

Yale University

## EliScholar – A Digital Platform for Scholarly Publishing at Yale

---

Yale Graduate School of Arts and Sciences Dissertations

---

Fall 10-1-2021

### Development of Enantioselective Synthetic Routes to (–)-Myrocin G and (–)-Euonyminol.

Martin Tomanik

Yale University Graduate School of Arts and Sciences, martin.tomanik@outlook.com

Follow this and additional works at: [https://elischolar.library.yale.edu/gsas\\_dissertations](https://elischolar.library.yale.edu/gsas_dissertations)

---

#### Recommended Citation

Tomanik, Martin, "Development of Enantioselective Synthetic Routes to (–)-Myrocin G and (–)-Euonyminol." (2021). *Yale Graduate School of Arts and Sciences Dissertations*. 430.  
[https://elischolar.library.yale.edu/gsas\\_dissertations/430](https://elischolar.library.yale.edu/gsas_dissertations/430)

This Dissertation is brought to you for free and open access by EliScholar – A Digital Platform for Scholarly Publishing at Yale. It has been accepted for inclusion in Yale Graduate School of Arts and Sciences Dissertations by an authorized administrator of EliScholar – A Digital Platform for Scholarly Publishing at Yale. For more information, please contact [elischolar@yale.edu](mailto:elischolar@yale.edu).

## Abstract

### Development of Enantioselective Synthetic Routes to (–)-Myrocin G and (–)-Euonyminol.

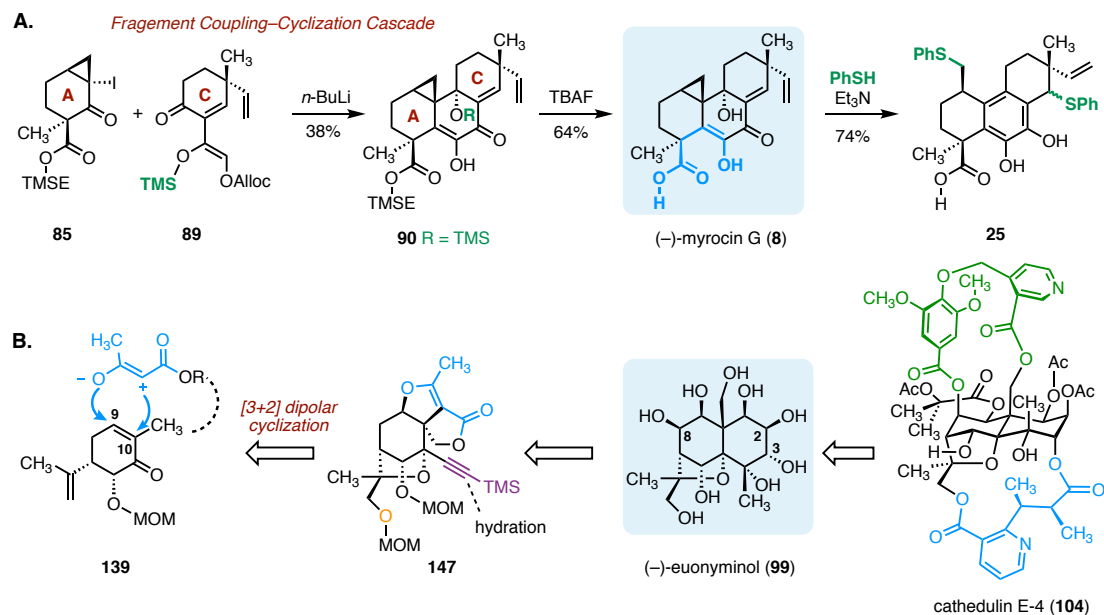
Martin Tomanik

2021

In the first chapter, I describe the development of a synthetic strategy towards (–)-myrocin G (**8**), the putative active form of the antiproliferative fungal metabolite (+)-myrocin C (**4**). Myrocin C (**4**) has been proposed to cross-link DNA by two-fold nucleotide addition; however, this proposed bioalkylation hypothesis has not been tested with native DNA. Our synthetic efforts provided a highly convergent total synthesis of myrocin G (**8**) in 15 steps from simple starting materials. A key steps in the sequence involved a carefully designed fragment coupling–cyclization cascade (see **85** + **89** → **90**). This transformation effectively unites the iodocyclopropane **85** with the enoxysilane **89** to provide in a single step and in 38% yield the protected form of the target. Next, I present our preliminary biological activity studies of the diosphenol (–)-myrocin G (**8**) including DNA cleavage and DNA cross-linking studies. The data collected from these studies indicates that myrocins do not cross-link or cleave DNA and rather suggests an alternative mode of action potentially involving a protein target.

In the second chapter, I present the development of an enantioselective synthesis of the heavily oxidized sesquiterpenoid (–)-euonyminol (**99**). Euonyminol (**99**) is the

dihydro- $\beta$ -agarofuran nucleus of the macrocyclic terpenoid alkaloids known as the cathedulins. This natural product is characterized by a tricyclic framework comprising of a *trans*-decalin fused to a tetrahydrofuran ring and by possessing nine free hydroxyl groups. Our synthetic route to access euonyminol features several highly diastereoselective transformations that were specifically designed to overcome problems encountered. For example, we developed a metal catalyzed [3+2] dipolar cycloaddition reaction provided the vinylogous carbonate **147** and simultaneously established the C9 oxidation and the C10 quaternary stereocenter, a tandem lactonization–epoxide opening to form the *trans*-C2–C3 vicinal diol residue, and a late-stage diastereoselective  $\alpha$ -ketol rearrangement necessary for the *syn*-C8–C9 oxidation pattern. The body of work presented in this chapter may set the stage for synthesizing the macrocyclic cathedulin alkaloids, such as cathedulin E-4 (**104**).



**Development of Enantioselective Synthetic Routes to (-)-Myrocin G and  
(-)-Euonyminol.**

A Dissertation

Presented to the Faculty of the Graduate School

Of

Yale University

In Candidacy for the Degree of

Doctor of Philosophy

by

Martin Tomanik

Dissertation Director: Professor Seth B. Herzon

December 2021

© 2021 by Martin Tomanik

All rights reserved.

## Table of Contents

<b>Abstract</b> .....	<b>i</b>
<b>Table of Contents</b> .....	<b>v</b>
<b>Acknowledgments</b> .....	<b>vii</b>
<b>List of Abbreviations</b> .....	<b>ix</b>
<b>List of Figures</b> .....	<b>xv</b>
<b>List of Schemes</b> .....	<b>xvi</b>
<b>List of Tables</b> .....	<b>xviii</b>
<b>Chapter 1: Development of a convergent and enantioselective synthesis of (-)-myrocin G</b> .....	<b>1</b>
<b>1.1 Introduction</b> .....	<b>2</b>
<b>1.2 Structural features and biological activities of the myrocins</b> .....	<b>3</b>
<b>1.3 Prior synthetic art of the myrocins</b> .....	<b>4</b>
1.3.1 Total Synthesis of ( $\pm$ )-myrocin C by Chu-Moyer and Danishefsky.....	<b>4</b>
1.3.2 Synthetic studies towards (+)-myrocin C by Aso and co-workers.....	<b>5</b>
<b>1.4 On the mechanism of action of the myrocins</b> .....	<b>6</b>
<b>1.5 Development of a convergent and enantioselective synthetic route to (-)-myrocin G</b> .....	<b>9</b>
1.5.1 General synthetic strategy and retrosynthetic analysis of (-)-myrocin G .....	<b>9</b>
1.5.2 Synthesis of the geminal dimethyl myrocin G analog .....	<b>10</b>
1.5.3 Synthesis of (-)-myrocin G.....	<b>21</b>
1.5.4 Explored strategies for the conversion of (-)-myrocin G to (+)-myrocin C.....	<b>23</b>
<b>1.6 Biological evaluation of (-)-myrocin G and related analogues</b> .....	<b>24</b>
<b>1.7 Conclusion</b> .....	<b>29</b>
<b>1.8 Experimental section</b> .....	<b>30</b>
1.8.1 General information.....	<b>30</b>

1.8.2	Synthetic procedures.....	34
<b>1.9</b>	<b>Bibliography .....</b>	<b>136</b>
<b>Chapter 2: Development of an enantioselective synthesis of (-)-euonyminol .....</b>		
<b>2.1</b>	<b>Introduction.....</b>	<b>142</b>
<b>2.1</b>	<b>Biological properties and structural features of the dihydro-<math>\beta</math>-agarofuran natural products .....</b>	<b>143</b>
2.2.1	Biological activity of the dihydro- $\beta$ -agarofurans and of the cathedulins ..	143
2.2.2	Structural features of the dihydro- $\beta$ -agarofurans and introduction to euonyminol .....	145
<b>2.3</b>	<b>Prior synthetic art towards the dihydro-<math>\beta</math>-agarofurans.....</b>	<b>146</b>
2.3.1	Total synthesis of ( $\pm$ )-euonyminol by White and co-workers .....	146
2.3.2	Synthetic studies towards (-)-euonyminol by Spivey and co-workers ...	147
2.3.3	Total synthesis of (-)-4-hydroxyzinowol by Inoue and co-workers.....	148
<b>2.4</b>	<b>Development of an enantioselective synthetic route to (-)-euonyminol.....</b>	<b>150</b>
2.4.1	Synthesis of the exocyclic olefin <b>179</b> via a novel oxyalkylation reaction of an allylic alcohol.....	150
2.4.2	Synthesis of the lactone <b>197</b> by an aldol–dehydration strategy.....	160
2.4.3	Completion of the synthesis of (-)-euonyminol.....	165
2.4.4	Improved synthesis of the unsaturated ketone <b>216</b> via a 6- <i>endo</i> -trig radical cyclization.....	170
2.4.5	Application of the synthetic strategy towards the macrocyclic cathedulins alkaloids.....	173
<b>2.5</b>	<b>Conclusion .....</b>	<b>174</b>
<b>2.6</b>	<b>Experimental section .....</b>	<b>176</b>
2.6.1	General information.....	176
2.6.2	Synthetic procedures.....	179
<b>2.7</b>	<b>Bibliography .....</b>	<b>296</b>
<b>Appendix A: Catalogue of Crystallographic Data .....</b>		<b>303</b>
<b>Appendix B: Catalogue of Spectroscopic Data .....</b>		<b>343</b>

## Acknowledgments

First and foremost, I would like to acknowledge and give my sincerest thanks to Seth. You have completely exceeded all of my expectations as a teacher, mentor, and a friend. The past five years have been a tremendous learning experience, and I feel extremely lucky to have had this opportunity. Your scientific curiosity, gifted creativity, and relentless work ethic are second to none and one day I hope to emulate these qualities in my own group. I am very thankful to have you in my corner as I navigate the next chapters of my career. I would also like to thank my thesis committee members Professors Jon Ellman and Tim Newhouse for their valuable feedback and support during my graduate education.

Next, I would like to thank Christos Economou for a great friendship and for inviting me to work with him on the myrocin project. I learned a tremendous amount from working with you. I am thankful for our never ending conversations, arguments, and laughs while sharing the same fume-hood together.

A special thank you goes to Olivia Goethe for her unwavering support and kindness. I can't thank you enough for your reassuring presence during the exciting "highs" but also the stressful "lows" while at Yale. I am truly lucky to have met you and I am looking forward to dragging you across the country.

I am also very grateful for the many friends that made in the department along the way, I will certainly cherish the memories we made here together. To the Herzon group members, notably, Kevin, Ian, Nick, Zikki, Xiaoshen, Alan, Josh, Zhixun, Chao, Zechun, Haruka, and Tim I am thankful for your friendship and for turning the lab into a second



home for me. I look forward to seeing what you all accomplish in the lab and in your independent careers. I hope to keep in touch.

Lastly, I would like to thank my family, the Ceplikas family, and all my college friends for their constant support and for always being there for me. I cannot put it into words how much you all mean to me and I definitely could not have achieved any of this without your encouragement.

## List of Abbreviations

A	alpha, specific rotation
$[\alpha]$	optical rotation
Ac	acetyl
Ac <sub>2</sub> O	acetic anhydride
AcOH	acetic acid
Ag <sub>2</sub> O	silver(I)oxide
Al(CH <sub>3</sub> ) <sub>3</sub>	trimethylaluminum
Alloc	allyloxycarbonyl
AllocCl	allyl chloroformate
$\beta$	beta
Br	bromide
Bn	benzyl
BnBr	benzyl bromide
Boc	<i>tert</i> -butoxycarbonyl
°C	degree celsius
CAM	cerium ammonium molybdate
CAN	ammonium cerium(IV) nitrate
CH <sub>3</sub>	methyl
CH <sub>3</sub> CN	acetonitrile
CH <sub>3</sub> I	iodomethane
CH <sub>3</sub> Li•LiBr	methyl lithium-lithium bromide complex

CH <sub>2</sub> N <sub>2</sub>	diazomethane
CH <sub>3</sub> OH	methanol
CH <sub>3</sub> OTf	methyl trifluoromethanesulfonate
(CH <sub>3</sub> ) <sub>3</sub> SOI	trimethylsulfoxonium iodide
<i>Cis</i>	on the same side
Cl	chloride
Cs <sub>2</sub> CO <sub>3</sub>	cesium carbonate
CsF	cesium fluoride
Cu[TBS]	bis( <i>N</i> -( <i>tert</i> -butyl)salicylaldiminato)copper(II)
D	doublet
DBU	1,8-diazobicyclo[5.4.0]undec-7-ene
DCC	<i>N,N'</i> -dicyclohexyldiimide
DIBAL	di- <i>iso</i> -butylaluminum hydride
DMAP	4-(dimethylamino)pyridine
DMDO	dimethyldioxirane
DMF	<i>N,N'</i> -dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
dr	diastereomeric excess
<i>E</i>	entegen, across
ee	enantiomeric excess
et al.	et alii (“and others”)

<i>ent</i>	enantiomer
Et <sub>3</sub> N	triethylamine
EtOAc	ethyl acetate
EtOH	ethanol
<i>gem</i>	geminal
HATU	1-[bis(dimethylamino)methylene]-1 <i>H</i> -1,2,3-triazolo[4,5- <i>b</i> ]pyridinium 3-oxid hexafluoro-phosphate
HCl	hydrochloric acid
HF•Et <sub>3</sub> N	hydrogen fluoride triethylamine complex
Hg(OTf) <sub>2</sub>	mercury triflate
HMBC	heteronuclear multiple bond correlation
HPLC	high-performance liquid chromatography
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum coherence
Hz	Hertz
<i>i</i> -Pr	<i>iso</i> -propyl
<i>i</i> -Pr <sub>2</sub> NEt	di- <i>iso</i> -propylethyl amine
<i>i</i> -PrMgCl	<i>iso</i> -propylmagnesium chloride
J	coupling constant
kcal	kilocalorie
K <sub>2</sub> CO <sub>3</sub>	potassium carbonate
K <sub>2</sub> OsO <sub>4</sub>	potassium osmate(IV)
LaCl <sub>3</sub> •2LiCl	lanthanum chloride lithium chloride complex

LiAlH <sub>4</sub>	lithium aluminum hydride
LiBH <sub>4</sub>	lithium borohydride
LiCl	lithium chloride
LDA	lithium di- <i>iso</i> -propylamide
LC/MS	liquid chromatography/mass spectrometry
M	multiplet
M	molar concentration
μM	micro molar concentration
<i>m</i> -CPBA	3-chloroperoxybenzoic acid
mg	milligram
MIC	minimum inhibitory concentration
mL	milliliter
μL	microliter
mmol	millimole
μmol	micromole
MMPP	magnesium monoperoxyphthalate
MOM	methoxymethyl
MOMCl	methoxymethyl chloride
MsCl	methanesulfonyl chloride
N	normal
<i>n</i> -BuLi	<i>n</i> -butyllithium
NaBH <sub>4</sub>	sodium borohydride
NaH	sodium hydride

NaOCH <sub>3</sub>	sodium methoxide
NH <sub>4</sub> Cl	ammonium chloride
NMO	<i>N</i> -methylmorpholine <i>N</i> -oxide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NaOEt	sodium ethoxide
NaO <i>t</i> -Bu	sodium <i>tert</i> -butoxide
OTf	trifluoromethanesulfonate
O <sub>3</sub>	ozone
PAA	<i>para</i> -anisaldehyde
Pb(OAc) <sub>4</sub>	lead tetraacetate
Pd/BaSO <sub>4</sub>	palladium on barium sulfate
Pd(OAc) <sub>2</sub>	palladium(II) acetate
Pd(PPh <sub>3</sub> ) <sub>3</sub>	palladium(0) tetrakis(triphenylphosphine)
Ph	phenyl
PhCH <sub>3</sub>	toluene
PhSH	thiophenol
PPTS	pyridinium <i>p</i> -toluenesulfonate
PTSA	<i>para</i> -toluenesulfonic acid
ppm	parts per million
R	general alkyl substituent
R <sub>f</sub>	retention factor
s	singlet

SeO <sub>2</sub>	selenium dioxide
Si(OTf) <sub>2</sub> ( <i>t</i> -Bu) <sub>2</sub>	di- <i>tert</i> -butylsilyl ditrifluoromethanesulfonate
T	temperature
<i>t</i> -BuOH	<i>tert</i> -butanol
TBAF	tetra- <i>n</i> -butylammonium fluoride
TBS	<i>tert</i> -butylsilyl
TBSCl	<i>tert</i> -butyl chloride
TBSOTf	<i>tert</i> -butyldimethylsilyl trifluoromethanesulfonate
TMU	tetramethylurea
TMSOTf	trimethylsilyl trifluoromethanesulfonate
TFA	trifluoroacetic acid
Tf <sub>2</sub> O	trifluoromethanesulfonic anhydride
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMS	trimethylsilyl
TMSCl	trimethylsilyl chloride
TMSE	2-trimethylsilylethyl
<i>trans</i>	across
UV	ultraviolet
v/v	volume/volume
Z	zusammen, on the same side

## List of Figures

<b>Figure 1.</b> Structure of isopimaric acid ( <b>1</b> ) and structures of myrocin A–G ( <b>2–8</b> ) .....	2
<b>Figure 2.</b> DNA plasmid cleavage assay employing circular pBR322 plasmid DNA and (–)-myrocin G ( <b>8</b> ).....	27
<b>Figure 3.</b> DNA cross-linking assay employing linear pUC19 DNA and myrocin analogs(–)- <b>65</b> and (+)- <b>65</b> .....	28
<b>Figure 4. A.</b> Structures of the dihydro- $\beta$ -agarofuran skeleton ( <b>98</b> ), (–)-euonyminol ( <b>98</b> ), and additional representative isolates ( <b>100–102</b> ). <b>B.</b> Structures of several representative cathedulin terpenoid alkaloids ( <b>103–105</b> ). <b>C.</b> Structure of evonine ( <b>106</b> ) .....	142
<b>Figure S1.</b> The complete numbering scheme of the cyclopropane <b>37</b> with 50% thermal ellipsoid probability levels.....	305
<b>Figure S2.</b> The complete numbering scheme of the vinyl iodine <b>41</b> with 50% thermal ellipsoid probability levels.....	309
<b>Figure S3.</b> The complete numbering scheme of the cyclobutanol <b>51</b> with 50% thermal ellipsoid probability levels.....	313
<b>Figure S4.</b> The complete numbering scheme of the geminal dimethyl analog (–)- <b>65</b> with 50% thermal ellipsoid probability levels .....	322
<b>Figure S5.</b> The complete numbering scheme of the cyclic ether <b>141</b> with 50% thermal ellipsoid probability levels.....	324
<b>Figure S6.</b> The complete numbering scheme of the vinylogous carbonate <b>147</b> with 50% thermal ellipsoid probability levels.....	328
<b>Figure S7.</b> The complete numbering scheme of the $\alpha$ -ketolactone <b>169</b> with 50% thermal ellipsoid probability levels.....	332
<b>Figure S8.</b> The complete numbering scheme of the epoxide <b>196</b> with 50% thermal ellipsoid probability levels.....	336
<b>Figure S9.</b> The complete numbering scheme of the lactone <b>197</b> with 50% thermal ellipsoid probability levels.....	340



## List of Schemes

<b>Scheme 1.</b> Total synthesis of (±)-myrocin C ( <b>4</b> ) by Chu-Moyer and Danishefsky.....	4
<b>Scheme 2.</b> Synthesis of the cyclopropane <b>22</b> by Aso and co-workers. ....	6
<b>Scheme 3.</b> <b>A.</b> The mechanism proposed for the formation of the bis(sulfide) <b>25</b> by Chu-Moyer and Danishefsky. <b>B.</b> Formation of sulfide <b>26</b> from (±)-desoxymyrocine C ( <b>17</b> ).....	7
<b>Scheme 4.</b> <b>A.</b> Studies on model system <b>27</b> by Hoffmann and co-workers show the sensitive nature of the 5-hydroxy- $\gamma$ -lactone moiety. <b>B.</b> Newly proposed bioalkylation mechanisms for the formation of the bis(sulfide) <b>25</b> .....	8
<b>Scheme 5.</b> Retrosynthetic analyses to the diosphenol (–)-myrocin G ( <b>8</b> ) .....	9
<b>Scheme 6.</b> <b>A.</b> Synthesis of the racemic cyclopropyl iodide fragment <b>37</b> . <b>B.</b> Synthesis of the model iodoenone <b>39</b> .....	10
<b>Scheme 7.</b> <b>A.</b> Fragment coupling reaction to form <b>41</b> and <b>43</b> . <b>B.</b> X-ray of vinyl iodide <b>41</b> . <b>C.</b> Stereochemical model for the highly diastereoselective fragment coupling transformation .....	11
<b>Scheme 8.</b> Synthesis of the vinyl silane <b>48</b> and cyclobutanol <b>51</b> from the fragment coupled adduct <b>41</b> .....	13
<b>Scheme 9.</b> Synthesis of the pentacycle <b>54</b> via the ketofuran <b>53</b> .....	14
<b>Scheme 10.</b> Synthesis of the aldol product <b>60</b> .....	15
<b>Scheme 11.</b> Synthesis of cyclodehydrated product <b>64</b> from the aldol product <b>60</b> .....	16
<b>Scheme 12.</b> Synthesis of the 1,2-addition adduct <b>67</b> possessing a 2-(trimethylsilyl)ethyl (TMSE) protecting group.....	17
<b>Scheme 13.</b> Synthesis of diosphenol <b>75</b> via an alloc group transfer and $\beta$ -elimination...18	
<b>Scheme 14.</b> <b>A.</b> Synthesis of the newly designed C-ring fragment <b>78</b> . <b>B.</b> Synthesis of (±)-myrocin G model ( <b>65</b> ) via a fragment coupling–cyclization cascade.....	20
<b>Scheme 15.</b> <b>A.</b> Synthesis of the cyclopropyl A-ring fragment <b>85</b> . <b>B.</b> Synthesis of the enoxysilane C-ring fragment <b>89</b> .....	22
<b>Scheme 16.</b> Synthesis of (–)-myrocin G ( <b>8</b> ) and formation of the bis(sulfide) <b>25</b> .....	23
<b>Scheme 17.</b> Attempted conversion of the myrocin G model <b>65</b> to the myrocin C model <b>91</b> via synthesis of the free acid <b>93</b> .....	24

<b>Scheme 18.</b> A. Separation of ( $\pm$ )- <b>75</b> by chiral stationary phase supercritical chromatography to provide the (+)- <b>75</b> and (-)- <b>75</b> . B. Synthesis of the enantiopure azide <b>96</b> . C. Synthesis of the enantiopure alkyne <b>97</b> .....	25
<b>Scheme 19.</b> Synthesis of ( $\pm$ )-euonyminol ( <b>99</b> ) by White and co-workers .....	146
<b>Scheme 20.</b> Synthesis of the tricycle <b>123</b> by Spivey and co-workers .....	148
<b>Scheme 21.</b> Synthesis of (-)-4-hydroxyzinowol ( <b>134</b> ) by Inoue and co-workers.....	149
<b>Scheme 22.</b> First retrosynthetic analysis of (-)-euonyminol ( <b>99</b> ) .....	150
<b>Scheme 23.</b> Synthesis of the epoxide <b>146</b> .....	152
<b>Scheme 24.</b> Synthesis of the vinylogous carbonate <b>147</b> .....	153
<b>Scheme 25.</b> A. Attempted conversion of the cyclopropane <b>165a</b> to the cycloaddition product <b>165</b> . B. Proposed mechanism for the formation of the vinylogous carbonate <b>147</b> . C. Proposed mechanism for the formation of the vinylogous carbonate <b>165</b> from the pinene derivative <b>164</b> .....	157
<b>Scheme 26.</b> Synthesis of the tetracyclic acetonide <b>174</b> from <b>147</b> .....	158
<b>Scheme 27.</b> Synthesis of the exocyclic olefin <b>179</b> .....	159
<b>Scheme 28.</b> Alternative retrosynthetic analysis of (-)-euonyminol ( <b>99</b> ) .....	161
<b>Scheme 29.</b> A. Unsuccessful alkyne hydration of <b>174</b> . B. Synthesis of the propargylic alcohol <b>190</b> via alkyne hydration of the primary alcohol <b>185</b> .....	162
<b>Scheme 30.</b> Synthesis of the lactone <b>197</b> via aldol–dehydration reaction of the ketoaldehyde <b>193</b> .....	164
<b>Scheme 31.</b> Synthesis of the bis(acetonide) <b>203</b> from the lactone <b>197</b> .....	167
<b>Scheme 32.</b> Completion of the synthesis of (-)-euonyminol ( <b>99</b> ).....	169
<b>Scheme 33.</b> A. Synthesis of <b>211</b> via 5- <i>exo</i> -trig cyclization. B. Improved synthesis of the unsaturated ketone <b>194</b> from the acetonide <b>174</b> via a 6- <i>endo</i> -trig radical cyclization ....	171
<b>Scheme 34.</b> Application of the synthetic strategy towards the synthesis of the macrocyclic cathedulin K-19 ( <b>105</b> ).....	174

## List of Tables

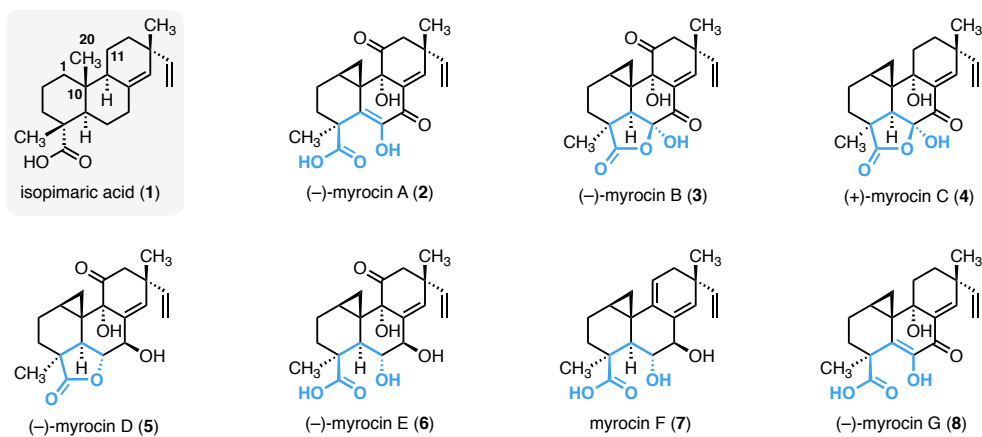
<b>Table 1.</b> IC <sub>50</sub> Values (in μM) of (-)-myrocin G ( <b>8</b> ), the geminal dimethyl analogs (-)- <b>65</b> and (+)- <b>65</b> , the azido probes (-)- <b>96</b> and (+)- <b>96</b> , and the alkynyl probes (-)- <b>97</b> and (+)- <b>97</b> .....	26
<b>Table 2.</b> Optimization of the [3+2] cyclization reaction .....	154
<b>Table 3.</b> Scope of the [3+2] cycloaddition reaction of allylic alcohols .....	156
<b>Table 4.</b> Conditions screen for the late-stage C8 oxidation of the lactone <b>197</b> .....	166
<b>Table S1.</b> Comparison of <sup>1</sup> H NMR data for the bis(sulfide) <b>25</b> .....	135
<b>Table S2:</b> Comparison of <sup>1</sup> H NMR data of natural and synthetic euonyminol ocataacetate ( <b>116</b> ).....	293
<b>Table S3:</b> Comparison of <sup>13</sup> C NMR data of natural and synthetic euonyminol ocataacetate ( <b>116</b> ).....	294
<b>Table S4:</b> Comparison of <sup>1</sup> H NMR data of synthetic euonyminol ( <b>99</b> ).....	295
<b>Table S5.</b> X-ray crystal data and structure refinement for the cyclopropane <b>37</b> .....	305
<b>Table S6.</b> X-ray crystal data and structure refinement for the vinyl iodine <b>41</b> .....	309
<b>Table S7.</b> X-ray crystal data and structure refinement for the cyclobutanol <b>51</b> .....	313
<b>Table S8.</b> X-ray crystal data and structure refinement for the geminal dimethyl myrocin G analog (-)- <b>65</b> .....	321
<b>Table S9.</b> Crystal data and structure refinement for the cyclic ether <b>141</b> .....	324
<b>Table S10.</b> Crystal data and structure refinement for the vinylogous carbonate <b>147</b> ....	328
<b>Table S11.</b> Crystal data and structure refinement for the α-ketolactone <b>169</b> .....	332
<b>Table S12.</b> Crystal data and structure refinement for the epoxide <b>196</b> .....	336
<b>Table S13.</b> Crystal data and structure refinement for the lactone <b>197</b> .....	340

## **Chapter 1.**

**Development of a convergent and enantioselective synthesis of (-)-myrocin G.**

## 1.1 Introduction.

The myrocins (**2–8**) are a small family of bioactive secondary metabolites originally isolated from the soil fungus *Myrothecium verucarrria* in 1989 (Figure 1).<sup>1-4</sup> At the time of their isolation, the myrocins were shown to possess moderate antibiotic activity against various Gram-positive bacteria, yeast, and fungi (MICs ~ 10–100  $\mu\text{g/mL}$ ).<sup>3,4</sup> They were also shown to prolong life in mouse models of Ehrlich ascites carcinoma.<sup>5,6</sup> Preliminary chemical reactivity studies conducted with a synthetic sample of ( $\pm$ )-myrocin C (**4**), by Chu-Moyer and Danishefsky lead to a hypothesis that the bioactivity of these natural products derives from cross-linking of DNA.<sup>10</sup> In the sections that follow, I will first review the structural features of these isolates, their biological activities, and prior synthetic studies that guided our approach. I will then provide a detailed development of our convergent and enantioselective strategy towards this family of compounds that ultimately provided (–)-myrocin G (**8**), the putative biologically-active form of (+)-myrocin C (**4**). Finally, I will present our preliminary cytotoxicity and DNA cross-linking studies of **8** and various other related compounds.



**Figure 1.** Structure of isopimaric acid (**1**) and the structures of myrocin A–G (**2–8**).

## 1.2 Structural features and biological activity of the myrocins.

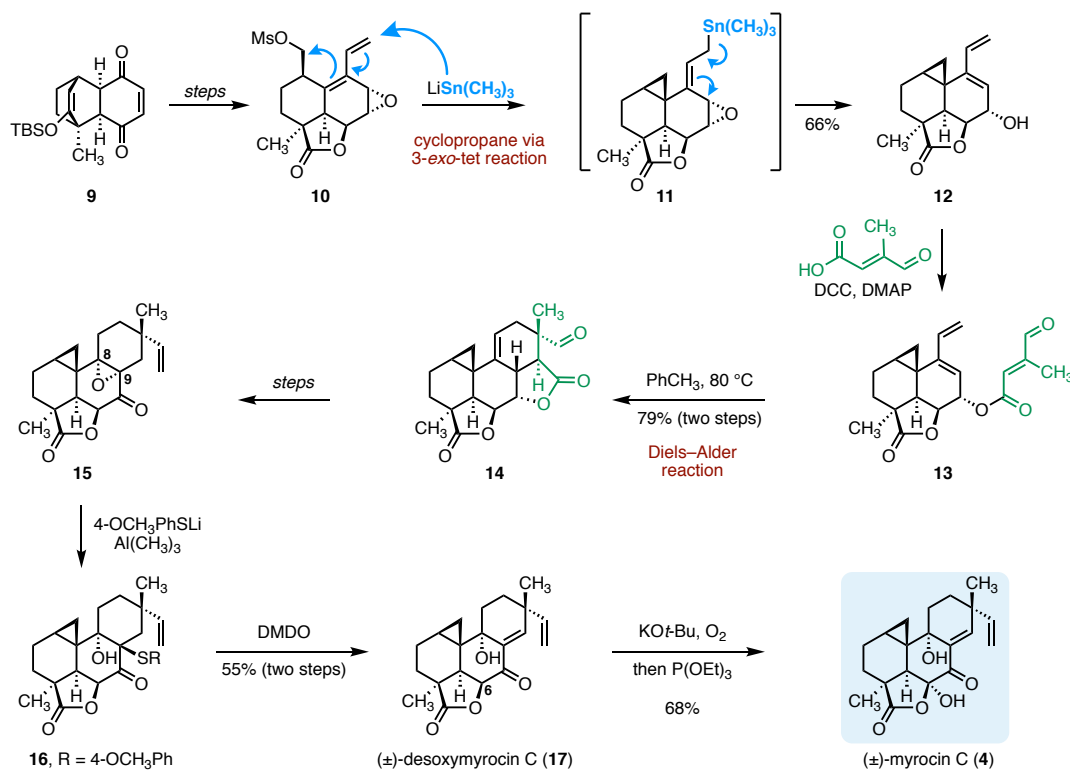
The myrocins belong to the pimarane family of diterpene natural products and are derived biosynthetically from isopimaric acid precursor (**1**, Figure 1).<sup>4</sup> A common feature of the myrocins is an activated cyclopropane moiety. This distinguishing feature arises from a biosynthetic conversion of the angular C20 methyl group to the residing C1–C10–C20 electrophilic cyclopropane. Additionally, myrocins also possess a highly oxygenated central ring, three all-carbon quaternary stereocenters, and a range of oxidation levels at the C11 position. Collectively, all of the above mentioned structural features define the myrocins as challenging targets for total synthesis.

At the time of their isolation in 1989, Nakayama and co-workers found that (–)-myrocin B (**2**) and (+)-myrocin C (**4**) exhibited a moderate antibiotic activity against several Gram-positive bacteria, yeast, and fungi (examples of tested organisms included: *Bacillus subtilis*, *Bacillus brevis*, *Staphylococcus aureus*, *Penicillium chrysogenum*, or *Candida albicans*) with MICs ~ 10–100 µg/mL. Additionally, **2** and **4** showed a promising *in vivo* antitumor activity in mouse model of Ehrlich ascites carcinoma (prolongation rate, test/control: 130% for **2** at 1.6 mg/kg, 169% for **4** at 2.4 mg/kg).<sup>5,6</sup> Although this therapeutic effect can be characterized as moderate, a detailed understating of the biological target, mechanism of action, and structure–activity relationship of the myrocins could lead to the identification of new compounds and targets for the treatment of cancer and bacterial infections. To the best of our knowledge, however, no further biological evaluation of these compounds have since been conducted.

### 1.3 Prior synthetic art of the myrocins.

#### 1.3.1 Total Synthesis of ( $\pm$ )-myrocin C by Chu-Moyer and Danishefsky.

In 1993, Chu-Moyer and Danishefsky reported the first total synthesis of ( $\pm$ )-myrocin C (**4**).<sup>7,8</sup> Their approach started with a Diels–Alder reaction between a 2-[(tert-butyl(dimethyl)silyl)oxy]-1-methylcyclohexa-1,3-diene and *p*-benzoquinone provided the cycloadduct **9** (94%, Scheme 1). This intermediate was then advanced to the mesylate **10** for a key cyclopropane forming reaction. In a key step, treatment of **10** with trimethylstannyl lithium provided the dienyl alcohol **12** (66%).



**Scheme 1.** Total synthesis of ( $\pm$ )-myrocin C (**4**) by Chu-Moyer and Danishefsky.

This transformation is believed to occur via addition of the stannyl lithium reagent to the terminal position of the 1,3-diene. Subsequent, displacement of the mesylate

substituent (3-*exo*-tet cyclization) would provide the allyl stannane intermediate **11**. Subsequent elimination of the stannyl substituent with concomitant epoxide opening would then provide the product **12**. To construct the right most ring of the natural product, **12** was first condensed with (*E*)-3-methyl-4-oxo-2-butenoic acid (DCC, DMAP) to provide ester **13**. Subsequent intramolecular Diels–Alder reaction (toluene, 80 °C) then generated the endo-bis(lactone) **14** (79%, two steps).

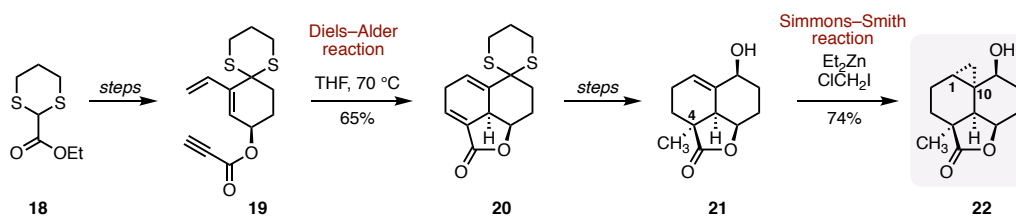
The intermediate **14** contains all of the carbon atoms of the target. The remaining steps of the synthesis focused on adjusting the oxidation state of central B-ring. To this end, bis(lactone) **14** was advanced to the epoxide **15** by a seven-step sequence. Treatment of the epoxide **15** with the aluminum thiolate of 4-methoxythiophenol resulted in the formation of the sulfide **16** via a site selective opening of the C8–C9 epoxide. Subsequent selective oxidation of the thioether moiety with DMDO initially formed the sulfoxide that under the reaction conditions underwent [2,3]-elimination to generate the (±)-desoxymyrocin C (**17**, 55% from **15**). Finally, (±)-desoxymyrocin C (**17**) was converted to (±)-myrocin C via a diastereoselective  $\alpha$ -hydroxylation–reduction reaction (KO*t*-Bu, O<sub>2</sub>, then triethyl phosphite; 68%).

### 1.3.2 Synthetic studies towards (+)-myrocin C by Aso and co-workers.

In 1998, the Aso group reported a synthetic approach towards (+)-myrocin C (**4**). In their approach, the central B-ring of the target was prepared by a diastereoselective intramolecular Diels–Alder reaction.<sup>9</sup> Their approach started with a known thioketal **18** that was advanced to the propionate ester **19** in seven steps and in 33% overall yield



(Scheme 2). After some experimentation, the authors found that desired cycloaddition could be effected by heating **19** to 70 °C in tetrahydrofuran. Under these conditions, the intramolecular [4+2] cycloadduct **20** was obtained in 65% yield. The lactone **20** was elaborated to the allylic alcohol **21** in additional four steps and in 66% yield. Treatment of the allylic alcohol **21** with diethyl zinc and chloriodomethane resulted in exclusive formation of the cyclopropyl intermediate **22** in 74% yield possessing the wrong stereochemistry at C1–C10 junction.

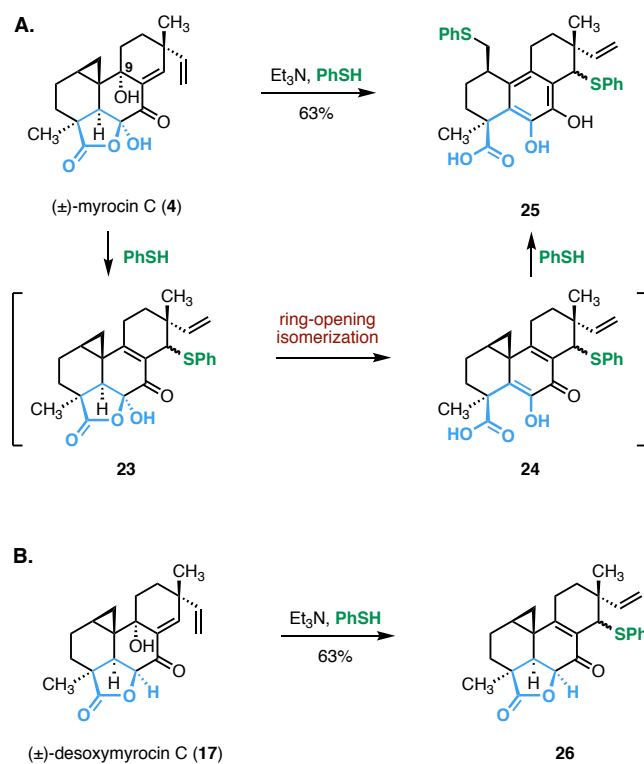


**Scheme 2.** Synthesis of the cyclopropane **22** by Aso and co-workers.

#### 1.4 On the mechanism of action of the myrocins.

Following the synthesis of ( $\pm$ )-myrocin C (**4**), Chu-Moyer and Danishefsky treated synthetic **4** with thiophenol in the presence of triethylamine and observed the formation of the bis(sulfide) **25** (63%, Scheme 3A).<sup>10</sup> The authors suggested that the bis(sulfide) **25** is formed via a 1,4-conjugate addition of the thiolate, followed by a E<sub>1</sub>cb elimination of the C9 hydroxyl substituent. A ring-opening isomerization of the 5-hydroxy- $\gamma$ -lactone moiety to the corresponding diosphenol **24**, followed by addition of a second equivalent of thiolate to the cyclopropane, would then provide the observed product. Not surprisingly, treatment

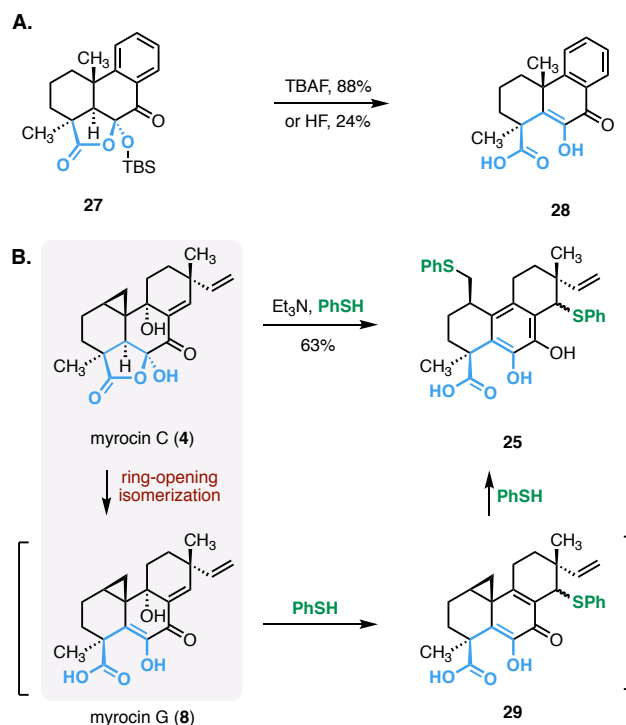
of the synthetic ( $\pm$ )-desoxymyrocin C (**17**) with identical reaction conditions provided the sulfide **26** in 63% as the sole product (Schem 3B).<sup>10</sup> This result indicates the ring-opening to the diosphenol is necessary to activate the cyclopropane for a second nucleophilic addition. Based on the observed reactivity, Chu-Moyer and Danishefsky postulated that myrocins might be capable of forming DNA cross-links via a sequential nucleotide addition.<sup>11,12</sup>



**Scheme 3. A.** The mechanism proposed for the formation of the bis(sulfide) **25** by Chu-Moyer and Danishefsky. **B.** Formation of sulfide **26** from ( $\pm$ )-desoxymyrocin C (**17**).

Hoffmann and co-workers investigated the stability of the sensitive 5-hydroxy- $\gamma$ -lactone substructure of the myrocins. The authors showed that the model system **27** underwent a ring-opening transformation to the corresponding diosphenol **28** under mildly

acidic or basic conditions (Scheme 4A).<sup>13,14</sup> This result, coupled with the isolation of (–)-myrocin A (**2**, Figure 1), the product of the ring-opening of (–)-myrocin B (**3**), lead us to hypothesize that the diosphenol (–)-myrocin G (**8**) is likely the biologically-active form of (+)-myrocin C (**4**), even though **8** has not been isolated from natural sources (Scheme 4B). Taken together, we reasoned that the order of bond forming events in the proposed bioalkylation mechanism might be reversed relative to that proposed by Chu-Moyer and Danishefsky. Specifically, an initial ring-opening isomerization of the 5-hydroxy- $\gamma$ -lactone to the diosphenol is suggested to precedes the first thiol addition as is shown in Scheme 4B.

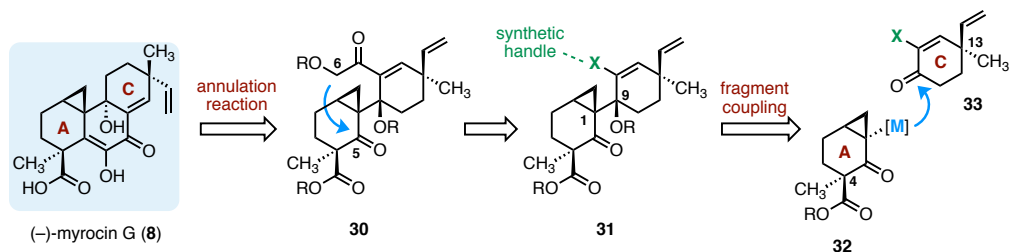


**Scheme 4.** **A.** Studies on model system **27** by Hoffmann and co-workers show the sensitive nature of the 5-hydroxy- $\gamma$ -lactone moiety. **B.** Newly proposed bioalkylation mechanisms for the formation of the bis(sulfide) **25**.

## 1.5 Development of a convergent and enantioselective synthetic route to (–)-myrocin G.

### 1.5.1 General synthetic strategy and retrosynthetic analysis of (–)-myrocin G.

Interested in the proposed DNA damaging activity of myrocins coupled with our own analysis of the potential bioalkylation mechanism, we initiated a research program to develop synthetic strategy capable of providing access to the diosphenol (–)-myrocin G (**8**) and other myrocin derivatives. Seeking to study the bioactivity of these molecules in detail after the synthesis, we desired to formulate a highly convergent and scalable synthesis capable of producing substantial quantities of the natural products.

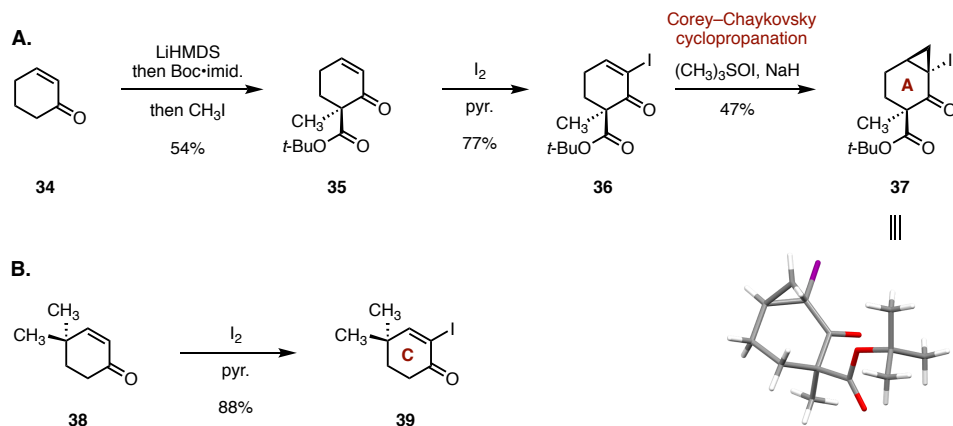


**Scheme 5.** Retrosynthetic analyses to the diosphenol (–)-myrocin G (**8**).

Our retrosynthetic analysis of **8** is shown in Scheme 5. We envisioned accessing the target from the  $\alpha$ -hydroxyketone **30** via an intramolecular aldol–dehydration reaction. The  $\alpha$ -hydroxyketone **30** residue was anticipated to be accessible by homologation of the vinyl halide **31**, followed by functionalization. Further simplification of **31** via a cleavage of the C1–C9 bond provides the cyclopropyl fragment **32** and the unsaturated ketone **33** as two precursors of similar complexity. Strategically, this disconnection allows for independent preparation of the two distal all-carbon quaternary stereocenters at C4 and C13, which would have been more challenging to do otherwise.

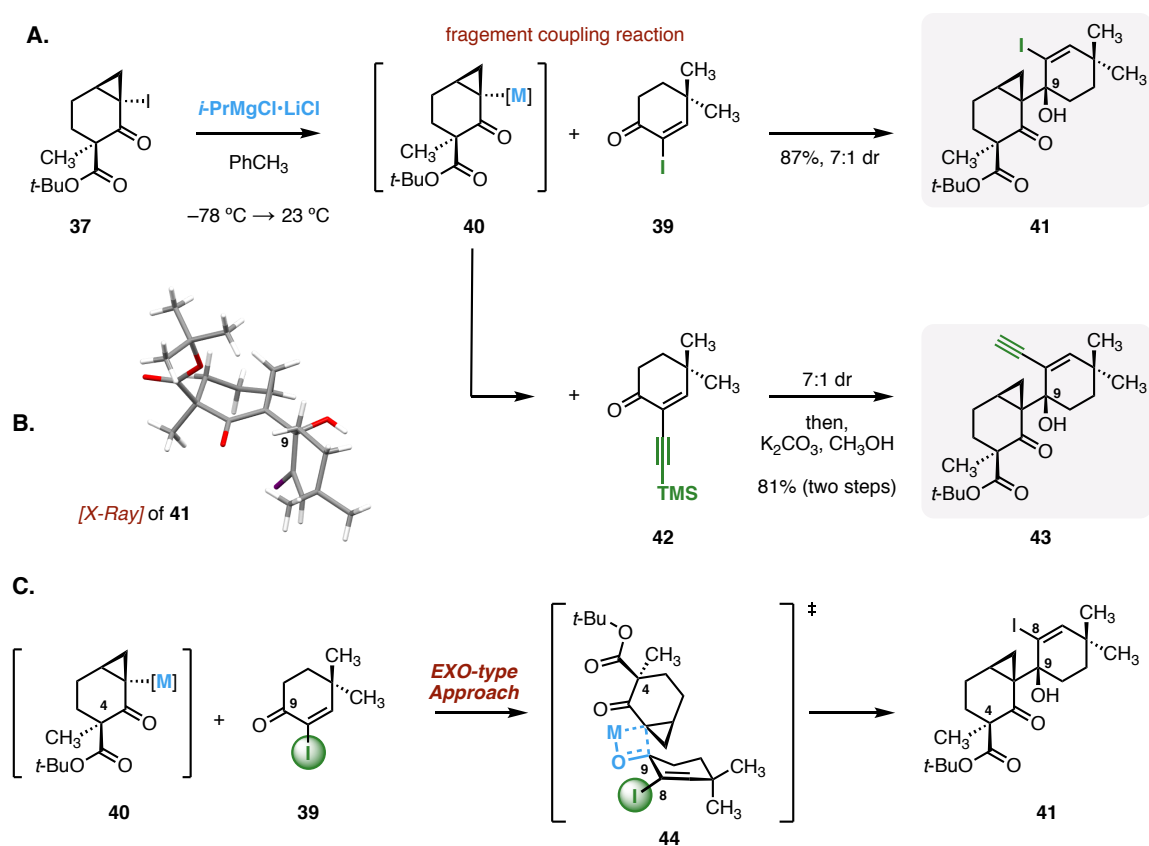
## 1.5.2 Synthesis of the myrocin G model system.

To expedite the development of the synthesis, we initiated our work with the model fragments ( $\pm$ )-**37** and the achiral  $\alpha$ -iodoenone **39** (Scheme 6). The preparation of the A-ring cyclopropyl fragment **37** began with a kinetic deprotonation of cyclohex-2-ene-1-one (**34**) with excess LiHMDS followed by a C-selective carboxylation with *N*-tert-butoxycarbonylimidazole and a subsequent second alkylation with iodomethane to provide the  $\alpha$ -methyl- $\beta$ -ketoester **35** (54%, Scheme 6A). Dehydroiodination under Johnson conditions (iodine, pyridine, 77%)<sup>16</sup> and a Corey–Chaykovsky cyclopropanation<sup>17</sup> then provided the corresponding iodocyclopropane **37** in 47% yield. The cyclopropanation proceeded with 2.4:1 diastereoselectivity and the relative stereochemistry of **37** was established by X-ray analysis. The model C-ring fragment was prepared in a single transformation from a commercially available 4,4-dimethylcyclohex-2-en-1-one (**38**) via a dehydroiodination to furnish **39** (iodine, pyridine, 88%, Scheme 6B).



**Scheme 6. A.** Synthesis of the racemic cyclopropyl iodide fragment **37**. **B.** Synthesis of the model  $\alpha$ -iodoenone **39**.

We found that exposure of **37** to *iso*-propylmagnesium chloride–lithium chloride complex in toluene at cryogenic temperatures ( $-78\text{ }^{\circ}\text{C}$ ), followed by addition of the  $\alpha$ -iodoenone **39** and subsequent warming of the reaction mixture to  $23\text{ }^{\circ}\text{C}$  generated the fragment coupled adduct **41** (87%, 7:1 dr, Scheme 7A). The complete relative stereochemistry of coupling adduct **41** was determined by X-ray crystallographic analysis (Scheme 7B). The same stereochemical preference was observed when the alkynyl electrophile **42** was employed, to provide (after desilylation with potassium carbonate in methanol) the enyne fragment coupling product **43** (81%, 7:1 dr two steps).

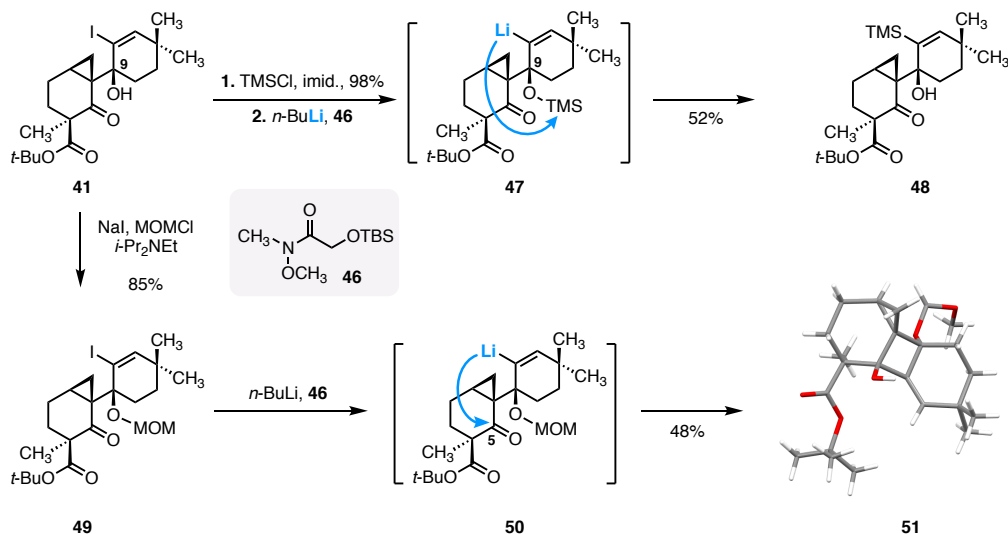


**Scheme 7.** **A.** Fragment coupling reaction to form **41** and **43**. **B.** X-ray analysis of the vinyl iodide **41**. **C.** Stereochemical model for highly diastereoselective fragment coupling transformation.

We rationalized the high degrees of stereochemical control in this fragment coupling with the model shown in Scheme 7C. If approach of the nucleophile occurs along the Bürgi–Dunitz trajectory, the relative *exo*-type orientation between the nucleophile **40** and the electrophile **39** shown would minimize the non-bonded interactions between the C4 quaternary stereocenter in the nucleophile **40** and the bulky C8 halogen in the electrophile **39**, leading to the observed diastereomer.<sup>18</sup> The alternative *endo*-type approach (not shown) is disfavored due to superposition of the steric bulk of the incoming nucleophile over the plane of the electrophile.

Having discovered a robust access to the fragment coupling adduct **41**, the next steps of the synthesis of (–)-myrocin G (**8**) focused on introducing the appropriate two carbon synthon to the vinyl iodide handle to arrive at the retrosynthetically desired  $\alpha$ -hydroxyketone **30** shown in Scheme 5. The tertiary hydroxyl in **41** was first protected as the corresponding trimethylsilyl ether (TMSCl, imidazole, 98%). However, subsequent lithiation of the vinyl iodide (*n*-butyllithium, –78 °C) followed by addition of the Weinreb amide **46**<sup>19</sup> did not introduce the desired glycolic-acid synthon, but rather we obtained the vinyl silane **48** in 52% yield. Compound **48** arise from an unproductive retro–Brook rearrangement of the vinyl lithium intermediate **47** with the C9 trimethylsilyl group as is shown in Scheme 8. To circumvent this, the fragment coupling product **41** was converted to the methoxymethyl ether **49** (sodium iodide, chloromethyl methyl ether, *N,N*-diisopropylethylamine, 85%). However, lithium–halogen exchange (*n*-butyllithium)

followed by addition of the identical Weinreb amide **46** provided the cyclobutanol **51** (48%). These two results indicated to us that strategies relying on metalation and subsequent trapping will not be capable of introducing the desired two carbon synthon in place of the vinyl iodide handle.

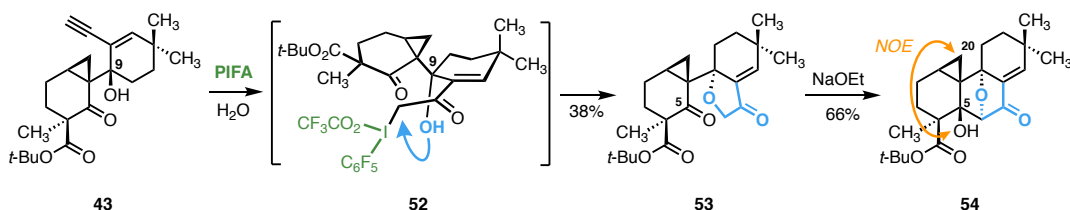


**Scheme 8.** Synthesis of the vinyl silane **48** and cyclobutanol **51** from the fragment coupling adduct **41**.

The next strategy pursued to arrive at the desired  $\alpha$ -hydroxyketone moiety employed the alkyne intermediate **43**. We envisioned the direct conversion of **43** to the  $\alpha$ -hydroxyketone **30** via an oxidative hydration of the alkyne residue, as described by Kita and co-workers.<sup>20</sup> However, only the ketofuran **53** was obtained (38%) when the enyne **43** was subjected to the oxidative hydration conditions (bis(trifluoroacetoxy)iodobenzene, water). The ketofuran **53** may form by intramolecular displacement of the activated alkyne by the C9 hydroxyl, as shown is in Scheme 9. Attempted oxidative functionalization of the alkyne moiety with the C9 hydroxyl group protected did not provide the desired  $\alpha$ -hydroxyketone group. Nevertheless, ketofuran **53** provided us with an opportunity to

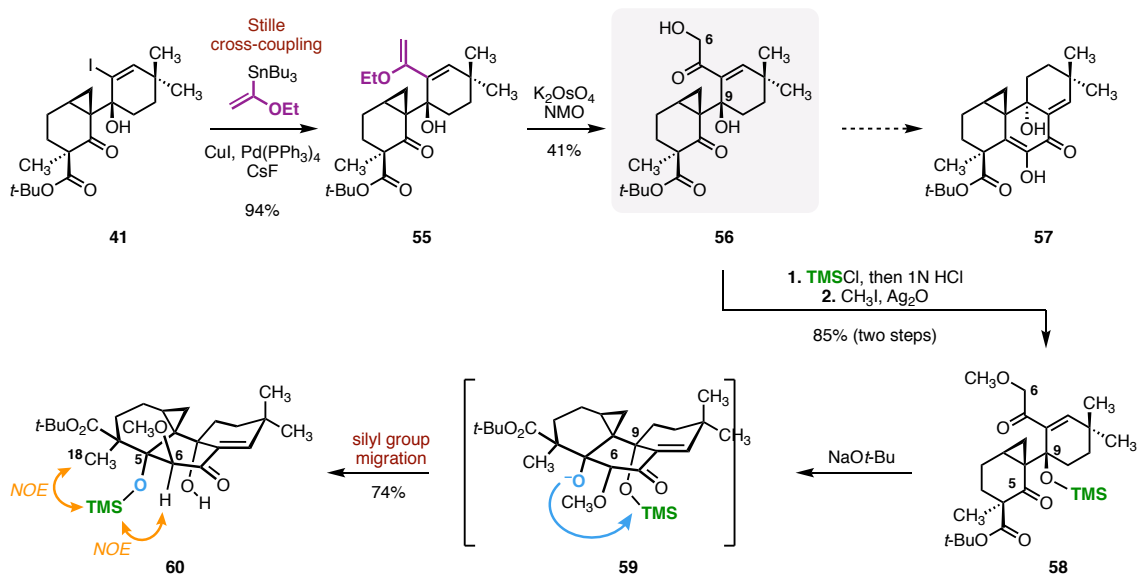


attempt an annulation reaction to access the ring-closed scaffold. We found that treatment of **53** with sodium hydroxide in ethanol produced the aldol product **54** in 66% yield as a single detectable diastereomer ( $^1\text{H}$  NMR analysis). The relative stereochemistry of **54** was established by nuclear Overhauser effect analysis, which showed a strong correlation between the C5 hydroxyl proton and the C20 cyclopropane proton (Scheme 9).



**Scheme 9.** Synthesis of the pentacycle **54** via the ketofuran **53**.

A successful strategy to access the desired  $\alpha$ -hydroxyketone was eventually realized via the following two step protocol (Scheme 20). First, a Stille cross-coupling between the fragment coupling product **41** and tributyl(1-ethoxyvinyl)tin [copper(I) iodide, tetrakis(triphenylphosphine)palladium(0), cesium fluoride] provided the ethyl vinyl ether intermediate **55** in 94% yield. This was followed by a dihydroxylation of the vinyl ether residue [potassium osmate(VI) dihydrate, 4-methylmorpholine *N*-oxide] to provide the sought-after  $\alpha$ -hydroxyketone **56** in moderate yield of 41%. However, in contrast to our experience with the ketofuran **53**, attempted ring-closures of **56** by aldol addition under numerous basic and acidic reaction conditions resulted only in decomposition without any of the desired aldol product detected ( $^1\text{H}$  NMR analysis). We reasoned that the acidic protons in **56** were impeding the desired addition.

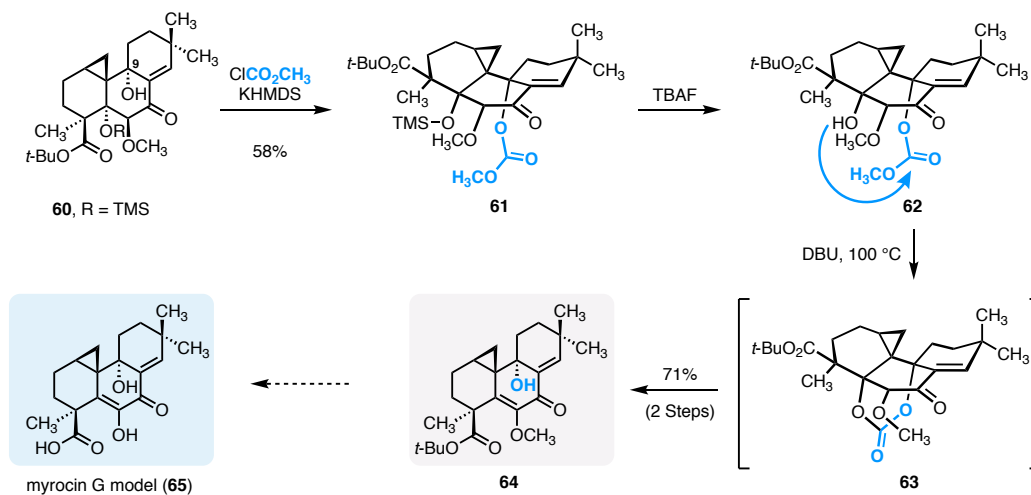


**Scheme 10.** Synthesis of the aldol product **60**.

To address this, the  $\alpha$ -hydroxyketone **56** was first subjected to a two-fold silylation with excess chlorotrimethylsilane and imidazole, followed by a selective hydrolysis of the unstable primary trimethylsilyl ether group (aqueous hydrochloric acid) to provide a C9 trimethylsilyl protected intermediate (not shown, Scheme 10). Ensuing exposure of the silyl ether to silver(I) oxide and iodomethane furnished the fully protected methyl ether intermediate **58** (85%, two steps). After much experimentation, we found that aldol addition product **60** was obtained in 74% yield by the treatment of the methyl ether **58** with sodium *tert*-butoxide in a mixture of tetrahydrofuran and *tert*-butanol. However, to our surprise this aldol addition reaction was accompanied by a transfer of the trimethylsilyl group from the C9 hydroxyl to the newly formed C5 alkoxide as is shown in Scheme 10. This unexpected result was rigorously confirmed using NMR spectroscopy, which revealed a strong nuclear Overhauser effect correlations between the C5 silyl ether

residue and the C18 methyl group as well as the C6 methine proton that is consistent with the stereochemical assignment shown in Scheme 10.

Intrigued by the trimethylsilyl group migration, we envisioned using this migration strategically to activate the C5 hydroxyl group towards an elimination, to generate the corresponding cyclodehydration product. To realize this approach, **60** was first treated with potassium bis(trimethylsilyl)amide and methyl chloroformate to arrive at the carbonate **61** (58%, Scheme 11). Subsequent removal of the trimethylsilyl substituent with tetrabutylammonium fluoride provided the free alcohol intermediate **62**. Finally, exposure of **62** to excess 1,8-diazabicyclo[5.4.0]undec-7-ene at elevated temperatures of 100 °C generated the cyclodehydration product **64** (71% from **61**). We believe that this transformation occurs via a transient formation of the shown cyclic carbonate intermediate **63**, which is poised to undergo a facile  $\beta$ -elimination.

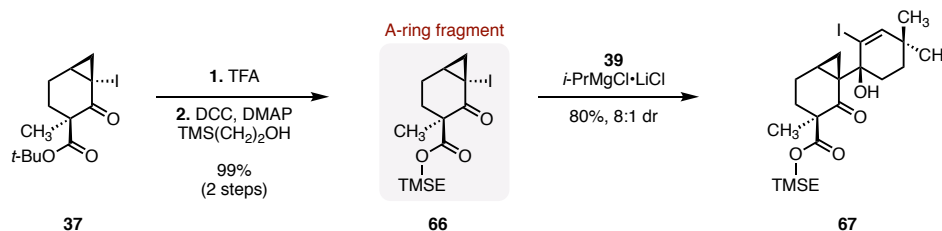


**Scheme 11.** Synthesis of cyclodehydrated product **64** from the aldol product **60**.

Unfortunately, our extensive efforts to remove the methyl enol ether and the *tert*-butyl ester substituents of **64** under various strongly acidic or Lewis acidic condition were

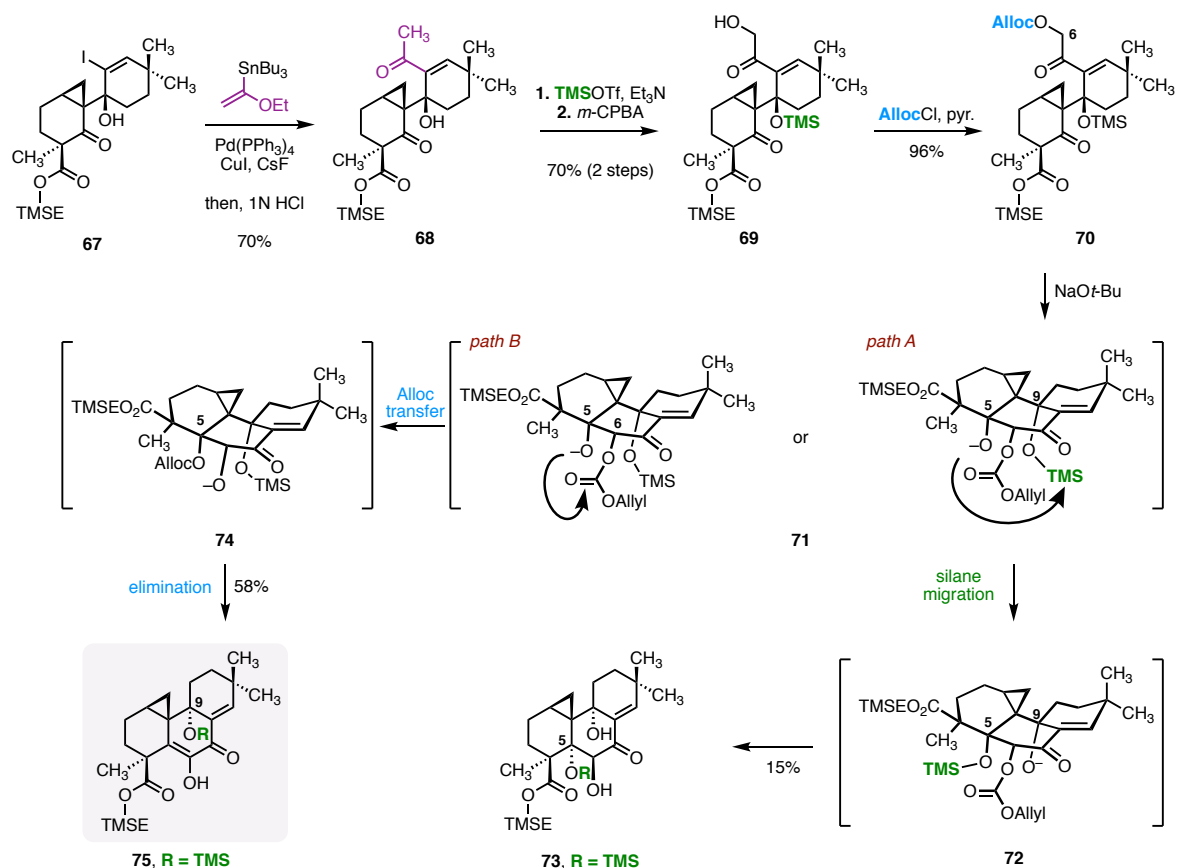
uniformly unsuccessful. Consequently, at this point we decided to look for alternative protecting groups for the carboxylic acid and the diosphenol functional groups.

