Progress Towards the Synthesis of Jogyamycin

By

Nels Collins Gerstner

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

Jennifer M. Schomaker, Professor, Chemistry
Steven D. Burke, Professor, Chemistry
Helen E. Blackwell, Professor, Chemistry
Tehshik P. Yoon, Professor, Chemistry

Abstract

Jogyamycin is an aminocyclopentitol natural product that belongs in a family of molecules that contains pactamycin, amongst others. These structurally complicated molecules have a wide variety of functional groups in a condensed amount of space, making them fascinating targets for the synthetic chemist. Jogyamycin also displays activity against drug resistant malaria, making it an interesting target for structure-activity relationship studies. Previous approaches towards the synthesis of pactamycin and jogyamycin are discussed. We have undertaken several routes towards the synthesis of jogyamycin, including allene aziridination, allylic aminations, and Ichikawa rearrangements, and the results of those studies are described herein.

Acknowledgements

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Abbreviations and Acronyms

$(Bu_3Sn)_2$	Bis(tributyltin)
$(COCl)_2$	Oxalyl Chloride
$(DHQ)_2PHAL$	Hydroquinine 1,4-phthalazinediyl diether
$(^{l}Ipc)_2BH$	(*l*)-Diisopinocampheylborane
$(Me_2N)_2CH_2$	Bis(dimethylamino)methane
(*S*)-CBS	(*S*)-1-Butyl-3,3-diphenylhexahydropyrrolo[1,2-*c*][1,3,2]oxazaborole
$[allylPdCl]_2$	Allylpalladium(II) chloride dimer
$[IrCl(cod)]_2$	Bis(1,5-cyclooctadiene)diiridium(I) dichloride
$[Pd(OH)_2/C]$	Palladium Hydroxide on carbon
1,2-DCE	1,2-dichloroethane
5% Pd/C	5% palladium on carbon
Å	Angstrom
ABq	AB quartet
Ac_2O	Acetic Anhydride
AcOH	Acetic Acid
$Al(O\textit{i}\text{-}Pr)_3$	Aluminum Triisopropoxide
$AlMe_3$	Trimethylaluminum
appt	apparent
aq.	Aqueous
$AsPh_3$	Triphenylarsine
$B(OEt)_3$	Triethyl Borate
$BF_3\text{-}OEt_2$	Boron Trifluoride Diethyl Etherate
$BH_3\text{-}Me_2S$	Borane Dimethyl Sulfide Complex
BINAP	1,1′-Binaphthalene-2,2′-diyl)bis(diphenylphosphine)
Bn	Benzyl

BnBr	Benzyl Bromide
Boc_2O	Di-*tert*-Butyl Dicarbonate
BOM	Benzyl Methyl Ether
BOMCl	Benzyl Chloromethyl Ether
Br_2	Bromine
bs	broad singlet
BSA	*N,O*-Bis(trimethylsilyl)acetamide
BzONa	Sodium Benzoate
C	Celsius
C_6D_6	Deuterated Benzene
C_6H_6	Benzene
CAM	Ceric Ammonium Molybdate
CBr_4	Carbon Tetrabromide
Cbz	Benzyloxycarbonyl
CD_2Cl_2	Deuterated Dichloromethane
$CDCl_3$	Deuterated Chloroform
$CeCl_3$	Cerium(III) chloride
$CeCl_3$-2LiCl	Cerium(III) chloride Bis(lithium chloride) complex
$CeCl_3$-$7H_2O$	Cerium(III) chloride heptahydrate
CH_2Cl_2	Dichloromethane
$CHCl_3$	Chloroform
Cl_3CCOCl	Trichloroacetyl chloride
Cl_3CN	Trichloroacetonitrile
$ClCO_2Me$	Methyl chloroformate
Cs_2CO_3	Cesium carbonate
CSA	Camphor-10-sulfonic acid

CsF	Cesium fluoride
CSI	Chlorosulfonyl isocyanate
$Cu(OTf)_2$	Copper(II) trifluoromethanesulfonate
CuCl	Copper(I) chloride
d	doublet
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
dd	doublet of doublets
ddd	doublet of doublet of doublets
dddd	doublet of doublet of doublet of doublets
ddq	doublet of doublet of quartets
DDQ	2,3-Dichloro-5,6-dicyano-*p*-benzoquinone
ddt	doublet of doublet of triplets
DIBAL	Diisobutylaluminum hydride
DIP-Cl	B-Chlorodiisopinocampheylborane
DMA	*N*,*N*-Dimethylacetamide
DMAP	4-(Dimethylamino)-pyridine
DMDO	Dimethyl dioxirane
DME	1,2-dimethyoxyethane
DMF	Dimethylformamide
DMP	Dess-Martin Periodinane
DMSO	Dimethylsulfoxide
Dpm	Benzhydryl
dp	doublet of pentets
dq	doublet of quartets
dqd	doublet of quartet of doublets
dt	doublet of triplets

dtd	doublet of triplet of doublets
dtt	doublet of triplet of triplets
ESI	Electron Spray Ionization
Et	Ethyl
Et_2BOMe	Diethyl methyoxyborane
Et_2O	Diethyl ether
Et_3N	Triethylamine
EtMgBr	Ethylmagnesium bromide
EtOAc	Ethyl acetate
EtOH	Ethanol
G-II	Grubbs Catalyst® 2^{nd} generation
H_2	Molecular hydrogen
$H_2CO_{(g)}$	Gaseous formaldehyde
H_2NSO_2Cl	Sulphamoyl chloride
H_2O	Water
H_2O_2	Hydrogen peroxide
H_2SO_4	Sulfuric acid
HCl	Hydrochloric acid
HCO_2H	Formic acid
HMPA	Hexamethylphosphoramide
HRMS	High Resolution Mass Spectrometry
hν	light
IBX	2-Iodoxybenzoic acid
i-Pr_2NEt	*N*,*N*-Diisopropylethylamine
i-PrOAc	Isopropyl acetate
i-PrOH	Isopropanol

K_2CO_3	Potassium carbonate
KHMDS	Potassium bis(trimethylsilyl)amide
KO*t*-Bu	Potassium *tert*-butoxide
LDA	Lithium diisopropylamide
$LiAl(Ot\text{-}Bu)_3H$	Lithium tri-*tert*-butoxyaluminum hydride
$LiAlH_4$	Lithium aluminum hydride
LiBr	Lithium bromide
LiCl	Lithium chloride
LiH	Lithium hydride
LiHMDS	Lithium bis(trimethylsilyl)amide
L-Selectride	Lithium tri-*sec*-butylborohydride
m	multiplet
m-CPBA	*meta*-chloroperbenzoic acid
Me	Methyl
Me_2NCONH_2	1,1-dimethylurea
Me_2NH	Dimethylamine
Me_2NH-HCl	Dimethylammonium chloride
Me_2S	Dimethyl sulfide
Me_4Sn	Tetramethyltin
MeCN	Acetonitrile
MeLi	Methyllithium
MeMgBr	Methylmagnesium bromide
MeNH(OMe)	*N*,*O*-Dimethylhydroxylamine
MeOH	Methanol
Mg	Magnesium
$MgBr_2$	Magnesium dibromide

MgO	Magnesium oxide
$MgSO_4$	Magnesium sulfate
MOMCl	Methyl chloromethyl ether
MS	Molecular sieves
MsCl	Methanesulfonyl chloride
$N_3PO(OPh)_2$	Diphenyl phosphoryl azide
Na_2SO_4	Sodium sulfate
$NaBH_4$	Sodium borohydride
NaCl	Sodium chloride
NaH	Sodium hydride
$NaHB(OAc)_3$	Sodium triacetoxyborohydride
$NaHCO_3$	Sodium bicarbonate
NaHMDS	Sodium bis(trimethylsilyl)amide
NaI	Sodium iodide
$NaIO_4$	Sodium periodate
NaN_3	Sodium azide
NaOAc	Sodium acetate
NaOH	Sodium hydroxide
NaOMe	Sodium methoxide
n-BuLi	*n*-Butyllithium
NH_4Cl	Ammonium chloride
NH_4F	Ammonium fluoride
NMO	4-methylmorpholine-*N*-oxide
O_2	Molecular oxygen
O_3	Ozone
OsO_4	Osmium tetroxide

p	pentet
$Pd(dba)_2$	Bis(dibenzylideneacetone)palladium(0)
$Pd(OAc)_2$	Palladium(II) acetate
$Pd(PPh_3)_4$	Tetrakis(triphenylphosphine)palladium(0)
Pd_2dba_3-$CHCl_3$	Tris(dibenzylideneacetone)palladium(0)-chloroform complex
Ph	Phenyl
Ph_2Se_2	Diphenyl diselenide
$PhI(OAc)_2$	(diacetoxyiodo)benzene
$PhI(OPiv)_2$	(dipivaloyloxyiodo)benzene
PhINTs	(Tosylimino)phenyl-λ^3-iodane
PhIO	Iodosobenzene
$PhNTf_2$	*N*-Phenyl-bis(trifluoromethanesulfonimide)
PhSeBr	Phenylselenyl bromide
PhSeCl	Phenylselenyl chloride
PhSH	Thiophenol
PMB	4-(methyoxy)-benzyl
PMBCl	4-(methyoxy)-benzyl chloride
$PMBOCH_2Cl$	4-(methyoxy)-benzyl chloromethyl ether
PMBz	4-(methyoxy)-benzoyl
p-$MeOC_6H_4COCl$	4-(methyoxy)-benzoyl chloride
PMP	4-(methyoxy)-phenyl
PPh_3	Triphenylphosphine
q	quartet
qd	quartet of doublets
qq	quartet of quartets
qt	quartet of triplets

$Rh_2(esp)_2$	Bis[rhodium(α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid)]
$Rh_2(HNCOCF_3)_4$	Rhodium(II) trifluoroacetamide dimer
$Rh_2(OAc)_4$	Rhodium(II) acetate dimer
$Rh_2(oct)_4$	Rhodium(II) octonate dimer
$Rh_2(TPA)_4$	Rhodium(II) triphenylacetate dimer
s	singlet
$Sc(OTf)_3$	Scandium(III) trifluoromethanesulfonate
SiO_2	Silicon dioxide
SmI_2	Samarium(II) iodide
$SOCl_2$	Thionyl chloride
t	triplet
TAI	Trichloroacetyl isocyanate
TASF	Tris(dimethylamino)sulfonium difluorotrimethylsilicate
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBD	1,5,7-Triazabicyclo[4.4.0]dec-5-ene
TBDP	*tert*-Butyldiphenylsilyl
TBDPSCl	*tert*-Butyldiphenylsilyl chloride
TBS	*tert*-Butyldimethylsilyl
TBSCl	*tert*-Butyldimethylsilyl chloride
TBSOTf	*tert*-Butyldimethylsilyl trifluoromethanesulfonate
t-BuLi	*tert*-Butyllithium
t-BuOCl	*tert*-Butyl hypochlorite
t-BuOOH	*tert*-Butyl hydrogenperoxide
td	triplet of doublets
TES	Triethylsilyl

TESCl	Triethylsilyl chloride
TESOTf	Triethylsilyl trifluoromethanesulfonate
Tf_2O	Trifluoromethanesulfonic anhydride
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
$TiCl_4$	Titanium(IV) chloride
TLC	Thin Layer Chromatography
TMSCCLi	Lithium trimethylsilylacetylide
TMSCl	Trimethylsilyl chloride
tp	triplet of pentets
tq	triplet of quartets
Troc	Trichloroethyloxycarbonyl
TrocCl	Trichloroethyl chloroformate
$VO(acac)_2$	Vanadyl acetylacetonate
XPhos	2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl
XPhos-Pd-GII	X-Phos aminobiphenyl palladium chloride precatalyst
$Yb(OTf)_3$	Ytterbium(III) trifluoromethanesulfonate
Zn	Zinc
$Zn(OTf)_2$	Zinc(II) trifluoromethanesulfonate

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Approaches to the Synthesis of Jogyamycin

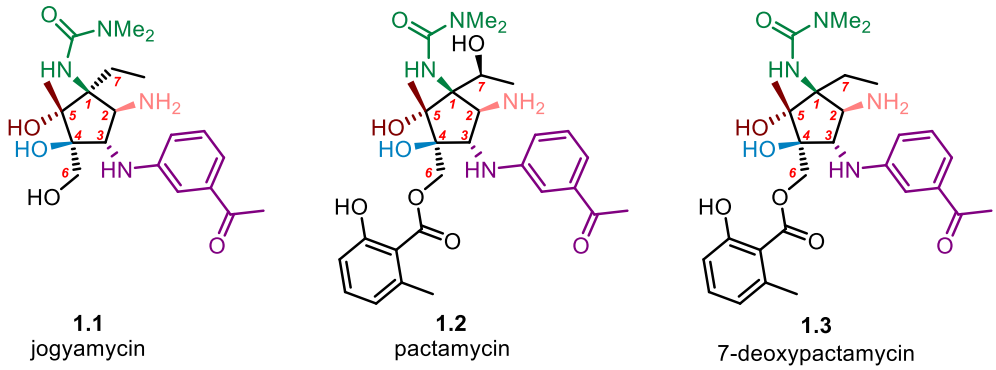
Chapter 1

Previous Approaches to the Synthesis of Pactamycin and the Aminocyclopentitol Core of Pactamycin and Jogyamycin

1.1 Introduction

In 2012 Otogura, Ōmura and co-workers reported the isolation of a new natural product from a strain of *Streptomyces* bacteria.[1] They named this new natural product jogyamycin (**1.1**, Figure **1.1**) after the city of Jogjakarta, Indonesia where the bacteria was first discovered. Structurally this natural product is related to pactamycin (**1.2**) and its known analogs, such as 7-deoxypactamycin (**1.3**). Pactamycin itself was first isolated from *Streptomyces pactum* in 1961, but its complex structure eluded characterization until 1970, when researchers at the Upjohn company utilized NMR analysis to identify the various functional groups located at each of the five carbons of the cyclopentane core.[2] The structure was further revised when the X-ray crystal structure was solved by Duchamp in 1972, revealing the structure to be **1.2**.[2d] Pactamycin, jogyamycin and their analogs show intriguing biological activity, exhibiting nanomolar levels of potency against strains of drug-resistant malaria.[1,3] Unfortunately, this family of molecules are also highly cytotoxic. Interestingly, small structural changes to this family of molecules yield analogues with altered selectivity, with some genetically engineered analogs showing significantly less cytotoxicity than pactamycin and jogyamycin.[4] To further probe the structure-activity relationships in this family of molecules beyond what

Figure 1.1 – Jogyamycin and Related Molecules



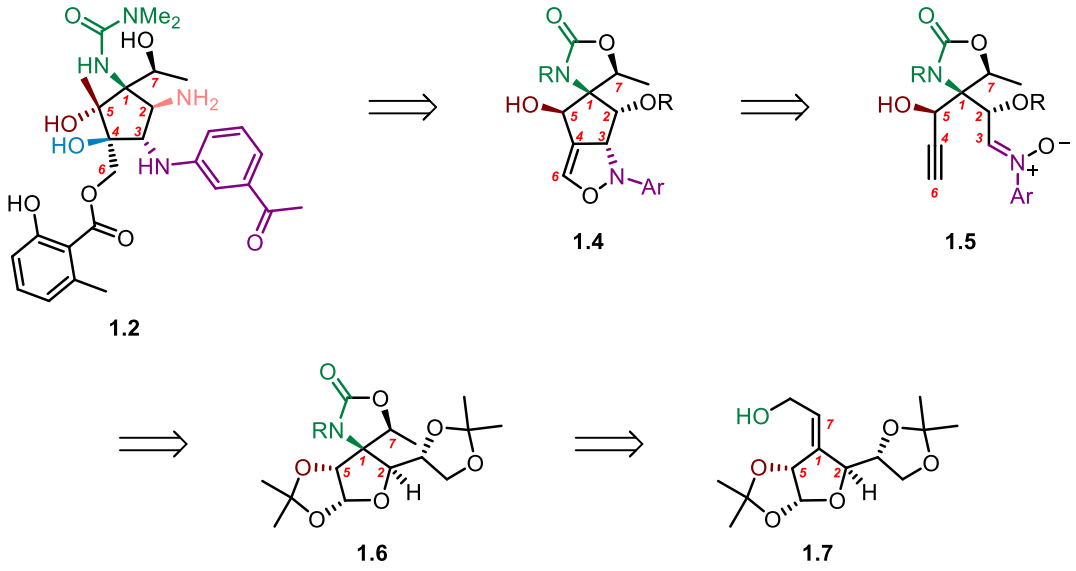
can solely be achieved through genetic engineering, modular chemical syntheses of this family of molecules need to be developed.

Structurally, the aminocyclopentitols jogyamycin and pactamycin are imposing molecules. The C-1/C-2/C-3 portion of the cyclopentane ring in **1.1** is comprised of three contiguous carbons bearing distinct amine functional groups, while the C-4/C-5/C-1 side of the ring bears three contiguous fully substituted carbons. All told, every carbon of the cyclopentane core bears a polar functional group. The stereochemical relationships between some of the adjacent heteroatom-bearing stereocenters also pose difficult challenges, such as the *cis* relationship between the C-1 urea and the C-2 amine or the *trans* relationship between the C-4 and C-5 tertiary alcohols. In addition to having the same cyclopentane core as jogyamycin, pactamycin also contains a stereodefined exocyclic alcohol at the C-7 position. At face value, this additional stereocenter would appear to make pactamycin an even more imposing target compared to jogyamycin. However, this stereocenter is used as an effective lynchpin in most syntheses of either pactamycin or its core to set the remaining stereocenters through diastereoselective reactions, the details of which will be discussed in this chapter. While the total synthesis of jogyamycin has not yet been accomplished, the potential applicability of the strategies reported for the syntheses of pactamycin or its core towards the synthesis of jogyamycin will be discussed.

1.2 Nishikawa's Synthesis of the Pactamycin Core

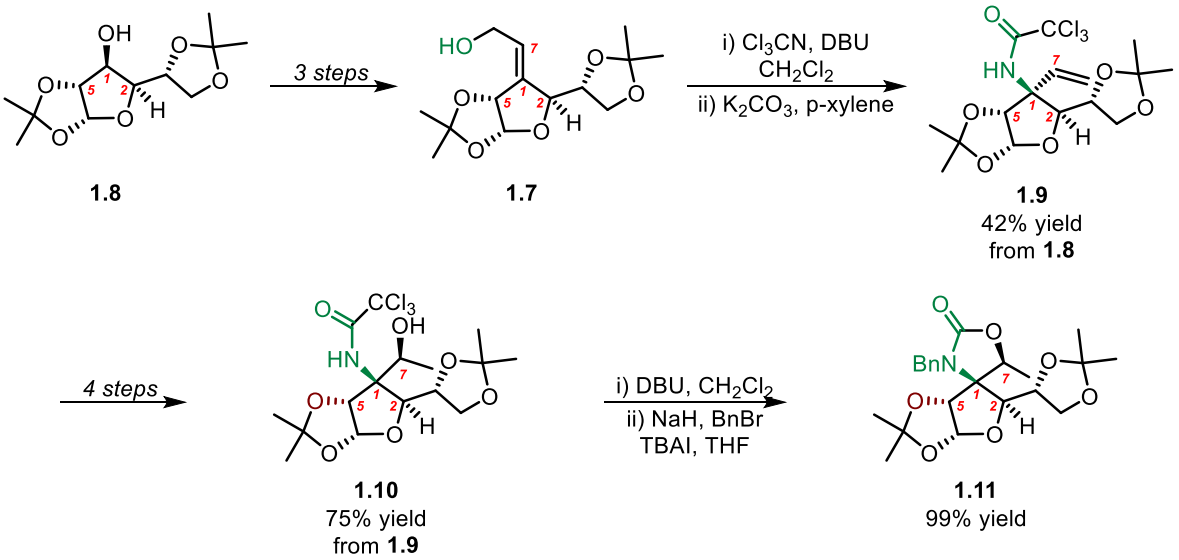
Nishikawa and co-workers were among the first to detail a route to the pactamycin core.[5] Nishikawa proposed forming the urea in **1.2** at a late stage from a carbamate formed between the C-1 amine and the C-7 alcohol in **1.4** (**Scheme 1.1**). They proposed the amine at C-2 could be formed from the alcohol at C-2 in **1.4**, presumably *via* either an S_N2 reaction or an oxidation/reductive amination sequence. The C-5 alcohol in **1.2** was to arise from an organometallic addition to a ketone, itself derived from the alcohol in **1.4**. The C-4 alcohol was to be formed *via* an oxidation of isooxazoline **1.4**. The isooxazoline **1.4** could be accessed *via* a [3+2] cycloaddition of nitrone **1.5**, although at the time, there was no precedent for predicting the stereochemistry that would be formed at C-3 by such a cycloaddition. This nitrone could be synthesized in a series of standard organic transformations from **1.6**. This protected amino sugar could be obtained *via* an Overman rearrangement from the allylic alcohol **1.7**.

Scheme 1.1 – Nishikawa's Retrosynthetic Analysis of Pactamycin



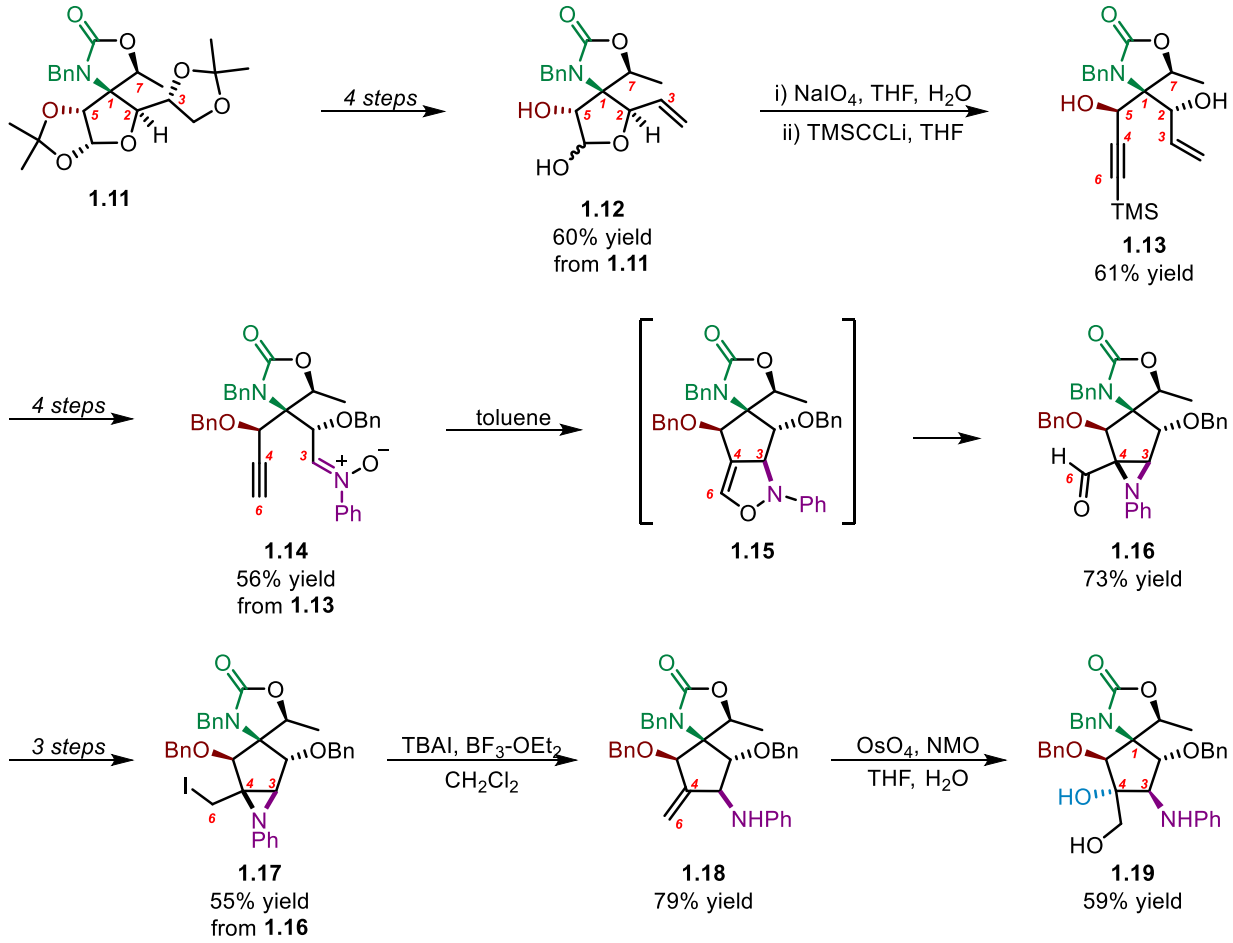
The synthesis begins with diacetone-D-glucose **1.8**, which is converted to the allylic alcohol **1.7** in three steps (**Scheme 1.2**). The Overman rearrangement of the allylic trichloroacetimidate proved to be highly diastereoselective, and **1.9** was accessed in an acceptable 42% yield from **1.8**. The alcohol at C-7 in **1.10** was formed in a series of steps by first oxidizing the alkene in **1.9** and the performing several functional group manipulations. The trichloromethyl group was displaced by the C-7 alcohol under basic conditions, yielding **1.11** after protection of the nitrogen with benzyl bromide. Through this series of steps Nishikawa was able to establish the challenging C-1 amine, as well as accessing the C-7 alcohol in a stereospecific manner. The step count to access carbamate **1.11** is relatively high, however, requiring nine steps to access this key intermediate. The majority of these steps involved oxidation state manipulations of the different alcohol functional groups, which is one drawback to starting with this readily available glucose derived material from the chiral pool.

Scheme 1.2 – Nishikawa's Overmann Rearrangement



The next phase of the synthesis involved fragmentation of the sugar and formation of the cyclopentane carbon skeleton of **1.2** (**Scheme 1.3**). Conversion of the acetal at C-3 of **1.11** into the olefin of **1.12** was accomplished; subsequent deprotection of the acetal at C-5 furnished the diol **1.12**. Periodate cleavage of the α-hydroxy aldehyde, followed by addition of lithium trimethylsilylacetylide gave **1.13** in good yield, albeit with 21% of a minor diastereomer also being isolated. A series of functional group manipulations gave access to nitrone **1.14**, which was primed for the key [3+2] cycloaddition. Heating **1.14** in toluene led to complete consumption of the starting material, but the isoxazoline was not isolated. Rather, the aziridine **1.16** was the major product, although the stereochemistry about the newly formed C3-C4 bond was unknown. This product was hypothesized to arise from an unexpected Baldwin rearrangement of **1.15**. Nonetheless, the authors surmised that this intermediate could prove useful, provided that the correct

Scheme 1.3 – Nishikawa's [3+2] Cycloaddition



1.11

1.12
60% yield
from **1.11**

1.13
61% yield

1.14
56% yield
from **1.13**

1.15

1.16
73% yield

1.17
55% yield
from **1.16**

1.18
79% yield

1.19
59% yield

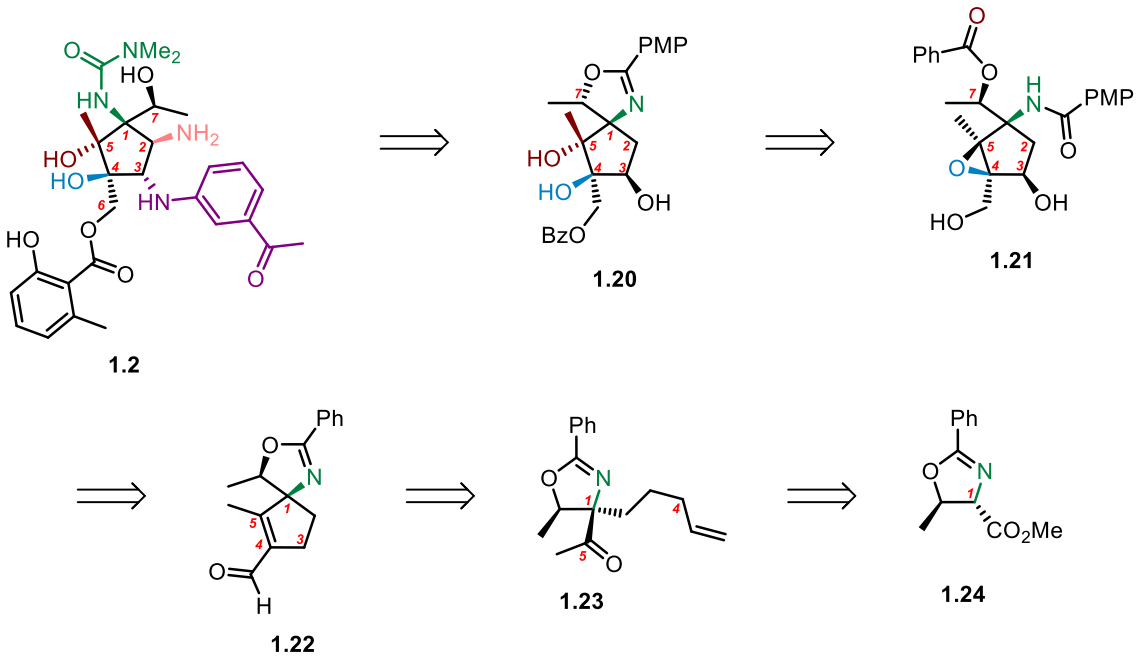
stereochemistry at C-3 was present. The elimination of the aziridine to form **1.18** was accomplished *via* conversion of the aldehyde into an iodide in three steps, followed by deiodination in the presence of BF_3-OEt_2. Dihydroxylation of the C-4/C-6 olefin yielded material whose stereochemistry could be determined *via* NOE experiments. Unfortunately, **1.19** contained a *cis* relationship between the carbamate at C-1 and the aniline at C-3, and a *trans* relationship between the alcohol at C-4 and the carbamate at C-1. While the configuration at C-4 could conceivably be corrected *via* ligand control of the dihydroxylation, the incorrect aniline configuration at C-3 would be far more challenging to resolve, especially since it occurs at such a late stage of the synthesis.

Despite these challenges, Nishikawa and co-workers were able to synthesize the core of pactamycin **1.2**, where each carbon of the ring possesses a heteroatom and two of the amine functional groups are included. Had their end game been successful, it is still unclear if this strategy could have been employed for the synthesis of jogyamycin (**1.1**). Intermediate **1.9** could have conceivably been shunted off towards **1.1** by hydrogenating the alkene, but formation of the cyclic carbamate would not have been a viable option, potentially affecting the success of various steps along this route.

1.3 Looper's Synthesis of the Pactamycin Core

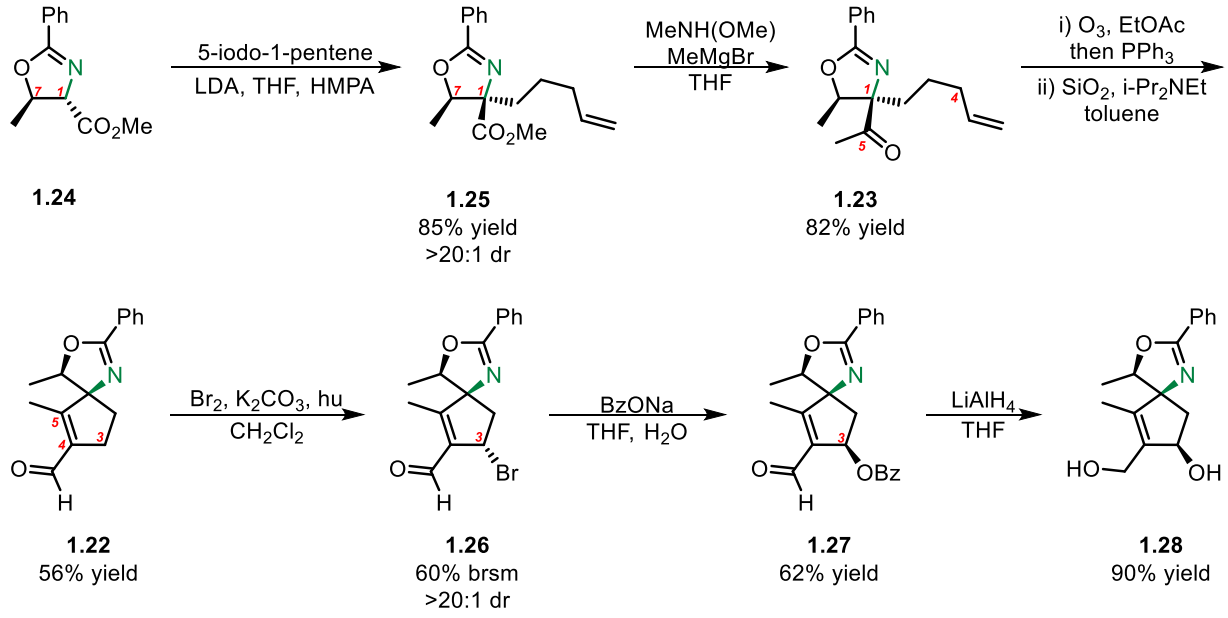
Looper and Haussener published a report in 2012 detailing access to the aminocyclopentitol core of pactamycin (**Scheme 1.4**).[6] They targeted aminocyclopentitol **1.20**, where the C-1 urea is masked as an oxazoline, the C-2 amine is absent, and the C-3 aniline is masked as an alcohol. The oxazoline and the C-5 tertiary alcohol in **1.20** were proposed to arise *via* an epoxide opening cascade of epoxide **1.21**, which could be accessed from cyclopentenal **1.22**. The cyclopentenal could be formed from oxazoline **1.23**, which is available in a few short steps from threonine-derived **1.24**. This is a similar starting point is similar to the successful route to pactamycin **1.2** developed by Hanessian and co-workers, which is detailed in section 1.8 of this chapter.

Scheme 1.4 – Looper's Retrosynthetic Analysis of Pactamycin



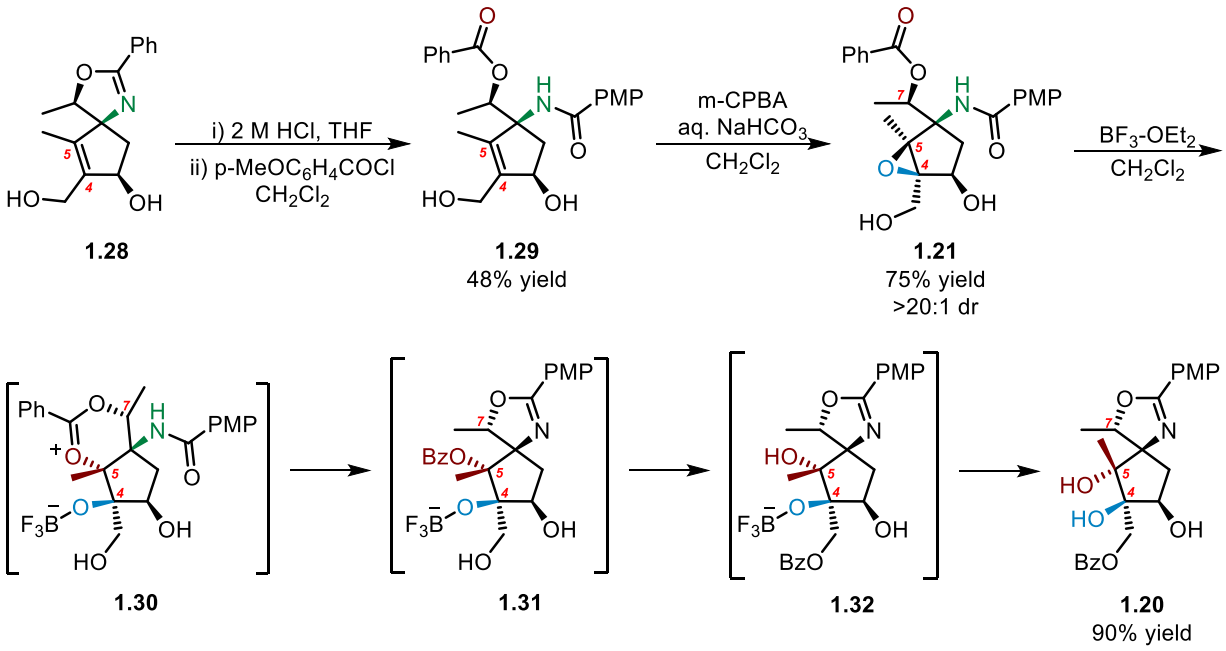
The protected amino acid **1.24** was used in a diastereoselective alkylation to yield **1.25** with C-1 set with the correct stereochemistry (**Scheme 1.5**). It should be noted that the stereochemistry at C-7 is opposite that of the pactamycin, but this will be altered later in the synthetic route. Conversion of **1.25** to ketone **1.23** occurred smoothly. Ozonolysis of the alkene and subsequent aldol condensation yielded cyclopentenal **1.22**

Scheme 1.5 – Looper's Formation of the Cyclopentane Ring



in moderate yield. Radical bromination conditions generated the C-3 allylic bromide **1.26** as a single stereoisomer possessing a *trans* relationship between the C-1 amine and the bromide. The observed facial selectivity poses a problem for installation of the aniline at C-3, as it would likely require a double displacement to install the aniline with the correct stereochemistry. Displacement of the bromide with sodium benzoate gave **1.27** in moderate yield. Reduction of both the aldehyde and ester with $LiAlH_4$ furnished allylic alcohol **1.28** in excellent yield.

Scheme 1.6 – Looper's Epoxide Opening Cascade



With allylic alcohol **1.28** in hand, the next key transformations involved oxidations of C-4 and C-5 (**Scheme 1.6**). The oxazoline **1.28** was hydrolyzed under acidic conditions, and the intermediate primary amine was acylated to give amide **1.29**. The directed epoxidation of the C-4/C-5 alkene proceeded smoothly with *m*-CPBA, and epoxide **1.21** was isolated in >20:1 *dr*. Exposure of the epoxide **1.21** to BF_3-OEt_2 initiates a ring-opening cascade, where the C-7 benzoate ester attacks the epoxide at C-5, establishing the correct stereochemistry for oxygen at C-5 in intermediate **1.30**. The oxygen at C-7 in **1.30** is then displaced by the amide oxygen to form the oxazolidinone **1.31**. Unexpectedly, the benzoate group migrates from the C-5 oxygen to the C-6 oxygen, which yields oxazolidinone **1.20** after workup. It is during this cascade

epoxide opening that the incorrect stereochemistry at C-7 from **1.28** is inverted, giving the correct stereochemistry at C-7.

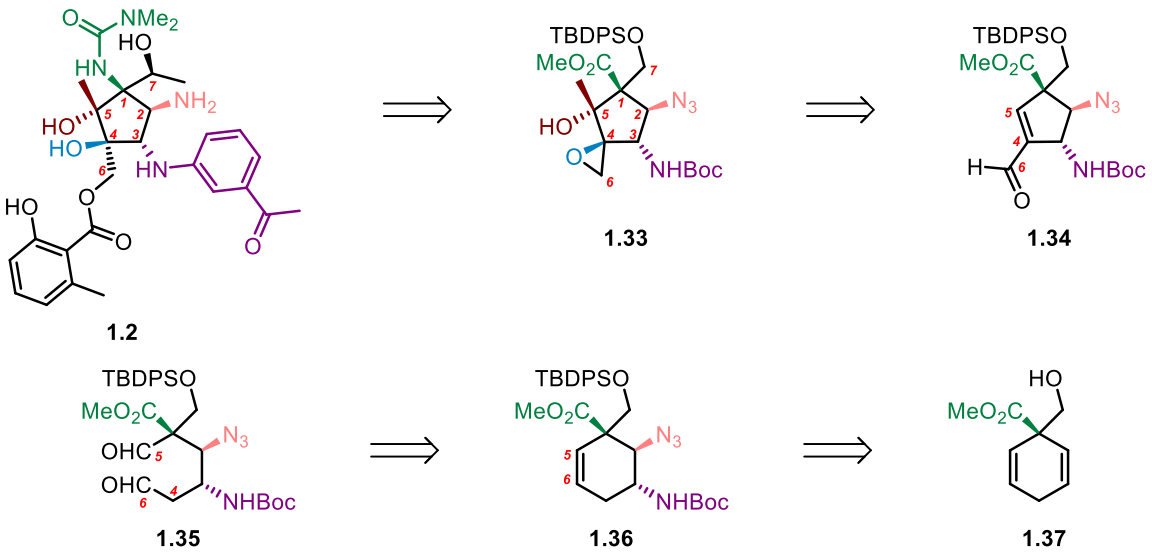
This route to the core of **1.2** is relatively rapid, with four of the stereocenters being set correctly in the nine steps between **1.24** and **1.20**. Despite this success, there has not been a follow-up publication detailing the completion of this synthesis. This is likely due to some of the challenges faced in functionalizing the C-2 and C-3 positions with the correct amine functionality. Although Looper and Haussener were able to functionalize the C-3 position with a radical bromination, the facial selectivity of this reaction generates an allylic bromide that requires a double displacement to yield the desired stereochemistry. This issue with the C-3 aniline is likely surmountable, but the functionalization of the C-2 position with an amine is expected to be more difficult. The C-2/C-3/C-4 carbons are introduced into the core *via* a diastereoselective alkylation in the absence of the amine functionality, which is challenging to install at a late stage. It is possible that an aldol or Mannich reaction as the first step could have brought the C-2 carbon into the synthesis with the correct oxidation state, making its later manipulation significantly easier.

Regardless of these issues, this route is notable for its rapid build-up of complexity and the creative leverage with which the C-7 alcohol is used to form the C-5 alcohol. The relationship between the C-7 and C-5 alcohols is unique amongst all reported syntheses of pactamycin (**1.2**) or its core, in that all other routes indirectly leverage the C-7 position to help dictate the stereochemistry of the C-5 position, typically through the formation of the C-1 urea. Unfortunately, the novel use of the C-7 alcohol also highlights the necessity of this functionality for this route. This precludes using a similar strategy to access jogyamycin (**1.1**) and other C-7 deoxygenated analogs.

1.4 Kan's Synthesis of the Pactamycin Core

In 2017, Kan and co-workers published a route to the core of **1.2** that utilizes a unique desymmetrization strategy (**Scheme 1.7**).[7] They planned to form the challenging C-1 urea *via* a Curtius rearrangement at a late stage, allowing them to move forward with the more predictable methyl ester. They also hypothesized the C-6 alcohol could be formed by opening an epoxide at the less substituted position in **1.33**. The aniline

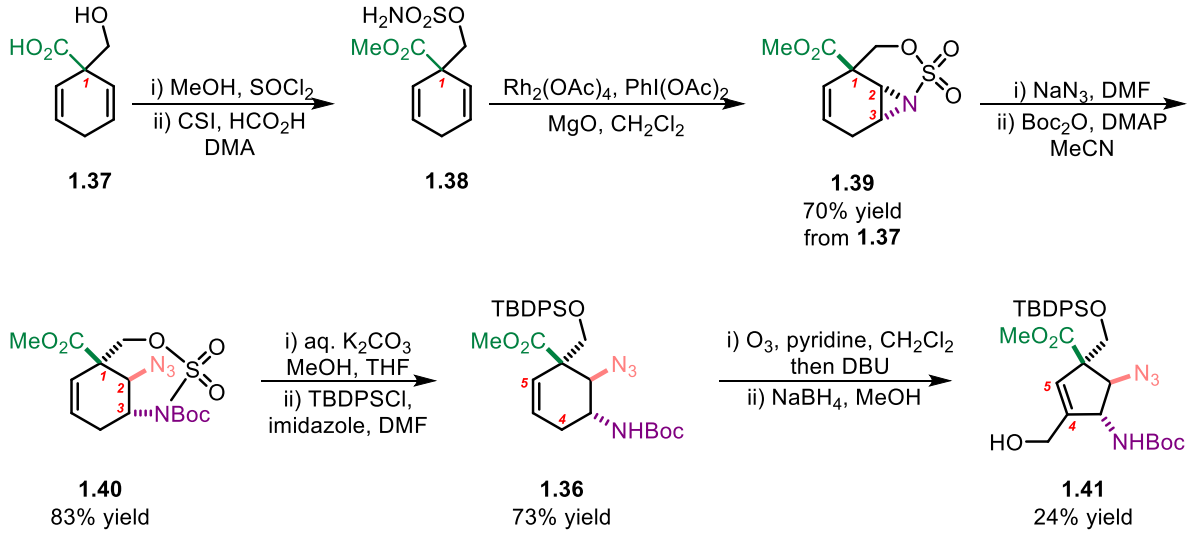
Scheme 1.7 – Kan's Retrosynthetic Analysis of Pactamycin



would arise from a late stage Buchwald-Hartwig coupling. Both the C-5 tertiary alcohol and the C-6/C-4 epoxide are both proposed to arise from the manipulation of the enal **1.34**. The enal could be formed *via* an aldol condensation reaction of **1.35**, which can be generated *via* ozonolysis of cyclohexene **1.36**. The *trans*-diamine **1.36** would be formed through the desymmetrization of diene **1.37** via a rhodium-mediated nitrene aziridination.

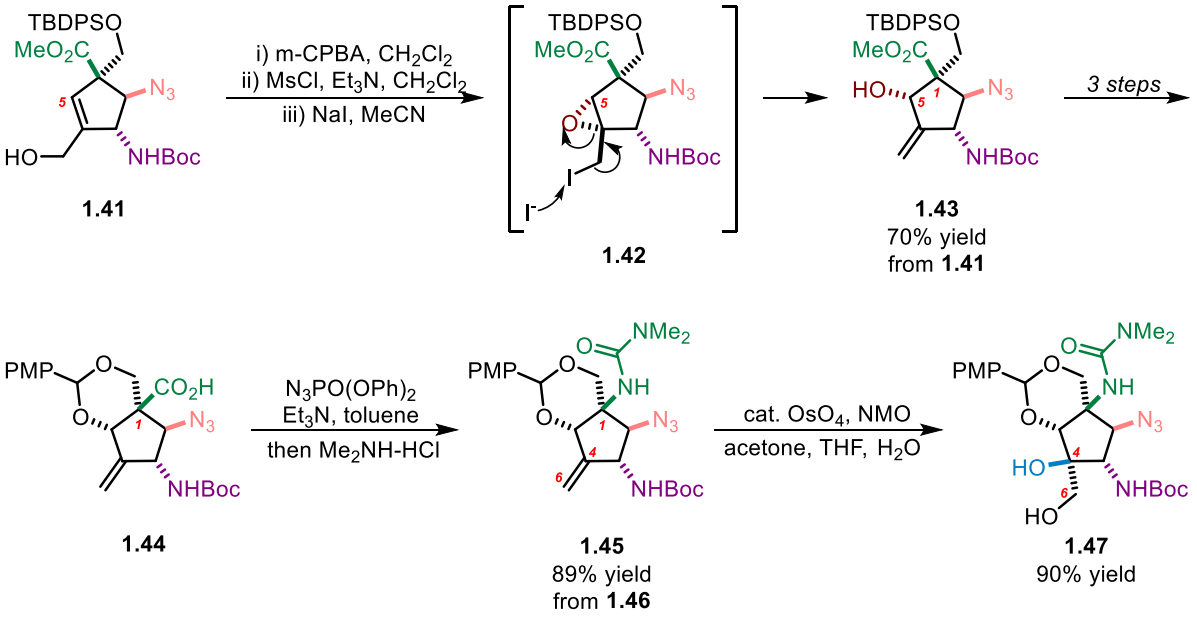
The desymmetrization of **1.37** was enacted at an early stage by forming sulfamate **1.38** from the corresponding alcohol, and then performing a $Rh_2(OAc)_4$-mediated aziridination to give **1.39** (**Scheme 1.8**).

Scheme 1.8 – Kan's Formation of the Diamino Cyclopentene Ring



The ring opening of **1.39** was regioselective for the position adjacent to the ester. Protection of the sulfamate nitrogen with a Boc group gives **1.40**, which is sufficiently activated for cleavage of the sulfamate. Hydrolysis of the sulfamate under basic conditions affords the primary alcohol, whose protection with a TBDPS group led to **1.36**. A tandem ozonolysis/aldol condensation was performed and reduction of the resulting enal with sodium borohydride yielded allylic alcohol **1.41** in low yield.

Scheme 1.9 – Kan's Curtius Rearrangement and C-4/C-6 Diol Formation



With access to cyclopentenol **1.41**, the next steps involved functionalization at the C-4 and C-5 positions (**Scheme 1.9**). The primary allylic alcohol **1.41** was isomerized stereoselectively to the endocyclic allylic alcohol **1.43** *via* a three-step sequence employing an epoxidation of an allylic alcohol followed by fragmentation of the intermediate epoxide. Protection of the C-5 and C-7 alcohols *via* a *p*-methoxybenzyl acetal and ester hydrolysis afforded the carboxylic acid **1.44**, which was primed for formation of the C-1 urea. An azide transfer reagent was used to initiate the Curtius rearrangement, with the addition of dimethylamine hydrochloride utilized to trap the intermediate isocyanate to furnish urea **1.45** in good yields. It should be noted that the Curtius rearrangement from the carboxylic acid used by Kan appears to be less problematic than the Hoffman rearrangement employed by Trost and co-workers from the amide (Section

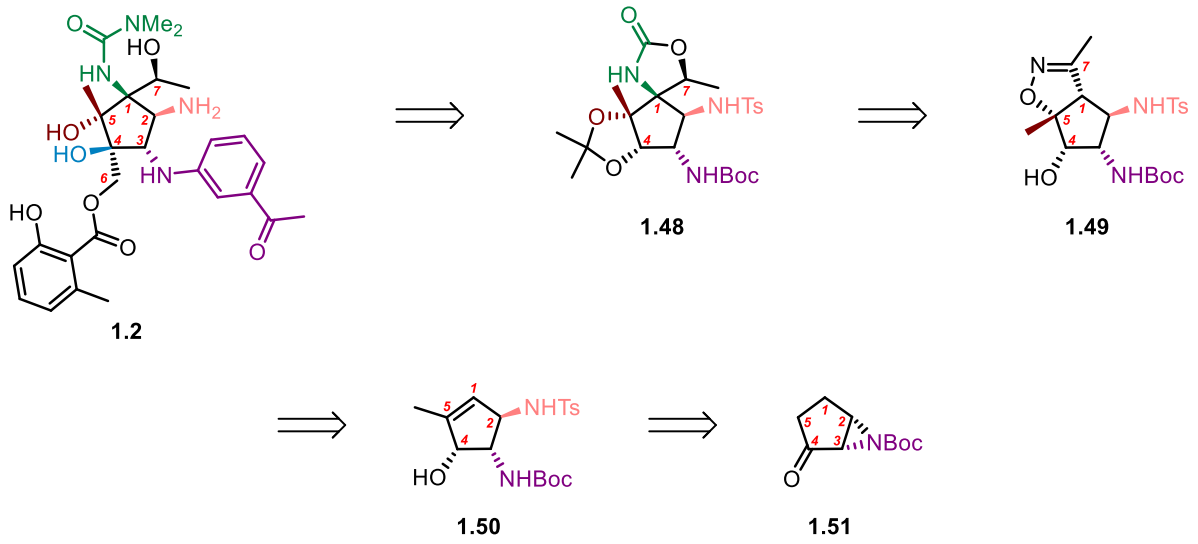
1.7). Dihydroxylation of the exocyclic alkene **1.45** with catalytic OsO_4 was highly diastereoselective and high yielding. This reaction was also performed on a relatively large scale for such a late intermediate, indicating that material throughput along this route is not an issue (2.1 mmol of **1.47** was isolated).

At this point, to complete the synthesis of **1.2** from intermediate **1.47**, three transformations need to take place. The Boc-protected amine must be coupled with an aryl group to form the aniline, the C-5 secondary alcohol needs to be transformed into a tertiary alcohol and the C-7 primary alcohol must be converted into a secondary alcohol. Conceivably, the latter two changes could be enacted in a single deprotection/oxidation/organometallic addition sequence. This strategy would rely on addition to the carbonyls occurring stereoselectively in concert, which could potentially prove to be problematic. This is to say nothing of the possibility of the organometallic addition to the extremely hindered ketone working, which Trost and co-workers found to be impossible, despite screening a wide array of conditions in a related system (Section 1.7). While a Buchwald-Hartwig coupling to form the aniline also has precedent in the route pioneered by Trost and co-workers, they performed the reaction on a considerably less hindered system. In Kan's case, the steric bulk around the nitrogen may prevent the coupling from occurring. Despite these potential challenges for the end game, this route synthesizes the challenging C-1/C-2/C-3 amine triad in a stereoselective manner, making this approach to the core a considerable achievement. Unfortunately, the reliance on the exocyclic C-7 alcohol to perform the desymmetrizing aziridination means that this route cannot be easily modified to access **1.1** or other 7-deoxy analogs.

1.5 Nemoto's Synthesis of the Pactamycin Core

Nemoto, Hamada and co-workers published a route to the core of pactamycin (**Scheme 1.10**).[8] Their key disconnect recognizes the *cis* relationship between the C-7 side chain and the C-5 alcohol, designing their synthesis around the installation of these two groups. They imagined that the C-1 urea could be formed at a late stage from cyclic carbamate **1.48**. The C-4 tertiary alcohol would arise from a secondary alcohol at C-4, minimizing the number of contiguous, fully substituted stereocenters until a later stage of the synthesis. The C-3 aniline would be formed through a late-stage Buchwald-Hartwig coupling. The carbamate in **1.48** would be derived from isooxazoline **1.49**, which could be formed from a 1,3-dipolar cycloaddition. This step would establish the *cis* relationship between the C-5 alcohol and the C-7 side chain. These reactions are known to be directed by allylic alcohols, necessitating the opposite orientation of the C-4 alcohol in **1.50** relative to that in **1.2**. The cyclopentenol **1.50** could be formed in a series of steps from chiral aziridine **1.51**. Using this aziridine gives facile access to the *trans* relationship between the differentiated amines at C-2 and C-3 at an early stage.

Scheme 1.10 – Nemoto's Retrosynthetic Analysis of Pactamycin

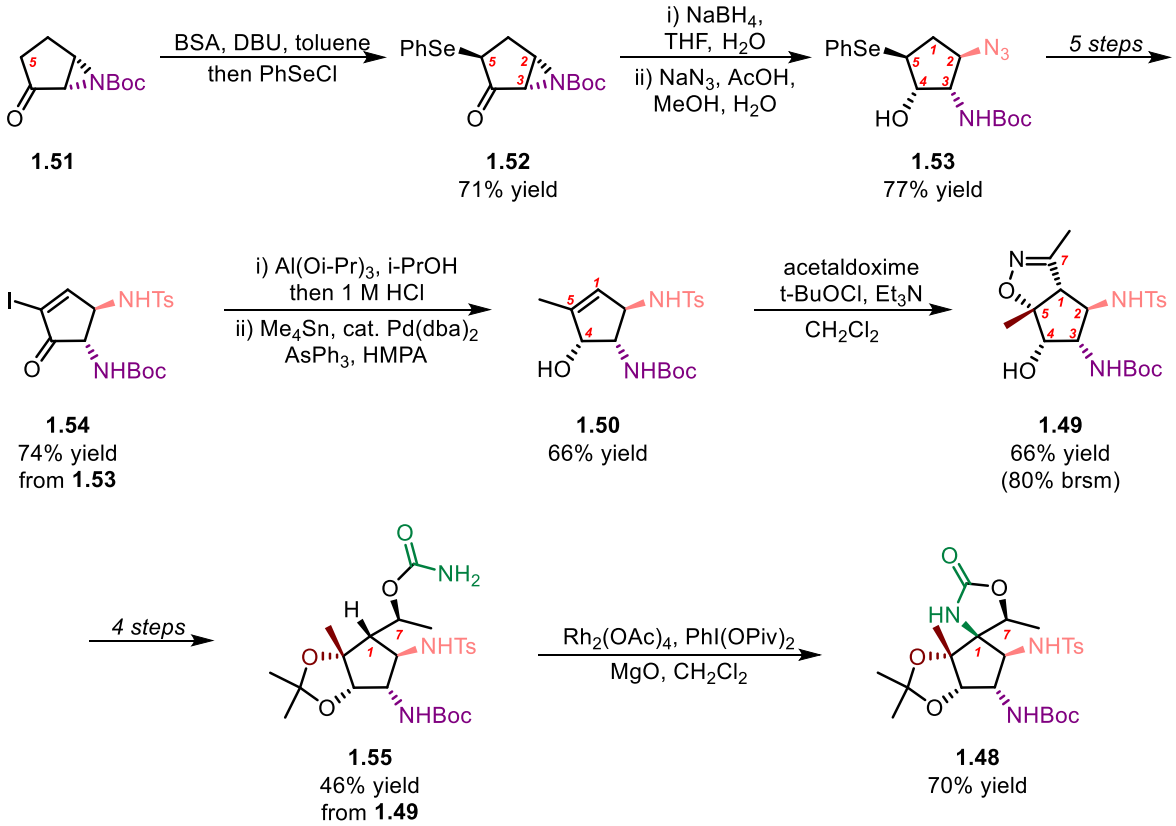


Chiral aziridine **1.51**, available in one step from cyclopentenone *via* an asymmetric intermolecular aziridination, was primed for forming an alkene between C-5 and C-1 by first generating the α-seleno ketone **1.52** (**Scheme 1.11**). Reduction of the C-4 ketone and regioselective opening of the aziridine at C-2 with

sodium azide yields **1.53**, containing the required *trans* relationship established between the differentiated C-2 and C-3 amine functional groups. With this stereochemical relationship in place, the subsequent five steps to transform **1.53** to **1.54** are spent on functional group interconversions and formation of the C-5/C-1 alkene. The non-nucleophilic C-2 azide was converted into a tosylsulfonamide. Hanessian's synthesis of **1.2** also employed a C-2 azide to allow for the installation of the C-1 urea at a late stage. It is probable that reduction of the planned isooxazoline could be problematic in the presence of the azide but having an azide installed at C-2 would make forming the C-1 urea far easier.

The α-iodo enone **1.54** was reduced diastereoselectively using a Meerwin-Pondorff-Verley reduction. Stille coupling of the vinyl iodide with tetramethyltin gives **1.50** in good yield. With the allylic alcohol in hand, the 1,3-dipolar cycloaddition with acetonitrile oxide generated from acetaldoxime and *tert*-butyl hypochlorite, gave isoxazoline **1.49**, presumably as a single diastereomer or regioisomer. Stepwise

Scheme 1.11 – Nemoto's Route to the Cyclopentane Core of Pactamycin



reduction of the isoxazoline, diol protection and carbamate formation gave **1.55**. The carbamate was then used to form the C-1 amine in **1.48** *via* a rhodium-catalyzed nitrene insertion.

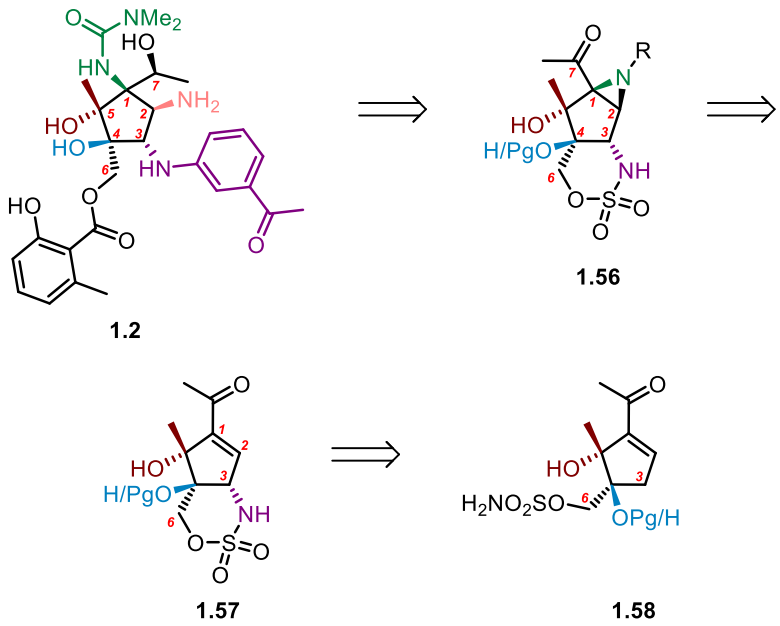
This synthesis is notable for its use of 1,3-dipolar cycloaddition to establish the C-5 alcohol stereocenter as well as the C-1/C-7 bond. In terms of strategy, this route is closest to the Looper route detailed in Section 1.3. However, the inherent difference between the two routes is in the other functional groups that were readily installed. Looper was able to form the C-4 and C-6 alcohols, whereas this route has both the incorrect orientation and substitution of the C-4 alcohol. In contrast, this route establishes the C-2/C-3 amine relationship, whereas Looper's intermediate contained only an alcohol at C-3.

At this point in the synthesis the installation of the remaining functional groups found in **1.2** would be expected to be quite challenging. A new C-C bond needs to be formed between C-4 and C-6 in a sterically hindered environment. The ability to react with a ketone formed at C-4, especially to give the correct C-4 stereochemistry, is of potential concerning. Equally challenging is the formation of the C-1 urea in the presence of the C-2 tosylsulfonamide. Any attempts to form an isocyanate at C-1 would rapidly result in a tosyl-protected cyclic urea. Protection of the C-2 sulfonamide would be required, which could be difficult in the crowded steric environment; at a minimum, these manipulations would increase the step count of the synthesis. The success of the Buchwald-Hartwig coupling to form the C-3 aniline could also be difficult at a late stage, due to the steric congestion of the molecule. Furthermore, the application of this route to jogyamycin (**1.1**) is unlikely to be feasible, as the key 1,3-dipolar cycloaddition requires an oxidized carbon at C-7. Nemoto uses this oxidized carbon as a linchpin to install the C-1 amine through a rhodium-mediated nitrene C-H insertion. Since the C-7 carbon must be in an elevated oxidation state for two key steps, it will be difficult to adapt this route to access the class of molecules that does not contain the same C-7 oxidation.

1.6 Du Bois' Synthesis of the Pactamycin Core

Du Bois and co-workers detailed a route to pactamycin that relies extensively on rhodium-catalyzed nitrene transfer reactions to install the urea and aniline amines.[9] Their initial plan utilized forming the C-2 amine in **1.2** from a C-1 aziridine in **1.56** through chemistry developed by their group (**Scheme 1.12**).

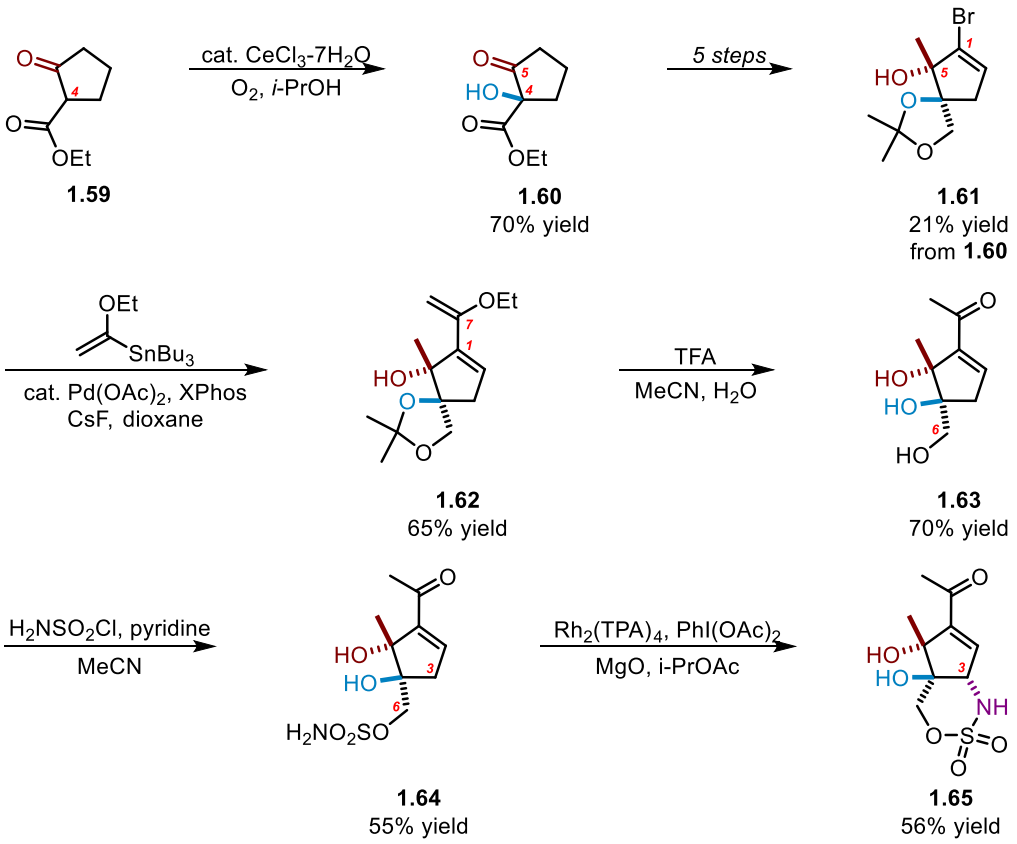
Scheme 1.12 – Du Bois' Retrosynthetic Analysis of Pactamycin



Similar to other groups, they planned to form the C-3 aniline at a late stage with a Buchwald-Hartwig coupling. Prior to the coupling, the amine would be tied up as a sulfamate between the C-3 amine and the C-6 oxygen. The C-1/C-2 aziridine was proposed to arise from the aziridination of enone **1.57**. An allylic amination of **1.58** would yield the C-3 amine in **1.57**. It was not clear if the alcohol at C-4 would have to protected or not for a successful synthesis; thus, different routes were developed to address this concern.

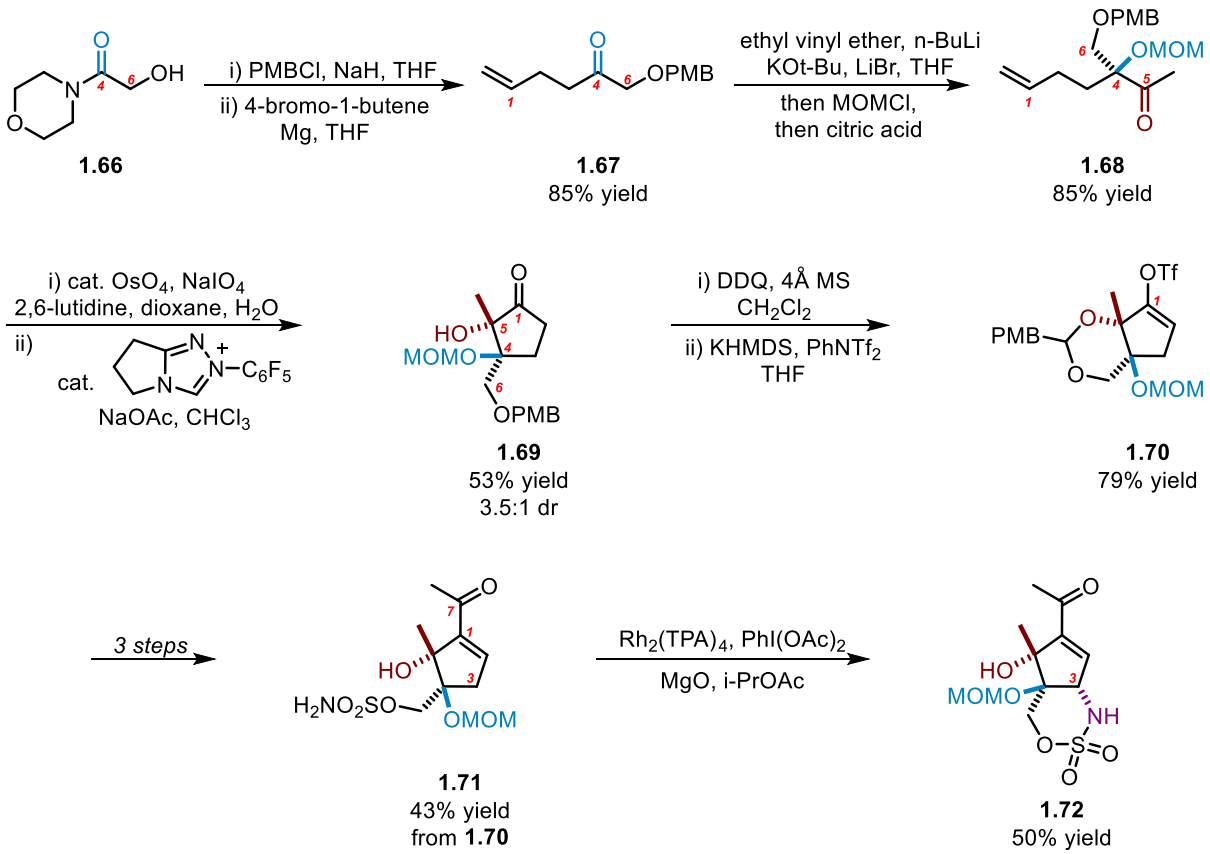
The first route begins with β-keto ester **1.59** which is oxidized to the tertiary alcohol **1.60** (**Scheme 1.13**). A series of five steps takes **1.60** to vinyl bromide **1.61**, where the C-7 side chain is then installed *via* a Stille cross coupling. Deprotection of the acetal frees the primary alcohol in **1.62** to be used in the formation of the sulfamate **1.64**. With this sulfamate in place, a diastereoselective allylic C-H insertion is accomplished using catalytic $Rh_2(TPA)_4$. This accomplishes the synthesis of the aminocyclopentitol core of **1.65** in ten steps from **1.59**.

Scheme 1.13 – Du Bois' Initial Route to the Allylic Sulfamate



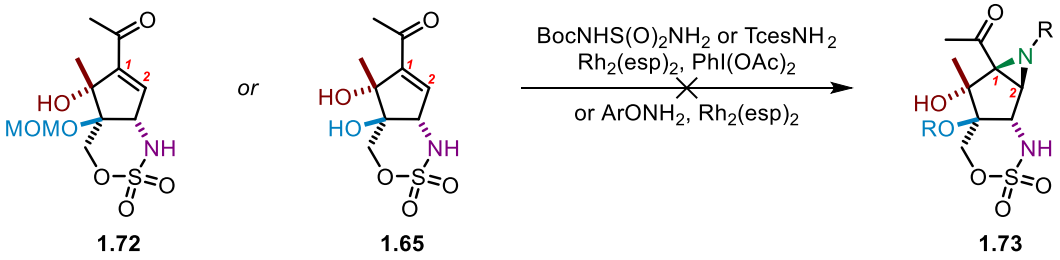
A second route to the core of pactamycin core, where the C-4 alcohol was protected, is illustrated in **Scheme 1.14**. Protection of **1.66** and organometallic addition to the morpholine amide resulted in unsymmetrical ketone **1.67**. Lithiation of ethyl vinyl ether and attack of the ketone resulted in a tertiary alkoxide that was protected with MOMCl *in situ*; subsequent hydrolysis of the enol ether under mild conditions gave **1.68**. Oxidation of the alkene of **1.68** to the aldehyde, followed by an NHC-catalyzed cyclization, afforded access to ketone **1.69** in moderate yield and *dr*. Acetal formation, followed by KHMDS and phenyl triflimide, gave the vinyl triflate **1.70**. This was transformed to the enone **1.71**, which undergoes $Rh_2(TPA)_4$ catalyzed nitrene C-H insertion to give **1.72** in moderate yield.

Scheme 1.14 – Du Bois' Second Route to the Allylic Sulfamate



With both the protected alcohol **1.72** and unprotected alcohol **1.65** in hand, a number of conditions to introduce the aziridine at C-1 were explored (**Scheme 1.15**). Conditions developed by the Du Bois group utilizing H_2NSO_2NHBoc to prepare *cis* 1,2-diamines proved to be unreactive. Exchange of this nitrene precursor with $TcesNH_2$ did not result in improved reactivity. The use of *O*-(2,4-dinitrophenyl)hydroxylamine as a nitrene precursor also led to no conversion. It was hypothesized that the enone was too electron-poor and that the allylic alcohol might prove to be a more forgiving substrate. Unfortunately, these same aziridination conditions also proved to be unreactive with the allylic alcohol, possibly due to the highly congested steric environment of the alkene.

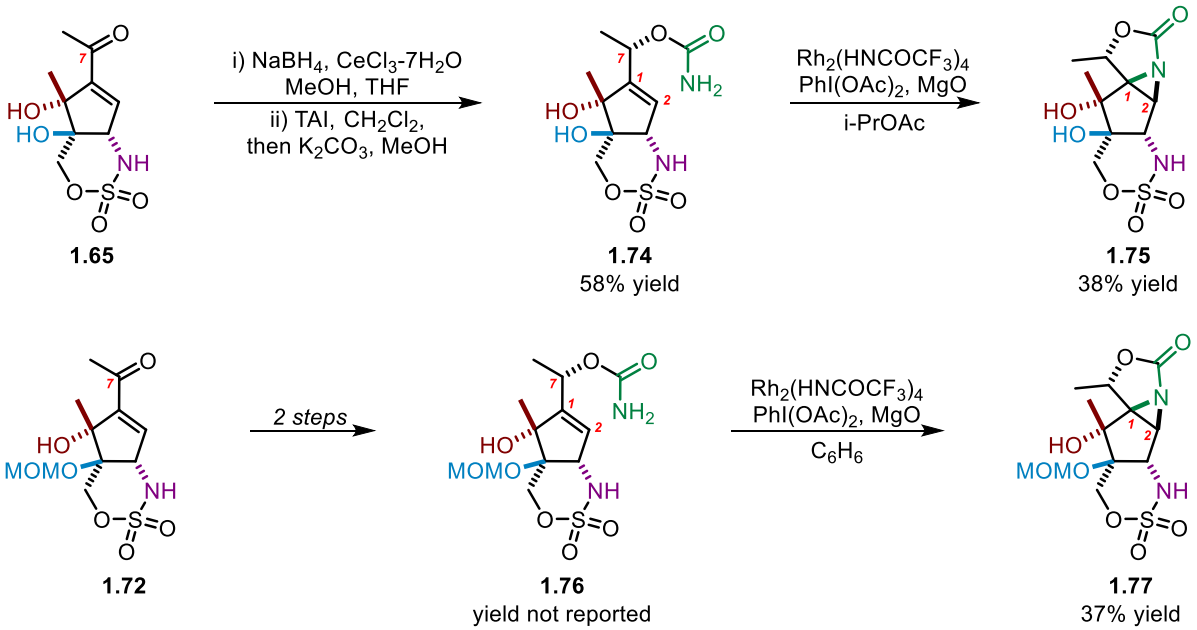
Scheme 1.15 – Du Bois' Attempted Intermolecular Aziridination of the Enone



In light of the difficulty of performing the intermolecular aziridination, the C-1 nitrogen was introduced *via* an intramolecular aziridination (**Scheme 1.16**). Reduction of enone **1.65** with Luche conditions, followed by formation of the carbamate, gave **1.74** in moderate yield. The intramolecular aziridination to give **1.75** proved to be more successful, albeit low-yielding. The rest of the mass balance was the result of oxidation of the C-7 position, resulting in the isolation of enone **1.65**. Aziridine **1.77** was also accessed, although the specific reaction conditions were not reported.

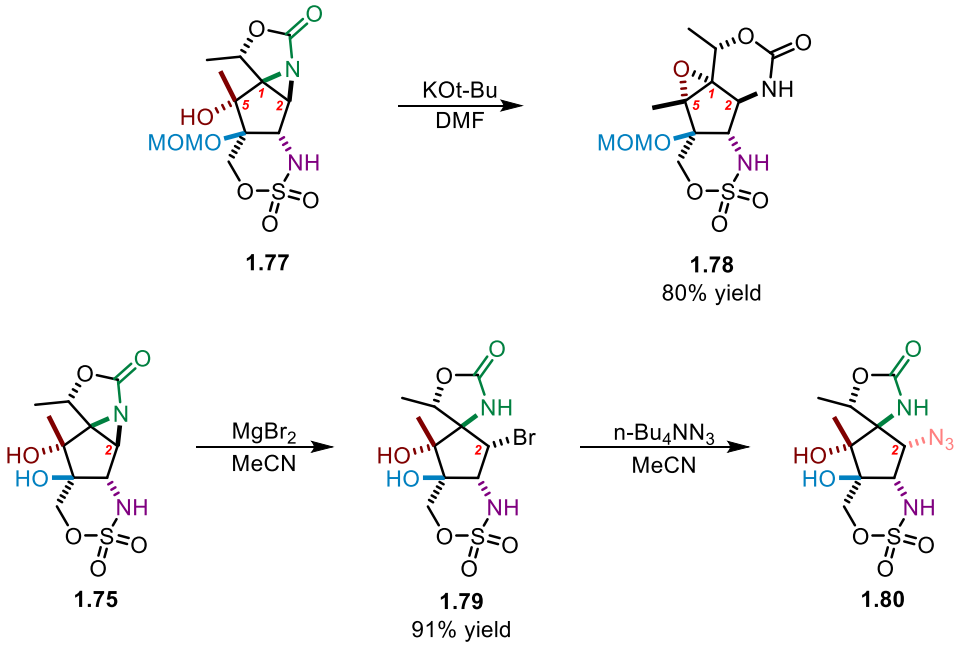
With aziridines **1.75** and **1.77** in hand, efforts were made to convert the C-1 aziridine into the C-1/C-2 *cis*-diamine *via* an S_N2 double inversion sequence (**Scheme 1.17**). Initial attempts to open the aziridine of **1.77** with the C-3 amine in the presence of a large excess of KO*t*-Bu failed. Instead of the C-3 amine acting

Scheme 1.16 – Du Bois' Formation of the C-1 Stereocenter *via* an Intramolecular Aziridination



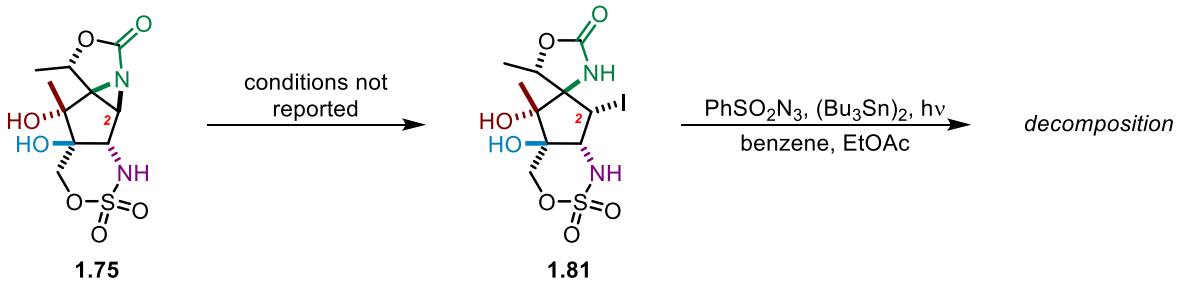
as an internal nucleophile, the C-5 alcohol attacked the aziridine to give rise to epoxide **1.78**. Du Bois did not discuss whether using catalytic amounts of KO*t*-Bu to deprotonate only the more acidic sulfamate also resulted in the formation of **1.78**. As strongly basic conditions were counterproductive, milder conditions were explored. It was found that the aziridine underwent opening with bromide using magnesium bromide as both a Lewis acid and a source of nucleophilic bromide anions. A challenging S_N2 reaction using azide as a nucleophile was then attempted; while azide product **1.80** was isolated, it was determined to have the incorrect C-2 stereochemistry. This result indicates that the reformation of the aziridine **1.75** is surprisingly easy in solution; likely this is the electrophile that undergoes attack by the azide anion. Attempts to perform the substitution *via* a radical pathway with iodide **1.81** also met with failure (**Scheme 1.18**).

Scheme 1.17 – Du Bois' Attempts to Form the C-2 Amine



The difficulties encountered in this route highlight the dangers of relying on reactions catalyzed by bulky transition metal catalysts to add functionality at a late stage in the synthesis of these sterically congested molecules. The lack of success in the intermolecular aziridination forced an approach that relied on an intramolecular aziridination to install the C-1 urea; however, this created a situation where it proved difficult to form the C-2 amine with the correct stereochemistry. The authors' attempts to salvage the route *via* the carbamate aziridine also highlights the potential for diverse functional groups to work against the synthetic chemist by participating in unexpected and undesired reactions, due to the close proximity of many reactive functional groups. In any case, application of this strategy to jogyamycin would have been challenging, as the intermolecular aziridination would still face the same steric hinderance issues in a system designed to access jogyamycin and the intramolecular aziridination would prove untenable due to oxidation required at C-7.

