, epoxidation of **1.52** followed by the addition of various nucleophiles allowed for the formation of diverse macrolide products.

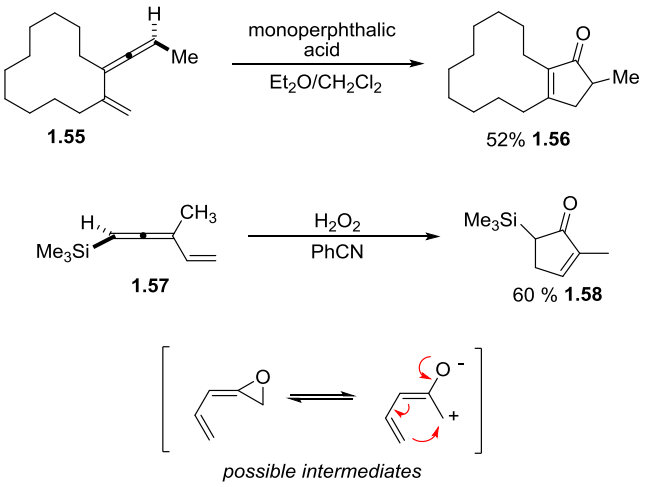
Scheme 1.10. Erythronolide synthesis by epoxidation of macrocyclic bisallenes.



1.2.4. Electrocyclizations of vinylallenes

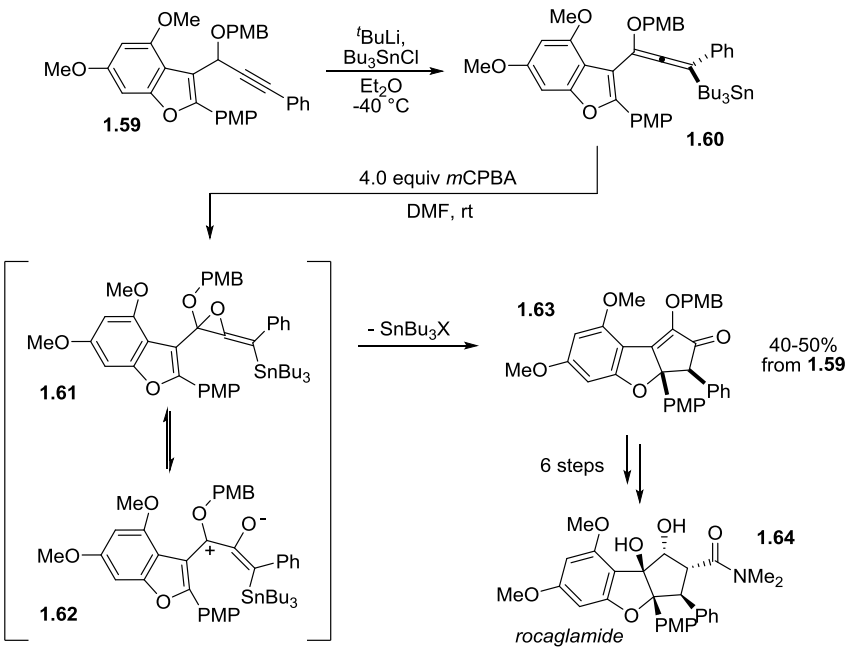
An alternative to the reactions of spirodiepoxides shown above is to trap the intermediate allene oxide in a different chemical process. This is traditionally challenging, as the reactivity of the allene oxide towards a second epoxidation generally outcompetes other processes. However, the groups of Gore,[18] Bertrand,[19] and Santelli[20] have found that allene oxides derived from vinylallenes can be trapped in a [4π] electrocyclization reaction, generating cyclopentenone products as demonstrated in Scheme 1.11.

Scheme 1.11. Formal [4π] electrocyclizations of allene oxides derived from vinylallenes.



While the cyclopentenone products shown above could be argued to be more readily accessed by a Nazarov cyclization or alternative process, the Frontier group has demonstrated the usefulness of this method towards the complex polycyclic core of rocaglamide (Scheme 1.12).[21] Oxidation of allene **1.60** with *m*CPBA led to formation of the highly substituted cyclopentenone **1.63** as a single diastereomer, through the likely intermediacy of allene oxide **1.61** and the resulting divinyl cation **1.62**. While the tributytin substituent was necessary for formation of the desired allene motif in the conversion of **1.59** to **1.60**, it was serendipitously lost during the cyclization, presumably *via* protodestannylation. The use of an allene precursor for this cyclization was crucial, as a more traditional Nazarov cyclization of a divinyl ketone precursor (not shown) was unable to access **1.63**.

Scheme 1.12. Allene epoxidation/electrocyclization as a route towards rocaglamide.

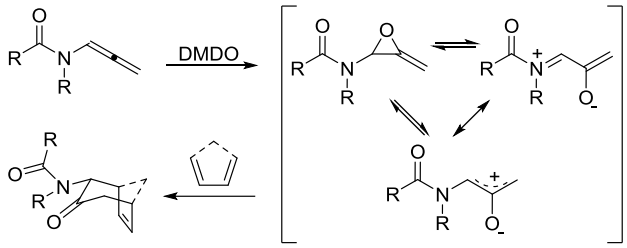


1.2.5. Cycloadditions *via* epoxidation of allenamides.

The use of oxyallyl cations in [4 + 3] cycloadditions is a well-precedented method for generating 7-membered carbocycles; however, these intermediates are most commonly generated

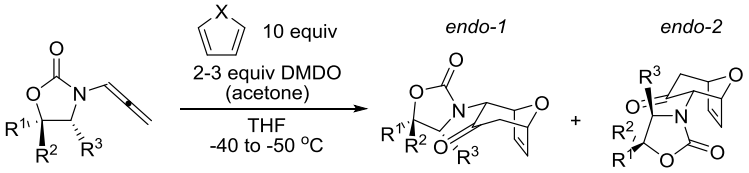
from α-halo ketones.[22] Hsung and co-workers have demonstrated that the epoxidation of allenamides generates nitrogen-stabilized oxyallyl cations that readily undergo [4+3] cycloadditions with dienes (Scheme 1.13). In addition to activating the allene for epoxidation and stabilizing the electrophilic oxyallyl cation, the nitrogen atom provides a scaffold for incorporating chiral auxiliaries to control the absolute stereochemistry of the reaction products.

Scheme 1.13. Generation of N-stabilized oxyallyl cations *via* allenamides epoxidation.



In their first report (Table 1.2), the Hsung group utilized an Evans auxiliary to control the stereochemical outcome of intermolecular [4 + 3] reactions of allenamides with furan.[23] The cyclization was found to be exclusively selective for the *endo* product, with several chiral oxazolidinones providing a major stereoisomer in high *dr*. Cyclopentadiene was tolerated, albeit in lower yields (entry 2). This elaboration of simple allenamides to complex cycloheptenes highlights the utility of the allene scaffold.

Table 1.2. Intermolecular [4+3] of allenamides using the Evans auxiliary.

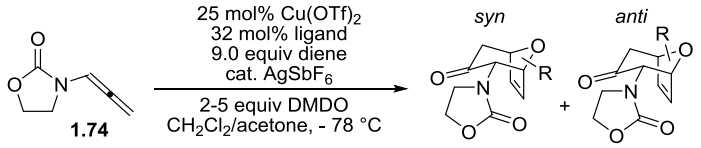


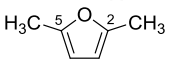
entry	R^1	R^2	R^3		X	yield	*endo-1:endo-2*	
1	H	H	Ph	**1.65**	O	77%[a]	94:6	**1.69**
2	H	H	Ph	**1.65**	CH_2	40%[a]	> 95:5	**1.70**
3	H	H	Bn	**1.66**	O	67%	77:23	**1.71**
4	H	H	$CHPh_2$	**1.67**	O	74%	> 95:5	**1.72**
5	Ph	Ph	^{i}Pr	**1.68**	O	72%	94:6	**1.73**

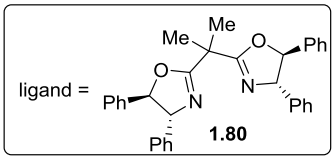
[a] 2.0 eq. of $ZnCl_2$ was used.

A catalytic asymmetric variant of this process was later reported.[24] Using a Cu(II)-BOX complex, *ee*'s of up to 99% could be achieved, offering an alternative to chiral auxiliaries for gaining access to enantioenriched products (Table 1.3). The system tolerated substituted furans, with the *syn/anti* ratios depending on the placement of the substituents. While 2-substituted furans favoured the *syn* product **1.76** shown in Table 13 (where the furan substituent is positioned adjacent to the oxazolidinone group), 3-substituted substrates favoured the *anti* products **1.77** and **1.78**.

Table 1.3. Catalytic asymmetric [4 + 3] reactions of allenamides using a Cu(II)-BOX catalyst.

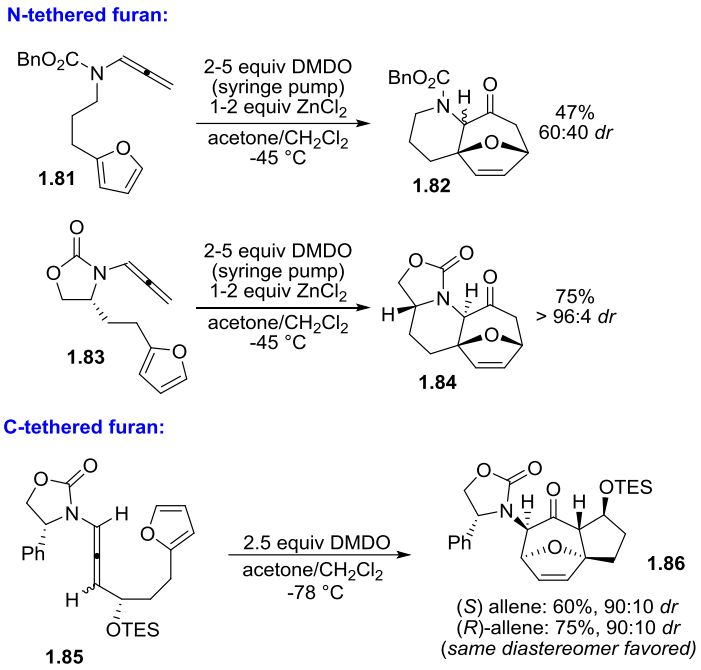


entry	diene	R	yield	*syn:anti*	%*ee*	
1		H	91	N/A	99	**1.75**
2		Me	88	20:1	71	**1.76**
3		Me	91	*anti* only	99	**1.77**
4		Br	58	1:14	84	**1.78**
5		-	81	N/A	36	**1.79**



Complementary intramolecular [4 + 3] reactions were also reported. By tethering both the allene and the diene to nitrogen, (Scheme 1.14, top), complex tricyclic systems such as **1.82** and **1.84** could be generated in varying *dr*'s.[25] Incorporating the furan through a 1,3-disubstituted allene (Scheme 1.14, bottom) gave similar motifs with generally good *dr*.[26] The allene stereochemistry had no impact on the stereochemical outcome of this reaction, indicating the likely intermediacy of a cationic intermediate.

Scheme 1.14. Top: intramolecular [4+3] cycloaddition *via* an N-tethered diene. Bottom: intramolecular [4+3] cycloaddition *via* a C-tethered 1,3-disubstituted allene.



1.2.6. Conclusions

The above examples demonstrate both the promise and challenge of achieving selective transformations *via* intermolecular allene oxidation. The α,α'-difunctionalized ketone products of allene epoxidation/ring-opening are valuable motifs that almost certainly could not be accessed in one step by any other method. However, achieving regioselective and stereoselective oxidation is still an inherent, substrate-controlled limitation. The most success in reactions of spirodiepoxides has been obtained with trisubstituted allenes bearing sterically differentiated groups, as this allows both epoxidation events to occur with moderate to good selectivity. Alternatively, using vinylallene or allenamide substrates predisposes the intermediate allene oxide to a variety of electrocyclization and cycloaddition processes. The sensitivity of allene epoxidation intermediates has largely limited the types of available oxidants to dioxiranes, which can be cumbersome to generate[27] and do not always provide high levels of stereoselectivity (recall

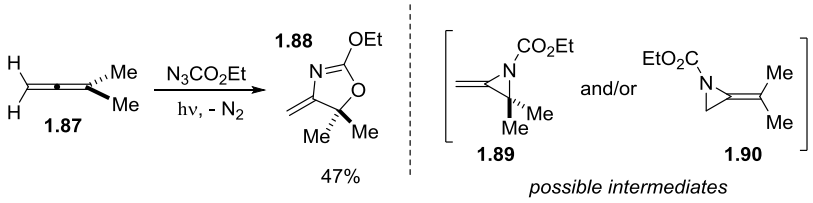
Scheme 1.5). The development of new methods for reagent-controlled stereoselective oxidations would be a powerful addition to this field.

1.3. Allene aziridination

1.3.1. Early work with intermolecular attempts.

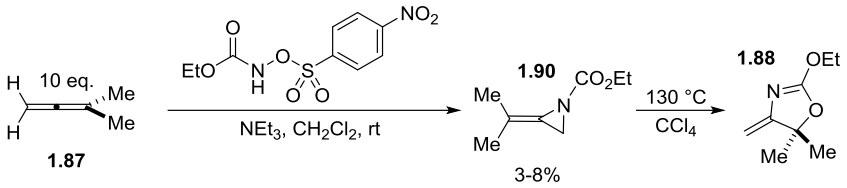
The first attempt of nitrogen atom transfer to an allene was described by Bleiholder and Shechter in the reaction of ethyl azidoformate and allene **1.87** under photolytic conditions (Scheme 1.15).[28] Instead of an aziridine, the methylene oxazoline **1.88** was obtained in 47% yield as the sole product. The authors speculated that the oxazoline arose from a transient methylene aziridine (MA) such as **1.89** or **1.90**, but could not rule out a direct [3 + 2] cycloaddition of carbethoxynitrene with allene **1.87** or other pathways.

Scheme 1.15. Photolysis of ethyl azidoformate in the presence of an allene.



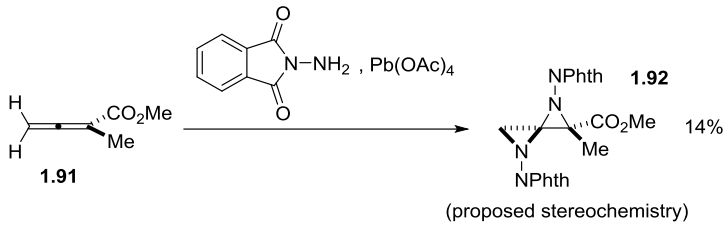
Gilbert and co-workers re-examined this transformation using a nosyloxycarbamate as the nitrene source.[29] Intriguingly, trace amounts of MA **1.90** could be isolated using this reagent, as confirmed by MS and NMR analysis (Scheme 1.16). Thermolysis of **1.90** gave Shechter's oxazoline product **1.88**, validating the possible intermediacy of MA **1.90** in that work. Due to the low isolated yields and poor stability of MA **1.90**, further transformations of this motif were not explored.

Scheme 1.16. First isolation of MAs from sulfonyloxycarbamates and allenes.



Concurrently with these reports, Atkinson and Malpass described the bis-aziridination of allenoate **1.91** to form 1,4-diazaspiro[2.2]pentane (DASP) **1.92**.[30] The addition of phthalimidonitrene, generated from N-amino phthalimide and $Pb(OAc)_4$, to **1.91** gave no isolable methylene aziridine products, but yielded the DASP product in greater than 9:1 *dr* (Scheme 1.13). At room temperature, this compound existed as a mixture of N-invertomers, but the major diastereomer could be observed by ^1H NMR at temperatures below -5 ºC. The reactivity of this spiro compound was not investigated, likely due to the low yields in its formation. No further syntheses of DASPs were reported until the work of Schomaker and coworkers in 2012 (*vide infra*).[31]

Scheme 1.17. Intermolecular DASP formation from an allenoate.

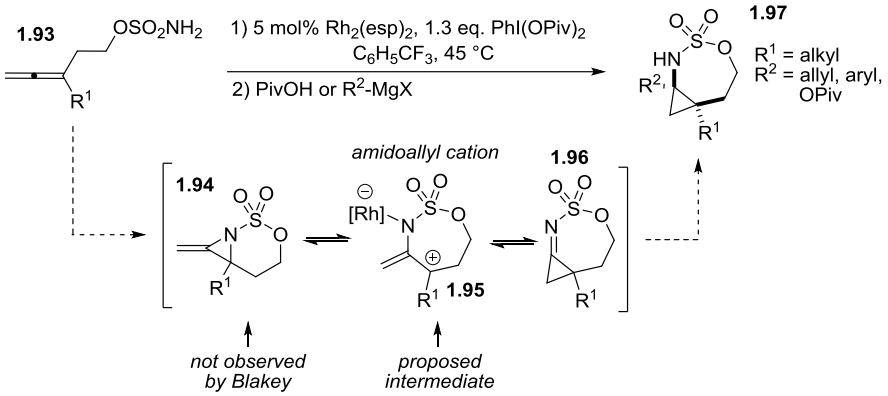


1.3.2. Work by the Blakey group

Allene aziridination has seen a resurgence of activity since the popularization of sulfamate and carbamate-based nitrene precursors by the group of Du Bois.[32] The first attempt of intramolecular allene aziridination using these reagents was reported by the Blakey group in 2009.[33] In the presence of $Rh_2(esp)_2$ and $PhI(OPiv)_2$, 1,1-disubstituted homoallenic sulfamates yielded iminocyclopropanes that were isolated as the pivalate aminals (Scheme 1.18). It was

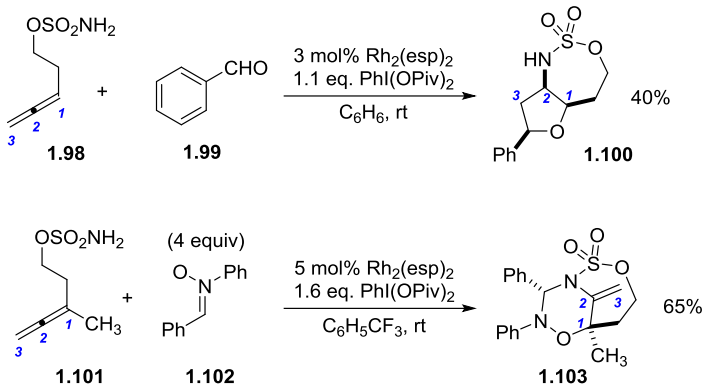
demonstrated that grignard reagents were capable of adding cleanly to these intermediates to give densely substituted aminocyclopropanes. Blakey proposed that the iminocyclopropane **1.96** was formed by rearrangement of an initial amidoallyl cation **1.95** and support for this intermediate was seen in the partial racemization of an enantioenriched allene substrate under the reaction conditions. The group did not report the observation of a bicyclic methylene aziridine such as **1.94** during the course of their reactions; however, the observance of the iminocyclopropane valence tautomer suggests it could have been present as a transient intermediate.

Scheme 1.18. Aminocyclopropane formation from allenes.



The 2-amidoallyl cation character of the reaction intermediates was demonstrated through a [3 + 2] cycloaddition of **1.98** with benzaldehyde, as well as a [3 + 3] cycloaddition of **1.101** with N,α-diphenyl nitrone as a coupling partner (Scheme 1.19). Interestingly, while the reaction with benzaldehyde favored bond formation at C1 and C3 of the allene, the [3 + 3] favored bond formation at C1 and the nitrogen atom of the presumed amidoallyl cation. Both reactions were highly selective, providing the cycloadducts with excellent regio- and diastereoselectivity.[34]

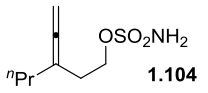
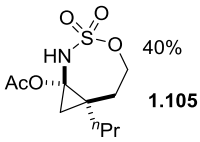
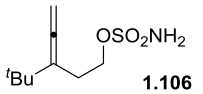
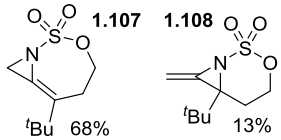
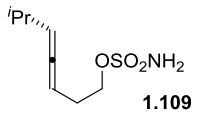
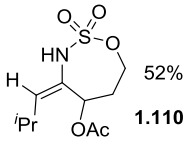
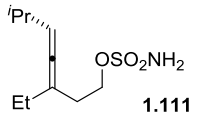
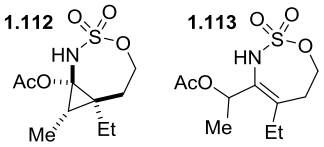
Scheme 1.19. Cyclizations of 2-amidoallyl cations generated from sulfamoyl allenes.



1.3.3. Work by the Robertson group

Soon after the initial publication by Blakey, the Robertson group reported similar findings in their experiments with homoallenic sulfamates.[35] They found that the nature of the allene substitution pattern had a profound effect on the regioselectivity of nitrene transfer. While several 1,1-disubstituted allenes gave the same aminocyclopropane products observed by Blakey (Table 1.4, entry 1), a more hindered ^{t}Bu substrate **1.106** gave the novel bicyclic methylene aziridine products **1.107** and **1.108** as a 5:1 mixture of regioisomers (entry 2). Aziridination of the distal, less substituted olefin was preferred. A 1,3-disubstituted allene (entry 3) gave an enesulfamate product **1.110**, likely formed by acetate ring-opening of a bicyclic MA similar to **1.108**. Finally, a trisubstituted allene reacted with poor regioselectivity, giving a 1:1 mixture of aminocyclopropane **1.112** and enesulfamate **1.113** (entry 4). The results illustrate the complex effects of allene substitution on the regiochemistry of allene aziridination.

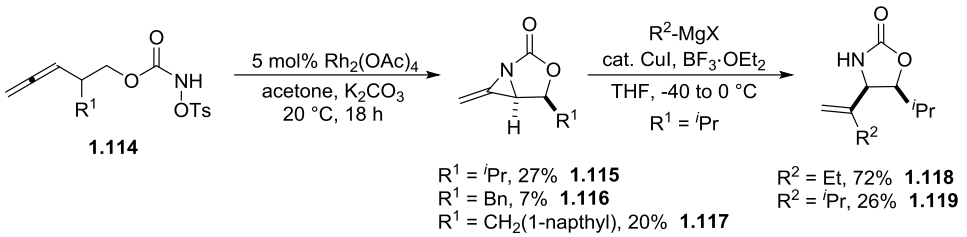
Table 1.4. Oxidative Cyclization of Homoallenic Sulfamates.

Entry	Substrate	Product(s)
1	 **1.104**	 40% **1.105**
2	 **1.106**	 **1.107** 68% **1.108** 13%
3	 **1.109**	 52% **1.110**
4	 **1.111**	 **1.112** 26% **1.113** 28%

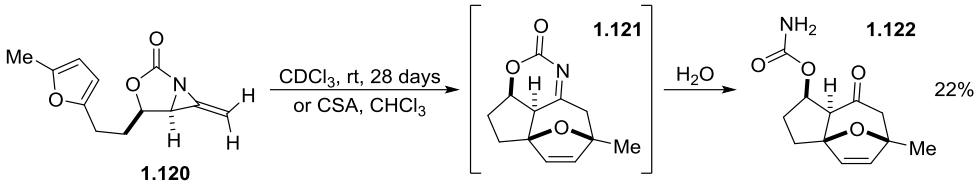
Conditions: $Rh_2(OAc)_4$ (5 mol%), $PhI(OAc)_2$ (1.3 eq.), MgO (2.3 eq.), CH_2Cl_2, 20 °C, 18 h.

Concurrent with the above work, the corresponding aziridination of homoallenic carbamates and tosyloxycarbamates was also investigated by Robertson.[36] Using rhodium catalysis, allene-tethered tosyloxycarbamates gave bicyclic MA products **1.115-117** in low yields (Scheme 1.20). Reaction of the MA products with cuprates gave unexpected ring-opening at the sp^2-hybridized carbon of the aziridine to give oxazolidinones **1.118** and **1.119**. The furan-tethered MA **1.120** was also observed to undergo an intramolecular [4 + 3] cycloaddition (Scheme 1.21), in analogy to the reactivity observed by Blakey (Scheme 1.19, *vide supra*). While these transformations demonstrated the utility of MAs as reactive intermediates, the low yields of MA formation limited their usefulness.

Scheme 1.20. Synthesis and ring-opening of carbamoyl bicyclic MAs.



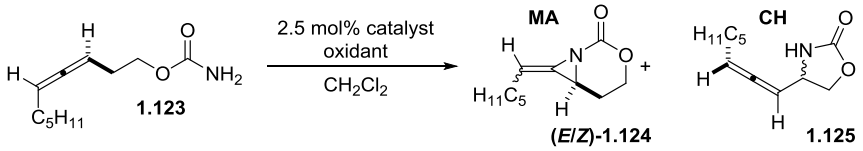
Scheme 1.21. Intramolecular [4 + 3] cycloaddition of a bicyclic MA.



1.3.4. Work by the Schomaker group

The Schomaker group also explored the intramolecular aziridination of homoallenic tosyloxycarbamates, noting similarly low yields for formation of the bicyclic MAs.[37] They found that yields could be significantly improved by using homoallenic carbamates in the presence of iodine (III) oxidants. Both the *E* and *Z* isomers of the bicyclic MA **1.124** were formed in these reactions, in addition to the allenic C-H insertion product **1.125** (Table 1.5). The bulkier catalyst rhodium (II) triphenylacetate (Rh_2TPA_4) in conjunction with PhIO as the oxidant was found to give the highest selectivity for the (*E*)-methylene aziridine (entry 4).

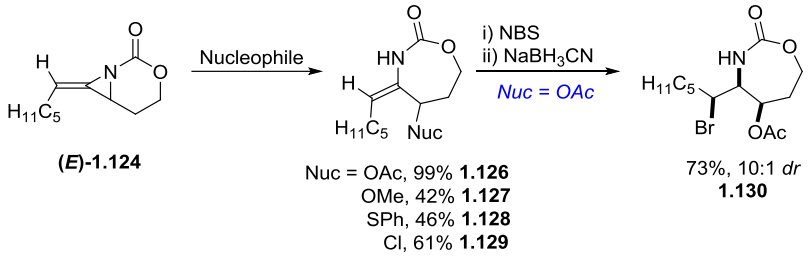
Table 1.5. Intramolecular aziridination of homoallenic carbamates.



entry	catalyst	oxidant	additive	temp (°C)	%MA (*E*:*Z*)	%CH
1	$Rh_2(esp)_2$	$PhI(OAc)_2$	2.6 eq. MgO	35	46% (1.5:1)	44%
2	$Rh_2(esp)_2$	$PhI(OPiv)_2$	2.6 eq. MgO	35	42% (4.1:1)	45%
3	$Rh_2(esp)_2$	PhIO	4 A MS	rt	66% (3.0:1)	16%
4	$Rh_2(TPA)_4$	PhIO	4 A MS	rt	80% (4.0:1)	15%

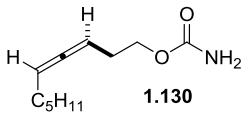
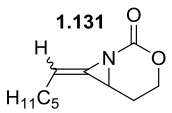
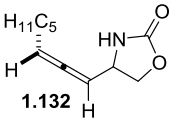
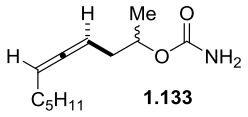
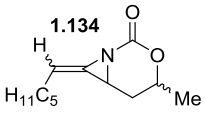
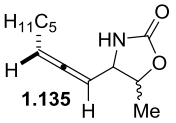
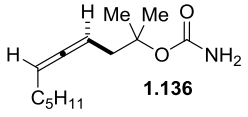
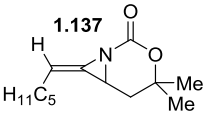
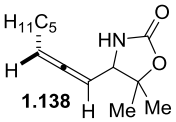
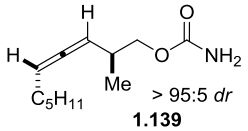
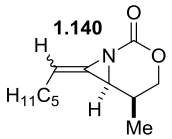
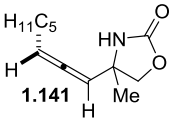
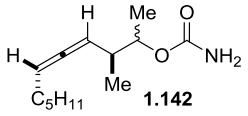
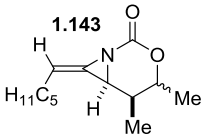
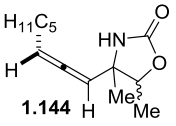
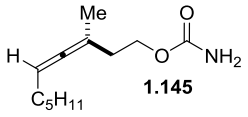
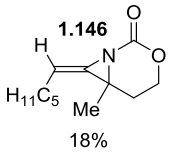
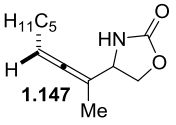
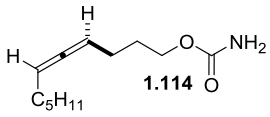
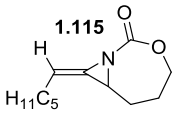
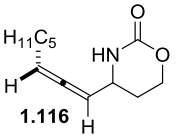
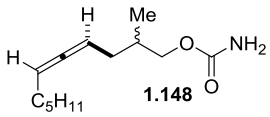
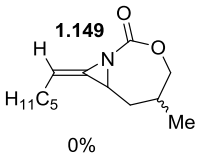
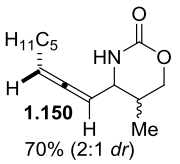
The Schomaker group then investigated the reactivity of the MA **1.124** (Scheme 1.22). In contrast to Robertson's example (Scheme 1.20), nucleophilic attack primarily occurred at the sp^3-hybridized carbon of the aziridine to give enecarbamates **1.126-129**. Functionalizing the remaining alkene of enecarbamate **1.126** delivered stereotriad **1.130** in high *dr*, demonstrating the utility of MAs for functionalizing all three carbons of the initial allene.

Scheme 1.22. Ring-opening of MA **1.92** with heteroatom nucleophiles.



To gain a better understanding of the factors controlling the chemoselectivity of carbamoyl allene aziridination, the effect of tether length and substitution was probed (Table 1.6).[38] In most cases, adding additional substituents in the tether between the allene and carbamate increased the amount of allenic C-H insertion (entries 1-5). The use of a trisubstituted allene gave low yields of both products (entry 6), and when a three-carbon tether was used, (entries 7-8), C-H insertion was the exclusive product.

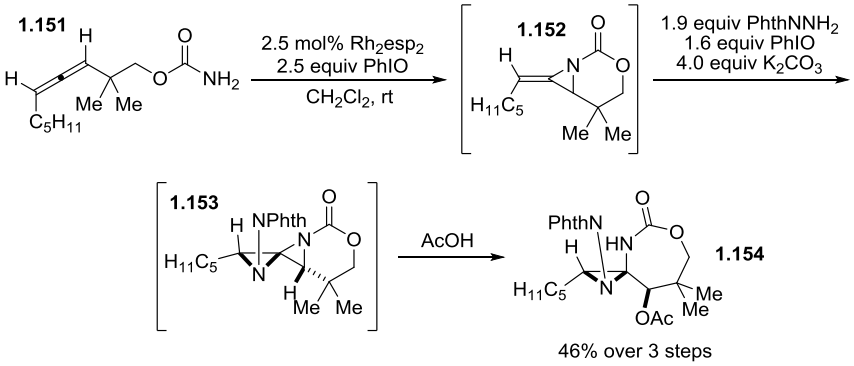
Table 1.6. Chemoselectivity in carbamoyl allene aziridination.

entry	substrate	conditions	products	
1	 **1.130**	$Rh_2(esp)_2$, $PhI(OPiv)_2$, MgO	 **1.131** 42%, (1.5:1 *E*/*Z*)	 **1.132** 45%
2	 **1.133**	$Rh_2(esp)_2$ $PhI(OPiv)_2$ MgO	 **1.134** 39%, (2.2:1 *E*/*Z*)	 **1.135** 29% (2:1 *dr*)
3	 **1.136**	$Rh_2(esp)_2$ $PhI(OPiv)_2$ MgO	 **1.137** 10%	 **1.138** 72%
4	 > 95:5 *dr* **1.139**	$Rh_2(esp)_2$ $PhI(OPiv)_2$ MgO	 **1.140** 21% (3:1 *E*/*Z*)	 **1.141** 57%
5	 **1.142**	$Rh_2(esp)_2$ PhIO 4A MS	 **1.143** 12%	 **1.144** 61% (1.3:1 *dr*)
6	 **1.145**	$Rh_2(esp)_2$ PhIO 4A MS	 **1.146** 18%	 **1.147** 28%
7	 **1.114**	$Rh_2(esp)_2$ $PhI(OPiv)_2$ MgO	 **1.115** 0%	 **1.116** 9%
8	 **1.148**	$Rh_2(esp)_2$ PhIO 4A MS	 **1.149** 0%	 **1.150** 70% (2:1 *dr*)

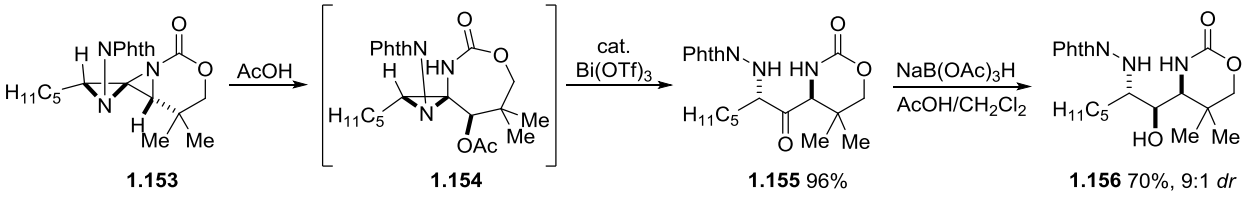
Functionalization of the exocyclic olefin of the MA was explored as a route to stereotriad products, taking advantage of the concave geometry of the bicyclic system to carry out highly diastereoselective transformations. Aziridination of carbamoyl MAs could be carried out with

excellent diastereoselectivity to give DASP products[31] (Scheme 1.23) in analogy to the work of Atkinson and Malpass (Scheme 1.13, *vide supra*). Ring-opening was generally regioselective for the more electron-poor aziridine, giving N,N-spiroaminal **1.154**. A hydrolysis/ring-contraction of aminal **1.154** could be achieved using $Bi(OTf)_3$, although the presence of an acetate group was necessary to promote this unusual rearrangement (Scheme 1.24).[39] Reduction of the resulting diaminoketone **1.155** with $NaB(OAc)_3H$ provided 1,3-diamino-2-ols in good diastereoselectivity.

Scheme 1.23. Synthesis and ring-opening of 1,4-diazaspiro[2.2]pentanes.

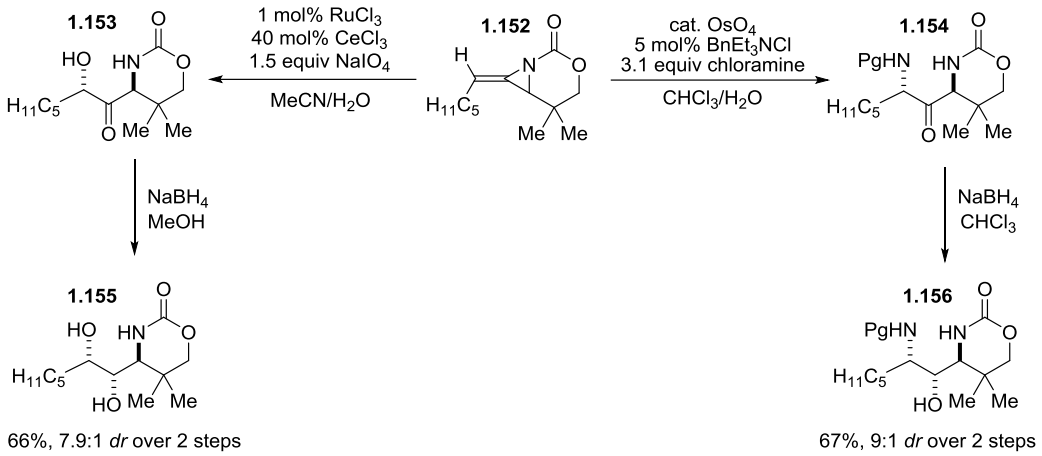


Scheme 1.24. $Bi(OTf)_3$-promoted rearrangement of spiroaminal **1.123** and reduction.



Similar products could be obtained in a more direct route by aminohydroxylation[40] or dihydroxylation[41] of bicyclic MA's, as shown in Scheme 1.25. In both cases, the diastereoselectivity of functionalization of the MA exocyclic alkene was high, and diastereoselective reduction of the resulting ketones could be carried out to arrive at single diastereomers of 1,3-diamino-2-ol or 1-amino-2,3-diol products.

Scheme 1.25. Aminohydroxylation and dihydroxylation of MA's.



1.3.5. Conclusions

In contrast to allene epoxidation, which is by necessity an intermolecular process, the majority of reports of allene aziridination have occurred *via* an intramolecular approach. This reaction design appears to provide more stable products than the intermolecular approach; however, the regioselectivity of the initial aziridination event is still highly dependent on the substitution of the allene (see Tables 1.4, 1.6). Competing allenic C-H amination also raises a chemoselectivity concern not seen to a great extent in the epoxidation reactions.[42] However, the bicyclic methylene aziridines obtained from this approach can be converted to complex amine stereotriads by a variety of different methods. The research described in the following chapters will highlight recent work in controlling the regio-, chemo-, and stereochemical outcomes of transformations of methylene aziridines.

1.4. A selection of common methods for allene synthesis

1.4.1. Introduction

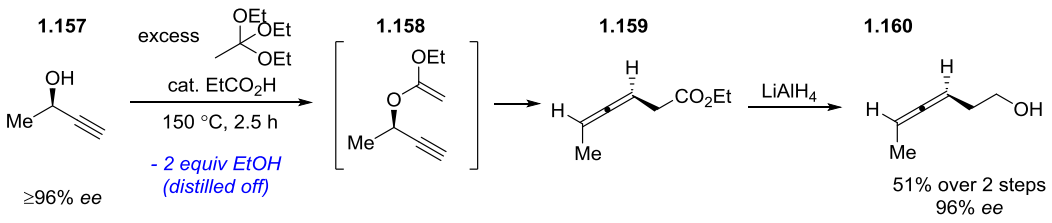
As the utilization of allenes in organic synthesis has expanded, so have the methods for their preparation.[4] A particularly valuable starting material for allene synthesis is the propargyl alcohol. Propargyl alcohols are advantageous substrates due to their ease of synthesis (most

commonly by ynone reduction or addition of an alkynyl organometallic reagent to a carbonyl) in both racemic and enantioselective fashion.[43] In addition, the absolute stereochemistry of a chiral propargyl alcohol can often be translated in stereospecific fashion to the axial chirality of an allene.[4] The following examples highlight common methods (often employed by our own group) for the synthesis of allenes from propargyl alcohols (or, as in the last two examples, propargyl amines).

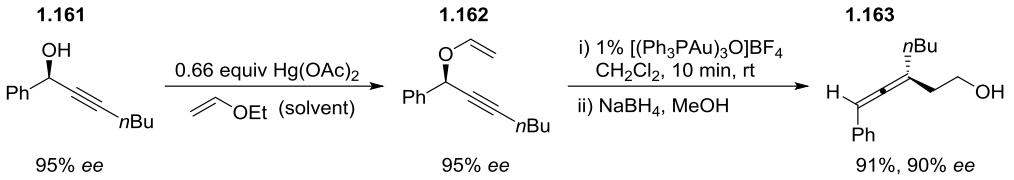
1.4.2 Propargyl Claisen

The Claisen rearrangement of propargyl vinyl ethers[44] is a straightforward method for the synthesis of β-allenic carbonyl compounds. Allene products can be obtained in one pot from propargyl alcohols *via* the propargyl Johnson-Claisen reaction with an orthoester reagent, as shown in Scheme 1.26.[45] Rearrangement of the intermediate **1.158** is stereospecific, and thus can be used for accessing β-allenols in high *ee* from enantioenriched alcohols. High temperatures are required in order to both promote the sigmatropic reaction and remove the alcohol byproducts (thus driving equilibrium towards the products). The high temperatures, combined with the requirement of catalytic acid, can often result in low yields and isomerization for the formation of phenyl-substituted allenes as well as allenes containing acid-sensitive functional groups.[45] A milder, catalytic variant of the propargyl Claisen was demonstrated by Toste and coworkers that accesses these motifs in good yields with minimal loss of *ee* of the propargyl alcohol (Scheme 1.27).[46]

Scheme 1.26. Propargyl Johnson-Claisen reaction.



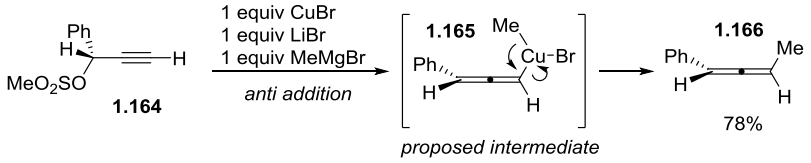
Scheme 1.27. Gold-catalyzed propargyl Claisen.



1.4.3. S_N2' Addition to activated propargyl alcohols

The S_N2' addition of cuprates to propargyl sulfonates is a reliable and popular method for allene formation.[4a] Most commonly, the cuprate attack occurs *anti* to the leaving group, as shown in Scheme 1.28.[47] A 1:1 ratio of grignard to copper was used for the formation of **1.166**, as diorganocuprates had been previously observed to give racemization of enantioenriched allenes. The addition of soft ligands, such as dimethyl sulfide, phosphines, and phosphites is an alternative method for minimizing allene racemization.[48] Examples using catalytic amounts of copper are also common,[49] and leaving groups other than sulfonates can be used, such as acetates, ethers, and epoxides.[4e]

Scheme 1.28. S_N2' displacement of a propargyl mesylate by a cuprate.

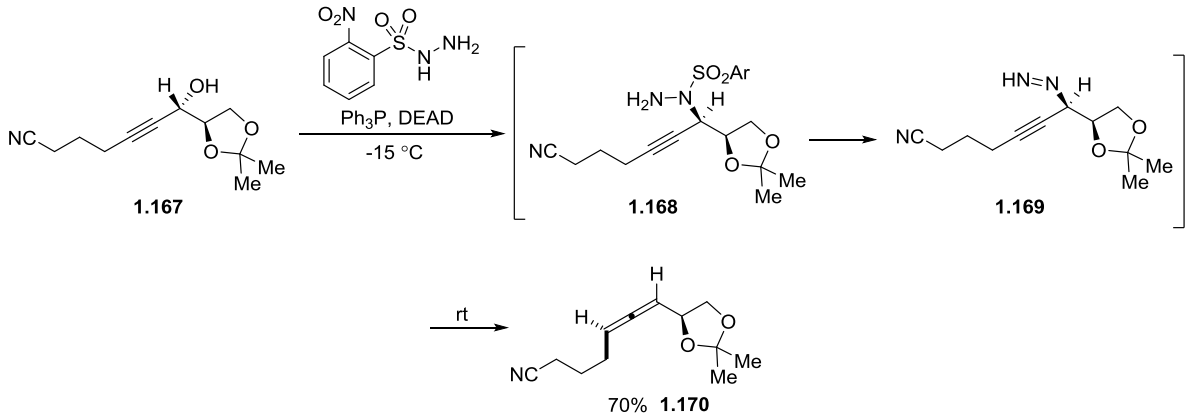


1.4.4. Mitsunobu displacement / rearrangement of propargyl alcohols

The group of Myers has demonstrated a straightforward one-pot method for the stereospecific conversion of propargyl alcohols to allenes (Scheme 1.29).[50] Mitsunobu displacement with *o*-nitrobenzenesulfonyl hydrazine (NBSH) delivers the intermediate **1.168**, which decomposes upon warming to room temperature to the propargyl diazine **1.169**. This diazine undergoes a [3,3] sigmatropic reaction to provide allenes of the form **1.170**. A variety of

1,3-disubstituted allenes can be obtained by this straightforward reaction with good functional group tolerance, as shown by **1.170**.

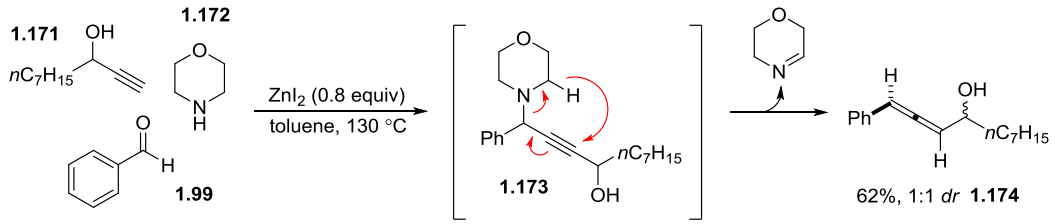
Scheme 1.29. Allene synthesis by Mitsunobu displacement of propargyl alcohols.



1.4.5. One-pot coupling of aldehydes, amines, and alkynes.

Recently, the Ma group[51] and others[52] have utilized the A^3 (amine-aldehyde-alkyne) coupling reaction to form allenes in a single pot from very simple precursors (Scheme 1.30). In the presence of ZnI_2 and under high temperatures, propargyl amines are formed *in situ* and undergo intramolecular hydride transfer to form allene products. While the harsh conditions impose some limits on substrate scope, the simple starting materials make this an ideal method for one-step allene synthesis. Further developments to this work have resulted in enantioenriched allene synthesis by using chiral, proline-based amines as substrates.[53]

Scheme 1.30. A^3 coupling and rearrangement to give allene products.



1.5. References

1. (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc*. **1980**, *102*, 5974. (b) Evans, D. A.; Faul, M. M.; Bilodeau, M. T.; Anderson, B. A.; Barnes, D. M. *J. Am. Chem. Soc.* **1993**, *115*, 5328. (c) Jacobsen, E. N.; Marko, I.; Mungall, W. S.; Schroeder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1968. (d) Bruncko, M.; Schlingloff, G.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **1997**, *36*, 1483.
2. For classical examples of stereochemical match/mismatch in more complex aldol reactions, see: (a) Masamune, S.; Choy, W.; Petersen, J. S.; Rita, L. R. *Angew. Chem. Int. Ed.* **1985**, *24*, 1. (b) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Rieger, D. L. *J. Am. Chem. Soc.* **1995**, *117*, 9073.
3. Recent reviews demonstrating the generation and transfer of allene axial chirality: (a) Hoffman-Röder, A.; Krause, N. *Angew. Chem., Int. Ed.* **2004**, *43*, 1196. (b) Yu, S.; Ma, S. *Angew. Chem., Int. Ed.* **2012**, *51*, 3074. (c) Allen, A. D.; Tidwell, T. T. *Chem. Rev.* **2013**, *113*, 7287. (d) Campolo, D.; Gastaldi, S.; Roussel, C.; Bertrand, M. P.; Nacheb, M. *Chem. Soc. Rev.* **2013**, *42*, 8434.
4. Recent reviews of both racemic and enantioselective allene synthesis: (a) N. Krause and A. Hoffmann-Röder, *Tetrahedron* **2004**, *60*, 11671–11694; (b) K. M. Brummond and J. E. DeForrest, *Synthesis* **2007**, 795–818; (c) M. Ogasawara, *Tetrahedron: Asymmetry* **2009**, *20*, 259–271; (d) S. Yu and S. Ma, *Chem. Commun.* **2011**, *47*, 5384–5418. (e) Krause, N.; Hashmi, S. K., Eds. *Modern Allene Chemistry*; Wiley-VCH, Weinheim, Germany, 2004. (f) Neff, R. K.; Frantz, D. E. *ACS Catal.* **2014**, *4*, 519.
5. Adams, C. S.; Weatherly, C. D.; Burke, E. G.; Schomaker, J. M. *Chem. Soc. Rev.* **2014**, *43*, 3136-3163

6. Bachrach, S. M. *J. Phys. Chem.* **1993**, *97*, 4996.

7. (a) Crandall, J. K.; Machleder, W. H. *Tetrahedron Lett.* **1966**, *48*, 6037. (b) Crandall, J. K.; Machleder, W. H. *J. Am. Chem. Soc.* **1968**, *90*, 7292.

8. Camp, R. L.; Greene, F. D. *J. Am. Chem. Soc.* **1968**, *90*, 7349.

9. Crandall, J. K.; Machleder, W. H. *J. Am. Chem. Soc.* **1968**, *90*, 7347.

10. Crandall, J. K.; Batal, D. J. *J. Org. Chem.* **1988**, *53*, 1340.

11. Crandall, J. K.; Batal, D. J.; Sebesta, D. P.; Lin, F. *J. Org. Chem.* **1991**, *56*, 1153.

12. Zhang, Y.; Cusick, J. R.; Ghosh, P.; Shangguan, N.; Katukojvala, S.; Inghrim, J.; Emge, T. J.; Williams, L. J. *J. Org. Chem.* **2009**, *74*, 7707.

13. (a) Crandall, J. K.; Batal, D. J. *Tetrahedron Lett.* **1988**, *29*, 4791. (b) Crandall, J. K.; Rambo, E. *J. Org. Chem.* **1990**, *55*, 5929. (c) Crandall, J. K.; Batal, D. J.; Lin, F.; Reix, T.; Nadol, G. S.; Ng, R. A. *Tetrahedron* **1992**, *48*, 1427.

14. Crandall, J. K.; Reix, T. *Tetrahedron Lett.* **1994**, *35*, 2513.

15. Katukojvala, S.; Barlett, K. N.; Lotesta, S. D.; Williams, L. J. *J. Am. Chem. Soc.* **2004**, *126*, 15348.

16. Lotesta, S. D.; Hou, Y.; Williams, L. J. *Org. Lett.* **2007**, *9*, 869.

17. (a) Ghosh, P.; Zhang, Y.; Emge, T. J.; Williams, L. J. *Org. Lett.* **2009**, *11*, 4402. (b) Liu, K.; Kim, H.; Ghosh, P.; Akhmedov, N. G.; Williams, L. J. *J. Am. Chem. Soc.* **2011**, *133*, 14968.

18. Doutheau, A.; Gore, J.; Malacria, M. *Tetrahedron* **1977**, *33*, 2393.

19. Bertrand, M.; Dulcere, J. P.; Gil, G.; Roumestant, M. L. *Tetrahedron Lett.* **1979**, *20*, 1845.

20. Dulcere, J. P.; Grimaldi, J.; Santelli, M. *Tetrahedron Lett.* **1981**, *22*, 3179.

21. (a) Malona, J. A.; Cariou, K.; Frontier, A. J. *J. Am. Chem. Soc.* **2009**, *131*, 7560. (b) Malona, J. A.; Cariou, K.; Spencer III, W. T.; Frontier, A. J. *J. Org. Chem.* **2012**, *77*, 1891.

22. For reviews dedicated to [4+3] cycloadditions, see: (a) Hartung, I. V.; Hoffmann, H. M. R. *Angew. Chem. Int. Ed.* **2004**, *43*, 1934. (b) Harmata, M. *Acc. Chem. Res.* **2001**, *34*, 595. (c) Harmata, M.; *Chem. Comm.* **2010**, *46*, 8886. (d) Hoffmann, H. M. R. *Angew. Chem. Int. Ed.* **1984**, *23*, 1.

23. Xiong, H.; Hsung, R. P.; Berry, C. R.; Rameshkumar, C. *J. Am. Chem. Soc.* **2001**, *123*, 7174.

24. Huang, J.; Hsung, R. P. *J. Am. Chem. Soc.* **2005**, *127*, 50.

25. Xiong, H.; Huang, J.; Ghosh, S. K.; Hsung, R. P. *J. Am. Chem. Soc.* **2003**, *125*, 12694.

26. Rameshkumar, C.; Hsung, R. P. *Angew. Chem. Int. Ed.* **2004**, *43*, 615.

27. (a) Murray, R. W.; Singh, M. *Org. Synth.* **1997**, *74*, 91. (b) Gilbert, M.; Ferrer, M.; Sánchez-Baeza, F.; Messeguer, A. *Tetrahedron* **1997**, *53*, 8643.

28. Bleiholder, R. F.; Shechter, H. *J. Am. Chem. Soc.* **1968**, *90*, 2131.

29. Bingham, E. M.; Gilbert, J. C. *J. Org. Chem.* **1975**, *40*, 224.

30. Atkinson, R. S.; Malpass, J. R. *Tetrahedron Lett.* **1975**, *16*, 4305.

31. Rigoli, J. W.; Boralsky, L. A.; Hershberger, J. C.; Marston, D.; Meis, A. R.; Guzei, I. A.; Schomaker, J. M. *J. Org. Chem.* **2012**, *77*, 2446.

32. (a) Espino, C. G.; Du Bois, J. *Angew. Chem. Int. Ed.* **2001**, *40*, 598. (b) Espino, C. G.; Wehn, P. M.; Chow, J.; Du Bois, J. *J. Am. Chem. Soc.* **2001**, *123*, 6935. (c) Guthikonda, K.; Du Bois, J. *J. Am. Chem. Soc.* **2002**, *124*, 13672. (d) Roizen, J. L.; Harvey, M. E.; Du Bois, J. *Acc. Chem. Res.* **2012**, *45*, 911.

33. Stoll, A. H.; Blakey, S. B. *J. Am. Chem. Soc.* **2010**, *132*, 2108-2109.

34. The scope of the [3 + 3] cycloaddition was investigated further: Stoll, A. H.; Blakey, S. B. *Chem. Sci.* **2011**, *2*, 112.

35. Feast, G. C.; Page, L. W.; Robertson, J. *Chem. Commun.* **2010**, *46*, 2835.

36. Robertson, J.; Feast, G. C.; White, L. V.; Steadman (née Doughty), V. A.; Claridge, T. D. W. *Org. Biomol. Chem.* **2010**, *8*, 3060.

37. Boralsky, L. A.; Marston, D.; Grigg, R. D.; Hershberger, J. C.; Schomaker, J. M. *Org. Lett.* **2011**, *13*, 1924-1927.

38. Grigg, R. D.; Schomaker, J. M.; Timokhin, V. *Tetrahedron*, **2011**, *67*, 4318.

39. Weatherly, C. D.; Rigoli, J. W.; Schomaker, J. M. *Org. Lett.* **2012**, *14*, 1704.

40. Weatherly, C. D.; Guzei, I. A.; Schomaker, J. M. *Eur. J. Org. Chem.* **2013**, 3667.

41. Rigoli, J. W.; Guzei, I. A.; Schomaker, J. M. *Org. Lett.* **2014**, *16*, 1696.

42. Exquisite control over the chemoselectivity of intramolecular allene aziridination was achieved by the Schomaker group *via* silver catalysis: Rigoli, J. W.; Weatherly, C. D.; Alderson, J.; Vo, B. T.; Schomaker, J. M. *J. Am. Chem. Soc.* **2013**, *135*, 17238.

43. Reviews on the catalytic, enantioselective synthesis of propargyl alcohols: (a) Pu, L.; *Tetrahedron* **2003**, *59*, 9873. (b) Trost, B. M.; Weiss, A. M. *Adv. Synth. Catal.* **2009**, *351*, 963.

44. Tejedor, D.; Méndez-Abt, G.; Cotos, L.; García-Tellado, F. *Chem. Soc. Rev.* **2013**, *42*, 458.

45. Henderson, M. A.; Heathcock, C. H. *J. Org. Chem.* **1988**, *53*, 4736-4745.

46. Sherry, B. D.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 15978.

47. Elsevier, C. J.; Vermeer, P. *J. Org. Chem.* **1989**, *54*, 3726.

48. (a) Oehlschlager, A. C.; Czyzewska, E. *Tetrahedron Lett.* **1983**, *24*, 5587. (b) Alexakis, A.; Marek, I.; Manganey, P. Normant, J. F. *Tetrahedron Lett.* **1989**, *30*, 2387. (c) Alexakis, A.;

Marek, I.; Manganey, P.; Normant, J. F. *Tetrahedron* **1991**, *47*, 1677. (d) Alexakis, A.; *Pure Appl. Chem.* **1992**, *64*, 387.

49. For examples of copper catalyzed S_N2' substitution of propargyl electrophiles, see references 5a, 5e, and the following selected examples: (a) Vermeer, P.; Meijer, J.; de Graag, C.; Schreurs, H. *Recl. Trav. Chim. Pays-Bas* **1974**, *93*, 46. (b) Sato, T.; Kawashima, M.; Fujisawa, T. *Tetrahedron Lett.* **1981**, *22*, 2375.

50. Myers, A. G.; Zheng, B. *J. Am. Chem. Soc.* **1996**, *118*, 4492.

51. Kuang, J.; Ma, S. *J. Am. Chem. Soc.* **2010**, *132*, 1786.

52. (a) Gurubrahamam, R.; Periasamy, M. *J. Org. Chem.* **2013**, *78*, 1463. (b) Periasamy, M.; Reddy, P. O.; Sanjeevakumar, N. *Eur. J. Org. Chem.* **2013**, 3866.

53. Ye, J.; Fan, W.; Ma, S. *Chem. Eur. J.* **2013**, *19*, 716.

Chapter 2

Heteroatom Diversity in the Conversion of Homoallenic Sulfamates to Aminated Stereotriads

This chapter is adapted with permissions from sections published in:

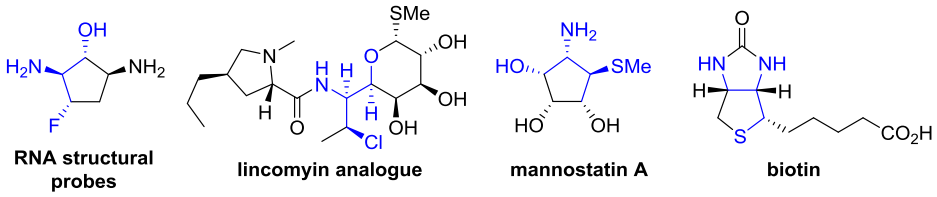
Adams, C. S.; Boralsky, L. A.; Guzei, I. A.; Schomaker, J. M.

J. Am. Chem. Soc. **2012**, *134*, 10807-10810

2.1. Introduction

Densely functionalized amines bearing adjacent, stereodefined heteroatom groups (X/N/Y stereotriads, where X and Y represent a halogen, oxygen, nitrogen or sulfur-containing group) occur frequently in natural products and biologically active molecules (Figure 2.1).[1] We were intrigued by the idea of developing highly modular and streamlined methods for the chemo-, regio- and stereoselective construction of these motifs. This chapter describes the modular preparation of X/N/Y stereotriads from allenes, with the ability to finely tune the identity of the X/Y substituents. Key to our method is the synthesis and elaboration of a highly strained bicyclic methylene aziridine, formed *via* intramolecular aziridination of sulfamoyl allenes.

Figure 2.1. Diverse X/N/Y Stereotriads in Bioactive Molecules

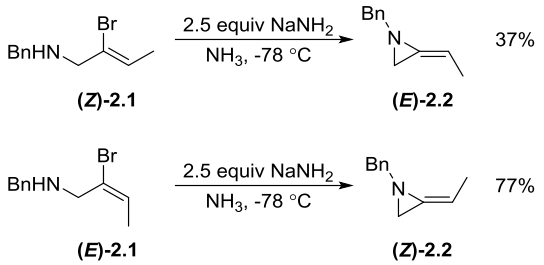


2.2. Background

2.2.1. Multi-component reactions of monocyclic methylene aziridines

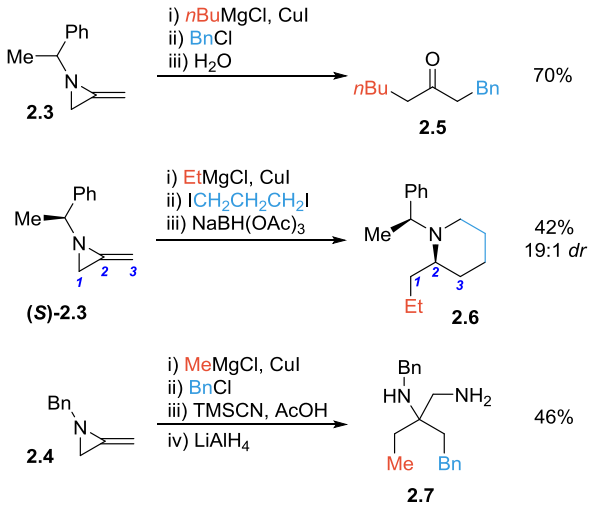
The first high-yielding synthesis of methylene aziridines (MA's) was reported by the group of Shipman.[2] They demonstrated that 2-bromoallylamines **(*E*/*Z*)-2.1** undergo cyclization to form MA's in the presence of sodium amide (Scheme 2.1). Interestingly, the geometry of the alkene was inverted by this nucleophilic attack, leading Shipman to propose an unusual S_N2-like vinylic displacement based on this finding and isotope labeling studies that ruled out an elimination-addition pathway.[3]

Scheme 2.1. Synthesis of monocyclic methylene aziridines from 2-bromoallylamines.



Shipman and coworkers demonstrated the utility of their methylene aziridine products *via* "multi-component reactions" – one-pot reactions in which multiple carbon-carbon bonds were formed by the sequential addition of reagents.[4] Several examples are shown in Scheme 2.2. Most commonly, the aziridine would be opened by the copper-catalyzed addition of a Grignard reagent, followed by alkylation of the resulting metalloenamine and nucleophilic trapping of the final imine. We were intrigued by the idea of using this same reactivity principle to form X/N/Y stereotriads. Additionally, because the harsh conditions employed by Shipman to generate monocyclic MAs could limit the scope of accessible products, we were interested in accessing this motif by an alternative method.

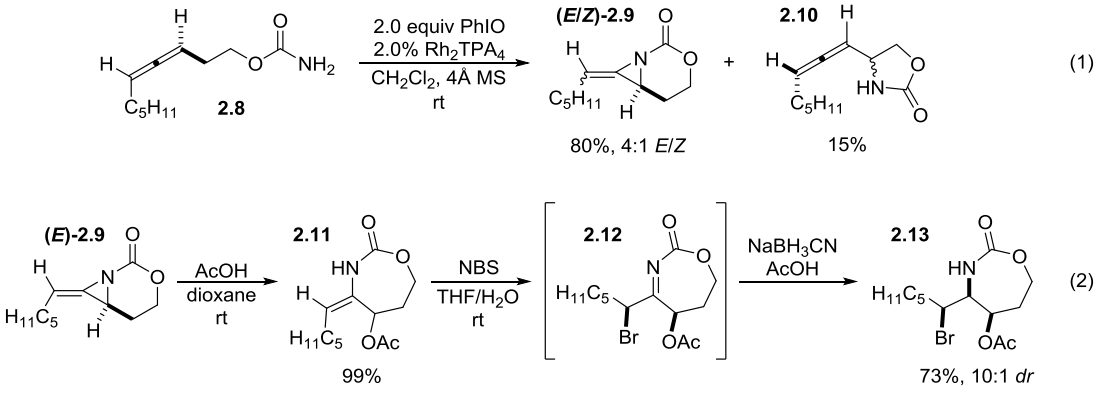
Scheme 2.2. Multi-component reactions of monocyclic methylene aziridines.



2.2.2. Previous work with bicyclic methylene aziridines by the Schomaker group

Prior to the work described in this chapter, the Schomaker group demonstrated that homoallenic carbamates could be carried through multi-component reactions to transform the three allene carbons into an X/N/Y stereotriad (Scheme 2.3).[5] Beginning with an intramolecular, Rh-catalyzed aziridination, a mixture of bicyclic MAs **(*E*/*Z*)-2.9** and C-H insertion product **2.10** were obtained, with the desired aziridine favored by a factor of ~4:1. The MA could then be treated with a nucleophile, such as acetate, that would open the aziridine to give enecarbamate **2.11**. The moderately nucleophilic alkene was shown to react with NBS to afford α-bromoimine **2.12**, which underwent reduction with $NaBH_3CN$ to give the OAc/N/Br stereotriad **2.13**. This single example demonstrated a potentially flexible entry to X/N/Y stereotriads, with the ability to obtain multiple products by variation of the reagents used to manipulate MA **2.9**.

Scheme 2.3. Multi-step process for converting homoallenic carbamates to X/N/Y stereotriads.



While the diastereoselectivity of the process shown in Scheme 2.3 was high, it was complicated by the poor chemo- and stereoselectivity of the initial aziridination. For example, it was necessary to separate the MA from oxazolidinone **2.10** in order to avoid formation of undesired byproducts in subsequent steps. Similarly, separation of the *E* and *Z* isomers of **2.9** (a challenging task in many cases) was necessary to obtain stereotriad **2.13** in high *dr*. These factors

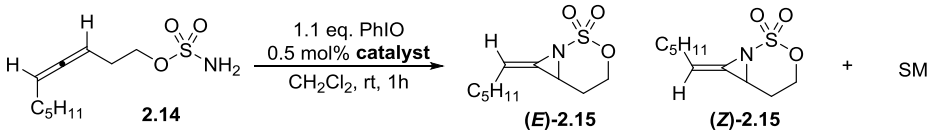
led us to investigate alternative nitrene precursors to carbamates for this process, in the hope that it might improve the selectivity of the aziridination.

2.3. Results and Discussion

2.3.1 Intramolecular aziridination of a homoallenic sulfamate

Homoallenic sulfamate **2.14** was prepared according to known methods[5,6] and subjected to a brief survey of rhodium-catalyzed conditions for intramolecular aziridination (Scheme 2.4). The findings were immediately striking: **2.14** behaved much more selectively than the corresponding carbamate **2.8**, giving no detectable C-H insertion products and favoring the *E* isomer of the MA by greater than a 30:1 ratio. While little variance was observed in the three rhodium catalysts screened, $Rh_2(TPA)_4$ was chosen for further work as it generally gave superior reaction rates and could be prepared from Rh_2OAc_4 in a single, high-yielding step.[7] The remainder of the mass balance could not be identified by NMR or isolation, and was assumed to arise from an unknown decomposition pathway of **2.15**.

Scheme 2.4 Rh-catalyzed intramolecular aziridination.

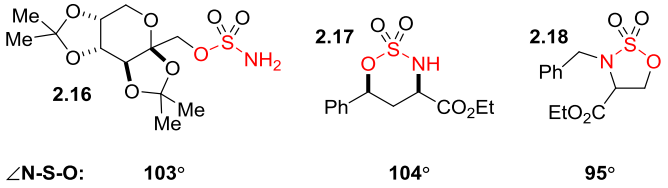


	(*E*)-2.15	(*Z*)-2.15	SM
Rh_2TPA_4:	79%	<1%	0%
Rh_2esp_2:	76%	<1%	0%
$Rh_2(OAc)_4$:	75%	2%	5%

The vastly improved chemoselectivity (i.e., favoring aziridination over C-H insertion) of **2.14** was initially surprising. An empirical explanation for this finding lies in the observation that sulfamates greatly favor the formation of six-membered rings over five-membered rings (the necessary ring size for C-H insertion in this case) under oxidizing conditions similar to those found in Scheme 2.4.[8] This is in contrast to carbamates, which typically prefer to form 5-membered

oxazolidinones under conditions of competitive C-H insertion.[9] The preference of sulfamates for six-membered ring formation may lie in the geometrical parameters of the sulfamate group. As shown in Figure 2.2, the uncyclized sulfamate in compound **2.16** possesses a 103° N-S-O bond angle.[10] The formation of a six-membered ring (exemplified by **2.17**) requires little deformation of that bond angle, while formation of a five-membered ring significantly compresses the sulfamate, potentially representing a higher-energy process. The near-perfect E/Z selectivity of the sulfamates in comparison to carbamates is less readily rationalized, but likely arises from a different trajectory of approach for the sulfamoyl nitrene to the allene in comparison to the carbamate.

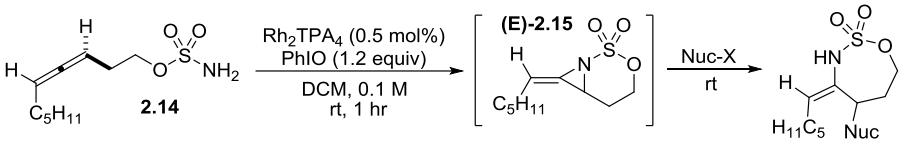
Figure 2.2. N-S-O bond angles of linear and cyclic sulfamates



2.3.2. Ring-opening of sulfamoyl MAs

The reactivity of sulfamoyl MA **(*E*)-2.15** was subsequently investigated. It proved to be highly susceptible to ring-opening with a variety of heteroatom nucleophiles, requiring no purification between its formation and nucleophile addition (Table 2.1). Successful oxygen nucleophiles included AcOH, MeOH, and H_2O (entries 1-3), which gave the enesulfamate products **2.19**-**2.21** in good yields. The unusually activated nature of the bicyclic methylene aziridine was demonstrated by its facile reaction at room temperature with amines that typically do not open aziridines in the absence of a Lewis acid (entries 4-6).[11] Thiophenol and TMSCl (entries 7, 8) were also shown to be competent nucleophiles for the installation of sulfur and chlorine substituents.

Table 2.1. One-Pot Aziridination/Ring-Opening of Homoallenic Sulfamate **2.14**.

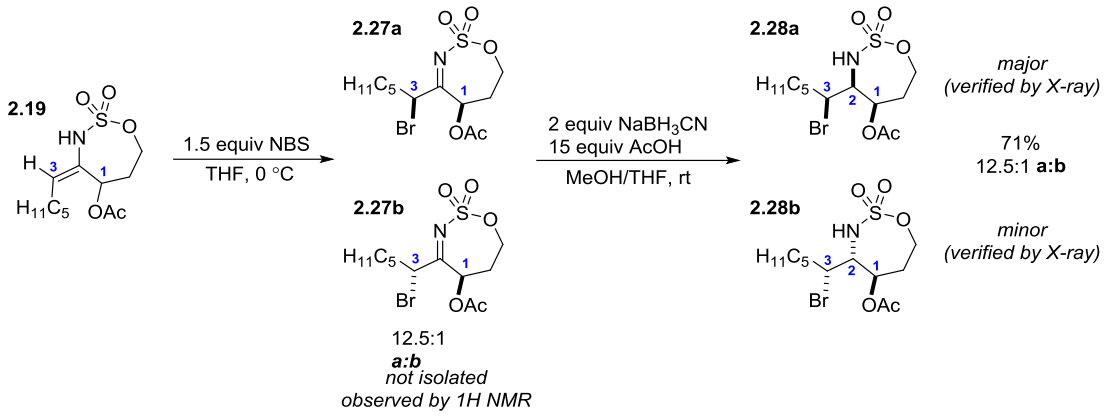


Entry	Nuc-X	Equiv.	Solvent	Time (h)	% Yield	Product
1	AcO-H	6	CH_2Cl_2	5	75	**2.19**
2	MeO-H	50	CH_2Cl_2	1	77	**2.20**
3	HO-H	20	MeCN	0.67	74	**2.21**
4	PhNH-H	1.3	CH_2Cl_2	2	68	**2.22**
5	Morpholine	1.6	CH_2Cl_2	2.5	71	**2.23**
6	Piperidine	1.3	CH_2Cl_2	1	75	**2.24**
7	PhS-H	10	CH_2Cl_2	1	69	**2.25**
8	Cl-$SiMe_3$	1.5	THF	8	56	**2.26**

2.3.3. Synthesis of an O/N/Br stereotriad and stereochemical models

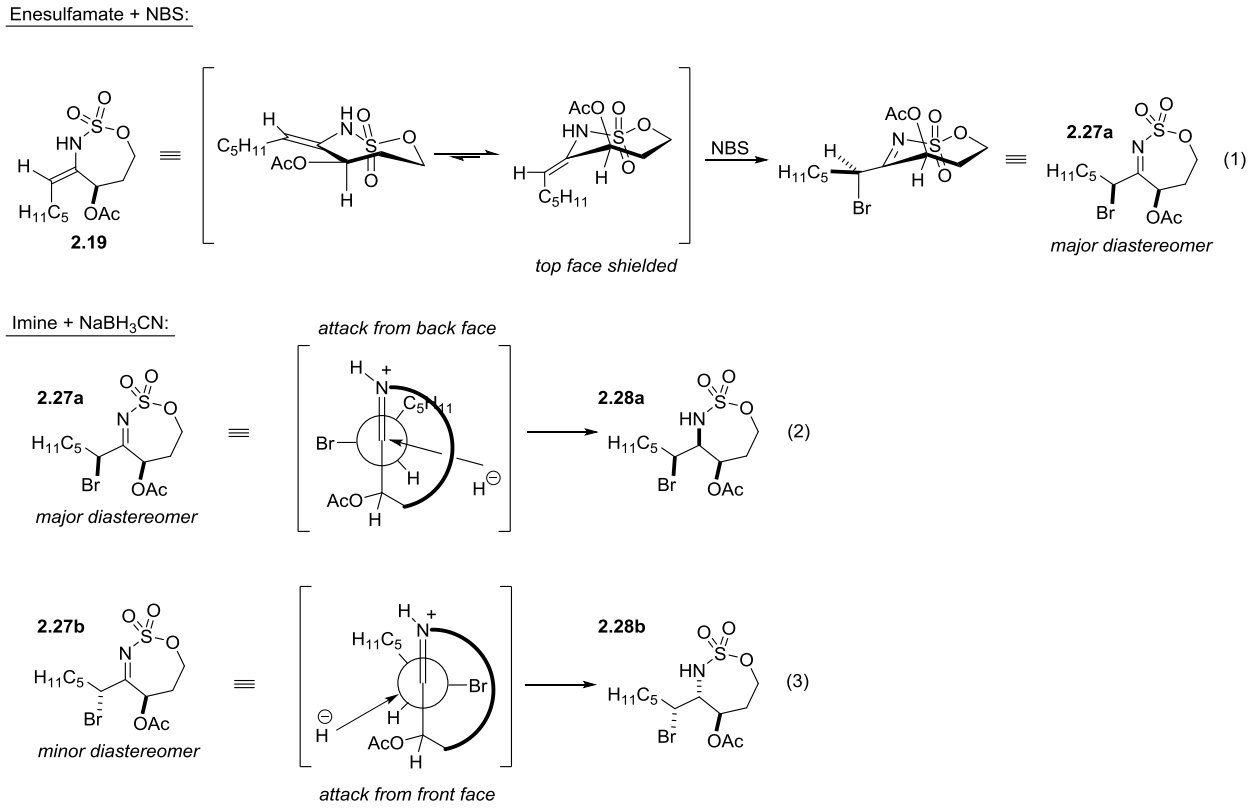
The formation of an X/N/Y stereotriad was first attempted with NBS and $NaBH_3CN$ (Scheme 2.5), in analogy to the synthesis of **2.13**. We were pleased to find that enesulfamate **2.19** reacted with excellent diastereoselectivity, providing **2.28** in greater than 10:1 *dr*. As the intermediate imines **2.27ab** were sensitive to hydrolysis and epimerization, the reductant was generally added in the same pot, with no intermediate purification steps. The *dr* of **2.28** closely matched the *dr* of the imine **2.27**, indicating that both imines were reduced with high diastereoselectivity. The relative stereochemistries of **2.28ab** were verified by X-ray crystallography.

Scheme 2.5. Synthesis of O/N/Br stereotriads and determination of relative stereochemistry.



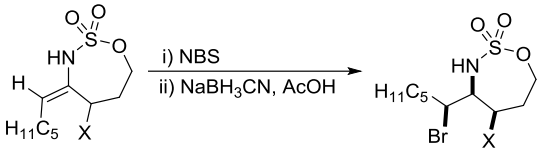
A stereochemical model was proposed in order to account for the observed diastereoselectivity (Scheme 2.6). It was assumed that the –OAc group of **2.19** would adopt a pseudo-axial orientation to avoid $A_{1,3}$ strain with the pentyl chain, thus biasing the approach of NBS to occur preferentially from the bottom face of the alkene (eq. 1). In the imine reduction, it might be assumed that the –OAc group again blocks the top face of the imine, but the formation of **2.28b** from **2.27b** (in which hydride approaches from the same face as -OAc) suggested this was not the case. Considering the conformationally flexible C3 stereocenter, a steric Felkin-Anh argument, in which the pentyl chain (R_L) is oriented perpendicular to the plane of the C=N bond, predicts the opposite outcome of what is observed. Instead, a polar Felkin-Anh case appeared to be in effect, in which the C-Br bond is oriented perpendicular to the C=N bond for maximal overlap of $\sigma^*_{C\text{-}Br}$ with $\pi_{C\text{-}N}$.[12] This orientation provides the observed facial selectivity for both imine diastereomers.

Scheme 2.6. Stereochemical models for O/N/Br stereotriad formation.



To confirm that a variety of X/N/Br stereotriads could be accessed by this reaction, and that high *dr* was not dependent on the presence of an allylic –OAc group, a variety of enesulfamates were subjected to the NBS/$NaBH_3CN$ conditions (Table 2.2). Ethers, alcohols, sulfides, and halogens were all well tolerated in the reaction and gave stereotriads **2.29**-**2.32** in good to excellent *dr*. Even a tertiary amine was tolerated (entry 5), although the yield of the N/N/Br triad **2.33** was significantly reduced, likely due to competing amine oxidation. The relative stereochemistries of the X/N/Br products were not empirically determined, instead being assigned by analogy to **2.28**.

Table 2.2. Synthesis of a variety of X/N/Br stereotriads.

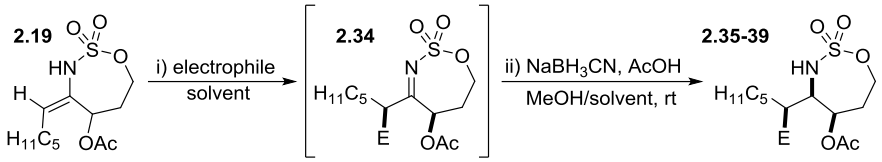


entry	enesulfamate	X =	yield	*dr*	product
1	**2.20**	OMe	65%	8:1	**2.29**
2	**2.21**	OH	71%	5.6:1	**2.30**
3	**2.25**	SPh	67%	>19:1	**2.31**
4	**2.26**	Cl	77%	>19:1	**2.32**
5	**2.24**	piperidine	44%	10:1	**2.33**

2.3.4. Synthesis of a variety of O/N/X stereotriads

Next, conditions were identified for the installation of a variety of heteroatom groups *via* electrophilic substitution of the enesulfamate (Table 2.3). To simplify these experiments, it was assumed that the stereochemical outcome matched that seen in Scheme 2.5. For the installation of a Cl substituent, NCS was found to give O/N/Cl triad **2.35** in only moderate yield and diastereoselectivity (entry 1). Substitution of NCS for the more electrophilic trichloroisocyanuric acid (TCICA, entry 2) was found to give superior yield and *dr*. The use of Selectfluor® (entry 3) resulted in a 2:1 *dr* of **2.36**, likely due to increased epimerization at C3 caused by the electron-withdrawing fluorine atom. Nitrogen was installed by the Cu-promoted ene reaction of **2.19** with an azodicarboxylate (entry 5), affording the vicinal diaminated stereotriad **2.37** in greater than 19:1 *dr*.[13] Phenylsulfenyl chloride (entry 5) gave **2.38** in good yield but poor *dr*, likely due to epimerization of the imine by HCl, a byproduct of the sulfenylation step.[14] The addition of a non-nucleophilic base restored a moderate *dr* (entry 6). Reaction of **2.19** with the epoxidant DMDO (entry 7) and sodium triacetoxyborohydride as the reductant gave the aminodiol **2.39** in lower *dr*, in this case due to poor facial selectivity in the addition of the electrophile to the enesulfamate. The scope and diastereoselectivity of this route to aminodiols were greatly improved in later work (see Chapter 3).[15]

Table 2.3. Results for the addition of a variety of heteroatom electrophiles to enesulfamate **2.19**.

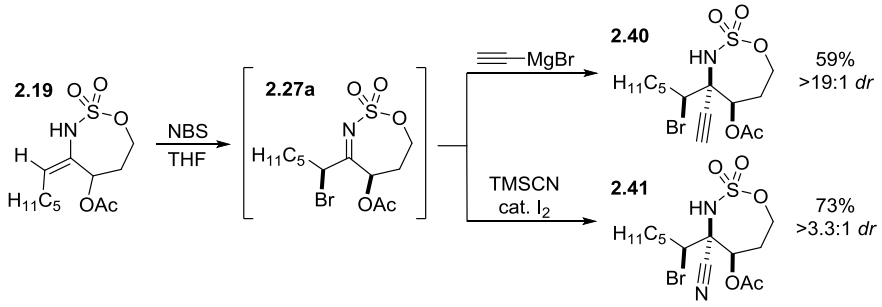


entry	electrophile	E =	solvent	temp (°C)	yield	dr	product
1	NCS	Cl	THF	66	65%[a]	5:1	**2.35**
2	TCICA	Cl	$CHCl_3$	rt	76%	7.7:1	**2.35**
3	Selectfluor®	F	MeCN	80	57%	2:1	**2.36**
4	DIAD[b]	$NNH(CO_2{}^iPr)_2$	Toluene	55	69%	>19:1	**2.37**
5	PhSCl	SPh	CH_2Cl_2	rt	74%	1.4:1[c]	**2.38**
6	PhSCl[d]	SPh	CH_2Cl_2	rt	80%	2.9:1[c]	**2.38**
7	DMDO[e]	OH	CH_2Cl_2	rt	44%	2:1[c]	**2.39**

[a]NMR yield of the unpurified product using mesitylene as the internal standard. [b] 10 mol% $Cu(OTf)_2$ and 11 mol% $Me_2N(CH_2)_2NMe_2$ were also added to the reaction. [c] Minor amounts of other diastereomers were observed. [d] 2,6-di-*tert*-butyl-4-methylpyridine was also added. [e] STABH used in place of $NaBH_3CN$.

Stereotriads containing quaternary, amine-bearing carbons could also be accessed by the addition of carbon nucleophiles to the imine **2.27a** (Scheme 2.7). For example, employing ethynylmagnesium bromide in place of $NaBH_3CN$ gave **2.40** in excellent diastereoselectivity, although the yield was modest due to the sensitivity of the –OAc group. Similarly, a Strecker reaction using TMSCN gave **2.41** in 73% yield and a *dr* of 3.3:1.[16] As with the stereotriads listed in Table 2.2, the stereochemistry of the major diastereomers was assumed by analogy to compound **2.28a**.

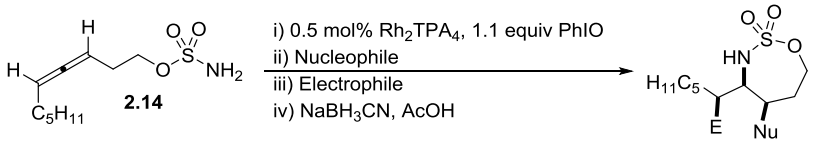
Scheme 2.7. Generation of Br/N/OAc stereotriads containing a quaternary carbon.



2.3.5. One-pot conversion of allenes to X/N/Y stereotriads.

We were pleased to find that the mild reaction conditions, coupled with the high chemo-, regio- and diastereoselectivity of the allene oxidation, allowed for conversion of the homoallenic sulfamate **2.14** directly to X/N/Y stereotriads in a single pot (Table 2.4). Obtaining high *dr*'s hinged on minimizing the reaction time of the enesulfamate functionalization, to prevent epimerization of the resulting imine (compare entries 1/2 and 3/4). Gratifyingly, the one-pot yields of **2.28** and **2.29** (entries 2, 4) were higher than when the reaction was performed in two steps (61% vs. 53% for **2.28**; 58% vs. 50% for **2.29**; see Table 2.1, Scheme 2.3, and Table 2.2 for individual yields). Complex O/N/N and O/N/S stereotriads (entries 5,6) were also accessible by this one-pot method in good yield and moderate *dr*.

Table 2.4. One-pot conversion of homoallenic sulfamates to X/N/Y stereotriads.

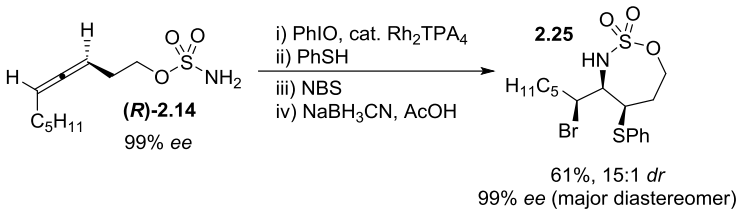


entry	nucleophile (Nu)	electrophile (E)	rxn time/temp for step iii	% yield	dr	product
1	AcOH (OAc)	NBS (Br)	2 h, rt	60	5:1	**2.28**
2	AcOH (OAc)	NBS (Br)	15 min, rt	61	20:1	**2.28**
3	MeOH (OMe)	NBS (Br)	45 min, rt	60	1.7:1	**2.29**
4	MeOH (OMe)	NBS (Br)	10 min, -10 °C	58	2.6:1	**2.29**
5	MeOH (OMe)	DIAD ($NNH(CO_2{}^iPr)_2$)	2 h, 70 °C	64	4.6:1	**2.42**
6	MeOH (OMe)	PhSCl (SPh)	30 min, rt	74	2.6:1	**2.43**

2.3.6. Demonstrating synthetic utility of the X/N/Y stereotriads

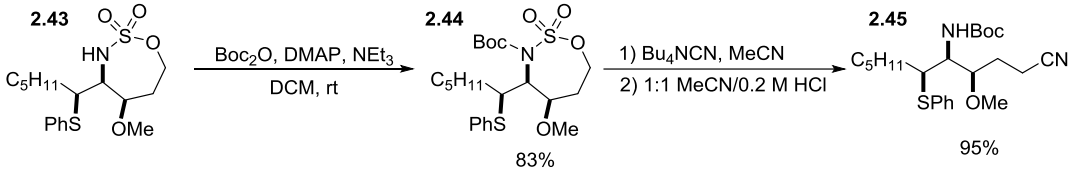
The ability to transfer the axial chirality of the allene to point chirality in the stereotriad is an important aspect of this chemistry, as it simplifies the task of obtaining enantioenriched material to a diastereoselective allene functionalization. As illustrated in Scheme 2.8, **(*R*)-2.14** was smoothly converted into the S/N/Br stereotriad **2.25** in a single pot with no erosion in *ee*.

Scheme 2.8. Transfer of axial to point chirality.



Finally, it was demonstrated that a simple, two-step process could cleave the sulfamate group from cyclic X/N/Y products to reveal the linear stereotriad. In the first step, substitution of the sulfamoyl N-H for an electron-withdrawing Boc group activated the sulfamate for nucleophilic displacement. The addition of Bu_4NCN gave the unraveled stereotriad **2.45** with a new nitrile handle for further possible derivitization (Scheme 2.9).[17] An acidic workup was necessary to cleave the N-S bond of **2.44**. This process has been demonstrated by other groups to be general for a wide variety of heteroatom[8a] and carbon nucleophiles,[18] adding a final diversification step to this reaction sequence.

Scheme 2.9. Removal of sulfamate from a O/N/S stereotriad.



2.4. Conclusions

Homoallenic sulfamate **2.14** was shown to be an ideal substrate for intramolecular aziridination, giving a single MA product in near-perfect chemo-, regio-, and stereoselectivity. Both the aziridine **2.15** and the resulting ring-opened enesulfamates were shown to be excellent scaffolds for the introduction of heteroatom substituents, leading to the synthesis of a wide variety of X/N/Y stereotriads often in one pot from the starting allene. The stereotriad products themselves were shown to be useful templates for further manipulation, as they could be accessed in high *ee*

and the sulfamate group could be removed with the simultaneous introduction of new functionality (Schemes 2.8, 2.9). Future work (see Chapter 3) focused on expanding the substrate scope of allenes that could be applied to this method, as well as obtaining selective access to any desired diastereomer of the X/N/Y products.

2.5. References

1. (a) Pasco, M.; Moumne, R.; Lecourt, T.; Micouin, L. *J. Org. Chem.* **2011**, *76*, 5137. (b) King, S. B.; Ganem, B. *J. Am. Chem. Soc.* **1994**, *116*, 562. (c) Magerlein, B. J.; Kagan, F. *J. Med. Chem.* **1969**, *12*, 780. (d) Zhang, Y.; Liu, S.; Che, Y.; Liu, X. *J. Nat. Prod.* **2007**, *70*, 1522. (e) Lewis, J. G.; Anandan, S. K.; O'dowd, H.; Gordeev, M. F. PCT Int. Appl. **2005**, WO 2005012320 A2 20050210.
2. (a) Ince, J.; Ross, T. M.; Shipman, M.; Ennis, D. N. *Tetrahedron: Asymmetry* **1996**, *7*, 3397. (b) Ince, J.; Ross, T. M.; Shipman, M.; Slawin, A. M. Z.; Ennis, D. N. *Tetrahedron* **1996**, *52*, 7037.
3. Shiers, J. J.; Shipman, M.; Hayes, J. F.; Slawin, A. M. Z. *J. Am. Chem. Soc.* **2004**, *126*, 6868.
4. Multi-component reactions of monocyclic methylene aziridines: (a) Hayes, J. F.; Shipman, M.; Twin, H. *Chem. Commun.* **2000**, 1791. (b) Hayes, J. F.; Shipman, M.; Twin, H. *Chem. Commun.* **2001**, 1784. (c) Hayes, J. F.; Shipman, M.; Twin, H. *J. Org. Chem.* **2002**, *67*, 935-942. (d) Margathe, J.-F.; Shipman, M.; Smith, S. C. *Org. Lett.* **2005**, *7*, 4987. (e) Shiers, J. J.; Clarkson, G. J.; Shipman, M.; Hayes, J. F. *Chem. Commun.* **2006**, 649. (f) Cariou, C. C. A.; Clarkson, G. J.; Shipman, M. *J. Org. Chem.* **2008**, *73*, 9762.
5. Boralsky, L. A.; Marston, D.; Grigg, R. D.; Hershberger, J. C.; Schomaker, J. M. *Org. Lett.* **2011**, *13*, 1924-1927.

6. Stoll, A. H.; Blakey, S. B. *Org. Lett.* **2010**, *132*, 2108.

7. Huard, K.; Lebel, H. *Org. Synth.* **2009**, *86*, 59-69.

8. (a) Espino, C. G.; Wehn, P. M.; Chow, J.; Du Bois, J. *J. Am. Chem. Soc.* **2001**, *123*, 6935. (b) Wehn, P. M.; Lee, J.; Du Bois, J. *Org. Lett.* **2003**, *5*, 4823.

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

10. Roizen, J. L.; Harvey, M. E.; Du Bois, J. *Acc. Chem. Res.* **2012**, *45*, 911.

11. Hu, X. E.; *Tetrahedron* **2004**, *60*, 2701.

12. Anh, N. T.; Eisenstein, O.; LeFour, J. M.; Tran Huu Dau, M. E. *J. Am. Chem. Soc.* **1973**, *95*, 6146.

13. Matsubara, R.; Kobayashi, S. *Angew. Chem. Int. Ed.* **2006**, *45*, 7993.

14. Hopkins, P. B.; Fuchs, P. L. *J. Org. Chem.* **1978**, *43*, 1208.

15. Adams, C. S.; Grigg, R. D.; Schomaker, J. M. *Chem. Sci.* **2014**, *5*, 3046.

16. Das, B.; Balasubramanyam, P.; Krishnaiah, M.; Veeranjaneyulu, B.; Reddy, G. C. *Synthesis* **2009**, *20*, 3467.

17. Tanino, T.; Ichikawa, S.; Matsuda, A. *Org. Lett.* **2011**, *13*, 4028.

18. (a) Malik, G.; Esteoule, A.; Retailleau, P.; Dauban, P. *J. Org. Chem.* **2011**, *76*, 7438. (b) Bower, J. F.; Švenda, J.; Williams, A. J.; Charmant, J. P. H.; Lawrence, R. M.; Szeto, P.; Gallagher, T. *Org. Lett.* **2004**, *6*, 4727

2.6. Experimental Details

2.6.1. General information

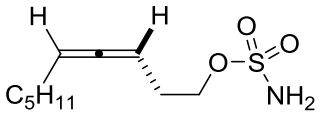
All glassware was either oven-dried overnight at 130 °C or flame-dried under a stream of dry nitrogen prior to use. Unless otherwise specified, reagents were used as obtained from the vendor

without further purification. Tetrahydrofuran and diethyl ether were freshly distilled from purple Na/benzophenone ketyl. Dichloromethane, acetonitrile and toluene were dried over CaH_2 and freshly distilled prior to use. All other solvents were purified in accordance with "Purification of Laboratory Chemicals".[1] Air- and moisture- sensitive reactions were performed using standard Schlenk techniques under an atmosphere of nitrogen. Analytical thin layer chromatography (TLC) was performed utilizing pre-coated silica gel 60 F_{254} plates containing a fluorescent indicator, while preparative chromatography was performed using SilicaFlash P60 silica gel (230-400 mesh) via Still's method.[2] Unless otherwise stated, the mobile phases for column chromatography were mixtures of hexanes/ethyl acetate. Columns were typically run using a gradient method, beginning with 100% hexanes and gradually increasing the polarity using ethyl acetate. Various stains were used to visualize reaction products, including *p*-anisaldehyde, $KMnO_4$, ceric ammonium molybdate (CAM stain) and iodine powder.

^{1}H NMR and ^{13}C NMR spectra were obtained using Bruker-300, Varian-300, Varian Inova-500, or Varian Unity-500 spectrometers. For ^{1}H NMR, chemical shifts are reported relative to residual proteo solvent (δ 7.26, 2.49, 7.15 and 7.09 ppm for $CDCl_3$, $(CD_3)_2SO$, C_6D_6 and $CD_3C_6D_5$ respectively). ^{13}C NMR spectra were measured at either 125 MHz or 75 MHz on the same instruments noted above for recording ^{1}H NMR spectra. Chemical shifts were again reported in accordance to residual proteo solvent (δ 77.2, 39.5, 128.0 and 137.9 ppm for $CDCl_3$, $(CD_3)_2SO$, C_6D_6, and $CD_3C_6D_5$, respectively). IR spectra were acquired on a Bruker Tensor 27. Melting ranges were measured on a DigiMelt MPA 160. Optical rotations were measured in CH_2Cl_2 on an AUTOPOL III automatic polarimeter. High-pressure liquid chromatography (HPLC) analyses were performed at 215 and 225 nm using a Shimadzu HPLC, Model LC-20AB. Further details are given in Section VIII. Accurate mass measurements were acquired at the University of

Wisconsin, Madison using a Micromass LCT (electrospray ionization, time-of-flight analyzer or electron impact methods). When two or more significant isotopes were present in the molecule, a monoisotopic approach was used, focusing on the isotope with the lowest mass (^{35}Cl and ^{79}Br). The NMR and Mass Spectrometry facilities are funded by the NSF (CHE-9974839, CHE-9304546, CHE-9208463, CHE-9629688) and the University of Wisconsin, as well as the NIH (RR08389-01).

2.6.2. Preparation of allene substrate



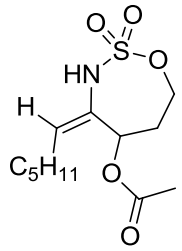
Compound 2.14 The desired allenic sulfamate was prepared from the corresponding alcohol according to literature procedure.[3,4]

2.6.3. Tandem aziridination/ring-opening of allenes to enesulfamates

Representative procedure for the one-pot aziridination/ring opening of allene sulfamates

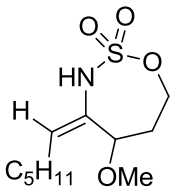
The allenic sulfamate **2.14** (0.100 g, 0.429 mmol) and Rh_2TPA_4 (3.0 mg, 0.0021 mmol, 0.5 mol %) were added to a dry 25 mL round bottom flask. The mixture was kept under an atmosphere of nitrogen and charged with 4.3 mL of CH_2Cl_2. The resulting blue-green mixture was stirred for 5 min at rt, and then powdered 4 Å MS (0.100 g) were added in one portion. After stirring for 5 min at rt, PhIO (0.113 g, 0.515 mmol, 1.2 equiv) was added in one portion, and the reaction was allowed to stir at rt. The reaction was monitored by TLC (CAM stain) for the consumption of the allene starting material. After it had been consumed (~1 h), a solvent exchange was carried out if necessary by removal of the reaction solvent under reduced pressure and addition of 4.3 mL of the specified solvent. The nucleophile was added at the specified temperature in one portion, and the

reaction was monitored for the disappearance of the methylene aziridine by TLC (CAM stain). Upon completion, the reaction was filtered through a pad of celite with EtOAc, concentrated by rotary evaporation, and purified *via* silica gel chromatography to yield the enesulfamate.

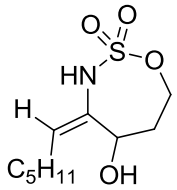


Compound 2.19. The allenic sulfamate **2.14** (0.800 g, 3.43 mmol) and Rh_2TPA_4 (14.8 mg, 0.026 mmol, 0.31 mol %) were added to a dry 100 mL round bottom flask. The mixture was kept under an atmosphere of nitrogen and charged with 34 mL of CH_2Cl_2. The resulting blue-green mixture was stirred for 5 min at rt, and then powdered 4 Å MS (0.800 g) were added in one portion. After stirring for 5 min at rt, PhIO (0.905 g, 4.12 mmol, 1.2 equiv) was added in one portion, and the reaction was allowed to stir at rt. After 1 h, TLC of the reaction mixture indicated consumption of the sulfamate (CAM stain). Glacial acetic acid (1.21 mL, 20.6 mmol, 6.0 equiv) was added in one portion at rt. The reaction was stirred at rt for 5 h, filtered through a pad of celite, washed with EtOAc and concentrated under rotary evaporation. Note: the ring-opening reaction is not complete at 5 h, but the act of concentrating the reaction by rotary evaporation (at ~40 °C) drives the reaction to completion). The concentrate was purified *via* silica gel chromatography (20% EtOAc/hexanes to 40% EtOAc/hexanes, gradient) to obtain 0.748 g (2.57 mmol, 75%) of the enesulfamate as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.33 (s, 1H), 5.94 (t, J = 7.8 Hz, 1H), 5.90 (t, J = 3.3 Hz, 1H), 4.65 (ddd, J = 12.9, 11.4, 1.5 Hz, 1H), 4.23 (dt, J = 12.9, 3.6 Hz, 1H), 2.30-2.06 (m, 4H), 2.13 (s, 3H), 1.44 (m, 2H), 1.31 (m, 4H), 0.89 (t, J = 6.9 Hz, 3H). ^{13}C

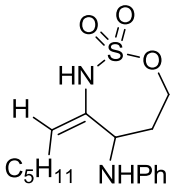
NMR (75 MHz, $CDCl_3$) δ 169.5, 136.7, 127.6, 66.8, 65.4, 34.6, 31.5, 28.6, 27.3, 22.5, 21.2, 14.1. IR (neat) ν = 3264, 2955, 2927, 2858, 1735, 1378, 1244, 1174, 998, 766. Melting range: 59-61 °C. HRMS (ESI) *m/z* calculated for $C_{12}H_{21}NO_5S$ [M+NH_4^+] 309.1479, found 309.1493.



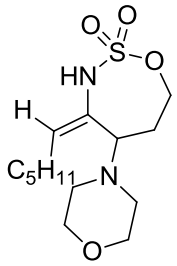
Compound 2.20. The allenic sulfamate **2.14** (0.604 g, 2.58 mmol) and Rh_2TPA_4 (26.8 mg, 0.019 mmol, 0.75 mol %) were added to a dry 100 mL round bottom flask. The mixture was kept under an atmosphere of nitrogen and charged with 26 mL of CH_2Cl_2. No molecular sieves were used in the reaction. After stirring for 5 min at rt, PhIO (0.680 g, 3.09 mmol, 1.2 equiv) was added in one portion, and the reaction was allowed to stir at rt. After 35 minutes, TLC of the reaction mixture indicated consumption of the sulfamate (CAM stain). Methanol (5.23 mL, 129.1 mmol, 50 equiv) was added in one portion at rt, and the reaction was stirred for 70 min. The reaction was filtered through a pad of celite with EtOAc and concentrated under rotary evaporation. The concentrate was purified *via* silica gel chromatography (20% EtOAc/hexanes to 30% EtOAc/hexanes, gradient) to give 0.497 g (1.89 mmol, 77% yield) of the enesulfamate as a clear liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.18 (s, 1H), 5.99 (app t, *J* = 7.8 Hz, 1H), 4.61 (ddd, *J* = 13.2, 8.4, 4.5 Hz, 1H), 4.28 (t, *J* = 3.3 Hz, 1H), 4.15 (dt, *J* = 13.2, 3.0 Hz, 1H), 3.28 (s, 3H), 2.20-2.00 (m, 4H), 1.50-1.38 (m, 2H), 1.38-1.23 (m, 4H), 0.89 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.8, 129.1, 73.0, 65.3, 56.6, 35.2, 31.5, 28.9, 26.9, 22.6, 14.1. IR (neat) ν = 3277, 2956, 2935, 2859, 1340, 1181, 1165, 1088, 753, 672. HRMS (ESI) *m/z* calculated for $C_{11}H_{21}NO_4S$ [M+NH_4^+] 281.1530, found 281.1525.



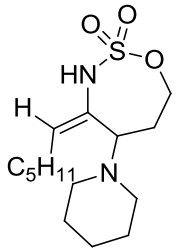
Compound 2.21. The allenic sulfamate **2.14** (0.152 g, 0.451 mmol) and Rh_2TPA_4 (3.0 mg, 0.00215 mmol, 0.5 mol %) were added to a dry 15 mL round bottom flask. The mixture was kept under an atmosphere of nitrogen and charged with 4.5 mL of CH_2Cl_2. No molecular sieves were used in the reaction. After stirring for 5 min at rt, PhIO (0.116 g, 0.527 mmol, 1.2 equiv) was added in one portion, and the reaction was allowed to stir at rt. After 80 min, TLC of the reaction mixture indicated consumption of the sulfamate (CAM stain). The reaction was concentrated by rotary evaporation, and acetonitrile (4.5 mL) was added. Deionized water (0.15 mL, 8.33 mmol, 18 equiv) was added in one portion at rt, and the reaction was stirred for 40 min, at which point TLC (CAM stain) indicated consumption of the methylene aziridine. The reaction was diluted with CH_2Cl_2, and the biphasic mixture was dried with Na_2SO_4. The mixture was filtered through a pad of celite with EtOAc and concentrated under rotary evaporation. The concentrate was purified *via* silica gel chromatography (30% EtOAc/hexanes to 50% EtOAc/hexanes, gradient) to obtain 82.4 mg (0.331 mmol, 74%) of the enesulfamate as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.34 (s, 1H), 5.77 (t, *J* = 7.8 Hz, 1H), 4.93 (app q, *J* = 3.6 Hz, 1H), 4.72 (ddd, *J* = 12.9, 12.5, 0.9 Hz, 1H), 4.18 (dt, *J* = 12.9, 3.3 Hz, 1H), 2.53 (d, *J* = 3.6 Hz, 1H), 2.22-1.86 (m, 4H), 1.50-1.36 (m, 2H), 1.36-1.20 (m, 4H), 0.89 (t, *J* = 6.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.0, 131.2, 65.1, 64.0, 36.7, 31.5, 28.9, 27.0, 22.6, 14.1. IR (neat) ν = 3503, 3277, 2929, 2860, 1412, 1333, 1180, 996, 758. HRMS (ESI) *m*/*z* calculated for $C_{10}H_{19}NO_4S$ [M+NH_4^+] 267.1374, found 267.1363.



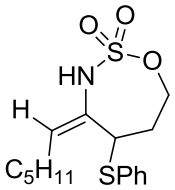
Compound 2.22. The allenic sulfamate **2.14** (101.4 mg, 0.435 mmol) and Rh_2TPA_4 (3.0 mg, 0.00215 mmol, 0.5 mol %) were added to a dry 15 mL round bottom flask. The mixture was kept under an atmosphere of nitrogen and charged with 4.3 mL of CH_2Cl_2. The resulting blue-green mixture was stirred for 5 min at rt, and then powdered 4 Å MS (100 mg) was added in one portion. After stirring for 5 min at rt, PhIO (104.0 mg, 0.473 mmol, 1.1 equiv) was added in one portion, and the reaction was allowed to stir at rt. After 60 min, an additional 10 mg of PhIO was added to push the reaction to completion. At 80 min, TLC of the reaction mixture indicated consumption of the sulfamate (CAM stain). Aniline (50.8 μL, 0.557 mmol, 1.3 equiv) was added in one portion at rt, and the reaction was stirred for 2 h until TLC (CAM stain) indicated consumption of the methylene aziridine. The reaction was filtered through a pad of celite with EtOAc and concentrated under rotary evaporation. The concentrate was purified *via* silica gel chromatography (20% EtOAc/hexanes to 25% EtOAc/hexanes, gradient) to obtain 95.4 mg (0.294 mmol, 68%) of the enesulfamate as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17 (dd, *J* = 8.7, 7.5 Hz, 2H), 6.79 (tt, *J* = 7.5, 0.8 Hz, 1H), 6.65 (m, 2H), 6.63 (bs, 1H), 5.83 (t, *J* = 7.8 Hz, 1H), 4.69 (t, *J* = 12.6 Hz, 1H), 4.50 (t, *J* = 3.6 Hz, 1H), 4.22 (dt, *J* = 12.6, 3.3 Hz, 1H), 3.93 (bs, 1H), 2.35 (ddt, *J* = 15.9, 12.3, 3.6 Hz, 1H), 2.31-2.12 (m, 2H), 2.06 (dt, *J* = 15.9, 3.0 Hz, 1H), 1.55-1.42 (m, 2H), 1.40-1.28 (m, 4H), 0.91 (app t, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.9, 133.8, 131.8, 129.5, 129.0, 128.0, 66.1, 47.5, 34.8, 31.4, 28.6, 27.5, 22.5, 14.1. IR (neat) ν = 3377, 3285, 2938, 2858, 1603, 1184, 1166, 925, 752. Melting range: 89-91 °C. HRMS (ESI) *m*/*z* calculated for $C_{16}H_{24}N_2O_3S$ [M+H$^+$] 325.1581, found 325.1577.



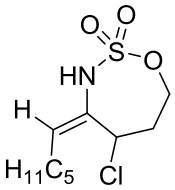
Compound 2.23. The allenic sulfamate **2.14** (50.1 mg, 0.215 mmol) and Rh_2TPA_4 (1.5 mg, 0.00107 mmol, 0.5 mol %) were added to a dry 10 mL round bottom flask. The mixture was kept under an atmosphere of nitrogen and charged with 2.1 mL of CH_2Cl_2. The resulting blue-green mixture was stirred for 5 min at rt, and then powdered 4 Å MS (50 mg) was added in one portion. After stirring for 5 min at rt, PhIO (51.9 mg, 0.236 mmol, 1.1 equiv) was added in one portion, and the reaction was allowed to stir for 70 min, until TLC of the reaction mixture indicated consumption of the sulfamate (CAM stain). Morpholine (30 μL, 0.343 mmol, 1.6 equiv) was added in one portion at rt, and the reaction was stirred for 2.5 h. The reaction was filtered through a pad of celite with EtOAc and concentrated under rotary evaporation. The concentrate was purified *via* silica gel chromatography (30% EtOAc/hexanes to 50% EtOAc/hexanes, gradient) to obtain 48.6 mg (0.153 mmol, 71%) of the enesulfamate as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.85 (bs, 1H), 5.91 (app t, *J* = 7.8 Hz, 1H), 4.50 (app t, *J* = 12.6 Hz, 1H), 4.14 (app dt, *J* = 12.6, 3.0 Hz, 1H), 3.74 (t, *J* = 4.6 Hz, 4H), 3.28 (t, *J* = 3.3 Hz, 1H), 2.52-2.37 (m, 4H), 2.27 (dt, *J* = 16.5, 3.3 Hz, 1H), 2.19-1.94 (m, 3H), 1.49-1.37 (m, 2H), 1.37-1.24 (m, 4H), 0.89 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.4, 130.3, 66.9, 65.1, 60.6, 51.1, 31.5, 30.4, 28.9, 26.6, 22.6, 14.1. IR (neat) ν = 3141, 2958, 2928, 2858, 1432, 1338, 1178, 1113, 1001, 744. Melting range: 90-92 °C. HRMS (ESI) *m*/*z* calculated for $C_{14}H_{26}N_2O_4S$ [M+H$^+$] 319.1687, found 319.1683.



Compound 2.24. The allenic sulfamate **2.14** (104.2 mg, 0.447 mmol) and Rh_2TPA_4 (3.5 mg, 0.00252 mmol, 0.56 mol %) were added to a dry 15 mL round bottom flask. The mixture was kept under an atmosphere of nitrogen and charged with 4.3 mL of CH_2Cl_2. The resulting blue-green mixture was stirred for 5 min at rt, and then powdered 4 Å MS (100 mg) was added in one portion. After stirring for 5 min at rt, PhIO (120.0 mg, 0.545 mmol, 1.2 equiv) was added in one portion, and the reaction was stirred for 1 h. Piperidine (55.0 μL, 0.556 mmol, 1.24 equiv) was added in one portion at rt, and the reaction was stirred for 50 min, filtered through a pad of celite with EtOAc and concentrated under rotary evaporation. The concentrate was purified *via* silica gel chromatography (30% EtOAc/hexanes to 50% EtOAc/hexanes, gradient) to obtain 106.6 mg (0.337 mmol, 75%) of the enesulfamate as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.85 (bs, 1H), 5.82 (app t, *J* = 7.5 Hz, 1H), 4.49 (app t, *J* = 12.6 Hz, 1H), 4.12 (dt, *J* = 12.6, 3.0 Hz, 1H), 3.23 (t, *J* = 3.3 Hz, 1H), 2.39 (bs, 4H) 2.30 (dt, *J* = 16.2, 3.6 Hz, 1H), 2.20-1.88 (m, 3H), 1.60 (m, 4H), 1.55-1.36 (m, 4H), 1.35-1.25 (m, 4H), 0.89 (app t, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 131.8, 130.4, 65.3, 60.4, 51.6, 31.6, 31.0, 29.0, 26.4, 26.2, 24.4, 22.6, 14.1. HRMS (ESI) *m*/*z* calculated for $C_{15}H_{28}N_2O_3S$ [M+H$^+$] 317.1894, found 317.1892.



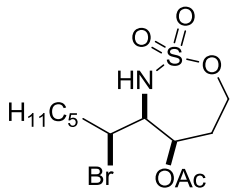
Compound 2.25. The allenic sulfamate **2.14** (55.2 mg, 0.237 mmol) and Rh_2TPA_4 (3.0 mg, 0.00215 mmol, 0.9 mol %) were added to a dry 10 mL round bottom flask. The mixture was kept under an atmosphere of nitrogen and charged with 2.3 mL of CH_2Cl_2. The resulting blue-green mixture was stirred for 5 min at rt, and then powdered 4 Å MS (50 mg) was added in one portion. After stirring for 5 min at rt, PhIO (63.0 mg, 0.286 mmol, 1.2 equiv.) was added in one portion, and the reaction was allowed to stir for 25 min. Thiophenol (0.244 mL, 2.37 mmol, 10.0 equiv) was added in one portion at rt, and the reaction was stirred for 30 min. The reaction was filtered through a pad of celite with EtOAc and concentrated under rotary evaporation. The concentrate was purified *via* silica gel chromatography (5% EtOAc/hexanes to 20% EtOAc/hexanes, gradient) to obtain 55.6 mg (0.163 mmol, 69%) of the enesulfamate as a light purple solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (m, 2H), 7.31 (m, 3H), 6.65 (s, 1H), 5.79 (app t, *J* = 7.8 Hz, 1H), 4.60 (t, *J* = 12.9 Hz, 1H), 4.50 (dd, *J* = 5.1, 2.7 Hz, 1H), 4.24 (dt, *J* = 12.9, 2.7 Hz, 1H), 2.51 (tdd, *J* = 12.0, 5.1, 3.0 Hz, 1H), 2.15 (dt, *J* = 15.9, 3.0 Hz, 1H), 1.89 (m, 1H), 1.76 (m, 1H), 1.34-0.95 (m, 6H), 0.83 (t, *J*= 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.9, 133.8, 131.8, 129.5, 129.0, 128.0, 66.1, 47.5, 34.8, 31.4, 28.6, 27.5, 22.5, 14.1. IR (neat) ν = 3255, 2958, 2929, 2855, 1397, 1186, 999, 924, 745, 658. Melting range: 52-54 °C. HRMS (ESI) *m/z* calculated for $C_{16}H_{23}NO_3S_2$ $[M+NH_4^+]$ 359.1458, found 359.1452.



Compound 2.26. The allenic sulfamate **2.14** (50.0 mg, 0.215 mmol) and Rh_2TPA_4 (3.0 mg, 0.00215 mmol, 1.0 mol %) were added to a dry 10 mL round bottom flask. The mixture was kept under an atmosphere of nitrogen and charged with 2.1 mL of CH_2Cl_2. The resulting blue-green mixture was stirred for 5 min at rt, and then powdered 4 Å MS (50 mg) was added in one portion. After stirring for 5 min at rt, PhIO (56.8 mg, 0.258 mmol, 1.2 equiv) was added in one portion, and the reaction was allowed to stir at rt. At 45 minutes, TLC of the reaction mixture indicated consumption of the sulfamate (CAM stain). The reaction was concentrated by rotary evaporation, and 1 mL of THF was added. This solution was transferred by pipette to a solution of Me_3SiCl (40.6 μL, 0.322 mmol, 1.5 equiv) in 1 mL of THF at -40 °C. After stirring at -40 °C for 5 min, the reaction was placed in an ice bath and was allowed to slowly warm to room temperature with stirring. After 8 h of stirring with Me_3SiCl, the reaction was filtered through a pad of celite with EtOAc and concentrated under rotary evaporation. The concentrate was purified *via* silica gel chromatography (20% EtOAc/hexane) to obtain 32.4 mg (0.121 mmol, 56%, 62% based on recovered starting material) of the enesulfamate as a clear liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.23 (s, 1H), 5.95 (td, *J* = 9.3, 0.5 Hz, 1H), 5.27 (t, *J* = 3.5 Hz, 1H), 4.75 (t, *J* = 12.7 Hz, 1H), 4.26 (dt, *J* = 12.7, 3.0 Hz, 1H), 2.50 (app ddt, *J* = 15.5, 12.5, 3.5 Hz, 1H) 2.23 (dtd, *J* = 16.0, 3.0, 0.5 Hz, 1H), 2.15 (m, 2H), 1.49-1.42 (m, 2H), 1.37-1.26 (m, 4H), 0.90 (app t, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.8, 128.2, 64.7, 56.0, 38.7, 31.4, 28.6, 27.7, 22.6, 14.1. IR (neat) ν = 3283, 2957, 2930, 2860, 1409, 1182, 998, 925, 737, 657. HRMS (ESI) *m*/*z* calculated for $C_{10}H_{18}ClNO_3S$ [M+NH_4^+] 285.1035, found 285.1043.

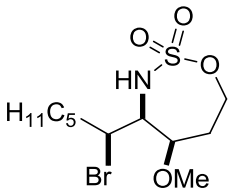
2.6.4. Stereotriads from enesulfamates

Note: Characterization data for minor diastereomers is given if they are formed in a significant amount relative to the major diastereomer (4:1 major/minor ratio or smaller).



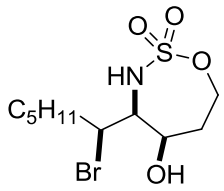
Compound 2.28. Enesulfamate **2.19** (49.6 mg, 0.170 mmol) was added to a 10 mL round bottom flask and dissolved in 2.5 mL of dry THF. The solution was cooled to 0 °C, and N-bromosuccinimide (45.9 mg, 0.258 mmol, 1.5 equiv) was added in one portion with stirring. This mixture was allowed to stir at 0 °C for 80 min. (Note: the reaction is generally complete within 15 min; although the longer reaction time was not harmful in this case, it can often result in a lower final *dr*). Sodium cyanoborohydride (21.6 mg, 0.344 mmol, 2 equiv) was then dissolved separately in 1.25 mL MeOH. Glacial acetic acid (150 μL, 2.58 mmol, 15 equiv) was added, and this solution was added to the reaction in one portion *via* pipette. The reaction was warmed to rt and stirred for 2 h, then concentrated by rotary evaporation. A 15 mL portion of EtOAc was added, the solution transferred to a separatory funnel and washed with saturated $NaHCO_3$ (2 x 10 mL) and brine (2 x 10 mL). The organics were dried over Na_2SO_4 and concentrated by rotary evaporation to give a crude yield of 88% of the major diastereomer (^{1}H NMR using mesitylene as the internal standard). The crude material was purified by silica gel chromatography (20% EtOAc/hexanes to 40% EtOAc/hexanes, gradient) to give 45.2 mg (0.122 mmol, 71%) of a white solid as a 12.5:1 mixture of diastereomers. The relative stereochemistry was assigned *via* an X-ray crystal structure of the major diastereomer **2.28a**. Major diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.66 (d, J = 11.1

Hz, 1H), 5.41 (t, *J* = 3.2 Hz, 1H), 4.61 (t, *J* = 12.7 Hz, 1H), 4.23 (dt, *J* = 12.7, 3.2 Hz, 1H), 3.99 (ddd, *J* = 9.0, 6.5, 3.5 Hz, 1H), 3.74 (dd, *J* = 11.1, 3.3 Hz, 1H), 2.24 (ddt, *J* = 15.0, 12.0, 3.0, 1H), 2.15 (s, 3H), 2.03 (dt, *J* = 15.9, 3.0 Hz, 1H), 1.89 (m, 2H), 1.60-1.49 (m, 1H), 1.48-1.38 (m, 1H), 1.37-1.20 (m, 4H), 0.90 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.7, 70.0, 65.1, 57.5, 56.1, 36.4, 34.6, 31.1, 27.1, 22.6, 21.6, 14.1. IR (neat) ν =3523, 2955, 2935, 2857, 1729, 1242, 1180, 1003, 927, 763. Melting range: 149-151 °C. HRMS (ESI) *m/z* calculated for $C_{12}H_{22}BrNO_5S$ [M+Na^+] 394.0295, found 394.0282.



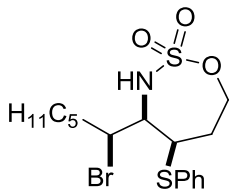
Compound 2.29. Enesulfamate **2.20** (105.9 mg, 0.403 mmol) was added to a 25 mL roundbottom flask and dissolved in 5.4 mL of dry THF. The solution was cooled to 0 °C, and N-bromosuccinimide (108.1 mg, 0.607 mmol, 1.5 equiv) was added in one portion with stirring. This mixture was allowed to stir at 0 °C for 25 min, at which point TLC (CAM stain) indicated consumption of the enesulfamate. Sodium cyanoborohydride (50 mg, 0.794 mmol, 2 equiv) dissolved in 2.7 mL MeOH was added at 0 °C, followed by glacial acetic acid (0.335 mL, 5.70 mmol, 15 equiv), and the reaction was stirred at rt for 3 h. The reaction was concentrated by rotary evaporation, and 15 mL EtOAc was added. The solution was added to a separatory funnel and washed with saturated $NaHCO_3$ (2 x 10 mL) and brine (2 x 10 mL). The solution was dried over Na_2SO_4 and concentrated by rotary evaporation. The crude material was purified by silica gel chromatography (20% EtOAc/hexanes to 40% EtOAc/hexanes, gradient) to give 90.5 mg (0.263 mmol, 65%) of the major diastereomer as a white solid. No minor diastereomer was isolated,

although it was observed in the crude ^{1}H NMR in a small amount. The stereochemistry of the major diastereomer was assigned by analogy to **2.28a**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.62 (d, *J* = 11.0 Hz, 1H), 4.57 (t, *J* = 13.0 Hz, 1H), 4.17 (dt, *J* = 13.0, 3.5 Hz, 1H) 4.05 (ddd, *J* = 8.5, 5.0, 3.5 Hz, 1H), 3.92 (dd, *J* = 2.5, 2.0 Hz, 1H), 3.67 (dd, *J* = 11.0, 5.0 Hz, 1H), 3.39 (s, 3H), 2.17 (dt, *J* = 17.0, 3.5 Hz, 1H), 1.98 (app ddt, *J* = 17.0, 15.0, 3.0 Hz, 1H), 1.85 (m, 1H), 1.75 (m, 1H), 1.63-1.54 (m, 1H), 1.45-1.23 (m, 5H), 0.90 (app t, *J* = 7.0 Hz). ^{13}C NMR 125 MHz, $CDCl_3$) δ 74.7, 64.5, 59.5, 56.5, 56.5, 34.4, 31.3, 31.0, 27.4, 22.4, 14.0. IR (neat) ν = 3268, 2948, 2929, 2860, 1351, 1188, 1013, 940, 768. Melting range: 100-102 °C. HRMS (ESI) *m*/*z* calculated for $C_{11}H_{22}BrNO_4S$ [M+NH_4^+] 361.0792, found 361.0809.



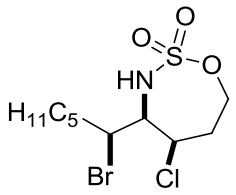
Compound 2.30. Enesulfamate **2.21** (30.0 mg, 0.120 mmol) was added to a 10 mL roundbottom flask and dissolved in 1.5 mL of dry THF. The solution was cooled to 0 °C, and N-bromosuccinimide (27.8 mg, 0.156 mmol, 1.3 equiv) was added in one portion with stirring. This mixture was allowed to stir at 0 °C for 15 min, after which sodium cyanoborohydride (15.1 mg, 0.240 mmol, 2 equiv) dissolved in 0.75 mL dry MeOH was added at 0 °C via pipette. Glacial acetic acid (35 μL, 0.60 mmol, 5 equiv) was then added, and the reaction was stirred at rt. After 3 h, the reaction was concentrated by rotary evaporation, and diluted with 5 mL of EtOAc. The solution was transferred to a separatory funnel, diluted to 20 mL with EtOAc and washed with saturated $NaHCO_3$ (2 x 10 mL) and brine (2 x 10 mL). The organic layer was dried over Na_2SO_4 and concentrated by rotary evaporation to give the crude product as a clear oil. The product was

purified *via* silica gel chromatography (20% EtOAc/hexanes to 40% EtOAc/hexanes, gradient) to give 28.0 mg (0.848 mmol, 70%) of the product as a white solid and a 4:1 mixture of diastereomers. The stereochemistry of the major diastereomer was assigned by analogy to **2.28a**. The product was characterized as a 4:1 mixture of diastereomers: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.63 (d, *J* = 10.5 Hz, 1H), 4.86 (d, *J* = 10.8 Hz, 0.25H), 4.70 (t, *J* = 12.0 Hz, 1H), 4.56 (ddd, *J* = 8.1, 5.7, 1.8 Hz, 0.25 H), 4.35 (m, 0.5H), 4.27 (m, 1H), 4.14 (m, 2H), 3.91 (m, 0.25H), 3.68 (dd, *J* = 10.5, 2.7 Hz, 1H), 3.28 (ddd, *J* = 10.8, 9.0, 1.6 Hz, 0.25H), 2.86 (dd, *J* = 2.7, 1.8 Hz, 1H), 2.29 (m, 0.25H), 2.22-1.90 (m, 4.75H), 1.60-1.20 (m, 7.75H), 0.90 (t, *J* = 6.8 Hz, 3.75H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 72.1, 69.3, 67.2, 64.8, 60.2, 59.4, 57.9, 57.3, 37.1, 36.5, 36.3, 36.0, 31.3, 31.2, 27.3, 27.2, 22.6, 22.6, 14.2, 14.2. IR (neat) ν = 3505, 3193, 2959, 2931, 2858, 1336, 1174, 1006, 943, 770. Melting range: 142-144 °C. HRMS (ESI) *m*/*z* calculated for $C_{10}H_{20}BrNO_4S$ [M+NH_4^+] 347.0635, found 347.0638.



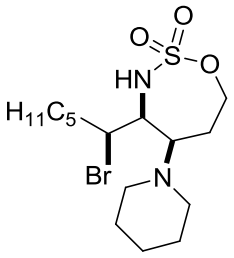
Compound 2.31. Enesulfamate **2.25** (52.5 mg, 0.154 mmol) was added to a 10 mL roundbottom flask and dissolved in 2 mL of dry THF. The solution was cooled to 0 °C, and N-bromosuccinimide (39.1 mg, 0.220 mmol, 1.5 equiv) was added in one portion with stirring. This mixture was allowed to stir at 0 °C for 25 min, after which sodium cyanoborohydride (18.5 mg, 0.294 mmol, 2 equiv) dissolved in 1 mL dry MeOH was added at 0 °C via pipette. Glacial acetic acid (86 μL, 1.47 mmol, 10 equiv) was then added, and the reaction was stirred at rt. After 1 h, the reaction was concentrated by rotary evaporation and diluted with 5 mL of EtOAc. The solution

was transferred to a separatory funnel and further diluted to 20 mL with EtOAc, washed with saturated $NaHCO_3$ (3 x 10 mL) and brine (3 x 10 mL). The organic layer was dried over Na_2SO_4 and concentrated by rotary evaporation to give the crude product as a clear oil. The product was purified *via* silica gel chromatography (5% EtOAc/hexanes to 25% EtOAc/hexanes, gradient) to give 43.6 mg (0.103 mmol, 67%) of product as a single diastereomer. No minor diastereomer was observed, either by crude ^{1}H NMR or by isolation. The product was a white solid. The stereochemistry of the major diastereomer was assigned by analogy to **2.28a**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (m, 2H), 7.35 (m, 3H), 5.32 (d, *J* = 9.9 Hz, 1H), 4.74 (app t, *J* = 12.0 Hz, 1H), 4.22 (app dt, J = 12.0, 3.0 Hz, 1H), 4.14 (m, 1H), 3.89 (ddd, *J* = 9.9, 8.4, 1.5 Hz, 1H), 3.82 (m, 1H), 2.39 (app ddt, *J* = 15.6, 13.2, 3.2, 1H), 2.17 (dtd, *J* = 15.6, 3.3, 0.9 Hz, 1H), 1.74 (m, 2H), 1.60-1.44 (m, 1H), 1.43-1.10 (m, 5H), 0.87 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.2, 132.2, 129.9, 128.8, 66.3, 61.2, 56.6, 50.6, 35.42, 35.41, 31.2, 27.1, 22.6, 14.1. IR (neat) ν = 3311, 2959, 2926, 2856, 1349, 1336, 1184, 994, 921, 772. Melting range: 123-125 °C. HRMS (ESI) *m*/*z* calculated for $C_{16}H_{24}BrNO_3S_2$ [M+NH_4^+] 439.0720, found 439.0721.



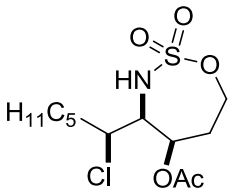
Compound 2.32. Enesulfamate **2.26** (60.3 mg, 0.225 mmol) was added to a 25 mL roundbottom flask and dissolved in 3.2 mL of dry THF. The solution was cooled to 0 °C, and N-bromosuccinimide (60.1 mg, 0.338 mmol, 1.5 equiv) was added in one portion with stirring. This mixture was allowed to stir at 0 °C for 75 min, at which point TLC (CAM stain) indicated consumption of the enesulfamate. Sodium cyanoborohydride (28.4 mg, 0.450 mmol, 2 equiv)

dissolved in 1.6 mL MeOH was added at 0 °C, followed by glacial acetic acid (0.200 mL, 3.38 mmol, 15 equiv), and the reaction was stirred at rt for 2.5 h. The reaction was concentrated by rotary evaporation, and 15 mL EtOAc was added. The solution was added to a separatory funnel and washed with saturated $NaHCO_3$ (2 x 10 mL) and brine (2 x 10 mL). The solution was dried over Na_2SO_4 and concentrated by rotary evaporation. The product was not observed by TLC, even with a wide variety of stains (CAM, Ninhydrin, para-anisaldehyde, I_2, etc.), so purification via silica gel chromatography was difficult. Instead, the crude yield of the major diastereomer was determined to be 77% by ^{1}H NMR using mesitylene as the internal standard. Only one diastereomer was observed by ^{1}H NMR. The stereochemistry of the major diastereomer was assigned by analogy to **2.28a**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.41 (d, *J* = 10.5 Hz, 1H), 4.75-4.65 (m, 2H), 4.26 (dt, *J* = 13.2, 3.2 Hz, 1H), 4.03-3.85 (m, 2H), 2.56 (ddt, *J* = 15.9, 11.4, 3.0, 1H), 2.24 (dt, *J* = 15.9, 3.2 Hz, 1H), 1.84 (m, 2H), 1.67-1.42 (m, 2H), 1.40-1.20 (m, 4H), 0.91 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 64.7, 60.2, 59.1, 55.6, 38.3, 34.7, 31.1, 27.2, 22.6, 14.2. IR (neat) ν = 3274, 2952, 2930, 2857, 1351, 1187, 1009, 943, 765. HRMS (ESI) *m*/*z* calculated for $C_{10}H_{19}BrClNO_3S$ [M+NH_4^+] 365.0296, found 365.0305.



Compound 2.33. Enesulfamate **2.24** (49.1 mg, 0.155 mmol) was added to a 10 mL roundbottom flask and dissolved in 2 mL of dry THF. The solution was cooled to 0 °C, and N-bromosuccinimide (42.2 mg, 0.237 mmol, 1.5 equiv) was added in one portion with stirring. This

mixture was allowed to stir at 0 °C for 15 min, after which sodium cyanoborohydride (19.9 mg, 0.316 mmol, 2 equiv) dissolved in 1 mL dry MeOH was added at 0 °C via pipette. Glacial acetic acid (93 μL, 1.58 mmol, 10 equiv) was then added, and the reaction was stirred at rt. After 1 h, the reaction was concentrated by rotary evaporation, and diluted with 5 mL of EtOAc. The solution was transferred to a separatory funnel and diluted to 20 mL with EtOAc, washed with sat. $NaHCO_3$ (3 x 10 mL) and brine (3 x 10 mL). The organic layer was dried over Na_2SO_4 and concentrated by rotary evaporation to give the crude product as a clear oil. The product was purified *via* silica gel chromatography (5% EtOAc/hexanes to 20% EtOAc/hexanes, gradient) to give 27.1 mg (0.0684 mmol, 44%) of the desired product as a single diastereomer. No minor diastereomer was isolated, although it was observed in the crude ^{1}H NMR (5.9:1 major:minor). The product was a white solid. The stereochemistry of the major diastereomer was assigned by analogy to **2.28a**. Major diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.83 (d, *J* = 10.8 Hz, 1H), 4.75 (ddd, *J* = 8.4, 6.3, 1.5 Hz, 1H) 4.38 (dt, *J* = 12.9, 4.2 Hz, 1H), 4.29 (m, 1H), 3.34 (td, *J* = 10.8, 1.5 Hz, 1H), 2.78 (td, *J* = 10.2, 5.4, 1H), 2.46 (m, 4H), 2.21-1.88 (m, 4H), 1.68-1.25 (m, 12H), 0.90 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 69.0, 67.1, 58.1, 57.6, 50.2, 36.1, 31.2, 27.4, 26.8, 26.2, 24.7, 22.6, 14.2. IR (neat) ν = 3285, 2932, 2857, 2805, 1355, 1185, 928, 757. HRMS (ESI) *m*/*z* calculated for $C_{15}H_{29}BrN_2O_3S$ [M+H$^+$] 397.1161, found 397.1168.

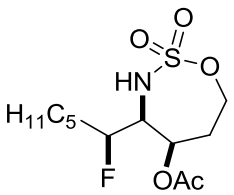


Compound 2.35. Procedure using NCS: Enesulfamate **2.19** (52.3 mg, 0.180 mmol) was added to a 10 mL round bottom flask and dissolved in 2.5 mL of dry THF. N-Chlorosuccinimide (35.2

mg, 0.263 mmol, 1.5 equiv) was added in one portion at rt. A water-cooled reflux condenser was attached, and the solution was heated to reflux under N_2. After 5 h, a solution of $NaBH_3CN$ (21.6 mg, 0.344 mmol, 2 equiv) in 1.25 mL MeOH was added to the reaction in one portion at rt, followed by glacial acetic acid (0.152 mL, 2.58 mmol, 15 equiv). The reaction was stirred at rt for 14 h, concentrated by rotary evaporation, transferred to a separatory funnel and diluted with 20 mL EtOAc. The organics were washed with saturated $NaHCO_3$ (2 x 10 mL) and brine (2 x 10 mL), dried over Na_2SO_4 and concentrated by rotary evaporation. ^{1}H NMR analysis (using mesitylene as the internal standard) of the resulting crude oil of the resulting crude oil indicated a 65% yield and a 5:1 *dr*. The stereochemistry was assigned by analogy to **2.28a**. Major diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.61 (d, *J* = 10.8 Hz, 1H), 5.43 (t, *J* = 3.0 Hz, 1H), 4.61 (t, *J* = 12.6 Hz, 1H), 4.23 (dt, *J* = 12.6, 3.3 Hz, 1H), 3.95 (m, 1H), 3.73 (dd, *J* = 10.8, 2.4 Hz, 1H), 2.26 (ddt, *J* = 15.6, 12.3, 3.0 Hz, 1H), 2.14 (s, 3H), 2.02 (dt, *J* = 15.6, 3.6 Hz, 1H), 1.82 (m, 2H), 1.58-1.36 (m, 2H), 1.36-1.20 (m, 4H), 0.89 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.7, 70.0, 65.1, 63.7, 57.5, 35.8, 34.7, 31.2, 26.0, 22.6, 21.5, 14.1. IR (neat) ν = 3526, 2953, 2931, 2858, 1729, 1360, 1244, 1181, 1007, 928, 764. Melting range: 148-151 °C. HRMS (ESI) *m*/*z* calculated for $C_{12}H_{22}ClNO_5S$ [M+Na^+] 350.0800, found 350.0807.

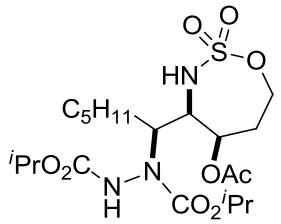
Procedure using TCCA: Enesulfamate **2.19** (104.0 mg, 0.357 mmol) was added to a 25 mL round bottom flask and dissolved in 5 mL of $CHCl_3$. Trichloroisocyanuric acid (122.0 mg, 0.526 mmol, 1.5 equiv) was added in one portion at rt, and the cloudy white mixture was stirred for 45 min. Sodium cyanoborohydride (65 mg, 1.03 mmol, 3 equiv) dissolved in 2.5 mL MeOH was added at rt, resulting in a slight exotherm. Glacial acetic acid (0.200 mL, 3.44 mmol, 10 equiv) was added, and the reaction was stirred at rt for 2 h. The reaction was concentrated by rotary evaporation, and

15 mL EtOAc was added. The solution was added to a separatory funnel and washed with saturated $NaHCO_3$ (2 x 10 mL) and brine (2 x 10 mL). The solution was dried over Na_2SO_4 and concentrated by rotary evaporation. The crude material was purified by silica gel chromatography (20% EtOAc/hexanes to 40% EtOAc/hexanes, gradient) to give 89.1 mg (0.272 mmol, 76%) of product in a 20:1 diastereomeric ratio. Spectroscopic data of the major diastereomer matched the values reported above for **2.35**.



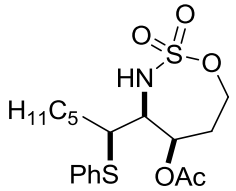
Compound 2.36. Enesulfamate **2.19** (151.0 mg, 0.519 mmol) and Selectfluor® (225.0 mg, 0.636 mmol, 1.2 equiv) were added to a 50 mL roundbottom flask and dissolved in 21 mL of MeCN. The reaction flask was fitted with a water-cooled reflux condenser and heated to 80 °C with stirring. After 2 h, TLC (CAM stain) of the resulting yellow solution indicated consumption of the enesulfamate. The reaction was cooled to rt, and sodium cyanoborohydride (67.8 mg, 1.08 mmol, 2 equiv) dissolved in 2 mL MeOH was added via pipette, followed by glacial acetic acid (0.30 mL, 5.1 mmol, 10 equiv). The reaction was stirred at rt for 4.5 h, concentrated by rotary evaporation, diluted with 20 mL of EtOAc and the solution was transferred to a separatory funnel. The organics were washed with saturated $NaHCO_3$ (2 x 10 mL) and brine (2 x 10 mL), dried over Na_2SO_4, and concentrated by rotary evaporation to give the crude product, which was purified by silica gel chromatography (20% EtOAc/hexanes to 40% EtOAc/hexanes, gradient) to give 92.7 mg (0.298 mmol, 57%) of desired product as a white solid as an inseparable 2:1 mixture of diastereomers. The identity of the major diastereomer was assigned as 1,2-*syn*:2,3-*syn* by analogy

to **2.28a**. The identity of the minor diastereomer is not known with certainty. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.48 (t, *J* = 3.0 Hz, 1.5 Hz), 5.38 (d, *J* = 11.0 Hz, 1H), 5.28 (d, *J* = 11.0 Hz, 0.5H), 4.61 (app t, *J* = 12.5 Hz, 1H), 4.59 (dddd, *J* = 47.0, 8.5, 5.0, 1.5 Hz, 1H), 4.53 (dd, *J* = 13.0, 3.5 Hz, 0.5H), 4.28 (dtd, J = 48, 8.0, 2.5 Hz, 0.5H), 4.23 (dt, *J* = 13.5, 3.0 Hz, 1H), 4.24 (m, 0.5H), 3.57-3.47 (m, 1.5H), 2.32-2.19 (m, 2H), 2.15 (s, 1.5H), 2.11 (s, 3H), 2.02 (dt, *J* = 16.5, 3.3 Hz, 1H), 1.92-1.58 (m, 3H), 1.45-1.24 (m, 9H), 0.89 (m, 4.5H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.6, 169.2, 94.9 (d, *J* = 177 Hz), 91.4 (d, *J* = 177 Hz), 70.1, 67.3, 65.13, 65.10, 57.3 (d, *J* = 26 Hz), 56.4 (d, *J* = 17 Hz), 34.5, 33.6, 32.1 (d, *J* = 21 Hz), 31.8 (d, *J* = 10 Hz), 31.6, 31.5, 24.53, 24.49, 22.65, 22.62, 21.2, 21.2, 14.13, 14.10. IR (neat) ν =3208, 2950, 2928, 2858, 1717, 1362, 1251, 1100, 999, 929, 771. HRMS (ESI) *m*/*z* calculated for $C_{12}H_{22}FNO_5S$ [M+NH_4^+] 329.1541, found 329.1548.



Compound 2.37. Copper (II) triflate (6.2 mg, 0.017 mmol, 0.1 equiv) was added to a roundbottom flask and dissolved in 2.5 mL toluene. After 5 min of stirring at rt, N,N'-dimethylethylenediamine (2.0 μL, 0.019 mmol, 0.11 equiv) was added via a 50 μL syringe. The solution rapidly turned dark purple. After stirring for 10 min at rt, diisopropylazodicarboxylate (37.0 μL, 0.189 mmol, 1.1 equiv.) was added via a 50 μL syringe, and the solution turned dark yellow-gray. After stirring at rt for an additional 5 min, enesulfamate **2.19** (51.7 mg, 0.178 mmol, 1.0 equiv) was added, and the flask was fitted with a water-cooled reflux condenser. The solution was stirred for 1 h at 55 ºC, during which time the reaction turned dark green. Subsequently, the solution was concentrated

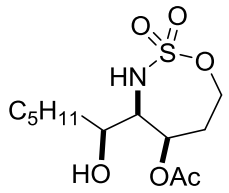
via rotary evaporation at 55 ºC, and 2.5 mL of THF was added. A solution of $NaBH_3CN$ (22 mg, 0.35 mmol, 2.0 equiv) in 1 mL MeOH was added at rt with stirring, followed by 0.1 mL HOAc. The reaction was allowed to stir at rt for 5 h, concentrated by rotary evaporation, and diluted with 15 mL of EtOAc. The organics were transferred to a separatory funnel and washed with saturated $NaHCO_3$ (2 x 10 mL) and brine (2 x 10 mL). The solution was dried over Na_2SO_4 and concentrated by rotary evaporation. The crude material was purified by silica gel chromatography (30% EtOAc/hexanes to 40% EtOAc/hexanes, gradient) to give 60.4 mg (0.122 mmol, 69%) of product as a single diastereomer. The stereochemistry of the major diastereomer was assigned by analogy to **2.28a**. The product was a white solid. (Note: This spectrum is complicated by the presence of multiple rotamers in the product structure. Acquiring spectra at 80 ºC in d^8-toluene alleviates some, but not all, of these issues. At higher temperatures, product decomposition occurs.) ^{1}H NMR (300 MHz, $CD_3C_6D_5$, 80 ºC) δ 6.71 (bs, 1H), 5.28 (bs, 1H), 5.04 (t, *J* = 2.5 Hz, 1H), 5.00-4.85 (m, 2H), 4.21 (m, 1H), 4.14 (t, *J* = 12.5 Hz, 1H), 3.48 (dt, *J* = 13.5, 2.5 Hz, 1H), 3.34 (t, *J* = 11.0 Hz, 1H), 1.71 (s, 3H), 1.55-1.40 (m, 4H), 1.34 (m, 5H), 1.19-1.09 (m, 13H), 0.92 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CD_3C_6D_5$, 80 ºC) δ 169.3, 158.1 (broad), 157.2 (broad), 71.0, 70.0, 68.8 (broad) 65.3, 58.7 (broad), 57.9, 34.3, 32.3, 29.3 (broad), 26.7, 23.2, 22.4, 22.34, 22.30, 22.2, 22.2, 14.4. HRMS (ESI) *m*/*z* calculated for $C_{20}H_{37}N_3O_9S$ [M+NH_4^+] 513.2589, found 513.2596.



Compound 2.38. N-Chlorosuccinimide (27.6 mg, 0.206 mmol, 2.0 equiv) was added to a 10 mL roundbottom flask and dissolved in 1.5 mL of dichloromethane. Thiophenol (21.2 μL, 0.206

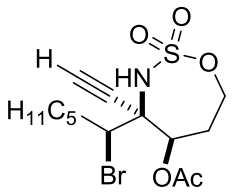
mmol, 2.0 equiv) was added at rt over 30 sec, and the reaction was allowed to stir at rt for 30 min, during which time it turned dark yellow. Enesulfamate **2.19** (30.9 mg, 0.109 mmol, 1.0 equiv) was added in one portion at rt, followed by 2,6-di-*tert*-butyl-4-methylpyridine (21.1 mg, 0.103 mmol, 1.0 equiv). The reaction was stirred at rt for 70 min, at which point a solution of $NaBH_3CN$ (19.5 mg, 0.309 mmol, 3.0 equiv) in 1.25 mL MeOH was added, followed by acetic acid (60 μL, 1.03 mmol, 10 equiv). The mixture was stirred at rt for 3 h, concentrated by rotary evaporation, and diluted with 15 mL of EtOAc. The organics were transferred to a separatory funnel and washed with saturated $NaHCO_3$ (2 x 10 mL) and brine (2 x 10 mL). The solution was dried over Na_2SO_4 and concentrated by rotary evaporation. The crude material was purified by silica gel chromatography (30% EtOAc/hexanes to 40% EtOAc/hexanes, gradient) to give 34.3 mg (0.0855 mmol, 80%) of the desired product as a 2.9:1 mixture of diastereomers. An additional minor diastereomer was also formed in a small (< 10% by mass) amount. The product was a white solid. If desired, the diastereomers could be separated by using a CH_2Cl_2/MeOH solvent system (100% CH_2Cl_2 to 2% MeOH/DCM, gradient). The stereochemistry of the major diastereomer was assigned by analogy to **2.28a**. Major diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.22 (m, 5H), 5.61 (d, *J* = 11.1 Hz, 1H), 5.55 (t, *J* = 3.0 Hz, 1H), 4.53 (ddd, *J* = 13.2, 10.5, 2.4 Hz, 1H), 4.16 (dt, *J* = 13.2, 3.3 Hz, 1H), 3.68 (dd, *J* = 11.1, 4.8 Hz, 1H), 3.22 (dt, *J* = 8.7, 4.8 Hz, 1H), 2.20-2.02 (m, 2H), 2.08 (s, 3H), 1.69 (m, 1H), 1.58-1.15 (m, 7H), 0.87 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6, 134.1, 131.7, 129.5, 127.6, 69.1, 65.0, 56.9, 52.3, 34.3, 31.6, 31.2, 27.1, 22.6, 21.5, 14.2. IR (neat) ν = 3302, 2963, 2929, 2857, 1749, 1354, 1263, 1179, 1105, 1088, 1048, 1012, 809, 760. Melting range: 129-131 °C. HRMS (ESI) *m*/*z* calculated for $C_{18}H_{27}NO_5S_2$ [M+NH_4^+] 419.1669, found 419.1674. Minor diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (m, 2H), 7.28 (m, 3H), 5.16 (d, *J* = 10.5 Hz, 1H), 4.77 (td, *J* = 9.6, 4.8 Hz, 1H), 4.36 (m, 1H), 4.28

(dt, *J* = 13.2, 3.3 Hz, 1H), 3.70 (td, *J* = 9.6, 1.2 Hz, 1H), 3.42 (ddd, *J* = 8.1, 6.3, 1.8 Hz, 1H), 2.45 (dtd, *J* = 15.0, 4.2, 1.0 Hz, 1H), 1.96-1.73 (m, 3H), 1.70-1.60 (m, 1H), 1.61 (s, 3H), 1.42-1.25 (m, 5H), 0.92 (t, *J* = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.1, 134.9, 132.4, 129.6, 128.0, 72.5, 66.8, 59.5, 52.0, 34.0, 33.6, 31.7, 27.2, 22.7, 20.6, 14.2.



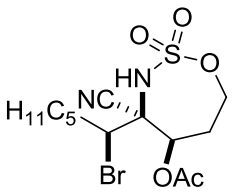
Compound 2.39. Enesulfamate **2.19** (40.0 mg, 0.137 mmol, 1.0 equiv.) was added to a 2-mL screw-top flask, followed by a magnetic stir bar and powdered 4Å molecular sieves (30 mg). A solution of DMDO in dichloromethane (0.20 M, 1.5 mL, 0.30 mmol, 2.25 equiv) was added *via* pipette, the flask was capped tightly, and the mixture was stirred at rt. After 2.5 h, consumption of the starting material was observed by TLC (CAM stain), and the reaction was concentrated by rotary evaporation. Freshly distilled 1,2-dichloroethane (1.5 mL) was added to the concentrate, followed by $NaB(OAc)_3H$ (29.0 mg, 0.137 mmol, 1 equiv) with stirring. Acetic acid (80 μL, 1.37 mmol, 10 equiv) was added immediately, and the reaction was stirred at rt for 15 min. Additional $NaB(OAc)_3H$ (87.0 mg, 0.410 mmol, 3.0 equiv) was added, and the mixture was stirred at rt overnight. After a total reaction time of 25 h, the reaction was transferred to a separatory funnel, diluted with 20 mL of CH_2Cl_2, and washed with sat. $NaHCO_3$ (2 x 10 mL) and brine (2 x 10 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated. The resulting crude oil was purified by silica gel chromatography (20% EtOAc/hexanes to 50% EtOAc/hexane, gradient) to give 18.5 mg (0.0599 mmol, 44%) of the desired product as a clear oil and a 6:3:1 mixture of diastereomers. The product was characterized as a 2:1 mixture of diastereomers (with a third

diastereomer present as a minor impurity). The identity of the major diastereomer could be assigned as 1,2-*syn*:2,3-*syn* by analogy to **2.28a**, but the identity of the minor diastereomer is not known using DMDO as the electrophile. Future studies will be undertaken to improve the selectivity of the reaction, determine the relative stereochemistry of the minor diastereomer, and utilize this information to identify the factors responsible for the stereochemical outcome of this reaction. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.61 (t, *J* = 3.3 Hz, 1H), 5.53 (d, *J* = 10.8 Hz, 0.5H), 5.39 (t, *J* = 3.3 Hz, 0.5H), 5.29 (d, *J* = 10.8 Hz, 1H), 4.61 (t, *J* = 12.3 Hz, 0.5H), 4.58 (t, *J* = 12.0 Hz, 1H), 4.23 (dt, *J* = 13.2, 3.3 Hz, 1H), 4.22 (m, 0.5H), 3.68 (m, 0.5H), 3.42 (dd, *J* = 10.8, 3.9 Hz, 0.5H), 3.30 (m, 2H), 2.65 (d, *J* = 4.8 Hz, 1H), 2.25 (m, 1.5H), 2.18 (s, 3H), 2.12 (s, 1.5H), 2.08 (m, 0.5H), 1.98 (m, 0.5H), 1.85 (m, 1H), 1.63-1.40 (m, 3H), 1.40-1.20 (m, 9H), 0.89 (m, 4.5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 170.0, 72.5, 70.3, 70.2, 68.0, 65.2, 65.1, 59.4, 58.3, 34.5, 34.3, 34.1, 33.5, 31.9, 31.7, 25.2, 25.0, 22.8, 22.7, 21.3, 21.3, 14.2, 14.2. IR (neat) ν = 3516, 3276, 2955, 2929, 2860, 1725, 1355, 1252, 1181, 1016, 934, 761. HRMS (ESI) *m*/*z* calculated for $C_{12}H_{23}NO_6S$ [M+NH_4^+] 327.1585, found 327.1590.



Compound 2.40. Enesulfamate **2.19** (45.0 mg, 0.155 mmol) was added to a 10 mL roundbottom flask and dissolved in 3.0 mL of dry THF. The solution was cooled to 0 °C, and N-bromosuccinimide (32.0 mg, 0.180 mmol, 1.2 equiv) was added in one portion with stirring. This mixture was allowed to stir at 0 °C for 10 min, at which point TLC (CAM stain) indicated consumption of the enesulfamate. The solution was cooled to -78 °C, and ethynylmagnesium

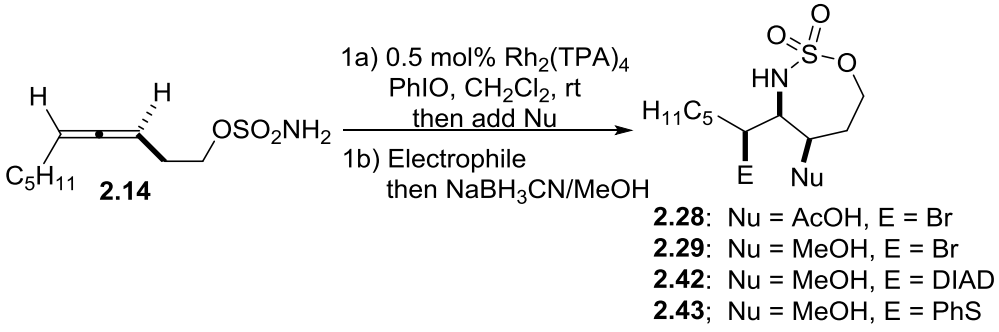
bromide (0.5 M in THF, 1.5 mL, 0.75 mmol, 5 equiv) was added dropwise over 3 min. The reaction was stirred at -78 °C for 1 h, at which point 2 mL of saturated NH_4Cl was added to quench the reaction. The organics were transferred to a separatory funnel and diluted with 20 mL of EtOAc. The organic layer was washed with saturated NH_4Cl (2 x 10 mL) and brine (2 x 10 mL), dried over Na_2SO_4, and concentrated by rotary evaporation. The crude material was purified by silica gel chromatography (20% EtOAc/hexanes to 40% EtOAc/hexanes, gradient) to give 36.1 mg (0.091 mmol, 59%) of the desired product as a single diastereomer. The product was a clear oil. The stereochemistry of the major diastereomer was assigned by analogy to **2.28a**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.75 (s, 1H), 5.42 (app dd, *J* = 4.2, 2.4 Hz, 1H), 4.61 (app t, *J* = 12.9 Hz, 1H), 4.24 (dt, *J* = 12.9, 3.3 Hz, 1H), 3.90 (dd, *J* = 11.1, 2.1 Hz, 1H), 2.86 (s, 1H), 2.82 (m, 1H), 2.19 (s, 3H), 2.12 (dt, *J* = 16.2, 3.6 Hz, 1H), 1.93 (m, 1H), 1.85-1.60 (m, 2H), 1.45-1.10 (m, 5H), 0.90 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.4, 80.6, 75.5, 72.2, 64.9, 62.0, 59.2, 33.5, 31.8, 30.9, 27.8, 22.6, 21.2, 14.1. IR (neat) ν = 3269, 2958, 2931, 2861, 2125, 1746, 1375, 1355, 1221, 1184, 1017, 740. HRMS (ESI) *m*/*z* calculated for $C_{14}H_{22}BrNO_5S$ [M+NH_4^+] 413.0741, found 413.0722.

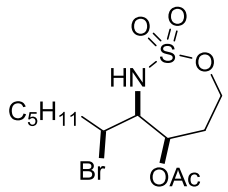


Compound 2.41. Enesulfamate **2.19** (99.1 mg, 0.341 mmol) was added to a 1.5 mL screw-top flask and dissolved in 0.5 mL of dry CH_2Cl_2. The solution was cooled to 0 °C, and N-bromosuccinimide (66.6 mg, 0.374 mmol, 1.1 equiv) was added in one portion with stirring. This mixture was allowed to stir at 0 °C for 15 min. After this time, trimethylsilyl cyanide (68.7 μL,

0.516 mmol, 1.5 equiv) was added via a 50 μL syringe (in two portions) at 0 ºC, followed by iodine (10.4 mg, 0.0409 mmol, 0.12 equiv). The flask was warmed to 30 ºC and stirred for 17 h. The reaction was then heated at reflux for 1 h to complete the consumption of the starting material. The solution was concentrated by rotary evaporation and purified by silica gel chromatography (30% EtOAc/hexanes to 50% EtOAc/hexanes, gradient) to give 75.6 mg of the major diastereomer and 23.3 mg of the minor diastereomer for an overall 73% yield and 3.3:1 *dr*. The stereochemistry of the major diastereomer was assigned by analogy to **2.28a**. Major diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.80 (bs, 1H), 5.60 (dd, *J* = 5.1, 2.1 Hz, 1H), 4.57 (ddd, *J* = 12.9, 11.4, 1.5 Hz, 1H), 4.36 (dt, *J* = 12.9, 3.6 Hz, 1H), 3.95 (dd, *J* = 10.5, 3.0 Hz, 1H), 2.76 (m, 1H), 2.38 (dddd, *J* = 16.5, 5.1, 3.9, 1.5 Hz, 1H), 2.20 (s, 3H), 2.03-1.85 (m, 2H), 1.80-1.65 (m, 1H), 1.50-1.20 (m, 6H), 0.91 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 113.6, 70.9, 65.6, 62.6, 55.8, 33.8, 31.9, 30.8, 27.6, 22.5, 21.0, 14.1. IR (neat) ν = 3244, 2961, 2928, 2874, 1768, 1360, 1183, 1007, 941, 787. Melting range: 169-170 °C. HRMS (ESI) *m/z* calculated for $C_{13}H_{21}BrN_2O_5S$ [M+NH_4^+] 414.0693, found 414.0691. Minor diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.84 (dd, *J* = 6.6, 2.4 Hz, 1H), 5.68 (bs, 1H), 4.55-4.30 (m, 3H), 2.45 (m, 2H), 2.23 (s, 3H), 1.98-1.76 (m, 1H), 1.80-1.62 (m, 1H), 1.50-1.25 (m, 6H), 0.91 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7, 115.3, 73.1, 65.9, 65.2, 53.6, 33.8, 32.0, 30.9, 27.2, 22.6, 21.0, 14.1.

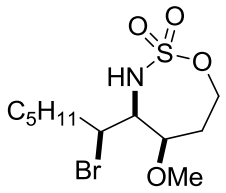
2.6.5. One-pot conversion of allenic sulfamates to stereotriads





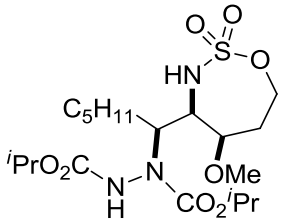
Compound 2.28. The allenic sulfamate **2.14** (102.7 mg, 0.441 mmol) and Rh_2TPA_4 (3.0 mg, 0.00215 mmol, 0.5 mol %) were added to a dry 25 mL round bottom flask. The mixture was kept under an atmosphere of nitrogen and charged with 4.4 mL of CH_2Cl_2. The resulting blue-green mixture was stirred for 5 min at rt, and then powdered 4 Å MS (100 mg) was added in one portion. After stirring for 5 min at rt, PhIO (113 mg, 0.515 mmol, 1.2 equiv) was added in one portion. After ten minutes, the initially green solution had turned yellow, so an additional 1.0 mg of Rh_2TPA_4 was added to ensure the presence of active catalyst. After a total reaction time of 90 min, TLC of the reaction mixture indicated consumption of the sulfamate (CAM stain). Glacial acetic acid (0.126 mL, 2.15 mmol, 5.0 equiv) was added in one portion at rt, and the reaction was fitted with a water-cooled reflux condenser and heated to reflux. After 3.5 h at reflux, the solution was concentrated by rotary evaporation (water bath temp ~40 °). An aliquot of 10 mL of THF was added to the roundbottom flask, and the solution was again concentrated by rotary evaporation. (Note: this second evaporation step is not strictly necessary, but helps to ensure completion of the ring-opening step.) Another 6 mL aliquot of THF was added to the flask, and the reaction was cooled to 0 °C under an atmosphere of N_2. N-Bromosuccinimide (115 mg, 0.644 mmol 1.5 equiv) was added in one portion, and the mixture was stirred at 0 °C. After 15 min, sodium cyanoborohydride (81 mg, 1.29 mmol, 3.0 equiv) dissolved in 3 mL dry MeOH was added via pipette, and the reaction as warmed to rt. The reaction was stirred at rt for 1 hr, at which point the reaction was concentrated by rotary evaporation. The mixture was diluted with 15 mL of EtOAc

and the solution transferred to a separatory funnel and washed with saturated NaHCO3 (2 x 10 mL) and brine (2 x 10 mL). The organic layer was dried over Na_2SO_4 and concentrated by rotary evaporation to give a crude product that was purified by silica gel chromatography (20% EtOAc/hexanes to 40% EtOAc/hexanes, gradient) to give 99.3 mg (0.267 mmol, 61%) of the desired product as a white solid. The product was obtained as a single diastereomer, although a crude ^{1}H NMR indicated a 20:1 mixture of diastereomers. Spectral data were identical to that listed above. Again, the relative stereochemistry was unambiguously assigned by obtaining an X-ray crystal structure of **2.28a**.



Compound 26. The allenic sulfamate **2.14** (105.0 mg, 0.451 mmol) and Rh_2TPA_4 (4.3 mg, 0.00309 mmol, 0.69 mol %) were added to a dry 25 mL roundbottom flask. The mixture was kept under an atmosphere of nitrogen and charged with 4.5 mL of CH_2Cl_2. No molecular sieves were used in the reaction. After stirring for 5 min at rt, PhIO (113 mg, 0.515 mmol, 1.2 equiv) was added in one portion, and the reaction was allowed to stir at rt. After 90 min, TLC of the reaction mixture indicated consumption of the sulfamate (CAM stain). Methanol (0.868 mL, 21.5 mmol, 50 equiv) was added via syringe, and the reaction was allowed to stir at rt for 3.5 h. After this time, the solution was concentrated by rotary evaporation, and 6 mL dry THF was added to the flask. The solution was cooled to -10 °C with a MeOH/ice bath, and N-bromosuccinimide (115 mg, 0.644 mmol 1.5 equiv) was added in one portion under N_2. After 10 min at -10 °C, sodium cyanoborohydride (81 mg, 1.29 mmol, 3.0 equiv) dissolved in 3 mL dry MeOH was added via

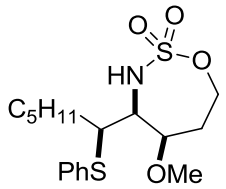
pipette, followed by glacial acetic acid (0.126 mL, 2.15 mmol, 5 equiv). The reaction was stirred at rt for 1 h, at which point the reaction was concentrated by rotary evaporation. An aliquot of 15 mL of EtOAc was added, and the solution was transferred to a separatory funnel and washed with saturated NaHCO3 (2 x 10 mL) and brine (2 x 10 mL). The organic layer was dried over Na_2SO_4 and concentrated by rotary evaporation to give a crude product that was purified by silica gel chromatography (20% EtOAc/hexanes to 40% EtOAc/hexanes, gradient) to give 89.8 mg (0.261 mmol, 58%) of the desired product as a white solid. The product was obtained as a 2.85:1 mixture of diastereomers, although a crude ^{1}H NMR indicated a 2.6:1 mixture of diastereomers. Spectral data for the major diastereomer was identical to that listed above. The stereochemistry of the major diastereomer was assigned by analogy to **2.28a**. Minor diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.03 (d, *J* = 10.5 Hz, 1H), 4.55 (ddd, *J* = 8.0, 6.0, 1.5 Hz, 1H), 4.41-4.30 (m, 2H), 3.45 (td, *J* = 9.0, 4.5 Hz, 1H), 3.43 (s ,3H), 3.32 (ddd, *J* = 11.0, 9.0, 2.0 Hz, 1H), 2.38 (dt, *J* = 15.0, 4.0 Hz, 1H), 2.12-1.88 (m, 3H), 1.58-1.22 (m, 6H), 0.90 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 80.5, 67.2, 59.7, 57.8, 57.2, 36.1, 32.6, 31.2, 27.3, 22.6, 14.1.



Compound 2.42. The allenic sulfamate **2.14** (307.5 mg, 1.32 mmol, 1.0 equiv.) and Rh_2TPA_4 (8.7 mg, 0.00625 mmol, 0.5 mol %) were added to a dry 50 mL round bottom flask. The mixture was kept under an atmosphere of nitrogen and charged with 13 mL of CH_2Cl_2. No molecular sieves were used in the reaction. After stirring for 5 min at rt, PhIO (312 mg, 1.42 mmol, 1.1 equiv) was added in one portion, and the reaction was allowed to stir at rt. After 75 min, TLC of the reaction

mixture indicated consumption of the sulfamate (CAM stain). Methanol (2.6 mL, 64.5 mmol, 50 equiv) was added via syringe, and the reaction was allowed to stir at rt for 1 h. After this time, the solution was filtered through a pad of celite with EtOAc and concentrated by rotary evaporation. The concentrate was transferred back to the original 50 mL flask by washing with EtOAc, followed by rotary evaporation. In a separate flask, a solution of copper (II) triflate (70.0 mg, 0.194 mmol, 0.15 equiv), N,N'-dimethylethylenediamine (22.8 μL, 0.213 mmol, 0.165 equiv), and diisopropylazodicarboxylate (304 μL, 1.55 mmol, 1.2 equiv) in 18 mL toluene was prepared according to the procedure listed above for the synthesis of compound **2.37**. This solution was rapidly added via pipette to the reaction concentrate. The flask was then fitted with a water-cooled reflux condenser, and the solution was stirred at 70 °C for 2 h. Subsequently, the reaction was cooled to rt, concentrated by rotary evaporation at 50 °C, and diluted with 18 mL of THF. A solution of $NaBH_3CN$ (244 mg, 3.87 mmol, 3.0 equiv) in 9 mL MeOH was added via pipette at rt, followed by glacial acetic acid (1.13 mL, 19.4 mmol, 15 equiv). The reaction was stirred at rt for 3.5 h, at which point the reaction was concentrated by rotary evaporation. EtOAc (30 mL) was added, and the solution was transferred to a separatory funnel and washed with saturated $NaHCO_3$ (2 x 30 mL) and brine (2 x 30 mL). The organic layer was dried over Na_2SO_4 and concentrated by rotary evaporation to give a crude product that was purified by silica gel chromatography (10% EtOAc/hexanes to 40% EtOAc/hexanes, gradient) to give 392.9 mg (0.841 mmol, 64%) of the desired product as a 4.6:1 mixture of diastereomers. The product was a white solid. The stereochemistry of the major diastereomer was assigned by analogy to **2.28a**. Major diastereomer: ^{1}H NMR (300 MHz, DMSO, 100 ºC) δ 7.50-7.10 (bs, 1H), 7.25 (d, 7.5 Hz, 1H), 4.97-4.77 (m, 2H), 4.40 (t, *J* = 12.0 Hz, 1H), 4.30-4.10 (bs, 1H), 4.13 (dt, *J* = 12.5, 3.0 Hz, 1H), 3.69 (t, *J* = 2.3 Hz, 1H), 3.39 (dd, *J* = 10.5, 8.0 Hz, 1H), 3.29 (s, 3H), 2.20 (dt, *J* = 16.0, 4.0 Hz, 1H), 1.94 (ddt, *J*

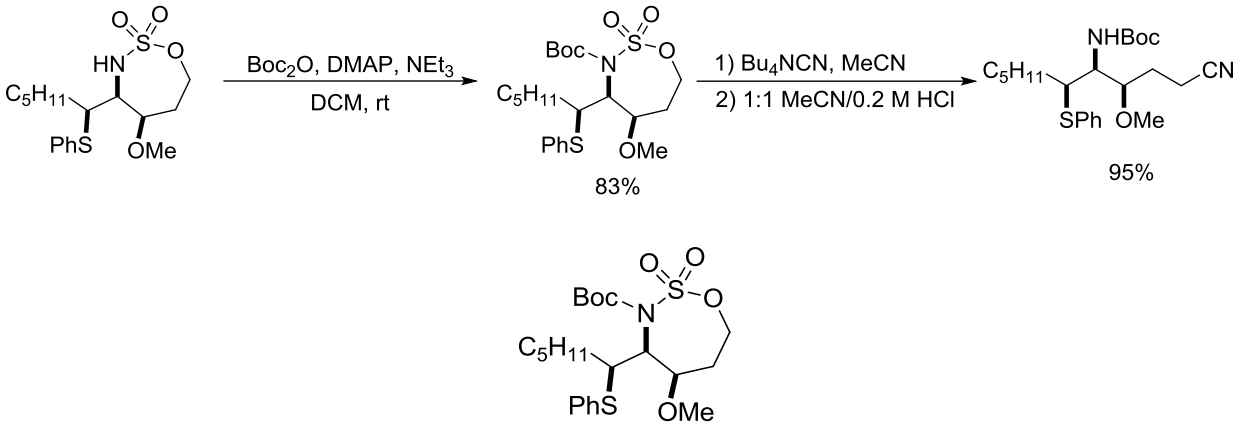
= 16.0, 11.5, 2.5 Hz, 1H), 1.60-1.50 (m, 2H), 1.49-1.35 (m, 2H), 1.35-1.15 (m, 16H), 0.89 (J = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, DMSO, 100 ºC) δ 155.3, 155.1, 75.0, 68.6, 68.0, 64.2, 58.2, 56.9, 55.4, 30.5, 29.9, 27.7, 24.8, 21.3, 21.2, 21.2, 21.1, 13.1. HRMS (ESI) *m*/*z* calculated for $C_{19}H_{37}N_3O_8S$ [M+NH_4^+] 485.2640, found 485.2637.



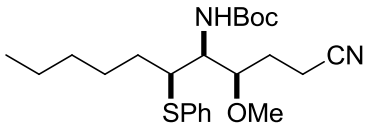
Compound 2.43. The allenic sulfamate **2.14** (49.8 mg, 0.214 mmol, 1.0 equiv) and Rh_2TPA_4 (1.5 mg, 0.00107 mmol, 0.5 mol %) were added to a dry 50 mL roundbottom flask. The mixture was kept under an atmosphere of nitrogen and charged with 2 mL of CH_2Cl_2. No molecular sieves were used in the reaction. After stirring for 5 min at rt, PhIO (55.0 mg, 0.250 mmol, 1.1 equiv) was added in one portion, and the reaction was allowed to stir at rt. After 100 min, TLC of the reaction mixture indicated consumption of the sulfamate (CAM stain). Methanol (0.43 mL, 10.8 mmol, 50 equiv) was added via syringe, and the reaction was allowed to stir at rt for 50 min. After this time, the solution was concentrated by rotary evaporation. In a separate flask, a solution of phenylsulfenyl chloride (prepared from N-chlorosuccinimide (86.4 mg, 0.645 mmol, 3.0 equiv) and thiophenol (66 μL, 0.645 mmol, 3.0 equiv) in 3 mL CH_2Cl_2) was prepared according to the procedure listed above for the synthesis of compound **2.38**. A portion of 2,6-di-*tert*-butyl-4-methylpyridine (44.1 mg, 0.215 mmol, 1.0 equiv) was added to the solution, and the solution was then rapidly transferred to the reaction concentrate *via* pipette. This mixture was stirred at rt for 30 min, at which point a solution of $NaBH_3CN$ (67.7 mg, 1.08 mmol, 5.0 equiv) in 1.5 mL MeOH was added *via* pipette at rt, followed by glacial acetic acid (0.190 mL, 3.2 mmol, 15 equiv). The

reaction was stirred at rt for 2 h, then concentrated by rotary evaporation. A portion of 30 mL of EtOAc was added, the solution transferred to a separatory funnel and washed with saturated $NaHCO_3$ (2 x 30 mL) and brine (2 x 30 mL). The organic layer was dried over Na_2SO_4 and concentrated by rotary evaporation to give a crude product that was purified by silica gel chromatography (10% EtOAc/hexanes to 40% EtOAc/hexanes, gradient) to give 59.5 mg (0.159 mmol, 74%) of the desired product as a 2.6:1 mixture of diastereomers. If desired, the diastereomers can be separated by using a CH_2Cl_2/hexanes solvent system (80% CH_2Cl_2/hexanes to 100% CH_2Cl_2, gradient). The stereochemistry of the major diastereomer was assigned by analogy to **2.28a**. Major diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (m, 2H), 7.31 (m, 2H), 7.23 (m, 1H), 5.53 (d, *J* = 11.0 Hz, 1H), 4.50 (t, *J* = 13.0 Hz, 1H), 4.08 (dt, *J* = 13.0, 3.0 Hz, 1H), 3.99 (app t, *J* = 2.5 Hz, 1H), 3.50 (dd, *J* = 11.0, 5.5 Hz, 1H), 3.32 (m, 1H), 3.31 (s, 3H), 2.12 (dt, *J* = 15.5, 3.5 Hz, 1H), 1.81 (ddt, *J* = 15.5, 12.5, 3.0 Hz, 1H), 1.74 (m, 1H), 1.68-1.58 (m, 1H), 1.50-1.42 (m, 1H), 1.40-1.22 (m, 5H), 0.90 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.7, 131.3, 129.4, 127.3, 74.0, 64.5, 57.8, 56.3, 52.6, 31.7, 31.2, 30.0, 27.4, 22.6, 14.2. IR (neat) ν = 3322, 2955, 2927, 2855, 1350, 1176, 1087, 934, 759, 691. Melting range: 49-51 °C. HRMS (ESI) *m*/*z* calculated for $C_{17}H_{27}NO_4S_2$ [M+Na^+] 396.1274, found 396.1256. Minor diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (m, 2H), 7.30 (m, 2H), 7.22 (m, 1H), 5.24 (d, *J* = 11.0 Hz, 1H), 4.32 (m, 2H), 3.72 (ddd, *J* = 8.5, 6.5, 2.0 Hz, 1H), 3.51 (ddd, *J* = 11.0, 9.5, 1.5 Hz, 1H), 3.27 (td, *J* = 9.0, 4.5 Hz, 1H), 2.66 (s, 3H), 2.27 (m, 1H), 1.90-1.70 (m, 3H), 1.68-1.52 (m, 2H), 1.38-1.30 (m, 4H), 0.90 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.8, 131.8, 129.3, 127.3, 78.7, 67.0, 60.7, 55.7, 50.9, 33.7, 32.5, 31.7, 27.2, 22.7, 14.2.

2.6.6. Removal of the sulfamate from a stereotriad product.

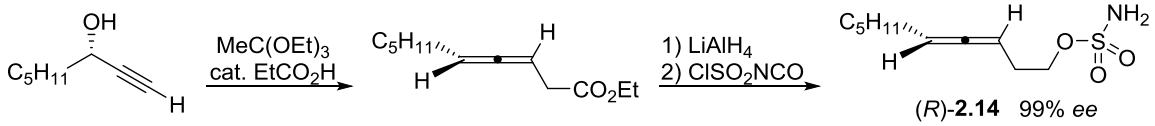


Compound 2.44. This reaction can be run without particular care for oxygen-free or water-free conditions. Stereotriad product **2.43** (75.0 mg, 0.201 mmol, 1.0 equiv) was added to a 10 mL roundbottom flask and dissolved in 3 mL CH_2Cl_2. Di-*tert*-butyl dicarbonate (52.6 mg, 0.241 mmol, 1.2 equiv), triethylamine (40 µL, 0.288 mmol, 1.4 equiv), and dimethylaminopyridine (4.0 mg, 0.033 mmol, 0.16 equiv) were added sequentially to the solution at rt. The reaction was not complete by TLC within 2 h, so an additional 13.5 mg di-*tert*-butyl dicarbonate was added. Within 15 min, the reaction was complete by TLC. The reaction was diluted with 20 mL of CH_2Cl_2, and washed with saturated NH_4Cl (2 x 20 mL) and brine (2 x 20 mL). The organic layer was dried over Na_2SO_4 and concentrated by rotary evaporation. The resulting crude oil was purified *via* silica gel chromatography (10 % EtOAc/hexanes to 20% EtOAc/hexanes, gradient) to give 79.0 mg (0.167 mmol, 83%) of the desired product. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (m, 2H), 7.28 (m, 3H), 4.77 (d, *J* = 11.0 Hz, 1H), 4.54 (m, 2H), 3.79 (ddd, *J* = 11.0, 8.5, 3.0 Hz, 1H), 3.71 (dt, *J* = 11.0, 3.0 Hz, 1H), 3.36 (s, 3H), 2.25 (m, 1H), 2.03 (m, 1H), 1.78 (m, 1H), 1.65-15.0 (m, 11H), 1.40-1.10 (m, 5H), 0.86 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.9, 134.7, 133.6, 128.9, 127.9, 85.5, 82.2, 69.8, 61.1, 57.8, 50.9, 31.8, 30.1, 30.0, 28.1, 25.7, 22.8, 14.2. IR (neat) ν = 2956, 2931, 2860, 1729, 1392, 1369, 1299, 1148, 1097, 750. HRMS (ESI) *m*/*z* calculated for $C_{22}H_{35}NO_6S_2$ [M+Na^+] 496.1799, found 496.1778.



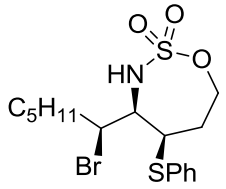
Compound 2.45. Compound **2.44** (19.5 mg, 0.0411 mmol, 1.0 equiv) was added to a 10 mL roundbottom flask and dissolved in 1 mL MeCN. Tetrabutylammonium cyanide (22.6 mg, 0.084 mmol, 2.0 equiv) was added to the solution, and the mixture was stirred at rt. After 1 h, the reaction was complete by TLC and 1 mL of 0.2M aqueous HCl was added to the reaction. The reaction was stirred at rt for 30 min, and then diluted with EtOAc. The biphasic mixture was transferred to a separatory funnel, further diluted with 20 mL of EtOAc, and the organic layer washed with saturated $NaHCO_3$ (2 x 20 mL) and brine (2 x 20 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The resulting crude oil was purified *via* silica gel chromatography (10 % EtOAc/hexanes, isocratic) to give 16.4 mg (0.0390 mmol, 95%) of desired product as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (m, 2H), 7.31 (m, 2H), 7.22 (m, 1H), 5.02 (d, *J* = 9.6 Hz, 1H), 3.75 (ddd, *J* = 8.1, 5.1, 2.7 Hz, 1H), 3.63 (td, *J* = 6.3, 2.7 Hz, 1H), 3.39 (s, 3H), 3.34 (m, 1H), 2.40-2.15 (m, 2H), 1.90-1.68 (m, 3H), 1.50-1.20 (m, 16H), 0.89 (t, *J* = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.9, 135.4, 131.2, 129.4, 127.0, 119.6, 79.8, 78.0, 58.1, 54.9, 51.3, 31.8, 31.2, 28.6, 27.3, 27.2, 22.7, 14.2, 13.4. IR (neat) ν = 3451, 2955, 2933, 2858, 1711, 1495, 1160, 1099, 1064, 743, 693. HRMS (ESI) *m*/*z* calculated for $C_{23}H_{36}N_2O_3S$ [M+NH_4^+] 438.2785, found 438.2785.

2.6.7. Reaction of an enantioenriched homoallenic sulfamate



(*R*)-**2.14** 99% *ee*

Compound (*R*)-2.14. Enantioenriched (>98% *ee*) propargyl alcohol was purchased from Alfa Aesar. It was converted to the homoallenic sulfamate in three steps, according to previously published procedures[3]. The *ee* of the homoallenic sulfamate was determined by chiral high-pressure liquid chromatography (HPLC) analysis. An AD-H column (4.6 μm diameter x 258 mm) at a temperature of 40 ºC was employed, using 4% isopropanol in hexanes (isocratic) as the eluent and a flow rate of 0.6 mL/min. The enantiomers were detected at 49.9 and 52.2 minutes, with observation at both 215 nm and 225 nm. Optical rotation: $[\alpha]_D^{22.4}$ +53.6 (*c* 3.08, CH_2Cl_2, 99% *ee*).



Compound 2.44. Enantioenriched allenic sulfamate **(*R*)-2.14** (31.5 mg, 0.135 mmol) and Rh_2TPA_4 (0.9 mg, 0.0006 mmol, 0.5 mol %) were added to a dry 10 mL roundbottom flask. The mixture was kept under an atmosphere of nitrogen and charged with 1.3 mL of CH_2Cl_2. No molecular sieves were used in the reaction. After stirring for 5 min at rt, PhIO (32.7 mg, 0.149 mmol, 1.1 equiv) was added in one portion, and the reaction was allowed to stir at rt. After 70 min, TLC of the reaction mixture indicated consumption of the sulfamate (CAM stain). Thiophenol (16.5 μL, 0.162 mmol, 1.2 equiv) was added via syringe, and the reaction was allowed to stir at rt for 1.5 h. After this time, TLC indicated incomplete consumption of the methylene aziridine (CAM stain), so an additional thiophenol (2.0 μL, 0.020 mmol, 0.15 equiv) was added and the mixture stirred for an additional 30 min. The reaction was then concentrated by rotary evaporation and 2 mL THF was added. The solution was cooled in an ice bath and N-bromosuccinimide (36.0 mg, 0.202 mmol, 1.5 equiv) was added in one portion under N_2. After

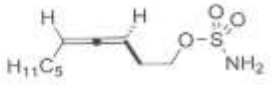
10 min, sodium cyanoborohydride (17.0 mg, 0.270 mmol, 2.0 equiv) dissolved in 1 mL MeOH was added via pipette, followed by glacial acetic acid (79 μL, 1.35 mmol, 10 equiv). The reaction was stirred at rt for 2 h, concentrated by rotary evaporation, transferred to a separatory funnel with 20 mL of EtOAc, and washed with saturated $NaHCO_3$ (2 x 10 mL) and brine (2 x 10 mL). The organic layer was dried over Na_2SO_4 and concentrated by rotary evaporation to give a crude product that was purified by silica gel chromatography (10% EtOAc/hexanes, isocratic) to give 32.9 mg of the major diastereomer and 2.1 mg of minor diastereomer for a combined 61% yield and 15:1 *dr*. Spectral data for the major diastereomer was identical to that listed above. Optical rotation: $[\alpha]_D^{22.4}$ -5.5 (*c* 1.3, CH_2Cl_2, 99% *ee*). The stereochemistry of the major diastereomer was assigned by analogy to **2.28a**. The enantiomeric excess of the major diastereomer was determined by chiral HPLC analysis. An AD-H column (4.6 μm diameter x 258 mm) at a temperature of 40 ºC was employed, using 10% isopropanol in hexanes (isocratic) as the eluent and a flow rate of 0.9 mL/min. The enantiomers were detected at 22.6 and 26.5 minutes, observing at both 215 nm and 225 nm.

2.6.8. HPLC traces of racemic and enantioenriched 2.14 and 2.44

==== Shimadzu LCsolution Analysis Report ====

C:\LabSolutions\Data\Chris\racemicsulfamate.lcd

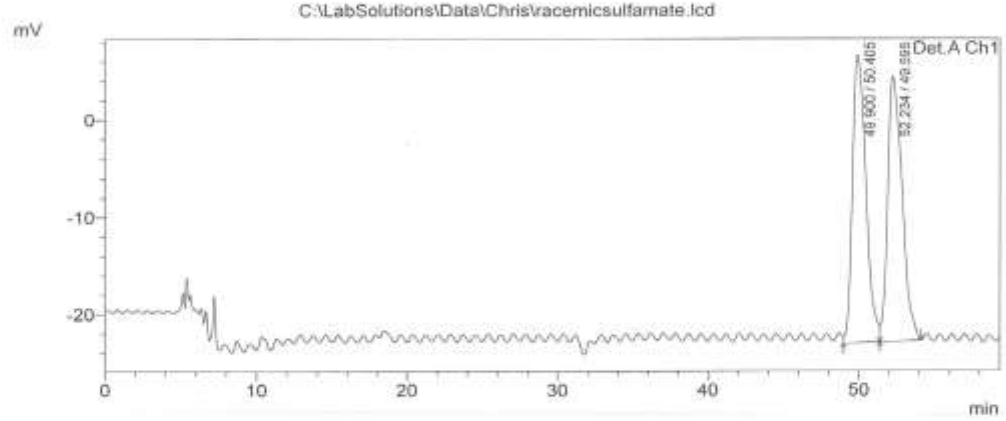
Acquired by	: Admin
Sample Name	: racsulf2
Sample ID	: csaracsulfam
Tray#	: 1
Vail #	: 62
Injection Volume	: 1 uL
Data File Name	: racemicsulfamate.lcd
Method File Name	: 96-4 method 0.6 flow 215 and 225 nm 90 min.lcm
Batch File Name	: batch 1.lcb
Report File Name	: Default.lcr
Data Acquired	: 4/30/2012 12:48:54 PM
Data Processed	: 5/17/2012 5:06:24 PM

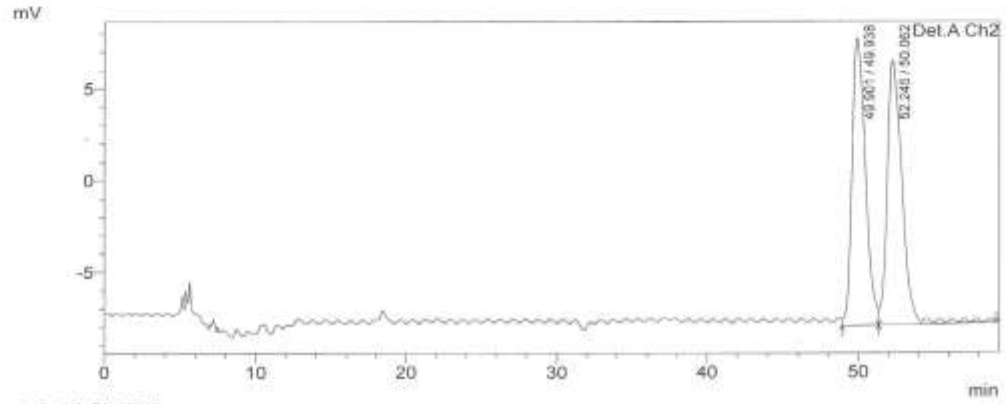


(racemic)

<Chromatogram>

C:\LabSolutions\Data\Chris\racemicsulfamate.lcd



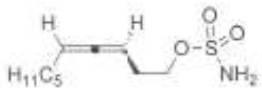


1 Det.A Ch1/215nm
2 Det.A Ch2/225nm

==== Shimadzu LCsolution Analysis Report ====

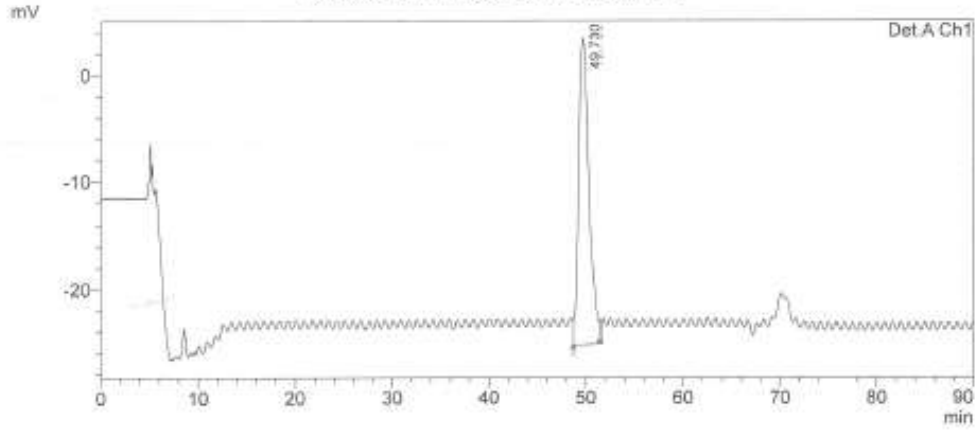
C:\LabSolutions\Data\Chris\eesulfamate2.lcd

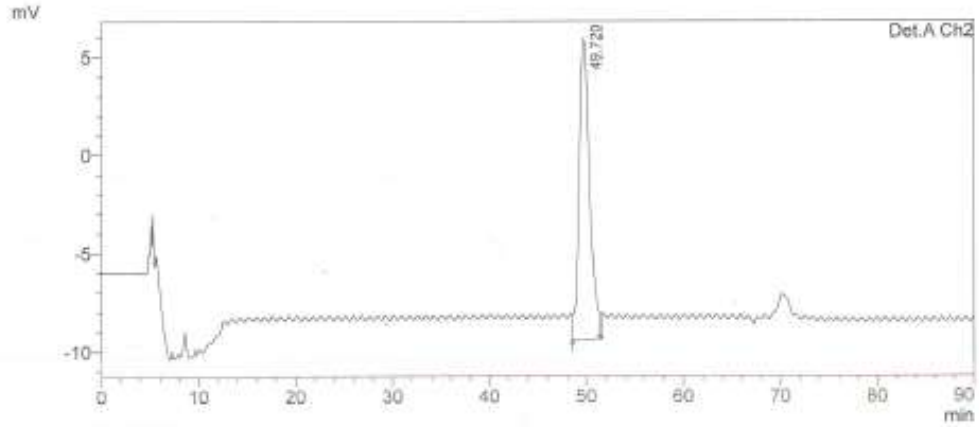
Acquired by	: Admin
Sample Name	: ee sulfamate2
Sample ID	: csa2166.pdt2
Tray#	: 1
Vail #	: 65
Injection Volume	: 1 uL
Data File Name	: eesulfamate2.lcd
Method File Name	: 96-4 method 0.6 flow 215 and 225 nm 90 min.lcm
Batch File Name	: Nov232009.lcb
Report File Name	: Default.lcr
Data Acquired	: 4/30/2012 5:42:07 PM
Data Processed	: 4/30/2012 7:12:10 PM



<Chromatogram>

C:\LabSolutions\Data\Chris\eesulfamate2.lcd



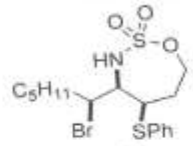


1 Det.A Ch1/215nm
2 Det.A Ch2/225nm

==== Shimadzu LCsolution Analysis Report ====

C:\LabSolutions\Data\Chris\CSA2031.PDT.lcd

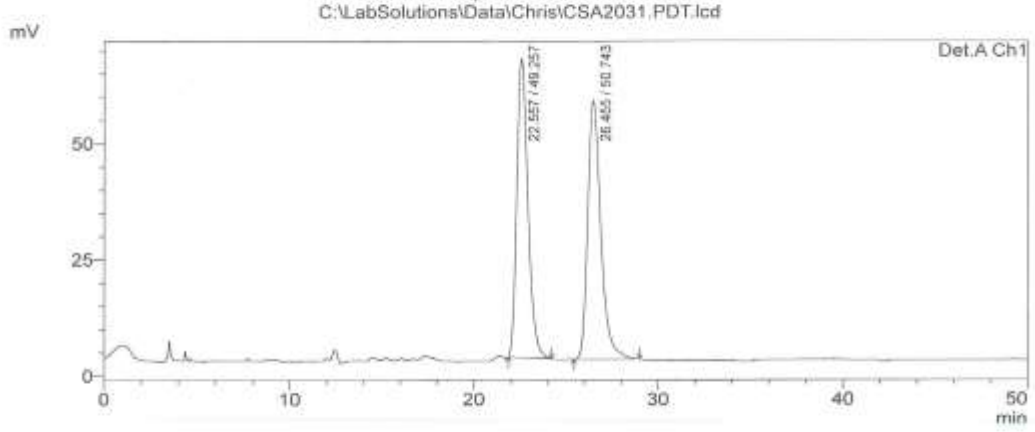
Acquired by	: Admin
Sample Name	: Br/N/SPh triad
Sample ID	:
Tray#	: 1
Vail #	: 62
Injection Volume	: 1 uL
Data File Name	: CSA2031.PDT.lcd
Method File Name	: 90-10 method 0.9 flow 215 and 225 nm 50 min.lcm
Batch File Name	: batch 1.lcb
Report File Name	: Default.lcr
Data Acquired	: 4/24/2012 11:20:32 AM
Data Processed	: 4/30/2012 11:32:29 AM

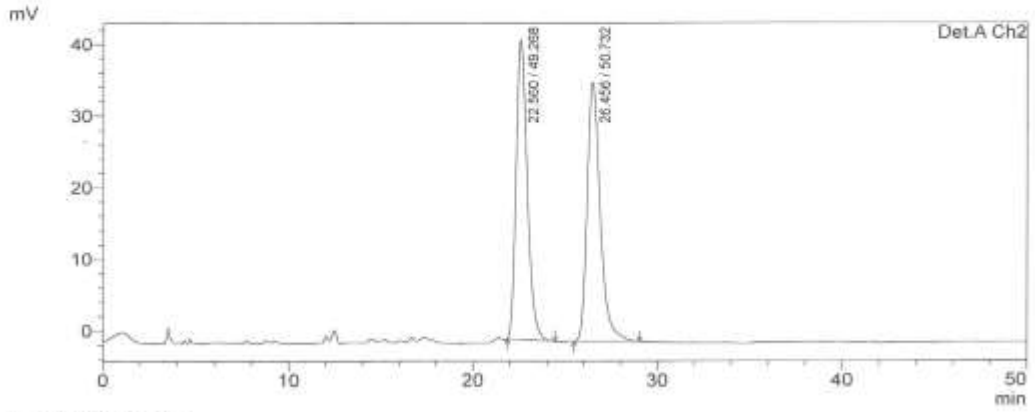


(racemic)

<Chromatogram>

C:\LabSolutions\Data\Chris\CSA2031.PDT.lcd



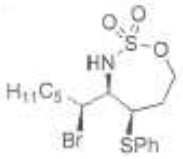


1 Det.A Ch1/215nm
2 Det.A Ch2/225nm

==== Shimadzu LCsolution Analysis Report ====

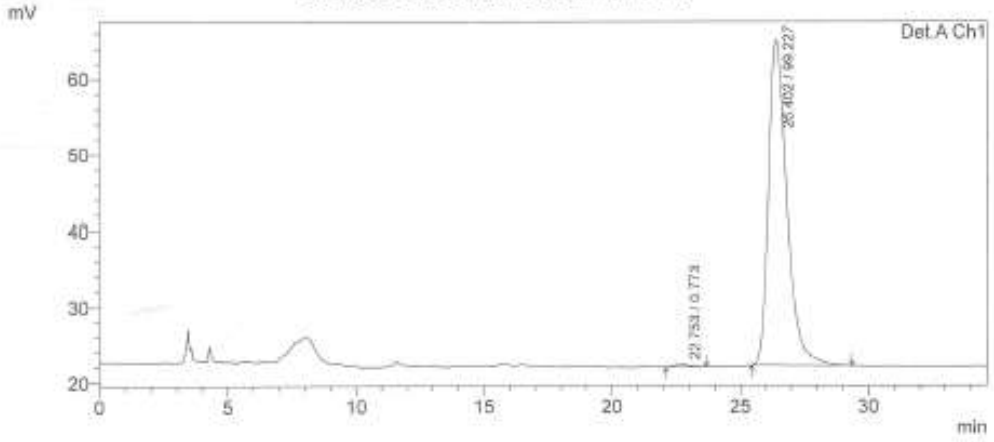
C:\LabSolutions\Data\Chris\CSA2176.PDT.lcd

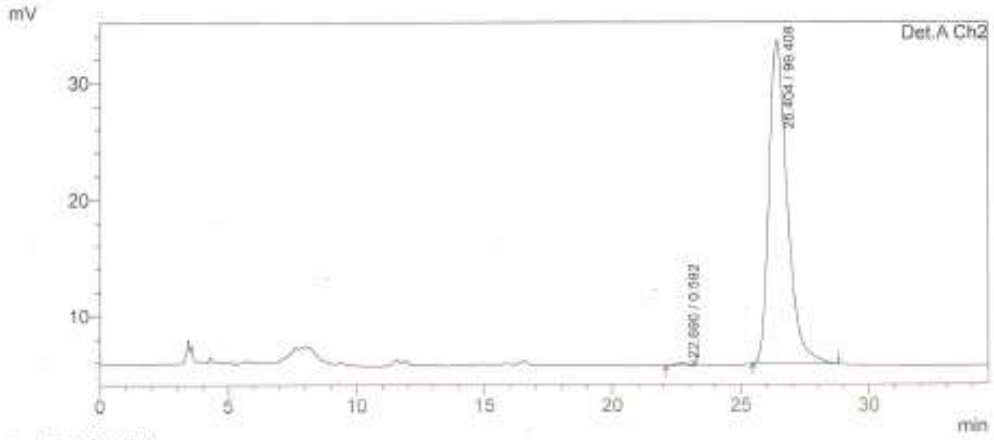
Acquired by	: Admin
Sample Name	: eetriad1
Sample ID	: csa2176.pdt
Tray#	: 1
Vail #	: 64
Injection Volume	: 1 uL
Data File Name	: CSA2176.PDT.lcd
Method File Name	: 90-10 method 0.9 flow 215 and 225 nm 50 min.lcm
Batch File Name	: batch 1.lcb
Report File Name	: Default.lcr
Data Acquired	: 4/27/2012 4:11:02 PM
Data Processed	: 4/30/2012 11:35:58 AM



<Chromatogram>

C:\LabSolutions\Data\Chris\CSA2176.PDT.lcd





1 Det.A Ch1/215nm
2 Det.A Ch2/225nm

2.6.9. References for experimental section

1. Armarego, W.L.F.; Chai, C.L.L. *Purification of Laboratory Chemicals* 6th ed., Elsevier: Burlington, MA, 2009.

2. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

3. Boralsky, L. A.; Marston, D.; Grigg, R. D.; Hershberger, J. C.; Schomaker, J. M. *Org. Lett.* **2011**, *13*, 1924-1927.

4. Espino, C. G.; Wehn, P. M.; Chow, J.; Du Bois, J. *J. Am. Chem. Soc.* **2001**, *123*, 6935-6936.

Chapter 3

Stereochemical Diversity in the Conversion of Homoallenic Sulfamates to 2-Amino-1,3-Diols

This chapter is adapted with permission from sections published in:

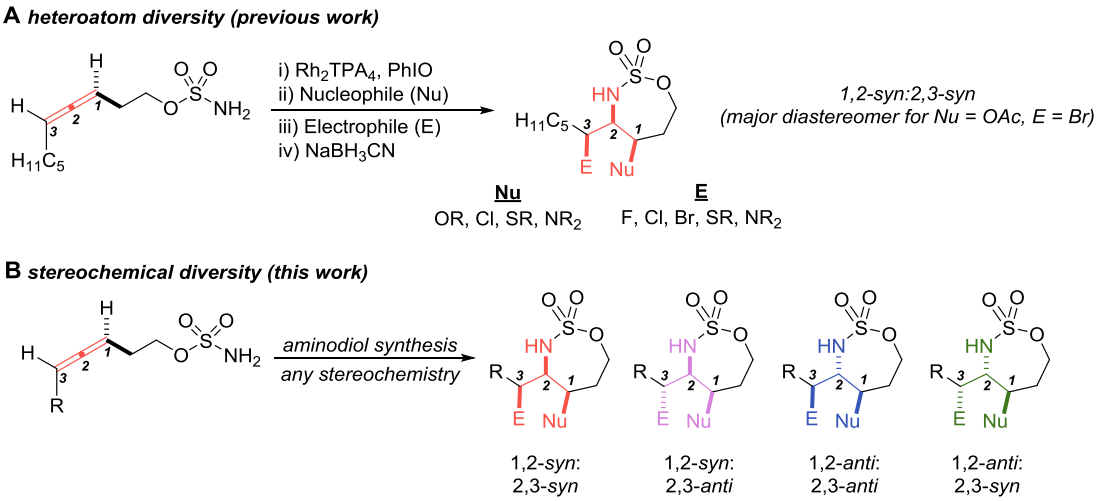
Adams, C. S.; Grigg, R. D.; Schomaker, J. M.

Chem. Sci. **2014**, *5*, 3046-3056.

3.1. Introduction

In the work described in Chapter 2, a variety of X/N/Y stereotriads (X, Y = nitrogen, oxygen, sulfur, and halogens) were shown to be accessible from a single homoallenic sulfamate *via* an intramolecular aziridination cascade. While this method was powerful in terms of the scope of heteroatoms that could be introduced into the amine products (Scheme 3.1, **A**), the stereochemical outcome was often limited to a single diastereomer, commonly the 1,2-*syn*:2,3-*syn* isomer.[1] We attributed this to an inherent substrate control of the reaction, a feature that could potentially limit the utility of the oxidative amination of allenes. Thus, we wanted to explore the possibility of overriding this substrate control to generate amine triads with both *heteroatom* and *stereochemical* diversity from a single allene substrate (Scheme 3.1, **B**).[2] The successful realization of this goal would yield useful methods for the construction of complex amine targets as well as libraries of both functional and stereochemical analogues.

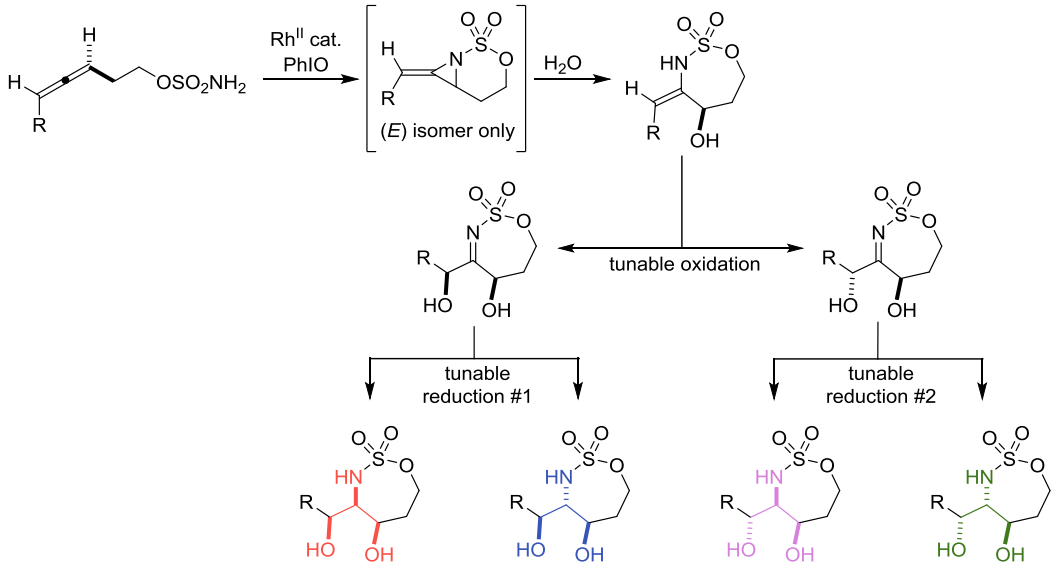
Scheme 3.1. Strategies for generating aminated stereotriads.



We decided to focus on the synthesis of 2-amino-1,3-diols, as these motifs commonly occur in aminosugars and other bioactive natural products but are not easily prepared *via* the aminohydroxylation of allylic alcohols due to issues with regio- and stereocontrol.[3] In order to

access all four possible diastereomers of this motif, we identified three key challenges in the reaction sequence shown in Scheme 3.2.[4,5] First, our previous studies had shown that the Rh-catalyzed aziridination step yielded only (*E*) bicyclic methylene aziridines; the (*Z*) isomer could not be obtained directly.[1] Second, irrespective of whether an (*E*) or (*Z*)-enesulfamate was employed as the substrate, the facial selectivity in its addition to a suitable electrophilic oxygen source must be controlled (Scheme 3.2, "tunable oxidation"). This necessitates an understanding of how the structure of the enesulfamate and identity of the electrophile influence the stereocontrol of the oxidation. Finally, the stereoselectivity of the reduction of the resulting *syn* and *anti* imines must be tunable, a task made difficult by the presence of two stereodefined alcohols flanking the imine. While the stereocontrolled reduction of cyclic imines with two adjacent oxygen-containing groups contained in the same ring are known, examples of high *dr* in the reduction of more conformationally flexible 1,3-dioxo-2-imines are rare.[6,7]

Scheme 3.2. Challenges in stereodivergent triad synthesis.

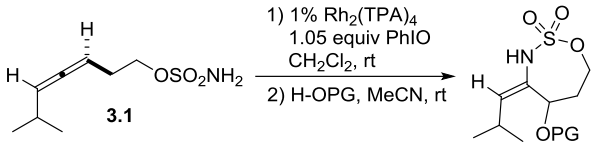


3.2. Results and Discussion

3.2.1. Optimization of the addition of (*E*)-enesulfamates to DMDO.

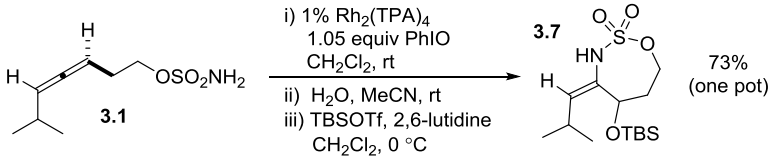
The first challenge in developing the stereodivergent 2-amino-1,3-diol synthesis was to understand what factors control the *dr* in the addition of an enesulfamate to a given electrophile. These attributes include (but are not limited to) the nature of the group at C1, the conformation of the exocyclic alkene (*E vs. Z*) and the identity of the electrophile. To begin, a small sample of O-functionalized enesulfamates were prepared in order to determine the impact that the O-substituent had on the diastereoselectivity of enesulfamate oxidation. Substrates **3.2**-**3.6** were synthesized by the straightforward intramolecular aziridination and ring-opening of *iso*propyl-substituted sulfamate **3.1** (Table 3.1). To install a TBS-protected oxygen, the methylene aziridine was first ring-opened with H_2O, then functionalized with TBSOTf (Scheme 3.3).

Table 3.1. Synthesis of oxygenated enesulfamates by aziridination/ring-opening.



entry	H-OPG	yield	product
1	H_2O	79%	**3.2**
2	AcOH	72%	**3.3**
3	4-MeOC$_6$H$_4$CO$_2$H	68%	**3.4**
4	9-phenCO$_2$H	68%	**3.5**
5	MeOH	79%	**3.6**

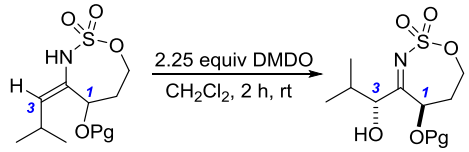
Scheme 3.3. Synthesis of –OTBS substituted enesulfamate **3.7**.



The oxidation of enesulfamates **3.2-3.7** was then investigated. DMDO was chosen as the oxidant due to its high reactivity and mild reaction conditions that would minimize epimerization of the resulting α-hydroxyimine.[8] Of the substrates tested, only the bulky, TBS-susbtitued enesulfamate **3.7** reacted with good selectivity. The major diastereomer of this oxidation was

identified as the 1,3-*anti* imine by X-ray analysis.[9] This result was surprising, given that N-bromosuccinimide (NBS) afforded the opposite, 1,3-*syn* imine in previous work.[1] This differential outcome will be discussed in section 3.2.3.

Table 3.2. Effect of allylic substituent on enesulfamate oxidation *dr*.



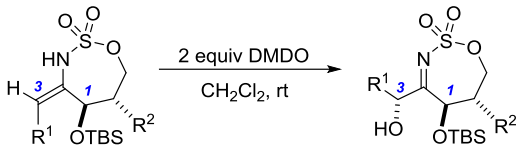
entry	OPg =	substrate	*anti/syn*[a]	product
1	OH	**3.2**	2.5 : 1	**3.8**
2	OAc	**3.3**	1 : 1	**3.9**
3	4-MeOC$_6$H$_4$CO$_2$	**3.4**	2.7 : 1	**3.10**
4	9-phenCO$_2$	**3.5**	2.5 : 1	**3.11**
5	OMe	**3.6**	4.0 : 1	**3.12**
6	OTBS	**3.7**	> 9 : 1	**3.13**

[a] Determined by ^{1}H NMR of the crude imine. The 1,3-*anti* diastereomer is assumed to be the major product in all cases, but was only experimentally determined for **3.13a**.

3.2.2. Synthesis of 1,2-*syn*:2,3-*anti* aminodiols from (*E*)-enesulfamates

The scope of the DMDO oxidation was explored for a series of (*E*)-enesulfamates (Table 3.3). Substitution of the ^{i}Pr group of **3.7** with the *n*-pentyl chain of **3.14** (entry 2) resulted in a lowered *dr* of 3:1 for imine **3.20** when the reaction was carried out at rt. Lowering the temperature to -20 °C delivered a more satisfactory 5:1 *dr* (entry 3). Placement of an *anti*-Me group on the carbon adjacent to the OTBS in **3.15** resulted in an improved *dr* of 9:1 (entry 4), while a phenethyl-substituted enesulfamate **3.16** (entry 5) and the PhMe$_2$Si-substituted **3.17** (entry 6) gave lower *dr*. Surprisingly, placement of a Ph group in conjugation with the exocyclic double bond of **3.18** reversed the selectivity, giving a 10:1 *dr* in favor of the *syn* diastereomer **3.24** (entry 7).

Table 3.3. Scope of DMDO oxidation for (*E*)-enesulfamates.

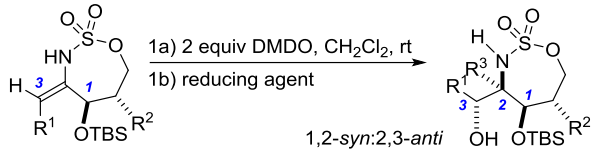


entry	R^1	R^2	substrate	temp (°C)	*anti:syn*	product
1	^{i}Pr	H	**3.7**	25	> 9 : 1	**3.19**
2	C_5H_{11}	H	**3.14**	25	3 : 1	**3.20**
3	C_5H_{11}	H	**3.14**	-20	5 : 1	**3.20**
4	C_5H_{11}	Me	**3.15**	25	> 9 : 1	**3.21**
5	CH_2CH_2Ph	H	**3.16**	40	3 : 1	**3.22**
6	$CH_2CH_2SiMe_2Ph$	H	**3.17**	-20	3.5 : 1	**3.23**
7	Ph	H	**3.18**	0	1 : 10	**3.24**

[a] *anti:syn* ratios determined by crude ^{1}H NMR of the imine (not isolated due to its sensitivity to hydrolysis)

With a method in hand to form the 1,3-*anti* imines in good *dr*, hydride sources were investigated to set the C2 stereocenter (Table 3.4). An *a priori* prediction of the reduction stereochemistry was made difficult by the unknown influences exerted by the two adjacent oxygen-containing groups. The bulky C1-OTBS group could control reduction by shielding one face of the imine from reduction, while the more conformationally flexible C3 stereocenter might control reduction *via* Felkin-Anh effects. Ultimately, it was found that the use of $Zn(BH_4)_2$ in non-coordinating solvents (CH_2Cl_2 or 1,2-DCE) provided the highest *dr*'s across a broad series of substrates. The major diastereomer contained a 1,2-*syn*:2,3-*anti* configuration as determined by X-ray analysis, with the *anti* relationship between the C2-amine and C3-OH suggestive of a chelation-controlled Felkin-Anh addition of hydride (see section 3.2.6 for a stereochemical model). As seen in Table 3.3, the *dr* of the stereotriad products closely matched that of the imine precursors, indicating a highly selective reduction. Additional versatility was provided by employing Grignard reagents in place of a hydride reductant to yield the triad products **3.26**-**3.28** (entries 2-4). The pure amines could be easily obtained by column chromatography or recrystallization.

Table 3.4. Synthesis of 1,2-*syn*:2,3-*anti* aminodiols.



entry[a,b]	R^1	R^2	R^3	substrate	yield	*dr*[c]	product
1	^{i}Pr	H	H	**3.7**	80%	> 9 : 1	**3.25**
2	^{i}Pr	H	Ph	**3.7**	84%	> 9 : 1	**3.26**
3	^{i}Pr	H	$CH{=}CH_2$	**3.7**	83%	8.2 : 1	**3.27**
4	^{i}Pr	H	C≡CH	**3.7**	81%	7.4 : 1	**3.28**
5	C_5H_{11}	H	H	**3.14**	82%	5 : 1	**3.29**
6	C_5H_{11}	Me	H	**3.15**	74%	> 9 : 1	**3.30**
7	CH_2CH_2Ph	H	H	**3.16**	80%	3.0 : 1	**3.31**
8	$CH_2CH_2SiMe_2Ph$	H	H	**3.17**	72%	3.5 : 1	**3.32**

[a] Entries 1, 5-8: 1 equiv $Zn(BH_4)_2$, $Cl(CH_2)_2Cl$, 0 °C *or* CH_2Cl_2, -78 °C. [b] Entries 2-4: 3.0 equiv Grignard reagent. [c] *anti:syn* ratios determined by ^{1}H NMR of the crude product.

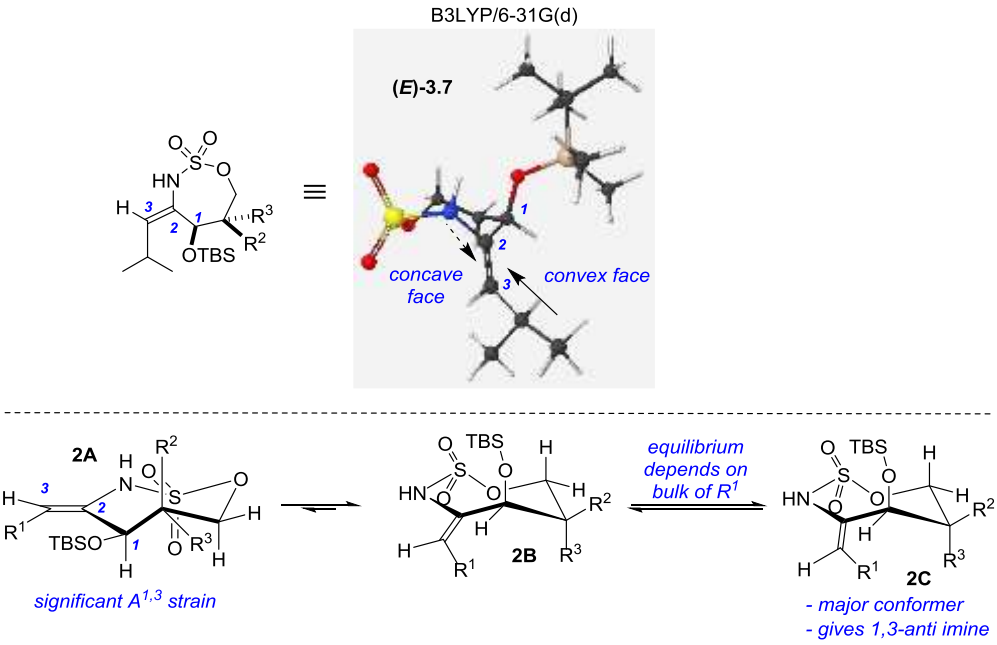
3.2.3. Stereochemical models for rationalizing selectivity of DMDO oxidations

These initial studies exploring the reaction of (*E*)-enesulfamates with DMDO provided an opportunity to establish design principles for achieving successful stereodivergent oxidative allene amination. In particular, the challenges in controlling the conformations of seven-membered heterocyclic rings,[10] as compared to well-studied six-membered systems, prompted us to undertake a more detailed analysis to understand why the specific nature of the electrophile and the substrate play such important roles in controlling the *dr* of the imine formation.

Figure 3.1 depicts the calculated optimized geometry for the (*E*)-enesulfamate **3.7** containing an OTBS group at C1.[#] Comparison of two possible chair-like conformations, **2A** and **2B**, indicates relief of $A^{1,3}$ strain in **A** may dispose the equilibrium towards conformer **B**, despite the fact this places the OTBS group in a pseudoaxial position. This is reasonable, given that alkylidenecyclohexanes have been known to adopt conformations where an oxygen-containing group prefers to reside in an axial position.[11,12] In addition, the bulky OTBS group of **3.23** may promote an additional perturbation of the exocyclic double bond to a pseudoaxial position to yield **2C**. This presents the electrophile with a choice between approaching the double bond from either

the convex or concave face, with reaction at the more accessible convex face occurring to yield the 1,3-*anti* stereochemistry.

Figure 3.1. Stereochemical model for DMDO oxidation of –OTBS (E)-enesulfamates.

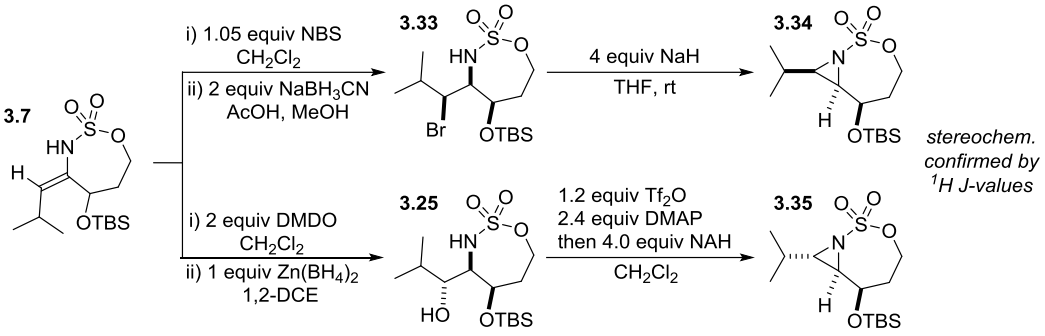


Conformers **2A-2C** also help to rationalize the impact of the size of the R^1 group on the *dr* of the DMDO oxidation. Substrates with bulkier R^1 groups (i.e., ^{i}Pr-substituted **3.7**) experience enhanced $A^{1,3}$ strain in conformer **2A**, shifting the equilibrium further towards **2C** and improving the selectivity in the approach of the DMDO from the *exo* face of **2C**. However, the complete inversion of selectivity observed in Ph-substituted **3.18** is less easily rationalized by this model. Conjugation of the phenyl group with the enesulfamate double bond may lead to a perturbation of the ring away from conformer **2C**. Alternatively, rapid epimerization of the α-Ph C3 stereocenter in imine **3.24**, while not confirmed experimentally, could favour the 1,3-*syn* imine.

While invoking **2C** as the preferred conformer explains the stereochemical outcome in the addition of **3.7** and other enesulfamates to DMDO, it does not explain the 1,3-*syn* geometry observed in our previous studies employing NBS as the electrophile.[1] To confirm that the

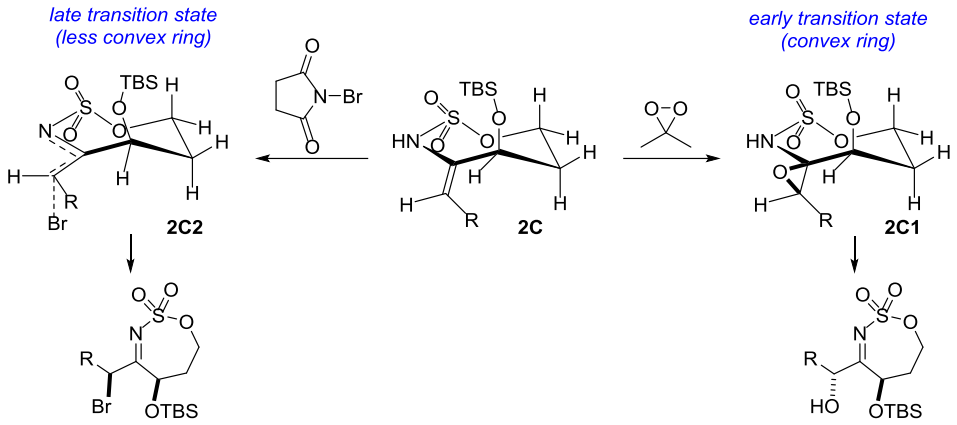
differential outcome resulted from the nature of the electrophile and not the C1-substituent (the NBS result was obtained with an –OAc group instead of a –OTBS group), the experiment in Scheme 3.4 was carried out. Enesulfamate **3.7** was reacted with both NBS and DMDO, then reduced with either $NaBH_3CN$ or $Zn(BH_4)_2$ (as in Table 3.4) to access the stereotriads **3.33** and **3.25** bearing the same configuration at C2. The –Br and –OH substituents were then displaced in S_N2 fashion to arrive at the diasteromeric aziridines **3.34** and **3.35**, thus demonstrating that NBS and DMDO give the opposite facial selectivity in the addition to enesulfamates.

Scheme 3.4. Demonstration of differential facial selectivity of NBS and DMDO.



To rationalize these observations, we propose the nature of the transition state in the addition of an (*E*)-enesulfamate to the electrophile impacts the stereochemical outcome (Scheme 3.5). For example, if the addition of **2C** to DMDO occurs in a concerted fashion with an early transition state that closely resembles the starting material, intermediate **2C1** would be produced and unravel to yield a 1,3-*anti* relationship in the imine product. In contrast, employing NBS in the reaction of **2C** may occur through a late transition state **2C2** that contains significant C=N double bond character. The bending of the C=C bond away from the pseudoaxial orientation in **2C** to be in conjugation with the forming C=N bond may influence facial selectivity by precluding approach of NBS from the top face of the alkene due to effective shielding by the bulky OTBS group, resulting in the 1,3-*syn* imine.

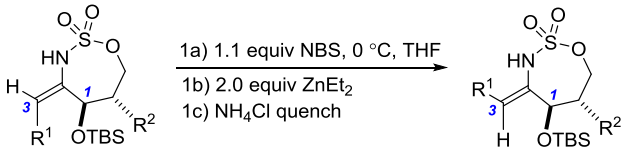
Scheme 3.5. Model for differential facial selectivity of NBS and DMDO.



3.2.4 *E*/Z Isomerization of (*E*)-enesulfamates

Extension of this method to the synthesis of diastereomeric aminodiols required access to the (*Z*)-enesulfamate, as we were unable to identify an oxidant that gave the opposite facial selectivity to DMDO. We were pleased to find that the (*E*)-enesulfamates could be cleanly isomerized to the corresponding (*Z*) isomers by simple sequential treatment with NBS and $ZnEt_2$ (Table 3.5 and Scheme 3.6). This isomerization method proved to be both selective and high-yielding, giving solely the (Z)-enesulfamates as the product (Table 3.5, entries 1-6). The (*Z*)-enesulfamates were often more sensitive to hydrolysis than their (*E*)-counterparts; consequently they were often used unpurified in subsequent functionalizations.

Table 3.5. Isomerization of (*E*) to (*Z*) enesulfamates.

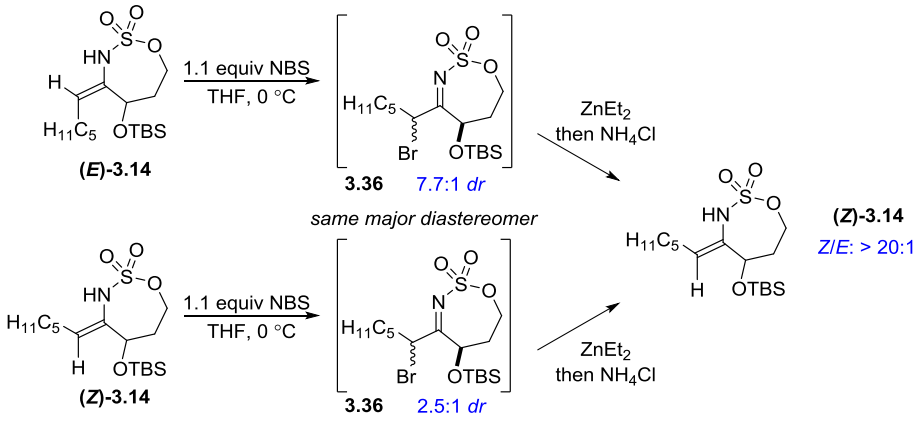


entry	R^1	R^2	substrate	yield	product	*Z*:*E*
1	^{i}Pr	H	**3.7**	97%	**(*Z*)-3.7**	> 20 : 1
2	C_5H_{11}	H	**3.14**	93%[a]	**(*Z*)-3.14**	> 20 : 1
3	C_5H_{11}	Me	**3.15**	79%	**(*Z*)-3.15**	> 20 : 1
4	CH_2CH_2Ph	H	**3.16**	89%[a]	**(*Z*)-3.16**	> 20 : 1
5	$CH_2CH_2SiMe_2Ph$	H	**3.17**	85%	**(*Z*)-3.17**	> 20 : 1
6	Ph	H	**3.18**	98%[a]	**(*Z*)-3.18**	> 20 : 1

[a] Crude NMR yield with mesitylene as an internal standard and used in subsequent steps without further purification.

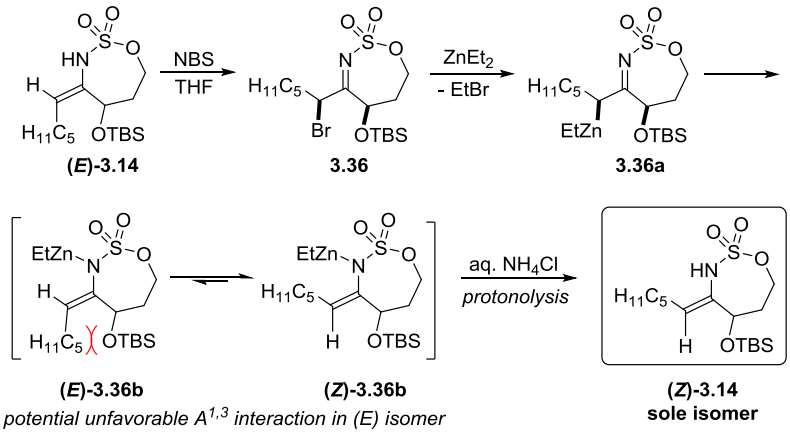
The mechanism of the NBS/$ZnEt_2$-mediated isomerization reaction was briefly probed by correlating the *E/Z* ratio of the isomerized product to the *dr* of the intermediate α-Br imine **3.36** (generated by reaction of **(*E*/*Z*)-3.14** with NBS). As illustrated in Scheme 3.6, there is no relationship between the *dr* of the α-Br imine and the final *E/Z* ratio for either the (*E*) or (*Z*)-enesulfamate. Importantly, the (*Z*)-enesulfamate does not undergo isomerization back to the (*E*)-isomer under these conditions.

Scheme 3.6. Explorations of enesulfamate isomerization.



Based on this data, we hypothesize that the final *E/Z* ratio reflects a high thermodynamic preference for the (*Z*)-isomer of an intermediate zinc enamine that results from insertion of $ZnEt_2$ into the C-Br bond of **3.36a** (Scheme 3.7).[13] A facile *E/Z* interconversion of this intermediate would explain why the *dr* of the α-Br imine **3.36** is not reflected in the product **(*Z*)-3.14**. The (*Z*)-isomer may be favored due to $A^{1,3}$ interactions between the R group and the OTBS in the (*E*)-isomer. Protonolysis of the highly favored (*Z*)-zinc enamine then gives the (*Z*)-enesulfamate **(*Z*)-3.14** as the sole product.

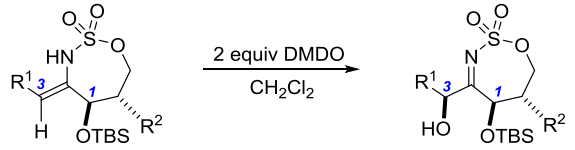
Scheme 3.7. Proposed mechanism of (*E*/*Z*) isomerization for enesulfamates.



3.2.5. DMDO oxidation of (*Z*)-enesulfamates

Gratifyingly, the (Z)-enesulfamates reacted with DMDO to afford the desired 1,3-*syn* imines **3.37-3.41** in moderate to high *dr* (Table 3.6).[14] While the isopropyl-substituted enesulfamate (***Z***)-**3.7** gave a reduced *dr* of 4.3:1 (entry 1) compared to the analogous (*E*)-enesulfamate, several other substrates exhibited much improved selectivities (entries 2-5). The Ph-substituted enesulfamate (***Z***)-**3.18** again delivered the *syn* diastereomer **3.24** in good *dr*, suggesting that epimerization of the Ph-substituted imine might be facile under these reaction conditions.

Table 3.6. Synthesis of 1,3-*syn* imines from (*Z*)-enesulfamates.

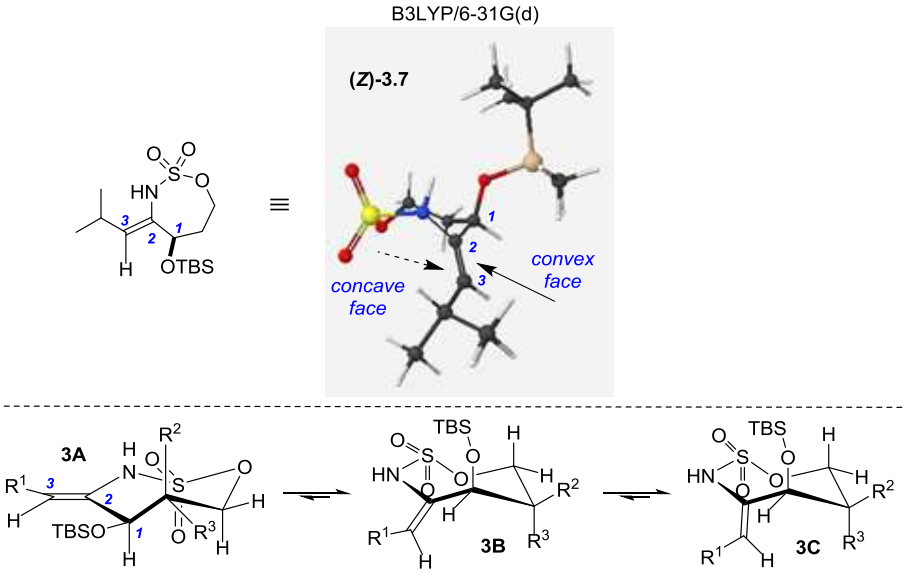


entry	R^1	R^2	substrate	°C	*syn:anti*[a]	product
1	^{i}Pr	H	(***Z***)-**3.7**	-20	4.3 : 1	**3.37**
2	C_5H_{11}	H	(***Z***)-**3.14**	0	9 : 1	**3.38**
3	C_5H_{11}	Me	(***Z***)-**3.15**	0	>9 : 1	**3.39**
4	CH_2CH_2Ph	H	(***Z***)-**3.16**	0	9 : 1	**3.40**
5	$CH_2CH_2SiMe_2Ph$	H	(***Z***)-**3.17**	0	>9 : 1	**3.41**
6	Ph	H	(***Z***)-**3.18**	0	7.7 : 1	**3.24**

[a]*anti:syn* ratios determined by ^{1}H NMR of the crude imine

A calculated optimized geometry[#] for the (*Z*)-enesulfamate **(*Z*)-3.7** (Figure 3.2) shows a similar conformation to the (*E*)-isomer **23**, rationalizing the conserved facial approach of DMDO. Although conformer **3A** is not predicted to possess as much $A^{1,3}$ strain as the analogous (*E*)-isomer, conformers **3B** and **3C** do relieve some of this strain, and we cannot rule out stereoelectronic preferences for placing the oxygenated group in a pseudoaxial position.[11,12] Oxidation is again proposed to occur from the *exo* face of **(*Z*)-3.7** to give the 1,3-*syn* imine as the major stereoisomer. Bulkier groups at R^1, such as the isopropyl group of **(*Z*)-3.7**, may favour conformer **3B** due to a steric interaction between R^1 and the neighbouring sulfamate group. This could tilt the exocyclic alkene back into the plane of the ring and lower the selectivity of the oxidation, resulting in the lower *dr* of 4.3:1 in **3.37**.

Figure 3.2. Stereochemical model for DMDO oxidation of (Z)-enesulfamates.

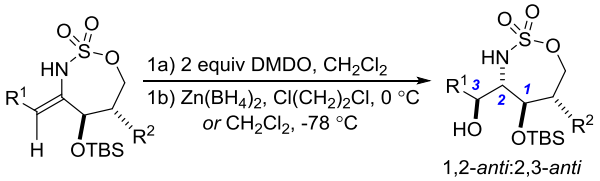


3.2.6. Synthesis of 1,2-*anti*:2,3-*anti* and 1,2-*syn*:2,3-*syn* aminodiols from (*Z*)-enesulfamates

The 1,3-*syn* imines listed in Table 3.6 were subjected to reduction with $Zn(BH_4)_2$, resulting in the formation of 1,2-*anti*;2,3-*anti* stereotriads in high *dr* (Table 3.7), as confirmed by X-ray crystallographic analysis of **3.45**. Again, the *anti* relationship observed between the C2-amine and

C3-OH suggests chelation between the imine and C3-hydroxyl group is the dominant stereochemical factor in this reduction (see section 3.2.6). Products **3.43** and **3.45** were observed as mixtures of three stereoisomers, owing to imperfect diastereocontrol in the reduction step. However, the yields of isolated product were typically good to excellent, and the major diastereomers could be cleanly isolated by chromatography or recrystallization. Triad **3.47** was derived from the (*E*)-enesulfamate, due to the reversed selectivity observed in its reaction with DMDO (see Table 3.3, entry 7).

Table 3.7. 1,2-*Anti*-2,3-*anti* stereotriads from (*Z*)-enesulfamates.



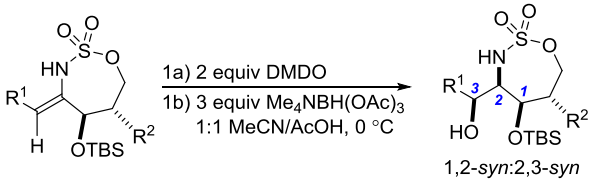
entry	R^1	R^2	substrate	yield	*dr*[a]	product
1	^{i}Pr	H	**(*Z*)-3.7**	89%	4.9 : 1	**3.42**
2	C_5H_{11}	H	**(*Z*)-3.14**	62%	11.7 : 1.7 : 1[b]	**3.43**
3	C_5H_{11}	Me	**(*Z*)-3.15**	61%	> 9 : 1	**3.44**
4	CH_2CH_2Ph	H	**(*Z*)-3.16**	85%	11.8 : 1.5 : 1[b]	**3.45**
5	$CH_2CH_2SiMe_2Ph$	H	**(*Z*)-3.17**	90%	9 : 1	**3.46**
6	Ph (*E*) isomer	H	**(*E*)-3.18**	85%	8.3 : 1	**3.47**

[a] *dr* determined by ^{1}H NMR of the product. [b] The major product is the 1,2-*syn*:2,3-*anti* stereoisomer.

The synthesis of 1,2-*syn*:2,3-*syn* aminodiols required a reversal of the reduction selectivity observed in in Table 3.7. The desired 2,3-*syn* reduction was achieved by preventing chelation between the C3 hydroxyl and the imine using $Me_4NBH(OAc)_3$ as the reductant in a polar protic solvent.[15] The stereotriads **3.48**-**3.52** were obtained in good yields and moderate to good *dr* (Table 3.8), and the major diastereomer could be purified in all cases by column chromatography. Interestingly, the presence of an *anti*-Me group in **(Z)-3.15** biased the reaction towards the 2,3-*anti* reduction product **3.44** in good yield and *dr* (entry 3). This result points to the effects that small perturbations in the substrate can have on the reactive conformations in these seven-

membered rings, thus prompting the development of alternate strategies to overcome cases of stereochemical mismatching.

Table 3.8. 1,2-*Syn*-2,3-*syn* stereotriads from (*Z*)-enesulfamates.



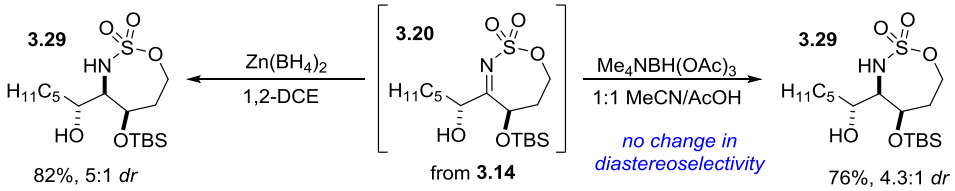
entry	R^1	R^2	substrate	yield	*dr*[a]	product
1	^{i}Pr	H	**(*Z*)-3.7**	82%	3.6 : 1.3[b] : 1[c]	**3.48**
2	C_5H_{11}	H	**(*Z*)-3.14**	73%	10.1 : 1.4 : 1[d]	**3.49**
3	C_5H_{11}	Me	**(*Z*)-3.15**	70%	< 1 : 9[e]	**3.44**
4	CH_2CH_2Ph	H	**(*Z*)-3.16**	73%	10.2 : 1.8 : 1[d]	**3.50**
5	$CH_2CH_2SiMe_2Ph$	H	**(*Z*)-3.17**	74%	3.1 : 1	**3.51**
6	Ph (from *E* isomer)	H	**(*E*)-3.18**	67%	8.7 : 1	**3.52**

[a] *dr* determined by ^{1}H NMR. [b] 1,2-*anti*:2,3-*anti* isomer. [c] 1,2-*syn*:2,3-*anti* isomer. [d] minor diastereomers not identified. [e] 1,2-*anti*:2,3-*anti* isomer.

3.2.7. Stereochemical models for imine reductions

With a pair of divergent reduction conditions in hand for the 1,3-*syn* imines, we applied the $Me_4NBH(OAc)_3$ conditions to 1,3-*anti* imine **3.14**, hopeful that these conditions would provide the fourth aminodiol diastereomer (Scheme 3.8). We were disappointed to find that in the case of this diastereomeric imine, the same 1,2-*syn*:2,3-*anti* aminodiol **3.29** predominated in both cases. Stereochemical models summarizing these outcomes are provided in Scheme 3.9 below.

Scheme 3.8. Lack of stereodivergence in reduction of 1,3-*anti* imine **3.36**.

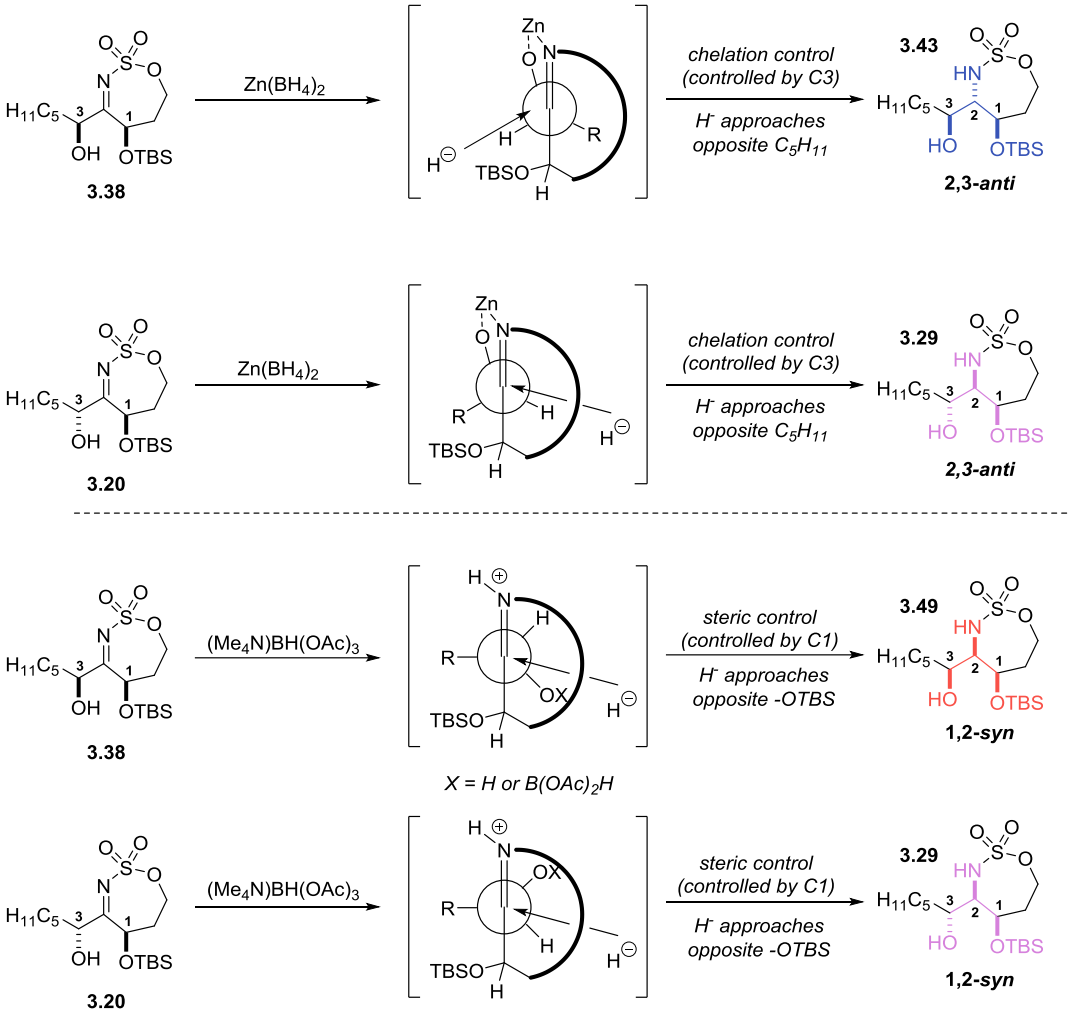


As stated previously, the 2,3-*anti* outcome observed in reductions with $Zn(BH_4)_2$ is readily rationalized by a chelation-controlled Felkin-Anh model (Scheme 3.9, top). A chelate is expected to form between the C3-OH and C2-imine, with hydride approaching opposite the bulky *n*-pentyl

chain to afford the observed diastereomers. The influence of this chelate appears to outweigh the steric influence of the bulky OTBS group, as hydride approaches from the same face as the OTBS in the formation of **3.60** (Scheme 3.9, top). Thus, in the $Zn(BH_4)_2$ reductions, C3 controls the outcome of the reduction.

Understanding the sense of $Me_4NBH(OAc)_3$ reduction is complicated by the possibility for both inter- and intramolecular hydride delivery, if the C3-OH is able to effectively coordinate to the borohydride in the acidic MeCN/AcOH reaction solvent. However, in either case, chelation between the C3-OH and C2-imine is assumed to not be occurring. Under these conditions, the steric influence of the C1-OTBS appears to dominate, as hydride approaches *anti* to this group in the case of **3.38** and **3.20** (Scheme 3.9, bottom). Thus, while the exact orientation and substitution of the flexible C3 substituent is unknown in this scenario, the C1 stereocenter controls the sense of reduction.

Scheme 3.9. Stereochemical models for $Zn(BH_4)_2$ and $Me_4NBH(OAc)_3$ reduction.

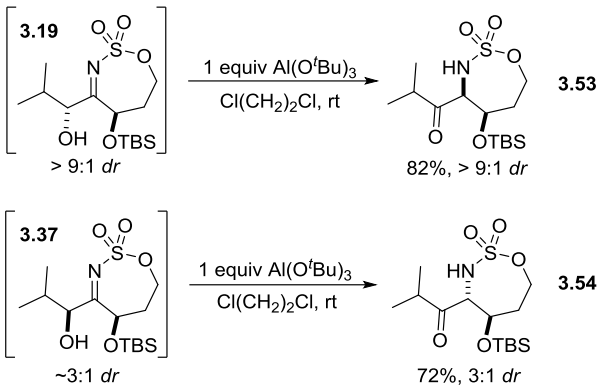


3.2.8. Synthesis of the 1,2-*anti*-2,3-*syn* diastereomer by imine isomerization

Since complementary imine reduction was not possible for 1,3-*anti* imines, alternative routes for accessing the final 1,2-*anti*:2,3-s*yn* diastereomer were examined. We hypothesized that isomerization of the α-hydroxyimine to a α-aminoketone might provide a way to carry out the intramolecular delivery of a hydride to the desired face of the imine (Scheme 3.10).[16] In addition, reducing ketones **3.53** or **3.54** instead of the imines **3.19** and **3.37** would curtail the problem of the two flanking heteroatom groups competing for stereocontrol. A variety of Lewis acids were explored for the Amadori-type rearrangement, with $Al(O^tBu)_3$ giving the best yields.[17] The

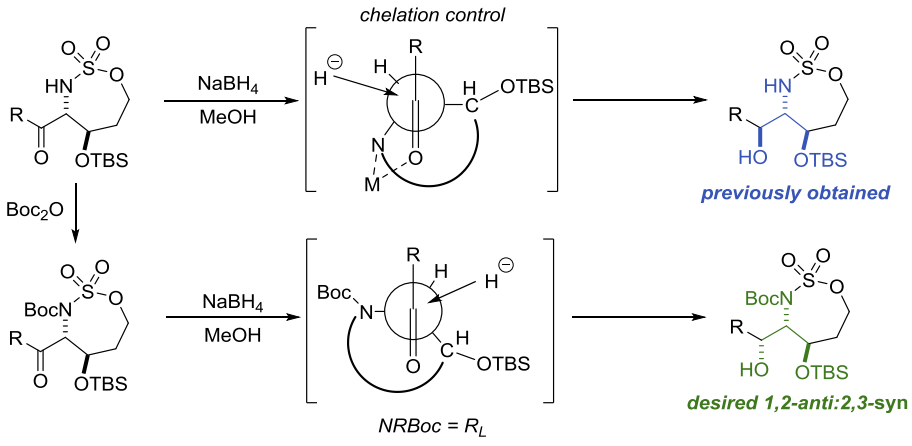
isomerization proved to be stereospecific, delivering either diastereomer of the α-aminoketone depending on the initial stereochemistry of the imine, with no noticeable epimerization observed under the reaction conditions.

Scheme 3.10. Isomerization of α-hydroxyimines to α-aminoketones.



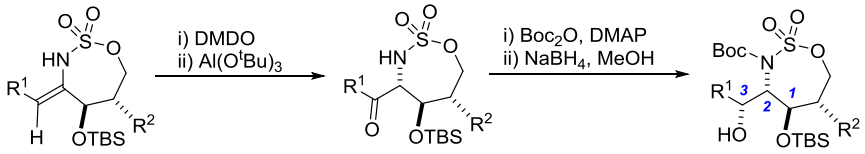
Success in obtaining the final 1,2-*anti*:2,3-*syn* 2-amino-1,3-diol triad was achieved through reduction of the 1,2-*anti* α-aminoketones with $NaBH_4$ in MeOH, provided the nitrogen of the sulfamate was Boc-protected. In the absence of the Boc protection, the reduction generally proceeded under chelation control (Scheme 3.11) to give the 1,2-*anti*:2,3-*anti* triad, providing an alternative route to this stereoisomer.

Scheme 3.11. Divergent reduction of aminoketones.



This protocol for 1,2-*anti*:2,3-*syn* aminodiol synthesis was carried out in two steps, with isolation of the aminoketone intermediate prior to the Boc protection/reduction steps. As illustrated in Table 3.9, step 2, the *dr* for the $NaBH_4$ reductions ranged from 4:1 to >20:1, with moderate to good yields for each enesulfamate.

Table 3.9. Access to 1,2-*anti*:2,3-*syn* aminodiols via ketone reduction.

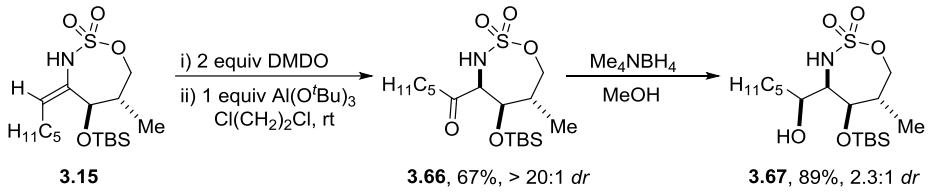


entry	substrate	R^1	R^2	yield	*dr*[c]	product
1	**(*Z*)-3.7**	^{i}Pr	H	72%[a]	3 : 1	**3.54**
				88%[b]	5.3 : 1	**3.55**
2	**(*Z*)-3.14**	C_5H_{11}	H	72%[a]	10.6 : 1	**3.56**
				77%[b]	> 20 : 1	**3.57**
3	**(*Z*)-3.15**	C_5H_{11}	Me	60%[a]	> 20 : 1	**3.58**
				79%[b]	6.2 : 1	**3.59**
4	**(*Z*)-3.16**	CH_2CH_2Ph	H	63%[a]	11 : 1	**3.60**
				78%[b]	> 20 : 1	**3.61**
5	**(*Z*)-3.17**	$CH_2CH_2SiMe_2Ph$	H	58%[a]	7.3 : 1	**3.62**
				76%[b]	> 20 : 1	**3.63**
6	**(*Z*)-3.18**	Ph	H	60%[a]	20 : 1	**3.64**
				48%[b]	4 : 1	**3.65**

[a]Yield of the ketone. [b]Yield of the reduction. [c]*dr* determined by ^{1}H NMR of the crude product.

The strategy described in Table 8 could be used to obtain the 1,2-*syn*:2,3-*syn* stereotriad **3.67** (Scheme 3.12), which was inaccessible *via* direct imine reduction. The 1,2-*syn* α-aminoketone **3.66** was prepared from the (*E*)-enesulfamate **3.15**, followed by a *syn*-selective reduction with Me_4NBH_4. Taken together, the paths in Table 3.9 and Scheme 3.12 represent a convenient alternative for obtaining stereotriads from precursors where the imine reduction proves problematic.

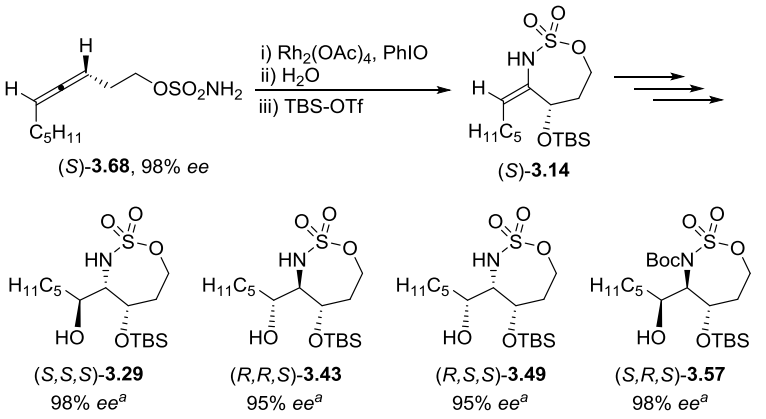
Scheme 3.12. 1,2-syn:2,3-syn aminodiols by a different route.



3.2.9. Transfer of allene axial chirality

With routes to all four possible diastereomers in hand, we wanted to clearly demonstrate that oxidative amination of an enantioenriched homoallenic sulfamate could be used to prepare enantioenriched 2-amino-1,3-diol triads. The homoallenic sulfamate **(*S*)-3.68** was prepared in three steps from the corresponding propargylic alcohol[18] and converted to the enesulfamate **(*S*)-3.14** in 98% *ee*. Subsequent transformation of **(*S*)-3.14** to each of the four possible diastereomers occurred as expected, and no significant erosion in the stereochemical fidelity in the axial to point chirality transfer (Scheme 3.13) was noted.

Scheme 3.13. Demonstration of transfer of axial chirality from enantioenriched allene.



[a] *ee* determined by chiral HPLC analysis of the corresponding 3,5-dinitrobenzoate ester

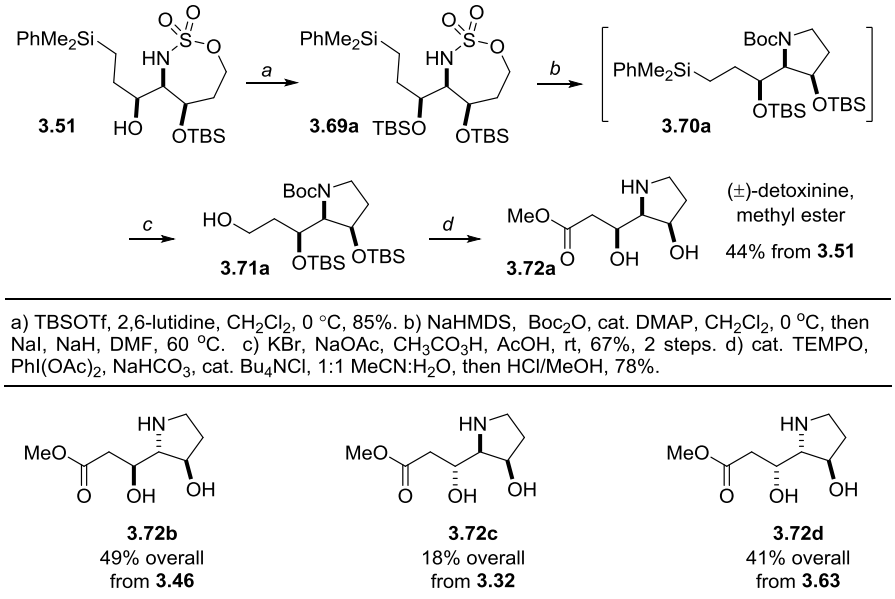
3.2.10. Stereodivergent total synthesis of (±)-detoxinine methyl ester

The potential of our methods to enable rapid access to all possible stereoisomers of an aminodiol-containing bioactive molecule was demonstrated in the syntheses of (±)-detoxinine methyl ester and its three diastereomers (Scheme 8).[19] Detoxinine is an unusual bis-hydroxylated

α-amino acid that constitutes the core of the detoxifying agent detoxin, which is co-administered with blasticidin S for the treatment of rice blast disease.[20] The synthesis of detoxinine itself is relatively straight-forward, but the flexibility of our methodology permits the same homoallenic sulfamate to be employed to access any possible stereoisomer. Application of this same strategy to other complex amines could prove very useful for exploration of stereochemical structure-activity relationships.

In the synthesis, the free alcohol of the all-*syn* stereotriad **3.51** was silyl protected to give the sulfamate **3.69a** in 85% yield. Boc protection of the amine, followed by NaI-mediated ring contraction, gave **3.70a**.[21] This intermediate was subjected to Fleming-Tamao conditions to furnish **3.71a** in 67% yield over the two steps.[22] A two-step oxidation sequence yielded the terminal carboxylic acid, which upon acidic workup afforded (±)-detoxinine methyl ester **3.72a**. The same sequence of reactions was applied to the three remaining diastereomers of **3.51** to yield the non-natural stereoisomers of detoxinine, **3.72b-d**.[23]

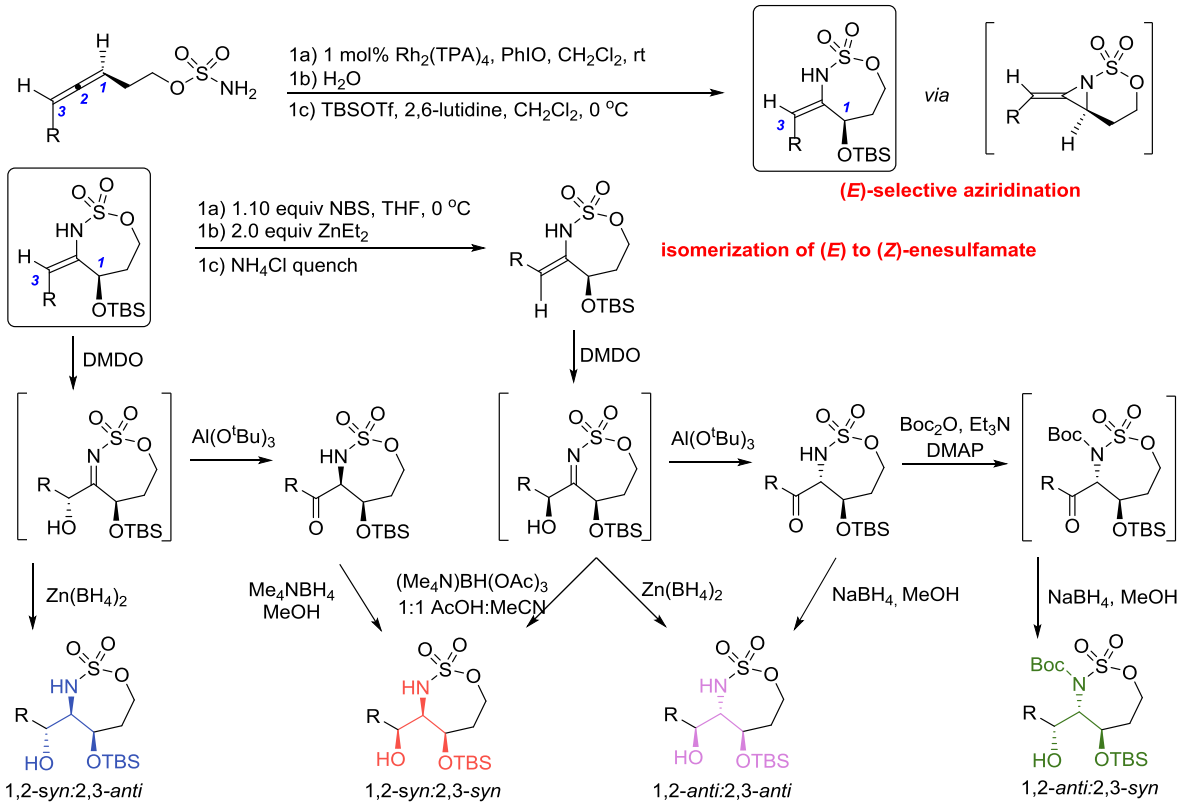
Scheme 3.14. Stereodivergent synthesis of all diastereomers of detoxinine methyl ester.



3.3. Conclusions

Scheme 3.15 summarizes our demonstration of the versatility of allene aziridination for the stereodivergent syntheses of all four possible diastereomers of a 2-amino-1,3-diol motif. The ability to obtain stereochemically diverse outcomes from a single precursor, in addition to the heteroatom diversity we have previously demonstrated,[1] further expands the scope of allene oxidation as a powerful tool for the construction of libraries of bioactive amines. Future work will apply the strategies and understandings developed in this work to access other common stereotriads, such as the O/N/N or N/N/N motifs. Ultimately, we anticipate that the ability to introduce heteroatom and stereochemical diversity by a single, unified allene aziridination strategy will be of great utility in diversity-oriented synthesis and the exploration of novel chemical space.

Scheme 3.15. "Roadmap" for the stereodivergent synthesis of 1-amino-2,3-diols.



3.4. References

1. Adams, C. S.; Boralsky, L. A.; Guzei, I. A.; Schomaker, J. M. *J. Am. Chem. Soc.* **2012**, *134*, 10807.

2. Recent reviews on transformations utilizing allenes as starting materials or intermediates: (a) Allen, A. D.; Tidwell, T. T. *Chem. Rev.* **2013**, *113*, 7287. (b) Yu, S.; Ma, S. *Angew. Chem. Int. Ed.* **2012**, *51*, 3074. (c) Ma, S. *Pure Appl. Chem.* **2006**, *78*, 197.

3. For selected references on the aminohydroxylation of allylic alcohols, see: (a) Donohoe, T. J.; Callens, C. K. A.; Flores, A.; Lacy, A. R.; Rathi, A. H. *Chem.-Eur. J.* **2011**, *17*, 58. (b) Donohoe, T. J.; Johnson, P. D.; Pye, R. J. *Org. Biomol. Chem.* **2003**, *1*, 2025. (b) Bodkin, J. A.; McLeod, M. D. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2733. (c) Ma, Z.; Naylor, B. C.; Loertscher, B. M.; Hafen, D. D.; Li, J. M.; Castle, S. L. *J. Org. Chem.* **2012**, *77*, 1208. (d) Masruri; Kanizaj, N.; McLeod, M. D. *Chirality* **2013**, *26*, 724.

4. For selected references on approaches to 1-amino-2,3-diols, see: a) Dai, L.; Lou, B.; Zhang, Y. *J. Am. Chem. Soc.* **1988**, *110*, 5195. b) Park, J.J.; Lee, J. H.; Seo, K.C.; Bricard, G.; Venkataswamy, M.M.; Porcelli, S.A.; Chung, S. K. *Bioorg. Med. Chem. Lett.* **2010**, 814. c) Hili, R.; Yudin, A.K. *Angew. Chem. Int. Ed.* **2008**, *47*, 4188. d) Llaveria, J.; Diaz, Y.; Matheu, M.I.; Castillon, S. *Org. Lett.* **2009**, *11*, 205.

5. For selected other methods of making O/N/O stereotriads, see: (a) Abe, J. et al. *Org. Biomol. Chem.* **2012**, *10*, 7826. (b) Zhou, X.; Liu, W.; Ye, J.; Huang, P. *J. Org. Chem.* **2007**, *72*, 8904.

6. For selected examples in cyclic systems, see: (a) Tsuda, Y.; Okuno, Y.; Iwaki, M.; Kanemitsu, K. *Chem. Pharm. Bull.* **1989**, *37*, 2673. (b) Groneberg, R. D.; Miyazaki, T.; Stylianides, N. A.; Schulze, T. J.; Stahl, W.; Schreiner, E. P.; Suzuki, T.; Iwabuchi, Y.;

Smith, A. L.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1993**, *115*, 7593. (c) Boering, B. K.; Li, J.; Ganem, B. *Tetrahedron Lett.* **1995**, *36*, 8905. (d) Noya, B.; Paredes, M. D.; Ozores, L.; Alonso, R. *J. Org. Chem.* **2000**, *65*, 5960. (e) Jäger, M.; Hartmann, M.; de Vries, J. G.; Minnaard, A. J. *Angew. Chem. Int. Ed.* **2013**, *52*, 7809.

7. For an example with more conformational flexibility: Yin, H.; Franck, R. W.; Chen, S.-L.; Quigley, G. J.; Todaro, L. *J. Org. Chem.* **1992**, *57*, 644.

8. DMDO is a common reagent for the oxidation of enamides and enecarbamates: a) Baldwin, J. E.; O'Neil, I. A. *Tetrahedron Letters* **1990**, *31*, 2047. b) Adam, W.; Reinhardt, D. *Tetrahedron*, **1995**, *51*, 12257. c) Sugisaki, C. H.; Carroll, P. J.; Correia, C. R. D. *Tetrahedron Letters* **1998**, *39*, 3413. d) Koseki, Y.; Kusano, S.; Ichi, D.; Yoshida, K.; Nagasaka, T. *Tetrahedron* **2000**, *56*, 8855.

9. The 1,3-*anti* stereochemistry of the imine was inferred from the crystal structure of compound **3.47**. See the Experimental Details for further information.

10. *Conformational Analysis of Medium-Sized Heterocycles.* Glass, R. S., ed., VHC: New York, 1988.

11. (a) Johnson, F. *Chem. Rev.* **1968**, *68*, 375. b) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841. c) Lambert, J. B. Conformational analysis of six-membered carbocyclic rings with exocyclic double bonds. In *The Conformational Analysis of Cyclohexenes, Cyclohexadienes, and Related Hydroaromatic Compounds*. Rabideau, P. W., ed. VCH: New York, 1989; pp 47-64.

12. A conformational preference for axial oxy groups has been observed for 2-oxymethylenecyclohexanes, rationalized by $\pi_{C\text{-}C} \rightarrow \sigma_{C\text{-}O}^*$ hyperconjugative donation. We cannot rule out the possibility of this effect in the conformation of the enesulfamates. For

a discussion of this effect, see: (a) Lessard, J.; Phan Viet, M. T.; Martino, R.; Saunders, J. K. *Can. J. Chem.* **1977**, *55*, 1015. (b) Phan Viet, M. T.; Lessard, J.; Saunders, J. K. *Tetrahedron Lett.* **1979**, *20*, 317. (c) Lessard, J.; Saunders, J. K.; Phan Viet, M. T. *Tetrahedron Lett.* **1982**, *23*, 2059. (d) Zefirov, N. S.; Barenenkov, I. V. *Tetrahedron* **1983**, *39*, 1769. (e) Ouédraogo, A.; Phan Viet, M. T.; Saunders, J. K.; Lessard, J. *Can. J. Chem.* **1987**, *65*, 1761.

13. The insertion of $ZnEt_2$ into the C-Br bond of α-bromoketones is a known process for the formation of zinc enolates: Hansen, M. V.; Bartlett, P. A.; Heathcock, C. H. *Organometallics* **1987**, *6*, 2069.

14. The 1,3-*syn* stereochemistry of the imines was inferred from the crystal structure of compound **3.67**, as well as by comparison to the known 1,3-anti diastereomer.

15. (a) Williams, D. R.; Osterhout, M. H.; Reddy, J. P. *Tetrahedron Lett.* **1993**, *34*, 3271. (b) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560.

16. (a) Paquette, L. A.; Hofferberth, J. E. *Organic Reactions* **2004**, *62*, 447. (b) Wrodnigg, T. M.; Eder, B. *Top. Curr. Chem.* **2001**, *215*, 115.

17. For examples of $Al(O^tBu)_3$ being used for a similar isomerization of an α-hydroxyketone, see: (a) Paquette, L. A.; Montgomery, F. J.; Wang, T.-Z. *J. Org. Chem.* **1995**, *60*, 7857. (b) Zeng, Q.; Bailey, S.; Wang, T.-Z.; Paquette, L. A. *J. Org. Chem.* **1998**, *63*, 137.

18. See Experimental Details for further information.

19. For selected syntheses of detoxinine: a) Hausler, J. *Liebigs Ann. Chem.* **1983**, 982. b) Ohfune, Y.; Nishio, H. *Tetrahedron Lett.* **1984**, *25*, 4133. c) Joullié, M. M.; Ewing, W. R.; Harris, B. D.; Bhat, K. L. *Tetrahedron* **1986**, *42*, 2421. d) Ewing, W. R.; Joullié, M. M. *Heterocycles* **1988**, *27*, 2843. e) Kogen, H.; Kadokawa, H.; Kurabayashi, M. *J. Chem. Soc.*

Chem. Commun. **1990**, 1240. f) Mulzer, J.; Meier, A.; Buschmann, J.; Luger, P. *J. Org. Chem.* **1996**, *61*, 566. g) Denmark, S.E.; Hurd, A.R.; Sacha, H. J *J. Org. Chem.* **1997**, *62*, 1668. h) Delle Monache, G.; Misiti, D.; Zappia, G. *Tetrahedron: Asymmetry* **1999**, *10*, 2961. i) Flögel, O.; Okala, M.; Amombo, G.; Reissig, H.-U.; Zahn, G.; Brüdgam, I.; Hartl, H. *Chem. Eur. J.* **2003**, *9*, 1405. j) Ceccon, J.; Poisson, J.F.; Greene, A.E. *Synlett* **2005**, 1413.

20. (a) Joullie, M. M.; Li, W.-R.; Han, S.-Y. *Heterocycles* **1993**, *36*, 359. (b) Yonehara, H.; Seto, H.; Aizawa, S.; Hidaka, T.; Shimazu, A.; Otake, N. *J. Antibiot.* **1968**, *21*, 369. (c) Yonehara, H.; Seto, H.; Shimazu, A.; Aizawa, S.; Hidaka, T.; Kakinuma, K.; Otake, N. *Agr. Biol. Chem.* **1973**, *37*, 2771.

21. Thornton, A. R.; Martin, V. I.; Blakey, S. B. *J. Am. Chem. Soc.* **2009**, *131*, 2434.

22. a) Takahata, H.; Banba, Y.; Ouchi, H.; Nemoto, H. *Org. Lett.* **2003**, *5*, 2527. b) Guaragna, A.; D'Errico, S.; D'Alonzo, D.; Pedatella, S.; Palumbo, G. *Org. Lett.* **2007**, *9*, 3473. c) Martín, R.; Murruzzu, C.; Pericàs, M. A.; Riera, A. *J. Org. Chem.* **2005**, *70*, 2325.

23. Interestingly, the stereochemical configuration of detoxinine was originally assigned with the arrangement shown in compound **3.91**. For the study that revised the stereochemistry through synthesis of both stereoisomers, see: Kakinuma, K.; Otake, N.; Yonehara, H. *Tetrahedron Lett.* **1980**, *21*, 167.

3.5. Experimental Details

3.5.1. General information

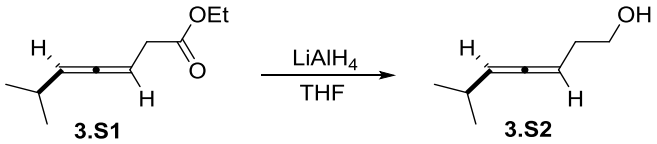
Unless otherwise specified, all glassware was either oven-dried overnight at 130 °C or flame-dried under vacuum and purged with dry nitrogen prior to use. Unless otherwise specified, reagents were used as obtained from the vendor without further purification. Tetrahydrofuran and

diethyl ether were freshly distilled from purple Na/benzophenone ketyl. Dichloromethane, acetonitrile and toluene were dried over CaH_2 and freshly distilled prior to use. 1,2-Dichloroethane was used as purchased from Sigma Aldrich. All other solvents were purified in accordance with "Purification of Laboratory Chemicals".[1] Air- and moisture- sensitive reactions were performed using standard Schlenk techniques under an atmosphere of nitrogen. Analytical thin layer chromatography (TLC) was performed utilizing pre-coated silica gel 60 F_{254} plates containing a fluorescent indicator, while preparative chromatography was performed using SilicaFlash P60 silica gel (230-400 mesh) via Still's method.[2] Unless otherwise stated, the mobile phases for column chromatography were mixtures of hexanes/ethyl acetate. Columns were typically run using a gradient increasing the polarity using ethyl acetate. Various stains were used to visualize reaction products, including *p*-anisaldehyde, $KMnO_4$, ceric ammonium molybdate (CAM stain) and iodine powder. High-pressure liquid chromatography (HPLC) analyses were performed at 215 and 225 nm using a Shimadzu HPLC, Model LC-20AB. Further details are given in Section XV.

^{1}H NMR and ^{13}C NMR spectra were obtained using Bruker-300, Varian Inova-500, Varian Unity-500 or Varian Inova-600 NMR spectrometers. For ^{1}H NMR, chemical shifts are reported relative to residual proteo solvent (δ 7.26, 2.49, 7.15 and 4.80 ppm for $CDCl_3$, $(CD_3)_2SO$, C_6D_6 and CD_3OD respectively). ^{13}C NMR spectra were measured at either 125 MHz or 150 MHz on the same instruments noted above for recording ^{1}H NMR spectra. Chemical shifts were again reported in accordance to residual proteo solvent (δ 77.0, 39.5, 128.0 and 49.0 ppm for $CDCl_3$, $(CD_3)_2SO$, C_6D_6, and CD_3OD, respectively). Accurate mass measurements were acquired at the University of Wisconsin, Madison using a Micromass LCT (electrospray ionization, time-of-flight analyzer or electron impact methods). When two or more significant isotopes were present in the

molecule, a monoisotopic approach was used, focusing on the isotope with the lowest mass (^{35}Cl and ^{79}Br). The NMR and Mass Spectrometry facilities are funded by the NSF (CHE-9974839, CHE-9304546, CHE-9208463, CHE-9629688) and the University of Wisconsin, as well as the NIH (RR08389-01).