After a period of experimentation, we speculated if we could employ 2-(trimethylsilyl)ethyl as an alternative protecting group for the carboxylic acid moiety. Accordingly, the *tert*-butyl ester of **37** was cleanly cleaved by a treatment with trifluoroacetic acid (Scheme 12). Subsequent esterification of the resulting carboxylate with 2-(trimethylsilyl)ethyl alcohol) using *N,N'*-dicyclohexylcarbodiimide and DMAP as promoters provided the new A-ring fragment **66** (99%, two steps). The fragment coupling of **66** with the iodoenone **39** proceeded as expected to furnish the 1,2-addition adduct **67** (80%, 8:1 dr).



**Scheme 12.** Synthesis of the 1,2-addition product **67** possessing a 2-(trimethylsilyl)ethyl (TMSE) protecting group.

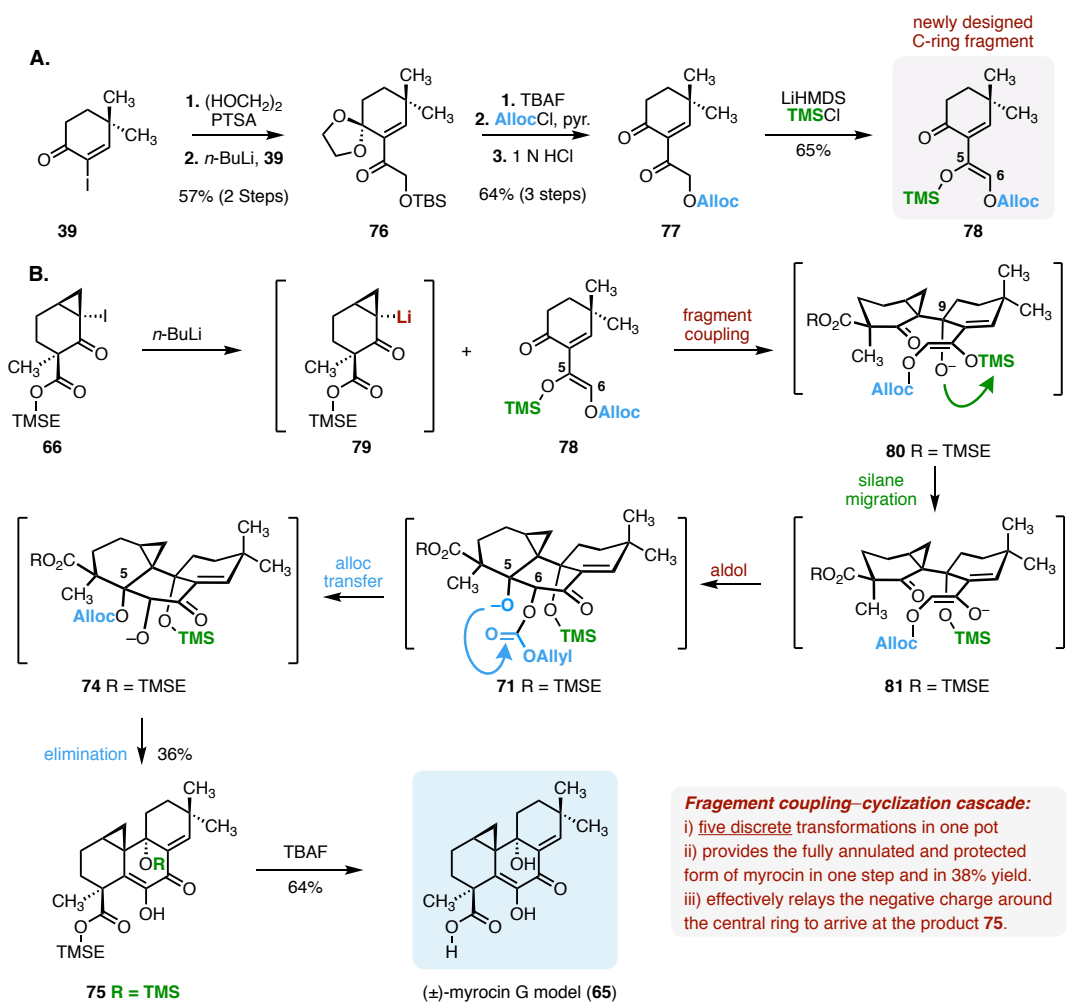
We modified the preceding  $\alpha$ -hydroxyketone synthesis to improve material throughput. The Stille cross-coupling product was hydrolyzed by direct addition of aqueous hydrochloric acid to the unpurified product, to generate the methyl ketone **68** (70%). Ensuing treatment of the methyl ketone **68** with excess trimethylsilyl trifluoromethanesulfonate and triethylamine resulted in silylation of the ketone and C9 hydroxyl group (not shown). Rubottom oxidation<sup>21</sup> (*meta*-chloroperoxybenzoic acid) provided the trimethylsilyl protected  $\alpha$ -hydroxyketone **69** (70%, two steps).



**Scheme 13.** Synthesis of diosphenol **75** via an Alloc group transfer and  $\beta$ -elimination.

Next, we substituted the previously discussed C6 methyl ether for an allyl carbonate (Alloc) group (allyl chloroformate, pyridine, 96%). We found that treatment of this compound with our previously described aldol conditions (sodium *tert*-butoxide) resulted in formation of the expected silane transfer product **73** as only the minor product (15%, Scheme 13, path A). Instead, the major product of this transformation was the diosphenol **75** (58%). We speculated that formation of the diosphenol **75** arises from the preferential migration of the Alloc group from the C6 primary alcohol to the newly-formed C5 alkoxide (Scheme 13, path B), to provide the carbonate **74**. Formal 1,2-proton transfer and  $\beta$ -elimination would then generate the observed product **75**.

The mechanistic insight gained from the synthesis of the diosphenol **75** lead to us consider an alternative C-ring fragment that contains a masked enolate equivalent. We hypothesized that such fragment could allow us to conduct the fragment coupling and annulation steps into a single operation by strategic use of the migration events we had discovered. This type of thinking lead us to rationally design the enoxysilane fragment **78** (Scheme 14A). Preparation of this model fragment was accomplished in six transformations from **39**. Ketalization of the ketone group (triethylorthoformate, ethylene glycol, para-toluenesulfonic acid), followed by lithium–halogen exchange (*n*-butyl lithium) and trapping with the Weinreb amide **46** provided the ketone **76** in 57% yield. Next, desilylation (TBAF), followed by installation of the allyl carbonate group (allyl chloroformate, pyridine), and ketal hydrolysis (aqueous hydrochloric acid) provided the diketone **77** (64%, three steps). Finally, to mask the acidic  $\alpha$ -protons we employed a site-selective enoxysilane formation via a kinetic deprotonation of **77** with LiHMDS and trapping with TMSCl to arrive at the model fragment **78** exclusively as the *Z*-isomer (65%, <sup>1</sup>H NMR analysis).



**Scheme 14.** **A.** Synthesis of the newly-designed C-ring fragment **78**. **B.** Synthesis of ( $\pm$ )-myrocinn G model (**65**) via a fragment coupling–cyclization cascade.

After some experimentation, it was found that exposure of the **66** to *n*-butyllithium at cryogenic temperatures ( $-78\text{ }^{\circ}\text{C}$ ) followed by addition of the model enoxysilane fragment **78** and warming the reaction mixture to  $0\text{ }^{\circ}\text{C}$  over 3 h provided the annulation product **75** in 36% yield (Scheme 14B). The mechanism we proposed for this one step fragment coupling–cyclization cascade begins with a diastereoselective 1,2-addition of **79** to **78** to generate the alkoxide intermediate **80**. Migration of the trimethylsilyl group from the C7

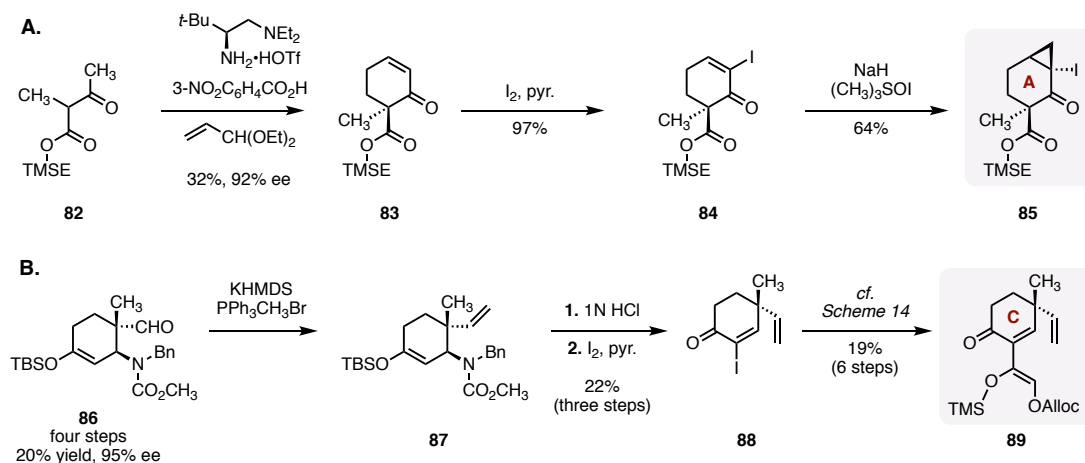
enoxysilane to the C9 alkoxide would reveal the masked enolate **81**. This enolate is poised to undergo an intramolecular ring-closing aldol addition to the C5 ketone. Subsequent Alloc group transfer from the C6 to the C5 alcohol followed by  $\beta$ -elimination would generate the desired diosphenol product **75**. This transformation is noteworthy as it accomplishes five discrete transformation in one flask and provides the fully annulated protected form of myrocin G in a single operation. Finally, the conversion of **75** to the myrocin G model **65** was accomplished via a global deprotection by treatment with excess TBAF in DMF (64%).<sup>22</sup>

### 1.5.3 Synthesis of (–)-myrocin G (**8**).

With a route to the myrocin G model **65** established, we shifted our focus to synthesis of (–)-myrocin G (**8**) via the developed sequence. The A-ring fragment was prepared in an enantioenriched form from the known  $\beta$ -ketoester **82**.<sup>23</sup> Asymmetric Robinson annulation<sup>24</sup> using acrolein diethyl acetal provide the unsaturated ketone **83** in 32% and in 92% ee. Subsequent Johnson dehydroiodination (iodine, pyridine) and Corey–Chaykovsky cyclopropanation gave the iodocyclopropane A-ring fragment **85** (62%, two steps). The electrophile C-ring fragment **89** was prepared in nine steps from the known Diels–Alder adduct **86**.<sup>25</sup> Wittig homologation of **86** (KHMDS, methyl triphenylphosphonium bromide) provided the olefin **89**. A tandem hydrolysis of the enoxysilane and  $\beta$ -carbamate elimination (aqueous hydrochloric acid) revealed the  $\alpha,\beta$ -unsaturated ketone moiety (not shown). Johnson dehydroiodination (iodine, pyridine) generated  $\alpha$ -iodo ketone **88** (22%, three steps). The corresponding enoxysilane ether C-

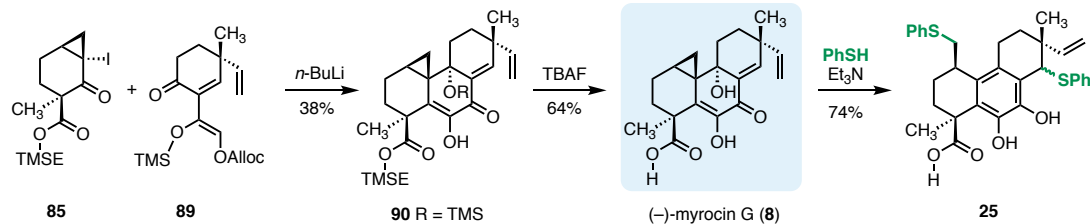


ring fragment **89** was then prepared from **88** in additional six steps and in 19% yield as shown for the model system **78** in Scheme 15.



**Scheme 15.** **A.** Synthesis of the cyclopropyl A-ring fragment **85**. **B.** Synthesis of the enoxysilane C-ring fragment **89**.

The fragment coupling–cyclization cascade employing **85** and **89** proceeded as expected, to provide the diosphenol **90** (38%). Global deprotection (TBAF, DMF) then generated (–)-myrocin G (**8**) (64%).<sup>26,27</sup> To test the mechanistic hypothesis discussed in the introduction section 1.4, we treated (–)-myrocin G (**8**) with thiophenol and triethylamine at 23 °C, as described by Chu-Moyer and Danishefsky for (±)-myrocin C (**3**). Under these conditions the bis(sulfide) **25** was obtained in 74% yield. The spectroscopic data precisely matched the bis(sulfide) **25** reported by Chu-Moyer and Danishefsky (see Table S1).<sup>10</sup> It is important to note that based solely on this result, we cannot rule out the pathway originally proposed, however, the successful formation of **25** from **8** indicates that the alternate order of events as we proposed is viable.



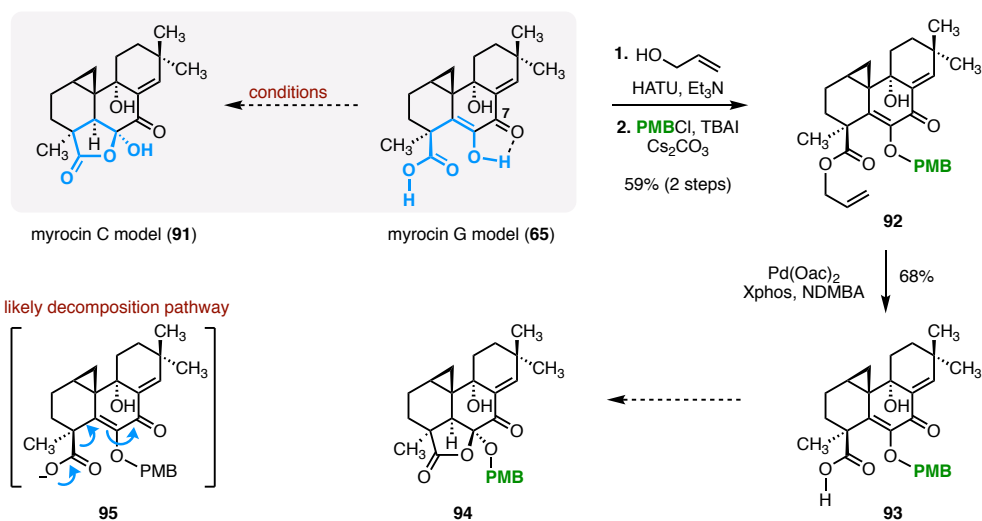
**Scheme 16.** Synthesis of (-)-myrocin G (**8**) and formation of the bis(sulfide) **25**.

#### 1.5.4 Explored strategies for the conversion of (-)-myrocin G to (+)-myrocin C.

Even though our synthetic target from the onset of our work was the diosphenol (-)-myrocin G (**8**), we were highly interested in attempting to convert the (-)-myrocin G (**8**) to (+)-myrocin C (**4**) in order to gain synthetic access to both of the compounds. Extensive experimentation was initially spent trying to convert the model system **65** to **91** via exposure of **65** to various polar solvents, reaction temperatures, or mildly acidic conditions. Unfortunately, all of these attempts were met with failure and resulted only in isolation of various unidentified decomposition products (Scheme 17).<sup>22</sup>

As an alternative, we envisioned that we might be able to access the  $\gamma$ -hydroxylactone moiety by temporarily disrupting the intramolecular hydrogen bond formed between the C7 ketone and the enol as is shown in Scheme 17. To this end, **65** was first subjected to esterification with allyl alcohol (HATU, triethylamine). This was followed by conversion of the diosphenol hydroxyl group to a *para*-methoxybenzyl group ether (*para*-methoxybenzyl chloride, tetrabutylammonium iodide, and cesium carbonate) to provide the allyl ester **92** (59%, two steps). Next, a palladium(II) acetate mediated cleavage of the allyl ester liberated the free carboxylic acid **93** (68%). Unfortunately, another extensive screen of reaction conditions attempted to convert **93** to the  $\gamma$ -

hydroxylactone **94** were uniformly unsuccessful. In many cases, we observed an unproductive decarboxylation reaction via the diosphenol moiety **95** leading to a mixture of undesired products.

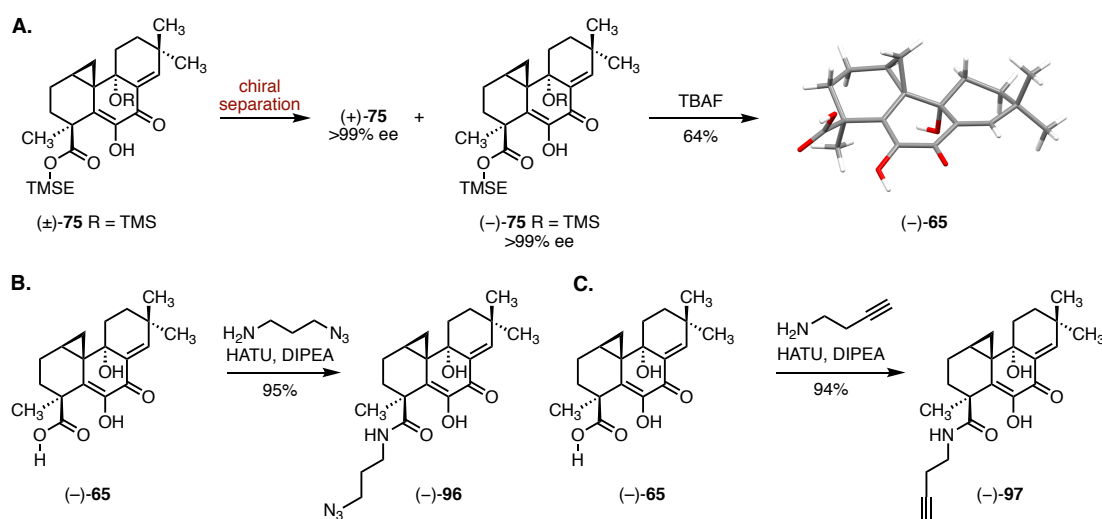


**Scheme 17.** Attempted conversion of the myrocin G model **65** to the myrocin C model **91** via synthesis of the free acid **93**.

## 1.6 Biological evaluation of (–)-myrocin G and related analogues.

Our synthetic route to (–)-myrocin G (**8**) and related structures, such as the protected geminal dimethyl model system **75**, enabled us to probe the mechanism of action of these compounds. We were specifically interested in evaluating the DNA cross-linking hypothesis advanced by Chu-Moyer and Danishefsky.<sup>10</sup> The protected model system **75** was prepared as a racemate. We were able to obtain enantiopure (>99% ee) (+)-**75** and (–)-**75** by chiral stationary phase supercritical fluid chromatography, which was carried out by our collaborators at Merck Research Laboratories (Scheme 18A). Both of the

enantiomers were treated with excess TBAF in DMF to remove the protecting groups. The absolute stereochemistry of (–)-**65** was determined by X-ray analysis. The resolved enantiomer (–)-**65** was then advanced to the azide (–)-**96** (Scheme 18B) and the corresponding alkyne (–)-**97** (Scheme 18C). The same set of transformations was performed on (+)-**90**, to afford the azide (+)-**96** and the alkyne (+)-**97** (for the purposes of clarity, these transformation are not shown in Scheme 18).



**Scheme 18.** **A.** Separation of (±)-**75** by chiral stationary phase supercritical chromatography to provide the (+)-**75** and (–)-**75**. **B.** Synthesis of the enantiopure azide (–)-**96**. **C.** Synthesis of the enantiopure alkyne (–)-**97**.

We evaluated the cytotoxicities of our compounds against cervical (HeLa), colorectal (HCT116), leukemia (K562) and prostate (LNCaP) cancer cell lines using a CellTiter-Glo assay, which utilizes ATP production as an indicator of cell viability. The results are shown in Table 1.<sup>22</sup> (–)-Myrocin G (**8**) showed low micromolar activity against the HeLa and K562 cell lines, but was less active against LNCaP and HCT116 cell lines.

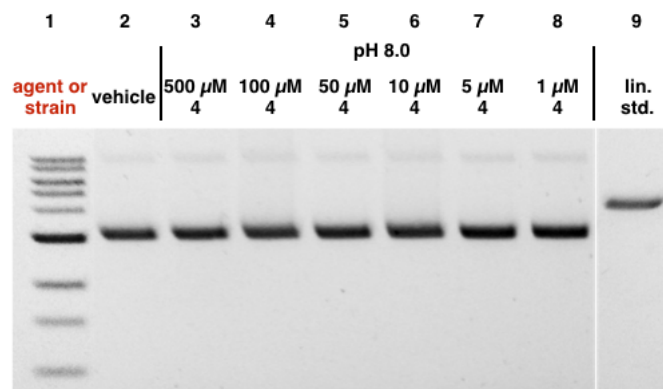
To our surprise, we observed no significant differences between the potencies of the two separated enantiomers, suggesting their toxicity may derive from non-specific binding to protein and/or DNA. Both the amides bearing an alkyne or azide showed stronger activity compared to the corresponding carboxylic acid. We speculate that this could be due to decreased cellular uptake of the carboxylic acid, although additional studies are required to fully establish this.

compound	HeLa	HCT116	K562	LNCap
(-)-myrocin G ( <b>8</b> )	3.2	1400	3.3	12
analog (-)- <b>65</b>	189	30	43	54
analog (+)- <b>65</b>	21	52	59	37
azide (-)- <b>96</b>	13	5.6	8.1	5.3
azide (+)- <b>96</b>	23	12	14	9.8
alkyne (-)- <b>97</b>	13	5.3	10	9.0
alkyne (+)- <b>97</b>	24	8	10	8.2

**Table 1.** IC<sub>50</sub> Values (in  $\mu\text{M}$ ) of (-)-myrocin G (**8**), the geminal dimethyl analogs (-)-**65** and (+)-**65**, the azido probes (-)-**96** and (+)-**96**, and the alkynyl probes (-)-**97** and (+)-**97**.

Cells were treated with compounds for 72h. Tamaxifen (60  $\mu\text{M}$ ) was used as a positive control.

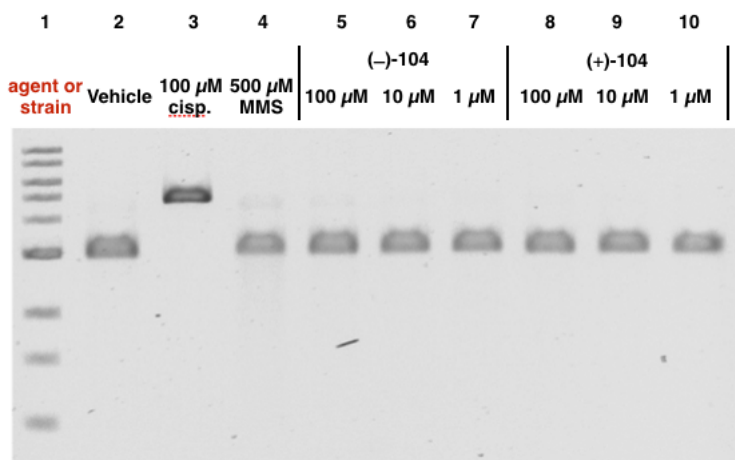
We then examined reactivity of our synthetic (-)-myrocin G (**8**) toward DNA.<sup>22</sup> Circular pBR322 plasmid DNA was incubated with varying concentration of **8** for 16 h at 37 °C. The DNA was then analyzed by native gel electrophoresis and the results are shown in Figure 2. Disappointingly, we did not observe detectable levels of DNA nicking or cleavage with concentration of **8** up to 500  $\mu\text{M}$ .



**Figure 2.** DNA plasmid cleavage assay employing circular pBR322 plasmid DNA and (–)-myrocin G (**8**). 5% DMSO was used as vehicle (negative control), and linearized pBR322 DNA was used as positive control. DNA ladder (Lane #1); 5% DMSO, pH 8.0 (Lane #2); 500  $\mu\text{M}$  **8**, pH 8.0 (Lane #3); 100  $\mu\text{M}$  **8**, pH 8.0 (Lane #4); 50  $\mu\text{M}$  **8**, pH 8.0 (Lane #5); 10  $\mu\text{M}$  **8**, pH 8.0 (Lane #6); 5  $\mu\text{M}$  **8**, pH 8.0 (Lane #7); 1  $\mu\text{M}$  **8**, pH 8.0 (Lane #8); linearized pBR322 DNA (Lane #9). Conditions (Lane #2): circular pBR322 DNA (15.2  $\mu\text{M}$  in base pairs), 5% DMSO (vehicle), TE buffer (10 mM Tris, 1 mM EDTA, pH 8.0), 16 h, 37 °C. Conditions (Lanes #3 – #8): circular pBR322 DNA (15.2  $\mu\text{M}$  in base pairs), **8** (500  $\mu\text{M}$ –1  $\mu\text{M}$ ), 5% DMSO, TE buffer (10 mM Tris, 1 mM EDTA, pH 8.0), 16 h, 37 °C. The DNA was analyzed by native gel electrophoresis (90 V, 1.5 h).

Next, we evaluated the cross-linking capability of the pair of enantiomeric geminal dimethyl derivatives (–)-**65** and (+)-**65** (Figure 3). We incubated the linearized pUC19 DNA with (–)-**65** or (+)-**65** (1–100  $\mu\text{M}$ ) for 16 h at 37 °C and then analyzed the treated DNA by denaturing gel electrophoresis. Under these conditions, we did not detect any DNA cross-links using either (–)-**65** or (+)-**65**. These studies suggest to us that DNA is unlikely to be the primary biological target of myrocins and that an alternative mode of

action, potentially involving a protein target, could explain their antiproliferative activities. To date, we are actively investigating the biological target by collaborating with the Adibekian lab at Scripps Florida.



**Figure 3.** DNA cross-linking assay employing linear pUC19 DNA and myrocin analogs(-)-65 and (+)-65. 5% DMSO was used as a negative control. Cisplatin (100  $\mu$ M) and methyl methanesulfonate (MMS, 500  $\mu$ M) were used as positive controls for cross-linking and monoalkylation, respectively. DNA ladder (Lane #1); 5% DMSO (Lane #2); 100  $\mu$ M cisplatin (Lane #3); 500  $\mu$ M MMS (Lane #4), 100  $\mu$ M (-)-65 (Lane #5); 10  $\mu$ M (-)-65 (Lane #6); 1  $\mu$ M (-)-65 (Lane #7); 100  $\mu$ M (+)-65 (Lane #8); 10  $\mu$ M (+)-65 (Lane #9); 1  $\mu$ M (+)-65 (Lane #10). Conditions (Lane #2): linearized pUC19 DNA (15.4  $\mu$ M in base pairs), 5% DMSO (vehicle), TE buffer (10 mM Tris, 1 mM EDTA, pH 8.0), 16 h, 37  $^{\circ}$ C. Conditions (Lane #4): linearized pUC19 DNA (15.4  $\mu$ M in base pairs), 5% DMSO (vehicle), 100  $\mu$ M cisplatin, TE buffer (10 mM Tris, 1 mM EDTA, pH 8.0), 16 h, 37  $^{\circ}$ C. Conditions (Lane #5): linearized pUC19 DNA (15.4  $\mu$ M in base pairs), 5% DMSO (vehicle), 500  $\mu$ M MMS, TE buffer (10 mM Tris, 1 mM EDTA, pH 8.0), 16 h, 37  $^{\circ}$ C. Conditions (Lanes #5–#7): linearized pUC19 DNA (15.4  $\mu$ M in

base pairs), 5% DMSO (vehicle), (-)-**65** (100  $\mu\text{M}$ –1  $\mu\text{M}$ ), TE buffer (10 mM Tris, 1 mM EDTA, pH 8.0), 16 h, 37 °C. Conditions (Lanes #8–#10): linearized pUC19 DNA (15.4  $\mu\text{M}$  in base pairs), 5% DMSO (vehicle), (+)-**65**. (100  $\mu\text{M}$ –1  $\mu\text{M}$ ), TE buffer (10 mM Tris, 1 mM EDTA, pH 8.0), 16 h, 37 °C. The DNA was analyzed by 0.4% NaOH denature agarose gel electrophoresis (90 V, 1.5 h).

## 1.7 Conclusion.

In summary, I have presented our work towards (-)-myrocin G (**8**), the putative active form of antitumor antibiotic (+)-myrocin C (**4**). I described the development of our synthetic strategy, which was guided by several failed approaches and attempts. This work ultimately resulted in the discovery of a complex stereoselective fragment coupling–cyclization cascade employing the iodocyclopropane **85** and the enoxysilane **89** as two precursors of similar complexity. This powerful reaction allowed us to synthesize the fully annulated protected form of (-)-myrocin G (**8**) in a single operation. I then described our synthetic efforts to convert the diosphenol moiety of (-)-myrocin G (**8**) to the  $\gamma$ -hydroxylactone present in (+)-myrocin C (**4**). Lastly, I detailed our preliminary biological activity studies, which suggest that DNA is not the primary biological target of myrocins. Efforts to identify their biological target are currently ongoing in collaboration with the Adibekian lab at Scripps Florida.



## 1.8 Experimental section.

### 1.8.1 General information.

**General experimental procedures.** All reactions were performed in single-neck, flame-dried, round-bottomed flasks fitted with rubber septa under a positive pressure of argon unless otherwise noted. Air- and moisture-sensitive liquids were transferred via syringe or stainless steel cannula, or were handled in a nitrogen-filled drybox (working oxygen level <10 ppm). Organic solutions were concentrated by rotary evaporation at 28–32 °C. Flash-column chromatography was performed as described by Still et al.,<sup>28</sup> employing silica gel (SiliaFlash® P60, 60 Å, 40–63 µm particle size) purchased from SiliCycle (Québec, Canada). Analytical thin-layered chromatography (TLC) was performed using glass plates pre-coated with silica gel (250 µm, 60 Å pore size) impregnated with a fluorescent indicator (254 nm). Preparative thin-layered chromatography (PTLC) was performed using glass plates precoated with silica gel (250 µm, 60 Å pore size) impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light (UV) and/or submersion in aqueous ceric ammonium molybdate solution (CAM), *para*-anisaldehyde (PAA), or aqueous potassium permanganate solution (KMnO<sub>4</sub>), followed by brief heating on a hot plate (120 °C, 10–15 s).

**Materials.** Commercial solvents and reagents were used as received with the following exceptions. Dichloromethane, diethyl ether (ether), *N,N*-dimethylformamide, tetrahydrofuran, and toluene were purified according to the method of Pangborn et al.<sup>29</sup> Pyridine was distilled from calcium hydride under an atmosphere of nitrogen immediately prior to use. Triethylamine was distilled from calcium hydride under an atmosphere of

nitrogen immediately prior to use. *N,N*-Di-*iso*-propylethylamine was distilled from calcium hydride and stored under argon. Sodium *tert*-butoxide, sodium hydride, lithium bis(trimethylsilyl)amide, and potassium bis(trimethylsilyl)amide were stored and handled in a nitrogen-filled drybox. The molarities of *n*-butyllithium and *iso*-propylmagnesium chloride–lithium chloride complex solutions were determined using the method of Love et al.<sup>30</sup> Trimethylsilyl trifluoromethanesulfonate was purified by vacuum transfer distillation and stored under argon at –20 °C. Trimethylsulfoxonium iodide was recrystallized from water, rinsed with acetone, dried under vacuum in the presence of calcium sulfate, and stored in a desiccator with protection from light. 3-Chloroperoxybenzoic acid (mCPBA) was recrystallized from dichloromethane and stored at –20 °C. Chlorotrimethylsilane was distilled from calcium hydride and stored under argon. Compounds iodoenone **39**<sup>31</sup>, the Weinreb amide **46**<sup>19</sup>, the amine catalyst **S9**<sup>24</sup>,  $\beta$ -ketoester **82**<sup>23</sup>, Diels–Alder adduct **86**<sup>25</sup> were prepared according to published procedures.

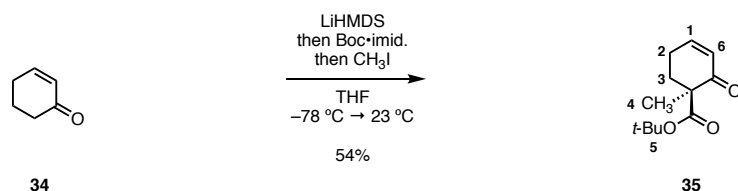
**Instrumentation.** Proton nuclear magnetic resonance (<sup>1</sup>H NMR) spectra were recorded at 400, 500, or 600 megahertz (MHz) at 23 °C, unless otherwise noted. Chemical shifts are expressed in parts per million (ppm,  $\delta$  scale) downfield from tetramethylsilane and are referenced to residual proton in the NMR solvent (CHCl<sub>3</sub>,  $\delta$  7.26; C<sub>6</sub>H<sub>5</sub>D,  $\delta$  7.16; CHD<sub>2</sub>OD,  $\delta$  3.31; (CD<sub>2</sub>H)SO(CD<sub>3</sub>),  $\delta$  2.50). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and/or multiple resonances, b = broad, app = apparent), coupling constant in Hertz (Hz), integration, and assignment. Proton-decoupled carbon nuclear magnetic resonance spectra (<sup>13</sup>C NMR) were recorded at 100, 125, or 150 MHz at 23 °C, unless otherwise noted. Chemical shifts are expressed in parts per million (ppm,  $\delta$  scale) downfield from tetramethylsilane and are

referenced to the carbon resonances of the solvent ( $\text{CDCl}_3$ ,  $\delta$  77.0;  $\text{C}_6\text{D}_6$ ,  $\delta$  128.1;  $\text{CD}_3\text{OD}$ ,  $\delta$  49.0;  $\text{DMSO}-d_6$ ,  $\delta$  39.5). Distortionless enhancement by polarization transfer [DEPT (135)] spectra were recorded at 125 or 150 MHz at 23 °C, unless otherwise noted. Heteronuclear single quantum coherence (HSQC), and heteronuclear multiple bond correlation (HMBC) spectra were recorded at 125 or 150 MHz at 23 °C, unless otherwise noted.  $^{13}\text{C}$  NMR and DEPT (135)/HSQC data are combined and represented as follows: chemical shift, carbon type [obtained from DEPT (135) or HSQC experiments]. Two-dimensional nuclear Overhauser effect spectroscopy (2D NOESY) and two-dimensional rotating-frame nuclear Overhauser effect spectroscopy (2D ROESY) experiments were performed at 500 MHz at 23 °C, unless otherwise noted. Attenuated total reflectance Fourier transform infrared (ATR-FTIR) spectra were obtained using a Thermo Electron Corporation Nicolet 6700 FTIR spectrometer referenced to a polystyrene standard. Data are represented as follows: frequency of absorption ( $\text{cm}^{-1}$ ), intensity of absorption (s = strong, m = medium, w = weak, br = broad). Analytical ultra-high-performance liquid chromatography/mass spectrometry (UPLC/MS) was performed on a Waters UPLC/MS instrument equipped with a reverse-phase C18 column (1.7  $\mu\text{m}$  particle size, 2.1  $\times$  50 mm), dual atmospheric pressure chemical ionization (API)/electrospray (ESI) mass spectrometry detector, and photodiode array detector. Samples were eluted with a linear gradient of 5% acetonitrile– water containing 0.1% formic acid  $\rightarrow$  100% acetonitrile containing 0.1% formic acid over 0.75 min, followed by 100% acetonitrile containing 0.1% formic acid for 0.75 min, at a flow rate of 800  $\mu\text{L}/\text{min}$ . High-resolution mass spectrometry (HRMS) were obtained on a Waters UPLC/HRMS instrument equipped with a dual API/ESI high-resolution mass spectrometry detector and photodiode array detector. Unless otherwise

noted, samples were eluted over a reverse-phase C18 column (1.7  $\mu\text{m}$  particle size, 2.1  $\times$  50 mm) with a linear gradient of 5% acetonitrile–water containing 0.1% formic acid  $\rightarrow$  95% acetonitrile–water containing 0.1% formic acid for 1 min, at a flow rate of 600  $\mu\text{L}/\text{min}$ . Optical rotations were measured on a Rudolph Research Analytical Autopol IV polarimeter equipped with a sodium (589 nm, D) lamp. Optical rotation data are represented as follows: specific rotation ( $[\alpha]_D^T$ ), concentration (mg/mL), and solvent.

## 1.8.2 Synthetic procedures.

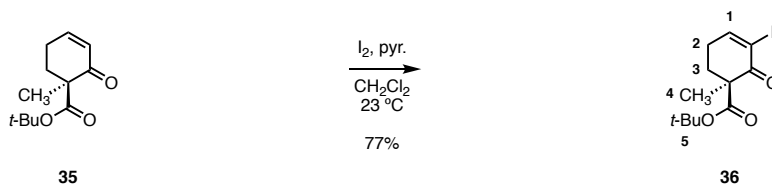
*Synthesis of the unsaturated ketone 35:*



Cyclohex-2-en-1-one (**34**) (4.84 mL, 50.0 mmol, 1 equiv) was added to a solution of lithium bis(trimethylsilyl)amide (19.2 g, 115 mmol, 2.30 equiv) in tetrahydrofuran (50 mL) at  $-78\text{ }^{\circ}\text{C}$ . The reaction mixture was stirred for 1 h at  $-78\text{ }^{\circ}\text{C}$ . A solution of the 1-(*tert*-butoxycarbonyl)imidazole (12.6 g, 75.0 mmol, 1.50 equiv) in tetrahydrofuran (35 mL) was then added dropwise via syringe pump over 20 min at  $-78\text{ }^{\circ}\text{C}$ . The reaction vessel was immediately removed from the cooling bath and the reaction mixture was allowed to warm over 1.5 h to  $23\text{ }^{\circ}\text{C}$ . Upon warming, a turbid, dark-red mixture formed. Iodomethane (9.34 mL, 150 mmol, 3.00 equiv) was then added at  $23\text{ }^{\circ}\text{C}$ . The reaction mixture was stirred for 18 h at  $23\text{ }^{\circ}\text{C}$ . The product mixture was diluted sequentially with saturated aqueous ammonium chloride solution (50 mL) and water (50 mL). The resulting mixture was poured into a solution of 75% ether–pentane (v/v, 300 mL). The biphasic mixture was stirred for 10 min at  $23\text{ }^{\circ}\text{C}$ . The stirred mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ether (100 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (50 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 14% ether–hexanes) to provide the unsaturated ketone **35** as a pale yellow oil (5.66 g, 54%).

$R_f = 0.26$  (20% ether–hexanes; UV, PAA).  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.90–6.86 (m, 1H, H1), 6.03 (ddd,  $J = 10.1, 2.6, 1.5$  Hz, 1H, H6), 2.51–2.40 (m, 2H, H2a,3a), 2.35–2.27 (m, 1H, H2b), 1.90–1.81 (m, 1H, H3b), 1.42 (s, 9H, H5), 1.34 (s, 3H, H4).  $^{13}\text{C NMR}$  (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  197.3 (C), 171.8 (C), 148.8 (CH), 129.1 (CH), 81.7 (C), 53.9 (C), 33.6 (CH<sub>2</sub>), 27.8 (3  $\times$  CH<sub>3</sub>), 23.8 (CH<sub>2</sub>), 20.3 (CH<sub>3</sub>). IR (ATR-FTIR),  $\text{cm}^{-1}$ : 3005 (m), 2998 (m), 1655 (m). HRMS-Cl ( $m/z$ ):  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{12}\text{H}_{19}\text{O}_3$ , 211.1334 found, 211.1334.

Synthesis of the  $\alpha$ -iodoenone **36**:



Iodine (6.27 g, 24.8 mmol, 1.80 equiv) was added to a solution of the enone **35** (2.61 g, 12.4 mmol, 1 equiv) in 50% pyridine–dichloromethane (v/v, 30 mL) at  $23^\circ C$ . The reaction mixture was stirred for 24 h at  $23^\circ C$ . The product mixture was diluted sequentially with saturated aqueous sodium thiosulfate solution (30 mL), water (10 mL), ether (100 mL) and ethyl acetate (100 mL). The resulting biphasic mixture was stirred for 20 min at  $23^\circ C$ . The stirred mixture was transferred to a separatory funnel and the layers were separated. The organic layer was washed sequentially with aqueous hydrochloric acid solution (1 N,  $5 \times 20$  mL) and saturated aqueous sodium chloride solution (20 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by elution over a short plug of silica gel (3.0' 5.0 cm, eluting with 20% ether–hexanes). The filtrate was collected and concentrated. The residue obtained was triturated with pentane ( $5 \times 10$  mL) to furnish the  $\alpha$ -iodoenone **36** as a colorless solid (3.20 g, 77%).

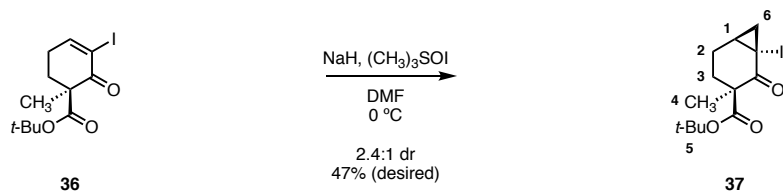
$R_f = 0.35$  (20% ether–hexanes; UV, PAA).  $^1H$  NMR (500 MHz,  $CDCl_3$ ):  $\delta$  7.59–7.56 (m, 1H, H<sub>1</sub>), 2.59–2.51 (m, 1H, H<sub>2a</sub>), 2.49–2.43 (m, 1H, H<sub>3a</sub>), 2.37–2.30 (m, 1H, H<sub>2b</sub>), 1.96–1.89 (m, 1H, H<sub>3b</sub>), 1.41 (s, 9H, H<sub>5</sub>), 1.38 (s, 3H, H<sub>4</sub>).  $^{13}C$  NMR (125 MHz,  $CDCl_3$ ):  $\delta$  190.8 (C), 171.0 (C), 156.8 (CH), 102.2 (C), 82.4 (C), 54.0 (C), 33.4 (CH<sub>2</sub>), 27.9 (CH<sub>2</sub>), 27.8 (3

× CH<sub>3</sub>), 21.0 (CH<sub>3</sub>). IR (ATR-FTIR), cm<sup>-1</sup>: 2973 (m), 2933 (m), 1720 (m), 1685 (m).

HRMS-Cl (m/z): [M + H]<sup>+</sup> calcd for C<sub>12</sub>H<sub>18</sub>IO<sub>3</sub>, 337.0301; found 337.0301.



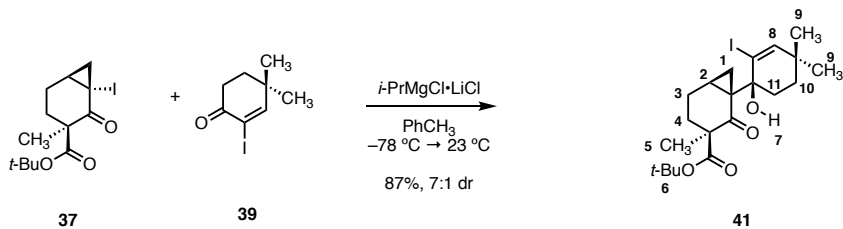
*Synthesis of the cyclopropane 37:*



Trimethylsulfoxonium iodide (3.54 g, 16.1 mmol, 1.40 equiv) was added in one portion to a suspension of sodium hydride (95%, 385 mg, 15.2 mmol, 1.33 equiv) in *N,N*-dimethylformamide (230 mL) at  $23\text{ }^\circ\text{C}$ . The resulting suspension was stirred for 40 min at  $23\text{ }^\circ\text{C}$ . The reaction mixture was cooled to  $-45\text{ }^\circ\text{C}$  and stirred for 2 h at  $-45\text{ }^\circ\text{C}$ . A solution of the  $\alpha$ -iodoenone **36** (3.85 g, 11.4 mmol, 1 equiv) in *N,N*-dimethylformamide (25 mL) was then added dropwise via syringe pump over 1 h at  $-45\text{ }^\circ\text{C}$ . The reaction mixture was placed in an ice bath and stirred for 18 h at  $0\text{ }^\circ\text{C}$ . The cold product mixture was then diluted sequentially with saturated aqueous ammonium chloride solution (25 mL), water (25 mL), and 50% ethyl acetate–hexanes (v/v, 200 mL). The resulting biphasic mixture was transferred to a separatory funnel the layers that formed were separated. The aqueous layer was extracted with 50% ethyl acetate–hexanes (v/v,  $3 \times 30.0\text{ mL}$ ). The organic layers were combined and the combined organic layers were washed sequentially with water ( $3 \times 20\text{ mL}$ ) and saturated aqueous sodium chloride solution (30 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated.  $^1\text{H}$  NMR analysis of the unpurified product mixture indicated the presence of a 2.4:1 mixture of diastereomers. The residue obtained was recrystallized (see Appendix A) from 5% ether–hexanes to furnish the cyclopropane **37** as an off-white solid (1.88 g, 47%).

$R_f = 0.36$  (20% ether–hexanes; faintly UV, PAA).  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ ):  $\delta$  2.25–2.17 (m, 2H,  $\text{H}_{1,2a}$ ), 2.09 (td,  $J = 13.7, 4.6$  Hz, 1H,  $\text{H}_{3a}$ ), 1.97 (app t,  $J = 6.6$  Hz, 1H,  $\text{H}_{6a}$ ), 1.93–1.87 (m, 1H,  $\text{H}_{3b}$ ), 1.67–1.61 (m, 1H,  $\text{H}_{2b}$ ), 1.54 (dd,  $J = 8.7, 6.8$  Hz, 1H,  $\text{H}_{6b}$ ), 1.42 (s, 9H,  $\text{H}_5$ ), 1.29 (s, 3H,  $\text{H}_4$ ).  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ ):  $\delta$  200.4 (C), 171.7 (C), 81.8 (C), 53.7 (C), 30.7 (CH), 28.7 ( $\text{CH}_2$ ), 27.8 ( $3 \times \text{CH}_3$ ), 21.9 ( $\text{CH}_2$ ), 21.3 ( $\text{CH}_2$ ), 18.1 ( $\text{CH}_2$ ), 7.8 (C). IR (ATR-FTIR),  $\text{cm}^{-1}$ : 2976 (m), 2867 (m), 1730 (m), 1701 (m). HRMS-CI (m/z):  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{13}\text{H}_{19}\text{I}\text{NaO}_3$ , 373.0277; found 373.0277.

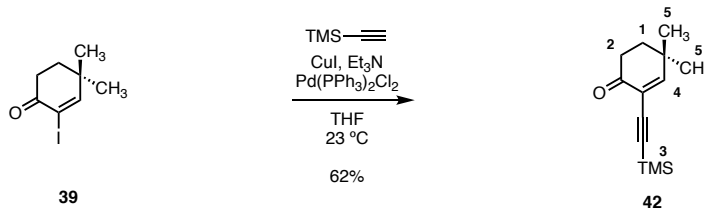
*Synthesis of the fragment coupling product 41:*



A solution of *iso*-propylmagnesium chloride–lithium chloride complex in tetrahydrofuran (1.21 M, 530  $\mu\text{L}$ , 641  $\mu\text{mol}$ , 1.11 equiv) was added dropwise to a solution of the iodocyclopropane **37** (225 mg, 642  $\mu\text{mol}$ , 1.11 equiv) in toluene (2.6 mL) at  $-78\text{ }^\circ\text{C}$ . The reaction mixture was stirred for 30 min at  $-78\text{ }^\circ\text{C}$ . A solution of the iodoenone **39** (145 mg, 580  $\mu\text{mol}$ , 1 equiv) in toluene (500  $\mu\text{L}$ ) was then added to the reaction mixture at  $-78\text{ }^\circ\text{C}$ . The reaction vessel was removed from its cooling bath and the reaction mixture was then warmed over 3 h to  $23\text{ }^\circ\text{C}$ . The product mixture was diluted with saturated aqueous ammonium chloride solution (500  $\mu\text{L}$ ), water (3.0 mL), and 25% hexanes–ether (v/v, 20.0 mL) at  $23\text{ }^\circ\text{C}$ . The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The organic layer was washed with water (3.0 mL) and saturated aqueous sodium chloride solution (3.0 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 14% ether–hexanes). The fractions containing product (TLC) were combined and the combined fractions were concentrated. The residue obtained was recrystallized (see Appendix A) from 5% ether–pentane to provide the adduct **41** as a white solid (240 mg, 87%).

$R_f = 0.43$  (20% ether–hexanes; faintly UV, PAA).  $^1\text{H NMR}$  (600 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.32 (s, 1H,  $\text{H}_8$ ), 2.73 (bs, 1H,  $\text{H}_7$ ), 2.21 (t,  $J = 13.7$  Hz, 1H,  $\text{H}_{11a}$ ), 2.13–1.99 (m, 3H,  $\text{H}_{4a,10}$ ), 1.74–1.58 (m, 4H,  $\text{H}_{3,4b,9b}$ ), 1.54–1.49 (m, 1H,  $\text{H}_{8b}$ ), 1.42 (s, 9H,  $\text{H}_6$ ), 1.36 (s, 3H,  $\text{H}_5$ ), 1.21 (s, 3H,  $\text{H}_{9a}$ ), 1.03 (s, 3H,  $\text{H}_{9b}$ ).  $^{13}\text{C NMR}$  (150 MHz,  $\text{CDCl}_3$ ):  $\delta$  205.7 (C), 172.8 (C), 152.0 (CH), 106.2 (C), 81.1 (C), 72.4 (C), 54.9 (C), 41.7 (C), 38.0 (C), 32.9 ( $\text{CH}_2$ ), 31.3 (C), 30.4 ( $\text{CH}_3$ ), 29.9 ( $\text{CH}_2$ ), 27.8 ( $3 \times \text{CH}_3$ ), 25.4 ( $\text{CH}_3$ ), 23.7 (CH), 22.8 ( $\text{CH}_3$ ), 17.5 ( $\text{CH}_2$ ), 11.5 ( $\text{CH}_2$ ). IR (ATR-FTIR),  $\text{cm}^{-1}$ : 2973 (m), 2931 (m), 2863 (m), 1737 (m), 1680 (m). HRMS-Cl ( $m/z$ ):  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{21}\text{H}_{32}\text{IO}_4$ , 475.1345; found 475.1345.

*Synthesis of the alkyne 42:*

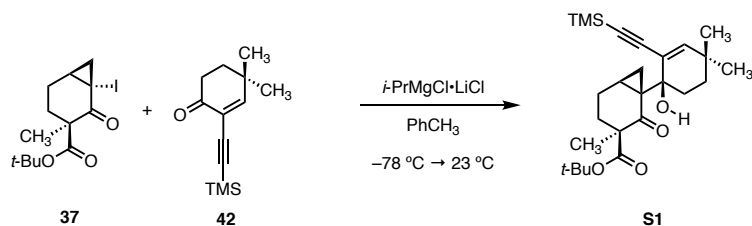


A round-bottom flask was charged with bis(triphenylphosphine)palladium(II) dichloride (206 mg, 293  $\mu$ mol, 0.05 equiv), copper(I) iodide (33.6 mg, 176  $\mu$ mol, 0.03 equiv), and the iodoenone **39** (1.47 g, 5.88 mmol, 1 equiv). The reaction vessel was sealed with a rubber septum. Tetrahydrofuran (30 mL) and triethylamine (2.90 mL, 20.8 mmol, 3.54 equiv) were then added in succession to the reaction vessel. The resulting suspension was deoxygenated by brief exposure to vacuum (~30 s) and subsequent backfilling with argon (1 atm). This process was repeated three times. Trimethylsilylacetylene (1.50 mL, 10.9 mmol, 1.87 equiv) was then added to the reaction mixture under argon at 23 °C. The reaction mixture was stirred for 7 h at 23 °C. The product mixture was diluted with 25% pentane–ether (v/v, 60 mL), saturated aqueous ammonium chloride solution (5.0 mL), and water (15 mL). The resulting biphasic mixture was stirred for 5 min at 23 °C. The mixture was then transferred to a separatory funnel and the layers that formed were separated. The organic layer was washed with saturated aqueous sodium chloride solution (10 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 10% ether–hexanes) to provide the ethynylenone **42** as a yellow solid (799 mg, 62%).

$R_f = 0.35$  (20% ether–hexanes; UV, PAA).  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.01 (s, 1H, H4), 2.50 (dd,  $J = 7.4, 6.2$  Hz, 2H, H2), 1.88–1.83 (m, 2H, H1), 1.18 (s, 6H, H5), 0.21 (s, 9H, H3).  $^{13}\text{C NMR}$  (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  195.1 (C), 163.9 (CH), 122.5 (C), 99.1 (C), 97.2 (C), 35.5 ( $\text{CH}_2$ ), 34.3 ( $\text{CH}_2$ ), 33.6 (C), 27.5 (2 x  $\text{CH}_3$ ),  $-0.11$  (3 x  $\text{CH}_3$ ). IR (ATR-FTIR),  $\text{cm}^{-1}$ : 2965 (m), 2865 (m), 1730 (m), 1737 (m), 1692 (m). HRMS-CI ( $m/z$ ):  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{13}\text{H}_{20}\text{NaOSi}$ , 243.1181; found 243.1180.

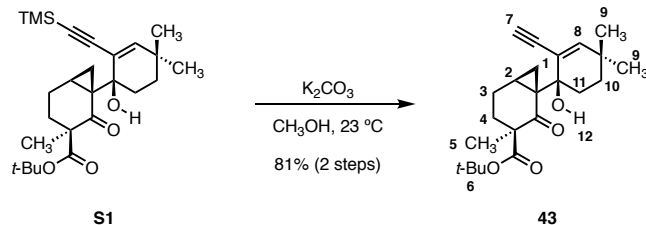
*Synthesis of the alkyne adduct 43:*

*Part 1: Fragment coupling of 37 and 42:*



A solution of *iso*-propylmagnesium chloride–lithium chloride complex in tetrahydrofuran (1.21 M, 50.0  $\mu\text{L}$ , 60.0  $\mu\text{mol}$ , 1.20 equiv) was added dropwise to a solution of the iodocyclopropane **37** (21.0 mg, 60.0  $\mu\text{mol}$ , 1.20 equiv) in toluene (500  $\mu\text{L}$ ) at  $-78\text{ }^\circ\text{C}$ . The reaction mixture was stirred for 30 min at  $-78\text{ }^\circ\text{C}$ . A solution of the alkyne **42** (11.0 mg, 50.0  $\mu\text{mol}$ , 1 equiv) in toluene (100  $\mu\text{L}$ ) was then added to the reaction mixture at  $-78\text{ }^\circ\text{C}$ . The reaction vessel was removed from its cooling bath and the reaction mixture was then warmed over 3 h to  $23\text{ }^\circ\text{C}$ . The product mixture was then diluted with saturated aqueous ammonium chloride solution (200  $\mu\text{L}$ ), water (1.0 mL), and 25% hexanes–ether (v/v, 5.0 mL) at  $23\text{ }^\circ\text{C}$ . The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The organic layer was washed sequentially with water (1.0 mL) and saturated aqueous sodium chloride solution (1.0 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was used directly in the next step.

Part 2: Removal of the trimethylsilyl group to provide **43**:



Potassium carbonate (8.3 mg, 60.0  $\mu\text{mol}$ , 1.20 equiv) was added to a solution of the unpurified fragment coupling product **S1** obtained in the preceding step (nominally 50.0  $\mu\text{mol}$ , 1 equiv) in methanol (250  $\mu\text{L}$ ) at 23  $^\circ\text{C}$ . The reaction mixture was stirred for 3 h at 23  $^\circ\text{C}$ . The product mixture was diluted sequentially with saturated aqueous ammonium chloride solution (200  $\mu\text{L}$ ), water (1.0 mL), and 25% hexanes–ether (v/v, 5.0 mL) at 23  $^\circ\text{C}$ . The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The organic layer was washed with water (1.0 mL) and saturated aqueous sodium chloride solution (1.0 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by preparative thin-layered chromatography (eluting with 20% ether–hexanes) to provide the alkyne **43** as a white solid (15.0 mg, 81% over two steps).

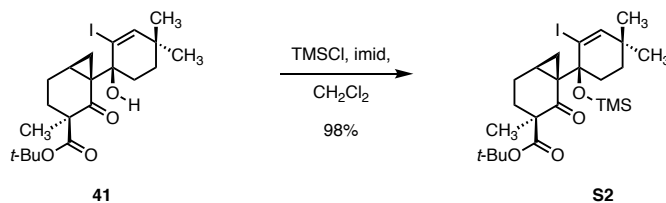
$R_f = 0.20$  (25% ether–hexanes; faintly UV, PAA).  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.07 (s, 1H,  $\text{H}_8$ ), 2.89 (s, 1H,  $\text{H}_7$ ), 2.36 (bs, 1H,  $\text{H}_{12}$ ), 2.11 (td,  $J = 13.0, 5.9$  Hz, 1H,  $\text{H}_{11a}$ ), 2.05–1.88 (m, 4H,  $\text{H}_{3a,4a,10}$ ), 1.68–1.45 (m, 7H,  $\text{H}_{1,3b,4b,8a,11}$ ), 1.44–1.40 (m, 10H,  $\text{H}_{8b,6}$ ), 1.12 (s, 3H,  $\text{H}_{9a}$ ), 1.03 (s, 3H,  $\text{H}_{9b}$ ).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  208.1 (C), 172.5 (C), 150.9 (CH), 121.1 (C), 83.0 (C), 81.2 (CH), 71.7 (C), 55.0 (C), 37.9 (C), 33.2 ( $\text{CH}_2$ ), 33.1 ( $\text{CH}_2$ ), 32.0 (C), 29.3 ( $\text{CH}_3$ ), 29.0 ( $\text{CH}_3$ ), 27.8 ( $3 \times \text{CH}_3$ ), 27.5 ( $\text{CH}_2$ ), 22.3 (CH), 21.4 ( $\text{CH}_3$ ), 17.4



(CH<sub>2</sub>), 10.2 (CH<sub>2</sub>). \* IR (ATR-FTIR), cm<sup>-1</sup>: 2935 (m), 2830 (m), 1739 (m), 1683 (m), 1446 (m). HRMS-CI (m/z): [M + H]<sup>+</sup> calcd for C<sub>23</sub>H<sub>33</sub>O<sub>4</sub>, 373.2379; found 373.2379. \*The quaternary *tert*-butyl carbon was not observed due to coincidence with the residual solvent peak.

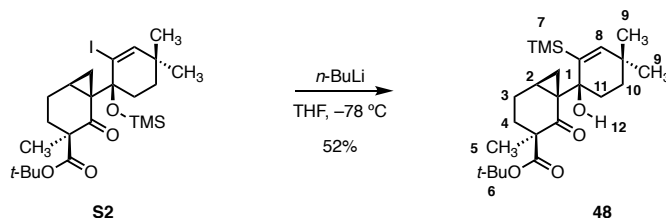
*Synthesis of the vinyl silane 48:*

*Part 1: Synthesis of the silyl ether S2:*



Imidazole (20.0 mg, 294  $\mu$ mol, 2.96 equiv) was added in one portion to a solution of the adduct **41** (47 mg, 99.1  $\mu$ mol, 1 equiv) and chlorotrimethylsilane (20.0  $\mu$ L, 158  $\mu$ mol, 1.59 equiv) in dichloromethane (500  $\mu$ L) at 23  $^{\circ}$ C. The reaction mixture was stirred for 2 d at 23  $^{\circ}$ C. The product mixture was diluted with water (1.0 mL) and 50% ether–pentane (v/v, 5.0 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The organic layer was washed with saturated aqueous sodium chloride solution (1.0 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered through a plug of silica gel (0.5 cm  $\times$  1.0 cm) and the filter cake was rinsed with ether (3  $\times$  3.0 mL). The filtrates were combined and the combined filtrates were concentrated to provide the silyl ether **S2** as a colorless oil. The unpurified silyl ether was used directly in the following step.

Part 2: Synthesis of the vinyl silane **48**:

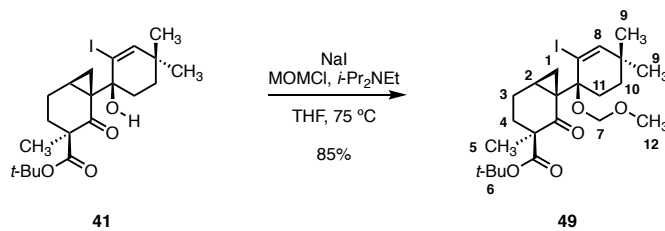


A solution of *n*-butyllithium in hexanes (2.4 M, 60.0  $\mu\text{L}$ , 0.143 mmol, 1.44 equiv) was added to a solution of the unpurified silyl ether **S2** obtained in the preceding step (nominally, 99.1  $\mu\text{mol}$ , 1 equiv) in tetrahydrofuran (500  $\mu\text{L}$ ) at  $-78\text{ }^\circ\text{C}$ . The reaction mixture was stirred for 20 min at  $-78\text{ }^\circ\text{C}$ . The product mixture was diluted sequentially with saturated aqueous ammonium chloride solution (500  $\mu\text{L}$ ), water (1.0 mL) and ethyl acetate (5.0 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The organic layer was washed with saturated aqueous sodium chloride solution (1.0 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by preparative thin-layered chromatography (eluting with 5% ether–hexanes) to provide the vinyl silane **48** as a colorless oil (21.6 mg, 52%, two steps).

$R_f = 0.41$  (10% ether–hexanes; faintly UV, PAA).  $^1\text{H NMR}$  (600 MHz,  $\text{CDCl}_3$ ):  $\delta$  5.72 (s, 1H, H<sub>8</sub>), 5.23 (s, 1H, H<sub>12</sub>), 2.15–2.06 (m, 1H, H<sub>4a</sub>), 2.02–1.91 (m, 3H, H<sub>3,11a</sub>), 1.76–1.68 (m, 1H, H<sub>11b</sub>), 2.01–1.94 (m, 1H, H<sub>3b</sub>), 1.58–1.46 (m, 4H, H<sub>2,4b,10</sub>), 1.42 (s, 9H, H<sub>6</sub>), 1.34–1.23 (s, 4H, H<sub>1a,5</sub>), 1.11 (,  $J = 8.3, 5.7\text{ Hz}$ , 1H, H<sub>1b</sub>) 1.01 (s, 3H, H<sub>9a</sub>), 0.95 (s, 3H, H<sub>9b</sub>), 0.14 (s, 9H, H<sub>7</sub>).  $^{13}\text{C NMR}$  (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  212.1 (C), 172.3 (C), 151.3 (CH), 139.2 (C),

81.4 (C), 77.5 (C), 55.4 (C), 36.2 (C), 34.9 (CH<sub>2</sub>), 33.7 (CH<sub>2</sub>), 33.3 (C), 29.7 (CH<sub>3</sub>), 29.3 (CH<sub>3</sub>), 28.3 (CH<sub>2</sub>), 27.8 (3 × CH<sub>3</sub>), 21.1 (CH<sub>2</sub>), 20.3 (CH), 16.7 (CH<sub>2</sub>), 9.9 (CH<sub>2</sub>), 1.6 (3 × CH<sub>3</sub>).

*Synthesis of the methoxymethyl ether 49:*

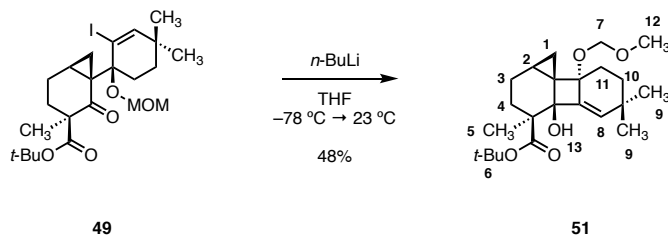


Chloromethyl methyl ether (40.0  $\mu$ L, 527  $\mu$ mol, 5.27 equiv) was added to a solution of sodium iodide (57.0 mg, 381  $\mu$ mol, 3.81 equiv) in tetrahydrofuran (400  $\mu$ L) at 23 °C. The reaction mixture was stirred for 5 min at 23 °C. A solution of the adduct **41** (47 mg, 99.1  $\mu$ mol, 1 equiv) and di-*iso*-propylethylamine (10.0  $\mu$ L, 574  $\mu$ mol, 5.74 equiv) in tetrahydrofuran (200  $\mu$ L) was added at 23 °C. The reaction vessel was sealed and the sealed vessel was placed in a heating block that had been preheated to 75 °C. The reaction mixture was stirred for 21 h at 75 °C. The product mixture was then cooled over 30 min to 23 °C. The cooled product mixture was diluted with saturated aqueous sodium bicarbonate solution (1.0 mL), water (1.0 mL), and ethyl acetate (5.0 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The organic layer was washed with saturated aqueous sodium chloride solution (1.0 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by preparative thin-layered chromatography (eluting with 5% ether–hexanes) to provide the methoxymethyl ether **49** as a colorless oil (44.0 mg, 85%).

$R_f$  = 0.46 (10% ether–hexanes; faintly UV, PAA). <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):  $\delta$  6.57 (s, 1H, H<sub>8</sub>), 4.81 (d,  $J$  = 6.8 Hz, 1H, H<sub>7a</sub>), 4.51 (d,  $J$  = 6.8 Hz, 1H, H<sub>7b</sub>), 3.36 (s, 1H, H<sub>12</sub>), 2.80

(td,  $J = 13.9, 4.5$  Hz, 1H, H<sub>11a</sub>), 2.31–2.20 (m, 2H, H<sub>2,4a</sub>), 2.08 (td,  $J = 13.7, 4.5$  Hz, 1H, H<sub>3a</sub>), 2.01–1.96 (m, 1H, H<sub>4b</sub>), 1.80–1.70 (m, 3H, H<sub>1a,10a,11b</sub>), 1.60–1.58 (m, 1H, H<sub>3b</sub>), 1.51–1.46 (m, 1H, H<sub>10b</sub>), 1.42 (s, 9H, H<sub>6</sub>), 1.36 (s, 3H, H<sub>5</sub>), 1.32–1.25 (m, 4H, H<sub>1b,9a</sub>), 1.03 (s, 3H, H<sub>9b</sub>). <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>):  $\delta$  204.9 (C), 173.1 (C), 155.5 (CH), 101.7 (C), 91.5 (CH<sub>2</sub>), 81.0 (C), 76.8 (C), 55.9 (CH<sub>3</sub>), 55.1 (C), 43.0 (C), 37.5 (C), 32.7 (CH<sub>2</sub>), 31.3 (CH<sub>2</sub>), 30.9 (CH<sub>3</sub>), 30.0 (CH<sub>3</sub>), 27.8 (3  $\times$  CH<sub>3</sub>), 25.5 (CH<sub>3</sub>), 24.0 (CH), 23.1 (CH<sub>3</sub>), 17.8 (CH<sub>2</sub>), 11.9 (CH<sub>2</sub>). IR (ATR-FTIR), cm<sup>-1</sup>: 2975 (m), 2933 (m), 2868 (m), 1732 (m), 1682 (m). HRMS-Cl (m/z): [M + H]<sup>+</sup> calcd for C<sub>23</sub>H<sub>35</sub>INaO<sub>5</sub>, 541.1427; found 541.1448.

*Synthesis of the cyclobutanol 51:*



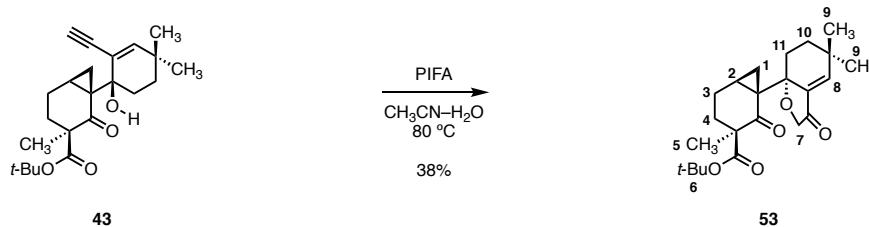
A solution *n*-butyllithium in hexanes (2.4 M, 40.0  $\mu$ L, 94.9  $\mu$ mol, 1.20 equiv) was added to a solution of the methoxymethyl ether **49** (41.0 mg, 79.1  $\mu$ mol, 1 equiv) in tetrahydrofuran (400  $\mu$ L) at  $-78$   $^{\circ}$ C. The reaction mixture was stirred for 30 min at  $-78$   $^{\circ}$ C. The reaction mixture was then warmed over 1 h to 23  $^{\circ}$ C. The product mixture was diluted sequentially with saturated aqueous ammonium chloride solution (500  $\mu$ L), water (1.0 mL) and ethyl acetate (5.0 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The organic layer was washed with saturated aqueous sodium chloride solution (1.0 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by preparative thin-layered chromatography (eluting with 25% ether–hexanes) to provide the cyclobutanol **51** as a white solid (15.0 mg, 48%). The relative stereochemistry of cyclobutanol **51** was established by X-ray analysis (see Appendix A)

$R_f$  = 0.20 (25% ether–hexanes; faintly UV, PAA).  $^1\text{H NMR}$  (600 MHz,  $\text{CDCl}_3$ ):  $\delta$  5.74 (s, 1H, H<sub>8</sub>), 4.61 (d,  $J$  = 6.7 Hz, 1H, H<sub>7a</sub>), 4.51 (d,  $J$  = 6.7 Hz, 1H, H<sub>7b</sub>), 3.38 (s, 1H, H<sub>12</sub>), 1.99–1.92 (m, 1H, H<sub>3a</sub>), 1.90–1.82 (m, 2H, H<sub>10a,11a</sub>), 1.78–1.72 (m, 1H, H<sub>3b</sub>), 1.47 (s, 3H, H<sub>6</sub>), 1.46–1.40 (m, 3H, H<sub>4,11b</sub>), 1.35 (s, 3H, H<sub>5</sub>), 1.31–1.27 (m, 1H, H<sub>2</sub>), 1.13 (m, 3H, H<sub>9a</sub>),

1.00 (s, 3H, H<sub>9b</sub>), 0.74 (d,  $J = 9.5, 5.1$  Hz, 1H, H<sub>1a</sub>), 0.55 (d,  $J = 6.4, 5.2$  Hz, 1H, H<sub>1b</sub>). <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>):  $\delta$  176.5 (C), 146.0 (C), 135.1 (CH), 93.2 (CH<sub>2</sub>), 82.1 (C), 82.0 (C), 80.0 (C), 55.8 (CH<sub>3</sub>), 46.4 (C), 40.1 (C), 33.8 (C), 32.9 (CH<sub>2</sub>), 30.4 (CH<sub>3</sub>), 29.3 (CH<sub>2</sub>), 29.3 (CH<sub>3</sub>), 28.1 (3  $\times$  CH<sub>3</sub>), 22.1 (CH<sub>2</sub>), 19.2 (CH<sub>2</sub>), 19.1 (CH<sub>3</sub>), 13.8 (CH), 9.0 (CH<sub>2</sub>).