Scheme 1.18 – Du Bois' Attempted Formation of the C-2 Amine *via* Radical Chemistry

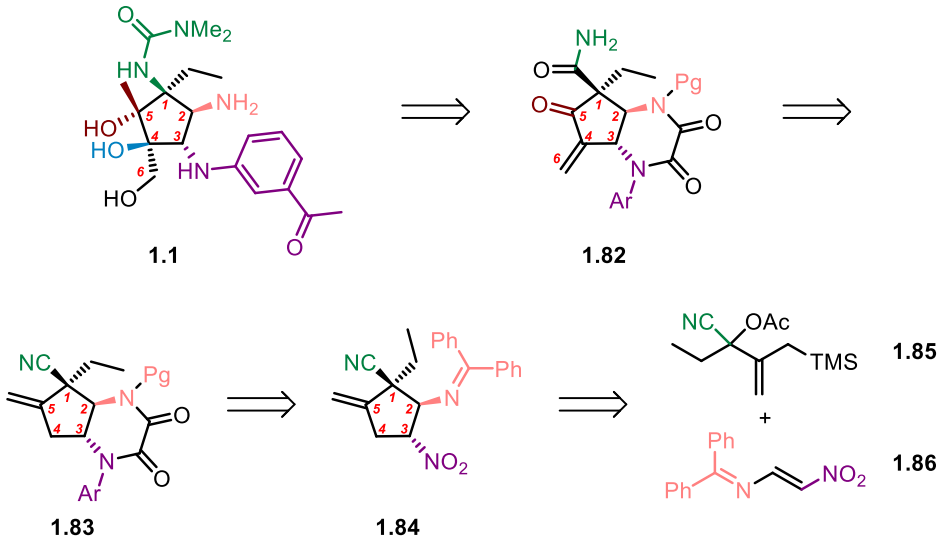


1.7 Trost's Synthesis of the Jogyamycin Core

In 2018, Trost and co-workers reported the first alternative route to the core of jogyamycin (**1.1**, **Scheme 1.19**) outside of our earlier report.[10] They proposed that the C-1 urea could be formed *via* a late-stage Hofmann rearrangement of an amide. The C-5 tertiary alcohol could be formed from an organometallic addition, and the oxidation at C-4 and C-6 would be formed through a dihydroxylation of an alkene. The C-3 aniline and C-2 amine would also be protected in **1.82** as an oxalamide. The amide in **1.82** could be formed *via* the hydrolysis of a nitrile. The C-5 ketone and C-4 alkene would arise from an ozonolysis of **1.83**, followed by an aldol condensation. The oxalamide in **1.83** would be generated from the

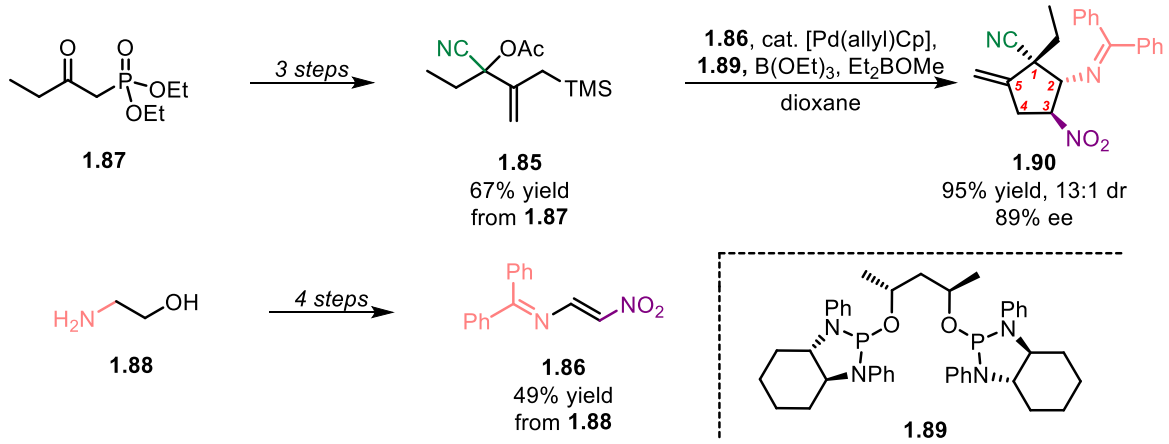
reduction of imine **1.84** followed by acylation. Imine **1.84** was proposed to be accessible *via* a palladium-catalyzed trimethylene methane (TMM) [3+2]-cycloaddition between TMM precursor **1.85** and β-nitroenamine **1.86**. The unique approach of this synthetic plan hinged on the formation of the chemically differentiated amines at the beginning of the route, thus leaving the synthesis of oxygenated functional groups for the endgame. As organometallic additions to carbonyls and dihydroxylations of alkenes are robust reactions, this proposed route saves less-precedented reactions for the beginning of the synthesis and more reliable reactions for the end.

Scheme 1.19 – Trost's Retrosynthetic Analysis of Jogyamycin



The synthesis commenced by developing routes to both of the precursors needed for the TMM cycloaddition (**Scheme 1.20**). Cyanoacetate **1.85** was accessible in three steps from ketophosphonate **1.87** *via* standard chemistry. A new, scalable route was developed to access **1.86** in four steps from 2-ethanolamine **1.88**. Conditions for the Pd-catalyzed TMM cycloaddition were developed that used a combination of $B(OEt)_3$ and Et_2BOMe as additives and the diamidophosphite ligand **1.89**. For reasons not stated in the text, the authors decided to use (*S*,*S*,*R*,*R*,*S*,*S*)-**1.89**, which they predict would give the opposite enantiomer of **1.1**, were the route to work. They obtained no crystal structures to confirm the absolute stereochemistry of the cycloadduct. Confusingly, they state that product derived from the use of ligand **1.89**

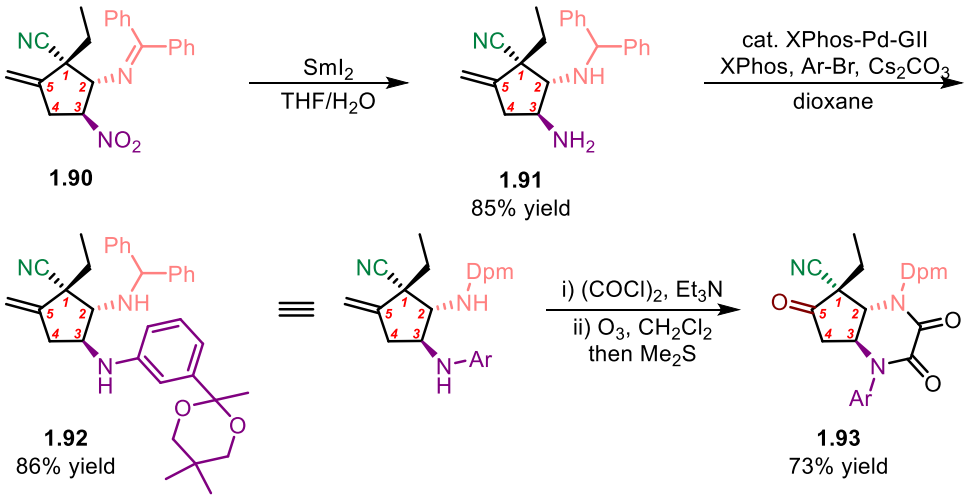
Scheme 1.20 – Trost's Asymmetric [3+2] Cycloaddition



"is predicted to be the enantiomer of the natural product" and that "[t]he natural enantiomer can be accessed by employment of readily prepared (*R,R,S,S,R,R*)-[**1.89**]". Presumably the former statement is a typographic error, and they proceeded through the synthesis with the unnatural enantiomeric series.

Initial efforts to move **1.90** forward through the synthesis focused on the reduction of the nitro group, which contained a stereocenter sensitive to epimerization. Samarium diiodide proved highly effective at both reducing the nitro group as well as the benzophenone imine, yielding diamine **1.91** (**Scheme 1.21**). The C-3 aniline could be formed through a Buchwald-Hartwig coupling, providing the protected aniline **1.92** in excellent yield. The protection of the diamine proved to be problematic, particularly that of the C-2 benhydryl amine. Using oxalyl chloride to form the oxalamide solved this issue by forcing the C-2 amine

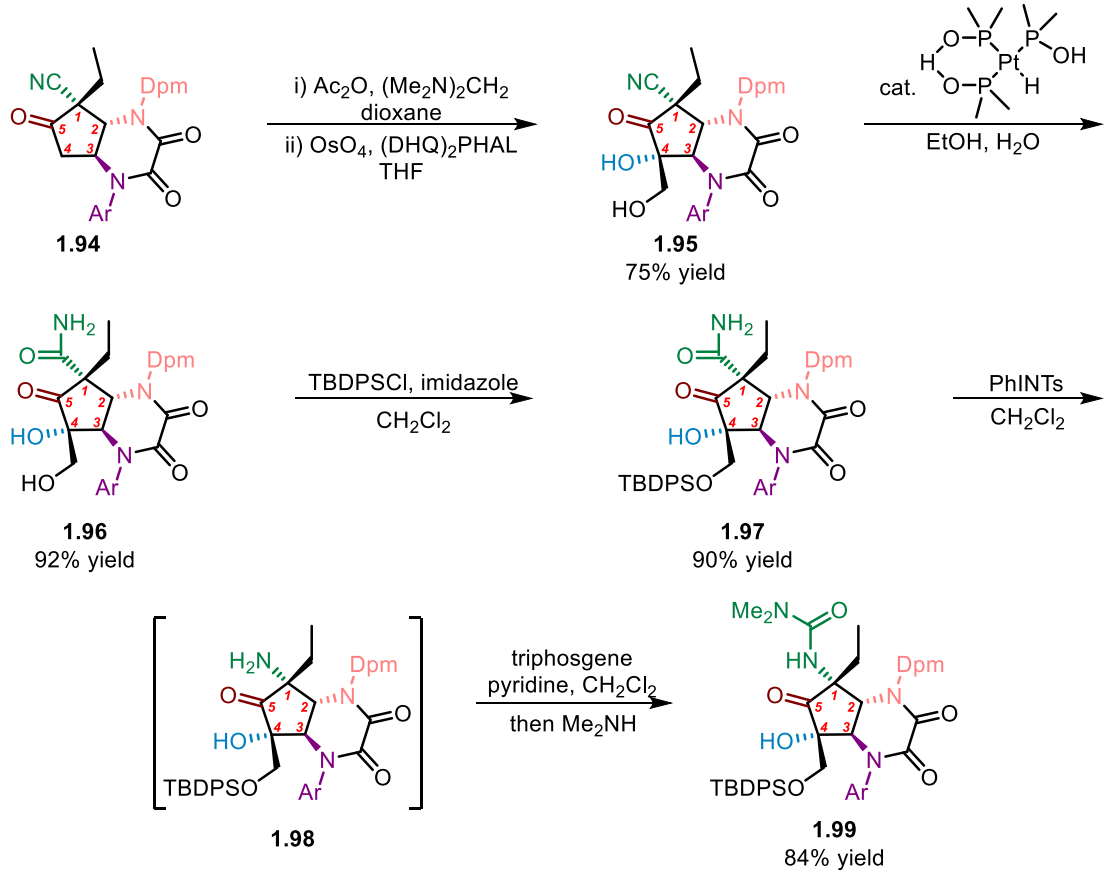
Scheme 1.21 – Trost's Oxalamide Formation and Alkene Ozonolysis



in closer proximity to the acyl chloride. Protection of the C-2/C-3 diamine is critical, as it increases the likelihood that the Hofmann rearrangement to form the C-1 urea will be successful by preventing the cyclic urea formation. Ozonolysis of the alkene at C-4 to yield **1.93** acts as an inflection point of the synthesis where focus is placed on the functionalization of C-1, C-4 and C-5.

The α-methylenation of ketone **1.93** at C-4 was unsuccessful *via* deprotonation with basic reagents, although acidic conditions using acetic anhydride and $(Me_2N)_2CH_2$ (**Scheme 1.22**) proved fruitful. The resulting exocyclic enone was sensitive to polymerization; in light of this, the optimal dihydroxylation conditions employed stoichiometric OsO_4. The inclusion of $(DHQ)_2PHAL$ was essential for isolating the correct diastereomer of **1.95**. With the diol in hand, focus was placed on enacting the Hofmann rearrangement. Hydrolysis of the nitrile with the Parkins-Ghaffar catalyst proceeded smoothly to provide **1.96** in high yield. The primary alcohol was protected before performing the Hofmann rearrangement of

Scheme 1.22 – Trost's Endgame Strategy



1.97. Using PhINTs, the isomerization to the isocyanate occurs. Unfortunately, the isocyanate was unstable and rapidly hydrolyzed to amine **1.98**. Ultimately, it was found that this amine could be turned into the urea by first forming the carbamoyl chloride with triphosgene and pyridine before quenching the carbamoyl chloride with dimethylamine, to furnish **1.99** in excellent yield. The only major functional group transformation left was the addition of a methyl group to form the C-5 tertiary alcohol, with all subsequent steps being deprotection steps. Unfortunately, the ketone was resistant towards reaction with a variety of nucleophiles, including Grignard reagents, MeLi and $AlMe_3$. The inclusion of $CeCl_3$ unfortunately did not result in improved reactivity. The only side product noted was cleavage of the oxalamide group.

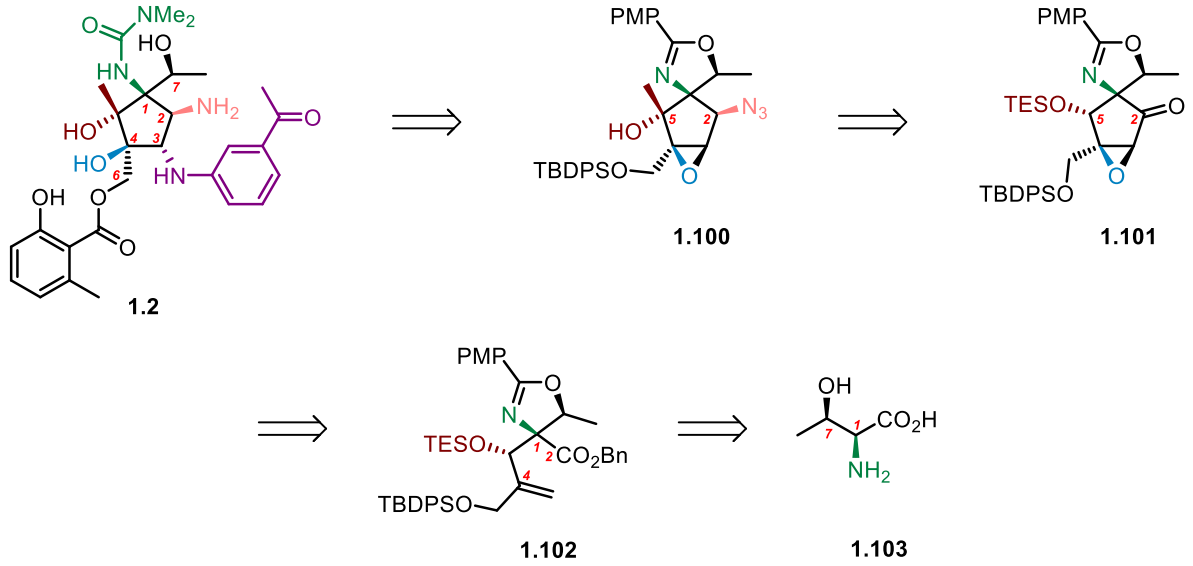
This route highlights how even extremely robust reactions, such as the addition of organometallic reagents to a ketone, can be challenging in this system. The steric hinderance posed by the flanking C-1 and C-4 fully substituted stereocenters certainly played a role in the failure of this reaction to occur. Careful consideration of the endgame of any synthesis within this family of molecules is critical, as many seemingly reliable reactions have met with unexpected failures. Despite the unfortunate setback, the Trost route is commendable in that it accesses four of the stereocenters on the ring without requiring oxygenation at the C-7 position. It also successfully differentiates the C-1, the C-2 and C-3 amines. Although this route failed to deliver the natural product, there is still potential to use this route to explore analogs of jogyamycin by either leaving the carbonyl intact or reducing it to the alcohol.

1.8 Hanessian's Synthesis of Pactamycin

Hanessian and co-workers achieved a considerable milestone by reporting the first total synthesis of **1.2** in 2011, 50 years after its isolation.[11] The key to their success was the realization that the C-4 alcohol and the C-3 aniline are *trans* to one another, a motif that could be accessed *via* a late stage aniline ring-opening of an epoxide (**Scheme 1.23**). The urea could be generated at a late stage through the hydrolysis of a cyclic oxazolidinone between C-1 and C-7, while the C-2 amine could be masked as an azide in **1.100**. The C-2 azide would originate from the functionalization of a carbonyl, and the C-5 tertiary alcohol could be formed *via* a secondary alcohol. Using a secondary alcohol would enable the use of a reliable aldol

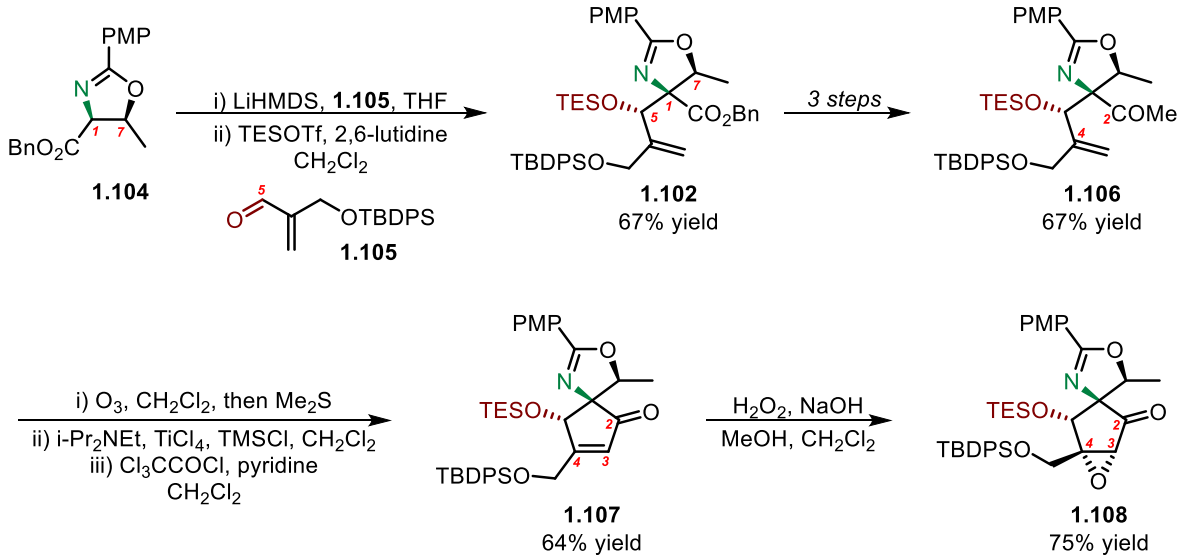
reaction to form the C-5/C-1 bond. This key intermediate could be obtained from threonine **1.103**, an abundant compound from the chiral pool.

Scheme 1.23 – Hanessian's Retrosynthetic Analysis of Pactamycin



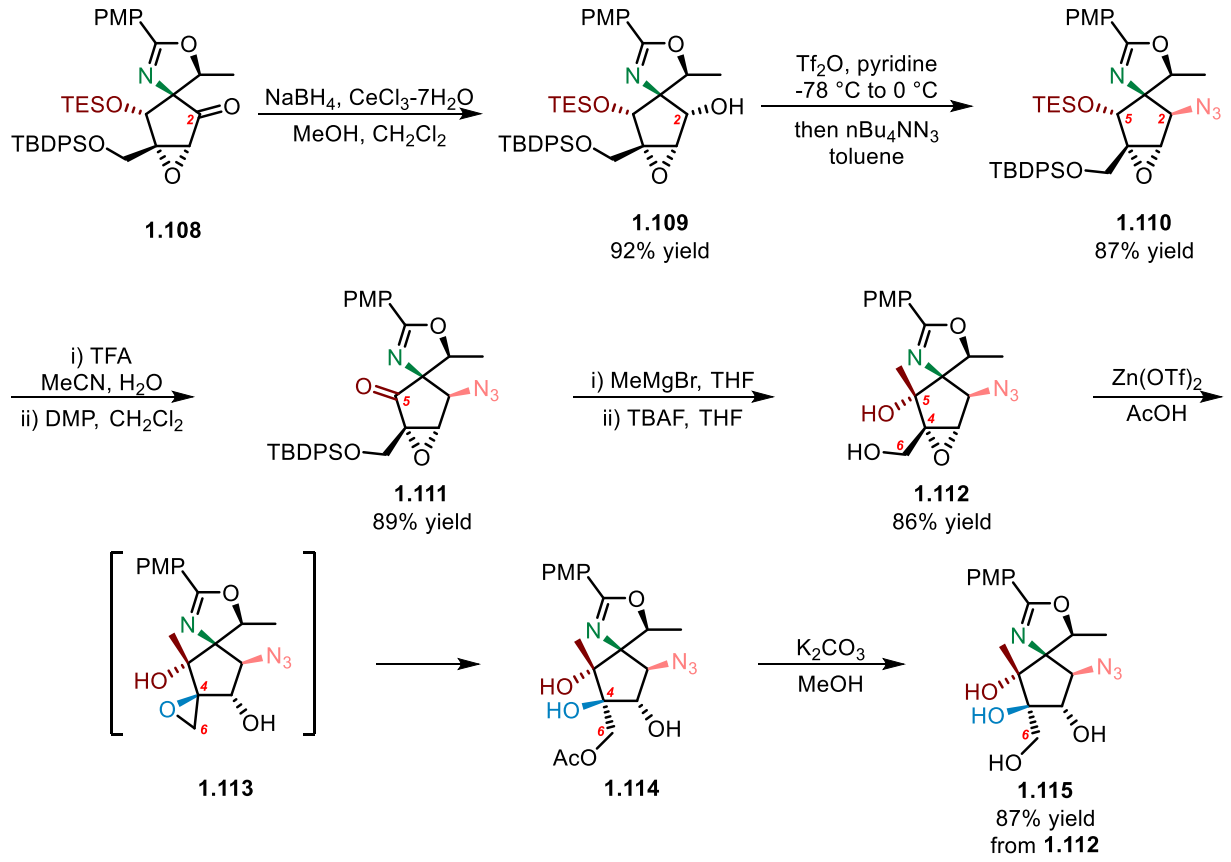
The synthesis commences with oxazolidinone **1.104**, which is available in three steps from **1.103**. This is used in an aldol reaction with enal **1.105**, affording **1.102** in good yields after protection (**Scheme 1.24**). This reaction is key, as it establishes the correct stereochemistry at the C-1 carbon. Although the C-5

Scheme 1.24 – Hanessian's Formation of the Cyclopentene Ring



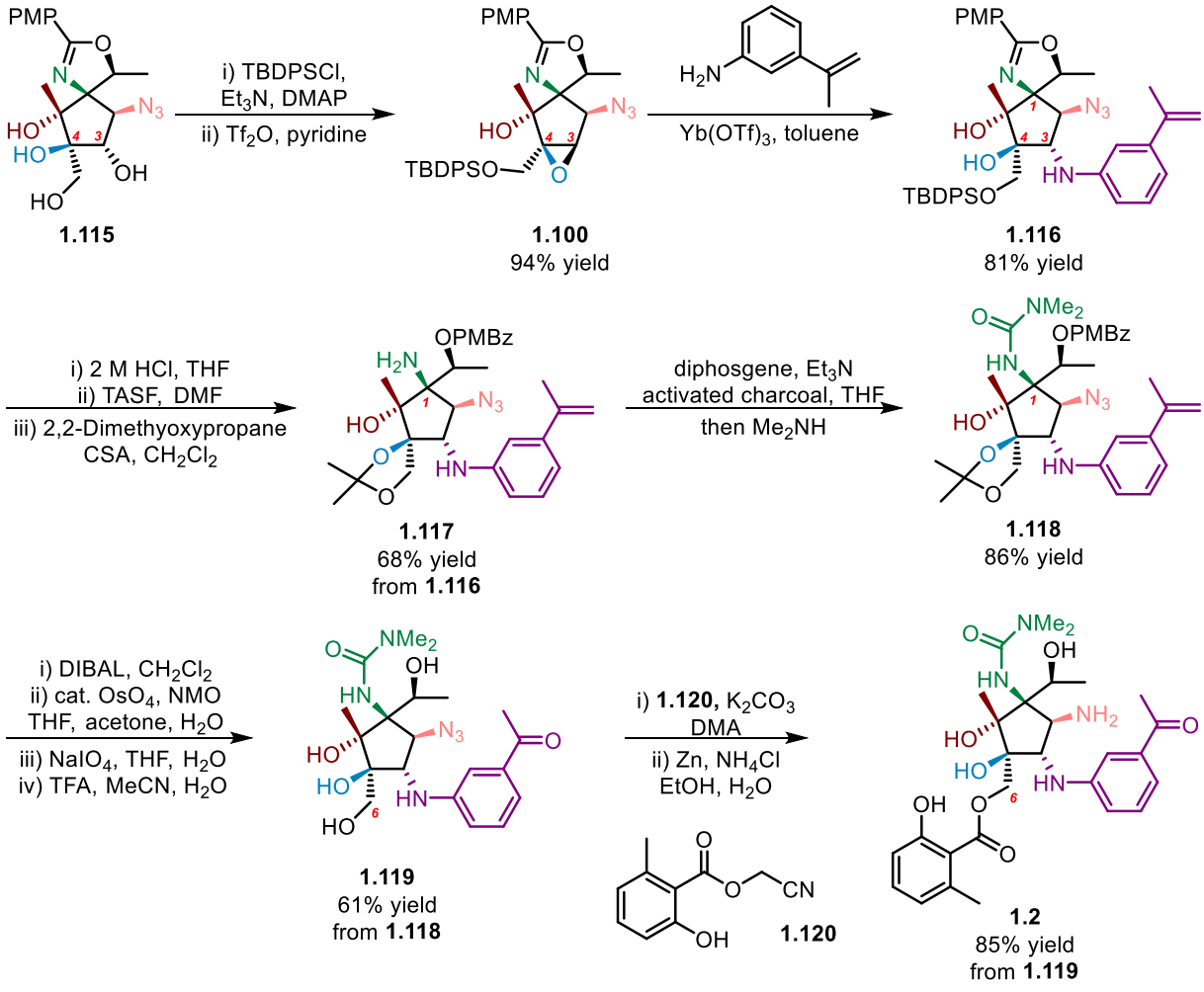
stereocenter is temporary, it is also potentially important, as it contributes to the overall steric environment of the system that is likely to impact the diastereoselectivity of several subsequent steps. The absolute stereochemistry of these stereocenters is dictated by the C-7 stereocenter. The aldol adduct **1.102** was converted to the ketone **1.106**, then cyclopentenone **1.107** was formed through a process involving the ozonolysis of the alkene and a two-step aldol condensation. Nucleophilic oxidation of the enone with $NaOH/H_2O_2$ resulted in epoxide **1.108**. While the stereochemistry about C-3 and C-4 in **1.108** is opposite to the correct orientation in **1.2**, the synthesis failed when the other diastereomer of the epoxide was employed at this point. Unfortunately, this necessitates a later inversion of the epoxide, a sequence that adds to the step count of the route.

Scheme 1.25 – Hanessian's Formation of the C-2 Azide and C-5 Tertiary Alcohol



Conversion of the ketone into the C-2 amine was accomplished in a two-step sequence (**Scheme 1.25**). Reduction of ketone **1.108** using $NaBH_4$ and $CeCl_3$-$7H_2O$ gave a **1.109** as a single diastereomer. Activation of the alcohol with triflic anhydride and displacement with tetrabutylammonium azide gave **1.110** in excellent yield. After turning the C-2 alcohol into the azide, Hanessian and co-workers were able to convert the C-5 secondary alcohol to the tertiary alcohol **1.112** in four steps without worrying about competing functionality. This reaction is notable in that the organometallic addition to the ketone **1.111** proceeds smoothly despite the ketone being flanked by two fully substituted carbons at C-1 and C-4, a step that failed in the Trost route. The key difference between the two systems may be that the Trost route employs an alcohol at C-4 whereas the Hanessian route has an epoxide. The strained nature of the epoxide may possibly be altering the orientation of the cyclopentane ring, making the ketone more accessible to attack relative to

Scheme 1.26 – Hanessian's Synthesis of Pactamycin



a system with more degrees of freedom. With the tertiary alcohol set, the stereochemistry of the C-4 position was inverted *via* a Payne rearrangement, initially forming epoxide **1.113**, which is opened with acetic acid at the less substituted carbon. Cleavage of the acetate ester gives **1.115** in good yield.

With the correct stereochemistry at the C-4 position established, the C-6 alcohol was protected and the C-3/C-4 epoxide was reformed to set the correct stereochemistry needed for the aniline ring opening (**Scheme 1.26**). The opening of **1.100** was catalyzed by $Yb(OTf)_3$ in excellent yield, setting the final stereocenter in the system. All that remained was to turn the oxazolidinone into the urea and to form the ester at C-6. Hydrolysis of the oxazolidinone was easily accomplished under acidic conditions, but conversion of the sterically hindered primary amine proved to be extremely problematic in the presence of the C-4 alcohol, with cyclic carbamates isolated as the major product. A workaround was developed by desilylation of **1.116** and formation of the acetal **1.117**. With the C-4 alcohol tied up, formation of the isocyanate and trapping with dimethylamine gave urea **1.118**. A series of steps cleaved the ester at C-7, unmasked the carbonyl on the aniline and deprotected the C-4/C-6 diol. The C-6 alcohol was then acylated with **1.120** and the C-2 azide was reduced to yield **1.2** in 32 steps from the chiral pool.

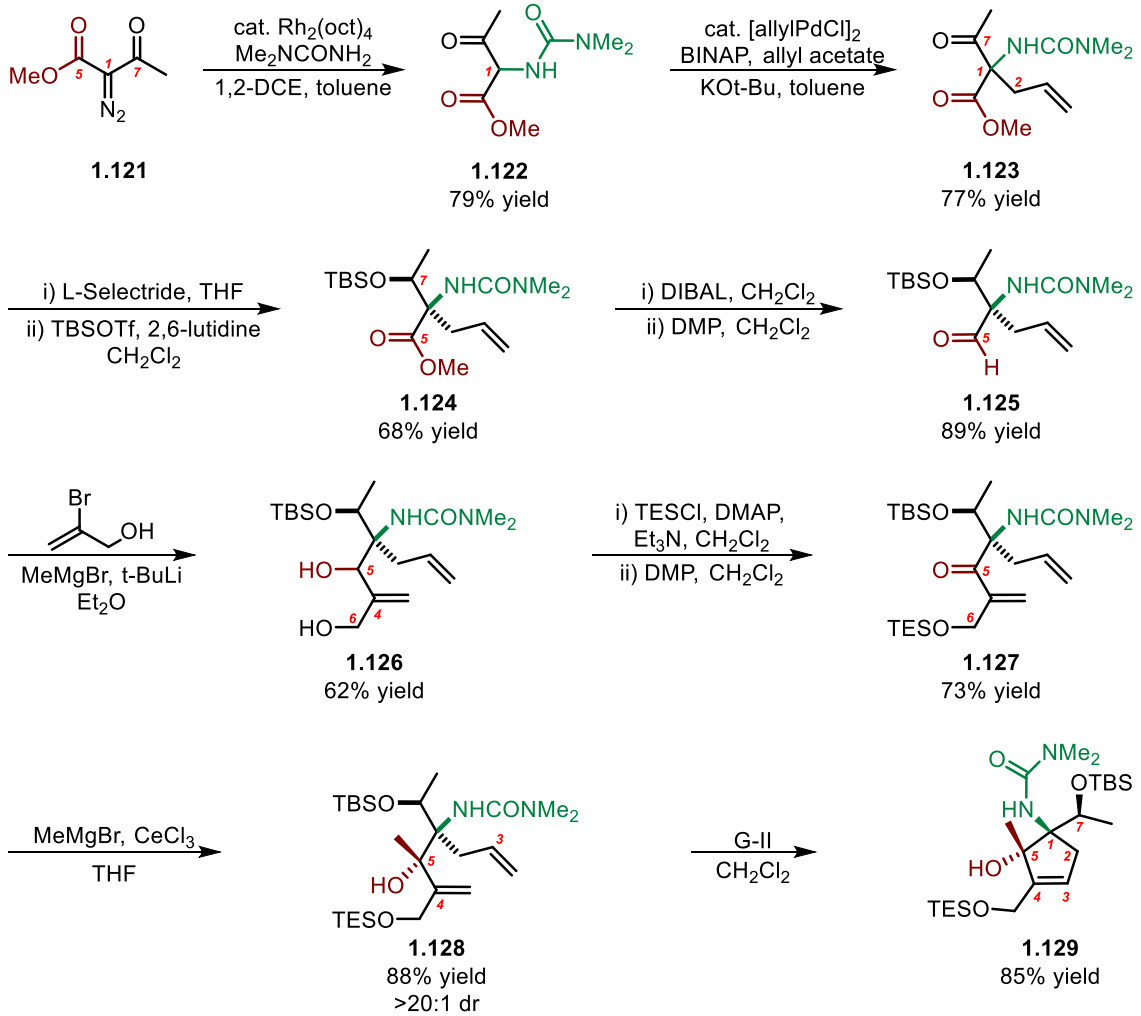
This landmark synthesis is an excellent blueprint for how to approach these molecules. There are several noteworthy strategies employed in this route that may either prove useful or should potentially be avoided when considering new routes to access jogyamycin. For instance, the urea was masked as an oxazolidinone for the majority of the synthesis and the deprotection and urea formation near the end of the synthesis proved to be highly problematic. Tying up the urea nitrogen as an oxazolidinone or a carbamate is a strategy employed in many approaches to the core of pactamycin; this strategy could be risky, depending on the functionality present in the system. Opening of the epoxide at C-3 with the aniline, in contrast, appears to be an effective end game strategy, as this reaction worked even with the majority of the functionality installed on the ring. Since epoxides are an easily accessed functional group, with an expansive body of work devoted to their enantioselective and diastereoselective syntheses, this approach to setting the C-3 and C-4 stereocenters is likely to be amendable to a wide variety of strategies, and not just those used by Hanessian. As far as applying this route to jogyamycin, Hanessian uses the exocyclic C-7 stereocenter

to considerable effect, where it dictates the stereochemistry of the C-1 position and thus, every subsequent stereocenter. It is also used to tie up the C-1 nitrogen and prevent it from undergoing undesired reactions. Therefore, it is doubtful that this route could be used to access jogyamycin.

1.9 Johnson's Synthesis of Pactamycin

Johnson and co-workers published a route to the core of pactamycin in 2012 that would inform their strategy for the final total synthesis (**Scheme 1.27**).[12] Part of this initial work would also inform our own strategy for the synthesis of the core of jogyamycin, as detailed in the next chapter. Instead of delaying the synthesis of the urea until a late stage, Johnson decided to embrace the challenging functionality at the

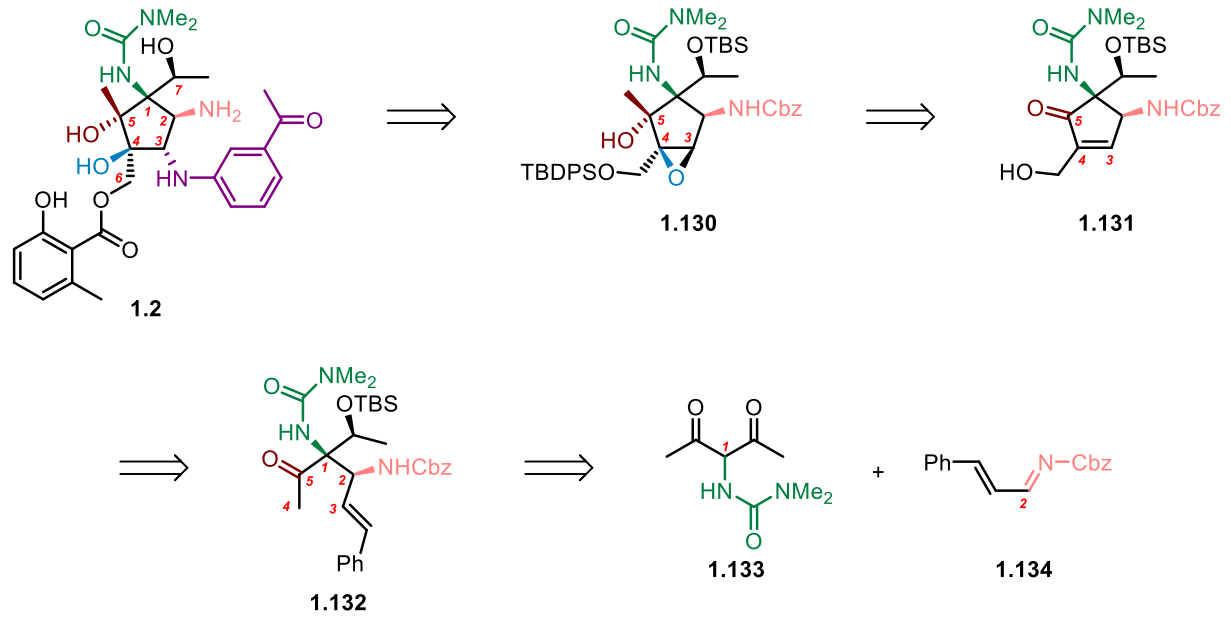
Scheme 1.27 – Johnson's Synthesis of the Pactamycin's Core



beginning, in the hopes of avoiding a troublesome installation later on. The C-1 C-N bond was formed *via* a rhodium-catalyzed N-H insertion, giving **1.122** in good yield. A palladium-catalyzed Tsuji-Trost alkylation gave C-alkylation adduct **1.123** as the sole product. Formation of the C-7 stereocenter was then accomplished *via* ketone reduction with L-Selectride. This process proved to be diastereoselective, resulting in the desired *syn* relationship between the C-1 and C-7 stereocenters. Silylation with TBSOTf afforded **1.124** in good yield. The ester was subsequently converted to the enone **1.127** in five steps. Addition of a methyl group to enone **1.127** occurred through chelation control, yielding **1.128** in excellent yield and >20:1 *dr*. The cyclopentene **1.129** was then formed *via* a ring closing metathesis.

To complete the synthesis, Johnson and coworkers proposed a similar endgame strategy to Hanessian by planning to open an epoxide at C-3/C-4 with an aniline (**Scheme 1.28**).[13] Key differences between the two successful routes is that Johnson did not plan to use a C-2 azide or mask the C-1 urea as an oxazolidinone like the Hanessian route. The C-5 alcohol in **1.130** was proposed to arise *via* an organometallic attack on a ketone, and the epoxide would be generated from the epoxidation of enone **1.131**. Enone **1.131** could be synthesized in a sequence of steps from the allyl amine **1.132**, which could be

Scheme 1.28 – Johnson's Retrosynthetic Analysis of Pactamycin

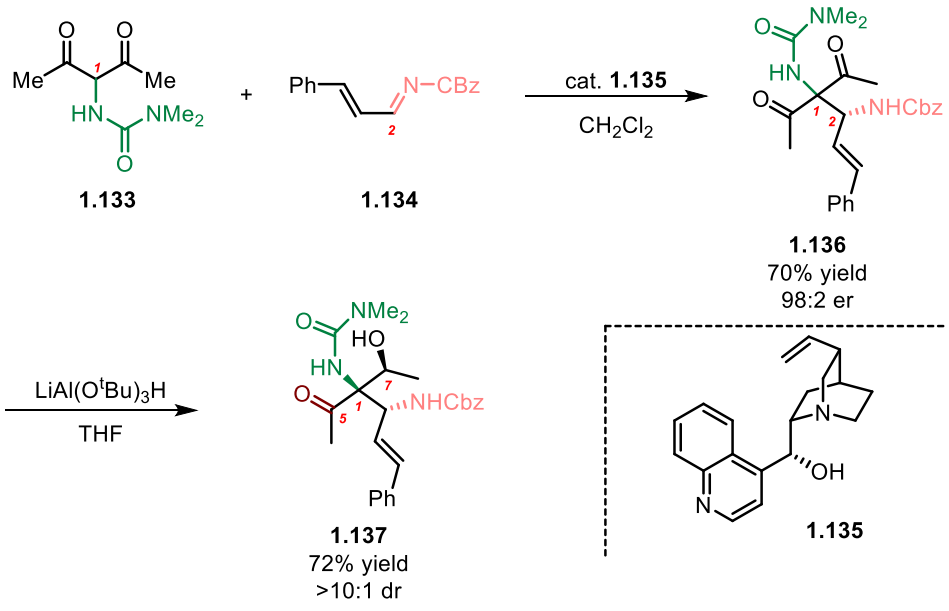


accessed *via* an asymmetric Mannich/desymmetrization sequence beginning with urea **1.133** and imine **1.134**.

The urea **1.133** was accessed in one step from the corresponding diazo. The 1,3-dicarbonyl proved to be a competent nucleophile in an asymmetric Mannich reaction using **1.135** as a catalyst (**Scheme 1.29**). The Mannich adduct **1.136** was isolated in 98:2 *er* after a single recrystallization, providing easy access to material with a high enantioenrichment. It is worth noting that the C-2 amine was formed with the opposite stereochemistry compared to the natural product. Despite this issue, the material was pushed forward. The 1,3-diketone could be desymmetrized using lithium tri-*tert*-butoxyaluminum hydride, establishing both the C-7 and C-1 stereochemistry in **1.137** in a single, powerful step.

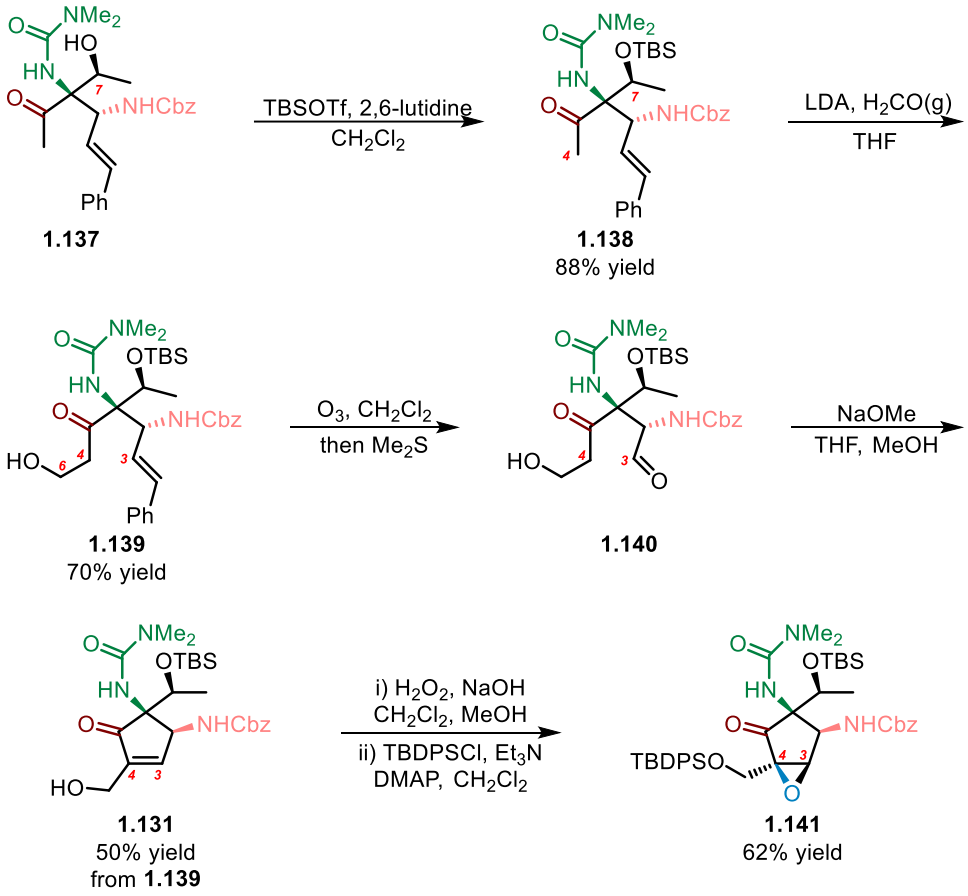
With the key C-1 stereocenter established, the ring cyclopentene ring needed to be formed (**Scheme 1.30**). Silylation of the C-7 alcohol in **1.137** occurred in good yield. An aldol between **1.138** and formaldehyde formed the C-4/C-6 C-C bond in **1.139**. Ozonolysis of the styrene followed by aldol condensation under basic conditions gave enone **1.131** in acceptable yield over the two steps. Surprisingly, the C-2 stereocenter epimerizes during this process to give the desired stereochemistry at C-2. Enone **1.31**

Scheme 1.29 – Johnson's Asymmetric Mannich and 1,3-Diketone Desymmetrization



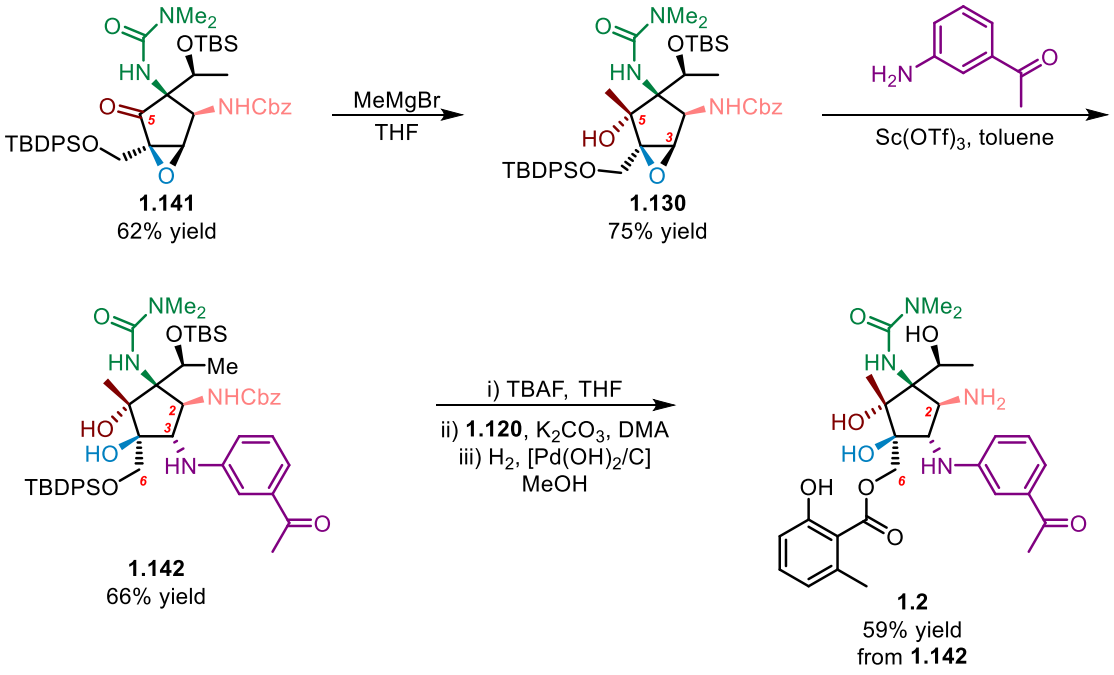
was then epoxidized selectively from the same face as the C-2 amine, and the C-6 alcohol was protected with a TBDPS group to give **1.141**.

Scheme 1.30 – Johnson's Aldol Condensation Cyclization



The final stereocenters to be formed are the C-5 alcohol and the C-3 aniline. Adding methylmagneisum bromide to ketone **1.141** proceeded as easily as it had for Hanessian, indicating that the C-3/C-4 epoxide may be key for the success of this transformation (**Scheme 1.31**). Interestingly, the nucleophile approached from the same face as the epoxide, whereas it approached from the opposite case in Hanessian's work. This result again highlights the difficulty in predicting the facial selectivity the addition of nucleophiles to sterically congested cyclopentanones. With the tertiary alcohol **1.130** in hand the epoxide was opened with *m*-acetylaniline, furnishing aniline **1.142** in good yield. Global desilylation, esterification of the C-6 alcohol and deprotection of the C-2 amine resulted in the isolation of **1.2**.

Scheme 1.31 – Johnson's Synthesis of Pactamycin



Overall this synthesis is completed in 14 steps from commercially available starting materials. This step count is less than half of the Hanessian synthesis, despite thematic similarities between the two syntheses. Hanessian and Johnson both use an aldol-type reaction to form a new C-C bond to C-1, and the C-7 stereocenter is essential for dictating the stereochemistry of the C-1 position. The cyclopentane rings are formed *via* aldol condensations. The C-5 stereocenter is formed *via* a Grignard addition to a ketone in both syntheses. Both syntheses make use of a diastereoselective nucleophilic epoxidation of an enone to oxidize the C-3 and C-4 carbons. The end game of both syntheses is also essentially the same, relying on the nucleophilic opening of an epoxide to establish the C-3 aniline. The difference in step count is largely due Johnson and co-workers focus on adding the functional groups to the core in their final form and in the correct orientation. This focus is highlighted by how the different routes accommodate the urea. The Hanessian route spends two steps at the beginning of the synthesis masking the C-1 urea as an oxazolidinone and four steps at the end cleaving the oxazolidinone and forming the urea. The Johnson route does not have any of these steps. The Hanessian route spends six steps turning the carboxylic acid of threonine into the

C-2 azide, whereas Johnson introduces this functionality into the synthesis in one step. Johnson was also able to introduce the C-3/C-4 epoxide with the correct stereochemistry, whereas Hanessian was forced to introduce this epoxide in from the opposite face and spend several steps to invert this stereochemistry. It would be fair to suggest that these two syntheses are somewhat similar, with the Johnson approach being essentially a streamlined version of the Hanessian synthesis.

As far as applying the Johnson strategy to synthesis of jogyamycin, the prospects are not encouraging, largely due to the lack of C-7 oxygenation in jogyamycin. The formation of the C-1 stereocenter *via* a desymmetrization that forms the C-7 stereocenter is key to the success of this synthesis, and a different kind of asymmetric Mannich reaction would have to be used to set the C-1 stereochemistry. If the same Mannich reaction were to be used in the synthesis of jogyamycin, the C-7 alcohol would have to be removed *via* a deoxygenation reaction. Johnson and co-workers explored this in a 2015 paper describing the synthesis of a number of pactamycin analogues. In this report, Johnson stated "Cognizant of the documented bioactivity difference across multiple cell lines observed between [**1.2**] and its 7-deoxy congener [**1.1**], reduction of the C-7 hydroxyl to its corresponding methylene was also probed. Unfortunately, all conditions explored (from a number of different intermediates in our route) failed to deliver the desired C-7 methylene." This offers a compelling argument that a successful synthesis of jogyamycin requires a new route.

1.10 Conclusion

A number of different routes have been developed to synthesize the core of pactamycin and jogyamycin. Two of these routes developed by Johnson and Hanessian have resulted in the successful synthesis of pactamycin. All seven of the routes developed to access pactamycin or its core have relied upon the exocyclic C-7 alcohol stereocenter as a key functional group in their syntheses, making it highly questionable that any of these routes could easily be adapted to the synthesis of jogyamycin. The only route designed to access jogyamycin failed at a late stage of the synthesis. In order to explore the biological activity of the 7-deoxy series of pactamycin, of which jogyamycin is a member, a new route to this scaffold needs to be developed.

1.11 References

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Chapter 2

Diastereoselective Synthesis of the Aminocyclitol Core of Jogyamycin via an Allene Aziridination Strategy

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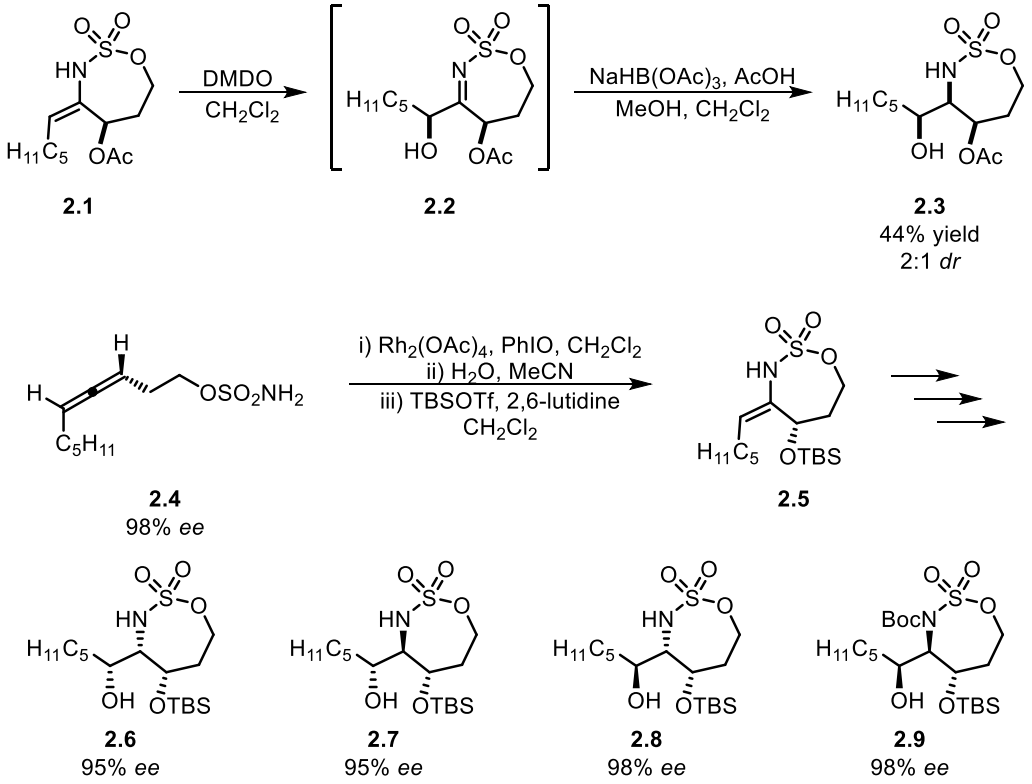
2.1 Derivatization of Enesulfamates

Previous work done in the group has explored the oxidative aziridination of homoallenic sulfamates and the elaboration of these bicyclic methylene aziridines into interesting aminated scaffolds.[1] These bicyclic methylene aziridines are particularly prone to ring opening, resulting in the formation of enesulfamates (**2.1**, **Scheme 2.1**).[1c] These enesulfamates can be used as nucleophiles with heteroatom electrophiles to provide imines such as **2.2**. Reduction of the imine with borohydride reductants resulted in

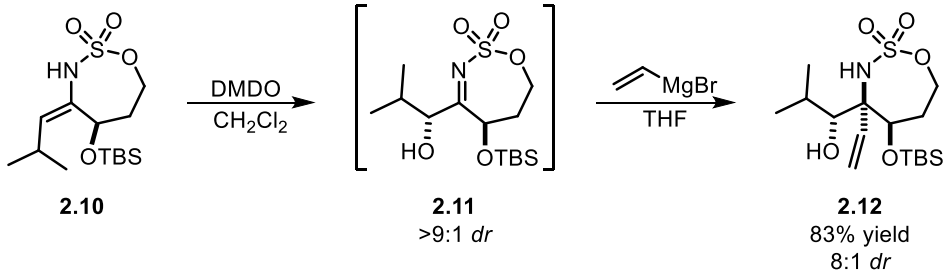
Scheme 2.1 – Diastereoselective Access to O/N/O Stereotriads from Homoallenic Sulfamates



the formation of O/N/O stereotriad **2.3** in moderate yield and low *dr*. This process was further optimized to afford access to every potential diastereomer of the O/N/O stereotriad (**2.6-9)** from a single homoallenic sulfamate **2.4**.[1e] Additionally, since the axial chirality of the allene transfers to the point chirality of the enesulfamate, these stereotriads could be synthesized in an enantiomerically pure form if starting with enantiopure homoallenic sulfamate.

For the purposes of jogyamycin, one of the more interesting results was the ability to add organometallic reagents to the imino alcohol **2.11** to give the O/N/O stereotriad **2.12** in high yield and excellent diastereoselectivity (**Scheme 2.2**).[1e] Although the organometallic addition to the 1,3-*anti* imine **2.11** was the only one explored and no O/N/N stereotriads to give a structure more closely resembling that of the motifs found in jogyamycin had been developed, we felt confident that this transformation would be general across a range of enesulfamates. The ability to form a host of heteroatom substituted stereotriads also appealed to us as presumably any synthesis of jogyamycin using this route could be easily diversified to give unique analogs of jogyamycin.

Scheme 2.2 – Organometallic Addition to Sulfamate-derived Imino Alcohols

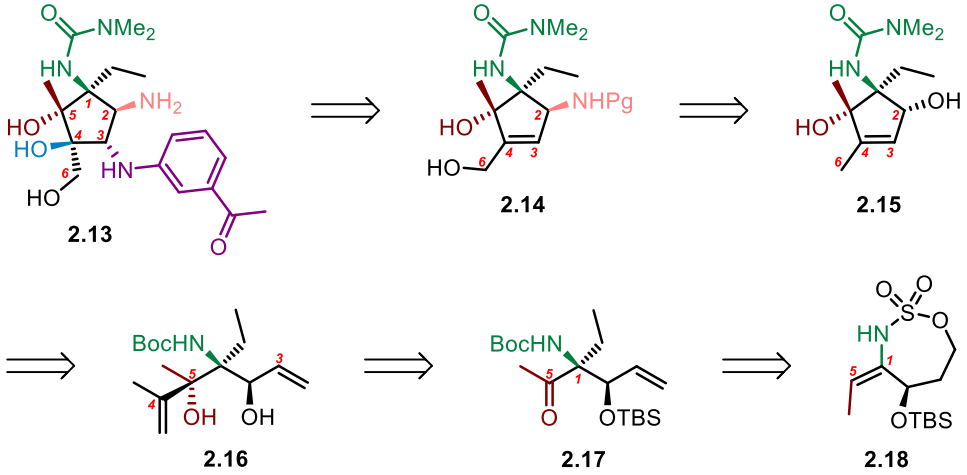


2.10 | **2.11** >9:1 *dr* | **2.12** 83% yield 8:1 *dr*

2.2 Retrosynthetic Analysis of Jogyamycin

When we developed our synthetic plan towards jogyamycin (**2.13**, **Scheme 2.3**), we thought that the safest route would target the same end game used by both Johnson and Hanessian where the C-3 C-N bond would be formed *via* an aniline opening of an epoxide.[2] However instead of forming the epoxide *via* a nucleophilic epoxidation of an enone, we proposed forming the C-3/C-4 epoxide through the directed epoxidation of allylic alcohol **2.14**. Introduction of the C-6 allylic alcohol at a late stage through an allylic

Scheme 2.3 – Retrosynthetic Analysis of Jogyamycin

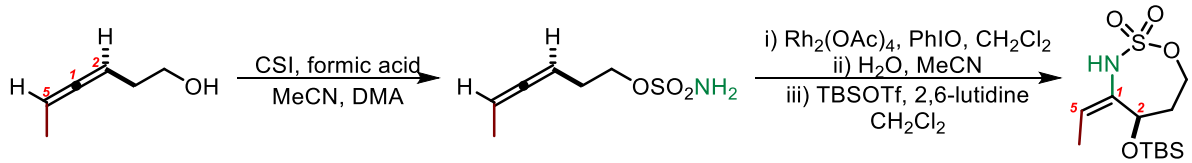


oxidation reaction would simplify the synthetic plan, allowing for greater flexibility in how to form the C-4/C-5 bond. We hypothesized that the allylic amine at C-2 would be formed by the manipulation of the C-2 alcohol in **2.15**. A ring closing metathesis of diene **2.16** would give the C-3/C-4 alkene in cyclopentene **2.15**. The C-4/C-5 bond could be accessed through a diastereoselective organometallic addition to ketone **2.17**. A similar diastereoselective organocerium addition/ring closing metathesis strategy was employed by Johnson and co-workers in their synthesis of the pactamycin core, albeit in a less sterically encumbered system.[3] Finally, we were confident that the amino ketone **2.17** could be easily accessed from enesulfamate **2.18** using chemistry developed in our group.

2.3 Synthetic Route

The synthesis began with homoallenic alcohol **2.19**, which could be prepared in 100 g quantities in two steps from commercial starting material. Formation of the sulfamate **2.20** proceeded in excellent yield. One

Scheme 2.4 – Formation of the Enesulfamate

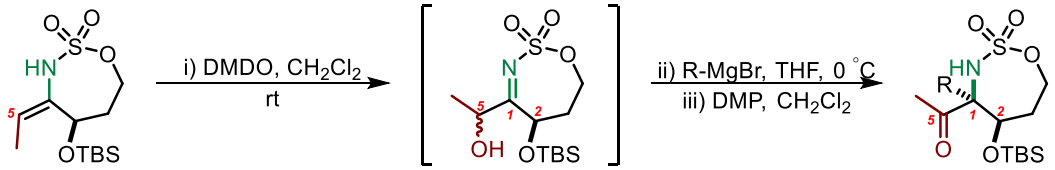


2.19 | **2.20** 89% yield | **2.18** 50% yield

issue with this chemistry is the temperature sensitivity of sulfamate **2.20**, which limited the scale of the reaction to 100 mmol to minimize the time the product spent at ambient temperature during the purification manipulations. The sulfamate **2.20** was then subjected to the oxidative aziridination/water opening/silylation sequence, yielding **2.18** in moderate yield in >20:1 *E:Z*. During this process both the C-2 alcohol stereocenter and C-1 C-N bond is formed in a single step.

We then proceeded to investigate the oxidation of the enesulfamate **2.18** with DMDO. Unfortunately, we discovered that these conditions resulted in the production of imino alcohol **2.21** in poor diastereoselectivity at room temperature. This result was essentially unchanged when running the oxidation at -78 °C. At first glance this could appear to be inconsequential as the C-5 secondary alcohol is to be oxidized to the ketone, thus ablating the mixture of diastereomers. However, upon closer examination this development was troubling because the organometallic addition to this class of sulfonyl imines have been shown to proceed through chelation control, meaning a low *dr* for the oxidation would result in a low *dr* for the formation of the C-1 amine bearing stereocenter. Considering this, we set off to explore organometallic additions to the imine. Addition of ethylmagnesium bromide (entry 1) resulted solely in hydride reduction of the imine. Addition of vinylmagnesium bromide (entry 2) did give amino ketone **2.23** after DMP oxidation, but the poor diastereoselectivity of the DMDO oxidation was transferred to the

Scheme 2.5 – Diastereoselective Organometallic Additions to the Imino Alcohol



2.18 | **2.21** ~2:1 *dr* | *desired diastereomer*

entry	R =	yield	*dr*[a]	product
1	Et	0%[b]	N/A	**2.22**
2	$HC{=}CH_2$	45%	2:1	**2.23**
3	C≡CH	48%	2.3:1	**2.24**
4[c]	C≡CH	68%	11.5:1	**2.24**

[a] Based on ^{1}H NMR analysis of the crude

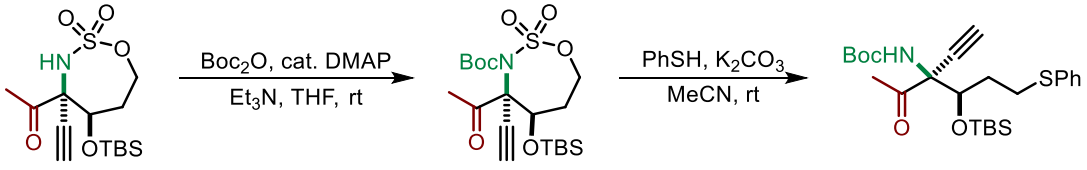
[b] Hydride reduction of the imine observed as sole product

[c] Grignard pre-stirred at 0 °C 30 min prior to addition

organometallic addition. The addition of ethynylmagnesium bromide (entry 3) to a solution of **2.24** also resulted in the same low *dr* of the product. However, it was found that pre-cooling the Grignard solution to 0 °C prior to the addition of the imine (entry 4) resulted the isolation of the amino ketone **2.24** in improved yield and diastereoselectivity. The working hypothesis is that cooling the solution of ethynylmagnesium bromide results in a shift of the Schlenck equilibrium. The diastereoselectivity of the addition to the imine by the organometallic species is not easily rationalized by a model evoking chelation control but rather through the preference of the organometallic to approach opposite the bulky C-2 silyl ether.

After figuring out how to form the C-1 stereocenter efficiently, we set about to remove the sulfamate moiety. Attempts to install the urea at this point with either dimethylcarbamoyl chloride or methyl isocyanate failed. However, activation of the nitrogen with Boc_2O afforded the carbamate **2.25** in excellent yield. Carbamate **2.25** also proved to be somewhat unstable, and the reaction had to be quenched quickly to avoid biproducts associated with sulfamate cleavage with *t*-BuOH generated *in situ*. As there is precedent for transforming the Boc group into a urea, we felt confident proceeding with the carbamate.[5] There are several things to note about this transformation. When this reaction was attempted with either a vinyl or ethyl group at C-1, all that was observed was recovered starting material. Not only is the alkyne essential for forming the C-1 stereocenter with high diastereoselectivity, it is also key to successfully removing the sulfamate by allowing the nitrogen to be functionalized with an electron withdrawing group. With the sulfamate sufficiently activated, we now had to explore how we were going to cleave this sulfamate and form the alkene required for the ring closing metathesis. We knew that an E2 elimination would be unlikely due to the cyclic nature of the sulfamate, so we set off to develop a route that opened the sulfamate with a nucleophile that could itself be eliminated at a later point in the synthesis. Ultimately after extensive

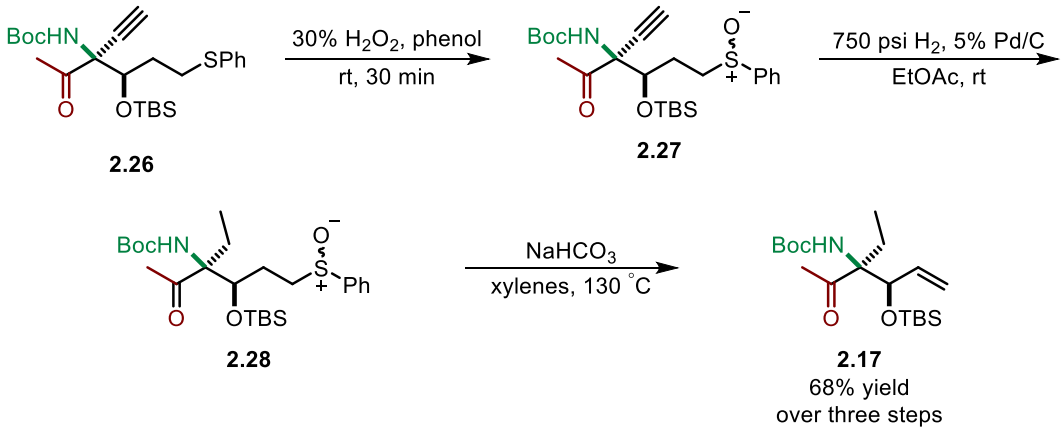
Scheme 2.6 – Sulfamate Cleavage



2.24 | **2.25** 91% yield | **2.26** 98% yield

screening of a variety of nucleophiles, thiophenol proved to be the ideal nucleophile for the cleavage of the sulfamate; thioether **2.26** was isolated in nearly quantitative yield.[4] Furthermore, we knew that we should be able to eliminate the thioether through an oxidation/sulfoxide elimination sequence.[5]

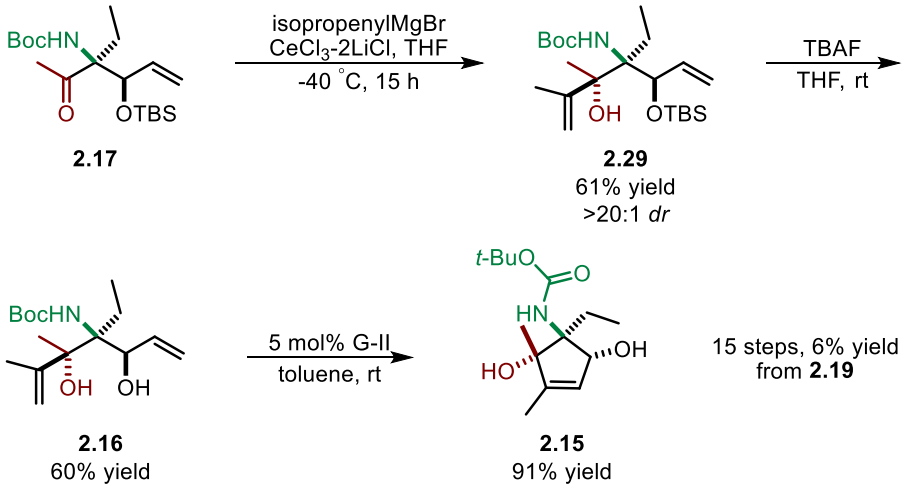
Scheme 2.7 – Alkyne Hydrogenation and Sulfoxide Elimination



With thioether in hand we set off to convert **2.26** into alkene **2.17** (**Scheme 2.7**), where the alkyne at C-1 has been fully reduced to the ethyl group and the alkene needed for the ring closing metathesis has been formed. Hydrogenation of the alkyne in the presence of thioether was sluggish. Therefore, the thioether was oxidized selectively to the sulfoxide **2.27** using hydrogen peroxide.[6] With the less Lewis basic sulfoxide the hydrogenation of the alkyne proceeded more smoothly, albeit under somewhat forcing conditions, to give the sulfoxide **2.28**. With the alkyne fully reduced we were then able to form the alkene *via* the sulfoxide elimination in hot xylenes. This gave **2.17** in good yield over the three-step sequence.

After forming one of the requisite alkenes needed for the ring closing metathesis, we had to introduce the other alkene into ketone **2.17** (**Scheme 2.8**). This was accomplished *via* the addition of isopropenylmagnesium bromide to the C-5 ketone mediated by $CeCl_3$-2LiCl.[7] This gave allylic alcohol **2.29** in acceptable yield and excellent yield. The diastereoselectivity observed for the organometallic addition is what one would expect if chelation control was operative. This reaction proved to be highly sensitive to temperature and the nature of the organometallic used. The exclusion of $CeCl_3$-2LiCl led to enolization and attack of the enolate oxygen on the carbamate carbon. When attempting to perform the organometallic addition with $CeCl_3$-2LiCl at temperatures above -40 °C, the intermediate tertiary alkoxide also attacked

Scheme 2.8 – Organocerium Addition and Ring Closing Metathesis



the Boc group to generate a cyclic carbamate. With conditions for this challenging organometallic addition parsed out, we set off to perform the ring closing metathesis. To prepare the diene for the ring closing metathesis the TBS group was removed with TBAF, giving **2.16**. Exposing **2.16** to G-II at room temperature led to clean conversion to the cyclopentendiol **2.15** in excellent yield. The stereochemistry of the diol was confirmed *via* NOESY experiments (see Experimental Section for details). Overall, diol **2.15** was synthesized in 15 steps from the homoallenic sulfamate **2.19** in 6% yield.

2.4 Analysis

While we were pleased that we could use the aziridination of homoallenic sulfamates to generate complex aminocyclitols, there were several issues with further pursing the synthesis of jogyamycin along this route. The route was lengthier than we originally anticipating, which is due to several factors. We originally hoped that we would be able to establish the C-1 stereocenter through the addition of ethylmagnesium bromide, form the urea and eliminate the sulfamate in a three-step sequence. Unfortunately, this proved to be infeasible. Since only hydride reduction of the imine was observed when using ethylmagnesium bromide, we had to use ethynylmagnesium bromide instead. This unsaturation adjacent to C-1 created an issue since this would need to be reduced to the alkane prior to forming the alkene needed for the RCM. Overall, this issue added three steps to the sequence that we hadn't anticipated. Furthermore,

Scheme 2.9 – Likely Issues with Alcohol Displacement

2.15 **2.30**

being unable to form the urea at an earlier stage of the sequence forced us into a similar situation as Hanessian where a late stage installation of the urea would significantly increase the step count.

The biggest problem, however, was that this route does not have a method for forming the C-2 amine with the correct orientation. Ideally one would be able to transform the C-2 alcohol to the amine *via* a substitution reaction. However, conversion of the alcohol would result in the rapid formation of aziridine **2.30** (**Scheme 2.9**). Oxidation of the allylic alcohol to the enone and following a route that mimicked the one developed by Hanessian would also run into significant challenges due to competing reactivity and unknown diastereomeric outcomes of individual steps. Such a route would also increase the step count of the synthesis significantly, and such a lengthy sequence would be a questionable application of what is otherwise excellent chemistry. Upon considering these options, it was decided that pursuing jogyamycin utilizing a different approach would be preferable.

2.5 References

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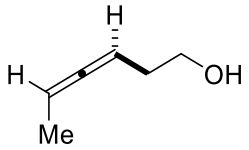
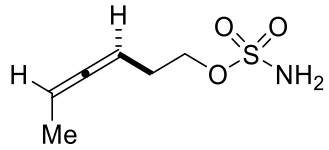
2.6 Experimental Details

All glassware was either oven dried at 130 ˚C, or flame dried under vacuum and purged with nitrogen before use. All glassware was then allowed to cool 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. Tetrahydrofuran was passed through an alumina column before use or freshly distilled from a Na/benzophenone ketyl. Dichloromethane was freshly distilled from calcium hydride or passed through an alumina column before use. Acetonitrile, toluene and benzene were all freshly distilled from calcium hydride before use. Xylenes was used without further purification. 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 nitrogen atmosphere. 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] 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 Avance-500 spectrometers. For ^{1}H NMR, chemical shifts are reported relative to the tetramethylsilane peak (δ 0.00 ppm), except in acetone-d_6 and toluene-d_8 where the chemical shifts are reported relative to the residual protiated solvent peak (2.05 ppm and 2.09 ppm, respectively). ^{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 peaks (δ 77.16 ppm for $CDCl_3$, 128.06 ppm for C_6D_6, 206.68 ppm for acetone-d_6, and 20.40 ppm for toluene-d_8). Accurate mass measurements were acquired at the University of Wisconsin, Madison using a Micromass LCT (electrospray ionization 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.

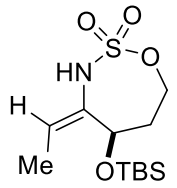


Compound 2.19. The homoallenic alcohol was once commercially available from Aldrich (#767336), but can be conveniently prepared on multi-gram scale according to the procedure of Blakey and coworkers.[3] Spectra were consistent with reported values.[3]



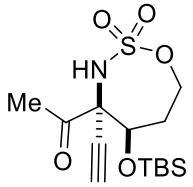
Compound 2.20. The sulfamate was prepared according to the procedure of Du Bois and coworkers.[4] To a flame-dried, three-neck round-bottom flask under N_2 was added chlorosulfonyl isocyanate (19.4 mL, 224.5 mmol, 2.2 equiv). The flask was cooled to 0 °C in an ice bath, and formic acid (8.46 mL, 224.5 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 **2.19** (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 H_2O, 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. ^{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.



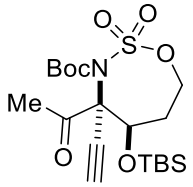
Compound 2.18. A flame-dried round-bottom flask equipped with a stir bar was charged with homoallenic sulfamate **2.20** (5.03 g, 28.4 mmol, 1 equiv) and $Rh_2(OAc)_4$ (94.0 mg, 0.213 mmol, 0.0075 equiv). Dry dichloromethane was added to prepare a 0.1 M solution, and the mixture stirred vigorously to yield a faint green-blue solution. Iodosylbenzene (6.52 g, 29.6 mmol, 1.04 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, can also easily be monitored by NMR). 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 0.4 M solution. Water (2.10 ml, 117 mmol, 4.1 equiv) was added, and the solution stirred at room temperature for 2.5 h until TLC indicated complete consumption of the intermediate bicyclic methylene aziridine (~30% EtOAc/hex or 100% CH_2Cl_2 solvent system, CAM stain, can also be easily monitored by NMR). 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 (3.30 mL, 28.3 mmol, 1.0 equiv) was added in one portion, followed by the slow addition of TBSOTf (6.50 mL, 28.2 mmol, 0.99 equiv) over approximately 1 min. The reaction was stirred at 0 °C for 45 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 (0% to 12% EtOAc/hexanes) to yield **2.18** (4.33 g, 14.1 mmol, 50%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.33 (s, 1H), 5.80 (q, *J* = 7.3 Hz, 1H), 4.83 (t, *J* = 3.1 Hz, 1H), 4.68 (t, *J* = 12.6 Hz, 1H), 4.15 (dt, *J* = 13.0, 3.2 Hz, 1H), 2.11 (ddt, *J* = 15.2, 12.2, 3.0 Hz, 1H), 1.84 (dt, *J* = 15.1, 3.4 Hz, 1H), 1.72 (d, *J* = 7.3 Hz, 3H), 0.89 (s, 9H), 0.10 (s, 4H), 0.07 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 132.25, 124.73, 77.16, 64.77, 64.45, 37.47, 25.77, 18.22, 12.21, -4.84, -5.04. HRMS (ESI) *m*/*z* calculated for $C_{12}H_{29}N_2O_5SSi$ $[M+NH_4]^+$ 325.1612, found 325.1621.



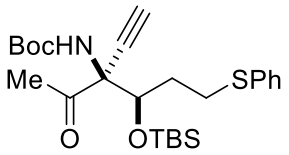
Compound 2.24. A flame dried round bottom flask with stir bar was charged with **2.18** (3.778 g, 12.30 mmol, 1.0 equiv.) and 4Å MS (3.96 g, ~1:1 4Å MS:**2.18**). Freshly prepared DMDO (0.22 M in CH_2Cl_2, 98 ml, 21.6 mmol, 1.76 equiv.) was added and the reaction was stirred for 2 hours. The reaction was then filtered through celite and the solvent was removed until the imine had solidified. An oven dried round bottom flask with stir bar was charged with ethynylmagnesium bromide solution (0.5 M in THF, 76 ml, 38 mmol, 3.0 equiv.) while the oxidation was running. The solution was cooled in an ice bath for 1 hour prior to addition of the imine. While the solution rapidly goes from transparent to murky within 10 minutes due to the precipitation of salts, it was found that for consistently reproducible results the extended stir time was required. The solid imine was dissolved in THF (24.0 ml, 0.51 M) and added dropwise to the grignard solution. This was allowed to stir for 1 hour, after which the reaction was quenched with sat. NH_4Cl and the aqueous phase was extracted 3x with CH_2Cl_2. The combined organics were washed with brine, dried with Na_2SO_4, filtered and the solvent removed. The crude oil was dissolved in CH_2Cl_2 (123 ml, 0.10 M)

and Dess-Martin Periodane (6.279 g, 14.80 mmol, 1.20 equiv.) was added. The reaction was stirred for 16 hours, after which a $Na_2S_2O_3$ solution was added and the biphasic mixture was stirred for 30 minutes. Then sat. $NaHCO_3$ solution was added, and the aqueous layer was extracted 3x with CH_2Cl_2. The combined organics were washed with brine, dried with Na_2SO_4, filtered and the solvent was removed. The crude material was purified by flash chromatography (49.25/49.25/0.5 to 99.5/0/0.5% CH_2Cl_2/Hexanes/EtOAc, major diastereomer eluting at ~80% CH_2Cl_2), yielding 2.793 g of a 23:1 mixture of the major diastereomer **2.24** and the minor diastereomer and 117 mg of the minor diastereomer, for an overall yield of 2.910 g (8.37 mmol, 68% yield) with a *dr* of 11.5:1. ^{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.

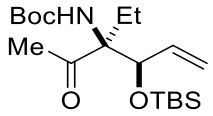


Compound 2.25. A flame dried round bottom flask with stir bar was charged with **2.24** (503 mg, 1.45 mmol, 1.0 equiv.), Boc_2O (478 mg, 2.19 mmol, 1.5 equiv.), triethylamine (0.22 ml, 1.58 mmol, 1.10 equiv.) and THF (14.5 ml, 0.099 M of (1)). DMAP (163 mg, 0.146 mmol, 0.09 equiv.) was then added to the solution. The reaction was followed closely by TLC, which showed complete consumption of starting material after 20 minutes. The reaction was quenched with saturated NH_4Cl and extracted 3x with CH_2Cl_2. The combined organics were washed with brine, dried with sodium sulfate and then filtered. The solvent was removed and the crude material was purified by flash chromatography (0 to 10% EtOAc/Hexanes in 2% increments). The product **2.25** was isolated as a white solid (592 mg, 1.32 mmol, 91% yield) that was stable at room temperature and could be stored for long periods of time in a freezer. Rotamer issues led to

an uninterpretable NMR spectrum at room temperature in $CDCl_3$. These issues were solved by taking NMR spectra in d_8-toluene at 90 °C. ^{1}H NMR (500 MHz, Toluene-d_8, 90 °C) δ 4.93 (dd, *J* = 7.7, 1.7 Hz, 1H), 4.20 (br t, *J* = 8.6 Hz, 1H), 3.90 (ddd, *J* = 11.5, 8.4, 2.6 Hz, 1H), 2.53 – 2.38 (m, 1H), 2.34 (s, 3H), 2.23 (s, 1H), 1.76 (dd, *J* = 16.4, 7.4 Hz, 1H), 1.37 (s, 9H), 0.83 (s, 9H), 0.12 (s, 3H), -0.00 (s, 3H). ^{13}C NMR (126 MHz, Toluene-d_8, 90 °C) δ 195.90, 151.51, 85.30, 81.75, 76.87, 75.99, 68.97, 68.43, 34.66, 28.11, 27.95, 26.15, 26.11, 18.27, -4.07, -5.06. HRMS (ESI) *m*/*z* calculated for $C_{19}H_{33}NO_7SiS$ $[M+Na]^+$ 470.1639, found 470.1636.

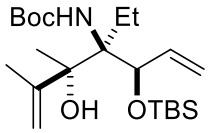


Compound 2.26. A 1.5 dram vial with a stir bar was charged with **2.25** (97.2 mg, 0.217 mmol, 1.0 equiv.), MeCN (1.10 ml, 0.20 M of **2.25**) and thiophenol (55 µl, 0.54 mmol, 2.5 equiv.). K_2CO_3 (63.0 mg, 0.456 mmol, 2.1 equiv.) was then added and the reaction was stirred for 15 hours, after which the reaction was quenched with 0.5 M HCl. The aqueous layer was extracted with EtOAc, and the combined organics were washed with sat. $NaHCO_3$. Following a brine wash, the organics were then dried with sodium sulfate, filtered and the solvent removed. The crude material was purified by flash chromatography (0 to 10% EtOAc/Hexanes), yielding **2.26** (101 mg, 0.212 mmol, 98% yield) as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.30 (m, 2H), 7.28 (d, *J* = 7.4 Hz, 2H), 7.21 – 7.16 (m, 1H), 5.54 (s, 1H), 4.39 (dd, *J* = 6.5, 3.8 Hz, 1H), 3.08 (ddd, *J*= 13.1, 9.3, 5.1, 1H), 2.92 (ddd, *J* = 13.1, 9.1, 6.9 Hz, 1H), 2.50 (s, 1H), 2.42 (s, 3H), 1.99 (dddd, *J* = 13.6, 9.4, 6.9, 4.0 Hz, 1H), 1.87 – 1.78 (m, 1H), 1.45 (s, 9H), 0.90 (s, 9H), 0.15 (s, 3H), 0.09 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 200.67, 153.35, 134.65, 128.58, 127.92, 125.20, 79.38, 74.52, 72.61, 65.13, 32.33, 29.35, 27.32, 25.74, 24.88, 17.15, -4.92, -5.21. HRMS (ESI) *m*/*z* calculated for $C_{25}H_{40}NO_4SiS$ $[M+H]^+$ 478.2442, found 478.2242.