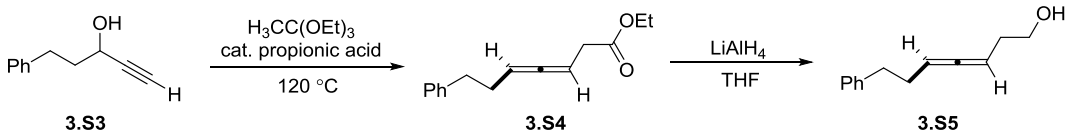
3.5.2. Preparation of allenols



3.S1 3.S2

Compound 3.S1. Homoallenic ester **3.S1** was prepared from 4-methyl-1-pentyn-3-ol using a literature procedure.[3]

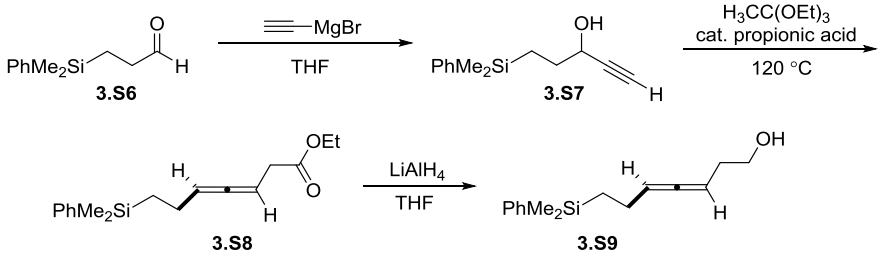
Compound 3.S2. An oven-dried 2 L flask was charged with $LiAlH_4$ (12.66 g, 333 mmol, 1.1 equiv) and 700 mL dry THF. The suspension was cooled to 0 ºC and a solution of **3.S1** (51.0 g, 303 mmol, 1.0 equiv) in 100 mL of THF was added dropwise over 10 min. The reaction mixture was stirred for 1h. The reaction quenched carefully by Fieser workup. 10 g $MgSO_4$ was added, and the mixture was stirred vigorously at rt for 30 min. The salts were removed by filtrateion and the filtrate dried over $MgSO_4$. The volatiles were removed under reduced pressure and the crude allenol was purified by vacuum distillation (83-86 °C, 10 mmHg) to yield **3.S2** (33.20 g, 263 mmol, 87%) as a colorless oil. ^1H NMR: (500.0 MHz, $CDCl_3$) δ 5.17 (m, 2H), 3.71 (t, J = 6.2 Hz, 2H), 2.23-2.34 (m, 3H), 1.69 (br s, 1H), 1.02 (d, J = 6.7 Hz, 6H). ^{13}C NMR: (125.7 MHz, $CDCl_3$) δ 203.0, 99.1, 88.4, 62.0, 32.4, 27.8, 22.4, 22.4. HRMS (ESI) *m/z* calculated for $C_8H_{14}O$ $[M]^+$ 126.1039, found 126.1040.



3.S3 3.S4 3.S5

Compound 3.S4. Propargyl alchol **3.S3** (5.89 g, 36.8 mmol, 1.0 equiv) was placed in a 50 mL round bottom flask. Triethyl orthoacetate (9.38 mL, 51.5 mmol, 1.4 equiv) was added, and a distillation head was attached to the flask. The flask was heated to 120 °C for 2 hours, then cooled and diluted with EtOAc. The solution was washed with 0.1 M HCl, $NaHCO_3$ (aq) and brine. The organic phase was dried with Na_2SO_4 and concentrated by rotoary evaporation. The crude residue was purified by silica gel chromatography (2% to 10% EtOAc in hexanes) to give **3.S4** (5.20 g, 21.3 mmol, 58%). ^{1}H NMR: (500.0 MHz, $CDCl_3$) δ 7.29 (m, 2H), 7.17-7.22 (m, 3H), 5.28 – 5.20 (m, 2H), 4.16 (q, *J* = 7.1 Hz, 2H), 2.95 (m, 2H), 2.73 (app t, *J* = 7.3 Hz, 2H), 2.34 (m, 2H), 1.28 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR: (125.7 MHz, $CDCl_3$) δ 205.1, 171.6, 141.6, 128.5, 128.3, 125.8, 91.4, 84.7, 60.7, 35.1, 34.9, 30.1, 14.2. HRMS (ESI) *m*/*z* calculated for $C_{15}H_{18}O_2$ [M]$^+$ 230.1302, found 230.1307.

Compound 3.S5. Following the general procedure outlined for the preparation of allenol **3.S2**, homoallenic ester **3.S4** gave **3.S5** as a colorless oil in 83% yield. ^{1}H NMR: (500.0 MHz, $CDCl_3$) δ 7.28 (m, 2H), 7.19 (m, 3H), 5.19 (qt, *J* = 6.5, 2.8 Hz, 1H), 5.09 (qt, *J* = 6.5, 3.0 Hz, 1H), 3.62 (t, *J* = 6.1 Hz, 2H), 2.73 (m, 2H), 2.33 (2.33, 2H), 2.19 (qd, *J* = 6.5, 2.8 Hz, 2H), 1.55 (br s, 1H). ^{13}C NMR: (125.7 MHz, $CDCl_3$) delta 204.7, 141.6, 128.5, 128.3, 125.8, 90.9, 87.7, 61.9, 35.3, 32.1, 30.5. HRMS (EI) *m*/*z* calculated for $C_{11}H_{12}$ [M-CH_2CH_2O]$^+$ 144.0934, found 144.0931.



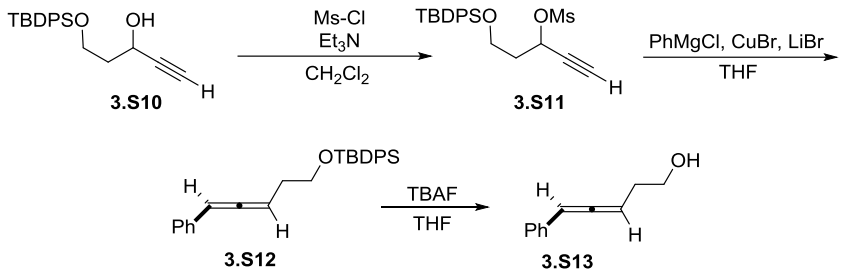
Compound 3.S7. Aldehyde **3.S6** (14.5 g, 75.4 mmol, 1.0 equiv) was placed in a 500 mL round bottom flask and dissolved in 100 mL dry THF. The solution was cooled to 0 °C and

ethynylmagnesium bromide (0.5 M in THF, 180 mL, 90.0 mmol, 1.20 equiv) was added dropwise. The solution stirred for 30 minutes, and was quenched with 200 mL NH_4Cl (aq). The phases were separated, and the aqueous phase extracted with EtOAc (3 x 150 mL). Combined organic fractions were washed with brine, dried with $MgSO_4$, and concentrated by rotary evaporation to a crude oil. Silica gel chromatography (20% EtOAc in hexanes) gave **3.S7** as a colorless oil (15.1 g, 69.4 mmol, 92%). ^{1}H NMR: (500.0 MHz, $CDCl_3$) δ 7.52 (m, 2H), 7.36 (m, 3H), 4.30 (qd, *J* = 5.9, 1.9 Hz, 1H), 2.45 (d, *J* = 1.9 Hz, 1H), 1.85 (d, *J* = 5.9 Hz, 1H), 1.71 (m, 2H), 0.90 (m, 2H), 0.29 (s, 6H). ^{13}C NMR: (125.7 MHz, $CDCl_3$) δ 138.7, 133.5, 129.0, 127.8, 84.8, 73.0, 64.5, 32.1, 10.6, -3.2. HRMS (EI) *m*/*z* calculated for $C_{12}H_{15}OSi$ $[M–CH_3]^+$ 203.0887, found 203.0892.

Compound 3.S8. Propargyl alcohol **3.S7** (10.3 g, 47.0 mmol, 1.0 equiv) was placed in a 100 mL round bottom flask. Triethyl orthoacetate (26 mL, 141 mmol, 3.0 equiv) was added with 5 drops of propionic acid. The flask was attached to a distillation head, and the solution was heated to 120 °C overnight. The reaction was cooled and diluted with 200 mL Et_2O. The solution was washed with 0.1 M HCl (3 x 150 mL) and dried with $MgSO_4$. Removal of volatiles by rotary evaporation gave crude ester **3.S8** that was used immediately without further purification.

Compound 3.S9. The crude ester **3.S8** was dissolved in 50 mL dry THF and added to a suspention of $LiAlH_4$ (3.57 g, 94.1 mmol, 2 equiv) in 200 mL THF at 0 °C. The suspension was stirred for 30 minutes, and the reductant was quenched by Fieser workup. The slurry was filtered, and volatiles removed by rotary evaporation. The crude residue was purified by silica gel chromatography (10% to 30% EtOAc in hexanes) to give **3.S9** as a pale yellow oil (8.85 g, 35.9 mmol, 76% over 2 steps). ^{1}H NMR: (500.0 MHz, $CDCl_3$) δ 7.51 (m, 2H), 7.35 (m, 3H), 5.21 (qt, *J* = 6.4, 2.9 Hz, 1H), 5.10 (qt, *J* = 6.4, 3.3 Hz, 1H), 3.69 (t, *J* = 6.2 Hz, 2H), 2.24 (qd, *J* = 6.4, 2.9 Hz, 2H), 2.02 (m, 2H), 1.56 (br s, 1H), 0.87 (m, 2H), 0.28 (s, 6H). ^{13}C NMR: (125.7 MHz, $CDCl_3$) δ 204.0, 139.1, 133.6, 128.9,

127.8, 94.5, 88.0, 62.0, 32.3, 23.2, 15.1, -3.1, -3.1. HRMS (ESI) *m/z* calculated for $C_{15}H_{26}NOSi$ $[M+NH_4]^+$ 264.1778, found 264.1790.



Compound 3.S11. Propargyl alcohol **3.S10** (10.0g, 29.6 mmol, 1.0 equiv) was dissolved in 90 mL CH_2Cl_2 and cooled to 0 °C. Triethylamine (4.91 mL, 35.5 mmol, 1.2 equiv) was added, followed by Ms-Cl (2.76 mL, 35.5 mmol, 1.2 equiv). After 35 minutes, the reaction was quenched with 1 M HCl. The phases were separated and the organic phase was washed with $NaHCO_3$ solution, dried with $MgSO_4$, and volatiles removed by rotary evaporation. The crude mesylate **3.S11** was used immediately without further purification.

Compound 3.S12. A 250 mL round bottom flask was charged with CuBr (4.65 g, 32.5 mmol, 1.1 equiv) and LiBr (2.83 g, 32.5 mmol, 1.1 equiv) under nitrogen. 74 mL dry THF was added, and the solution was cooled to 0 °C. PhMgBr (2.1 M in THF, 15.5 mL, 32.5 mmol, 1.1 equiv) was added dropwise and the solution stirred for 30 minutes. Mesylate **3.S11** was added to the solution in 6 mL THF. The reaction stirred for 90 minutes, and was quenched by the addition of 200 mL of a 2% aqueous NH_4Cl solution that contained 6.5 g NaCN. 200 mL Et_2O was added, and the phases were separated. The organic phase was washed with NH_4Cl (aq), brine, dried with $MgSO_4$ and concentrated by rotary evaporation. Silica gel chromatography (0% to 10% EtOAc in hexanes) gave **3.S12** as a clear, colorless oil (9.78 g, 24.6 mmol, 83%). ^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.68 (m, 4H), 7.41 (m, 2H), 7.38 – 7.33 (m, 4H), 7.26 (m, 4H), 7.17 (m, 1H), 6.10 (dt, *J* = 6.4, 2.7 Hz, 1H), 5.61 (q, *J* = 6.4 Hz, 1H), 3.80 (t, *J* = 6.6 Hz, 2H), 2.39 (qd, *J* = 6.6, 2.7 Hz, 2H), 1.06 (s, 9H).

^{13}C NMR: (125.7 MHz, $CDCl_3$) δ 205.9, 135.8, 135.8, 135.0, 134.0, 134.0, 129.8, 128.7, 127.9, 126.9, 126.9, 94.7, 92.1, 63.8, 32.5, 27.0, 19.4. HRMS (EI) *m*/*z* calculated for $C_{23}H_{21}OSi$ [M-C_4H_9]$^+$ 341.1357, found 341.1358.

Compound 3.S13. Silyl ether **3.S12** (6.14 g, 15.4 mmol, 1.0 equiv) was dissolved in 60 mL THF and cooled to 0 °C. TBAF (1.0 M in THF, 18.5 mL, 18.5 mmol, 1.2 equiv) was added over 2 minutes. After 2 hours, the reaction was quenched with NH_4Cl (aq) and extracted with EtOAc. The organic fractions were washed with brine, dried with Na_2SO_4, and concentrated by rotary evaporation. Silica gel chromatography (0% to 20% EtOAc in hexanes) gave **3.S13** as a pale yellow oil (1.77g, 11.1 mmol, 72%). Characterization data was consistent with previous reports.[4]

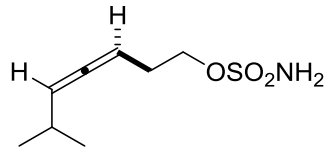
3.5.3. Preparation of homoallenic sulfamates

General procedure A: The following procedure is taken from a published literature procedure by Du Bois.[5] Formic acid (1.5 equiv) was added over 10 min to a rapidly stirred solution of neat chlorosulfonyl isocyanate (1.5 equiv) at 0 °C (Caution: significant gas evolution!). After the addition was completed, the mixture was stirred for an additional 5 min to yield a white solid. Dichloromethane was added (1.9 M) and the resulting solution stirred at room temperature for 6-8 h. The solution was cooled to 0 °C and a mixture of the homoallenic alcohol (1.0 equiv) and pyridine (1.5 equiv) in dichloromethane (1.4 M in alcohol) was added dropwise. The flask was warmed to room temperature and stirred for 1 h. The mixture was quenched with EtOAc and H_2O, the biphasic mixture extracted with three portions of EtOAc and the combined organics washed with brine. Silica gel chromatography (hexanes/ethyl acetate gradient) afforded the sulfamate esters.

General procedure B: The following procedure is taken from a published literature procedure by Du Bois.[6] Formic acid (2.5 equiv) was added over 2-3 min to a rapidly stirred solution of neat

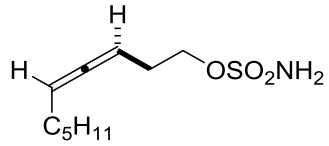
chlorosulfonyl isocyanate (2.5 equiv) at 0 °C. Vigorous gas evolution was observed during the addition process, resulting in solidification of the mixture to a white solid within 5 min. Acetonitrile was added to the resulting white mass (6 mL per mmol of alcohol) and the contents warmed to 23 °C. After stirring for 4-8 h, the mixture was cooled to 0 °C and a solution of the corresponding homoallenic alcohol (1.0 equiv) in N,N-dimethylacetamide (DMA, same volume as for acetonitrile) was added *via* syringe. The reaction was warmed to 23 °C and stirred for 1.5-2 h (Note: TLC monitoring can be attempted, but the product and starting material often have the same R_f values). After the reaction was complete, the mixture was carefully quenched by the addition of H_2O and poured into a separatory funnel containing Et_2O. The organic phase was collected and the aqueous layer was extracted twice with portions of H_2O. The combined organic extracts were washed five times with H_2O, once with a saturated solution of NaCl and then dried over Na_2SO_4. The solution was decanted and concentrated by rotary evaporation to give a crude oil that was purified by silica gel chromatography (hexanes/EtOAc gradient) to afford the sulfamate ester.

(Note: Either method can be used for all substrates described in the SI; the choice of method was based on the preference of the individual authors.)

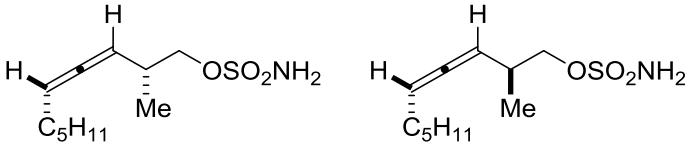


Compound 3.1. Following general procedure A, 2.54 g of the homoallenic alcohol (20.1 mmol) yielded upon silica gel chromatography (10-30% EtOAc in Hexanes) 3.18 g of the sulfamate (15.5 mmol, 77%). ^{1}H NMR (400.2 MHz, $CDCl_3$) δ 5.21 (m, 1H), 5.14 (m, 1H), 5.03 (br s, 2H), 4.25 (t, *J* = 6.7 Hz, 2H), 2.44 (app qd, *J* = 6.7, 2.9 Hz, 2H), 2.29 (m, 1H), 1.01 (d, *J* = 6.7 Hz, 6H). ^{13}C

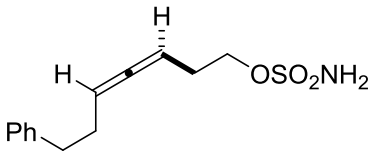
NMR (100.6 MHz, $CDCl_3$) δ 203.1, 99.8, 86.7, 70.4, 28.5, 27.7, 22.3, 22.3. HRMS (ESI) *m/z* calculated for $C_8H_{19}N_2O_3S$ [M+NH_4^+] 223.1111, found 223.1105.



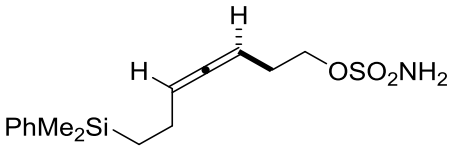
Compound 3.68. Following general procedure B, 2.0 g of homoallenic alcohol (13.0 mmol) yielded upon silica gel chromatography (10% to 30% EtOAc in Hexanes) 2.63 g of the sulfamate (11.3 mmol, 87%). Spectral data was consistent with the reported values.[7]



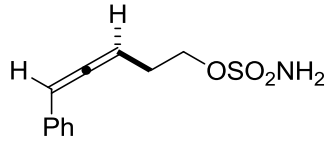
Compounds 3.S14. Following general procedure A, 6.80 g of homoallenic alcohol (40.4 mmol, ~1.25:1 mixture of isomers) yielded upon silica gel chromatography (10% to 30% EtOAc in Hexanes) 6.84 g of the two homoallenic sulfamates **3.S14** as an inseparable mixture of isomers (27.7 mmol, 68%, in a ratio of ~ 1.25:1). ^{1}H NMR (500.0 MHz, $CDCl_3$) δ 5.22 (m, 1H), 5.10 (m, 1H), 4.80 (br s, 2H), 4.14 (app dd, *J* = 9.1, 6.1 Hz, 1H), 4.01 (m, 1H), 2.59 (m, 1H), 1.99 (app qd, *J* = 7.2, 2.8 Hz, 2H), 1.36-1.44 (m, 2H), 1.27-1.34 (m, 4H), 1.10 (d, *J* = 6.7 Hz, 3H), 0.89 (t, *J* = 6.2 Hz, 3H). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 203.5, 93.5, 93.4, 91.9, 75.3, 75.3, 32.8, 32.7, 31.3, 28.8, 28.7, 28.7, 22.5, 16.6, 16.5, 14.0. HRMS (ESI) *m/z* calculated for $C_{11}H_{25}N_2O_3S$ [M+NH_4^+] 265.1581, found 265.1572.



Compound 3.S15. Following general procedure B, 3.07 g of homoallenic alcohol (16.3 mmol) yielded upon silica gel chromatography (10% to 40% EtOAc/hexane) 3.45 g of the sulfamate (12.9 mmol, 79%). ^{1}H NMR (500.0 MHz, $CDCl_3$) δ 7.28 (m, 2H), 7.19 (m, 3H), 5.22 (qt, *J* = 6.3, 2.8 Hz, 1H), 5.09 (qt, *J* = 6.3, 2.8 Hz), 4.67 (bs, 2H), 4.16 (app td, *J* = 6.8, 2.8 Hz, 2H), 2.73 (m, 2H), 2.35 (m, 4H). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 204.8, 141.5, 128.5, 128.3, 125.9, 91.7, 86.1, 70.3, 35.1, 30.1, 28.3. HRMS (ESI) *m*/*z* calculated for $C_{13}H_{21}N_2O_3S$ [M + NH_4^+] 285.1268, found 285.1279.

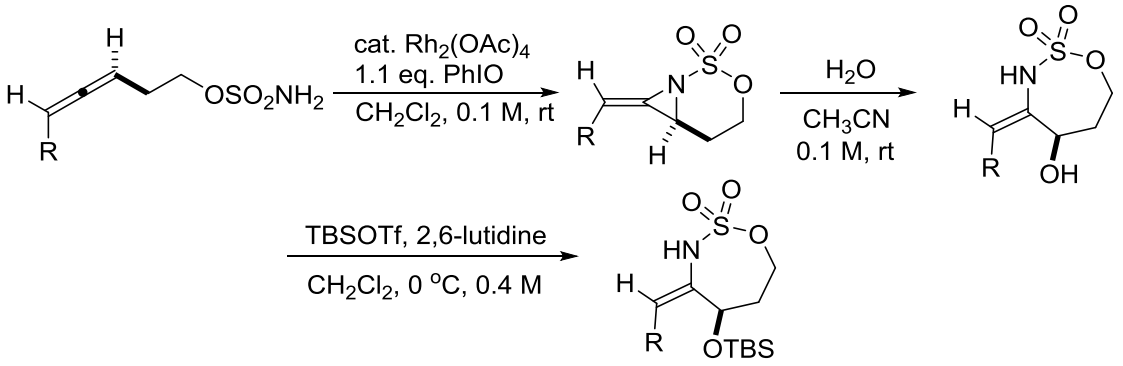


Compound 3.S16. Following general procedure A, 1.26 g of homoallenic alcohol (5.11 mmol) yielded upon silica gel chromatography (5% to 20% EtOAc in hexanes) 1.20 g of the sulfamate (3.69 mmol, 72%). ^{1}H NMR (500.0 MHz, $CDCl_3$) δ 7.51 (m, 2H), 7.36 (m, 3H), 5.24 (m, 1H), 5.10 (m, 1H), 4.66 (br s, 2H), 4.23 (t, *J* = 6.7 Hz, 2H), 2.42 (app qd, *J* = 6.7, 2.8 Hz, 2H), 2.02 (m, 2H), 0.87 (m, 2H), 0.28 (s, 6H). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 204.1, 139.1, 133.6, 128.9, 127.8, 95.2, 86.4, 70.4, 28.5, 23.0, 15.0, -3.1. HRMS (ESI) *m*/*z* calculated for $C_{15}H_{27}N_2O_3SSi$ [M+NH_4^+] 343.1507, found 343.1496.



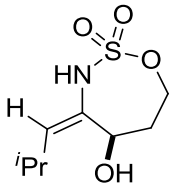
Compound 3.S17. Following general procedure B, 2.00 g of the homoallenic alcohol (12.5 mmol) yielded upon silica gel chromatography (0% to 30% EtOAc/hexane) 2.20 g of the sulfamate (9.21 mmol, 74%). ^{1}H NMR (500.0 MHz, $CDCl_3$) δ 7.35-7.29 (m, 4H), 7.22 (m, 1H), 6.24 (dt, *J* = 6.4, 3.0 Hz, 1H), 5.61 (q, *J* = 6.4 Hz, 1H), 4.52 (bs, 2H), 4.34 (t, *J* = 6.4 Hz, 2H), 2.59 (qd, *J* = 6.4, 3.0 Hz, 2H). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 205.8, 134.0, 128.7, 127.3, 126.8, 96.0, 90.0, 69.7, 28.1. HRMS (ESI) *m*/*z* calculated for $C_{11}H_{17}N_2O_3S$ [M+NH_4^+] 257.0955, found 257.0961.

3.5.4. One-pot synthesis of enesulfamates from homoallenic sulfamates



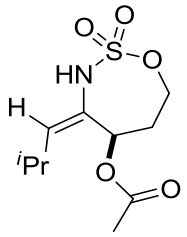
General procedure: A flame-dried roundbottom flask equipped with a stir bar was charged with the appropriate homoallenic sulfamate (1.0 equiv) and $Rh_2(OAc)_4$ (0.005 equiv). Dry dichloromethane was added to prepare a 0.1 M solution, and the mixture stirred vigorously to yield a faint green-blue solution. Iodosylbenzene (1.1 equiv) was added in one portion, and the resulting suspension stirred at room temperature for approximately 1 h. The reaction was monitored by TLC for consumption of starting material (~30% EtOAc/hex or 100% CH_2Cl_2 solvent system, CAM stain). Upon complete consumption of the starting material, the solution was concentrated by rotary evaporation, and CH_3CN was added to the residue to prepare a 0.1 M solution. Water (50 equiv) was added, and the solution stirred at room temperature for approximately 1 h until TLC indicated complete consumption of the intermediate bicyclic methylene aziridine (~30%

EtOAc/hex or 100% CH_2Cl_2 solvent system, CAM stain). Upon completion, the reaction was poured into a beaker of appropriate size and diluted by a factor of 2-3 with CH_2Cl_2. The solution was dried by the addition of Na_2SO_4 until the initially cloudy solution turned clear, and the resulting suspension decanted. The residual material was washed twice with CH_2Cl_2, the organic portions combined and concentrated by rotary evaporation. The residue was then dissolved in dry CH_2Cl_2 (0.4 M) and cooled to 0 ºC. A portion of 2,6-lutidine was added all at once, followed by the slow addition of TBSOTf over approximately 1 min. The reaction was stirred at 0 °C until complete consumption of the starting material was observed by TLC, usually within 30 min (~30% EtOAc/hex or 100% CH_2Cl_2 solvent system, CAM stain). The reaction mixture was diluted with CH_2Cl_2 and washed twice with portions of saturated NH_4Cl and NaCl solutions. The organic layer was dried over Na_2SO_4 and concentrated by rotary evaporation to yield a crude oil that is purified by silica gel chromatography to yield the (*E*)-enesulfamate typically as oils.

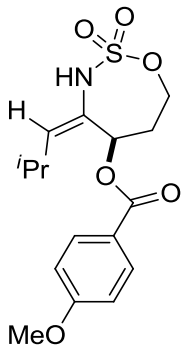


Compound 3.2. A 0.430 g portion of the homoallenic sulfamate (2.09 mmol) was subjected to aziridination/ring-opening conditions. The water-opened intermediate was purified by column chromatography (10-40% EtOAc in Hexanes) to yield 0.367 g product as a white solid (1.66 mmol, 79%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.59 (br s, 1H), 5.61 (d, *J* = 10.5 Hz, 1H), 4.94 (td, *J* = 3.2, 2.8 Hz, 1H), 4.72 (dd, *J* = 13.0, 12.5 Hz, 1H), 4.19 (dt, *J* = 13.0, 3.2 Hz, 1H), 2.55 (d sep, *J* = 10.5, 6.8 Hz, 1H), 2.52 (d, *J* = 3.2 Hz, 1H), 2.15 (ddt, *J* = 15.2, 12.5, 3.2 Hz, 1H), 2.04 (dt, *J* = 15.3, 2.8 Hz, 1H), 1.05 (d, *J* = 6.8 Hz, 1H), 1.03 (d, *J* = 6.8 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.4,

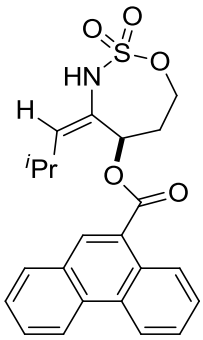
129.2, 64.8, 64.0, 36.8, 26.7, 22.7, 22.7. HRMS (ESI) *m*/*z* calculated for $C_8H_{19}N_2O_4S$ [M+NH_4^+] 239.1061, found 239.1061.



Compound 3.3. A portion of 0.267 g of the homoallenic sulfamate precursor (1.30 mmol) was subjected to aziridination conditions. After 2 h, 0.446 mL AcOH (7.80 mmol, 6 equiv) was added and the reaction was stirred overnight. The reaction mixture was then filtered through Celite and concentrated to yield a crude oil. Purification by column chromatography (5% to 25% EtOAc in Hexanes) yielded the product as a white solid (0.234 g, 0.931 mmol, 72%). ^{1}H NMR (500.0 MHz, $CDCl_3$) δ 6.01 (br s, 1H), 5.93 (t, *J* = 3.4 Hz, 1H), 5.79 (d, *J* = 10.5 Hz, 1H), 4.62 (dd, *J* = 13.1, 12.2 Hz, 1H), 4.23 (dt, *J* = 13.1, 3.4 Hz, 1H), 2.64 (d sep, *J* = 10.5, 6.6 Hz, 1H), 2.22 (ddt, *J* = 15.9, 12.2, 3.4 Hz, 1H), 2.10-2.15 (m, 4H), 1.06 (d, *J* = 6.6 Hz, 3H), 1.04 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 169.1, 143.0, 125.5, 66.8, 65.0, 34.7, 27.1, 22.6, 22.3, 21.1. HRMS (ESI) *m*/*z* calculated for $C_{10}H_{21}N_2O_5S$ [M+NH_4^+] 281.116, found 281.1164.

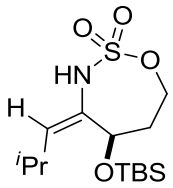


Compound 3.4. A portion of 0.267 g of the homoallenic sulfamate (1.30 mmol) was subjected to aziridination conditions. After 2 h, 0.297 g of *p*-anisic acid (1.95 mmol, 1.50 equiv) was added and the mixture filtered through Celite. The filtrate was concentrated and the residue redissolved in 1.3 mL of dry CH_3CN. The solution was heated to 50 °C for 1 h. The crude reaction mixture was then diluted with dichloromethane, washed with aqueous $NaHCO_3$, and concentrated. Purification of the crude residue by column chromatography (5 to 25% EtOAc in Hexanes) yielded the product as a white solid (0.316 g, 0.889 mmol, 68%). ^{1}H NMR (500.0 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.8 Hz, 2H), 6.96 (d, *J* = 8.8 Hz, 2H), 6.15 (t, *J* = 3.3 Hz, 1H), 6.12 (br s, 1H), 5.81 (d, *J* = 10.5 Hz, 1H), 4.74 (ddd, *J* = 13.1, 10.8, 1.4 Hz, 1H), 4.30 (dt, *J* = 13.1, 3.3 Hz, 1H), 3.89 (s, 3H), 2.73 (d sep, *J* = 10.5, 6.7 Hz, 1H), 2.25-2.38 (m, 2H), 1.09 (d, *J* = 6.7 Hz, 3H), 1.07 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ164.5, 164.0, 143.1, 131.8, 125.8, 121.3, 114.0, 67.0, 65.3, 55.5, 34.8, 27.2, 22.7, 22.4. HRMS (ESI) *m*/*z* calculated for $C_{16}H_{25}N_2O_6S$ [M+NH_4^+] 373.1428, found 373.1436.

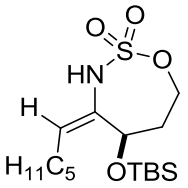


Compound 3.5. Silver triflate (0.565 g, 2.20 mmol, 2.2 equiv) was mixed with 10 mL of dry dichloromethane and the mixture cooled to 0 °C. A portion of 0.481 g of 9-phenanthroyl chloride (2.00 mmol, 1.0 equiv) was added and the slurry stirred for 30 min. The 9-phenanthroyl triflate solution was then cooled to -78 °C, and 0.433 g of **1** (2.00 mmol) was added in 5 mL dry dichloromethane containing 2,6-lutidine (0.255 mL, 2.20 mmol, 1.10 equiv). After stirring for 20

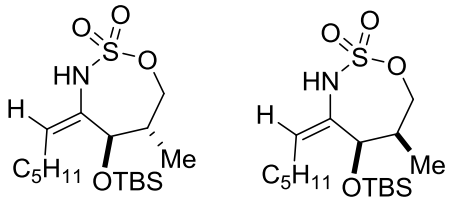
min, the cold bath was removed and the reaction warmed to room temperature for 30 min. The crude solution was filtered over Celite, washed with aqueous NH_4Cl, dried with $MgSO_4$ and concentrated to a crude oil. The residue was purified by column chromatography (6 to 30% EtOAc in hexanes) to give the product as an off-white solid (0.623 g, 1.46 mmol, 73%). ^{1}H NMR (500.0 MHz, $CDCl_3$) δ 8.81 (d, *J* = 8.1 Hz, 1H), 8.76 (d, *J* = 7.9 Hz, 1H), 8.71 (d, *J* = 8.4 Hz, 1H), 8.42 (s, 1H), 8.02 (d, *J* = 7.9 Hz, 1H), 7.80 (t, *J* = 7.9 Hz, 1H), 7.67-7.76 (m, 3H), 6.32 (t, *J* = 3.1 Hz, 1H), 6.14 (br s, 1H), 5.89 (d, *J* = 10.4 Hz, 1H), 4.80 (m, 1H), 4.36 (dt, *J* = 13.2, 3.2 Hz, 1H), 2.83 (d sep, *J* = 10.4, 6.5 Hz, 1H), 2.40-2.47 (m, 2H), 1.14 (app d, *J* = 6.5 Hz, 6H). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 165.7, 143.6, 132.6, 132.4, 130.8, 130.2, 129.7, 129.5, 128.7, 127.7, 127.3, 127.3, 126.1, 125.7, 125.1, 123.1, 122.7, 67.7, 65.4, 34.8, 27.4, 22.7, 22.5. HRMS (ESI) *m*/*z* calculated for $C_{23}H_{26}NNaO_5S$ [M+Na^+] 448.1190, found 448.1190.



Compound 3.7. The general procedure was employed to convert 0.100 g of the precursor homoallenic sulfamate (0.487 mmol) to 0.119 g of enesulfamate as a clear oil (0.355 mmol, 73% yield) after silica gel chromatography (9:1 hexanes:EtOAc). ^{1}H NMR (500.0 MHz, $CDCl_3$) δ 6.33 (br s, 1H), 5.60 (d, *J* = 10.6 Hz, 1H), 4.83 (t, J = 2.8 Hz, 1H), 4.68 (t, *J* = 12.7 Hz, 1H), 4.15 (dt, *J* = 12.7, 2.8 Hz, 1H), 2.51 (m, 1H), 2.09 (ddt, *J* = 15.1, 12.7, 2.8 Hz, 1H), 1.86 (dt, *J* = 15.1, 2.8 Hz, 1H), 1.05 (d, *J* = 6.6 Hz, 3H), 1.03 (d, *J* = 6.4 Hz, 3H), 0.90 (s, 9H), 0.10 (s, 3H), 0.08 (s, 3H). 13C NMR (125.7 MHz, $CDCl_3$) δ 136.9, 129.4, 64.9, 64.5, 38.2, 26.8, 25.7, 22.8, 22.5, 18.1, -4.9, -5.1. HRMS (ESI) *m*/*z* calculated for $C_{14}H_{30}NO_4SSi$ [M+H^+] 336.1660, found 336.1657.



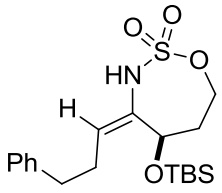
Compound 3.14. According to the general procedure, 1.51 g of the homoallenic sulfamate precursor (6.48 mmol) yielded 1.29 g of enesulfamate (3.55 mmol, 55% yield) after silica gel chromatography (0% to 15% EtOAc/hexane). The product was a colorless liquid that solidified upon storage in a 0 °C freezer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.35 (s, 1H), 5.75 (t, 7.8 Hz, 1H), 4.81 (t, *J* = 3.0 Hz, 1H), 4.68 (t, *J* = 12.7 Hz, 1H), 4.16 (dt, *J* = 12.7, 3.0 Hz, 1H), 2.08 (m, 3H), 1.84 (dt, *J* = 15.0, 3.3 Hz, 1H), 1.47-1.39 (m, 2H), 1.36-1.26 (m, 4H), 0.92-0.88 (m, 12H), 0.10 (s, 3H), 0.08 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 131.2, 130.3, 64.7, 64.6, 37.7, 31.4, 28.7, 26.7, 25.7, 22.4, 18.1, 13.9, -4.9, -5.1. HRMS (ESI) *m*/*z* calculated for $C_{16}H_{37}N_2O_4SSi$ [M+NH_4^+] 381.2238, found 381.2248.



3.15 **3.S5**

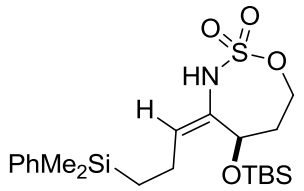
Compounds 3.15 and 3.S18. The compounds were prepared by a modification of the general procedure. The homoallenic sulfamate precursor **3.S14** (2.00 g, 8.01 mmol), prepared as a 1.25:1 mixture of diastereomers, was subjected to the aziridination/water ring-opening conditions. After dilution with dichloromethane, drying, filtration, and concentration, the crude enesulfamate was purified by column chromatography on silica gel (10%-50% EtOAc in hexanes) to separate the *anti* and *syn* stereoisomers prior to silylation (1.67 g, 6.34 mmol, 79% yield, *dr* ~ 1.25:1 *anti:syn*).

The silyl protection was performed on each individual alcohol using TBSOTf and 2,6-lutidine as outlined in the general procedure. Silylation of 0.770 g of the *anti*-isomer yielded 0.903 g (2.39 mmol, 82%) of **3.15** as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.29 (s, 1H), 5.85 (dd, *J* = 8.3, 6.9 Hz, 1H), 4.75 (d, *J* = 12.9 Hz, 1H), 4.49 (d, *J* = 3.0 Hz, 1H), 3.92 (dd, *J* = 12.9, 2.6 Hz, 1H), 2.08 (m, 2H), 1.92 (m, 1H), 1.30-1.50 (m, 6H), 1.08 (d, *J* = 7.3 Hz, 3H), 0.89 (m, 12H), 0.10 (s, 3H), 0.07 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 132.9, 128.9, 69.7, 68.9, 41.3, 31.5, 28.7, 27.5, 25.7, 22.4, 18.1, 13.9, 13.1, -4.9, -5.1. HRMS (ESI) *m*/*z* calculated for $C_{17}H_{39}N_2O_4SSi$ [M+NH_4^+] 395.2395, found 395.2384. Silylation of 0.412 g of the *syn*-isomer (1.56 mmol) yielded 0.414 g (1.10 mmol, 70%) of **3.S18** as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.26 (br s, 1H), 5.76 (t, *J* = 7.6 Hz, 1H), 4.53 (s, 1H), 4.42 (dd, *J* = 12.6, 11.3 Hz, 1H), 3.84 (dd, *J* = 12.6, 2.8 Hz, 1H), 2.00-2.17 (m, 3H), 1.44 (app p, *J* = 7.0 Hz, 2H), 1.25-1.36 (m, 4H), 0.87-0.96 (m, 15H), 0.11 (s, 3H), 0.05 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 131.6, 130.1, 77.3, 77.0, 76.7, 69.0, 68.8, 40.3, 31.4, 28.7, 26.6, 25.7, 22.4, 18.1, 13.9, 13.8, -5.0. HRMS (ESI) *m*/*z* calculated for $C_{17}H_{39}N_2O_4SSi$ [M+NH_4^+] 395.2395, found 395.2396. [Note: the *syn* isomer **3.S18** was not used in the studies reported in this work.]

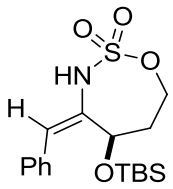


Compound 3.16. According to the general procedure, 2.50 g of the homoallenic sulfamate precursor (9.36 mmol) yielded 2.27 g of enesulfamate as a faint yellow liquid (5.70 mmol, 61% yield) after silica gel chromatography (10% to 40% EtOAc in Hexane). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (m, 2H), 7.22-7.16 (m, 3H), 6.33 (s, 1H), 5.80 (t, *J* = 7.9 Hz, 1H), 4.66 (t, *J* = 2.9

Hz, 1H), 4.60 (t, *J* = 12.5 Hz, 1H), 4.04 (dt, *J* = 12.5, 3.1 Hz, 1H), 2.75 (m, 2H), 2.44 (m, 1H), 2.34 (m, 1H), 1.65 (dt, *J* = 15.0, 3.0 Hz, 1H), 1.55 (ddt, *J* = 15.0, 12.0, 3.0 Hz, 1H), 0.87 (s, 9H), 0.05 (s, 3H), 0.02 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.7, 132.0, 129.0, 128.7, 128.6, 126.2, 64.6, 64.5, 37.3, 35.2, 29.3, 25.6, 18.1, -5.0, -5.1. HRMS (ESI) *m*/*z* calculated for $C_{19}H_{35}N_2O_4SSi$ [M+NH_4^+] 415.2082, found 415.2089.



Compound 3.17. According to the general procedure, 1.00 g of the homoallenic sulfamate precursor (3.07 mmol) yielded 0.918 g of enesulfamate as an oil (2.03 mmol, 66% yield) after purification by silica gel chromatography (9:1 hexanes:EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (m, 2H), 7.37 (m, 3H), 6.30 (br s, 1H), 5.76 (dd, *J* = 8.3, 7.2 Hz, 1H), 4.62-4.68 (m, 2H), 4.12 (dt, *J* = 13.0, 3.2 Hz, 1H), 1.95-2.10 (m, 3H), 1.76 (dt, *J* = 15.0, 3.2 Hz, 1H), 0.82-0.89 (m, 10H), 0.28-0.32 (m, 7H), 0.04 (s, 3H), 0.02 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.2, 133.5, 132.5, 130.1, 129.1, 127.9, 64.5, 64.5, 37.7, 25.6, 21.1, 18.1, 15.7, -3.3, -3.3, -5.0, -5.1. HRMS (ESI) *m*/*z* calculated for $C_{21}H_{41}N_2O_4SSi_2$ [M+NH_4^+] 473.2321, found 473.2321.



Compound 3.18. Due to the instability of the intermediate methylene aziridine, a modified procedure was used to access compound **3.18**. To a 100 mL roundbottom flask was added the

homoallenic sulfamate precursor **3.S17** (598 mg, 2.50 mmol, 1 equiv) and rhodium (II) triphenylacetate (34.0 mg, 0.0251 mmol, 0.01 equiv, prepared according to the procedure of Huard and Lebel[8]). A portion of CH_2Cl_2 (25 mL, 0.1 M) was added, and the green solution was stirred for 2-3 min prior to addition of PhIO (1.10 g, 5.02 mmol, 2 equiv) in one portion at rt. The solution was stirred at rt for 30 min, at which point TLC (100% CH_2Cl_2, CAM stain) indicated complete consumption of the starting allene. The solution was filtered through a pad of Celite with CH_2Cl_2 and concentrated by rotary evaporation at room temperature (higher temperatures promoted product decomposition). The residue was dissolved in 15 mL CH_3CN and cooled to 0 °C in an ethylene glycol/water bath cooled by a chiller. Water (15 mL) was added, and the mixture was stirred at 0 °C for two days (higher temperatures gave lower yields due to decomposition of the methylene aziridine). After two days, the mixture was poured into a beaker and diluted five-fold with CH_2Cl_2. Na_2SO_4 was added, and the mixture was stirred until the cloudy solution turned transparent. The solution was decanted and concentrated by rotary evaporation. The residue was dissolved in 7 mL CH_2Cl_2, cooled to 0 °C and 2,6-lutidine (0.29 mL, 2.51 mmol, 1 equiv) was added slowly, followed by TBSOTf (0.58 mL, 2.51 mmol, 1 equiv). A TLC sample taken at 15 min (100% CH_2Cl_2, CAM stain) indicated incomplete reaction, so an additional 0.5 equiv of 2,6-lutidine and TBSOTf were added. After an additional 40 min at 0 °C, the reaction was quenched by the addition of a saturated solution of NH_4Cl. The mixture was extracted with CH_2Cl_2, the combined organic layers washed with saturated NH_4Cl and brine. The organic layer was dried over Na_2SO_4, decanted and the volatiles removed under reduced pressure. Purification of the crude oil was attempted *via* silica gel chromatography (0% to 15% EtOAc in hexanes), but the product was contaminated with Rh_2TPA_4 and an unknown yellow oil. Pure product was obtained by recrystallization from a mixture of hexanes/EtOAc. The solid was heated in boiling hexanes, and

small portions of EtOAc added gradually until complete dissolution was achieved. Upon cooling, the white solid was filtered and the recrystallization repeated to yield a combined 310.2 mg (0.838 mmol, 33%) of a white crystalline solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (m, 3H), 7.18 (app d, *J* = 7.0 Hz, 2H), 6.84 (s, 1H), 6.64 (bs, 1H), 4.91 (t, *J* = 2.9 Hz, 1H), 4.79 (t, *J* = 12.6 Hz, 1H), 4.27 (dt, *J* = 12.6, 3.1 Hz, 1H), 2.37 (ddt, *J* = 15.2, 12.5, 3.1 Hz, 1H), 1.95 (dt, *J* = 15.2, 3.0 Hz, 1H), 0.83 (s, 9H), -0.06 (s, 3H), -0.07 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.7, 133.2, 130.1, 128.6, 128.5, 128.2, 64.8, 64.7, 38.1, 25.6, 18.0, -5.1, -5.2. HRMS (ESI) *m*/*z* calculated for $C_{17}H_{31}N_2O_4SSi$ [$M+NH_4^+$] 387.1769, found 387.1768.

3.5.5. Computational models for enesulfamates 3.7 and (*Z*)-3.7

The geometries for enesulfamate **3.7** and **(*Z*)-3.7** were optimized using a suite of Gaussian 09 software at B3LYP/6-31G(d) level of theory.[9]

Enesulfamate **3.7** RB3LYP Energy = -1594.27176634 Hartree.

Cartesian coordinates for enesulfamate **3.7**:

C 0.00000000 0.00000000 0.00000000

C -1.00001800 0.01710100 -1.14616600

N -0.98779600 -1.19354600 -1.92352300

S -2.08224000 -2.40756200 -1.49816600

O -2.14227500 -2.32269700 0.14254700

C -0.87813400 -2.29170000 0.85671200

C -0.47487400 -0.85707600 1.19038800

H 0.34284800 -0.89221200 1.92160200

H	-1.32760700	-0.36140600	1.66972900
H	-0.10616400	-2.82111100	0.28966000
H	-1.06868100	-2.85617000	1.77253200
O	-3.42355100	-2.04341000	-1.90831400
O	-1.45158000	-3.65619400	-1.90891700
H	-0.05726800	-1.60790700	-1.96418500
C	-1.87822700	0.98073500	-1.45226800
C	-2.12660500	2.27995800	-0.73085800
C	-1.99328600	3.46514900	-1.70611000
H	-2.71644800	3.37768000	-2.52618700
H	-2.18352300	4.41407200	-1.19137900
H	-0.99121100	3.51058900	-2.14704300
C	-3.52415100	2.26383400	-0.07754600
H	-4.30689800	2.13483400	-0.83448400
H	-3.61957300	1.44292200	0.64077700
H	-3.71457200	3.20733600	0.44752000
H	-1.38481500	2.41117300	0.06749100
H	-2.52399300	0.78988500	-2.30917700
O	1.24058000	-0.54668000	-0.46285500
Si	2.54732500	0.32503300	-1.10505400
C	2.19843600	0.75760300	-2.91021300
H	2.10554400	-0.13759100	-3.53589600
H	1.26200800	1.32000400	-3.00329100

H 2.99929700 1.37604800 -3.33337300

C 2.78761300 1.91835300 -0.11468800

H 2.86296400 1.72779400 0.96180600

H 3.70895000 2.42570800 -0.42525400

H 1.96540700 2.62609700 -0.27416200

C 4.03477800 -0.86186000 -0.92926300

C 3.72098400 -2.20383700 -1.62570500

H 2.85020800 -2.69796800 -1.18042600

H 3.52440300 -2.07505200 -2.69713300

H 4.57456500 -2.89053100 -1.53258000

C 5.28471000 -0.23297500 -1.58412000

H 6.14854000 -0.90401600 -1.47526500

H 5.14429300 -0.05752500 -2.65758100

H 5.55849200 0.72310600 -1.12038100

C 4.32400900 -1.12678100 0.56380100

H 5.16395300 -1.82794400 0.67169500

H 4.59673300 -0.20849600 1.09827900

H 3.45822800 -1.56744600 1.07121900

H 0.15528100 1.02047100 0.36685000

Enesulfamate **(*Z*)-3.7** RB3LYP Energy = -1594.27473013 Hartree

Cartesian coordinates for enesulfamate **(*Z*)-3.7**:

C 0.00000000 0.00000000 0.00000000

C -1.10981700 0.38327800 -0.96764000

N -1.22418700 -0.50186600 -2.09463300

S -2.24922200 -1.84107600 -1.97174300

O -2.14035100 -2.28275900 -0.39602300

C -0.81077000 -2.45758200 0.16470400

C -0.36415800 -1.19674800 0.89916800

H 0.51966700 -1.44545600 1.50049500

H -1.16175500 -0.89645600 1.58907000

H -0.10566200 -2.75864500 -0.61604500

H -0.91832200 -3.29068800 0.86305900

O -3.63386600 -1.43409000 -2.11359000

O -1.64908800 -2.86196800 -2.82220700

H -0.30673700 -0.84381400 -2.38158800

C -1.91032100 1.44344800 -0.80631200

H -1.74097500 2.05410400 0.08326900

C -3.02795000 1.89915000 -1.70571900

C -4.38551100 1.78478600 -0.98528600

H -4.60136800 0.74519800 -0.72377500

H -4.40086800 2.38748200 -0.06756400

H -5.19068600 2.14665100 -1.63532400

C -2.76768900 3.34499400 -2.17024500

H -1.82189100 3.42548000 -2.71755700

H -3.57274600 3.68526500 -2.83170400

H -2.72448900 4.03470500 -1.31698700

H -3.05283200 1.24449600 -2.58258300

O 1.16938300 -0.35510200 -0.74930000

Si 2.49746800 0.65653200 -1.04631400

C 1.95786300 2.14048700 -2.08315100

H 1.57417800 1.83771700 -3.06388200

H 1.16110800 2.70148200 -1.58076800

H 2.79288000 2.83187400 -2.24900100

C 3.19206300 1.27380000 0.60096300

H 3.48172300 0.44710700 1.25916800

H 4.07988100 1.89690200 0.43852300

H 2.46501000 1.89127500 1.14242300

C 3.73753300 -0.46288700 -1.97271000

C 3.10339300 -0.99648600 -3.27569600

H 2.21324500 -1.60435800 -3.07605700

H 2.81470500 -0.18680700 -3.95698300

H 3.81917000 -1.63392600 -3.81405200

C 5.00403200 0.34905800 -2.32464000

H 5.72759200 -0.28722300 -2.85359500

H 4.78138800 1.19958100 -2.98077200

H 5.50802700 0.73689400 -1.43059700

C 4.13459900 -1.66113200 -1.08363800

H 4.83564200 -2.31716400 -1.61910300

H 4.63059000 -1.34051200 -0.15939800

H 3.26236500 -2.26336000 -0.80582500

H 0.20477000 0.85848700 0.65359200

3.5.6. Preparation of dimethyldioxirane

Dimethyldioxirane was prepared as a solution in acetone using a variation on the procedure of Murray and Singh,[10] then extracted into CH_2Cl_2 according to the procedure of Messeguer.[11,12] A 2 L, three-necked, roundbottom flask equipped with a magnetic stir bar was charged with water (160 mL), acetone (100 mL) and sodium bicarbonate (192 g). The flask was fitted with a pressure-equalizing addition funnel containing water (120 mL) and acetone (120 mL) and an air condenser. The outlet of the air condenser was attached to a receiving flask (cooled in a dry ice/acetone bath) and a dry ice/acetone trap. The dry ice/acetone trap was connected using Tygon tubing (not rubber) to an oil bubbler capable of carefully monitoring gas flow. Oxone (monopersulfate compound, 360 g total) was added portionwise to the stirred solution over ~30 minutes while the acetone/water mixture was simultaneously added to the flask in a dropwise fashion. A yellow solution of dimethyldioxirane in acetone collected in the receiving flask throughout the course of the addition. Vigorous stirring was continued for an additional 15 min while a slight vacuum (ca. 30 mm using a water aspirator) was applied to the cold trap. Approximately 100 mL of a yellow DMDO-acetone (0.05 – 0.1 M) solution was obtained that could be stored for several months at -70 °C or 1-2 weeks at 0 °C.

Extraction of DMDO into CH_2Cl_2: The freshly distilled DMDO solution in acetone (cooled to at least 0 °C) was diluted with an equal volume of cold water (the solution bubbles vigorously upon addition) and transferred to a separatory funnel. The solution was extracted four times with CH_2Cl_2

(4 x 1/20th of the initial volume of the acetone solution). The first extract typically could not be separated and was collected with the second extract. The combined extracts were washed five times with cold 0.01 M phosphate buffer, pH 7.0 (1.5 volume with respect to the volume to be washed) to remove excess acetone and water. The remaining solution was stored over Na_2SO_4 in a roundbottom flask sealed with a glass stopper. The flask was stored in a -70 ºC freezer (decomposition of the DMDO occurs more readily at 0 ºC, but it is typically stable for at least a week).

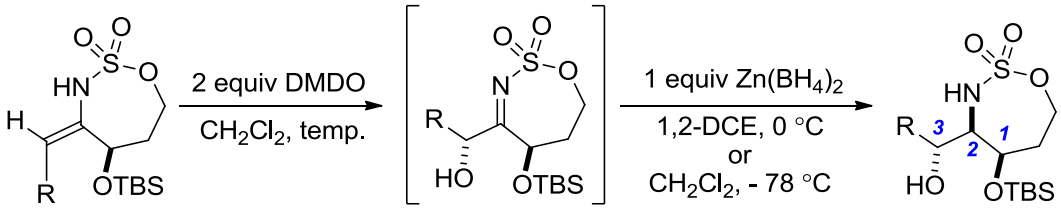
Titration of the DMDO/CH_2Cl_2 solution: The concentration of DMDO in solution was measured by the oxidation of a known amount of thioanisole to methyl phenyl sulfoxide (and a minor amount of methyl phenyl sulfone). In a typical titration, 10.0 mg (0.0805 mmol) of thioanisole is added to a 2 mL screw cap flask equipped with a stir bar. CH_2Cl_2 (0.5 mL) is added, and then DMDO (~0.25 M in CH_2Cl_2 if prepared by the above method, 0.1 mL, ~0.025 mmol) is added. The solution is stirred at rt for 1 h, then concentrated by rotary evaporation at rt. A crude ^{1}H NMR in $CDCl_3$ is taken with a relaxation delay (d1) of at least 5 s. Comparison of the ratio of thioanisole (~2.5 ppm) to methyl phenyl sulfoxide (~2.8 ppm) and methyl phenyl sulfone (~3.0 ppm), and based on the known mass of starting thioanisole, the concentration of the DMDO solution can be determined (typically 0.2 – 0.3 M).

3.5.7. Determination of *dr* for reaction of -OTBS protected enesulfamates with DMDO

General procedure: The purified (*E*)-enesulfamate (1 equiv) is added to a roundbottom flask and the flask is cooled to the specified temperature (see Tables 1, 2 and 5 in the manuscript). A solution of DMDO in CH_2Cl_2 (2 equiv) is added, the flask is capped and the solution stirred until complete consumption of the starting material is observed by TLC (~30% EtOAc/hex, CAM stain). At this

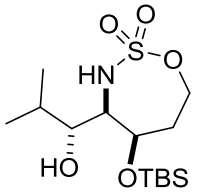
point, the solution is concentrated by rotary evaporation and the ratio of the imine diastereomers is measured by crude ^{1}H NMR in $CDCl_3$.

3.5.8. Synthesis of 1,2-*syn*:2,3-*anti* stereotriads

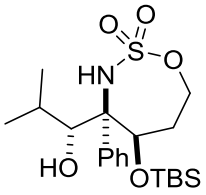


General procedure A: The appropriate (*E*)-enesulfamate (1 equiv) is added to a roundbottom flask and cooled to the specified temperature (see the individual entries for temperature). DMDO is added (2 equiv as a solution in CH_2Cl_2), the flask is capped and the resulting solution stirred at the specified temperature until complete consumption of the starting material was indicated by TLC (~ 30% EtOAc/hex, CAM stain). The solution is concentrated by rotary evaporation at room temperature, and 1,2-dichloroethane (0.05 - 0.1 M) is added. The solution is cooled to 0 °C, and 1 equiv of $Zn(BH_4)_2$ (0.5 M in THF, prepared according to the procedure of Narasimhan and Balakumar)[13] is added *via* syringe. The reaction is stirred at 0 °C until the reaction is complete and then quenched by the addition of a saturated solution of NH_4Cl. The mixture is transferred to a separatory funnel, diluted with additional CH_2Cl_2, then washed twice with saturated NH_4Cl and once with brine. The organic layer is dried over Na_2SO_4 and concentrated by rotary evaporation to give a crude oil, which is purified by silica gel chromatography to give the desired 1,2-*syn*;2,3-*anti* stereotriad, along with minor diastereomers. The *dr* and yield for the reaction are calculated based on the isolated masses of each diastereomer. As a rule, the isolated *dr* closely matches the *dr* of the crude material, as measured by ^{1}H NMR.

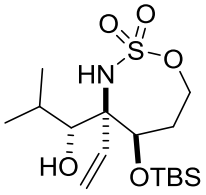
General procedure B: The reaction is run in a fashion identical to procedure A until completion of the DMDO oxidation. The reaction mixture is concentrated under vacuum at rt and CH_2Cl_2 added to the residue. The solution is cooled to -78 °C in an acetone/dry ice bath and 1 equiv of $Zn(BH_4)_2$ (0.5 M in THF) added. The mixture is stirred under TLC indicates complete consumption of the starting material, at which point the reaction is quenched by the addition of a saturated solution of NH_4Cl. Workup, purification, and determination of product yield and *dr* are performed in a manner identical to that described in General Procedure A.



Compound 3.25. 0.500 g of enesulfamate **3.7** (1.49 mmol) was subjected to General Procedure A, using 1.5 equiv DMDO in CH_2Cl_2 at 25 °C over 2.5 hours. This yielded 0.423 g of the stereotriad **3.25** as an oil (1.20 mmol, 80% yield) after silica gel chromatography (4-20% EtOAc in Hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.22 (d, *J* = 10.4 Hz, 1H), 4.58 (app t, *J* = 12.5 Hz, 1H), 4.56 (s, 1H), 4.16 (dt, *J* = 12.5, 3.1 Hz, 1H), 3.22-3.32 (m, 2H), 2.22 (sep d, *J* = 7.1, 1.9 Hz, 1H), 2.12 (ddt, *J* = 15.3, 12.5, 3.1 Hz, 1H), 1.89 (dt, *J* = 15.3, 3.1 Hz, 1H), 1.33 (d, *J* = 5.2 Hz, 1H), 1.00 (d, *J* = 7.1 Hz, 1H), 0.91-0.94 (m, 12H), 0.12 (s, 3H), 0.12 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 73.7, 65.7, 64.3, 57.8, 36.7, 28.2, 25.8, 20.2, 18.0, 13.4, -4.4, -4.9. HRMS (ESI) *m*/*z* calculated for $C_{14}H_{35}N_2O_5SSi$ [$M+NH_4^+$] 371.2031, found 371.2031.

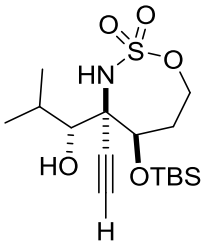


Compound 3.26. 0.100 g of enesulfamate **3.7** (0.298 mmol) was oxidized using 1.5 equiv DMDO in CH_2Cl_2 at 25 °C over 2.5 hours. After concentration, the crude imine was dissolved in 3.0 mL dry 1,2-dichloroethane, and the solution was cooled to 0 °C. 0.373 mL PhMgCl (2.0 M in THF, 0.745 mmol, 2.5 equiv) was injected and the solution was stirred for 1 hour. Workup was performed as described in General Procedure A. This yielded 0.108 g of the stereotriad **3.26** as a white solid (0.251 mmol, 84% yield) after silica gel chromatography (4-20% EtOAc in Hexanes). ^{1}H NMR: (500.0 MHz, $CDCl_3$) δ 7.30-7.70 (m, 5H), 5.16 (d, *J* = 5.7 Hz, 1H), 5.04 (s, 1H), 4.73 (td, *J* = 12.2, 1.0 Hz, 1H), 4.03 (dt, *J* = 12.2, 3.4 Hz, 1H), 3.44 (dd, *J* = 10.4, 2.0 Hz, 1H), 2.41 (dddd, *J* = 15.9, 12.2, 3.4, 1.0 Hz, 1H), 2.12 (sep d, *J* = 6.9, 2.0 Hz, 1H), 1.84 (m, 1H), 1.26 (d, *J* = 10.4 Hz, 1H), 1.00 (s, 9H), 0.97 (d, *J* = 6.9 Hz, 3H), 0.22 (s, 3H), 0.19 (s, 3H), 0.06 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR: (125.7 MHz, $CDCl_3$) δ 133.7, 128.1, 128.1, 128.1, 77.7, 71.6, 70.2, 65.1, 31.7, 27.1, 25.9, 23.8, 18.2, 15.4, -4.2, -5.1. HRMS (ESI) *m*/*z* calculated for $C_{20}H_{39}N_2O_5SSi$ [M+NH_4^+] 447.2344, found 447.2339.



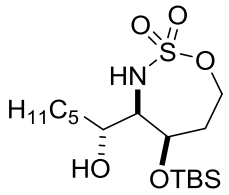
Compound 3.27. 0.0500 g of enesulfamate **3.7** (0.149 mmol) was oxidized using 2.0 equiv DMDO in CH_2Cl_2 at 25 °C over 2.0 hours. After concentration, the crude imine was dissolved in 1.5 mL dry diethyl ether, and the solution was cooled to -78 °C. 0.447 mL vinylmagnesium bromide (1.0

M in THF, 0.447 mmol, 3.0 equiv) was injected and the solution was stirred for 30 minutes. Workup was performed as described in General Procedure A. This yielded 0.0417 g of the stereotriad **3.27** as a colorless oil (0.110 mmol, 74% yield) after silica gel chromatography (4-20% EtOAc in Hexanes) along with 5.0 mg of a separable minor diastereomer (0.013 mmol, 9% yield). Major Isomer: ^{1}H NMR: (500.0 MHz, $CDCl_3$) δ 6.56 (dd, *J* = 18.4, 12.0 Hz, 1H), 5.46 (d, *J* = 12.0 Hz, 1H), 5.17 (br s, 1H), 5.13 (d, *J* = 18.4 Hz, 1H), 4.55-4.67 (m, 2H), 4.10 (dt, *J* = 12.8, 3.3 Hz, 1H), 3.33 (dd, *J* = 11.1, 3.7 Hz, 1H), 2.56 (dddd, *J* = 15.7, 12.8, 3.3, 2.0 Hz, 1H), 2.11 (sep d, *J* = 6.9, 3.7 Hz, 1H), 1.68 (dt, *J* = 15.7, 3.3 Hz, 1H), 1.47 (d, *J* = 11.1 Hz, 1H), 1.02 (d, *J* = 6.9 Hz, 3H), 0.94 (s, 9H), 0.86 (d, *J* = 6.9 Hz, 3H), 0.16 (s, 3H), 0.13 (s, 3H). ^{13}C NMR: (125.7 MHz, $CDCl_3$) δ 132.9, 117.9, 77.3, 69.2, 67.9, 64.4, 32.1, 28.7, 25.9, 22.8, 18.1, 17.7, -4.5, -5.1. HRMS (ESI) *m*/*z* calculated for $C_{16}H_{34}NO_5SSi$ [M+H$^+$] 380.1922, found 380.1925. Minor Diastereomer: ^{1}H NMR: (400.2 MHz, $CDCl_3$) δ 5.85 (dd, *J* = 17.3, 10.8 Hz, 1H), 5.34 (d, *J* = 17.3 Hz, 1H), 5.30 (d, *J* = 10.8 Hz, 1H), 5.06 (br s, 1H), 4.63 (app t, *J* = 11.9 Hz, 1H), 4.36 (d, *J* = 5.2 Hz, 1H), 4.28 (br s, 1H), 4.15 (ddd, *J* = 11.9, 4.0, 3.0 Hz, 1H), 2.51 (m, 1H), 2.13 (sep d, *J* = 6.8, 1.3 Hz, 1H), 1.89 (dt, *J* = 15.6, 4.7 Hz, 1H), 1.58 (s, 1H), 1.05 (d, *J* = 6.8 Hz, 3H), 0.91 (d, *J* = 6.8 Hz, 3H), 0.88 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H). HRMS (ESI) *m*/*z* calculated for $C_{16}H_{37}N_2O_5SSi$ [M+NH_4^+] 397.2187, found 397.2187.



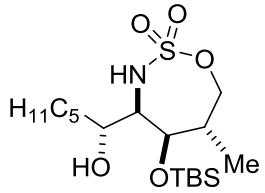
Compound 3.28. 0.100 g of enesulfamate **3.7** (0.298 mmol) was oxidized using 2.0 equiv DMDO in CH_2Cl_2 at 25 °C over 2.0 hours. After concentration, the crude imine was dissolved in 3.0 mL

dry THF, and the solution was cooled to 0 °C. 1.79 mL ethynylmagnesium bromide (0.5 M in THF, 0.894 mmol, 3.0 equiv) was injected and the solution was stirred for 60 minutes. Workup was performed as described in General Procedure A. This yielded 0.0906 g of the stereotriad **3.28** as a colorless oil (0.240 mmol, 81% yield) after silica gel chromatography (4-20% EtOAc in Hexanes) along with 12.0 mg of a separable minor diastereomer (0.0318 mmol, 11% yield). Major Isomer: ^{1}H NMR: (500.0 MHz, $CDCl_3$) δ 5.16 (br s, 1H), 4.63 (app t, *J* = 12.6 Hz, 1H), 4.49 (dd, *J* = 4.3, 1.8 Hz, 1H), 4.18 (dt, *J* = 12.6, 3.0 Hz, 1H), 3.28 (dd, *J* = 11.3, 4.0 Hz, 1H), 2.80 (s, 1H), 2.73 (dddd, *J* = 16.0, 12.6, 3.0, 1.8 Hz, 1H), 2.25 (sep d, *J* = 6.9, 4.0 Hz, 1H), 1.78 (dt, *J* = 16.0, 4.3 Hz, 1H), 1.66 (d, *J* = 11.3 Hz, 1H), 1.07 (d, *J* = 6.9 Hz, 3H), 1.05 (d, *J* = 6.9 Hz, 3H), 0.93 (s, 9H), 0.15 (s, 3H), 0.13 (s, 3H). ^{13}C NMR: (125.7 MHz, $CDCl_3$) δ 81.5, 76.4, 75.1, 70.6, 64.1, 62.1, 33.3, 29.8, 25.8, 22.1, 18.0, 16.7, -4.5, -5.1. HRMS (ESI) *m/z* calculated for $C_{16}H_{35}N_2O_5SSi$ [M+NH_4^+] 395.2031, found 395.2036. Minor Isomer: ^{1}H NMR: (500.0 MHz, $CDCl_3$) δ 5.62 (br d, *J* = 10.8 Hz, 1H), 4.62-4.69 (m, 1H), 4.16 (dt, *J* = 12.8, 3.2 Hz, 1H), 3.55 (d, *J* = 10.8 Hz, 1H), 2.49 (s, 1H), 2.14 (s, 1H), 2.04-2.14 (m, 2H), 1.92 (dt, *J* = 15.7, 3.2 Hz, 1H), 1.05-1.10 (2 x d, *J* = 6.9 Hz, 6H), 0.93 (s, 9H), 0.17 (s, 3H), 0.12 (s, 3H). ^{13}C NMR: (125.7 MHz, $CDCl_3$) δ 82.9, 75.7, 74.6, 65.5, 64.3, 58.6, 37.3, 35.3, 26.0, 18.1, 17.5, 16.2, -3.8, -4.0. HRMS (ESI) *m/z* calculated for $C_{16}H_{35}N_2O_5SSi$ [M+NH_4^+] 395.2031, found 395.2015.

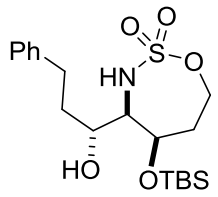


Compound 3.29 A portion of 0.150 g of the enesulfamate **3.14** (0.413 mmol) was subjected to General Procedure A using 4.0 equiv of DMDO in CH_2Cl_2 at -20 °C. The stereotriad **3.29** was

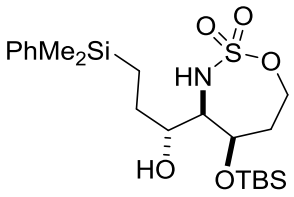
isolated as an oil (0.108 g, 0.283 mmol, 68%) along with the separable 1,2-*anti*:2,3-*anti* isomer (21.2 mg, 0.0556 mmol, 13%) after silica gel chromatography (4-20% EtOAc in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.29 (d, *J* = 10.6 Hz, 1H), 4.58 (m, 2H), 4.16 (dt, *J* = 12.9, 2.9 Hz, 1H), 3.37 (m, 1H), 3.13 (t, *J* = 10.6 Hz, 1H), 2.11 (ddt, *J* = 15.2, 12.6, 2.3 Hz, 1H), 1.95 (app t, *J* = 12.6 Hz, 1H), 1.88 (dt, *J* = 15.2, 3.7 Hz, 1H), 1.52 (m, 1H), 1.44 (m, 1H), 1.43 (d, *J* = 5.4 Hz, 1H), 1.32 (m, 5H), 0.92 (s, 9H), 0.90 (t, *J* = 6.7 H, 3H), 0.13 (s, 3H), 0.12 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 69.9, 65.3, 64.3, 60.5, 36.7, 33.9, 31.6, 25.8, 24.7, 22.5, 18.0, 14.0, -4.4, -4.9. HRMS (ESI) *m*/*z* calculated for $C_{16}H_{36}NO_5SSi$ [M+H$^+$] 382.2078, found 382.2068.



Compound 3.30. 0.100 g of the enesulfamate **3.15** (0.265 mmol) was subjected to General Procedure A using 2.5 equiv DMDO at 25 °C over 5.5 hours. This yielded 0.0776 g of stereotriad **3.30** as an oil (0.196 mmol, 74% yield) after purification by silica gel chromatography (4-20% EtOAc in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.25 (d, *J* = 10.1 Hz, 1H), 4.66 (d, *J* = 12.9 Hz, 1H), 4.23 (d, *J* = 3.0 Hz, 1H), 3.96 (dd, *J* = 12.9, 3.0 Hz, 1H), 3.36 (m, 1H), 3.13 (app t, *J* = 10.1 Hz, 1H), 1.85-2.00 (m, 2H), 1.22-1.60 (m, 8H), 1.14 (d, *J* = 7.4 Hz, 3H), 0.92 (s, 9H), 0.90 (t, *J* = 6.1 Hz, 3H), 0.12 (s, 3H), 0.11 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 70.3, 69.6, 68.4, 56.3, 39.4, 34.0, 31.6, 25.8, 24.8, 22.5, 18.0, 14.0, 13.3, -4.5, -4.9. HRMS (ESI) *m*/*z* calculated for $C_{17}H_{41}N_2O_5SSi$ [M+NH_4^+] 413.2500, found 413.2520.



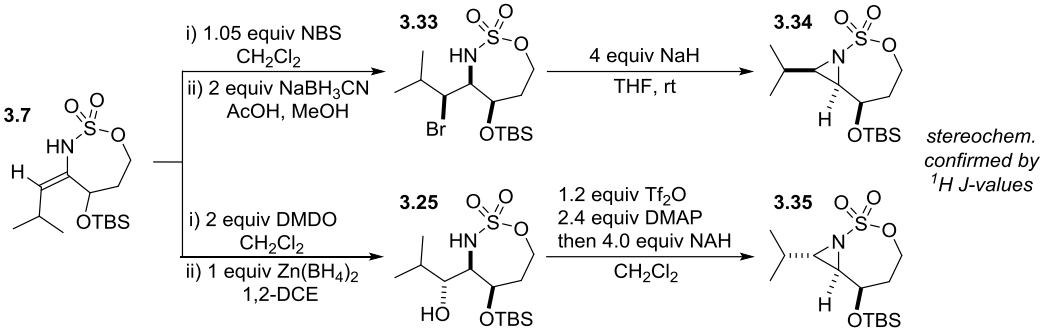
Compound 3.31. The enesulfamate **3.16** (67.7 mg, 0.170 mmol, 1 equiv.) was subjected to General Procedure B using 2.5 equiv. DMDO at 40 °C over 70 minutes. This yielded 56.6 mg of stereotriad **3.31** and a minor diastereomer (0.136 mmol, 80%) as an inseparable mixture after purification by silica gel chromatography (5% to 30% EtOAc in hexanes). The diastereomers were eventually separated by silica gel chromatography on a Combiflash RF (0% to 5% MeOH in CH_2Cl_2). Major diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (m, 2H), 7.20 (m, 3H), 5.23 (d, *J* = 10.7 Hz, 1H), 4.55 (t, *J* = 12.5 Hz, 1H), 4.54 (app t, *J* = 3.0 Hz, 1H), 4.15 (dt, *J* = 12.5, 3.1 Hz), 3.34 (m, 1H), 3.17 (app t, *J* = 10.7 Hz, 1H), 2.87 (ddd, *J* = 13.7, 8.5, 5.3 Hz, 1H), 2.72 (dt, *J* = 13.7, 8.2 Hz, 1H), 2.31 (dtd, *J* = 14.7, 8.4, 2.4 Hz, 1H), 2.09 (ddt, *J* = 15.2, 12.4, 2.7 Hz, 1H), 1.86 (dt, *J* = 15.7, 3.5 Hz, 1H), 1.78 (dtd, *J* = 14.2, 8.2, 5.5 Hz, 1H), 1.36 (d, *J* = 5.8 Hz, 1H), 0.85 (s, 9H), 0.07 (s, 3H), 0.02 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.0, 128.6, 128.5, 126.2, 69.0, 65.2, 64.4, 60.3, 36.7, 35.3, 31.3, 25.7, 17.9, -4.4, -5.0. HRMS (ESI) *m*/*z* calculated for $C_{19}H_{37}N_2O_5SSi$ [M+NH_4^+] 433.2187, found 433.2196.



Compound 3.32. The enesulfamate **3.17** (0.0500 g, 0.110 mmol, 1.0 equiv) was subjected to General Procedure A using 4.0 equiv of DMDO in CH_2Cl_2 at -20 °C. The stereotriad **3.32** was isolated as an oil (0.0288 g, 0.0616 mmol, 56%) along with the separable 1,2-*anti*:2,3-*anti* isomer

(8.3 mg, 0.0176 mmol, 16%) after silica gel chromatography (4-20% EtOAc in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (m, 2H), 7.36 (m, 3H), 5.23 (d, *J* = 10.8 Hz, 1H), 4.56 (app t, *J* = 12.6 Hz, 1H), 4.54 (t, *J* = 3.1 Hz, 1H), 4.14 (dt, *J* = 12.6, 3.1 Hz, 1H), 3.33 (m, 1H), 3.16 (app t, *J* = 10.8 Hz, 1H), 2.08 (ddt, *J* = 15.3, 12.6, 3.1 Hz, 1H), 1.83-1.92 (m, 2H), 1.50-1.63 (m, 1H), 1.42 (br d, *J* = 5.4 Hz, 1H), 0.88-0.98 (m, 10H), 0.67 (td, *J* = 13.2, 4.4 Hz, 1H), 0.30 (s, 3H), 0.30 (s, 3H), 0.09 (s, 3H), 0.08 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.7, 133.6, 129.0, 127.9, 71.1, 65.4, 64.3, 59.4, 36.7, 27.8, 25.8, 18.0, 9.4, -3.2, -3.3, -4.5, -4.9. HRMS (ESI) *m*/*z* calculated for $C_{21}H_{43}N_2O_5SSi_2$ [M+NH_4^+] 491.2426, found 491.2424.

3.5.9. Preparation of diastereomeric aziridines



Compound 3.33. Enesulfamate **3.7** (0.200 g, 0.596 mmol, 1.0 equiv) was placed in a 25 mL round bottom flask and dissolved in 8 mL dry CH_2Cl_2. The solution was cooled to 0 °C and *N*-bromosuccinimide (0.111 g, 0.626 mmol, 1.05 equiv) was added in one portion. After 25 mintues, sodium cyanoborohydride (74.8 mg, 1.19 mmol, 2.0 equiv), dissolved separately in 4.0 mL MeOH, was added, followed by glacial acetic acid (0.48 mL, 8.34 mmol, 14 equiv). The reaction stirred for 45 minutes, and was diluted with 15 mL water, and extracted with CH_2Cl_2 (3 x 10 mL). Combined organic fractions were washed with $NaHCO_3$(aq), dried with $MgSO_4$, and concentrated by rotary evaporation. The crude residue was purified by silica gel chromatography (4% to 20%

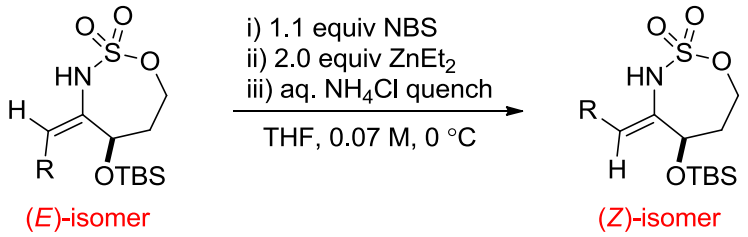
EtOAc in hexanes) to give **3.33** as a white solid (85.5 mg, 0.205 mmol, 34%) with the remaining mass balance as recovered starting material (Note: Improved conversion can be obtained using THF as bromination solvent. The same stereochemical outcome is obtained in either case). ^{1}H NMR: (500.0 MHz, $CDCl_3$) δ 5.43 (br d, *J* = 10.6 Hz, 1H), 4.57 (dd, *J* = 13.1, 12.7 Hz, 1H), 4.25 (dd, *J* = 3.7, 2.6 Hz, 1H), 4.14 (dt, *J* = 13.1, 3.2 Hz, 1H), 3.84 (dd, *J* = 9.0, 2.9 Hz, 1H), 3.59 (dd, *J* = 10.6, 9.0 Hz, 1H), 2.13 (ddt, *J* = 15.6, 12.7, 2.6 Hz, 1H), 1.92 (dt, *J* = 15.8, 3.7 Hz, 1H), 1.83 (sep d, *J* = 6.6, 2.9 Hz, 1H), 1.09 (d, *J* = 6.6 Hz, 3H), 0.98 (d, *J* = 6.6 Hz, 3H), 0.92 (s, 9H), 0.12 (s, 3H), 0.12 (s, 3H). ^{13}C NMR: (125.7 MHz, $CDCl_3$) δ 67.7, 64.2, 63.6, 60.2, 37.2, 31.0, 25.8, 22.4, 18.0, 16.4, -3.9, -4.8. HRMS (ESI) *m*/*z* calculated for $C_{14}H_{34}BrN_2O_4SSi$ [$M+NH_4^+$] 433.1187, found 433.1184

Compound 3.34. Stereotriad **3.33** (85.5 mg, 0.205 mmol, 1.0 equiv) was placed in a 10 mL round bottom flask and dissolved in 2.0 mL dry THF. NaH (60% wt. dispersion in mineral oil, 32.8 mg, 0.820 mmol, 4.0 equiv) was cautiously added, and the suspension was stirred for 4.5 hours. The reaction was diluted with EtOAc and cautiously quenched with water. The aqueous phase was extracted with EtOAc (3 x 5 mL) and combined organic phases were dried with $MgSO_4$. Silica gel chromatography (4% to 20% EtOAc in hexanes) afforded **3.34** as a white solid (38.8 mg, 0.115 mmol, 56%). ^{1}H NMR: (500.0 MHz, $CDCl_3$) δ 4.59-4.65 (m, 2H), 4.35 (ddd, *J* = 12.1, 9.4, 2.4 Hz, 1H), 2.77 (dd, *J* = 6.1, 3.1 Hz, 1H), 2.71 (dd, *J* = 10.6, 6.2 Hz, 2H), 2.49 (m, 1H), 2.06-2.20 (m, 2H), 1.20 (d, *J* = 6.2 Hz, 3H), 1.08 (d, *J* = 6.2 Hz, 3H), 0.89 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H). ^{13}C NMR: (125.7 MHz, $CDCl_3$) δ 68.1, 67.9, 56.5, 46.0, 38.0, 25.6, 24.9, 21.7, 19.9, 17.8, -4.8, -4.9. HRMS (ESI) *m*/*z* calculated for $C_{14}H_{30}NO_4SSi$ [$M+H^+$] 336.1660, found 336.1659.

Compound 3.35. Stereotriad **3.25** (32.0 mg, 0.0905 mmol, 1.0 equiv) was placed in a 10 mL round bottom flask, dissolved in 1.0 mL dry THF, and cooled to 0 °C. DMAP (29.0 mg, 0.217 mmol,

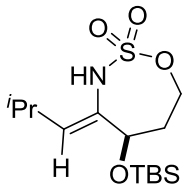
2.4 equiv) was added, followed by triflic anhydride (21.0 μL, 0.109 mmmol, 1.2 equiv). The solution was stirred vigorously for 3 hours. NaH (60% wt. dispersion in mineral oil, 7.2 mg, 0.181 mmol, 2.0 equiv) was cautiously added, and the suspension was stirred for 2 hours. The reaction was diluted with CH_2Cl_2 and cautiously quenched with water. The aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL) and combined organic phases were dried with $MgSO_4$. Silica gel chromatography (4% to 20% EtOAc in hexanes) afforded **3.35** as a white solid (12.9 mg, 0.0380 mmol, 42%). ^{1}H NMR: (500.0 MHz, $CDCl_3$) δ 4.50 (dt, *J* = 10.6, 3.3 Hz, 1H), 4.14-4.24 (m, 2H), 2.74 (dd, *J* = 7.5, 4.5 Hz, 1H), 2.70 (dd, *J* = 4.5, 3.3 Hz, 1H), 1.91-2.07 (m, 2H), 1.55 (app oct, *J* = 7.1 Hz, 1H), 1.08 (d, *J* = 7.1 Hz, 3H), 0.99 (d, *J* = 7.1 Hz, 3H), 0.90 (s, 9H), 0.13 (s, 3H), 0.11 (s, 3H). ^{13}C NMR: (125.7 MHz, $CDCl_3$) δ 68.6, 67.2, 49.0, 48.5, 36.2, 30.4, 25.5, 19.4, 18.7, 17.8, -4.9, -4.9. HRMS (ESI) *m/z* calculated for $C_{14}H_{30}NO_4SSi$ [M+H$^+$] 336.1660, found 336.1664.

3.5.10. *E*/*Z* Isomerization of enesulfamates

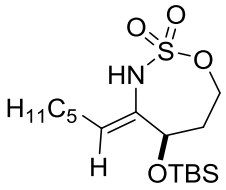


General procedure: The appropriate (*E*)-enesulfamate is added to a roundbottom flask and enough THF added to prepare a 0.07 M solution. The solution is cooled to 0 °C, and N-bromosuccinimide (1.1 equiv) added in one portion. The reaction mixture is stirred for 15 min and $ZnEt_2$ (1.0 M in hexane, 2 equiv) added *via* syringe. The solution is stirred at 0 °C for an additional 20 min and the reaction quenched by the addition of a saturated solution of NH_4Cl. (Note: reaction monitoring with TLC is generally not necessary for this reaction.) The mixture is transferred to a separatory funnel, diluted with CH_2Cl_2 and washed twice with saturated NH_4Cl and once with brine. The organic layer is dried over Na_2SO_4 and concentrated by rotary evaporation to yield the (*Z*)-isomer

as a crude oil. The product can be purified by silica gel chromatography or used as the crude material due to the clean and high-yielding nature of the reaction. In this instance, the yield of the (*Z*)-isomer was determined by ^{1}H NMR with mesitylene as an internal standard, and the material used in subsequent transformations as a solution of known concentration in $CDCl_3$.

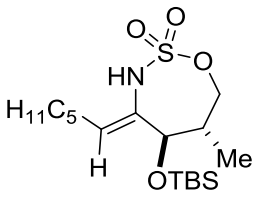


Compound (*Z*)-3.7. The (*E*)-enesulfamate **3.7** (0.500 g, 1.49 mmol, 1.0 equiv) was subjected to the general procedure to provide **(*Z*)-3.7** (0.483 g, 1.44 mmol, 97% yield) as a white solid after chromatography (10% EtOAc in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.01 (br s, 1H), 5.33 (d, *J* = 10.2 Hz, 1H), 4.67 (app t, *J* = 12.9 Hz, 1H), 4.37 (t, *J* = 2.4 Hz, 1H), 4.17 (dt, *J* = 12.9, 2.4 Hz, 1H), 3.05 (d sep, *J* = 10.2, 6.6 Hz, 1H), 2.17 (ddt, *J* = 14.9, 12.9, 2.4 Hz, 1H), 1.85 (dt, *J* = 14.9, 2.4 Hz, 1H), 1.03 (d, *J* = 6.6 Hz, 3H), 0.95 (d, *J* = 6.6 Hz, 3H), 0.89 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.0, 129.0, 71.1, 64.7, 38.3, 26.1, 25.7, 22.3, 21.9, 18.1, -5.0. HRMS (ESI) *m*/*z* calculated for $C_{14}H_{33}N_2O_4SSi$ [M+NH_4^+] 353.1925, found 353.1913.

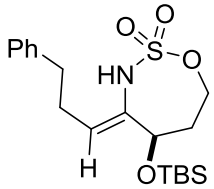


Compound (*Z*)-3.14. The (*E*)-enesulfamate **3.14** (0.300 g, 0.824 mmol, 1.0 equiv) was subjected to the general procedure to provide **(*Z*)-3.14** (0.763 mmol, 97% yield by ^{1}H NMR with a mesitylene standard). The product was not purified further and was used in later reactions as a

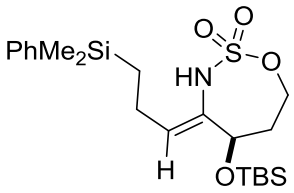
0.25 M solution in $CDCl_3$. ^1H NMR (500 MHz, $CDCl_3$) δ 6.08 (s, 1H), 5.55 (dd, *J* = 8.9, 5.8 Hz, 1H), 4.67 (t, *J* = 12.6 Hz, 1H), 4.42 (t, *J* = 3.2 Hz, 1H), 4.17 (dt, *J* = 12.6, 3.3 Hz, 1H), 2.44 (m, 1H), 2.18 (m, 2H), 1.85 (dt, *J* = 15.0, 3.6 Hz, 1H), 1.42 (m, 1H), 1.30 (m, 5H), 0.89 (s, 9H), 0.88 (t, *J* = 6.9 Hz, 3H), 0.09 (s, 3H), 0.06 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 131.0, 71.0, 64.7, 38.2, 31.3, 28.3, 26.5, 25.6, 22.4, 18.1, 14.0, -5.0, -5.1. HRMS (ESI) *m*/*z* calculated for $C_{16}H_{37}N_2O_4SSi$ [M+NH_4^+] 381.2238, found 381.2224.



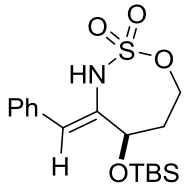
Compound (*Z*)-3.15. The (*E*)-enesulfamate **3.15** (0.983 g, 2.60 mmol, 1.0 equiv) was subjected to the general procedure to provide the (*Z*)-isomer **(*Z*)-3.15** (0.779 g, 2.06 mmol, 79%) as a colorless oil after chromatography (10% EtOAc in hexanes). ^1H NMR (500 MHz, $CDCl_3$) δ 6.02 (br s, 1H), 5.47 (dd, *J* = 8.0, 5.9 Hz, 1H), 4.74 (d, *J* = 12.9 Hz, 1H), 3.99 (d, *J* = 3.0 Hz, 1H), 3.93 (dd, *J* = 12.9, 2.7 Hz, 1H), 2.45 (app dq, *J* = 15.0, 8.0 Hz, 1H), 2.26 (dtq, *J* = 15.0, 8.0, 5.9 Hz, 1H), 1.84 (m, 1H), 1.25-1.48 (m, 6H), 1.06 (d, *J* = 7.2 Hz, 3H), 0.85-0.91 (m, 12H), 0.08 (s, 3H), 0.06 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.0, 128.3, 76.5, 68.8, 40.2, 31.4, 28.4, 26.7, 25.7, 22.4, 18.1, 14.0, 13.3, -5.0, -5.1. HRMS (ESI) *m*/*z* calculated for $C_{17}H_{39}N_2O_4SSi$ [M+NH_4^+] 395.2395, found 395.2405.



Compound (*Z*)-3.16. The (*E*)-enesulfamate **3.16** (1.00 g, 2.51 mmol, 1.0 equiv) was subjected to the general procedure to provide **(*Z*)-3.16** (2.23 mmol, 89% yield by ^{1}H NMR with a mesitylene standard). The product was not purified further and was used in later reactions as a 0.74 M solution in $CDCl_3$. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (m, 2H), 7.19 (m, 3H), 6.05 (bs, 1H), 5.52 (app dd, *J* = 8.1, 6.1 Hz, 1H), 4.66 (t, *J* = 12.9 Hz, 1H), 4.36 (t, *J* = 3.1 Hz, 1H), 4.17 (dt, *J* = 12.9, 3.3 Hz, 1H), 2.76 (m, 2H), 2.67 (m, 1H), 2.60 (m, 1H), 2.14 (ddt, *J* = 15.0, 12.0, 3.0, 1H), 1.83 (dt, *J* = 15.0, 3.5 Hz, 1H), 0.86 (s, 9H), 0.03 (s 3H), -0.02 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.1, 131.7, 129.5, 128.5, 128.4, 126.0, 70.9, 64.8, 38.3, 34.7, 28.1, 25.7, 18.1, -5.06, -5.07. HRMS (ESI) *m*/*z* calculated for $C_{19}H_{35}N_2O_4SSi$ [M+NH_4^+] 415.2082, found 415.2086.

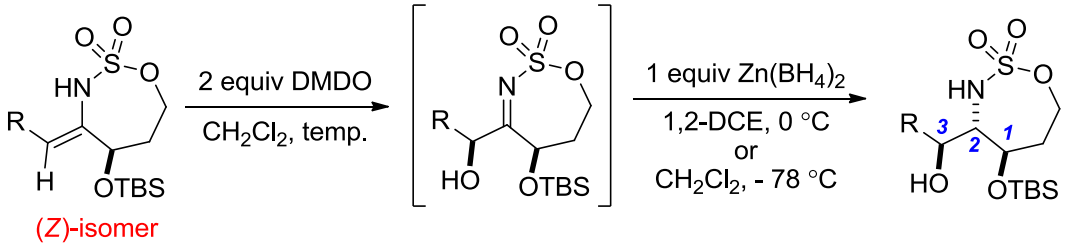


Compound (*Z*)-3.17. The (*E*)-enesulfamate **3.17** (0.810 g, 1.78 mmol, 1.0 equiv) was subjected to the general procedure, providing the product **(*Z*)-3.17** (0.690 g, 1.51 mmol, 85%) after chromatography (10% EtOAc in hexanes) as a colorless oil that solidified upon standing. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (m, 2H), 7.35 (m, 3H), 6.01 (br s, 1H), 5.51 (t, *J* = 7.2 Hz, 1H), 4.66 (t, *J* = 12.4 Hz, 1H), 4.35 (t, *J* = 3.2 Hz, 1H), 4.15 (dt, *J* = 12.4, 3.2 Hz, 1H), 2.26-2.42 (m, 2H), 2.12 (ddt, *J* = 15.1, 12.4, 3.2 Hz, 1H), 1.82 (dt, *J* = 15.1, 3.2 Hz, 1H), 0.82-0.92 (m, 10H), 0.76 (ddd, *J* = 14.4, 11.1, 5.8 Hz, 1H), 0.30 (s, 3H), 0.29 (s, 3H), 0.07 (s, 3H), 0.04 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.1, 133.6, 133.3, 129.8, 128.9, 127.8, 71.0, 64.7, 38.2, 25.7, 21.2, 18.1, 15.0, -3.2, -3.2, -5.0. HRMS (ESI) *m*/*z* calculated for $C_{21}H_{41}N_2O_4SSi_2$ [M+NH_4^+] 474.2399, found 474.2391.



Compound (*Z*)-3.18. The (*E*)-enesulfamate **3.18** (20.1 mg, 0.0543 mmol, 1.0 equiv) was subjected to the general procedure to provide **(*Z*)-3.18** (0.0535 mmol, 98% yield by ^{1}H NMR with a mesitylene standard). The product was not purified further and was used in later reactions as a 0.0535 M solution in $CDCl_3$. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (app d, *J* = 7.4 Hz, 1H), 7.36 (app t, *J* = 7.4 Hz, 1H), 7.29 (app tt, *J* = 7.4, 1.2 Hz, 1H), 6.41 (bs, 1H), 6.30 (s, 1H), 4.66 (m, 2H), 4.30 (ddd, *J* = 12.6, 5.9, 3.0 Hz, 1H), 2.26 (ddt, *J* = 15.1, 9.7, 2.7, 1H), 2.04 (dtd, *J* = 15.1, 5.8, 1.8, 1H), 0.93 (s, 9H), 0.14 (s, 3H), 0.11 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.3, 131.9, 129.3, 128.5, 128.4, 122.2, 71.4, 65.9, 38.4, 25.7, 18.1, -4.9. -5.0. HRMS (ESI) *m/z* calculated for $C_{17}H_{31}N_2O_4SSi$ [M+NH_4^+] 387.1769, found 387.1762.

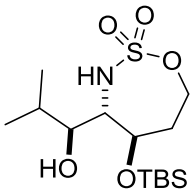
3.5.11. Synthesis of 1,2-*anti*:2,3-*anti* stereotriads



General procedure A: The appropriate (*Z*)-enesulfamate is added to a roundbottom flask and cooled to the desired temperature (see the individual entries). DMDO is added to the flask (2 equiv as a solution in CH_2Cl_2), the flask capped and the solution stirred until TLC indicates complete consumption of the starting material (30% EtOAc/hex, CAM stain). Upon completion of the

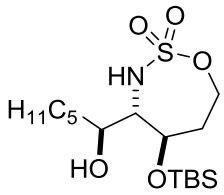
reaction, the solution is concentrated by rotary evaporation at rt and 1,2-dichloroethane (0.05 – 0.1 M) is added. The solution is cooled to 0 °C and 1 equiv of $Zn(BH_4)_2$ (0.5 M in THF) is added *via* syringe. The reaction is stirred at 0 °C until TLC indicates complete consumption of the starting material and then quenched by the addition of a saturated solution of NH_4Cl. The mixture is transferred to a separatory funnel, diluted with additional CH_2Cl_2, then washed twice with saturated NH_4Cl and once with brine. The organic layer is dried over Na_2SO_4 and concentrated by rotary evaporation to give a crude oil, which is purified by silica gel chromatography to give the desired 1,2-*anti*;2,3-*anti* stereotriad, in addition to minor diastereomers. The *dr* and yield for the reaction are calculated based on the isolated masses of each diastereomer. As a rule, the isolated *dr* closely matches the *dr* of the crude material, as measured by ^1H NMR.

General procedure B: The reaction is run in a manner identical to procedure A until completion of the DMDO oxidation. After concentration of the reaction mixture under reduced pressure at rt, CH_2Cl_2 (0.05 – 0.1 M) is added to the residue and the resulting solution is cooled to -78 °C in an acetone/dry ice bath. A solution of 1 equiv of $Zn(BH_4)_2$ (0.5 M in THF) is added, and the reaction mixture is stirred until TLC indicates complete consumption of the starting material. Workup, purification, and determination of product yield and *dr* are performed in a manner identical to that described in General Procedure A.



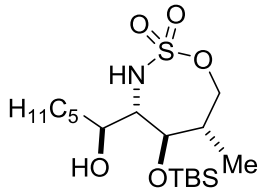
Compound 3.42. The enesulfamate **(*Z*)-3.7** (0.200 g, 0.596 mmol, 1.0 equiv) was subjected to General Procedure A using 4.0 equiv of DMDO in CH_2Cl_2 at -20 °C for 23 h. Purification by

column chromatography (4% to 20% EtOAc in hexanes) resulted in the isolation of the 1,2-*anti*;2,3-*anti* stereotriad **3.42** (0.156 g, 0.441 mmol, 74%) with 31.6 mg of the 1,2-*anti*;2,3-*syn* stereotriad isolated (0.0894 mmol, 15%) as a separable mixture of diastereomers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.18 (d, *J* = 7.2 Hz, 1H), 4.51 (dd, *J* = 12.8, 9.4 Hz, 1H), 4.25 (td, *J* = 6.2, 2.6 Hz, 1H), 4.19 (ddd, *J* = 12.8, 6.2, 1.8 Hz, 1H), 3.80 (m, 1H), 3.27 (dt, *J* = 7.2, 6.2 Hz, 1H), 2.22-2.32 (m, 2H), 2.17 (sep d, *J* = 6.6, 3.9 Hz, 1H), 1.96 (dt, *J* = 15.9, 6.2 Hz, 1H), 1.01 (d, *J* = 6.6 Hz, 3H), 0.93 (d, *J* = 6.6 Hz, 3H), 0.91 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 75.3, 71.2, 65.0, 60.4, 35.3, 29.3, 25.7, 19.7, 17.9, 15.0, -4.4, -4.9. HRMS (ESI) *m*/*z* calculated for $C_{14}H_{35}N_2O_5SSi$ [M+NH_4^+] 371.2031, found 371.2036.

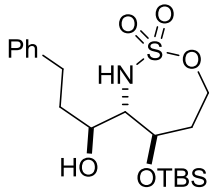


Compound 3.43. The enesulfamate **(*Z*)-3.14** (0.44 mL of a 0.25 M solution in $CDCl_3$, 0.110 mmol, 1.0 equiv) was subjected to General Procedure A using 2.0 equiv of DMDO at 0 °C for 1 h for the oxidation step. Purification by column chromatography (0% to 10% EtOAc in CH_2Cl_2) yielded 26.2 mg (0.0686 mmol, 62%) of the major diastereomer **3.43**. Two minor diastereomers (8.4 mg) were also obtained, but the material was slightly contaminated with an unknown impurity, so this mass was not included in the yield. ^{1}H NMR analysis of the crude product mixture showed an 11.7:1.7:1 *dr*. Major diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.22 (d, *J* = 8.0 Hz, 1H), 4.44 (ddd, *J* = 12.9, 5.2, 1.5 Hz, 1H), 4.23 (ddd, *J* = 12.9, 8.4, 1.5 Hz, 1H), 4.10 (td, *J* = 7.0, 3.1 Hz, 1H), 3.98 (bs, 1H), 3.25 (app q, *J* = 7.0 Hz, 1H), 2.24 (m, 2H), 1.98 (dtd, *J* = 15.6, 7.8, 1.7 Hz, 1H), 1.72 (m, 1H), 1.56 (m, 1H), 1.32 (m, 6H), 0.90 (app s, 12H), 0.10 (app s, 6H). ^{13}C NMR (125

MHz, $CDCl_3$) δ 70.7, 70.5, 65.6, 63.3, 36.3, 33.2, 31.8, 25.7, 25.2, 22.6, 17.9, 14.0, -4.1, -4.9. HRMS (ESI) *m*/*z* calculated for $C_{16}H_{36}NO_5SSi$ [M+H^+] 382.2078, found 382.2065.

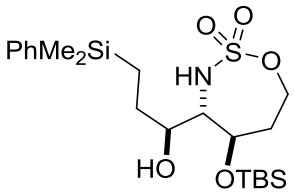


Compound 3.44. Following the general procedure for the synthesis of the 1,2-*syn*:2,3-*syn* stereotriads (see Section 3.4.12), the enesulfamate **(*Z*)-3.15** (0.050 g, 0.132 mmol, 1.0 equiv) was oxidized with 2.0 equiv DMDO at 25 °C over 2 hours. Reduction and chromatography (4% to 20% EtOAc in hexanes) yielded 0.0367 g (0.0927 mmol, 70%) of the 1,2-*anti*;2,3-*anti* stereotriad **3.44**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.28 (d, *J* = 10.4 Hz, 1H), 4.41 (s, 1H), 4.37 (dd, *J* = 12.9, 10.9 Hz, 1H), 3.83 (dd, *J* = 12.9, 2.0 Hz, 1H), 3.35 (m, 1H), 3.11 (t, *J* = 10.4 Hz, 1H), 2.12 (m, 1H), 2.01 (m, 1H), 1.25-1.58 (m, 8H), 0.85-0.95 (m, 12H), 0.90 (t, *J* = 6.4 Hz, 3H), 0.15 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 69.9, 69.4, 68.7, 61.3, 40.3, 34.0, 31.5, 26.3, 24.7, 22.5, 18.5, 15.0, 14.0, -3.7, -4.0. HRMS (ESI) *m*/*z* calculated for $C_{17}H_{38}NO_5SSi$ [M+H^+] 396.2235, found 396.2244.



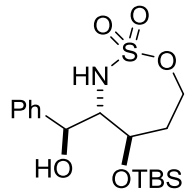
Compound 3.45. The enesulfamate **(*Z*)-3.16** (40.0 mg, 0.101 mmol, 1.0 equiv.) was subjected to General Procedure A using 2.0 equiv of DMDO at 0 °C for 1.5 h for the oxidation step. Purification by column chromatography (0% to 5% EtOAc in CH_2Cl_2) yielded 30.0 mg of the clean 1,2-

anti:2,3-*anti* product **3.45**, and 7.0 mg of two minor diastereomers in a 1:0.4 ratio. Taken together, this equates to a total of 37.0 mg (0.0889 mmol, 88%) and a 15:2.5:1 *dr*. Major diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (m, 2H), 7.22 (m, 2H), 7.18 (m, 1H), 5.16 (d, *J* = 8.0 Hz, 1H), 4.35 (ddd, *J* = 12.9, 7.3, 1.8 Hz, 1H), 4.18 (ddd, *J* = 12.9, 8.5, 1.4 Hz, 1H), 4.02 (m, 2H), 3.26 (app q, *J* = 7.4 Hz, 1H), 2.89 (ddd, *J* = 13.8, 10.4, 5.5 Hz, 1H), 2.70 (ddd, *J* = 13.8, 10.0, 6.1 Hz, 1H), 2.41 (d, *J* = 5.8 Hz, 1H), 2.19 (dddd, *J* = 15.5, 7.3, 3.5, 1.5 Hz, 1H), 2.04 (m, 1H), 1.95 (m, 1H), 1.69 (m, 1H), 0.89 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 141.7, 128.5 (2 peaks), 126.0, 71.1, 70.1, 65.7, 63.0, 36.3, 35.0, 31.8, 25.7, 17.8, -4.2, -4.9. HRMS (ESI) *m*/*z* calculated for $C_{19}H_{34}NO_5SSi$ [$M+H^+$] 416.1922, found 416.1911.



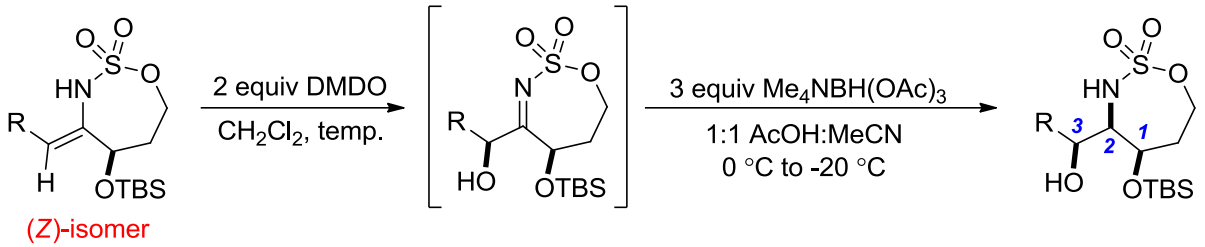
Compound 3.46. The enesulfamate **(*Z*)-3.17** (0.100 g, 0.220 mmol, 1.0 equiv) was subjected to General Procedure B using 2.0 equiv DMDO at 0 °C over 2 hours. Purification by column chromatography (4% to 20% EtOAc in hexanes) resulted in the isolation of 0.0842 g of the 1,2-*anti*;2,3-*anti* stereotriad **3.46** (0.178 mmol, 81%), along with 9.4 mg of the 1,2-*anti*;2,3-*syn* stereotriad (0.020 mmol, 9%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (m, 2H), 7.36 (m, 3H), 4.93 (d, *J* = 6.3 Hz, 1H), 4.48 (ddd, *J* = 12.8, 9.1, 2.6 Hz, 1H), 4.10-4.20 (m, 2H), 3.93 (m, 1H), 3.16 (app q, *J* = 6.3 Hz, 1H), 2.22 (ddt, *J* = 15.6, 9.2, 2.6 Hz, 1H), 1.84-1.95 (m, 3H), 1.34 (tdd, *J* = 13.2, 8.9, 4.3 Hz, 1H), 1.00 (td, *J* = 13.2, 4.3 Hz, 1H), 0.88 (s, 9H), 0.71 (td, *J* = 13.2, 4.3 Hz, 1H), 0.30 (s, 3H), 0.29 (s, 3H), 0.06 (s, 3H), 0.03 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.7, 133.6,

129.0, 127.9, 72.2, 70.2, 65.0, 63.1, 35.4, 28.2, 25.7, 17.9, 11.0, -3.1, -3.3, -4.3, -4.9. HRMS (ESI) *m*/*z* calculated for $C_{21}H_{43}N_2O_5SSi_2$ [M+NH_4^+] 491.2426, found 491.2415.

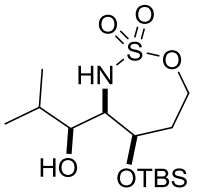


Compound 3.47. The (*E*)-enesulfamate **3.18** (42.0 mg, 0.114 mmol, 1.0 equiv.) was subjected to General Procedure B using 2.0 equiv of DMDO at 0 °C for 6 h for the oxidation step. Purification by column chromatography (10% to 30% EtOAc in Hexane) yielded 37.5 mg (0.0966 mmol, 85%) of the product **3.47** as an 8.3:1 mixture of diastereomers. The major diastereomer was obtained in pure form by recrystallization from a hexane/EtOAc mixture (the product is heated in boiling hexane, with EtOAc added gradually until dissolution is complete). Major diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (app d, *J* = 7.2 Hz, 2H), 7.39 (app t, *J* = 7.2 Hz, 2H), 7.33 (app t, *J* = 7.2 Hz, 1H), 5.13 (app dd, *J* = 5.0, 4.0 Hz, 1H), 4.82 (d, *J* = 8.0 Hz, 1H), 4.47 (ddd, *J* = 12.7, 8.5, 1.2 Hz, 1H), 4.16 (ddd, *J* = 12.7, 7.8, 1.3 Hz, 1H), 4.12 (td, *J* = 6.7, 3.0 Hz, 1H), 3.58 (dt, *J* = 8.0, 5.9 Hz, 1H), 2.80 (d, *J* = 4 Hz, 1H), 2.32 (ddt, *J* = 15.5, 8.6, 1.8 Hz, 1H), 2.02 (dtd, *J* = 15.5, 7.1, 1.4 Hz, 1H), 0.87 (s, 9H), 0.04 (s, 3H), -0.03 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.6, 128.7, 128.4, 126.7, 72.9, 70.9, 65.4, 64.1, 36.2, 25.7, 17.9, -4.0, -5.0. HRMS (ESI) *m*/*z* calculated for $C_{17}H_{33}N_2O_5SSi$ [M+NH_4^+] 405.1874, found 405.1878.

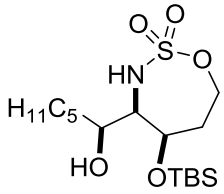
3.5.12. Synthesis of 1,2-*syn*:2,3-*syn* stereotriads



General procedure: The appropriate (*Z*)-enesulfamate is added to a roundbottom flask, either as the neat compound or as a crude stock solution in $CDCl_3$, depending on how it was prepared. (If the latter approach is used, the residual $CDCl_3$ is removed by rotary evaporation prior to the next step.) The flask is cooled to the appropriate temperature (see the individual entries), DMDO added (2 equiv as a solution in CH_2Cl_2), the flask capped and the solution stirred until complete consumption of the starting material is observed by TLC (30% EtOAc/hex, CAM stain). Upon completion, the solution is concentrated under reduced pressure at rt and acetonitrile added to the residue. The resulting solution is cooled to the appropriate temperature (see individual entries) and an equal volume of glacial acetic acid added, followed by $Me_4NBH(OAc)_3$ (3.0 equiv) The reaction is stirred until complete consumption of the starting material is indicated by TLC. The solution is then diluted with CH_2Cl_2 and washed with three portions of saturated $NaHCO_3$ and one portion of brine. The organic layer is dried over Na_2SO_4 and concentrated under reduced pressure to give a crude oil, which is purified by silica gel chromatography to give the desired 1,2-*syn*:2,3-*syn* stereotriad, in addition to minor diastereomers. The *dr* and yield for the reaction are calculated based on the isolated masses of each diastereomer. As a rule, the isolated *dr* closely matches the *dr* of the crude material, as measured by ^1H NMR.

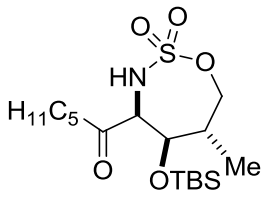


Compound 3.48. The enesulfamate **(*Z*)-3.7** (0.100 g, 0.298 mmol, 1.0 equiv) was subjected to the general procedure using 4.0 equiv DMDO at -20 °C over 26 h. Reduction at -20 °C and chromatography (4% to 20% EtOAc in hexanes) yielded the desired 1,2-*syn*:2,3-*syn* stereotriad **3.48** (52.7 mg, 0.149 mmol, 50%) along with the separable 1,2-*anti*:2,3-*anti* stereotriad (18.9 mg, 0.0535 mmol, 18%) and 1,2-*syn*:2,3-*anti* stereotriad (14.7 mg, 0.0417 mmol, 14%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.42 (d, *J* = 10.4 Hz, 1H), 4.61 (app t, *J* = 12.4 Hz, 1H), 4.15-4.22 (m, 2H), 3.40 (dd, *J* = 10.4, 5.8 Hz, 1H), 3.35 (td, *J* = 5.8, 2.1 Hz, 1H), 2.42 (br d, *J* = 2.1 Hz, 1H), 2.17 (ddt, *J* = 15.5, 12.4, 2.7 Hz, 1H), 1.91 (dt, *J* = 15.5, 3.8 Hz, 1H), 1.82 (m, 1H), 1.03 (d, *J* = 6.7 Hz, 3H), 0.94 (d, *J* = 6.7 Hz, 3H), 0.92 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 75.8, 69.2, 64.2, 58.4, 37.0, 29.8, 25.7, 19.7, 17.9, 15.8, -4.1, -4.9. HRMS (ESI) *m*/*z* calculated for $C_{14}H_{35}N_2O_5SSi$ [$M+NH_4^+$] 371.2031, found 371.2036.



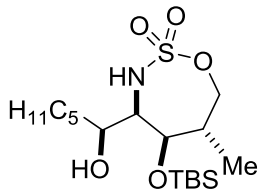
Compound 3.49. The enesulfamate **(*Z*)-3.14** (0.44 mL of a 0.25 M solution in $CDCl_3$, 0.110 mmol, 1.0 equiv) was subjected to the general procedure using 2.0 equiv. DMDO at 0 °C over 1 h. Reduction at 0 °C yielded, after column chromatography (0% to 5% EtOAc in CH_2Cl_2), 24.8 mg of the major diastereomer **3.49** and 5.8 mg of two minor diastereomers in a 1:0.7 ratio. This equates to a combined total of 30.6 mg (0.0801 mmol, 73%) and a 10.1:1.4:1 *dr*. Major

diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.45 (d, *J* = 10.6 Hz, 1H), 4.60 (t, *J* = 12.5 Hz, 1H), 4.22 (bs, 1H), 4.18 (dt, *J* = 12.5, 2.8 Hz, 1H), 3.57 (m, 1H), 3.25 (dd, *J* = 10.6, 6.4 Hz, 1H), 2.49 (bs, 1H), 2.16 (ddt, *J* = 15.0, 12.4, 2.2 Hz, 1H), 1.90 (dt, *J* = 15.0, 3.0 Hz, 1H), 1.50 (m, 2H), 1.31 (m, 6H), 0.92 (app s, 12H), 0.12 (app s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 71.3, 68.7, 64.2, 60.8, 37.0, 33.2, 31.8, 25.7, 24.9, 22.5, 17.9, 14.0, -4.0, -4.8. HRMS (ESI) *m*/*z* calculated for $C_{16}H_{39}N_2O_5SSi$ [M+NH_4^+] 399.2344, found 399.2327.

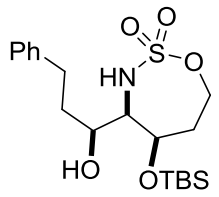


Compound 3.66. The enesulfamate **3.15** (0.150 g, 0.397 mmol, 1.0 equiv) was dissolved in 4.25 mL of 0.28 M DMDO in dichloromethane (1.19 mmol, 3.0 equiv) at rt. The solution was stirred for 6 h prior to concentration under reduced pressure. The crude residue was dissolved in 4 mL 1,2-dichloroethane, $Al(O^tBu)_3$ (97.8 mg, 0.397 mmol, 1.0 equiv) was added and the solution stirred for 2 h. The reaction mixture was diluted with 20 mL of dichloromethane and 20 mL of saturated Rochelle's salt. After stirring for 15 min, the phases were separated and the aqueous phase extracted with portions of dichloromethane. The combined organic phases were dried with $MgSO_4$, filtered and concentrated. The crude residue was purified by column chromatography (2% to 10% EtOAc in hexanes) to yield 0.105 g of **3.66** as a colorless oil that solidified upon refrigeration (0.267 mmol, 67%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.69 (d, *J* = 10.9 Hz, 1H), 4.68 (d, *J* = 12.9 Hz, 1H), 4.37 (d, *J* = 2.9 Hz, 1H), 4.00 (dd, *J* = 12.9, 2.4 Hz, 1H), 3.82 (d, *J* = 10.9 Hz, 1H), 2.75 (ddd, *J* = 18.2, 8.6, 6.4 Hz, 1H), 2.50 (ddd, *J* = 18.2, 8.6, 6.4 Hz, 1H), 1.90 (qdd, *J* = 6.9, 2.9, 2.4 Hz, 1H), 1.56 (m, 2H), 1.24-1.38 (m, 4H), 1.15 (d, *J* = 7.3 Hz, 3H), 0.89 (t, *J* = 6.9

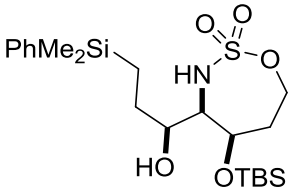
Hz, 3H), 0.86 (s, 9H), 0.09 (s, 3H), -0.02 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.5, 71.8, 68.5, 60.4, 40.6, 39.3, 31.1, 25.7, 22.8, 22.4, 17.8, 13.9, 13.4, -4.7, -5.0. HRMS (ESI) *m*/*z* calculated for $C_{17}H_{39}N_2O_5SSi$ [M+NH_4^+] 411.2344, found 411.2346.



Compound 3.67. Compound **3.66** (39.5 mg, 0.100 mmol, 1.0 equiv) was dissolved in 1.0 mL of dry MeOH and cooled to -78 °C. Tetrabutylammonium borohydride (77.5 mg, 0.301 mmol, 3.0 equiv) was added in a single portion. After stirring 25 min at -78 °C, the cooling bath was removed and stirring continued for another 10 min. The reaction was diluted with 10 mL of diethyl ether and quenched with 10 mL of brine. The phases were separated and the aqueous layer extracted with portions of diethyl ether. The combined organic phases were dried with $MgSO_4$, filtered, and concentrated. The crude residue was purified by column chromatography (4% to 20% EtOAc in hexanes) to provide the desired 1,2-*syn*:2,3-*syn* stereotriad **3.67** (24.5 mg, 0.0620 mmol, 62%) along with the separable 1,2-*anti*;2,3-*syn* stereotriad (10.7 mg, 0.027 mmol, 27%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.41 (d, *J* = 10.6 Hz, 1H), 4.68 (d, *J* = 12.7 Hz, 1H), 3.97 (dd, *J* = 12.7, 2.6 Hz, 1H), 3.82 (d, *J* = 3.0 Hz, 1H), 3.52 (m, 1H), 3.26 (dd, *J* = 10.6, 7.2 Hz, 1H), 2.45 (s, 1H), 1.89 (qdd, *J* = 7.2, 3.0, 2.6 Hz, 1H), 1.23-1.55 (m, 6H), 1.15 (d, *J* = 7.2 Hz, 3H), 1.86-1.93 (m, 12H), 0.11 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 73.1, 70.7, 68.1, 56.9, 39.6, 33.1, 31.8, 25.7, 24.7, 22.5, 17.9, 14.0, 13.4, -4.1, -4.8. HRMS (ESI) *m*/*z* calculated for $C_{17}H_{41}N_2O_5SSi$ [M+NH_4^+] 413.2500, found 413.2504.

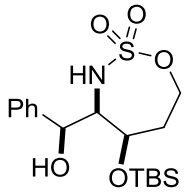


Compound 3.50. The enesulfamate **(*Z*)-3.16** (0.17 mL of a 0.58 M solution in $CDCl_3$, 0.101 mmol, 1.0 equiv) was subjected to the general procedure using 2.0 equiv. DMDO at 0 °C over 1.5 h. Reduction at 0 °C yielded, after column chromatography (0% to 25% EtOAc in Hexane), 24.0 mg of the major diastereomer **3.50** and 6.6 mg of two minor diastereomers in a 1.8:1 ratio. This equates to a combined total of 30.6 mg (0.0736 mmol, 73%) and a 10.2:1.8:1 *dr*. Major diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (m, 2H), 7.20 (m, 3H), 5.46 (d, *J* = 10.8 Hz, 1H), 4.58 (t, *J* = 12.5 Hz, 1H), 4.16 (m, 2H), 3.56 (m, 1H), 3.25 (dd, *J* = 10.6, 6.4 Hz, 1H), 2.87 (ddd, *J* = 13.9, 8.6, 6.0, 1H), 2.73 (dt, *J* = 13.9, 7.9 Hz, 1H), 2.59 (bs, 1H), 2.07 (ddt, *J* = 15.2, 12.0, 2.7 Hz, 1H), 1.83 (m, 3H), 0.88 (s, 9H), 0.07 (s, 3H), 0.01 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.5, 128.6, 128.5, 126.0, 70.0, 68.4, 64.2, 61.0, 36.9, 35.3, 31.4, 25.7, 17.9, -4.1, -5.0. HRMS (ESI) *m*/*z* calculated for $C_{19}H_{37}N_2O_5SSi$ [M+NH_4^+] 433.2187, found 433.2185.



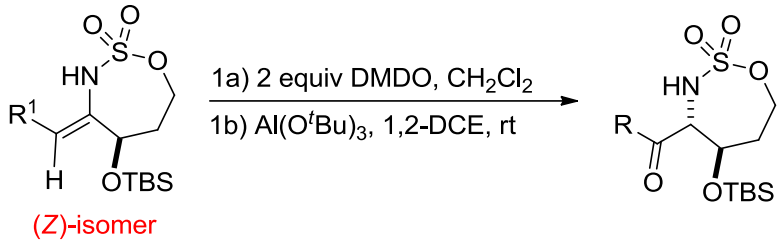
Compound 3.51. Enesulfamate **(*Z*)-3.17** (50.0 mg, 0.110 mmol, 1.0 equiv) was subjected to the general procedure with 2.0 equiv DMDO at 0 °C over 2.5 hours for the oxidation step. Reduction was carried out at -20 °C, and chromatography (4% to 20% EtOAc in hexanes) yielded the desired 1,2-*syn*:2,3-*syn* stereotriad **3.51** (29.2 mg, 0.0616 mmol, 56%) along with the separable 1,2-*anti*:2,3-*anti* stereotriad (9.1 mg, 0.0193 mmol, 18%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (m,

2H), 7.35 (m, 3H), 5.38 (d, *J* = 10.6 Hz, 1H), 4.57 (app t, *J* = 12.5 Hz, 1H), 4.15 (dt, *J* = 12.5, 3.2 Hz, 1H), 4.04 (app t, *J* = 3.2 Hz, 1H), 3.47 (td, *J* = 6.0, 4.5 Hz, 1H), 3.27 (dd, *J* = 10.6, 6.0 Hz, 1H), 2.48 (br s, 1H), 2.10 (ddt, *J* = 15.6, 12.5, 3.2 Hz, 1H), 1.84 (dt, *J* = 15.6, 3.2 Hz, 1H), 1.60 (tt, *J* = 12.7, 4.5 Hz, 1H), 1.43 (tdd, *J* = 12.7, 7.3, 4.5 Hz, 1H), 0.87-0.96 (m, 10H), 0.77 (td, *J* = 12.7, 4.5 Hz, 1H), 0.29 (s, 3H), 0.28 (s, 3H), 0.05 (s, 3H), 0.02 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.7, 133.5, 129.0, 127.8, 73.4, 68.8, 64.2, 59.7, 36.9, 27.3, 25.7, 17.9, 10.8, -3.2, -3.4, -4.1, -5.0. HRMS (ESI) *m*/*z* calculated for $C_{21}H_{43}N_2O_5SSi_2$ [M+NH_4^+] 491.2426, found 491.2410.

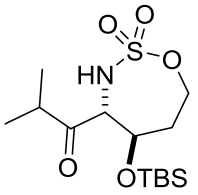


Compound 3.52. The (*E*)-enesulfamate **3.18** (41.2 mg, 0.111 mmol, 1.0 equiv.) was subjected to the general procedure using 2.0 equiv. DMDO at 0 °C over 18 h. Reduction at -10 °C yielded, after column chromatography (0% to 3% EtOAc in CH_2Cl_2), 29.0 mg (0.0747 mmol, 67%) of a colorless oil. This contained the desired product **3.52** as an 8.7:1 mixture of two diastereomers. The diastereomers were eventually separated by column chromatography using an EtOAc/Hexane gradient (5% to 30%). Major diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (m, 5H), 5.66 (d, *J* = 10.7 Hz, 1H), 4.60 (t, *J* = 12.8 Hz, 1H), 4.46 (d, *J* = 9.3 Hz, 1H), 4.17 (dt, *J* = 12.8, 3.1 Hz, 1H), 3.82 (dd, *J* = 3.5, 2.5 Hz, 1H), 3.53 (dd, *J* = 10.7, 9.5, 1H), 3.01 (bs, 1H), 1.96 (ddt, *J* = 15.5, 12.1, 2.7 Hz, 1H), 1.77 (dt, *J* = 15.5, 3.4 Hz, 1H), 0.97 (s, 9H), 0.12 (s, 3H), 0.04 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.9, 129.0, 128.9, 127.5, 73.2, 66.6, 64.2, 63.5, 36.6, 25.9, 18.1, -3.7, -4.6. HRMS (ESI) *m*/*z* calculated for $C_{17}H_{30}NO_5SSi$ [M+H^+] 388.1609, found 388.1613.

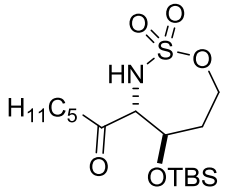
3.5.13. Two-pot synthesis of 1,2-*anti*:2,3-*syn* stereotriads



General procedure: The appropriate (*Z*)-enesulfamate is added to a roundbottom flask, either as the neat compound or as a crude stock solution in $CDCl_3$, depending on how it was prepared. (If the latter approach is used, the residual $CDCl_3$ is removed by rotary evaporation prior to the next step.) The flask is cooled to the appropriate temperature (see the individual entries), DMDO is added (2 equiv as a solution in CH_2Cl_2), the flask is capped and the solution is stirred until complete conversion of the starting material is observed by TLC (30% EtOAc/hex, CAM stain). Upon completion, the solution is concentrated at rt under reduced pressure. A portion of 1,2-dichloroethane (0.1 M) is added, followed by 1.0 equiv of $Al(O^tBu)_3$. The suspension is sonicated for 5 min to facilitate dissolution of the aluminum reagent and then stirred at rt until TLC indicates complete consumption of the starting material. The reaction is quenched by the addition of an aqueous solution of Rochelle's salt and the biphasic mixture stirred at rt for 30 min. The reaction is diluted with CH_2Cl_2 and the organic layer is washed once with Rochelle's salt and once with brine. The organic layer is dried over Na_2SO_4 and concentrated by rotary evaporation to give a crude oil. Purification *via* silica gel chromatography yields the desired 1,2-*anti* α-aminoketone, along with a minor 1,2-syn diastereomer. The yield and *dr* are determined by the isolated masses of the two diastereomers. As a rule, the isolated *dr* closely matches the *dr* of the crude material, as measured by ^1H NMR.

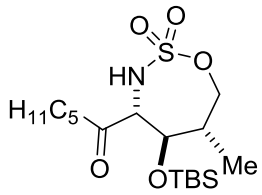


Compound 3.54. The enesulfamate **(*Z*)-3.7** (0.477 g, 1.42 mmol, 1.0 equiv) was subjected to the general procedure. The oxidation was conducted at 0 °C over 5 h. Purification by column chromatography (4%-20% EtOAc in hexanes) provided 0.267 g of the desired 1,2-*anti* α-aminoketone **3.54** (0.760 mmol, 54%), along with 89.8 mg of the minor 1,2-*syn* diastereomer (0.256 mmol, 18%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.00 (d, *J* = 10.0 Hz, 1H), 4.31-4.34 (m, 2H), 4.21 (app t, *J* = 9.4 Hz, 1H), 3.97 (td, *J* = 9.2, 5.0 Hz, 1H), 2.83 (sep, *J* = 6.9 Hz, 1H), 2.05-2.22 (m, 2H), 1.23 (d, *J* = 6.9 Hz, 3H), 1.11 (d, *J* = 6.9 Hz, 3H), 0.85 (s, 9H), 0.06 (s, 3H), -0.03 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.4, 72.7, 66.7, 60.0, 41.9, 37.4, 25.6, 17.8, 17.7, 16.4, -4.6, -4.9. HRMS (ESI) *m*/*z* calculated for $C_{14}H_{33}N_2O_5SSi$ [M+NH_4^+] 369.1874, found 369.1857.

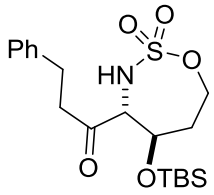


Compound 3.56. The enesulfamate **(*Z*)-3.14** (0.40 mL of a 0.688 M solution in $CDCl_3$, 0.275 mmol, 1.0 equiv) was subjected to the general procedure and the oxidation occurred at -10 °C over 2.33 h. Purification by column chromatography (0% to 20% EtOAc in hexanes) provided 67.0 mg of the desired 1,2-*anti* α-aminoketone **3.56** along with 8.5 mg of a 3.3:1 mixture of the two diastereomers, favoring the minor, 1,2-*syn* α-aminoketone. This equates to a total of 75.5 mg (0.199 mmol, 72%) in a 10.6:1 *dr*. Major diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.21 (d, *J* = 9.5 Hz, 1H), 4.32 (m, 2H), 4.02 (t, *J* = 9.5 Hz, 1H), 3.93 (td, *J* = 8.8, 5.0 Hz, 1H), 2.67 (t, *J* = 7.5

Hz, 2H), 2.14 (m, 2H), 1.64 (m, 1H), 1.55 (m, 1H), 1.29 (m, 4H), 0.89 (t, *J* = 6.7 Hz, 3H), 0.86 (s, 9H), 0.06 (s, 3H), -0.03 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.4, 72.9, 66.7, 62.2, 44.6, 37.4, 31.1, 25.6, 22.5, 22.4, 17.8, 13.9, -4.6, -5.1. HRMS (ESI) *m/z* calculated for $C_{16}H_{37}N_2O_5SSi$ [M+NH_4^+] 397.2187, found 397.2197.

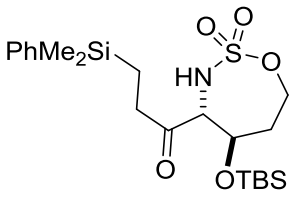


Compound 3.58. The enesulfamate **(*Z*)-3.15** (0.580 g, 1.0 equiv) was subjected to the general procedure and oxidation occurred at rt over 2 h. Purification by column chromatography (4%-20% EtOAc in hexanes) provided 0.364 g of the desired 1,2-*anti* α-aminoketone **3.58** (0.925 mmol, 60%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.70 (d, *J* = 10.7 Hz, 1H), 4.66 (s, 1H), 4.39 (dd, *J* = 12.8, 10.7 Hz, 1H), 3.88 (ddd, *J* = 12.8, 2.7, 0.7 Hz, 1H), 3.77 (d, *J* = 10.7 Hz, 1H), 2.78 (ddd, *J* = 18.3, 9.0, 6.0 Hz, 1H), 2.55 (ddd, *J* = 18.3, 8.5, 5.8 Hz, 1H), 2.14 (m, 1H), 1.57 (m, 1H), 1.18-1.38 (m, 5H), 0.97 (d, *J* = 7.4 Hz, 3H), 0.87-0.91 (m, 12H), 0.14 (s, 3H), -0.10 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.7, 70.0, 68.9, 64.9, 40.5, 39.9, 31.1, 26.1, 22.7, 22.4, 18.4, 14.4, 13.9, -4.1, -4.6. HRMS (ESI) *m/z* calculated for $C_{17}H_{39}N_2O_5SSi$ [M+NH_4^+] 411.2344, found 411.2331.

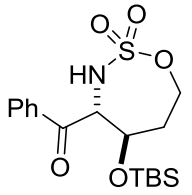


Compound 3.60. The enesulfamate **(*Z*)-3.15** (0.65 mL of a 0.58M solution in $CDCl_3$, 0.377 mmol, 1.0 equiv) was subjected to the general procedure and the oxidation occurred at 0 °C over 2 h.

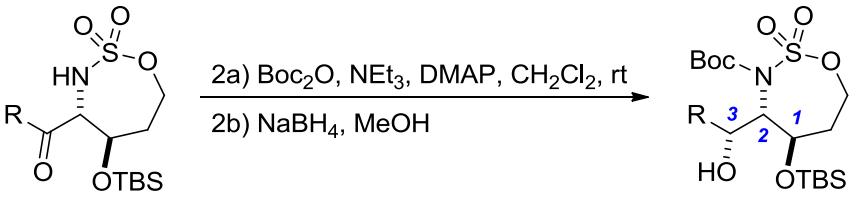
Purification by column chromatography (5% to 20% EtOAc in hexanes) provided 89.8 mg of the desired 1,2-*anti* α-aminoketone **3.60** along with 8.2 mg of the separable 1,2-*syn* α-aminoketone. This equates to a total of 98.0 mg (0.237 mmol, 63%) in an 11:1 *dr*. Major diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (m, 2H), 7.21 (m, 1H), 7.17 (m, 2H), 5.10 (d, *J* = 9.0 Hz, 1H), 4.32 (m, 2H), 3.99 (t, *J* = 8.8 Hz, 1H), 3.95 (td, *J* = 8.8 Hz, 4.2 Hz, 1H), 3.02 (app td, *J* = 7.4, 1.2 Hz, 2H), 2.96 (m, 1H), 2.86 (m, 1H), 2.18 (app dq, *J* = 15.4, 3.3 Hz, 1H), 2.12 (m, 1H), 0.85 (s, 9H), 0.06 (s, 3H), -0.01 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.1, 140.0, 128.6, 128.2, 126.3, 72.8, 66.7, 62.5, 46.0, 37.2, 29.0, 25.6, 17.8, -4.6, -5.0. HRMS (ESI) *m*/*z* calculated for $C_{19}H_{32}NO_5SSi$ [M+H$^+$] 431.2031, found 431.2019.



Compound 3.62. The enesulfamate **(*Z*)-3.17** (0.100 g, 1.0 equiv) was subjected to the general procedure and the oxidation occurred at 0 °C over 2.5 h. Purification by column chromatography (4%-20% EtOAc in hexanes) provided 53.1 mg of the desired 1,2-*anti* α-aminoketone **3.62** (0.113 mmol, 51%), along with 7.6 mg (0.0161 mmol, 7%) of the separable 1,2-*syn* α-aminoketone. Major diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (m, 2H), 7.36 (m, 3H), 5.16 (d, *J* = 9.6 Hz, 1H), 4.25-4.34 (m, 2H), 3.99 (app t, *J* = 9.2 Hz, 1H), 3.87 (td, *J* = 9.2, 5.3 Hz, 1H), 2.60 (m, 2H), 2.04-2.16 (m, 2H), 1.08 (m, 1H), 0.92 (m, 1H), 0.80 (s, 9H), 0.29 (s, 6H), 0.02 (s, 3H), -0.10 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.0, 137.7, 133.5, 129.2, 127.9, 73.0, 66.7, 61.9, 39.3, 37.4, 25.5, 17.7, 8.5, -3.3, -3.3, -4.7, -5.0. HRMS (ESI) *m*/*z* calculated for $C_{21}H_{41}N_2O_5SSi_2$ [M+NH_4^+] 490.2348, found 490.2352.

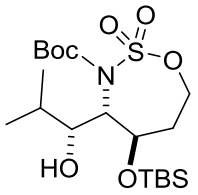


Compound 3.64. The (*Z*)-enesulfamate **(*Z*)-3.18** (49.4 mg, 0.134 mmol, 1.0 equiv) was subjected to the general procedure and oxidation occurred at 0 °C over 11 h. Purification by column chromatography (0% to 2% EtOAc in CH_2Cl_2) provided 31.3 mg of a white solid. ^{1}H NMR analysis showed a 20:1 *dr* in favor of the diastereomer **3.64**. The mixture was considered pure enough to preclude further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (app d, *J* = 7.3 Hz, 2H), 7.63 (app tt, *J* = 7.3, 0.9 Hz, 1H), 7.50 (app t, *J* = 7.3 Hz, 2H), 5.36 (d, *J* = 9.3 Hz, 1H), 4.99 (t, *J* = 9.3 Hz, 1H), 4.43 (ddd, *J* = 13.0, 10.4, 1.9 Hz, 1H), 4.38 (dt, *J* = 13.0, 3.8 Hz, 1H), 4.02 (td, *J* = 9.3, 4.9 Hz, 1H), 2.25 (m, 2H), 0.60 (s, 9H), -0.04, (s, 3H), -0.34 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.1, 135.4, 134.5, 129.5, 128.7, 73.9, 66.9, 58.2, 37.8, 25.3, 17.6, -4.8, -5.5. HRMS (ESI) *m*/*z* calculated for $C_{17}H_{28}NO_5SSi$ [M+H$^+$] 386.1452, found 386.1454.



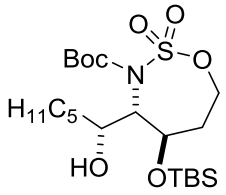
<u>General procedure</u>: The appropriate 1,2-*anti* α-aminoketone is added to a roundbottom flask, followed by Boc_2O (1.2 equiv) and CH_2Cl_2 (0.05 – 0.1 M). Triethylamine (1.2 equiv) is added, followed by DMAP (0.1 equiv), and the reaction is stirred at rt until TLC indicates complete consumption of the starting material, generally within 15 min (~30% EtOAc/hex, CAM stain). The solution is passed through a short (~1 inch) silica plug while washing with CH_2Cl_2. The

resulting solution is concentrated under reduced pressure, the residue dissolved in MeOH (0.05 – 0.1M) and the solution cooled to 0 °C. $NaBH_4$ (5 equiv) is added, and the reaction is monitored by TLC for completion. The reaction is generally complete within 15 min. The reaction is quenched by the addition of a saturated solution of NH_4Cl, diluted with EtOAc and the layers separated. The aqueous layer is extracted twice with additional EtOAc. The combined organic layers are washed with brine, dried over Na_2SO_4 and concentrated by rotary evaporation to give a crude oil. Purification by silica gel chromatography yields the Boc-protected 1,2-*anti*:2,3-*syn* stereotriad, in addition to the minor 1,2-*anti*:2,3-*anti* product (observed in some cases). Yield and *dr* are determined by the isolated masses of the two diastereomers. As a rule, the isolated *dr* closely matches the *dr* of the crude material, as measured by ^{1}H NMR.

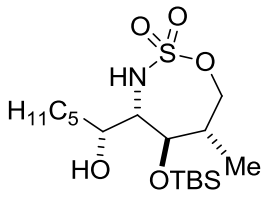


Compound 3.55. Following the general procedure, the ketone **3.54** (60.0 mg, 1.0 equiv) yielded 57.4 mg of the Boc-protected 1,2-*anti*:2,3-*syn* stereotriad **3.55** (0.127 mmol, 74%) after chromatography (2% to 10% EtOAc in hexanes) in addition to the separable minor 1,2-*anti*:2,3-*anti* product (10.9 mg, 0.0239 mmol, 14%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.92 (d, *J* = 10.0 Hz, 1H), 4.76 (d, *J* = 9.0 Hz, 1H), 4.36 (ddd, *J* = 12.3, 5.8, 2.0 Hz, 1H), 4.28 (dd, *J* = 12.3, 10.0 Hz, 1H), 3.77 (app td, *J* = 7.9, 5.8 Hz, 1H), 3.54 (dd, *J* = 9.0, 7.9 Hz, 1H), 2.25 (dt, *J* = 15.9, 5.8 Hz, 1H), 2.15 (m, 1H), 2.05 (dddd, *J* = 15.9, 10.0, 7.9, 2.0 Hz, 1H), 1.48 (s, 9H), 1.01 (d, *J* = 6.7 Hz, 3H), 0.95 (d, *J* = 6.7 Hz, 3H), 0.90 (s, 9H), 0.09 (5.3, s, 3H), 0.06 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.8, 82.5, 79.0, 70.4, 66.2, 58.1, 37.6, 29.5, 27.7, 25.8, 18.6, 17.9, -3.8, -5.1. HRMS

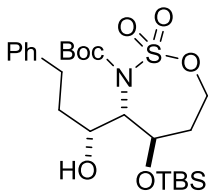
(ESI) *m*/*z* calculated $C_{19}H_{43}N_2O_7SSi$ [M+NH_4^+] 471.2555, found 471.2574. Minor stereoisomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.92 (app t, *J* = 12.4 Hz, 1H), 4.63 (s, 1H), 4.47 (t, *J* = 4.1 Hz, 1H), 4.33 (dt, *J* = 12.4, 3.3 Hz, 1H), 4.05 (ddd, *J* = 10.7, 5.9, 0.9 Hz, 1H), 2.41 (app t, *J* = 12.4 Hz, 1H), 1.96 (sep, *J* = 6.7 Hz, 1H), 1.71 (br d, *J* = 12.4 Hz, 1H), 1.53 (s, 1H), 1.36 (s, 1H), 1.01 (d, *J* = 6.7 Hz, 3H), 0.89 (s, 9H), 0.86 (d, *J* = 6.7 Hz, 3H), 0.12 (s, 3H), 0.09 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.7, 84.8, 74.5, 68.4, 66.2, 62.3, 31.8, 29.0, 27.9, 25.7, 20.2, 17.9, 13.8, -5.1. HRMS (ESI) *m*/*z* calculated $C_{19}H_{39}NO_7SSiNa$ [M+Na^+] 476.2109, found 476.2107.



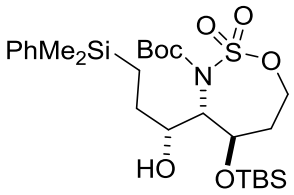
Compound 3.57. Following the general procedure, the ketone **3.56** (31.1 mg, 0.0818 mmol, 1.0 equiv) yielded, after purification by column chromatography (0% to 15% EtOAc/hexane), 30.3 mg (0.0630 mmol, 77%) of **3.57** as a white solid. ^{1}H NMR indicated a single diastereomer was present, in agreement with a ^{1}H NMR of the crude material. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.91 (app dd, *J* = 7.5, 6.5 Hz, 1H), 4.87 (d, *J* = 10.6 Hz, 1H), 4.30 (m, 2H), 3.81 (td, *J* = 9.1, 5.1 Hz, 1H), 3.37 (t, *J* = 10.6 Hz, 1H), 2.22 (m, 1H), 2.05 (m, 1H), 1.77 (m, 2H), 1.48 (s, 9H), 1.44-1.22 (m, 6H), 0.89 (m, 12H), 0.07 (s, 3H), 0.05 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.2, 82.6, 74.5, 69.7, 66.6, 58.4, 37.8, 31.3, 30.0, 27.7, 25.7, 24.6, 22.4, 17.8, 13.9, -3.9, -5.2. HRMS (ESI) *m*/*z* calculated for $C_{21}H_{47}N_2O_7SSi$ [M+NH_4^+] 499.2868, found 499.2885.



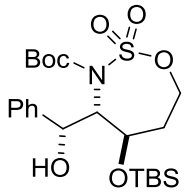
Compound 3.59. This isomer was prepared using an alternative route to the scheme shown above. Starting from ketone **3.58** (0.0250 g, 0.0635 mmol, 1.0 equiv), the substrate was dissolved in 1.0 mL dry MeOH and cooled to -78 °C. $NaBH_4$ (7.2 mg, 0.191 mmol, 3.0 equiv) was added and the reaction stirred for 1 h before warming to 0 °C. The reaction was quenched with a mixture of saturated NH_4Cl and dichloromethane. The product was extracted with portions of dichloromethane, dried with $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (5-25% EtOAc in hexanes) isolated the desired 1,2-*syn*:2,3-*anti* stereotriad **3.59** (17.1 mg, 0.0432 mmol, 68%) along with the separable 1,2-*anti*;2,3-*anti* stereotriad (2.8 mg, 0.0070 mmol, 11%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.48 (d, *J* = 10.2 Hz, 1H), 4.40 (dd, *J* = 12.7, 10.9 Hz, 1H), 3.97 (s, 1H), 3.86 (dd, *J* = 12.7, 2.3 Hz, 1H), 3.45 (br dd, *J* = 9.3, 7.8 Hz, 1H), 3.20 (dd, *J* = 10.2, 9.3 Hz, 1H), 2.46 (br s, 1H), 2.17 (m, 1H), 1.52-1.58 (m, 2H), 1.25-1.45 (m, 6H), 0.94-0.98 (m, 12H), 0.90 (t, *J* = 6.7 Hz, 3H), 0.14 (s, 3H), 0.11 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 71.6, 69.4, 68.6, 63.1, 40.6, 33.3, 32.0, 26.2, 24.8, 22.5, 18.5, 15.0, 14.0, -3.3, -3.7. HRMS (ESI) *m*/*z* calculated for $C_{17}H_{38}NO_5SSi$ [M+H$^+$] 396.2235, found 396.2243.



Compound 3.61. Following the general procedure, the ketone **3.60** (30.7 g, 0.0742 mmol, 1.0 equiv) yielded, after column chromatography (5% to 20% EtOAc/hexane), 29.9 mg (0.0579 mmol, 78%) of **3.61** as a colorless oil. ^{1}H NMR indicated a single diastereomer in both the crude material and the final product. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (m, 4H), 7.18 (m, 1H), 4.96 (d, *J* = 11.2 Hz, 1H), 4.95 (m, 1H), 4.31 (m, 2H), 3.82 (td, *J* = 9.0, 5.0 Hz, 1H), 3.45 (td, *J* = 10.1, 0.9 Hz, 1H), 2.76 (ddd, *J* = 13.7, 10.8, 5.5 Hz, 1H), 2.60 (ddd, *J* = 13.7, 10.3, 6.4 Hz, 1H), 2.25-2.00 (m, 4H), 1.47 (s, 9H), 0.85 (s, 9H), 0.05 (s, 3H), 0.01 (s, 3H). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 152.1, 140.6, 128.5, 128.4, 126.0, 82.7, 74.1, 69.6, 66.6, 58.4, 37.8, 32.0, 31.2, 27.7, 25.7, 127.8, -4.0, -5.2. HRMS (ESI) *m*/*z* calculated for $C_{24}H_{45}N_2O_7SSi$ [M+NH_4^+] 533.2712, found 533.2717.

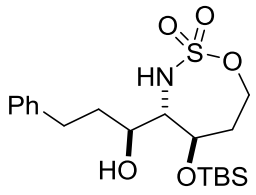


Compound 3.63. Following the general procedure, the ketone **3.62** (29.9 mg, 0.0634 mmol, 1.0 equiv) yielded 27.6 mg (0.0481 mmol, 76%) of the Boc-protected 1,2-*anti*:2,3-*syn* stereotriad **3.63** after chromatography (2% to 10% EtOAc in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (m, 2H), 7.35 (m, 3H), 4.77-4.86 (m, 2H), 4.27-4.32 (m, 2H), 3.80 (td, *J* = 9.1, 4.9 Hz, 1H), 3.52 (td, *J* = 10.4, 0.7 Hz, 1H), 2.21 (m, 1H), 2.04 (m, 1H), 1.77 (m, 2H), 1.45 (s, 9H), 0.80-0.90 (m, 10H), 0.62 (m, 1H), 0.30 (s, 3H), 0.29 (s, 3H), 0.06 (s, 3H), 0.03 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.1, 138.5, 133.6, 128.9, 127.8, 82.6, 76.9, 69.6, 66.6, 57.4, 37.9, 27.7, 25.7, 24.4, 17.8, 10.6, -3.2, -3.4, -4.0, -5.2. HRMS (ESI) *m*/*z* calculated $C_{26}H_{51}N_2O_7SSi_2$ [M+NH_4^+] 591.3029, found 591.3015.

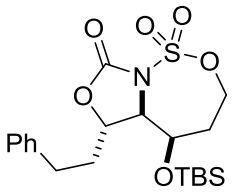


Compound 3.65. Following the general procedure, the ketone **3.64** (29.3 mg, 0.0759 mmol, 1.0 equiv) yielded, after column chromatography (0% to 20% EtOAc/hexane), 17.6 mg (0.0361 mmol, 48%) of a white solid containing **3.65** in a 4:1 *dr*. The diastereomers were eventually separated by column chromatography (0% to 0.5% MeOH/CH_2Cl_2). Major diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (m, 2H), 7.32 (m, 3H), 5.90 (d, *J* = 2.1 Hz, 1H), 5.00 (d, *J* = 10.2 Hz, 1H), 4.30 (m, 2H), 3.89 (td, *J* = 9.2, 4.8 Hz, 1H), 3.44 (ddd, *J* = 10.2, 9.2, 2.2 Hz, 1H), 2.23 (m, 1H), 2.04 (m, 1H), 1.42 (s, 9H), 0.94 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.6, 137.2, 128.6, 128.4, 125.8, 83.2, 75.0, 70.0, 66.3, 62.5, 37.4, 27.6, 25.7, 17.8, -4.0, -5.2. HRMS (ESI) *m*/*z* calculated for $C_{22}H_{41}N_2O_7SSi$ [M+NH_4^+] 505.2399, found 505.2376.

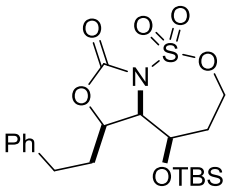
3.5.14. Synthesis of crystalline stereotriad derivatives for X-ray analysis



3.46



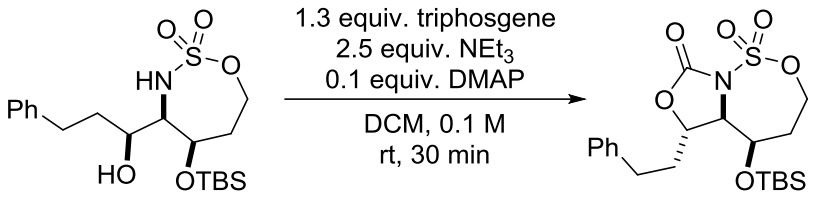
3.S19
(derived from 3.50)



3.S20
(derived from 3.31)

The stereotriads shown above were subjected to X-ray crystallography to confirm the stereochemical outcome of these reactions. (The fourth diastereomer in this series, stereotriad **3.61**, was not crystallized, as its stereochemistry was inferred by process of elimination.) Stereotriad **3.46** was crystallized without need for derivitization, but stereotriads **3.50** and **3.31** were not crystalline solids at room temperature. It was found that treatment of **3.50** and **3.31** with

triphosgene under basic conditions yielded the corresponding oxazolidinones, which were readily crystallized to determine their relative stereochemistry. An example procedure for this reaction is given below:



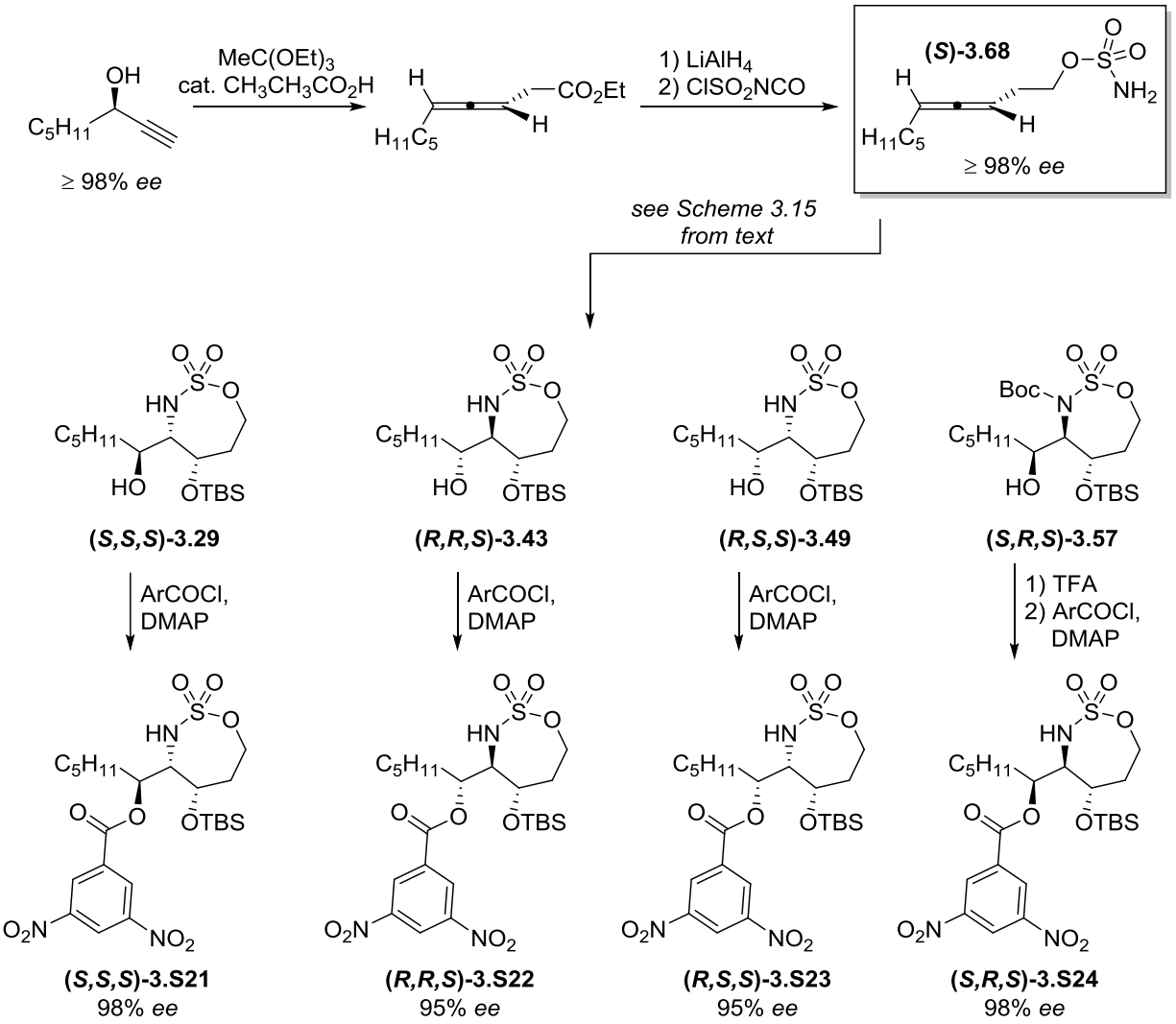
Stereotriad **3.50** (50.0 mg, 0.120 mmol, 1.0 equiv) was added to a 10-mL roundbottom flask and dissolved in dry CH_2Cl_2 (0.1 M). Triethylamine (42 μL, 0.30 mmol, 2.5 equiv) and 4-dimethylaminopyridine (1.5 mg, 0.012 mmol, 0.1 equiv) were added sequentially. In a well-ventilated fume hood, triphosgene (46.3 mg, 0.156 mmol, 1.3 equiv) was carefully added to this solution, and the mixture was stirred at room temperature for 30 min, at which point TLC analysis (30% EtOAc in Hexane) indicated completion of the reaction. The reaction was quenched by the addition of aqueous NH_4Cl, and the mixture was transferred to a separatory funnel. The mixture was extracted twice with CH_2Cl_2, washed once with brine, dried over $MgSO_4$, and concentrated by rotary evaporation. The resulting crude oil was purified by column chromatography (10% to 40% EtOAc in hexane) to give the corresponding oxazolidinone (31.7 mg, 0.0717 mmol, 60%) as a white solid. In lieu of spectroscopic data, the crystal structure is provided (see Appendix 2).

3.5.15. Transfer of chirality studies

Transfer-of-chirality experiments were carried out using an enantioenriched homoallenic sulfamate derived from 98+% *ee* (*R*)-(+)-1-octyn-3-ol (Alfa Aesar #L19045) by known methods.[7] The % *ee* of the homoallenic sulfamate could not be readily determined by chiral HPLC, so it was

assumed to be ≥98% *ee*.[14] This material was carried through the sequence of steps depicted in Scheme 3.15 to arrive at enantioenriched triads **(*S,S,S*)-3.29**, **(*R,R,S*)-3.43**, **(*R,S,S*)-3.49**, and **(*S,R,S*)-3.57**. These compounds were O-benzoylated with 3,5-dinitrobenzoyl chloride as described in the General Procedure below in order to obtain compounds suitable for UV/Vis detection. Compound **(*S,R,S*)-3.57** decomposed under these conditions and had to be first treated with trifluoroacetic acid in order to cleave the N-Boc group. As seen in Scheme S1, there was minimal erosion of stereochemistry in generating the four stereotriads. The slight erosion observed in compounds **(*R,R,S*)-3.S8** and **(*R,S,S*)-3.S9** cannot necessarily be attributed to any one particular step in the stereotriad synthesis, as compound **(*S,R,S*)-3.S10**, which was derived from the longest sequence of steps from the starting allene, was obtained in an excellent 98% *ee*.

Scheme 3.16. Conversion of enantioenriched homoallenic sulfamate to all four stereotriads with good transfer of chirality.

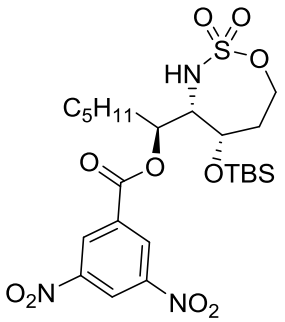


General procedure for O-benzoylation of O/N/O triads: The appropriate O/N/O triad (1 equiv) is added to a roundbottom flask and dissolved in dry CH_2Cl_2 (0.1 M). 3,5-Dinitrobenzoyl chloride (1.1 equiv) and 4-(dimethylamino)pyridine (1.1 equiv) are added sequentially, and the resulting light yellow solution is stirred at room temperature. The reaction is monitored by TLC (30% EtOAc/hexane, CAM stain). When full consumption of the starting triad is observed, the reaction is worked up by filtration through a silica plug (~1 in. in height) with 5% EtOAc/DCM. Rotary evaporation yields clean, O-benzoylated product with no trace of competing N-benzoylation or

bis-benzoylation. The crude material is generally pure enough for HPLC analysis, but can be further purified by silica gel chromatography if desired (0-30% EtOAc in hexanes). Yields were not recorded for this step, as only an analytical amount of the benzoylated product was needed; however, clean conversion was always observed by NMR.

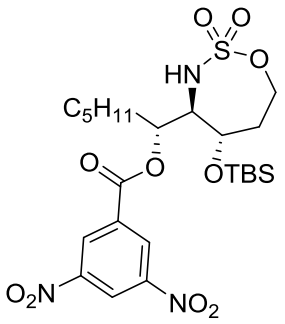
Example procedure for TFA-mediated Boc deprotection: The N-Boc protected triad **57** (8.5 mg, 17.6 μmol, 1 equiv.) is added to a 2 mL screw-cap flask and dissolved in a 4:1 mixture of CH_2Cl_2/CF_3CO_2H. The resulting clear solution is stirred at room temperature for 4 hours, or until TLC analysis (30% EtOAc/hexane, CAM stain) indicates full consumption of the starting material. The reaction mixture is then concentrated by rotary evaporation and any remaining acid residue is removed under vacuum (<1 mmHg). The crude material (4.7 mg, 12.3 μmol, 70%) is then carried on to the benzoylation step without further purification.

Characterization and HPLC methods for O-benzoylated stereotriads:

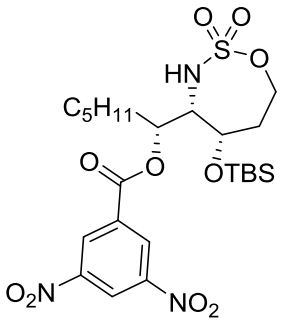


(*S,S,S*)-3.S21. ^{1}H NMR: (500.0 MHz, $CDCl_3$) δ 9.27 (t, *J* = 2.1 Hz, 1H), 9.13 (d, 2.1 Hz, 2H), 5.43 (d, *J* = 11.0 Hz, 1H), 5.11 (ddd, *J* = 9.2, 7.4, 3.4 Hz, 1H), 4.59 (t, *J* = 12.6 Hz, 1H), 4.21 (dt, *J* = 12.6, 3.0 Hz, 1H), 4.16 (t, *J* = 2.6 Hz, 1H), 3.70 (dd, *J* = 10.8, 9.2 Hz, 1H), 2.18 (ddt, *J* = 15.5, 12.7, 2.8 Hz, 1H), 2.03 (m, 1H), 1.92 (dt, *J* = 15.5, 3.5 Hz, 1H), 1.88 (m, 1H), 1.46 (m, 1H), 1.33-1.24 (m, 5H), 0.94 (s, 9H), 0.85 (m, 3H), 0.05 (app s, 6H). ^{13}C NMR: (125.7 MHz, $CDCl_3$) δ 161.8,

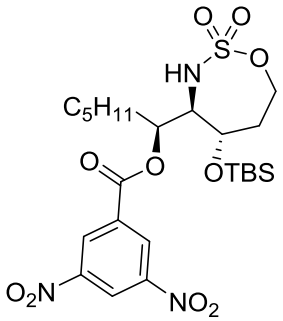
148.9, 133.3, 129.3, 122.8, 75.4, 66.2, 64.0, 58.0, 36.6, 31.5, 30.6, 25.8, 24.0, 22.4, 18.0, 13.9, -4.0, -5.0. HRMS (ESI) *m/z* calculated $C_{23}H_{41}N_4O_{10}SSi$ [M+NH_4^+] 593.2308, found 593.2309. An OJ-H column (4.6 µm diameter x 258 mm) at a temperature of 40 ºC was employed, using 25% isopropanol in hexanes (isocratic) as the eluent and a flow rate of 0.9 mL/min. The enantiomers were detected at 7.88 and 8.99 minutes, with observation at both 215 nm and 225 nm.



(*R,R,S*)-3.S22. ^{1}H NMR: (500.0 MHz, $CDCl_3$) δ 9.24 (t, *J* = 2.1 Hz, 1H), 9.17 (d, *J* = 2.1 Hz, 2H), 5.63 (ddd, *J* = 10.6, 4.0, 2.6 Hz, 1H), 5.00 (d, *J* = 9.5 Hz, 1H), 4.37 (ddd, *J* = 13.1, 5.5, 2.9 Hz, 1H), 4.32 (app q, *J* = 13.1 Hz, 1H), 3.90 (td, *J* = 8.7, 4.2 Hz, 1H), 3.69 (td, *J* = 9.1, 4.2 Hz, 1H), 2.24 (dt, *J* = 15.5, 4.3 Hz, 1H), 2.07 (m, 1H), 1.76 (m, 2H), 0.95 (s, 9H), 1.50-1.20 (m, 6H), 0.88 (app t, *J* = 6.6 Hz, 3H), 0.13 (s, 6H). ^{13}C NMR: (125.7 MHz, $CDCl_3$) δ 162.2, 148.7, 133.6, 129.5, 122.6, 74.9, 70.8, 66.3, 60.5, 37.4, 31.6, 28.2, 25.6, 25.4, 22.4, 17.9, 13.9, -3.6, -4.9. HRMS (ESI) *m/z* calculated $C_{23}H_{41}N_4O_{10}SSi$ [M+NH_4^+] 593.2308, found 593.2310. An AD-H column (4.6 µm diameter x 258 mm) at a temperature of 40 ºC was employed, using a steady gradient from 5%-30% isopropanol in hexane over 40 minutes and a flow rate of 0.9 mL/min. The enantiomers were detected at 8.18 and 10.06 minutes, with observation at both 215 nm and 225 nm.



(*R,S,S*)-3.S23. ^{1}H NMR: (500.0 MHz, $CDCl_3$) δ 9.23 (t, *J* = 2.1 Hz, 1H), 9.20 (t, *J* = 2.1 Hz, 2H), 5.39 (d, *J* = 10.8 Hz, 1H), 5.23 (ddd, *J* = 12.4, 4.8, 3.8 Hz, 1H), 4.55 (t, *J* = 12.7 Hz, 1H), 4.25 (t, *J* = 2.7 Hz, 1H), 4.18 (dt, *J* = 12.7, 3.2 Hz, 1H), 3.54 (t, *J* = 10.4 Hz, 1H), 2.18 (ddt, *J* = 15.7, 12.6, 2.7 Hz, 1H), 1.94 (dt, *J* = 15.7, 3.3 Hz, 1H), 1.76 (m, 2H), 1.50-1.18 (m, 6H), 0.98 (s, 9H), 0.88 (app t, *J* = 6.9 Hz, 3H), 0.20 (s, 3H), 0.15 (s, 3H). ^{13}C NMR: (125.7 MHz, $CDCl_3$) δ 162.8, 148.7, 133.6, 129.8, 122.5, 73.9, 66.4, 64.0, 60.3, 36.9, 31.5, 31.2, 25.7, 24.9, 22.4, 18.0, 13.9, -3.9, -4.8. HRMS (ESI) *m/z* calculated $C_{23}H_{41}N_4O_{10}SSi$ [M+NH_4^+] 593.2308, found 593.2302. An AD-H column (4.6 µm diameter x 258 mm) at a temperature of 40 ºC was employed, using a steady gradient from 5%-30% isopropanol in hexane over 40 minutes and a flow rate of 0.9 mL/min. The enantiomers were detected at 7.72 and 8.87 minutes, with observation at both 215 nm and 225 nm.



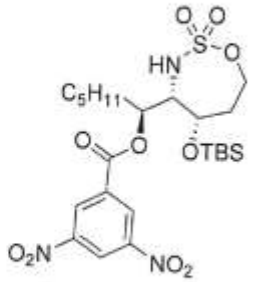
(*S,R,S*)-3.S24. ^{1}H NMR: (500.0 MHz, $CDCl_3$) δ 9.24 (t, *J* = 1.8 Hz, 1H), 9.15 (d, *J* = 1.8 Hz, 2H), 5.54 (t, *J* = 6.7 Hz, 1H), 5.27 (d, *J* = 10.5 Hz, 1H), 4.39 (m, 2H), 3.89 (td, *J* = 8.4, 4.6 Hz, 1H), 3.55 (t, *J* = 9.7 Hz, 1H), 2.26 (m, 1H), 2.08 (m, 1H), 1.91 (m, 2H), 1.50-1.20 (m, 6H), 0.89 (m,

12H), 0.05 (s, 3H), -0.05 (s, 3H). ^{13}C NMR: (125.7 MHz, $CDCl_3$) δ 161.9, 148.8, 133.6, 129.3, 122.7, 75.2, 70.2, 66.5, 59.3, 37.5, 31.3, 29.7, 25.7, 24.5, 22.4, 17.8, 13.9, -3.7, -4.9. HRMS (ESI) *m*/*z* calculated $C_{23}H_{41}N_4O_{10}SSi$ [$M+NH_4^+$] 593.2308, found 593.2310. An AD-H column (4.6 µm diameter x 258 mm) at a temperature of 40 ºC was employed, using a steady gradient from 5%-30% isopropanol in hexane over 40 minutes and a flow rate of 0.9 mL/min. The enantiomers were detected at 8.30 and 8.92 minutes, with observation at both 215 nm and 225 nm.

4/17/2014 19:18:32 1 / 1

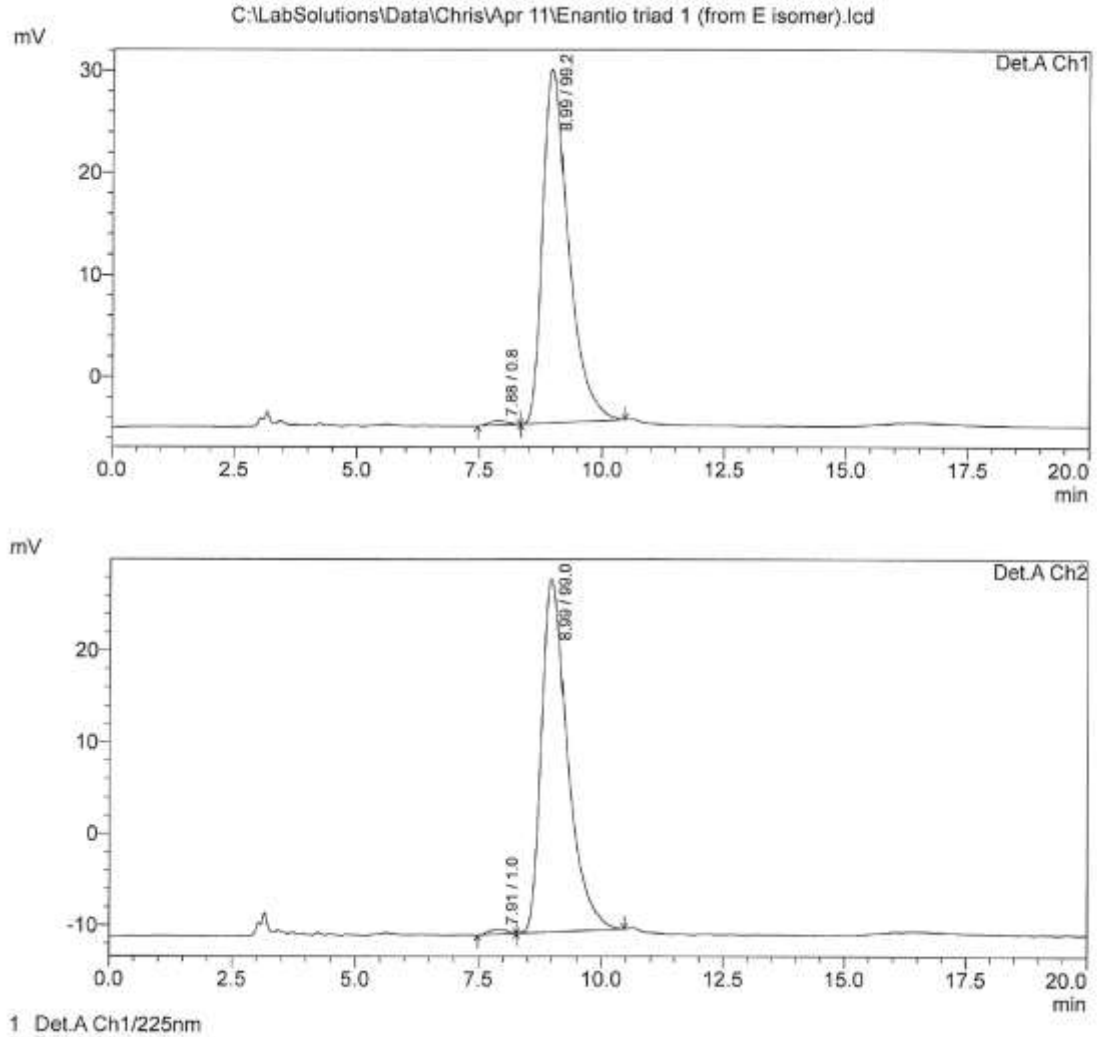
C:\LabSolutions\Data\Chris\Apr 11\Enantio triad 1 (from E isomer).lcd

Acquired by	: Admin
Sample Name	: CSR7009
Sample ID	:
Tray#	: 1
Vail #	: 64
Injection Volume	: 1 uL
Data File Name	: Enantio triad 1 (from E isomer).lcd
Method File Name	: 75-25 iso 20 min 225 215.lcm
Batch File Name	: Batch 2 enantio.lcb
Report File Name	: Default.lcr
Data Acquired	: 4/11/2014 5:22:04 PM
Data Processed	: 4/11/2014 5:42:07 PM



(enantioenriched)

<Chromatogram>

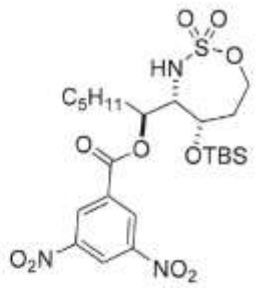


1 Det.A Ch1/225nm
2 Det.A Ch2/215nm

4/17/2014 19:15:21 1 /

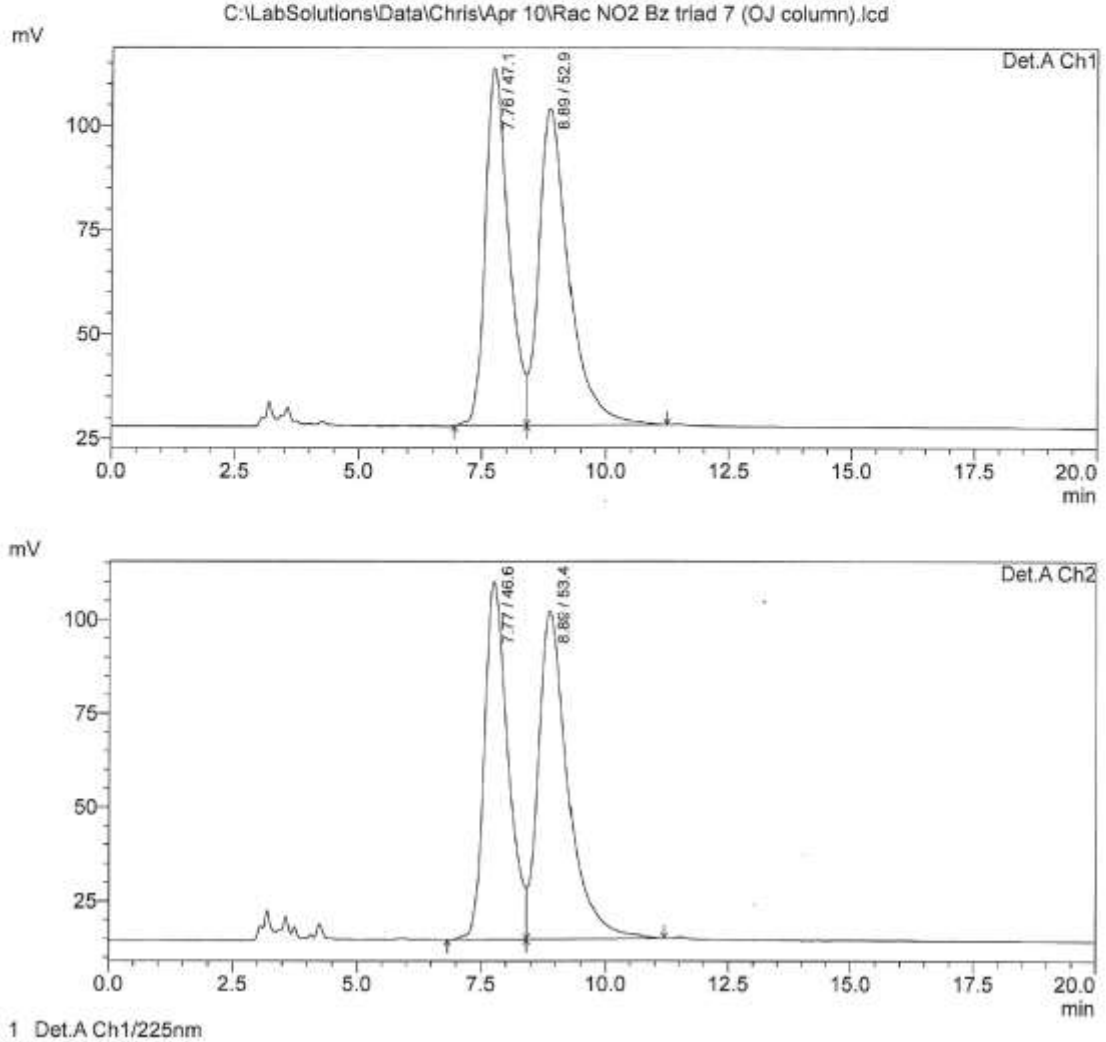
C:\LabSolutions\Data\Chris\Apr 10\Rac NO2 Bz triad 7 (OJ column).lcd

Acquired by	: Admin
Sample Name	: CSA7008
Sample ID	:
Tray#	: 1
Vail #	: 63
Injection Volume	: 1 uL
Data File Name	: Rac NO2 Bz triad 7 (OJ column).lcd
Method File Name	: 75-25 iso 20 min 225 215.lcm
Batch File Name	: batch 7 Rac Bz NO2 triad (OJ column) 3.lcb
Report File Name	: Default.lcr
Data Acquired	: 4/10/2014 10:10:17 PM
Data Processed	: 4/10/2014 10:30:19 PM



(racemic)

<Chromatogram>

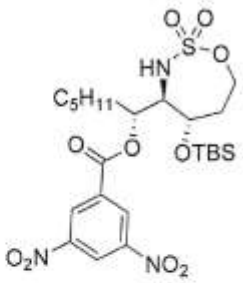


1 Det.A Ch1/225nm
2 Det.A Ch2/215nm

4/17/2014 18:57:49 1 / 1

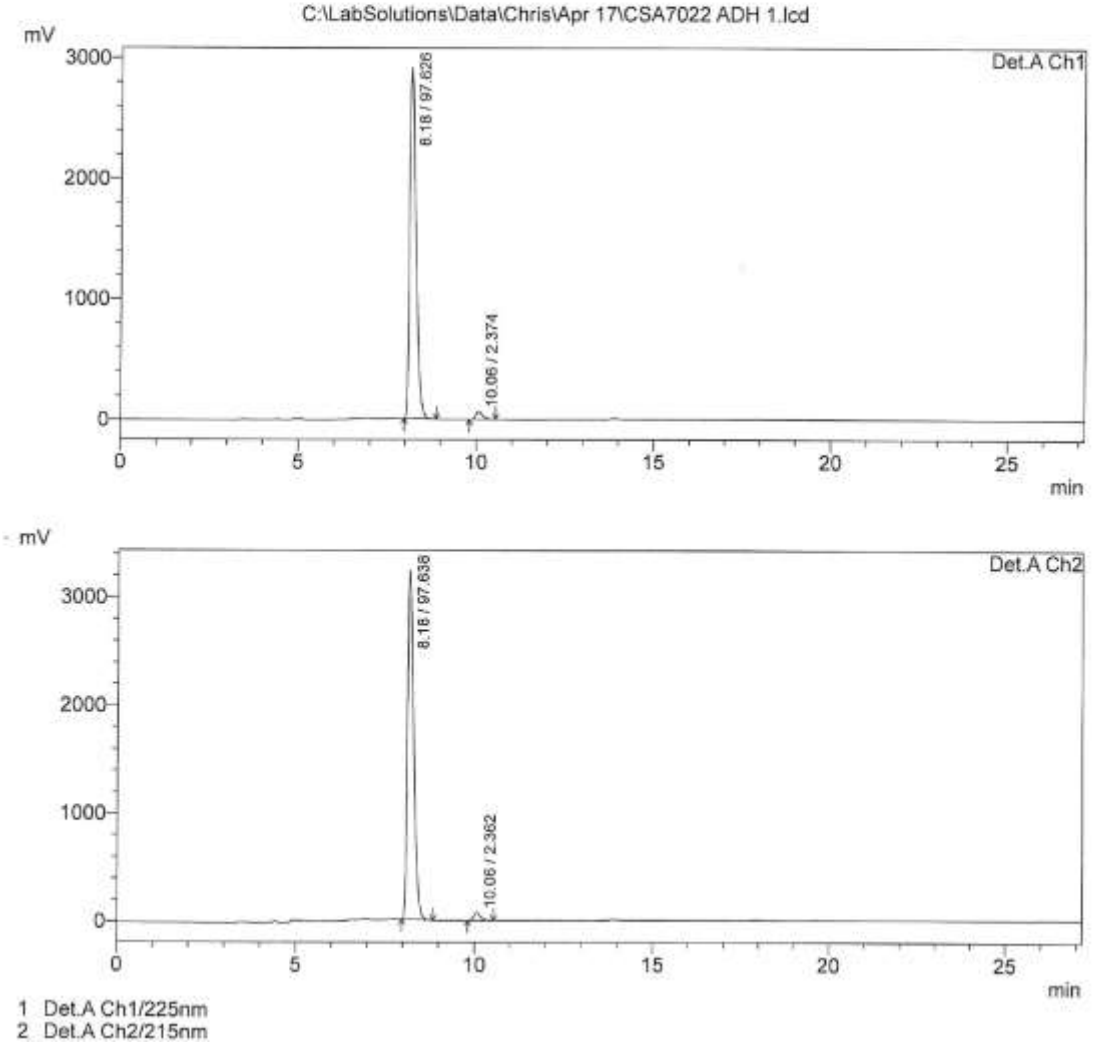
C:\LabSolutions\Data\Chris\Apr 17\CSA7022 ADH 1.lcd

Acquired by	: Admin
Sample Name	: CSA7022
Sample ID	:
Tray#	: 1
Vail #	: 49
Injection Volume	: 5 uL
Data File Name	: CSA7022 ADH 1.lcd
Method File Name	: 95-5 to 70-30 over 40 min 0.9 flow 215 225 nm.lcm
Batch File Name	: Batch 3 enantio triads ADH.lcb
Report File Name	: Default.lcr
Data Acquired	: 4/17/2014 6:07:00 PM
Data Processed	: 4/17/2014 6:34:11 PM



(enantioenriched)

<Chromatogram>

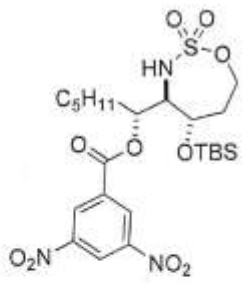


1 Det.A Ch1/225nm
2 Det.A Ch2/215nm

4/18/2014 00:07:54 1 / 1

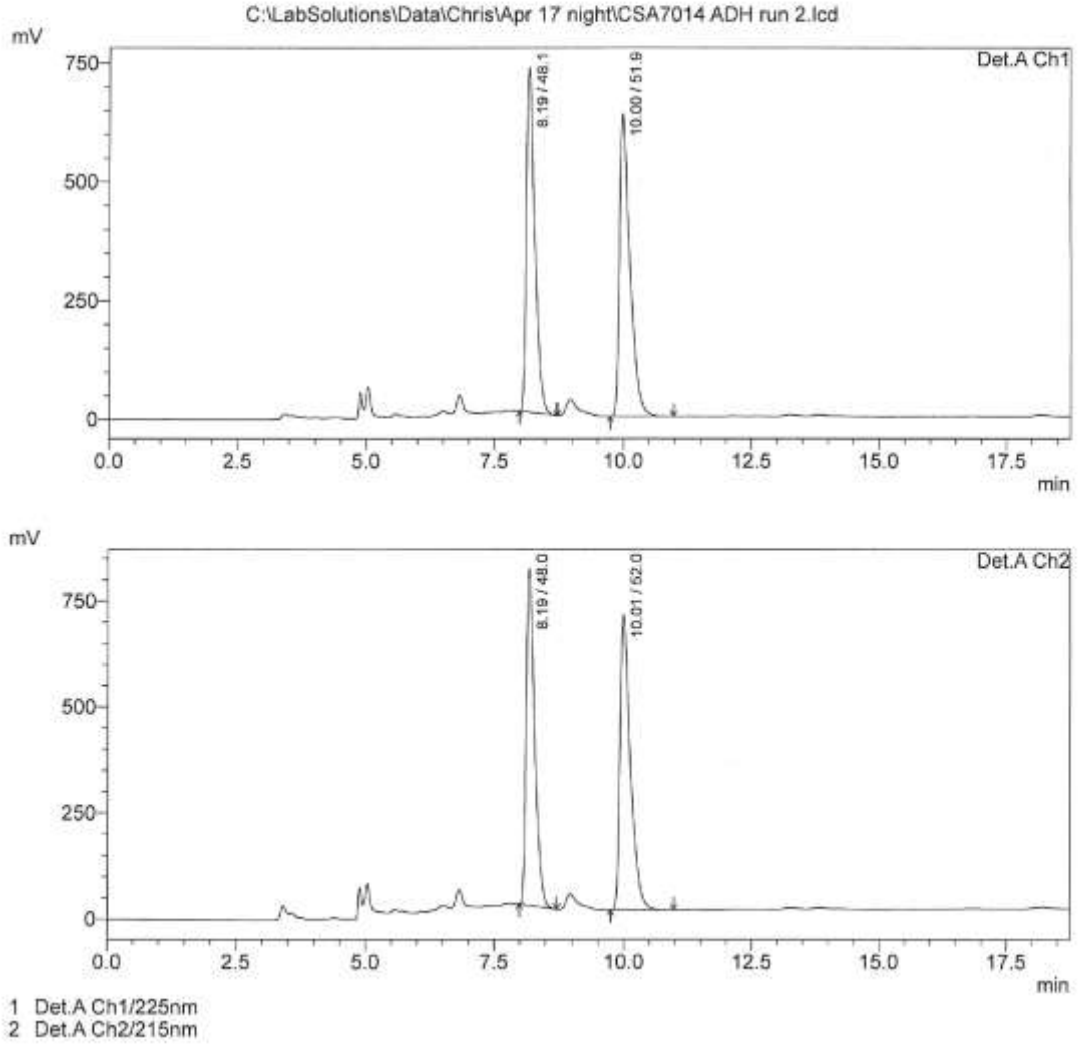
C:\LabSolutions\Data\Chris\Apr 17 night\CSA7014 ADH run 2.lcd

Acquired by	: Admin
Sample Name	: 7014 run2
Sample ID	:
Tray#	: 1
Vail #	: 66
Injection Volume	: 5 uL
Data File Name	: CSA7014 ADH run 2.lcd
Method File Name	: 95-5 to 70-30 over 40 min 0.9 flow 215 225 nm.lcm
Batch File Name	: Batch 3 7014.lcb
Report File Name	: Default.lcr
Data Acquired	: 4/17/2014 11:46:47 PM
Data Processed	: 4/18/2014 12:05:32 AM



(racemic)

<Chromatogram>

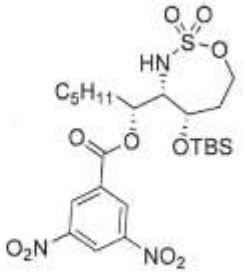


1 Det.A Ch1/225nm
2 Det.A Ch2/215nm

4/17/2014 23:32:22 1 / 1

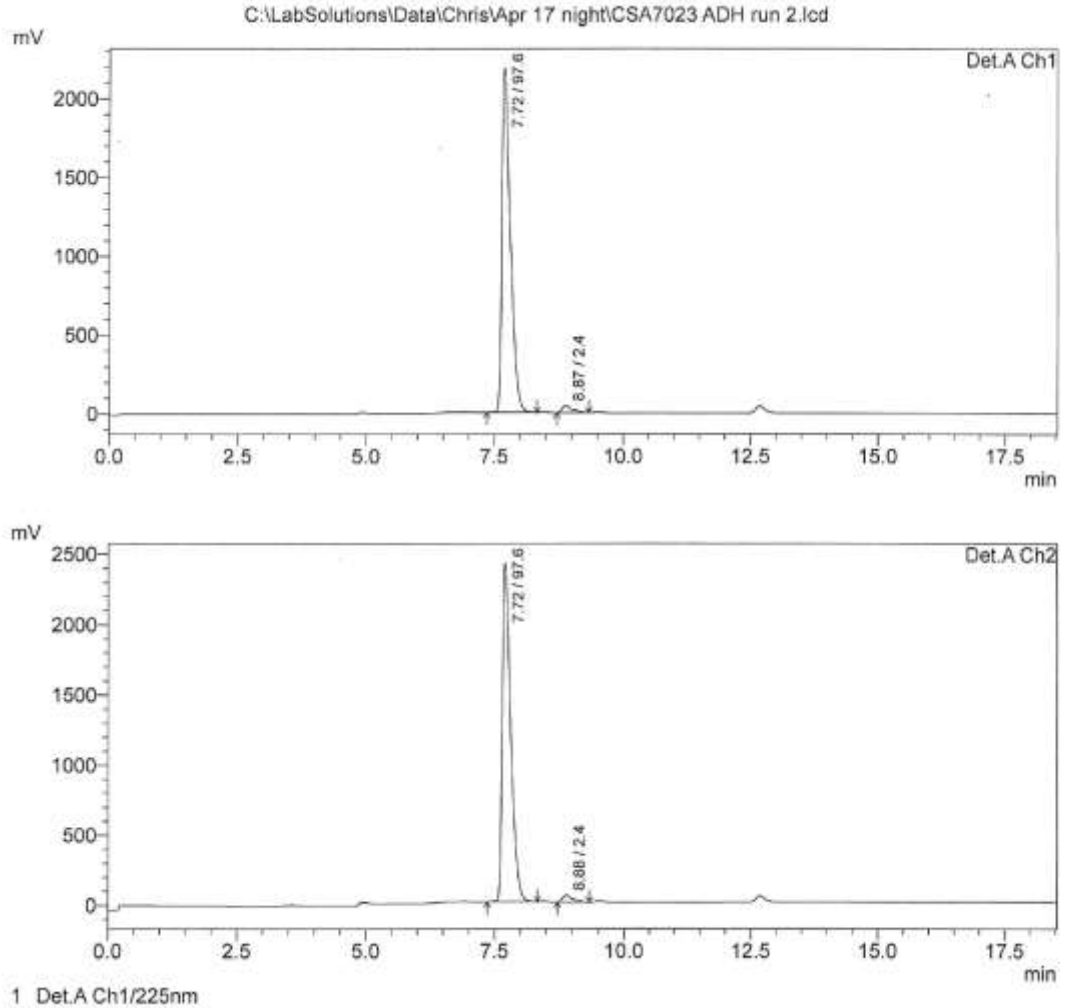
C:\LabSolutions\Data\Chris\Apr 17 night\CSA7023 ADH run 2.lcd

Acquired by	: Admin
Sample Name	: 7023 (column)
Sample ID	:
Tray#	: 1
Vail #	: 50
Injection Volume	: 5 uL
Data File Name	: CSA7023 ADH run 2.lcd
Method File Name	: 95-5 to 70-30 over 40 min 0.9 flow 215 225 nm.lcm
Batch File Name	: Batch 2 7013 and 7023.lcb
Report File Name	: Default.lcr
Data Acquired	: 4/17/2014 11:09:57 PM
Data Processed	: 4/17/2014 11:28:30 PM



(enantioenriched)

<Chromatogram>

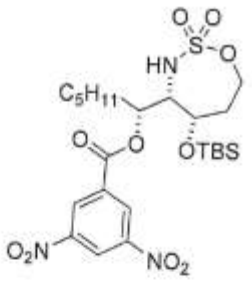


1 Det.A Ch1/225nm
2 Det.A Ch2/215nm

4/17/2014 23:30:18 1 / 1

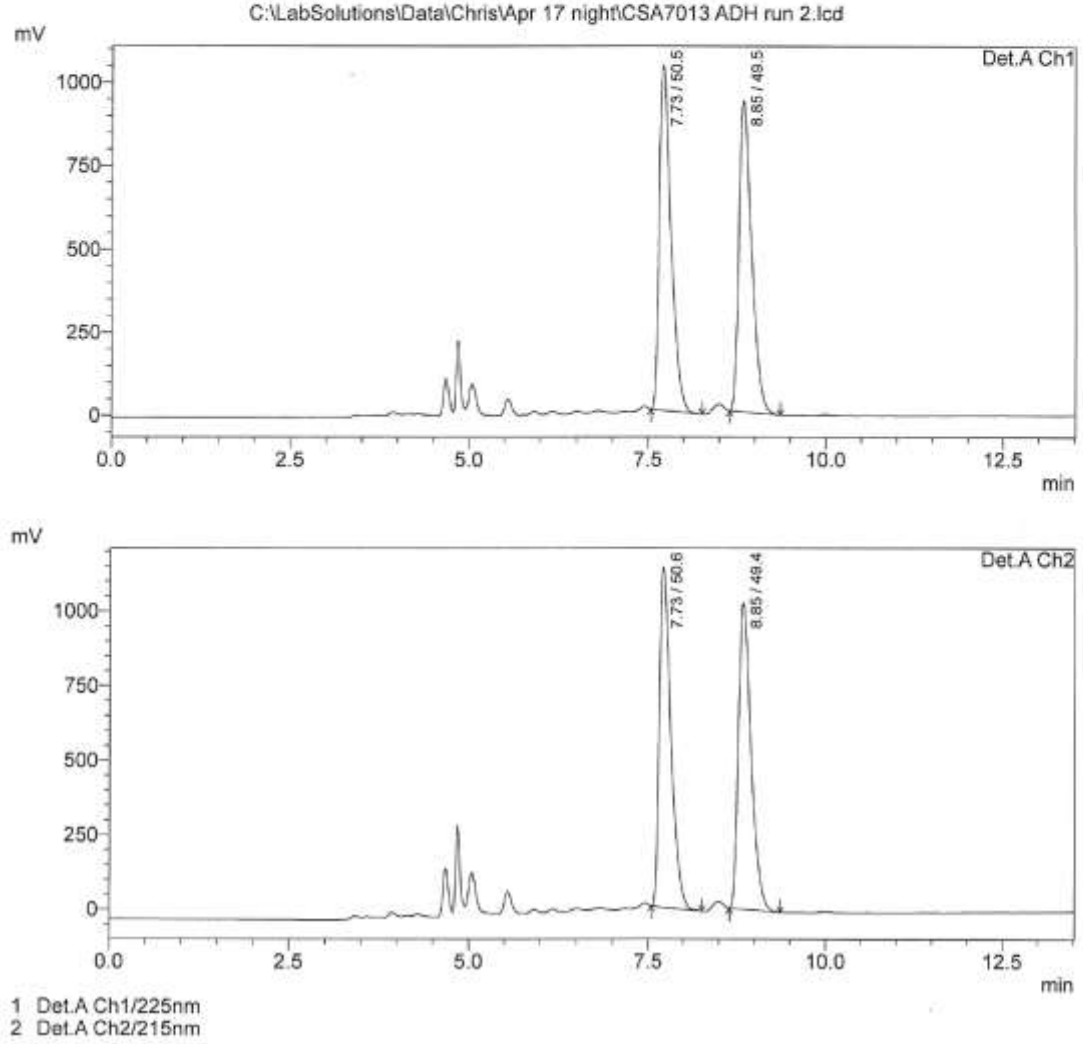
C:\LabSolutions\Data\Chris\Apr 17 night\CSA7013 ADH run 2.lcd

Acquired by	: Admin
Sample Name	: 7013
Sample ID	:
Tray#	: 1
Vail #	: 65
Injection Volume	: 5 uL
Data File Name	: CSA7013 ADH run 2.lcd
Method File Name	: 95-5 to 70-30 over 40 min 0.9 flow 215 225 nm.lcm
Batch File Name	: Batch 2 7013 and 7023.lcb
Report File Name	: Default.lcr
Data Acquired	: 4/17/2014 10:50:35 PM
Data Processed	: 4/17/2014 11:04:07 PM



(racemic)

<Chromatogram>

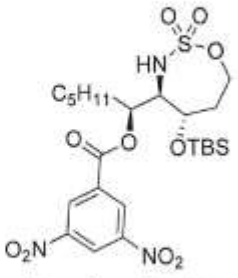


1 Det.A Ch1/225nm
2 Det.A Ch2/215nm

4/17/2014 22:28:53 1 / 1

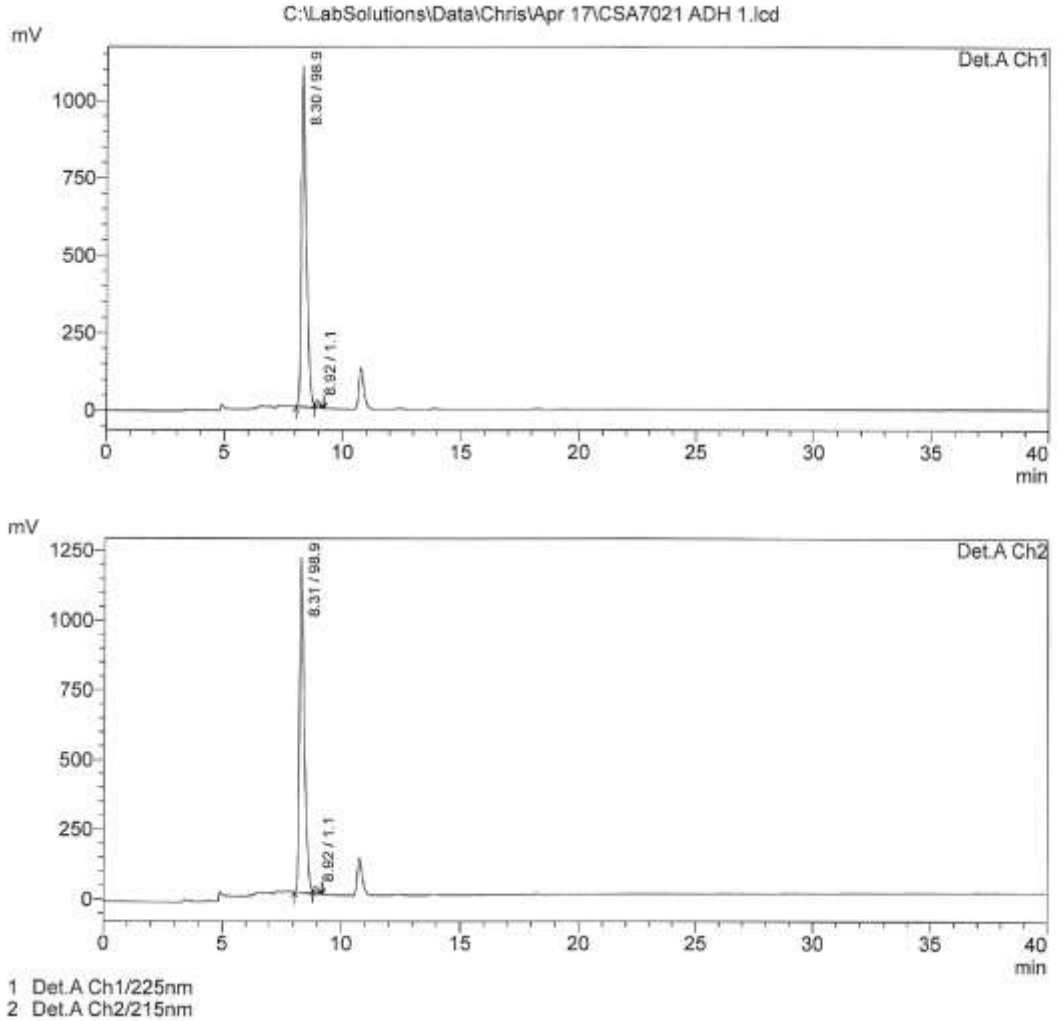
C:\LabSolutions\Data\Chris\Apr 17\CSA7021 ADH 1.lcd

Acquired by	: Admin
Sample Name	: CSA7021
Sample ID	:
Tray#	: 1
Vail #	: 48
Injection Volume	: 5 uL
Data File Name	: CSA7021 ADH 1.lcd
Method File Name	: 95-5 to 70-30 over 40 min 0.9 flow 215 225 nm.lcm
Batch File Name	: Batch 3 enantio triads ADH.lcb
Report File Name	: Default.lcr
Data Acquired	: 4/17/2014 5:21:09 PM
Data Processed	: 4/17/2014 6:01:11 PM



(enantioenriched)

<Chromatogram>

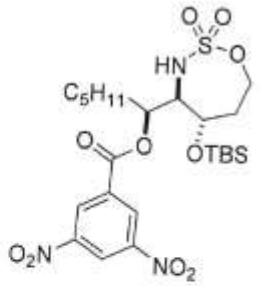


1 Det.A Ch1/225nm
2 Det.A Ch2/215nm

4/17/2014 22:25:41 1 / 1

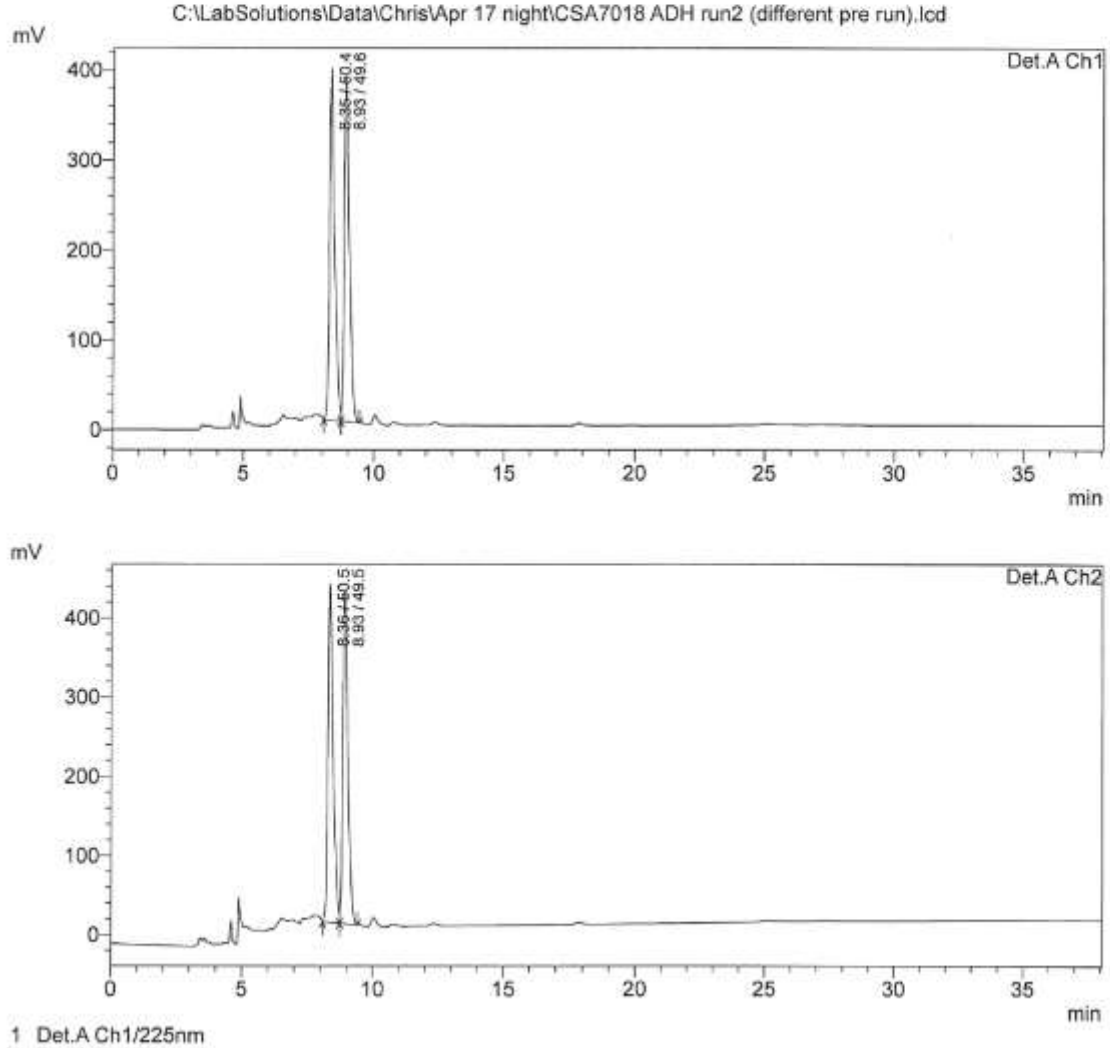
C:\LabSolutions\Data\Chris\Apr 17 night\CSA7018 ADH run2 (different pre run).lcd

Acquired by	: Admin
Sample Name	: CSA7018 2
Sample ID	:
Tray#	: 1
Vail #	: 69
Injection Volume	: 5 uL
Data File Name	: CSA7018 ADH run2 (different pre run).lcd
Method File Name	: 95-5 to 70-30 over 40 min 0.9 flow 215 225 nm.lcm
Batch File Name	: Batch 1 7018.lcb
Report File Name	: Default.lcr
Data Acquired	: 4/17/2014 9:46:11 PM
Data Processed	: 4/17/2014 10:24:15 PM



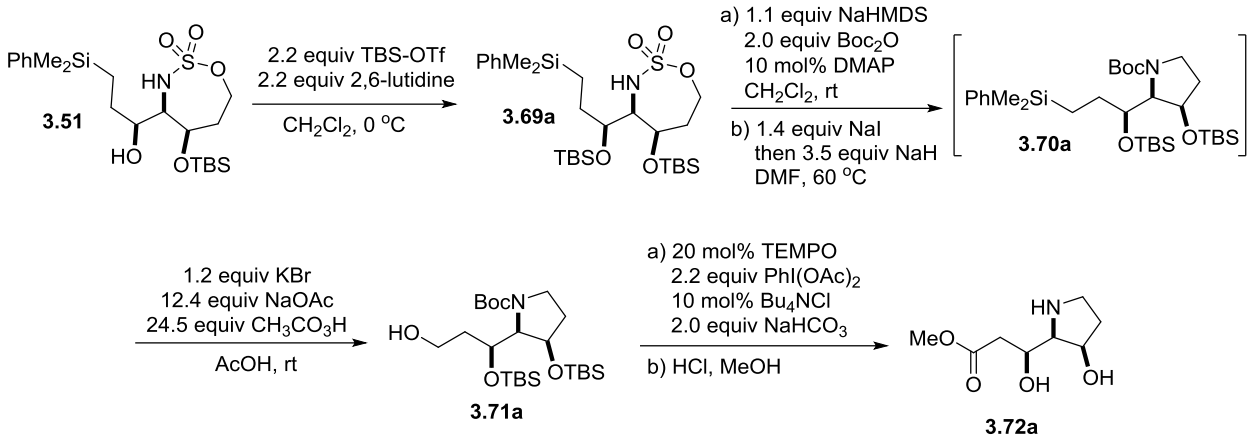
(racemic)

<Chromatogram>



1 Det.A Ch1/225nm
2 Det.A Ch2/215nm

3.5.16. Total synthesis of (±)-detoxinine methyl ester and diastereomers



Compound 3.69a. The 1,2-*syn*:2,3-*syn* stereotriad **3.51** (0.722 g, 1.52 mmol, 1.0 equiv) was dissolved in 5.0 mL of dry dichloromethane. The solution was cooled to 0 °C and 0.387 mL of 2,6-lutidine (3.34 mmol, 2.2 equiv) and 0.768 mL of TBSOTf (3.34 mmol, 2.2 equiv) were added. The reaction mixture was stirred for 25 min, diluted with 20 mL dichloromethane and quenched with 30 mL of water. The phases were separated and the aqueous phase extracted with dichloromethane (2 x 15 mL). The combined organic fractions were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography (2% to 10% EtOAc in hexanes) on silica gel. The product **3.69a** (0.761 g, 1.29 mmol, 85%) was isolated as a white solid. ^{1}H NMR: (500.0 MHz, $CDCl_3$) δ 7.48 (m, 2H), 7.35 (m, 3H), 5.21 (d, *J* = 10.6 Hz, 1H), 4.52 (t, *J* = 12.4 Hz, 1H), 4.14 (t, *J* = 3.1 Hz, 1H), 4.10 (dt, *J* = 12.4, 3.1 Hz, 1H), 3.61 (ddd, *J* = 8.0, 5.8, 2.8 Hz, 1H), 3.32 (dd, *J* = 10.6, 8.0 Hz, 1H), 1.99 (ddt, *J* = 15.7, 12.4, 3.1 Hz, 1H), 1.83 (dt, *J* = 15.7, 3.1 Hz, 1H), 1.50 (tdd, J = 14.0, 3.7, 2.8 Hz, 1H), 1.34 (tdd, *J* = 14.0, 5.8, 4.2 Hz,), 0.90 (s, 9H), 0.86 (s, 9H), 0.80 (td, *J* = 14.0, 3.7 Hz, 1H), 0.72 (td, *J* = 14.0, 4.2 Hz, 1H), 0.27 (s, 3H), 0.26 (s, 3H), 0.09 (s, 3H), 0.02 (s, 3H), 0.01 (s, 3H), -0.06 (s, 3H). ^{13}C NMR: (125.7 MHz, $CDCl_3$) δ 138.6, 133.5, 129.0, 127.9, 72.9, 66.1, 63.9, 59.8, 37.1,

27.0, 25.8, 25.8, 18.0, 17.9, 10.0, -2.9, -3.5, -3.8, -4.2, -4.6, -4.8. HMRS (ESI) *m/z* calculated for $C_{27}H_{54}NO_5SSi_3$ $[M + H]^+$ 588.3026, found 588.3032.

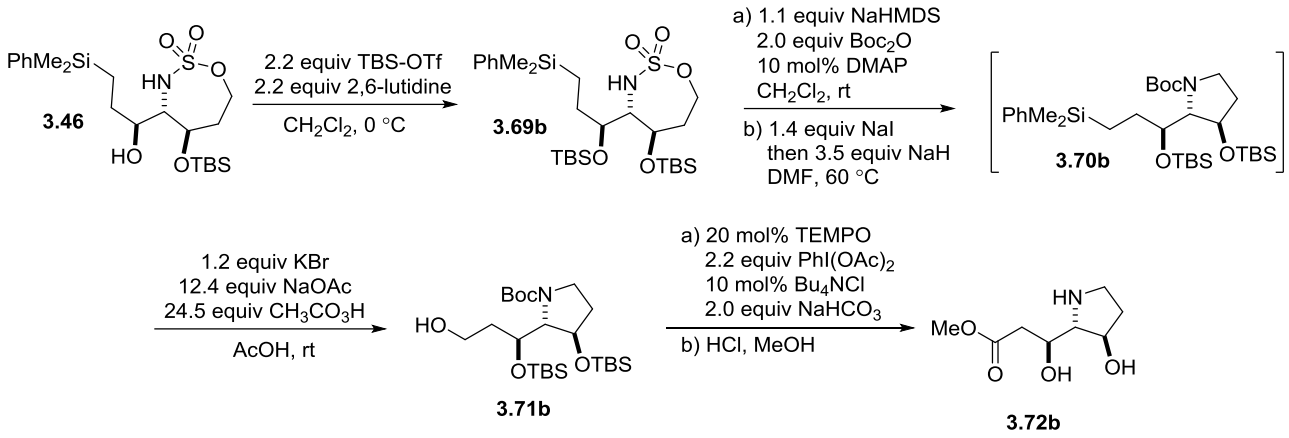
Compound 3.71a. The sulfamate **3.69a** (0.689 g, 1.17 mmol, 1.0 equiv) was dissolved in 6.0 mL of dry dichloromethane. The solution was cooled to 0 °C and DMAP was added (14.3 mg, 0.117 mmol, 10 mol%), followed by dropwise addition of NaHMDS (1.30 mL of 1.0 M solution in THF, 1.30 mmol, 1.1 equiv). After completion of the addition, Boc_2O was added (0.511 g, 2.34 mmol, 2.0 equiv). The solution was warmed to rt and allowed to stir for 3.5 h. The solution containing the protected sulfamate was concentrated under reduced pressure to a tan syrup. The material was redissolved in 5.9 mL of dry DMF and 0.246 g NaI (1.64 mmol, 1.4 equiv) was added. The thick solution was warmed to 45 °C and stirred for 15 min prior to the cautious addition of NaH (0.164 g of 60% wt suspension in mineral oil, 4.10 mmol, 3.5 equiv). The solution was then warmed to 60 °C and stirred for 10 h. The reaction mixture was cooled and cautiously quenched with 50 mL of water. The mixture was extracted with diethyl ether (4 x 50 mL), dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residual HMDS was removed from the crude residue by flash chromatography (5% EtOAc in hexanes) to yield oil **3.70a** of sufficient purity for the Fleming-Tamao oxidation.

The crude pyrrolidine **3.70a** was dissolved in 8.7 ml of glacial acetic acid containing KBr (0.164 g, 1.38 mmol, 1.2 equiv) and NaOAc (0.292 g, 3.56 mmol, 3.1 equiv). Peroxyacetic acid (1.47 mL of 32% wt in acetic acid, 7.01 mmol, 6.1 equiv) was added dropwise with ice bath cooling to control the exotherm. After stirring for 5 min, a second portion of NaOAc was added (0.876 g, 10.7 mmol, 9.3 equiv), followed by a second portion of peroxyacetic acid (4.45 mL, 21.2 mmol, 18.4 equiv). The solution was stirred at rt for 2 h before dilution with 100 mL diethyl ether and

100 mL of water containing 11.7 g sodium thiosulfate pentahydrate. The phases were separated, and the aqueous phase extracted with diethyl ether (3 x 50 mL). The combined organic phases were washed with saturated aqueous $NaHCO_3$ before drying with $MgSO_4$. The crude residue was purified by column chromatography (4% to 20% EtOAc in hexanes) to yield **3.71a** as a colorless oil (0.386 g, 0.788 mmol, 67% from sulfamate). ^{1}H NMR: (500.0 MHz, toluene-d_8, 60 °C) δ 4.44 (ddd, *J* = 9.2, 3.5, 2.8 Hz, 1H), 4.37 (m, 1H), 4.13 (app q, *J* = 9.2 Hz, 1H), 3.92 (m, 1H), 3.71 (m, 1H), 3.45 (td, *J* = 10.3, 3.1 Hz, 1H), 3.35 (m, 1H), 3.15 (m, 1H), 2.21 (m, 1H), 2.00-2.10 (m, 1H), 1.70-1.85 (m, 2H), 1.43 (s, 9H), 0.95 (s, 9H), 0.91 (s, 9H), 0.15 (s, 3H), 0.10 (s, 3H), 0.03 (s, 3H), 0.00 (s, 3H). ^{13}C NMR: (125.7 MHz, toluene-d_8) δ 156.2, 79.4, 72.0, 71.1, 61.2, 60.0, 44.8, 38.5, 32.2, 28.4, 26.1, 26.0, 18.3, 18.2, -3.7, -4.2, -4.9, -5.0. HMRS (ESI) *m/z* calculated for $C_{24}H_{52}NO_5Si_2$ $[M + H]^+$ 490.3379, found 490.3372.

Compound 3.72a. A 5 mL round bottom flask equipped with a magnetic stir bar was charged with **66** (91.5 mg, 0.187 mmol), sodium bicarbonate (31.4 mg, 0.374 mmol, 2.0 equiv), Bu_4NCl (5.2 mg, 0.0187 mmol, 10 mol%), and 1.10 mL 1:1 CH_3CN:H_2O. The mixture was stirred vigorously, and TEMPO (5.8 mg, 0.0374, 20 mol%) was added, followed by $PhI(OAc)_2$ (0.130 g, 0.411 mmol, 2.20 equiv). After stirring under nitrogen for 24 hours, the reaction was diluted with 5 mL CH_2Cl_2 and 5 mL of 0.2 M HCl. The phases were separated, and the aqueous phase extracted with CH_2Cl_2 (4 x 5 mL). The combined organic fractions were dried with $MgSO_4$ and concentrated to a crude oil. The oil was treated with 5.60 mL of 0.5 M HCl in methanol (prepared by reaction of TMS-Cl in methanol) and stirred for 1 hour. Concentration by rotary evaporation afforded a crude oil. Non-polar organics were removed by column chromatography (10% CH_3CN in CH_2Cl_2, then 10% MeOH in CH_3CN) yielding crude white solid **68** that was triturated with cold CH_3CN and isolated

by filtration (26.9 mg, 0.142 mmol, 76%). ^{1}H NMR: (500.0 MHz, D_2O) δ 4.51 (t, *J* = 3.3 Hz, 1H), 4.40 (ddd, *J* = 9.9, 9.2, 3.2 Hz, 1H), 3.73 (s, 3H), 3.40-3.58 (m, 3H), 2.84 (dd, *J* = 15.8, 3.2 Hz, 1H), 2.63 (dd, *J* = 15.8, 9.2 Hz, 1H), 2.23 (dtd, *J* = 14.3, 10.1, 3.3 Hz, 1H), 2.12 (ddd, *J* = 14.3, 7.8, 3.0 Hz, 1H). ^{13}C NMR: (125.7 MHz, D_2O) δ 173.2, 69.3, 68.0, 64.9, 52.5, 42.9, 39.1, 33.1. HMRS (ESI) *m/z* calculated for $C_8H_{16}NO_4$ $[M + H]^+$ 190.1074, found 190.1079.



Compound 3.69b. The 1,2-*anti*:2,3-*anti* stereotriad **3.46** (0.150 g, 0.317 mmol, 1.0 equiv) was dissolved in 3.1 mL of dry dichloromethane. The solution was cooled to 0 °C and 0.0806 mL of 2,6-lutidine (0.696 mmol, 2.2 equiv) and 0.160 mL of TBSOTf (0.696 mmol, 2.2 equiv) were added. The reaction mixture was stirred for 25 min, diluted with 10 mL dichloromethane and quenched with 10 mL of water. The phases were separated and the aqueous phase extracted with dichloromethane (2 x 15 mL). The combined organic fractions were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography (2% to 10% EtOAc in hexanes) on silica gel. The product **3.69b** (0.165 g, 0.281 mmol, 89%) was isolated as a white solid. ^{1}H NMR: (500.0 MHz, $CDCl_3$) δ 7.48 (m, 2H), 7.34 (m, 3H), 4.77 (d, *J* = 6.0 Hz, 1H), 4.43 (ddd, *J* = 12.4, 8.8, 1.3 Hz, 1H), 4.18 (ddd, *J* = 12.4, 7.3, 1.8 Hz, 1H), 4.05-4.10 (m, 2H), 3.27 (app q, *J* = 6.0 Hz, 1H), 2.13 (ddt, *J* = 15.6, 8.8, 2.1 Hz, 1H), 1.90 (m, 1H), 1.65 (m, 1H), 1.52 (m, 1H), 0.87 (s, 9H), 0.86 (s, 9H), 0.77 (td, *J* = 14.0, 4.2 Hz,

1H), 0.67 (td, *J* = 14.0, 3.9 Hz, 1H), 0.27 (s, 3H), 0.26 (s, 3H), 0.06 (s, 3H), 0.03 (s, 3H), -0.00 (s, 3H), -0.01 (s, 3H); ^{13}C NMR: (125.7 MHz, $CDCl_3$) δ 138.8, 133.6, 129.0, 127.8, 71.7, 69.7, 65.3, 62.0, 35.5, 26.3, 25.8, 25.7, 18.0, 17.9, 9.7, -3.2, -3.2, -4.0, -4.2, -4.6, -4.9. HMRS (ESI) *m/z* calculated for $C_{27}H_{54}NO_5SSi_3$ $[M + NH_4]^+$ 605.3291, found 605.3307.

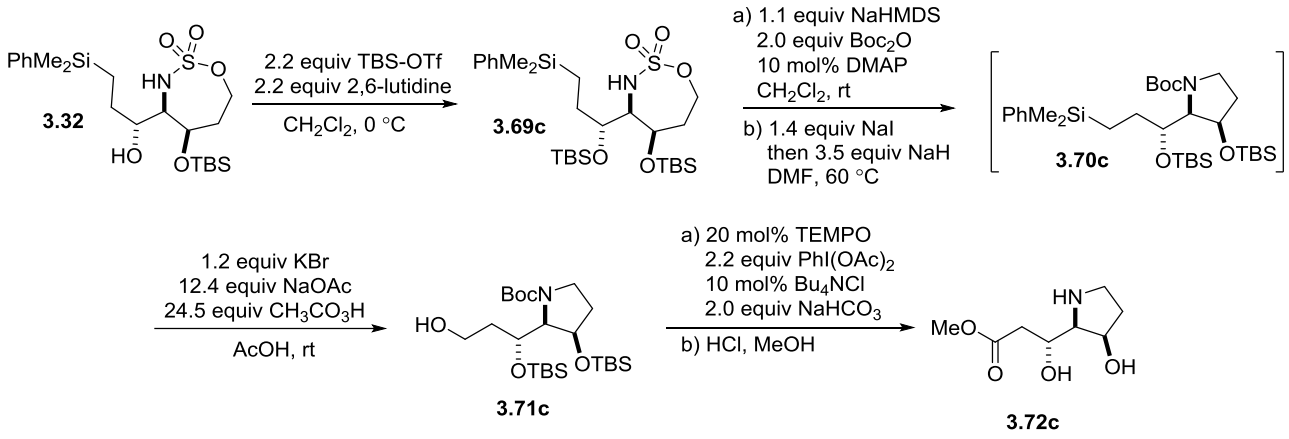
Compound 3.71b. The sulfamate **3.69b** (0.144 g, 0.246 mmol, 1.0 equiv) was dissolved in 1.5 mL of dry dichloromethane. The solution was cooled to 0 °C and DMAP was added (3.0 mg, 0.0246 mmol, 10 mol%), followed by dropwise addition of NaHMDS (0.271 mL of 1.0 M solution in THF, 0.271 mmol, 1.1 equiv). After completion of the addition, Boc_2O was added (0.107 g, 0.492 mmol, 2.0 equiv). The solution was warmed to rt and allowed to stir for 50 minutes. The solution containing the protected sulfamate was concentrated under reduced pressure to a tan syrup. The material was redissolved in 1.3 mL of dry DMF and 0.0516 g NaI (0.344 mmol, 1.4 equiv) was added. The thick solution was warmed to 45 °C and stirred for 15 min prior to the cautious addition of NaH (0.0344 g of 60% wt suspension in mineral oil, 0.861 mmol, 3.5 equiv). The solution was then warmed to 60 °C and stirred for 10 h. The reaction mixture was cooled and cautiously quenched with 10 mL of water. The mixture was extracted with diethyl ether (4 x 10 mL), dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residual HMDS was removed from the crude residue by flash chromatography (5% EtOAc in hexanes) to yield 0.0983 g of oil **3.70b** of sufficient purity for the Fleming-Tamao oxidation.

The crude pyrrolidine **3.70b** was dissolved in 1.2 ml of glacial acetic acid containing KBr (0.0231 g, 0.194 mmol, 1.2 equiv) and NaOAc (0.0411 g, 0.501 mmol, 3.1 equiv). Peroxyacetic acid (0.207 mL of 32% wt in acetic acid, 0.986 mmol, 6.1 equiv) was added dropwise with ice bath cooling to control the exotherm. After stirring for 5 min, a second portion of NaOAc was

added (0.123 g, 1.50 mmol, 9.3 equiv), followed by a second portion of peroxyacetic acid (0.625 mL, 2.97 mmol, 18.4 equiv). The solution was stirred at rt for 2 h before dilution with 10 mL diethyl ether and 12 mL of water containing 1.62 g sodium thiosulfate pentahydrate. The phases were separated, and the aqueous phase extracted with diethyl ether (3 x 10 mL). The combined organic phases were washed with saturated aqueous $NaHCO_3$ before drying with $MgSO_4$. The crude residue was purified by column chromatography (4% to 20% EtOAc in hexanes) to yield **3.71b** as a colorless oil (0.0698 g, 0.142 mmol, 58% from sulfamate). (Note: This spectrum is complicated by the presence of two rotamers in the product structure. However, the rotamers are fairly well resolved for this compound). ^{1}H NMR: (500.0 MHz, $CDCl_3$) δ 4.45 (br s, 1H), 4.17 (m, 1H), 3.80 (dt, *J* = 10.8, 6.7 Hz, 0.6H), 3.68-3.75 (m, 2H), 3.58 (app q, *J* = 8.7 Hz, 0.4H), 3.42-3.50 (m, 1H), 3.25-3.33 (m, 1H), 2.80 (br s, 0.4H), 2.04 (m, 1H), 1.64-1.85 (m, 3.6H), 1.43-1.49 (2 x s, 9H), 0.87 (s, 9H), 0.86 (s, 9H), -0.05-0.07 (overlapping s, 12H). ^{13}C NMR: (125.7 MHz, $CDCl_3$) δ 155.2, 154.8, 79.5, 79.4, 72.6, 71.8, 70.2, 69.6, 69.5, 69.2, 59.6, 59.5, 45.2, 45.0, 38.2, 37.8, 34.1, 33.5, 28.6, 28.5, 25.9, 25.8, 25.7, 25.6, 17.9 x 2, 17.8, 17.8, -4.4, -4.5, -4.6, -4.7 x 2, -4.8, -4.9, -5.0. HMRS (ESI) *m/z* calculated for $C_{24}H_{52}NO_5Si_2$ $[M + H]^+$ 490.3379, found 490.3273.

Compound 3.72b. A 5 mL round bottom flask equipped with a magnetic stir bar was charged with **3.71b** (65.0 mg, 0.133 mmol), sodium bicarbonate (22.3 mg, 0.266 mmol, 2.0 equiv), Bu_4NCl (3.7 mg, 0.0133 mmol, 10 mol%), and 0.78 mL 1:1 CH_3CN:H_2O. The mixture was stirred vigorously, and TEMPO (4.2 mg, 0.0266, 20 mol%) was added, followed by $PhI(OAc)_2$ (92.4 mg, 0.293 mmol, 2.20 equiv). After stirring under nitrogen for 24 hours, the reaction was diluted with 4 mL CH_2Cl_2 and 4 mL of 0.2 M HCl. The phases were separated, and the aqueous phase extracted with CH_2Cl_2 (4 x 5 mL). The combined organic fractions were dried with $MgSO_4$ and concentrated to a crude

oil. The oil was treated with 4.0 mL of 0.5 M HCl in methanol (prepared by reaction of TMS-Cl in methanol) and stirred for 1 hour. Concentration by rotary evaporation afforded a crude oil. Non-polar organics were removed by column chromatography (10% CH_3CN in CH_2Cl_2, then 10% MeOH in CH_3CN) yielding crude white solid **3.72b** that was purified by trituration with cold CH_2Cl_2 (23.9 mg, 0.126 mmol, 95%). ^{1}H NMR: (500.0 MHz, D_2O) δ 4.59 (ddd, *J* = 6.0, 4.8, 4.2 Hz, 1H), 4.46 (dt, *J* = 8.7, 4.2 Hz, 1H), 3.75 (s, 3H), 3.58 (t, *J* = 4.2 Hz, 1H), 3.41-3.52 (m, 2H), 2.81 (dd, *J* = 16.2, 4.2 Hz, 1H), 2.76 (dd, *J* = 16.2, 8.7 Hz, 1H), 2.29 (ddt, *J* = 13.0, 6.9, 6.0 Hz, 1H), 2.04 (dddd, *J* = 13.0, 11.5, 5.9, 4.8 Hz, 1H); ^{13}C NMR: (125.7 MHz, D2O) δ 173.0, 69.1, 68.3, 64.8, 52.5, 44.5, 38.4, 33.0. HMRS (ESI) *m/z* calculated for $C_8H_{16}NO_4$ $[M + H]^+$ 190.1074, found 190.1078.



Compound 3.69c. The 1,2-*anti*:2,3-*anti* stereotriad **3.32** (0.260 g, 0.549 mmol, 1.0 equiv) was dissolved in 5.0 mL of dry dichloromethane. The solution was cooled to 0 °C and 0.127 mL of 2,6-lutidine (1.10 mmol, 2.0 equiv) and 0.252 mL of TBSOTf (1.10 mmol, 2.0 equiv) were added. The reaction mixture was stirred for 25 min, diluted with 10 mL dichloromethane and quenched with 10 mL of water. The phases were separated and the aqueous phase extracted with dichloromethane (2 x 15 mL). The combined organic fractions were dried with $MgSO_4$, filtered,

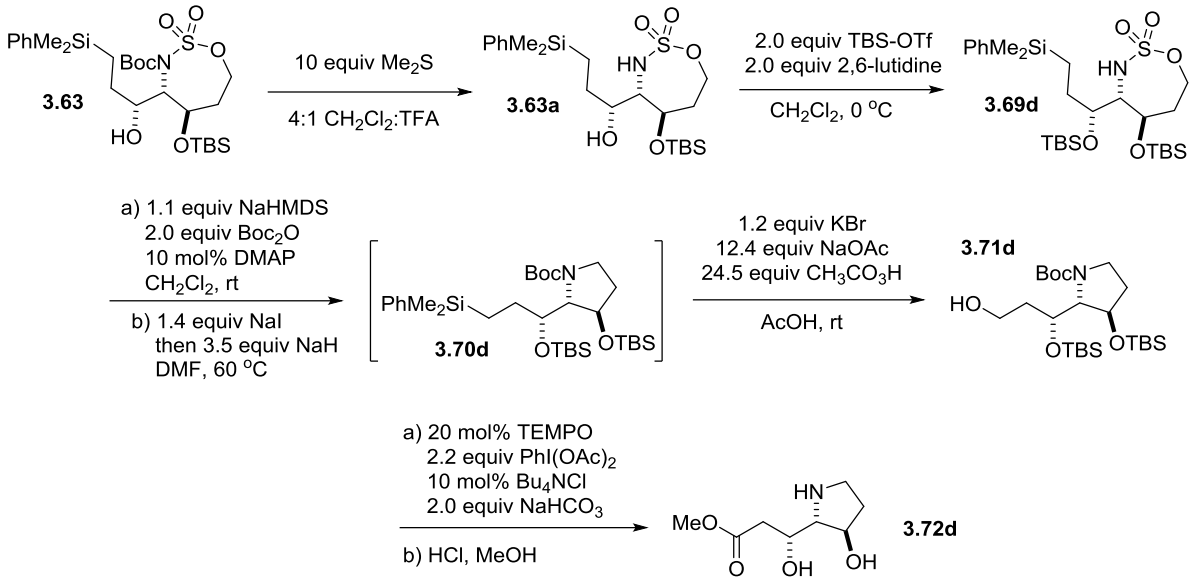
and concentrated under reduced pressure. The crude residue was purified by column chromatography (3% to 15% EtOAc in hexanes) on silica gel. The product **3.69c** (0.313 g, 0.532 mmol, 97%) was isolated as a clear, colorless oil. ^{1}H NMR: (500.0 MHz, $CDCl_3$) δ 7.54 (m, 2H), 7.34 (m, 3H), 5.24 (d, *J* = 11.0 Hz, 1H), 11.2 (t, *J* = 12.5 Hz, 1H), 4.39 (dd, *J* = 3.3, 2.4 Hz, 1H), 4.14 (dt, *J* = 12.5, 3.1 Hz, 1H), 3.65 (ddd, *J* = 9.3, 3.9, 2.7 Hz, 1H), 3.33 (dd, *J* = 11.0, 9.3 Hz, 1H), 2.07 (dddd, *J* = 15.6, 12.5, 3.1, 2.4 Hz, 1H), 1.89 (ddd, *J* = 15.6, 3.3, 3.1 Hz, 1H), 1.77 (tdd, *J* = 14.0, 3.5, 2.7 Hz, 1H), 1.55 (tt, *J* = 14.0, 3.9 Hz, 1H), 1.03 (td, *J* = 14.0, 3.9 Hz, 1H), 0.90 (s, 9H), 0.86 (s, 9H), 0.75 (td, *J* = 14.0, 3.5 Hz, 1H), 0.28 (s, 3H), 0.27 (s, 3H), 0.10 (s, 3H), 0.10 (s, 3H), 0.02 (s, 3H), -0.03 (s, 3H). ^{13}C NMR: (125.7 MHz, $CDCl_3$) δ 139.1, 133.7, 128.8, 127.7, 71.5, 66.5, 63.8, 58.8, 36.6, 27.3, 25.9, 25.8, 18.1, 18.1, 6.5, -3.3, -3.3, -3.3, -3.8, -4.5, -4.6. HMRS (ESI) *m/z* calculated for $C_{27}H_{54}NO_5SSi_3$ $[M + NH_4]^+$ 605.3291, found 605.3282.

Compound 3.71c. The sulfamate **3.69c** (0.298 g, 0.507 mmol, 1.0 equiv) was dissolved in 2.6 mL of dry dichloromethane. The solution was cooled to 0 °C and DMAP was added (6.2 mg, 0.0507 mmol, 10 mol%), followed by dropwise addition of NaHMDS (0.557 mL of 1.0 M solution in THF, 0.557 mmol, 1.1 equiv). After completion of the addition, Boc_2O was added (0.220 g, 1.01 mmol, 2.0 equiv). The solution was warmed to rt and allowed to stir for 4 hours. The solution containing the protected sulfamate was concentrated under reduced pressure to a tan syrup. The material was redissolved in 2.5 mL of dry DMF and 0.106 g NaI (0.709 mmol, 1.4 equiv) was added. The thick solution was warmed to 45 °C and stirred for 15 min prior to the cautious addition of NaH (0.071 g of 60% wt suspension in mineral oil, 1.77 mmol, 3.5 equiv). The solution was then warmed to 60 °C and stirred for 10 h. The reaction mixture was cooled and cautiously quenched with 10 mL of water. The mixture was extracted with diethyl ether (4 x 15 mL), dried

with $MgSO_4$, filtered, and concentrated under reduced pressure. The residual HMDS was removed from the crude residue by flash chromatography (5% EtOAc in hexanes) to yield 0.198 g of oil **3.70c** of sufficient purity for the Fleming-Tamao oxidation.

The crude pyrrolidine **3.70c** was dissolved in 2.4 ml of glacial acetic acid containing KBr (0.0463 g, 0.389 mmol, 1.2 equiv) and NaOAc (0.0820 g, 1.00 mmol, 3.1 equiv). Peroxyacetic acid (0.416 mL of 32% wt in acetic acid, 1.98 mmol, 6.1 equiv) was added dropwise with ice bath cooling to control the exotherm. After stirring for 5 min, a second portion of NaOAc was added (0.246 g, 3.01 mmol, 9.3 equiv), followed by a second portion of peroxyacetic acid (1.26 mL, 5.96 mmol, 18.4 equiv). The solution was stirred at rt for 2 h before dilution with 20 mL diethyl ether and 25 mL of water containing 3.60 g sodium thiosulfate pentahydrate. The phases were separated, and the aqueous phase extracted with diethyl ether (3 x 15 mL). The combined organic phases were washed with saturated aqueous $NaHCO_3$ before drying with $MgSO_4$. The crude residue was purified by column chromatography (6% to 30% EtOAc in hexanes) to yield **3.71c** as a colorless oil (0.0707 g, 0.144 mmol, 28% from sulfamate). (Note: This spectrum is complicated by the presence of two rotamers in the product structure. However, the rotamers are fairly well resolved for this compound). ^{1}H NMR: (500.0 MHz, $CDCl_3$) δ 4.41 (dt, *J* = 10.5, 7.4 Hz, 1H), 4.28 (m, 1H), 3.62-9.95 (m, 3H), 3.38 (t, *J* = 10.2 Hz, 1H), 3.20 (m, 1H), 2.12-2.38 (m, 2H), 1.83-1.95 (m, 2H), 1.46 (s, 9H), 0.91 (s, 9H), 0.90 (s, 9H), 0.01-0.09 (overlapping s, 12H). ^{13}C NMR (Major Rotamer): (125.7 MHz, $CDCl_3$) δ 154.6, 79.4, 72.8, 71.7, 60.5, 59.7, 43.3, 37.3, 32.9, 28.5, 25.9, 25.8, 17.9, 17.8, -4.6, -4.7, -5.0, -5.0. HMRS (ESI) *m/z* calculated for $C_{24}H_{52}NO_5Si_2$ $[M + H]^+$ 490.3379, found 490.3382.

Compound 3.72c. A 5 mL round bottom flask equipped with a magnetic stir bar was charged with **3.71c** (67.3 mg, 0.137 mmol), sodium bicarbonate (23.1 mg, 0.274 mmol, 2.0 equiv), Bu_4NCl (3.8 mg, 0.0137 mmol, 10 mol%), and 0.80 mL 1:1 CH_3CN:H_2O. The mixture was stirred vigorously, and TEMPO (4.3 mg, 0.0274, 20 mol%) was added, followed by $PhI(OAc)_2$ (95.3 mg, 0.302 mmol, 2.20 equiv). After stirring under nitrogen for 36 hours, the reaction was diluted with 4 mL CH_2Cl_2 and 4 mL of 0.2 M HCl. The phases were separated, and the aqueous phase extracted with CH_2Cl_2 (4 x 5 mL). The combined organic fractions were dried with $MgSO_4$ and concentrated to a crude oil. The oil was treated with 4.5 mL of 0.5 M HCl in methanol (prepared by reaction of TMS-Cl in methanol) and stirred for 1 hour. Concentration by rotary evaporation afforded a crude oil. Non-polar organics were removed by column chromatography (10% CH_3CN in CH_2Cl_2, then 10% MeOH in CH_3CN) yielding crude white solid **3.72c** that was purified by trituration with cold CH_2Cl_2 (16.3 mg, 0.0861 mmol, 63%). ^{1}H NMR: (500.0 MHz, D_2O) δ 4.69 (t, *J* = 1.5 Hz, 1H), 4.49 (td, *J* = 8.6, 3.7 Hz, 1H), 3.76 (s, 3H), 3.46-3.64 (m, 3H), 2.84 (dd, *J* = 15.9, 3.7 Hz, 1H), 2.75 (dd, *J* = 15.9, 8.6 Hz, 1H), 2.23 (dtd, *J* = 13.7, 10.1, 3.9 Hz, 1H), 2.14 (ddd, *J* = 13.7, 6.9, 1.5 Hz, 1H). ^{13}C NMR: (125.7 MHz, D_2O) δ 173.1, 69.7, 66.0, 64.0, 52.5, 43.9, 39.1, 32.4. HMRS (ESI) *m/z* calculated for $C_8H_{16}NO_4$ $[M + H]^+$ 190.1074, found 190.1071.



Compound 3.63a. The 1,2-*anti*:2,3-*syn* stereotriad **3.63** (0.104 g, 0.181 mmol, 1.0 equiv) was dissolved in 1.8 mL of dry dichloromethane. Dimethyl sulfide (0.112 g, 1.81 mmol, 10 equiv) was added to the solution. The solution was cooled to 0 °C and 0.45 mL of TFA was added. The reaction mixture was stirred for 60 min at 0 °C and 2 hours at room temperature. The reaction was diluted with 30 mL dichloromethane and quenched with saturated aqueous $NaHCO_3$. The phases were separated and the organic phase dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography (6% to 30% EtOAc in hexanes) on silica gel. The product **3.63a** (0.0580 g, 0.122 mmol, 68%) was isolated as a clear, colorless oil. ^{1}H NMR: (500.0 MHz, $CDCl_3$) δ 7.51 (m, 2H), 7.36 (m, 3H), 5.00 (br s, 1H), 4.22-4.33 (m, 2H), 3.94 (td, *J* = 6.7, 1.9 Hz, 1H), 3.86 (td, *J* = 8.9, 4.6 Hz, 1H), 3.25 (td, *J* = 9.7, 2.0 Hz, 1H), 2.11 (dtd, *J* = 15.7, 4.5, 2.0 Hz, 1H), 1.99 (dddd, *J* = 15.7, 9.7, 8.9, 4.0 Hz, 1H), 1.60-1.70 (m, 2H), 1.54 (tdd, *J* = 13.0, 6.7, 4.6 Hz,), 0.88 (s, 9H), 0.79 (td, *J* = 13.0, 4.7 Hz, 1H), 0.70 (td, *J* = 13.0, 4.5 Hz, 1H), 0.30 (s, 3H), 0.30 (s, 3H), 0.07 (s, 3H), 0.07 (s, 3H). ^{13}C NMR: (125.7 MHz, $CDCl_3$) δ 138.63, 133.57, 129.02, 127.85, 70.66, 69.93, 66.60, 59.73, 37.43, 28.12, 25.67,

17.87, 11.09, -3.17, -3.31, -4.36, -4.96. HMRS (ESI) *m/z* calculated for $C_{21}H_{43}N_2O_5SSi_2$ $[M + NH_4]^+$ 491.2426, found 491.2427.

Compound 3.69d. The 1,2-*anti*:2,3-*syn* stereotriad **3.63a** (0.140 g, 0.295 mmol, 1.0 equiv) was dissolved in 2.95 mL of dry dichloromethane. The solution was cooled to 0 °C and 0.069 mL of 2,6-lutidine (0.591 mmol, 2.0 equiv) and 0.136 mL of TBSOTf (0.591 mmol, 2.0 equiv) were added. The reaction mixture was stirred for 25 min, diluted with 10 mL dichloromethane and quenched with 10 mL of water. The phases were separated and the aqueous phase extracted with dichloromethane (2 x 15 mL). The combined organic fractions were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography (2% to 10% EtOAc in hexanes) on silica gel. The product **3.69d** (0.138 g, 0.235 mmol, 80%) was isolated as a clear, colorless oil. ^{1}H NMR: (500.0 MHz, $CDCl_3$) δ 7.50 (m, 2H), 7.34 (m, 3H), 4.81 (d, *J* = 8.9 Hz, 1H), 4.40 (dd, *J* = 12.6, 6.5 Hz, 1H), 4.25 (dd, *J* = 12.6, 9.6 Hz, 1H), 3.94 (td, *J* = 7.7, 4.4 Hz, 1H), 3.88 (dd, *J* = 10.5, 4.2 Hz, 1H), 3.47 (dd, *J* = 8.9, 7.7 Hz, 1H), 2.21 (ddd, *J* = 15.8, 6.5, 4.2 Hz, 1H), 2.05 (ddd, *J* = 15.8, 10.5, 9.6 Hz, 1H), 1.66 (tdd, *J* = 13.6, 7.7, 4.9 Hz, 1H), 1.41 (tt, *J* = 13.6, 3.4 Hz, 1H), 0.88 (s, 9H), 0.84 (s, 9H), 0.79 (td, *J* = 13.6, 4.9 Hz, 1H), 0.47 (td, *J* = 13.6, 3.3 Hz, 1H), 0.29 (s, 3H), 0.28 (s, 3H), 0.07 (s, 6H), -0.01 (s, 3H), -0.03 (s, 3H). 13C NMR: (125.7 MHz, CDCl3) delta 138.5, 133.5, 129.0, 127.8, 73.7, 71.5, 66.1, 58.9, 37.5, 28.5, 25.9, 25.7, 18.0, 17.9, 10.9, -3.1, -3.4, -3.5, -3.6, -4.3, -4.7. HMRS (ESI) *m/z* calculated for $C_{27}H_{57}N_2O_5SSi_3$ $[M + NH_4]^+$ 605.3291, found 605.3293.

Compound 3.71d. The sulfamate **3.69d** (0.124 g, 0.212 mmol, 1.0 equiv) was dissolved in 2.1 mL of dry dichloromethane. The solution was cooled to 0 °C and DMAP was added (2.6 mg, 0.0212

mmol, 10 mol%), followed by dropwise addition of NaHMDS (0.233 mL of 1.0 M solution in THF, 0.233 mmol, 1.1 equiv). After completion of the addition, Boc_2O was added (0.0925 g, 0.424 mmol, 2.0 equiv). The solution was warmed to rt and allowed to stir for 60 minutes. The solution containing the protected sulfamate was concentrated under reduced pressure to a tan syrup. The material was redissolved in 2.1 mL of dry DMF and 0.0445 g NaI (0.297 mmol, 1.4 equiv) was added. The thick solution was warmed to 45 °C and stirred for 25 min prior to the cautious addition of NaH (0.0300 g of 60% wt suspension in mineral oil, 0.742 mmol, 3.5 equiv). The solution was then warmed to 60 °C and stirred for 5 h. The reaction mixture was cooled and cautiously quenched with 10 mL of brine. The mixture was extracted with diethyl ether (4 x 10 mL), dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residual HMDS was removed from the crude residue by flash chromatography (5% EtOAc in hexanes) to yield 0.0926 g of oil **3.70d** of sufficient purity for the Fleming-Tamao oxidation.

The crude pyrrolidine **3.70d** was dissolved in 1.1 ml of glacial acetic acid containing KBr (0.0218 g, 0.183 mmol, 1.2 equiv) and NaOAc (0.0387 g, 0.472 mmol, 3.1 equiv). Peroxyacetic acid (0.195 mL of 32% wt in acetic acid, 0.929 mmol, 6.1 equiv) was added dropwise with ice bath cooling to control the exotherm. After stirring for 5 min, a second portion of NaOAc was added (0.116 g, 1.42 mmol, 9.3 equiv), followed by a second portion of peroxyacetic acid (0.589 mL, 2.80 mmol, 18.4 equiv). The solution was stirred at rt for 2 h before dilution with 10 mL diethyl ether and 12 mL of water containing 1.62 g sodium thiosulfate pentahydrate. The phases were separated, and the aqueous phase extracted with diethyl ether (3 x 10 mL). The combined organic phases were washed with saturated aqueous $NaHCO_3$ before drying with $MgSO_4$. The crude residue was purified by column chromatography (4% to 20% EtOAc in hexanes) to yield **3.71d** as a white solid (0.0577 g, 0.118 mmol, 56% from sulfamate). (Note: This spectrum is

complicated by the presence of two rotamers in the product structure) ^{1}H NMR: (500.0 MHz, $CDCl_3$) δ 4.30-4.42 (2 s, 1H), 4.05-4.18 (m, 1H), 3.30-3.95 (m, 5H), 2.62 (br s, 0.29H), 1.80-2.10 (m, 0.71 H), 1.69-1.80 (m, 1H), 1.45-1.65 (m, 12H), 0.85-0.93 (2 s, 18H), 0.05-0.15 (3 s, 12H). ^{13}C NMR: (125.7 MHz, $CDCl_3$) δ 155.8, 155.3, 79.8, 79.3, 73.3, 72.9, 70.8, 70.7, 68.8, 68.8, 60.7, 60.5, 45.9, 45.4, 35.9, 35.2, 34.1, 33.3, 28.7, 28.5, 26.0, 25.7, 17.9, 17.8, -3.5, -4.0, -4.2, -4.4, -4.6, -4.6, -4.9, -5.2. HMRS (ESI) *m/z* calculated for $C_{24}H_{52}NO_5Si_2$ $[M + H]^+$ 490.3379, found 490.3378.

Compound 3.72d. A 10 mL round bottom flask equipped with a magnetic stir bar was charged with **3.71d** (55.0 mg, 0.112 mmol), sodium bicarbonate (18.8 mg, 0.224 mmol, 2.0 equiv), Bu_4NCl (1.5 mg, 0.0056 mmol, 5 mol%), and 0.56 mL 1:1 CH_3CN:H_2O. The mixture was stirred vigorously, and TEMPO (3.5 mg, 0.0224 mmol, 20 mol%) was added, followed by $PhI(OAc)_2$ (77.7 mg, 0.246 mmol, 2.20 equiv). After stirring under nitrogen for 36 hours, 0.25 mL dichloromethane was added with an additional 0.90 mg TEMPO (0.00576 mmol, 5 mol%) and 19.4 mg $PhI(OAc)_2$ (0.0615 mmol, 0.55 equiv). After an additional 24 hours the reaction was diluted with 4 mL CH_2Cl_2 and 4 mL of 0.2 M HCl. The phases were separated, and the aqueous phase extracted with CH_2Cl_2 (4 x 5 mL). The combined organic fractions were dried with $MgSO_4$ and concentrated to a crude oil. The oil was treated with 3.4 mL of 0.5 M HCl in methanol (prepared by reaction of TMS-Cl in methanol) and stirred for 1 hour. Concentration by rotary evaporation afforded a crude oil. Non-polar organics were removed by column chromatography (10% CH_3CN in CH_2Cl_2, then 10% MeOH in CH_3CN) yielding crude white solid **3.72d** that was purified by trituration with cold CH_2Cl_2 (19.6 mg, 0.104 mmol, 92%). ^{1}H NMR: (500.0 MHz, D_2O) δ 4.40 (dt, *J* = 6.0, 4.6 Hz, 1H), 4.26 (ddd, *J* = 8.9, 7.8, 3.8 Hz, 1H), 3.75 (s, 3H), 3.42-3.54

(m, 3H), 2.86 (dd, *J* = 16.2, 3.8 Hz, 1H), 2.67 (dd, *J* = 16.2, 8.9 Hz, 1H), 2.32 (dtd, *J* = 14.2, 8.2, 6.0 Hz, 1H), 2.06 (dddd, *J* = 14.2, 8.0, 5.2, 4.6 Hz, 1H). ^{13}C NMR: (125.7 MHz, D_2O) δ 173.0, 71.3, 69.1, 65.1, 52.5, 43.7, 39.1, 32.1. HMRS (ESI) *m/z* calculated for $C_8H_{16}NO_4$ $[M + H]^+$ 190.1074, found 190.1080.

3.5.17. References for experimental section

1. Armarego, W.L.F.; Chai, C.L.L. *Purification of Laboratory Chemicals* 6th ed., Elsevier: Burlington, MA, 2009.
2. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
3. Henderson, M. A.; Heathcock, C. H. *J. Org. Chem.* **1988**, *53*, 4736.
4. Sherry, B. D.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 15978.
5. Espino, C. G.; Wehn, P. M.; Chow, J.; Du Bois, J. *J. Am. Chem. Soc.* **2001**, *123*, 6935.
6. Fiori, K. W.; Espino, C. G.; Brodsky, B. H.; Du Bois, J. *Tetrahedron*, **2009**, *65*, 3042.
7. Boralsky, L. A.; Marston, D.; Grigg, R. D.; Hershberger, J. C.; Schomaker, J. M. *Org. Lett.* **2011**, *13*, 1924.
8. Huard, K.; Lebel, H. *Org. Synth.* **2009**, *86*, 59.
9. Gaussian 09, Revision C.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, T. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J.

Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, and D. J. Fox, Gaussian, Inc., Wallingford CT, 2010.

10. Murray, R. W.; Singh, M. *Org. Synth.* **1997**, *74*, 91; **1998**, Coll. Vol. *9*, 288.

11. Ferrer, M.; Gibert, M.; Sanchez-Baeza, F.; Messeguer, A. *Tetrahedron Letters* **1996**, *20*, 3585.

12. Gibert, M.; Ferrer, M.; Sanchez-Baeza, F.; Messeguer. A. *Tetrahedron* **1997**, *53*, 8643.

13. Narasimhan, S.; Belakumar, R. *Aldrichimica Acta* **1998**, *31*, 19.

14. In a previous publication from our group (see ref. 1 in the text), it was demonstrated that this homoallenic sulfamate could be generated in >98% *ee* from the same enantioenriched starting material and by the same sequence of transformations employed here. However, the HPLC conditions used previously were found to no longer separate the allene enantiomers, likely due to slight degradation of the HPLC since this previous publication.

Chapter 4

Progress Towards a Flexible Entry to Aminocyclopentitol Scaffolds *via* Allene Amination

Portions of the work described in this chapter were carried out in collaboration with Nels C. Gerstner, Jared W. Rigoli, and R. David Grigg.

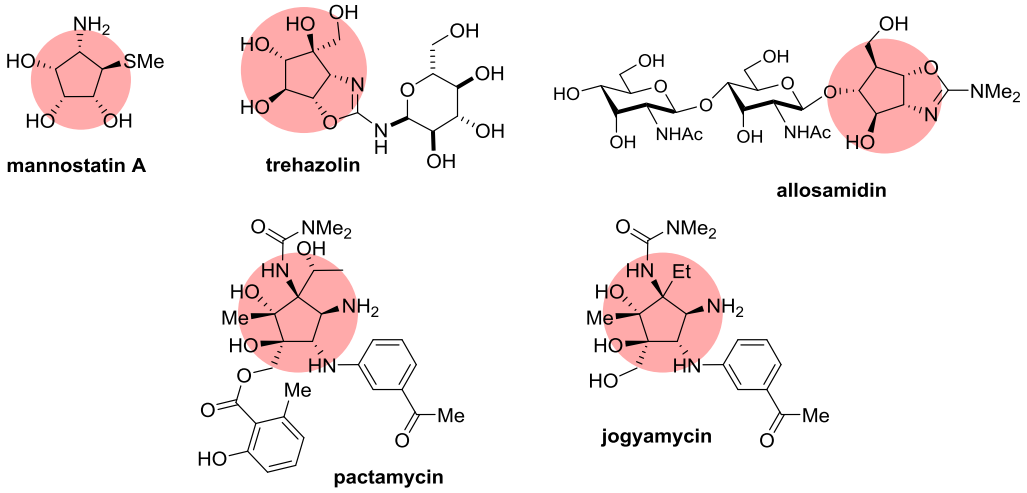
4.1 Introduction

Chapters 2 and 3 of this work describe the development of allene functionalization methods for the synthesis of amine stereotriads, with control over both the functionality installed and its relative stereochemistry.[1] We felt a natural extension of this work would be its application to the diversity-oriented synthesis of medicinally relevant complex amines. Ideally, this work would provide access to a target compound as well as new analogues with potentially interesting properties. In addition to this goal, the challenge of accessing a specific target would likely spur the development of new allene amination strategies for accessing challenging functional and stereochemical motifs.

In choosing a target, we were intrigued by the aminocyclopentitol class of natural products, a sample of which are shown below in Figure 4.1. These compounds are sugar-derived secondary metabolites that display a variety of glycosidase-inhibitory and ribosomal-inhibitory activities. For example, mannostatin A, trehazolin, and allosamidin are all potent glycosidase inhibitors, targeting mannosidase, α,α-trehalase, and chitinase, respectively.[2] While these compounds have been useful targets for both medicinal and agricultural purposes,[3] a variety of methods for their synthesis have already been reported, starting either from sugar precursors[4c-g] or by *de novo* synthesis using specifically tailored methodologies.[4a,b] In contrast, pactamycin and its recently discovered analogue jogyamycin[5] have received significantly less synthetic attention,[6] due in large part to their considerable complexity. Indeed, despite the discovery of pactamycin over 50 years ago,[7] only in the past five years has this compound yielded to chemical synthesis. The biological profile of pactamycin is quite notable, as it displays potent antitumor, antimicrobial, antiviral, and antiprotozoal properties in addition to acute cytotoxicity in both eukaryotic and prokaryotic cells.[8] This broad-spectrum behavior is known to arise from binding of pactamycin to universally

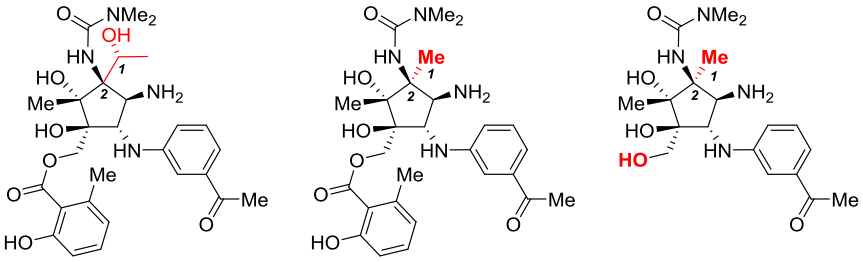
conserved rRNA residues in a binding pocket of the smaller ribosomal subunit, where it inhibits translocation.[9]

Figure 4.1. Important aminocyclopentitol-containing compounds.



While traditionally pactamycin and its analogues have been considered too cytotoxic for therapeutic use, recent efforts in the biosynthesis of novel pactamycin analogues[10] have uncovered analogues with improved specificities towards protozoal species implicated in malaria. Specifically, modification of the exocyclic hydroxyethyl substituent of pactamycin (see TM-025 and TM-026, Table 4.1) have resulted in compounds that show a 10-30 fold decrease in cytotoxicity and antibacterial properties, while still maintaining high inhibitory levels against the parasite *P. falciparum*.[11] As of yet, there is no clear understanding of the impact that these structural changes have on the ribosomal binding and resulting differential activities of these compounds. Consequently, synthetic routes towards pactamycin derivatives with an emphasis on building structure-activity relationships at these and other sites within the molecule would be valuable for the development of potential therapeutics and a better understanding of pactamycin's mode of activity across different kingdoms.

Table 4.1. Pactamycin analogues with increased protozoal selectivity.



pactamycin TM-025 TM-026

Compound	*(Antimalarial)* *P. falciparum* D6 IC_{50} (nM)	*(Antibacterial)* *S. aureus* MIC (μM)	*(Cytotoxicity)* HCT116 IC_{50} (μM)
Pactamycin	< 2.5	~10	0.07
TM-025 / TM-026	25-30	> 1000	1-3

HCT116 = human colorectal cancer cells, IC_{50} = half maximal inhibitory concentration
MIC = minimum inhibitory concentration

In this vein, we decided it would be valuable to devise an allene amination-based approach to pactamycin-based aminocyclopentitols that would tolerate variation at multiple sites, including the C1 and C2 centers highlighted in Table 4.1. As jogyamycin has not previously been synthesized, and it also lacks the exocyclic hydroxyl group seen in TM-025 and TM-026 (Table 4.1), it was chosen as the target around which to devise a general synthetic strategy.

4.2 Synthetic strategy

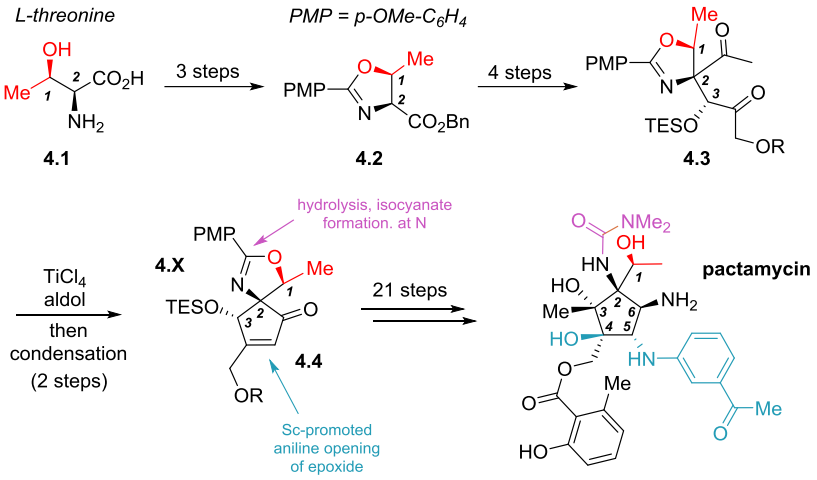
To begin, a brief summary of the two previous syntheses of pactamycin will be presented, to highlight the points at which analogue synthesis has been carried out. It should be noted that the two syntheses reported below would not be readily tailored to the synthesis of jogyamycin, as their starting materials both contain the exocyclic hydroxyl group that is absent in jogyamycin. Late stage de-oxygenation of pactamycin derivatives has been attempted to access jogyamycin, and could not be achieved, making novel routes to jogyamycin necessary.[12a]

4.2.1. Previous routes to jogyamycin

The first total synthesis of pactamycin was accomplished by the group of Hanessian in 2011 (Scheme 4.1).[6g] Starting from L-threonine, a sequence of functional group interconversions

and $SOCl_2$-mediated rearrangement yielded oxazoline **4.2**. This intermediate was elaborated into the 1,4-diketone **4.3** which underwent a Ti-mediated intramolecular aldol addition to arrive at the spirocyclopentenone **4.4**. Twenty-one further transformations were required to access pactamycin, highlighting the challenges in carrying out early-stage structural modifications by this route. While late-stage modification of the C2-urea by isocyanate addition and the C5 aniline by an epoxide ring-opening were possible,[12b] the C2-hydroxyethyl group (highlighted in red) could not be modified as it was derived from the threonine starting material **4.1**.

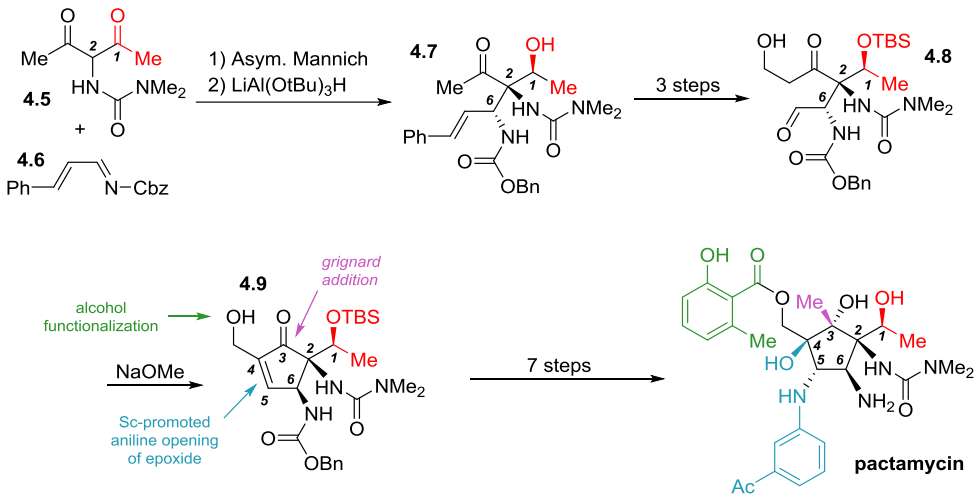
Scheme 4.1. Hanessian's route to pactamycin.



A significantly shorter approach to pactamycin was reported in 2013 by the group of Johnson (Scheme 4.2).[6b] It utilized an asymmetric Mannich reaction and desymmetrizing β-diketone monoreduction to set the three stereocenters of **4.7** in high *dr* and *ee*. Intramolecular aldol condensation was again utilized to form the five-membered ring, with only seven subsequent steps (13 total) needed to obtain pactamycin. In analogy to Hanessian's synthesis, a $Sc(OTf)_3$-mediated epoxide opening could be utilized to install a variety of aniline derivatives. Additionally, late-stage organometallic addition to form the C3-quat center and alcohol functionalization could

be used to synthesize analogues, but the C2-hydroxyethyl group could not be modified as it arose from the starting acetylacetone derivative **4.5**.[12a]

Scheme 4.2. Johnson's route to pactamycin.



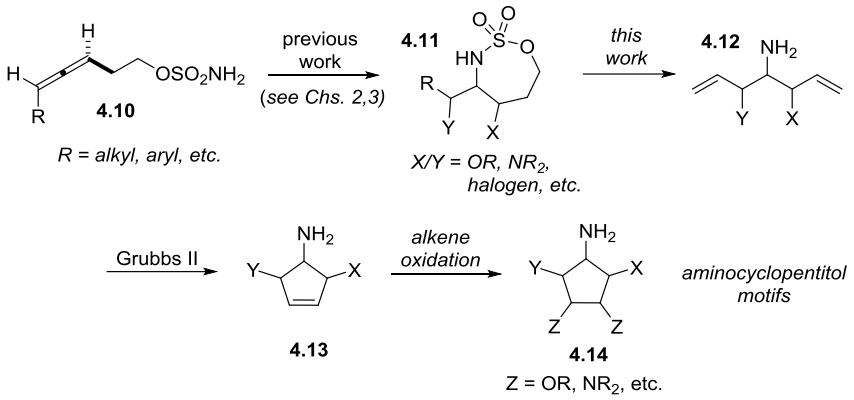
4.2.2. Allene amination route to jogyamycin

While the above routes allowed for the synthesis of pactamycin analogues at select positions on the cyclopentane ring, there is still a need for syntheses that permit greater diversification. With this goal in mind, we devised a route to jogyamycin-related aminocyclitols based on our allene amination methodology.

A primary goal in developing a new approach to aminocyclitols was to couple the diversity of products available *via* allene amination with an efficient process for converting them to cyclopentanes. A simplified version of our general strategy is presented in Scheme 4.3. Intramolecular aziridination of allenes of the form **4.10** would provide modular access to aminated stereotriads **4.11**, in keeping with previous work.[1] If these heterocycles could be rapidly converted to stereotriad-bearing dienes such as **4.12**, ring-closing metathesis would provide cyclopentenes **4.3**, from which subsequent alkene functionalization would deliver fully substituted aminocyclopentitols of the form **4.14**. With allene functionalization setting three substituents and

stereocenters of the ring in a modular manner, and the remaining two carbons of the ring being set by flexible alkene oxidation methods, we felt this would provide access to diverse libraries of aminocyclopentitols.

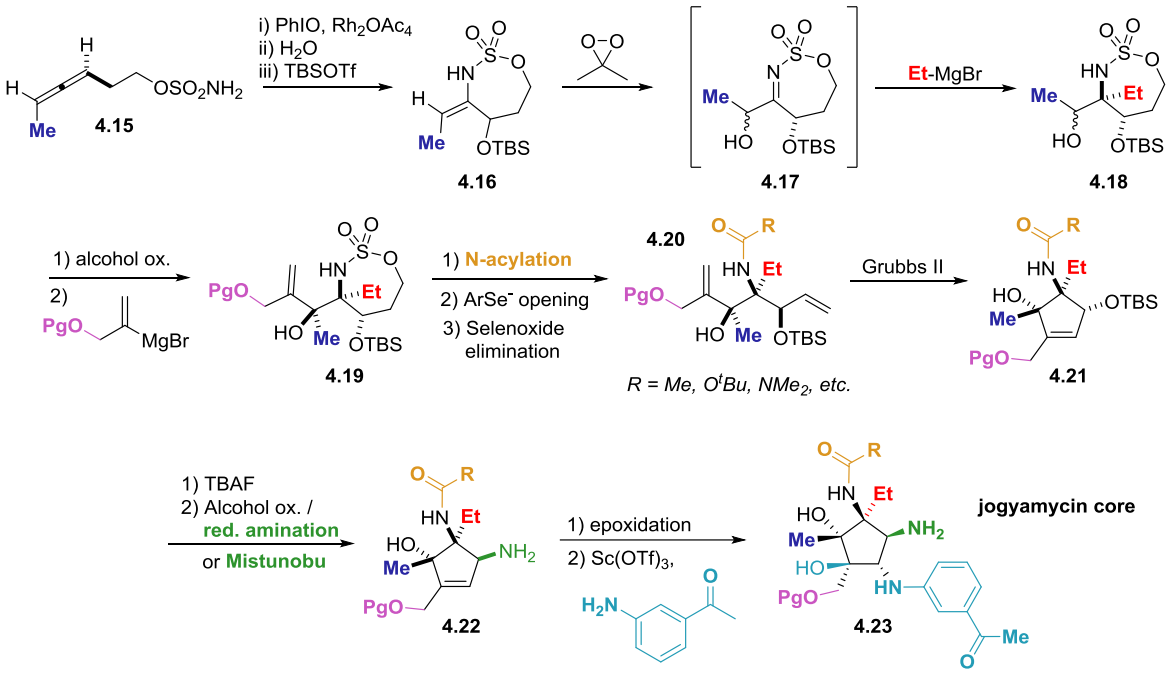
Scheme 4.3. General strategy for aminocyclopentitol synthesis *via* allene amination.



Scheme 4.4 below demonstrates the application of this strategy towards the complex aminocyclopentitol jogyamycin. Functional groups highlighted in color could be potentially diversified using this route. Starting from the simple methyl-substituted allene **4.15**, our 2-amino-1,3-diol methodology (recall Chapter 3) would provide access to stereotriad **4.18**, with the first quaternary center set by the addition of a Grignard to imine **4.17**. This Grignard addition could be used to install a variety of groups corresponding to the hydroxyethyl chain of pactamycin that cannot be modified by the previous pactamycin syntheses. From **4.18**, the next quaternary center would be set by alcohol oxidation and organometallic addition. This would also install one of the alkene units needed for ring-closing metathesis. Removal of the sulfamate group of **4.19** would be achieved by N-acylation and nucleophilic opening by a selenide, chosen for its ability to undergo mild selenoxide elimination[13] to provide diene **4.20**. Ring-closing metathesis would yield cyclopentene **4.21**. At this point, the undesired –OTBS group could be exchanged for the 1° amine of jogyamycin by deprotection/oxidation/reductive amination to access **4.22**, or it could be kept as a novel oxygenated analogue. Epoxidation and aniline ring-opening of the remaining alkene (in

analogy to the syntheses of Hanessian and Johnson)[6b,g] would provide the jogyamycin core. The following work details our efforts to achieve this synthesis.

Scheme 4.4. Proposed route to jogyamycin *via* allene amination.

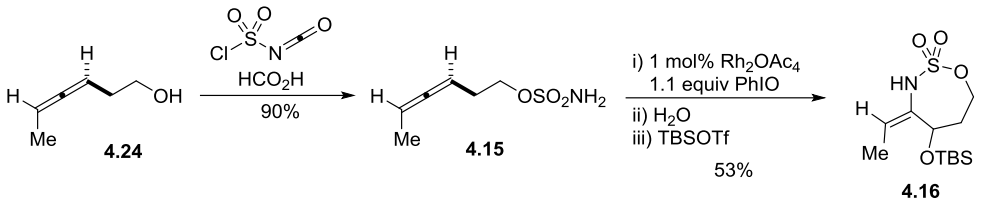


4.3. Results and Discussion

4.3.1. Approach using homoallenic sulfamates

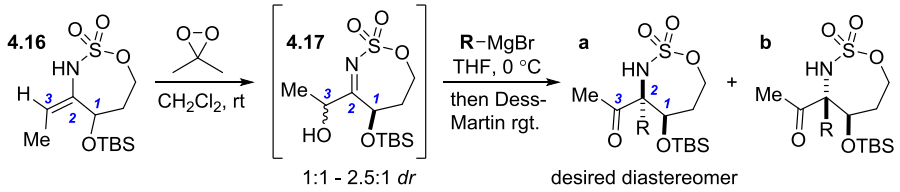
The starting homoallenic sulfamate **4.15** was prepared in one step from the commercially available alcohol **4.24**. The sulfamate then underwent intramolecular aziridination, water ring-opening, and TBS protection to afford enesulfamate **4.16** in analogy to our previous work on the synthesis of 2-amino-1,3-diols (Scheme 4.5).[1b] This process could be carried efficiently out on a multi-gram scale to access large quantities of this early intermediate.

Scheme 4.5. Aziridination/ring-opening of allene **4.24**.



The DMDO oxidation of **4.16** was then investigated, in order to install the C3-OH and the C2 quaternary center. Although DMDO reacted with poor facial selectivity to give imine **4.17** in ~2:1 *dr*, the *dr* of this imine was largely irrelevant as the alcohol was oxidized in a subsequent step. A variety of Grignard reagents were reacted with imine **4.17** in order to install the desired quaternary center (Table 4.2). The desired ethyl group could not be installed using ethylmagnesium bromide (entry 1), due to competing hydride reduction by this reagent.[14] Diastereoselective addition was achieved using ethynylmagnesium bromide, provided that the Grignard was pre-stirred at 0 °C prior to addition (compare entries 3,4). Magnesium salts were observed to precipitate during this pre-stirring, indicating that the Schlenk equilibrium of this particular Grignard was likely being biased in a way favorable to high diastereoselectivity.[15]

Table 4.2. Oxidation of enesulfamate and formation of first quaternary center.

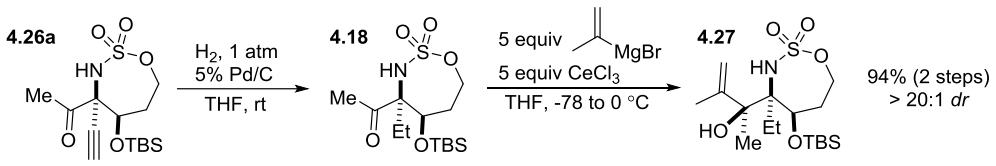


entry	R =	yield	*a:b*[a]	product
1	Et	0%[b]	N/A	**4.18**
2	$CH{=}CH_2$	45%	2:1	**4.25**
3	C≡CH	48%	2.3:1	**4.26**
4[c]	C≡CH	45%	>10:1	**4.26**

[a] Based on 1H NMR analysis of crude product.
[b] Hydride reduction of imine observed as sole product.
[c] Grignard pre-stirred at 0 °C for 30 minutes prior to addition.

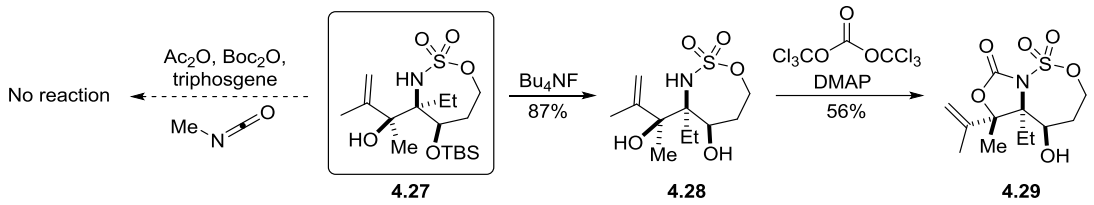
The terminal alkyne of **4.26a** was hydrogenated to access the desired ethyl group present in jogyamycin, then the addition of a Grignard reagent to aminoketone **4.18** was carried out (Scheme 4.6). The use of anhydrous $CeCl_3$ to form an organocerium nucleophile proved necessary to accomplishing the addition in high yield; in the absence of $CeCl_3$ conversions were generally below 50%, likely due to competing enolization of the hindered ketone.[16] The diastereoselectivity of this substrate-controlled addition was very high, giving **4.27** in greater than 20:1 *dr* with the relative stereochemistry determined by X-ray analysis. This product lacked the desired terminal allylic alcohol present in jogyamycin, but it was decided to move forward with **4.27** with the understanding that the alcohol could be potentially installed at a later stage by allylic C-H oxidation.[17]

Scheme 4.6. Formation of key O/N/O stereotriad by organocerium addition.