*Synthesis of the ketofuran 53:*

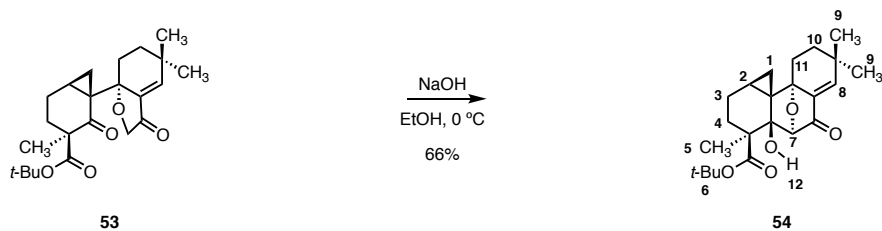


A 10-mL round bottom flask fused to a Teflon-coated valve was charged with [bis(trifluoroacetoxy)iodo]benzene (94.6 mg, 220  $\mu\text{mol}$ , 2.20 equiv), the adduct **43** (37.2 mg, 100  $\mu\text{mol}$ , 1 equiv), and 1% water–acetonitrile (v/v, 2.0 mL). The reaction chamber was sealed and the reaction vessel was immersed in an oil bath that had been preheated to 80  $^\circ\text{C}$ . The reaction mixture was stirred for 1.5 h at 80  $^\circ\text{C}$ . The product mixture was cooled over 30 min to 23  $^\circ\text{C}$ . The cooled product mixture was diluted sequentially with saturated aqueous sodium bicarbonate solution (2.0 mL) and 50% ether–ethyl acetate (v/v, 10.0 mL) at 23  $^\circ\text{C}$ . The resulting biphasic mixture was then transferred to a separatory funnel and the layers that formed were separated. The organic layers were combined and the combined layers were washed sequentially with water ( $3 \times 2.0$  mL) and saturated aqueous sodium chloride solution (3.0 mL). The organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was used purified by preparative thin-layered chromatography (eluting with 50% ether–hexanes) to provide the ketofuran **53** as an amorphous solid (14.7 mg, 38%).

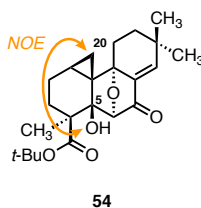
$R_f = 0.26$  (50% ether–hexanes; UV, PAA).  $^1\text{H NMR}$  (600 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.51 (s, 1H,  $\text{H}_1$ ), 4.29 (dd,  $J = 17.4, 1.0$  Hz, 1H,  $\text{H}_{7a}$ ), 4.06 (dd,  $J = 17.4, 1.0$  Hz, 1H,  $\text{H}_{7b}$ ), 2.38 (dt,  $J = 13.2, 3.4$  Hz, 1H,  $\text{H}_{10a}$ ), 2.13–2.08 (m, 1H,  $\text{H}_{4a}$ ), 1.99–1.95 (m, 2H,  $\text{H}_3$ ), 1.71–1.65 (m, 1H,  $\text{H}_{10b}$ ), 1.63–1.51 (m, 3H,  $\text{H}_{4b,11}$ ), 1.46–1.41 (m, 10H,  $\text{H}_{1a,6}$ ), 1.27–1.23 (m, 4H,  $\text{H}_{2,5}$ ), 1.17

(s, 3H, H<sub>9a</sub>), 1.08 (s, 3H, H<sub>9b</sub>), 0.75 (dd, J = 8.3, 6.6 Hz, 1H, H<sub>1b</sub>). <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>): δ 204.2 (C), 203.7 (C), 172.4 (C), 146.3 (CH), 134.2 (C), 83.3 (C), 81.4 (C), 70.7 (CH<sub>2</sub>), 55.3 (C), 34.2 (C), 33.9 (C), 33.6 (CH<sub>2</sub>), 31.4 (CH<sub>2</sub>), 28.7 (CH<sub>2</sub>), 28.4 (2 × CH<sub>3</sub>), 27.8 (3 × CH<sub>3</sub>), 21.0 (CH), 20.7 (CH<sub>3</sub>), 16.7 (CH<sub>2</sub>), 8.9 (CH<sub>2</sub>). IR (ATR-FTIR), cm<sup>-1</sup>: 2961 (m), 2955 (m), 2870 (m), 1732 (s), 1691 (m), 1654 (m). HRMS-CI (m/z): [M + Na]<sup>+</sup> calcd for C<sub>23</sub>H<sub>33</sub>O<sub>5</sub>, 389.2328; found, 389.2338.

*Synthesis of the aldol product 54:*



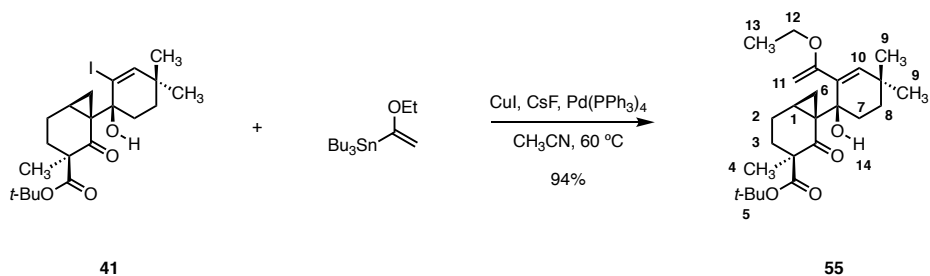
Powdered sodium hydroxide (1.0 mg, 25.0  $\mu\text{mol}$ , 2.03 equiv) was added to a solution of the ketofuran **53** (5.0 mg, 12.3  $\mu\text{mol}$ , 1 equiv) in ethanol (240  $\mu\text{L}$ ) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C. The product mixture was diluted sequentially with saturated aqueous ammonium chloride solution (200  $\mu\text{L}$ ), water (1.0 mL), and ethyl acetate (5.0 mL) at 23 °C. The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3.0 mL). The organic layers were combined and the combined organic layers were washed with water (2.0 mL) and saturated aqueous sodium chloride solution (2.0 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by preparative thin-layered chromatography (eluting with 50% ether–hexanes) to provide the aldol product **54** as a white solid (3.2 mg, 66%).



The relative stereochemistry of the newly generated alcohol was determined by NOE analysis. Correlations between the cyclopropane hydrogen H1 and the hydroxyl proton H12 support the relative assignment shown.

$R_f = 0.58$  (33% ether-hexanes; faintly UV, PAA).  $^1\text{H NMR}$  (600 MHz, dimethylsulfoxide- $d_6$ ):  $\delta$  6.20 (s, 1H, H<sub>8</sub>), 4.89 (s, 1H, H<sub>12</sub>), 4.74 (s, 1H, H<sub>9</sub>), 1.80–1.64 (m, 4H, H<sub>3,13</sub>), 1.52–1.41 (m, 3H, H<sub>2,4a,14a</sub>), 1.41 (s, 9H, H<sub>6</sub>), 1.22–1.18 (m, 1H, H<sub>4b</sub>), 1.16–1.10 (m, 1H, H<sub>14b</sub>), 1.10 (s, 3H, H<sub>9a</sub>), 1.03 (s, 3H, H<sub>9b</sub>), 0.99 (s, 3H, H<sub>5</sub>), 0.69 (t,  $J = 6.2$  Hz, 1H, H<sub>1a</sub>), 0.35 (dd,  $J = 9.4, 6.0$  Hz, 1H, H<sub>1b</sub>).  $^{13}\text{C NMR}$  (150 MHz, dimethylsulfoxide- $d_6$ ):  $\delta$  198.2 (C), 174.2 (C), 137.2 (C), 136.4 (CH), 84.4 (CH), 83.0 (C), 79.7 (C), 78.3 (C), 47.1 (C), 36.3 (C), 33.3 (CH<sub>2</sub>), 32.7 (C), 29.2 (CH<sub>3</sub>), 27.7 (3  $\times$  CH<sub>3</sub>), 27.3 (CH<sub>3</sub>), 22.6 (CH<sub>2</sub>), 21.2 (CH<sub>2</sub>), 18.3 (CH<sub>2</sub>), 17.6 (CH<sub>3</sub>), 12.7 (CH), 8.9 (CH<sub>2</sub>). IR (ATR-FTIR),  $\text{cm}^{-1}$ : 2930 (m), 1752 (m), 1726 (m), 1555 (m). HRMS-Cl ( $m/z$ ):  $[\text{M} + \text{Na}]^+$  calcd for  $\text{C}_{23}\text{H}_{32}\text{NaO}_5$ , 411.2147; found, 411.2154.

*Synthesis of the vinyl ether 55:*

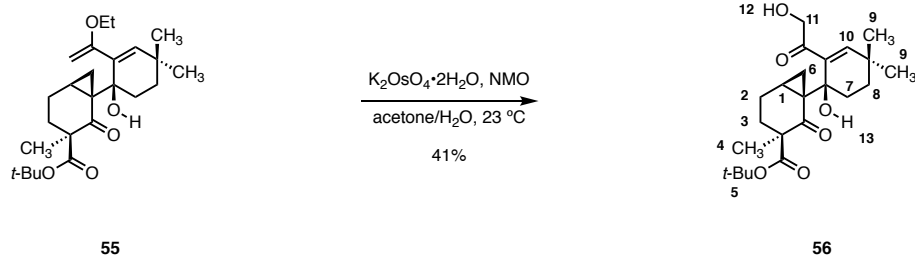


A screw-capped pressure vessel was charged with copper(I) iodide (24.0 mg, 124  $\mu$ mol, 0.10 equiv), cesium fluoride (414 mg, 2.73 mmol, 2.20 equiv), tetrakis(triphenylphosphine)-palladium(0) (72.0 mg, 62.0  $\mu$ mol, 0.05 equiv), the adduct **41** (590 mg, 1.24 mmol, 1 equiv), and acetonitrile (6.2 mL). The reaction vessel was fitted with a rubber septum and the headspace in the vessel was evacuated. The headspace was back-filled with argon. Tributyl(1-ethoxyvinyl) tin (460  $\mu$ L, 1.36 mmol, 1.10 equiv) was added to the suspension under argon at 23  $^{\circ}$ C. The reaction chamber was then sealed and the reaction vessel was immediately placed into a bath that had been preheated to 60  $^{\circ}$ C. The reaction mixture was stirred for 6 h at 65  $^{\circ}$ C. The product mixture was then cooled over 30 min to 23  $^{\circ}$ C. The cooled product mixture was diluted with ether (30 mL). The diluted mixture was filtered through a pad of celite (2.5  $\times$  4.0 cm) and the filter cake was rinsed with ether (3  $\times$  10 mL). The filtrates were combined and the combined filtrates were transferred to a separatory funnel that had been charged with pentane (20 mL). The diluted filtrates were washed sequentially with saturated aqueous sodium bicarbonate solution (15 mL), saturated aqueous ammonium chloride solution (15 mL), and saturated aqueous sodium chloride solution (25 mL). The washed organic layer was dried over sodium sulfate. The solution was filtered and the filtrate was concentrated. The residue obtained

was purified by flash-column chromatography (eluting with 16% ether–hexanes) to provide the vinyl ether **55** as a yellow oil (490 mg, 94%).

$R_f = 0.58$  (33% ether–hexanes; faintly UV, PAA).  $^1\text{H NMR}$  (600 MHz,  $\text{C}_6\text{D}_6$ ):  $\delta$  5.92 (s, 1H, H<sub>10</sub>), 4.04 (s, 1H, H<sub>11a</sub>), 3.67 (s, 1H, H<sub>11b</sub>), 3.17 (q,  $J = 7.0$  Hz, 2H, H<sub>12</sub>), 2.96 (s, 1H, H<sub>14</sub>), 2.84 (t,  $J = 15.4$  Hz, 1H, H<sub>7a</sub>), 2.14–2.05 (m, 1H, H<sub>8a</sub>), 2.04–1.93 (m, 2H, H<sub>1,2a</sub>), 1.69 (d,  $J = 10.2$  Hz, 1H, H<sub>7b</sub>), 1.66–1.60 (m, 2H, H<sub>6a,3a</sub>), 1.56–1.47 (m, 1H, H<sub>3b</sub>), 1.41–1.37 (m, 2H, H<sub>6b,8b</sub>), 1.36 (s, 3H, H<sub>4</sub>), 1.32 (s, 3H, H<sub>9</sub>), 1.28 (s, 9H, H<sub>5</sub>), 0.98 (s, 3H, H<sub>9</sub>), 0.79 (t,  $J = 7.0$  Hz, 3H, H<sub>13</sub>).  $^{13}\text{C NMR}$  (150 MHz,  $\text{C}_6\text{D}_6$ ):  $\delta$  205.4 (C), 172.9 (C), 164.7 (C), 142.7 (CH), 136.1 (C), 84.7 (CH<sub>2</sub>), 80.4 (C), 70.1 (C), 63.1 (CH<sub>2</sub>), 55.2 (C), 39.9 (CH<sub>2</sub>), 33.8 (C), 32.9 (CH<sub>2</sub>), 31.8 (CH<sub>2</sub>), 31.3 (CH<sub>3</sub>), 30.5 (CH<sub>2</sub>), 27.8 (3  $\times$  CH<sub>3</sub>), 25.7 (CH<sub>3</sub>), 23.5 (CH<sub>3</sub>), 22.5 (CH), 18.9 (CH<sub>2</sub>), 14.3 (CH<sub>3</sub>), 10.9 (CH<sub>2</sub>). IR (ATR-FTIR),  $\text{cm}^{-1}$ : 2990 (m), 1851 (m), 1776 (m), 1501 (m). HRMS-CI ( $m/z$ ):  $[\text{M} + \text{Na}]^+$  calcd for  $\text{C}_{25}\text{H}_{39}\text{O}_5$ , 419.2797; found, 419.2777.

Synthesis of the  $\alpha$ -hydroxyketone **56**:



Potassium osmate(VI) dihydrate (15.7 mg, 42.5  $\mu$ mol, 5.0 mol%) was added to a mixture of the vinyl ether **55** (355 mg, 850  $\mu$ mol, 1 equiv) and *N*-methyl-morpholine *N*-oxide (498 mg, 4.25 mmol, 5.00 equiv) in 66% acetone–water (v/v, 3.0 mL) at 23 °C. The reaction mixture was stirred for 18 h at 23 °C. The product mixture was poured into a stirring mixture of ethyl acetate (15 mL) and saturated aqueous sodium thiosulfate solution (10 mL). The diluted product mixture was stirred for 10 min at 23 °C. The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (10 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 20% ethyl acetate–hexanes) to provide the diol **56** as a white solid (143 mg, 41%).

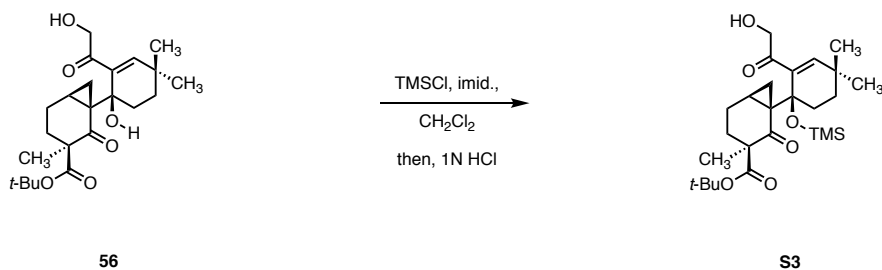
$R_f$  = 0.10 (33% ethyl acetate–hexanes; faintly UV, PAA). <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):  $\delta$  6.39 (s, 1H, H<sub>10</sub>), 4.67 (dd,  $J$  = 18.6, 4.4 Hz, 1H, H<sub>11a</sub>), 4.14 (dd,  $J$  = 18.6, 4.5 Hz, 1H, H<sub>11b</sub>), 3.15 (t,  $J$  = 4.7 Hz, 1H, H<sub>12</sub>), 2.76 (s, 1H, H<sub>13</sub>), 2.36 (tt,  $J$  = 14.1, 2.8 Hz, 1H, H<sub>7a</sub>), 2.23–2.10 (m, 1H, H<sub>1</sub>), 2.07 (td,  $J$  = 13.7, 4.7 Hz, 1H, H<sub>3a</sub>), 2.01–1.89 (m, 2H, H<sub>2</sub>), 1.71 (td,  $J$  =

13.8, 3.4 Hz, 1H, H<sub>8a</sub>), 1.61–1.52 (m, 2H, H<sub>6a,7b</sub>), 1.51–1.44 (m, 2H, H<sub>3a,8b</sub>), 1.40 (s, 9H, H<sub>5</sub>), 1.27 (s, 3H, H<sub>9a</sub>), 1.23 (dd, J = 8.5, 5.1 Hz, 1H, H<sub>6b</sub>), 1.11 (s, 3H, H<sub>9b</sub>), 1.04 (s, 3H, H<sub>4</sub>). <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>): δ 207.3 (C), 203.5 (C), 172.7 (C), 151.4 (CH), 137.7 (C), 81.1 (C), 69.7 (C), 64.5 (CH<sub>2</sub>), 55.0 (C), 39.8 (C), 33.4 (C), 32.5 (CH<sub>2</sub>), 31.8 (CH<sub>2</sub>), 30.3 (CH<sub>3</sub>), 29.1 (CH<sub>3</sub>), 27.8 (3 × CH<sub>3</sub>), 25.2 (CH<sub>3</sub>), 23.8 (CH), 21.5 (CH<sub>3</sub>), 17.7 (CH<sub>2</sub>), 11.7 (CH<sub>2</sub>). IR (ATR-FTIR), cm<sup>-1</sup>: 2905 (m), 1745 (m), 1733 (m), 1616 (m). HRMS-Cl (m/z): [M + Na]<sup>+</sup> calcd for C<sub>23</sub>H<sub>34</sub>NaO<sub>6</sub>, 429.2253; found, 429.2205.



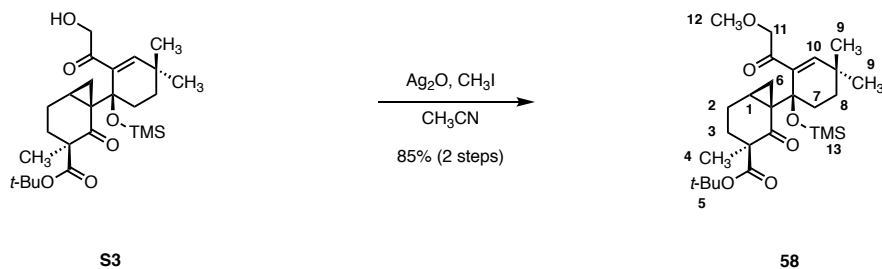
*Synthesis of the silyl methyl ether **58**:*

*Step 1: Synthesis of the silyl ether **S3**:*



Chlorotrimethylsilane (102  $\mu$ L, 812  $\mu$ mol, 2.21 equiv) was added to a solution of the hydroxyketone **56** (150 mg, 369  $\mu$ mol, 1 equiv), 4-dimethylaminopyridine (9.0 mg, 73.9  $\mu$ mol, 20.0 mol%), and imidazole (121 mg, 1.77 mmol, 4.80 equiv) in dichloromethane (3.7 mL) at 23  $^{\circ}$ C. The reaction mixture was stirred for 22 h at 23  $^{\circ}$ C. The product mixture was diluted sequentially with 1 N aqueous hydrochloric acid solution (1.0 mL) and ethyl acetate (5.0 mL). The diluted product mixture was stirred for 30 min at 23  $^{\circ}$ C. The resulting biphasic mixture was transferred to a separatory funnel that had been charged with ethyl acetate (10 mL) and the layers that formed were separated. The organic layer was washed with saturated aqueous sodium chloride solution (10 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The silyl ether **S3** obtained in this way was used directly in the following step.

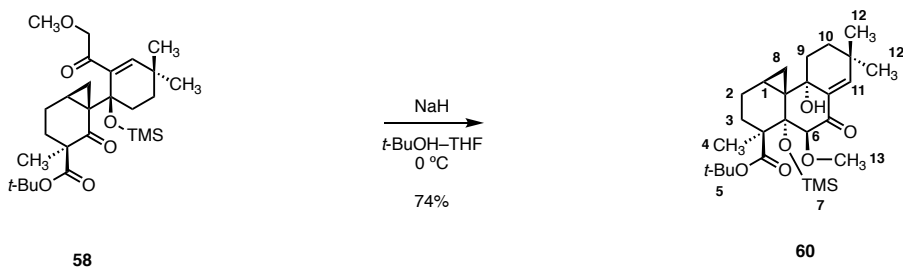
Part 2: Synthesis of the silyl methyl ether **58**:



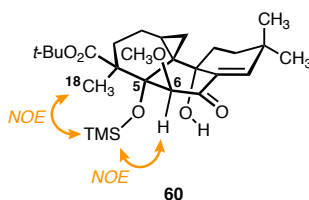
Silver(I) oxide (427 mg, 1.85 mmol, 5.01 equiv) was added in one portion to a solution of the unpurified silyl ether **S3** obtained in the preceding step (nominally, 369  $\mu\text{mol}$ , 1 equiv) in 50% iodomethane–acetonitrile (v/v, 7.5 mL) at 23 °C. The reaction mixture was stirred vigorously for 18 h at 23 °C. The product mixture was filtered through a plug of celite (2.0 cm  $\times$  3.0 cm). The filter cake was rinsed with dichloromethane (3  $\times$  5.0 mL). The filtrates were combined and the combined filtrates were concentrated. The residue obtained was purified by flash-column chromatography (eluting with 15% ethyl acetate–hexanes) to provide the methyl ether **58** as a colorless oil (154.3 mg, 85% two steps).

$R_f = 0.20$  (15% ethyl acetate–hexanes; faintly UV, PAA).  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.38 (s, 1H, H<sub>10</sub>), 4.40 (d,  $J = 16.5$  Hz, 1H, H<sub>11a</sub>), 4.14 (d,  $J = 16.4$  Hz, 1H, H<sub>11b</sub>), 3.38 (s, 3H, H<sub>12</sub>) 2.45–2.38 (m, 1H, H<sub>7a</sub>), 2.34–2.27 (m, 1H, H<sub>1</sub>), 2.24–2.16 (m, 1H, H<sub>2a</sub>), 2.09–2.02 (m, 1H, H<sub>3a</sub>), 1.93–1.88 (m, 1H, H<sub>2b</sub>), 1.70–1.59 (m, 2H, H<sub>6a,8a</sub>), 1.52–1.52 (m, 3H, H<sub>3b,7b,8b</sub>), 1.39 (s, 9H, H<sub>5</sub>), 1.24 (s, 3H, H<sub>9a</sub>), 1.17–1.12 (m, 4H, H<sub>4,6b</sub>), 1.11 (s, 3H, H<sub>9b</sub>), 0.02 (s, 2H, H<sub>13</sub>).

Synthesis of the silyl migration product **60**:



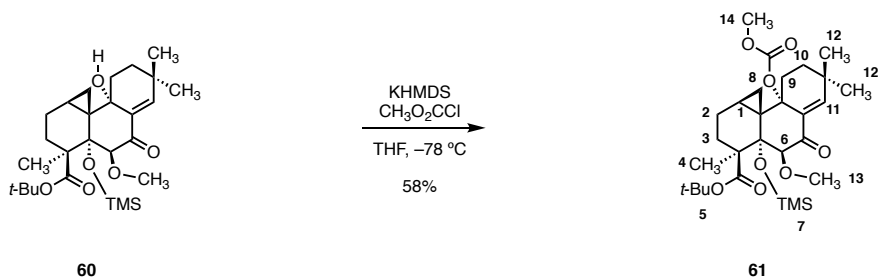
A dispersion of sodium hydride in mineral oil (60% wt., 16.0 mg, 443  $\mu\text{mol}$ , 1.20 equiv) was added in one portion to a solution of the methyl ether **58** (181.6 mg, 369  $\mu\text{mol}$ , 1 equiv) in 5% *tert*-butanol–tetrahydrofuran (v/v, 4.9 mL) at 0 °C. The reaction mixture was stirred for 2 h at 23 °C. The product mixture was diluted sequentially with saturated aqueous ammonium chloride solution (2.0 mL), water (2.0 mL), and ethyl acetate (15 mL). The resulting biphasic mixture was transferred to a separatory funnel that had been charged with ethyl acetate (10 mL) and the layers that formed were separated. The organic layer was washed with saturated aqueous sodium chloride solution (5.0 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 25% ether–hexanes) to provide the silyl migration product **60** as a colorless oil (134.3 mg, 74%).



The relative stereochemistry of the silyl migration product **60** was assigned via conclusive NOE correlations between the C6 methine and the C7 trimethylsilyl group as well as the correlation between C4 methyl group and the C7 trimethylsilyl group supporting the relative stereochemistry depicted.

$R_f = 0.25$  (25% ether–hexanes; PAA).  $^1\text{H NMR}$  (600 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.83 (s, 1H, H<sub>11</sub>), 4.92 (s, 1H, H<sub>6</sub>), 3.52 (s, 3H, H<sub>13</sub>), 1.97–1.89 (m, 1H, H<sub>2a</sub>), 1.81–1.75 (m, 2H, H<sub>2b,9a</sub>), 1.59–1.53 (m, 3H, H<sub>3,10a</sub>), 1.45 (s, 9H, H<sub>5</sub>), 1.43–1.40 (m, 1H, H<sub>10b</sub>), 1.39–1.30 (m, 1H, H<sub>1</sub>), 1.25 (s, 3H, H<sub>4</sub>), 1.15–1.08 (m, 6H, H<sub>8a,3b,12a</sub>), 1.01 (s, 3H, H<sub>12b</sub>), 0.67 (dd,  $J = 9.8, 6.3$  Hz, 1H, H<sub>8b</sub>), 0.13 (s, 9H, H<sub>7</sub>).  $^{13}\text{C NMR}$  (150 MHz,  $\text{CDCl}_3$ ):  $\delta$  197.3 (C), 176.5 (C), 145.6 (CH), 134.1 (C), 85.3 (CH), 80.1 (C), 76.2 (C), 74.6 (C), 59.2 (CH<sub>3</sub>), 35.4 (C), 33.8 (CH<sub>3</sub>), 32.1 (C), 28.3 (CH<sub>3</sub>), 29.7 (3  $\times$  CH<sub>3</sub>), 27.5 (CH<sub>3</sub>), 27.3 (CH<sub>2</sub>), 26.2 (CH<sub>2</sub>), 18.9 (CH<sub>2</sub>), 18.9 (CH<sub>3</sub>), 15.4 (CH), 12.1 (CH<sub>2</sub>), 2.6 (3  $\times$  CH<sub>3</sub>). IR (ATR-FTIR),  $\text{cm}^{-1}$ : 2999 (m), 2750 (m), 1645 (m), 1605 (m). HRMS-Cl ( $m/z$ ):  $[\text{M} + \text{Na}]^+$  calcd for  $\text{C}_{27}\text{H}_{44}\text{NaO}_6\text{Si}$ , 515.2805; found, 515.2801.

Synthesis of the methyl carbonate **61**:



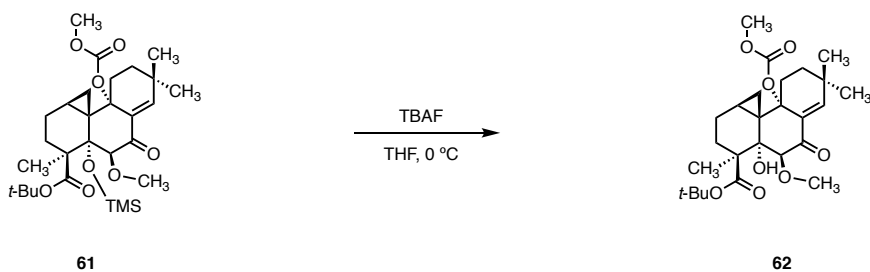
A solution of potassium bis(trimethylsilyl)amide in tetrahydrofuran (1.0 M, 250  $\mu$ L, 250  $\mu$ mol, 1.50 equiv) was added dropwise via syringe pump over 5 min to a solution of the silyl migration product **60** (82.0 mg, 167  $\mu$ mol, 1 equiv) in tetrahydrofuran (1.7 mL) at  $-78$   $^{\circ}$ C. The reaction mixture was stirred for 5 min at  $-78$   $^{\circ}$ C. Methyl chloroformate (128  $\mu$ L, 1.67 mmol, 10.0 equiv) was then added at  $-78$   $^{\circ}$ C. The reaction mixture was stirred for 5 h at  $-78$   $^{\circ}$ C. The product mixture was diluted sequentially with saturated aqueous ammonium chloride solution (500  $\mu$ L), water (1.0 mL), and ethyl acetate (10 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The organic layer was washed with saturated aqueous sodium chloride solution (2.0 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 16% ether–hexanes) to provide the methyl carbonate **61** as a colorless oil (149 mg, 58%).

$R_f$  = 0.40 (20% ether–hexanes; UV, PAA).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.75 (s, 1H, H<sub>11</sub>), 4.41 (s, 1H, H<sub>6</sub>), 3.61 (s, 3H, H<sub>14</sub>), 3.56 (s, 3H, H<sub>13</sub>), 2.06 (td,  $J$  = 13.9, 5.8 Hz, 1H, H<sub>3a</sub>), 1.95–1.86 (m 1H, H<sub>2a</sub>), 1.84–1.80 (m, 1H, H<sub>2b</sub>), 1.63–1.53 (m, 3H, H<sub>9,10a</sub>), 1.41 (s, 9H, H<sub>5</sub>), 1.37 (s, 3H, H<sub>4</sub>), 1.22–1.14 (m, 2H, H<sub>1,3b,10b</sub>), 1.12 (s, 3H, H<sub>12a</sub>), 1.01 (s, 3H, H<sub>12b</sub>)

0.84–0.80 (m, 1H, H<sub>8a</sub>), 0.67 (t, J = 7.0 Hz, 1H, H<sub>8b</sub>), 0.12 (s, 9H, H<sub>7</sub>). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 194.9 (C), 173.9 (C), 153.3 (C), 143.6 (CH), 135.0 (C), 85.7 (C), 80.4 (CH), 79.7 (C), 74.6 (C), 60.58 (CH<sub>3</sub>), 54.2 (CH<sub>3</sub>), 48.1 (C), 33.9 (C), 33.8 (CH<sub>2</sub>), 31.8 (C), 28.1 (CH<sub>3</sub>), 27.8 (3 × CH<sub>3</sub>), 27.7 (CH<sub>3</sub>), 27.5 (CH<sub>2</sub>), 25.2 (CH<sub>2</sub>), 19.1 (CH<sub>3</sub>), 18.6 (CH<sub>2</sub>), 14.8 (CH<sub>3</sub>), 13.8 (CH<sub>2</sub>), 2.7 (3 × CH<sub>3</sub>).

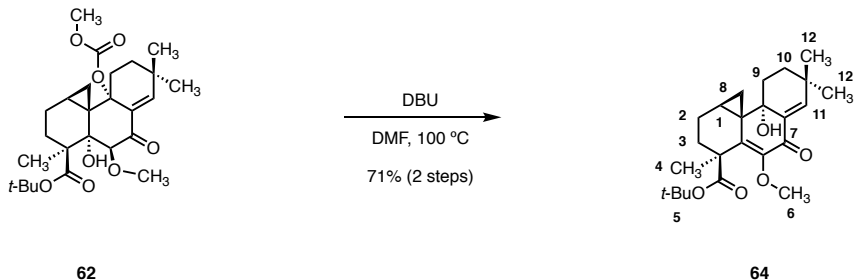
*Synthesis of the methyl vinyl ether 64:*

*Part 1: Synthesis of methyl carbonate 62:*



A solution of tetrabutylammonium fluoride in tetrahydrofuran (1.0 M, 130  $\mu$ L, 130  $\mu$ mol, 1.24 equiv) was added to a solution of the methyl carbonate **61** (53.5 mg, 97.2  $\mu$ mol, 1 equiv) in tetrahydrofuran (1.0 mL) at 0 °C. The reaction mixture was stirred for 2 h at 0 °C. The product mixture was diluted sequentially with saturated aqueous ammonium chloride solution (500  $\mu$ L), water (500  $\mu$ L), and ethyl acetate (5.0 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The organic layer was washed with saturated aqueous sodium chloride solution (1.0 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The methyl carbonate **62** obtained in this way was used in the next step without further purification.

Part 2: Synthesis of the methyl vinyl ether **64**:



1,8-Diazabicyclo[4.5.0]undec-7-ene (259  $\mu\text{L}$ , 1.67 mmol, 17.2 equiv) was added to a solution of the unpurified methyl carbonate **62** obtained in the preceding step (nominally, 97.2  $\mu\text{mol}$ , 1 equiv) dissolved in *N,N*-dimethylformamide (1.7 mL) at 23 °C. The reaction vessel was placed in a heating block that had been preheated to 100 °C. The reaction mixture was stirred and heated for 2 h at 100 °C. The product mixture was cooled over 30 min to 23 °C. The cooled product mixture was diluted sequentially with saturated aqueous ammonium chloride solution (500  $\mu\text{L}$ ), water (3.0 mL), and ethyl acetate (10.0 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3  $\times$  3.0 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (1.0 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by preparative thin-layered chromatography (eluting with 33% ether–hexanes) to furnish the methyl vinyl ether **64** as colorless oil (23.0 mg, 71% over two steps).

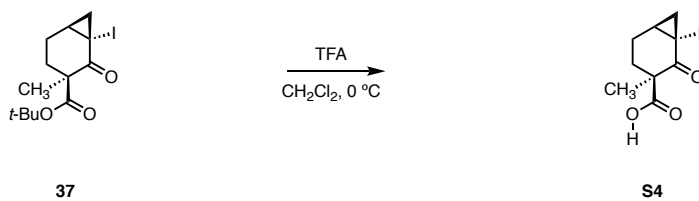
$R_f = 0.20$  (33% ether–hexanes; UV, PAA).  $^1\text{H NMR}$  (600 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.87 (s, 1H,  $\text{H}_{11}$ ), 3.67 (s, 3H,  $\text{H}_{22}$ ), 2.01–1.86 (m, 3H,  $\text{H}_3$ ), 1.77 (td,  $J = 13.9, 4.8$  Hz, 1H,  $\text{H}_{9a}$ ), 1.71–



1.63 (m, 2H, H<sub>1,3a</sub>), 1.51–1.43 (m, 2H, H<sub>3b,10</sub>), 1.40–1.37 (m, 10H, H<sub>5,9b</sub>), 1.29 (s, 3H, H<sub>4</sub>), 1.12 (m, 3H, H<sub>12a</sub>), 1.00 (s, 3H, H<sub>12b</sub>), 0.96 (dd,  $J = 8.9, 5.9$  Hz, 1H, H<sub>8a</sub>), 0.86 (t,  $J = 6.2$  Hz, 1H, H<sub>8b</sub>). <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>):  $\delta$  181.4 (C), 174.7 (C), 148.8 (CH), 148.2 (C), 146.0 (C), 134.8 (C), 80.1 (CH), 70.7 (C), 58.7 (CH<sub>3</sub>), 44.7 (C), 32.8 (C), 31.4 (CH<sub>2</sub>), 29.6 (CH<sub>3</sub>), 29.7 (CH<sub>3</sub>), 28.8 (CH<sub>2</sub>), 27.8 (3  $\times$  CH<sub>3</sub>), 26.2 (CH<sub>3</sub>), 26.1 (CH<sub>2</sub>), 21.4 (CH<sub>3</sub>), 17.4 (CH<sub>2</sub>), 14.9 (CH), 12.7 (CH<sub>2</sub>). IR (ATR-FTIR), cm<sup>-1</sup>: 2980 (m), 2900 (m), 2350 (w), 1735 (s), 1680 (m). HRMS-Cl (m/z): [M + Na]<sup>+</sup> calcd for C<sub>24</sub>H<sub>34</sub>NaO<sub>5</sub>, 425.2304; found, 425.2302.

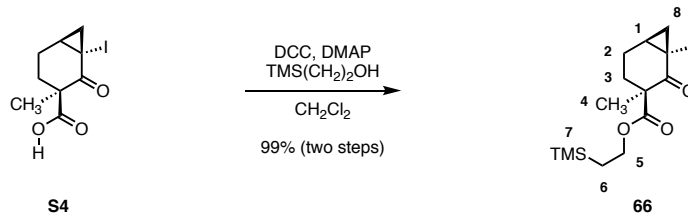
*Synthesis of the iodocyclopropane 66:*

*Part 1: Synthesis of the carboxylic acid S4:*



Trifluoroacetic acid (110  $\mu$ L, 1.43 mmol, 10.0 equiv) was added to a solution of the cyclopropane **37** (50.0 mg, 143  $\mu$ mol, 1 equiv) in dichloromethane (800  $\mu$ L) at 0 °C. The reaction mixture was stirred for 2 h at 0 °C. The product mixture was concentrated. The residue obtained was re-concentrated twice from 50% ether–pentane (v/v, 4.0 mL). The carboxylic acid **S4** was obtained as an off-white solid and was used in the next step without purification.

Part 2: Synthesis of the iodocyclopropane **66**:

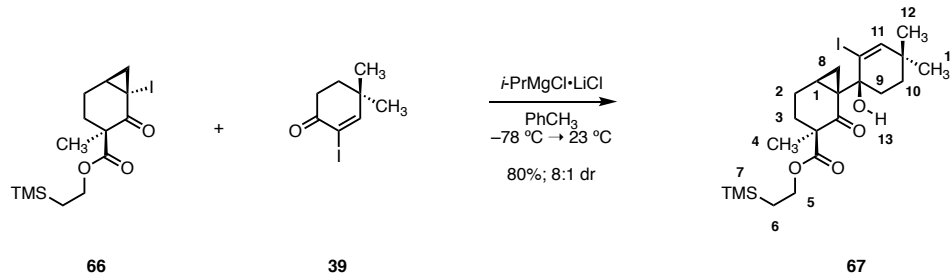


*N,N'*-Cyclohexylcarbodiimide (30.0 mg, 145  $\mu\text{mol}$ , 1.01 equiv), 4-dimethylamino pyridine (2.0 mg, 16.3  $\mu\text{mol}$ , 0.10 equiv), and 2-trimethylsilylethanol (68.5  $\mu\text{L}$ , 429  $\mu\text{mol}$ , 3.00 equiv) were added in sequence to a solution of the unpurified carboxylic acid **S4** obtained in the preceding step (nominally, 143  $\mu\text{mol}$ , 1 equiv) in dichloromethane (800  $\mu\text{L}$ ) at 23  $^\circ\text{C}$ . The reaction mixture was stirred for 3 h at 23  $^\circ\text{C}$ . The product mixture was diluted sequentially with saturated aqueous ammonium chloride solution (200  $\mu\text{L}$ ), water (1.0 mL), and ethyl acetate (5.0 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The organic layer was washed sequentially with water (1.0 mL) and saturated aqueous sodium chloride solution (2.0 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was partitioned into two portions and each portion was purified by flash-column chromatography (eluting with 25% ether–hexanes) to furnish the cyclopropane **66** as a white solid (55.7 mg, 99% over two steps).

$R_f = 0.36$  (20% ether–hexanes; faintly UV, PAA).  $^1\text{H NMR}$  (600 MHz,  $\text{CDCl}_3$ ):  $\delta$  4.17 (ddt,  $J = 10.3, 7.1, 3.7$  Hz, 2H,  $\text{H}_5$ ), 2.27–2.19 (m, 2H,  $\text{H}_1, \text{H}_{2a}$ ), 2.13 (td,  $J = 13.6, 4.4$  Hz, 1H,  $\text{H}_{3a}$ ), 2.01 (t,  $J = 6.8$  Hz, 1H,  $\text{H}_{8a}$ ), 1.92 (dq,  $J = 12.0, 2.9, 2.5$  Hz, 1H,  $\text{H}_{2b}$ ), 1.65 (dt,  $J = 14.3, 3.9$  Hz, 1H,  $\text{H}_{3b}$ ), 1.56 (dd,  $J = 8.8, 7.0$  Hz, 1H,  $\text{H}_{8b}$ ), 1.35 (s, 3H,  $\text{H}_4$ ) 1.04–0.93 (m, 2H,  $\text{H}_6$ ), 0.03 (s, 9H,  $\text{H}_7$ ).  $^{13}\text{C NMR}$  (150 MHz,  $\text{CDCl}_3$ ):  $\delta$  200.2 (C), 172.8 (C), 64.0

(CH<sub>2</sub>), 53.1 (C), 30.7 (CH), 28.6 (CH<sub>2</sub>), 22.1 (CH<sub>3</sub>), 21.5 (CH<sub>2</sub>), 18.1 (CH<sub>2</sub>), 17.3 (CH<sub>2</sub>), 7.5 (C), -1.6 (3 × CH<sub>3</sub>). IR (ATR-FTIR), cm<sup>-1</sup>: 2953 (w), 1737 (s), 1692 (s). HRMS-Cl (m/z): [M + Na]<sup>+</sup> calcd for C<sub>14</sub>H<sub>23</sub>INaO<sub>3</sub>Si, 417.0353; found, 417.0396.

Synthesis of the adduct **67**:

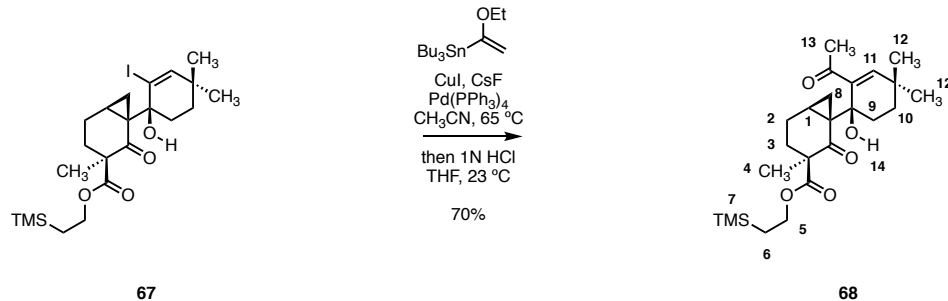


A solution of *iso*-propylmagnesium chloride–lithium chloride complex in tetrahydrofuran (1.25 M, 8.40 mL, 10.5 mmol, 1.05 equiv) was added dropwise to a solution of the iodo-cyclopropane **66** (4.14 g, 10.5 mmol, 1.1 equiv) in toluene (50 mL) at  $-78\text{ }^\circ\text{C}$ . The reaction mixture was stirred for 30 min at  $-78\text{ }^\circ\text{C}$ . A solution of the iodoenone **39** (2.5 g, 10.0 mmol, 1 equiv) in toluene (5.0 mL) was then added to the reaction mixture over 30 min at  $-78\text{ }^\circ\text{C}$ . The reaction mixture was then removed from the cooling bath and warmed over 1 h to  $23\text{ }^\circ\text{C}$ . The warmed mixture was stirred for 19 h at  $23\text{ }^\circ\text{C}$ . The product mixture was diluted with saturated aqueous ammonium chloride solution (15 mL), water (50 mL), and 66% ether–pentane (v/v, 150 mL) at  $23\text{ }^\circ\text{C}$ . The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The organic layer was washed sequentially with water (25 mL) and saturated aqueous sodium chloride solution (25 mL). The organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 14% ether–hexanes) to provide the adduct **67** as a pale yellow oil (4.35 g, 80%).

$^1\text{H}$  NMR analysis of the unpurified product mixture indicated the presence of a 8:1 mixture of diastereomers.

$R_f = 0.25$  (20% ether–hexanes; PAA).  $^1\text{H NMR}$  (600 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.33 (s, 1H,  $\text{H}_{11}$ ), 4.21–4.11 (m, 2H,  $\text{H}_5$ ), 2.78 (bs, 1H,  $\text{H}_{13}$ ), 2.28–1.98 (m, 4H,  $\text{H}_{3a,9a,10}$ ), 1.72–1.49 (m, 7H,  $\text{H}_{1,2,3b,8,9b}$ ), 1.43 (s, 3H,  $\text{H}_4$ ), 1.21 (s, 3H,  $\text{H}_{9a}$ ), 1.04 (s, 3H,  $\text{H}_{9b}$ ), 1.01–0.93 (m, 2H,  $\text{H}_6$ ), 0.04 (s, 9H,  $\text{H}_7$ ).  $^{13}\text{C NMR}$  (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  205.3 (C), 173.9 (C), 152.2 (CH), 149.9 (C), 106.7 (C), 72.4 ( $\text{CH}_2$ ), 63.5(C), 54.4 (C), 38.0 (C), 32.9 ( $\text{CH}_2$ ), 31.5 (C), 30.4 ( $\text{CH}_3$ ), 29.9 ( $\text{CH}_2$ ), 25.4 ( $\text{CH}_3$ ), 23.5 (CH), 23.1 ( $\text{CH}_3$ ), 17.4 ( $\text{CH}_2$ ), 17.1 ( $\text{CH}_2$ ), 11.5 ( $\text{CH}_2$ ), –1.5 ( $3 \times \text{CH}_3$ ). IR (ATR-FTIR),  $\text{cm}^{-1}$ : 3515 (m), 2953 (m), 2930 (m), 1738 (m), 1681 (m), 1446 (w). HRMS-CI (m/z):  $[\text{M} + \text{Na}]^+$  calcd for  $\text{C}_{22}\text{H}_{35}\text{INaO}_4\text{Si}_1$ , 541.1247; found, 541.1266.

Synthesis of the methyl ketone **68**:



A screw-capped pressure vessel was charged with copper(I) iodide (22.0 mg, 120  $\mu\text{mol}$ , 0.20 equiv), cesium fluoride (973 mg, 6.41 mmol, 1.10 equiv), tetrakis(triphenylphosphine)-palladium(0) (336 mg, 290  $\mu\text{mol}$ , 0.05 equiv), the adduct **67** (3.02 g, 5.82 mmol, 1 equiv), and acetonitrile (30 mL). The reaction vessel was fitted with a rubber septum and the headspace in the vessel was evacuated. The headspace was back-filled with argon. Tributyl(1-ethoxyvinyl) tin (2.20 mL, 6.48 mmol, 1.11 equiv) was added to the suspension under argon at 23  $^\circ\text{C}$ . The reaction chamber was then sealed and the reaction vessel was immediately placed into an oil bath that had been preheated to 65  $^\circ\text{C}$ . The reaction mixture was stirred and heated for 9 h at 65  $^\circ\text{C}$ . The product mixture was cooled over 30 min to 23  $^\circ\text{C}$ . The cooled product mixture was diluted with ethyl acetate (30 mL). The diluted mixture was filtered through a pad of celite (2.5  $\times$  4.0 cm) and rinsed with ethyl acetate (3  $\times$  15 mL). The filtrates were combined and the combined filtrates were transferred to a separatory funnel. The filtrates were washed sequentially with 30% aqueous ammonium hydroxide solution (w/v, 3  $\times$  10 mL), saturated aqueous sodium bicarbonate solution (25 mL), and saturated aqueous sodium chloride solution (25 mL). The organic layer was dried over sodium sulfate. The dried solution was filtered and concentrated. The residue obtained was dissolved in tetrahydrofuran (30 mL). 1 N

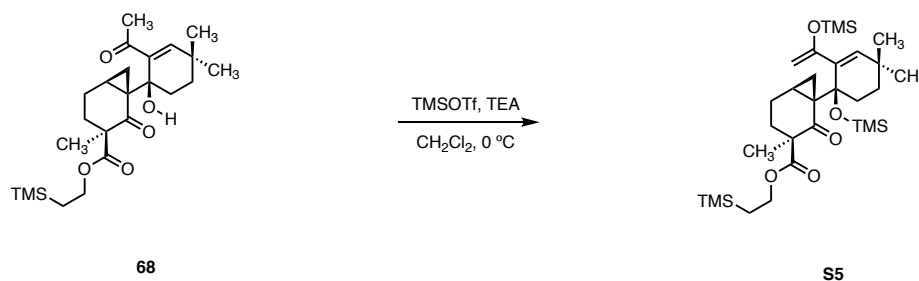
aqueous hydrochloric acid solution (7.00 mL, 7.00 mmol, 1.20 equiv) was added at 23 °C. The reaction mixture was stirred for 1.5 h at 23 °C. The product mixture was then diluted sequentially with saturated aqueous sodium bicarbonate (30 mL, *CAUTION*: gas evolution!), water (15 mL), and ethyl acetate (60 mL) at 23 °C. The resulting biphasic mixture was transferred to a separatory funnel and the layers were separated. The aqueous layer was extracted with ethyl acetate (2 × 15 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (15 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and concentrated. The residue obtained was purified by flash-column chromatography (eluting with 33% ether–hexanes) to provide the methyl ketone **68** as a white solid (1.77 g, 70%).

$R_f = 0.20$  (33% ether–hexanes; UV, PAA).  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.49 (d,  $J = 1.3$  Hz, 1H,  $\text{H}_{11}$ ), 4.24–4.03 (m, 2H,  $\text{H}_5$ ), 3.16 (s, 1H,  $\text{H}_{14}$ ), 2.41 (t,  $J = 14.2$  Hz, 1H,  $\text{H}_{9a}$ ), 2.22 (s, 3H,  $\text{H}_{13}$ ), 2.21–2.17 (m, 1H,  $\text{H}_1$ ), 2.09 (dt,  $J = 13.5, 9.1$  Hz, 1H,  $\text{H}_{3a}$ ), 2.02–1.96 (m, 2H,  $\text{H}_2$ ), 1.66 (td,  $J = 13.8, 3.3$  Hz, 1H,  $\text{H}_{10a}$ ), 1.54–1.39 (m, 4H,  $\text{H}_{3b,8a,9b,10b}$ ), 1.29 (s, 3H,  $\text{H}_{12a}$ ), 1.21 (dd,  $J = 8.5, 5.0$  Hz, 1H,  $\text{H}_{8b}$ ), 1.12 (s, 3H,  $\text{H}_{14}$ ), 1.10 (s, 3H,  $\text{H}_{12b}$ ), 0.95 (ddd,  $J = 8.8, 7.4, 4.3$  Hz, 1H,  $\text{H}_6$ ), 0.02 (s, 9H,  $\text{H}_7$ ).  $^{13}\text{C NMR}$  (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  206.5 (C), 204.4 (C), 173.9 (C), 151.8 (CH), 140.3 (C), 69.9 (C), 63.5 ( $\text{CH}_2$ ), 54.7 (C), 39.6 (C), 33.3 (C), 32.8 ( $\text{CH}_2$ ), 32.1 ( $\text{CH}_2$ ), 30.6 ( $\text{CH}_3$ ), 28.7 ( $\text{CH}_2$ ), 26.6 ( $\text{CH}_3$ ), 25.2 ( $\text{CH}_3$ ), 22.8 (CH), 21.4 ( $\text{CH}_3$ ), 17.4 ( $\text{CH}_2$ ), 17.1 ( $\text{CH}_2$ ), 11.3 ( $\text{CH}_2$ ),  $-1.5$  ( $3 \times \text{CH}_3$ ). IR (ATR-FTIR),  $\text{cm}^{-1}$ : 2953 (w), 1737 (s), 1692 (s). HRMS-CI ( $m/z$ ): 9530 (w), 1730 (s), 1671 (s), 1370 (s);  $[\text{M} + \text{Na}]^+$  calcd for  $\text{C}_{24}\text{H}_{38}\text{NaO}_5\text{Si}$ , 457.2386; found, 457.2394.



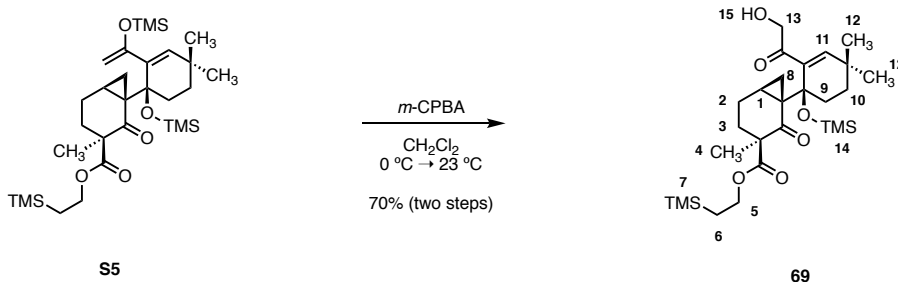
*Synthesis of the hydroxyketone 69:*

*Part 1: Synthesis of the enoxysilane S5:*



Trimethylsilyl trifluoromethanesulfonate (1.86 mL, 10.3 mmol, 8.00 equiv) was added to a solution of triethylamine (2.17 ml, 15.4 mmol, 12.0 equiv) and the methyl ketone **68** (650.0 mg, 1.28 mmol, 1 equiv) in dichloromethane (6.5 mL) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C. The cold product mixture was then diluted sequentially with saturated aqueous sodium bicarbonate solution (5.0 mL), water (5.0 mL) and dichloromethane (15 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The organic layer was washed with saturated aqueous sodium chloride solution (15 mL). The organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The enoxysilane ether residue **S5** was found to readily hydrolyze to the corresponding methyl ketone and was consequently used directly in the next step without purification.

Part 2: Synthesis of the hydroxyketone **69**:

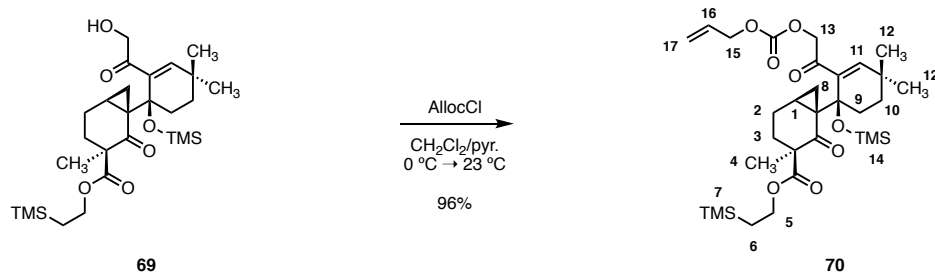


3-Chloroperoxybenzoic acid (332.1 mg, 1.92 mmol, 1.5 equiv) was added in one portion to a solution of the unpurified enoxysilane **S5** obtained in the preceding step (nominally, 1.28 mmol, 1 equiv) in dichloromethane (6.5 mL) at 0 °C. The reaction mixture was immediately removed from the cooling bath and allowed to warm over 30 min to 23 °C. The reaction mixture was stirred for 2 h at 23 °C. The product mixture was diluted sequentially with 10% aqueous sodium thiosulfate solution (w/v, 6 mL), water (5.0 mL), and ethyl acetate (15 mL) at 23 °C. The resulting biphasic mixture was stirred for 1 h at 23 °C. The mixture was then transferred to a separatory funnel and the layers that formed were separated. The organic layer was washed sequentially with 10% aqueous potassium carbonate solution (w/v, 2 × 6 mL) and saturated aqueous sodium chloride solution (15 mL). The organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 33% ethyl acetate–hexanes) to provide the hydroxyketone **69** as a white solid (468 mg, 70% over two steps).

$R_f = 0.20$  (33% ethyl acetate–hexanes; UV, PAA).  $^1\text{H NMR}$  (600 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.45 (s, 1H,  $\text{H}_{11}$ ), 4.49 (dd,  $J = 17.6, 4.4$  Hz, 1H,  $\text{H}_{13a}$ ), 4.25 (dd,  $J = 17.6, 4.3$  Hz, 1H,  $\text{H}_{13b}$ ), 4.15–4.08 (m, 2H,  $\text{H}_5$ ), 3.41 (t,  $J = 4.5$  Hz, 1H,  $\text{H}_{15}$ ), 2.49 (td,  $J = 14.3, 3.3$  Hz, 1H,  $\text{H}_{9a}$ ), 2.30 (ddt,  $J = 8.9, 6.3, 3.3$  Hz, 1H,  $\text{H}_1$ ), 2.24–2.03 (m, 2H,  $\text{H}_{2a}, \text{H}_{3a}$ ), 1.96 (dq,  $J = 13.4, 3.4$  Hz,

1H, H<sub>2b</sub>), 1.66 (td,  $J = 14.0, 3.1$  Hz, 1H, H<sub>10</sub>), 1.60–1.57 (m, 1H, H<sub>8a</sub>), 1.53–1.45 (m, 2H, H<sub>3b</sub>, H<sub>9b</sub>, H<sub>10b</sub>), 1.25 (s, 3H, H<sub>12a</sub>), 1.16 (dd,  $J = 8.5, 5.0$  Hz, 1H, H<sub>8b</sub>), 1.14 (s, 3H, H<sub>12b</sub>), 1.08 (s, 3H, H<sub>4</sub>), 0.94 (ddd,  $J = 10.6, 6.8, 2.3$  Hz, 2H, H<sub>6</sub>), 0.02 (s, 9H, H<sub>14</sub>), 0.00 (s, 9H, H<sub>7</sub>). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  207.1 (C), 199.0 (C), 174.2 (C), 153.1 (CH), 136.6 (C), 72.0 (C), 64.5 (CH<sub>2</sub>), 63.4 (CH<sub>2</sub>), 54.5 (C), 40.8 (C), 34.1 (CH<sub>2</sub>), 33.5 (C), 32.2 (CH<sub>2</sub>), 29.7 (CH<sub>3</sub>), 29.5 (CH<sub>2</sub>), 25.5 (CH<sub>3</sub>), 24.3 (CH), 21.9 (CH<sub>3</sub>), 17.8 (CH<sub>2</sub>), 17.1 (CH<sub>2</sub>), 12.2 (CH<sub>2</sub>), 2.2 (3  $\times$  CH<sub>3</sub>), -1.5 (3  $\times$  CH<sub>3</sub>). IR (ATR-FTIR), cm<sup>-1</sup>: 2954 (m), 2930 (m), 2361 (m), 2339 (m), 1398 (w). HRMS-Cl (m/z): [M + Na]<sup>+</sup> calcd for C<sub>27</sub>H<sub>46</sub>NaO<sub>6</sub>Si<sub>2</sub>, 545.2730; found, 545.2794.

*Synthesis of the allyl carbonate 70:*

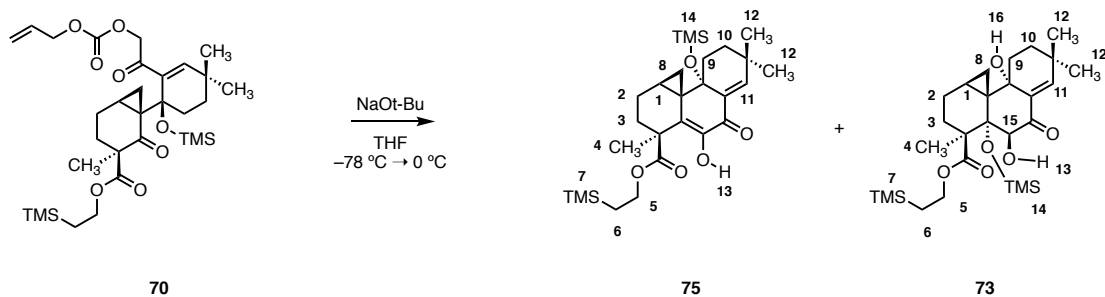


Allyl chloroformate (935  $\mu$ L, 8.80 mmol, 5.00 equiv) was added dropwise via syringe to a solution of the hydroxyketone **69** (920.0 mg, 1.76 mmol, 1 equiv) in 5% pyridine–dichloromethane (v/v, 6.0 mL) at 0 °C. The reaction mixture was allowed to warm with its bath over ~1 h to 23 °C. The reaction mixture was stirred for an additional 1 h at 23 °C. The product mixture was diluted sequentially with ethyl acetate (20 mL) and water (20 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The organic layer was washed sequentially with 1 N aqueous hydrogen chloride solution (3  $\times$  7 mL), saturated aqueous sodium bicarbonate solution (15 mL), and saturated aqueous sodium chloride solution (20 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 33% ether–hexanes) to provide the allyl carbonate **70** as a colorless oil (1.05 g, 96%).

$R_f$  = 0.33 (20% ether–hexanes; UV, PAA). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  6.41 (s, 1H, H<sub>11</sub>), 6.02–5.87 (m, 1H, H<sub>16</sub>), 5.46–5.34 (m, 1H, H<sub>17a</sub>), 5.33–5.23 (m, 1H, H<sub>17b</sub>), 5.14 (d,  $J$  = 16.1 Hz, 1H, H<sub>13a</sub>), 4.68 (d,  $J$  = 16.3 Hz, 1H, H<sub>13b</sub>), 4.66–4.64 (m, 2H, H<sub>15</sub>), 4.18–4.06 (m, 2H, H<sub>5</sub>), 2.47 (td,  $J$  = 15.4, 14.6, 4.0 Hz, 1H, H<sub>9a</sub>), 2.29 (td,  $J$  = 7.0, 6.4, 3.2 Hz, 1H, H<sub>1</sub>), 2.15 (tt,  $J$  = 13.5, 3.6 Hz, 1H, H<sub>2a</sub>), 2.06 (td,  $J$  = 13.5, 4.1 Hz, 1H, H<sub>3a</sub>), 1.90 (dq,  $J$  =

13.2, 3.4 Hz, 1H, H<sub>2b</sub>), 1.71–1.63 (m, 1H, H<sub>10a</sub>), 1.56 (app t,  $J = 6.0$  Hz, 1H, H<sub>8a</sub>), 1.54–1.44 (m, 3H, H<sub>3b,9b,10b</sub>), 1.25 (s, 3H, H<sub>12a</sub>), 1.16–1.12 (m, 7H, H<sub>4,8b,12b</sub>), 0.93 (ddd,  $J = 9.8, 6.6, 1.3$  Hz, 2H, H<sub>6</sub>), 0.02 (s, 9H, H<sub>14</sub>), 0.01 (s, 9H, H<sub>7</sub>). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  207.2 (C), 192.1 (C), 174.3 (C). 154.6 (C), 151.9 (CH), 137.1 (C), 131.4 (CH), 118.7 (CH<sub>2</sub>), 72.0 (C), 68.7 (CH<sub>2</sub>), 68.2 (CH<sub>2</sub>), 63.4 (CH<sub>2</sub>), 54.6 (C), 40.8 (C), 34.0 (CH<sub>2</sub>), 33.5 (C), 32.2 (CH<sub>2</sub>), 29.8 (CH<sub>3</sub>), 29.7 (CH<sub>2</sub>), 25.7 (CH<sub>3</sub>), 24.5 (CH), 22.1 (CH<sub>3</sub>), 17.8 (CH<sub>2</sub>), 17.1 (CH<sub>2</sub>), 12.4 (CH<sub>2</sub>), 2.2 (3  $\times$  CH<sub>3</sub>), -1.5 (3  $\times$  CH<sub>3</sub>). IR (ATR-FTIR), cm<sup>-1</sup>: 2953 (m), 2901 (w), 1754 (s), 1695 (s), 1624 (w). HRMS-Cl (m/z): [M + Na]<sup>+</sup> calcd for C<sub>31</sub>H<sub>50</sub>NaO<sub>8</sub>Si<sub>2</sub>, 629.2942; found, 629.2994.

Synthesis of the diosphenol **75** and the silyl transfer product **73**:



A solution of the carbonate **70** (509 mg, 840  $\mu\text{mol}$ , 1 equiv) in tetrahydrofuran (1.6 mL) was added via syringe pump over 20 min to a solution of sodium *tert*-butoxide (173 mg, 1.80 mmol, 2.14 equiv) in tetrahydrofuran (4.4 mL) at  $-78\text{ }^{\circ}\text{C}$ . The reaction mixture was stirred for 2 h at  $-78\text{ }^{\circ}\text{C}$ . The reaction mixture was then transferred to an ice bath at  $0\text{ }^{\circ}\text{C}$ . The reaction mixture was stirred for additional 20 min at  $0\text{ }^{\circ}\text{C}$ . The product mixture was diluted with saturated aqueous ammonium chloride solution (4.0 mL), water (3.0 mL) and ethyl acetate (20 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate ( $2 \times 10\text{ mL}$ ). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL). The organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting initially with 14% ether–hexanes, grading to 33% ether–hexanes, one step) to provide separately the diosphenol **75** as a yellow oil (246 mg, 58%) and the silane transfer product **73** (79 mg, 15%).

Separation of the enantiomers of **75** was achieved by preparative chiral stationary phase supercritical fluid chromatography (eluting with 15% methanol–supercritical carbon dioxide) to furnish separately (+)-**75** ( $[\alpha]_D^{20} = +23.4$  (c= 0.4, chloroform)) and (–)-**75** ( $[\alpha]_D^{20} = -28.1$  (c= 0.4, chloroform)).

*Diosphenol 75*:  $R_f = 0.37$  (50% ether–hexanes; UV, PAA).  $^1\text{H NMR}$  (600 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.78 (d,  $J = 1.3$  Hz 1H, H<sub>11</sub>), 6.21 (s, 1H, H<sub>13</sub>), 4.19 (td,  $J = 10.8, 6.1$  Hz, 1H, H<sub>5a</sub>), 4.11 (td,  $J = 10.8, 6.4$  Hz, 1H, H<sub>5b</sub>), 3.57 (d,  $J = 5.6$  Hz, 1H, H<sub>13</sub>), 1.97 (ddd,  $J = 17.7, 10.7, 3.9$  Hz, 1H, H<sub>9a</sub>), 1.91–1.85 (m, 1H, H<sub>9b</sub>), 1.78 (td,  $J = 12.6, 5.0$  Hz, 1H, H<sub>3b</sub>), 1.65 (td,  $J = 12.6, 5.0$  Hz, 2H, H<sub>1, 10a</sub>), 1.53–1.47 (m, 2H, H<sub>2</sub>), 1.43 (td,  $J = 12.4, 10.0, 3.1$  Hz, 2H, H<sub>3a, 10b</sub>), 1.38 (s, 3H, H<sub>4</sub>), 1.14 (s, 3H, H<sub>12</sub>), 1.00 (s, 3H, H<sub>12</sub>), 0.98–0.86 (m, 4H, H<sub>6,8</sub>), 0.00 (s, 9H, H<sub>7</sub>), –0.02 (s, 9H, H<sub>14</sub>).  $^{13}\text{C NMR}$  (150 MHz,  $\text{CDCl}_3$ ):  $\delta$  183.2 (C), 177.0 (C), 149.0 (CH), 143.3 (C), 134.4 (C), 133.8 (C), 75.1 (C), 63.2 (CH<sub>2</sub>), 44.0 (C), 32.8 (C), 31.6 (CH<sub>2</sub>), 29.7 (C), 29.2 (CH<sub>2</sub>), 29.1 (CH<sub>3</sub>), 27.4 (CH<sub>2</sub>), 26.8 (CH<sub>3</sub>), 19.8 (CH<sub>3</sub>), 17.7 (CH<sub>2</sub>), 17.3 (CH<sub>2</sub>), 15.7 (CH<sub>2</sub>), 13.2 (CH<sub>2</sub>), 2.85 (3 × CH<sub>3</sub>), –1.35 (3 × CH<sub>3</sub>). IR (ATR-FTIR),  $\text{cm}^{-1}$ : 2954 (m), 2901 (m), 1734 (s), 1718 (m), 1636 (w). HRMS-CI (m/z):  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{28}\text{H}_{49}\text{O}_6\text{Si}_2$ , 505.2805; found, 505.2877.

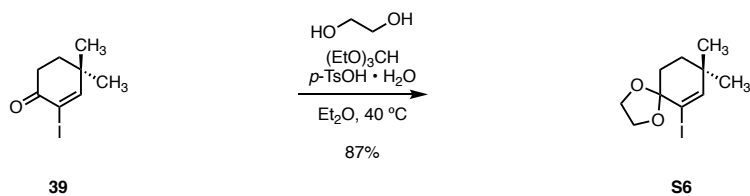
*Silyl transfer product 73*:  $R_f = 0.29$  (50% ether–hexanes; UV, PAA).  $^1\text{H NMR}$  (600 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.89 (s, 1H, H<sub>11</sub>), 5.59 (s, 1H, H<sub>16</sub>), 5.29 (d,  $J = 5.6$  Hz, 1H, H<sub>15</sub>), 4.32–4.06 (m, 2H, H<sub>5</sub>), 3.57 (d,  $J = 5.6$  Hz, 1H, H<sub>13</sub>), 1.98–1.91 (m, 1H, H<sub>2a</sub>), 1.83–1.77 (m, 2H, H<sub>2b,3a</sub>), 1.63–1.54 (m, 3H, H<sub>9,10a</sub>), 1.45–1.41 (m, 1H, H<sub>10b</sub>), 1.40–1.36 (m, 4H, H<sub>1,4</sub>), 1.18–1.13 (m, 2H, H<sub>3b,8a</sub>), 1.11 (s, 3H, H<sub>12a</sub>), 1.07–0.97 (m, 5H, H<sub>6,12b</sub>), 0.69 (dd,  $J = 9.4, 6.6$  Hz, 1H, H<sub>8b</sub>), 0.11 (s, 9H, H<sub>14</sub>), 0.04 (s, 9H, H<sub>7</sub>).  $^{13}\text{C NMR}$  (150 MHz,  $\text{CDCl}_3$ ):  $\delta$  198.5 (C), 179.6

(C), 147.2 (CH), 133.1 (C), 76.2 (C), 75.9 (CH), 74.4 (C), 63.7 (CH<sub>2</sub>), 44.8 (C), 35.0 (C), 33.7 (CH<sub>2</sub>), 32.3 (C), 28.3 (CH<sub>3</sub>), 27.5 (CH<sub>3</sub>), 27.2 (CH<sub>2</sub>), 26.2 (CH<sub>2</sub>), 18.7 (CH<sub>2</sub>), 18.3 (CH<sub>3</sub>), 17.0 (CH<sub>2</sub>), 15.2 (CH<sub>2</sub>), 12.5 (CH<sub>2</sub>), 2.6 (3 × CH<sub>3</sub>), -1.5 (3 × CH<sub>3</sub>). IR (ATR-FTIR), cm<sup>-1</sup>: 2903 (m), 2901 (m), 1705 (s), 1632 (m). [M + Na]<sup>+</sup> calcd for C<sub>27</sub>H<sub>46</sub>NaO<sub>6</sub>Si<sub>2</sub>, 545.2731; found, 545.2744.