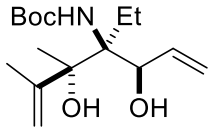
Compound 2.17. A 1.5 dram vial with stir bar was charged with **2.26** (264 mg, 0.553 mmol, 1.0 equiv.) and phenol (1.28 g, 13.6 mmol, 24.6 equiv.). Then H_2O_2 (30% in H_2O, 0.25 ml, 2.21 mmol, 4.0 equiv.) was added and the solids became a slurry within 10 minutes. The reaction was quenched with a $Na_2S_2O_3$ solution after 30 minutes. The solution was diluted with water and K_2CO_3 (1.8 g, 13.0 mmol, 23.5 equiv.) and extracted 2x with EtOAc. The combined organics were washed with brine, dried with Na_2SO_4, and filtered. The solvent was removed and the crude material was passed through a silica gel column to remove the residual phenol (5 to 50% EtOAc/Hexanes). The product was a ~1:1 mixture of diastereomers, which was carried on to the next step. The sulfoxide was dissolved in EtOAc (55 ml, 0.01 M) in a parr reactor. $CHCl_3$ (0.70 ml, 0.8 M) was then added and the solution was sparged with nitrogen. 5% Pd/C (555 mg, 200%) was added to the reaction and which was pressurized with hydrogen gas to 750 psi. After 13 hours the pressure was relieved and the solution was filtered through celite. The solvent was removed and the crude material was dissolved in xylenes (22.0 ml, 0.025 M) in an oven dried 100 ml pressure tube with stir bar. $NaHCO_3$ (187 mg, 2.22 mmol, 4.0 equiv.) was added and the reaction was heated to 130 ^oC for 15 hours. The reaction was cooled to room temperature and then diluted with H_2O and extracted with EtOAc. The combined organics were washed with brine, dried with Na_2SO_4 and filtered. The EtOAc was removed under reduced pressure. The crude material was next put through a silica plug to remove the xylenes (100% Hexanes until all the xylenes had eluted, and the 100% EtOAc to elute the remaining material). The crude material was purified by flash chromatography (0 to 20% EtOAc/Hex, product eluting at 6% EtOAc/Hex), yielding a slightly impure **2.17** (140 mg, 0.38 mmol, 68% yield) as an oil. ^1H NMR (500 MHz, $CDCl_3$) δ 5.88 (s, 1H), 5.63 (ddd, *J* = 16.9, 10.4, 6.4 Hz, 1H), 5.19 (dt, *J* = 17.1, 1.5 Hz, 1H), 5.13 (dt, *J* = 10.5, 1.5 Hz, 1H), 4.84 (d, *J* = 6.3 Hz, 1H), 2.54 (dq, *J* = 15.0, 7.6 Hz, 1H), 2.27 (s, 3H), 2.19 – 2.08 (m, 1H), 1.43 (d, *J* = 3.5 Hz, 9H), 0.94 (s, 9H), 0.70 (t, *J* = 7.5 Hz, 3H), 0.18 (s, 3H), 0.05 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 207.57,

153.87, 136.52, 117.02, 78.87, 74.36, 71.74, 28.40, 27.08, 25.90, 23.42, 18.09, 7.96, -4.27, -4.77. HRMS (ESI) *m*/*z* calculated for $C_{19}H_{38}NO_4Si$ $[M+H]^+$ 372.2565, found 372.2568.

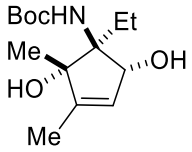


Compound 2.29. A 50 ml round bottom flask taken into a nitrogen filled glovebox and charged with a solution of $CeCl_3$-2LiCl (0.35 M in THF, 3.1 ml, 1.1 mmol, 10 equiv.). The flask was sealed with a septum before removing from the glovebox and placed under nitrogen. The flask was then cooled to -78 °C before isopropenylmagnesium bromide (0.5 M in THF, 2.15 ml, 1.1 mmol, 10 equiv.) was added dropwise over approximately one minute. While the organometallic solution stirred at -78 °C, a conical vial was charged with **2.17** (40.4 mg, 0.109 mmol, 1 equiv.) and taken out of the glovebox and placed under nitrogen. After the cerium solution had stirred for 1 h at -78 °C, the brown slurry was quickly placed in a pre-cooled bath at -40 °C. Then **2.17** was dissolved in THF (1.0 ml) and cannulaed over to the organocerium solution dropwise. The flask was rinsed with more THF (1.0 ml), which was again cannulaed dropwise. This was allowed to stand for 15 h before the reaction was quenched with dropwise addition of acetic acid (1.0 ml), during which the solution turned from in color to a colorless, clear solution. The solution was diluted with water and the aqueous solution was extracted three times with EtOAc. The combined organics were washed with sat. sodium bicarbonate and then brine, dried with sodium sulfate and concentrated by rotary evaporation. The crude material was purified by silica gel (0 to 5% EtOAc/Hex), yielding 27.4 mg of **2.29** (0.0662 mmol, 61%) as a clear oil in >20:1 *dr*. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.06 (ddd, *J* = 17.5, 10.4, 7.5 Hz, 1H), 5.41 (s, 1H), 5.32 – 5.25 (m, 2H), 5.24 (s, 1H), 5.10 (d, *J* = 1.6 Hz, 1H), 4.94 (t, *J* = 1.5 Hz, 1H), 4.37 (d, *J* = 7.5 Hz, 1H), 2.49 (dq, *J* = 14.9, 7.5 Hz, 1H), 1.88 (d, *J* = 1.3 Hz, 3H), 1.85 – 1.76 (m, 1H), 1.42 (s, 10H), 1.40 (s, 3H), 0.93 (s, 8H), 0.88 (t, *J* = 7.3 Hz, 3H), 0.11 (s, 3H), 0.05 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.24, 150.40, 138.04, 118.43, 114.27, 80.72, 79.27, 78.07, 65.11, 28.52, 26.19, 25.97, 21.98,

18.24, 8.89, 1.17, -3.50, -4.95. HRMS (ESI) *m/z* calculated for $C_{22}H_{44}NO_4Si$ $[M+H]^+$ 414.3034, found 414.3030.

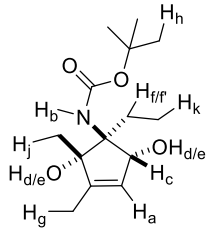


Compound 2.16. To a 20 ml syntillation vial containing **2.29** (25.6 mg, 0.0619 mmol, 1 equiv.) was added THF (1.25 ml, 0.05 M of **2.29**). The solution was stirred and a solution of TBAF (1.0 M in THF, 0.62 ml, 0.62 mmol, 10 equiv.) was added. This was stirred for 30 min until the reaction was complete by TLC (10% EtOAc/Hex). The solution was diluted with EtOAc and water, and the resulting aqueous layer was extracted three times with EtOAc. The combined organics were washed with brine, dried with sodium sulfate and the solvent was then removed. The crude oil was purified by column chromatography (0 to 10% EtOAc/Hex), and **2.16** (11.1 mg, 0.0371 mmol, 60% yield) was isolated as a clear oil with a minor impurity by NMR. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.07 (ddd, *J* = 17.6, 10.3, 7.5 Hz, 1H), 5.45 (s, 1H), 5.36 (dt, *J* = 17.2, 1.3 Hz, 1H), 5.25 (ddd, *J* = 10.3, 1.6, 0.8 Hz, 1H), 5.16 (d, *J* = 0.9 Hz, 1H), 5.08 (p, *J* = 1.5 Hz, 1H), 4.88 (s, 1H), 4.39 (t, *J* = 8.0 Hz, 1H), 4.33 (s, 1H), 1.90 – 1.87 (s, 3H), 1.77 (dq, *J* = 15.2, 7.7 Hz, 1H), 1.58 (s, 3H), 1.51 (dq, *J* = 15.2, 7.6 Hz, 1H), 1.45 (s, 9H), 0.92 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.76, 148.18, 137.18, 118.24, 115.35, 81.69, 80.15, 76.20, 65.21, 28.49, 27.14, 25.48, 21.79, 9.69. HRMS (ESI) *m/z* calculated for $C_{16}H_{30}NO_4$ $[M+H]^+$ 300.2169, found 300.2165.



Compound 2.15. A 1.5 dram vial containing **2.16** (10.5 mg, 0.0351 mmol, 1 equiv.) was taken into a nitrogen filled glovebox and charged with Grubb's-II catalyst (1.6 mg, 0.0019 mmol, 0.05 equiv.). Toluene (0.62 ml, 0.06 M of **2.16**) was then added and the vial was sealed before removing from the glovebox. The

reaction was monitored by TLC, which showed the complete consumption of starting material after 1.25 h. The solvent was then removed under reduced pressure. The crude, red oil was purified by column chromatography (0 to 25% EtOAc/Hex), yielding **2.15** (8.7 mg, 0.032 mmol, 91%) as a clear oil with a minor impurity by NMR. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.32 (s, 1H), 5.09 (s, 1H), 4.51 (s, 1H), 3.32 – 2.85 (m, 2H), 1.92 (q, *J* = 7.5 Hz, 2H), 1.73 (t, *J* = 2.0 Hz, 3H), 1.45 (s, 9H), 1.17 (s, 3H), 0.91 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.16, 146.06, 124.78, 84.00, 80.55, 80.09, 72.75, 28.47, 23.27, 22.30, 11.64, 11.33. HRMS (ESI) *m*/*z* calculated for $C_{14}H_{26}NO_4$ $[M+H]^+$ 272.1856, found 372.1852. The stereochemistry at the C-5 position was confirmed by nNoesy analysis shown below.

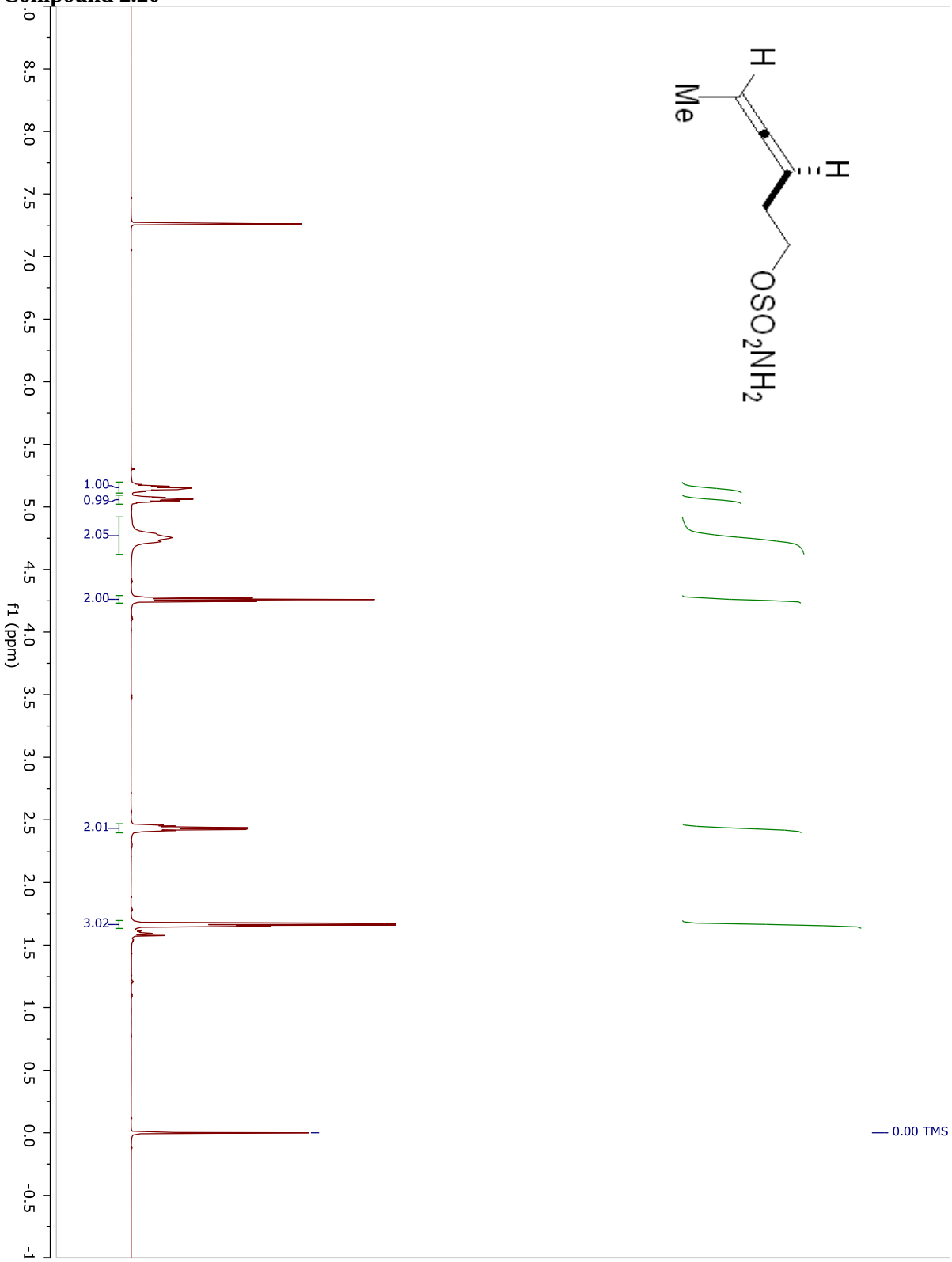


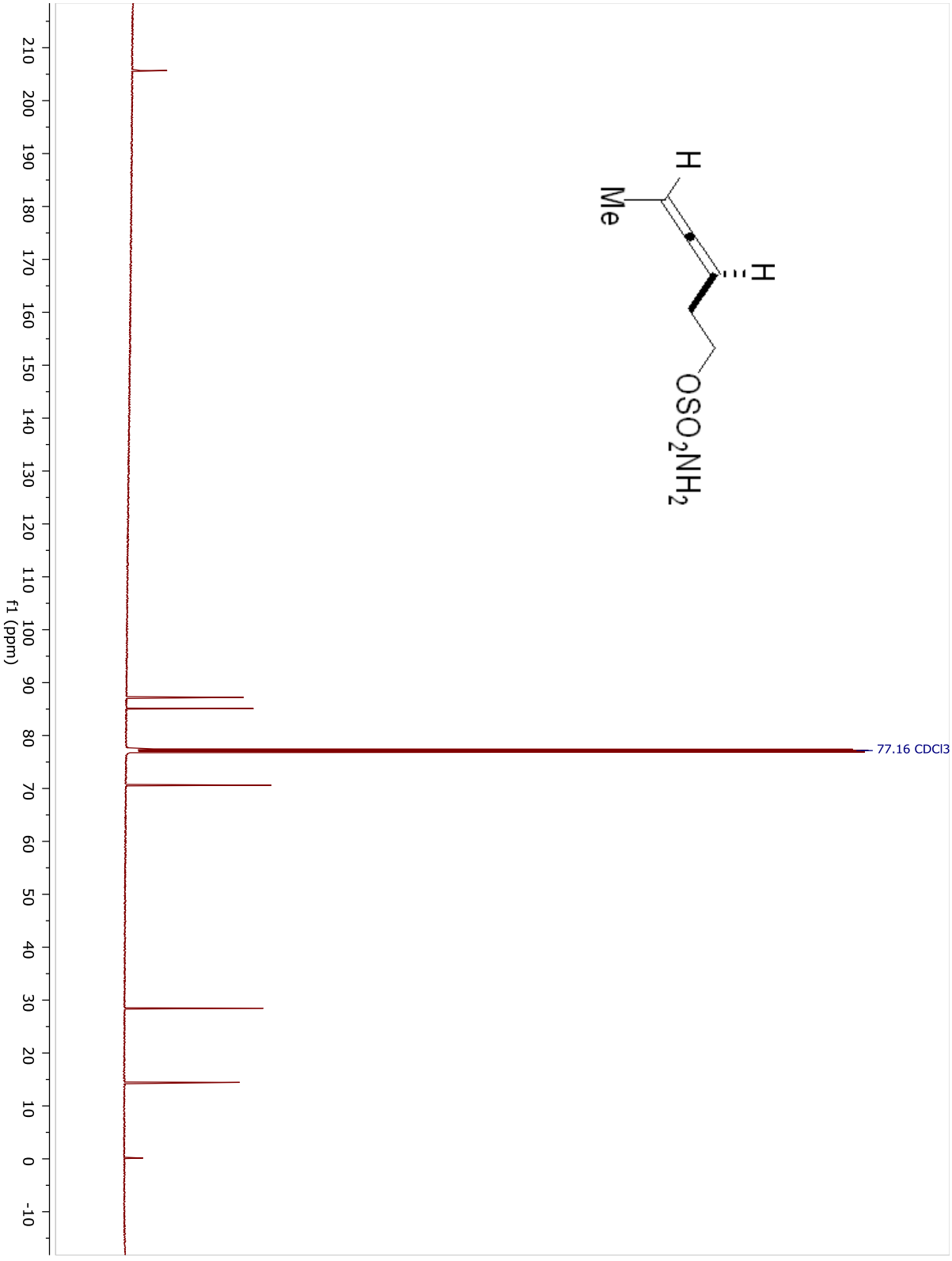
Observed NOE correlations

	H_a	H_b	H_c	H_d	H_e	$H_{f/f'}$	H_g	H_h	H_j	H_k
H_b	0%	N/A	4.7%	0%	0%	1.4%	0%	0.9%	3.5%	1.0%
H_c	3.5%	3.5%	N/A	0.8%	1.0%	0.4%	0.2%	0.2%	2.8%	0.3%
H_f	0.4%	1.3%	0.4%	1.3%	1.7%	N/A	0.3%	0.4%	0.2%	7.0%
H_j	0.4%	3.8%	3.5%	0.6%	0.7%	0.3%	3.3%	0.7%	N/A	0.3%

2.7 Spectra

Compound 2.20




H
Me
H
OSO2NH2
77.16 CDCl3
f1 (ppm)
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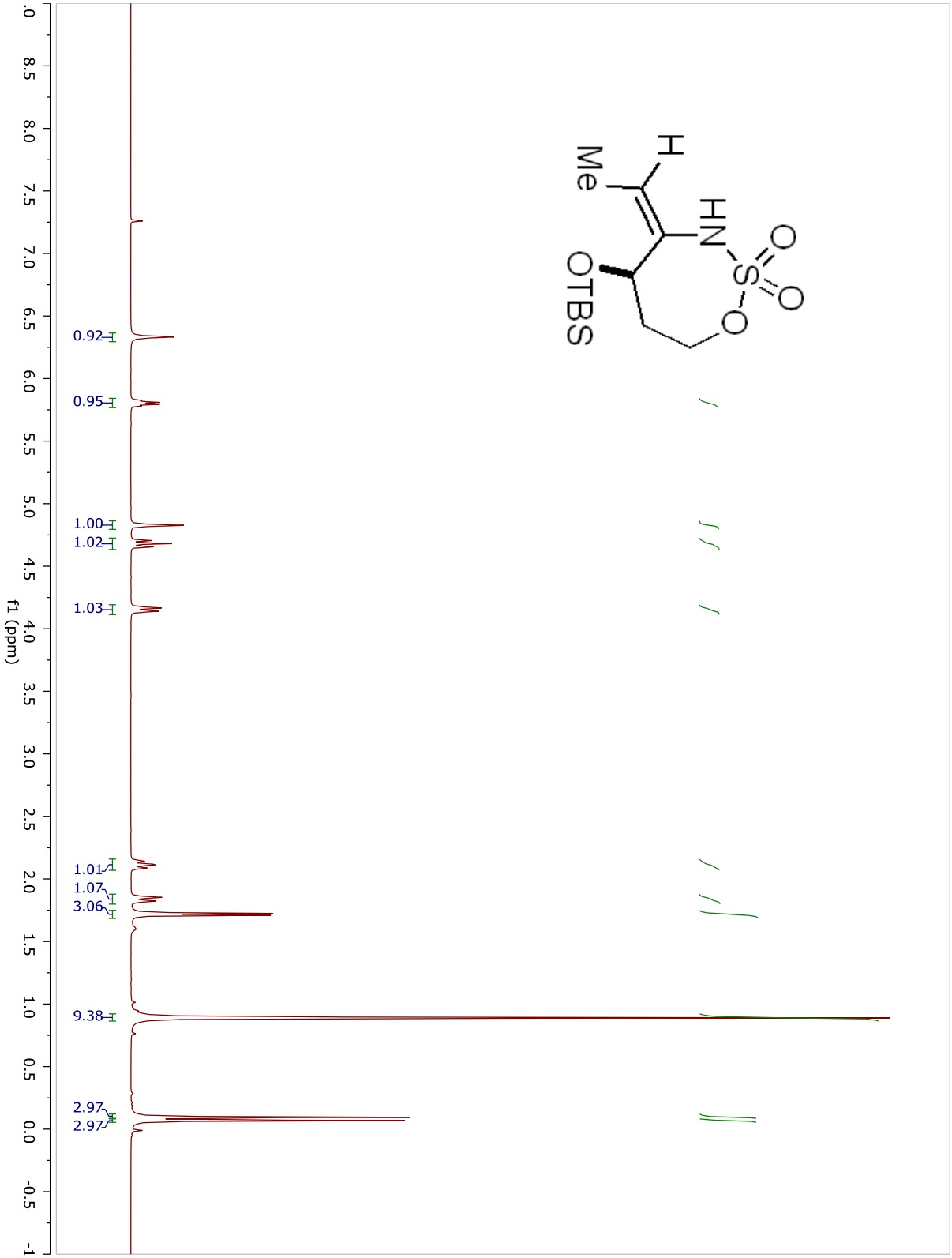
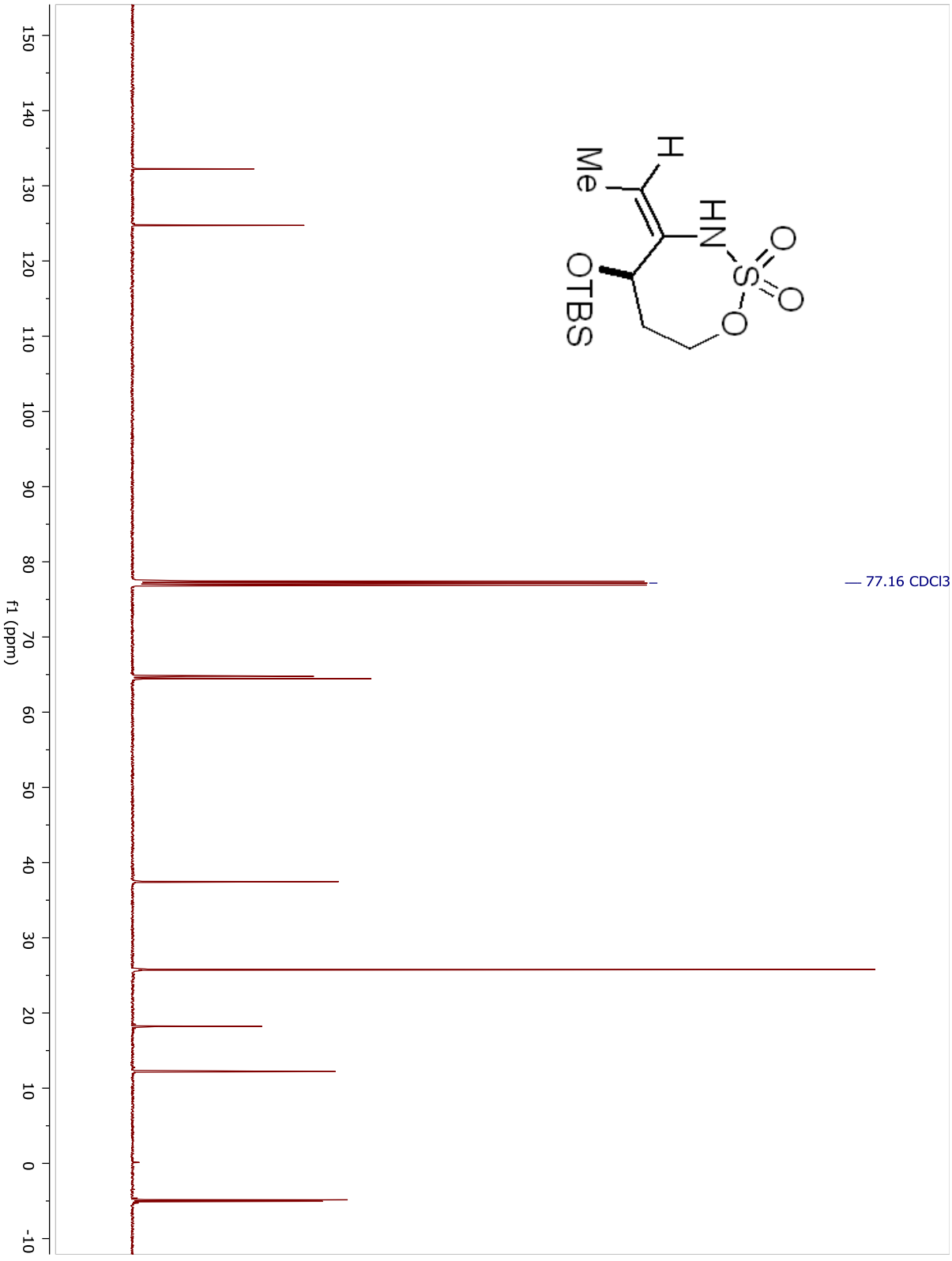
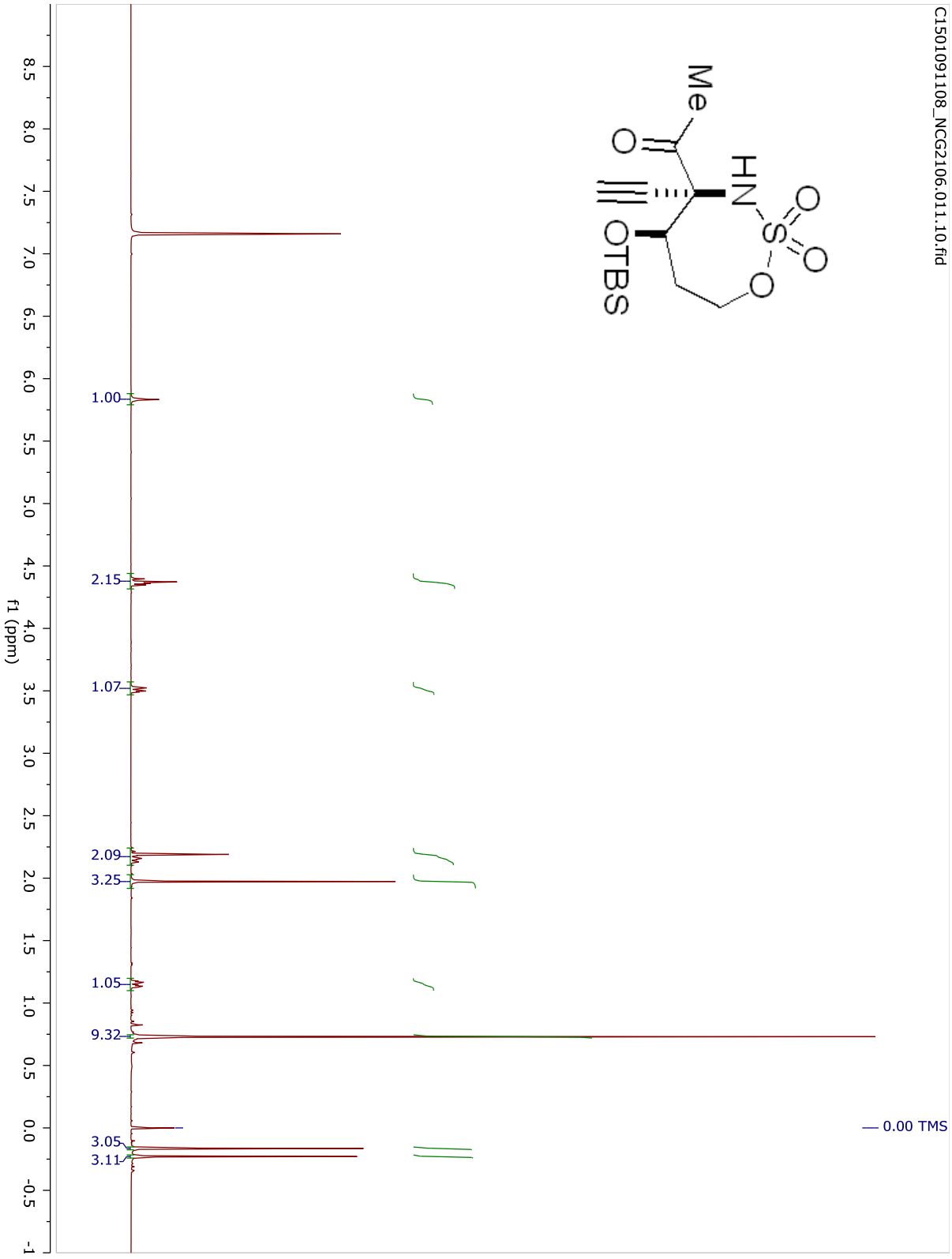
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

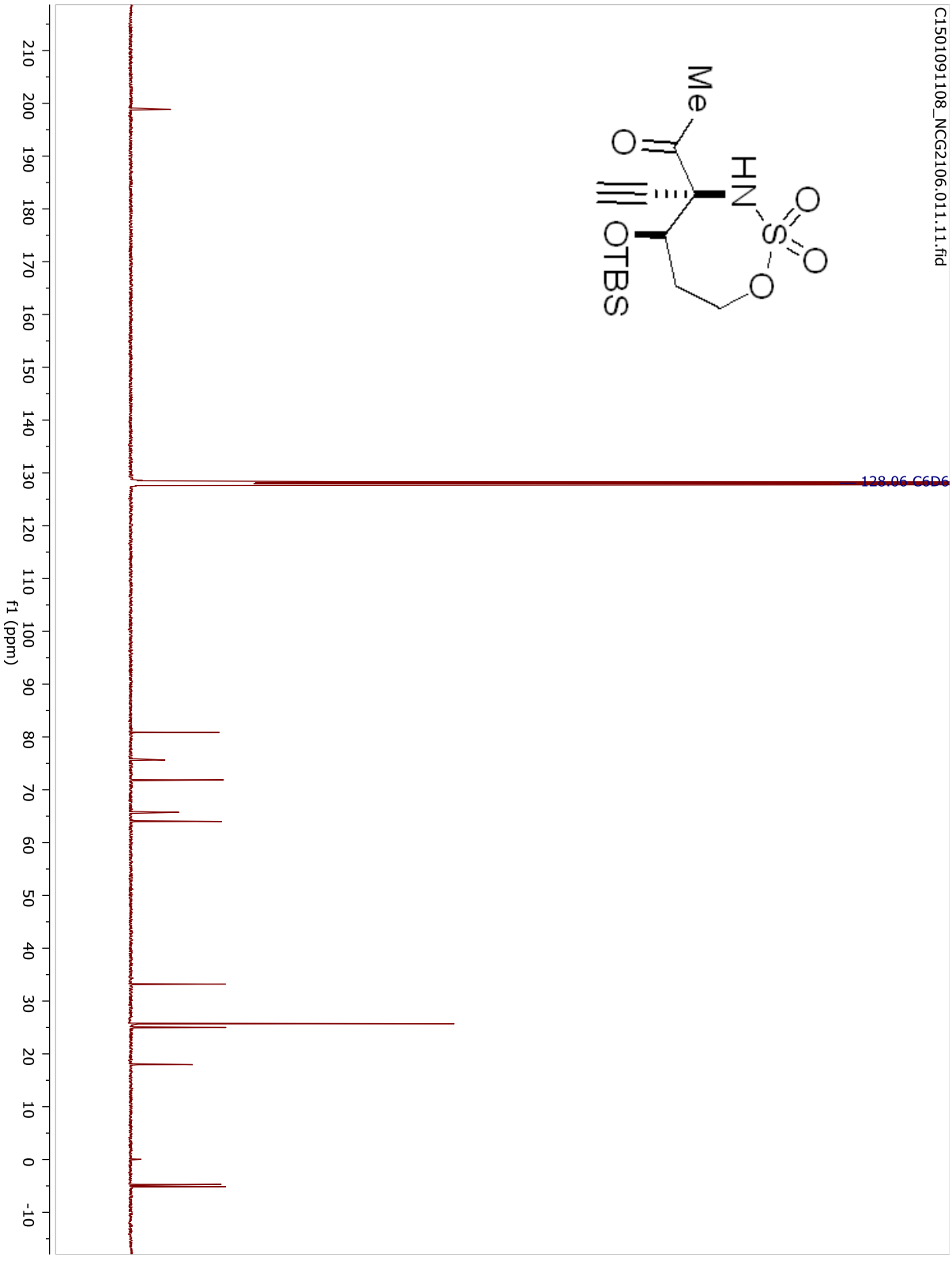
Compound 2.18



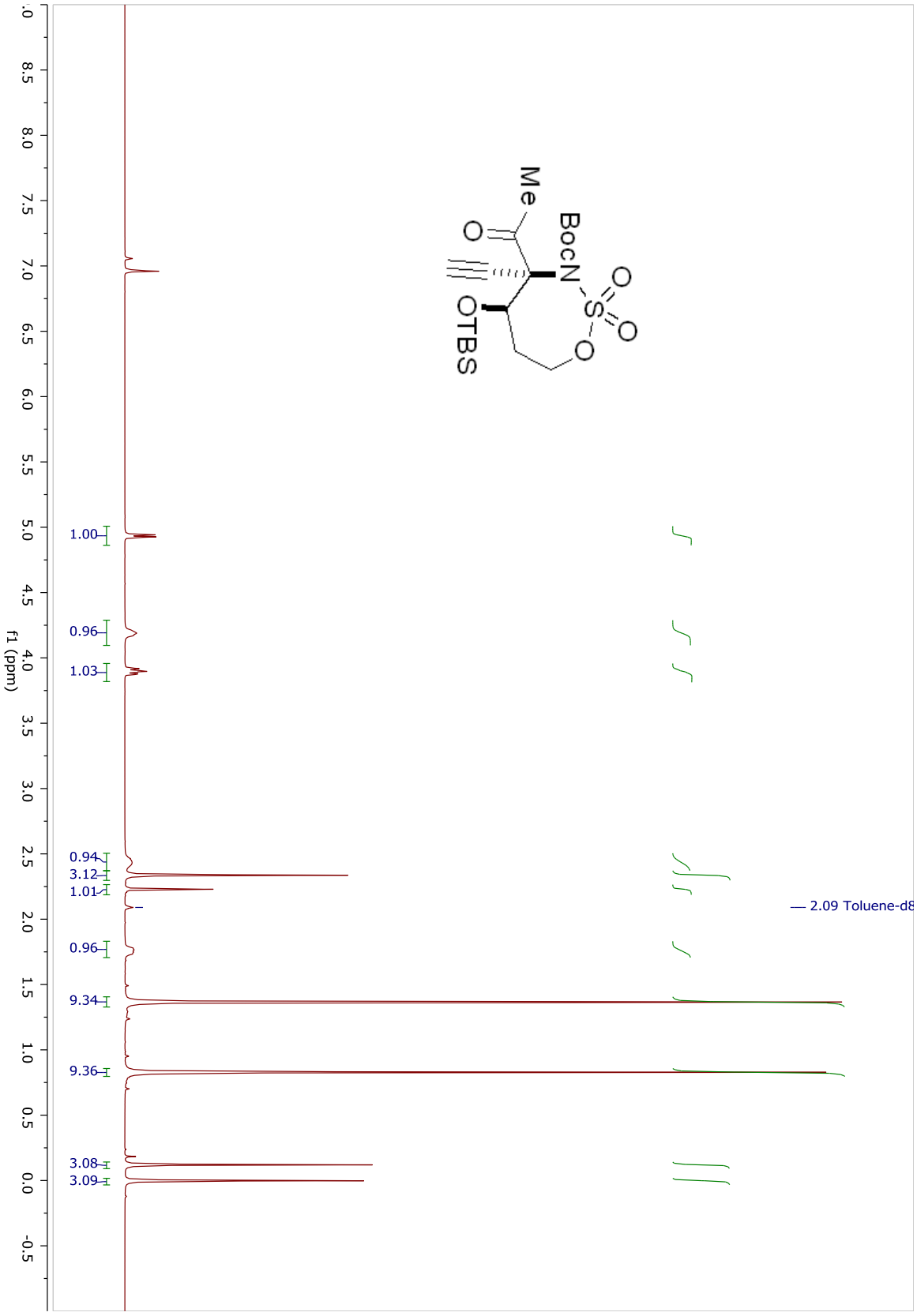

H
Me
HN
S
O
O
O
OTBS
77.16 CDCl3
f1 (ppm)
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

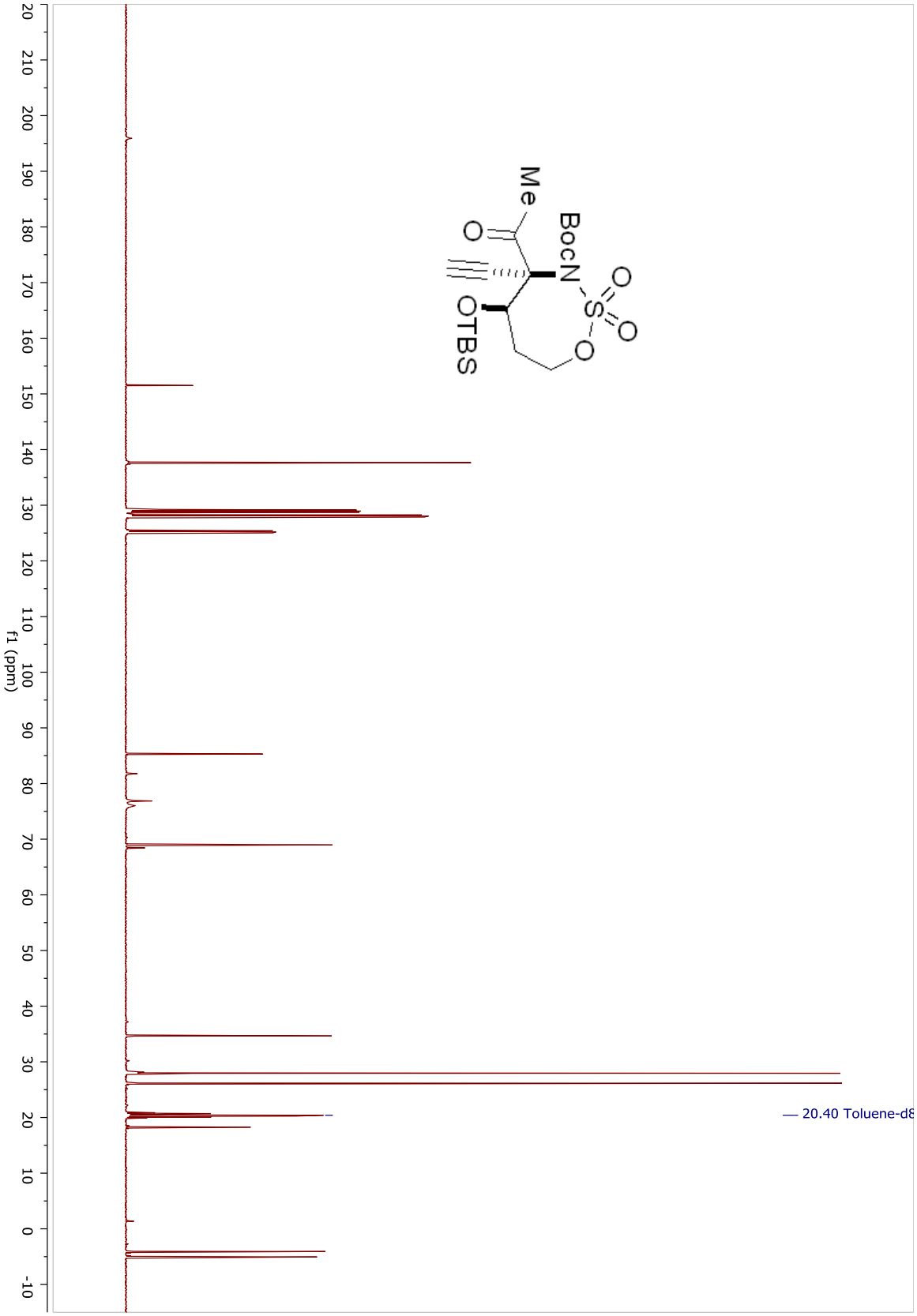
Compound 2.24



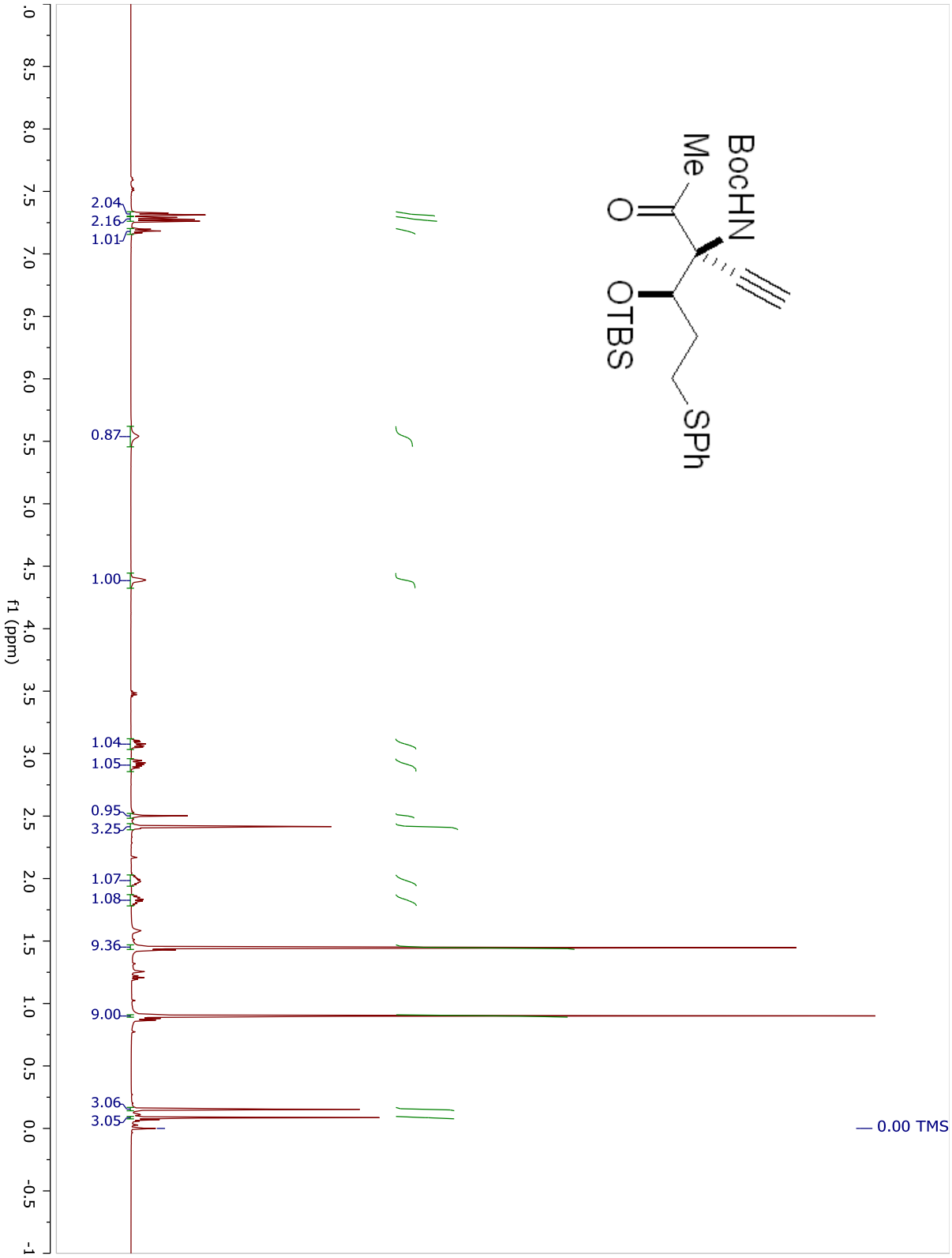

C15010911108_NCG2106.011.11.fid
128.06 C6D6
Me
O
HN
S
O
O
O
OTBS
f1 (ppm)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

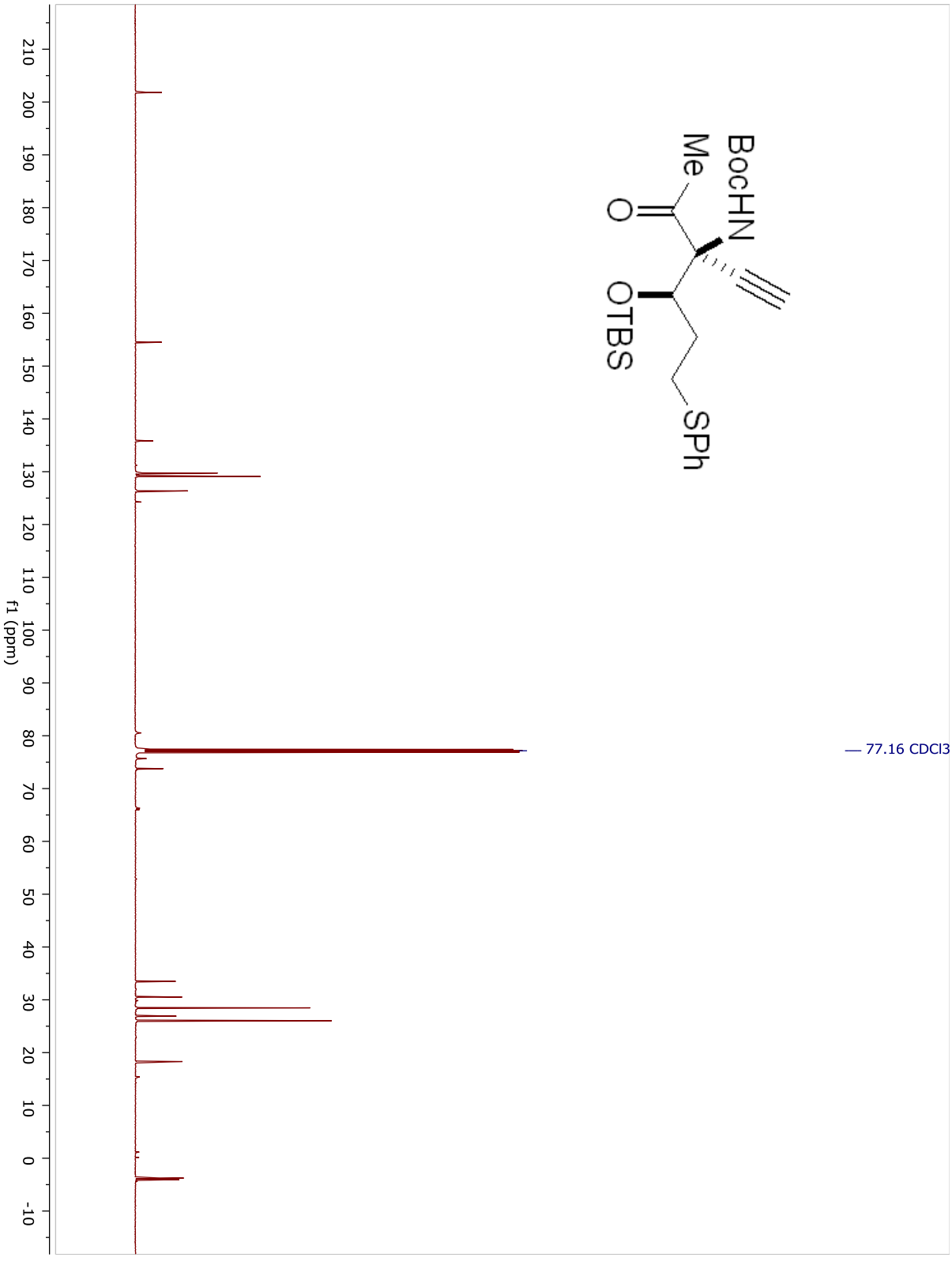
Compound 2.25



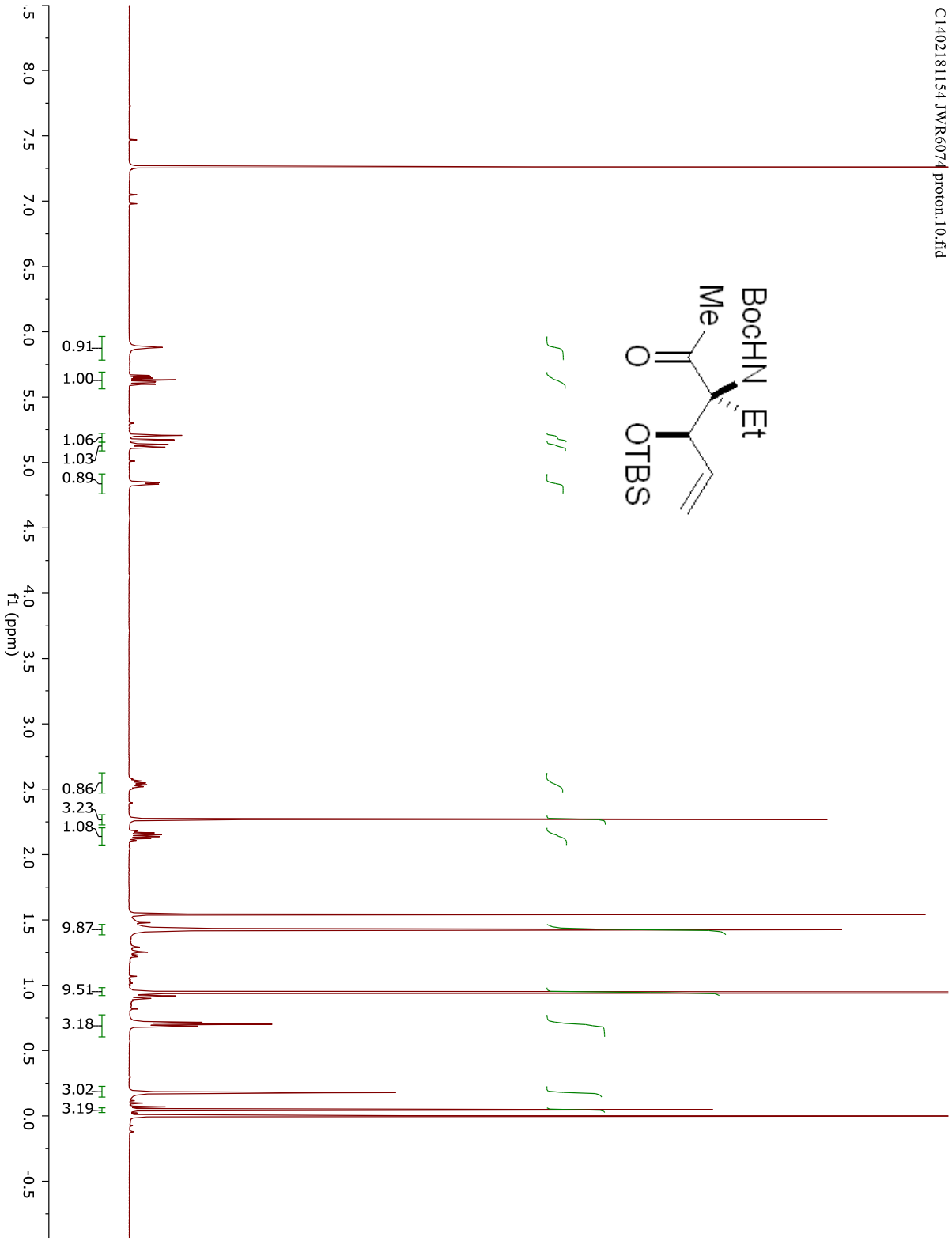

Me
O
BocN
S
O
O
O
OTBS
20.40 Toluene-d8
f1 (ppm)
20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

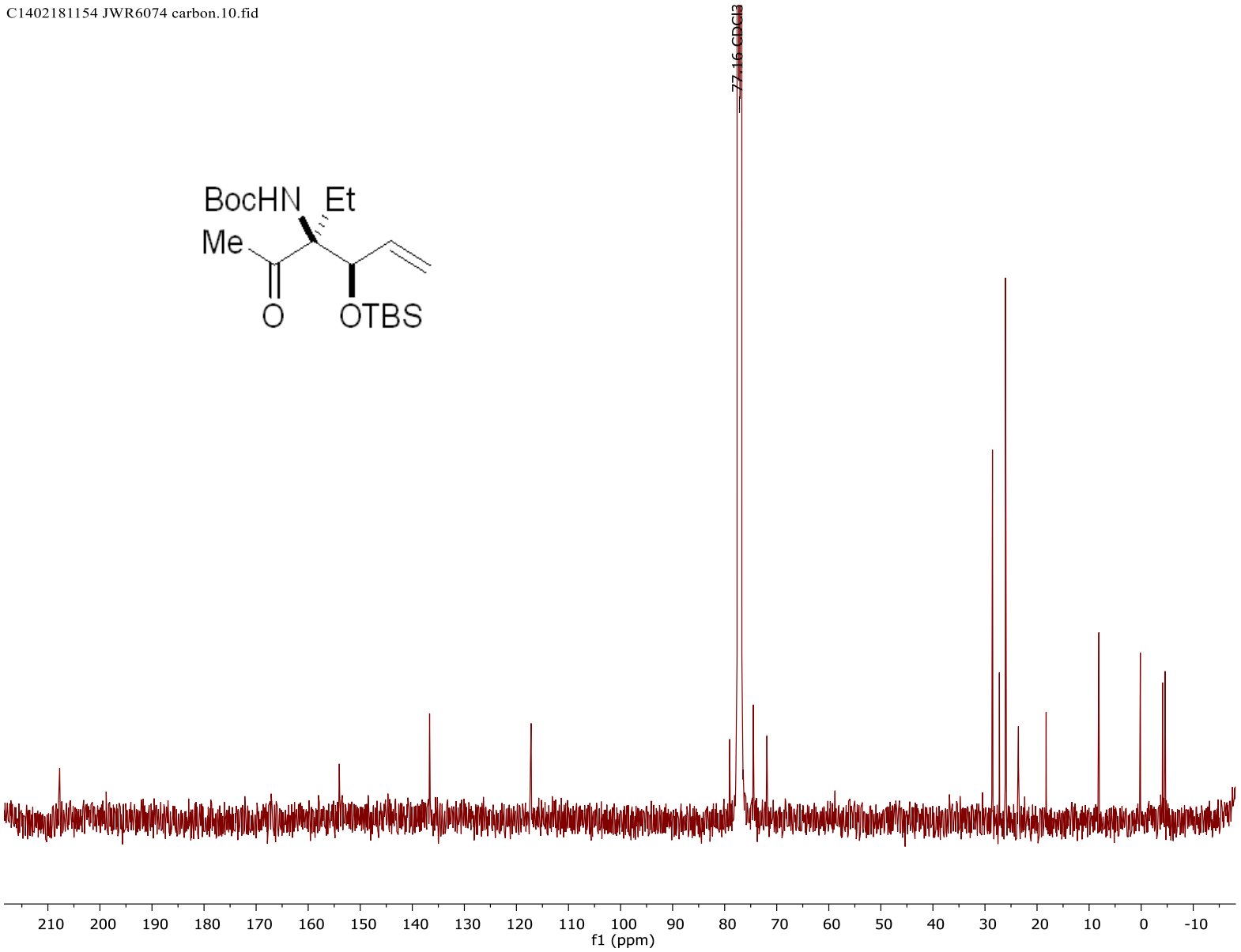
Compound 2.26



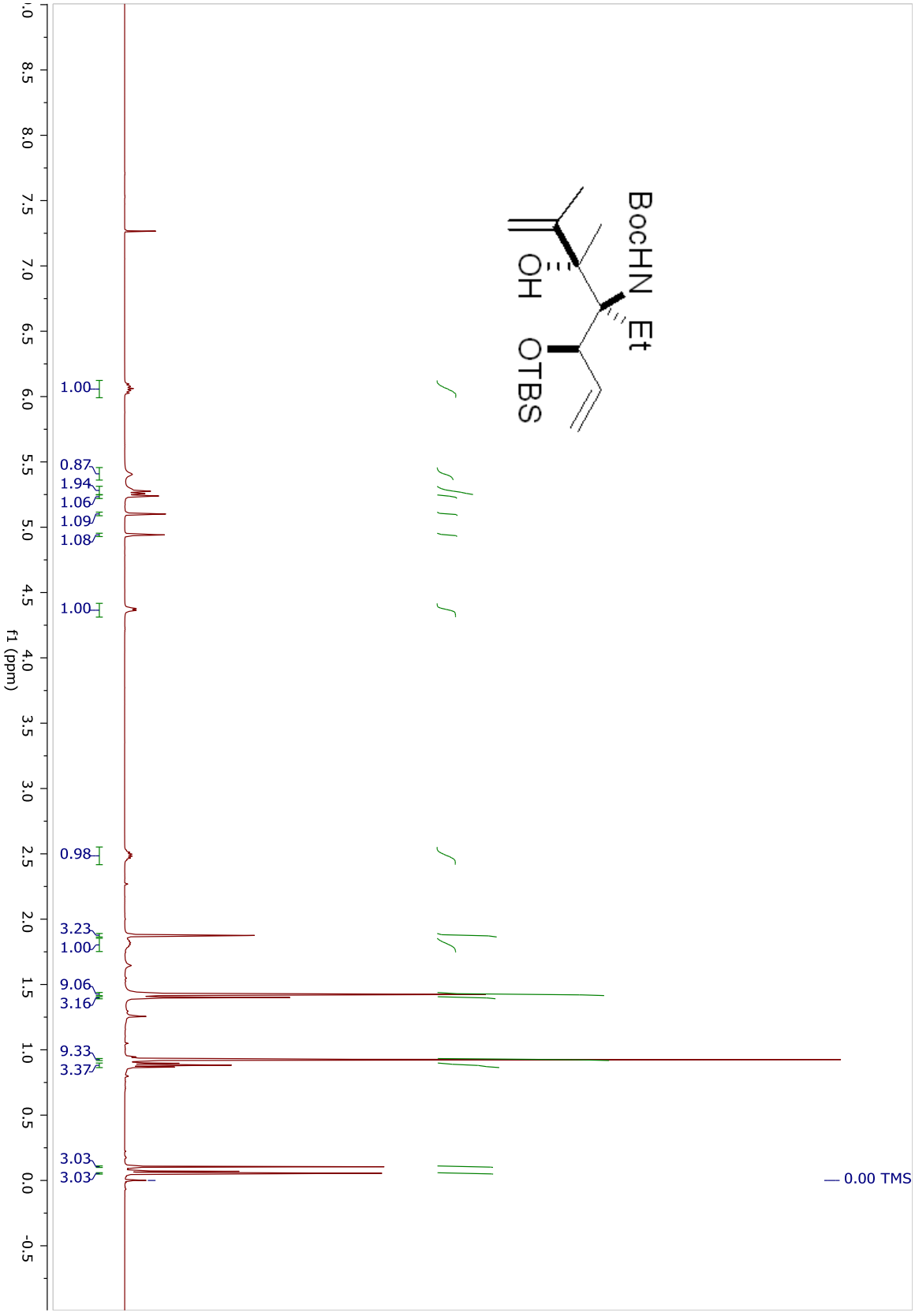

BocHN
Me
O
OTBS
SPh
77.16 CDCl3
f1 (ppm)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

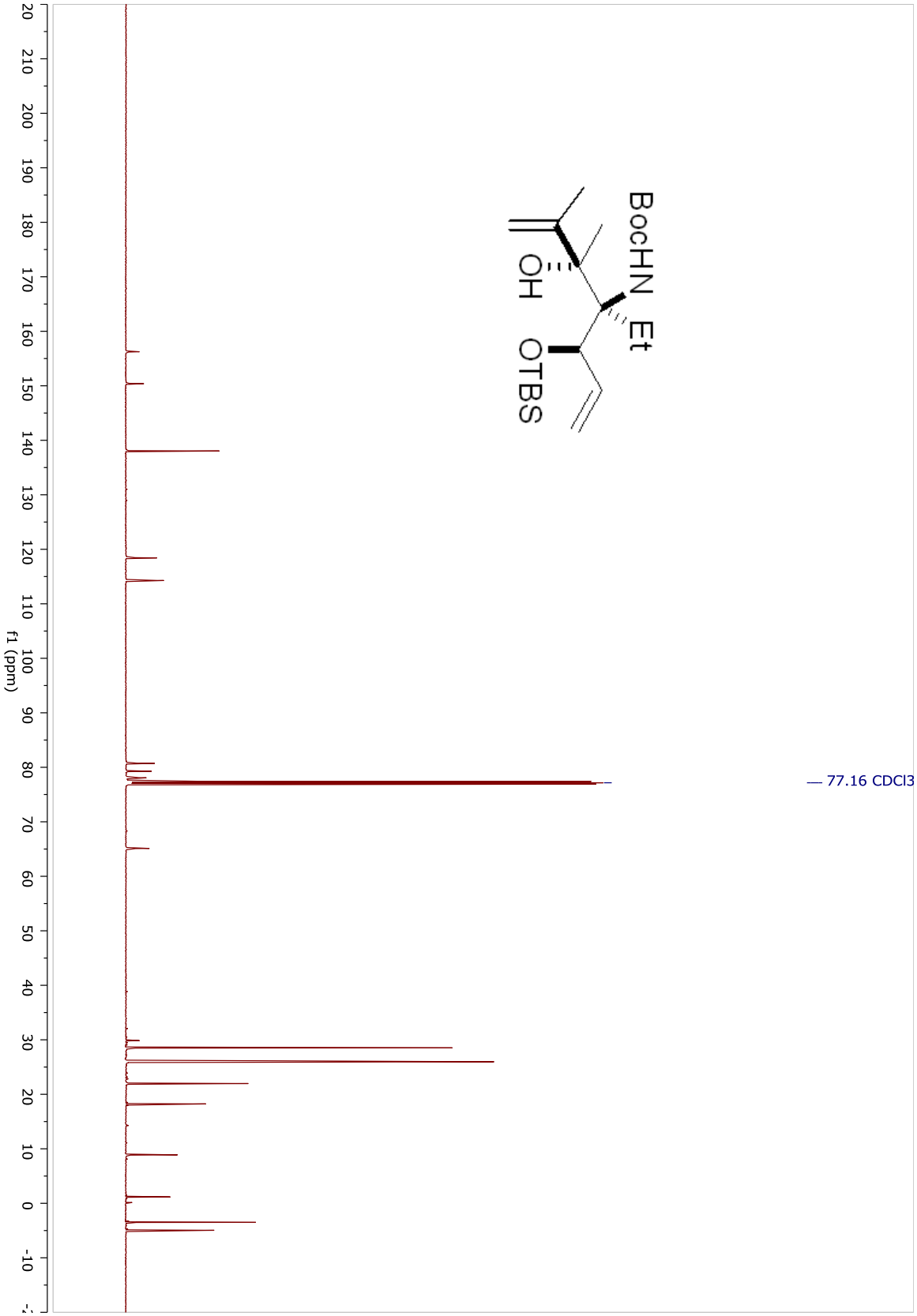
Compound 2.17



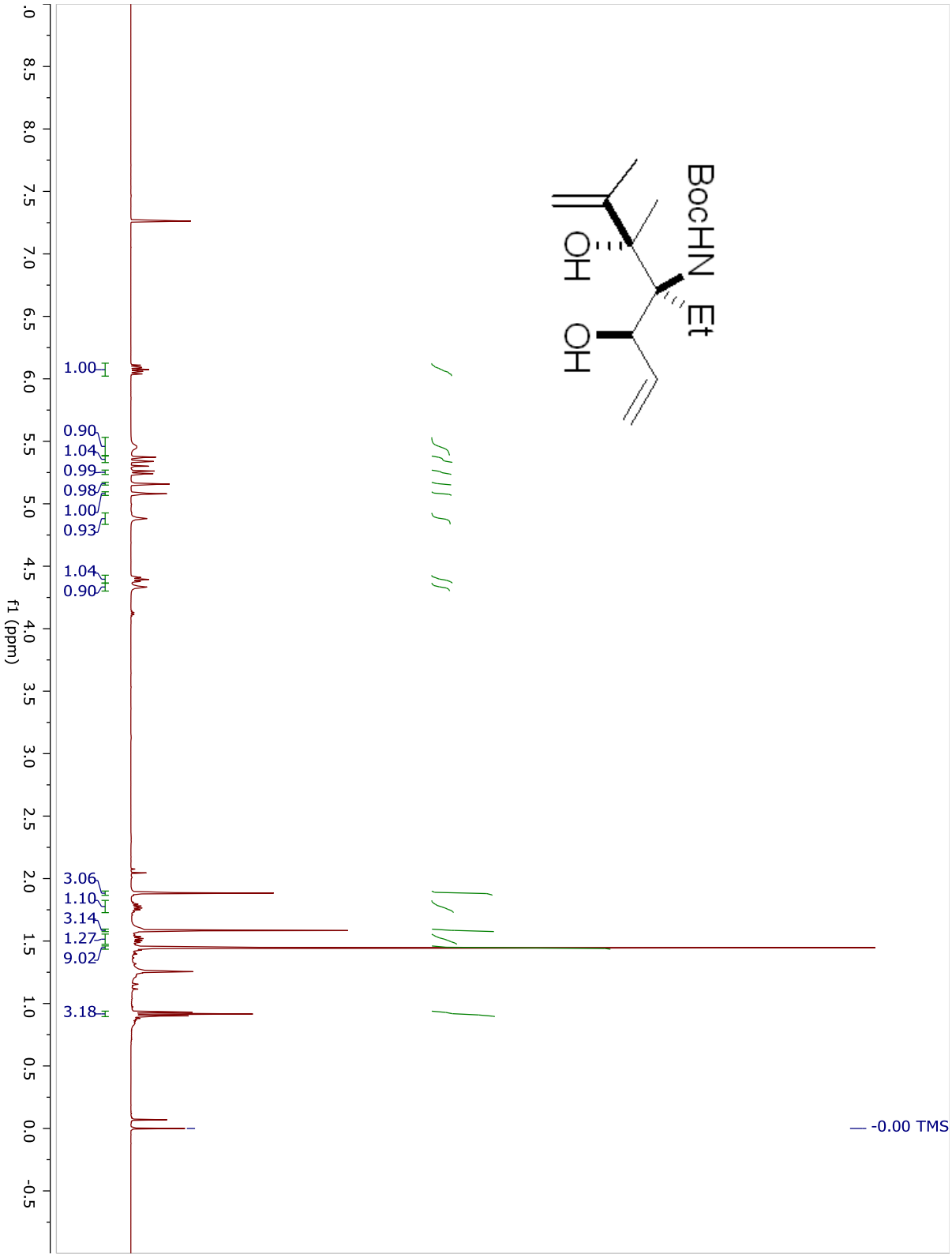

C1402181154 JWR6074 carbon.10.fid
77.16 CDCl3
BocHN
Et
Me
O
OTBS
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

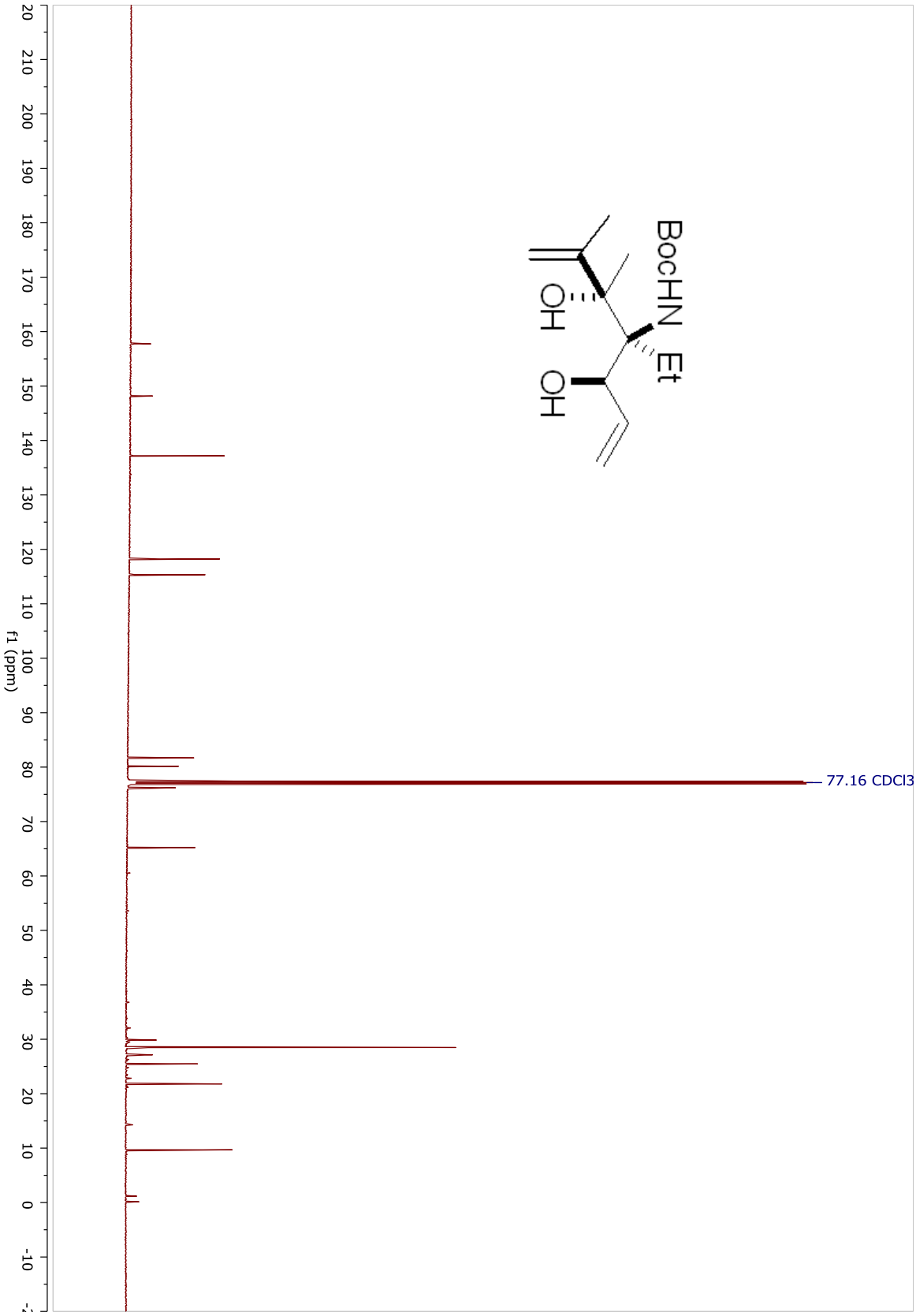
Compound 2.29



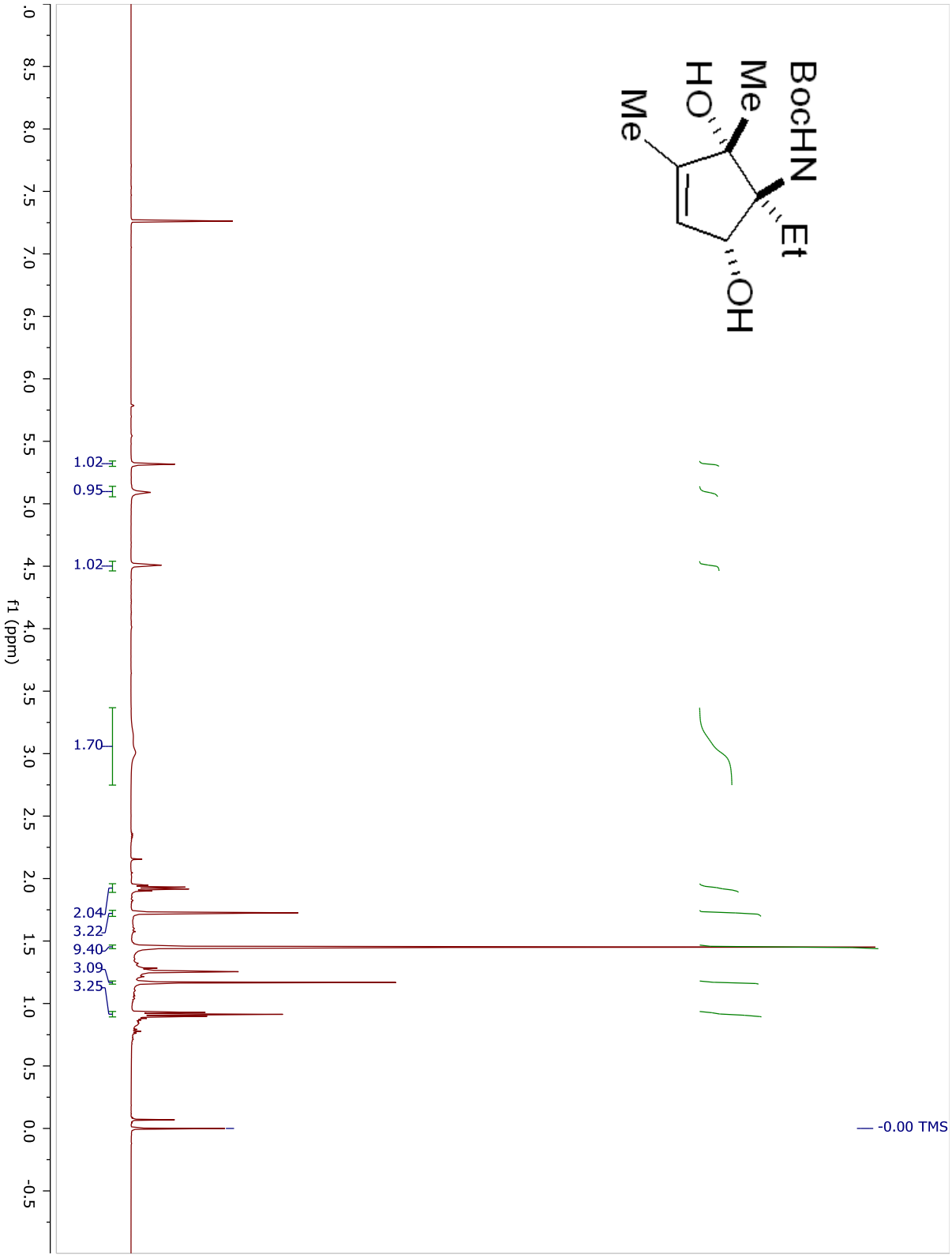

BocHN
Et
OH
OTBS
77.16 CDCl3
f1 (ppm)

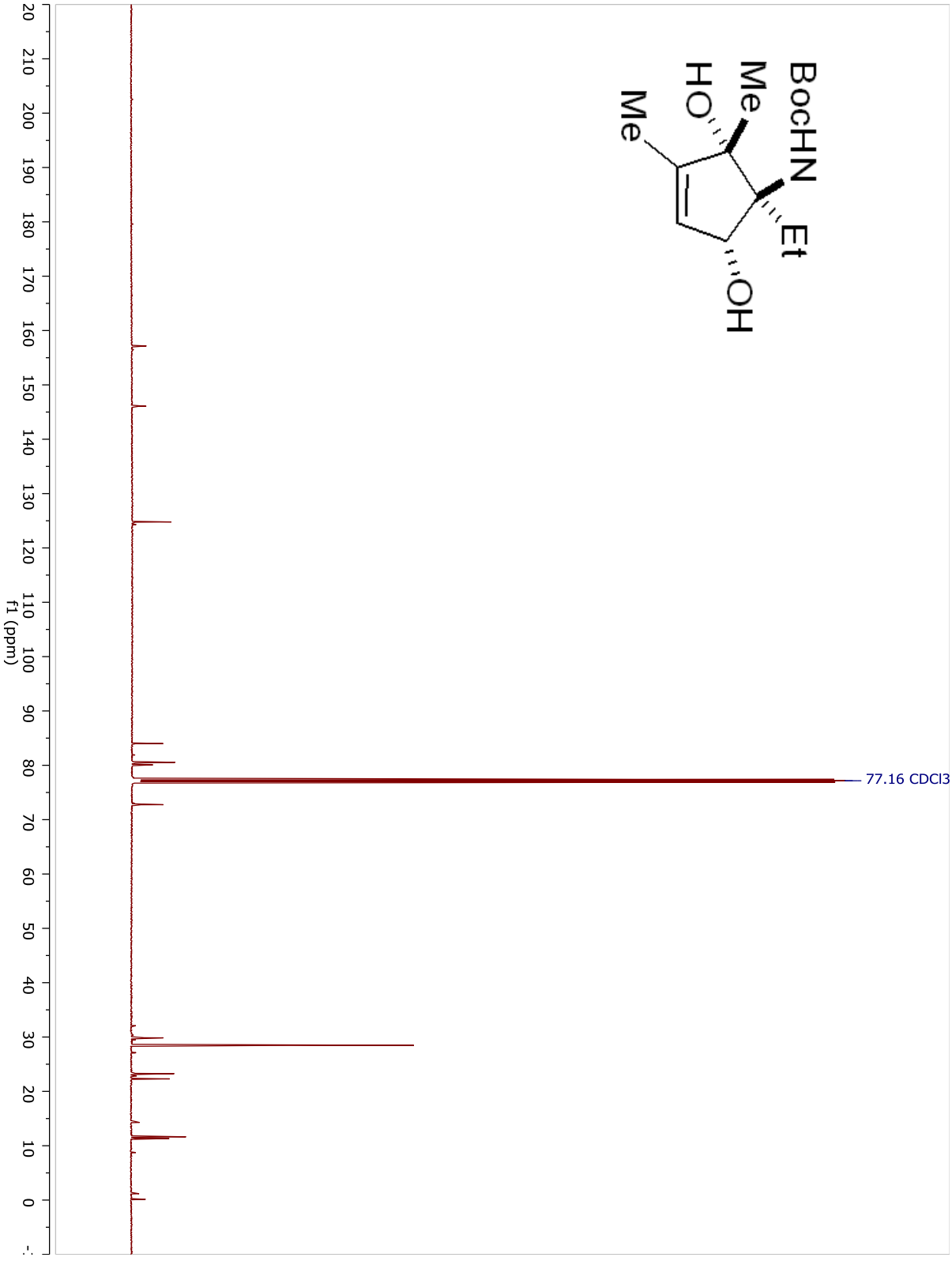
Compound 2.16




BocHN
Et
OH
OH
77.16 CDCl3
f1 (ppm)
20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

Compound 2.15




BocHN
Et
Me
HO
Me
OH
77.16 CDCl3
f1 (ppm)
20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

2.8 Experimental Details References

1. W.L.F. Armarego; C.L.L. Chai *Purification of Laboratory Chemicals* 6th ed., Elsevier: Burlington, MA, **2009**.
2. 2. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923
3. 3. Stoll, A. H.; Blakey, S. B. *J. Am. Chem. Soc.* **2010**, *132*, 2108-2109.
4. 4. Fiori, K. W.; Espino, C. G.; Brodsky, B. H.; Du Bois, J. *Tetrahedron* **2009**, *65*, 3042.

Chapter 3

Progress Towards the Synthesis of Jogyamycin

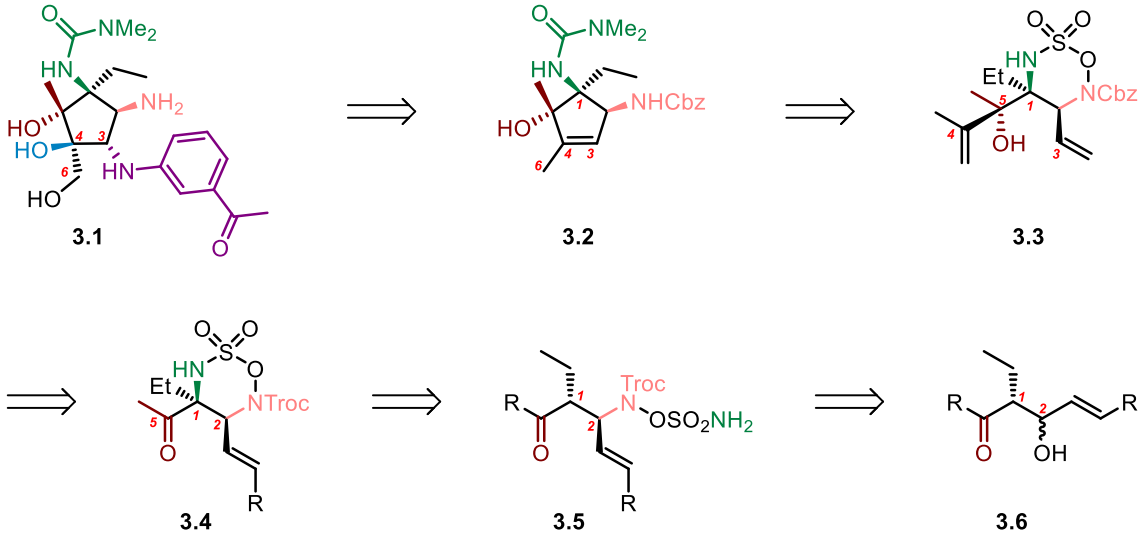
Gerstner, N. C.; Schomaker, J. M. *In preparation*

3.1 Diamination Strategy

3.1.a Diamination Retrosynthesis

After completing our efforts to the core of jogyamycin (**3.1**) using our allene aziridination chemistry, we set out to develop a route that better accommodated the *cis* C-1/C-2 amine functionality (**Scheme 3.1**). We felt that this was the most challenging stereochemical relationship in **3.1** and developing a synthesis that accounted for it would offer the greatest chance of success. We still felt that the end game of our initial route, requiring an allylic oxidation/epoxidation/epoxide opening sequence starting with **3.2**, had a high likelihood of working. We thought that the C-3/C-4 bond of cyclopentene **3.2** could be formed *via* a ring closing metathesis, similar to the strategy we employed in the synthesis of the core of **3.1** in Chapter 2. The key difference is that we thought the C-1/C-2 amine relationship could be synthesized *via* the *N*-hydroxysulfamate **3.3**, an unusual synthon that has been pioneered by Du Bois and Trost as an effective way to form 1,2-diamines.[1] Continuing with the retrosynthesis, we anticipated that the C-4/C-5 bond could be formed in a diastereoselective organometallic addition to ketone **3.4**, the stereochemistry being dictated

Scheme 3.1 – Diamination Retrosynthesis

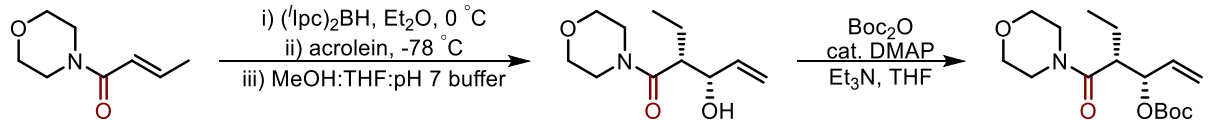


via chelation control. The sulfamate **3.5** would be used to form the C-1 amine with a chemoselective metal catalyzed nitrene C-H amination.[1] Although Du Bois and Trost did not show any examples of these sulfamates undergoing a C-H insertion in the presence of an alkene, we thought that this was feasible using the chemoselective silver catalysts that have been developed in our group for nitrene transfer reactions.[2] Du Bois and Trost showed that these C-N bonds could be formed from alcohols or their derivatives by either using through a Tsuji-Trost allylic amination reaction or a Mitsunobu reaction.[1] With this in mind, we thought that the C-2 C-N bond of **3.5** would be formed via a nucleophilic displacement of the alcohol in aldol adduct **3.6**.