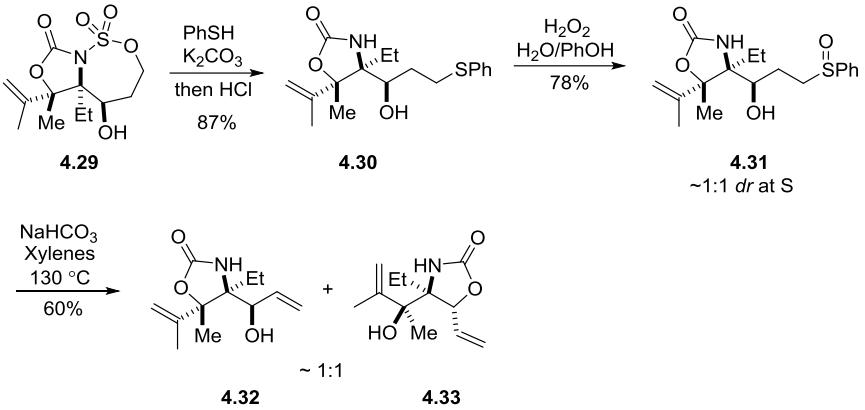
From stereotriad **4.27**, removal of the sulfamate group was necessary to install the second alkene for ring-closing metathesis. This required N-acylation of the sulfamate in order to activate it for nucleophilic displacement. Unfortunately, a variety of acylating agents proved incapable of functionalizing the highly hindered sulfamoyl nitrogen of **4.27** (Scheme 4.7, left). The steric environment around the nitrogen was mitigated by O-TBS deprotection, delivering aminodiol **4.28** which yielded to reaction with triphosgene to afford oxazolidinone **4.29** (Scheme 4.7, right). Oxazolidinone formation with the more hindered 3° alcohol was surprising and appeared to result from rearrangement during silica gel chromatography.

Scheme 4.7. Attempts to acylate compound **4.27**.



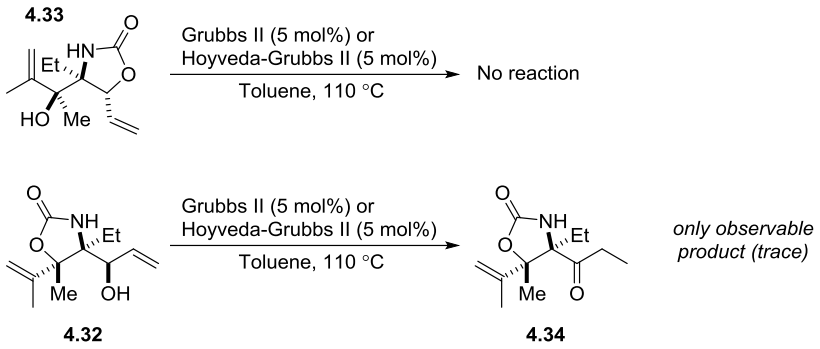
With sulfamate acylation achieved, the terminal diene was installed by the process shown in Scheme 4.8. Ring-opening of **4.29** was accomplished with thiophenol, as other selenium-based reagents were observed to decompose the sensitive oxazolidinone.[18] The resulting sulfide was eliminated *via* a two-step sulfoxide elimination to afford **4.32** and the thermal isomerization product **4.33**.

Scheme 4.8. Accessing a stereotriad-containing diene.



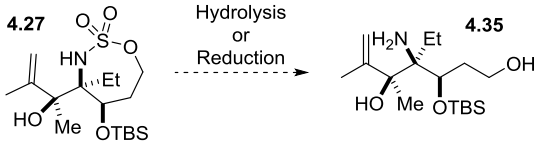
Unfortunately, progress towards the jogyamycin core by this route halted at dienes **4.32** and **4.33**. Neither substrate underwent the desired ring-closing metathesis (Scheme 4.9), likely due to conformational constraints imposed by the oxazolidinone ring. Attempts to hydrolyze the oxazolidinone were unsuccessful, and N-functionalization of either oxazolidinone (to activate it for hydrolysis) gave mixtures of products owing to competing O-substitution. We concluded that oxazolidinone formation was an undesired route by which to open the sulfamate ring.

Scheme 4.9. Attempted RCM of dienes **4.32** and **4.33**.



Returning to the key O/N/O stereotriad **4.27**, direct sulfamate cleavage was attempted under either hydrolytic or reductive conditions, hoping to extrude the sulfonyl group and reveal compound **4.35** that could be rapidly converted to a diene (Table 4.3). Unfortunately, the sulfamate proved too robust; the only commonly observed product was the TBS-cleaved aminodiol **4.28**. Based on the lack of success in functionalizing the sulfamoyl N-H as anything other than an oxazolidinone, and the inability to cleave the sulfamate by any other chemical method, we decided to investigate alternative nitrene precursors to sulfamates for this synthetic route.

Table 4.3. Unsuccessful attempts to open sulfamate **4.27** by hydrolysis or reduction.

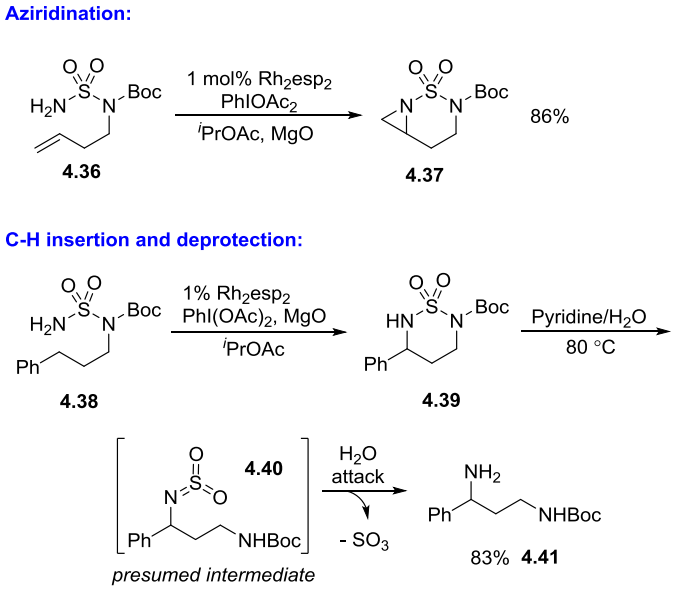


entry	Conditions	Outcome
1	H_2O, 100 °C, μw, 30 min	No rxn (SM recovered)
2	MeCN/H_2O, 100 C, 8 h	No rxn (SM recovered)
3	30% NH_4OH, 100 °C, 14 h	Trace SM recovered, no desired pdt
4	1N HCl/EtOH, 100 °C, 13 h	Unknown pdt, sulfamate still present
5	8N KOH, EtOH, 100 °C, 16 h	TBS loss only
6	$LiAlH_4$, THF, reflux, overnight	TBS loss only
7	RedAl, $PhCH_3$, 100 °C, 2.5 h	TBS loss only
8	RedAl, $PhCH_3$, 100 °C, overnight	Decomp
9	$AlH_3 \cdot NMe_2Et$, $PhCH_3$, 100 °C, overnght	TBS loss only

4.3.2. Approach using homoallenic N-Boc sulfamides

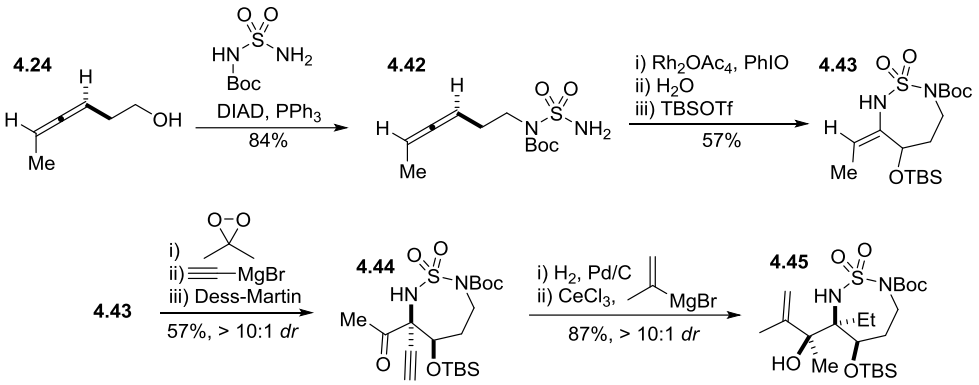
As stated above, a key challenge to converting stereotriad **4.27** to a diene motif was the difficulty in either functionalizing or cleaving the highly robust sulfamate group. An alternative strategy would be to use a more labile sulfamate analogue. In this context, the use of N-Boc sulfamides appeared to be an attractive route. While less frequently used than the corresponding sulfamates, N-Boc sulfamides have demonstrated similar reactivity parameters in intramolecular aziridination and C-H insertion reactions (Scheme 4.10).[19] Notably, the heterocyclic products resulting from these processes can be readily "deprotected" due to the pre-installation of the Boc group. Treatment with mild base and heat cleaves the sulfonyl group from compounds such as **4.39** likely *via* the electrophilic intermediate **4.30**, thus leaving a differentially protected diamine compound **4.41**. As this nitrene precursor had not been previously investigated in our allene amination chemistry, we were curious to see if this group would prove superior to sulfamates for this project.

Scheme 4.10. Previously reported reactivity of N-Boc sulfamides.



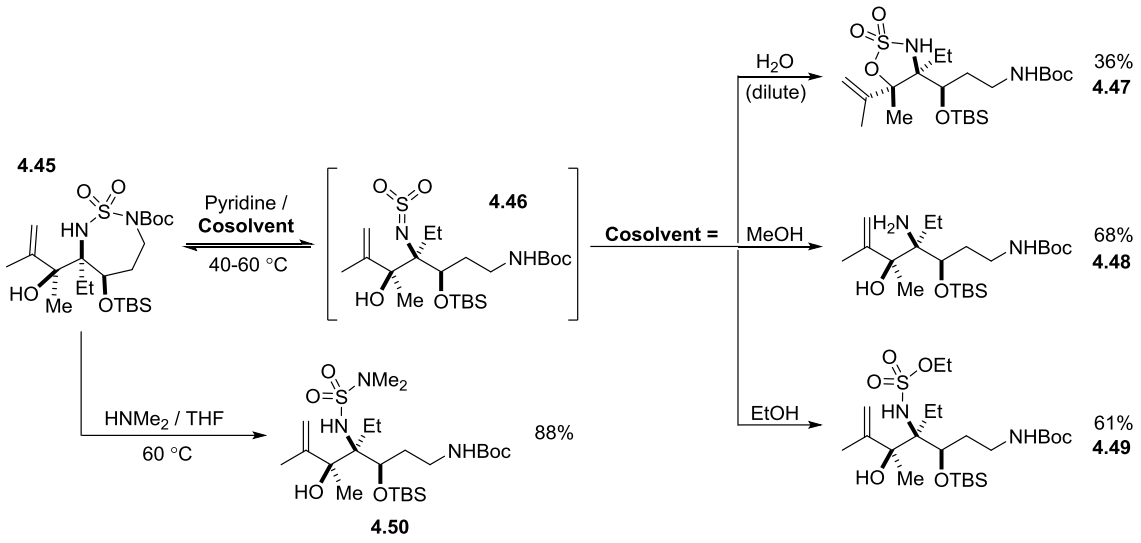
We were pleased to find that, starting from the same homoallenic alcohol **4.24**, the N-Boc sulfamide group could be installed and carried through an identical sequence of transformations to arrive at the O/N/O triad **4.45** (Scheme 4.11). While the relative stereochemistry of **4.45** was not determined empirically and only assumed by analogy to the sulfamoyl analogue **4.27**, the high levels of diastereoselectivity, similar to those observed for the synthesis **4.27**, suggested that the same stereochemical outcome was obtained.

Scheme 4.11. Stereotriad synthesis using homoallenic N-Boc sulfamides.



The ring-opening of **4.45** was then investigated, and it was observed to proceed in a predictable fashion (Scheme 4.12). Under mildly basic conditions, deprotonation of the sulfamide N-H led to formation of the putative intermediate **4.46**. In 10:1 pyridine/water, the water was unable to intercept this electrophilic species, and thus **4.47** was formed by undesired intramolecular capture by the 3° alcohol. Ethanol and dimethylamine, if present in high enough concentration, were able to outcompete the 3° alcohol and form the linear products **4.49** and **4.50**, respectively. Methanol was also a competent trapping nucleophile, but the resulting –OMe sulfamate decomposed upon silica gel chromatography to reveal the unprotected amine **4.48**. This result was fortuitous, as it would potentially allow for the installation of a variety of different protecting groups on this amine, including the N,N-dimethyl urea present in jogyamycin.

Scheme 4.12. Ring-opening of N-Boc sulfamide stereotriads.

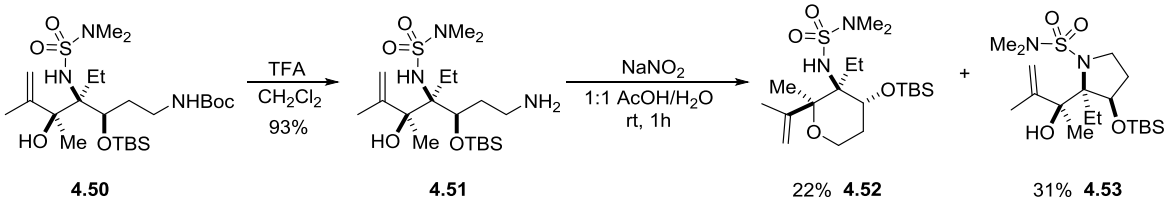


Having shown that the stereotriad **4.45** could be readily "unraveled" under mild conditions, the next step was the challenging task of elimination of the Boc-protected amine to form the terminal alkene necessary for RCM. We chose to investigate two methods for this deamination: diazonium elimination and Cope elimination. A Hofmann elimination was not attempted, as the synthesis of terminal, unconjugated alkenes by this method is uncommon and often requires temperatures in excess of 150 °C.[20] In addition to the risk of decomposition or alkene isomerization at these temperatures, intramolecular S_N2 displacement of the ammonium leaving group is a known competing reaction to Hofmann eliminations.[20d]

An attempted diazonium elimination is shown in Scheme 4.13.[21] The Boc group of ring-opened product **4.50** was cleaved using TFA, and the resulting 1° amine was treated with $NaNO_2$ under acidic conditions. Not surprisingly, the only isolable products were the result of intramolecular S_N2 displacement of the reactive alkyl diazonium. Although competing S_N2 processes were anticipated, there are several reports of 1°, alkyl diazoniums undergoing partial E2 elimination (even in the presence of nearby nucleophilic groups) that led us attempt this

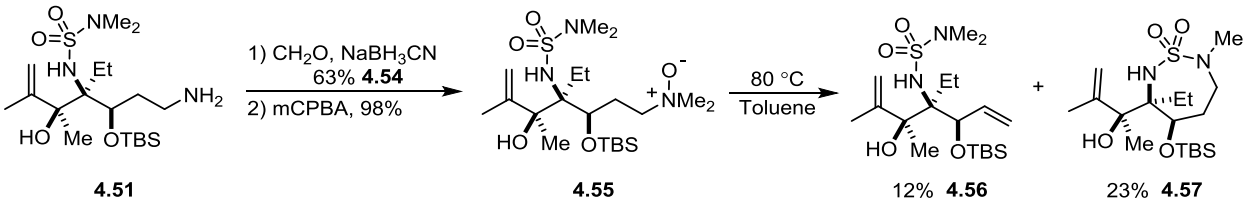
transformation.[21d,e] It is possible that the highly branched nature of **4.51** favored intramolecular S_N2 pathways *via* a Thorpe-Ingold effect.[22]

Scheme 4.13. Attempted diazonium elimination.

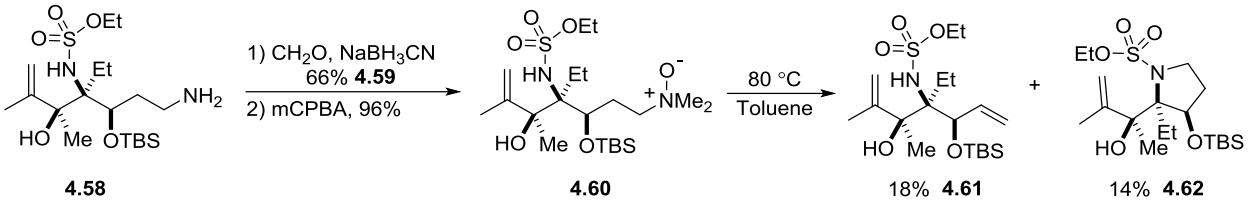


With the failure of the diazonium elimination, a Cope elimination was attempted to access the desired RCM precursor (Scheme 4.14).[23] Reductive amination of **4.51** with formaldehyde, followed by treatment with *m*CPBA, led to the desired N-oxide **4.55** with no observed epoxidation of the disubstituted alkene. Thermal heating of **4.55** gave partial formation of the desired diene, but the major product **4.57**resulted from intramolecular S_N2 displacement of the amine N-oxide by the sulfamide protecting group. The Cope elimination was attempted again with the ethanol ring-opened product **4.60** (Scheme 4.15), in the hope that this protecting group would be less nucleophilic, but unfortunately a significant amount of S_N2 product **4.62** still formed. This poor selectivity for elimination, in combination with the poor mass balances observed for these reactions, suggests that a different deamination protocol must be identified. Alternatively, a protecting group strategy that shuts down the undesired S_N2 pathways would also address this problem.

Scheme 4.14. Synthesis and Cope elimination of compound **4.55**.

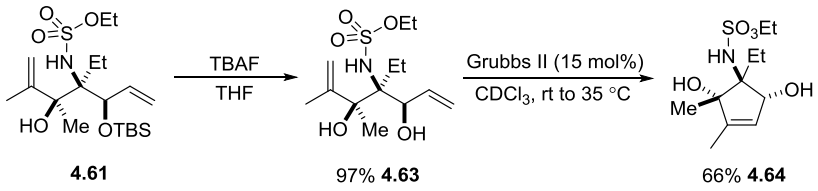


Scheme 4.15. Synthesis and Cope elimination of compound **4.61**.



In order to validate the ring-closing metathesis step as a route for converting these stereotriads to aminocyclitols, diene **4.61** was treated with a variety of Ru-based catalysts. No reaction was observed, even with stoichiometric catalyst loadings. Fortunately, removal of the TBS group restored the desired reactivity, with **4.63** undergoing RCM to afford **4.64** in moderate yield (Scheme 4.16). Current work is focused on carrying this material forward to jogyamycin, while also investigating methods for obtaining the key diene in higher yield.

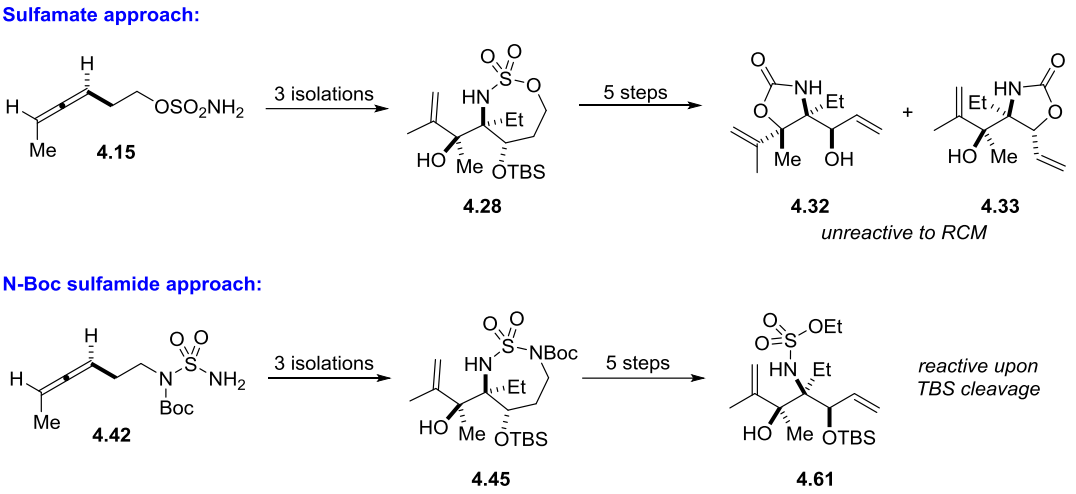
Scheme 4.16. Successful RCM of diene **4.63**.



4.4. Conclusion

The two approaches taken towards jogyamycin are summarized below in Scheme 4.17. An initial approach using homoallenic sulfamate **4.15** delivered, after eight isolations, two isomeric dienes **4.32** and **4.33** that proved unreactive to RCM, likely due to conformational constraints arising from the use of an oxazolidinone protecting group. Using a more readily cleaved N-Boc sulfamide substrate **4.42**, diene **4.61** was accessed in an equal number of steps (due to the necessity of carrying out a step-laborious Cope elimination) that could be cyclized to an aminocyclopentitol motif. Currently, the low yield of the Cope elimination (< 20% of the desired diene) requires optimization if this process is to be applied to a scalable synthesis of jogyamycin.

Scheme 4.17. Summary of the two routes taken toward jogyamycin.



Despite these setbacks, a number of new accomplishments have been made during this work. It was demonstrated that our group's allene amination methodology could be utilized to access stereotriads bearing multiple, contiguous quaternary centers, a previously unaccomplished feat. Similarly, it was demonstrated that N-Boc sulfamides behave analogously to sulfamates in this methodology. The ability to convert complex sulfamide-derived stereotriads of the form **4.45** to linear 1,4-diamino-3,5-diols such as **4.47-50** in a single step (Scheme 4.12) is an impressive feat that could potentially have applications towards the synthesis of other complex targets.

4.5. References

1. (a) Adams, C. S.; Boralsky, L. A.; Guzei, I. A.; Schomaker, J. M. *J. Am. Chem. Soc.* **2012**, *134*, 10807. (b) Adams, C. S.; Grigg, R. D.; Schomaker, J. M. *Chem. Sci.* **2014**, *5*, 3046.
2. For an early review of mannostatin, allosamidin, and trehazolin syntheses, as well as discussion of the biological properties of key analogues, see: Berecibar, A.; Grandjean, C.; Siriwardena, A. *Chem. Rev.* **1999**, *99*, 779.
3. For a more recent review on synthetic work towards aminocyclopentitols, as well as a discussion of their potential use, see: Delgado, A. *Eur. J. Org. Chem.* **2008**, 3893.

4. A selection of previous syntheses of mannostatin, allosamidin, and trehazolin (or related derivatives): (a) Trost, B. M.; Van Vranken, D. L. *J. Am. Chem. Soc.* **1993**, *115*, 444. (b) Ledford, B. E.; Carreira, E. M. *J. Am. Chem. Soc.* **1995**, *117*, 11811. (c) Ogawa, S.; Yuming, Y. *J. Chem. Soc., Chem. Commun.* **1991**, 890. (d) Dickson, L. G.; Leroy, E.; Reymond, J.-L. *Org Biomol. Chem.* **2004**, *2*, 1217. (e) Knapp, S.; Dhar, T. G. M. *J. Org. Chem.* **1991**, *56*, 4096. (f) Kassab, D. J.; Ganem, B. *J. Org. Chem.* **1999**, *64*, 1782. (g) Donohoe, T. J.; Rosa, C. P. *Org. Lett.* **2007**, *9*, 5509.

5. Iwatsuki, M.; Nishihara-Tsukashima, A.; Ishiyama, A.; Namatame, M.; Watanabe, Y.; Handasah, S.; Pranamuda, H.; Marwoto, B.; Matsumoto, A.; Takahashi, Y.; Otoguro, K.; Ōmura, S. *J. Antibiot.* **2012**, *65*, 169.

6. Previous total and partial syntheses of pactamycin: (a) Sharpe, R. J.; Malinowski, J. T.; Johnson, J. S. *J. Am. Chem. Soc.* **2013**, *135*, 17990-17998. (b) Malinowski, J. T.; Sharpe, R. J.; Johnson, J. S. *Science* **2013**, *340*, 180-182. (c) Malinowski, J. T.; McCarver, S. J.; Johnson, J. S. *Org. Lett.* **2012**, *14*, 2878-2881. (c) Boyce, G. R.; Liu, S.; Johnson, J. S. *Org. Lett.* **2012**, *14*, 652-655. (d) Haussener, T. J.; Looper, R. E. *Org. Lett.* **2012**, *14*, 3632-3635. (e) Matsumoto, N.; Tsujimoto, T.; Nakazaki, A.; Isobe, M.; Nishikawa, T. *RSC Adv.* **2012**, *2*, 9448-9462. (f) Hanessian, S.; Vakiti, R. R.; Dorich, S.; Banerjee, S.; Deschênes-Simard, B. *J. Org. Chem.* **2012**, *77*, 9458-9472. (g) Hanessian, S.; Vakiti, R. R.; Dorich, S.; Banerjee, S.; Lecomte, F.; DelValle, J. R.; Zhang, J.; Deschênes-Simard, B. *Angew. Chem. Int. Ed.* **2011**, *50*, 3497-3500.

7. White, F. R. *Cancer Chemoth. Rep.* **1962**, 75.

8. Otoguro, K.; Iwatsuki, M.; Ishiyama, A.; Namatame, M.; Nishihara-Tukashima, A.; Shibihara, S.; Kondo, S.; Yamada, H.; Ōmura, S. *J. Antibiot.* **2010**, *63*, 381.

9. Work detailing the binding of pactamycin to eukaryotic and prokaryotic ribosomes: (a) Dinos, G.; Wilson, D. N.; Teraoka, Y.; Szaflarski, W.; Fucini, P.; Kalplaxis, D.; Nierhaus, K. H. *Mol. Cell* **2004**, *13*, 113-124. (b) Garreau de Loubresse, N.; Prokhorova, I.; Holtkamp, W.; Rodnina, M.; Yusupova, G.; Yusupov, M. *Nature* **2014**,_513, 517. (c) Broderson, D. E.; Clemons, W. M.; Carter, A. P.; Morgan-Warren, R. J.; Wimberly, B. T.; Ramakrishnan, V. *Cell* **2000**, *103*, 1143. (d) Carter, A. P.; Clemons, W. M.; Broderson, D. E.; Morgan-Warren, R. J.; Wimberly, B. T.; Ramakrishnan, V. *Nature* **2000**, *407*, 340.

10. (a) Kudo, F.; Kasama, Y.; Hirayama, T.; Eguchi, T. *J. Antibiot.* **2007**, *60*, 492. (b) Ito, T.; Roongsawang, N.; Shirasaki, N.; Lu, W.; Flatt, P. M.; Kasanah, N.; Miranda, C.; Mahmud, T. *ChemBioChem* **2009**, *10*, 2253. (c) Mahmud, T. *Curr. Opin. Chem. Biol.* **2009**, *13*, 161. (d) Mahmud, T.; Flatt, P. M.; Wu, X. *J. Nat. Prod.* **2007**, 1384.

11. Lu, W.; Roongsawang, N.; Mahmud, T. *Chem. Biol.* **2011**, *18*, 425.

12. Biological studies on synthetically derived pactamycin analogues: (a) Sharpe, R. J.; Malinowski, J. T.; Sorana, F.; Luft, J. C.; Bowerman, C. J.; DeSimone, J. M.; Johnson, J. S. *Bioorg. Med. Chem.* **2015**, *23*, 1849-1857. (b) Hanessian, S.; Vakiti, R. R.; Chattopadhyay, A. K.; Dorich, S; Lavallée, C. *Bioorg. Med. Chem.* **2013**, *21*, 1775-1786.

13. Reich, H. J.; Wollowitz, S. *Preparation of α,β-Unsaturated Carbonyl Compounds and Nitriles by Selenoxide Elimination*. Organic Reactions. **2004**, 44:1:1–296.

14. Krasovskiy, A.; Kopp, F.; Knochel, P. *Angew. Chem. Int. Ed.* **2006**, *45*, 497.

15. (a) Wakefield, B. J. *Grignard Reagents — New Developments*, H. G. Richey (ed), Wiley, Chichester, 2000, xvi + 418pp. (b) Cannon, K. C.; Krow, G. R. The Composition of Grignard Reagents in Solution: The Schlenk Equilibrium and its Effect on Reactivity. In

Handbook of Grignard Reagents; Silverman, G. S.; Rakita, P. E., Eds.; Marcel Dekker: New York, 1996.

16. A requirement for $CeCl_3$ was also observed in a related transformation carried out by the Johnson group towards pactamycin (see ref. 6c).

17. Examples of allylic C-H oxidation methods for acyclic alkenes: (a) Umbreit, M. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1977**, *99*, 5526. (b) Andrus, M. B.; Lashley, J. C. *Tetrahedron* **2002**, *58*, 845.

18. For examples of selenide reagents used, see the Experimental Details.

19. Kurokawa, T.; Kim, M.; Du Bois, J. *Angew. Chem. Int. Ed.* **2009**, *48*, 2777.

20. Hofmann elimination examples: (a) Sapi, J.; Grébille, Y.; Laronze, J.-Y.; Lévy, J. *Synthesis* **1992**, 383. (b) Sekine, A.; Ohshima, T.; Shibasaki, M. *Tetrahedron*, **2002**, *58*, 75. (c) Gupta, R. B.; Franck, R. W. *J. Am. Chem. Soc.* **1989**, *111*, 7668. (d) Liu, J.-H., Kovacic, P. *J. Org. Chem.* **1975**, *40*, 1183.

21. Diazonium elimination examples: (a) Baldwin, J. E.; Killin, S. J.; Adlington, R. M.; Spiegel, U. *Tetrahedron* **1988**, *44*, 2633. (b) Aurelio, L.; Box, J. S.; Brownlee, R. T. C.; Hughes, A. B.; Sleebs, M. M. *J. Org. Chem.* **2003**, *68*, 2652. (c) Fennel, K. A.; Möllmann, U.; Miller, M. J. *J. Org. Chem.* **2008**, *73*, 1018. (d) Allevi, P.; Galligani, M.; Anastasia, M. *Tetrahedron: Asymmetry* **2002**, *13*, 1901. (e) Adger, B.; Dyer, U.; Hutton, G.; Woods, M. *Tetrahedron Lett.* **1996**, *37*, 6399.

22. Jung, M. E.; Piizzi, G. *Chem. Rev.* **2005**, *105*, 1735.

23. Cope elimination examples: (a) Kircher, H. W.; Rosenstein, F. U. *J. Org. Chem.* **1982**, *47*, 1722. (b) Langlois, N.; Rakotondradany, F. *Tetrahedron*, **2000**, *56*, 2437. (c) Martínez, A. G.; Vilar, E. T.; Fraile, A. G.; Cerero, S. M.; Maroto, B. L. *Tetrahedron: Asymmetry* **2002**,

13, 17. (d) White, J. D.; Ihle, D. C. *Org. Let.* **2006**, *8*, 1081. (e) Suzuki, M.; Kawamoto, Y.; Sakai, T.; Yamamoto, Y.; Tomioka, K. *Org. Lett.* **2009**, *11*, 653.

4.6. Experimental Details

4.6.1. General Information

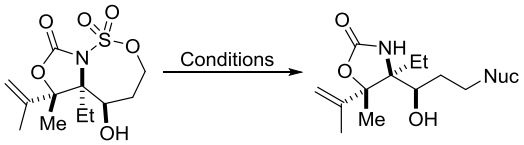
Unless otherwise specified, all glassware was either oven-dried overnight at 130 °C or flame-dried under vacuum and purged with dry nitrogen prior to use. Unless otherwise specified, reagents were used as obtained from the vendor without further purification. Tetrahydrofuran and diethyl ether were freshly distilled from purple Na/benzophenone ketyl. Dichloromethane, acetonitrile and toluene were dried over CaH_2 and freshly distilled prior to use. All other solvents were purified in accordance with "Purification of Laboratory Chemicals".[1] Air- and moisture-sensitive reactions were performed using standard Schlenk techniques under an atmosphere of nitrogen. Analytical thin layer chromatography (TLC) was performed utilizing pre-coated silica gel 60 F_{254} plates containing a fluorescent indicator, while preparative chromatography was performed using SilicaFlash P60 silica gel (230-400 mesh) via Still's method.[2] Unless otherwise stated, the mobile phases for column chromatography were mixtures of hexanes/ethyl acetate. Columns were typically run using a gradient increasing the polarity using ethyl acetate. Various stains were used to visualize reaction products, including *p*-anisaldehyde, $KMnO_4$, ceric ammonium molybdate (CAM stain) and iodine powder.

^{1}H NMR and ^{13}C NMR spectra were obtained using Bruker-300, Varian Inova-500, Varian Unity-500 or Varian Inova-600 NMR spectrometers. For ^{1}H NMR, chemical shifts are reported relative to residual proteo solvent (δ 7.26, 2.49, 7.15 and 4.80 ppm for $CDCl_3$, $(CD_3)_2SO$, C_6D_6 and CD_3OD respectively). ^{13}C NMR spectra were measured at either 125 MHz or 150 MHz on

the same instruments noted above for recording ^{1}H NMR spectra. Chemical shifts were again reported in accordance to residual proteo solvent (δ 77.16, 39.5, 128.0 and 49.0 ppm for $CDCl_3$, $(CD_3)_2SO$, C_6D_6, and CD_3OD, respectively). Accurate mass measurements were acquired at the University of Wisconsin, Madison using a Micromass LCT (electrospray ionization, time-of-flight analyzer or electron impact methods). The NMR and Mass Spectrometry facilities are funded by the NSF (CHE-1048642, CHE-0342998, CHE-9304546 and CHE-9208463), the University of Wisconsin as well as a generous gift by Paul J. Bender.

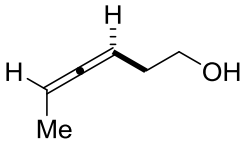
4.6.2. Selenium reagents used for ring-opening of compound 4.29

Table 4.4. Selenium reagents used for ring-opening of compound **4.29**.

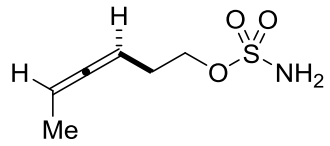


Nuc =	Reagent	Solvent	Temp (°C)	Time (h)	%Yield (NMR)
o-NO_2PhSe-	$NaBH_4$/ArSeCN	EtOH	rt	12	26
"	$NaBH_4$/ArSeCN	EtOH	0	18	0 (18% SM)
PhSe-	DIBAL/Ph_2Se_2	THF	rt	3	0 (15% SM)
"	DIBAL/Ph_2Se_2	CH_2Cl_2	rt	16	34
"	DIBAL/Ph_2Se_2	CH_2Cl_2	-40	16	19 (12% SM)
PhS-	**K_2CO_3/PhSH**	**MeCN**	**rt**	**1.5**	**86**

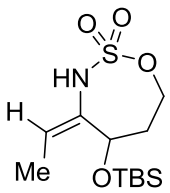
4.6.3. Synthesis of all reported compounds.



Compound 4.24. The homoallenic alcohol is commercially available from Aldrich (#767336), but can be conveniently prepared on multi-gram scale according to the procedure of Blakey and coworkers.[3] Spectra were consistent with reported values.[3]

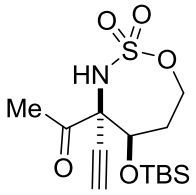


Compound 4.15. The sulfamate was prepared according to the procedure of Du Bois and coworkers.[4] To a flame-dried, three-neck roundbottom flask under N_2 was added chlorosulfonyl isocyanate (19.4 mL, 224.5 mmol, 2.2 equiv). The flask was cooled to 0 °C in an ice bath, and formic acid (8.46 mL, 224.5 mmol, 2.2 equiv) was added slowly over ~15 minutes via syringe (caution: vigorous evolution of CO_2/CO; reaction must be carried out in a well-ventilated hood). After completion of the addition, the mixture was stirred at 0 °C until a white solid had formed, and then 200 mL dry MeCN were added. This solution was stirred overnight at rt (12 h), after which the solution was cooled to 0 °C and alcohol **4.24** (10 g, 102.0 mmol, 1 equiv), dissolved in 200 mL DMA, was added over 2-3 minutes. The solution was stirred at 0 °C for 1.5 h and then at rt for 2 h. The reaction mixture was quenched by the addition of 500 mL of H_2O and poured into a separatory funnel containing 500 mL of Et_2O. The organic phase was collected and the aqueous layer was extracted with 2 x 300 mL of Et_2O. The combined organic extracts were washed with 5 x 200 mL of H2O, dried over $MgSO_4$, and concentrated under reduced pressure. Purification of the oily residue by chromatography on silica gel (0% to 30% EtOAc/hexanes) afforded 16.17 g (91.4 mmol, 90%) of the product as a light yellow oil. Spectra were identical to that previously reported.[3]



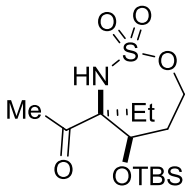
Compound 4.16. A flame-dried roundbottom flask equipped with a stir bar was charged with homoallenic sulfamate **4.15** (5.10 g, 28.8 mmol, 1 equiv) and $Rh_2(OAc)_4$ (125 mg, 0.282 mmol, 0.01 equiv). Dry dichloromethane was added to prepare a 0.1 M solution, and the mixture stirred vigorously to yield a faint green-blue solution. Iodosylbenzene (6.93 g, 31.5 mmol, 1.1 equiv) was added in one portion, and the resulting suspension stirred at room temperature for 1 h. The reaction was monitored by TLC for consumption of starting material (100% CH_2Cl_2 solvent system, CAM stain). Upon complete consumption of the starting material, the solution was concentrated by rotary evaporation (without heating the sample above 30 °C to avoid decomposition of the aziridine), and CH_3CN was added to the residue to prepare a 0.1 M solution. Water (4 equiv) was added, and the solution stirred at room temperature for 1.5 h until TLC indicated complete consumption of the intermediate bicyclic methylene aziridine (~30% EtOAc/hex or 100% CH_2Cl_2 solvent system, CAM stain). Upon completion, the reaction was poured into a beaker of appropriate size and diluted by a factor of 2-3 with CH_2Cl_2. The solution was dried by the addition of Na_2SO_4 until the initially cloudy solution turned clear, and the resulting suspension decanted. The residual material was washed twice with CH_2Cl_2, the organic portions combined and concentrated by rotary evaporation. The residue was then dissolved in dry CH_2Cl_2 (0.4 M) and cooled to 0 ºC. 2,6-Lutidine (2.79 mL, 24.0 mmol, 0.85 equiv) was added in one portion, followed by the slow addition of TBSOTf (5.50 mL, 24.0 mmol, 0.85 equiv) over approximately 1 min. The reaction was stirred at 0 °C for 80 minutes, at which point complete consumption of the starting material was observed by TLC (~30% EtOAc/hex or 100% CH_2Cl_2 solvent system, CAM stain). The reaction mixture was diluted with CH_2Cl_2 and washed twice with saturated NH_4Cl and NaCl solutions. The organic layer was dried over Na_2SO_4, concentrated by rotary evaporation, and the crude material was purified by column chromatography (3% to 30%

EtOAc/hexanes) to yield the desired product (4.06 g, 13.2 mmol, 47%) as a white solid. Spectra was identical to that previously reported.[5]

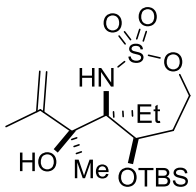


Compound 4.26a. A 250 mL, one-neck roundbottom flask was charged with enesulfamate **4.16** (5.95 g, 19.3 mmol, 1 equiv) and 5g of powdered 4Å MS. A 0.28 M solution of DMDO in CH_2Cl_2 (83.6 mL, 23.4 mmol, 1.2 equiv, prepared according to the procedures of Murray and Singh[6] and Messegeur[7] as described in Chapter 3.4.5) was added and the mixture was stirred at rt for 2 h. The mixture was passed through a celite pad with CH_2Cl_2 and concentrated by rotary evaporation. The resulting crude oil was dissolved in 5-10 mL dry THF, and added dropwise to a solution of ethynylmagnesium bromide (0.5 M in THF, 117 mL, 58.5 mmol, 3 equiv) that had been stirred at 0 ºC for 30 minutes. (Note: the pre-cooling of the grignard solution is essential for high *dr* in this step.) After stirring for 40 minutes at 0 ºC, the reaction was quenched by the addition of sat. NH_4Cl solution. The mixture was extracted twice with EtOAc, and the combined organics were washed with sat. NaCl and dried over Na_2SO_4. The solution was concentrated by rotary evaporation, and the resulting oil was dissolved in CH_2Cl_2 (0.1 M). Dess-Martin reagent (12.4 g, 29.3 mmol, 1.5 equiv) was added, and the mixture was stirred overnight at rt. The solution was quenched by the addition of sat. $Na_2S_2O_3$ and sat. $NaHCO_3$, and the layers were separated in a separatory funnel. The organic layer was washed with sat. NaCl, dried over Na_2SO_4, and concentrated by rotary evaporation. The resulting crude material was purified by column chromatography (50% to 100% CH_2Cl_2/hexanes) to give 3.00 g (8.63 mmol, 45%) of a white solid. The *dr* of the product was

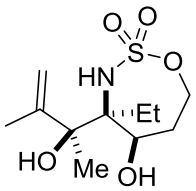
>10:1 judging by ^{1}H NMR of the crude product. ^{1}H NMR (500 MHz, C_6D_6) δ 5.83 (s, 1H), 4.41 – 4.34 (m, 2H), 3.51 (dt, *J* = 12.8, 3.5 Hz, 1H), 2.19 (s, 1H), 2.20 – 2.11 (m, 1H), 1.97 (s, 3H), 1.15 (dt, *J* = 15.9, 4.4 Hz, 1H), 0.73 (s, 9H), -0.16 (s, 3H), -0.23 (s, 3H). ^{13}C NMR (125 MHz, C_6D_6) δ 198.8, 80.9, 75.6, 71.9, 65.7, 64.0, 33.2, 25.7, 25.0, 18.0, -4.7, -5.1. HRMS (ESI) *m*/*z* calculated for $C_{14}H_{29}N_2O_5SSi$ $[M+NH_4]^+$ 365.1561, found 365.1548.



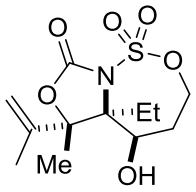
Compound 4.18. A 100 mL, one-neck roundbottom flask was charged with aminoketone **4.26a** (995 mg, 2.86 mmol, 1 equiv) and 29 mL THF (0.1 M). Palladium on carbon (5 wt%, 305 mg, 0.144 mmol Pd, 0.05 equiv Pd) was added, and the flask was fitted with a septum. The atmosphere in the flask was evacuated and back-filled with hydrogen three times using a Schlenk line and a 1 atm hydrogen balloon. The reaction was stirred at rt for 2 h, at which point the balloon was removed, and the atmosphere in the roundbottom flask was purged with N_2. The reaction was passed through a pad of Celite with EtOAc, and concentrated by rotary evaporation to give the desired product (1.03 g, 2.93 mmol, 98%) as a white solid. The material was pure enough to preclude further purification. Spectra was identical to that previously reported.[5]



Compound 4.27. In a glovebox, anhydrous $CeCl_3$ (3.51 g, 14.2 mmol, 5 equiv) was added to a three-neck, 250 mL roundbottom flask. The flask was capped and removed from the glovebox, and 30 mL dry THF was added. The $CeCl_3$-THF slurry was stirred overnight at rt under N_2. The next day, the reaction was cooled to -78 °C in a dry ice/acetone coldbath, and isopropenylmagnesium bromide (0.4 M in THF, 35.6 mL, 14.2 mmol, 5 equiv) was added via syringe. The mixture was stirred at -78 °C for 1.5 h, then aminoketone **4.18** (1.00 g, 2.84 mmol, 1 equiv) was added as a solution in 6 mL THF. The mixture was stirred at -78 °C for 2 h, then warmed to 0 °C and stirred for 1 h. The reaction was quenched by the addition of 75 mL 0.5 M AcOH. The mixture was poured into a separatory funnel and extracted three times with CH_2Cl_2. The combined organic layers were washed with sat. $NaHCO_3$ then sat. NaCl, dried over Na_2SO_4, and concentrated by rotary evaporation. The resulting crude material was purified by column chromatography (5% to 30% EtOAc/hexanes) to give 1.05 g (2.66 mmol, 94%) of **4.14** as a white powder. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.02 (s, 1H), 5.07 (bs, 1H), 5.01 (s, 1H), 4.67 (dd, *J* = 12.7, 11.5 Hz, 1H), 4.55 (dd, *J* = 4.7, 1.9 Hz, 1H), 4.10 (ddd, *J* = 12.7, 4.3, 2.3 Hz, 1H), 3.67 (s, 1H), 2.46 – 2.23 (m, 2H), 2.00 (s, 3H), 1.99 – 1.83 (m, 2H), 1.59 (s, 3H), 0.97 (s, 9H), 0.94 (t, *J* = 7.8 Hz, 3H), 0.23 (s, 3H), 0.18 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.3, 114.9, 80.0, 73.9, 65.3, 63.7, 33.2, 26.6, 26.2, 24.2, 21.0, 18.3, 9.1, -2.7, -4.5. HRMS (ESI) *m*/*z* calculated for $C_{17}H_{39}N_2O_5SSi$ $[M+NH_4]^+$ 411.2344, found 411.2358.

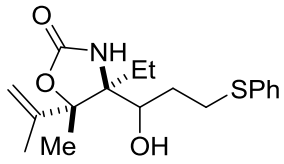


Compound 4.28. A 50 mL, one-neck roundbottom flask was charged with compound **4.14** (432 mg, 1.10 mmol, 1 equiv) and 8.5 mL THF (0.13 M). The flask was cooled to 0 °C in an ice bath, then tetrabutylammonium fluoride (1.0 M in THF, 1.32 mL, 1.32 mmol, 1.2 equiv) was added *via* syringe. The flask was removed from the cold bath and stirred at rt for 40 minutes, at which point it was poured into a separatory funnel, diluted with EtOAc, and washed successively with two portions of sat. NH_4Cl solution and one portion of brine. The organic layer was dried over Na_2SO_4, concentrated by rotary evaporation, and purified by column chromatography (30% to 80% EtOAc/hexanes) to give 263 mg (0.942 mmol, 86%) of the desired product as a faintly yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.93 (bs, 1H), 5.12 (bs, 1H), 5.11 (s, 1H), 4.79 (t, *J* = 12.5 Hz, 1H), 4.52 (m, 1H), 4.12 (dt, *J* = 12.5, 3.1 Hz, 1H), 3.28 (t, *J* = 1.5 Hz, 1H), 2.64 (s, 1H), 2.36 (m, 2H), 2.02 (s, 3H), 1.87 (m, 2H), 1.68 (s, 3H), 0.97 (t, *J* = 7.7 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.4, 115.9, 81.1, 70.8, 65.1, 64.1, 33.3, 27.0, 24.0, 21.2, 9.1. HRMS (ESI) *m*/*z* calculated for $C_{11}H_{25}N_2O_5S$ $[M+NH_4]^+$ 297.1479, found 297.1471.



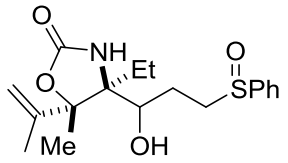
Compound 4.29. Compound **4.28** (127 mg, 0.455 mmol, 1 equiv) and DMAP (139 mg, 1.14 mmol, 2.5 equiv) were added to a 50 mL screwcap pressure vial and dissolved in 9.1 mL MeCN (0.05 M). Triphosgene (149 mg, 0.501 mmol, 1.1 equiv) was added in one portion, and the vial was immediately sealed and immersed in a 70 °C oil bath. After 1 h, the vial was cooled to rt and the solvent removed by rotary evaporation. The resulting crude material was purified by column chromatography (30% to 90% EtOAc/hexanes) to give 77.1 mg (0.253 mmol, 56%) of the desired

product as a white powder. ^{1}H NMR (500 MHz, d_6-acetone) δ 5.23 (s, 1H), 5.20 (q, *J* = 1.4 Hz, 1H), 5.00 (t, *J* = 12.4 Hz, 1H), 4.81 (d, *J* = 3.6 Hz, 1H), 4.51 (m, 1H), 4.48 (dt, *J* = 12.4, 3.2 Hz, 1H), 2.52 (m, 1H), 2.48 (m, 1H), 1.99 (m, 1H), 1.94 (d, *J* = 1.4 Hz, 3H), 1.89 (s, 3H), 1.85 (m, 1H), 0.95 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (125 MHz, d_6-acetone) δ 151.6, 147.1, 117.3, 88.0, 73.3, 68.6, 67.4, 33.3, 24.2, 21.6, 20.0, 8.1. HRMS (ESI) *m/z* calculated for $C_{12}H_{23}N_2O_6S$ $[M+NH_4]^+$ 323.1272, found 323.1277.

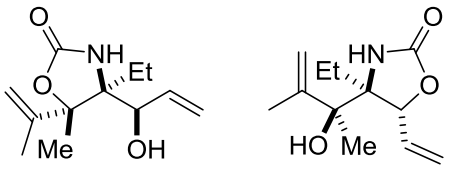


Compound 4.30. A 10 mL roundbottom flask was charged with compound **4.29** (82.0 mg, 0.269 mmol, 1 equiv) and 3 mL MeCN (0.09 M). Thiophenol (66.0 μL, 0.648 mmol, 2.4 equiv) and potassium carbonate (74.0 mg, 0.538 mmol, 2 equiv) were added in sequence, then the flask was capped with a septum and sonicated at rt for 1 h. The resulting white, sludgy mixture was diluted with 5 mL EtOAc and 5 mL 0.5 M HCl, then stirred vigorously at rt for 8 h. The biphasic solution was quenched with sat. $NaHCO_3$ solution, then extracted twice with EtOAc. The combined organic layers were washed with sat. $NaHCO_3$ and brine, concentrated by rotary evaporation, and purified by silica gel chromatography (10% to 70% EtOAc/hexanes) to afford the desired product (78.5 mg, 0.234 mmol, 87%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (d, *J* = 7.7 Hz, 2H), 7.29 (t, *J* = 7.7 Hz, 2H), 7.18 (t, *J* = 7.2 Hz, 1H), 6.39 (bs, 1H), 5.03 (s, 1H), 5.01 (s, 1H), 4.14 (t, *J* = 6.3 Hz, 1H), 3.25 (dt, *J* = 13.4, 5.8 Hz, 1H), 3.07 (dt, *J* = 13.4, 7.5 Hz, 1H), 2.17 (s, 1H), 1.80 (s, 3H), 1.78 (m, 2H), 1.66 (m, 1H), 1.54 (s, 3H), 1.51 (m, 1H), 0.83 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.3, 144.6, 135.8, 129.3, 129.2, 126.4, 115.2, 90.5, 71.5, 68.1,

30.9, 30.3, 24.9, 22.4, 20.9, 8.6. HRMS (ESI) *m*/*z* calculated for $C_{18}H_{29}N_2O_3S$ $[M+NH_4]^+$ 353.1894, found 353.1898.

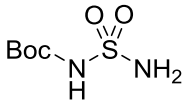


Compound 4.31. A 1.5 dram screwcap vial was charged with compound **4.30** (78.5 mg, 0.234 mmol, 1 equiv) and phenol (303 mg, 3.23 mmol, 13.8 equiv). The mixture was homogenized by adding 20 μL H_2O and sonicating the vial for 30 s, then 30% aq. H_2O_2 was added (53.5 μL, 0.538 mmol, 2.3 equiv) , and the vial was capped and stirred at rt for 1 h. The crude reaction was loaded onto a silica gel column with ~1 mL CH_2Cl_2 and purified (50% to 100% EtOAc, then 5% MeOH/EtOAc) to afford the desired product (64.5 mg, 0.183 mmol, 78%) as a white foam. Characterized as a 1:1 mixture of diastereomers (epimeric at S). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (m, 4H), 7.55 – 7.47 (m, 6H), 6.95 (s, 1H), 6.77 (s, 1H), 5.07 (s, 1H), 5.05 (s, 1H), 5.04 (s, 2H), 4.53 (d, *J* = 7.4 Hz, 1H), 4.48 (d, *J* = 7.0 Hz, 1H), 4.06 (ddd, *J* = 10.4, 7.1, 2.7 Hz, 1H), 3.90 (ddd, *J* = 11.1, 7.0, 2.5 Hz, 1H), 3.26 (ddd, *J* = 13.6, 7.6, 5.8 Hz, 1H), 3.16 – 2.99 (m, 2H), 2.89 (dt, *J* = 14.1, 7.2 Hz, 1H), 2.06 (m, 1H), 1.95 (m, 1H), 1.92 (s, 3H), 1.89 (s, 3H), 1.87 (m, 1H), 1.82 (s, 1H), 1.69 (s, 3H), 1.67 (m, 2H), 1.62 (s, 3H), 1.53 (m, 2H), 0.82 (t, *J* = 7.6 Hz, 3H), 0.80 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.8, 159.6, 146.0, 145.8, 143.0, 142.8, 131.3, 131.3, 129.6, 129.5, 124.3, 124.2, 115.1, 115.0, 89.9, 89.8, 71.3, 70.6, 67.9, 67.9, 53.5, 53.4, 25.1, 25.0, 24.9, 24.8, 22.1, 22.1, 20.7, 20.7, 8.6, 8.5. HRMS (ESI) *m*/*z* calculated for $C_{18}H_{26}NO_4S$ $[M+H]^+$ 352.1578, found 352.1585.

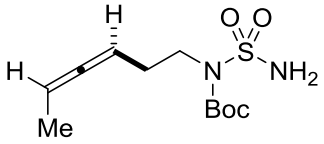


4.32 **4.33**

Compounds 4.32/4.33. A 50 mL screwcap pressure vial was charged with compound **4.31** (64.5 mg, 0.183 mmol, 1 equiv) and 12 mL toluene (0.015 M). Sodium bicarbonate (61.7 mg, 0.734 mmol, 4 equiv) was added, and the vial was capped and heated to 125 °C for 16 h. The solution was cooled to rt and diluted with EtOAc, then washed with H_2O and brine successively. The organic layer was dried over Na_2SO_4, concentrated by rotary evaporation, and purified by silica gel chromatography (10% to 50% EtOAc/hexanes) to afford 13.6 mg of the major diene isomer **4.33**, and 10.9 mg of the minor isomer **4.32** (combined: 24.5 mg, 0.109 mmol, 60% combined yield, 1.25:1 ratio), both as colorless oils. Compound **4.33**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.96 (ddd, *J* = 16.9, 10.8, 5.7 Hz, 1H), 5.93 (bs, 1H), 5.54 (dt, *J* = 16.9, 1.4 Hz, 1H), 5.39 (dt, *J* = 10.8, 1.4 Hz, 1H), 5.30 (app d, *J* = 5.7 Hz, 1H), 5.09 (m, 2H), 2.28 (s, 1H), 1.88 (d, *J* = 0.8 Hz, 3H), 1.77 (m, 1H), 1.73 – 1.64 (m, 1H), 1.39 (s, 3H), 0.96 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.1, 148.3, 131.9, 119.9, 114.9, 81.6, 77.8, 69.1, 24.3, 23.1, 21.8, 8.6. HRMS (ESI) *m*/*z* calculated for $C_{12}H_{20}NO_3$ $[M+H]^+$ 226.1438, found 226.1435. Compound **4.32**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.99 (ddd, *J* = 17.2, 10.4, 7.3 Hz, 1H), 5.93 (s, 1H), 5.46 (dt, *J* = 17.2, 1.2 Hz, 1H), 5.36 (dt, *J* = 10.4, 1.2 Hz, 1H), 5.14 (s, 1H), 5.04 (p, *J* = 1.2 Hz, 1H), 4.47 (d, *J* = 7.3 Hz, 1H), 2.52 (s, 1H), 1.88 (bs, 3H), 1.75 (m, 1H), 1.68 (s, 3H), 1.54 (dq, *J* = 14.8, 7.5 Hz, 1H), 0.91 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.8, 144.7, 136.0, 119.6, 114.8, 89.8, 74.7, 67.4, 25.2, 22.5, 20.8, 8.4. HRMS (ESI) *m*/*z* calculated for $C_{12}H_{20}NO_3$ $[M+H]^+$ 226.1438, found 226.1431.

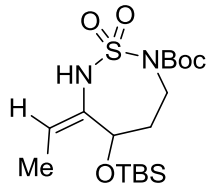


Compound 4.S1. The literature procedure by Masui and coworkers was followed.[8] A flame-dried 500 mL, three-neck roundbottom flask under N_2 was charged with toluene (194 mL) and *tert*-butanol (13.4 mL, 141 mmol, 1 equiv). The flask was cooled to 0 °C, and chlorosulfonyl isocyanate (12.3 mL, 141 mmol, 1 equiv) was added dropwise over 10 minutes. The mixture was stirred at 0 °C for 30 minutes, then dry pyridine (25.0 mL, 311 mmol, 2.2 equiv) was added dropwise over 5 minutes. The mixture was stirred for 1 h at 0 °C, then 25% aqueous ammonium hydroxide (58 mL, 770 mmol, 5.5 equiv) was added and the resulting biphasic solution stirred vigorously at 0 °C for 2 h. The solution was transferred to a separatory funnel and the layers were separated. The aqueous layer was washed once with a portion of toluene, then the combined organic layers were back-extracted with two portions of water. The combined aqueous layers were then acidified to pH ~1 by the cautious addition of 62% H_2SO_4 (33.6 g). The resulting white precipitate was collected by filtration, washed twice with portions of water, and dried overnight under high-vacuum to give 15.6 g (79.4 mmol, 56%) of the desired N-Boc sulfamide as a white solid. Spectra were identical to that previously reported.[9]



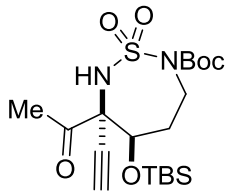
Compound 4.42. A flame-dried, 250 mL roundbottom flask was charged with homoallenic alcohol **4.24** (1.22 g, 12.5 mmol, 1 equiv), N-Boc sulfamide **4.S1** (3.18 g, 16.2 mmol, 1.3 equiv), triphenylphosphine (4.24 g, 16.2 mmol, 1.3 equiv), and 62.5 mL dry THF. The solution was cooled to 0 °C with stirring, then diisopropylazodicarboxylate (3.15 mL, 16.2 mmol, 1.3 equiv) was added

dropwise over 5 minutes. The solution was warmed to rt and stirred for 4 h, at which point TLC monitoring (30% EtOAc/hexanes, CAM stain) indicated the starting alcohol had been consumed. The solution was concentrated by rotary evaporation, and the resulting crude oil was purified by silica gel chromatography (5% to 60% EtOAc/hexanes) to give the desired product (2.85 g, 10.3 mmol, 83%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.24 (s, 2H), 5.13 – 4.98 (m, 2H), 3.78 (app t, *J* = 7.0 Hz, 2H), 2.32 (app qd, *J* = 7.0, 2.4 Hz, 2H), 1.64 (dd, *J* = 7.0, 3.3 Hz, 3H), 1.54 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.9, 152.5, 86.8, 86.3, 84.4, 47.1, 29.6, 28.2, 14.5. HRMS (ESI) *m*/*z* calculated for $C_{11}H_{24}N_3O_4S$ $[M+NH_4]^+$ 294.1483, found 294.1489.



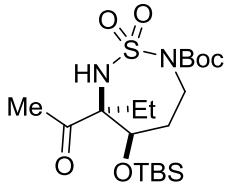
Compound 4.43. A one-neck, 100 mL roundbottom flask was charged with compound **4.30** (995 mg, 3.61 mmol, 1 equiv), Rh_2OAc_4 (24.0 mg, 0.0543 mmol, 0.015 equiv), and 36 mL CH_2Cl_2 (0.1 M). The blue-green solution was cooled to 0 °C with stirring, then the reaction was initiated by the addition of PhIO (1.19 g, 5.43 mmol, 1.5 equiv) in one portion. After stirring for 2 h at 0 °C, the reaction was passed through a glass-fritted funnel with CH_2Cl_2 in order to remove excess PhIO. The resulting solution was concentrated by rotary evaporation in a 10 °C water bath (to avoid decomposition of the sensitive methylene aziridine). The concentrated material was re-dissolved in 9 mL MeCN (0.4 M), then cooled to 0 °C, and H_2O (1.30 mL, 72.4 mmol, 20 equiv) was added in one portion. The reaction was stirred at 0 °C for 2.5 h, then the solution was diluted by a factor of 2-3 with CH_2Cl_2 and dried by the addition of Na_2SO_4 (the solution should turn from cloudy to clear when the water is removed). The solution was decanted and dried by rotary evaporation,

then the concentrated material was re-dissolved in 9 mL dry CH_2CL_2 (0.4 M). The solution was cooled to 0 °C , then 2,6-lutidine (0.42 mL, 3.6 mmol, 1 equiv) and TBSOTf (0.83 mL, 3.6 mmol, 1 equiv) were added in sequence. After 1 h, the reaction was transferred to a separatory funnel, diluted with CH_2Cl_2, then washed twice with sat. NH_4Cl and once with brine. The organic layer was dried over Na2SO4, concentrated by rotary evaporation, and purified by silica gel chromatography (5% to 20% EtOAc/hexanes) to give the desired product (844 mg, 2.07 mmol, 57%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.46 (s, 1H), 5.80 (q, *J* = 7.3 Hz, 1H), 4.74 (t, *J* = 3.0 Hz, 1H), 3.93 (ddd, *J* = 15.9, 4.4, 2.8 Hz, 1H), 3.82 (ddd, *J* = 15.9, 10.6, 1.7 Hz, 1H), 1.98 – 1.78 (m, 2H), 1.71 (d, *J* = 7.3 Hz, 3H), 1.51 (s, 9H), 0.89 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.6, 132.4, 124.1, 84.1, 64.6, 41.2, 37.2, 28.1, 25.8, 18.3, 12.3, -4.8, -4.9. HRMS (ESI) *m/z* calculated for $C_{17}H_{38}N_3O_5SSi$ $[M+NH_4]^+$ 424.2296, found 424.2295.



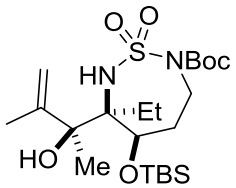
Compound 4.44. The enesulfamide **4.43** (1.16 g, 2.86 mmol, 1 equiv) was added to a 100 mL roundbottom flask with 1 g of powdered 4Å MS. A 0.31 M solution of DMDO in CH_2Cl_2 (14.8 mL, 4.58 mmol, 1.6 equiv, prepared according to the procedures of Murray and Singh[6] and Messegeur[7] as described in Chapter 3.4.5) was added and the mixture was stirred at rt for 35 minutes. The mixture was passed through a celite pad with CH_2Cl_2 and concentrated by rotary evaporation. The resulting crude oil was dissolved in 3 mL dry THF, and added dropwise to a solution of ethynylmagnesium bromide (0.5 M in THF, 17.2 mL, 8.58 mmol, 3 equiv) that had been pre-stirred at 0 ºC for 30 minutes. (Note: the pre-cooling of the Grignard solution is essential

for high *dr* in this step.) After stirring for 50 minutes at 0 ºC, the reaction was quenched by the addition of sat. NH_4Cl solution. The mixture was extracted twice with EtOAc, and the combined organics were washed with sat. NaCl and dried over Na_2SO_4. The solution was concentrated by rotary evaporation, and the resulting oil was dissolved in 25 mL CH_2Cl_2 (0.1 M). Dess-Martin reagent (1.21 g, 2.86 mmol, 1.0 equiv) was added, and the mixture was stirred overnight at rt. The solution was diluted with 20 mL Et_2O, and a 1:1 mixture of sat. $Na_2S_2O_3$/sat. $NaHCO_3$ was added. The biphasic mixture was stirred vigorously for 5 minutes, then transferred to a separatory funnel and the layers separated. The organic layer was washed once with brine, dried over Na_2SO_4, and concentrated by rotary evaporation. The resulting crude material was purified by column chromatography (0% to 20% EtOAc/hexanes) to give the desired product (731.3 mg, 1.64 mmol, 57%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.89 (s, 1H), 4.61 (dd, *J* = 4.3, 2.0 Hz, 1H), 3.84 (ddd, *J* = 15.7, 4.8, 2.7, 1H), 3.76 (dd, 15.7, 11.1 Hz, 1H), 2.79 (s, 1H), 2.58 (ddt, *J* = 15.5, 11.1, 2.4 Hz, 1H), 2.41 (s, 3H), 1.80 (dt, *J* = 15.5, 4.6 Hz, 1H), 1.52 (s, 9H), 0.85 (s. 9H), 0.11 (s, 3H), 0.04 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.3, 151.6, 84.1, 81.2, 75.2, 72.1, 65.9, 40.6, 32.5, 28.2, 25.8, 25.5, 18.1, -4.3, -4.9. HRMS (ESI) *m*/*z* calculated for $C_{19}H_{38}N_3O_6SSi$ $[M+NH_4]^+$ 464.2246, found 464.2256.



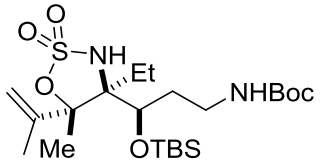
Compound 4.S2. A 100 mL, one-neck roundbottom flask was charged with aminoketone **4.44** (730.0 mg, 1.633 mmol, 1 equiv) and 16 mL THF (0.1 M). Palladium on carbon (5 wt%, 173 mg, 0.0816 mmol Pd, 0.05 equiv Pd) was added, and the flask was fitted with a septum. The

atmosphere in the flask was evacuated and back-filled with hydrogen three times using a Schlenk line and a 1 atm hydrogen balloon. The reaction was stirred at rt for 30 minutes, at which point the balloon was removed and the atmosphere in the roundbottom flask was purged with N_2. The reaction was passed through a pad of Celite with EtOAc, and concentrated by rotary evaporation to give the desired product (729.0 mg, 1.616 mmol, 99%) as a white solid. The material was pure enough to preclude further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.06 (s, 1H), 4.46 (dd, *J* = 8.2, 3.2 Hz, 1H), 3.93 (ddd, *J* = 15.6, 4.8, 4.1 Hz, 1H), 3.61 (ddd, *J* = 15.6, 11.3, 3.2 Hz, 1H), 2.31 (s, 3H), 2.22 – 2.00 (m, 3H), 1.60 (m, 1H), 1.53 (s, 9H), 0.89 (s, 9H), 0.88 (m, 3H), 0.10 (s, 3H), 0.09 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.9, 151.9, 84.2, 74.1, 71.9, 42.0, 32.9, 28.1, 27.5, 26.5, 25.9, 18.1, 7.9, -4.3, -4.8. HRMS (ESI) *m*/*z* calculated for $C_{19}H_{42}N_3O_6SSi$ $[M+NH_4]^+$ 468.2559, found 468.2557.

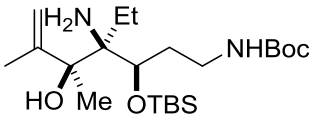


Compound 4.45. In a glovebox, anhydrous $CeCl_3$ (1.38 g, 5.59 mmol, 4 equiv) was added to a three-neck, 250 mL roundbottom flask. The flask was capped and removed from the glovebox, and 14 mL dry THF was added. The $CeCl_3$-THF slurry was stirred under N_2 for 1 h at rt. The flask was then cooled to -78 °C in a dry ice/acetone bath, and isopropenylmagnesium bromide (0.5 M in THF, 11.2 mL, 5.60 mmol, 4 equiv) was added via syringe. The mixture was stirred at -78 °C for 1 h, then aminoketone **4.S2** (630.0 mg, 1.397 mmol, 1 equiv) was added (dissolved in 3 mL THF). The mixture was stirred at -78 °C for 1 h, then warmed to 0 °C and stirred for 1 h. The reaction was quenched by the addition of 30 mL 0.5 M AcOH. The mixture was poured into a

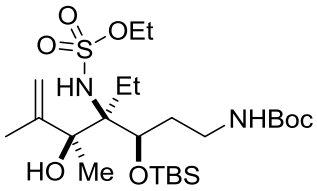
separatory funnel and extracted three times with CH_2Cl_2. The combined organic layers were washed with sat. $NaHCO_3$ then sat. NaCl, dried over Na_2SO_4, and concentrated by rotary evaporation. The resulting crude material was purified by column chromatography (5% to 20% EtOAc/hexanes) to give the desired product (565.3 g, 1.147 mmol, 82%) as a white powder. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.04 (s, 1H), 5.07 (s, 1H), 5.01 (s, 1H), 4.47 (dd, *J* = 4.5, 1.8 Hz, 1H), 3.94 (ddd, *J* = 15.5, 6.4, 1.7 Hz, 1H), 3.83 (dd, *J* = 15.5, 10.6 Hz, 1H), 2.81 (m, 1H), 2.14 (m, 2H), 2.00 (s, 3H), 1.99 (m, 2H), 1.59 (s, 3H), 1.52 (s, 9H), 0.96 (s, 9H), 0.94 (t, *J* = 7.7 Hz, 3H), 0.22 (s, 3H), 0.19 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.5, 147.2, 114.9, 84.2, 80.2, 73.9, 66.1, 40.5, 32.7, 28.1, 26.4, 26.3, 24.8, 21.0, 18.4, 9.3, -2.8, -4.7. HRMS (ESI) *m*/*z* calculated for $C_{22}H_{48}N_3O_6SSi$ $[M+NH_4]^+$ 510.3028, found 510.3036.



Compound 4.47. A 3-dram vial was charged with compound **4.45** (51.2 mg, 0.104 mmol, 1 equiv) and 1.1 mL of a 10:1 pyridine/H_2O mixture. The vial was capped and heated to 50 °C for 16 h, then the solvent was removed by rotary evaporation and the crude product was purified by silica gel chromatography (5% to 25% EtOAc/hexanes) to afford the desired product (18.6 mg, 0.0377 mmol, 36%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.21 (s, 1H), 5.15 (m, 1H), 4.97 (s, 1H), 4.61 (bs, 1H), 4.13 (d, *J* = 7.6 Hz, 1H), 3.28 (m, 1H), 3.13 (m, 1H), 2.04 (m, 2H), 1.92 (s, 3H), 1.78 (s, 3H), 1.78 – 1.68 (m, 1H), 1.66 – 1.56 (m, 1H), 1.44 (s, 9H), 1.06 (t, *J* = 7.5 Hz, 3H), 0.92 (s, 9H), 0.22 (s, 3H), 0.17 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.1, 143.4, 117.0, 99.5, 79.8, 73.1, 72.9, 38.4, 34.8, 28.5, 26.2, 25.5, 23.9, 21.7, 18.5, 9.6, -3.6, -3.8. HRMS (ESI) *m*/*z* calculated for $C_{22}H_{45}N_2O_6SSi$ $[M+H]^+$ 493.2763, found 493.2765.

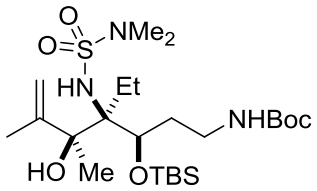


Compound 4.48. A 20 mL scintillation vial was charged with compound **4.45** (48.9 mg, 0.0992 mmol, 1 equiv) and 3 mL of a 7:1 MeOH/pyridine mixture (0.033 M). The vial was capped and heated to 60 °C for 16 h, then the solvent was removed by rotary evaporation and the crude product was purified by silica gel chromatography (10% to 50% EtOAc/hexanes) to afford the desired product (29.2 mg, 0.0677 mmol, 68%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.10 (bs, 1H), 5.02 (s, 1H), 4.99 (s, 1H), 4.66 (bs, 1H), 3.95 (bs, 1H), 3.28 (m, 1H), 3.14 (m, 1H), 2.14 (m, 1H), 1.88 (s, 3H), 1.81 (dq, *J* = 14.8, 7.3 Hz, 1H), 1.68 (m, 1H), 1.44 (s, 9H), 1.35 – 1.25 (m, 1H), 1.33 (s, 3H), 0.95 (t, *J* = 7.3 Hz, 3H), 0.92 (s, 9H), 0.15 (s, 3H), 0.13 (s, 3H). [Note: due to rapid exchange, the $–NH_2$ cannot be observed]. ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.1, 151.0, 113.5, 79.1, 78.8, 74.3, 61.8, 38.8, 35.1, 28.6, 27.4, 26.1, 23.9, 22.6, 18.4, 9.3, -3.6, -4.0. HRMS (ESI) *m*/*z* calculated for $C_{22}H_{47}N_2O_4Si$ $[M+H]^+$ 431.3300, found 431.3295.

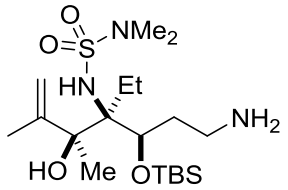


Compound 4.49. A 20 mL scintillation vial was charged with compound **4.45** (201 mg, 0.408 mmol, 1 equiv) and 6.15 mL of a 7:1 EtOH/pyridine mixture (0.066 M). The vial was capped and heated to 50 °C overnight in an oilbath. After 16 h, the solvent was removed by rotary evaporation and the crude material was purified by silica gel chromatography (5% to 25% EtOAc/hexanes) to afford the desired product (134 mg, 0.249 mmol, 61%) as a white foam. ^{1}H NMR (500 MHz,

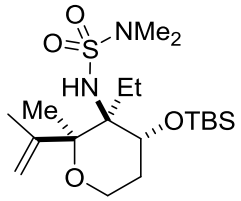
$CDCl_3$) δ 5.80 (s, 1H), 5.09 (m, 2H), 4.63 (bs, 1H), 0.24 (q, *J* = 7.0 Hz, 2H), 4.21 (m, 1H), 3.93 (s, 1H), 3.33 (m, 1H), 3.20 (m, 1H), 2.34 (m, 1H), 2.23 (m, 1H), 2.05 – 1.92 (m, 1H), 1.94 (s, 3H),1.78 (m, 1H), 1.55 (s, 3H), 1.44 (s, 9H), 1.37 (t, *J* = 7.0 Hz, 3H), 1.04 (t, *J* = 7.5 Hz, 3H), 0.93 (s, 9H), 0.24 (s, 3H), 0.22 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.9, 148.8, 115.4, 80.8, 79.4, 75.8, 69.7, 66.8, 39.1, 34.4, 28.5, 26.5, 26.2, 23.2, 21.9, 18.5, 14.9, 9.9, -3.2, -4.1. HRMS (ESI) *m*/*z* calculated for $C_{24}H_{51}N_2O_7SSi$ $[M+H]^+$ 539.3181, found 539.3182.



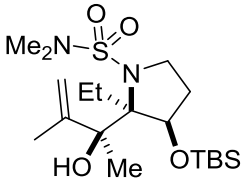
Compound 4.50. A 20 mL scintillation vial was charged with compound **4.45** (153 mg, 0.311 mmol, 1 equiv) and 4 mL of a 2.0 M solution of $HNMe_2$ in THF. The vial was capped and heated to 60 °C overnight in an oilbath. After 9 h, the solvent was removed by rotary evaporation and the crude material was purified by silica gel chromatography (0% to 30% EtOAc/hexanes) to afford the desired product (147 mg, 0.273 mmol, 88%) as a white foam. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.27 (s, 1H), 5.09 (s, 1H), 5.08 (s, 1H), 4.76 (bs, 1H), 4.23 (dd, *J* = 5.7, 3.5 Hz, 1H), 4.01 (s, 1H), 3.32 (m, 1H), 3.21 (m, 1H), 2.84 (s, 6H), 2.34 (m, 1H), 2.19 (m, 1H), 2.05 (m, 1H), 1.95 (s, 3H), 1.79 (m, 1H), 1.53 (s, 3H), 1.44 (s, 9H), 1.06 (t, *J* = 7.6 Hz, 3H), 0.93 (s, 9H), 0.23 (s, 3H), 0.21 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.0, 149.6, 115.3, 80.9, 79.3, 76.2, 69.2, 68.1, 39.2, 38.5, 34.3, 28.6, 26.6, 26.2, 24.1, 22.1, 18.6, 10.2, -3.3, -4.0. HRMS (ESI) *m*/*z* calculated for $C_{24}H_{52}N_3O_6SSi$ $[M+H]^+$ 538.3341, found 538.3335.



Compound 4.51. A 20 mL scintillation vial was charged with compound **4.50** (147 mg, 0.273 mmol, 1 equiv) and 2.25 mL CH_2Cl_2 (0.12M). Trifluoroacetic acid (0.45 mL, 1:5 v/v relative to CH_2Cl_2) was added in one portion, and the vial was capped and stirred at rt for 1 h. The solution was diluted with CH_2Cl_2, then washed twice with portions of sat. $NaHCO_3$ and once with brine. The organic layer is dried over Na_2SO_4 and concentrated by rotary evaporation to afford the desired product (109.3 mg, 0.250 mmol, 91%) as a white foam. The material was pure enough to preclude further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.09 (bs, 1H), 5.07 (p, *J* = 1.2 Hz, 1H), 4.21 (dd, *J* = 5.2, 4.0 Hz, 1H), 2.98 (ddd, *J* = 12.3, 9.0, 5.2 Hz, 1H), 2.83 (s, 6H), 2.75 (dt, *J* = 12.3, 7.7 Hz, 1H), 2.32 – 2.22 (m, 2H), 2.05 (dq, *J* = 14.9, 7.5 Hz, 1H), 1.96 (bs, 3H), 1.76 (ddt, *J* = 13.7, 8.2, 5.3 Hz, 1H), 1.54 (s, 3H), 1.05 (t, *J* = 7.5 Hz, 3H), 0.93 (s, 9H), 0.19 (s, 3H), 0.19 (s, 3H). [Note: due to rapid exchange, the NH_2, NH, and OH peaks were not observed in the ^{1}H NMR]. ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.7, 115.1, 80.7, 76.7, 69.6, 40.4, 38.5, 37.5, 26.6, 26.1, 24.0, 22.2, 18.5, 10.0, -3.2, -4.1. HRMS (ESI) *m*/*z* calculated for $C_{19}H_{44}N_3O_4SSi$ $[M+H]^+$ 438.2817, found 438.2819.

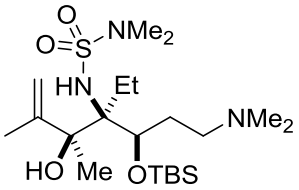


4.52

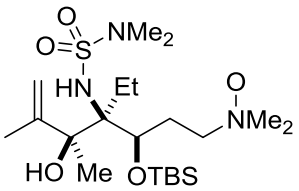


4.53

Compounds 4.52/4.53. A ½-dram vial was charged with compound **4.51** (23.0 mg, 0.0525 mmol, 1 equiv) and 0.53 mL 1:1 AcOH/H_2O (0.1M). Sodium nitrite (18.0 mg, 0.261 mmol, 5 equiv) was added in one portion, and the vial was capped and stirred at rt for 25 minutes. At this point, TLC (10% MeOH/CH_2Cl_2, CAM stain) indicated the reaction was incomplete, so an additional 5 equiv $NaNO_2$ were added in one portion, and the vial was stirred at rt for an additional 15 minutes. The reaction was then diluted with EtOAc, then washed with sat. $NaHCO_3$ followed by brine. The organic layer was dried over Na_2SO_4, concentrated by rotary evaporation, and purified by silica gel chromatography (0% to 30% EtOAc/hexanes) to afford tetrahydropyran **4.52** (4.9 mg, 0.012 mmol, 22%) and pyrollidine **4.53** (6.8 mg, 0.016 mmol, 31%) as clear oils. Compound **4.52** eluted first (R_f = 0.2 in 20% EtOAc/hexanes), and compound **4.53** eluted second (Rf = 0.15 in 20% EtOAc/hexanes). Compound **4.52**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.16 (s, 1H), 5.09 (s, 1H), 4.72 (s, 1H), 4.62 (t, *J* = 2.6 Hz, 1H), 4.02 (m, 1H), 3.72 (dd, *J* = 11.9, 5.8 Hz, 1H), 2.77 (s, 6H), 2.42 (tdd, *J* = 13.8, 6.1, 3.0 Hz, 1H), 1.94 (q, *J* = 7.5 Hz, 2H), 1.90 (s, 3H), 1.69 (s, 3H), 1.52 – 1.46 (m, 1H), 1.11 (t, *J* = 7.5 Hz, 3H), 0.92 (s, 9H), 0.14 (s, 3H), 0.11 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.9, 115.4, 82.3, 68.9, 65.1, 56.7, 38.1, 28.5, 26.1, 25.0, 22.7, 19.5, 18.3, 9.2, -3.2, -5.1. HRMS (ESI) *m*/*z* calculated for $C_{19}H_{41}N_2O_4SSi$ $[M+H]^+$ 421.2551, found 421.2550. Compound **4.53**: ^{1}H NMR (500 MHz, $CDCl_3$) 5.28 (s, 1H), 4.99 (s, 1H), 4.74 (d, *J* = 1.4 Hz, 1H), 4.39 (dd, *J* = 11.7, 7.6 Hz, 1H), 3.24 – 3.12 (m, 2H), 2.90 (s, 6H), 2.48 (q, *J* = 7.5 Hz, 2H), 2.25 (p, *J* = 10.7 Hz, 1H), 2.01 (s, 3H), 1.95 (dt, *J* = 11.8, 7.6, 1H), 1.49 (s, 3H), 1.11 (t, *J* = 7.5 Hz, 3H), 0.93 (s, 9H), 0.17 (s, 3H), 0.14 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.5, 114.2, 81.3, 78.1, 74.6, 46.3, 38.6, 29.4, 26.4, 25.8, 24.0, 22.3, 18.0, 9.7, -3.9, -5.2. HRMS (ESI) *m*/*z* calculated for $C_{19}H_{41}N_2O_4SSi$ $[M+H]^+$ 421.2551, found 421.2554.

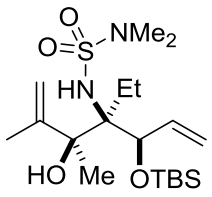


Compound 4.54. A 20 mL scintillation vial was charged with compound **4.51** (178 mg, 0.406 mmol, 1 equiv) and 8 mL of a 3:1 MeOH/MeCN mixture (0.05 M). The vial was cooled to 0 °C, then $NaBH_3CN$ (65.5 mg, 1.04 mmol, 2.5 equiv) and AcOH (30.0 μL, 0.0.519 mmol, 1.25 equiv) were added sequentially. A 37 wt% aqueous solution of formaldehyde (155 μL, 2.08 mmol, 5 equiv) was then added, and the vial was capped and stirred at 0 °C, slowly warming to rt over 1-2 h. After 4.5 h total, the reaction was diluted with EtOAc, then washed twice with sat. $NaHCO_3$ solution and once with brine. The organic layer was dried over Na_2SO_4, concentrated by rotary evaporation, and the crude material purified by silica gel chromatography (0% to 15% MeOH/CH_2Cl_2) to afford the desired product (118.4 mg, 0.2541 mmol, 63%) as a white foam.. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.08 (bs, 1H), 5.09 (s, 1H), 5.04 (m, 1H), 4.17 (t, *J* = 4.3 Hz, 1H), 2.83 (s, 6H), 2.79 (m, 1H), 2.33 (bs, 8H), 2.13 (dq, *J* = 14.6, 7.3 Hz, 1H), 2.04 – 1.94 (m, 2H), 1.95 (s, 3H), 1.55 (s, 3H), 1.05 (t, *J* = 7.3 Hz, 3H), 0.93 (s, 9H), 0.17 (s, 3H), 0.15 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.1, 114.9, 79.9, 70.2, 57.0, 44.9, 38.5, 30.6, 26.2, 26.1, 25.0, 22.4, 18.5, 10.0, -3.2, -4.3. HRMS (ESI) *m*/*z* calculated for $C_{21}H_{48}N_3O_4SSi$ $[M+H]^+$ 466.3130, found 466.3131.

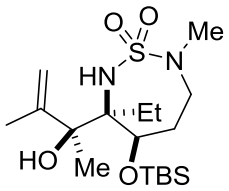


Compound 4.55. A 20 mL scintillation vial was charged with compound **4.54** (112 mg, 0.240 mmol, 1 equiv) and 3.7 mL CH_2Cl_2 (0.065 M). mCPBA (62.4 mg, 0.361 mmol, 1.5 equiv) was

added in one portion at rt, and the solution was stirred at rt for 25 minutes. The solution was then diluted with CH_2Cl_2 and washed twice with sat. Na_2CO_3 solution, then washed once with brine. The organic layer was dried over Na_2SO_4 and concentrated by rotary evaporation to afford the desired product (113.1 mg, 0.235 mmol, 98%) as a tan solid. The material was pure enough to preclude further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.95 (bs, 1H), 5.07 (s, 1H), 5.01 (bs, 1H), 4.28 (t, *J* = 5.2 Hz, 1H), 3.50 (td, *J* = 11.5, 5.2 Hz, 1H), 3.41 (td, *J* = 11.5, 4.6 Hz, 1H), 3.21 (s, 3H), 3.19 (s, 3H), 2.91 – 2.85 (m, 1H), 2.83 (s, 6H), 2.36 (ddt, *J* = 14.3, 11.6, 5.8 Hz, 1H), 1.95 (s, 3H), 1.92 (app q, J = 7.3 Hz, 2H), 1.62 (s, 3H), 1.06 (t, *J* = 7.3 Hz, 3H), 0.92 (s, 10H), 0.20 (s, 3H), 0.17 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.6, 114.8, 79.7, 76.8, 70.1, 69.7, 59.7, 57.9, 38.5, 28.9, 26.2, 26.1, 25.8, 22.4, 18.5, 10.2, -3.2, -3.9. HRMS (ESI) *m*/*z* calculated for $C_{21}H_{48}N_3O_5SSi$ $[M+H]^+$ 482.3079, found 482.3065.



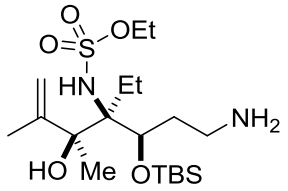
4.56



4.57

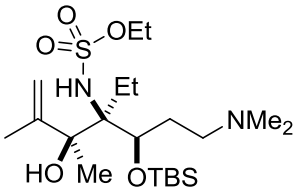
Compounds 4.56/4.57. A 20 mL scintillation vial was charged with compound **4.55** (35.1 mg, 0.0728 mmol, 1 equiv) and 2.1 mL toluene (0.035 M). The vial was capped and heated to 80 °C in an oil bath with stirring for 2.5 h. The resulting yellow solution was concentrated by rotary evaporation and purified by silica gel chromatography (0% to 30% EtOAc/hexanes) to afford the desired Cope product **4.56** (3.7 mg, 0.0088 mmol, 12%) as a colorless oil, and the undesired pyrrolidine **4.57** (6.9 mg, 0.017 mmol, 23%) as a white solid. Compound **4.56** eluted first (R_f = 0.4 in 20% EtOAc/hexanes), and compound **4.57** eluted second (R_f = 0.2 in 20% EtOAc/hexanes).

Compound **4.56**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.24 (dt, *J* = 17.2, 9.6 Hz, 1H), 5.38 – 5.28 (m, 3H), 5.11 (s, 1H), 5.10 (s, 1H), 4.64 (d, *J* = 9.2 Hz, 1H), 4.48 (s, 1H), 2.84 (s, 6H), 2.16 (m, 1H), 2.06 (m, 1H), 1.97 (s, 3H), 1.57 (s, 3H), 1.00 (t, *J* = 7.5 Hz, 3H), 0.91 (s, 9H), 0.16 (s, 3H), 0.13 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.2, 137.3, 120.0, 115.3, 80.9, 80.5, 68.0, 38.5, 27.2, 26.1, 22.9, 21.8, 18.2, 9.6, -2.5, -4.5. HRMS (ESI) *m/z* calculated for $C_{19}H_{41}N_2O_4SSi$ $[M+H]^+$ 421.2551, found 421.2549. Compound **4.57**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.68 (s, 1H), 5.06 (s, 1H), 5.01 (s, 1H), 4.47 (d, *J* = 4.2 Hz, 1H), 3.95 (s, 1H), 3.91 (dd, *J* = 15.5, 11.3 Hz, 1H), 2.91 (s, 3H), 2.78 (dd, *J* = 15.5, 5.5 Hz, 1H), 2.27 (dq, *J* = 15.3, 7.8 Hz, 1H), 2.10 (m, 1H), 2.03 (s, 3H), 1.94 – 1.84 (m, 2H), 1.57 (s, 3H), 0.96 (s, 9H), 0.94 (m, 3H), 0.22 (s, 3H), 0.18 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.9, 114.7, 80.3, 74.9, 64.9, 44.4, 36.3, 31.7, 26.6, 26.2, 24.6, 21.2, 18.3, 9.4, -2.8, -4.6. HRMS (ESI) *m/z* calculated for $C_{18}H_{39}N_2O_4SSi$ $[M+H]^+$ 407.2395, found 407.2387.



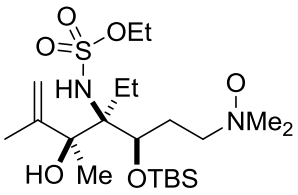
Compound 4.58. A 20 mL scintillation vial was charged with compound **4.49** (125 mg, 0.232 mmol, 1 equiv) and 2.0 mL CH_2Cl_2 (0.12M). Trifluoroacetic acid (0.40 mL, 1:5 v/v relative to CH_2Cl_2) was added in one portion, and the vial was capped and stirred at rt for 1 h. The solution is diluted with CH_2Cl_2, then washed twice with portions of sat. $NaHCO_3$ and once with brine. The organic layer is dried over Na_2SO_4 and concentrated by rotary evaporation to afford the desired product (97.9 mg, 0.223 mmol, 96%) as a light yellow oil. The material was pure enough to preclude further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.14 (s, 1H), 5.04 (p, *J* = 1.3 Hz, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 4.14 (dd, *J* = 5.6, 4.2 Hz, 1H), 3.03 (ddd, *J* = 12.1, 6.6, 5.3 Hz, 1H), 2.66

(ddd, *J* = 12.1, 8.7, 6.1 Hz, 1H), 2.43 – 2.27 (m, 2H), 2.05 (dq, *J* = 15.0, 7.5 Hz, 1H), 1.96 (d, *J* = 1.3 Hz, 3H), 1.80 – 1.70 (m, 1H), 1.53 (s, 3H), 1.36 (t, *J* = 7.1 Hz, 3H), 1.04 (t, *J* = 7.5 Hz, 3H), 0.93 (s, 9H), 0.18 (s, 3H), 0.17 (s, 3H). [Note: Due to rapid exchange, the OH, NH, and NH_2 protons are not observed in the ^{1}H NMR.] ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.0, 114.9, 80.9, 77.7, 69.2, 66.1, 40.0, 37.3, 26.4, 26.1, 22.9, 22.3, 18.4, 14.9, 9.4, -3.3, -4.3. HRMS (ESI) *m/z* calculated for $C_{19}H_{43}N_2O_5SSi$ $[M+H]^+$ 439.2657, found 439.2661.

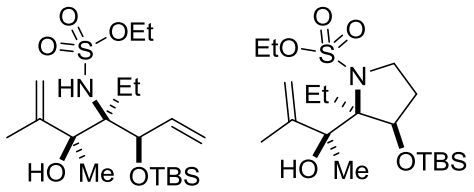


Compound 4.59. A 20 mL scintillation vial was charged with compound **4.58** (97.0 mg, 0.221 mmol, 1 equiv) and 4.5 mL of a 3:1 MeOH/MeCN mixture (0.05 M). The vial was cooled to 0 °C, then $NaBH_3CN$ (34.8 mg, 0.553 mmol, 2.5 equiv) and AcOH (15.8 μL, 0.276 mmol, 1.25 equiv) were added sequentially. A 37 wt% aqueous solution of formaldehyde (82 μL, 1.1 mmol, 5 equiv) was then added, and the vial was capped and stirred at 0 °C for 30 minutes. The reaction was then warmed to rt and stirred for an additional 2 h, at which point, the solution was diluted with EtOAc, then washed twice with sat. $NaHCO_3$ solution and once with brine. The organic layer was dried over Na_2SO_4, concentrated by rotary evaporation, and the crude material purified by silica gel chromatography (0% to 6% MeOH/CH_2Cl_2) to afford the desired product (67.8 mg, 0.145 mmol, 66%) as a white foam. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.18 (s, 1H), 5.02 (s, 1H), 4.21 (q, *J* = 7.2 Hz, 2H), 4.01 (d, *J* = 6.7 Hz, 1H), 2.62 – 2.38 (m, 3H), 2.31 (m, 1H), 2.28 (s, 6H), 2.08 (dq, *J* = 14.6, 7.2 Hz, 1H), 1.99 (s, 3H), 1.68 (d, *J* = 15.1 Hz, 1H), 1.50 (s, 3H), 1.35 (t, *J* = 7.2 Hz, 3H), 1.03 (t, *J* = 7.4 Hz, 3H), 0.93 (s, 9H), 0.17 (s, 3H), 0.14 (s, 3H). [Note: Due to rapid exchange, the

OH and NH protons are not observed in the ^{1}H NMR.] ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.0, 114.4, 80.8, 79.2, 68.7, 65.7, 57.8, 45.1, 31.9, 26.3, 26.0, 22.9, 22.5, 18.2, 14.7, 8.9, -3.6, -4.6. HRMS (ESI) *m*/*z* calculated for $C_{21}H_{47}N_2O_5SSi$ $[M+H]^+$ 467.2970, found 467.2968.

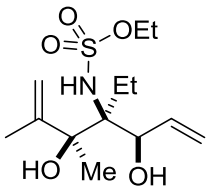


Compound 4.60. A 20 mL scintillation vial was charged with compound **4.59** (65.0 mg, 0.139 mmol, 1 equiv) and 2.1 mL CH_2Cl_2 (0.065 M). mCPBA (36.1 mg, 0.209 mmol, 1.5 equiv) was added in one portion at rt, and the solution was stirred at rt for 20 minutes. The solution was then diluted with CH_2Cl_2 and washed twice with sat. Na_2CO_3 solution, then washed once with brine. The organic layer was dried over Na_2SO_4 and concentrated by rotary evaporation to afford the desired product (64.3 mg, 0.133 mmol, 96%) as a tan solid. The material was pure enough to preclude further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.13 (s, 1H), 5.03 (m, 1H), 4.42 (dd, *J* = 6.0, 4.3 Hz, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 3.55 (dt, *J* = 12.2, 7.2 Hz, 1H), 3.46 (m, 1H), 3.24 (s, 3H), 3.19 (s, 3H), 3.01 (m, 1H), 2.31 – 2.08 (m, 2H), 2.08 – 1.98 (m, 1H), 1.99 (d, *J* = 1.3 Hz, 3H), 1.58 (s, 3H), 1.35 (t, *J* = 7.1 Hz, 3H), 1.06 (t, *J* = 7.4 Hz, 3H), 0.93 (s, 9H), 0.21 (s, 3H), 0.19 (s, 3H). [Note: Due to rapid exchange, the –OH and NH protons were not observed in the 1H NMR.] ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.4, 114.7, 80.4, 76.2, 70.4, 68.9, 66.5, 59.3, 58.6, 29.1, 26.1, 26.1, 24.4, 22.3, 18.4, 14.8, 9.6, -3.2, -4.3. HRMS (ESI) *m*/*z* calculated for $C_{21}H_{47}N_2O_6SSi$ $[M+H]^+$ 483.2919, found 483.2919.

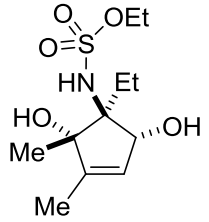


4.61 **4.62**

Compounds 4.61/4.62. A 20 mL scintillation vial was charged with compound **4.60** (50.0 mg, 0.104 mmol, 1 equiv) and 3.0 mL toluene (0.035 M). The vial was capped and heated to 80 °C in an oil bath with stirring for 2.5 h. The resulting yellow solution was concentrated by rotary evaporation and purified by silica gel chromatography (80% CH_2Cl_2/hexanes to 100% CH_2Cl_2) to afford the desired Cope product **4.61** (7.7 mg, 0.018 mmol, 18%) as a colorless oil, and the undesired pyrrolidine **4.62** (6.1 mg, 0.014 mmol, 14%) as a white solid. Compound **4.61** eluted first (R_f = 0.5 in 20% EtOAc/hexanes), and compound **4.62** eluted second (Rf = 0.2 in 20% EtOAc/hexanes). Compound **4.61**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.22 (dt, *J* = 17.0, 9.7 Hz, 1H), 5.84 (s, 1H), 5.35 (app d, *J* = 9.7 Hz, 1H), 5.32 (app d, J = 17.0 Hz, 1H), 5.12 (s, 1H), 5.10 (s, 1H), 4.61 (d, *J* = 9.2 Hz, 1H), 4.47 (s, 1H), 4.22 (m, 2H), 2.16 (m, 1H), 1.97 (m, 1H), 1.95 (s, 3H), 1.58 (s, 3H), 1.35 (t, *J* = 7.1 Hz, 3H), 0.99 (t, *J* = 7.6 Hz, 3H), 0.91 (s, 9H), 0.16 (s, 3H), 0.13 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.6, 137.0, 119.8, 115.4, 80.7, 80.2, 68.3, 66.5, 26.8, 26.1, 22.3, 21.6, 18.2, 14.9, 9.4, -2.4, -4.5. HRMS (ESI) *m*/*z* calculated for $C_{19}H_{40}NO_5SSi$ $[M+H]^+$ 422.2391, found 422.2393. Compound **4.62**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.21 (dd, *J* = 1.4, 0.8 Hz, 1H), 5.00 (p, *J* = 1.4 Hz, 1H), 4.73 (q, *J* = 1.3 Hz, 1H), 4.41 (dd, *J* = 11.7, 7.6 Hz, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 3.48 – 3.25 (m, 2H), 2.51 (m, 1H), 2.37 – 2.15 (m, 2H), 1.99 (dd, *J* = 1.4, 0.8 Hz, 3H), 1.97 – 1.87 (m, 1H), 1.44 (d, *J* = 1.4 Hz, 3H), 1.37 (t, *J* = 7.1 Hz, 3H), 1.01 (t, *J* = 7.3 Hz, 3H), 0.94 (s, 9H), 0.18 (s, 3H), 0.15 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.1, 114.2, 81.1, 77.4, 74.7, 66.5, 47.2, 29.1, 26.5, 25.8, 22.9, 21.8, 18.0, 14.9, 8.6, -4.2, -5.2. HRMS (ESI) *m*/*z* calculated for $C_{19}H_{43}N_2O_5SSi$ $[M+NH_4]^+$ 439.2657, found 439.2647.[10]



Compound 4.63. A 20 mL scintillation vial was charged with compound **4.61** (13.9 mg, 0.0329 mmol, 1 equiv) and 0.66 mL THF (0.05 M). A 1.0 M solution of TBAF (100 μL, 0.1 mmol, 3 equiv) was then added in one portion, and the solution was stirred at rt. After 30 minutes, TLC analysis (20% EtOAc/hexanes, CAM stain) indicated that the starting material was still present, so an addition portion of TBAF was added (200 μL, 0.2 mmol, 6 equiv) and the solution stirred for an additional 20 minutes at rt. The reaction was then diluted with EtOAc and washed twice with sat. NH4Cl and once with brine. The organic layer was dried over Na_2SO_4, concentrated by rotary evaporation, and purified by silica gel chromatography (0% to 30% EtOAc/hexanes) to afford the desired product (9.8 mg, 0.319 mmol, 97%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.28 (ddd, *J* = 17.0, 10.3, 7.5 Hz, 1H), 5.94 (s, 1H), 5.42 (dt, *J* = 17.0, 1.2 Hz, 1H), 5.35 (ddd, *J* = 10.3, 1.2, 0.8 Hz, 1H), 5.17 (bs, 1H), 5.11 (p, *J* = 1.4 Hz, 1H), 4.68 (dd, *J* = 7.5, 3.6 Hz, 1H), 4.22 (m, 2H), 3.42 (s, 1H), 2.44 (d, *J* = 3.6 Hz, 1H), 2.13 – 2.05 (m, 2H), 2.08 (app q, J = 7.6 Hz, 2H), 1.65 (s, 3H), 1.35 (t, *J* = 7.1 Hz, 3H), 1.00 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.6, 135.9, 119.5, 115.1, 80.8, 76.2, 68.4, 66.7, 27.1, 22.8, 21.5, 14.9, 9.5. HRMS (ESI) *m*/*z* calculated for $C_{13}H_{26}NO_5S$ $[M+H]^+$ 308.1527, found 308.1531.



Compound 4.64. In a N_2-filled glovebox, a ½-dram vial was charged with Grubbs Catalyst, 2nd generation (0.8 mg, 0.001 mmol, 0.15 equiv). The vial was removed from the glovebox, then a solution of compound **4.63** (2.0 mg, 0.0065 mmol, 1 equiv) in 0.2 mL $CDCl_3$ was added, and the vial was stirred at rt. After 15 min, TLC analysis (30% EtOAc/hexanes, CAM stain) indicated that the starting material was unreacted, so the vial was heated to 35 °C in an oil bath for 1 h, at which point TLC indicated completion. The crude material was purified by silica gel chromatography (0% to 50% EtOAc/hexanes) to afford the desired aminocyclitol **4.64** (1.2 mg, 0.0043 mmol, 66%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.41 (m, 1H), 4.77 (m, 1H), 4.64 (s, 1H), 4.25 (m, 2H), 2.58 (d, *J* = 5.2 Hz, 1H), 2.08 (s, 1H), 2.02 (m, 2H), 1.74 (t, *J* = 1.6 Hz, 3H), 1.40 (t, *J* = 7.1 Hz, 3H), 1.27 (s, 3H), 0.98 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.9, 125.4, 84.5, 78.2, 76.4, 67.4, 24.4, 23.2, 14.8, 11.8, 11.6. HRMS (ESI) *m*/*z* calculated for $C_{11}H_{25}N_2O_5S$ $[M+NH_4]^+$ 297.1479, found 297.1480.

4.6.4. References for experimental section

1. Armarego, W.L.F.; Chai, C.L.L. *Purification of Laboratory Chemicals* 6th ed., Elsevier: Burlington, MA, 2009.
2. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
3. Stoll, A. H.; Blakey, S. B. *J. Am. Chem. Soc.* **2010**, *132*, 2108-2109.
4. Fiori, K. F.; Espino, C. G.; Brodsky, B. H.; Du Bois, J. *Tetrahedron* **2009**, 3042-3051.
5. Rigoli, J. W. Allene Functionalization *via* Bicyclic Methylene Aziridines: Development of Methods for the Synthesis of Heteroatom Stereotriads, Discover of Dynamic Ag Catalysis, and Applications Toward the Total Synthesis of Jogyamycin. Ph.D. Thesis, University of Wisconsin – Madison, Madison, WI, 2014.
6. Murray, R. W.; Singh, M. *Org. Synth.* **1997**, *74*, 91; **1998**, Coll. Vol. *9*, 288.

7. Gibert, M.; Ferrer, M.; Sanchez-Baeza, F.; Messeguer. A. *Tetrahedron* **1997**, *53*, 8643.

8. Masui, Y.; Watanabe, H.; Masui, T. *Tetrahedron Letters* **2004**, *45*, 1853-1856.

9. Kurokawa, T.; Kim, M.; Du Bois, J. *Angew. Chem. Int. Ed.* **2009**, *48*, 2777-2779.

10. The primary peak observed by electrospray ionization (ESI) was a dehydrated species $[M-H_2O+H]^+$; however, the $[M+NH_4]^+$ and $[M+Na]^+$ peaks were clearly visible as minor species. Dehydration was assumed to occur thermally under the ionization conditions (it was not observed by NMR).

Chapter 5

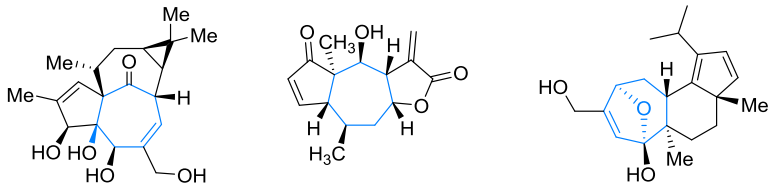
Stereocontrolled Cycloheptene Synthesis by Intermolecular [4 + 3] Cycloadditions of Methylene Aziridines

The work described in this chapter was carried out in collaboration with Nels C. Gerstner.

5.1. Introduction

Densely functionalized seven-membered rings are valuable synthetic targets that commonly occur in a range of natural products with intriguing biological activities (Figure 5.1). The long-standing challenge of controlling the stereochemical outcome in the synthesis of seven-membered rings has given rise to a variety of creative approaches towards this goal, including annulations, ring-closing metatheses and an array of cycloaddition reactions.[1] A particularly powerful strategy involves the [4 + 3] cycloaddition of a diene with a suitable three-carbon coupling partner; similar to the venerable Diels-Alder reaction, potential exists for the stereocontrolled formation of four new stereocenters and rapid assembly of significant skeletal complexity from simple building blocks.[2,3]

Figure 5.1. Cycloheptane-containing bioactive molecules.



Ingenol
anticancer, anti-HIV

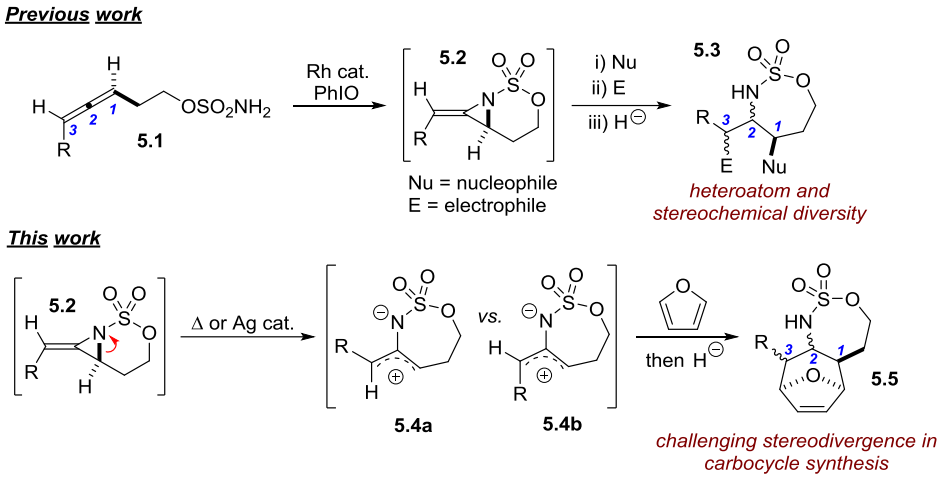
Helenalin
inhibits telomerase
anti-inflammatory, anti-tumor

allocyathin B_3
stimulates nerve growth

Oxyallyl cations are well-precedented coupling partners in [4 + 3] cycloadditions; however, the use of the analogous amidoallyl cations, typically generated from α-chloroenamines or α-chloroimines, is far less common.[3-5] This is unfortunate, as amine functionalities often impart interesting and potentially tunable biological activities to molecules. Our group has been engaged in developing highly chemo-, regio- and stereocontrolled oxidative allene amination reactions (Scheme 5.1) to transform **5.2** into a diverse array of amine stereotriads **5.3** with control over both the identity and relative stereochemistry of the heteroatoms at C1-3.[6] We surmised that an alternative ring-opening of the C-N bond of **5.2** could be promoted using either heat or Lewis acids

to give 2-amidoallyl cations **5.4a** and **5.4b** (Scheme 5.1), which could undergo an intermolecular reaction with furan, followed by subsequent reduction, to yield a scaffold **5.5** containing five adjacent stereogenic carbons.[7] Diastereocontrolled reaction of the remaining alkene could presumably lead to a fully substituted cycloheptane core in a few straightforward steps.

Scheme 5.1. Stereochemical diversity *via* allene aziridination.

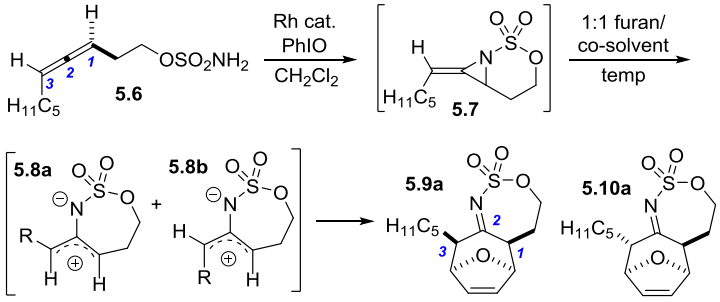


Two recent reports by Shipman and Robertson describe the use of methylene aziridines as 2-amidoallyl cation precursors for [4 + 3] cycloadditions, but these reactions were intramolecular in nature, did not typically retain nitrogen in the product and exhibited a lack of tunability in the relative stereochemistries of the newly formed asymmetric centers.[4c,d] Our work sought to advance this chemistry in three major ways: 1) achieve intermolecular [4 + 3] cycloadditions of 2-amidoallyl cations obtained *via* allene aziridination, 2) determine if the stereodiversity previously seen in our allene amination chemistry could be extended to the syntheses of all four possible C1-3 diastereomers of **5.5**, and 3) explore further manipulations of aminated cycloheptene scaffolds as useful tools for preparing nitrogenated analogues of bioactive natural products.

5.2. Results and Discussion

Table 5.1 illustrates our initial efforts to convert **5.6a** to the imines **5.9a** and **5.10a** through the intermediacy of **5.8a** and **5.8b**. Solvents including CH_2Cl_2, EtOAc and benzene were not effective at room temperature (see Experimental Details); however, a 1:1 THF/furan mixture successfully transformed **7a** (generated *in situ* from **6a**) to the *endo* [4+3] adduct **9a**, containing a *syn* relationship between the C1 and C3 substituents. Increasing the temperature to 50 °C broadened the range of solvents capable of converting **5.6a** to imines **5.9a** or **5.10a** (Table 5.1, right). Interestingly, while the polar aprotic solvents $MeNO_2$ and MeCN also yielded an *endo* mode of cyclization, imine **5.10a** containing a 1,3-*anti* relationship was the major product; the relative stereochemistries of **5.9a** and **5.10a** were determined by X-ray crystallography. An increase in the yield of **5.10a** to 45% over the two steps was observed when the reaction was heated to 65 °C in $MeNO_2$, albeit with slightly lower *dr*.

Table 5.1. Solvent screen for the formal [4 + 3] cycloaddition.



co-solvent	% yield at 24 h, rt[a,b]	% **7a**	**5.9a**: **5.10a**	% yield at 24 h, 50 °C[b]	% **7a**	**5.9a**: **5.10a**
none	0	77	-	-	0	-
THF	**35**	**26**	**> 20:1**	**31**	**0**	**>10:1**
Et_2O	0	69	-	7	0	>10:1
dioxane	0	75	-	17	0	>10:1
MeCN	0	44	-	21	0	~1:3
$MeNO_2$[c]	**0**	**53**	-	**31**	**0**	**<1:10**
CF_3CH_2OH	0	0	-	26	0	<1:10

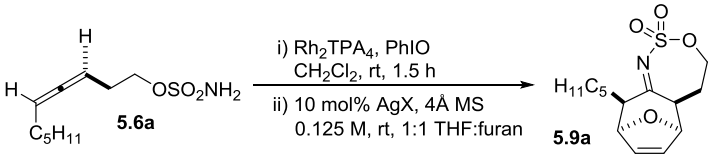
[a]Reactions at rt performed in sealed vials. [b]Yields and *dr* determined by ^1H NMR with an internal trimethoxybenzene standard. [c] When run at 65 °C for 7 h, the yield was 45% with a ~1:6 ratio of **9a**:**10a**.

The differing stereochemical outcomes using THF or $MeNO_2$ were intriguing; control experiments showed that neither **5.9a** nor **5.10a** underwent facile epimerization of the C3

stereocenter. Shimizu and coworkers have previously noted solvent effects on the dr of [4 + 3] cycloadditions of 2-oxyallyl cations.[8] $MeNO_2$ yielded 1,3-*syn* products, while THF:Et_2O favored a 1,3-*anti* relationship; however, the diastereoselectivities were quite poor in both cases, on the order of 2:1. We hypothesize that the high *dr* for the *anti* **5.10a** in our chemistry results from a rapid and concerted cycloaddition process, while the use of ethereal solvents permits the 2-amidoallyl cation **5.8b** to equilibrate to the more stable conformer **5.8a** in order to relieve $A_{1,3}$ strain, thus resulting in the observed syn product **5.9a**.

A variety of Lewis acids were explored to improve the [4 + 3] reaction, including Fe, Ti, Ce, Ni and Cu salts (see Experimental Details), but no improvements were noted. However, AgOTf accelerated the reaction rate with only a moderate decrease in yield (Table 5.2, entries 1-2). More coordinating counterions (entries 3-4) reduced the yields, while non-coordinating anions (entries 5-8) were slightly better than triflate. A 10 mol% loading of $AgPF_6$ proved best, while heating the reaction to 40 °C further increased the yield of the two-step process to 45% from **5.6a** (entry 11). A control experiment with *n*-Bu_4NPF_6 demonstrated that the silver cation was necessary for catalysis (entry 12). Reactions carried out in $MeNO_2$ did not benefit from added Lewis acids and simple thermal conditions were employed with this solvent.

Table 5.2. Silver catalysts for the [4 + 3] cycloaddition.



entry	catalyst	time (h)	yield	entry	catalyst	time (h)	yield
1	AgOTf	6	32%	7[b]	AgBArF	3.5	36%
2[a]	AgOTf	53	30%	8	$AgPF_6$	7	35%
3	AgOAc	11	21%	9[c]	$AgPF_6$	4	29%
4	AgTFA	8	23%	10[d]	$AgPF_6$	11	35%
5	$AgSbF_6$	8	36%	11[e]	$AgPF_6$	3.5	45%
6	$AgClO_4$	9	34%	12	(*n*-Bu)$_4NPF_6$	24	30%

[a] Reaction run at -5 °C. [b] BArF = $B[C_6H_3\text{-}3,5\text{-}(CF_3)_2]_4$. [c] 0.2 equiv. $AgPF_6$. [d] 0.05 equiv. $AgPF_6$ [e] Run at 40 °C.

With the 1,3-*syn* and 1,3-*anti endo* diastereomers **5.9a** and **5.10a** in hand, general conditions for stereocontrolled reduction of both imines needed to be established. Tunable reduction of the 1,3-*syn* imine obtained from THF/furan (Scheme 5.2, Condition A) proved straightforward: bulky borohydrides favored equatorial reduction from the face opposite the alkene bridge to give the all *syn* triads, while smaller borohydrides ($NaBH_3CN$) gave the 1,2-*anti*:2,3-*anti* diastereomers. In the case of the 1,3-*anti* imine (Condition B), the axial R substituent blocked the bottom face of the imine, and both $NaBH_3CN$ or $LiBHEt_3$ resulted in the 1,2-*anti*:2,3-*syn* triad. However, the use of $AlH_3{\cdot}Me_2NEt$ yielded the final 1,2-*syn*:2,3-*anti* isomer, possibly *via* chelation to the oxygen bridge of the [3.2.1] bicycle or to one of the sulfur-bound oxygens of the sulfamate.

Scheme 5.2. Conditions for stereodivergent imine reduction.

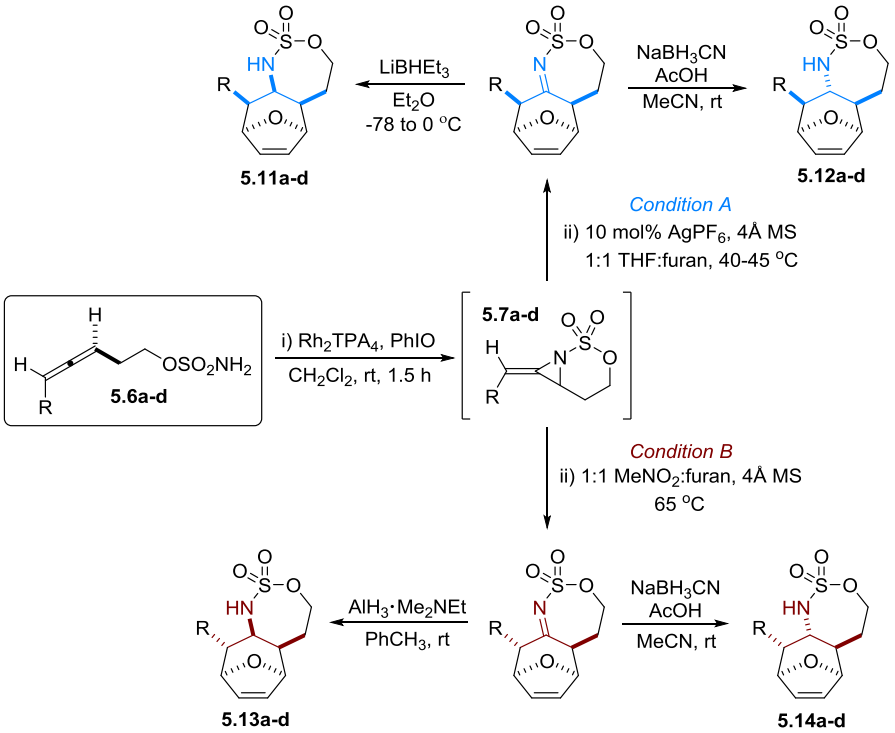
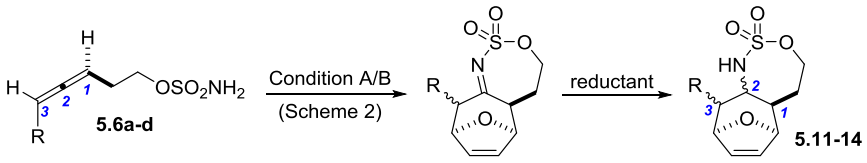
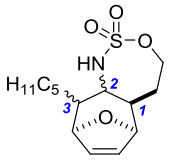
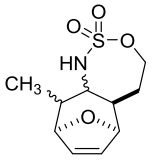
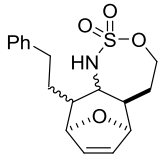
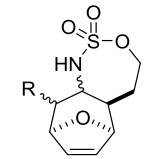


Table 5.3 illustrates the application of the conditions outlined in Scheme 2 to a survey of homoallenic sulfamates **5.6a-d**. Although the overall yields are modest, the three-step process can be carried out in a single pot, with good to average yields-per-step (shown in parenthesis in Table

5.3), and the conditions are amenable to multi-gram scale in order to obtain substantial quantities of products. The pentyl side chain of **5.6a** resulted in good to excellent *dr*'s for all four diastereomeric products **5.11a**-**5.14a**, with yields-per-step ranging from 67% to 74%. The smaller methyl substituent of **5.6b** afforded comparable and often superior diastereoselectivities, although the yields were consistently lower due to the decreased stability of the intermediate methylene aziridine. The stereodivergent reaction conditions were shown to tolerate the tethered phenyl group of **5.6c**, as well as the TBDPS-protected alcohol of **5.6d**, although the $AlH_3 \cdot Me_2NEt$ conditions led to decomposition in the attempted synthesis of [4 + 3] adduct **5.13d**.

Table 5.3. One-pot, stereodivergent synthesis of aminated cycloheptenes.

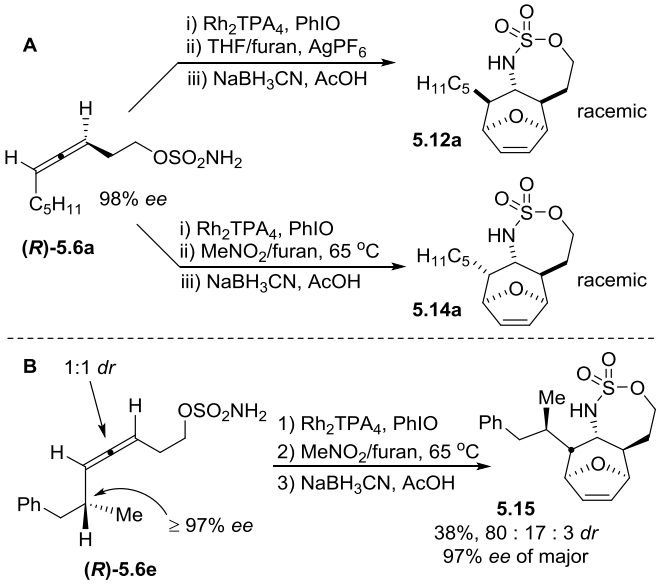


substrate	product	diastereomer	yield (yield/step)	*dr*
5.6a		1,2-*syn*:2,3-*syn* **(5.11a)**[a]	39% (73%)	**10** : 1
		1,2-*anti*:2,3-*anti* **(5.12a)**[b]	41% (74%)	**16** : 1
		1,2-*syn*:2,3-*anti* **(5.13a)**[c]	30% (67%)	**4.9** : 1.1 : 1
		1,2-*anti*:2,3-*syn* **(5.14a)**[d]	41% (74%)	**4.7** : 1
5.6b		1,2-*syn*:2,3-*syn* **(5.11b)**	20% (58%)	**15** : 1
		1,2-*anti*:2,3-*anti* **(5.12b)**	26% (64%)	**10** : 1
		1,2-*syn*:2,3-*anti* **(5.13b)**	29% (66%)	**54** : 11 : 1
		1,2-*anti*:2,3-*syn* **(5.14b)**	33% (69%)	**6.7** : 1
5.6c		1,2-*syn*:2,3-*syn* **(5.11c)**	22% (60%)	**7.5** : 1
		1,2-*anti*:2,3-*anti* **(5.12c)**	29% (66%)	**3.2** : 1
		1,2-*syn*:2,3-*anti* **(5.13c)**	23% (61%)	**12** : 2.4 : 2 : 1
		1,2-*anti*:2,3-*syn* **(5.14c)**	46% (77%)	**4.3** : 1
5.6d	 R = $(CH_2)_4OTBDPS$	1,2-*syn*:2,3-*syn* **(5.11d)**	34% (70%)	**12** : 1
		1,2-*anti*:2,3-*anti* **(5.12d)**	46% (77%)	**18** : 1
		1,2-*syn*:2,3-*anti* **(5.13d)**	<5%	*n/a*
		1,2-*anti*:2,3-*syn* **(5.14d)**	52% (80%)	**4.3** : 1

[a]1,3-*syn*-imine, reduction with $LiBHEt_3$. [b]1,3-*syn*-imine, reduction with $NaBH_3CN$. [c]1,3-*anti*-imine, reduction with AlH_3NMe_2Et. [d]1,3-*anti*-imine, reduction with $NaBH_3CN$.

In our previous work, aziridination and subsequent functionalization of enantioenriched allenes gave complete transfer of axial to point chirality.[6a,c] However, the proposed intermediacy of an amidoallyl cation in the [4 + 3] reaction was expected to preclude this chirality transfer. Indeed, racemic product was obtained in both THF and $MeNO_2$ using enantioenriched **(*R*)-5.6a** (Scheme 5.3A). However, the racemization of the allene could be used to advantage. For example, the two diastereomers of allene **5.6e**, epimeric in the stereochemistry of the allene but bearing a stereodefined carbon adjacent to the allene, could be reacted in a stereoconvergent manner to obtain **5.15** as the major diastereomer in excellent *ee* (Scheme 5.3B).

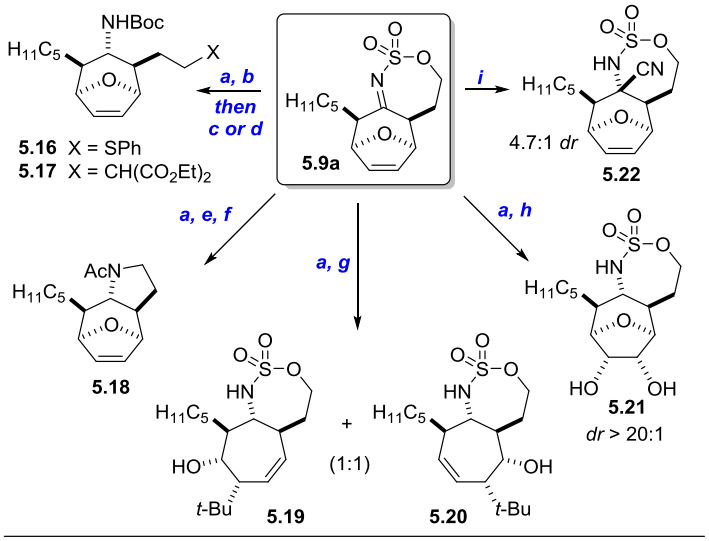
Scheme 5.3. Racemic and enantioenriched cycloheptenes via [4 + 3] reactions.



The cycloheptane products from the tandem allene aziridination/formal [4 + 3] cyclization were envisaged to function as flexible scaffolds for further diversification, as the imine **5.9a** (Scheme 5.4) has multiple reactive functional handles that can be manipulated before or after reduction of the imine. For example, reduction of **5.9a** and activation of the sulfamate *via* Boc-protection is followed by nucleophilic displacement with thiophenol or diethyl malonate to yield **5.16** and **5.17**, respectively, in good yields.[11,12] Activation of the sulfamate by acetate protection

and double displacement by NaI yielded pyrrolidine **5.18** in excellent yield.[13] Such nucleophilic displacements provide access to cycloadducts with differentially substituted side chains at C1 and C3, which is a challenge for conventional [4+3] cycloadditions that utilize symmetrical dienophiles.[8] The ether bridge can be cleaved in an S_N2' fashion using *t*-BuLi as a nucleophile, resulting in a 1:1 mixture of regioisomers **5.19** and **5.20**.[14] Dihydroxylation of the alkene yields **5.21** in high *dr*, with OsO_4 approaching from the less hindered face of the alkene to yield a cycloheptane with seven contiguous stereocenters set in high *dr* over four steps from **5.6a**.[15] Carbon nucleophiles also add to the imine **5.9a**, as evidenced by a Strecker reaction that affords **5.22** in high yield and good *dr*.

Scheme 5.4. Synthetic utility of cycloheptene products.



a: $NaBH_3CN$, AcOH, MeCN; 41%, 16:1 *dr* from **5.6a**. ***b***: Boc_2O, cat. DMAP, Et_3N, CH_2Cl_2, rt. ***c***: thiophenol, K_2CO_3, CH_3CN, rt; 75% from **5.12a**. ***d***: diethyl malonate, TBAB, Cs_2CO_3, MeCN, rt; 58% from **5.12a**. ***e***: KO*t*-Bu, DMAP, CH_2Cl_2, 0 °C, then Ac_2O, rt; 96%. ***f***: NaI, DMF, 60 °C, then NaH, 40 to 60 °C; 83%. ***g***: *t*-BuLi, THF, -40 °C; 61% of a 1:1 mixture of regioisomers. ***h***: 10 mol% OsO_4, NMO, acetone, H_2O, *t*-BuOH, rt; 65%, >20:1 *dr*. ***i***: *n*-Bu_4NCN, MeCN, rt; 80% yield from **5.9a**.

5.3. Conclusions

In conclusion, we have described the first examples of intermolecular formal [4 + 3] cycloadditions that occur *via* the intermediacy of a 2-amidoallyl cation arising from a bicyclic

methylene aziridine. A key advantage of employing allenes as substrates is the ability to manipulate the stereochemistry of the amidoallyl cation, leading to stereodivergent syntheses of all four possible diastereomeric cycloheptenes resulting from *endo* cyclization. The rich functional group diversity of these products enables their transformation into an array of densely functionalized synthetic building blocks in a few simple steps. While the stereoablative nature of the chemistry prevents direct transfer of axial to point chirality, the presence of an additional stereocenter can be employed to yield enantioenriched and densely functionalized aminated carbocycles. Future work is focused on expanding the scope of both allenes and coupling partners, as well as applying this methodology to the syntheses of aminated analogues of bioactive natural products.

5.4. References

1. For selected reviews on the synthesis of seven-membered carbocycles, see: (a) Nguyen, T. V.; Hartmann, J. M.; Enders, D. *Synthesis* **2013**, *45*, 845. (b) Battiste, M. A.; Pelphrey, P. M.; Wright, D. L. *Chem. Eur. J.* **2006**, *12*, 3438. (c) Pellissier, H. *Adv. Synth. Catal.* **2011**, *353*, 189. (d) Foley, D. A.; Maguire, A. R. *Tetrahedron* **2010**, *66*, 1131.
2. For reviews dedicated to [4+3] cycloadditions, see: (a) Hartung, I. V.; Hoffmann, H. M. R. *Angew. Chem. Int. Ed.* **2004**, *43*, 1934. (b) Harmata, M. *Acc. Chem. Res.* **2001**, *34*, 595. (c) Harmata, M.; *Chem. Comm.* **2010**, *46*, 8886. (d) Hoffmann, H. M. R. *Angew. Chem. Int. Ed.* **1984**, *23*, 1.
3. For selected reviews on the use of heteroatom-substituted allyl cations in [4+3] cycloadditions, see: a) Lohse, A. G.; Hsung, R. P. *Chem. Eur. J.* **2011**, *17*, 3812. b) Harmata, M. *Chem. Comm.* **2010**, *46*, 8904.

4. a) Kende, A. S.; Huang, H. *Tetrahedron Lett.* **1997**, *38*, 3353. b) Schmid, R.; Schmid, H. *Helv. Chim. Acta.* **1981**, *64*, 813. c) Robertson, J.; Feast, G. C.; White, L. V.; Steadman, V. A.; Claridge, T. D. W. *Org. Biomol. Chem.* **2010**, *8*, 3060. d) Prié, G.; Prévost, N.; Twin, H.; Fernandes, S. A.; Hayes, J. F.; Shipman, M. *Angew. Chem. Int. Ed.* **2004**, *43*, 6517.

5. For other recent examples of reactions believed to occur through the intermediacy of 2-amidoallyl cations, see: a) Stoll, A. H.; Blakey, S. B. *Chem. Sci.* **2011**, *2*, 112. b) Stoll, A. H.; Blakey, S. B. *J. Am. Chem. Soc.* **2010**, *132*, 2108. c) Thorton, A. R.; Martin, V. I.; Blakey, S. B. *J. Am. Chem. Soc.* **2009**, *131*, 2434.

6. Adams, C. S.; Grigg, R. D.; Schomaker, J. M. *Chem. Sci.* **2014**, *5*, 3046. b) Adams, C. S.; Grigg, R. D.; Schomaker, J. M. *Tetrahedron* **2014**, *70*, 4128. c) Adams, C. S.; Boralsky, L. A.; Guzei, I. A.; Schomaker, J. M. *J. Am. Chem. Soc.* **2012**, *134*, 10807.

7. For selected examples of generating 2-oxaallyl cations from allenes and their use in [4+3] cycloadditions, see: a) Fernández, I.; Mascareñas, J. L. *Org. Biomol. Chem.* **2012**, *10*, 699. b) Xiong, H.; Hsung, R. P.; Berry, C. R.; Rameshkumar, C. *J. Am. Chem. Soc.* **2001**, *123*, 7174. c) Huang, J.; Hsung, R. P. *J. Am. Chem. Soc.* **2005**, *127*, 50. d) Lohse, A. G.; Hsung, R. P.; Leider, M. D.; Ghosh, S. K. *J. Org. Chem.* **2011**, *76*, 3246.

8. Shimizu, N.; Tanaka, M.; Tsuno, Y. *J. Am. Chem. Soc.* **1982**, *104*, 1330.

9. For examples of stereocenters adjacent to either the diene or the 2-oxaallyl cation affecting the diastereoselectivity of the [4+3] cycloaddition, see: a) Giguere, R. J.; Tasseley, S. M.; Tose, M. I. *Tetrahedron Lett.* **1990**, *31*, 4577. b) Lautens, M.; Aspiotis, R.; Colucci, J. *J. Am. Chem. Soc.* **1996**, *118*, 10930. c) Chung, W. K.; Lam, S. K.; Lo, B.; Liu, L. L.; Wong, W.-T.; Chiu, P. *J. Am. Chem. Soc.* **2009**, *131*, 4556. d) Cho, S. Y.; Lee, J. C.; Cha, J. K. *J. Org. Chem.* **1999**, *64*, 3394. e) Harmata, M.; Rashatasakhon, P. *Org. Lett.* **2000**, *2*, 2913.

e) Stark, C. B. W.; Eggert, U.; Hoffmann, H. M. R. *Angew. Chem. Int. Ed.* **1998**, *37*, 1266. f) Harmata, M.; Jones, D. E.; Kahraman, M.; Sharma, U.; Barnes, C. L. *Tetrahedron Lett.* **1999**, *40*, 1831. f) Montaña, A. M.; Grima, P. M. *Tetrahedron Lett.* **2002**, *43*, 2017.

10. The relative stereochemistry of the product was determined using NOE studies (see Experimental Details).
11. For an example of thiophenol cleaving a sulfamate, see: Duran, F.; Leman, L.; Ghini, A.; Burton, G.; Dauban, P.; Dodd, R. H. *Org. Lett.* **2002**, *4*, 2481.
12. For examples of 1,3-dicarbonyls being used to cleave sulfamates, see: a) Bower, J. F.; Švenda, J.; Williams, A. J.; Charmant, J. P. H.; Lawrence, R. M.; Szeto, P.; Gallagher, T. *Org. Lett.* **2004**, *6*, 4727. b) Moss, T. A.; Alonso, B.; Fenwick, D. R.; Dixon, D. J. *Angew. Chem. Int. Ed.* **2010**, *49*, 568.
13. For examples of SO_3-extrusion and pyrolidine formation, see ref. [6a] and Thorton, A. R.; Martin, V. I.; Blakey, S. B. *J. Am. Chem. Soc.* **2009**, *131*, 2434.
14. Lautens, M.; Abd-El-Aziz, A. S.; Lough, A. *J. Org. Chem.* **1990**, *55*, 5305.
15. He, S.; Hsung, R. P.; Presser, W. R.; Ma, Z.-X.; Haugen, B. J. *Org. Lett.* **2014**, *16*, 2180.

5.5. Experimental Details

5.5.1. General information

All glassware was either oven dried at 130 ^{o}C overnight, or flame dried under vacuum and purged with nitrogen before use. All glassware was then allowed to cool to rt in a desiccator filled with Drierite as a desiccant or under nitrogen after placing under vacuum. Unless otherwise specified, reagents were used as obtained from the vendor without further purification. Diethyl ether was freshly distilled from a Na/benzophenone ketyl. Tetrahydrofuran was either freshly

distilled from a Na/benzophenone ketyl or passed through an alumina column before use. Dichloromethane was either dried over CaH_2 and freshly distilled before use or passed through an alumina column before use. Acetonitrile, toluene and benzene were all dried over CaH_2 and freshly distilled before use. All other solvents were purified using accepted procedures from the sixth edition of "Purification of Laboratory Chemicals".[1] Air- and moisture- sensitive reactions were performed using standard Schlenk Techniques under an atmosphere of nitrogen. Analytical thin layer chromatography (TLC) was performed using pre-coated silica gel 60 F_{24} plates containing a fluorescent indicator. Either $KMnO_4$ or ceric ammonium molybdate (CAM stain) were used to visualize the reaction products. Preparative chromatography for most compounds, unless otherwise specified, was performed using SilicaFlash P60 silica gel (230-400 mesh) via Still's method.[2] Some specified separations required the use of Davisil Grade 635 silica gel (pore size 60 Å, 60-100 mesh, available from Sigma Aldrich) for satisfactory separation. Unless stated otherwise, columns were typically run using a gradient method using EtOAc/hexanes.

^{1}H NMR and ^{13}C NMR spectra were obtained using Bruker AC+ 300a, Varian MercuryPlus 300, and Bruker Avance-500 spectrometers. For ^{1}H NMR, chemical shifts are reported relative to the tetramethylsilane peak (δ 0.00 ppm), except in DMSO-d_6 where the chemical shifts are reported relative to the residual proteo solvent (2.50 ppm). ^{13}C NMR spectra were measured at 125 MHz on the same instruments noted above for recording ^{1}H NMR spectra. Chemical shifts are reported relative to the solvent residual proteo solvent (δ 77.16 ppm for $CDCl_3$, 128.06 ppm for C_6D_6, and 39.50 ppm for $(CD_3)_2SO$). High-pressure liquid chromatography (HPLC) analyses were performed at 215 and 225 nm using a Shimadzu HPLC, Model LC-20AB. Further details are given in Section IX. Accurate mass measurements were acquired at the University of Wisconsin, Madison using a Micromass LCT (electrospray ionization, time-of-flight analyzer or electron impact methods). The

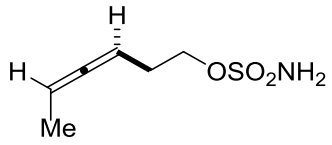
NMR and Mass Spectrometry facilities are funded by the NSF (CHE-1048642, CHE-0342998, CHE-9304546 and CHE-9208463), the University of Wisconsin as well as a generous gift by Paul J. Bender.

5.5.2. Synthesis of homoallenic sulfamates

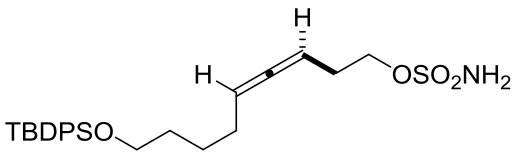
Sulfamates were synthesized from the corresponding alcohol according to the procedure of Du Bois and coworkers.[3] An oven dried 2- or 3-necked round bottom flask with stir bar is placed under nitrogen and charged with chlorosulfonyl isocyanate (2 equiv.) and then cooled to 0 ^{o}C. Formic acid (2 equiv.) is then added dropwise to the flask, with vigorous evolution of gas observed. Within 5 min. a white solid forms, and then MeCN (0.5 M with respect to the homoallenic alcohol) is then added. The solution is then removed from the ice bath and allowed to stir for at least 4 hours, but generally overnight. The mixture is then cooled to 0 ^{o}C again and a solution of homoallenic alcohol (1 equiv.) in *N*,*N*-dimethylacetamide (same volume as MeCN) is added via syringe. The reaction is allowed to warm to room temp and stirred for 1-1.5 h (Note: reaction can be monitored by TLC but the starting material and product often have the same R_f values. The reaction is likely done sooner, but the difficulty of separating the starting material and products means that letting the reaction go longer to ensure the complete consumption of the starting material is often advantageous). After the reaction was complete, the reaction was quenched with H_2O (roughly the same volume as MeCN) and the resulting aqueous layer was extracted 3x with Et_2O. The combined organics were then washed 5-10 times with H_2O (~1/5th of volume of original volume of water used to quench reaction), and then washed once more with brine. The organics were then dried with $MgSO_4$ and the solvent was removed under reduced pressure at rt. The crude mixture is then purified by silica gel chromatography, eluting with a gradient of Et_2O and either hexanes or pentanes (Note: EtOAc can also be used, but it is much easier to remove Et_2O from the

viscous product). The solvent was then removed *in vacuo* at rt, yielding the sulfamate as a colorless oil (Note: The solvent must be removed below 30 ^{o}C as at higher temperatures decomposition of the product starts to take place. The material that is heated above 30-35 ^{o}C will appear pure by ^{1}H or ^{13}C NMR but will be a darker yellow instead of a clear oil. This material will react in the aziridination, but result in lower yields. This minor decomposition product can be removed by re-purifying by silica gel chromatography). The purified product is then stored at either 0 ^{o}C for about a month before repurification is necessary or at -78 ^{o}C for extended periods of time.

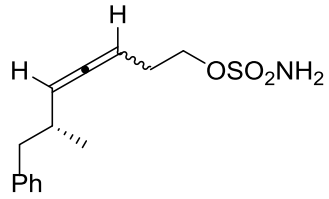
Compounds 5.6a and **5.6c** have previously been prepared in this manner and spectral data was consistent with the reported values.[4]



Compound 5.6b. Following the general procedure, 11.25 ml (101.7 mmol) of the homoallenic alcohol yielded, after chromatography (20 to 50% Et_2O/pentanes), 15.76 g (88.93 mmol, 87%) of **5.6b** as an clear oil that solidified as a white solid upon cooling in a freezer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.15 (tp, *J* = 6.8, 2.9 Hz, 1H), 5.06 (qq, *J* = 6.5, 3.2 Hz, 1H), 4.76 (bs, 2H), 4.26 (t, *J* = 6.8 Hz, 2H), 2.43 (qd, *J* = 6.7, 2.8 Hz, 2H), 1.66 (dd, *J* = 7.0, 3.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 205.69, 87.22, 85.10, 70.62, 28.47, 14.44. HRMS (ESI) *m*/*z* calculated for $C_6H_{15}N_2O_3S$ [M + NH_4^+] 195.0799, found 195.0798.



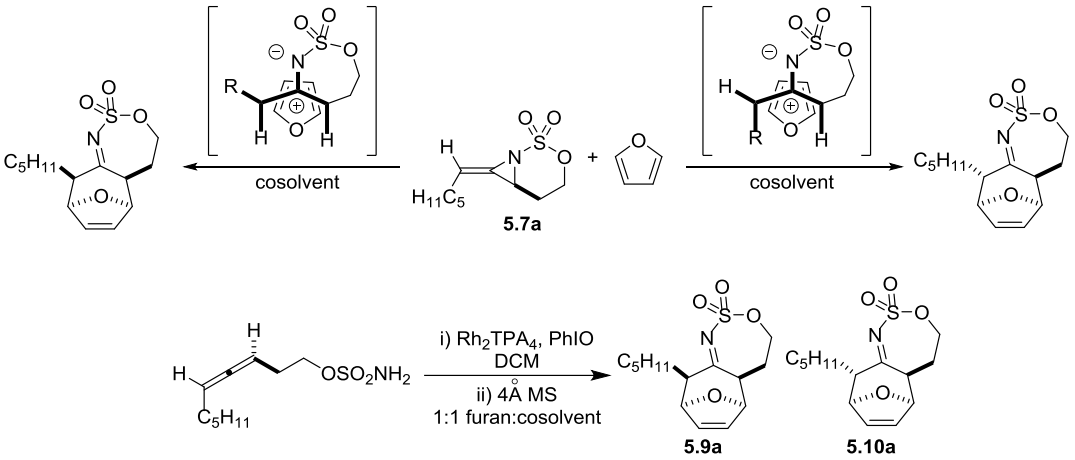
Compound 5.6d. Following the general procedure, 2.92 g (7.40 mmol) of the homoallenic alcohol yielded, after chromatography (10 to 50% Et_2O/hexanes), 2.07 g (4.36 mmol, 59%) of homoallenic alcohol **5.6d** . ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 – 7.63 (m, 4H), 7.39 (m, 6H), 5.16 (qt, *J* = 6.5, 3.0 Hz, 1H), 5.08 (qt, *J* = 6.4, 3.1 Hz, 1H), 4.62 (s, 2H), 4.23 (t, *J* = 6.8 Hz, 2H), 3.68 (t, *J* = 6.3 Hz, 2H), 2.42 (qd, *J* = 6.7, 2.9 Hz, 2H), 1.99 (qd, *J* = 7.0, 3.1 Hz, 2H), 1.68 – 1.40 (m, 4H), 1.05 (s, *J* = 1.1 Hz, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.89, 135.69, 135.69, 134.19, 134.19, 129.71, 129.71, 127.76, 127.76, 92.48, 85.88, 70.54, 63.96, 32.11, 28.61, 28.47, 27.05, 25.38, 19.40. HRMS (ESI) *m*/*z* calculated for $C_{25}H_{36}NO_4SSi$ [M + H^+] 474.2129, found 474.2126.



Compound 5.6e. Following the general procedure, 0.982 g (4.85 mmol) of the enantioenriched alcohol as a 1:1 mixture of diastereomers yielded, after silica gel chromatography (10 to 50% Et_2O/hexanes), 1.136 g (4.04 mmol, 83% yield) of **5.6e** as an inseprable 1:1 mixture of diastereomers . ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.27 (m, 4H), 7.23 – 7.18 (m, 2H), 7.16 (dt, *J* = 8.2, 1.2 Hz, 4H), 5.22 (tt, *J* = 5.8, 2.9 Hz, 1H), 5.15 (tt, *J* = 6.3, 2.7 Hz, 1H), 5.09 (m, 2H), 4.66 (m, 4H), 4.17 (m, 2H), 4.12 (m, 2H), 2.70 (dd, *J* = 13.5, 7.0 Hz, 1H), 2.52 – 2.42 (m, 2H), 2.38 (qd, *J* = 6.7, 2.9 Hz, 2H), 2.30 (m, 2H), 1.03 (d, *J* = 6.7 Hz, 3H), 1.00 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 203.92, 203.84, 140.80, 140.59, 129.38, 129.38, 128.32, 128.29, 126.07, 126.05, 98.01, 97.79, 87.08, 86.81, 70.57, 70.51, 43.69, 43.36, 35.55, 34.68, 28.60, 28.55, 20.24, 19.87. HRMS (ESI) *m*/*z* calculated for $C_{14}H_{23}N_2O_3S$ [M + NH_4^+] 299.1424, found 299.1427. HPLC/SFC analysis is shown in Section VIII.

5.5.3. Selected optimization

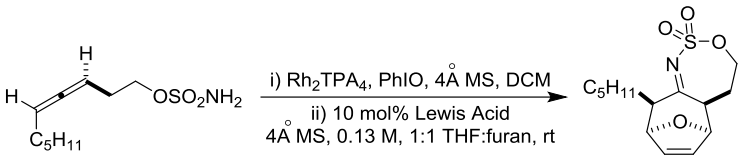
Table 5.4. Optimization of solvent conditions.



cosolvent	% yield at 24 h, rt	% **7a**	**9a:10a**	% yield at 24 h, 50 °C	% **7a**	**9a:10a**
none	0	77	-	12	0	~1:2
CH_2Cl_2	0	70	-	22	0	~1:2
EtOAc	0	63	-	14	0	~1:1
PhH	0	64	-	11	0	~1:2
toluene	0	72	-	10	0	~1:2
THF	**35**	**26**	**> 20:1**	**31**	**0**	**>10:1**
Et_2O	0	69	-	7	0	>10:1
dioxane	0	75	-	17	0	>10:1
MeCN	0	44	-	21	0	~1:3
$MeNO_2$	**0**	**53**	-	**31**	**0**	**<1:10**
DMF	0	0	-	0	0	n/a
CF_3CH_2OH	0	0	-	26	0	<1:10

[a] NMR yields using 1,3,5-Trimethoxybenzene internal standard

Table 5.5. Selected Lewis acid optimization.



5.6a **5.9a**

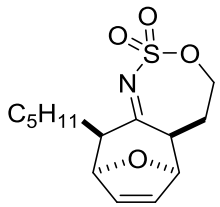
Lewis Acid	time	yield 5.9a[a,b]
AgOTf	5.5 h	32%
$Ti(O\textit{i}\text{-}Pr)_4$	48	38%
$CeCl_3$ - $7H_2O$	21 h	16%
$[Cu(OTf)]_2$-tol	6 h	0%
$Cu(OTf)_2$	6 h	0%
$[Cu(MeCN)_4]PF_6$	10 h	23%
IMesAuCl, $AgPF_6$	2 h	0%
Ph_3PAuCl, $AgPF_6$	2 h	0%
$Ni(acac)_2$	18 h	16%, 14% MA
$FeCl_2$	18 h	23%, 6% MA
$FeBr_3$	20 h	20%
AgTFA	7 h	23%
$AgClO_4$	9 h	34%
$AgSbF_6$	8 h	36%
$AgPF_6$	**7 h**	**35%**

[a] NMR yields using 1,3,5-Trimethoxybenzene internal standard [b] Formation of **5.10a** was not observed in any of these experiments.

5.5.4. Synthesis of 1,2-*syn*;2,3-*syn* aminated cycloheptenes

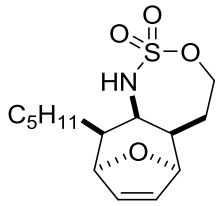
General Procedure A: A round bottom flask was charged with the homoallenic sulfamate (0.2 to 1.0 mmol, 1.0 equiv.) and Rh_2TPA_4 (0.01 equiv.). The flask was placed under nitrogen and then CH_2Cl_2 (0.1 M) was added. The flask was cooled in an ice bath and stirred for five minutes, afterwhich PhIO (1.1 or 1.2 equiv.) was then added at once. The reaction was then monitored either visually for disappearance of the PhIO or by ^1H NMR, and was generally complete between 1-1.5 hr. 4Å MS (1:1 mass ratio with PhIO) was then added and stirred five minutes before filtering the reaction through celite with CH_2Cl_2. The solvent was then removed *in vacuo* at rt (Note: Decomposition of the sensitive methylene aziridine is observed when heated above rt. No decomposition products are present if an NMR is taken, but the yields will be lower. If a NMR of the methylene aziridine is desired, the authors recommend taking the NMR in C_6D_6 to avoid any decomposition in $CDCl_3$ due to adventitious acid). The crude green oil is next dissolved in furan

(0.25 M), and 4Å MS (1:1 mass ratio with PhIO) was added and followed by $AgPF_6$ (0.1 equiv.) dissolved in THF (0.25 M). The reaction was then refluxed at 45 °C under nitrogen. The reaction was then monitored by ^1H NMR for consumption of the methylene aziridine, and was generally complete between 2-4 h. Following filtration through celite, the solvent was next removed *in vacuo*. The crude oil was then dissolved in Et_2O (0.2 M) and then cooled in a dry ice/acetone bath followed by dropwise addition of $LiBHEt_3$ (1.0 M in THF, 3.0 equiv.). The reaction was stirred for an hour in the dry ice/acetone bath, and the reaction was allowed to warm to rt for an hour. The reaction was quenched with sat. NH_4Cl, and the resulting aqueous layer was extracted 3x with EtOAc. The combined organics were then washed with brine and dried with Na_2SO_4. After removing the solvent, the crude product was purified by flash chromatography. When separations were perfomed using Davisil silica gel, a slow flow rate of eluent and slowly increasing the proportion of EtOAc to cosolvent were found to give the greatest separation.

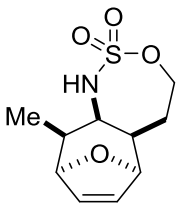


Compound 5.9a. The homoallenic sulfamate **5.6a** (2.10 g, 9.01 mmol, 1 equiv) was subjected to General Procedure A using 1.1 equiv. PhIO until completion of the [4+3] reaction (e.g., the reduction step was not carried out). After workup of the [4+3] step, the concentrated crude material was triturated with 20 mL Et_2O in order to precipitate the product as a white solid. The Et_2O was decanted and the resulting white solid was washed twice with 10 mL portions of Et_2O, again removing excess solvent by decanting. The resulting product was dried to give 832 mg (2.78 mmol, 31%) of **5.9a** as a single diastereomer. ^1H NMR (400 MHz, $CDCl_3$) δ 6.47 (dd, J = 6.1, 1.6

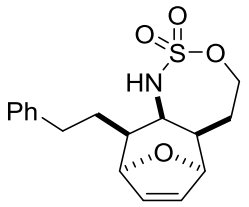
Hz, 1H), 6.32 (dd, *J* = 6.1, 1.6 Hz, 1H), 4.95 (dd, *J* = 4.8, 1.6 Hz, 1H), 4.78 (dd, *J* = 5.1, 1.6 Hz, 1H), 4.47 (dd, *J* = 11.0, 6.5 Hz, 1H), 4.19 (ddd, *J* = 12.9, 11.0, 5.0 Hz, 1H), 3.24 (ddd, *J* = 11.2, 5.1, 0.8 Hz, 1H), 2.75 (dt, *J* = 9.4, 4.8 Hz, 1H), 2.30 (dddd, *J* =15.2, 12.9, 11.5, 6.5 Hz, 1H), 2.18 – 2.04 (m, 1H), 1.69 (dd, *J* = 15.2, 5.1 Hz, 1H), 1.46 – 1.22 (m, 6H), 1.12 (m, 1H), 0.90 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.4, 135.3, 132.8, 80.8, 79.9, 68.4, 50.6, 48.5, 31.9, 27.9, 27.8, 26.7, 22.6, 14.1. HRMS (ESI) *m*/*z* calculated for $C_{14}H_{22}NO_4S$ $[M+H]^+$ 300.1265, found 300.1260.



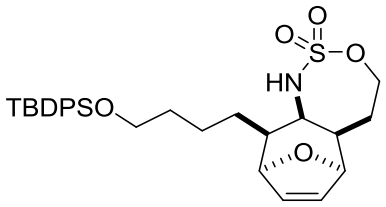
Compound 5.11a. The homoallenic sulfamate **5.6a** (0.0509 g, 0.218 mmol) was subjected to general procedure A using 1.1 equiv. PhIO, which delivered, after silica gel chromatography (10% to 50% EtOAc/hexanes), 0.0254 g (0.0843 mmol, 39%) of **5.11a** in a 10:1 mixture with a minor diastereomer. The material was not purified further. ^{1}H NMR (500.0 MHz, $CDCl_3$) δ 6.51 (app s, 2H), 4.93 (d, *J* = 12.2 Hz, 1H), 4.53 (t, *J* = 4.1 Hz, 2H), 4.35 – 4.21 (m, 2H), 4.05 (dt, *J* = 12.2, 6.5 Hz, 1H), 2.53 (dtd, *J* = 13.0, 6.7, 3.4 Hz, 1H), 2.28 (m, 1H), 2.18 (m, 1H), 1.68 (m, 1H), 1.46 (m, 1H), 1.41 – 1.14 (m, 7H), 0.89 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 136.8, 134.3, 81.4, 80.5, 67.3, 51.9, 41.8, 41.3, 32.0, 29.8, 28.4, 26.2, 22.6, 14.2. HRMS (ESI) *m*/*z* calculated for $C_{14}H_{27}N_2O_4S$ $[M + NH_4^+]$ 319.1687, found 319.1695.



Compound 11b. Homoallenic sulfamate **5.6b** (0.199 g, 1.12 mmol) was subjected to General Procedure A using 1.1 equiv. PhIO. This delivered, after silica gel chromatography (10% to 80% EtOAc/hexanes), 0.0564 g (0.230 mmol, 20%) of **5.11b** in a 15:1 mixture with a minor diastereomer. The material was not purified further. ^{1}H NMR (500.0 MHz, $CDCl_3$) δ 6.55 (dd, *J* = 6.1, 1.5 Hz, 1H), 6.52 (dd, *J* = 6.1, 1.5 Hz, 1H), 4.96 (d, *J* = 12.2 Hz, 1H), 4.53 (m, 1H), 4.48 (dd, *J* = 2.9, 1.5 Hz, 1H), 4.28 (m, 2H), 4.00 (dt, *J* = 12.6, 6.6 Hz, 1H), 2.55 (m, 1H), 2.47 (m, 1H), 2.18 (m, 1H), 1.69 (m, 1H), 0.96 (d, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 136.7, 134.5, 82.1, 80.2, 67.4, 53.2, 41.8, 36.0, 29.7, 13.8. HRMS (ESI) *m/z* calculated for $C_{10}H_{19}N_2O_4S$ [M + NH_4^+] 263.1061, found 263.1064.



Compound 5.11c. The homoallenic sulfamate **5.6c** (0.268 g, 1.00 mmol) was subjected to General Procedure A using 1.1 equiv. PhIO. This delivered, after silica gel chromatography (0 to 5% EtOAc/CH_2Cl_2 in 0.5% increments, Davisil silica gel), 0.0748 g (0.223 mmol, 22%) of **5.11c** in a 7.5:1 mixture of diastereomers. The material was not purified further. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.24 (m, 2H), 7.23 – 7.16 (m, 3H), 6.51 (dd, *J* = 6.1, 1.7 Hz, 1H), 6.47 (m, 1H), 5.21 – 5.05 (m, 1H), 4.53 – 4.47 (m, 2H), 4.32 – 4.18 (m, 2H), 4.09 (ddd, *J* = 21.3, 13.7, 6.1 Hz, 1H), 2.81 (ddt, *J* = 14.2, 9.9, 5.0 Hz, 1H), 2.58 (ddd, *J* = 13.6, 9.4, 7.2 Hz, 1H), 2.49 (m, 1H), 2.27 (m, 1H), 2.18 – 2.08 (m, 1H), 1.73-1.53 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.80, 136.43, 134.45, 128.58, 128.55, 126.09, 81.38, 80.46, 67.41, 51.37, 41.65, 40.22, 32.32, 30.18, 29.68. HRMS (ESI) *m/z* calculated for $C_{17}H_{25}N_2O_4S$ [M+NH_4^+] 353.1530, found 353.1534.

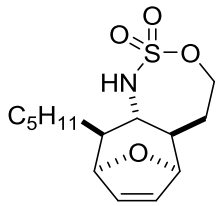


Compound 5.11d. Homoallenic sulfamate **5.6d** (0.235 g, 0.497 mmol) was subjected to General Procedure A using 1.2 equiv. PhIO. This delivered, after silica gel chromatography (0 to 5% EtOAc/CH_2Cl_2 in 0.5% increments, Davisil silica gel), 0.0739 g of **5.11d** in a 11:1 mixture with a minor diastereomer and 0.0176 g in a 17:1 mixture with the same minor diastereomer. Combined, this amounts to 0.0915 g (0.169 mmol, 34%) in a 12:1 *dr*. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (m, 4H), 7.43 – 7.35 (m, 6H), 6.49 (dd, *J* = 6.1, 1.7 Hz, 1H), 6.45 (dd, *J* = 6.1, 1.7 Hz, 1H), 5.05 – 4.95 (m, 1H), 4.53 – 4.47 (m, 2H), 4.32 – 4.18 (m, 2H), 4.02 (dt, *J* = 12.6, 6.4 Hz, 1H), 3.68 (appt. t, *J* = 6.1 Hz, 2H), 2.50 (dtd, *J* = 13.0, 6.7, 3.4 Hz, 1H), 2.24 (ddd, *J* = 11.3, 10.3, 3.1 Hz, 1H), 2.13 (dt, *J* = 16.5, 6.6 Hz, 1H), 1.72 – 1.16 (m, 7H), 1.05 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 136.58, 136.56, 135.69, 135.68, 134.34, 134.17, 129.65, 129.64, 127.75, 127.73, 81.13, 80.44, 67.27, 63.76, 51.88, 41.79, 41.18, 32.68, 29.73, 28.22, 27.01, 22.83, 19.34. HRMS (ESI) *m/z* calculated for $C_{29}H_{43}N_2O_5SSi$ [$M+NH_4^+$] 559.2657, found 559.2658.

5.5.5. Synthesis of the 1,2-*anti*;2,3-*anti* aminated cycloheptenes

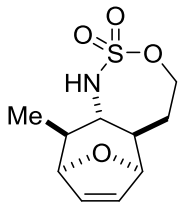
General Procedure B: A round bottom flask was charged with the homoallenic sulfamate (0.4 to 1.0 mmol, 1.0 equiv.) and Rh_2TPA_4 (0.01 equiv.). The flask was placed under nitrogen and CH_2Cl_2 (0.1 M) was added. The flask was cooled in an ice bath and stirred for five minutes, afterwhich PhIO (1.1 or 1.2 equiv.) was added in one portion. The reaction was then monitored either visually for disappearance of the PhIO or by ^{1}H NMR, and was generally complete between 1-1.5 h 4Å MS (1:1 mass ratio with PhIO) was then added and stirred five minutes before filtering the reaction

through celite with CH_2Cl_2 and removing the solvent *in vacuo* at rt (Note: Decomposition of the sensitive methylene aziridine is observed when heated above rt. No decomposition products are present if an NMR is taken, but the yields will be lower. If a NMR of the methylene aziridine is desired, the authors recommend taking the NMR in C_6D_6 to avoid any decomposition in $CDCl_3$ due to adventitious acid). The crude green oil is next dissolved in furan (0.25 M), and 4Å MS (1:1 mass ratio with PhIO) was added and followed by $AgPF_6$ (0.1 equiv.) dissolved in THF (0.25 M). The reaction was then refluxed at 45 ^oC under nitrogen. The reaction was then monitored by ^1H NMR for consumption of the methylene aziridine, and was generally complete between 2-4 h. Following filtration through celite, the solvent was next removed *in vacuo*. The crude oil was dissolved in MeCN (0.2 M), $NaBH_3CN$ (4.0 equiv.) was added followed by dropwise addition of AcOH (30 equiv.). The reaction was then allowed to stir 12-14 h overnight. The reaction was quenched with dropwise addition of sat. $NaHCO_3$ and the resulting aqueous layer was then extracted 3x with EtOAc. The combined organics were washed with brine and dried with Na_2SO_4. After removing the solvent, the crude product was then purified by flash chromatography. When separations were performed using Davisil silica gel, a slow flow rate of eluent and slowly increasing the proportion of EtOAc to cosolvent were found to give the greatest separation.

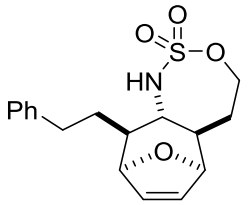


Compound 5.12a. Homoallenic sulfamate **5.6a** (0.102 g, 0.436 mmol) was subjected to General Procedure B using 1.1 equiv. PhIO. This delivered, after silica gel chromatography (gradient, 80% CH_2Cl_2/hexanes to 100% CH_2Cl_2 to 12% EtOAc/CH_2Cl_2), 0.0516 g of the clean major

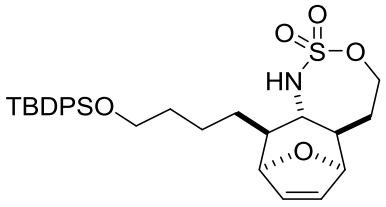
diastereomer **5.12a** and 0.0031 g of a slightly impure minor diastereomer. Combined, this amounts to 0.0547 g of the product (0.181 mmol, 41%) in a 16:1 *dr*. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.29 (dd, *J* = 6.2, 1.8 Hz, 1H), 6.22, (dd, *J* = 6.2, 1.8 Hz, 1H), 4.79 (dd, *J* = 3.8, 1.8 Hz, 1H), 4.55 (dd, *J* = 3.3, 1.8 Hz, 1H), 4.37 (d, *J* = 11.3 Hz, 1H), 4.33 (m, 2H), 2.90 (dt, *J* = 11.3, 9.7 Hz, 1H), 1.86 (m, 2H), 1.72 (m, 1H), 1.65 – 1.52 (m, 2H), 1.44 (m, 1H), 1.37 – 1.20 (m, 6H), 0.98 (m, 1H), 0.89 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 131.7, 130.2, 81.3, 80.6, 69.2, 56.6, 46.6, 42.7, 32.0, 31.1, 28.7, 27.0, 22.7, 14.2. HRMS (ESI) *m*/*z* calculated for $C_{14}H_{27}N_2O_4S$ [M + NH_4^+] 319.1687, found 319.1701.



Compound 5.12b. Homoallenic sulfamate **5.6b** (0.100 g, 0.565 mmol) was subjected to General Procedure B using 1.1 equiv. PhIO. This delivered, after silica gel chromatography (10% to 90% EtOAc/hexanes), 0.0357 g (0.146 mmol, 26%) of the [4+3] product **5.12b** in a 10:1 mixture with a minor diastereomer. The material was not purified further. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.32 (dd, *J* = 6.2, 1.8 Hz, 1H), 6.24 (dd, *J* = 6.2, 1.8 Hz, 1H), 4.64 (dd, *J* = 3.7, 1.8 Hz, 1H), 4.56 (dd, *J* = 3.3, 1.8 Hz, 1H), 4.34 (m, 3H), 2.88 (dt, *J* = 11.3, 9.6 Hz, 1H), 1.88 (m 2H), 1.7 – 1.58 (m, 2H), 0.98 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 131.6, 130.4, 82.5, 81.4, 69.2, 57.4, 45.9, 37.7, 31.0, 13.7. HRMS (ESI) *m*/*z* calculated for $C_{10}H_{19}N_2O_4S$ [M + NH_4^+] 263.1061, found 263.1067.



Compound 5.12c. Homoallenic sulfamate **5.6c** (0.269 g, 1.01 mmol) was subjected to General Procedure B using 1.1 equiv. PhIO. This delivered, after silica gel chromatography (0 to 10% EtOAc/CH_2Cl_2, 0.5% increments), 0.0790 g of the pure major **5.12c** and 0.020 g of a 5:1 mixture of minor diastereomers. Combined, this amounts to 0.0990 g (0.300 mmol, 29%) in a 19.4:5:1 *dr* (3.2:1 *dr* when combining the minor diastereomers). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (dd, *J* = 8.2, 6.9 Hz, 2H), 7.23 – 7.17 (m, 3H), 6.30 (dd, *J* = 6.2, 1.8 Hz, 1H), 6.23 (dd, *J* = 6.1, 1.8 Hz, 1H), 4.79 (dd, *J* = 3.8, 1.8 Hz, 1H), 4.54 (dd, *J* = 3.4, 1.8 Hz, 1H), 4.35 – 4.27 (m, 3H), 2.94 (dt, *J* = 11.2, 9.6 Hz, 1H), 2.80 (ddd, *J* = 14.3, 8.9, 5.5 Hz, 1H), 2.67 (dt, *J* = 13.9, 8.2 Hz, 1H), 2.06 (dtd, *J* = 14.3, 8.4, 3.5 Hz, 1H), 1.91 – 1.79 (m, 2H), 1.65 – 1.55 (m, 2H), 1.36 (dddd, *J* = 14.0, 9.8, 8.3, 5.5 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.30, 131.59, 130.45, 128.70, 128.54, 126.29, 81.32, 80.47, 69.17, 56.43, 46.42, 41.74, 33.35, 31.06, 30.13. HRMS (ESI) *m/z* calculated for $C_{17}H_{25}N_2O_4S$ [M+NH_4^+] 353.1530, found 353.1539.



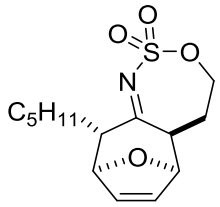
Compound 5.12d. Homoallenic sulfamate **5.6d** (0.235 g, 0.496 mmol) was subjected to General Procedure B using 1.2 equiv. PhIO. This delivered, after silica gel chromatography (Davisil Silica Gel, 0 to 5% EtOAc/CH_2Cl_2 in 0.5% increments), 0.1140 g of pure **5.12d** and 0.0109 g as a 1.5:1 mixture of the minor and major diastereomer. Combined, this amounts to 0.125 g (0.230 mmol,

46%) in a 18:1 *dr*. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 – 7.63 (m, 4H), 7.44 – 7.37 (m, 6H), 6.26 (dd, *J* = 6.2, 1.8 Hz, 1H), 6.21 (dd, *J* = 6.2, 1.8 Hz, 1H), 4.76 (dd, *J* = 3.8, 1.8 Hz, 1H), 4.55 (dd, *J* = 3.4, 1.8 Hz, 1H), 4.34 – 4.29 (m, 2H), 4.29 – 4.24 (m, 1H), 3.67 (t, *J* = 6.1 Hz, 2H), 2.87 (q, *J* = 10.1 Hz, 1H), 1.89-1.82 (m, 2H), 1.70 (dddd, *J* = 13.5, 9.8, 6.4, 3.2 Hz, 1H), 1.65 – 1.46 (m, 5H), 1.44 – 1.32 (m, 1H), 1.05 (s, 9H), 0.96 (dtd, *J* = 14.8, 10.4, 4.5 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.75, 135.72, 134.20, 134.17, 131.68, 130.26, 129.71, 129.70, 127.80, 127.80, 81.34, 80.44, 69.15, 63.62, 56.50, 46.52, 42.61, 32.60, 31.08, 28.33, 27.04, 23.44, 19.39. HRMS (ESI) *m/z* calculated for $C_{29}H_{43}N_2O_4SSi$ [M+NH_4^+] 559.2656, found 559.2657.

5.5.6. Synthesis of 1,2-*syn*;2,3-*anti* aminated cycloheptenes

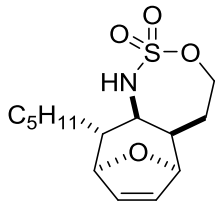
General Procedure C: A round bottom flask was charged with the homoallenic sulfamate (0.4 to 1.0 mmol, 1.0 equiv.) and Rh_2TPA_4 (0.01 equiv.). The flask was placed under nitrogen and CH_2Cl_2 (0.1 M) was added. The flask was cooled in an ice bath and stirred for five minutes, afterwhich PhIO (1.1 or 1.2 equiv.) was added in one portion. The reaction was then monitored either visually for disappearance of the PhIO or by ^{1}H NMR, and was generally complete between 1-1.5 h 4Å MS (1:1 mass ratio with PhIO) was then added and stirred five minutes before filtering the reaction through celite with CH_2Cl_2 and removing the solvent *in vacuo* at rt (Note: Decomposition of the sensitive methylene aziridine is observed when heated above rt. No decomposition products are present if an NMR is taken, but the yields will be lower. If a NMR of the methylene aziridine is desired, the authors recommend taking the NMR in C_6D_6 to avoid any decomposition in $CDCl_3$ due to adventitious acid). The crude green oil was next dissolved in furan (0.25 M), followed by 4Å MS (1:1 mass ratio with PhIO) and $MeNO_2$ (0.25 M). The reaction was then refluxed at 65 ºC and the reaction was monitored by NMR for consumption of the methylene aziridine, which was generally consumed within 6-8 h. The reaction was then cooled to rt and then loaded onto a silica

plug, which was eluted using 10% EtOAc/ CH_2Cl_2. Next, 1,3,5-Trimethoxybenzene (0.6 equiv.) was added as an internal standard, followed by putting the solution in a flame dried round bottom flask. The solvent was removed at under reduced pressure at rt to first remove the CH_2Cl_2, and then the temperature was elevated to 80 ^oC for an extended period of time to ensure that minimal $MeNO_2$ was remaining. Following removal of all the solvent, the red oil was placed under nitrogen and dissolved in toluene. AlH_3-NMe_2Et (0.5 M in toluene, 5.0 equiv.) was added dropwise, with a small evolution of gas observed at the start. The reaction was then allowed to stir 12-14 h overnight. The reaction was then quenched with dropwise addition of a saturated Rochelle salt solution and then diluted with water. The resulting aqueous layer was extracted 3x with EtOAc. The combined organics were then washed with brine and dried with Na_2SO_4. After removing the solvent, the crude product was purified by flash chromatography.

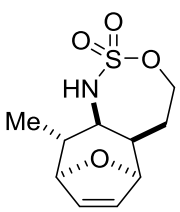


Compound 5.10a. The homoallenic sulfamate **5.6a** (860 mg, 3.69 mmol, 1 equiv) was subjected to General Procedure C using 1.1 equiv. PhIO until completion of the [4+3] reaction (e.g., the reduction step was not carried out). After workup of the [4+3] step, the concentrated crude material was purified by silica gel chromatography (80% CH_2Cl_2/hexanes to 100% CH_2Cl_2 to elute nonpolar impurities, then 0% to 2% EtOAc/CH_2CL_2 to elute the desired product) to give 290 mg (0.96 mmol, 26%) of the desired product as a white solid. ^1H NMR (400 MHz, $CDCl_3$) □ 6.44 (dd, *J* = 6.1, 1.8 Hz, 1H), 6.26 (dd, *J* = 6.1, 1.7 Hz, 1H), 4.18 (s, 1H), 4.74 (dd, *J* = 5.0, 1.7 Hz, 1H), 4.48 (dd, *J* = 11.0, 6.6 Hz, 1H), 4.17 (ddd, *J* = 12.9, 11.0, 5.0 Hz, 1H), 3.25 (ddt, *J* = 11.5,

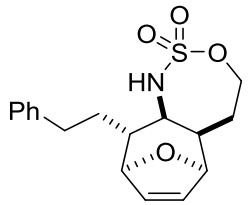
5.0, 1.3 Hz, 1H), 2.42 (dd, *J* = 9.2, 5.8 Hz, 1H), 2.37 (dddd, *J* = 15.3, 12.8, 11.6, 6.7 Hz, 1H), 1.94 – 1.84 (m, 1H), 1.75 – 1.66 (m, 1H), 1.54 – 1.36 (m, 2H), 1.36 – 1.24 (m, 5H), 0.89 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.3, 136.6, 131.8, 80.5, 79.9, 68.5, 50.1, 48.4, 34.2, 31.6, 27.8, 27.0, 22.6, 14.1. HRMS (ESI) *m/z* calculated for $C_{14}H_{22}NO_4S$ $[M+H]^+$ 300.1265, found 300.1262.



Compound 5.13a. The homoallenic sulfamate **5.6a** (0.120 g, 0.516 mmol) was subjected to General Procedure C using 1.1 equiv. PhIO. This delivered, after silica gel chromatography (0 to 5% EtOAc/CH_2Cl_2, 0.5% increments), 0.0321 g of **5.13a** and 0.0139 g of a 1.1:1 mixture of minor diastereomers. Combined this amounts to 0.0460 g (0.15 mmol, 30%) with a 4.9:1.1:1 *dr*. ^{1}H NMR (500 MHz, CDCl) δ 6.50 (dd, *J* = 6.1, 1.5 Hz, 1H), 6.48 (d, *J* = 6.2 Hz, 1H), 5.16 (d, *J* = 11.9 Hz, 1H), 4.61 (s, 1H), 4.47 (d, *J* = 3.6 Hz, 1H), 4.33 – 4.21 (m, 2H), 3.76 (dd, *J* = 11.9, 6.7 Hz, 1H), 2.58 (dtd, *J* = 13.4, 6.7, 3.6 Hz, 1H), 2.12 (dt, *J* = 17.8, 6.4 Hz, 1H), 1.76 – 1.57 (m, 4H), 1.49 – 1.24 (m, 6H), 0.90 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.49, 133.10, 80.76, 80.27, 67.34, 53.36, 42.74, 40.20, 33.20, 31.86, 29.60, 27.15, 22.66, 14.17. HRMS (ESI) *m/z* calculated for $C_{14}H_{23}N_2O_4S$ $[M+NH_4^+]$ 319.1687, found 319.1685.



Compound 5.13b. The homoallenic sulfamate **5.6b** (0.0886 g, 0.500 mmol) was subjected to General Procedure C using 1.1 equiv. PhIO. This delivered, after chromatography (0 to 6% EtOAc/DCM, 0.5% increments), 0.0286 g of **5.13b** and 0.0064 g of a slightly impure 11:1 mixture of minor diastereomers. Combined, this is 0.0350 g (0.14 mmol, 29%) with a 54:11:1 *dr*. ^{1}H NMR (500 MHz, C_6D_6) δ 5.72 (dd, *J* = 6.1, 1.8 Hz, 1H), 5.67 (dd, *J* = 6.1, 1.7 Hz, 1H), 5.02 (d, *J* = 11.9 Hz, 1H), 3.96 (s, 1H), 3.87 (dt, *J* = 3.0, 1.3 Hz, 1H), 3.71 (ddd, *J* = 13.0, 8.5, 1.9 Hz, 1H), 3.56 (dd, *J* = 11.9, 6.8 Hz, 1H), 3.49 (ddd, *J* = 13.2, 5.9, 1.9 Hz, 1H), 1.88 (dtd, *J* = 11.0, 7.2, 3.5 Hz, 1H), 1.38 (q, *J* = 7.4 Hz, 1H), 1.05 (d, *J* = 7.3 Hz, 3H), 1.00 – 0.91 (m, 2H). ^{13}C NMR (126 MHz, C_6D6) δ 137.09, 132.84, 82.05, 80.15, 66.89, 54.75, 39.54, 37.59, 29.22, 19.23. HRMS (ESI) *m/z* calculated for $C_{10}H_{19}N_2O_4S$ [M+NH_4^+] 263.1061, found 263.1058.



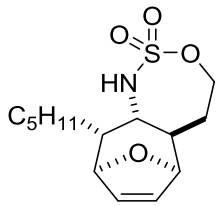
Compound 5.13c. The homoallenic sulfamate **5.6c** (0.136 g, 0.507 mmol) was subjected to General Procedure C using 1.1 equiv. PhIO. This delivered, after silica gel chromatography (0 to 5% EtOAc/CH_2Cl_2, 5% increments), 0.0239 g of **5.13c,** 0.0047 g of a 1.2:1 mixture of **5.13c** and a minor diastereomer, and 0.0097 g of a 1.2:1 mixture of minor diastereomers. Combined this amounts to 0.0383 g (0.114 mmol, 23%) with a 12:2.4:2:1 *dr*. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (appt. t, *J* = 7.5 Hz, 2H), 7.24 – 7.18 (m, 3H), 6.50 (dd, *J* = 6.0, 1.7 Hz, 1H), 6.44 (dd, *J* = 6.0, 1.8 Hz, 1H), 5.13 (d, *J* = 11.9 Hz, 1H), 4.61 (d, *J* = 1.8 Hz, 1H), 4.48 (dd, *J* = 3.7, 1.8 Hz, 1H), 4.31 – 4.22 (m, 2H), 3.87 (dd, *J* = 11.9, 6.8 Hz, 1H), 2.81 – 2.72 (m, 2H), 2.60 (dtd, *J* = 13.0, 6.8, 3.6 Hz, 1H), 2.16 – 2.08 (m, 1H), 2.01 (q, *J* = 7.6 Hz, 2H), 1.73 – 1.61 (m, 2H). ^{13}C NMR (126 MHz,

$CDCl_3$) δ 141.42, 137.35, 133.19, 128.64, 128.60, 126.15, 80.98, 80.29, 67.36, 52.87, 41.78, 40.19, 34.78, 33.38, 29.59. HRMS (ESI) *m/z* calculated for $C_{17}H_{25}N_2O_4S$ [$M+NH_4^+$] 353.1530, found 353.1527. HRMS (ESI) *m/z* calculated for $C_{17}H_{25}N_2O_4S$ [$M+NH_4^+$] 353.1530, found 353.1527.

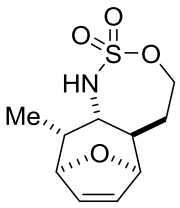
5.5.7. Synthesis of the 1,2-*anti*;2,3-*syn* aminated cycloheptenes

General Procedure D: A round bottom flask was charged with the homoallenic sulfamate (0.4 to 1.0 mmol, 1.0 equiv.) and Rh_2TPA_4 (0.01 equiv.). The flask was placed under nitrogen and CH_2Cl_2 (0.1 M) was added. The flask was cooled in an ice bath and stirred for five minutes, afterwhich PhIO (1.1 or 1.2 equiv.) was added in one portion. The reaction was then monitored either visually for disappearance of the PhIO or by ^1H NMR, and was generally complete between 1-1.5 h 4Å MS (1:1 mass ratio with PhIO) was then added and stirred five minutes before filtering the reaction through celite with CH_2Cl_2 and removing the solvent *in vacuo* at rt (Note: Decomposition of the sensitive methylene aziridine is observed when heated above rt. No decomposition products are present if an NMR is taken, but the yields will be lower. If a NMR of the methylene aziridine is desired, the authors recommend taking the NMR in C_6D_6 to avoid any decomposition in $CDCl_3$ due to adventitious acid). The crude green oil was next dissolved in furan (0.25 M), followed by 4Å MS (1:1 mass ratio with PhIO) and $MeNO_2$ (0.25 M). The reaction was then refluxed at 65 ^oC and the reaction was monitored by NMR for consumption of the methylene aziridine, which was generally consumed within 6-8 h. The reaction was then cooled to rt and filtered through celite. The solvent was then removed *in vacuo*. The crude oil was dissolved in MeCN (0.2 M), $NaBH_3CN$ (4.0 equiv.) was added followed by dropwise addition of AcOH (30 equiv.). The reaction was then allowed to stir 12-14 h overnight. The reaction was quenched with dropwise addition of sat. $NaHCO_3$ and the resulting aqueous layer was then extracted 3x with EtOAc. The combined organics were washed with brine and dried with Na_2SO_4. After removing the solvent, the crude

product was then purified by flash chromatography. When separations were performed using Davisil silica gel, a slow flow rate of eluent and slowly increasing the proportion of EtOAc to cosolvent were found to give the greatest separation.

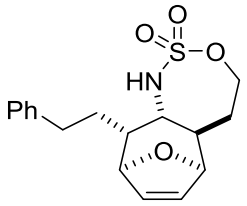


Compound 5.14a. The homoallenic sulfamate **5.6a** (0.1175 g, 0.5036 mmol) was subjected to General Procedure D using 1.2 equiv. PhIO. This delivered, after silica gel chromatography (0 to 50% EtOAc/Hex, 5% increments, Davisil silica gel), 0.0518 g of **5.14a** and 0.0111 g of a minor diastereomer. Combined, this amounts to 0.0629 g (0.209 mmol, 41%) in a 4.7:1 *dr*. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.29 (dd, *J* = 6.1, 1.8 Hz, 1H), 6.21 (dd, *J* = 6.1, 1.5 Hz, 1H), 4.91 (d, *J* = 11.0 Hz, 1H), 4.77 (bs, 1H), 4.49 (dd, *J* = 3.1, 1.5 Hz, 1H), 4.29 (m, 2H), 3.53 (td, *J* = 11.0, 6.2 Hz, 1H), 1.95 (m, 1H), 1.83 (m, 1H), 1.71 (m, 1H), 1.58 (m, 3H), 1.46 (m, 1H), 1.39 – 1.20 (m, 5H), 0.90 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 133.6, 129.5, 80.9, 80.0, 68.9, 52.6, 42.2, 37.6, 32.0, 30.9, 26.7, 25.4, 22.7, 14.2. HRMS (ESI) *m*/*z* calculated for $C_{14}H_{27}N_2O_4S$ [M + NH_4^+] 319.1687, found 319.1684.

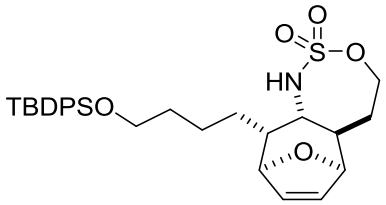


Compound 5.14b. The homoallenic sulfamate **5.6b** (0.0509 g, 0.218 mmol) was subjected to General Procedure D using 1.1 equiv. PhIO. This delivered, after silica gel chromatography (10%

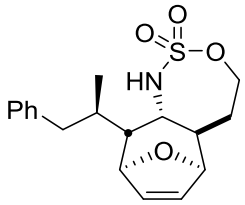
to 50% EtOAc/hexanes), 0.0254 g (0.0843 mmol, 39%) of **5.14b** in a 10:1 mixture with a minor diastereomer. The material was not purified further. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.51 (app s, 2H), 4.93 (d, *J* = 12.2 Hz, 1H), 4.53 (t, *J* = 4.1 Hz, 2H), 4.35 – 4.21 (m, 2H), 4.05 (dt, *J* = 12.2, 6.5 Hz, 1H), 2.53 (dtd, *J* = 13.0, 6.7, 3.4 Hz, 1H), 2.28 (m, 1H), 2.18 (m, 1H), 1.68 (m, 1H), 1.46 (m, 1H), 1.41 – 1.14 (m, 7H), 0.89 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 136.8, 134.3, 81.4, 80.5, 67.3, 51.9, 41.8, 41.3, 32.0, 29.8, 28.4, 26.2, 22.6, 14.2. HRMS (ESI) *m/z* calculated for $C_{14}H_{27}N_2O_4S$ [M + NH_4^+] 319.1687, found 319.1695.



Compound 5.14c. The homoallenic sulfamate **5.6c** (0.270 g, 1.01 mmol) was subjected to General Procedure D using 1.1 equiv. PhIO. This delivered, after silica gel chromatography (0 to 50% EtOAc/hexanes in 5% increments), 0.155 g (0.462 mmol, 46%) of **5.14c** in a 4.3:1 mixture with the minor diastereomer. The diastereomers could be separated using Davisil silica gel (0 to 50% EtOAc/hexanes in 5% increments). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (t, *J* = 7.5 Hz, 2H), 7.23 (appt d, *J* = 7.2 Hz, 3H), 6.31 (d, *J* = 6.2 Hz 1H), 6.24 (d, *J* = 6.2 Hz, 1H), 4.89 (s, 1H), 4.73 (d, *J* = 11.5 Hz, 1H), 4.53 (s, 1H), 4.30 – 4.21 (m, 2H), 3.56 (td, *J* = 10.8, 6.0 Hz, 1H), 2.85 (m, 1H), 2.62-2.50 (m, 1H), 1.97–1.90 (m, 2H), 1.86-1.80 (m, 2H), 1.64-1.57 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.65, 133.45, 129.62, 128.70, 128.53, 126.29, 81.00, 79.92, 68.84, 52.46, 42.44, 37.44, 33.24, 30.89, 27.84. HRMS (ESI) *m/z* calculated for $C_{17}H_{25}N_2O_4S$ [M+NH_4^+] 353.1530, found 353.1533.



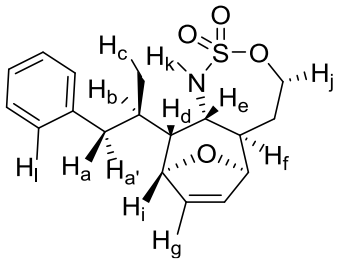
Compound 5.14d. The homoallenic sulfamate **5.6d** (0.238 g, 0.501 mmol) was subjected to General Procedure D using 1.2 equiv. PhIO. This delivered, following silica gel chromatography (Davisil Silica Gel, 0 to 45% EtOAc/hexanes in 5% increments), 0.1042 g of clean **5.14d**, 0.0187 g of a 1.4:1 mixture of minor to major diastereomer, and 0.0197 g of the clean minor diastereomer. Combined, this amounts to 0.1426 g (0.2632 mmol, 52%) in a 4.2:1 *dr*. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 – 7.65 (m, 4H), 7.43 – 7.36 (m, 6H), 6.27 (dd, *J* = 6.1, 1.9 Hz, 1H), 6.19 (dd, *J* = 6.1, 1.7 Hz, 1H), 4.87 – 4.68 (m, 2H), 4.47 (dd, *J* = 3.6, 1.8 Hz, 1H), 4.32 – 4.15 (m, 2H), 3.72 – 3.63 (m, 2H), 3.51 (td, *J* = 10.9, 6.1 Hz, 1H), 1.89 (ddt, *J* = 10.2, 7.0, 3.3 Hz, 1H), 1.79 (ddd, *J* = 16.5, 4.6, 2.6 Hz, 1H), 1.71 – 1.64 (m, 1H), 1.62-1.50 (m, 5H), 1.45-1.38 (m, 1H), 1.36-1.30 (m, 1H), 1.05 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.72, 135.71, 134.13, 134.13, 133.56, 129.70, 129.68, 129.49, 127.77, 127.76, 80.91, 79.90, 68.86, 63.81, 42.25, 42.20, 37.55, 32.72, 30.89, 27.03, 25.23, 23.30, 19.36. HRMS (ESI) *m/z* calculated for $C_{29}H_{39}N_2O_5SSi$ [M+NH_4^+] 559.2657, found 559.2654.



Compound 5.15. The homoallenic sulfamate **5.6e** (0.144 g, 0.511 mmol, 1:1 mixture of diastereomers, ≥97% *ee*) was subjected to General Procedure D using 1.2 equiv. PhIO. This delivered, after silica gel chromatography (0 to 7% EtOAc/CH_2Cl_2, 0.5% increments), 0.0494 g of clean **17**, 0.0142 g of a 6:1:1 mixture of diastereomers, with **5.15** as a minor component, and 0.0048

g of a 2.5:1 mixture of diastereomers, with **5.15** as a major component. Combined, this amounts to a 0.0684 g (0.196 mmol, 38%, 97% *ee*) with a 30:6.7:1 *dr*. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (appt t, *J*= 7.4, 2H), 7.21 (t, *J*= 7.5, 1H), 7.17 (d, J=7.2, 2H), 6.27 (dd, *J* = 6.0, 1.9 Hz, 1H), 6.23 (dd, *J* = 6.1, 1.6 Hz, 1H), 5.00 (d, *J* = 1.9 Hz, 1H), 4.76 (d, *J* = 11.8 Hz, 1H), 4.55 (dd, *J* = 3.7, 1.6 Hz, 1H), 4.30 (m, 2H), 3.66 (td, *J* = 11.1, 7.5 Hz, 1H), 2.77 (dd, *J* = 13.4, 5.6 Hz, 1H), 2.64 (dd, *J* = 13.4, 9.1 Hz, 1H), 2.35 – 2.26 (m, 1H), 2.16 – 2.08 (m, 1H), 1.86 – 1.77 (m, 2H), 1.57 (dtd, *J* = 15.3, 11.7, 3.6 Hz, 1H), 1.07 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.40, 134.51, 129.93, 129.18, 128.59, 126.33, 80.93, 79.21, 69.06, 52.58, 44.68, 42.68, 40.15, 33.91, 31.42, 18.67. HRMS (ESI) *m/z* calculated for $C_{18}H_{27}N_2O_4S$ [M+NH_4^+] 367.1687, found 367.1684. See Section IX for the transfer of chirality studies for determing the % *ee* of the **15**.

NOE data:



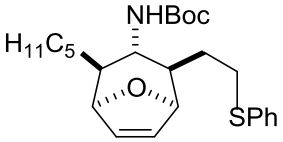
H_i NOE Correlations

H_a	4.3%	H_d	3.4%
$H_{a'}$	2.8%	H_g	3.6%
H_b	0.4%	H_l	0.9%
H_c	1.9%		

H_k NOE Correlations

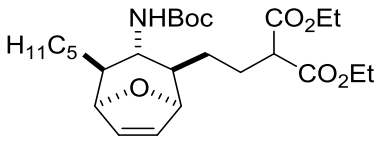
H_a	0.4%	H_d	0.4%	H_j	3.2%
$H_{a'}$	0.3%	H_e	2.0%		
H_b	9.1%	H_f	5.8%		
H_c	3.5%	H_l	0.4%		

5.5.8. Derivatization of the aminated cycloheptenes

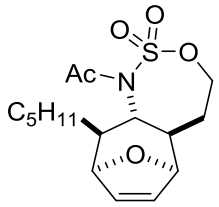


Compound 5.16. A 1.5 dram vial equipped with a stir bar was charged with 0.0422 g (0.140 mmol, 1.0 equiv.) of **5.12a**, 0.0501 g (0.230 mmol, 1.6 equiv.) of Boc_2O, and 1.5 ml of CH_2Cl_2 (0.09 M). Next, 50 µl (0.36 mmol, 2.6 equiv.) of triethylamine was then added followed by 0.0042 g (0.034 mmol, 0.24 equiv.) of 4-dimethylaminopyridine. The reaction was stirred for 45 min. at rt, afterwhich the reaction was quenched with sat. NH_4Cl solution. The resulting aqueous layer was

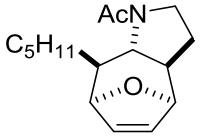
extracted three times with diethyl ether. The combined organics were then washed with a brine solution and dried with Na_2SO_4. The solution was then filtered and the solvent was removed under reduced pressure. A modified procedure by Duran, F. et. al. was used for the cleavage of the sulfamate.[5] The crude material was then dissolved in 0.75 ml of MeCN (0.19 M) and 40 µl (0.39 mmol, 2.8 equiv.) of thiophenol and 0.0419 g (0.303 mmol, 2.2 equiv.) of potassium carbonate was then added. The reaction was stirred at rt for 12 hours, after which the reaction was diluted with EtOAc and quenched with 1M HCl. The aqueous layer was then extracted three times with EtOAc, and the combined organics were then washed once with a solution of sat. $NaHCO_3$ and then washed once with a brine solution. The combined organics were then dried with Na_2SO_4, the solids were filtered off and the solvent was removed under reduced pressure. The crude material was then purified by column (0 to 16% EtOAc/hexanes, 2% increments), yielding 0.0453 g (0.105 mmol, 75% yield) of **5.16**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.33 (m, 2H), 7.31 (d, *J* = 7.4 Hz, 2H), 7.22 – 7.18 (m, 1H), 6.25 (dd, *J* = 6.2, 1.8 Hz, 1H), 6.18 (dd, *J* = 6.1, 1.8 Hz, 1H), 4.76 – 4.72 (m, 2H), 4.25 (d, *J* = 10.5 Hz, 1H), 3.16 (q, *J* = 10.0 Hz, 1H), 3.04 (ddd, *J* = 13.4, 8.3, 5.4 Hz, 1H), 2.93 (dt, *J* = 12.9, 7.7 Hz, 1H), 1.82 – 1.68 (m, 2H), 1.55 – 1.44 (m, 2H), 1.41 (s, 10 H), 1.39 – 1.21 (m, 6H), 1.06 – 0.94 (m, 1H), 0.90 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.21, 136.23, 131.07, 130.21, 129.47, 129.03, 126.18, 80.73, 80.45, 79.35, 53.36, 44.83, 43.66, 32.14, 31.88, 29.14, 28.70, 28.46, 27.10, 22.59, 14.15. HRMS (ESI) *m/z* calculated for $C_{25}H_{41}N_2O_3S$ $[M+NH_4^+]$ 449.2833, found 449.2833.



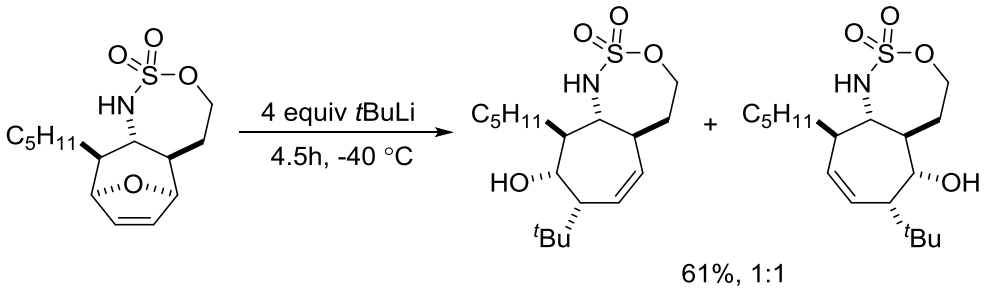
Compound 5.17. A 1.5 dram vial equipped with a stir bar was charged with 0.0518 g (0.172 mmol, 1.0 equiv.) of **5.12a**, 0.0588 g (0.269 mmol, 1.6 equiv.) of Boc_2O and 1.7 ml of CH_2Cl_2 (0.1 M). Then 50 µl (0.36 mmol, 2.1 equiv.) of triethylamine was added, followed by 0.0047 g (0.038 mmol, 0.22 equiv.) of 4-dimethylaminopyridine. The reaction was then stirred for 30 min. at rt, afterwhich the reaction was quenched with a sat. NH_4Cl solution. The aqueous layer was extracted three times with CH_2Cl_2 and the combined organics were then washed with brine. The organics were then dried with Na_2SO_4, the solids were filtered off and the mixture was concentrated in vacuo. The crude material was then dissolved in 1.7 ml of MeCN (0.1 M) and then 0.0643 g (0.199 mol, 1.2 equiv.) of tetrabutylammonium bromide and 0.0822 g (0.252 mmol, 1.5 equiv.) of Cs_2CO_3 were added. Then 50 µl (0.33 mmol, 1.9 equiv.) of diethyl malonate was added and the reaction was stirred for 2.5 days at rt. The reaction was diluted with EtOAc and quenched with 1M HCl. The aqueous layer was extracted 3x with EtOAc and the combined organics were then washed once with a sat. $NaHCO_3$ solution and then washed once with a brine solution. The organics were then dried with Na_2SO_4 and the solids were filtered off. The solvent was removed in vacuo and the crude material was purified via column (0 to 35% EtOAc/hexanes, 5% increments, Davisil silica gel), yielding 0.0478 g (0.0992 mmol, 58% yield) of **17**. ^{1}H NMR (500 MHz, CDCl3) δ 6.22 (s, 2H), 4.75 (d, J = 3.4 Hz, 1H), 4.71 (d, J = 3.6 Hz, 1H), 4.26 (d, J = 10.7 Hz, 1H), 4.24-4.16 (m, 4H), 3.28 (dd, J = 8.3, 6.5 Hz, 1H), 3.10 (q, J = 10.0 Hz, 1H), 2.05 (tdd, J = 13.1, 10.1, 6.5 Hz, 1H), 1.82 (ddt, J = 13.6, 11.6, 6.0 Hz, 1H), 1.52 – 1.44 (m, 2H), 1.50-1.46 (m, 2H), 1.42 (appt. s, 11H), 1.27 (appt. q, J = 7.0 Hz, 12H), 1.05 – 0.92 (m, 2H), 0.88 (t, J = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.39, 169.22, 156.29, 130.83, 130.33, 80.73, 80.26, 79.29, 61.50, 61.49, 53.45, 52.18, 44.83, 44.53, 32.15, 29.19, 28.46, 27.10, 27.09, 26.65, 22.59, 14.21, 14.19, 14.14. HRMS (ESI) m/z calculated for $C_{26}H_{47}N_2O_7$ $[M+NH_4]^+$ 499.3378, found 499.3375.



Compound 5.S1. A modified procedure by Brawn, R. A. et. al. was used.[6] An oven-dried 1.5-dram screwcap vial equipped with a stirbar was charged with compound **5.12a** (0.0970 g, 0.32 mmol, 1 equiv) and 2.2 mL CH_2Cl_2. The solution was cooled to 0 °C and dry KO^{t}Bu (0.0590 g, 0.53 mmol, 1.6 equiv) was added in one portion, followed by DMAP (0.0049 g, 0.040 mmol, 0.12 equiv). The mixture was stirred at 0 °C for 45 minutes, and then acetic anhydride (0.16 mL, 1.7 mmol, 5.3 equiv) was added and the reaction warmed to rt. The reaction was quenched after 21 h by the addition of sat. NH_4Cl. The mixture was extracted three times with CH_2Cl_2, then the combined organic layers were washed with brine and dried over Na_2SO_4. Rotary evaporation yielded a crude oil that was purified by column chromatography (10% to 50% EtOAc/hexanes) to give compound **5.S1** (0.106 g, 0.310 mmol, 96%) as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.33 (dd, *J* = 6.2, 1.8 Hz, 1H), 6.26 (dd, *J* = 6.2, 1.8 Hz), 4.80 (dd, *J* = 4.4, 1.8 Hz, 1H), 4.63 (dd, *J* = 4.1, 1.8 Hz, 1H), 4.44 – 4.36 (m, 2H), 3.50 (t, *J* = 10.0 Hz, 1H), 2.95 (ddt, *J* = 12.4, 10.0, 4.4 Hz, 1H), 2.63 (m, 1H), 2.47 (s, 3H), 1.82 (ddt, *J* = 15.3, 4.4, 1.9 Hz), 1.54 (m, 1H), 1.45 – 1.15 (m, 7H), 1.03 (m, 1H), 0.88 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.82, 131.85, 130.31, 80.91, 80.72, 71.45, 63.28, 37.51, 36.06, 31.94, 30.21, 29.72, 27.95, 26.64, 22.55, 14.09. HRMS (ESI) *m*/*z* calculated for $C_{16}H_{29}N_2O_5S$ $[M+NH_4]^+$ 361.1792, found 361.1793.



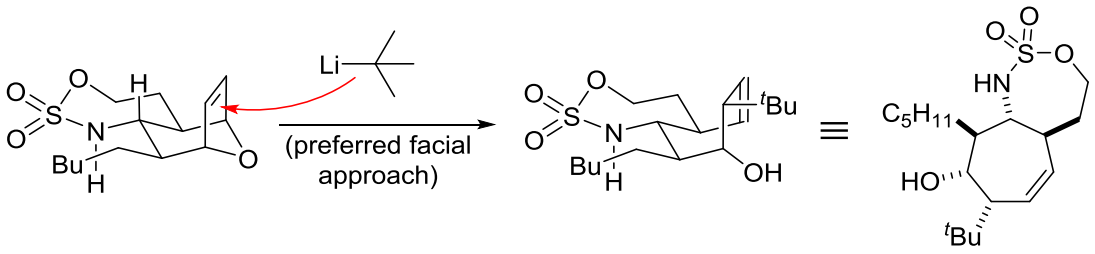
Compound 5.18. A modified procedure was used for the pyrolidine ring formation was used.[4a] An oven-dried ½-dram screwcap vial equipped with a stirbar was charged with compound **5.S1** (15.0 mg, 0.0437 mmol, 1 equiv) and NaI (13.1 mg, 0.0875 mmol, 2 equiv). Dry DMF (0.22 mL, 0.2 M) was added, and the sealed vial was heated to 60 °C for 18 h. The vial was then cooled to rt, and NaH (60 wt% dispersion in mineral oil, 5.2 mg, 0.13 mmol, 3 equiv) was added in one portion. The reaction was then stirred at 40 °C for 8 h, and then heated to 60 °C for 13h. The reaction was quenched by the cautious addition of H_2O, and then diluted with EtOAc and washed with $NaHCO_3$ followed by brine. The organic layer was dried over Na_2SO_4, concentrated by rotary evaporation, and then purified by column chromatography (30% to 90% EtOAc/hexane) to give 9.6 mg (0.036 mmol, 83%) of compound **5.19** as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.23 (dd, *J* = 6.2, 1.9 Hz, 1H), 6.15 (dd, *J* = 6.2, 1.8 Hz, 1H), 4.87 (dd, *J* = 3.5, 1.8 Hz, 1H), 4.81 (bs, 1H), 3.44 (m, 1H), 3.51 – 3.29 (m, 2H), 2.64 (t, *J* = 10.5 Hz, 1H), 2.41 (tt, *J* = 10.5, 3.1 Hz, 1H), 2.27 – 2.11 (m, 1H), 2.00 (s, 3), 1.96 (m, 1H), 1.77 (tdd, *J* = 10.5, 6.0, 2.9, 1H), 1.44 (m, 2H), 1.39 – 1.15 (m, 6H), 0.95 – 0.86 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7, 132.0, 129.7, 80.5, 80.0, 64.7, 47.0, 43.0, 41.4, 32.3, 31.9, 27.3, 25.1, 24.0, 22.9, 14.3. HRMS (ESI) *m*/*z* calculated for $C_{16}H_{26}NO_2$ $[M+H]^+$ 264.1959, found 264.1955.

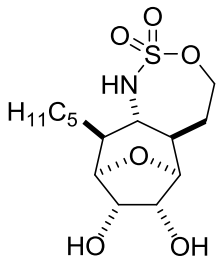


Compounds 5.19 and 5.20. A flame-dried 10 mL roundbottom flask under N_2, equipped with a stirbar, was charged with compound **5.12a** (51.3 mg, 0.170 mmol, 1 equiv) and 2.5 mL Et_2O. The

insoluble mixture was cooled to -78 °C with stirring and *tert*-butyllithium (1.27 M in pentane, 0.520 mL, 0.660 mmol, 4 equiv) was added over 1-2 minutes. The mixture was stirred at -78 °C for 10 minutes, then warmed to -40 °C in a MeCN/CO_2 bath and stirred for 4.5 h. The bath was then allowed to warm to 0 °C over 30 minutes, then quenched by the cautious addition of sat. aq. $NaHCO_3$ solution. The mixture was extracted twice with EtOAc, and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated by rotary evaporation. The crude oil was purified by column chromatography (5% to 45% EtOAc/hexanes, using Davisil grade 635 silica gel) to give 37.1 mg (0.103 mmol, 61%) of the desired product(s) as a clear oil. The product was obtained and characterized as a 1:1 mixture of regioisomers **5.19** and **5.20**. The stereochemistry of the -^{t}Bu group was not experimentally verified, but is presumed to arise from a preferred trajectory of approach from the back face of the alkene bridge (see Scheme S-1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.78 (dt, *J* = 11.7, 2.8 Hz, 1H), 5.57 (app s, 2H), 5.53 (dd, *J* = 11.7, 4.1 Hz, 1H), 5.04 (d, *J* = 10.0 Hz, 1H), 4.93 (d, *J* = 10.2 Hz, 1H), 4.31 (m, 4H), 4.12 (d, *J* = 6.8 Hz, 1H), 3.76 (d, *J* = 8.7 Hz, 1H), 3.36 (m, 1H), 3.23 (q, *J* = 10.0 Hz, 1H), 3.07 (m, 1H), 2.47 (m, 1H), 2.22 – 2.13 (m, 3H), 2.12 – 1.97 (m, 5H), 1.93 (d, *J* = 9.7 Hz, 1H), 1.75 – 1.55 (m, 4H), 1.48 (m, 2H), 1.40 – 1.15 (m, 10H), 1.08 (m, 1H), 0.99 (s, 9H), 0.98 (s, 9H), 0.89 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.1, 134.7, 128.6, 126.0, 74.4, 70.8, 68.8, 68.6, 60.0, 57.0, 53.9, 52.5, 48.7, 48.3, 44.8, 44.7, 36.2, 33.3, 32.8, 32.4, 32.3, 32.1, 30.2, 28.3, 27.7, 25.1, 22.7, 14.2. HRMS (ESI) *m*/*z* calculated for $C_{18}H_{37}N_2O_4S$ $[M+NH_4]^+$ 377.2469, found 377.2468.

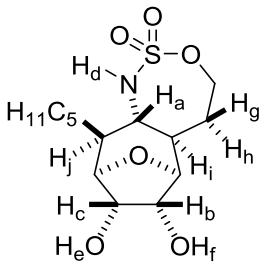
Scheme 5.5. Stereochemical model for S_N2' cleavage of ether bridge.





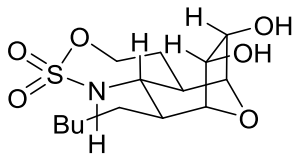
Compound 5.21. A 1.5 dram screw top vial equipped with a stir bar was charged with 0.0309 g (0.103 mmol, 1 equiv.) of **5.12a**, which was then dissolved in 1.65 ml of acetone, 0.60 ml of deionized water and 0.08 ml of *tert*-butanol. Then 0.10 ml (50% in water, 0.50 mmol, 5 equiv.) of NMO was added, followed by 0.06 ml (4% in water, 0.01 mmol, 0.1 equiv.) of OsO_4. The reaction was stirred at rt for five days, afterwhich the reaction was quenched with a solution of sodium thiosulfate. The solution was then transferred to a round bottom flask and the acetone was removed *in vacuo*. The aqueous layer was then extracted three times with EtOAc and the combined organics were washed with brine. The organics were then dried with Na_2SO_4 and the solvent was removed under reduced pressure. The highly insoluble solid was then dissolved in a minimum amount of acetone and recrystallized by vapor diffusion with hexanes over several days, yielding 0.0224 g (0.0679 mmol, 65%) of **5.21**. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.93 (d, J = 8.4 Hz, 1H), 4.95 – 4.88 (m, 1H), 4.86 – 4.78 (m, 1H), 4.31 – 4.23 (m, 1H), 4.18 (t, J = 12.1 Hz, 1H), 4.00 – 3.93 (m, 2H), 3.91 (d, J = 3.8 Hz, 1H), 3.76 (d, J = 3.4 Hz, 1H), 2.41 (q, J = 10.1 Hz, 1H), 1.92 – 1.79 (m, 2H), 1.70 – 1.52 (m, 2H), 1.47 – 1.17 (m, 8H), 1.14 – 1.01 (m, 1H), 0.87 (t, J = 6.8 Hz, 4H). ^{13}C NMR (126 MHz, DMSO) δ 85.27, 84.14, 70.10, 69.70, 68.34, 54.96, 44.70, 43.10, 39.52, 31.39, 30.22, 27.42, 26.44, 21.96, 13.92. HRMS (ESI) *m*/*z* calculated for $C_{14}H_{29}N_2O_6S$ $[M+NH_4]^+$ 353.1741, found 353.1732.

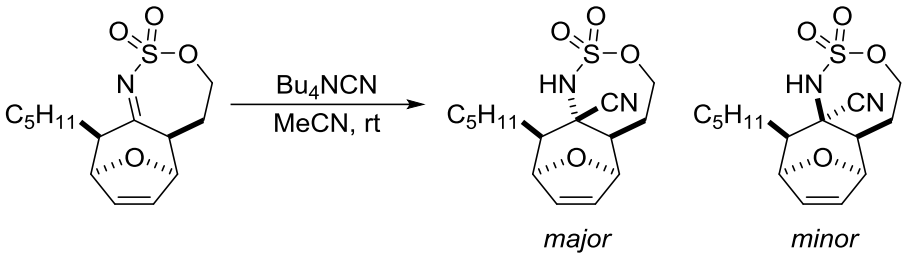
NOE data and 3-D structure:



H_a NOE correlations

$H_b + H_c$	13.9%	H_g	4.0%
H_d	1.5%	H_h	0%
H_e	0%	H_i	1.3%
H_f	0%	H_j	2.0%





80%, 4.7:1 *dr*

Compound 5.22. A 10 mL, one-neck roundbottom flask equipped with a stirbar was charged with compound **5.9a** (32.7 mg, 0.109 mmol, 1 equiv) and 1 mL MeCN. Tetrabutylammonium cyanide (40.3 mg, 0.150 mmol, 1.5 equiv) was then added in one portion, and the mixture was stirred at rt for 1.5 h. The solution was diluted with CH_2Cl_2 and washed successively with sat. NH_4Cl and brine in a separatory funnel. The organic layers were dried over Na_2SO_4, concentrated by rotary evaporation, and purified by silica gel chromatography (5% to 40% EtOAc/hexanes) to give 23.7 mg of the major diastereomer **5.22** as a white solid, and 5.0 mg of the minor diastereomer as a colorless oil. Combined, this amounts to 28.7 mg (0.0880 mmol, 80%) in a 4.7:1 *dr*. It was assumed that the major diastereomer resulted from axial addition of cyanide, as similarly sterically small hydride sources (ie, $NaBH_3CN$) had been observed to give axial reduction. Major diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.46 (dd, *J* = 6.1, 1.1 Hz, 1H), 6.35 (dd, *J* = 6.1, 1.0 Hz, 1H), 4.81 (bs, 1H), 4.77 (s, 1H), 4.62 (bs, 1H), 4.50 (ddd, *J* = 12.4, 5.1, 2.7 Hz, 1H), 4.43 (td, *J* = 12.4, 3.1 Hz, 1H), 2.58 (dt, *J* = 12.2, 2.6 Hz, 1H), 2.33 (m, 1H), 1.96 (dq, *J* = 15.4, 2.6 Hz, 1H), 1.86 (dt, *J* = 10.4, 3.4 Hz, 1H), 1.74 (m, 1H), 1.50 – 1.30 (m, 7H), 0.92 (app t, *J* = 6.6 Hz,

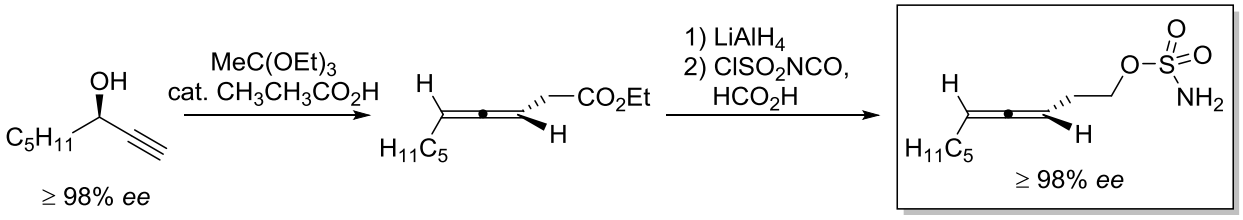
3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.6, 132.2, 116.6, 81.6, 79.5, 69.8, 59.3, 47.0, 46.9, 31.9, 29.7, 27.8, 27.1, 22.6, 14.1. HRMS (ESI) *m*/*z* calculated for $C_{15}H_{26}N_3O_4S$ $[M+NH_4]^+$ 344.1639, found 344.1643. Minor diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.47 (dd, *J* = 6.1, 1.9 Hz, 1H), 6.33, (d, *J* = 6.1 Hz, 1H), 4.95 (bs, 1H), 4.86 (s, 1H), 4.57 (dd, *J* = 3.6, 1.9 Hz, 1H), 4.40 (m, 2H), 2.84 (dd, *J* = 11.4, 3.3 Hz, 1H), 2.30 (m, 1H), 2.00 (dd, *J* = 10.3, 4.3 Hz, 1H), 1.86 (app d, *J* = 15.9 Hz, 1H), 1.81 (m, 1H), 1.69 (m, 1H), 1.40 – 1.20 (m, 6H), 0.91 (app t, *J* = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.2, 131.3, 120.7, 81.3, 79.3, 69.8, 57.4, 43.5, 39.8, 31.8, 30.8, 27.1, 27.1, 22.7, 14.1. HRMS (ESI) *m*/*z* calculated for $C_{15}H_{26}N_3O_4S$ $[M+NH_4]^+$ 344.1639, found 344.1638.

5.5.9. Transfer of chirality studies

Demonstration of erosion of chirality for –C_5H_{11} substrate 6a

The enantioenriched substrate used for transfer-of-chirality experiments was synthesized from 98+% *ee* (*R*)-(+)-1-octyn-3-ol (Alfa Aesar #L19045) by known methods, as indicated in Scheme S-2.[4b] The % *ee* of the homoallenic sulfamate **5.6a** could not be readily determined by chiral HPLC, so it was assumed to be ≥98% *ee*.[7]

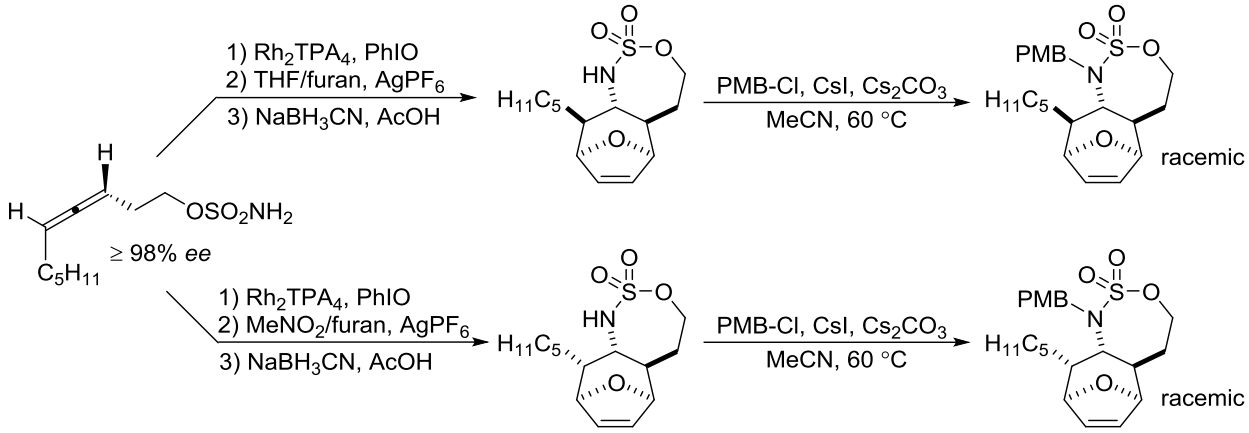
Scheme 5.6. Synthesis of enantioenriched C_5H_{11}-substituted allene.



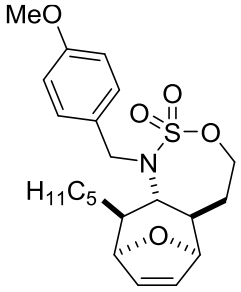
The enantioenriched substrate **5.6a** was carried through the reaction sequence illustrated below in Scheme S-3 in order to obtain compounds **5.12a** and **5.14a**. These compounds were then alkylated using *p*-methoxybenzyl chloride as described in the procedures below in order to obtain compounds suitable for UV/Vis detection. As demonstrated by the HPLC traces given below,

both products were obtained as a racemate, indicating that the stereochemistry of the allene was not transferred to the [4+3] products.

Scheme 5.7. Synthesis of PMB-protected [4+3] products.

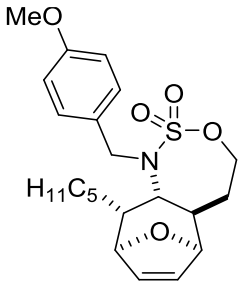


Procedure for PMB-protection and HPLC analysis of the PMB-protected products:



Compound 5.S2. A ½-dram screwcap vial equipped with a stirbar was charged with compound **5.12a** (9.8 mg, 0.0326 mmol, 1 equiv), cesium iodide (0.9 mg, 0.003 mmol, 0.1 equiv), and cesium carbonate (21.6 mg, 0.0664 mmol, 2 equiv). Dry MeCN (0.42 mL) was then added, and the vial was capped and warmed to 60 °C with stirring in an oil bath. At 30 minutes, TLC analysis (10% EtOAc/CH_2Cl_2, CAM stain) indicated that the starting material had been consumed. The vial was then cooled to rt, and the solution transferred to a separatory funnel with EtOAc. The solution was further diluted with EtOAc and washed with one portion of water and one portion of brine. The organic layer was dried over Na_2SO_4, concentrated by rotary evaporation, and purified by column chromatography (20% to 70% EtOAc/hexanes) to give the desired product (11.0 mg, 0.261 mmol,

80%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (d, J= 8.5 Hz, 2H), 6.86 (d, *J* = 8.5 Hz, 2H), 6.25 (m, 2H), 4.87 (d, *J* = 16.2 Hz, 1H), 4.71 (dd, *J* = 4.0, 0.8 Hz, 1H), 4.59 (dd, *J* = 3.8, 1.2 Hz, 1H), 4.25 (d, *J* = 16.2 Hz, 1H), 4.24 (dt, *J* = 12.4, 3.4 Hz, 1H), 4.15 (app t, *J* = 12.4 Hz, 1H), 3.79 (s, 3H), 3.39 (t, *J* = 10.2 Hz, 1H), 2.26 (m, 1H), 1.82 (dt, *J* = 14.9, 3.5 Hz, 1H), 1.72 (tdd, *J* = 10.8, 3.9, 2.4 Hz, 1H), 1.61 (m, 1H), 1.31 (m, 1H), 1.07 (m, 3H), 0.88 (m, 2H), 0.77 (t, *J* = 7.4 Hz, 3H), 0.71 (m, 1H), 0.33 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.2, 131.8, 130.4, 130.3, 129.0, 114.1, 81.1, 80.2, 68.4, 60.6, 55.4, 49.9, 39.7, 38.7, 32.0, 31.2, 28.9, 26.5, 22.7, 14.1. HRMS (ESI) *m*/*z* calculated for $C_{22}H_{35}N_2O_5S$ [M+NH_4^+] 439.2340, found 439.2319. An AD-H column (4.6 mm diameter x 258 mm) at a temperature of 40 ºC was employed, using a steady gradient from 5%-60% isopropanol in hexanes over 20 minutes and a flow rate of 0.9 mL/min. The enantiomers were detected at 11.18 and 14.34 minutes, with observation at both 215 nm and 225 nm.

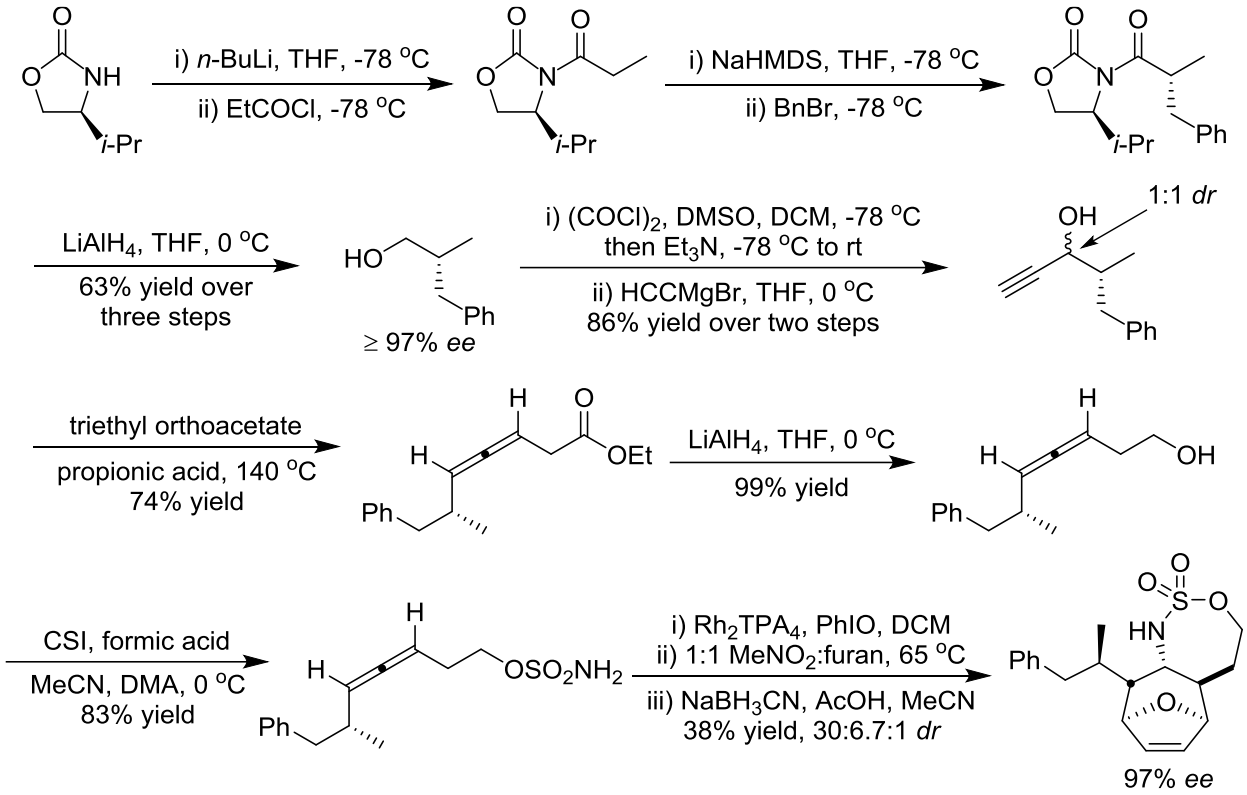


Compound 5.S3. An oven dried 10 ml round bottom flask with stir bar was charged with 0.0193 g (0.0640 mmol, 1 equiv.) of 5.**14a**, 0.0446 g (0.137 mmol, 2.1 equiv.) of Cs_2CO_3, 0.0016 g (0.0062 mmol, 0.1 equiv.) of CsI and 0.85 ml of MeCN (0.08 M). Then 10.8 µl of *p*-methoxybenzyl chloride (0.0797 mmol, 1.2 equiv.) was added and the reaction was heated to 60 ºC for 7 h. The reaction was then quenched with water and the resulting aqueous layer was extracted 3x with EtOAc. The combined organics were then washed with brine, dried with Na_2SO_4 and filtered. The solvent was then removed under reduced pressure and then the crude material was purified by flash chromatography (0 to 50% EtOAc/Hex), yielding 0.0270 g (0.064 mmol, quantitative) of **5.S2**

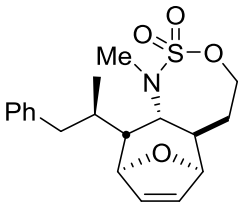
contaminated with a small amount of an impurity. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.3 Hz, 2H), 6.86 (d, *J* = 8.2 Hz, 2H), 6.18 (d, *J* = 6.0 Hz, 1H), 5.98 (d, *J* = 5.9 Hz, 1H), 4.65 (s, 1H), 4.50 (d, *J* = 15.0 Hz, 1H), 4.47 (d, *J* = 3.5 Hz, 1H), 4.27 (d, *J* = 14.9 Hz, 1H), 3.81 (s, 3H), 3.08 (dd, *J* = 11.4, 5.3 Hz, 1H), 2.88 (td, *J* = 11.0, 3.6 Hz, 1H), 1.63 (q, *J* = 7.7 Hz, 2H), 1.56 (d, *J* = 15.1 Hz, 1H), 1.47 – 1.37 (m, 1H), 1.34 – 1.23 (m, 4H), 1.20 (q, *J* = 7.0 Hz, 1H), 1.09 – 0.94 (m, 2H), 0.89 (appt. t, *J* = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.64, 133.56, 130.96, 128.69, 127.92, 113.91, 83.18, 79.90, 69.43, 60.49, 55.39, 54.99, 38.62, 35.61, 33.00, 32.04, 27.08, 25.06, 22.86, 14.23. HRMS (ESI) *m*/*z* calculated for $C_{22}H_{35}N_2O_5S$ $[M+NH_4]^+$ 439.2262, found 439.2261. An AD-H column (4.6 mm diameter x 258 mm) at a temperature of 40 ºC was employed, using a flow rate of 0.9 mL/min and a steady gradient from 5%-60% isopropanol in hexanes over 20 minutes, followed by a five minute holding period at 60% isopropanol/hexanes. The enantiomers were detected at 15.63 and 18.83 minutes, with observation at both 215 nm and 225 nm.

Demonstration of transfer of chirality for substrate 5.6e.

Scheme 5.8. Synthesis of enantioenriched substrate **5.6e** and **5.17**.



In order to set the stereocenter adjacent to the allene, an Evans auxiliary approach was employed based off of literature precedent.[8] The enantioenriched mixture of diastereomeric alcohols was then transformed into the sulfamate as described earlier in Section II. This was carried then through the [4+3] cycloaddition as described in Section VI to yield **5.17**. The major diastereomer proved to be particularly insoluble, precluding it from HPLC analysis. However, methylation as described below provided a compound that was soluble enough for HPLC analysis.

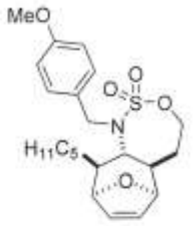


Compound 5.S3. An oven dried ½ dram screwtop vial with stir bar was charged with 0.0171 g (0.0489 mmol, 1 equiv.) of **5.17**, 0.0387 g (0.119 mmol, 2.4 equiv.) of Cs_2CO_3, and 0.72 ml of MeCN (0.07 M). Then 18 µl (0.29 mmol, 6 equiv.) of MeI was added and then the vial was capped and heated to 60 °C. The reaction was complete by TLC after 4.5 h, afterwhich the reaction was quenched with water. The resulting aqueous layer was extracted once with EtOAc. The combined organics were then washed with brine, dried with Na_2SO_4 and filtered. The solvent was then removed before passing the crude material through a silica plug (10% EtOAc/DCM). Removing the solvent and azeotroping the resulting oil two times with $CDCl_3$ yielded 0.0184 g (0.0506 mmol, quantitative yield) of pure **5.S3**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (m, 2H), 7.23 – 7.17 (m, 3H), 6.27 (d, *J* = 6.0 Hz, 1H), 6.15 (d, *J* = 6.0 Hz, 1H), 5.00 (s, 1H), 4.61 (s, 1H), 4.28 (t, *J* = 12.3 Hz, 1H), 4.15 (d, *J* = 11.8 Hz, 1H), 3.05 (t, *J* = 12.1 Hz, 1H), 2.94 – 2.84 (m, 1H), 2.77 – 2.61 (m, 5H), 2.46 – 2.35 (m, 1H), 1.80 (d, *J* = 15.1 Hz, 1H), 1.54 – 1.46 (m, 1H), 1.38 (q, *J* = 14.3, 13.7 Hz, 1H), 1.19 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.29, 134.57, 129.35, 129.26, 128.48, 126.07, 82.64, 78.96, 69.13, 64.45, 43.26, 39.68, 39.18, 35.71, 34.52, 33.19, 18.86. HRMS (ESI) *m*/*z* calculated for $C_{19}H_{26}NO_4S$ [M+H$^+$] 364.1578, found 364.1577. An AD-H column (4.6 mm diameter x 258 mm) at a temperature of 40 °C was employed, using a flow rate of 0.7 mL/min and a steady gradient from 0.02% to 4% isopropanol in hexanes over 90 minutes. The enantiomers were detected at 63.895 and 69.230 minutes, with observation at 215 nm.

1/27/2015 12:20:55 1 / 1

C:\LabSolutions\Data\Chris\July 1 2014\Nels Rac THF NaBH3CN pdt ADH 1.lcd

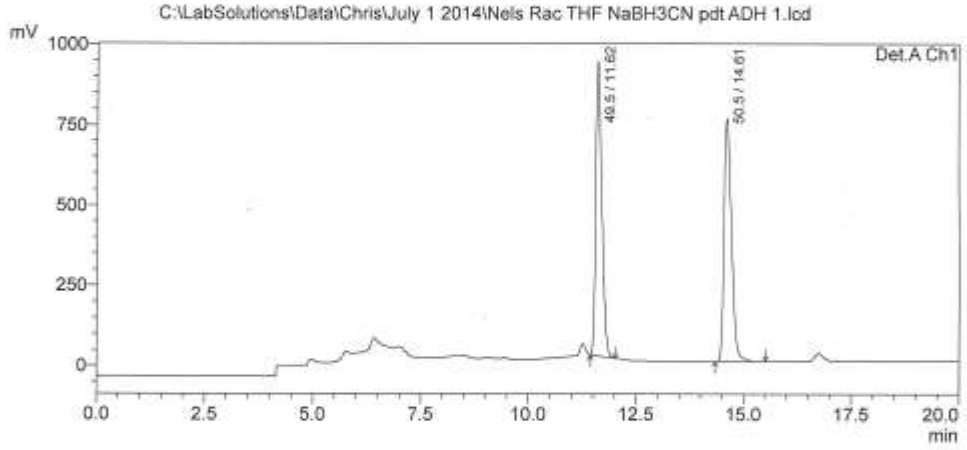
Acquired by	: Admin
Sample Name	: Nels rxn
Sample ID	:
Tray#	: 1
Vail #	: 61
Injection Volume	: 3 uL
Data File Name	: Nels Rac THF NaBH3CN pdt ADH 1.lcd
Method File Name	: 95-5 to 40-60 over 20 min 0.9 flow 215 225 nm.lcm
Batch File Name	: Batch 1 7018.lcb
Report File Name	: Default.lcr
Data Acquired	: 7/1/2014 2:41:00 PM
Data Processed	: 7/1/2014 3:01:02 PM

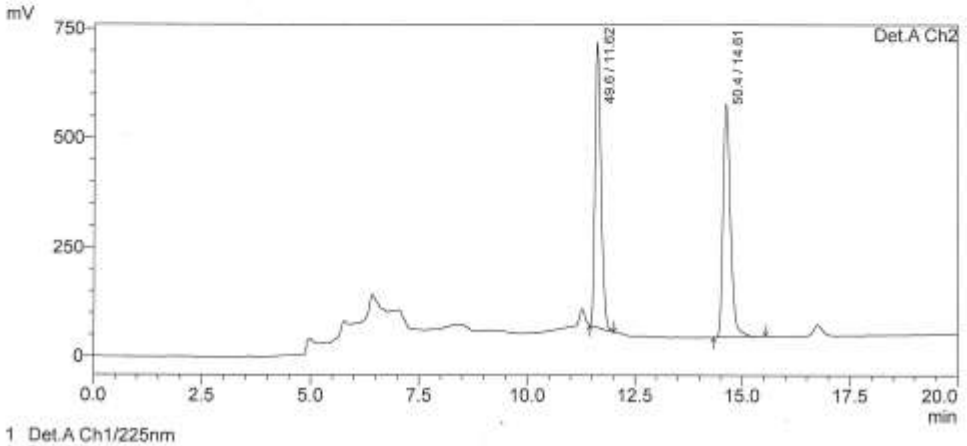


(from racemic allene)

<Chromatogram>

C:\LabSolutions\Data\Chris\July 1 2014\Nels Rac THF NaBH3CN pdt ADH 1.lcd



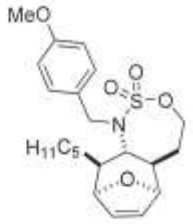


1 Det.A Ch1/225nm
2 Det.A Ch2/215nm

1/27/2015 12:24:40 1 / 1

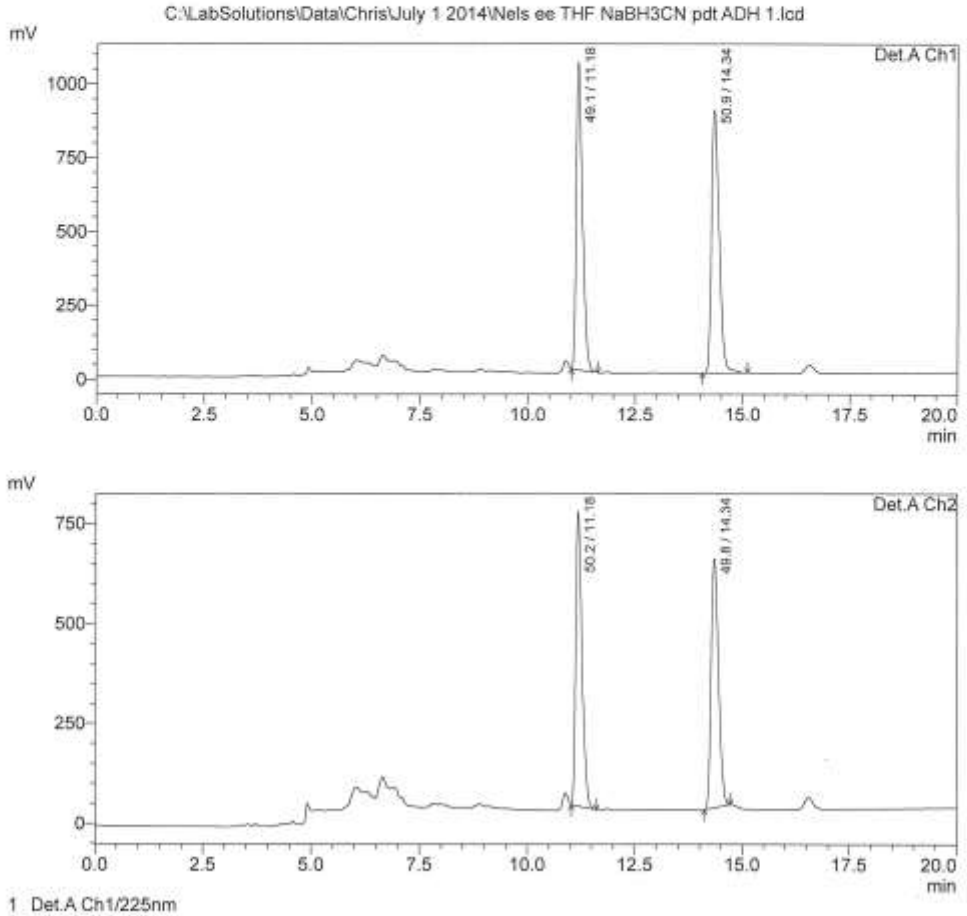
C:\LabSolutions\Data\Chris\July 1 2014\Nels ee THF NaBH3CN pdt ADH 1.lcd

Acquired by	: Admin
Sample Name	: ee THF pdt
Sample ID	:
Tray#	: 1
Vail #	: 62
Injection Volume	: 5 uL
Data File Name	: Nels ee THF NaBH3CN pdt ADH 1.lcd
Method File Name	: 95-5 to 40-60 over 20 min 0.9 flow 215 225 nm.lcm
Batch File Name	: Batch 2 ee THF pdt.lcb
Report File Name	: Default.lcr
Data Acquired	: 7/1/2014 9:30:20 PM
Data Processed	: 7/1/2014 9:50:22 PM



(from enantioenriched allene)

<Chromatogram>

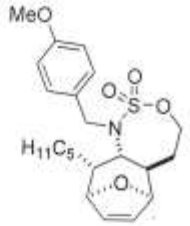


1 Det.A Ch1/225nm
2 Det.A Ch2/215nm

1/27/2015 12:30:21 1 / 1

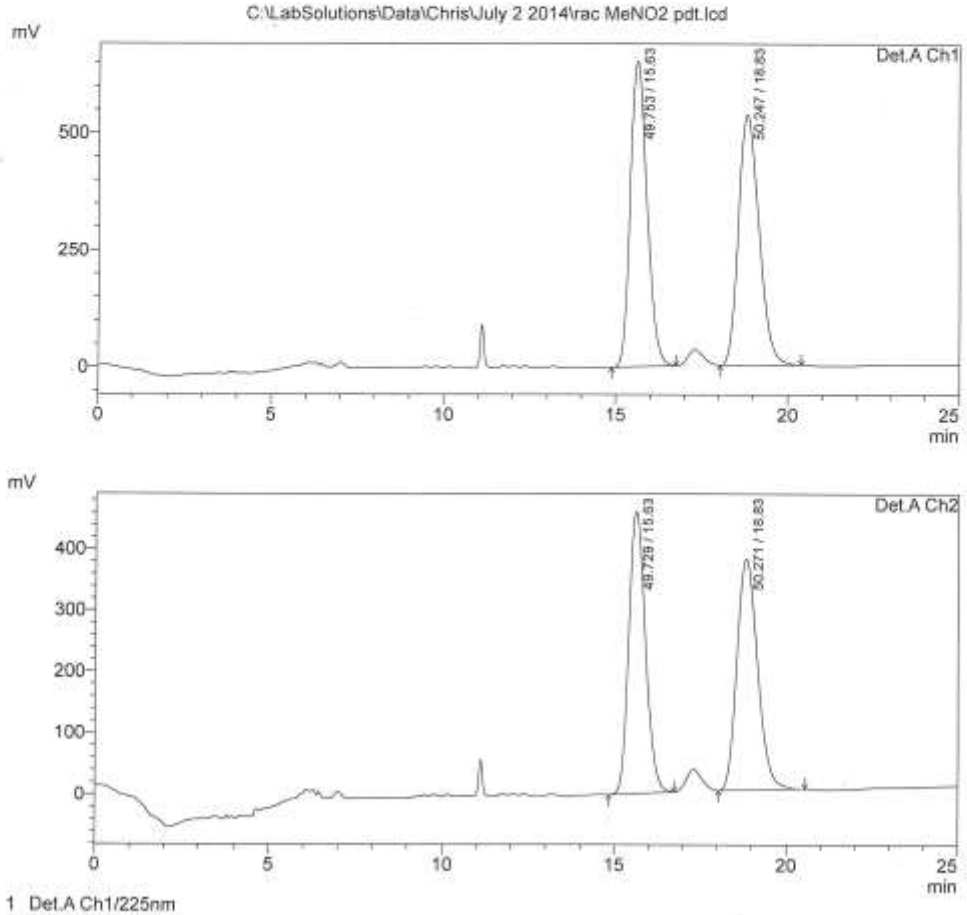
C:\LabSolutions\Data\Chris\July 2 2014\rac MeNO2 pdt.lcd

Acquired by	: Admin
Sample Name	: rac MeNO2 pdt
Sample ID	:
Tray#	: 1
Vail #	: 63
Injection Volume	: 4 uL
Data File Name	: rac MeNO2 pdt.lcd
Method File Name	: CSA method for MeNO2 pdt.lcm
Batch File Name	: Batch 1 MeNO2 pdts.lcb
Report File Name	: Default.lcr
Data Acquired	: 7/2/2014 11:34:53 AM
Data Processed	: 7/2/2014 11:59:55 AM



(from racemic allene)

<Chromatogram>

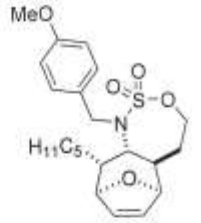


1 Det.A Ch1/225nm
2 Det.A Ch2/215nm

1/27/2015 12:28:37 1 / 1

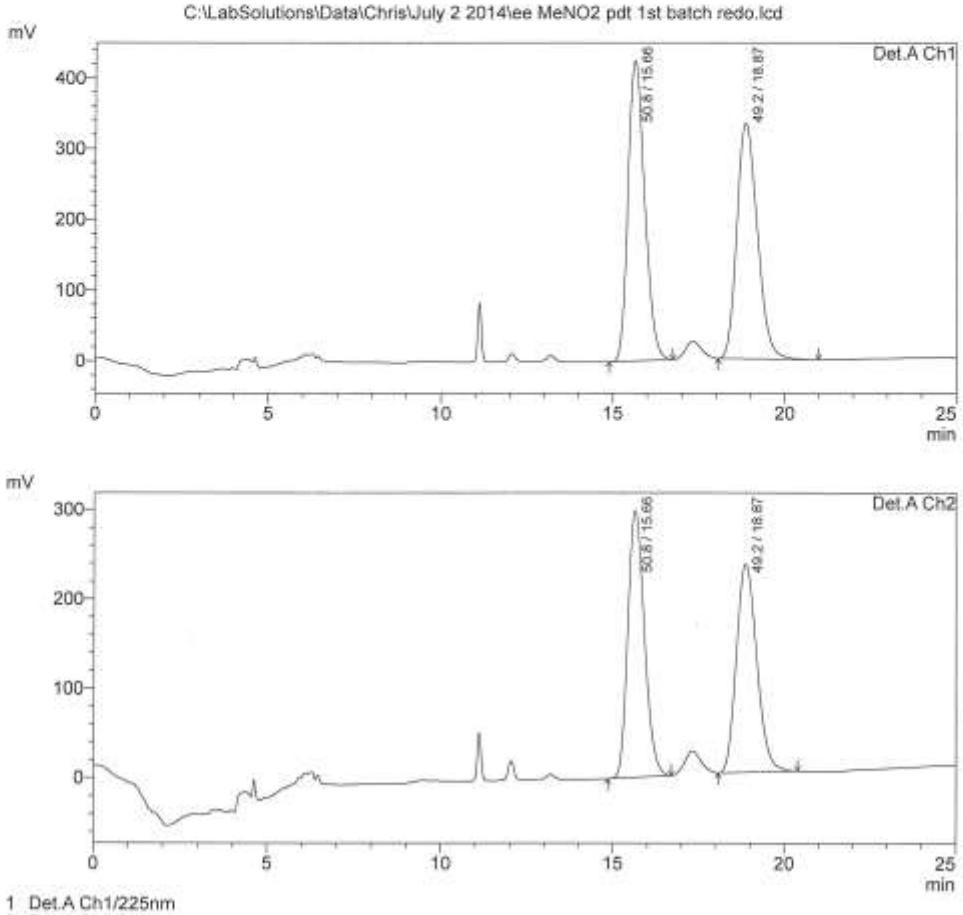
C:\LabSolutions\Data\Chris\July 2 2014\ee MeNO2 pdt 1st batch redo.lcd

Acquired by	: Admin
Sample Name	: ee MeNO2 pdt #1 (redo)
Sample ID	:
Tray#	: 1
Vail #	: 64
Injection Volume	: 4 uL
Data File Name	: ee MeNO2 pdt 1st batch redo.lcd
Method File Name	: CSA method for MeNO2 pdt.lcm
Batch File Name	: Batch 1 MeNO2 pdts.lcb
Report File Name	: Default.lcr
Data Acquired	: 7/2/2014 11:07:02 AM
Data Processed	: 7/2/2014 11:32:03 AM



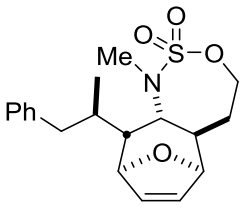
(from enantioenriched allene)

<Chromatogram>

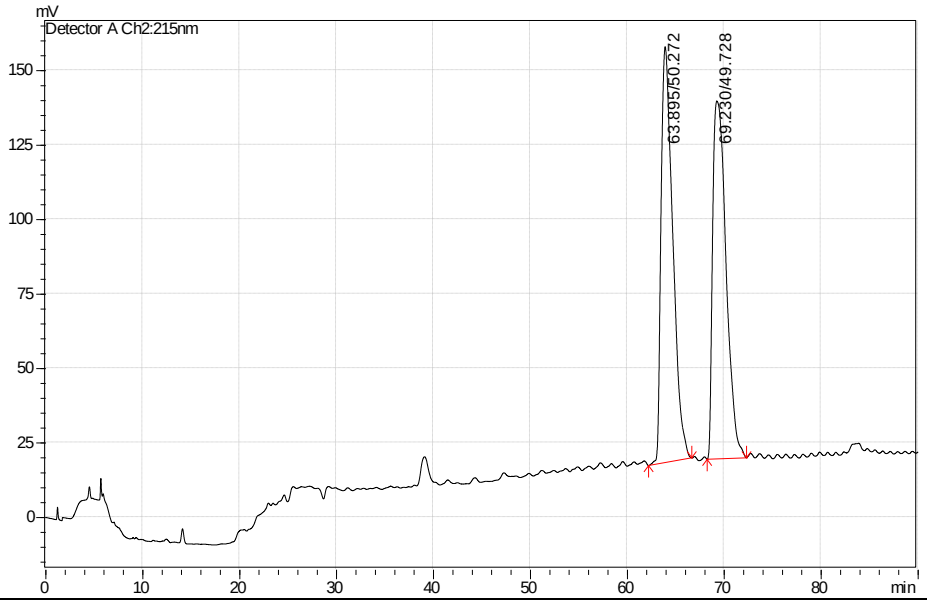


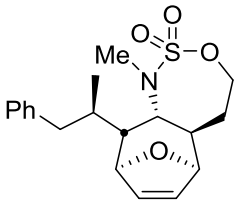
1 Det.A Ch1/225nm
2 Det.A Ch2/215nm

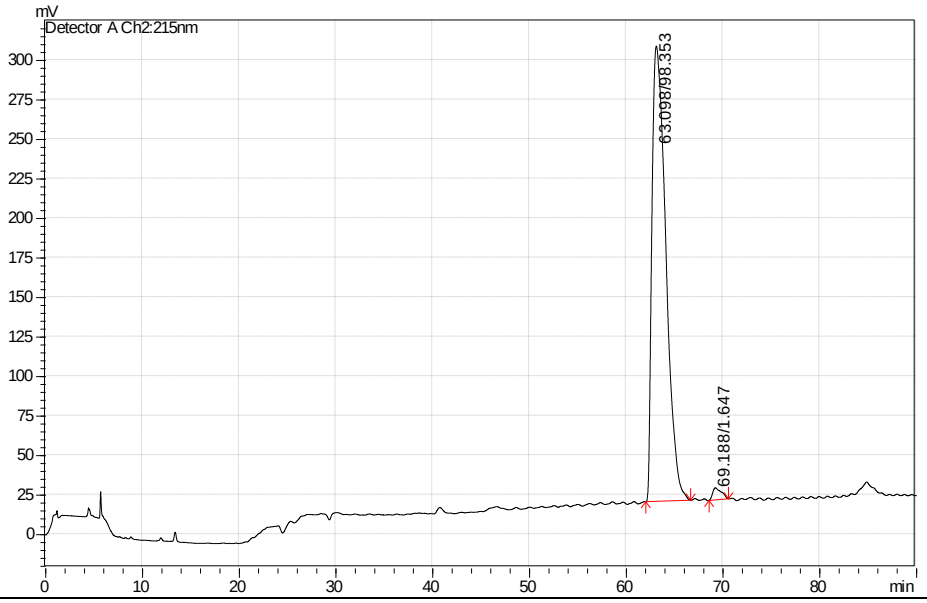
5S.3:



(racemic)







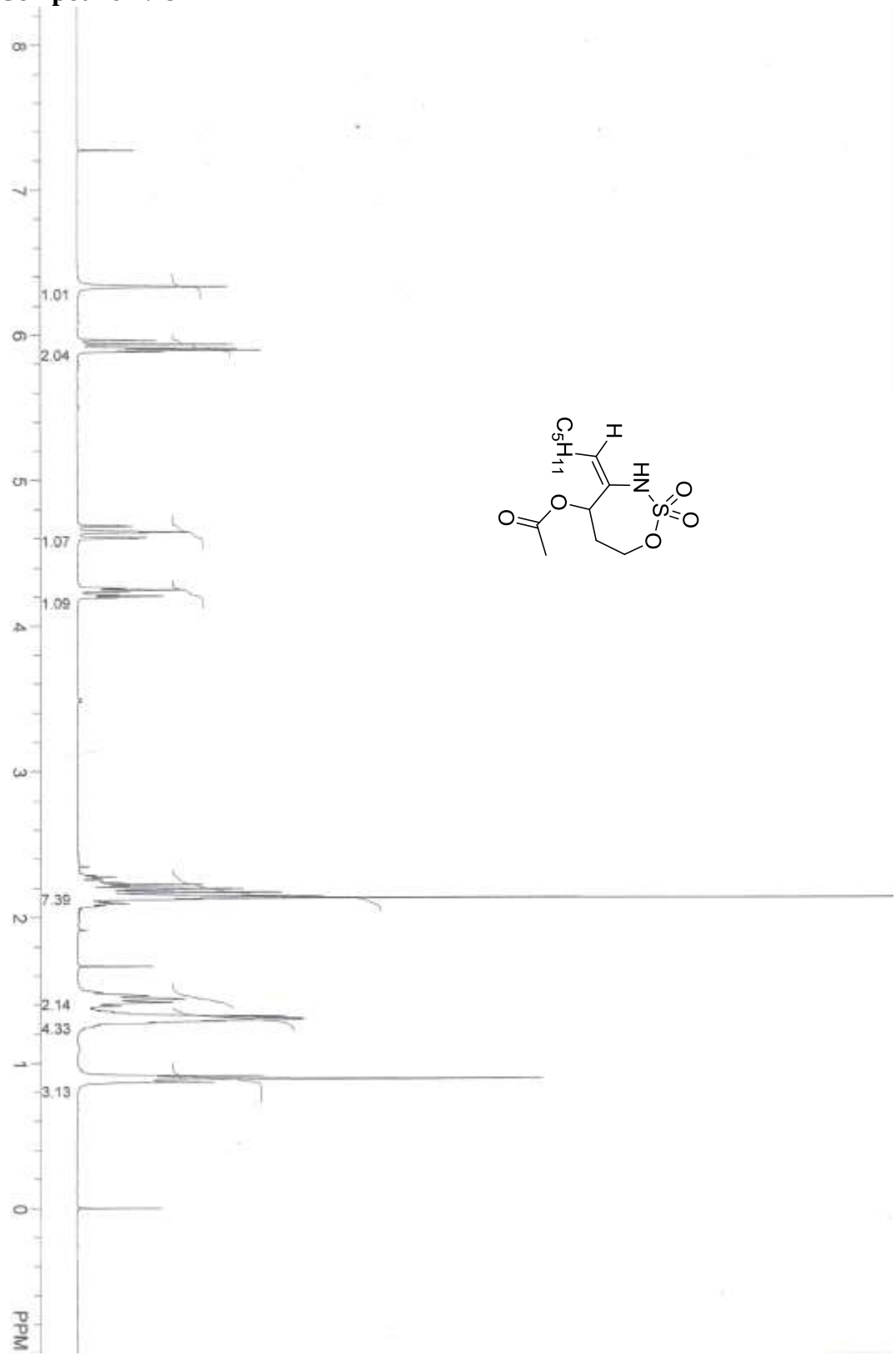
Conditions: Chromatograms were acquired on a Shimadzu Prominence HPLC equipped with a Chiracel AD-H column. Flow rate: 0.7 mL/min.; Oven temp: 40.0 ˚C; Solvent: 0.02% to 4% *i*-PrOH in hexanes over 90 min; Detector: UV @ 215 nm

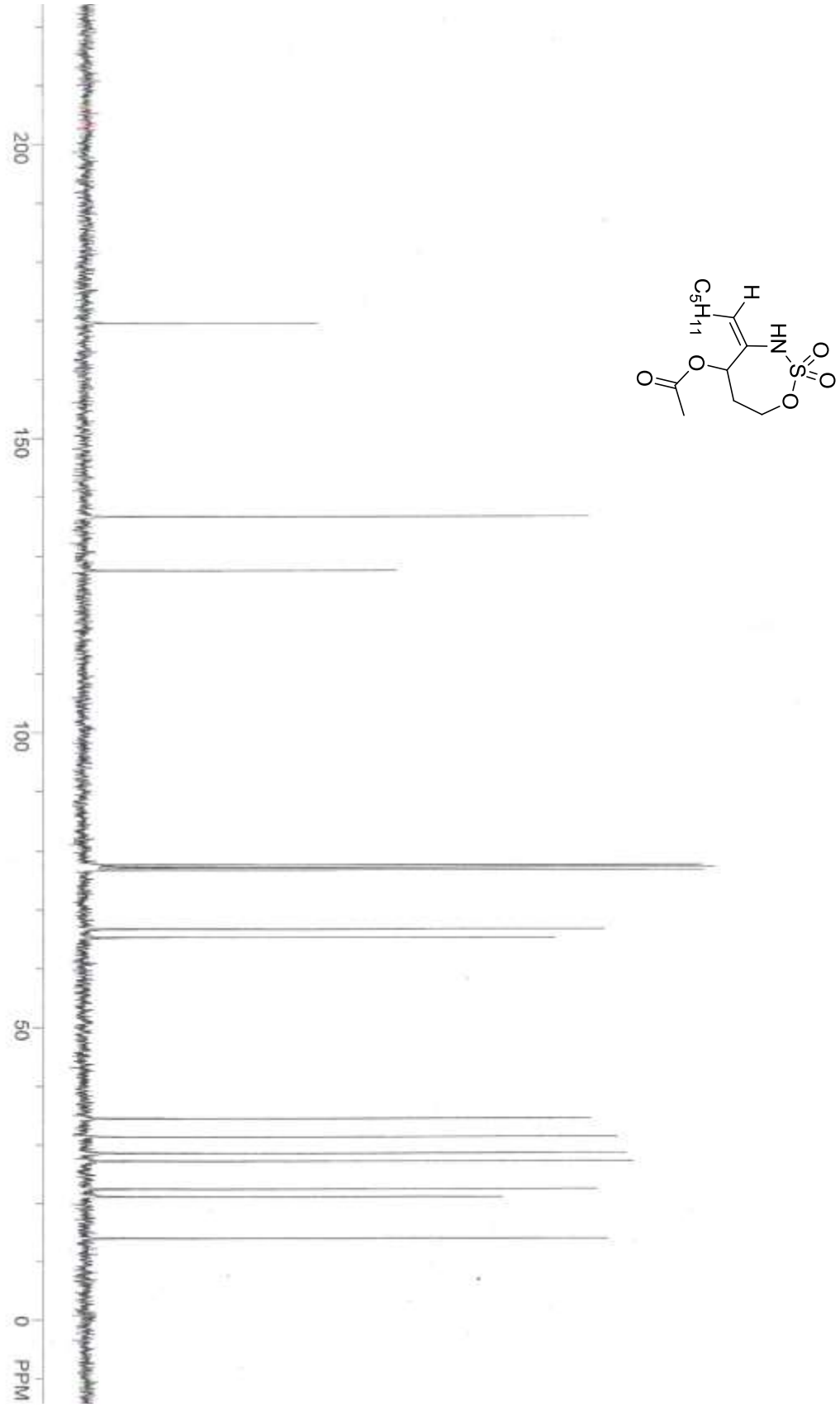
5.5.10. References

1. Armarego, W. L. F.; Chai, C. L. L. *Purification of Laboratory Chemicals* 6th ed., Elsevier: Burlington, MA, **2009**.
2. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem*. **1978**, *43*, 2923.
3. Fiori, K. W.; Espino, C. G.; Brodsky, B. H.; Du Bois, J. *Tetrahedron* **2009**, *65*, 3042.
4. (a) Adams, C. S.; Grigg, R. D.; Schomaker, J. M. *Chem. Sci.* **2014**, *5*, 3046. (b) Boralsky, L. A.; Marston, D.; Grigg, R. D.; Hershberger, J. C.; Schomaker, J. M. *Org. Lett.* **2011**, *13*, 1924. (c) Adams, C. S.; Boralsky, L. A.; Guzei, I. A.; Schomaker, J. M. *J. Am. Chem. Soc.* **2012**, *134*, 10807.
5. Duran, F.; Leman, L.; Ghini, A.; Burton, G.; Dauban, P.; Dodd, R. H. *Org. Lett.* **2002**, *4*, 2481.
6. Brawn, R. A.; Zhu, K.; Panek, J. S. *Org. Lett.* **2014**, *16*, 74.
7. In a previous publication in our group (see reference 4c), it was demonstrated that the homoallenic sulfamate could be generated in >98% *ee* from the same starting material and sequence of steps shown here. However, the HPLC conditions previously used were no longer able to separate the enantiomers of the allene. This is likely due to the degradation of the HPLC through continued use since this previous publication.
8. Simpson, T. J.; Smith, R. W.; Westaway, S. M.; Willis, C. L.; Buss, A. D.; Cannell, R. J. P.; Dawson, M. J.; Rudd, B. A. M. *Tetrahedron* **1997**, *38*, 5367.