*Synthesis of the ketone 76:*

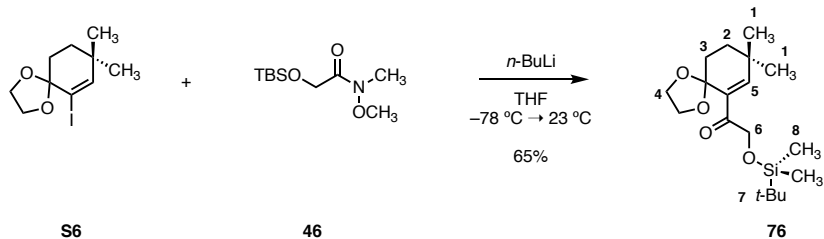
*Part 1: Synthesis of the ketal S6:*



Triethyl orthoformate (3.00 mL, 27.4 mmol, 5.04 equiv) was added to a solution of ethylene glycol (1.20 mL, 21.5 mmol, 3.95 equiv), *para*-toluenesulfonic acid monohydrate (52.0 mg, 273  $\mu$ mol, 0.05 equiv) and the iodoenone **39** (1.36 g, 5.44 mmol, 1 equiv) in ether (7.0 mL) under argon in a screw-capped pressure vessel at 23 °C. The reaction vessel was sealed under argon and the sealed vial was placed in an oil bath that had been preheated to 40 °C. The reaction mixture was stirred and heated for 2 d at 40 °C. The product mixture was cooled over 30 min to ~23 °C. The cooled product mixture was diluted with ethyl acetate (20 mL). The diluted mixture was transferred to a separatory funnel and washed sequentially with saturated aqueous sodium bicarbonate solution (10 mL) and saturated aqueous sodium chloride solution (10 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 10% ether–hexanes) to provide the known ketal **S6** as a yellow oil (1.39 g, 87%).

<sup>1</sup>H NMR spectroscopic data for **S6** obtained in this way were in agreement with those reported by Takahashi et al.

Part 2: Synthesis of the ketone **76**:



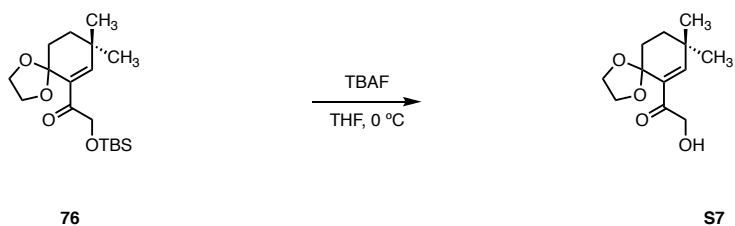
A solution of *n*-butyllithium in hexanes (2.33 M, 3.00 mL, 6.99 mmol, 1.07 equiv) was added dropwise via syringe to a solution of the ketal **S6** (2.00 g, 6.53 mmol, 1 equiv) in tetrahydrofuran (30 mL) at  $-78\text{ }^{\circ}\text{C}$ . The reaction mixture was stirred at  $-78\text{ }^{\circ}\text{C}$  for 2 min. A solution of the amide **46** (1.82 g, 7.79 mmol, 1.19 equiv) in tetrahydrofuran (8.0 mL) was then added to the reaction mixture slowly at  $-78\text{ }^{\circ}\text{C}$ . The reaction mixture was stirred for 2 h at  $-78\text{ }^{\circ}\text{C}$  and warmed gradually with its cooling bath over 21 h to  $23\text{ }^{\circ}\text{C}$ . The product mixture was diluted sequentially with saturated aqueous ammonium chloride solution (5.0 mL), water (10 mL), and ethyl acetate (75 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted ethyl acetate ( $2 \times 15\text{ mL}$ ). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL). The organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting initially with 10% ether–hexanes initially, grading to 14% ether–hexanes, 1 step) to provide the ketone **76** as a colorless oil (1.45 g, 65%).

$R_f = 0.39$  (20% ether–hexanes; UV, PAA).  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.47 (s, 1H,  $\text{H}_5$ ), 4.48 (s, 1H,  $\text{H}_6$ ), 4.17–4.08 (m, 2H,  $\text{H}_{4a}$ ), 4.03–3.96 (m, 2H,  $\text{H}_{4b}$ ), 1.81–1.73 (m, 2H,

H<sub>3</sub>), 1.63–1.57 (m, 2H, H<sub>2</sub>), 1.06 (s, 6H, H<sub>1</sub>), 0.90 (s, 9H, H<sub>6</sub>), 0.07 (s, 6H, H<sub>8</sub>). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 198.8 (C), 151.6 (CH), 134.2 (C), 106.2 (C), 68.5 (CH<sub>2</sub>), 64.6 (2 × CH<sub>2</sub>), 33.6 (CH<sub>2</sub>), 32.7 (C), 30.6 (CH<sub>2</sub>), 28.0 (2 × CH<sub>3</sub>), 25.8 (3 × CH<sub>3</sub>), 18.5 (C), –5.4 (2 × CH<sub>3</sub>). IR (ATR-FTIR), cm<sup>-1</sup>: 2956 (m), 2857 (m), 1705 (m), 1627 (w). HRMS-CI (m/z): [M + H]<sup>+</sup> calcd for C<sub>18</sub>H<sub>33</sub>O<sub>4</sub>Si, 341.2143; found, 341.2144.

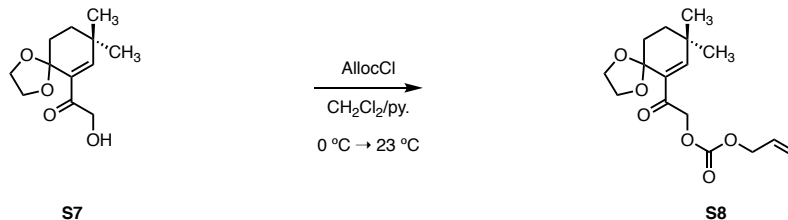
*Synthesis of the diketone 77:*

*Part 1: Synthesis of the ketone S7:*



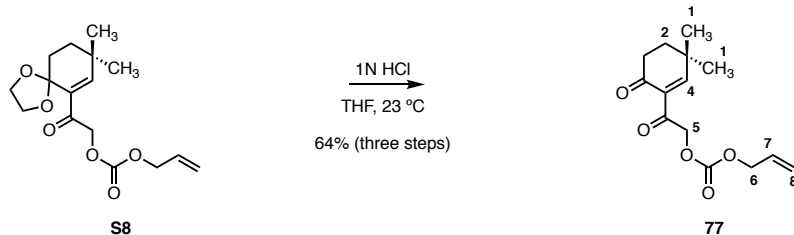
A solution of tetrabutylammonium fluoride in tetrahydrofuran (1 M, 5.30 ml, 5.30 mmol, 1.11 equiv) was added to a solution of the ketone **76** (1.69 g, 4.79 mmol, 1 equiv) in tetrahydrofuran (24 mL) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C. The product mixture was diluted sequentially with saturated aqueous ammonium chloride solution (15 mL), water (15 mL), and ethyl acetate (50 mL) at 0 °C. The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (2 × 20 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL). The organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The ketone product **S7** obtained in this way was used directly in the following step.

Part 2: Synthesis of the allyl carbonate **S8**:



Allyl chloroformate (2.60 mL, 24.5 mmol, 5.11 equiv) was added dropwise via syringe to a solution of the unpurified ketone **S7** obtained in the preceding step (nominally 4.79 mmol, 1 equiv) in 5% pyridine–dichloromethane (w/v, 15 mL) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C and warmed gradually with its cooling bath over 14 h to 23 °C. Additional allyl chloroformate (1.00 mL, 9.41 mmol, 1.96 equiv) was added carefully to the reaction mixture at 23 °C. The reaction mixture was stirred for 3 h at 23 °C. The product mixture was diluted sequentially with ethyl acetate (75 mL) and 1 N aqueous hydrogen chloride solution (30 mL), with stirring. The resulting biphasic mixture was stirred for 30 min at 23 °C and then transferred to a separatory funnel. The layers that formed were separated. The organic layer was washed sequentially with 1 N aqueous hydrogen chloride solution (3 × 20 mL), saturated aqueous sodium bicarbonate solution (20 mL), and saturated aqueous sodium chloride solution (20 mL). The organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The carbonate **S8** obtained in this way was used without further purification.

Part 3: Synthesis of the diketone **77**:

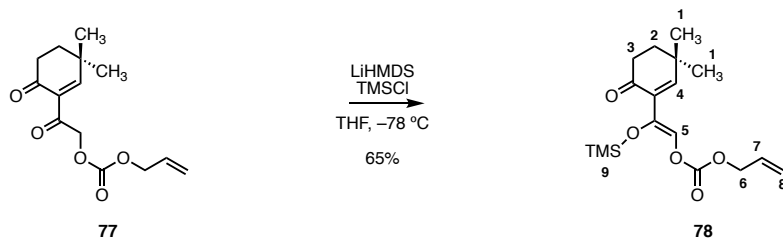


Aqueous hydrogen chloride solution (1 N, 24.0 mL, 24.0 mmol, 5.01 equiv) was added to a solution of the unpurified carbonate **S8** obtained in the preceding step (nominally 4.79 mmol, 1 equiv) in tetrahydrofuran (50 mL) at 23 °C. The reaction mixture was stirred for 5 h at 23 °C. The product mixture was diluted sequentially with saturated aqueous sodium bicarbonate solution (50 mL), water (30 mL), and ethyl acetate (150 mL), with stirring. The resulting biphasic mixture was stirred for 30 min at 23 °C. The mixture was then transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (2 × 30 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was used purified by flash-column chromatography (eluting with 50% ether–hexanes) to furnish the diketone **77** as a colorless oil (422 mg, 64% over three steps).

$R_f = 0.47$  (50% ether–hexanes; UV, PAA).  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.64 (s, 1H, H<sub>4</sub>), 6.00–5.89 (m, 1H, H<sub>7</sub>), 5.44–5.34 (m, 1H, H<sub>8a</sub>), 5.31–5.24 (m, 1H, H<sub>8b</sub>), 5.16 (s, 2H, H<sub>5</sub>), 4.66 (d,  $J = 5.3$  Hz, 2H, H<sub>6</sub>), 2.54 (t,  $J = 7.0$  Hz, 2H, H<sub>3</sub>), 1.89 (t,  $J = 6.8$  Hz, 2H, H<sub>2</sub>), 1.23 (s, 6H, H<sub>1</sub>).  $^{13}\text{C NMR}$  (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  196.9 (C), 191.7 (C), 168.5 (CH), 154.7 (C), 133.2 (C), 131.4 (CH), 118.8 (CH<sub>2</sub>), 71.9 (CH<sub>2</sub>), 68.8 (CH<sub>2</sub>), 35.2 (CH<sub>2</sub>), 35.1 (CH<sub>2</sub>),

34.60 (C), 27.2 (2 × CH<sub>3</sub>). IR (ATR-FTIR), cm<sup>-1</sup>: 2962 (w), 1750 (s), 1704 (s), 1679 (s), 1598 (m). HRMS-Cl (m/z): [M + H]<sup>+</sup> calcd for C<sub>14</sub>H<sub>19</sub>O<sub>5</sub>, 289.1046; found, 289.1049.

*Synthesis of the enoxysilane ether 78:*



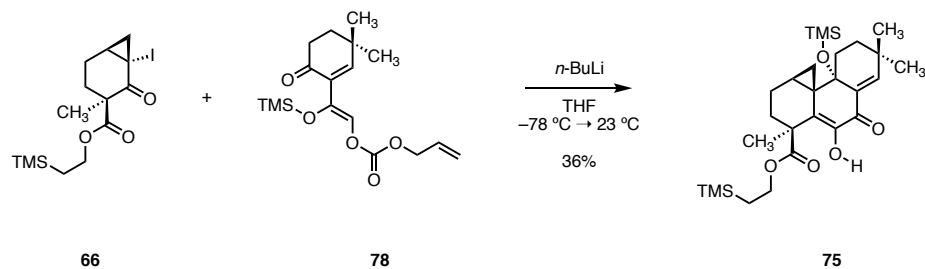
A solution of lithium bis(trimethylsilyl)amide (95%, 74.0 mg, 420  $\mu\text{mol}$ , 1.40 equiv) in tetrahydrofuran (800  $\mu\text{L}$ ) at 23  $^{\circ}\text{C}$  was transferred via cannula to a solution of chlorotrimethylsilane (50.0  $\mu\text{L}$ , 394  $\mu\text{mol}$ , 1.31 equiv) and the diketone **77** (80.0 mg, 300  $\mu\text{mol}$ , 1 equiv) in tetrahydrofuran (1.2 mL) at  $-78^{\circ}\text{C}$ . The reaction mixture was stirred for 1 h at  $-78^{\circ}\text{C}$ . The product mixture was diluted sequentially with triethylamine (600  $\mu\text{L}$ ) and ethyl acetate (10 mL) at  $-78^{\circ}\text{C}$ . The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The organic layer was washed sequentially with saturated aqueous sodium bicarbonate solution (3.0 mL) and saturated aqueous sodium chloride solution (3.0 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 20% ether–hexanes) to provide the enoxysilane **78** as a colorless oil (66.0 mg, 65%).

$R_f = 0.31$  (25% ether–hexanes; UV, PAA).  $^1\text{H NMR}$  (600 MHz,  $\text{C}_6\text{D}_6$ ):  $\delta$  8.46 (s, 1H, H<sub>5</sub>), 6.79 (s, 1H, H<sub>4</sub>), 5.59–5.55 (m, 1H, H<sub>7</sub>), 5.05 (d,  $J = 17.8$  Hz, 1H, H<sub>8a</sub>), 4.89 (d,  $J = 10.5$  Hz, 1H, H<sub>8b</sub>), 4.31 (d,  $J = 5.3$  Hz, 2H, H<sub>6</sub>), 2.18 (t,  $J = 5.5$  Hz, 2H, H<sub>3</sub>), 1.26 (t,  $J = 6.8$  Hz, 2H, H<sub>2</sub>), 0.75 (s, 6H, H<sub>1</sub>), 0.35 (s, 9H, H<sub>9</sub>).  $^{13}\text{C NMR}$  (150 MHz,  $\text{C}_6\text{D}_6$ ):  $\delta$  195.4 (C), 154.8 (CH), 152.6 (C), 134.9 (C), 131.6 (CH), 131.1 (C), 126.9 (CH), 118.4 (CH<sub>2</sub>), 68.8 (CH<sub>2</sub>), 36.0 (CH<sub>2</sub>), 35.5 (CH<sub>2</sub>), 32.9 (C), 27.7 ( $2 \times \text{CH}_3$ ), 0.5 ( $3 \times \text{CH}_3$ ). IR (ATR-FTIR),  $\text{cm}^{-1}$ :



2962 (m), 1752 (s), 1705 (s), 1681 (s), 1603 (m). HRMS-Cl (m/z): [M + H]<sup>+</sup> calcd for C<sub>17</sub>H<sub>26</sub>NaO<sub>5</sub>Si, 361.1447; found, 361.1446.

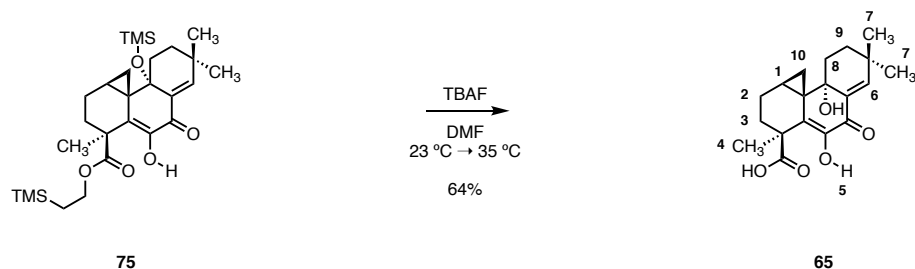
*Synthesis of the diosphenol 75 by the fragment coupling–cyclization cascade:*



A solution of *n*-butyllithium in hexanes (2.20 M, 50.0  $\mu\text{L}$ , 110  $\mu\text{mol}$ , 2.20 equiv) was added to a solution of the iodocyclopropane **66** (43.0 mg, 110  $\mu\text{mol}$ , 2.20 equiv) in tetrahydrofuran (500  $\mu\text{L}$ ) at  $-78\text{ }^{\circ}\text{C}$ . A solution of the enoxysilane **78** (17.0 mg, 50.0  $\mu\text{mol}$ , 1 equiv) in tetrahydrofuran (150  $\mu\text{L}$ ) was added then immediately added dropwise down the inside wall of the flask. The reaction mixture was stirred for 2 h at  $-78\text{ }^{\circ}\text{C}$ . The reaction mixture was then immersed in a cooling bath at  $0\text{ }^{\circ}\text{C}$ . The reaction mixture was stirred for 3 h at  $0\text{ }^{\circ}\text{C}$ . The product mixture was diluted sequentially with saturated aqueous ammonium chloride solution (150  $\mu\text{L}$ ), water (500  $\mu\text{L}$ ), and ethyl acetate (8.0 mL). The resulting biphasic solution was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3.0 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (2.0 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by preparatory thin-layered chromatography (eluting with 16% ether–hexanes) to furnish the diosphenol **75** as light-yellow oil (9.0 mg, 36%).

$^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectroscopic data for **75** obtained in this way agreed with those obtained by the cyclodehydration sequence **70**  $\rightarrow$  **75**.

*Synthesis of the geminal dimethyl myrocin G analog 65:*

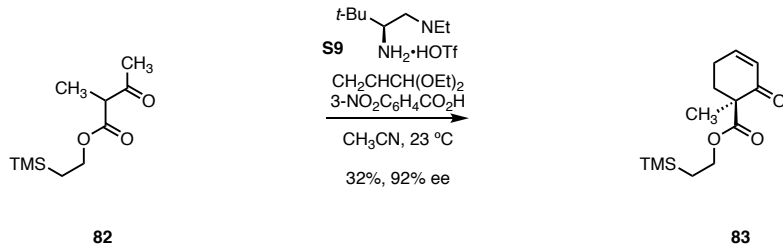


A solution of tetrabutylammonium fluoride in tetrahydrofuran (1.0 M, 0.168 ml, 0.168 mmol, 2.10 equiv) was added to a solution of the diosphenol **75** (38.0 mg, 0.0753 mmol, 1 equiv) in *N,N*-dimethylformamide (350  $\mu$ L) at 23 °C. The reaction mixture was stirred for 6 h at 23 °C. The reaction vessel was placed in an oil bath that had been preheated to 35 °C. The reaction mixture was stirred and heated for 2 h at 35 °C. The reaction vessel was removed from the oil bath and allowed to cool over 5 min to ~23 °C. The cooled product mixture was diluted sequentially with saturated aqueous ammonium chloride solution (3.0 mL), water (3.0 mL), and ethyl acetate (15 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3  $\times$  4.0 mL). The organic layers were combined and the combined organic layers were washed sequentially with water (3  $\times$  3.0 mL) and saturated aqueous sodium chloride solution (10 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 1% acetic acid–50% acetone–hexanes). The fractions containing product (TLC analysis) were combined and the combined fractions were diluted with 60 mL of toluene and then concentrated to provide the geminal dimethyl myrocin G analog **65** as an off-white solid

(15.9 mg, 64%). The structure of the methyl analog product **65** was confirmed by X-ray analysis (see Appendix A). Deprotection of the enantiomers of (+)-**75** and (-)-**75** under the above described conditions furnished (+)-**65** ( $[\alpha]_D^{20} = +68.8$  (c= 0.12, methanol)) and (-)-**65** ( $[\alpha]_D^{20} = -82.8$  (c= 0.10, methanol)).

$R_f = 0.20$  (1% acetic acid–50% acetone–hexanes; UV, PAA).  $^1\text{H NMR}$  (600 MHz, methanol- $d_4$ ):  $\delta$  6.81 (d,  $J = 5.6$  Hz, 1H, H<sub>11</sub>), 2.06 (ddd,  $J = 18.5, 9.5$  Hz, 1H, H<sub>2a</sub>), 1.91–1.83 (m, 2H, H<sub>2b,3a</sub>), 1.79–1.71 (m, 1H, H<sub>10a</sub>), 1.68 (dd,  $J = 10.4, 5.0$  Hz, 1H, H<sub>1</sub>), 1.57 (td,  $J = 13.9, 12.8$  Hz, 1H, H<sub>9a</sub>), 1.51–1.39 (m, 2H, H<sub>10b,9b</sub>), 1.37 (s, 3H, H<sub>4</sub>), 1.31–1.27 (m, 1H, H<sub>3b</sub>), 1.12 (s, 3H, H<sub>12</sub>), 1.06 (dd,  $J = 8.9, 5.7$  Hz, 1H, H<sub>8a</sub>), 1.04 (s, 3H, H<sub>12</sub>), 0.93 (t,  $J = 6.2$  Hz, 1H, H<sub>8b</sub>).  $^{13}\text{C NMR}$  (150 MHz, methanol- $d_4$ ):  $\delta$  183.7 (C), 180.9 (C), 150.2 (CH), 145.5 (C), 135.3 (C), 135.2 (C), 72.3 (C), 45.1 (C), 45.1 (C), 33.8 (C), 32.3 (CH<sub>2</sub>), 30.6 (CH<sub>2</sub>), 29.9 (CH<sub>3</sub>), 29.4 (C), 27.7 (CH<sub>2</sub>), 26.5 (CH<sub>3</sub>), 20.1 (CH<sub>3</sub>), 18.5 (CH<sub>2</sub>), 16.6 (CH), 13.4 (CH<sub>2</sub>). IR (ATR-FTIR),  $\text{cm}^{-1}$ : 2945 (m), 2933 (m), 1712 (s), 1658 (s), 1604 (s). HRMS- CI (m/z):  $[\text{M} + \text{H}]^+$  calcd for C<sub>19</sub>H<sub>25</sub>O<sub>5</sub>, 333.1702; found, 333.1728.

*Synthesis of the unsaturated ketone 83:*

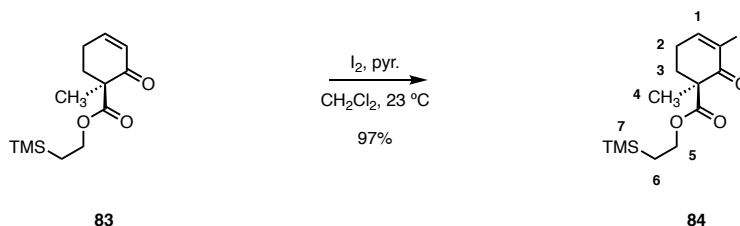


A solution of acrolein diethyl acetal (4.16 mL, 27.3 mmol, 1 equiv) in acetonitrile (35.0 mL) was added dropwise via syringe pump over 24 h to a solution of the  $\beta$ -ketoester **82** (10.3 g, 47.8 mmol, 1.75 equiv), the amine catalyst **S9** (2.14 g, 6.64 mmol, 24.3 mol %), and 3-nitrobenzoic acid (913 mg, 5.46 mmol, 20.0 mol %) in acetonitrile (60.0 mL) with exclusion of light at 23 °C. The reaction mixture was stirred for 3 days at 23 °C. The product mixture was transferred to a separatory funnel that had been charged with ethyl acetate (400 mL). The diluted mixture was washed sequentially with water (100 mL) and 2 M aqueous sodium hydroxide solution (3  $\times$  30 mL). The aqueous layers were combined and the combined aqueous layers were extracted with ethyl acetate (2  $\times$  50 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (50 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting initially with 14% ether–hexanes, grading to 25% ether–hexanes, one step) to provide the unsaturated ketone **83** as a yellow oil (2.23 g, 32%).

The enantiomeric excess (ee) of **83** obtained in this way was determined to be 92% by chiral stationary phase HPLC analysis (Chiralpak® IG column, eluting with 5% ethanol–hexanes, flow rate of 500  $\mu$ L/min, 30 min).

$R_f$  = 0.33 (20% ether–hexanes; UV, PAA).  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.92–6.89 (m, 1H, H<sub>1</sub>), 6.04 (d,  $J$  = 10.0 Hz, 1H, H<sub>8</sub>), 4.21–4.17 (m, 2H, H<sub>5</sub>), 2.52–2.48 (m, 2H, H<sub>2a</sub>, H<sub>3a</sub>), 2.37–2.30 (m, 1H, H<sub>2b</sub>), 1.91–1.86 (m, 1H, H<sub>3b</sub>), 1.38 (s, 3H, H<sub>4</sub>), 1.02–0.93 (m, 2H, H<sub>6</sub>), 0.02 (s, 9H, H<sub>7</sub>).  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ ):  $\delta$  197.0 (C), 172.8 (C), 149.3 (CH), 128.9 (CH), 63.7 (CH<sub>2</sub>), 53.3 (C), 33.3 (CH<sub>2</sub>), 23.7 (CH<sub>2</sub>), 20.3 (CH<sub>3</sub>), 17.3 (CH<sub>2</sub>), –1.6 (3  $\times$  CH<sub>3</sub>). IR (ATR-FTIR),  $\text{cm}^{-1}$ : 2956 (m), 1728 (s), 1684 (s). HRMS-CI ( $m/z$ ):  $[\text{M} + \text{Na}]^+$  calcd for  $\text{C}_{13}\text{H}_{22}\text{NaO}_3\text{Si}$ , 277.1230; found, 277.1249.  $[\alpha]_D^{20}$  = +25.1 ( $c$  = 1.33,  $\text{CDCl}_3$ ).

*Synthesis of the  $\alpha$ -iodoenone **84**:*



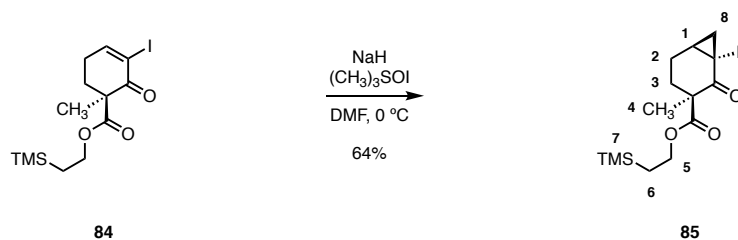
Iodine (420 mg, 1.65 mmol, 2.00 equiv) was added to a solution of the unsaturated ketone **83** (210 mg, 830  $\mu$ mol, 1 equiv) in 5% pyridine–dichloromethane (v/v, 2.8 mL) at 23 °C. The reaction mixture was stirred for 15 h at 23 °C. The product mixture was diluted sequentially with saturated aqueous sodium thiosulfate solution (5.0 mL), water (5.0 mL), and ethyl acetate (15 mL). The resulting biphasic mixture was stirred for 20 min at 23 °C. The stirred mixture was transferred to a separatory funnel and the layers were separated. The organic layer was washed with saturated aqueous sodium chloride solution (5.0 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 20% ether–hexanes) to furnish the  $\alpha$ -iodoenone **84** as a pale-yellow oil (307 mg, 97%).

$R_f$  = 0.35 (20% ether–hexanes; UV, PAA).  $^1H$  NMR (500 MHz,  $CDCl_3$ ):  $\delta$  7.64–7.61 (m, 1H,  $H_1$ ), 4.24–4.12 (m, 2H,  $H_5$ ), 2.65–2.47 (m, 2H,  $H_{2a,3a}$ ), 2.44–2.26 (m, 2H,  $H_{2b}$ ), 1.99–1.92 (m, 1H,  $H_{3b}$ ), 1.42 (s, 3H,  $H_4$ ), 0.96 (ddd,  $J$  = 11.1, 6.4, 3.3 Hz, 2H,  $H_6$ ), 0.03 (s, 9H,  $H_7$ ).  $^{13}C$  NMR (125 MHz,  $CDCl_3$ ):  $\delta$  190.4 (C), 171.9 (C), 157.7 (CH), 102.0 (C), 64.1 ( $CH_2$ ), 53.4 (C), 33.2 ( $CH_2$ ), 27.8 ( $CH_2$ ), 21.1 ( $CH_3$ ), 17.3 ( $CH_2$ ), –1.56 ( $3 \times CH_3$ ). IR

(ATR-FTIR),  $\text{cm}^{-1}$ : 2953 (m), 1727 (s), 1695 (s), 1596 (w). HRMS-CI (m/z):  $[\text{M} + \text{Na}]^+$   
calcd for  $\text{C}_{13}\text{H}_{21}\text{INaO}_3\text{Si}$ , 403.0197; found, 403.0209.  $[\alpha]_D^{20} = +68.1$  ( $c = 0.93$ ,  $\text{CHCl}_3$ ).



Synthesis of the iodocyclopropane **85**:

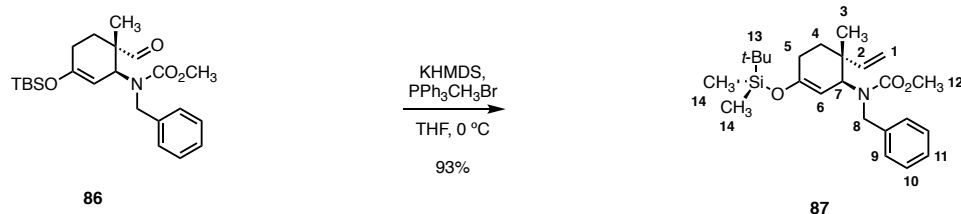


Trimethylsulfoxonium iodide (2.99 g, 13.6 mmol, 1.20 equiv) was added in one portion to a suspension of sodium hydride (95%, 313 mg, 12.4 mmol, 1.10 equiv) in *N,N*-dimethylformamide (90 mL) at  $23\text{ }^\circ\text{C}$ . The resulting white suspension was stirred for 1 h at  $23\text{ }^\circ\text{C}$ . The resulting mixture was then cooled over 30 min to  $0\text{ }^\circ\text{C}$ . A solution of the  $\alpha$ -iodoenone **84** (4.29 g, 11.3 mmol, 1 equiv) in *N,N*-dimethylformamide (22 mL) was then added dropwise via syringe pump over 1 h at  $0\text{ }^\circ\text{C}$ . Upon completion of the addition, the reaction mixture was stirred for 1.5 h at  $0\text{ }^\circ\text{C}$ . The cold product mixture was diluted sequentially with saturated aqueous ammonium chloride solution (25 mL), water (25 mL), and ethyl acetate (200 mL). The resulting biphasic mixture was transferred to a separatory funnel and diluted with hexanes (50 mL). The layers that formed were separated. The aqueous layer was extracted with ethyl acetate ( $3 \times 30\text{ mL}$ ). The organic layers were combined and the combined organic layers were washed sequentially with water ( $3 \times 20\text{ mL}$ ) and saturated aqueous sodium chloride solution (30 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 14% ether–hexanes) to provided  $\alpha$ -iodocyclopropane **85** as an off-white solid (2.84 g, 64%).

$^1\text{H}$  NMR analysis of the unpurified product mixture indicated the presence of a 2.3:1 mixture of diastereomers (500 MHz).

$R_f = 0.36$  (20% ether–hexanes; faintly UV, PAA).  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ ):  $\delta$  4.17 (ddt,  $J = 10.3, 7.1, 3.7$  Hz, 2H,  $\text{H}_5$ ), 2.27–2.19 (m, 2H,  $\text{H}_1, \text{H}_{2a}$ ), 2.13 (td,  $J = 13.6, 4.4$  Hz, 1H,  $\text{H}_{3a}$ ), 2.01 (t,  $J = 6.8$  Hz, 1H,  $\text{H}_{8a}$ ), 1.92 (dq,  $J = 12.0, 2.9, 2.5$  Hz, 1H,  $\text{H}_{2b}$ ), 1.65 (dt,  $J = 14.3, 3.9$  Hz, 1H,  $\text{H}_{3b}$ ), 1.56 (dd,  $J = 8.8, 7.0$  Hz, 1H,  $\text{H}_{8b}$ ), 1.35 (s, 3H,  $\text{H}_4$ ) 1.04–0.93 (m, 2H,  $\text{H}_6$ ), 0.03 (s, 9H,  $\text{H}_7$ ).  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ ):  $\delta$  200.2 (C), 172.8 (C), 64.0 ( $\text{CH}_2$ ), 53.1 (C), 30.7 (CH), 28.6 ( $\text{CH}_2$ ), 22.1 ( $\text{CH}_3$ ), 21.5 ( $\text{CH}_2$ ), 18.1 ( $\text{CH}_2$ ), 17.3 ( $\text{CH}_2$ ), 7.5 (C),  $-1.6$  ( $3 \times \text{CH}_3$ ). IR (ATR-FTIR),  $\text{cm}^{-1}$ : 2953 (w), 1737 (s), 1692 (s). HRMS-Cl ( $m/z$ ):  $[\text{M} + \text{Na}]^+$  calcd for  $\text{C}_{14}\text{H}_{23}\text{INaO}_3\text{Si}$ , 417.0353; found, 417.0396.

*Synthesis of the olefin 87:*



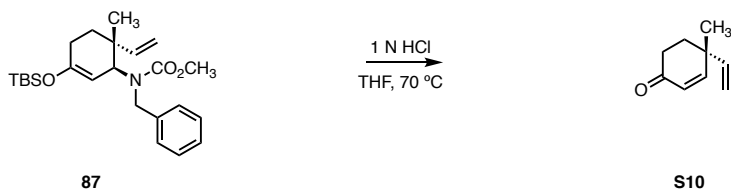
A solution of potassium bis(trimethylsilyl)amide (6.36 g, 31.9 mmol, 1.20 equiv) in tetrahydrofuran (90 mL) was transferred via cannula to a solution of methyltriphenylphosphonium bromide (11.5 g, 31.9 mmol, 1.20 equiv) in tetrahydrofuran (130 mL) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C. A solution of the aldehyde **86** (11.1 g, 26.6 mmol, 1 equiv) in tetrahydrofuran (18 mL) was then added dropwise. The reaction mixture was stirred for 45 min at 0 °C. The product mixture was diluted sequentially with saturated aqueous ammonium chloride solution (200 mL), water (100 mL), and ethyl acetate (200 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The organic layer was washed with saturated aqueous sodium chloride solution (200 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 33% ether–hexanes) to furnish the olefin **87** as a yellow oil (12.2 g, 93%).

$R_f = 0.30$  (33% ethyl acetate–hexanes; PAA).  $^1\text{H NMR}$  (500 MHz,  $(\text{CD}_3)_2\text{SO}$ , 120 °C)  $\delta$  7.26 (t,  $J = 7.6$  Hz, 2H, H<sub>10</sub>), 7.15 (dd,  $J = 20.8, 7.4$  Hz 3H, H<sub>9,11</sub>), 6.01 (dd,  $J = 17.6, 11.0$  Hz, 1H, H<sub>2</sub>), 5.06–4.96 (m, 2H, H<sub>1</sub>), 4.68 (s, 1H, H<sub>7 or 6</sub>), 4.64 (d,  $J = 4.4$  Hz, 1H, H<sub>6 or 7</sub>),

4.41 (d,  $J = 16.3$  Hz, 1H, H<sub>8a</sub>), 4.29 (d,  $J = 16.3$  Hz, 1H, H<sub>8b</sub>), 3.53 (s, 3H, H<sub>12</sub>), 2.08 (h,  $J = 9.9, 9.3$  Hz, 2H, H<sub>5</sub>), 1.80 (dt,  $J = 14.9, 7.6$  Hz 1H, H<sub>4a</sub>), 1.57–1.45 (m, 1H, H<sub>4b</sub>), 1.07 (s, 3H, H<sub>3</sub>), 0.84 (s, 9H, H<sub>13</sub>), –0.02 (d, 1H,  $J = 9.4$  Hz, H<sub>14</sub>). IR (ATR-FTIR),  $\text{cm}^{-1}$ : 2954 (m), 2930 (m), 2857 (m), 1721 (s), 1694 (s), 1665 (s) 1450 (m).  $[\alpha]_D^{20} = -92.7$  (c= 0.42,  $\text{CHCl}_3$ ).

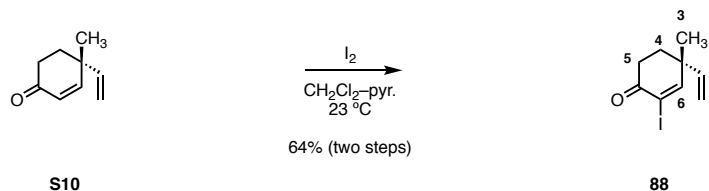
*Synthesis of the  $\alpha$ -iodoenone **88**:*

*Part 1: Synthesis of the unsaturated ketone **S10**:*



A 500-mL flask fused to a Teflon-coated valve was charged with the olefin **87** (6.60 g, 15.9 mmol, 1 equiv) and tetrahydrofuran (160 mL). Aqueous hydrochloric acid solution (1 N, 33.0 mL, 33.0 mmol, 2.08 equiv) was then added at 23 °C. The reaction vessel was sealed and the sealed reaction vessel was placed in an oil bath that had been preheated to 70 °C. The reaction mixture was stirred for 3 days at 70 °C. The product mixture was then cooled over 45 min to ~23 °C. The cooled product mixture was diluted slowly and sequentially with saturated aqueous sodium bicarbonate solution (100 mL, CAUTION: Gas evolution!), water (50 mL), and ethyl acetate (150 mL), with stirring. The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (2 × 50 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (150 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was used directly in the following step.

Part 2: Synthesis of the  $\alpha$ -iodoenone **88**:

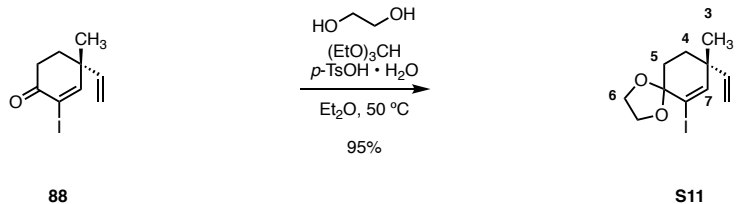


Iodine (12.0 g, 47.6 mmol, 3.00 equiv) was added to a solution of the unsaturated ketone **S10** (nominally 15.9 mmol, 1 equiv) in 5% pyridine–dichloromethane (v/v, 80 mL) at 23 °C. The reaction mixture was stirred for 5 days at 23 °C. The product mixture was diluted sequentially with saturated aqueous sodium thiosulfate solution (50 mL), water (50 mL), and ethyl acetate (100 mL). The resulting biphasic mixture was stirred for 20 min at 23 °C. The stirred mixture was transferred to a separatory funnel and the layers were separated. The organic layer was washed sequentially with 1 N aqueous hydrochloric acid solution (2 × 40 mL) and saturated aqueous sodium chloride solution (100 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 14% ether–hexanes) to furnish the  $\alpha$ -iodoenone **88** as a pale-yellow oil (2.65 g, 64% two steps).

$R_f = 0.35$  (20% ether–hexanes; UV, PAA).  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.43 (s, 1H, H<sub>6</sub>), 5.76 (dd,  $J = 17.3, 10.5$  Hz 1H, H<sub>2</sub>), 5.16 (d,  $J = 17.4$  Hz, 1H, H<sub>1a</sub>), 5.06 (d,  $J = 17.4$  Hz, 1H, H<sub>1b</sub>), 2.64 (t,  $J = 6.4$  Hz, 2H, H<sub>5</sub>), 2.00 (t,  $J = 6.6$  Hz, 2H, H<sub>4</sub>), 1.27 (s, 3H, H<sub>3</sub>).  $^{13}\text{C NMR}$  (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  192.3 (C), 164.5 (CH), 141.7 (CH), 115.3 (CH<sub>2</sub>), 103.4 (C), 44.5 (C), 34.9 (CH<sub>2</sub>), 33.6 (CH<sub>2</sub>), 26.7 (CH<sub>3</sub>). IR (ATR-FTIR),  $\text{cm}^{-1}$ : 2962 (m), 2933

(m), 1686 (s), 1583 (m). HRMS-Cl (m/z):  $[M + H]^+$  calcd for  $C_9H_{12}IO$ , 262.9932; found, 262.9975.  $[\alpha]_D^{20} = -55.7$  (c= 0.75,  $CHCl_3$ ).

Synthesis of the ketal **S11**:



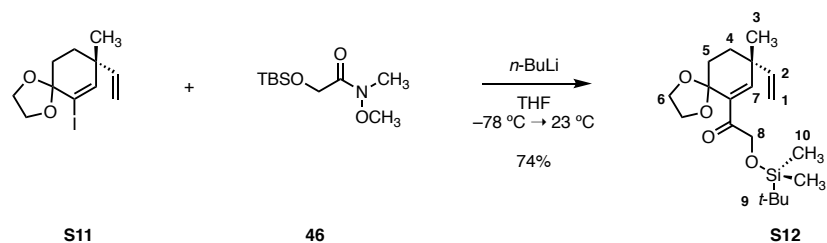
Triethyl orthoformate (8.50 mL, 51.1 mmol, 7.09 equiv) was added to a solution of ethylene glycol (2.00 mL, 35.8 mmol, 4.97 equiv), *para*-toluenesulfonic acid monohydrate (68.9 mg, 360  $\mu\text{mol}$ , 5.0 mol %), and the iodoenone **88** (1.89 g, 7.21 mmol, 1 equiv) in ether (14 mL) at 23  $^\circ\text{C}$ . The reaction vessel was sealed and the sealed reaction vessel was placed in an oil bath that had been preheated to 50  $^\circ\text{C}$ . The reaction mixture was stirred for 29 h at 50  $^\circ\text{C}$ . The product mixture was cooled to 23  $^\circ\text{C}$  over 30 min. The cooled product mixture was diluted with ethyl acetate (25 mL). The diluted mixture was transferred to a separatory funnel and washed sequentially with saturated aqueous sodium bicarbonate solution (15 mL) and saturated aqueous sodium chloride solution (15 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 5% ether–hexanes) to provide the ketal **S11** as a colorless oil (2.10 g, 95%).

$R_f$  = 0.50 (10% ether–hexanes; UV, PAA).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.38 (s, 1H, H<sub>7</sub>), 5.66 (dd,  $J$  = 17.4, 10.5 Hz, 1H, H<sub>2</sub>), 5.14–4.90 (m, 2H, H<sub>1</sub>), 4.30–4.14 (m, 2H, H<sub>6a</sub>), 4.08–3.88 (m, 2H, H<sub>6b</sub>), 2.03–1.83 (m, 2H, H<sub>5</sub>), 1.83–1.67 (m, 2H, H<sub>4</sub>), 1.12 (s, 3H, H<sub>3</sub>).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  150.3 (CH), 143.4 (CH), 113.6 (CH<sub>2</sub>), 105.9 (C), 103.4



(C), 65.8 (CH<sub>2</sub>), 65.4 (CH<sub>2</sub>), 43.5 (C), 32.7 (CH<sub>2</sub>), 30.6 (CH<sub>2</sub>), 26.7 (CH<sub>3</sub>). IR (ATR-FTIR), cm<sup>-1</sup>: 2957 (m), 2926 (m), 2888 (m), 1636 (w), 1344 (m). HRMS-Cl (m/z): [M + H]<sup>+</sup> calcd for C<sub>11</sub>H<sub>16</sub>IO<sub>2</sub>, 307.0189; found, 307.0177.  $[\alpha]_D^{20} = -40.4$  (*c* = 4.55, CHCl<sub>3</sub>).

*Synthesis of the ketone S12:*

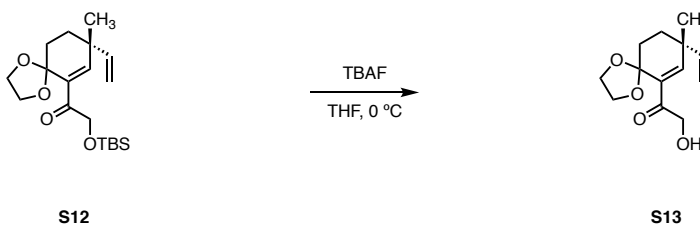


A solution of *n*-butyllithium in hexanes (2.33 M, 3.00 mL, 6.99 mmol, 1.07 equiv) was added dropwise via syringe to a solution of the ketal **S11** (2.00 g, 6.53 mmol, 1 equiv) in tetrahydrofuran (30 mL) at  $-78\text{ }^{\circ}\text{C}$ . The reaction mixture was stirred for 2 min at  $-78\text{ }^{\circ}\text{C}$ . A solution of the Weinreb amide **46** (1.82 g, 7.79 mmol, 1.19 equiv) in tetrahydrofuran (8.0 mL) was then added dropwise via syringe pump over 20 min at  $-78\text{ }^{\circ}\text{C}$ . The reaction mixture was stirred for 2 h at  $-78\text{ }^{\circ}\text{C}$ . The reaction mixture was then allowed to warm to  $23\text{ }^{\circ}\text{C}$  over 21 h. The product mixture was diluted sequentially with saturated aqueous ammonium chloride solution (5.0 mL), water (10 mL), and ethyl acetate (75 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted ethyl acetate ( $2 \times 15\text{ mL}$ ). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting initially with 10% ether–hexanes, grading to 14% ether–hexanes, one step) to provide the ketone **S12** as a colorless oil (1.70 g, 74%).

$R_f = 0.39$  (20% ether–hexanes; UV, PAA).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.47 (s, 1H, H<sub>7</sub>), 5.72 (dd,  $J = 17.5, 10.5$  Hz, 1H, H<sub>2</sub>), 5.04 (dd,  $J = 10.5, 1.0$  Hz, 1H, H<sub>1a</sub>), 4.95 (dd,  $J = 17.5, 1.0$  Hz, 1H, H<sub>1b</sub>), 4.51 (dd,  $J = 18.0, 9.5$  Hz, 2H, H<sub>8</sub>), 4.18–4.09 (m, 2H, H<sub>6a</sub>), 4.05–3.90 (m, 2H, H<sub>6b</sub>), 1.76–1.66 (m, 4H, H<sub>4,5</sub>), 1.16 (s, 3H, H<sub>3</sub>), 0.91 (s, 9H, H<sub>9</sub>), 0.86 (s, 6H, H<sub>10</sub>).  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ ):  $\delta$  198.7 (C), 148.1 (CH), 143.4 (CH), 136.0 (C), 113.8 (CH<sub>2</sub>), 106.1 (C), 68.6 (CH<sub>2</sub>), 64.9 (CH<sub>2</sub>), 64.5 (CH<sub>2</sub>), 39.1 (C), 32.2 (CH<sub>2</sub>), 30.1 (CH<sub>2</sub>), 26.7 (CH<sub>3</sub>), 25.9 (3  $\times$  CH<sub>3</sub>), 18.6 (C), –5.35 (CH<sub>3</sub>), –5.36 (CH<sub>3</sub>). IR (ATR-FTIR),  $\text{cm}^{-1}$ : 2957 (m), 2928 (m), 2858 (w), 1706 (m). HRMS-Cl ( $m/z$ ):  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{19}\text{H}_{33}\text{O}_4\text{Si}$  353.2143; found, 353.2192.  $[\alpha]_D^{20} = -97.0$  ( $c = 0.33, \text{CHCl}_3$ ).

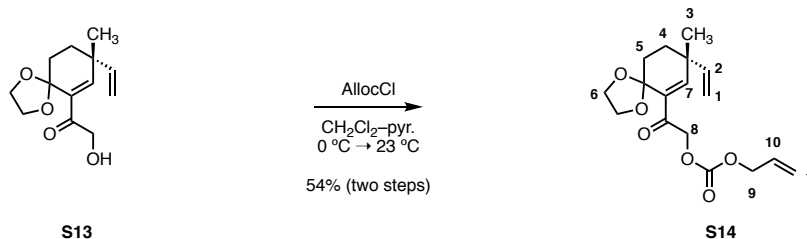
*Synthesis of the allyl carbonate S14:*

*Part 1: Synthesis of the ketone S13:*



A solution of tetrabutylammonium fluoride in tetrahydrofuran (1 M, 5.30 mL, 5.30 mmol, 1.11 equiv) was added to a solution of the ketone **S12** (1.69 g, 4.79 mmol, 1 equiv) in tetrahydrofuran (24 mL) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C. The cold product mixture was diluted sequentially with saturated aqueous ammonium chloride solution (15 mL), water (15 mL), and ethyl acetate (50 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (2 × 20 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was used directly in the next step without further purification.

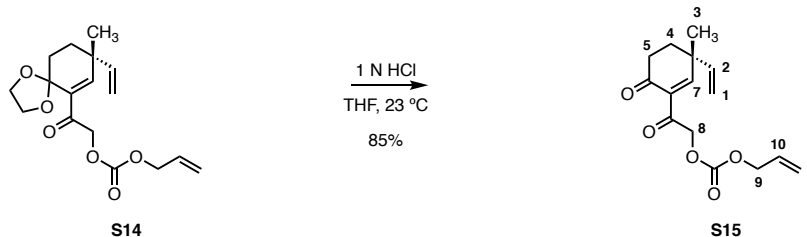
Part 2: Synthesis of the allyl carbonate **S14**:



Allyl chloroformate (2.60 mL, 24.5 mmol, 5.11 equiv) was added dropwise via syringe to the ketone **S13** residue obtained in the previous step (nominally, 4.79 mmol, 1 equiv) dissolved in 5% pyridine–dichloromethane (v/v, 15 mL) and the resulting solution was cooled to 0 °C. The resulting mixture was stirred for 1 h at 0 °C. The reaction mixture was then allowed to warm to 23 °C over 14 h. An additional portion of allyl chloroformate (1.00 mL, 9.41 mmol, 1.96 equiv) was then added. The reaction mixture was stirred for 3 h at 23 °C. The product mixture was diluted sequentially with ethyl acetate (75 mL) and 1 N aqueous hydrochloric acid solution (30 mL). The resulting biphasic mixture was stirred for 30 min at 23 °C. The stirred biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The organic layer was washed sequentially with 1 N aqueous hydrochloric acid solution (3 × 20 mL), saturated aqueous sodium bicarbonate solution (20 mL), and saturated aqueous sodium chloride solution (20 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting initially with 20% ether–hexanes, grading to 50% ether hexanes, one step) to provide the allyl carbonate **S14** as a colorless oil (829 mg, 54% two steps).

$R_f = 0.72$  (33% ethyl acetate–hexanes; UV, PAA).  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.64 (s, 1H, H<sub>7</sub>), 5.97–5.87 (m, 1H, H<sub>10</sub>), 5.70 (dd,  $J = 17.5, 10.6$  Hz, 1H, H<sub>2</sub>), 5.37 (dt,  $J = 17.2, 1.4$  Hz, 1H, H<sub>11a</sub>), 5.25 (dt,  $J = 10.5, 1.2$  Hz, 1H, H<sub>11b</sub>), 5.05–4.85 (m, 4H, H<sub>1,8</sub>), 4.64 (dq,  $J = 5.7, 1.3$  Hz, 2H, H<sub>9</sub>), 4.19–3.99 (m, 4H, H<sub>6</sub>), 1.82–1.62 (m, 4H, H<sub>4,5</sub>), 1.16 (s, 3H, H<sub>3</sub>).  $^{13}\text{C NMR}$  (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  192.6 (C), 154.6 (C), 150.1 (CH), 143.0 (CH), 134.9 (C), 131.3 (CH), 118.7 (CH<sub>2</sub>), 114.0 (CH<sub>2</sub>), 105.8 (C), 69.8 (CH<sub>2</sub>), 68.7 (CH<sub>2</sub>), 64.4 (CH<sub>2</sub>), 64.1 (CH<sub>2</sub>), 39.2 (C), 32.0 (CH<sub>2</sub>), 29.5 (CH<sub>2</sub>), 26.6 (CH<sub>3</sub>). IR (ATR-FTIR),  $\text{cm}^{-1}$ : 2961 (m), 2902 (w), 1754 (s), 1704 (m), 1625 (w), 1418 (w). HRMS-CI ( $m/z$ ):  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{17}\text{H}_{23}\text{O}_6$ , 323.1489; found, 323.1481.  $[\alpha]_D^{20} = -74.2$  ( $c = 0.50, \text{CHCl}_3$ ).

*Synthesis of the diketone S15:*



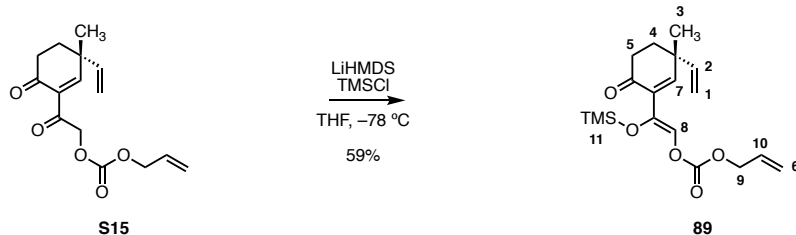
1 N aqueous hydrochloric acid solution (12.4 mL, 12.4 mmol, 5.00 equiv) was added to a solution of the ketone **S14** (800 mg, 2.48 mmol, 1 equiv) in tetrahydrofuran (25 mL) at 23 °C. The reaction mixture was stirred for 14 h at 23 °C. The product mixture was diluted sequentially with saturated aqueous sodium bicarbonate (30 mL), water (10 mL), and ethyl acetate (50 mL). The resulting biphasic mixture was stirred for 30 min at 23 °C. The stirred mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (2 × 30 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 50% ether–hexanes) to furnish the diketone **S15** as a colorless oil (588 mg, 85%).

$R_f = 0.47$  (50% ether–hexanes; UV, PAA).  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.58 (s, 1H, H<sub>7</sub>), 5.97–5.87 (m, 1H, H<sub>10</sub>), 5.77 (dd,  $J = 17.6, 10.6$  Hz, 1H, H<sub>2</sub>), 5.36 (dq,  $J = 17.2, 1.5$  Hz, 1H, H<sub>6a</sub>), 5.25 (dq,  $J = 10.5, 1.4$  Hz, 1H, H<sub>6b</sub>), 5.17–5.12 (m, 3H, H<sub>1a,8</sub>), 4.97 (d,  $J = 17.5$  Hz, 1H, H<sub>1b</sub>), 4.63 (dt,  $J = 5.7, 1.5$  Hz, 2H, H<sub>9</sub>), 2.57–2.43 (m, 2H, H<sub>5</sub>), 2.01–1.88 (m, 2H, H<sub>4</sub>), 1.29 (s, 3H, H<sub>3</sub>).  $^{13}\text{C NMR}$  (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  196.8 (C), 191.5 (C), 164.6 (CH), 154.6 (C), 141.0 (CH), 134.6 (C), 131.3 (CH), 118.7 (CH<sub>2</sub>), 115.4 (CH<sub>2</sub>), 71.7 (CH<sub>2</sub>),

68.7 (CH<sub>2</sub>), 40.1 (C), 34.9 (CH<sub>2</sub>), 33.6 (CH<sub>2</sub>), 26.4 (CH<sub>3</sub>). IR (ATR-FTIR), cm<sup>-1</sup>: 2959 (w), 1753 (s), 1706 (s), 1684 (s), 1598 (w). HRMS-Cl (m/z): [M + H]<sup>+</sup> calcd for C<sub>15</sub>H<sub>19</sub>O<sub>5</sub>, 279.1227; found, 279.1201.  $[\alpha]_D^{20} = -87.9$  (*c* = 0.33, CHCl<sub>3</sub>).



*Synthesis of the enoxysilane ether 89:*

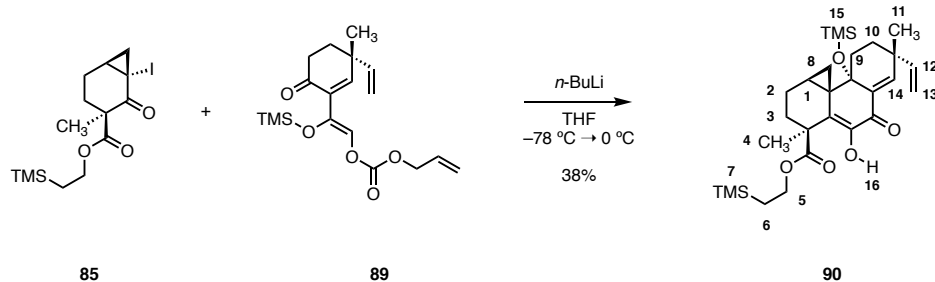


A solution of lithium bis(trimethylsilyl)amide (108 mg, 611  $\mu\text{mol}$ , 1.22 equiv) in tetrahydrofuran (1.20 mL) was added dropwise via cannula to a solution of chlorotrimethylsilane (90.0  $\mu\text{L}$ , 709  $\mu\text{mol}$ , 1.42 equiv) and the diketone **S15** (140 mg, 503  $\mu\text{mol}$ , 1 equiv) in tetrahydrofuran (2.5 mL) at  $-78\text{ }^{\circ}\text{C}$ . The resulting mixture was stirred for 1 h at  $-78\text{ }^{\circ}\text{C}$ . The cold product mixture was diluted with saturated aqueous sodium bicarbonate solution (500  $\mu\text{L}$ ), water (2.0 mL), and ethyl acetate (5.0 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted ethyl acetate (10 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (3.0 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 14% ether–hexanes) to provide the enoxysilane **89** as a colorless oil (103.0 mg, 59%).

The enoxysilane **89** was isolated as a single olefin isomer. The orientation of this isomer was assigned via conclusive NOE correlations between the C11 trimethylsilyl group and the C8 allyl carbonate substituent supporting the relative orientation depicted.

$R_f = 0.32$  (25% ether–hexanes; UV, PAA).  $^1\text{H NMR}$  (500 MHz,  $\text{C}_6\text{D}_6$ ):  $\delta$  8.53 (s, 1H, H<sub>8</sub>), 6.85 (s, 1H, H<sub>7</sub>), 5.62–5.52 (m, 1H, H<sub>10</sub>), 5.40 (dd,  $J = 17.4, 10.5$  Hz, 1H, H<sub>2</sub>), 5.05 (d,  $J = 17.2$  Hz, 1H, H<sub>6a</sub>), 4.89 (d,  $J = 10.5$  Hz, 1H, H<sub>6b</sub>), 4.86–4.77 (m, 2H, H<sub>1</sub>), 4.32–4.29 (m, 2H, H<sub>9</sub>), 2.30–2.21 (m, 2H, H<sub>5</sub>), 1.39–1.29 (m, 2H, H<sub>4</sub>), 0.86 (s, 3H, H<sub>3</sub>), 0.86 (s, 9H, H<sub>11</sub>).  $^{13}\text{C NMR}$  (125 MHz,  $\text{C}_6\text{D}_6$ ):  $\delta$  195.5 (C), 152.6 (C), 151.1 (CH), 143.2 (CH), 134.8 (C), 132.6 (C), 131.7 (CH), 127.2 (CH), 118.5 (CH<sub>2</sub>), 113.9 (CH<sub>2</sub>), 68.8 (CH<sub>2</sub>), 39.7 (C), 35.9 (CH<sub>2</sub>), 34.1 (CH<sub>2</sub>), 27.1 (CH<sub>3</sub>), 0.6 ( $3 \times \text{CH}_3$ ). IR (ATR-FTIR),  $\text{cm}^{-1}$ : 2960 (w), 1761 (s), 1686 (s).  $[\alpha]_D^{20} = -83.5$  ( $c = 0.60$ ,  $\text{CHCl}_3$ ).

Synthesis of the diosphenol **90** by the fragment coupling–cyclization cascade:

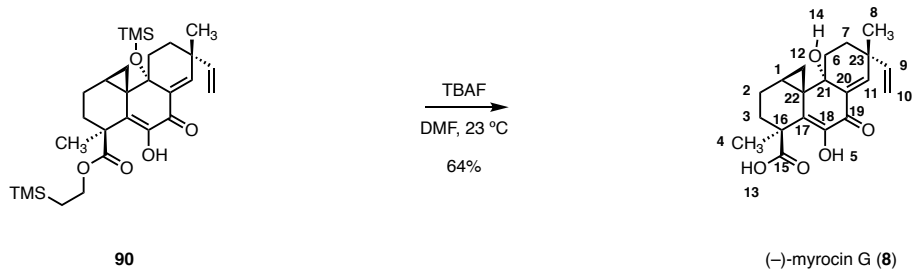


A solution of *n*-butyllithium in hexanes (2.20 M, 50.0  $\mu\text{L}$ , 110  $\mu\text{mol}$ , 2.20 equiv) was added to a solution of the iodocyclopropane **85** (43.0 mg, 110  $\mu\text{mol}$ , 2.20 equiv) in tetrahydrofuran (500  $\mu\text{L}$ ) at  $-78\text{ }^{\circ}\text{C}$ . A solution of the enoxysilane **89** (17.5 mg, 50.0  $\mu\text{mol}$ , 1 equiv) in tetrahydrofuran (150  $\mu\text{L}$ ) was added then immediately added dropwise down the inside wall of the flask. The reaction mixture was stirred for 2 h at  $-78\text{ }^{\circ}\text{C}$ . The reaction mixture was then immersed in a cooling bath at  $0\text{ }^{\circ}\text{C}$ . The reaction mixture was stirred for 3 h at  $0\text{ }^{\circ}\text{C}$ . The product mixture was then diluted sequentially with saturated aqueous ammonium chloride solution (150  $\mu\text{L}$ ), water (500  $\mu\text{L}$ ), and ethyl acetate (8.0 mL). The resulting biphasic solution was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3.0 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (2.0 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by preparative thin-layered chromatography (eluting with 16% ether–hexanes) to furnish the diosphenol **90** as light yellow oil (9.5 mg, 38%).

$R_f = 0.50$  (33% ether–hexanes; UV, PAA).  $^1\text{H NMR}$  (600 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.86 (s, 1H,  $\text{H}_{14}$ ), 6.21 (d,  $J = 17.5\text{ Hz}$ , 1H,  $\text{H}_{16}$ ), 5.86 (dd,  $J = 17.5, 10.7\text{ Hz}$ , 1H,  $\text{H}_{12}$ ), 5.12–5.06 (m,

2H, H<sub>13</sub>), 4.24–4.14 (m, 1H, H<sub>5a</sub>), 4.16–4.07 (m, 1H, H<sub>5b</sub>), 1.97 (ddd,  $J = 17.5, 8.7, 3.7$  Hz, 1H, H<sub>9a</sub>), 1.91–1.86 (m, 1H, H<sub>2a</sub>), 1.85–1.75 (m, 2H, H<sub>3a,9b</sub>), 1.68–1.62 (m, 1H, H<sub>1</sub>), 1.56 (dd,  $J = 9.9, 4.4$  Hz, 2H, H<sub>10</sub>), 1.54–1.49 (m, 1H, H<sub>2b</sub>), 1.43 (dt,  $J = 13.6, 2.9$  Hz, 1H, H<sub>3b</sub>), 1.39 (s, 3H, H<sub>3</sub>), 1.10 (s, 3H, H<sub>11</sub>), 1.01–0.88 (m, 4H, H<sub>6,8</sub>), 0.01 (s, 9H, H<sub>7</sub>), –0.03 (s, 9H, H<sub>15</sub>). <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>):  $\delta$  182.9 (C), 179.9 (C), 145.8 (CH), 144.8 (CH), 143.3 (C), 135.1 (C), 134.0 (C), 112.9 (CH<sub>2</sub>), 75.1 (C), 63.2 (CH<sub>2</sub>), 44.1 (C), 38.8 (C), 29.7 (CH<sub>2</sub>), 29.6 (CH<sub>2</sub>), 29.2 (CH<sub>2</sub>), 27.1 (CH<sub>3</sub>), 25.1 (CH<sub>3</sub>), 19.8 (CH<sub>3</sub>), 17.8 (CH<sub>2</sub>), 17.3 (CH<sub>2</sub>), 15.8 (CH), 13.2 (CH<sub>2</sub>), 2.8 (3  $\times$  CH<sub>3</sub>), 1.4 (3  $\times$  CH<sub>3</sub>). IR (ATR-FTIR), cm<sup>-1</sup>: 2952 (m), 1731 (s), 1655 (s), 1609 (s). HRMS-Cl (m/z): [M + H]<sup>+</sup> calcd for C<sub>28</sub>H<sub>45</sub>O<sub>5</sub>Si<sub>2</sub>, 517.2805; found, 517.2855.  $[\alpha]_D^{20} = -13.3$  ( $c = 0.50$ , CHCl<sub>3</sub>).

Synthesis of (-)-myrocin G (**8**):



A solution of tetrabutylammonium fluoride in tetrahydrofuran (1 M, 49.0  $\mu\text{L}$ , 49.0  $\mu\text{mol}$ , 2.10 equiv) was added to a solution of the diosphenol **90** (12.0 mg, 23.2  $\mu\text{mol}$ , 1 equiv) in *N,N*-dimethylformamide (200  $\mu\text{L}$ ) at 23 °C. The reaction mixture was stirred for 5 h at 23 °C. The product mixture was diluted sequentially with saturated aqueous ammonium chloride solution (500  $\mu\text{L}$ ), water (1.0 mL), and ethyl acetate (7.0 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3  $\times$  4.0 mL). The organic layers were combined and the combined organic layers were washed sequentially with water (3  $\times$  2.0 mL) and saturated aqueous sodium chloride solution (3.0 mL). The organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 1% acetic acid–50% acetone–hexanes). The fractions containing product (TLC analysis) were combined. The combined fractions were dissolved in toluene (5.0 mL) and the resulting solution was concentrated to provide (-)-myrocin G (**8**) as a white solid (5.0 mg, 64%).

$R_f = 0.20$  (1% acetic acid–50% acetone–hexanes; UV, PAA).  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  6.84 (d,  $J = 1.3$  Hz, 1H,  $\text{H}_{11}$ ), 5.89 (dd,  $J = 17.5, 10.7$  Hz, 1H,  $\text{H}_9$ ), 5.16–5.14

(m, 2H, H<sub>10</sub>), 2.10–2.03 (m, 1H, H<sub>2a</sub>), 1.93–1.83 (m, 3H, H<sub>2b,3</sub>), 1.72–1.67 (m, 1H, H<sub>1</sub>), 1.63 (td,  $J = 13.7, 12.6, 3.6$  Hz, 1H, H<sub>6a</sub>), 1.56–1.48 (m, 2H, H<sub>6b,7a</sub>), 1.48–1.41 (m, 1H, H<sub>7b</sub>), 1.37 (s, 3H, H<sub>4</sub>), 1.09 (s, 3H, H<sub>8</sub>), 1.09 (dd,  $J = 8.9, 5.8$  Hz 1H, H<sub>12a</sub>), 0.94 (t,  $J = 6.1$ Hz, 1H, H<sub>12b</sub>). <sup>13</sup>C NMR (100 MHz, CD<sub>3</sub>OD):  $\delta$  183.6 (C, C<sub>19</sub>), 180.9 (C, C<sub>15</sub>), 147.1 (CH, C<sub>11</sub>), 146.9 (CH, C<sub>9</sub>), 145.5 (C, C<sub>18</sub>), 136.0 (C, C<sub>20</sub>), 135.4 (C, C<sub>17</sub>), 112.9 (CH<sub>2</sub>, C<sub>10</sub>), 72.2 (C, C<sub>21</sub>), 45.1 (C, C<sub>16</sub>), 39.9 (C, C<sub>23</sub>), 30.7 (CH<sub>2</sub>, C<sub>3</sub>), 30.6 (CH<sub>2</sub>, C<sub>7</sub>), 29.4 (C, C<sub>22</sub>), 27.3 (CH<sub>2</sub>, C<sub>6</sub>), 24.4 (CH<sub>3</sub>, C<sub>8</sub>), 20.1 (CH<sub>3</sub>, C<sub>4</sub>), 18.5 (CH<sub>2</sub>, C<sub>2</sub>), 16.6 (CH, C<sub>1</sub>), 13.4 (CH<sub>2</sub>, C<sub>12</sub>). IR (ATR-FTIR), cm<sup>-1</sup>: 3393 (m), 2922 (m), 2868 (w), 1701 (s), 1653 (s), 1635 (m), 1601 (m). HRMS-Cl (m/z): [M + H]<sup>+</sup> calcd for C<sub>20</sub>H<sub>25</sub>O<sub>5</sub> 345.1702, found 345.1723.  $[\alpha]_D^{20} = -78.7$  ( $c = 0.20$ , CHCl<sub>3</sub>).