3.1.b Intermolecular Allylic Amination

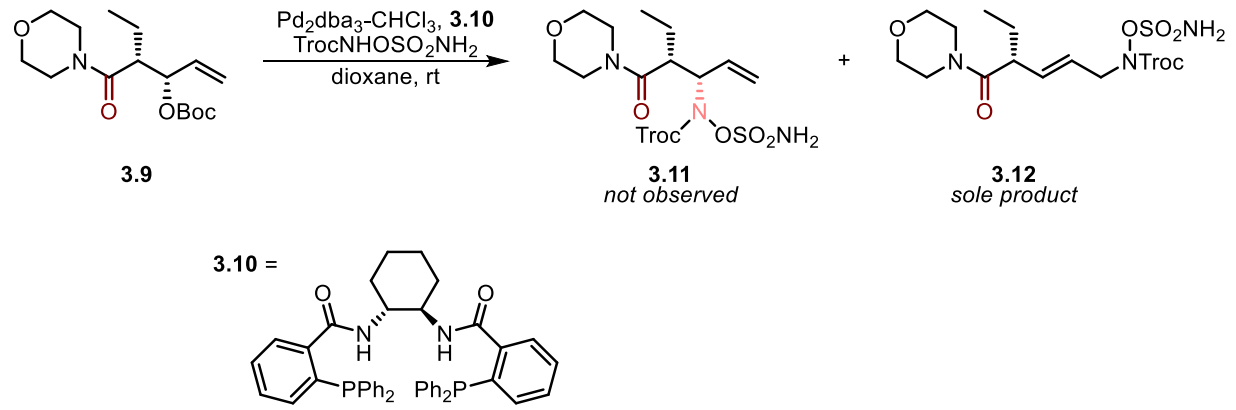
In selecting which aldol protocol to use, we settled on a system developed by Roush and co-workers that afforded the aldol adduct enantioselectively without the use of a chiral auxiliary.[3] The α,β-unsaturated morpholine amide **3.7** was reduced with $(^{l}Ipc)_2BH$, and freshly distilled acrolein was added to the resulting boron enolate (**Scheme 3.2**). The yield of the aldol adduct **3.8** proved to be exceedingly erratic, the cause supposedly being the relative instability of acrolein. Activation of the alcohol with Boc_2O yielded carbonate

Scheme 3.2 – Reductive Aldol and Carbonate Formation



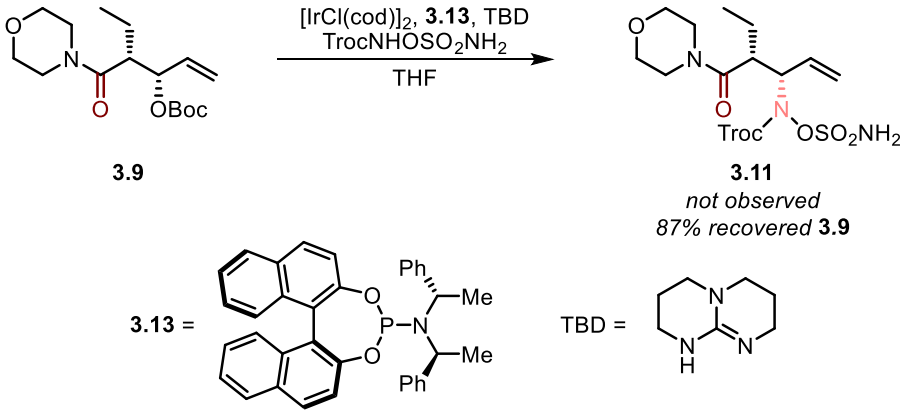
3.7 | **3.8** 10-60% yield | **3.9** 62% yield

Scheme 3.3 – Tsuji-Trost Allylic Amination



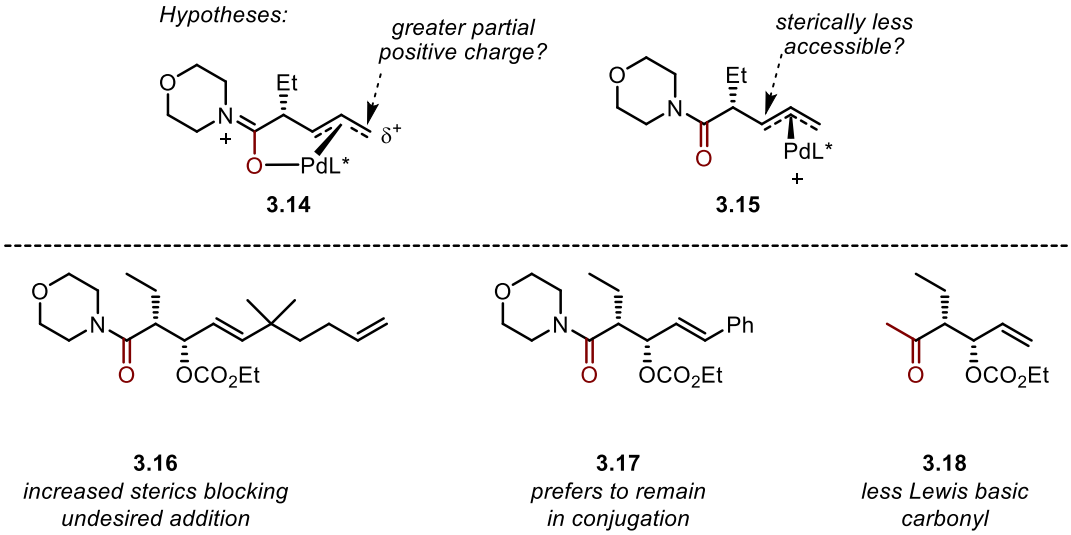
3.9 in moderate yield. Subjecting **3.9** to the Tsuji-Trost allylic amination reaction with Pd_2dba_3 and ligand **3.10** led to complete consumption of the allylic carbonate (**Scheme 3.3**).[1b,c] Unfortunately, ^{1}H NMR analysis revealed complete conversion not to the desired branch isomer **3.11**, but rather to the linear isomer **3.12**. This result was not anticipated as these nucleophiles were known to produce exclusively the branched allylic amination product.[1b,c] Attempts to perform the same reaction using $[IrCl(cod)]_2$ and ligand **3.13** led to recovered starting material (**Scheme 3.4**).[4] While this catalyst combination has been used to perform allylic aminations with *N*-hydroxyamines to yield branched amines, linear carbonates were used as starting materials instead of branched carbonates. The lack of reactivity is likely due to the inability of the iridium catalyst to productively react with the branched allylic carbonate.

Scheme 3.4 – Attempted Iridium Catalyzed Allylic Amination



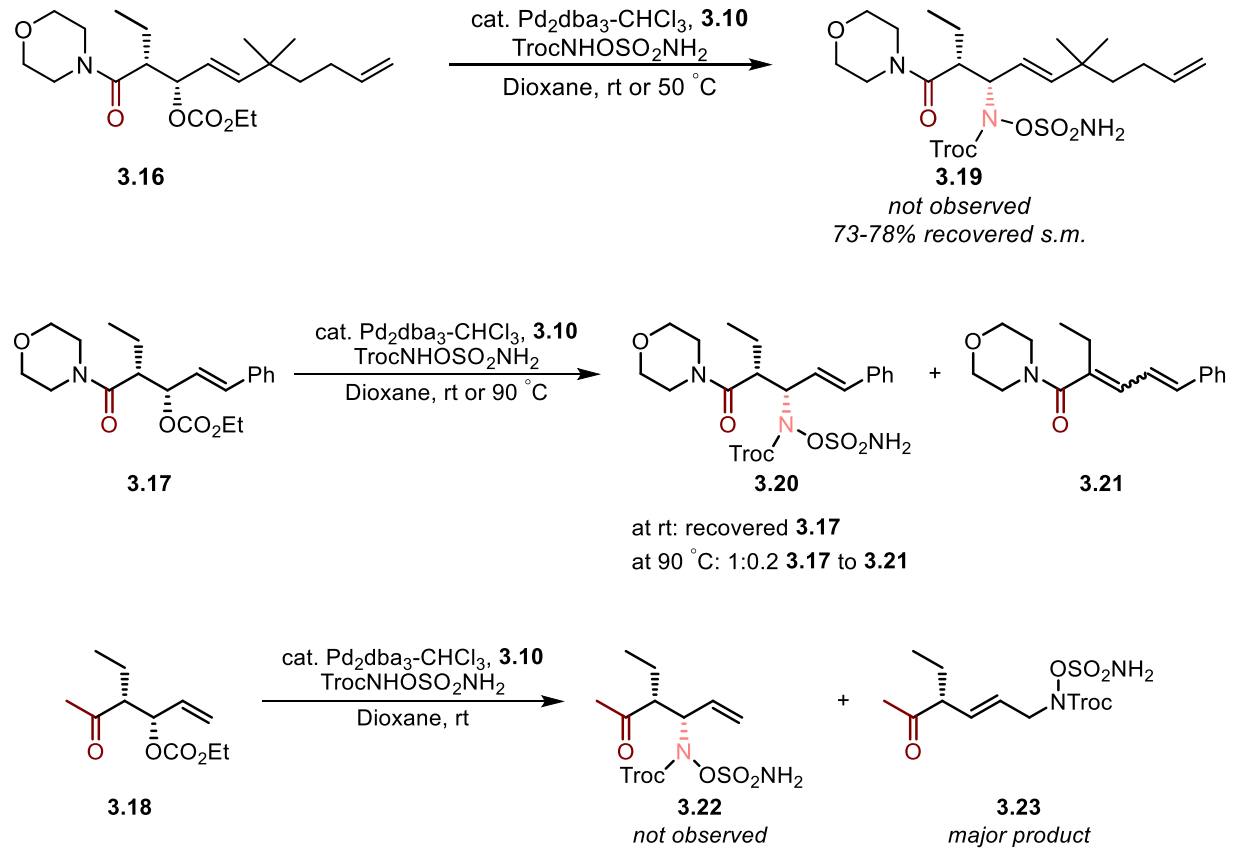
As we were getting complete conversion of the branched carbonate when using palladium catalysts but were observing the undesired linear product, we hypothesized that this was a substrate issue and not a catalyst issue. We hypothesized that there were potentially two reasons we were seeing exclusively linear product (**Figure 3.1**). One potential issue could be that the amide could be acting as a potent Lewis base, and that coordination of the carbonyl to the palladium complex in **3.14** could alter the electronics of the palladium π-allyl complex. This could create a greater partial positive charge on the terminal carbon of the π-allyl and lead to preferential attack at this carbon by the nitrogen nucleophile. Our other hypothesis was that the trajectory of approach by the nitrogen nucleophile in **3.15** was hindered by the branched carbon, resulting in the linear product being formed exclusively. We developed several substrates (**3.16-18**) to test these hypotheses. If the preference was simply due to the bulk of the branched carbon adjacent to the alkene, carbonate **3.16** would offer a bulkier side chain that would hopefully give the desired C-2 amine. Styrenyl **3.17** would offer a strategy revolving around the fact that the alkene in the allylic amination product would prefer to remain in conjugation with the phenyl group. If the issue the Lewis basicity of the carbonyl, using the less basic ketone **3.18** could afford the desired branched allylic amination product.

Figure 3.1 – Alternative Aldol Adducts for the Allylic Amination



Substrates **3.16-18** were synthesized in a similar manner as **3.9**. Exposure of carbonate **3.16** to the allylic amination conditions only resulted in recovered starting material and elevated temperatures did not improve conversion (**Scheme 3.5**). It appears that while one side of the alkene was blocked by the fully substituted carbon adjacent to it, this also prevented the palladium from attacking the carbonate. Styrene **3.17** was then subjected to the reaction conditions. No reaction occurred at room temperature, but at elevated temperatures it appeared that a small amount of diene **3.21** was observed in addition to recovered carbonate **3.17**. Ketone **3.18** proved to be a more reactive substrate, with complete conversion observed at room temperature. Unfortunately, only the linear product **3.23** was observed. These results appear to indicate that the biggest issue for obtaining the branched amine with the correct C-2 configuration was the branched carbon C-1 carbon hindering the approach of the nucleophile. Unfortunately, that was a feature of the substrate that could not be removed, necessitating a new approach to jogyamycin.

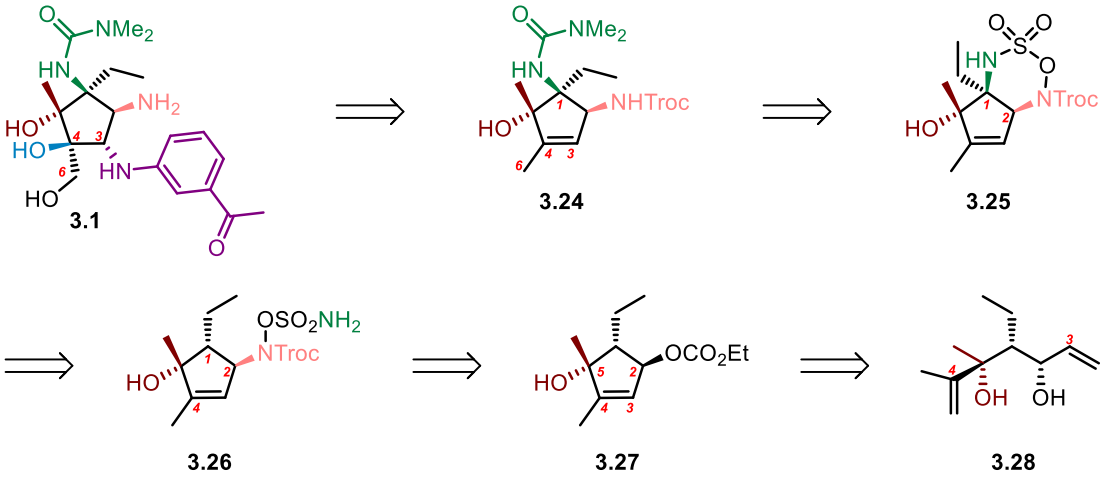
Scheme 3.5 – Attempted Allylic Aminations



3.1.c Revised Allylic Amination Retrosynthesis

With the allylic amination of the aldol adducts not performing as we had planned, we designed a new route (**Scheme 3.6**). The C-1 C-N bond in **3.25** would be formed at a later stage of the sequence, after the cyclopentene had already been formed. The sulfamate **3.26** would be accessed from carbonate **3.27**. Although all previously published examples of using $TrocNHOSO_2NH_2$ as a nucleophile in these Pd-catalyzed allylic aminations have resulted in the branched allylic amine, we observed that the preference for the more substituted product can be overridden by the steric environment adjacent to the π-allyl complex. We proposed that C-5 stereocenter in **3.27** would block attack at C-4, resulting in amination at C-2. Carbonate **3.27** could be easily accessed from diol **3.28** *via* a ring closing metathesis, which could be derived from aldol adduct **3.8**.

Scheme 3.6 – Revised Diamination Retrosynthetic Strategy

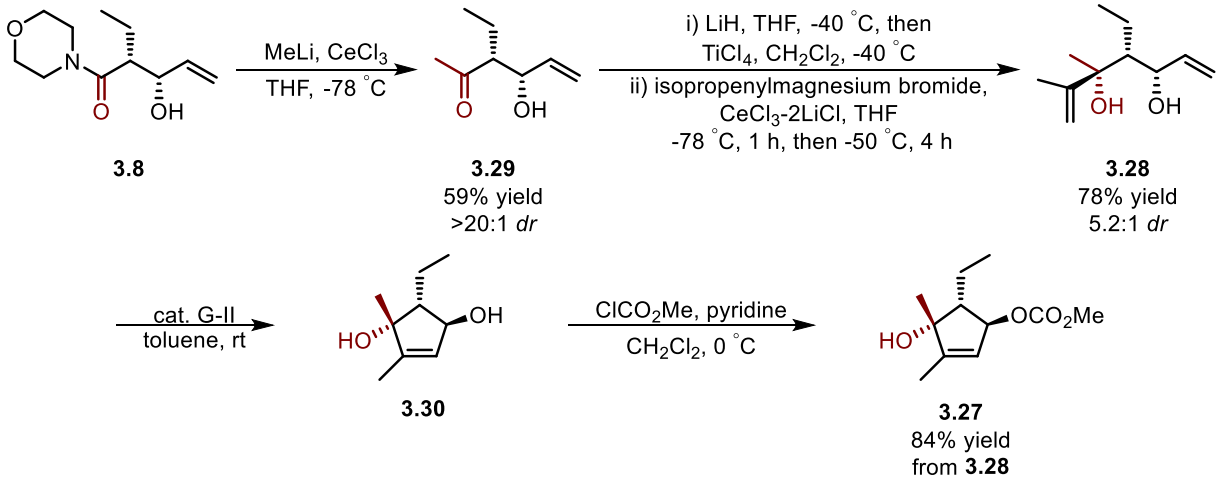


3.1.d Cyclic Allyl Carbonates as Allylic Amination Substrates

The synthesis of diol **3.28** was initiated by adding MeLi to aldol adduct **3.8** mediated by $CeCl_3$ to yield ketone **3.29** (**Scheme 3.7**).[5] This procedure developed by Kishi and coworkers was preferable to using MeMgBr as it limited the epimirization of **3.29** upon work up. The isopropenyl group was added to ketone **3.29** diastereoselectively utilizing conditions developed by Bartoli and co-workers, affording diol **3.28** in good yield and *dr*.[6] Diol **3.28** was transformed into cyclopentene **3.30** with a ring closing metathesis, and

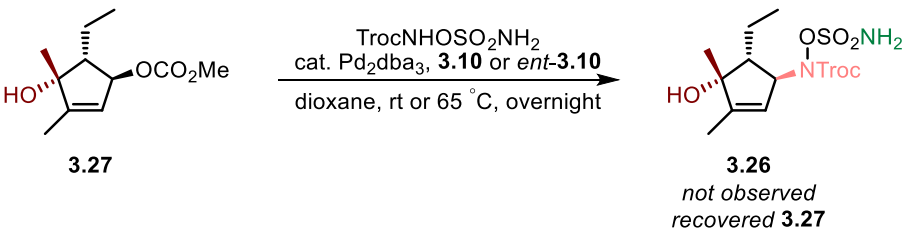
the crude mixture was immediately subjected to the acylation to give carbonate **3.27** in good yield. While we were pleased with the step efficiency of this route, in practice the large amount of $CeCl_3$ needed for the first two steps and the resulting dilute conditions needed to accommodate this large amount of $CeCl_3$ limited the practical scale of these transformations.

Scheme 3.7 – Synthesis of the Cyclopentendiol



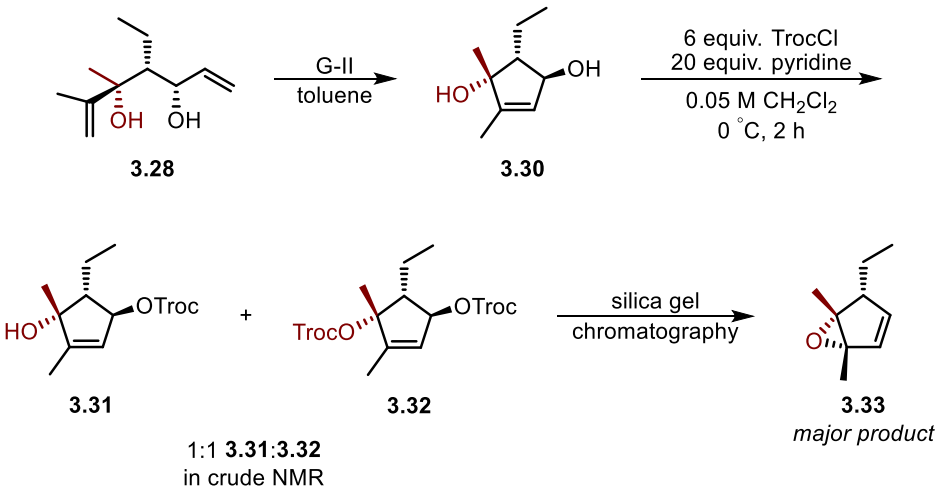
With carbonate **3.27** in hand, we set off to explore the allylic amination (**Scheme 3.8**). We were unsure which enantiomeric series of the ligand **3.10** would provide the ideal interaction between the substrate and the palladium catalyst, so both enantiomers were tried. Unfortunately, at both ambient and elevated temperatures, no conversion of the allylic carbonate was observed. Although it appears that the allylic carbonate **3.27** would be more accessible for the nitrogen nucleophile to attack at the desired position due to the ethyl group being *trans* to the incoming nucleophile, this same ethyl group would be on the same face as the palladium complex and could be impeding reactivity.

Scheme 3.8 – Attempted Allylic Amination of the Cyclopentene Carbonate



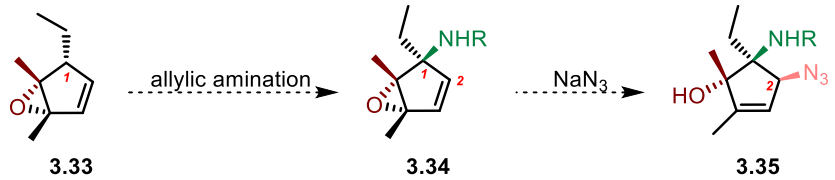
To get around this issue, we hypothesized that raising the reactivity of the allylic carbonate would produce better results. This strategy has been employed before by substituting a Troc carbonate for a generally unreactive alkyl carbonate.[7] Diol **3.28** was again converted to the cyclopentene **3.30**, which was exposed to excess 2,2,2-trichloroethyl chloroformate (**Scheme 3.9)**. Upon work up we observed what appeared to be a 1:1 mix of the mono-acylated material **3.31** and the bis-acylated material **3.32**. Purification of this material surprisingly did not lead to the isolation of either compound in useable yield. Rather, epoxide **3.33** was isolated as the major product, presumably formed *via* a S_N2' reaction.

Scheme 3.9 – Accidental Synthesis of the Cyclopentene Oxide



We were intrigued by the cyclopentene oxide **3.33** as we realized that this could be used as a key intermediate in our synthesis (**Scheme 3.10**). We hypothesized that performing an allylic amination on **3.33** would yield the amine **3.34**. With the C-1 amine in place, the opening of the allylic epoxide with the azide anion in an S_N2' reaction would furnish the azido amine **3.35**. Both the allylic amination and the S_N2' of allylic epoxides with azide nucleophiles were precedented, reassuring us that this route could be feasible.[8,9]

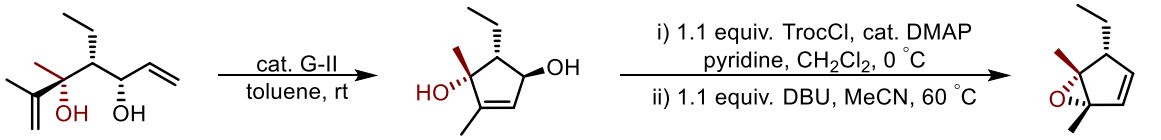
Scheme 3.10 – Proposed Elaboration of the Cyclopentene Oxide



3.33 **3.34** **3.35**

To explore this new intermediate, we set about developing a better synthesis that did not rely upon substrate decomposition upon exposure to silica gel (**Scheme 3.11**). To accomplish this, cyclopentene **3.30** was isolated prior to the acylation to more carefully control the equivalents to 2,2,2-trichloroethyl chloroformate required for the transformation. Subjecting the crude carbonate to DBU in warm acetonitrile led to complete conversion of the intermediate carbonate, and **3.33** was isolated in excellent yield after column chromatography. The stability of **3.33** to acidic silica gel was not noteworthy at the time, but became so in our future work.

Scheme 3.11 – Optimized Synthesis of the Cyclopentene Oxide



3.28

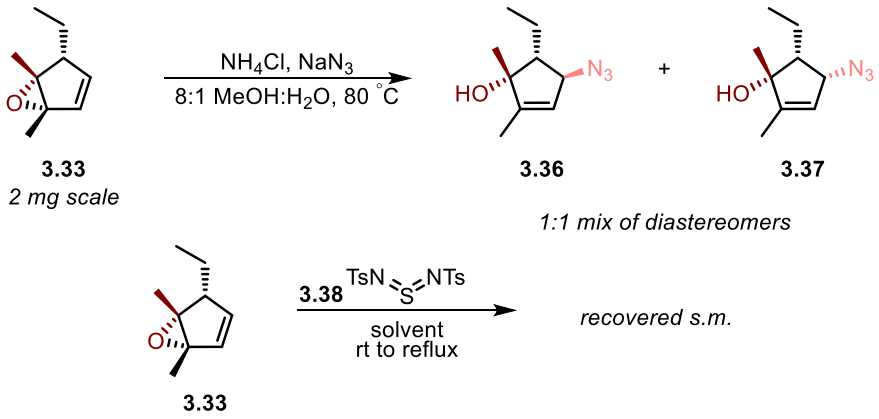
3.30
91% yield

3.33
86% yield

With access to epoxide **3.33** we were able to test both amination events needed to form the C-1 and C-2 amines (**Scheme 3.12**). Heating epoxide **3.33** in a methanol/water mixture in the presence of ammonium chloride and sodium azide led to the clean conversion of the starting material into two new products that appeared to be the diastereomers **3.36** and **3.37**. They did not appear to be regioisomers due to the trisubstituted alkene in both products. While it is disappointing that it appears that these reactions go through a S_N1' reaction rather than a stereospecific S_N2' reaction, we were encouraged that we were finally able to form the C-2 amine product. With this result in hand, we went about exploring the allylic amination of **3.33**. Metal catalyzed nitrene C-H insertions were unappealing either due to the large excess of the epoxide that would be needed or due to the substantial difficulties in accessing the nitrene precursor.[2,10] We

settled on using sulfur diimide **3.38** to perform the allylic amination.[9] Unfortunately, we observed no reaction between the substrate and diimide at temperatures as high as 160 ˚C in 1,2-dichlorobenzene. Clean recovery of **3.33** was observed even at these elevated temperatures. While a number of examples exist of using diimide **3.38** to perform C-H aminations in complex substrates, it appears that this reagent is not adept at forming amines from tertiary C-H bonds.[9] Overall, we were encouraged by our ability to form the C-2 amine through the opening of the allylic epoxide. To pursue this route further, however, we needed to develop a route to access the allylic epoxide with the C-1 urea already in place.

Scheme 3.12 – S_N2' Opening of the Epoxide and Attempted Allylic Amination



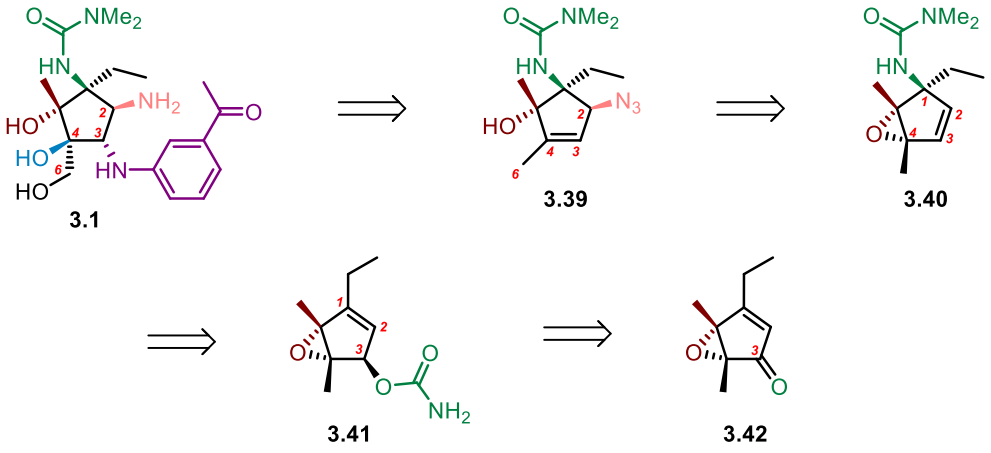
3.2 Ichikawa Rearrangement/Epoxide Opening Strategy

3.2.a Ichikawa Rearrangement/Epoxide Opening Retrosynthesis

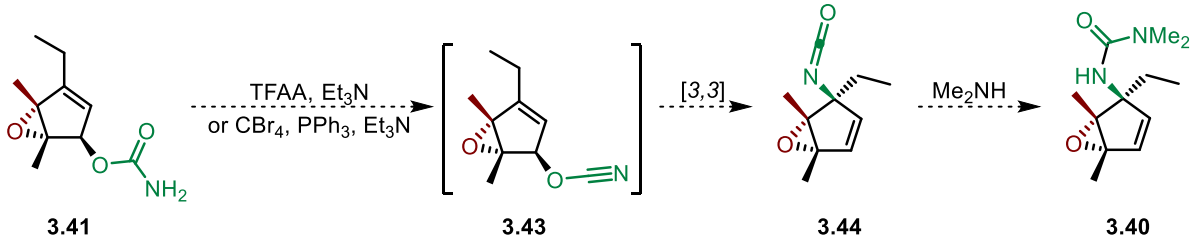
As stated in the previous section, we were encouraged by ability to form the C-2 amine through the azide opening of an allylic epoxide. We were also somewhat frustrated in our inability to scale some of the reactions to procure large amounts of material even three to four steps into the synthesis. With the idea of scalability in mind, we developed a new route to **3.1** (**Scheme 3.13**). The biggest difference between our previous end game strategies was that the C-2 amine in **3.1** would be formed through the reduction of an azide rather than the deprotection of a carbamate. We proposed that we would be able to develop conditions to access azide **3.39** stereoselectively from epoxide **3.40**. If the C-1 urea interfered with this transformation,

the C-1 amine could easily be tied up as a non-nucleophilic nitrogen since a late stage formation of the C-1 urea would be easier in the presence of the C-2 azide. Since our previous attempts to form the C-1 amine through an intermolecular allylic amination failed we wished to develop a more reliable approach that wasn't as sensitive to the sterics of the system, leading us to explore various intramolecular reactions. Eventually we came upon the Ichikawa rearrangement, which was initially discovered by Overmann and co-workers but later developed into a synthetically useful transformation by Ichikawa and co-workers.[11] Although this reaction has been used in a variety of syntheses and has been recently reviewed, it appears that this reaction is still somewhat unknown in the broader synthetic community. This is unfortunate as it is a similar retrosynthetic disconnect to the famous Overmann rearrangement, but it proceeds at significantly lower temperatures and the functionalization of the intermediate isocyanate offers greater product diversity than can be achieved through the Overmann rearrangement. The overall appeal of the Ichikawa rearrangement led us to target allylic carbonate **3.41** as a key intermediate. We thought we would be able to develop conditions to access the allylic carbamate **3.41** through the stereoselective reduction of cyclopentenone **3.42**. There are several reports in the literature of accessing cyclopentenones with α,β-epoxides similar to **3.42**.[12] Although we didn't find the synthetic routes used previously to be appealing and there was little reports on the diversification of these products, we felt that this synthetic intermediate was a reasonable target and that conditions for the stereoselective reduction could easily be developed.

Scheme 3.13 – Ichikawa Rearrangement/S_N2' Epoxide Opening Retrosynthetic Analysis



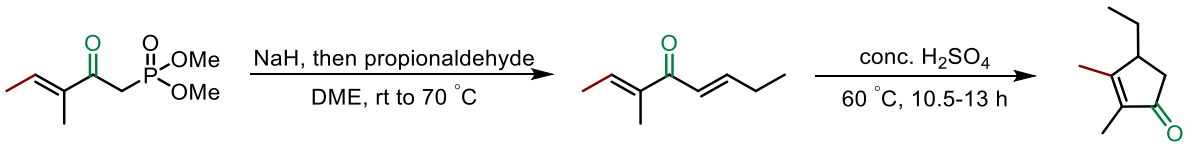
Scheme 3.14 – Proposed Ichikawa Rearrangement



3.2.b Route to the epoxide

As stated previously, the unappealing nature of the previous routes to access α,β-epoxycyclopentenones led us to develop an alternate synthetic route (**Scheme 3.15**). A Horner-Wadsworth-Emmons olefination of propionaldehyde with phosphonate **3.43** led to the isolation of **3.44** in reproducible yields on significant scales.[13] Subjecting the dienone **3.44** to warm concentrated sulfuric acid led to isolation of Nazarov product **3.45** as a single regioisomer.[13] With the rapid formation of the cyclopentene ring with all of the necessary exocyclic alkyl groups at C-1, C-4 and C-5, the rest of the synthesis would compose of oxidation state manipulations of the carbon scaffold, a synthetic strategy that is currently in vogue.[14]

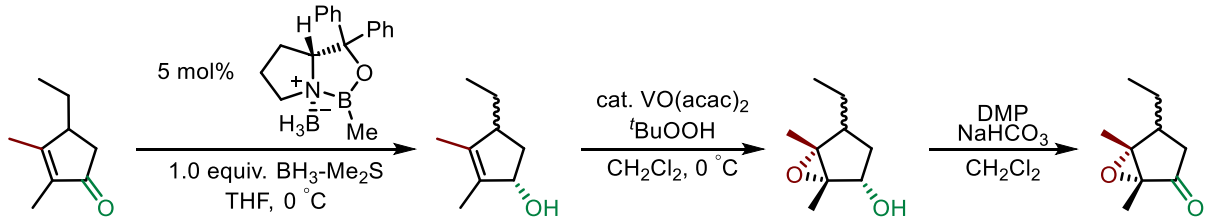
Scheme 3.15 – Cyclopentenone Formation *via* a Nazarov Strategy



Although the Nazarov cyclization afforded rapid access to cyclopentenone **3.45**, it did so in a racemic fashion. Advantageously, the racemic C-1 center would be ablated later in the synthesis. Wishing to perform an enantioselective synthesis of **3.1**, we initially considered performing an enantioselective epoxidation of the enone.[15] Ultimately, we decided that an inefficient stepwise enantioselective reduction/diastereoselective epoxidation/alcohol oxidation route would procure enantioselective more rapidly to initially test the feasibility of this route (**Scheme 3.16**). The CBS reduction of enone **3.45** resulted in the isolation of **3.46**; the acid sensitive allylic alcohol could be purified *via* Kugelrohr distillation to

afford a 1:1 mix of diastereomers.[16] The vanadium-catalyzed directed epoxidation afforded **3.47** in excellent yield. This protocol was a significant improvement over *m*-CPBA, which was somewhat inconsistent because the acid generated was prone to decomposing the sensitive allylic alcohol. Oxidation of alcohol **3.47** led to the quantitative isolation of ketone **3.48**.

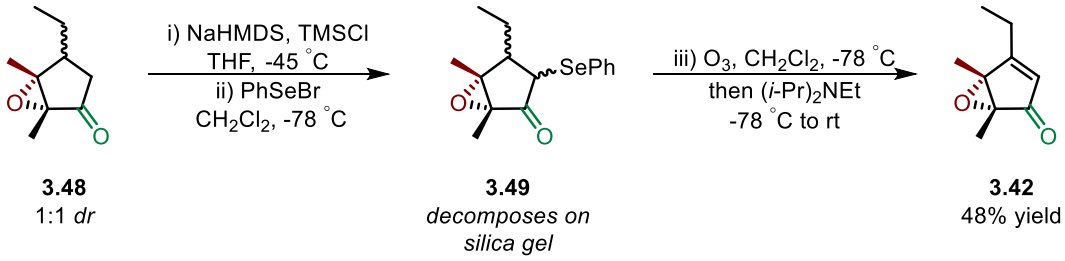
Scheme 3.16 – Enone Reduction/Epoxidation/Oxidation Sequence



3.45 | **3.46** 79% yield 1:1 *dr* | **3.47** 91% yield 1:1 *dr* | **3.48** quantitative 1:1 *dr*

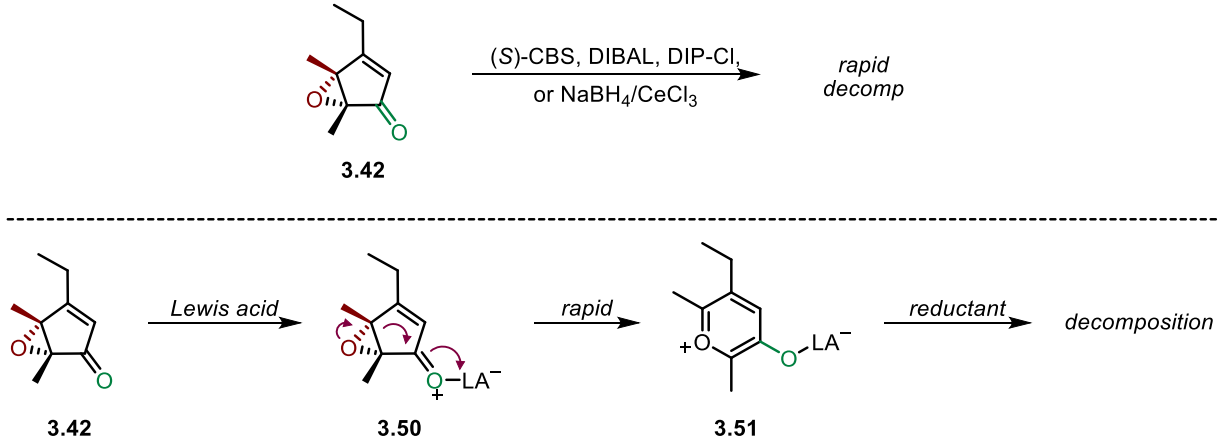
With the stereoselective formation of the α,β-epoxy ketone developed, we then set out to destroy the C-1 stereocenter by forming the α,β-unsaturated ketone (**Scheme 3.17**). Formation of the silyl enol ether of **3.48** proved to be relatively easy when using NaHMDS as a base. Unfortunately, Saegusa-Ito conditions led to decomposition of the silyl enol ether. Similar results were observed employing conditions utilizing the hypervalent iodine reagents developed by Nicolau.[17] Silyl enol ether did give clean conversion to the α-phenylselenoketone **3.49** when it was exposed to phenylselenyl bromide. This substrate was sensitive to silica gel chromatography, so the crude material was subjected to mild oxidizing conditions employing the aprotic ozone as an oxidant. The addition of a tertiary amine base and warming the mixture to room temperature led to the formation of the sensitive enone **3.42** in acceptable yield after Kugelrohr distillation.

Scheme 3.17 – Oxidation to the Enone



We were somewhat dismayed at the difficulty of accessing enone **3.42** from the ketone, but with the material in hand we proceeded to explore different conditions to access the allylic alcohol (**Scheme 3.18**). A variety of reductants known for the selective reduction of enones to allylic alcohols all resulted in the rapid decomposition of the enone. Unfortunately, there was no discernible products that could be identified in this mixture. We noted that all of the reagents employed to this point contained a Lewis acid. This information, coupled with the knowledge that the enone **3.42** decomposed upon exposure to silica gel, indicated to us that the enone could be unstable in the presence of Lewis acids. Lewis acid complexation to **3.42** would likely occur at the carbonyl, resulting in complex **3.50** which could undergo rapid electrocyclic ring opening to afford the 3-oxypyrillium zwitterion **3.51**.[18] Presumably **3.51** is unstable to the reductants employed leading the extensive decomposition that we observed. This was disheartening as we needed to reduce enone **3.42** from the concave face, indicating we would need to direct this reduction through

Scheme 3.18 – Attempted Reduction of the Enone

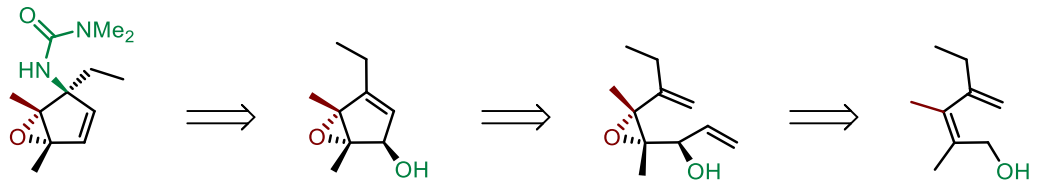


substrate binding. We believe that the general instability of α,β-epoxy cyclopentenone **3.42** to Lewis acids is likely why similar molecules have not been utilized previously in any previous syntheses despite the fact that they appear to be an appealing synthetic intermediate.

3.2.c Reroute of epoxide synthesis

The instability of **3.42** led us to develop an alternate route to the allylic alcohol. We hypothesized that the allylic alcohol **3.52** would not be prone to the same electrocyclic ring opening issues due to the C-3 carbon being sp^3 hybridized (**Scheme 3.52**). This belief was buoyed by the general stability we had observed when handling epoxide **3.33**, which was formed, not decomposed, upon exposure to silica gel. Epoxide **3.33** was also stable to elevated temperatures, which gave us further confidence that allylic alcohol **3.52** would be stable. We proposed that we would be able to form the allylic alcohol **3.52** *via* a ring closing metathesis of allylic alcohol **3.53** to form the C-2/C-3 bonds. Allylic alcohol **3.53** could be formed in a series of steps from diene **3.54**.

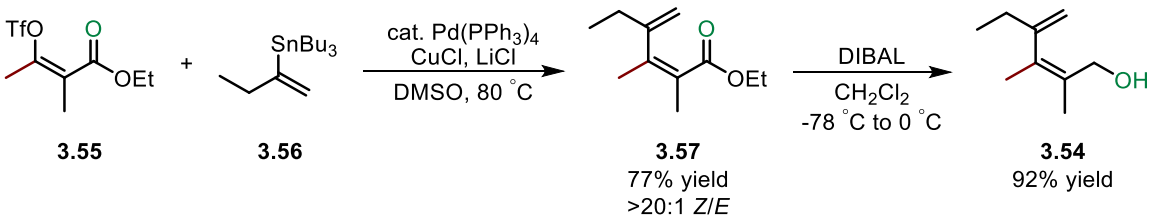
Scheme 3.19 – Revised Approach to the Ichikawa Rearrangement Precursor



3.40 **3.52** **3.53** **3.54**

The synthesis was started using a Stille coupling between the known stereodefined vinyl triflate **3.55** and vinyl stannane **3.56**, yielding **3.57** in good yield and excellent stereoselectivity (**Scheme 3.20**).[19] There are reported conditions performing this transformation with a vinyl copper reagent starting with a vinyl organometallic. Unfortunately, the price of 2-bromo-1-butene meant that the cross-coupling route was more economically feasible.[20] Reduction of the ester with DIBAL proceeded smoothly and the allylic alcohol **3.54** was isolated in excellent yield.

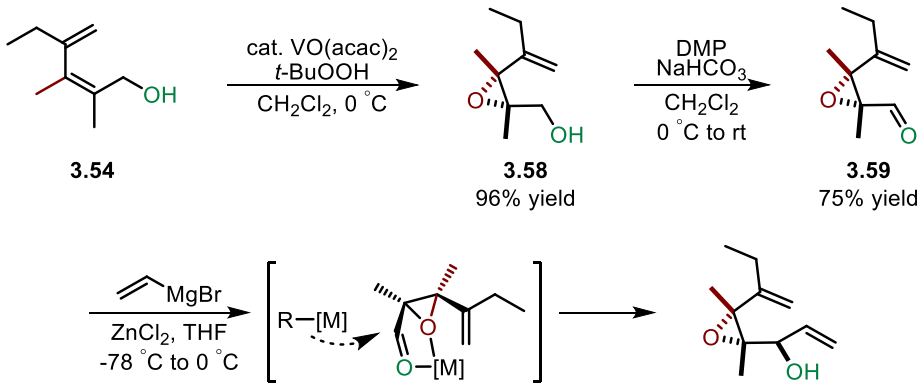
Scheme 3.20 – Diene Formation *via* a Stille Coupling



3.55 **3.56** **3.57** 77% yield >20:1 *Z*/*E* **3.54** 92% yield

The epoxidation of **3.54** could be enacted regioselectively using a vanadium catalyst (**Scheme 3.21**). Although we initially accessed racemic material, we knew of an example of a similar allylic alcohol being epoxidized enantioselectively using a chiral vanadium complex.[19c,21] However, we prioritized rapid access to the racemic material to explore the subsequent steps over the ability access the enantioenriched material. Oxidation of epoxy alcohol **3.58** proceeded smoothly with DMP, yielding aldehyde **3.59** in acceptable yield after careful removal of the solvent under reduced pressure. The C-3 allylic alcohol **3.53** could be accessed stereoselectively by using $ZnCl_2$ and vinylmagnesium bromide, with the diastereoselectivity observed likely due to chelation of the aldehyde with the adjacent epoxide.[22]

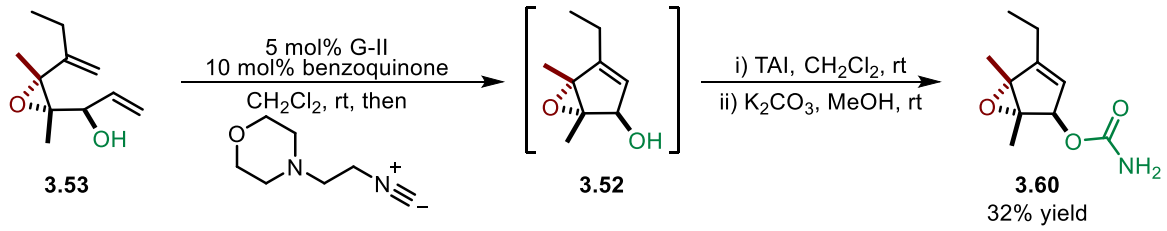
Scheme 3.21 – Epoxidation and Allylic Alcohol Formation



3.54 **3.58** 96% yield **3.59** 75% yield **3.53** 78% yield 5.7:1 *dr*

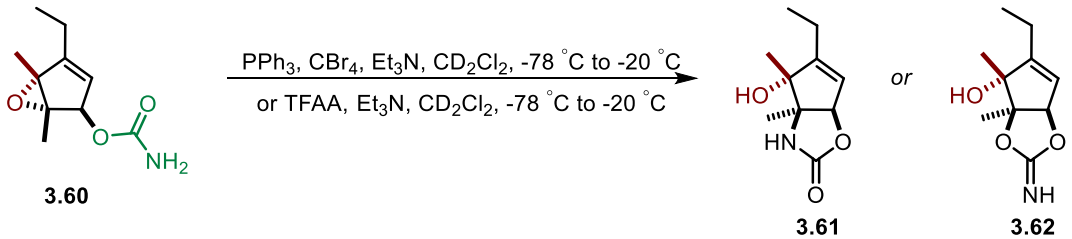
With access to **3.53**, we set off to explore the ring closing metathesis to form the cyclopentenol **3.52** (**Scheme 3.22**). It was discovered that when using the G-II catalyst at ambient temperature the starting

Scheme 3.22 – Ring Closing Metathesis and Carbamate Formation



material was consumed, but messy conversion was observed. The inclusion of benzoquinone significantly improved the situation, as well as adding a neutral isocyanate to quench the active catalyst after the starting material had been consumed as indicated by TLC analysis.[23] With these conditions the allylic alcohol could be observed in 67% yield using an NMR internal standard. This species was stable overnight in benzene-d_6, although decomposition was observed after two weeks at room temperature. Unfortunately, this material decomposed when it was exposed to silica gel chromatography. While we were disappointed by this development, we attempted to cap the allylic alcohol with the carbamate in the hopes that **3.60** would be more stable to isolation. This did prove to be true, with **3.60** being isolated after alumina gel chromatography in low yield over the two-step process. This material was stable when stored at -78 ˚C for at least a week, which was enough to explore the next step. Unfortunately attempts to perform the Ichikawa rearrangement resulted in difficult to interpret spectra after the addition of dimethylamine. We decided to explore this reaction by following the progress of the initial step using NMR spectroscopy (**Scheme 3.23**). Addition of either CBr_4 to a solution of **3.60** in CD_2Cl_2 at -78 ˚C in the presence of PPh_3 and Et_3N and the subsequently warming the NMR tube in the NMR probe to -20 ˚C resulted in the clean conversion to a new product that contained the tri-substituted alkene but was instead missing the epoxide. The same phenomena was observed when employing TFAA and Et_3N. This new product contained a new carbon peak at 92 ppm,

Scheme 3.23 – Attempted Ichikawa Rearrangement



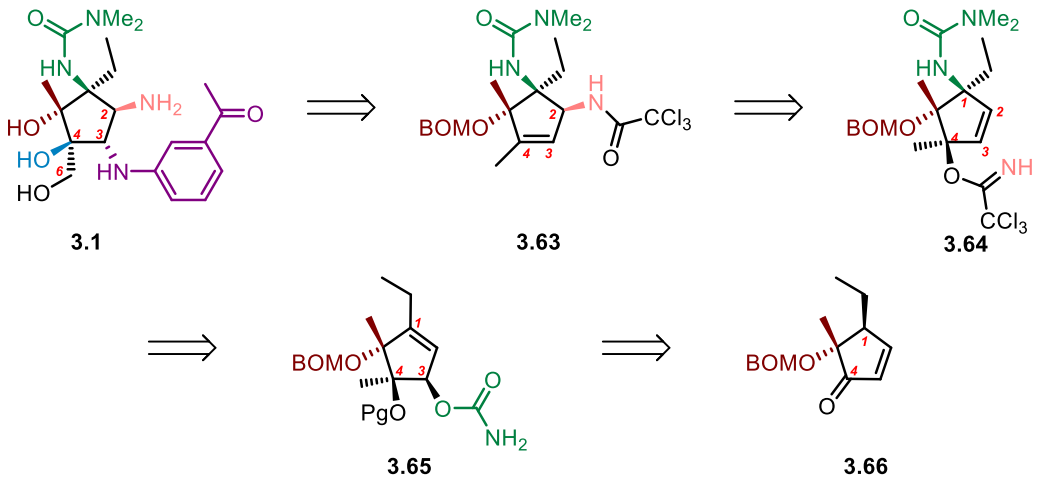
which is indicative of either **3.61** or **3.62**. Attempts to isolate this material *via* chromatography was unsuccessful. The fact that the epoxide seemed to be preferentially activated rather than the carbamate surprised us and indicated that moving away from this motif would be advisable.

3.3 Sequential Ichikawa/Overmann Rearrangement Strategy

3.3.a Sequential Rearrangement Retrosynthesis

With the challenges we encountered in dealing with the different cyclopentene oxides, we decided that further pursuit of such a route was folly. This required us to reevaluate our approach to forming the C-2 amine (**Scheme 3.24**). We thought that the C-2 amine could be formed from the allylic trichloroacetamide **3.63**, which could be formed from an Overmann rearrangement of allylic trichloroacetimidate **3.64**. Our conviction in this disconnect was strengthened by the option of also forming the C-2 amine *via* an Ichikawa rearrangement, alleviating some of the risk if the Overmann rearrangement proved to be infeasible. The C-1 urea **3.64** would also be formed through a sigmatropic rearrangement, this time with the Ichikawa rearrangement that we had initially planned on using in our previous route. We planned on forming the *cis* C-3/C-4 diol in **3.65** in a series of steps from enone **3.66**, which we thought we could access in a short sequence of steps from 2-metyl-2-cyclopenten-1-one.

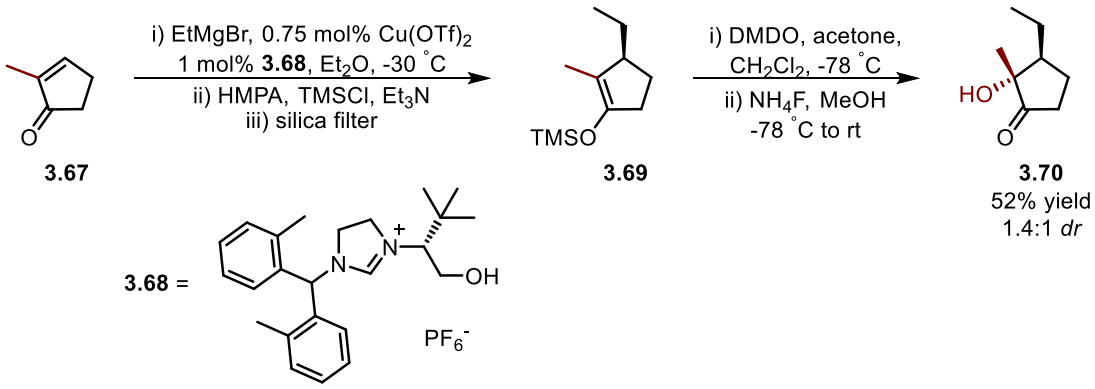
Scheme 3.24 – Sequential Ichikawa and Overman Rearrangements Strategy



3.3.b Forward route of the Ichikawa/Overmann Rearrangement Strategy

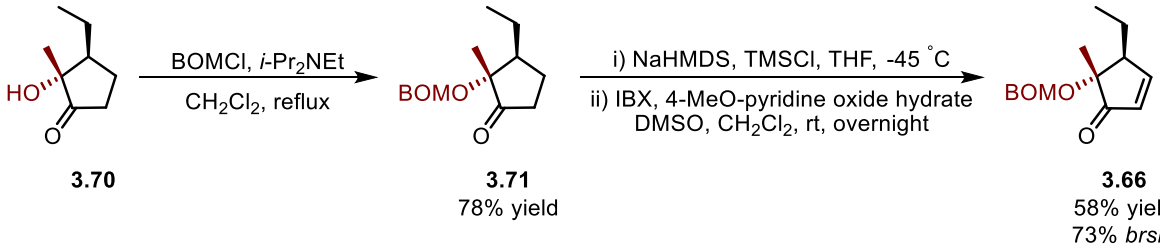
The forward route proceeded with enone **3.67** which was subjected to an enantioselective cuprate addition using $Cu(OTf)_2$ and ligand **3.68** (**Scheme 3.25**).[24] The intermediate magnesium enolate was trapped as the silyl enol ether **3.69**, which was isolated in ~57% crude yield. Oxidation of the silyl enol ether with DMDO resulted in the mixture of α-hydroxy ketone diastereomers, with **3.70** being the major diastereomer.[25] The stereochemistry of **3.70** was confirmed *via* NOESY analysis of a later intermediate (see supporting information for details). Unfortunately, *m*-CPBA and MoOPH led to the predominate formation of the undesired diastereomer with the oxidation taking place from the more hindered face of the silyl enol ether. Inoue and co-workers have also observed this stereochemistry from performing the oxidation of a silyl enol ethers derived from a cyclopentenones with *m*-CPBA, with calculations indicating that tortional strain in the transition state leads to the unexpected observed diastereoselectivity.

Scheme 3.25 – α-Hydroxy Cyclopentanone Synthesis



To convert the α-hydroxy ketone **3.70** to the enone, the alcohol was initially protected as the BOM ether **3.71** (**Scheme 3.26**). Oxidation of ketone to the enone proceeded first by formation of the silyl enol ether and subsequent oxidation of this material utilizing IBX and 4-methoxypyridine oxide.[17] This resulted in the incomplete conversion of **3.71** to the enone **3.66**. However, the starting material was easily separated from the product and re-subjected to the reaction conditions, improving the overall efficiency of the process. This was a considerable improvement over the Saegusa-Ito oxidation of the silyl enol ether, which led to considerable byproduct formation.

Scheme 3.26 – Enone Formation



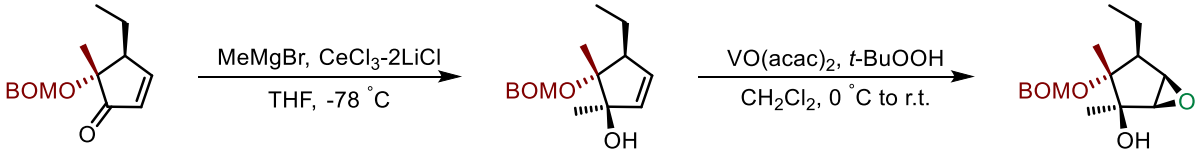
3.70

3.71
78% yield

3.66
58% yield
73% *brsm*

With enone **3.66** in hand, the C-4/C-6 bond needed to be formed (**Scheme 3.27**). This was accomplished by the addition of methylmagnesium bromide. In the absence of $CeCl_3$-2LiCl, this reaction resulted in formation of a 3:1 mixture of 1,2- and 1,4-addition products, albeit in >20:1 *dr* for both products. The inclusion of $CeCl_3$-2LiCl led to the same observed diastereoselectively but with a complete preference for the 1,2-addition product **3.72**. Our previous experience with isolating cyclopentenols led us to perform the directed epoxidation on the crude material. Epoxide **3.73** was thus isolated in good yield and essentially perfect diastereoselectivity. The extreme facial bias for the organometallic addition to **3.66** is notable in that this occurs adjacent to a quaternary carbon where the two groups are somewhat similar sterically. The extreme preference is likely due to the ethyl group at C-1 effectively blocking the approach of the organometallic along the Burgi-Dunitz angle, although chelation between the adjacent ether and the carbonyl could also be operative. Similar diastereoselectivity for the 1,2-addition has also been observed in other cyclopentenones.[26]

Scheme 3.27 – Organocerium Addition and Directed Epoxidation



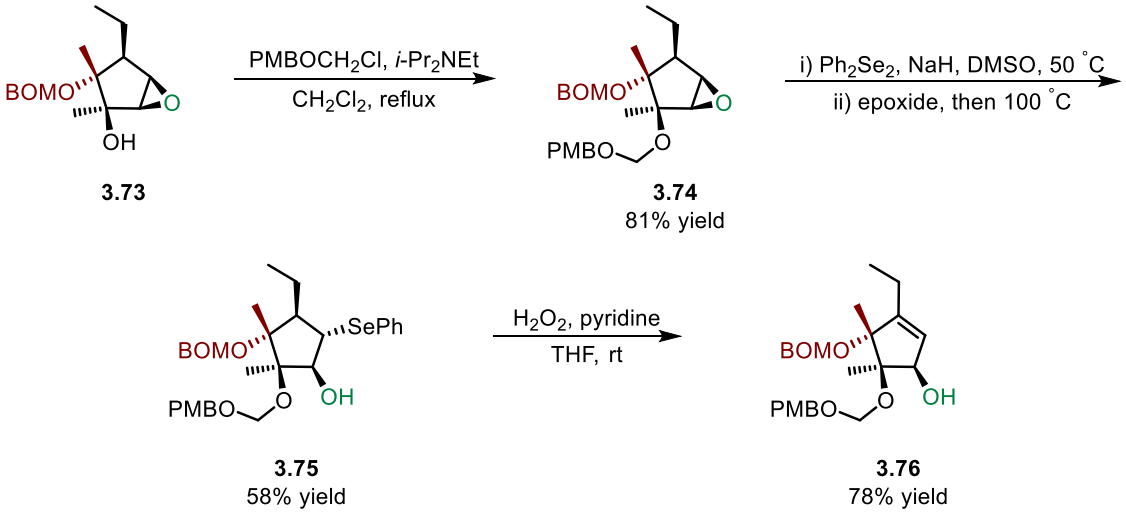
3.66

3.72

3.73
78% yield
>20:1 *dr*

To perform the Ichikawa rearrangement, the epoxide **3.73** needed to be eliminated to form the allylic alcohol. The *cis* relationship between the ethyl group at C-1 and the epoxide at C-2 meant that a concerted elimination with lithium amide bases was not feasible and that an approach utilizing a nucleophilic opening of the epoxide with selenium was needed. Protection of the tertiary C-4 alcohol with the orthogonal $PMBOCH_2$ protecting group proceeded sluggishly, albeit in good yield (**Scheme 3.28**). The epoxide was opened utilizing PhSeNa generated in situ in hot DMSO, affording alcohol **3.75** as a single regioisomer.[27] This transformation proved to be more challenging than we had anticipated, with standard conditions such as $Ph_2Se_2/NaBH_4$ in hot ethanol or *n*-butanol and PhSeLi in THF and HMPA being generally unreactive. With **3.75** in hand, we completed the stepwise transformation of the epoxide to the allylic alcohol **3.76** by oxidation of the selenide with hydrogen peroxide.

Scheme 3.28 – Epoxide Elimination



3.73

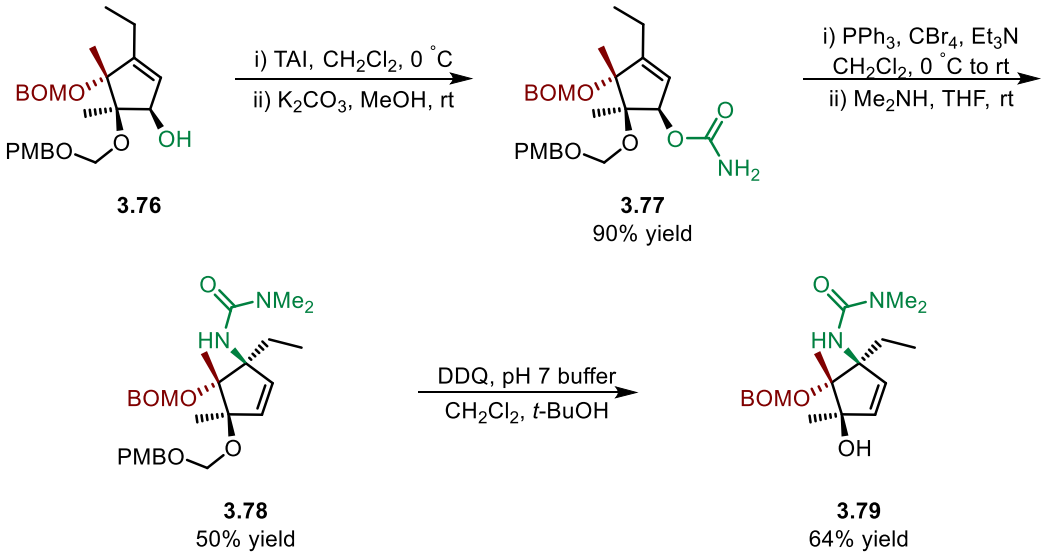
3.74
81% yield

3.75
58% yield

3.76
78% yield

After accessing **3.76**, we formed the carbamate **3.77** in excellent yield (**Scheme 3.29**). This material was thus primed for the Ichikawa rearrangement. We avoided using trifluoroacetic anhydride as a dehydrating reagent due to fears that this would react with the acetal protecting groups we had employed. Using the $CBr_4/PPh_3/Et_3N$ system, we were pleased to see conversion to the intermediate isocyanate which was then trapped with dimethyl amine to afford the C-1 urea **3.78** in acceptable yield. The $PMBOCH_2$ protecting group could be cleaved using DDQ to unmask the tertiary alcohol in **3.79**.[28] It was found that addition of a buffered solution was important for improving the yield of the deprotection. The use of the non-standard $PMBOCH_2$ as an orthogonal protecting group was key to accessing **3.79** as attempts to deprotect a SEM group at this stage led to either cleavage of the urea or oxazolidinone formation depending on whether acidic or basic conditions were employed.

Scheme 3.29 – Successful Icikawa Rearrangment and Alcohol Deprotection



3.76

3.77
90% yield

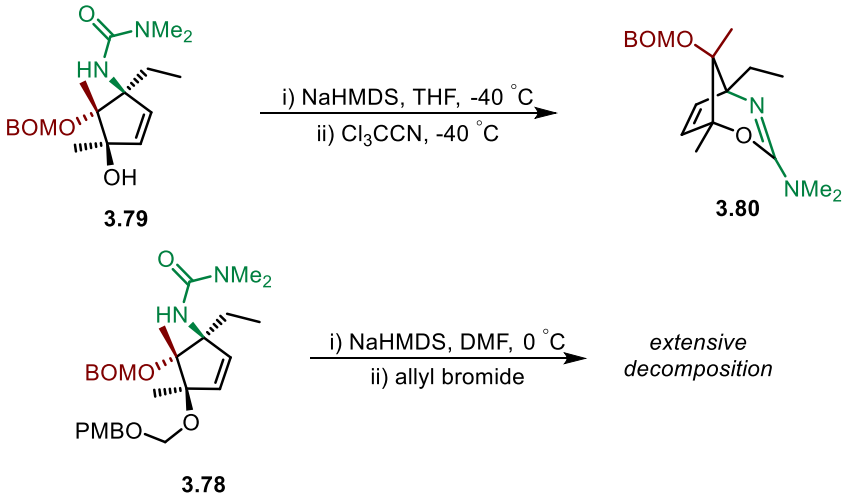
3.78
50% yield

3.79
64% yield

To test the feasibility of the Overmann rearrangement, we set out to convert the allylic alcohol **3.79** to the allylic trichloroacetimidate (**Scheme 3.30**). Exposing alcohol **3.79** to NaHMDS in cold THF, followed by the addition of trichloroacetonitrile led to the formation of a new product which was later identified as oxazoline **3.80**. Attempts to increase the nucleophilicity of the C-4 alcohol by using KHMDS as a base resulted in the formation of the same product. The use of DBU as a base at room temperature led to no reaction, and elevated temperatures led to decomposition being observed. Our hypothesis is that they C-4

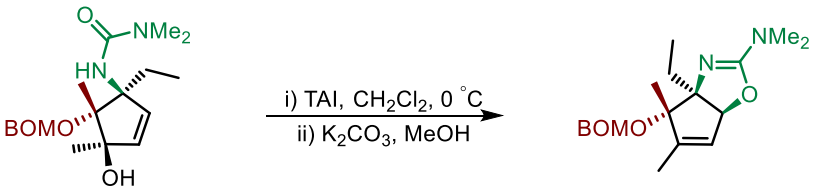
tertiary alcohol is simply too hindered to react with trichloroacetonitrile, and that the urea oxygen attacking the electrophile is kinetically more favored. Upon work up the C-4 alcohol attacks the suddenly electrophilic carbon of the urea, and after the expulsion of trichloroacetamide the oxazoline **3.80** is isolated. Protection of the urea would limit the nucleophilicity of the urea carbonyl, potentially allowing for the formation of the desired trichloroimidate. Unfortunately, attempts to alkylate the urea with allyl bromide led to extensive decomposition.

Scheme 3.30 – Attempted Trichloroimidate Formation and Urea Protection



In light of these issues, we decided to attempt the Ichikawa rearrangement of the C-4 alcohol (**Scheme 3.31**). We knew that the inability to protect the C-1 urea would result in the formation of a second urea between C-1 and C-2. However, we just wished to verify that we would be able to perform the rearrangement without devoting more time and material into trying to develop conditions to protect the C-1 urea. When we attempted to form the C-4 carbamate from **3.79** though we observed the formation a new product that was not the desired carbamate. Analysis of the NMR spectrum indicated that the product contained a tri-substituted alkene. This was later confirmed to be **3.81**, a product we had already observed earlier during failed attempts to remove a SEM group at C-4. It appears that the urea carbonyl is nucleophilic enough to displace even extremely poor leaving groups at C-4 *via* an allylic substitution reaction.

Scheme 3.31 – Attempted Carbamoylation of the C-4 Allylic Alcohol

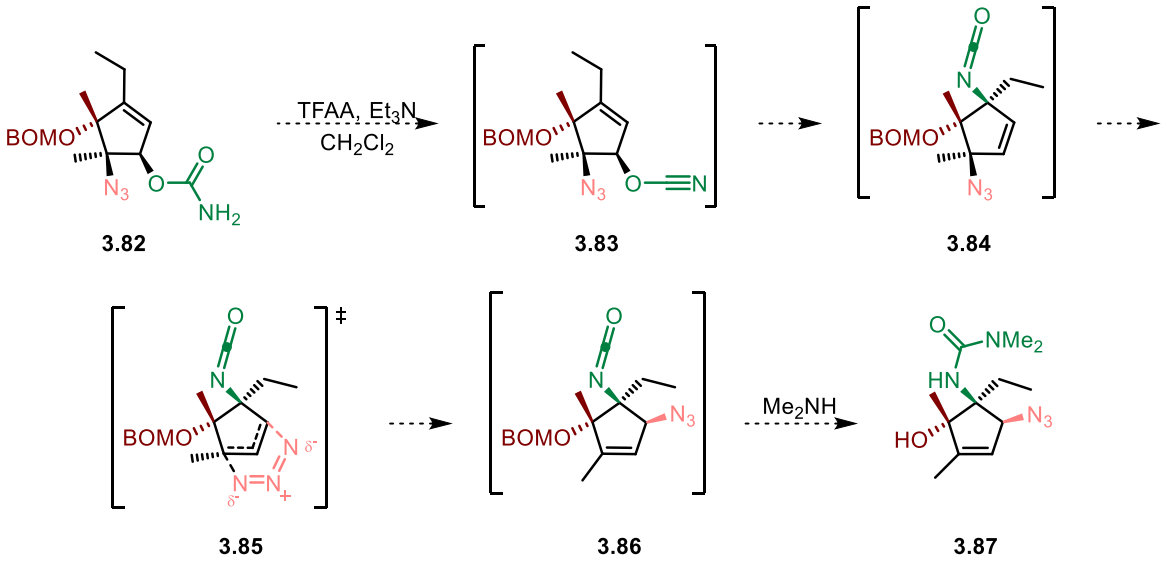


3.79 **3.81**
major product

3.4 Future Directions

Ultimately there was several issues with attempting the second rearrangement, whether it was an Overman or an Ichikawa rearrangement. The first issue was the potential for the alkoxide at the C-4 position to interact with the urea. The second issue was the propensity the urea oxygen displayed to displace even mediocre leaving groups at the C-4 position. These observations indicate that for a successful second rearrangement to take place, two conditions need to be met; 1) the group at C-4 cannot be nucleophilic, and 2) the urea oxygen cannot displace the group at C-4. While these two conditions may seem to be challenging to engineer, a solution appears to exist with the sigmatropic rearrangement of allylic azides. If the Ichikawa rearrangement is performed on azido carbamate **3.82**, the intermediate **3.84** would have a disubstituted

Scheme 3.32 – Proposed Sequential Ichikawa/Azide Rearrangements



3.82 **3.83** **3.84**

3.85 **3.86** **3.87**

alkene adjacent to a tertiary azide. Importantly, azides are non-nucleophilic and should not react with the electrophilic isocyanate at the C-1 position. We have evidence of this as Hanessian formed the C-1 urea *via* an isocyanate in the presence of an azide at C-2 without any issue.[29] Additionally, the urea oxygen in **3.84** is contained in the linear isocyanate functional group. The 180° dihedral angle found in this functional group does not permit the formation of a C-O bond between the oxygen and the C-2 carbon, which would prevent it from displacing the azide. This would allow the azide to undergo a sigmatropic rearrangement to form the thermodynamically favored trisubstituted alkene **3.86**. Quenching the reaction with dimethylamine would generate the urea **3.87**. The exploration of this route is currently underway in our group.

3.5 References

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20. 2-Bromo-1-butene is $282 for 25 g from Alfa Aesar as of May 23rd, 2019.

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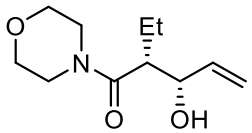
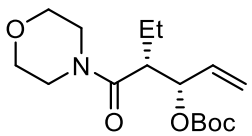
3.6 Experimental Details

All glassware was either oven dried at 130 ˚C, or flame dried under vacuum and purged with nitrogen before use. All glassware was then allowed to cool 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. Tetrahydrofuran was passed through an alumina column before use or freshly distilled from a Na/benzophenone ketyl. Diethyl ether was freshly distilled from a Na/benzophenone ketyl. Dichloromethane was freshly distilled from calcium hydride or passed through an alumina column before use. Acetonitrile, toluene and benzene were all freshly distilled from calcium hydride before use. 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 nitrogen atmosphere. 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] Unless stated otherwise, columns were typically run using a gradient method using EtOAc/hexanes.

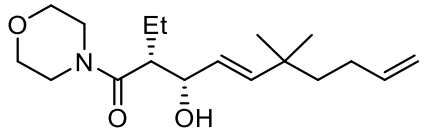
^{1}H NMR and ^{13}C NMR spectra were obtained using Bruker Avance III 400 and 500 spectrometers. For ^{1}H NMR, chemical shifts are reported relative to the tetramethylsilane peak (δ 0.00 ppm), except in some cases when there was no tetramethylsilane peaks in some samples of C_6D_6 where the chemical shifts are reported relative to the residual protiated solvent peak (7.16 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 peaks (δ 77.16 ppm for $CDCl_3$ and 128.06 ppm for C_6D_6,). Accurate mass measurements were acquired at the University of Wisconsin, Madison using a Micromass LCT (electrospray ionization or electron impact methods). The NMR and Mass Spectrometry facilities are funded by the NSF (CHE-1048642), the University of Wisconsin as well as a generous gift by Paul J. Bender.



Compound 3.8. An oven dried round bottom flask with a stir bar was taken into a glovebox and charged with (^{l}Ipc)$_2$BH (1.988 g, 6.94 mmol, 1.19 equiv.). The flask was sealed with a septum, removed from the box and vac cycled with argon. The solid was dissolved in Et_2O (28.0 ml) and the flask was cooled to 0 ˚C in an ice bath. A separate flame dried flask was charged with **3.7** (1.1868 g, 7.65 mmol, 1.31 equiv.) and vac cycled with argon before adding Et_2O (10.0 ml). The solution of **3.7** was cannulaed over to the solution of (^{l}Ipc)$_2$BH and the resulting mixture was stirred for 8.5 h at 0 ˚C. The flask was then cooled to -78 ˚C in a cryogenic bath. After 30 min, freshly distilled acrolein (0.39 ml, 5.8 mmol, 1.0 equiv.) was added dropwise. A THF/MeOH/0.1 M pH 7 phosphate buffer solution (6.0 ml of each component) was prepared and this was added to the reaction mixture after 17.5 h. The mixture was allowed to warm to room temp, diluted with Et_2O after 4.5 hours and diluted with water. The aqueous mixture was extracted three times with Et_2O. The combined organics were washed with brine and dried with Na_2SO_4. The solvent was removed and the crude mixture was purified by column chromatography (0 to 100% EtOAc/hexanes, 10% increments). Aldol adduct **3.8** (0.7466 g, 3.50 mmol, 60% yield) was isolated as an oil that solidified upon standing in the freezer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.85 (dddd, *J* = 17.4, 10.6, 5.3, 1.5 Hz, 1H), 5.35 (dt, *J* = 17.1, 1.6 Hz, 1H), 5.19 (dt, *J* = 10.5, 1.6 Hz, 1H), 4.38 – 4.34 (m, 1H), 3.76 – 3.63 (m, 7H), 3.58 (dt, *J* = 5.8, 3.8 Hz, 2H), 2.69 (dt, *J* = 8.9, 4.2 Hz, 1H), 1.85 – 1.68 (m, 2H), 0.91 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.44, 138.20, 116.06, 73.20, 67.19, 66.97, 46.70, 46.57, 42.24, 20.28, 12.45. HRMS (ESI) *m/z* calculated for $C_{11}H_{19}NO_3$ $[M+H]^+$ 214.1438, found 214.1434.

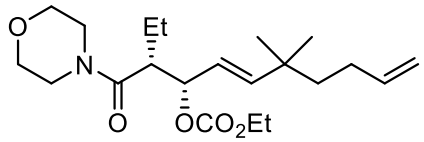


Compound 3.9. A syn vial containing **3.8** (132.0 mg, 0.619 mmol, 1.0 equiv.) and a stir bar was charged with THF (6.25 ml). Boc_2O (402 mg, 1.84 mmol, 2.97 equiv.) and Et_3N (0.17 ml, 1.2 mmol, 1.94 equiv.) were added to the vial before adding DMAP (15.6 mg, 0.128 mmol, 0.21 equiv.). This was stirred at room temp for 40 hours before quenching with sat. NH_4Cl and extracting three times with EtOAc. The combined orgs were washed with brine and dried with Na_2SO_4. The solvent was removed and the yellow oil was purified by column chromatography (50% to 100% EtOAc/hexanes). Carbonate **3.9** (119.7 mg, 0.382 mmol, 62% yield) was isolated as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.84 (ddd, *J* = 17.3, 10.5, 7.0 Hz, 1H), 5.31 (dt, *J* = 17.1, 1.2 Hz, 1H), 5.23 (dt, *J* = 10.5, 1.1 Hz, 1H), 5.16 (t, *J* = 7.4 Hz, 1H), 3.78 – 3.46 (m, 8H), 2.95 (ddd, *J* = 9.7, 7.9, 4.1 Hz, 1H), 1.86 – 1.73 (m, 1H), 1.69 – 1.59 (m, 1H), 1.48 (s, 9H), 0.88 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.75, 152.73, 134.09, 118.54, 82.52, 79.09, 67.27, 67.02, 46.73, 46.44, 42.40, 28.38, 27.94, 23.02, 11.74. HRMS (ESI) *m/z* calculated for $C_{16}H_{27}NO_5$ $[M+H]^+$ 314.1962, found 314.1959.



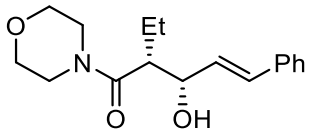
Compound S-01. An oven dried round bottom flask with a stir bar was taken into a glovebox and charged with $(^l\text{Ipc})_2\text{BH}$ (3.44 g, 12.0 mmol, 1.20 equiv.). The flask was sealed with a septum, removed from the box and vac cycled with argon. The solid was dissolved in Et_2O (45.0 ml) and the flask was cooled to 0 °C in an ice bath. A separate flame dried flask was charged with **3.7** (2.107 g, 13.6 mmol, 1.36 equiv.) and vac cycled with argon before adding Et_2O (20.0 ml). The solution of **3.7** was cannulaed over to the solution of $(^l\text{Ipc})_2\text{BH}$ and the resulting mixture was stirred for 5 h at 0 °C. The flask was then cooled to -78 °C in a cryogenic bath. After 10 min, 4,4-dimethyl-2,7-octadien-1-al (1.75 ml, 0.874 g/ml, 10.0 mmol, 1.0 equiv.) was added dropwise. A THF/MeOH/0.1 M pH 7 phosphate buffer solution (10.0 ml of each component) was prepared and this was added to the reaction mixture after 17 h. The mixture was allowed to warm to room temp, diluted with Et_2O after 7.5 hours and diluted with water. The aqueous mixture was extracted

three times with Et_2O. The combined organics were washed with brine and dried with Na_2SO_4. The solvent was removed, and the crude mixture was purified by column chromatography (0 to 50% EtOAc/hexanes, 5% increments). Aldol adduct **3.16** (2.498 g, 8.07 mmol, 81% yield) was isolated. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.80 (ddt, *J* = 16.9, 10.2, 6.5 Hz, 1H), 5.68 (dd, *J* = 15.7, 1.3 Hz, 1H), 5.37 (dd, *J* = 15.7, 6.2 Hz, 1H), 4.98 (dq, *J* = 17.1, 1.7 Hz, 1H), 4.91 (ddt, *J* = 10.1, 2.2, 1.3 Hz, 1H), 4.32 (ddt, *J* = 6.0, 4.2, 1.6 Hz, 1H), 3.78 – 3.55 (m, 8H), 3.48 (d, *J* = 2.0 Hz, 1H), 2.67 (dt, *J* = 9.1, 4.6 Hz, 1H), 1.95 (dtt, *J* = 9.2, 6.5, 1.3 Hz, 2H), 1.83 – 1.67 (m, 2H), 1.42 – 1.34 (m, 2H), 1.01 (s, 3H), 1.00 (s, 3H), 0.91 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.43, 142.18, 139.54, 126.25, 114.07, 73.46, 67.21, 67.00, 47.25, 46.69, 42.21, 42.19, 35.87, 29.28, 27.34, 27.21, 20.58, 12.53. HRMS (ESI) *m/z* calculated for $C_{18}H_{31}NO_3$ $[M+H]^+$ 310.2377, found 310.2372.

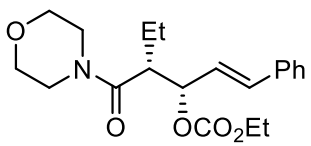


Compound 3.16. A flame dried flask with a stir bar was charged with **S-01** (929.3 mg, 3.00 mmol, 1.0 equiv.), CH_2Cl_2 (60 ml) and pyridine (4.75 ml, 58.7 mmol, 19.6 equiv.). This was cooled to 0 ˚C in an ice bath before adding ethyl chloroformate (1.75 ml, 18.3 mmol, 6.1 equiv.). After 8.5 h, the reaction was quenched with 120 ml of water and the resulting aqueous layer was extracted three times with CH_2Cl_2. The combined organics were washed with brine and dried with Na_2SO_4. The solvent was removed, and the crude mixture was purified by column chromatography (0 to 50% EtOAc/hexanes). Carbonate **3.16** (899.5 mg, 2.36 mmol, 79% yield) was isolated. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.77 (ddt, *J* = 17.1, 10.3, 6.6 Hz, 1H), 5.72 (d, *J* = 15.7 Hz, 1H), 5.38 – 5.33 (m, 1H), 5.31 (d, *J* = 11.6 Hz, 0H), 5.18 (t, *J* = 8.0 Hz, 1H), 4.97 (dq, *J* = 17.1, 1.7 Hz, 1H), 4.90 (ddt, *J* = 10.2, 2.3, 1.3 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.78 – 3.47 (m, 8H), 2.97 (ddd, *J* = 9.8, 8.1, 4.1 Hz, 1H), 1.97 – 1.85 (m, 2H), 1.76 (ddq, *J* = 14.7, 9.9, 7.4 Hz, 1H), 1.68 – 1.59 (ddq, *J* = 15.0, 7.6, 4.2 Hz, 1H), 1.37 – 1.32 (m, 2H), 1.30 (t, *J* = 7.1 Hz, 3H), 0.98 (s, 3H), 0.98 (s, 3H),

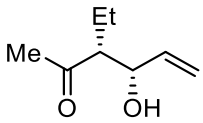
0.87 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.89, 154.37, 146.23, 139.38, 121.77, 114.15, 80.70, 67.27, 67.02, 64.07, 46.72, 46.56, 42.34, 42.08, 36.10, 29.21, 27.09, 27.01, 23.15, 14.42, 11.85. HRMS (ESI) *m/z* calculated $C_{21}H_{35}NO_5$ $[M+H]^+$ 382.2588, found 382.2583.



Compound S-02. An oven dried round bottom with a stir bar was taken into the glovebox and charged with $(^{l}Ipc)_2BH$ (10.57 g, 36.9 mmol, 1.25 equiv.). The flask was sealed with a septum, removed from the box and vac cycled with nitrogen. The solid was dissolved in Et_2O (100 ml) and the flask was cooled to 0 ˚C in an ice bath. A separate flame dried flask was charged with **3.7** (6.208 g, 40.0 mmol, 1.36 equiv.) and then charged with Et_2O (100 ml). The solution of **3.7** was cannulaed over to the borane solution and the resulting mixture was stirred at 0 ˚C for 5 h. The flask was then cooled to -78 ˚C before a dropwise addition of cinnamaldehyde (3.90 ml, 29.5 mmol, 1.0 equiv.). The reaction was stirred overnight before adding a THF/MeOH/0.1 M pH 7 phosphate buffer solution (31.5 ml of each). The solution was allowed to warm to room temp over the course of 6 h before diluting with water and extracting three times with Et_2O. The combined organics were washed with brine and dried with Na_2SO_4. The solvent was removed, and the crude material was purified by column chromatography (0 to 100% Et_2O/hexanes in 5% increments). The aldol adduct **S-02** (8.410 g, 29.1 mmol, 99% yield) was isolated as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.36 (m, 2H), 7.34 – 7.29 (m, 2H), 7.26 – 7.22 (m, 1H), 6.68 (dd, *J* = 16.0, 1.4 Hz, 1H), 6.22 (dd, *J* = 15.9, 5.8 Hz, 1H), 4.55 (t, *J* = 4.2 Hz, 1H), 3.87 (s, 1H), 3.76 – 3.53 (m, 8H), 2.78 (dt, *J* = 9.0, 4.4 Hz, 2H), 1.89 – 1.73 (m, 2H), 0.92 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.45, 136.80, 131.11, 129.48, 128.74, 127.81, 126.59, 73.11, 67.18, 66.96, 46.96, 46.72, 42.26, 20.47, 12.50. HRMS (ESI) *m/z* calculated for $C_{17}H_{23}NO_3$ $[M+H]^+$ 290.1751, found 290.1746.