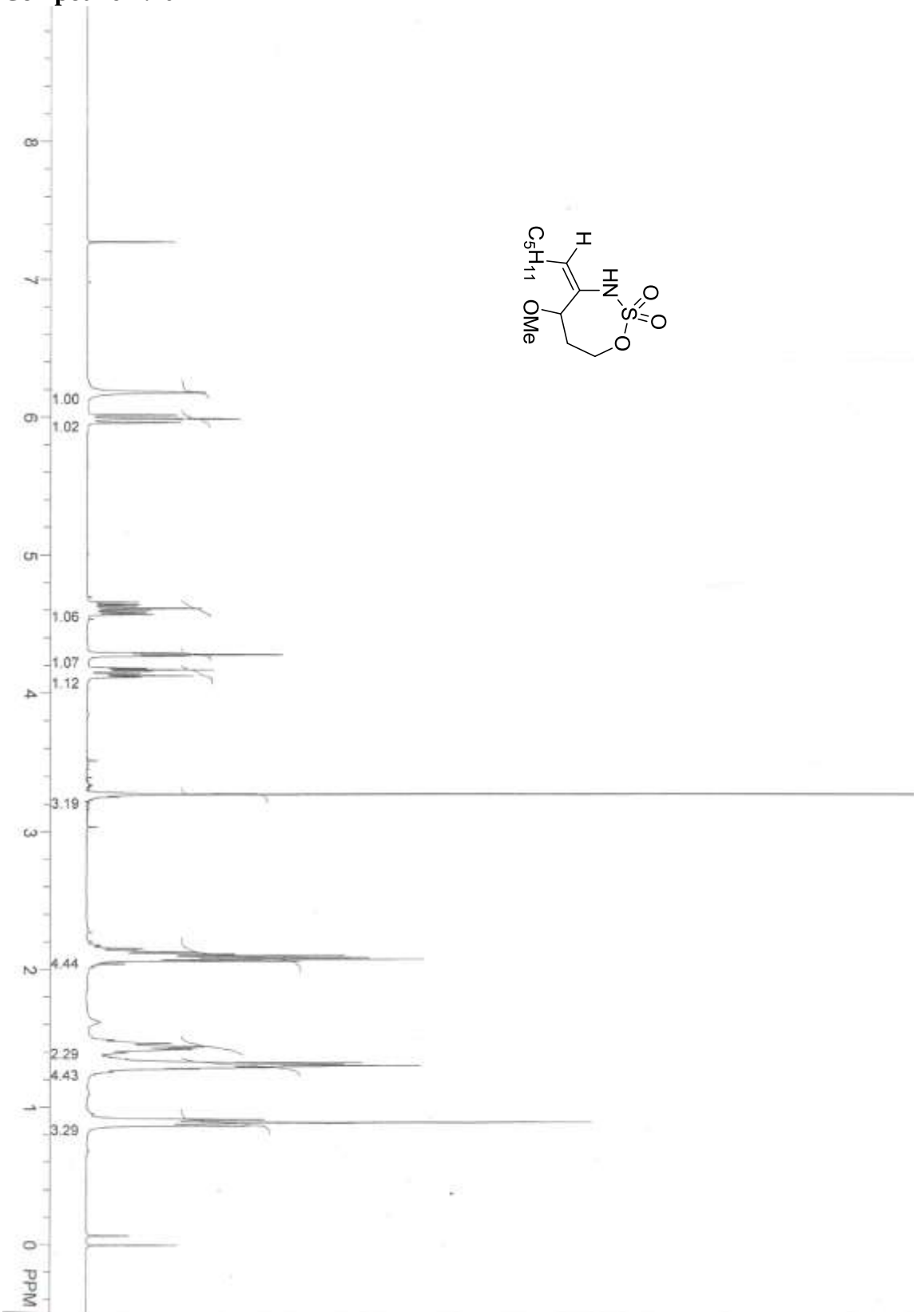
APPENDIX 1 – Selected ^{1}H and ^{13}C Spectra

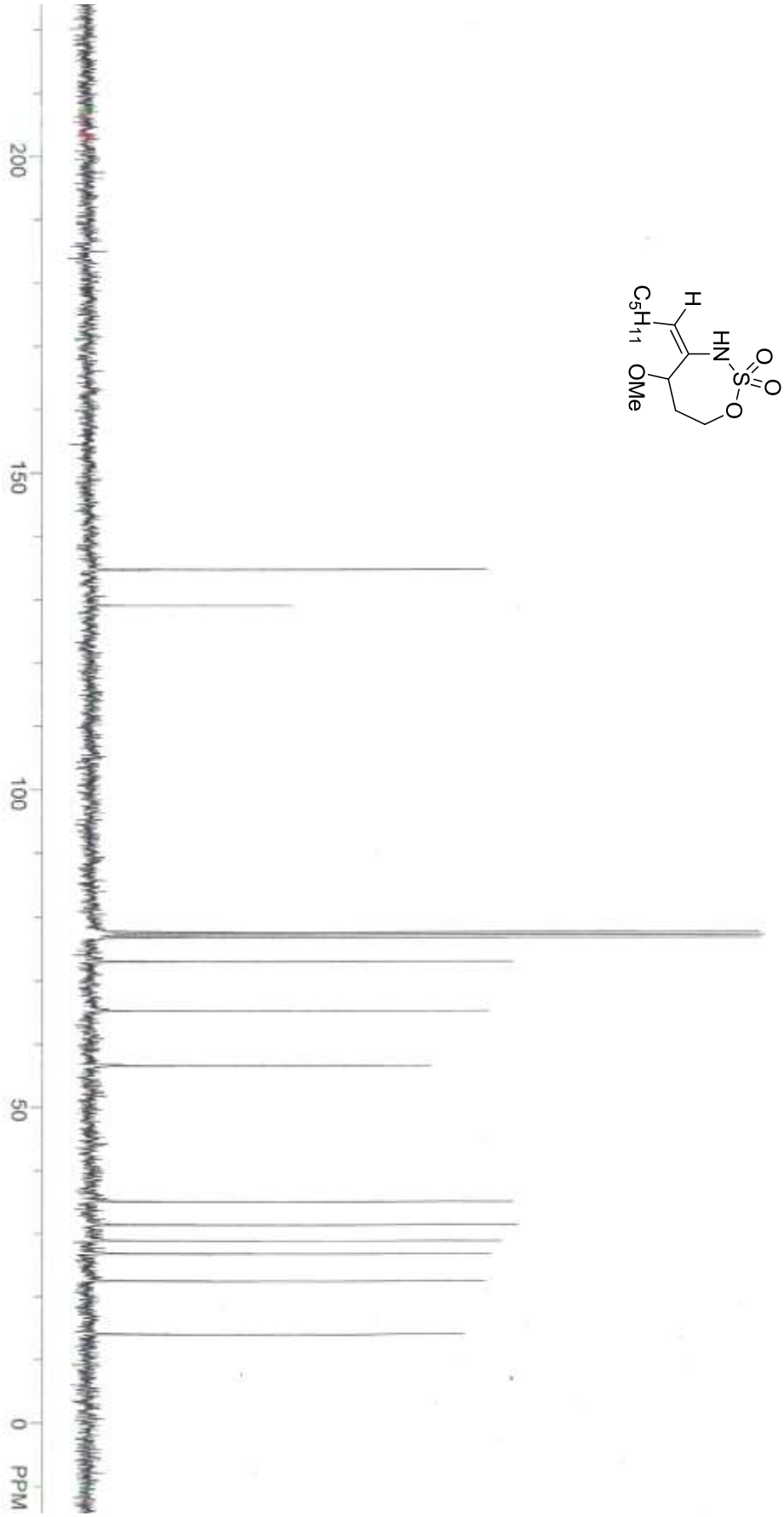
Compound 2.19



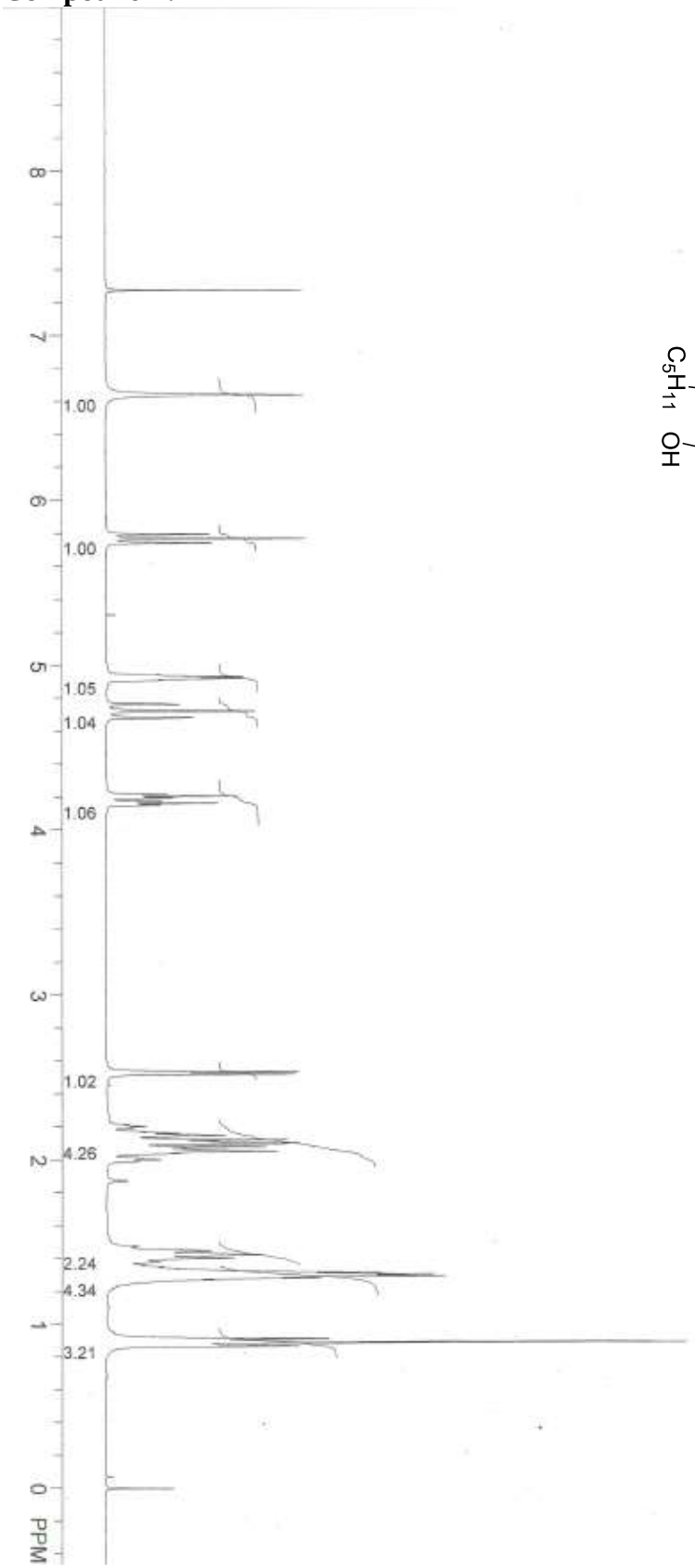

200
150
100
50
0
PPM
H
C_5H_{11}
HN
O
O
O
O
S
O

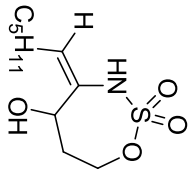
Compound 2.20

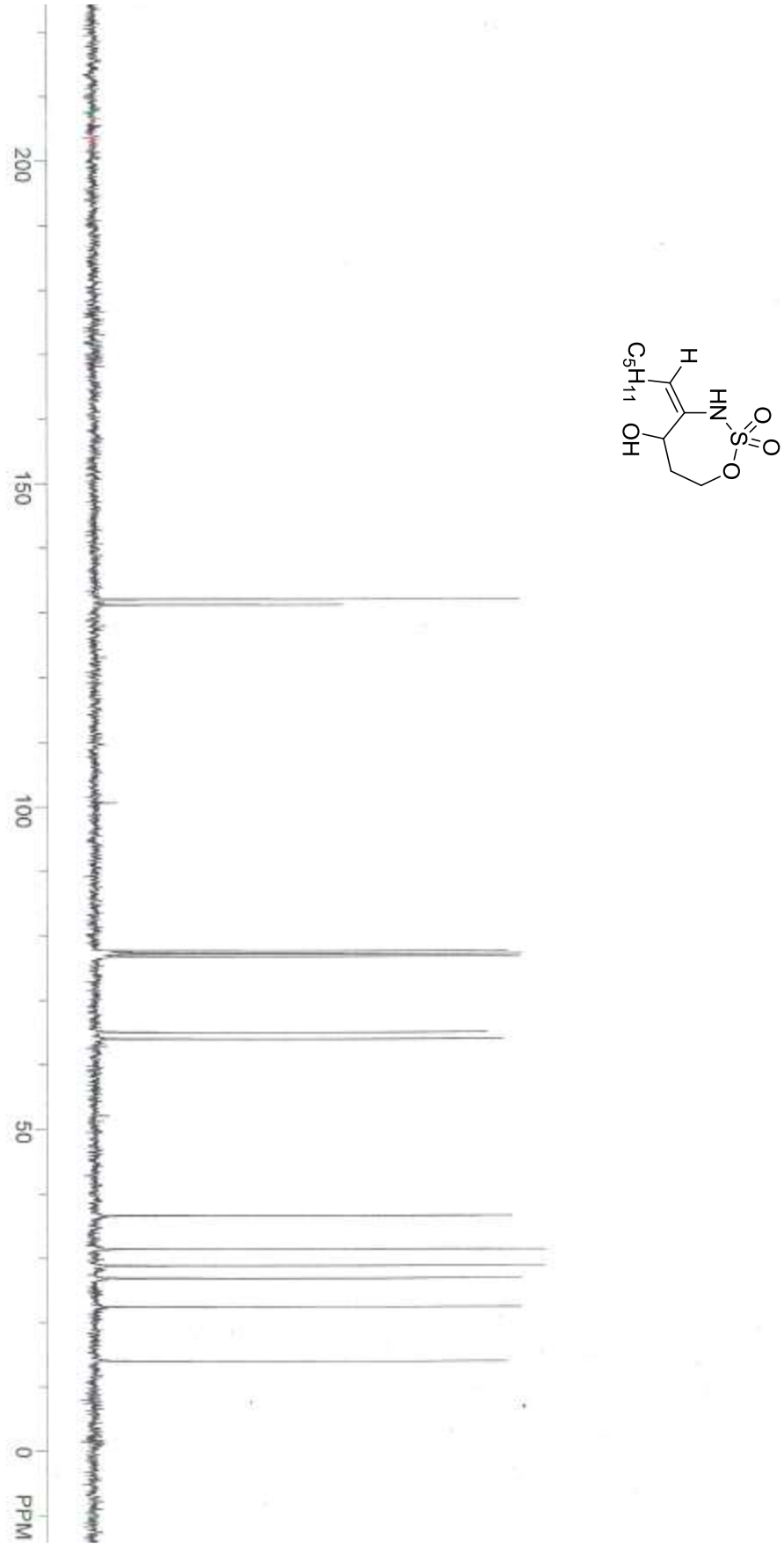



200
150
100
50
0
PPM
H
C5H11
OMe
HN
S
O
O
O

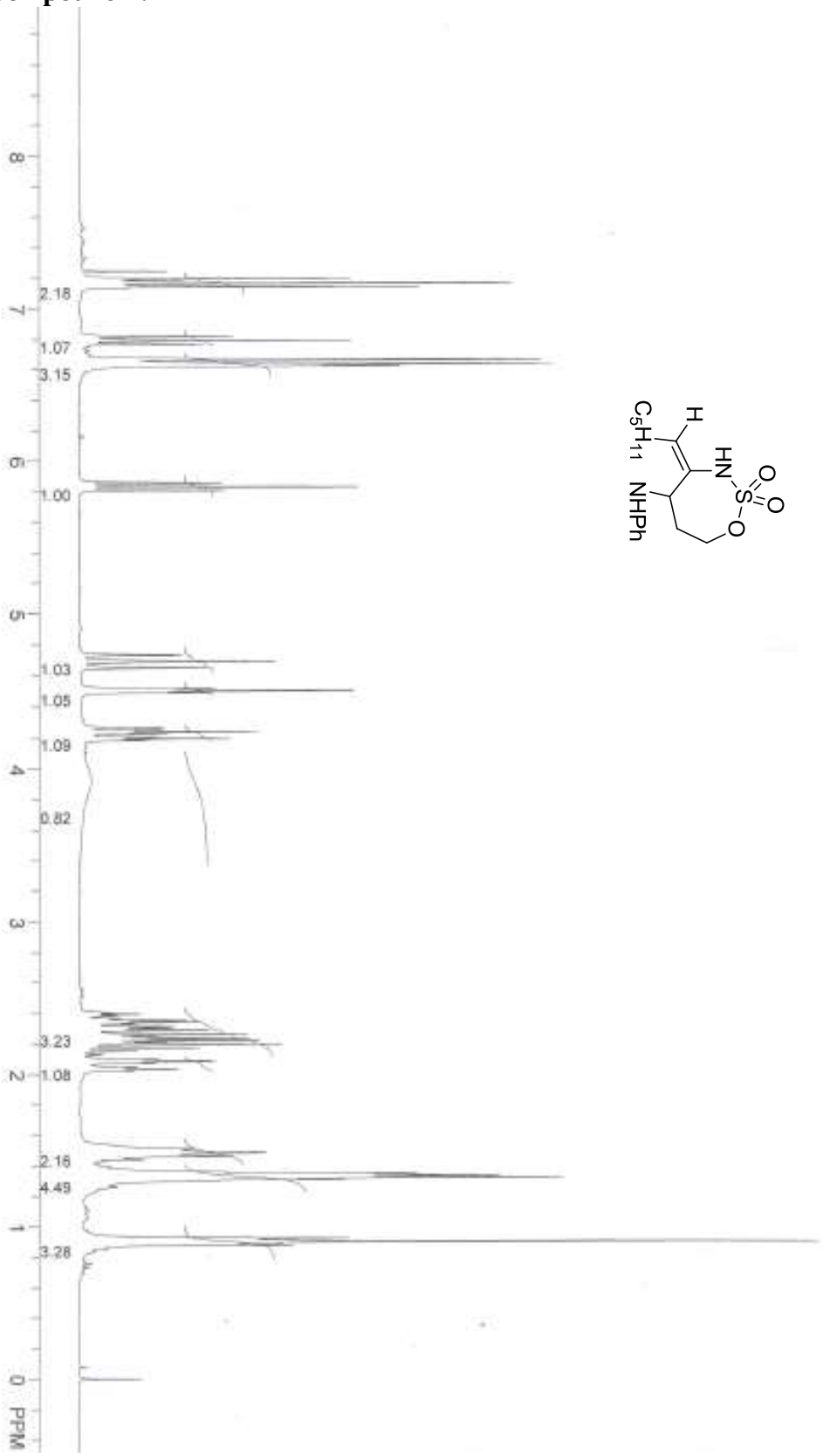
Compound 2.21

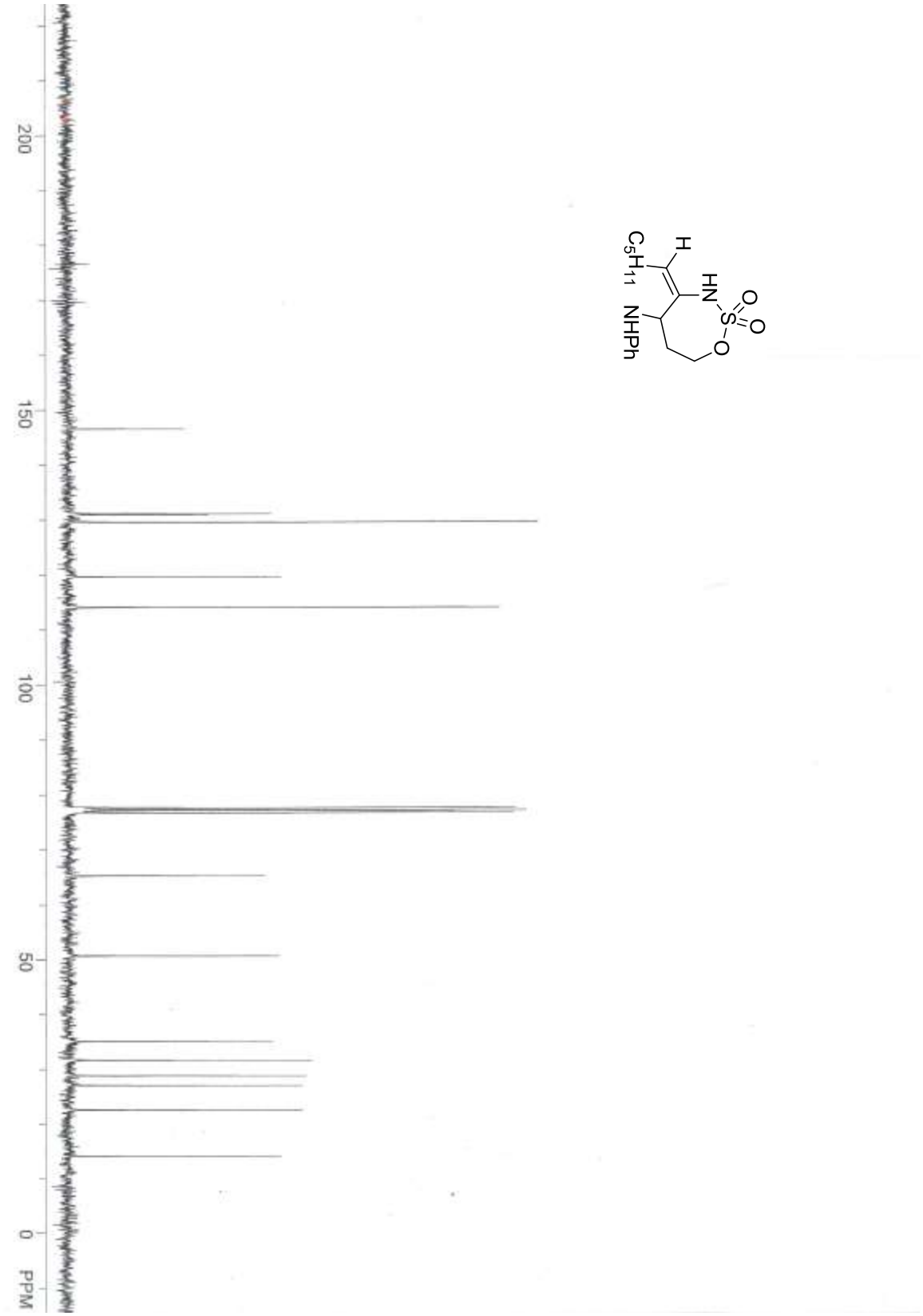




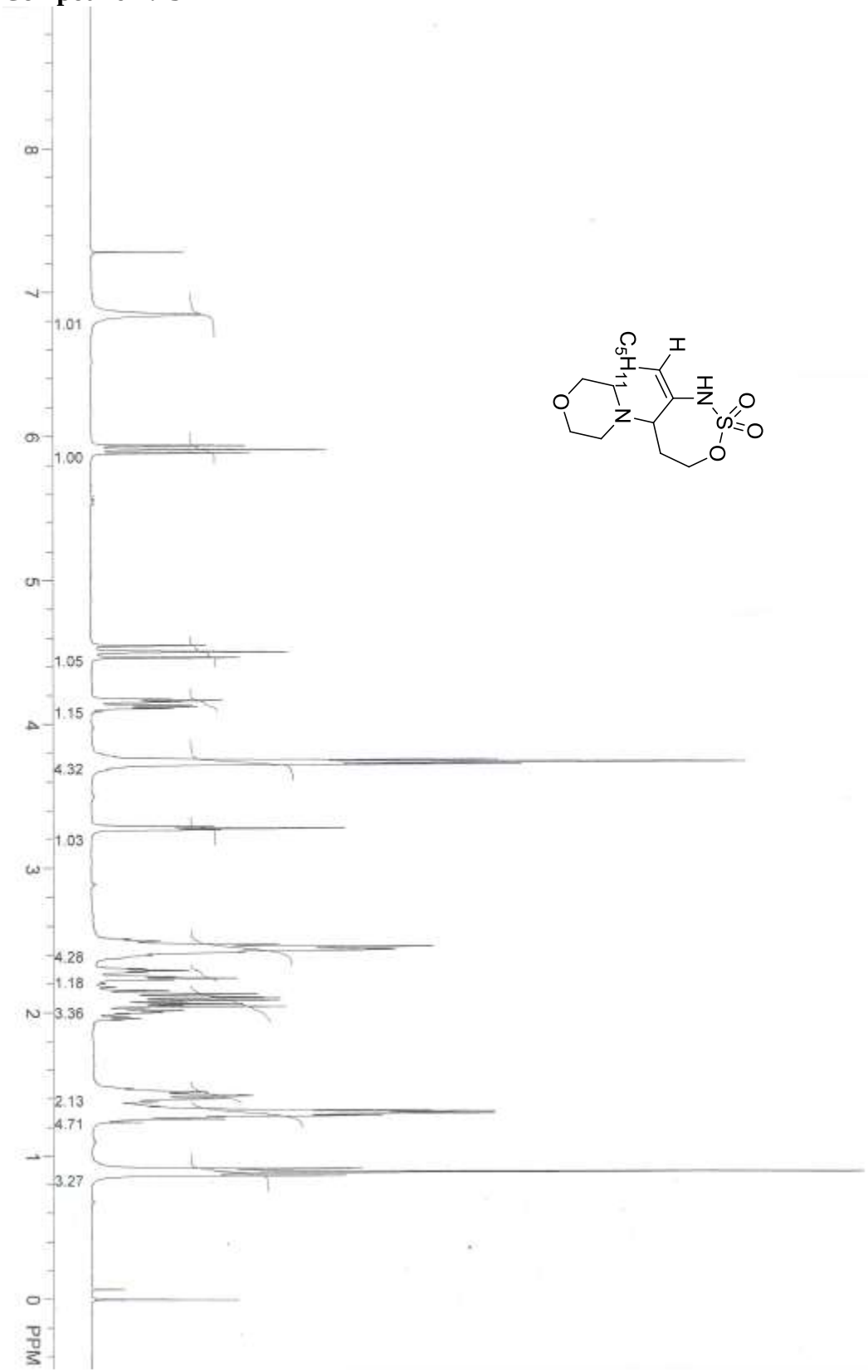

200
150
100
50
0
PPM
H
C_5H_{11}
HN
O
O
S
O
OH

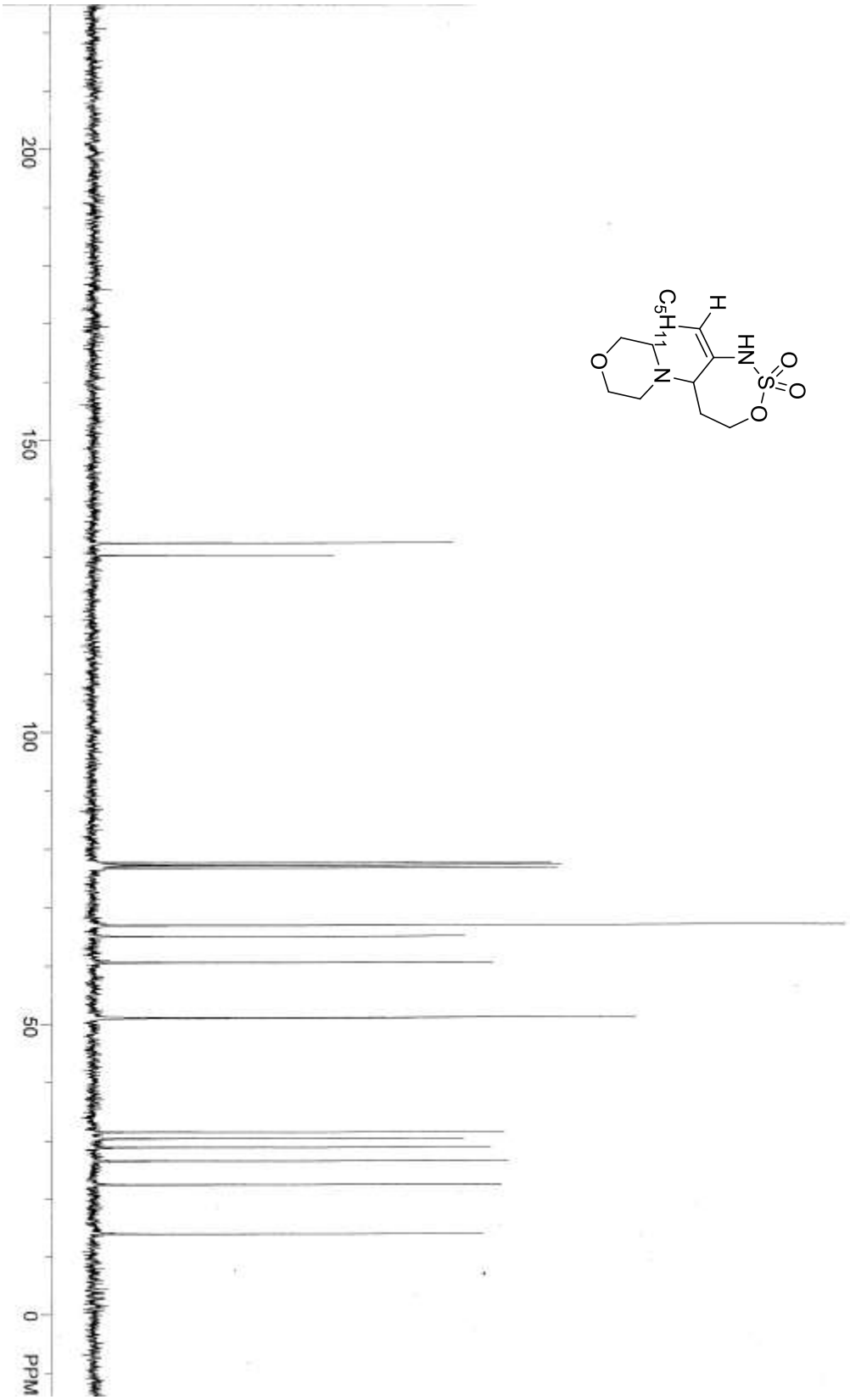
Compound 2.22



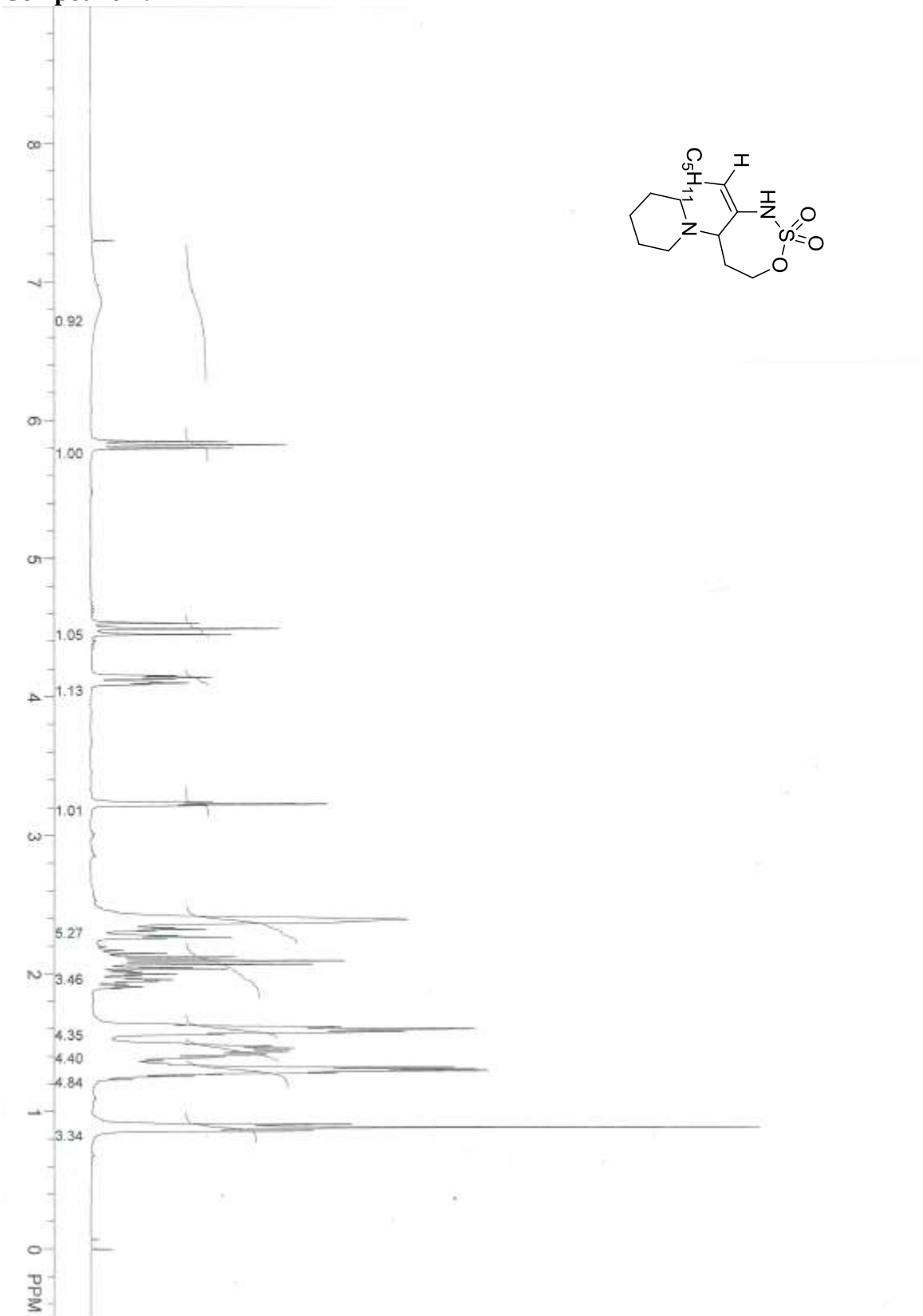

200
150
100
50
0
PPM
H
HN
S
O
O
O
C5H11
NHPh

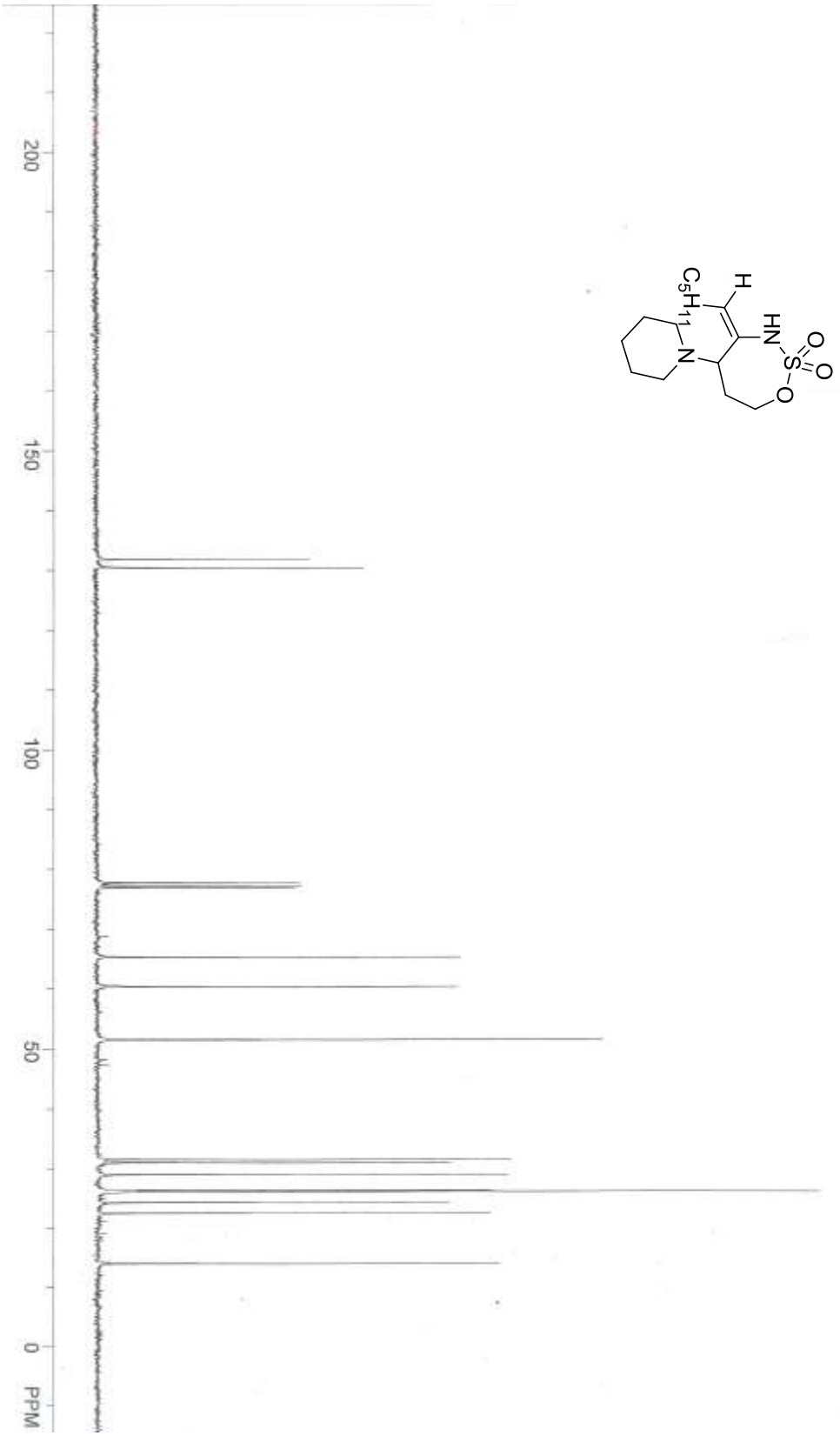
Compound 2.23



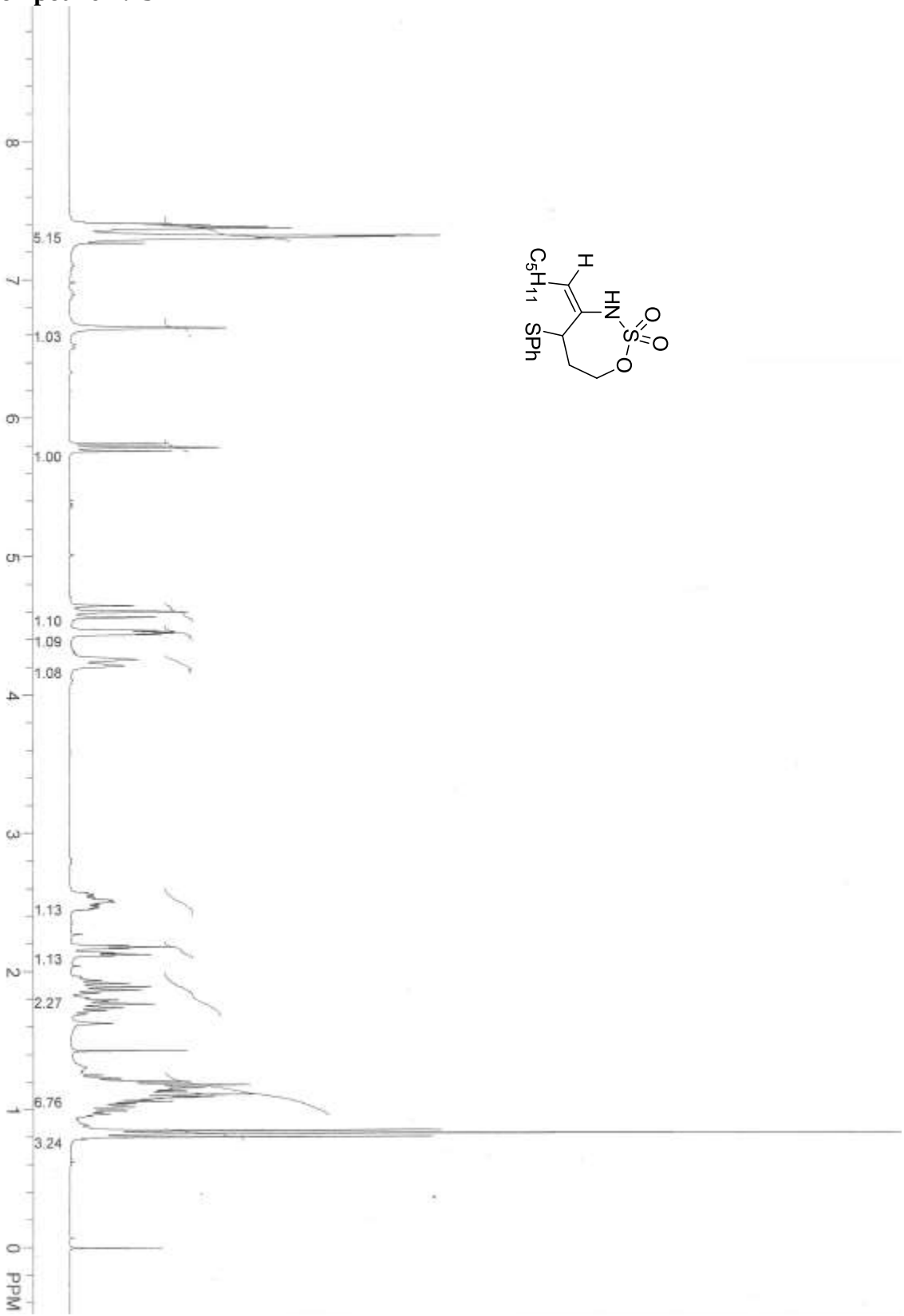

200
150
100
50
0
PPM
C5H11
H
HN
S
O
O
O
N
O

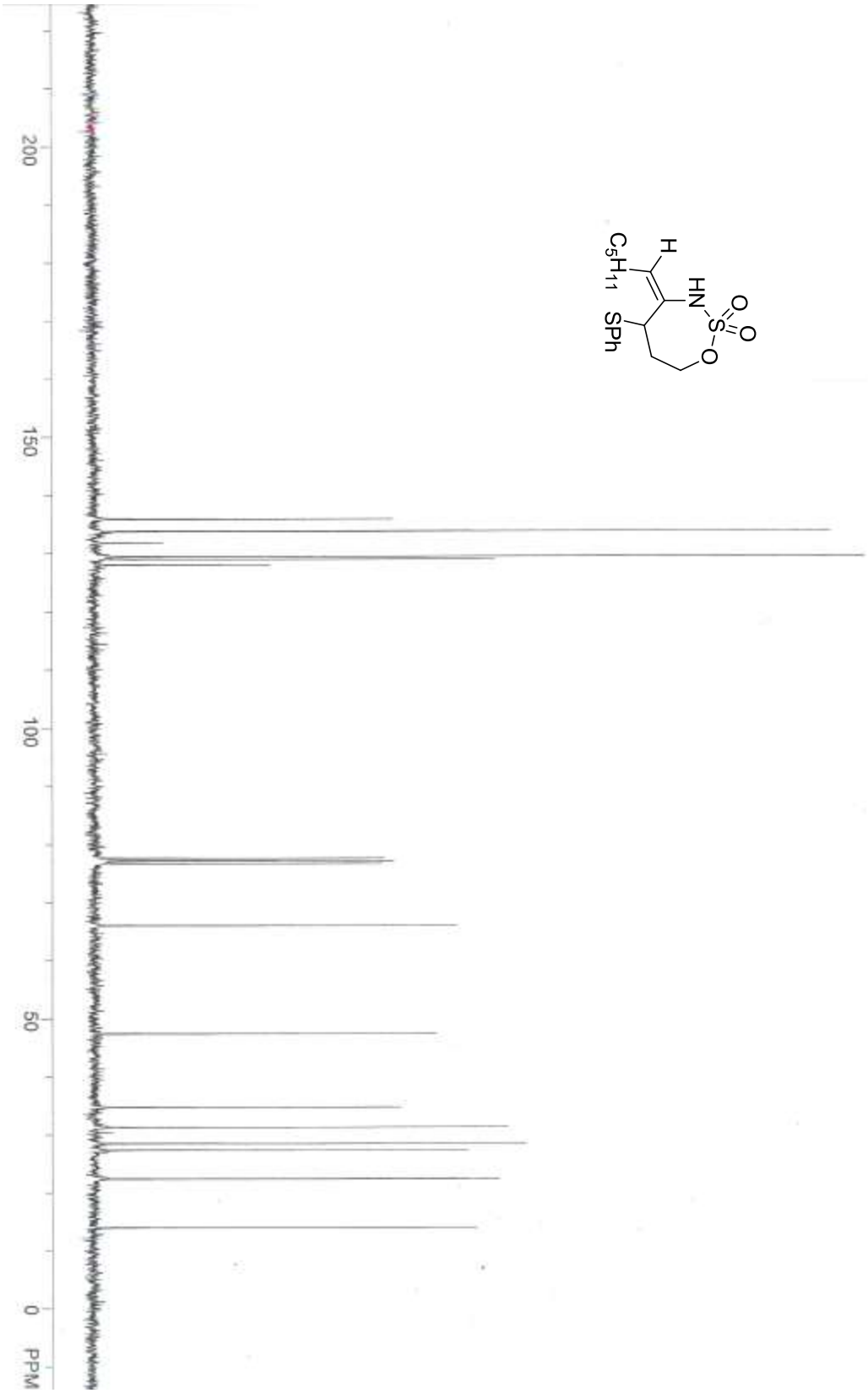
Compound 2.24



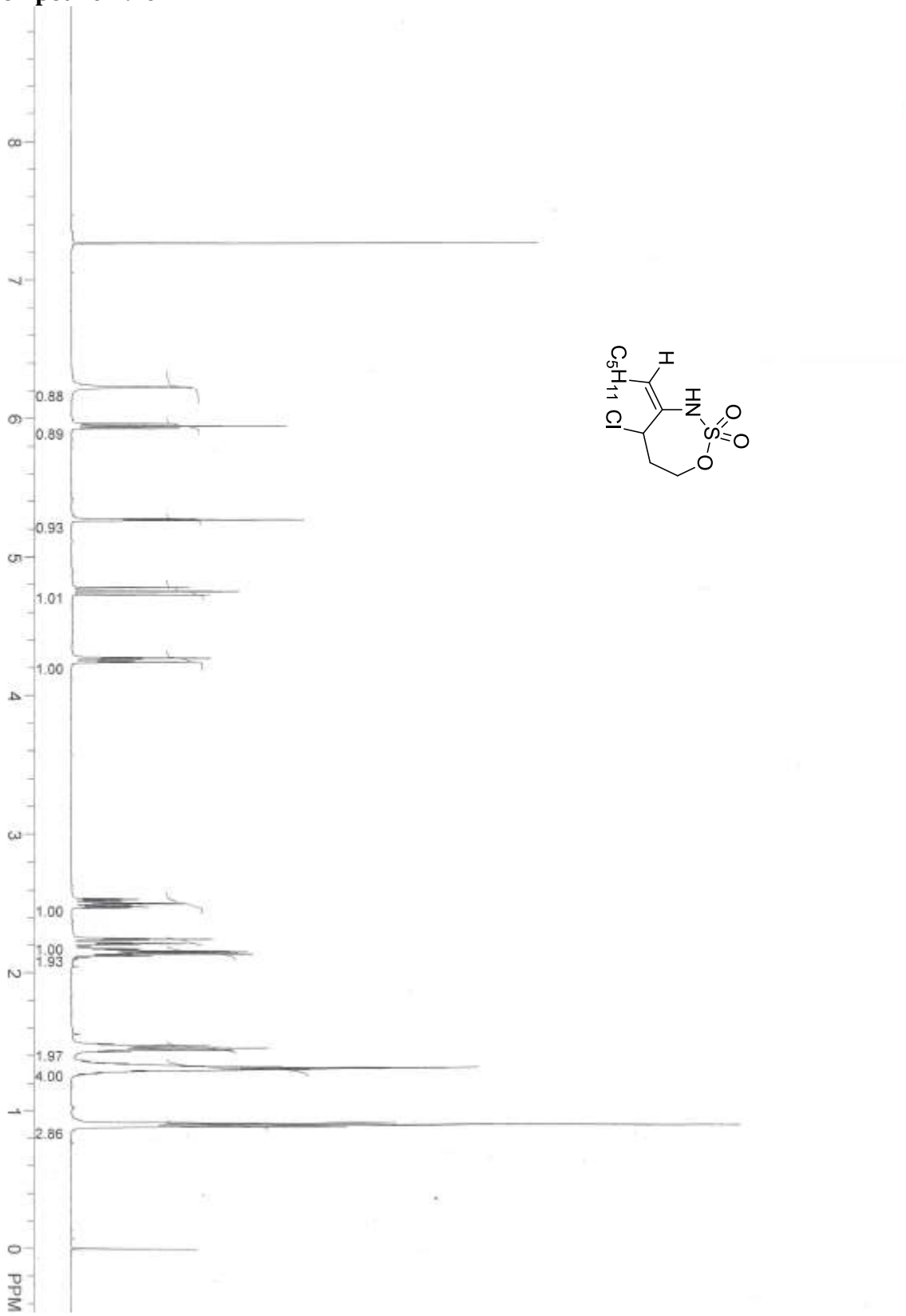

200
150
100
50
0
PPM
H
C_5H_{11}
N
HN
S
O
O
O

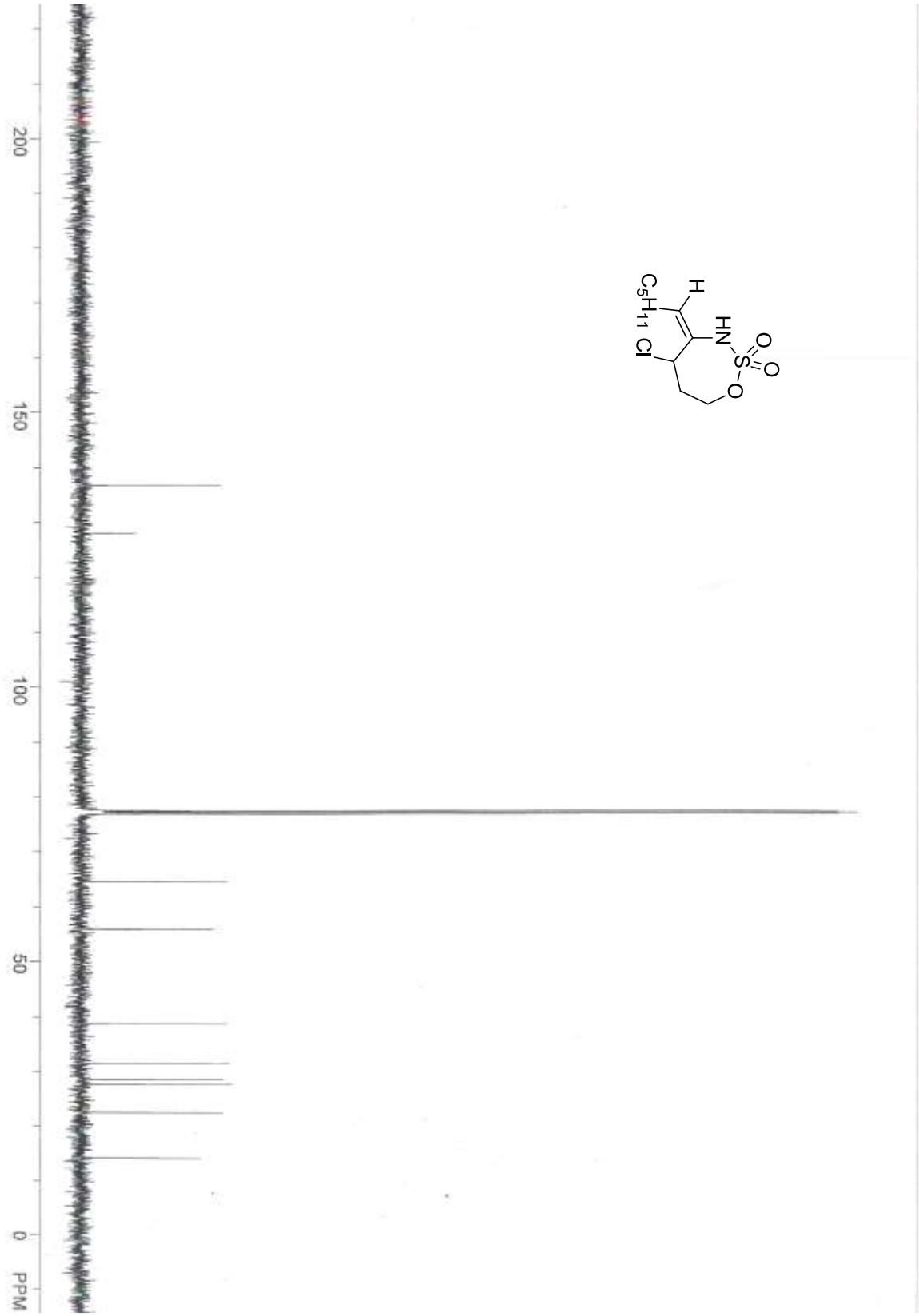
Compound 2.25



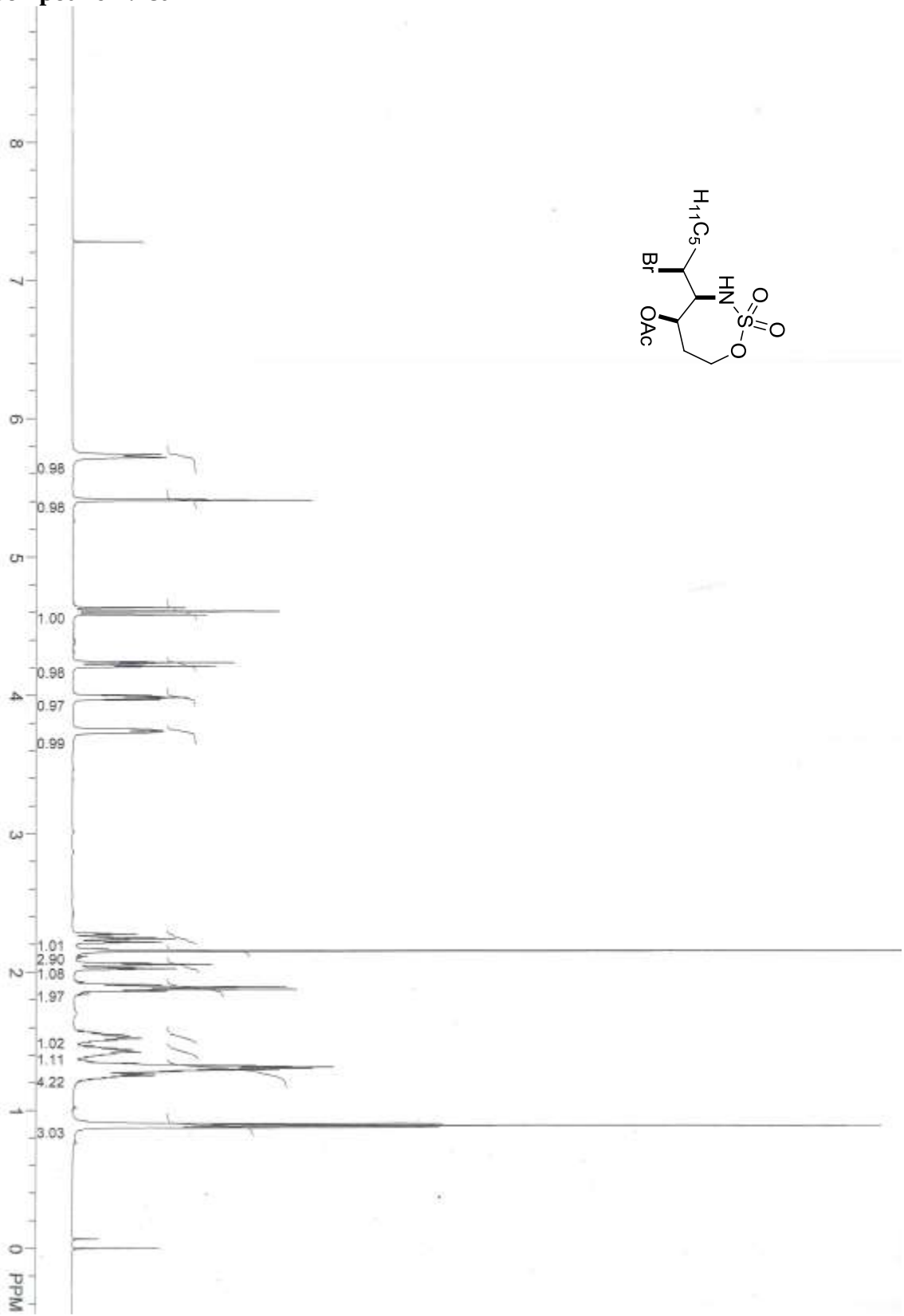

200
150
100
50
0
PPM
H
C_5H_{11}
SPh
HN
S
O
O
O

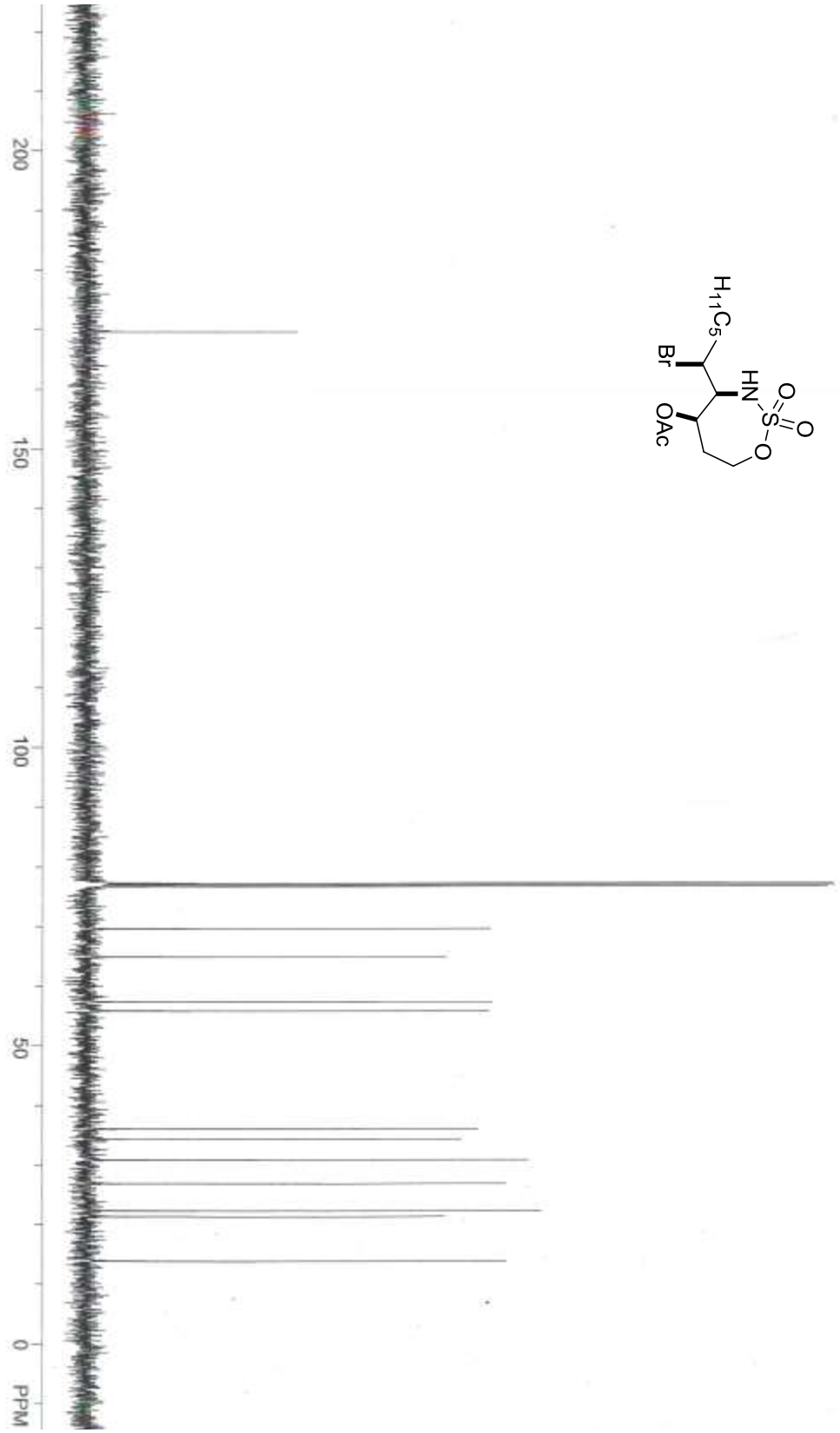
Compound 2.26



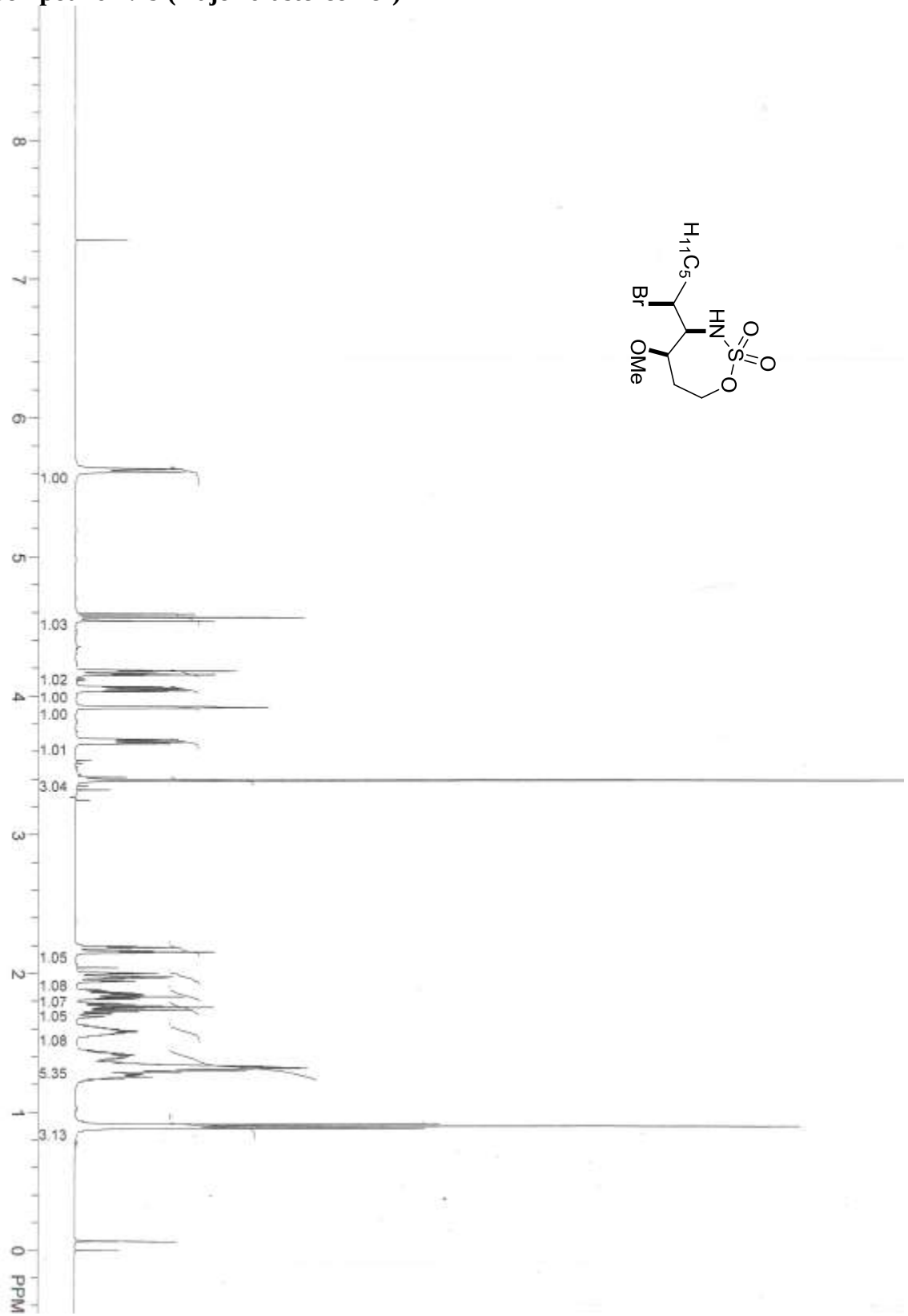

200
150
100
50
0
PPM
H
C_5H_{11}
Cl
HN
S
O
O
O

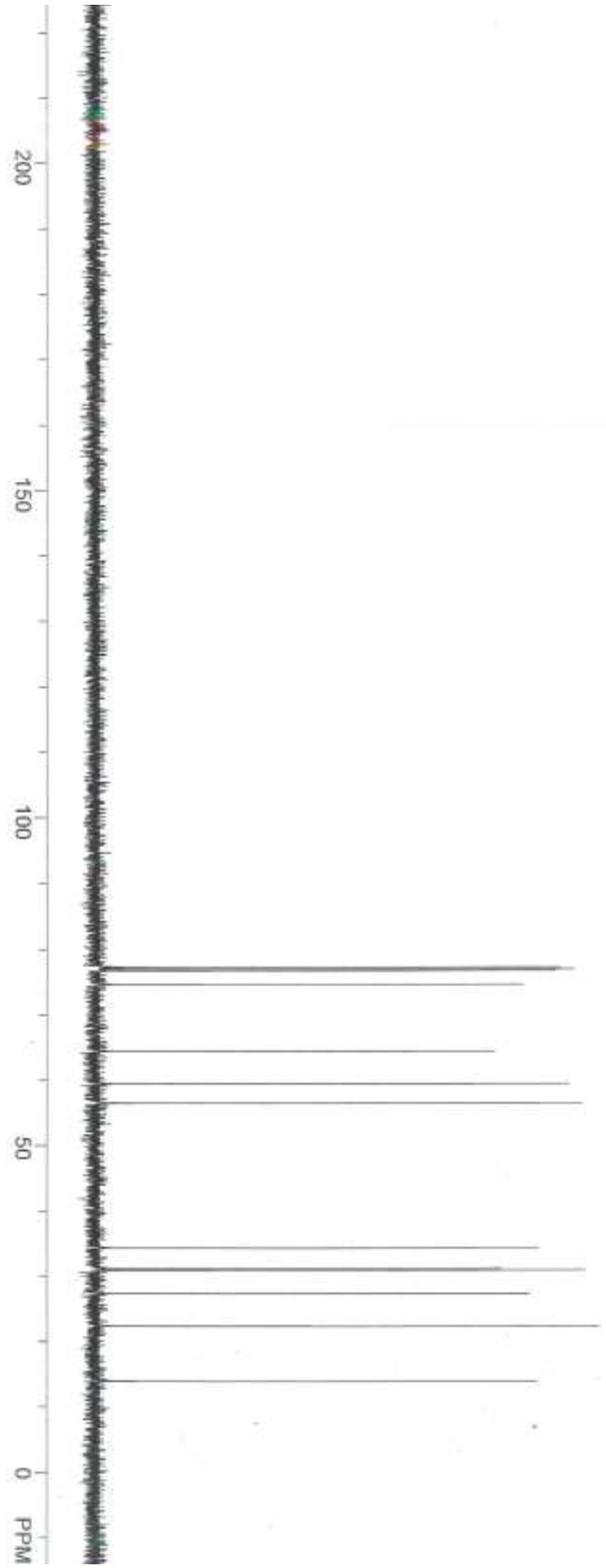
Compound 2.28a

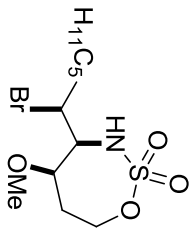



200
150
100
50
0
PPM
$H_{11}C_5$
Br
OAc
HN
S
O
O
O

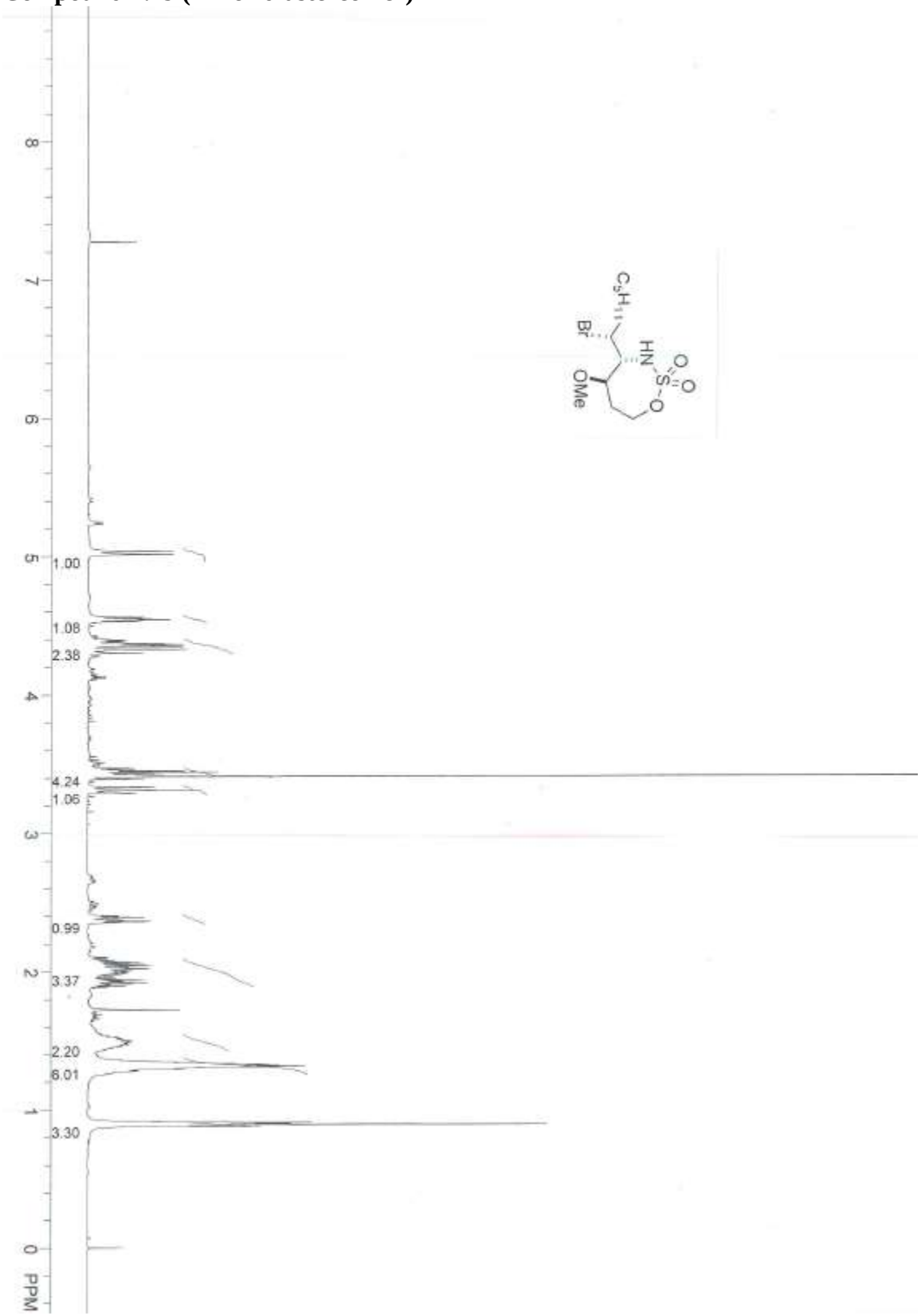
Compound 2.29 (major diastereomer)

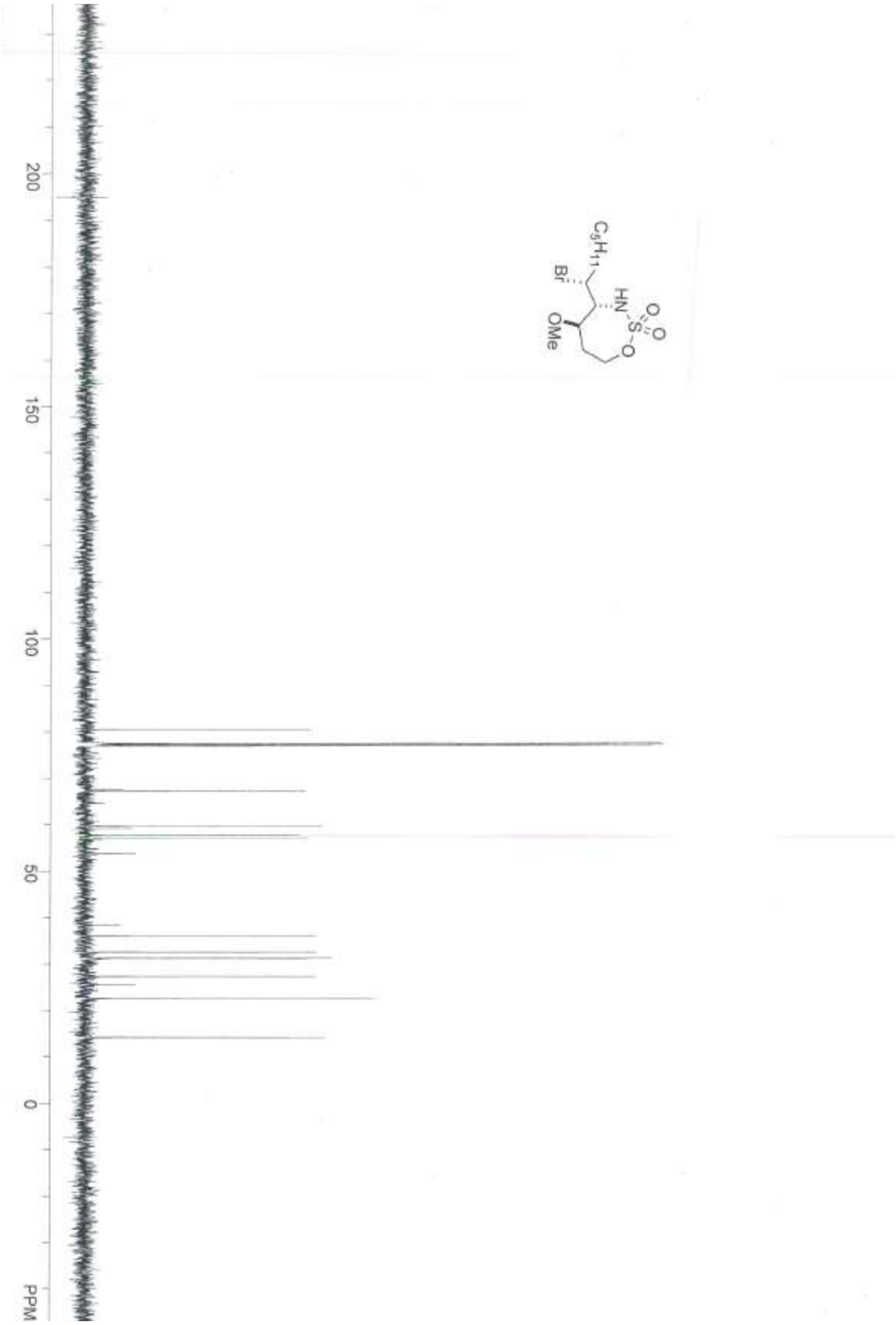



200
150
100
50
0
PPM

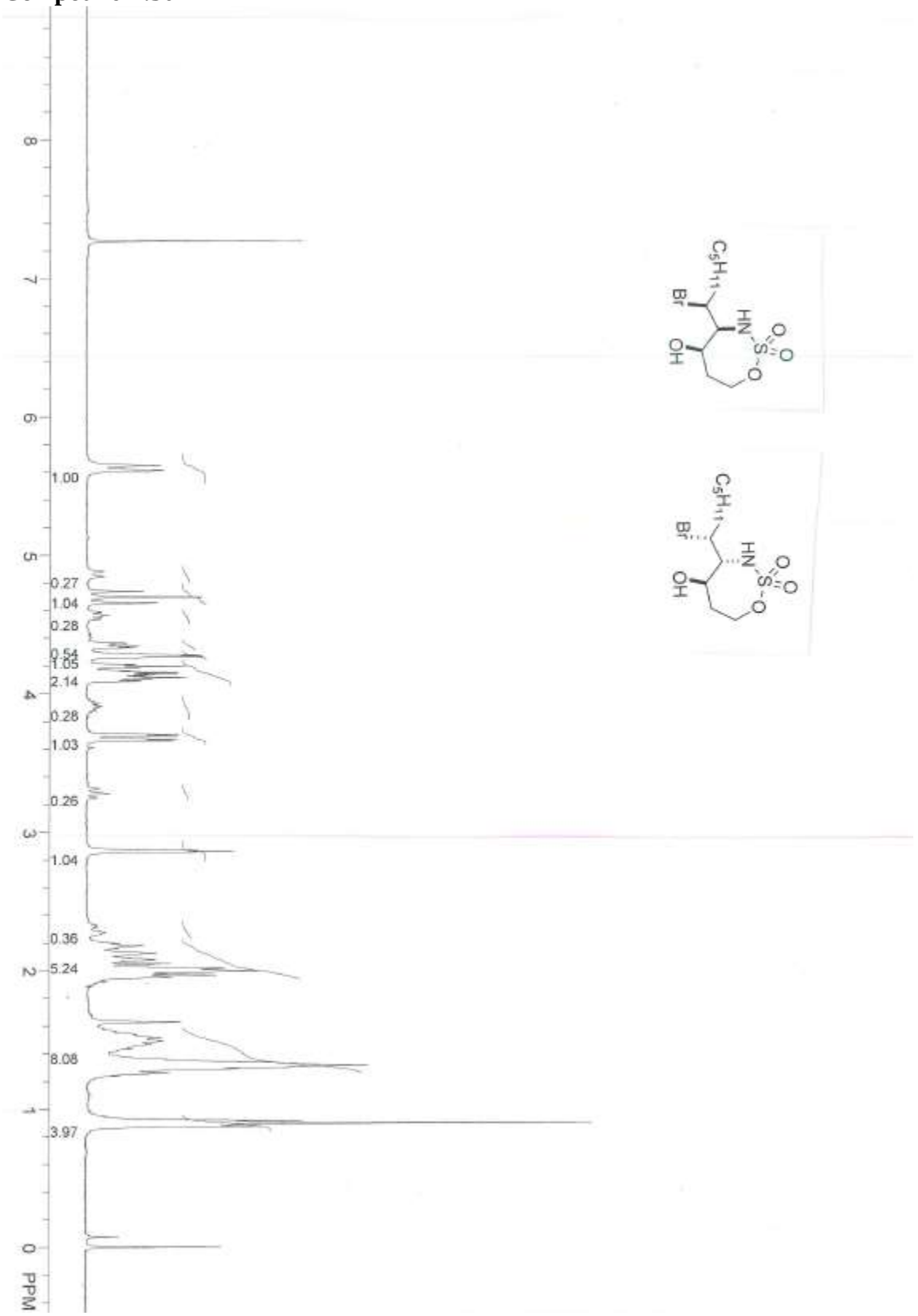

H11C5
Br
OMe
HN
S
O
O
O

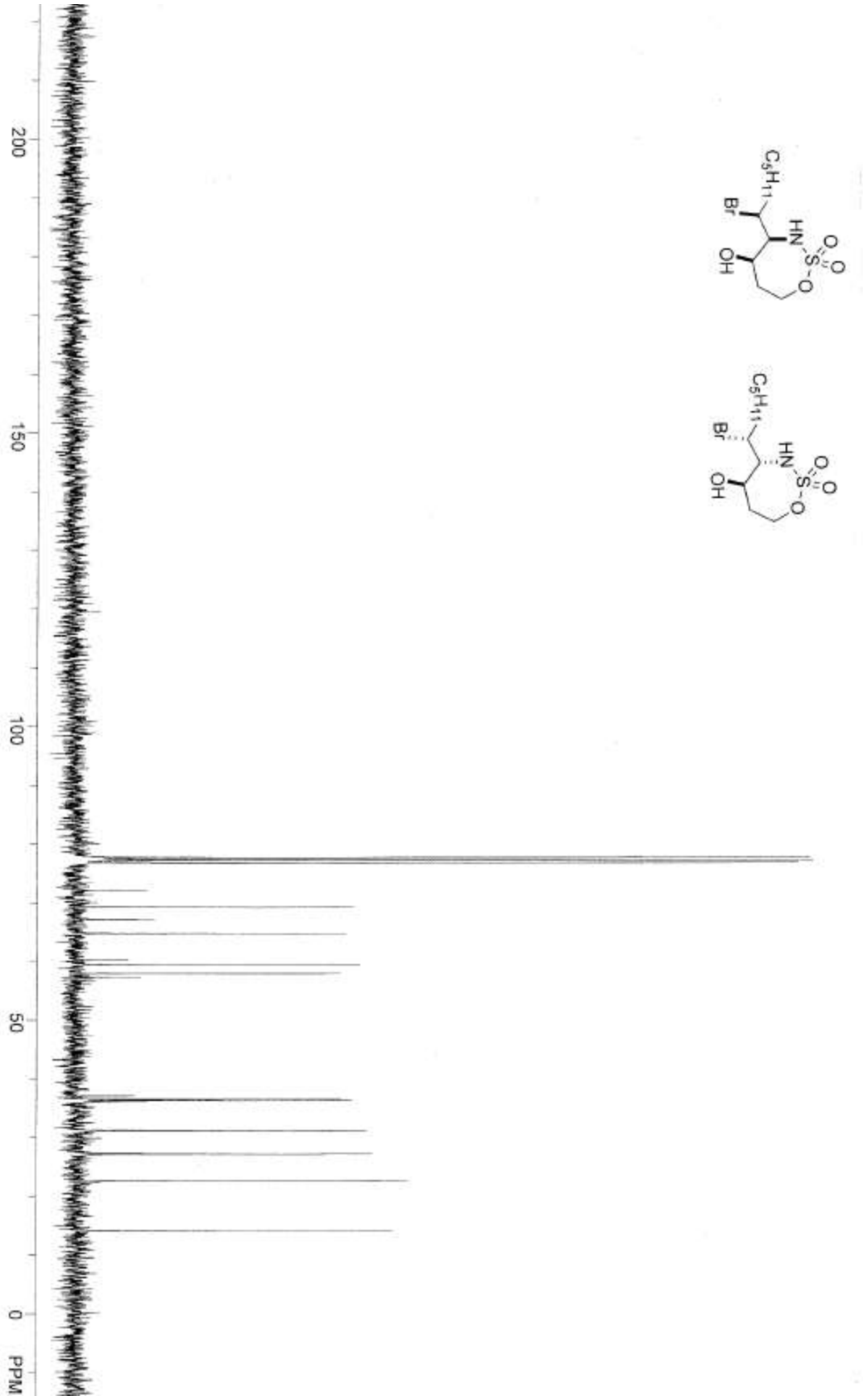
Compound 2.29 (minor diastereomer)



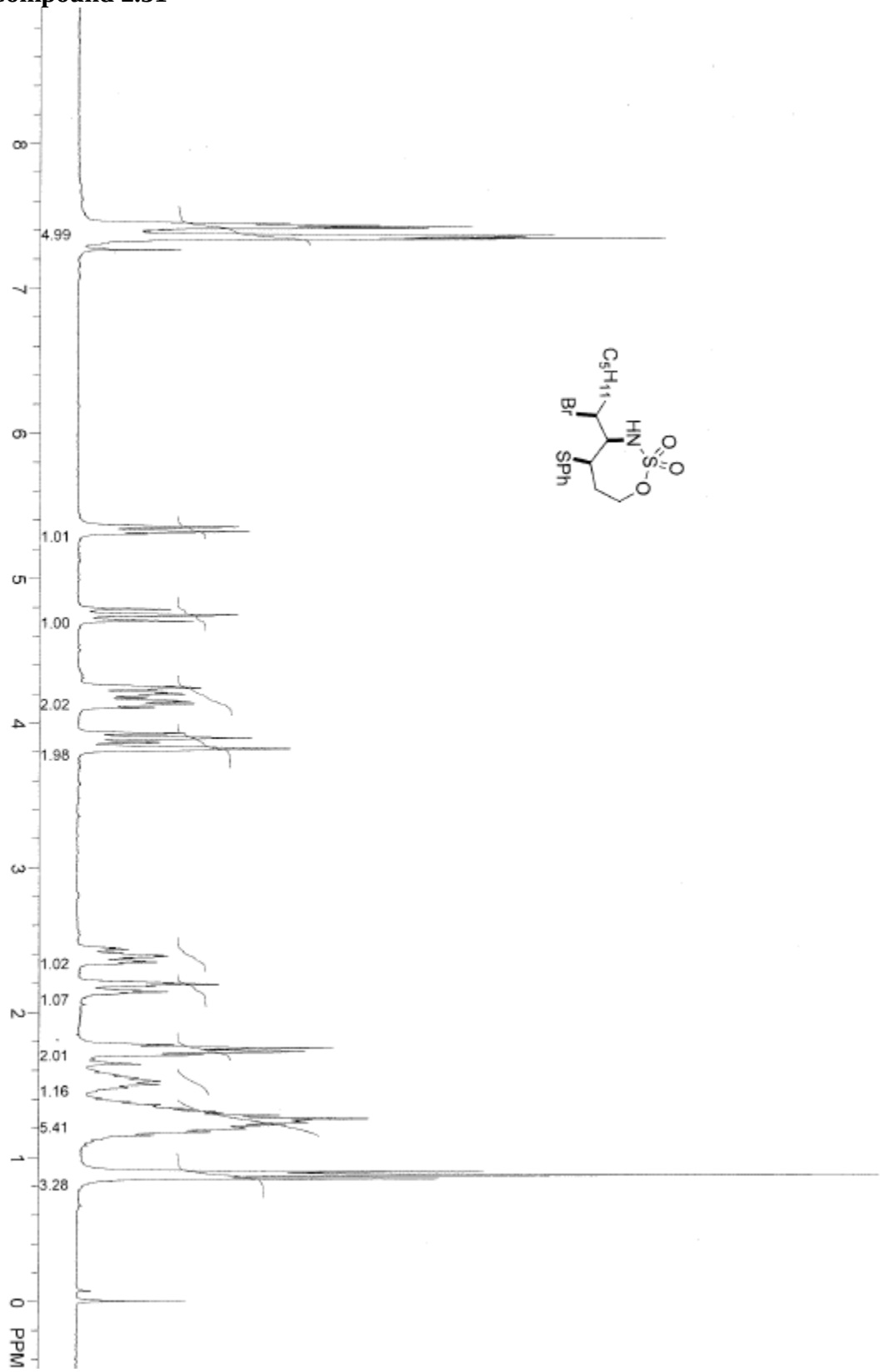

200
150
100
50
0
PPM
C5H11
Br
OMe
HN
S
O
O
O

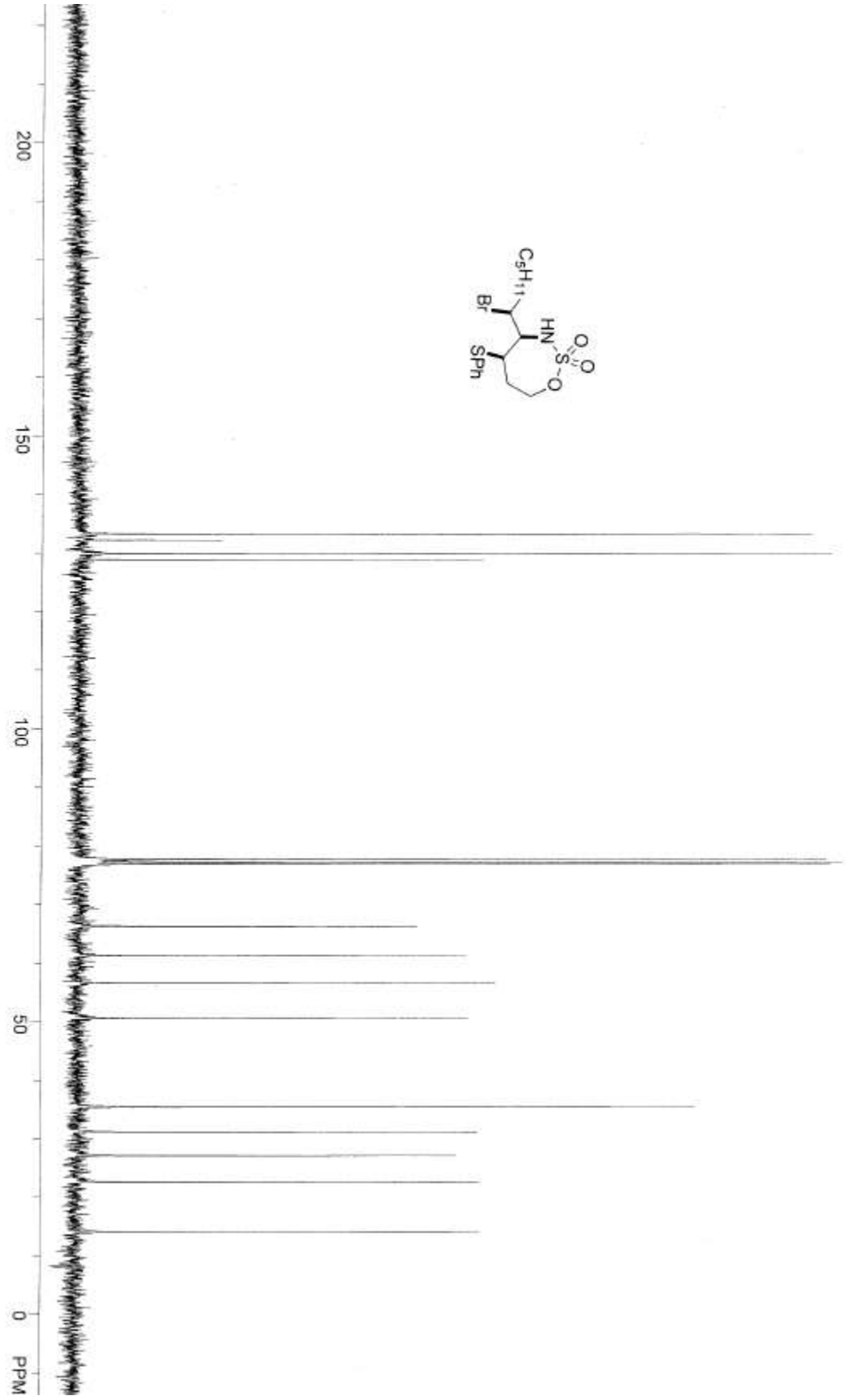
Compound 2.30



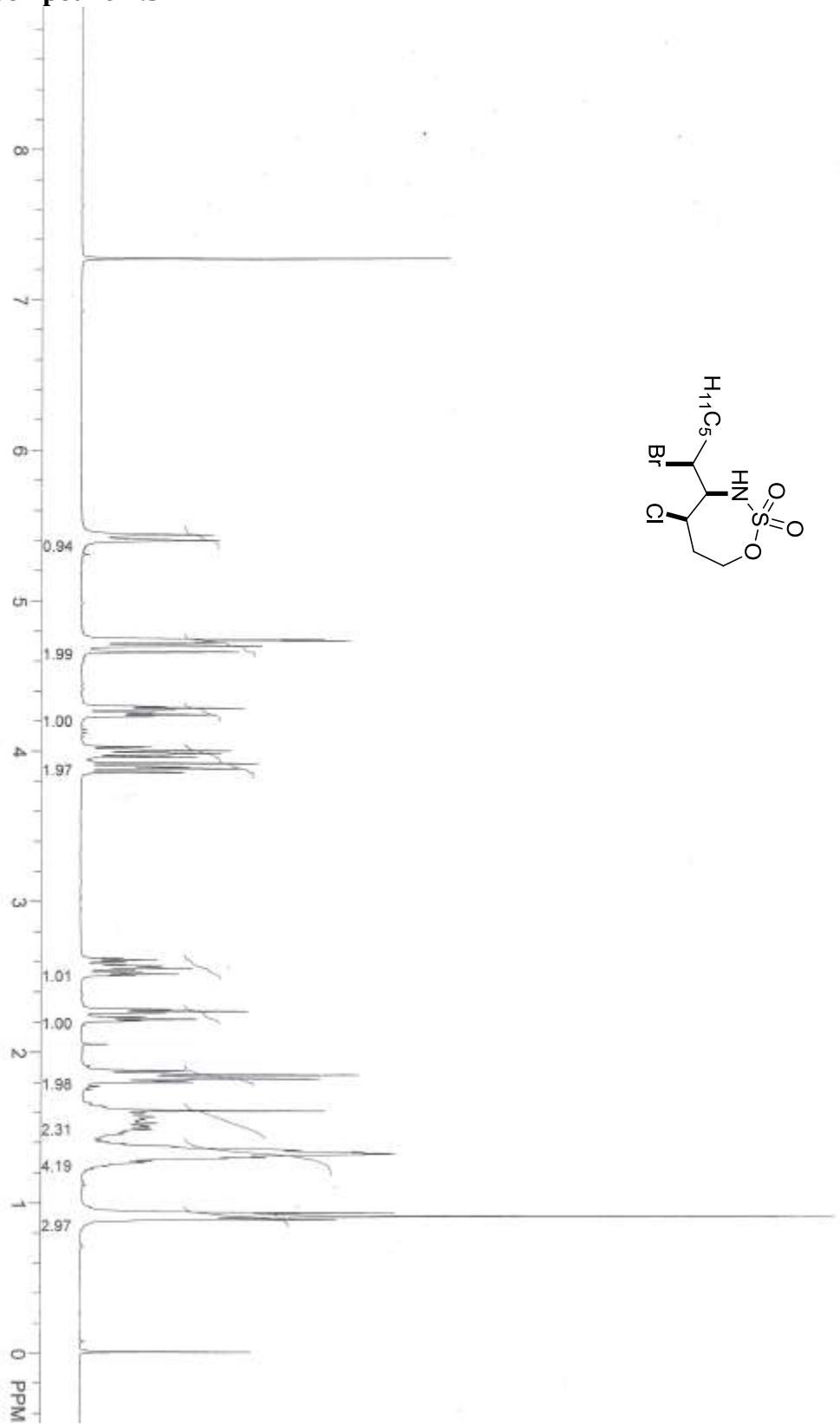

200
150
100
50
0
PPM
C5H11
Br
OH
HN
S
O
O
O
C5H11
Br
OH
HN
S
O
O
O

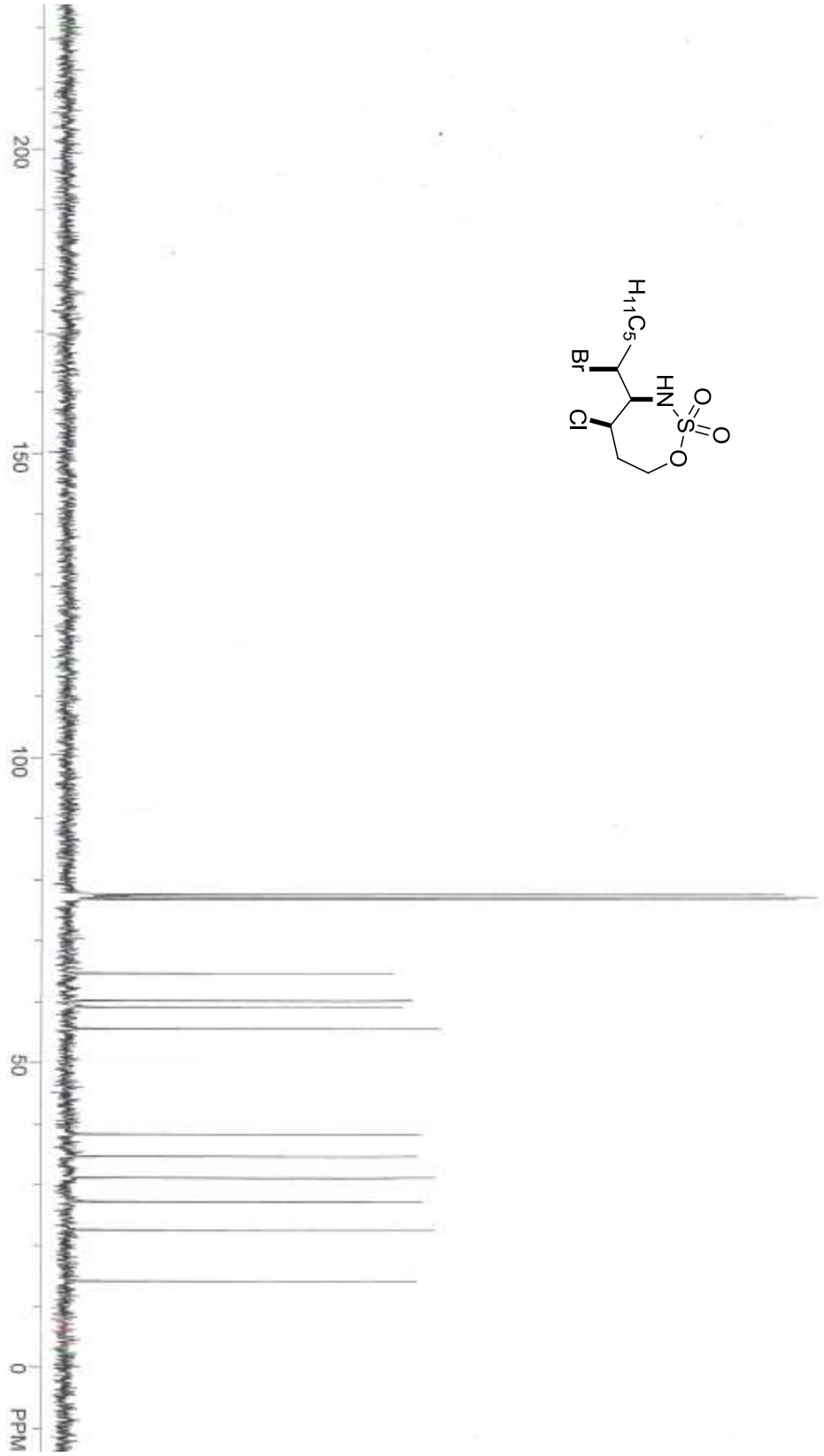
Compound 2.31



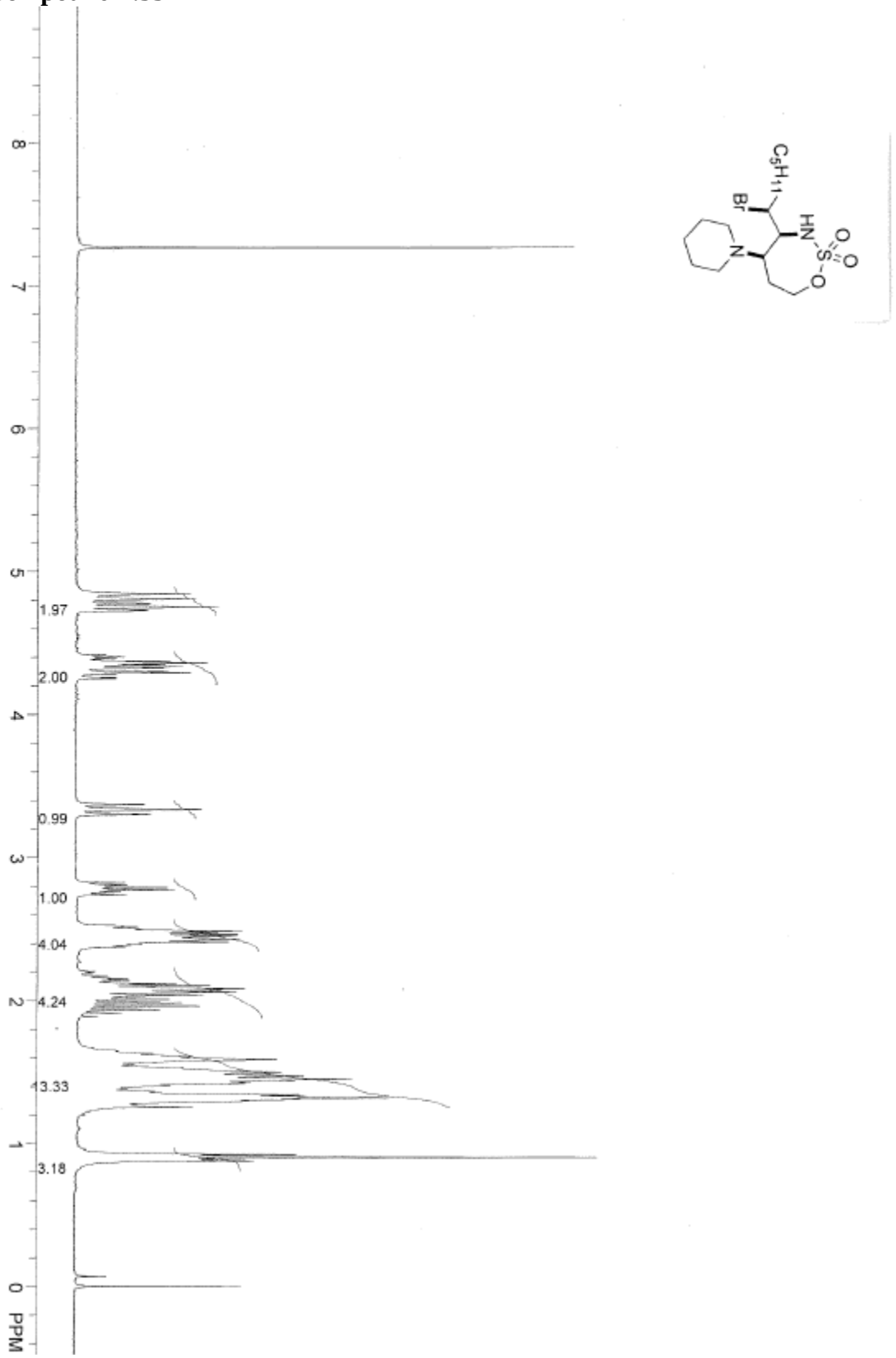

200
150
100
50
0
PPM
C_5H_{11}
Br
SPh
HN
S
O
O
O

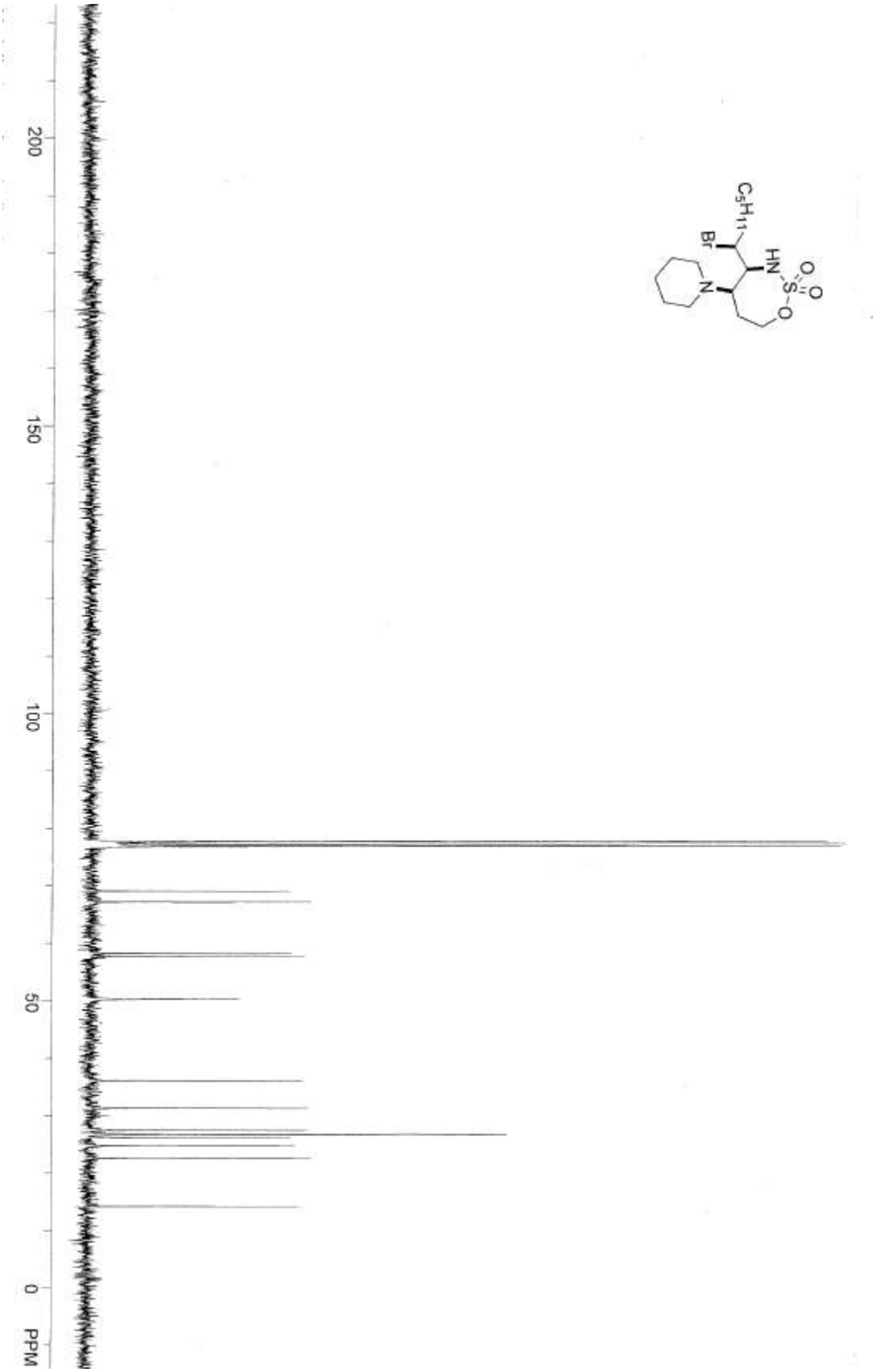
Compound 2.32



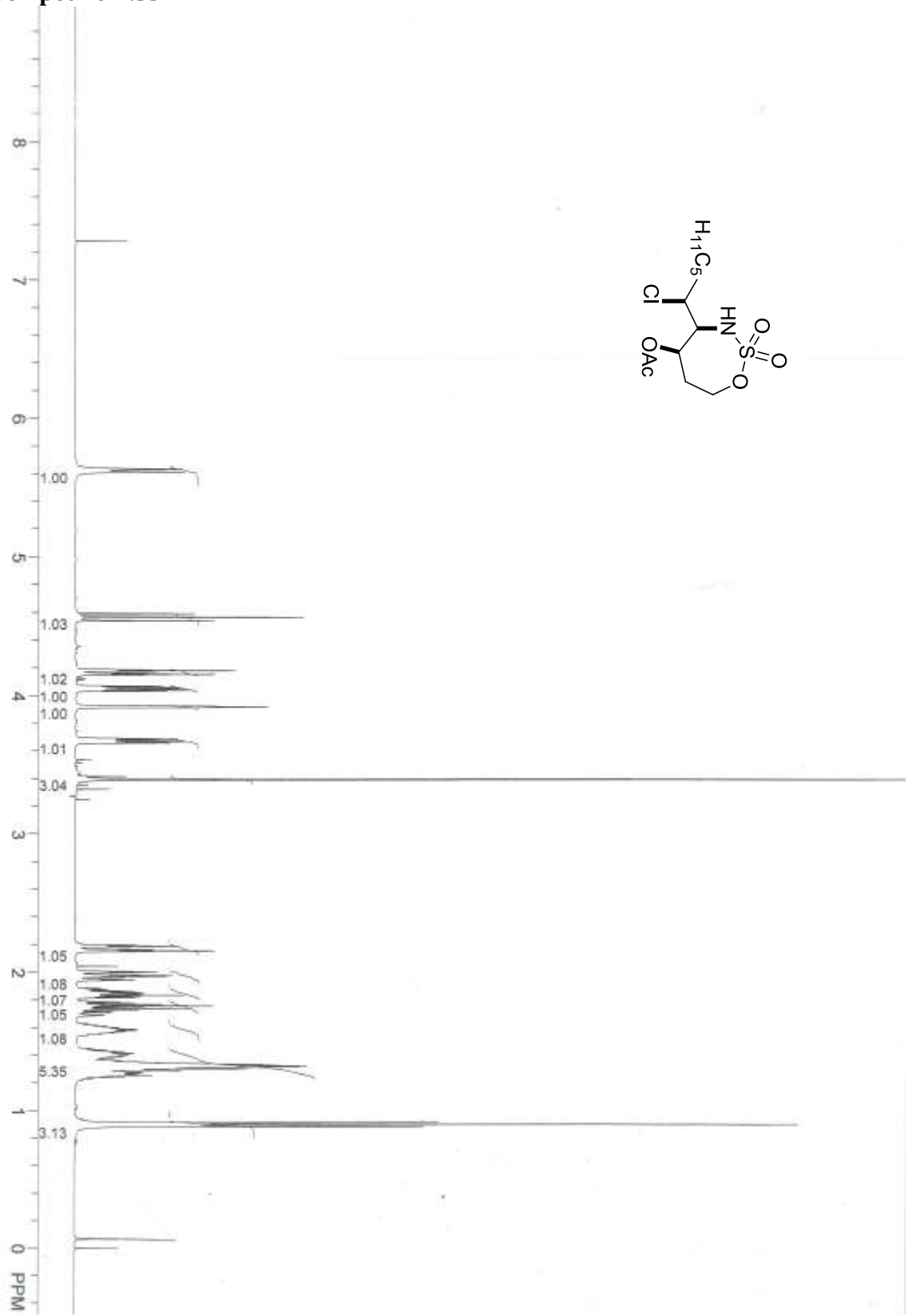

200
150
100
50
0
PPM
H11C5
Br
Cl
HN
S
O
O
O

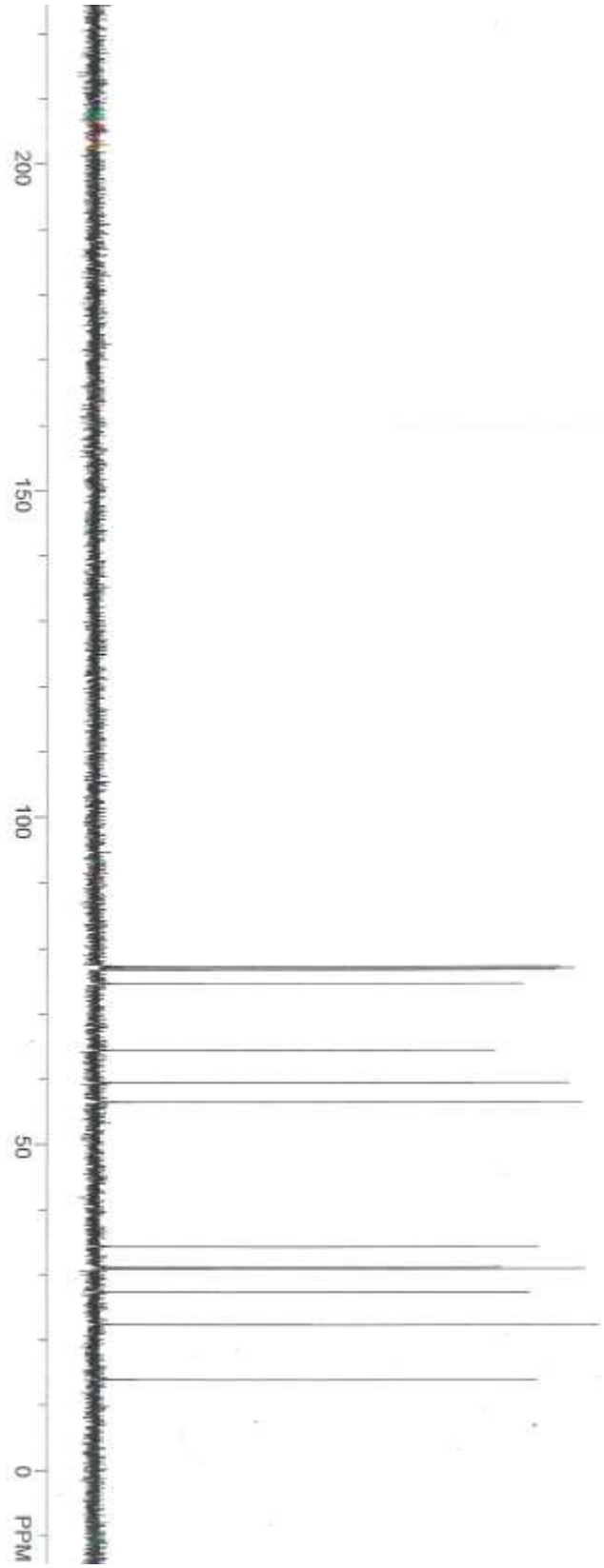
Compound 2.33

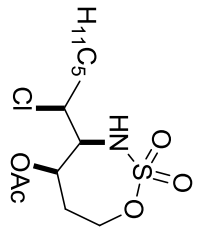



200
150
100
50
0
PPM
C5H11
Br
HN
N
S
O
O
O

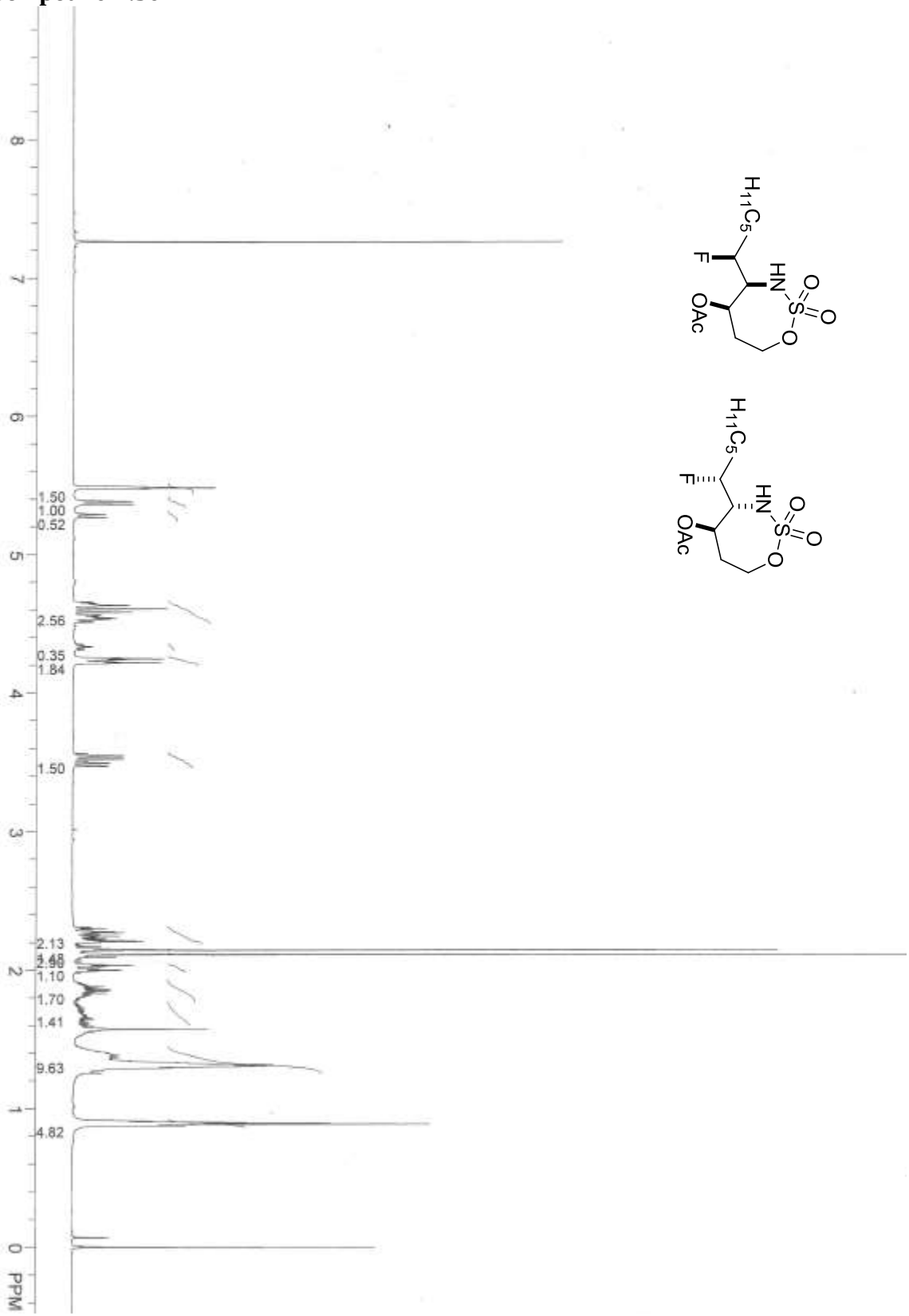
Compound 2.35

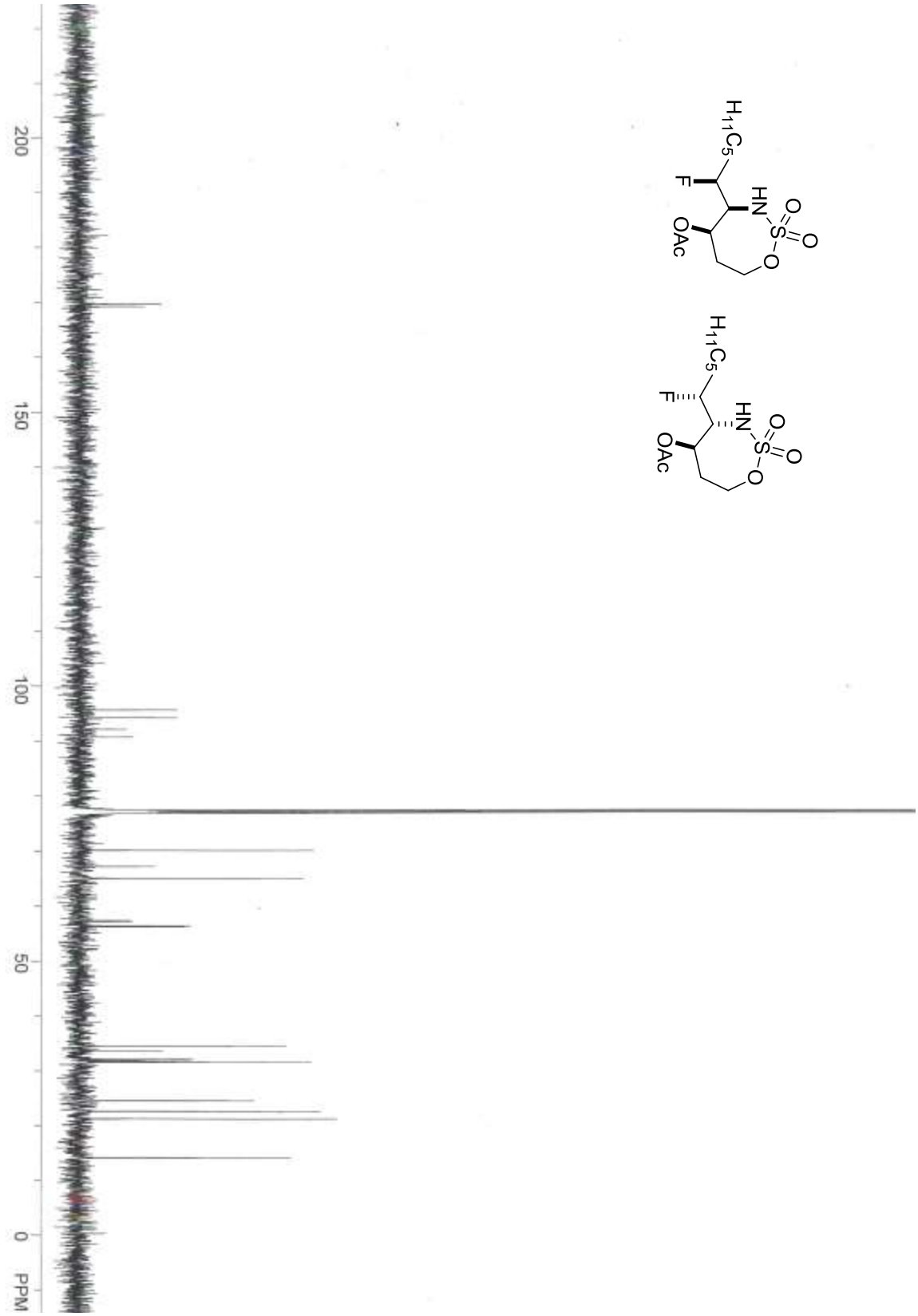



200
150
100
50
0
PPM

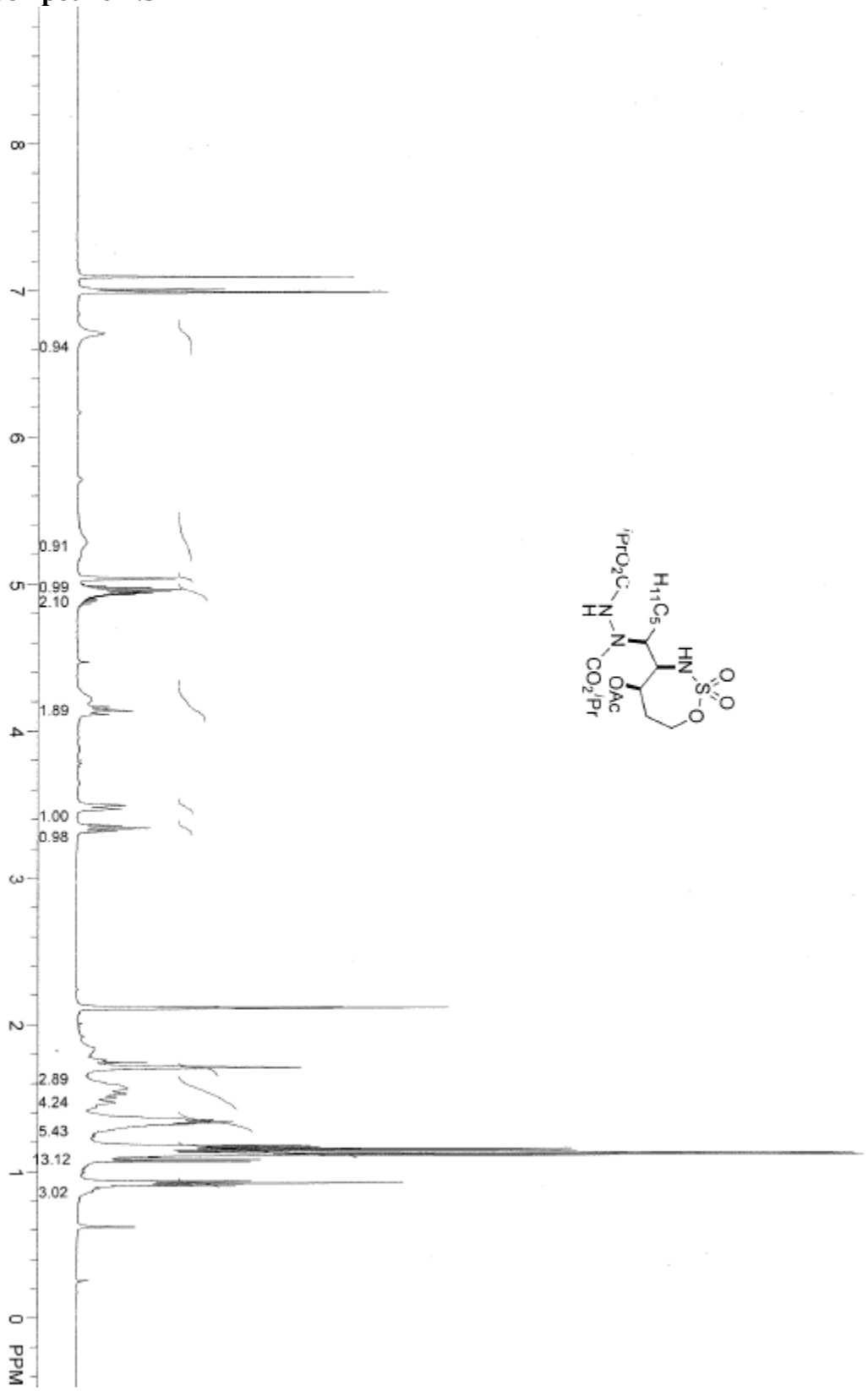

H11C5
Cl
OAc
HN
S
O
O
O

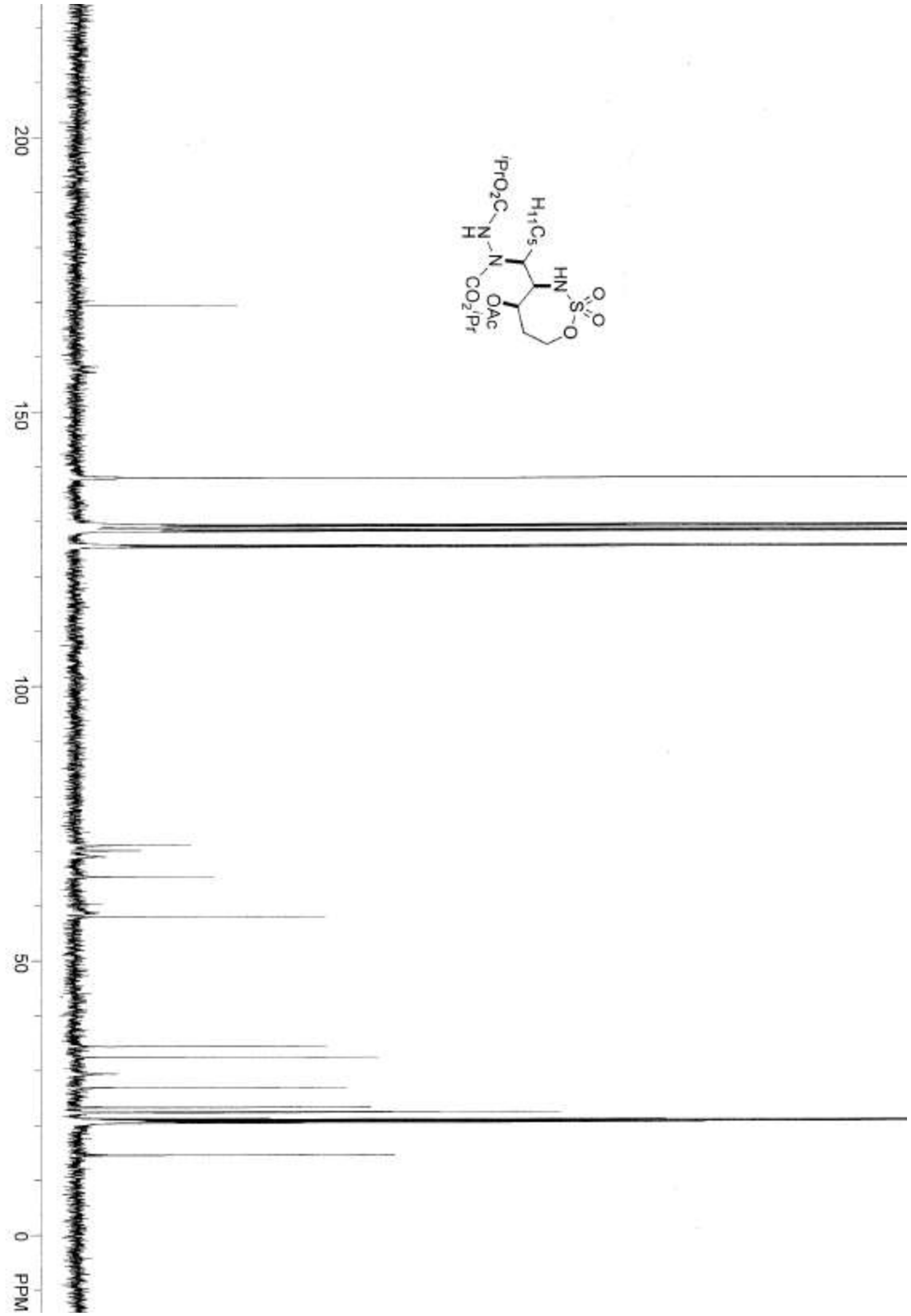
Compound 2.36



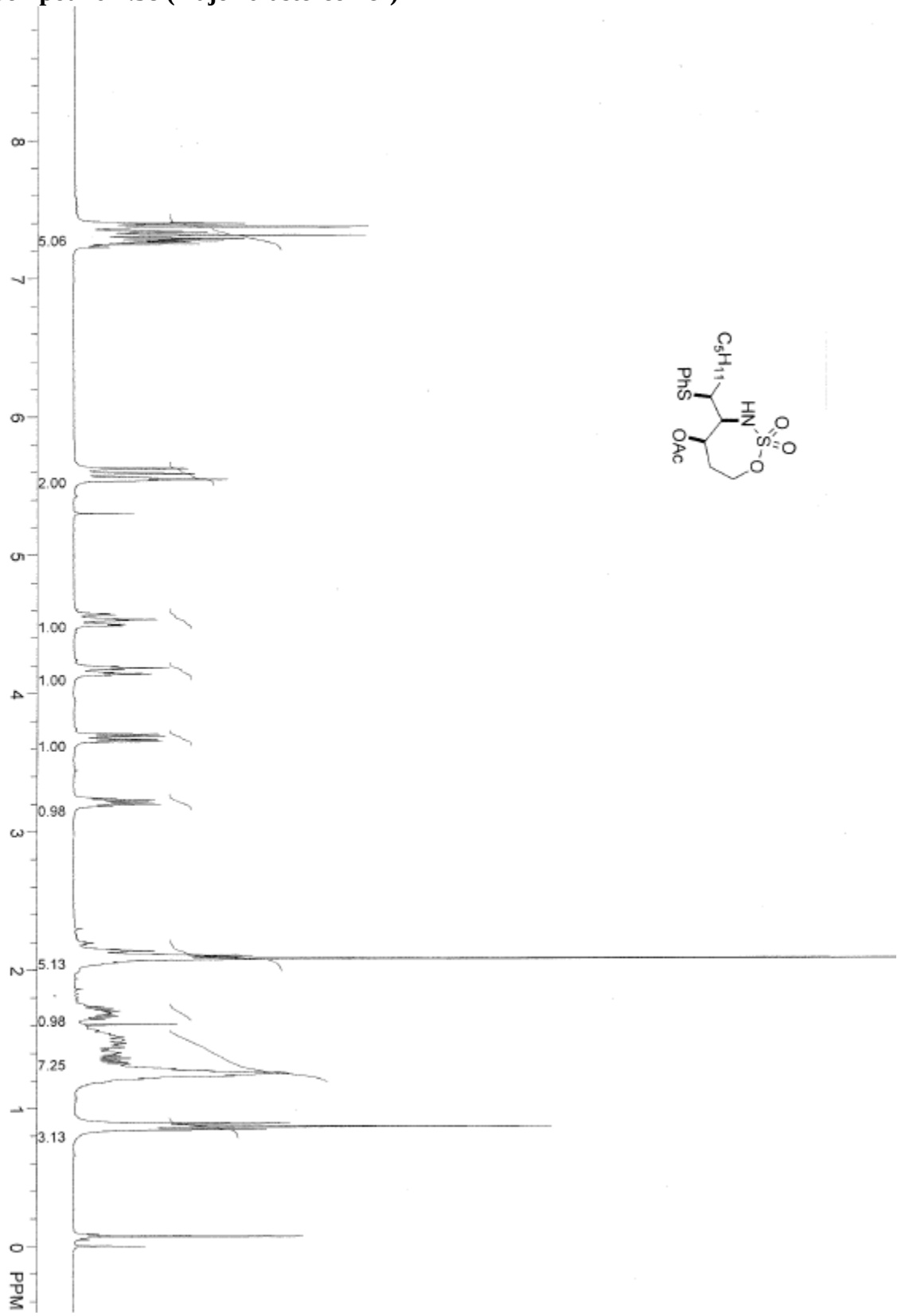

200
150
100
50
0
PPM
H11C5
F
HN
S
O
O
OAc
H11C5
F
HN
S
O
O
OAc

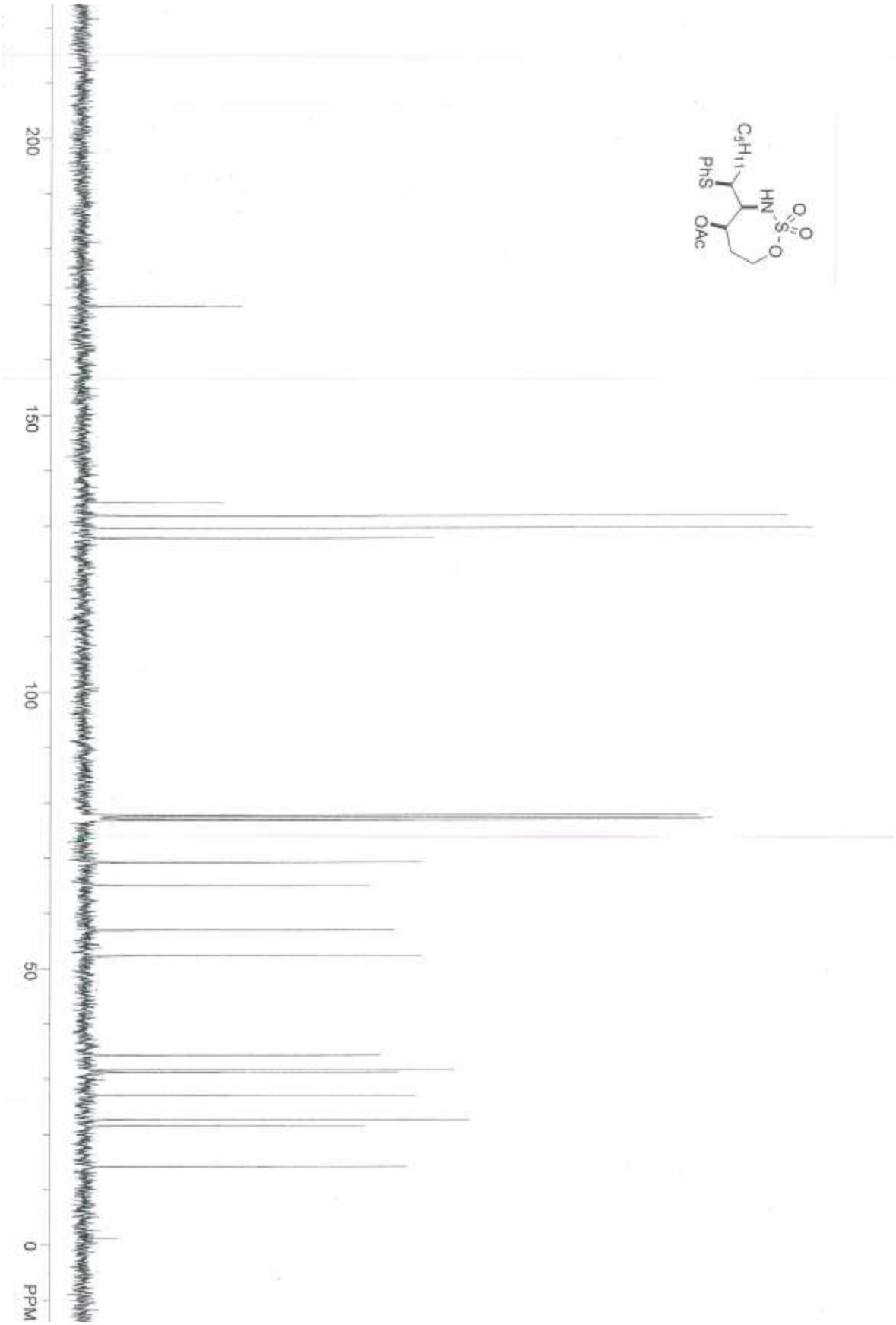
Compound 2.37



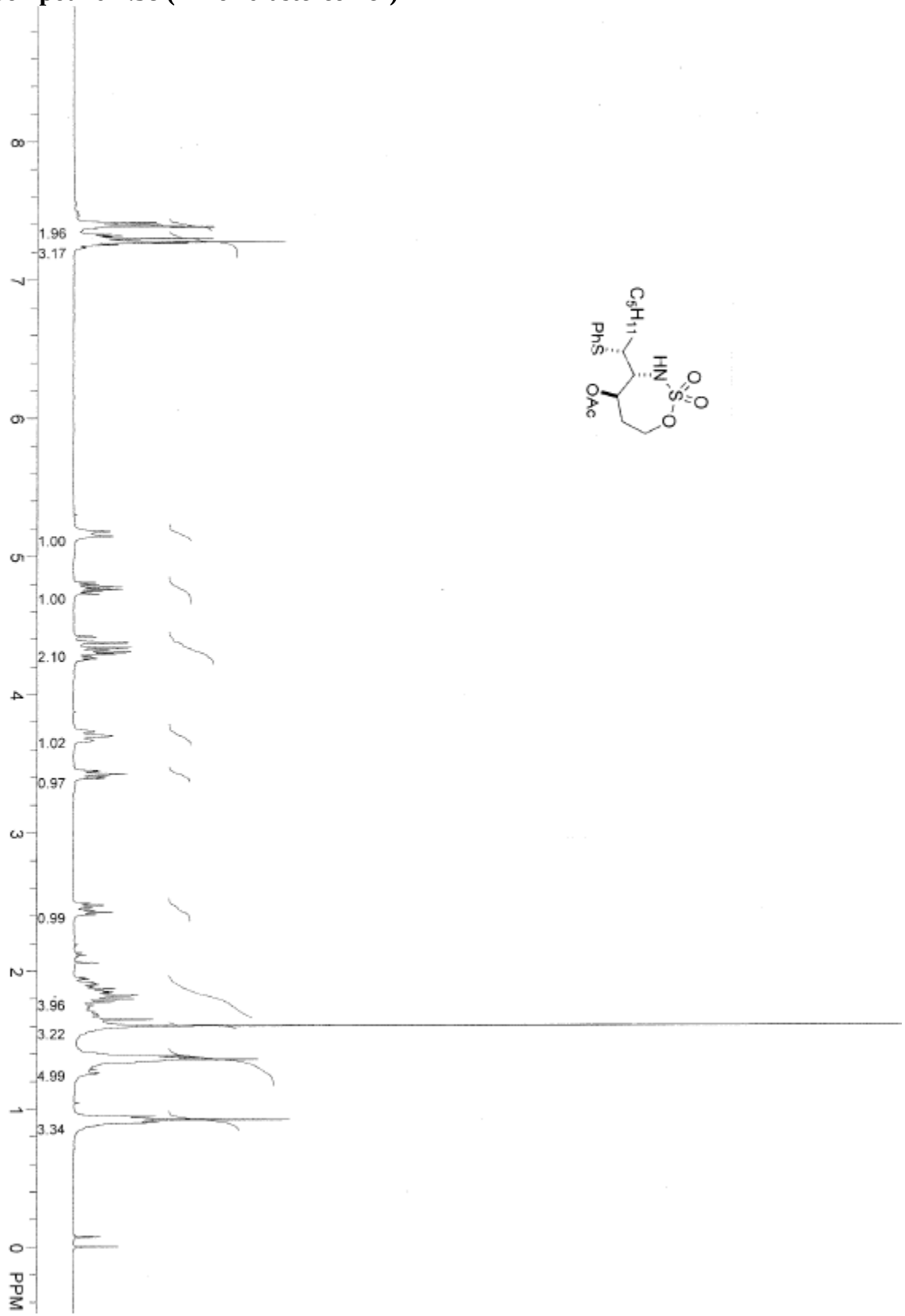

200
150
100
50
0
PPM

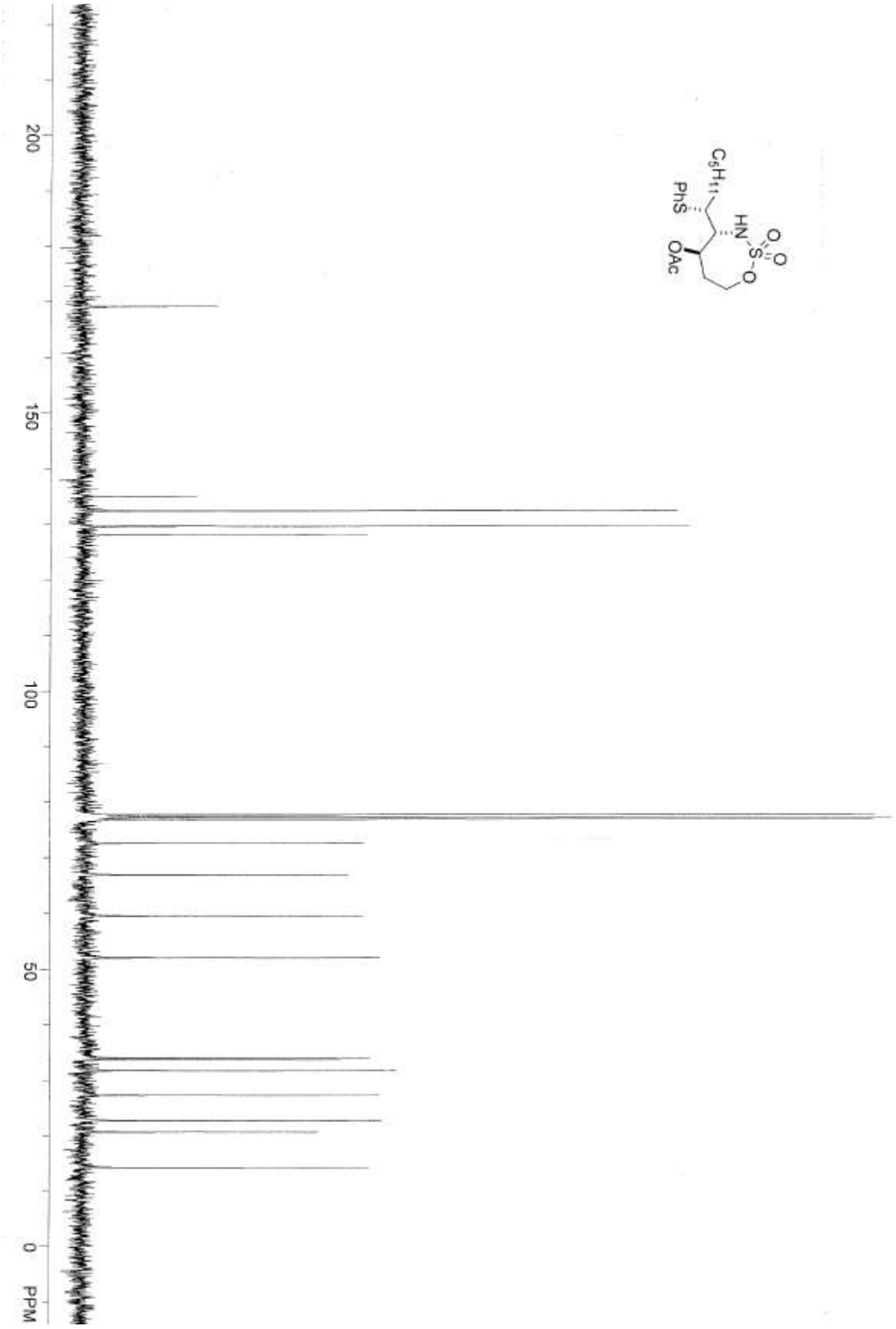
Compound 2.38 (major diastereomer)



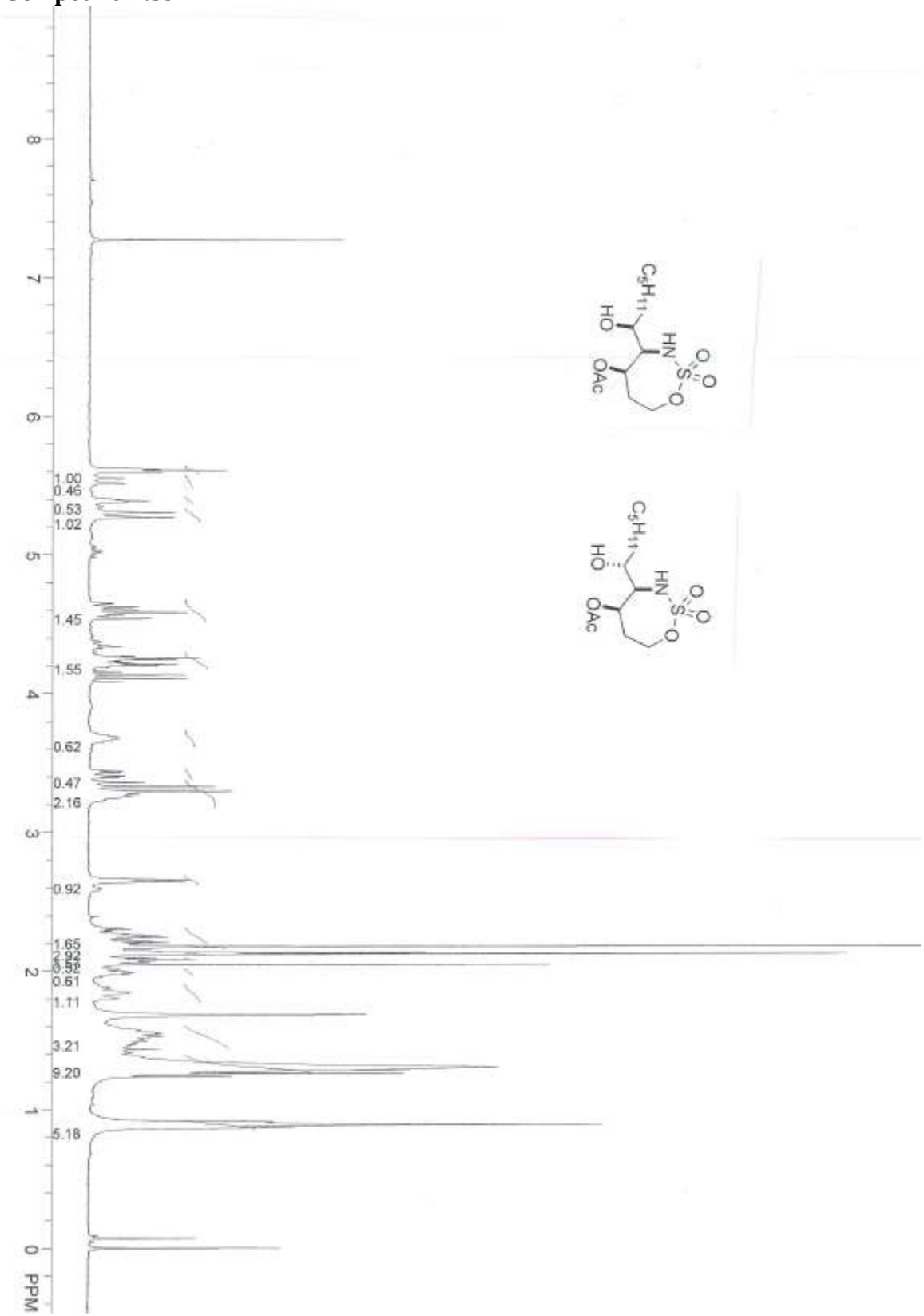

200
150
100
50
0
PPM
C5H11
PhS
OAc
HN
S
O
O
O

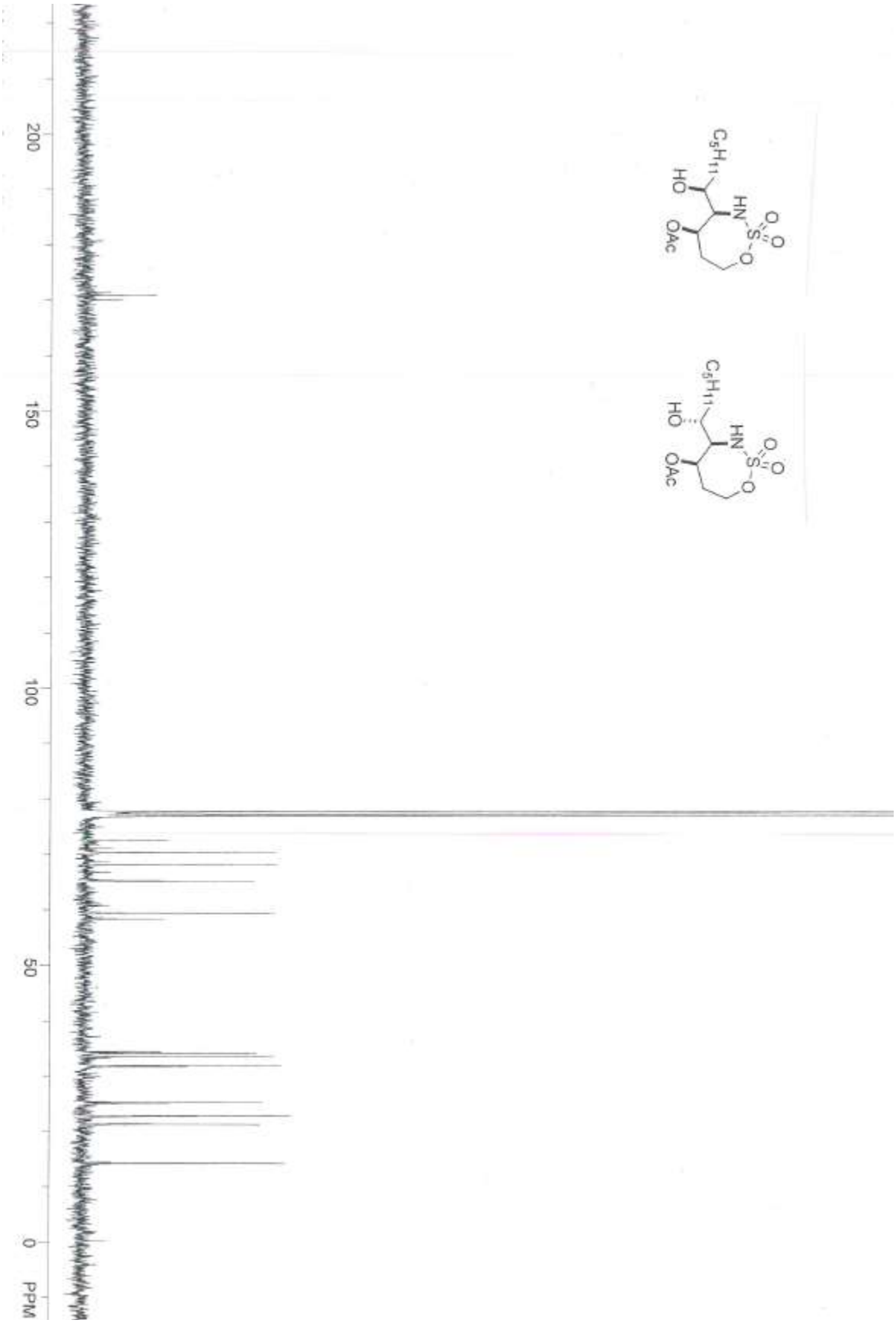
Compound 2.38 (minor diastereomer)



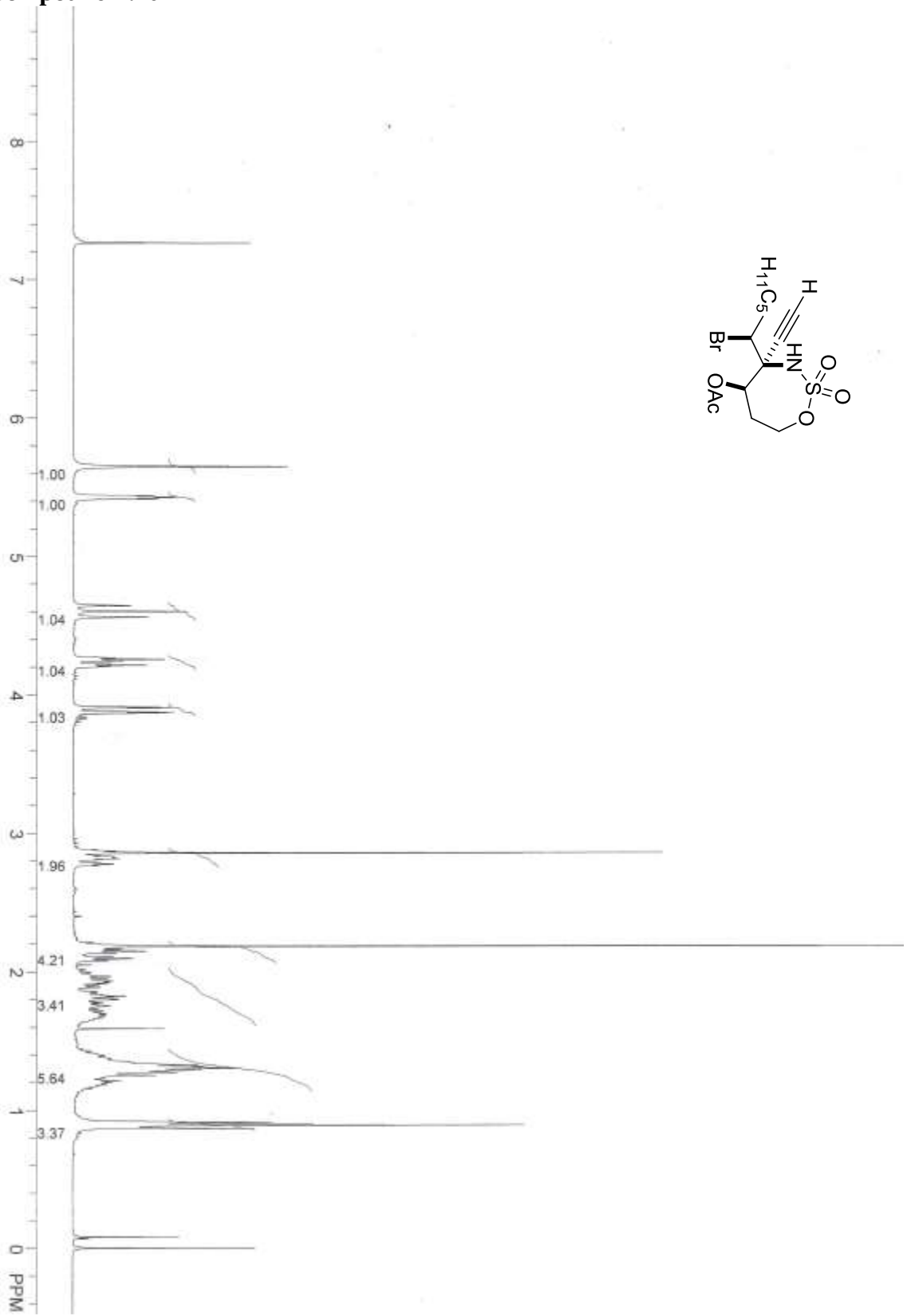

200
150
100
50
0
PPM
C5H11
PhS
OAc
HN
S
O
O
O

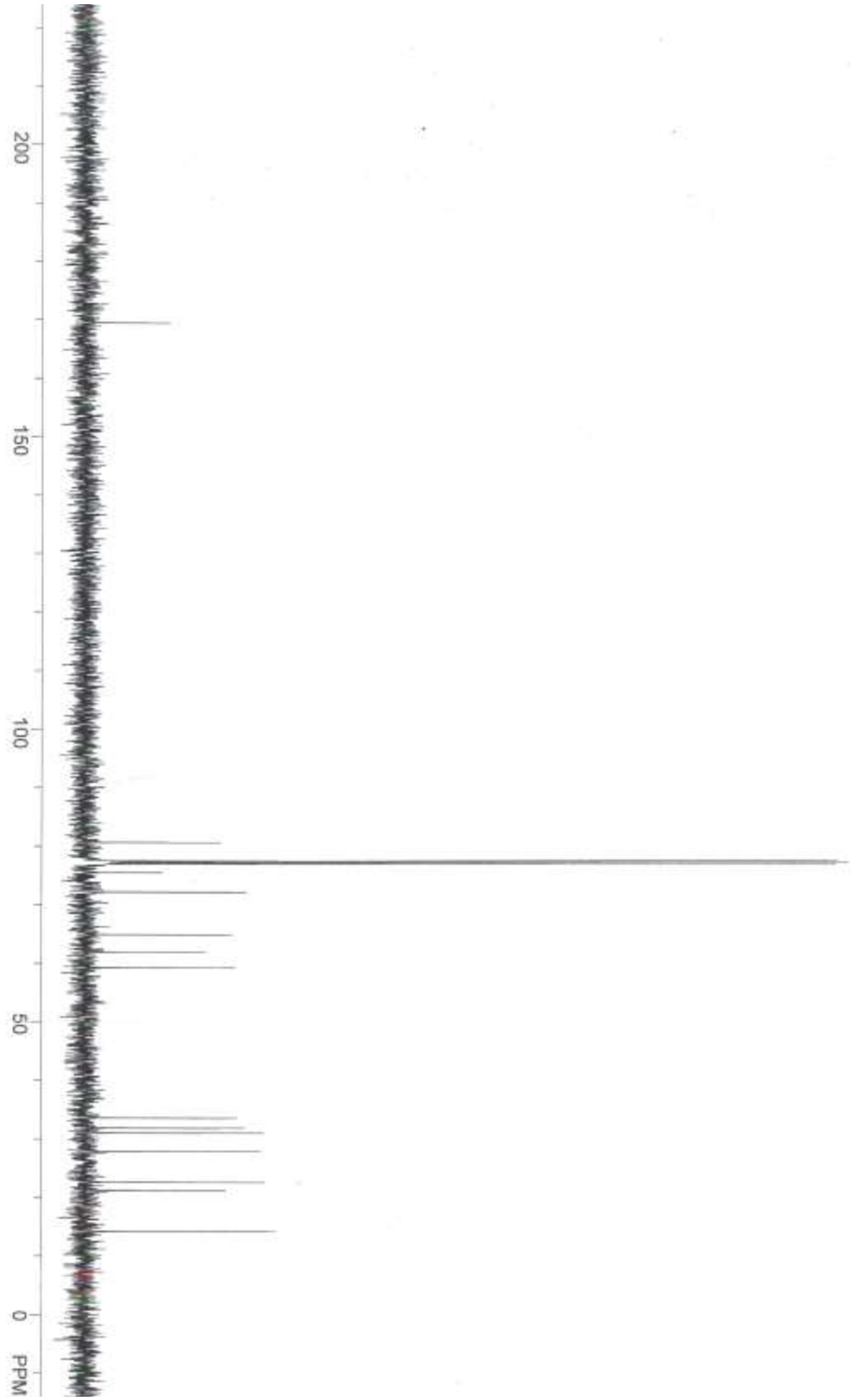
Compound 2.39



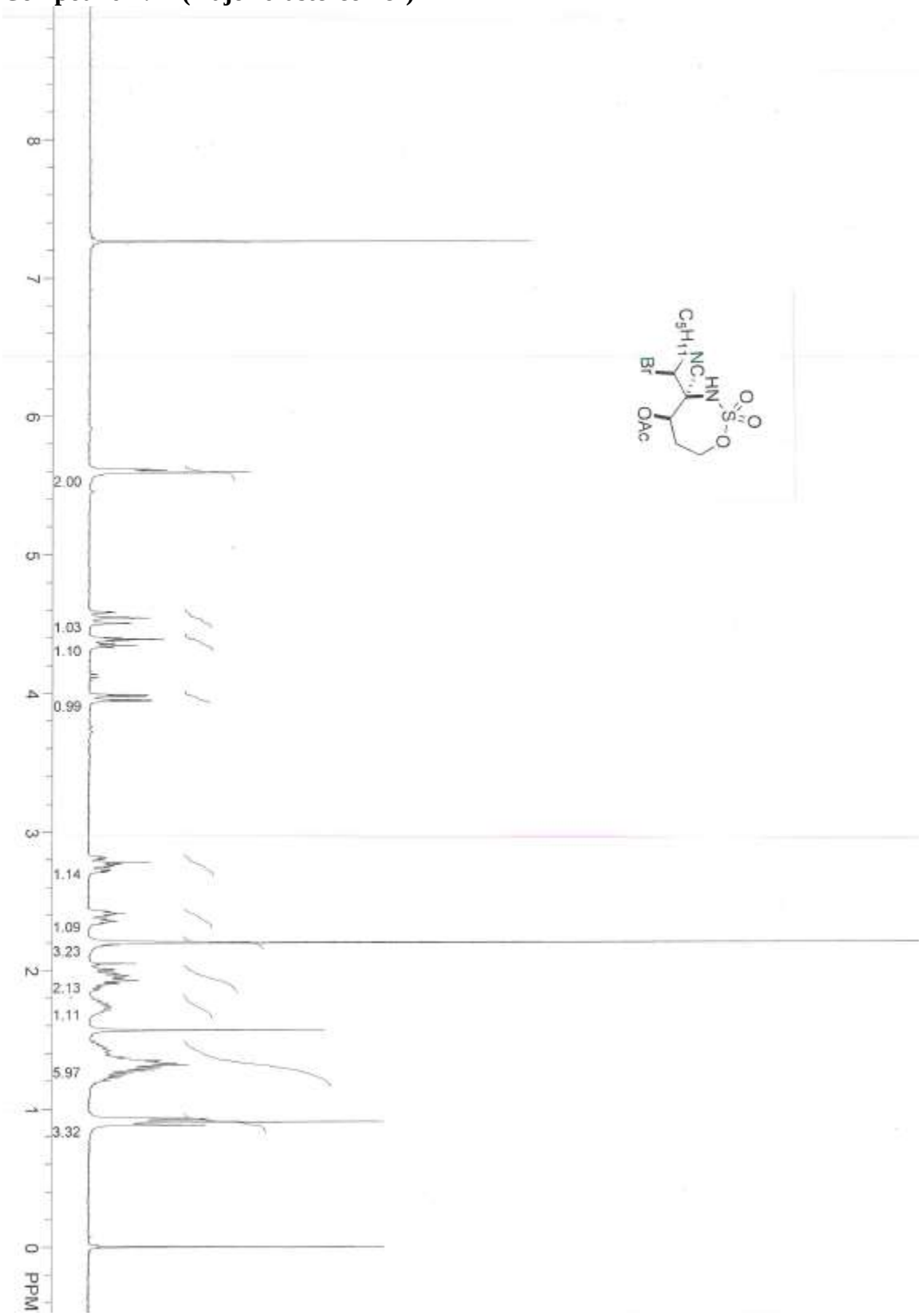

200
150
100
50
0
PPM
C_5H_{11}
HO
OAc
HN
S
O
O
O
C_5H_{11}
HO
OAc
HN
S
O
O
O

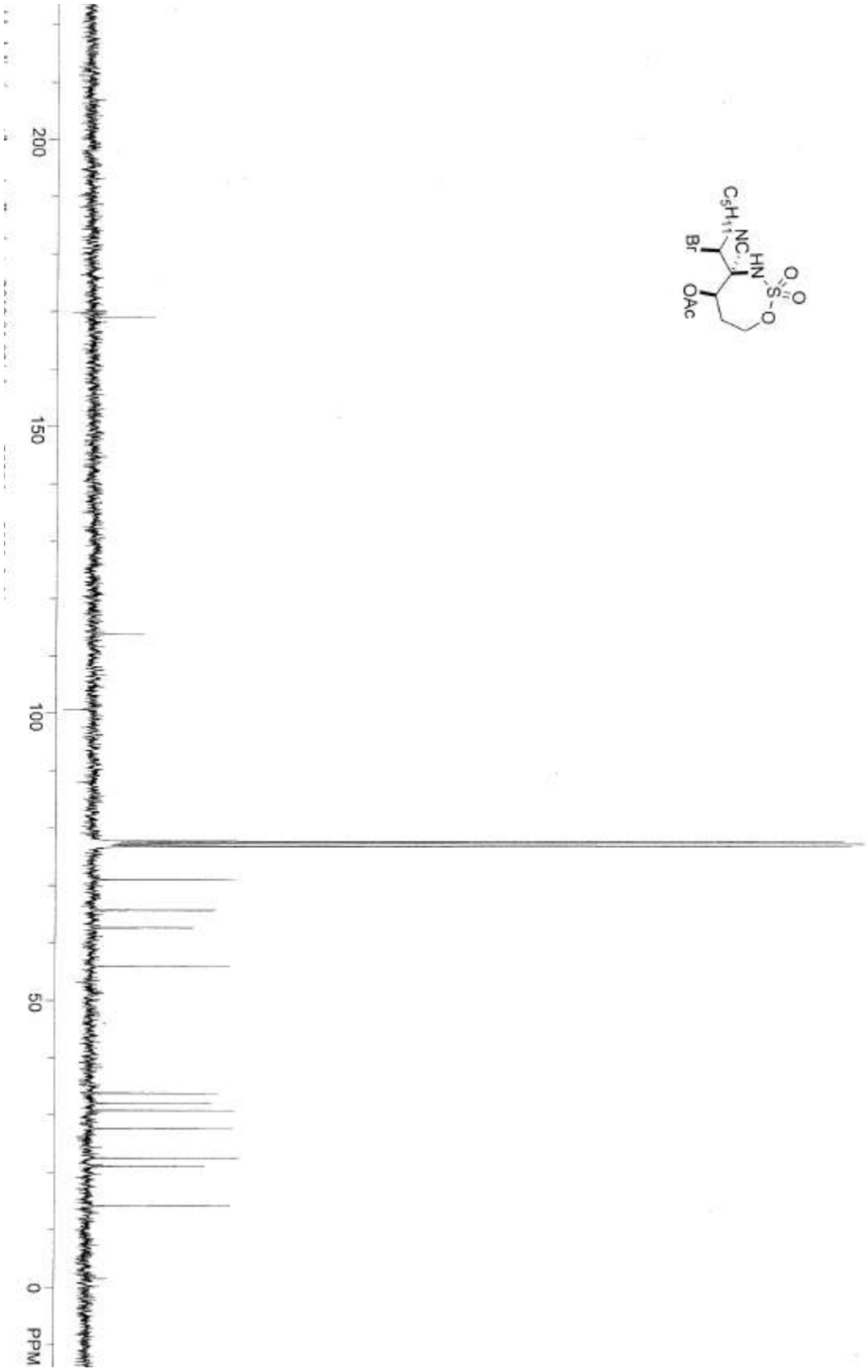
Compound 2.40



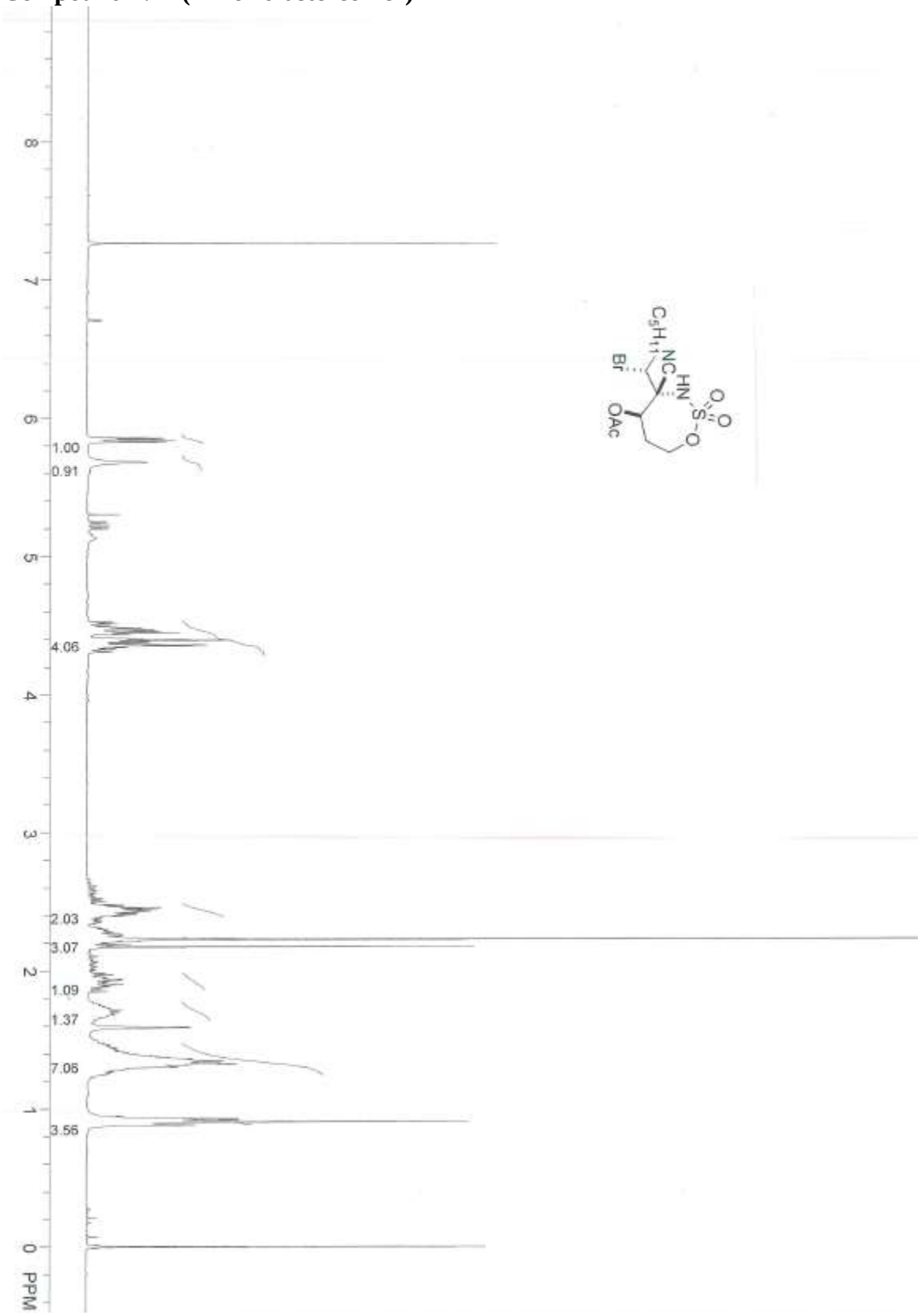

200
150
100
50
0
PPM

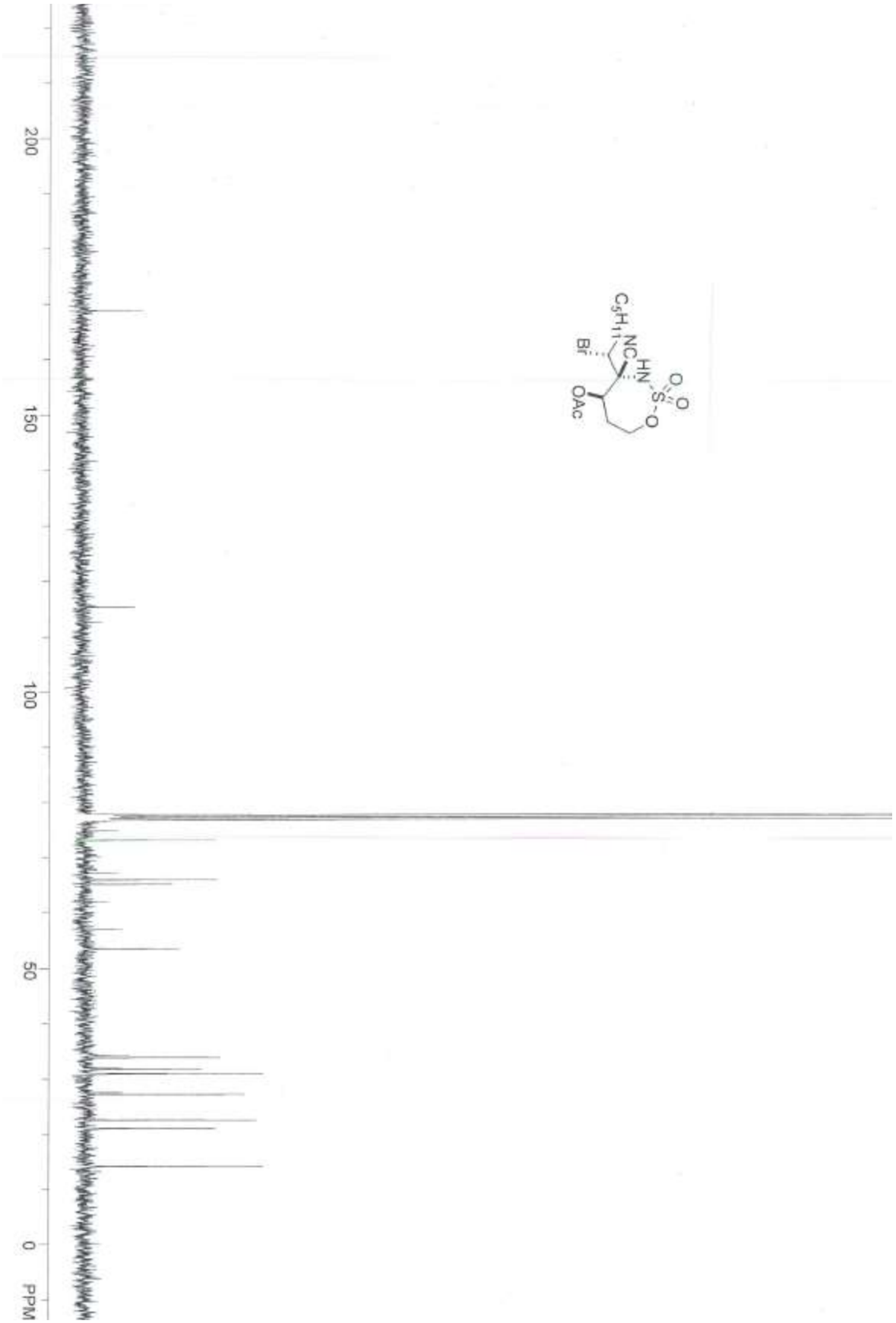
Compound 2.41 (major diastereomer)



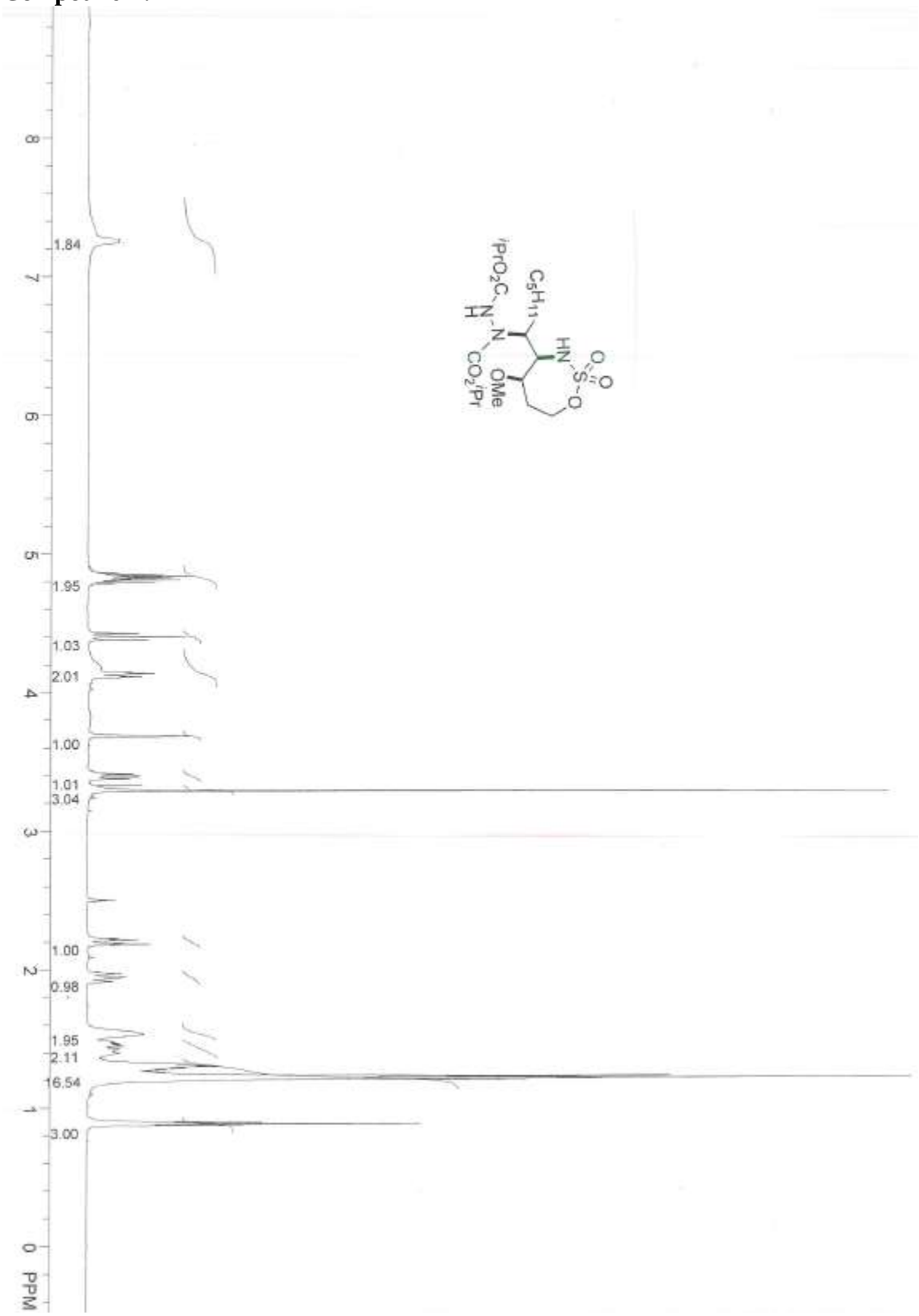

200
150
100
50
0
PPM
C5H11
NC
HN
Br
OAc
S
O
O
O

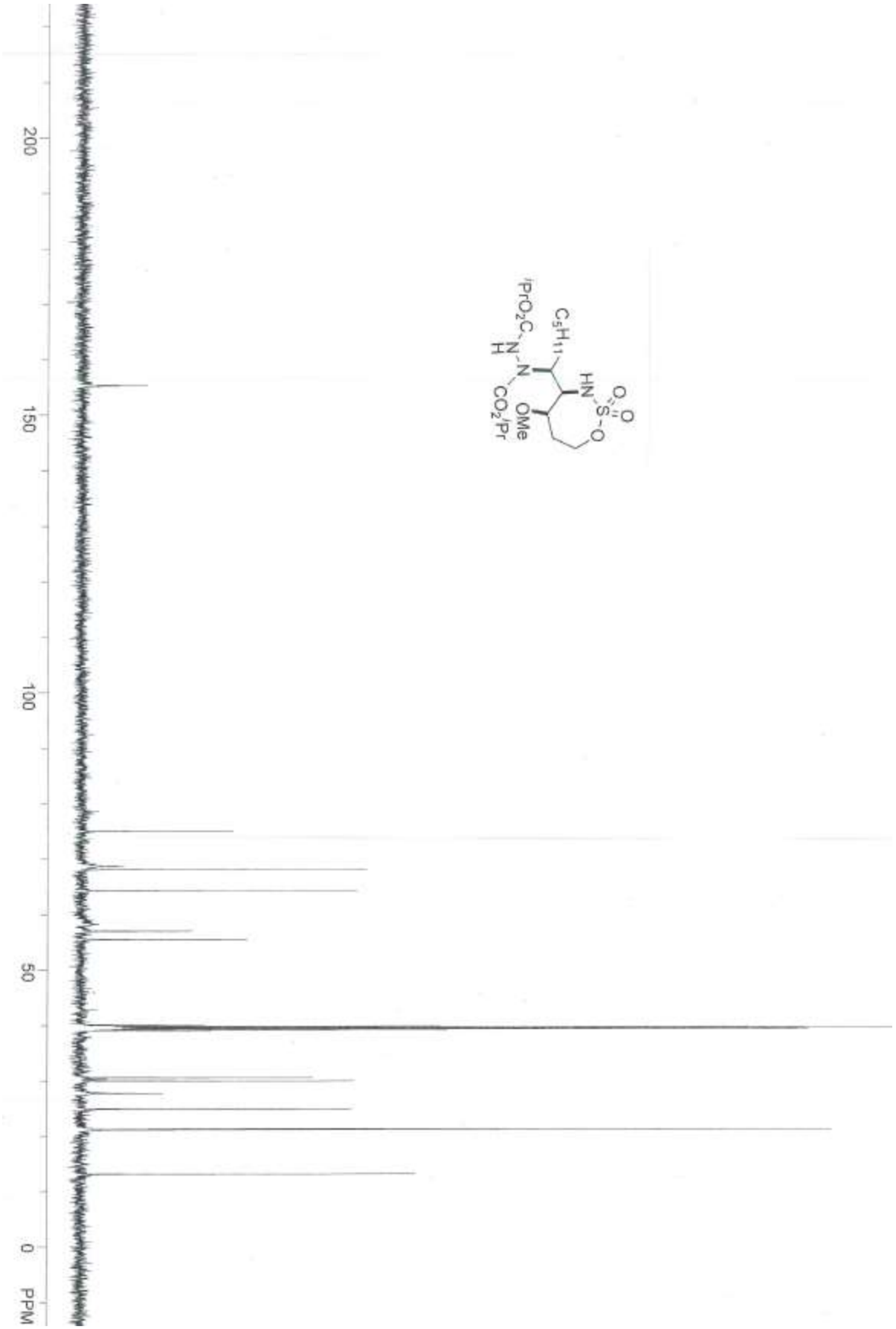
Compound 2.41 (minor diastereomer)



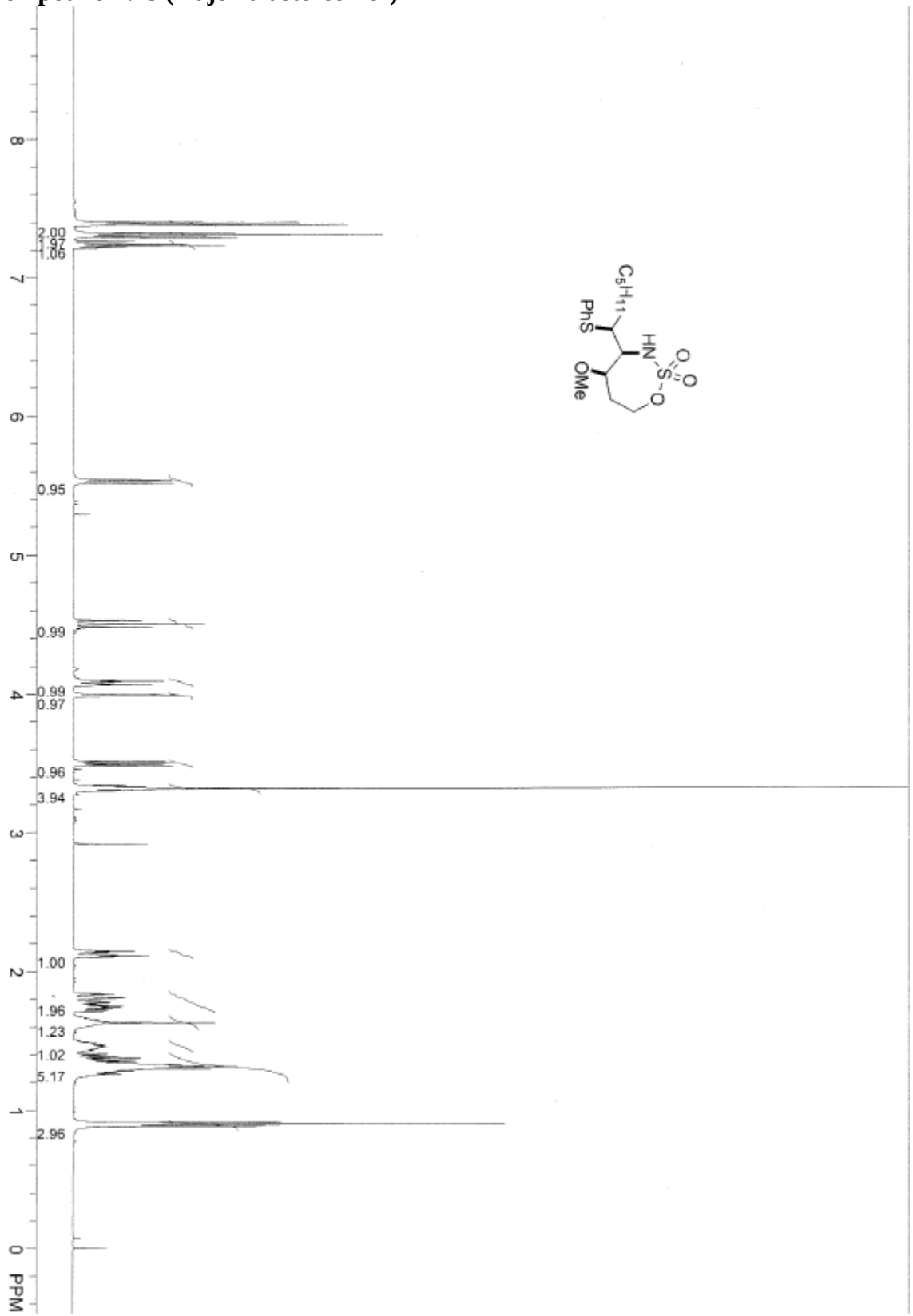

200
150
100
50
0
PPM
C5H11
NC
HN
Br
OAc
O
O
S
O

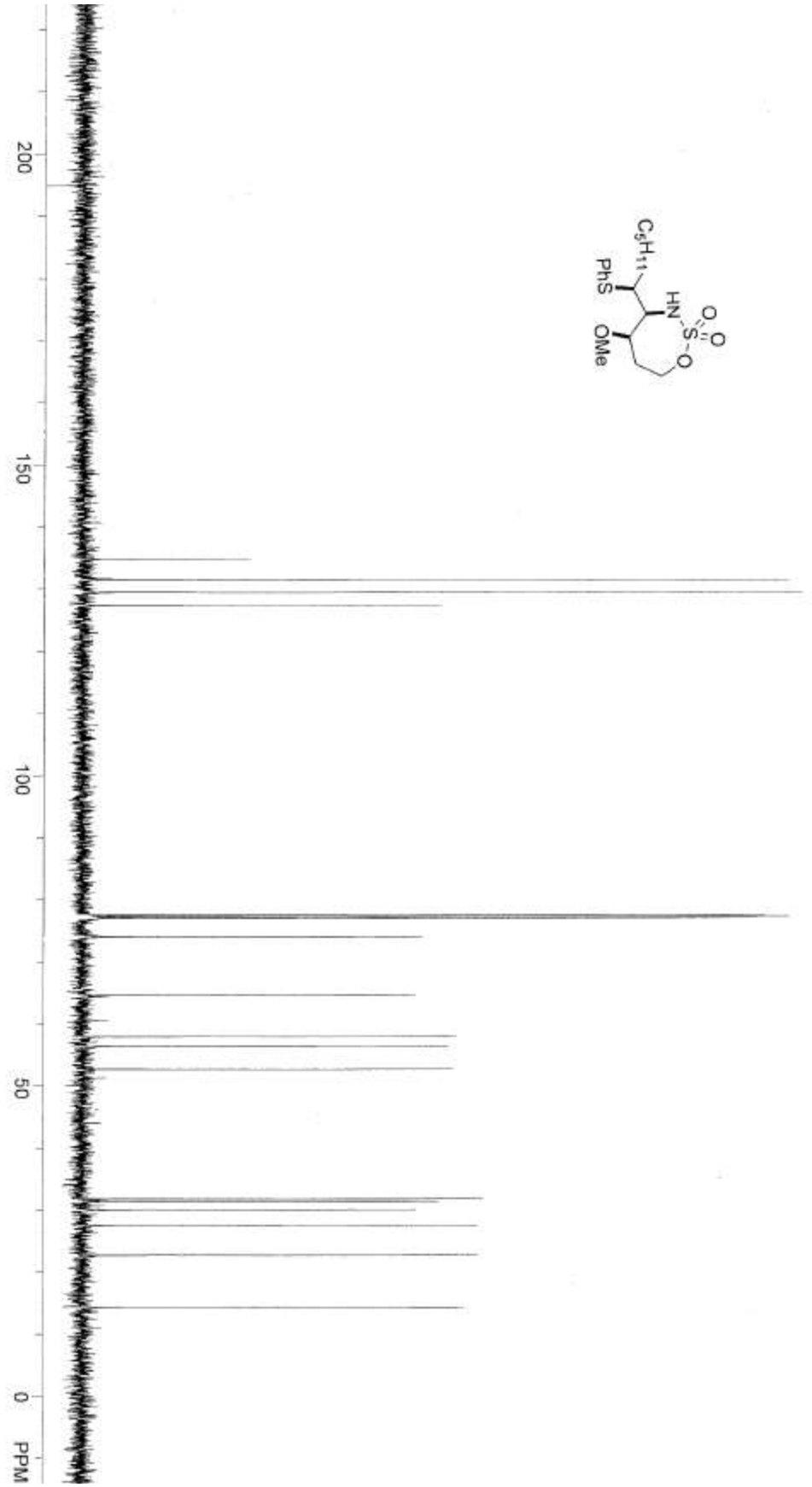
Compound 2.42



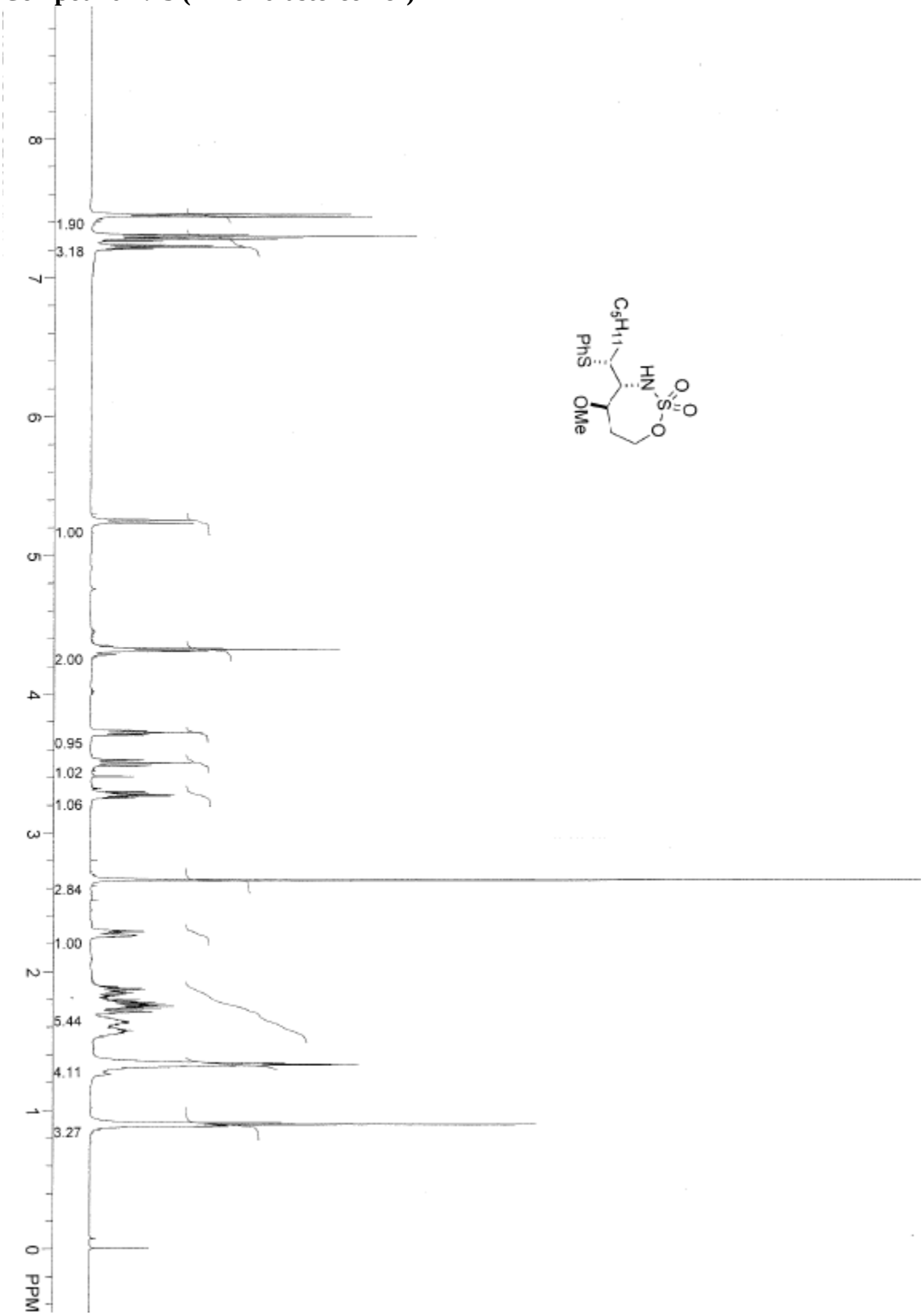

200
150
100
50
0
PPM
$^{i}PrO_2C$
N
H
N
$CO_2{}^{i}Pr$
OMe
C_5H_{11}
HN
S
O
O
O

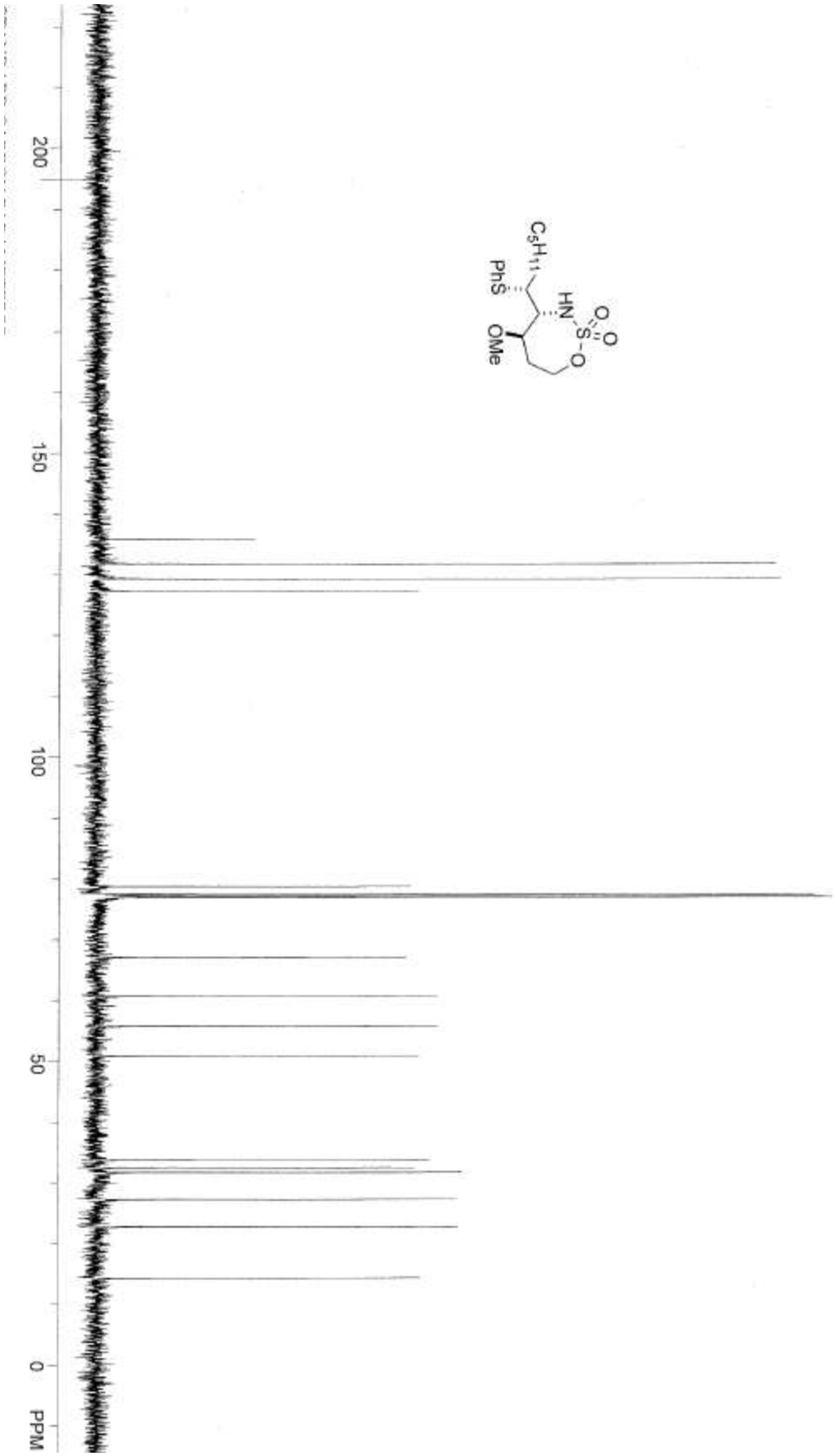
Compound 2.43 (major diastereomer)



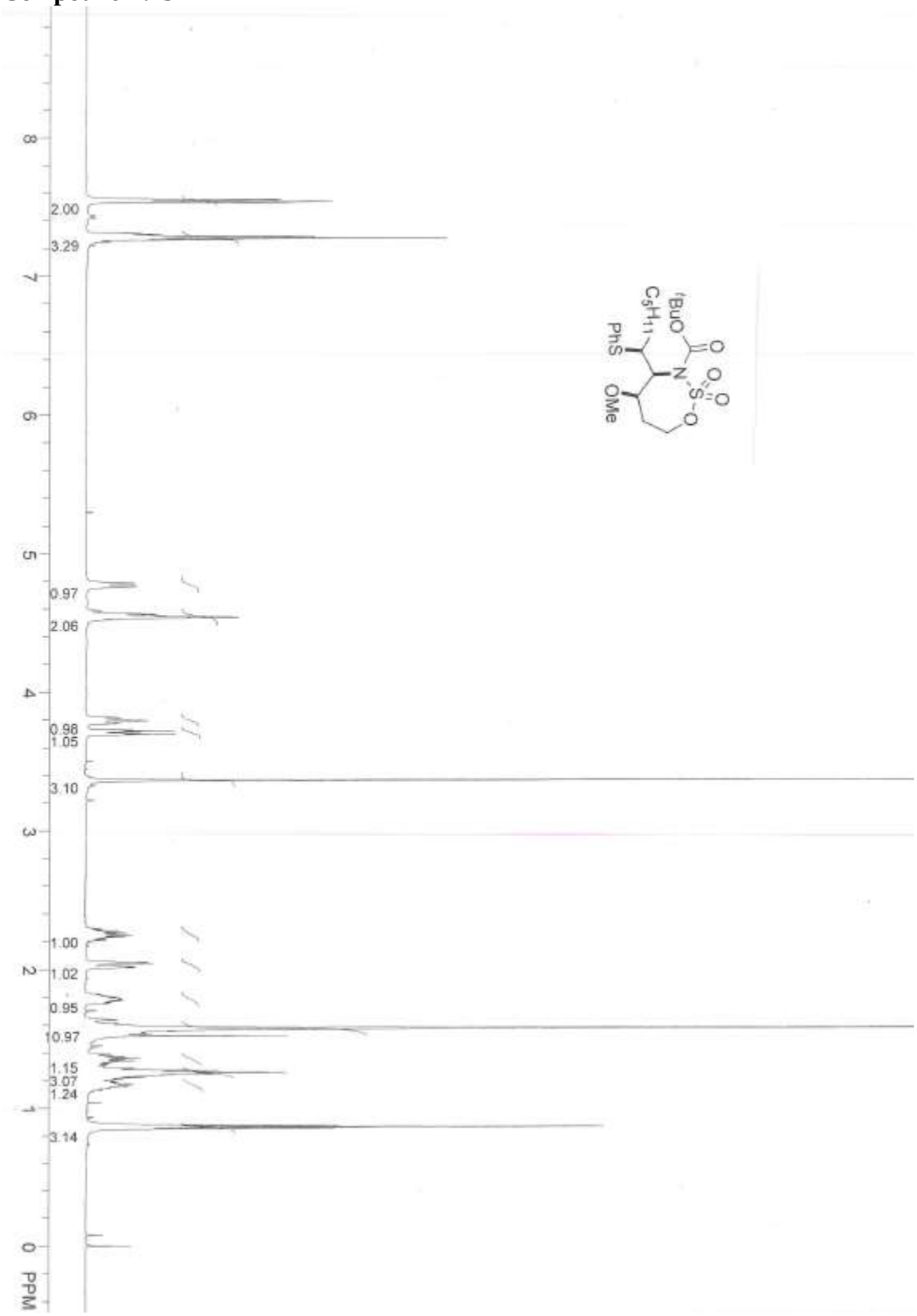

200
150
100
50
0
PPM
C5H11
PhS
OMe
HN
S
O
O
O

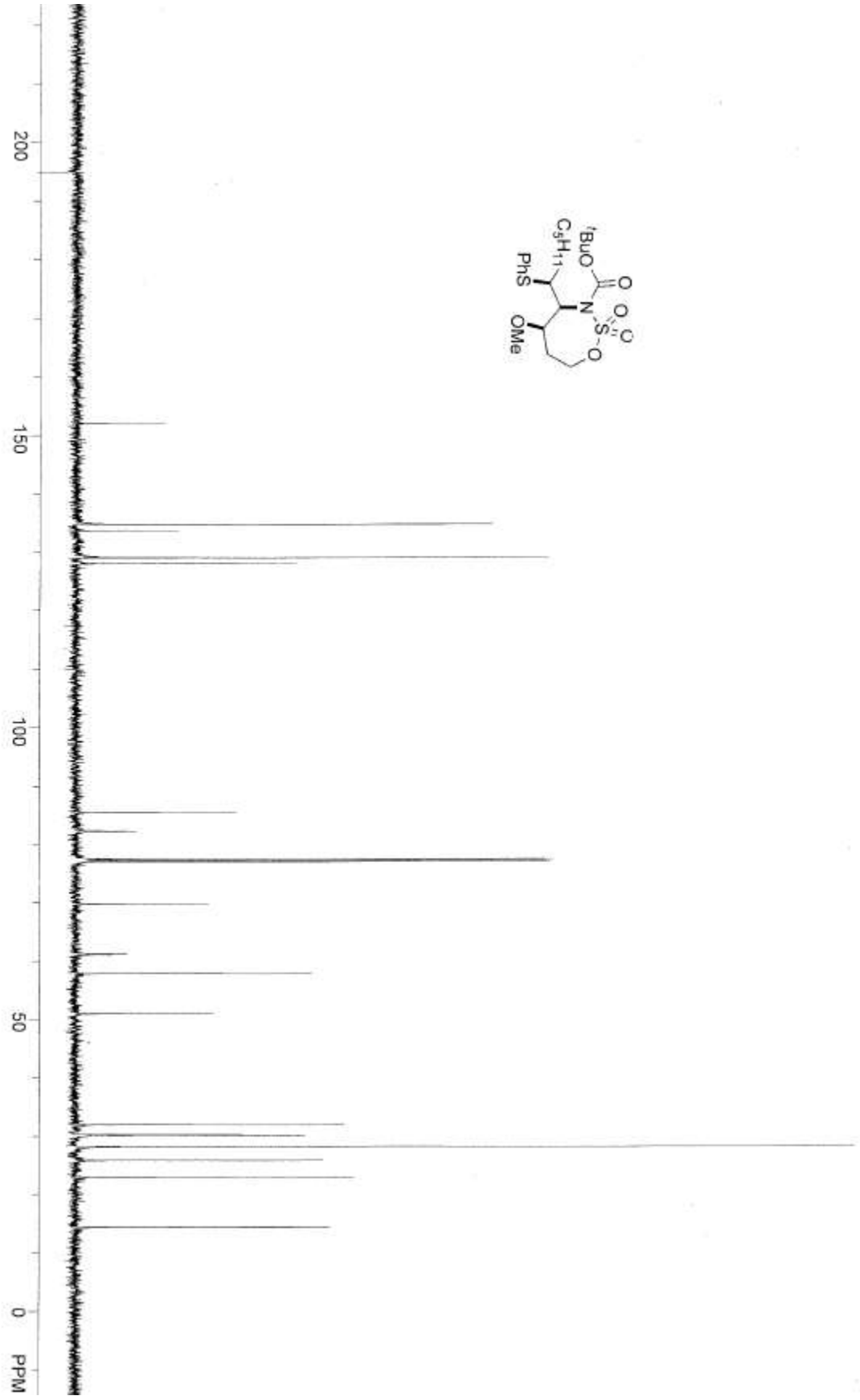
Compound 2.43 (minor diastereomer)



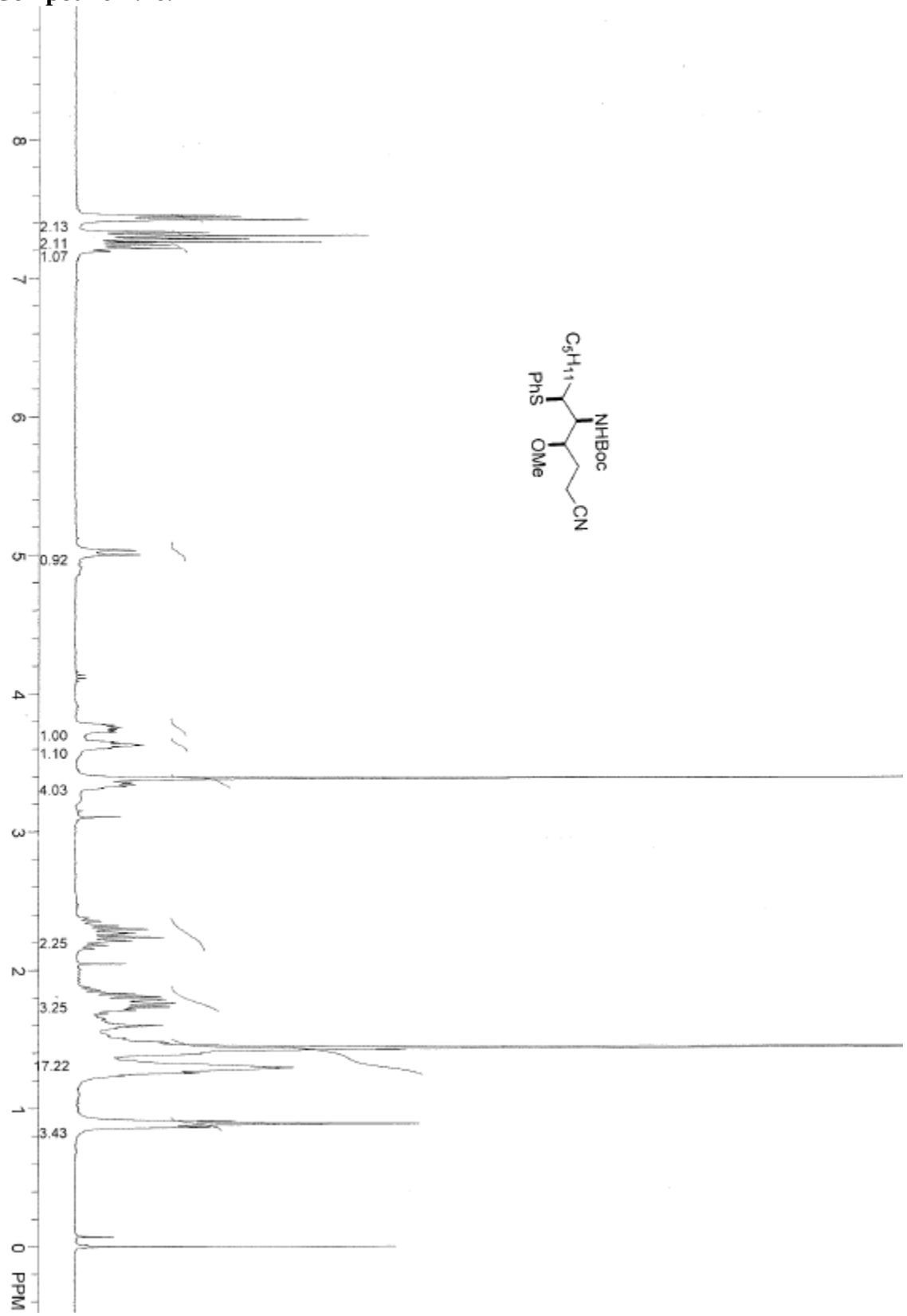

200
150
100
50
0
PPM
C_5H_{11}
PhS
OMe
HN
S
O
O
O

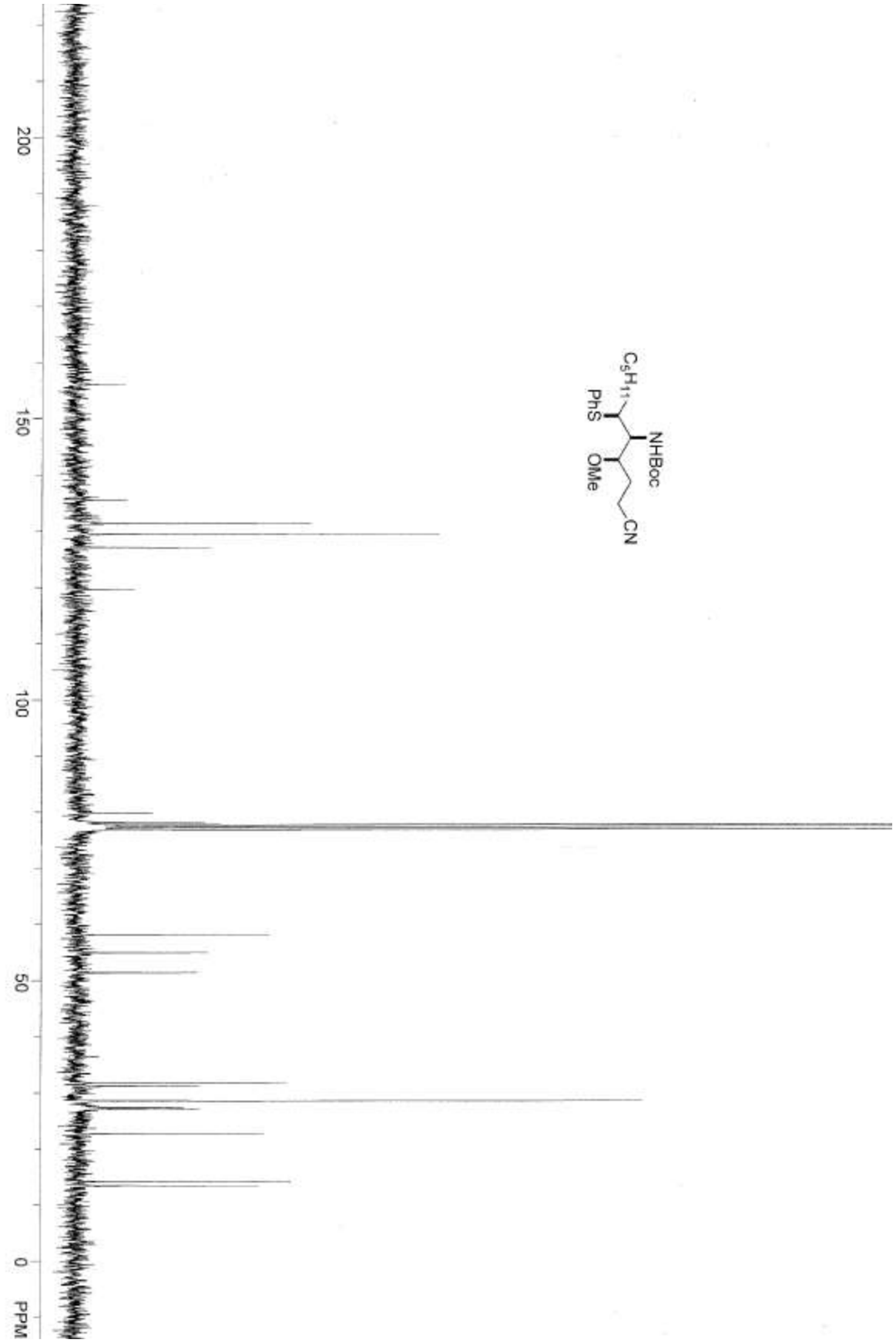
Compound 2.45



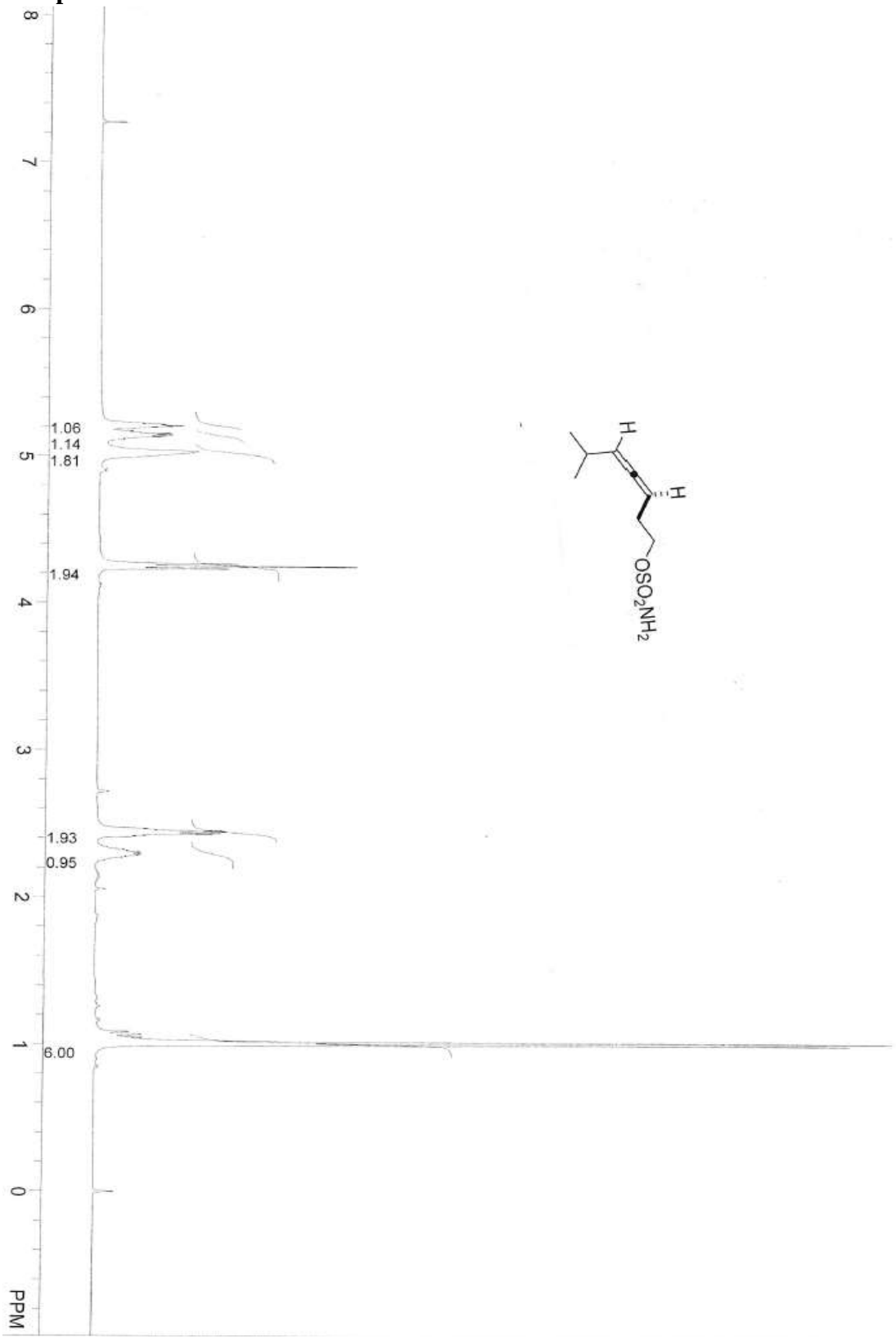

200
150
100
50
0
PPM
tBuO
C5H11
PhS
OMe
N
S
O

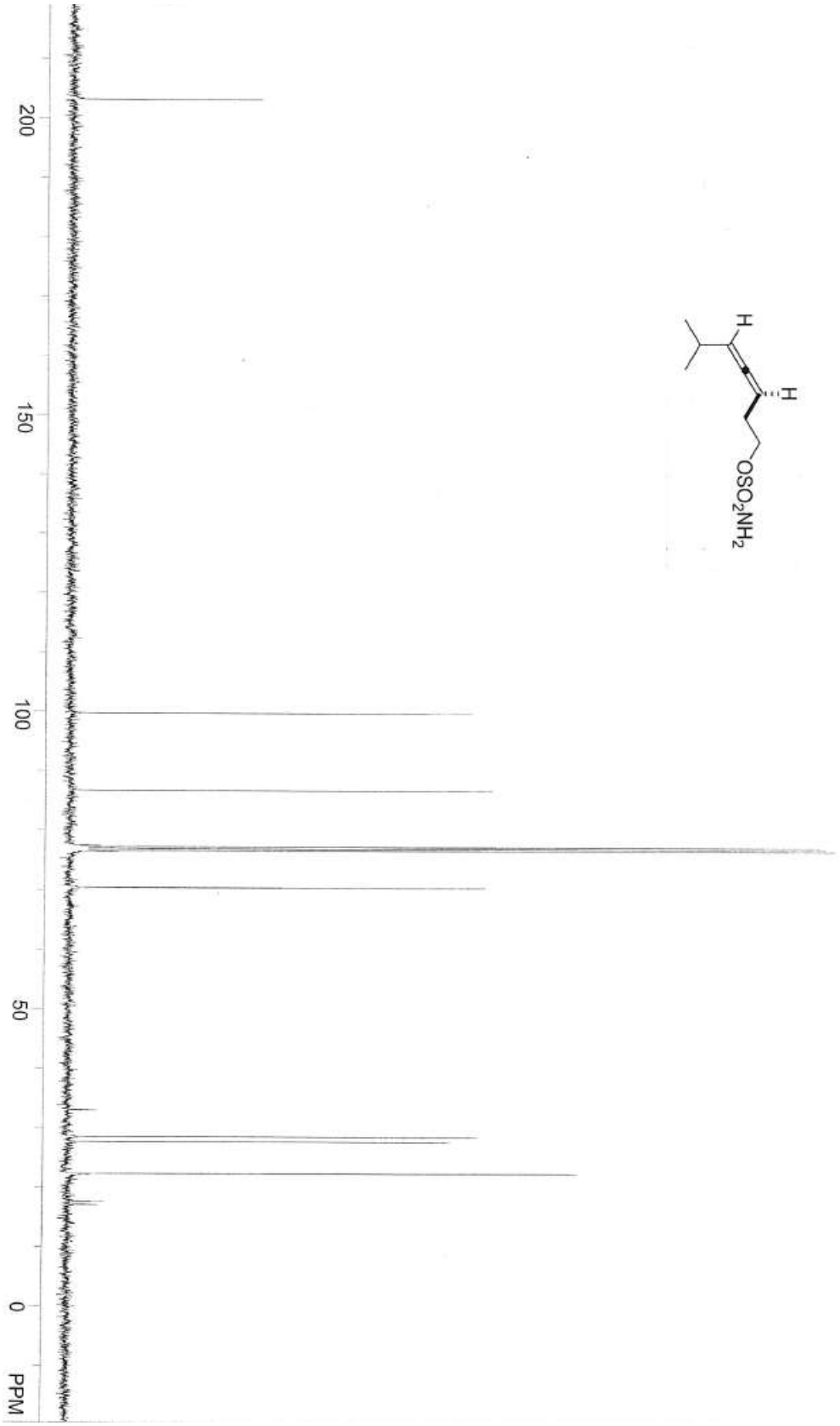
Compound 2.46.



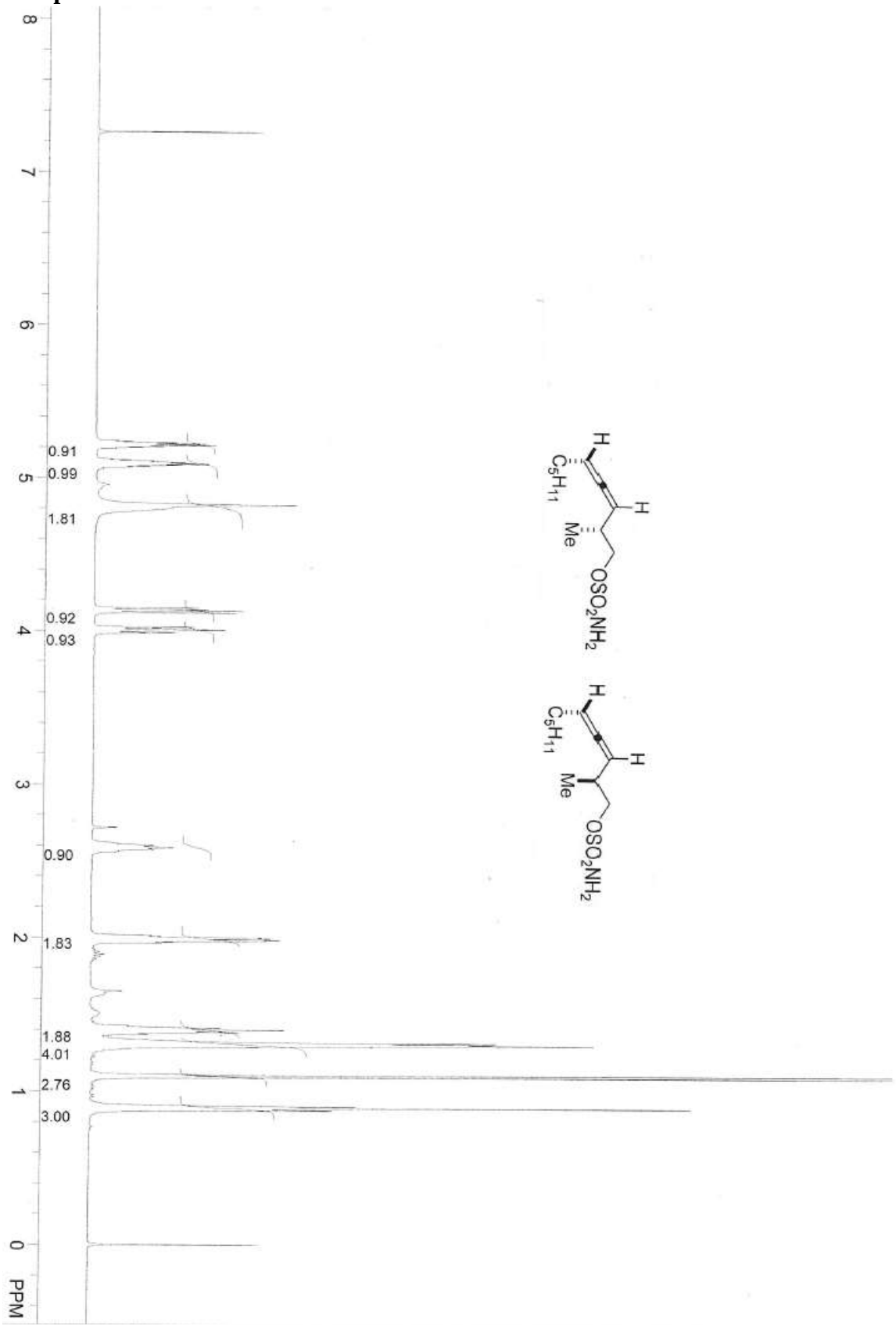

200
150
100
50
0
PPM
C5H11
PhS
NHBoc
OMe
CN

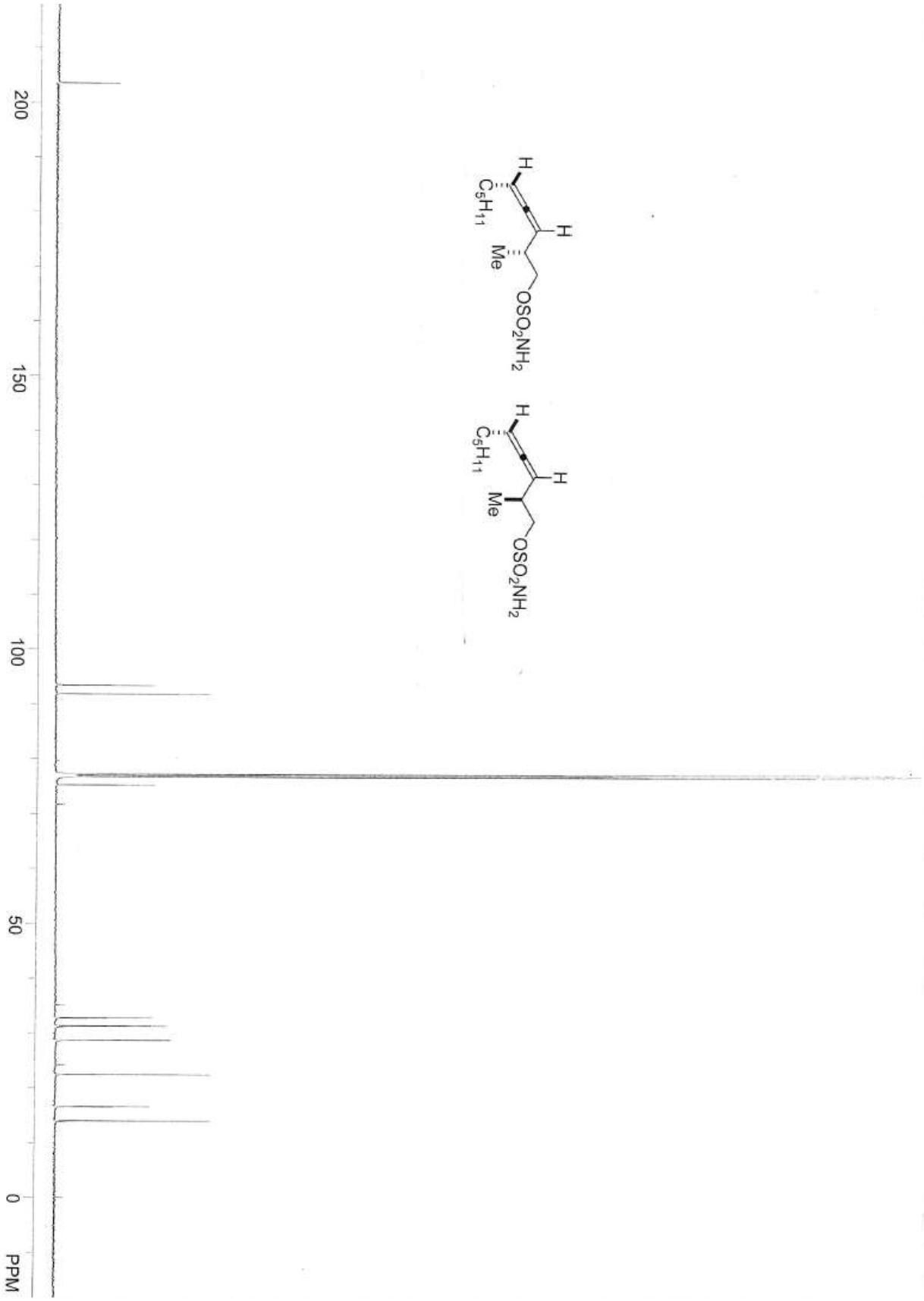
Compound 3.1.



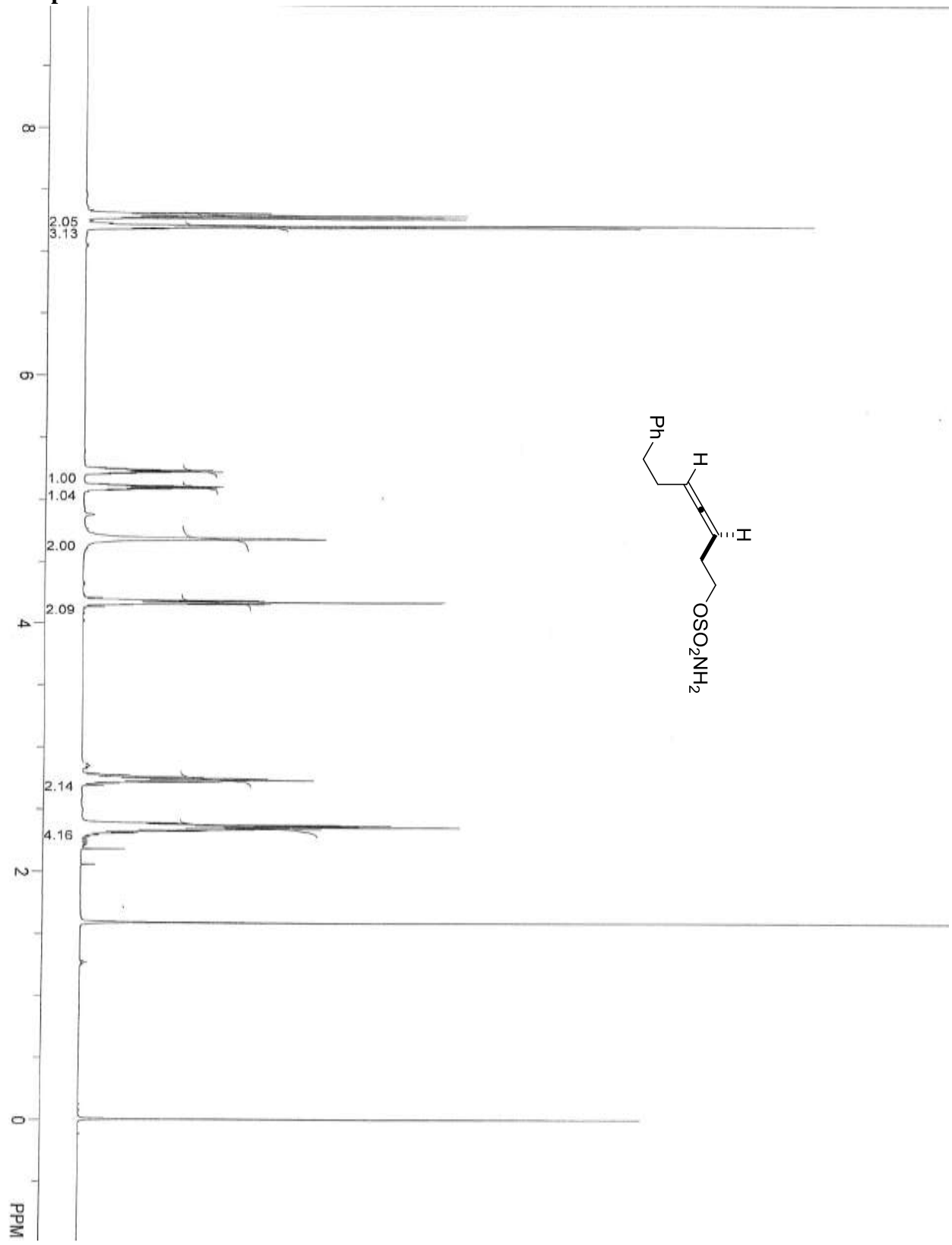

200
150
100
50
0
PPM
H
H
OSO2NH2

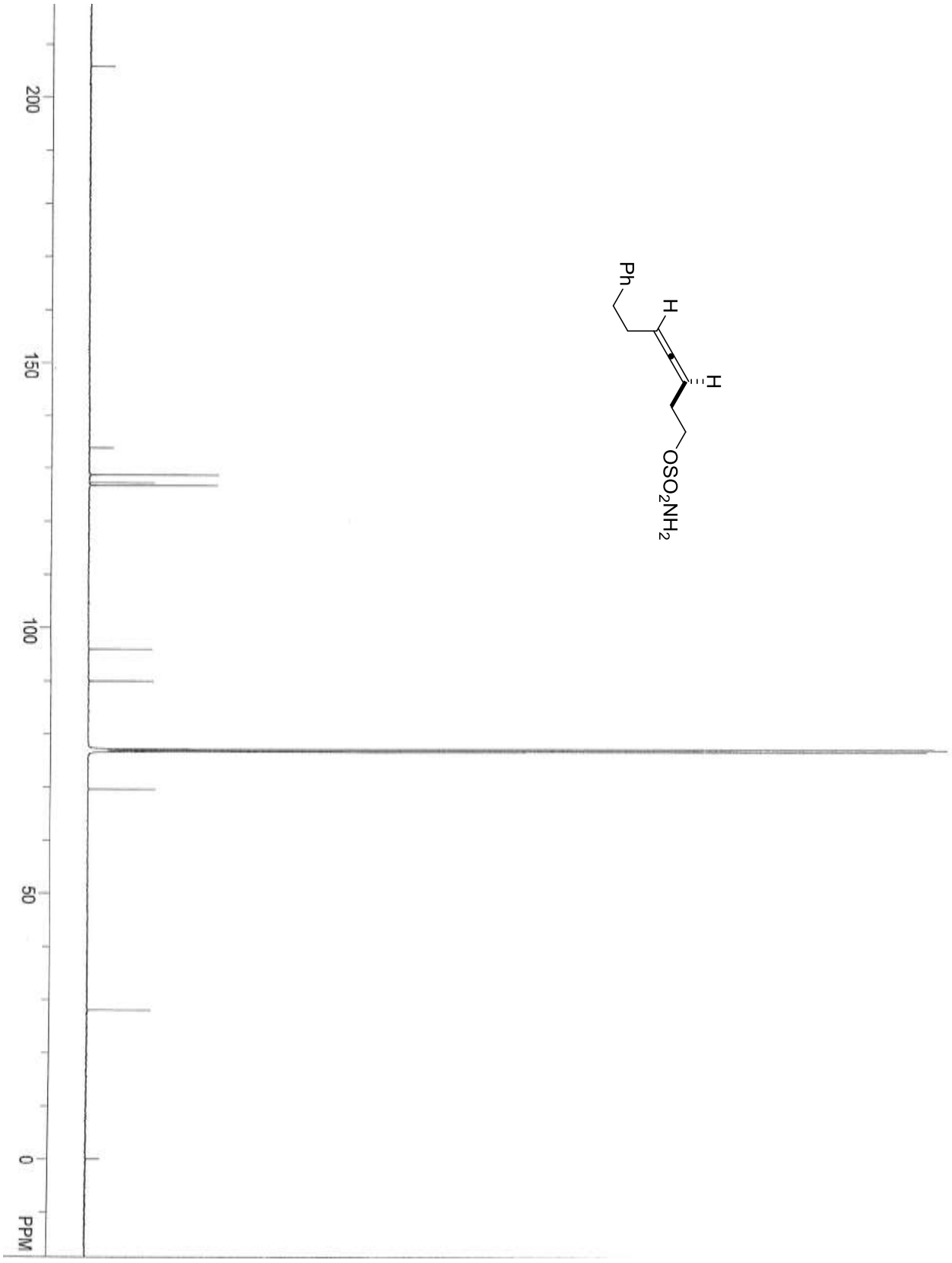
Compound 3.S1.



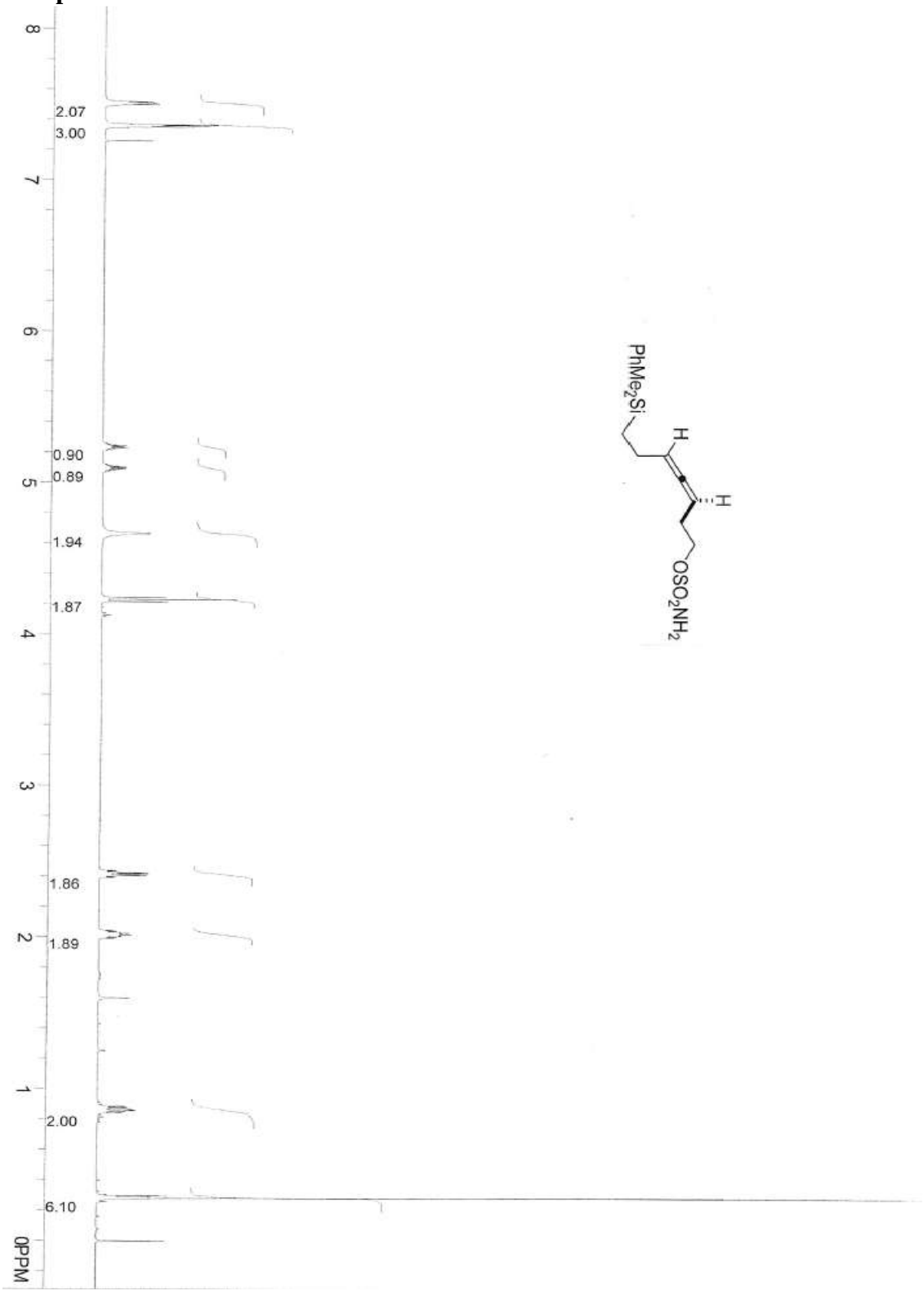

200
150
100
50
0
PPM
H
C5H11
Me
OSO2NH2
H
H
C5H11
Me
OSO2NH2

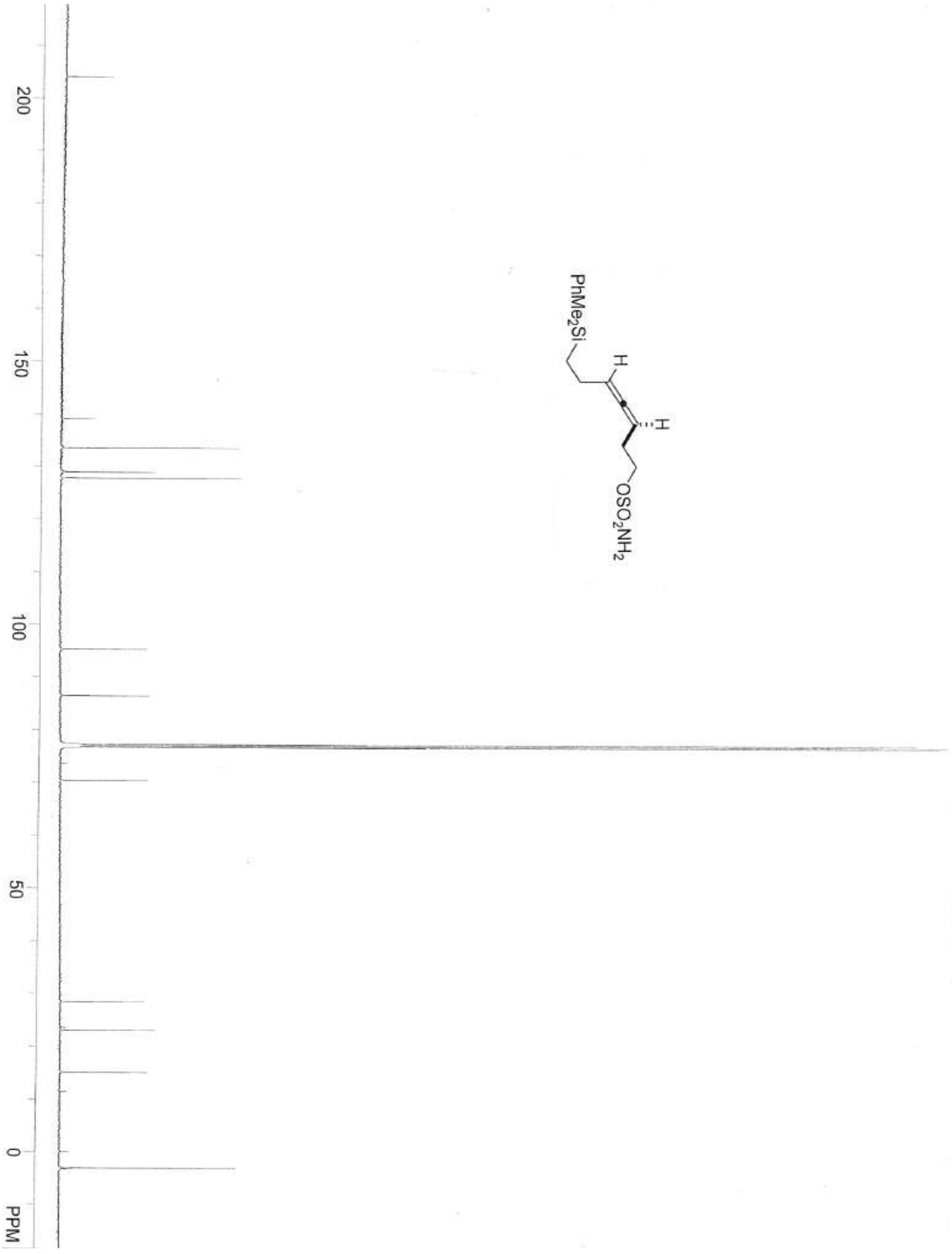
Compound 3.S2.



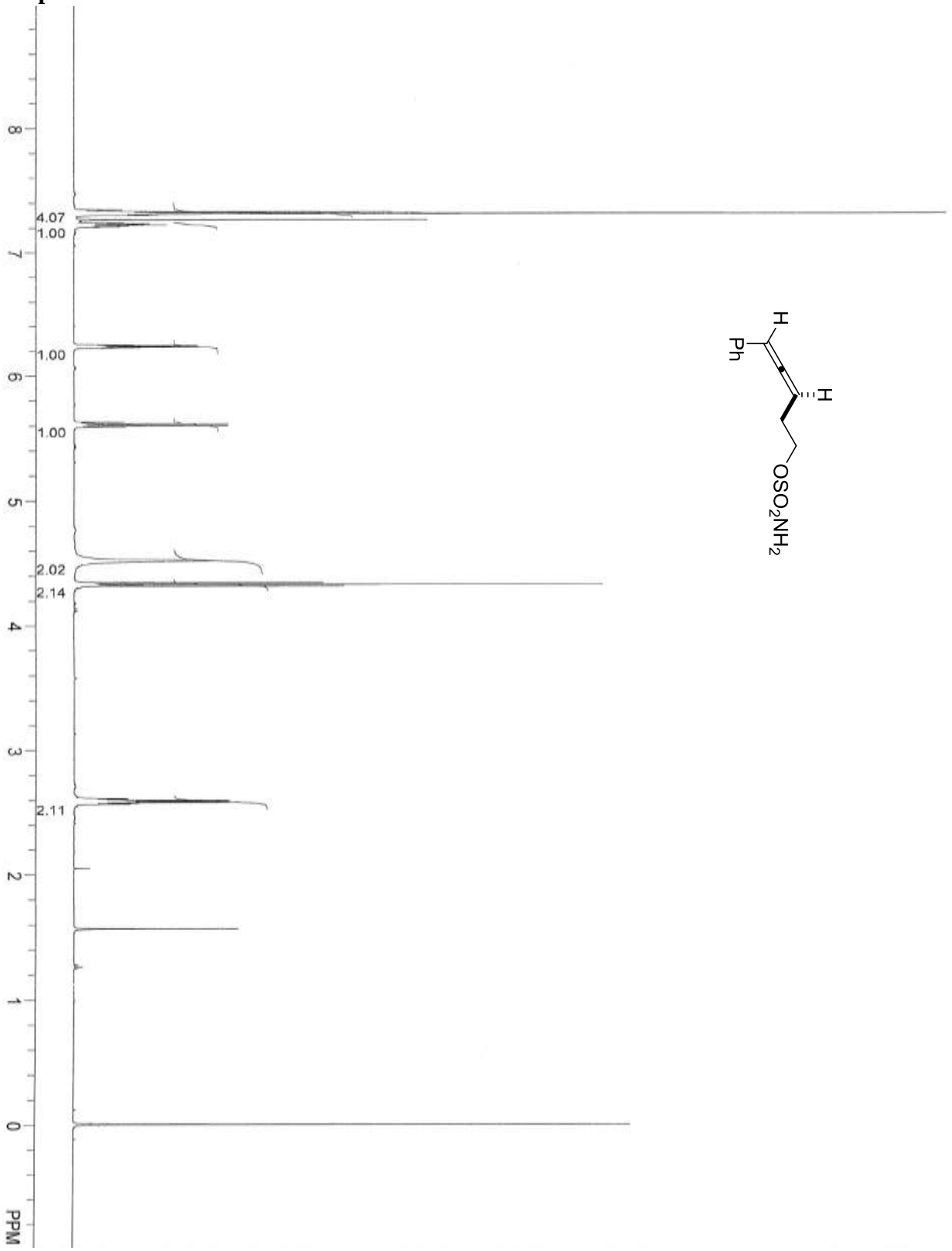

Ph
H
H
OSO2NH2
200
150
100
50
0
PPM

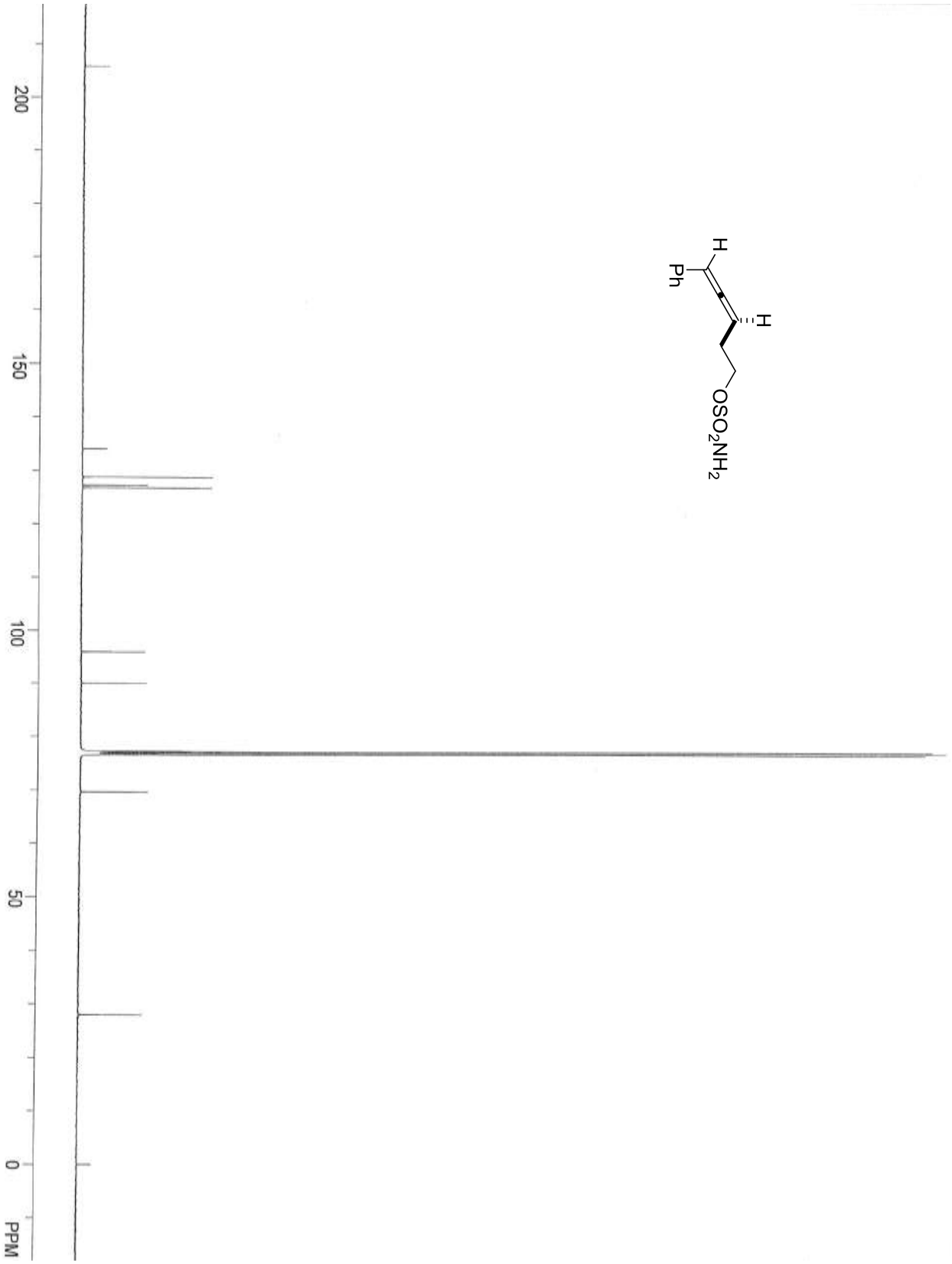
Compound 3.S3.



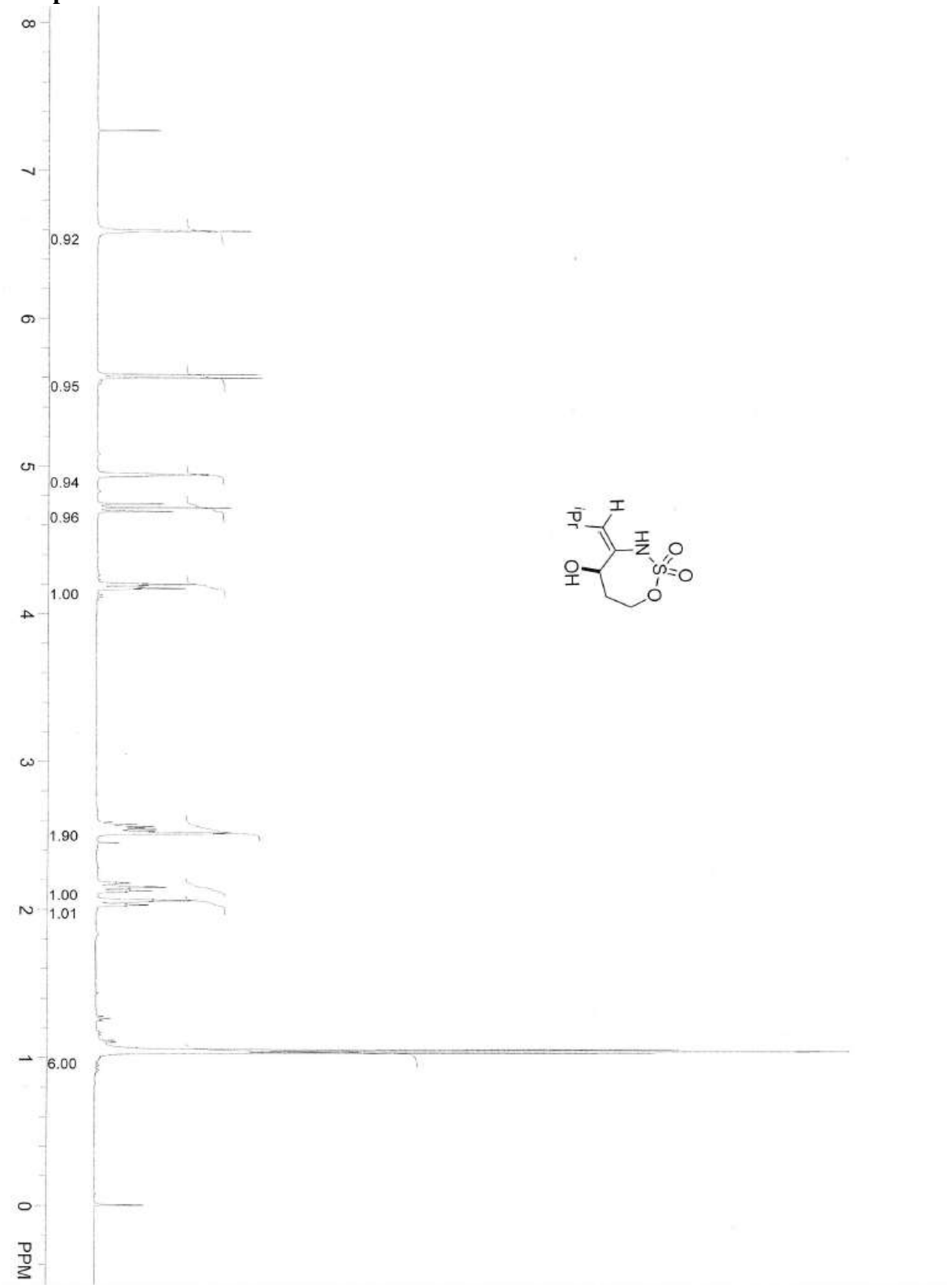

PhMe2Si
H
H
OSO2NH2
200
150
100
50
0
PPM

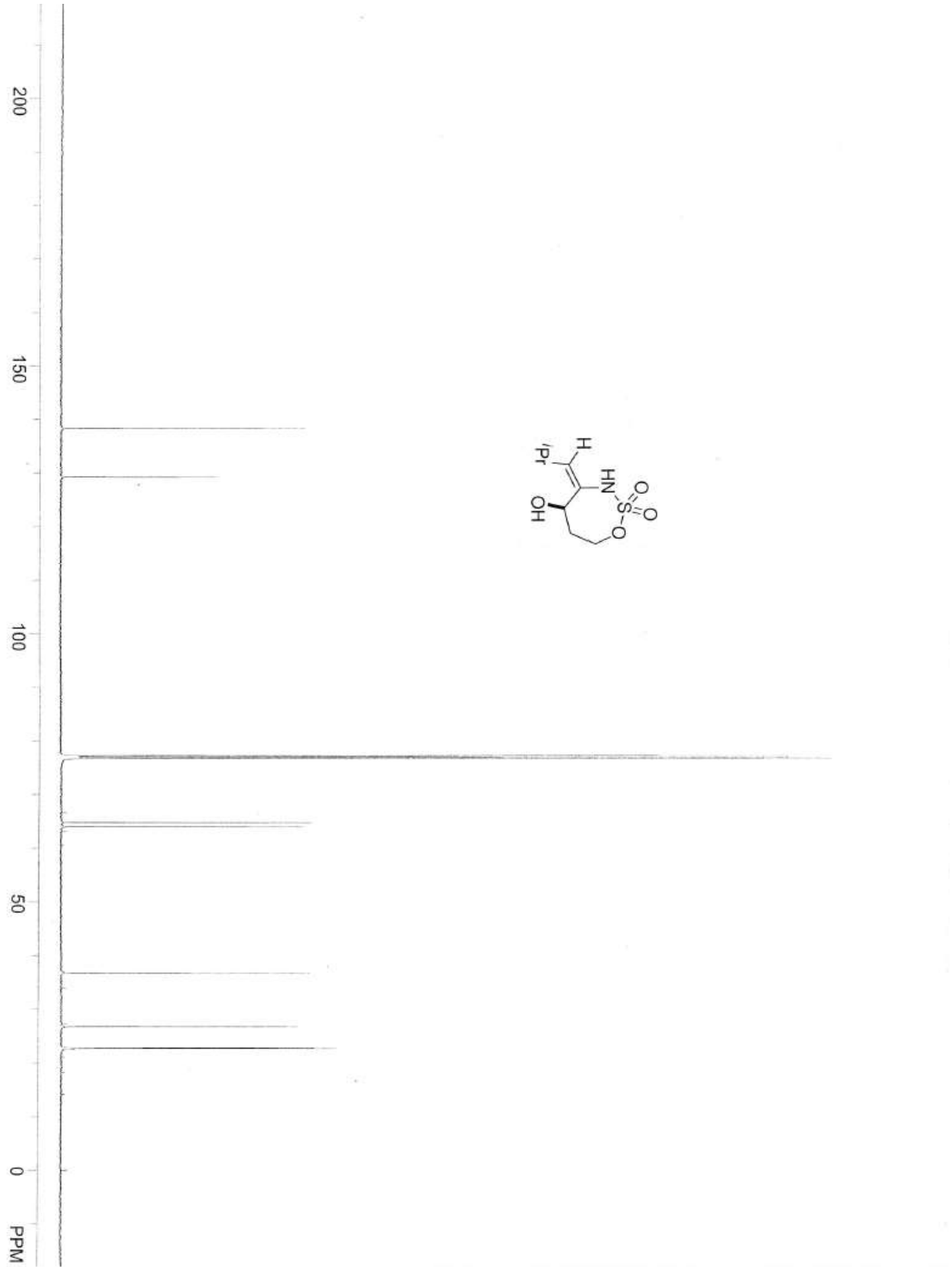
Compound 3.S4



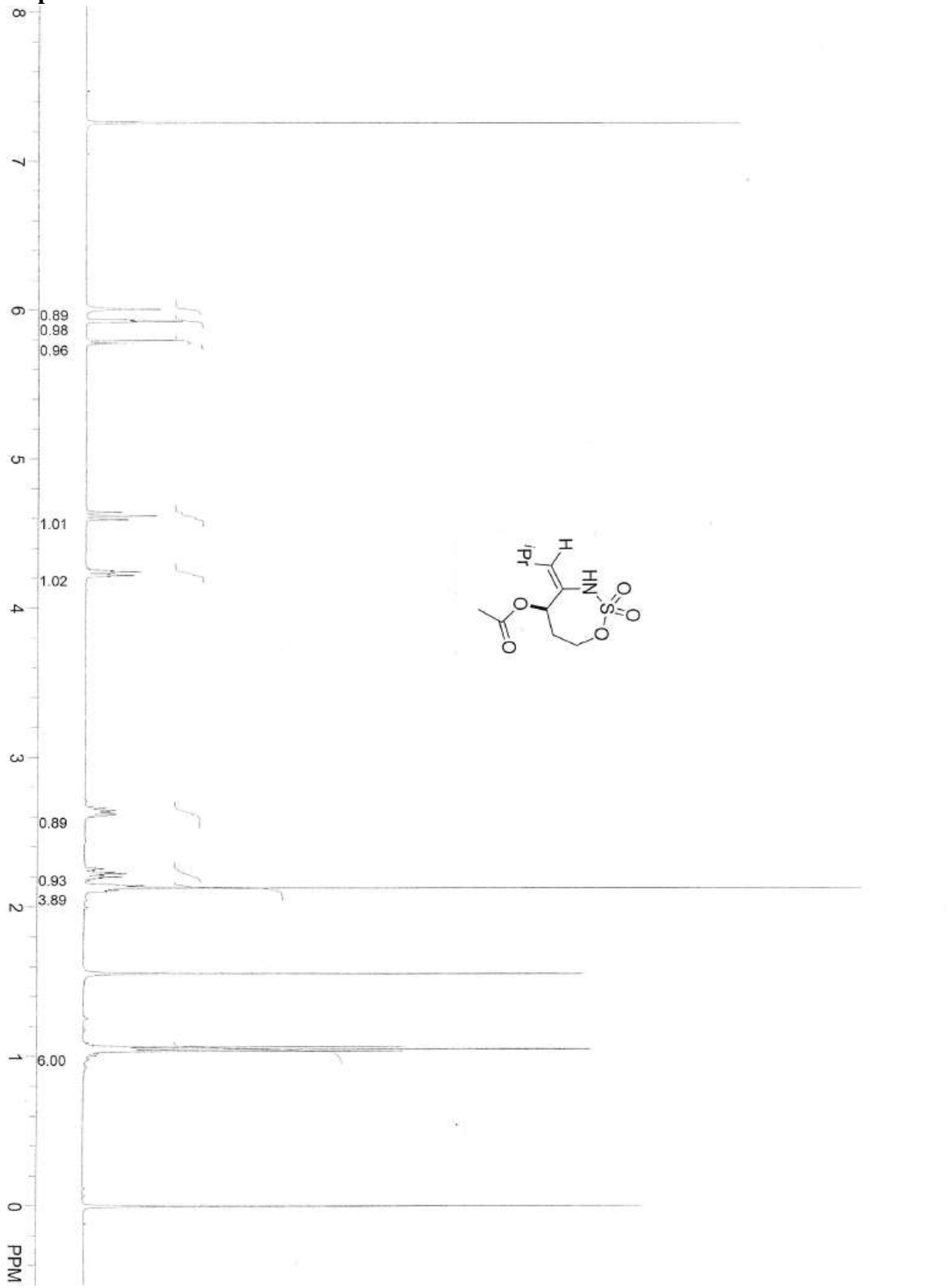

H
Ph
H
OSO2NH2
200
150
100
50
0
PPM

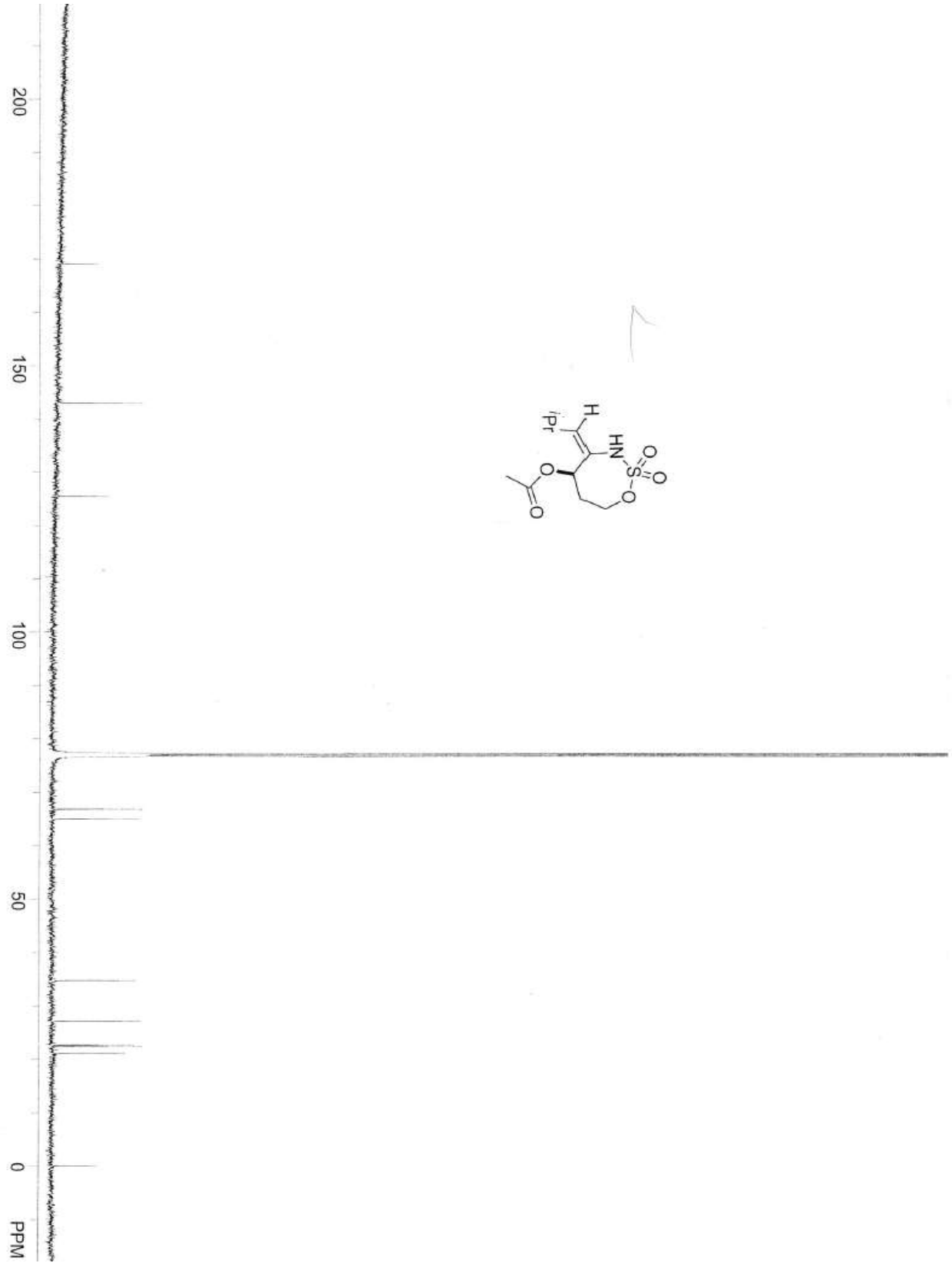
Compound 3.2.


8
7
6
5
4
3
2
1
0
PPM
0.92
0.95
0.94
0.96
1.00
1.90
1.00
1.01
6.00
H
iPr
HN
S
O
O
O
OH

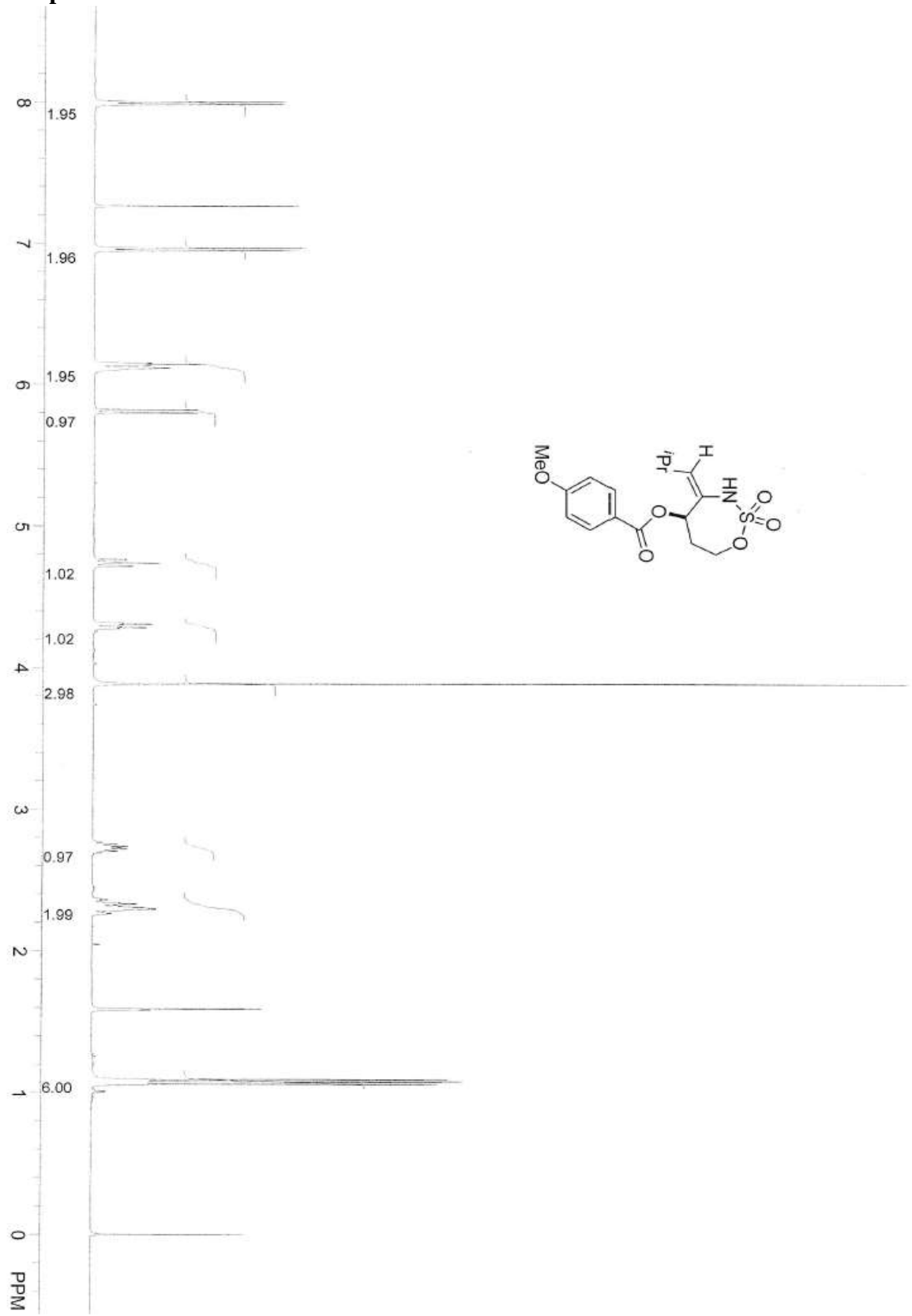

200
150
100
50
0
PPM
H
iPr
HN
O
O
S
O
OH

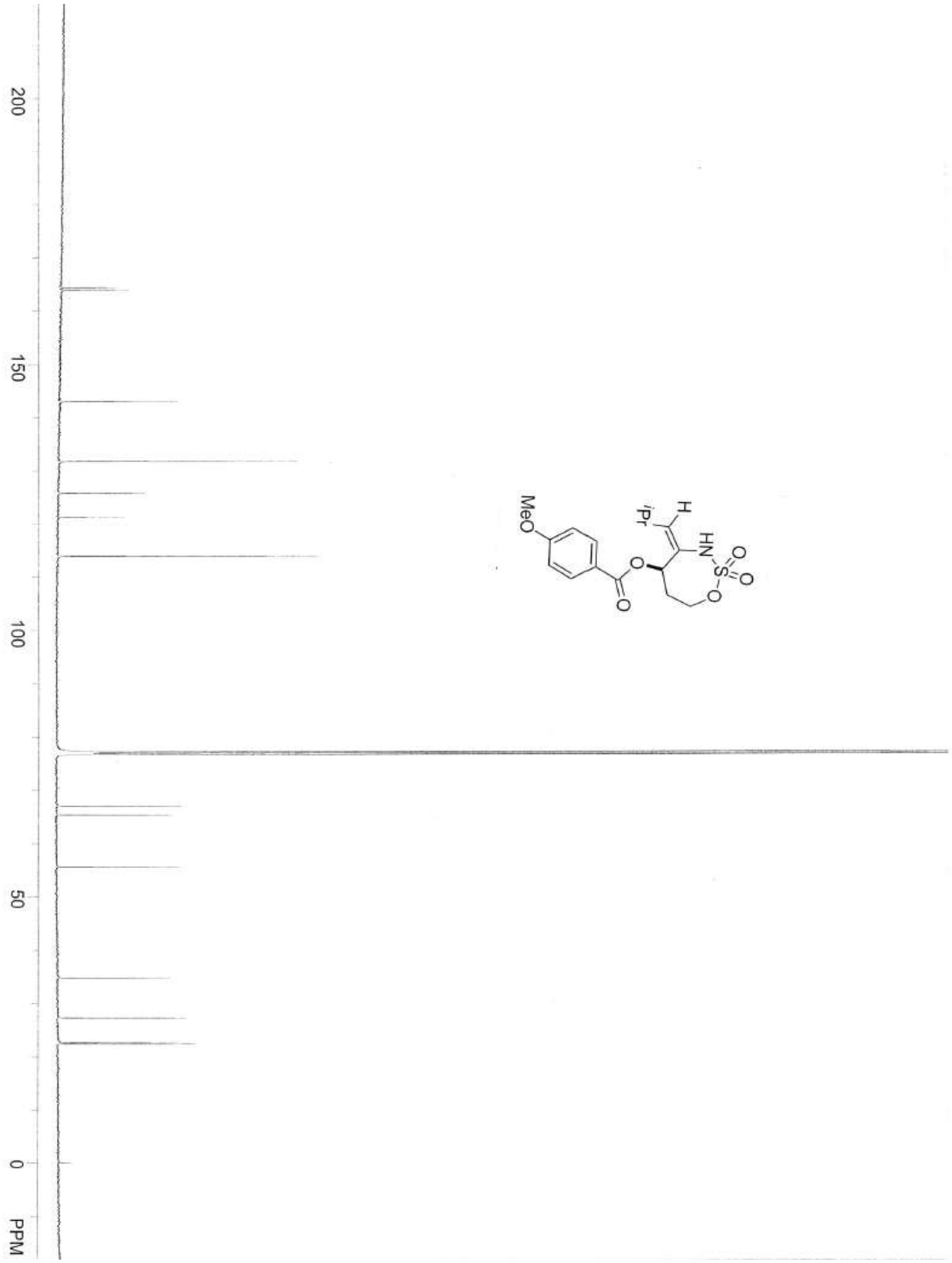
Compound 3.3.


8
7
6
5
4
3
2
1
0
PPM
0.89
0.98
0.96
1.01
1.02
0.89
0.93
3.89
6.00
H
iPr
HN
O
O
O
O
O
O

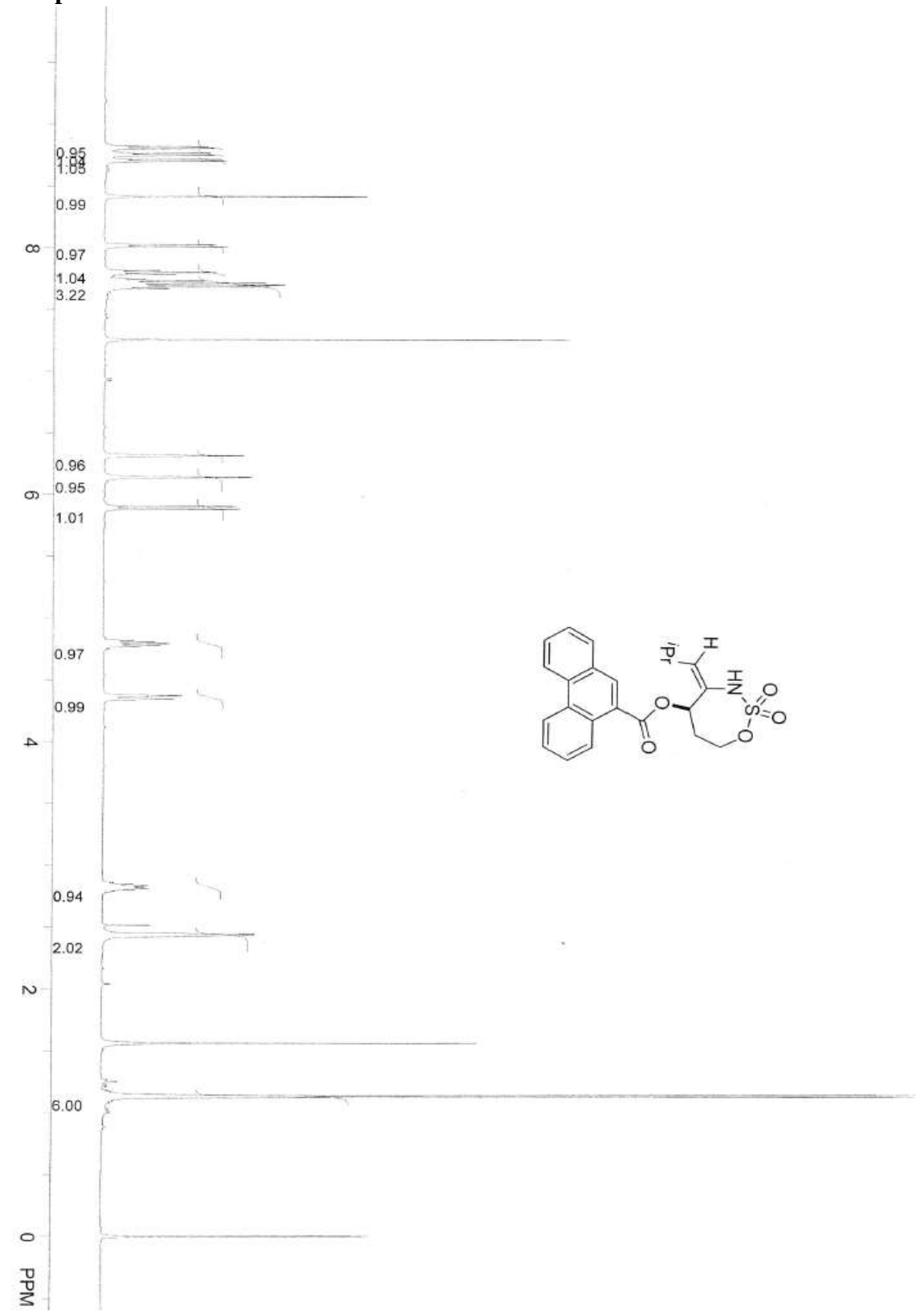

200
150
100
50
0
PPM
H
iPr
HN
O
O
S
O
O
O

Compound 3.4.


8
7
6
5
4
3
2
1
0
PPM
1.95
1.96
1.95
0.97
1.02
1.02
2.98
0.97
1.99
6.00
MeO
iPr
H
HN
S
O
O
O
O
O

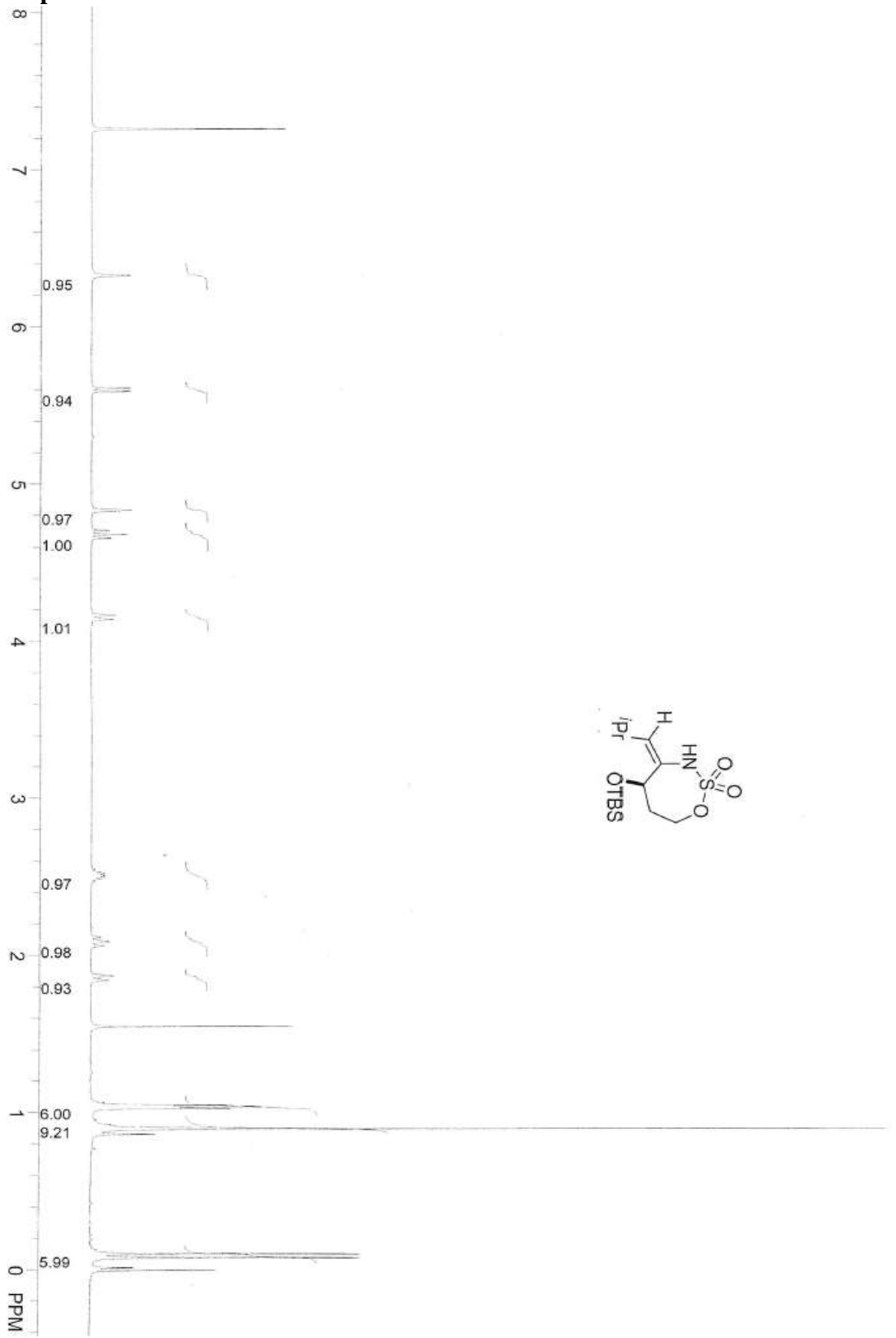

200
150
100
50
0
PPM
MeO
O
O
H
iPr
HN
S
O
O
O

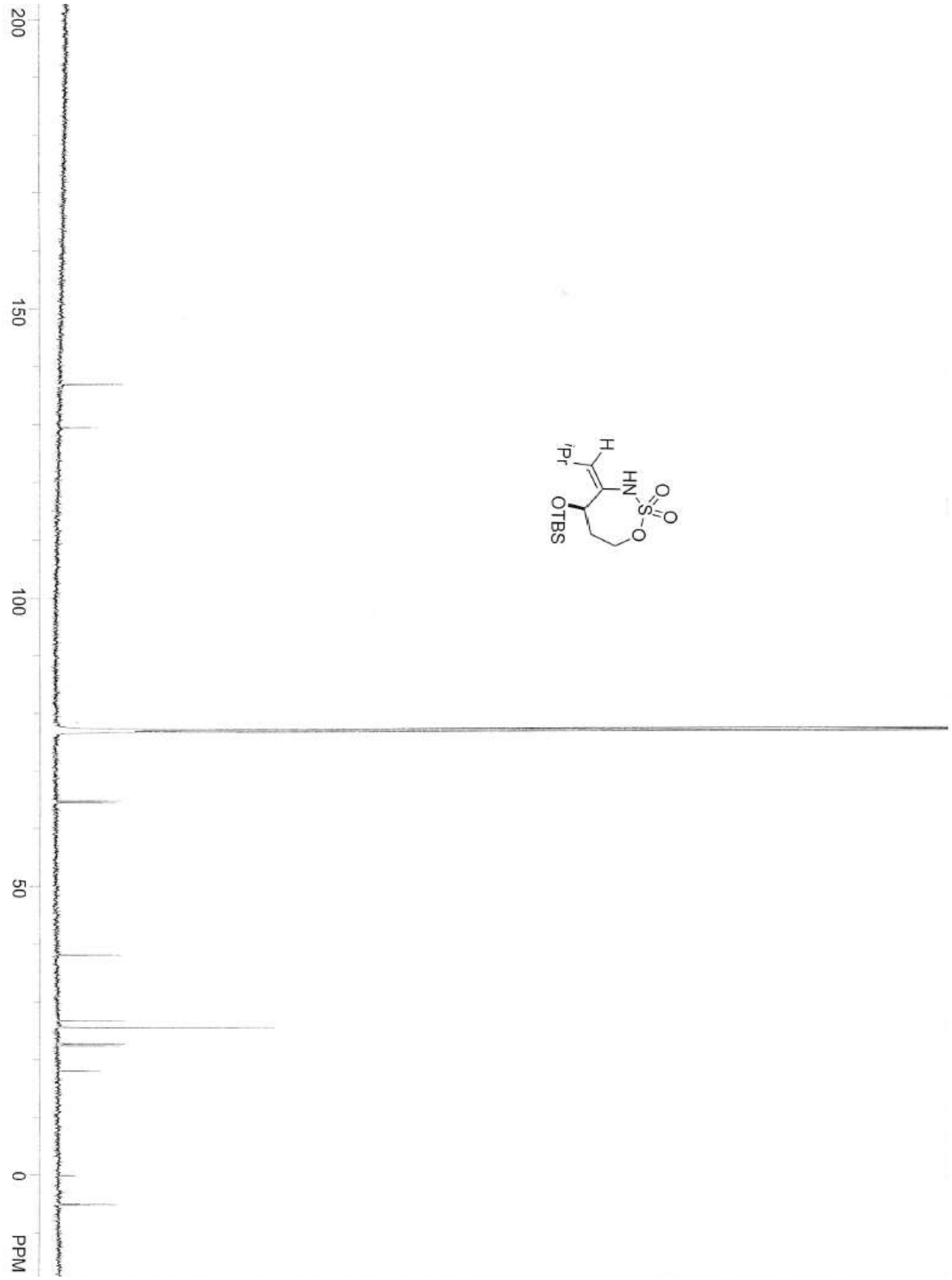
Compound 3.5.