Synthesis of the bis(sulfide) **25**:



Thiophenol (9.0  $\mu\text{L}$ , 87.0  $\mu\text{mol}$ , 10.0 equiv) and triethylamine (12.0  $\mu\text{L}$ , 87.0  $\mu\text{mol}$ , 10.0 equiv) were added in sequence to a solution of (–)-myrocin G (**8**, 3.0 mg, 8.7  $\mu\text{mol}$ , 1 equiv) in tetrahydrofuran (200  $\mu\text{L}$ ) at 23 °C. The headspace in the reaction vessel was evacuated and the evacuated vessel was filled with argon. This process was repeated twice. The reaction mixture was stirred for 15 h at 23 °C. The product mixture was diluted sequentially with 1 N aqueous hydrochloric acid solution (100  $\mu\text{L}$ ), water (500  $\mu\text{L}$ ) and dichloromethane (1.5 mL). The resulting biphasic mixture was transferred to a separatory funnel that had been charged with dichloromethane (5.0 mL). The layers that formed were separated, and the aqueous layer was extracted with dichloromethane ( $3 \times 3.0$  mL). The organic layers were combined and the combined organic layers were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by preparative thin-layered chromatography (eluting with 1% acetic acid–33% acetone–hexanes) to provide the bis(sulfide) **25** as a white solid (3.5 mg, 74%).

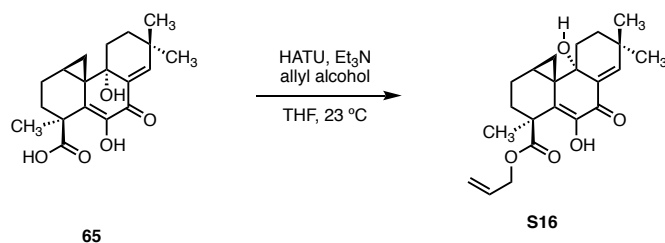
$R_f = 0.14$  (1% acetic acid–33% acetone–hexanes; UV, PAA).  $^1\text{H NMR}$  (600 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.41 (d,  $J = 7.4$ , 2H,  $\text{H}_9$ ), 7.36–7.32 (m, 2H,  $\text{H}_{14}$ ), 7.29 (t,  $J = 7.6$ , 2H,  $\text{H}_{10}$ ), 7.24–7.17 (m, 4H,  $\text{H}_{11,15,16}$ ), 5.85 (dd,  $J = 17.5, 10.8$  Hz, 1H,  $\text{H}_{12}$ ), 5.01 (d,  $J = 17.5$  Hz, 1H,  $\text{H}_{13a}$ ), 4.86 (d,  $J = 10.8$  Hz, 1H,  $\text{H}_{13b}$ ), 4.23 (s, 1H,  $\text{H}_5$ ), 3.04–2.87 (m, 3H,  $\text{H}_{1,8}$ ), 2.46 (dd,  $J =$

17.3, 6.0 Hz, 1H, H<sub>6a</sub>), 2.37–2.23 (m, 3H, H<sub>2a,3a,6b</sub>), 2.01–1.95 (m, 1H, H<sub>7a</sub>), 1.81 (app t,  $J = 14.3$  Hz, 1H, H<sub>2b</sub>), 1.74 (app d  $J = 13.5$  Hz, 1H, H<sub>3b</sub>), 1.53–1.45 (m, 4H, H<sub>4,7b</sub>), 0.98 (s, 3H, H<sub>17</sub>). <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>):  $\delta$  183.2 (C, C<sub>28</sub>), 146.1 (CH, C<sub>12</sub>), 141.6 (C, C<sub>20</sub>), 139.7 (C, C<sub>21</sub>), 136.1 (C, C<sub>26</sub>), 135.5 (C, C<sub>27</sub>), 131.7 (CH, C<sub>9</sub>), 130.9 (CH, C<sub>14</sub>), 130.1 (C, C<sub>24</sub>), 128.9 (CH, C<sub>10</sub>), 128.8 (CH, C<sub>15</sub>), 127.3 (CH, C<sub>11</sub>), 126.6 (CH, C<sub>16</sub>), 126.2 (C, C<sub>19</sub>), 125.2 (C, C<sub>23</sub>), 123.1 (C, C<sub>22</sub>), 112.0 (CH<sub>2</sub>, C<sub>13</sub>), 53.8 (CH, C<sub>5</sub>), 44.7 (C, C<sub>18</sub>), 39.7 (C, C<sub>25</sub>), 37.4 (CH<sub>2</sub>, C<sub>8</sub>), 33.3 (CH, C<sub>1</sub>), 29.9 (CH<sub>2</sub>, C<sub>3</sub>), 27.1 (CH<sub>2</sub>, C<sub>7</sub>), 23.3 (CH<sub>3</sub>, C<sub>4</sub>), 22.9 (CH<sub>3</sub>, C<sub>17</sub>), 21.6 (CH<sub>2</sub>, C<sub>6</sub>), 20.8 (CH<sub>2</sub>, C<sub>2</sub>). IR (ATR-FTIR), cm<sup>-1</sup>: 2931 (s), 1701 (s), 1439 (m). HRMS-Cl (m/z): [M + Na]<sup>+</sup> calcd for C<sub>32</sub>H<sub>34</sub>NaO<sub>4</sub>O<sub>2</sub> 569.1798, found 569.1805.  $[\alpha]_D^{20} = -29.2$  ( $c = 0.10$ , CHCl<sub>3</sub>).



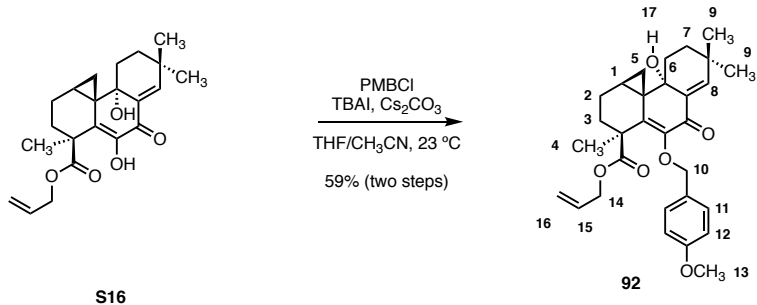
*Synthesis of the allyl ester 92:*

*Part 1: Synthesis of diosphenol allyl ester S16:*



Allyl alcohol (30.0  $\mu\text{L}$ , 441  $\mu\text{mol}$ , 16.3 equiv) was added to a solution of the analogue **65** (9.0 mg, 27.1  $\mu\text{mol}$ , 1 equiv) and 1-[bis(dimethylamino)-methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium-3-oxide hexafluorophosphate (HATU) (22.0 mg, 136  $\mu\text{mol}$ , 5.00 equiv) in tetrahydrofuran (300  $\mu\text{L}$ ) at 23 °C. The reaction mixture was stirred for 5 d at 23 °C. The product mixture was diluted with saturated aqueous ammonium chloride solution (2.0 mL), water (1.0 mL), and ethyl acetate (5.0 mL). The diluted product mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3  $\times$  2.0 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (1.0 mL). The organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was eluted over a short plug of silica gel (1.0 cm  $\times$  3.0 cm, eluting with 50% ether–hexanes). The filtrate was collected and concentrated. The diosphenol allyl ester **S16** obtained in this way was used in the following step without further purification.

Part 2: Synthesis of the allyl ester **92**:

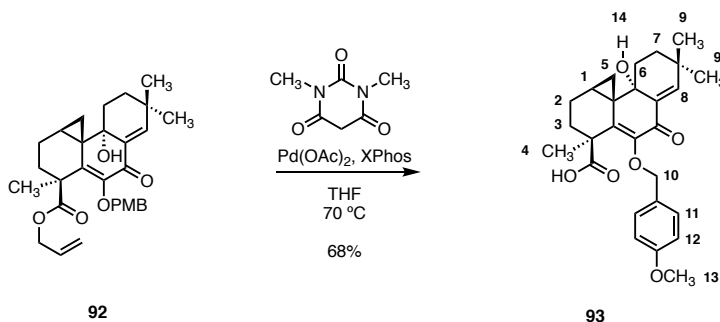


Tetrabutylammonium iodide (1.2 mg, 3.40  $\mu\text{mol}$ , 0.20 equiv), cesium carbonate (6.6 mg, 20.0  $\mu\text{mol}$ , 1.20 equiv) and *para*-methoxybenzoyl chloride (2.70  $\mu\text{L}$ , 20.0  $\mu\text{mol}$ , 1.20 equiv) were added in sequence to a solution of the unpurified allyl ester diosphenol **S16** obtained in the preceding step (nominally, 17.0  $\mu\text{mol}$ , 1 equiv) in 33% tetrahydrofuran–acetonitrile (v/v, 300  $\mu\text{L}$ ) at 23  $^{\circ}\text{C}$ . The reaction mixture was stirred for 16 h at 23  $^{\circ}\text{C}$ . The product mixture was diluted sequentially with saturated aqueous ammonium chloride solution (1.0 mL), water (1.0 mL) and ethyl acetate (5.0 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate ( $2 \times 3.0$  mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (2.0 mL). The washed organic layers were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by preparative thin-layered chromatography (eluting with 25% ethyl acetate–hexanes initially, grading to 50% ethyl acetate–hexanes, 1 step) to provide the allyl ester **92** as a colorless oil (7.5 mg, 59% two steps).

$R_f = 0.40$  (50% ethyl acetate–hexanes; UV, PAA).  $^1\text{H NMR}$  (600 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.33 (d,  $J = 8.6$  Hz, 2H, H<sub>11</sub>), 6.92 (s, 1H, H<sub>8</sub>), 6.86 (d,  $J = 8.6$  Hz, 2H, H<sub>12</sub>), 5.81–5.74 (m, 1H,

H<sub>15</sub>), 5.16 (d,  $J = 17.2$  Hz, 1H, H<sub>16a</sub>), 5.09 (d,  $J = 10.5$  Hz, 1H, H<sub>16b</sub>), 4.92 (d,  $J = 10.6$  Hz, 1H, H<sub>10a</sub>), 4.82 (d,  $J = 10.6$  Hz, 1H, H<sub>10b</sub>), 4.43–4.38 (m, 1H, H<sub>14a</sub>), 4.35–4.31 (m, 1H, H<sub>14b</sub>), 3.79 (s, 3H, H<sub>13</sub>), 1.98–1.84 (m, 2H, H<sub>6</sub>), 1.80 (td,  $J = 13.9, 4.7$  Hz, 1H, H<sub>3a</sub>), 1.72–1.62 (m, 2H, H<sub>2a,6b</sub>), 1.51–1.36 (m, 5H, H<sub>1,2b,3b,7</sub>), 1.22 (s, 3H, H<sub>4</sub>), 1.15 (s, 3H, H<sub>9a</sub>), 1.01 (s, 3H, H<sub>9b</sub>), 0.95 (dd,  $J = 8.9, 5.9$  Hz, 1H, H<sub>5a</sub>), 0.84 (t,  $J = 6.2$  Hz, 1H, H<sub>5b</sub>). <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>):  $\delta$  181.6 (C), 175.3 (C), 159.5 (C), 149.1 (CH), 146.6 (C), 145.2 (C), 134.9 (C), 132.7 (C), 130.7 (CH), 129.2 (C), 117.3 (CH), 113.6 (CH<sub>2</sub>), 71.9 (C), 70.6 (CH<sub>2</sub>), 65.4 (CH<sub>2</sub>), 55.2 (CH<sub>3</sub>), 43.8 (C), 32.9 (C), 31.3 (CH<sub>2</sub>), 28.4 (CH<sub>3</sub>), 28.0 (CH<sub>2</sub>), 26.1 (CH<sub>3</sub>), 26.0 (CH<sub>2</sub>), 21.0 (CH<sub>3</sub>), 17.2 (CH<sub>2</sub>), 14.5 (CH<sub>2</sub>), 12.7 (CH<sub>2</sub>).

*Synthesis of the free acid 93:*

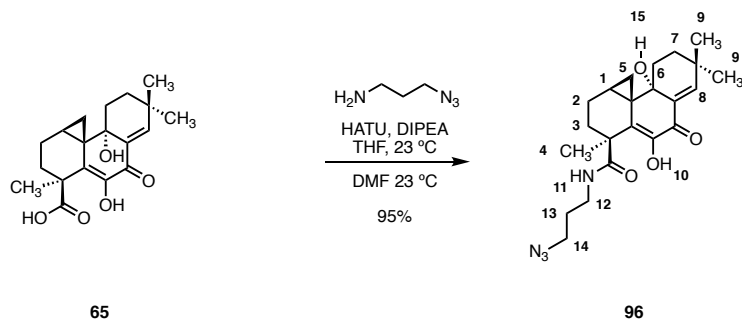


A one-dram vial was sequentially charged with 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (1.9 mg, 4.0  $\mu\text{mol}$ , 0.40 equiv), the allyl ester **92** (4.0 mg, 10.0  $\mu\text{mol}$ , 1 equiv), palladium(II) acetate (1.0 mg, 4.0  $\mu\text{mol}$ , 0.40 equiv), 1,3-dimethylbarbituric acid (7.8 mg, 50.0  $\mu\text{mol}$ , 5.00 equiv), and tetrahydrofuran (200  $\mu\text{L}$ ). The reaction vessel was sealed and the sealed vessel was placed on a heating block that had been preheated to 40 °C. The reaction mixture was stirred and heated for 1 h at 40 °C. The reaction mixture was then warmed to 50 °C. The reaction mixture was stirred and heated for 2.5 h at 50 °C. The reaction mixture was then warmed to 70 °C. The reaction mixture was stirred and heated for 2.5 h at 70 °C. The product mixture was cooled over 30 min to 23 °C. The cooled product mixture was diluted sequentially with saturated aqueous ammonium chloride solution (1.0 mL), water (1.0 mL) and ethyl acetate (5.0 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (2  $\times$  3.0 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (2.0 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The

residue obtained was purified by preparative thin-layered chromatography (eluting with 50% ethyl acetate–hexanes) to provide the free acid **93** as a white solid (2.5 mg, 68%).

$R_f = 0.10$  (50% ethyl acetate–hexanes; UV, PAA).  $^1\text{H NMR}$  (600 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.33 (d,  $J = 8.6$  Hz, 2H,  $\text{H}_{11}$ ), 6.92 (s, 1H,  $\text{H}_8$ ), 6.85 (d,  $J = 8.6$  Hz, 2H,  $\text{H}_{12}$ ), 4.94–4.90 (m, 2H,  $\text{H}_{10}$ ), 3.78 (s, 3H,  $\text{H}_{13}$ ), 1.99–1.87 (m, 2H,  $\text{H}_6$ ), 1.80 (td,  $J = 13.9, 4.8$  Hz, 1H,  $\text{H}_{3a}$ ), 1.72–1.64 (m, 2H,  $\text{H}_{2a,6b}$ ), 1.51–1.37 (m, 5H,  $\text{H}_{1,2b,3b,7}$ ), 1.21 (s, 3H,  $\text{H}_4$ ), 1.15 (s, 3H,  $\text{H}_{9a}$ ), 1.01 (s, 3H,  $\text{H}_{9b}$ ), 0.97 (dd,  $J = 8.8, 6.0$  Hz, 1H,  $\text{H}_{5a}$ ), 0.86 (t,  $J = 5.9$  Hz, 1H,  $\text{H}_{5b}$ ).  $^{13}\text{C NMR}$  (150 MHz,  $\text{CDCl}_3$ ):  $\delta$  181.7 (C), 178.7 (C), 159.5 (C), 149.2 (CH), 146.7 (C), 144.7 (C), 134.9 (C), 130.7 (C), 129.1 (CH), 113.6 (CH), 72.1 (C), 70.7 ( $\text{CH}_2$ ), 55.2 ( $\text{CH}_3$ ), 43.4 (C), 32.9 (C), 31.9 ( $\text{CH}_2$ ), 31.3 ( $\text{CH}_3$ ), 28.4 ( $\text{CH}_3$ ), 28.0 ( $\text{CH}_2$ ), 26.1 ( $\text{CH}_3$ ), 26.0 ( $\text{CH}_2$ ), 14.5 ( $\text{CH}_2$ ), 20.7 ( $\text{CH}_3$ ), 17.2 ( $\text{CH}_2$ ), 14.5 ( $\text{CH}_2$ ), 12.7 ( $\text{CH}_2$ ).

Synthesis of the azide probe (–)-**96**:

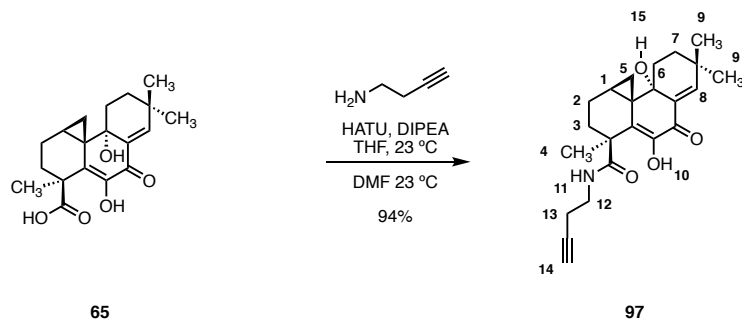


3-Azido-1-propanamine (3.1  $\mu\text{L}$ , 0.0301 mmol, 2.0 equiv) was added to a solution of the analogue (–)-**65** (5.0 mg, 15.0  $\mu\text{mol}$ , 1 equiv), 1-[bis(dimethylamino)-methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium-3-oxide hexafluorophosphate (HATU) (1.5 mg, 23.0  $\mu\text{mol}$ , 1.50 equiv), and *N,N*-diisopropylethylamine (13.0  $\mu\text{L}$ , 75.0  $\mu\text{mol}$ , 5.00 equiv) in *N,N*-dimethylformamide (300  $\mu\text{L}$ ) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C and then was warmed to 23 °C. The reaction mixture was stirred for 30 min at 23 °C. The product mixture was diluted sequentially with saturated aqueous ammonium chloride solution (2.0 mL), water (1.0 mL), and ethyl acetate (5.0 mL). The diluted product mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3  $\times$  2.0 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (2.0 mL). The organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by preparative thin-layered chromatography (eluting with 50% ethyl acetate–hexanes) to provide the azido ester (–)-**96** as a colorless oil (5.9 mg, 95%).

Azido ester (+)-**96** was prepared in an analogous fashion. <sup>1</sup>H NMR and <sup>13</sup>C NMR data for (+)-**96** obtained matched that of the (–)-**96**

$R_f = 0.30$  (50% ethyl acetate–hexanes, UV, PAA). <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD):  $\delta$  7.30 (t,  $J = 5.5$  Hz, 1H, H<sub>11</sub>), 6.81 (s, 1H, H<sub>8</sub>), 3.37 – 3.31 (m, 2H, H<sub>12</sub>), 3.22 (q,  $J = 6.4$  Hz, 2H, H<sub>14</sub>), 2.04 (tt,  $J = 14.2, 4.2$  Hz, 1H, H<sub>7a</sub>), 1.85 (ddt,  $J = 13.7, 4.8, 2.5$  Hz, 1H, H<sub>7b</sub>), 1.79–1.69 (m, 3H, H<sub>13,3a</sub>), 1.75–1.68 (m, 1H, H<sub>1</sub>), 1.67 (tt,  $J = 6.0, 3.1$  Hz, 1H, H<sub>3b</sub>), 1.58 (td,  $J = 13.6, 12.6, 3.4$  Hz, 1H, H<sub>2a</sub>), 1.51–1.36 (m, 2H, H<sub>2b,15</sub>), 1.39–1.37 (m, 5H, H<sub>4,6</sub>), 1.29 (s, 3H, H<sub>9</sub>), 1.12–1.07 (m, 1H, H<sub>5a</sub>), 1.03–0.983 (m, 4H, H<sub>9,5b</sub>). <sup>13</sup>C NMR (150 MHz, CD<sub>3</sub>OD):  $\delta$  182.5 (C), 178.9 (C), 178.8 (C), 148.9 (CH), 133.8 (C), 133.0 (C), 70.8 (C), 49.06 (CH<sub>2</sub>), 44.7(C), 44.7 (C), 36.9 (CH<sub>2</sub>), 32.3(C), 30.9 (CH<sub>2</sub>), 30.3 (CH<sub>2</sub>), 28.4 (CH<sub>3</sub>), 28.1(CH<sub>2</sub>), 26.3(CH<sub>2</sub>), 25.0 (CH<sub>3</sub>), 18.2 (CH<sub>3</sub>), 17.2 (CH<sub>2</sub>), 15.14 (CH<sub>3</sub>), 12.1 (CH<sub>2</sub>). IR (ATR-FTIR), cm<sup>-1</sup>: 3404 (m), 2957 (m), 2926 (m), 1652 (s), 1605 (s). HRMS- CI (m/z): [M + Na]<sup>+</sup> calcd for C<sub>22</sub>H<sub>30</sub>N<sub>4</sub>NaO<sub>4</sub>, 437.2165; found, 437.2179.

Synthesis of the alkyne probe (–)-**97**:

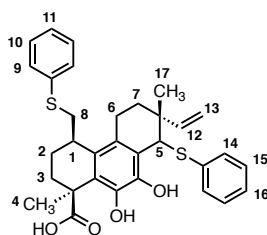


1-Amino-3-butyne (2.50  $\mu$ L, 30.1  $\mu$ mol, 2.00 equiv) was added to a solution of the analogue (–)-**65** (5.0 mg, 15.0  $\mu$ mol, 1 equiv), 1-[bis(dimethylamino)-methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium-3-oxide hexafluorophosphate (HATU) (1.5 mg, 26.0  $\mu$ mol, 1.50 equiv), and *N,N*-diisopropylethylamine (13.0  $\mu$ L, 75.0  $\mu$ mol, 5.00 equiv) in *N,N*-dimethylformamide (300  $\mu$ L) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C and was then warmed to 23 °C. The reaction mixture was stirred for 30 min at 23 °C. The product mixture was diluted sequentially with saturated aqueous ammonium chloride solution (2.0 mL), water (1.0 mL), and ethyl acetate (5.0 mL). The diluted product mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3  $\times$  2.0 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (1.0 mL). The organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by preparative thin-layered chromatography (eluting with 30% hexanes–ethyl acetate) to provide the alkynyl ester (–)-**97** as a yellow oil (5.8 mg, 94%).



Alkynyl ester (+)-**97** was prepared in an analogous fashion. <sup>1</sup>H NMR and <sup>13</sup>C NMR data for (+)-**97** obtained matched that of the (–)-**97**.

$R_f = 0.35$  (50% ethyl acetate–hexanes, UV, PAA). <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD):  $\delta$  7.32 (t,  $J = 5.9$  Hz, 1H, H<sub>11</sub>), 6.81 (d,  $J = 1.5$  Hz, 1H, H<sub>8</sub>), 3.25–3.23 (m, 2H, H<sub>12</sub>), 2.81 (s, 1H, H<sub>15</sub>), 2.37 (ddt,  $J = 9.0, 6.7, 2.4$  Hz, 2H, H<sub>13</sub>), 2.23 (t,  $J = 2.7$  Hz, 1H, H<sub>14</sub>), 2.05 (tt,  $J = 13.9, 4.1$  Hz, 1H, H<sub>6a</sub>), 1.87–1.82 (m, 1H, H<sub>6b</sub>), 1.79–1.70 (m, 2H, H<sub>7a,2a</sub>), 1.67 (tt,  $J = 6.1, 3.1$  Hz, 1H, H<sub>1</sub>), 1.59 (td,  $J = 13.6, 12.6, 3.5$  Hz, 1H, H<sub>3a</sub>), 1.49–1.4 (m, 3H, H<sub>7b,2a,3b</sub>), 1.39 (s, 3H, H<sub>4</sub>), 1.13–1.08 (m, 4H, H<sub>9,5a</sub>), 1.03–0.983 (m, 4H, H<sub>9,5a</sub>). <sup>13</sup>C NMR (150 MHz, CD<sub>3</sub>OD):  $\delta$  183.9 (C), 180.2 (C), 150.4 (CH), 145.6 (C), 135.2 (C), 134.3 (C), 82.6 (C), 72.3 (C), 70.4 (CH), 46.0 (C), 39.9 (CH<sub>2</sub>), 33.7 (C), 32.3 (CH<sub>2</sub>), 31.6 (CH<sub>2</sub>), 29.8 (CH<sub>3</sub>), 29.5 (C), 27.7 (CH<sub>2</sub>), 26.4 (CH<sub>3</sub>), 19.6 (CH<sub>3</sub>), 19.4 (CH<sub>2</sub>), 18.6 (CH<sub>2</sub>), 16.5 (CH), 13.6 (CH<sub>2</sub>). IR (ATR-FTIR), cm<sup>-1</sup>: 2924 (m), 22805 (m), 1738 (m), 1655 (s), 1605 (s). HRMS-  
CI (m/z): [M + Na]<sup>+</sup> calcd for C<sub>23</sub>H<sub>30</sub>NO<sub>4</sub>, 384.2175; found, 384.2176.

**Table S1.** Comparison of  $^1\text{H}$  NMR data for the bis(sulfide) **25**:**25**

Position	$^1\text{H}$ NMR (-)- <b>25</b> [CDCl <sub>3</sub> , 600 MHz]	$^1\text{H}$ NMR (±)- <b>25</b> <sup>8,10</sup> [CDCl <sub>3</sub> , 250 MHz] <sup>a</sup>
1	3.04–2.87 (m)	3.16–2.85 (m)
2	2.37–2.23 (m)	2.38–2.18 (m)
	1.81 (app t, 14.3)	1.83–1.67 (m)
3	2.37–2.23 (m)	2.38–2.18 (m)
	1.74 (app d, 13.5)	1.83–1.67 (m)
4	1.53–1.45 (m) [1.50 (s)]	1.48 (s)
5	4.23 (s)	4.21 (s)
6	2.46 (dd, 17.3, 6.0)	2.45 (dd, 17.8, 5.2)
	2.37–2.23 (m)	2.38–2.18 (m)
7	2.01–1.95 (m)	1.97 (m)
	1.53–1.45 (m)	1.46 [buried (i.e. m)]
8	3.04–2.87 (m)	3.16–2.85 (m)
9	7.41 (d, 7.4)	7.45–7.14 (m)
10	7.29 (t, 7.6)	7.45–7.14 (m)
11	7.24–7.17 (m)	7.45–7.14 (m)
12	5.85 (dd, 17.5, 10.8)	5.82 (dd, 17.4, 10.7)
13	5.01 (d, 17.4)	4.98 (d, 17.3)
	4.86 (d, 10.7)	4.83 (d, 10.8)
14	7.36–7.32 (m)	7.45–7.14 (m)
15	7.24–7.17 (m)	7.45–7.14 (m)
16	7.24–7.17 (m)	7.45–7.14 (m)
17	0.98 (s)	0.96 (s)

<sup>a</sup> $^{13}\text{C}$  NMR data for (±)-**25** were not reported.

## 1.9 Bibliography.

1. Hsu, Y.-H.; Hirota, A.; Shima, S.; Nakagawa, M.; Nozaki, H.; Tada, T.; Nakayama, M. Structure of Myrocin C, a New Diterpene Antibiotic Produced by a Strain of *Myrothecium* Sp. *Agric. Biol. Chem.* **1987**, *51*, 3455-3457.
2. Nakagawa, M. H., Y. H.; Hirota, A.; Shima, S.; Nakayama, M. Myrocin C, a New Diterpene Antitumor Antibiotic from *Myrothecium Verrucaria*. I. Taxonomy of the Producing Strain, Fermentation, Isolation and Biological Properties. *J. Antibiot.* **1989**, *42*, 218-222.
3. Hsu, Y.-H. H., A.; Shima, S.; Nakagawa, M.; Adachi, T.; Nozaki, H.; Nakayama, M.; Myrocin C, a New Diterpene Antitumor Antibiotic from *Myrothecium Verrucaria*. *J. Antibiot.* **1989**, *42*, 223-229.
4. Wang, X.; Yu, H.; Zhang, Y.; Lu, X.; Wang, B.; Liu, X. Bioactive Pimarane-Type Diterpenes from Marine Organisms. *Chem. Biodiversity* **2018**, *15*, 1-12.
5. Hsu, Y.-H.; Nakagawa, M.; Hirota, A.; Shima, S.; Nakayama, M. Structure of Myrocin B, a New Diterpene Antibiotic Produced by *Myrothecium Verrucaria*. *Agric. Biol. Chem.* **1988**, *52*, 1305-1307.
6. Lehr, N.-A.; Meffert, A.; Antelo, L.; Sterner, O.; Anke, H.; Weber, R. W. S. Antiamoebins, Myrocin B and the Basis of Antifungal Antibiosis in the Coprophilous Fungus *Stilbella Erythrocephala* (Syn. *S. Fimetaria*). *FEMS Microbiol. Ecol.* **2006**, *55*, 105-112.
7. Chu-Moyer, M. Y.; Danishefsky, S. J. A Remarkable Cyclopropanation: The Total Synthesis of Myrocin C. *J. Am. Chem. Soc.* **1992**, *114*, 8333-8334.

8. Chu-Moyer, M. Y.; Danishefsky, S. J.; Schulte, G. K. Total Synthesis of (±)-Myrocin C. *J. Am. Chem. Soc.* **1994**, *116*, 11213-11218.
9. Yamada, S.; Nagashima, S.; Takaoka, Y.; Torihara, S.; Tanaka, M.; Suemune, H.; Aso, M. Synthetic Study toward Myrocin Analogues. Highly Enantio- and Diastereo-Selective Synthesis of a Tetracyclic Ring System. *J. Chem. Soc., Perkin Trans. I* **1998**, 1269-1274.
10. Chu-Moyer, M. Y.; Danishefsky, S. J. On the Mode of Action of Myrocin C: Evidence for a CC-1065 Connection. *Tetrahedron Lett.* **1993**, *34*, 3025-3028.
11. Chidester, C. G.; Krueger, W. C.; Mizensak, S. A.; Duchamp, D. J.; Martin, D. G. The Structure of CC-1065, a Potent Antitumor Agent and Its Binding to DNA. *J. Am. Chem. Soc.* **1981**, *103*, 7629-7635.
12. Gargiulo, D.; Musser, S. S.; Yang, L.; Fukuyama, T.; Tomasz, M. Alkylation and Crosslinking of DNA by the Unnatural Enantiomer of Mitomycin C: Mechanism of the DNA-Sequence Specificity of Mitomycins. *J. Am. Chem. Soc.* **1995**, *117*, 9388-9398.
13. (a) Zander, N.; Langschwager, W.; Hoffmann, H. M. R. The Enol Lactone Approach to Protected Hydroxy  $\gamma$ -Lactones (5-Hydroxy-dihydro-furan-2-ones). *Synth. Commun.* **1996**, *26*, 4577-4590.
14. Langschwager, W.; Hoffmann, H. M. R. Ring-Chain Tautomerism Provides a Route to 7a-hydroxy-3a-methyl-2,7-dioxoperhydrobenzofuran. Synthesis of the Hydroxy  $\gamma$ -Lactone Substructure of Myrocin and Other Bioactive Natural Products. *Liebigs Ann.* **1995**, *1995*, 797-802.

15. Klemke, C.; Kehraus, S.; Wright, A. D.; König, G. M. New Secondary Metabolites from the Marine Endophytic Fungus *Apiospora Montagnei*. *J. Nat. Prod.* **2004**, *67*, 1058-1063.
16. Johnson, C. R.; Adams, J. P.; Braun, M. P.; Senanayake, C. B. W.; Wovkulich, P. M.; Uskoković, M. R. Direct  $\alpha$ -Iodination of Cycloalkenones. *Tetrahedron Lett.* **1992**, *33*, 917-918.
17. Corey, E. J.; Chaykovsky, M. Dimethyloxosulfonium Methylide ((CH<sub>3</sub>)<sub>2</sub>SOCH<sub>2</sub>) and Dimethylsulfonium Methylide ((CH<sub>3</sub>)<sub>2</sub>SCH<sub>2</sub>). Formation and Application to Organic Synthesis. *J. Am. Chem. Soc.* **1965**, *87*, 1353-1364.
18. Burgi, H. B.; Dunitz, J. D.; Lehn, J. M.; Wipff, G. Stereochemistry of Reaction Paths at Carbonyl Centres. *Tetrahedron* **1974**, *30*, 1563-1572.
19. Nahm, S.; Weinreb, S. M. *N*-Methoxy-*N*-methyamides as Effective Acylating Agents. *Tetrahedron Lett.* **1981**, *22*, 3815-3818.
20. Kita, Y.; Yakura, T.; Terashi, H.; Haruta, J.-i.; Tamura, Y. Hypervalent Iodine Oxidation of Ethynylcarbinols: A Short and Efficient Conversion of Dihydroxyacetyl Groups from Keto Groups. *Chem. Pharm. Bull.* **1989**, *37*, 891-894.
21. Rubottom, G. M.; Gruber, J. M.; Boeckman, R. K.; Ramaiah, M.; Medwid, J. B. Clarification of the Mechanism of Rearrangement of Enol Silyl Ether Epoxides. *Tetrahedron Lett.* **1978**, *19*, 4603-4606.
22. Tomanik, M.<sup>#</sup>; Economou, C.<sup>#</sup>; Frischling, M. C.; Xue, M.; Marks, V. A.; Mercado, Q. B.; Herzon, S. B. Development of a Convergent Enantioselective Synthetic Route to (-)-Myrocin G. *J. Org. Chem.* **2020**, *85*, 8952-8989.

23. Meng, Z.; Yu, H.; Li, L.; Tao, W.; Chen, H.; Wan, M.; Yang, P.; Edmonds, D. J.; Zhong, J.; Li, A. Total Synthesis and Antiviral Activity of Indolosesquiterpenoids from the Xiamycin and Oridamycin Families. *Nat. Commun.* **2015**, *6*, 6096.
24. Xu, C.; Zhang, L.; Luo, S. Asymmetric Enamine Catalysis with  $\beta$ -Ketoesters by Chiral Primary Amine: Divergent Stereocontrol Modes. *J. Org. Chem.* **2014**, *79*, 11517-11526.
25. Kozmin, S. A.; Rawal, V. H. Asymmetric Diels–Alder Reactions of Chiral 1-Amino-3-siloxy-1,3-butadiene: Application to the Enantioselective Synthesis of (–)-Elemene. *J. Am. Chem. Soc.* **1997**, *119*, 7165-7166.
26. Economou, C.; Tomanik, M.; Herzon, S. B. Synthesis of Myrocin G, the Putative Active Form of the Myrocin Antitumor Antibiotics. *J. Am. Chem. Soc.* **2018**, *140*, 16058-16061.
27. Tomanik, M.; Herzon, S. B. Synthesis of (–)-Myrocin G via a Cascade Coupling. *Trends in Chemistry.* **2020**, *2*, 776-777.
28. Still, W. C.; Kahn, M.; Mitra, A. Rapid Chromatographic Technique for Preparative Separations with Moderate Resolution. *J. Org. Chem.* **1978**, *43*, 2923-2925.
29. Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. Safe and Convenient Procedure for Solvent Purification. *Organometallics* **1996**, *15*, 1518-1520.
30. Love, B. E.; Jones, E. G. The Use of Salicylaldehyde Phenylhydrazone as an Indicator for the Titration of Organometallic Reagents. *J. Org. Chem.* **1999**, *64*, 3755-3756.

31. Braun, M.-G.; Katcher, M. H.; Doyle, A. G. Carbofluorination Via a Palladium-Catalyzed Cascade Reaction. *Chem. Sci.* **2013**, *4*, 1216-1220.

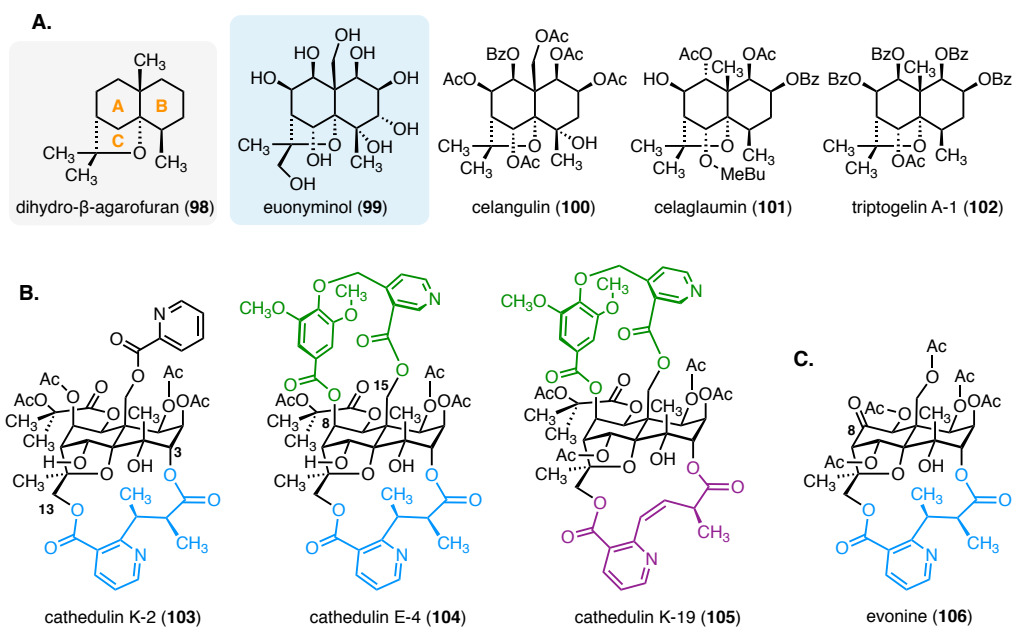
## **Chapter 2.**

**Development of an enantioselective synthesis of (-)-euonyminol.**



## 2.1 Introduction.

Dihydro- $\beta$ -agarofurans (e.g., **98–102**) are a diverse family of secondary metabolites isolated from the *Celastraceae* plant family, which is native to the sub-tropical regions of the world (Figure 4).<sup>1-3</sup> These isolates are characterized by a highly-oxidized tricyclic carbogenic skeleton. The related isolates known as the cathedulins (e.g., **103–105**) are macrocyclic terpenoid alkaloids possessing the common dihydro- $\beta$ -agarofurans nucleus known as euonyminol (**99**).<sup>4-8</sup> In the sections that follow, I will review the interesting biological properties of these natural products, their characteristic structural features, and the prior related synthetic work. I will then describe in detail the development of the first enantioselective synthetic route to (–)-euonyminol (**99**) and discuss the potential adaptation of this route towards the synthesis of the macrocyclic cathedulins.



**Figure 4.** A. Structures of the dihydro- $\beta$ -agarofuran skeleton (**98**), (–)-euonyminol (**99**), and additional representative isolates (**100–102**). B. Structures of several representative cathedulin terpenoid alkaloids (**103–105**). C. Structure of evonine (**106**).

## 2.2 Biological properties and structural features of the dihydro- $\beta$ -agarofuran natural products.

### 2.2.1 Biological properties of the dihydro- $\beta$ -agarofurans and of the cathedulins.

The *Celastraceae* plant family, the source of the dihydro- $\beta$ -agarofurans, has been extensively used in traditional farming methods.<sup>9-11</sup> For example, the crude extracts of the plant *Celastrus angulatus* were employed as insecticides in Chinese agriculture.<sup>12</sup> Detailed analysis of these extracts revealed the dihydro- $\beta$ -agarofuran celangulin (**100**) as the metabolite responsible for the potent insecticidal property.<sup>13,2</sup> Further screening experiments in 1990 revealed that **100** exhibits pesticidal activity against the fall armyworm *Mythimma separata* at 5 parts per million (ppm), the cabbage leaf worm *Pieris rapae* at 222 ppm, and against the Asian corn borer *Ostrinia furnacalis* at 222 ppm.<sup>13</sup> These activities were not unique to celangulin (**100**) as subsequent studies identified additional dihydro- $\beta$ -agarofurans possessing insect antifeedant properties similar to the known commercial pesticide azadirachtin.<sup>14</sup>

*Celastraceae* extracts have also been used in traditional medicine owing to their anti-inflammatory, anti-bacterial, and digestive healing properties.<sup>2-3,11</sup> Additionally, the widespread search for cancer treatments lead to the identification of various dihydro- $\beta$ -agarofurans as promising anti-tumor agents.<sup>15-16</sup> For example, celaglaumin (**101**) exhibited modest activity against murine leukemia cell line L1210 (IC<sub>50</sub> = 2.11  $\mu$ g/mL) and against lymphatic leukemia cell line P-388 (IC<sub>50</sub> = 4.12  $\mu$ g/mL).<sup>17</sup> Related studies done by Takaishi and co-workers established that the dihydro- $\beta$ -agarofuran triptogelin A-1 (**102**) reduced both the incidence and the frequency of skin cancer in mice without excessive

cytotoxicity.<sup>15,18</sup> Collectively, these studies suggest that these natural products may constitute for the development of additional anti-cancer therapeutics.<sup>15,18</sup>

The cathedulin terpenoid alkaloids are complex macrocyclic natural products isolated from the small shrub *Catha edulis*.<sup>4</sup> Extracts from freshly cut leaves of this shrub are known to produce a substance that is commonly referred to as Khat. Simple chewing of Khat is widely popular in East Africa and in several parts of the Middle East as it leads to a mental stimulation and produces feelings of euphoria.<sup>4</sup> Pharmacological studies of Khat have identified that the stimulatory effects are primarily caused by norpseudeiohedrine (cathine) but these studies have also implicated cathedulins as possibly responsible for some of the observed physiological effects associated with Khat digestion.<sup>5,19</sup> To date, over twenty macrocyclic cathedulins have been identified from natural sources possessing either one or two macrocycles in studies carried out by Crombie and co-workers.<sup>6-8</sup> The former structures are exemplified by cathedulin K-2 (**103**)<sup>6</sup> wherein the macrocycle bridges the C13 and C3 hydroxyl groups. The more complex bis(macrocyclic structures) structures possess an additional bridge between C8 and C15 hydroxyl groups, as exemplified by cathedulins E-4 (**104**)<sup>8</sup> and K-19 (**105**)<sup>8</sup>. A unifying structural feature across this family is the presence of a common tricyclic nucleus identified as the sesquiterpenoid euonyminol (**99**, Figure 4), which will be discussed in the subsequent section.

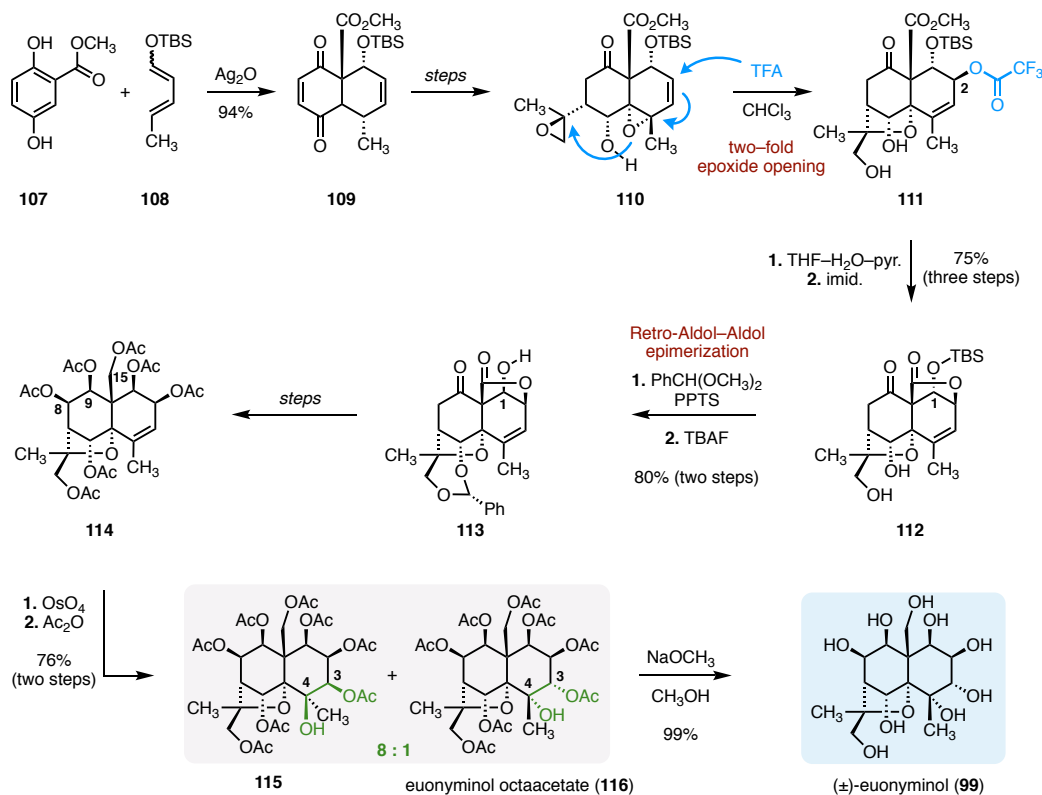
### 2.2.2 Structural features of the dihydro- $\beta$ -agarofurans and introduction to euonyminol.

Structurally, the dihydro- $\beta$ -agarofurans are characterized by the tricyclic scaffold shown in Figure 4. This skeleton is comprised of a *trans*-decalin (A- and B- rings) that is further appended by a tetrahydrofuran (C-ring). As is seen in structures **99–102**, these natural products possess an unusually high degree of oxygenation around the tricyclic scaffold, leading to a large structure diversity among the family, as evidenced by the isolation of over four hundred distinct metabolites.<sup>2-3</sup> Euonyminol (**99**) is the most heavily-oxygenated family member with a total of ten oxygen atoms, nine of which are free hydroxyl groups. To the best of our knowledge, this natural product was first described in the literature by Beroza and co-workers 1952.<sup>20</sup> These researches concluded that euonyminol (**99**) is a polyhydroxy substance without a definite melting point and having a molecular formula C<sub>15</sub>H<sub>26</sub>O<sub>10</sub>. In 1971, Hirata first advanced a structure for euonyminol based on degradation and NMR spectroscopy studies.<sup>21</sup> The structure was unambiguously confirmed by the same group in 1972 via X-ray crystallographic analysis of the related alkaloid evonine (**106**), which was isolated from a different *Celastraceae* plant species.<sup>22</sup> Though evonine (**106**) possess a ketone oxidation state at the C8 position, a direct link between these two natural products was found when evonine (**106**) was treated with lithium aluminum hydride (LiAlH<sub>4</sub>) resulting in formation of euonyminol (**99**) (30%) as the major product along with the C8 *epi*-euonyminol as the minor byproduct (15%).<sup>22-23</sup>

## 2.3 Prior synthetic art towards the dihydro- $\beta$ -agarofurans.

### 2.3.1 Total synthesis of ( $\pm$ )-euonyminol by White and co-workers.

In 1995, White and co-workers reported the first synthesis of ( $\pm$ )-euonyminol (**99**).<sup>24,25</sup> Their synthesis began with a silver-mediated Diels–Alder reaction between methyl 2,5-dihydroxybenzoate (**107**) and the diene **108**, to generate the adduct **109** (94%, Scheme 19). This adduct was then advanced to the bis(epoxide) **110** which served as a substrate for a key transformation. Exposure of **110** to trifluoroacetic acid resulted in a two-fold epoxide opening ring-forming cascade with trapping of the final allylic cation by trifluoroacetate, to provide the tricyclic diol **111**. A two-step sequence comprising of a cleavage of the trifluoroacetate ester (aqueous tetrahydrofuran and pyridine) followed by imidazole-promoted lactonization then provided the lactone diol **112** (75% from **110**).



**Scheme 19.** Synthesis of ( $\pm$ )-euonyminol (**99**) by White and co-workers.

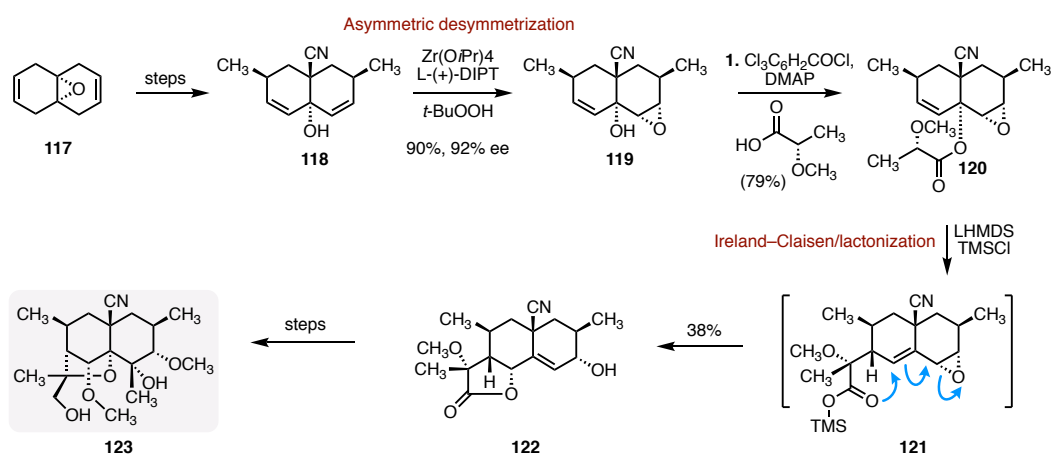
The diol residue was then protected as a benzylidene acetal (benzaldehyde dimethyl acetal, pyridinium *para*-toluenesulfonate). After some experimentation, the authors found that the stereochemistry at C1 could be corrected via a retro-Aldol–Aldol addition initiated by exposing the acetal intermediate to tetrabutylammonium fluoride, to provide the ketone **113** (80%, two steps). The ketone **113** possesses all of the carbons of the target, however, the oxidation state of **113** needed to be significantly increased in subsequent manipulations.

To this end, **113** was advanced to the heptaacetate intermediate **114** in six steps (28% overall). The authors then pursued dihydroxylation of the C3–C4 olefin as a means to install the final missing 1,2-diol residue. In the event, treatment of **114** with osmium tetroxide in the presence of pyridine, followed by acetylation with acetic anhydride and DMAP provided euonyminol octaacetate (**116**) and its stereoisomer **115** in 76% combined yield and 1:8 ratio favoring the undesired diastereomer **115**. As the authors were unable to improve the stereoselectivity of the osmylation or perform this transformation at an earlier point of the synthesis, they elected to carry on with this result and complete the synthesis. Consequently, the minor isomer **116** was treated with sodium methoxide in methanol to deliver ( $\pm$ )-euonyminol (**99**) in 99% yield.

### 2.3.2 Synthetic studies towards (–)-euonyminol by Spivey and co-workers.

In 2013, the Spivey laboratory reported an enantioselective synthesis of the tricycle **123** possessing the fully functionalized lower region of euonyminol (**99**).<sup>26</sup> Their synthesis commenced with the epoxide **117**, which was advanced to the meso diallylic alcohol **118** in five transformations (52% overall, Scheme 20). The authors desymmetrized **118** by an asymmetric epoxidation employing zirconium(IV) isopropoxide, (+)-diisopropyl L-tartarate

and *tert*-butyl hydroperoxide, to generate the monoepoxide **119** in 90% yield and in 92% ee. The intermediate **119** was then converted to the ester **120** for a pivotal transformation. A silylketene acetal (not shown) was generated by treatment of the ester **118** with LiHMDS and TMSCl; subsequent Ireland ester Claisen rearrangement afforded the allylic epoxide intermediate **121** which underwent lactonization via  $S_N'$  epoxide opening to the tricycle **122** (38%). This transformation is notable as it simultaneously established the C6 and C7 stereocenters while also introducing an allylic alcohol for further manipulations. Subsequent manipulations provided the tricycle **123**, which possess the fully functionalized lower region of euonyminol (**99**).

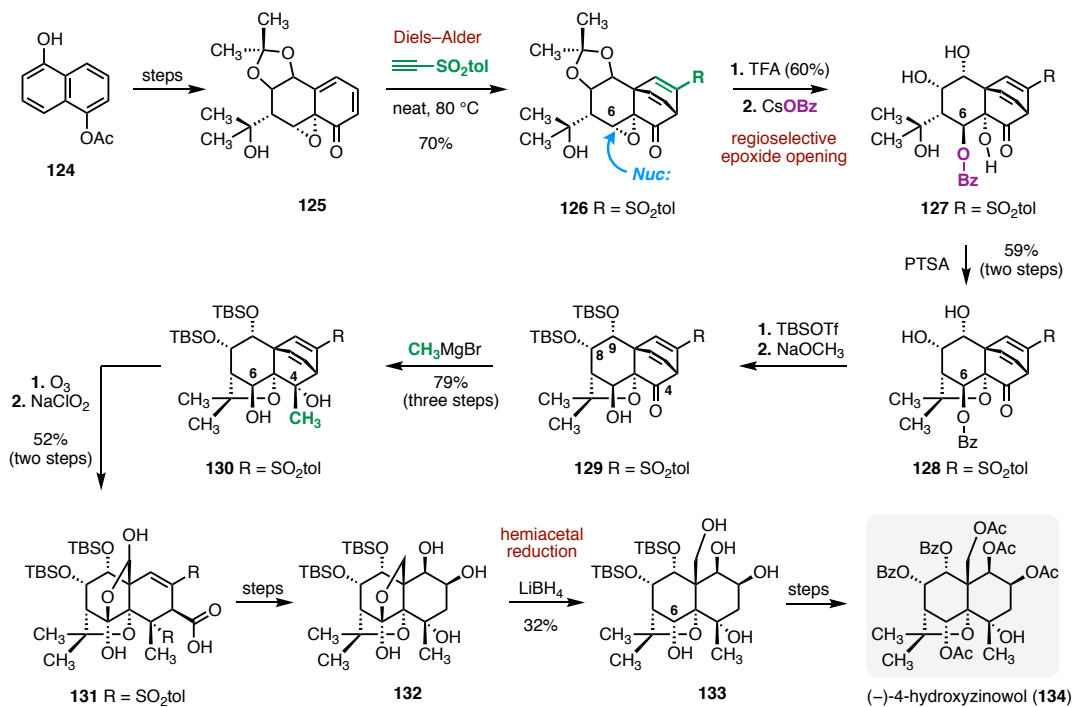


**Scheme 20.** Synthesis of the tricycle **123** by Spivey and co-workers.

### 2.3.3 Total synthesis of (–)-4-hydroxyzinowol by Inoue and co-workers.

In 2014, Inoue and co-workers reported a total synthesis of the polyoxygenated dihydro- $\beta$ -agarofuran (–)-4-hydroxyzinowol (**134**).<sup>27</sup> Their synthesis began with the naphthalene derivative **124**, which was advanced to the epoxide **125** in thirteen steps (Scheme 21). Heating of the epoxide to 80 °C in the presence of ethynyl *para*-tolyl sulfone provided the Diels–Alder adduct **126** as a single isomer in 70% yield. Cleavage of the

acetone (trifluoroacetic acid), followed by regioselective epoxide opening with cesium benzoate as nucleophile, provided the triol **127**. An intramolecular substitution was achieved by exposure of the triol **127** to PTSA, resulting in production of the tricycle **128** (59%, two steps).



**Scheme 21.** Total synthesis of (-)-4-hydroxyzinowol (**134**) by Inoue and co-workers.

Silylation of the C8–C9 diol (*tert*-butyldimethylsilyl trifluoromethanesulfonate), followed by cleavage of the C6 benzoate ester (sodium methoxide) provided the secondary alcohol **129**. The remaining carbon of the natural product was introduced via a diastereoselective addition of methyl magnesium bromide to the C4 ketone. This reaction presumably occurred via formation of a magnesium chelate between the C6 alcohol and the ketone, which would then direct approach of the nucleophile to the  $\beta$ -face, forming the tertiary alcohol **130** (79% from **128**). With all of the carbon atoms present in **128**, several

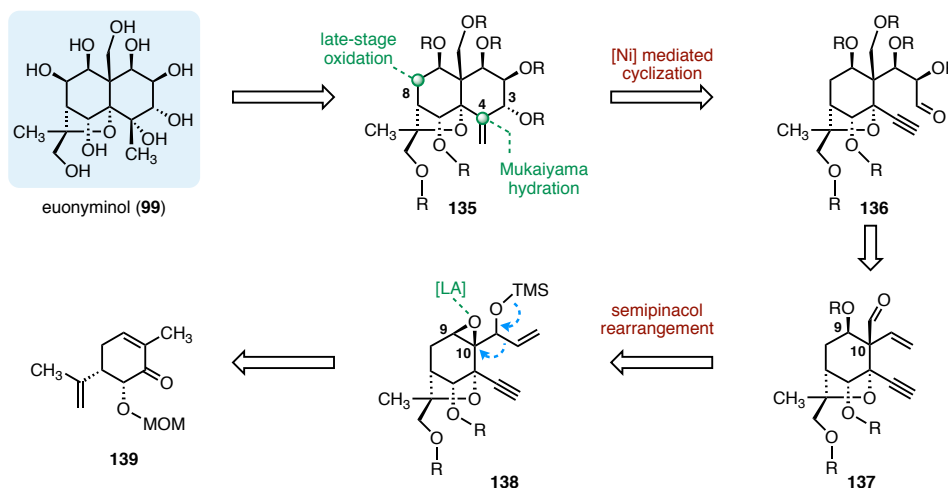


additional reactions highlighted in Scheme 21 were required to adjust the oxidation state of **128** and to complete the synthesis of (–)-4-hydroxyzinowol (**134**).

## 2.4 Development of an enantioselective synthetic route to (–)-euonyminol.

### 2.4.1 Synthesis of the exocyclic olefin **179** via a novel oxyalkylation reaction of an allylic alcohol.

Our interest in (–)-euonyminol (**99**) was motivated by the synthetic challenge associated with construction of the heavily oxygenated dihydro-β-agarofuran skeleton, which resembles a carbosaccharide. The goal from the start of this research project was to develop a robust strategy that would not only provide access to (–)-euonyminol (**99**) but would also be easily adaptable for the synthesis of the cathedulin alkaloids. With this goal in mind, we devised an initial approach as summarized in Scheme 22.



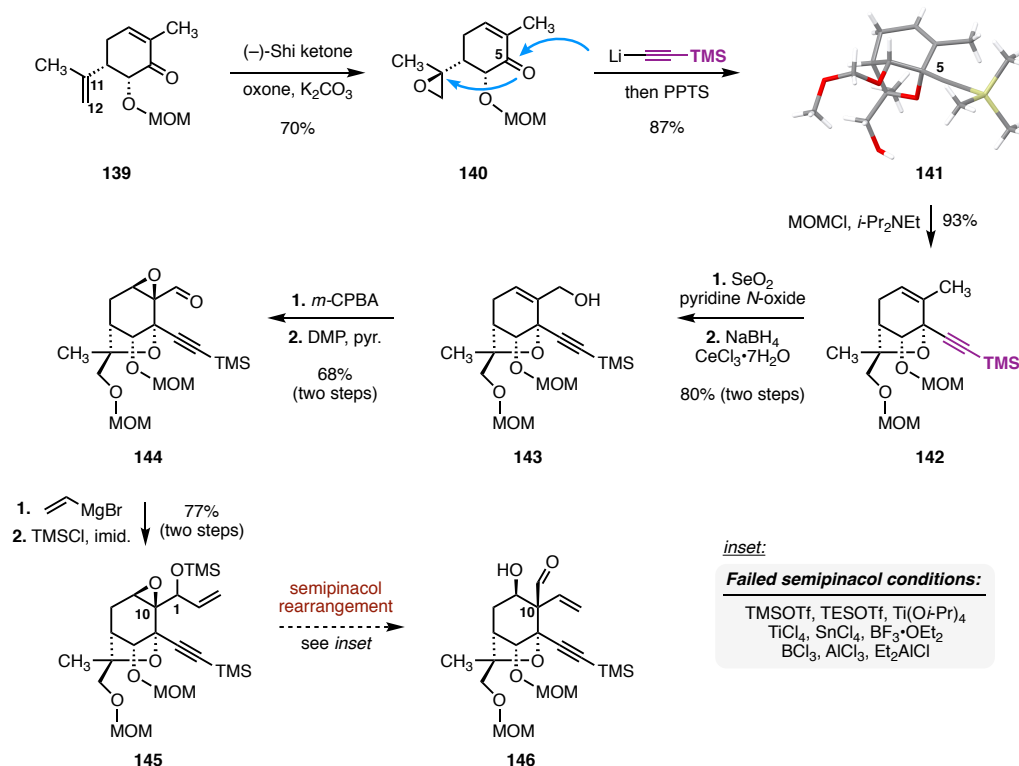
**Scheme 22.** First retrosynthetic analysis of (–)-euonyminol (**99**).

We envisioned accessing the target from the exocyclic olefin **135** via a late-stage oxidation at the C8 position, followed by a Mukaiyama hydration<sup>28</sup> of the olefin to establish

the C4 stereocenter. This intermediate, in turn, could be derived from the alkyne **136** via a ring closing nickel-catalyzed alkyne–aldehyde reductive cyclization.<sup>29</sup> The intermediate **136** could be traced back to the neopentyl aldehyde **137**. The C10 quaternary stereocenter of **137** was anticipated to be accessible by a Lewis-acid mediated semipinacol rearrangement of the epoxide **138**, which in turn could be simplified to the known carvone derivative **139**<sup>30</sup> as the starting point for our synthesis.<sup>31</sup>

We began by evaluating the diastereoselective epoxidation of the C11–C12 alkene within **139** (Scheme 23). Epoxidation with the levorotary enantiomer of the Shi ketone provided the epoxide **140** as well as its diastereomer (not shown) in a 2.4:1 ratio. Following chromatographic separation the epoxide **140** was obtained in 70% yield on a multigram scale. The addition of lithium trimethylsilyl acetylide to the ketone **140** proceeded with 13:1 diastereoselectivity to provide a C5 alcohol intermediate (not shown). Exposure of the unpurified alcohol to pyridinium *para*-toluenesulfonate then promoted the formation of the C-ring via a regioselective ring-opening of the C11–C12 epoxide, to yield the cyclic ether **141** (87% overall). The relative stereochemistry of **141** was confirmed by X-ray analysis. Protection of the primary alcohol group as the methoxymethyl ether (methoxymethyl chloride, Hünig's base, 93%) was followed by an allylic oxidation (selenium dioxide) and a reduction of the unsaturated aldehyde under Luche conditions (sodium borohydride, cerium chloride) to generate the allylic alcohol intermediate **143** (80%, two steps). A two-step sequence comprising stereoselective epoxidation (mCBPA) and oxidation (Dess–Martin periodinane, pyridine) generated the aldehyde **144** (68% overall). The addition of vinylmagnesium bromide to **144** followed by silylation of the resulting allylic alcohol (TMSCl, imidazole) formed **145**, the key precursor for the

semipinacol rearrangement (77%, 3.4:1 dr at C1). The relative stereochemistry of the major diastereomer was not assigned.

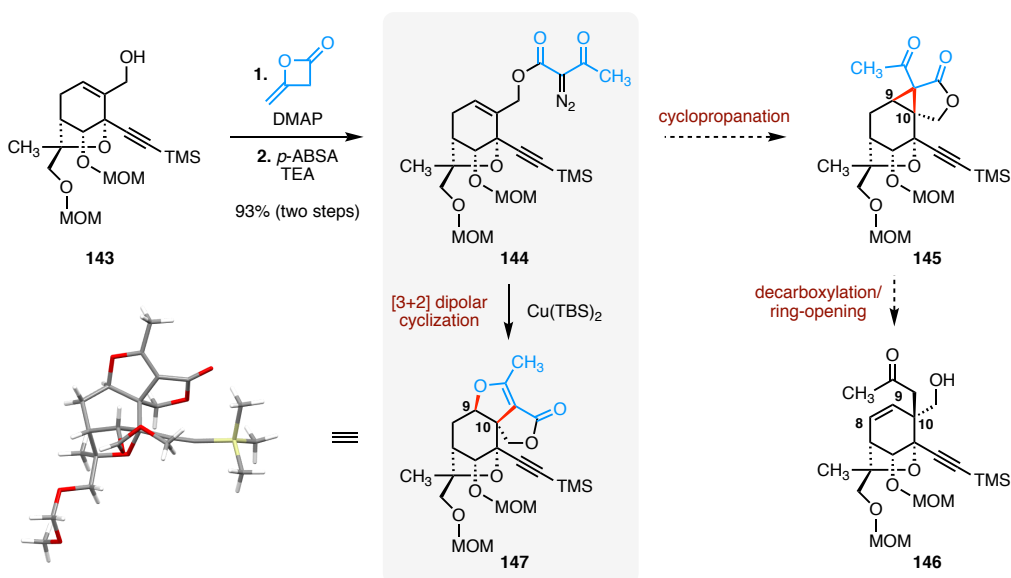


**Scheme 23.** Synthesis of the epoxide **146**.

Unfortunately, all of our attempts to promote the desired semipinacol transformation to establish the C10 quaternary stereocenter were unsuccessful.<sup>31</sup> A variety of Lewis acids commonly employed in this transformation (see inset, Scheme 23) resulted in decomposition of substrate **145** via ring-opening of the tetrahydrofuran C-ring. We hypothesize that the two methoxymethyl ether substituents create a binding pocket capable of chelating the Lewis acids in the vicinity of the tetrahydrofuran ring, thereby promoting its ring-opening. Attempts to simply exchange the protecting groups were unsuccessful.

This result motivated us to formulate a different approach to construct the C10 quaternary stereocenter.

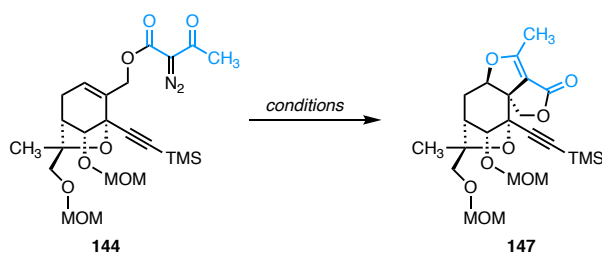
Based on our difficulties in the semipinacol approach, an alternative strategy based on a cyclopropanation of the C9–C10 olefin was devised. We envisioned elaborating the possible cyclopropane intermediate via a decarboxylation and a subsequent cyclopropane ring-opening to liberate the C10 stereocenter, which would also introduce a C8–C9 olefin handle for future oxidation (Scheme 24).



**Scheme 24.** Synthesis of the vinylogous carbonate **147**.

Accordingly, the  $\alpha$ -diazo- $\beta$ -ketoester **144** was prepared by treatment of the allylic alcohol **143** with diketene in the presence of DMAP, followed by a diazo transfer ((4-acetamido)benzenesulfonyl azide, triethylamine; 93% over two steps). Thermolysis of the  $\alpha$ -diazo- $\beta$ -ketoester **144** in the presence of bis(*N*-(*tert*-butyl)salicylaldiminato)copper did not, however, provide the expected product. Instead we isolated the vinylogous carbonate **147**, which arises from formal [3+2] addition of a carbenoid to the alkene (40%, Scheme

24). The structure of the vinylogous carbonate intermediate **147**, including complete relative stereochemistry, was unambiguously confirmed by X-ray analysis. While not the anticipated product, we recognized that this transformation served to simultaneously introduce the C10 quaternary stereocenter and the C9 oxidation of the target in a single step. Accordingly, we conducted a thorough optimization of reaction conditions to improve the yield of this transformation, as summarized in Table 2.

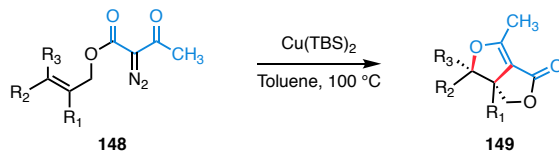


entry	catalyst	solvent	T	Yield of <b>147</b> (%) <sup>b</sup>
1	Cu(OTf) <sub>2</sub>	DCE	50 °C	nd <sup>c</sup>
2	Rh <sub>2</sub> (OAc) <sub>4</sub>	CH <sub>2</sub> Cl <sub>2</sub>	23 °C	nd
3	Rh <sub>2</sub> (esp) <sub>2</sub>	CH <sub>2</sub> Cl <sub>2</sub>	23 °C	nd
4	Cu(TBS) <sub>2</sub>	PhCH <sub>3</sub>	110 °C	40%
5	Cu(TBS) <sub>2</sub>	PhCH <sub>3</sub> <sup>d</sup>	100 °C	67%
6	Cu(TBS) <sub>2</sub>	PhCH <sub>3</sub> <sup>d,e</sup>	100 °C	83%
7	Cu(TBS) <sub>2</sub>	PhCH <sub>3</sub> <sup>d,e,f</sup>	100 °C	78%

**Table 2.** Optimization of the [3+2] cyclization reaction. <sup>a</sup>Conditions: (30 mol%) catalyst loading, [**144**] = 0.10 M. <sup>b</sup>Isolated yields following purification by flash-column chromatography. <sup>c</sup>None detected. <sup>d</sup>Reaction concentration lowered: [**144**] = 0.02M. <sup>e</sup>Solvent was deoxygenated by sparging with argon for 1h. <sup>f</sup>Reaction done on a 3.0g scale.

We observed no product formation when we treated the  $\alpha$ -diazo- $\beta$ -ketoester **144** with dirhodium tetraacetate, copper triflate, or  $\text{Rh}_2(\text{esp})_2$  as the catalysts (entries 1–3). Only the product of hydrodediazotization was observed. The yield of product **147** increased to 67% when the reaction concentration was decreased from 0.10 M to 0.02 M and the reaction temperature was lowered to 100 °C (entry 5). Deoxygenation of the solvent (toluene) by sparging with argon increased the yield to 83% (entry 6). Comparable yields were obtained when the reaction was conducted on a 3.0g scale (78%, entry 7).

To the best of our knowledge, related [3+2] cycloadditions have only been observed when heteroatom-substituted alkenes, such as alkyl enol ether or furans, are employed.<sup>32,32a</sup> Accordingly, we sought to probe the scope of this transformation (Table 3). Several derivatives of **147** transformed smoothly to [3+2] cycloaddition products in comparable yield (entries 1–5, 63–86%). The terminal acetylene **160** did not convert to product, presumably due to competitive interaction of the alkyne with the copper catalyst (entry 6). The perillaldehyde derivative **162**, which lacks the bicyclic structure the dihydro- $\beta$ -agarofuran scaffold, transformed to a complex mixture of products (entry 7). The pinene derivative **164** provided the expected cycloaddition product **165** (23%) as well as the corresponding cyclopropane **165a** (54%, entry 8).