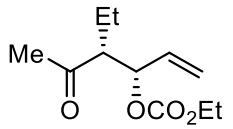
Compound 3.17. A round bottom flask with a stir bar was charged with **S-02** (299.6 mg, 1.04 mmol, 1.0 equiv.), CH_2Cl_2 (20 ml) and pyridine (1.60 ml, 19.8 mmol, 19 equiv.). Ethyl chloroformate (0.57 ml, 6,0 mmol, 5.8 equiv.) was added and the reaction was stirred overnight. After 14 h, more ethyl chloroformate (0.30 ml, 3.1 mmol, 3.0 equiv.) was added and stirred for an additional 4 h before quenching with 10 ml of 2 M HCl. The aqueous layer was extracted three times with CH_2Cl_2. The combined organics were washed with sat. $NaHCO_3$ and dried with Na_2SO_4. The solvent was then removed under reduced pressure and the crude material was purified *via* column chromatography (0 to 50% EtOAc/hexanes). This yielded pure carbonate **3.17** (345.8 mg, 0.957 mmol, 92% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, *J* = 7.0 Hz, 1H), 7.31 (t, *J* = 7.4 Hz, 1H), 7.25 – 7.23 (m, 0H), 6.66 (d, *J* = 15.9 Hz, 0H), 6.21 (dd, *J* = 15.9, 7.9 Hz, 0H), 5.38 (t, *J* = 7.9 Hz, 1H), 4.20 (q, *J* = 7.1 Hz, 1H), 3.78 – 3.68 (m, 1H), 3.68 – 3.47 (m, 3H), 3.07 (ddd, *J* = 9.7, 8.0, 4.1 Hz, 1H), 1.83 (ddq, *J* = 14.6, 9.6, 7.3 Hz, 0H), 1.68 (dqd, *J* = 14.8, 7.4, 4.1 Hz, 0H), 1.30 (t, *J* = 7.1 Hz, 1H), 0.90 (t, *J* = 7.4 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.69, 154.45, 136.09, 134.52, 128.76, 128.36, 126.88, 124.63, 80.14, 77.16, 67.23, 66.96, 64.28, 46.77, 42.42, 23.06, 14.41, 11.79. HRMS (ESI) *m/z* calculated $C_{20}H_{27}NO_5$ $[M+Na]^+$ 384.1781, found 384.1777.



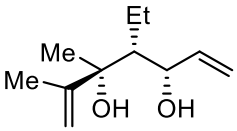
Compound 3.29. An oven dried round bottom flask with a stir bar was taken into the glove box and charged with anhydrous $CeCl_3$ (3.206, 13.0 mmol)[3]. After the flask was sealed with a septum, removed from the box and vac cycled, THF (57 ml) was added. This was cooled to -78 °C and given enough time to sufficiently cool. A solution of MeLi (8.0 ml, 1.6 M in Et_2O, 13 mmol) was added and the solution turned a dark yellow-brown color. After 20 min the solution was warmed to 0 °C in an ice bath. After 10 minutes at this temperature, it was cooled back down to -78 °C. Stirring was ceased and the solid was allowed to settle over the next hour, with the supernatant being used for the next step. A separate oven dried flask with a stir bar was charged with **3.8** (424.2 mg, 1.99 mmol, 1.0 equiv.) and the flask was vac cycled. After charging with

THF (10.0 ml), the flask was allowed to cool to -78 ˚C. The MeLi/$CeCl_3$ supernatant (~0.2 M, 48 ml, ~9.6 mmol, 4.8 equiv.) was added dropwise. The reaction was monitored by TLC, which after an hour showed conversion to a new, less polar spot but with some starting material remaining. After an additional 2.5 h, the TLC remained essentially unchanged. The reaction was quenched with acetic acid (0.69 ml, 12.1 mmol, 6.1 equiv.) and the solution was poured into Et_2O and water. The aqueous layer was extracted two times with Et_2O. The combined organics were washed with brine and dried with Na_2SO_4. After removing the solvent, the crude NMR revealed a 3.6:1 ratio of ketone **3.29** to amide **3.8**. The crude material was purified by column chromatography (5% to 50% Et_2O/hexanes). Ketone **3.29** (165.9 mg, 1.17 mmol, 59% yield) was isolated as an oil.

Alternatively, ketone **3.29** could also be synthesized through the following procedure. An oven dried round bottom flask with stir bar was vac cycled and charged with **3.8** (207.1 mg, 0.971 mmol, 1.0 equiv.) and THF (10.0 ml). This was cooled to 0 ˚C in an ice bath before adding MeMgBr (1.25 ml, 3.0 M in Et_2O, 3.75 mmol, 3.86 equiv.) dropwise. This was allowed to warm to room temperature overnight, before cooling back down to 0 ˚C after 12.5 h. The reaction was quenched with the dropwise addition of aq. 1 M HCl solution. The reaction was then diluted with water and the resulting aqueous layer was extracted three times with EtOAc. The combined organics were washed first with sat. $NaHCO_3$ followed by washing with brine. After drying with Na_2SO_4, the solvent was removed, and the crude material was purified by column chromatography (0 to 60% EtOAc/hexanes in 10% increments, then 60 to 100% EtOAc/hexanes in 20% increments). Some unreacted **3.8** was isolated (36.8 mg, 0.175 mmol, 18% recovered). Ketone **3.29** (68.9 mg, 0.485 mmol, 50% yield, 61% brsm) was isolated as a 6.5:1 mixture of diastereomers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.84 (ddd, *J* = 17.1, 10.5, 6.0 Hz, 1H), 5.29 (dt, *J* = 17.1, 1.5 Hz, 1H), 5.19 (dt, *J* = 10.5, 1.4 Hz, 1H), 4.34 (td, *J* = 5.4, 1.4 Hz, 1H), 2.63 (dt, *J* = 9.5, 4.9 Hz, 1H), 2.32 (s, 1H), 2.21 (s, 3H), 1.78 – 1.60 (m, 2H), 0.93 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 212.75, 138.06, 116.46, 73.05, 59.10, 31.80, 20.35, 12.42. HRMS (ESI) *m/z* calculated for $C_6H_{14}O_2$ $[M\text{-}OH]^+$ 125.0961, found 125.0958.

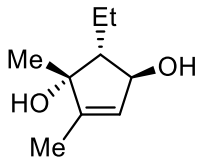


Compound 3.18. A round bottom flask was charged with **3.29** (68.9 mg, 0.485 mmol, 1.0 equiv., 6.5:1 *dr*) with CH_2Cl_2, and the solvent was removed under reduced pressure. Distilled CH_2Cl_2 (14.0 ml) and pyridine (0.78 ml, 9.6 mmol, 19.9 equiv.) were added and the solution was cooled to 0 ˚C in an ice bath. Ethyl chloroformate (0.28 ml, 2.9 mmol, 6.0 equiv.) was then added. After 3 hours, TLC showed complete conversion of **3.29**. The reaction mixture was diluted with CH_2Cl_2 and quenched with water. The aqueous layer was extracted three times with CH_2Cl_2 and the combined orgs were washed with brine. After drying with Na_2SO_4, the solvent was removed. The crude material was purified by column chromatography (0/2/100 to 80/2/20 ratios of CH_2Cl_2/Et_2O/hexanes, with the amount of Et_2O being kept constant and the percentage of CH_2Cl_2 relative to hexanes being increased in 10% increments). Carbonate **3.18** (73.2 mg, 0.342 mmol, 70% yield) was isolated as an 8:1 mixture of diastereomers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.79 (ddd, *J* = 17.4, 10.5, 7.1 Hz, 1H), 5.32 (dt, *J* = 17.3, 1.2 Hz, 1H), 5.26 (dt, *J* = 10.5, 1.1 Hz, 1H), 5.22 (tt, *J* = 7.0, 1.1 Hz, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 2.82 (ddd, *J* = 9.4, 7.4, 4.3 Hz, 1H), 2.18 (s, 3H), 1.72 (ddq, *J* = 14.7, 9.3, 7.4 Hz, 1H), 1.67 – 1.55 (m, 1H), 1.31 (t, *J* = 7.1 Hz, 3H), 0.89 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 209.15, 154.47, 133.52, 119.32, 78.56, 64.32, 57.88, 31.86, 21.37, 14.39, 11.71. HRMS (ESI) *m/z* calculated $C_{11}H_{18}O_4$ $[M+NH_4]^+$ 232.1543, found 232.1540.

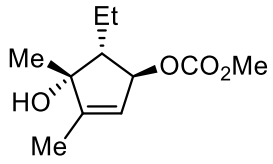


Compound 3.28. An oven dried round bottom with a stir bar was taken into a glove box and charged with anhydrous $CeCl_3$ (5.915 g, 24.0 mmol, 6.0 equiv.)[3] and LiCl (2.037 g, 48.1 mmol, 12.0 equiv.). The flask was septumed, removed from the box and vac cycled before adding THF (68.0 ml). This was vigorously stirred at room temp overnight. The next morning an oven dried Schlenck flask with a stir bar and an oven dried round bottom flask were taken into the glove box. The Schlenck flask was charged with LiH (41.1

mg, 5.17 mmol, 1.29 equiv.) and then septumed. The round bottom flask was charged with **3.29** (569.3 mg, 4.00 mmol, 1.0 equiv., >20:1 *dr*) and then septumed. Both flasks were removed from the glovebox and charged with THF (23.0 ml in the flask containing LiH and 12.0 ml in the flask containing **3.29**). The Schlenck flask containing LiH was then cooled down to -40 ˚C. Meanwhile, the flask containing $CeCl_3$-2LiCl was cooled to -78 ˚C and after reaching that temperature isopropenylmagnesium bromide (48.0 ml, 0.47 M in THF, 22.6 mmol, 5.6 equiv.) was added dropwise. The solution of **3.29** in THF was cannulaed over dropwise to the solution of LiH, and the round bottom flask containing **3.29** was rinsed with THF (12.0 ml) and cannulaed over dropwise. The cannula transfer of **3.29** ended 40 min after the isopropenylmagnesium bromide was added to the $CeCl_3$. After stirring for 15 min, $TiCl_4$ (5.2 ml, 1 M in CH_2Cl_2, 5.2 mmol, 1.3 equiv.) was added dropwise to the flask with **3.29** and LiH. After 45 minutes the flask with **3.29** was cooled to -78 ˚C, and the organocerium solution was added rapidly *via* cannula transfer. The reaction mixture was kept at -78 ˚C for 1 hour before warming up to -50 ˚C and maintaining that temperature for 5 hours. The reaction was quenched by adding acetic acid (1.30 ml, 22.7 mmol, 5.7 equiv.) and pouring into Et_2O and aqueous 0.25 M HCl. The aqueous layer was extracted three times with Et_2O, and the combined organics were washed with sat. $NaHCO_3$ and two times with brine. After drying with Na_2SO_4, the solvent was removed. The crude material was purified by column chromatography (0 to 30% Et_2O/hexanes in 2% increments). This yielded 185.9 mg of a 12.5:1 mixture of the major and minor diastereomers, 372.1 mg of a 5:1 mixture of the major and minor diastereomers and 17.6 mg of the minor diastereomer. This amounts to 575.6 mg (3.12 mmol, 78% yield) of both diastereomers, which were formed in 5.2:1 *dr*. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.93 (ddd, *J* = 17.0, 10.6, 4.6 Hz, 1H), 5.32 (dt, *J* = 17.1, 1.7 Hz, 1H), 5.16 (dt, *J* = 10.7, 1.8 Hz, 1H), 5.07 (dt, *J* = 1.6, 0.8 Hz, 1H), 4.89 (t, *J* = 1.5 Hz, 1H), 4.78 (dd, *J* = 4.7, 2.2 Hz, 1H), 3.14 (s, 1H), 2.59 (s, 1H), 1.75 (s, 3H), 1.55 – 1.48 (m, 1H), 1.47 (s, 3H), 1.43 (ddd, *J* = 5.4, 3.3, 2.0 Hz, 1H), 1.36 (dqd, *J* = 15.1, 7.5, 3.4 Hz, 1H), 0.89 – 0.84 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.10, 140.39, 114.04, 110.03, 79.40, 72.45, 49.59, 27.20, 20.03, 16.04, 15.99. HRMS (ESI) *m/z* calculated $C_{11}H_{20}O_2$ $[M\text{-}OH]^+$ 167.1430, found 167.1429.

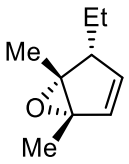


Compound 3.30. A round bottom flask was charged with **3.29** (262.9 mg, 1.43 mmol, >20:1 *dr*, 1.0 equiv.) in CH_2Cl_2. The solvent was removed under reduced pressure, a stir bar was added followed by the Grubbs-II catalyst (122.1 mg, 0.144 mmol, 0.10 equiv.). The solids were dissolved in toluene (30.0 ml). After 1.5 h, an NMR aliquot revealed that all of **3.29** had been consumed. The solvent was removed under reduced pressure and the crude material was purified by column chromatography (0 to 21% acetone/DCM in 3% increments). Diol **3.30** (203.8 mg, 1.30 mmol, 91% yield) was isolated as a brown solid that was pure by NMR. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.43 (p, *J* = 1.5 Hz, 1H), 4.14 (tq, *J* = 5.8, 1.8 Hz, 1H), 1.74 (t, *J* = 1.7 Hz, 3H), 1.72 – 1.64 (m, 2H), 1.59 – 1.52 (m, 1H), 1.49 (d, *J* = 7.4 Hz, 1H), 1.45 (s, 1H), 1.12 (t, *J* = 7.3 Hz, 3H), 1.11 (s, 3 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.75, 128.20, 82.78, 78.89, 63.94, 21.52, 21.38, 13.40, 11.51. HRMS (ESI) *m/z* calculated for $C_9H_{16}O_2$ $[M+Na]^+$ 179.1043, found 179.1038.



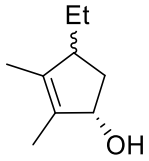
Compound 3.27. A round bottom flask with a stir bar was charged with Grubbs-II catalyst (37.7 mg, 0.0444 mmol, 0.074 equiv.) and **3.29** (110.2 mg, 0.598 mmol, 1.0 equiv.) in toluene (12.0 ml). After stirring for 3.5 h, an NMR aliquot showed a 10:1 ratio of cyclopentene to **3.29** present. No further conversion was observed after stirring for 7 hours. The solvent was then removed under reduced pressure. The flask was vac cycled with nitrogen and CH_2Cl_2 (12.0 ml) and pyridine (0.97 ml, 12 mmol, 20 equiv.) were added. The mixture was cooled to 0 ˚C in an ice bath before adding methyl chloroformate (0.34 ml, 3.6 mmol, 6.0 equiv.). After 1 hour, an NMR aliquot showed that the reaction was complete. The reaction was quenched by pouring into 100 ml of aqueous 5% $CuSO_4$ solution. The aqueous layer was extracted three times with CH_2Cl_2. The combined organics were washed with brined and dried with Na_2SO_4 before removing the

solvent. The crude oil was purified by column chromatography (0 to 28% EtOAc/hexanes, 2% increments), yielding carbonate **3.27** (108.3 mg, 0.505 mmol, 85% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.49 (p, *J* = 1.6 Hz, 1H), 5.03 (dp, *J* = 5.5, 1.8 Hz, 1H), 3.78 (s, 3H), 2.01 (dt, *J* = 8.7, 6.3 Hz, 1H), 1.76 (t, *J* = 1.7 Hz, 3H), 1.74 – 1.66 (m, 1H), 1.59 – 1.45 (m, 3H), 1.15 (s, 3H), 1.05 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.76, 151.35, 123.89, 84.53, 82.26, 59.04, 54.79, 21.38, 21.34, 12.93, 11.61. HRMS (ESI) *m/z* calculated for $C_{11}H_{18}O_4$ $[M+Na]^+$ 237.1097, found 237.1094.



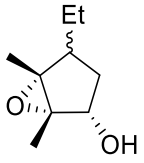
Compound 3.33. A flame dried round bottom with a stir bar was charged with **3.30** (99.3 mg, 0.636 mmol, 1.0 equiv.), DMAP (8.6 mg, 0.070 mmol, 0.11 equiv.), CH_2Cl_2 (13.0 ml) and pyridine (0.10 ml, 1.2 mmol, 1.9 equiv.). This was cooled to 0 °C before adding 2,2,2-trichloroethyl chloroformate (0.10 ml, 0.73 mmol, 1.1 equiv.). After 30 min, an NMR aliquot showed complete conversion. The reaction was quenched with aqueous 5% NaH_2PO_4 and the aqueous layer was extracted three times with Et_2O. The combined orgs were washed with sat. $NaHCO_3$ followed by washing with brine. After drying with Na_2SO_4 and removing the solvent, the flask was charged with a stir bar, vac cycled and stored overnight at -78 °C. After warming to room temperature, the flask was charged with MeCN (13.0 ml) and DBU (0.11 ml, 0.74 mmol, 1.2 equiv.) before heating reaction to 60 °C. After 3.5 hours, an NMR aliquot shows complete conversion of the intermediate carbonate. The reaction was cooled to room temperature and quenched with sat. NH_4Cl. The aqueous layer was extracted three times with Et_2O and the combined organics were washed with brine and dried with Na_2SO_4. The solvent was removed, and the crude material was purified by column chromatography (0 to 24% Et_2O/hexanes in 4% increments). Epoxide **3.33** (75.4 mg, 0.546 mmol, 86% yield) was isolated as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.15 (dd, *J* = 6.0, 2.6 Hz, 1H), 5.77 (dd, *J* = 6.0, 1.5 Hz, 1H), 2.93 – 2.82 (m, 1H), 1.77 – 1.67 (m, 1H), 1.46 (s, 3H), 1.42 (s, 3H), 1.09 – 0.92 (m,

4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.85, 131.62, 94.84, 92.26, 55.07, 24.89, 20.10, 16.81, 12.21. HRMS (ASAP-MS) *m/z* calculated for $C_9H_{14}O$ $[M+H]^+$ 139.1117, found 139.1115.

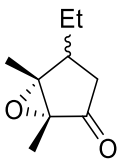


Compound 3.46. A flame dried 1 L Schlenck flask with a stir bar was taken into a glovebox and charged with (*R*)-(+)-2-methyl-CBS:BH_3 complex[4] (760.0 mg, 2.61 mmol, 0.05 equiv.). The flask was septumed, removed from the box and put under nitrogen. THF (250 ml) was added to the flask followed by BH_3-Me_2S (5.15 ml, 51.5 mmol, 1.0 equiv.). A second flame dried round bottom was put under nitrogen, and then charged with THF (250 ml) and **3.45** (7.70 ml, 0.924 g/ml, 51.5 mmol, 1.0 equiv.). Both flasks were cooled to 0 ˚C in ice baths before cannulating over the solution of **3.45** in THF over five minutes. TLC showed complete conversion after 12 minutes. The reaction was quenched with 75 ml of MeOH, and the solution was allowed to stir until gas stopped evolving. The solvent was then removed under reduced pressure, before dissolving the crude material in another 75 ml of MeOH. After removing the MeOH under reduced pressure, the crude material was purified *via* Kugelrohr distillation with the product distilling at 86-87 ˚C at ~1-2 torr. This yielded **3.46** (5.676 g, 40.5 mmol, 79% yield) as a 1:1 mix of diastereomers. (*Note*: The proton NMRs of this material are provided in both $CDCl_3$ and C_6D_6. The trace acid in $CDCl_3$ was found to catalyze the decomposition of the compound, making it an unreliable solvent if you wished to isolate the material from the NMR sample.) ^{1}H NMR (400 MHz, C_6D_6) δ 4.47 – 4.37 (m, 1H), 4.31 (q, *J* = 7.3 Hz, 1H), 2.42 (s, 1H), 2.25 (dt, *J* = 13.3, 7.8 Hz, 1H), 2.15 – 2.06 (m, 1H), 1.72 (appt t, *J* = 5.9 Hz, 2H), 1.62 – 1.58 (m, 6H), 1.58 – 1.46 (m, 2H), 1.44 (m, 6H), 1.20 – 0.89 (m, 4H), 0.81 (appt t, *J* = 7.4 Hz, 4H), 0.74 (appt t, *J* = 7.4 Hz, 4H). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.56 (bs, 1H), 4.49 (t, *J* = 6.0 Hz, 1H), 2.63 – 2.54 (m, 1H), 2.43 (dt, *J* = 13.6, 7.8 Hz, 1H), 2.34 – 2.24 (m, 1H), 1.89 – 1.77 (m, 2H), 1.75 – 1.69 (m, 1H), 1.67 (m, 6H), 1.65 – 1.61 (m, 1H), 1.63 – 1.58 (m, 6H), 1.29 (bs, 2H), 1.25 – 1.01 (m, 4H), 0.87 (t, *J* = 7.4 Hz, 3H), 0.82 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.27, 138.59, 133.71, 133.49, 80.33,

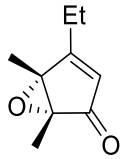
79.94, 77.16, 48.30, 48.25, 39.19, 38.62, 26.95, 26.35, 12.54, 12.52, 11.52, 11.34, 11.28, 11.20. HRMS (ESI) *m/z* calculated for $C_9H_{16}O$ $[M\text{-}OH]^+$ 123.1168, found 123.1168.



Compound 3.47. A flame dried round bottom flask with a stir bar was charged with **3.46** (1.0014 g, 7.14 mmol, 1 equiv.) and CH_2Cl_2 (24.0 ml) before cooling to 0 °C in an ice bath and adding *t*-BuOOH (1.70 ml, ~5.5 M in decane, 9.35 mmol, 1.31 equiv.). A separate flame dried round bottom flask was charged with $VO(acac)_2$ (76.0 mg, 0.285 mmol, 0.04 equiv.) and CH_2Cl_2 (70 ml). The $VO(acac)_2$ solution was added dropwise to the solution with **3.46**, turning red in color. After 5 hours, TLC showed the reaction had gone to completion. The reaction was diluted with CH_2Cl_2 and quenched with sat. $Na_2S_2O_3$ and brine. The aqueous layer was extracted three times with CH_2Cl_2, and the combined organics were washed with brine. After drying with Na_2SO_4, the solvent was removed. The crude material was purified by column chromatography (10 to 20% Et_2O/hexanes, then 20 to 70% Et_2O/hexanes in 5% increments). Epoxide **3.47** (1.0116 g, 6.48 mmol, 91% yield) was isolated as a 1:1 mixture of diastereomers. ^{1}H NMR (500 MHz, C_6D_6) δ 3.81 (dt, *J* = 10.3, 7.9 Hz, 1H), 3.63 (dt, *J* = 10.1, 7.9 Hz, 1H), 1.90 (td, *J* = 8.6, 3.8 Hz, 1H), 1.75 (dt, *J* = 12.3, 7.5 Hz, 1H), 1.55 (dd, *J* = 12.9, 7.7 Hz, 1H), 1.49 (dtt, *J* = 12.8, 7.5, 4.0 Hz, 1H), 1.36 – 1.27 (m, 2H), 1.26 (s, 3H), 1.23 (s, 3H), 1.22 – 1.17 (m, 1H), 1.16 – 1.08 (m, 3H), 1.07 (s, 3H), 1.03 (s, 3H), 0.79 (appt t, *J* = 7.5 Hz, 4H), 0.76 – 0.66 (m, 1H), 0.59 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, C_6D_6) δ 75.65, 75.33, 69.00, 68.87, 68.66, 68.03, 43.65, 42.57, 35.05, 34.04, 24.07, 22.53, 13.88, 13.87, 12.73, 12.62, 12.19, 11.53. HRMS (ESI) *m/z* calculated for $C_9H_{16}O_2$ $[M+H]^+$ 157.1223, found 157.1219.

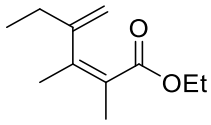


Compound 3.48. A round bottom flask with a stir bar was charged with **3.47** (1.0104 g, 6.47 mmol, 1.0 equiv.), $NaHCO_3$ (5.48 g, 65.2 mmol, 10.1 equiv.) and CH_2Cl_2 (130 ml). Dess-Martin periodinane (4.162 g, 9.81 mmol, 1.52 equiv.) was added and the reaction was allowed to stir for 16 hours. After an NMR aliquot indicated that the alcohol had been consumed, the reaction was quenched with sat. $NaHCO_3$ and sat. $Na_2S_2O_3$. The resulting mixture was stirred vigorously for 2 hours, after which the aqueous layer was diluted with brine and extracted four times with CH_2Cl_2. The combined organics were washed with brine and dried with Na_2SO_4. After removing the solvent, the resulting crude material was purified *via* Kugelrohr distillation. The pressure was initially 14 torr and the collection bath was kept at -78 ˚C. The bath was gradually heated to 85 ˚C, after which the pressure was lowered from 14 torr to 2 torr in 3-4 torr steps. When no liquid remained in the distillation flask, the distillation was ended and ketone **3.48** (1.017 g, 92% pure, 5.98 mmol, 92% yield) was collected with a small amount of acetic acid as an impurity. ^{1}H NMR (500 MHz, C_6D_6) δ 2.34 (dd, *J* = 17.7, 8.3 Hz, 1H), 1.95 (td, *J* = 8.5, 3.5 Hz, 1H), 1.83 (dd, *J* = 17.5, 8.2 Hz, 1H), 1.76 (dd, *J* = 17.5, 7.9 Hz, 1H), 1.56 (dd, *J* = 17.7, 1.1 Hz, 1H), 1.48 – 1.37 (m, 1H), 1.31 – 1.25 (m, 1H), 1.24 – 1.16 (m, 7H), 1.10 – 1.03 (m, 1H), 1.02 (s, 3H), 0.99 (s, 3H), 0.76 – 0.65 (m, 1H), 0.62 (t, *J* = 7.4 Hz, 3H), 0.44 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, C_6D_6) δ 210.75, 209.94, 71.02, 70.45, 65.98, 64.75, 40.43, 39.87, 37.49, 37.22, 24.30, 22.47, 13.85, 13.66, 12.10, 10.14, 8.37, 8.15. HRMS (ESI) *m/z* calculated for $C_9H_{14}O_2$ $[M+Na]^+$ 177.0886, found 177.0881.

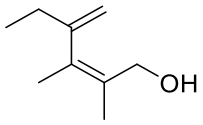


Compound 3.42. A flame dried round bottom with a stir bar was charged with **3.48** (1.017 g, 92% pure, 5.98 mmol, 1.0 equiv.) and THF (60 ml). The flask was cooled to -45 ˚C in a MeCN/dry ice bath for 15 min and then NaHMDS (8.4 ml, 1 M in THF, 8.4 mmol, 1.40 equiv.) was added. Freshly distilled trimethylchlorosilane (1.30 ml, 10.2 mmol, 1.70 equiv.) was added 40 minutes later. The solution went from orange to a faint yellow in color. After 3 hours the reaction was warmed up to room temperature, and

then pentanes were added after 30 minutes. The reaction was quenched with sat. NH_4Cl, which was extracted three times with pentanes. The combined organics were washed with water, then sat. NH_4Cl before drying with Na_2SO_4. The solvent was removed under reduced pressure, a stir bar was added and the residue was dissolved in CH_2Cl_2 (40 ml). Pyridine (0.68 ml, 8.4 mmol, 1.4 equiv.) was added before cooling the flask down to -78 ˚C. PhSeBr (1.6988 g, 7.20 mmol, 1.20 equiv.) was dissolved in CH_2Cl_2, which was added dropwise to the solution containing the silyl enol ether. An NMR aliquot of the reaction after 45 min showed full conversion of the silyl enol ether. The reaction was quenched with sat. $NaHCO_3$ and brine, which was extracted three times with CH_2Cl_2. The combined organics were washed with brine and dried with Na_2SO_4 before removing the solvent under reduced pressure. The crude material was dissolved in CH_2Cl_2 (310 ml) and transferred into a 3-neck flask with a stir bar. The solution was cooled to -78 ˚C before adding a stream of ozone gas. Once the color of the solution had gone from a yellow to a faint blue, the solution was purged with nitrogen until the blue color dissipated. Once the flask was clear, *i*-Pr_2Net (11.25 ml, 64.6 mmol, 10.8 equiv.) was added and the flask was warmed to 0 ˚C in an ice bath. After 30 min, the flask was warmed to room temp for 5 minutes before quenching the reaction with sat. $NaHCO_3$ and brine. The aqueous layer was extracted three times with CH_2Cl_2. The combined organics were washed with 60 ml of 1 M HCl and brine followed by sat. $NaHCO_3$ and brine. The organics were dried with sat. Na_2SO_4 before removing the solvent under reduced pressure. The crude material was purified *via* Kugelrohr distillation. Starting at 14 torr, the bath was heated until 85 ˚C. Nothing had distilled over, so the pressure was lowered until it was <1 torr. The resulting distillate was somewhat impure, so a second Kugelrohr distillation was performed. The material that distilled at <55 ˚C and 1 torr was separated, and the material that distilled at 65-70 ˚C at 1 torr was collected. The later material was shown to be **3.42** (473.9 mg, 2.88 mmol, 48% yield based on starting material purity). ^{1}H NMR (500 MHz, C_6D_6) δ 5.41 (t, *J* = 1.9 Hz, 1H), 1.78 (dqd, *J* = 18.5, 7.3, 2.0 Hz, 1H), 1.64 (dqd, *J* = 18.4, 7.2, 1.8 Hz, 1H), 1.31 (s, 3H), 0.97 (s, 3H), 0.67 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, C_6D_6) δ 200.20, 176.15, 124.80, 65.51, 62.10, 22.93, 10.86, 10.37, 8.36. HRMS (ESI) *m/z* calculated for $C_9H_{12}O_2$ $[M+H]^+$ 153.0910, found 153.0906.

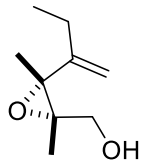


Compound 3.57. A flame dried Schlenk flask with a stir bar was taken into the glove box and charged with [$Pd(PPh_3)_4$] (976 mg, 0.845 mmol, 0.10 equiv.), CuCl (4.161 g, 42.0 mmol, 5.0 equiv.), and LiCl (2.14 g, 50.5 mmol, 6.0 equiv.). The flask was septumed and removed from the box before charging with distilled DMSO (67.0 ml), **3.55** (1.77 ml, 1.310 g/ml, 8.39 mmol, 1.0 equiv.) and **3.57** (3.25 ml, 1.052 g/ml, 9.91 mmol, 1.18 equiv.). The septum was quickly replaced with a glass stopper and the solution went through three freeze/pump/thaw cycles; after the last such cycle the solution was stirred at room temperature for 1.5 hours. The flask was then heated to 80 ˚C for 39 hours. After cooling to room temperature the solution was filtered through celite, with the round bottom being rinsed with Et_2O. The filtrate was quenched with sat. NH_4Cl and the aqueous layer was extracted three times with Et_2O. The combined organics were washed two times with water and one time with brine before diluting with pentanes and drying with Na_2SO_4. Removing the solvent revealed a brown residue that was dry loaded with celite and purified *via* column chromatography (120 g gold column, 0 to 25% EtOAc/hexanes). Diene **3.57** (1.1813 g, 6.48 mmol, 77% yield) was isolated as a slightly off yellow oil. ^{1}H NMR (500 MHz, C_6D_6) δ 4.83 (dt, *J* = 2.1, 1.2 Hz, 1H), 4.76 (q, *J* = 1.7 Hz, 1H), 4.00 (q, *J* = 7.1 Hz, 2H), 2.18 (qt, *J* = 7.4, 1.5 Hz, 2H), 1.81 (d, *J* = 1.1 Hz, 3H), 1.56 (d, *J* = 1.1 Hz, 3H), 1.04 (t, *J* = 7.5 Hz, 3H), 0.98 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, C_6D_6) δ 169.86, 154.33, 144.18, 125.17, 108.91, 59.97, 27.80, 18.86, 15.75, 14.07, 12.15. HRMS (ESI) *m/z* calculated for $C_{11}H_{18}O_2$ $[M+H]^+$ 183.1380, found 183.1379.



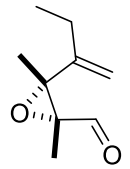
Compound 3.54. A flame dried round bottom flask was taken into a glovebox and charged with neat DIBAL (3.50 ml, 19.6 mmol, 3.0 equiv.). The flask was septumed and removed from the glovebox before dissolving the DIBAL with CH_2Cl_2 (20.0 ml). A separate flame dried round bottom flask with stir bar was

charged with **3.57** (1.1813 g, 6.48 mmol, 1.0 equiv.) and cooled to -78 ˚C. The solution of DIBAL in CH_2Cl_2 was cannulaed over to ester and the resulting solution was kept at -78 ˚C for 1.5 hours. The solution was then warmed to 0 ˚C for 45 min, when TLC showed complete conversion of the diene. The reaction was quenched with 40 ml of sat. Rochelle's salt, and the resulting mixture was stirred for several hours. Afterwards, the aqueous layer was diluted with water and extracted three times with Et_2O. The organics were washed with brine and dried with Na_2SO_4. The solvent was removed under reduced pressure and the resulting crude material was purified by column chromatography (0 to 30% EtOAc/hexanes, 10% increments). Allylic alcohol **3.54** (835.3 mg, 5.96 mmol, 92% yield) was isolated as a clear oil with a yellow tinge. ^{1}H NMR (500 MHz, C_6D_6) δ 4.82 (q, *J* = 1.7 Hz, 1H), 4.65 (dt, *J* = 2.2, 1.0 Hz, 1H), 4.02 (s, 2H), 2.00 (qt, *J* = 7.5, 1.3 Hz, 2H), 1.70 (d, *J* = 1.1 Hz, 3H), 1.62 (t, *J* = 1.0 Hz, 3H), 0.89 (t, *J* = 7.5 Hz, 3H), 0.69 (s, 1H). ^{13}C NMR (126 MHz, C_6D_6) δ 153.05, 134.99, 130.31, 110.29, 64.72, 28.79, 18.34, 15.73, 12.37. HRMS (ESI) *m/z* calculated for $C_9H_{16}O$ $[M + NH_4]^+$ 158.1539, found 158.1535.

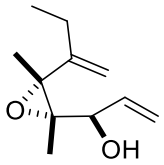


Compound 3.58. A flame dried round bottom flask with a stir bar was charged with **3.54** (809.6 mg, 5.77 mmol, 1.0 equiv.) in CH_2Cl_2 (19.0 ml) and *t*-BuOOH (1.35 ml, ~5.5 M in decane, 7.43 mmol, 1.29 equiv.). This was cooled to 0 ˚C before adding a solution of $VO(acac)_2$ (63.0 mg, 0.238 mmol, 0.04 equiv.) in CH_2Cl_2. After 4 hours, TLC shows complete conversion of the allylic alcohol. The reaction was diluted with CH_2Cl_2 and quenched with sat. $Na_2S_2O_3$. The aqueous layer was extracted three times with CH_2Cl_2. The combined organics were washed with brine before drying with Na_2SO_4. The solvent was removed and the crude oil was purified by column chromatography (0 to 40% EtOAc/hexanes, 10% increments). Epoxide **3.58** (861.4 mg, 5.51 mmol, 96% yield) was isolated as a clear oil. ^{1}H NMR (500 MHz, C_6D_6) δ 5.12 (s, 1H), 4.83 (q, *J* = 1.7 Hz, 1H), 3.35 (d, *J* = 5.6 Hz, 2H), 2.00 – 1.81 (m, 2H), 1.31 (s, 3H), 1.24 (s, 3H), 1.01 (t, *J* = 6.0 Hz, 1H), 0.88 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, C_6D_6) δ 150.37, 109.37, 67.40, 65.52,

65.20, 26.24, 19.58, 15.57, 11.82. HRMS (ESI) *m/z* calculated for $C_9H_{16}O_2$ $[M+Na]^+$ 179.1043, found 179.1041.

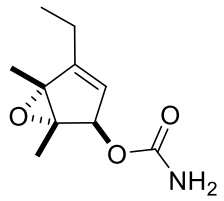


Compound 3.59. A flame dried round bottom flask with a stir bar was charged with **3.58** (861.4 mg, 5.51 mmol, 1.0 equiv.) in CH_2Cl_2 (55.0 ml) and $NaHCO_3$ (2.317 g, 27.6 mmol, 5.0 equiv.). This was cooled to 0 °C for 15 min before adding Dess-Martin periodinane (4.914 g, 11.6 mmol, 2.10 equiv.). After 3.5 hours, the reaction was complete by TLC. The reaction was quenched with sat. $Na_2S_2O_3$ and sat. $NaHCO_3$, and the mixture as stirred at room temperature for 30 minutes before extracting the aqueous layer three times with Et_2O. The combined organics were washed with brine and dried with Na_2SO_4. The solvent was removed under reduced pressure, and the crude material was purified *via* column chromatography (0 to 20% EtOAc/hexanes, 5% increments). Aldehyde **3.59** (636.2 mg, 4.13 mmol, 75% yield) was isolated as a clear oil. ^{1}H NMR (500 MHz, C_6D_6) δ 9.17 (s, 1H), 5.12 (q, *J* = 1.3 Hz, 1H), 4.73 (q, *J* = 1.6 Hz, 1H), 1.90 – 1.79 (m, 1H), 1.76 – 1.67 (m, 1H), 1.24 (s, 3H), 1.08 (s, 3H), 0.75 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, C_6D_6) δ 201.55, 147.81, 110.91, 67.80, 66.31, 25.99, 19.76, 11.71, 11.52. HRMS (ESI) *m/z* calculated for $C_9H_{14}O_2$ $[M+H]^+$ 155.1067, found 155.1065.



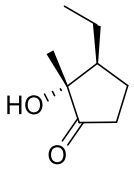
Compound 3.53. A flame dried round bottom flask with a stir bar was taken into the glovebox and charged with freshly fused $ZnCl_2$ (462.8 mg, 3.40 mmol, 2.26 equiv.). The flask was septumed, removed from the box and charged with THF (2.0 ml) with vigorous stirring. Vinylmagnesium bromide (6.75 ml, 1 M in THF, 6.75 mmol, 4.5 equiv.) was added dropwise, resulting in a largely homogeneous solution. The solution as

stirred vigorously at room temp for 20 min, breaking up any white percipitates. The solution was cooled to -78 ˚C for 15 min before adding **3.59** (242 µl, 0.957 g/ml, 1.50 mmol, 1.0 equiv.). After stirring for 1 hour at -78 ˚C, the solution was warmed to 0 ˚C. After 30 min, TLC indicated the starting material was completely consumed. The reaction mixture was poured into sat. NH_4Cl and the aqueous layer was extracted three time with Et_2O. The combined organics were washed with brine, diluted with pentane and dried with Na_2SO_4. The solvent was removed and the residue purified by column chromatography (0 to 12% EtOAc/hexanes, 2% increments). This yielded the major diastereomer **3.53** (181.2 mg, 0.994 mmol, 66% yield) and a minor diastereomer (31.9 mg, 0.175 mmol, 12% yield). Combined, this amounts to 213.1 mg (1.17 mmol, 78% yield) with a 5.7:1 *dr*. ^{1}H NMR (500 MHz, C_6D_6) δ 6.05 (ddd, *J* = 17.4, 10.7, 3.9 Hz, 1H), 5.28 (dt, *J* = 17.4, 1.8 Hz, 1H), 5.20 (s, 1H), 5.11 (dt, *J* = 10.8, 1.8 Hz, 1H), 4.89 (q, *J* = 1.8 Hz, 1H), 3.95 – 3.88 (m, 1H), 2.10 – 1.95 (m, 2H), 1.29 (s, 3H), 1.27 (s, 3H), 0.97 (appt t, *J* = 7.4 Hz, 4H). ^{13}C NMR (126 MHz, C_6D_6) δ 150.50, 138.53, 114.78, 109.74, 72.71, 67.90, 66.09, 26.18, 12.25, 11.96. HRMS (ESI) *m/z* calculated for $C_{11}H_{18}O_2$ $[M+Na]^+$ 205.1199, found 205.1193.



Compound 3.60. A round bottom flask with a stir bar was charged with **3.53** (50.7 mg, 0.278 mmol, 1.0 equiv.), 1,4-benzoquinone (3.4 mg, 0.031 mmol, 0.11 equiv.), Grubbs-II (11.6 mg, 0.0137 mmol, 0.05 equiv.), and finally CH_2Cl_2 (1.40 ml). After 4 hours, another batch of Grubbs-II (3.0 mg, 0.0035 mmol, 0.01 equiv.) was added. After 1.5 h, 2-morpholinoethyl isocyanide (10.0 µl, 0.0725 mmol, 0.26 equiv.) was added. The reaction was cooled to 0 ˚C after 10 min, and trichloroacetyl isocyanate (41.0 µl, 0.344 mmol, 1.24 equiv.) was added 5 min later. The reaction was warmed to room temperature after 10 min. After 1 h, the solvent was removed under reduced pressure. K_2CO_3 (24.4 mg, 0.177 mmol, 0.64 equiv.) and MeOH (0.79 ml) were then added and the reaction was stirred at room temperature for 2.5 h before diluting with DCM and storing in a -78 ˚C freezer overnight. The next day the solvent was removed under reduced

pressure and the crude material was dry loaded with celite (1.2 g) due to a large amount of insoluble material. This was loaded onto a column of neutral alumina and purified *via* column chromatography (0 to 60% EtOAc/hexanes, 10% increments, purified rapidly in order to minimize decomposition). Carbamate **3.60** (16.8 mg, 0.0852 mmol, 31% yield) was isolated as an oil that was then stored at -78 ˚C. ^{1}H NMR (500 MHz, C_6D_6) δ 5.47 (q, *J* = 2.1 Hz, 1H), 5.43 (q, *J* = 2.0 Hz, 1H), 4.46 (s, 2H), 1.95 – 1.80 (m, 1H), 1.78 – 1.67 (m, 1H), 1.30 (s, 3H), 1.02 (s, 3H), 0.85 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, C_6D_6) δ 157.18, 153.26, 125.62, 78.79, 67.99, 63.23, 21.65, 14.51, 11.64, 11.18. HRMS (ESI) *m/z* calculated for $C_{10}H_{15}NO_3$ $[M+H]^+$ 198.1125, found 198.1124.

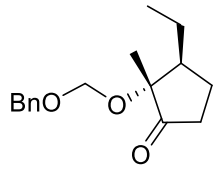


Compound 3.70. An oven dried 3-neck round bottom flask was equipped with a mechanical stirrer, an oven dried addition funnel and a septum before vac cycling three times. The flask was charged with **3.68** (599.3 mg, 1.17 mmol, 0.010 equiv.) and $Cu(OTf)_2$ (329.3 mg, 0.910 mmol, 0.0078 equiv.) before vac cycling again. The addition funnel was charged with 2-methyl-2-cyclopenten-1-one **3.67** (11.4 ml, 116 mmol, 1.0 equiv.) and Et_2O (110 ml). The flask was also charged with Et_2O (280 ml). The flask was stirred while it was cooled to -30 ˚C using a cryocool. After reaching a stable temperature, ethylmagnesium bromide (48.0 ml, 3.0 M in Et_2O, 144 mmol, 1.24 equiv.) was added, with the color changing from a dark brown to a yellow and back to a dark brown within the first couple of milliliters of the Grignard solution. After 25 min, the enone solution was added dropwise over the next 1 hour. After stirring for 4 hours, distilled HMPA (42.0 ml, 241 mmol, 2.08 equiv.) was added. The addition funnel was charged with Et_3N (34.0 ml, 244 mmol, 2.10 equiv.) and trimethylchlorosilane (29.5 ml, 232 mmol, 2.0 equiv., freshly distilled from CaH_2), which was added to the solution 25 min after the HMPA. This was stirred for 2 hours before adding pentanes (600 ml) and pouring the cold slurry into 150 ml of pentanes and 350 ml of water. The layers were separated and the aqueous layer was extracted again with 400 ml of pentanes. The combined

organics were washed with 200 ml of water followed by 200 ml of brine. The organics were dried with Na_2SO_4 and the solvent was removed under reduced pressure. The crude material was stored in a -78 ˚C overnight. A fritted funnel was loaded with 100 g of silica and wetted with pentanes. The crude material was loaded onto the silica and rapidly filtered using 1.5 L of pentanes. The solvent was removed under reduced pressure, yielding a slightly peach colored liquid that was the silyl enol ether **3.69** (14.309 g, 72.1 mmol, 62% crude yield). Due to the dilute nature of DMDO solutions, the oxidation was broken up into two separate flasks run at the same time that would later be combined for a single purification. A stock solution of 3.86 g of NH_4F in 700 ml of MeOH was prepared and set aside. One round bottom flask with a stir bar was cooled to -78 ˚C and charged with a DMDO solution (1.25 L, 0.046 M in acetone, 57.5 mmol, 1.3 equiv.) and CH_2Cl_2 (88 ml). A portion of the silyl enol ether (8.7748 g, 44.2 mmol, 1.0 equiv.) was added slowly once the internal temperature of the solution had reached -75 ˚C. After 1.5 h, the NH_4F solution (370 ml) was added and the flask was allowed to warm to room temp over 11 hours. Another round bottom flask with a stir bar was cooled to -78 ˚C and charged with another DMDO solution (625 ml, 0.059 M in acetone, 36.9 mmol, 1.3 equiv.) and CH_2Cl_2 (56 ml). Once the internal temperature of the solution had reached -75 ˚C, the balance of the silyl enol ether (5.5342 g, 27.9 mmol, 1.0 equiv.) was added. After 1.5 hours, the NH_4F solution (230 ml) was added and the solution was allowed to warm to room temp over 11 hours. The two solutions were combined, and the solvent was carefully removed under reduced pressure. When ~100 ml remained, the crude material was diluted with CH_2Cl_2 (600 ml) and water (400 ml). The layers were separated, and the aqueous layer was extracted two more times with CH_2Cl_2 before washing the combined organics with brine. The organics were dried with Na_2SO_4 and the solvent was carefully removed under reduced pressure. The crude material was dry loaded with celite (30 g) and purified *via* column chromatography (330 g gold column, 0 to 100% Et_2O/hexanes). The major diastereomer **3.70** (5.0301 g, 35.4 mmol, 30% yield) and the minor diastereomer (3.7074 g, 26.1 mmol, 22% yield) were completely separated, with both diastereomers being yellow oils. Combined, this amounts to 8.7375 g (61.4 mmol, 53% yield from the enone, 85% yield from the crude silyl enol ether) in a 1.36:1 *dr*. Major diastereomer - ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.50 (s, 1H), 2.44 (ddd, *J* = 19.5, 9.9, 1.6 Hz, 1H), 2.24 (dt,

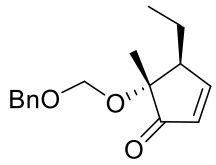
J = 19.6, 9.8 Hz, 1H), 2.17 – 2.10 (m, 1H), 1.86 (dddd, *J* = 12.1, 8.9, 7.0, 5.4 Hz, 1H), 1.70 (dqd, *J* = 12.9, 7.5, 5.3 Hz, 1H), 1.42 – 1.30 (m, 2H), 1.08 (s, 3H), 1.02 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 221.25, 79.51, 48.04, 33.40, 23.32, 22.52, 18.02, 12.13. HRMS (ESI) *m/z* calculated for $C_8H_{14}O_2$ $[M+NH_4]^+$ 160.1332, found 160.1332. Minor diastereomer (**SI-03**): ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.38 (ddd, *J* = 19.3, 8.7, 4.7 Hz, 1H), 2.25 (ddd, *J* = 19.3, 9.3, 7.4 Hz, 1H), 2.09 – 1.99 (m, 1H), 1.90 (d, *J* = 1.7 Hz, 1H), 1.82 – 1.75 (m, 1H), 1.75 – 1.65 (m, 2H), 1.27 (s, 3H), 1.26 – 1.18 (m, 1H), 0.98 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 219.63, 77.70, 48.30, 33.67, 23.16, 22.84, 20.75, 12.21. HRMS (ESI) *m/z* calculated for $C_8H_{14}O_2$ $[M+NH_4]^+$ 160.1332, found 160.1331.

For confirmation of the stereochemistry of **compound 3.70**, please see **compound 3.76**.



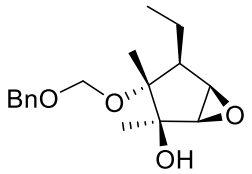
Compound 3.71. A flame dried round bottom flask with a stir bar and a reflux condenser was charged with *i*-Pr_2NEt (17.5 ml, 100 mmol, 5.0 equiv.) and **3.70** (2.8632 g, 20.1 mmol, 1.0 equiv.) in CH_2Cl_2 (100 ml). Benzyl chloromethylether (8.25 ml, 59.8 mmol, 3.0 equiv.) was added and the solution was refluxed. After confirming the reaction was complete after 6 hours *via* NMR, the solution was cooled to room temp and diluted with Et_2O and sat. NH_4Cl. The aqueous layer was extracted three times with Et_2O. The combined organics were washed with water and then brine before drying with Na_2SO_4. The solvent was removed under reduced pressure. The crude material was dry loaded with celite (20 g) and purified *via* column chromatography (330 g gold column, 0 to 60% Et_2O/hexanes). Acetal **3.71** (4.1394 g, 15.8 mmol, 79% yield) was isolated as a slightly cloudy liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.30 (m, 4H), 7.30 – 7.26 (m, 1H), 5.00 (d, *J* = 7.7 Hz, 1H), 4.77 (d, *J* = 7.7 Hz, 1H), 4.62 (ABq, $\Delta\delta_{AB}$ = 0.02, J_{AB} = 11.8 Hz, 2H), 2.38 – 2.13 (m, 4H), 1.67 (dqd, *J* = 14.8, 7.4, 4.1 Hz, 1H), 1.39 – 1.21 (m, 2H), 1.16 (s, 3H), 0.98 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 219.09, 137.97, 128.53, 128.06, 127.80, 90.37, 84.03, 70.16,

44.55, 34.96, 23.16, 22.16, 16.45, 12.10. HRMS (ESI) *m/z* calculated for $C_{16}H_{22}O_3$ $[M+NH_4]^+$ 280.1907, found 280.1905.



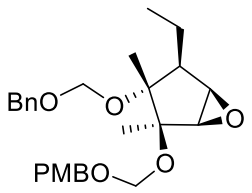
Compound 3.66. A flame dried round bottom flask with stir bar was taken into the glovebox and charged with **3.71** (264.7 mg, 1.01 mmol, 1.0 equiv.). The flask was septumed, removed from the box and charged with THF (10 ml) before cooling to -45 ˚C. NaHMDS (1.30 ml, 1 M in THF, 1.30 mmol, 1.3 equiv.) was added. After 30 min, chlorotrimethylsilane (0.20 ml, 1.6 mmol, 1.6 equiv., freshly distilled from CaH_2) was added. After 1 hour, the cold reaction was poured into pentanes (25 ml) and sat. NH_4Cl (12 ml). The mixture was extracted quickly and the aqueous layer was extracted two more times with pentanes (15 ml). The combined orgs were washed with water and then sat. NH_4Cl. The organics were dried with Na_2SO_4 and the solvent was removed under reduced pressure. The crude material was then azeotroped with toluene (2.0 ml) under high vac to remove any silanol biproducts. Meanwhile a second flask with a stir bar was charged with IBX (424.5 mg, 1.52 mmol, 1.5 equiv.) and 4-methoxypyridine *N*-oxide hydrate (218.4 mg, 1.5 equiv.). The flask was covered with aluminum foil and the light in the hood was extinguished before adding DMSO (3.75 ml). Once the IBX-MPO solution was homogenous and clear, the silyl enol ether was diluted with DMSO (0.50 ml) and CH_2Cl_2 (0.20 ml). The IBX-MPO solution was then poured into the flask containing the silyl enol ether, which was then covered with aluminum foil. After stirring for 18 hours, the solution was diluted with Et_2O (25 ml), sat. $NaHCO_3$ (15 ml) and sat. $Na_2S_2O_3$ (15 ml). The resulting aqueous layer was extracted three times with Et_2O. The combined organics were washed once with sat. $NaHCO_3$, twice with water, and one time with brine. The organics were then dried with Na_2SO_4 and the solvent was removed under reduced pressure. The crude material was dry loaded with celite and purified *via* column chromatography (40 g gold column, 0 to 50% Et_2O/hexanes). Recovered ketone **3.71** (54.7 mg, 0.209 mmol, 21%) and enone **3.66** (151.9 mg, 0.583 mmol, 58% yield, 73% brsm) were isolated. ^1H NMR (500 MHz,

$CDCl_3$) δ 7.59 (dd, *J* = 6.2, 2.2 Hz, 1H), 7.38 – 7.25 (m, 5H), 6.18 (dd, *J* = 6.2, 2.3 Hz, 1H), 4.99 (d, *J* = 7.6 Hz, 1H), 4.79 (d, *J* = 7.6 Hz, 1H), 4.61 (ABq, $\Delta\delta_{AB}$ = 0.03, J_{AB} = 11.8 Hz, 2H), 3.08 (ddt, *J* = 10.1, 5.8, 2.3 Hz, 1H), 1.84 – 1.72 (m, 1H), 1.34 (dtd, *J* = 13.7, 7.2, 2.4 Hz, 1H), 1.29 (s, 3H), 1.08 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 209.23, 164.66, 137.88, 130.72, 128.54, 128.03, 127.83, 90.94, 82.86, 70.12, 51.36, 21.95, 19.31, 12.35. HRMS (ESI) *m/z* calculated for $C_{16}H_{20}O_3$ $[M+NH_4]^+$ 278.1751, found 278.1747.

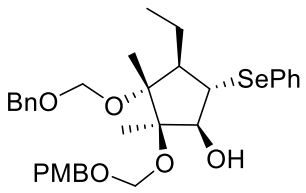


Compound 3.73. A flame dried round bottom flask with a stir bar was taken into the glovebox and charged with anhydrous $CeCl_3$ (2.9105 g, 11.8 mmol, 1.53 equiv.)[3] and LiCl (1.0191 g, 24.0 mmol, 3.10 equiv.). The flask was sealed with a septum, removed from the glovebox and charged with THF (47 ml). This solution stirred at room temp for 19 hours, turning homogenous and a yellow, opaque color. A flame dried conical flask was taken into the glovebox and charged with **3.66** (2.0116 g, 7.73 mmol, 1.0 equiv.). The flask was sealed with a septum, removed from the box and charged with THF (3.0 ml). This solution was then transferred *via* cannula over to the $CeCl_3$-2LiCl solution with a rinse of THF (3.0 ml). After stirring for 1 hour, the flask was cooled to -78 ˚C. Methylmagnesium bromide (7.0 ml, 3 M in Et_2O, 21 mmol, 2.7 equiv.) was added dropwise after 50 min. A pH 7 buffer solution (10 ml, 0.1 M phosphate buffer) was added after 5 hours and the reaction was warmed to room temp before pouring into Et_2O and pH 7 buffer. The aqueous layer was extracted three times with Et_2O. The combined organics were then washed with brine, diluted with CH_2Cl_2, and dried with Na_2SO_4. The solvent was then removed under reduced pressure. The crude alcohol **3.72** was diluted with CH_2Cl_2 (26 ml) and transferred to a flame dried round bottom flask with a stir bar. The flask was cooled to 0 ˚C and charged with *t*-BuOOH (1.60 ml, ~5.5 M in decane, 8.80 mmol, 1.14 equiv.). A separate flask was charged with $VO(acac)_2$ (83.5 mg, 0.315 mmol, 0.041 equiv.) and CH_2Cl_2 (77 ml). The $VO(acac)_2$ solution was added *via* cannula transfer to the allylic alcohol, resulting in

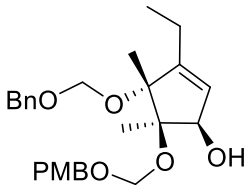
a red solution. This gradually warmed to room temp as the ice bath warmed. After 4.5 hours another batch of $VO(acac)_2$ (82.5 mg, 0.311 mmol, 0.040 equiv.) was added, restoring the red color. More *t*-BuOOH (1.60 ml, ~5.5 M in decane, 8.80 mmol, 1.14 equiv.) and $VO(acac)_2$ (85.3 mg, 0.322 mmol, 0.042 equiv.) were added after 2.5 hours. Another batch of *t*-BuOOH (1.60 ml, ~5.5 M in decane, 8.80 mmol, 1.14 equiv.) and $VO(acac)_2$ (80.1 mg, 0.302 mmol, 0.039 equiv.) were added after 1 hour. Another batch of $VO(acac)_2$ (83.2 mg, 0.314 mmol, 0.041 equiv.) was added after 1.5 hours. The reaction was quenched after 1.5 hours with sat. $Na_2S_2O_3$. The aqueous layer was extracted three times with Et_2O. The combined organics were washed with water and then brine. CH_2Cl_2 was added to the organics, which were then dried with Na_2SO_4. The solvent was removed under reduced pressure before dry loading the crude material with celite (13 g). The crude material was purified *via* column chromatography (120 g gold column, 0 to 70% EtOAc/hexanes). This yielded epoxy alcohol **3.73** (1.7626 g, 6.03 mmol, 78% yield) as an oil. *Note: Attempts to circumvent the portion wise addition of VO(acac)₂ and t-BuOOH by adding an equivalent amount at the beginning of the epoxidation were still hampered by stalled conversion that required additional portions of catalyst and oxidant to be added periodically. We hypothesize that this is due to the extremely hindered tertiary alcohol as the same batch of VO(acac)₂ and t-BuOOH did not display these issues with less hindered substrates.* ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.27 (m, 5H), 4.93 (d, *J* = 6.9 Hz, 1H), 4.75 (d, *J* = 6.9 Hz, 1H), 4.66 (d, *J* = 11.8 Hz, 1H), 4.52 (d, *J* = 11.8 Hz, 1H), 3.44 (dd, *J* = 3.4, 1.4 Hz, 1H), 3.30 (d, *J* = 3.4 Hz, 1H), 2.22 (s, 1H), 1.93 (ddd, *J* = 10.4, 4.9, 1.4 Hz, 1H), 1.67 – 1.58 (m, 1H), 1.57 – 1.50 (m, 1H), 1.31 (s, 3H), 1.26 (s, 3H), 1.05 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.90, 128.62, 127.89, 127.89, 89.83, 84.43, 81.62, 69.69, 60.75, 55.17, 50.03, 21.14, 19.71, 17.68, 12.51. HRMS (ESI) *m/z* calculated $C_{17}H_{24}O_4$ $[M+NH_4]^+$ 310.2013, found 310.2011.



Compound 3.74. A round bottom flask with a stir bar and a reflux condenser was charged with **3.73** (121.9 mg, 0.417 mmol, 1.0 equiv.) and *i*-Pr_2NEt (0.36 ml, 2.1 mmol, 5.0 equiv.). A separate round bottom flask with a stir bar is charged with $PMBOCH_2SMe$ (249.7 mg, 1.26 mmol, 3.0 equiv.), vac cycled, and then charged with CH_2Cl_2 (3.10 ml). This flask was cooled to -78 °C for 10 min before adding SO_2Cl_2 (0.11 ml, 1.4 mmol, 3.4 equiv.) dropwise over 2 min. After 1 hour, the flask was warmed to room temp and the solvent was removed under reduced pressure. Once dry, the $PMBOCH_2Cl$ was vac cycled three times before diluted with CH_2Cl_2 (2.25 ml). The solution was transferred to the tertiary alcohol *via* cannula transfer, followed by a CH_2Cl_2 rinse (2.0 ml). The reaction was refluxed for 51 hours, when it was quenched with water. The aqueous layer was extracted three times with CH_2Cl_2. The combined orgs were dried with Na_2SO_4 and the solvent was removed under reduced pressure. The crude material was dry loaded with celite (1 g) before purifying *via* column chromatography (40 g gold column, 0 to 15% Et_2O/toluene). Protected alcohol **X** (149.2 mg, 0.337 mmol, 81% yield) was isolated as a slightly impure sample. *Note: The reaction is lengthy and does take the full time allotted. Do not use sat. NH_4Cl during the workup as that led to rapid opening of the epoxide with chloride that was challenging to separate.* ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.26 (m, 7H), 6.90 – 6.86 (m, 2H), 5.04 (d, J = 7.2 Hz, 1H), 4.96 (ABq, $\Delta\delta_{AB}$ = 0.01, J_{AB} = 7.6 Hz, 2H), 4.76 – 4.70 (m, 2H), 4.68 (d, J = 11.2 Hz, 1H), 4.55 (d, J = 11.2 Hz, 1H), 4.49 (d, J = 11.8 Hz, 1H), 3.80 (s, 3H), 3.55 (d, J = 3.4 Hz, 1H), 3.42 (dd, J = 3.4, 1.4 Hz, 1H), 1.89 (ddd, J = 10.5, 4.7, 1.4 Hz, 1H), 1.75 – 1.64 (m, 1H), 1.64 – 1.56 (m, 1H), 1.37 (s, 3H), 1.28 (s, 3H), 1.07 (t, J = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.37, 138.30, 130.08, 129.94, 128.50, 127.88, 127.68, 113.97, 90.24, 89.90, 86.15, 85.15, 69.57, 69.24, 58.43, 55.42, 54.86, 49.43, 19.56, 19.31, 18.61, 12.59. HRMS (ESI) *m/z* calculated $C_{26}H_{34}O_6$ $[M+H]^+$ 460.2694, found 460.2691.



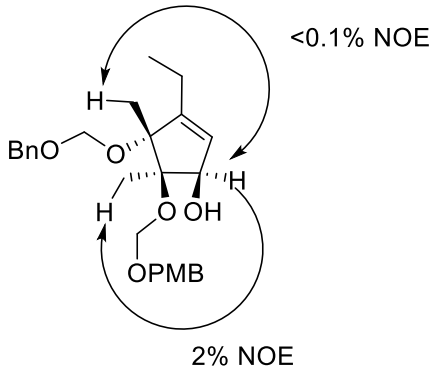
Compound 3.75. A flame dried round bottom flask with a stir bar was charged with Ph_2Se_2 (276.3 mg, 0.885 mmol, 5.75 equiv.) and NaH (47.7 mg, 1.19 mmol, 7.73 equiv.) before vac cycling with argon. DMSO (1.80 ml) was added and the flask was heated to 50 °C. A separate flame dried flask with a stir bar was taken into a glovebox and charged with **3.74** (68.3 mg, 0.154 mmol, 1.0 equiv.). The flask was sealed with a septum and vac cycled with argon. After 1 hour, the solution of PhSeNa was cooled to room temperature and 1.0 ml of this solution was added to the flask containing to **3.74**. The resulting solution was heated to 100 °C for 17 hours before cooling to room temp and quenching with brine. The aqueous layer was extracted three times with EtOAc, and the combined organics were washed one additional time with brine before drying with Na_2SO_4. The solvent was removed under reduced pressure and the crude material was dry loaded with celite (1 g). The crude material was purified *via* column chromatography (40 g gold column, 0 to 60% Et_2O/hexanes), yielding selenoether **3.75** (53.5 mg, 0.0892 mmol, 58% yield) as an oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 – 7.59 (m, 2H), 7.37 – 7.26 (m, 5H), 7.24 – 7.17 (m, 5H), 6.88 – 6.84 (m, 2H), 4.93 (d, *J* = 7.3 Hz, 1H), 4.75 (d, *J* = 7.3 Hz, 1H), 4.64 (d, *J* = 7.6 Hz, 1H), 4.62 (d, *J* = 11.8 Hz, 1H),), 4.53 (ABq, $\Delta\delta_{AB}$ = 0.04, J_{AB} = 11.8 Hz, 2H), 4.49 (d, *J* = 7.4 Hz, 1H), 4.46 (d, *J* = 11.4 Hz, 1H), 4.05 (dd, *J* = 8.3, 7.4 Hz, 1H), 3.80 (s, 3H), 3.62 (d, *J* = 8.4 Hz, 1H), 2.94 (t, *J* = 7.4 Hz, 1H), 1.88 (ddd, *J* = 8.9, 7.3, 5.9 Hz, 1H), 1.66 (ddd, *J* = 13.6, 7.5, 6.0 Hz, 1H), 1.54 (ddt, *J* = 13.5, 8.9, 7.4 Hz, 1H), 1.28 (s, 3H), 1.28 (s, 3H), 1.06 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.60, 138.11, 135.49, 129.73, 129.73, 129.53, 128.98, 128.51, 128.02, 127.73, 127.65, 114.12, 89.43, 89.00, 88.56, 87.06, 82.22, 70.25, 69.69, 55.43, 52.62, 51.97, 25.78, 14.92, 14.69, 13.56. HRMS (ESI) *m/z* calculated for $C_{32}H_{40}O_6Se$ $[M+H]^+$ 601.2063, found 601.2059.



Compound 3.76. A 20 dram vial with **3.75** (53.5 mg, 0.0892 mmol, 1.0 equiv.) was charged with THF (0.90 ml) and pyridine (0.015 ml, 0.19 mmol, 2.1 equiv.). This was stirred at room temp before adding 30%

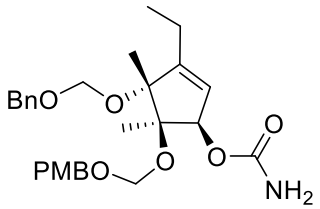
H_2O_2 (0.028 ml, 0.27 mmol, 3.0 equiv.). After 18 h the reaction was diluted with EtOAc and quenched with a 1:1 mix of sat. NaS_2O_3 and sat. $NaHCO_3$. The aqueous layer was extracted three times with EtOAc and the combined organics were washed with brine and dried with Na_2SO_4. The material was purified *via* column chromatography (12 g gold column, 0 to 50% EtOAc/hexanes), yielding allylic alcohol **3.76** (30.7 mg, 0.0694 mmol, 78% yield) as an oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.32 (m, 4H), 7.31 – 7.24 (m, 3H), 6.88 (d, *J* = 8.6 Hz, 2H), 5.56 (q, *J* = 2.2 Hz, 1H), 5.02 (d, *J* = 7.0 Hz, 1H), 4.98 (d, *J* = 6.8 Hz, 1H), 4.85 (d, *J* = 6.9 Hz, 1H), 4.78 (d, *J* = 7.1 Hz, 1H), 4.73 (d, *J* = 11.8 Hz, 1H), 4.68 (d, *J* = 11.3 Hz, 1H), 4.55 (d, *J* = 11.7 Hz, 1H), 4.51 (d, *J* = 11.2 Hz, 1H), 4.28-4.24 (m, 1H), 3.80 (s, 3H), 2.23 – 2.13 (m, 1H), 2.13 – 2.04 (m, 1H), 1.56 (s, 3H), 1.27 (s, 3H), 1.10 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.58, 154.91, 138.24, 129.83, 129.19, 128.50, 127.96, 127.70, 123.56, 114.09, 90.16, 90.07, 89.82, 88.44, 78.57, 69.97, 69.50, 55.41, 20.78, 19.98, 18.71, 11.41. HRMS (ESI) *m/z* calculated for $C_{26}H_{34}O_6$ $[M+NH_4]^+$ 460.2694, found 460.2690.

The overall stereochemistry of the molecule was confirmed with nNoesy analysis shown below.

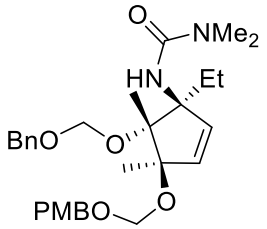


This analysis confirms the stereochemical assignment of **compound 3.70** even though the ethyl stereocenter has been ablated. This is due to two reasons; a) vanadium catalyzed directed epoxidations of allylic alcohols in cyclopentenol scaffolds give exclusively *cis* epoxy alcohols, and b) the selenoxide elimination occurs through a syn elimination and the proton adjacent to the selenoxide intermediate formed from **compound 3.75** has too high of a pKa to be epimerized under the conditions used. That means the epoxide and the ethyl group are on the same face of **compound 3.74**. Since the data above indicates that the allylic alcohol

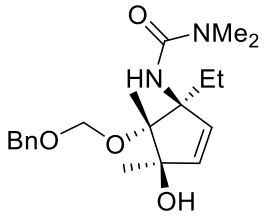
and the C-5 methyl are on the same face, this would indicate that the C-5 methyl and the ethyl group also were on the same face and thus the stereochemistry indicated for **compound 3.70** is correct.



Compound 3.77. A 20 dram vial with allylic alcohol **3.76** (367.1 mg, 0.830 mmol, 1.0 equiv.) and a stir bar was charged with CH_2Cl_2 (4.50 ml) and cooled to 0 ˚C. Trichloroacetyl isocyanate (0.12 ml, 0.996 mmol, 1.20 equiv.) was then added and the reaction was stirred for an hour. When **3.76** was complete by TLC, the solvent was removed under reduced pressure. Once dry, the dram vial was charged with K_2CO_3 (69.0 mg, 0.499 mmol, 0.60 equiv.) and MeOH (2.10 ml). After stirring for five hours at room temperature the reaction was complete by TLC. The solvent was removed under reduced pressure and the crude mixture was dissolved in Et_2O and water. The aqueous layer was extracted three times with Et_2O. The combined organics were washed with brine and dried with Na_2SO_4 before removing the solvent *in vacuo*. The crude material was dry loaded onto celite before purifying *via* column chromatography (24 g gold column, 0 to 70% EtOAc/hexanes). This yielded the allylic carbamate **3.77** (361.4 mg, 0.744 mmol, 90% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.27 (m, 5H), 7.25 (d, *J* = 8.5 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 5.54 (dd, *J* = 3.1, 1.8 Hz, 1H), 5.25 (dt, *J* = 2.7, 1.1 Hz, 1H), 5.10 (d, *J* = 7.1 Hz, 1H), 4.91 (d, *J* = 7.3 Hz, 1H), 4.81 (d, *J* = 7.1 Hz, 1H), 4.79 (d, *J* = 7.3 Hz, 1H), 4.76 (d, *J* = 11.8 Hz, 1H), 4.65 (d, *J* = 11.4 Hz, 1H), 4.55 (appt d, *J* = 11.7 Hz, 3H), 4.49 (d, *J* = 11.4 Hz, 1H), 3.79 (s, 3H), 2.27 – 2.16 (m, 1H), 2.16 – 2.06 (m, 1H), 1.54 (s, 3H), 1.39 (s, 3H), 1.10 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.31, 158.29, 156.48, 138.22, 130.19, 129.53, 128.55, 128.02, 127.75, 119.90, 113.95, 90.50, 90.25, 90.04, 85.99, 80.29, 69.59, 69.58, 55.43, 20.66, 20.24, 20.08, 11.32. HRMS (ESI) *m/z* calculated for $C_{27}H_{35}NO_7$ $[M+NH_4]^+$ 503.2752, found 503.2744.



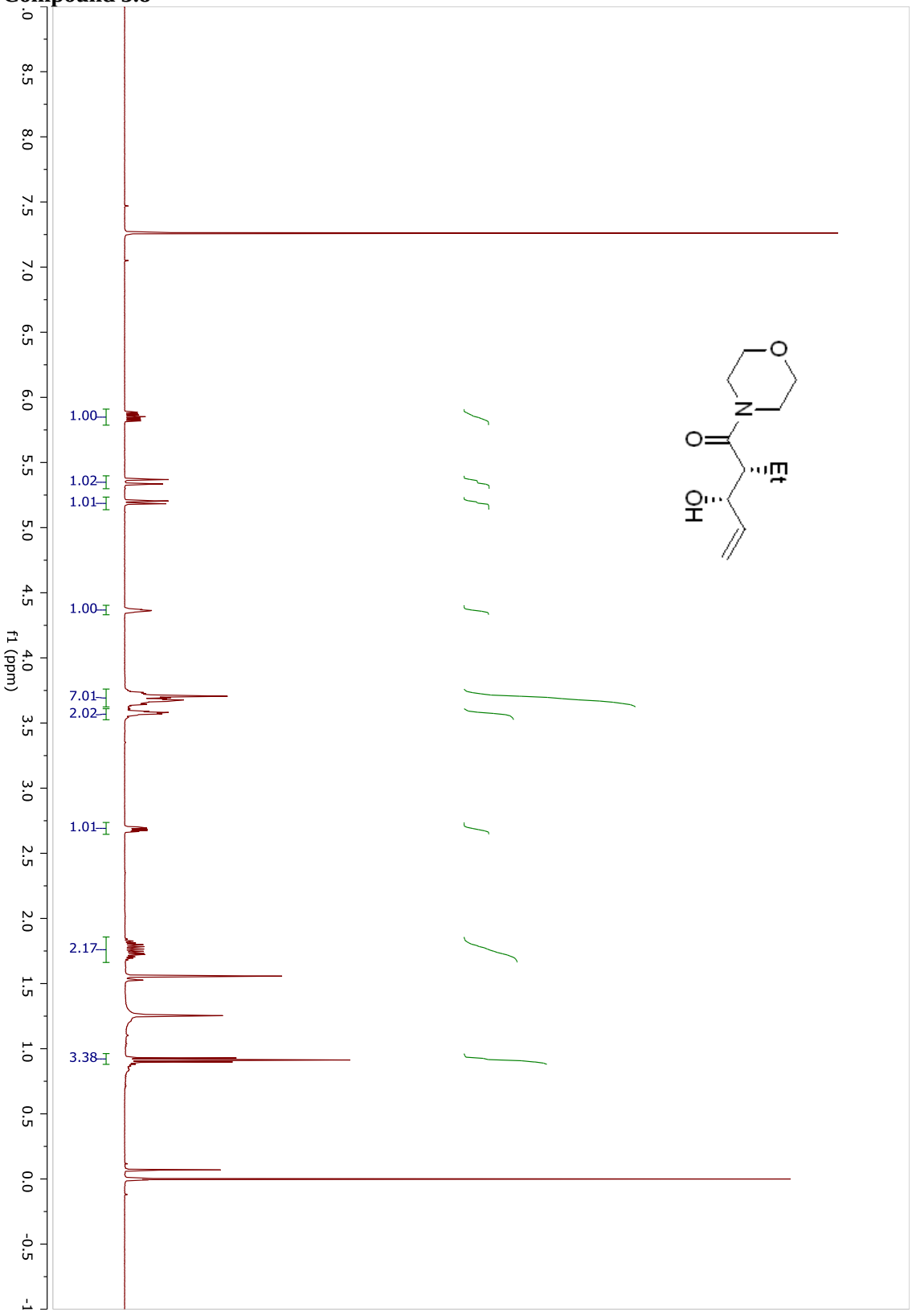
Compound 3.78. A flame dried round bottom flask with a stir bar was charged with PPh_3 (488.0 mg, 1.86 mmol, 2.50 equiv.) and **3.77** (361.4 mg, 0.744 mmol, 1.0 equiv.) in CH_2Cl_2 (10 ml). The flask was cooled to 0 ˚C before adding Et_3N (0.62 ml, 4.5 mmol, 5.8 equiv.). After 15 min, CBr_4 (691.4 mg, 2.08 mmol, 2.80 equiv.) in CH_2Cl_2 (5.0 ml) was added dropwise. The reaction was warmed to room temp after 1 hour. After 30 min, Me_2NH (3.35 ml, 2 M in THF, 6.70 mmol, 9.0 equiv.) was added and the reaction was stirred for 18 hours. The reaction was quenched with sat. NH_4Cl and the resulting aqueous layer was extracted three times with Et_2O. The combined organics were washed with brine, dried with Na_2SO_4 and the solvent was removed under reduced pressure. The crude material was dry loaded with silica (2.5 g) and purified *via* column chromatography (40 g gold column, 0 to 100% EtOAc/hexanes), yielding **3.78** (189.1 mg, 0.369 mmol, 50% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.31 (m, 4H), 7.31 – 7.27 (m, 1H), 7.25 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 6.27 (d, *J* = 6.4 Hz, 1H), 5.93 (d, *J* = 6.4 Hz, 1H), 5.03 (d, *J* = 7.1 Hz, 1H), 4.98 (d, *J* = 7.2 Hz, 1H), 4.84 (d, *J* = 7.3 Hz, 1H), 4.77 (d, *J* = 7.3 Hz, 1H), 4.72 (d, *J* = 11.5 Hz, 1H), 4.63 (d, *J* = 11.6 Hz, 1H), 4.59 (d, *J* = 11.4 Hz, 1H), 4.48 (d, *J* = 11.4 Hz, 1H), 4.39 (s, 1H), 3.80 (s, 3H), 2.77 (s, 6H), 2.11 (dq, *J* = 14.8, 7.5 Hz, 1H), 1.71 (dq, *J* = 14.6, 7.3 Hz, 1H), 1.42 (s, 3H), 1.40 (s, 3H), 0.93 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.30, 157.99, 138.17, 137.38, 131.61, 130.27, 129.58, 128.57, 128.09, 127.85, 113.94, 92.84, 90.71, 90.14, 90.09, 71.89, 70.30, 68.92, 55.44, 36.35, 28.72, 23.06, 16.06, 9.25. HRMS (ESI) *m/z* calculated $C_{29}H_{40}N_2O_6$ $[M+Na]^+$ 535.2779, found 535.2779.

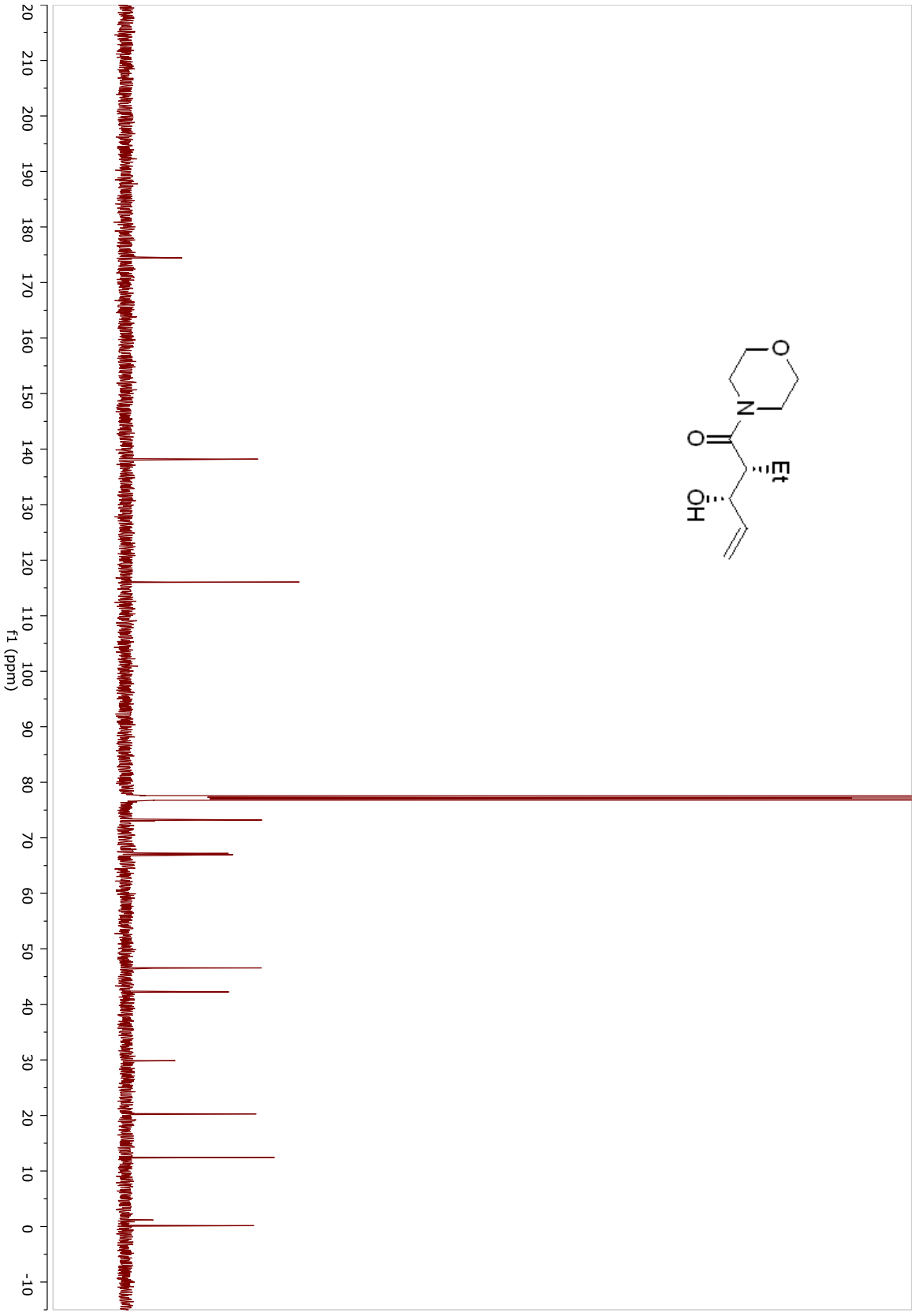


Compound 3.79. A round bottom flask with a stir bar was charged with **3.78** (20.0 mg, 0.0390 mmol, 1.0 equiv.), CH_2Cl_2 (0.56 ml), *t*-BuOH (0.06 ml) and pH 7 buffer (0.06 ml, 0.2 M sodium phosphate buffer). DDQ (14.0 mg, 0.0617 mmol, 1.6 equiv.) was added with vigorous stirring. An NMR aliquot after 3 hours showed complete conversion of the starting material. The reaction was diluted with Et_2O and filtered through celite. The filtrate was washed with 5 ml of sat. $NaHCO_3$ and 10 ml of brine. The aqueous layer was extracted three times with Et_2O. The combined organics were dried with Na_2SO_4 and the solvent was removed under reduced pressure. The crude material was purified *via* column chromatography (0 to 40% EtOAc/hexanes in 20% increments, then 40 to 100% EtOAc/hexanes in 10% increments), yielding **3.79** (9.0 mg, 0.025 mmol, 64% yield) as a thin film. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.27 (m, 5H), 5.90 (d, *J* = 6.1 Hz, 1H), 5.80 (d, *J* = 6.1 Hz, 1H), 4.99 (d, *J* = 7.4 Hz, 1H), 4.89 (d, *J* = 7.3 Hz, 1H), 4.69 – 4.58 (m, 3H), 4.34 (s, 1H), 2.85 (s, 6H), 1.87 – 1.75 (m, 2H), 1.38 (s, 3H), 1.34 (s, 3H), 1.01 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.06, 138.14, 137.12, 133.03, 128.57, 127.90, 127.83, 91.50, 90.77, 84.63, 77.16, 72.66, 70.35, 36.44, 29.29, 22.63, 14.52, 9.33. HRMS (ESI) *m/z* calculated for $C_{20}H_{30}N_2O_4$ $[M+H]^+$ 363.2278, found 363.2274.