0.95
1.04
1.05
0.99
0.97
1.04
3.22
0.96
0.95
1.01
0.97
0.99
0.94
2.02
6.00
8
6
4
2
0
PPM
iPr
H
HN
S
O
O
O
O
O

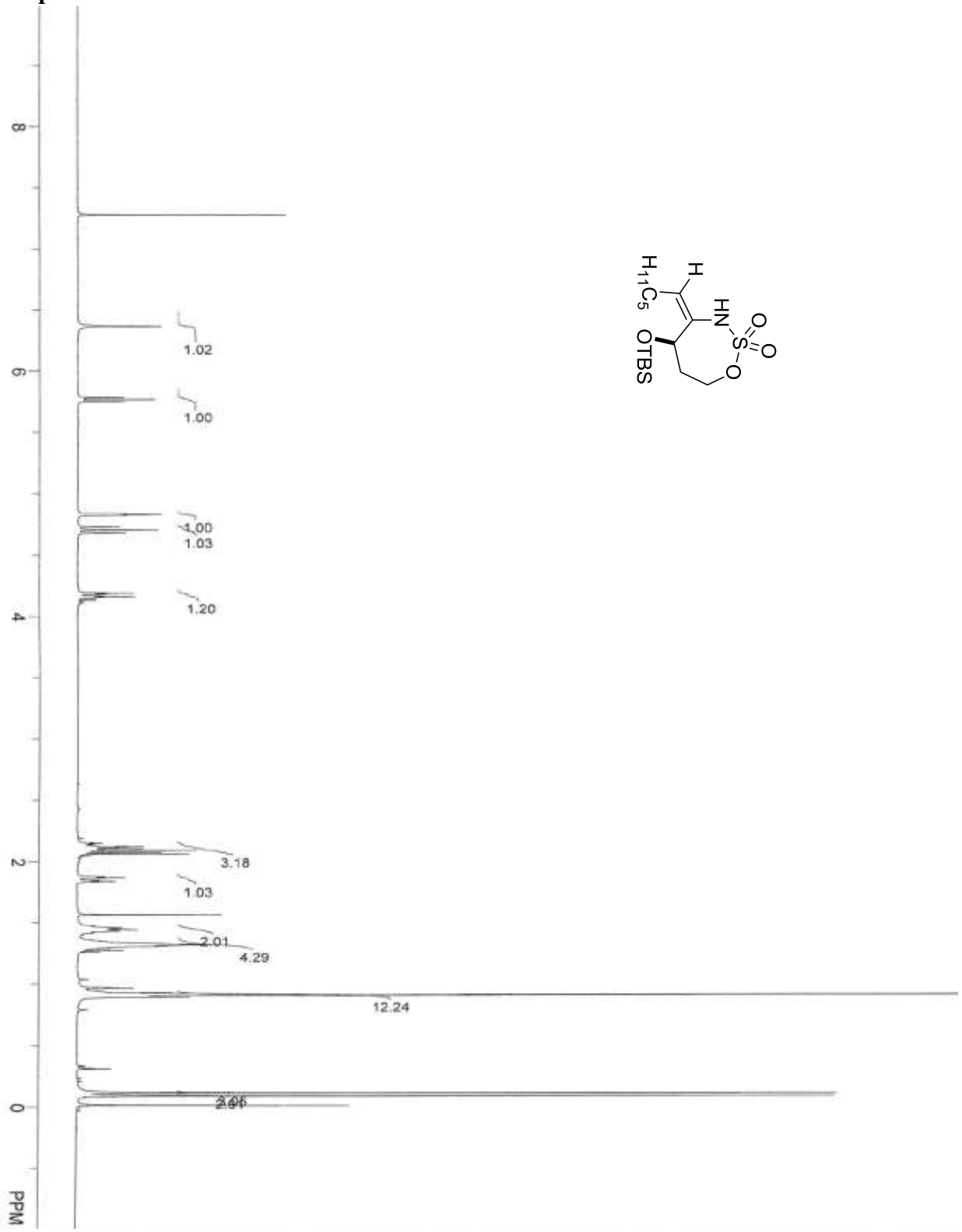

200
150
100
50
0
PPM
iPr
H
HN
O
S
O
O
O

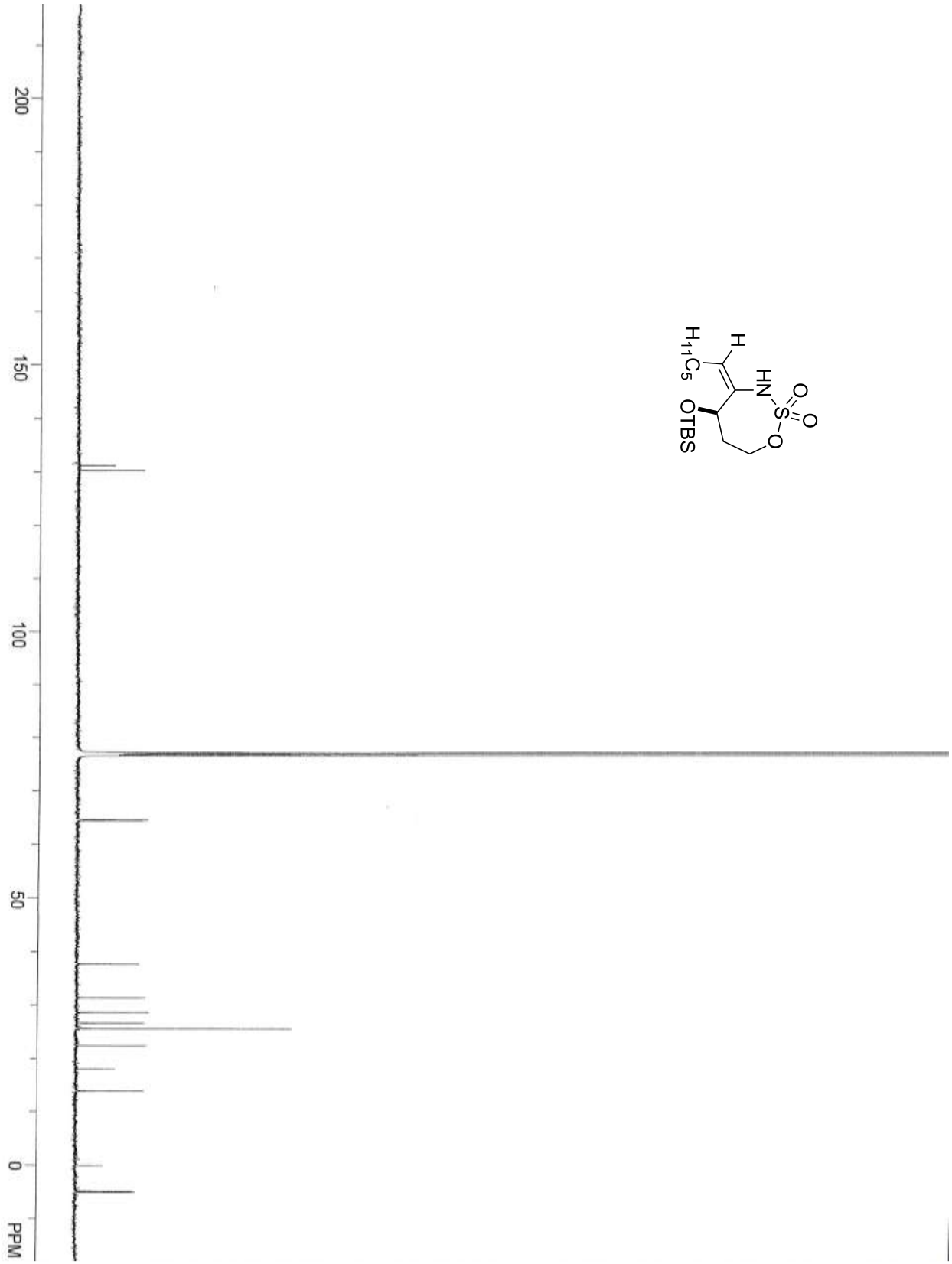
Compound 3.7.


8
7
6
5
4
3
2
1
0
PPM
0.95
0.94
0.97
1.00
1.01
0.97
0.98
0.93
6.00
9.21
5.99
H
iPr
OTBS
HN
S
O
O
O

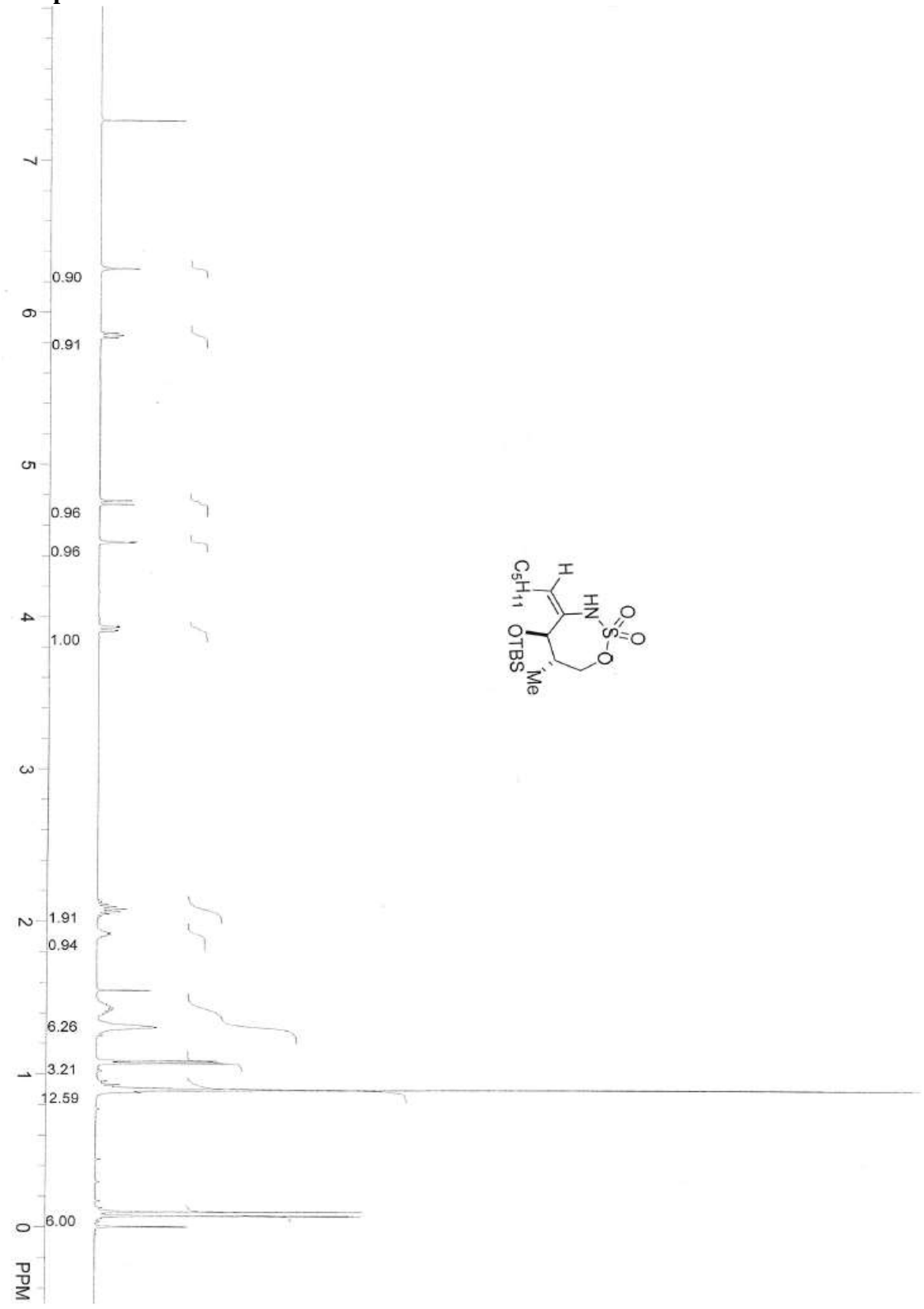

200
150
100
50
0
PPM
H
iPr
HN
S
O
O
O
OTBS

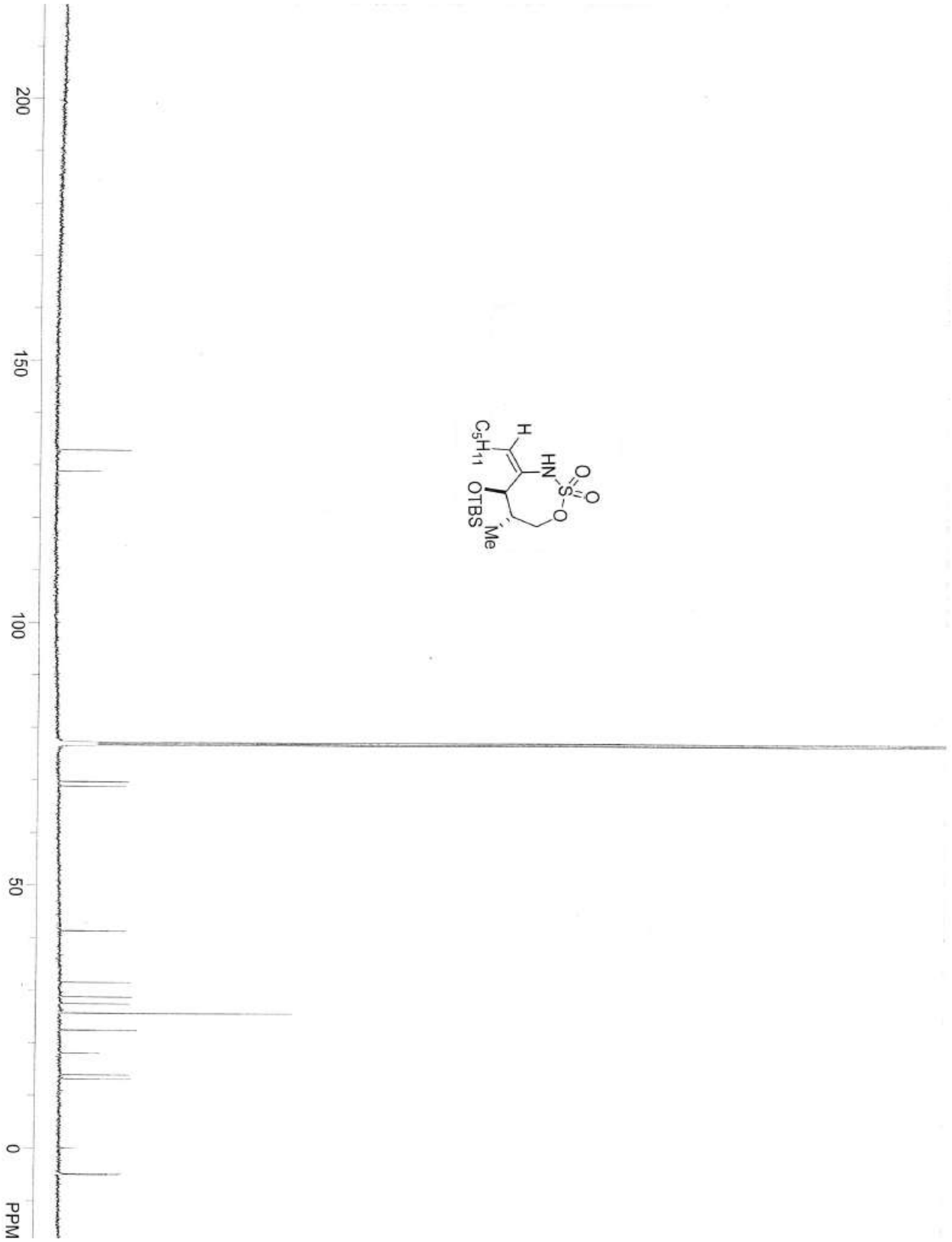
Compound 3.14.



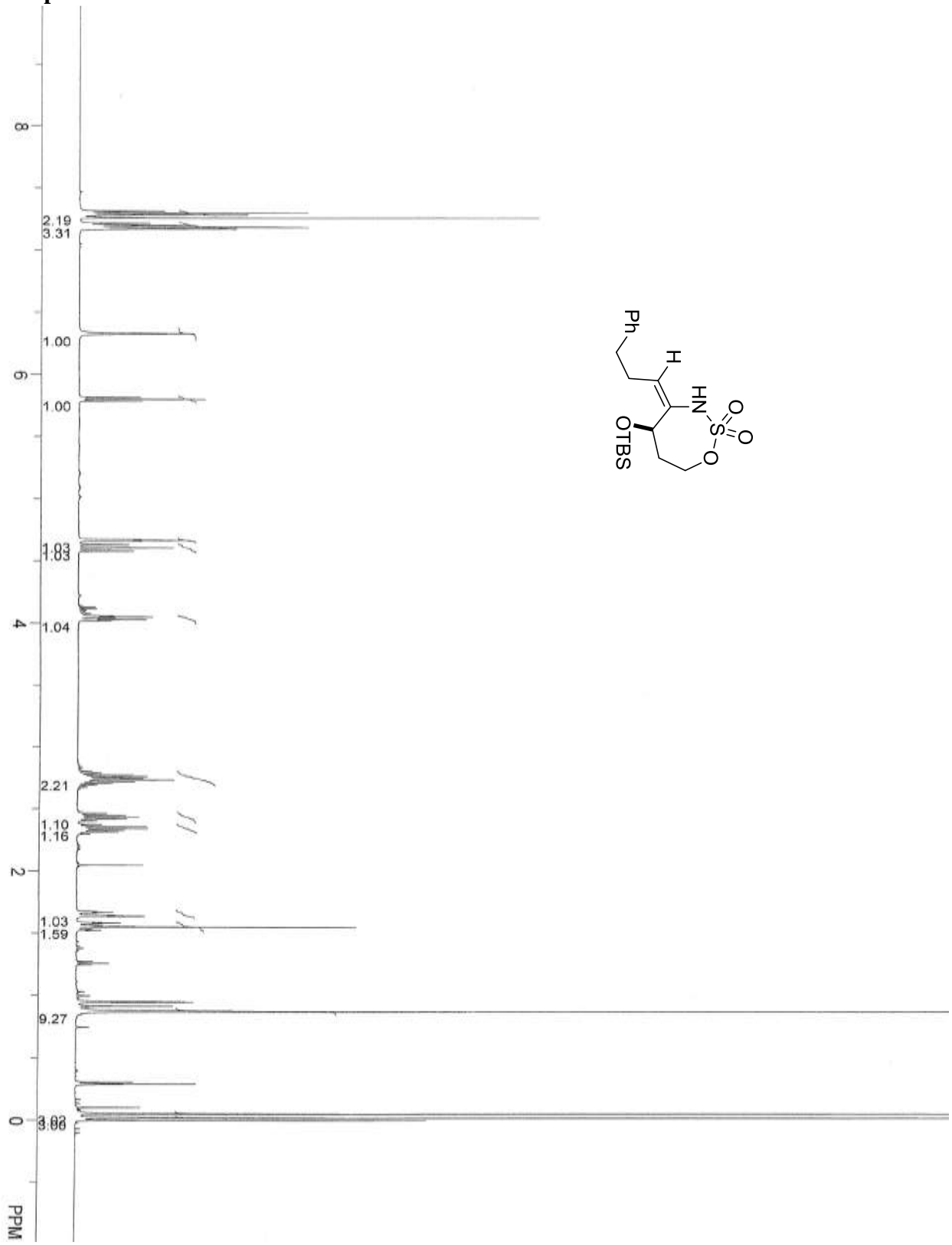

200
150
100
50
0
PPM
H
HN
O
O
S
O
H11C5
OTBS

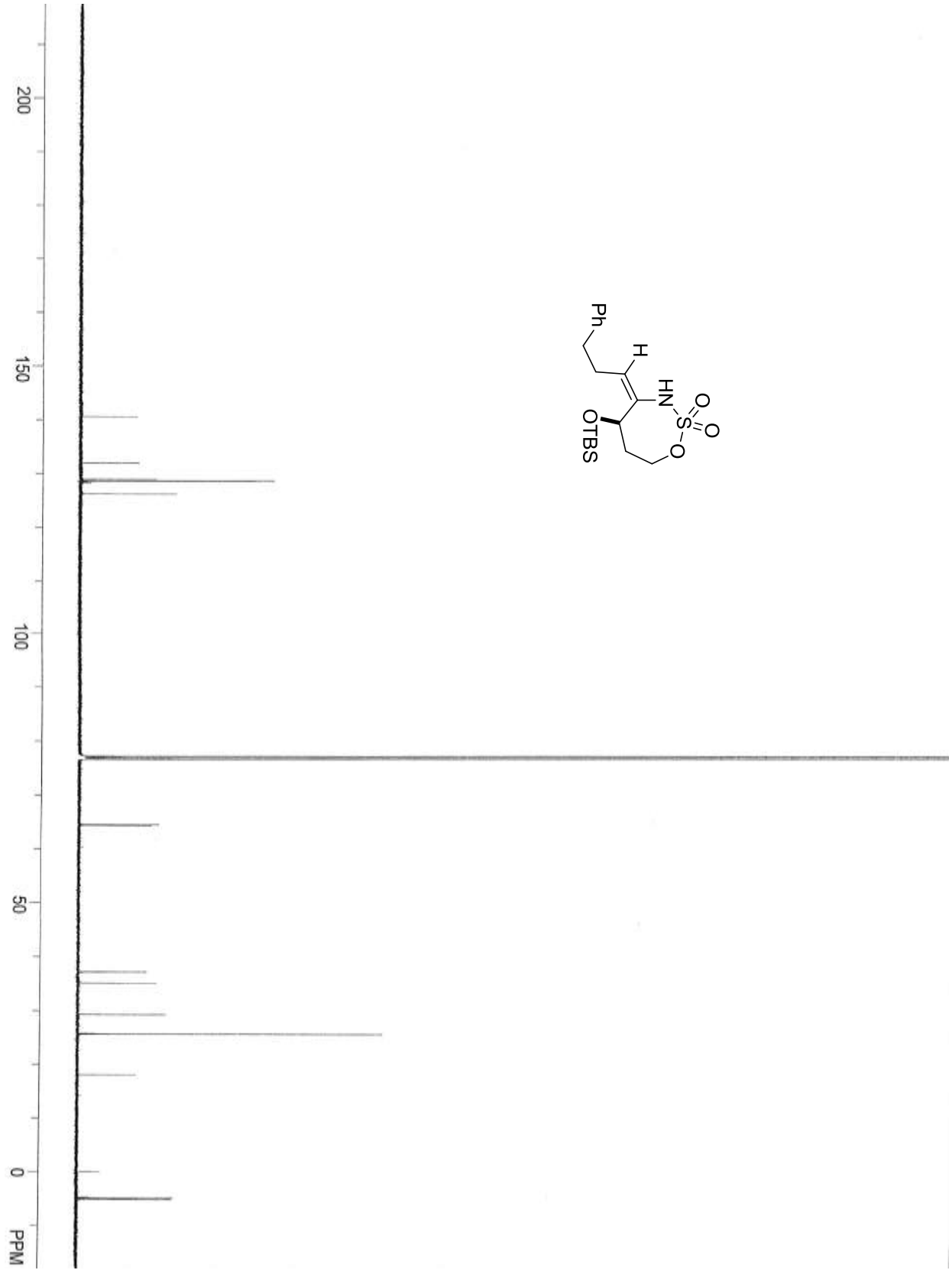
Compound 3.15.



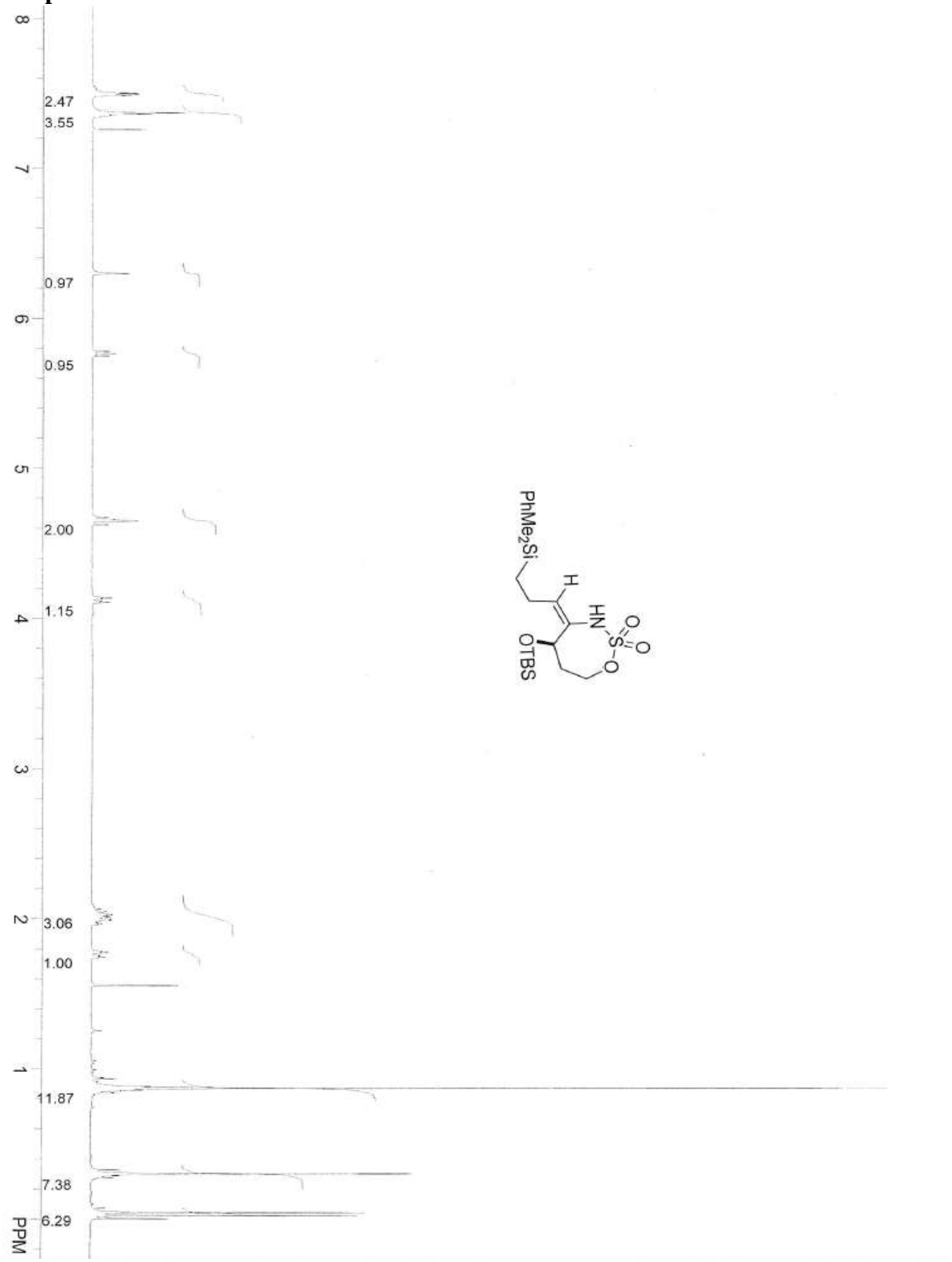

200
150
100
50
0
PPM
H
HN
O
O
S
O
C5H11
OTBS
Me

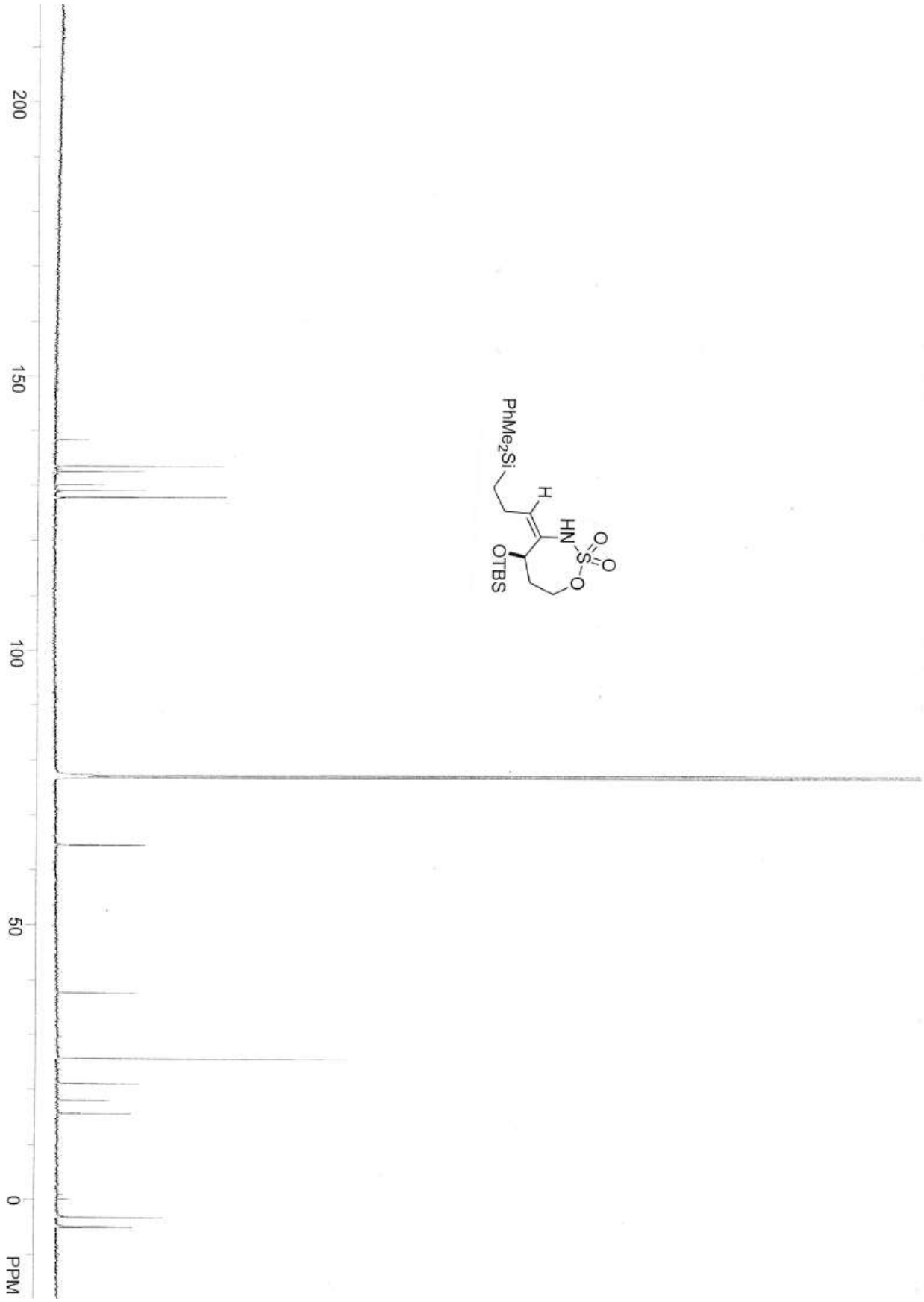
Compound 3.16.



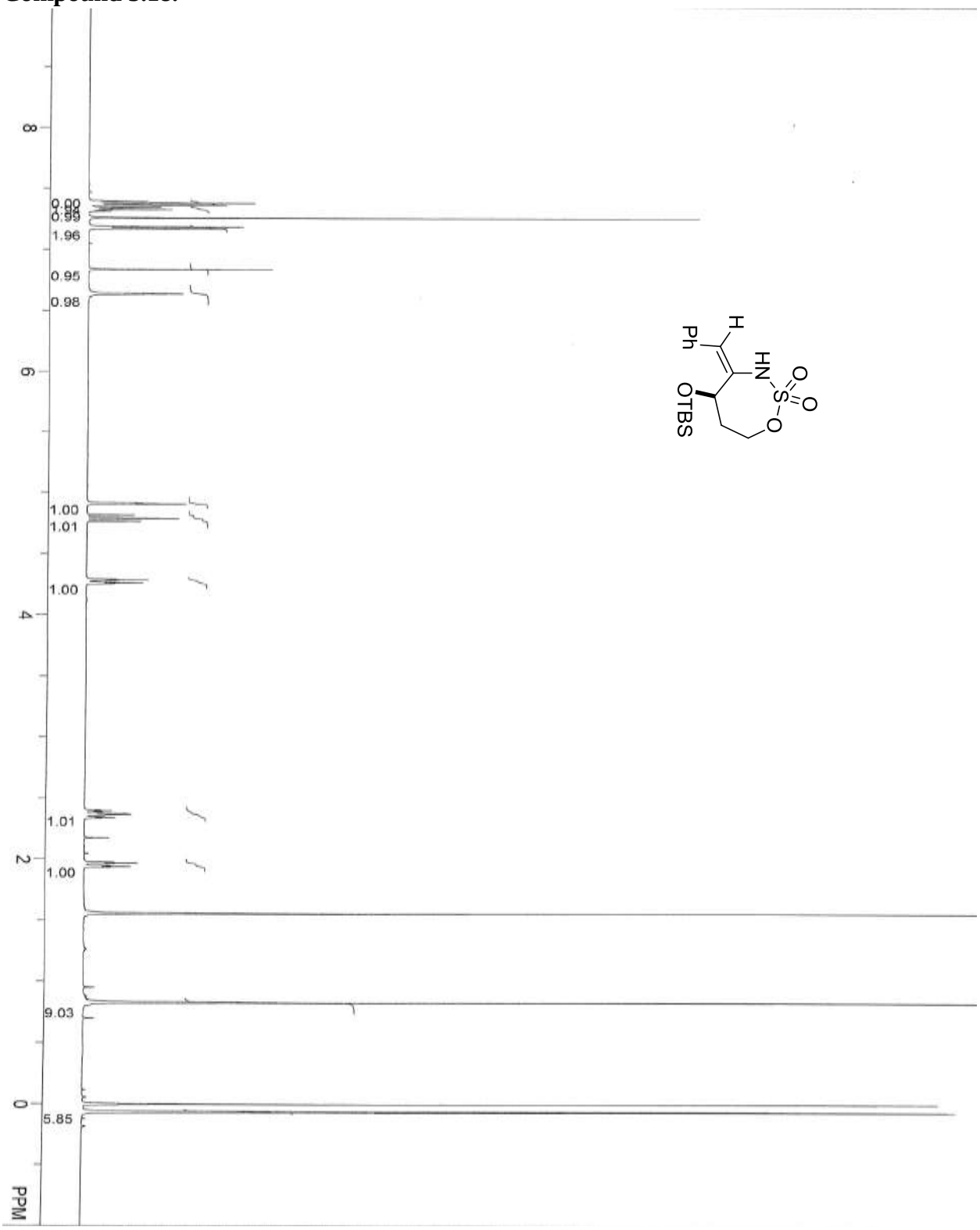

Ph
H
HN
S
O
O
O
OTBS
200
150
100
50
0
PPM

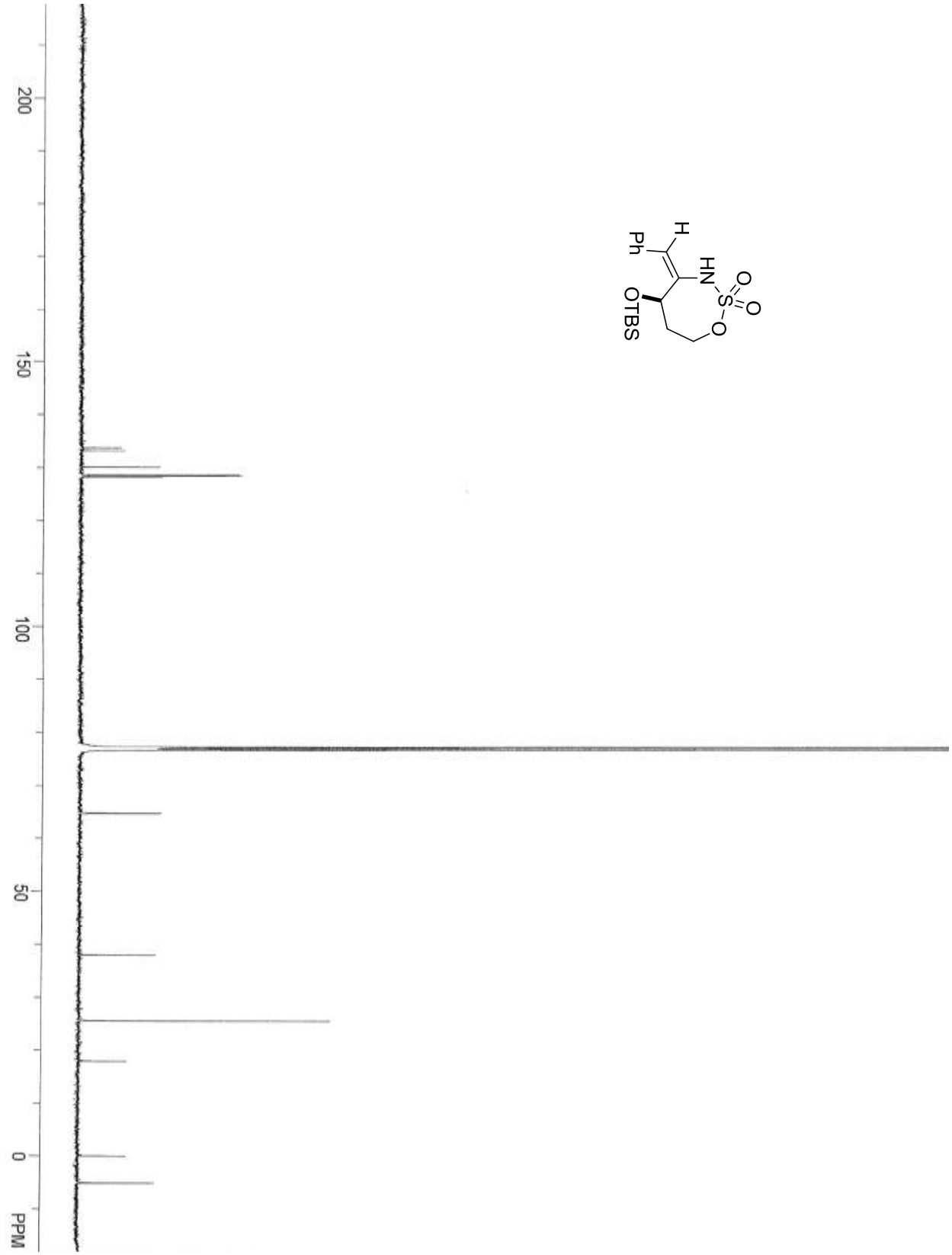
Compound 3.17.



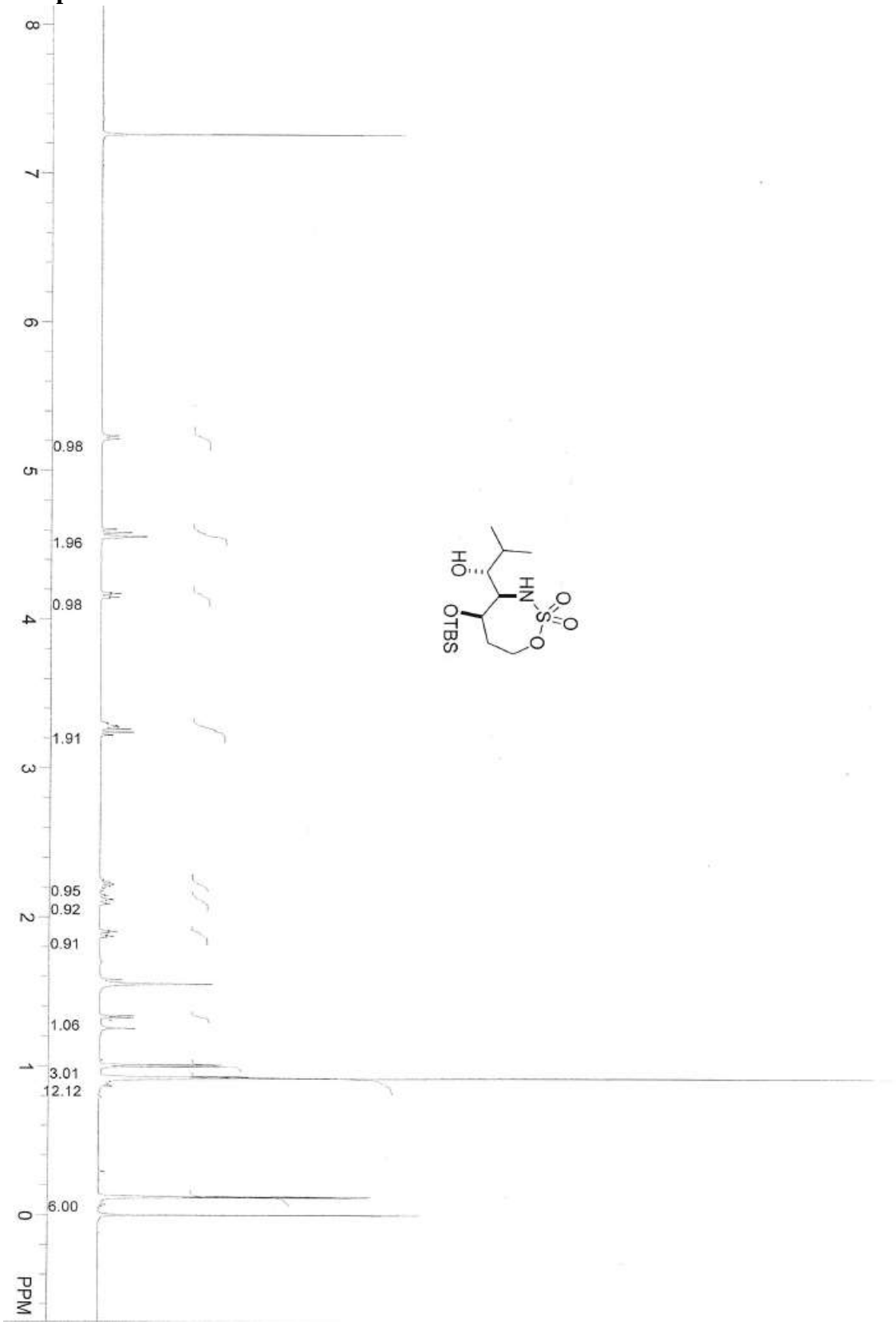

PhMe2Si
H
HN
S
O
O
O
OTBS
200
150
100
50
0
PPM

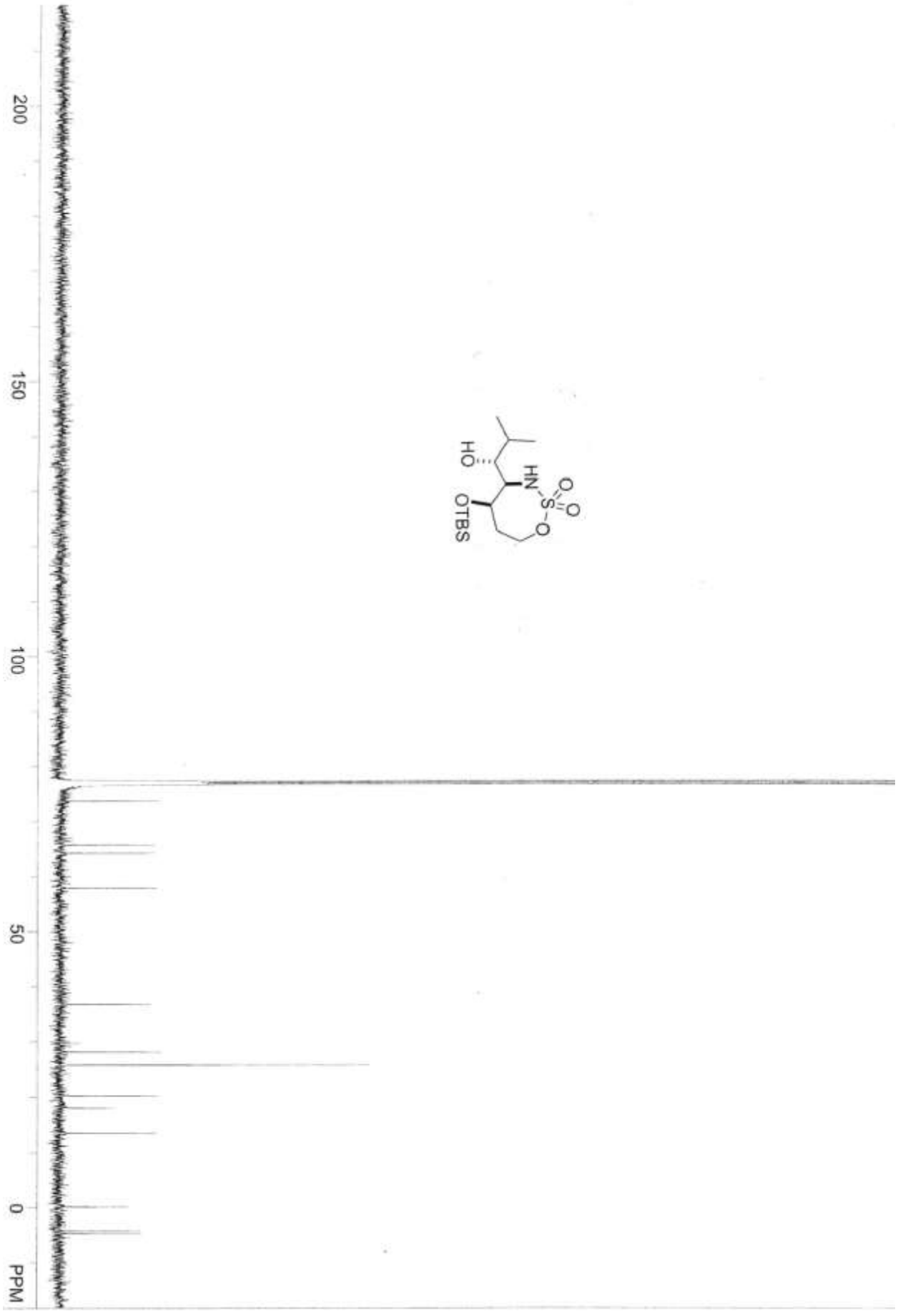
Compound 3.18.



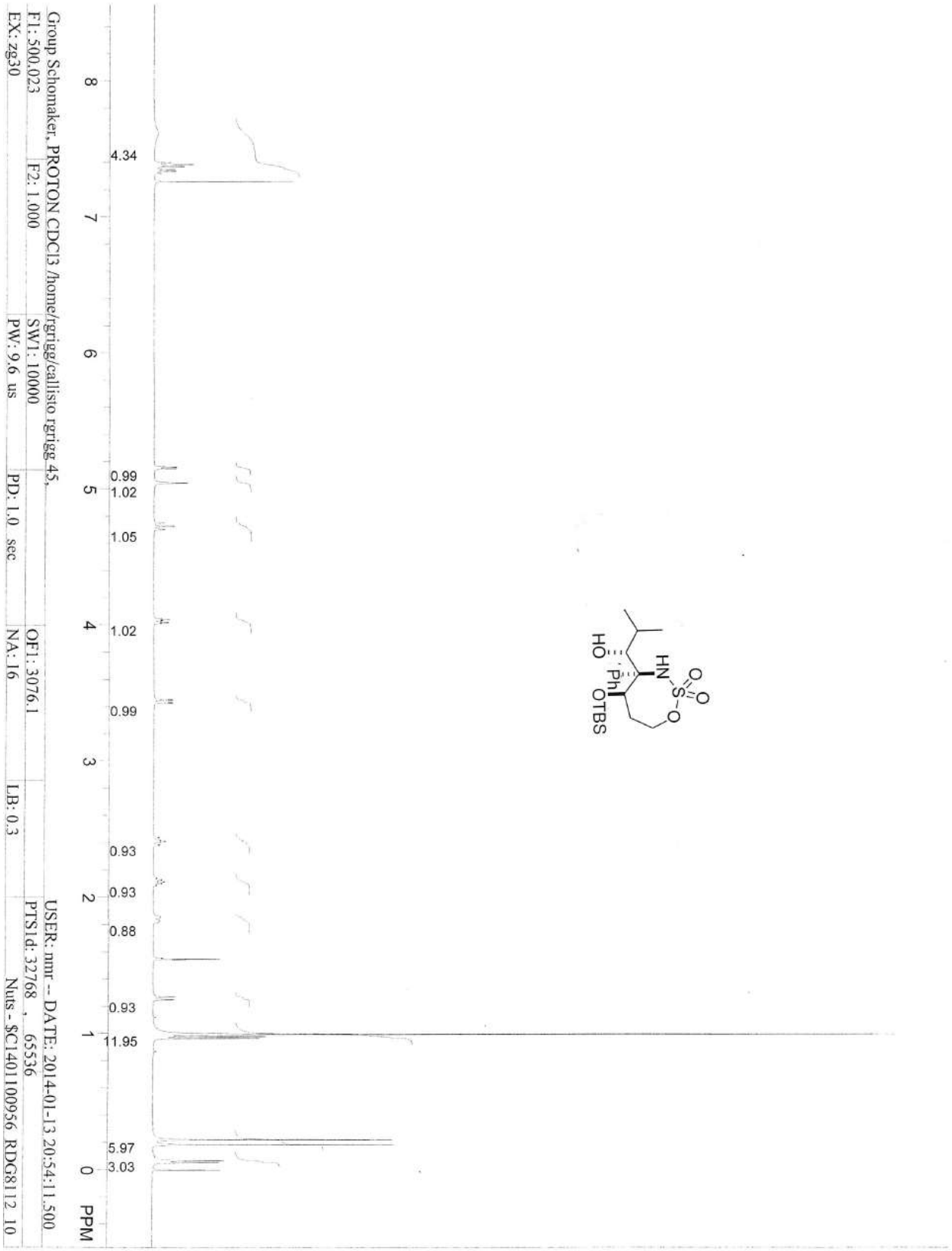

200
150
100
50
0
PPM
H
Ph
HN
S
O
O
O
OTBS

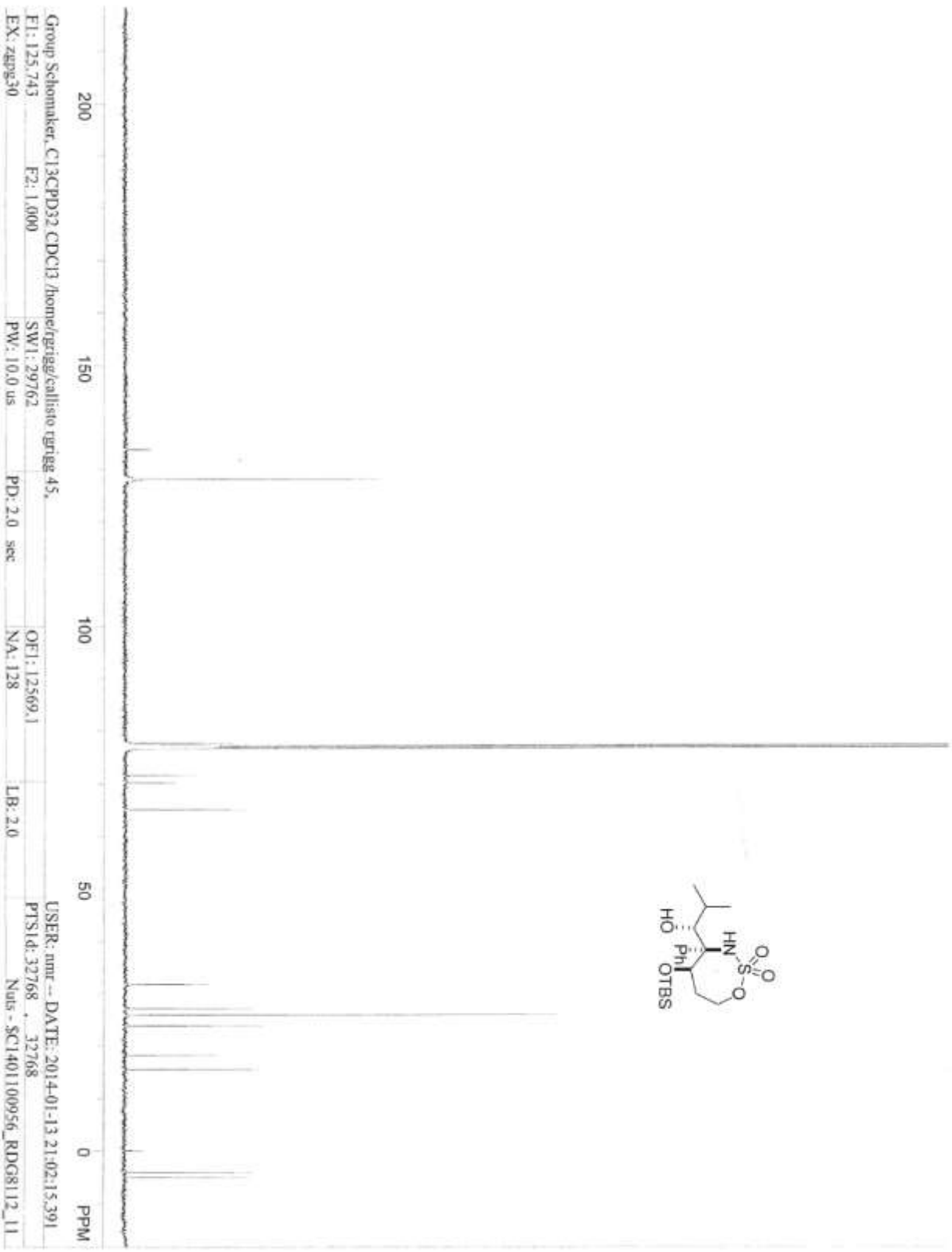
Compound 3.25.



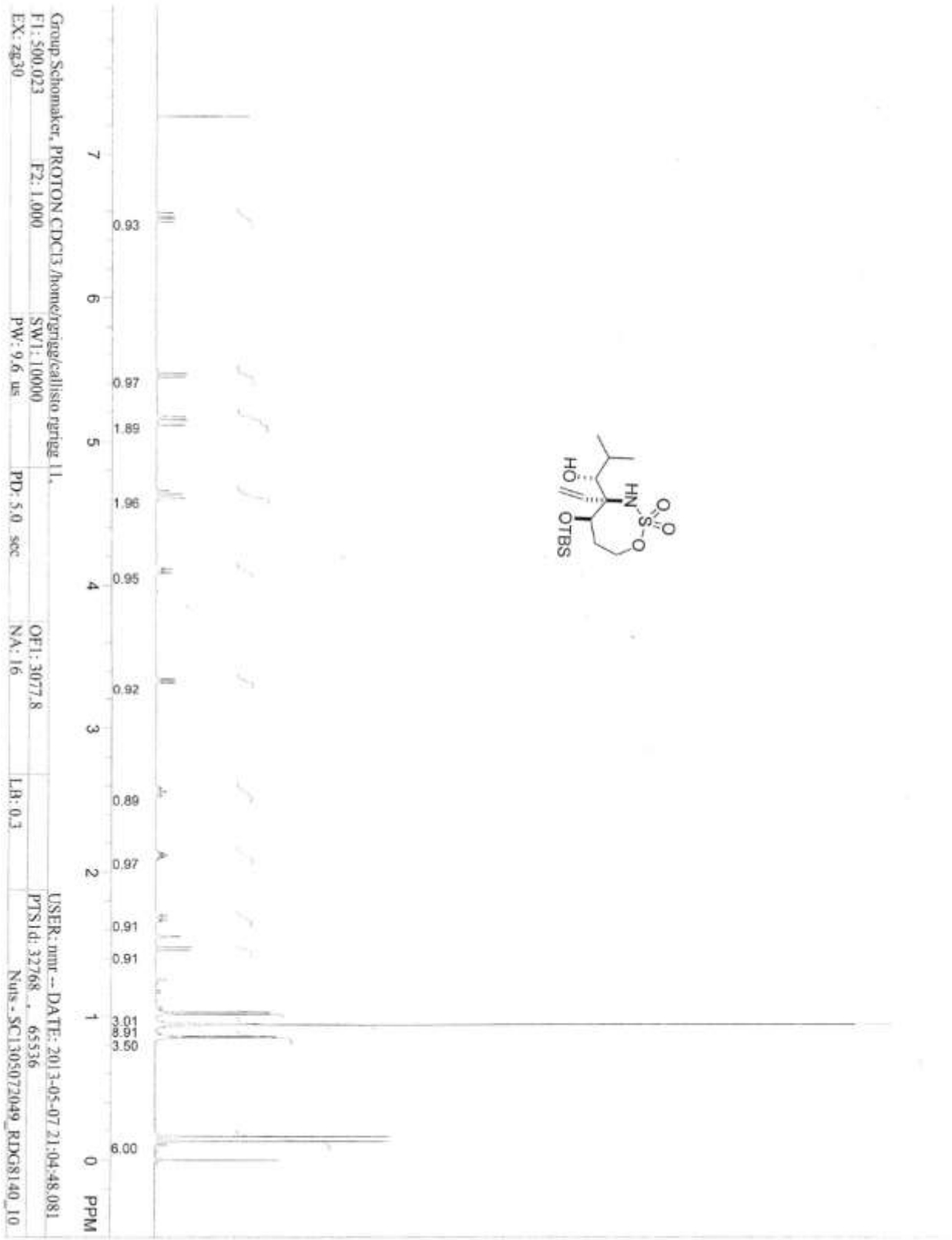

200
150
100
50
0
PPM
HO
HN
O
O
S
O
OTBS

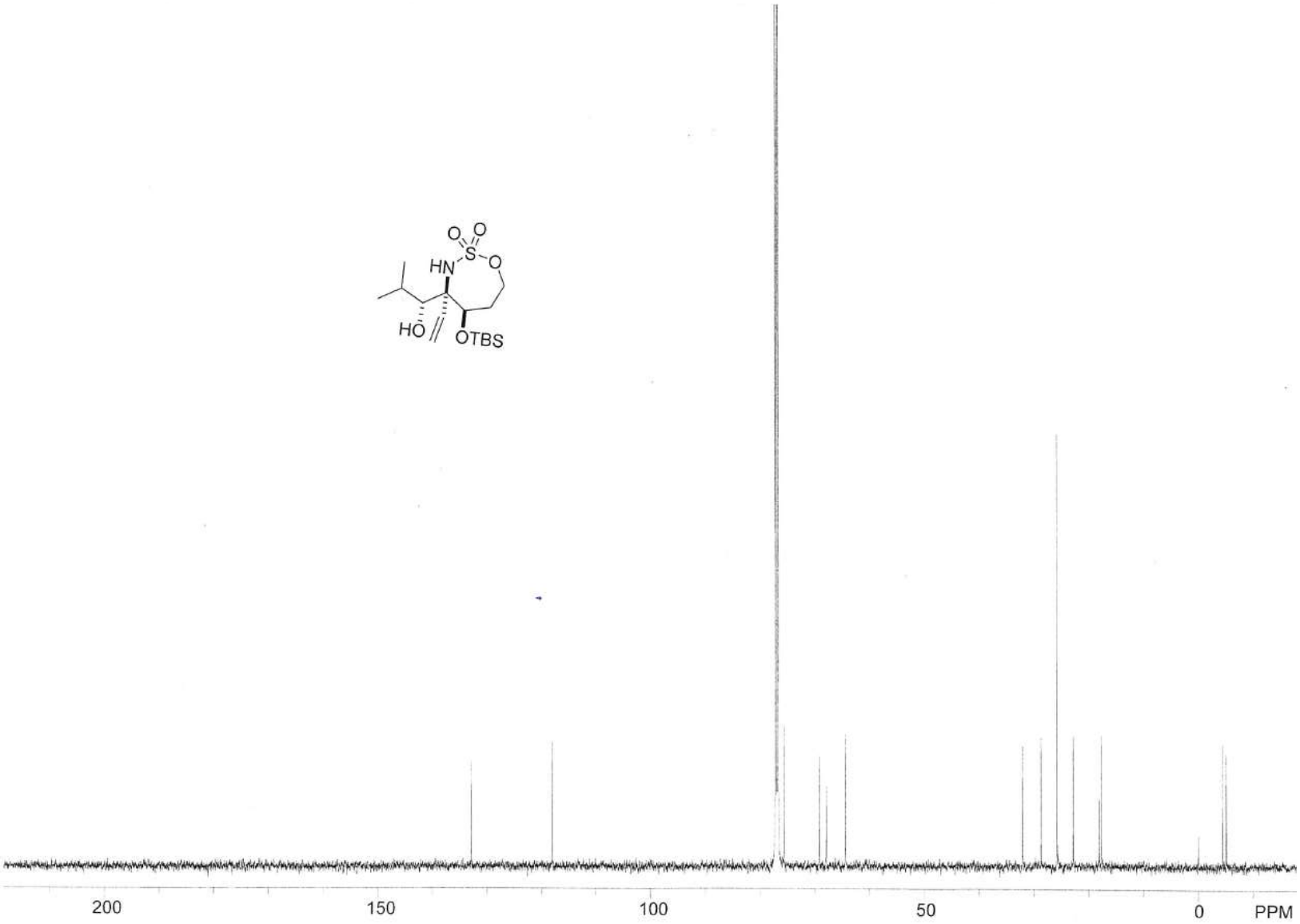
Compound 3.26.




HO
Ph
OTBS
HN
S
O
O
O
200
150
100
50
0
PPM
Group Schomaker, C13CPD32 CDCl3 /home/rgrigg/calisto rgrigg 45,
F1: 125.743
F2: 1.000
EX: zgpg30
SW1: 29762
PW: 10.0 us
PD: 2.0 sec
OF1: 12569.1
NA: 128
LB: 2.0
USER: nmr -- DATE: 2014-01-13 21:02:15.391
PTS1d: 32768
32768
Nuts - SC140110956_RDG8112_11

Compound 3.27.

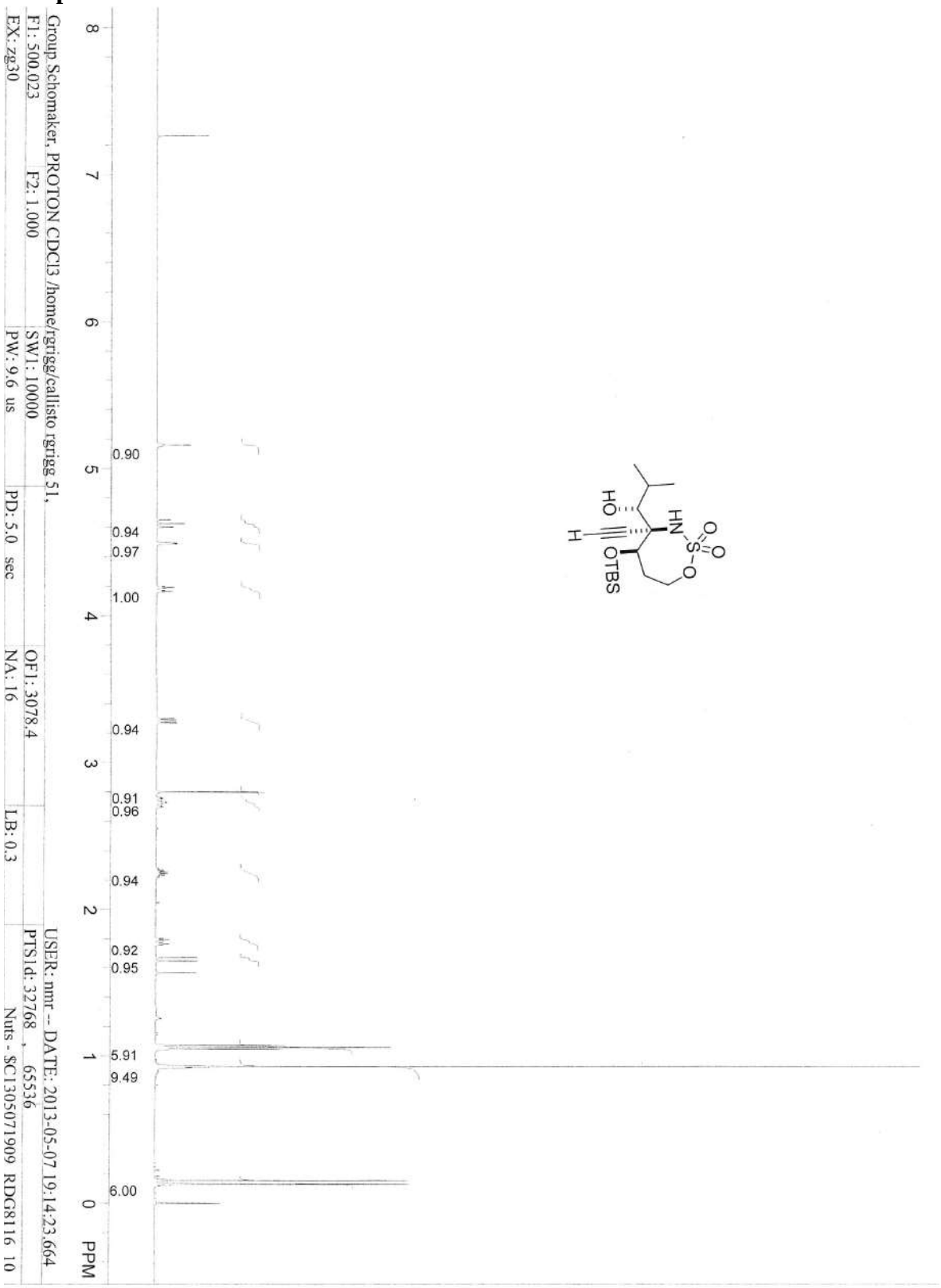


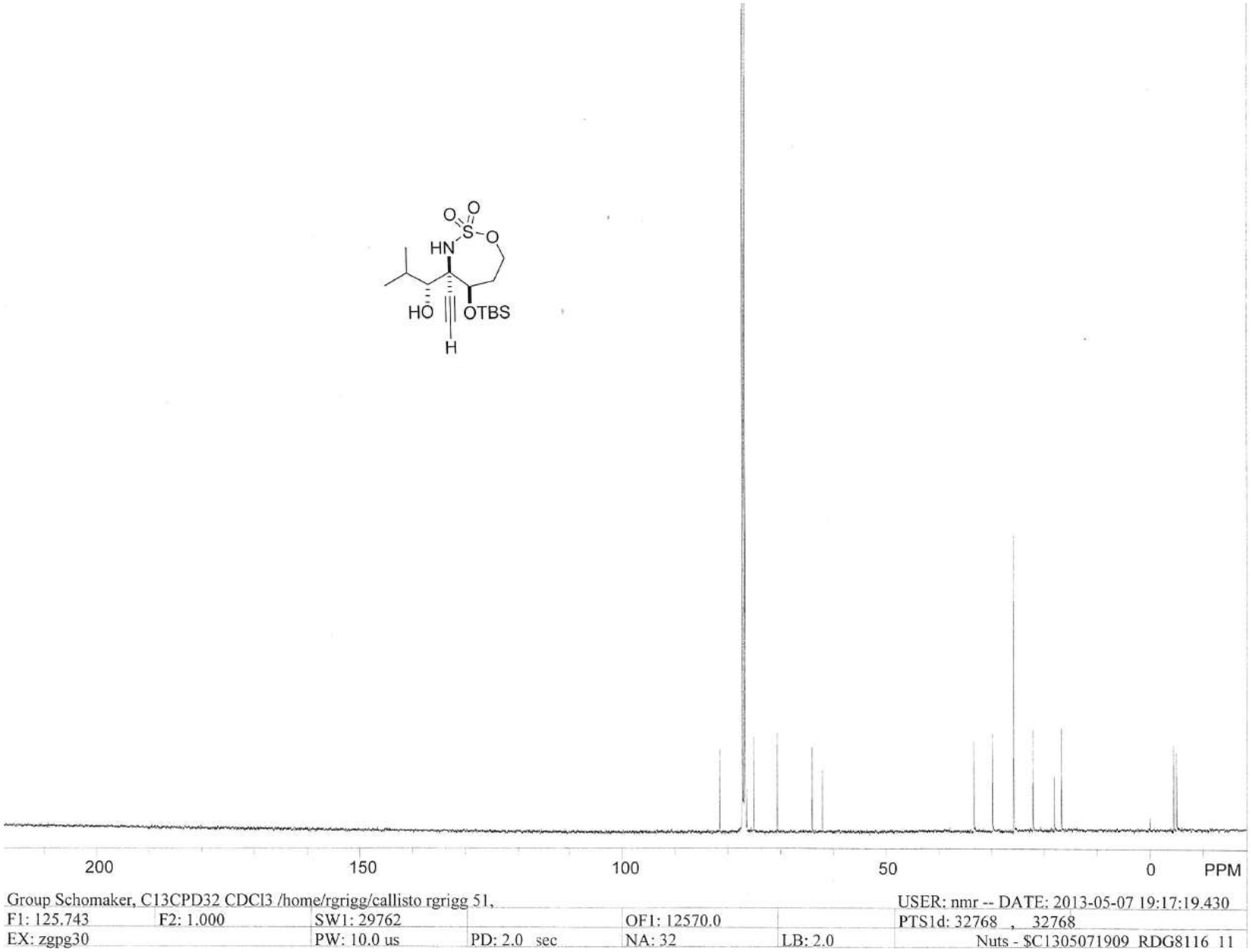


Group Schomaker, C13CPD32 CDCl3 /home/rgrigg/callisto rgrigg 11, USER: nmr -- DATE: 2013-05-07 21:07:43.350

F1: 125.743	F2: 1.000	SW1: 29762		OF1: 12570.0		PTS1d: 32768 , 32768
EX: zgpg30		PW: 10.0 us	PD: 2.0 sec	NA: 32	LB: 2.0	Nuts - $C1305072049_RDG8140_11

Compound 3.28.

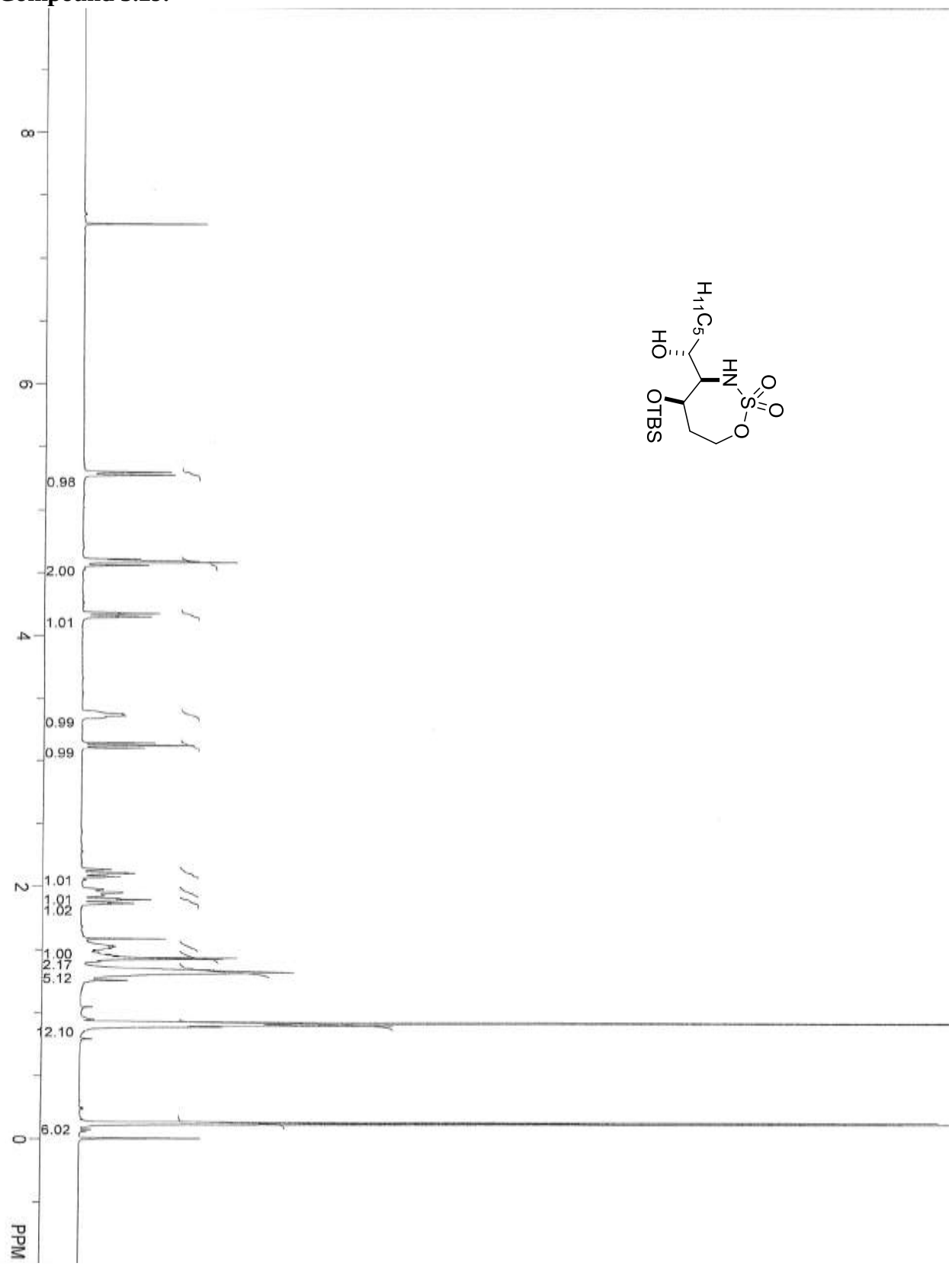


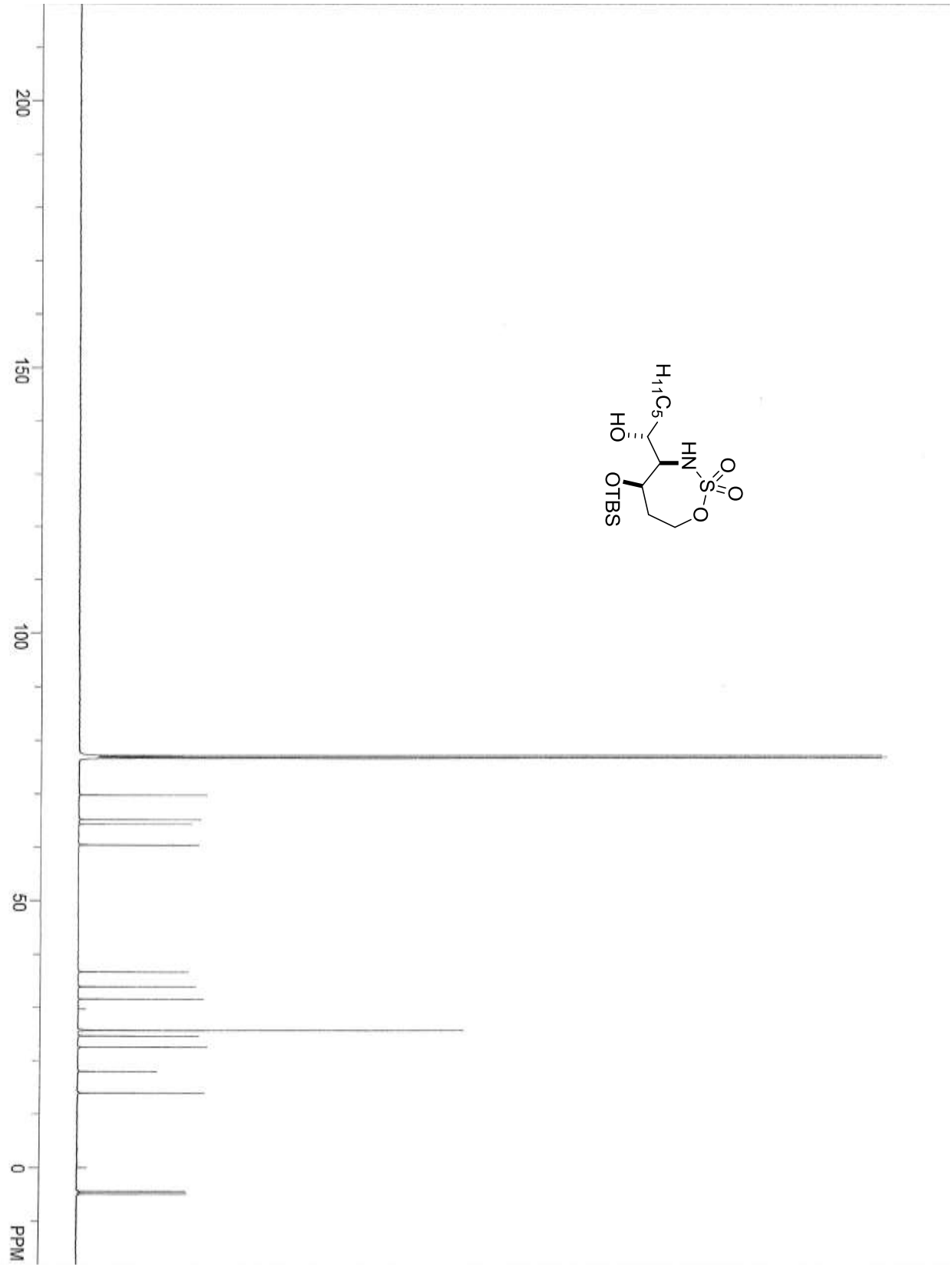


Group Schomaker, C13CPD32 CDCl3 /home/rgrigg/callisto rgrigg 51, USER: nmr -- DATE: 2013-05-07 19:17:19.430

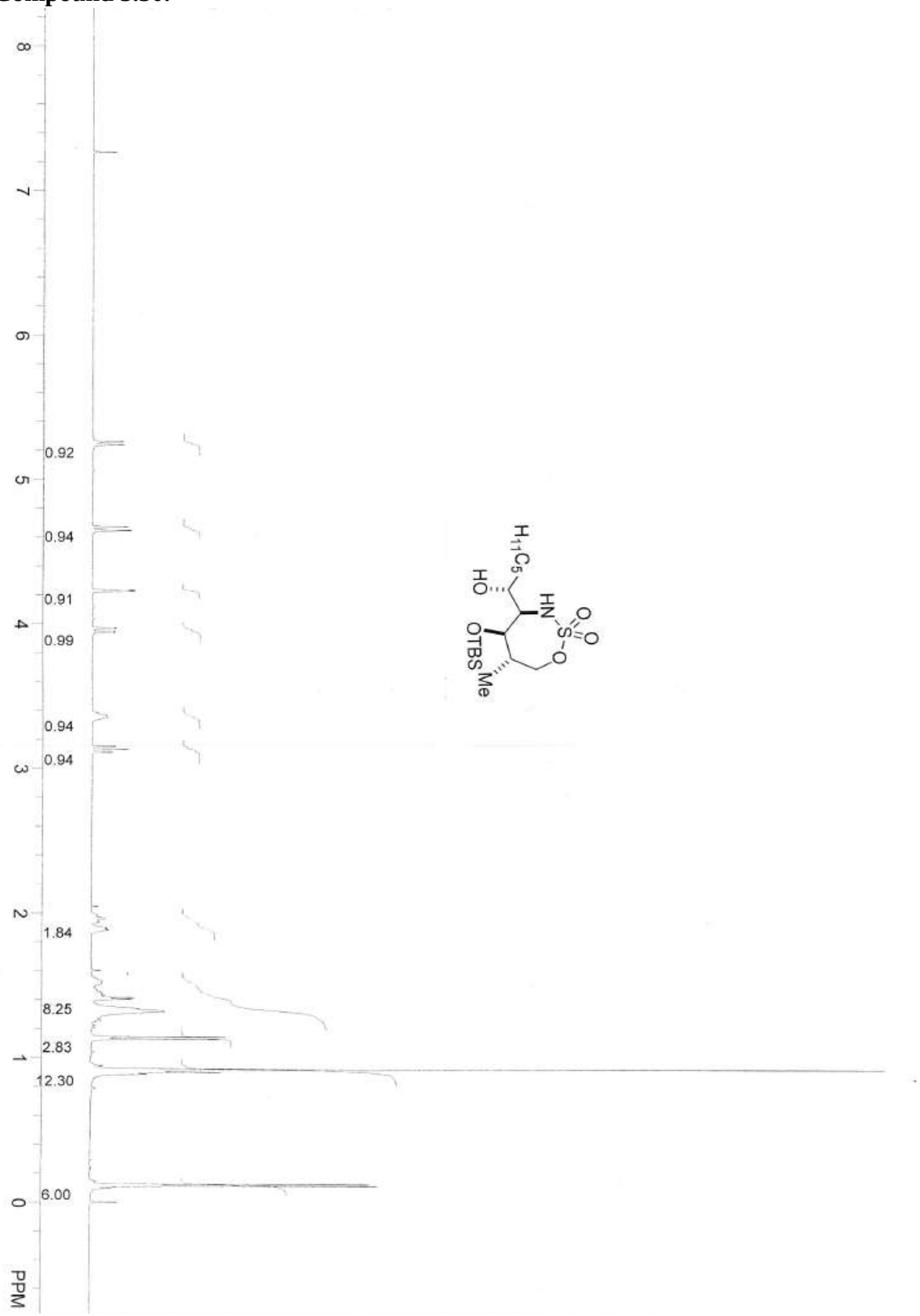
F1: 125.743	F2: 1.000	SW1: 29762		OF1: 12570.0		PTS1d: 32768 , 32768
EX: zgpg30		PW: 10.0 us	PD: 2.0 sec	NA: 32	LB: 2.0	Nuts - $C1305071909 RDG8116 11

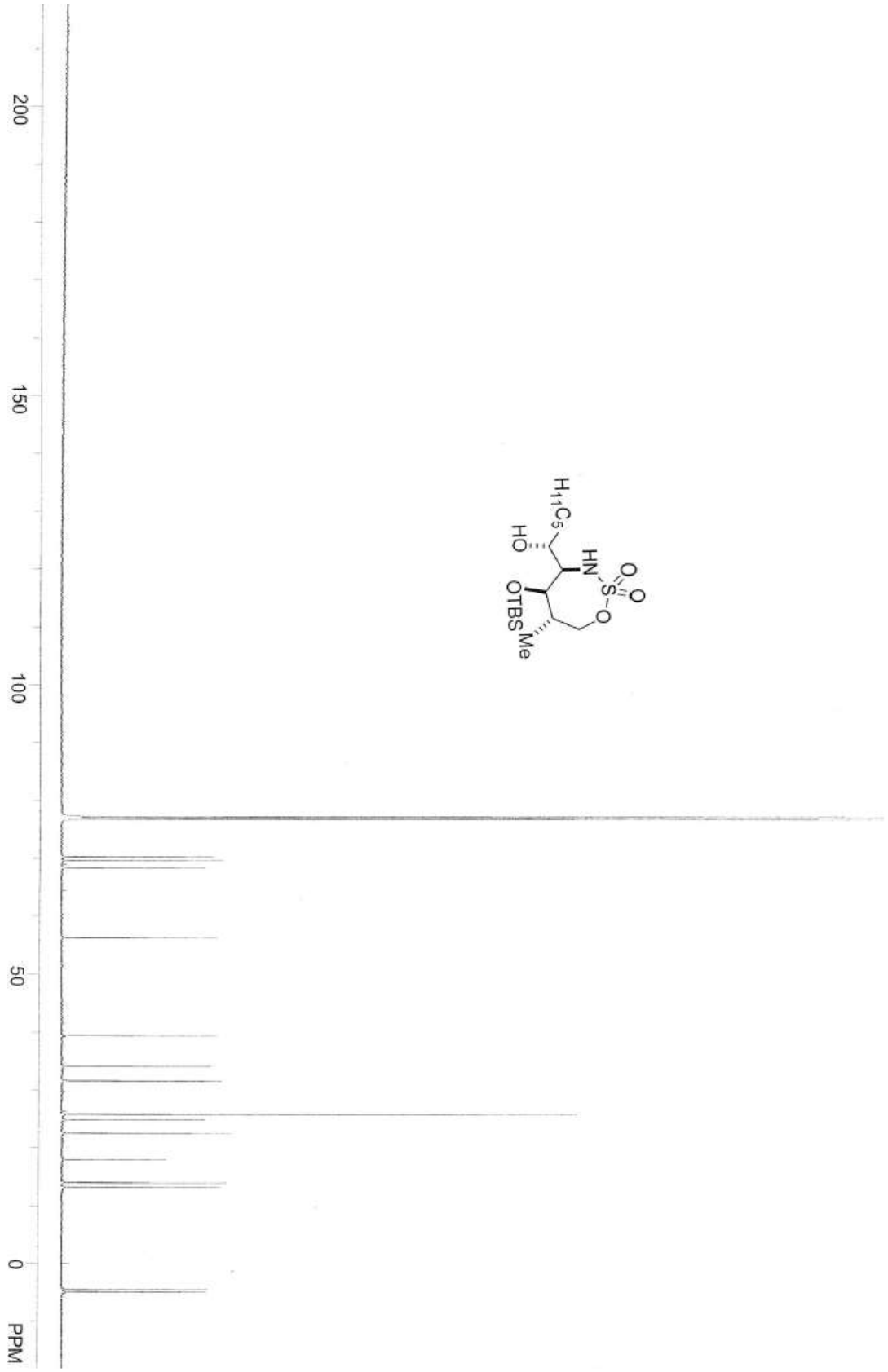
Compound 3.29.



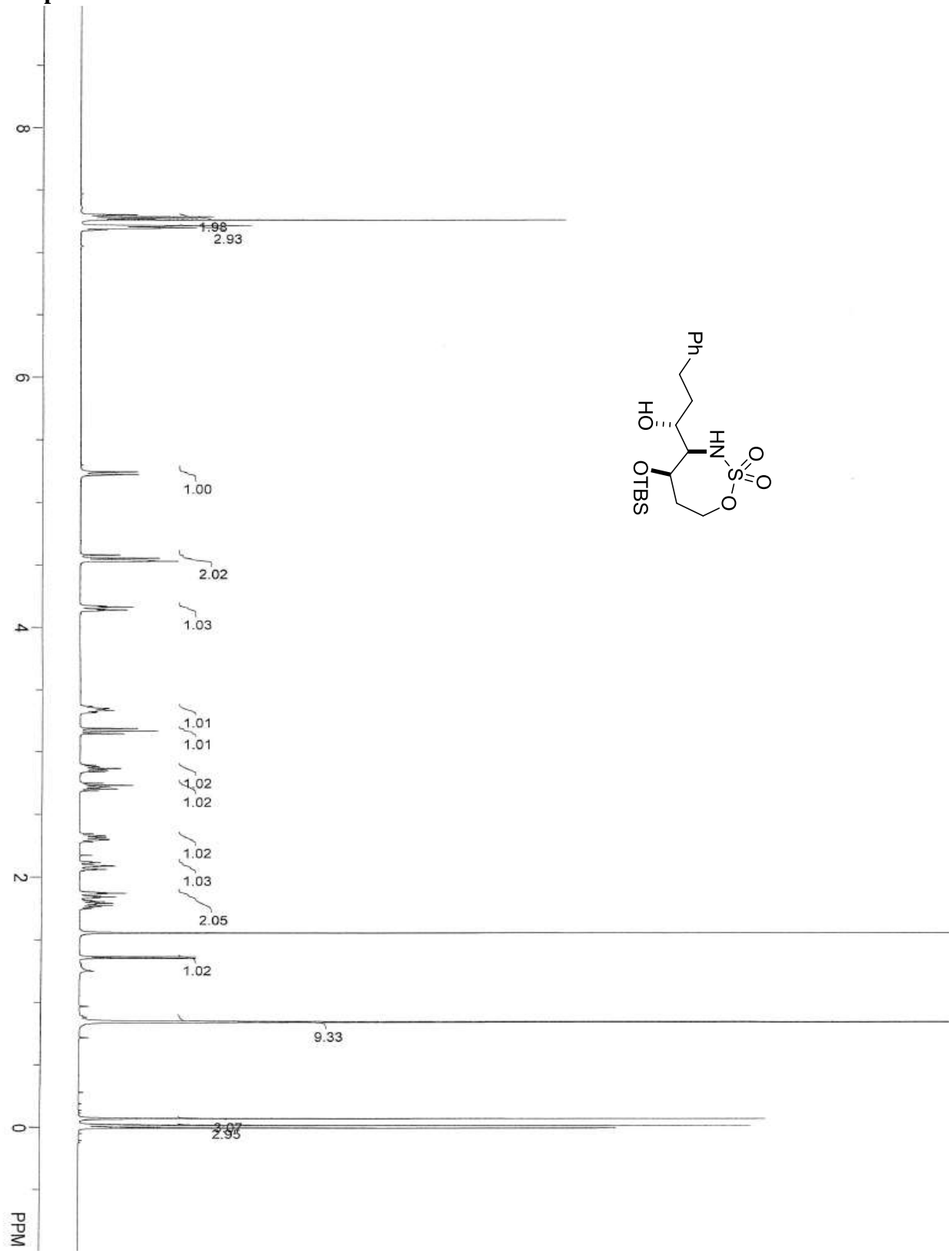

200
150
100
50
0
PPM
H11C5
HO
HN
S
O
O
O
OTBS

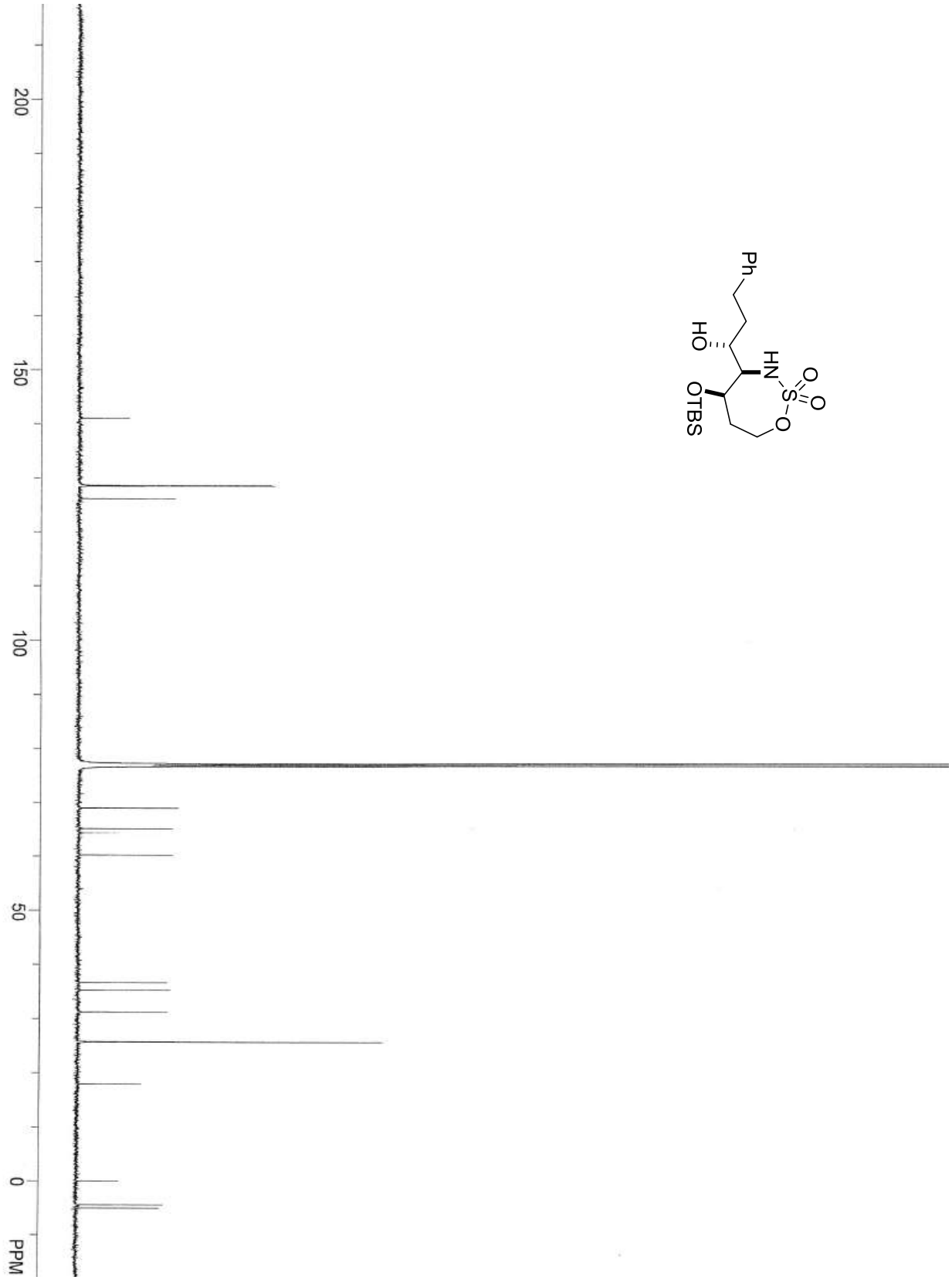
Compound 3.30.



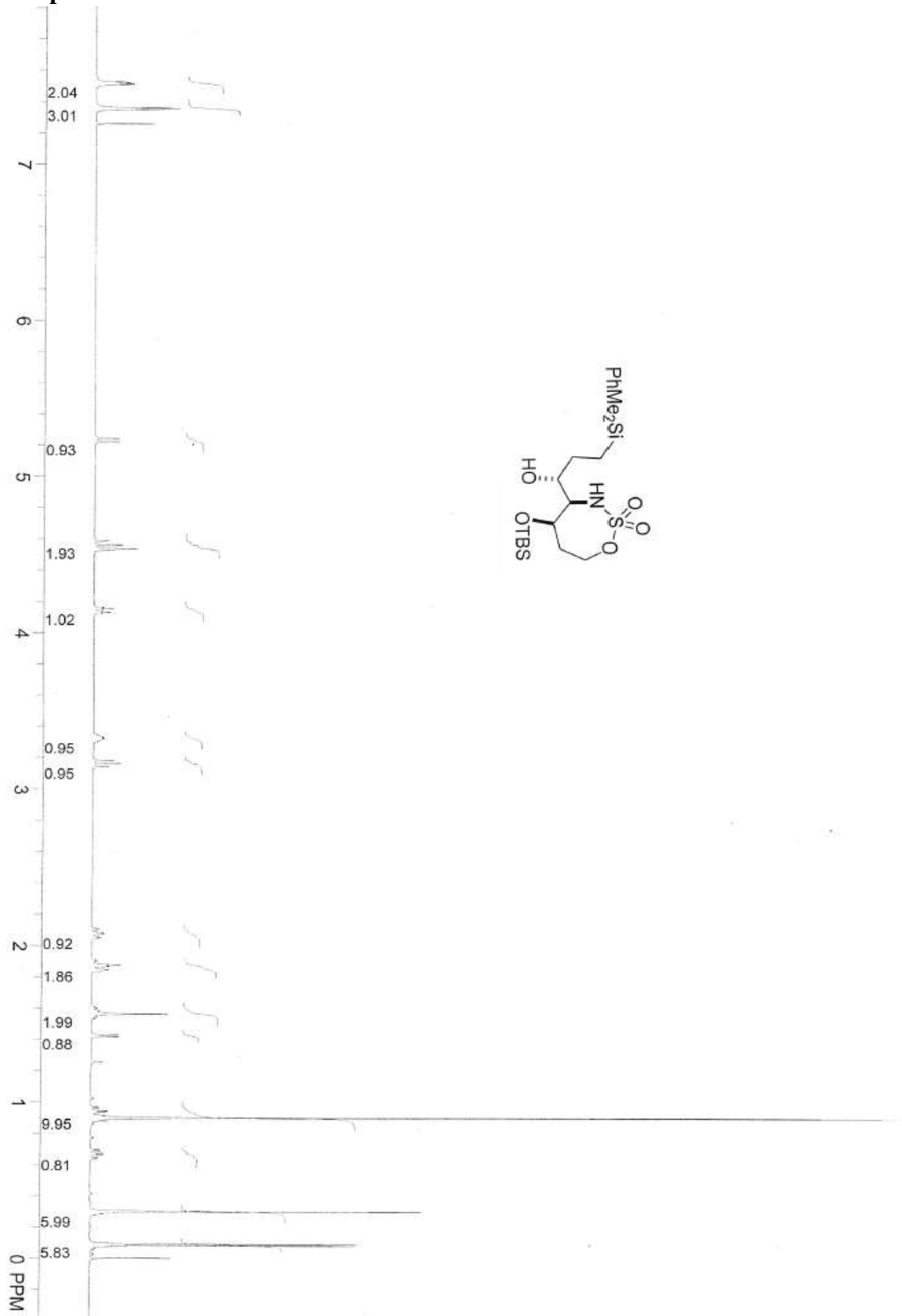

200
150
100
50
0
PPM
H11C5
HO
HN
O
O
S
O
OTBS
Me

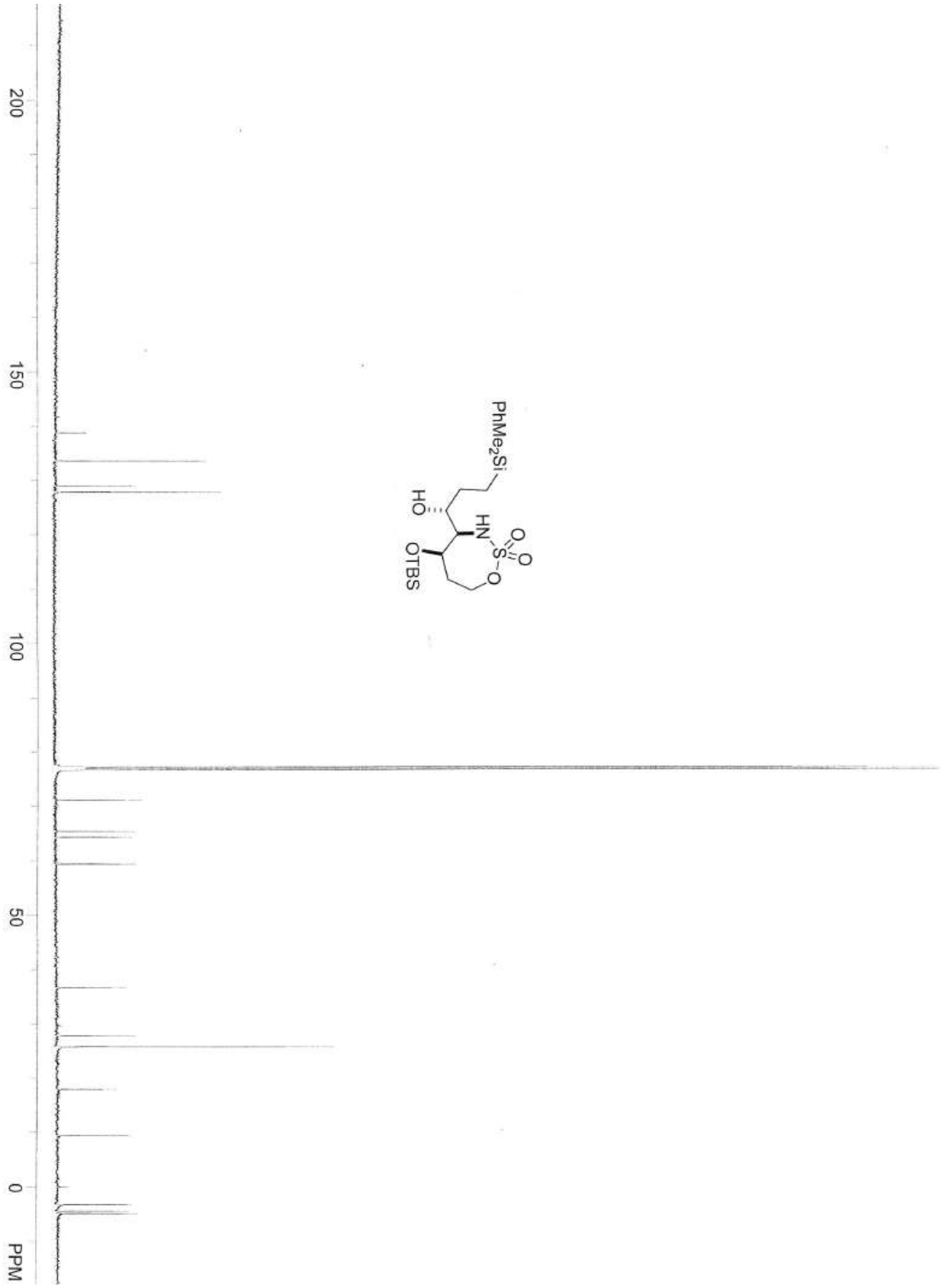
Compound 3.31.



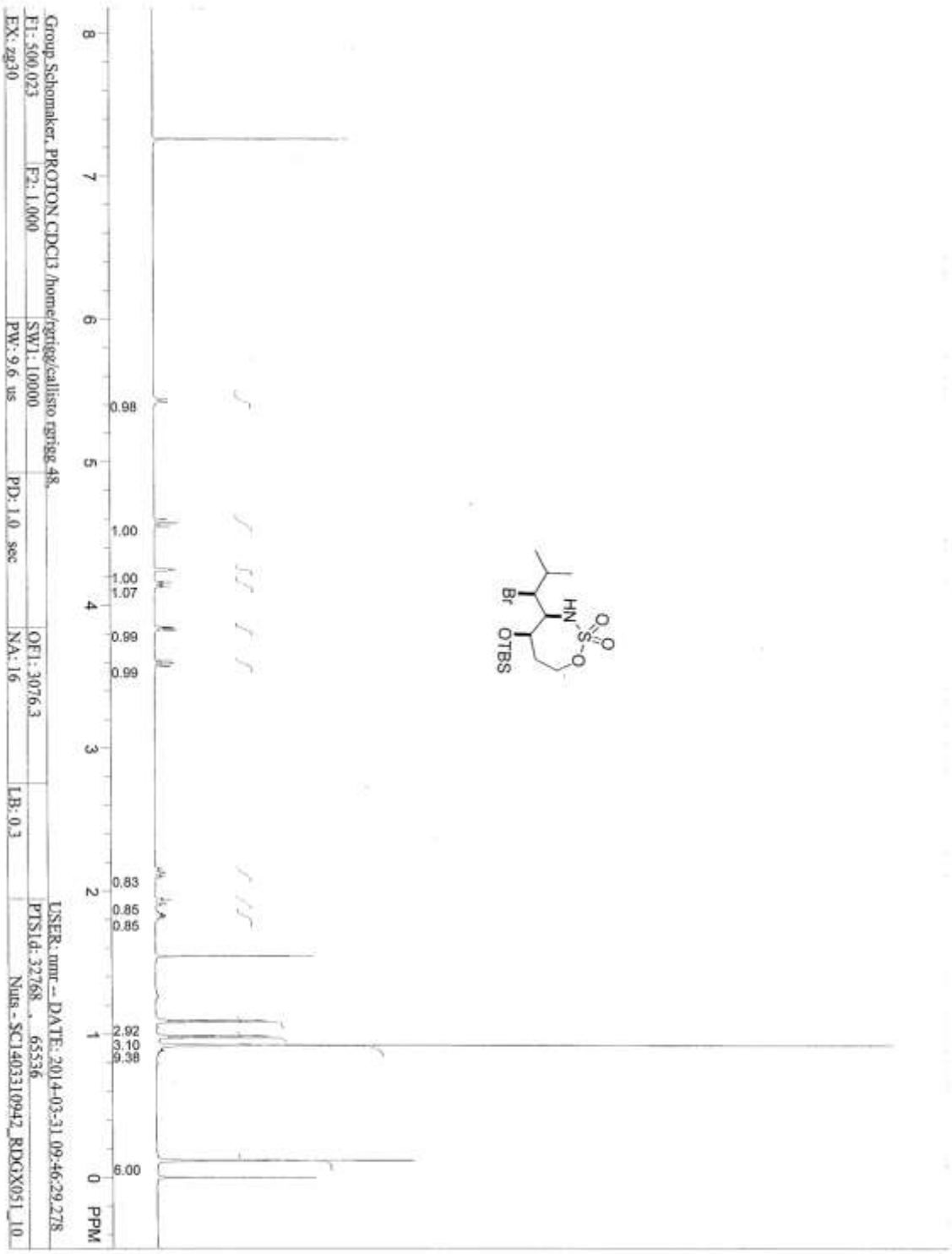

Ph
HO
HN
O
O
S
O
OTBS
200
150
100
50
0
PPM

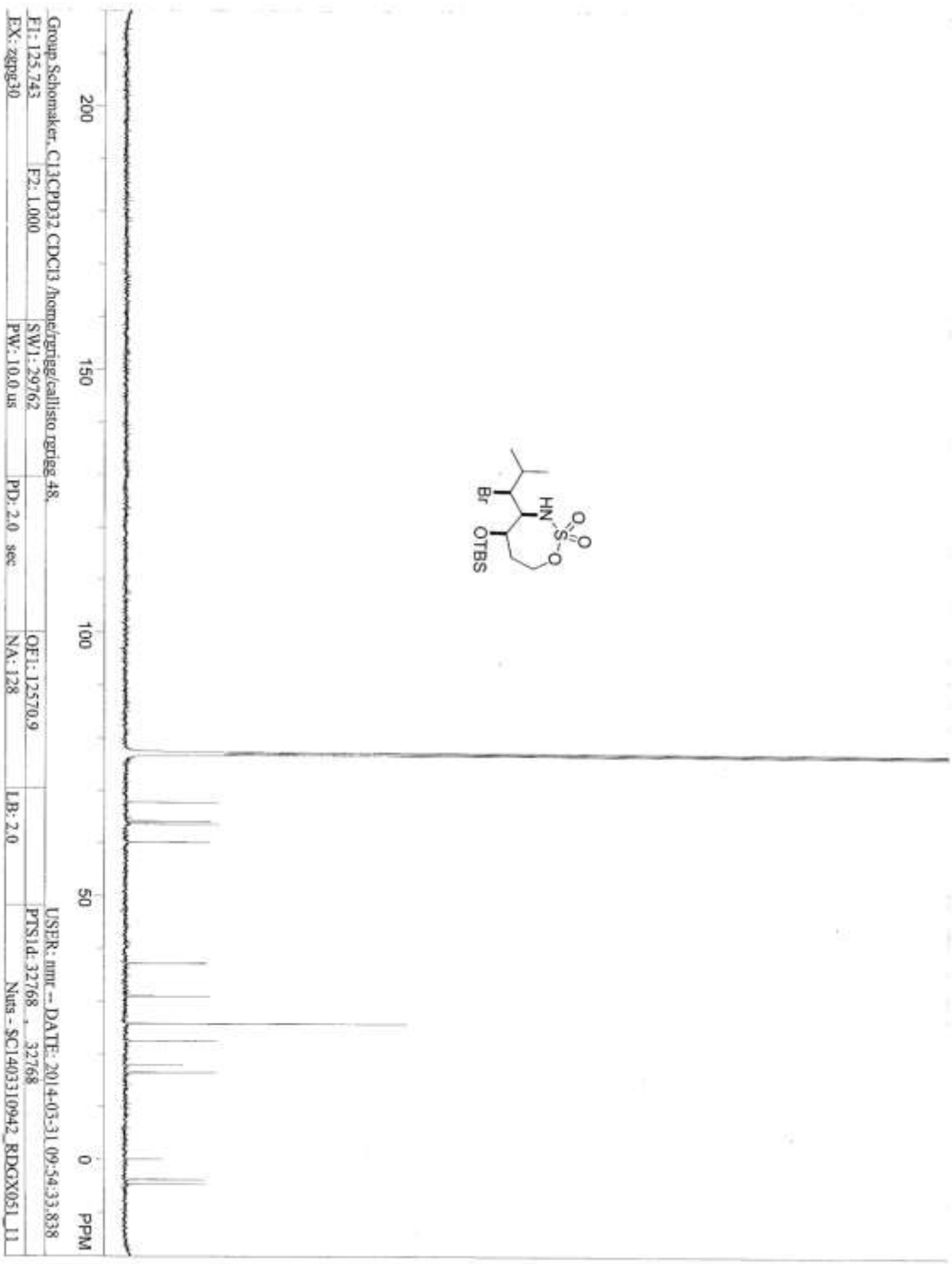
Compound 3.32.



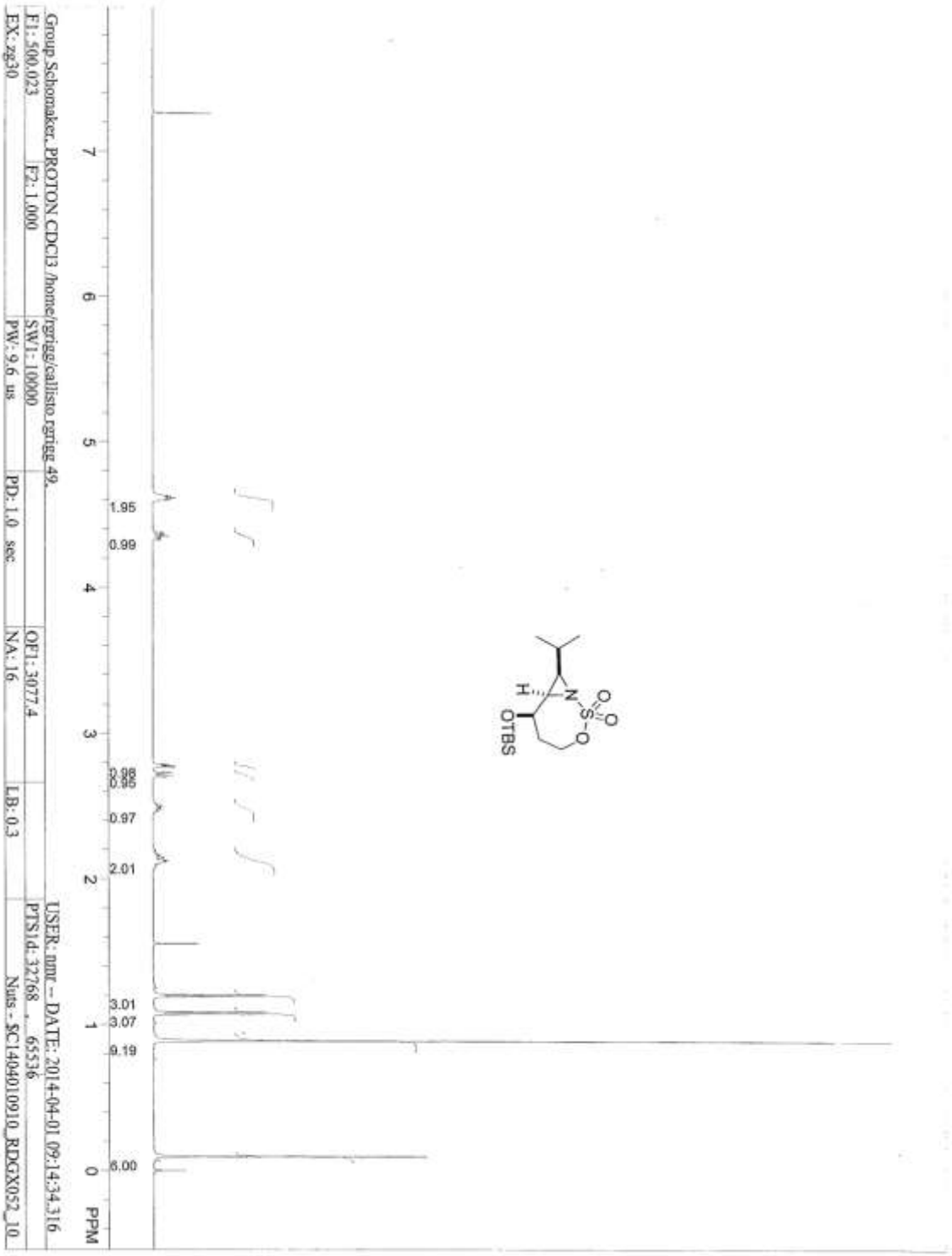

PhMe2Si
HO
HN
OTBS
O
O
S
O
200
150
100
50
0
PPM

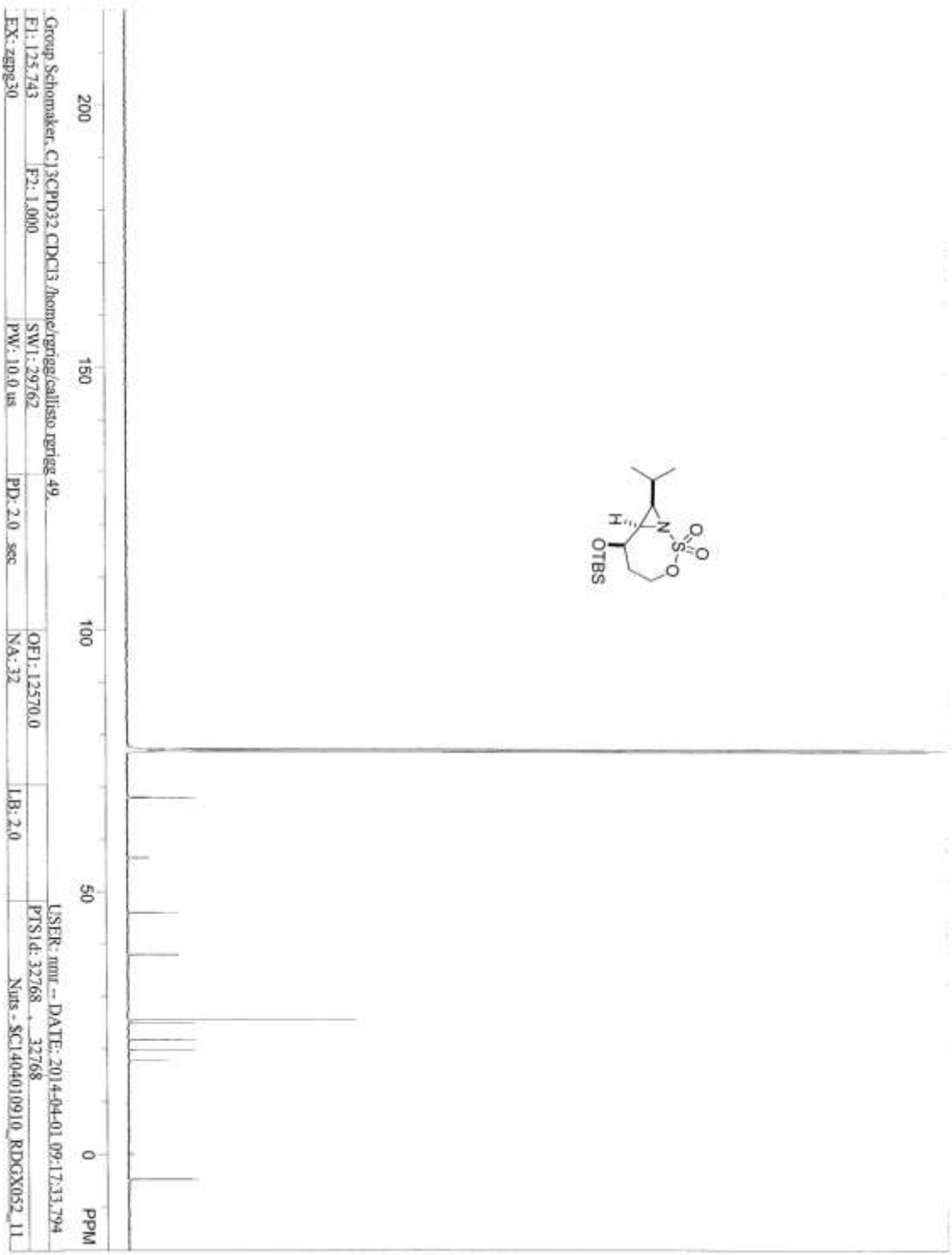
Compound 3.33



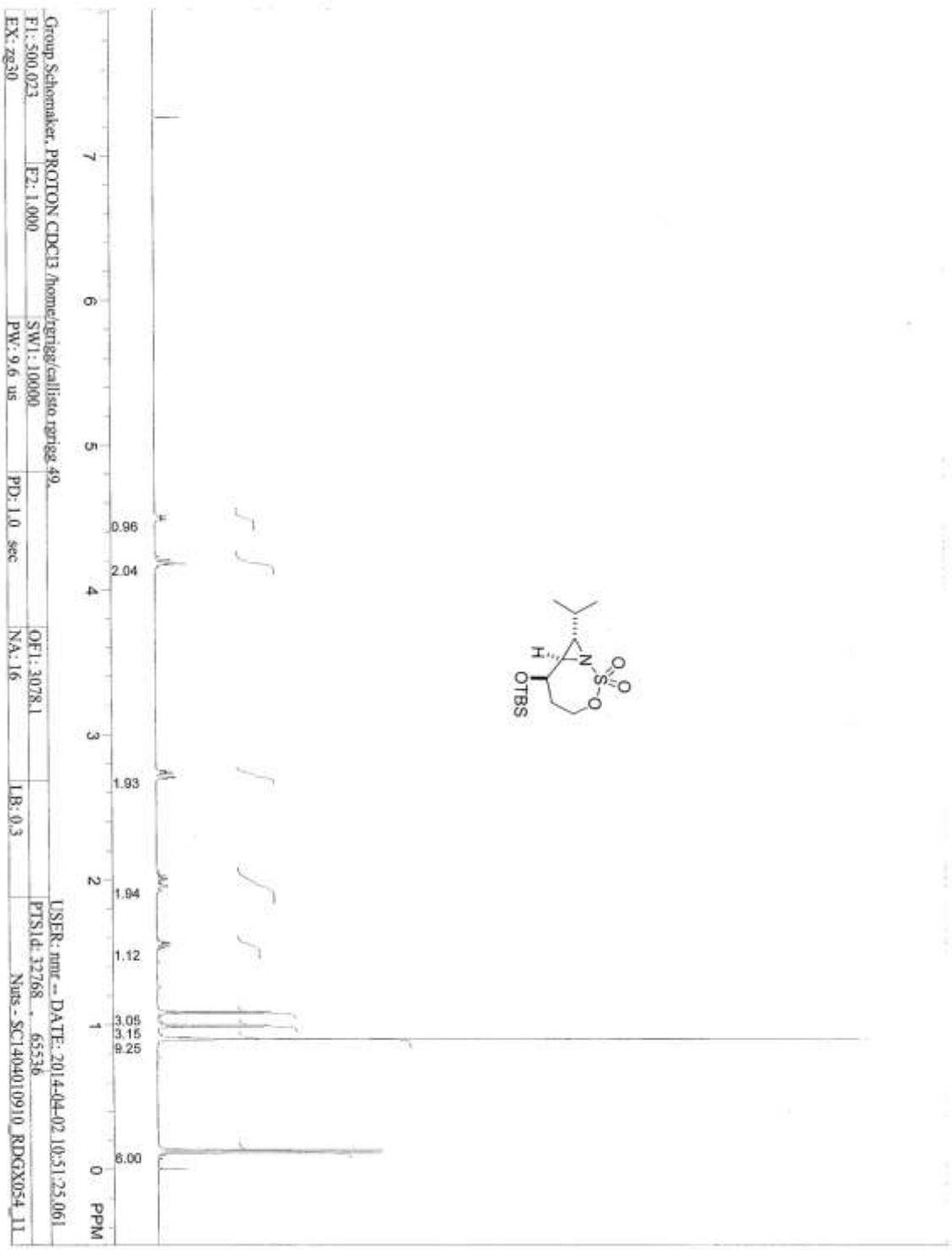

HN
S
O
O
O
Br
OTBS
200
150
100
50
0
PPM
Group Schomaker_C13CPD32 CDCl3 /home/rgrigg/callisto.rgrigg.48.
F1: 125.743
F2: 1.000
EX: zgpg30
SW1: 29762
PW: 10.0 us
PD: 2.0 sec
OF1: 12570.9
NA: 128
LB: 2.0
USER: nmr -- DATE: 2014-03-31 09:54:33.838
PTS1d: 32768 + 32768
Nuts - $C1403310942_RDGX051_11

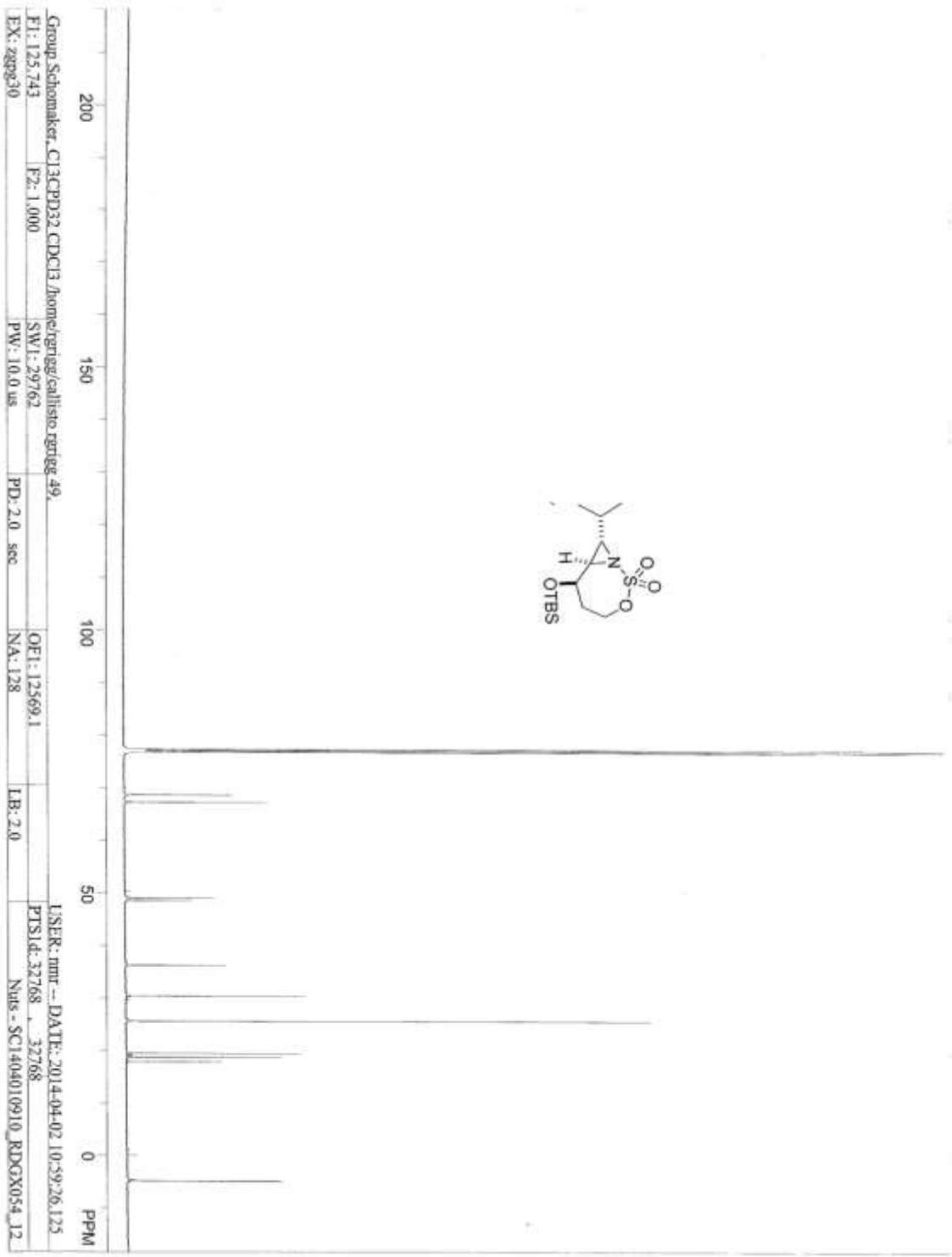
Compound 3.34.



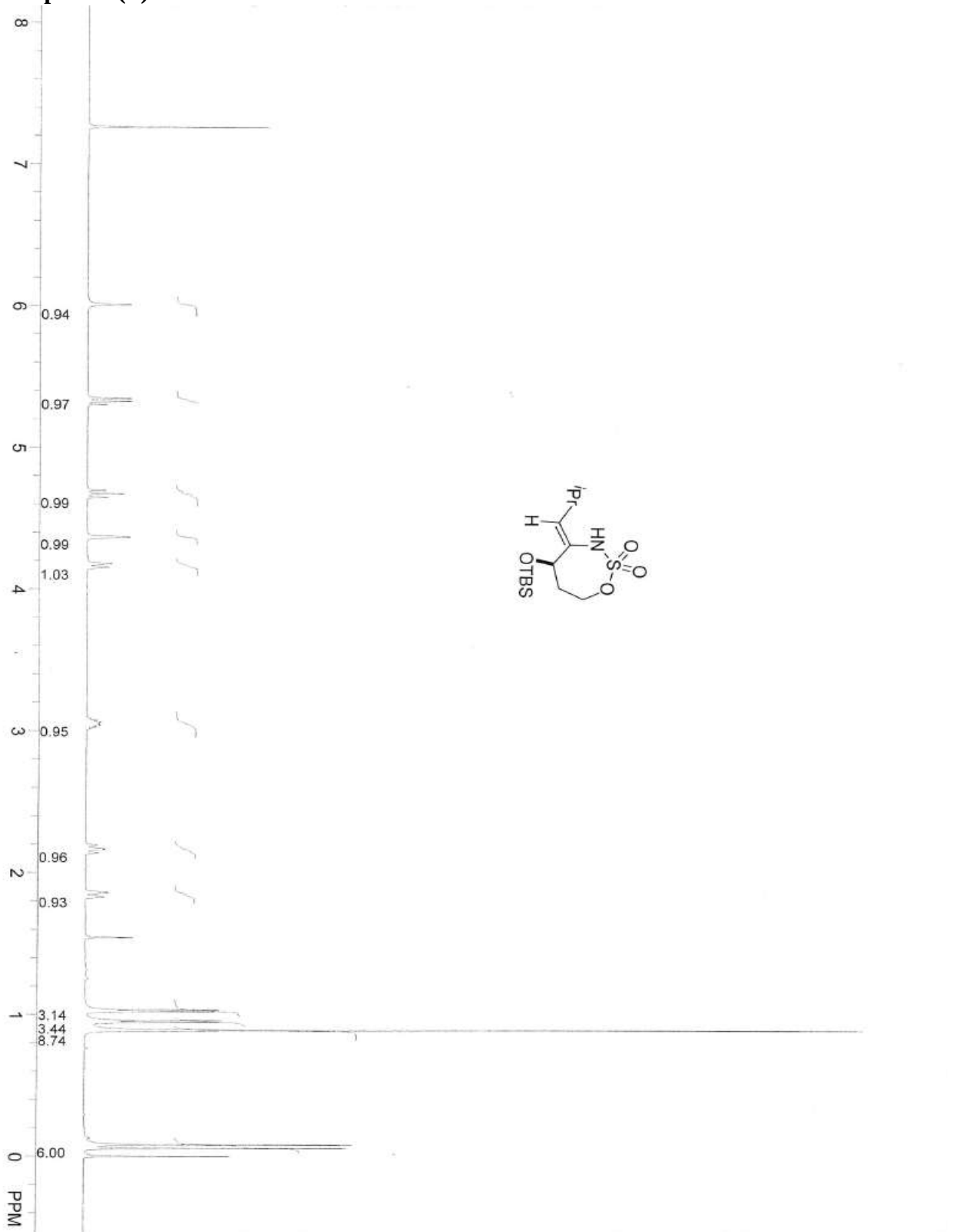

OTBS
200
150
100
50
0
PPM
Group Schomaker, C13CPD32 CDCl3 /home/rgrigg/callisto rgrigg 49
F1: 125.743
F2: 1.000
PW: 10.0 us
SW1: 29762
PD: 2.0 sec
OF1: 12570.0
NA: 32
LB: 2.0
USER: nmr -- DATE: 2014-04-01 09:17:33.794
PTS1d: 32768 , 32768
Nuts - SC140401091O_RDGX052_1L
EX: zgpg30

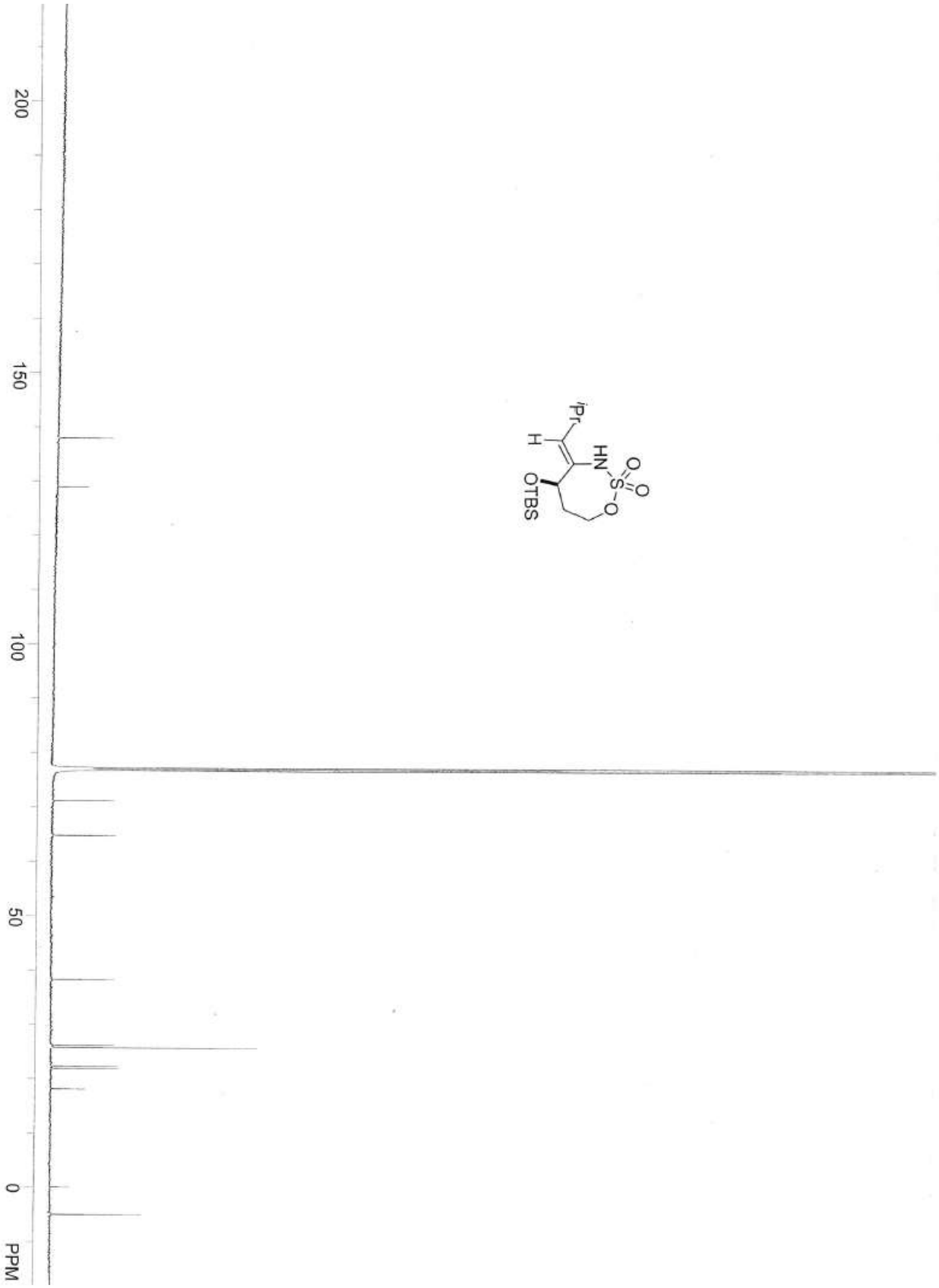
Compound 3.35



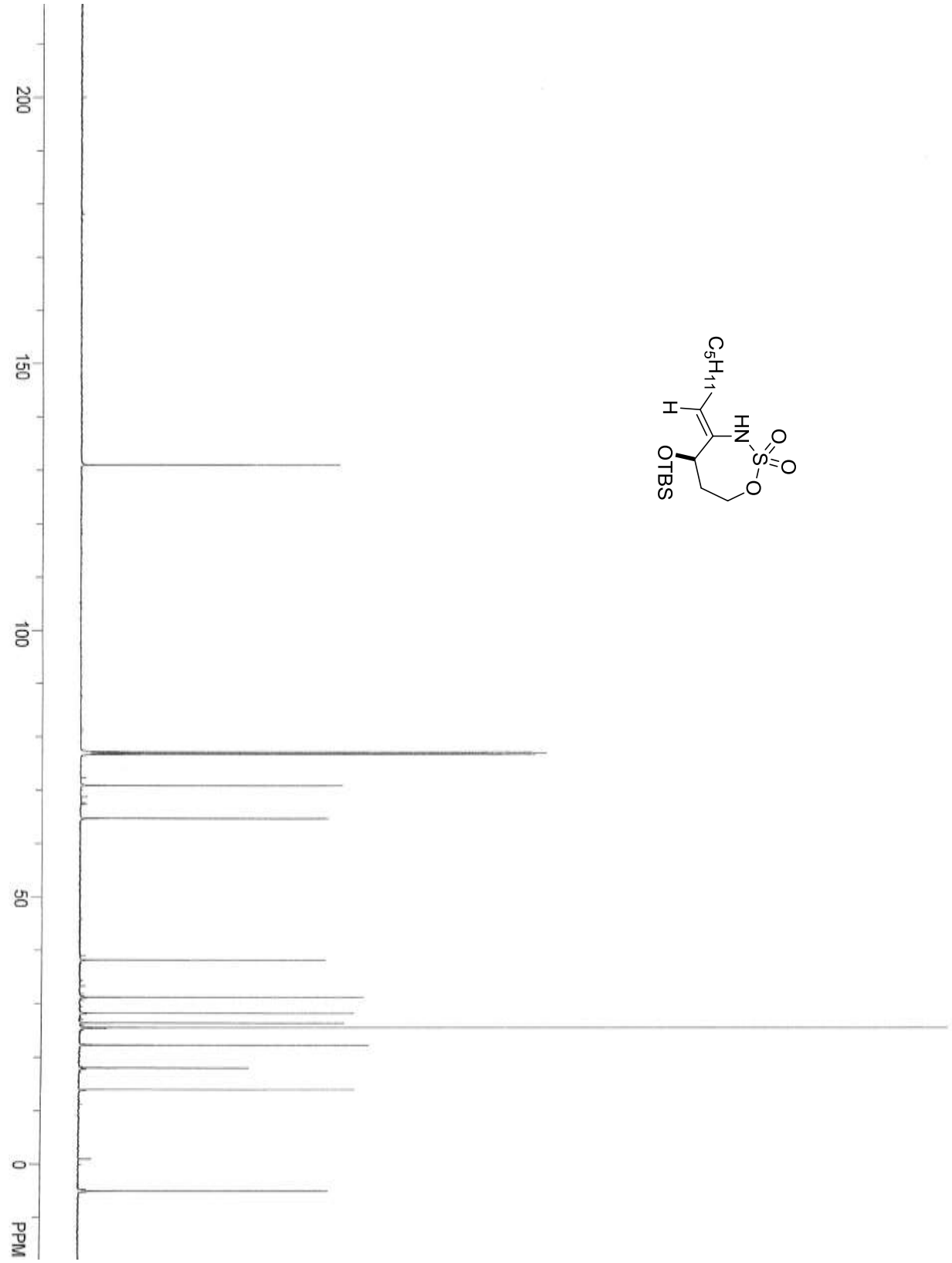

OTBS
200
150
100
50
0
PPM
Group Schomaker_C13CPD32 CDCl3 /home/rgrigg/callisto rgrigg 49
F1: 125.743
F2: 1.000
SW1: 29762
PW: 10.0 us
PD: 2.0 sec
OF1: 12569.1
NA: 128
LB: 2.0
USER: nmr -- DATE: 2014-04-02 10:59:26.125
PTS1d: 32768 _ 32768
Nuts - SC140401091O_RDGX054_12
EX: zgpg30

Compound (*Z*)-3.7.

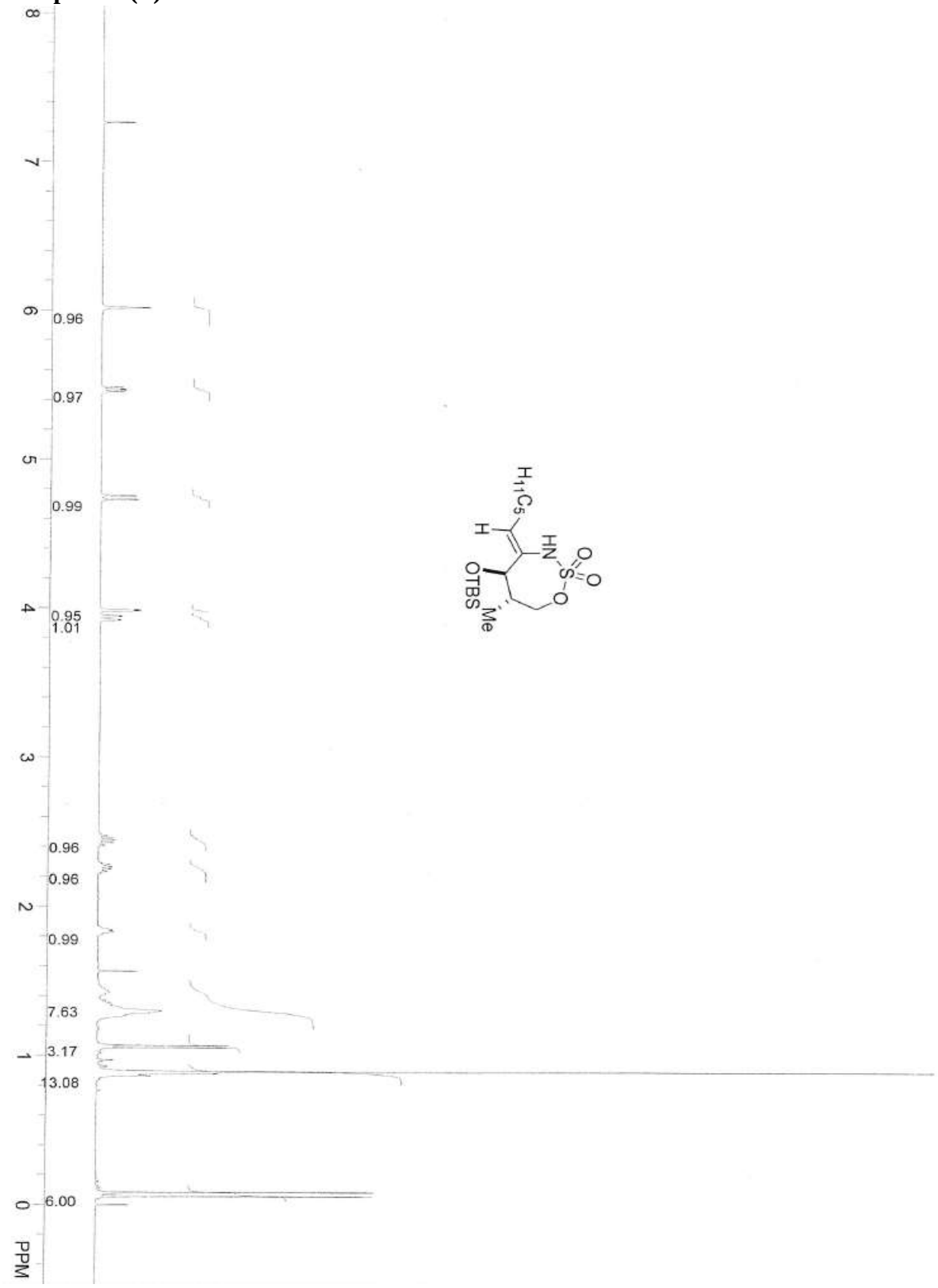


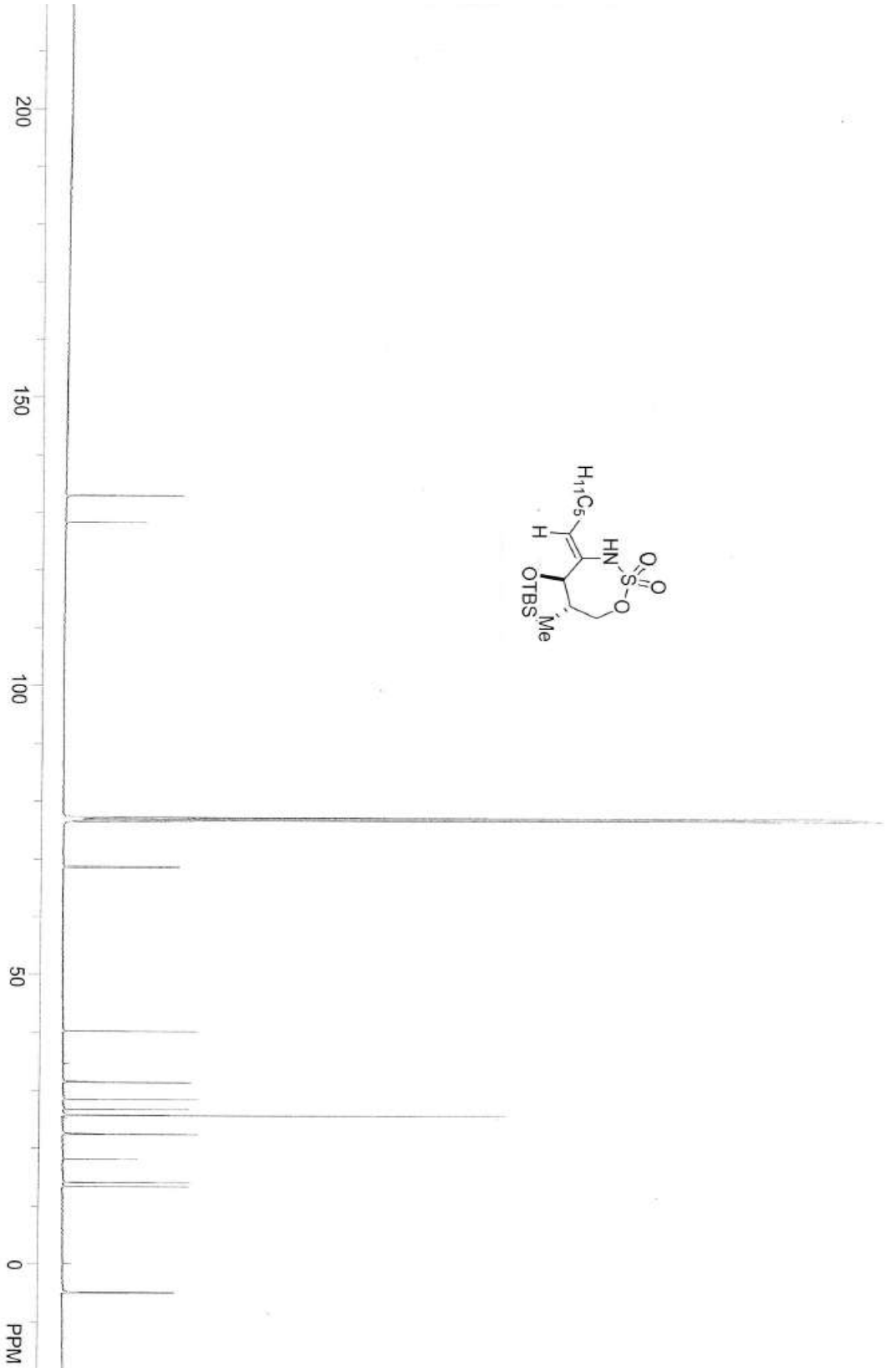

200
150
100
50
0
PPM
iPr
H
OTBS
HN
S
O
O
O

Compound (*Z*)-3.14.

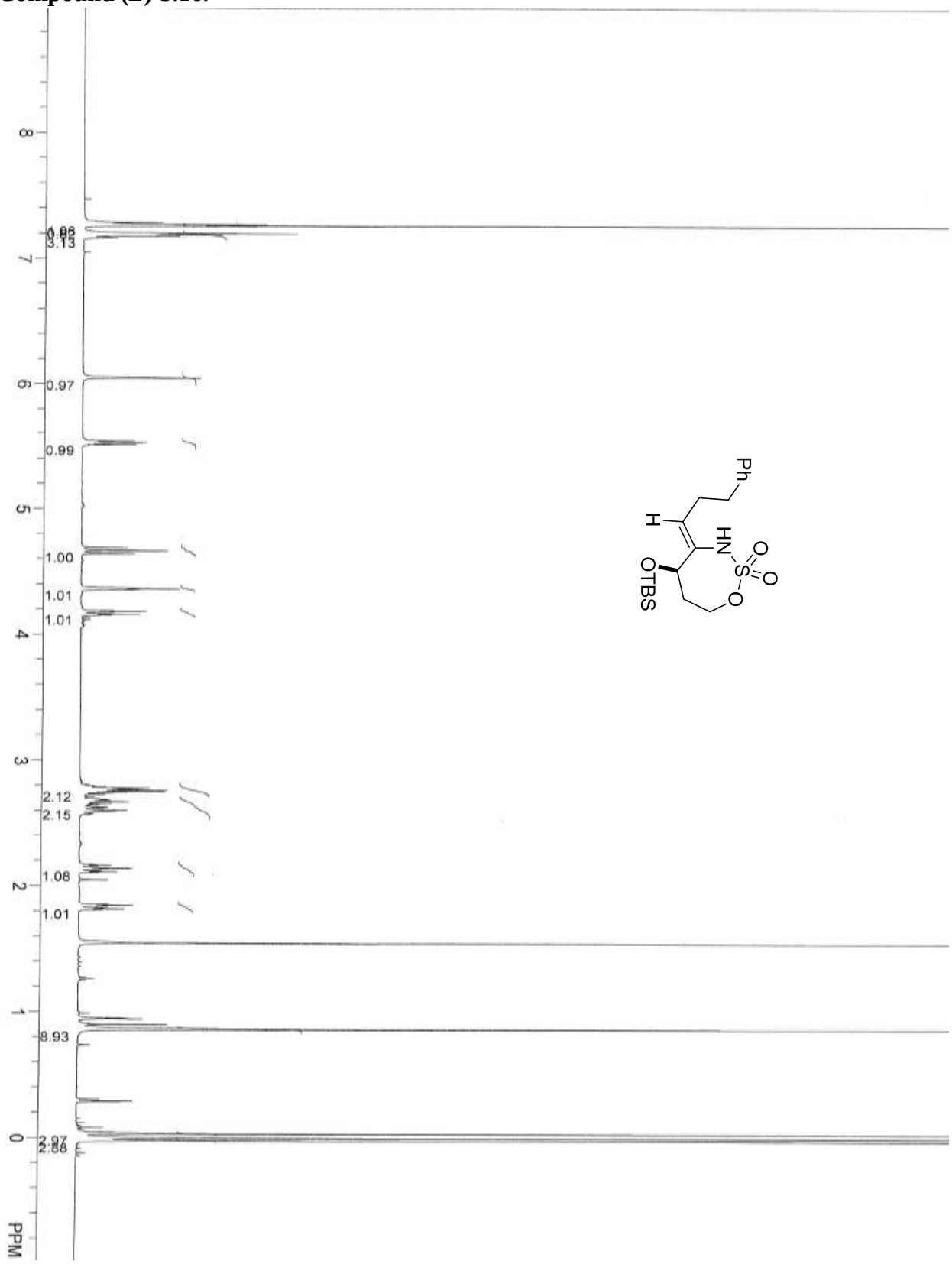

200
150
100
50
0
PPM
C5H11
H
HN
O
O
S
O
OTBS

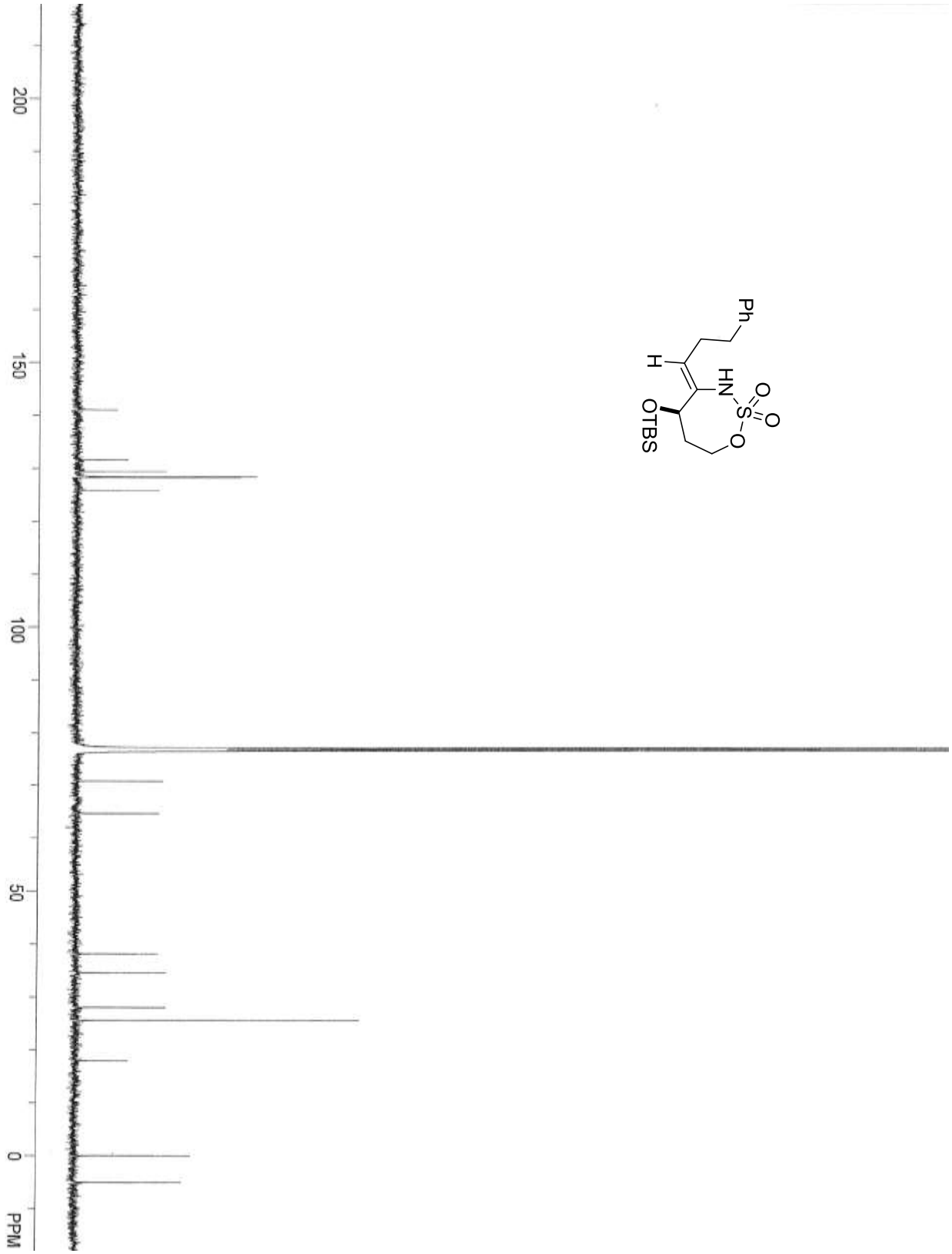
Compound (*Z*)-3.15.



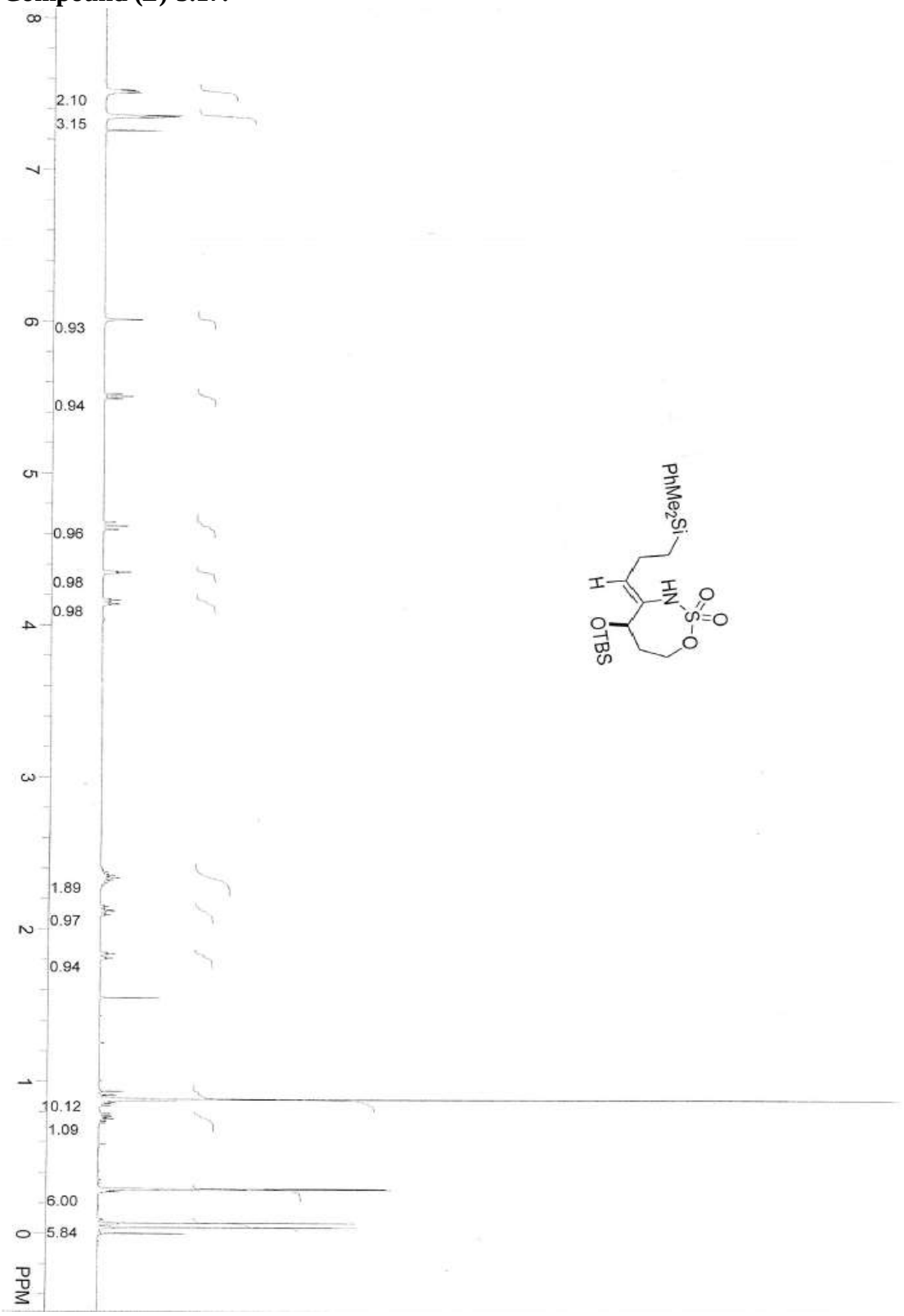

200
150
100
50
0
PPM
H11C5
H
HN
S
O
O
O
OTBS
Me

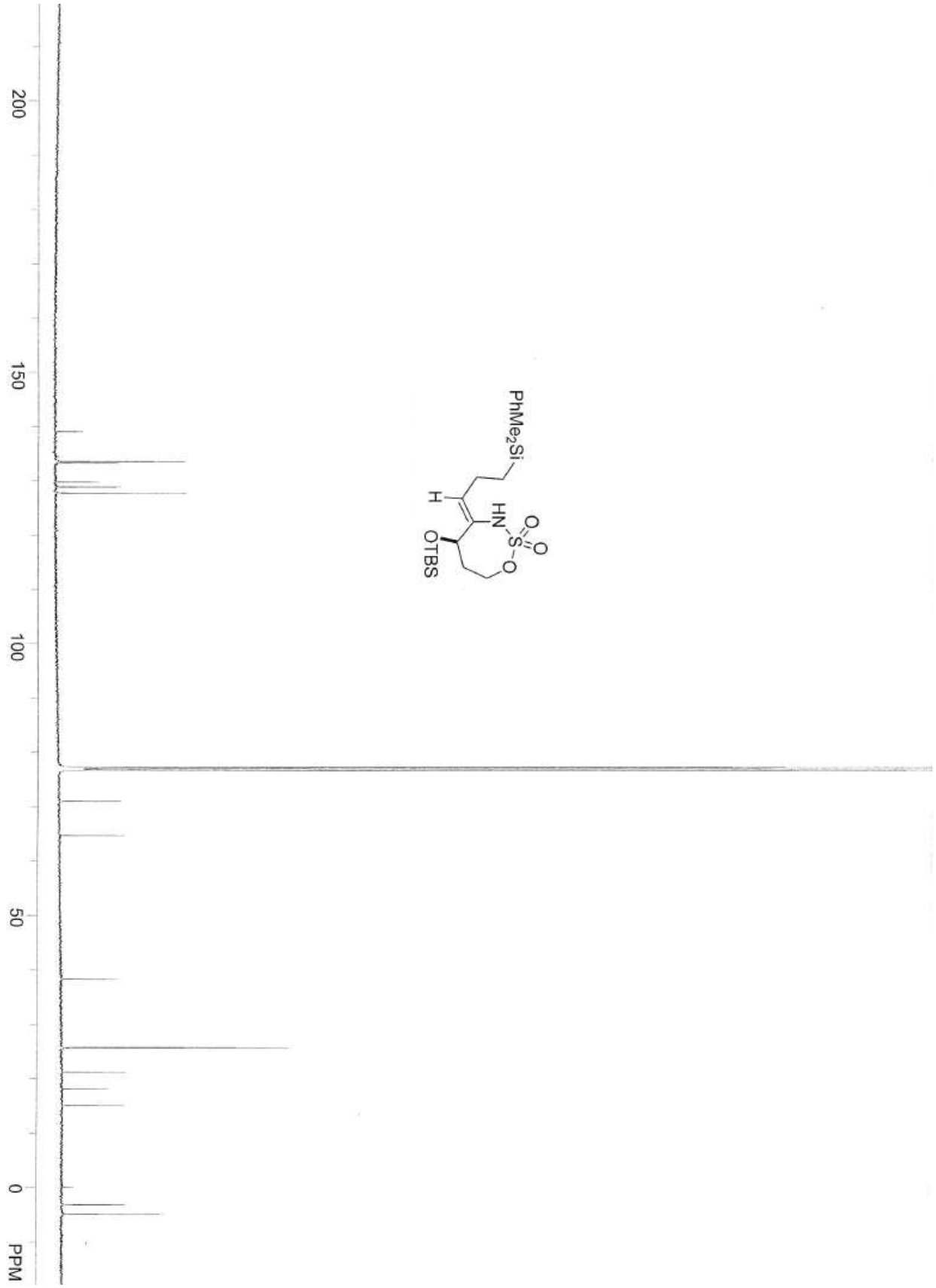
Compound (*Z*)-3.16.



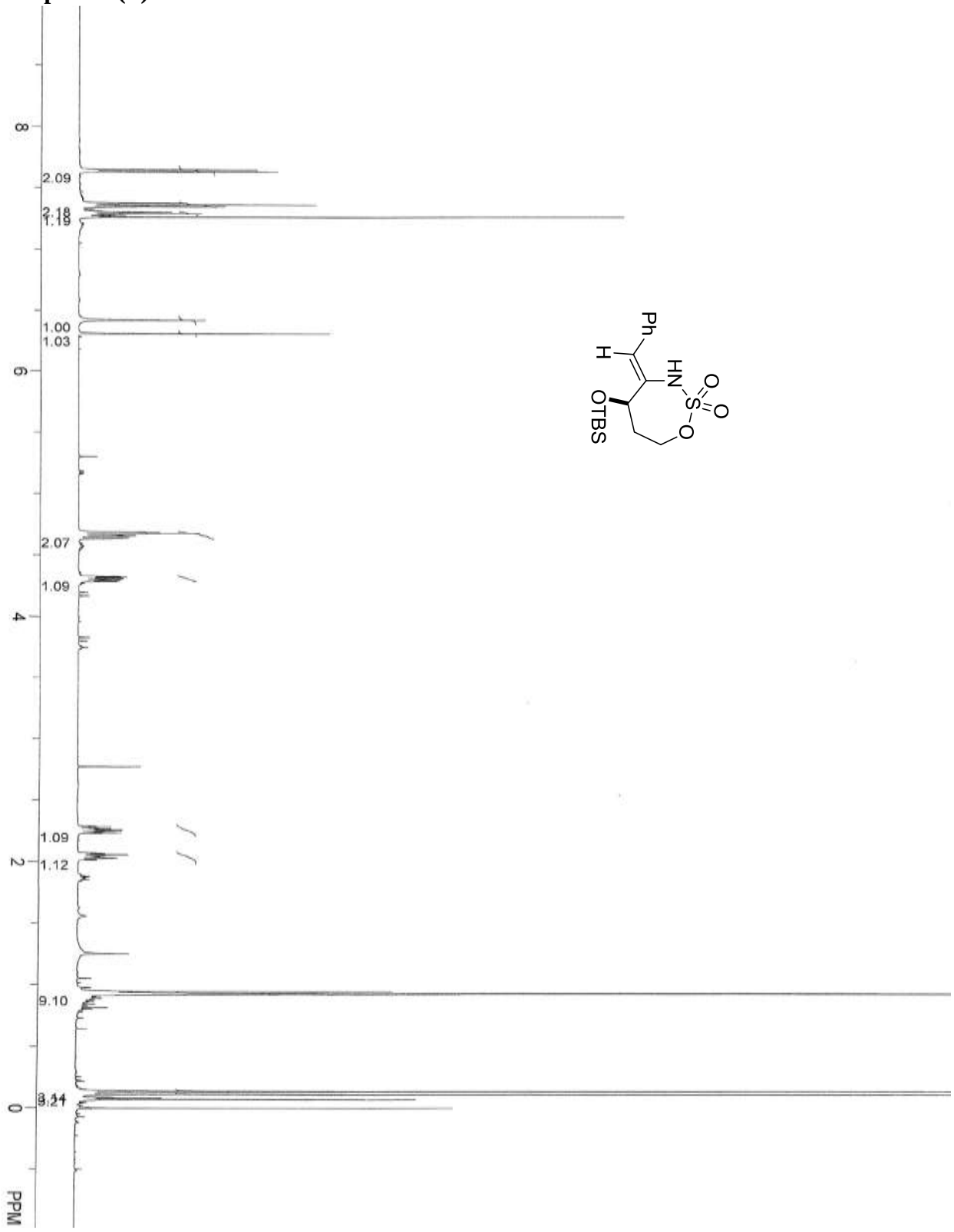

Ph
H
HN
O
O
S
O
OTBS
200
150
100
50
0
PPM

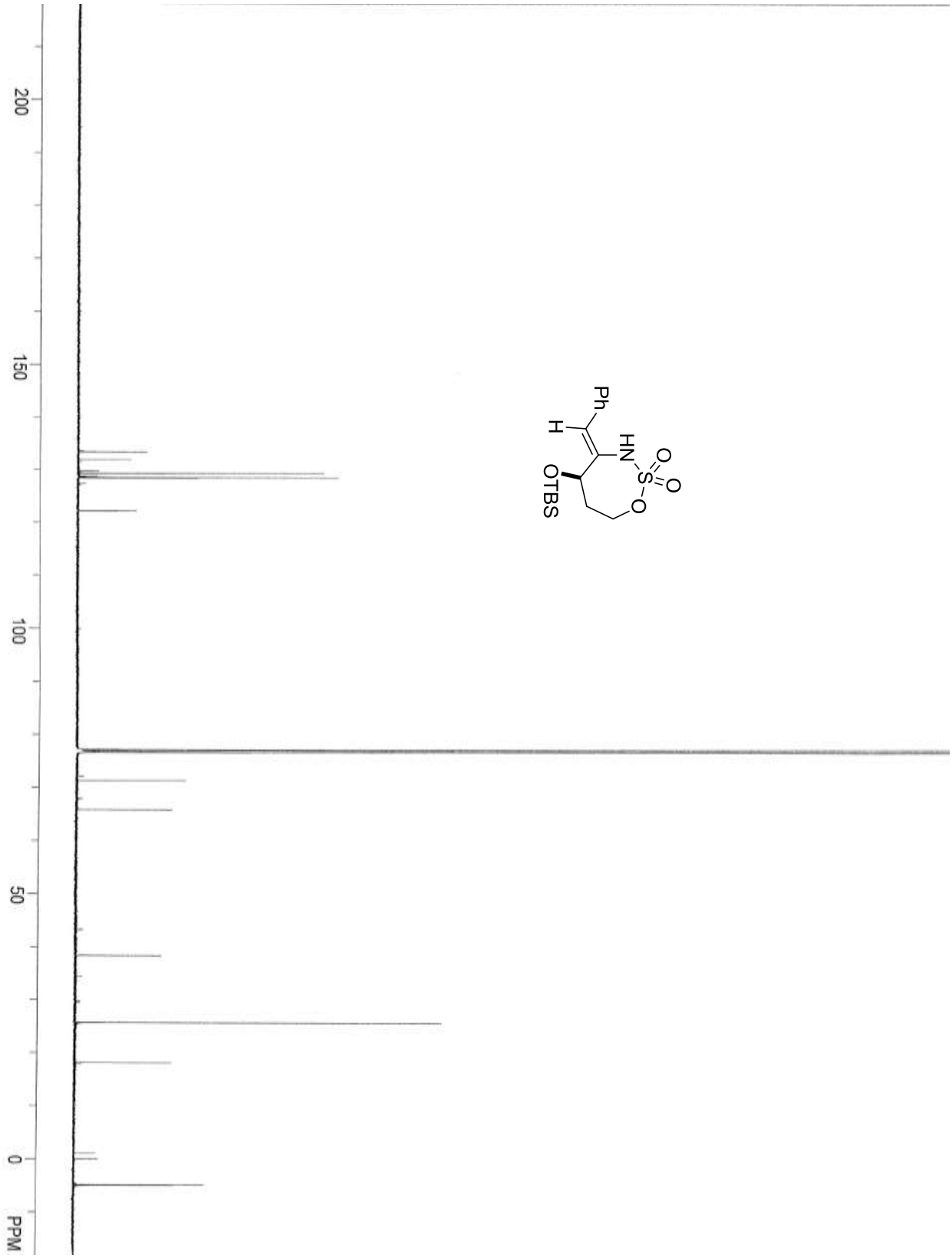
Compound (*Z*)-3.17.



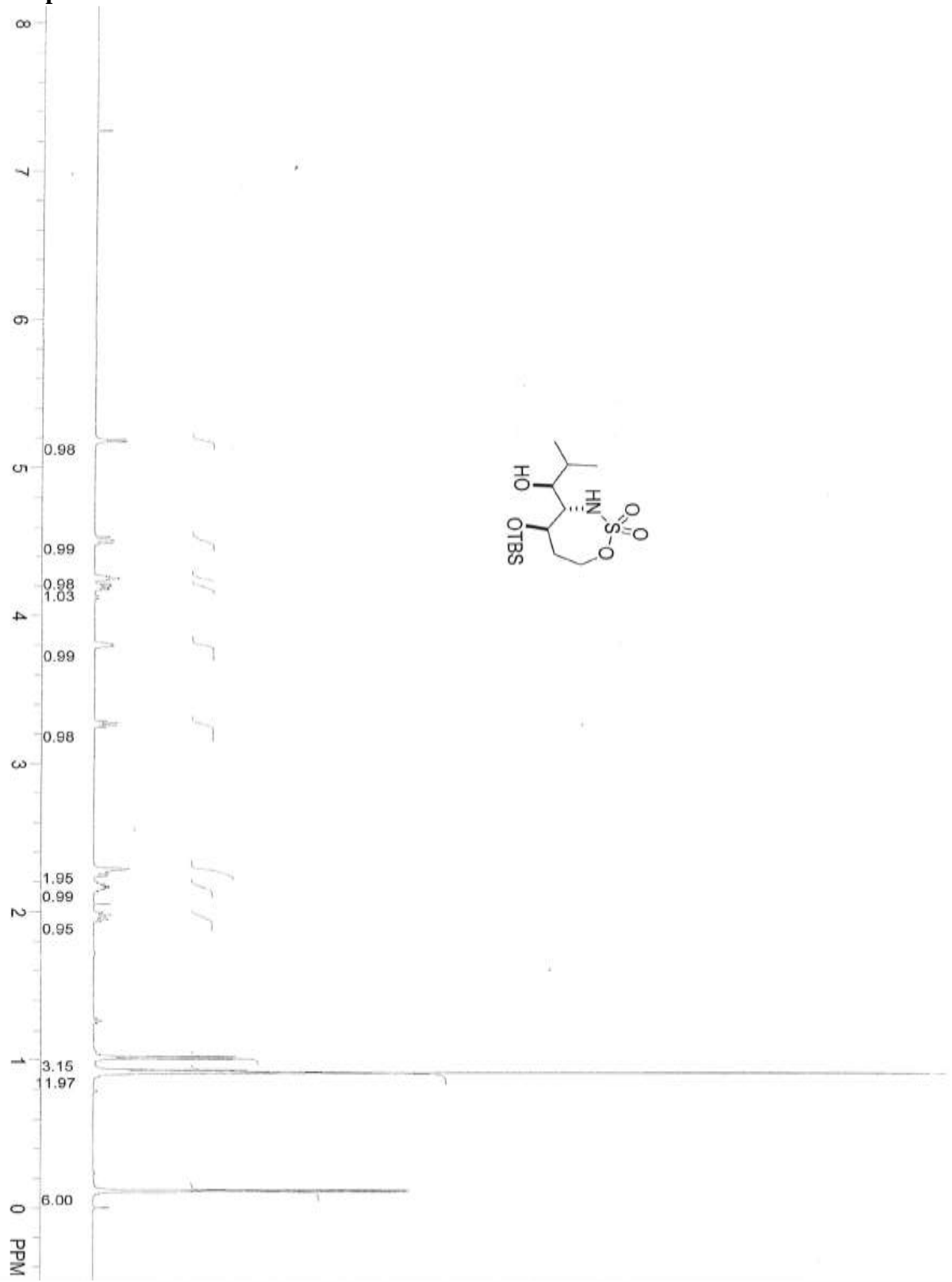

PhMe2Si
H
HN
S
O
O
O
OTBS
200
150
100
50
0
PPM

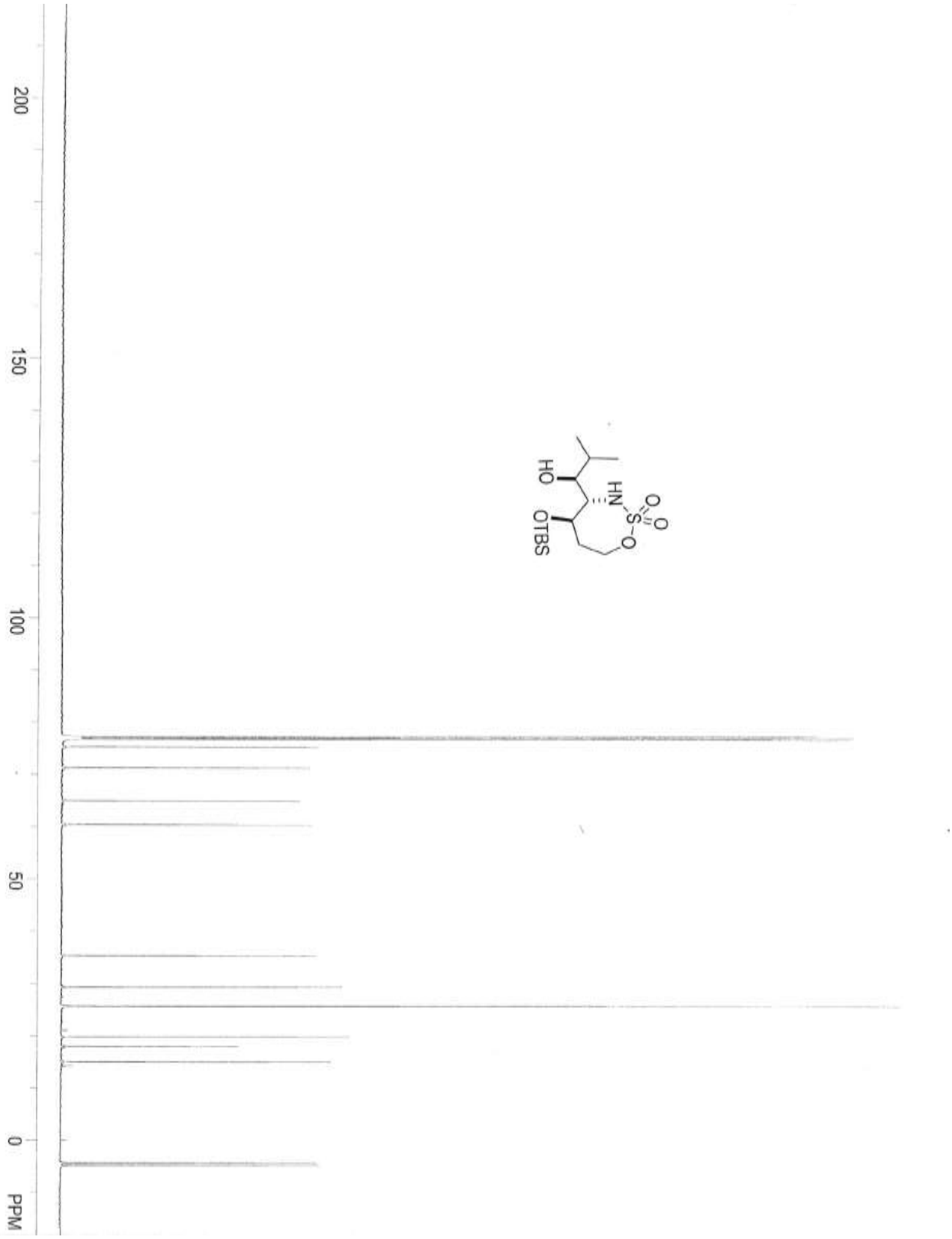
Compound (*Z*)-3.18.



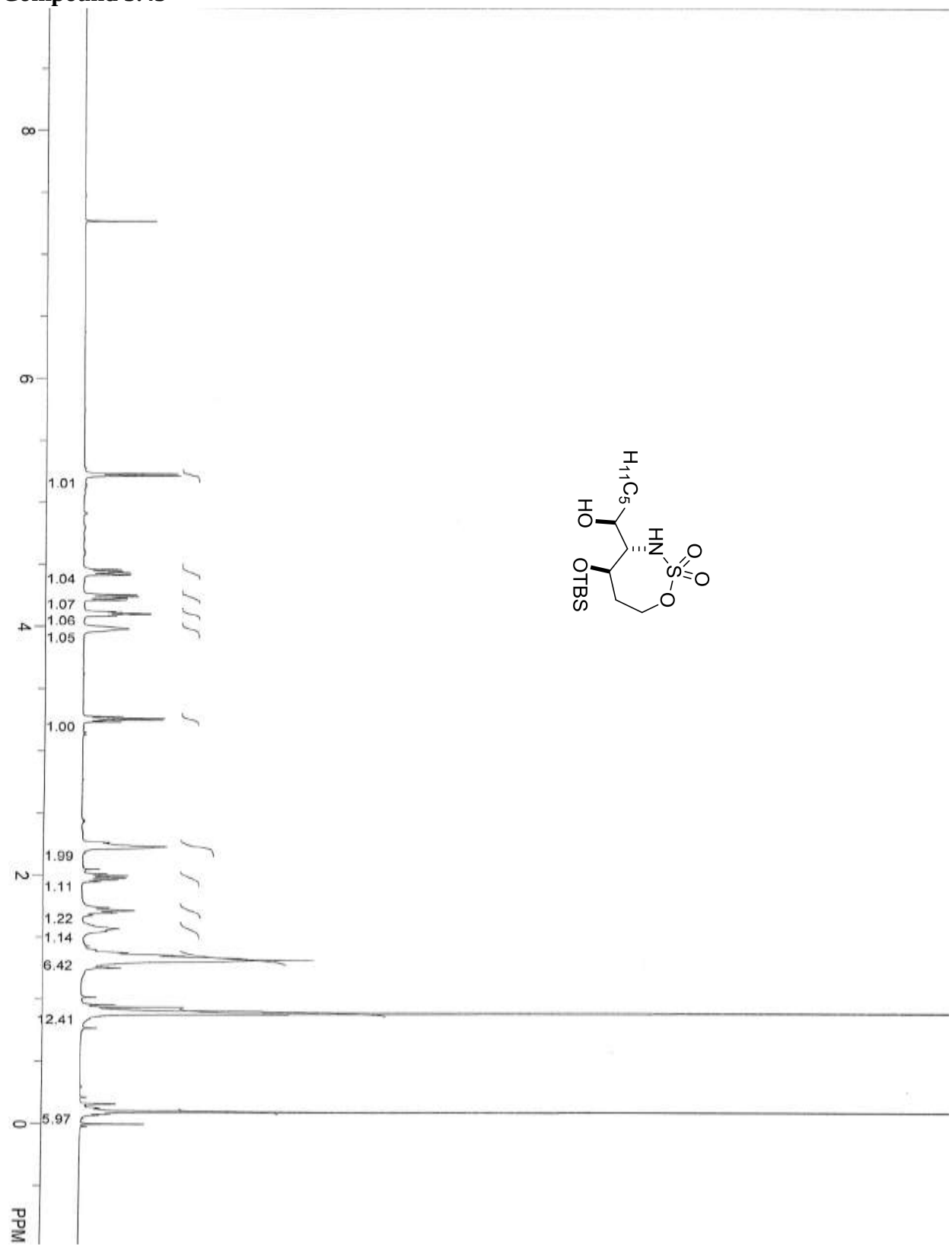

200
150
100
50
0
PPM
Ph
H
HN
S
O
O
O
OTBS

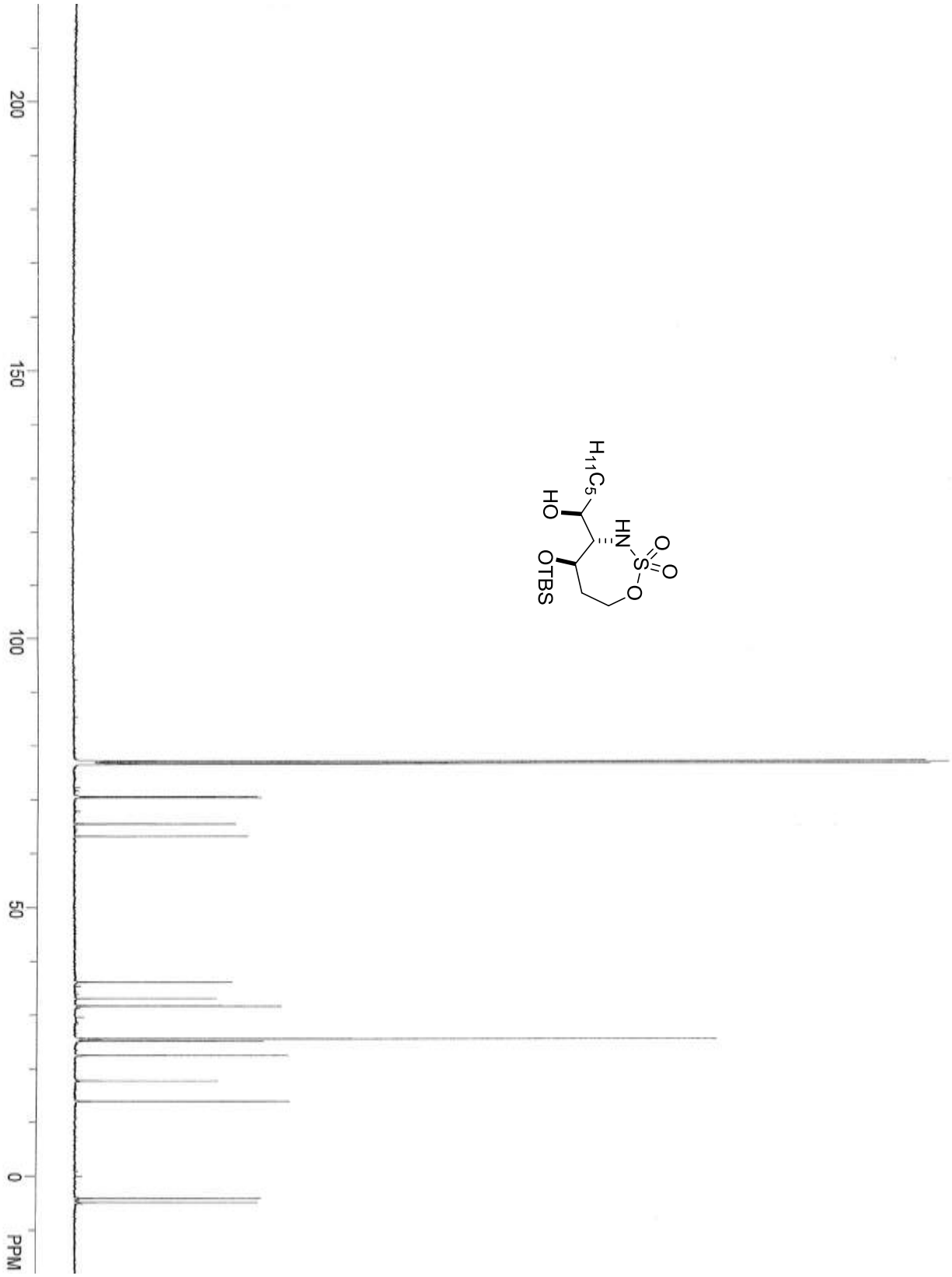
Compound 3.42.



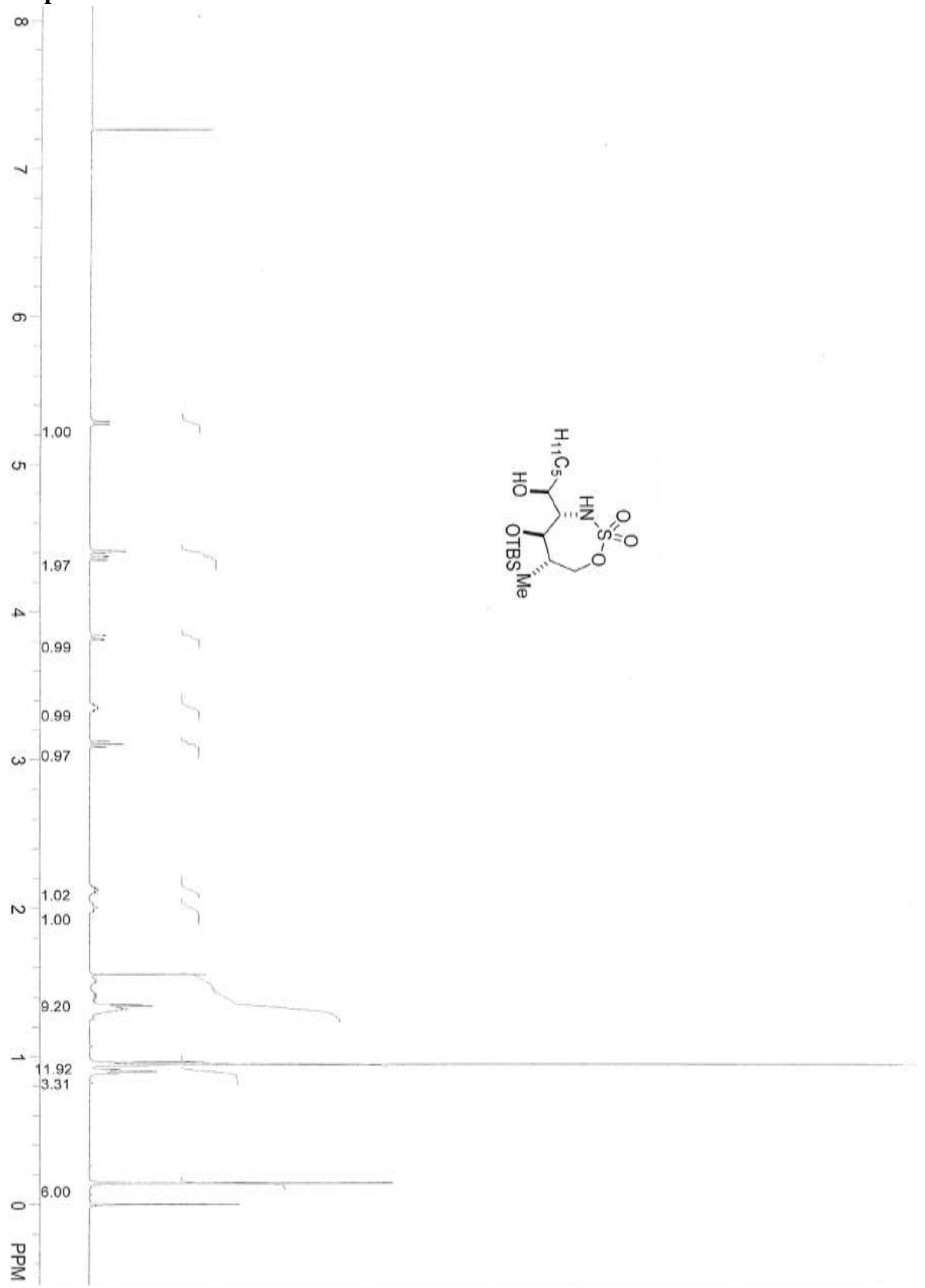

200
150
100
50
0
PPM
HO
HN
O
O
S
O
OTBS

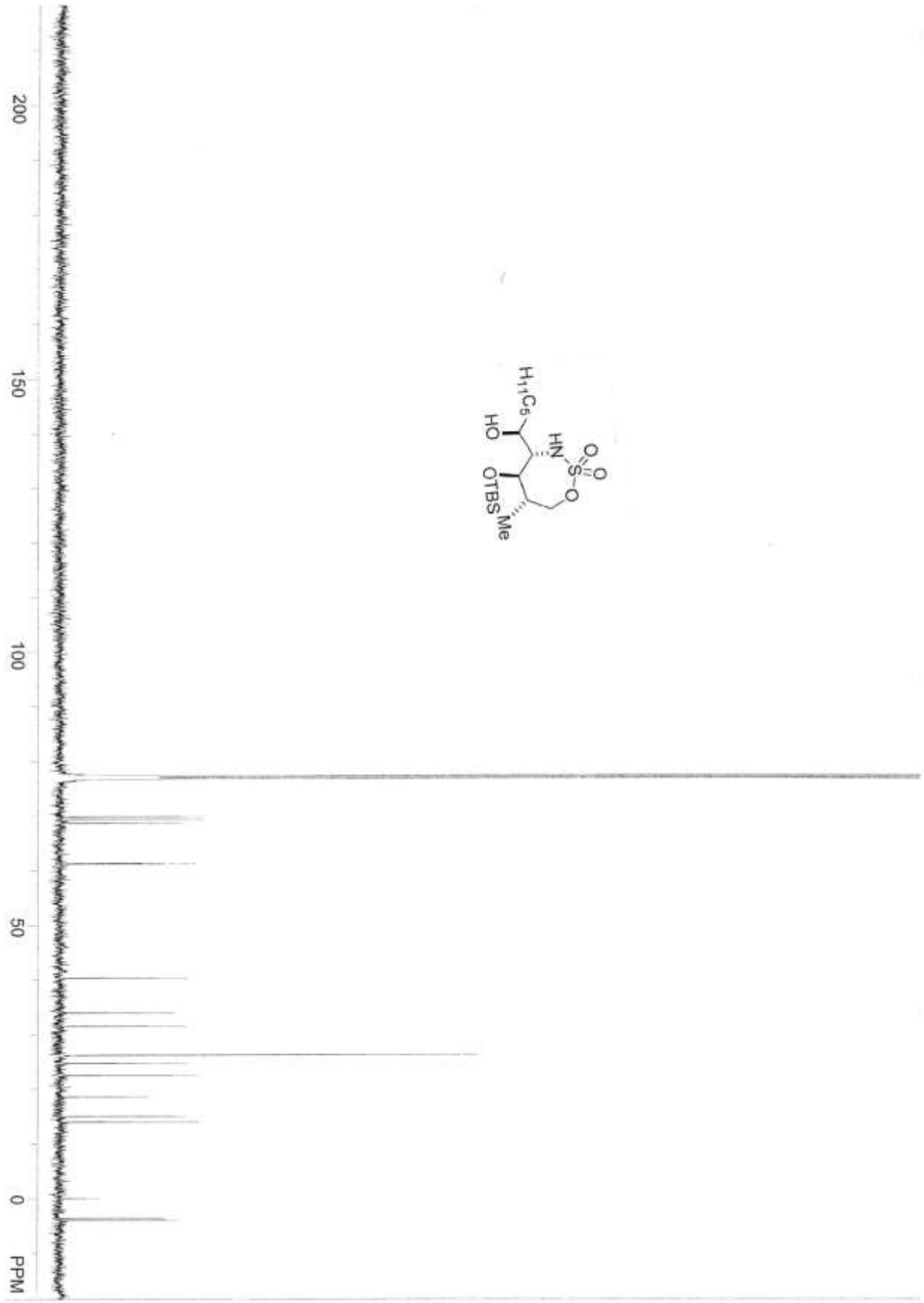
Compound 3.43



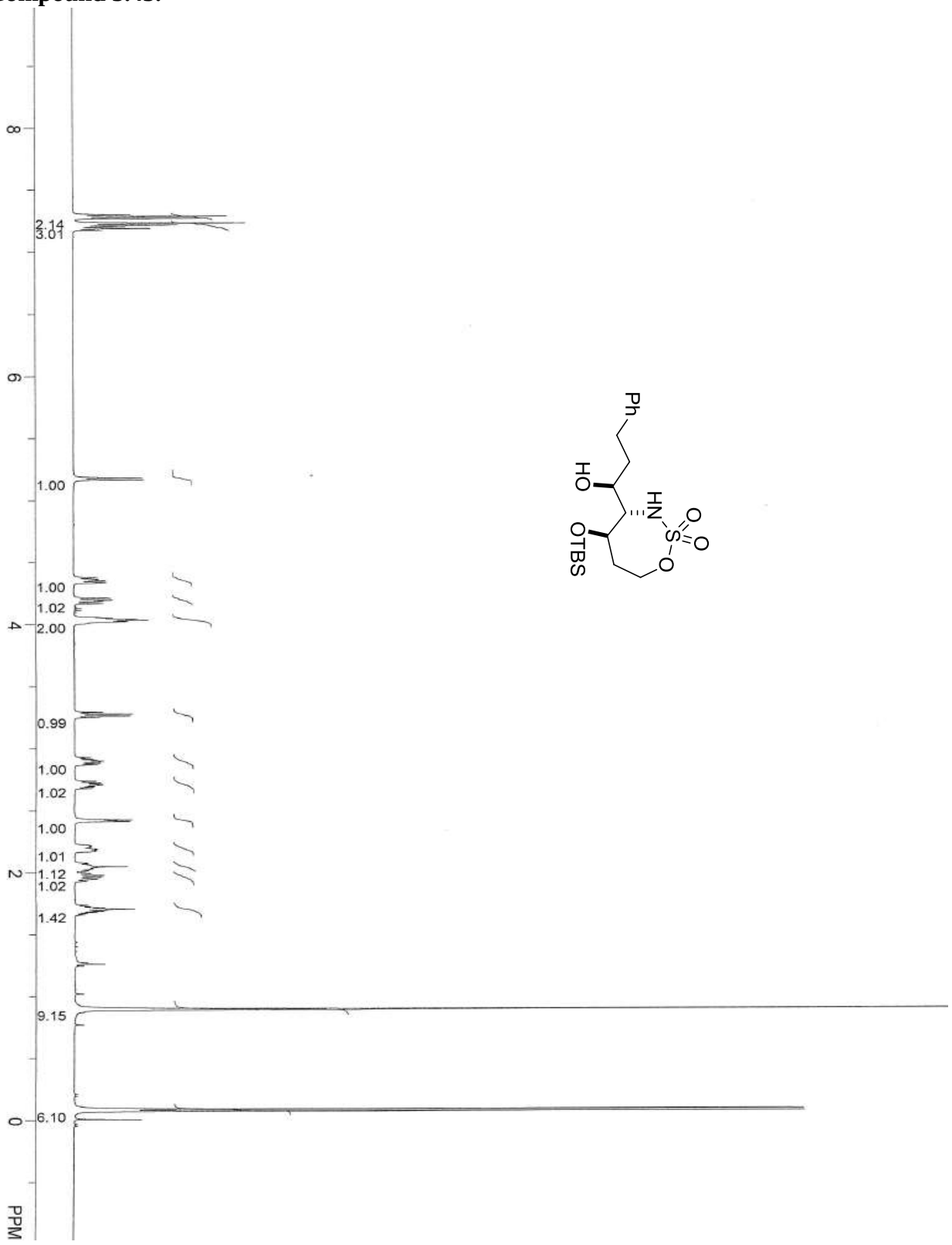

200
150
100
50
0
PPM
H11C5
HO
HN
O
O
S
O
OTBS

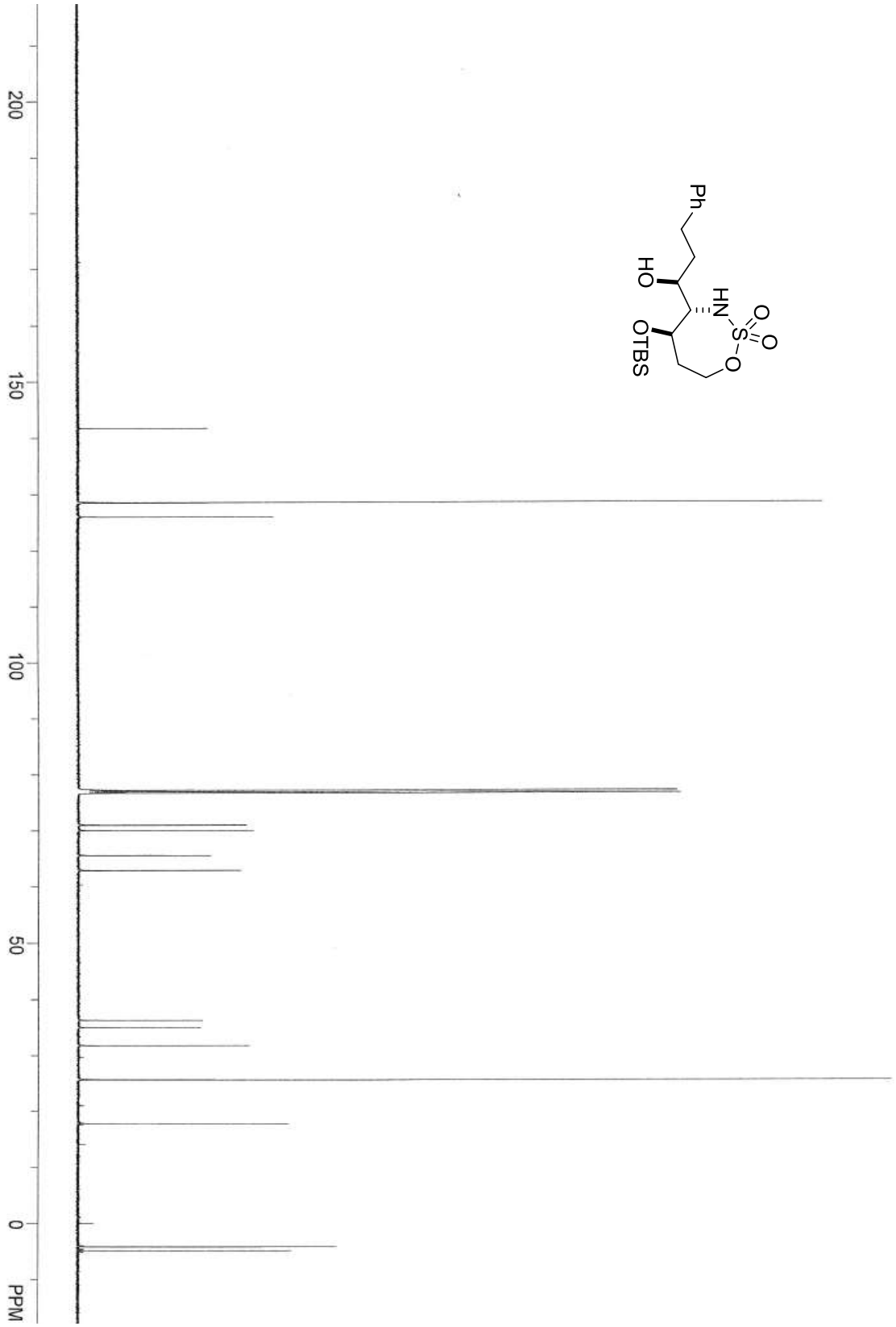
Compound 3.44.



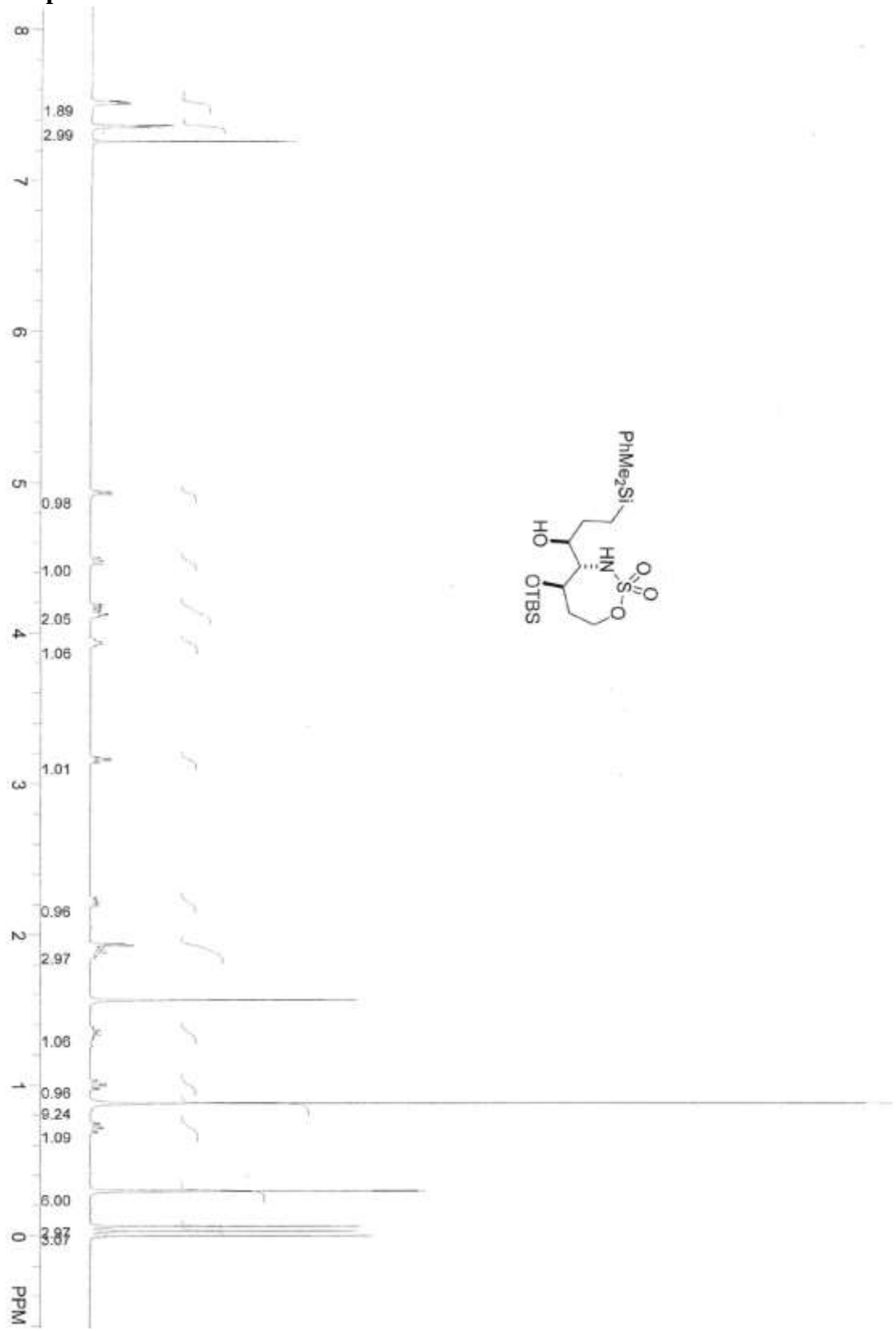

200
150
100
50
0
PPM
H11C5
HO
HN
O
O
S
O
OTBS
Me

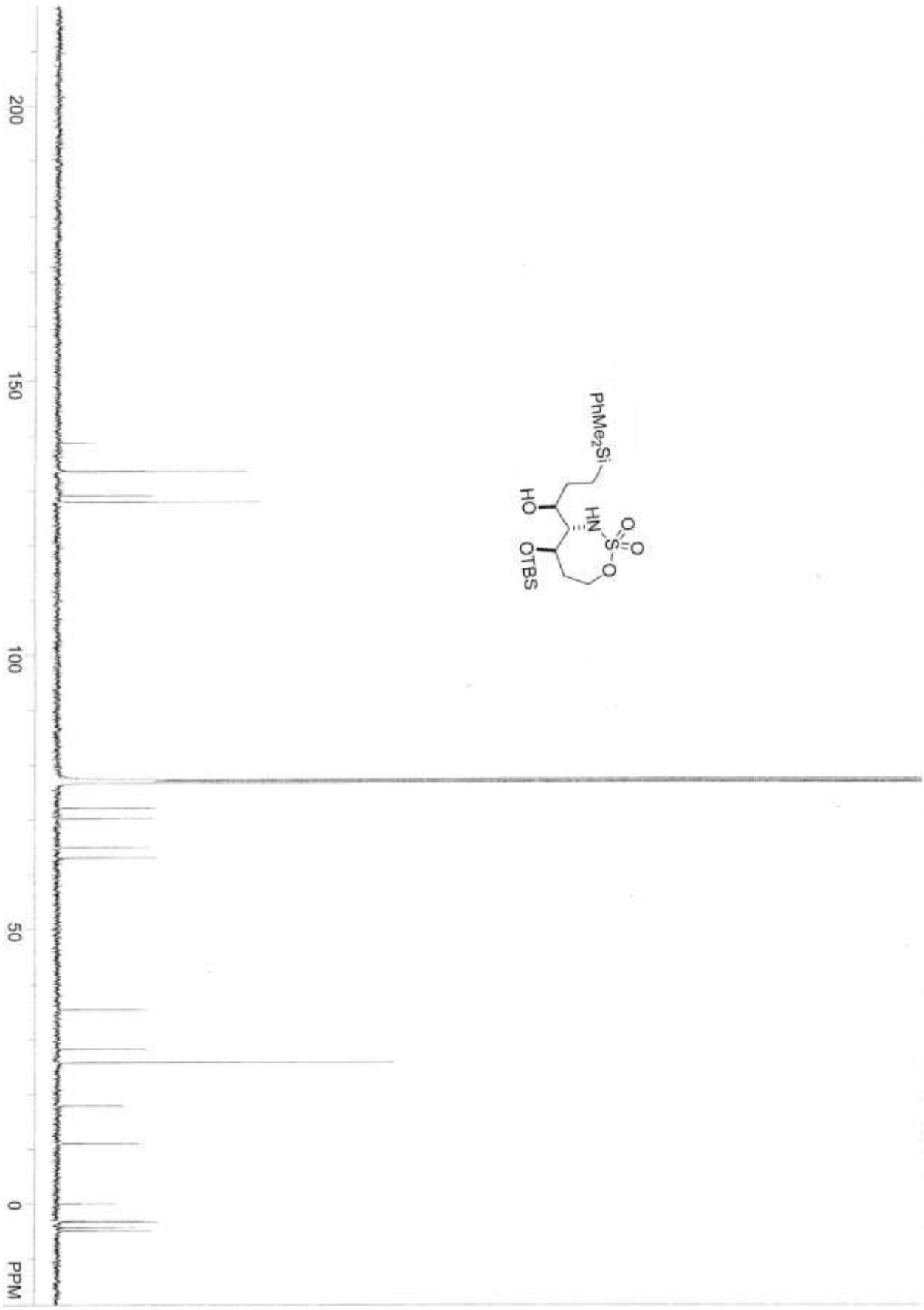
Compound 3.45.



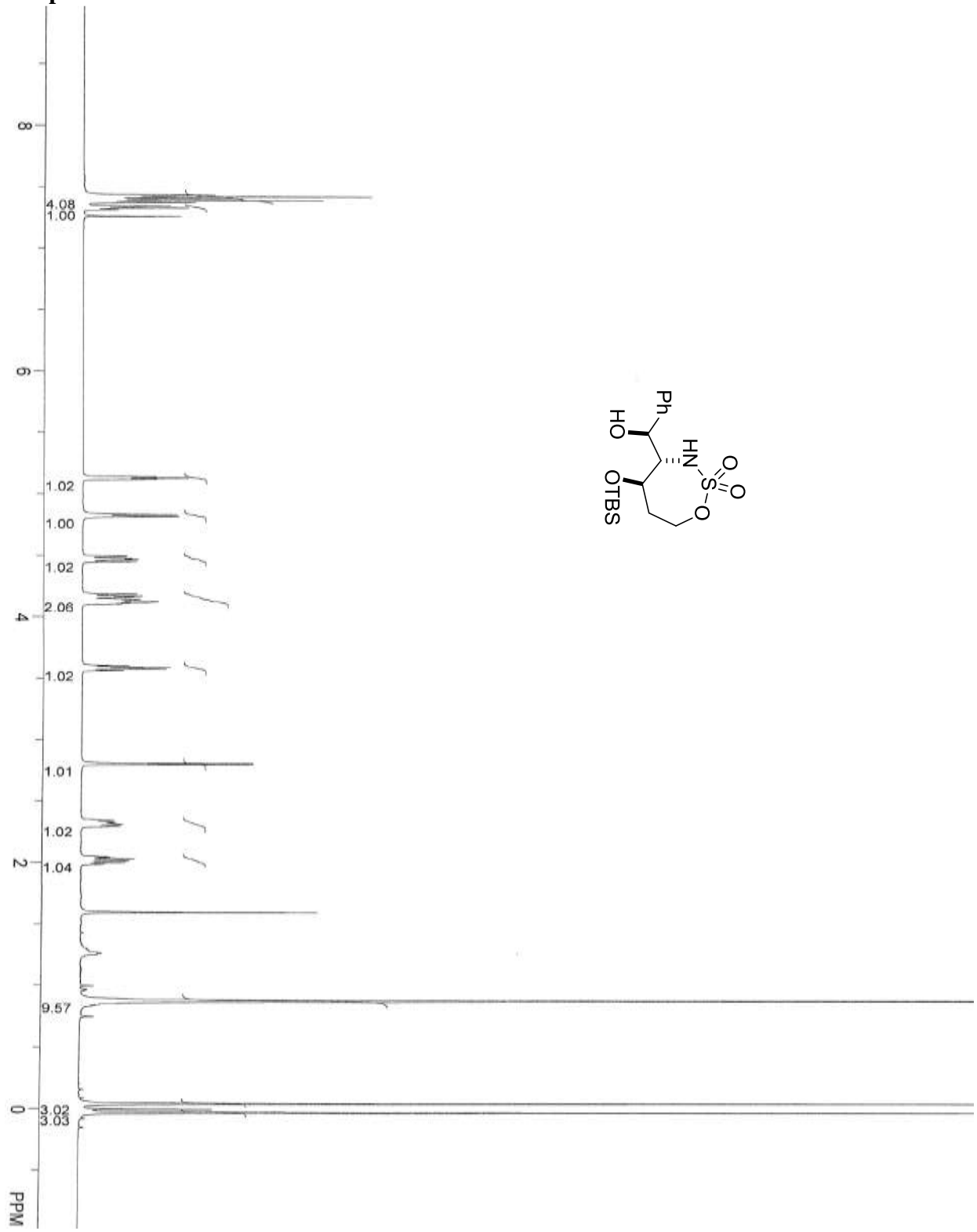

Ph
HO
HN
O
O
S
O
OTBS
200
150
100
50
0
PPM

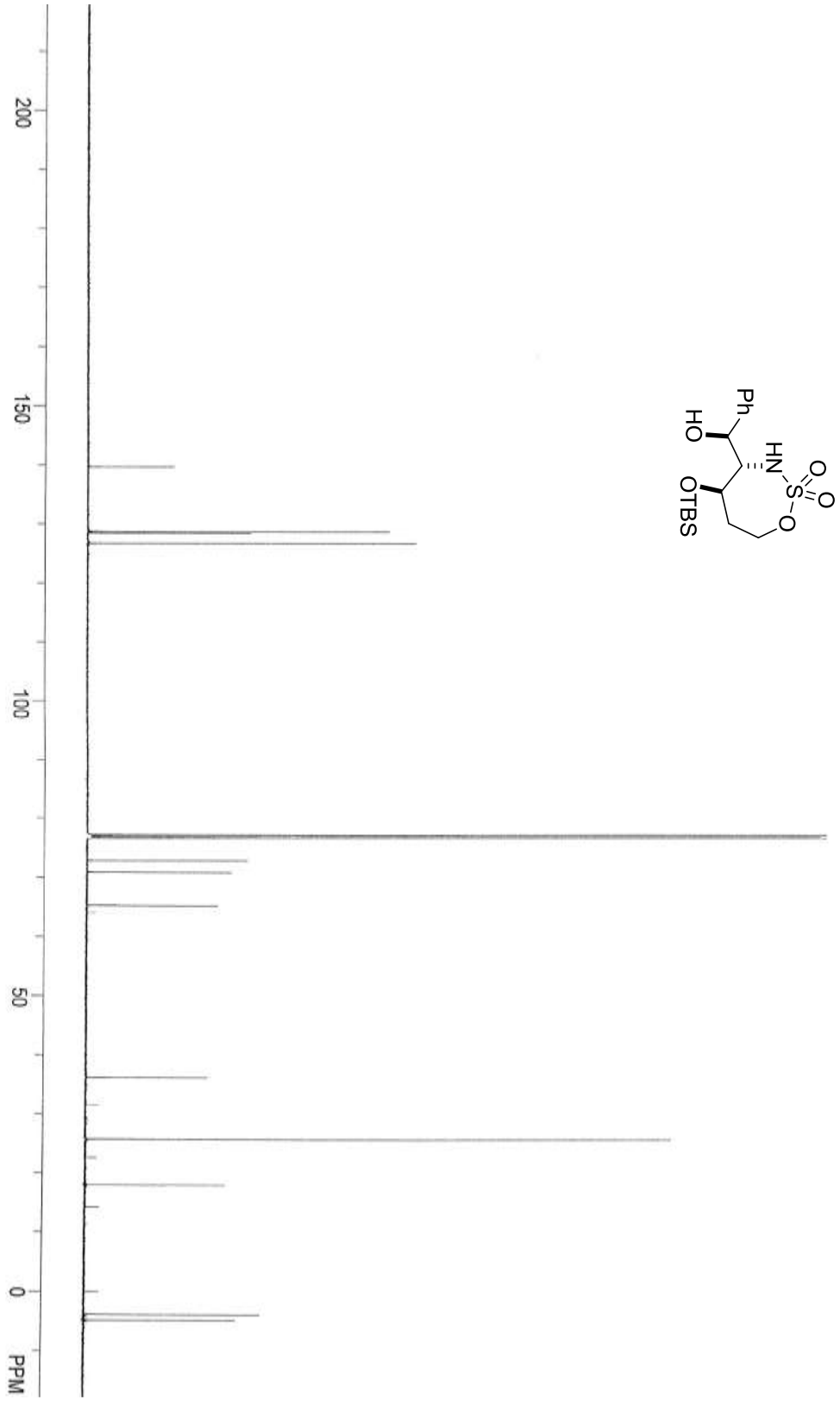
Compound 3.46.



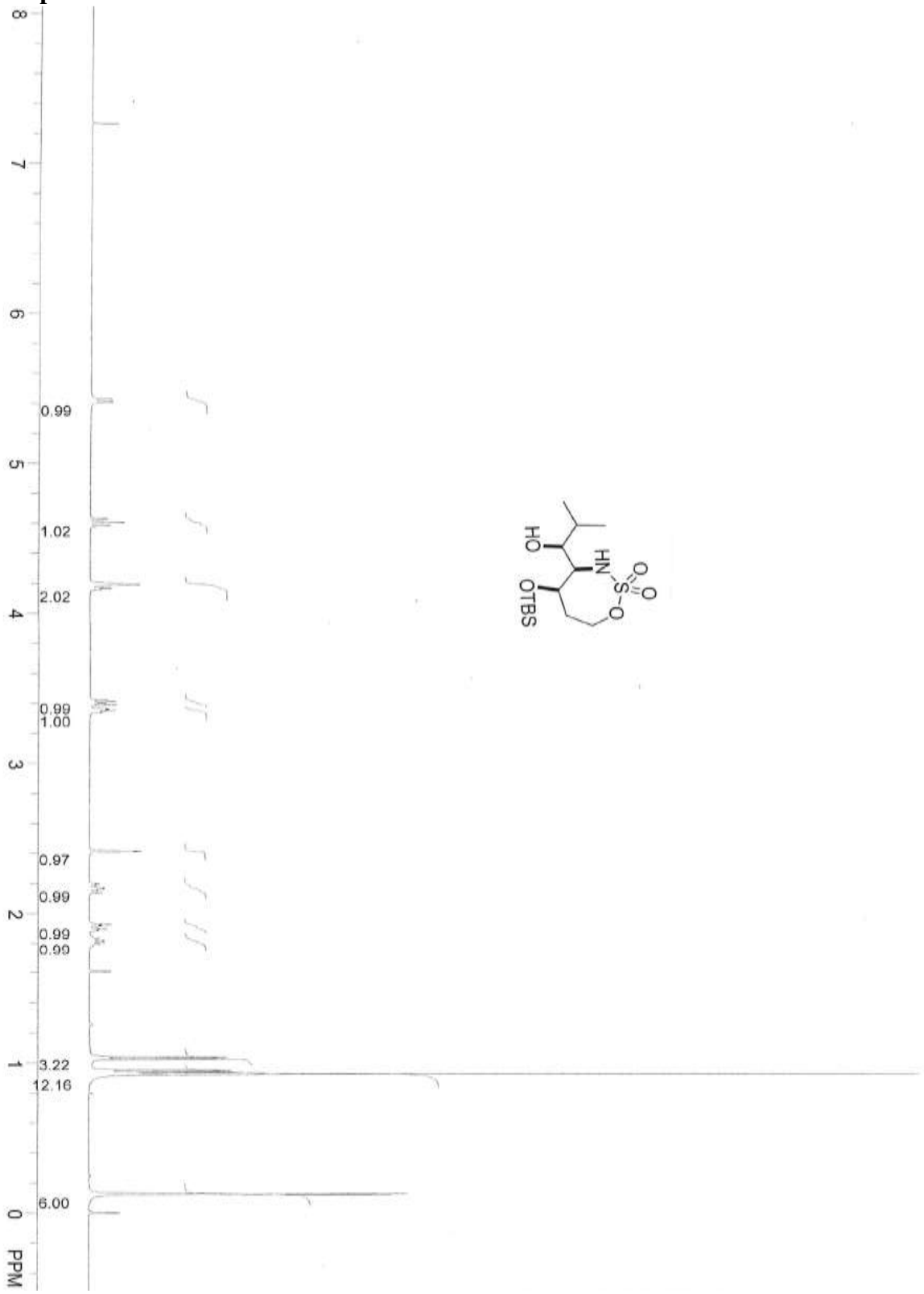

PhMe2Si
HO
HN
OTBS
O
S
O
O
200
150
100
50
0
PPM

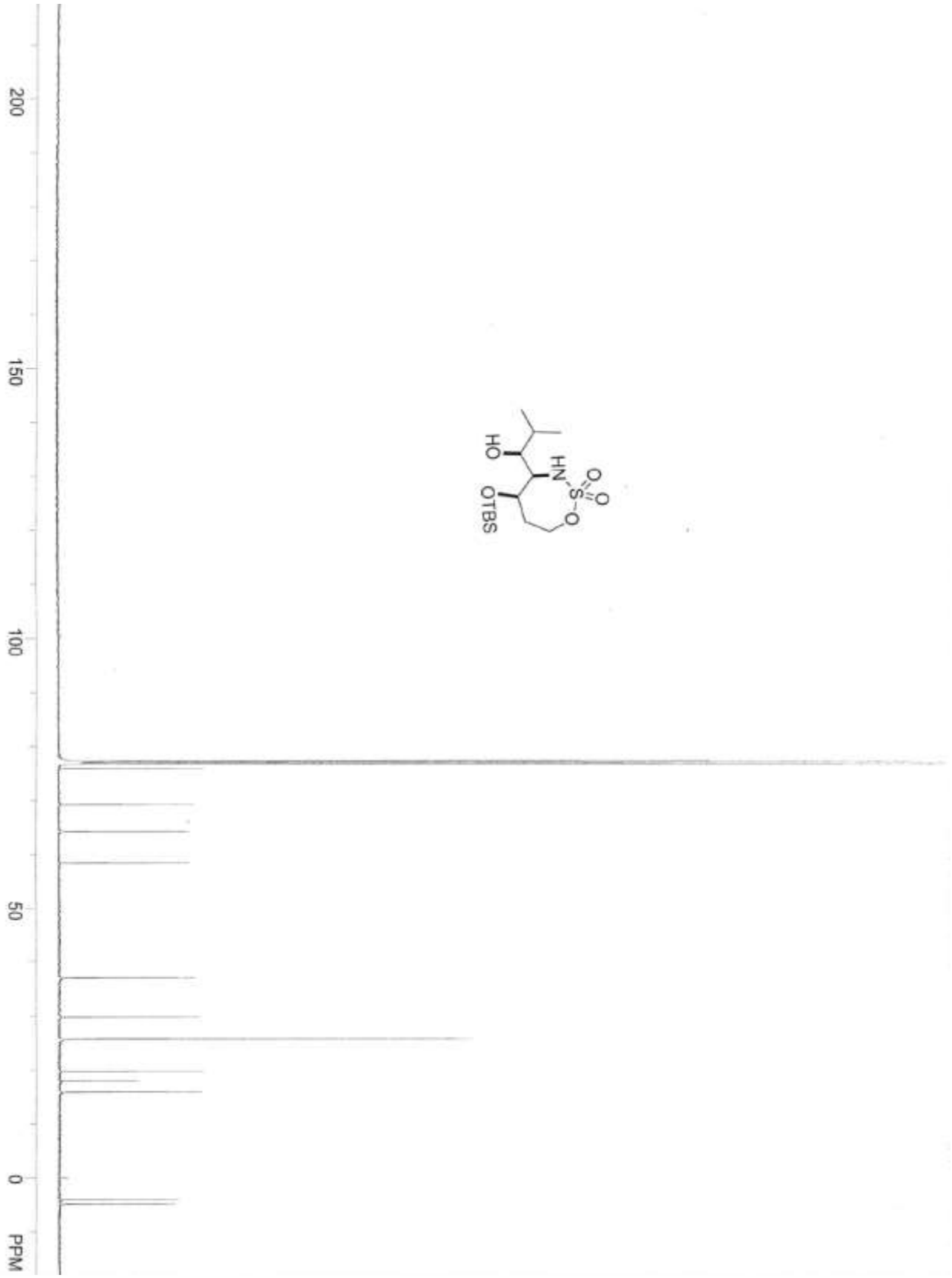
Compound 3.47.



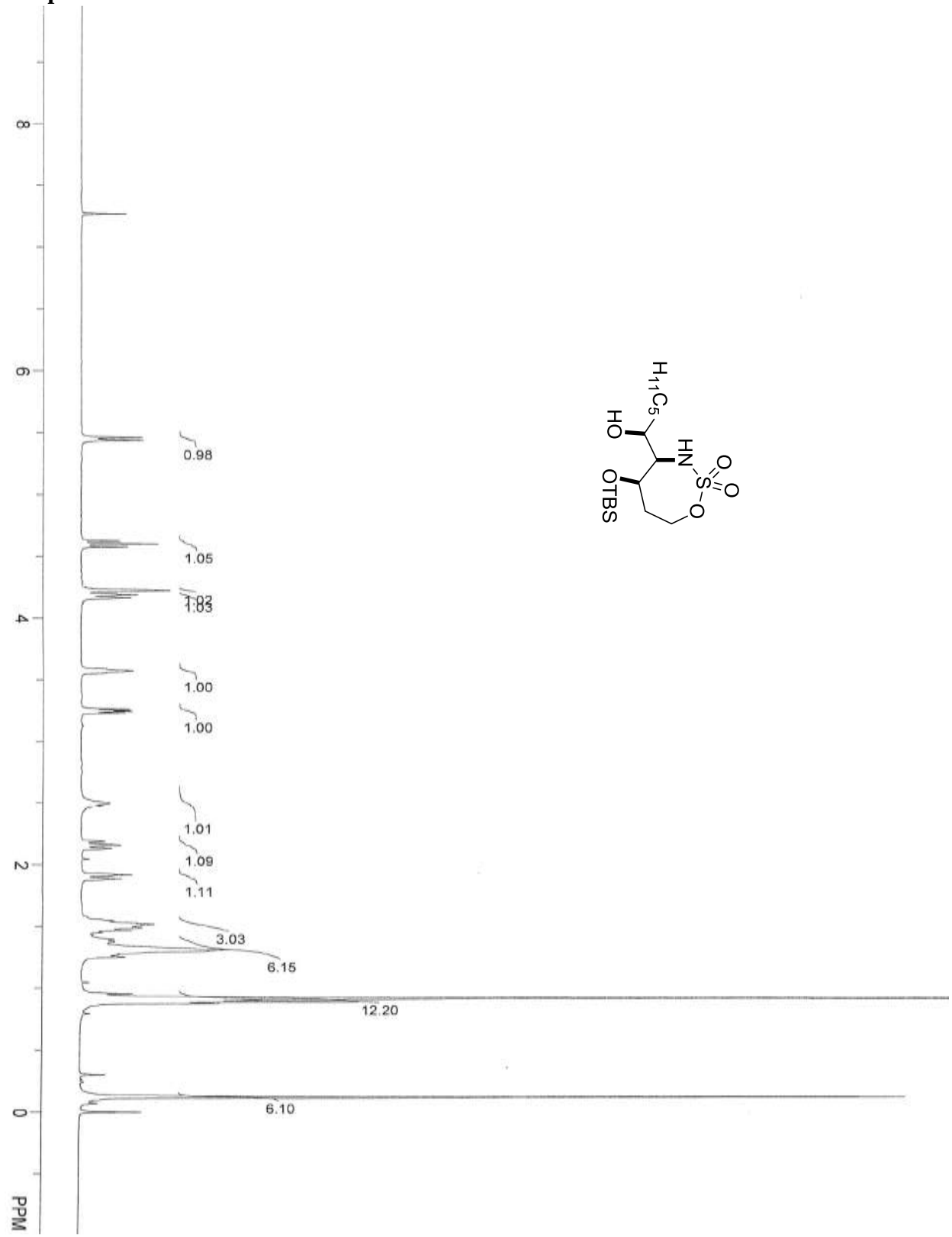

200
150
100
50
0
PPM
Ph
HO
HN
O
O
S
O
OTBS

Compound 3.48.



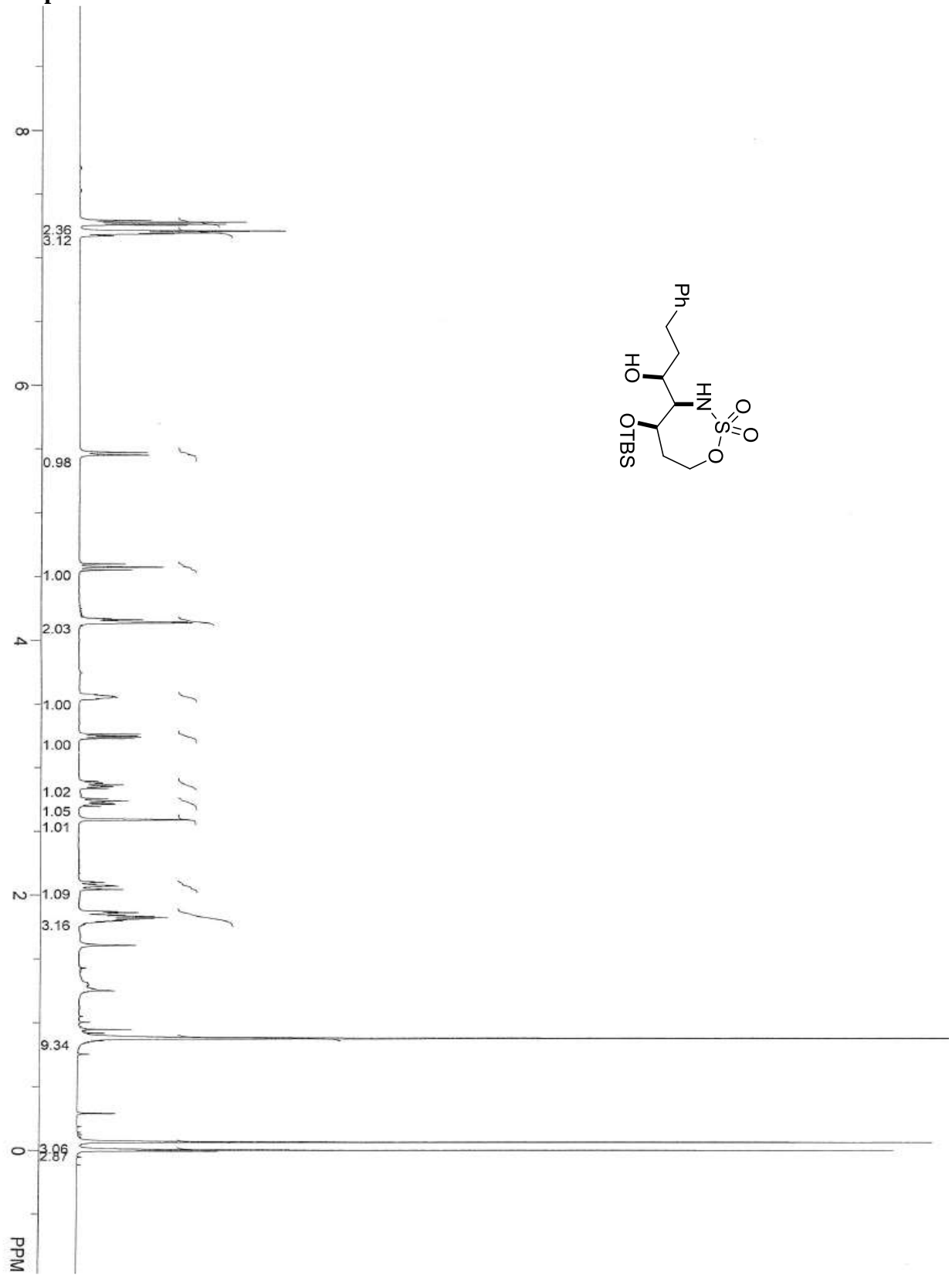

200
150
100
50
0
PPM
HO
HN
O
O
S
O
OTBS

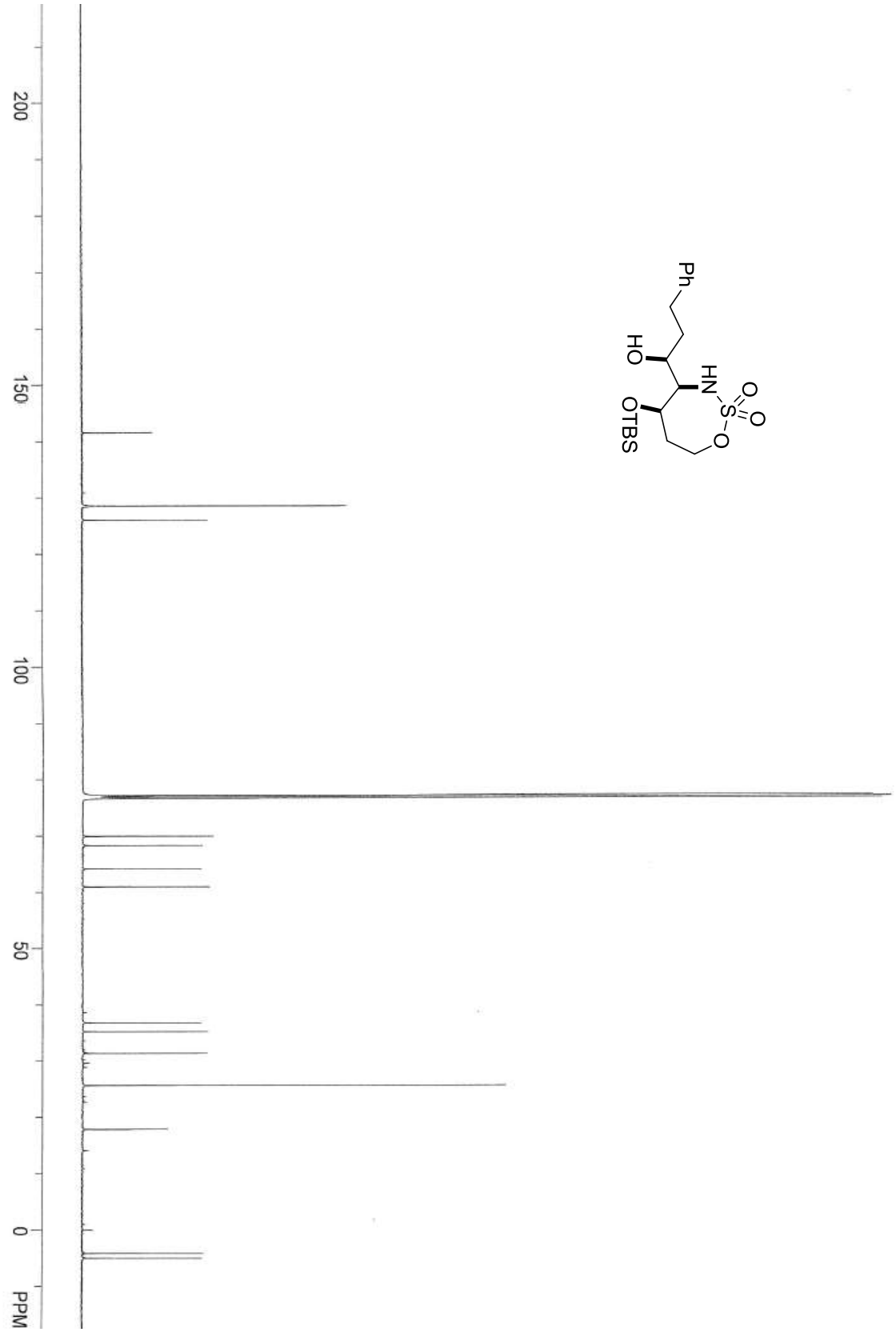
Compound 3.49.



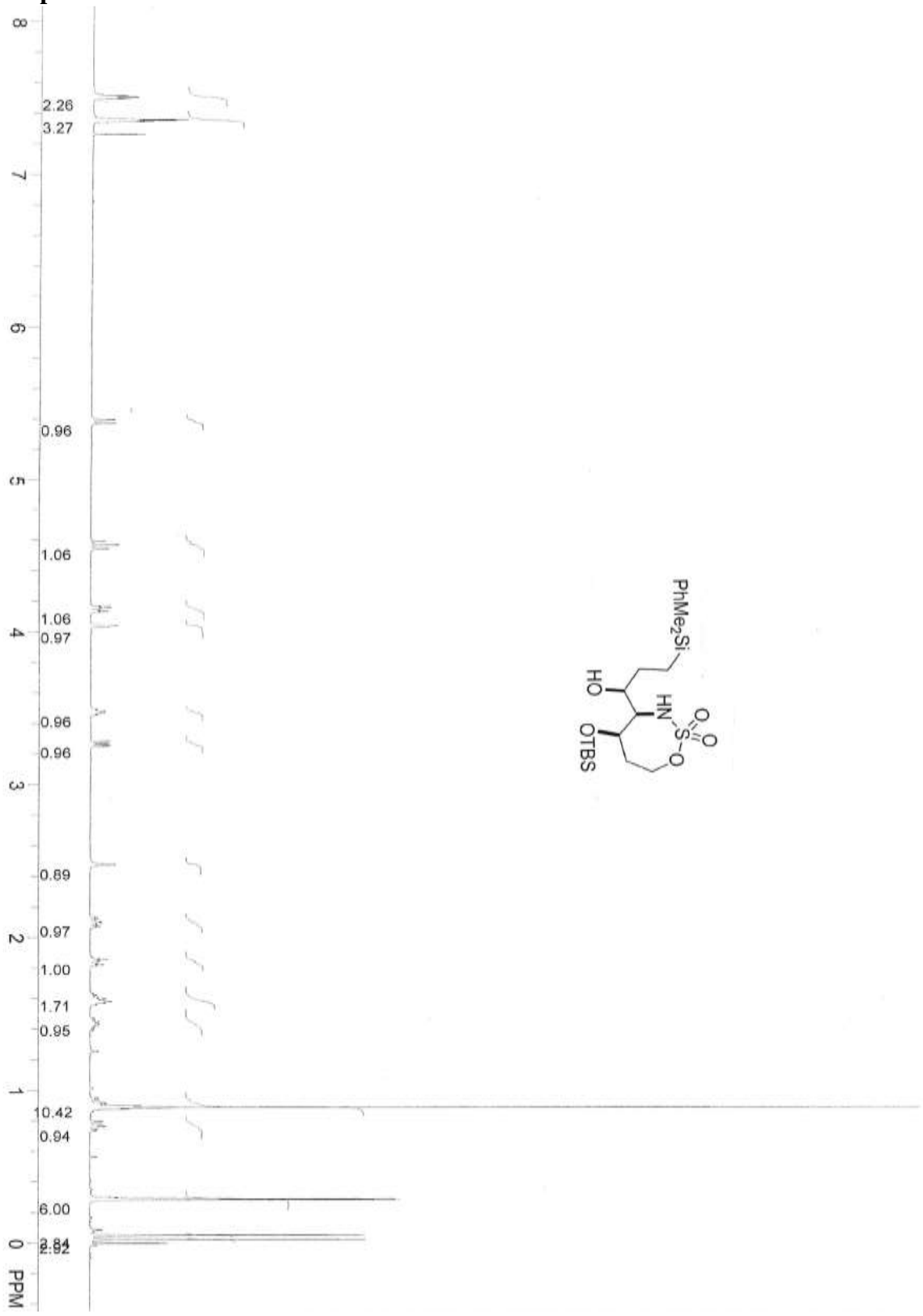

200
150
100
50
0
PPM
H11C5
HO
HN
S
O
O
O
OTBS

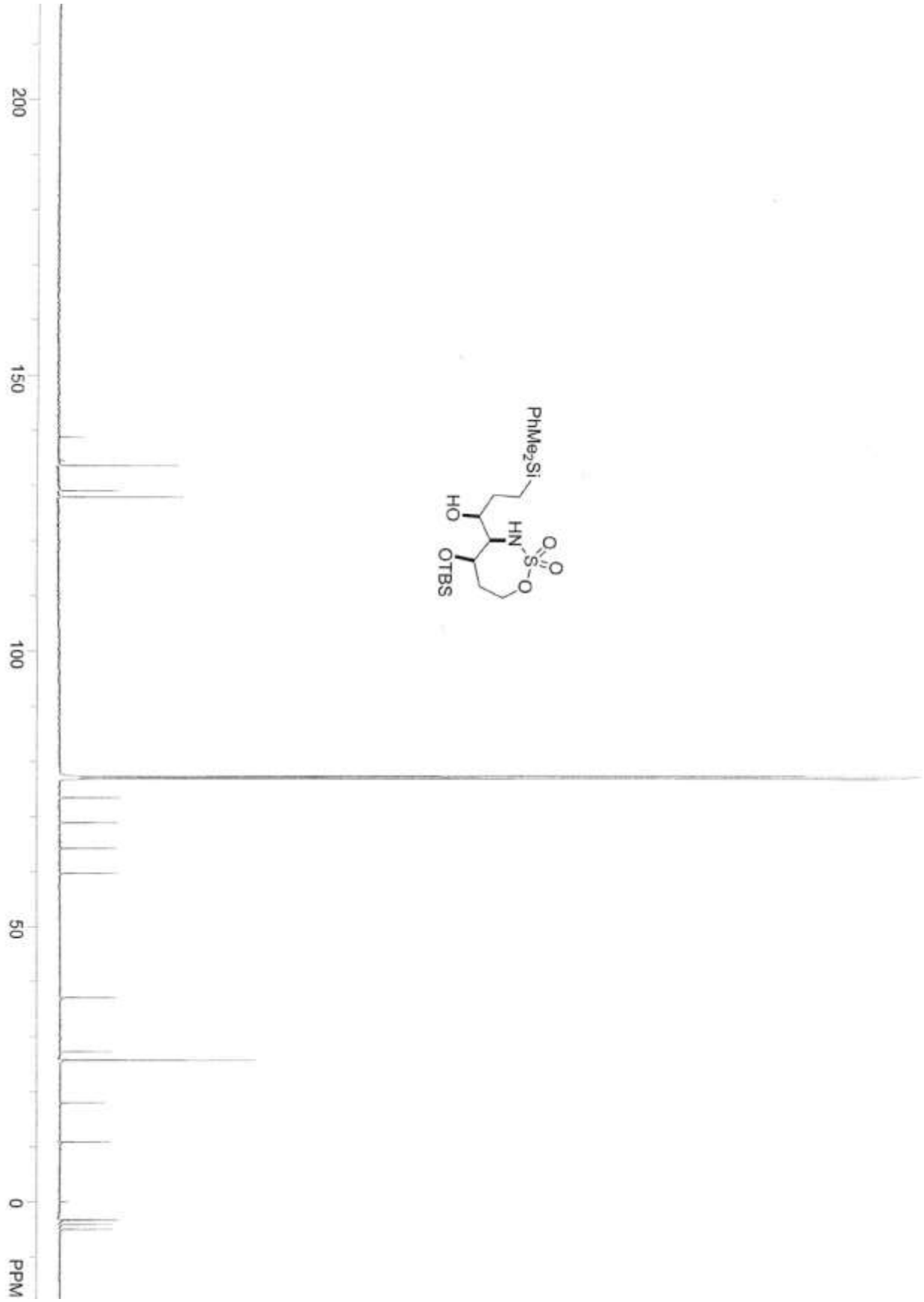
Compound 3.50.



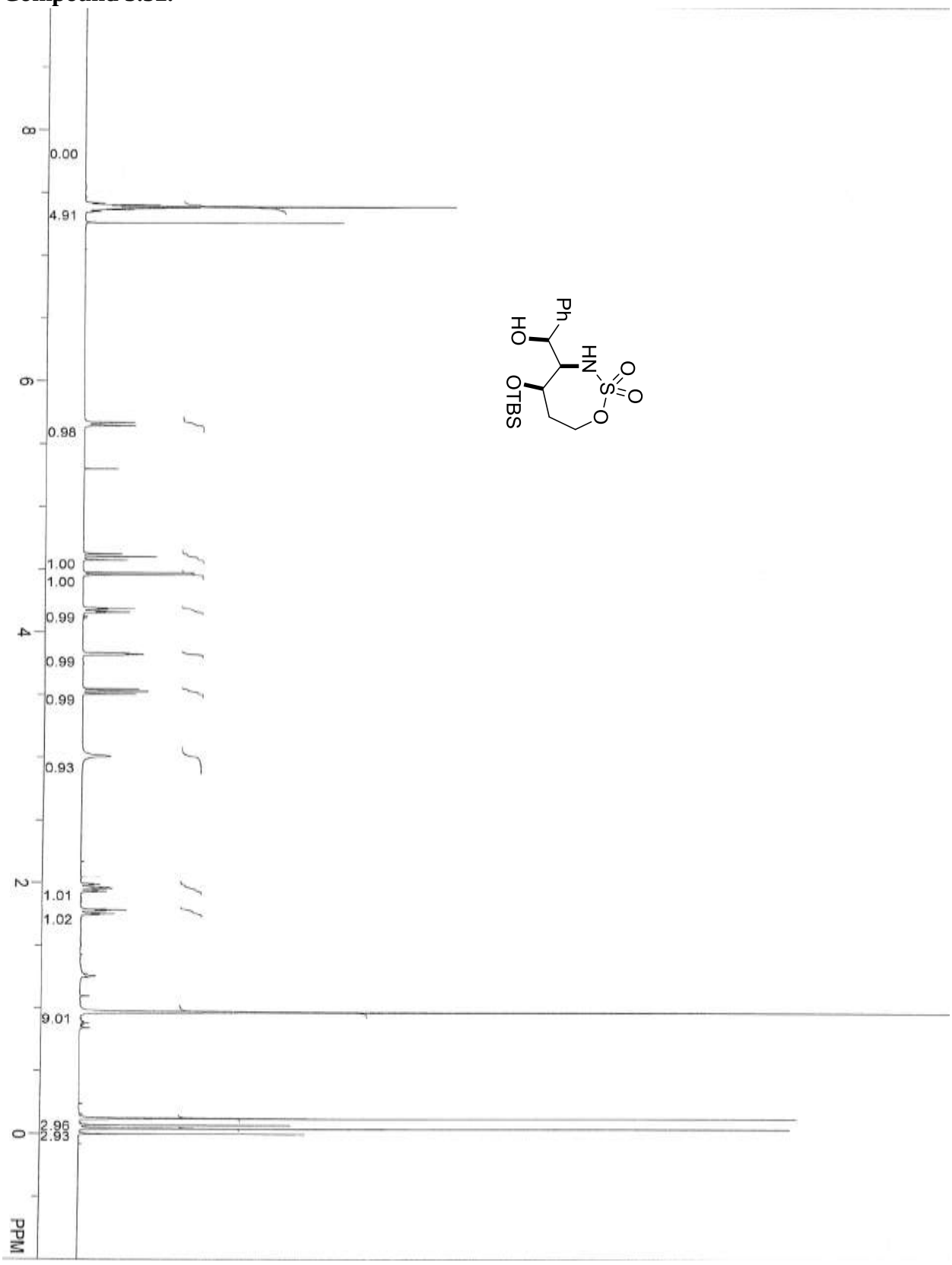

Ph
HO
HN
O
O
S
O
OTBS
200
150
100
50
0
PPM

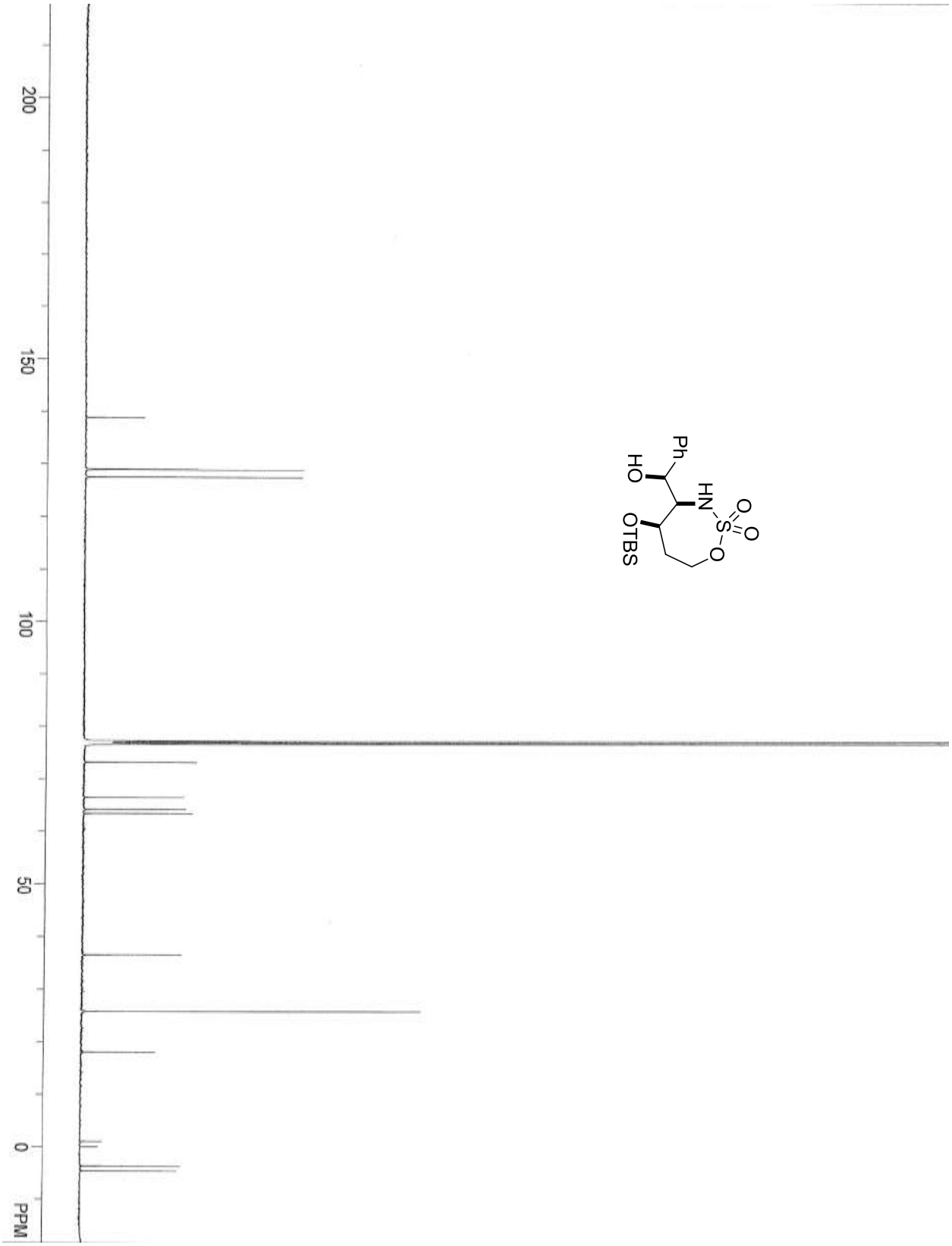
Compound 3.51.



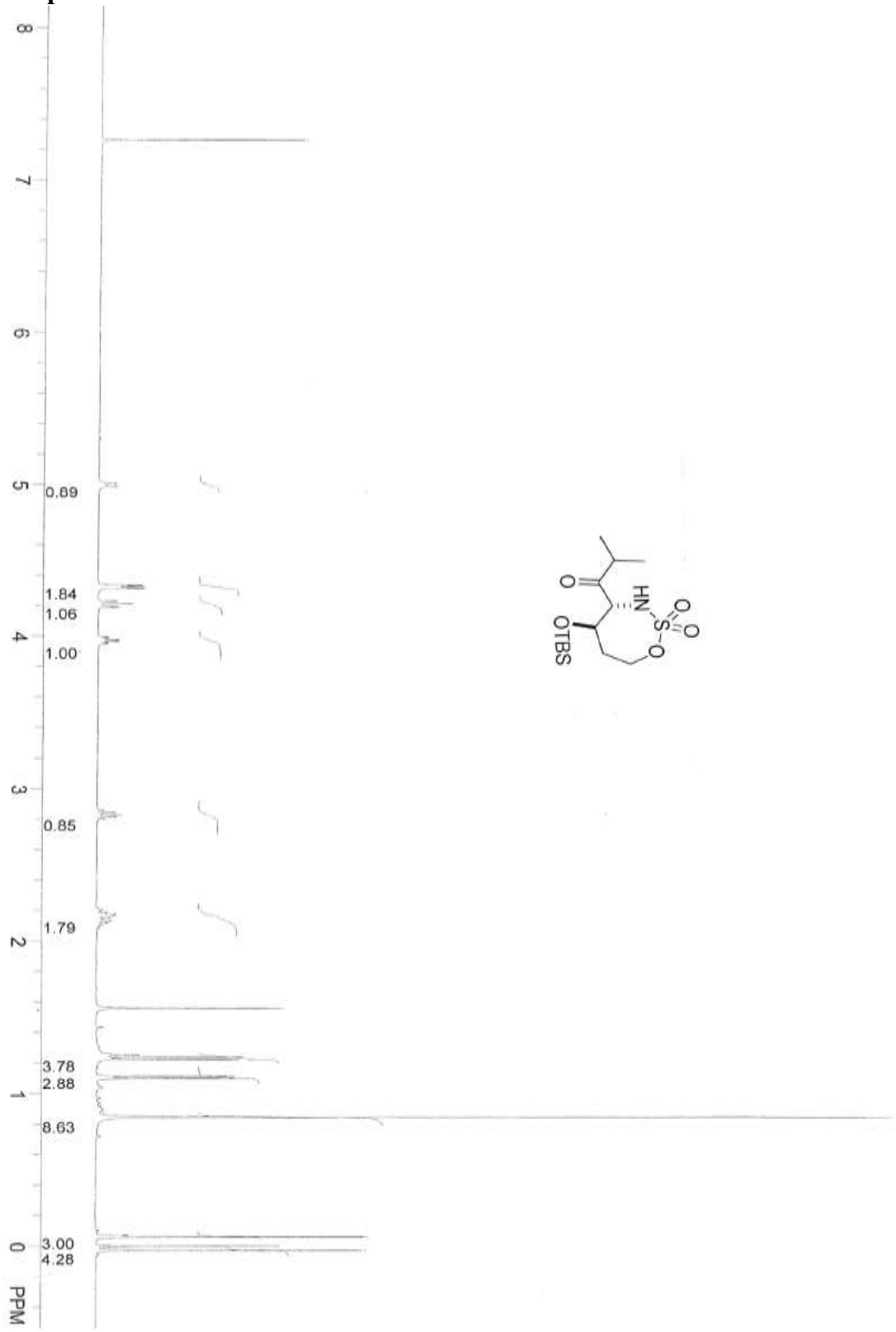

PhMe2Si
HO
HN
O
O
S
O
OTBS
200
150
100
50
0
PPM

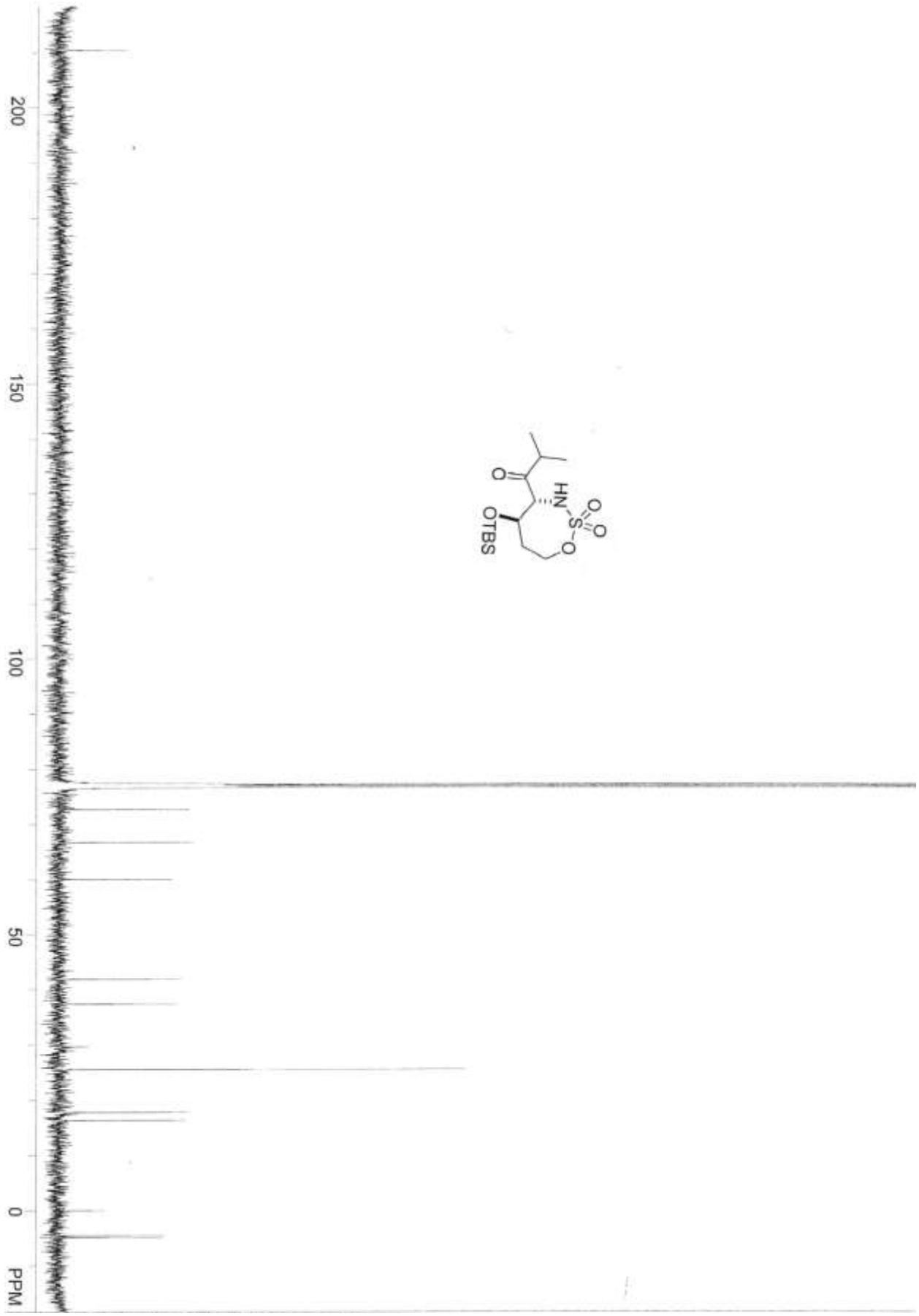
Compound 3.52.



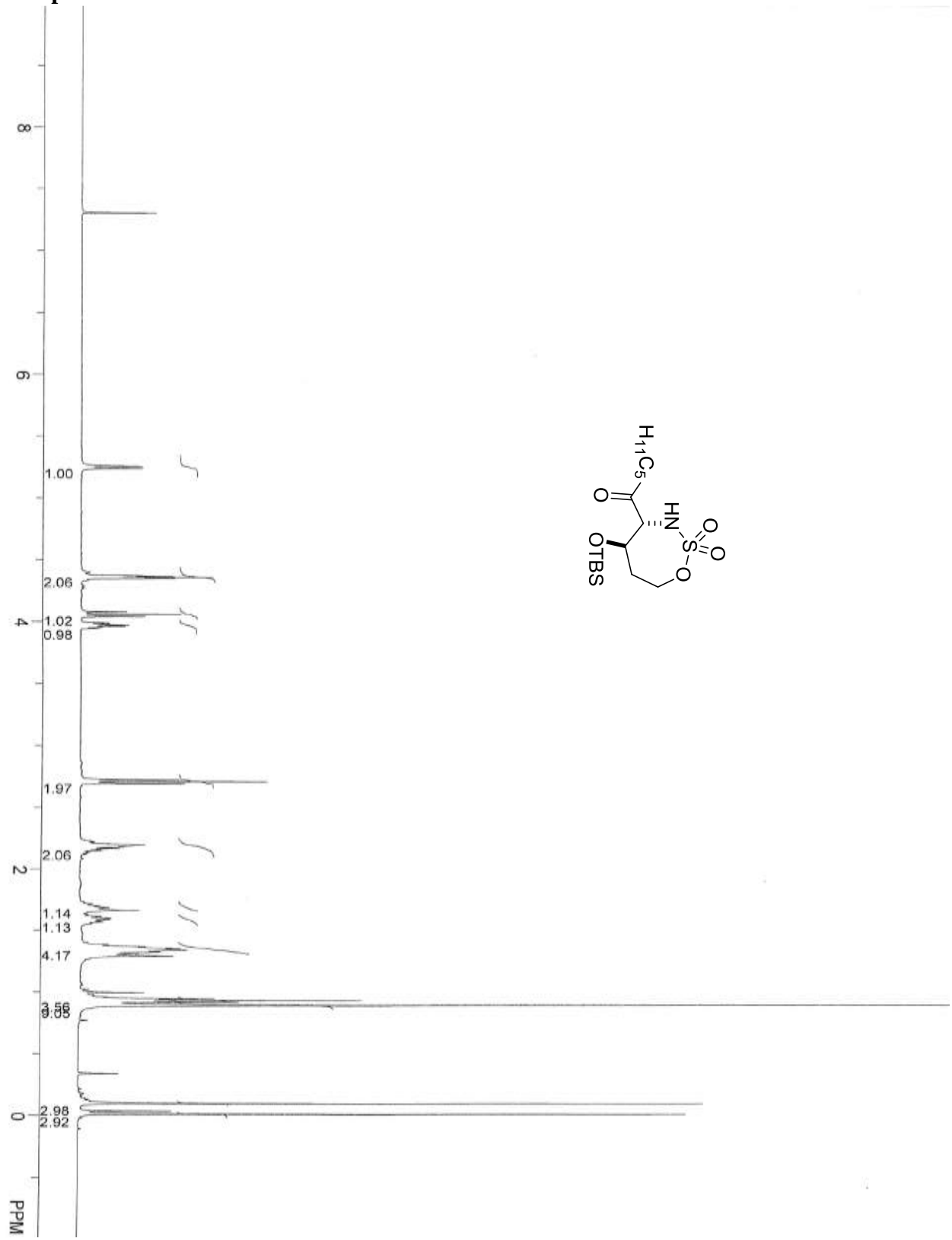

200
150
100
50
0
PPM
Ph
HO
HN
S
O
O
O
OTBS

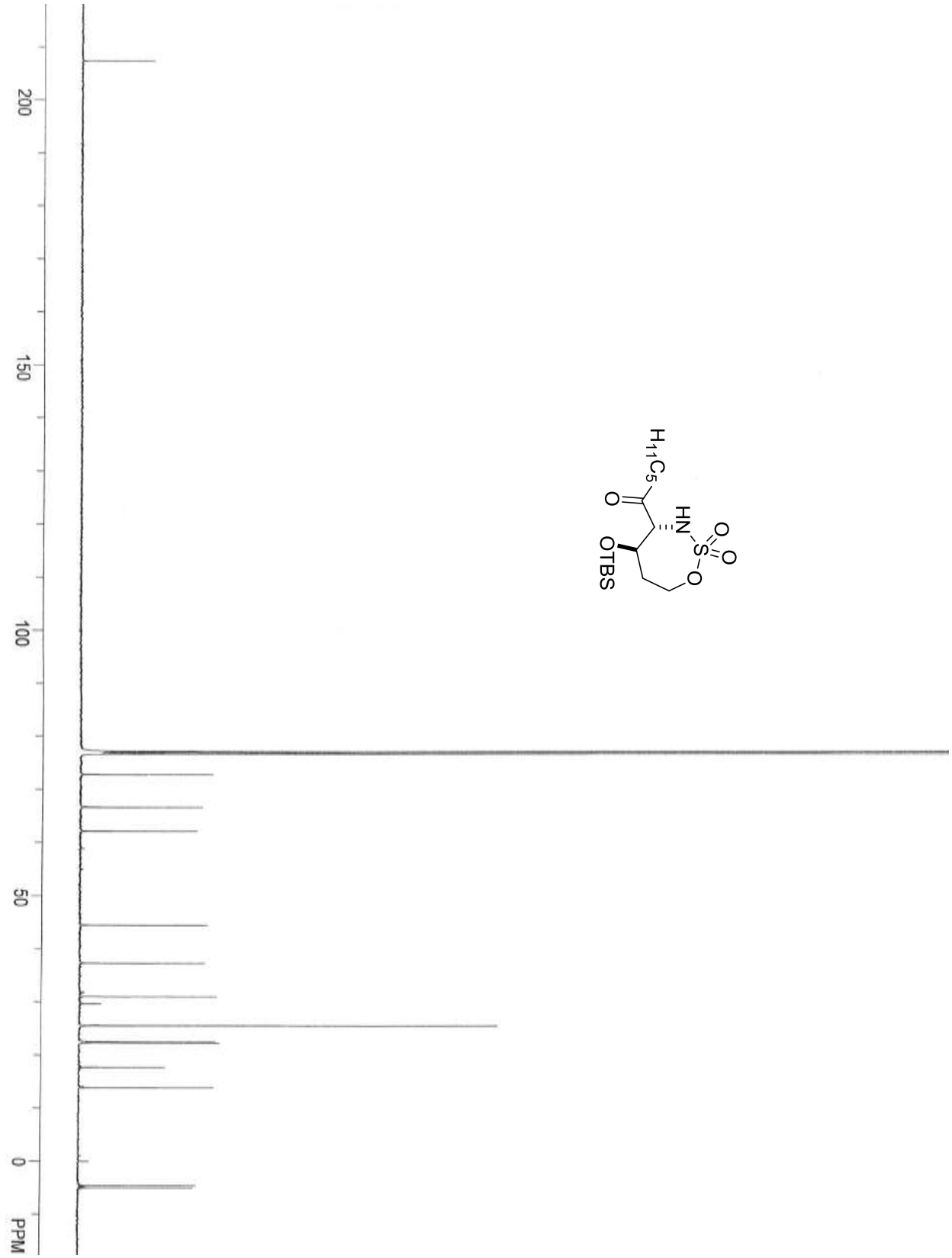
Compound 3.54.



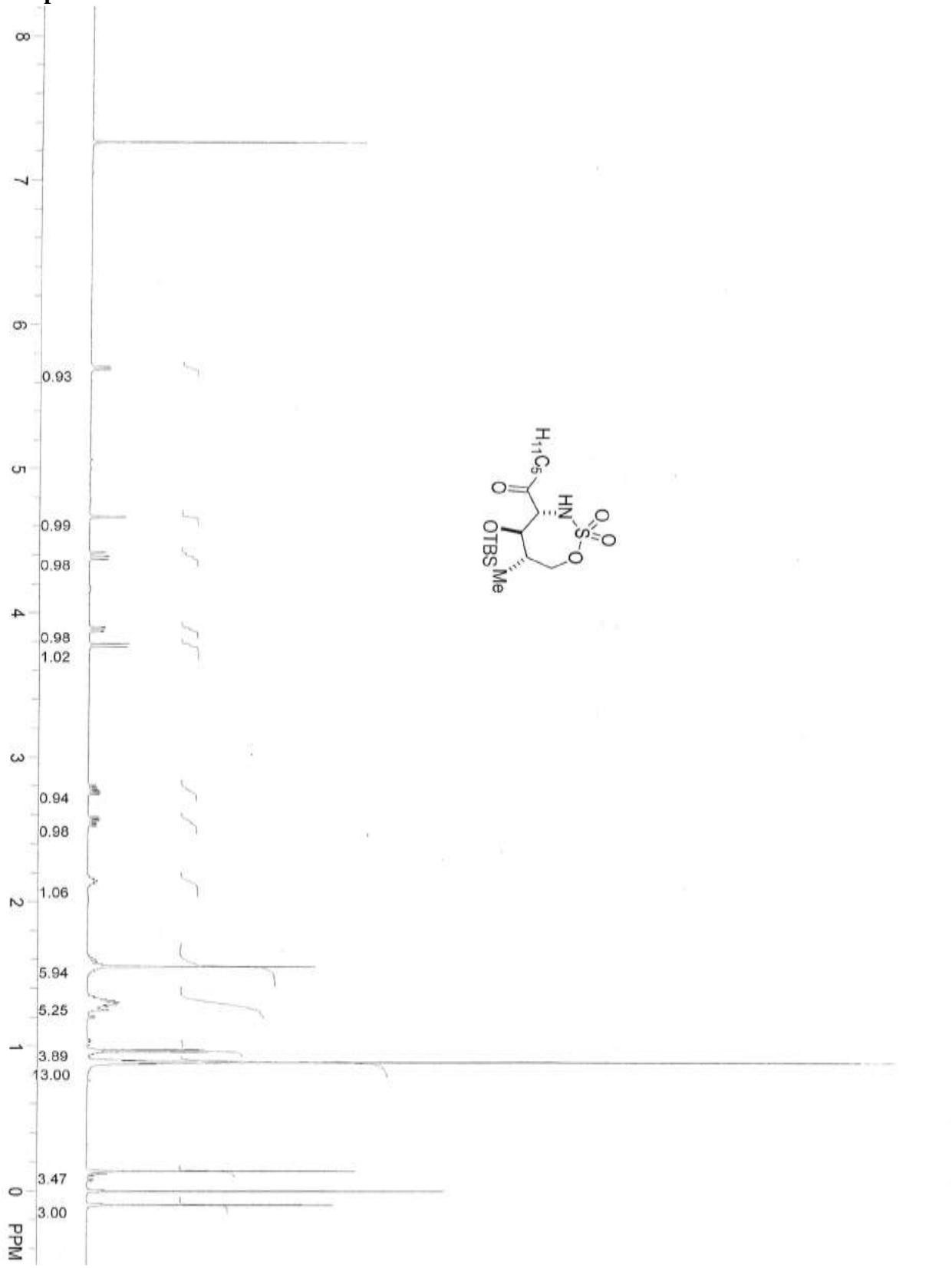

200
150
100
50
0
PPM
O
HN
S
O
O
O
OTBS

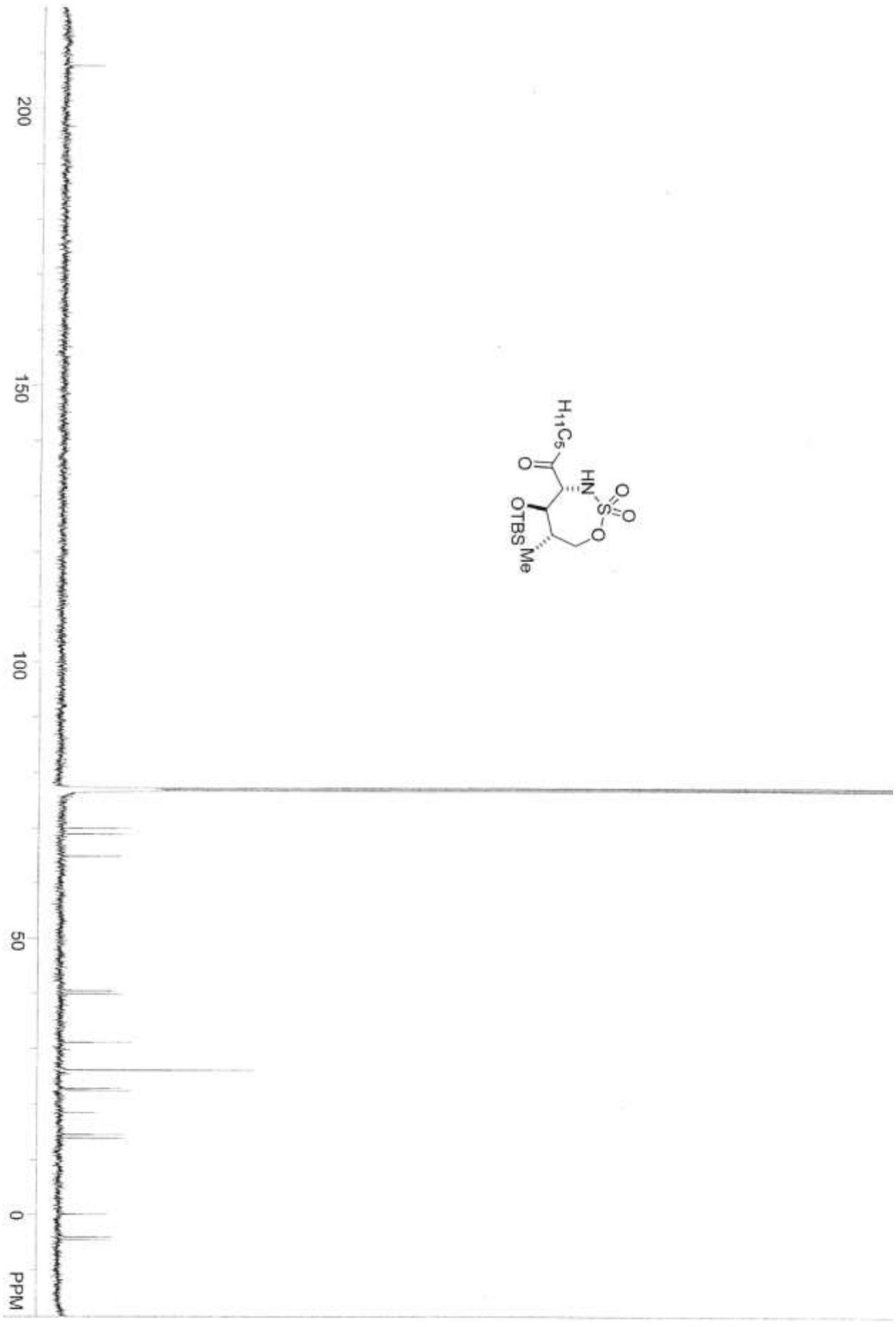
Compound 3.56.