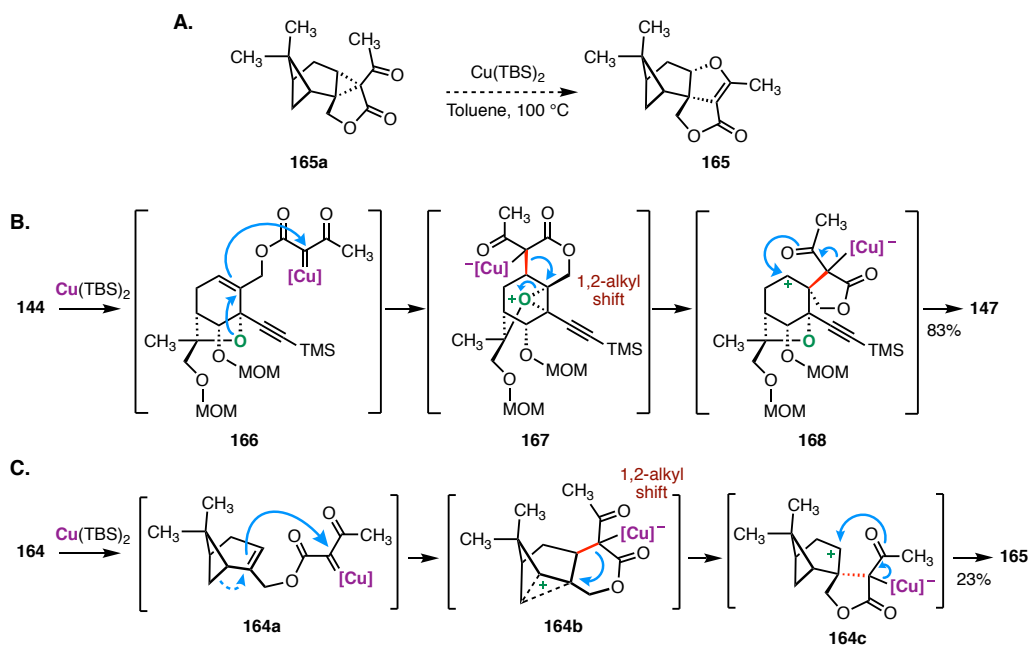


Entry	Substrate	Product	Yield <sup>b</sup>	Entry	Substrate	Product	Yield
1			75%	5			81%
2			86%	6			nd <sup>c</sup>
3			77%	7			nd <sup>c</sup>
4			63%	8			23% <sup>d,f</sup>

**Table 3.** Scope of the [3+2] cycloaddition reaction of allylic alcohols. <sup>a</sup>Conditions: (30 mol%), toluene solvent was deoxygenated by sparging with argon for 1h, 100 °C. <sup>b</sup>Isolated yields following purification by flash-column chromatography. <sup>c</sup>None detected. <sup>d</sup>Yield determined by <sup>1</sup>H NMR analysis of the unpurified reaction mixture. <sup>f</sup>The corresponding cyclopropane **165a** was obtained in 54%.

We hypothesized that this reaction may proceed by rearrangement of a cyclopropanation product. However, the pinene-derived cyclopropane **165a** did not convert to the [3+2] cycloaddition product when resubjected to the reaction conditions

(Scheme 25A). Based on these results as well as the existing literature, we reasoned that the [3+2] cycloaddition product may arise from a pathway that involves participation of the tetrahydrofuran oxygen (Scheme 25B). Specifically, we suggest that the product is generated by formation of an electrophilic carbenoid **166**, followed by addition of the alkene with participation of the tetrahydrofuran oxygen, to form the oxonium ion **167** (Scheme 25B). Next, a 1,2-alkyl shift is accompanied by trapping with the carbonyl oxygen and elimination of the copper catalyst to generate the cyclization product. In the case of the pinene-derived substrate **164**, we suggest that a non-classical cation<sup>33</sup> is formed (instead of an oxonium ion) leading to a parallel mechanistic pathway (Scheme 25C). The reduced electron-donating ability of the carbon-carbon bond in **164** vs. the oxygen lone pair in the more complex substrates would explain why some of the cyclopropane was observed in the transformation of **164**.

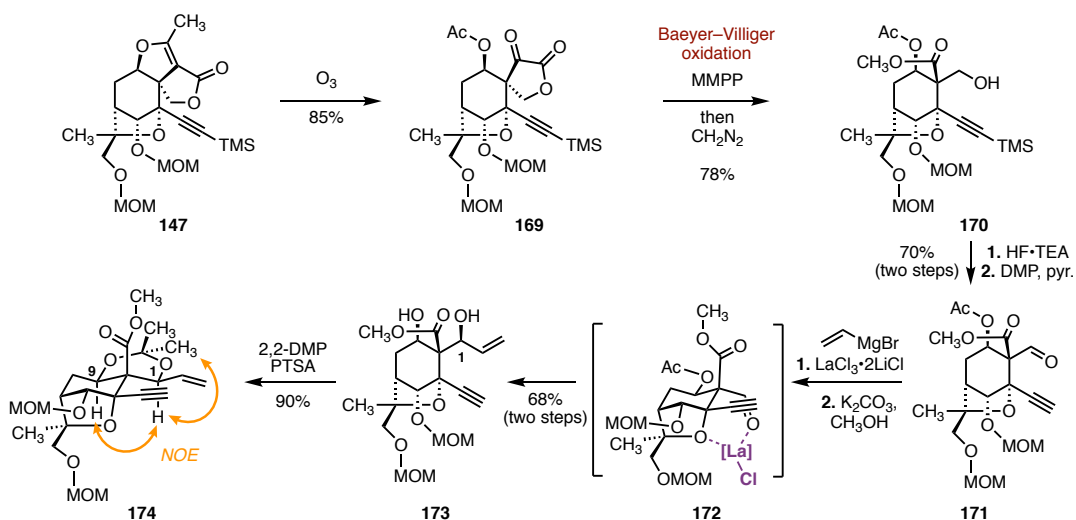


**Scheme 25.** A. Attempted conversion of the cyclopropane **165a** to the cycloaddition product **165**. B. Proposed mechanism for the formation of the vinylogous carbonate **147**.



C. Proposed mechanism for the formation of the vinylogous carbonate **165** from the pinene derivative **164**.

The vinylogous carbonate **147** was advanced by the pathway shown in Scheme 26. Oxidative cleavage of **147** (ozone) provided the  $\alpha$ -ketolactone **169** (85%). Baeyer–Villiger oxidation of **169** using magnesium monoperoxyphthalate (MMPP) followed by hydrolytic ring-opening proceeded smoothly to generate a corresponding carboxylic acid intermediate (not shown) that was esterified with diazomethane to generate the methyl ester **170** (78%). Next, removal of alkynyl silane (hydrogen fluoride–triethylamine complex) and oxidation of the primary alcohol (DMP, pyridine) generated the aldehyde **171** (70%, two steps).

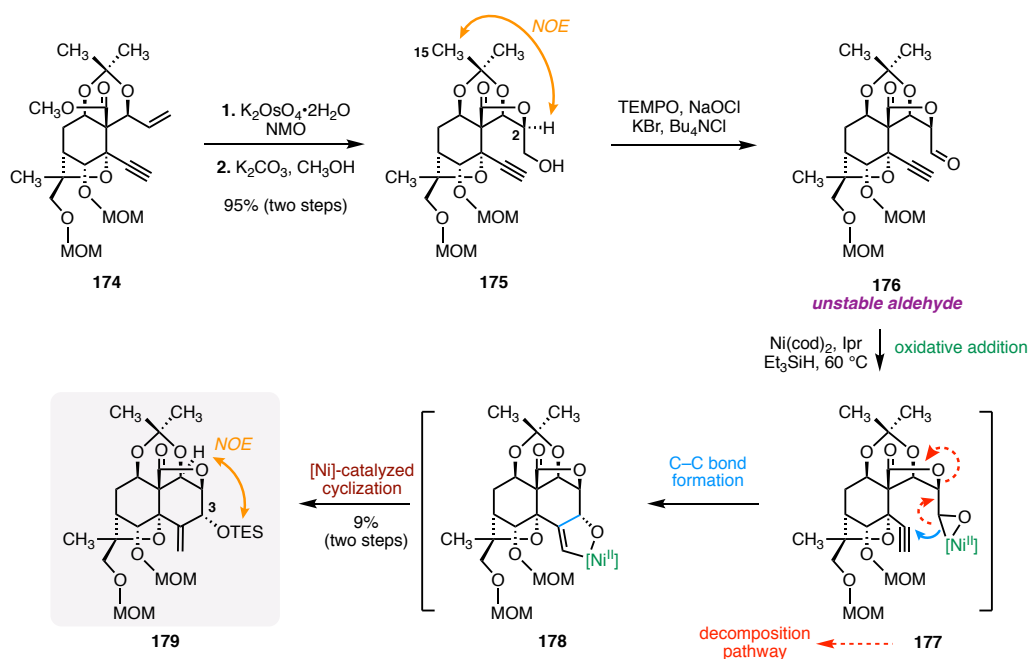


**Scheme 26.** Synthesis of the tetracyclic acetone **174** from **147**.

The addition of vinylmagnesium bromide to the aldehyde **171** in the presence of lanthanum chloride–lithium chloride<sup>34</sup> provided, after cleavage of the acetate ester, the allylic alcohol **173** in 68% yield (3.1:1 dr,  $^1H$  NMR analysis). Protection of the 1,3-diol

(PTSA, 2,2-dimethoxypropane, 90%) gave the tetracyclic acetonide **174**. An NOE analysis established that the C1 center possessed the desired (*S*)-configuration (see orange arrows, Scheme 26). We speculate that the addition proceeds via formation of the chelate **172**, which guides the nucleophile to the less-hindered  $\alpha$ -face of the molecule, to yield the desired C1 stereochemistry.

To synthesis of the cyclization precursor **136** was completed by the pathway shown in Scheme 27. Dihydroxylation of the acetonide **174** (osmium tetroxide, *N*-methylmorpholine *N*-oxide) provided the vicinal diol as a single detectable diastereomer ( $^1\text{H}$  NMR analysis) that upon exposure to potassium carbonate in methanol underwent a selective lactonization reaction to produce the lactone **175** (95%, two steps). The relative stereochemistry of **175** was determined by NOE correlations between the C2 methine proton and the C15 methyl substituent supporting the stereochemical assignment shown.



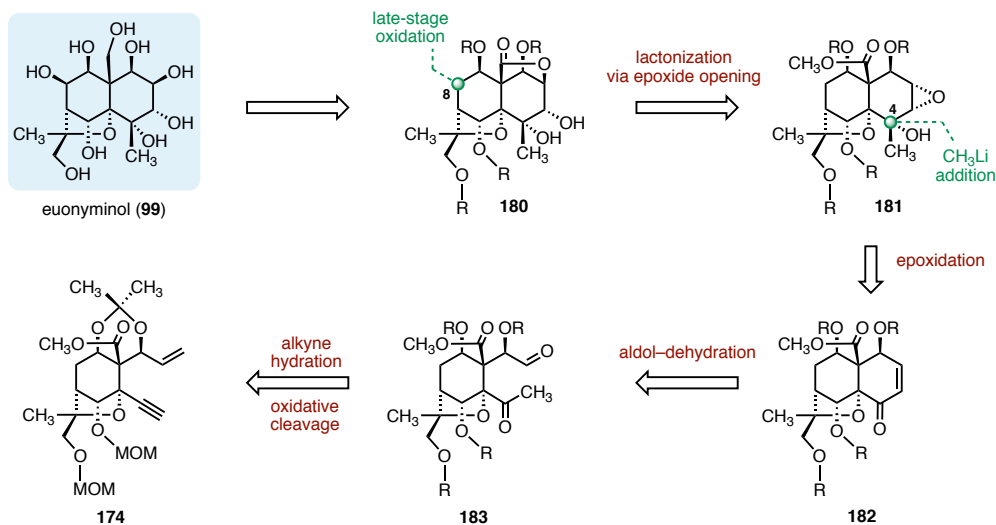
**Scheme 27.** Synthesis of the exocyclic olefin **179**.

Oxidation of the primary alcohol (TEMPO, sodium hypochlorite, potassium bromide, tetrabutylammonium chloride) generated the aldehyde **176**.<sup>35</sup> Because the aldehyde was unstable toward all purification conditions examined (flash-column chromatography, PTLC) and was also found to undergo appreciable decomposition at room temperature within 2 h in various solvents, it was used without purification in the ensuing reductive cyclization. Reductive cyclization of **176** under conditions developed by Montgomery and co-workers<sup>29,36</sup> (nickel bis(1,4-cyclooctadiene), 1,3-bis(2,6-diisopropylphenyl)-1,3-dihydro-2H-imidazol-2-ylidene, and triethylsilane) provided the desired exocyclic olefin **179** in 9% along with a large number of unidentified decomposition products (as determined by <sup>1</sup>H NMR analysis of the unpurified product mixture). The instability of the aldehyde **176** prevented us from characterizing these products in detail. However, we speculate that the decomposition derives from the lactone-opening pathway highlighted in red arrows in Scheme 27. Moreover, a comprehensive search of the literature did not reveal any  $\alpha$ -oxygen-substituted aldehyde as substrates in related cyclization reactions. Even though the olefin **179** closely resembles the natural product, we were unable to improve the yield of this intermediate and were forced to adjust our synthetic strategy accordingly.

#### **2.4.2 Synthesis of the lactone 197 by an aldol–dehydration strategy.**

Our second retrosynthetic analysis is summarized in Scheme 28. In this approach, we envisioned accessing the target from the lactone **180** via late-stage oxidation at C8, as discussed above. We then anticipated accessing the lactone **180** from the epoxide **181** by cleavage of the methyl ester and a subsequent lactonization via epoxide-opening. The

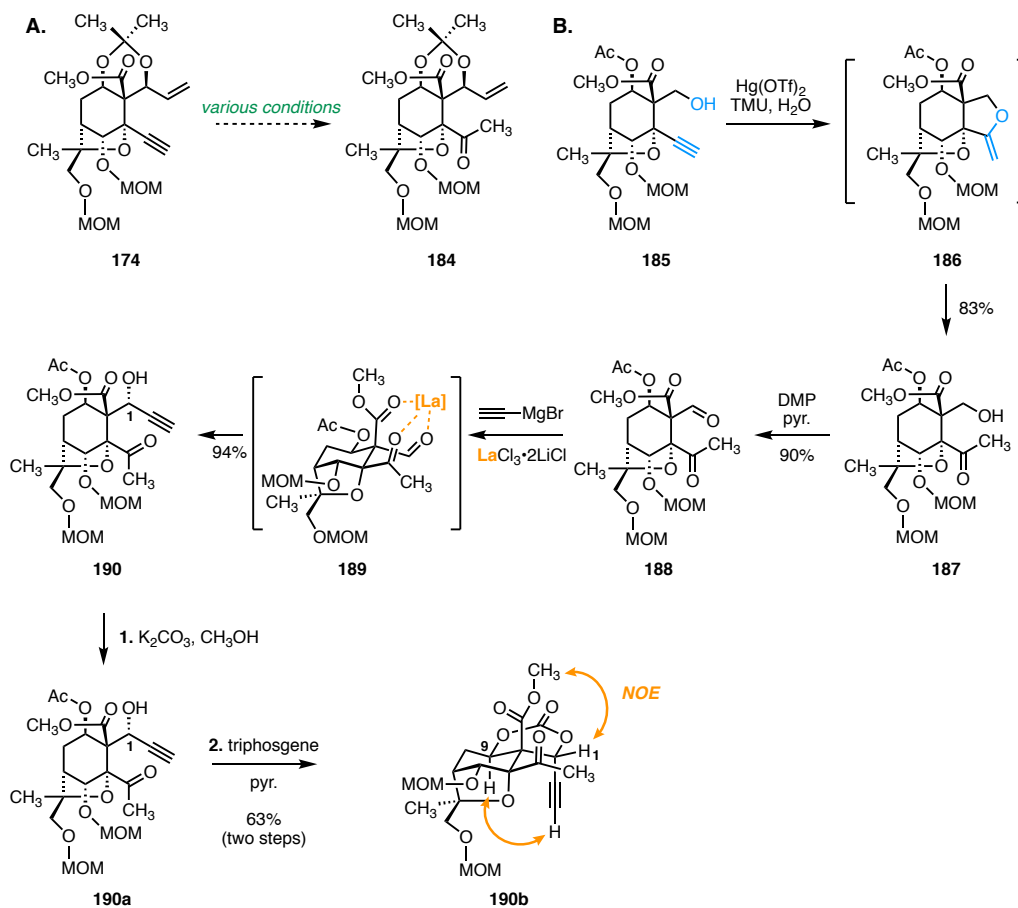
intermediate **181** was simplified retrosynthetically to the unsaturated ketone **182**, via a diastereoselective 1,2-addition of methyl lithium, followed by epoxidation. Further simplification of **182** via an aldol–dehydration revealed the ketoaldehyde **183**, which in turn could be prepared by hydration of the acetonide **174**, followed by oxidative cleavage.



**Scheme 28.** Alternative retrosynthetic analysis of (-)-euonyminol (**99**)

Hydration of the alkyne within **174** proved challenging (Scheme 28A). A survey of conditions employing mercury or gold catalysts failed to yield any of the desired methyl ketone ( $^1\text{H}$  NMR and LC/MS analysis).<sup>36a</sup> In most instances, the need for strongly acid conditions resulted in decomposition of the starting material or in a deprotection of the acid-labile methoxymethyl ether protecting groups. Fortunately, we found that the primary alcohol (**185**, derived from the methyl ester **170**) underwent smooth hydration using mercury triflate and tetramethylurea as promoters, to provide the Markovnikov-selective hydration product **187** (83%).<sup>37</sup> We speculate that this successful hydration proceeds via an intramolecular attack of the primary alcohol on the activated alkyne, to form the vinyl

ether **186**, which under the reaction conditions further hydrolyzes to the methyl ketone product.

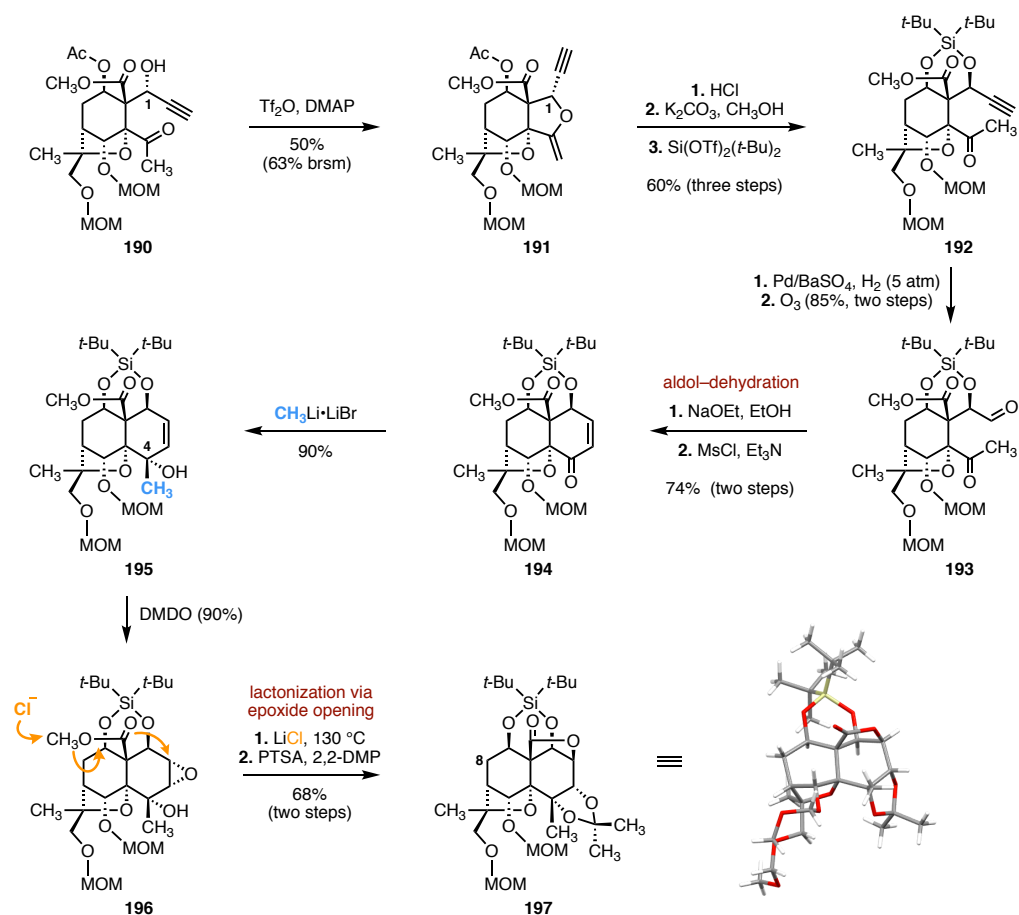


**Scheme 29.** A. Unsuccessful alkyne hydration of **174**. B. Synthesis of the propargylic alcohol **190** via alkyne hydration of the primary alcohol **185**.

Oxidation of the alcohol (DMP, pyridine) then gave the aldehyde **188** (90%). Nucleophilic additions to the hindered aldehyde **188** also proved challenging. It was discovered that the addition proceeded only with ethynylmagnesium bromide in the presence of lanthanum chloride–lithium chloride<sup>34</sup> additive, to give the propargylic alcohol **190** in 94% yield as a single detectable diastereomer (<sup>1</sup>H NMR analysis of unpurified reaction mixture). The C1 configuration of the addition product **190** was determined by

conversion of the propargylic alcohol **190** to the rigidified cyclic carbonate **190b** in two steps. Conclusive NOE correlations of **190b** shown in Scheme 29 supported the relative configuration shown. We hypothesize that the stereoselectivity arises from addition of the acetylide to the  $\alpha$ -face of the chelated structure **189**. Extensive efforts to alter the stereoselectivity, for example, by employing alternative nucleophiles such as vinyl lithium, vinylmagnesium bromide, or dithiane, were all uniformly unsuccessful and did not result in productive addition to the sterically encumbered neopentyl aldehyde. When trimethylsilylcyanide was used as the nucleophile, we observed formation of 3:1 mixture of addition diastereomers in 64% combined yield. However, all of our attempts to advance or determine the stereochemistry of this addition product suffered from a facile retro-Aldol elimination of the cyanide.

We found that the C1 configuration could be inverted by treatment of **190** with trifluoromethanesulfonic anhydride and DMAP, which provided the vinyl ether **191** in 50% (63% yield based on recovered starting material; Scheme 30) This transformation likely proceeds via an intramolecular displacement of a transient C1 triflate with the oxygen of the methyl ketone moiety. Despite this moderate yield, this inversion strategy was singularly successful among a large range of conditions surveyed, such as oxidation/reduction or Mitsunobu inversion.



**Scheme 30.** Synthesis of the lactone **197** via aldol–dehydration reaction of the ketoaldehyde **193**.

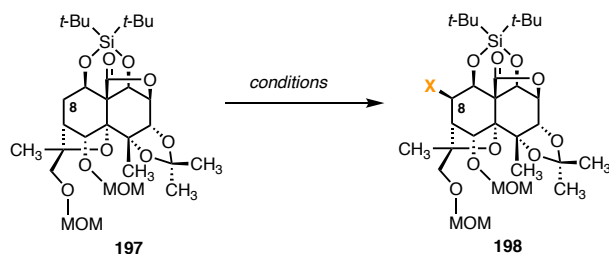
The vinyl ether **191** was elaborated to the tricyclic **192** via a three-step sequence comprising hydrolytic opening of the vinyl ether (hydrochloric acid), removal of the acetate ester (potassium carbonate, methanol), and silylene ether formation (di-*tert*-butylsilyl ditrifluoromethanesulfonate; 60%, three steps; Scheme 29). Partial hydrogenation of the alkyne (palladium–barium sulfonate, dihydrogen) and ozonolysis of the resulting alkene then formed the ketoaldehyde **193** (85%, two steps). We found that exposure of the ketoaldehyde **193** to a freshly prepared sodium ethoxide in ethanol gave the expected aldol addition product (not shown); activation of the alcohol with methanesulfonyl chloride and

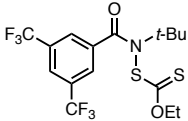
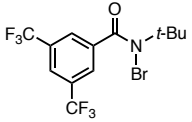
triethylamine provided the unsaturated ketone **194** (74%, two steps). The addition of methyllithium to the C4 ketone within **194** proceeded with 9:1 diastereoselectivity (<sup>1</sup>H NMR analysis) to provide the tertiary alcohol **195** (90%) as well as its separable C4 diastereomer. Oxidation of the allylic alcohol **195** (dimethyldioxirane) proceeded smoothly to afford the epoxide **196** as a single detectable diastereomer (<sup>1</sup>H NMR analysis). The relative stereochemistry of **196** was determined by X-ray analysis (vide infra). Heating of this epoxide **196** with lithium chloride in DMF at 130 °C effected dealkylation of the ester with concomitant epoxide opening–lactonization, to provide a C3–C4 vicinal diol (not shown). Protection of the C3–C4 diol (PTSA, 2,2-dimethoxypropane) generated the crystalline lactone **197** (68%, two steps).

### 2.4.3 Completion of the synthesis of (–)-euonyminol.

The lactone **197** contains all of the carbon atoms of (–)-euonyminol (**99**) and only lacks a single oxidation at the C8 position on the A-ring. We envisioned installing this hydroxyl equivalent via an intermolecular or a directed C–H oxidation.<sup>38-43</sup> Our attempts to achieve this oxidation are shown in Table 4. Unfortunately, all of these conditions were unsuccessful. Many of the attempted transformations only returned the unreacted starting material (entries 4–6) or provided products of oxidative cleavage of the primary methoxymethyl ether group, without detectable (<sup>1</sup>H NMR and LC/MS analysis) oxidation at C8 (entries 1–2). We anticipated that we would be able to reduce the lactone to reveal a primary hydroxyl group, which could be used in a directed oxidation.<sup>44</sup> Unfortunately, efforts to reduce this lactone were not successful, likely due to the substantial steric crowding arising from the neighboring silylene acetal.



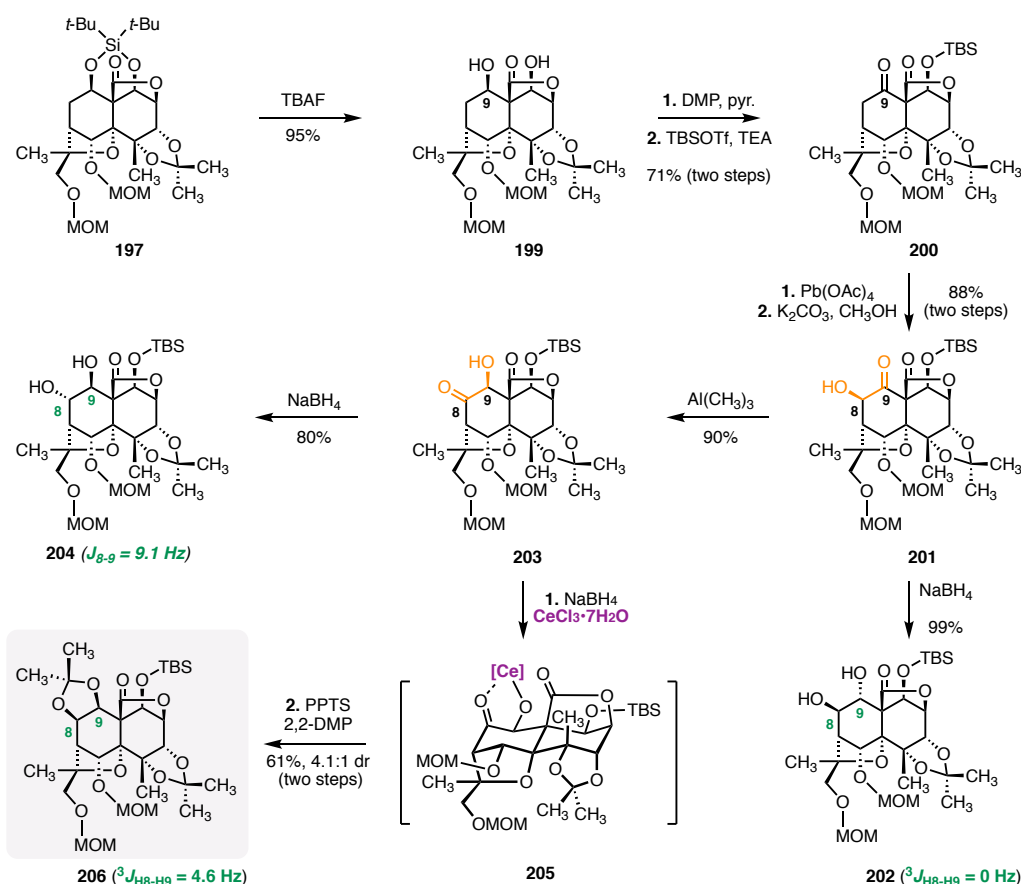


entry	conditions	results
1.	Fe( <i>S,S</i> -PDP), H <sub>2</sub> O <sub>2</sub>	oxidation of the MOM residues, then decomposition
2.	Fe( <i>R,R</i> -PDP), H <sub>2</sub> O <sub>2</sub>	oxidation of the primary MOM residue to the corresponding formate, then decomposition
3.	TFDO	complex mixture
4.	DMDO	no reaction
5.	 , blue LED	no reaction
6.	 , visible light	no reaction

**Table 4.** Conditions evaluated for the late-stage C8 oxidation of the lactone **197**.

In light of these difficulties, we devised an alternative strategy to introduce the remaining oxygen (Scheme 31). Removal of the silylene ether protecting group (TBAF, 95%), followed by site-selective oxidation of the C9 hydroxyl group (DMP, pyridine), and silylation of the remaining C1 hydroxyl group at C1 (TBSOTf, triethylamine) provided the ketone **200** (71%, two steps).  $\alpha$ -Acetoxylation of **200** (lead tetraacetate) provided an  $\alpha$ -acetoxyketone (not shown) as a single detectable diastereomer (<sup>1</sup>H NMR analysis). Cleavage of the acetate ester (potassium carbonate, methanol) provided the  $\alpha$ -hydroxyketone **201** (88%, two steps). Reduction of the C9 ketone within **201** delivered

exclusively the undesired C8–C9 *trans*-diol, under a large range of conditions. For example, treatment of **201** with sodium borohydride in methanol provided the unproductive *anti*-vicinal diol **202** in 99% yield. The stereochemistry of the reduction product was readily determined by analysis of the  $^3J_{\text{H8-H9}}$  coupling constant (0 Hz). Identical results were obtained with additional reductants such as di-*iso*-butylaluminum hydride, lithium aluminum hydride, or Superhydride.



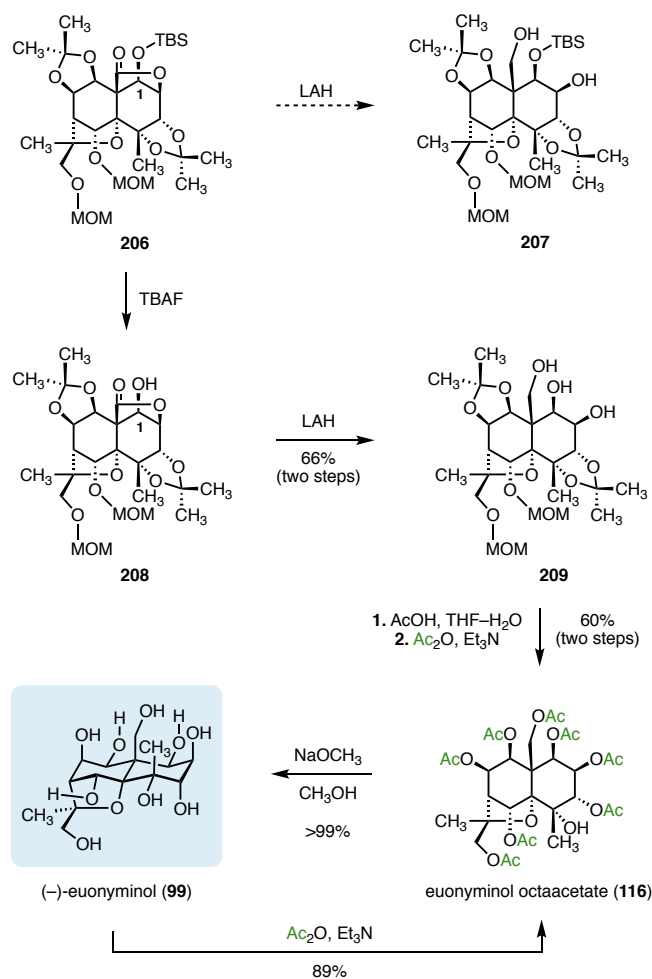
**Scheme 31.** Synthesis of the bis(acetonide) **203** from the lactone **197**.

Due to the problematic C9 reduction, we implemented an  $\alpha$ -ketol rearrangement, as first reported by White and co-workers<sup>24</sup> on a similar substrate. Treatment of the  $\alpha$ -

hydroxyketone **201** with trimethylaluminum provided the isomeric  $\alpha$ -hydroxyketone **203** (90%) as a single detectable diastereomer ( $^1\text{H}$  NMR analysis). The stereochemical configuration of the C9 hydroxyl group was determined by NOE correlations between the C13 methyl substituent and the C8 methine proton. Reduction of the transposed intermediate **203** with sodium borohydride in methanol gave the *anti*-vicinal diol **204** in 80% yield and 8:1 dr ( $^1\text{H}$  NMR analysis). The stereochemistry of this reduction product was readily determined by analysis of the  $^3J_{\text{H8-H9}}$  (9.1 Hz) which is consistent with the *anti*-stereochemical assignment shown. Fortunately, we found that the addition of cerium chloride heptahydrate<sup>45</sup> to this sodium borohydride reduction led to a reversal of the diastereoselectivity and preferential formation of the *syn*-C8–C9 diol stereochemistry (4.1:1 dr,  $^1\text{H}$  NMR analysis). We found that the diol intermediate (not shown) rapidly underwent translactonization upon exposure to acidic or basic conditions. Consequently we treated the unpurified diol with PTSA and 2,2-dimethoxypropane to generate the bis(acetonide) **206**, which was stable toward purification (61%, two steps).

The synthesis of (–)-euonyminol (**99**) was completed by the pathway shown in Scheme 32. Our attempts to reduce the lactone in the presence of the C1 silyl ether group were met with failure, again likely due to the steric congestion introduced by the acetonide and the silyl ether groups. Therefore, we first treated **206** with TBAF, to generate the lactone **208**. Treatment of **208** with excess of lithium aluminum hydride afforded the fully reduced triol intermediate **209** (66% yield, two steps). Finally, removal of all of the acid-labile protecting groups was accomplished by heating the triol **209** to 80 °C in aqueous acetic acid. Because of the very high polarity of (–)-euonyminol (**99**), we subjected the

unpurified product to exhaustive acylation (acetic anhydride), to generate the euonyminol octaacetate (**116**), which could be purified using normal phase chromatography. The sample obtained in this way was analytically pure and its spectroscopic data precisely matched natural euonyminol octaacetate (**116**) reported in the literature by Hirata and co-workers (see Table S2 and Table S3).<sup>23</sup> Removal of the eight acetate residues (sodium methoxide, methanol) then provided (–)-euonyminol (**99**), estimated to be >95% pure by <sup>1</sup>H NMR analysis (99%).<sup>46</sup>



**Scheme 32.** Completion of the synthesis of (–)-euonyminol (**99**).

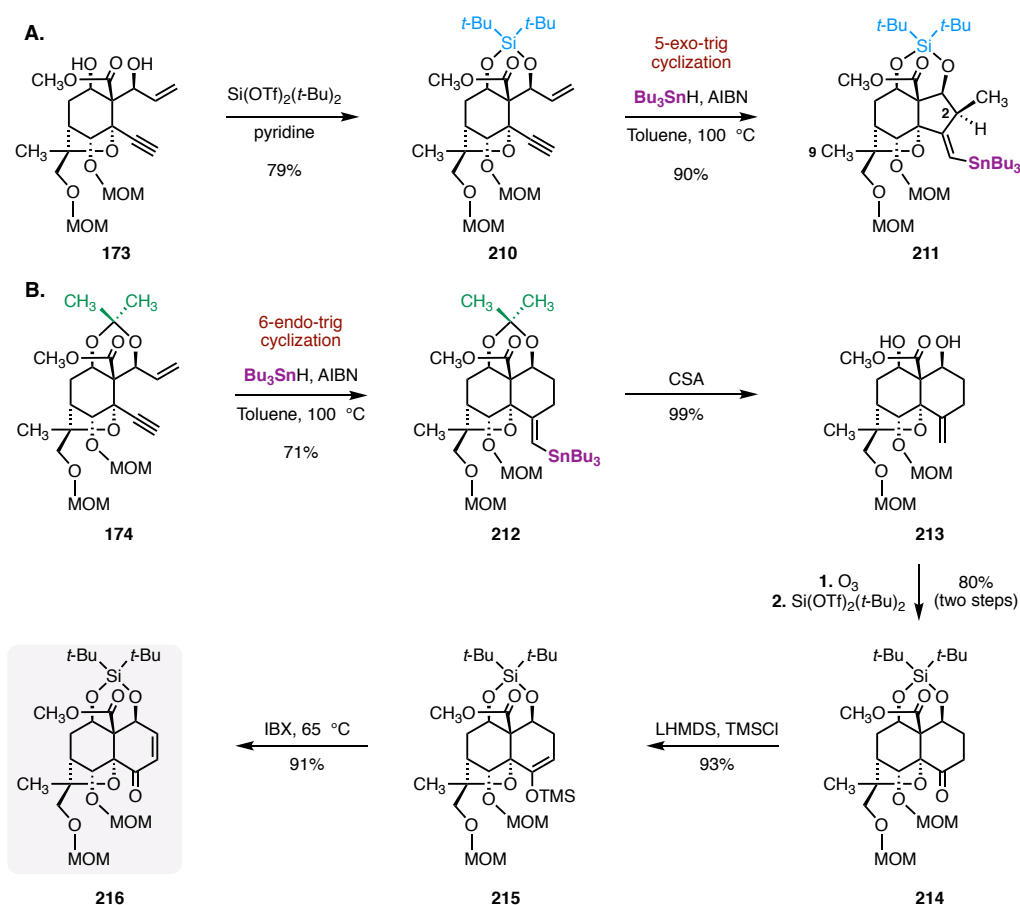
To the best of our knowledge, spectroscopic data for natural (–)-euonyminol (**99**) were not disclosed by the isolation chemists or published in the literature. White and co-workers provided <sup>1</sup>H NMR chemical shifts for synthetic (±)-euonyminol in deuterium oxide.<sup>25</sup> <sup>1</sup>H NMR spectroscopic data for our synthetic (–)-euonyminol (**99**) in the same solvent did not perfectly match the data reported by White and co-workers (see Table S4). The basis for this discrepancy is not known; however, White and co-workers failed to produce graphical representation of their <sup>1</sup>H NMR spectrum and they also did not disclose <sup>13</sup>C chemical shifts for their synthetic compound. They also acquired their data on <1 mg of material, which may render the NMR shifts sensitive to impurities.

To rigorously confirm we had indeed synthesized (–)-euonyminol (**99**), the synthetic material was reacylated (89%). The octaacetate **116** obtained in this way provided spectroscopic data that was indistinguishable from our earlier sample or from the data in the literature. This result indicates that no unexpected transformations or rearrangements had occurred in the original deacetylation step. We obtained complete NMR spectroscopic data for (–)-euonyminol (**99**) in deuterium oxide and methanol-*d*<sub>4</sub>, which we believe will be of use to future synthetic research in this area.

#### **2.4.4 Improved synthesis of the unsaturated ketone **216** via a 6-*endo*-trig radical cyclization.**

The synthesis of (–)-euonyminol (**99**) that we developed suffers from some limitations that make its adaptation to the cathedulins challenging. Specifically, the most significant bottleneck of our synthesis corresponds to the inversion of stereochemistry at

the C1 (see 190→191, Scheme 30). This reaction proceeds in 50% yield. As discussed in section 2.4.2, we were unable to overcome the preferential sense of the nucleophilic addition to the aldehyde **188** with various nucleophiles and were forced to proceed with this inversion strategy.



**Scheme 33.** **A.** Synthesis of **211** via 5-*exo*-trig cyclization. **B.** Improved synthesis of the unsaturated ketone **194** from the acetonide **174** via a 6-*endo*-trig radical cyclization.

To identify an alternative approach, we revisited the enyne intermediate **173**, which possesses the correct stereochemistry at C1. Previously, we were forced to abandon this intermediate because we were unable to hydrolyze the hindered neopentyl alkyne to the methyl ketone needed for the ring-closing aldol–dehydration sequence. We evaluated this

compound in an alternative ring-closing free-radical cyclization (Scheme 33). To this end, the 1,3-diol of **173** was protected as the silylene ether (di-*tert*-butylsilyl ditrifluoromethanesulfonate) to generate **210** (79%). Heating of **210** with tri-*n*-butyltin hydride and AIBN provided exclusively the 5-*exo*-trig-cyclization product **211** (90%, Scheme 33A). We believed that we could change the outcome of this radical cyclization to favor the desired 6-membered ring formation by varying the 1,3-diol protecting group. We found that the acetonide **174** underwent 6-*endo*-trig cyclization preferentially, to provide **212**, under identical conditions (tri-*n*-butyltin hydride, AIBN; 71%, Scheme 33B). Computational studies aiming to elucidate the exact reasoning behind the shift from 5-*exo*-trig to 6-*endo*-trig are currently ongoing by the Batista research group. We speculate that the differences in bond lengths between carbon–oxygen and carbon–silicon bonds influence the selectivity in the ring closure, but further studies are required to fully understand the different reaction outcomes.

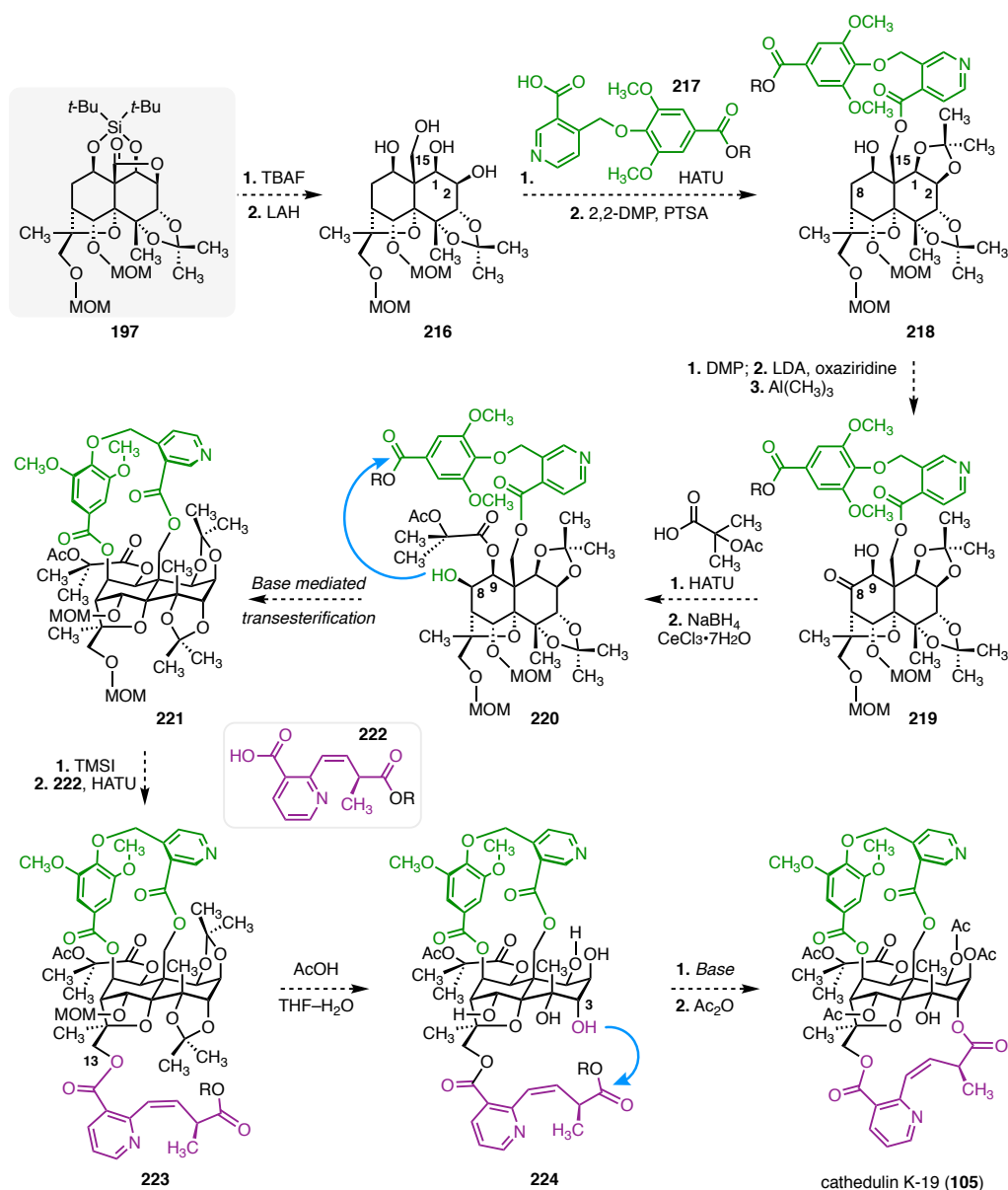
Protodestannylation of the vinyl stannane **212** with accompanying removal of the acetonide protecting group (camphorsulfonic acid) provided the exocyclic olefin **213** (99%). Ozonolysis and silylene ether formation proceeded uneventfully to generate the ketone **214** (80%, two steps). A two-step sequence comprising enoxysilane formation (LiHMDS, TMSCl, 93%) and oxidation<sup>47</sup> (2-iodobenzoic acid, 91%) then provided the unsaturated ketone **194**, that can be advanced to the natural product. This alternative synthesis of the unsaturated ketone **194** avoids the low-yielding stereochemical inversion at C1 and also nearly doubles the overall yield from the primary alcohol **170** to **194** (21.7% vs 12.7%), thereby expediting the material throughput and shortening the synthetic step count.

#### 2.4.5 Application of the synthetic strategy towards the macrocyclic cathedulin alkaloids.

As stated above, it is our desire to apply the developed synthetic strategy towards the synthesis of the cathedulin alkaloids. Our current synthetic plan towards the cathedulin K-19 (**105**) is shown in Scheme 34. Beginning with the lactone **197**, removal of the silylene ether group (TBAF) followed by a reduction of the lactone (lithium aluminum hydride) will provide the tetraol **216**. Selective esterification of the C15 primary hydroxyl group with the evioninic acid derivative **217** and protection of the *syn*-1,2 diol as an acetonide would provide the bis(acetonide) **218**. Similar to the euonyminol sequence, we propose to install the C8 hydroxyl group via an  $\alpha$ -oxidation reaction followed by a trimethyl aluminum mediated rearrangement and reduction, to obtain the ketone **219**. Installation of the methyl 2-acetoxypropanoate and a cerium chloride mediated sodium borohydride reduction will then give **220**.

We plan to access the top macrocycle via a base mediated lactonization to arrive at **221**. Next, we propose to selectively remove the primary methoxy methyl ether group (trimethylsilyl iodide) and esterify the C13 primary hydroxyl with the cathic acid derivative **222**, to generate **223**. Deprotection of all of the acid labile protecting groups with aqueous acetic acid is expected to then generate the shown pentaol **224**. Finally, a second base-mediated lactonization reaction between the C3 axial hydroxyl and the cathic acid would complete the lower-rim macrocycle and subsequent exposure of this intermediate to excess acetic anhydride will provide the cathedulin K-19 (**105**).





**Scheme 34.** Application of the synthetic strategy towards the synthesis of the macrocyclic cathedulin K-19 (**105**).

## 2.5 Conclusion.

In this chapter, I described the development of our enantioselective total synthesis of the nonhydroxylated natural product (–)-euonyminol (**99**). Our strategy began with the readily-available carvone derivative **139** and featured several transformations that were

specifically developed to overcome challenges met in the synthesis. These include a novel oxyalkylation reaction of an allylic alcohol that established the C10 quaternary stereocenter along with the oxidation state of the neighboring carbon. We also developed a tandem lactonization–epoxide opening reaction to form the *trans*-C2–C3 vicinal diol residue as well as a highly diastereoselective late-stage  $\alpha$ -ketol rearrangement, which was essential to establish the correct stereochemistry at the C8 position. I presented an unpublished radical cyclization approach that provides the tricyclic framework of the target from the enyne **174**. Successful implementation of this reaction nearly doubled the overall yield through the middle steps of the synthesis and avoided the problematic stereochemical inversion of the C1 alcohol. Finally, I described the application of this synthetic strategy toward the macrocyclic cathedulin alkaloids.

## 2.6 Experimental section.

### 2.6.1 General information.

**General experimental procedures.** All reactions were performed in single-neck, flame-dried, round-bottomed flasks fitted with rubber septa under a positive pressure of argon unless otherwise noted. Air- and moisture-sensitive liquids were transferred via syringe or stainless steel cannula, or were handled in a nitrogen-filled drybox (working oxygen level <10 ppm). Organic solutions were concentrated by rotary evaporation at 28–32 °C. Flash-column chromatography was performed as described by Still et al.,<sup>48</sup> employing silica gel ('SiliaFlash® P60', 60 Å, 40–63 µm particle size) purchased from SiliCycle (Québec, Canada). Analytical thin-layered chromatography (TLC) was performed using glass plates pre-coated with silica gel (250 µm, 60 Å pore size) impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light (UV) and/or submersion in aqueous ceric ammonium molybdate solution (CAM), *para*-anisaldehyde (PAA), or aqueous potassium permanganate solution (KMnO<sub>4</sub>), followed by brief heating on a hot plate (120 °C, 10–15 s).

**Materials.** Commercial solvents and reagents were used as received with the following exceptions. Dichloromethane, diethyl ether (ether), *N,N*-dimethylformamide, tetrahydrofuran, and toluene were purified according to the method of Pangborn et al.<sup>49</sup> Pyridine was distilled from calcium hydride under an atmosphere of nitrogen immediately prior to use. Triethylamine was distilled from calcium hydride immediately prior to use. Di-*iso*-propylethylamine was distilled from calcium hydride and stored in a round-bottomed flask fused to a Teflon-coated valve under an atmosphere of argon. The

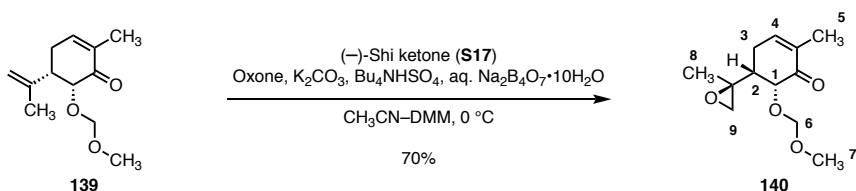
molarities of *n*-butyllithium, ethynylmagnesium bromide, and methyllithium lithium bromide solutions were determined by titration against a standard solution of menthol and 1,10-phenanthroline in tetrahydrofuran (average of three determinations).<sup>50</sup> Bis (*N*-*tert*-butylsalicylaldiminato) copper (II) was prepared according to the method of Beenakker et al.<sup>51</sup> Diazomethane was prepared according to the procedure of Arndt.<sup>52</sup> Dimethyldioxirane was prepared according to the procedure of Taber et al.<sup>53</sup> Trifluoromethanesulfonic anhydride and *tert*-butyldimethylsilyl trifluoromethanesulfonate were purified by vacuum transfer distillation and stored in a round-bottomed flask fused to a Teflon-coated valve under an atmosphere of argon at  $-20\text{ }^{\circ}\text{C}$ . Compounds methoxymethyl ether **139**<sup>30</sup> and the Shi ketone (**S17**)<sup>54</sup> were prepared according to published procedures.

**Instrumentation.** Proton nuclear magnetic resonance spectra ( $^1\text{H}$  NMR) were recorded at 400, 500, or 600 megahertz (MHz) at  $23\text{ }^{\circ}\text{C}$ , unless otherwise noted. Chemical shifts are expressed in parts per million (ppm,  $\delta$  scale) downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent ( $\text{CHCl}_3$ ,  $\delta$  7.26;  $\text{C}_6\text{D}_5\text{H}$ ,  $\delta$  7.16;  $\text{CD}_2\text{HOD}$ ,  $\delta$  3.31;  $\text{DHO}$ ,  $\delta$  4.79). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and/or multiple resonances, b = broad, app = apparent), coupling constant in Hertz (Hz), integration, and assignment. Proton-decoupled carbon nuclear magnetic resonance spectra ( $^{13}\text{C}$  NMR) were recorded at 100, 125, or 150 MHz at  $23\text{ }^{\circ}\text{C}$ , unless otherwise noted. Chemical shifts are expressed in parts per million (ppm,  $\delta$  scale) downfield from tetramethylsilane and are referenced to the carbon resonances of the solvent ( $\text{CDCl}_3$ ,  $\delta$  77.0;  $\text{C}_6\text{D}_6$ ,  $\delta$  128.1;  $\text{CD}_3\text{OD}$ ,  $\delta$  49.0). Distortionless enhancement by polarization transfer [DEPT (135)], heteronuclear

single quantum coherence (HSQC), and heteronuclear multiple bond correlation (HMBC) spectra were recorded at 125 or 150 MHz at 23 °C, unless otherwise noted. <sup>13</sup>C NMR and DEPT (135)/HSQC data are combined and represented as follows: chemical shift, carbon type [obtained from DEPT (135) or HSQC experiments]. Attenuated total reflectance Fourier transform infrared (ATR-FTIR) spectra were obtained using a Thermo Electron Corporation Nicolet 6700 FTIR spectrometer referenced to a polystyrene standard. Data are represented as follows: frequency of absorption (cm<sup>-1</sup>), intensity of absorption (s = strong, m = medium, w = weak, br = broad). Analytical ultra high-performance liquid chromatography/mass spectrometry (UPLC/MS) was performed on a Waters UPLC/MS instrument equipped with a reverse-phase C<sub>18</sub> column (1.7 μm particle size, 2.1 × 50 mm), dual atmospheric pressure chemical ionization (API)/electrospray (ESI) mass spectrometry detector, and photodiode array detector. Samples were eluted with a linear gradient of 5% acetonitrile–water containing 0.1% formic acid→100% acetonitrile containing 0.1% formic acid over 0.75 min, followed by 100% acetonitrile containing 0.1% formic acid for 0.75 min, at a flow rate of 800 μL/min. High-resolution mass spectrometry (HRMS) were obtained on a Waters UPLC/HRMS instrument equipped with a dual API/ESI high-resolution mass spectrometry detector and photodiode array detector. Unless otherwise noted, samples were eluted over a reverse-phase C<sub>18</sub> column (1.7 μm particle size, 2.1 × 50 mm) with a linear gradient of 5% acetonitrile–water containing 0.1% formic acid→95% acetonitrile–water containing 0.1% formic acid for 1 min, at a flow rate of 600 μL/min. Optical rotations were measured on a Rudolph Research Analytical Autopol IV polarimeter equipped with a sodium (589 nm, D) lamp. Optical rotation data are represented as follows: specific rotation ( $[\alpha]_{\lambda}^T$ ), concentration (g/mL), and solvent.

## 2.6.2 Synthetic procedures.

### *Synthesis of the epoxide 140:*



The (–)-Shi ketone (**S17**, 12.3 g, 47.6 mmol, 1.00 equiv), a solution of sodium tetraborate decahydrate and ethylenediamine tetraacetic acid disodium salt dihydrate (EDTA–Na<sub>2</sub>) in water (50 mM in sodium tetraborate decahydrate, 400 μM in EDTA–Na<sub>2</sub>, 1.24 L) and tetrabutylammonium hydrogensulfate (3.23 g, 9.51 mmol, 0.200 equiv) were added in sequence to a solution of the unsaturated ketone **139** (10.0 g, 47.6 mmol, 1 equiv) in acetonitrile–dimethoxymethane (1:2 v/v, 950 mL) at 23 °C. The reaction mixture was then cooled to 0 °C. A solution of oxone and EDTA–Na<sub>2</sub> in water (212 mM in oxone, 400 μM in EDTA–Na<sub>2</sub>, 448 mL, 95.1 mmol, 2.00 equiv oxone) and aqueous potassium carbonate (890 mM, 428 mL, 380 mmol, 8.00 equiv) were then added dropwise simultaneously using two addition funnels over 1 h. Upon completion of the addition, the reaction mixture was stirred for 1 h at 0 °C. The product mixture was warmed to 23 °C over 1 h. The warmed product mixture was diluted sequentially with water (1.0 L) and ethyl acetate (1.0 L). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 1.0 L). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (500 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The

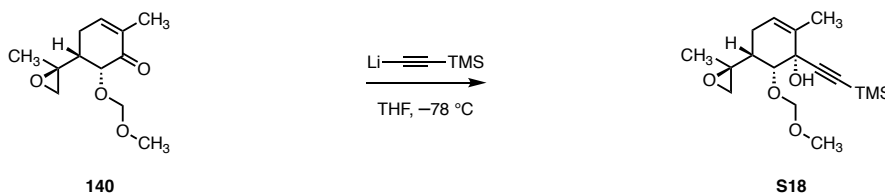
residue obtained was purified by flash-column chromatography (eluting with 10% ethyl acetate–hexanes) to provide the epoxide **140** as a yellow oil (7.50 g, 70%).

<sup>1</sup>H NMR analysis of the unpurified product mixture indicated the presence of a 2.4:1 mixture of diastereomers. The relative stereochemistry of **140** was established by X-ray analysis of the ether **141**.

R<sub>f</sub> = 0.40 (25% ethyl acetate–hexanes; UV, PAA). <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>): δ 6.70 (td, *J* = 3.4 Hz, H<sub>4</sub>, 1H), 4.75 (d, *J* = 6.7 Hz, H<sub>6a</sub>, 1H), 4.68 (d, *J* = 6.7 Hz, H<sub>6b</sub>, 1H), 4.20 (d, *J* = 3.7 Hz, H<sub>1</sub>, 1H), 3.36 (s, H<sub>7</sub>, 3H), 2.75 (d, *J* = 4.8 Hz, H<sub>9a</sub>, 1H), 2.73–2.65 (m, H<sub>3a</sub>, 1H), 2.62 (d, *J* = 4.7 Hz, H<sub>9b</sub>, 1H), 2.49–2.40 (m, H<sub>3b</sub>, 1H), 2.11 (ddd, *J* = 7.4, 5.5, 3.7 Hz, H<sub>2</sub>, 1H), 1.80 (q, *J* = 1.9 Hz, H<sub>5</sub>, 3H), 1.33 (s, H<sub>8</sub>, 3H). <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>): δ 197.2 (C), 143.6 (CH), 134.1 (C), 95.8 (CH<sub>2</sub>), 77.0 (CH), 57.4 (C), 56.2 (CH<sub>3</sub>), 53.9 (CH<sub>2</sub>), 46.2 (CH), 25.6 (CH<sub>2</sub>), 20.2 (CH<sub>3</sub>), 15.9 (CH<sub>3</sub>). IR (ATR-FTIR), cm<sup>-1</sup>: 3733 (s), 3710 (m), 3628 (m), 2984 (m), 1683 (m). HRMS-Cl (m/z): [M + Na]<sup>+</sup> calcd for C<sub>12</sub>H<sub>18</sub>NaO<sub>4</sub>, 249.1103; found, 249.1110. [α]<sub>D</sub><sup>20</sup> = 18.6 (*c* = 0.06, CHCl<sub>3</sub>).

*Synthesis of the cyclic ether 141:*

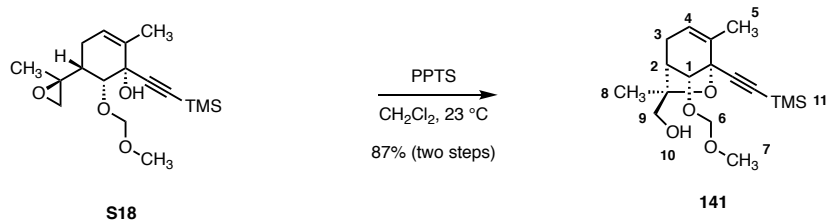
*Part 1: Synthesis of the tertiary alcohol S18:*



A solution of *n*-butyllithium in hexanes (2.50 M, 42.4 mL, 106 mmol, 1.20 equiv) was added dropwise via a syringe over 30 min to a solution of trimethylsilylacetylene (14.5 mL, 101 mol, 1.15 equiv) in tetrahydrofuran (380 mL) at  $-78\text{ }^\circ\text{C}$ . The resulting solution was stirred for 1 h at  $-78\text{ }^\circ\text{C}$ . The reaction vessel was then placed in an ice bath. The mixture was stirred for 30 min at  $0\text{ }^\circ\text{C}$  and then was cooled to  $-78\text{ }^\circ\text{C}$  over 30 min. A solution of the epoxide **140** (20.0 g, 88.4 mmol, 1 equiv) in tetrahydrofuran (65 mL) was added dropwise over 30 min. The reaction mixture was stirred for 1 h at  $-78\text{ }^\circ\text{C}$ . The reaction vessel was then placed in an ice bath and the product mixture was allowed to warm to  $0\text{ }^\circ\text{C}$  over 30 min. The warmed product mixture was diluted sequentially with saturated ammonium chloride (200 mL) and ethyl acetate (200 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate ( $3 \times 300\text{ mL}$ ). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (200 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was used directly in the next step without further purification.



Part 2: Synthesis of the cyclic ether **141**:

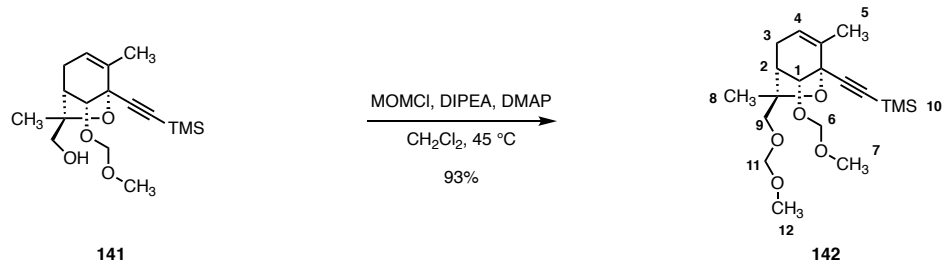


Pyridinium p-toluenesulfonate (PPTS, 4.40 g, 18.0 mmol, 0.200 equiv) was added in one portion to a solution of the residue obtained in the preceding step (nominally 62.4 mmol, 1 equiv) in dichloromethane (440 mL) at 23 °C. The resulting solution was stirred for 2 h at 23 °C. The product mixture was diluted sequentially with saturated aqueous sodium bicarbonate solution (200 mL) and dichloromethane (200 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with dichloromethane (3 × 200 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (200 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 15% ethyl acetate–hexanes initially, grading to 20% ethyl acetate–hexanes, one step) to provide the cyclic ether **141** as a yellow oil (25.0 g, 87% over two steps). The relative stereochemistry of cyclic ether **141** was established by X-ray analysis (see Appendix A).

$R_f = 0.30$  (50% ethyl acetate–hexanes; PAA).  $^1\text{H NMR}$  (600 MHz,  $\text{CDCl}_3$ ):  $\delta$  5.40 (s,  $\text{H}_4$ , 1H), 4.90 (d,  $J = 8.7$  Hz,  $\text{H}_{6a}$ , 1H), 4.77 (d,  $J = 8.7$  Hz,  $\text{H}_{6b}$ , 1H), 4.27 (s,  $\text{H}_1$ , 1H), 3.81 (d,  $J = 10.9$  Hz,  $\text{H}_{9a}$ , 1H), 3.46 (d,  $J = 10.9$  Hz,  $\text{H}_{9b}$ , 1H), 3.44 (s,  $\text{H}_7$ , 1H), 2.55 (s,  $\text{H}_{10}$ , 1H),

2.43 (d,  $J = 17.9$  Hz, H<sub>3a</sub>, 1H), 2.35 (s, H<sub>2</sub>, 1H), 2.29 (d,  $J = 23.7$  Hz, H<sub>3b</sub>, 1H), 1.86 (s, H<sub>5</sub>, 3H), 1.32 (s, H<sub>8</sub>, 3H), 0.16 (s, H<sub>11</sub>, 9H). <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>):  $\delta$  137.5 (C), 122.3 (CH), 101.3 (C), 95.2 (CH<sub>2</sub>), 93.1 (C), 86.2 (C), 84.2 (CH), 80.0 (C), 69.6 (CH<sub>2</sub>), 55.6 (CH<sub>3</sub>), 43.6 (CH), 30.5 (CH<sub>2</sub>), 21.0 (CH<sub>3</sub>), 20.0 (CH<sub>3</sub>), - 0.3 (3  $\times$ CH<sub>3</sub>). IR (ATR-FTIR), cm<sup>-1</sup>: 3726 (m), 3212 (m), 3011 (m). HRMS-CI (m/z): [M + Na]<sup>+</sup> calcd for C<sub>17</sub>H<sub>28</sub>NaO<sub>4</sub>Si, 347.1655; found, 347.1673.  $[\alpha]_D^{20} = 17.6$  ( $c = 0.20$ , CHCl<sub>3</sub>).

*Synthesis of the methoxymethyl ether 142:*



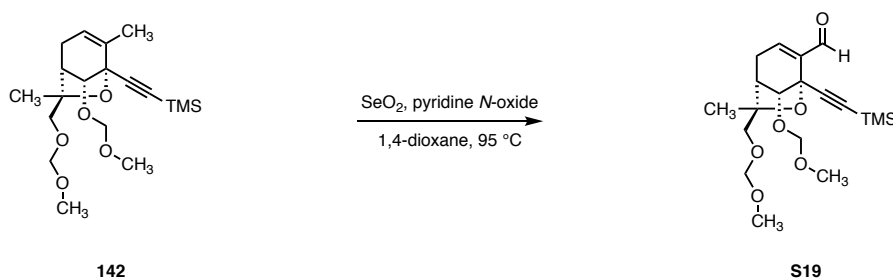
4-Dimethylaminopyridine (565 mg, 4.62 mmol, 0.03 equiv) and diisopropylethylamine (134 mL, 770 mmol, 5.00 equiv) were added in sequence to a solution of the ether **141** (50.0 g, 154 mmol, 1 equiv) in dichloromethane (500 mL) at 23 °C. The reaction vessel was then placed in an ice bath and allowed to cool to 0 °C over 20 min. Chloromethyl methyl ether (15.2 mL, 200 mmol, 1.30 equiv) was added dropwise via a syringe pump over 30 min. Upon completion of the addition, the ice bath was removed and the reaction mixture was allowed to warm to 23 °C over 30 min. The warmed reaction vessel was then immersed in an oil bath that had been preheated to 45 °C. The reaction mixture was stirred and heated for 3 d at 45 °C. The product mixture was cooled to 23 °C over 30 min. The cooled product mixture was diluted sequentially with dichloromethane (200 mL) and saturated aqueous ammonium chloride solution (100 mL). The diluted product mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with dichloromethane (3 × 300 mL). The organic layers were combined and the combined organic layers were washed sequentially with 1 N aqueous hydrochloric acid solution (200 mL) and saturated aqueous sodium chloride solution (200 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by a flash-

column chromatography (eluting with 20% ethyl acetate–hexanes) to provide the cyclic ether **142** as a yellow oil (52.7 g, 93%).

R<sub>f</sub> = 0.70 (50% ethyl acetate–hexanes; PAA). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 5.37 (ddt, *J* = 4.2, 2.6, 1.4 Hz, H<sub>4</sub>, 1H), 4.90 (d, *J* = 6.8 Hz, H<sub>6a</sub>, 1H), 4.78 (d, *J* = 6.8 Hz, H<sub>6b</sub>, 1H), 4.62 (q, *J* = 6.3 Hz, H<sub>11</sub>, 2H), 4.27 (s, H<sub>1</sub>, 1H), 3.86 (d, H<sub>9a</sub>, *J* = 8.9 Hz, 1H), 3.48 (d, H<sub>9b</sub>, *J* = 8.9 Hz, 1H), 3.44 (s, H<sub>12</sub>, 3H), 3.34 (s, H<sub>7</sub>, 3H), 2.59 – 2.46 (m, H<sub>2</sub>, 1H), 2.44 – 2.37 (m, H<sub>3a</sub>, 1H), 2.30 – 2.23 (m, H<sub>3b</sub>, 1H), 1.86 (s, H<sub>5</sub>, 1H), 1.34 (s, H<sub>8</sub>, 3H), 0.15 (s, H<sub>10</sub>, 9H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 138.4 (C), 122.0 (CH), 101.8 (C), 96.8 (CH<sub>2</sub>), 95.3 (CH<sub>2</sub>), 92.9 (C), 85.2 (C), 84.4 (CH), 80.1 (C), 74.6 (CH<sub>2</sub>), 55.5 (CH<sub>3</sub>), 55.3 (CH<sub>3</sub>), 43.4 (CH), 30.8 (CH<sub>3</sub>), 22.3 (CH<sub>3</sub>), 20.1 (CH<sub>3</sub>), – 0.1 (3 × CH<sub>3</sub>). IR (ATR-FTIR), cm<sup>-1</sup>: 3734 (s), 3685 (m), 2956 (s), 2901 (s). HRMS-Cl (m/z): [M + Na]<sup>+</sup> calcd for C<sub>19</sub>H<sub>32</sub>NaO<sub>5</sub>Si, 391.1917; found, 391.1935. [α]<sub>D</sub><sup>20</sup> = 21.8 (*c* = 0.25, CHCl<sub>3</sub>).