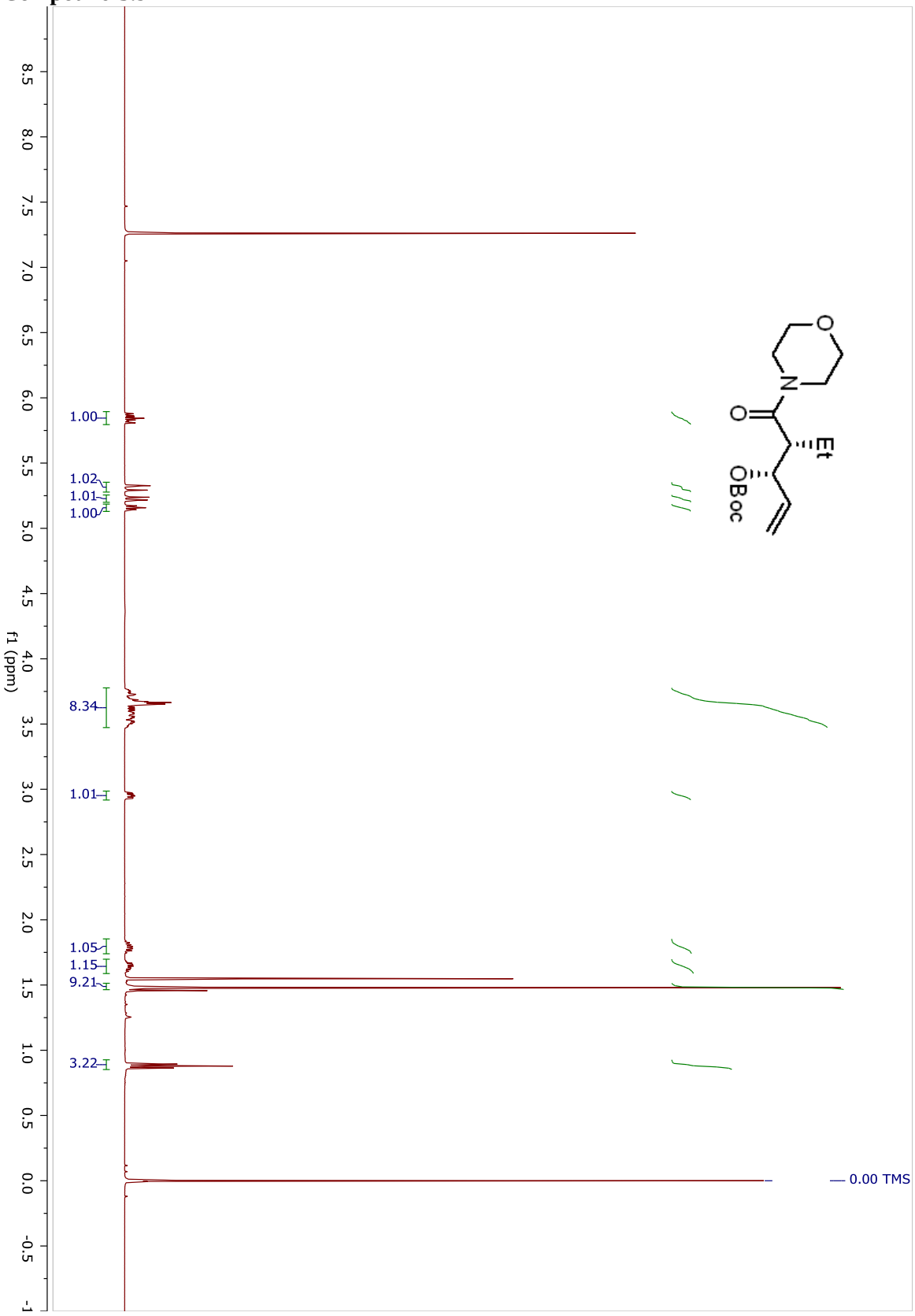
3.7 Spectra

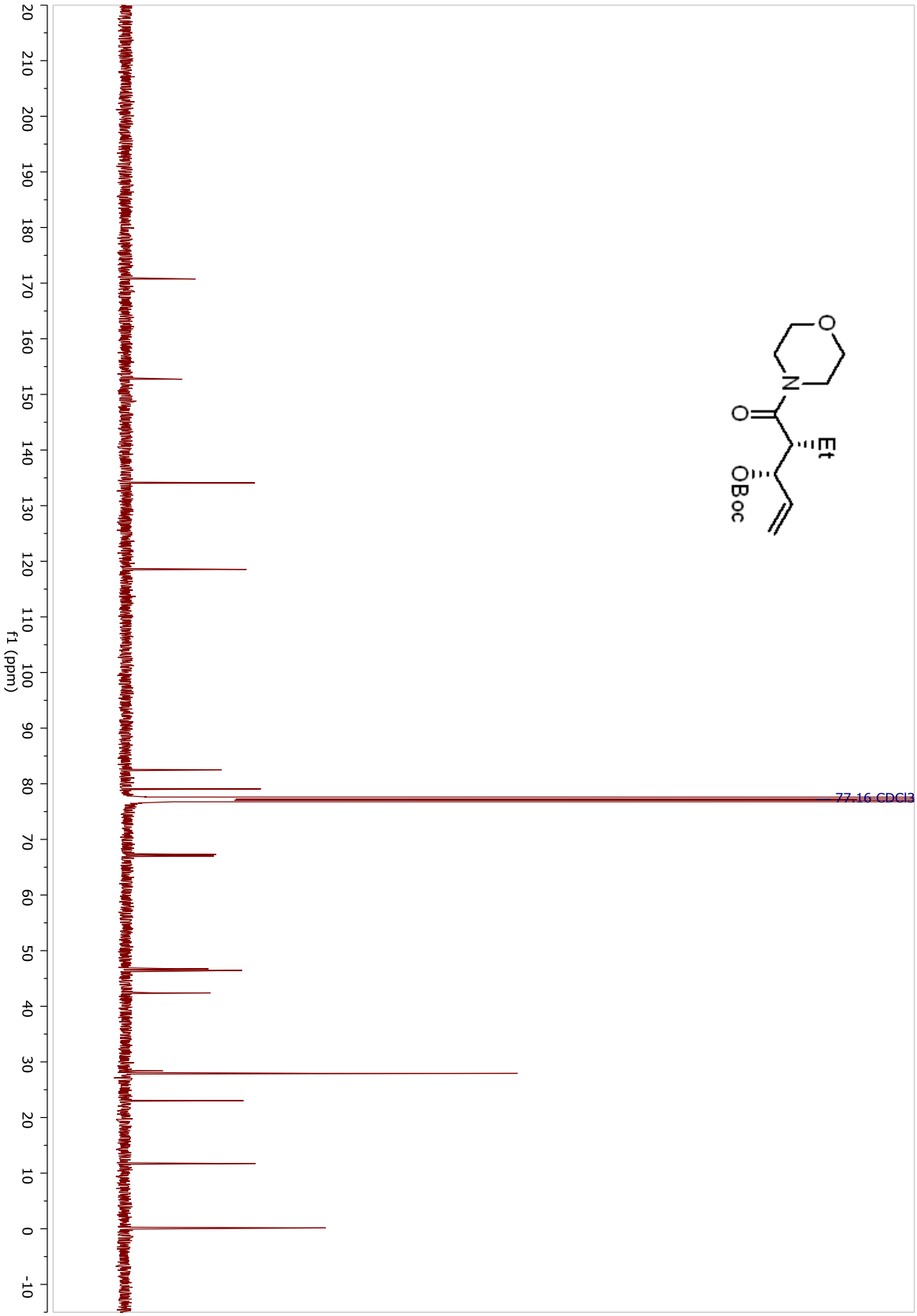
Compound 3.8



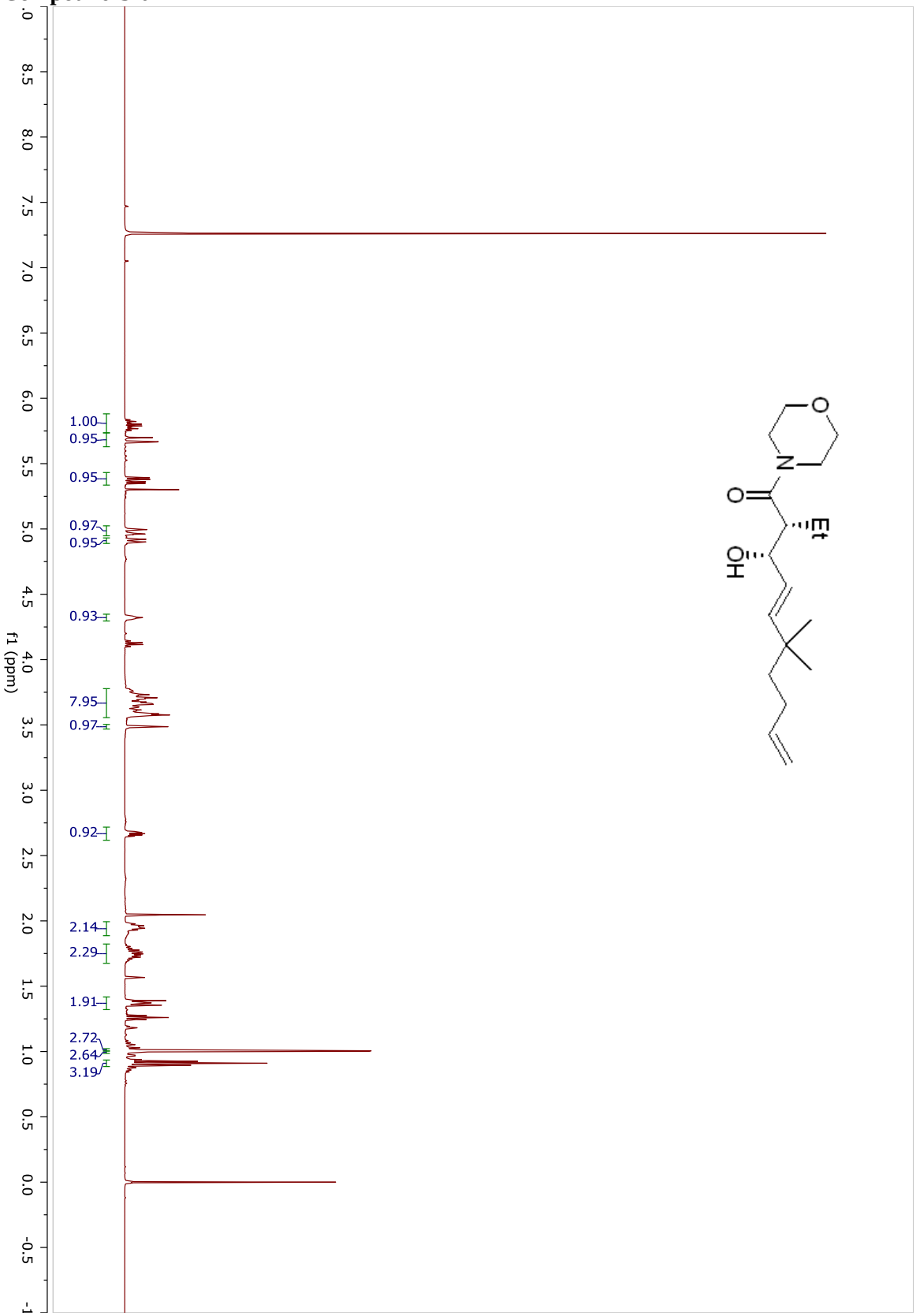

O
N
O
Et
OH
20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

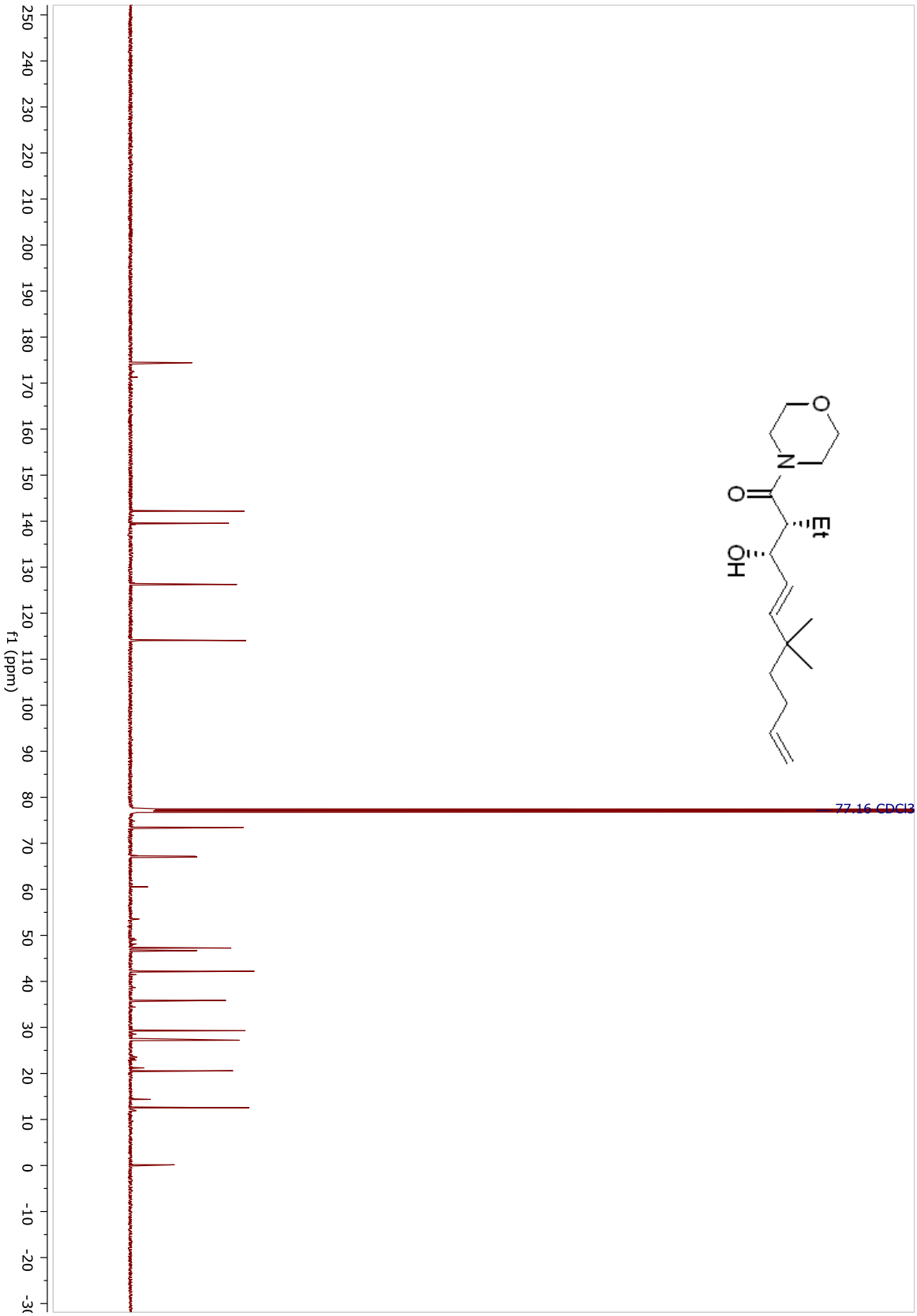
Compound 3.9



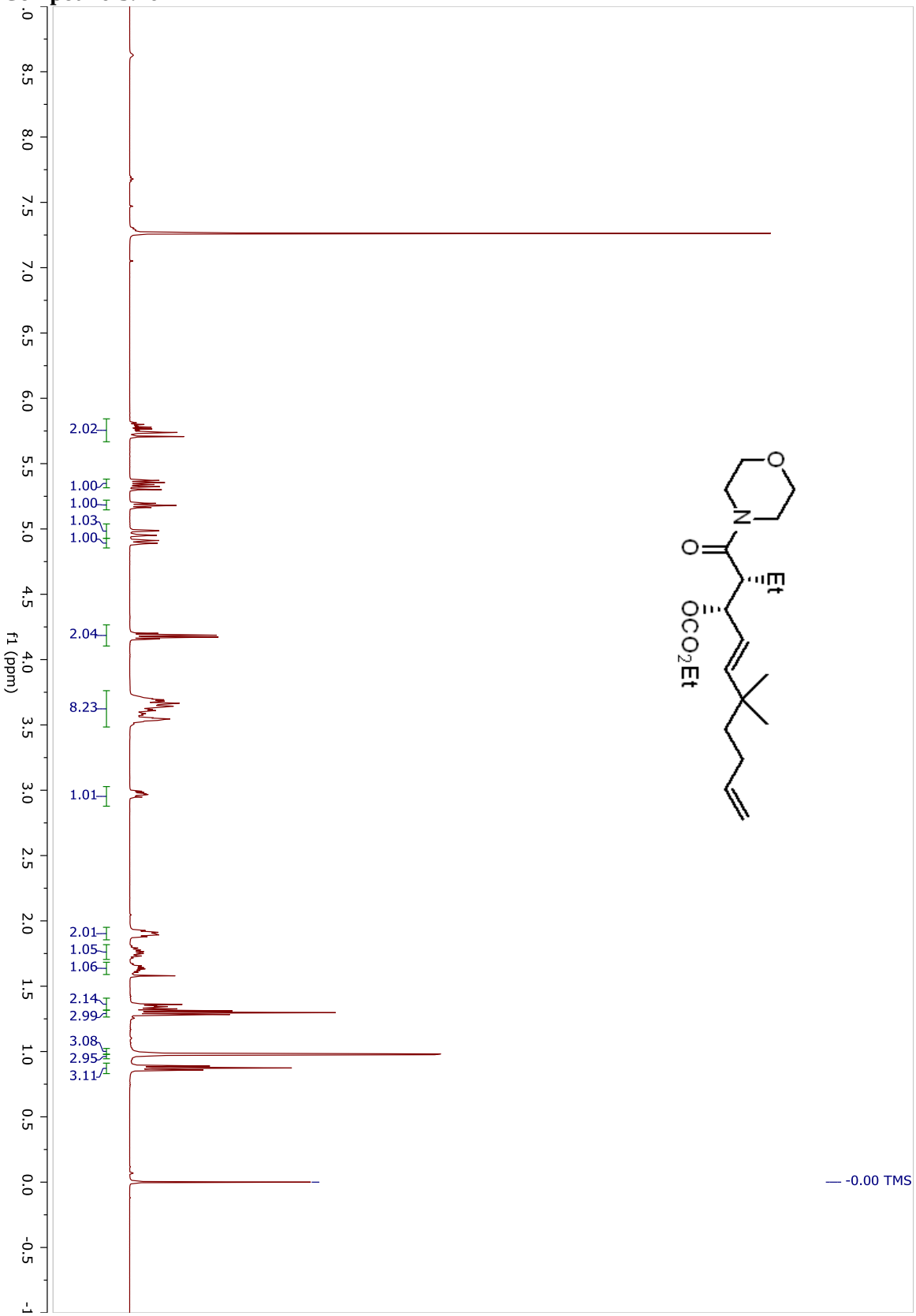

77.16 CDCl3
f1 (ppm)
20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
O
N
O
Et
OBoc

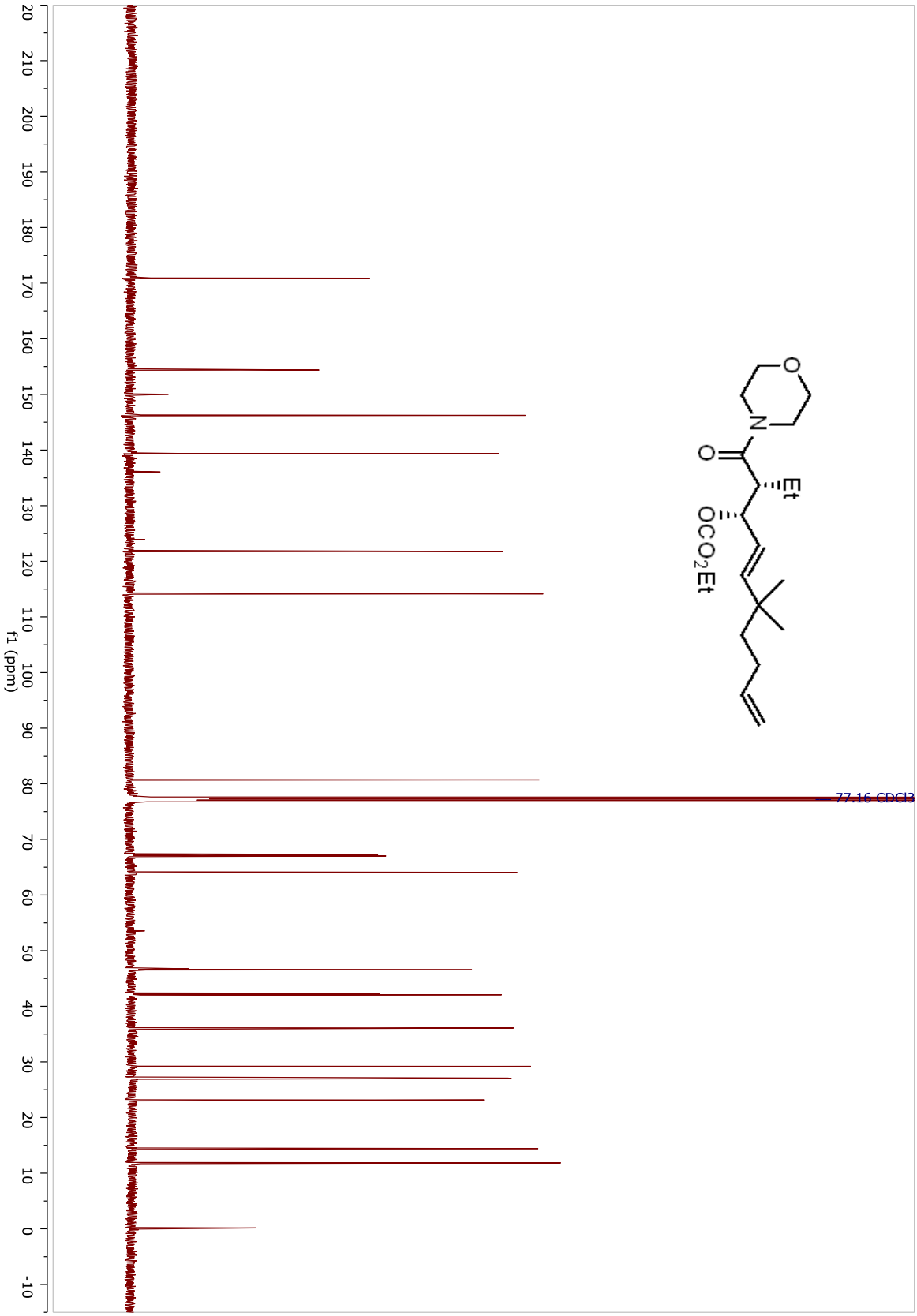
Compound S-01



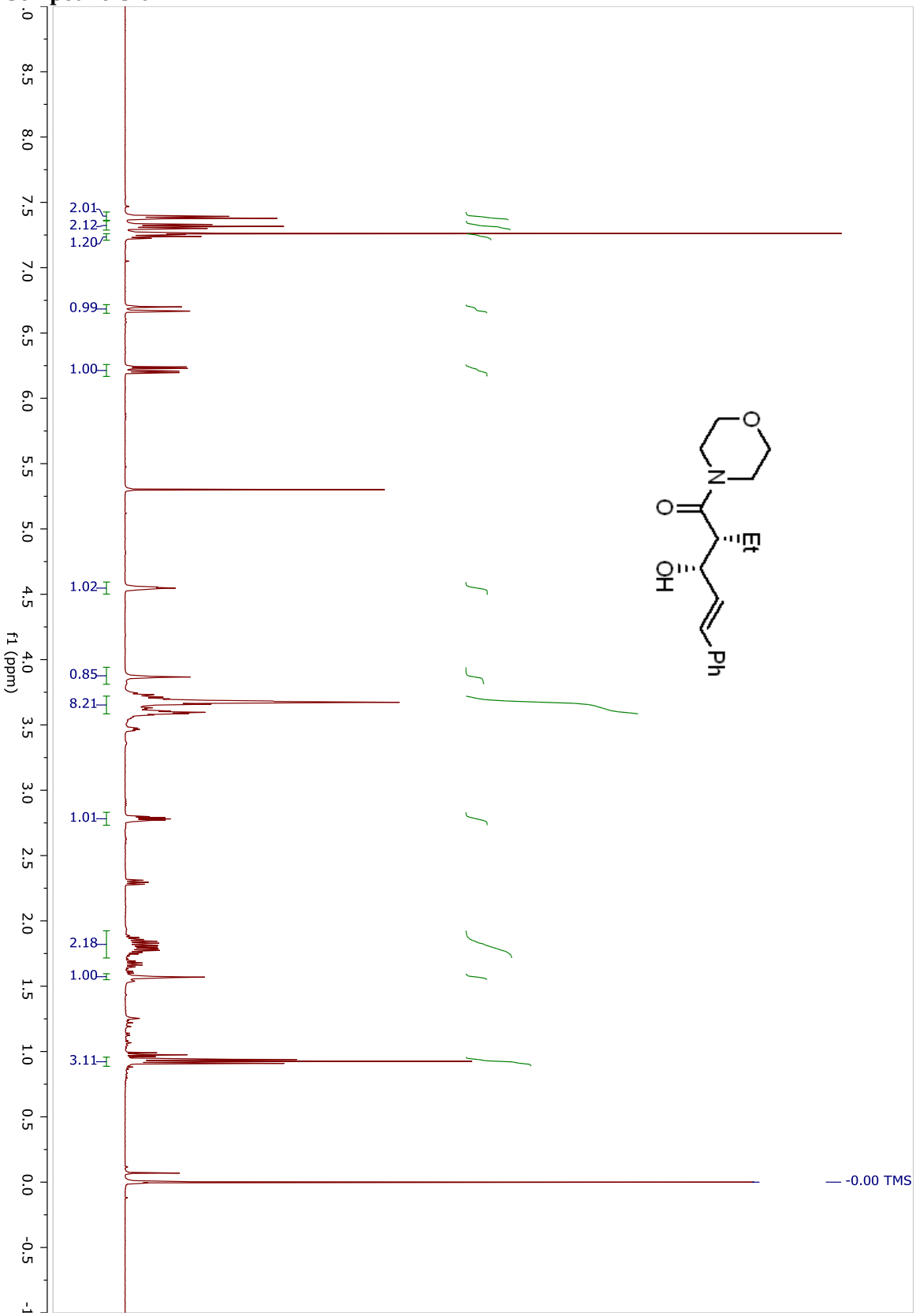

77.16 CDCl3
f1 (ppm)
250 240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30
O
N
O
Et
OH

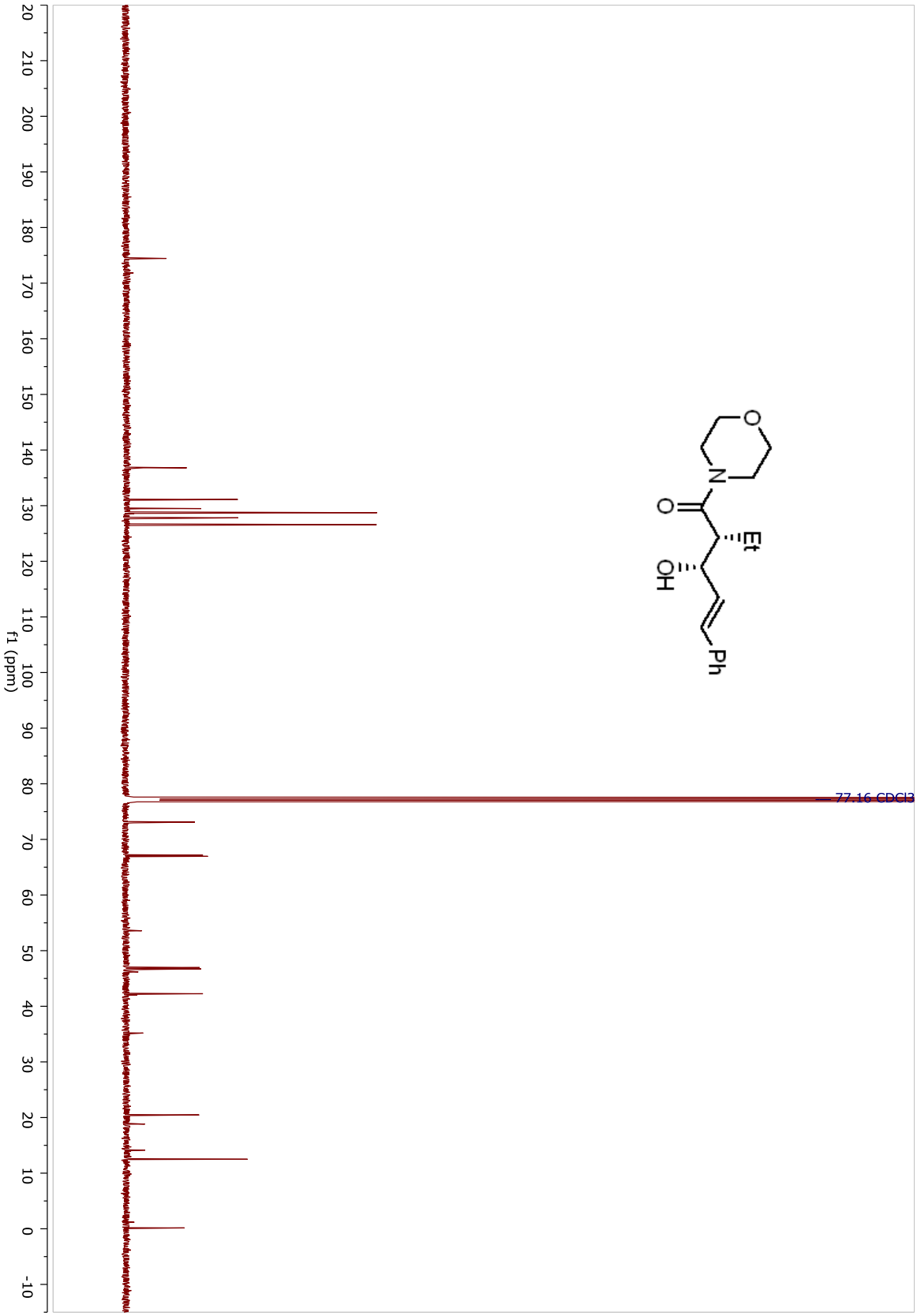
Compound 3.16



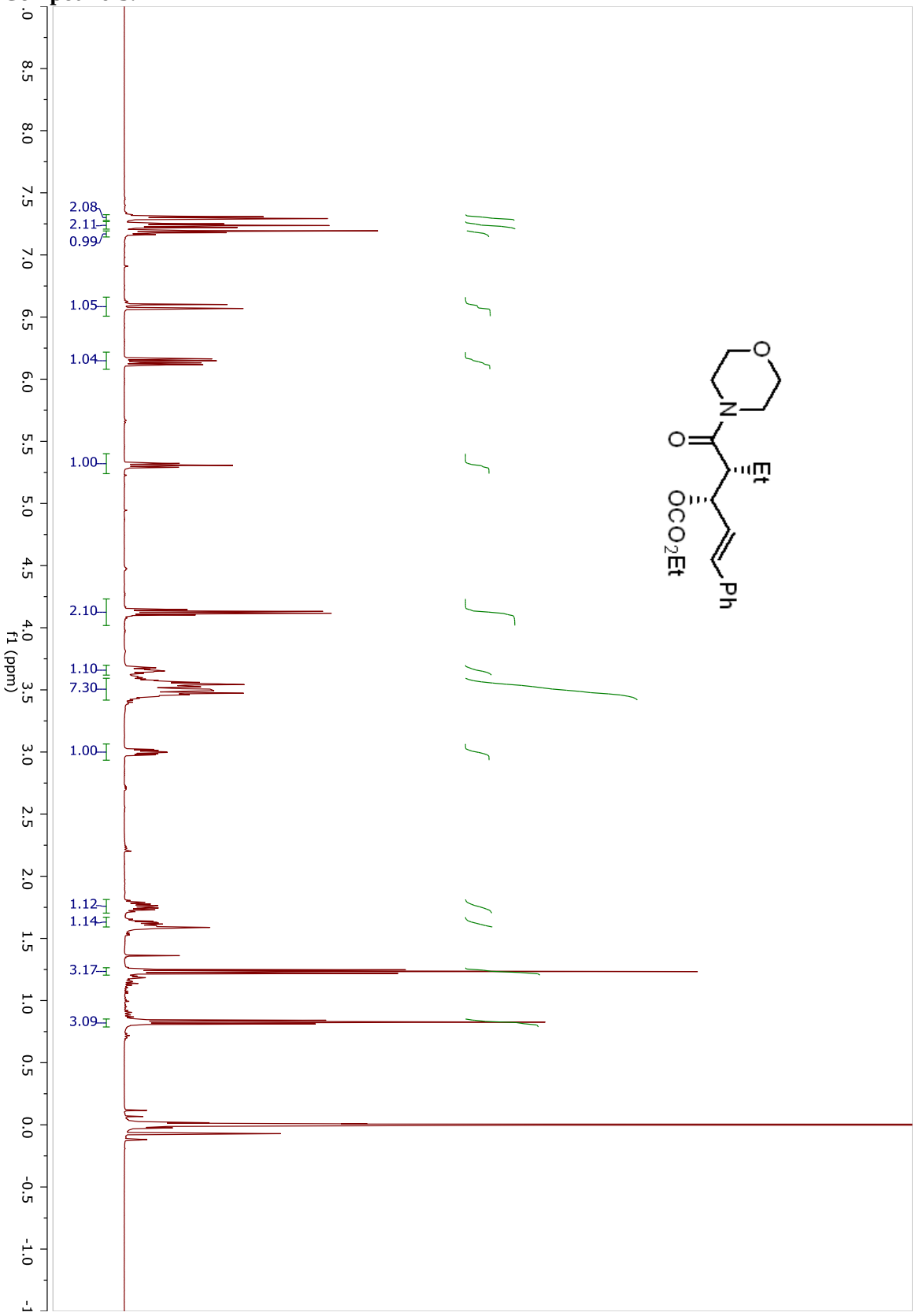

77.16 CDCl3
f1 (ppm)
20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
O
N
O
Et
OCO2Et

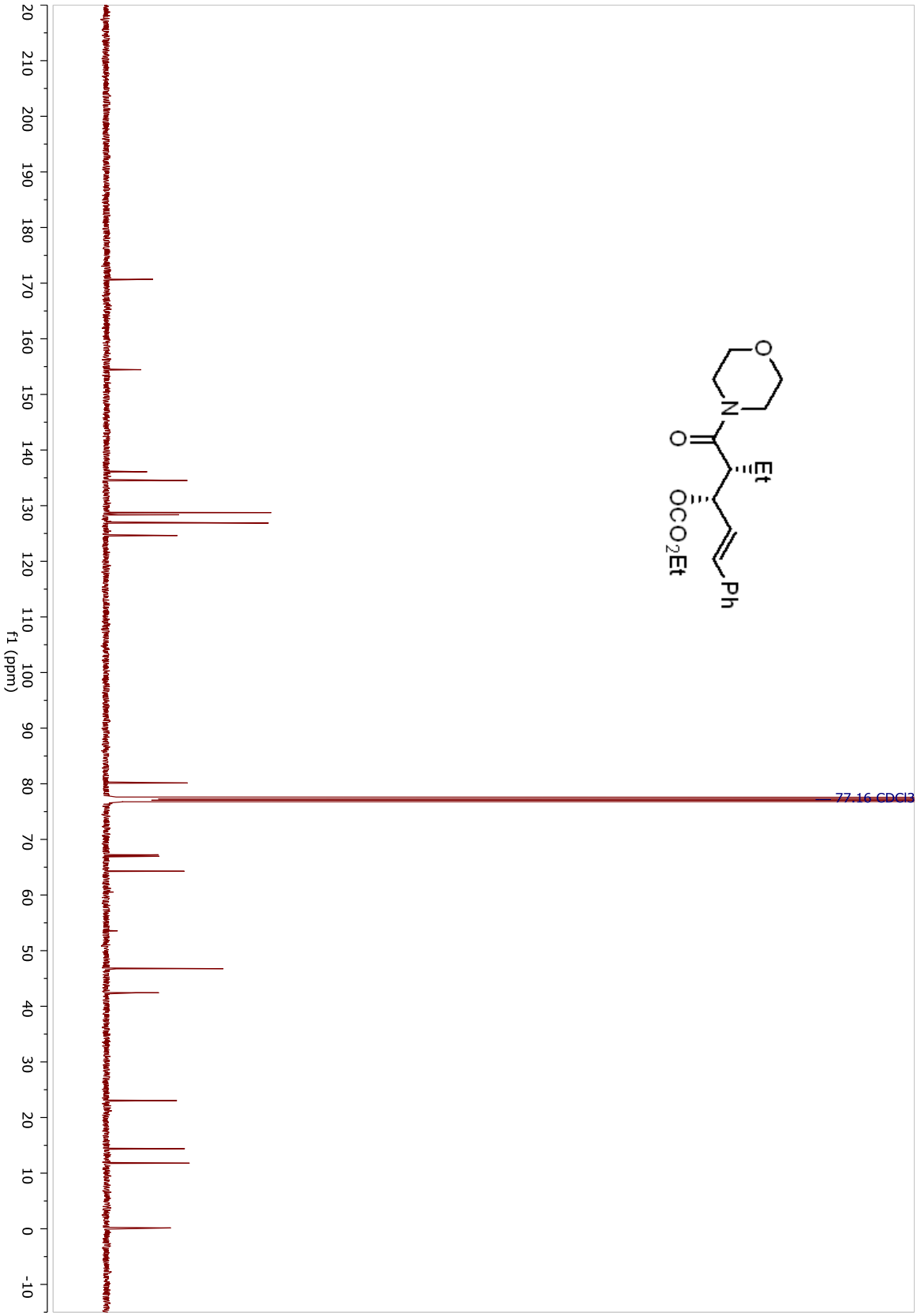
Compound S-02



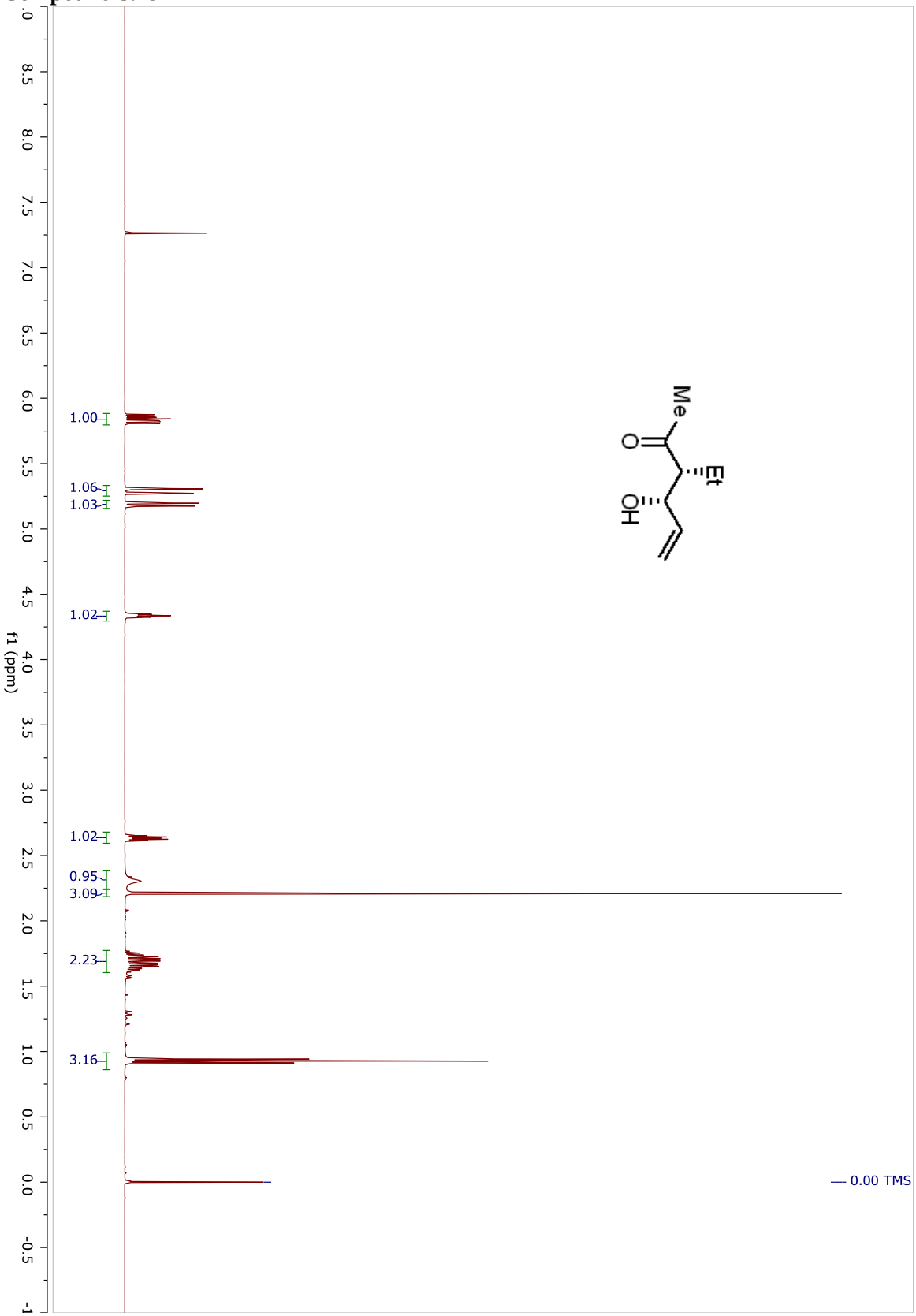

77.16 CDCl3
f1 (ppm)
20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
O
N
O
Et
OH
Ph

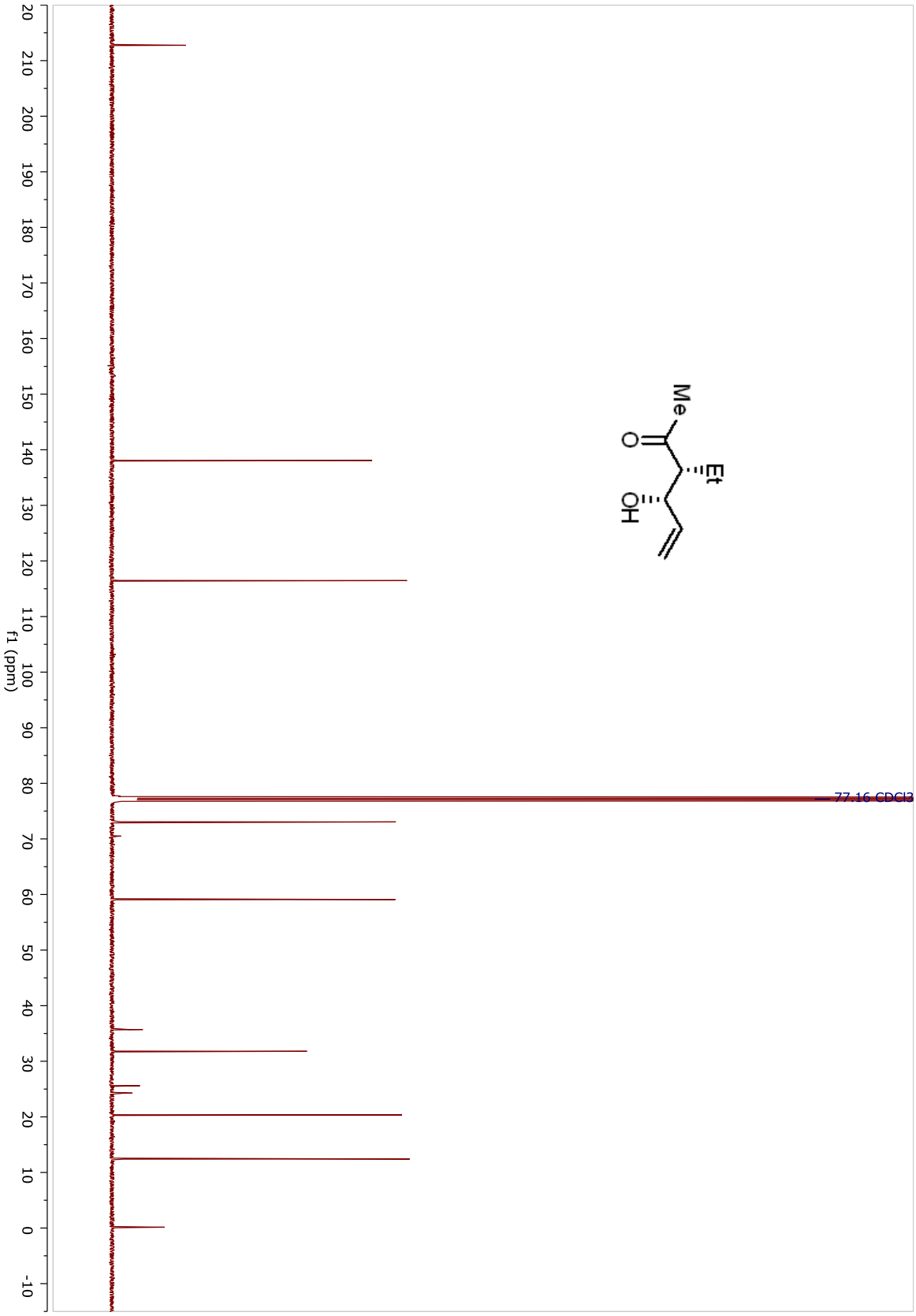
Compound 3.17



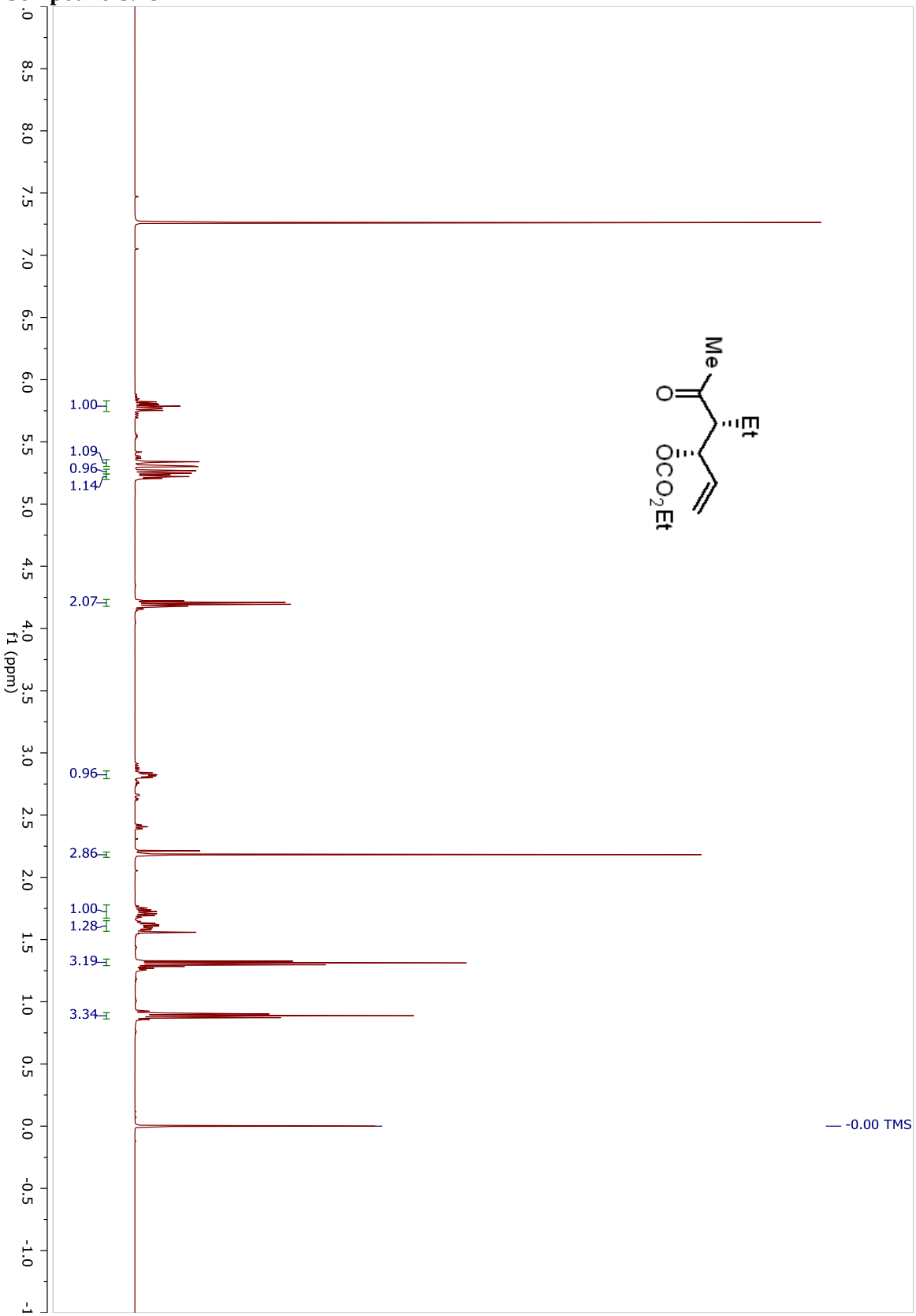

77.16 CDCl3
f1 (ppm)
20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
O
N
O
Et
OCO2Et
Ph

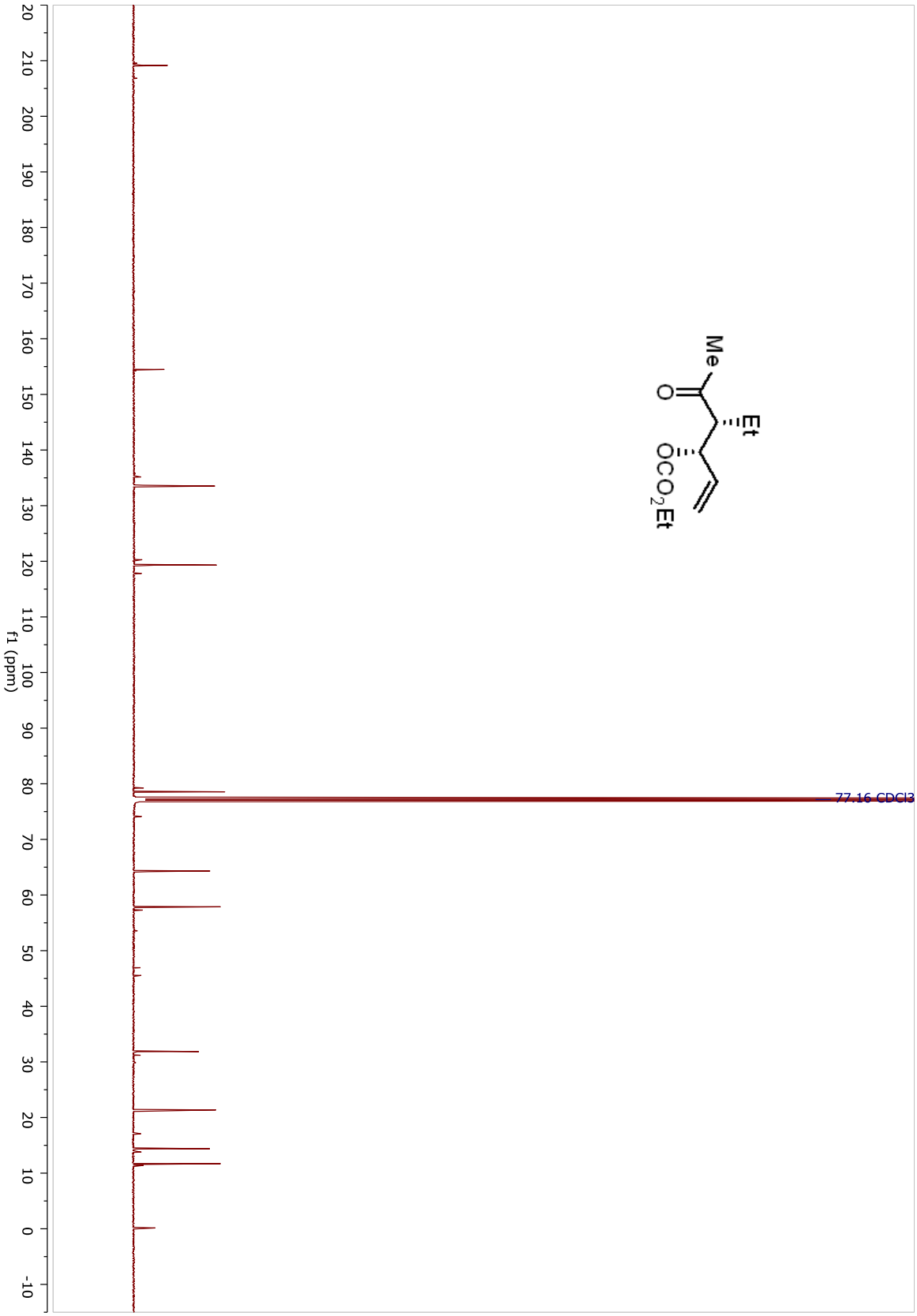
Compound 3.29



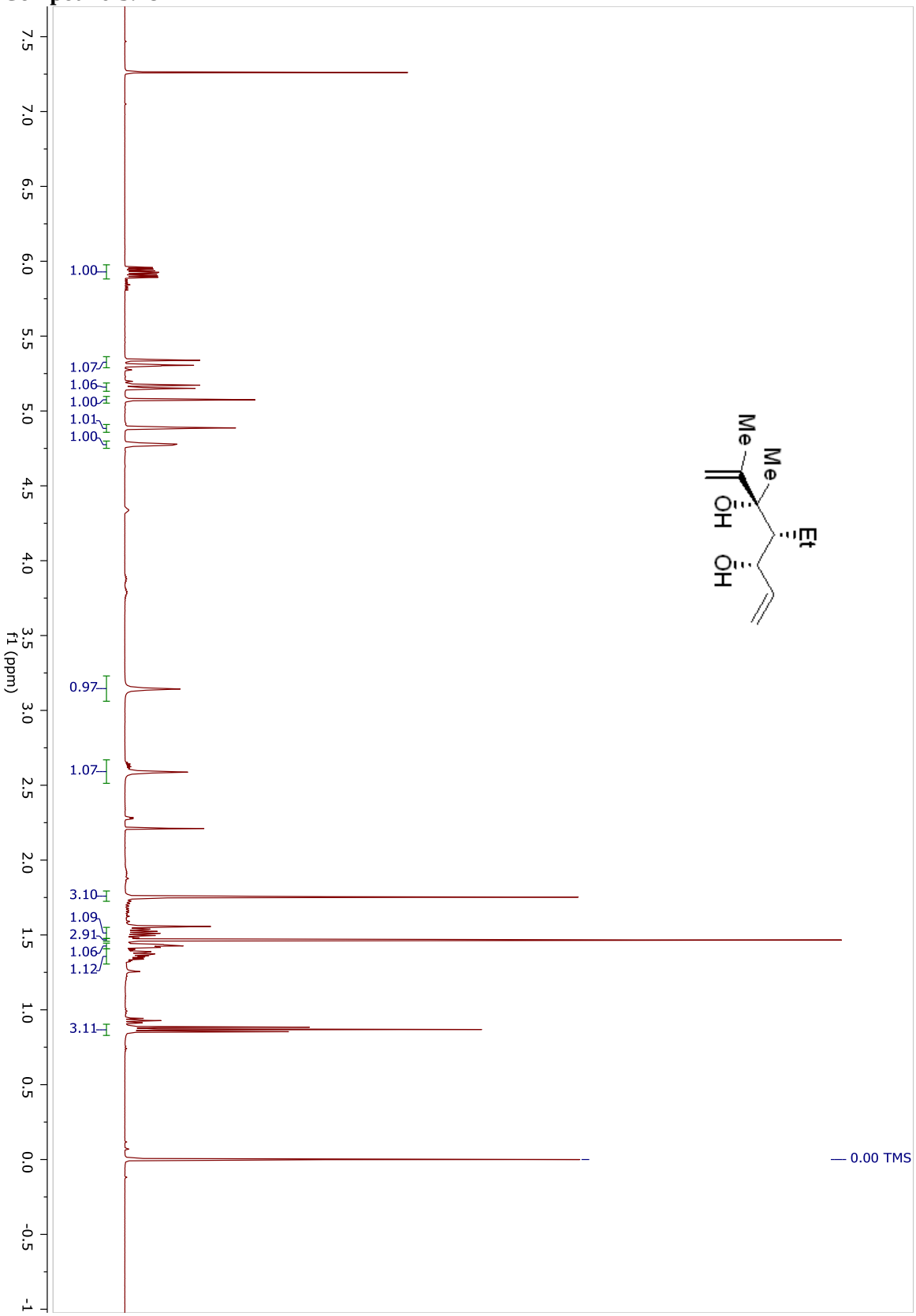

Me
O
Et
OH
77.16 CDCl3
f1 (ppm)
20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

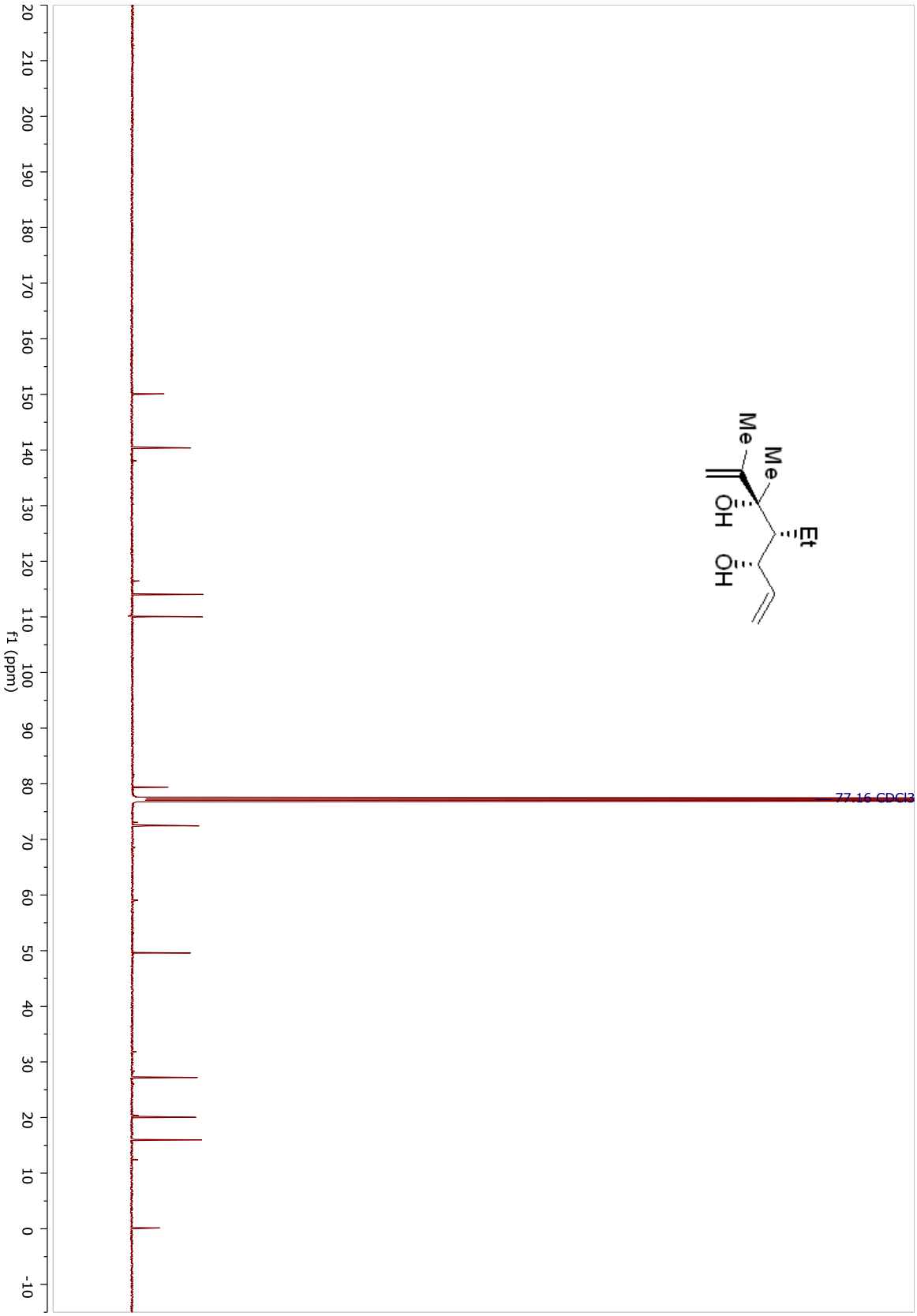
Compound 3.18



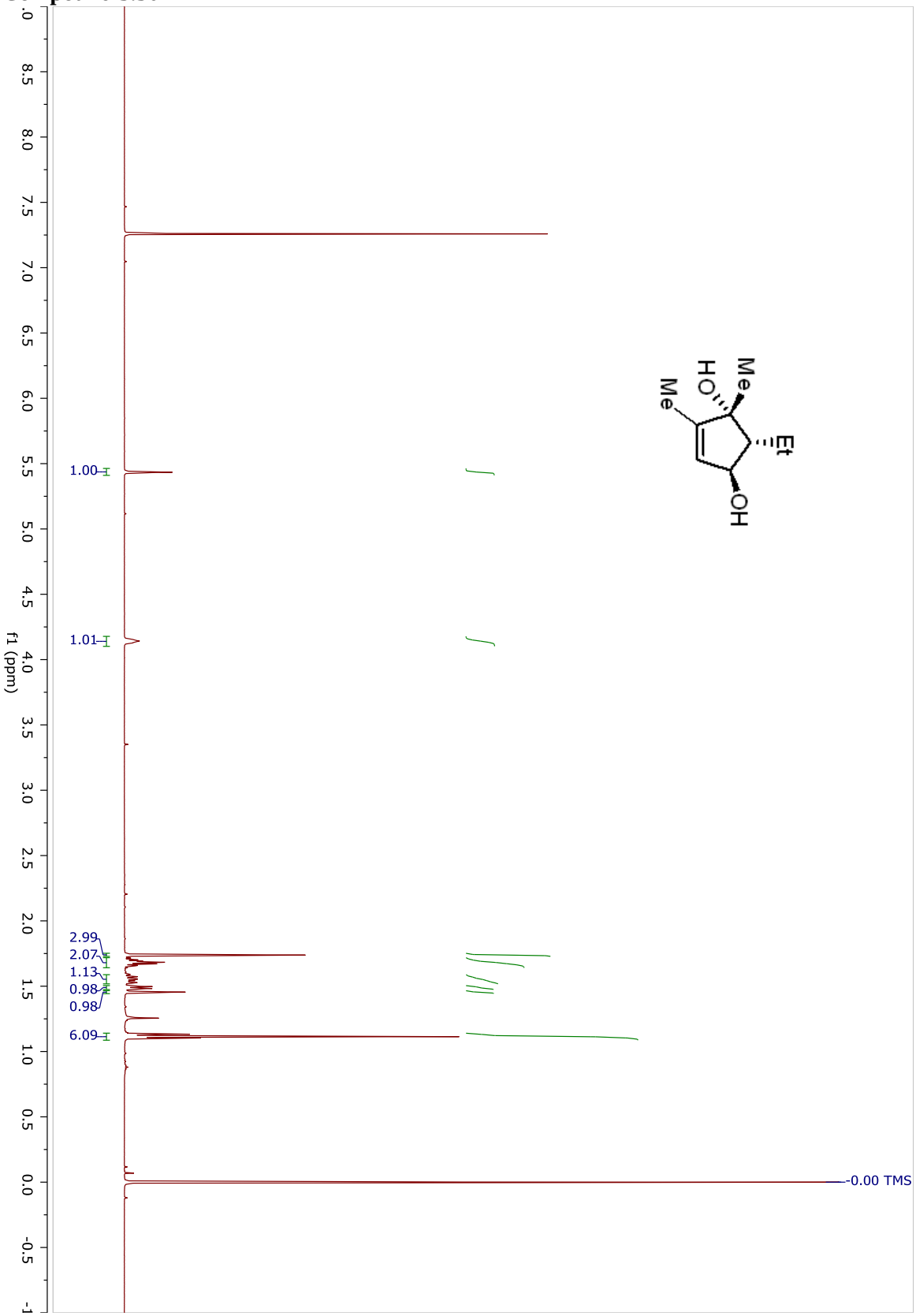

Me
Et
O
OCO2Et
77.16 CDCl3
f1 (ppm)
20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

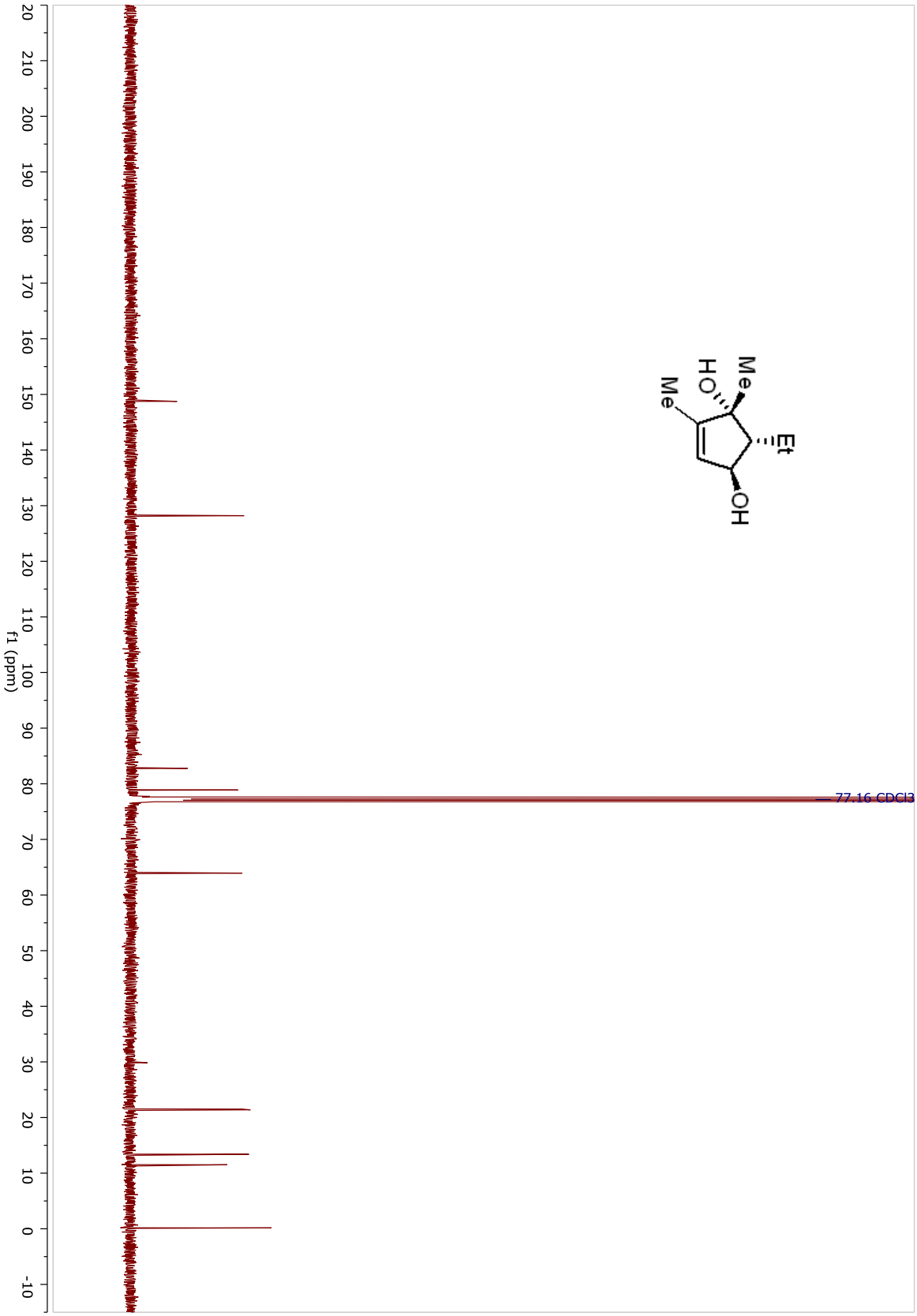
Compound 3.28



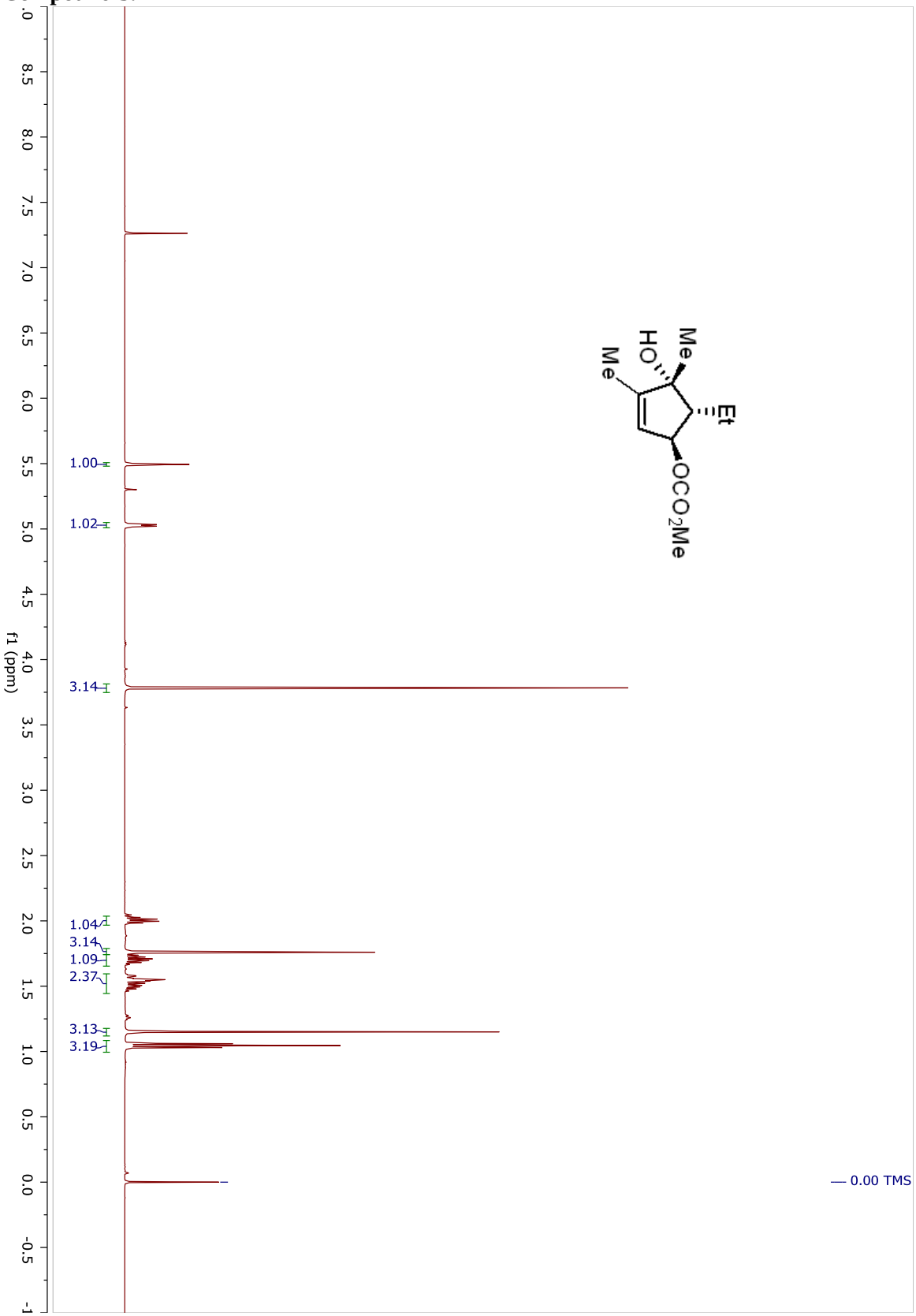

Me
Me
OH
OH
Et
77.16 CDCl3
f1 (ppm)
20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

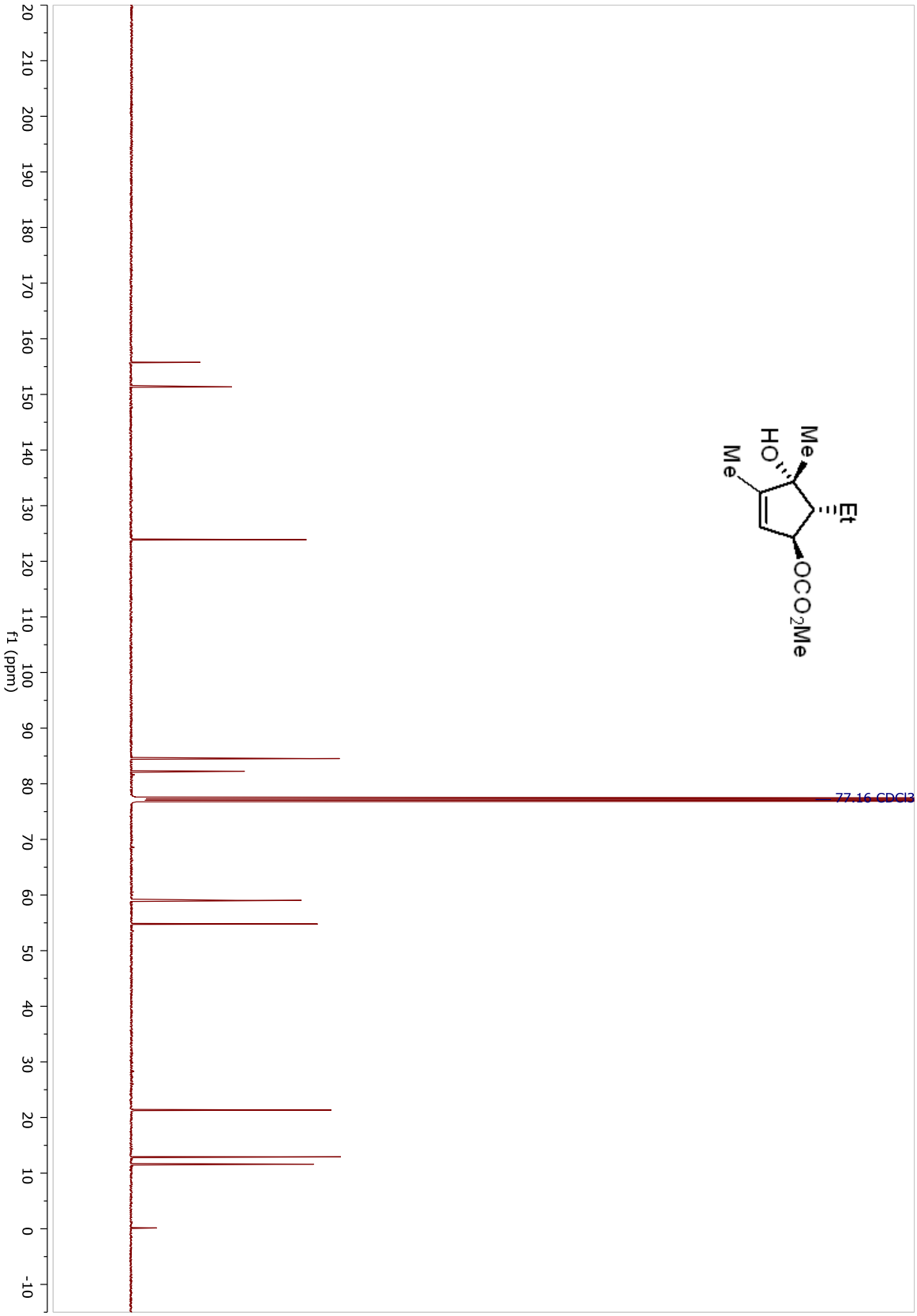
Compound 3.30



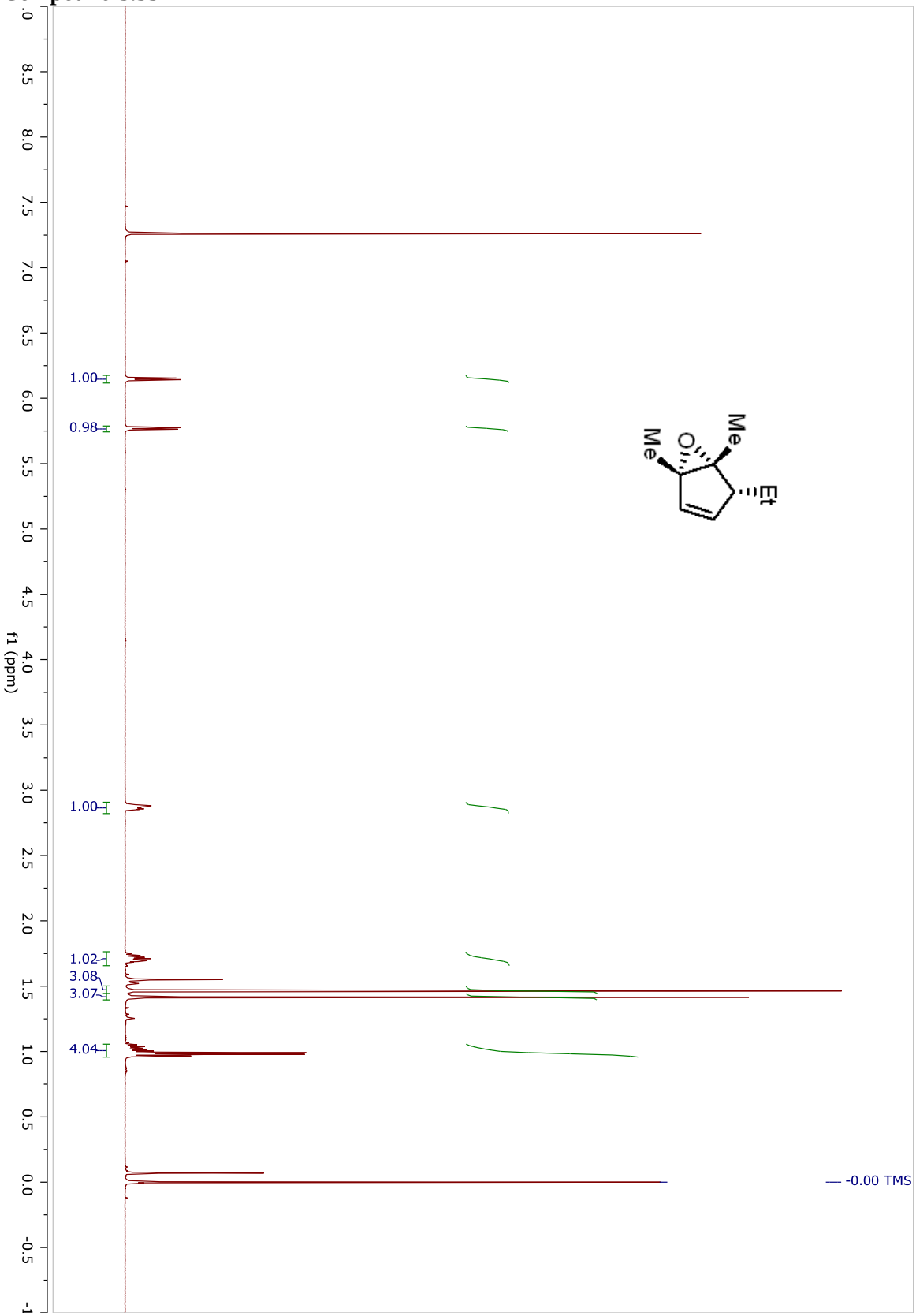

Me
HO
Me
Et
OH
77.16 CDCl3
f1 (ppm)
20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