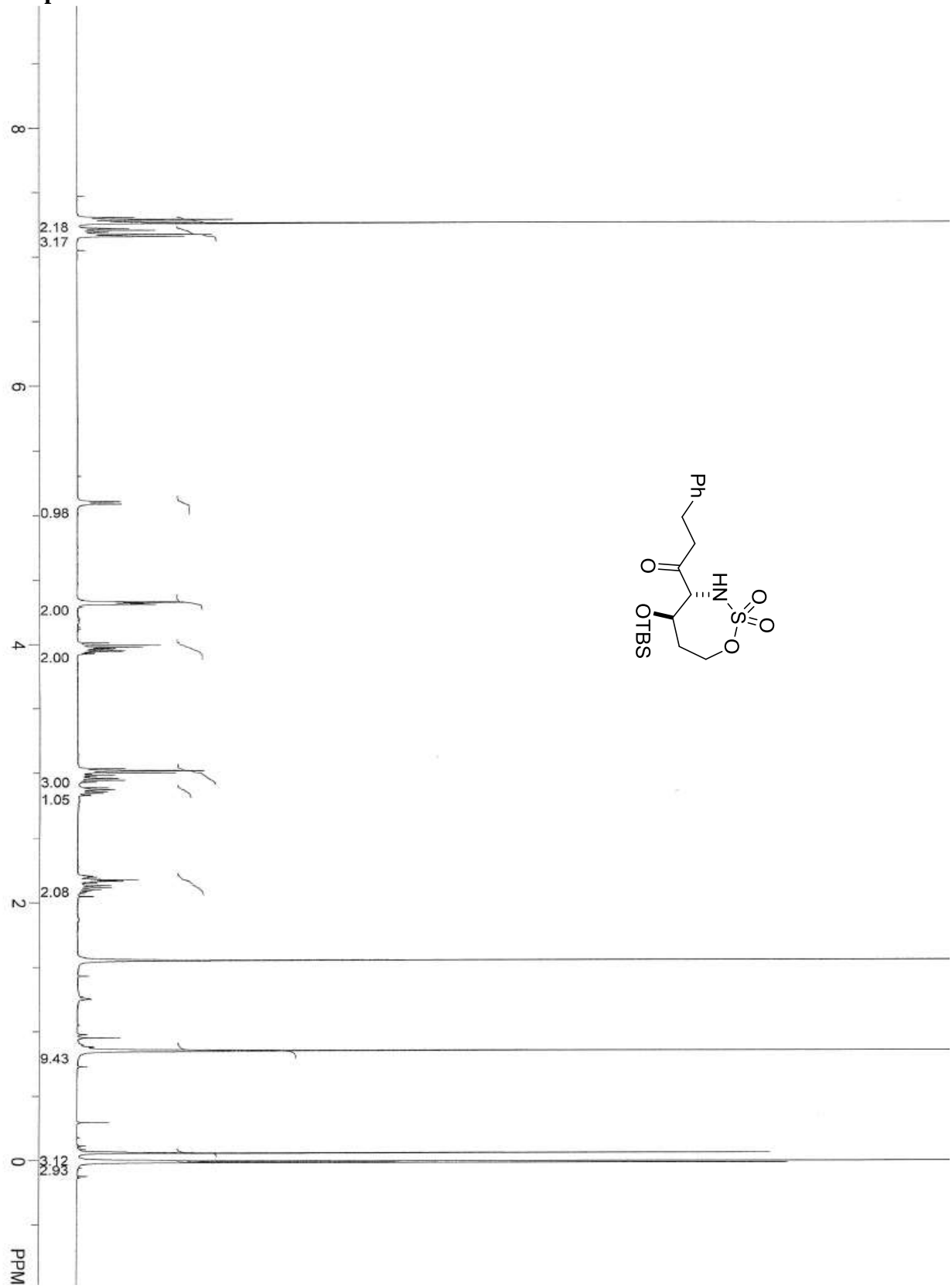

200
150
100
50
0
PPM
H11C5
O
HN
S
O
O
O
OTBS

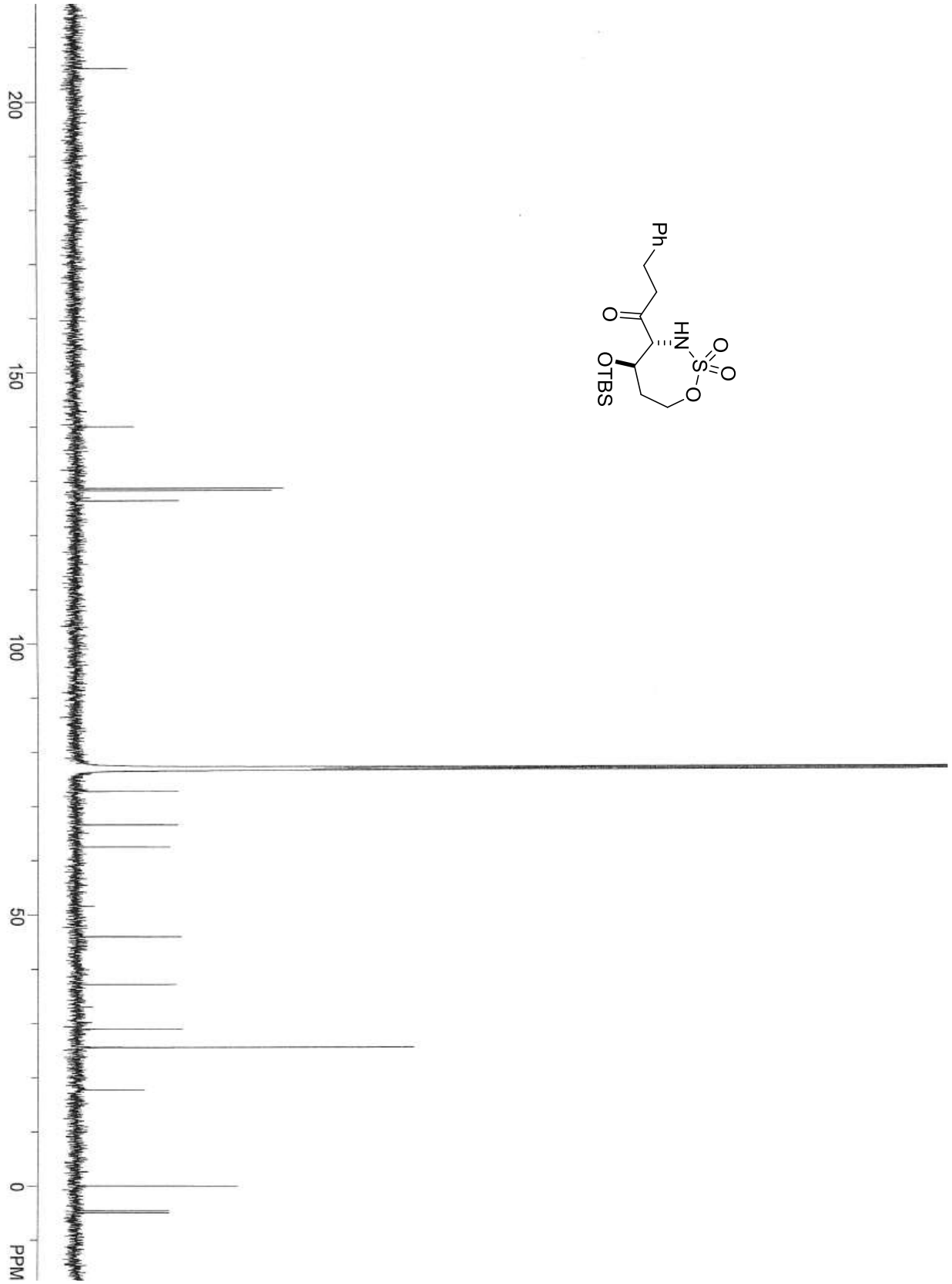
Compound 3.58.



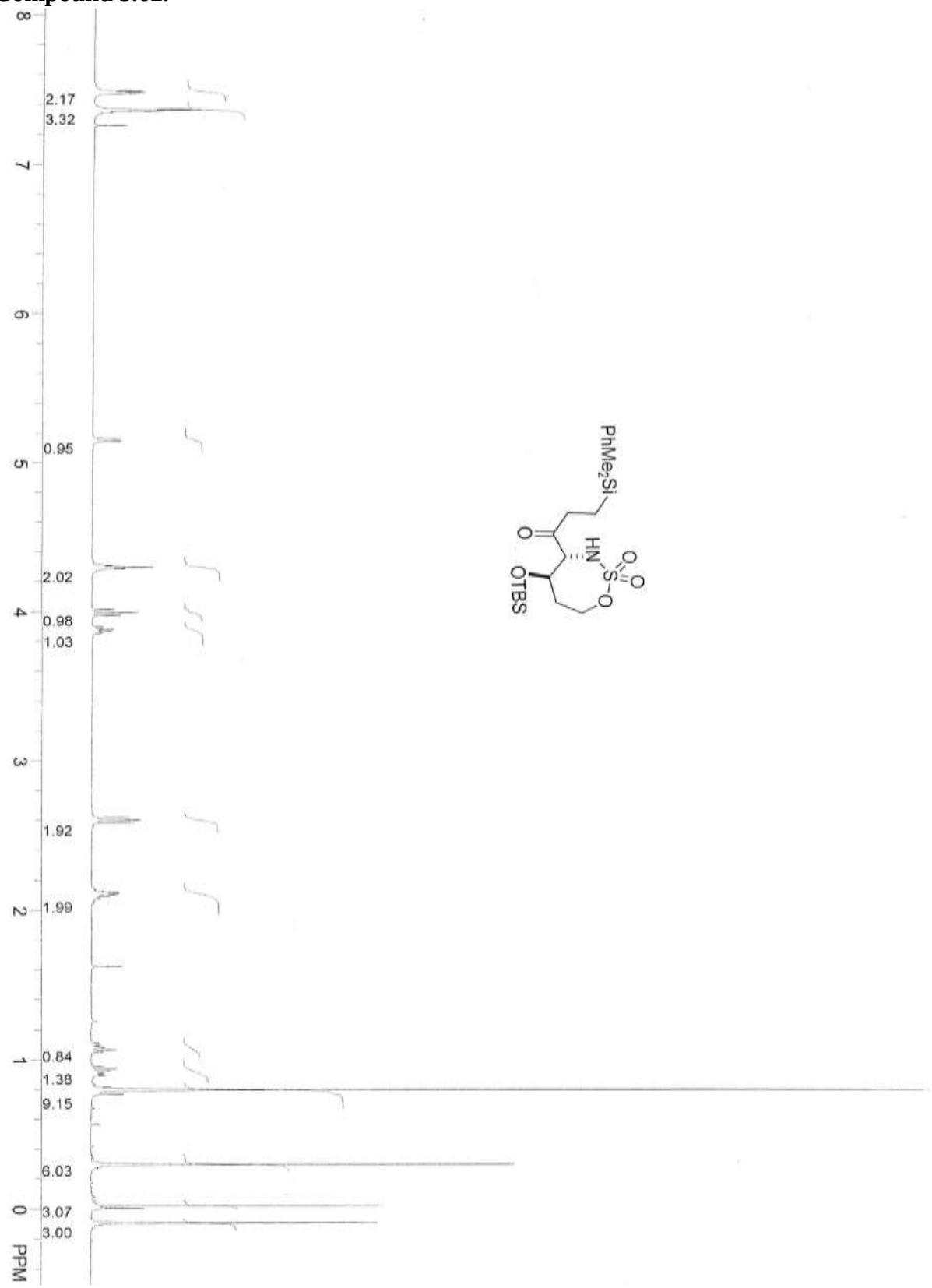

200
150
100
50
0
PPM
H11C5
O
HN
S
O
O
O
OTBS
Me

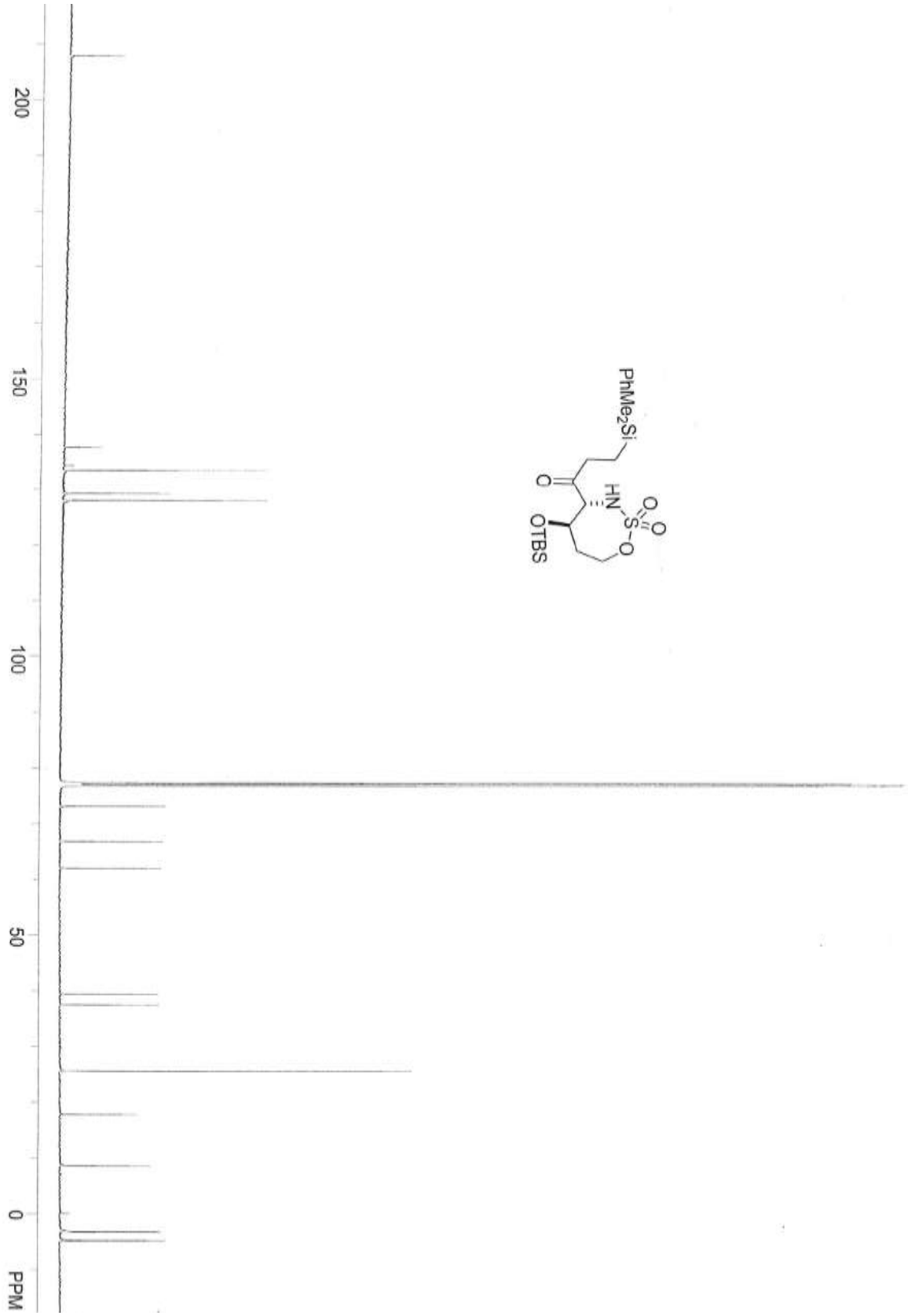
Compound 3.60.



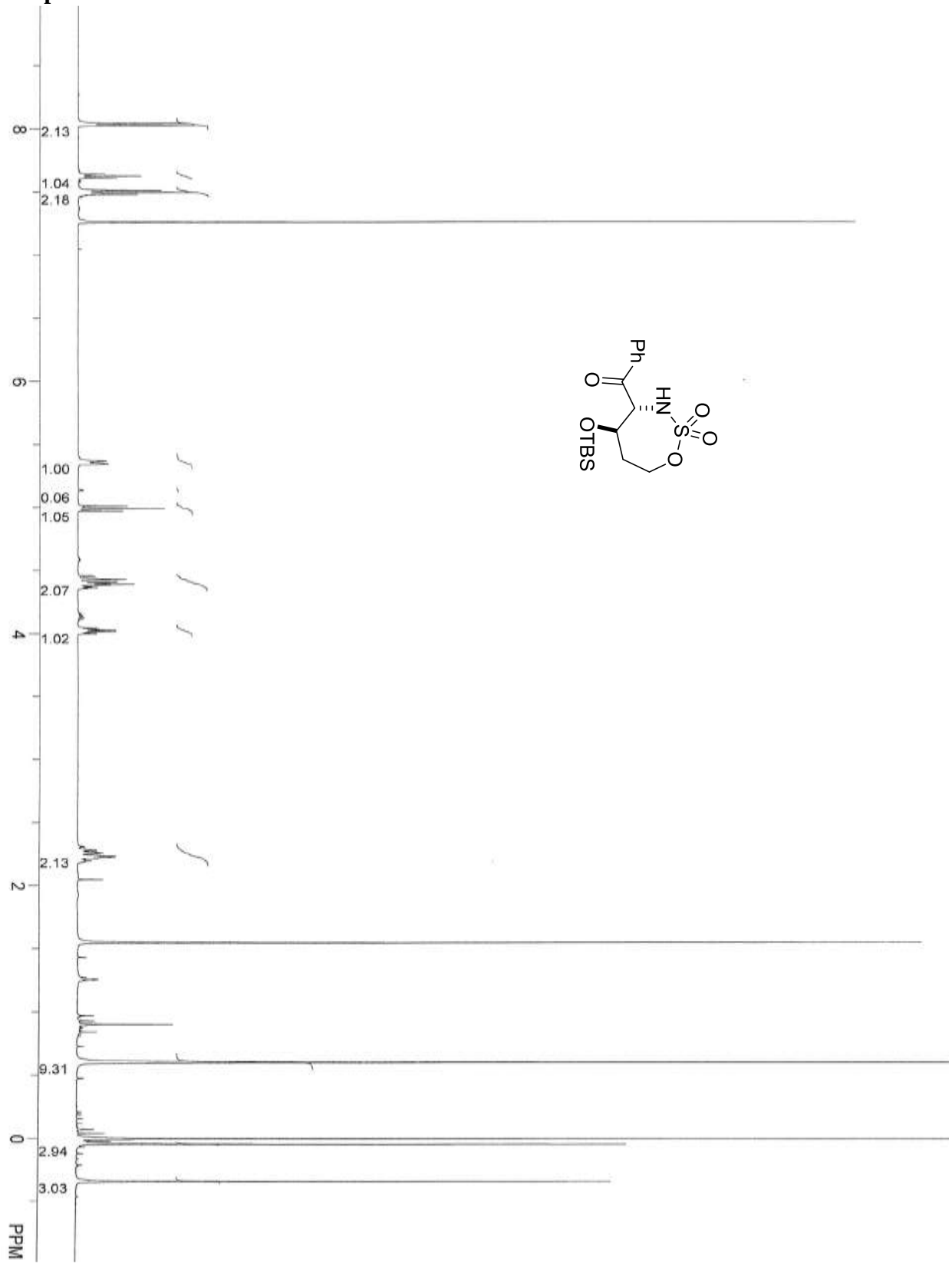

Ph
O
HN
O
O
S
O
OTBS
200
150
100
50
0
PPM

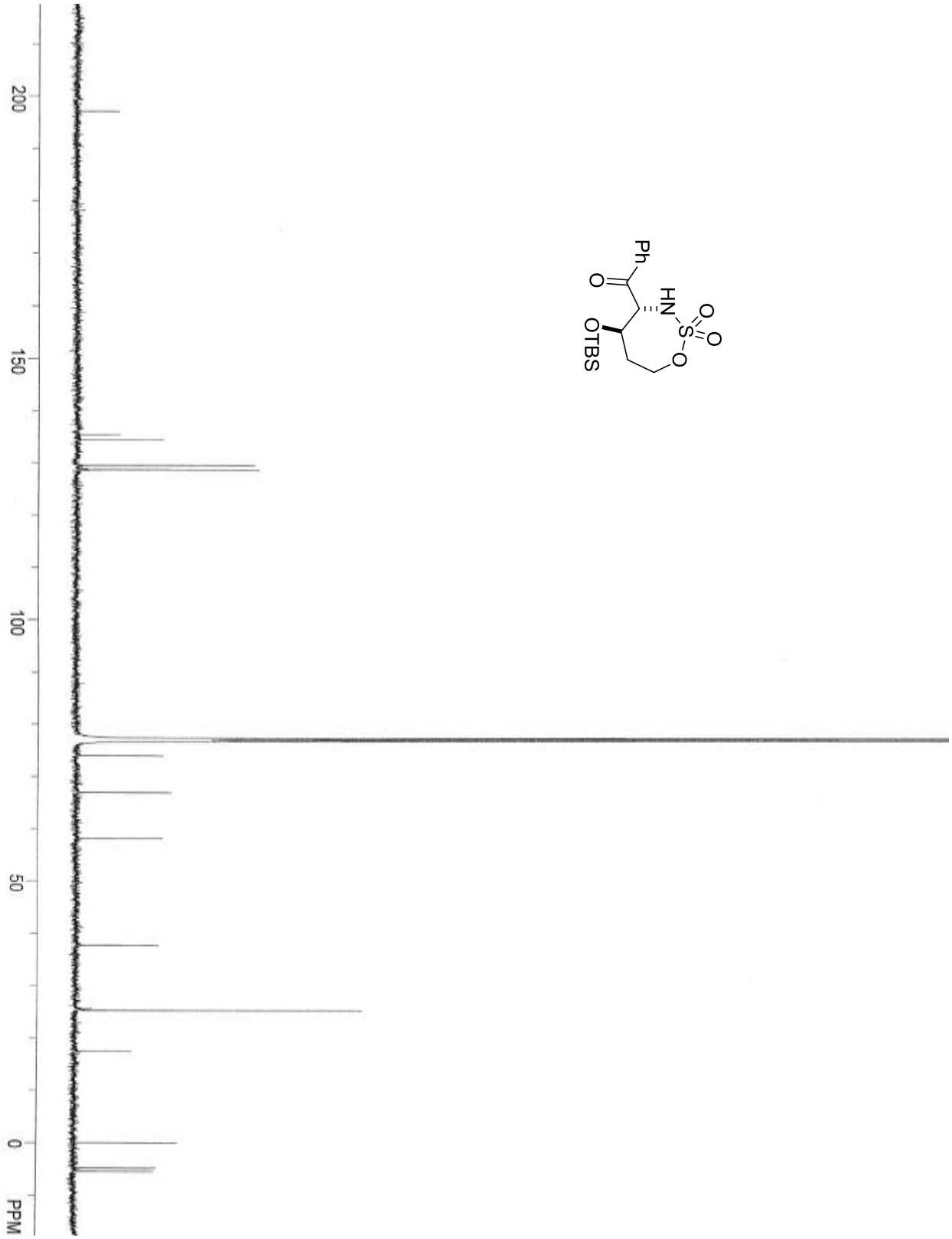
Compound 3.62.



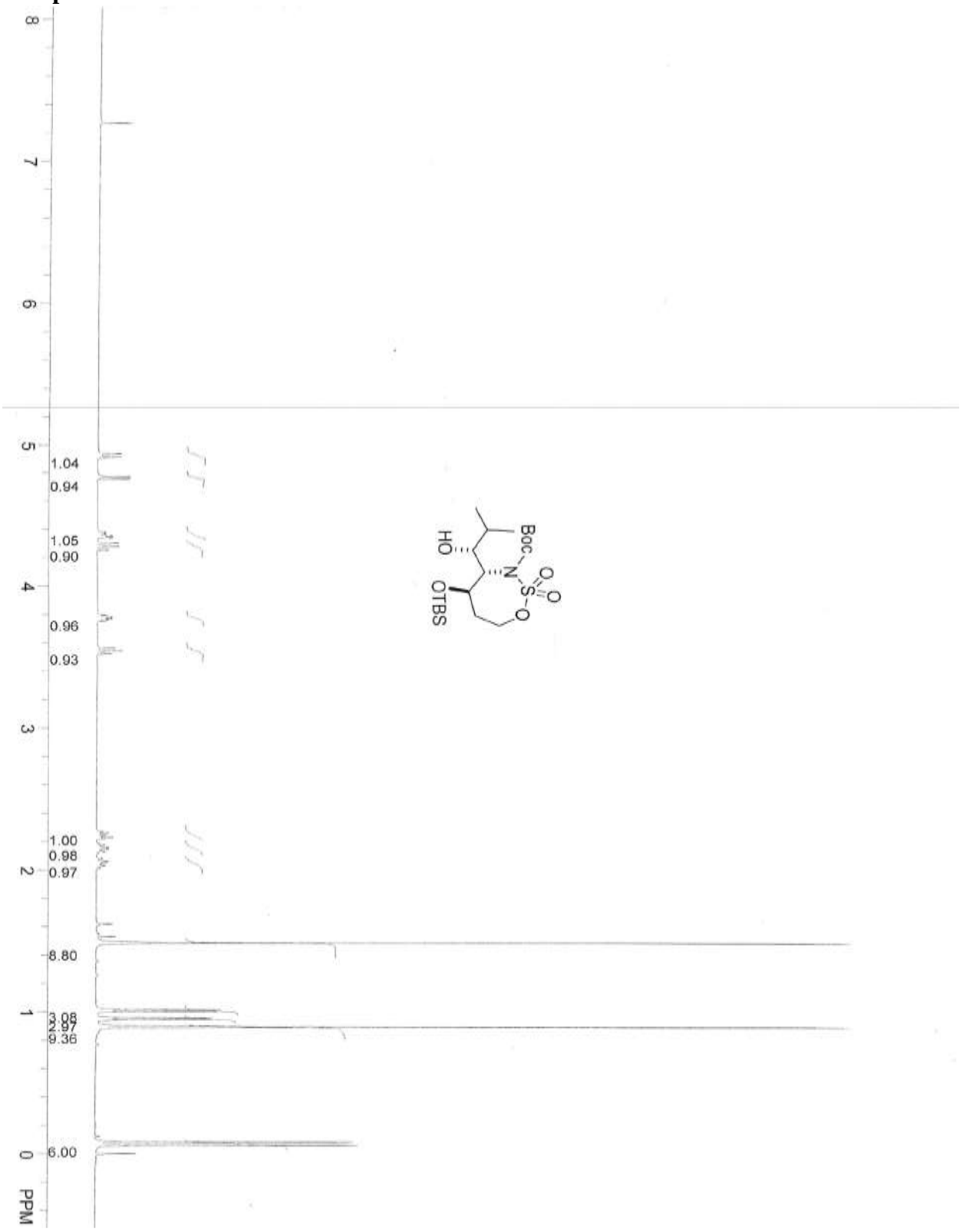

PhMe2Si
O
HN
S
O
O
O
OTBS
200
150
100
50
0
PPM

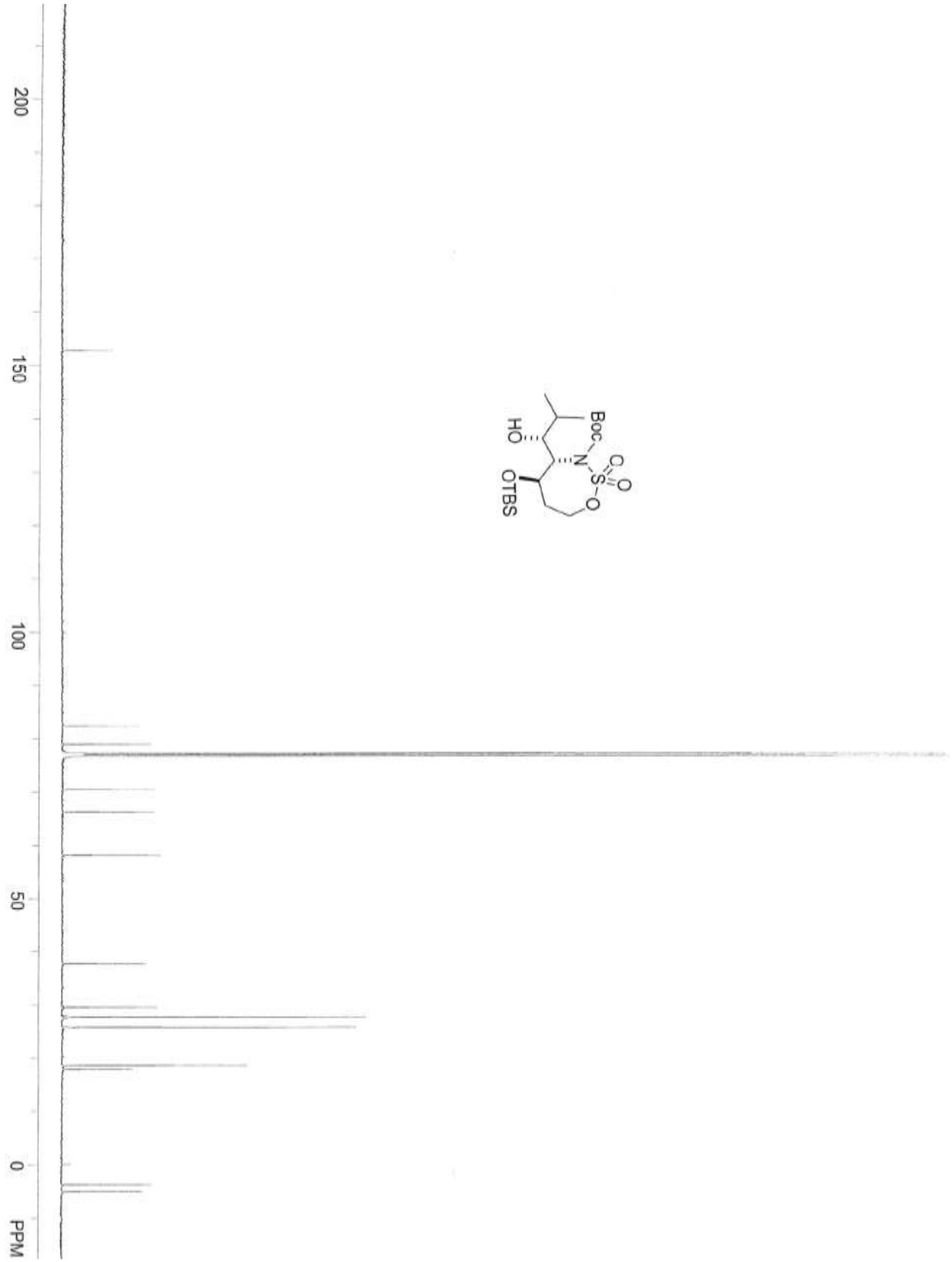
Compound 3.64.



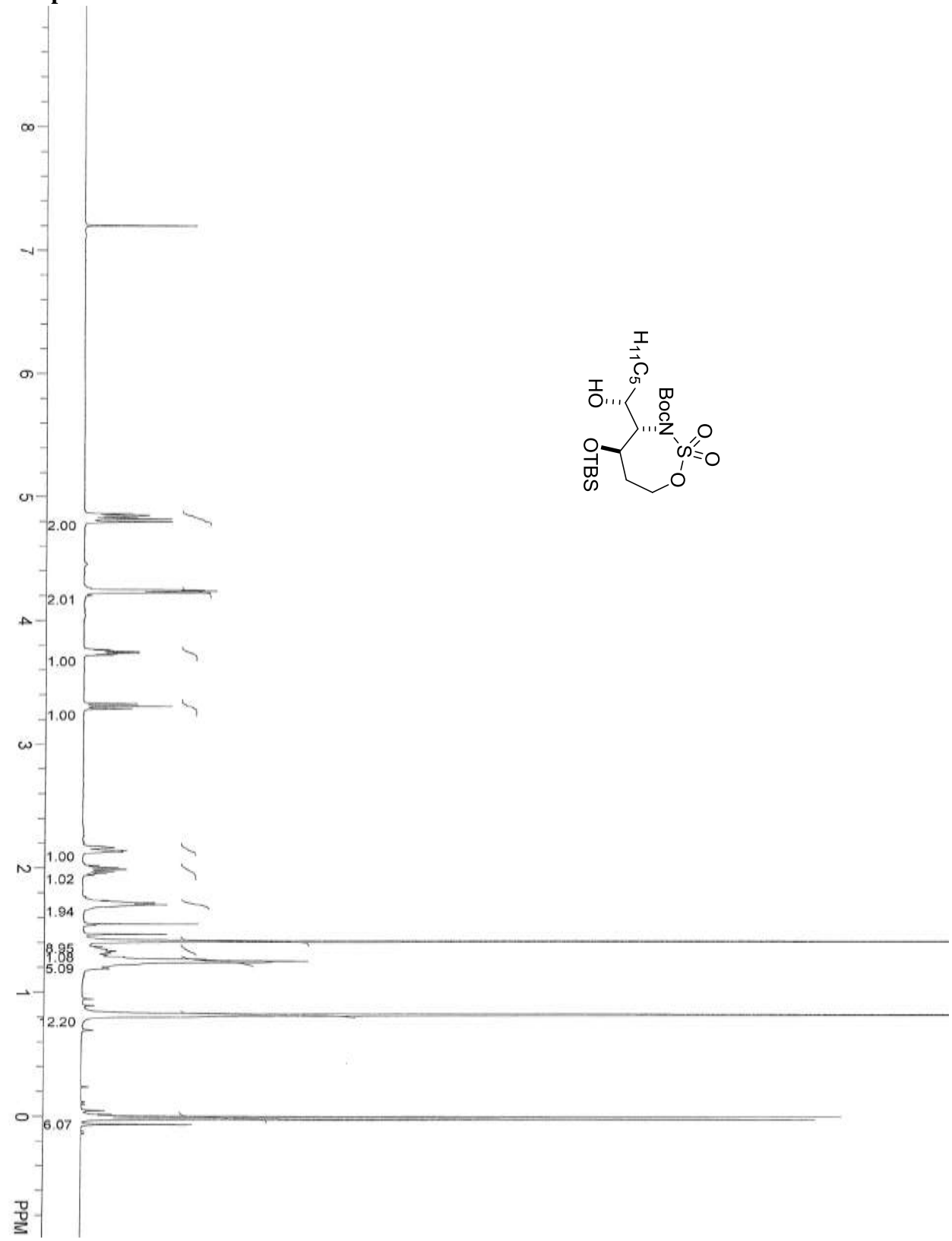

Ph
O
HN
S
O
O
O
OTBS
200
150
100
50
0
PPM

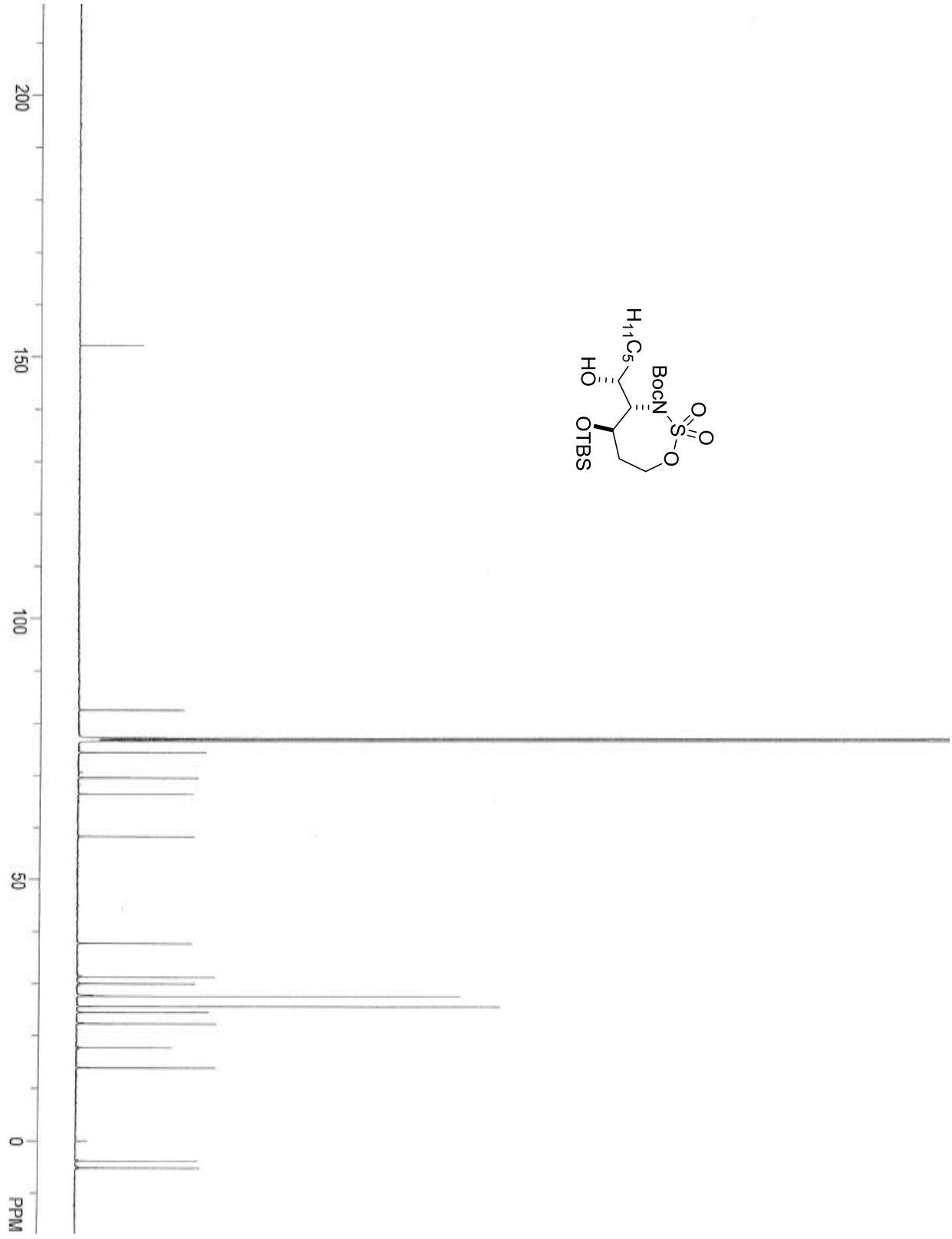
Compound 3.55.



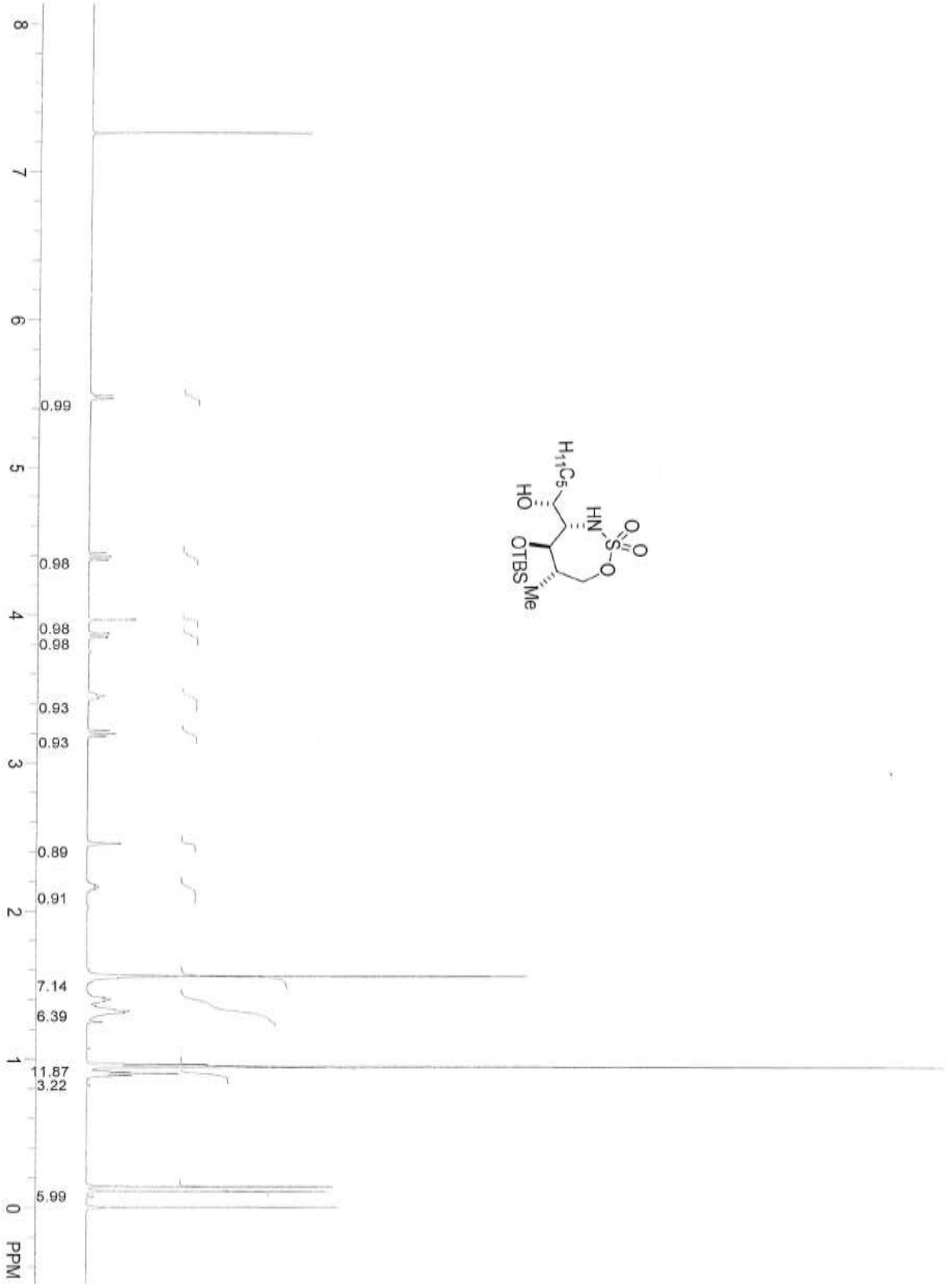

200
150
100
50
0
PPM
HO
Boc
N
S
O
O
OTBS

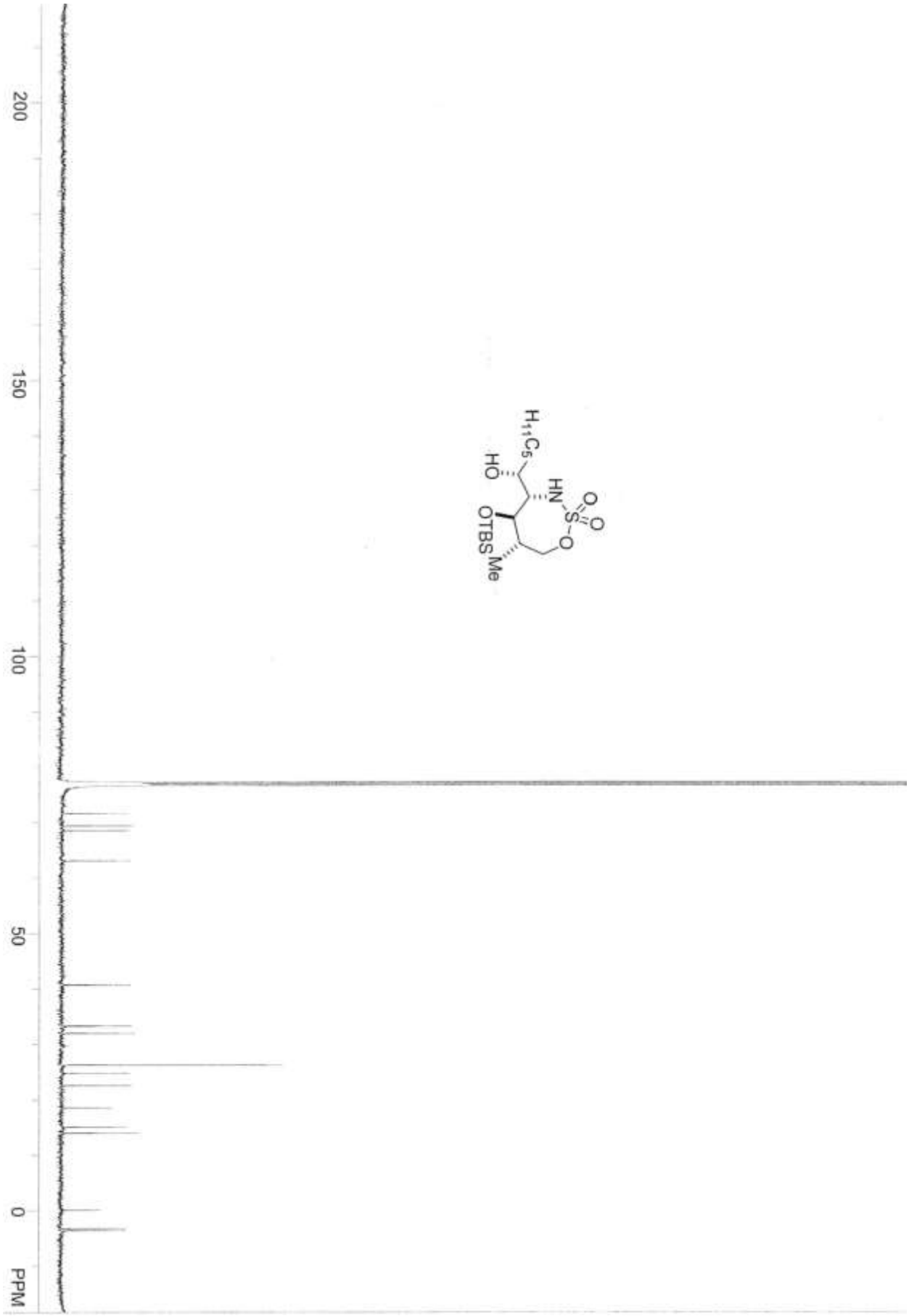
Compound 3.57.



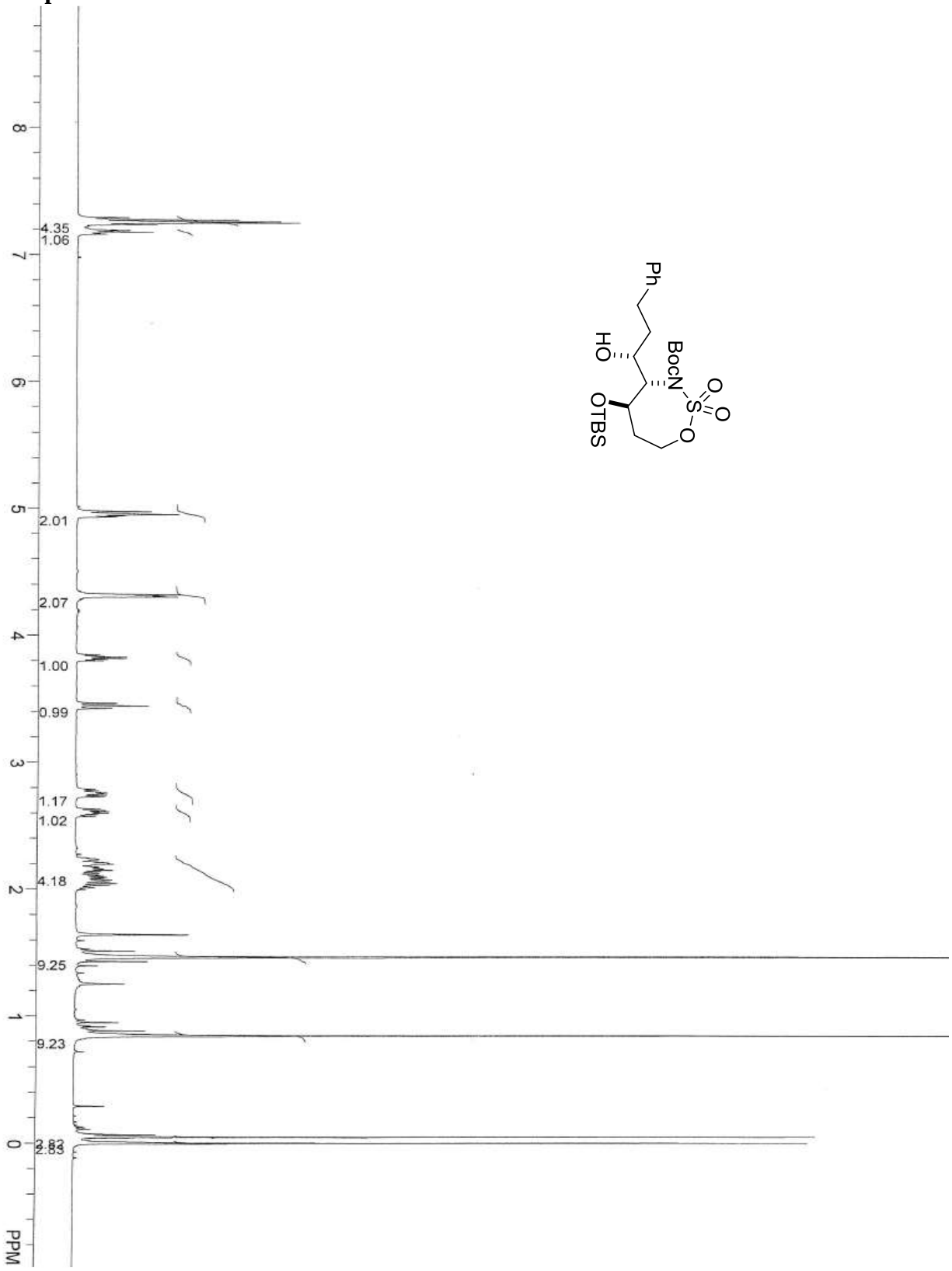

200
150
100
50
0
PPM
H11C5
HO
OTBS
BocN
S
O
O
O

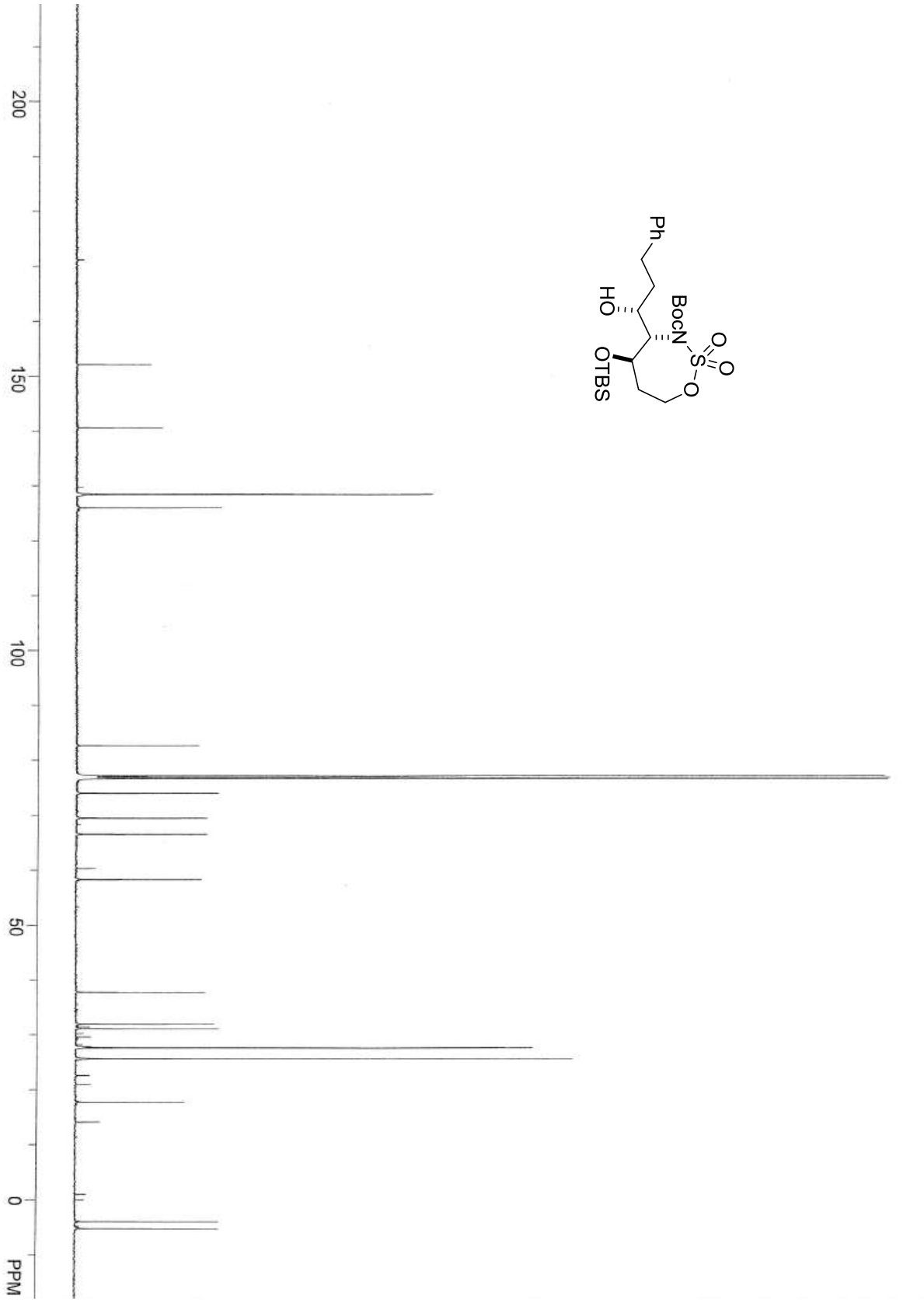
Compound 3.59.



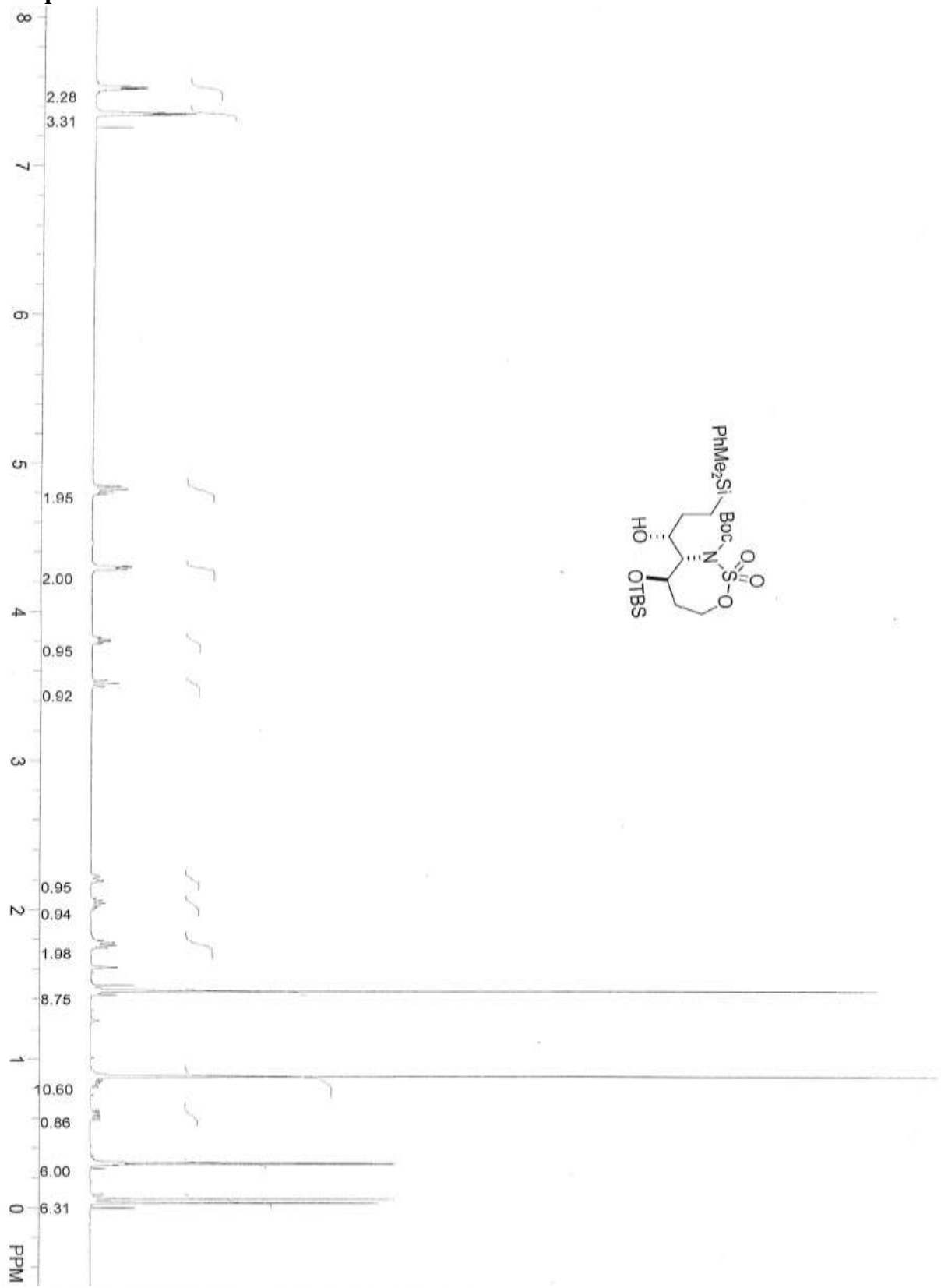

200
150
100
50
0
PPM
H11C5
HO
HN
O
O
S
O
OTBS
Me

Compound 3.61.



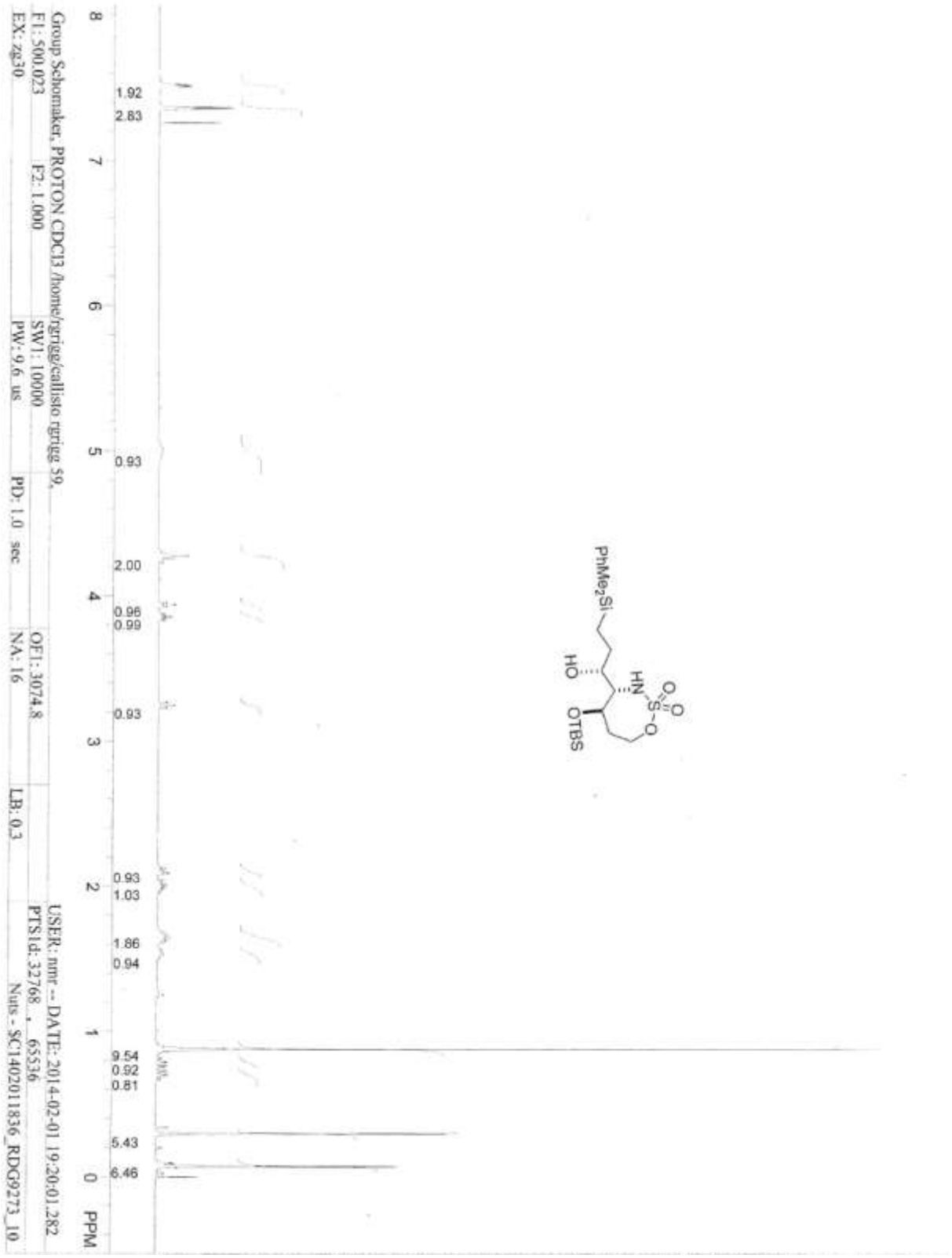

Ph
HO
BocN
S
O
O
O
OTBS
200
150
100
50
0
PPM

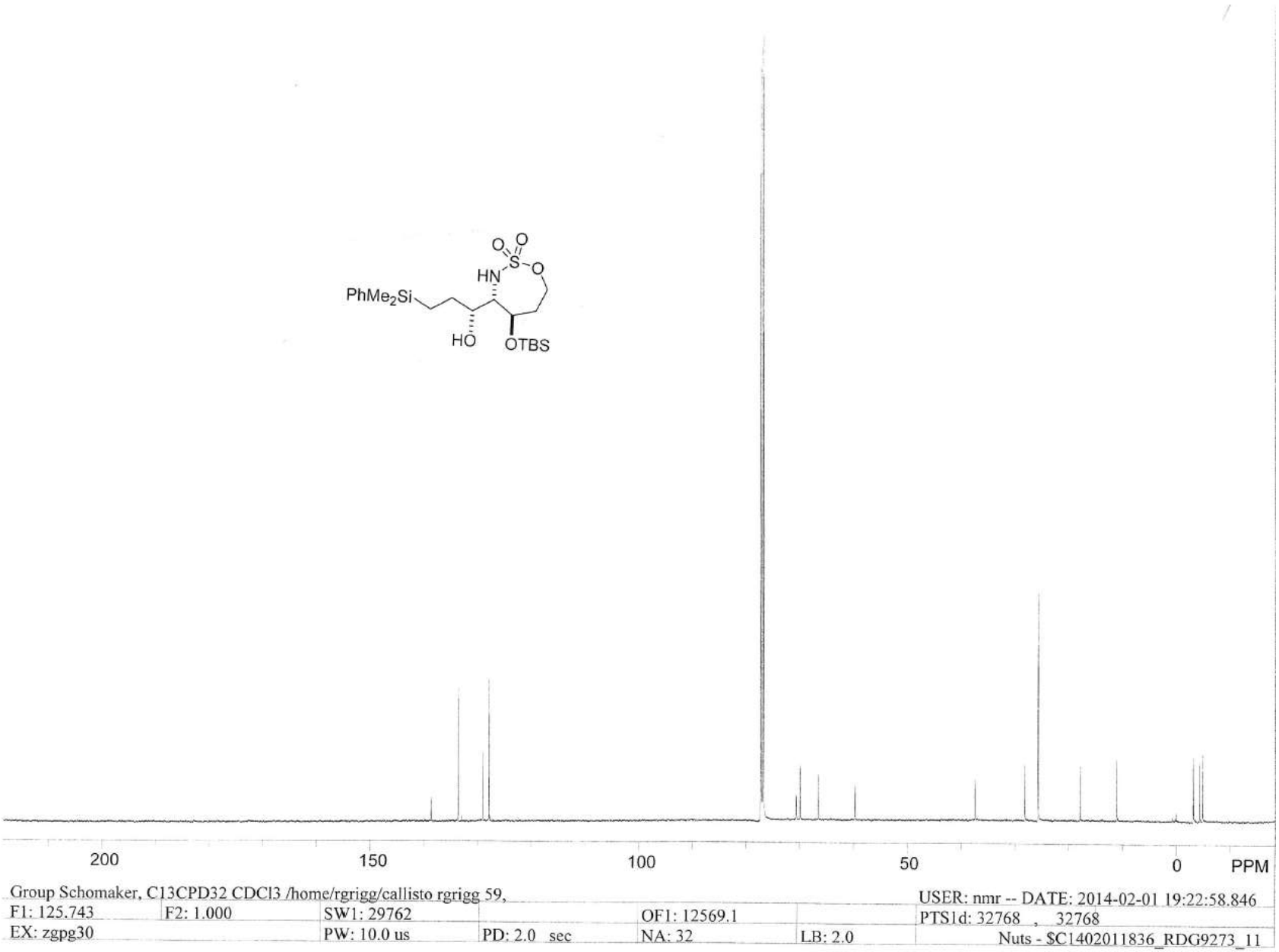
Compound 3.63.



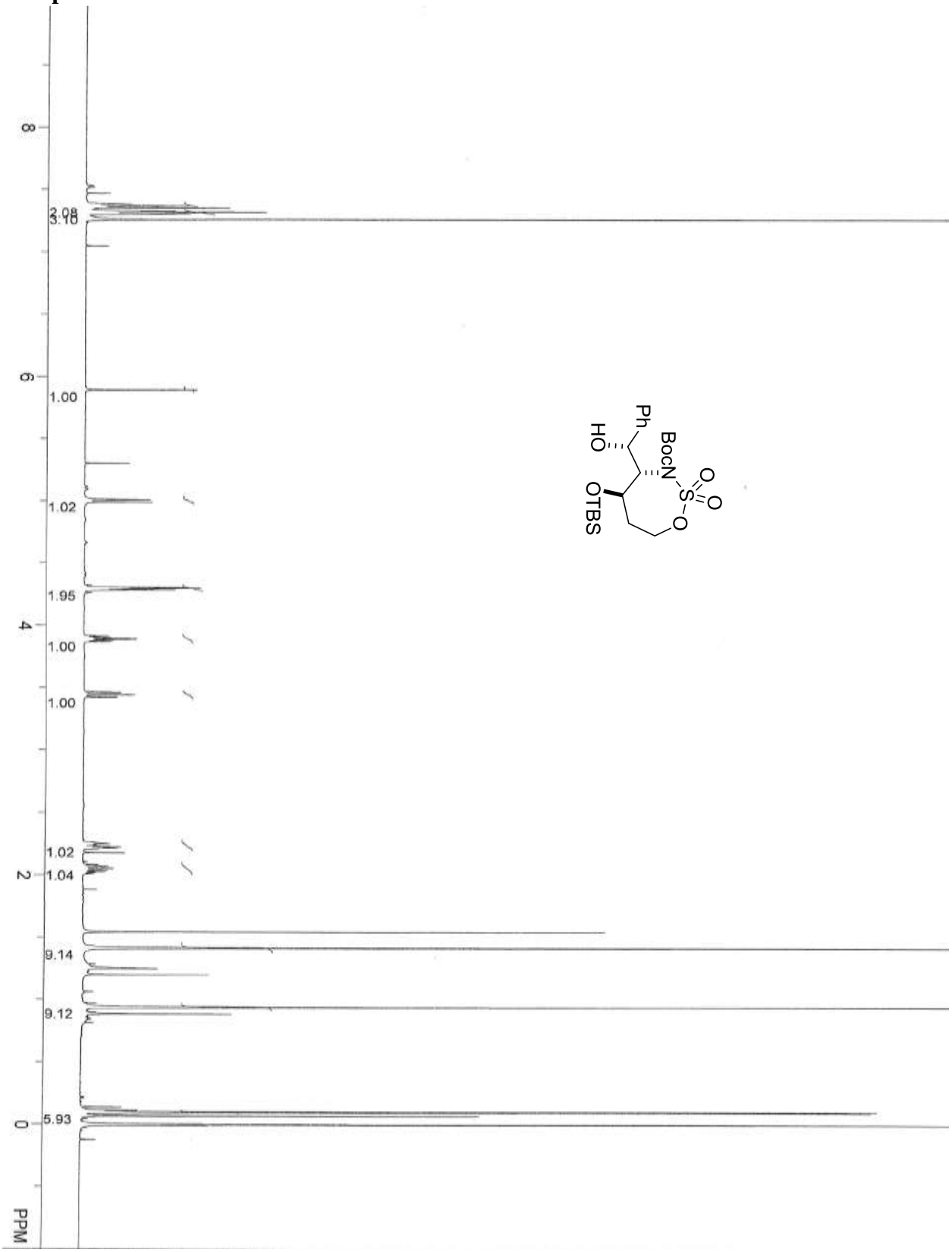

PhMe2Si
Boc
N
S
O
O
O
HO
OTBS
200
150
100
50
0
PPM

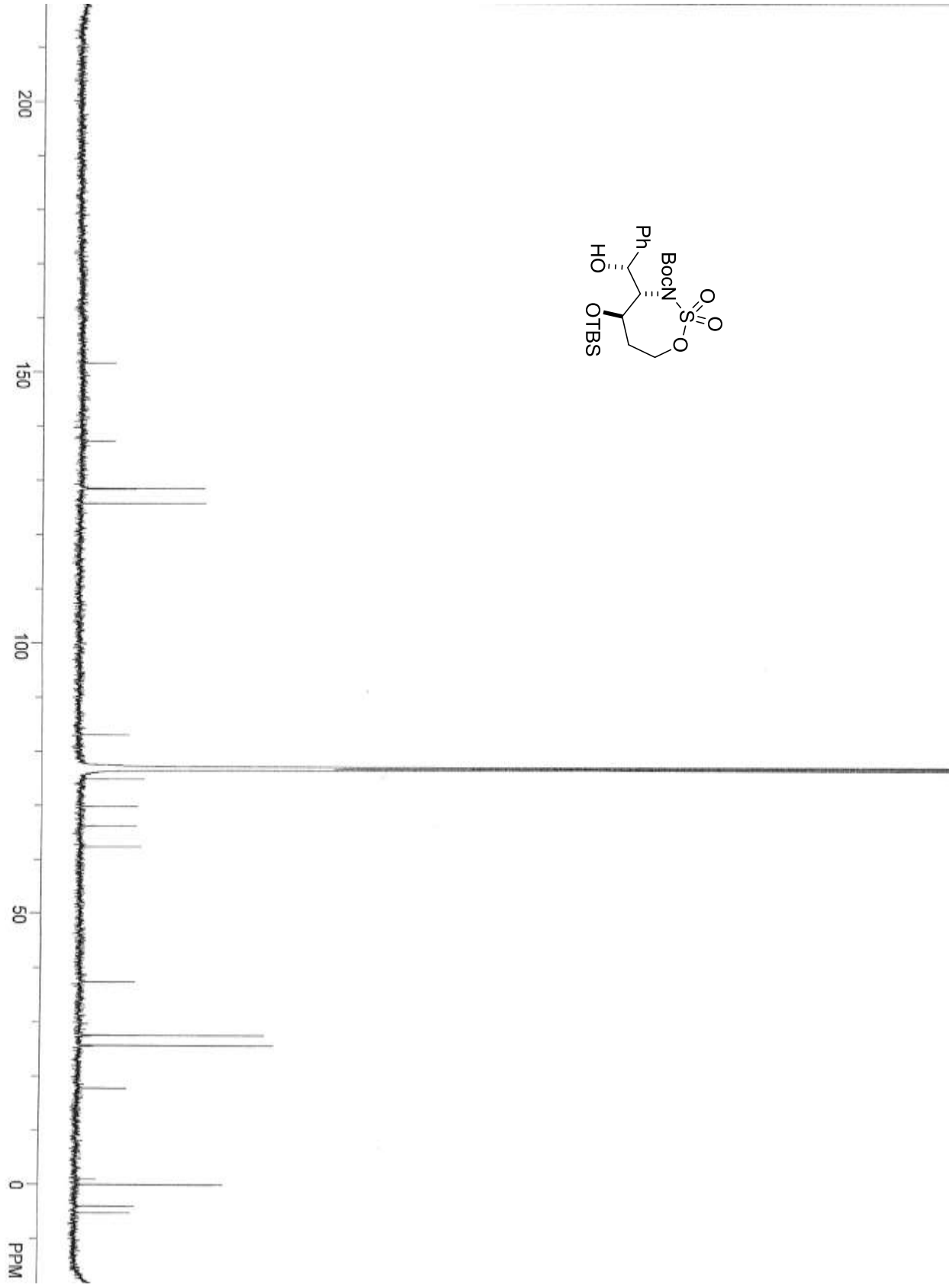
Compound 3.63a.



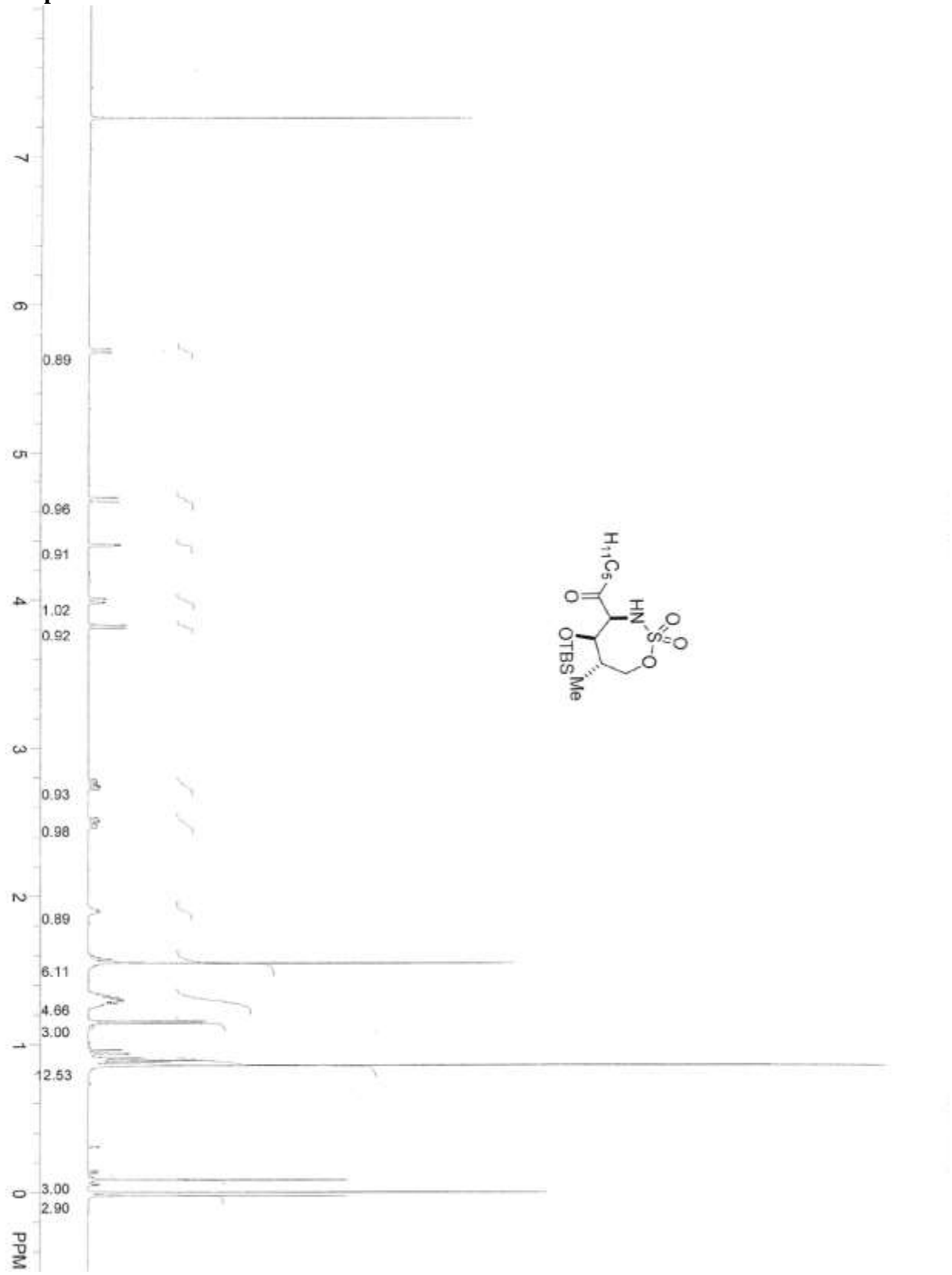

PhMe2Si
HO
HN
OTBS
200
150
100
50
0
PPM
Group Schomaker, C13CPD32 CDCl3 /home/rgrigg/callisto rgrigg 59,
USER: nmr -- DATE: 2014-02-01 19:22:58.846
F1: 125.743
F2: 1.000
SW1: 29762
OF1: 12569.1
PTS1d: 32768 , 32768
EX: zgpg30
PW: 10.0 us
PD: 2.0 sec
NA: 32
LB: 2.0
Nuts - $C1402011836_RDG9273_11

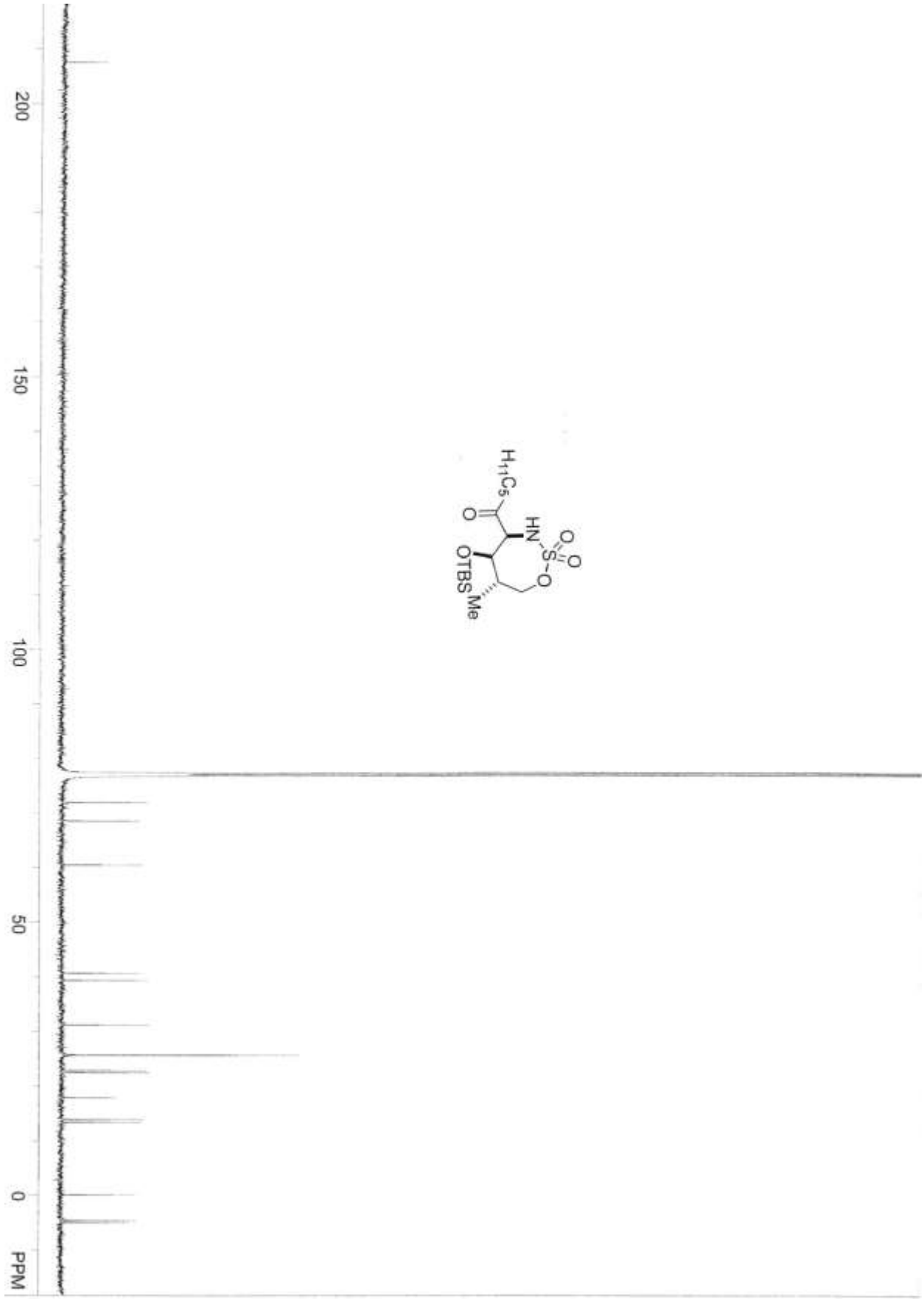
Compound 3.65.



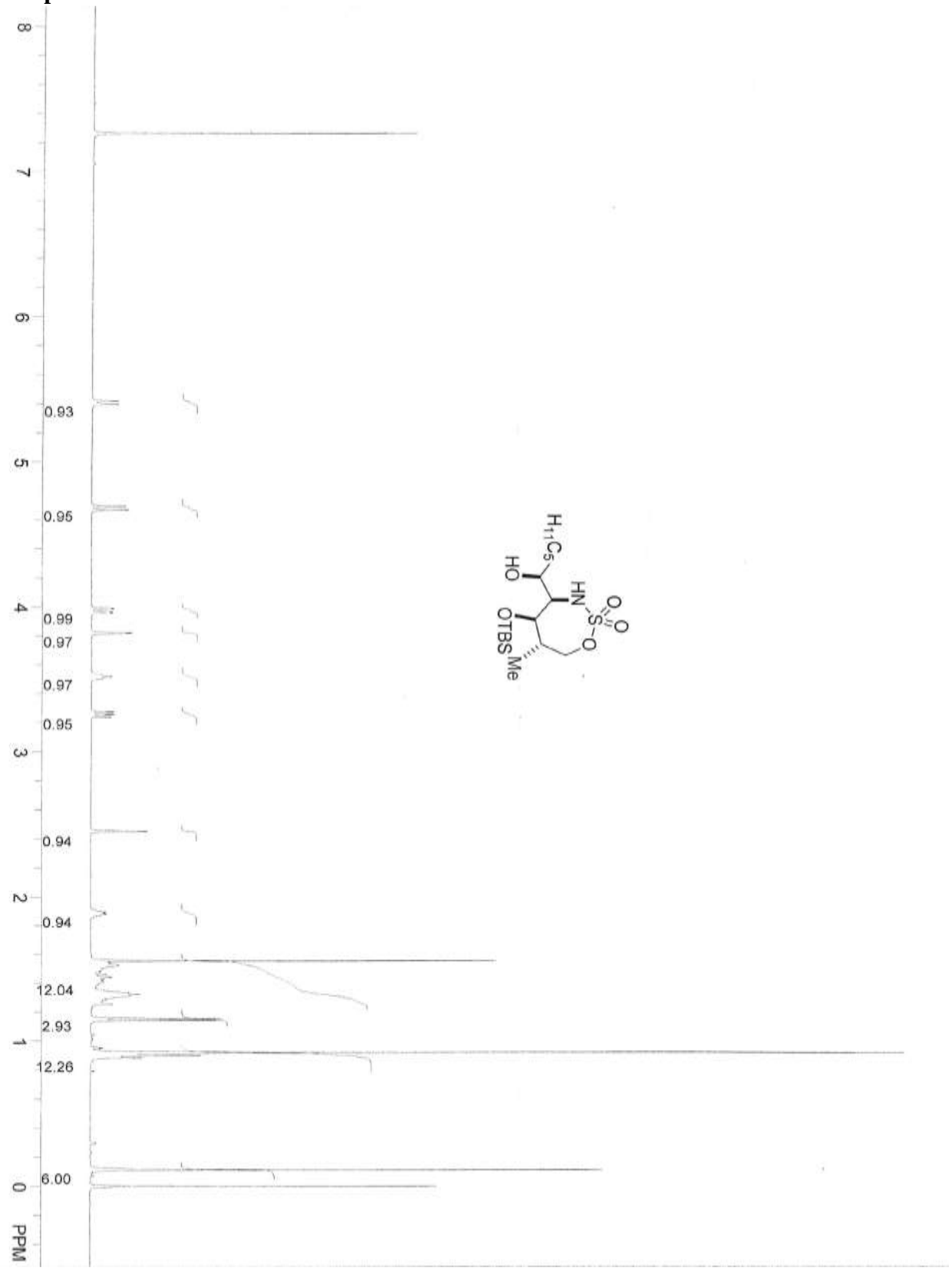

Ph
BocN
HO
OTBS
O
O
S
O
200
150
100
50
0
PPM

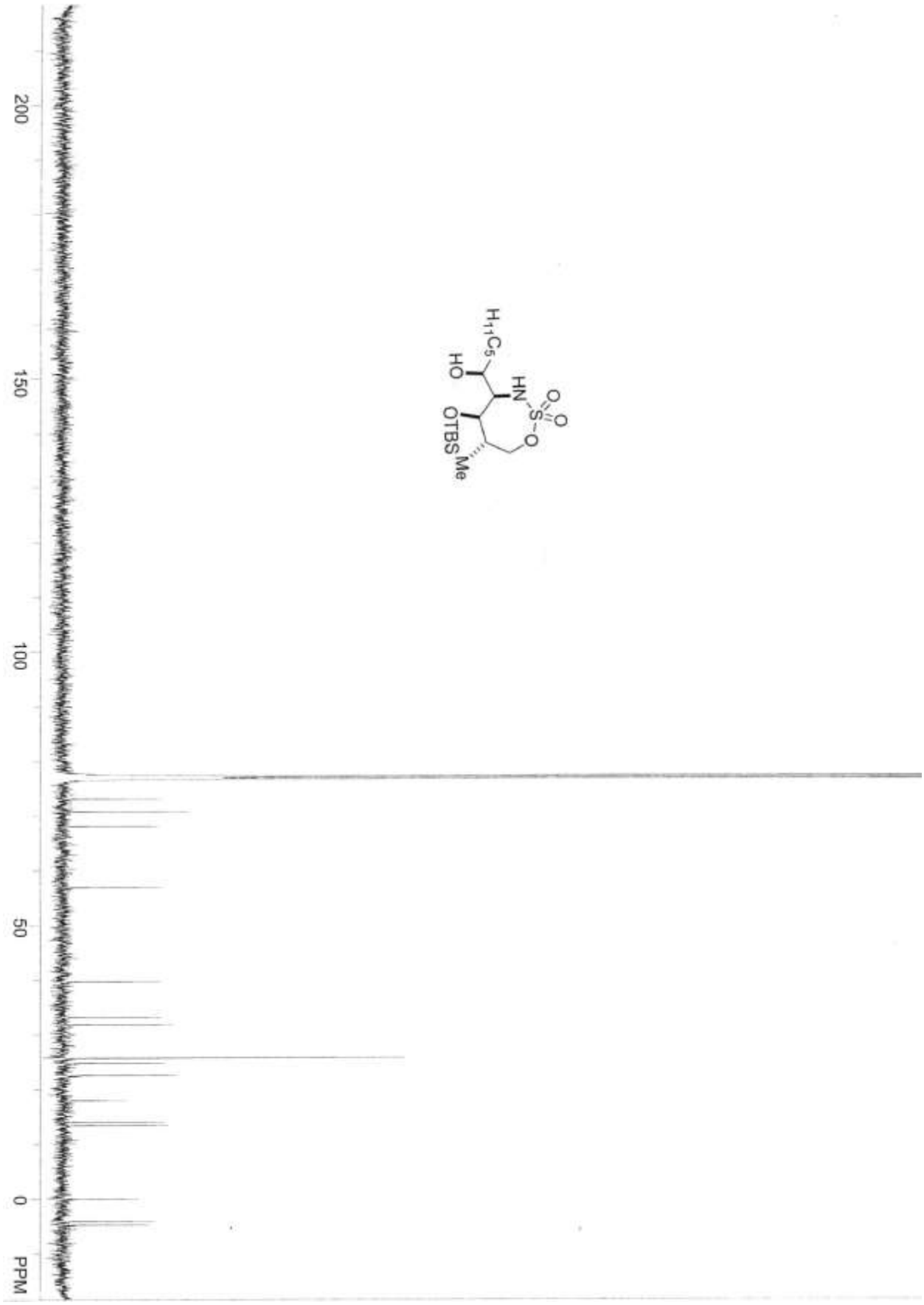
Compound 3.66.



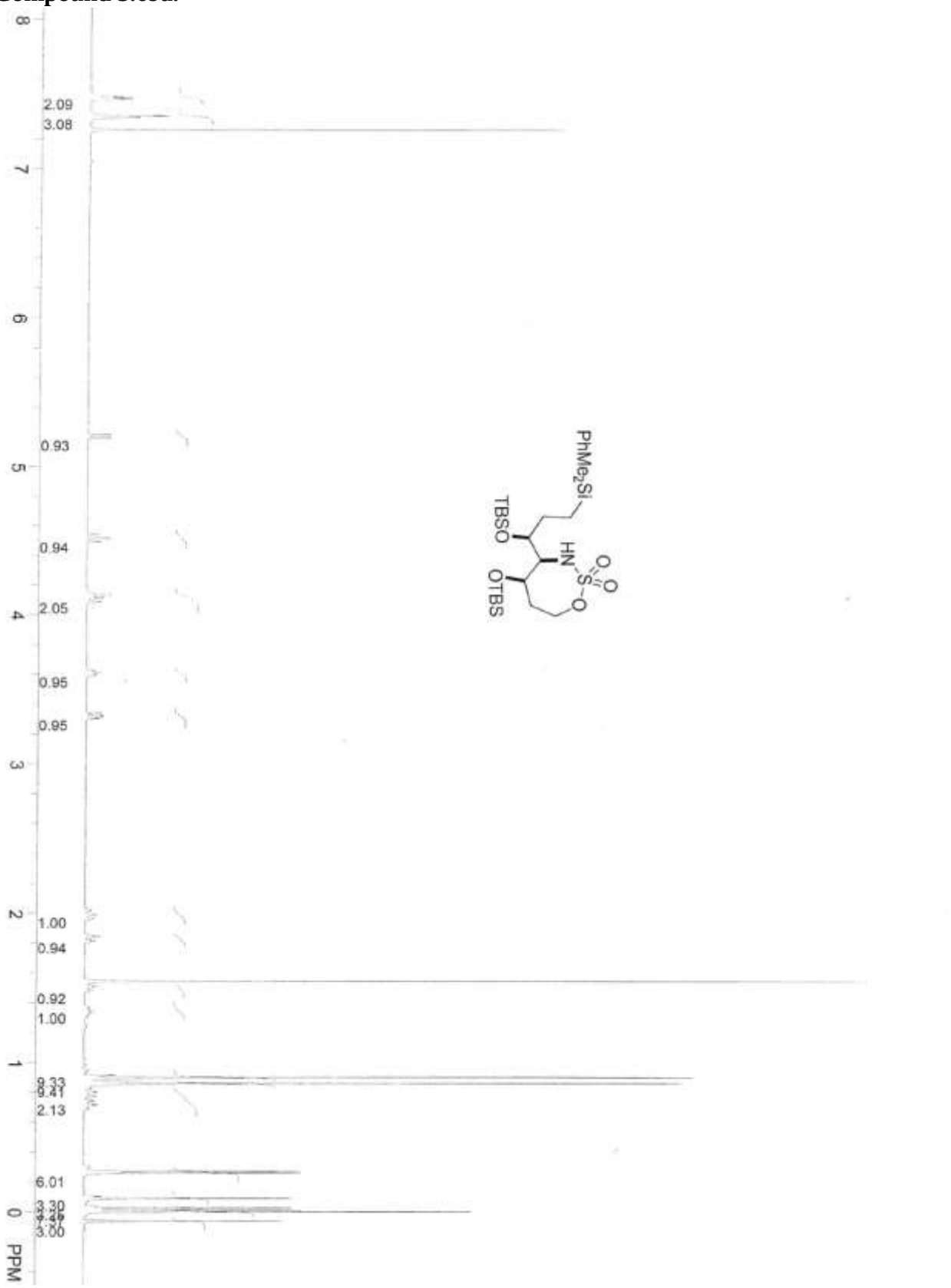

200
150
100
50
0
PPM
H11C5
O
HN
S
O
O
O
OTBS
Me

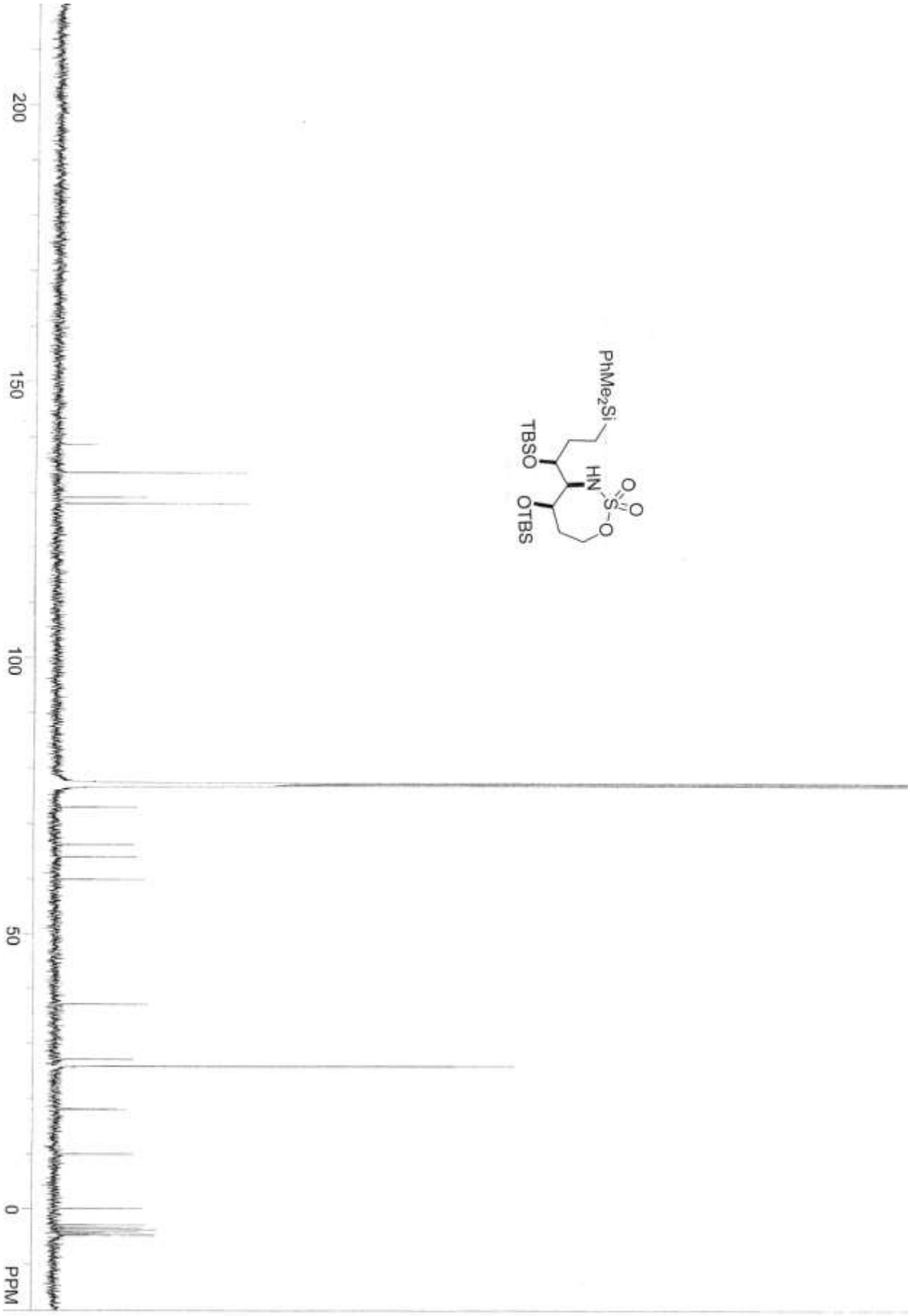
Compound 3.67.



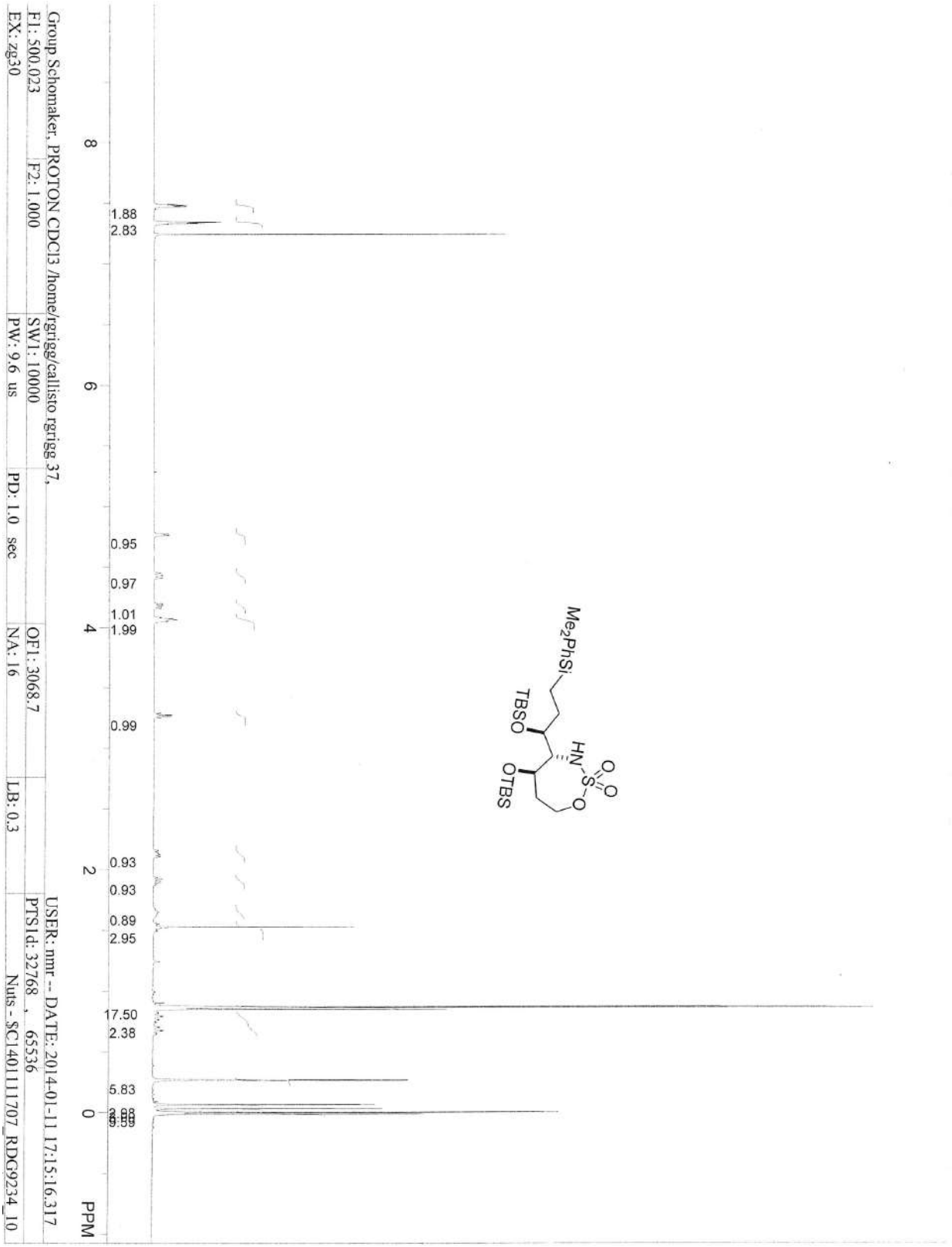

200
150
100
50
0
PPM
H11C5
HO
HN
S
O
O
O
OTBS
Me

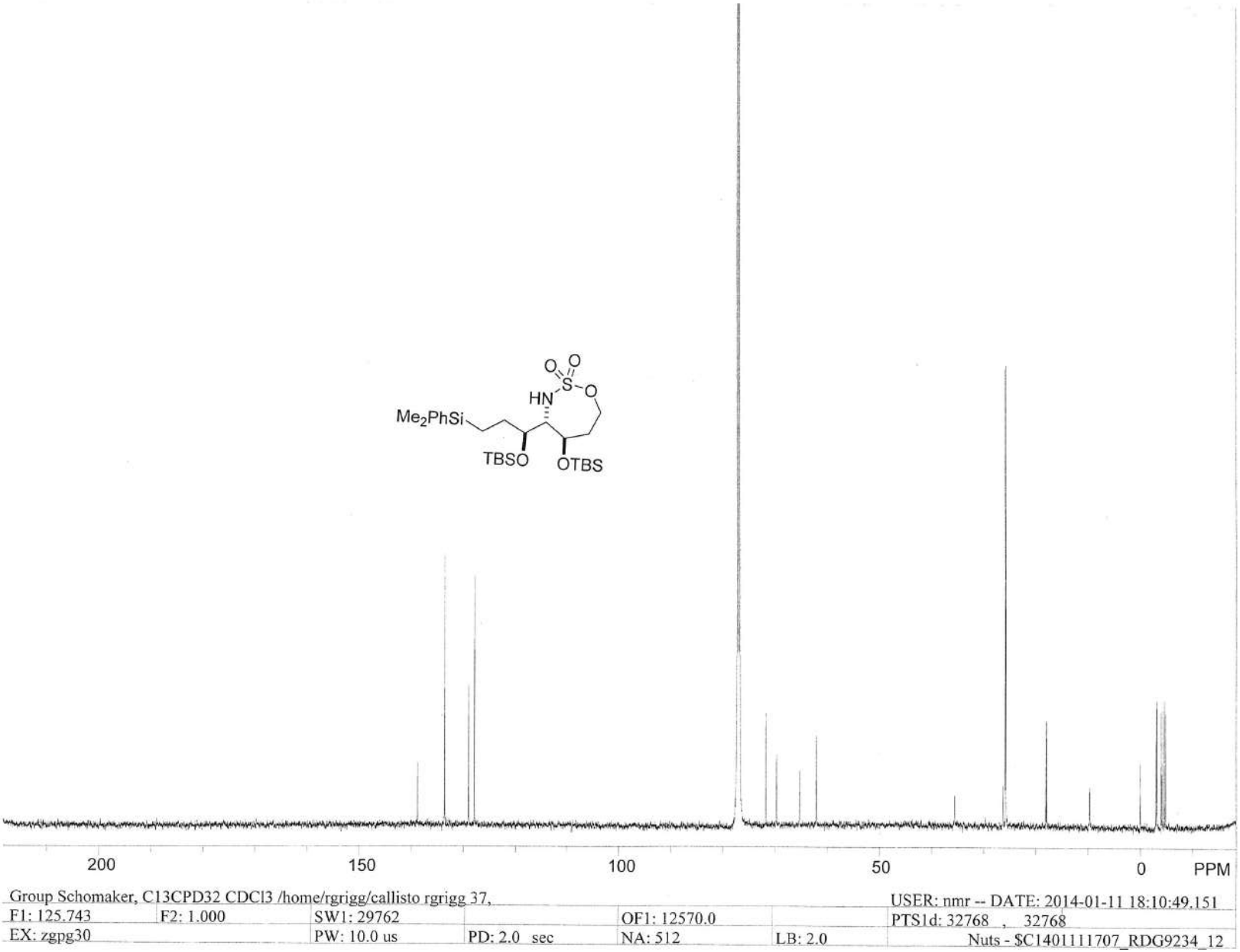
Compound 3.69a.




PhMe2Si
TBSO
HN
S
O
O
OTBS
200
150
100
50
0
PPM

Compound 3.69b.

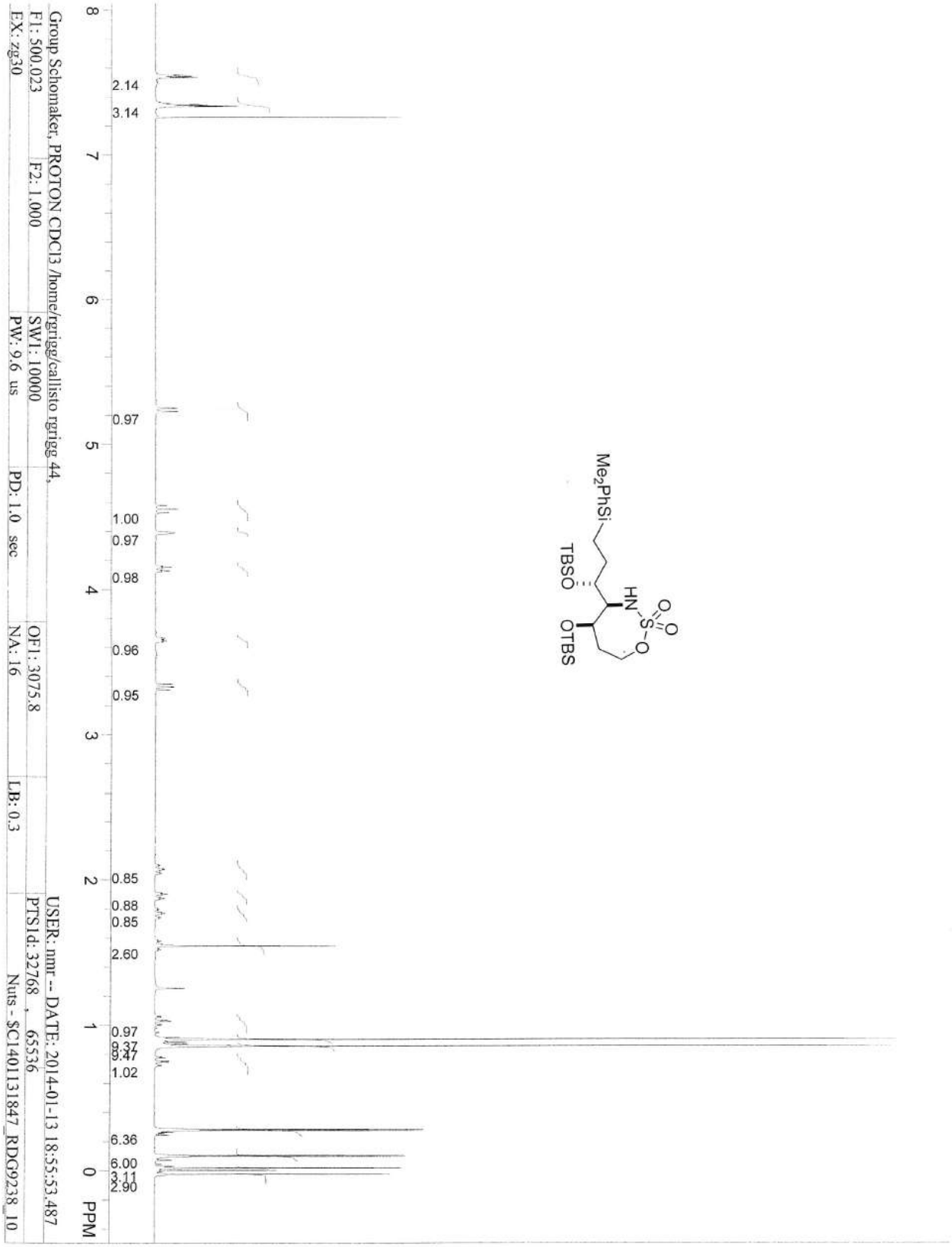


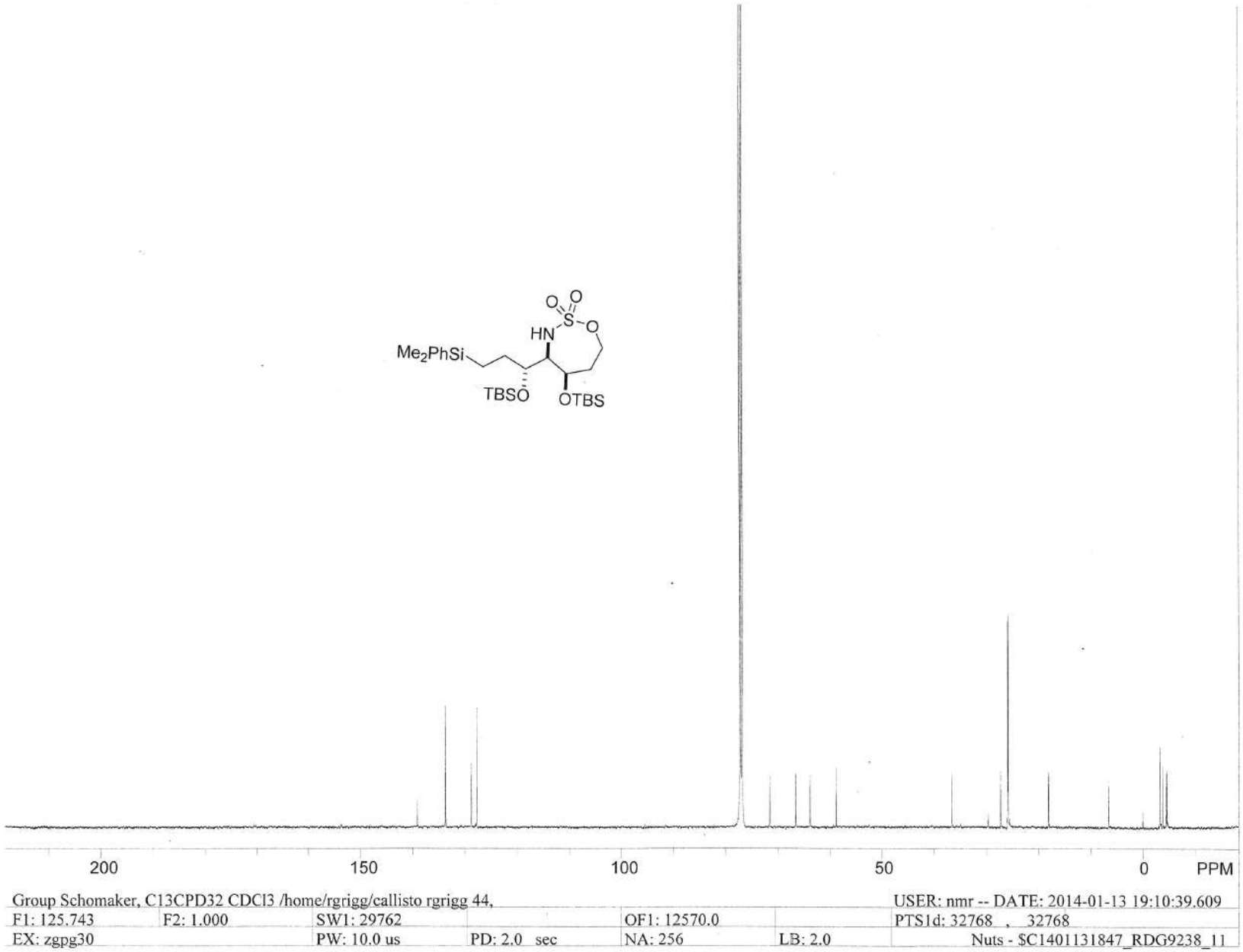


Group Schomaker, C13CPD32 CDCl3 /home/rgrigg/callisto rgrigg 37, USER: nmr -- DATE: 2014-01-11 18:10:49.151

F1: 125.743	F2: 1.000	SW1: 29762		OF1: 12570.0		PTS1d: 32768 , 32768
EX: zgpg30		PW: 10.0 us	PD: 2.0 sec	NA: 512	LB: 2.0	Nuts - $C1401111707_RDG9234_12

Compound 3.69c.

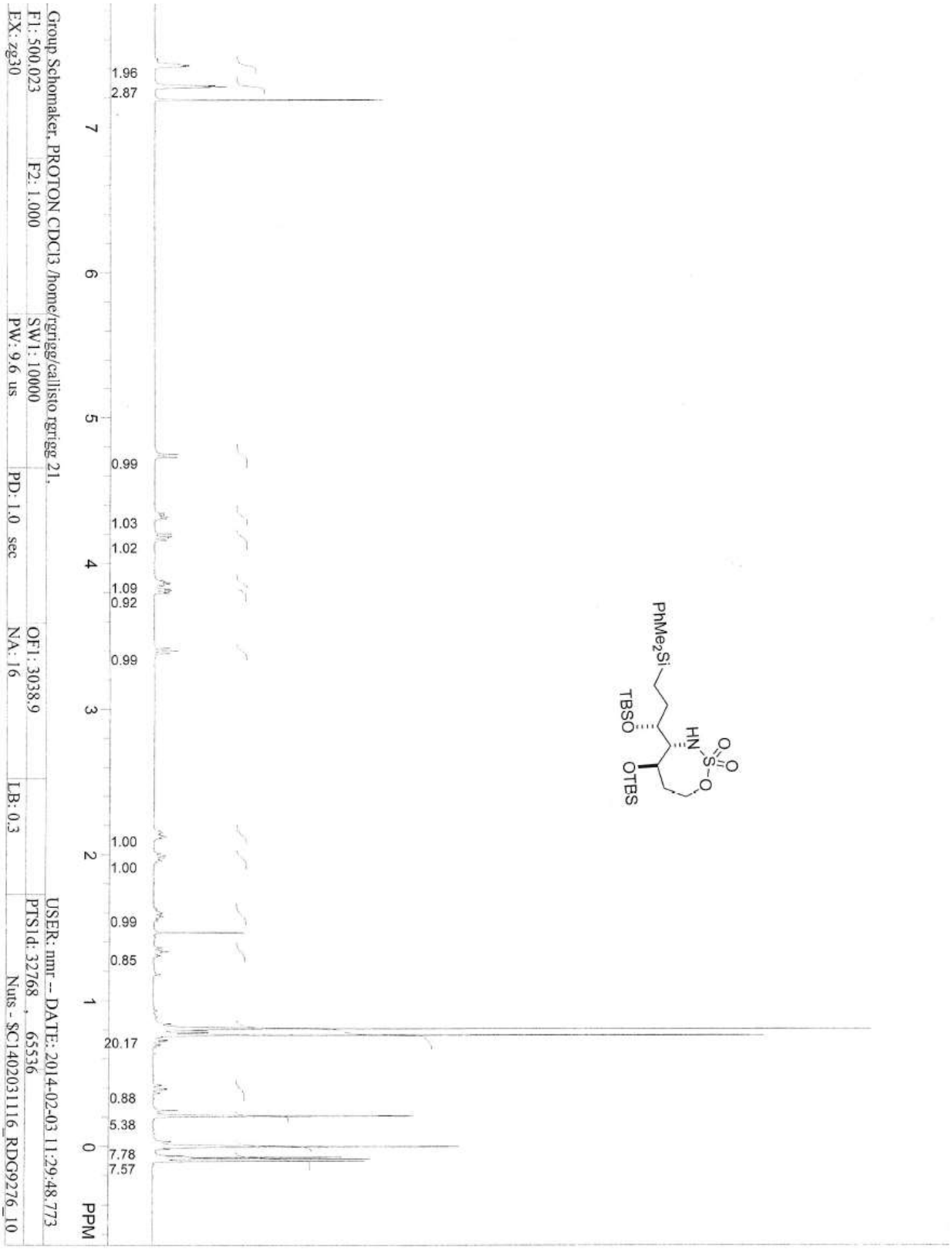


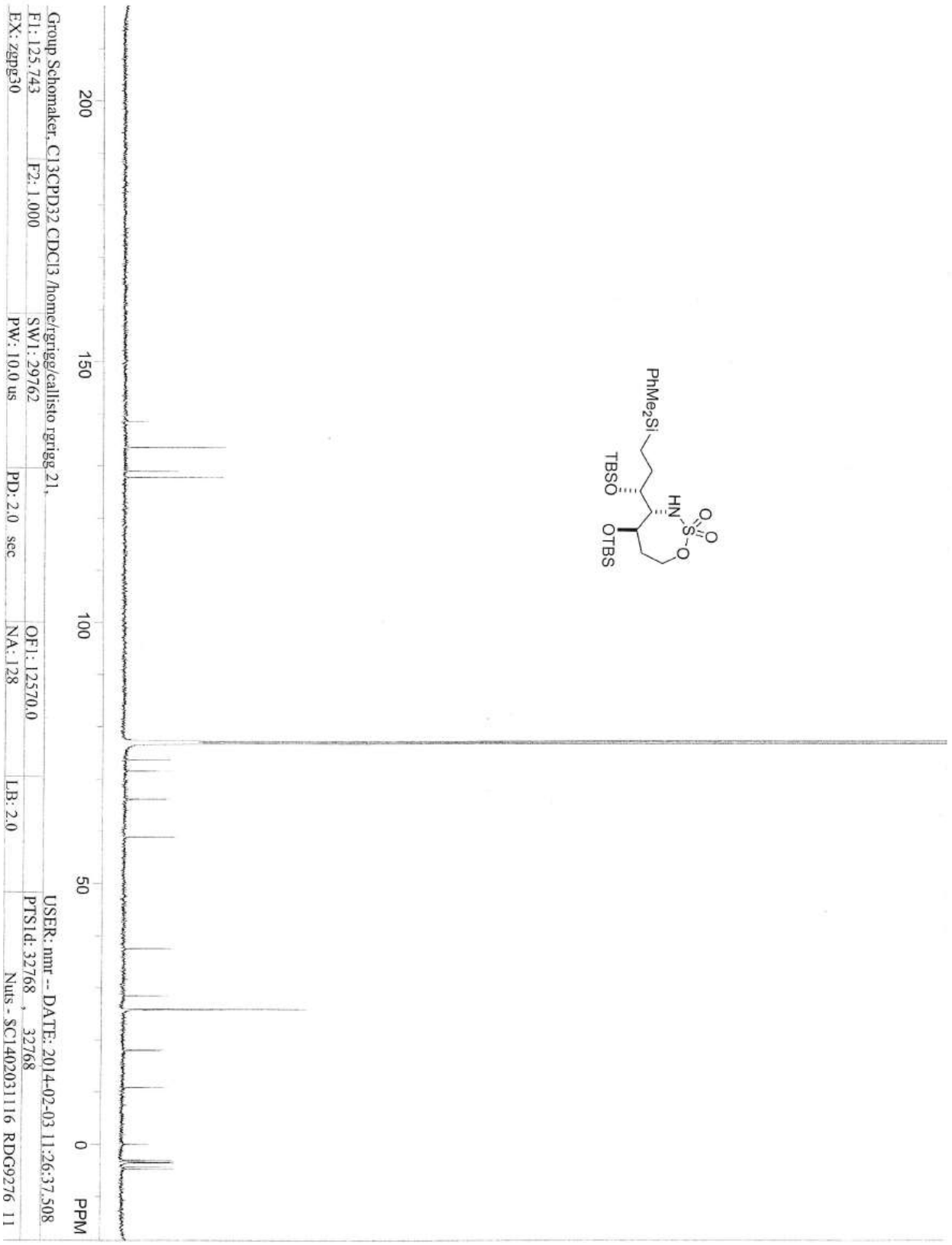


Group Schomaker, C13CPD32 CDCl3 /home/rgrigg/callisto rgrigg 44, USER: nmr -- DATE: 2014-01-13 19:10:39.609

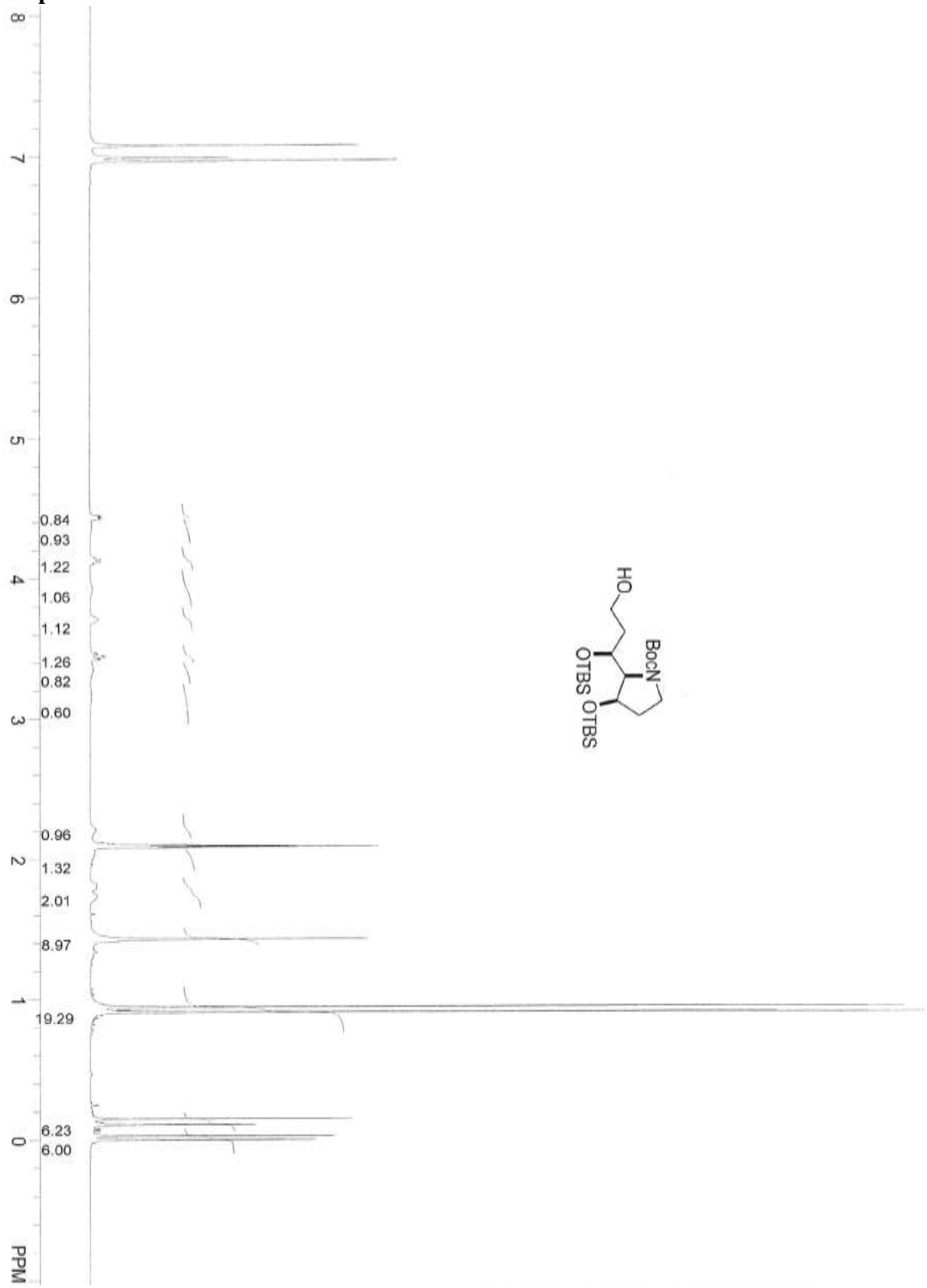
F1: 125.743	F2: 1.000	SW1: 29762		OF1: 12570.0		PTS1d: 32768 , 32768
EX: zgpg30		PW: 10.0 us	PD: 2.0 sec	NA: 256	LB: 2.0	Nuts - $C1401131847_RDG9238_11

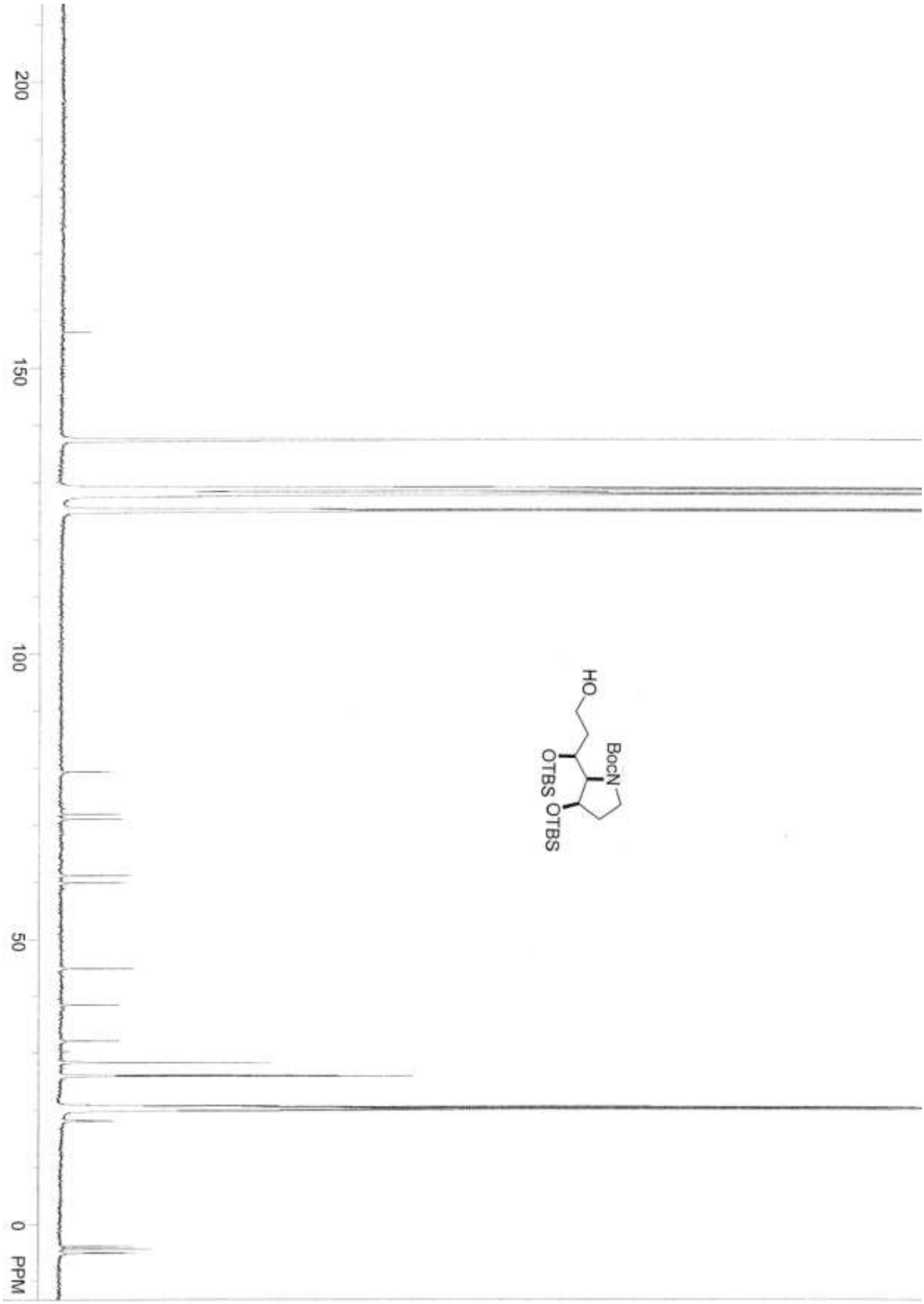
Compound 3.69d.



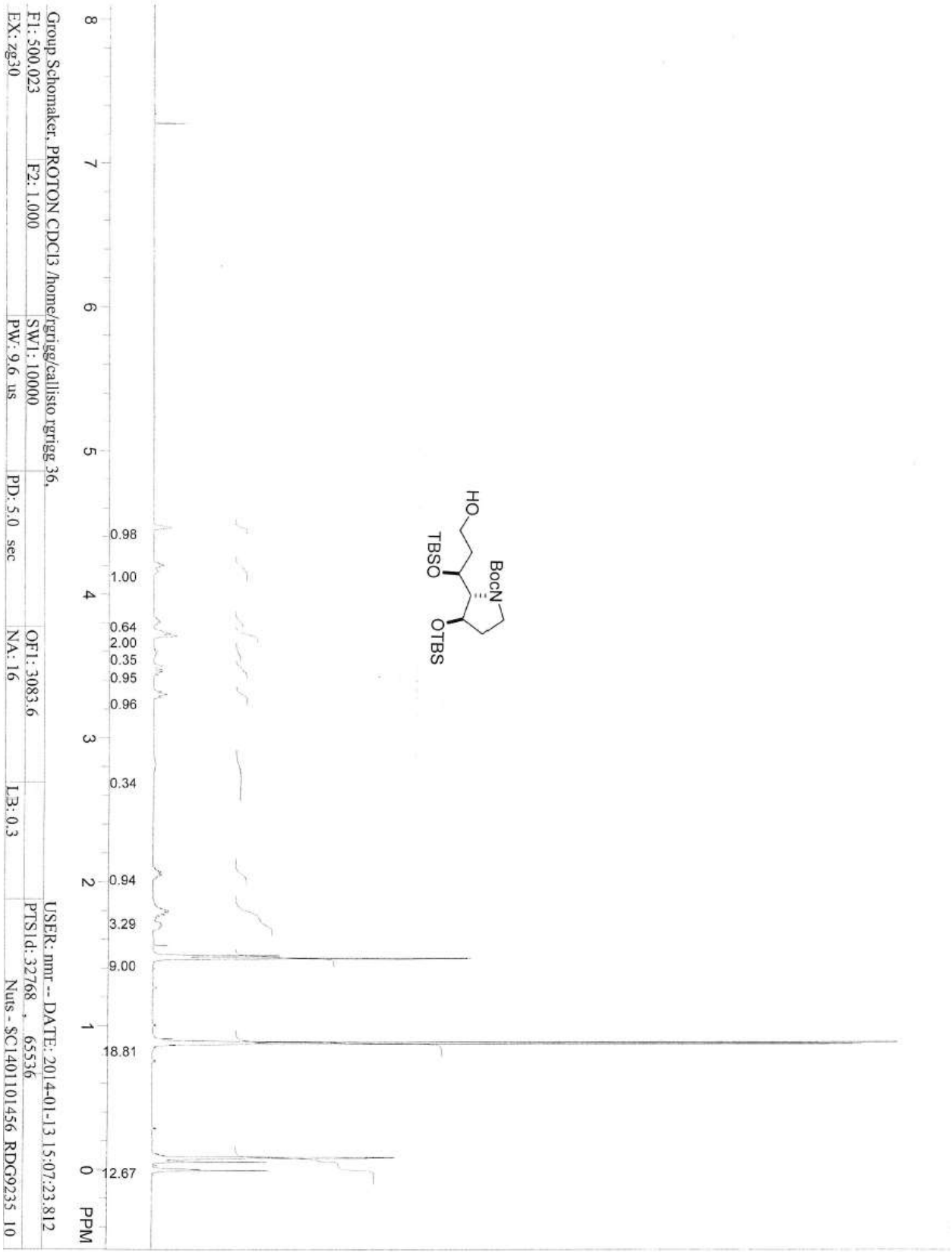

PhMe2Si
TBSO
OTBS
HN
S
O
O
O
200
150
100
50
0
PPM
Group Schomaker_C13CPD32 CDCl3 /home/rgrigg/callisto rgrigg 21.
USER: nmr -- DATE: 2014-02-03 11:26:37.508
F1: 125.743
F2: 1.000
SW1: 29762
OF1: 12570.0
PTSI d: 32768 , 32768
EX: zgpg30
PW: 10.0 us
PD: 2.0 sec
NA: 128
LB: 2.0
Nuts - SC1402031116 RDG9276 11

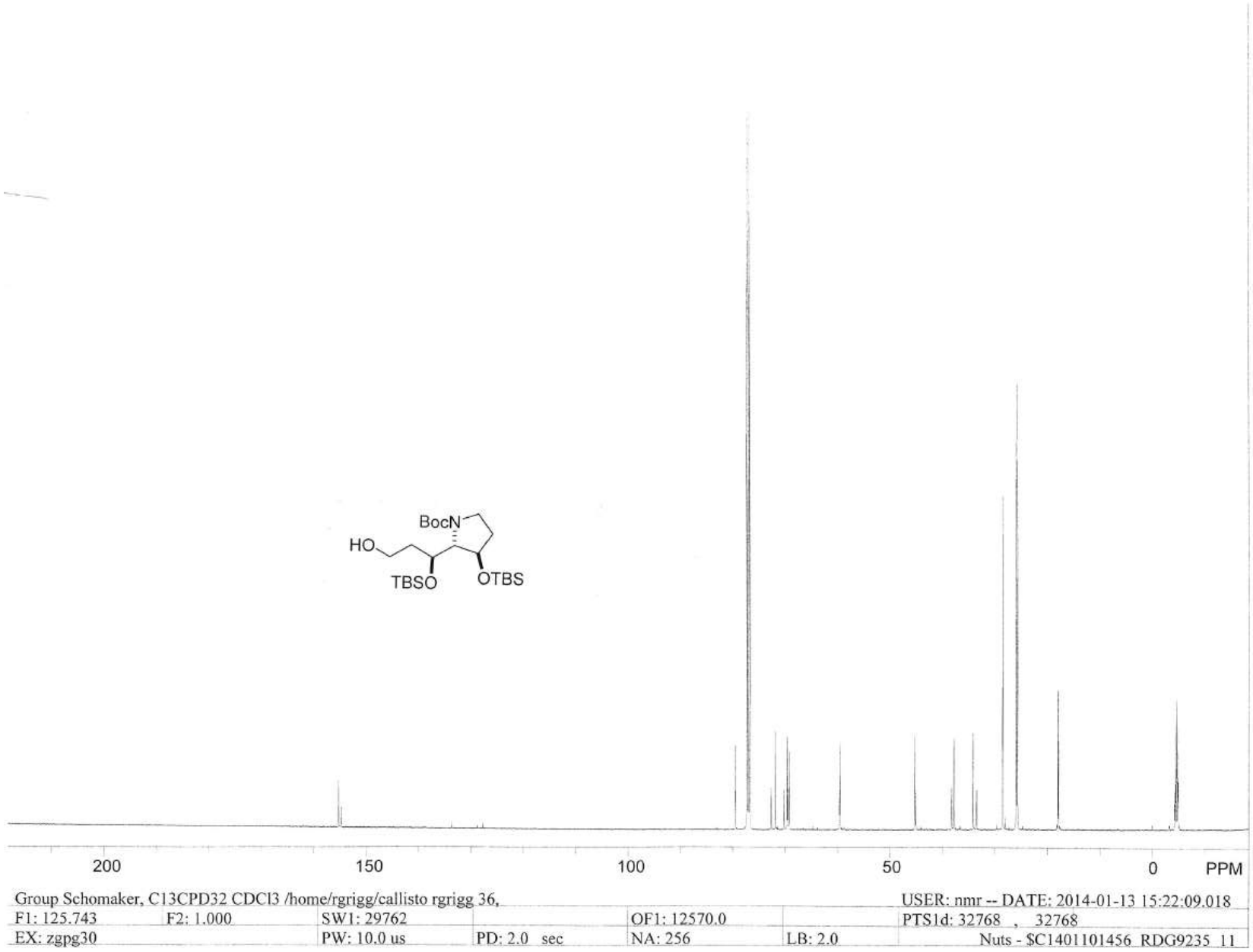
Compound 3.71a.




200
150
100
50
0
PPM
HO
BocN
OTBS
OTBS

Compound 3.71b.

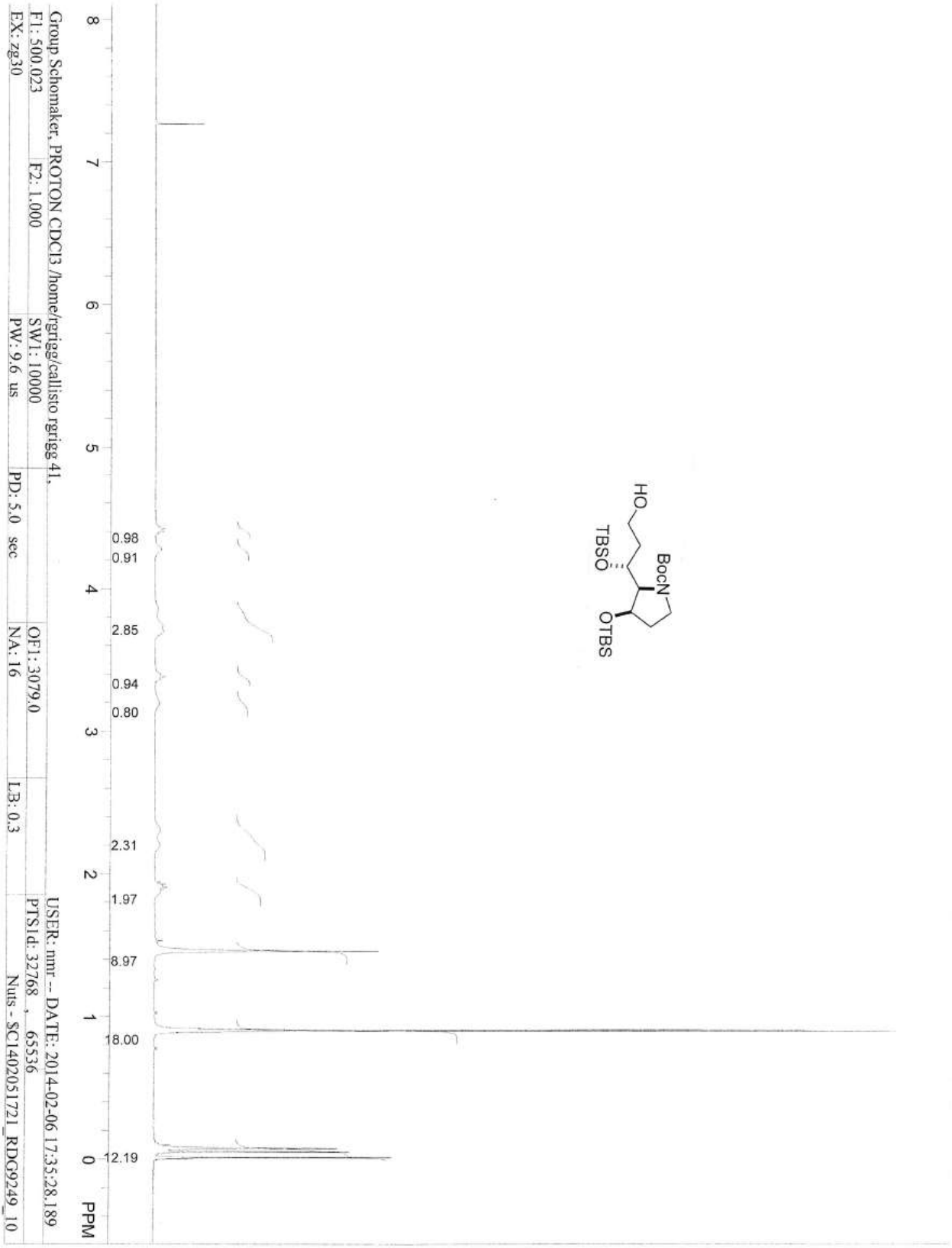


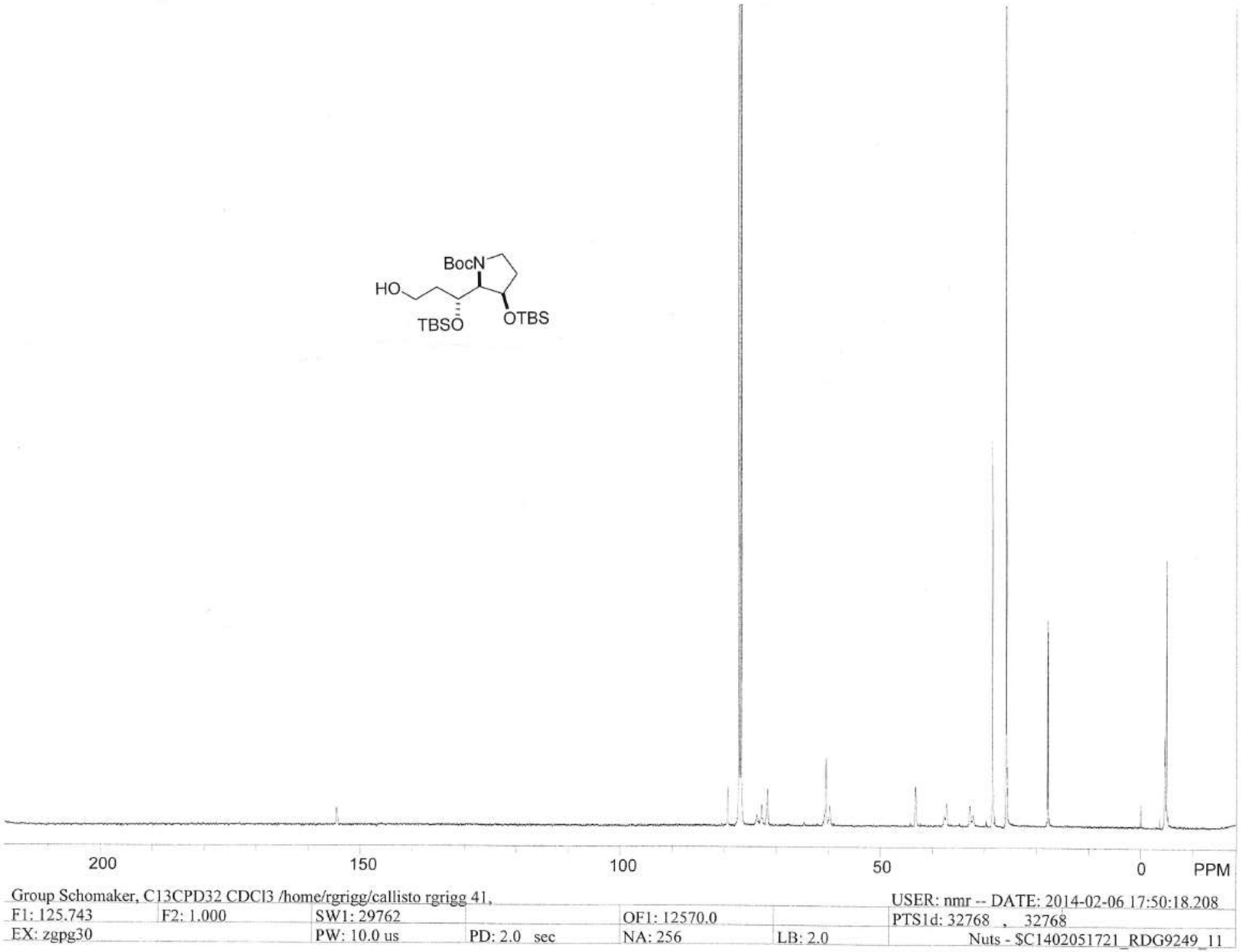


Group Schomaker, C13CPD32 CDCl3 /home/rgrigg/callisto rgrigg 36, USER: nmr -- DATE: 2014-01-13 15:22:09.018

F1: 125.743	F2: 1.000	SW1: 29762		OF1: 12570.0		PTS1d: 32768 , 32768
EX: zgpg30		PW: 10.0 us	PD: 2.0 sec	NA: 256	LB: 2.0	Nuts - $C1401101456_RDG9235_11

Compound 3.71c.



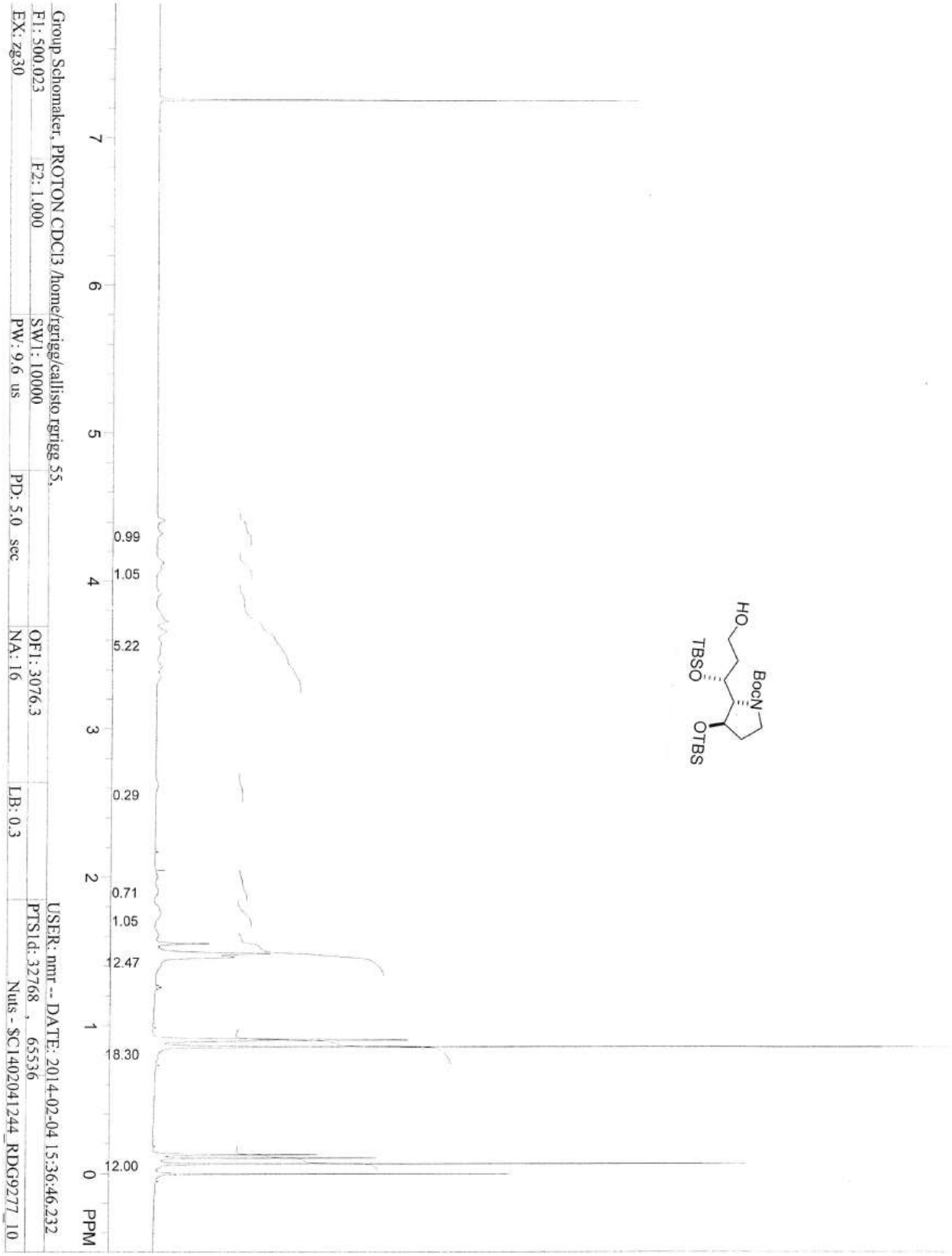


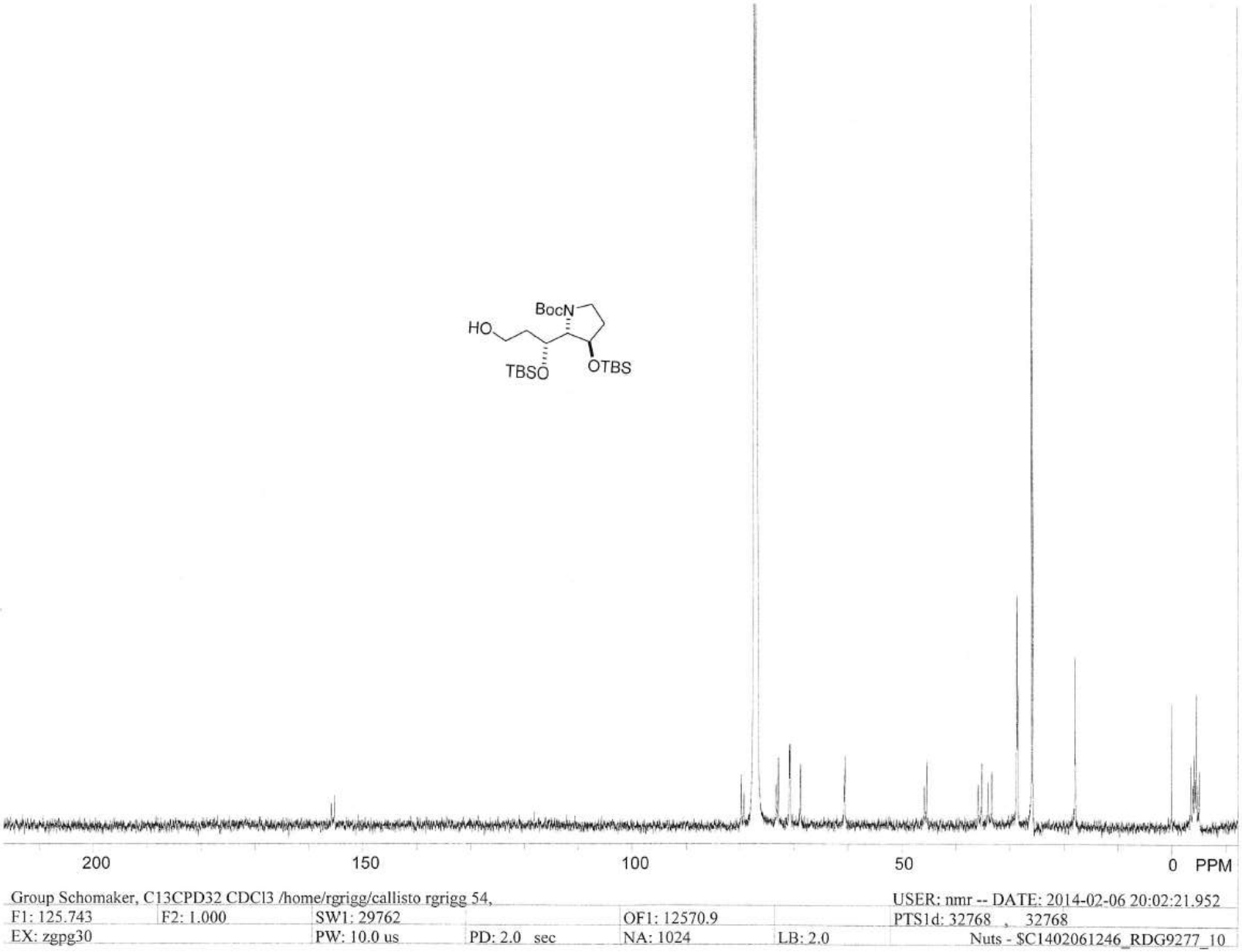
Group Schomaker, C13CPD32 CDCl3 /home/rgrigg/callisto rgrigg 41,

USER: nmr -- DATE: 2014-02-06 17:50:18.208

F1: 125.743	F2: 1.000	SW1: 29762		OF1: 12570.0		PTS1d: 32768 , 32768
EX: zgpg30		PW: 10.0 us	PD: 2.0 sec	NA: 256	LB: 2.0	Nuts - $C1402051721_RDG9249_11

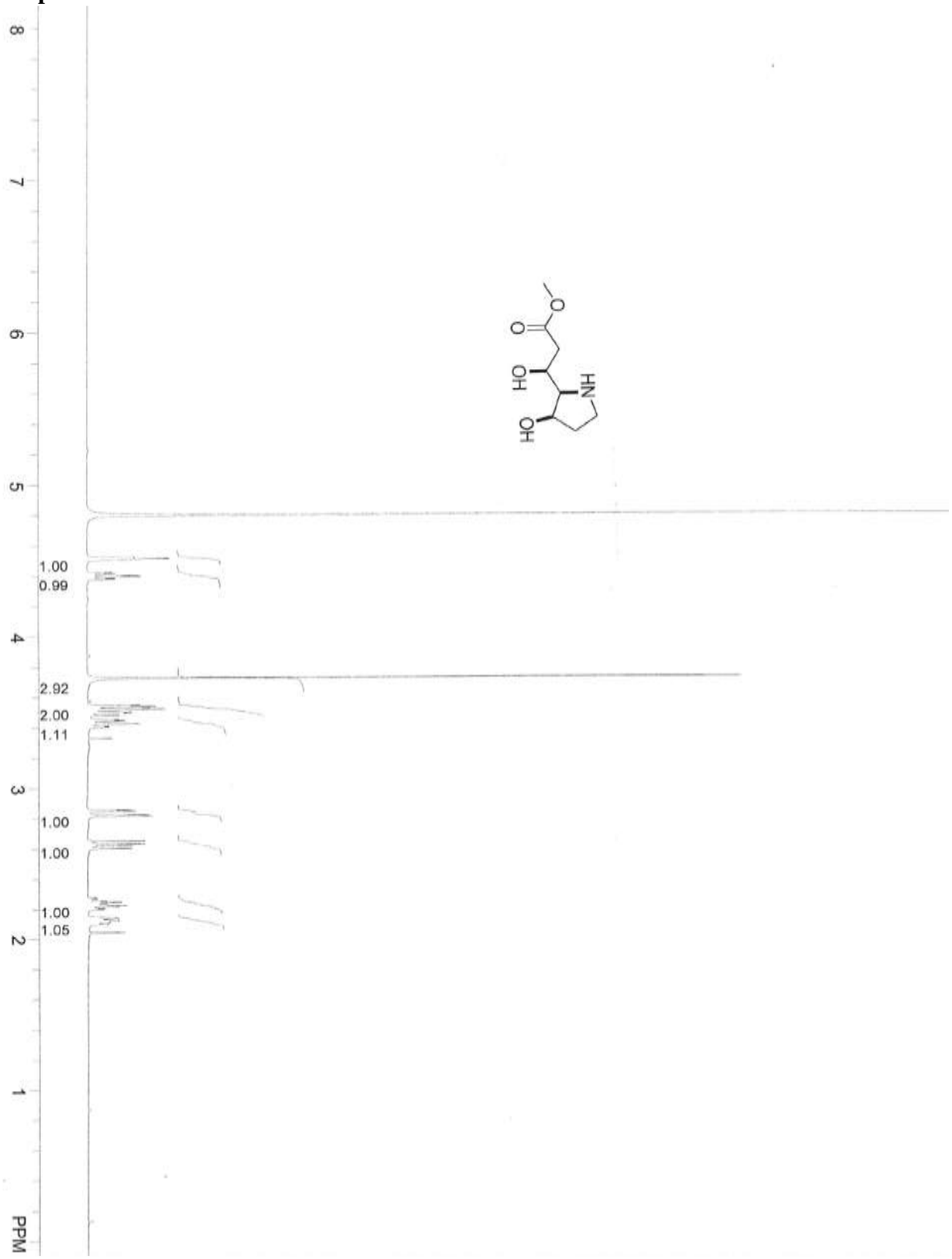
Compound 3.71d.

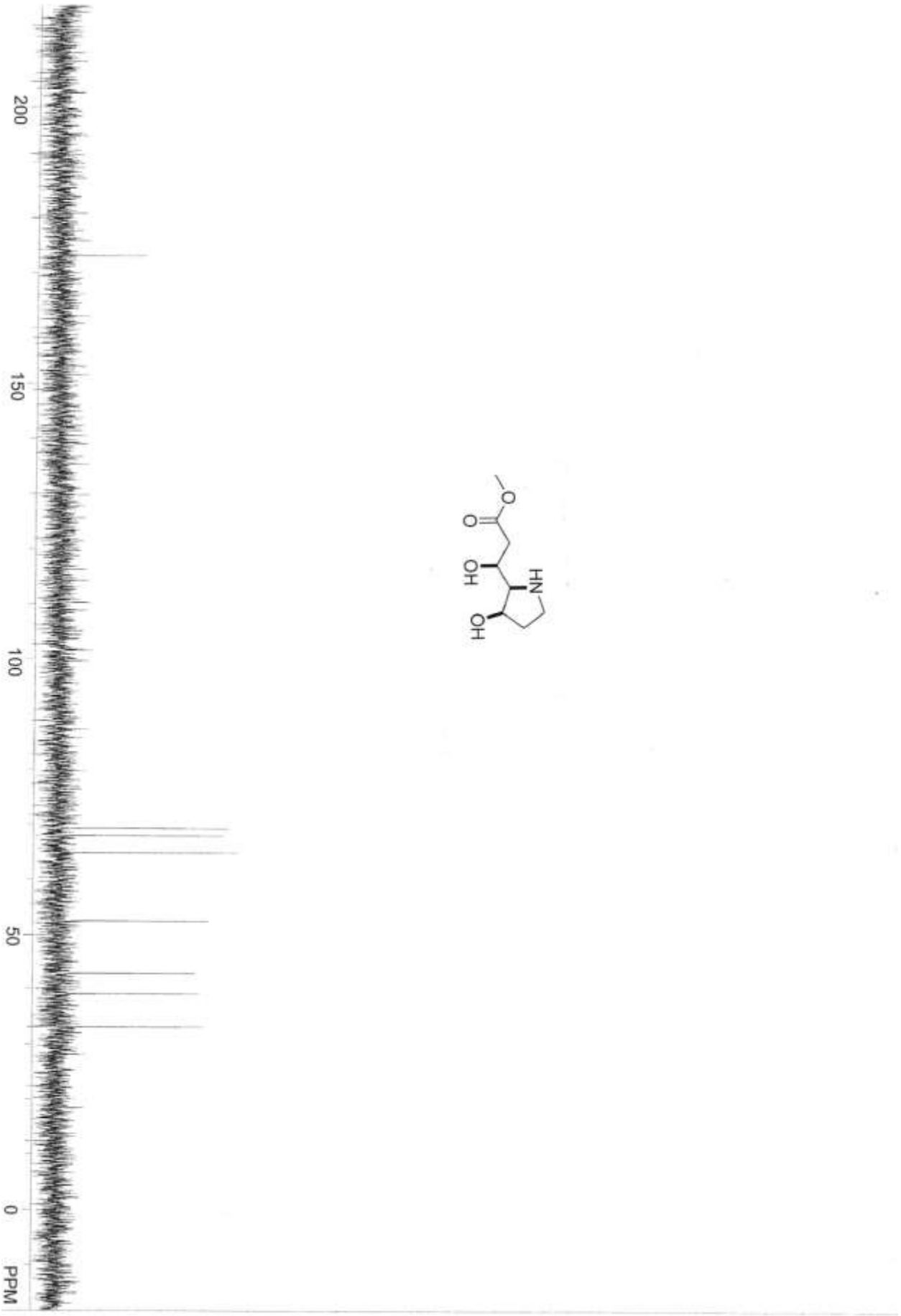




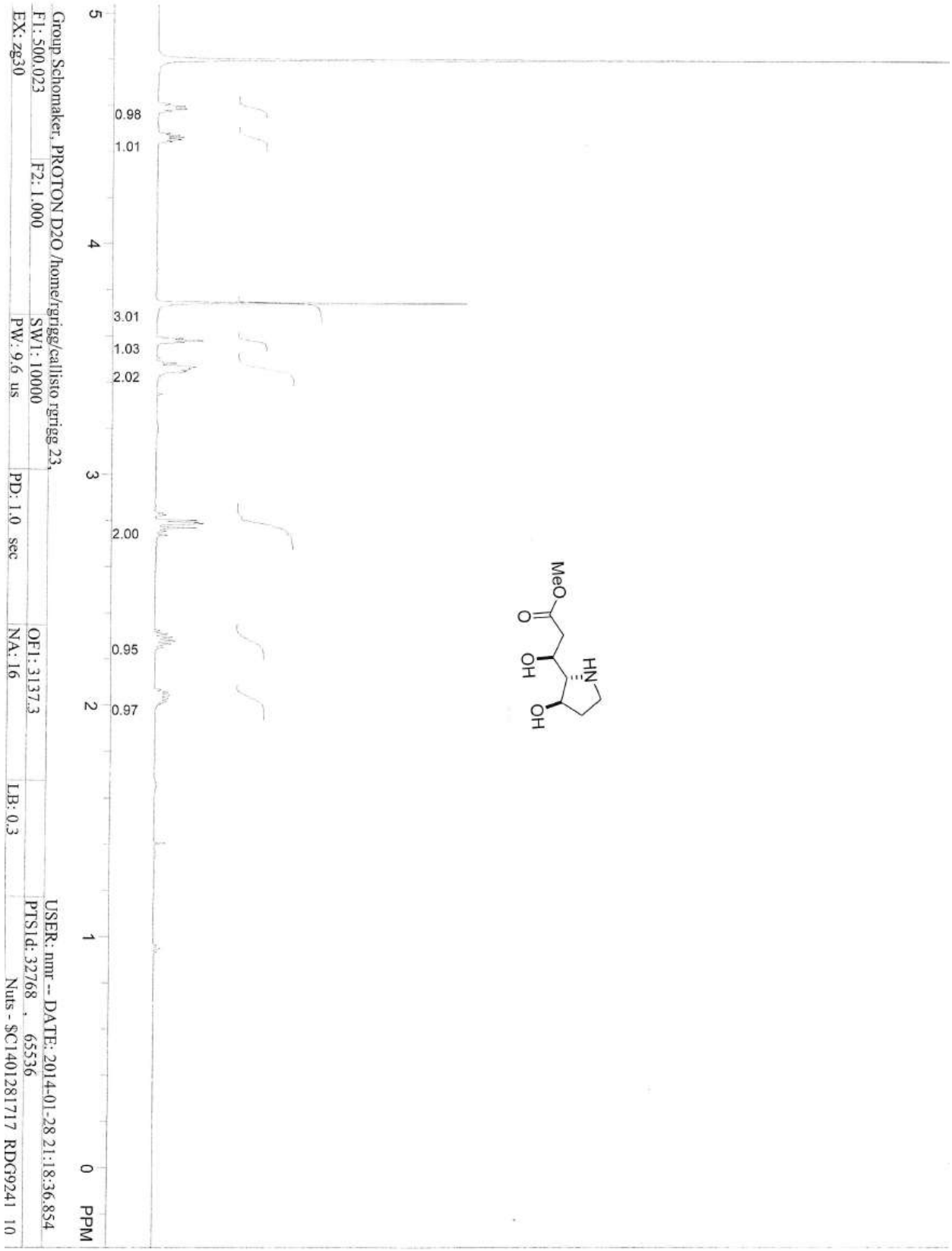
Group Schomaker, C13CPD32 CDCl3 /home/rgrigg/callisto rgrigg 54,						USER: nmr -- DATE: 2014-02-06 20:02:21.952
F1: 125.743	F2: 1.000	SW1: 29762		OF1: 12570.9		PTS1d: 32768 , 32768
EX: zgpg30		PW: 10.0 us	PD: 2.0 sec	NA: 1024	LB: 2.0	Nuts - $C1402061246_RDG9277_10

Compound 3.72a.




200
150
100
50
0
PPM
O
O
OH
HN
OH

Compound 3.72b.

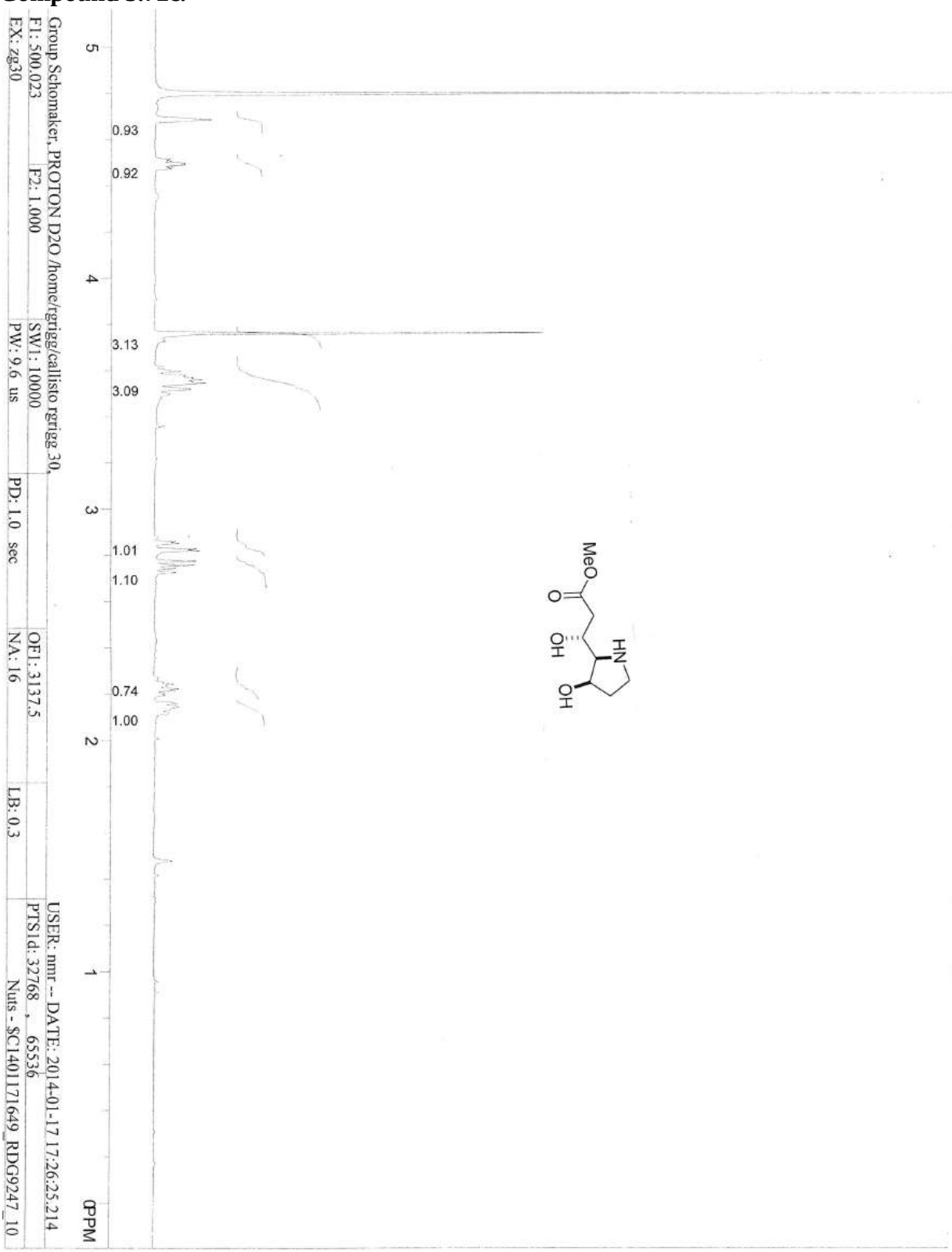


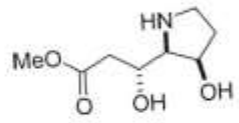
Group Schomaker, C13CPD32 D2O /home/rgrigg/callisto rgrigg 53,

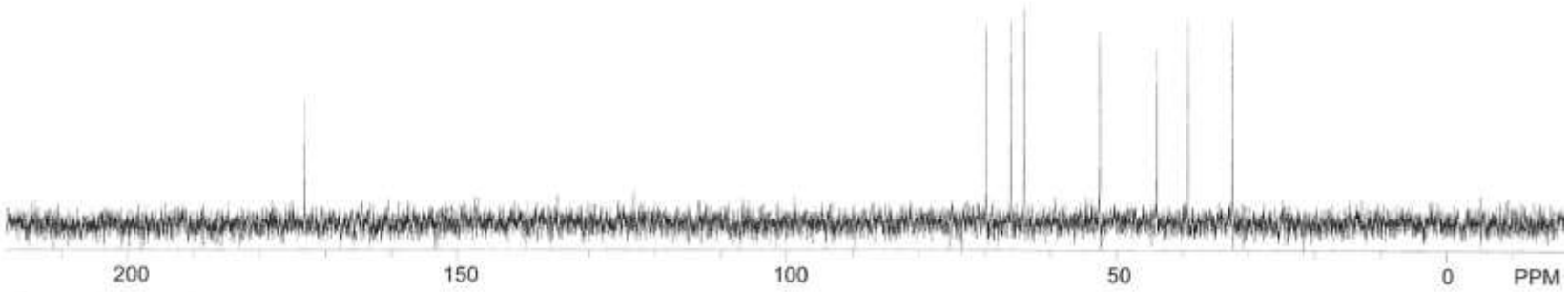
USER: nmr -- DATE: 2014-01-15 12:52:59.664

F1: 125.743	F2: 1.000	SW1: 29762		OF1: 12578.5		PTS1d: 32768 , 32768
EX: zgpg30		PW: 10.0 us	PD: 2.0 sec	NA: 256	LB: 2.0	Nuts - $C1401151233_RDG9241_11

Compound 3.72c.



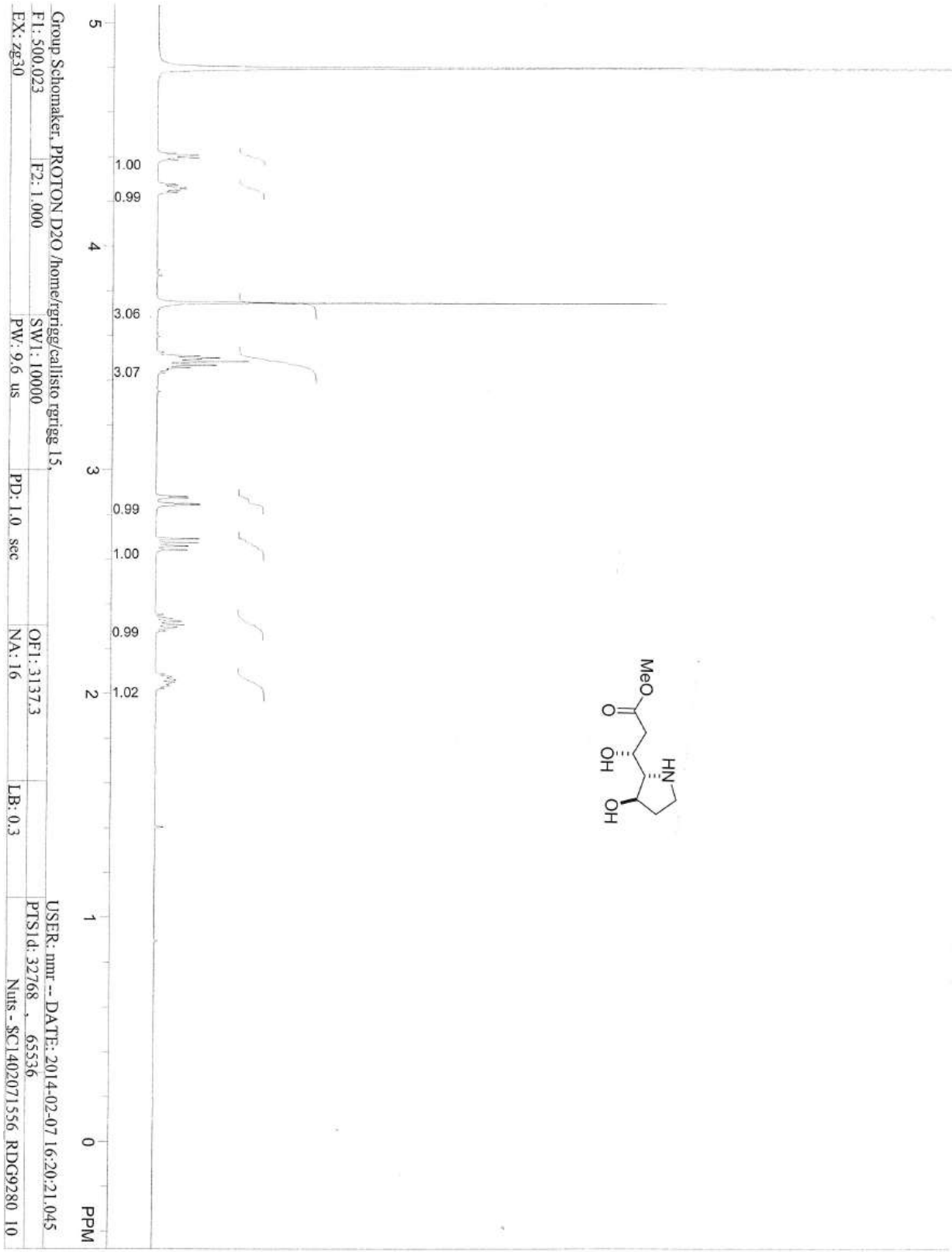


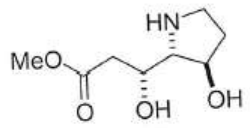


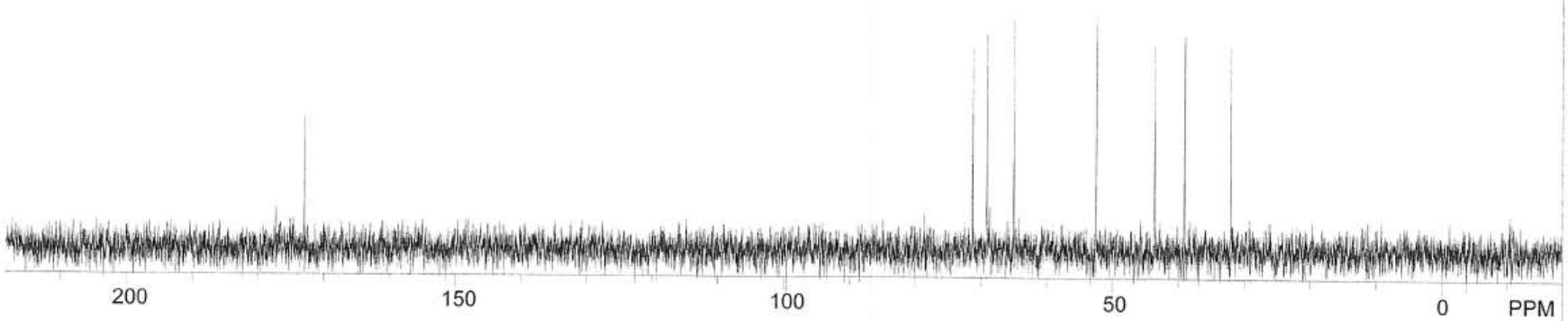
Group Schomaker, C13CPD32 D2O /home/rgrigg/callisto rgrigg 30, USER: nmr -- DATE: 2014-01-17 17:34:42.819

F1: 125.743	F2: 1.000	SW1: 29762		OF1: 12578.6		PTS1d: 32768 , 32768
EX: zgpg30		PW: 10.0 us	PD: 2.0 sec	NA: 128	LB: 2.0	Nuts - SC1401171649_RDG9247_11

Compound 3.72d.



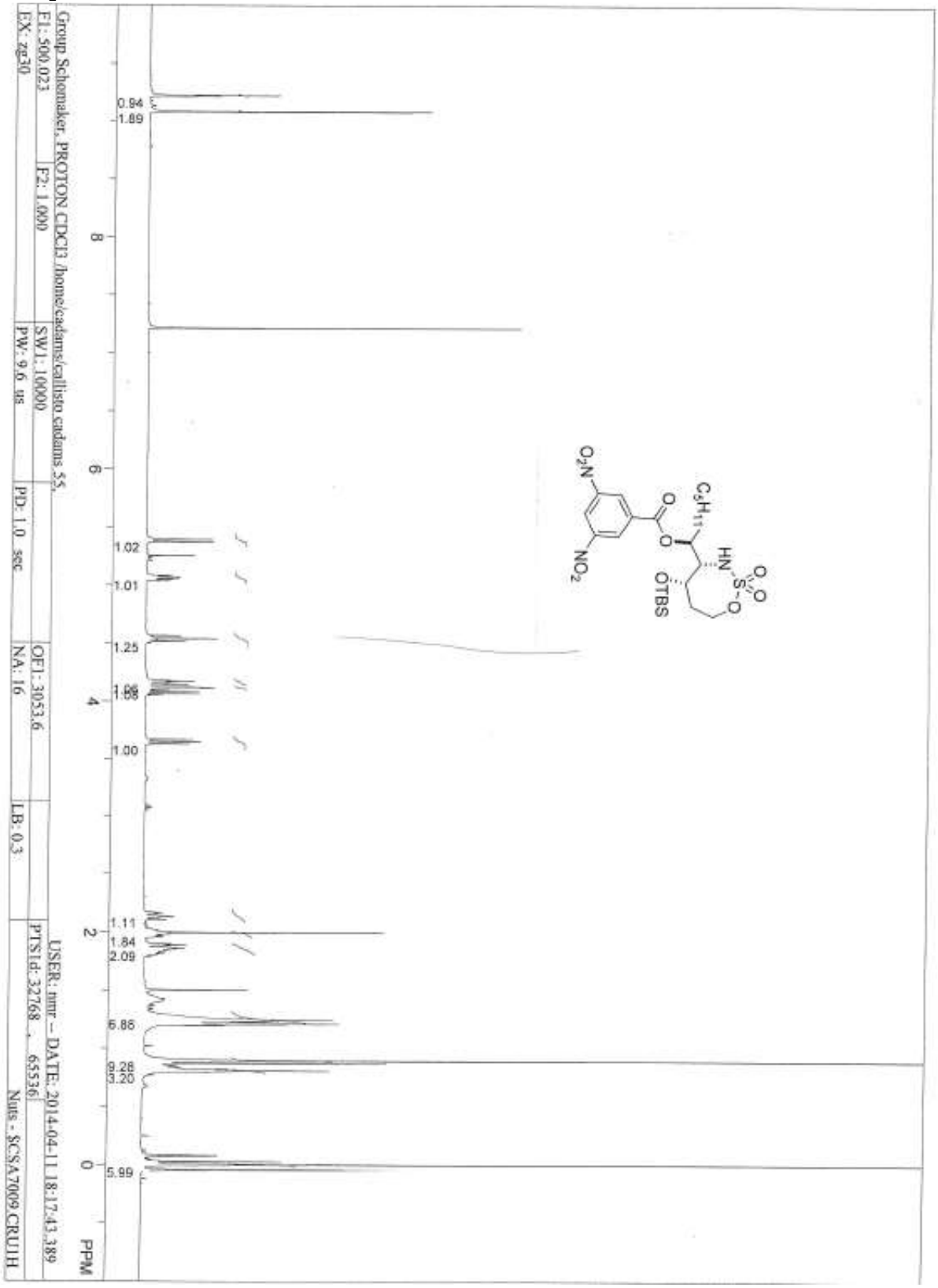


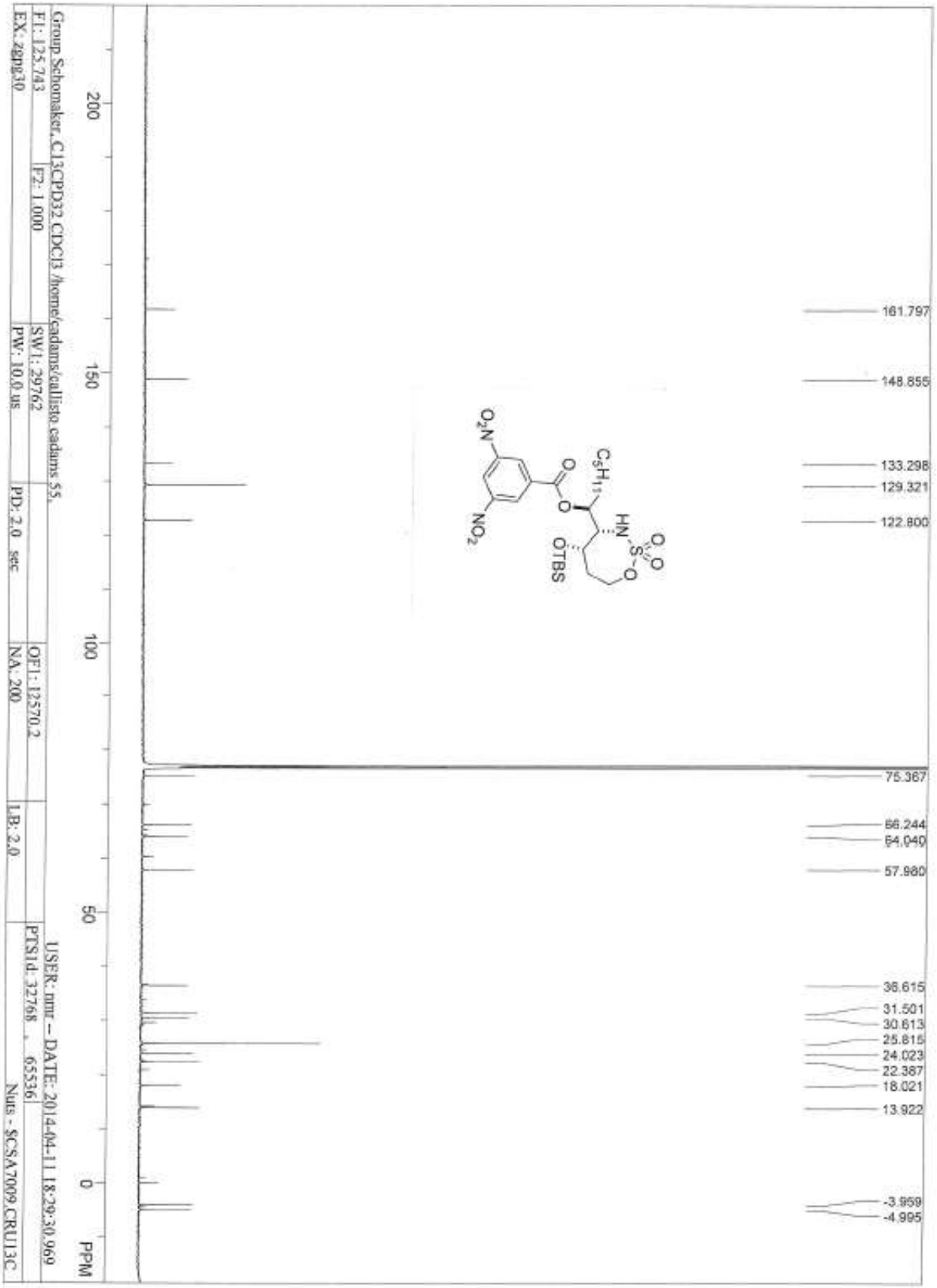


Group Schomaker, C13CPD32 D2O /home/rgrigg/callisto rgrigg 15,

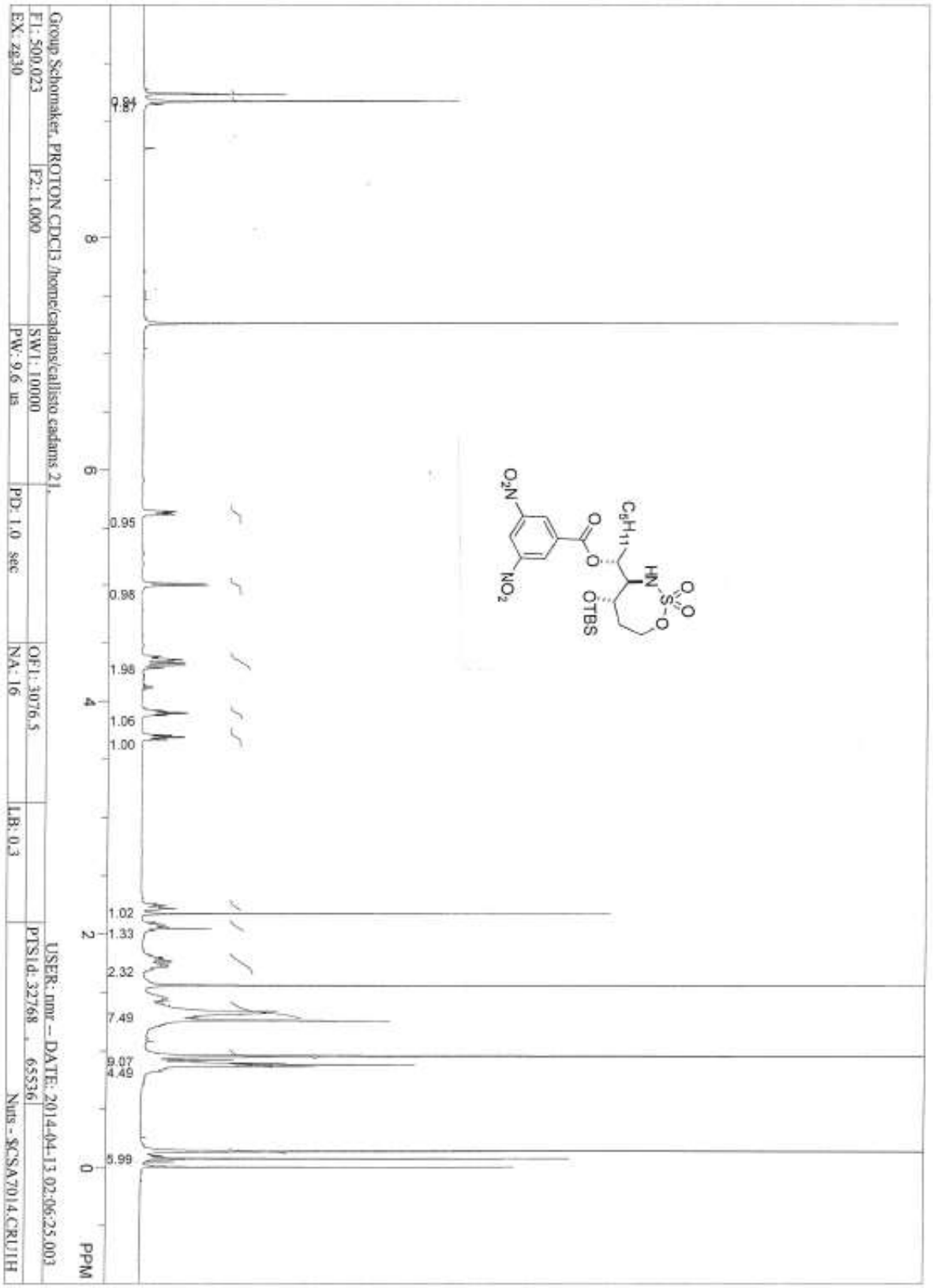
F1: 125.743	F2: 1.000	SW1: 29762		OF1: 12579.7		USER: nmr -- DATE: 2014-02-07 16:25:02.667
EX: zgpg30		PW: 10.0 us	PD: 2.0 sec	NA: 64	LB: 2.0	PTS1d: 32768 , 32768
						Nuts - $C1402071556 RDG9280 11

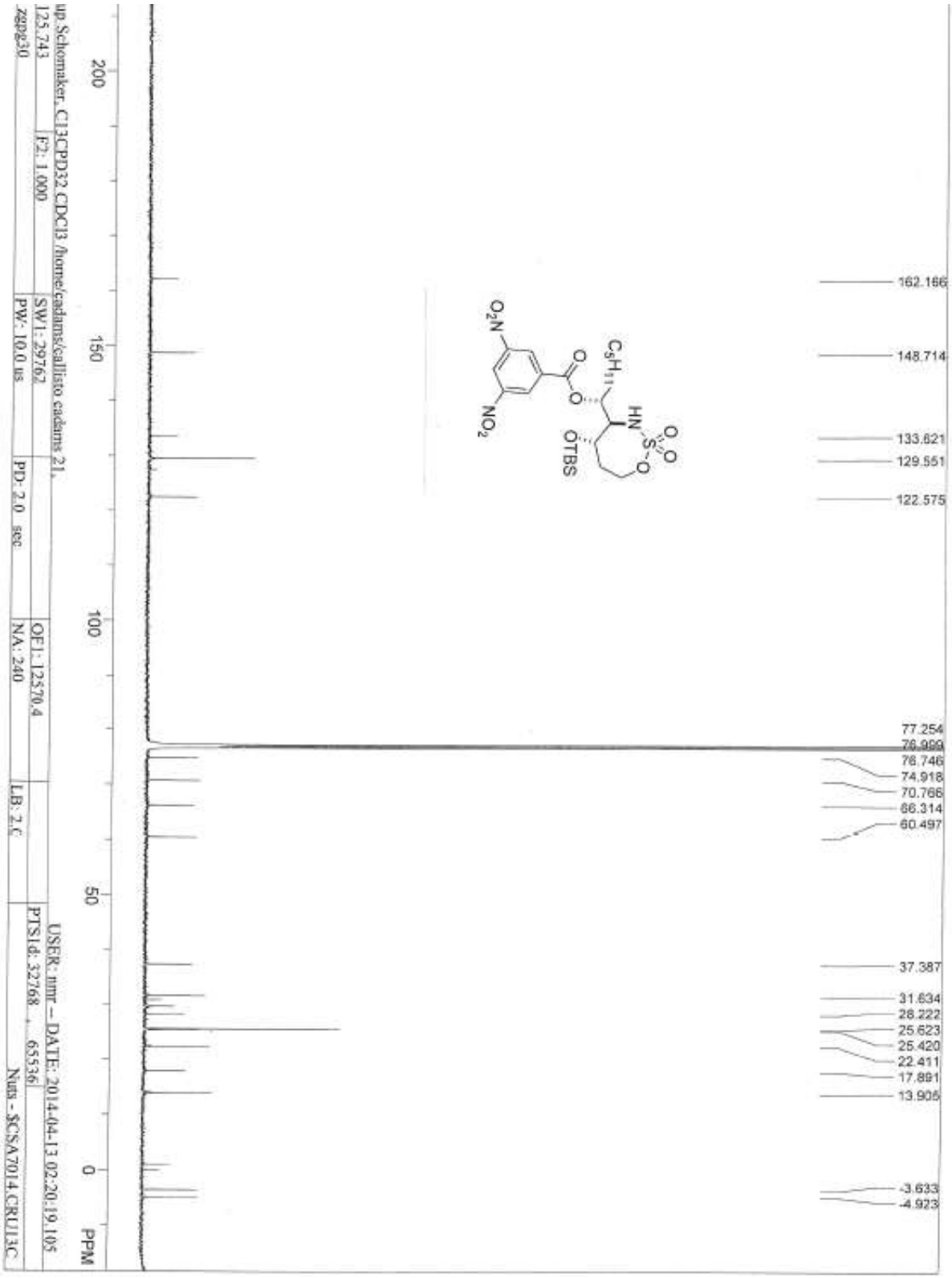
Compound 3.S21.



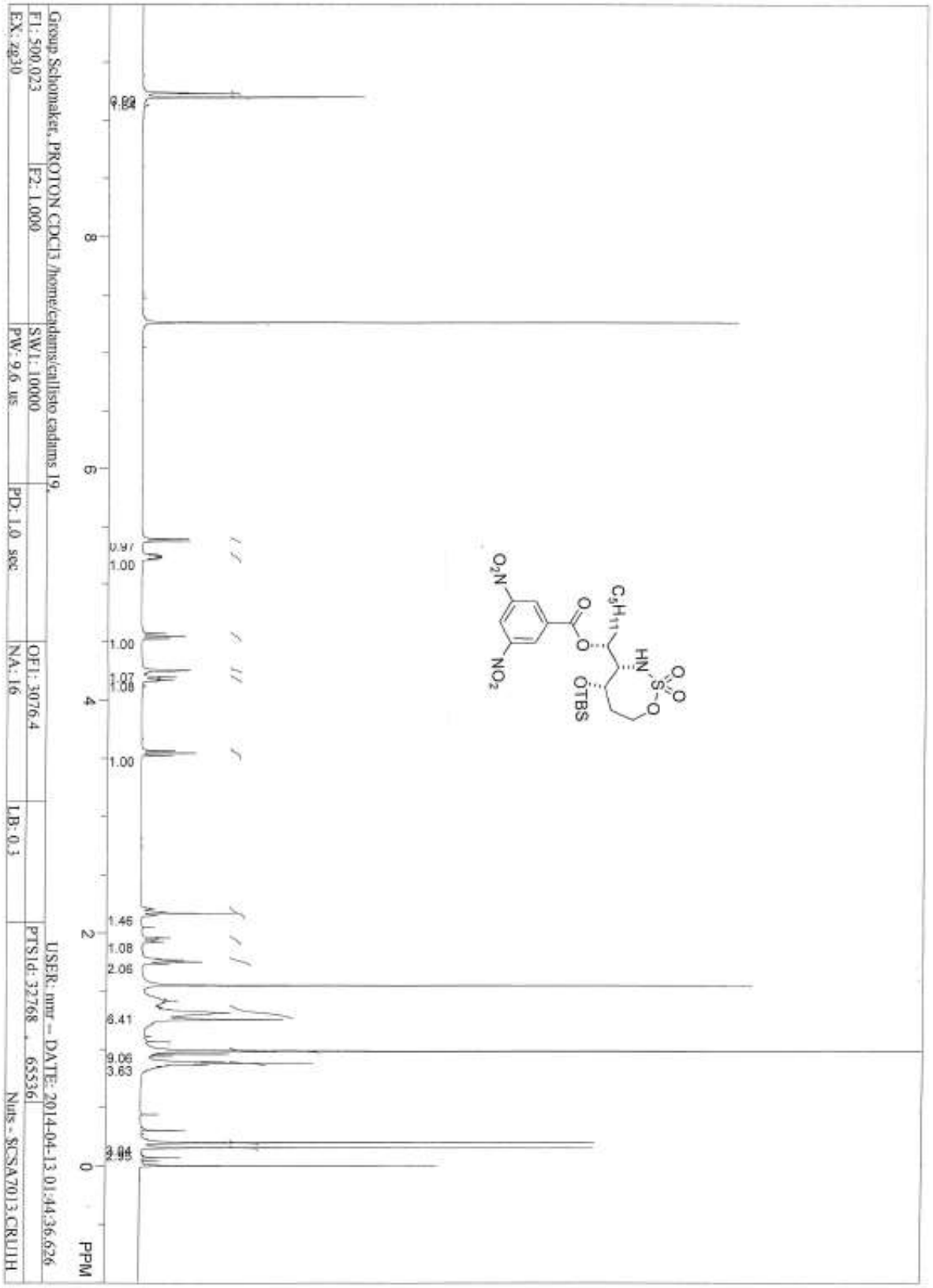

161.797
148.855
133.298
129.321
122.800
75.367
66.244
64.040
57.980
36.615
31.501
30.613
25.815
24.023
22.387
18.021
13.922
-3.959
-4.995
200
150
100
50
0
PPM
Group Schomaker, C13CPD32 CDCl3 /home/cadams/callisto.cadams 55.
F1: 125.743
F2: 1.000
EX: zgpg30
SW1: 29762
PW: 10.0 us
PD: 2.0 sec
OF1: 125702
NA: 200
LB: 2.0
USER: nmr – DATE: 2014-04-11 18:29:30.969
PTS1d: 32768
65536
Nuts - SCSA7009.CRU13C

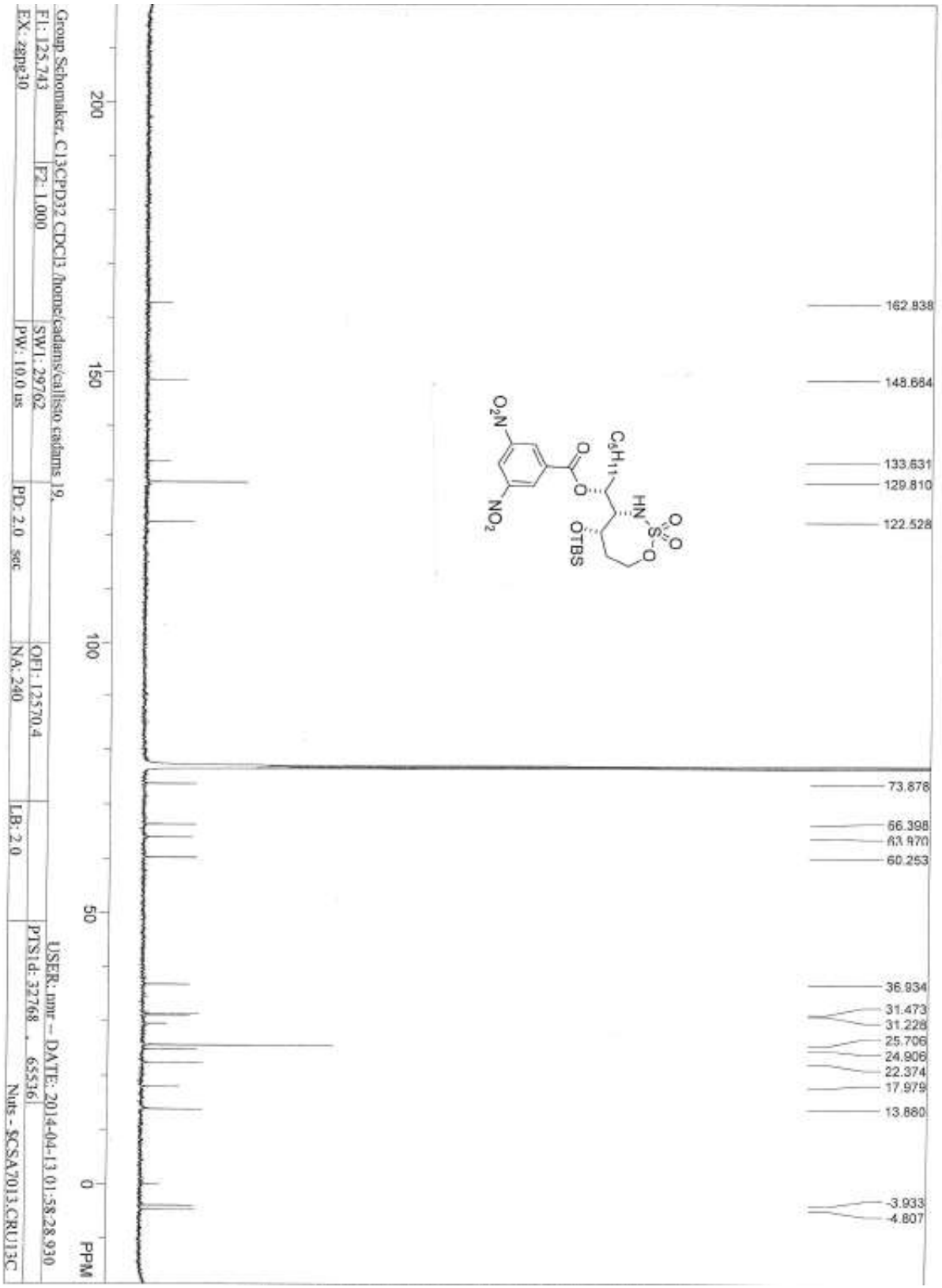
Compound 3.S22.



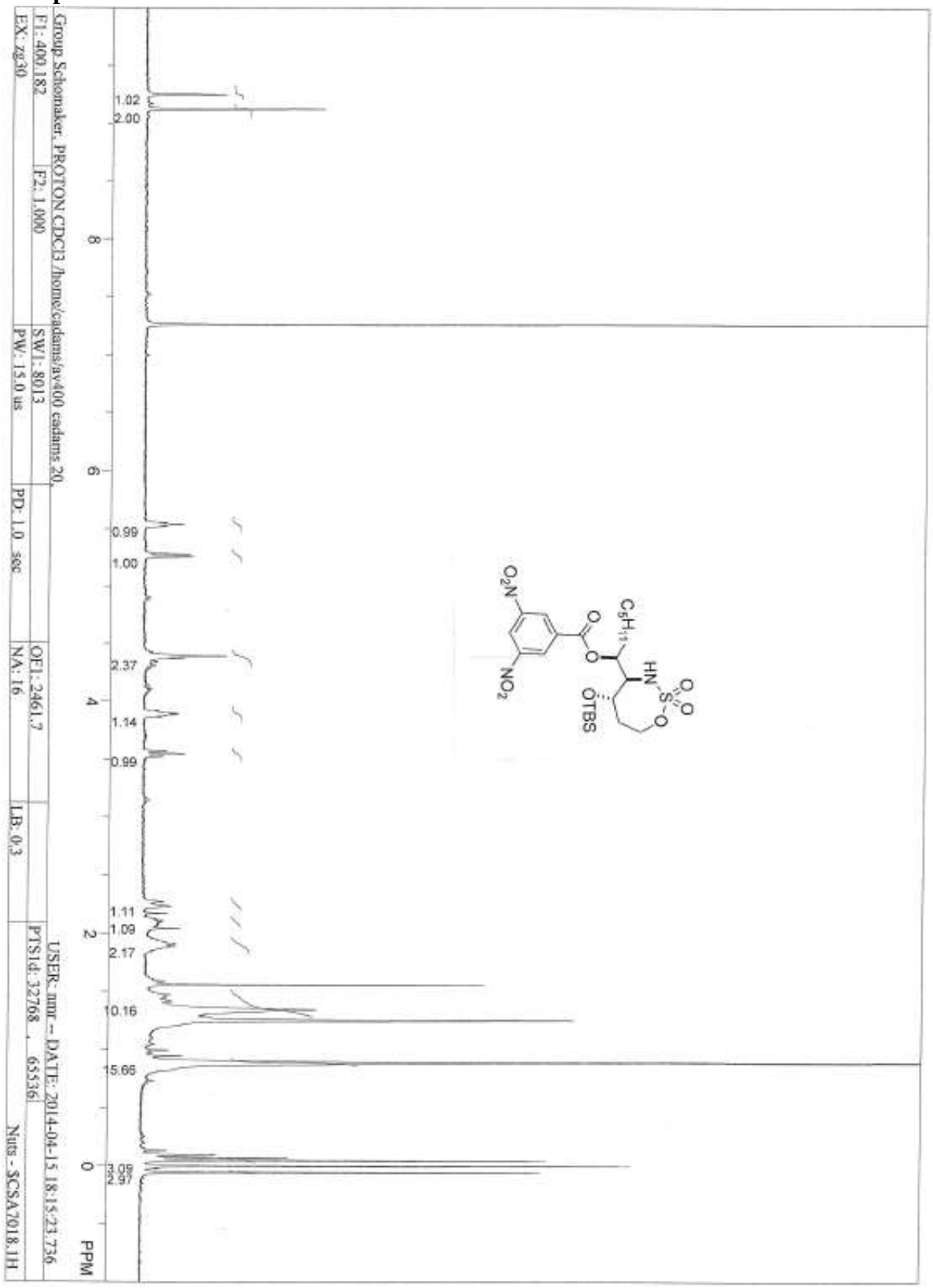

162.166
148.714
133.621
129.551
122.575
77.254
76.999
76.746
74.918
70.766
66.314
60.497
37.387
31.634
28.222
25.623
25.420
22.411
17.891
13.906
-3.633
-4.923
200
150
100
50
0
PPM
up.Schomaker.C13CPD32.CDCl3 /home/cadams/callisto cadams 21.
125.743
zgpg30
F2: 1.000
SW1: 29762
PW: 10.0 us
PD: 2.0 sec
OF1: 12570.4
NA: 240
LB: 2.0
USER: nmr – DATE: 2014-04-13 02:20:19.105
PTS1d: 32768 65536
Nuts - $CSA7014.CRU13C

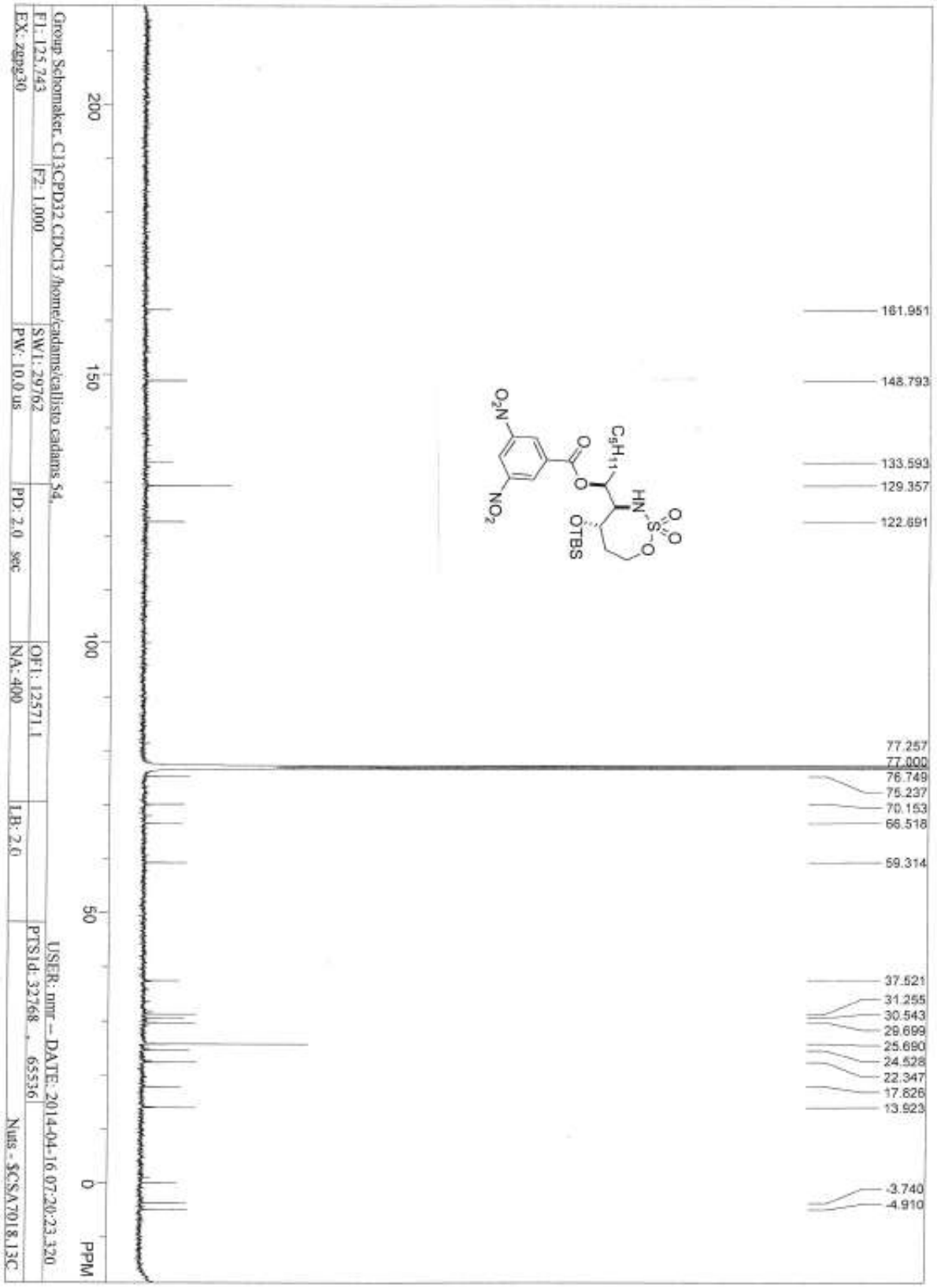
Compound 3.S23.



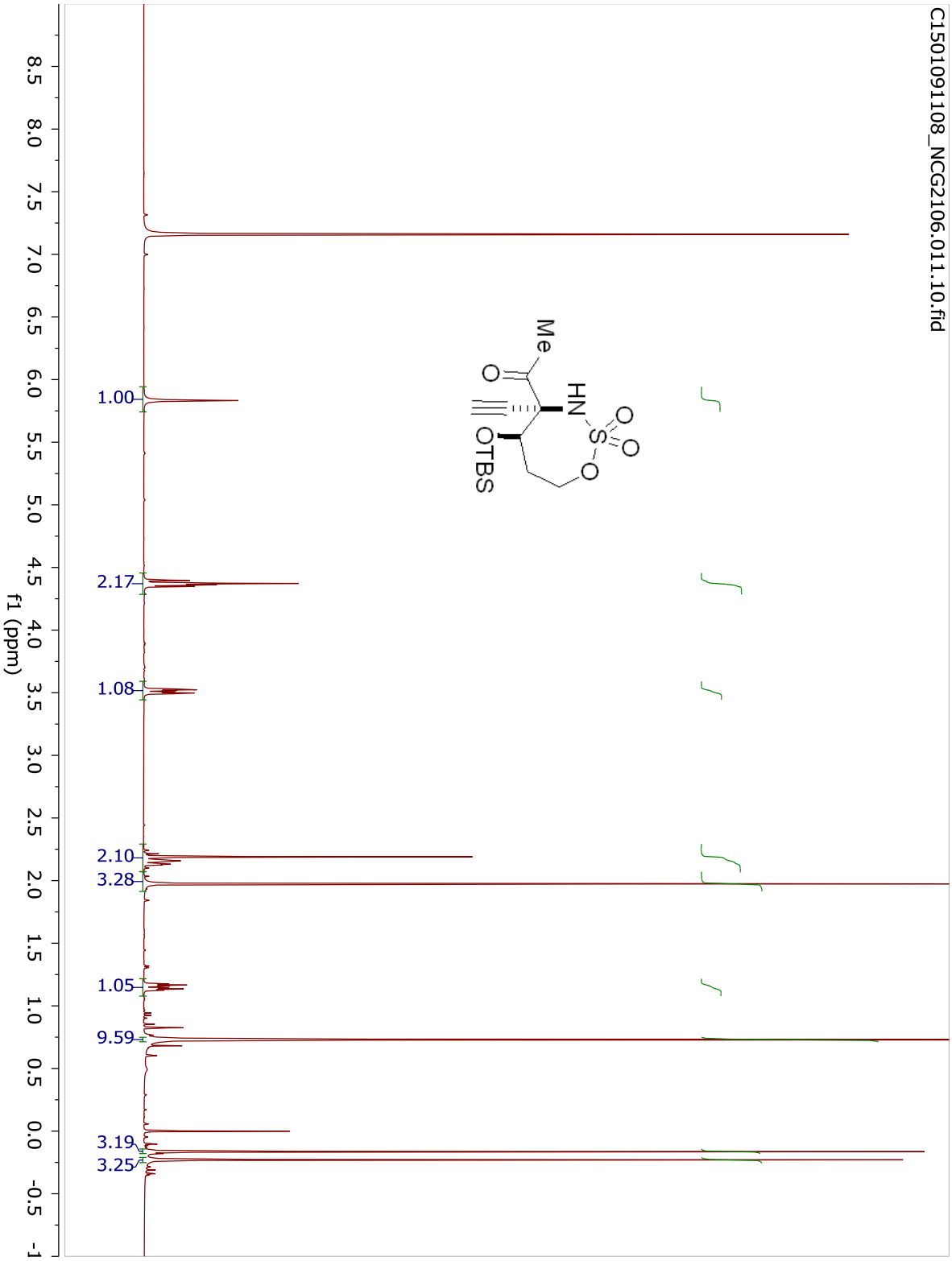

162.838
148.684
133.631
129.810
122.528
73.878
66.398
63.970
60.253
36.934
31.473
31.228
25.706
24.906
22.374
17.979
13.880
-3.933
-4.807
200
150
100
50
0
PPM
Group Schomaker, C13CPD32 CDCl3 /home/cadams/calliso cadams 19
F1: 125.743
F2: 1.000
EX: zgpg30
SW1: 29762
PW: 10.0 us
PD: 2.0 sec
QF1: 12570.4
NA: 240
LB: 2.0
USER: nmr -- DATE: 2014-04-13 01:58:28.930
PTS1d: 32768 , 65536
Nuts - $CSA7013.CRU13C

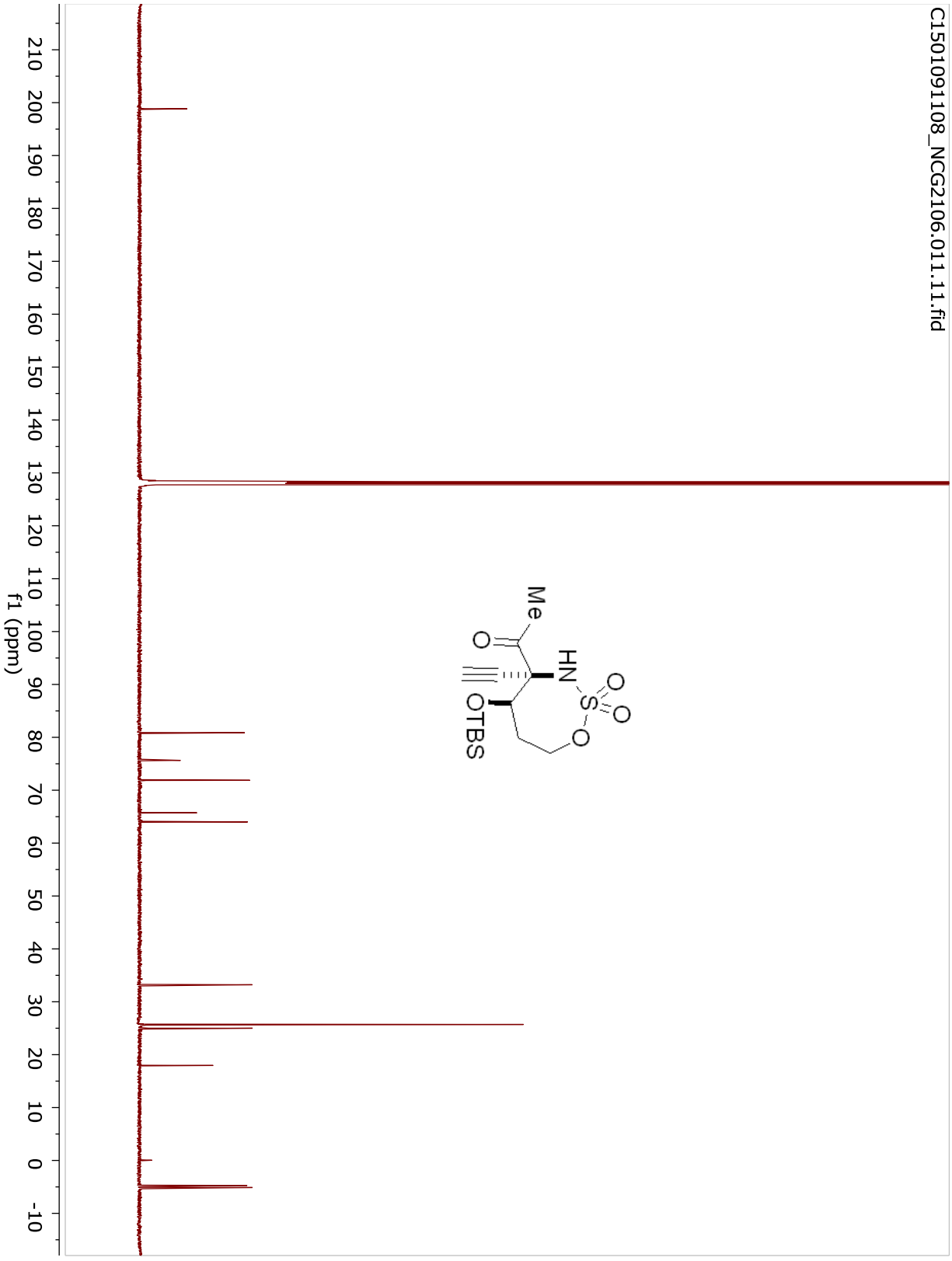
Compound 3.S24.



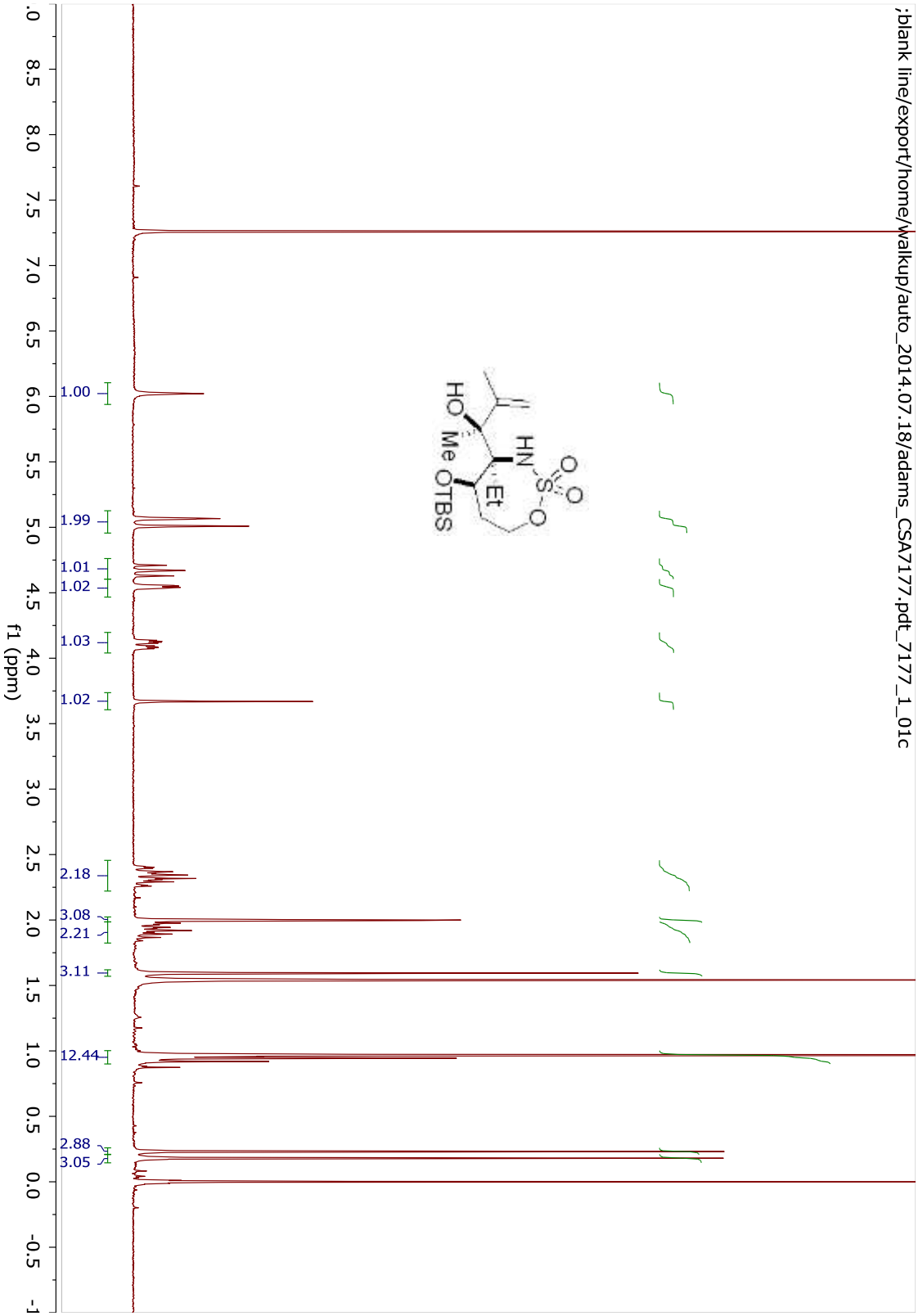


Compound 4.26a

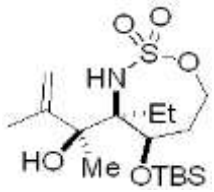

C1501091108_NCG2106.011.10.fid
Me
O
HN
S
O
O
O
OTBS
1.00
2.17
1.08
2.10
3.28
1.05
9.59
3.19
3.25
f1 (ppm)
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1


C1501091108_NCG2106.011.11.fid
Me
O
HN
S
O
O
O
OTBS
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

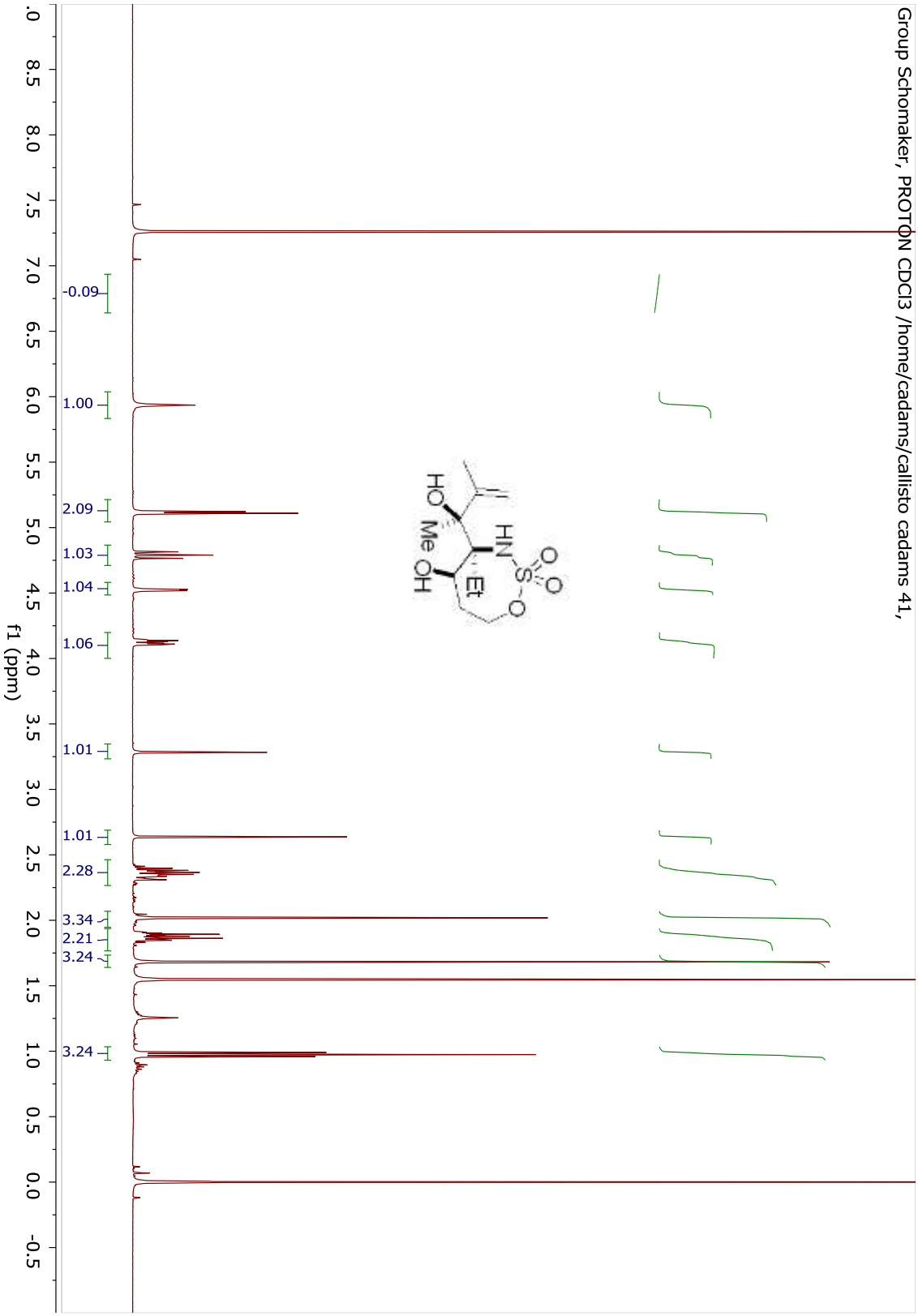
Compound 4.27.



Group Schomaker, C13CPD32 CDCl3 /home/cadams/callisto cadams 28,

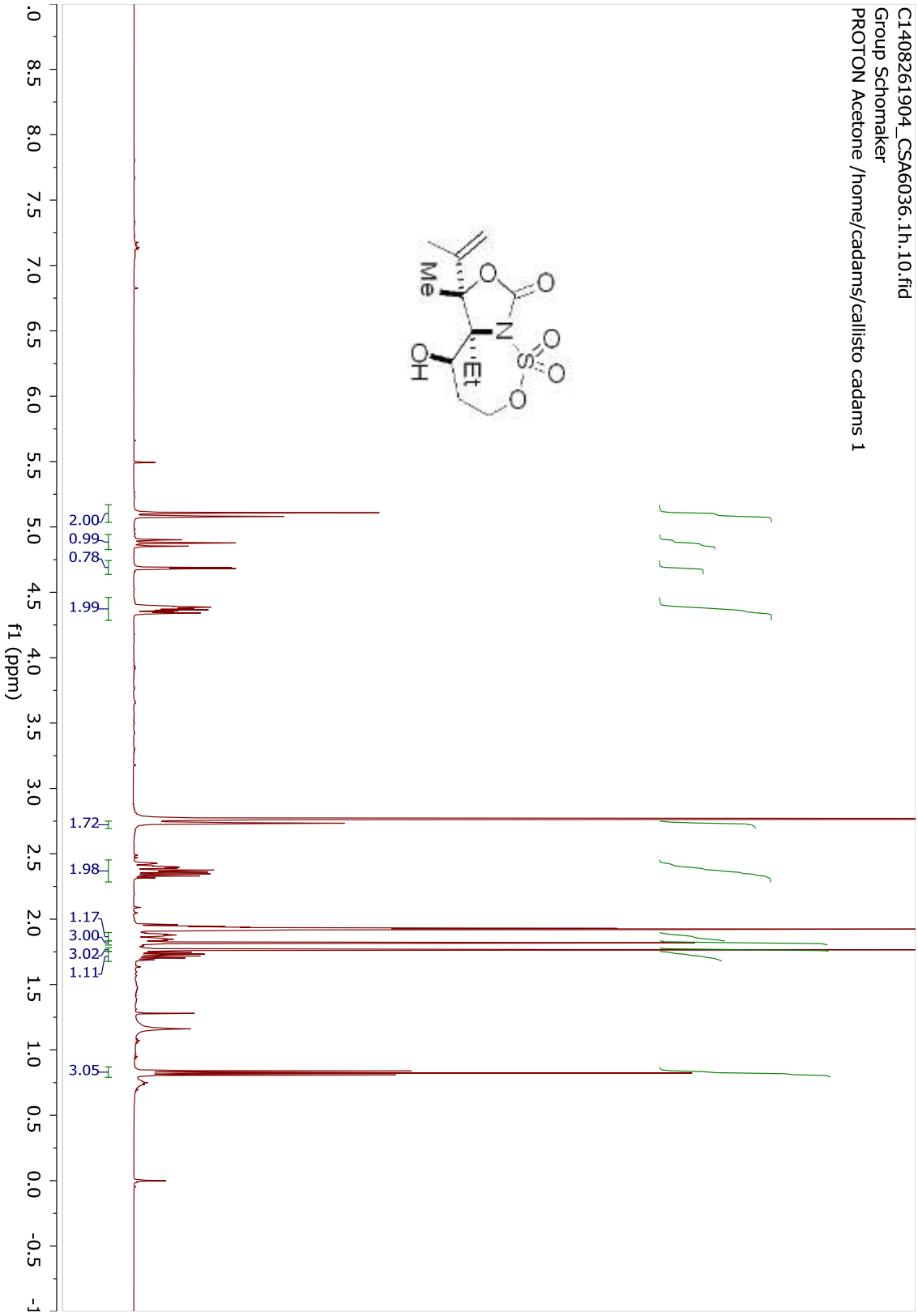


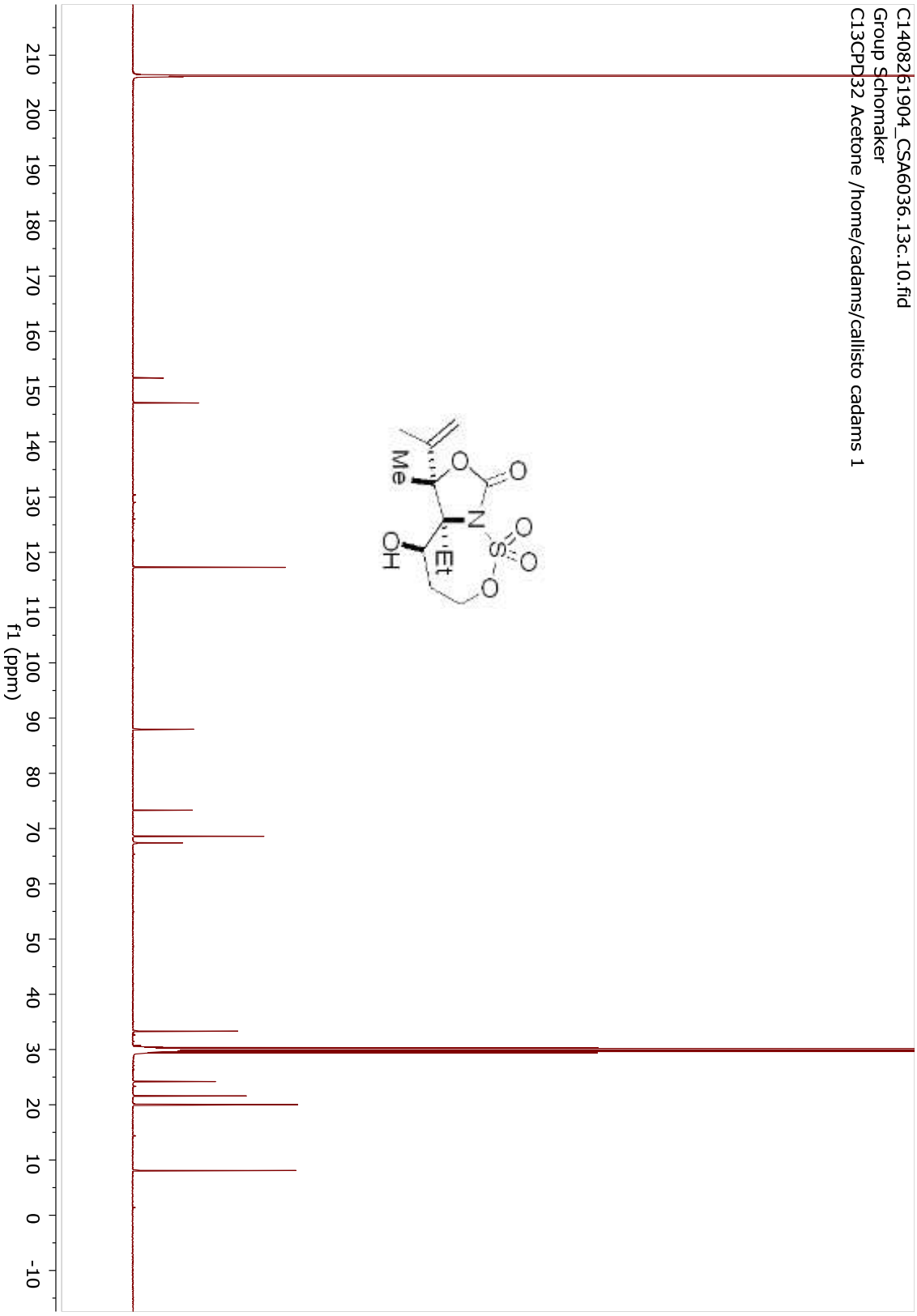
Compound 4.28.



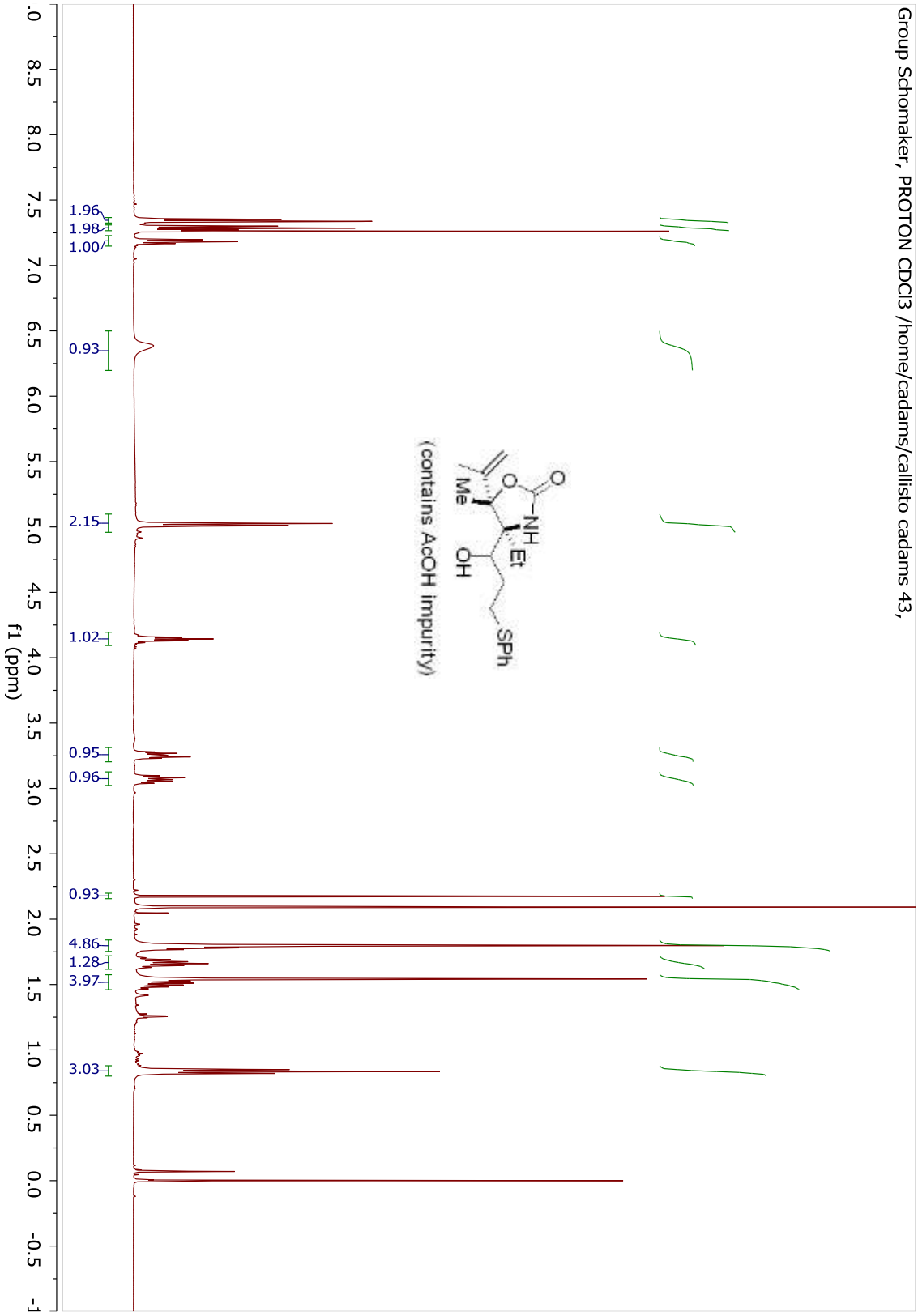
Group Schomaker, C13CPD32 CDCl3 /home/cadams/callisto cadams 41,
HO
Me
OH
HN
S
O
O
O
Et
f1 (ppm)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

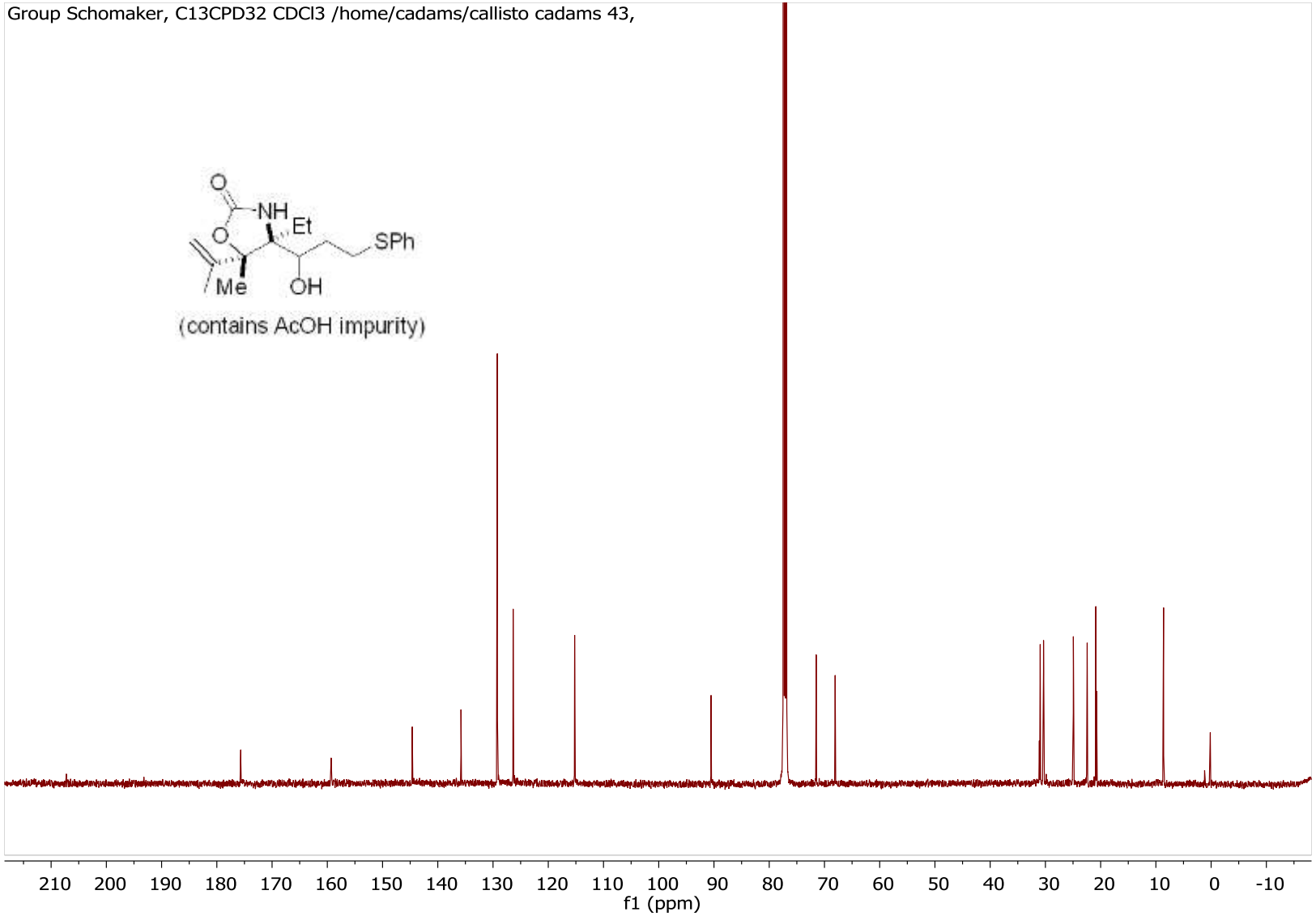
Compound 4.29.



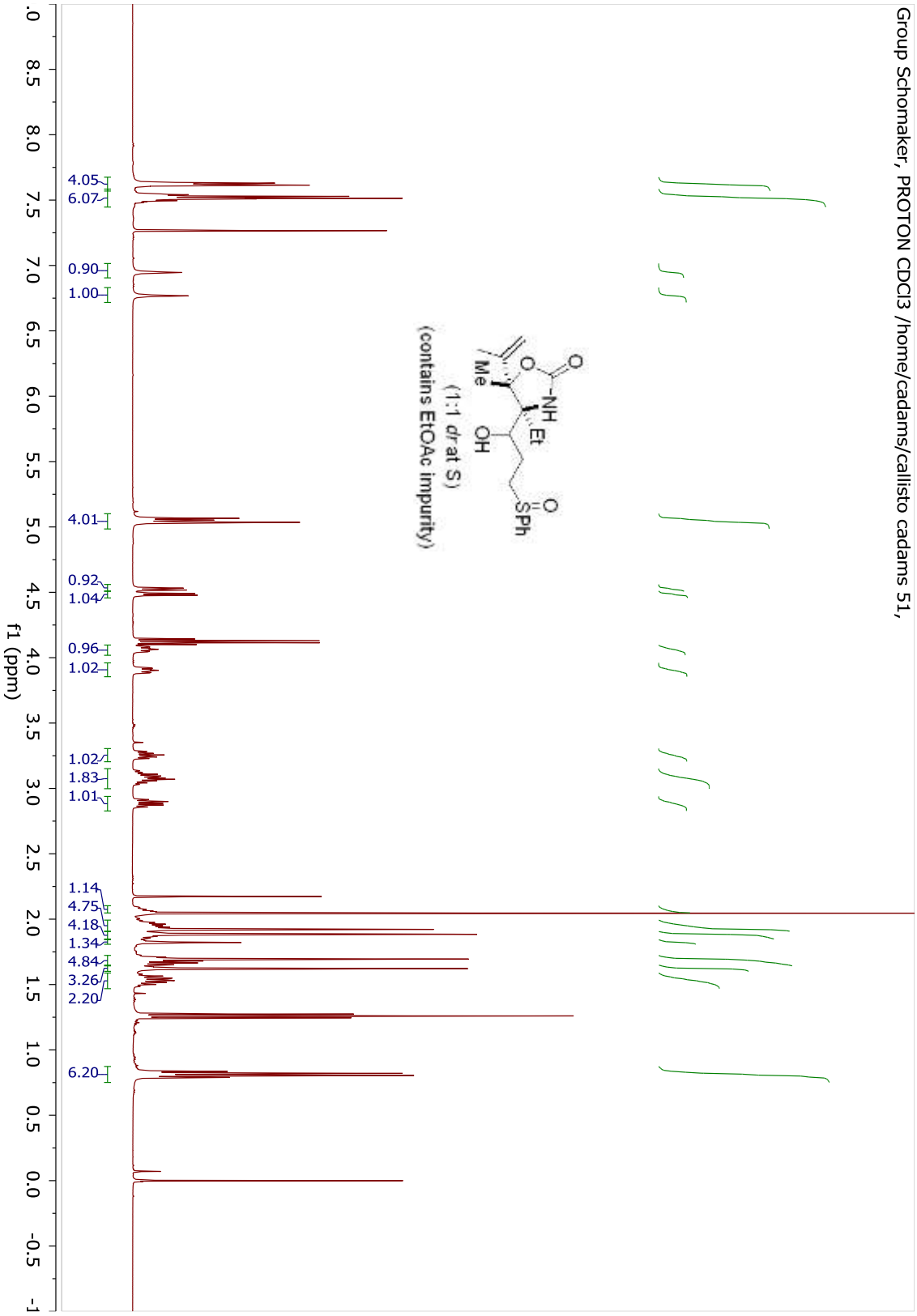

C140825 1904_CSA6036.13c.10.fid
Group Schomaker
C13CPD32 Acetone /home/cadams/callisto cadams 1
Me
Et
OH
f1 (ppm)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

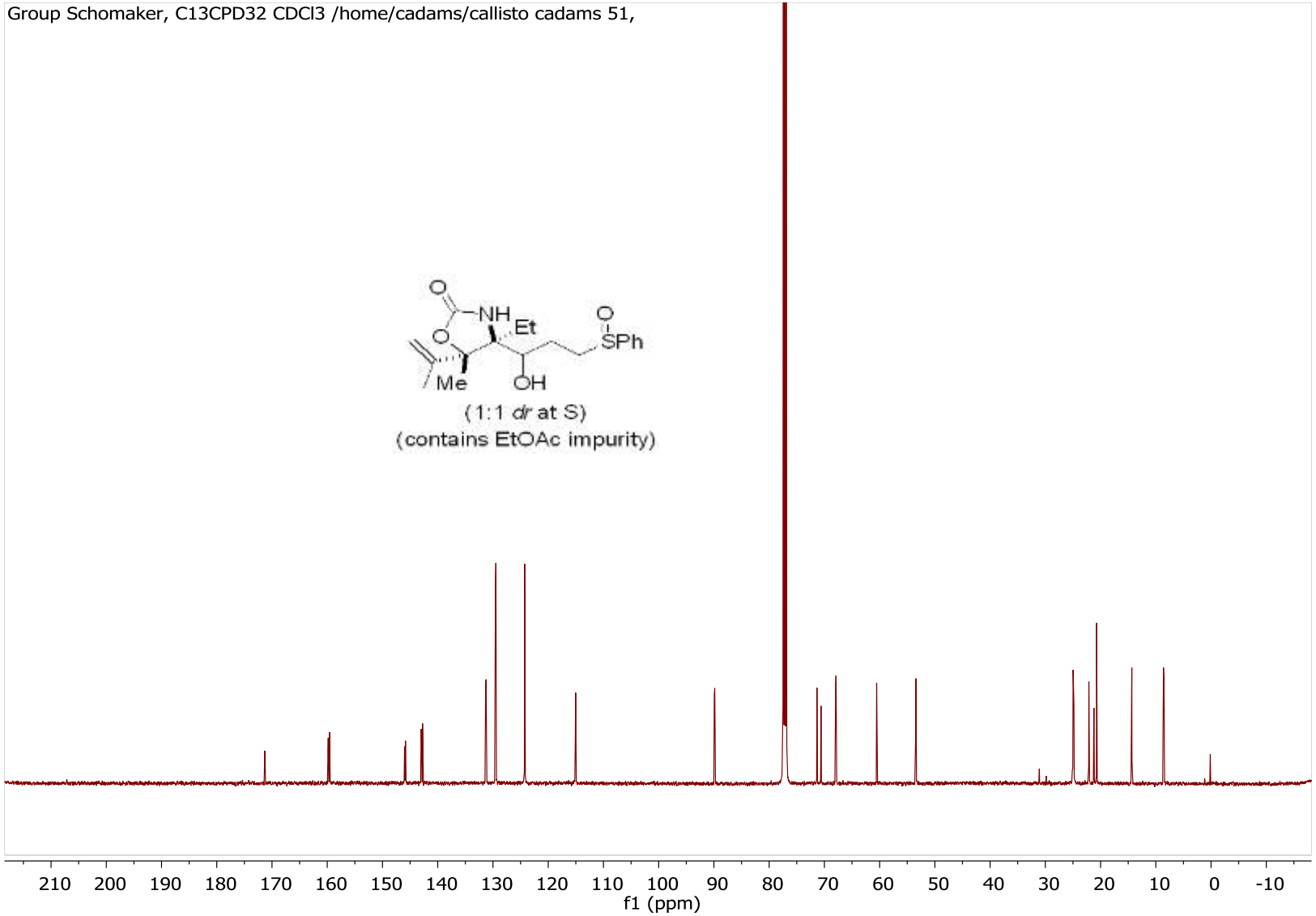
Compound 4.30



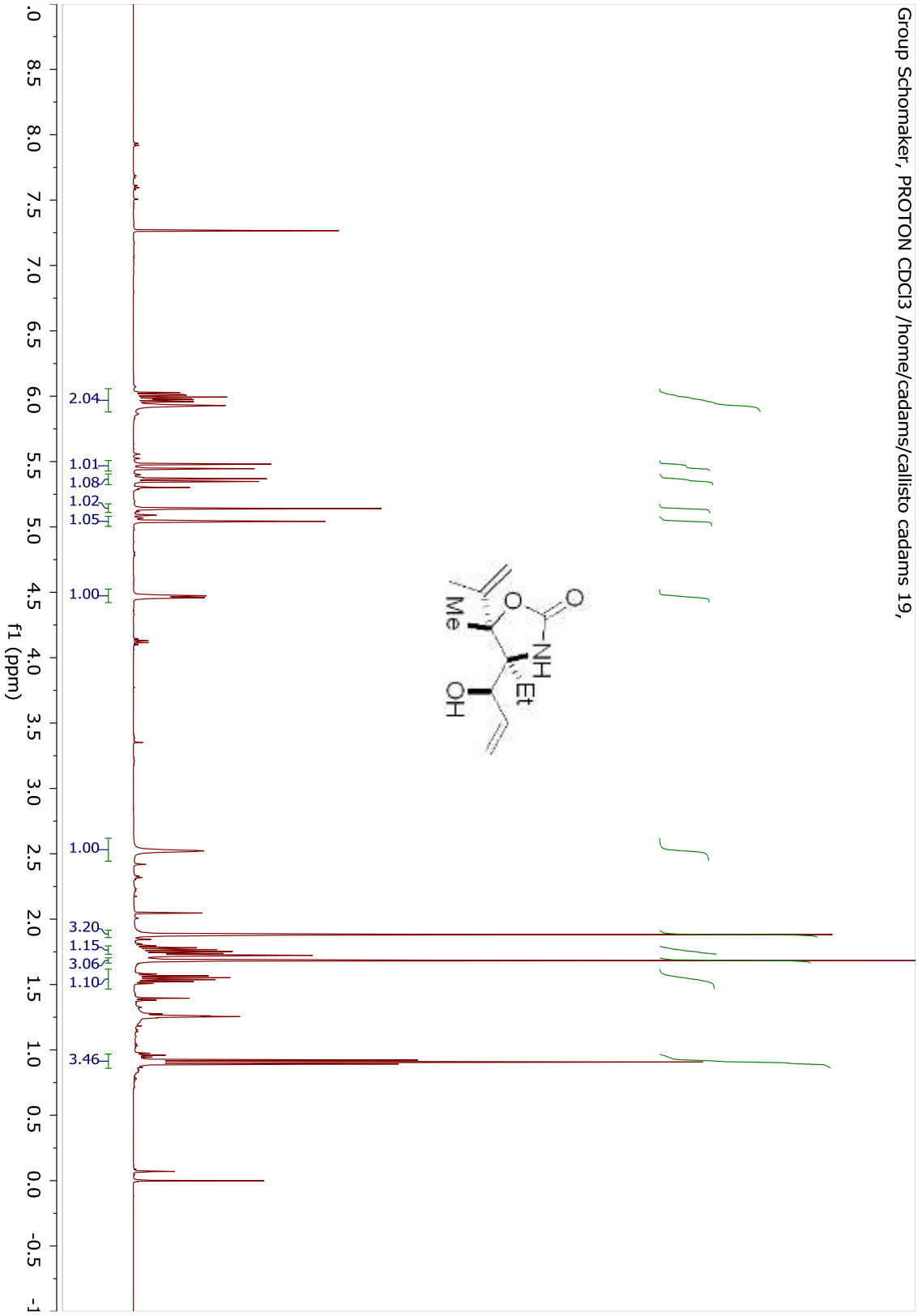

Group Schomaker, C13CPD32 CDCl3 /home/cadams/callisto cadams 43,
O
NH
Et
O
SPh
Me
OH
(contains AcOH impurity)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

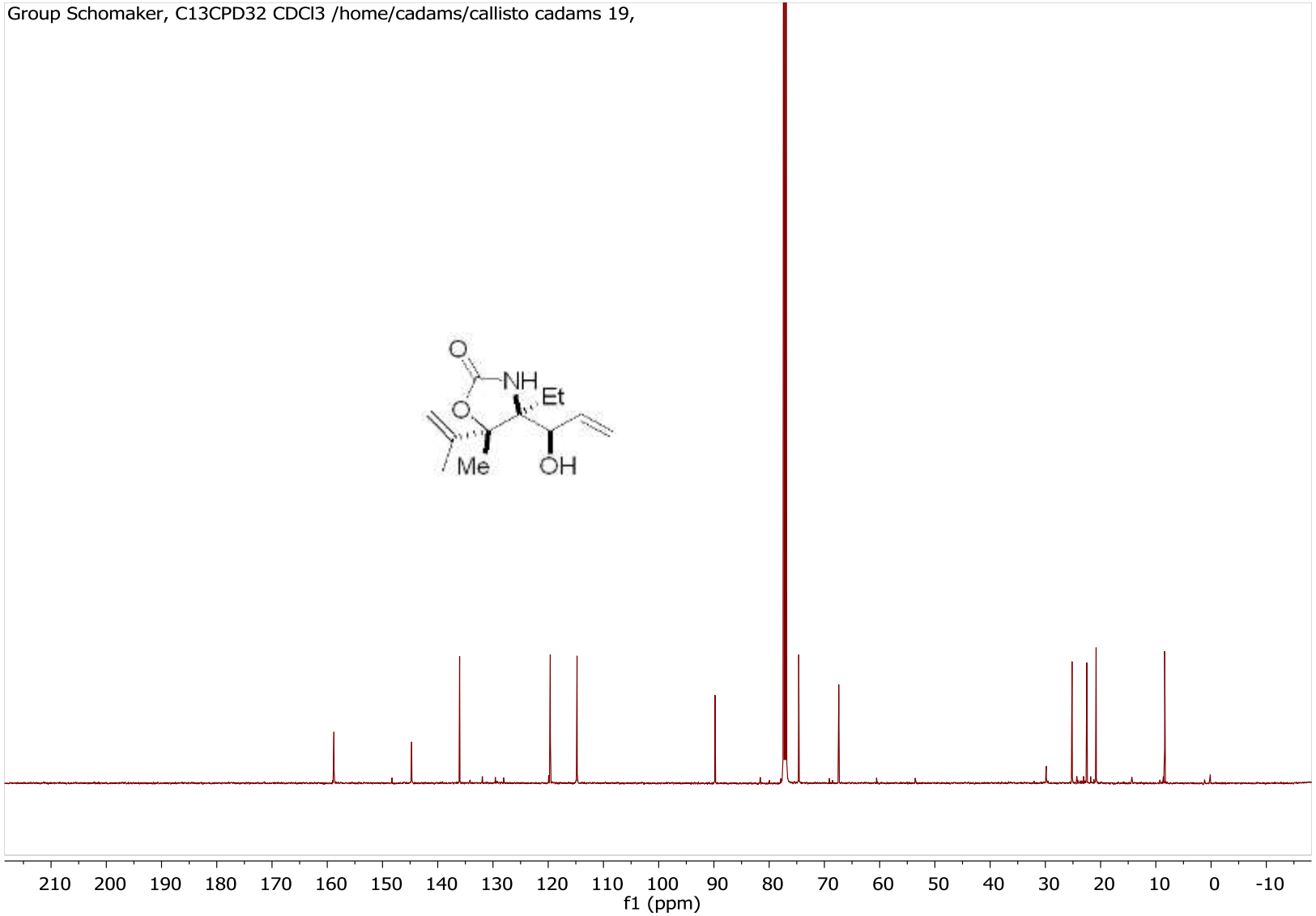
Compound 4.31



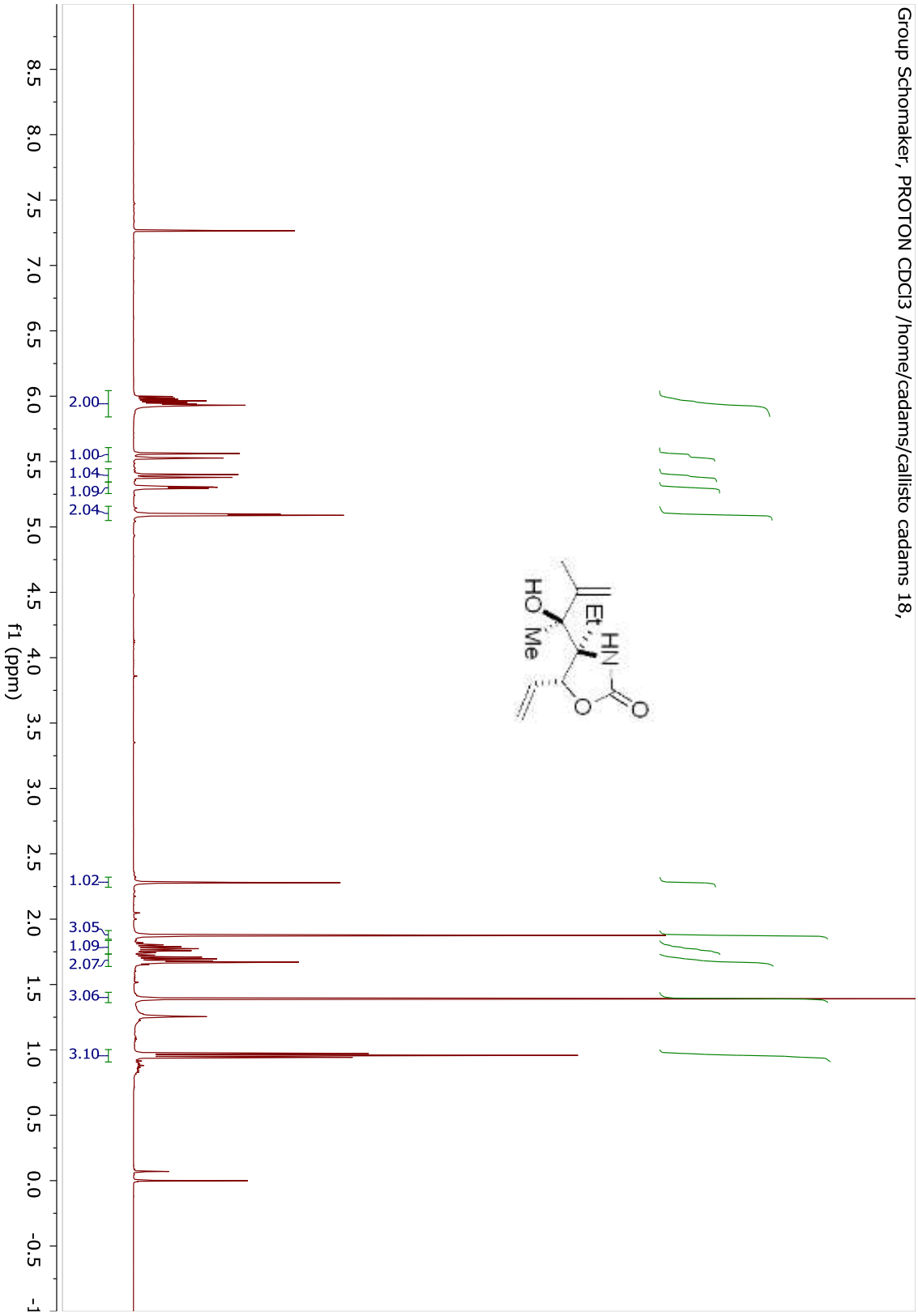

Group Schomaker, C13CPD32 CDCl3 /home/cadams/callisto cadams 51,
NH
Et
O
SPh
Me
OH
(1:1 dr at S)
(contains EtOAc impurity)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

Compound 4.32.



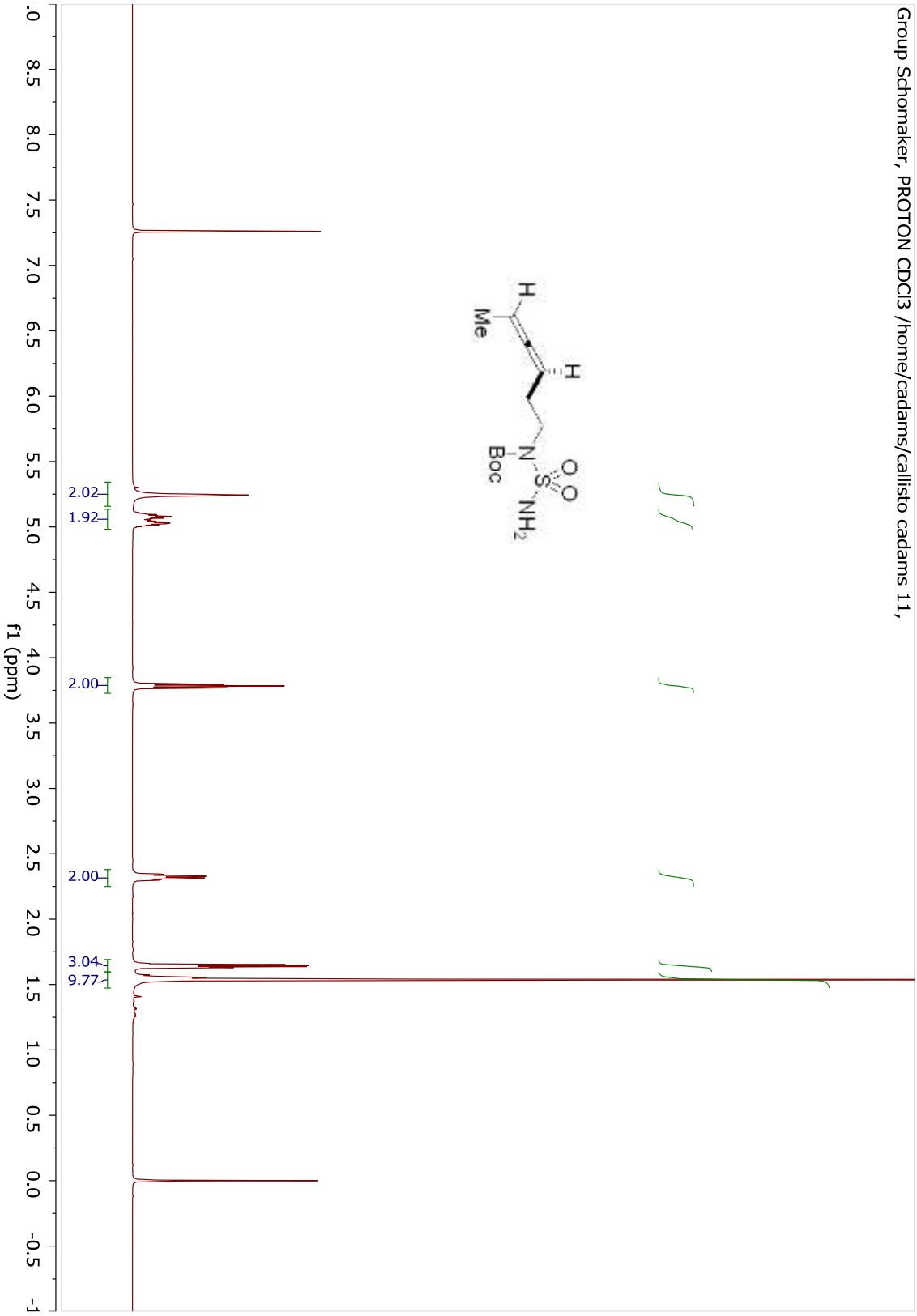

Group Schomaker, C13CPD32 CDCl3 /home/cadams/callisto cadams 19,
O
NH
Et
O
Me
OH
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

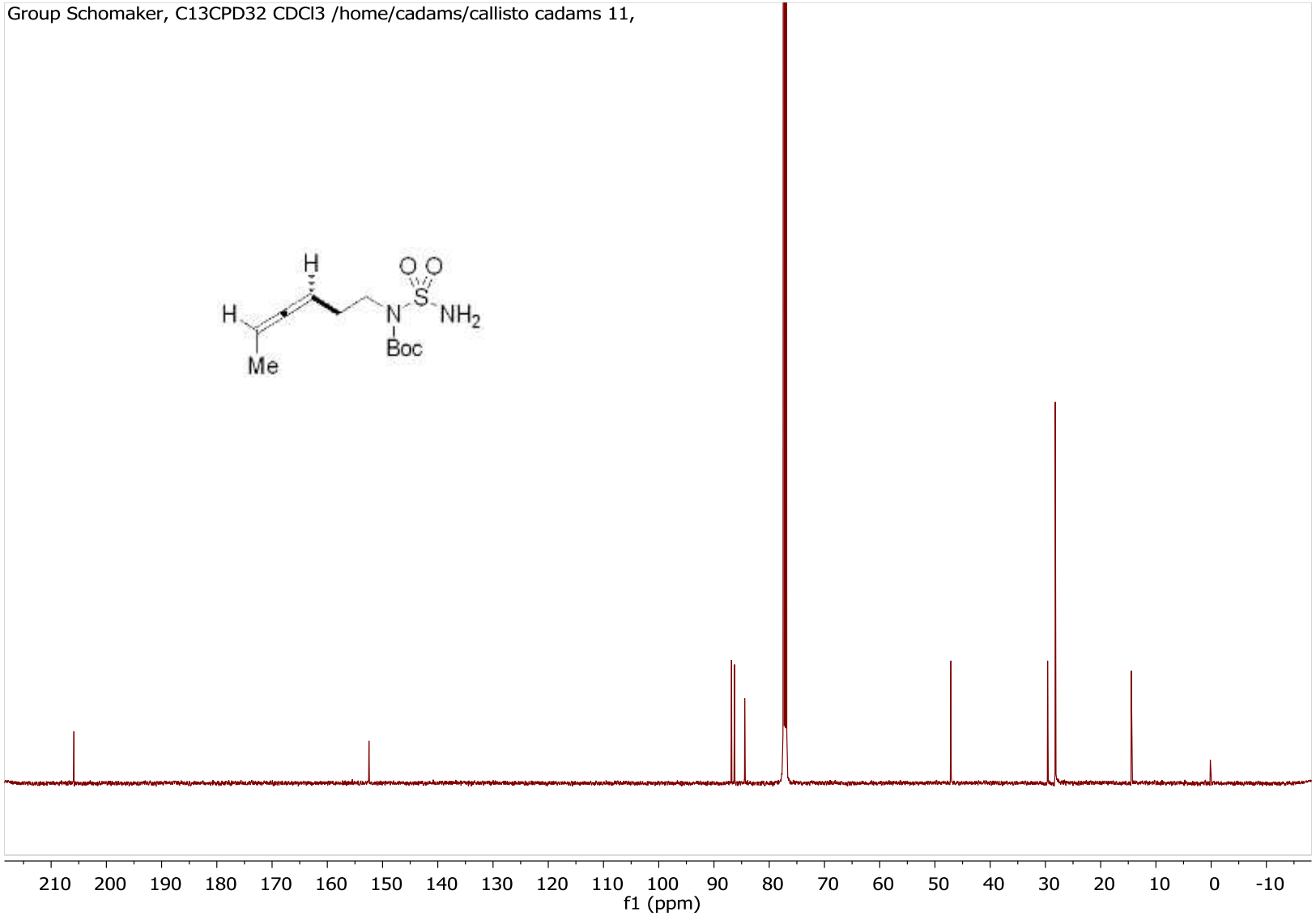
Compound 4.33.