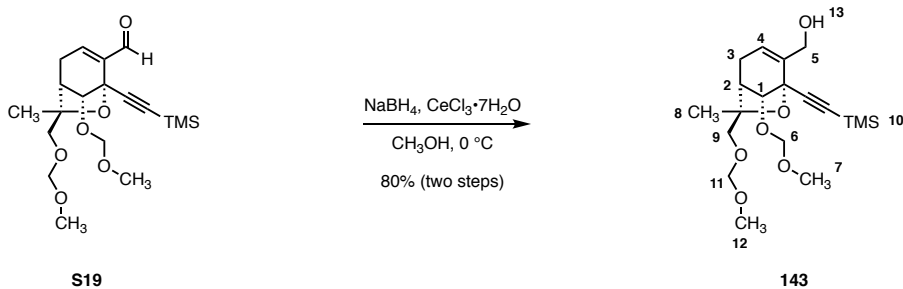
*Synthesis of the allylic alcohol 143:*

*Part 1: Synthesis of the unsaturated aldehyde S19:*



Pyridine *N*-oxide (23.7 g, 250 mmol, 4.00 equiv) and selenium dioxide (13.9 g, 125 mmol, 2.00 equiv) were added in sequence to a solution of the cyclic ether **142** (23.0 g, 62.4 mmol, 1 equiv) in 1,4-dioxane (520 mL) at 23 °C. The reaction vessel was fitted with a reflux condenser and then immersed in an oil bath that had been preheated to 95 °C. The reaction mixture was stirred and heated for 12 h at 95 °C. The product mixture was cooled to 23 °C over 30 min. The cooled product mixture was diluted sequentially with ethyl acetate (200 mL), water (100 mL), and saturated aqueous sodium bicarbonate solution (100 mL). The diluted mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 300 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (200 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was used directly in the following step.

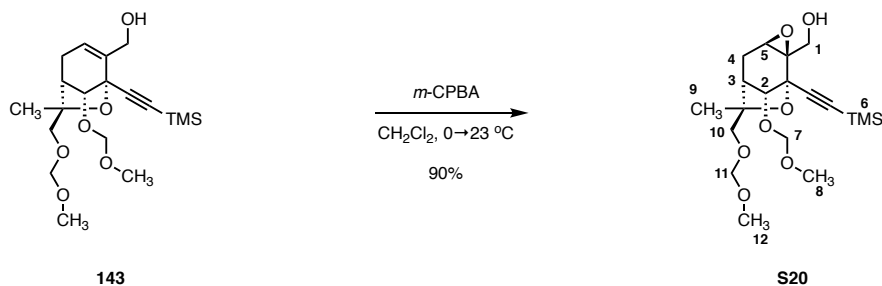
Part 2: synthesis of the allylic alcohol **143**:



Cerium (III) chloride heptahydrate (23.2 g, 62.4 mmol, 1.00 equiv) was added in one portion to a solution of the residue obtained in the preceding step (nominally 62.4 mmol, 1 equiv) in methanol (310 mL) at  $0\text{ }^\circ\text{C}$ . The resulting solution was allowed to stir for 30 min at  $0\text{ }^\circ\text{C}$ . Sodium borohydride (472 mg, 12.5 mmol, 0.20 equiv) was then added portionwise at 5 min intervals, until a total of 2.36 g (62.4 mmol, 1.00 equiv) had been introduced. Upon completion of the addition, the reaction mixture was stirred for 1 h at  $0\text{ }^\circ\text{C}$ . The cold product mixture was diluted sequentially with saturated aqueous ammonium chloride solution (100 mL), water (100 mL), and ethyl acetate (200 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate ( $3 \times 200\text{ mL}$ ). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (200 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 15% ethyl acetate–hexanes) to provide the allylic alcohol **143** as a yellow oil (19.2 g, 80% over two steps).

R<sub>f</sub> = 0.45 (50% ethyl acetate–hexanes; PAA). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 5.69 (s, H<sub>4</sub>, 1H), 4.89 (d, *J* = 6.8 Hz, H<sub>6a</sub>, 1H), 4.78 (d, *J* = 6.8 Hz, H<sub>6b</sub>, 1H), 4.62 (q, *J* = 6.3 Hz, H<sub>11</sub>, 2H), 4.30 (s, H<sub>1</sub>, 1H), 4.25 (s, H<sub>5</sub>, 2H), 3.85 (d, *J* = 8.9 Hz, H<sub>9a</sub>, 1H), 3.50 (d, *J* = 8.9 Hz, H<sub>9b</sub>, 1H), 3.43 (s, H<sub>12</sub>, 3H), 3.34 (s, H<sub>7</sub>, 3H), 2.55 – 2.30 (m, H<sub>2,3</sub>, 3H), 1.35 (s, H<sub>8</sub>, 3H), 0.17 (s, H<sub>10</sub>, 9H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 141.6 (C), 124.2 (CH), 101.0 (C), 96.6 (CH<sub>2</sub>), 95.2 (CH<sub>2</sub>), 93.2 (C), 85.4 (C), 84.3 (CH), 78.0 (C), 74.3 (CH<sub>2</sub>), 63.9 (CH<sub>2</sub>), 55.4 (CH<sub>3</sub>), 55.2 (CH<sub>3</sub>), 43.4 (CH), 30.5 (CH<sub>2</sub>), 22.2 (CH<sub>3</sub>), – 0.4 (3 × CH<sub>3</sub>). IR (ATR-FTIR), cm<sup>–1</sup>: 3733 (s), 3710 (m), 3628 (m), 2953 (s). HRMS-Cl (m/z): [M + Na]<sup>+</sup> calculated for C<sub>19</sub>H<sub>32</sub>NaO<sub>6</sub>Si, 407.1866; found, 407.1883. [ $\alpha$ ]<sub>D</sub><sup>20</sup> = 19.0 (*c* = 0.35, CHCl<sub>3</sub>).

*Synthesis of the epoxide S20:*



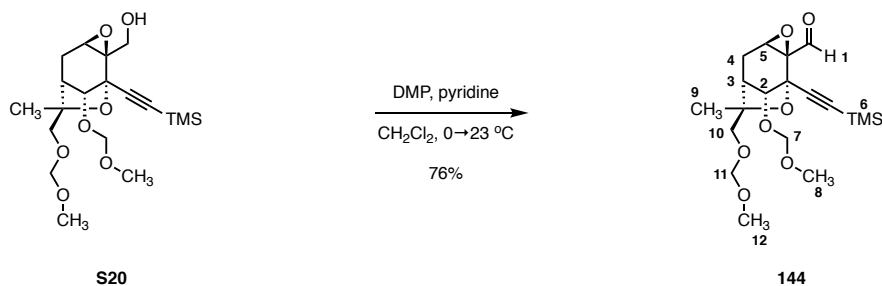
*meta*-Chloroperoxybenzoic acid (923 mg, 3.75 mmol, 1.80 equiv) was added in one portion to a solution of the allylic alcohol **143** (800 mg, 3.75 mmol, 1 equiv) in dichloromethane (10.5 mL) at 0 °C. The resulting solution was allowed to stir for 30 min at 0 °C. The cooling bath was then removed and the reaction mixture was allowed to warm to 23 °C over 30 min. The reaction mixture was stirred for 10 h at 23 °C. The product mixture was diluted sequentially with saturated aqueous ammonium chloride solution (50 mL), water (50 mL), and dichloromethane (100 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with dichloromethane (3 × 50 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (50 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 25% ethyl acetate–hexanes) to provide the epoxide **S20** as a yellow oil (750 mg, 90%).



Within the limits of detection, the epoxide **S20** was formed as a single diastereomers (<sup>1</sup>H NMR analysis, 400 MHz). The relative stereochemistry at the C5 position of the epoxide **S20** was established via conversion to the aldehyde **144**.

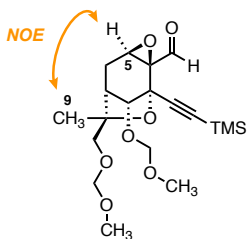
$R_f = 0.40$  (50% ethyl acetate–hexanes; PAA). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  4.80 (d,  $J = 6.8$  Hz, H<sub>7a</sub>, 1H), 4.69 (d,  $J = 6.8$  Hz, H<sub>7b</sub>, 1H), 4.66 – 4.59 (m, H<sub>11</sub>, 2H), 4.26 (s, H<sub>2</sub>, 1H), 4.10 (d,  $J = 2.7$  Hz, H<sub>1</sub>, 2H), 3.80 (d,  $J = 9.0$  Hz, H<sub>10a</sub>, 1H), 3.55 (d,  $J = 9.0$  Hz, H<sub>10b</sub>, 1H), 3.39 (s, H<sub>8</sub>, 3H), 3.34 (s, H<sub>5</sub>, H<sub>12</sub>, 4H), 2.33 (d,  $J = 1.7$  Hz, H<sub>3</sub>, 1H), 2.12 (t,  $J = 3.3$  Hz, H<sub>4</sub>, 2H), 1.33 (s, H<sub>9</sub>, 3H), 0.17 (s, H<sub>6</sub>, 9H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  99.3 (C), 96.8 (CH<sub>2</sub>), 95.8 (CH<sub>2</sub>), 94.4 (C), 85.1 (C), 82.1 (CH), 81.0 (C), 74.0 (CH<sub>2</sub>), 66.0 (C), 59.9 (CH<sub>2</sub>), 55.6 (CH<sub>3</sub>), 55.4 (CH<sub>3</sub>), 54.8 (CH), 44.2 (CH), 27.3 (CH<sub>2</sub>), 22.6 (CH<sub>3</sub>), -0.2 (3×CH<sub>3</sub>). IR (ATR-FTIR), cm<sup>-1</sup>: 3015 (m), 2975 (s), 1412 (s). HRMS-Cl (m/z): calcd for C<sub>19</sub>H<sub>32</sub>NaO<sub>7</sub>Si, 423.1815; found: 423.1810.  $[\alpha]_D^{20} = 5.77$  ( $c = 0.17$ , CHCl<sub>3</sub>).

*Synthesis of the aldehyde 144:*



The Dess–Martin periodinane (826 mg, 1.95 mmol, 1.50 equiv) was added in five equal portions over 1 h to a solution of the epoxide **S20** (520 mg, 1.30 mmol, 1 equiv) and pyridine (731  $\mu$ L, 9.09 mmol, 7.0 equiv) in dichloromethane (13 mL) at 0 °C. Upon completion of the addition, the cooling bath was removed and the reaction mixture was warmed to 23 °C over 30 min. The warmed mixture was stirred for 2 h at 23 °C. The product mixture was then diluted sequentially with dichloromethane (50 mL), saturated aqueous sodium bicarbonate solution (20 mL), and saturated aqueous sodium thiosulfate solution (20 mL). The diluted product mixture was stirred for 30 min at 23 °C. The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with dichloromethane (3  $\times$  50 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (30 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 20% ethyl acetate–hexanes) to provide the aldehyde **144** as a colorless oil (750 mg, 76%).

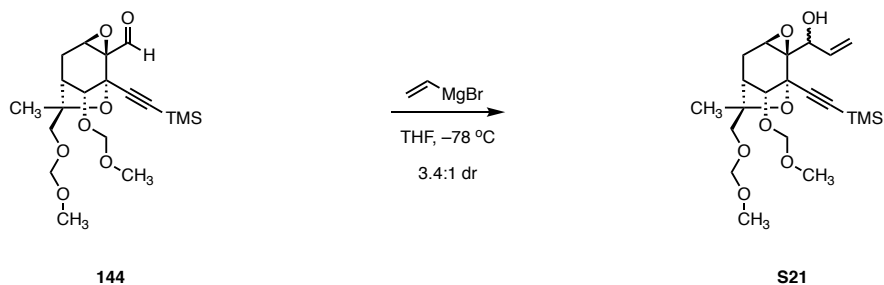
NOE correlations between the C5 hydrogen atom and the C9 methyl substituent support the relative configuration depicted.



$R_f = 0.30$  (25% ethyl acetate–hexanes; PAA).  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  9.98 (s, H<sub>1</sub>, 1H), 4.83 (d, H<sub>7a</sub>,  $J = 6.8$  Hz, 1H), 4.71 (d, H<sub>7b</sub>,  $J = 6.8$  Hz, 1H), 4.67 – 4.58 (m, H<sub>11</sub>, 2H), 4.25 (s, H<sub>2</sub>, 1H), 3.85 (d, H<sub>10a</sub>,  $J = 9.1$  Hz, 1H), 3.59 (d, H<sub>10b</sub>,  $J = 9.0$  Hz, 1H), 3.40 (s, H<sub>12</sub>, 3H), 3.35 (s, H<sub>8</sub>, 3H), 3.32 (s, H<sub>5</sub>, 1H), 2.39 (s, H<sub>3</sub>, 1H), 2.18 (t,  $J = 3.0$  Hz, H<sub>4</sub>, 2H), 1.32 (s, H<sub>9</sub>, 3H), 0.15 (s, H<sub>6</sub>, 9H).  $^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  196.4 (CH), 98.8 (C), 96.7 (CH<sub>2</sub>), 95.7 (CH<sub>2</sub>), 95.0 (C), 85.6 (C), 81.5 (CH), 78.5 (C), 73.6 (CH<sub>2</sub>), 66.6 (C), 58.4 (CH), 55.6 (CH<sub>3</sub>), 55.3 (CH<sub>3</sub>), 44.1 (CH), 27.5 (CH<sub>2</sub>), 22.7 (CH<sub>3</sub>), -0.4 (3×CH<sub>3</sub>). IR (ATR-FTIR),  $\text{cm}^{-1}$ : 3734 (s), 3628 (m), 2932 (s), 1733 (s). HRMS-CI ( $m/z$ ): calcd for  $\text{C}_{19}\text{H}_{30}\text{NaO}_7\text{Si}$ , 421.1658; found: 421.1653.  $[\alpha]_D^{20} = 21.1$  ( $c = 0.30$ ,  $\text{CHCl}_3$ ).

*Synthesis of the trimethylsilyl ether 145:*

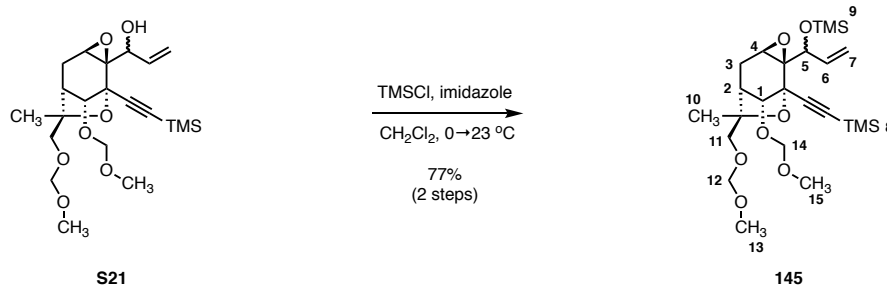
*Part 1: Synthesis of the allylic alcohol S21:*



A solution of vinylmagnesium bromide in tetrahydrofuran (700 mM, 2.84 mL, 1.98 mmol, 2.00 equiv) was added dropwise via a syringe over 30 min to a solution of aldehyde **144** (395 mg, 991  $\mu\text{mol}$ , 1 equiv) in tetrahydrofuran (8 mL) at  $-78\text{ }^{\circ}\text{C}$ . The reaction mixture was stirred for 2 h at  $-78\text{ }^{\circ}\text{C}$ . The product mixture was then warmed to  $0\text{ }^{\circ}\text{C}$  over 30 min, where it was diluted sequentially with saturated aqueous ammonium chloride solution (20 mL), water (20 mL), and ethyl acetate (50 mL). The resulting mixture was warmed up  $23\text{ }^{\circ}\text{C}$  over 30 min. The warmed product mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate ( $3 \times 20\text{ mL}$ ). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (50 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was used directly in the following step.

Within the limits of detection, the product **S21** was formed as 3.4:1 inconsequential mixture of diastereomers ( $^1\text{H}$  NMR analysis, 400 MHz).

Part 2: Synthesis of the trimethylsilyl ether **145**:



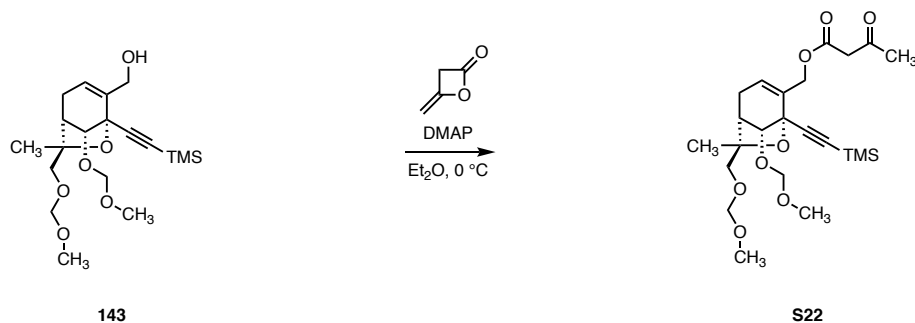
Trimethylsilyl chloride (252  $\mu$ L, 1.98 mmol, 2.00 equiv) was added dropwise via syringe to a solution of the residue obtained in the preceding step (nominally, 991  $\mu$ mol, 1 equiv) and imidazole (270 mg, 3.96 mmol, 4.00 equiv) in dichloromethane (6 mL) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C and then the cooling bath was removed. The reaction mixture was allowed to warm to 23 °C and stirred for 8 h at 23 °C. The product mixture was diluted sequentially with saturated aqueous ammonium chloride solution (15 mL), water (15 mL), and dichloromethane (50 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with dichloromethane (3  $\times$  20 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (50 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 15% ethyl acetate–hexanes) to provide the silyl ether **145** as a colorless oil (370 mg, 77% over two steps).

$R_f$  = 0.50 (40% ethyl acetate–hexanes; PAA). \*Denotes second diastereomer. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  6.30 (ddd, H<sub>6</sub>,  $J$  = 16.8, 10.4, 4.6 Hz, 1H), 6.13–5.97 (m, H<sub>6</sub>\*, 1H),

5.34 – 5.22 (m, H<sub>7a,7a\*</sub>, 2H), 5.20 – 5.08 (m, H<sub>7b,7b\*</sub>, 2H), 4.98 (d, H<sub>5\*</sub>, J = 5.0 Hz, 1H), 4.85 (d, H<sub>5</sub>, J = 4.7 Hz, 1H), 4.80 (dd, H<sub>12a,12a\*</sub>, J = 14.6, 6.7 Hz, 2H), 4.68 (d, H<sub>12b,12b\*</sub>, J = 6.8 Hz, 2H), 4.63 – 4.55 (m, H<sub>14,14\*</sub>, 4H), 4.34 (s, H<sub>1</sub>, 1H), 4.22 (s, H<sub>1\*</sub>, 1H), 3.84 (t, H<sub>11a,12a\*</sub>, J = 9.5 Hz, 2H), 3.51 (d, H<sub>12b\*</sub>, J = 8.9 Hz, 1H), 3.46 (d, H<sub>11b</sub>, J = 8.9 Hz, 1H), 3.38 (s, H<sub>13</sub>, 3H), 3.37 (s, H<sub>13\*</sub>, 3H), 3.34 (s, H<sub>15\*</sub>, 3H), 3.32 (s, H<sub>15</sub>, 3H), 3.29 – 3.24 (m, H<sub>4,4\*</sub>, 2H), 2.31 (s, H<sub>2,2\*</sub>, 2H), 2.13 – 1.89 (m, H<sub>3,3\*</sub>, 4H), 1.33 (s, H<sub>10</sub>, 3H), 1.22 (s, H<sub>10\*</sub>, 3H), 0.18 (s, H<sub>9</sub>, 9H), 0.17 (s, H<sub>9\*</sub>, 9H), 0.13 (s, H<sub>8\*</sub>, 9H), 0.10 (s, H<sub>8</sub>, 9H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 138.0 (CH), 136.9 (CH)\*, 115.6 (CH<sub>2</sub>)\*, 113.8 (CH<sub>2</sub>), 100.5 (C)\*, 99.9 (C), 96.69 (CH<sub>2</sub>)\*, 96.67 (CH<sub>2</sub>), 95.76 (CH<sub>2</sub>), 95.76 (CH<sub>2</sub>)\*, 93.9 (C)\*, 93.6 (C), 84.9 (C)\*, 84.7 (C), 82.9 (CH), 82.6 (CH)\*, 81.8 (C)\*, 80.9 (C), 74.2. (CH<sub>2</sub>), 74.2 (CH<sub>2</sub>)\*, 70.4 (CH)\*, 69.6 (CH), 68.7 (C)\*, 66.9 (C), 55.42 (CH<sub>3</sub>), 55.39 (CH<sub>3</sub>)\*, 55.2 (CH<sub>3</sub>), 54.8 (CH<sub>3</sub>)\*, 52.5 (CH), 52.5 (CH)\*, 43.9 (CH), 43.7 (CH)\*, 27.2 (CH<sub>2</sub>)\*, 26.8 (CH<sub>2</sub>), 22.6 (CH<sub>3</sub>)\*, 22.4 (CH<sub>3</sub>), 0.45 (3×CH<sub>3</sub>)\*. 0.041 (3×CH<sub>3</sub>), 0.3 (3×CH<sub>3</sub>), -0.4 (3×CH<sub>3</sub>)\*. IR (ATR-FTIR), cm<sup>-1</sup>: 3734 (m), 3646 (m), 2956 (m), 1683 (m). HRMS-Cl (m/z): calcd for C<sub>24</sub>H<sub>42</sub>NaO<sub>7</sub>Si<sub>2</sub>, 521.2367; found: 521.2376.  $[\alpha]_D^{20} = 25.2$  (*c* = 0.08, CHCl<sub>3</sub>).

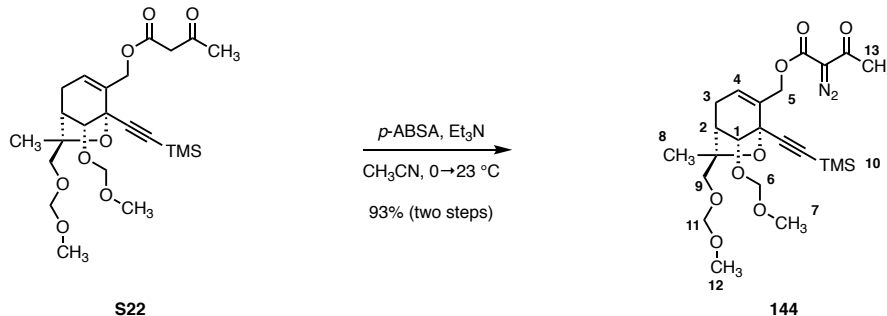
*Synthesis of the diazoester 144:*

*Part 1: Synthesis of the  $\beta$ -keto ester S22:*



Diketene (11.4 mL, 148 mmol, 3.00 equiv) was added dropwise via a syringe over 30 min to a solution of the allylic alcohol **143** (19.0 g, 49.4 mmol, 1 equiv) and (4-dimethylamino)pyridine (DMAP, 302 mg, 2.47 mmol, 0.05 equiv) in ether (250 mL) at 0 °C. Upon completion of the addition, the cooling bath was removed and the reaction mixture was allowed to warm to 23 °C over 30 min. The reaction mixture was stirred for 2 h at 23 °C. The product mixture was diluted sequentially with water (200 mL) and ethyl acetate (200 mL). The diluted mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 200 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (100 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was used directly in the following step.

Part 2: Synthesis of diazoester **144**:



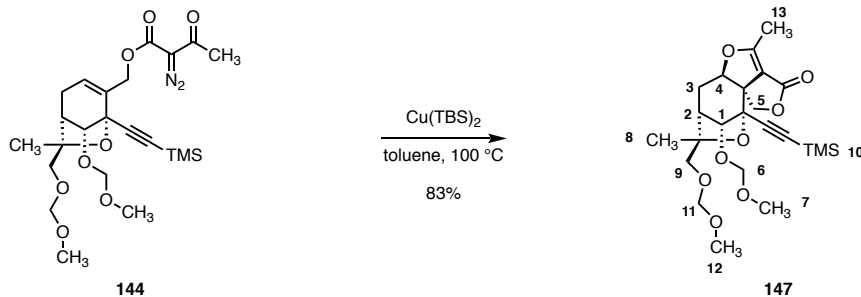
Triethylamine (20.6 mL, 148 mmol, 3.00 equiv) was added dropwise via syringe over 1 h to a solution of (4-acetamido)benzenesulfonyl azide (*p*-ABSA, 14.2 g, 59.3 mmol, 1.20 equiv) and the residue obtained in the preceding step (nominally 49.4 mmol, 1 equiv) in acetonitrile (490 mL) at 0 °C. Upon completion of the addition, the cooling bath was removed and the reaction mixture was allowed to warm to 23 °C. The reaction mixture was stirred for 6 h at 23 °C. The product mixture was diluted sequentially with water (100 mL) and ethyl acetate (200 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 200 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (200 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 15% ethyl acetate–hexanes) to provide the diazo ester **144** as a yellow oil (22.8 g, 93% over two steps).

$R_f = 0.20$  (50% ethyl acetate–hexanes; UV, PAA).  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  5.77 (ddd,  $J = 4.0, 2.6, 1.3$  Hz,  $\text{H}_4$ , 1H), 4.93 (d,  $J = 12.7$  Hz,  $\text{H}_{6a}$ , 1H), 4.90 (d,  $J = 6.9$  Hz,  $\text{H}_{5a}$ ,



1H), 4.77 (d,  $J = 6.9$  Hz, H<sub>5b</sub>, 1H), 4.76 (d,  $J = 12.7$  Hz, H<sub>6b</sub>, 1H), 4.63 – 4.59 (m, H<sub>11</sub>, 2H), 4.27 (s, H<sub>1</sub>, 1H), 3.87 (d,  $J = 8.9$  Hz, H<sub>9a</sub>, 1H), 3.44 (d,  $J = 8.9$  Hz, H<sub>9b</sub>, 1H), 3.43 (s, H<sub>7</sub>, 3H), 3.34 (s, H<sub>12</sub>, 3H), 2.56 (s, H<sub>3</sub>, 1H), 2.52 – 2.48 (m, H<sub>2a</sub>, 1H), 2.48 (s, H<sub>13</sub>, 3H), 2.44 – 2.35 (m, H<sub>2b</sub>, 1H), 1.30 (s, H<sub>8</sub>, 3H), 0.15 (s, H<sub>10</sub>, 9H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  190.3 (C), 161.3 (C), 136.6 (C), 128.5 (CH), 100.4 (C), 96.8 (CH<sub>2</sub>), 95.3 (CH<sub>2</sub>), 93.3 (C), 85.5 (C), 84.3 (CH), 78.3 (C), 77.4 (C), 74.5 (CH<sub>2</sub>), 65.9 (CH<sub>2</sub>), 55.6 (CH<sub>3</sub>), 55.4 (CH<sub>3</sub>), 43.4 (CH), 30.9 (CH<sub>2</sub>), 28.5 (CH<sub>3</sub>), 22.4 (CH<sub>3</sub>), -0.2 (3  $\times$  CH<sub>3</sub>). IR (ATR-FTIR), cm<sup>-1</sup>: 2953 (m), 2889 (m), 2141 (s), 1717 (s), 1655 (s). HRMS-CI (m/z): [M + Na]<sup>+</sup> calculated for C<sub>23</sub>H<sub>34</sub>N<sub>2</sub>NaO<sub>8</sub>Si, 517.1982; found, 517.1975.  $[\alpha]_D^{20} = 17.5$  ( $c = 0.28$ , CHCl<sub>3</sub>).

Synthesis of the vinylogous carbonate **147**:

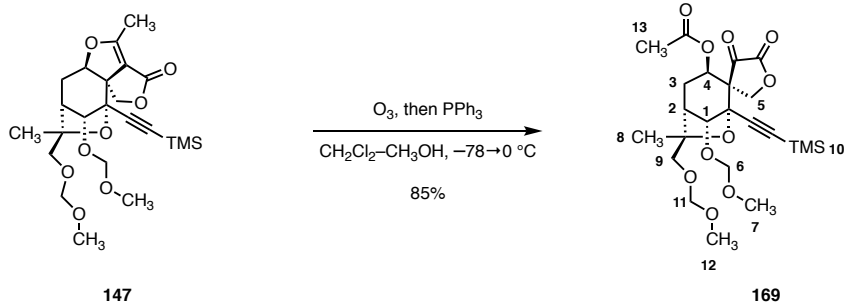


Bis (*N-tert*-butylsalicylaldiminato) copper (II) (522 mg, 1.25 mmol, 0.300 equiv), the diazo ester **144** (2.07 g, 4.18 mmol, 1 equiv), and toluene (220 mL) were combined in a 500-mL screw-capped pressure vessel in a nitrogen-filled glovebox. The reaction vessel was sealed and the sealed vessel was removed from the glovebox. The reaction vessel was placed in an oil bath that had been preheated to  $100\text{ }^\circ\text{C}$ . The reaction mixture was stirred and heated for 1 h at  $100\text{ }^\circ\text{C}$ . *CAUTION*: gas evolution will occur! The product mixture was cooled to  $23\text{ }^\circ\text{C}$  over 30 min. The cooled product mixture was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 15% ethyl acetate–hexanes initially, grading to 20% ethyl acetate–hexanes, one step) to provide the vinylogous carbonate **147** as a colorless solid (1.62 g, 83%). The relative stereochemistry of the vinylogous carbonate **147** was established by X-ray analysis (see Appendix A).

$R_f = 0.20$  (33% ethyl acetate–hexanes; UV,  $\text{KMnO}_4$ ).  $^1\text{H NMR}$  (600 MHz,  $\text{CDCl}_3$ ):  $\delta$  4.99 (dd,  $J = 9.4, 1.2$  Hz,  $\text{H}_{5a}$ , 1H), 4.91 – 4.82 (m,  $\text{H}_{6a,4}$ , 2H), 4.72 (dd,  $J = 6.9, 1.0$  Hz,  $\text{H}_{6b}$ , 1H), 4.63 (qd,  $J = 6.4, 1.0$  Hz,  $\text{H}_{11}$ , 2H), 4.26 (s,  $\text{H}_1$ , 1H), 3.94 (d,  $J = 9.4$  Hz,  $\text{H}_{5b}$ , 1H), 3.87 (d,  $J = 9.0$  Hz,  $\text{H}_{9a}$ , 1H), 3.60 (d,  $J = 9.0$  Hz,  $\text{H}_{9b}$ , 1H), 3.41 (s,  $\text{H}_7$ , 3H), 3.36 (s,  $\text{H}_{12}$ , 3H), 2.52 (d,  $J = 6.4$  Hz,  $\text{H}_2$ , 1H), 2.45 – 2.32 (m,  $\text{H}_3$ , 2H), 2.13 (s,  $\text{H}_{13}$ , 3H), 1.13 (s,  $\text{H}_8$ ,

3H), 0.15 (s, H<sub>10</sub>, 9H). <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>): δ 165.6 (C), 164.7 (C), 108.6 (C), 99.1 (C), 96.8 (CH<sub>2</sub>), 95.7 (CH<sub>2</sub>), 93.9 (C), 89.2 (CH), 84.3 (C), 83.6 (C), 80.9 (CH), 73.91 (CH<sub>2</sub>), 73.90 (CH<sub>2</sub>), 63.7 (C), 55.7 (CH<sub>3</sub>), 55.4 (CH<sub>3</sub>), 42.4 (CH), 30.0 (CH<sub>2</sub>), 22.9 (CH<sub>3</sub>), 13.3 (CH<sub>3</sub>), -0.4 (3 × CH<sub>3</sub>). IR (ATR-FTIR), cm<sup>-1</sup>: 2855 (m), 2769 (m), 1759 (s), 1678 (s). HRMS-Cl (m/z): [M + Na]<sup>+</sup> calculated for C<sub>23</sub>H<sub>34</sub>NaO<sub>8</sub>Si, 489.1921; found 489.1942.  $[\alpha]_D^{20} = -9.91$  (*c* = 0.38, CHCl<sub>3</sub>).

Synthesis of the diketone **169**:

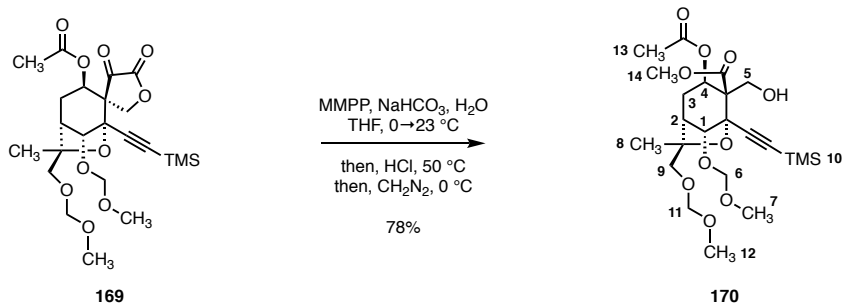


Ozone was passed through a solution of the vinyllogous carbonate **147** (5.60 g, 12.0 mmol, 1 equiv) in dichloromethane (350 mL) and methanol (80 mL) at  $-78\text{ }^\circ\text{C}$ . The addition of ozone was continued until a blue color persisted. Dioxygen was then passed through the solution to remove any dissolved ozone, resulting in a colorless solution. Triphenylphosphine (6.30 g, 24.0 mmol, 2.00 equiv) was then added to the cold mixture. Upon completion of the addition, the cooling bath was removed and the product mixture was allowed to warm to  $23\text{ }^\circ\text{C}$  over 1 h. The warmed product mixture was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 15% ethyl acetate–hexanes) to provide the diketone **169** as a white solid (5.09 g, 85%). The relative stereochemistry of the diketone **169** was established by X-ray analysis (see Appendix A).

$R_f = 0.55$  (50% ethyl acetate–hexanes; UV, PAA).  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  5.23 (d,  $J = 10.4$  Hz,  $\text{H}_{5a}$ , 1H), 5.12 (dd,  $J = 10.7, 7.1$  Hz,  $\text{H}_4$ , 1H), 4.89 (s,  $\text{H}_1$ , 1H), 4.69 (s,  $\text{H}_6$ , 2H), 4.62 (s,  $\text{H}_{11}$ , 2H), 4.40 (d,  $J = 10.4$  Hz,  $\text{H}_{5b}$ , 1H), 3.94 (d,  $J = 9.2$  Hz,  $\text{H}_{9a}$ , 1H), 3.60 (d,  $J = 9.2$  Hz,  $\text{H}_{9b}$ , 1H), 3.38 (s,  $\text{H}_7$ , 3H), 3.36 (s,  $\text{H}_{12}$ , 3H), 2.58 (t,  $J = 3.4$  Hz,  $\text{H}_2$ , 1H), 2.39 (ddd,  $J = 13.8, 7.2, 4.1$  Hz,  $\text{H}_{3a}$ , 1H), 2.01 (s,  $\text{H}_{13}$ , 3H), 1.99 – 1.95 (m,  $\text{H}_{3b}$ , 1H), 1.49

(s, H<sub>8</sub>, 3H), 0.13 (s, H<sub>10</sub>, 9H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 192.5 (C), 170.2 (C), 159.4 (C), 98.2 (C), 97.0 (C), 96.8 (CH<sub>2</sub>), 95.7 (CH<sub>2</sub>), 87.5 (C), 83.1(C), 80.4 (CH), 73.6 (CH<sub>2</sub>), 72.6 (CH<sub>2</sub>), 72.0 (CH), 57.7 (C), 55.8 (CH<sub>3</sub>), 55.4 (CH<sub>3</sub>), 42.4 (CH), 30.6 (CH<sub>2</sub>), 20.9 (CH<sub>3</sub>), 20.2 (CH<sub>3</sub>), -0.6 (3 × CH<sub>3</sub>). IR (ATR-FTIR), cm<sup>-1</sup>: 2956 (s), 2362 (m), 2338 (m), 1794 (s), 1768 (m), 1749 (s). HRMS-CI (m/z): [M + Na]<sup>+</sup> calculated for C<sub>23</sub>H<sub>34</sub>NaO<sub>10</sub>Si, 521.1819; found 521.1816.  $[\alpha]_D^{20} = -57.4$  (*c* = 0.14, CHCl<sub>3</sub>).

*Synthesis of the methyl ester 170:*

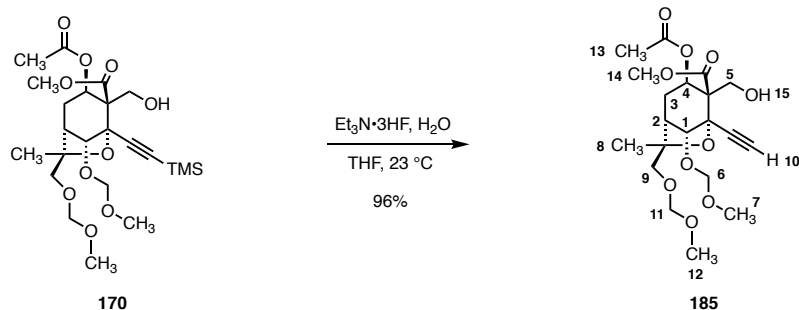


Magnesium monoperoxyphthalate (MMPP, 37.2 g, 75.2 mmol, 5.00 equiv) was added to a mixture of water (4.07 mL, 225 mmol, 15.0 equiv), sodium bicarbonate (15.8 g, 150.0 mmol, 10.0 equiv), and the diketone **169** (7.50 g, 15.0 mmol, 1 equiv) in tetrahydrofuran (190 mL) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C. The cooling bath was removed and the reaction mixture was allowed to warm to 23 °C over 30 min. The warmed mixture was stirred for 3 h at 23 °C. Aqueous hydrochloric acid solution (1 N, 22.6 mL, 22.6 mmol, 1.50 equiv) was then added. Upon completion of the addition, the reaction vessel was placed in an oil bath that had been preheated to 50 °C. *CAUTION*: gas evolution will occur! The reaction mixture was stirred and heated for 3 h at 50 °C. The product mixture was cooled to 0 °C over 1 h. The cooled mixture was diluted with a solution of diazomethane in ether (~0.66 M, 113.6 mL, 75.0 mmol, 5.00 equiv). *CAUTION*: gas evolution will occur! Upon completion of the addition, the reaction mixture was stirred for 2 h at 0 °C. The product mixture was warmed to 23 °C over 30 min. The warmed product mixture was diluted sequentially with ethyl acetate (100 mL) and water (100 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 100 mL). The organic layers were combined and the combined organic layers

were washed with saturated aqueous sodium chloride solution (100 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 20% ethyl acetate–hexanes) to provide the methyl ester **170** as a yellow oil (5.87 g, 78%).

$R_f = 0.55$  (50% ethyl acetate–hexanes; PAA).  $^1\text{H NMR}$  (600 MHz,  $\text{CDCl}_3$ ):  $\delta$  5.63 (dd,  $J = 10.5, 7.6$  Hz,  $\text{H}_4$ , 1H), 5.22 (s,  $\text{H}_1$ , 1H), 4.79 (d,  $J = 6.7$  Hz,  $\text{H}_{6a}$ , 1H), 4.68 (d,  $J = 6.7$  Hz,  $\text{H}_{6b}$ , 1H), 4.62 (s,  $\text{H}_{11}$ , 2H), 4.29 (d,  $J = 12.1$  Hz,  $\text{H}_{5a}$ , 1H), 4.03 (d,  $J = 12.1$  Hz,  $\text{H}_{5b}$ , 1H), 3.98 (d,  $J = 9.2$  Hz,  $\text{H}_{9a}$ , 1H), 3.76 (s,  $\text{H}_{14}$ , 3H), 3.54 (d,  $J = 9.2$  Hz,  $\text{H}_{9b}$ , 1H), 3.39 (s,  $\text{H}_7$ , 3H), 3.35 (s,  $\text{H}_{12}$ , 3H), 2.50 (d,  $J = 3.1$  Hz,  $\text{H}_2$ , 1H), 2.48 – 2.39 (m,  $\text{H}_{3a}$ , 1H), 2.03 – 1.94 (m,  $\text{H}_{3b,13}$ , 4H), 1.53 (s,  $\text{H}_8$ , 3H), 0.15 (s,  $\text{H}_{10}$ , 9H).  $^{13}\text{C NMR}$  (150 MHz,  $\text{CDCl}_3$ ):  $\delta$  170.1 (C), 169.9 (C), 99.3 (C), 96.7 ( $\text{CH}_2$ ), 95.5 ( $\text{CH}_2$ ), 94.7 (C), 86.5 (C), 85.1 (C), 82.2 (CH), 73.7 ( $\text{CH}_2$ ), 68.5 (CH), 64.5 ( $\text{CH}_2$ ), 60.8 (C), 55.4 ( $\text{CH}_3$ ), 55.2 ( $\text{CH}_3$ ), 52.2 ( $\text{CH}_3$ ), 42.7 (CH), 31.5 ( $\text{CH}_2$ ), 21.0 ( $\text{CH}_3$ ), 20.0 ( $\text{CH}_3$ ),  $-0.4$  ( $3 \times \text{CH}_3$ ). IR (ATR-FTIR),  $\text{cm}^{-1}$ : 2954 (m), 2892 (m), 1733 (s). HRMS-CI ( $m/z$ ):  $[\text{M} + \text{Na}]^+$  calculated for  $\text{C}_{23}\text{H}_{38}\text{NaO}_{10}\text{Si}$ , 525.2132; found 525.2134.  $[\alpha]_D^{20} = -5.00$  ( $c = 0.14$ ,  $\text{CHCl}_3$ ).

*Synthesis of the alkyne 185:*



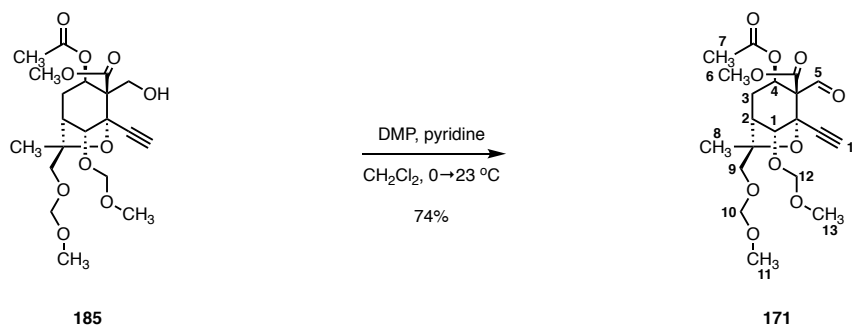
Triethylamine trihydrofluoride (2.90 mL, 23.4 mmol, 2.00 equiv) was added dropwise via syringe to a solution of the methyl ester **170** (5.87 g, 11.7 mmol, 1 equiv) and water (300  $\mu\text{L}$ ) in tetrahydrofuran (58 mL) at 23 °C. The resulting mixture was stirred for 60 h at 23 °C. The product mixture was then cooled to 0 °C over 30 min. The cooled product mixture was diluted sequentially with ethyl acetate (50 mL) and saturated aqueous sodium bicarbonate solution (20 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3  $\times$  100 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (100 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 33% ethyl acetate–hexanes) to provide the alkyne **185** as a white solid (4.80 g, 95%).

$R_f = 0.35$  (50% ethyl acetate–hexanes; PAA).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  5.63 (dd,  $J = 10.6, 7.5$  Hz,  $\text{H}_4$ , 1H), 5.21 (s,  $\text{H}_1$ , 1H), 4.78 (d,  $J = 6.8$  Hz,  $\text{H}_{6a}$ , 1H), 4.72 (d,  $J = 6.8$  Hz,  $\text{H}_{6b}$ , 1H), 4.61 (s,  $\text{H}_{11}$ , 2H), 4.29 (dd,  $J = 12.1, 5.5$  Hz,  $\text{H}_{5a}$ , 1H), 4.06 (dd,  $J = 12.1, 8.3$  Hz,



H<sub>5b</sub>, 1H), 3.96 (d, J = 9.2 Hz, H<sub>9a</sub>, 1H), 3.79 (s, H<sub>14</sub>, 3H), 3.56 (d, J = 9.2 Hz, H<sub>9b</sub>, 1H), 3.40 (s, H<sub>7</sub>, 3H), 3.35 (s, H<sub>12</sub>, 3H), 2.73 (dd, J = 8.3, 5.6 Hz, H<sub>15</sub>, 1H), 2.65 (s, H<sub>10</sub>, 1H), 2.53 (d, J = 3.5 Hz, H<sub>2</sub>, 1H), 2.45 (ddd, J = 13.7, 7.6, 4.0 Hz, H<sub>3a</sub>, 1H), 1.99 (s, H<sub>13</sub>, 3H), 1.98 (d, J = 4.2 Hz, H<sub>3b</sub>, 1H), 1.60 (s, H<sub>8</sub>, 3H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 170.2 (C), 170.0 (C), 96.9 (CH<sub>2</sub>), 95.9 (CH<sub>2</sub>), 86.8 (C), 84.8 (C), 82.6 (CH), 78.2 (C), 77.8 (CH), 73.8 (CH<sub>2</sub>), 68.6 (CH), 64.7 (CH<sub>2</sub>), 60.7 (C), 55.7 (CH<sub>3</sub>), 55.4 (CH<sub>3</sub>), 52.5 (CH<sub>3</sub>), 42.8 (CH), 31.6 (CH<sub>2</sub>), 21.1 (CH<sub>3</sub>), 20.1 (CH<sub>3</sub>). IR (ATR-FTIR), cm<sup>-1</sup>: 3734 (m), 3628 (m), 2953 (m), 1733 (s). HRMS-Cl (m/z): [M + Na]<sup>+</sup> calculated for C<sub>20</sub>H<sub>30</sub>NaO<sub>10</sub>, 453.1737; found 453.1728.  $[\alpha]_D^{20} = -17.8$  (*c* = 0.14, CHCl<sub>3</sub>).

*Synthesis of the aldehyde 171:*



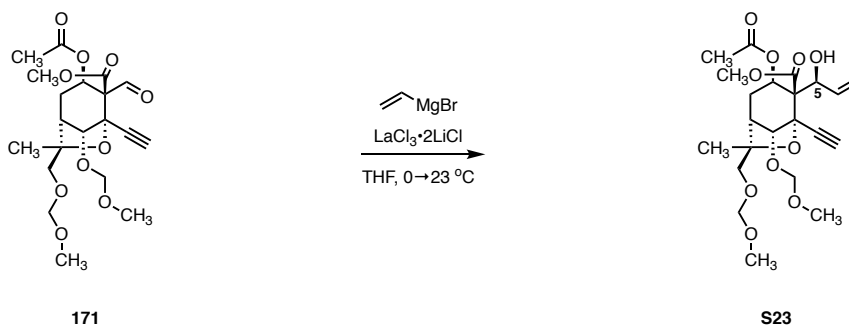
The Dess–Martin periodinane (3.70 g, 8.71 mmol, 1.50 equiv) was added in five equal portions over 1 h to a solution of the alcohol **185** (2.50 g, 5.81 mmol, 1 equiv) and pyridine (3.30 mL, 40.7 mmol, 7.0 equiv) in dichloromethane (40 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h. The product mixture was then diluted sequentially with dichloromethane (100 mL), saturated aqueous sodium bicarbonate solution (40 mL), and saturated aqueous sodium thiosulfate solution (40 mL). The diluted product mixture was stirred for 30 min at 23 °C. The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with dichloromethane (3 × 50 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (50 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 25% ethyl acetate–hexanes) to provide the aldehyde **171** as a colorless oil (1.85 g, 74%).

$R_f = 0.50$  (50% ethyl acetate–hexanes; PAA).  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  9.99 (s,  $\text{H}_5$ , 1H), 5.78 (dd,  $J = 10.6, 7.1$  Hz,  $\text{H}_4$ , 1H), 5.28 (s,  $\text{H}_1$ , 1H), 4.84 (d,  $J = 6.7$  Hz,  $\text{H}_{12a}$ , 1H),

4.76 (d,  $J = 6.7$  Hz, H<sub>12b</sub>, 1H), 4.60 (s, H<sub>10</sub>, 2H), 3.92 (d,  $J = 9.2$  Hz, H<sub>9a</sub>, 1H), 3.82 (s, H<sub>6</sub>, 3H), 3.52 (d,  $J = 9.1$  Hz, H<sub>9b</sub>, 1H), 3.42 (s, H<sub>11</sub>, 3H), 3.34 (s, H<sub>13</sub>, 3H), 2.81 (s, H<sub>14</sub>, 1H), 2.54 – 2.52 (m, H<sub>3a</sub>, 1H), 2.53 (s, H<sub>2</sub>, 1H), 1.97 (s, H<sub>7</sub>, 3H), 1.89 – 1.87 (m, H<sub>3b</sub>, 1H), 1.46 (s, H<sub>8</sub>, 3H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  193.8 (C), 169.3 (C), 167.1 (C), 96.7 (CH<sub>2</sub>), 96.0 (CH<sub>2</sub>), 87.1 (C), 82.3 (CH), 81.7 (C), 79.2 (CH), 77.4 (C), 73.5 (CH<sub>2</sub>), 68.6 (C), 65.9 (CH), 55.7 (CH<sub>3</sub>), 55.3 (CH<sub>3</sub>), 52.8 (CH<sub>3</sub>), 42.5 (CH), 31.2 (CH<sub>2</sub>), 20.8 (CH<sub>3</sub>), 20.0 (CH<sub>3</sub>). IR (ATR-FTIR), cm<sup>-1</sup>: 3734 (s), 2953 (s), 2119 (m), 1748 (s), 1728 (s). HRMS-CI (m/z): calcd for C<sub>20</sub>H<sub>28</sub>NaO<sub>10</sub>, 451.1580; found: 451.1574.  $[\alpha]_D^{20} = 36.3$  ( $c = 0.17$ , CHCl<sub>3</sub>).

*Synthesis of the diol 173:*

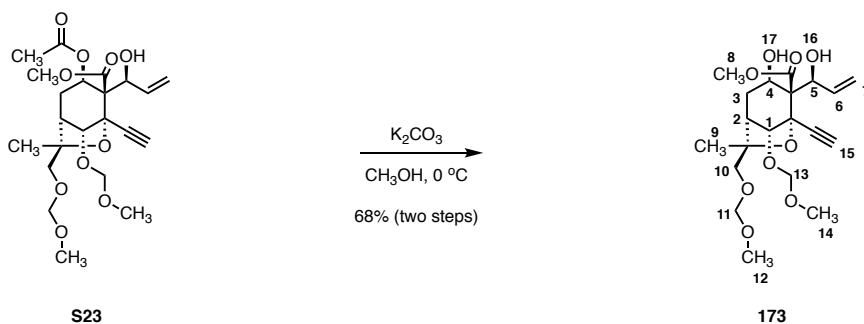
*Part 1: Synthesis of the allylic alcohol S23:*



A solution of lanthanum(III) chloride bis(lithium chloride) complex in tetrahydrofuran (600 mM, 14.0 mL, 8.40 mmol, 3.00 equiv) was added to a solution of the aldehyde **171** (1.20 g, 2.80 mmol, 1 equiv) in tetrahydrofuran (20 mL) at 23 °C. The resulting solution was stirred for 1 h at 23 °C and then cooled to 0 °C. A solution of vinylmagnesium bromide in tetrahydrofuran (700 mM, 12.0 mL, 8.40 mmol, 3.00 equiv) was then added dropwise via syringe over 30 min at 0 °C. The reaction mixture was stirred for 2 h at 0 °C. The product mixture was diluted sequentially with saturated aqueous potassium sodium tartrate solution (50 mL), saturated aqueous sodium chloride solution (50 mL), and ethyl acetate (100 mL). The resulting mixture was warmed up 23 °C over 30 min, and then stirred vigorously for 45 min at 23 °C. The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 50 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (50 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was used directly in the following step.

Within the limits of detection, the product **S23** was formed as a 3.6:1 mixture of diastereomers (<sup>1</sup>H NMR analysis, 400 MHz). The relative stereochemistry at the C5 position of the allylic alcohol **S23** was established via conversion to the acetonide **174**.

Part 2: Synthesis of the diol **173**:

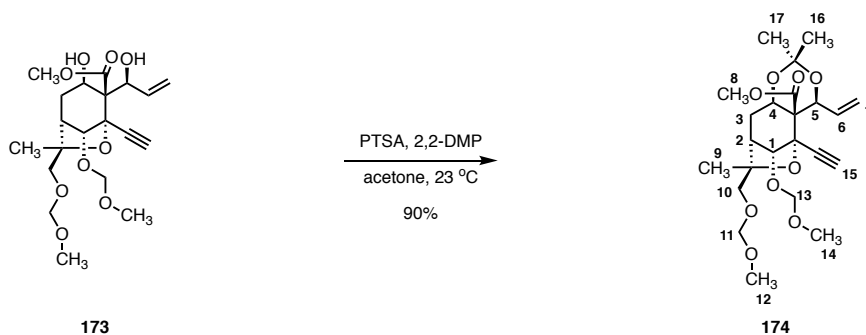


Potassium carbonate (774 mg, 5.60 mmol, 2.00 equiv) was added in one portion to a solution of the residue obtained in the preceding step (nominally, 2.80 mmol, 1 equiv) in methanol (20 mL) at 0 °C. The reaction mixture stirred for 1 h at 0 °C. The cold product mixture was diluted sequentially with saturated aqueous ammonium chloride solution (10 mL), water (10 mL), and ethyl acetate (30 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 20 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (30 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 30% ethyl acetate–hexanes) to provide the diol **173** as a yellow oil (788 mg, 68% over two steps).

$R_f = 0.20$  (40% ethyl acetate–hexanes; PAA).  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.16 (ddd,  $J = 17.4, 10.4, 7.2$  Hz,  $\text{H}_6$ , 1H), 5.27 (d,  $J = 17.1$  Hz,  $\text{H}_{7a}$ , 1H), 5.21 (d,  $J = 7.2$  Hz,  $\text{H}_5$ , 1H), 5.12 (d,  $J = 9.5$  Hz,  $\text{H}_{7b}$ , 1H), 4.72 (d,  $J = 6.8$  Hz,  $\text{H}_{13a}$ , 1H), 4.69 (d,  $J = 6.8$  Hz,  $\text{H}_{13b}$ , 1H), 4.67 – 4.65 (m,  $\text{H}_4$ , 1H), 4.61 (s,  $\text{H}_{11}$ , 2H), 4.17 (s,  $\text{H}_1$ , 1H), 3.97 (d,  $J = 9.3$  Hz,  $\text{H}_{10a}$ , 1H),

3.74 (s, H<sub>8</sub>, 3H), 3.54 (d,  $J = 9.2$  Hz, H<sub>10b</sub>, 1H), 3.37 (s, H<sub>12</sub>, 3H), 3.35 (s, H<sub>14</sub>, 3H), 2.77 (s, H<sub>15</sub>, 1H), 2.49 – 2.47 (m, H<sub>2</sub>, 1H), 2.33 (ddd,  $J = 13.9, 7.0, 3.7$  Hz, H<sub>3a</sub>, 1H), 1.92 (ddd,  $J = 14.1, 11.2, 3.0$  Hz, H<sub>3b</sub>, 1H), 1.47 (s, H<sub>9</sub>, 3H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  172.2 (C), 137.5 (CH), 116.4 (CH<sub>2</sub>), 96.6 (CH<sub>2</sub>), 95.3 (CH<sub>2</sub>), 87.8 (C), 86.2 (C), 83.3 (CH), 78.6 (CH), 77.2 (C), 75.9 (CH), 73.3 (CH<sub>2</sub>), 64.7 (CH), 63.2 (C), 55.5 (CH<sub>3</sub>), 55.3 (CH<sub>3</sub>), 52.2 (CH<sub>3</sub>), 43.2 (CH), 35.1 (CH<sub>2</sub>), 19.2 (CH<sub>3</sub>). IR (ATR-FTIR), cm<sup>-1</sup>: 3735 (s), 3628 (s), 2950 (m), 1717 (s). HRMS-Cl (m/z): calcd for C<sub>20</sub>H<sub>30</sub>NaO<sub>9</sub>, 437.1788; found: 437.1783.  $[\alpha]_D^{20} = -6.27$  ( $c = 0.17$ , CHCl<sub>3</sub>).

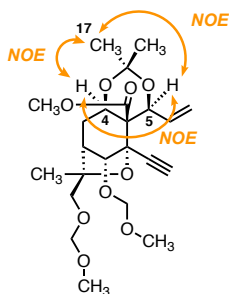
*Synthesis of the acetonide 174:*



*para*-Toluenesulfonic acid monohydrate (46.6 mg, 241  $\mu$ mol, 0.20 equiv) was added in one portion to a solution of the diol **173** (500 mg, 121 mmol, 1 equiv) in acetone (4.0 mL) and 2,2-dimethoxypropane (4.0 mL) at 23 °C. The reaction mixture was stirred for 15 h at 23 °C. The product mixture was then diluted sequentially with ethyl acetate (40 mL), water (10 mL), and saturated aqueous sodium bicarbonate solution (10 mL). The diluted product mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3  $\times$  20 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 20% ethyl acetate–hexanes) to provide the acetonide **174** as a colorless oil (490 mg, 90%).

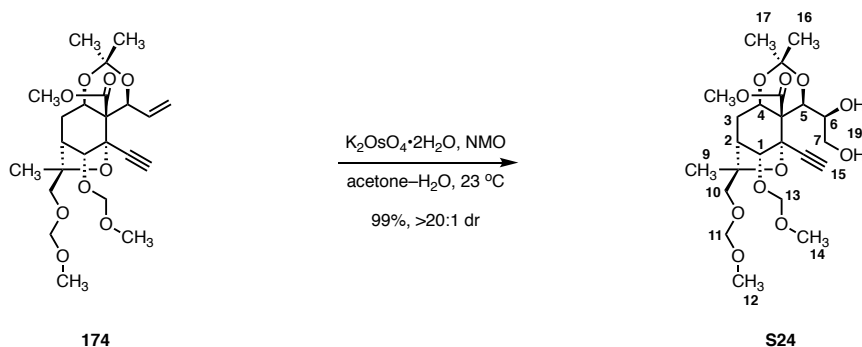
NOE correlations between the C4 hydrogen atom and the C17 methyl substituent, as well the C5 hydrogen and the C17 methyl substituent, and also C4 hydrogen atom and the C5 hydrogen support the relative configuration depicted.





$R_f = 0.50$  (33% ethyl acetate–hexanes; PAA).  $^1\text{H NMR}$  (600 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.59 (ddd,  $J = 16.9, 10.5, 6.2$  Hz,  $\text{H}_6$ , 1H), 5.36 (d,  $J = 17.0$  Hz,  $\text{H}_{7a}$ , 1H), 5.21 (d,  $J = 10.5$  Hz,  $\text{H}_{7b}$ , 1H), 4.74 (d,  $J = 6.8$  Hz,  $\text{H}_{13a}$ , 1H), 4.67 (d,  $J = 7.0$  Hz,  $\text{H}_{13b, 5}$  2H), 4.62 (s,  $\text{H}_{11}$ , 2H), 4.46 (dd,  $J = 12.1, 5.9$  Hz,  $\text{H}_4$ , 1H), 4.12 (s,  $\text{H}_1$ , 1H), 4.02 (d,  $J = 9.2$  Hz,  $\text{H}_{10a}$ , 1H), 3.77 (s,  $\text{H}_8$ , 3H), 3.60 (d,  $J = 9.2$  Hz,  $\text{H}_{10b}$ , 1H), 3.36 (s,  $\text{H}_{12}$ , 3H), 3.35 (s,  $\text{H}_{14}$ , 3H), 2.64 (s,  $\text{H}_{15}$ , 1H), 2.54 (t,  $J = 3.4$  Hz,  $\text{H}_2$ , 1H), 2.13 (td,  $J = 12.5, 2.8$  Hz,  $\text{H}_{3a}$ , 1H), 1.99 (ddd,  $J = 13.3, 5.9, 3.9$  Hz,  $\text{H}_{3b}$ , 1H), 1.53 (s,  $\text{H}_{16}$ , 3H), 1.51 (s,  $\text{H}_9$ , 3H), 1.43 (s,  $\text{H}_{17}$ , 3H).  $^{13}\text{C NMR}$  (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  169.6 (C), 135.0 (CH), 118.1 ( $\text{CH}_2$ ), 100.2 (C), 96.7 ( $\text{CH}_2$ ), 95.3 ( $\text{CH}_2$ ), 87.6 (C), 84.5 (CH), 82.6 (C), 79.8 (C), 78.5 (CH), 76.3 (CH), 73.8 ( $\text{CH}_2$ ), 69.8 (CH), 59.0 (C), 55.5 ( $\text{CH}_3$ ), 55.3 ( $\text{CH}_3$ ), 51.5 ( $\text{CH}_3$ ), 43.1 (CH), 30.6 ( $\text{CH}_2$ ), 29.5 ( $\text{CH}_3$ ), 19.7 ( $\text{CH}_3$ ), 19.1 ( $\text{CH}_3$ ). IR (ATR-FTIR),  $\text{cm}^{-1}$ : 3735 (s), 3648 (m), 2948 (m), 1735 (s). HRMS-CI ( $m/z$ ): calcd for  $\text{C}_{23}\text{H}_{34}\text{NaO}_9$ , 477.2101; found: 477.2100.  $[\alpha]_D^{20} = 8.00$  ( $c = 0.15$ ,  $\text{CHCl}_3$ ).

*Synthesis of the diol S24:*

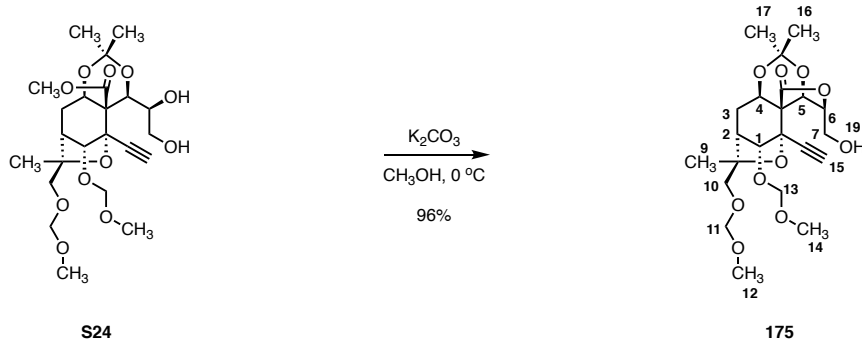


Potassium osmate(VI) dihydrate (12.2 mg, 33.0  $\mu\text{mol}$ , 10.0 mol %) was added to a solution of the acetonide **174** (150 mg, 330  $\mu\text{mol}$ , 1 equiv) and N-methyl-morpholine N-oxide (116 mg, 990  $\mu\text{mol}$ , 3.00 equiv) in 66% acetone–water (v/v, 3.0 mL) at 23 °C. The reaction mixture was stirred for 18 h at 23 °C. The product mixture was then poured into a stirring mixture of ethyl acetate (15 mL) and saturated aqueous sodium thiosulfate solution (10 mL). The diluted product mixture was stirred for 10 min at 23 °C. The resulting biphasic mixture was transferred to a separatory funnel, and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3  $\times$  10 mL). The organic layers were combined, and the combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue obtained was purified by flash column chromatography (eluting with 50% ethyl acetate–hexanes) to provide the diol **S24** as a colorless oil (159 mg, 99%).

Within the limits of detection, the diol **S24** was formed as a >20:1 mixture of diastereomers ( $^1\text{H}$  NMR analysis, 400 MHz). The relative stereochemistry at the C6 position of the diol **S24** was established via conversion to the lactone **175**.

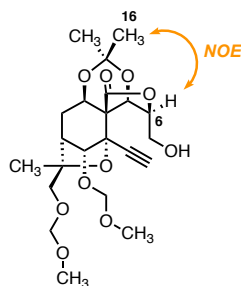
$R_f = 0.10$  (50% ethyl acetate–hexanes; PAA).  $^1\text{H}$  NMR (400 MHz,  $\text{C}_6\text{D}_6$ ):  $\delta$  5.35 (t,  $J = 5.2$  Hz, H<sub>4</sub>, 1H), 4.62 (d,  $J = 6.8$  Hz, H<sub>13a</sub>, 1H), 4.56 – 4.40 (m, H<sub>1</sub>, H<sub>5</sub>, H<sub>6</sub>, H<sub>11</sub>, H<sub>13b</sub>, 6H), 4.22 (d,  $J = 9.3$  Hz, H<sub>10a</sub>, 1H), 4.08 – 4.01 (m, H<sub>7a</sub>, 1H), 3.97 – 3.90 (m, H<sub>7b</sub>, 1H), 3.70 (d,  $J = 5.1$  Hz, H<sub>18</sub>, 1H), 3.62 (d,  $J = 9.3$  Hz, H<sub>10b</sub>, 1H), 3.43 (s, H<sub>8</sub>, 3H), 3.16 (s, H<sub>12</sub>, 3H), 3.12 (s, H<sub>14</sub>, 3H), 2.48 (s, H<sub>19</sub>, 1H), 2.38 (t,  $J = 3.4$  Hz, H<sub>2</sub>, 1H), 2.30 (td,  $J = 12.6, 2.8$  Hz, H<sub>3a</sub>, 1H), 2.14 (s, H<sub>15</sub>, 1H), 1.93 – 1.80 (m, H<sub>3b</sub>, 1H), 1.44 (s, H<sub>9</sub>, 3H), 1.32 (s, H<sub>16</sub>, 3H), 1.28 (s, H<sub>17</sub>, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{C}_6\text{D}_6$ ):  $\delta$  170.3 (C), 136.4 (C), 100.5 (CH<sub>2</sub>), 96.9 (CH<sub>2</sub>), 95.6 (C), 88.1 (CH), 84.7 (C), 82.5 (CH), 81.8 (C), 81.1 (CH), 78.2 (CH<sub>2</sub>), 74.2 (CH<sub>2</sub>), 71.8 (CH), 70.2 (CH), 64.1 (CH<sub>2</sub>), 59.9 (C), 55.4 (CH<sub>3</sub>), 55.0 (CH<sub>3</sub>), 51.2 (CH<sub>2</sub>), 43.3 (CH), 31.3 (CH<sub>3</sub>), 29.5 (CH<sub>3</sub>), 19.4 (CH<sub>3</sub>), 19.3 (CH<sub>3</sub>). IR (ATR-FTIR),  $\text{cm}^{-1}$ : 3733 (s), 3260 (s), 2990 (s), 2950 (m), 1733 (s). HRMS-CI ( $m/z$ ): calcd for  $\text{C}_{23}\text{H}_{36}\text{NaO}_{11}$ , 511.2155; found: 511.2146.  $[\alpha]_D^{20} = 1.35$  ( $c = 0.27$ ,  $\text{CHCl}_3$ ).

*Synthesis of the lactone 175:*



Potassium carbonate (56.6 mg, 409  $\mu\text{mol}$ , 2.00 equiv) was added in one portion to a solution of the diol **S24** (100 mg, 205  $\mu\text{mol}$ , 1 equiv) in methanol (2.0 mL) at 0  $^\circ\text{C}$ . The reaction mixture stirred for 1 h at 0  $^\circ\text{C}$ . The cold product mixture was diluted sequentially with saturated aqueous ammonium chloride solution (5.0 mL), water (5.0 mL), and ethyl acetate (20 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3  $\times$  10 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 25% ethyl acetate–hexanes) to provide the lactone **175** as a yellow oil (90 mg, 96%).

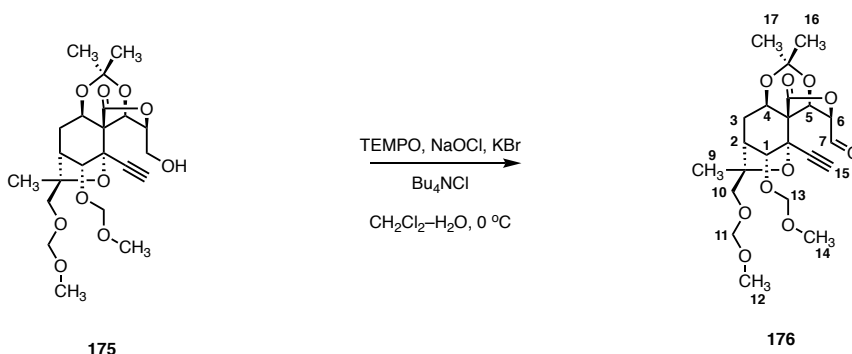
NOE correlations between the C6 hydrogen atom and the C16 methyl substituent support the relative configuration depicted.



$R_f = 0.40$  (50% ethyl acetate–hexanes; PAA).  $^1\text{H NMR}$  (400 MHz,  $\text{C}_6\text{D}_6$ ):  $\delta$  5.96 (s,  $\text{H}_1$ , 1H), 4.84 (d,  $J = 1.5$  Hz,  $\text{H}_5$ , 1H), 4.72 (d,  $J = 6.5$  Hz,  $\text{H}_{13a}$ , 1H), 4.69 – 4.62 (m,  $\text{H}_{4,6}$ , 2H), 4.60 (d,  $J = 6.5$  Hz,  $\text{H}_{13b}$ , 1H), 4.56 – 4.47 (m,  $\text{H}_{11}$ , 2H), 4.26 (d,  $J = 9.3$  Hz,  $\text{H}_{10a}$ , 1H), 3.83 (ddd,  $J = 11.8, 8.0, 3.7$  Hz,  $\text{H}_{7a}$ , 1H), 3.67 (d,  $J = 9.3$  Hz,  $\text{H}_{10b}$ , 1H), 3.60 (dt,  $J = 12.3, 6.8$  Hz,  $\text{H}_{7b}$ , 1H), 3.22 (s,  $\text{H}_{12}$ , 3H), 3.17 (s,  $\text{H}_{14}$ , 3H), 2.49 (t,  $J = 3.4$  Hz,  $\text{H}_2$ , 1H), 2.41 (td,  $J = 13.0, 2.5$  Hz,  $\text{H}_{3a}$ , 1H), 1.92 (s,  $\text{H}_{19}$ , 1H), 1.79 (ddd,  $J = 13.2, 6.1, 4.2$  Hz,  $\text{H}_{3b}$ , 1H), 1.48 (s,  $\text{H}_9$ , 3H), 1.32 (s,  $\text{H}_{16}$ , 3H), 1.26 (s,  $\text{H}_{17}$ , 3H).  $^{13}\text{C NMR}$  (100 MHz,  $\text{C}_6\text{D}_6$ ):  $\delta$  174.3 (C), 104.1 (C), 96.8 ( $\text{CH}_2$ ), 96.3 ( $\text{CH}_2$ ), 87.7 (C), 84.6 (CH), 82.6 (C), 82.0 (CH), 80.2 (C), 78.5 (CH), 77.3 (CH), 74.4 ( $\text{CH}_2$ ), 66.0 (CH), 63.4 ( $\text{CH}_2$ ), 59.1 (C), 55.5 ( $\text{CH}_3$ ), 55.0 ( $\text{CH}_3$ ), 43.1 (CH), 28.4 ( $\text{CH}_3$ ), 28.1 ( $\text{CH}_2$ ), 27.7 ( $\text{CH}_3$ ), 19.6 ( $\text{CH}_3$ ). IR (ATR-FTIR),  $\text{cm}^{-1}$ : 3736 (s), 3260 (s), 2949 (s), 2159 (m), 1762 (s). HRMS-CI ( $m/z$ ): calcd for  $\text{C}_{23}\text{H}_{32}\text{NaO}_{10}$ , 479.1893; found: 479.1891.  $[\alpha]_D^{20} = 17.2$  ( $c = 0.33$ ,  $\text{CHCl}_3$ ).