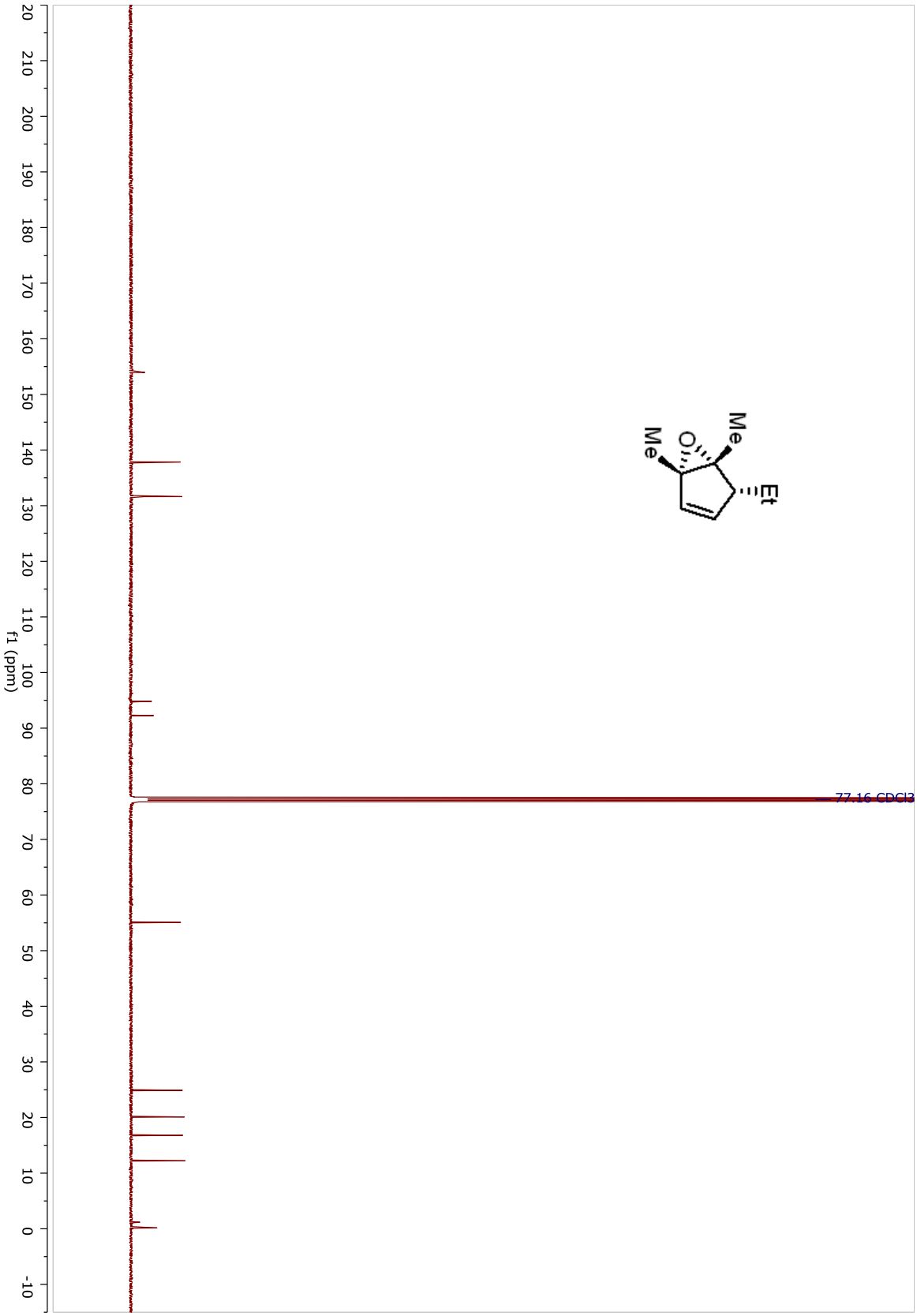
Compound 3.27



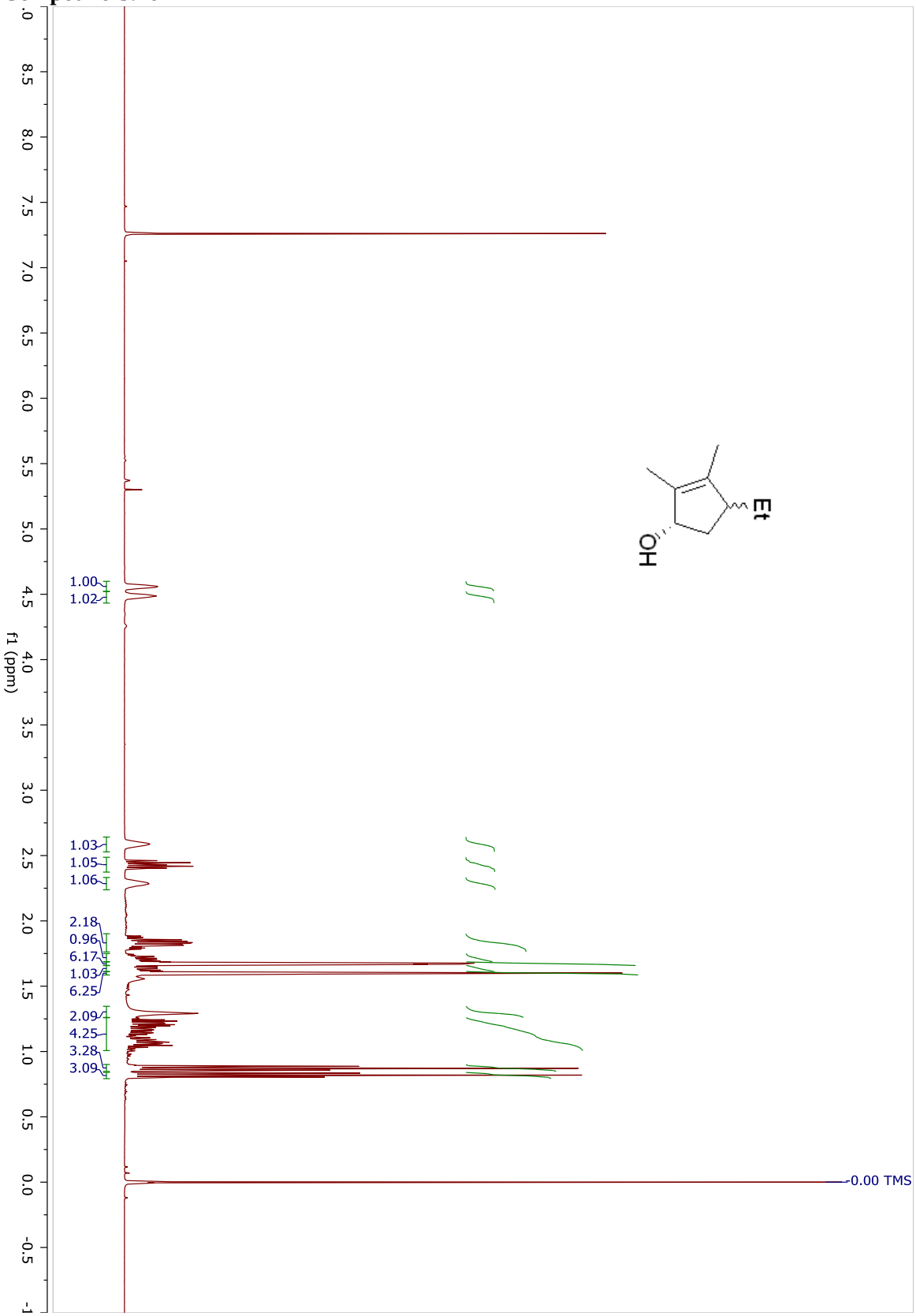

Me
HO
Me
Et
OCO2Me
77.16 CDCl3
f1 (ppm)
20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

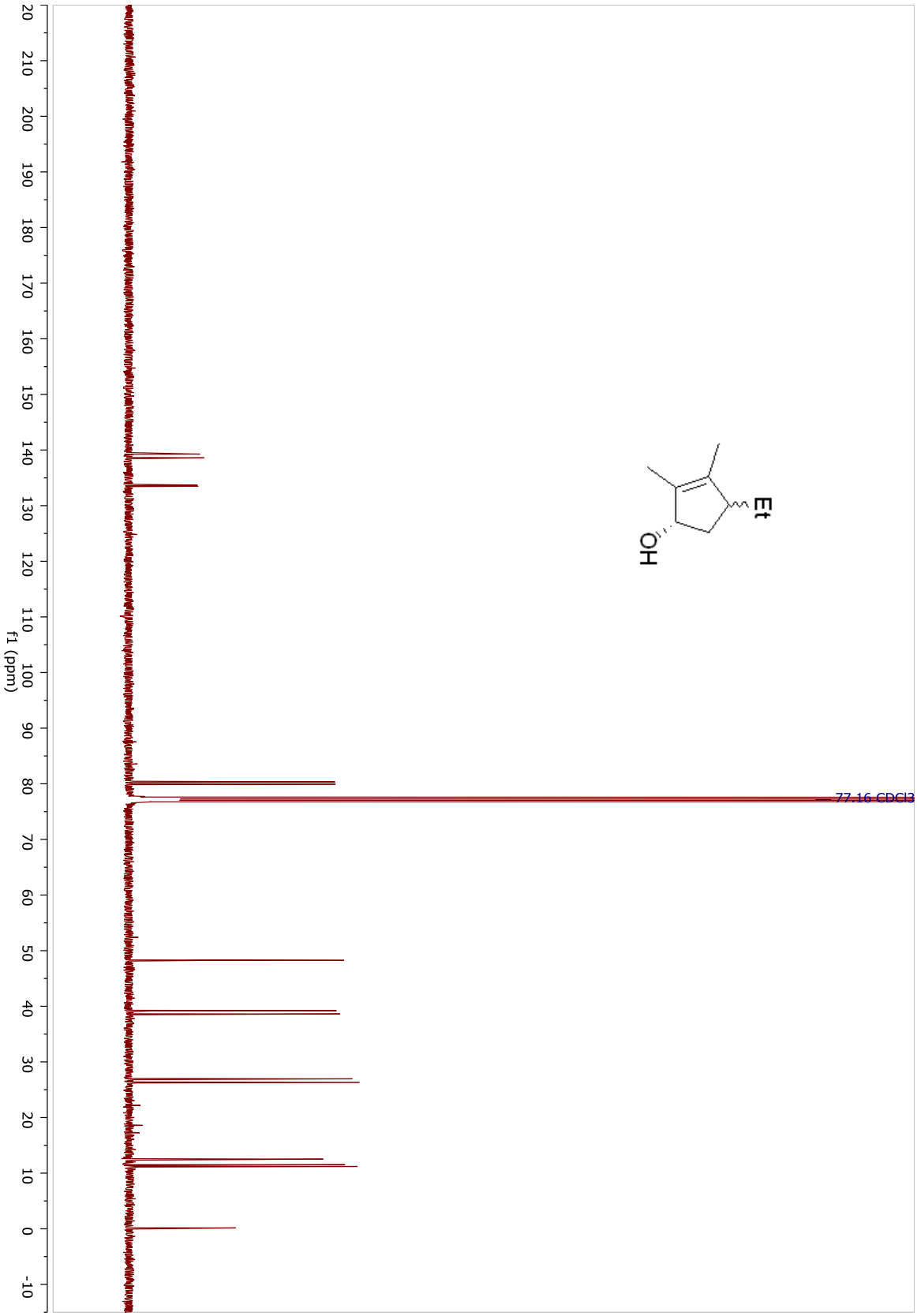
Compound 3.33

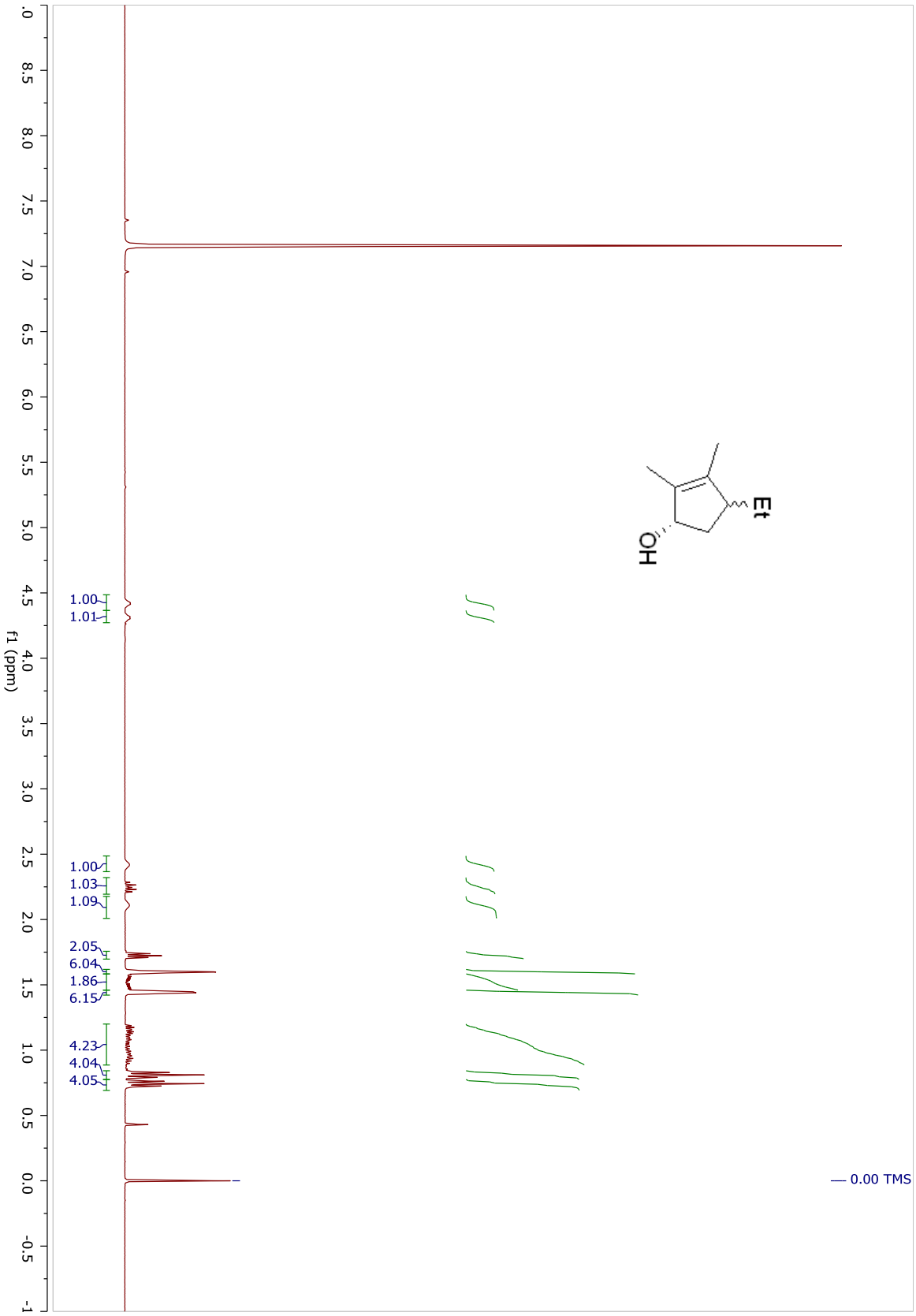



Me
O
Me
Et
77.16 CDCl3
f1 (ppm)
20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

Compound 3.46




Et
OH
77.16 CDCl3
f1 (ppm)
20
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)
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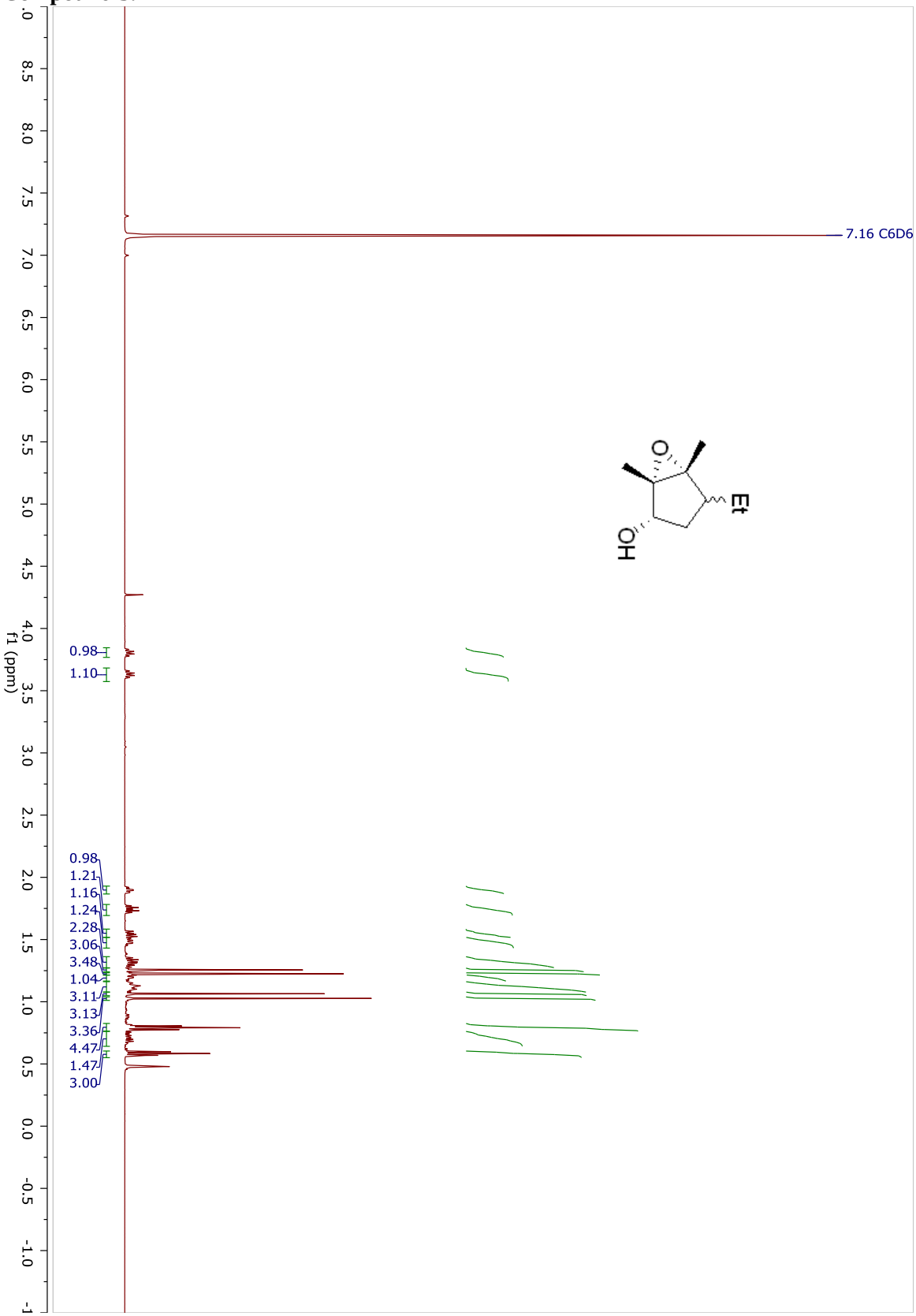
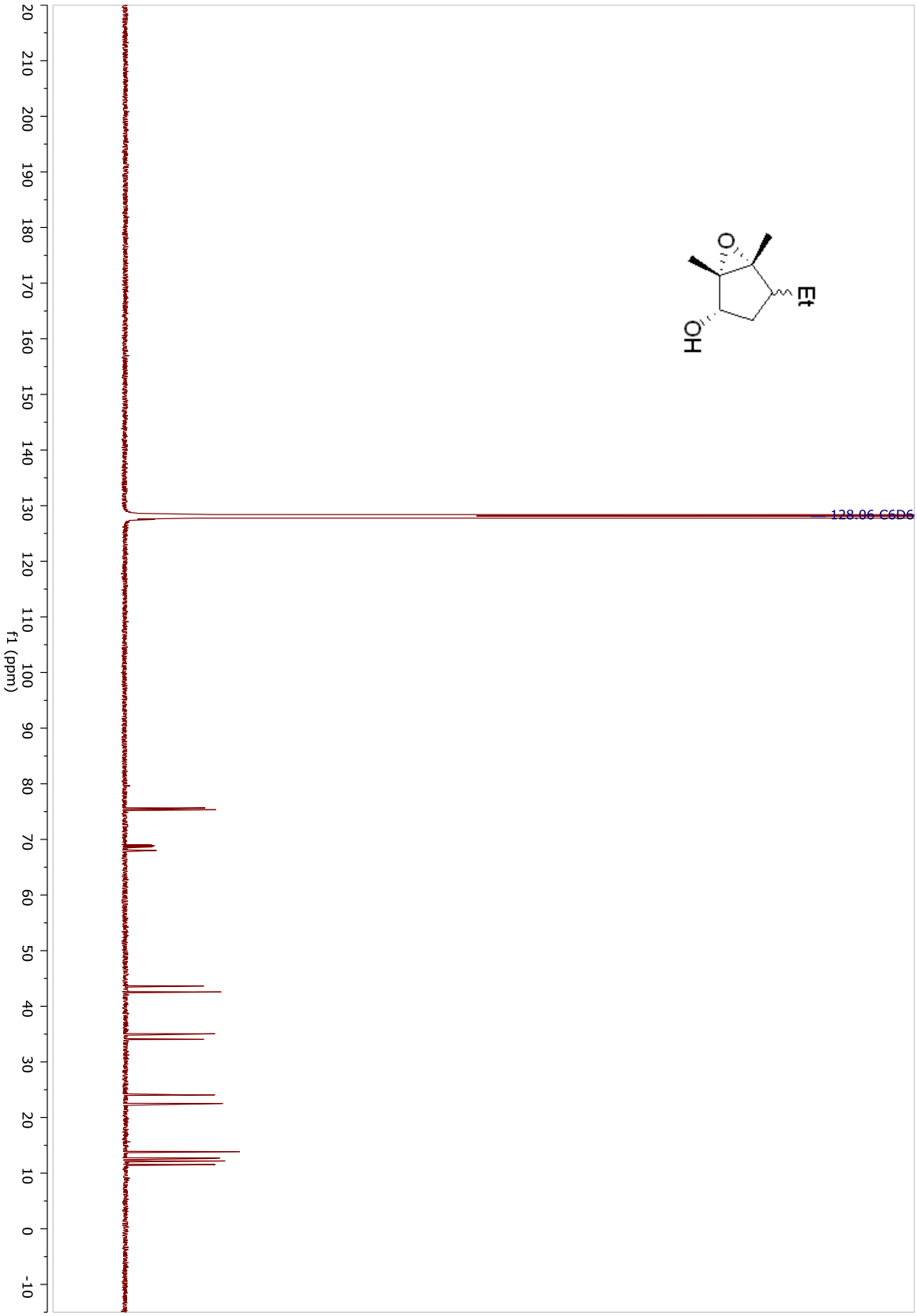
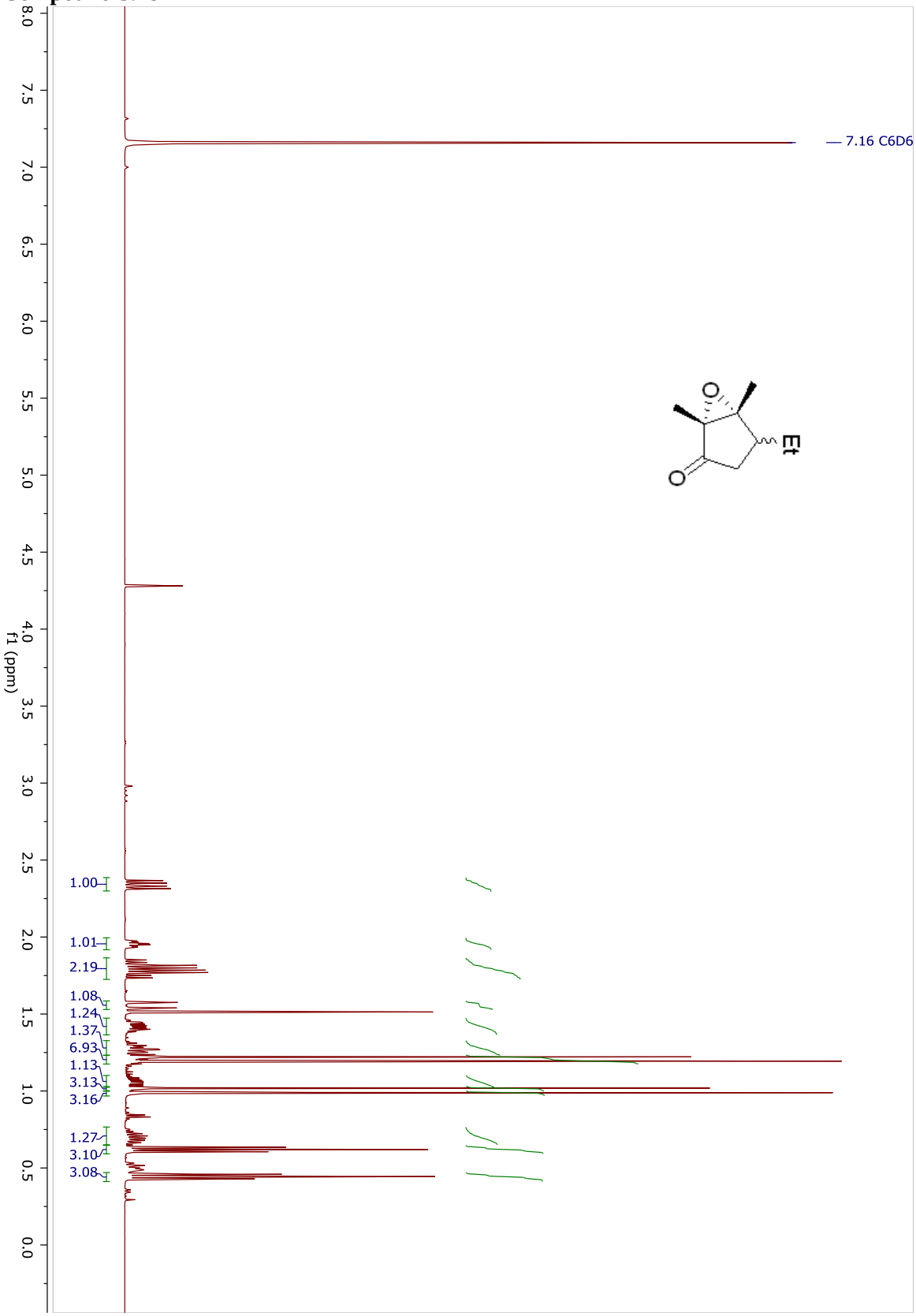
1.01
1.00
1.03
1.09
2.05
6.04
1.86
6.15
4.23
4.04
4.05
0.00 TMS
Et
OH

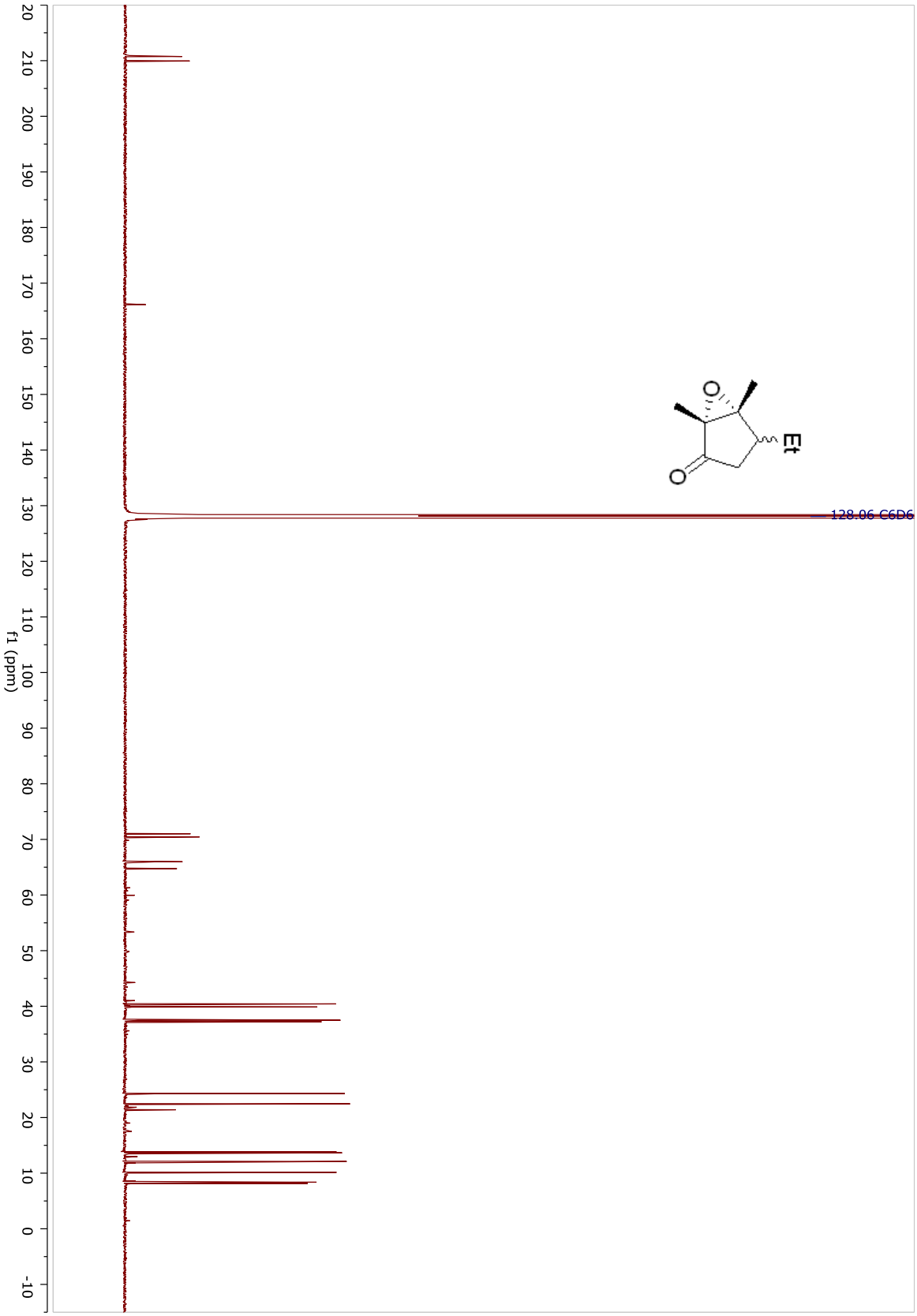
Compound 3.47



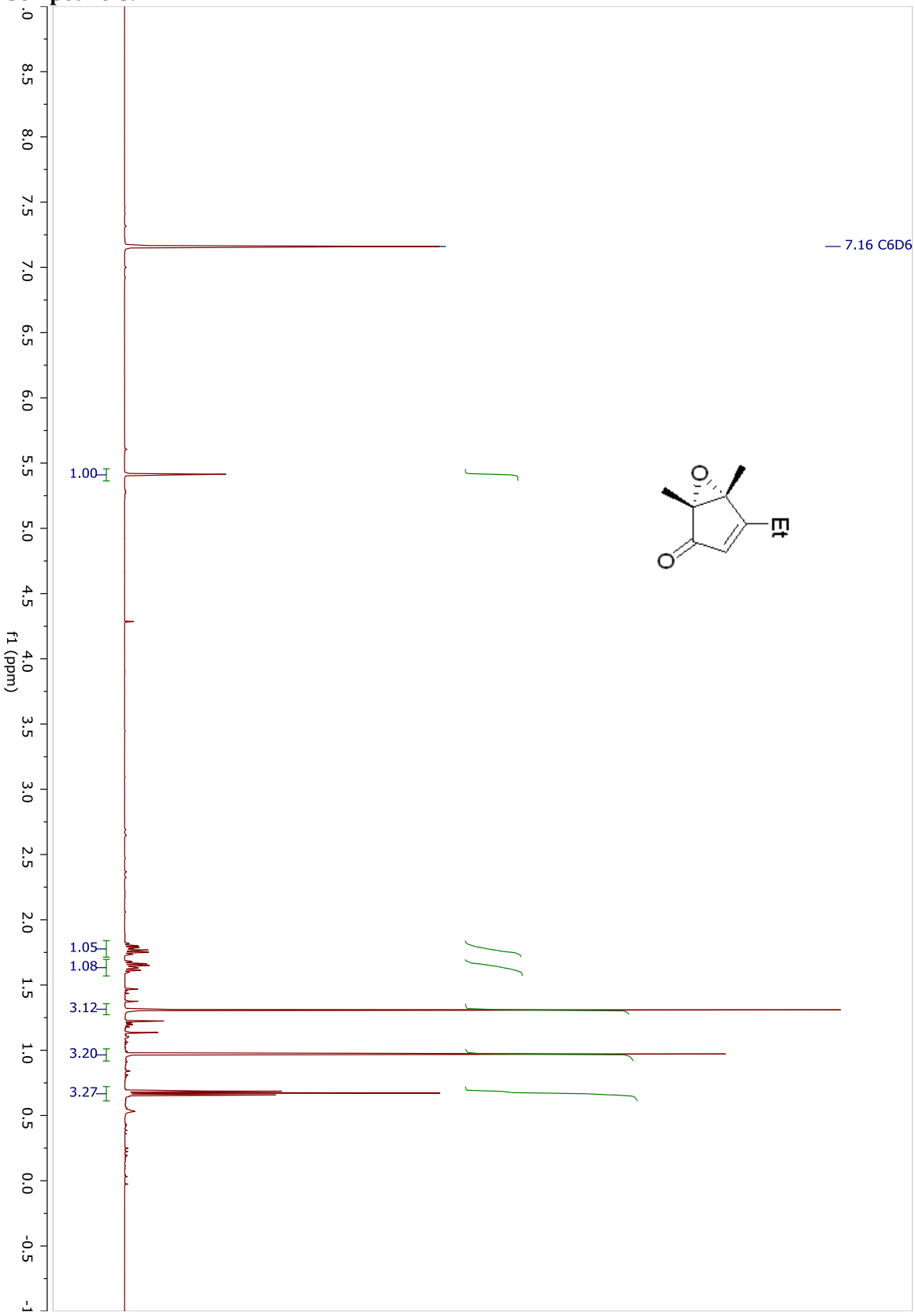

128.06 C6D6
Et
OH
O
f1 (ppm)
20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

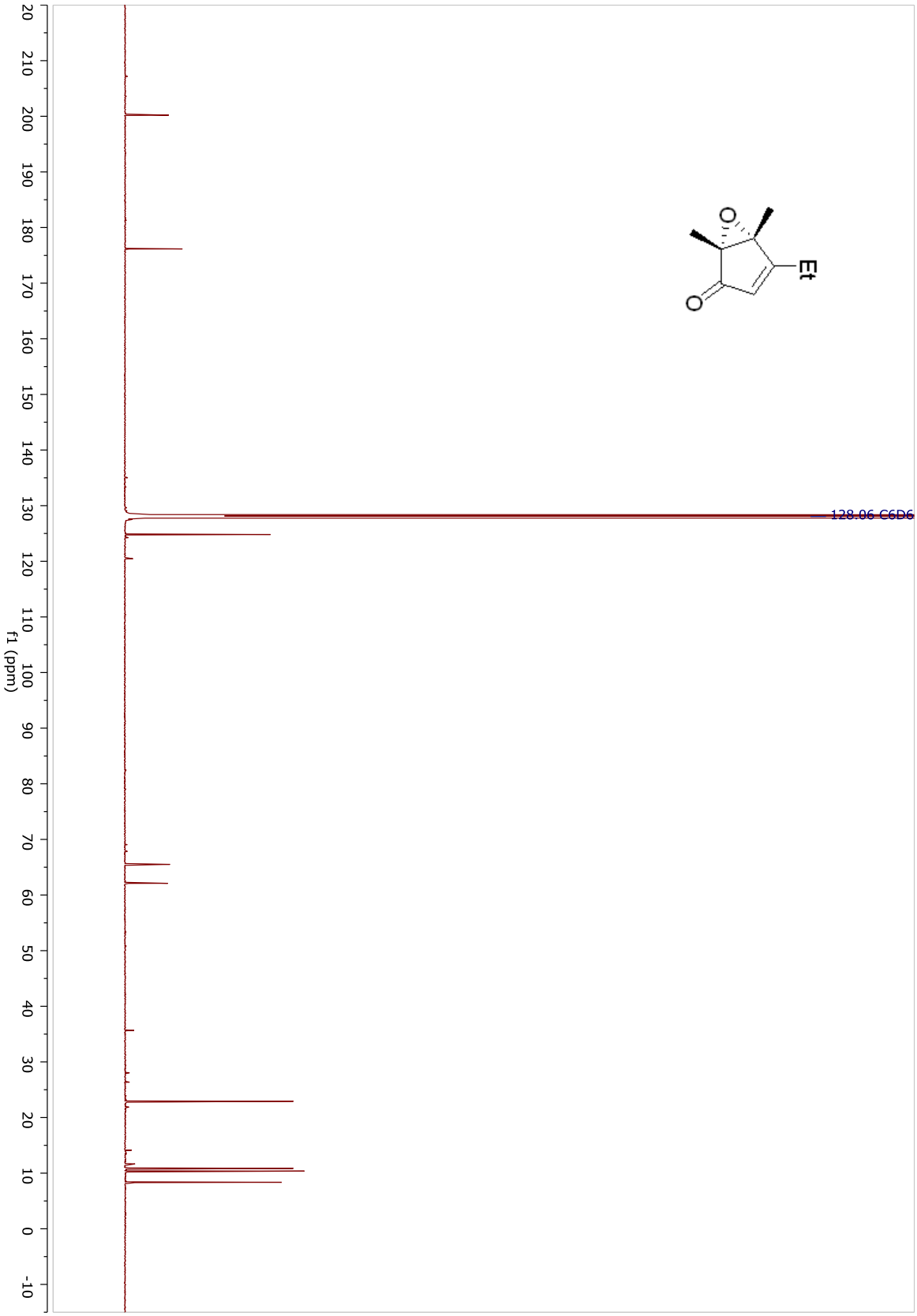
Compound 3.48



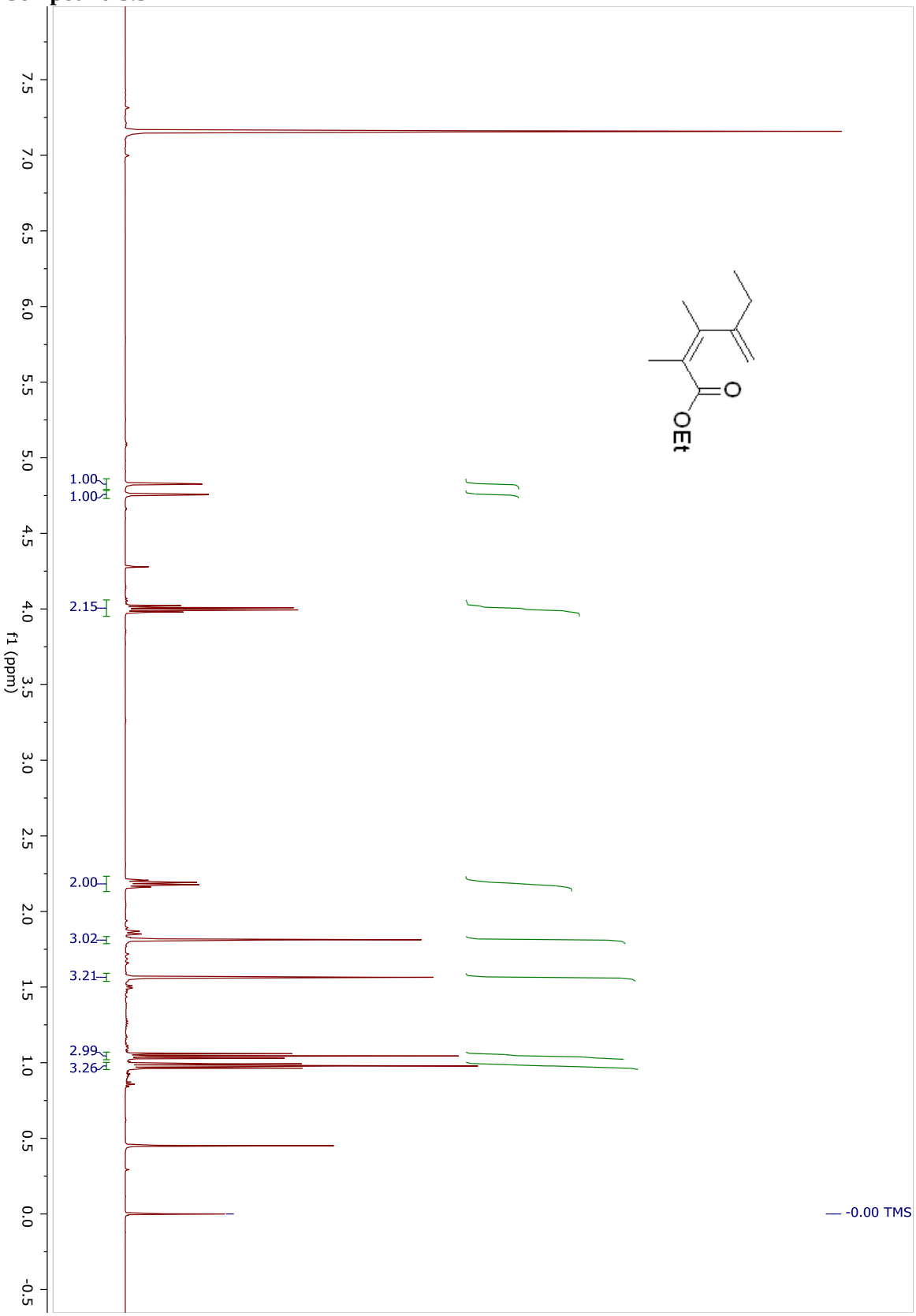

Et
128.06 C6D6
f1 (ppm)
20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

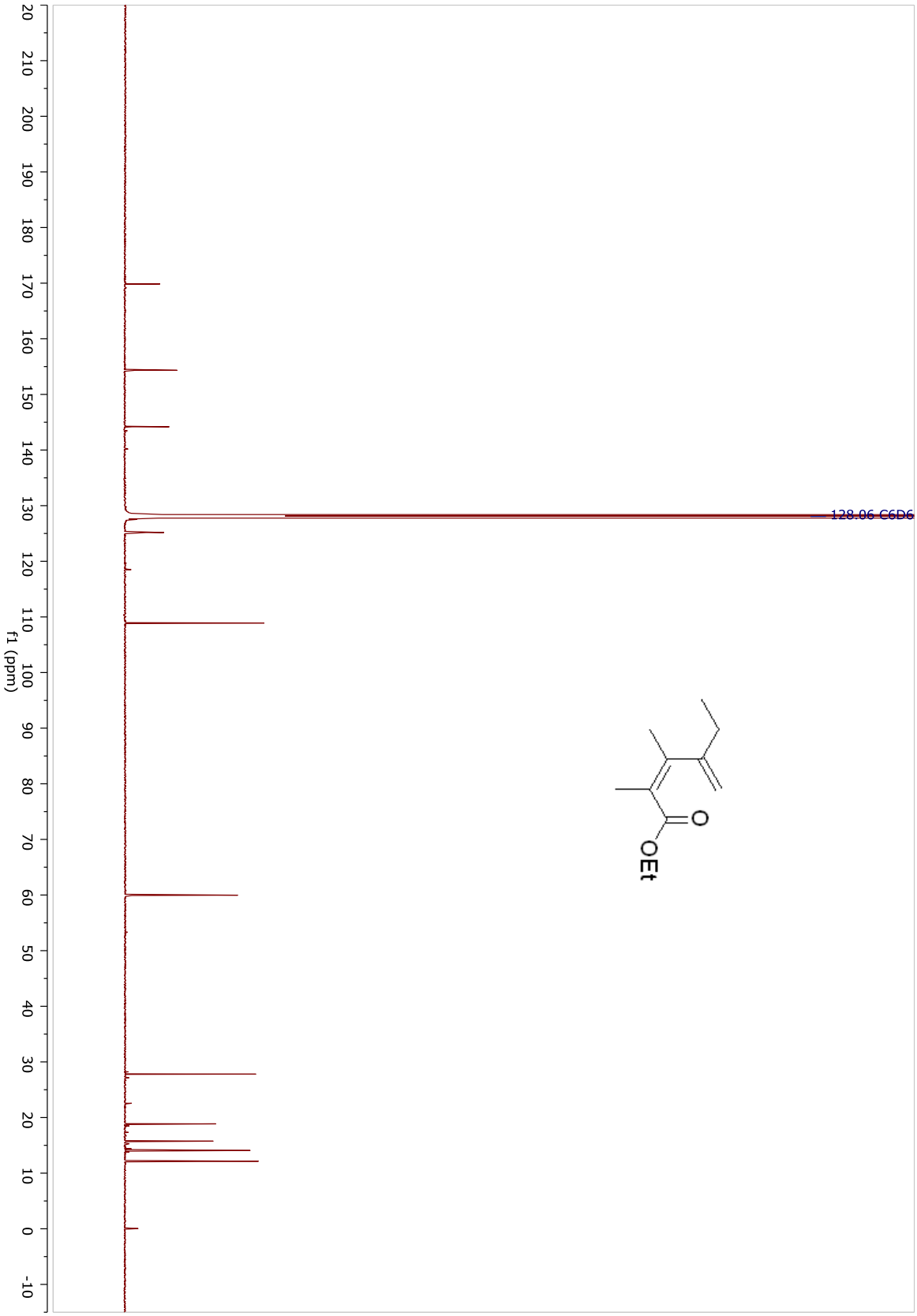
Compound 3.42



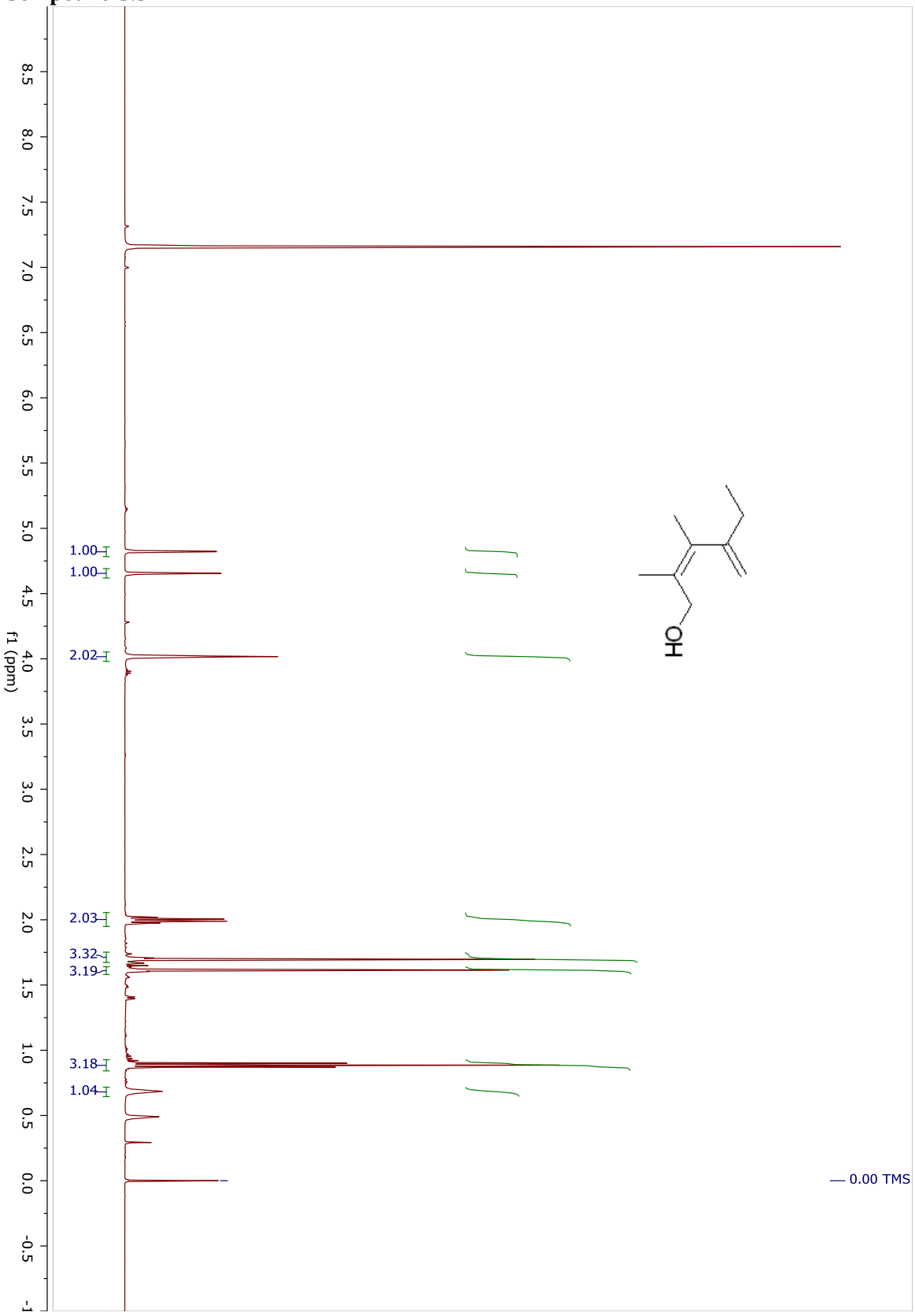

128.06 C6D6
Et
f1 (ppm)
20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

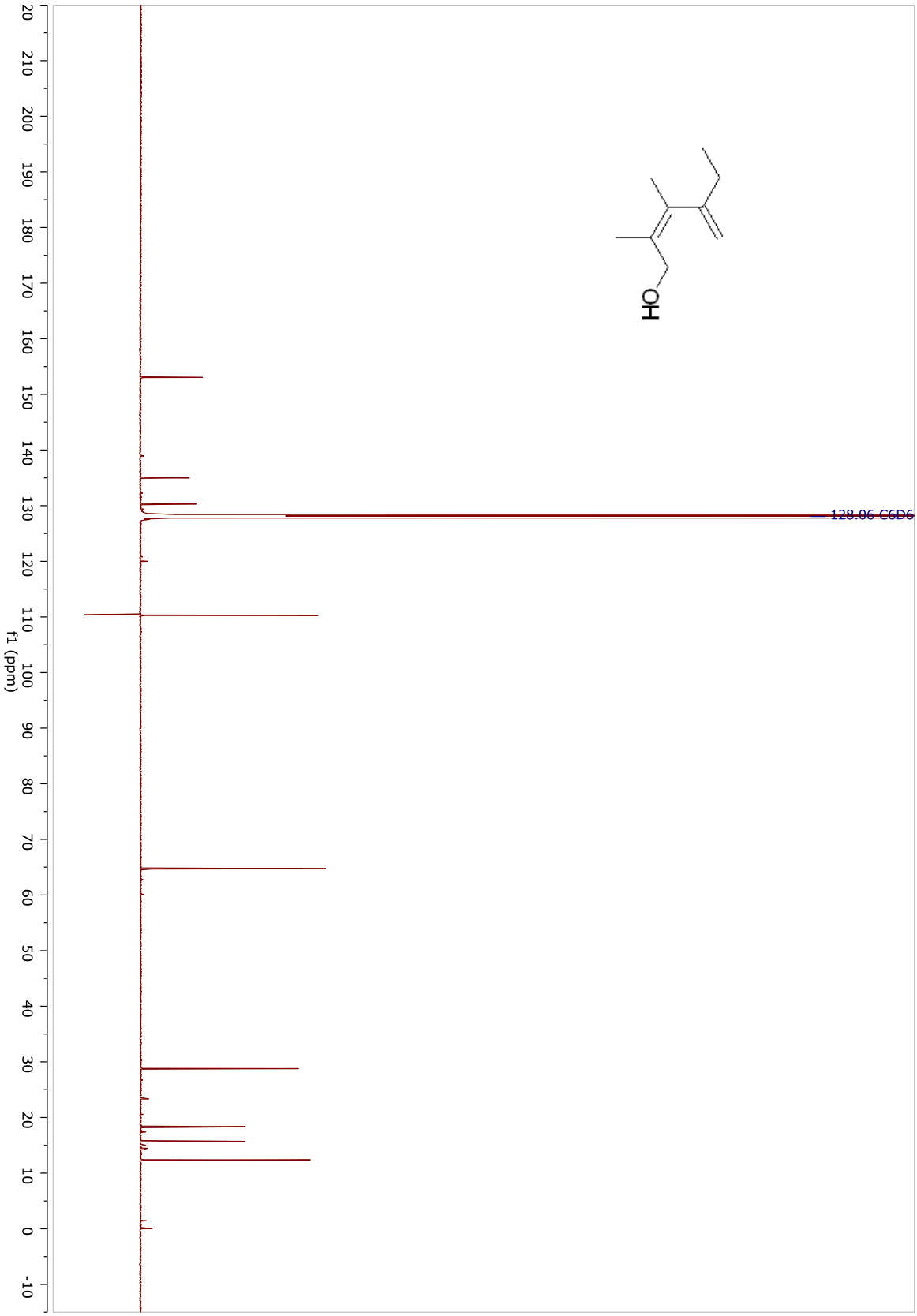
Compound 3.57



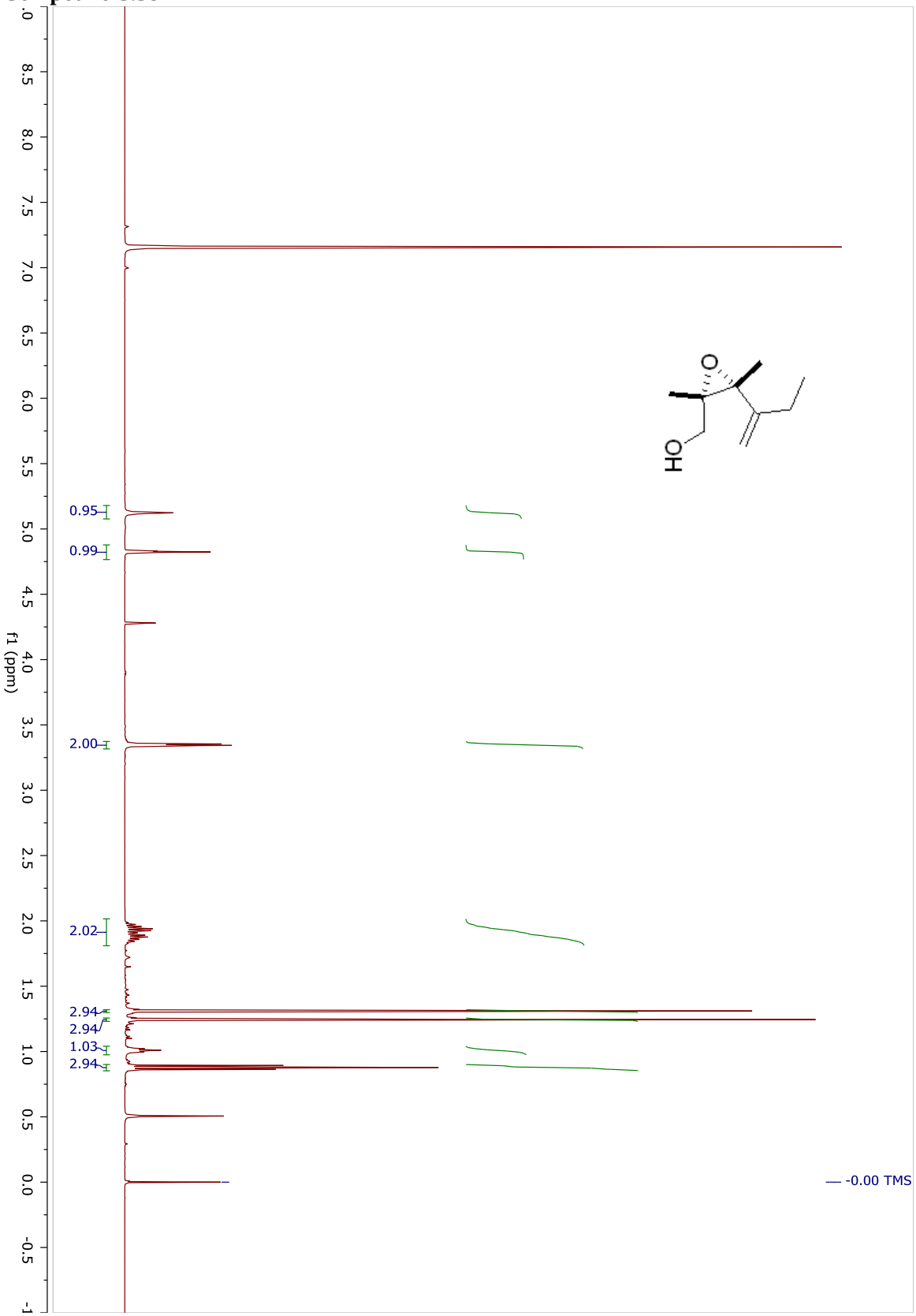

128.06 C6D6
O
OEt
f1 (ppm)
20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

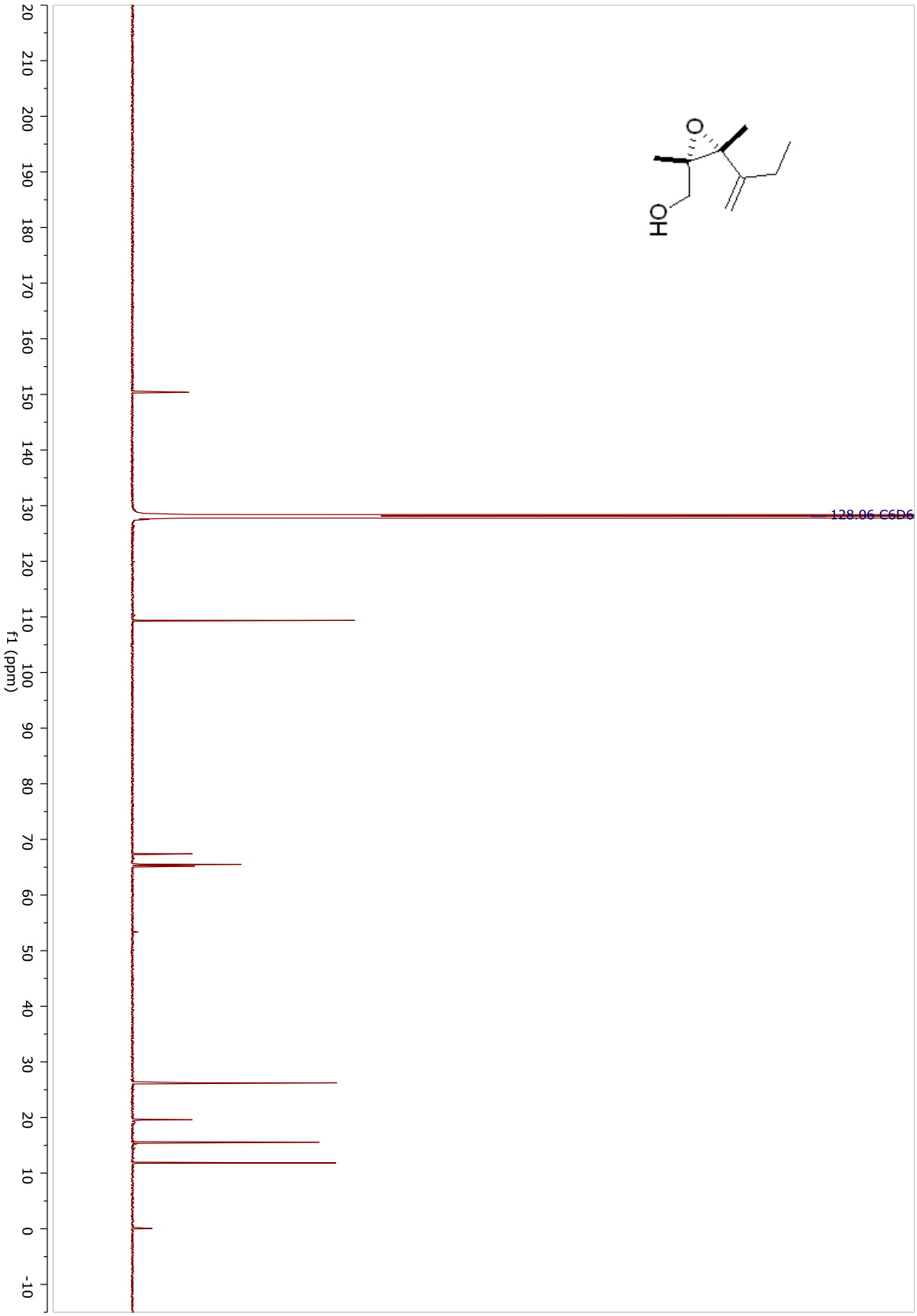
Compound 3.54



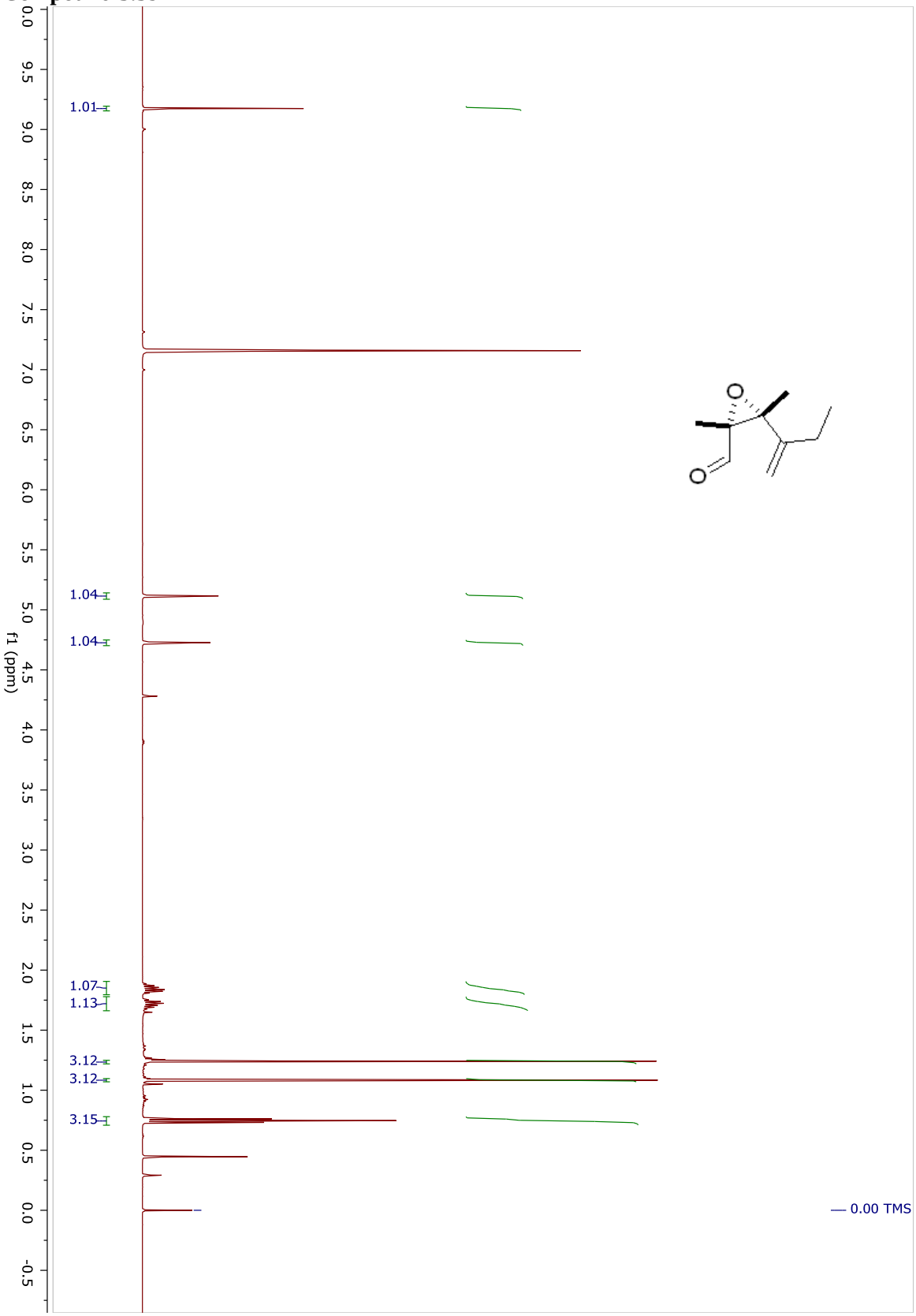

HO
128.06 C6D6
f1 (ppm)
20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

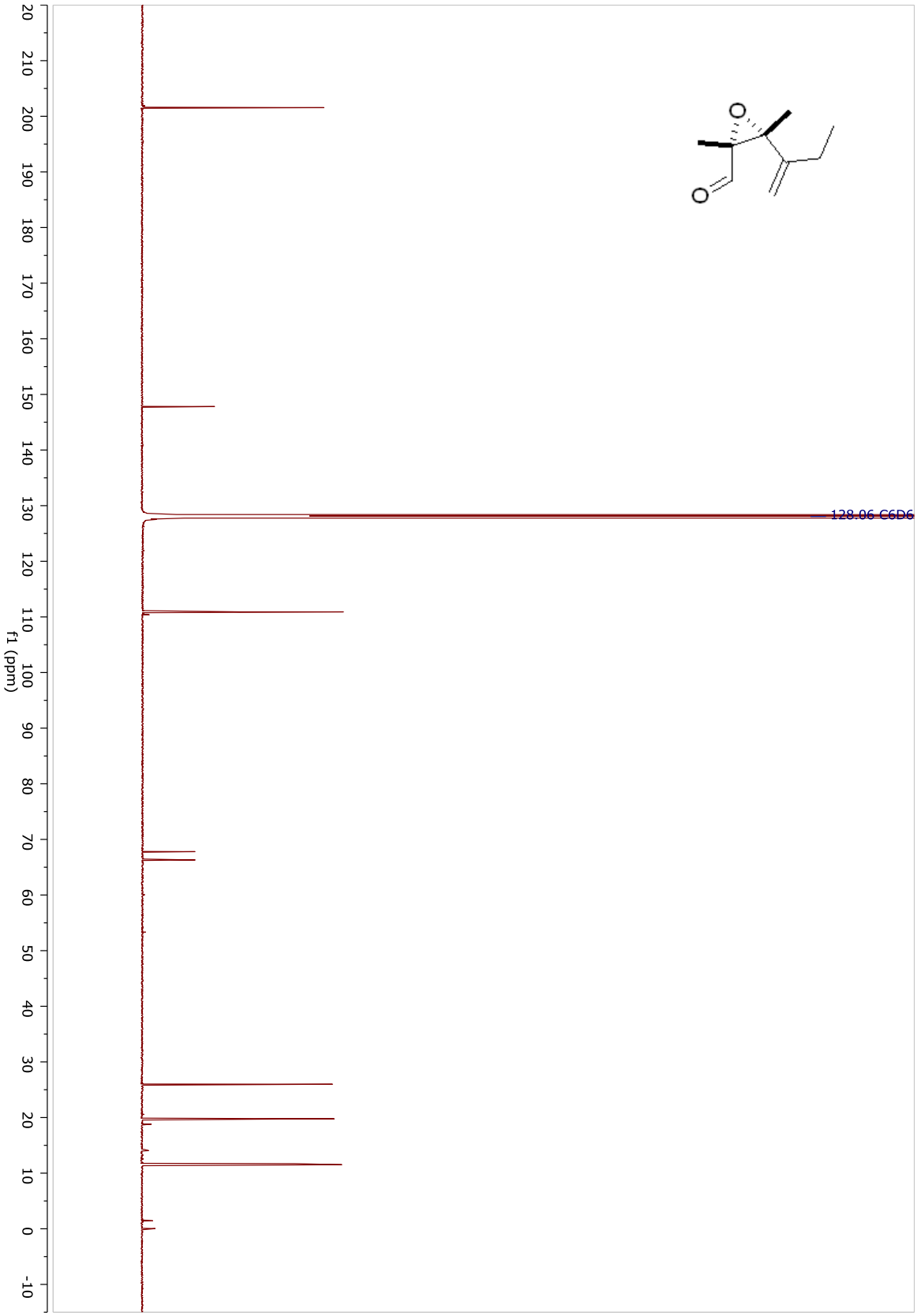
Compound 3.58



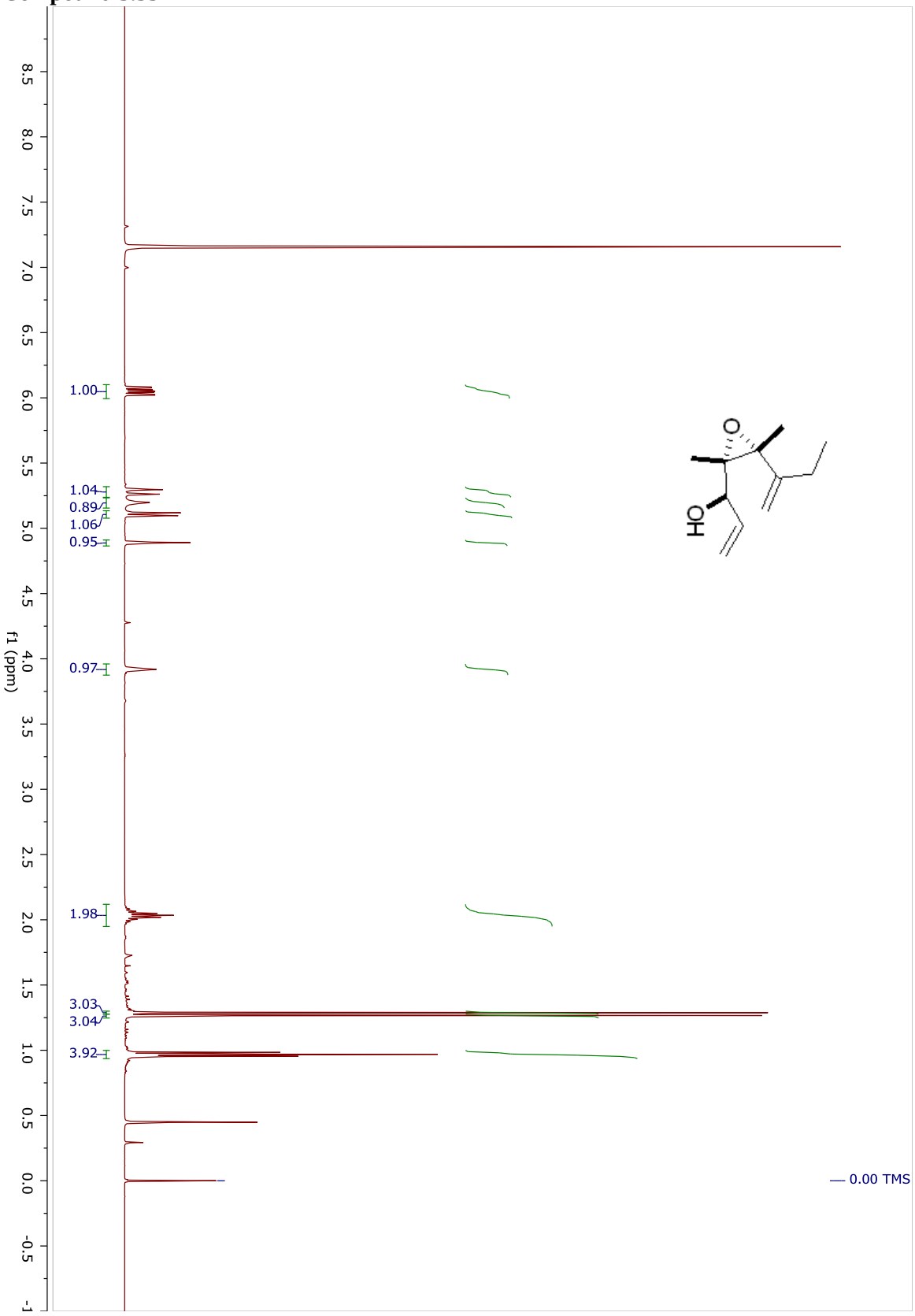

O
HO
128.06 C6D6
f1 (ppm)
20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

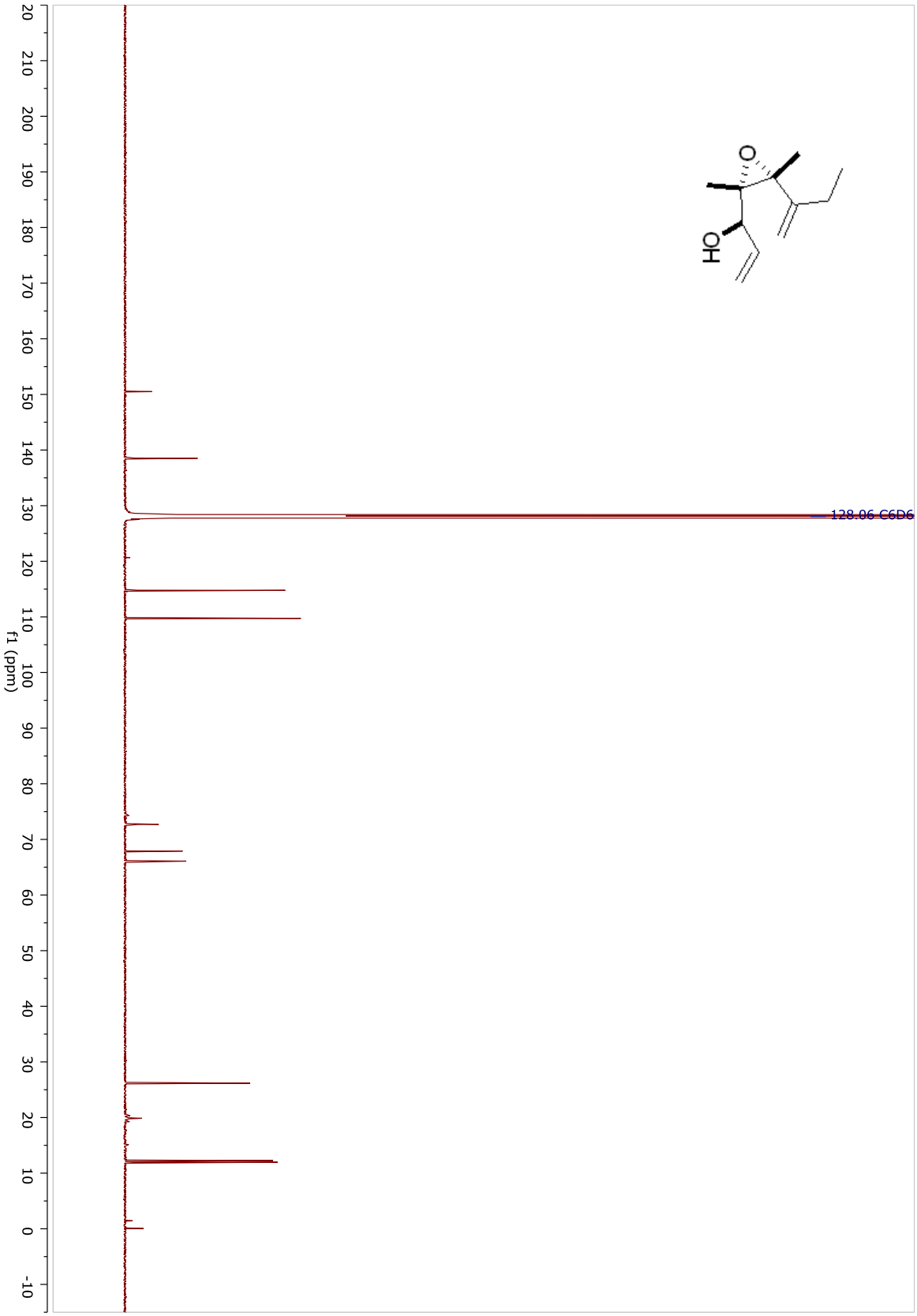
Compound 3.59



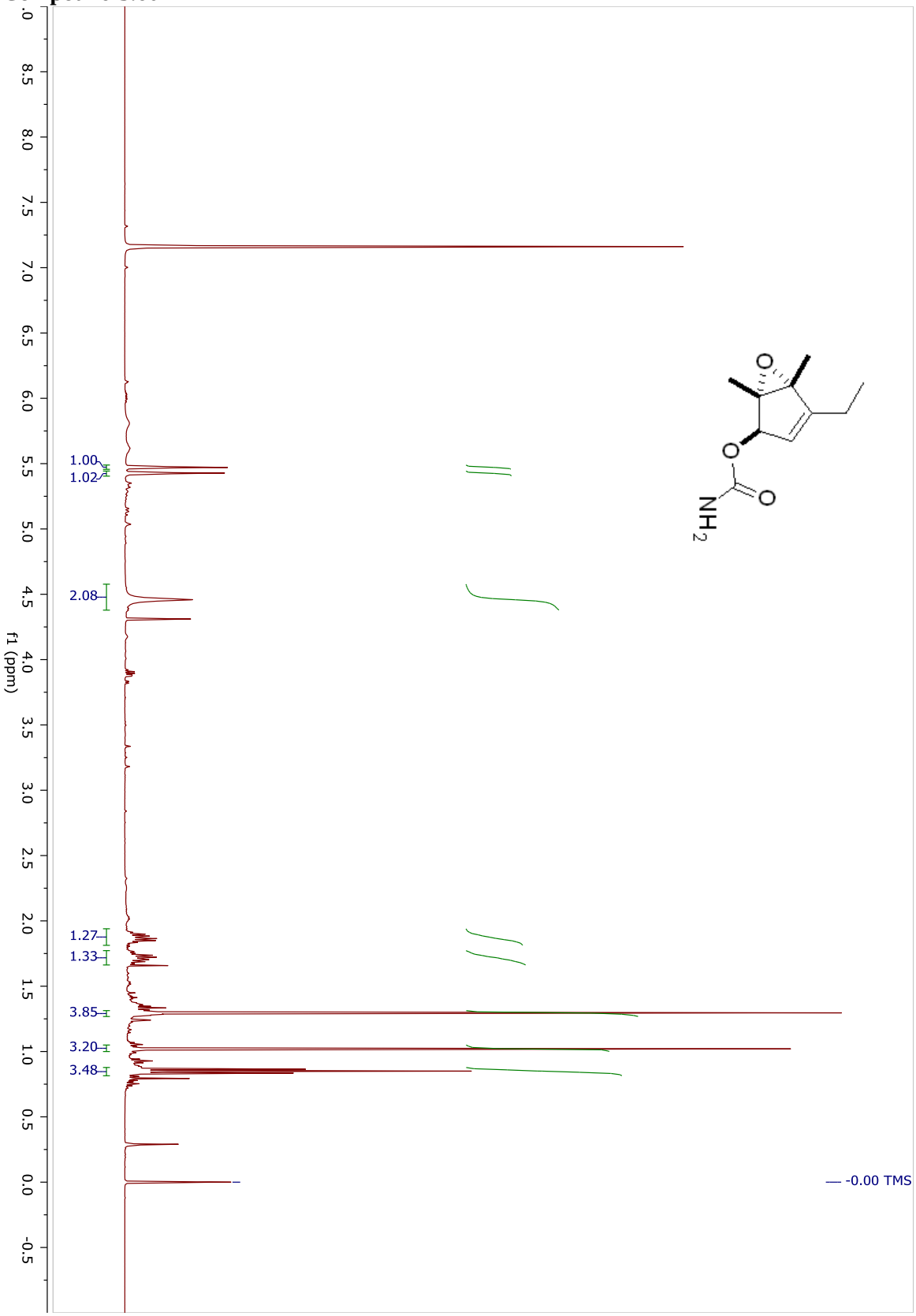

128.06 C6D6
f1 (ppm)
20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

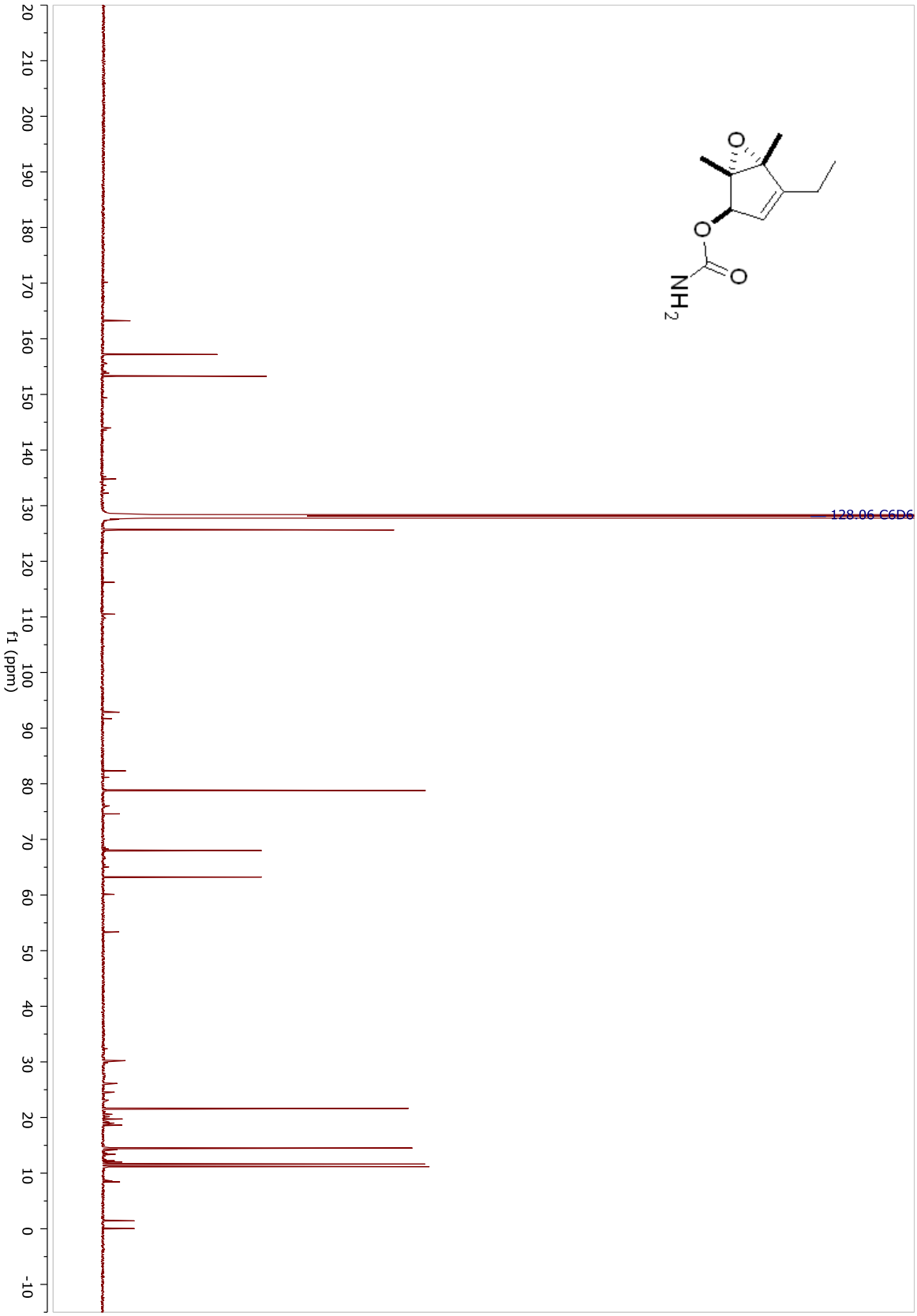
Compound 3.53



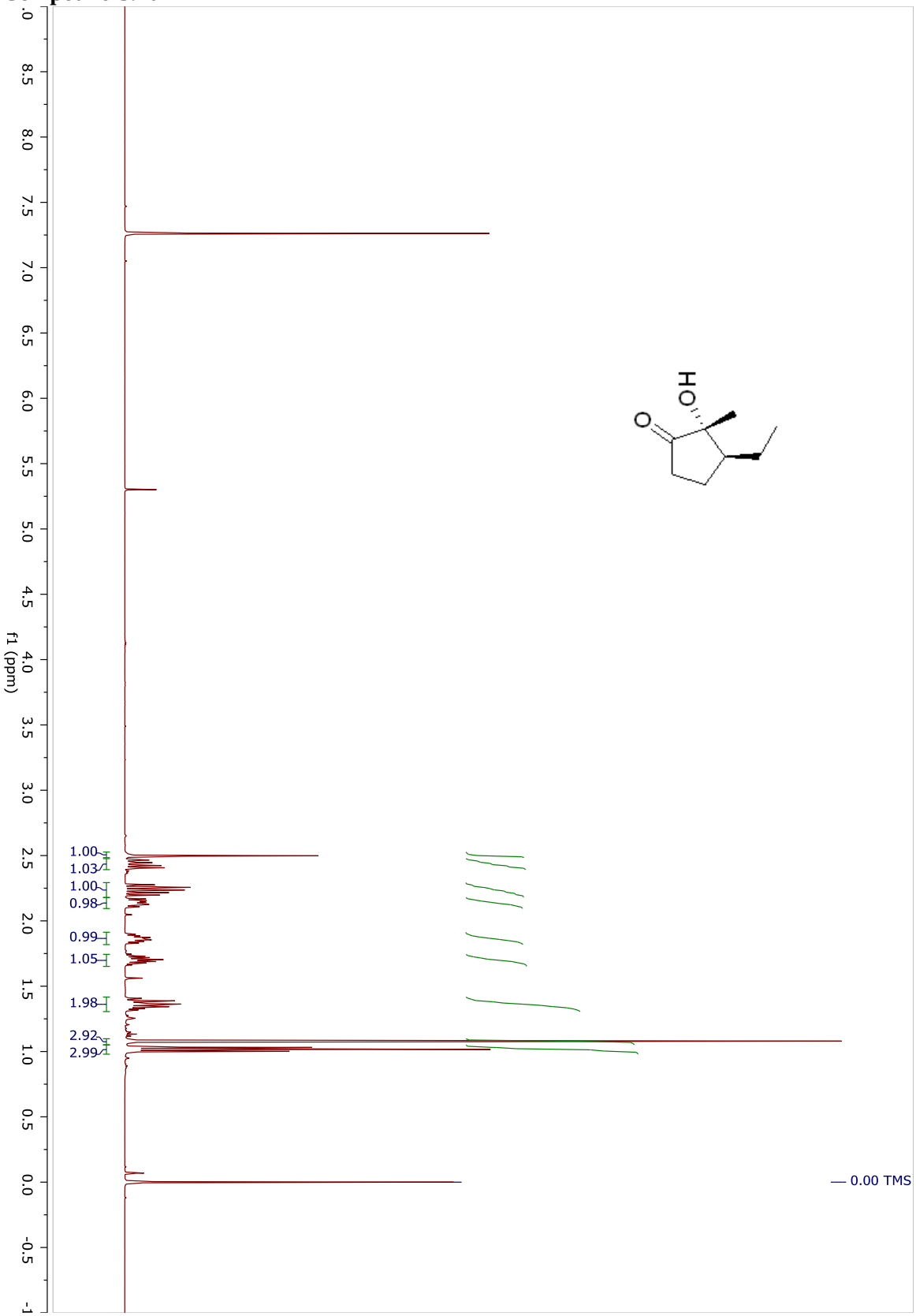

O
OH
128.06 C6D6
f1 (ppm)
20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