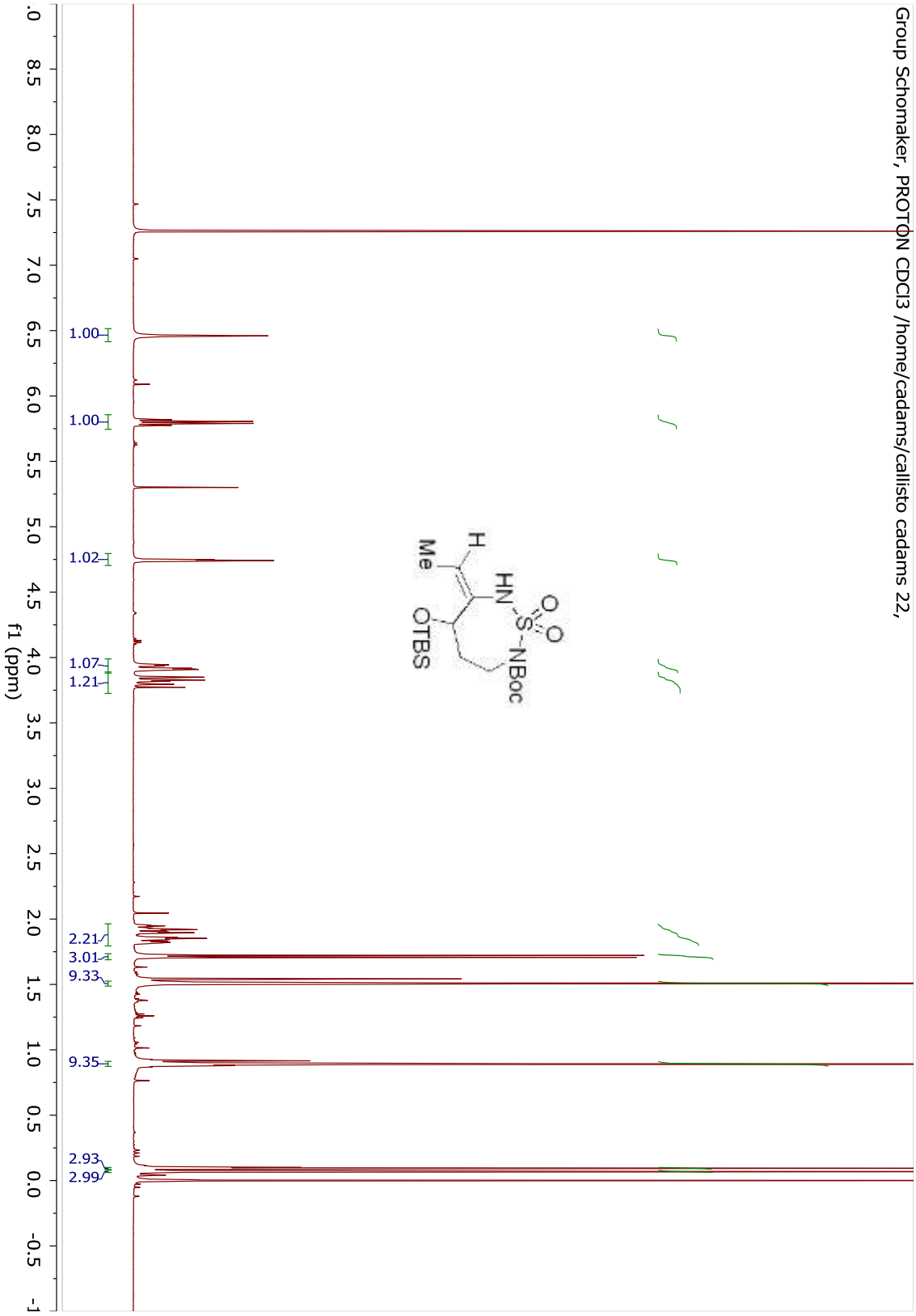
Group Schomaker, C13CPD32 CDCl3 /home/cadams/callisto cadams 18,
Et
HN
HO
Me
O
O
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

Compound 4.42.



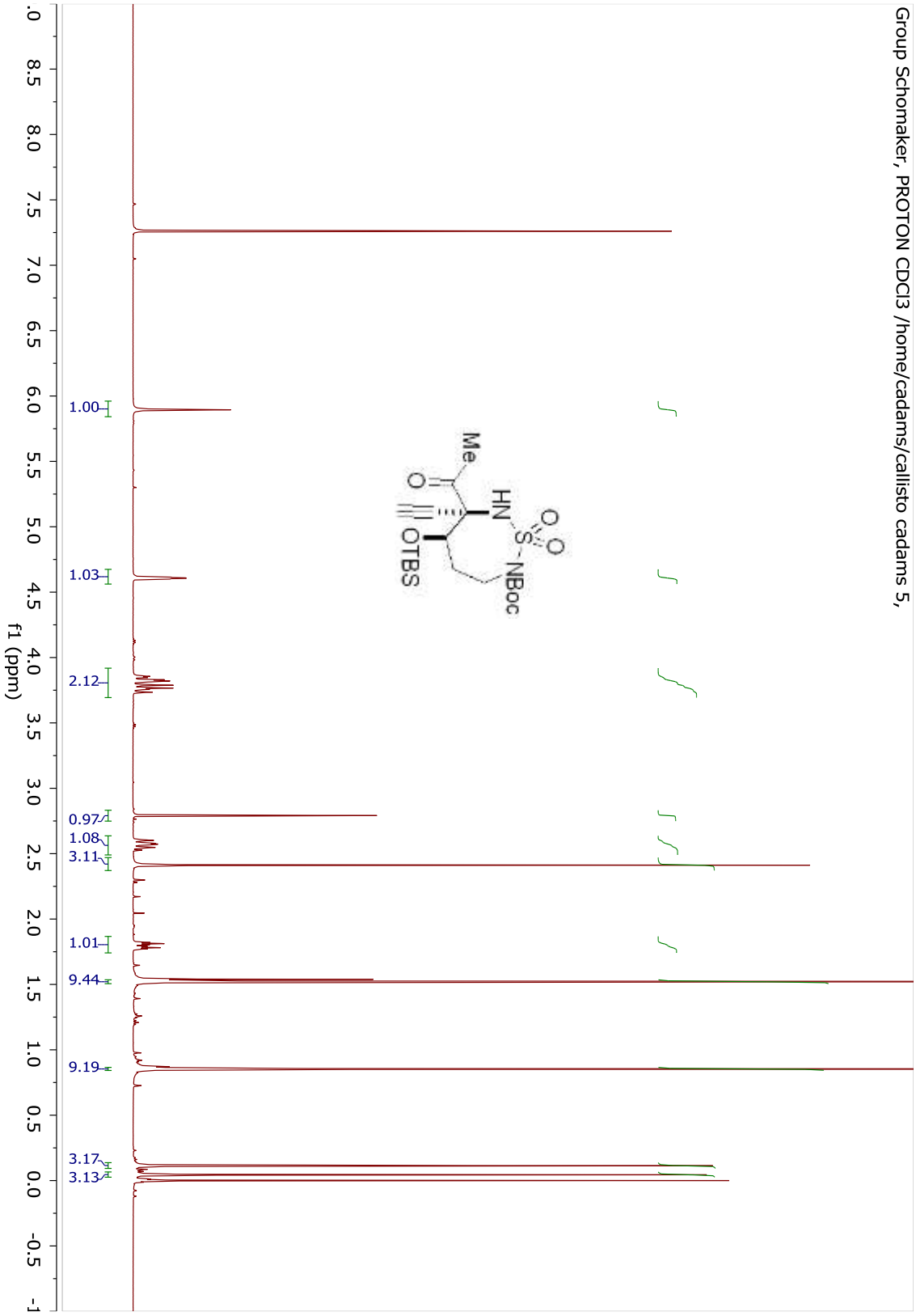

Group Schomaker, C13CPD32 CDCl3 /home/cadams/callisto cadams 11,
H
O O
S
H
N
NH2
Boc
Me
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

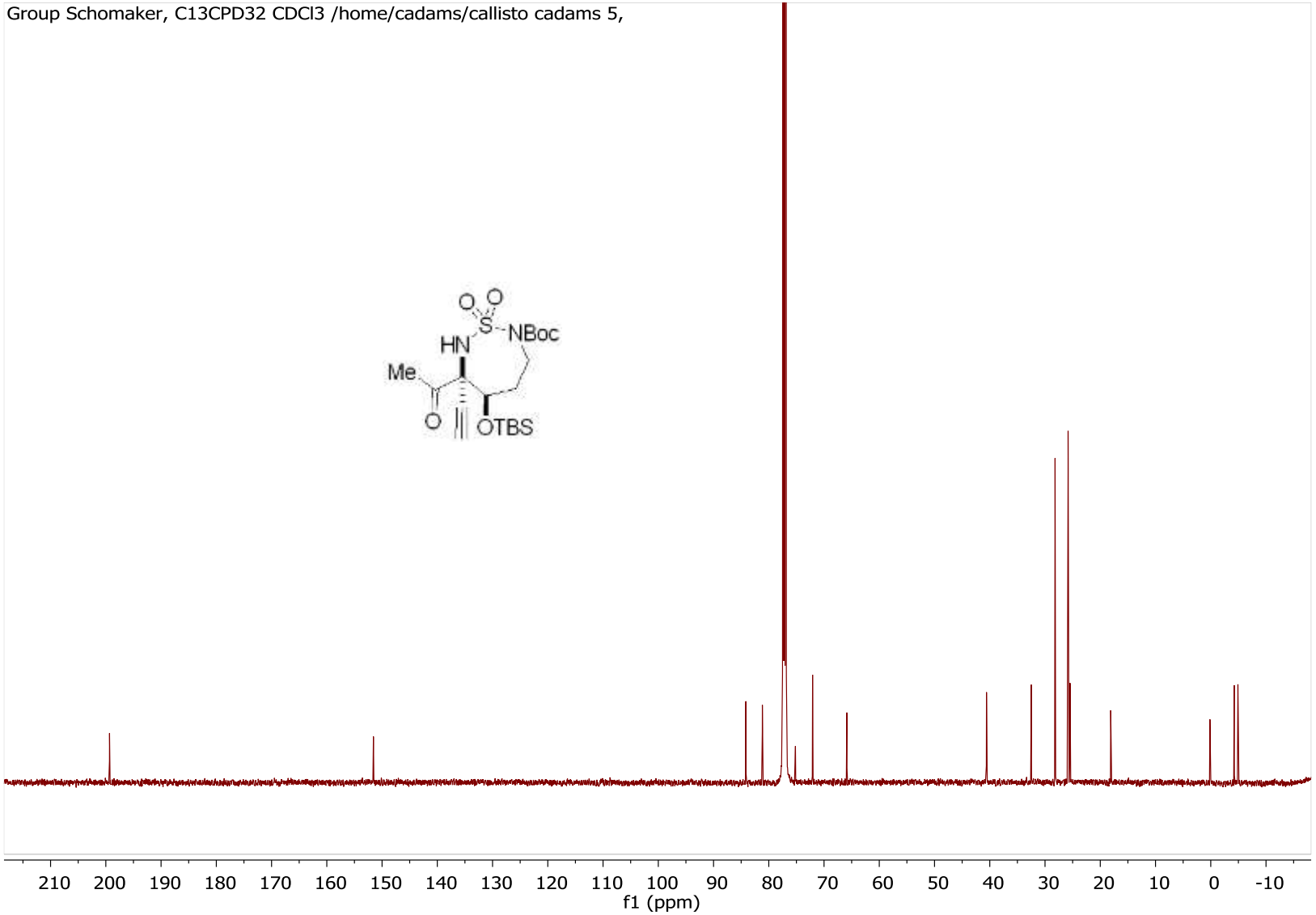
Compound 4.43.



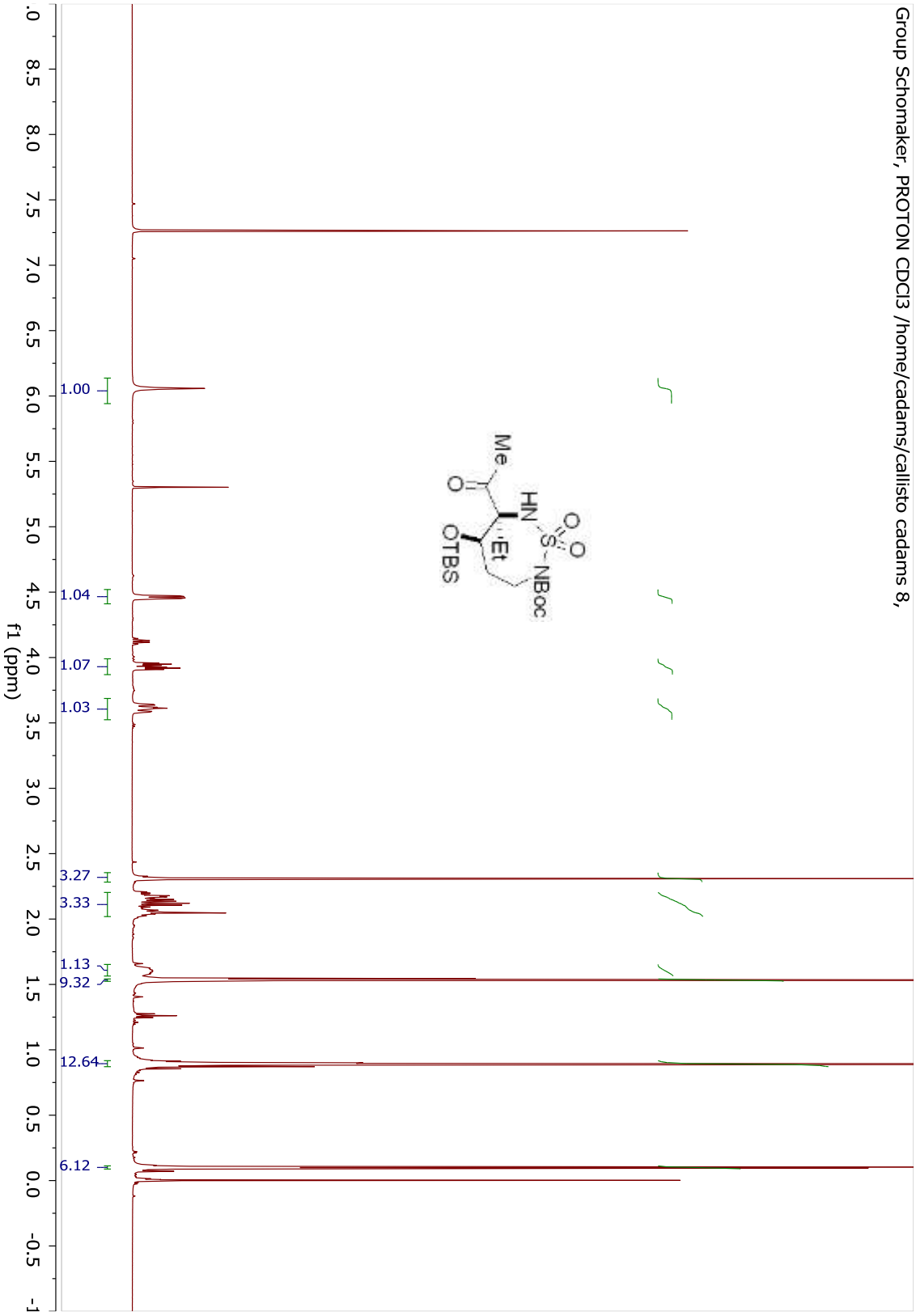
Group Schomaker, C13CPD32 CDCl3 /home/cadams/callisto cadams 58,
O
O
HN
S
NBoc
H
Me
OTBS
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

Compound 4.44.



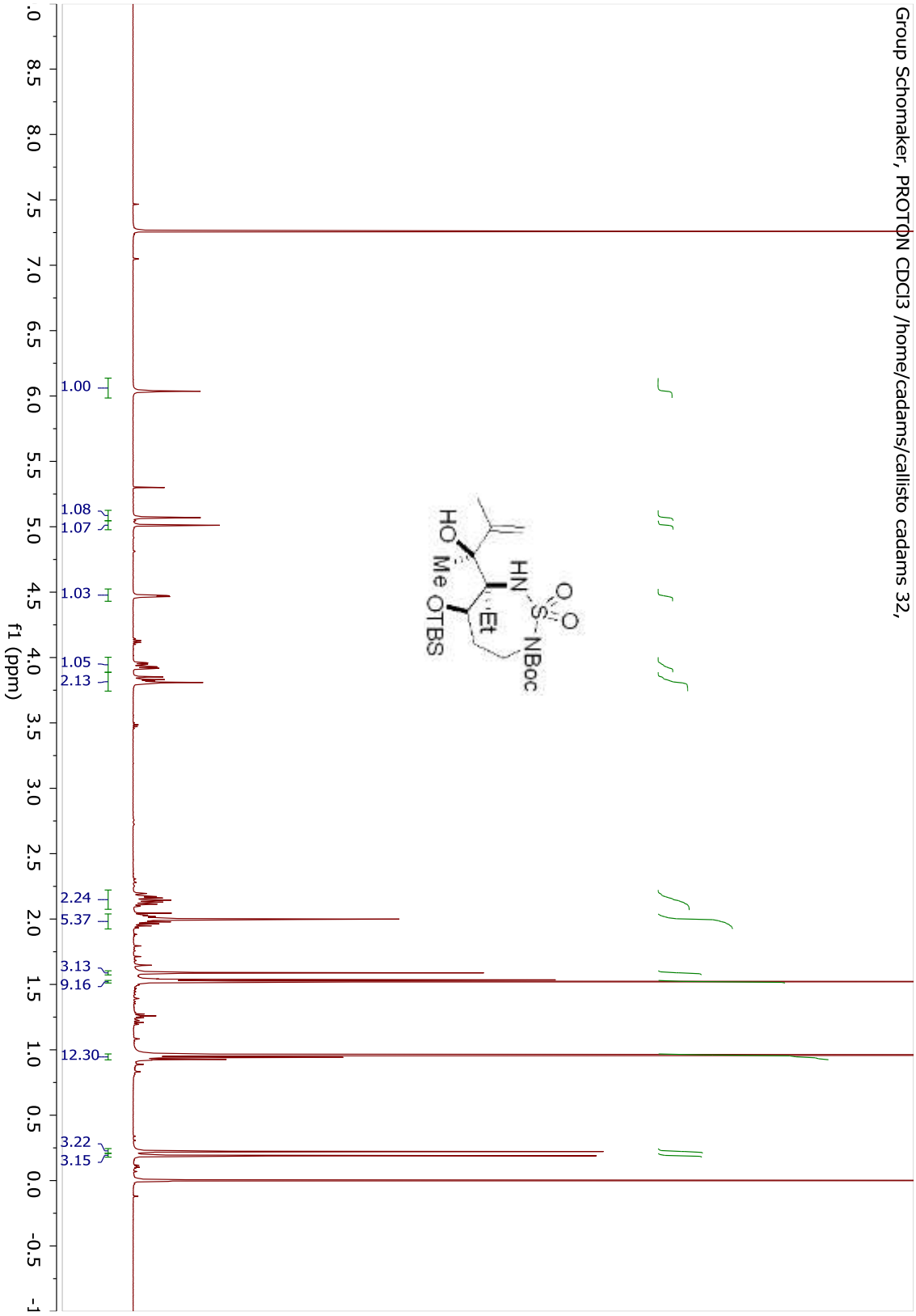

Group Schomaker, C13CPD32 CDCl3 /home/cadams/callisto cadams 5,
O
O
S
NBoc
HN
Me
O
OTBS
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

Compound 4.S2.



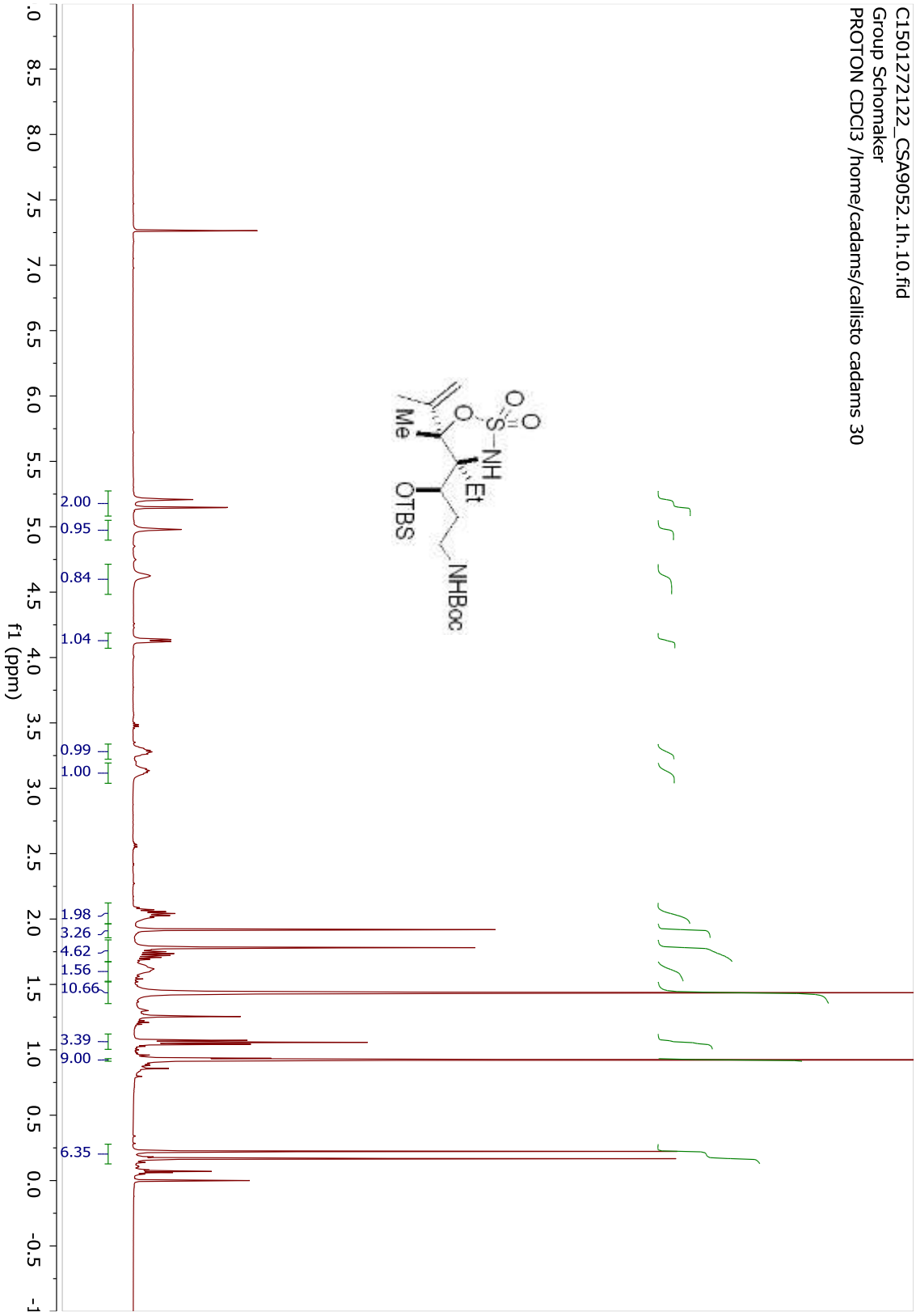
Group Schomaker, C13CPD32 CDCl3 /home/cadams/callisto cadams 8,
Me
O
OTBS
Et
HN
S
O
O
NBoc
f1 (ppm)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

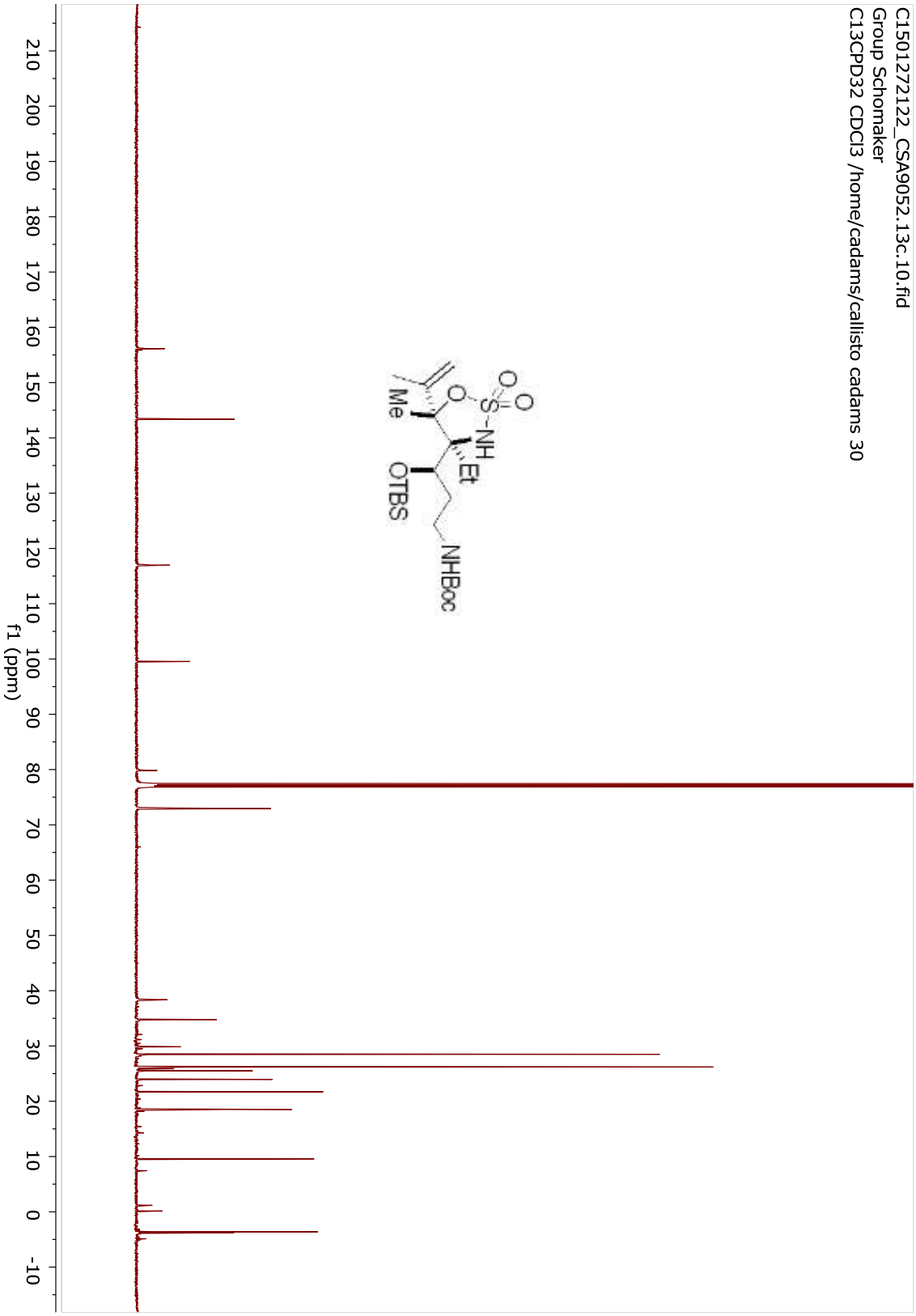
Compound 4.45.



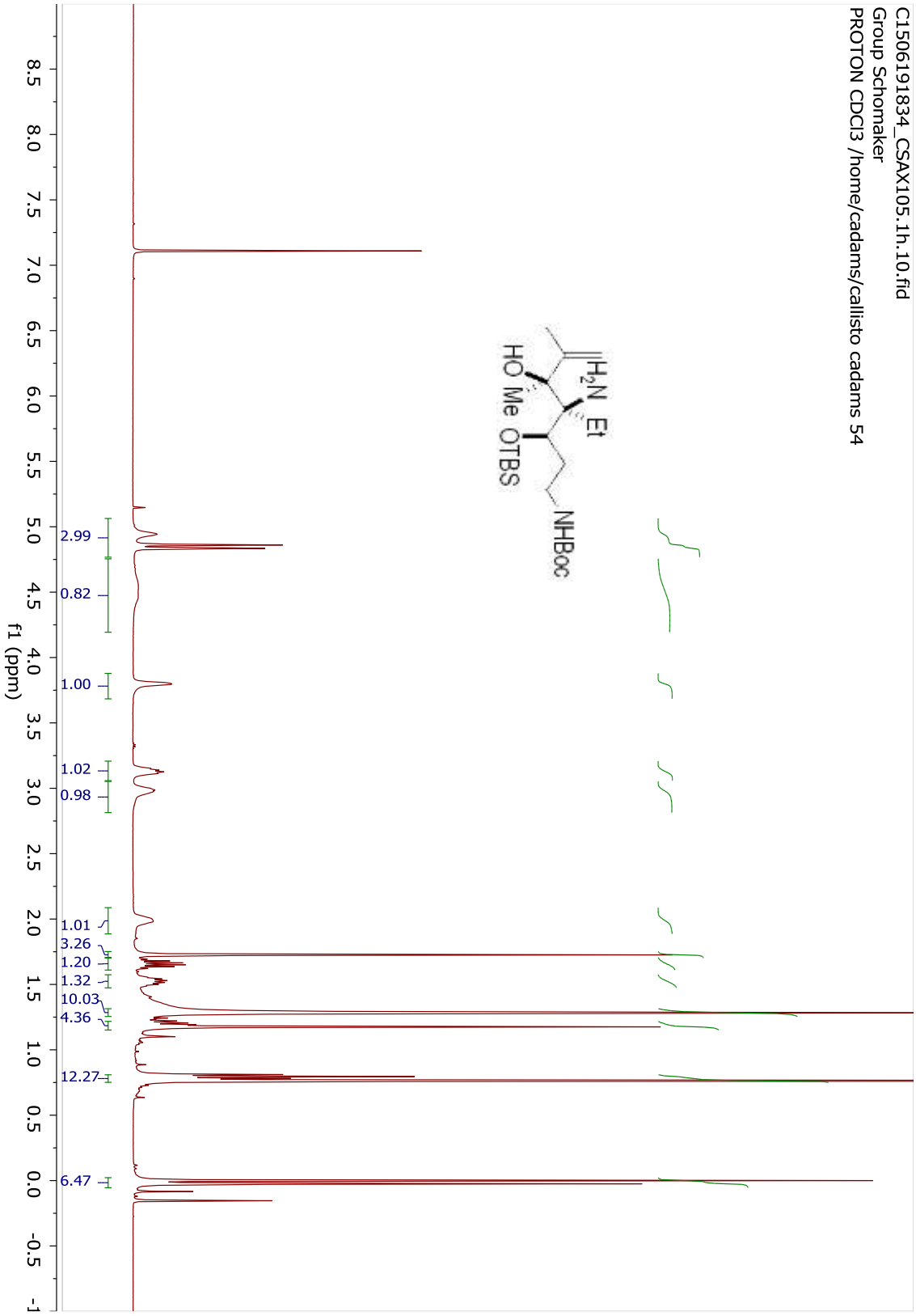
Group Schomaker, C13CPD32 CDCl3 /home/cadams/callisto cadams 32,
HO
Me
OTBS
Et
HN
S
O
O
NBoc
f1 (ppm)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

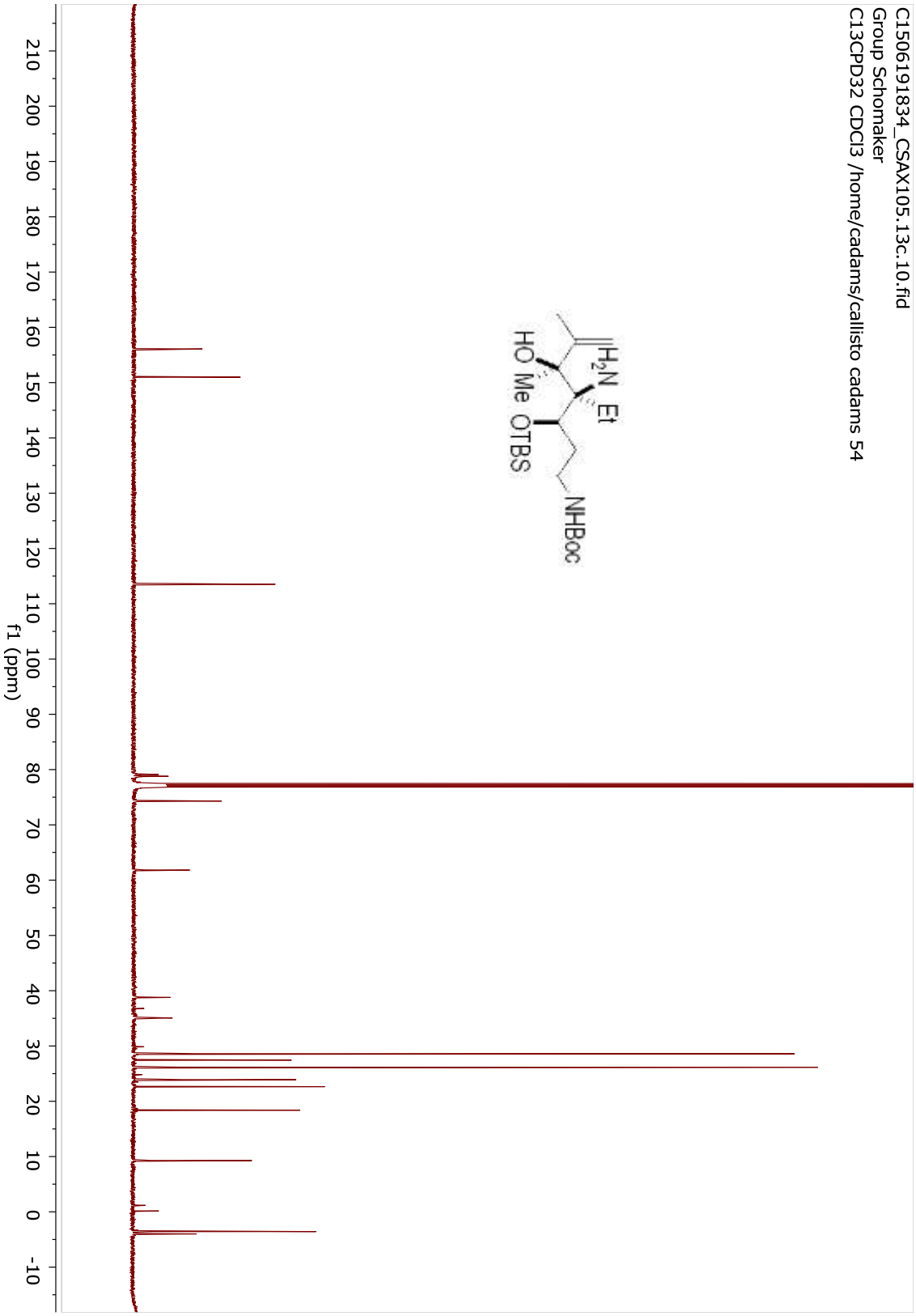
Compound 4.47.



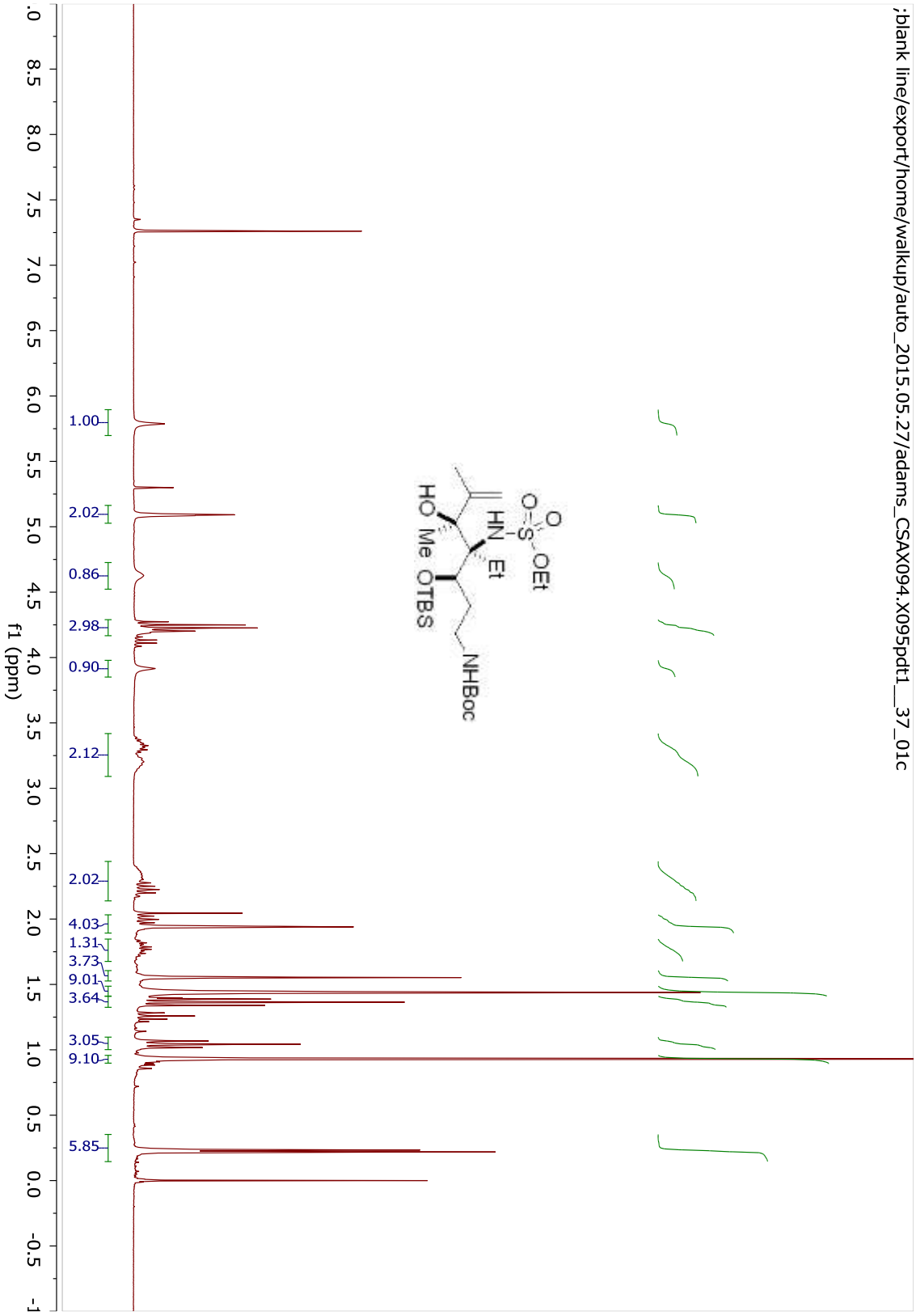

C1501272122_CSA9052.13c.10.fid
Group Schomaker
C13CPD32 CDCl3 /home/cadams/callisto cadams 30
O
O
S
NH
Et
O
Me
OTBS
NHBoc
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

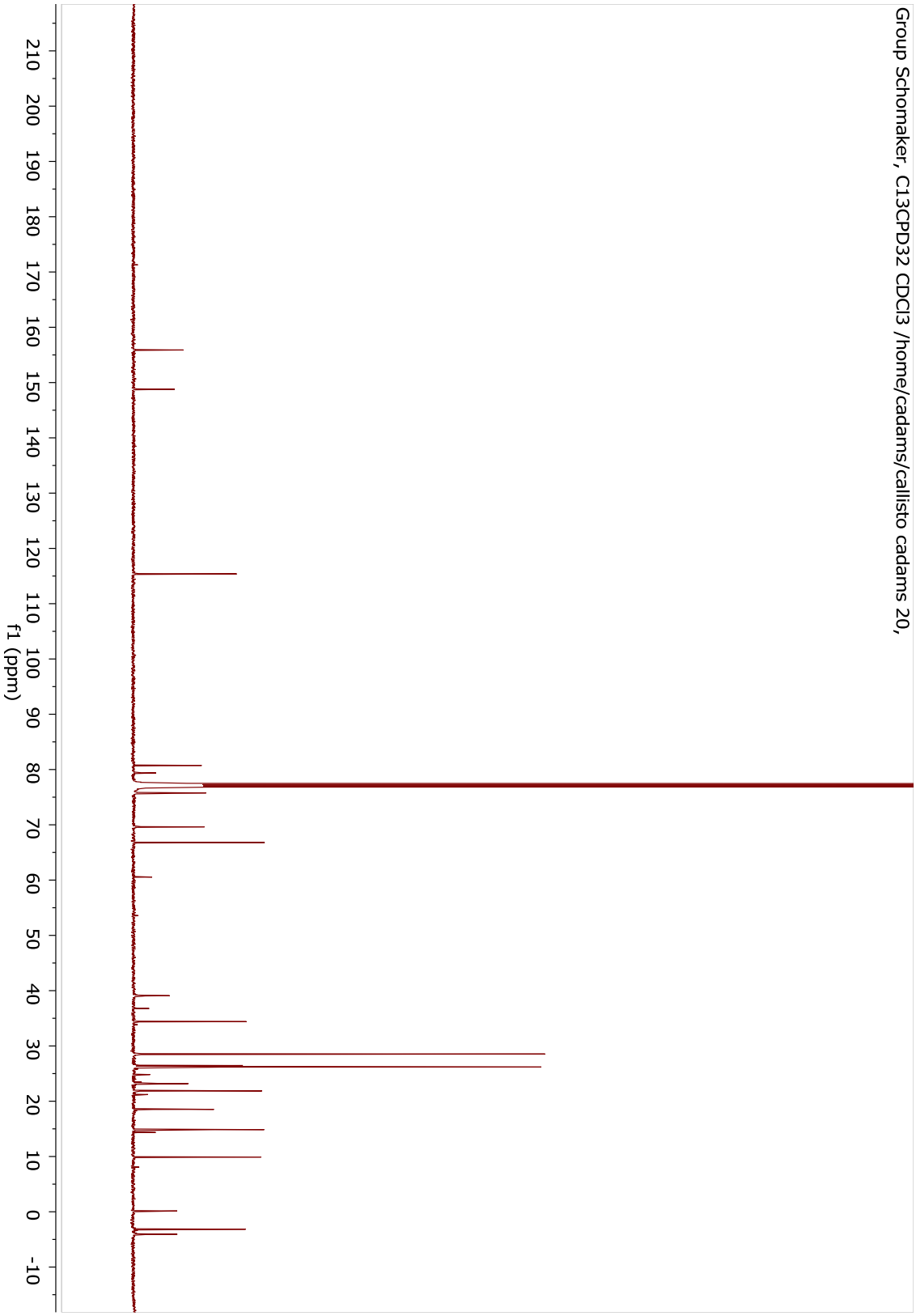
Compound 4.48.



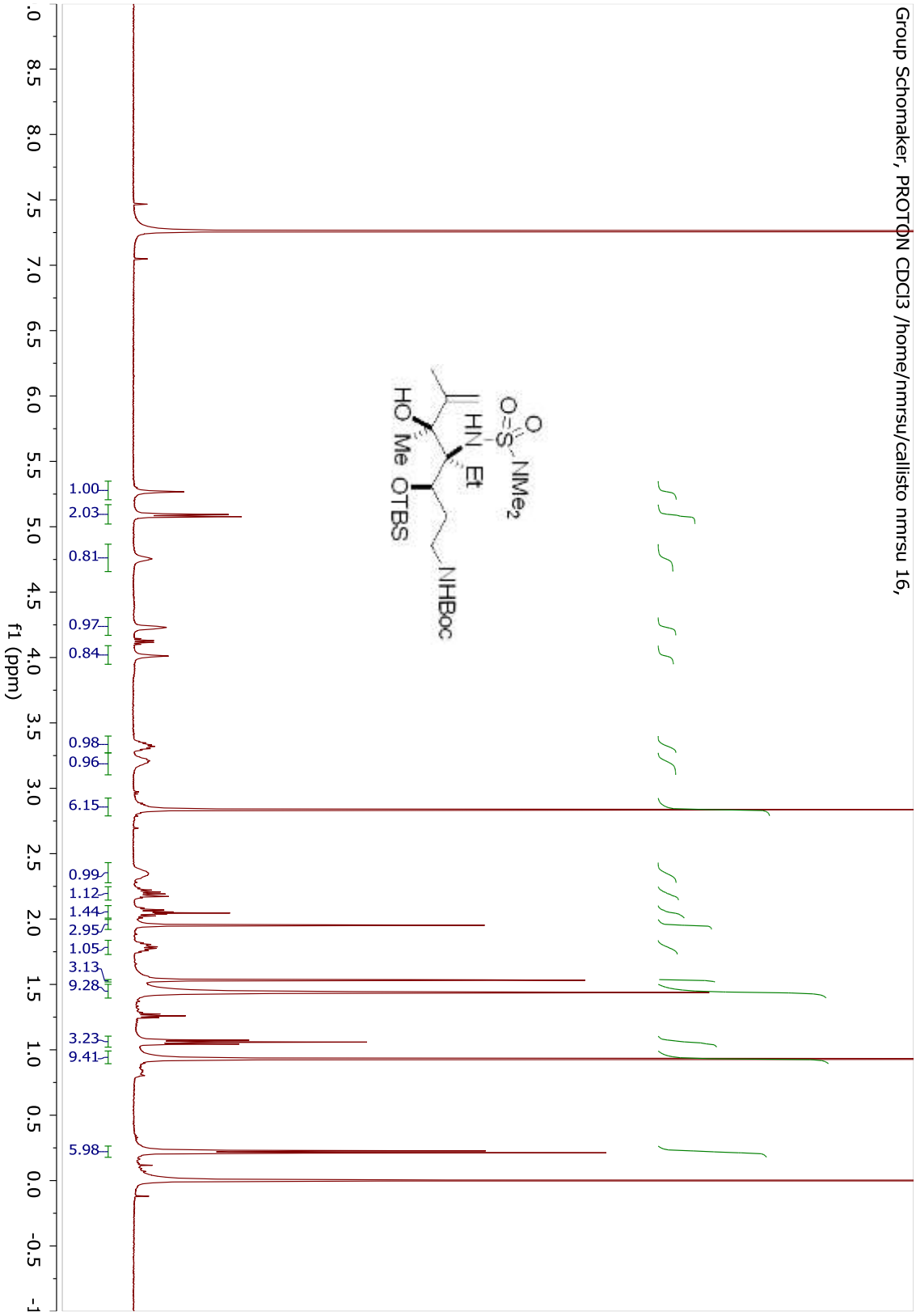

C1506191834_CSAX105.13c.10.fid
Group Schomaker
C13CPD32 CDCl3 /home/cadams/callisto cadams 54
H2N
Et
HO
Me
OTBS
NHBoc
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

Compound 4.49.



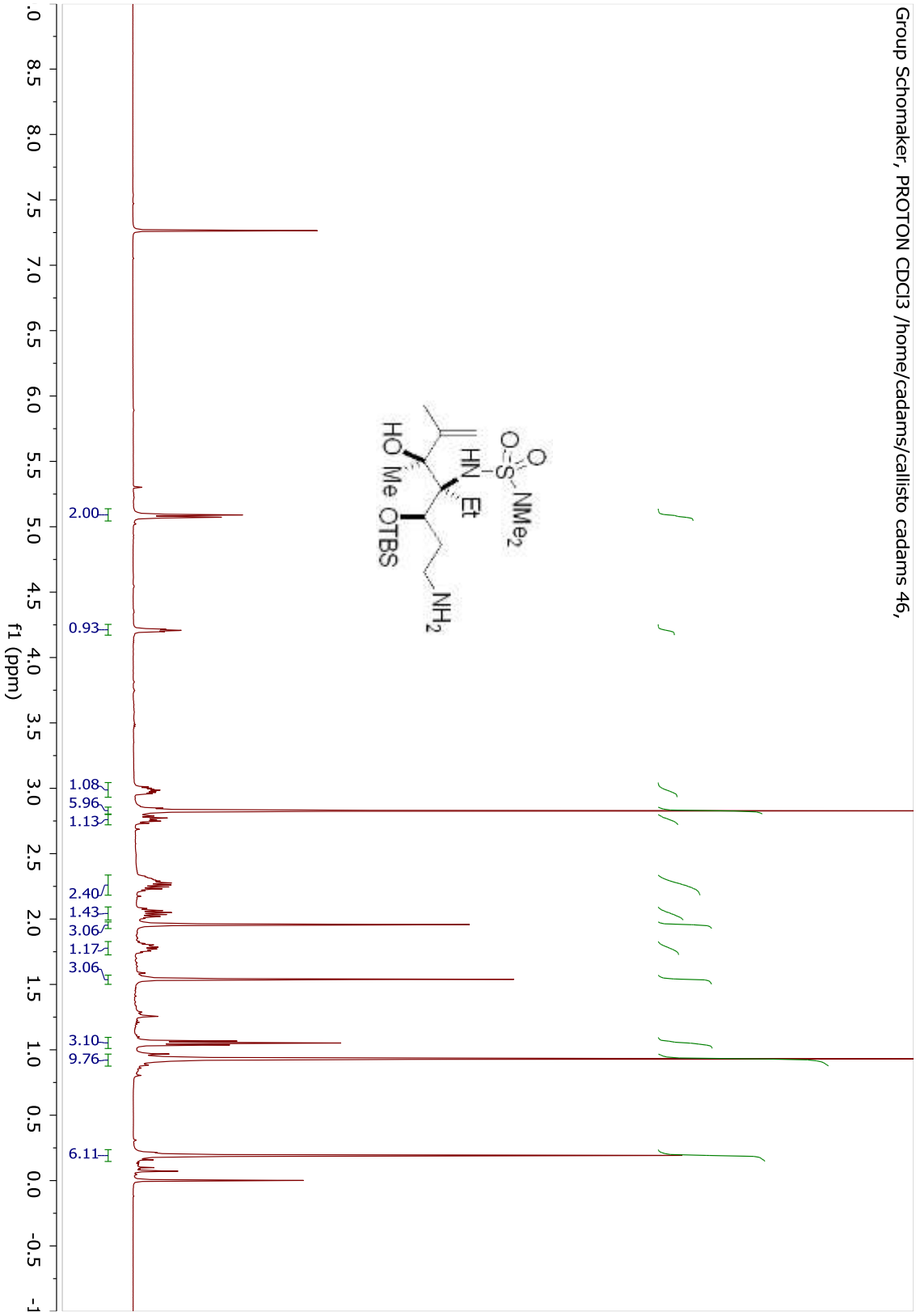

Group Schomaker, C13CPD32 CDCl3 /home/cadams/callisto cadams 20,
f1 (ppm)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

Compound 4.50.



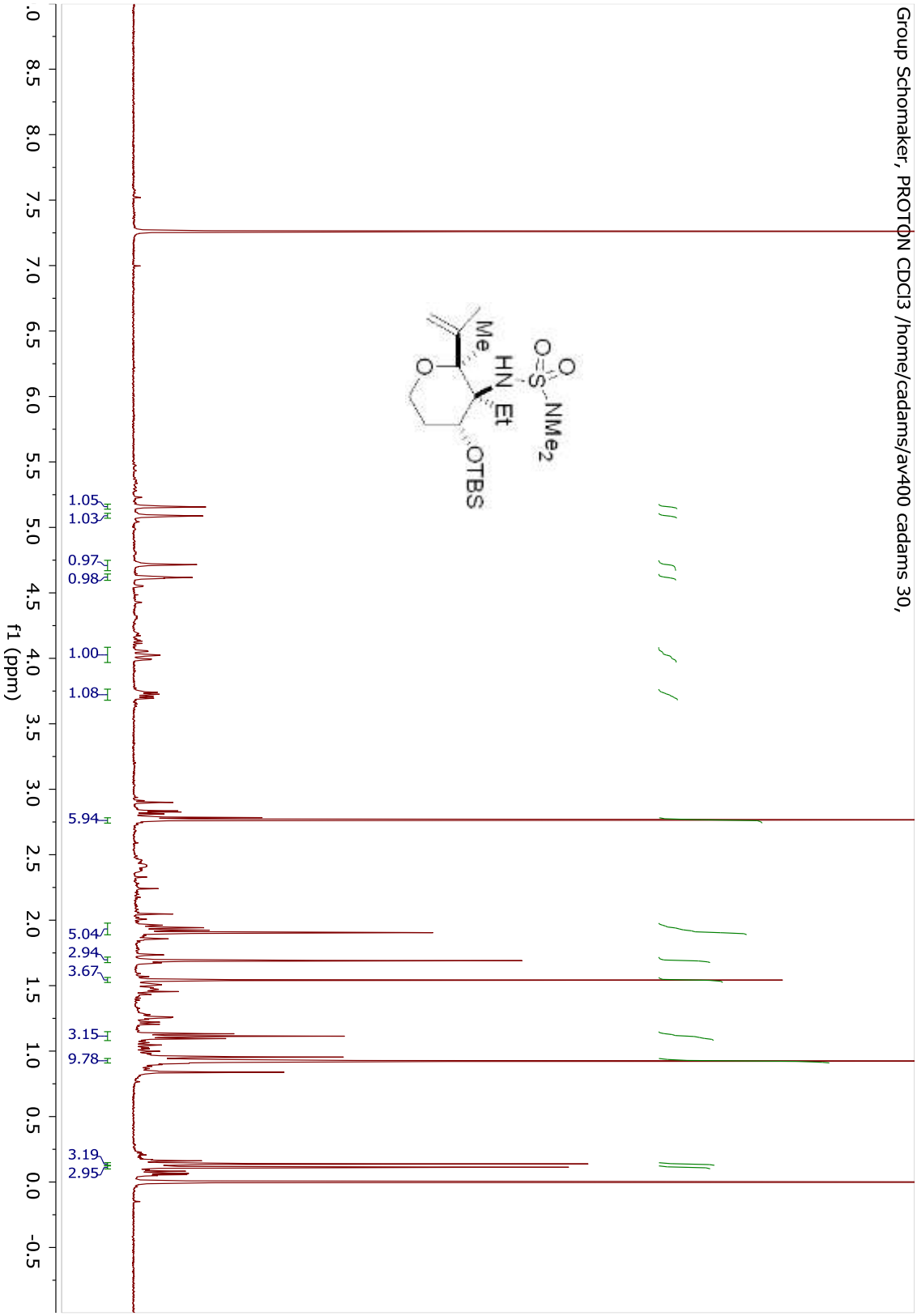
Group Schomaker, C13CPD32 CDCl3 /home/cadams/callisto cadams 46,
O
O=S
NMe2
HN
Et
HO
Me
OTBS
NHBoc
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

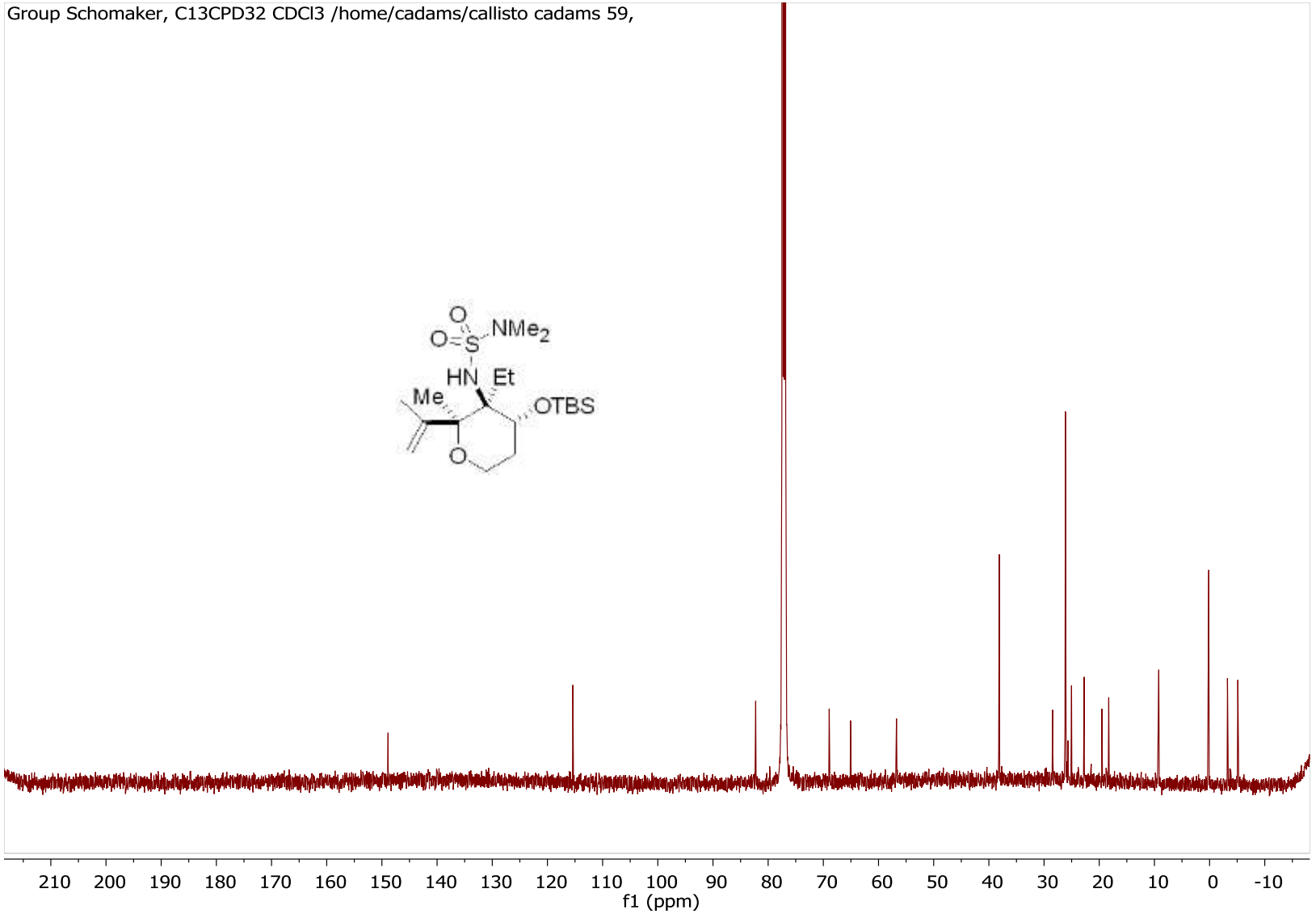
Compound 4.51.



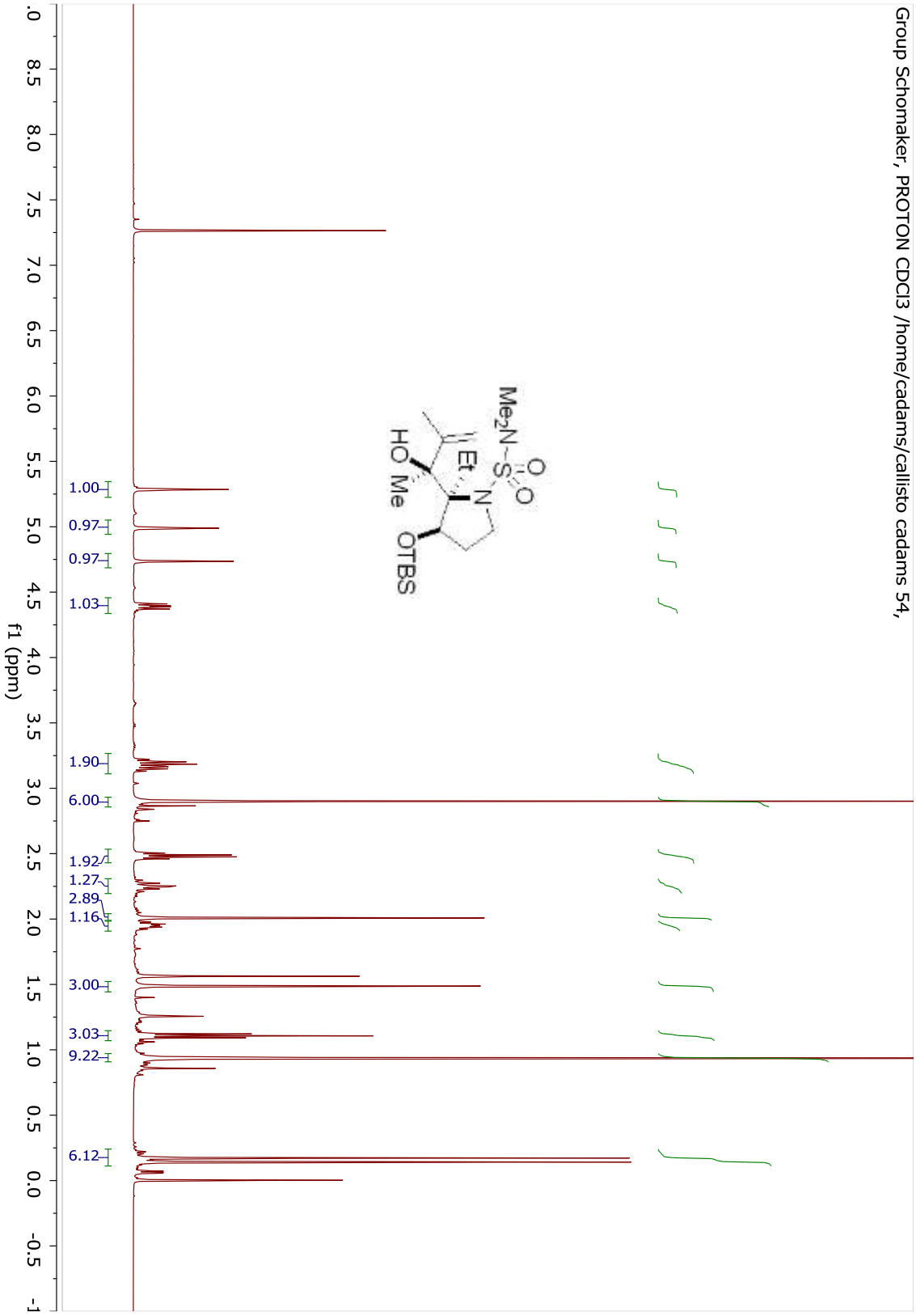
Group Schomaker, C13CPD32 CDCl3 /home/cadams/callisto cadams 46,
O
O=S
NMe2
HN
Et
HO
Me
OTBS
NH2
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

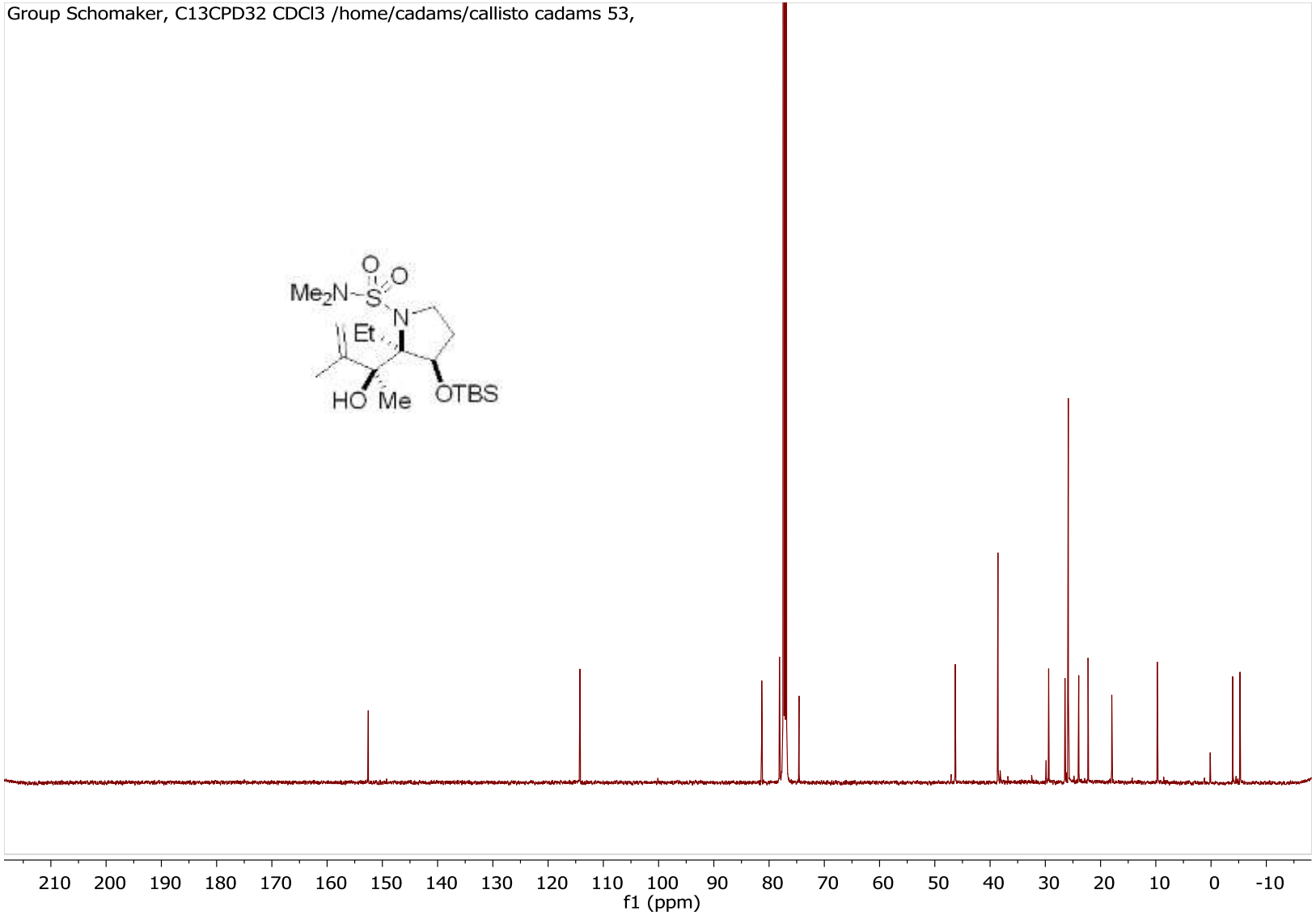
Compound 4.52.



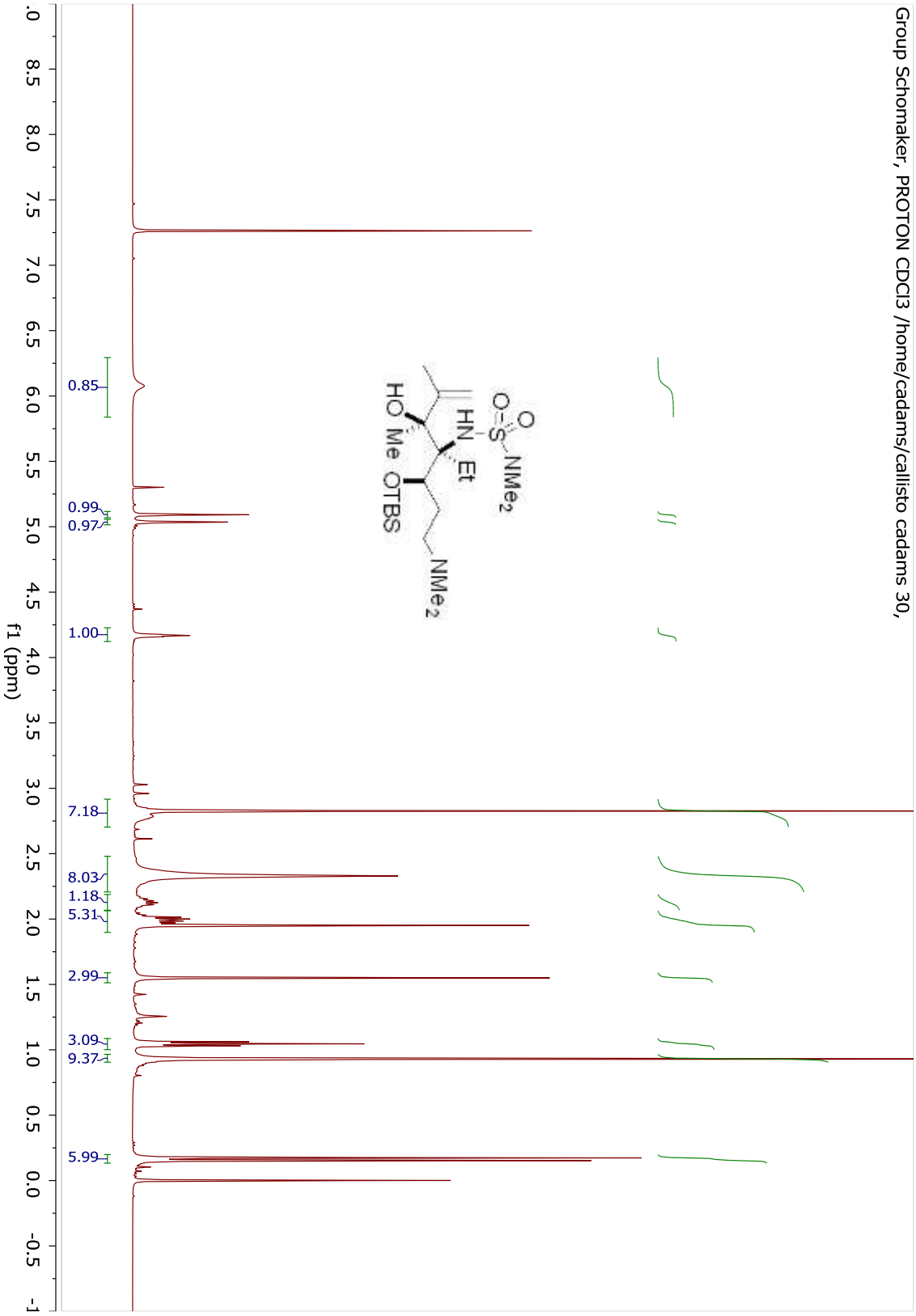

Group Schomaker, C13CPD32 CDCl3 /home/cadams/callisto cadams 59,
O
O
S
NMe2
HN
Et
Me
OTBS
O
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

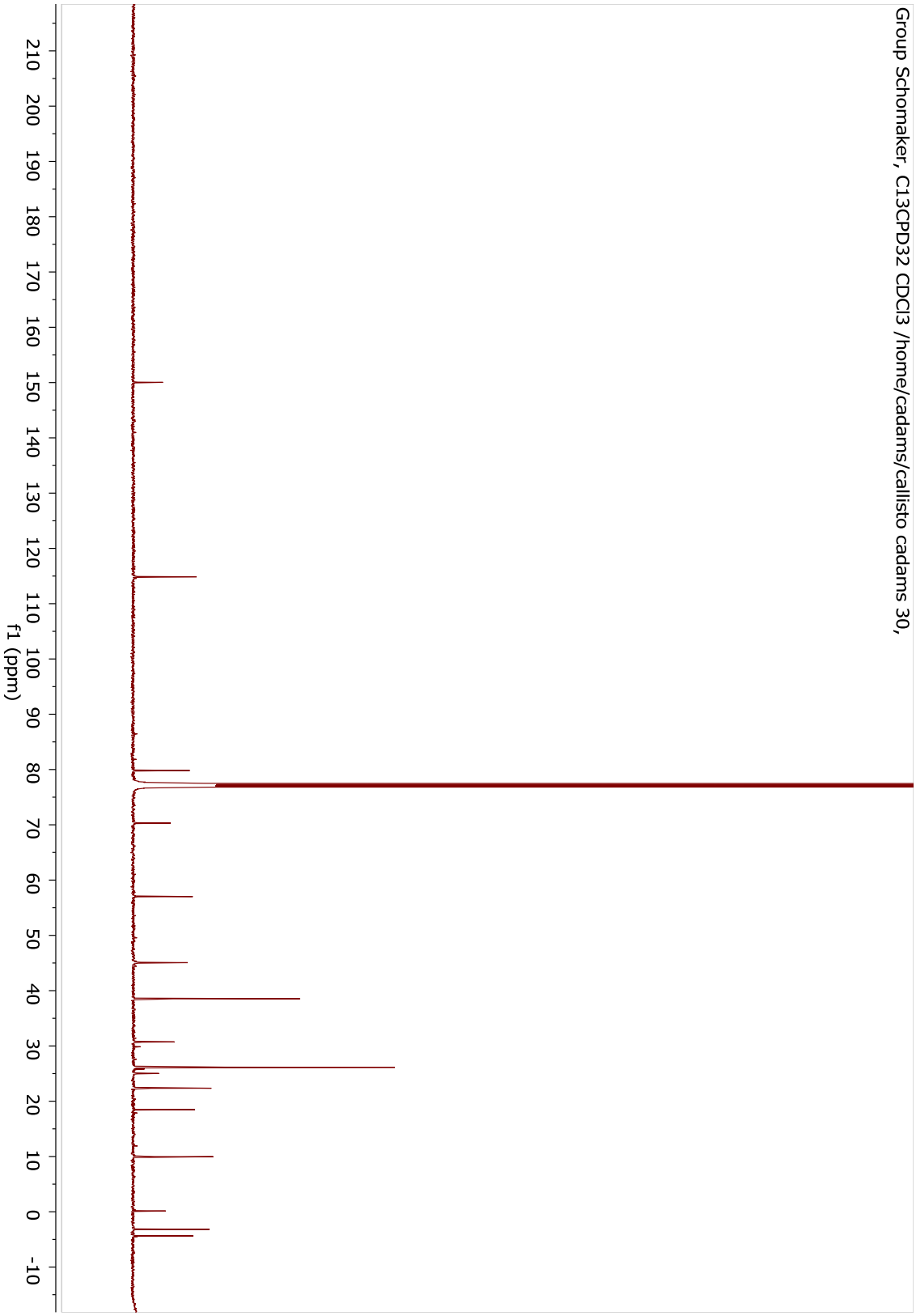
Compound 4.53.



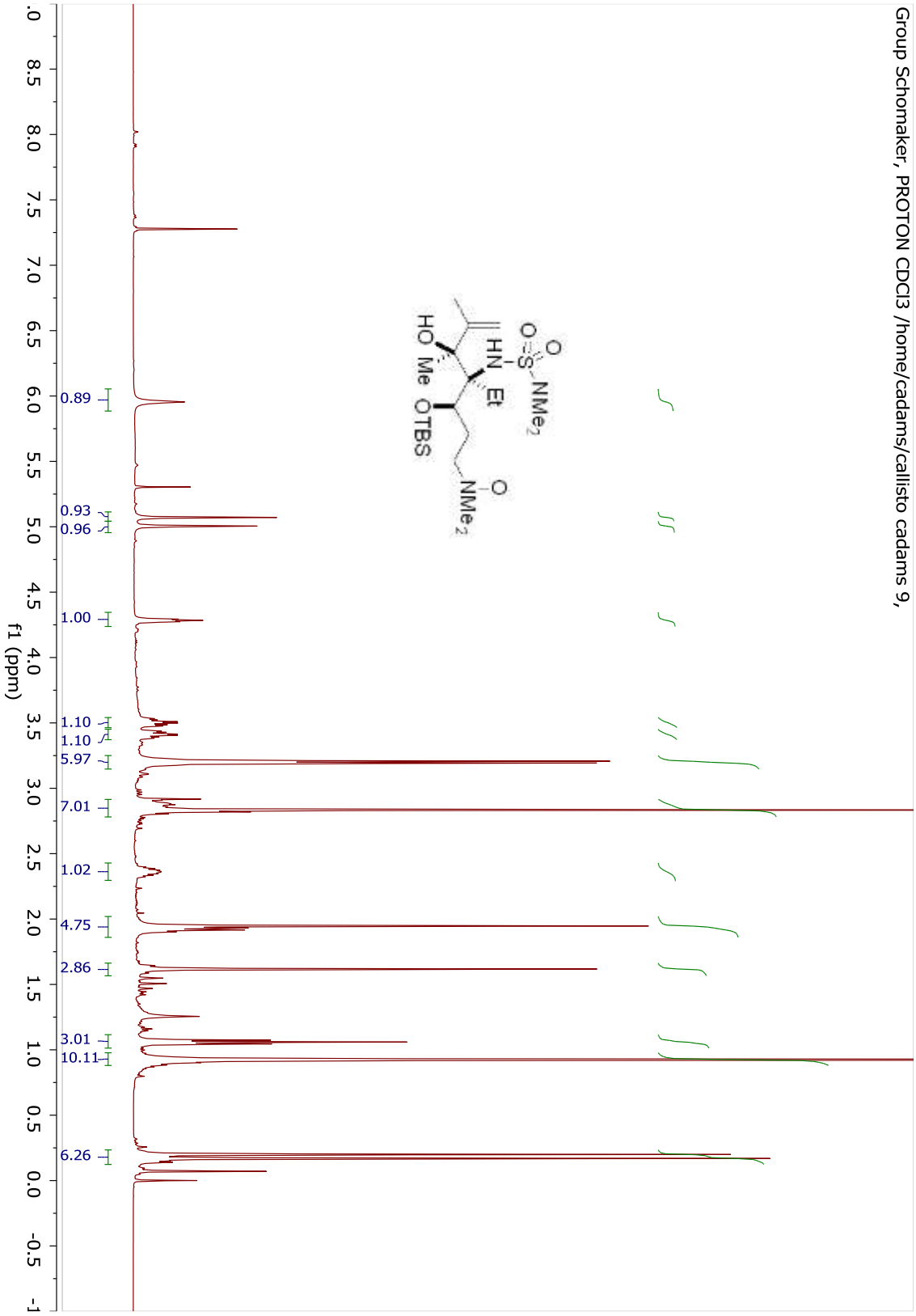

Group Schomaker, C13CPD32 CDCl3 /home/cadams/callisto cadams 53,
Me2N
S
O
O
N
Et
HO
Me
OTBS
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

Compound 4.54.



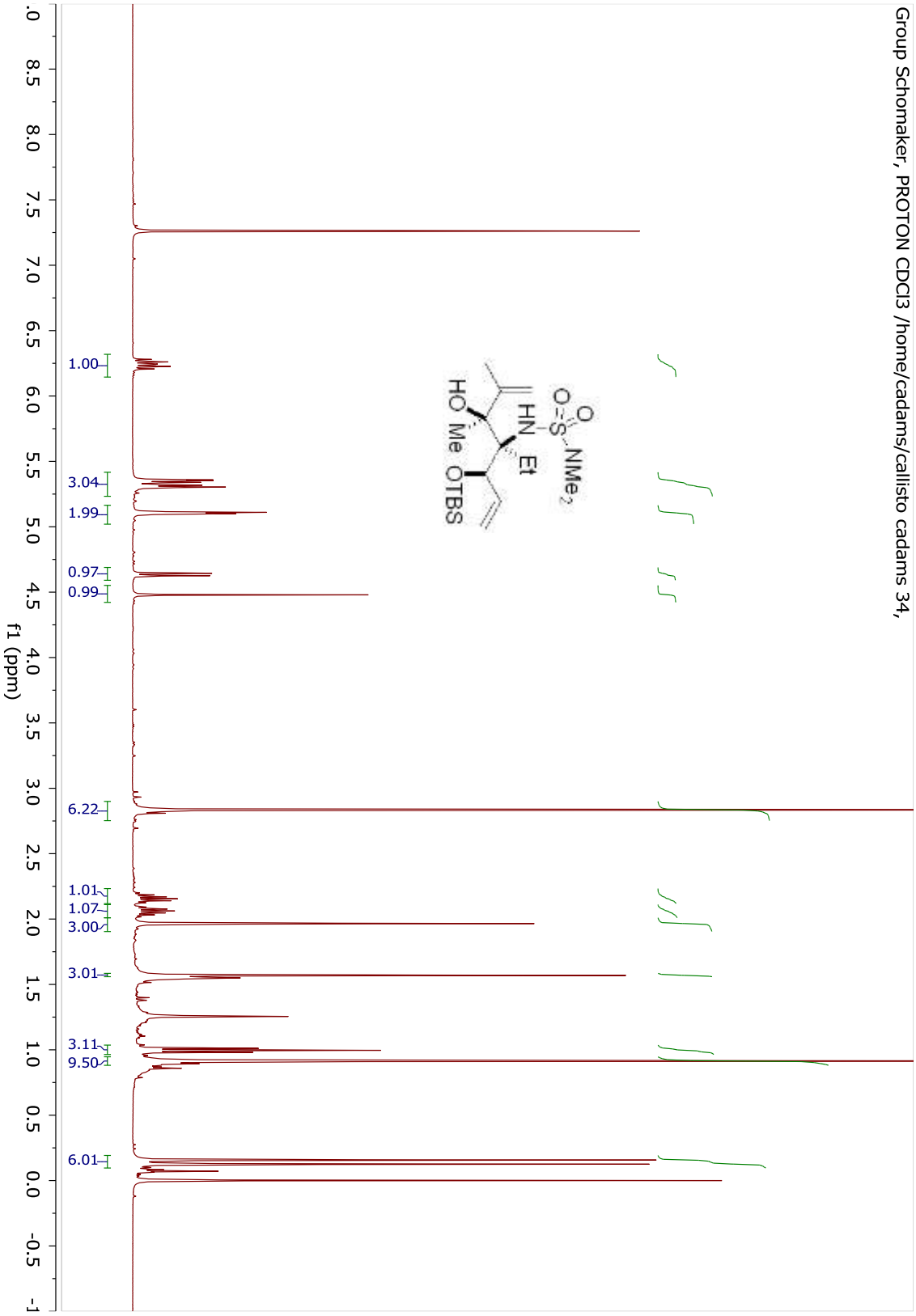

Group Schomaker, C13CPD32 CDCl3 /home/cadams/callisto cadams 30,
f1 (ppm)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

Compound 4.55.



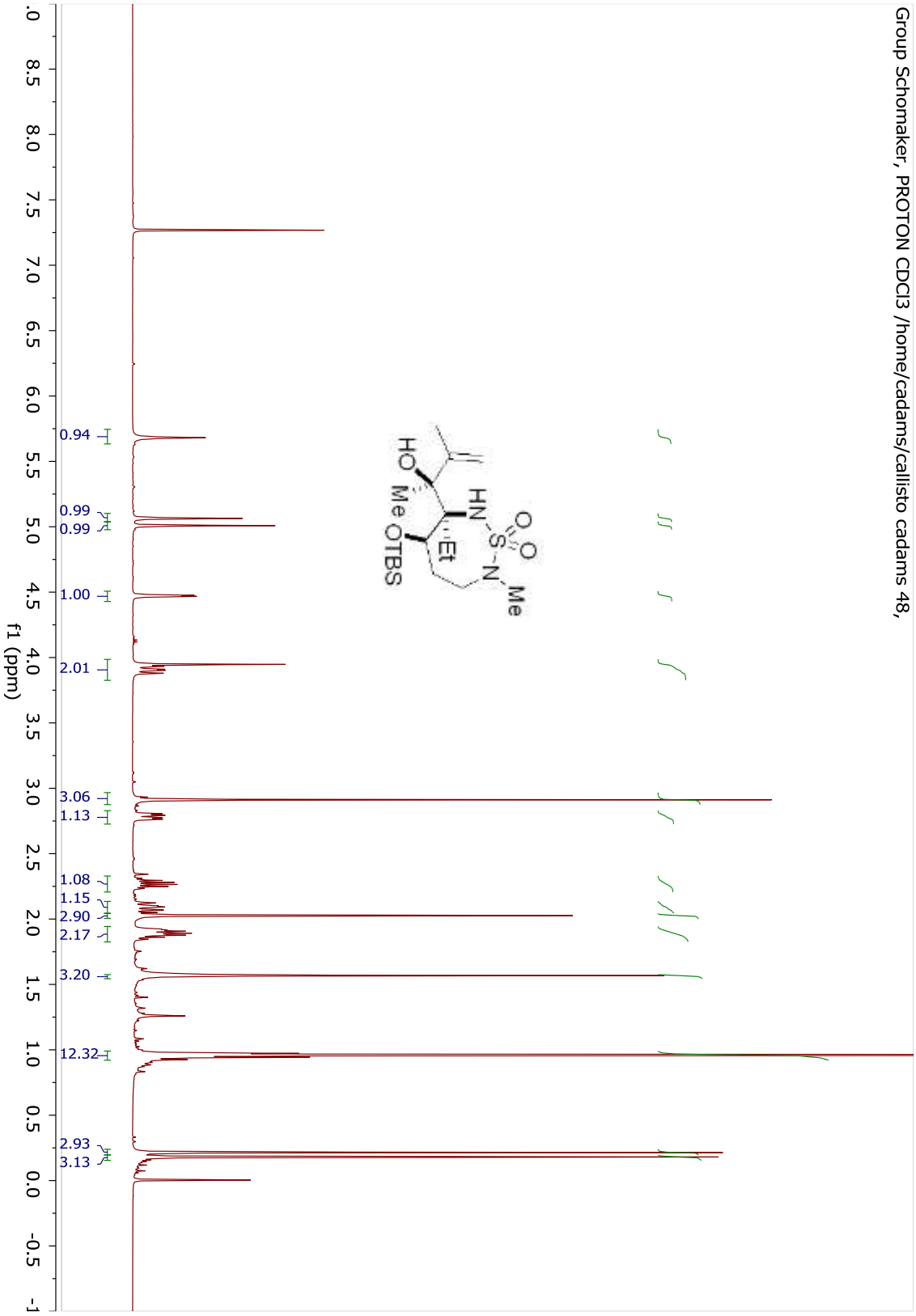
Group Schomaker, C13CPD32 CDCl3 /home/cadams/callisto cadams 9,
O
O=S
NMe2
HN
Et
HO
Me
OTBS
O
NMe2
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

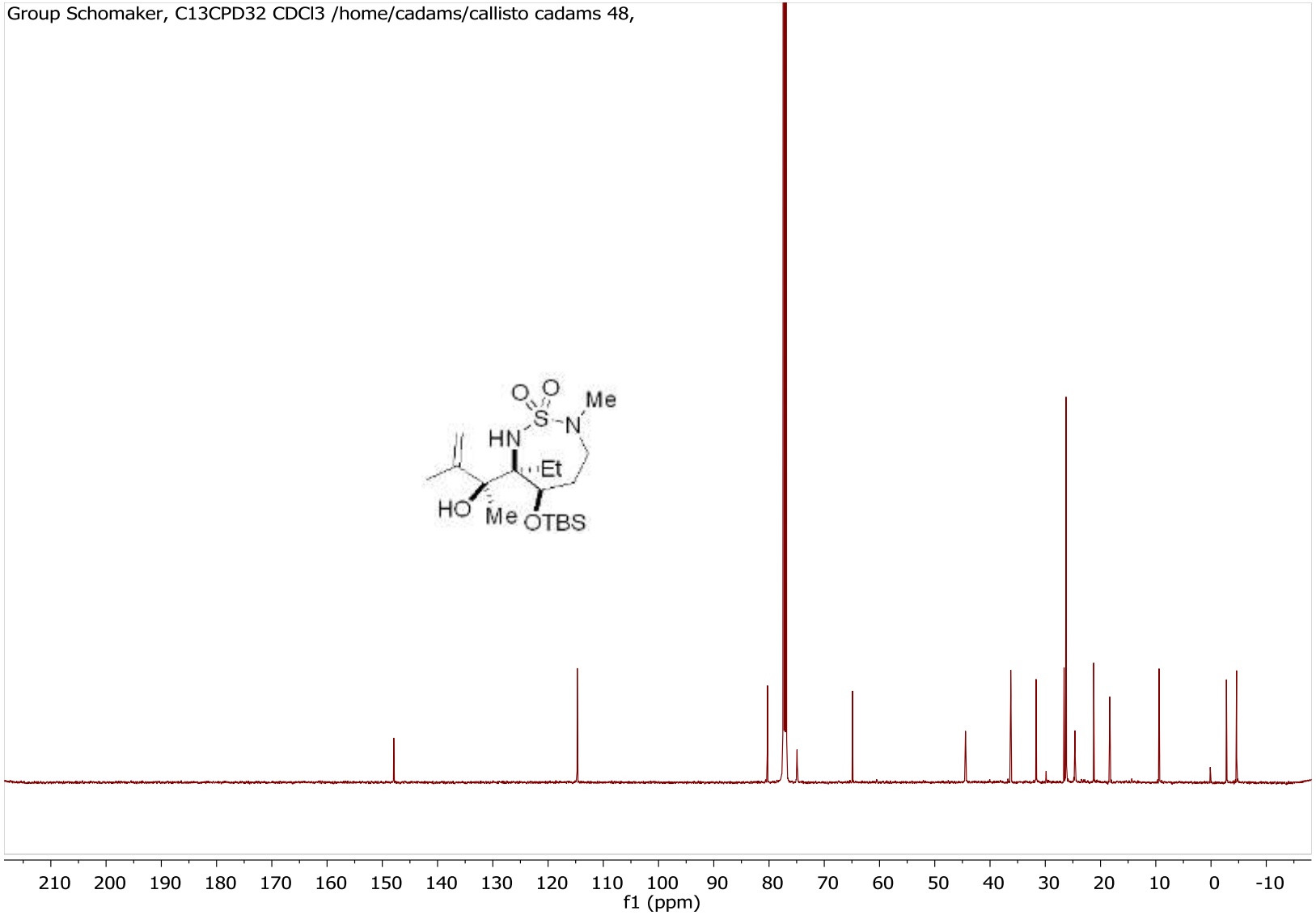
Compound 4.56.



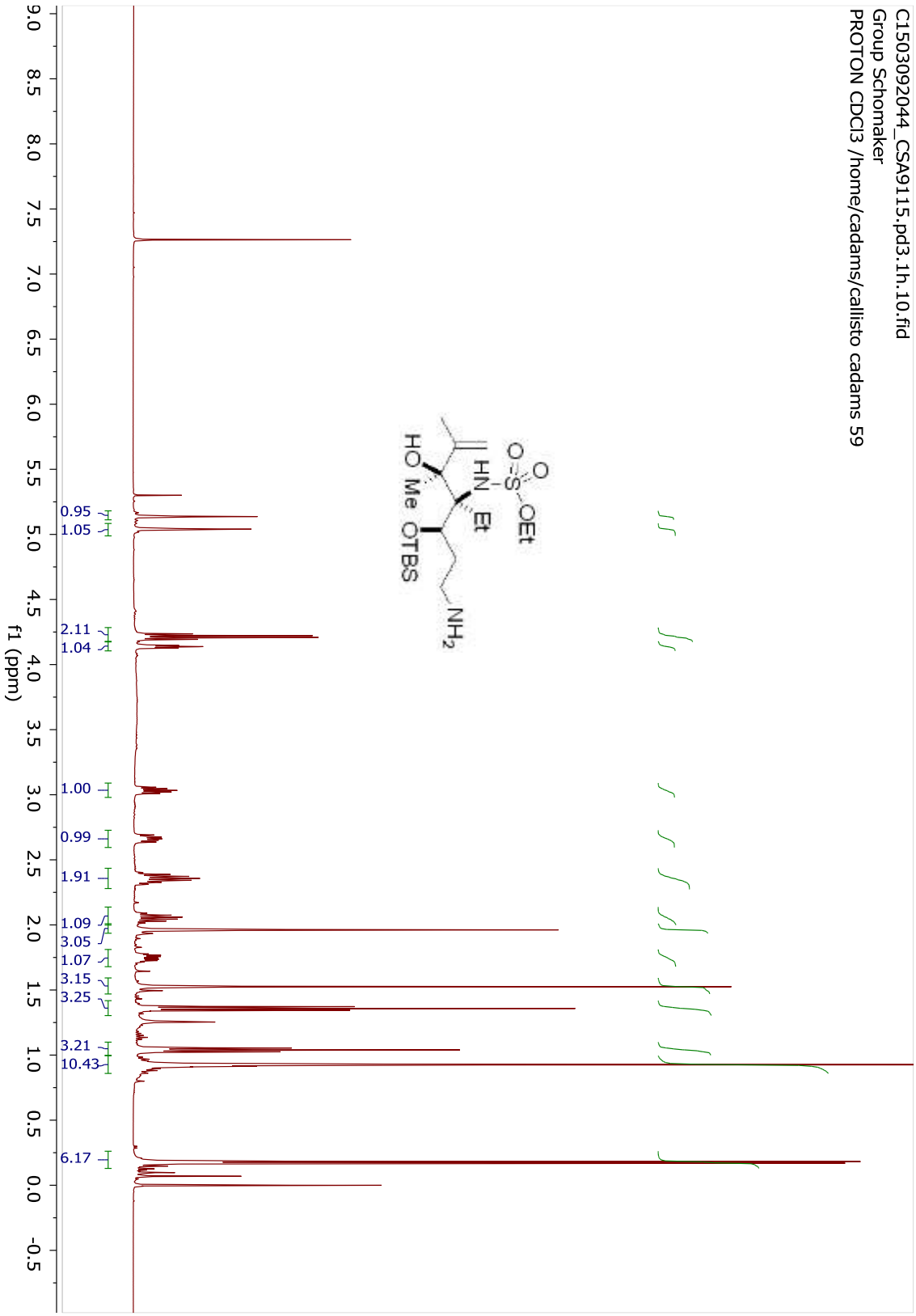
Group Schomaker, C13CPD32 CDCl3 /home/cadams/callisto cadams 34,
O
O=S
NMe2
HN
Et
HO
Me
OTBS
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

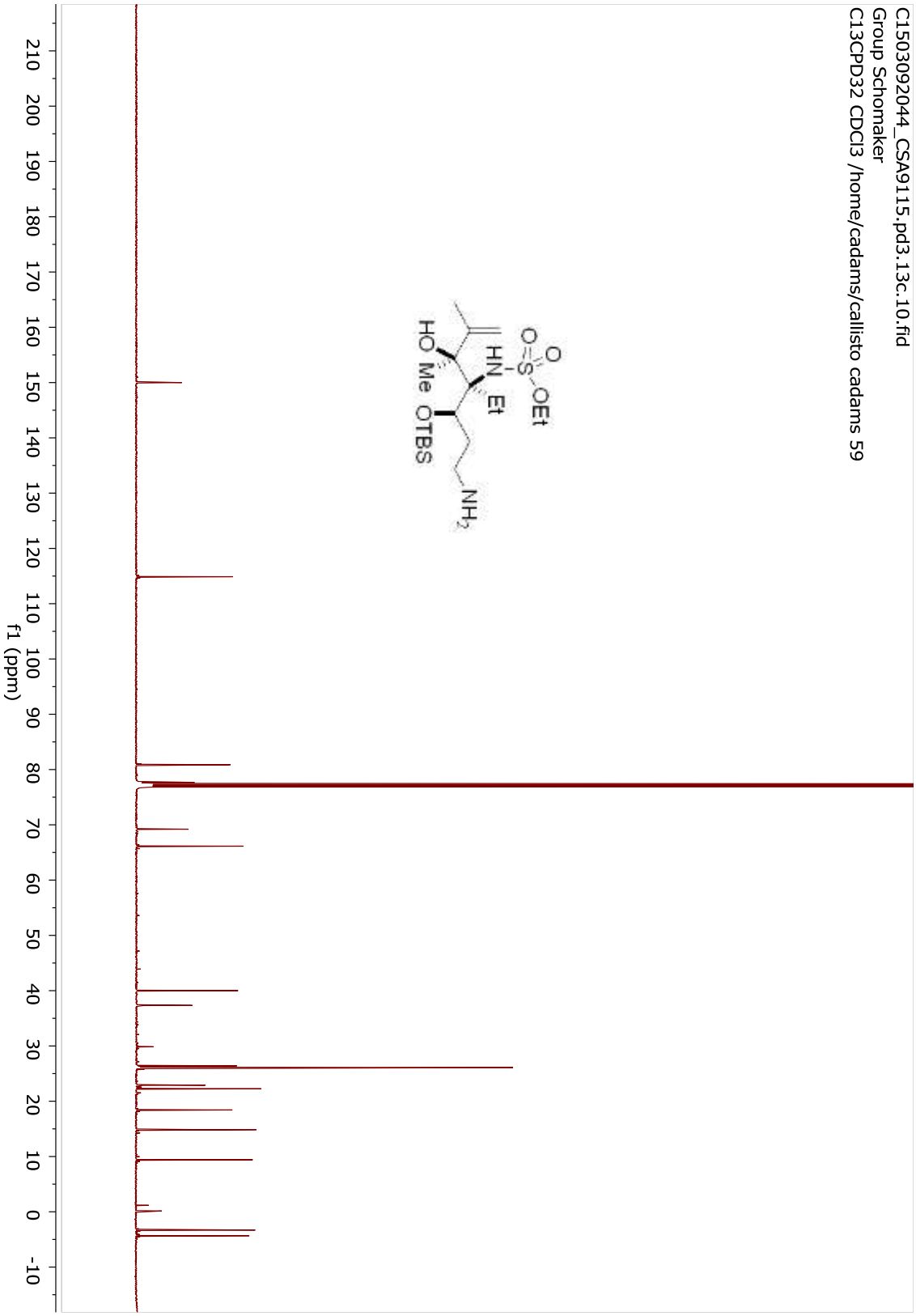
Compound 4.57.



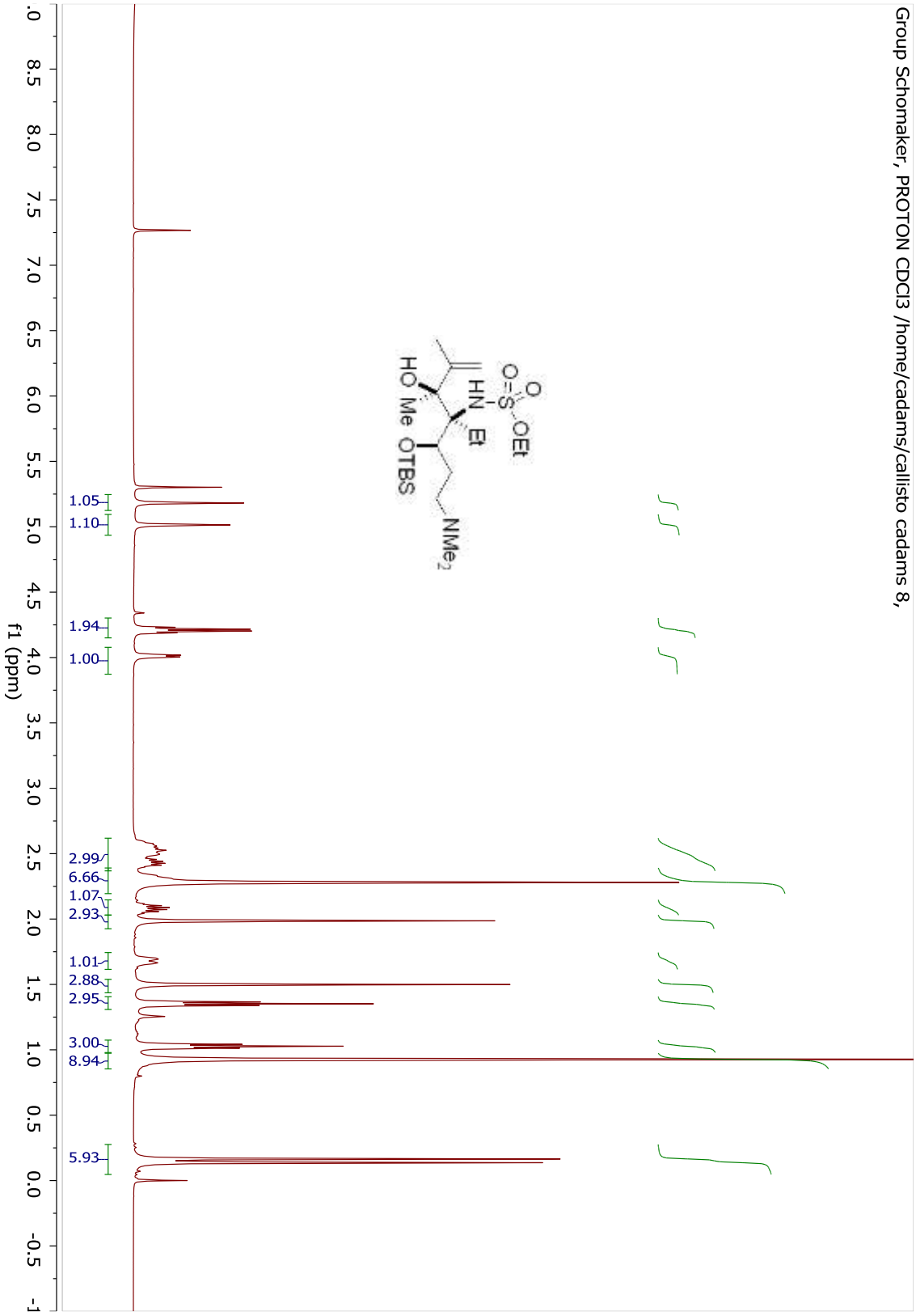

Group Schomaker, C13CPD32 CDCl3 /home/cadams/callisto cadams 48,
O
O
S
N
Me
HN
Et
HO
Me
OTBS
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

Compound 4.58.



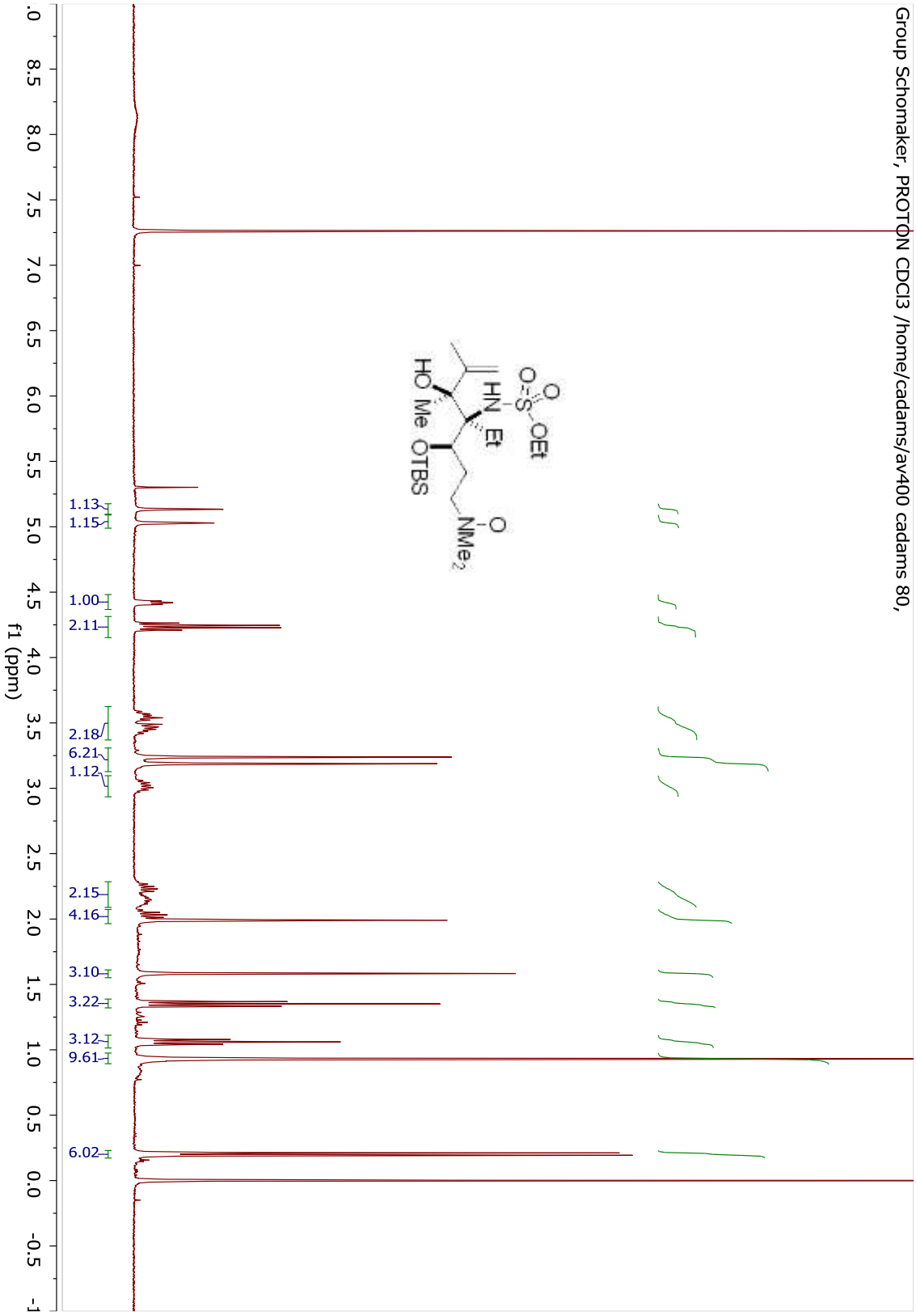

C1503092044_CSA91115.pd3.13c.10.fid
Group Schomaker
C13CPD32 CDCl3 /home/cadams/callisto cadams 59
O
O=S
OEt
HN
Et
HO
Me
OTBS
NH2
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

Compound 4.59.



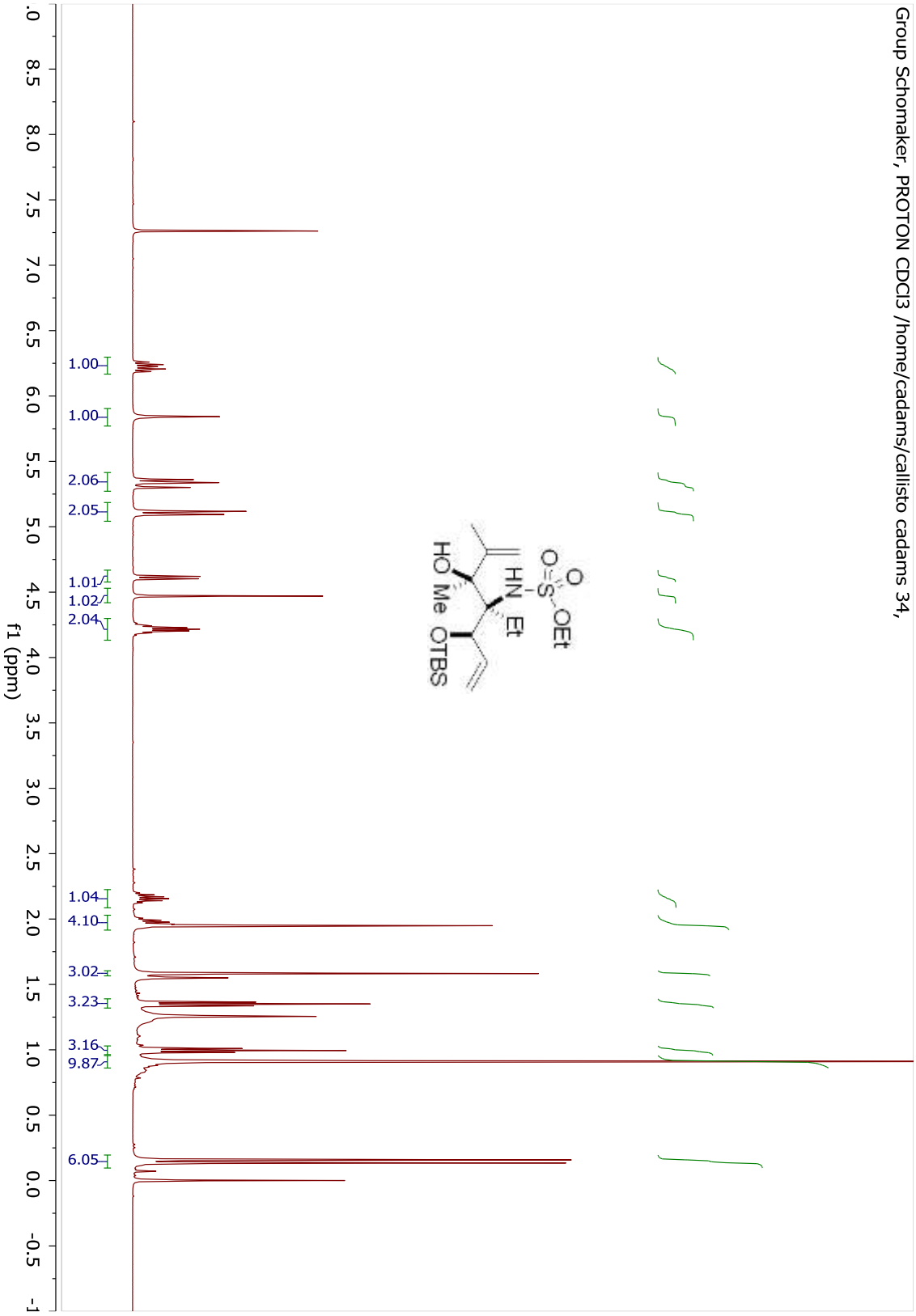
Group Schomaker, C13CPD32 CDCl3 /home/cadams/callisto cadams 8,
O
O
S
OEt
HN
Et
HO
Me
OTBS
NMe2
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

Compound 4.60.



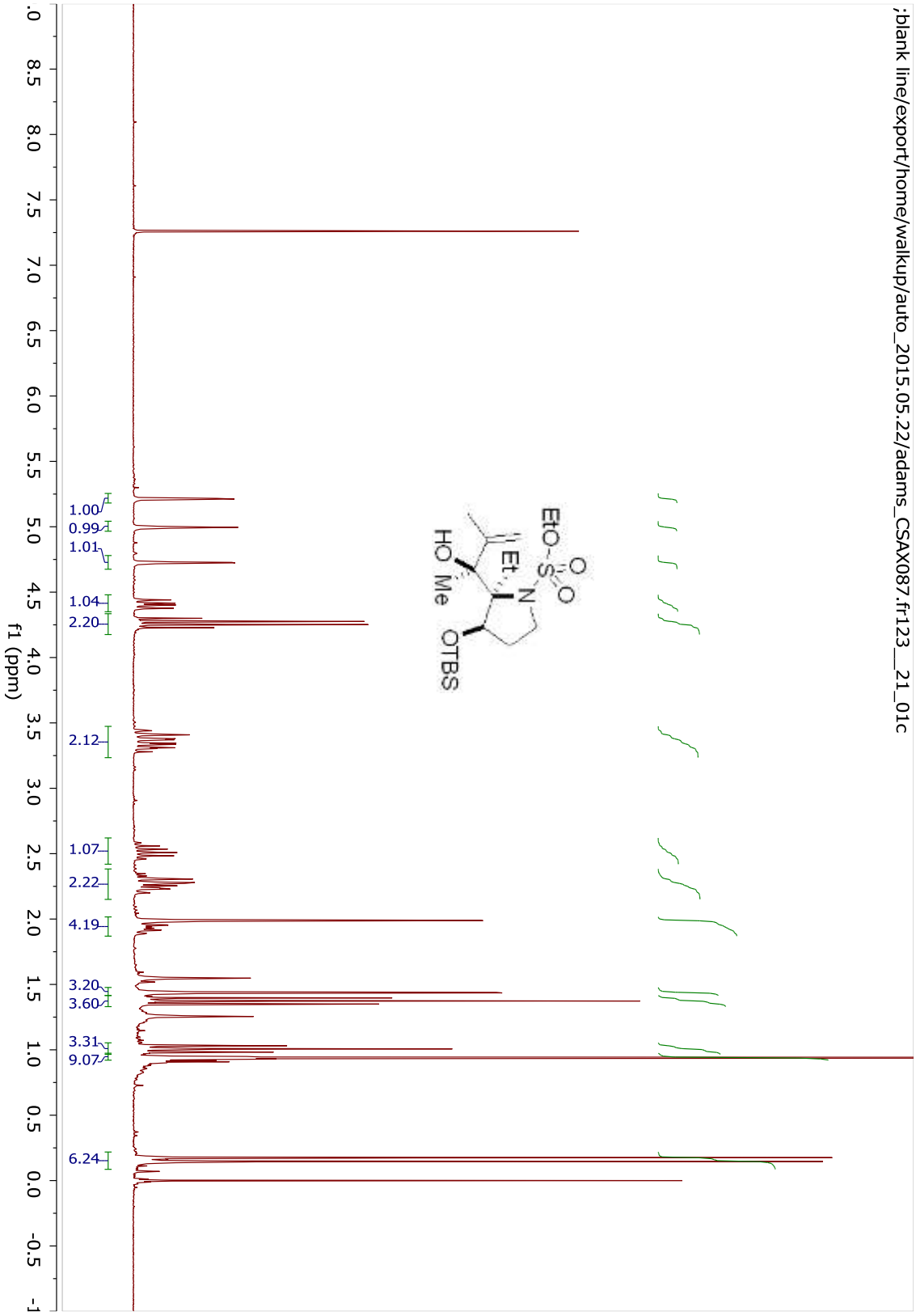
Group Schomaker, C13CPD32 CDCl3 /home/cadams/callisto cadams 9,
O
O=S
OEt
HN
Et
HO
Me
OTBS
O
NMe2
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

Compound 4.61.



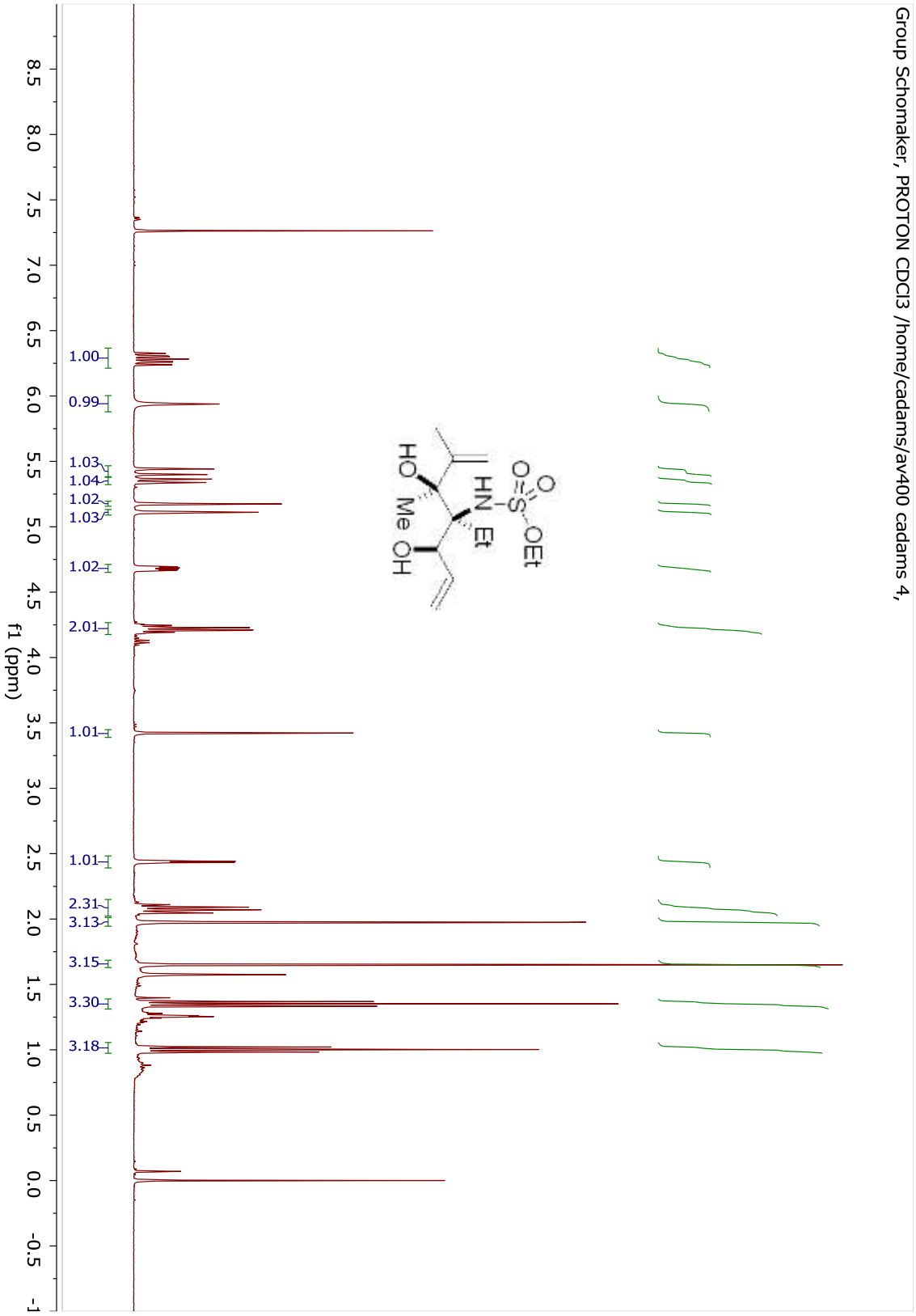
Group Schomaker, C13CPD32 CDCl3 /home/cadams/callisto cadams 34,
O
O=S
OEt
HN
Et
HO
Me
OTBS
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

Compound 4.62.



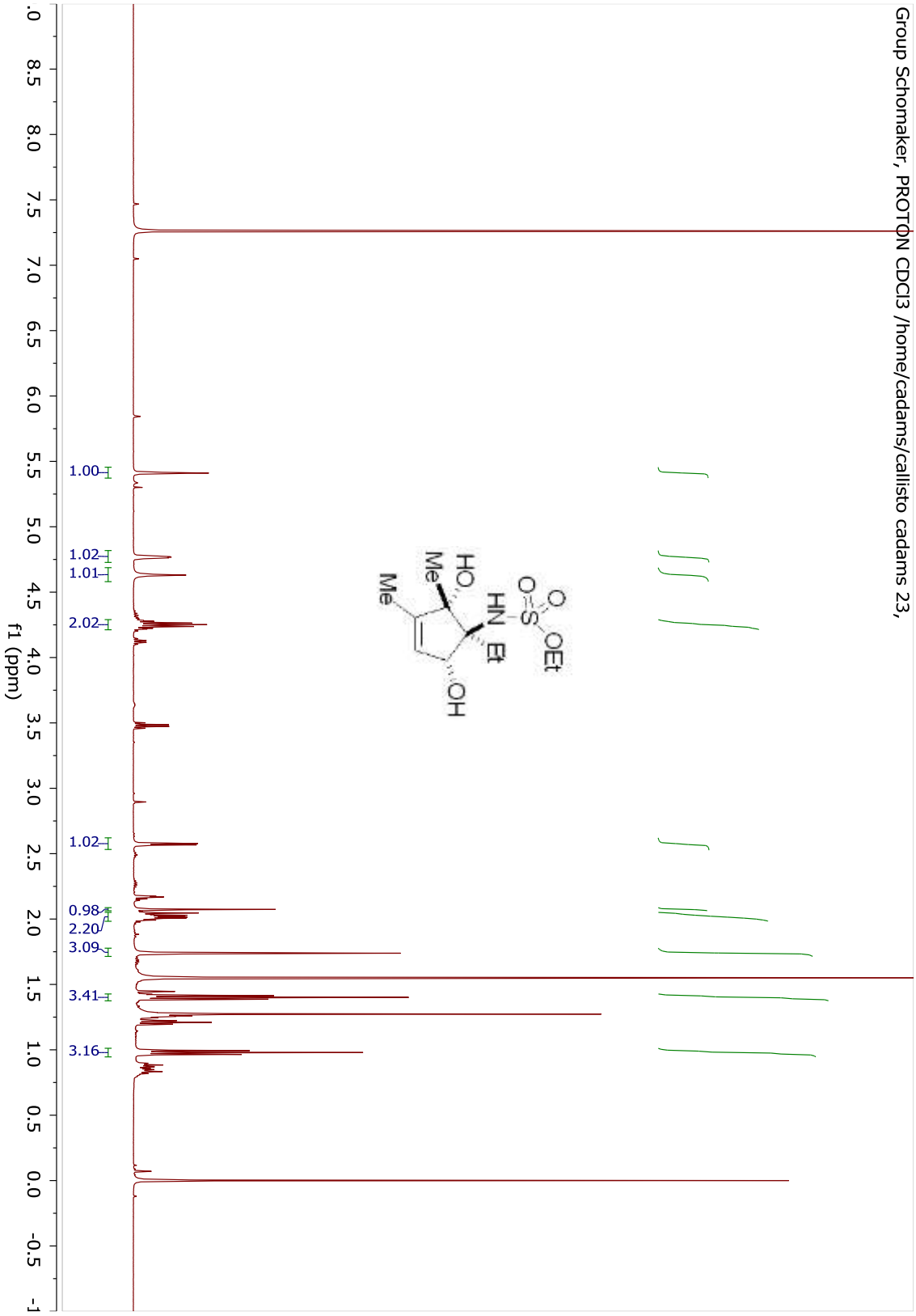
Group Schomaker, C13CPD32 CDCl3 /home/cadams/callisto cadams 33,
EtO
S
O
O
N
Et
HO
Me
OTBS
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

Compound 4.63.



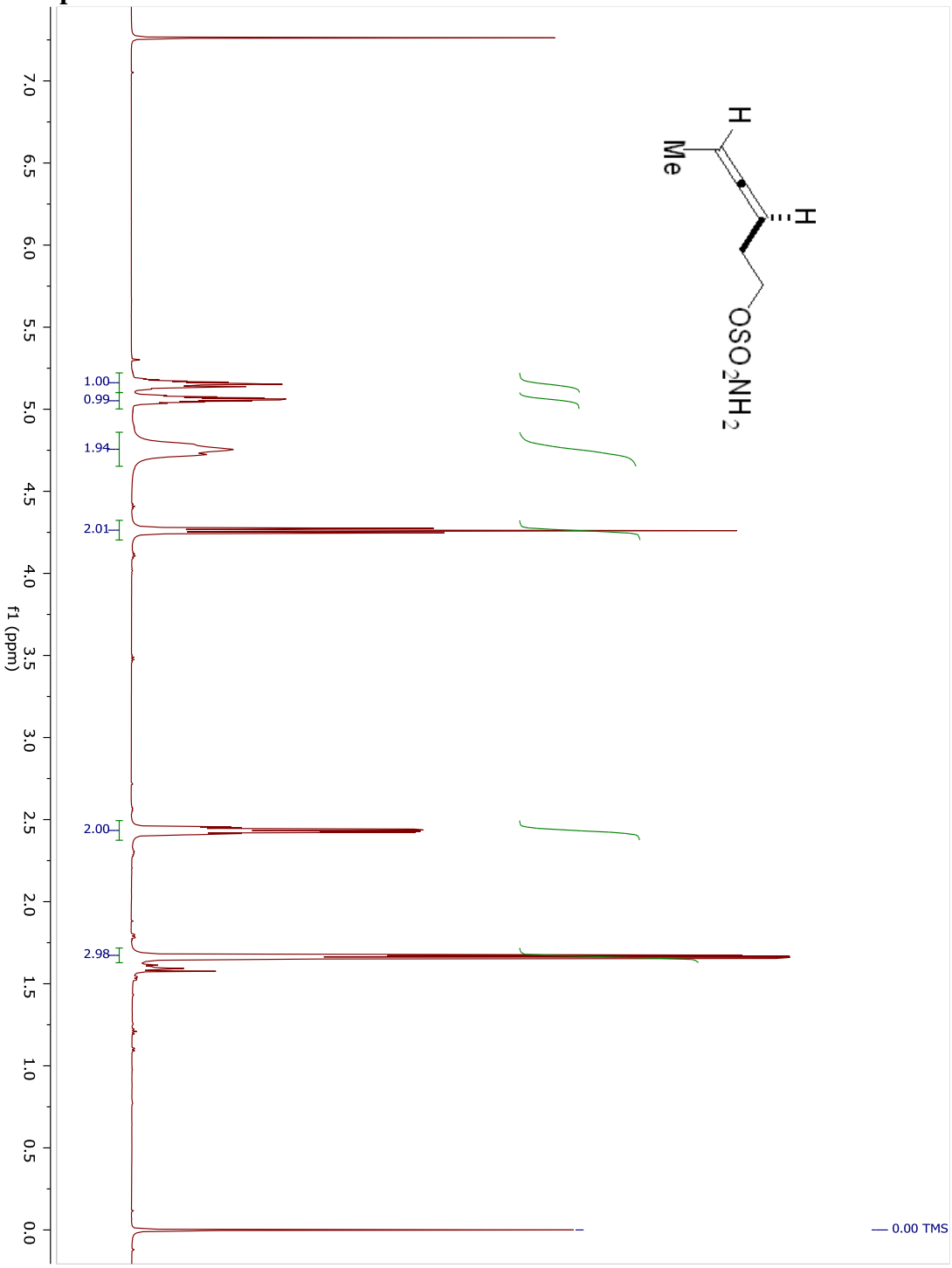
Group Schomaker, C13CPD32 CDCl3 /home/cadams/av400 cadams 4,
HO
Me
OH
HN
Et
O
S
O
OEt
f1 (ppm)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

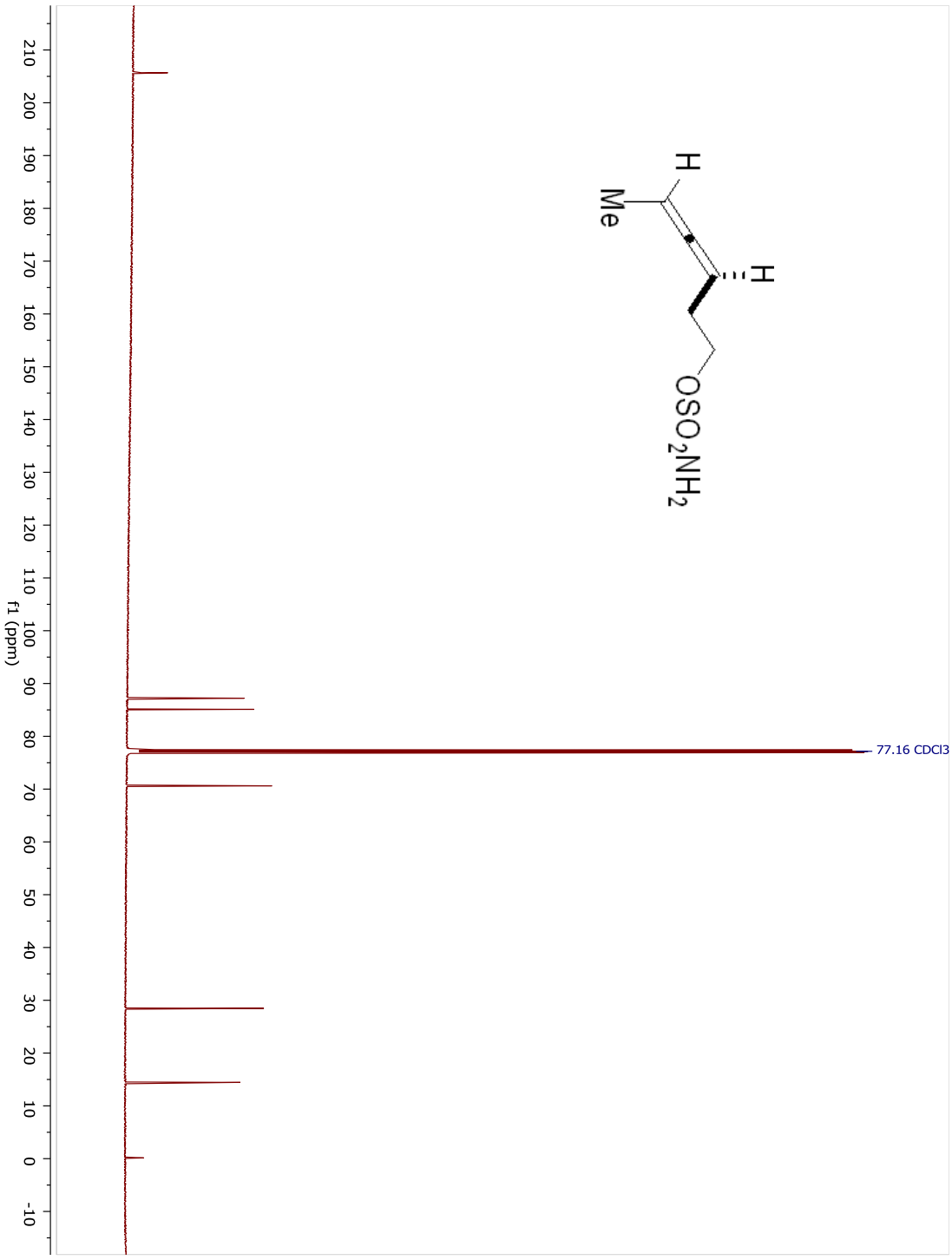
Compound 4.64.



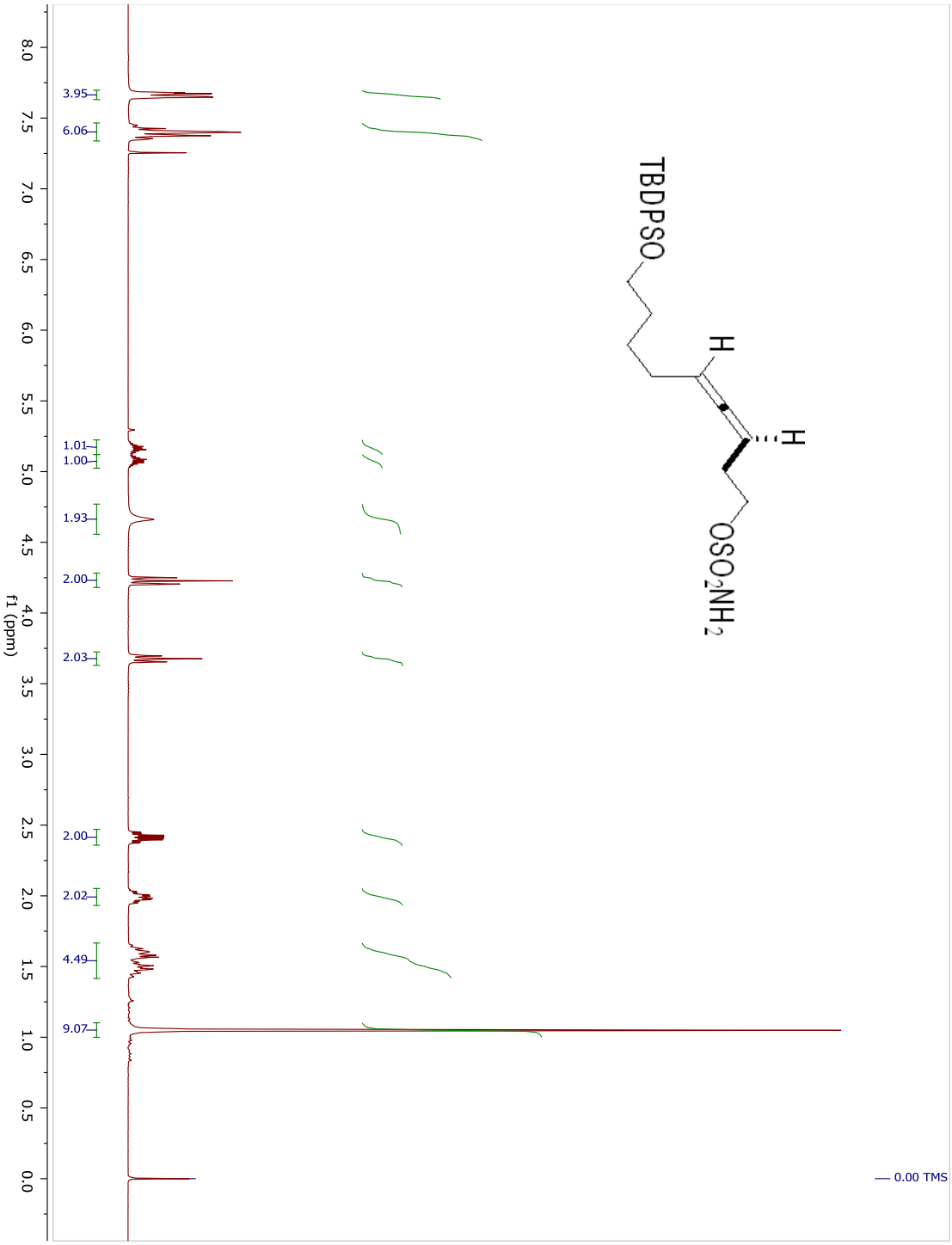
Group Schomaker, C13CPD32 CDCl3 /home/cadams/callisto cadams 23,
HO
Me
Me
HN
Et
O
O=S
OEt
OH
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

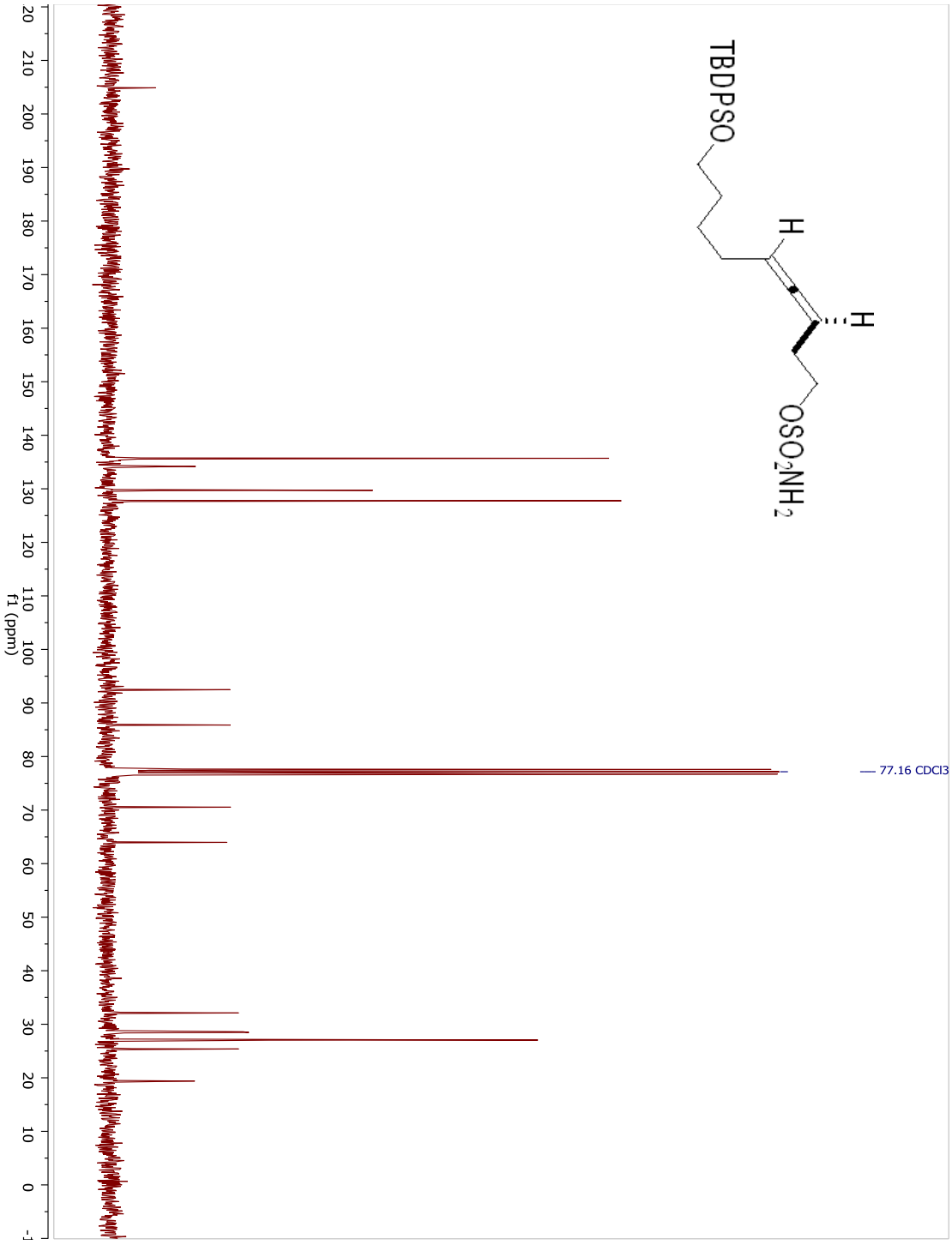
Compound 5.6b.



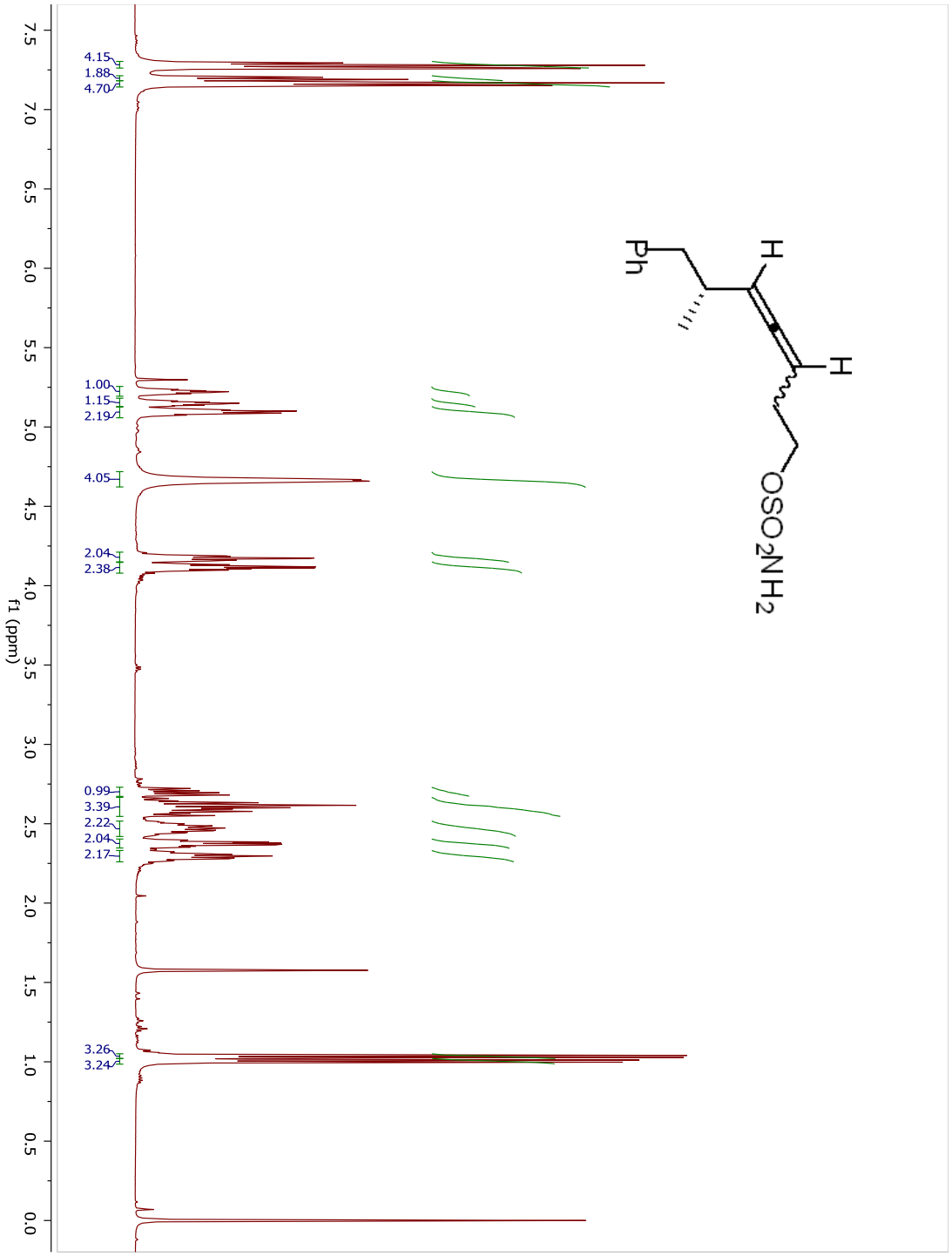


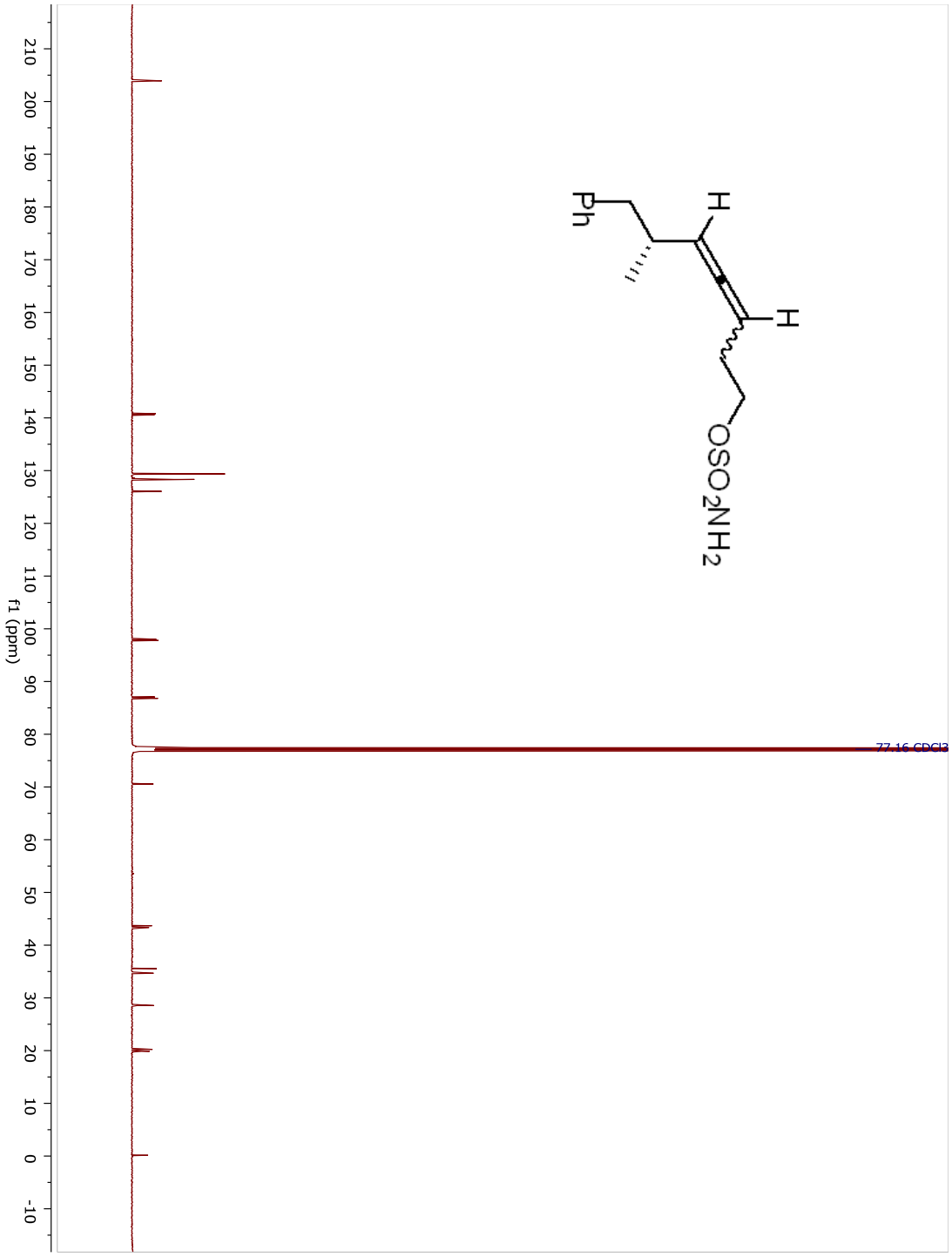
Compound 5.6d.


TBDPSO
H
H
OSO2NH2
3.95
6.06
1.01
1.00
1.93
2.00
2.03
2.00
2.02
4.49
9.07
0.00 TMS
f1 (ppm)

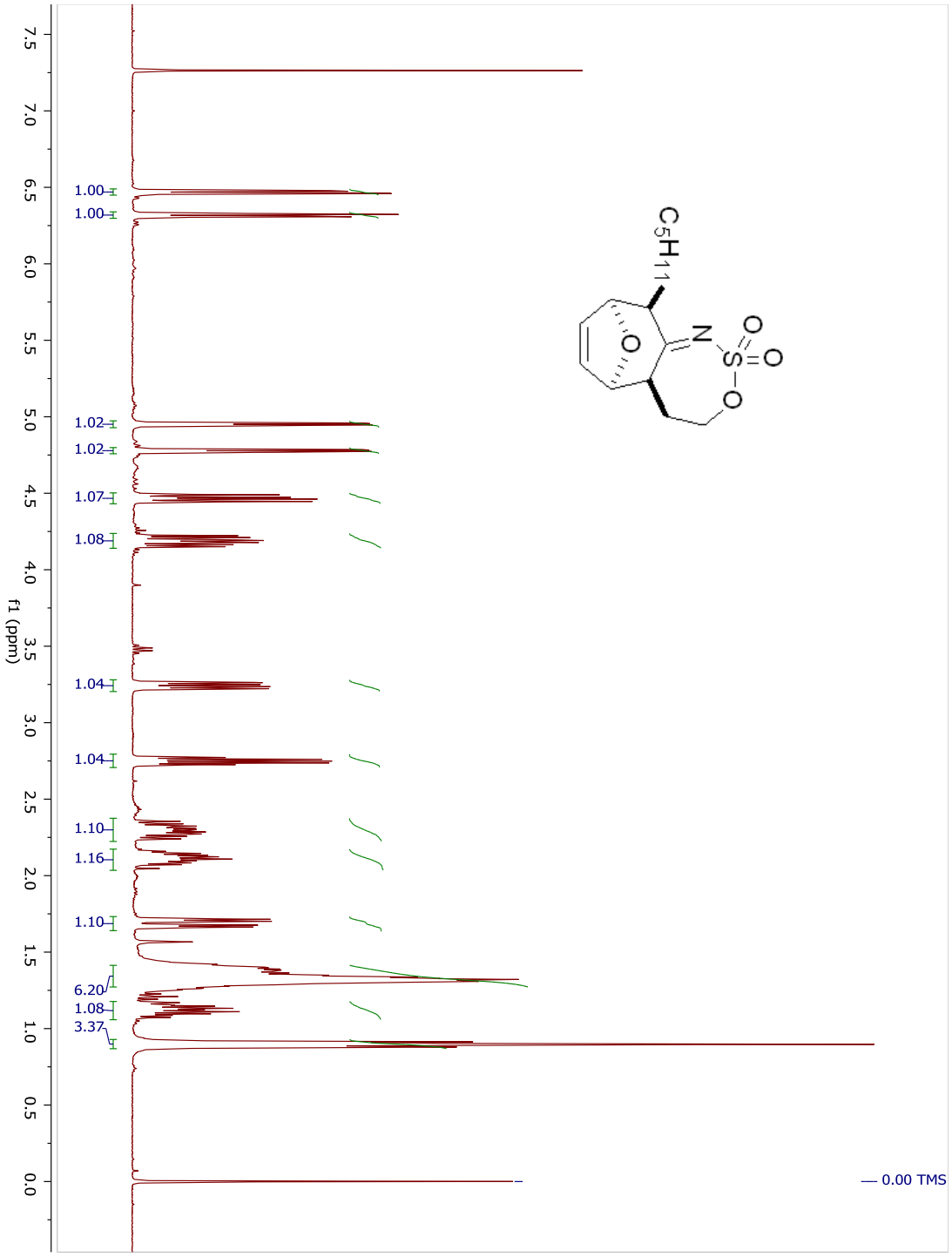


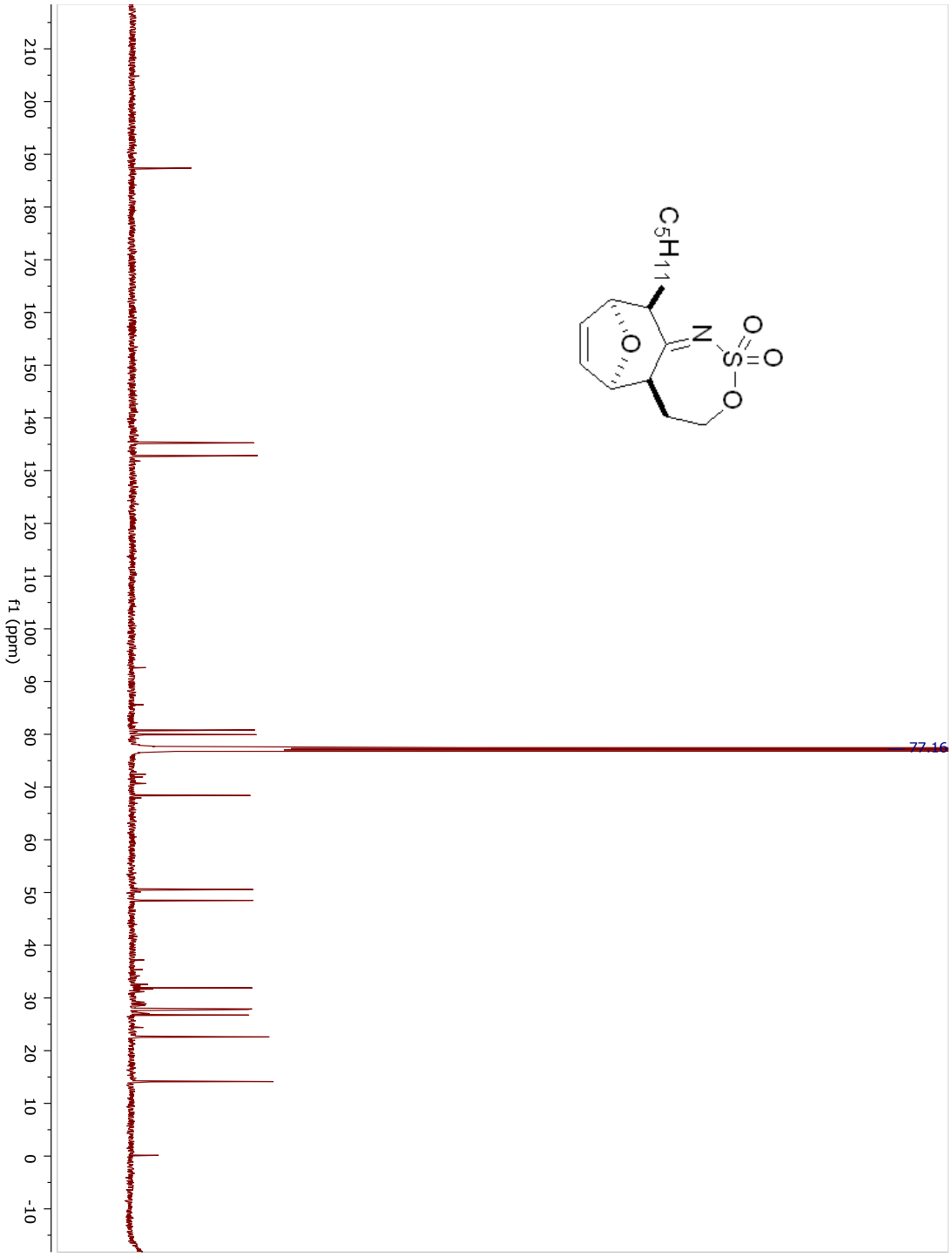
Compound 5.6e.


4.15
1.88
4.70
1.00
1.15
2.19
4.05
2.04
2.38
0.99
3.39
2.22
2.04
2.17
3.26
3.24
f1 (ppm)
Ph
H
H
OSO2NH2

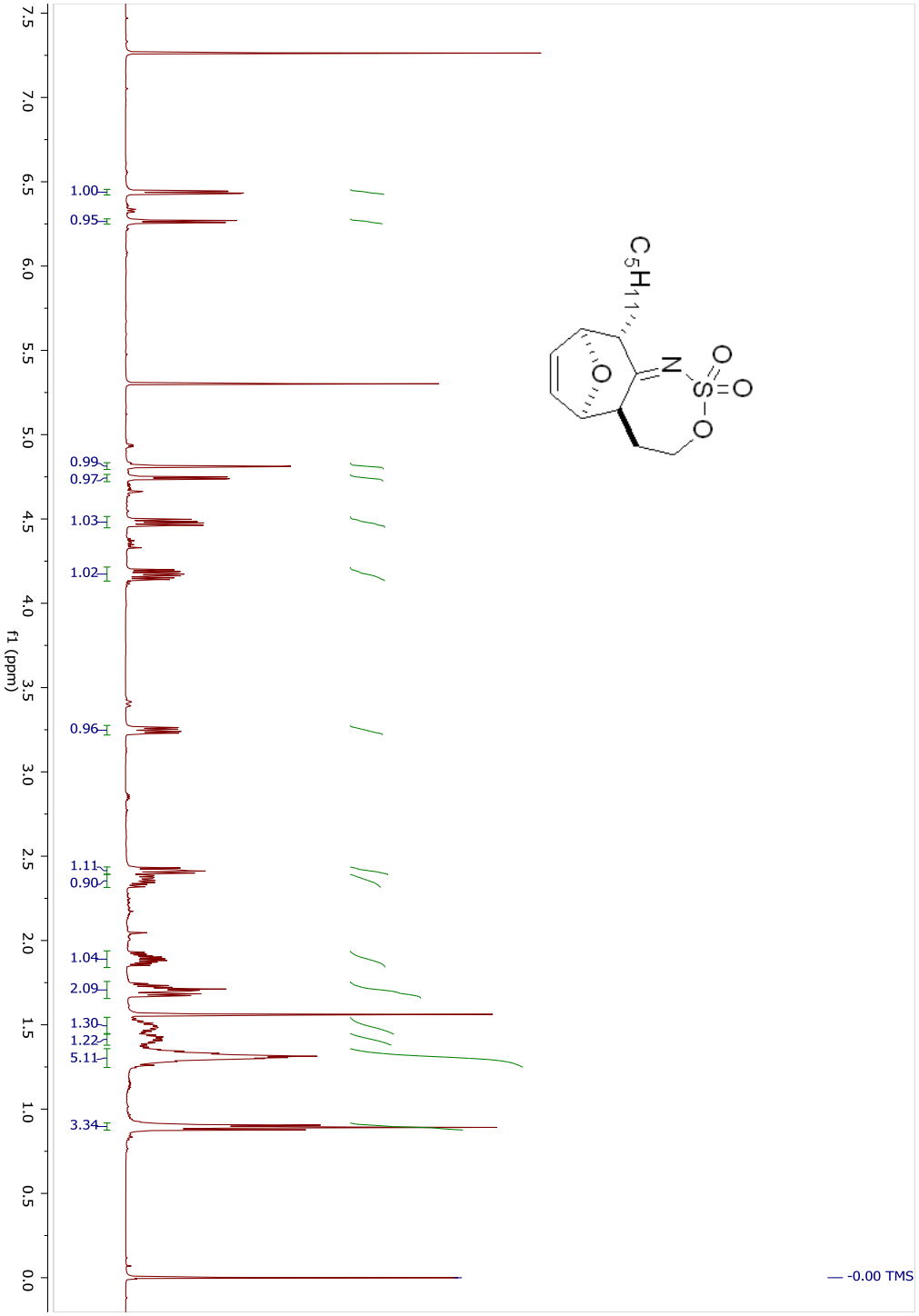


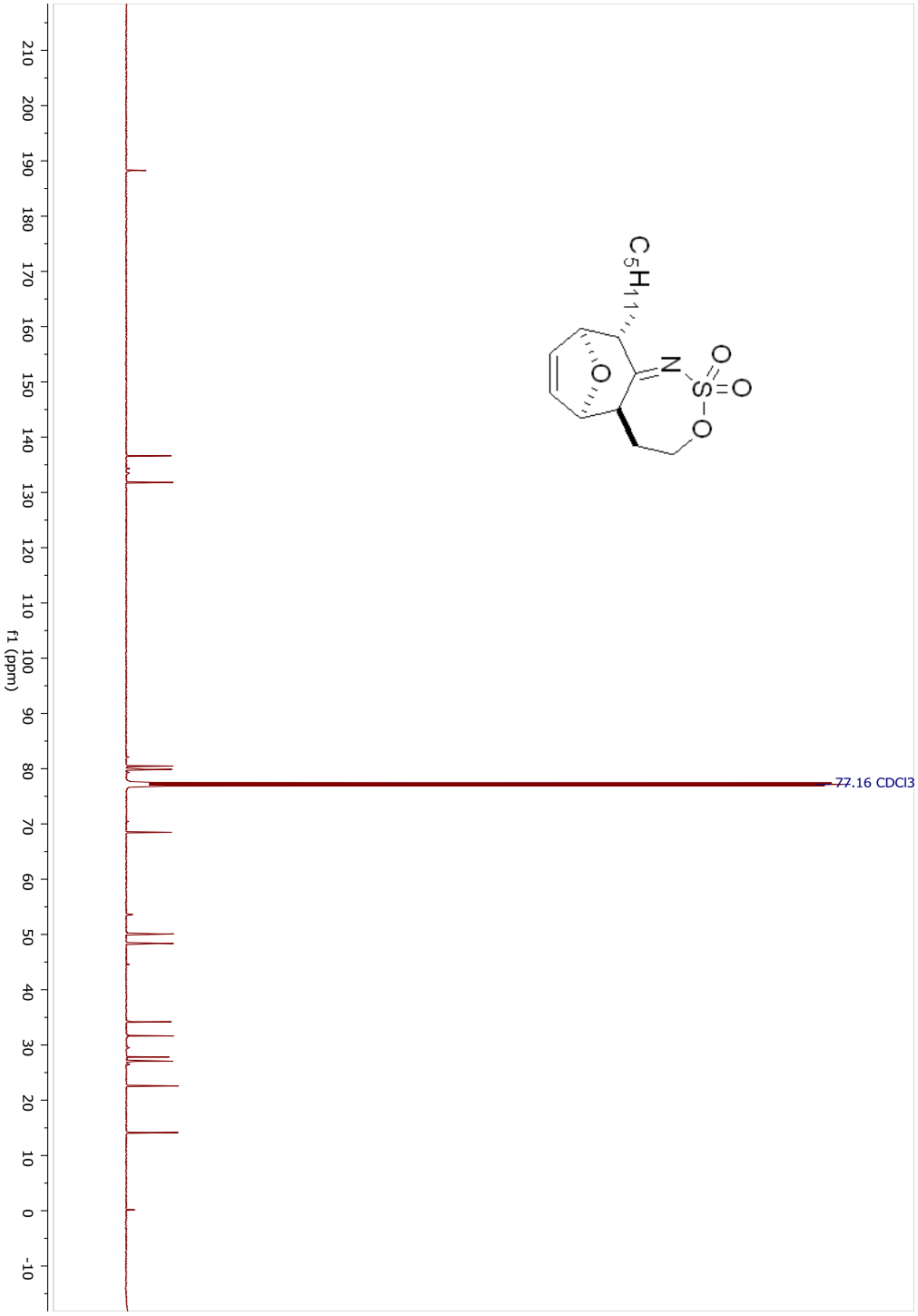
Compound 5.9a.


f1 (ppm)
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1.00
1.00
1.02
1.02
1.07
1.08
1.04
1.04
1.10
1.16
1.10
6.20
1.08
3.37
0.00 TMS
C5H11
O
N
S
O
O
O

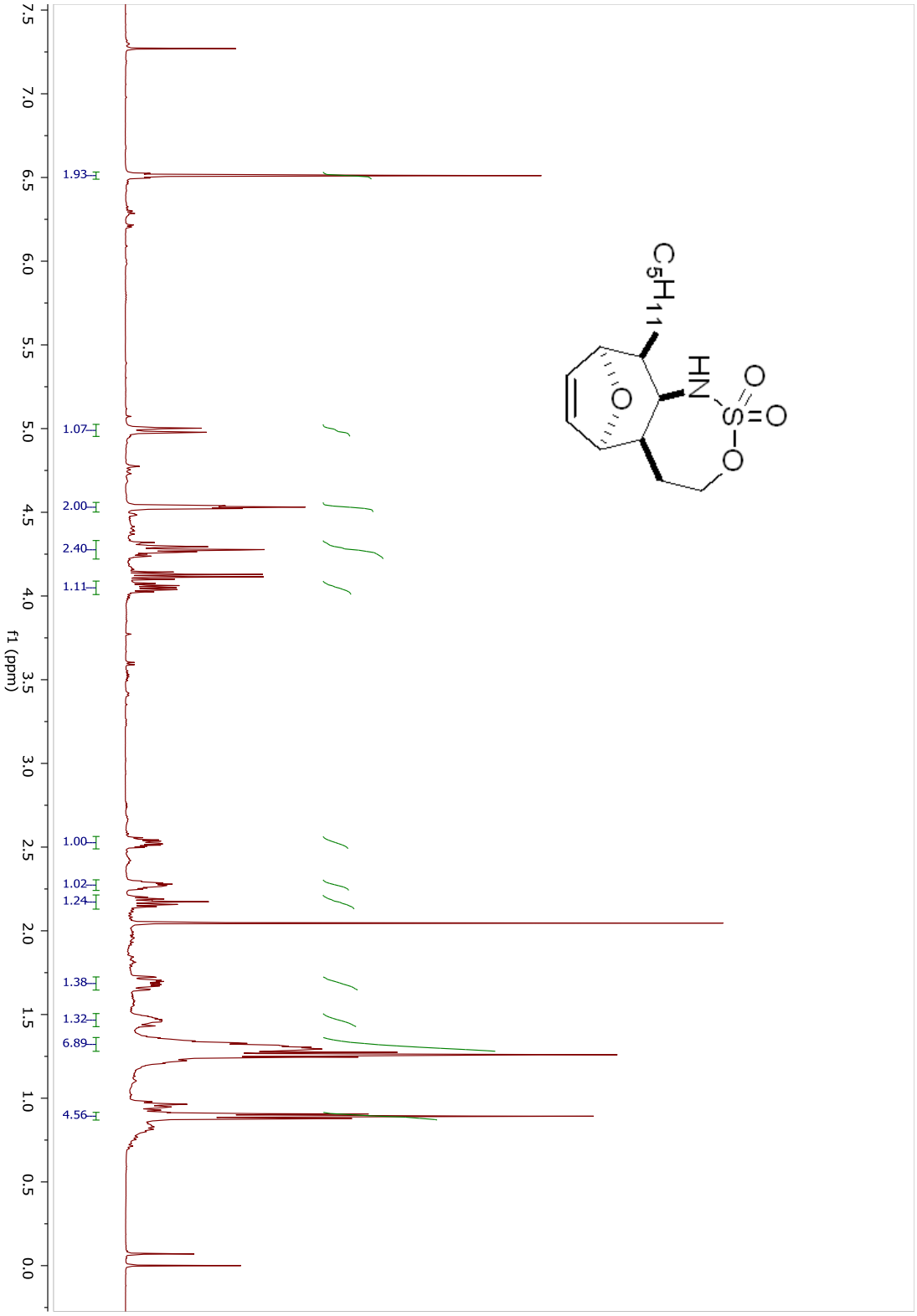


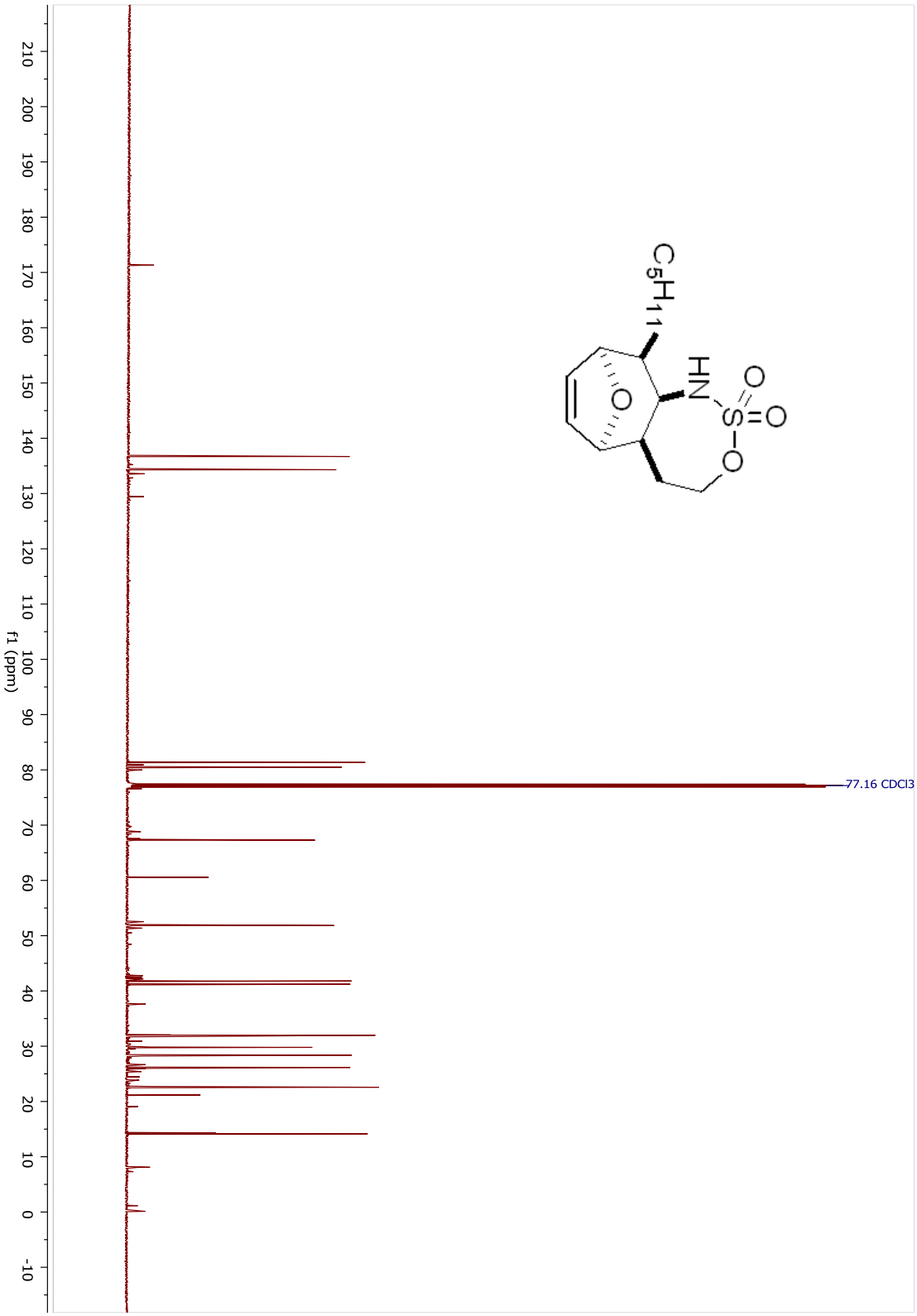
Compound 5.10a.


f1 (ppm)
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1.00
0.95
0.99
0.97
1.03
1.02
0.96
1.11
0.90
1.04
2.09
1.30
1.22
5.11
3.34
— -0.00 TMS
C5H11
O
N
S
O
O

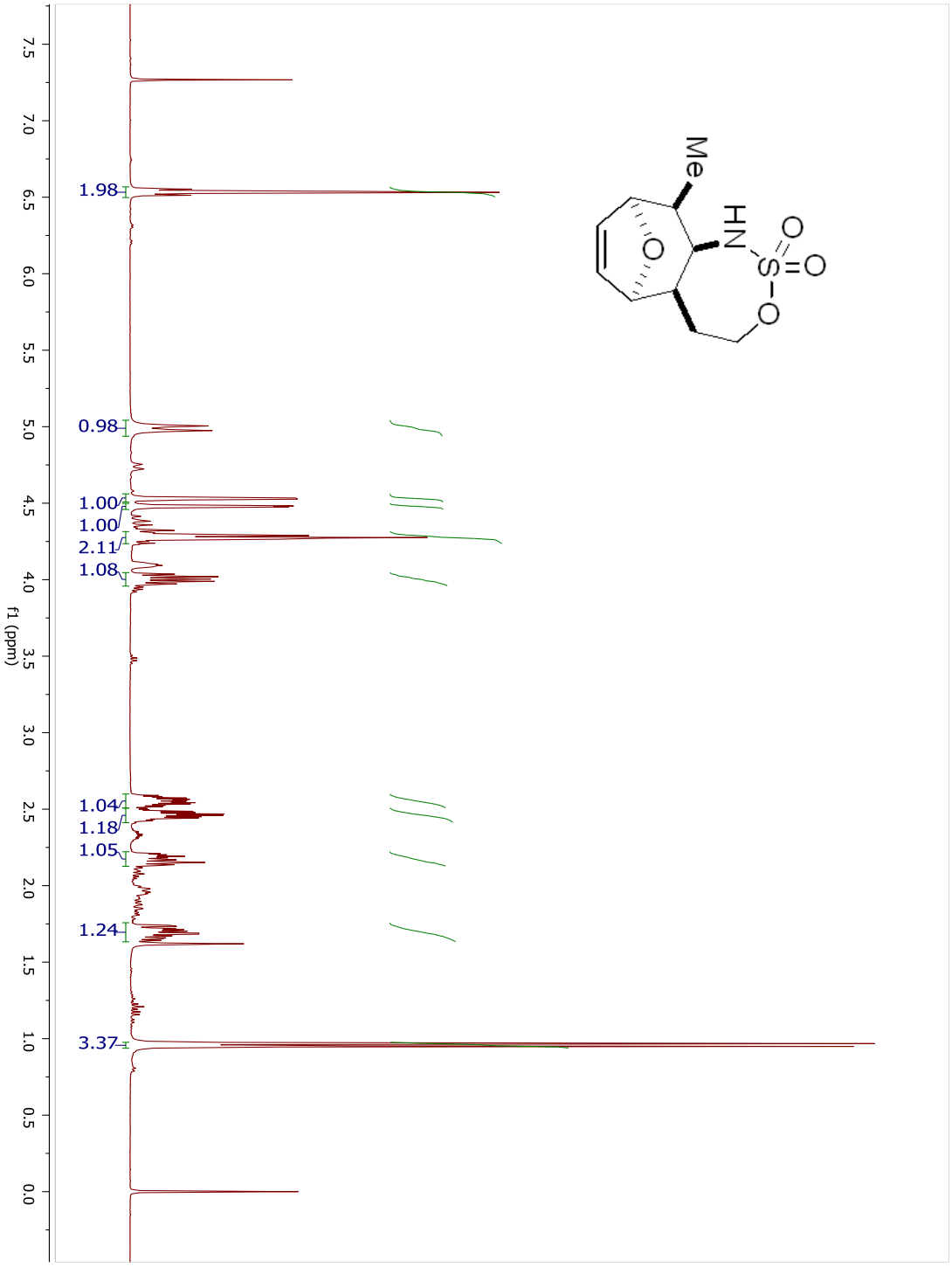


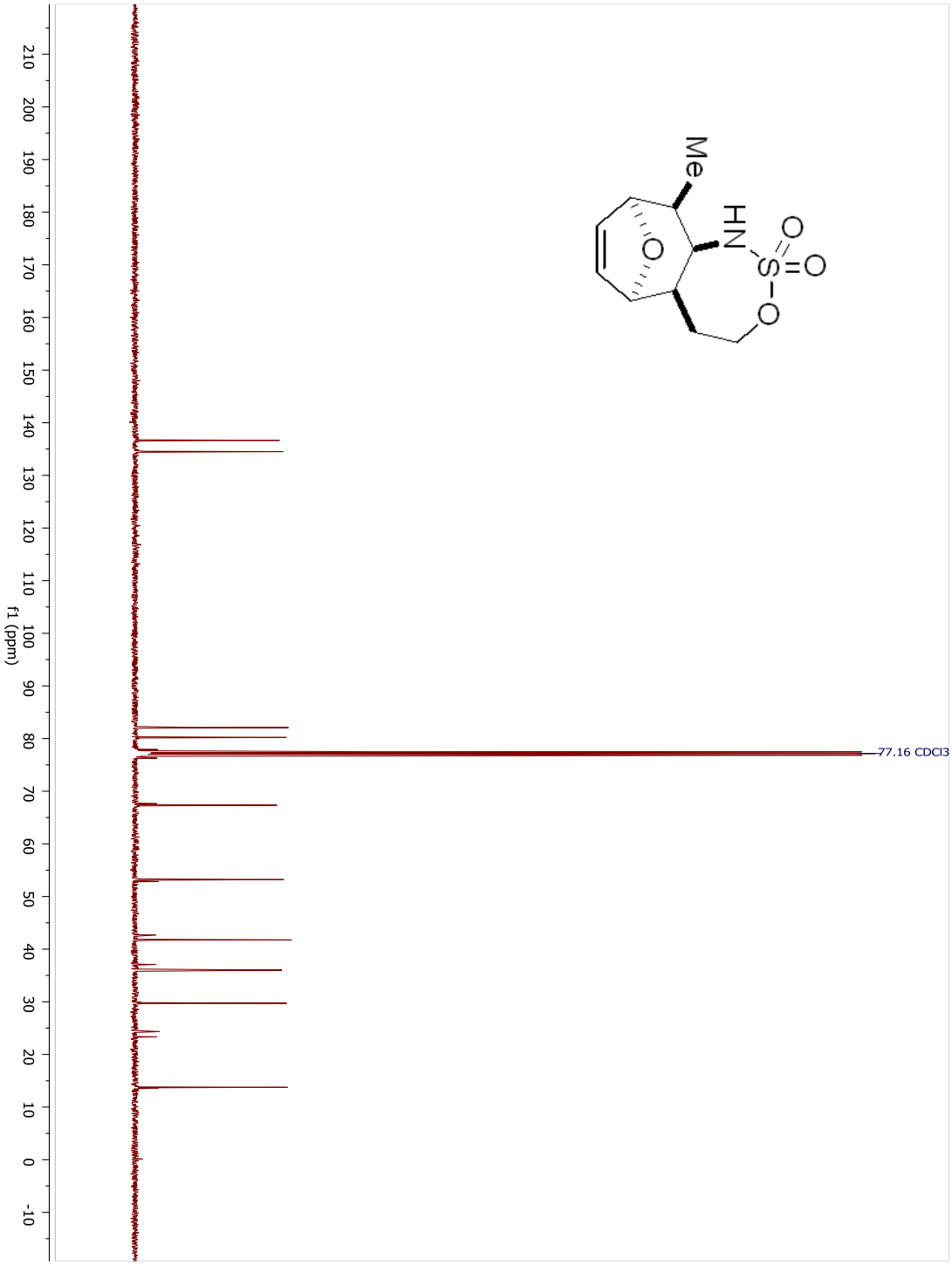
Compound 5.11a.


f1 (ppm)
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1.93
1.07
2.00
2.40
1.11
1.00
1.02
1.24
1.38
1.32
6.89
4.56
C5H11
HN
O
S
O
O
O

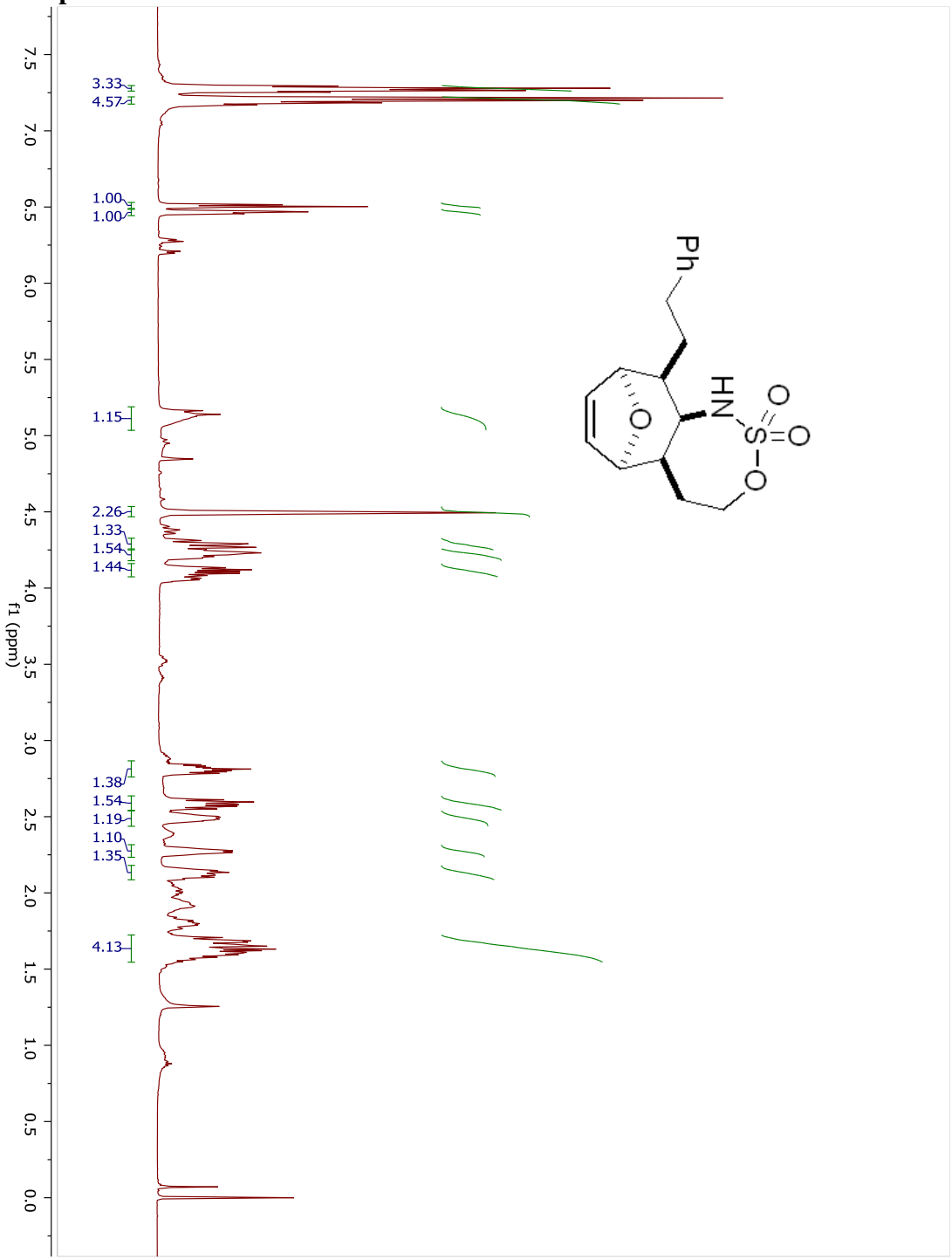

C5H11
HN
O
S
O
O
O
77.16 CDCl3
f1 (ppm)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

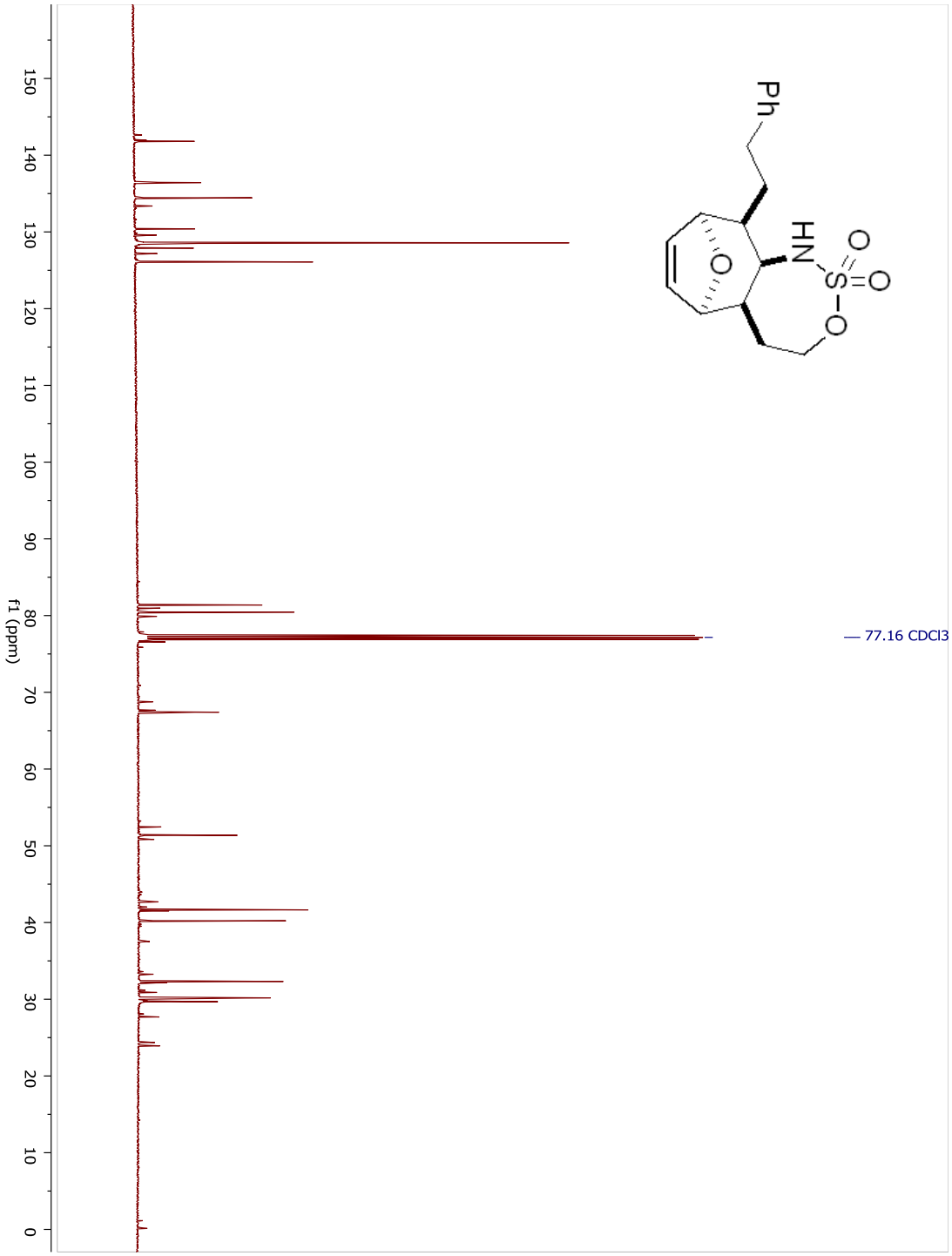
Compound 5.11b.



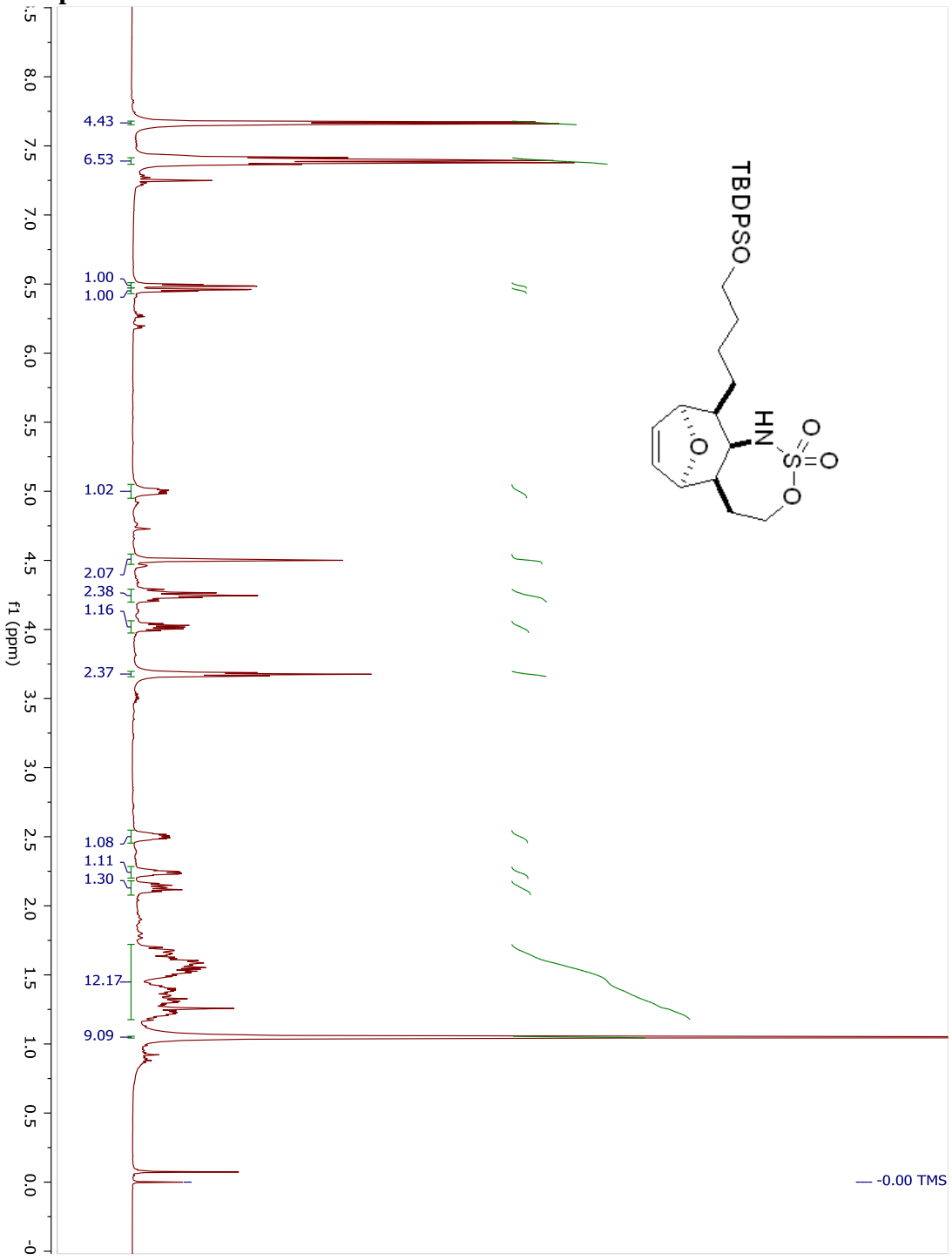

Me
HN
O
O
S
O
O
77.16 CDCl3
f1 (ppm)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

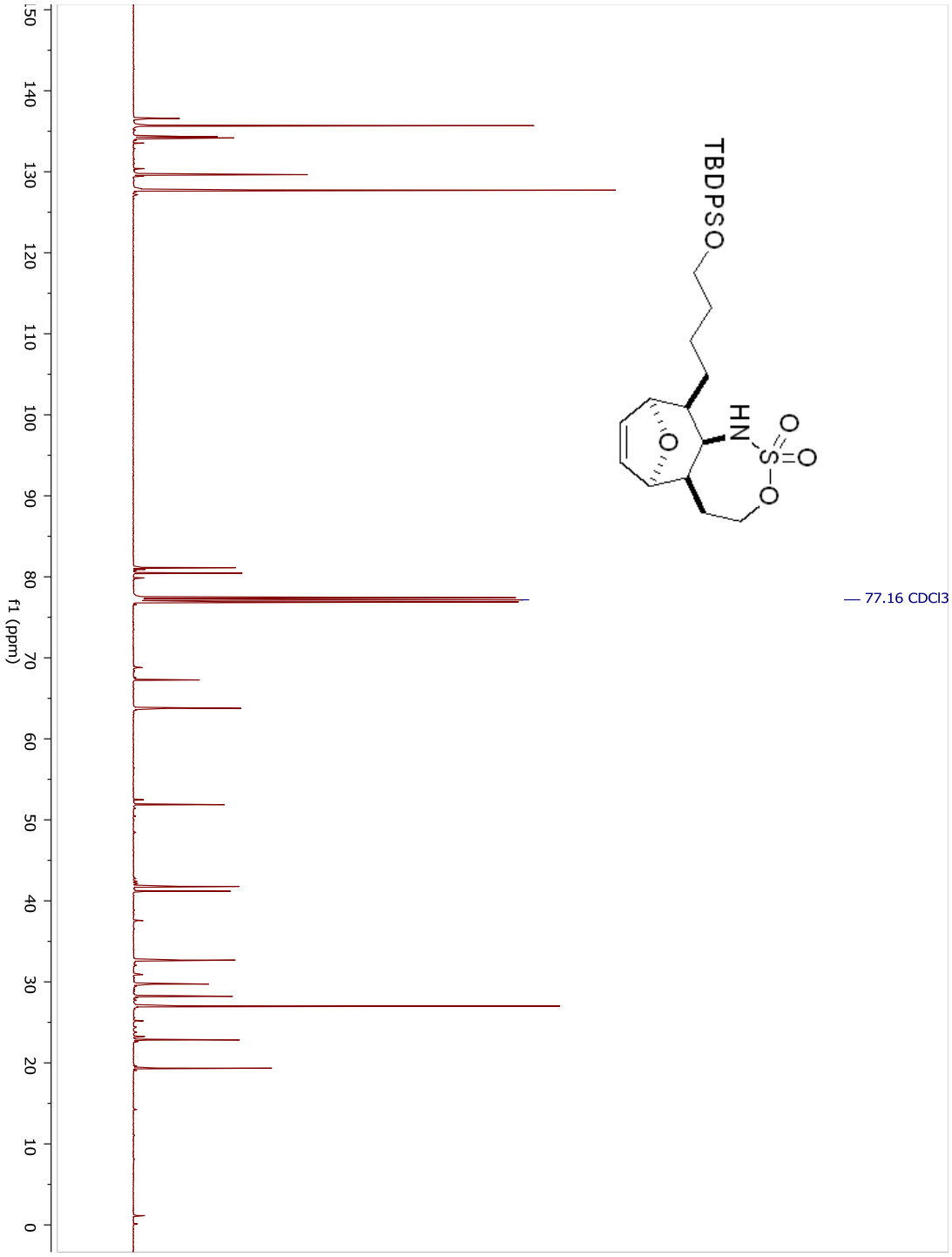
Compound 5.11c.



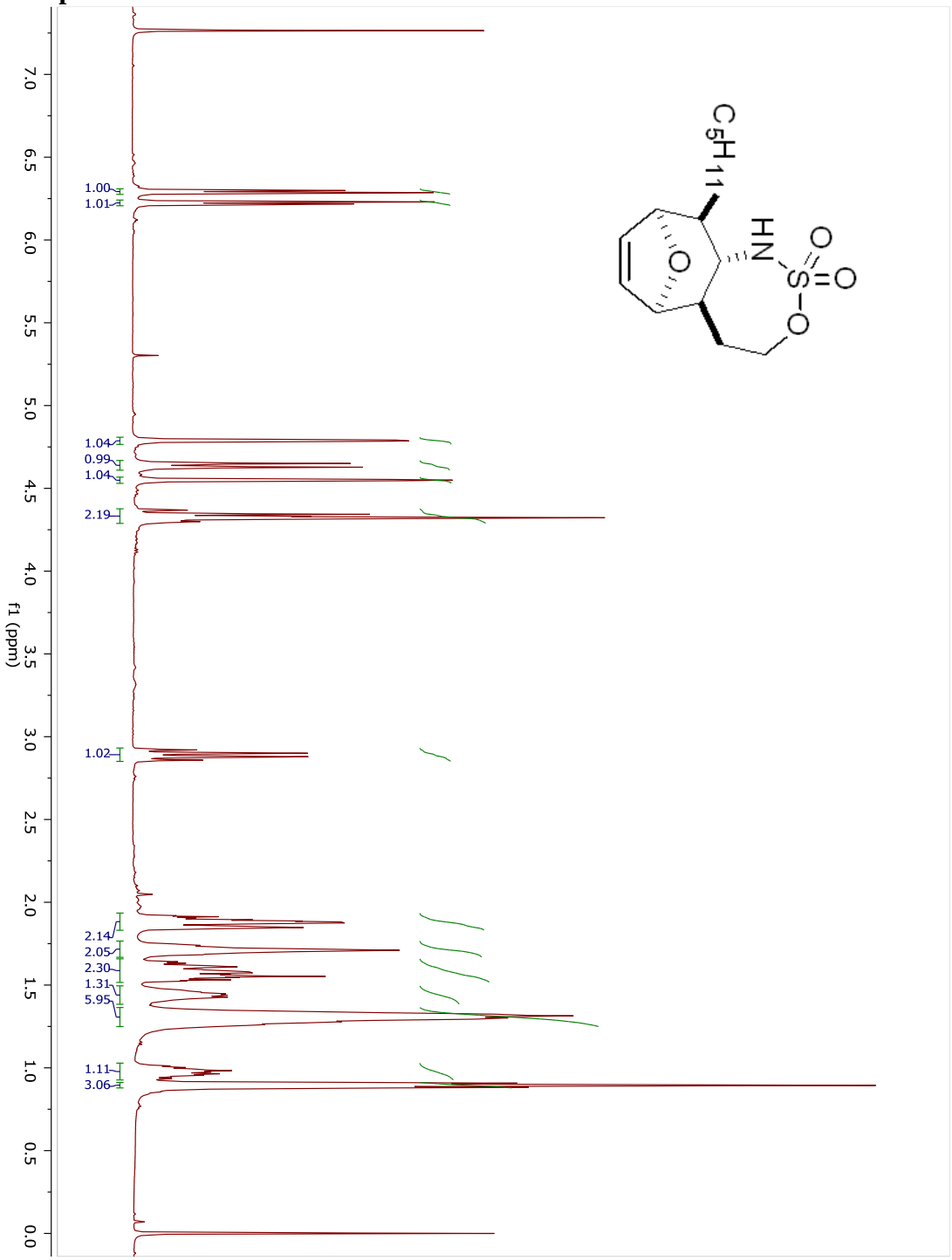

Ph
HN
O
S
O
O
O
f1 (ppm)
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
77.16 CDCl3

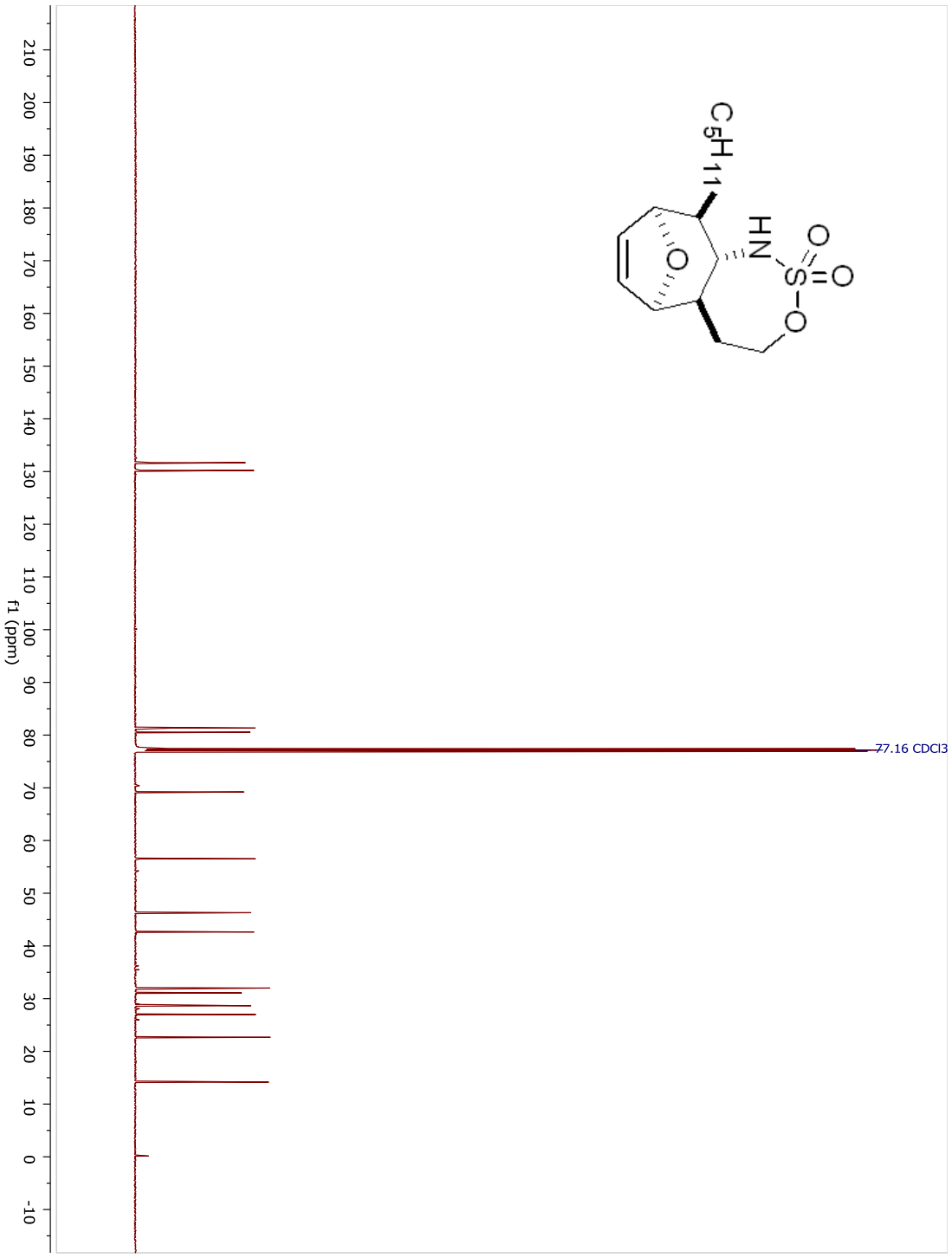
Compound 5.11d.



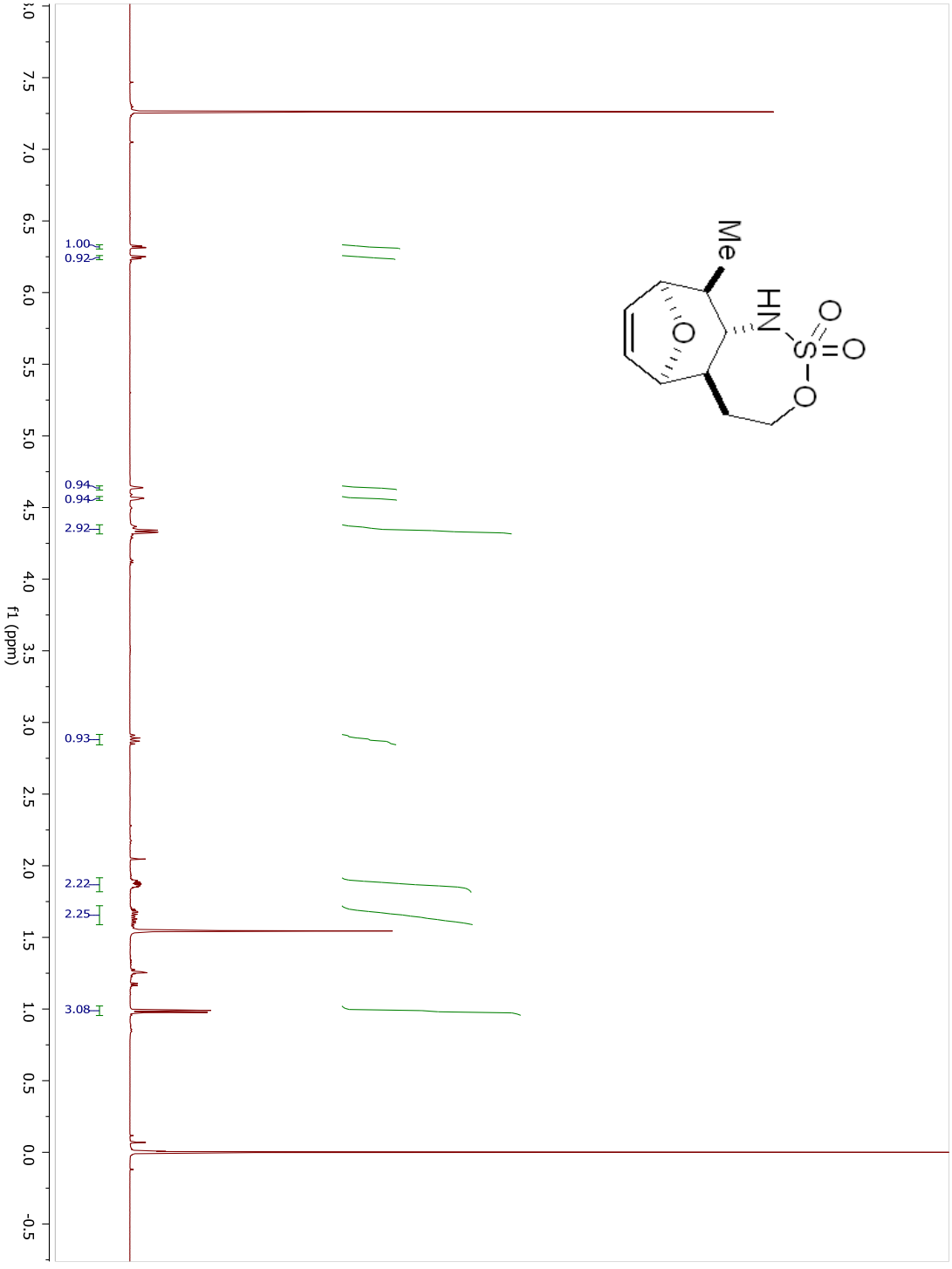

TBDPSO
HN
O
S
O
O
O
77.16 CDCl3
f1 (ppm)
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

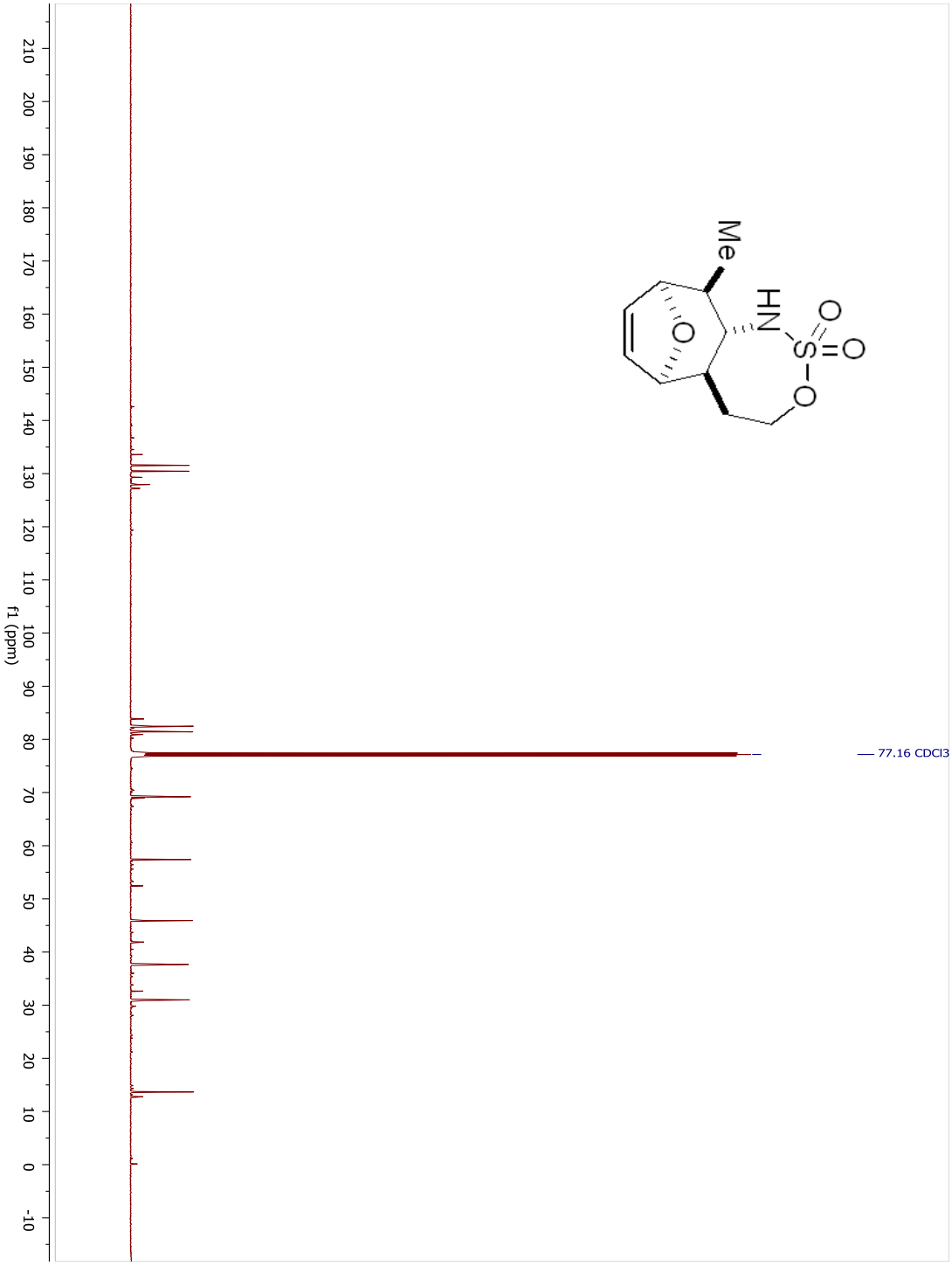
Compound 5.12a



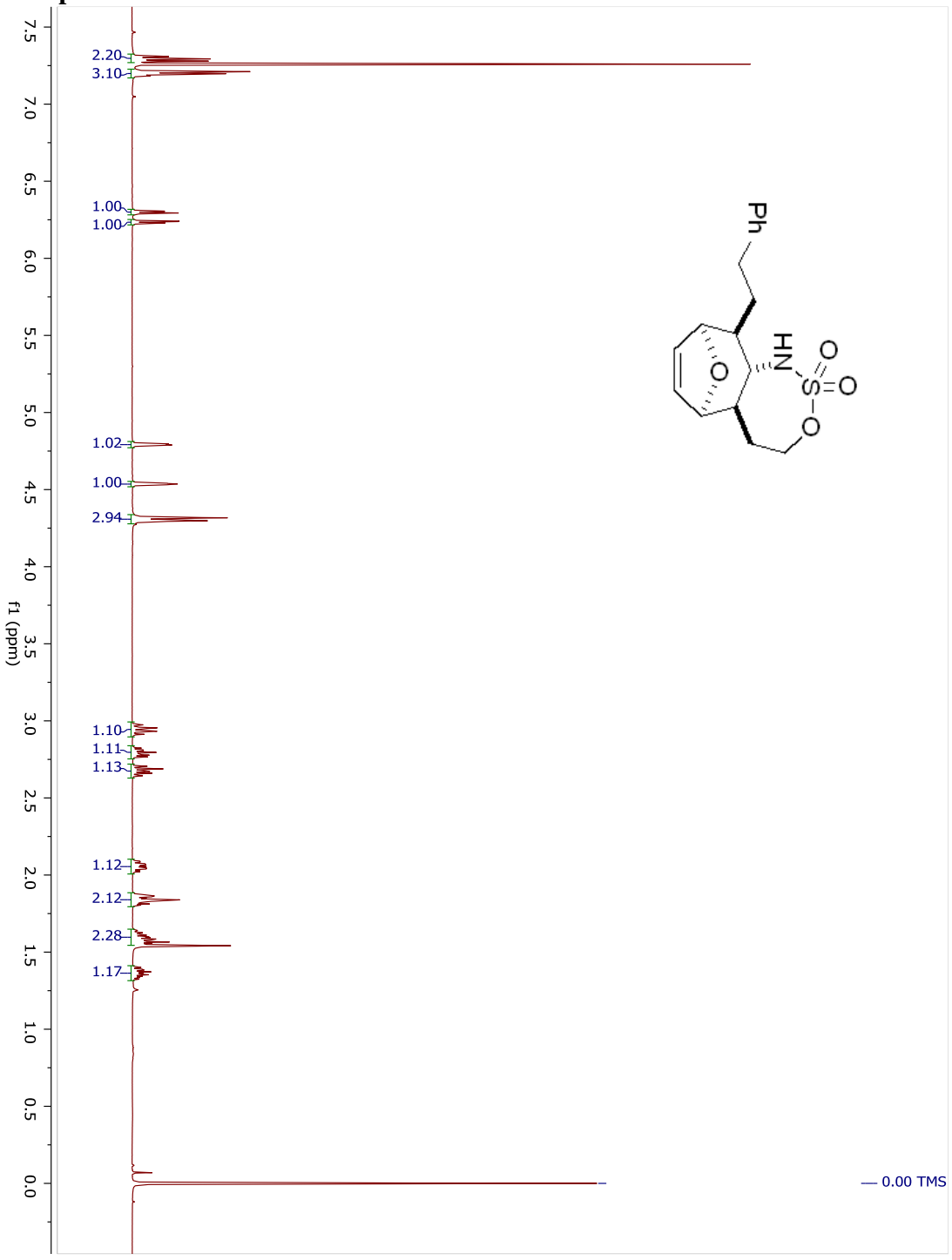

C5H11
HN
O
S
O
O
77.16 CDCl3
f1 (ppm)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

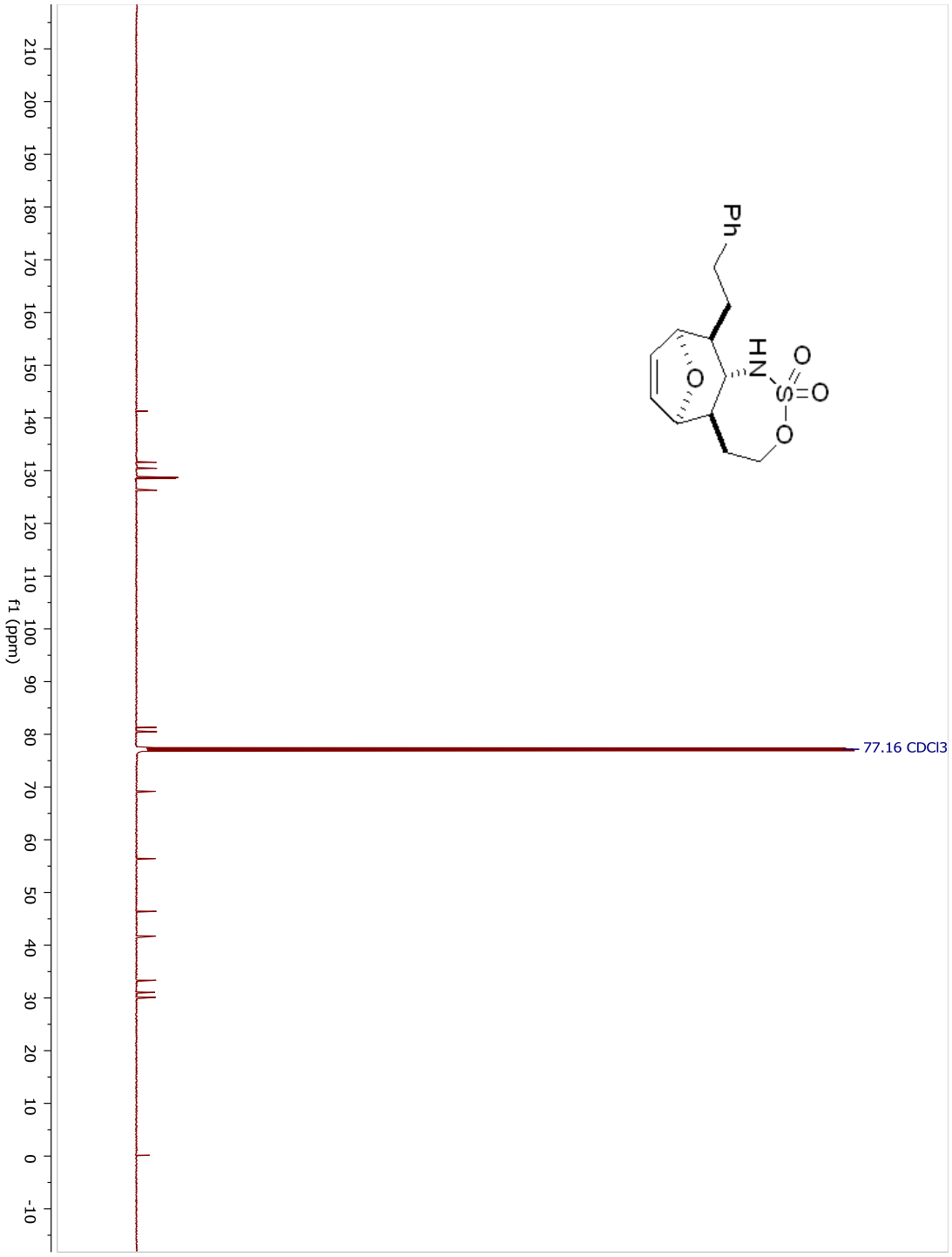
Compound 5.12b.



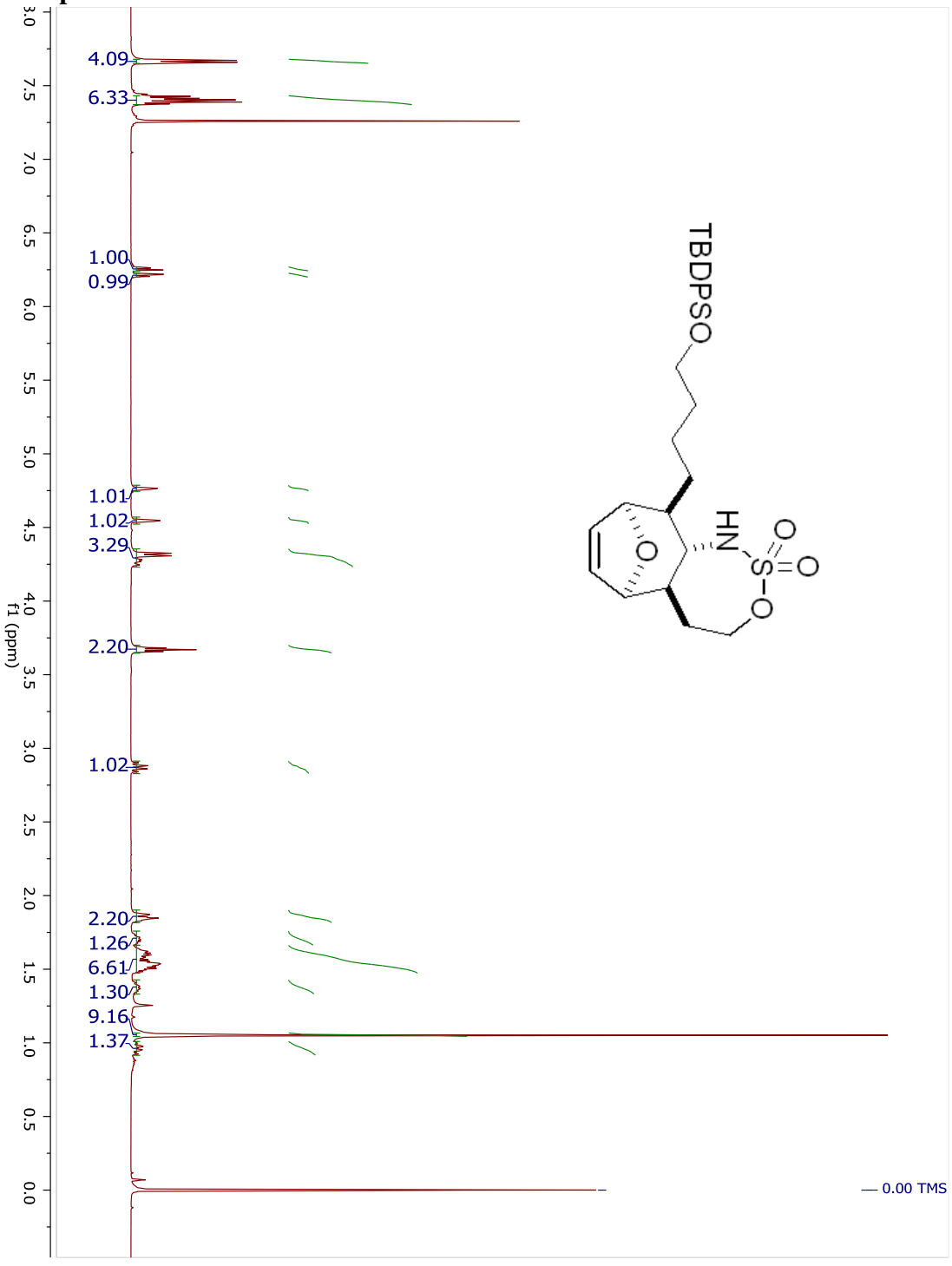

Me
HN
O
S
O
O
O
77.16 CDCl3
f1 (ppm)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

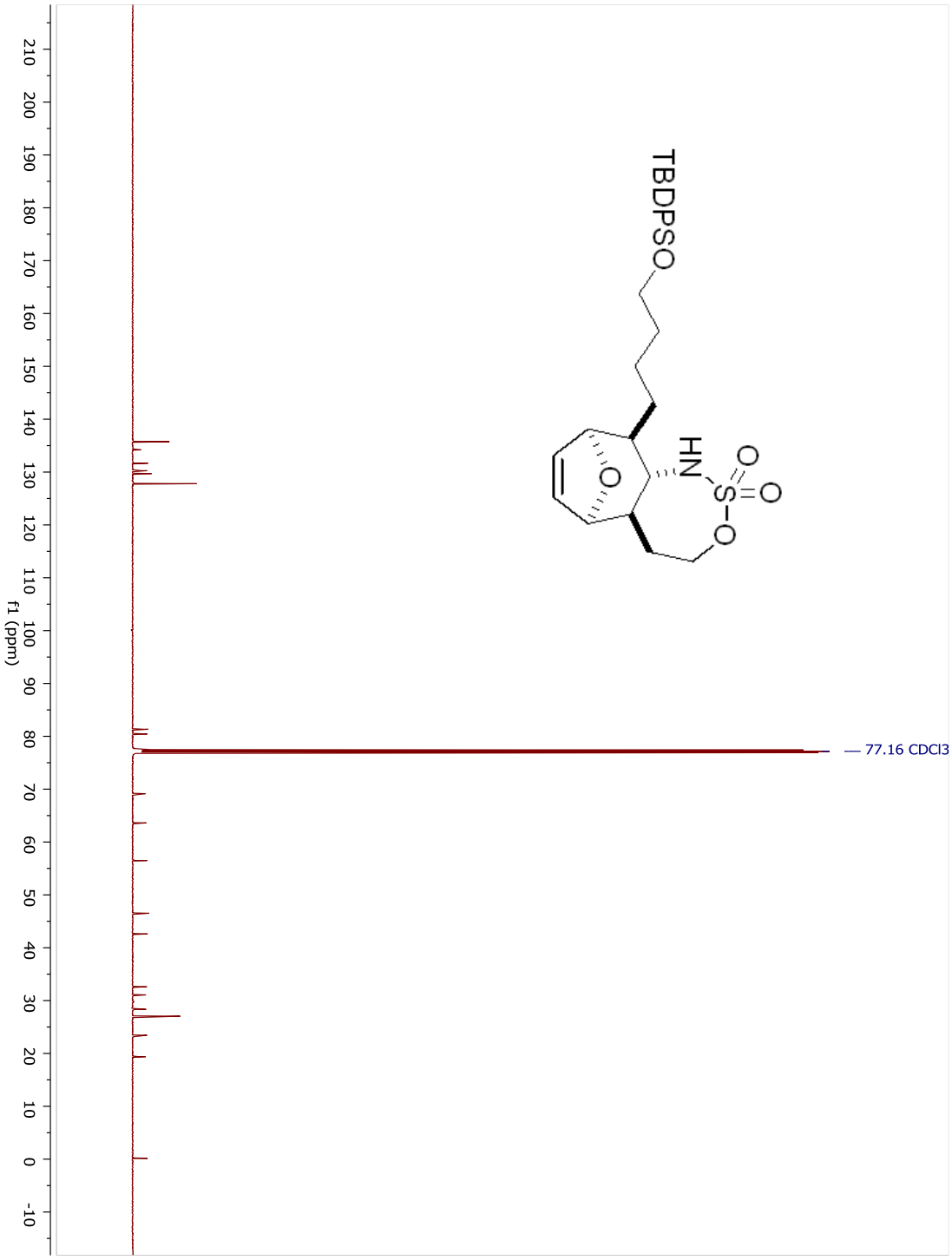
Compound 5.12c.



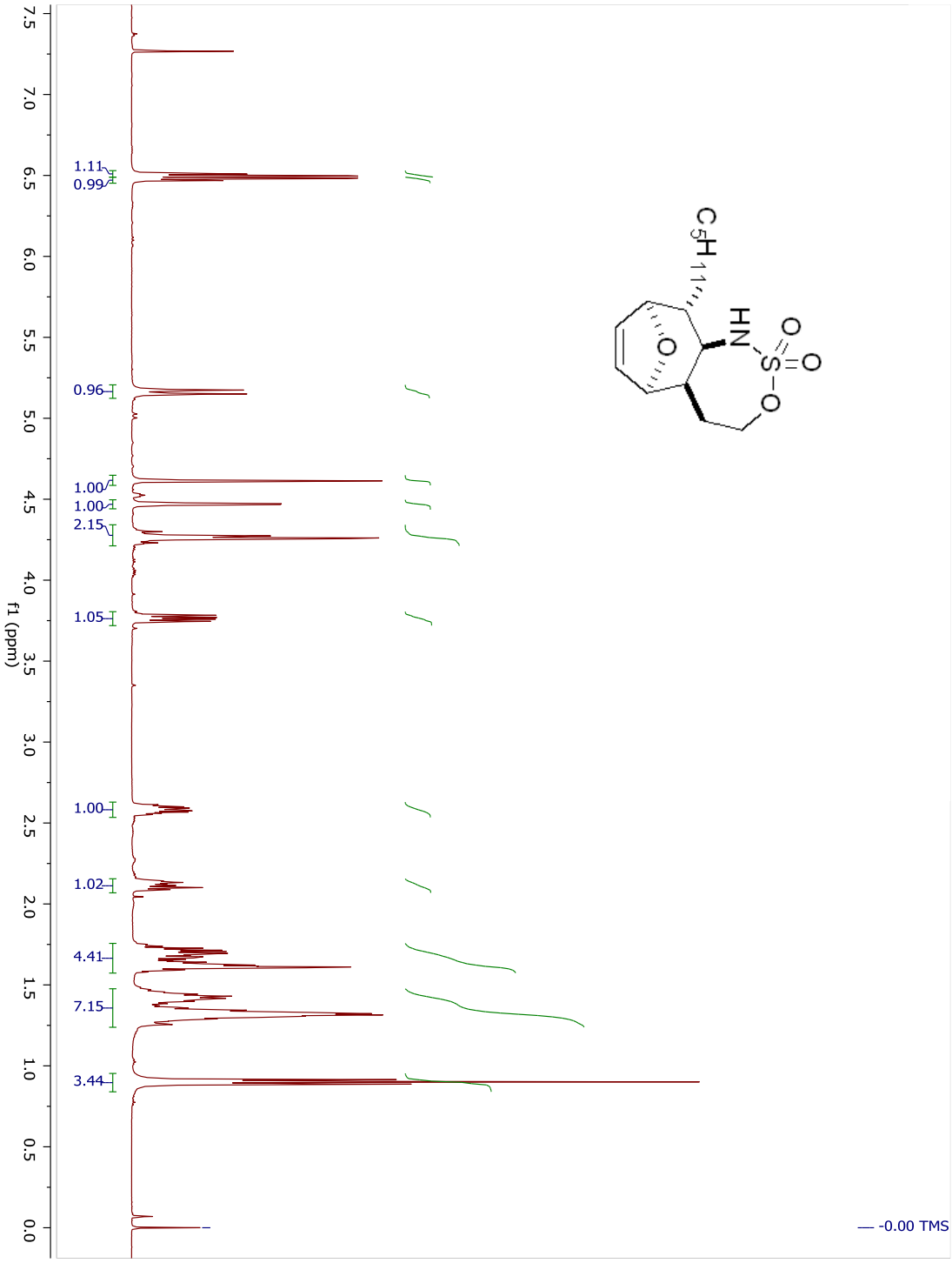

Ph
HN
O
O
S
O
O
77.16 CDCl3
f1 (ppm)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

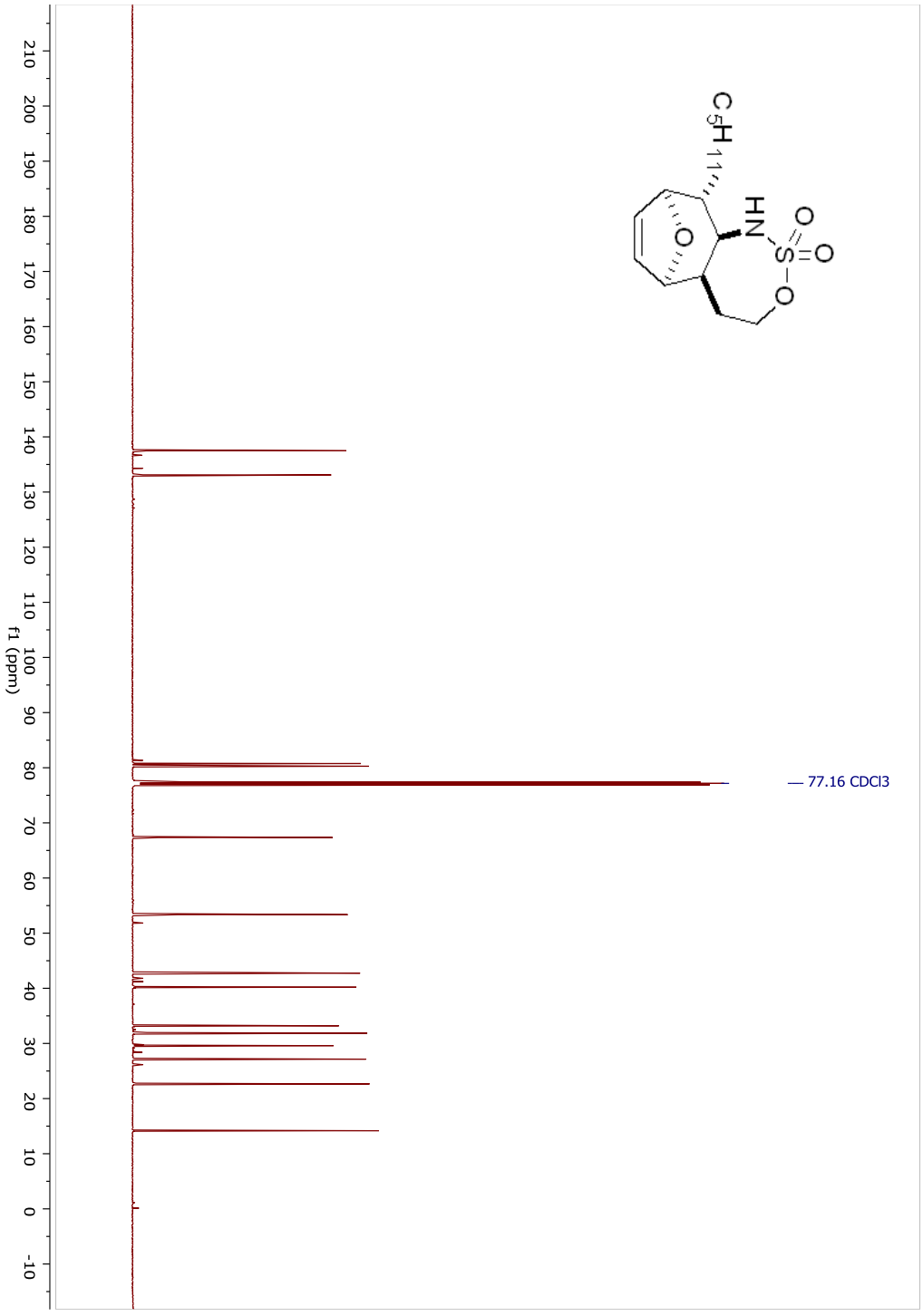
Compound 5.12d.



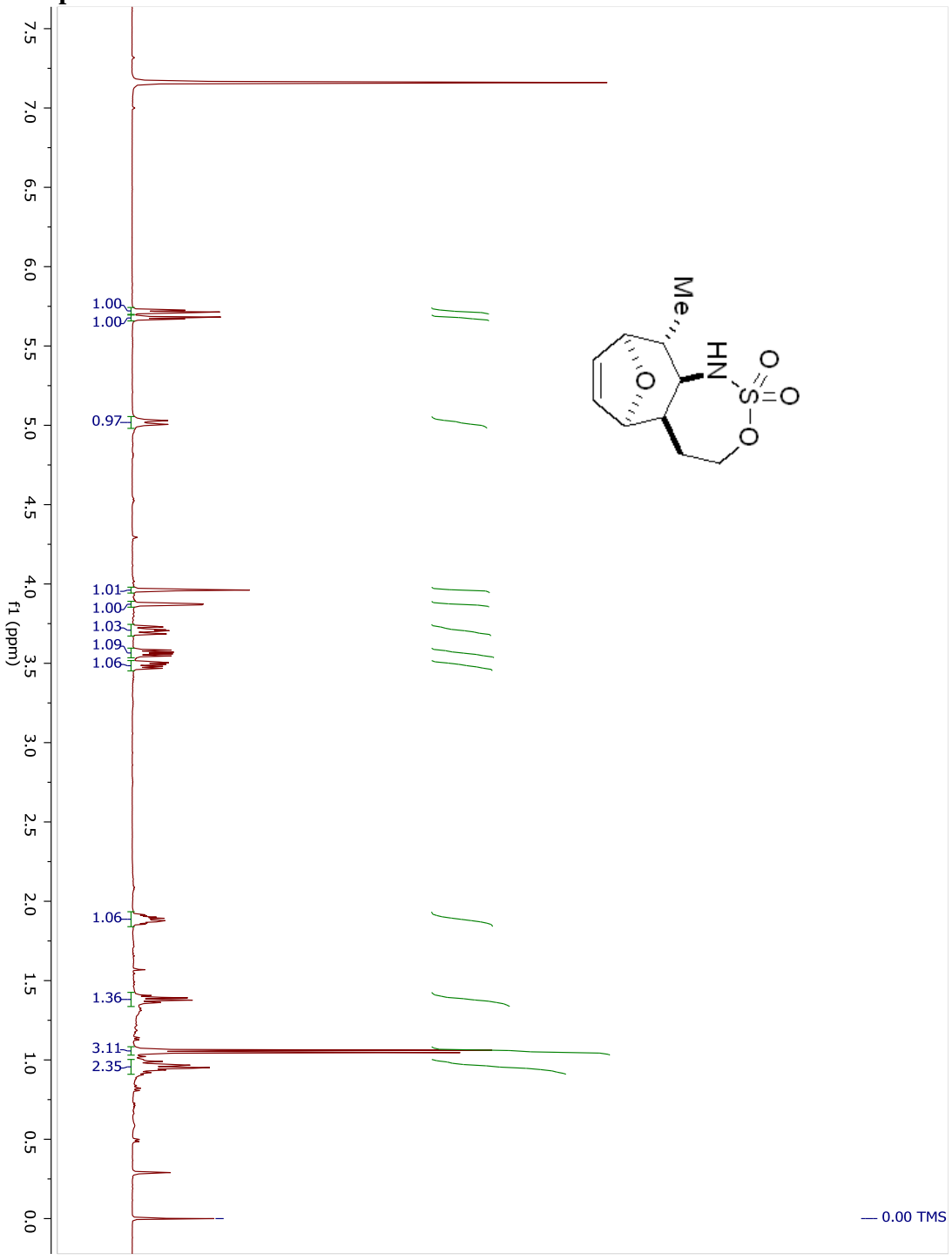


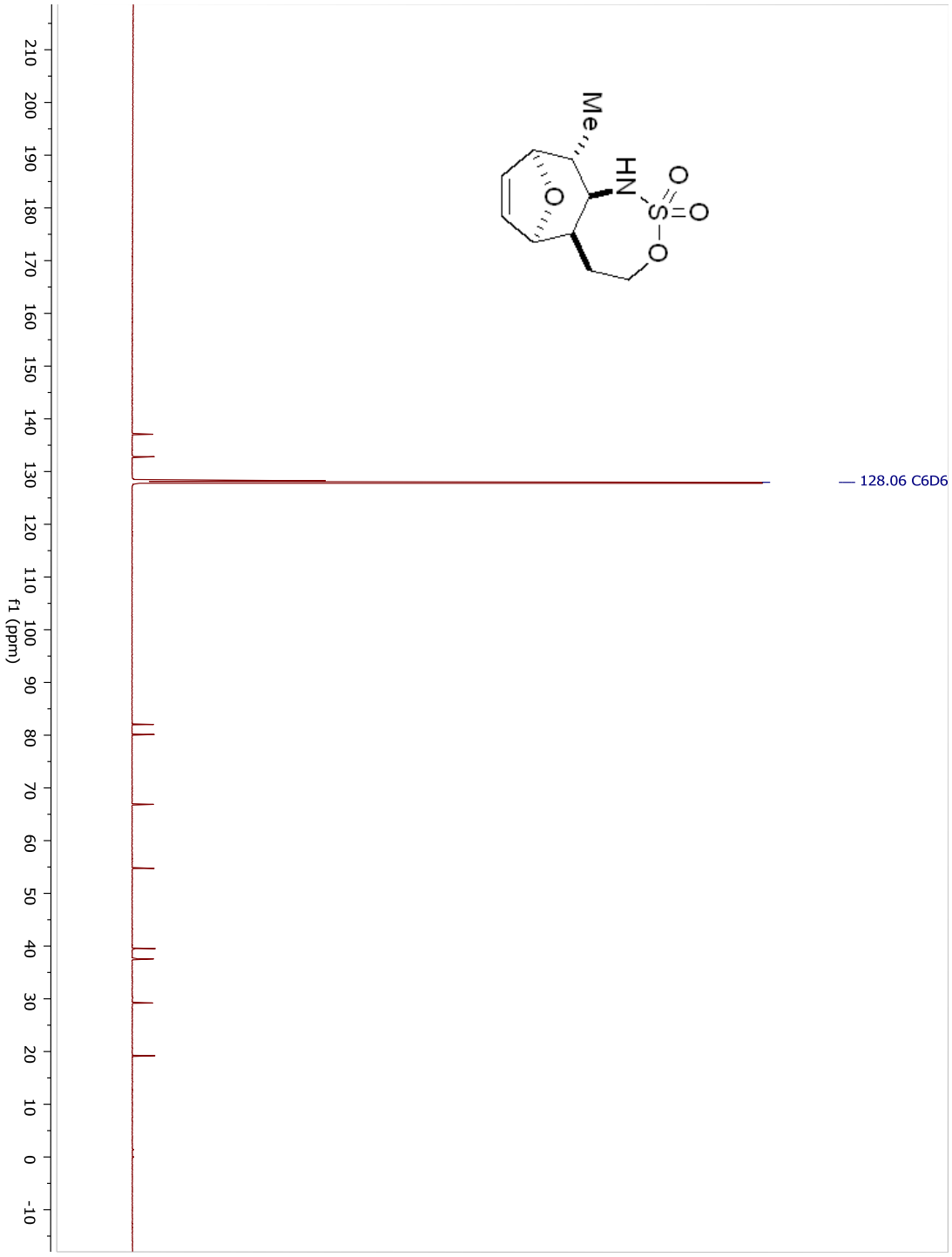
Compound 5.13a.


1.11
0.99
0.96
1.00
1.00
2.15
1.05
1.00
1.02
4.41
7.15
3.44
f1 (ppm)
-0.00 TMS
C5H11
HN
O
S
O
O

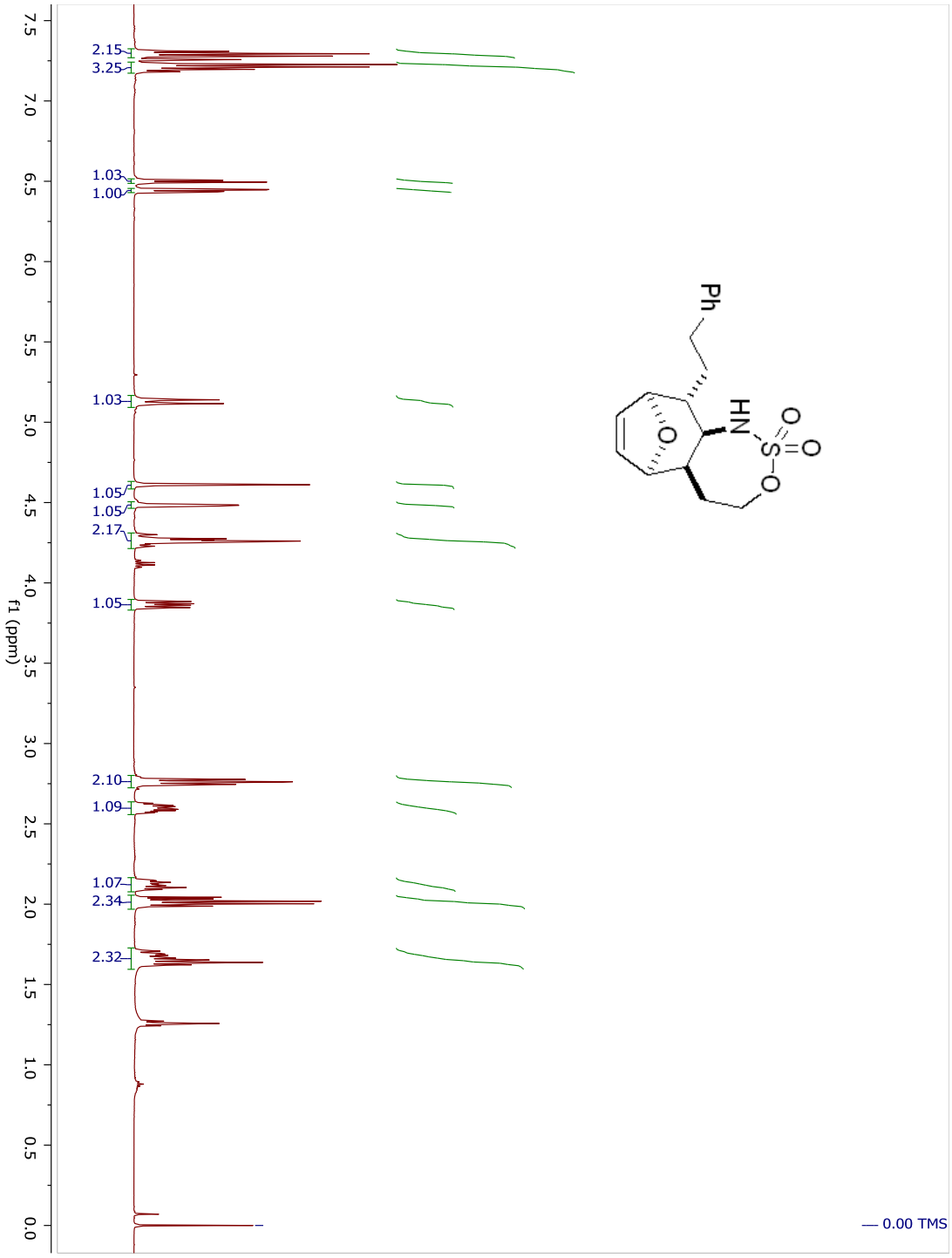

C5H11
HN
O
S
O
O
O
f1 (ppm)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
77.16 CDCl3

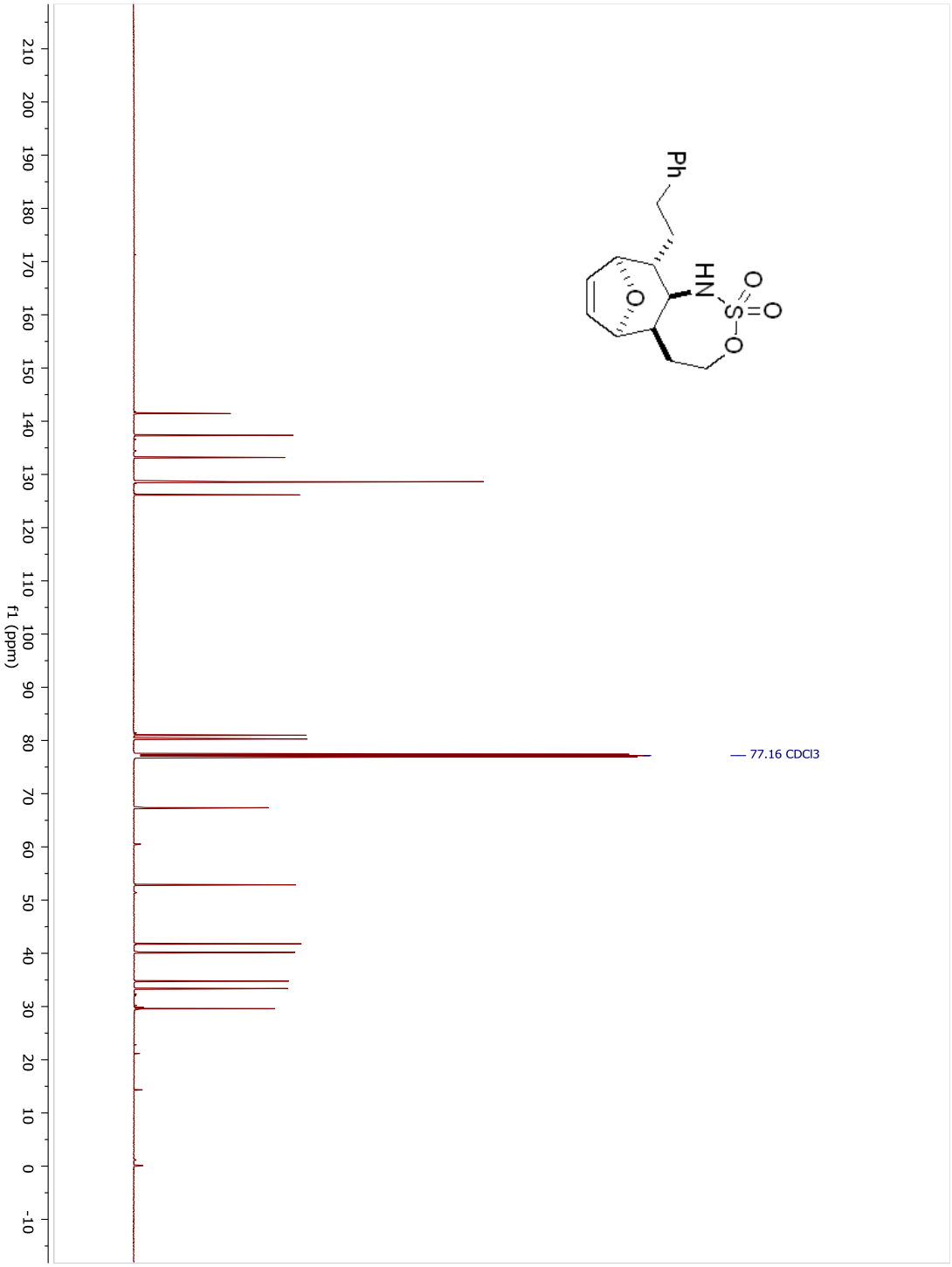
Compound 5.13b.



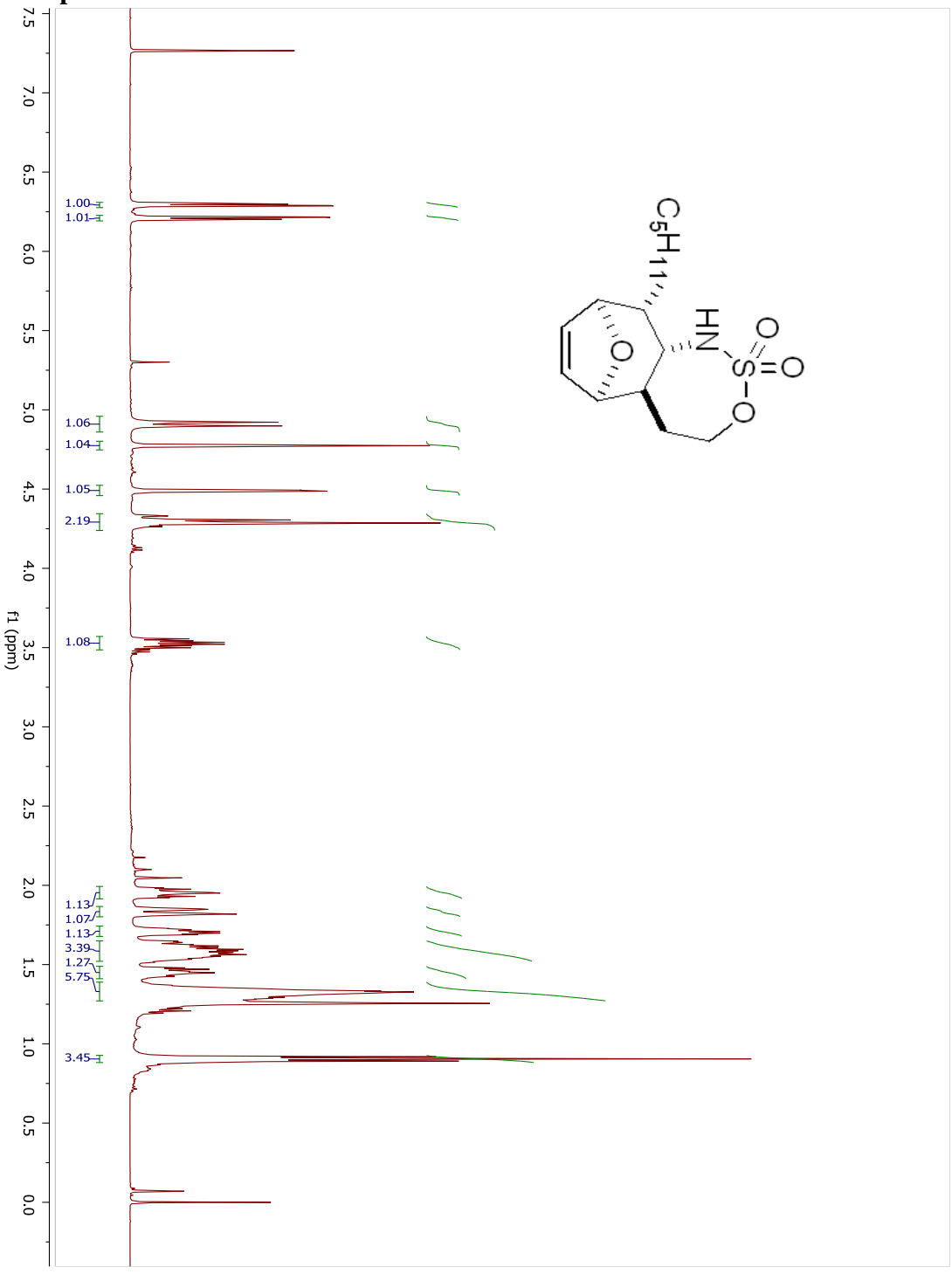


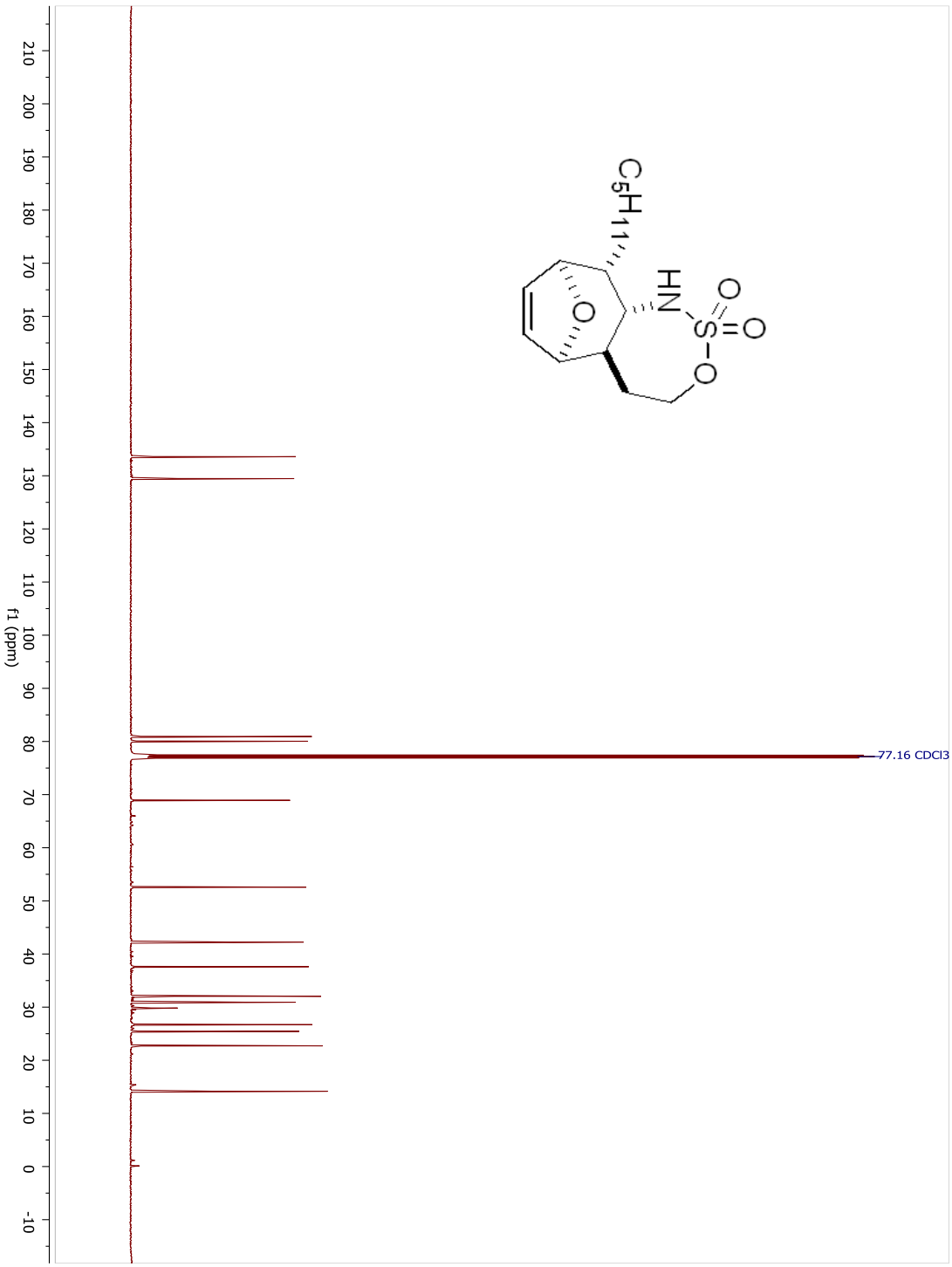
Compound 5.13c.


2.15
3.25
1.03
1.00
1.03
1.05
1.05
2.17
1.05
2.10
1.09
1.07
2.34
2.32
f1 (ppm)
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
Ph
HN
O
O
O
S
O
0.00 TMS

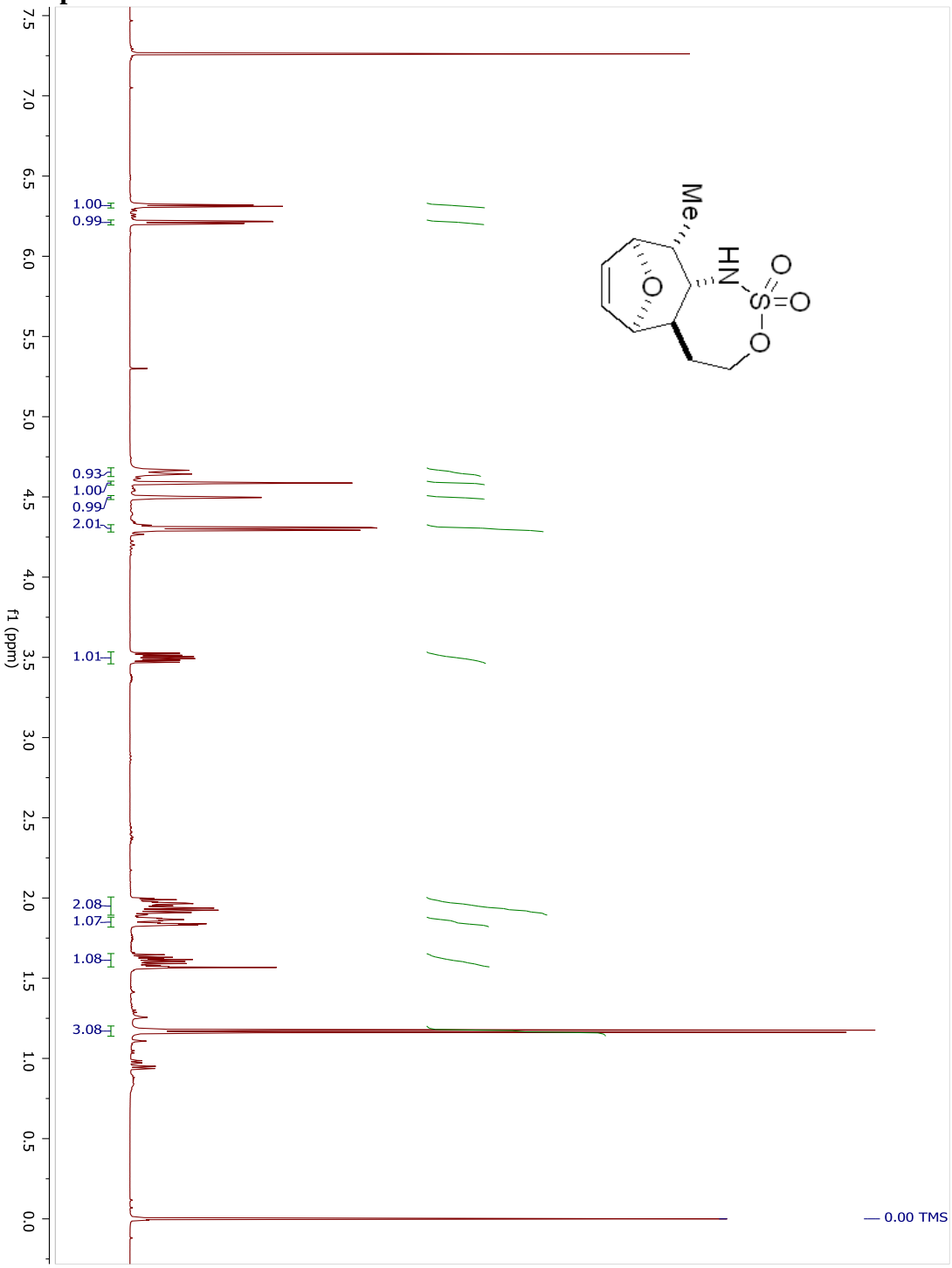

Ph
HN
O
O
O
S
O
77.16 CDCl3
f1 (ppm)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

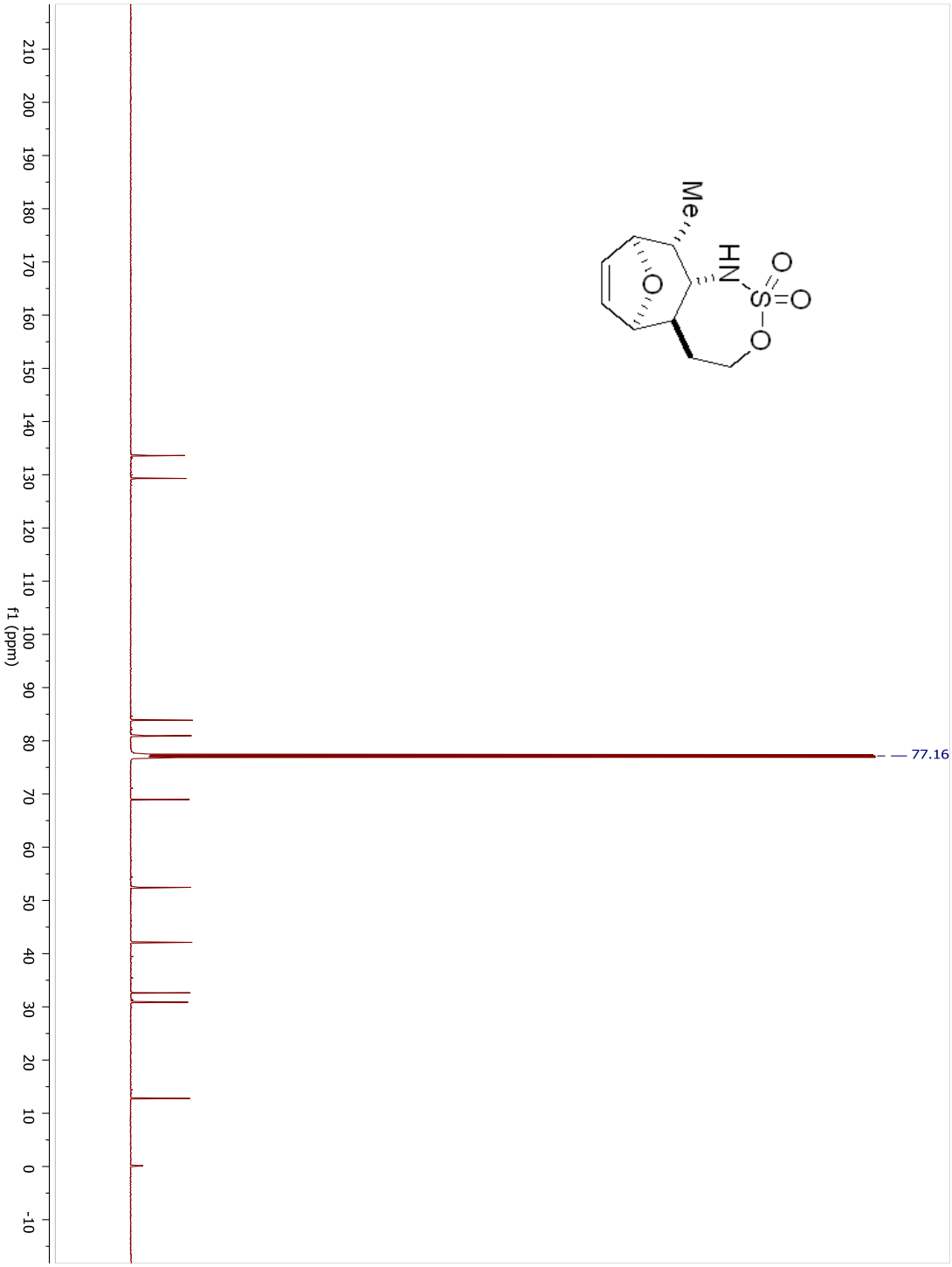
Compound 5.14a.



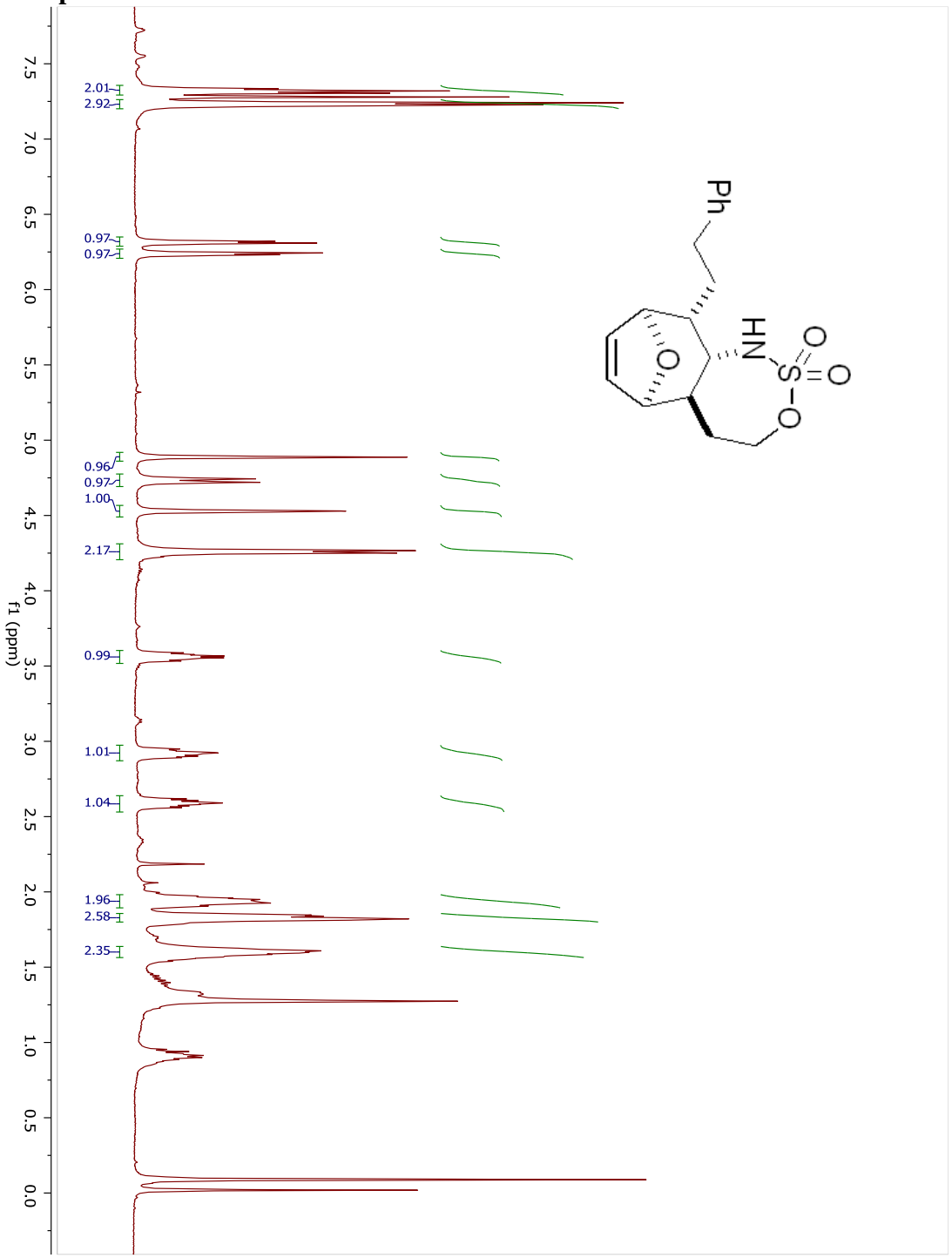

77.16 CDCl3
f1 (ppm)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
C5H11
HN
O
S
O
O

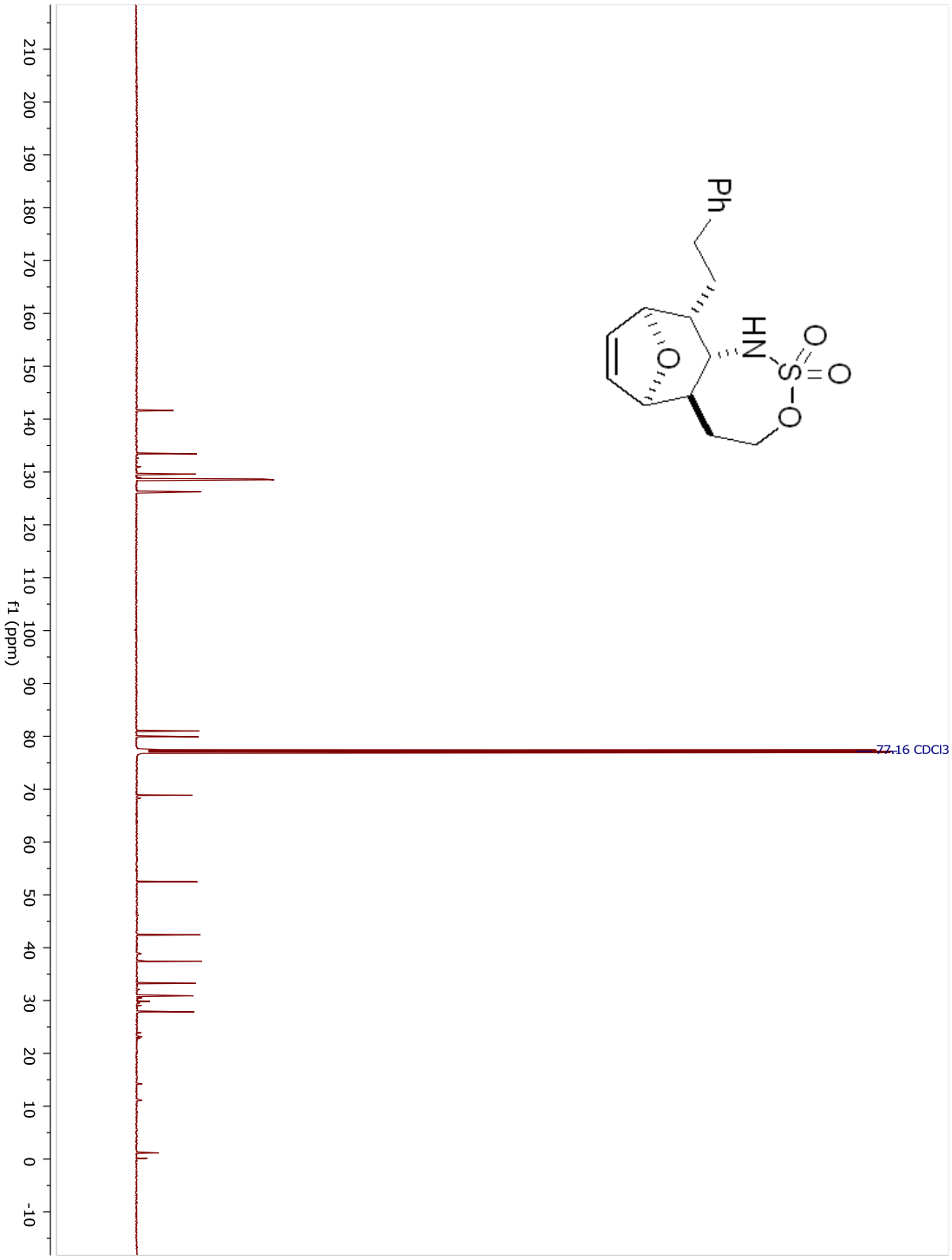
Compound 5.14b.



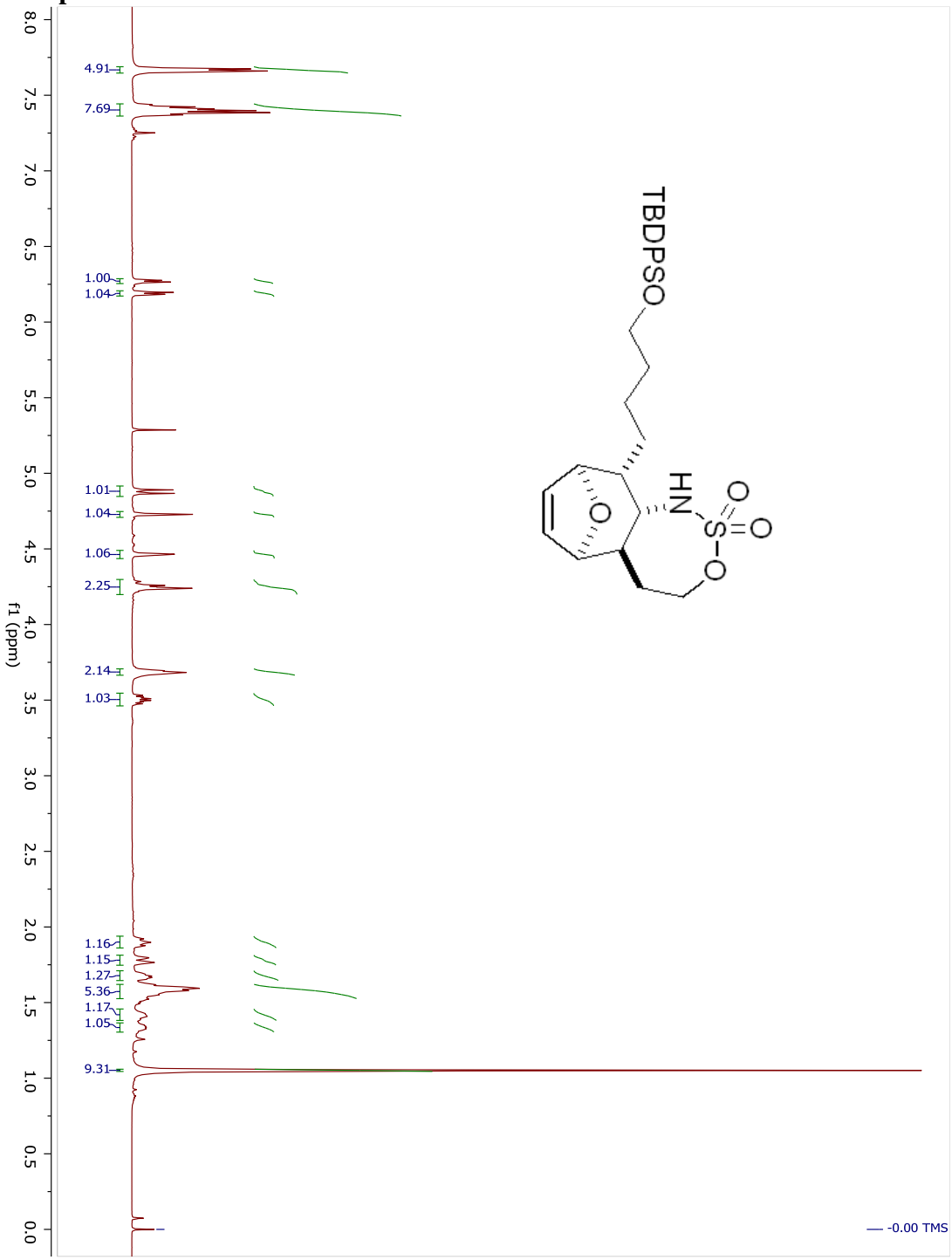

Me
HN
O
O
O
O
77.16
f1 (ppm)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

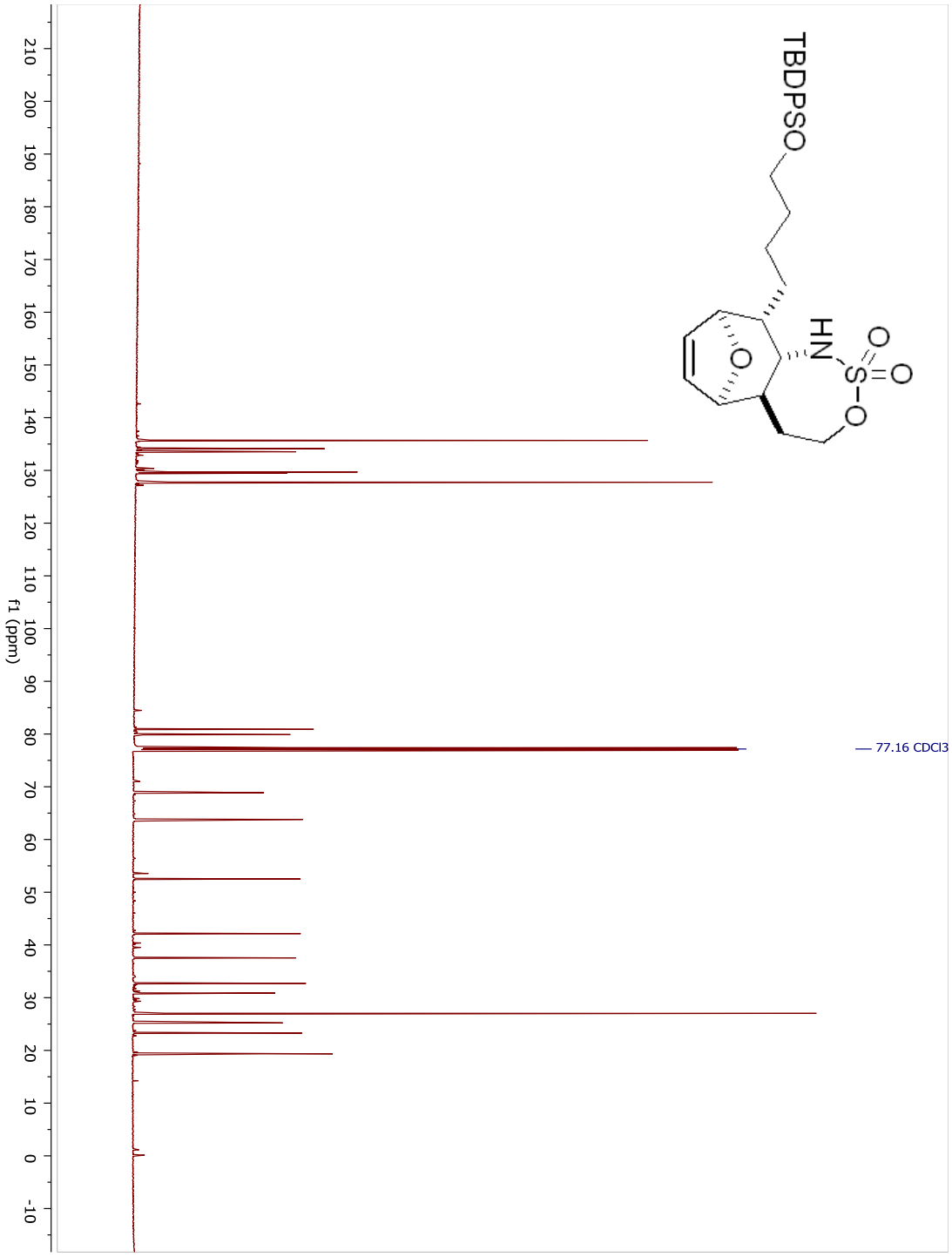
Compound 5.14c.



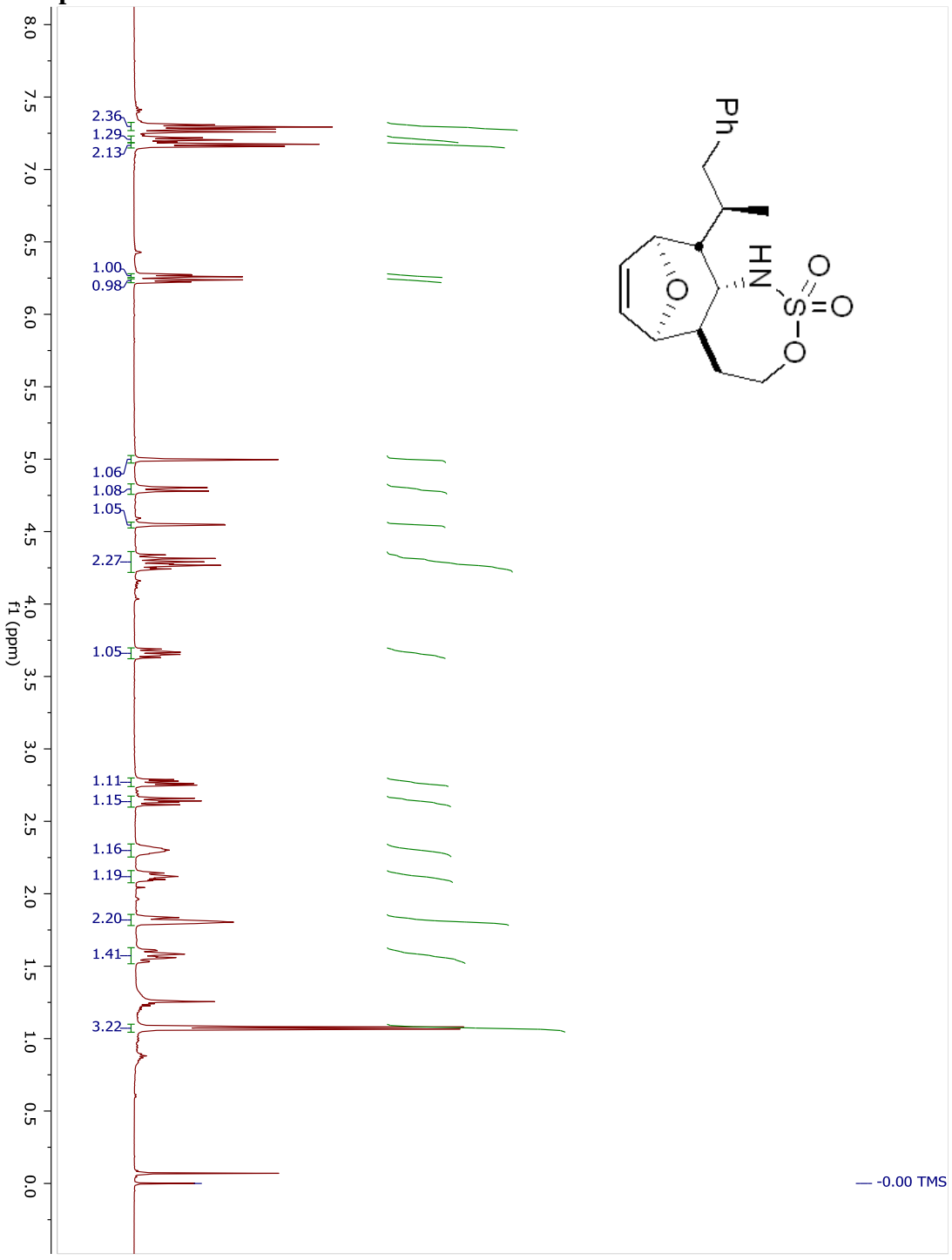

Ph
HN
O
O
O
O
77.16 CDCl3
f1 (ppm)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

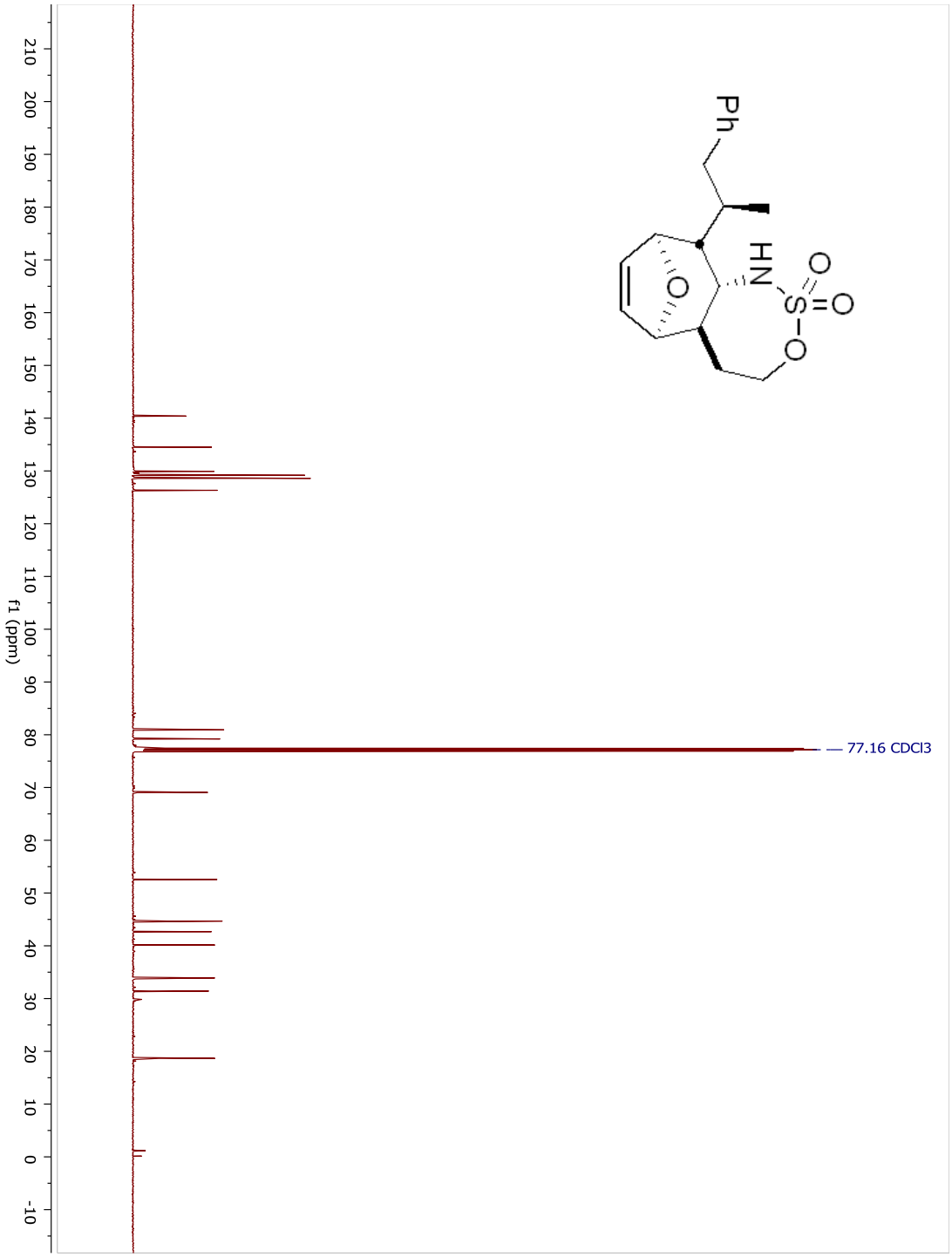
Compound 5.14d.



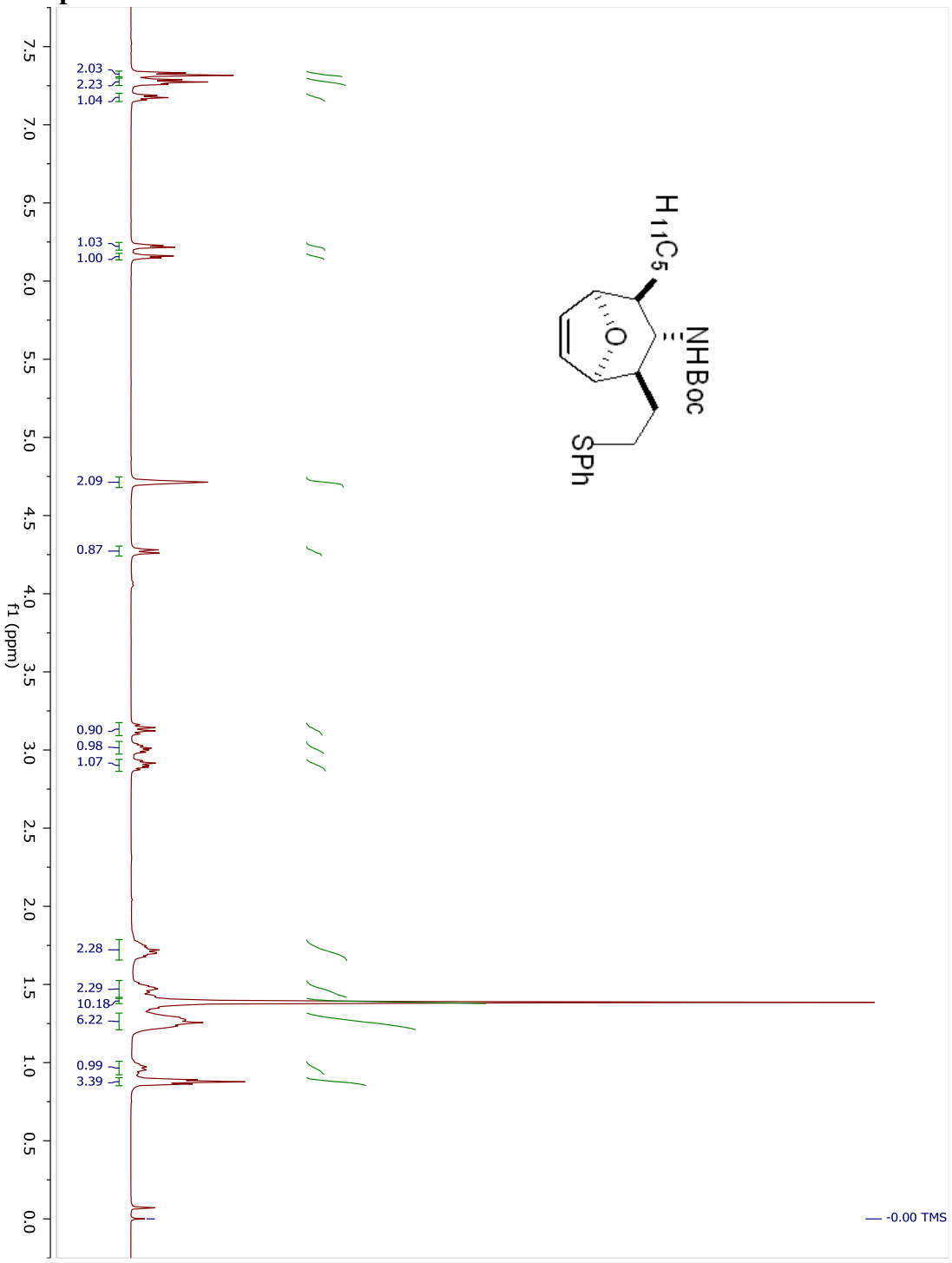

TBDPSO
HN
O
O
O
S
O
77.16 CDCl3
f1 (ppm)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

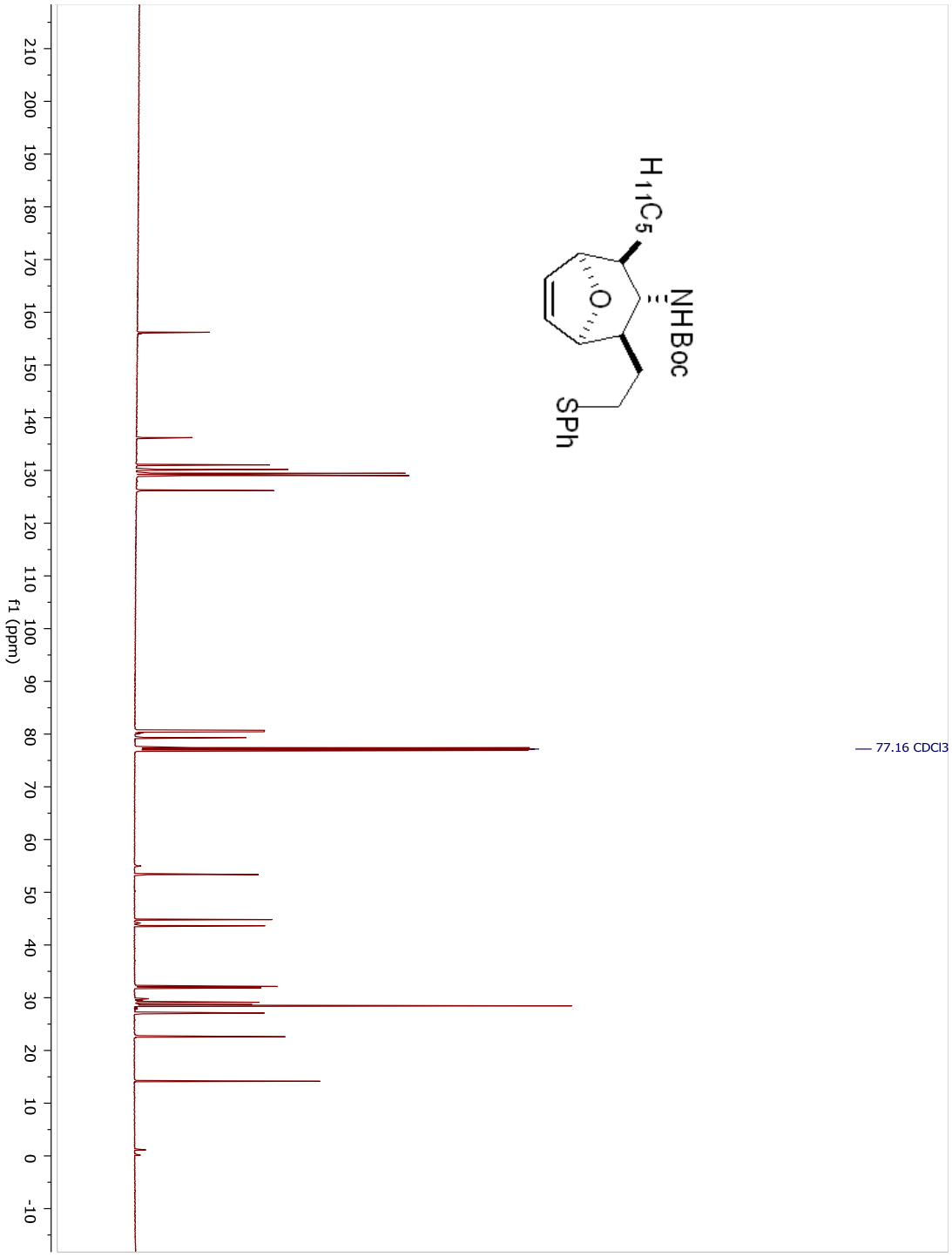
Compound 5.15.



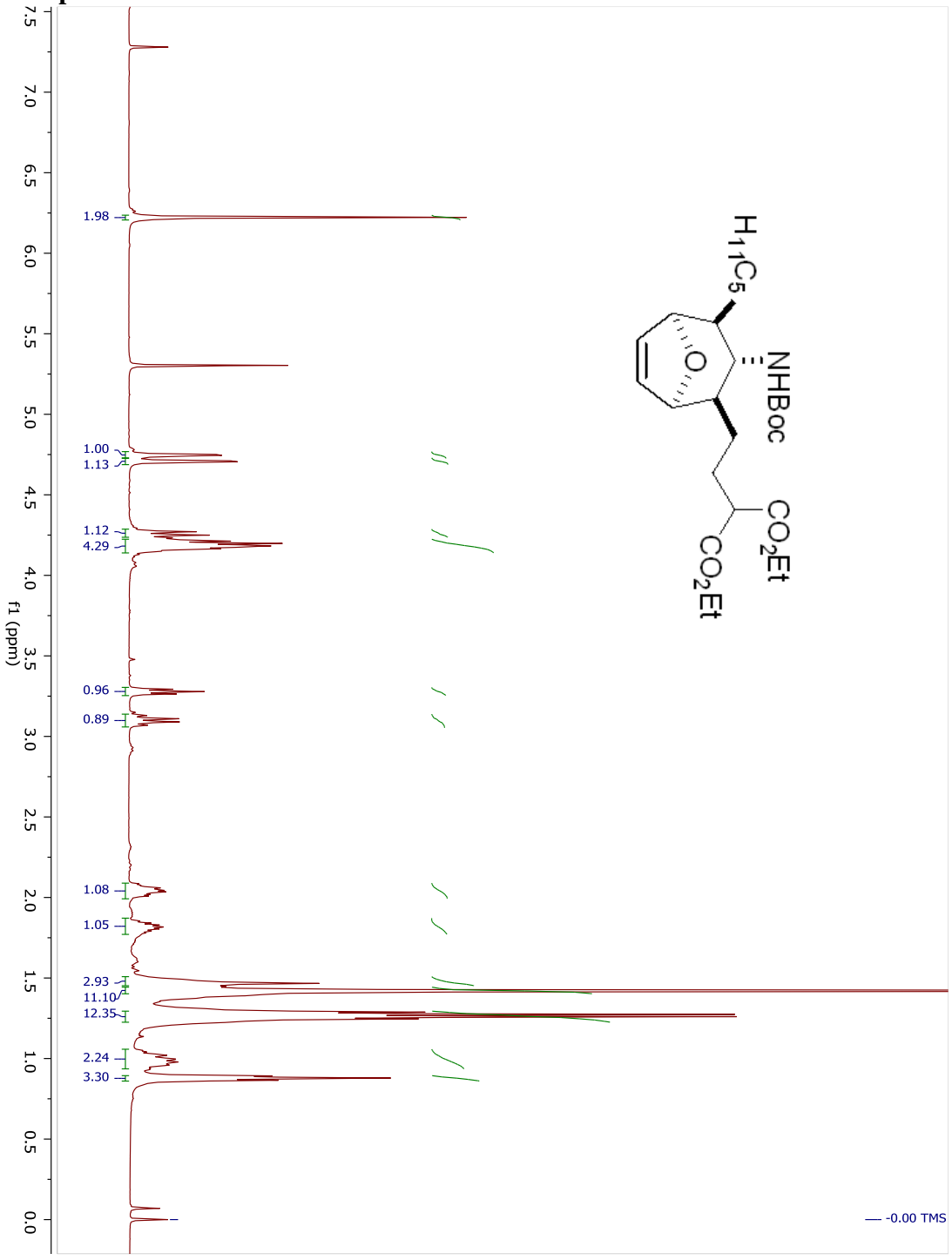

Ph
HN
O
S
O
O
O
77.16 CDCl3
f1 (ppm)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

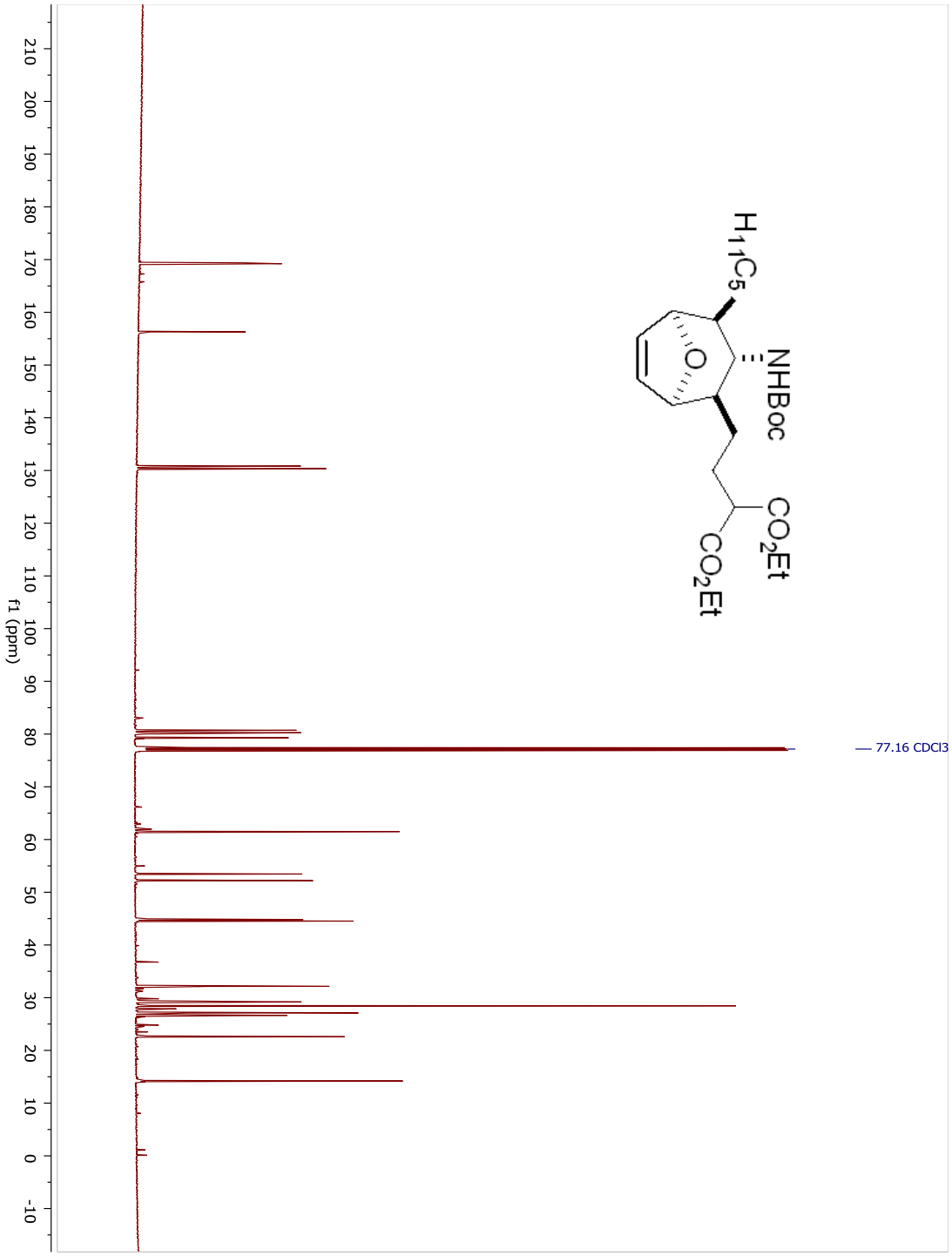
Compound 5.16.



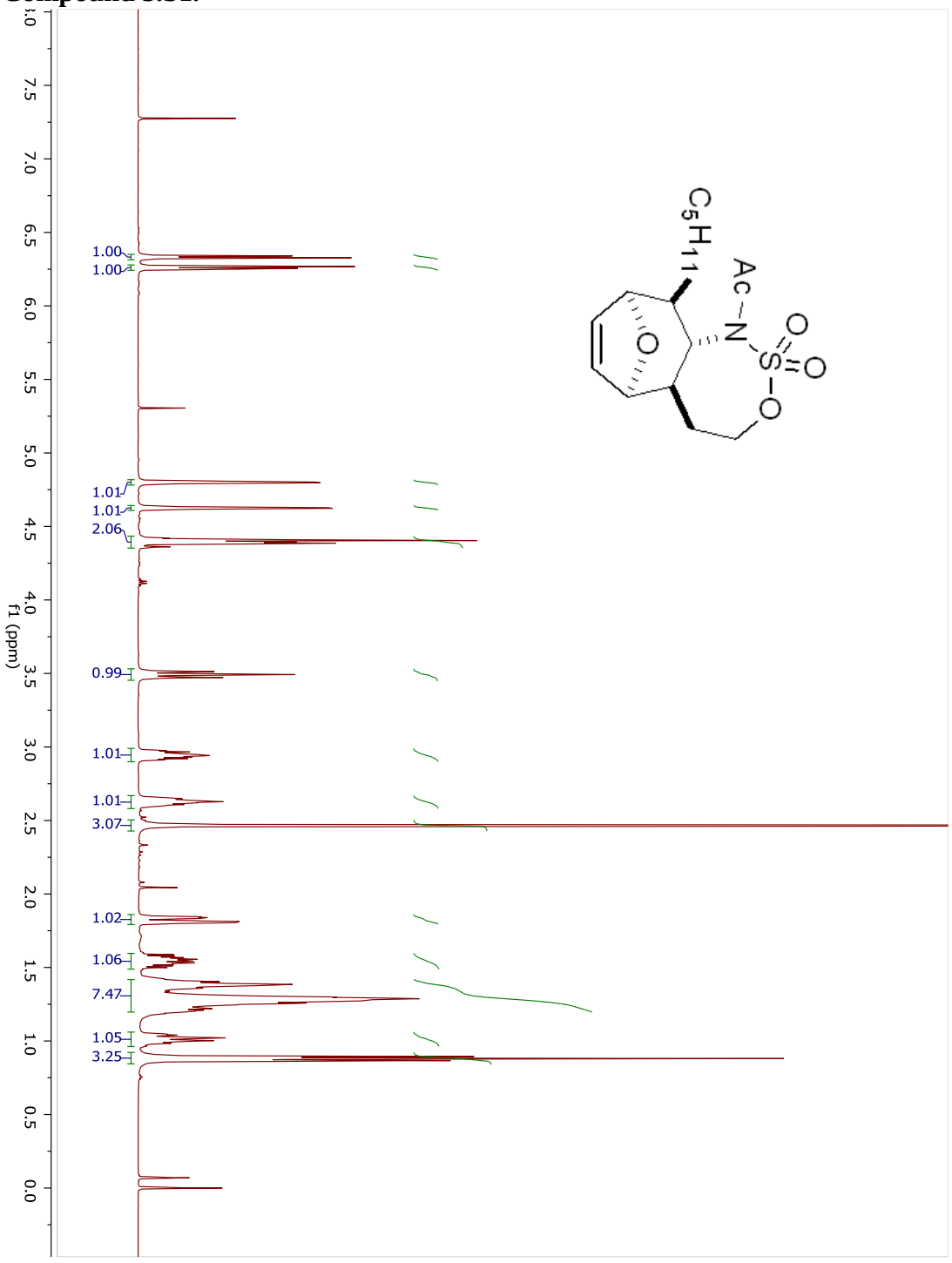

H11C5
NHBoc
O
SPh
77.16 CDCl3
f1 (ppm)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

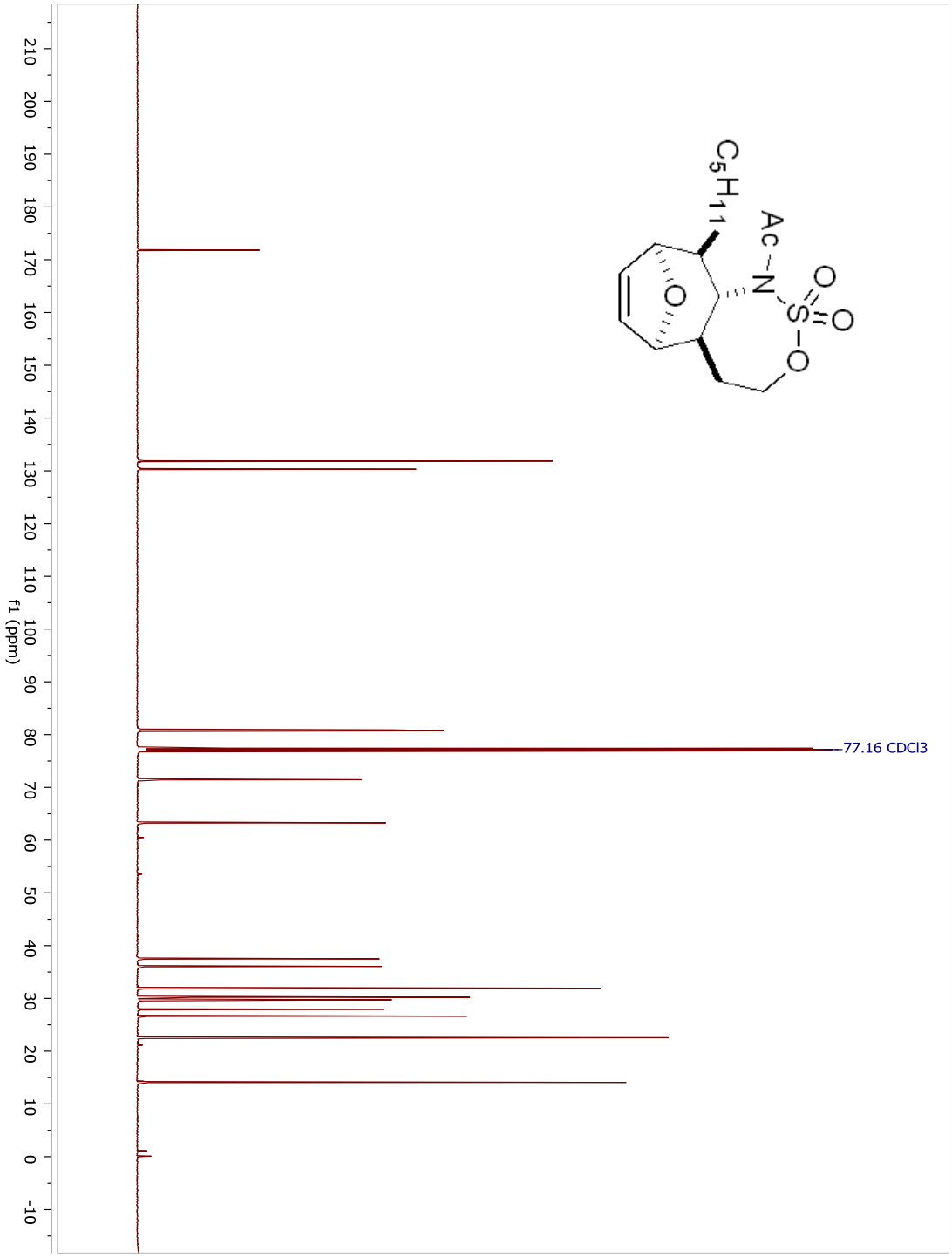
Compound 5.17.



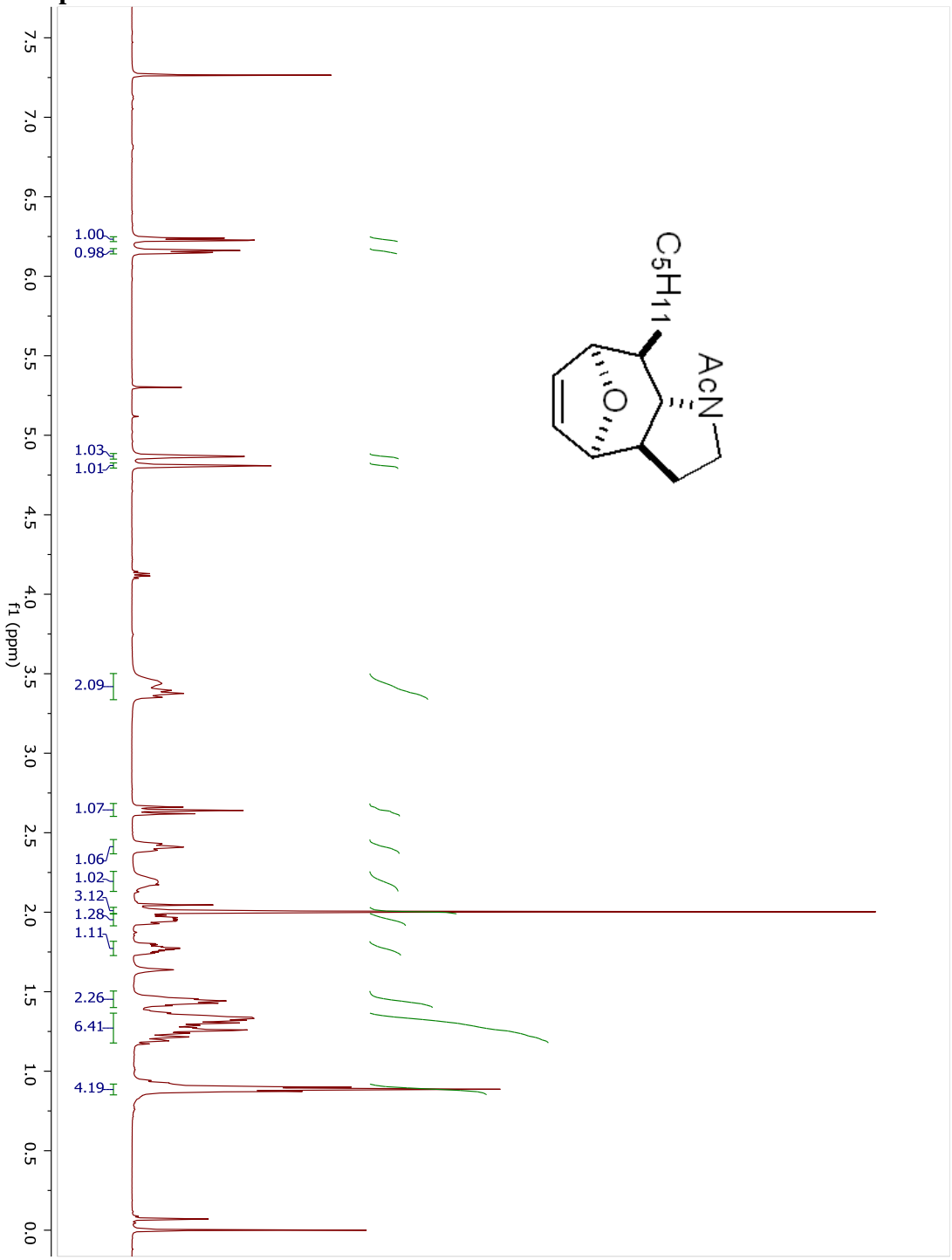

H11C5
NHBoc
CO2Et
CO2Et
O
77.16 CDCl3
f1 (ppm)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

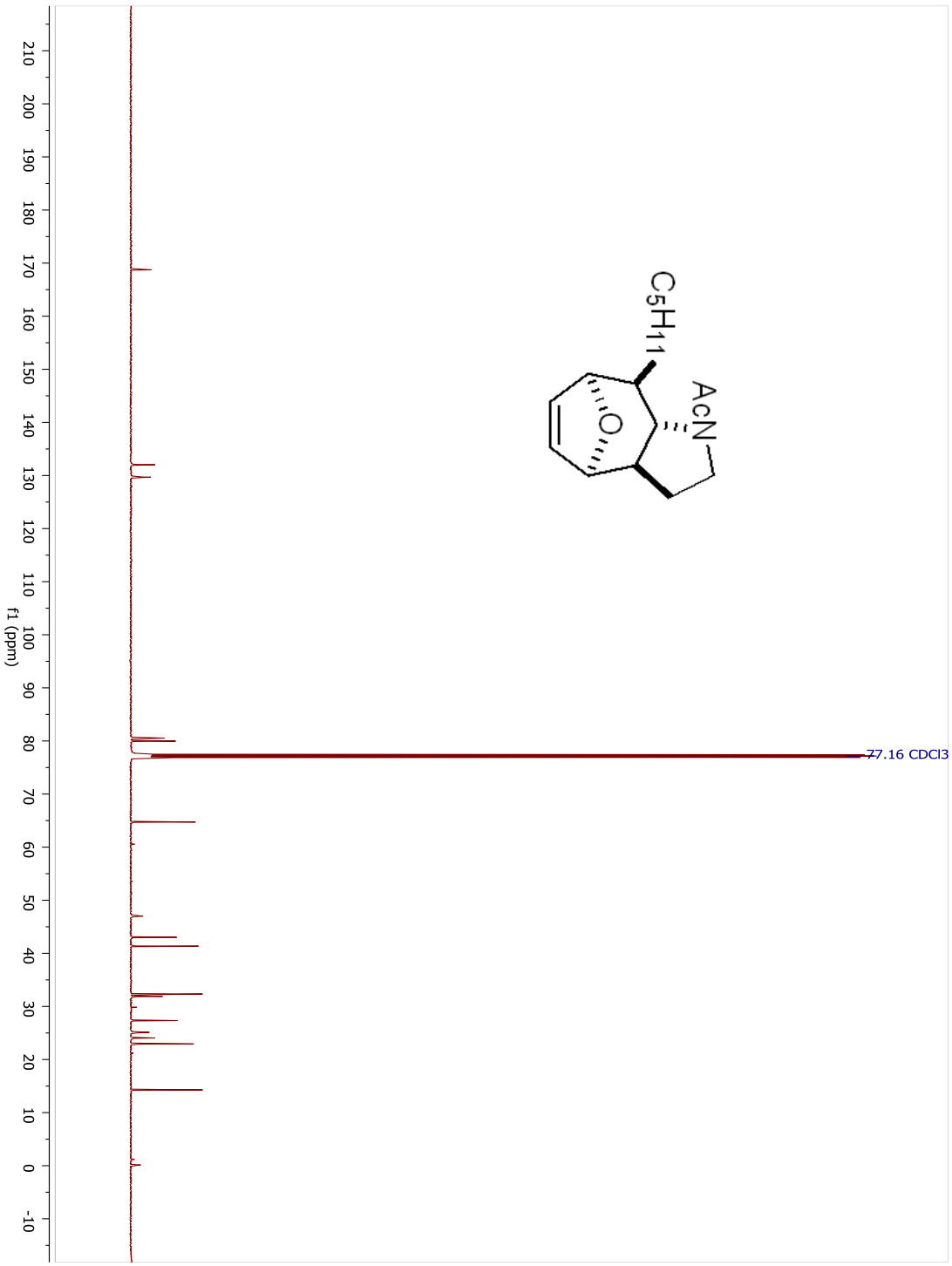
Compound 5.S1.



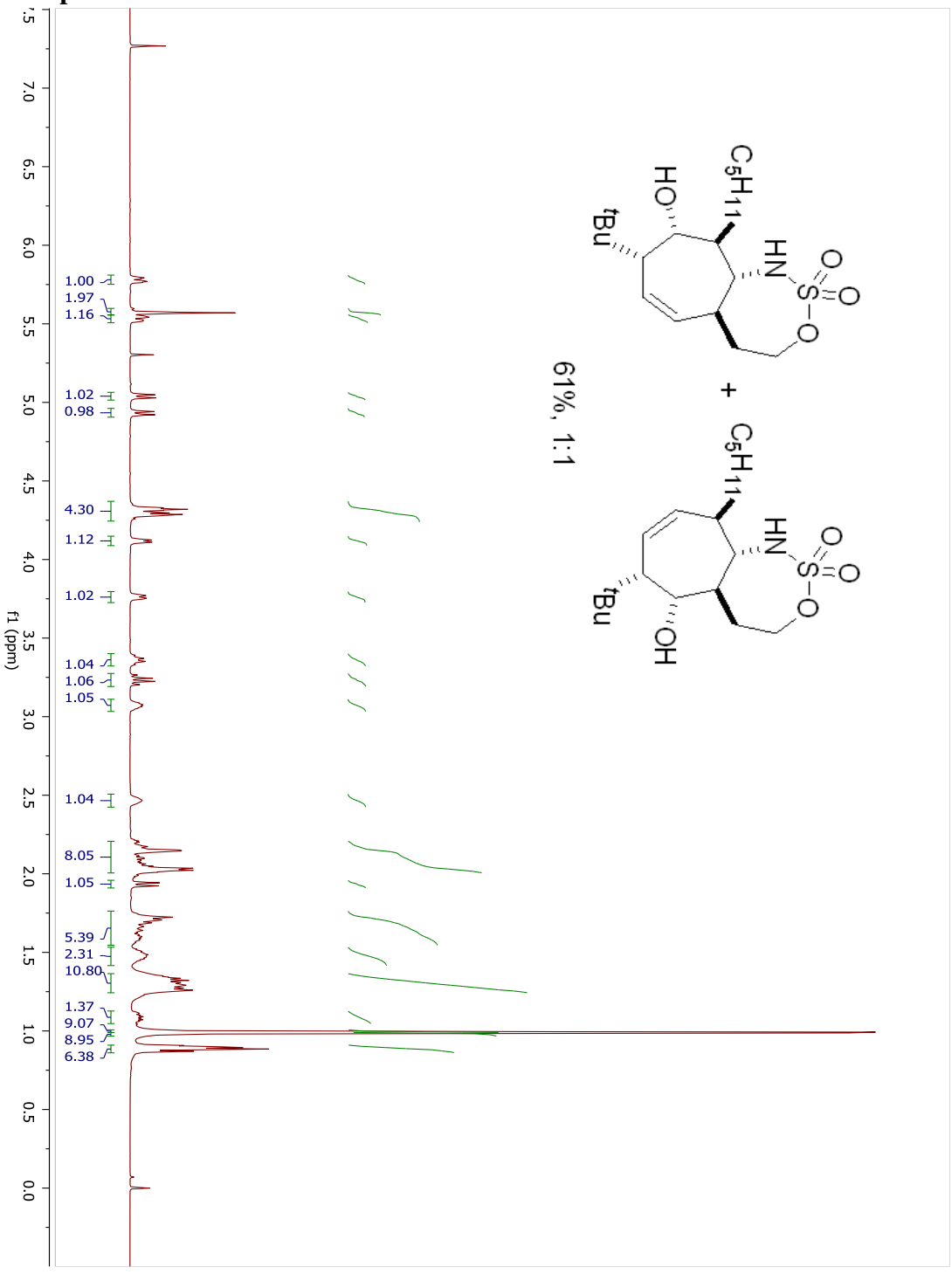

77.16 CDCl3
f1 (ppm)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
C5H11
Ac
N
S
O
O
O
O

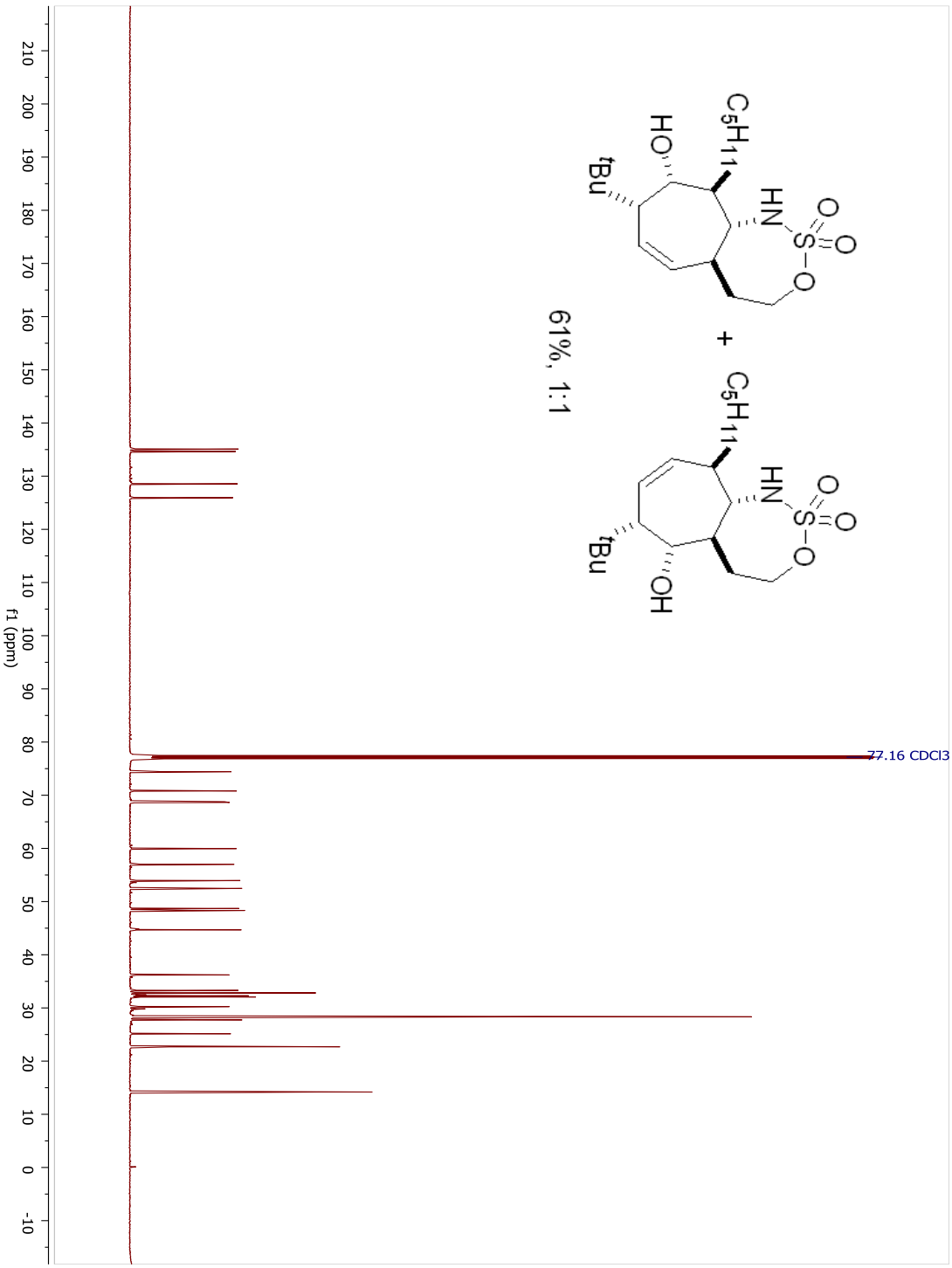
Compound 5.18.



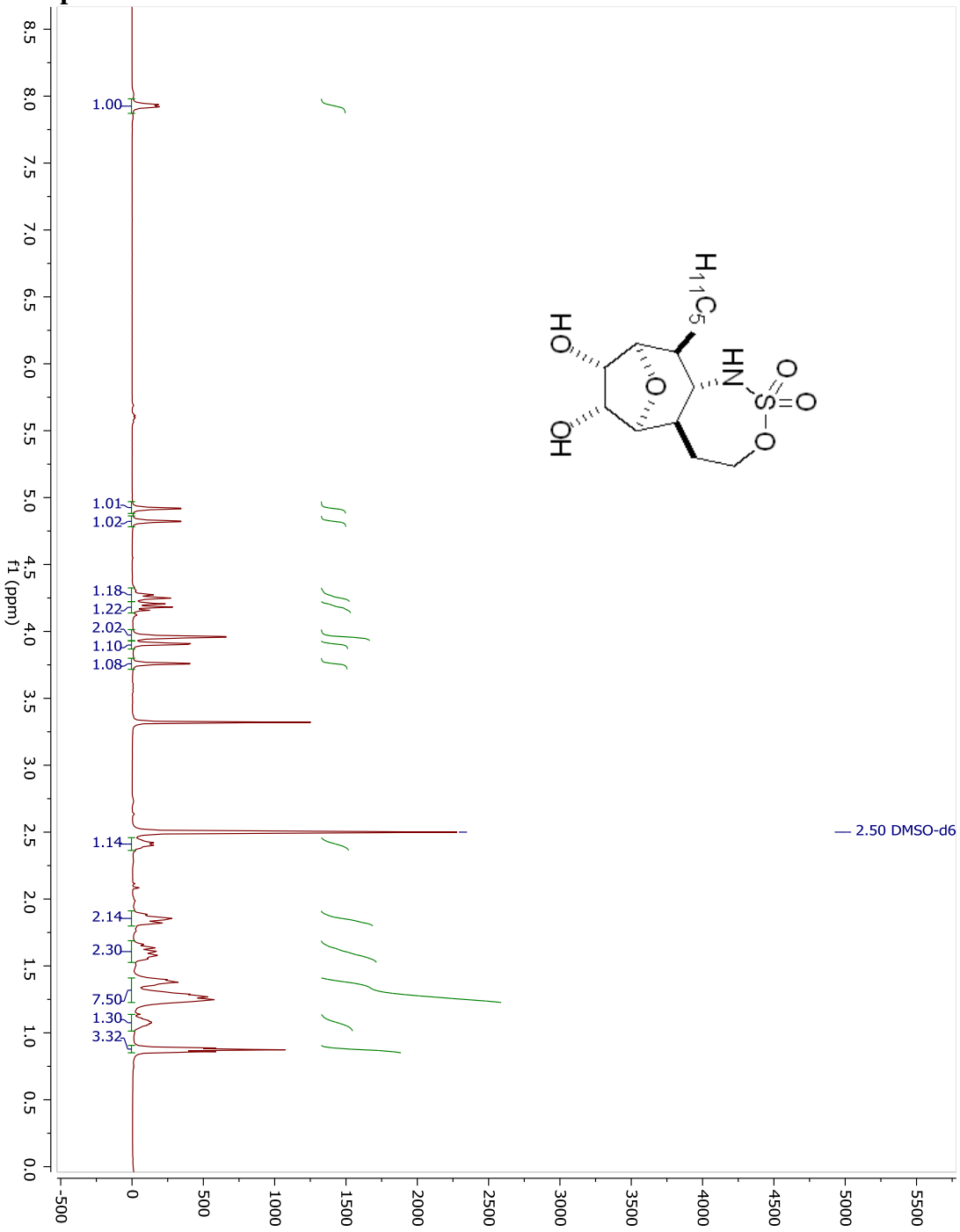

C5H11
AcN
O
77.16 CDCl3
f1 (ppm)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

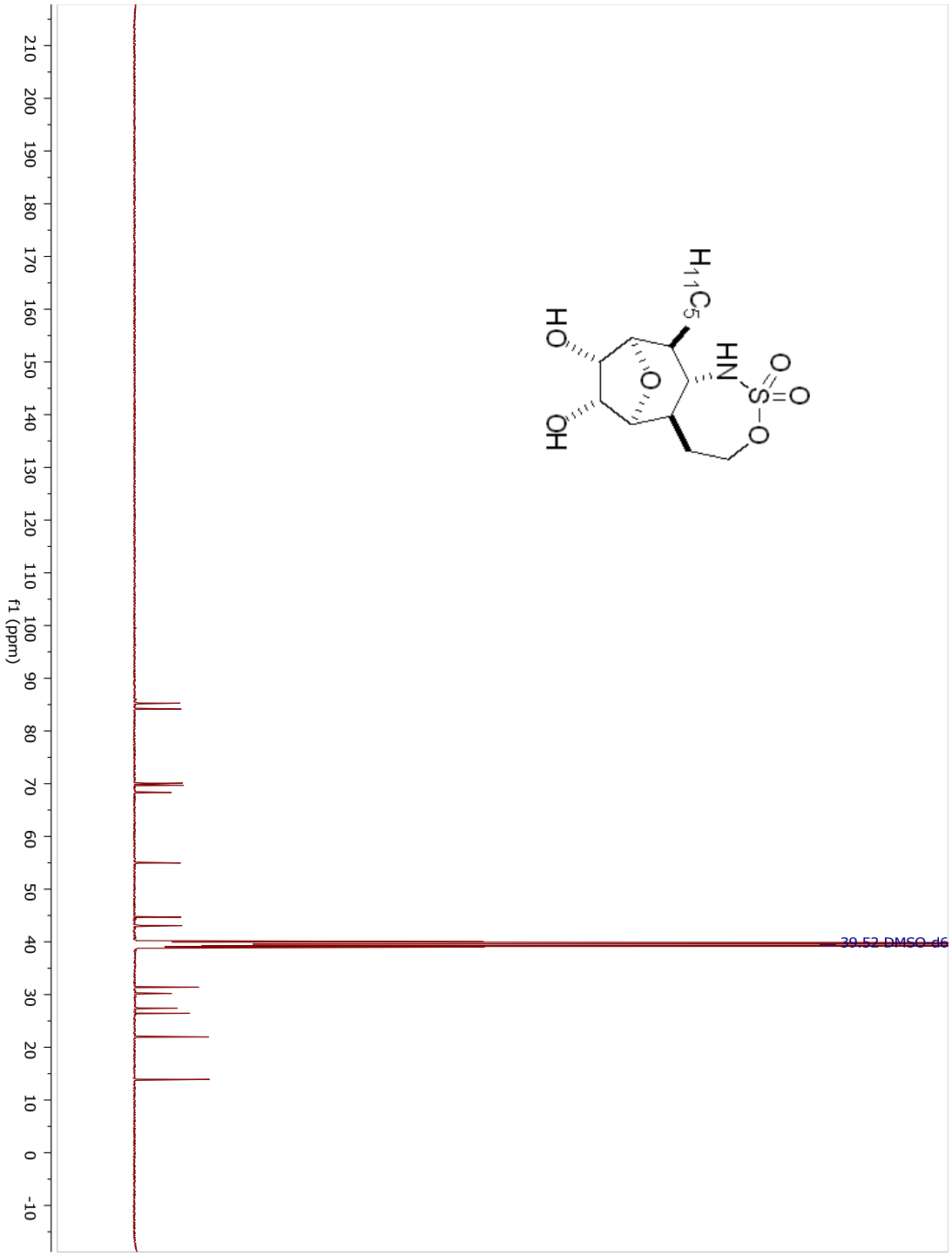
Compounds 5.19 and 5.20.



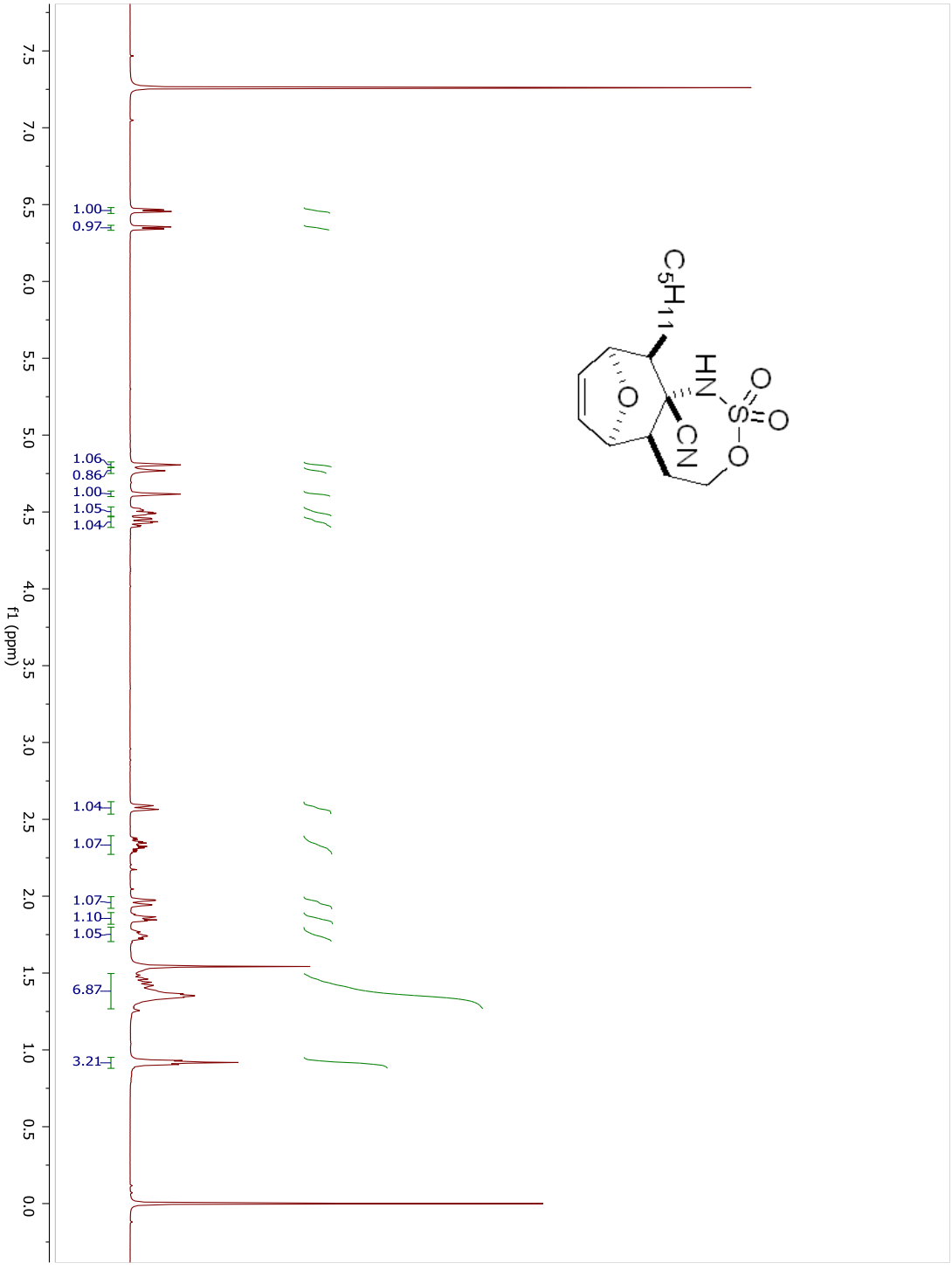

61%, 1:1
77.16 CDCl3
f1 (ppm)

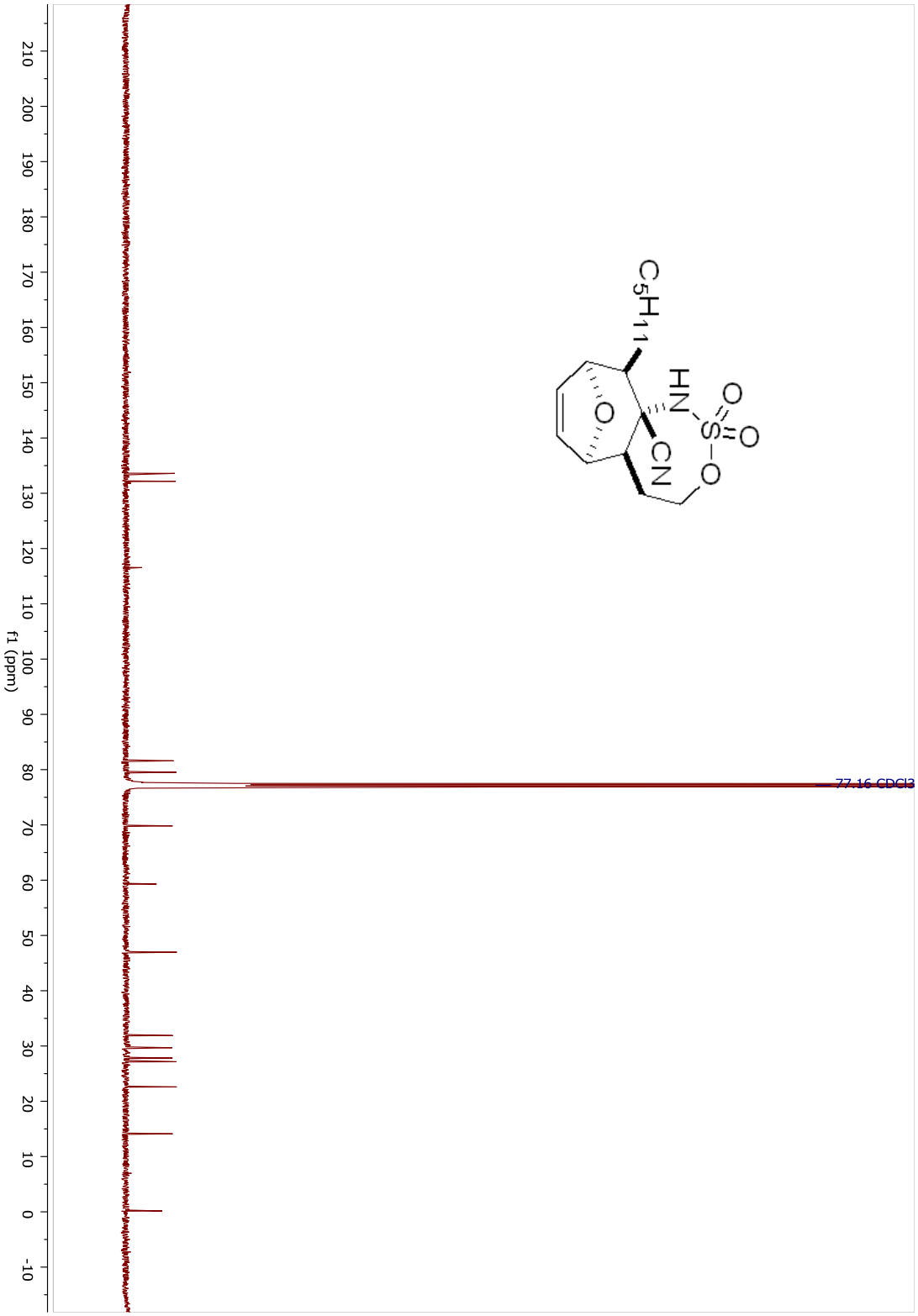
Compound 5.21.



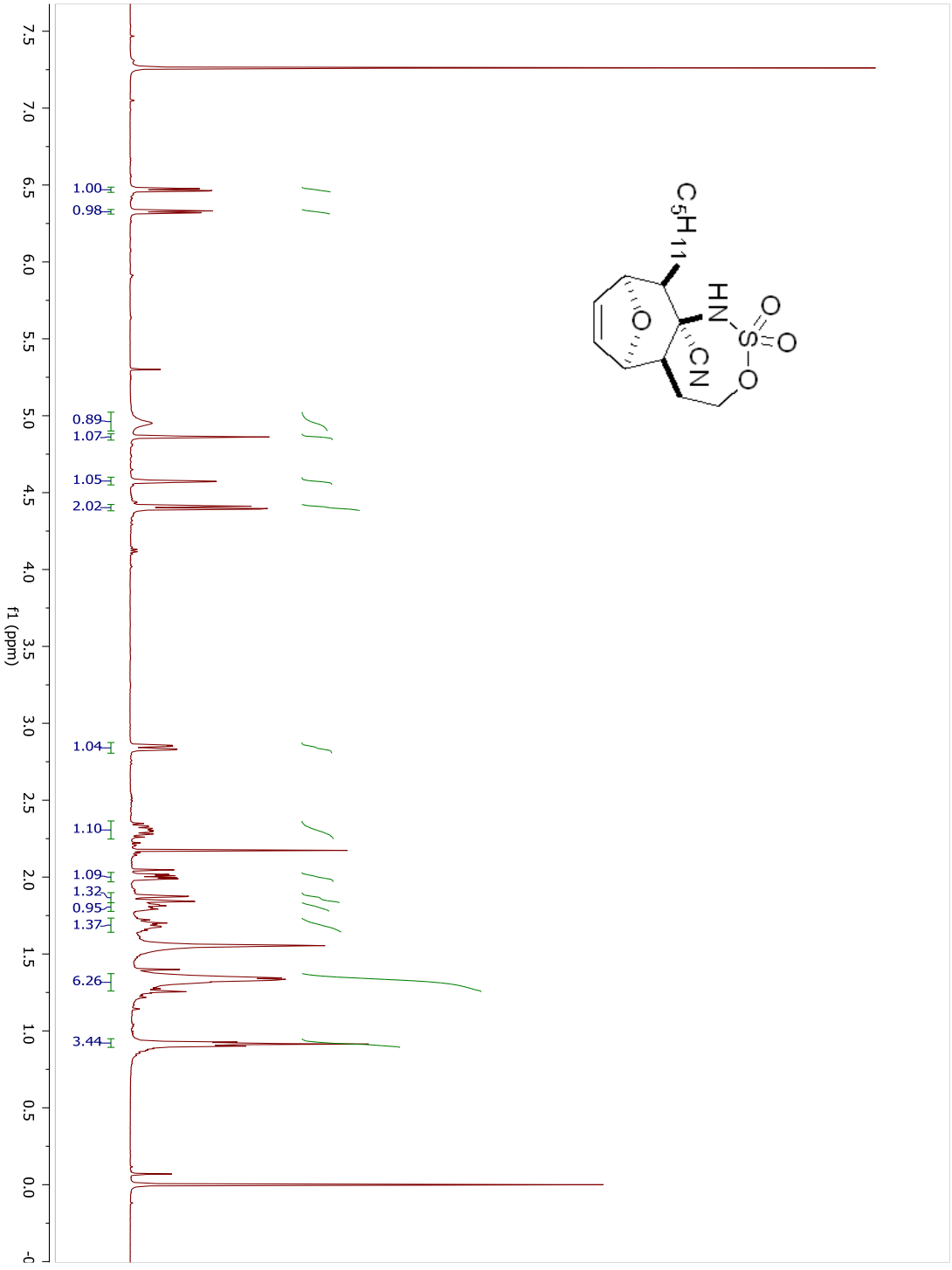

39.52 DMSO-d6
f1 (ppm)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
HO
OH
O
HN
S
O
O
O
H11C5

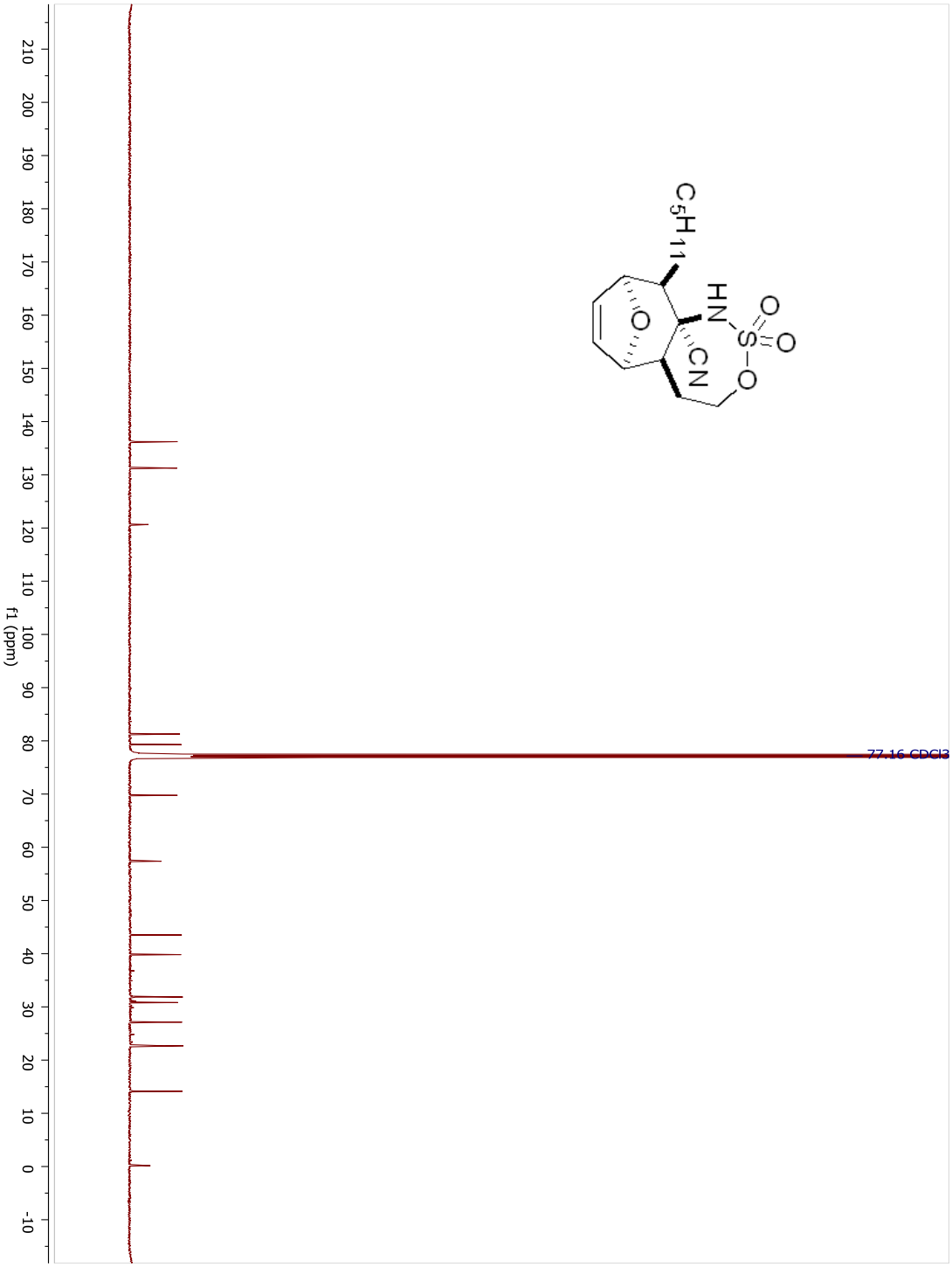
Compound 5.22 - major



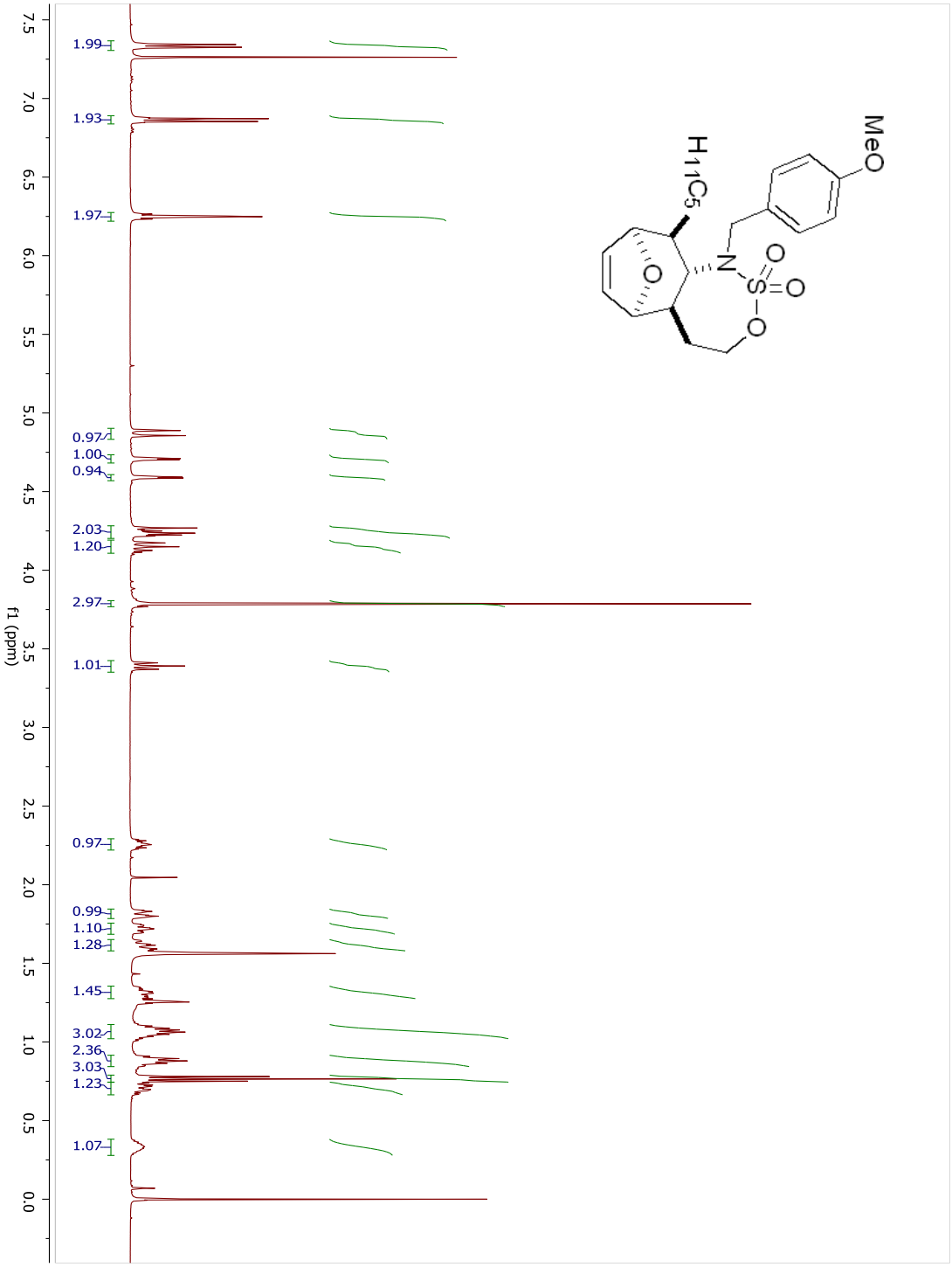

77.16 CDCl3
f1 (ppm)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
C5H11
HN
O
S
O
O
O
CN

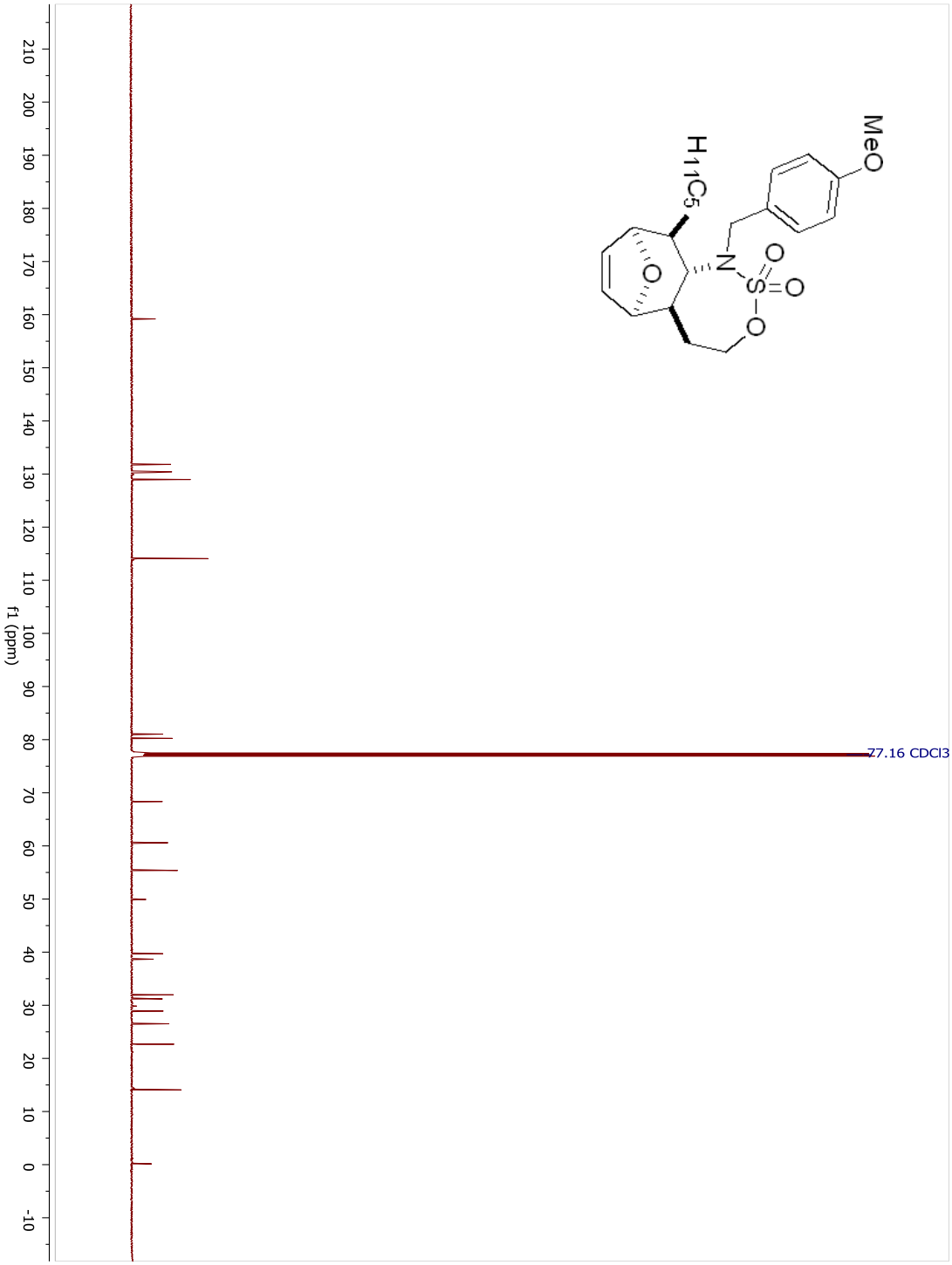
Compound 5.22 - minor



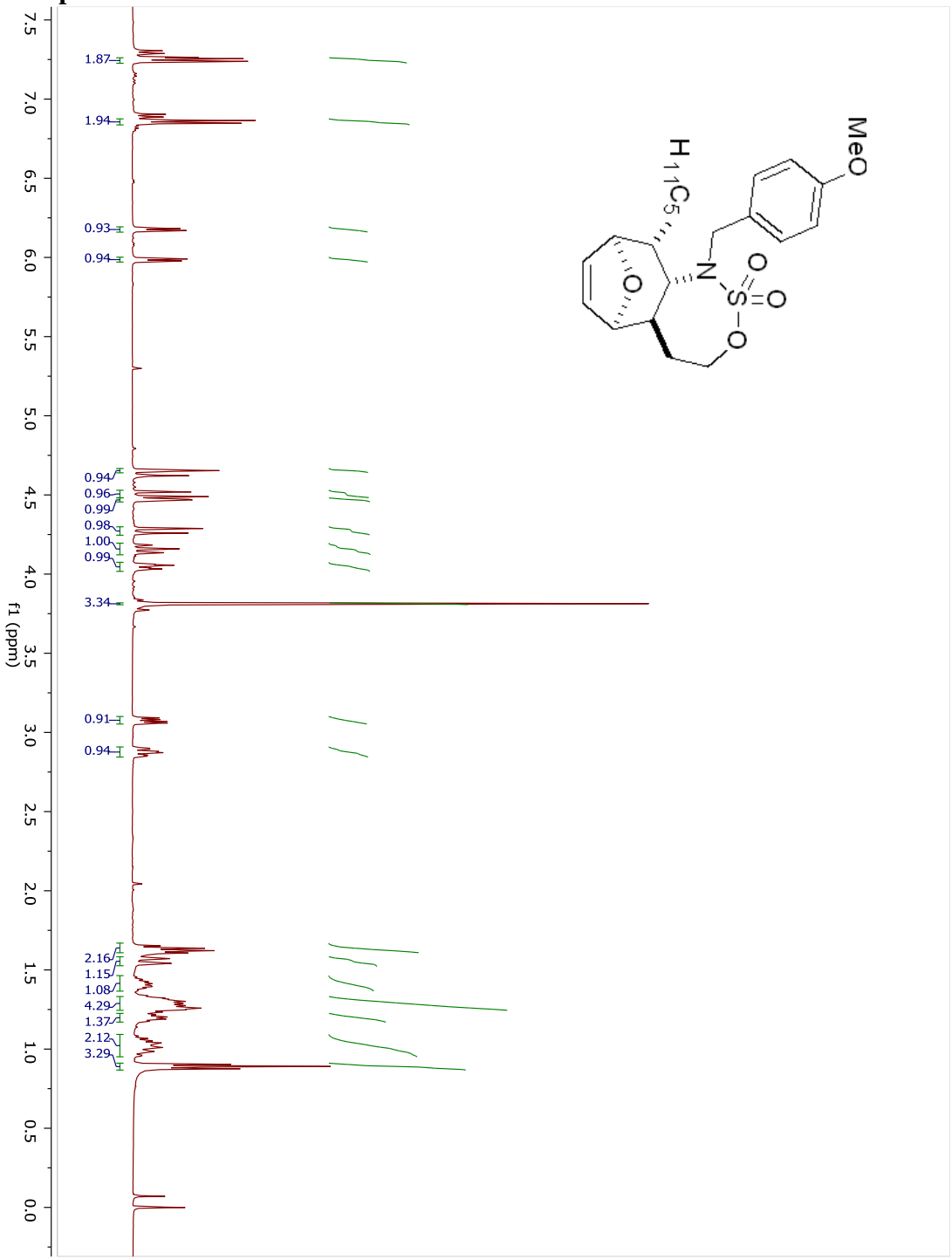

C5H11
HN
S
O
O
O
CN
O
77.16 CDCl3
f1 (ppm)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

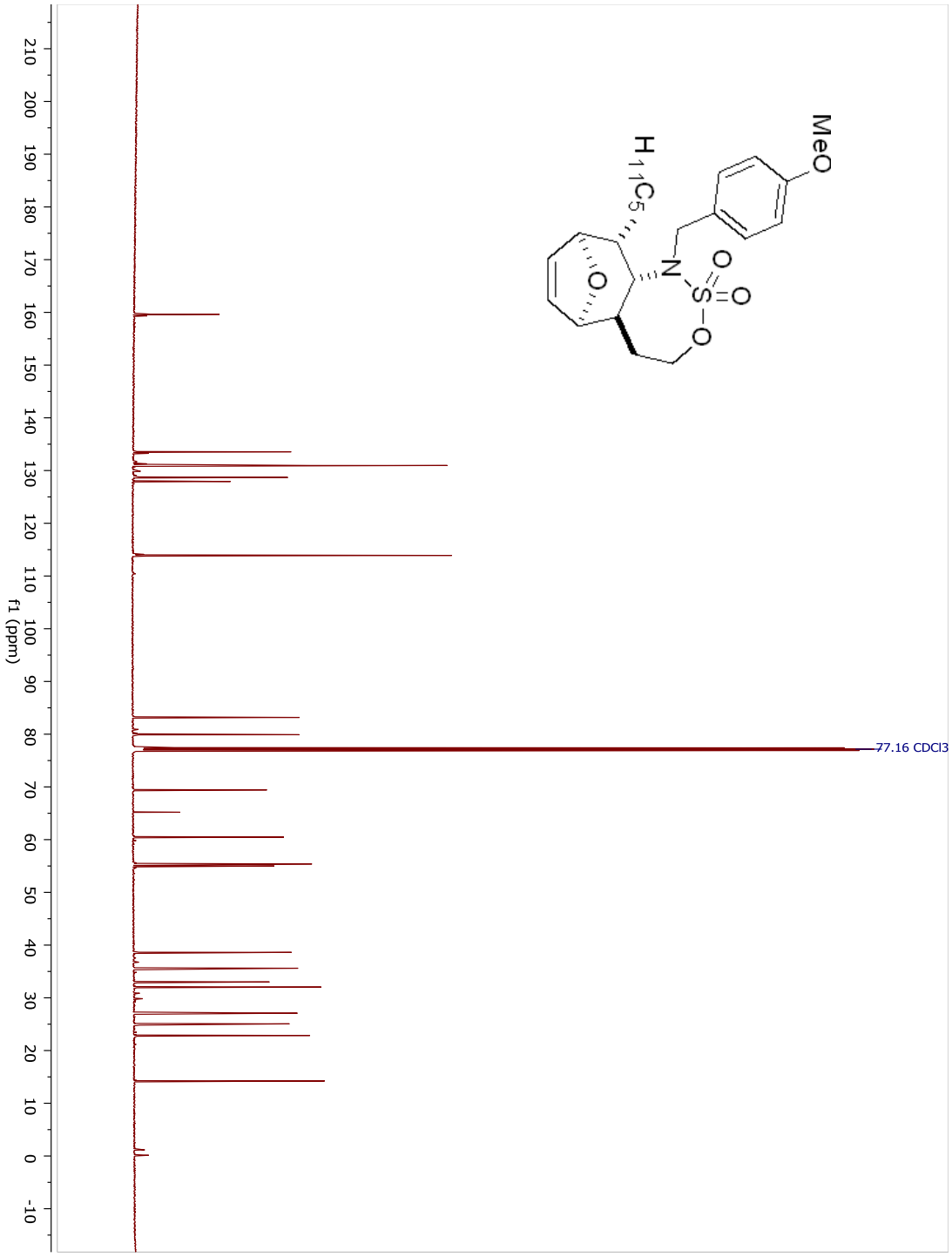
Compound 5.S2.



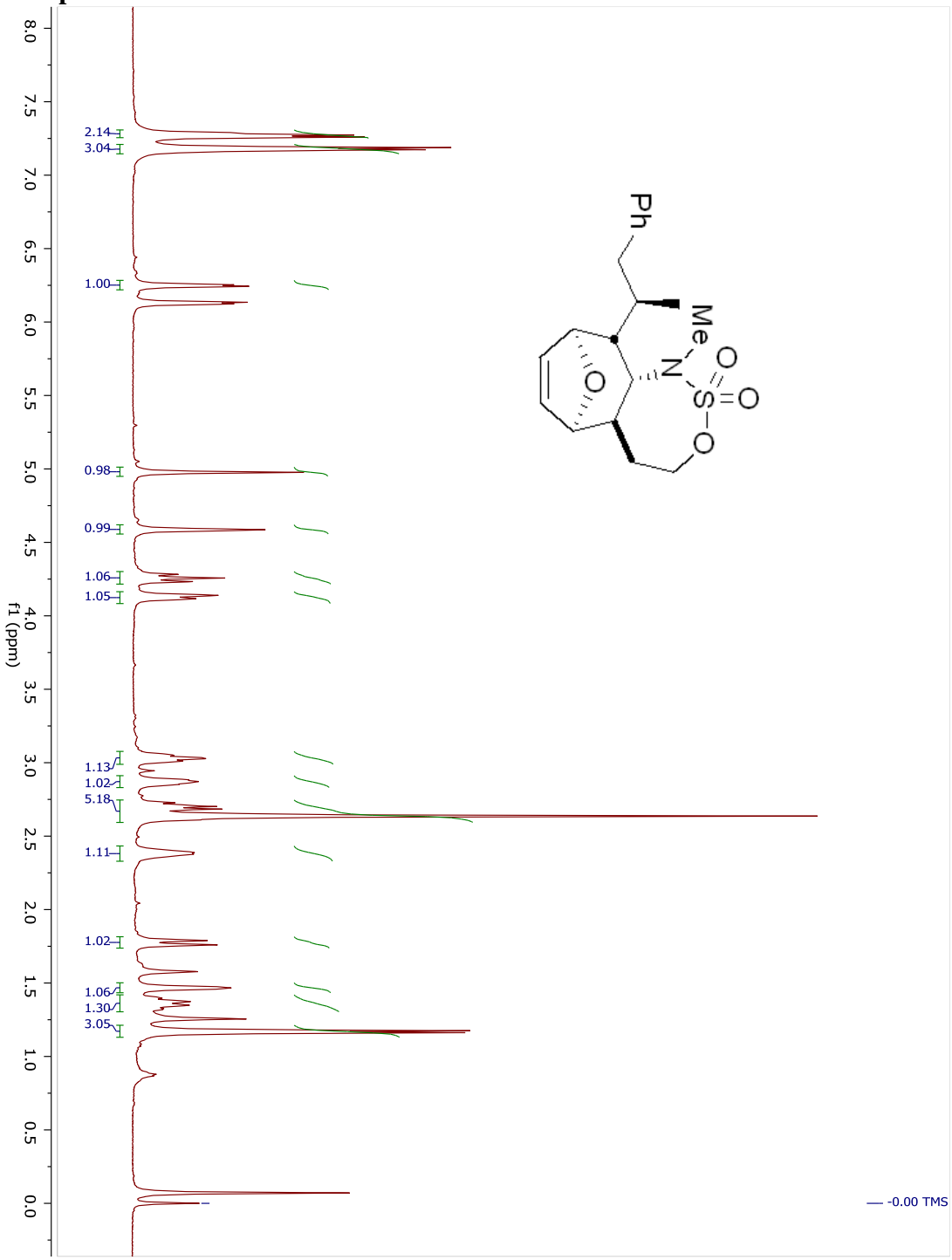

MeO
H11C5
O
N
S
O
O
O
7.16 CDCl3
f1 (ppm)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

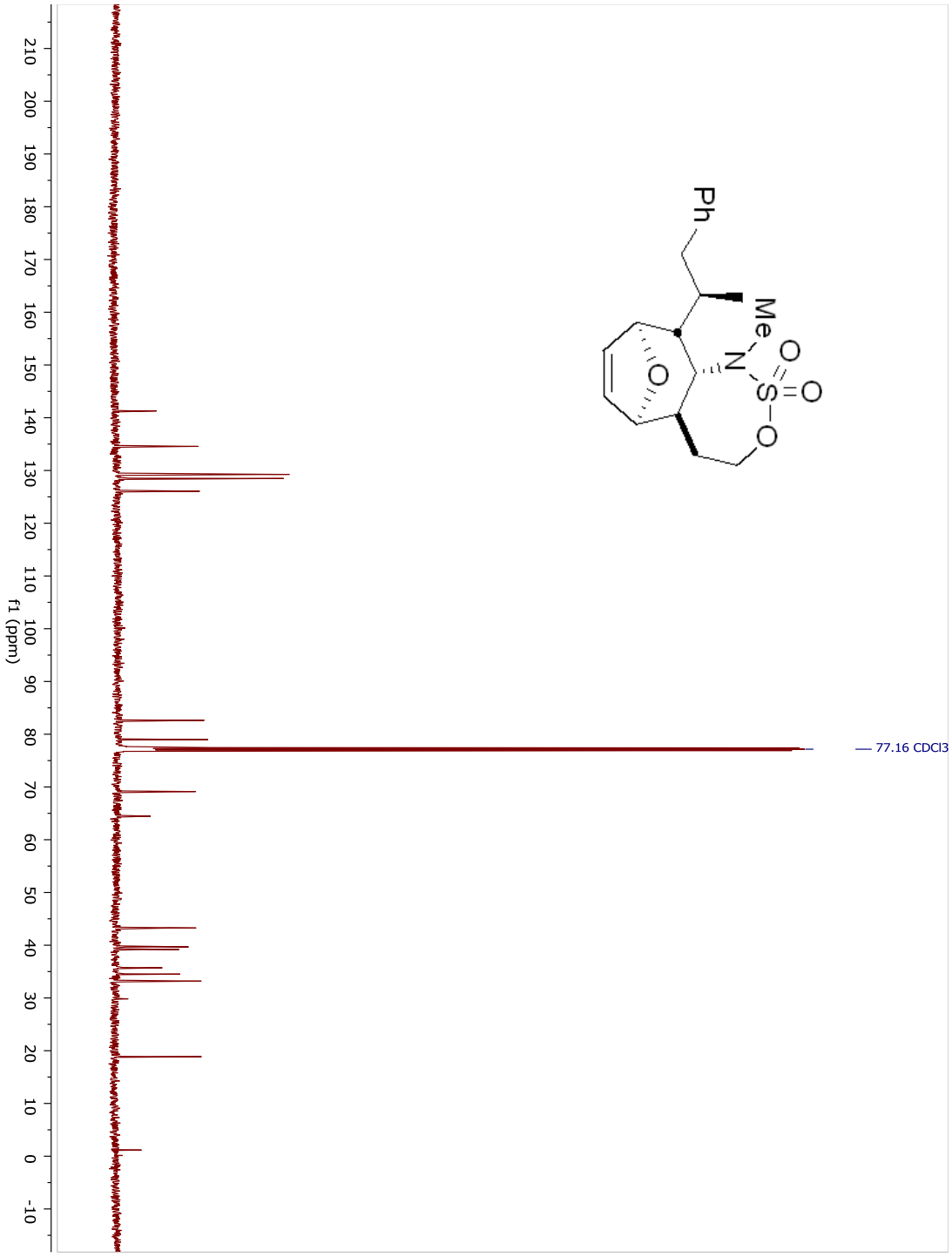
Compound 5.S3.




MeO
H11C5
O
N
S
O
O
O
77.16 CDCl3
f1 (ppm)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

Compound 5.S4.




Ph
Me
N
S
O
O
O
O
77.16 CDCl3
f1 (ppm)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

APPENDIX 2 - X-Ray Crystallography Data

MOLECULAR STRUCTURE LABORATORY

ILIA A. GUZEI, PH.D.

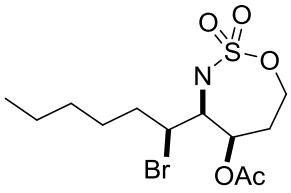
University of Wisconsin-Madison
2124 Chemistry Department
1101 University Ave
Madison, WI 53706

☎ 608-263-4694
Fax 608-262-0381

E-mail: iguzei@chem.wisc.edu

Structural report on Schomaker10

OCTOBER 17, 2011



Crystallographic Experimental Section

Data Collection

A colorless crystal with approximate dimensions 0.59 x 0.20 x 0.07 mm^3 was selected under oil under ambient conditions and attached to the tip of a MiTeGen MicroMount©. The crystal was mounted in a stream of cold nitrogen at 100(1) K and centered in the X-ray beam by using a video camera.

The crystal evaluation and data collection were performed on a Bruker SMART APEXII diffractometer with Cu K_α ($\lambda = 1.54178$ Å) radiation and the diffractometer to crystal distance of 4.03 cm.

The initial cell constants were obtained from three series of ω scans at different starting angles. Each series consisted of 50 frames collected at intervals of 0.5º in a 25º range about ω with the exposure time of 3 seconds per frame. The reflections were successfully indexed by an automated indexing routine built in the APEXII program. The final cell constants were calculated from a set of 9941 strong reflections from the actual data collection.

The data were collected by using the full sphere data collection routine to survey the reciprocal space to the extent of a full sphere to a resolution of 0.82 Å. A total of 28433 data were harvested by collecting 11 sets of frames with 0.9º scans in ω with an exposure time 3/6 sec per frame. These highly redundant datasets were corrected for Lorentz and polarization effects. The absorption correction was based on fitting a function to the empirical transmission surface as sampled by multiple equivalent measurements. [1]

Structure Solution and Refinement

The systematic absences in the diffraction data were uniquely consistent for the space group *Pbca* that yielded chemically reasonable and computationally stable results of refinement [2].

A successful solution by the direct methods provided most non-hydrogen atoms from the *E*-map. The remaining non-hydrogen atoms were located in an alternating series of least-squares cycles and difference Fourier maps. All non-hydrogen atoms were refined with anisotropic displacement coefficients. All hydrogen atoms except H1 were included in the structure factor calculation at idealized positions and were allowed to ride on the neighboring atoms with relative

isotropic displacement coefficients. Atom H1 was located in the difference map and refined independently.

Atoms C2 and C3 are disordered over two positions each. The major components of the disordered atoms are present 91.4(5)% of the time. The disorder in the butyl part was refined with restraints and constraints.

The final least-squares refinement of 193 parameters against 2956 data resulted in residuals *R* (based on F^2 for $I \geq 2\sigma$) and *wR* (based on F^2 for all data) of 0.0345 and 0.0853, respectively. The final difference Fourier map was featureless.

The molecular diagram is drawn with 50% probability ellipsoids.

References

[1] Bruker-AXS. (2007-2011) APEX2, SADABS, and SAINT Software Reference Manuals. Bruker-AXS, Madison, Wisconsin, USA.

[2] Sheldrick, G. M. (2008) SHELXL. *Acta Cryst.* **A64**, 112-122.

[3] Dolomanov, O.V.; Bourhis, L.J.; Gildea, R.J.; Howard, J.A.K.; Puschmann, H. "OLEX2: a complete structure solution, refinement and analysis program". *J. Appl. Cryst.* (2009) **42**, *339-341*.

[4] Guzei, I.A. (2006-2011). Internal laboratory computer programs "G1", "ResIns", "FCF_filter", "Modicifer".

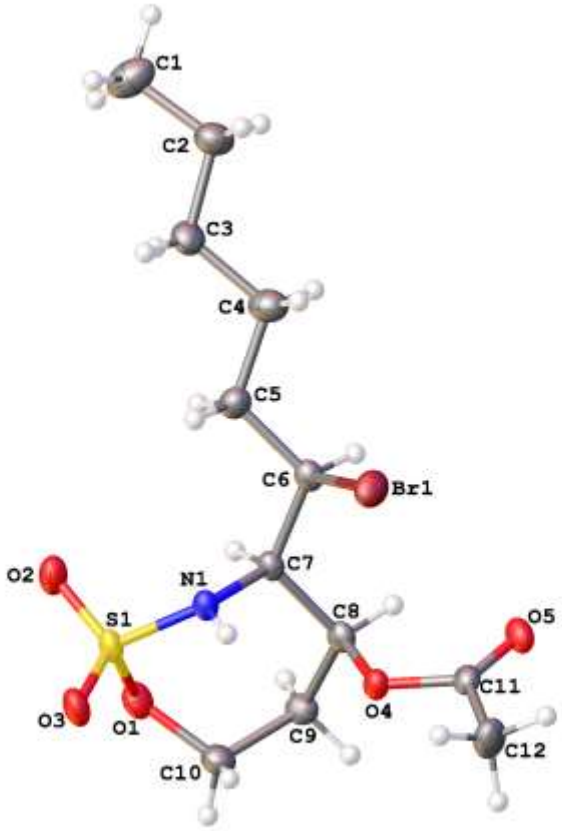


Figure 1. A molecular drawing of Schomaker10. The minor component of the C2/C3 disorder is omitted.

Table 1. Crystal data and structure refinement for schomaker10.

Identification code	schomaker10	
Empirical formula	C_{12} H_{22} Br N O_5 S	
Formula weight	372.28	
Temperature	100(1) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	Pbca	
Unit cell dimensions	a = 13.891(2) Å	α= 90°.
	b = 10.0196(18) Å	β= 90°.
	c = 22.790(2) Å	γ = 90°.
Volume	3172.0(8) $Å^3$	
Z	8	
Density (calculated)	1.559 Mg/m^3	
Absorption coefficient	4.932 mm^{-1}	
F(000)	1536	
Crystal size	0.59 x 0.20 x 0.07 mm^3	
Theta range for data collection	3.88 to 69.51°.	
Index ranges	-16<=h<=16, -12<=k<=12, -25<=l<=27	
Reflections collected	28433	
Independent reflections	2956 [R(int) = 0.0469]	
Completeness to theta = 67.00°	100.0 %	
Absorption correction	Numerical with SADABS	
Max. and min. transmission	0.7117 and 0.1583	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2956 / 5 / 193	
Goodness-of-fit on F^2	1.057	
Final R indices [I>2sigma(I)]	R1 = 0.0345, wR2 = 0.0814	
R indices (all data)	R1 = 0.0409, wR2 = 0.0853	
Largest diff. peak and hole	0.610 and -0.331 e.$Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for schomaker10. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Br(1)	886(1)	8148(1)	9509(1)	29(1)
S(1)	347(1)	5702(1)	7719(1)	21(1)
O(1)	922(1)	6339(2)	7189(1)	26(1)
O(2)	-630(2)	5961(2)	7571(1)	29(1)
O(3)	646(2)	4355(2)	7809(1)	28(1)
O(4)	2450(1)	7700(2)	8470(1)	20(1)
O(5)	3004(1)	9617(2)	8862(1)	25(1)
N(1)	673(2)	6538(2)	8288(1)	18(1)
C(1)	-4106(2)	9768(4)	9377(2)	42(1)
C(2)	-3049(2)	9996(3)	9512(2)	33(1)
C(3)	-2425(2)	9111(3)	9140(1)	29(1)
C(4)	-1336(2)	9334(3)	9208(1)	32(1)
C(5)	-780(2)	8461(3)	8784(1)	25(1)
C(6)	300(2)	8696(3)	8757(1)	20(1)
C(7)	762(2)	7993(2)	8239(1)	18(1)
C(8)	1792(2)	8408(2)	8089(1)	19(1)
C(9)	2081(2)	8073(3)	7462(1)	23(1)
C(10)	1947(2)	6623(3)	7281(1)	27(1)
C(11)	3029(2)	8420(3)	8826(1)	21(1)
C(12)	3697(2)	7517(3)	9150(2)	34(1)
C(2A)	-3086(9)	9650(40)	9129(11)	33(1)
C(3A)	-2293(10)	9250(40)	9541(10)	29(1)

Table 3. Bond lengths [Å] and angles [°] for schomaker10.

Br(1)-C(6)	1.974(3)	C(2A)-H(2AA)	0.9900
S(1)-O(2)	1.422(2)	C(2A)-H(2AB)	0.9900
S(1)-O(3)	1.427(2)	C(3A)-H(3AA)	0.9900
S(1)-O(1)	1.581(2)	C(3A)-H(3AB)	0.9900
S(1)-N(1)	1.609(2)		
O(1)-C(10)	1.467(4)	O(2)-S(1)-O(3)	118.97(12)
O(4)-C(11)	1.351(3)	O(2)-S(1)-O(1)	103.15(12)
O(4)-C(8)	1.446(3)	O(3)-S(1)-O(1)	110.17(12)
O(5)-C(11)	1.203(3)	O(2)-S(1)-N(1)	111.35(13)
N(1)-C(7)	1.468(3)	O(3)-S(1)-N(1)	107.10(12)
N(1)-H(1)	0.81(3)	O(1)-S(1)-N(1)	105.30(11)
C(1)-C(2)	1.518(5)	C(10)-O(1)-S(1)	117.36(17)
C(1)-C(2A)	1.530(9)	C(11)-O(4)-C(8)	118.4(2)
C(1)-H(1AA)	0.9800	C(7)-N(1)-S(1)	118.60(18)
C(1)-H(1AB)	0.9800	C(7)-N(1)-H(1)	117(2)
C(1)-H(1AC)	0.9800	S(1)-N(1)-H(1)	114(2)
C(1)-H(1BD)	0.9800	C(2)-C(1)-C(2A)	36.0(12)
C(1)-H(1BE)	0.9800	C(2)-C(1)-H(1AA)	109.5
C(1)-H(1BF)	0.9800	C(2A)-C(1)-H(1AA)	75.9
C(2)-C(3)	1.502(4)	C(2)-C(1)-H(1AB)	109.5
C(2)-H(2A)	0.9900	C(2A)-C(1)-H(1AB)	135.0
C(2)-H(2B)	0.9900	H(1AA)-C(1)-H(1AB)	109.5
C(3)-C(4)	1.537(4)	C(2)-C(1)-H(1AC)	109.5
C(3)-H(3A)	0.9900	C(2A)-C(1)-H(1AC)	110.2
C(3)-H(3B)	0.9900	H(1AA)-C(1)-H(1AC)	109.5
C(4)-C(5)	1.516(4)	H(1AB)-C(1)-H(1AC)	109.5
C(4)-C(3A)	1.533(9)	C(2)-C(1)-H(1BD)	141.3
C(4)-H(4AA)	0.9900	C(2A)-C(1)-H(1BD)	109.5
C(4)-H(4AB)	0.9900	H(1AA)-C(1)-H(1BD)	33.6
C(4)-H(4BC)	0.9900	H(1AB)-C(1)-H(1BD)	84.6
C(4)-H(4BD)	0.9900	H(1AC)-C(1)-H(1BD)	98.4
C(5)-C(6)	1.520(4)	C(2)-C(1)-H(1BE)	80.1
C(5)-H(5A)	0.9900	C(2A)-C(1)-H(1BE)	109.5
C(5)-H(5B)	0.9900	H(1AA)-C(1)-H(1BE)	123.8
C(6)-C(7)	1.518(4)	H(1AB)-C(1)-H(1BE)	29.5
C(6)-H(6)	1.0000	H(1AC)-C(1)-H(1BE)	119.0
C(7)-C(8)	1.528(4)	H(1BD)-C(1)-H(1BE)	109.5
C(7)-H(7)	1.0000	C(2)-C(1)-H(1BF)	101.6
C(8)-C(9)	1.521(4)	C(2A)-C(1)-H(1BF)	109.5
C(8)-H(8)	1.0000	H(1AA)-C(1)-H(1BF)	121.3
C(9)-C(10)	1.522(4)	H(1AB)-C(1)-H(1BF)	104.9
C(9)-H(9A)	0.9900	H(1AC)-C(1)-H(1BF)	12.0
C(9)-H(9B)	0.9900	H(1BD)-C(1)-H(1BF)	109.5
C(10)-H(10A)	0.9900	H(1BE)-C(1)-H(1BF)	109.5
C(10)-H(10B)	0.9900	C(3)-C(2)-C(1)	110.8(3)
C(11)-C(12)	1.492(4)	C(3)-C(2)-H(2A)	109.5
C(12)-H(12A)	0.9800	C(1)-C(2)-H(2A)	109.5
C(12)-H(12B)	0.9800	C(3)-C(2)-H(2B)	109.5
C(12)-H(12C)	0.9800	C(1)-C(2)-H(2B)	109.5
C(2A)-C(3A)	1.501(9)	H(2A)-C(2)-H(2B)	108.1

C(2)-C(3)-C(4)	115.1(3)
C(2)-C(3)-H(3A)	108.5
C(4)-C(3)-H(3A)	108.5
C(2)-C(3)-H(3B)	108.5
C(4)-C(3)-H(3B)	108.5
H(3A)-C(3)-H(3B)	107.5
C(5)-C(4)-C(3A)	136.5(14)
C(5)-C(4)-C(3)	110.7(3)
C(3A)-C(4)-C(3)	35.8(10)
C(5)-C(4)-H(4AA)	109.5
C(3A)-C(4)-H(4AA)	109.1
C(3)-C(4)-H(4AA)	109.5
C(5)-C(4)-H(4AB)	109.5
C(3A)-C(4)-H(4AB)	76.2
C(3)-C(4)-H(4AB)	109.5
H(4AA)-C(4)-H(4AB)	108.1
C(5)-C(4)-H(4BC)	103.0
C(3A)-C(4)-H(4BC)	103.0
C(3)-C(4)-H(4BC)	89.9
H(4AA)-C(4)-H(4BC)	25.7
H(4AB)-C(4)-H(4BC)	132.1
C(5)-C(4)-H(4BD)	103.0
C(3A)-C(4)-H(4BD)	103.0
C(3)-C(4)-H(4BD)	138.8
H(4AA)-C(4)-H(4BD)	79.4
H(4AB)-C(4)-H(4BD)	34.3
H(4BC)-C(4)-H(4BD)	105.1
C(4)-C(5)-C(6)	116.0(2)
C(4)-C(5)-H(5A)	108.3
C(6)-C(5)-H(5A)	108.3
C(4)-C(5)-H(5B)	108.3
C(6)-C(5)-H(5B)	108.3
H(5A)-C(5)-H(5B)	107.4
C(7)-C(6)-C(5)	112.1(2)
C(7)-C(6)-Br(1)	111.81(18)
C(5)-C(6)-Br(1)	109.22(18)
C(7)-C(6)-H(6)	107.8
C(5)-C(6)-H(6)	107.8
Br(1)-C(6)-H(6)	107.8
N(1)-C(7)-C(6)	111.4(2)
N(1)-C(7)-C(8)	111.5(2)
C(6)-C(7)-C(8)	116.4(2)
N(1)-C(7)-H(7)	105.5
C(6)-C(7)-H(7)	105.5
C(8)-C(7)-H(7)	105.5
O(4)-C(8)-C(9)	106.8(2)
O(4)-C(8)-C(7)	108.9(2)
C(9)-C(8)-C(7)	113.4(2)
O(4)-C(8)-H(8)	109.2
C(9)-C(8)-H(8)	109.2
C(7)-C(8)-H(8)	109.2
C(8)-C(9)-C(10)	115.6(2)
C(8)-C(9)-H(9A)	108.4
C(10)-C(9)-H(9A)	108.4
C(8)-C(9)-H(9B)	108.4
C(10)-C(9)-H(9B)	108.4
H(9A)-C(9)-H(9B)	107.4
O(1)-C(10)-C(9)	110.0(2)
O(1)-C(10)-H(10A)	109.7
C(9)-C(10)-H(10A)	109.7
O(1)-C(10)-H(10B)	109.7
C(9)-C(10)-H(10B)	109.7
H(10A)-C(10)-H(10B)	108.2
O(5)-C(11)-O(4)	123.8(3)
O(5)-C(11)-C(12)	126.1(3)
O(4)-C(11)-C(12)	110.1(2)
C(11)-C(12)-H(12A)	109.5
C(11)-C(12)-H(12B)	109.5
H(12A)-C(12)-H(12B)	109.5
C(11)-C(12)-H(12C)	109.5
H(12A)-C(12)-H(12C)	109.5
H(12B)-C(12)-H(12C)	109.5
C(3A)-C(2A)-C(1)	118.1(13)
C(3A)-C(2A)-H(2AA)	107.8
C(1)-C(2A)-H(2AA)	107.8
C(3A)-C(2A)-H(2AB)	107.8
C(1)-C(2A)-H(2AB)	107.8
H(2AA)-C(2A)-H(2AB)	107.1
C(2A)-C(3A)-C(4)	108.1(10)
C(2A)-C(3A)-H(3AA)	110.1
C(4)-C(3A)-H(3AA)	110.1
C(2A)-C(3A)-H(3AB)	110.1
C(4)-C(3A)-H(3AB)	110.1
H(3AA)-C(3A)-H(3AB)	108.4

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for schomaker10. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Br(1)	27(1)	41(1)	17(1)	0(1)	-1(1)	-4(1)
S(1)	25(1)	16(1)	23(1)	-3(1)	-5(1)	-2(1)
O(1)	33(1)	26(1)	19(1)	-2(1)	-4(1)	-2(1)
O(2)	29(1)	25(1)	34(1)	-2(1)	-10(1)	-3(1)
O(3)	34(1)	18(1)	30(1)	-5(1)	-8(1)	-3(1)
O(4)	20(1)	14(1)	25(1)	0(1)	-4(1)	-1(1)
O(5)	30(1)	18(1)	25(1)	-2(1)	1(1)	-6(1)
N(1)	20(1)	14(1)	19(1)	1(1)	-4(1)	0(1)
C(1)	30(2)	47(2)	50(2)	14(2)	4(2)	3(2)
C(2)	34(2)	33(2)	32(2)	-4(2)	3(2)	6(2)
C(3)	30(2)	32(2)	24(2)	-4(1)	2(1)	-2(1)
C(4)	32(2)	29(2)	35(2)	1(1)	7(1)	3(1)
C(5)	22(1)	24(1)	29(2)	1(1)	-1(1)	1(1)
C(6)	24(1)	16(1)	19(1)	2(1)	-2(1)	0(1)
C(7)	21(1)	14(1)	18(1)	1(1)	-3(1)	1(1)
C(8)	23(1)	13(1)	20(1)	3(1)	-2(1)	-1(1)
C(9)	25(1)	21(1)	22(1)	3(1)	3(1)	0(1)
C(10)	28(2)	27(1)	25(1)	-4(1)	4(1)	2(1)
C(11)	18(1)	22(1)	22(1)	-1(1)	3(1)	-4(1)
C(12)	27(2)	32(2)	43(2)	-1(1)	-14(1)	0(1)
C(2A)	34(2)	33(2)	32(2)	-4(2)	3(2)	6(2)
C(3A)	30(2)	32(2)	24(2)	-4(1)	2(1)	-2(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for schomaker10.

	x	y	z	U(eq)
H(1)	1070(20)	6160(30)	8488(15)	23(8)
H(1AA)	-4200	9748	8951	63
H(1AB)	-4489	10495	9546	63
H(1AC)	-4312	8916	9546	63
H(1BD)	-4568	9815	9053	63
H(1BE)	-4154	10580	9615	63
H(1BF)	-4249	8989	9621	63
H(2A)	-2883	10941	9438	40
H(2B)	-2927	9806	9932	40
H(3A)	-2600	9252	8723	34
H(3B)	-2571	8170	9237	34
H(4AA)	-1182	10283	9133	38
H(4AB)	-1141	9121	9615	38
H(4BC)	-1392	10190	8994	38
H(4BD)	-863	9505	9524	38
H(5A)	-1048	8596	8386	30
H(5B)	-892	7516	8892	30
H(6)	409	9677	8709	24
H(7)	366	8248	7890	21
H(8)	1865	9390	8154	23
H(9A)	2767	8312	7409	27
H(9B)	1700	8641	7192	27
H(10A)	2307	6448	6914	32
H(10B)	2205	6030	7590	32
H(12A)	3362	6685	9248	51
H(12B)	3912	7955	9511	51
H(12C)	4256	7316	8903	51
H(2AA)	-3103	8986	8806	40
H(2AB)	-2910	10517	8955	40
H(3AA)	-2399	8325	9683	34
H(3AB)	-2282	9852	9885	34

Table 6. Torsion angles [°] for schomaker10.

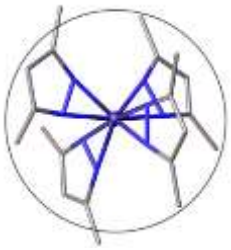
O(2)-S(1)-O(1)-C(10)	161.45(19)
O(3)-S(1)-O(1)-C(10)	-70.6(2)
N(1)-S(1)-O(1)-C(10)	44.6(2)
O(2)-S(1)-N(1)-C(7)	-69.0(2)
O(3)-S(1)-N(1)-C(7)	159.4(2)
O(1)-S(1)-N(1)-C(7)	42.1(2)
C(2A)-C(1)-C(2)-C(3)	-24(2)
C(1)-C(2)-C(3)-C(4)	175.6(3)
C(2)-C(3)-C(4)-C(5)	-176.1(3)
C(2)-C(3)-C(4)-C(3A)	41(2)
C(3A)-C(4)-C(5)-C(6)	-156.2(14)
C(3)-C(4)-C(5)-C(6)	173.3(3)
C(4)-C(5)-C(6)-C(7)	-168.2(2)
C(4)-C(5)-C(6)-Br(1)	67.3(3)
S(1)-N(1)-C(7)-C(6)	134.7(2)
S(1)-N(1)-C(7)-C(8)	-93.4(2)
C(5)-C(6)-C(7)-N(1)	-64.0(3)
Br(1)-C(6)-C(7)-N(1)	59.1(3)
C(5)-C(6)-C(7)-C(8)	166.7(2)
Br(1)-C(6)-C(7)-C(8)	-70.2(2)
C(11)-O(4)-C(8)-C(9)	117.5(2)
C(11)-O(4)-C(8)-C(7)	-119.7(2)
N(1)-C(7)-C(8)-O(4)	-47.2(3)
C(6)-C(7)-C(8)-O(4)	82.1(3)
N(1)-C(7)-C(8)-C(9)	71.6(3)
C(6)-C(7)-C(8)-C(9)	-159.1(2)
O(4)-C(8)-C(9)-C(10)	65.8(3)
C(7)-C(8)-C(9)-C(10)	-54.1(3)
S(1)-O(1)-C(10)-C(9)	-95.7(2)
C(8)-C(9)-C(10)-O(1)	74.4(3)
C(8)-O(4)-C(11)-O(5)	2.9(4)
C(8)-O(4)-C(11)-C(12)	-176.0(2)
C(2)-C(1)-C(2A)-C(3A)	37(2)
C(1)-C(2A)-C(3A)-C(4)	-174(2)
C(5)-C(4)-C(3A)-C(2A)	-81(3)
C(3)-C(4)-C(3A)-C(2A)	-27.2(17)

Symmetry transformations used to generate equivalent atoms:

Table 7. Hydrogen bonds for schomaker10 [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(1)-H(1)...O(5)#1	0.81(3)	2.19(3)	2.965(3)	162(3)

Symmetry transformations used to generate equivalent atoms:
#1 -x+1/2,y-1/2,z



MOLECULAR STRUCTURE LABORATORY

ILIA A. GUZEI, PH.D.

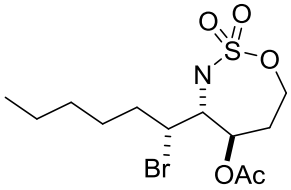
University of Wisconsin-Madison
2124 Chemistry Department
1101 University Ave
Madison, WI 53706

☎ 608-263-4694
Fax 608-262-0381

E-mail: iguzei@chem.wisc.edu

Structural report on Schomaker22

DECEMBER 18, 2012



Crystallographic Experimental Section

Data Collection

A colorless crystal with approximate dimensions 0.57 x 0.37 x 0.26 mm^3 was selected under oil under ambient conditions and attached to the tip of a MiTeGen MicroMount©. The crystal was mounted in a stream of cold nitrogen at 100(1) K and centered in the X-ray beam by using a video camera.

The crystal evaluation and data collection were performed on a Bruker Quazar SMART APEXII diffractometer with Mo K_α (λ = 0.71073 Å) radiation and the diffractometer to crystal distance of 4.96 cm.

The initial cell constants were obtained from three series of ω scans at different starting angles. Each series consisted of 12 frames collected at intervals of 0.5° in a 6° range about ω with the exposure time of 10 seconds per frame. The reflections were successfully indexed by an automated indexing routine built in the APEXII program suite. The final cell constants were calculated from a set of 9590 strong reflections from the actual data collection.

The data were collected by using the full sphere data collection routine to survey the reciprocal space to the extent of a full sphere to a resolution of 0.68 Å. A total of 22130 data were harvested by collecting 6 sets of frames with 0.3° scans in ω and φ with exposure times of 6 sec per frame. These highly redundant datasets were corrected for Lorentz and polarization effects. The absorption correction was based on fitting a function to the empirical transmission surface as sampled by multiple equivalent measurements. [1]

Structure Solution and Refinement

The systematic absences in the diffraction data were uniquely consistent for the space group $P2_1/c$ that yielded chemically reasonable and computationally stable results of refinement [2-4].

A successful solution by the direct methods provided most non-hydrogen atoms from the *E*-map. The remaining non-hydrogen atoms were located in an alternating series of least-squares cycles and difference Fourier maps. All non-hydrogen atoms were

refined with anisotropic displacement coefficients. All hydrogen atoms hydrogen [except H1(N1) which was refined freely] were included in the structure factor calculation at idealized positions and were allowed to ride on the neighboring atoms with relative isotropic displacement coefficients.

The final least-squares refinement of 187 parameters against 5729 data resulted in residuals *R* (based on F^2 for $I \geq 2\sigma$) and *wR* (based on F^2 for all data) of 0.0186 and 0.0499, respectively. The final difference Fourier map was featureless.

Summary

Crystal Data for $C_{12}H_{22}BrNO_5S$ (M =372.27): monoclinic, space group $P2_1/c$ (no. 14), a = 8.893(3) Å, b = 13.584(4) Å, c = 13.016(4) Å, β = 99.411(8)°, V = 1551.2(8) Å^3, Z = 4, T = 100.0 K, μ(Mo Kα) = 2.802 mm^{-1}, *Dcalc* = 1.594 g/mm^3, 47610 reflections measured ($4.364 \leq 2\Theta \leq 66.374$), 5729 unique ($R_{int}$ = 0.0272) which were used in all calculations. The final R_1 was 0.0186 ($I > 2\sigma(I)$) and wR_2 was 0.0499 (all data).

References

[1] Bruker-AXS. (2009) APEX2, SADABS, and SAINT Software Reference Manuals. Bruker-AXS, Madison, Wisconsin, USA.

[2] Sheldrick, G. M. (2008) SHELXL. *Acta Cryst*. **A64**, 112-122.

[3] Dolomanov, O.V.; Bourhis, L.J.; Gildea, R.J.; Howard, J.A.K.; Puschmann, H. "OLEX2: a complete structure solution, refinement and analysis program". *J. Appl. Cryst*. (2009) **42**, *339-341*.

[4] Guzei, I.A. (2006-2008). Internal laboratory computer programs "Inserter", "FCF_filter", "Modicifer".

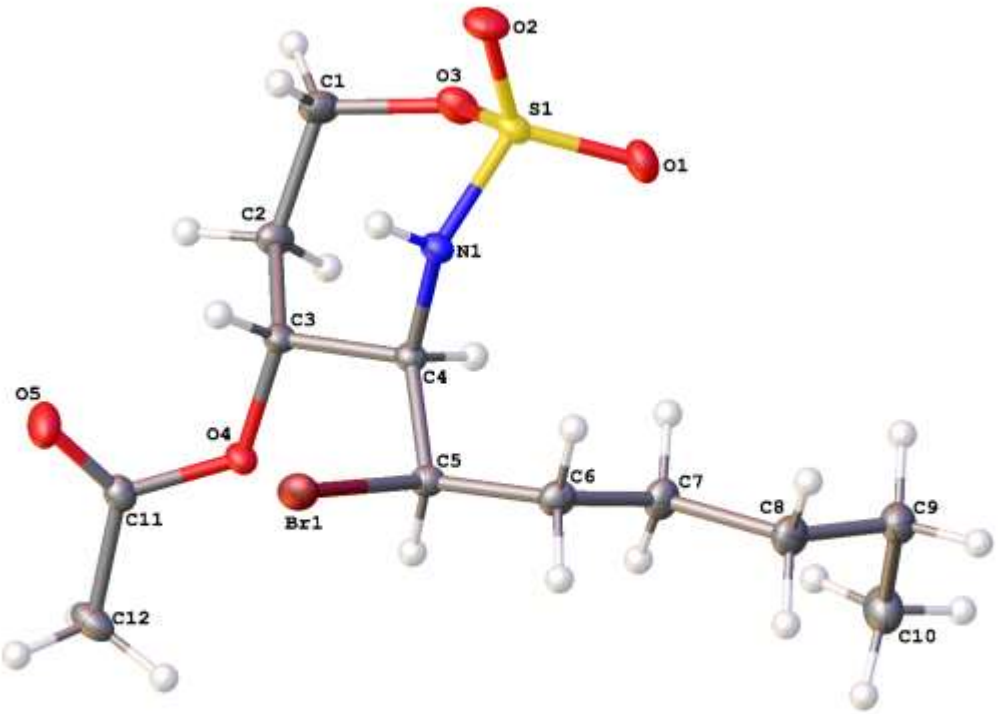


Figure 1. A molecular drawing of Schomaker22 shown with 50% probability ellipsoids.

Table 1 Crystal data and structure refinement for Schomaker22

Identification code	Schomaker22
Empirical formula	$C_{12}H_{22}BrNO_5S$
Formula weight	372.27
Temperature/K	100.0
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	8.893(3)
b/Å	13.584(4)
c/Å	13.016(4)
α/°	90
β/°	99.411(8)
γ/°	90
Volume/Å^3	1551.2(8)
Z	4
ρ_{calc}mg/mm^3	1.594
m/mm^{-1}	2.802
F(000)	768.0
Crystal size/mm^3	0.568 × 0.371 × 0.262
2Θ range for data collection	4.364 to 66.374°
Index ranges	$-13 \leq h \leq 13$, $-20 \leq k \leq 20$, $-19 \leq l \leq 20$
Reflections collected	47610
Independent reflections	5729[R(int) = 0.0272]
Data/restraints/parameters	5729/0/187
Goodness-of-fit on F^2	1.055
Final R indexes [I>=2σ (I)]	R_1 = 0.0186, wR_2 = 0.0493
Final R indexes [all data]	R_1 = 0.0206, wR_2 = 0.0499
Largest diff. peak/hole / e Å^{-3}	0.46/-0.33

Table 2 Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for Schomaker22. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
Br1	3382.1(2)	4025.0(2)	2903.3(2)	18.15(3)
S1	2262.1(2)	7490.9(2)	3336.5(2)	14.56(4)
O1	840.1(8)	7720.6(5)	2702.6(6)	20.85(13)
O2	3600.3(8)	8016.8(5)	3191.6(6)	21.22(13)
O3	1920.5(8)	7634.3(5)	4481.1(5)	18.43(12)
O4	1839.6(7)	4475.3(5)	5137.2(5)	13.52(11)
O5	4157.7(8)	3956.7(6)	5886.6(6)	22.55(14)
N1	2650.3(8)	6336.5(5)	3249.8(6)	12.68(12)
C1	2971.8(11)	7178.1(7)	5334.4(7)	18.76(16)
C2	2385.6(10)	6172.4(7)	5595.1(7)	15.94(15)
C3	2530.9(9)	5364.3(6)	4803.3(6)	12.71(13)
C4	1731.3(9)	5596.3(6)	3693.6(6)	11.78(13)
C5	1436.6(9)	4703.0(6)	2975.4(6)	13.56(14)
C6	650.3(10)	4943.4(7)	1877.5(7)	15.57(14)
C7	-916.7(10)	5412.7(7)	1871.7(7)	17.26(15)
C8	-1818.2(11)	5518.0(7)	774.3(7)	18.99(16)
C9	-3310.6(12)	6086.4(7)	740.0(8)	21.47(17)
C10	-4427.3(12)	5584.1(8)	1341.3(9)	25.00(19)
C11	2806.9(10)	3805.3(7)	5648.0(7)	14.23(14)
C12	2008.9(11)	2887.8(7)	5883.2(8)	20.20(17)

Table 3 Anisotropic Displacement Parameters ($Å^2 \times 10^3$) for Schomaker22. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+...+2hka\times b\times U_{12}]$

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
Br1	17.36(5)	15.16(5)	22.15(5)	-4.80(3)	3.85(3)	2.40(3)
S1	17.52(9)	10.56(9)	15.85(9)	1.89(7)	3.49(7)	-0.51(6)
O1	21.6(3)	17.5(3)	22.5(3)	5.1(3)	0.6(2)	4.8(2)
O2	23.4(3)	15.7(3)	25.4(3)	2.6(3)	6.7(3)	-5.9(2)
O3	25.0(3)	13.6(3)	17.4(3)	-0.8(2)	6.0(2)	1.5(2)
O4	13.4(2)	12.1(3)	15.1(3)	3.4(2)	2.4(2)	-0.8(2)
O5	14.8(3)	26.4(4)	25.3(4)	9.3(3)	-0.2(2)	0.8(2)

N1	13.3(3)	10.7(3)	14.4(3)	1.2(2)	3.5(2)	-0.3(2)
C1	25.1(4)	15.8(4)	14.7(4)	-2.2(3)	1.2(3)	-4.3(3)
C2	21.0(4)	15.0(4)	11.8(3)	-0.7(3)	2.6(3)	-2.7(3)
C3	14.0(3)	11.6(3)	12.4(3)	1.5(3)	1.9(2)	-1.9(2)
C4	12.7(3)	11.1(3)	11.8(3)	0.4(3)	2.8(2)	-0.9(2)
C5	14.2(3)	12.6(3)	14.1(3)	-1.5(3)	2.9(3)	-0.8(3)
C6	17.9(4)	17.0(4)	12.0(3)	-2.1(3)	2.9(3)	-1.3(3)
C7	18.5(4)	21.3(4)	11.5(3)	-1.0(3)	1.1(3)	1.1(3)
C8	22.7(4)	21.4(4)	12.0(3)	0.1(3)	0.3(3)	-0.5(3)
C9	22.8(4)	20.2(4)	19.8(4)	3.6(3)	-1.2(3)	0.2(3)
C10	21.5(4)	26.8(5)	26.1(5)	5.4(4)	2.3(3)	2.2(4)
C11	15.9(3)	14.5(3)	12.8(3)	2.1(3)	3.8(3)	1.7(3)
C12	22.8(4)	13.2(4)	26.2(5)	5.3(3)	9.0(3)	1.9(3)

Table 4 Bond Lengths for Schomaker22.

Atom	**Atom**	**Length/Å**	**Atom**	**Atom**	**Length/Å**
Br1	C5	1.9757(10)	C1	C2	1.5203(13)
S1	O1	1.4269(8)	C2	C3	1.5256(13)
S1	O2	1.4267(8)	C3	C4	1.5347(12)
S1	O3	1.5805(8)	C4	C5	1.5281(12)
S1	N1	1.6137(9)	C5	C6	1.5202(12)
O3	C1	1.4670(12)	C6	C7	1.5313(13)
O4	C3	1.4535(10)	C7	C8	1.5261(13)
O4	C11	1.3502(11)	C8	C9	1.5298(15)
O5	C11	1.2082(12)	C9	C10	1.5226(15)
N1	C4	1.4720(11)	C11	C12	1.4905(13)

Table 5 Bond Angles for Schomaker22.

Atom	**Atom**	**Atom**	**Angle/°**	**Atom**	**Atom**	**Atom**	**Angle/°**
O1	S1	O3	103.26(5)	N1	C4	C3	107.95(7)
O1	S1	N1	110.58(4)	N1	C4	C5	110.67(7)
O2	S1	O1	119.58(5)	C5	C4	C3	114.80(7)
O2	S1	O3	110.85(4)	C4	C5	Br1	109.59(6)

O2	S1	N1	106.54(4)	C6	C5	Br1	109.10(6)
O3	S1	N1	105.19(4)	C6	C5	C4	114.27(7)
C1	O3	S1	117.69(6)	C5	C6	C7	111.86(7)
C11	O4	C3	116.15(7)	C8	C7	C6	112.45(7)
C4	N1	S1	119.83(6)	C7	C8	C9	113.27(8)
O3	C1	C2	110.44(7)	C10	C9	C8	113.24(8)
C1	C2	C3	115.20(7)	O4	C11	C12	112.23(8)
O4	C3	C2	108.01(7)	O5	C11	O4	122.57(8)
O4	C3	C4	107.37(6)	O5	C11	C12	125.19(8)
C2	C3	C4	114.25(7)				

Table 6 Hydrogen Bonds for Schomaker22.

D	**H**	**A**	**d(D-H)/Å**	**d(H-A)/Å**	**d(D-A)/Å**	**D-H-A/°**
N1	H1	O5[1]	0.814(15)	2.119(15)	2.9045(14)	162.3(14)

[1]1-X,1-Y,1-Z

Table 7 Torsion Angles for Schomaker22.

A	**B**	**C**	**D**	**Angle/°**	**A**	**B**	**C**	**D**	**Angle/°**
Br1	C5	C6	C7	176.38(6)	C1	C2	C3	O4	-176.62(7)
S1	O3	C1	C2	-94.36(8)	C1	C2	C3	C4	-57.24(10)
S1	N1	C4	C3	-93.61(7)	C2	C3	C4	N1	74.00(9)
S1	N1	C4	C5	139.99(6)	C2	C3	C4	C5	-162.05(7)
O1	S1	O3	C1	161.72(6)	C3	O4	C11	O5	5.31(12)
O1	S1	N1	C4	-68.70(8)	C3	O4	C11	C12	-175.41(7)
O2	S1	O3	C1	-69.05(8)	C3	C4	C5	Br1	-56.97(8)
O2	S1	N1	C4	159.88(6)	C3	C4	C5	C6	-179.75(7)
O3	S1	N1	C4	42.14(7)	C4	C5	C6	C7	-60.57(9)
O3	C1	C2	C3	73.39(10)	C5	C6	C7	C8	-171.49(8)
O4	C3	C4	N1	-166.25(6)	C6	C7	C8	C9	-173.67(8)
O4	C3	C4	C5	-42.31(9)	C7	C8	C9	C10	-62.33(11)
N1	S1	O3	C1	45.73(7)	C11	O4	C3	C2	-99.01(8)
N1	C4	C5	Br1	65.52(8)	C11	O4	C3	C4	137.34(7)
N1	C4	C5	C6	-57.26(9)					

Table 8 Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for Schomaker22.

Atom	*x*	*y*	*z*	U(eq)
H1	3566(17)	6244(11)	3355(11)	22(3)
H1A	3076	7606	5957	23
H1B	3990	7107	5129	23
H2A	1298	6237	5664	19
H2B	2948	5964	6280	19
H3	3636	5238	4792	15
H4	723	5902	3745	14
H5	769	4237	3289	16
H6A	529	4332	1458	19
H6B	1298	5401	1550	19
H7A	-1506	5003	2294	21
H7B	-781	6071	2200	21
H8A	-2050	4854	477	23
H8B	-1178	5861	332	23
H9A	-3078	6752	1033	26
H9B	-3800	6165	5	26
H10A	-4523	4888	1143	37
H10B	-5426	5904	1177	37
H10C	-4052	5637	2090	37
H12A	1518	2995	6495	30
H12B	2749	2351	6024	30
H12C	1235	2715	5285	30

Department of Chemistry

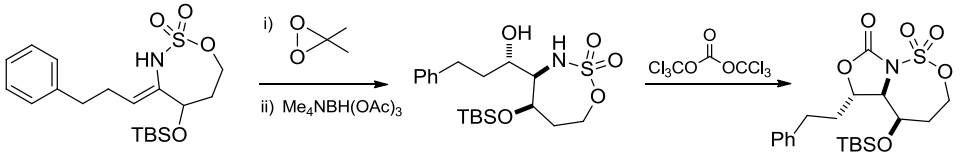
Structure Report 2013

X-RAY
UW-Madison

SCHOMAKER
1101 University Ave,
Madison, WI, 53706, USA
Dr. Maik Tretbar
email: mtretbar@chem.wisc.edu

Crystallographic Experimental Section

Crystal Structure of Schomaker32 [CSA5060]



[46] **[CSA5060]**

Preparation of Crystals: The racemic compound (CSA5060) was dissolved in acetonitrile and crystallized overnight at room temperature by slow vapor diffusion using n-hexanes as solvent. The obtained crystals were air-stable and selected under microscope.

Data Collection: A colorless crystal with approximate dimensions 0.135 x 0.158 x 0.437 mm^3 (block) with a mosaicity of 0.70 was selected under oil under ambient conditions and attached to the tip of a X-ray capillary (MiTeGenMicroMount©). The crystal was mounted in a stream of cold nitrogen at 100.0(15) K and centered in the X-ray beam by using a video camera. The crystal evaluation and data collection were performed on a three-circle Bruker Quazar SMART APEXII diffractometer with Molybdenum K_α(λ = 0.71073 Å) radiation and the diffractometer to crystal distance of 4.96 cm. The initial cell constants were obtained from three series of ω scans at different starting angles. Each series consisted of 12 frames collected at intervals of 0.5° in 6° range about ω with the exposure time of 10 seconds per frame. The reflections were successfully indexed by an automated indexing routine built in the APEXII program suite. The final cell constants were calculated from a set of 9893 strong from the actual data collection. The data were collected by using the full sphere data collection routine to survey the reciprocal space to the extent of a full sphere to a resolution of 0.70 Å. A total of 35770 reflection data were harvested by collecting 6 sets of frames with 0.6° scans in ω and ϕ with exposure times of 25 sec per frame. These highly redundant datasets were corrected for Lorentz and polarization effects. The absorption correction was based on fitting a function to the empirical transmission surface as sampled by multiple equivalent measurements. [1,2]

Structure Solution and Refinement: The systematic absences in the diffraction data were consistent for the monoclinic space groups *P2₁/n*. The *E*-statistics strongly suggested the centrosymmetric space group that yielded chemically reasonable and computationally stable results of refinement. [3,4] The systematic absences in the diffraction data were uniquely consistent for the space group *P2₁/n*. A successful solution by the direct methods by using SHELX-2013 provided most non-hydrogen atoms from the *E*-map. Using Olex2, all non-hydrogen atoms were refined with anisotropic displacement coefficients. All hydrogen atoms were included in the structure factor calculation at idealized positions and were allowed to ride on the neighboring atoms with relative isotropic displacement coefficients. All atoms of the phenyl group C8-C13 including C6 and C7 are disordered over two positions each. The disorder of the phenyl part was refined with restraints and constraints to give a **reasonably** stable model.

Table 1. Crystal data collection and structure solution refinement for Schomaker32 [CSA5060]

Parameter	CSA5060	Parameter	CSA5060
empiric formula	$C_{20}H_{31}NO_6SSi$	$\rho_{calc.}$ [g · cm^{-1}]	1.27
MW [g · mol^{-1}]	441.61	crystal size [mm]	0.158 x 0.437 x 0.437
X-ray lab code	Schomaker32	T [K]	100.0(15)
a [Å]	6.9812(5)	radiation type / λ [nm]	Mo K$_\alpha$ / 0.71072
b [Å]	22.2092(24)	μ [mm^{-1}]	0.227
c [Å]	14.9476(8)	F(000)	945.3
α [°]	90.000(0)°	Reflections collected	35165
β [°]	96.282(4)°	Independent reflections	4513 [R_{int} = 0.021, R_{sigma} = 0.0108]
γ [°]	90.000(8)°	Data/restraints/parameters	4513/84/330
V [Å^3]	2303.66(11)	GooF on F^2	1.049
Z	4	Largest diff. peak/hole [eÅ^{-3}]	0.36 / -0.32
crystal system	monoclinic		
crystal color	colorless	Final R_1[a]/ wR_2[b] all data	0.0298/ 0.0739
space group	$P2_1/n$	Final R_1[a]/ wR_2[b] I>2s(I)	0.0287/ 0.0731

[a] $R_1 = \sum \left| F_o \right| - \left| F_c \right| / \left| F_o \right|$; [b] $wR_2 = [\sum\{w(F_o^2 - F_o^2)^2\} / \sum\{w(F_o^2)^2\}]^{1/2}$

The final least-squares refinement of 330 parameters against 4513 data resulted in R = 0.0287 (based on F^2 for I>2s) and wR2 = 0.0739 (based on F^2 for all data), respectively. The final structure was visualized using Interactive Molecular Graphics. [5]

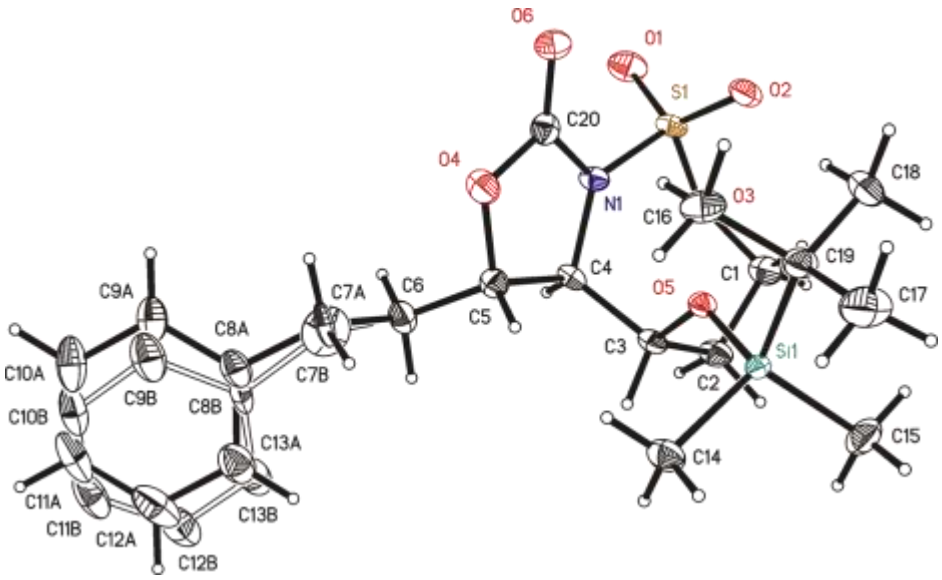


Figure 1. Thermal-ellipsoid of Schomaker32 [CSA5060] are set with 50 % probability. The hydrogen atoms in the disordered phenyl ring were omitted for clarity.

Table 2. Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) for Schomaker32 [CSA5060]. U_{eq} is defined as 1/3 of of the trace of the orthogonalized U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
S1	5027.9(4)	7961.36(14)	7966.90(19)	17.27(8)
Si1	677.4(4)	6468.01(14)	9301.3(2)	13.72(9)
O1	6214.1(13)	8462.5(4)	7817.7(7)	28.1(2)
O2	5865.4(12)	7378.1(4)	8055.8(6)	23.2(2)
O3	3313.7(12)	7976.9(4)	7219.2(6)	22.5(2)
O4	3652.1(13)	8239.7(4)	10308.8(6)	23.9(2)
O5	1604.3(11)	7095.6(4)	8923.3(5)	15.03(17)
O6	6584.5(13)	8072.9(4)	9871.6(6)	24.7(2)
N1	3849.0(14)	8101.8(5)	8854.2(6)	16.1(2)
C1	2042.6(18)	7440.7(6)	7073.8(8)	23.6(3)
C2	237.6(17)	7548.9(6)	7517.9(8)	21.0(3)
C3	591.7(16)	7603.2(5)	8540.9(7)	15.6(2)
C4	1748.9(16)	8161.3(5)	8870.7(8)	15.3(2)
C5	1661.4(17)	8263.9(5)	9890.2(8)	17.6(2)
C6	741.1(18)	8851.9(5)	10123.1(8)	20.6(3)
C14	-997.1(18)	6664.2(6)	10138.6(9)	23.8(3)
C15	-631(2)	6033.5(6)	8360.0(9)	28.6(3)
C16	3835.2(18)	6446.7(6)	10614.0(9)	25.8(3)
C17	2340(2)	5452.3(7)	10209.7(13)	38.4(4)
C18	4296.7(19)	5975.2(6)	9123.6(10)	30.1(3)
C19	2880.2(17)	6065.0(5)	9832.7(9)	20.8(3)
C20	4868.6(18)	8129.4(5)	9696.3(8)	18.9(2)
C7A	684(11)	8891(3)	11168(5)	22.5(10)
C8A	-420(8)	9424(3)	11444(4)	23(1)
C9A	449(8)	9885.7(16)	11956(2)	26.1(8)
C10A	-636(11)	10350.3(14)	12266(2)	34.5(11)
C11A	-2618(11)	10357.1(17)	12057(3)	37.3(13)
C12A	-3505(7)	9905.5(18)	11535(4)	42(1)
C13A	-2417(7)	9433.9(18)	11235(4)	32.5(9)
C7B	510(30)	8945(9)	11047(13)	41(4)
C8B	-950(20)	9433(5)	11311(9)	25(2)
C9B	-320(20)	9859(4)	11976(6)	34.1(19)
C10B	-1600(20)	10307(3)	12215(5)	32(2)
C11B	-3450(20)	10324(4)	11811(8)	38(2)
C12B	-4026(16)	9923(4)	11143(10)	43(2)
C13B	-2775(15)	9480(4)	10895(9)	35(2)

Table 3. Anisotropic Displacement Parameters ($Å^2 \times 10^3$) for csa5060.
The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+...]$

Atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
S1	11.66(14)	24.32(16)	16.50(15)	1.91(10)	4.57(11)	2.73(11)
Si1	11.27(15)	15.92(16)	14.00(16)	-1.44(11)	1.55(11)	-3.26(11)
O1	22.1(5)	33.4(5)	30.8(5)	-3.1(4)	11.3(4)	6.9(4)
O2	15.4(4)	28.2(5)	26.2(5)	5.0(3)	2.4(3)	-2.3(4)
O3	17.7(4)	36.0(5)	14.3(4)	3.8(4)	3.7(3)	5.3(3)
O4	22.6(5)	33.1(5)	15.5(4)	6.7(4)	-0.8(3)	-2.4(4)
O5	11.9(4)	16.7(4)	16.2(4)	1.7(3)	0.3(3)	0.1(3)
O6	18.2(4)	29.1(5)	25.3(5)	2.4(4)	-4.1(4)	-0.3(4)
N1	12.4(5)	21.3(5)	14.7(5)	0.4(4)	2.2(4)	1.6(4)
C1	18.3(6)	38.0(7)	14.3(6)	1.4(5)	0.7(5)	-4.0(5)
C2	14.3(6)	33.1(7)	14.9(6)	3.2(5)	-1.0(4)	0.2(5)
C3	11.4(5)	21.1(6)	14.5(5)	3.8(4)	1.8(4)	1.6(4)
C4	13.1(5)	18.3(6)	15.1(5)	4.2(4)	4.2(4)	2.5(4)
C5	18.5(6)	19.0(6)	15.2(5)	0.4(5)	2.6(4)	0.4(4)
C6	23.8(6)	18.4(6)	20.7(6)	0.7(5)	7.8(5)	-1.0(5)
C14	19.8(6)	30.2(7)	22.7(6)	0.7(5)	8.1(5)	0.1(5)
C15	28.2(7)	31.7(7)	25.3(7)	-10.3(6)	0.9(5)	-9.0(5)
C16	17.7(6)	33.9(7)	24.5(7)	-1.3(5)	-3.5(5)	5.3(5)
C17	27.3(7)	22.3(7)	65.6(11)	-0.6(6)	4.3(7)	14.9(7)
C18	21.0(6)	26.1(7)	44.5(8)	5.5(5)	8.9(6)	-4.7(6)
C19	16.2(6)	16.2(6)	30.0(7)	-0.0(4)	3.0(5)	2.6(5)
C20	21.5(6)	16.3(6)	18.5(6)	1.2(5)	0.2(5)	0.5(4)
C7A	41(2)	18.4(19)	9.9(14)	8.2(13)	11.7(14)	-2.0(15)
C8A	30(2)	22.2(15)	19.0(14)	2.6(14)	10.6(13)	2.4(10)
C9A	43(2)	21.4(12)	14.9(11)	3.0(13)	5.6(13)	2.2(8)
C10A	66(3)	17.8(12)	20.5(12)	6.4(14)	9.7(14)	1.3(8)
C11A	56(4)	23.9(14)	38(2)	13(2)	30(2)	5.2(13)
C12A	39.8(19)	35.7(18)	56(2)	9.5(13)	28.6(17)	11.2(16)
C13A	36(2)	25.0(13)	39(2)	-0.1(11)	16.3(16)	0.3(14)
C7B	54(6)	29(4)	40(7)	-5(4)	6(4)	14(3)
C8B	37(5)	13(3)	29(4)	-2(3)	21(3)	-6(2)
C9B	50(5)	31(3)	24(3)	3(3)	16(3)	2.9(19)
C10B	54(6)	21(3)	25(3)	2(3)	20(4)	-2.8(18)
C11B	53(5)	18(3)	50(4)	4(3)	33(3)	2(2)

C12B	43(4)	25(3)	67(5)	-1(2)	31(3)	-4(3)
C13B	36(4)	20(3)	53(5)	-4(2)	24(3)	-5(3)

Table 4. Bond Lengths for Schomaker32 [CSA5060].

Atom	Atom	Length/Å	Atom	Atom	Length/Å
S1	O1	1.4194(10)	C6	C7A	1.569(7)
S1	O2	1.4215(9)	C6	C7B	1.423(18)
S1	O3	1.5459(9)	C16	C19	1.5351(18)
S1	N1	1.6651(10)	C17	C19	1.5357(18)
Si1	O5	1.6616(9)	C18	C19	1.5396(18)
Si1	C14	1.8556(13)	C7A	C8A	1.495(8)
Si1	C15	1.8613(13)	C8A	C9A	1.380(6)
Si1	C19	1.8786(13)	C8A	C13A	1.395(5)
O3	C1	1.4868(16)	C9A	C10A	1.389(4)
O4	C5	1.4613(14)	C10A	C11A	1.385(5)
O4	C20	1.3378(15)	C11A	C12A	1.376(6)
O5	C3	1.4172(14)	C12A	C13A	1.396(5)
O6	C20	1.2044(15)	C7B	C8B	1.57(2)
N1	C4	1.4750(14)	C8B	C9B	1.408(13)
N1	C20	1.3779(15)	C8B	C13B	1.358(12)
C1	C2	1.5064(17)	C9B	C10B	1.408(11)
C2	C3	1.5269(16)	C10B	C11B	1.366(11)
C3	C4	1.5313(16)	C11B	C12B	1.367(11)
C4	C5	1.5485(16)	C12B	C13B	1.391(11)
C5	C6	1.5127(16)			

Table 5. Bond Angles for Schomaker32 [CSA5060].

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
O2	S1	O1	119.23(6)	C6	C5	O4	109.95(10)
O3	S1	O1	106.72(5)	C6	C5	C4	114.65(10)
O3	S1	O2	111.46(5)	C16	C19	Si1	109.02(8)
N1	S1	O1	109.03(6)	C17	C19	Si1	110.79(9)
N1	S1	O2	109.29(5)	C17	C19	C16	108.28(12)
N1	S1	O3	99.25(5)	C18	C19	Si1	109.17(9)
C14	Si1	O5	109.26(5)	C18	C19	C16	109.70(10)

C15	Si1	O5	110.80(5)	C18	C19	C17	109.86(11)
C15	Si1	C14	109.77(6)	O6	C20	O4	124.12(11)
C19	Si1	O5	102.25(5)	N1	C20	O4	109.28(10)
C19	Si1	C14	111.94(6)	N1	C20	O6	126.60(12)
C19	Si1	C15	112.58(6)	C9A	C8A	C7A	122.2(4)
C1	O3	S1	119.36(8)	C13A	C8A	C7A	118.9(5)
C20	O4	C5	111.03(9)	C13A	C8A	C9A	118.7(4)
C3	O5	Si1	127.50(7)	C10A	C9A	C8A	120.9(3)
C4	N1	S1	127.52(8)	C11A	C10A	C9A	120.1(3)
C20	N1	S1	119.01(8)	C12A	C11A	C10A	119.7(3)
C20	N1	C4	113.32(9)	C13A	C12A	C11A	120.2(4)
C2	C1	O3	108.81(10)	C12A	C13A	C8A	120.4(4)
C3	C2	C1	113.72(10)	C9B	C8B	C7B	118.7(10)
C2	C3	O5	111.11(9)	C13B	C8B	C7B	122.7(10)
C4	C3	O5	106.96(9)	C13B	C8B	C9B	118.5(9)
C4	C3	C2	114.09(10)	C10B	C9B	C8B	119.7(8)
C3	C4	N1	114.36(9)	C11B	C10B	C9B	120.1(7)
C5	C4	N1	100.13(9)	C12B	C11B	C10B	119.6(7)
C5	C4	C3	111.09(9)	C13B	C12B	C11B	120.8(8)
C4	C5	O4	106.13(9)	C12B	C13B	C8B	121.1(8)

Table 6. Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for Schomaker32

Atom	*x*	*y*	*z*	U(eq)
H1a	1708.4(18)	7371.6(6)	6421.1(8)	28.4(3)
H1b	2718.5(18)	7079.2(6)	7335.5(8)	28.4(3)
H2a	-381.8(17)	7923.5(6)	7271.5(8)	25.2(3)
H2b	-671.0(17)	7213.0(6)	7363.3(8)	25.2(3)
H3	-687.3(16)	7621.2(5)	8782.6(7)	18.7(3)
H4	1259.8(16)	8524.3(5)	8521.7(8)	18.4(3)
H5	926.3(17)	7924.9(5)	10130.6(8)	21.1(3)
H6aa	1491.7(18)	9193.8(5)	9917.9(8)	24.7(3)
H6ab	-584.6(18)	8876.2(5)	9813.2(8)	24.7(3)
H6bc	1531.5(18)	9185.7(5)	9922.6(8)	24.7(3)
H6bd	-543.6(18)	8878.2(5)	9772.1(8)	24.7(3)
H14a	-2066(8)	6904(4)	9847.1(17)	35.7(4)
H14b	-1503(11)	6294.4(6)	10382(5)	35.7(4)
H14c	-306(4)	6898(4)	10629(3)	35.7(4)
H15a	-1024(14)	5643(2)	8584.0(18)	42.8(4)
H15b	-1776(9)	6259(2)	8113(5)	42.8(4)
H15c	217(5)	5970(4)	7888(3)	42.8(4)
H16a	2948(6)	6490(4)	11075(3)	38.7(4)
H16b	5020(8)	6248(2)	10876(4)	38.7(4)
H16c	4147(13)	6845.6(17)	10389.9(16)	38.7(4)

H17a	3496(4)	5260(3)	10515(7)	57.7(6)
H17b	1393(14)	5510.9(8)	10639(6)	57.7(6)
H17c	1788(16)	5194(2)	9715.4(16)	57.7(6)
H18a	4641(12)	6367.7(7)	8888(5)	45.2(5)
H18b	5462(7)	5774(4)	9402(2)	45.2(5)
H18c	3689(6)	5727(4)	8630(4)	45.2(5)
H7Aa	88(11)	8519(3)	11377(5)	27.0(12)
H7Ab	2019(11)	8912(3)	11467(5)	27.0(12)
H9A	1809(8)	9886.2(16)	12098(2)	31.4(10)
H10A	-18(11)	10663.6(14)	12621(2)	41.4(13)
H11A	-3363(11)	10672.5(17)	12274(3)	44.7(15)
H12A	-4860(7)	9914.5(18)	11378(4)	50.4(12)
H13A	-3040(7)	9118.1(18)	10887(4)	39(1)
H7Ba	120(30)	8555(9)	11294(13)	49(4)
H7Bb	1790(30)	9047(9)	11361(13)	49(4)
H9B	960(20)	9844(4)	12263(6)	41(2)
H10B	-1170(20)	10598(3)	12659(5)	39(3)
H11B	-4330(20)	10614(4)	11993(8)	46(3)
H12B	-5296(16)	9946(4)	10844(10)	51(3)
H13B	-3204(15)	9207(4)	10427(9)	42(2)

Table 7. Atomic Occupancy for Schomaker32 [CSA5060].

Atom	*Occupancy*	Atom	*Occupancy*	Atom	*Occupancy*
H6aa	0.674(14)	H6ab	0.674(14)	H6bc	0.326(14)
H6bd	0.326(14)	C7A	0.674(14)	H7Aa	0.674(14)
H7Ab	0.674(14)	C8A	0.674(14)	C9A	0.674(14)
H9A	0.674(14)	C10A	0.674(14)	H10A	0.674(14)
C11A	0.674(14)	H11A	0.674(14)	C12A	0.674(14)
H12A	0.674(14)	C13A	0.674(14)	H13A	0.674(14)
C7B	0.326(14)	H7Ba	0.326(14)	H7Bb	0.326(14)
C8B	0.326(14)	C9B	0.326(14)	H9B	0.326(14)
C10B	0.326(14)	H10B	0.326(14)	C11B	0.326(14)
H11B	0.326(14)	C12B	0.326(14)	H12B	0.326(14)
C13B	0.326(14)	H13B	0.326(14)		

References:

[1] BRUKER-AXS. (2007-2013), APEX2 (Ver. 2013.2-0), SADABS (2012-1)

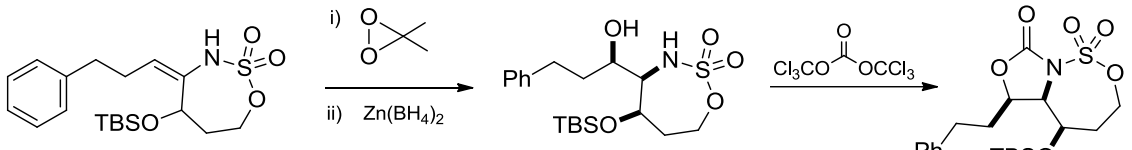
[2] SAINT+ (Ver. 8.30C) Software Reference Manuals, BRUKER-AXS, Madison, Wisconsin, USA.

[3] G. M. Sheldrick, *Acta Cryst.*, **2008**, *A64*, 112-122.

[4] O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. L. Howard, H. Puschmann, *J. Appl. Cryst.* **2009**, *42*, 339-341.

[5] XP – X-Ray Crystal Structure Visualization BRUKER, AXS, **1998**, V5.1

Crystal Structure of Schomaker31 [CSA5062]



[26] [CSA5062]

Preparation of Crystals: The racemic compound (CSA5062) was dissolved in acetonitrile and crystallized by slow evaporation at 7 °C. The obtained air-stable crystals were selected under microscope.

Data Collection: A colorless crystal with approximate dimensions 0.032 x 0.125 x 0.403 mm^3 (block) with a mosaicity of 0.68 was selected under oil under ambient conditions and attached to the tip of a X-ray capillary (MiTeGenMicroMount©). The crystal was mounted in a stream of cold nitrogen at 100.0(15) K and centered in the X-ray beam by using a video camera. The crystal evaluation and data collection were performed on a three-circle Bruker Quazar SMART APEXII ("GROMIT") diffractometer with Molybdenum K_a(λ = 0.71073 Å) radiation and the diffractometer to crystal distance of 4.96 cm. The initial cell constants were obtained from three series of ω scans at different starting angles. Each series consisted of 12 frames collected at intervals of 0.5° in 6° range about ω with the exposure time of 10 seconds per frame. The reflections were successfully indexed by an automated indexing routine built in the APEXII program suite. The final cell constants were calculated from a set of 9196 strong from the actual data collection. The data were collected by using the full sphere data collection routine to survey the reciprocal space to the extent of a full sphere to a resolution of 0.70 Å. A total of 27764 reflection data were harvested by collecting 6 sets of frames with 0.6° scans in ω and ϕ with exposure times of 20 sec per frame. These highly redundant datasets were corrected for Lorentz and polarization effects. The absorption correction was based on fitting a function to the empirical transmission surface as sampled by multiple equivalent measurements. [6,7]

Structure Solution and Refinement: The systematic absences in the diffraction data were consistent for the triclinic space groups P1 and $P\bar{1}$. The R_{int}-value was 0.043 and suggested a successful structure refinement. The *E*-statistics strongly suggested the centrosymmetric space group that yielded chemically reasonable and computationally stable results of refinement. [8] A successful solution by the "direct methods" by using SHELX-2013 [9] provided most non-hydrogen atoms from the *E*-map. Using Olex2, [10] all non-hydrogen atoms were refined with anisotropic displacement coefficients. All hydrogen atoms were included in the structure factor calculation at idealized positions and were allowed to ride on the neighboring atoms with relative isotropic displacement coefficients.

Table 8. Crystal data collection and structure solution refinement for Schomaker31 [CSA5062]

Parameter	CSA5062	Parameter	CSA5062
empiric formula	$C_{20}H_{31}NO_6SSi$	$\rho_{calc.}$ [g · cm^{-1}]	1.46
MW [g · mol^{-1}]	441.61	crystal size [mm]	0.032 x 0.125 x 0.403
X-ray lab code	Schomaker31	T [K]	100.0(15)
a [Å]	7.2477(28)	radiation type / λ [nm]	Mo K_α / 0.71072
b [Å]	12.2307(40)	μ [mm^{-1}]	0.230
c [Å]	12.4387(41)	F(000)	911.8
α [°]	87.0850(13)	Reflections collected	27763
β [°]	81.980(7)	Independent reflections	5586 [R_{int} = 0.041]
γ [°]	89.975(11)	Data/restraints/parameters	5586/0/262
V [Å^3]	1091.06(14)	GooF on F^2	1.047
Z	2	Largest diff. peak/hole [eÅ^{-3}]	0.76 / -0.22
crystal system	triclinic		
crystal color	colorless	Final R_1[a]/ wR_2[b] all data	0.0424/ 0.0879
space group	$P\bar{1}$	Final R_1[a]/ wR_2[b] I>2s(I)	0.0341/ 0.0830

[a] $R_1 = \sum | F_o | - | F_c | / | F_o |$; [b] $wR_2 = [\sum\{w(F_o^2 - F_o^2)^2\} / \sum\{w(F_o^2)^2\}]^{1/2}$

The final least-squares refinement of 262 parameters against 5586 data resulted in R = 0.0341 (based on F^2 for I>2s) and wR2 = 0.0879 (based on F^2 for all data), respectively. The final structure was visualized using Interactive Molecular Graphics. [5]

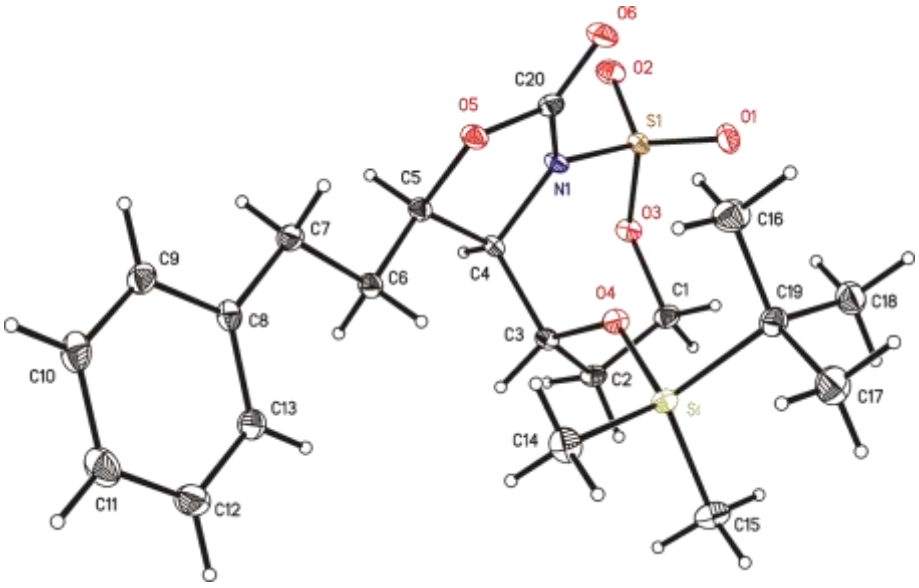


Figure 2. Thermal-ellipsoid of Schomaker31 [CSA5062] are set with 50 % probability

Table 9. Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) for Schomaker31 [CSA5062]. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
S1	7915.6(4)	9368.8(3)	1494.0(3)	10.60(8)
Si	11637.2(5)	7514.7(3)	4206.1(3)	10.91(9)
O4	10953.6(13)	7902.7(8)	3028.7(8)	11.56(19)
O6	6323.1(13)	7137.6(8)	2019.4(9)	15.8(2)
O2	6924.9(14)	9582.3(9)	600.6(9)	16.2(2)
O5	9088.0(13)	6349.5(8)	1498.5(8)	12.9(2)
N1	8952.9(15)	8160.5(9)	1346.1(9)	10.3(2)
O3	9651.2(13)	10130.6(8)	1306.5(8)	12.4(2)
O1	6968.2(14)	9432.3(8)	2569.7(8)	15.9(2)
C6	12406.6(18)	6000.0(11)	1188.9(11)	11.9(3)
C2	12472.7(18)	9480.7(11)	2010.1(11)	11.6(3)
C20	7948.5(18)	7210.0(11)	1667.9(11)	11.4(3)
C7	12127.6(19)	4807.9(11)	914.9(12)	13.5(3)
C14	12909(2)	6193.3(12)	4102.9(12)	17.3(3)
C4	10974.2(17)	7951.4(11)	1104.5(11)	9.7(2)
C3	12037.3(18)	8255.0(11)	2038.0(11)	10.0(2)
C8	13638.1(19)	4034.8(11)	1193.5(11)	12.1(3)
C10	14877(2)	2189.2(12)	1189.1(13)	17.5(3)
C19	9360(2)	7380.2(12)	5140.9(11)	14.2(3)
C5	10864.4(18)	6721.0(11)	881.7(11)	10.9(3)
C13	15122(2)	4366.7(12)	1703.9(12)	15.1(3)
C1	10797.9(19)	10211.6(11)	2202.3(12)	13.7(3)
C9	13542(2)	2931.6(11)	938.4(12)	14.3(3)
C11	16334(2)	2529.4(13)	1713.3(13)	20.6(3)
C18	8429(2)	8503.7(13)	5270.1(13)	19.0(3)
C17	9715(2)	6926.1(14)	6264.0(12)	21.0(3)
C15	13223(2)	8539.2(13)	4669.3(13)	19.0(3)
C16	8035(2)	6604.7(13)	4677.1(13)	20.6(3)
C12	16452(2)	3620.9(13)	1965.7(13)	19.9(3)

Table 10. Anisotropic Displacement Parameters (Å^2×10^3) for Schomaker31 [CSA5062].
The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+...+2hka\times b\times U_{12}]$

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
S1	8.49(15)	10.62(15)	12.50(16)	0.18(12)	-0.92(11)	1.67(11)
Si	11.65(17)	10.54(18)	10.84(18)	0.41(14)	-2.86(13)	-0.93(13)
O4	11.7(4)	12.5(5)	10.3(5)	1.7(4)	-1.3(3)	-2.1(3)
O6	9.2(4)	16.5(5)	21.5(5)	-0.2(4)	-1.5(4)	-1.8(4)
O2	13.4(5)	17.7(5)	18.1(5)	2.3(4)	-5.8(4)	2.7(4)

O5	9.5(4)	10.5(5)	18.5(5)	-1.5(4)	-0.9(4)	-1.1(3)
N1	6.6(5)	9.3(5)	15.1(6)	-0.2(4)	-1.5(4)	1.1(4)
O3	11.8(4)	11.0(5)	14.3(5)	1.9(4)	-2.4(4)	-0.8(3)
O1	14.5(5)	16.4(5)	15.7(5)	-2.6(4)	2.5(4)	0.8(4)
C6	11.0(6)	10.0(6)	14.8(7)	-1.6(5)	-2.3(5)	1.2(5)
C2	11.0(6)	9.8(6)	14.4(7)	0.6(5)	-3.4(5)	-2.5(5)
C20	11.7(6)	11.3(6)	11.8(6)	-0.3(5)	-4.3(5)	-0.2(5)
C7	13.2(6)	10.4(6)	17.5(7)	-2.9(5)	-3.8(5)	0.2(5)
C14	19.5(7)	15.5(7)	16.4(7)	2.5(6)	-1.9(5)	2.5(5)
C4	7.2(6)	10.5(6)	11.0(6)	-0.4(5)	-0.5(4)	1.3(4)
C3	8.3(6)	10.3(6)	11.1(6)	0.8(5)	-1.0(5)	-0.6(4)
C8	13.0(6)	10.8(6)	11.8(6)	-0.4(5)	1.3(5)	0.6(5)
C10	20.9(7)	9.0(6)	21.5(8)	-1.3(5)	1.1(6)	0.4(5)
C19	14.8(6)	17.0(7)	10.5(6)	0.6(5)	-1.7(5)	-0.6(5)
C5	9.5(6)	10.5(6)	12.5(6)	-1.1(5)	-0.5(5)	-0.6(5)
C13	15.3(6)	11.6(6)	19.0(7)	-3.2(5)	-3.4(5)	1.4(5)
C1	14.5(6)	11.1(6)	16.1(7)	-1.8(5)	-4.7(5)	-0.8(5)
C9	15.0(6)	11.4(6)	16.3(7)	-2.2(5)	-0.8(5)	-2.4(5)
C11	19.6(7)	15.6(7)	26.7(8)	0.4(6)	-3.7(6)	5.9(6)
C18	17.6(7)	21.3(7)	17.8(7)	-1.8(6)	-1.6(5)	3.7(6)
C17	22.4(8)	26.8(8)	13.3(7)	3.5(6)	-1.8(6)	2.1(6)
C15	18.3(7)	19.5(7)	20.5(8)	-0.7(6)	-8.0(6)	-3.8(6)
C16	18.3(7)	23.4(8)	19.7(8)	1.7(6)	-1.9(6)	-7.0(6)
C12	17.0(7)	18.1(7)	26.2(8)	-3.0(6)	-7.7(6)	2.8(6)

Table 11. Bond Lengths for Schomaker31 CSA5062].

Atom	Atom	Length/Å	Atom	Atom	Length/Å
S1	O2	1.4210(11)	C6	C5	1.5053(19)
S1	N1	1.6626(12)	C2	C3	1.5303(19)
S1	O3	1.5517(11)	C2	C1	1.5046(19)
S1	O1	1.4210(11)	C7	C8	1.5143(19)
Si	O4	1.6630(11)	C4	C3	1.5369(19)
Si	C14	1.8599(16)	C4	C5	1.5445(19)
Si	C19	1.8853(16)	C8	C13	1.391(2)
Si	C15	1.8610(16)	C8	C9	1.4016(19)
O4	C3	1.4183(16)	C10	C9	1.386(2)
O6	C20	1.2001(17)	C10	C11	1.388(2)
O5	C20	1.3421(16)	C19	C18	1.534(2)
O5	C5	1.4668(16)	C19	C17	1.539(2)
N1	C20	1.3878(18)	C19	C16	1.533(2)
N1	C4	1.4780(17)	C13	C12	1.390(2)
O3	C1	1.4861(17)	C11	C12	1.388(2)
C6	C7	1.5296(19)			

Table 12. Bond Angles for Schomaker31 [CSA5062].

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
O2	S1	N1	108.74(6)	N1	C4	C3	112.65(11)
O2	S1	O3	106.16(6)	N1	C4	C5	97.98(10)
O3	S1	N1	99.80(6)	C3	C4	C5	116.37(11)
O1	S1	O2	119.40(7)	O4	C3	C2	111.89(11)
O1	S1	N1	109.62(6)	O4	C3	C4	107.88(10)
O1	S1	O3	111.28(6)	C2	C3	C4	111.77(11)
O4	Si	C14	111.39(6)	C13	C8	C7	122.93(12)
O4	Si	C19	102.46(6)	C13	C8	C9	118.01(13)
O4	Si	C15	111.85(6)	C9	C8	C7	119.06(13)
C14	Si	C19	111.67(7)	C9	C10	C11	120.07(14)
C14	Si	C15	107.27(8)	C18	C19	Si	109.93(10)
C15	Si	C19	112.27(7)	C18	C19	C17	109.01(12)
C3	O4	Si	129.47(9)	C17	C19	Si	109.70(10)
C20	O5	C5	109.18(10)	C16	C19	Si	110.45(10)
C20	N1	S1	119.71(9)	C16	C19	C18	108.63(13)
C20	N1	C4	112.01(11)	C16	C19	C17	109.10(13)
C4	N1	S1	127.12(9)	O5	C5	C6	109.20(11)
C1	O3	S1	118.07(9)	O5	C5	C4	104.76(10)
C5	C6	C7	111.81(11)	C6	C5	C4	117.45(11)
C1	C2	C3	115.10(11)	C12	C13	C8	120.82(13)
O6	C20	O5	124.10(13)	O3	C1	C2	110.32(11)
O6	C20	N1	127.14(13)	C10	C9	C8	121.25(14)
O5	C20	N1	108.75(11)	C10	C11	C12	119.31(14)
C8	C7	C6	114.75(12)	C11	C12	C13	120.53(14)

Table 13. Torsion Angles for Schomaker31 [CSA5062].

A	B	C	D	Angle/°	A	B	C	D	Angle/°
S1	N1	C20	O6	3.3(2)	C7	C6	C5	C4	-179.53(11)
S1	N1	C20	O5	-178.25(9)	C7	C8	C13	C12	178.51(14)
S1	N1	C4	C3	66.76(15)	C7	C8	C9	C10	-179.17(13)
S1	N1	C4	C5	-170.25(10)	C14	Si	O4	C3	-68.43(12)
S1	O3	C1	C2	98.53(12)	C14	Si	C19	C18	175.74(10)
Si	O4	C3	C2	-85.52(13)	C14	Si	C19	C17	55.88(12)
Si	O4	C3	C4	151.15(9)	C14	Si	C19	C16	-64.41(12)
O4	Si	C19	C18	-64.94(11)	C4	N1	C20	O6	171.82(14)
O4	Si	C19	C17	175.21(10)	C4	N1	C20	O5	-9.71(15)
O4	Si	C19	C16	54.92(11)	C3	C2	C1	O3	-65.04(15)
O2	S1	N1	C20	-82.42(12)	C3	C4	C5	O5	94.42(13)
O2	S1	N1	C4	110.93(12)	C3	C4	C5	C6	-26.92(16)
O2	S1	O3	C1	170.64(9)	C8	C13	C12	C11	0.6(2)

N1	S1	O3	C1	-76.43(10)	C10	C11	C12	C13	0.4(2)
N1	C4	C3	O4	41.40(14)	C19	Si	O4	C3	172.05(11)
N1	C4	C3	C2	-82.01(13)	C5	O5	C20	O6	169.53(13)
N1	C4	C5	O5	-25.82(12)	C5	O5	C20	N1	-9.00(14)
N1	C4	C5	C6	-147.15(12)	C5	C6	C7	C8	179.51(11)
O3	S1	N1	C20	166.67(11)	C5	C4	C3	O4	-70.60(13)
O3	S1	N1	C4	0.02(12)	C5	C4	C3	C2	165.98(11)
O1	S1	N1	C20	49.75(12)	C13	C8	C9	C10	0.3(2)
O1	S1	N1	C4	-116.89(12)	C1	C2	C3	O4	-55.99(15)
O1	S1	O3	C1	39.23(11)	C1	C2	C3	C4	65.12(15)
C6	C7	C8	C13	2.8(2)	C9	C8	C13	C12	-0.9(2)
C6	C7	C8	C9	-177.78(12)	C9	C10	C11	C12	-1.0(2)
C20	O5	C5	C6	149.62(11)	C11	C10	C9	C8	0.7(2)
C20	O5	C5	C4	23.00(14)	C15	Si	O4	C3	51.60(13)
C20	N1	C4	C3	-100.75(13)	C15	Si	C19	C18	55.22(12)
C20	N1	C4	C5	22.24(14)	C15	Si	C19	C17	-64.64(12)
C7	C6	C5	O5	61.46(14)	C15	Si	C19	C16	175.08(10)

Table 14. Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for Schomaker31

Atom	*x*	*y*	*z*	U(eq)
H6A	12453	6041	1962	14
H6B	13589	6265	806	14
H2A	13270	9615	2557	14
H2B	13170	9683	1307	14
H7A	10942	4552	1300	16
H7B	12059	4778	143	16
H14A	12127	5644	3866	26
H14B	13235	5974	4801	26
H14C	14022	6280	3589	26
H4	11492	8358	437	12
H3	13217	7855	1964	12
H10	14796	1462	1006	21
H5	10797	6646	107	13
H13	15225	5097	1872	18
H1A	10054	9999	2888	16
H1B	11202	10963	2245	16
H9	12564	2693	594	17
H11	17221	2031	1894	25
H18A	9246	8998	5559	28
H18B	7282	8431	5757	28
H18C	8177	8785	4575	28
H17A	10296	6222	6189	31
H17B	8552	6854	6736	31
H17C	10519	7418	6567	31
H15A	12608	9234	4731	28

H15B	14334	8609	4152	28
H15C	13545	8303	5364	28
H16A	8602	5898	4592	31
H16B	7785	6893	3983	31
H16C	6888	6538	5165	31
H12	17430	3855	2313	24

References:

[6] BRUKER-AXS. (2007-2013) APEX2 (Ver. 2013.2-0), SADABS (2012-1)

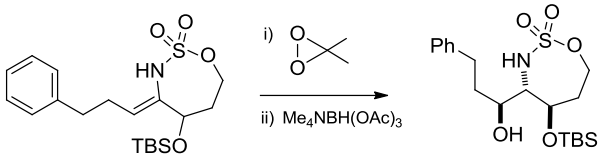
[7] SAINT+ (Ver. 8.30C) Software Reference Manuals, BRUKER-AXS, Madison, Wisconsin, USA.

[8] G. M. Sheldrick, *Acta Cryst.*, 2008, *A64*, 112-122.

[9] O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. L. Howard, H. Puschmann, *J. Appl. Cryst.* 2009, *42*, 339-341.

[10] XP – X-Ray Crystal Structure Visualization BRUKER, AXS, 1998, V5.1

Crystal Structure of Schomaker30 [CSA4199]



[41] = [CSA4199]

Preparation of Crystals: The racemic compound (CSA4199) was dissolved in a mixture n-hexane / ethyl acetate and crystallized at room temperature by slow vapor diffusion. The obtained crystals were air-stable and selected under microscope.

Data Collection: A colorless crystal with approximate dimensions 0.229 x 0.157 x 0.129 mm^3 (block) was selected under oil under ambient conditions and attached to the tip of a X-ray capillary (MiTeGenMicroMount©). The crystal was mounted in a stream of cold nitrogen at 200.0(15) K and centered in the X-ray beam by using a video camera. The crystal evaluation and data collection were performed on a three-circle Bruker Quazar SMART APEXII diffractometer with Molybdenum K_α(λ = 0.71073 Å) radiation and the diffractometer to crystal distance of 4.96 cm. The initial cell constants were obtained from three series of ω scans at different starting angles. Each series consisted of 12 frames collected at intervals of 0.5° in 6° range about ω with the exposure time of 10 seconds per frame. The reflections were successfully indexed by an automated indexing routine built in the APEXII program suite. The final cell constants were calculated from a set of 9172 strong from the actual data collection. The data were collected by using the full sphere data collection routine to survey the reciprocal space to the extent of a full sphere to a resolution of 0.70 Å. A total of 54259 reflection data were harvested by collecting 6 sets of frames with 0.6° scans in ω and ϕ with exposure times of 25 sec per frame. These highly redundant datasets were corrected for Lorentz and polarization effects. The absorption correction was based on fitting a function to the empirical transmission surface as sampled by multiple equivalent measurements. [11,12]

Structure Solution and Refinement: The systematic absences in the diffraction data were consistent for the triclinic space groups P1 and $P\bar{1}$. The *E*-statistics strongly suggested the centrosymmetric space group that yielded chemically reasonable and computationally stable results of refinement. [13,14] A successful solution by the "direct methods" by using SHELX-2013 provided most non-hydrogen atoms from the *E*-map. Using Olex2, all non-hydrogen atoms were refined with anisotropic displacement coefficients. All hydrogen atoms were included in the structure factor calculation at idealized positions and were allowed to ride on the neighboring atoms with relative isotropic displacement coefficients. The severe disorder in the TBS-protecting group (Si1A) in the second molecule of the unit was modeled with 3 components in A:B:C in three ways with restraints and constraints. Crystal diffraction data outlier elimination was carried out using "G4 - FCF filter". [16]

Table 16. Crystal data collection and structure solution refinement for Schomaker30 [CSA4099]

Parameter	CSA4099	Parameter	CSA4099
empiric formula	$C_{19}H_{33}NO_5SSi$	$\rho_{calc.}$ [g · cm^{-1}]	1.204
MW [g · mol^{-1}]	416.12	crystal size [mm]	0.229 × 0.157 × 0.129
X-ray lab code	Schomaker30	T [K]	200.0(15)
a [Å]	11.8101(17)	radiation type / λ [nm]	Mo K_α / 0.71072
b [Å]	12.7217(17)	μ [mm^{-1}]	0.220
c [Å]	16.841(2)	F(000)	898.0
α [°]	72.829(6)	Reflections collected	54072
β [°]	75.377(7)	Independent reflections	11307 [R_{int} = 0.0266]
γ [°]	75.493(6)	Data/restraints/parameters	11307/379/646
V [Å^3]	2296.4(6)	GooF on F^2	1.022
Z	2	Largest diff. peak/hole [eÅ^{-3}]	0.34 / -0.31
crystal system	triclinic		
crystal color	colorless	Final R_1[a]/ wR_2[b] all data	0.0433/ 0.1006
space group	$P\bar{1}$	Final R_1[a]/ wR_2[b] I>2s(I)	0.0367/ 0.0956

[a] $R_1 = \sum \left| F_o \right| - \left| F_c \right| / \left| F_o \right|$; [b] $wR_2 = [\sum\{w(F_o^2 - F_o^2)^2\} / \sum\{w(F_o^2)^2\}]^{1/2}$

The final least-squares refinement of 646 parameters against 11307 data resulted in R = 0.0357 (based on F^2 for I>2s) and wR2 = 0.01006 (based on F^2 for all data), respectively. The final structure was visualized using Interactive Molecular Graphics. [15]

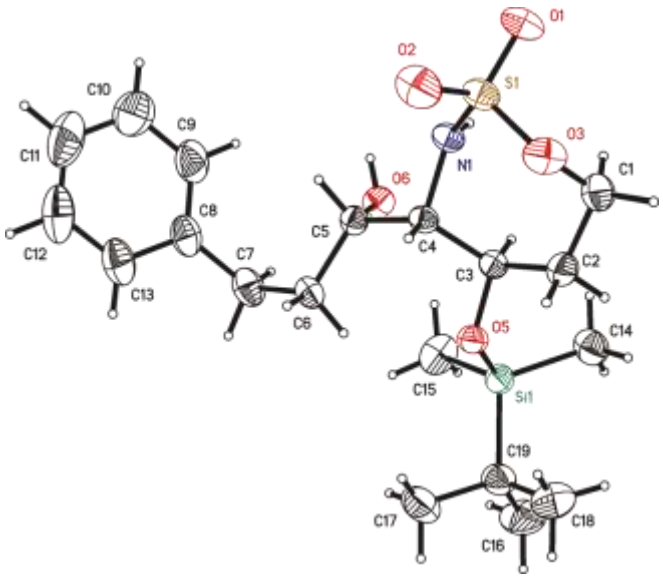


Figure 3. Thermal-ellipsoid of Schomaker30 [CSA4199] are set with 50 % probability

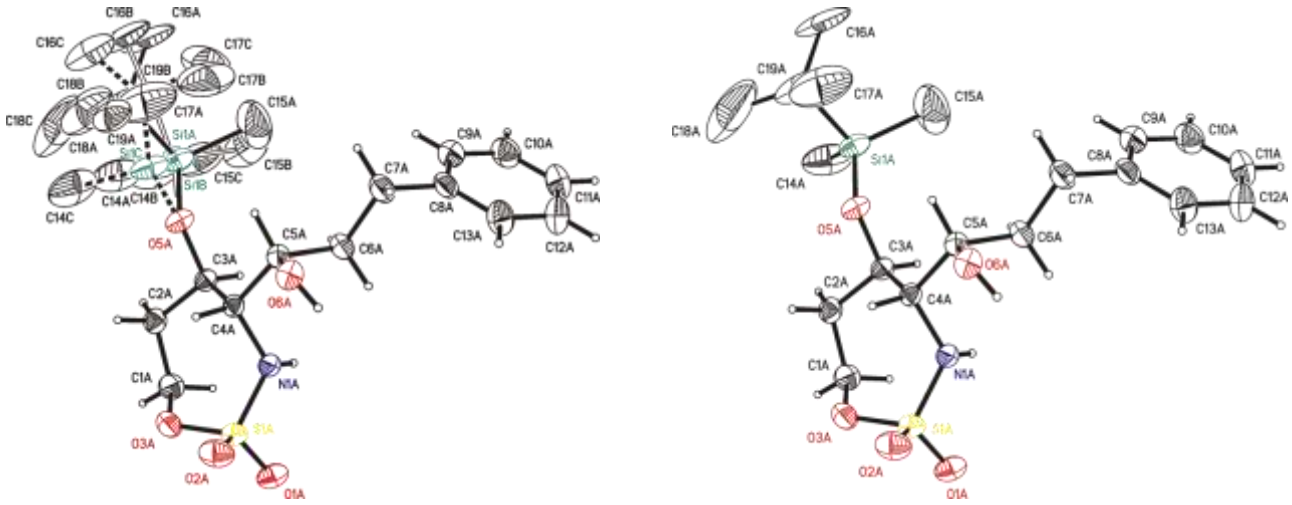


Figure 4. Thermal-ellipsoid of the disordered molecule (left) of Schomaker30 [CSA4199] are set with 50 % probability. The disorder parts Si1B and Si1C of the protecting group were omitted for more clarity (right).

Table 17. Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for Schomaker30 [CSA4099]. U_{eq} is defined as 1/3 of of the trace of the orthogonalized U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
Si1	1272.6(3)	-775.7(3)	6990.2(2)	31.60(9)
O3	4474.8(9)	2308.5(9)	5170.4(7)	40.0(2)
C14	885.7(16)	-497.0(14)	5927.4(10)	46.4(4)
C15	-100.0(15)	-304.2(16)	7722.9(12)	51.4(4)
C16	1064(2)	-3034.4(16)	7459.9(15)	63.7(5)
C17	2258(2)	-2484.4(16)	8252.1(12)	62.2(5)
C18	3101.0(19)	-2616.6(16)	6764.7(14)	60.6(5)
C19	1951.1(15)	-2290.8(12)	7383.3(10)	41.0(3)
S1	3771.1(3)	3314.2(3)	5568.2(2)	31.29(8)
O1	3343.6(9)	4237.2(8)	4922.7(7)	39.9(2)
O2	4571.2(10)	3446.6(10)	6018.4(8)	48.6(3)
O5	2333.7(8)	-86.6(7)	6921.9(6)	30.19(19)
O6	672.0(8)	2214.9(8)	7471.1(6)	32.3(2)
N1	2627.6(10)	2884.6(9)	6198.0(7)	27.9(2)
C1	3753.8(15)	1750.6(13)	4891.5(9)	40.9(3)
C2	3413.5(14)	754.2(12)	5591.0(9)	35.8(3)

C3	2442.2(11)	977(1)	6352.9(8)	27.0(2)
C4	2717.4(11)	1762.1(10)	6796.7(8)	25.2(2)
C5	1859.5(11)	1929(1)	7622.5(8)	26.9(2)
C6	1956.5(13)	947.8(12)	8400.6(8)	33.3(3)
C7	1030.9(15)	1178.0(15)	9185.0(9)	44.1(4)
C8	1206.6(14)	2084.5(15)	9528.2(9)	42.9(3)
C9	825.3(18)	3213.3(17)	9178.6(11)	56.1(5)
C10	1030(2)	4032(2)	9490.2(14)	75.4(7)
C11	1595(2)	3733(2)	10168.7(15)	79.8(7)
C12	1956(2)	2628(2)	10531.7(13)	71.2(6)
C13	1778.7(17)	1809.1(19)	10212.1(11)	55.5(4)
Si1A	-4337(14)	3095(10)	8474(9)	35.0(14)
C14A	-5584(9)	2685(12)	8236(6)	76(3)
C15A	-4898(12)	4542(8)	8601(10)	109(5)
C16A	-4942(14)	2700(12)	10184(7)	102(4)
C17A	-2702(10)	2458(14)	9548(6)	102(3)
C18A	-3752(15)	980(9)	9475(9)	172(7)
C19A	-3913(10)	2194(10)	9508(7)	84(3)
S1A	-614.2(3)	3519.6(3)	5111.43(19)	26.89(8)
O1A	-807.0(9)	4180.9(9)	4292.0(6)	35.7(2)
O2A	577.3(9)	3083.9(9)	5240.9(6)	38.5(2)
O3A	-1183.5(9)	2452.1(8)	5348.9(6)	34.9(2)
O5A	-3116.6(8)	2962.4(8)	7798.9(5)	30.48(19)
O6A	-309.5(8)	4452.0(7)	7155.7(6)	28.57(19)
N1A	-1353.6(10)	4244.0(8)	5772.6(6)	23.7(2)
C1A	-2496.1(13)	2623.7(11)	5569.3(8)	32.3(3)
C2A	-2892.2(12)	2420.4(10)	6517.7(8)	28.4(3)
C3A	-2872.6(11)	3359.1(10)	6905.6(7)	23.5(2)
C4A	-1645.5(10)	3693.5(9)	6680.9(7)	21.4(2)
C5A	-1537.7(11)	4453.2(9)	7206.6(7)	23.4(2)
C6A	-2236.7(12)	5644.5(10)	6969.8(8)	27.2(2)
C7A	-2275.7(14)	6319.8(11)	7596.8(9)	34.9(3)
C8A	-2840.9(13)	7534.9(11)	7303.4(8)	31.2(3)
C9A	-4055.4(14)	7913.8(12)	7516.5(10)	39.5(3)
C10A	-4565.2(15)	9030.9(13)	7234.4(11)	44.6(4)
C11A	-3858.4(15)	9782.8(12)	6727.4(11)	44.5(4)
C12A	-2650.5(15)	9419.0(13)	6497.5(12)	46.3(4)
C13A	-2143.6(14)	8300.3(12)	6780.9(11)	40.4(3)
Si1B	-4409(10)	3011(7)	8510(7)	32.2(11)
C14B	-5217(8)	2005(10)	8403(5)	84(3)
C15B	-5307(8)	4426(8)	8243(5)	98(4)
C16B	-4873(10)	2279(11)	10303(6)	99(3)
C17B	-3277(10)	3535(9)	9559(4)	102(3)
C18B	-3015(10)	1477(9)	9626(5)	112(3)
C19B	-3873(8)	2609(7)	9514(6)	56.2(16)
Si1C	-4274(4)	2560(5)	8498(2)	46.7(10)

C14C	-4455(15)	1151(12)	8498(8)	107(5)
C15C	-5622(8)	3570(14)	8250(6)	90(4)
C16C	-4570(12)	1652(13)	10258(7)	89(3)
C17C	-4095(14)	3628(10)	9697(8)	93(3)
C18C	-2556(9)	1878(9)	9512(7)	54(2)
C19C	-3865(14)	2481(12)	9517(8)	73(3)

Table 18. Anisotropic Displacement Parameters ($Å^2 \times 10^3$) for Schomaker30 [CSA4099]. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+...+2hka \times b \times U_{12}]$

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
Si1	34.4(2)	31.44(18)	31.23(18)	-6.90(14)	-8.06(15)	-9.67(14)
O3	26.8(5)	37.1(5)	47.3(6)	-6.1(4)	0.3(4)	-3.0(4)
C14	54(1)	48.9(9)	44.4(8)	-5.9(7)	-21.1(7)	-19.0(7)
C15	38.2(9)	59.5(10)	60.5(10)	-24.2(8)	2.5(7)	-17.6(7)
C16	77.2(14)	41.3(9)	81.2(14)	-5.3(9)	-27.2(11)	-26.4(9)
C17	89.2(15)	49.8(10)	50(1)	2.1(8)	-34.7(10)	-13.4(10)
C18	63.9(12)	44.3(9)	68.6(12)	-16.9(9)	-15.3(10)	4.9(8)
C19	51.6(9)	33.4(7)	41.4(8)	-4.4(6)	-15.7(7)	-13.0(6)
S1	25.66(16)	30.04(16)	34.81(17)	0.34(12)	-9.95(13)	-5.20(12)
O1	34.5(5)	34.5(5)	41.1(6)	6.6(4)	-10.3(4)	-5.5(4)
O2	40.9(6)	55.1(7)	54.2(7)	-1.2(5)	-21.5(5)	-19.4(5)
O5	33.3(5)	26.8(4)	31.0(5)	-4.4(3)	-9.1(4)	-6.9(4)
O6	24.5(5)	33.4(5)	38.7(5)	-9.8(4)	-9.7(4)	-0.1(4)
N1	24.4(6)	26.7(5)	29.7(5)	-2.2(4)	-8.8(4)	-2.0(4)
C1	46.2(9)	41.8(8)	30.3(7)	-10.0(6)	1.4(6)	-8.0(6)
C2	40.2(8)	33.6(7)	32.0(7)	-11.5(5)	-1.4(6)	-5.7(6)
C3	28.1(6)	26.2(6)	26.2(6)	-5.2(4)	-7.3(5)	-3.5(5)
C4	23.4(6)	24.3(5)	26.9(6)	-3.7(4)	-8.8(5)	-1.8(4)
C5	25.0(6)	28.7(6)	27.5(6)	-7.5(5)	-7.7(5)	-2.8(5)
C6	37.4(7)	34.9(7)	26.9(6)	-4.4(5)	-10.0(5)	-5.6(5)
C7	43.2(9)	56.3(9)	30.1(7)	-4.7(6)	-2.9(6)	-16.0(7)
C8	38.0(8)	61(1)	25.4(6)	-13.3(6)	3.9(6)	-8.7(7)
C9	61.4(11)	64.1(11)	36.8(8)	-21.9(8)	-4.7(8)	4.9(9)
C10	99.2(18)	64.5(13)	55.3(12)	-30.8(10)	1.7(11)	-0.4(12)
C11	93.3(18)	98.3(19)	61.5(13)	-50.4(13)	0.4(12)	-21.5(14)
C12	67.6(14)	111.3(19)	45.4(10)	-40.6(12)	-8.2(9)	-13.7(13)
C13	55.3(11)	77.5(13)	31.6(8)	-16.3(8)	-5.1(7)	-8.9(9)
Si1A	28(2)	49(3)	24.7(18)	-3.3(17)	-0.7(15)	-12.8(18)
C14A	50(5)	139(8)	52(4)	-28(6)	4(3)	-51(6)
C15A	88(8)	58(5)	148(12)	-39(6)	43(7)	-5(5)
C16A	110(6)	144(8)	18(4)	10(5)	6(4)	-17(6)
C17A	85(5)	165(8)	49(4)	-5(6)	-39(4)	-12(6)
C18A	156(10)	129(9)	124(9)	72(7)	0(8)	16(8)
C19A	56(4)	125(6)	32(3)	13(4)	1(3)	2(4)
S1A	25.76(16)	31.28(15)	23.00(14)	-7.96(11)	-3.14(11)	-4.41(11)

O1A	36.5(5)	47.1(6)	23.0(4)	-5.3(4)	-4.9(4)	-11.8(4)
O2A	26.0(5)	50.1(6)	36.7(5)	-14.4(4)	-4.9(4)	0.8(4)
O3A	38.0(5)	29.5(5)	37.8(5)	-14.7(4)	-1.1(4)	-6.2(4)
O5A	30.4(5)	39.1(5)	21.6(4)	-3.1(4)	-3.5(3)	-12.8(4)
O6A	26.2(5)	29.4(4)	31.4(5)	-3.6(3)	-11.2(4)	-6.8(3)
N1A	25.7(5)	22.0(5)	21.5(5)	-3.6(4)	-5.0(4)	-3.1(4)
C1A	36.8(7)	34.3(6)	31.9(6)	-11.6(5)	-6.5(5)	-13.4(5)
C2A	31.0(7)	27.1(6)	29.7(6)	-6.0(5)	-6.8(5)	-10.5(5)
C3A	24.3(6)	24.9(5)	21.2(5)	-3.9(4)	-5.8(4)	-5.3(4)
C4A	23.1(6)	19.9(5)	20.4(5)	-3.1(4)	-5.8(4)	-3.3(4)
C5A	24.1(6)	23.3(5)	23.7(5)	-5.4(4)	-6.6(4)	-4.5(4)
C6A	29.5(6)	23.9(5)	30.2(6)	-9.5(5)	-9.6(5)	-1.8(5)
C7A	48.5(8)	26.5(6)	33.8(7)	-11.2(5)	-14.8(6)	-2.8(5)
C8A	41.5(8)	26.8(6)	30.9(6)	-13.1(5)	-11.2(5)	-4.8(5)
C9A	43.3(8)	35.5(7)	38.0(7)	-11.4(6)	-0.6(6)	-9.0(6)
C10A	38.3(8)	39.3(8)	53.3(9)	-18.5(7)	-3.4(7)	0.9(6)
C11A	49.1(9)	27.4(6)	61.2(10)	-14.1(6)	-19.4(8)	-2.1(6)
C12A	48.1(9)	31.0(7)	62.2(10)	-5.9(7)	-14.9(8)	-14.4(6)
C13A	34.3(8)	33.1(7)	56.1(9)	-12.3(6)	-11.1(7)	-7.0(6)
Si1B	27.2(16)	39(2)	26.4(15)	-2.1(14)	0.1(11)	-11.6(14)
C14B	78(6)	138(7)	58(4)	-28(5)	15(4)	-82(5)
C15B	71(6)	92(6)	70(4)	5(4)	10(3)	42(5)
C16B	90(5)	134(8)	25(4)	21(5)	9(3)	-6(6)
C17B	129(6)	157(6)	47(3)	-30(4)	-16(4)	-73(5)
C18B	94(6)	125(7)	69(4)	30(4)	-24(4)	11(5)
C19B	57(3)	92(4)	22(2)	-6(2)	-6(2)	-29(3)
Si1C	41.7(16)	77(3)	24.0(9)	-8.6(16)	0.5(9)	-28.5(19)
C14C	156(12)	129(9)	64(6)	-18(7)	15(7)	-119(9)
C15C	52(5)	129(8)	54(5)	-3(6)	3(4)	6(6)
C16C	83(6)	121(8)	39(4)	13(6)	-6(4)	-23(6)
C17C	112(7)	108(7)	71(5)	-51(5)	-29(6)	5(6)
C18C	54(5)	63(5)	34(4)	1(4)	-19(3)	2(4)
C19C	64(5)	110(5)	31(4)	-4(5)	-4(4)	-16(5)

Table 19. Bond Lengths for Schomaker30 [CSA4099]

Atom	Atom	Length/Å	Atom	Atom	Length/Å
Si1	C14	1.8696(16)	S1A	O1A	1.4287(10)
Si1	C15	1.8574(17)	S1A	O2A	1.4240(10)
Si1	C19	1.8805(16)	S1A	O3A	1.5676(10)
Si1	O5	1.6643(10)	S1A	N1A	1.6010(11)
O3	S1	1.5711(11)	O3A	C1A	1.4752(17)
O3	C1	1.4668(19)	O5A	C3A	1.4165(14)
C16	C19	1.538(2)	O5A	Si1B	1.686(13)
C17	C19	1.531(2)	O5A	Si1C	1.642(4)
C18	C19	1.536(3)	O6A	C5A	1.4309(15)

S1	O1	1.4289(10)	N1A	C4A	1.4735(15)
S1	O2	1.4188(11)	C1A	C2A	1.5086(18)
S1	N1	1.5975(12)	C2A	C3A	1.5282(16)
O5	C3	1.4230(15)	C3A	C4A	1.5367(16)
O6	C5	1.4263(15)	C4A	C5A	1.5356(15)
N1	C4	1.4816(15)	C5A	C6A	1.5231(16)
C1	C2	1.513(2)	C6A	C7A	1.5319(17)
C2	C3	1.5334(18)	C7A	C8A	1.5092(18)
C3	C4	1.5452(17)	C8A	C9A	1.384(2)
C4	C5	1.5365(17)	C8A	C13A	1.389(2)
C5	C6	1.5254(18)	C9A	C10A	1.388(2)
C6	C7	1.538(2)	C10A	C11A	1.378(2)
C7	C8	1.510(2)	C11A	C12A	1.377(2)
C8	C9	1.386(3)	C12A	C13A	1.388(2)
C8	C13	1.394(2)	Si1B	C14B	1.848(9)
C9	C10	1.390(3)	Si1B	C15B	1.837(9)
C10	C11	1.378(4)	Si1B	C19B	1.841(9)
C11	C12	1.362(4)	C16B	C19B	1.569(10)
C12	C13	1.385(3)	C17B	C19B	1.544(9)
Si1A	C14A	1.845(12)	C18B	C19B	1.530(10)
Si1A	C15A	1.850(12)	Si1C	C14C	1.858(10)
Si1A	C19A	1.889(11)	Si1C	C15C	1.831(10)
Si1A	O5A	1.601(17)	Si1C	C19C	1.865(11)
C16A	C19A	1.590(12)	C16C	C19C	1.581(13)
C17A	C19A	1.570(13)	C17C	C19C	1.523(13)
C18A	C19A	1.524(13)	C18C	C19C	1.543(14)

Table 20. Bond Angles for Schomaker30 [CSA4099]

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
C14	Si1	C19	111.58(7)	O2A	S1A	O3A	103.98(6)
C15	Si1	C14	107.86(9)	O2A	S1A	N1A	111.25(6)
C15	Si1	C19	112.58(8)	O3A	S1A	N1A	106.00(5)
O5	Si1	C14	110.18(6)	C1A	O3A	S1A	116.79(8)
O5	Si1	C15	110.42(7)	Si1A	O5A	Si1B	4.0(7)
O5	Si1	C19	104.20(6)	Si1A	O5A	Si1C	23.3(5)
C1	O3	S1	115.81(9)	C3A	O5A	Si1A	131.0(4)
C16	C19	Si1	109.78(12)	C3A	O5A	Si1B	131.5(3)
C17	C19	Si1	110.01(12)	C3A	O5A	Si1C	134.30(16)
C17	C19	C16	109.16(15)	Si1C	O5A	Si1B	19.3(3)
C17	C19	C18	108.55(16)	C4A	N1A	S1A	120.13(8)
C18	C19	Si1	109.96(11)	O3A	C1A	C2A	109.48(11)
C18	C19	C16	109.35(15)	C1A	C2A	C3A	116.47(10)
O3	S1	N1	105.16(6)	O5A	C3A	C2A	108.27(9)
O1	S1	O3	109.57(7)	O5A	C3A	C4A	105.79(9)
O1	S1	N1	106.87(6)	C2A	C3A	C4A	112.95(10)

O2	S1	O3	103.65(7)	N1A	C4A	C3A	110.81(9)
O2	S1	O1	119.37(7)	N1A	C4A	C5A	109.44(9)
O2	S1	N1	111.35(7)	C5A	C4A	C3A	113.47(10)
C3	O5	Si1	123.56(8)	O6A	C5A	C4A	110.09(9)
C4	N1	S1	121.88(9)	O6A	C5A	C6A	111.00(9)
O3	C1	C2	109.85(12)	C6A	C5A	C4A	113.70(9)
C1	C2	C3	118.18(12)	C5A	C6A	C7A	112.15(10)
O5	C3	C2	106.55(10)	C8A	C7A	C6A	111.84(11)
O5	C3	C4	110.79(10)	C9A	C8A	C7A	121.82(13)
C2	C3	C4	113.25(11)	C9A	C8A	C13A	118.15(13)
N1	C4	C3	106.31(10)	C13A	C8A	C7A	120.00(13)
N1	C4	C5	105.70(10)	C8A	C9A	C10A	121.22(14)
C5	C4	C3	116.67(10)	C11A	C10A	C9A	119.89(15)
O6	C5	C4	108.16(10)	C12A	C11A	C10A	119.77(14)
O6	C5	C6	109.79(11)	C11A	C12A	C13A	120.17(15)
C6	C5	C4	116.31(10)	C12A	C13A	C8A	120.78(15)
C5	C6	C7	112.39(12)	O5A	Si1B	C14B	108.0(6)
C8	C7	C6	115.05(13)	O5A	Si1B	C15B	108.2(6)
C9	C8	C7	122.17(15)	O5A	Si1B	C19B	101.6(6)
C9	C8	C13	117.26(17)	C15B	Si1B	C14B	108.4(7)
C13	C8	C7	120.56(17)	C15B	Si1B	C19B	116.1(6)
C8	C9	C10	121.03(19)	C19B	Si1B	C14B	114.0(6)
C11	C10	C9	120.3(2)	C16B	C19B	Si1B	112.3(7)
C12	C11	C10	119.5(2)	C17B	C19B	Si1B	109.6(6)
C11	C12	C13	120.4(2)	C17B	C19B	C16B	113.9(8)
C12	C13	C8	121.4(2)	C18B	C19B	Si1B	112.0(7)
C14A	Si1A	C15A	105.7(9)	C18B	C19B	C16B	97.8(7)
C14A	Si1A	C19A	112.1(9)	C18B	C19B	C17B	110.8(8)
C15A	Si1A	C19A	107.3(9)	O5A	Si1C	C14C	112.4(5)
O5A	Si1A	C14A	114.7(8)	O5A	Si1C	C15C	108.9(5)
O5A	Si1A	C15A	113.4(8)	O5A	Si1C	C19C	102.1(5)
O5A	Si1A	C19A	103.6(7)	C14C	Si1C	C19C	109.1(6)
C16A	C19A	Si1A	101.9(9)	C15C	Si1C	C14C	108.4(7)
C17A	C19A	Si1A	107.0(8)	C15C	Si1C	C19C	116.0(7)
C17A	C19A	C16A	108.7(11)	C16C	C19C	Si1C	109.0(9)
C18A	C19A	Si1A	106.6(9)	C17C	C19C	Si1C	112.3(8)
C18A	C19A	C16A	120.9(11)	C17C	C19C	C16C	111.3(12)
C18A	C19A	C17A	110.5(10)	C17C	C19C	C18C	111.9(11)
O1A	S1A	O3A	109.34(6)	C18C	C19C	Si1C	109.4(9)
O1A	S1A	N1A	106.71(6)	C18C	C19C	C16C	102.5(10)
O2A	S1A	O1A	118.87(6)				

Table 21. Torsion Angles for Schomaker30 [CSA4099]

A	B	C	D	Angle/°	A	B	C	D	Angle/°
Si1	O5	C3	C2	-99.48(11)	S1A	O3A	C1A	C2A	-94.68(11)

Si1	O5	C3	C4	136.93(9)	S1A	N1A	C4A	C3A	-92.51(11)
O3	S1	N1	C4	46.01(11)	S1A	N1A	C4A	C5A	141.62(9)
O3	C1	C2	C3	74.69(17)	O1A	S1A	O3A	C1A	-72.91(10)
C14	Si1	C19	C16	-60.01(15)	O1A	S1A	N1A	C4A	161.42(9)
C14	Si1	C19	C17	179.84(13)	O2A	S1A	O3A	C1A	159.16(9)
C14	Si1	C19	C18	60.33(14)	O2A	S1A	N1A	C4A	-67.46(11)
C14	Si1	O5	C3	33.39(12)	O3A	S1A	N1A	C4A	44.95(10)
C15	Si1	C19	C16	61.44(15)	O3A	C1A	C2A	C3A	77.53(14)
C15	Si1	C19	C17	-58.71(15)	O5A	Si1A	C19A	C16A	158.7(10)
C15	Si1	C19	C18	-178.21(12)	O5A	Si1A	C19A	C17A	44.7(10)
C15	Si1	O5	C3	-85.66(12)	O5A	Si1A	C19A	C18A	-73.6(10)
C19	Si1	O5	C3	153.21(10)	O5A	C3A	C4A	N1A	-173.41(9)
S1	O3	C1	C2	-93.78(13)	O5A	C3A	C4A	C5A	-49.82(12)
S1	N1	C4	C3	-95.24(11)	O5A	Si1B	C19B	C16B	-165.0(7)
S1	N1	C4	C5	140.14(9)	O5A	Si1B	C19B	C17B	67.3(8)
O1	S1	N1	C4	162.41(10)	O5A	Si1B	C19B	C18B	-56.0(8)
O2	S1	N1	C4	-65.61(12)	O5A	Si1C	C19C	C16C	-156.6(8)
O5	Si1	C19	C16	-178.88(12)	O5A	Si1C	C19C	C17C	79.7(11)
O5	Si1	C19	C17	60.97(14)	O5A	Si1C	C19C	C18C	-45.3(10)
O5	Si1	C19	C18	-58.54(13)	O6A	C5A	C6A	C7A	-64.53(14)
O5	C3	C4	N1	-171.50(10)	N1A	S1A	O3A	C1A	41.78(10)
O5	C3	C4	C5	-53.95(14)	N1A	C4A	C5A	O6A	-73.16(11)
O6	C5	C6	C7	-54.60(15)	N1A	C4A	C5A	C6A	52.10(13)
N1	C4	C5	O6	67.49(12)	C1A	C2A	C3A	O5A	-172.37(11)
N1	C4	C5	C6	-168.49(11)	C1A	C2A	C3A	C4A	-55.56(15)
C1	O3	S1	O1	-69.91(11)	C2A	C3A	C4A	N1A	68.32(12)
C1	O3	S1	O2	161.63(10)	C2A	C3A	C4A	C5A	-168.09(10)
C1	O3	S1	N1	44.63(11)	C3A	O5A	Si1B	C14B	72.4(6)
C1	C2	C3	O5	-177.75(12)	C3A	O5A	Si1B	C15B	-44.7(7)
C1	C2	C3	C4	-55.70(17)	C3A	O5A	Si1B	C19B	-167.4(3)
C2	C3	C4	N1	68.85(13)	C3A	O5A	Si1C	C14C	74.8(6)
C2	C3	C4	C5	-173.60(10)	C3A	O5A	Si1C	C15C	-45.3(7)
C3	C4	C5	O6	-50.39(13)	C3A	O5A	Si1C	C19C	-168.4(5)
C3	C4	C5	C6	73.64(14)	C3A	C4A	C5A	O6A	162.50(9)
C4	C5	C6	C7	-177.78(11)	C3A	C4A	C5A	C6A	-72.24(13)
C5	C6	C7	C8	-67.35(17)	C4A	C5A	C6A	C7A	170.69(11)
C6	C7	C8	C9	81.2(2)	C5A	C6A	C7A	C8A	173.20(12)
C6	C7	C8	C13	-98.08(18)	C6A	C7A	C8A	C9A	89.45(16)
C7	C8	C9	C10	-178.05(18)	C6A	C7A	C8A	C13A	-88.31(16)
C7	C8	C13	C12	179.51(17)	C7A	C8A	C9A	C10A	-179.25(14)
C8	C9	C10	C11	-1.5(3)	C7A	C8A	C13A	C12A	179.30(14)
C9	C8	C13	C12	0.2(3)	C8A	C9A	C10A	C11A	0.5(2)
C9	C10	C11	C12	0.2(4)	C9A	C8A	C13A	C12A	1.5(2)
C10	C11	C12	C13	1.3(4)	C9A	C10A	C11A	C12A	0.6(3)
C11	C12	C13	C8	-1.5(3)	C10A	C11A	C12A	C13A	-0.5(3)
C13	C8	C9	C10	1.2(3)	C11A	C12A	C13A	C8A	-0.5(3)

Si1A	O5A	C3A	C2A	-95.9(6)	C13A	C8A	C9A	C10A	-1.5(2)
Si1A	O5A	C3A	C4A	142.8(6)	Si1B	O5A	C3A	C2A	-90.6(4)
Si1A	O5A	Si1B	C14B	157(9)	Si1B	O5A	C3A	C4A	148.1(4)
Si1A	O5A	Si1B	C15B	40(9)	Si1B	O5A	Si1C	C14C	165.6(11)
Si1A	O5A	Si1B	C19B	-83(9)	Si1B	O5A	Si1C	C15C	45.5(10)
Si1A	O5A	Si1C	C14C	167.6(13)	Si1B	O5A	Si1C	C19C	-77.7(10)
Si1A	O5A	Si1C	C15C	47.5(12)	C14B	Si1B	C19B	C16B	-49.1(11)
Si1A	O5A	Si1C	C19C	-75.6(12)	C14B	Si1B	C19B	C17B	-176.8(8)
C14A	Si1A	C19A	C16A	-77.1(13)	C14B	Si1B	C19B	C18B	59.8(11)
C14A	Si1A	C19A	C17A	168.9(10)	C15B	Si1B	C19B	C16B	77.9(10)
C14A	Si1A	C19A	C18A	50.6(13)	C15B	Si1B	C19B	C17B	-49.8(11)
C14A	Si1A	O5A	C3A	51.8(10)	C15B	Si1B	C19B	C18B	-173.2(9)
C14A	Si1A	O5A	Si1B	-47(9)	Si1C	O5A	C3A	C2A	-64.4(4)
C14A	Si1A	O5A	Si1C	-57.0(11)	Si1C	O5A	C3A	C4A	174.3(3)
C15A	Si1A	C19A	C16A	38.6(13)	Si1C	O5A	Si1B	C14B	-34.8(8)
C15A	Si1A	C19A	C17A	-75.5(12)	Si1C	O5A	Si1B	C15B	-152.0(12)
C15A	Si1A	C19A	C18A	166.2(10)	Si1C	O5A	Si1B	C19B	85.3(9)
C15A	Si1A	O5A	C3A	-69.7(9)	C14C	Si1C	C19C	C16C	-37.4(12)
C15A	Si1A	O5A	Si1B	-169(10)	C14C	Si1C	C19C	C17C	-161.2(11)
C15A	Si1A	O5A	Si1C	-178.6(16)	C14C	Si1C	C19C	C18C	73.9(11)
C19A	Si1A	O5A	C3A	174.3(4)	C15C	Si1C	C19C	C16C	85.2(11)
C19A	Si1A	O5A	Si1B	75(9)	C15C	Si1C	C19C	C17C	-38.5(14)
C19A	Si1A	O5A	Si1C	65.5(11)	C15C	Si1C	C19C	C18C	-163.4(9)

Table 22. Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for Schomaker30

Atom	*x*	*y*	*z*	U(eq)
H14J	289	-935	5970	70
H14K	1604	-713	5523	70
H14L	562	303	5733	70
H15J	-336	513	7547	77
H15K	55	-523	8300	77
H15L	-743	-654	7708	77
H16J	338	-2841	7866	96
H16K	1426	-3823	7658	96
H16L	864	-2913	6905	96
H17J	2806	-1997	8210	93
H17K	2638	-3269	8443	93
H17L	1527	-2311	8660	93
H18J	2915	-2515	6209	91
H18K	3457	-3403	6979	91
H18L	3665	-2140	6712	91
H6	438	2912	7383	49
H1B	4213	1497	4380	49
H1C	3025	2285	4744	49

H2A	4142	319	5807	43
H2B	3152	269	5335	43
H3	1671	1324	6155	32
H4	3550	1494	6904	30
H5	2021	2588	7755	32
H6B	2766	793	8525	40
H6C	1844	271	8276	40
H7A	229	1390	9040	53
H7B	1050	475	9639	53
H9	418	3431	8719	67
H10	778	4802	9234	90
H11	1733	4294	10382	96
H12	2332	2419	11007	85
H13	2053	1043	10464	67
H14A	-6252	2675	8719	114
H14B	-5323	1937	8128	114
H14C	-5838	3226	7734	114
H15A	-5069	5044	8061	163
H15B	-4292	4785	8774	163
H15C	-5628	4563	9034	163
H16A	-5210	3501	9945	153
H16B	-4636	2601	10696	153
H16C	-5613	2311	10327	153
H17A	-2046	2065	9190	153
H17B	-2580	2206	10134	153
H17C	-2724	3267	9343	153
H18A	-4535	790	9555	259
H18B	-3339	486	9926	259
H18C	-3279	884	8924	259
H6A	-43	4857	6685	43
H1AA	-2780	2101	5364	39
H1AB	-2843	3399	5293	39
H2AA	-2376	1731	6784	34
H2AB	-3715	2276	6669	34
H3A	-3490	4029	6723	28
H4A	-1037	2990	6797	26
H5A	-1874	4120	7811	28
H6AA	-3061	5617	6954	33
H6AB	-1865	6028	6396	33
H7AA	-2734	5990	8156	42
H7AB	-1454	6271	7665	42
H9A	-4549	7399	7862	47
H10A	-5400	9277	7390	54
H11A	-4203	10550	6537	53
H12A	-2162	9935	6144	56
H13A	-1310	8055	6616	48

H14D	-5395	2226	7832	126
H14E	-5964	2003	8821	126
H14F	-4722	1253	8498	126
H15D	-4865	4977	8256	148
H15E	-6058	4476	8657	148
H15F	-5478	4582	7676	148
H16D	-5441	2956	10403	148
H16E	-4512	1901	10803	148
H16F	-5290	1774	10196	148
H17D	-2445	3423	9262	153
H17E	-3306	3500	10152	153
H17F	-3702	4270	9290	153
H18D	-3329	945	9461	169
H18E	-2934	1189	10221	169
H18F	-2234	1570	9269	169
H14G	-4654	1184	7959	161
H14H	-5098	911	8965	161
H14I	-3710	614	8570	161
H15G	-5608	4286	8350	134
H15H	-6326	3284	8612	134
H15I	-5653	3679	7654	134
H16G	-5376	1744	10158	133
H16H	-4619	1819	10799	133
H16I	-4152	878	10275	133
H17G	-4030	4204	9161	140
H17H	-3506	3642	10010	140
H17I	-4898	3776	10036	140
H18G	-2408	1211	9295	81
H18H	-2404	1654	10090	81
H18I	-2026	2385	9148	81
H1	2064(17)	3094(15)	5992(12)	43(5)
H1A	-1897(15)	4737(14)	5580(10)	31(4)

References:

[11] BRUKER-AXS. (2007-2013), APEX2 (Ver. 2013.2-0), SADABS (2012-1)

[12] SAINT+ (Ver. 8.30C) Software Reference Manuals, BRUKER-AXS, Madison, Wisconsin, USA.

[13] G. M. Sheldrick, *Acta Cryst.*, 2008, *A64*, 112-122.

[14] O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. L. Howard, H. Puschmann, *J. Appl. Cryst.* 2009, *42*, 339-341.

[15] XP – X-Ray Crystal Structure Visualization BRUKER, AXS, 1998, V5.1

[16] I. Guzei, UW-Madison, 2013, G4.

Department of Chemistry

Structure Report 2014

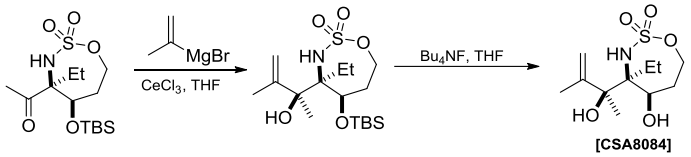
X-RAY
UW-Madison

SCHOMAKER
1101 University Ave,
Madison, WI, 53706, USA
Dr. Maik Tretbar
email: xray.tretbar@web.de

Crystallographic Experimental Section XXXYYY

CCDC-no.

Crystal Structure of Schomaker48



[CSA8084]

Preparation of Crystals: A sample consisting of 25 mg racemic CSA8084 (column purified) was dissolved in 2 mL dichloromethane and crystallized by slow evaporation at room temperature slowly over three days. The air-stable crystals were selected using a microscope to choose the best sample for X-ray crystallography.

Data Collection: A colorless crystal with approximate dimensions 0.140 x 0.07 x 0.05 mm^3 (needles) was selected under oil under ambient conditions and attached to the tip of a X-ray capillary (MiTeGenMicroMount©). The crystal was mounted in a stream of cold nitrogen at 100.0(15) K and centered in the X-ray beam by using a video camera. The crystal evaluation and data collection were performed on a three-circle Bruker Quazar SMART APEXII diffractometer with copper radiation K_α(α = 1.54184 Å) and the diffractometer to crystal distance of 4.96 cm. The initial cell constants were obtained from three series of ω scans at different starting angles. Each series consisted of 35 frames collected at intervals of 0.7° in 25° range about ω with the exposure time of 10 seconds per frame. The reflections were successfully indexed by an automated indexing routine built in the APEXII program suite. The final cell constants were calculated from a set of 9893 strong from the actual data collection. The data were collected by using the full sphere data collection routine to survey the reciprocal space to the extent of a full sphere to a high-resolution of 0.83 Å. A total of 42352 reflection data were harvested by collecting 19 sets of frames with 0.7° scans in ω and φ with exposure times of 10/20 sec per frame. These highly redundant datasets were corrected for Lorentz and polarization effects. The absorption correction was based on fitting a function to the empirical transmission surface as sampled by multiple equivalent measurements. [1,2]

Structure Solution and Refinement: The systematic absences in the diffraction data were consistent for the orthorhomic space groups $P2_12_12_1$. The E-statistics strongly suggested the chiral space group that yielded chemically reasonable and computationally stable results of refinement. [3,4] The systematic absences in the diffraction data were uniquely consistent for the space group $P2_12_12_1$. A successful solution by the direct

methods by using SHELX-2013 provided most non-hydrogen atoms from the E-map. Using Olex2, all non-hydrogen atoms were refined with anisotropic displacement coefficients. All hydrogen atoms were included in the structure factor calculation at idealized positions and were allowed to ride on the neighboring atoms with relative isotropic displacement coefficients. The only crystal large enough for the single-crystal X-ray diffraction experiment proved to be a non-merohedral twin with a 38.6(2)% second component contribution.

Table 1. Crystal data collection and structure solution refinement for Schomaker48 [CSA8084]

Parameter	**CSA8084**	**Parameter**	**CSA8084**
empiric formula	$C_{11}H_{21}NO_5S$	$\rho_{calc.}$ [g · cm^{-1}]	1.427
MW [g · mol^{-1}]	279.35	crystal size [mm]	0.14 x 0.07 x 0.05
X-ray lab code	Schomaker48	T [K]	100.0(2)
a [Å]	7.4335(15)	radiation type / λ [nm]	Cu K$_{\alpha}$ / 1.54184
b [Å]	12.118(2)	μ [mm^{-1}]	2.358
c [Å]	14.438(3)	F(000)	604.0
□ [°]	90.000(0)°	Reflections collected	42352
□ [°]	90.000(0)	Independent reflections	2451
□ [°]	90.000(0)°	Data/restraints/parameters	2461/0/179
V [Å^3]	1300.6(5)	GooF on F^2	1.045
Z	4	Largest diff. peak/hole [eÅ^{-3}]	0.22 / -0.31
crystal system	orthorhombic	Flack *x* parameter	0.160(21)
crystal color	colorless	Final R_1[a]/ wR_2[b] all data	0.0280/ 0.0723
space group	$P2_12_12_1$	Final R_1[a]/ wR_2[b] I>2s(I)	0.0274/ 0.0726

[a] $R_1 = \sum \left| F_o \right| - \left| F_c \right| / \left| F_o \right|$;[b] $wR_2 = [\sum\{w(F_o^2 - F_o^2)^2\}/ \sum\{w(F_o^2)^2\}]^{½}$

The final least-squares refinement of 221 parameters against 1442 data resulted in R = 0.0274 (based on F^2 for I>2s) and wR2 = 0.0723 (based on F^2 for all data), respectively. The final structure was visualized using Interactive Molecular Graphics. [5]

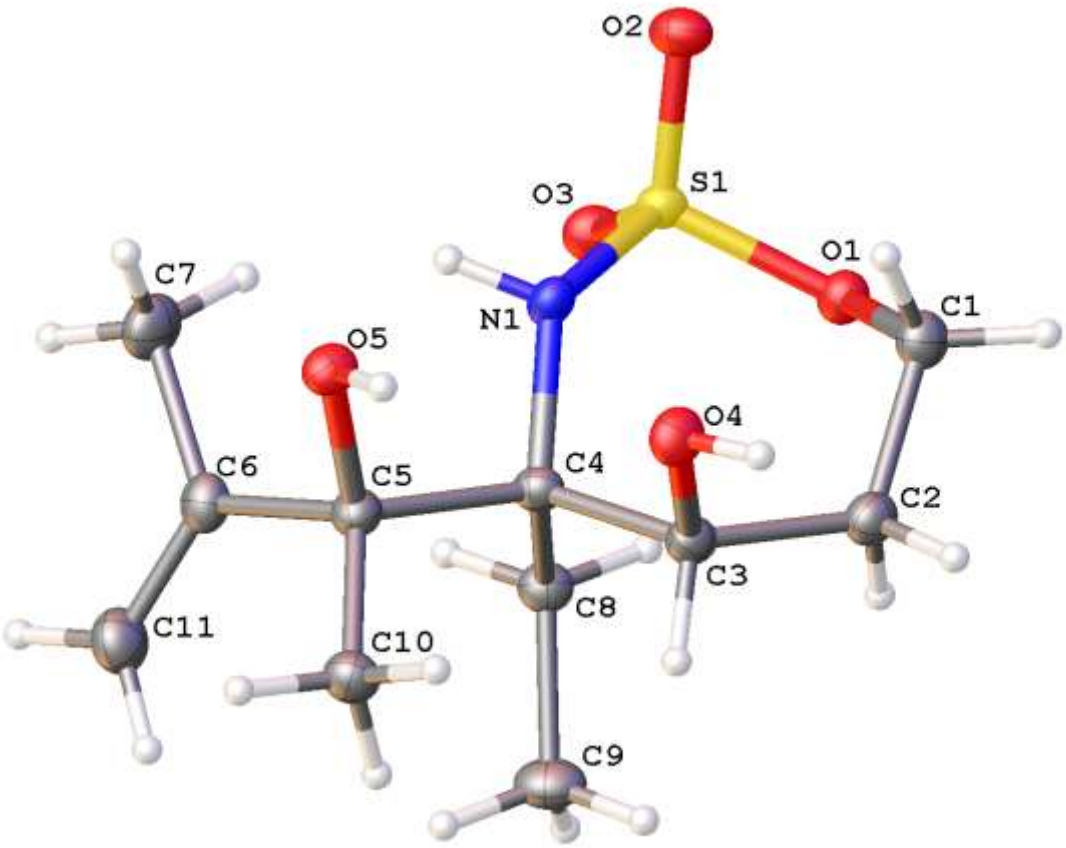


Figure 1. Thermal-ellipsoid of CSA8084 [Schomaker48] are set with 50 % probability.

Table 2. Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) for CSA8084 (Schomaker48). U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
S1	8641.2(8)	3744.4(5)	1987.1(4)	15.42(16)
O1	10731(2)	3794.4(15)	-706.5(12)	17.4(4)
O2	12505(3)	2389.3(14)	510.5(12)	19.5(4)
O3	8109(3)	4806.1(15)	2309.6(13)	21.8(4)
O4	7277(3)	2932.7(15)	1814.9(13)	21.8(4)
O5	9967(2)	3316.8(15)	2758.3(11)	18.1(4)
N6	9784(3)	3800.0(18)	1037.6(14)	16.4(4)

C7	11725(4)	4586(2)	-159.9(17)	17.0(5)
C8	11944(4)	5220(2)	1572.4(18)	17.7(5)
C9	13657(4)	4596(2)	-525.7(18)	20.4(5)
C10	12949(4)	2857(2)	2126.4(18)	19.8(6)
C11	10765(4)	5689(2)	-329.3(18)	19.0(6)
C12	12957(4)	3279(2)	1128.8(18)	17.6(5)
C13	13829(4)	5721(2)	1610(2)	24.9(6)
C14	11655(4)	6614(2)	-473(2)	26.0(6)
C15	11193(4)	2411(2)	2498.6(19)	19.9(5)
C16	11634(3)	4234(2)	913.7(17)	15.6(5)
C17	8727(4)	5684(2)	-358(2)	27.0(6)

Table 3. Anisotropic Displacement Parameters ($Å^2 \times 10^3$) for CSA8084 (Schomaker48). The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+...+2hka \times b \times U_{12}]$

Atom	**U_{11}**	**U_{22}**	**U_{33}**	**U_{23}**	**U_{13}**	**U_{12}**
S1	12.9(3)	17.1(3)	16.2(3)	-0.7(2)	1.4(2)	-0.5(2)
O1	17.7(9)	15.4(8)	19.3(8)	-3.9(7)	-1.4(7)	1.2(8)
O2	21.5(10)	15.4(8)	21.6(9)	-2.4(8)	-1.4(8)	4.4(8)
O3	19.6(9)	21.4(9)	24.3(9)	-3.2(8)	3.2(8)	2.3(8)
O4	18.0(9)	25.4(9)	22.1(9)	-1.9(8)	1.5(8)	-4.4(8)
O5	17.6(9)	20.0(8)	16.8(9)	-0.3(7)	0.1(8)	1.7(8)
N6	13.7(10)	19.5(10)	15.9(9)	0.8(9)	-1.5(8)	2.1(9)
C7	17.0(13)	17.0(12)	17.1(12)	-0.6(10)	-1.8(10)	-1.1(11)
C8	17.6(12)	16.9(11)	18.5(12)	-2.7(10)	0.7(10)	0.1(10)
C9	18.5(13)	21.8(13)	21.0(12)	0.7(11)	1.7(11)	-0.9(12)
C10	18.1(12)	19.3(12)	22.1(13)	0.8(11)	-2.2(11)	1.7(11)
C11	22.7(14)	19.0(13)	15.2(12)	-0.3(10)	-0.6(11)	3.2(11)
C12	15.2(12)	16.8(11)	20.8(12)	1(1)	-0.5(10)	0.5(11)
C13	21.6(13)	25.9(13)	27.1(14)	-6.7(12)	-0.2(12)	-6.3(12)
C14	29.5(17)	20.5(13)	27.9(14)	2.9(11)	-1.6(13)	2.1(12)
C15	20.8(13)	17.9(11)	20.8(12)	0.4(10)	-0.2(12)	3.1(11)
C16	13.8(12)	17.5(12)	15.4(11)	-1.1(10)	1(1)	-0.9(10)
C17	24.4(14)	22.9(14)	33.7(15)	2.6(12)	-4.6(13)	6.5(13)

Table 4. Bond Lengths for CSA8084 (Schomaker48).

Atom	**Atom**	**Length/Å**	**Atom**	**Atom**	**Length/Å**

S1	O3	1.424(2)	C7	C11	1.535(4)
S1	O4	1.4344(19)	C7	C16	1.609(3)
S1	O5	1.5748(18)	C8	C13	1.528(4)
S1	N6	1.614(2)	C8	C16	1.545(3)
O1	C7	1.446(3)	C10	C12	1.528(4)
O2	C12	1.440(3)	C10	C15	1.512(4)
O5	C15	1.475(3)	C11	C14	1.318(4)
N6	C16	1.483(3)	C11	C17	1.516(4)
C7	C9	1.530(4)	C12	C16	1.550(3)

Table 5. Bond Angles for CSA8084 (Schomaker48).

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
O3	S1	O4	118.67(12)	C15	C10	C12	117.2(2)
O3	S1	O5	103.89(10)	C14	C11	C7	122.2(2)
O3	S1	N6	112.72(11)	C14	C11	C17	120.0(3)
O4	S1	O5	109.83(11)	C17	C11	C7	117.7(2)
O4	S1	N6	104.69(11)	O2	C12	C10	109.5(2)
O5	S1	N6	106.54(10)	O2	C12	C16	106.7(2)
C15	O5	S1	116.86(15)	C10	C12	C16	115.9(2)
C16	N6	S1	127.26(17)	O5	C15	C10	111.0(2)
O1	C7	C9	107.3(2)	N6	C16	C7	104.43(19)
O1	C7	C11	104.7(2)	N6	C16	C8	109.8(2)
O1	C7	C16	109.18(19)	N6	C16	C12	107.4(2)
C9	C7	C11	112.0(2)	C8	C16	C7	112.4(2)
C9	C7	C16	112.0(2)	C8	C16	C12	111.1(2)
C11	C7	C16	111.4(2)	C12	C16	C7	111.4(2)
C13	C8	C16	117.8(2)				

Table 6. Torsion Angles for CSA8084 (Schomaker48).

A	B	C	D	Angle/°	A	B	C	D	Angle/°
S1	O5	C15	C10	90.7(2)	C9	C7	C11	C17	156.8(2)
S1	N6	C16	C7	-155.30(19)	C9	C7	C16	N6	-156.2(2)
S1	N6	C16	C8	-34.6(3)	C9	C7	C16	C8	84.9(3)
S1	N6	C16	C12	86.3(2)	C9	C7	C16	C12	-40.5(3)
O1	C7	C11	C14	-137.1(3)	C10	C12	C16	N6	-64.7(3)
O1	C7	C11	C17	40.9(3)	C10	C12	C16	C7	-178.5(2)
O1	C7	C16	N6	-37.5(2)	C10	C12	C16	C8	55.3(3)
O1	C7	C16	C8	-156.5(2)	C11	C7	C16	N6	77.6(2)
O1	C7	C16	C12	78.1(3)	C11	C7	C16	C8	-41.4(3)
O2	C12	C16	N6	57.4(2)	C11	C7	C16	C12	-166.8(2)
O2	C12	C16	C7	-56.4(3)	C12	C10	C15	O5	-78.1(3)

O2	C12	C16	C8	177.4(2)	C13	C8	C16	N6	174.8(2)
O3	S1	O5	C15	-160.91(17)	C13	C8	C16	C7	-69.4(3)
O3	S1	N6	C16	69.5(2)	C13	C8	C16	C12	56.1(3)
O4	S1	O5	C15	71.17(19)	C15	C10	C12	O2	-61.4(3)
O4	S1	N6	C16	-160.1(2)	C15	C10	C12	C16	59.2(3)
O5	S1	N6	C16	-43.8(2)	C16	C7	C11	C14	105.0(3)
N6	S1	O5	C15	-41.7(2)	C16	C7	C11	C17	-76.9(3)
C9	C7	C11	C14	-21.2(4)					

Table 7. Hydrogen Atom Coordinates (Å×10⁴) and Isotropic Displacement Parameters (Å²×10³) for CSA8084 (Schomaker48).

Atom	***x***	***y***	***z***	**U(eq)**
H1	11365	3254	-808	26
H2	13132	1851	629	29
H6	9111	4090	619	20
H8A	11110	5801	1399	21
H8B	11626	4986	2194	21
H9A	14141	3862	-504	31
H9B	14378	5076	-149	31
H9C	13663	4856	-1154	31
H10A	13847	2279	2176	24
H10B	13330	3457	2526	24
H12	14177	3529	981	21
H13A	14111	6049	1022	37
H13B	14689	5153	1747	37
H13C	13871	6276	2084	37
H15A	10625	1954	2031	24
H15B	11429	1954	3037	24
H17A	8324	5167	-818	41
H17B	8300	6409	-513	41
H17C	8265	5473	237	41
H14A	12900(50)	6640(30)	-480(20)	23(8)
H14B	11010(50)	7350(30)	-590(20)	35(9)

References.

1) BRUKER-AXS. (2007-2013), APEX2 (Ver. 2013.2-0), SADABS (2012-1).

2) SAINT+ (Ver. 8.30C) Software Reference Manuals, BRUKER-AXS, Madison, Wisconsin, USA.

3) G. M. Sheldrick, *Acta Cryst.*, **2008**, *A64*, 112-122.

4) O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. L. Howard, H. Puschmann, *J. Appl. Cryst.* **2009**, *42*, 339-341.

5) XP – X-Ray Crystal Structure Visualization BRUKER, AXS, **1998**, V5.1

Department of Chemistry

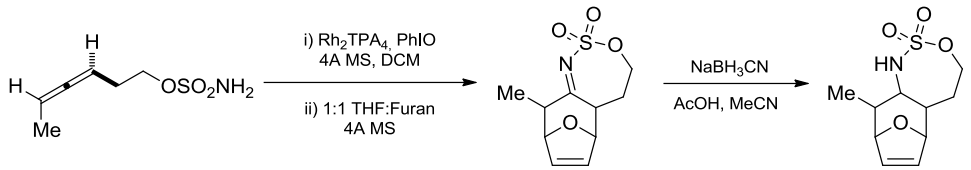
Structure Report 2014

X-RAY
UW-Madison

SCHOMAKER
1101 University Ave,
Madison, WI, 53706, USA
Dr. Maik Tretbar
email: mtretbar@chem.wisc.edu

Crystallographic Experimental Section

Crystal Structure of Schomaker35 [NCG1056]



Preparation of Crystals: The racemic compound (NCG1056) was dissolved in ethyl acetate and crystallized slowly at room temperature by vapor diffusion using n-hexanes as solvent. The obtained crystals were air-stable and selected under microscope.

Data Collection: A colorless crystal with approximate dimensions 0.061 x 0.103 x 0.208 mm^3 (block) with a mosaicity of 0.39 was selected under oil under ambient conditions and attached to the tip of a X-ray capillary (MiTeGenMicroMount©). The crystal was mounted in a stream of cold nitrogen at 100.0(15) K and centered in the X-ray beam by using a video camera. The crystal evaluation and data collection were performed on a three-circle Bruker Quazar SMART APEXII diffractometer with Molybdenum K_α(λ = 0.71073 Å) radiation and the diffractometer to crystal distance of 4.96 cm. The initial cell constants were obtained from three series of ω scans at different starting angles. Each series consisted of 12 frames collected at intervals of 0.5° in 6° range about ω with the exposure time of 10 seconds per frame. The reflections were successfully indexed by an automated indexing routine built in the APEXII program suite. The final cell constants were calculated from a set of 9994 strong from the actual data collection. The data were collected by using the full sphere data collection routine to survey the reciprocal space to the extent of a full sphere to a resolution of 0.70 Å. A total of 31583 reflection data were harvested by collecting 6 sets of frames with 0.6° scans in ω and ϕ with exposure times of 25 sec per frame. These highly redundant datasets were corrected for Lorentz and polarization effects. The absorption correction was based on fitting a function to the empirical transmission surface as sampled by multiple equivalent measurements. [1,2]

Structure Solution and Refinement: The systematic absences in the diffraction data were consistent for the monoclinic space groups *P2₁/n*. The *E*-statistics strongly suggested the centrosymmetric space group that yielded chemically reasonable and computationally stable results of refinement. [3,4] The systematic absences in the diffraction data were uniquely consistent for the space group *P2₁/n*. A successful solution by the direct methods by using SHELX-2013 provided most non-hydrogen atoms from the *E*-map. Using Olex2, all non-hydrogen atoms were refined with anisotropic displacement coefficients. All hydrogen atoms were included in the structure factor calculation at idealized positions and were allowed to ride on the neighboring atoms with relative isotropic displacement coefficients.

Table 1. Crystal data collection and structure solution refinement for Schomaker35 [NCG1056]

Parameter	NCG1056	Parameter	NCG1056
empiric formula	$C_{10}H_{15}NO_4S$	$\rho_{calc.}$ [g · cm^{-1}]	1.482
MW [g · mol^{-1}]	245.29	crystal size [mm]	0.208 × 0.103 × 0.061
X-ray lab code	Schomaker35	T [K]	100.0(15)
a [Å]	10.704(4)	radiation type / λ [nm]	Mo K_α / 0.71072
b [Å]	7.393(2)	μ [mm^{-1}]	0.293
c [Å]	14.201(4)	F(000)	520.0
α [°]	90.000(0)°	Reflections collected	30333
β [°]	101.927(13)°	Independent reflections	3360 [R_{int} = 0.0305]
γ [°]	90.000(8)°	Data/restraints/parameters	3360/0/157
V [Å^3]	1099.5(6)	GooF on F^2	1.014
Z	4	Largest diff. peak/hole [eÅ^{-3}]	0.52 / -0.32
crystal system	monoclinic	2Θ range for data collection	4.36 to 61.04°
crystal color	colorless	Final R_1[a]/ wR_2[b] all data	0.0354/ 0.0871
space group	$P2_1/n$	Final R_1[a]/ wR_2[b] I>2s(I)	0.0315/ 0.0846

[a] $R_1 = \sum \big| F_o \big| - \big| F_c \big| / \big| F_o \big|$; [b] $wR_2 = [\sum\{w(F_o^2 - F_o^2)^2\} / \sum\{w(F_o^2)^2\}]^{½}$

The final least-squares refinement of 157 parameters against 3360 data resulted in R = 0.0315 (based on F^2 for I>2s) and wR2 = 0.0871 (based on F^2 for all data), respectively. The final structure was visualized using Interactive Molecular Graphics. [5]

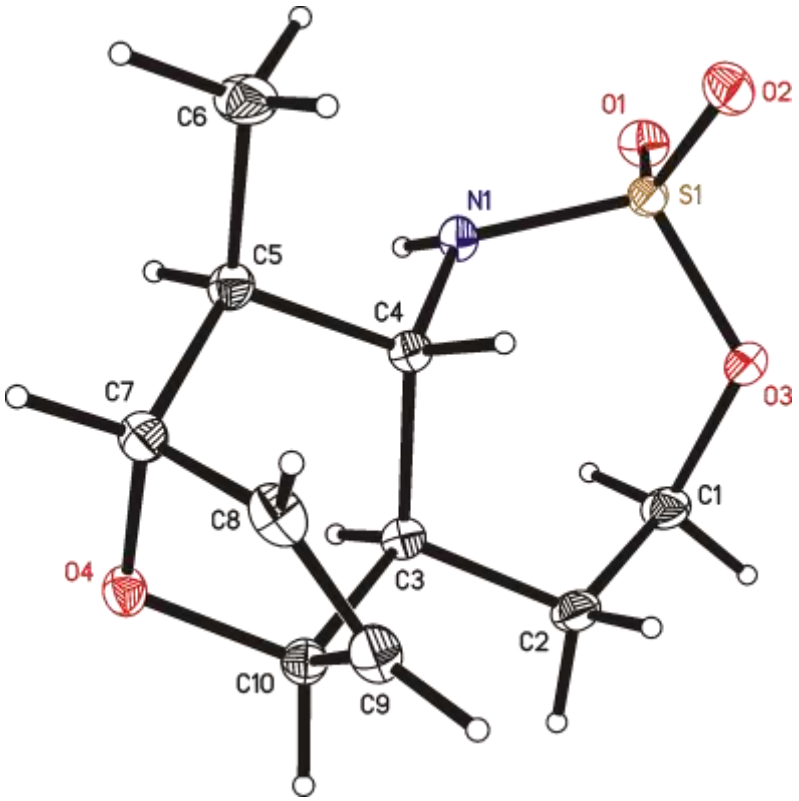


Figure 1. Thermal-ellipsoid of Schomaker35 [NCG1056] are set with 50 % probability.

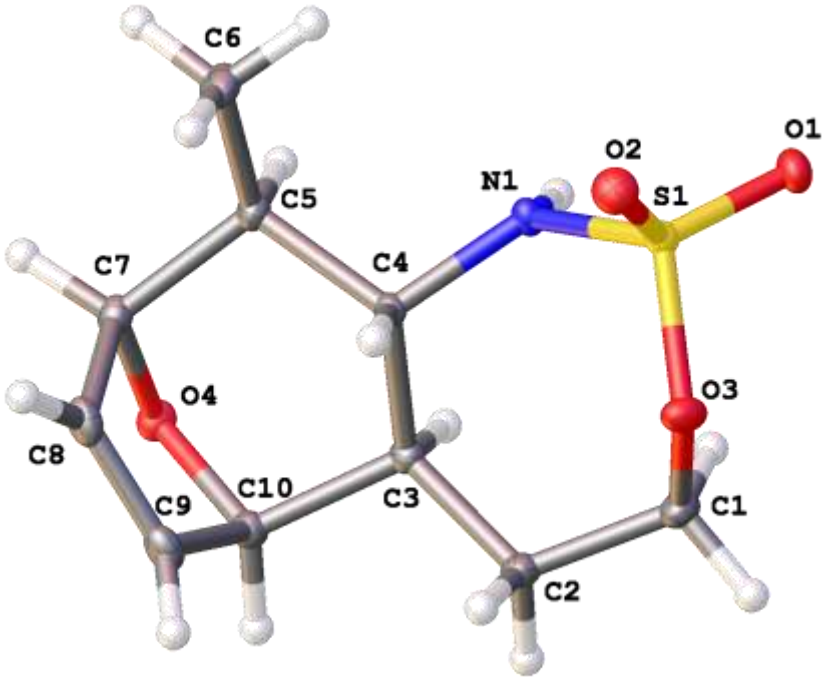


Figure 2. Thermal-ellipsoid of Schomaker35 [NCG1056] are set with 50 % probability.

Table 2. Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) for Schomaker35 [NCG1056]. U_{eq} is defined as 1/3 of of the trace of the orthogonalized U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
S1	5447.4(2)	1760.5(4)	2408.21(19)	11.25(8)
O3	6451.8(8)	3345.5(11)	2535.8(6)	15.82(17)
O1	5552.8(8)	770.0(12)	3287.7(6)	15.89(17)
O2	5664.6(8)	837.9(12)	1574.6(6)	16.69(17)
O4	2121.3(7)	7305.6(11)	1205.4(6)	13.08(16)
C4	3784.9(10)	4240.1(14)	1538.1(7)	10.55(19)
N1	4071.2(9)	2705.8(13)	2207.9(7)	11.22(17)
C5	2376.8(10)	4107.1(15)	1004.6(8)	12.5(2)
C7	1972.0(11)	5906.8(15)	479.9(8)	13.0(2)
C10	3481.6(10)	7618.1(15)	1413.8(8)	12.48(19)
C3	4100.1(10)	6056.1(14)	2069.0(8)	11.37(19)
C1	6225.6(11)	4933.0(16)	3101.4(8)	15.9(2)
C2	5531.7(11)	6385.2(16)	2439.9(8)	14.7(2)
C9	3790.1(11)	7527.0(16)	420.8(8)	15.4(2)
C8	2900.3(11)	6519.7(16)	-129.4(8)	15.5(2)
C6	2151.7(12)	2486.3(17)	330.7(9)	19.3(2)

Table 3. Anisotropic Displacement Parameters ($Å^2 \times 10^3$) for Schomaker35 [NCG1056].
The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+...]$

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
S1	10.78(12)	10.60(13)	12.09(13)	0.90(9)	1.68(9)	0.08(9)
O3	11.3(3)	13.1(4)	22.9(4)	-0.5(3)	3.0(3)	-1.6(3)
O1	18.4(4)	14.8(4)	13.4(4)	3.6(3)	0.7(3)	1.3(3)
O2	18.0(4)	17.2(4)	15.8(4)	-1.9(3)	5.7(3)	1.4(3)
O4	11.8(3)	14.2(4)	13.4(4)	-1.5(3)	2.9(3)	1.2(3)
C4	11.3(4)	10.4(4)	9.6(4)	1.0(3)	1.5(3)	-0.2(3)
N1	10.6(4)	12.2(4)	11.1(4)	2.7(3)	2.8(3)	1.0(3)
C5	11.9(4)	12.9(5)	11.7(5)	0.3(4)	0.1(4)	-0.3(4)
C7	13.2(5)	13.9(5)	11.3(4)	-0.8(4)	0.9(4)	0.9(4)
C10	12.6(5)	12.3(5)	12.7(5)	0.7(4)	2.9(4)	-0.2(4)
C3	12.2(4)	11.2(4)	10.5(4)	0.2(4)	1.9(4)	-0.8(4)
C1	14.7(5)	13.2(5)	17.5(5)	-1.1(4)	-1.7(4)	-2.0(4)
C2	13.8(5)	12.2(5)	16.8(5)	0.8(4)	-0.2(4)	-2.5(4)
C9	16.4(5)	16.0(5)	14.9(5)	5.1(4)	6.1(4)	2.5(4)
C8	19.1(5)	16.8(5)	10.9(5)	3.4(4)	4.1(4)	4.8(4)
C6	21.4(6)	15.0(5)	17.8(5)	-3.7(4)	-4.3(4)	0.6(4)

Table 4. Bond Lengths for Schomaker35 [NCG1056].

Atom	Atom	Length/Å	Atom	Atom	Length/Å
S1	O3	1.5752(9)	C4	C3	1.5427(15)
S1	O1	1.4320(9)	C5	C7	1.5427(16)
S1	O2	1.4263(9)	C5	C6	1.5214(16)
S1	N1	1.6018(11)	C7	C8	1.5155(16)
O3	C1	1.4703(15)	C10	C3	1.5437(16)
O4	C7	1.4451(14)	C10	C9	1.5148(16)
O4	C10	1.4432(14)	C3	C2	1.5333(16)
C4	N1	1.4714(14)	C1	C2	1.5161(16)
C4	C5	1.5438(16)	C9	C8	1.3284(17)

Table 5. Bond Angles for Schomaker35 [NCG1056].

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
O3	S1	N1	106.05(5)	C6	C5	C7	112.54(9)
O1	S1	O3	110.56(5)	O4	C7	C5	107.11(9)
O1	S1	N1	106.37(5)	O4	C7	C8	101.78(9)
O2	S1	O3	103.11(5)	C8	C7	C5	112.45(9)
O2	S1	O1	118.83(6)	O4	C10	C3	107.02(9)
O2	S1	N1	111.28(5)	O4	C10	C9	101.93(9)
C1	O3	S1	118.11(7)	C9	C10	C3	112.27(9)
C10	O4	C7	102.65(8)	C4	C3	C10	109.47(9)
N1	C4	C5	108.66(9)	C2	C3	C4	114.09(9)
N1	C4	C3	111.08(9)	C2	C3	C10	111.22(9)
C3	C4	C5	112.83(9)	O3	C1	C2	109.98(9)
C4	N1	S1	120.81(7)	C1	C2	C3	115.29(9)
C7	C5	C4	109.29(9)	C8	C9	C10	107.74(10)
C6	C5	C4	111.75(9)	C9	C8	C7	107.86(10)

Table 6. Torsion Angles for Schomaker35 [NCG1056].

A	B	C	D	Angle/°	A	B	C	D	Angle/°
S1	O3	C1	C2	-94.10(10)	C5	C4	N1	S1	144.70(8)
O3	S1	N1	C4	43.89(9)	C5	C4	C3	C10	-43.43(11)
O3	C1	C2	C3	76.76(12)	C5	C4	C3	C2	-168.78(9)
O1	S1	O3	C1	-72.99(9)	C5	C7	C8	C9	-89.13(12)
O1	S1	N1	C4	161.63(8)	C7	O4	C10	C3	-77.67(10)
O2	S1	O3	C1	158.97(8)	C7	O4	C10	C9	40.36(10)
O2	S1	N1	C4	-67.53(10)	C10	O4	C7	C5	77.85(10)
O4	C7	C8	C9	25.16(12)	C10	O4	C7	C8	-40.33(10)
O4	C10	C3	C4	60.30(11)	C10	C3	C2	C1	179.31(9)
O4	C10	C3	C2	-172.71(9)	C10	C9	C8	C7	-0.05(13)
O4	C10	C9	C8	-25.13(12)	C3	C4	N1	S1	-90.60(10)
C4	C5	C7	O4	-60.40(11)	C3	C4	C5	C7	43.45(12)
C4	C5	C7	C8	50.59(12)	C3	C4	C5	C6	168.68(9)
C4	C3	C2	C1	-56.28(13)	C3	C10	C9	C8	89.07(12)
N1	S1	O3	C1	41.91(9)	C9	C10	C3	C4	-50.74(12)
N1	C4	C5	C7	167.10(8)	C9	C10	C3	C2	76.25(12)
N1	C4	C5	C6	-67.67(12)	C6	C5	C7	O4	174.83(9)
N1	C4	C3	C10	-165.73(8)	C6	C5	C7	C8	-74.18(12)
N1	C4	C3	C2	68.92(11)					

Table 7. Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for Schomaker35.

Atom	*x*	*y*	*z*	U(eq)
H4	4335	4128	1051	13
H5	1844	3937	1499	15
H7	1077	5851	97	16
H10	3703	8824	1722	15
H3	3692	6036	2642	14
H1A	7051	5412	3460	19
H1B	5707	4577	3574	19
H2A	5943	6500	1879	18
H2B	5641	7554	2788	18
H6A	2423	1380	696	29
H6B	2646	2632	-173	29
H6C	1241	2403	35	29
H1	3736(17)	2740(30)	2665(13)	25(4)
H8	2842(17)	6170(20)	-784(13)	25(4)
H9	4509(18)	8060(30)	264(13)	29(5)

References:

[1] BRUKER-AXS. (2007-2013), APEX2 (Ver. 2013.2-0), SADABS (2012-1)

[2] SAINT+ (Ver. 8.30C) Software Reference Manuals, BRUKER-AXS, Madison, Wisconsin, USA.

[3] G. M. Sheldrick, *Acta Cryst.*, **2008**, *A64*, 112-122.

[4] O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. L. Howard, H. Puschmann, *J. Appl. Cryst.* **2009**, *42*, 339-341.

[5] XP – X-Ray Crystal Structure Visualization BRUKER, AXS, **1998**, V5.1

Department of Chemistry

Structure Report 2014

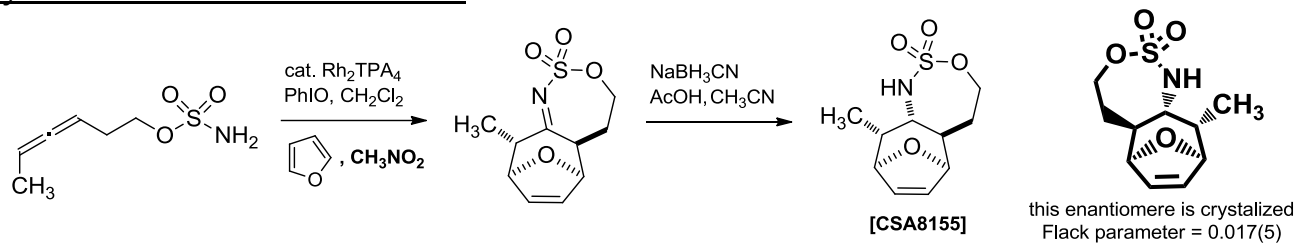
X-RAY
UW-Madison

SCHOMAKER
1101 University Ave,
Madison, WI, 53706, USA
Dr. Maik Tretbar
email: xray.tretbar@web.de

Crystallographic Experimental Section
XXXYYY

CCDC-no.

Crystal Structure of Schomaker50



Preparation of Crystals: A sample consisting of 20 mg racemic CSA8155 (column purified, purity ~ 90%) was dissolved in 2 mL dichloromethane and crystallized by slow evaporation at room temperature in a second vial with saturated atmosphere of n-hexane over 4 day at room temperature. The air-stable crystals were selected using a microscope to choose the best sample for X-ray crystallography.

Data Collection: A colorless crystal with approximate dimensions 0.140 x 0.07 x 0.05 mm^3 (needles) was selected under oil under ambient conditions and attached to the tip of a X-ray capillary (MiTeGenMicroMount©). The crystal was mounted in a stream of cold nitrogen at 100.0(15) K and centered in the X-ray beam by using a video camera. The crystal evaluation and data collection were performed on a three-circle Bruker Quazar SMART APEXII diffractometer with copper radiation K_α(α = 1.54184 Å) and the diffractometer to crystal distance of 4.96 cm. The initial cell constants were obtained from three series of ω scans at different starting angles. Each series consisted of 35 frames collected at intervals of 0.7° in 25° range about ω with the exposure time of 20 seconds per frame. The reflections were successfully indexed by an automated indexing routine built in the APEXII program suite. The final cell constants were calculated from a set of 9623 strong from the actual data collection. The data were collected by using the full sphere data collection routine to survey the reciprocal space to the extent of a full sphere to a high-resolution of 0.83 Å. A total of 16060 reflection data were harvested by collecting 15 sets of frames with 0.7° scans in ω and φ with exposure times of 12/35 sec per frame. These highly redundant datasets were corrected for Lorentz and polarization effects. The absorption correction was based on fitting a function to the empirical transmission surface as sampled by multiple equivalent measurements. [1,2]

Structure Solution and Refinement: The systematic absences in the diffraction data were consistent for the orthorhomic space groups $P2_12_12_1$. The E-statistics strongly suggested the chiral space group that yielded

chemically reasonable and computationally stable results of refinement. [3,4] The systematic absences in the diffraction data were uniquely consistent for the space group $P2_12_12_1$. A successful solution by the direct methods by using SHELX-2013 provided most non-hydrogen atoms from the E-map. Using Olex2, all non-hydrogen atoms were refined with anisotropic displacement coefficients. All hydrogen atoms were included in the structure factor calculation at idealized positions and were allowed to ride on the neighboring atoms with relative isotropic displacement coefficients.

Table 1. Crystal data collection and structure solution refinement for Schomaker50 [CSA8155]

Parameter	**CSA8155**	**Parameter**	**CSA8155**
empiric formula	$C_{10}H_{15}NO_4S$	$\rho_{calc.}$ [g · cm^{-1}]	1.503
MW [g · mol^{-1}]	245.29	crystal size [mm]	0.17 x 0.07 x 0.04
X-ray lab code	Schomaker50	T [K]	100.0(2)
a [Å]	9.0738(18)	radiation type / λ [nm]	Cu K_{α} / 1.54184
b [Å]	9.3215(19)	μ [mm^{-1}]	2.683
c [Å]	12.812(2)	F(000)	520.0
α [°]	90.000(0)°	Reflections collected	15.957
β [°]	90.000(0)	Independent reflections	2139 (R_{int} = 0.0282)
γ [°]	90.000(0)°	Data/restraints/parameters	2139/0/149
V [Å^3]	1083.6(4)	GooF on F^2	1.066
Z	4	Largest diff. peak/hole [eÅ^{-3}]	0.34 / -0.21
crystal system	orthorhombic	Flack *x* parameter	0.017(5)
crystal color	colorless	Final R_1[a]/ wR_2[b] all data	0.0275/ 0.0698
space group	$P2_12_12_1$	Final R_1[a]/ wR_2[b] I>2s(I)	0.0269/ 0.0694

[a] $R_1 = \sum \left| F_o \right| - \left| F_c \right| / \left| F_o \right|$;[b] $wR_2 = [\sum\{w(F_o^2 - F_o^2)^2\}/ \sum\{w(F_o^2)^2\}]^{½}$

The final least-squares refinement of 149 parameters against 2139 data resulted in R = 0.0269 (based on F^2 for I>2s) and wR2 = 0.0698 (based on F^2 for all data), respectively. The final structure was visualized using Interactive Molecular Graphics. [5]

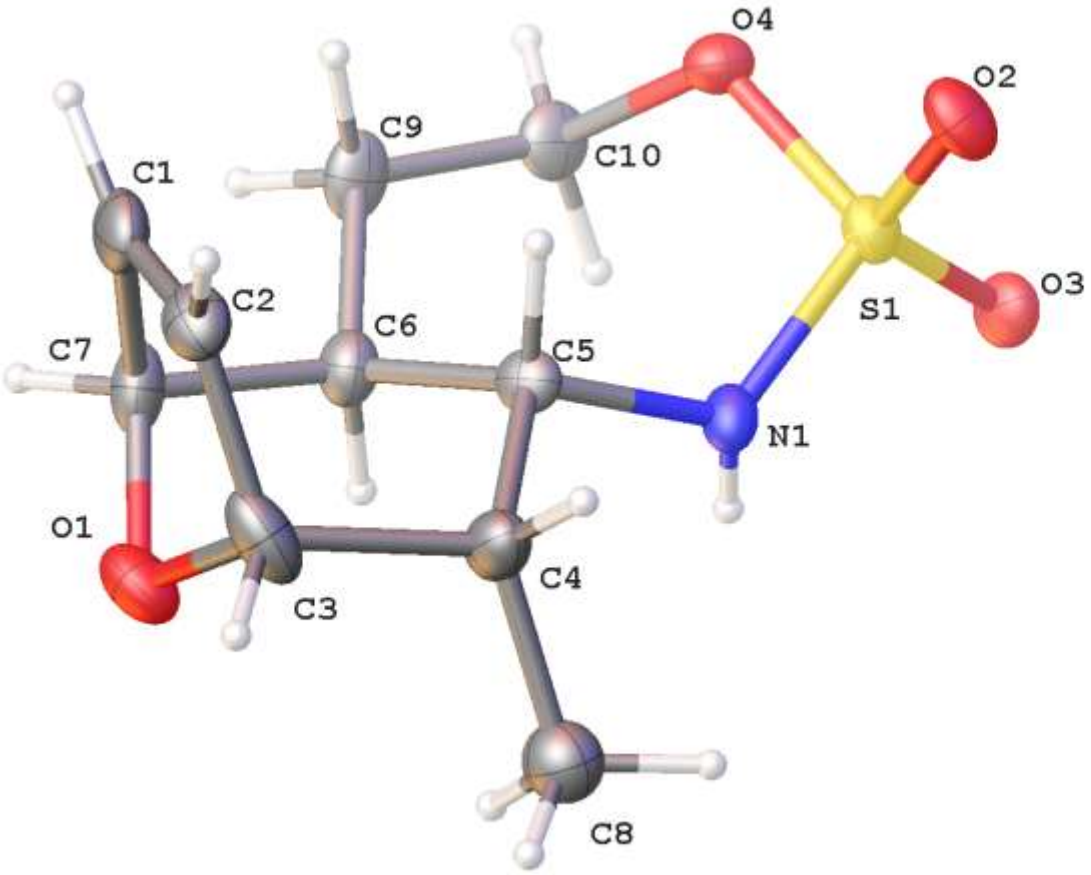


Figure 1. Thermal-ellipsoid of CSA8155 [Schomaker50] are set with 50 % probability.

Table 2, Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) for Schomaker50 . U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
S1	4077.2(6)	5284.0(5)	2259.1(4)	14.07(15)
O1	6850(2)	4535.4(19)	5983.5(14)	24.3(4)
O2	4006(2)	6784.6(17)	2036.8(13)	23.0(4)
O3	4090.2(19)	4287.9(17)	1411.6(12)	20.6(4)
O4	2667.4(17)	5042.3(16)	2951.8(12)	17.0(4)

N1	5469(2)	4916(2)	2980.7(14)	14.3(4)
C1	4893(3)	6073(3)	6245.0(19)	22.2(5)
C2	6045(3)	6875(3)	6031.7(17)	23.1(5)
C3	7224(3)	5932(3)	5573(2)	23.7(5)
C4	7110(3)	5846(3)	4372.1(19)	19.6(5)
C5	5515(2)	5397(2)	4079.4(17)	14.2(4)
C6	4837(3)	4223(3)	4795.9(19)	17.3(5)
C7	5268(3)	4548(3)	5938.7(18)	21.0(5)
C8	8292(3)	4866(3)	3926(2)	23.8(5)
C9	3174(3)	4070(3)	4679.2(18)	20.0(5)
C10	2616(2)	3733(2)	3592.5(18)	17.2(5)

Table 3. Anisotropic Displacement Parameters ($Å^2 \times 10^3$) for Schomaker50 . The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+...+2hka \times b \times U_{12}]$

Atom	**U_{11}**	**U_{22}**	**U_{33}**	**U_{23}**	**U_{13}**	**U_{12}**
S1	15.0(2)	13.6(3)	13.5(2)	2.09(19)	-2.3(2)	-1.6(2)
O1	27.0(9)	24.4(9)	21.4(8)	2.3(7)	-6.3(7)	5.7(8)
O2	27.8(8)	17.3(8)	24.1(8)	6.9(6)	-7.5(8)	-4.0(8)
O3	21.3(7)	24.5(8)	16.1(8)	-3.0(6)	-2.7(7)	-0.4(7)
O4	14.9(7)	15.0(8)	21.0(8)	1.4(6)	-0.3(6)	0.9(6)
N1	14.1(8)	14.8(10)	13.9(9)	0.2(7)	0.7(7)	0.9(7)
C1	27.7(12)	24.7(12)	14.3(11)	-2.5(9)	-0.5(9)	2.9(11)
C2	29.9(12)	21.6(11)	17.9(11)	-3.3(9)	-7.7(11)	-1.0(11)
C3	21.8(12)	26.1(13)	23.1(12)	1.2(10)	-7.9(10)	-1.3(10)
C4	17.5(11)	18.9(11)	22.5(12)	1.9(9)	-2.7(9)	-2.8(9)
C5	16.2(10)	13.3(10)	13.1(9)	-0.1(8)	-1.9(8)	0.3(9)
C6	22.3(11)	14.2(10)	15.4(11)	0.0(9)	-0.6(9)	2.0(9)
C7	25.0(12)	25.1(12)	13(1)	3.3(10)	-0.6(9)	-4.2(11)
C8	17.4(11)	28.0(13)	26.0(12)	0(1)	-1.3(9)	0.3(10)
C9	22.5(12)	18.3(12)	19.2(12)	2.7(9)	4.0(9)	-4.6(10)
C10	15.9(10)	13.9(10)	21.8(11)	3.1(9)	0.2(9)	-5.1(9)

Table 4. Bond Lengths for Schomaker50 .

Atom	Atom	Length/Å	Atom	Atom	Length/Å
S1	O2	1.4289(17)	C1	C7	1.513(3)
S1	O3	1.4287(17)	C2	C3	1.505(4)
S1	O4	1.5731(16)	C3	C4	1.543(3)
S1	N1	1.6020(19)	C4	C5	1.553(3)
O1	C3	1.444(3)	C4	C8	1.520(3)
O1	C7	1.437(3)	C5	C6	1.555(3)
O4	C10	1.472(3)	C6	C7	1.545(3)
N1	C5	1.478(3)	C6	C9	1.523(3)
C1	C2	1.314(4)	C9	C10	1.514(3)

Table 5. Bond Angles for Schomaker50 .

Atom	Atom	Atom	Angle/˚	Atom	Atom	Atom	Angle/˚
O2	S1	O4	102.47(10)	C3	C4	C5	108.49(19)
O2	S1	N1	111.10(11)	C8	C4	C3	111.0(2)
O3	S1	O2	119.02(10)	C8	C4	C5	113.9(2)
O3	S1	O4	110.02(9)	N1	C5	C4	109.76(18)
O3	S1	N1	107.04(11)	N1	C5	C6	109.74(18)
O4	S1	N1	106.54(9)	C4	C5	C6	114.56(18)
C7	O1	C3	102.27(19)	C7	C6	C5	108.75(19)
C10	O4	S1	117.33(13)	C9	C6	C5	113.6(2)
C5	N1	S1	120.47(16)	C9	C6	C7	111.2(2)
C2	C1	C7	107.6(2)	O1	C7	C1	102.8(2)
C1	C2	C3	108.3(2)	O1	C7	C6	106.79(19)
O1	C3	C2	102.5(2)	C1	C7	C6	111.9(2)
O1	C3	C4	107.5(2)	C10	C9	C6	116.2(2)
C2	C3	C4	111.9(2)	O4	C10	C9	109.28(18)

Table 6. Torsion Angles for Schomaker50 .

A	B	C	D	Angle/˚	A	B	C	D	Angle/˚
S1	O4	C10	C9	94.49(19)	C3	O1	C7	C1	-38.4(2)
S1	N1	C5	C4	-142.68(17)	C3	O1	C7	C6	79.5(2)
S1	N1	C5	C6	90.6(2)	C3	C4	C5	N1	-164.36(19)
O1	C3	C4	C5	58.8(3)	C3	C4	C5	C6	-40.4(3)
O1	C3	C4	C8	-67.1(2)	C4	C5	C6	C7	40.9(3)

O2	S1	O4	C10	-161.48(15)	C4	C5	C6	C9	165.3(2)
O2	S1	N1	C5	69.00(19)	C5	C6	C7	O1	-59.6(3)
O3	S1	O4	C10	70.98(17)	C5	C6	C7	C1	52.2(3)
O3	S1	N1	C5	-159.54(17)	C5	C6	C9	C10	57.6(3)
O4	S1	N1	C5	-41.86(19)	C6	C9	C10	O4	-76.4(3)
N1	S1	O4	C10	-44.72(17)	C7	O1	C3	C2	38.6(2)
N1	C5	C6	C7	164.88(18)	C7	O1	C3	C4	-79.5(2)
N1	C5	C6	C9	-70.7(3)	C7	C1	C2	C3	0.3(3)
C1	C2	C3	O1	-24.4(3)	C7	C6	C9	C10	-179.3(2)
C1	C2	C3	C4	90.5(3)	C8	C4	C5	N1	-40.2(3)
C2	C1	C7	O1	24.1(3)	C8	C4	C5	C6	83.8(2)
C2	C1	C7	C6	-90.2(3)	C9	C6	C7	O1	174.6(2)
C2	C3	C4	C5	-53.0(3)	C9	C6	C7	C1	-73.6(3)
C2	C3	C4	C8	-178.9(2)					

Table 7. Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for Schomaker50 .

Atom	*x*	*y*	*z*	U(eq)
H1	5710(30)	4150(30)	2850(20)	17
H1A	4008	6385	6532	27
H2	6118	7858	6145	28
H3	8209	6234	5796	28
H4	7278	6811	4094	24
H5	4892	6252	4136	17
H6	5285	3303	4604	21
H7	4836	3851	6423	25
H8A	8085	3891	4120	36
H8B	9237	5141	4197	36
H8C	8300	4946	3179	36
H9A	2844	3316	5146	24
H9B	2718	4956	4909	24
H10A	3224	2994	3278	21
H10B	1612	3379	3630	21

References.

1) BRUKER-AXS. (2007-2013), APEX2 (Ver. 2013.2-0), SADABS (2012-1).

2) SAINT+ (Ver. 8.30C) Software Reference Manuals, BRUKER-AXS, Madison, Wisconsin, USA.

3) G. M. Sheldrick, *Acta Cryst.*, **2008**, *A64*, 112-122.

4) O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. L. Howard, H. Puschmann, *J. Appl. Cryst.* **2009**, *42*, 339-341.

5) XP – X-Ray Crystal Structure Visualization BRUKER, AXS, **1998**, V5.1