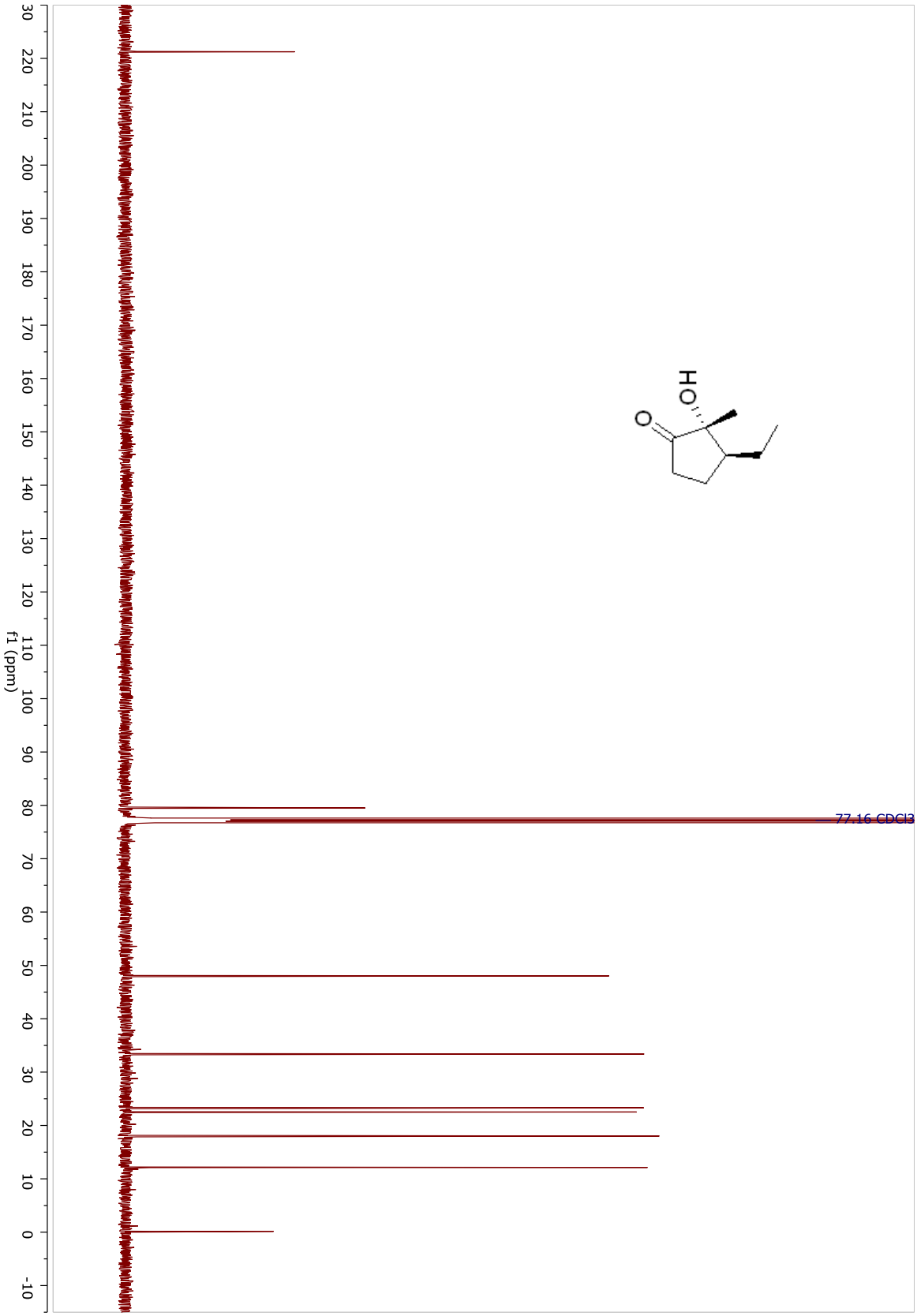
Compound 3.60



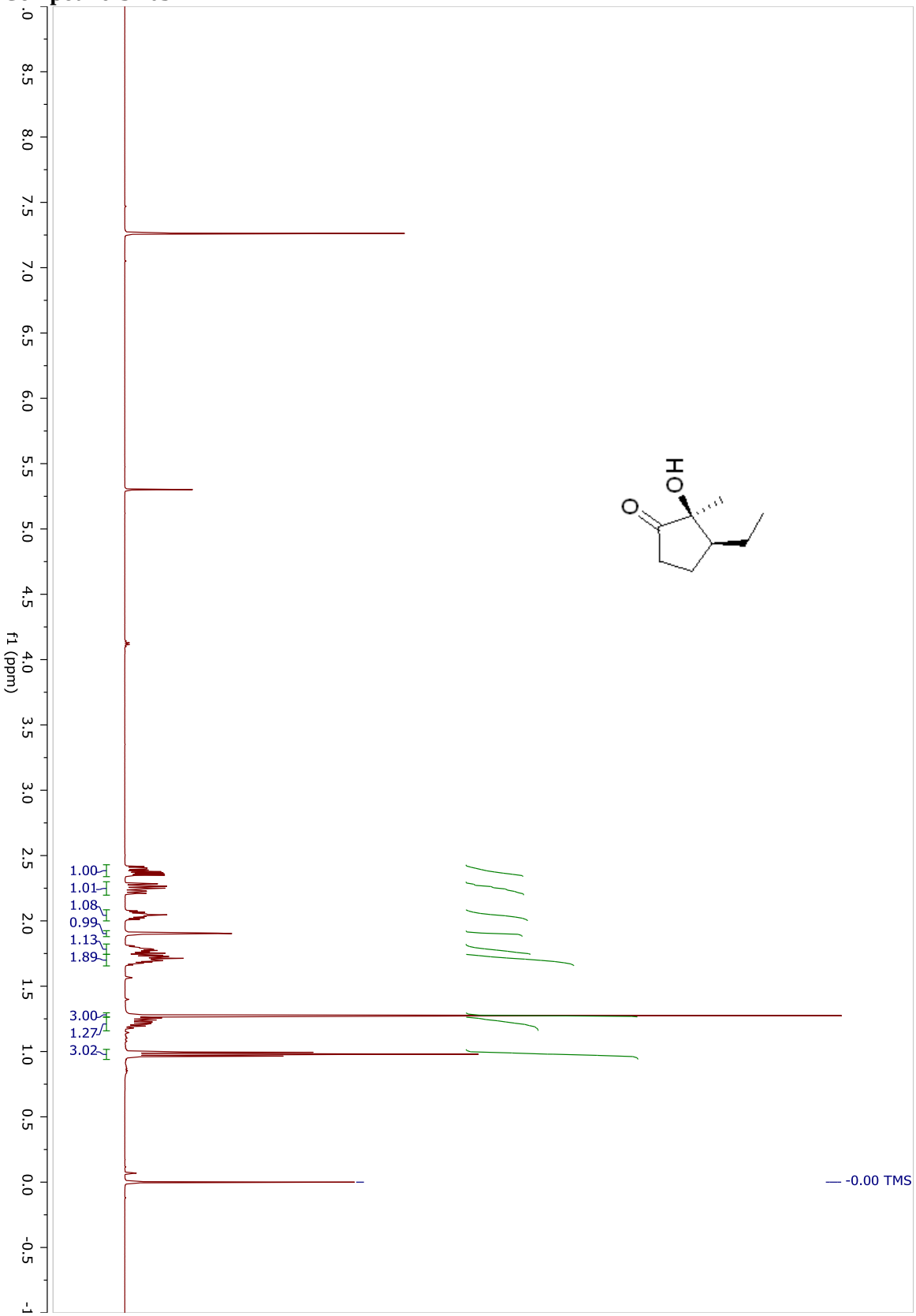

128.06 C6D6
f1 (ppm)
20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
O
O
O
NH2

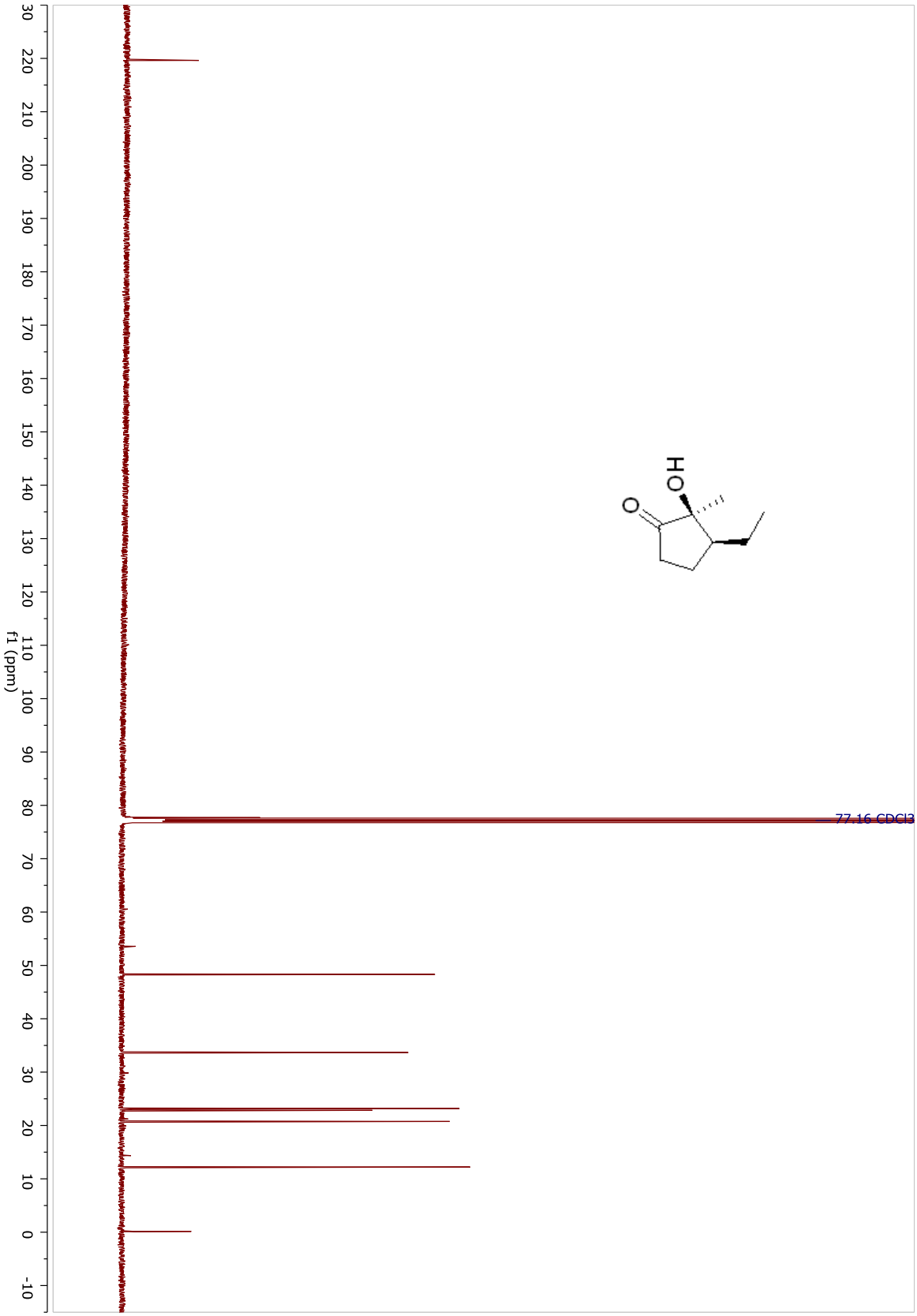
Compound 3.70



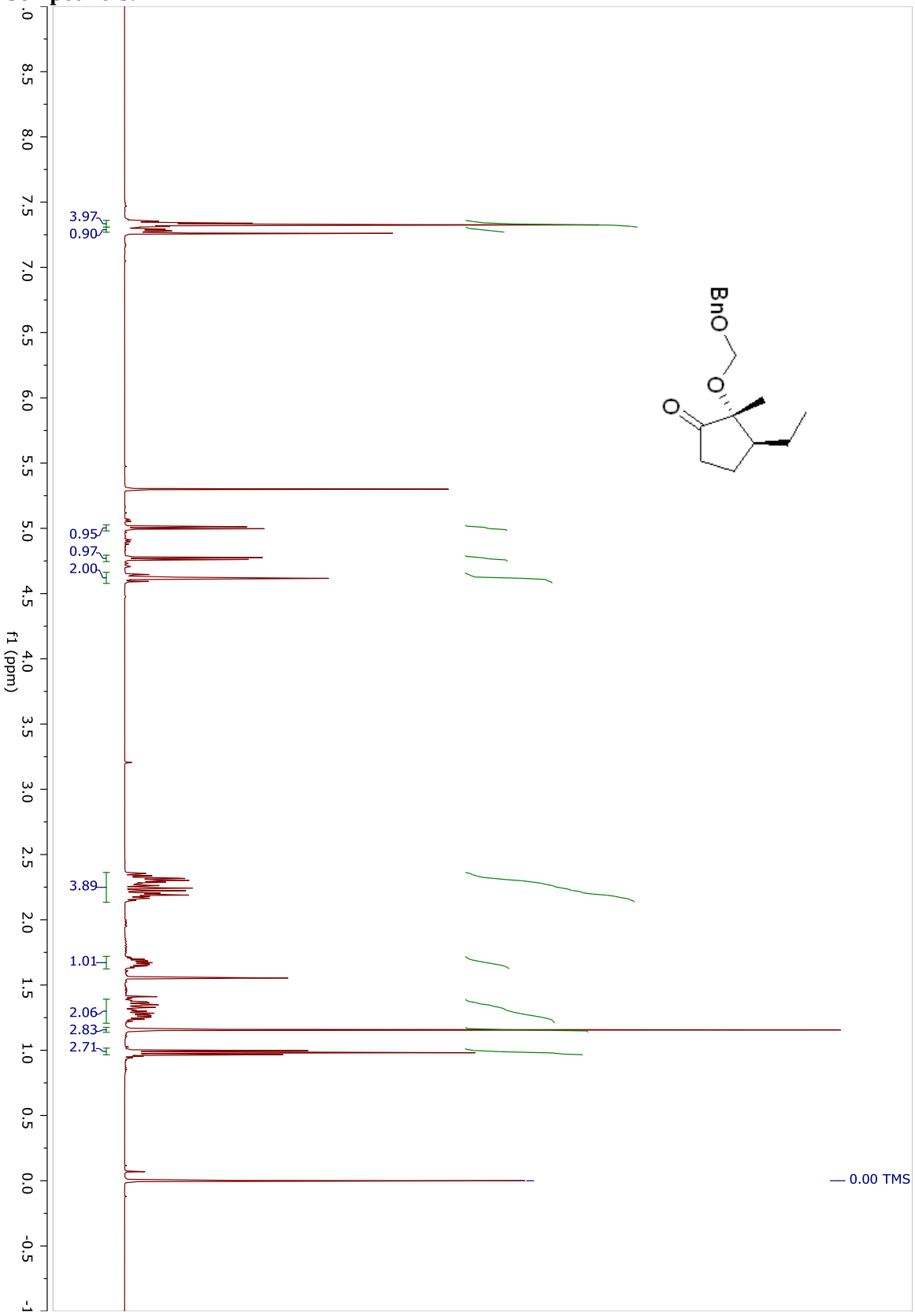

f1 (ppm)
77.16 CDCl3
HO
O

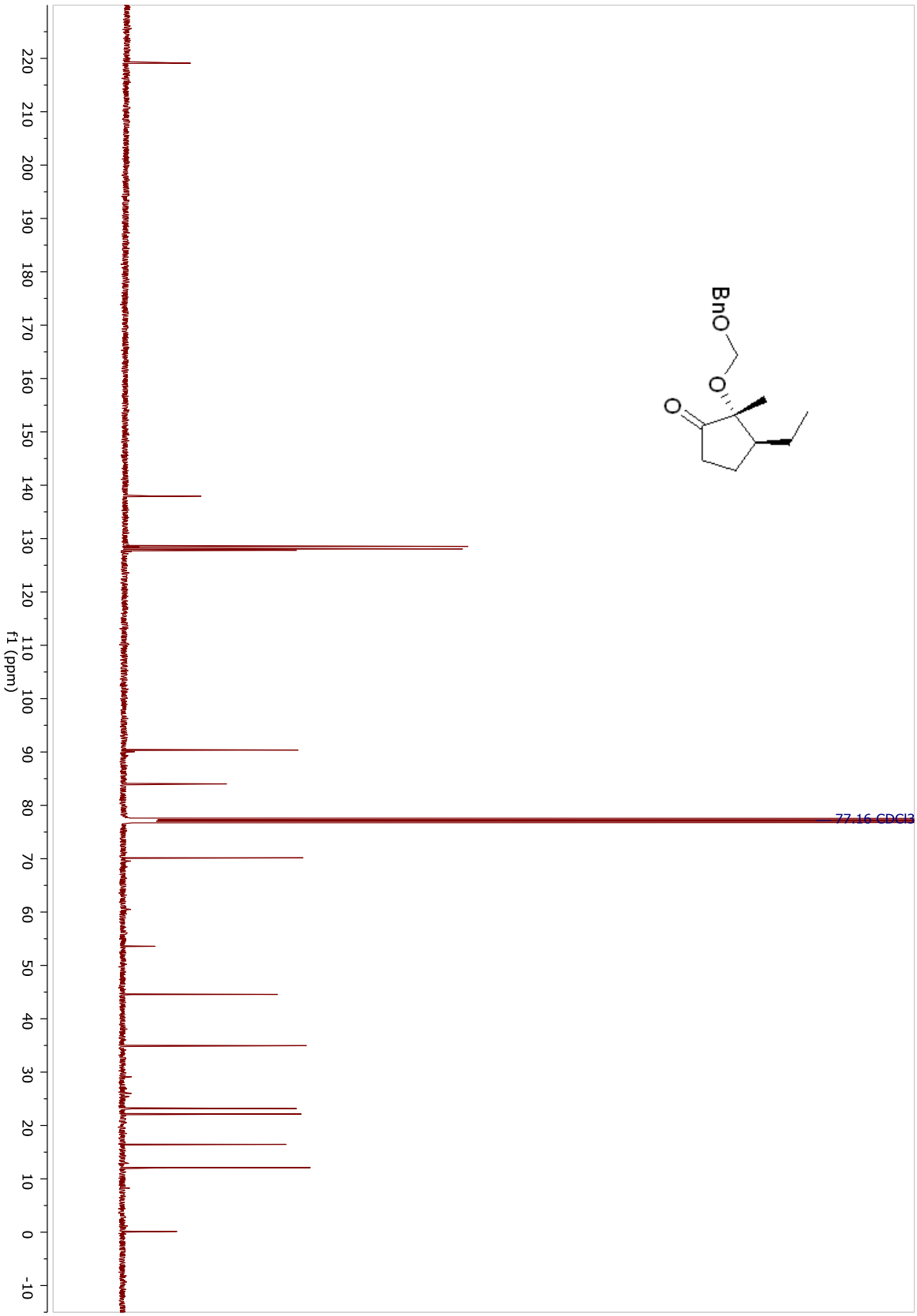
Compound SI-03



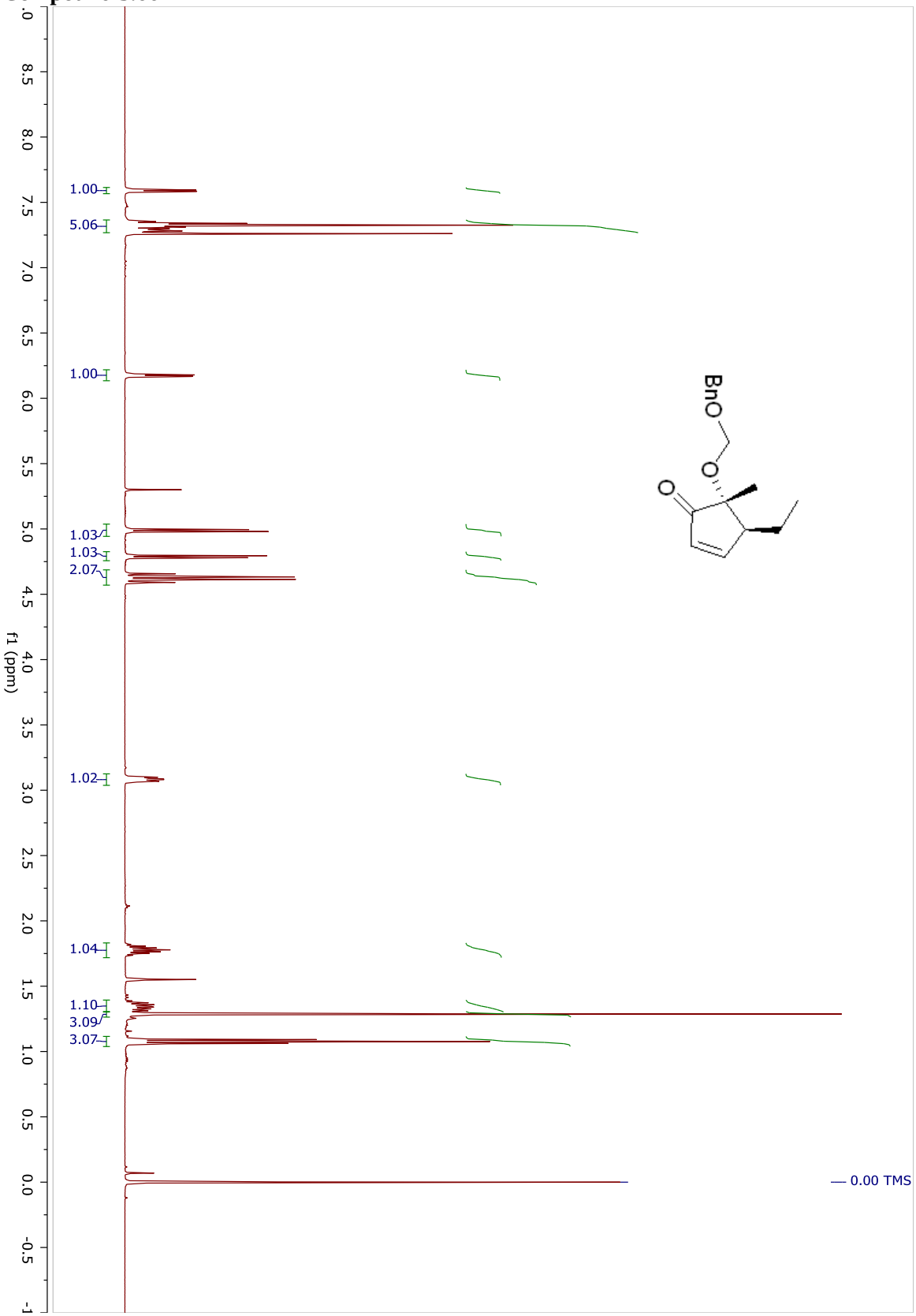

f1 (ppm)
77.16 CDCl3
OH
O

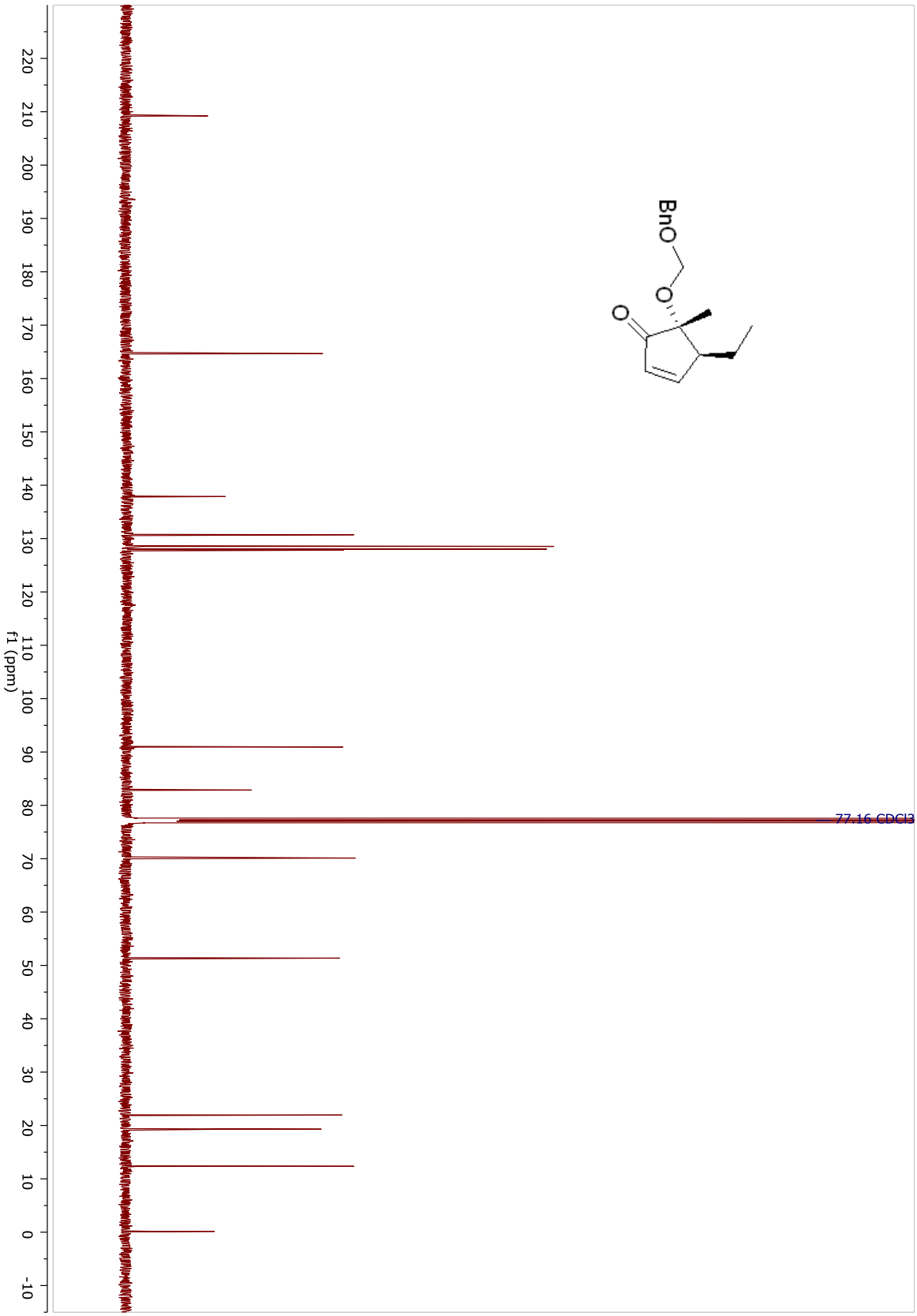
Compound 3.71



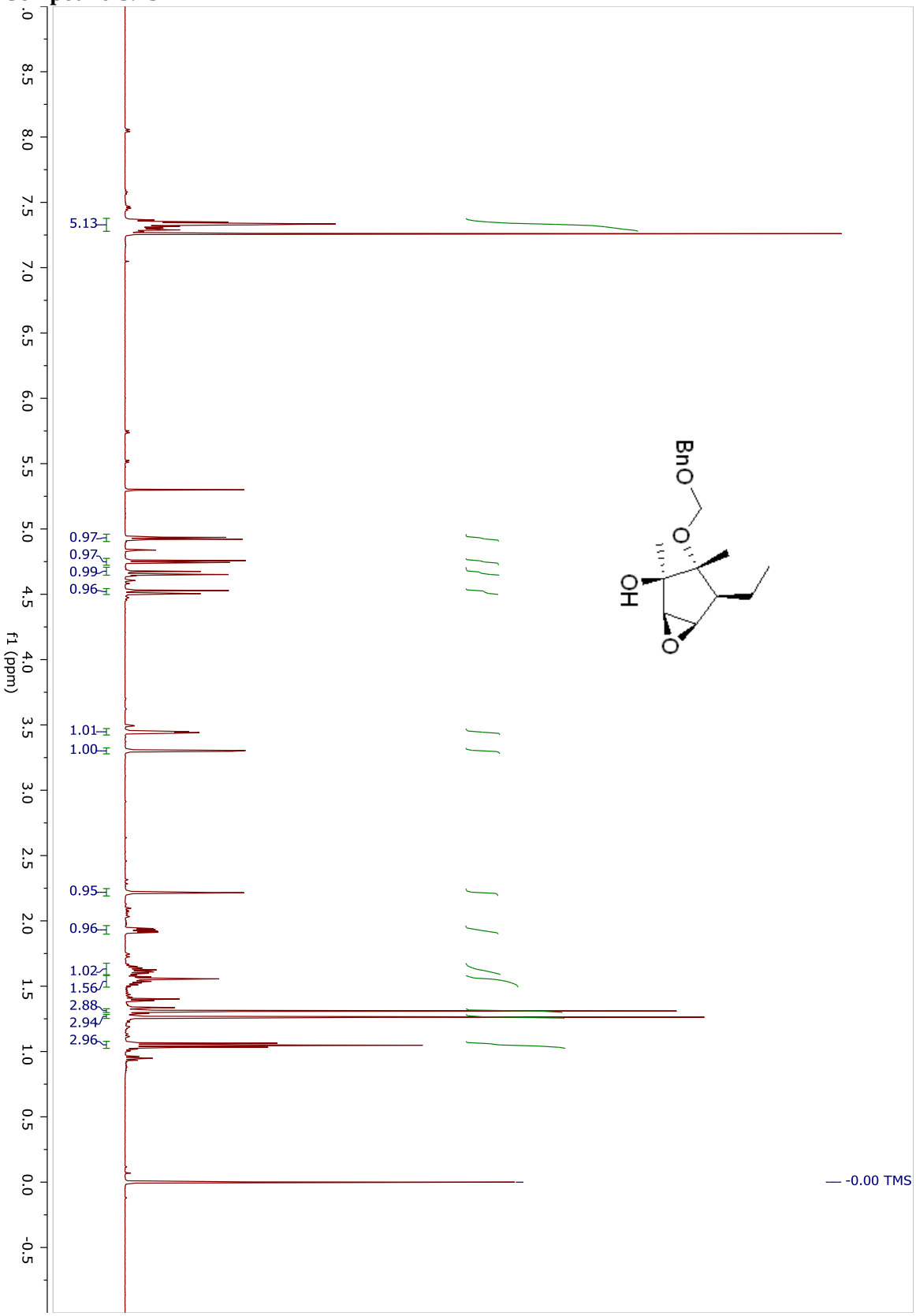

BnO
O
O
77.16 CDCl3
f1 (ppm)
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

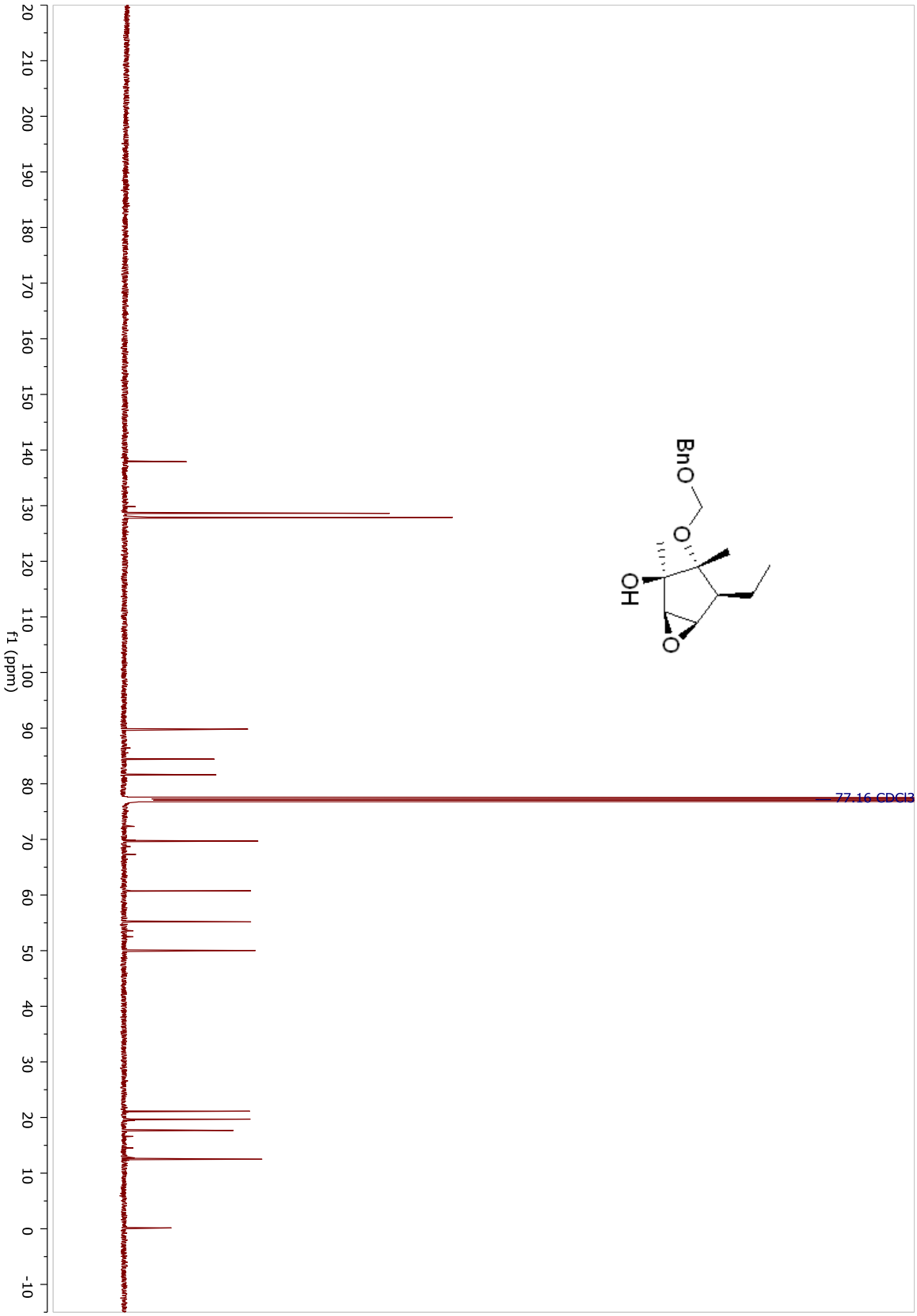
Compound 3.66



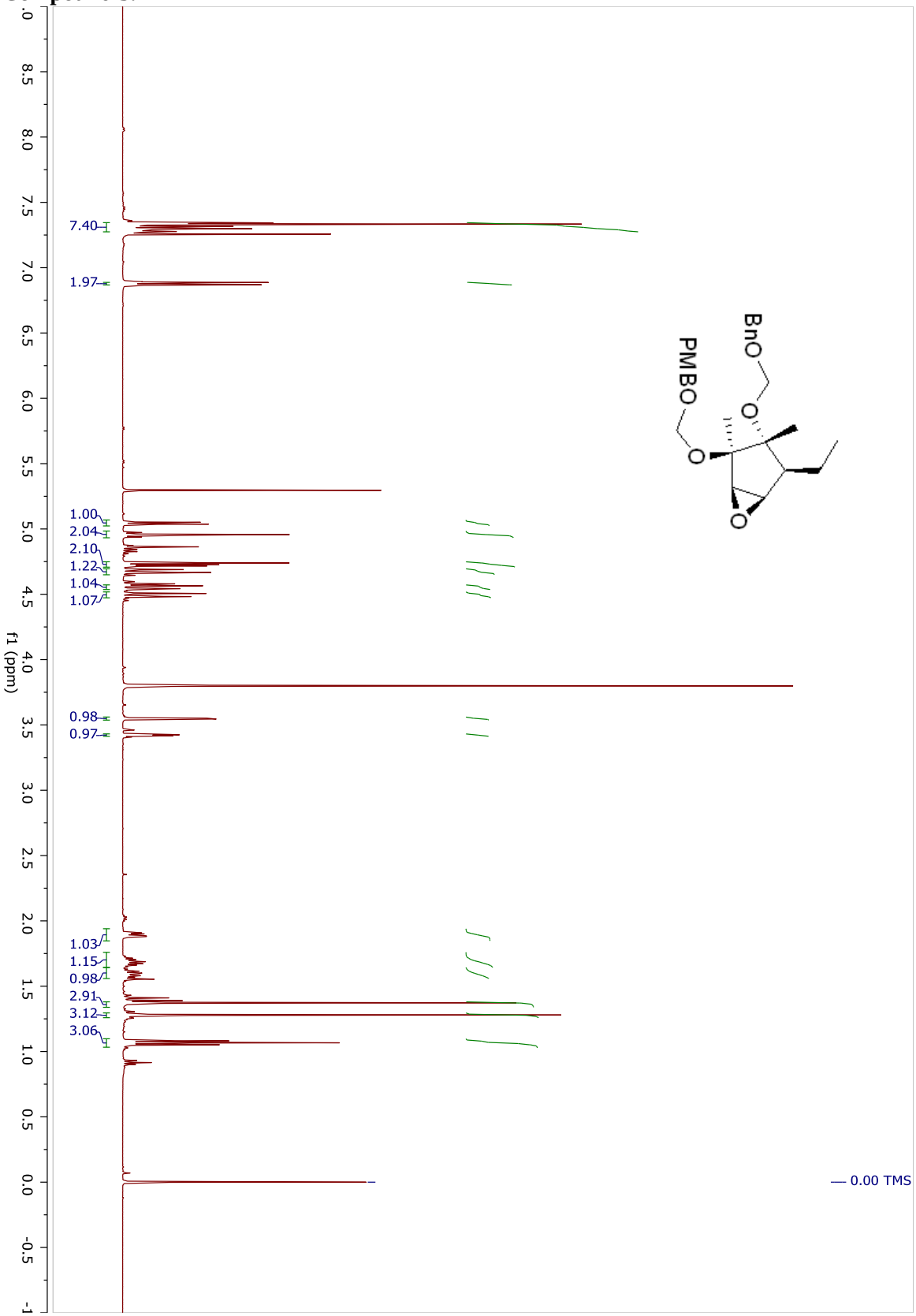

BnO
O
O
77.16 CDCl3
f1 (ppm)
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

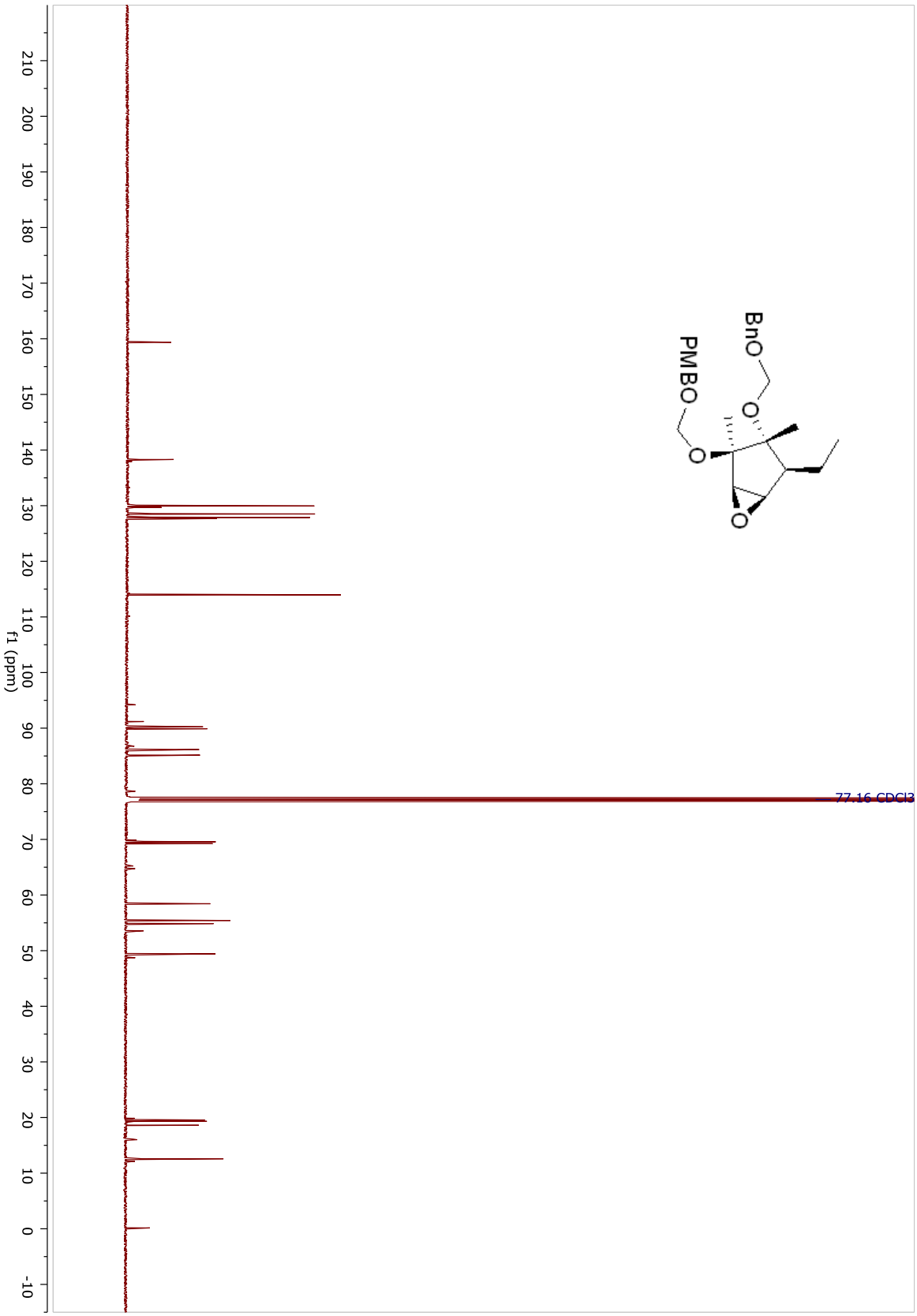
Compound 3.73



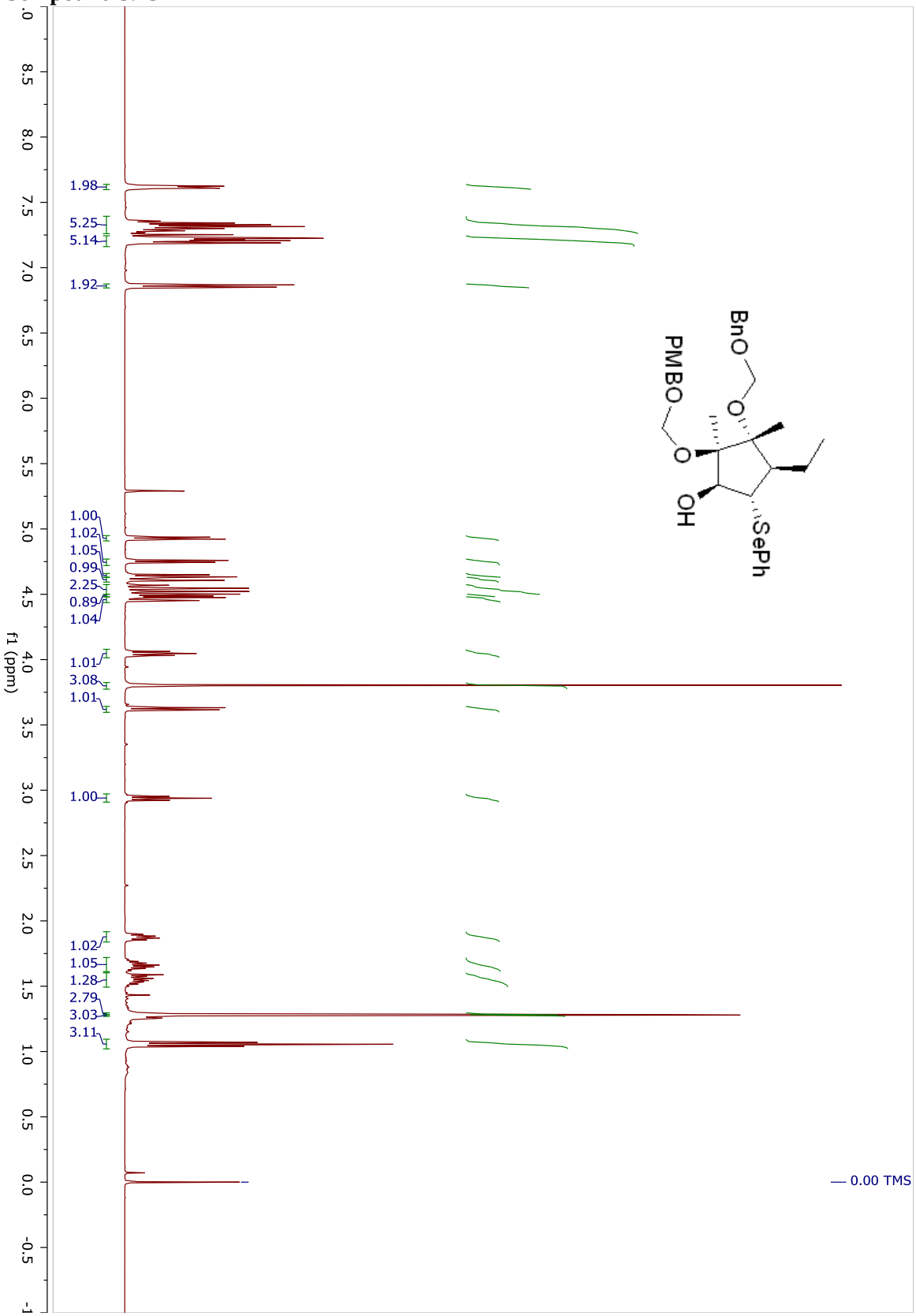

BnO
O
OH
O
77.16 CDCl3
f1 (ppm)
20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

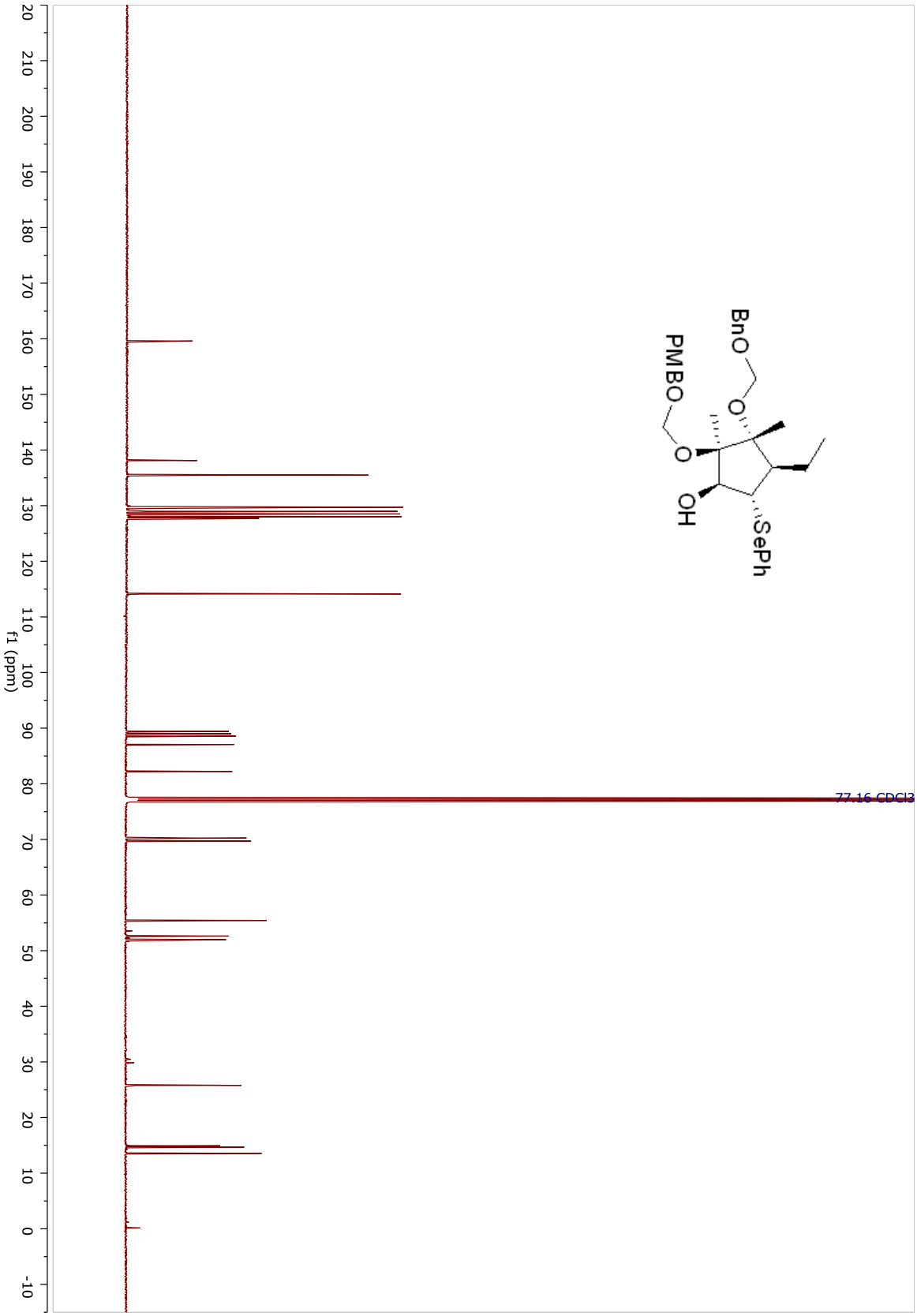
Compound 3.74



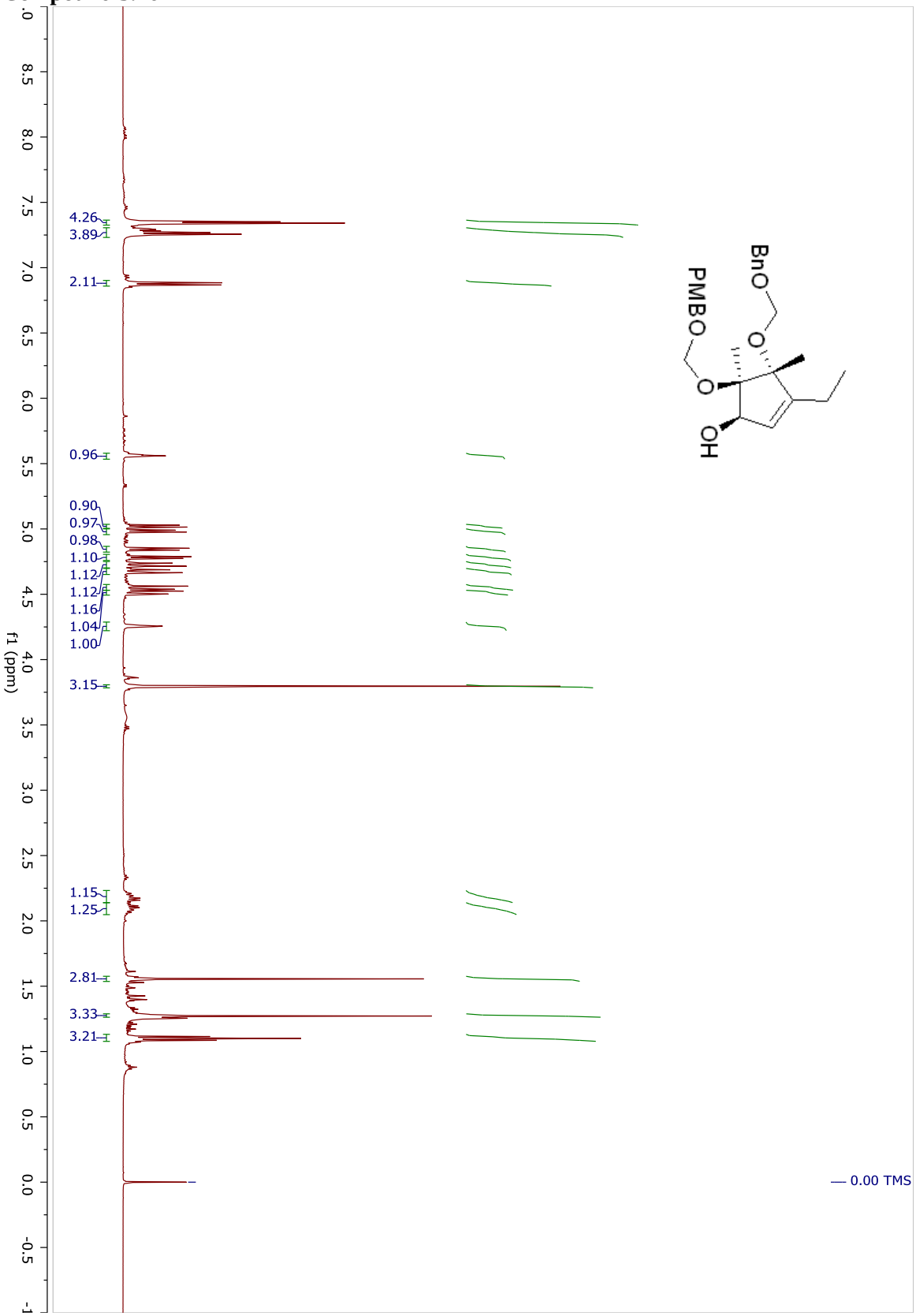

BnO
PMBO
O
O
O
77.16 CDCl3
f1 (ppm)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

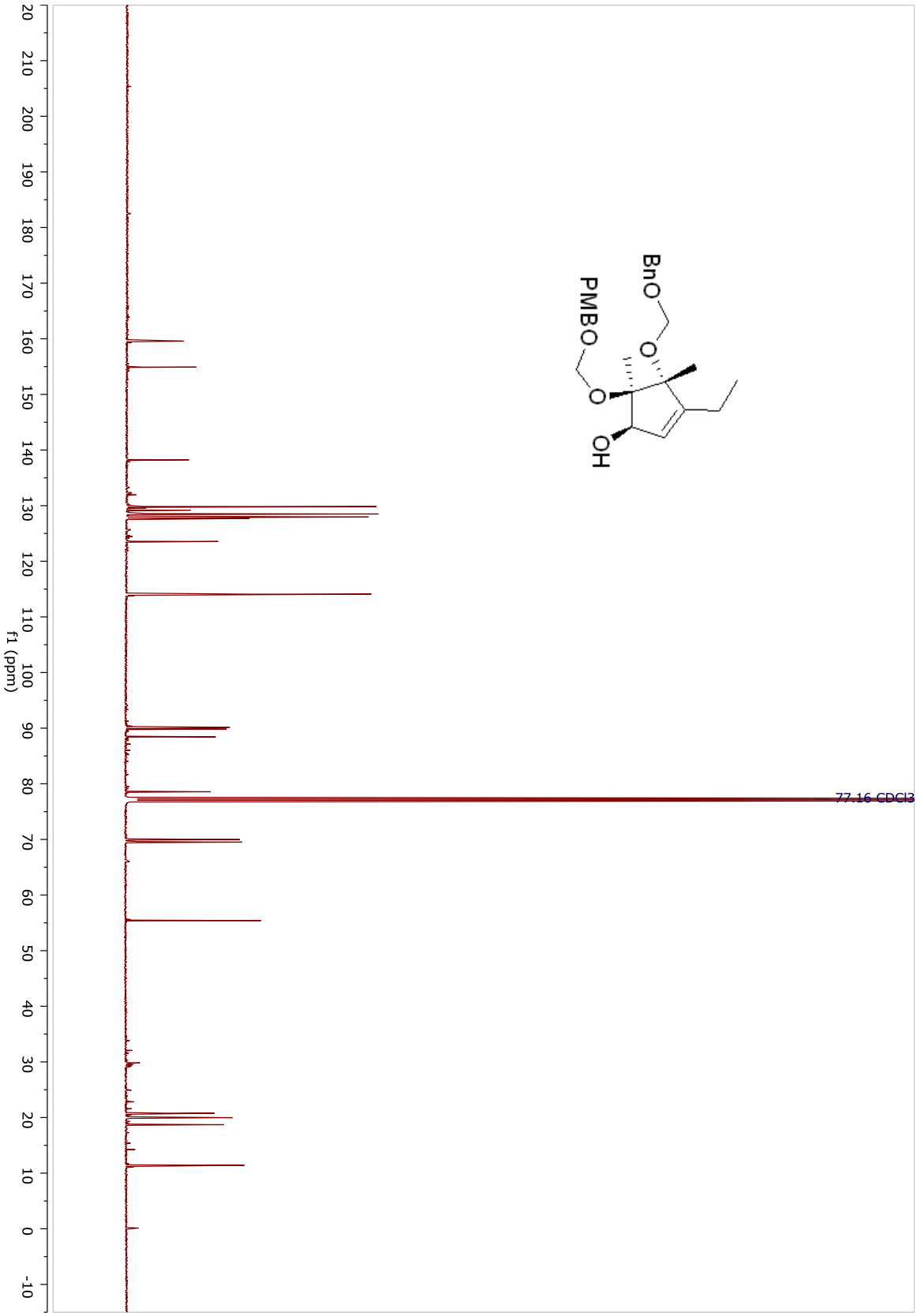
Compound 3.75



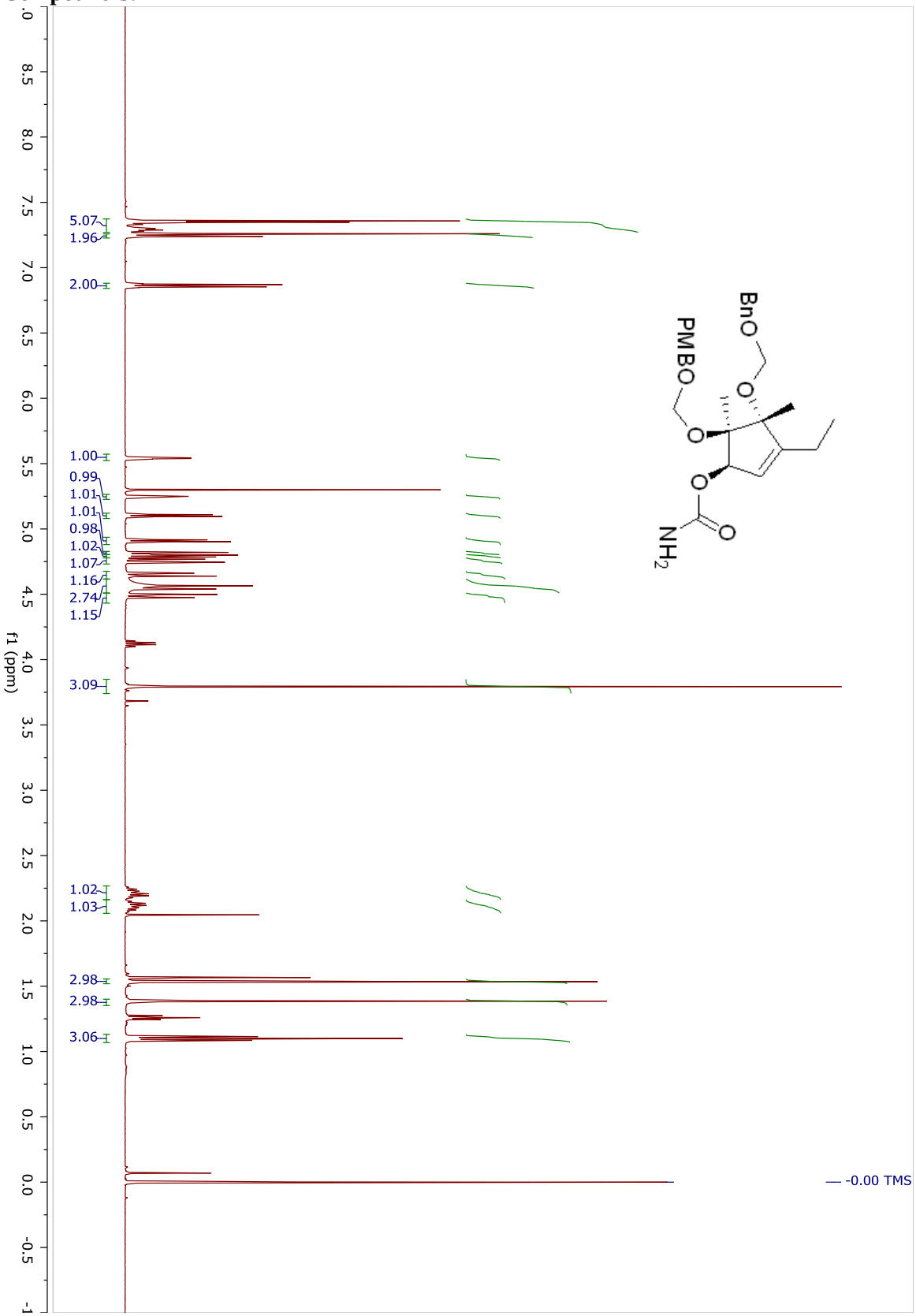

BnO
PMBO
O
O
OH
SePh
77.16 CDCl3
f1 (ppm)
20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

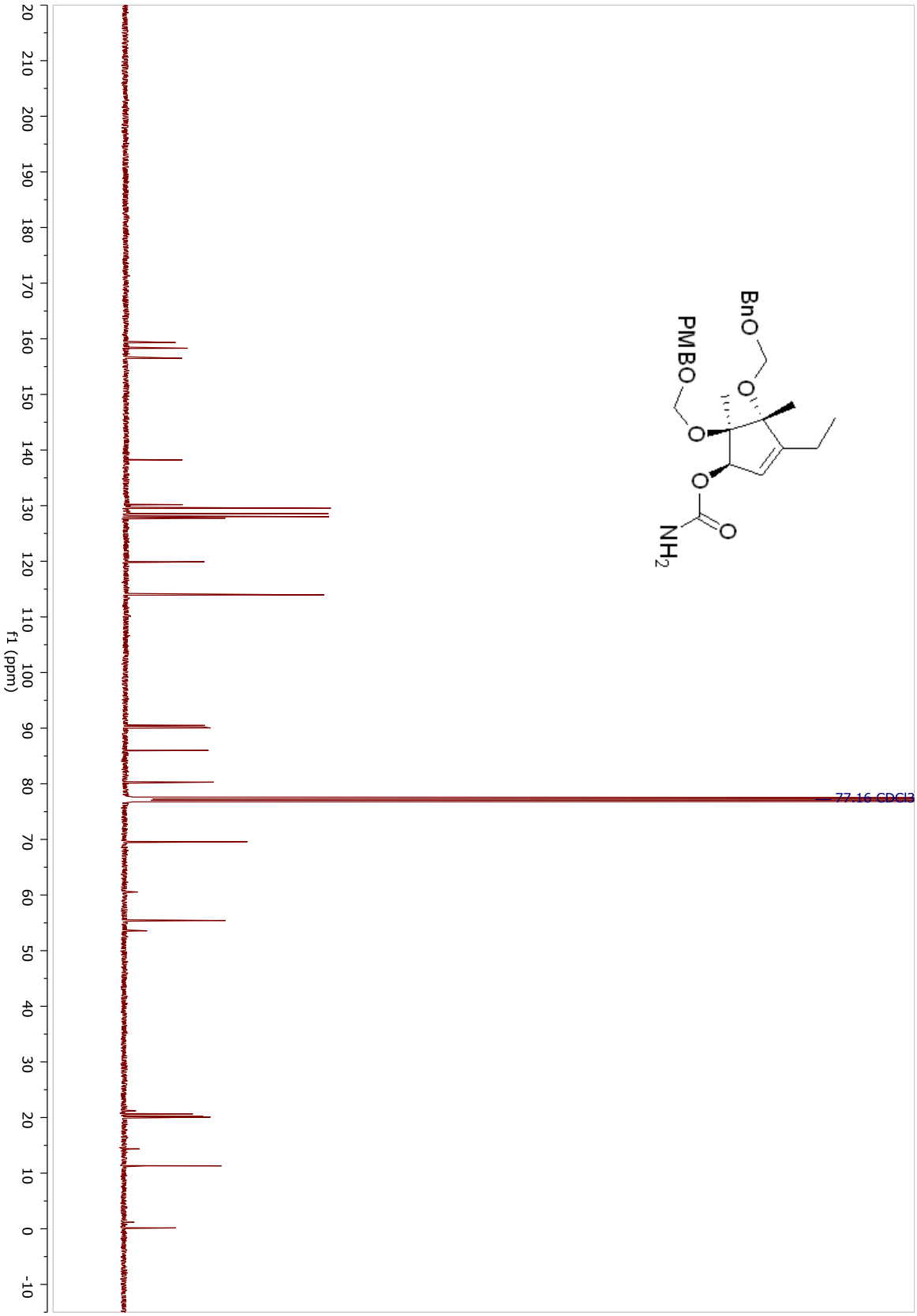
Compound 3.76



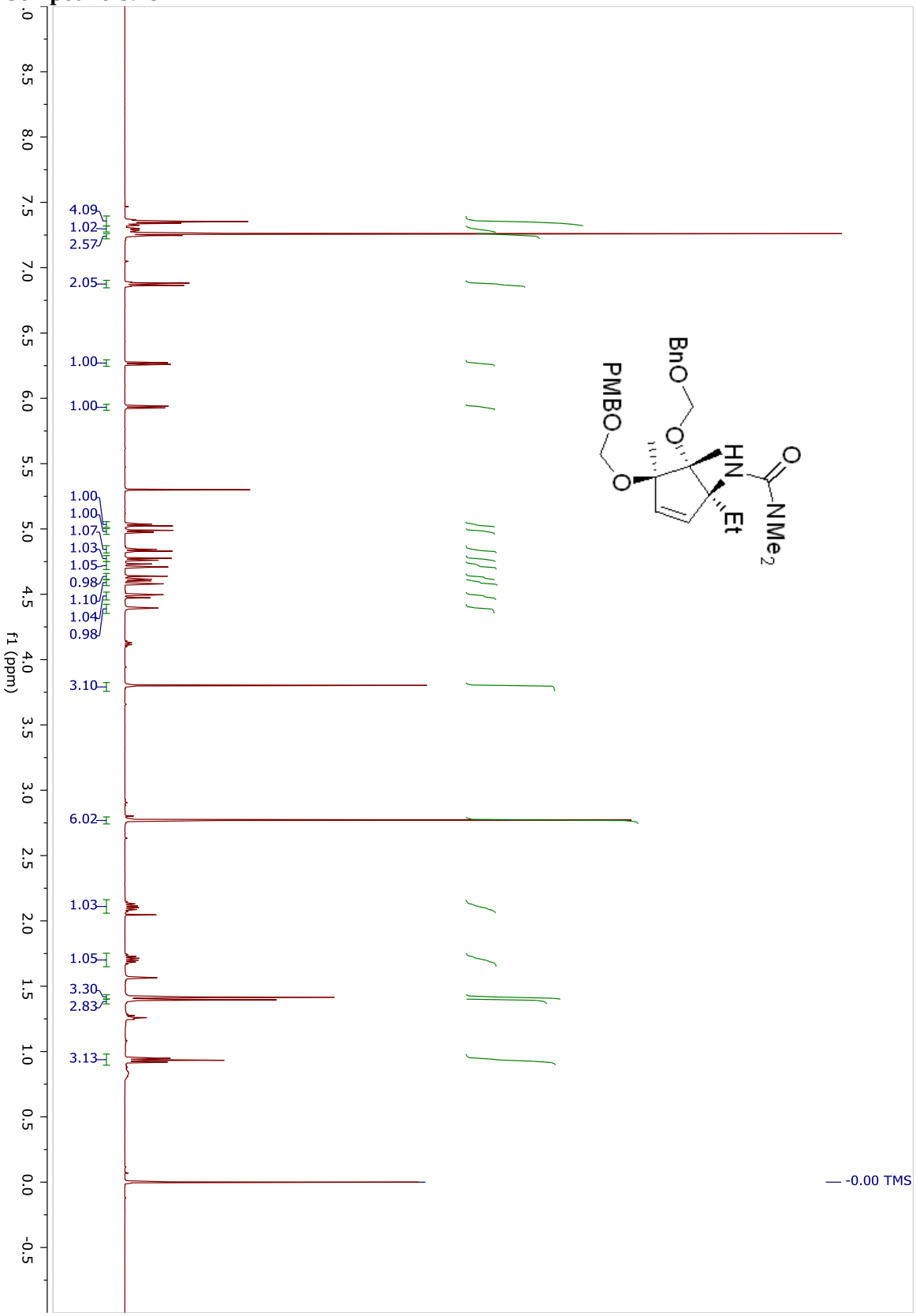

BnO
PMBO
O
O
OH
77.16 CDCl3
f1 (ppm)
20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

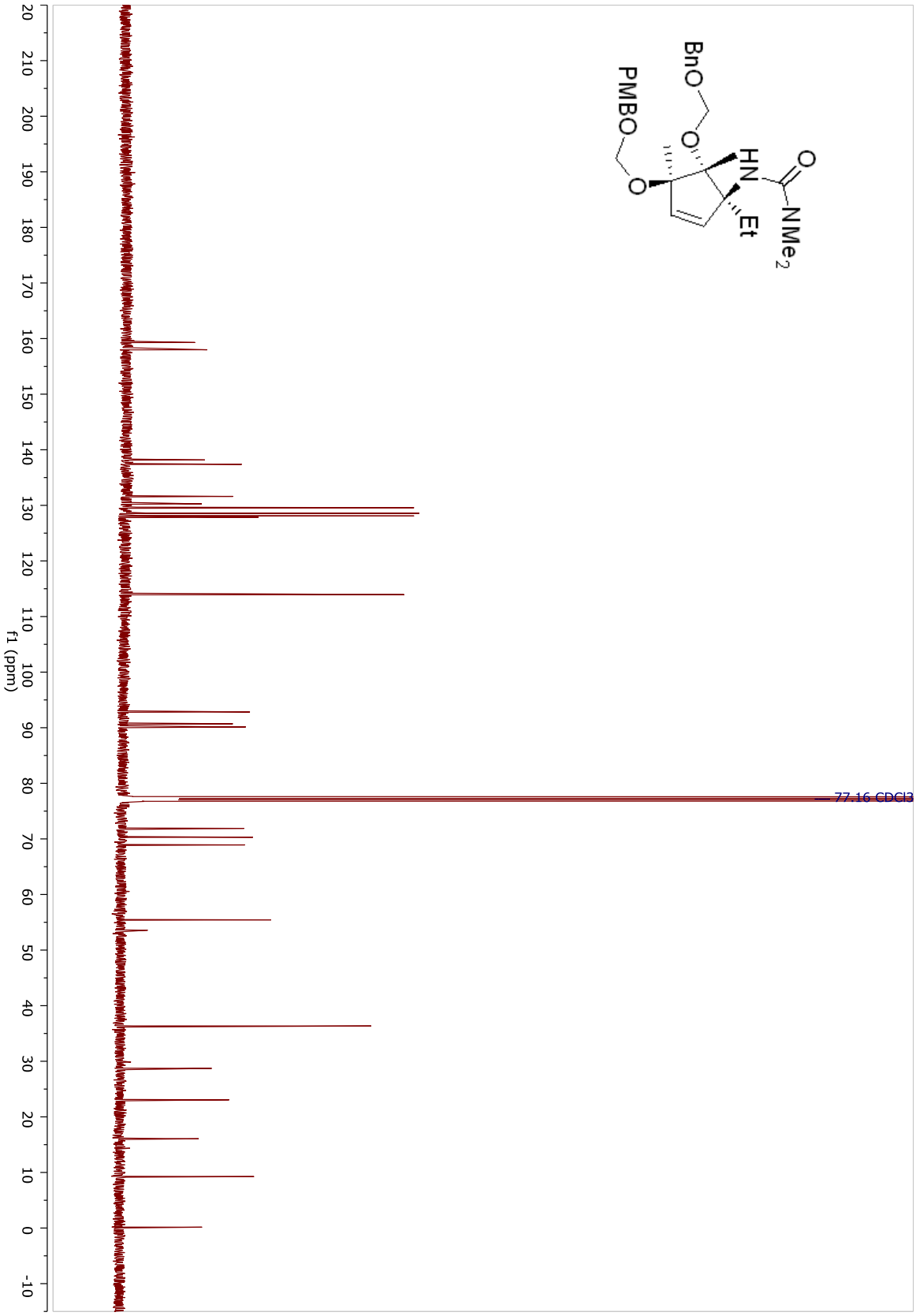
Compound 3.77



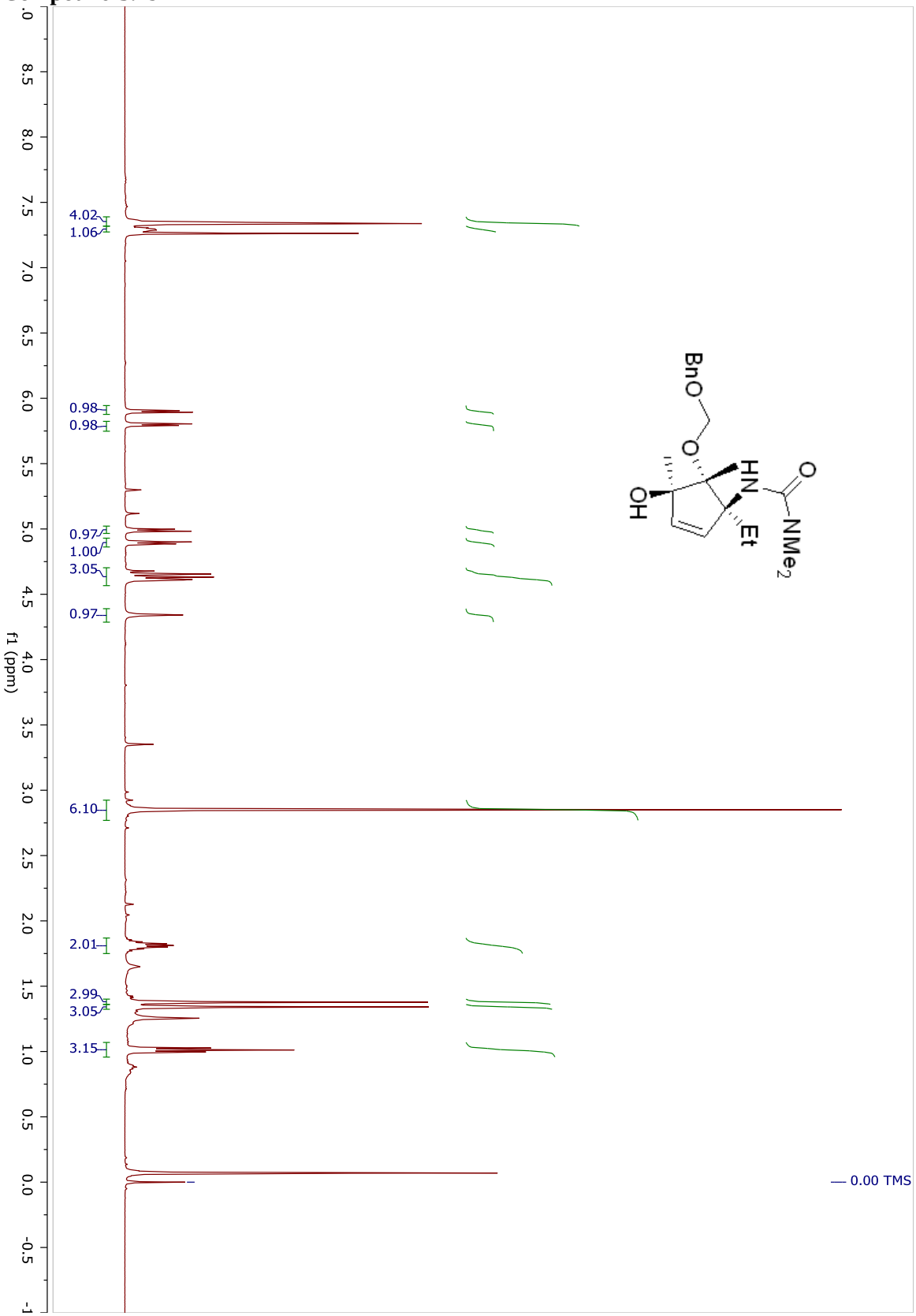

BnO
PMBO
O
O
O
O
NH2
77.16 CDCl3
f1 (ppm)
20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

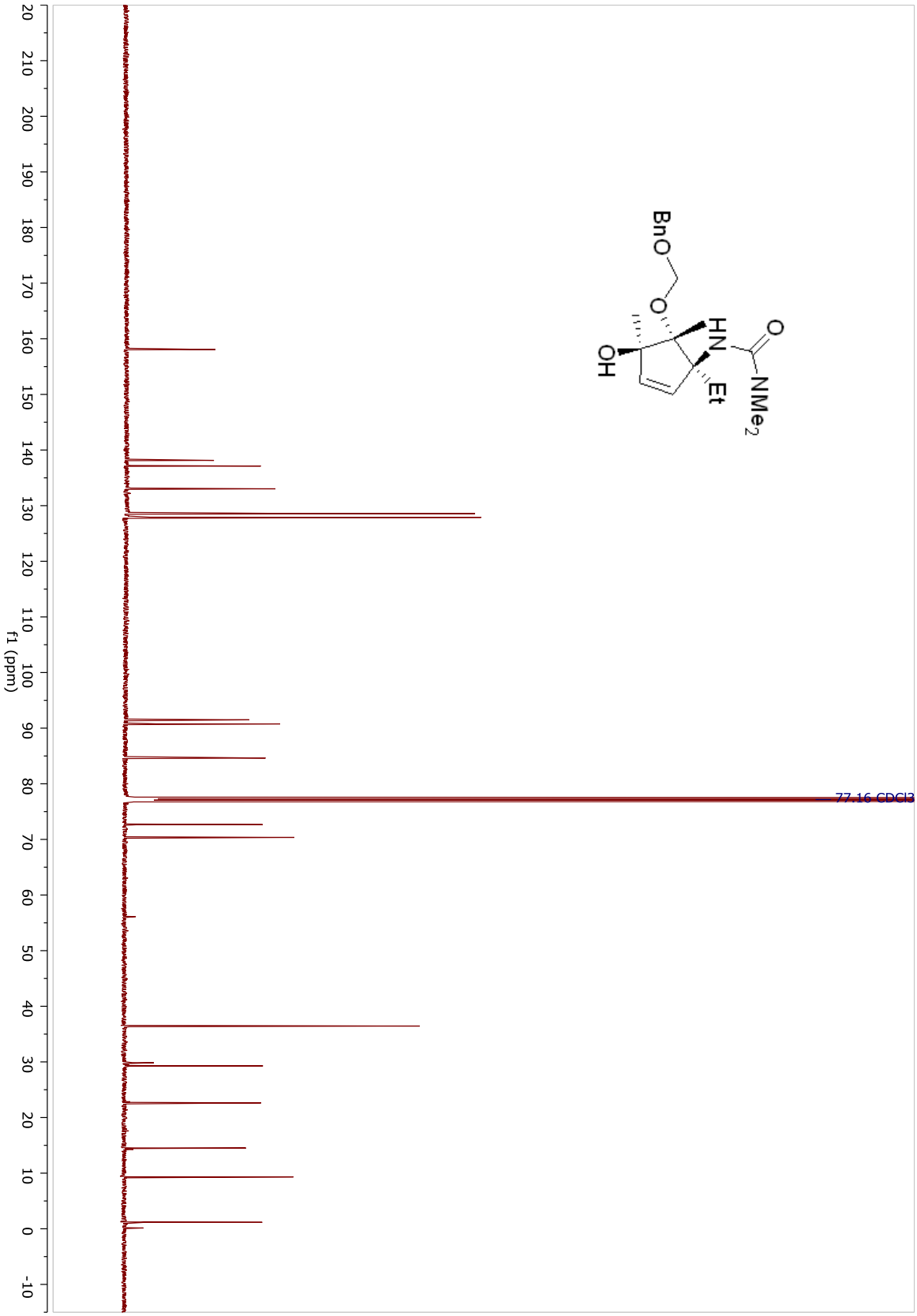
Compound 3.78




BnO
PMBO
O
HN
Et
O
NMe2
77.16 CDCl3
f1 (ppm)
20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

Compound 3.79




BnO
O
HN
OH
Et
O
NMe2
77.16 CDCl3
f1 (ppm)
20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

3.8 Experimental Details References

1. W.L.F. Armarego; C.L.L. Chai *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. Takeda, N.; Imamoto, T. *Org. Synth.* **1999**, *76*, 228.
4. Xavier, L. C.; Mohan, J. J.; Mathre, D. J.; Thompson, A. S.; Carroll, J. D.; Corley, E. G.; Desmond, R. *Org. Synth.* **1997**, *74*, 676.