*Synthesis of the olefin 179:*

*Part 1: Synthesis of the aldehyde 176:*



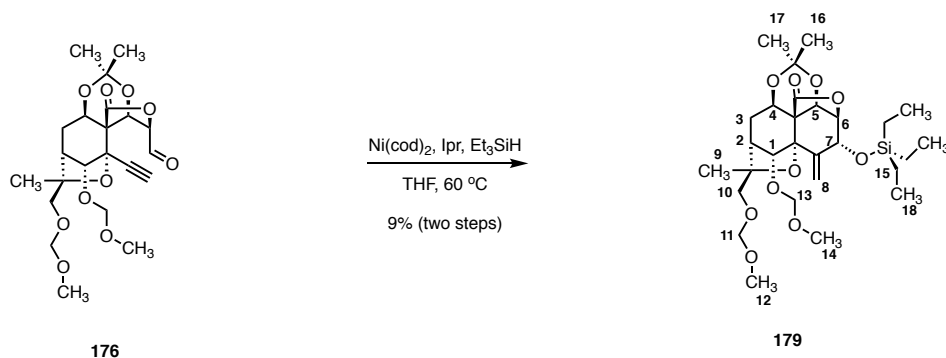
A stock solution of potassium bromide (29.0 mg, 0.244 mmol) and tetrabutylammonium chloride (30.0 mg, 0.108 mmol) in saturated aqueous sodium bicarbonate solution (4.0 mL) was prepared. A second stock solution of aqueous sodium hypochlorite (10-15 % chlorine, 2.75 mL), saturated aqueous sodium bicarbonate solution (4.0 mL) and saturated aqueous sodium chloride solution (11.0 mL) was also prepared. 274  $\mu$ L of the potassium bromide solution and 183  $\mu$ L of the aqueous sodium hypochlorite solution were sequentially added to a stirring solution of the lactone **175** (25 mg, 55.0  $\mu$ mol, 1 equiv) and TEMPO (1.0 mg, 6.0  $\mu$ mol, 0.10 eq) in dichloromethane (200  $\mu$ L) at 0 °C. The biphasic reaction mixture was stirred vigorously for 90 min at 0 °C. The product mixture was then diluted sequentially with dichloromethane (5.0 mL), saturated aqueous sodium bicarbonate solution (5.0 mL), and saturated aqueous sodium thiosulfate solution (5.0 mL). The diluted product mixture was stirred for 30 min at 0 °C. The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with dichloromethane (3  $\times$  5 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (10

mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The aldehyde residue obtained was used directly in the following step.

The lactone product **176** proved unstable towards silica gel purification and was also found decompose appreciably within 2h at 23 °C.

$R_f = 0.50$  (33% ethyl acetate–hexanes; PAA).  $^1\text{H NMR}$  (600 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  9.29 (s, H<sub>7</sub>, 1H), 5.70 (s, H<sub>1</sub>, 1H), 5.25 (s, H<sub>6</sub>, 1H), 4.62 (d,  $J = 6.6$  Hz, H<sub>13a</sub>, 1H), 4.54 (dd,  $J = 12.5$ , 6.3 Hz, H<sub>4</sub>, 1H), 4.51 – 4.47 (m, H<sub>11a,13b</sub>, 2H), 4.45 (d,  $J = 6.3$  Hz, H<sub>11b</sub>, 1H), 4.38 (d,  $J = 1.1$  Hz, H<sub>5</sub>, 1H), 4.18 (d,  $J = 9.3$  Hz, H<sub>10a</sub>, 1H), 3.58 (d,  $J = 9.3$  Hz, H<sub>10b</sub>, 1H), 3.16 (s, H<sub>12</sub>, 3H), 3.14 (s, H<sub>14</sub>, 3H), 2.44 (t,  $J = 3.3$  Hz, H<sub>2</sub>, 1H), 2.36 (td,  $J = 13.0$ , 2.5 Hz, H<sub>3a</sub>, 1H), 1.83 – 1.72 (m, H<sub>3b,15</sub>, 2H), 1.40 (s, H<sub>9</sub>, 3H), 1.21 (s, H<sub>16</sub>, 4H), 1.17 (s, H<sub>17</sub>, 3H).

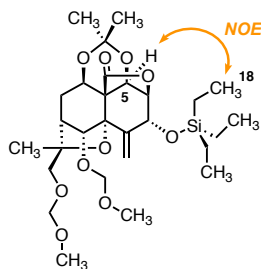
Part 2: Synthesis of the olefin **179**:



A stock solution of the catalyst was prepared in a nitrogen-filled glovebox by stirring a solution of bis(1,5-cyclooctadiene)nickel(0) (46.0 mg, 167  $\mu\text{mol}$ , 1.00 equiv) and 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene (IPr, 65.4 mg, 167  $\mu\text{mol}$ , 1.00 equiv) in tetrahydrofuran (1.0 mL) at  $20\text{ }^\circ\text{C}$  for 30 min. A portion of the catalyst stock solution (100  $\mu\text{L}$ , 30 mol%) was added to a 25-mL screw-capped pressure vessel containing a stirring solution of the aldehyde residue obtained in the preceding step (nominally 55.0  $\mu\text{mol}$ , 1 equiv) and triethylsilane (26.0  $\mu\text{L}$ , 165  $\mu\text{mol}$ , 3.00 equiv) in tetrahydrofuran (1.8 mL) at  $20\text{ }^\circ\text{C}$ . The reaction vessel was subsequently sealed and the sealed vessel was removed from the glovebox. The reaction vessel was placed in an oil bath that had been preheated to  $60\text{ }^\circ\text{C}$ . The resulting solution was stirred for 2 h at  $60\text{ }^\circ\text{C}$ . The product mixture was then cooled to  $23\text{ }^\circ\text{C}$  over 30 min. The cooled product mixture was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 15% ethyl acetate–hexanes) to provide the olefin **179** as a colorless oil (2.90 mg, 9% over two steps).

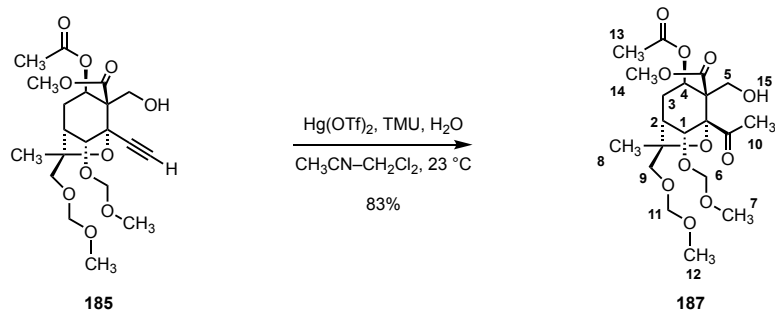
NOE correlations between the C5 hydrogen atom and the C18 methyl substituent of the triethylsilyl group support the relative configuration depicted.





$R_f = 0.50$  (33% ethyl acetate–hexanes; PAA).  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.18 (s,  $\text{H}_{8a}$ , 1H), 5.70 (s,  $\text{H}_{8b}$ , 1H), 4.78 (s,  $\text{H}_5$ , 1H), 4.66 (s,  $\text{H}_1$ , 1H), 4.65 – 4.58 (m,  $\text{H}_4, 11a, 11b, 13a$ , 4H), 4.50 (d,  $J = 7.7$  Hz,  $\text{H}_7, 13b$ , 2H), 4.25 (d,  $J = 3.6$  Hz,  $\text{H}_6$ , 1H), 4.02 (d,  $J = 9.2$  Hz,  $\text{H}_{10a}$ , 1H), 3.62 (d,  $J = 9.2$  Hz,  $\text{H}_{10b}$ , 1H), 3.36 (s,  $\text{H}_{12}$ , 3H), 3.32 (s,  $\text{H}_{14}$ , 3H), 2.64 (s,  $\text{H}_2$ , 1H), 2.48 (t,  $J = 12.7$  Hz,  $\text{H}_{3a}$ , 1H), 2.05 – 1.96 (m,  $\text{H}_{3b}$ , 1H), 1.56 (s,  $\text{H}_{16}$ , 3H), 1.51 (s,  $\text{H}_9$ , 3H), 1.43 (s,  $\text{H}_{17}$ , 3H), 0.97 (t,  $J = 7.9$  Hz,  $\text{H}_{18}$ , 9H), 0.66 (q,  $J = 8.0$  Hz,  $\text{H}_{15}$ , 6H).  $^{13}\text{C NMR}$  (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  174.2 (C), 140.8 (C), 129.9 ( $\text{CH}_2$ ), 101.2 (C), 96.7 ( $\text{CH}_2$ ), 96.4 ( $\text{CH}_2$ ), 85.6 (C), 84.0 (CH), 82.9 (C), 79.8 (CH), 74.1 ( $\text{CH}_2$ ), 71.4 (CH), 71.4 (CH), 64.8 (CH), 55.9 ( $\text{CH}_3$ ), 55.3 ( $\text{CH}_3$ ), 54.0 (C), 44.5 (CH), 29.5 ( $\text{CH}_3$ ), 28.7 ( $\text{CH}_2$ ), 20.5 ( $\text{CH}_3$ ), 19.3 ( $\text{CH}_3$ ), 6.8 ( $3 \times \text{CH}_3$ ), 4.9 ( $3 \times \text{CH}_2$ ). IR (ATR-FTIR),  $\text{cm}^{-1}$ : 3734 (s), 3628 (s), 2975 (m), 1717 (m). HRMS-Cl ( $m/z$ ): calcd for  $\text{C}_{28}\text{H}_{46}\text{NaO}_{10}\text{Si}$ , 593.2758; found: 593.2752.  $[\alpha]_D^{20} = -6.81$  ( $c = 0.07$ ,  $\text{CHCl}_3$ ).

*Synthesis of the methyl ketone 187:*

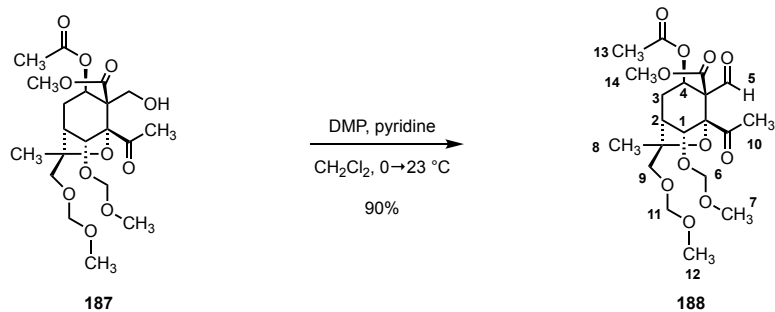


Water (502  $\mu\text{L}$ , 27.9 mmol, 2.50 equiv), *N,N,N',N'*-tetramethylurea (268  $\mu\text{L}$ , 2.23 mmol, 0.200 equiv), and mercury (II) trifluoromethanesulfonate (556 mg, 1.11 mmol, 0.100 equiv) were added in sequence to a solution of the alkyne **185** (4.80 g, 11.2 mmol, 1 equiv) in acetonitrile (56 mL) and dichloromethane (2.8 mL) at  $23\text{ }^\circ\text{C}$ . The reaction mixture was stirred for 2 h at  $23\text{ }^\circ\text{C}$ . The product mixture was diluted sequentially with saturated aqueous sodium bicarbonate solution (100 mL) and ethyl acetate (100 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate ( $3 \times 200\text{ mL}$ ). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (100 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 33% ethyl acetate–hexanes) to provide the methyl ketone **187** as a colorless solid (4.15 g, 83%).

$R_f = 0.30$  (50% ethyl acetate–hexanes; PAA).  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  5.40 (s,  $\text{H}_1$ , 1H), 4.92 (dd,  $J = 10.6, 7.4\text{ Hz}$ ,  $\text{H}_4$ , 1H), 4.64 (s,  $\text{H}_{11}$ , 2H), 4.56 (d,  $J = 6.7\text{ Hz}$ ,  $\text{H}_{6a}$ , 1H), 4.48 (d,  $J = 6.7\text{ Hz}$ ,  $\text{H}_{6b}$ , 1H), 4.03 (d,  $J = 9.0\text{ Hz}$ ,  $\text{H}_{9a}$ , 1H), 3.87 (s,  $\text{H}_{14}$ , 3H), 3.66 (d,  $J =$

9.0 Hz, H<sub>9b</sub>, 1H), 3.37 (s, H<sub>12</sub>, 3H), 3.29 (s, H<sub>7</sub>, 3H), 2.61 (bs, H<sub>15</sub>, 1H), 2.53 (s, H<sub>2</sub>, 1H), 2.33 (ddd, J = 13.6, 7.4, 4.0 Hz, H<sub>3a</sub>, 1H), 2.24 (s, H<sub>10</sub>, 3H), 1.98 (s, H<sub>13</sub>, 3H), 1.94 (ddd, J = 13.5, 10.6, 2.8 Hz, H<sub>3b</sub>, 1H), 1.57 (s, H<sub>8</sub>, 3H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 210.1 (C), 171.5 (C), 170.2 (C), 96.9 (CH<sub>2</sub>), 96.0 (CH<sub>2</sub>), 92.9 (C), 87.3 (C), 84.0 (CH), 73.9 (CH<sub>2</sub>), 70.5 (CH), 64.1 (CH<sub>2</sub>), 61.4 (C), 55.8 (CH<sub>3</sub>), 55.5 (CH<sub>3</sub>), 52.5 (CH<sub>3</sub>), 42.3 (CH), 31.3 (CH<sub>2</sub>), 28.9 (CH<sub>3</sub>), 21.1 (CH<sub>3</sub>), 20.5 (CH<sub>3</sub>). IR (ATR-FTIR), cm<sup>-1</sup>: 3734 (s), 3628 (m), 2953 (m), 1733 (s). HRMS-Cl (m/z): [M + Na]<sup>+</sup> calculated for C<sub>20</sub>H<sub>32</sub>NaO<sub>11</sub>, 471.1842; found 471.1830. [ $\alpha$ ]<sub>D</sub><sup>20</sup> = -112.8 (c = 0.08, CHCl<sub>3</sub>).

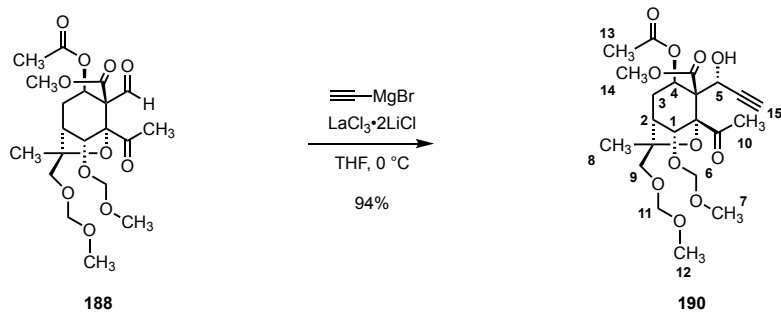
*Synthesis of the aldehyde 188:*



The Dess–Martin periodinane (7.57 g, 17.9 mmol, 2.00 equiv) was added in five equal portions over 1 h to a solution of the methyl ketone **187** (4.00 g, 8.92 mmol, 1 equiv) and pyridine (7.06 mL, 89.2 mmol, 10.0 equiv) in dichloromethane (45 mL) at 0 °C. Upon completion of the addition, the cooling bath was removed and the reaction mixture was warmed to 23 °C over 30 min. The warmed mixture was stirred for 12 h at 23 °C. The product mixture was diluted sequentially with dichloromethane (50 mL), saturated aqueous sodium bicarbonate solution (100 mL), and saturated aqueous sodium thiosulfate solution (100 mL). The diluted product mixture was stirred for 1 h at 23 °C. The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with dichloromethane (3 × 200 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (100 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 33% ethyl acetate–hexanes) to provide the aldehyde **188** as a colorless oil (3.60 g, 90%).

R<sub>f</sub> = 0.50 (50% ethyl acetate–hexanes; PAA). <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>): δ 9.31 (s, H<sub>5</sub>, 1H), 5.61 – 5.50 (m, H<sub>4,1</sub>, 2H), 4.62 (s, H<sub>11</sub>, 2H), 4.59 (d, J = 6.6 Hz, H<sub>6a</sub>, 1H), 4.52 (d, J = 6.6 Hz, H<sub>6b</sub>, 1H), 4.05 (d, J = 9.0 Hz, H<sub>9a</sub>, 1H), 3.83 (s, H<sub>14</sub>, 3H), 3.62 (d, J = 9.0 Hz, H<sub>9b</sub>, 1H), 3.36 (s, H<sub>12</sub>, 3H), 3.29 (s, H<sub>7</sub>, 3H), 2.59 (t, J = 3.5 Hz, H<sub>2</sub>, 1H), 2.44 (ddd, J = 13.6, 7.2, 4.0 Hz, H<sub>3a</sub>, 1H), 2.33 (s, H<sub>10</sub>, 3H), 2.03 (s, H<sub>13</sub>, 3H), 2.00 (ddd, J = 13.6, 10.8, 2.8 Hz, H<sub>3b</sub>, 1H), 1.54 (s, H<sub>8</sub>, 3H). <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>): δ 209.6 (C), 192.2 (CH), 170.0 (C), 167.4 (C), 96.9 (CH<sub>2</sub>), 96.1 (CH<sub>2</sub>), 92.5 (C), 87.9 (C), 83.3 (CH), 73.5 (CH<sub>2</sub>), 69.0 (C), 68.0 (CH), 55.9 (CH<sub>3</sub>), 55.6 (CH<sub>3</sub>), 52.9 (CH<sub>3</sub>), 42.5 (CH), 30.3 (CH<sub>2</sub>), 28.7 (CH<sub>3</sub>), 21.0 (CH<sub>3</sub>), 20.3 (CH<sub>3</sub>). IR (ATR-FTIR), cm<sup>-1</sup>: 2952 (m), 1747 (s), 1727 (s). HRMS-CI (m/z): [M + Na]<sup>+</sup> calculated for C<sub>20</sub>H<sub>30</sub>NaO<sub>11</sub>, 469.1686; found 469.1687. [α]<sub>D</sub><sup>20</sup> = -107.6 (c = 0.36, CHCl<sub>3</sub>).

*Synthesis of the propargylic alcohol 190:*

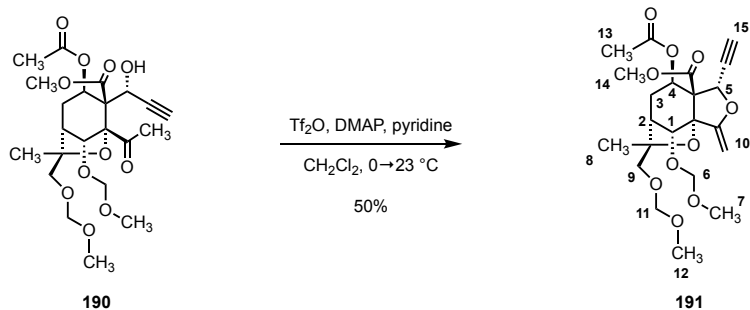


A solution of lanthanum(III) chloride bis(lithium chloride) complex in tetrahydrofuran (600 mM, 40.3 mL, 24.2 mmol, 3.00 equiv) was added to a solution of the aldehyde **188** (3.60 g, 8.06 mmol, 1 equiv) in tetrahydrofuran (40 mL) at  $23\text{ }^\circ\text{C}$ . The resulting solution was stirred for 1 h at  $23\text{ }^\circ\text{C}$  and then cooled to  $0\text{ }^\circ\text{C}$ . A solution of ethynylmagnesium bromide in tetrahydrofuran (500 mM, 74.2 mL, 37.1 mmol, 4.60 equiv) was then added dropwise via syringe over 30 min. The reaction mixture was stirred for 2 h at  $0\text{ }^\circ\text{C}$ . The product mixture was diluted sequentially with saturated aqueous potassium sodium tartrate solution (250 mL), saturated aqueous sodium chloride solution (500 mL), and ethyl acetate (500 mL). The resulting mixture was warmed up  $23\text{ }^\circ\text{C}$  over 30 min, and then stirred vigorously for 45 min at  $23\text{ }^\circ\text{C}$ . The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate ( $3 \times 250\text{ mL}$ ). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (300 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 20% ethyl acetate–hexanes) to provide the propargylic alcohol **190** as a colorless oil (3.56 g, 94%).

Within the limits of detection, the product **190** was formed as a single diastereomer (<sup>1</sup>H NMR analysis, 500 MHz).

R<sub>f</sub> = 0.45 (50% ethyl acetate–hexanes; PAA). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 5.24 (s, H<sub>1</sub>, 1H), 4.93 (dd, J = 10.1, 7.8 Hz, H<sub>4</sub>, 1H), 4.81 – 4.75 (m, H<sub>5</sub>, 1H), 4.63 (s, H<sub>11</sub>, 2H), 4.55 (d, J = 6.7 Hz, H<sub>6a</sub>, 1H), 4.46 (d, J = 6.7 Hz, H<sub>6b</sub>, 1H), 4.01 (d, J = 9.0 Hz, H<sub>9a</sub>, 1H), 3.92 (s, H<sub>14</sub>, 3H), 3.65 (d, J = 9.0 Hz, H<sub>9b</sub>, 1H), 3.37 (s, H<sub>12</sub>, 3H), 3.29 (s, H<sub>7</sub>, 3H), 2.52 (t, J = 3.1 Hz, H<sub>2</sub>, 1H), 2.46 – 2.37 (m, H<sub>3a</sub>, 1H), 2.32 (d, J = 2.3 Hz, H<sub>15</sub>, 1H), 2.21 (s, H<sub>10</sub>, 3H), 1.97 (s, H<sub>13</sub>, 3H), 1.90 (t, J = 12.0 Hz, H<sub>3b</sub>, 1H), 1.58 (s, H<sub>8</sub>, 3H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 209.1 (C), 170.1 (C), 169.7 (C), 96.8 (CH<sub>2</sub>), 95.8 (CH<sub>2</sub>), 92.6 (C), 87.6 (C), 84.1 (CH), 82.1 (CH), 73.6 (CH<sub>2</sub>), 72.8 (C), 70.0 (CH), 64.7 (CH), 64.1 (C), 55.7 (CH<sub>3</sub>), 55.4 (CH<sub>3</sub>), 52.3 (CH<sub>3</sub>), 41.9 (CH), 31.8 (CH<sub>2</sub>), 28.7 (CH<sub>3</sub>), 21.2 (CH<sub>3</sub>), 20.5 (CH<sub>3</sub>). IR (ATR-FTIR), cm<sup>-1</sup>: 3726 (m), 3628 (m), 3274 (m), 2952 (m), 1717 (s). HRMS-Cl (m/z): [M + Na]<sup>+</sup> calculated for C<sub>22</sub>H<sub>32</sub>NaO<sub>11</sub>, 495.1842; found 495.1838. [α]<sub>D</sub><sup>20</sup> = -69.2 (c = 0.16, CHCl<sub>3</sub>).

*Synthesis of the vinyl ether 191:*



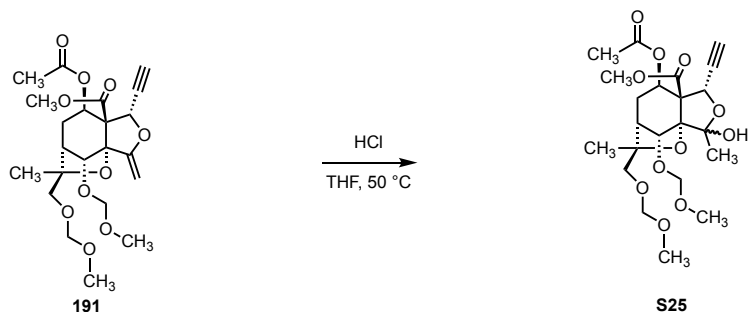
(4-Dimethylamino)pyridine (DMAP, 10.0 mg, 9.1  $\mu\text{mol}$ , 0.05 equiv), pyridine (1.20 mL, 14.6 mmol, 8.00 equiv), and triflic anhydride (490  $\mu\text{L}$ , 2.91 mmol, 1.60 equiv) were added in sequence to a solution of the propargylic alcohol **190** (860 mg, 1.82 mmol, 1 equiv) in dichloromethane (13 mL) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C. The cooling bath was then removed, and the reaction mixture was allowed to warm to 23 °C over 30 min. The reaction mixture was stirred for 2 h at 23 °C. The product mixture was diluted sequentially with dichloromethane (20 mL) and water (20 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with dichloromethane (3  $\times$  50 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (500 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 33% ethyl acetate–hexanes initially, grading to 50% ethyl acetate–hexanes, 2 steps) to provide separately the vinyl ether **191** (colorless oil, 413 mg, 50%) and the propargylic alcohol **190** (colorless oil, 177 mg, 21%).



R<sub>f</sub> = 0.40 (50% ethyl acetate–hexanes; PAA). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 5.85 (dd, J = 10.6, 6.4 Hz, H<sub>4</sub>, 1H), 5.51 (s, H<sub>5</sub>, 1H), 4.90 (s, H<sub>1</sub>, 1H), 4.74 (d, J = 6.7 Hz, H<sub>6a</sub>, 1H), 4.65 (s, H<sub>10a</sub>, 1H), 4.63 (d, J = 6.7 Hz, H<sub>6b</sub>, 1H), 4.59 (s, H<sub>11</sub>, 2H), 4.51 (s, H<sub>10b</sub>, 1H), 4.12 (d, J = 9.1 Hz, H<sub>9a</sub>, 1H), 3.80 (s, H<sub>14</sub>, 3H), 3.46 (d, J = 9.1 Hz, H<sub>9b</sub>, 1H), 3.37 (s, H<sub>12</sub>, 3H), 3.34 (s, H<sub>7</sub>, 3H), 2.74 (s, H<sub>15</sub>, 1H), 2.72 (s, H<sub>2</sub>, 1H) 2.42 (d, J = 13.0 Hz, H<sub>3a</sub>, 1H), 2.25 (t, J = 12.3 Hz, H<sub>3b</sub>, 1H), 2.03 (s, H<sub>13</sub>, 3H), 1.60 (s, H<sub>8</sub>, 3H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 170.3 (C), 169.7 (C), 156.5 (C), 97.0 (CH<sub>2</sub>), 95.4 (CH<sub>2</sub>), 88.5 (C), 86.8 (CH<sub>2</sub>), 84.9 (C), 80.4 (CH), 78.83 (CH), 78.76 (C), 74.4 (CH<sub>2</sub>), 73.1 (CH), 71.4 (CH), 65.2 (C), 56.0 (CH<sub>3</sub>), 55.5 (CH<sub>3</sub>), 53.1 (CH<sub>3</sub>), 44.0 (CH), 30.8 (CH<sub>2</sub>), 21.1 (CH<sub>3</sub>), 19.5 (CH<sub>3</sub>). IR (ATR-FTIR), cm<sup>-1</sup>: 3734 (m), 3627 (m), 3271 (m), 2953 (s), 1732 (s). HRMS-CI (m/z): [M + Na]<sup>+</sup> calculated for C<sub>22</sub>H<sub>30</sub>NaO<sub>10</sub>, 477.1737; found 477.1723. [ $\alpha$ ]<sub>D</sub><sup>20</sup> = -60.2 (c = 0.18, CHCl<sub>3</sub>).

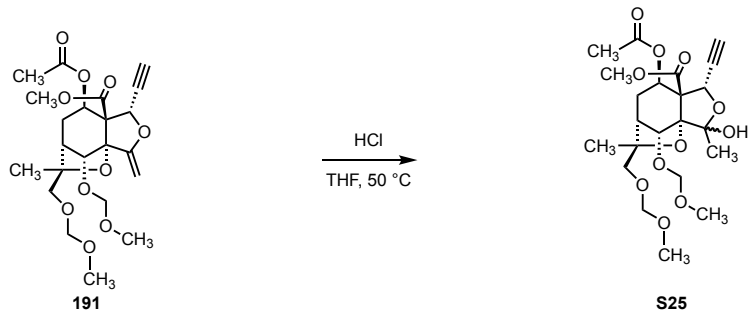
*Synthesis of the silylene ether 192:*

*Part 1: Synthesis of the hemiketal S25:*



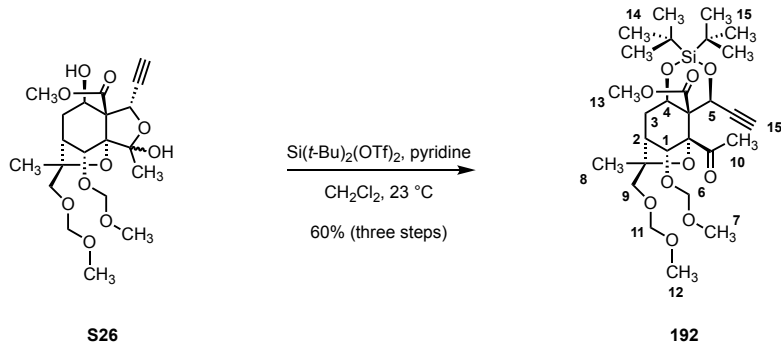
Aqueous hydrochloric acid solution (1 N, 24.2 mL, 24.2 mmol, 5.00 equiv) was added to a solution of the vinyl ether **191** (2.20 g, 4.84 mmol, 1 equiv) in tetrahydrofuran (73 mL) at 23 °C. The reaction vessel was then placed in an oil bath that had been preheated to 50 °C. The reaction mixture was stirred and heated for 2 h at 50 °C. The product mixture was then cooled to 0 °C over 15 min. The cooled product mixture was diluted sequentially with ethyl acetate (100 mL), water (100 mL), and saturated aqueous sodium bicarbonate solution (100 mL). The diluted product mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (5 × 100 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (50 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was used directly in the following step.

Part 2: Synthesis of the alcohol **S26**:



Potassium carbonate (1.34 g, 9.68 mmol, 2.50 equiv) was added in one portion to a solution of the residue obtained in the preceding step (nominally 4.84 mmol, 1 equiv) in methanol (48 mL) at 0 °C. The reaction mixture was stirred for 3 h at 0 °C. The cold product mixture was diluted sequentially with saturated aqueous ammonium chloride solution (50 mL), water (100 mL), and ethyl acetate (100 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (5 × 100 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (100 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was used directly in the following step.

Part 3: Synthesis of the silylene ether **192**:

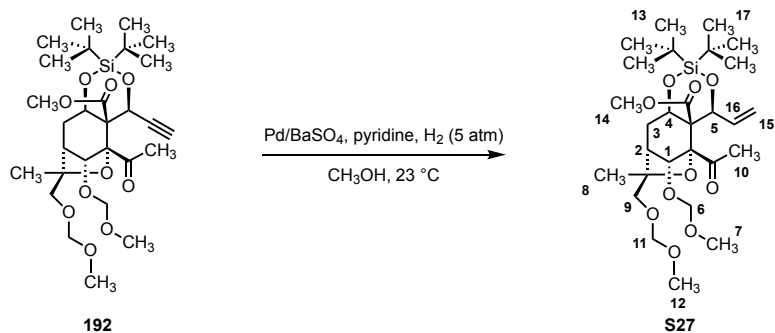


Di-*tert*-butylsilyl bis(trifluoromethanesulfonate) (2.40 mL, 7.26 mmol, 1.50 equiv) was added dropwise via syringe to a solution of the residue obtained in the preceding step (nominally 4.84 mmol, 1 equiv) and pyridine (1.90 mL, 24.2 mmol, 5.00 equiv) in dichloromethane (48 mL) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C and then the cooling bath was removed. The reaction mixture was allowed to warm to 23 °C and then stirred for 7 d at 23 °C. The product mixture was diluted sequentially with saturated aqueous ammonium chloride solution (50 mL), water (50 mL), and ethyl acetate (100 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 100 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (50 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 20% ethyl acetate–hexanes) to provide the silylene ether **192** as a colorless oil (1.66 g, 60% over three steps).

$R_f = 0.50$  (33% ethyl acetate–hexanes; PAA).  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  5.25 (s,  $\text{H}_{1,5}$ , 2H), 4.63 (s,  $\text{H}_{11}$ , 2H), 4.57 (dd,  $J = 11.4, 6.4$  Hz,  $\text{H}_4$ , 1H), 4.49 (d,  $J = 6.5$  Hz,  $\text{H}_{6a}$ , 1H), 4.42 (d,  $J = 6.5$  Hz,  $\text{H}_{6b}$ , 1H), 3.95 (d,  $J = 9.1$  Hz,  $\text{H}_{9a}$ , 1H), 3.77 (s,  $\text{H}_{13}$ , 3H), 3.72 (d,  $J = 9.1$  Hz,  $\text{H}_{9b}$ , 1H), 3.36 (s,  $\text{H}_{12}$ , 3H), 3.27 (s,  $\text{H}_7$ , 3H), 2.57 (d,  $J = 2.2$  Hz,  $\text{H}_{15}$ , 1H), 2.50 (d,  $J = 3.3$  Hz,  $\text{H}_2$ , 1H), 2.41 (ddd,  $J = 13.4, 6.3, 3.9$  Hz,  $\text{H}_{3a}$ , 1H), 2.24 (s,  $\text{H}_{10}$ , 3H), 2.08 (ddd,  $J = 13.4, 6.3, 3.9$  Hz,  $\text{H}_{3b}$ , 1H), 1.55 (s,  $\text{H}_8$ , 3H), 1.11 (s,  $\text{H}_{14}$ , 9H), 0.95 (s,  $\text{H}_{15}$ , 9H).  $^{13}\text{C NMR}$  (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  207.8 (C), 169.3 (C), 96.9 ( $\text{CH}_2$ ), 96.5 ( $\text{CH}_2$ ), 94.0 (C), 88.9 (C), 84.6 (CH), 82.4 (C), 76.2 (CH), 74.2 (CH), 74.0 ( $\text{CH}_2$ ), 69.6 (CH), 63.3 (C), 55.9 ( $\text{CH}_3$ ), 55.6 ( $\text{CH}_3$ ), 52.0 ( $\text{CH}_3$ ), 42.5 (CH), 32.9 ( $\text{CH}_2$ ), 30.5 ( $\text{CH}_3$ ), 29.1 ( $3 \times \text{CH}_3$ ), 27.0 ( $3 \times \text{CH}_3$ ), 22.9 (C), 19.9 (C). IR (ATR-FTIR),  $\text{cm}^{-1}$ : 3726 (m), 3628 (m), 2937 (s), 2859 (m), 1721 (s). HRMS-CI ( $m/z$ ):  $[\text{M} + \text{Na}]^+$  calculated for  $\text{C}_{28}\text{H}_{46}\text{NaO}_{10}\text{Si}$ , 593.2758; found 593.2745.  $[\alpha]_D^{20} = -34.4$  ( $c = 0.80$ ,  $\text{CHCl}_3$ ).

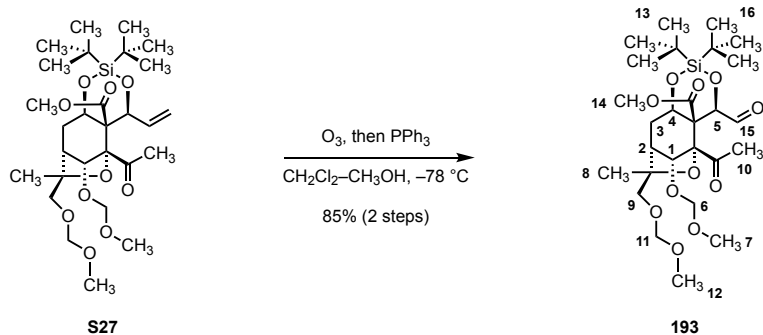
*Synthesis of the aldehyde 193:*

*Part 1: Synthesis of the olefin S27:*



Palladium on barium sulfate (10% w/w, 143 mg) was added to a solution of the silylene ether **192** (1.43 g, 2.51 mmol, 1 equiv) in methanol (28 mL) and pyridine (2.8 mL) at 23 °C. The reaction vessel was then transferred to a stainless steel hydrogenation apparatus. The apparatus was purged with dihydrogen by pressurizing to 5 atm and venting. This process was repeated three times. The vessel was then pressurized to 5 atm dihydrogen and sealed. The reaction mixture was stirred for 1 h at 23 °C. The apparatus was then slowly vented. The product mixture was diluted with ethyl acetate (20 mL) and the diluted solution was filtered through a pad of Celite. The filtrate was concentrated and the residue obtained was used directly in the following step.

Part 2: Synthesis of the aldehyde **193**:



Ozone was passed through a solution of the residue obtained in the preceding step (nominally 2.51 mmol, 1 equiv) in dichloromethane (50 mL) and methanol (8.0 mL) at  $-78\text{ }^\circ\text{C}$  until a dark blue color persisted. Dioxygen was then passed through the solution to remove any unreacted ozone, resulting in a colorless solution. Triphenylphosphine (1.32 g, 5.03 mmol, 2.00 equiv) was then added in one portion. The cooling bath was removed, and the mixture was allowed to warm to  $23\text{ }^\circ\text{C}$  over 1 h. The warmed product mixture was concentrated and the residue obtained was purified by flash-column chromatography (eluting with 25% ethyl acetate–hexanes) to provide the aldehyde **193** as a colorless solid (1.23 g, 85%, two steps).

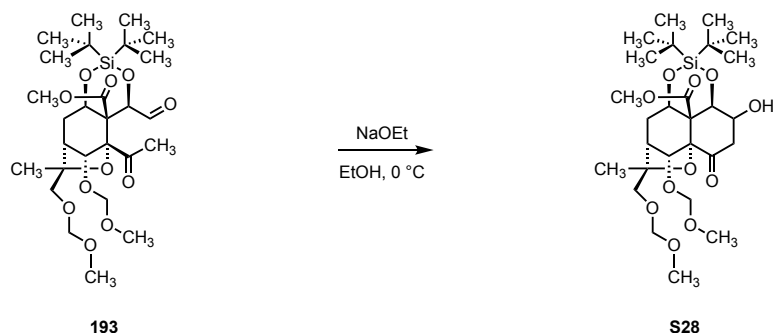
$R_f = 0.40$  (33% ethyl acetate–hexanes; PAA).  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  9.48 (s,  $\text{H}_{15}$ , 1H), 5.17 (s,  $\text{H}_1$ , 1H), 4.63 (s,  $\text{H}_{11}$ , 2H), 4.62 – 4.58 (m,  $\text{H}_4$ , 1H), 4.56 (d,  $J = 1.4\text{ Hz}$ ,  $\text{H}_5$ , 1H), 4.49 (d,  $J = 6.6\text{ Hz}$ ,  $\text{H}_{6a}$ , 1H), 4.37 (d,  $J = 6.6\text{ Hz}$ ,  $\text{H}_{6b}$ , 1H), 3.99 (d,  $J = 9.0\text{ Hz}$ ,  $\text{H}_{9a}$ , 1H), 3.76 (s,  $\text{H}_{14}$ , 3H), 3.71 (d,  $J = 9.0\text{ Hz}$ ,  $\text{H}_{9b}$ , 1H), 3.36 (s,  $\text{H}_{12}$ , 3H), 3.25 (s,  $\text{H}_7$ , 3H), 2.49 (s,  $\text{H}_2$ , 1H), 2.40 – 2.31 (m,  $\text{H}_{3a}$ , 1H), 2.27 (s,  $\text{H}_{10}$ , 3H), 2.17 – 2.06 (m,  $\text{H}_{3b}$ , 1H), 1.56 (s,  $\text{H}_8$ , 3H), 1.10 (s,  $\text{H}_{13}$ , 9H), 0.97 (s,  $\text{H}_{16}$ , 9H).  $^{13}\text{C NMR}$  (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  207.5 (C),

201.8 (CH), 169.4 (C), 96.8 (CH<sub>2</sub>), 96.2 (CH<sub>2</sub>), 93.3 (C), 89.0 (C), 84.7 (CH), 81.3 (CH), 73.7 (CH<sub>2</sub>), 72.9 (CH), 55.7 (CH<sub>3</sub>), 55.4 (CH<sub>3</sub>), 52.5 (C), 41.9 (CH), 32.8 (CH<sub>2</sub>), 29.6 (CH<sub>3</sub>), 28.7 (3 × CH<sub>3</sub>), 26.9 (3 × CH<sub>3</sub>) 22.5 (C), 19.82 (CH<sub>3</sub>), 19.77 (C). IR (ATR-FTIR), cm<sup>-1</sup>: 3734 (s), 3628 (m), 2937 (s), 2859 (m), 1734 (s). HRMS-Cl (m/z): [M + Na]<sup>+</sup> calculated for C<sub>27</sub>H<sub>46</sub>NaO<sub>11</sub>Si, 597.2707; found 597.2686.  $[\alpha]_D^{20} = -63.6$  (*c* = 0.22, CHCl<sub>3</sub>).



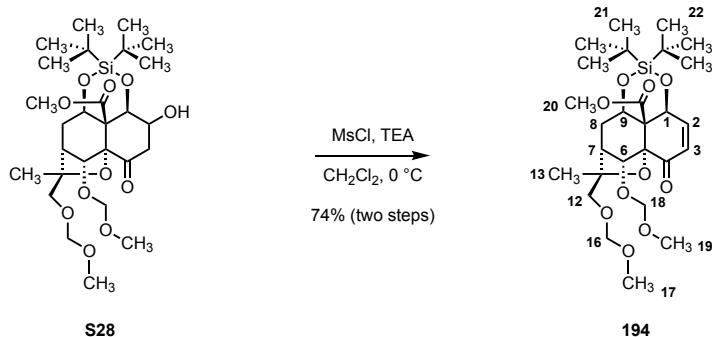
*Synthesis of the unsaturated ketone 194:*

*Part 1: Synthesis of the  $\beta$ -hydroxyketone S28:*



A solution of sodium ethoxide in ethanol (500 mM, 4.40 mL, 2.18 mmol, 2.00 equiv) was added dropwise via syringe over 10 min to a solution of the aldehyde **193** (628 mg, 1.09 mmol, 1 equiv) in ethanol (13.5 mL) at 0 °C. The resulting mixture was stirred for 45 min at 0 °C. The product mixture was diluted sequentially with water (25 mL) and ethyl acetate (50 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (5  $\times$  50 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was used directly in the following step.

Part 2: Synthesis of the unsaturated ketone **194**:

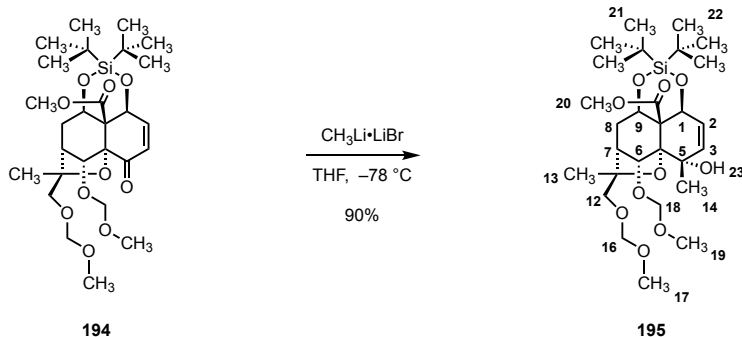


Triethylamine (456  $\mu$ L, 3.28 mmol, 3.00 equiv) and methanesulfonyl chloride (135  $\mu$ L, 1.75 mmol, 1.60 equiv) were added in sequence to a solution of the residue obtained in the preceding step (nominally 1.09 mmol, 1 equiv) in dichloromethane (18 mL) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C. The cold product mixture was diluted sequentially with saturated aqueous ammonium chloride solution (20 mL), water (20 mL), and dichloromethane (50 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with dichloromethane (3  $\times$  500 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (50 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 20% ethyl acetate–hexanes) to provide the unsaturated ketone **194** as a colorless oil (450 mg, 74% over two steps).

$R_f$  = 0.40 (33% ethyl acetate–hexanes; UV, CAM). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  6.91 (dd,  $J$  = 10.6, 1.9 Hz, H<sub>2</sub>, 1H), 5.93 (dd,  $J$  = 10.6, 3.0 Hz, H<sub>3</sub>, 1H), 5.43 (d,  $J$  = 2.5 Hz, H<sub>1</sub>,

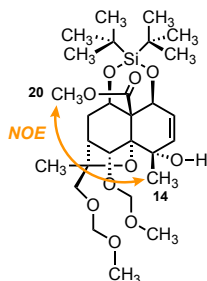
1H), 4.92 (dd, J = 11.7, 6.4 Hz, H<sub>9</sub>, 1H), 4.66 – 4.57 (m, H<sub>16,18a</sub>, 3H), 4.55 (s, H<sub>6</sub>, 1H), 4.43 (d, J = 7.0 Hz, H<sub>18b</sub>, 1H), 3.99 (d, J = 9.4 Hz, H<sub>12a</sub>, 1H), 3.67 (s, H<sub>20</sub>, 3H), 3.64 (d, J = 9.4 Hz, H<sub>12b</sub>, 1H), 3.34 (s, H<sub>17</sub>, 3H), 3.31 (s, H<sub>19</sub>, 3H), 2.52 (d, J = 3.4 Hz, H<sub>7</sub>, 1H), 2.48 (ddd, J = 14.5, 11.8, 2.9 Hz, H<sub>8a</sub>, 1H), 2.17 (ddd, J = 13.3, 6.4, 3.8 Hz, H<sub>8b</sub>, 1H), 1.52 (s, H<sub>13</sub>, 3H), 1.15 (s, H<sub>21</sub>, 9H), 0.96 (s, H<sub>22</sub>, 9H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 190.9 (C), 170.1 (C), 149.8 (CH), 128.0 (CH), 96.8 (CH<sub>2</sub>), 96.2 (CH<sub>2</sub>), 87.8 (C), 82.6 (CH), 82.5 (CH), 75.4 (CH), 74.8 (CH), 74.0 (CH<sub>2</sub>), 64.5 (C), 55.6 (CH<sub>3</sub>), 55.4 (CH<sub>3</sub>), 52.2 (C), 45.3 (CH), 32.7 (CH<sub>2</sub>), 29.2 (3 × CH<sub>3</sub>), 27.2 (3 × CH<sub>3</sub>), 23.3 (C), 19.8 (C), 19.1 (CH<sub>3</sub>). IR (ATR-FTIR), cm<sup>-1</sup>: 3734 (m), 3690 (m), 3648 (m), 2940 (s), 2160 (m), 2009 (m). HRMS-CI (m/z): [M + Na]<sup>+</sup> calculated for C<sub>27</sub>H<sub>44</sub>NaO<sub>10</sub>Si, 579.2601; found 579.2591. [ $\alpha$ ]<sub>D</sub><sup>20</sup> = 127.5 (c = 0.04, CHCl<sub>3</sub>).

*Synthesis of the tertiary alcohol 195:*



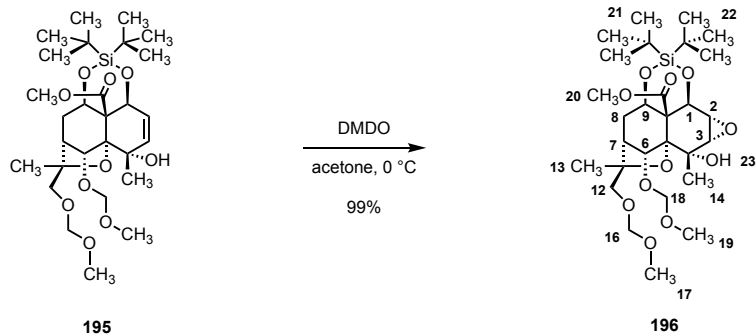
A solution of methyllithium–lithium bromide complex in diethyl ether (1.50 M, 6.00 mL, 8.98 mmol, 5.00 equiv) was added dropwise via syringe over 10 min to a solution of the enone **194** (1.00 g, 1.80 mmol, 1 equiv) in tetrahydrofuran (36 mL) at  $-78\text{ }^\circ\text{C}$ . The reaction mixture was stirred for 30 min at  $-78\text{ }^\circ\text{C}$ . The cold product mixture was diluted sequentially with saturated aqueous ammonium chloride solution (50 mL), saturated aqueous sodium chloride solution (50 mL), and ethyl acetate (50 mL). The diluted product mixture was then allowed to warm to  $23\text{ }^\circ\text{C}$  over 20 min. The warmed biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate ( $3 \times 50\text{ mL}$ ). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (100 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 20% ethyl acetate–hexanes) to provide the tertiary alcohol **195** as a colorless oil (925 mg, 90%, minor diastereomer not isolated).

$^1\text{H}$  NMR analysis of the unpurified product mixture indicated the presence of a 9:1 mixture of diastereomers. NOE correlations between the C14 methyl substituent and the ester substituent (C20) support the relative configuration depicted.



$R_f = 0.40$  (50% ethyl acetate–hexanes; CAM).  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ ):  $\delta$  5.80 (dd,  $J = 10.7, 1.7$  Hz,  $\text{H}_2$ , 1H), 5.33 (dd,  $J = 10.6, 3.0$  Hz,  $\text{H}_3$ , 1H), 5.19 (dd,  $J = 3.0, 1.8$  Hz,  $\text{H}_1$ , 1H), 4.88 (d,  $J = 0.9$  Hz,  $\text{H}_6$ , 1H), 4.79 (dd,  $J = 12.0, 6.4$  Hz,  $\text{H}_9$ , 1H), 4.75 (d,  $J = 6.7$  Hz,  $\text{H}_{18a}$ , 1H), 4.70 – 4.59 (m,  $\text{H}_{18b,16}$ , 3H), 3.95 (d,  $J = 9.2$  Hz,  $\text{H}_{12a}$ , 1H), 3.83 (d,  $J = 9.2$  Hz,  $\text{H}_{12b}$ , 1H), 3.67 (s,  $\text{H}_{20}$ , 3H), 3.40 (s,  $\text{H}_{17}$ , 3H), 3.36 (s,  $\text{H}_{19}$ , 3H), 3.29 (d,  $J = 0.9$  Hz,  $\text{H}_{23}$ , 1H), 2.57 (dd,  $J = 4.0, 2.7$  Hz,  $\text{H}_7$ , 1H), 2.53 – 2.44 (m,  $\text{H}_{8a}$ , 1H), 2.12 (ddd,  $J = 13.3, 6.4, 4.1$  Hz,  $\text{H}_{8b}$ , 1H), 1.56 (s,  $\text{H}_{13}$ , 3H), 1.28 (s,  $\text{H}_{14}$ , 3H), 1.12 (s,  $\text{H}_{21}$ , 9H), 0.94 (s,  $\text{H}_{22}$ , 9H).  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ ):  $\delta$  170.5 (C), 132.6 (CH), 128.1 (CH), 97.1 (CH<sub>2</sub>), 96.8 (CH<sub>2</sub>), 90.0 (C), 86.5 (C), 84.13 (CH), 77.2 (CH), 75.7 (CH), 74.2 (CH<sub>2</sub>), 70.0 (C), 62.9 (C), 56.8 (CH<sub>3</sub>), 55.5 (CH<sub>3</sub>), 51.7 (C), 43.3 (CH), 32.3 (CH<sub>2</sub>), 29.3 (3  $\times$  CH<sub>3</sub>), 27.0 (3  $\times$  CH<sub>3</sub>), 24.5 (CH<sub>3</sub>), 22.9 (C), 19.6 (CH<sub>3</sub>), 19.2 (C). IR (ATR-FTIR),  $\text{cm}^{-1}$ : 3726 (m), 3710 (m), 3628 (m), 2933 (s), 2858 (m), 1718 (s). HRMS-Cl ( $m/z$ ):  $[\text{M} + \text{Na}]^+$  calculated for  $\text{C}_{28}\text{H}_{48}\text{NaO}_{10}\text{Si}$ , 595.2914; found 595.2908.  $[\alpha]_D^{20} = 6.37$  ( $c = 0.11$ ,  $\text{CHCl}_3$ ).

*Synthesis of the epoxide 196:*



A solution of dimethyldioxirane in acetone (~60 mM, 102 mL, 6.11 mmol, 5.00 equiv) was added to a solution of the allylic alcohol **195** (700 mg, 1.23 mmol, 1 equiv) in acetone (19 mL) at 0 °C. The reaction mixture was stirred for 14 h at 0 °C. The product mixture was then warmed to 23 °C. The warmed product mixture was concentrated to provide the epoxide **196** as a pale yellow oil (709 mg, 99%).

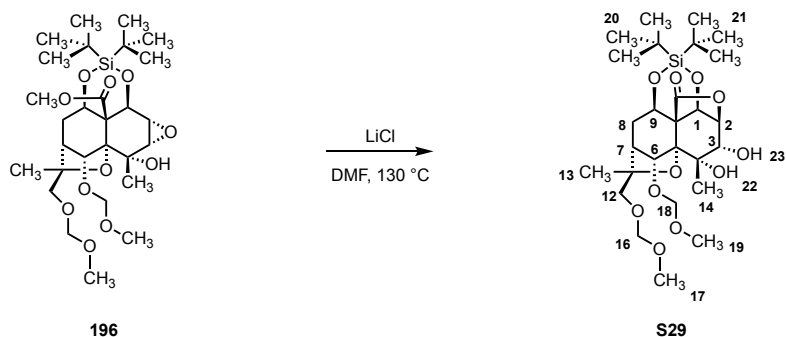
Within the limits of detection, the epoxide **196** was formed as a single diastereomer (<sup>1</sup>H NMR analysis, 500 MHz). The relative stereochemistry of the epoxide **196** was established via X-ray analysis (see Appendix A).

R<sub>f</sub> = 0.20 (50% ethyl acetate–hexanes; CAM). <sup>1</sup>H NMR (500 MHz, benzene-*d*<sub>6</sub>): δ 5.03 (s, H<sub>1</sub>, 1H), 4.91 (s, H<sub>6</sub>, 1H), 4.84 (dd, J = 12.0, 6.4 Hz, H<sub>9</sub>, 1H), 4.46 (d, J = 6.5 Hz, H<sub>16a</sub>, 1H), 4.42 – 4.35 (m, H<sub>18,16b</sub>, 3H), 3.96 (s, H<sub>23</sub>, 1H), 3.89 (d, J = 9.6 Hz, H<sub>12a</sub>, 1H), 3.81 (d, J = 9.6 Hz, H<sub>12b</sub>, 1H), 3.73 (s, H<sub>3</sub>, 1H), 3.33 (s, H<sub>20</sub>, 3H), 3.21 (s, H<sub>17</sub>, 3H), 3.16 (s, H<sub>2</sub>, 1H), 3.10 (s, H<sub>19</sub>, 3H), 3.58 (s, H<sub>8a</sub>, 1H), 2.27 (s, H<sub>7</sub>, 1H), 2.26 (ddd, J = 13.2, 6.4, 4.1 Hz, H<sub>8b</sub>, 1H), 1.47 (s, H<sub>13</sub>, H<sub>14</sub>, 6H), 1.17 (s, H<sub>22</sub>, 9H), 1.08 (s, H<sub>21</sub>, 9H). <sup>13</sup>C NMR (125 MHz,

benzene-*d*<sub>6</sub>):  $\delta$  170.9 (C), 97.1 (CH<sub>2</sub>), 96.9 (CH<sub>2</sub>), 90.3 (C), 87.2 (C), 85.1 (CH), 78.3 (CH), 76.3 (CH), 75.1 (CH<sub>2</sub>), 70.0 (C), 63.0 (CH), 62.0 (C), 60.2 (CH), 56.5 (CH<sub>3</sub>), 55.2 (CH<sub>3</sub>), 51.4 (CH<sub>3</sub>), 42.9 (CH), 32.9 (CH<sub>2</sub>), 29.3 (3  $\times$  CH<sub>3</sub>), 27.3 (3  $\times$  CH<sub>3</sub>), 23.1 (C), 23.0 (CH<sub>3</sub>), 19.9 (C), 19.0 (CH<sub>3</sub>). IR (ATR-FTIR), cm<sup>-1</sup>: 3734 (s), 3628 (m), 2925 (s), 2655 (m), 1724 (s). HRMS-Cl (m/z): [M + Na]<sup>+</sup> calculated for C<sub>28</sub>H<sub>48</sub>NaO<sub>11</sub>Si, 611.2864; found 611.2846.  $[\alpha]_D^{20} = -10.6$  (*c* = 0.10, CHCl<sub>3</sub>).

*Synthesis of the lactone 197:*

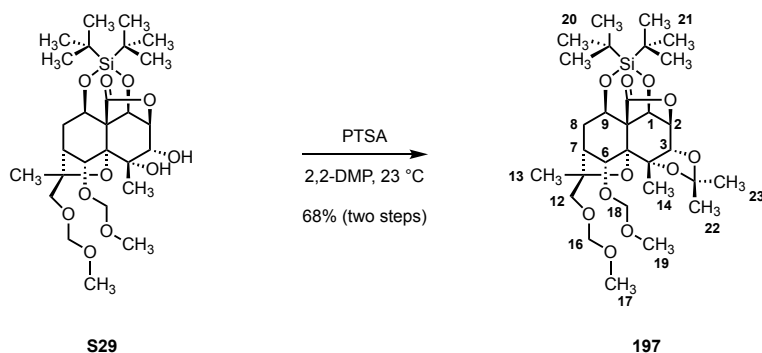
*Part 1: Synthesis of the diol S29:*



Lithium chloride (306 mg, 7.23 mmol, 6.00 equiv) was added to a solution of the epoxide **196** (709 mg, 1.24 mmol, 1 equiv) in *N,N*-dimethylformamide (28 mL) at 23 °C. The reaction vessel was sealed and the sealed vessel was placed in an oil bath that had been preheated to 130 °C. The reaction mixture was stirred and heated for 14 h at 130 °C. The product mixture cooled to 23 °C over 30 min. The cooled product mixture was diluted sequentially with ethyl acetate (50 mL), water (20 mL), and saturated aqueous sodium chloride solution (20 mL). The diluted product mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 50 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (50 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was used directly in the following step.



Part 2: Synthesis of the lactone **197**:

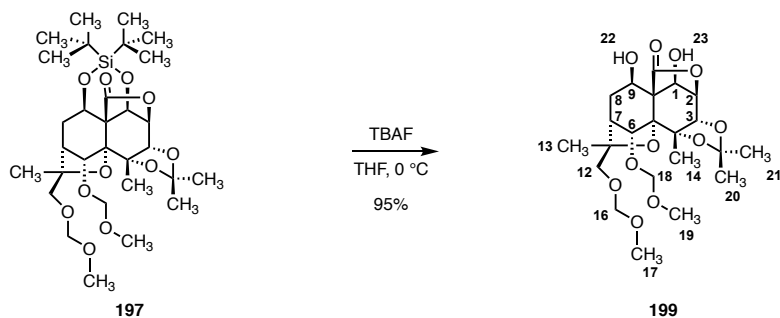


*para*-Toluenesulfonic acid (35.4 mg, 186  $\mu$ mol, 0.15 equiv) was added to a solution of the residue obtained in the preceding step (nominally 1.24 mmol, 1 equiv) in 2,2-dimethoxypropane (2,2-DMP, 8.3 mL) at 23 °C. The reaction mixture was stirred for 24 h at 23 °C. The product mixture was diluted sequentially with ethyl acetate (30 mL), water (20 mL), and saturated aqueous sodium bicarbonate solution (20 mL). The diluted product mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3  $\times$  30 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (50 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 33% ethyl acetate–hexanes) to provide the lactone **197** as a colorless oil (521 mg, 68% over two steps). The relative stereochemistry of the lactone **197** was established via X-ray analysis (see Appendix A).

$R_f$  = 0.30 (33% ethyl acetate–hexanes; CAM).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  5.07 (s,  $\text{H}_{1,}$  1H), 4.84–4.73 (m,  $\text{H}_{9,2,16a,}$  3H), 4.64 (d,  $J$  = 6.7 Hz,  $\text{H}_{16b,}$  1H), 4.61 (d,  $J$  = 6.3 Hz,  $\text{H}_{18a,}$

1H), 4.56(d, J = 6.3 Hz, H<sub>18b</sub>, 1H), 4.43 (s, H<sub>6</sub>, 1H), 4.25 (d, J = 5.0 Hz, H<sub>3</sub>, 1H), 4.11 (d, J = 8.6 Hz, H<sub>12a</sub>, 1H), 3.43 (d, J = 9.9 Hz, H<sub>12b</sub>, 1H), 3.39 (s, H<sub>17</sub>, 3H), 3.34 (s, H<sub>19</sub>, 3H), 2.65 (d, J = 3.4 Hz, H<sub>7</sub>, 1H), 2.13 (dd, J = 8.0, 3.3 Hz, H<sub>8</sub>, 2H), 1.62 (s, H<sub>14</sub>, 3H), 1.56 (s, H<sub>23</sub>, 3H), 1.49 (s, H<sub>13</sub>, 3H), 1.40 (s, H<sub>22</sub>, 3H), 1.11 (s, H<sub>20</sub>, 9H), 0.98 (s, H<sub>21</sub>, 9H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 173.6 (C), 112.5 (C), 96.9 (CH<sub>2</sub>), 96.7 (CH<sub>2</sub>), 88.6 (C), 86.7 (C), 85.0 (CH), 82.7 (CH), 80.9 (C), 79.8 (CH), 77.3 (CH), 74.0 (CH<sub>2</sub>), 67.5 (CH), 60.7 (C), 56.9 (CH<sub>3</sub>), 55.5 (CH<sub>3</sub>), 41.2 (CH), 32.2 (CH<sub>2</sub>), 28.5 (3 × CH<sub>3</sub>), 27.04 (CH<sub>3</sub>), 27.02 (CH<sub>3</sub>), 26.97 (3 × CH<sub>3</sub>), 25.9 (CH<sub>3</sub>), 22.5 (C), 20.5 (CH<sub>3</sub>), 20.1 (C). IR (ATR-FTIR), cm<sup>-1</sup>: 3734 (s), 3649 (m), 3628 (m), 2938 (s), 2889 (m), 2860 (m), 1786 (s). HRMS-CI (m/z): [M + Na]<sup>+</sup> calculated for C<sub>30</sub>H<sub>50</sub>NaO<sub>11</sub>Si, 637.3020; found 637.3015. [ $\alpha$ ]<sub>D</sub><sup>20</sup> = -4.75 (c = 0.08, CHCl<sub>3</sub>).

Synthesis of the 1,3-diol **199**:

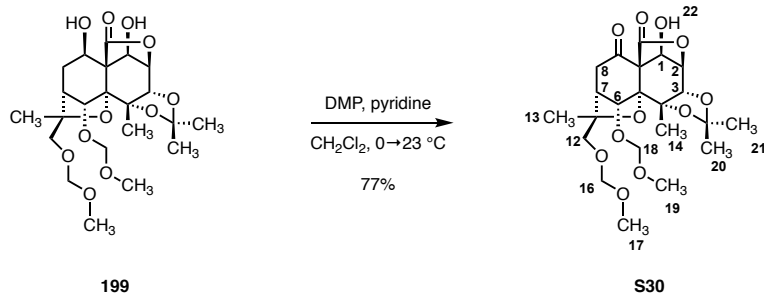


A solution of tetra-*n*-butylammonium fluoride in tetrahydrofuran (1.00 M, 1.70 mL, 1.71 mmol, 2.50 equiv) was added dropwise via syringe to a solution of the acetonide **197** (350 mg, 569  $\mu$ mol, 1 equiv) in tetrahydrofuran (5.7 mL) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C. The cooling bath was removed, and the reaction mixture was allowed to warm to 23 °C over 20 min. The warmed reaction mixture was stirred for 2 h at 23 °C. The product mixture was diluted sequentially with saturated aqueous ammonium chloride solution (10 mL), saturated aqueous sodium chloride solution (10 mL), and ethyl acetate (10 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3  $\times$  100 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (50 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 33% ethyl acetate–hexanes) to provide the 1,3-diol **199** as a colorless oil (256 mg, 95%).

R<sub>f</sub> = 0.30 (75% ethyl acetate–hexanes; CAM). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  4.93 (d, J = 5.4 Hz, H<sub>1</sub>, 1H), 4.82 (d, J = 4.8 Hz, H<sub>2</sub>, 1H), 4.79 (d, J = 6.8 Hz, H<sub>18a</sub>, 1H), 4.67 (d, J =

6.9 Hz, H<sub>18b</sub>, 1H), 4.60 (d, J = 6.3 Hz, H<sub>16a</sub>, 1H), 4.56 (d, J = 6.3 Hz, H<sub>16b</sub>, 1H), 4.45 (td, J = 10.8, 8.0 Hz, H<sub>9</sub>, 1H), 4.25 (d, J = 4.9 Hz, H<sub>3</sub>, 1H), 4.22 (s, H<sub>6</sub>, 1H), 4.07 (dd, J = 8.9, 1.0 Hz, H<sub>12a</sub>, 1H), 3.43 (d, J = 8.9 Hz, H<sub>12b</sub>, 1H), 3.40 (s, H<sub>19</sub>, 3H), 3.34 (s, H<sub>17</sub>, 3H), 3.15 (d, J = 5.4 Hz, H<sub>23</sub>, 1H), 2.65 (t, J = 3.5 Hz, H<sub>7</sub>, 1H), 2.51 (d, J = 10.6 Hz, H<sub>22</sub>, 1H), 2.45 (ddd, J = 14.0, 8.0, 3.9 Hz, H<sub>8a</sub>, 1H), 1.88 (ddd, J = 14.1, 11.0, 3.2 Hz, H<sub>8b</sub>, 1H), 1.61 (s, H<sub>14</sub>, 3H), 1.55 (s, H<sub>20</sub>, 3H), 1.48 (s, H<sub>13</sub>, 3H), 1.40 (s, H<sub>21</sub>, 3H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 175.2 (C), 112.7 (C), 96.9 (CH<sub>2</sub>), 96.8 (CH<sub>2</sub>), 89.2 (C), 86.1 (C), 85.2 (CH), 82.5 (CH), 81.2 (CH), 80.9 (C), 74.6 (CH), 73.9 (CH<sub>2</sub>), 66.4 (CH), 62.5 (C), 57.0 (CH<sub>3</sub>), 55.6 (CH<sub>3</sub>), 41.2 (CH), 35.7 (CH<sub>2</sub>), 27.1 (CH<sub>3</sub>), 26.6 (CH<sub>3</sub>), 26.0 (CH<sub>3</sub>), 21.3 (CH<sub>3</sub>). IR (ATR-FTIR), cm<sup>-1</sup>: 3734 (s), 3628 (m), 2929 (s), 2859 (m), 1772 (s). HRMS-CI (m/z): [M + Na]<sup>+</sup> calculated for C<sub>22</sub>H<sub>34</sub>NaO<sub>11</sub>, 497.1999; found 497.1998.  $[\alpha]_D^{20} = -3.25$  (c = 0.13, CHCl<sub>3</sub>).

*Synthesis of the ketone S30:*

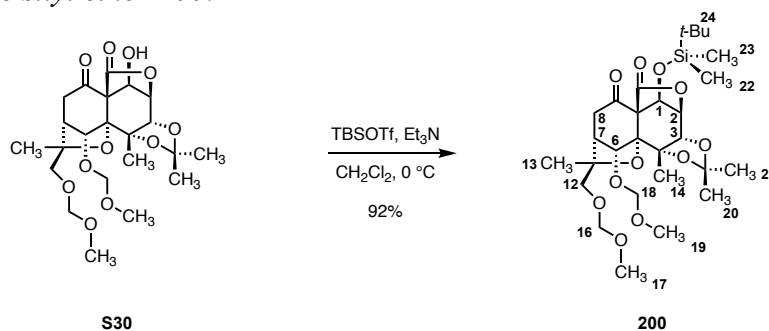


The Dess–Martin periodinane (217 mg, 285  $\mu\text{mol}$ , 1.00 equiv) was added in five equal portions over 1 h to a solution of the 1,3-diol **199** (135 mg, 285  $\mu\text{mol}$ , 1 equiv) and pyridine (137  $\mu\text{L}$ , 1.71 mmol, 6.00 equiv) in dichloromethane (2.8 mL) at 0  $^{\circ}\text{C}$ . Upon completion of the addition, the cooling bath was removed and the reaction mixture was allowed to warm to 23  $^{\circ}\text{C}$  over 20 min. The warmed reaction mixture was stirred for 2 h at 23  $^{\circ}\text{C}$ . The product mixture was diluted sequentially with dichloromethane (10 mL), saturated aqueous sodium bicarbonate solution (20 mL), and saturated aqueous sodium thiosulfate solution (20 mL). The diluted product mixture was vigorously stirred for 1 h at 23  $^{\circ}\text{C}$ . The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with dichloromethane (3  $\times$  50 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (50 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 40% ethyl acetate–hexanes) to provide the ketone **S30** as a colorless oil (104 mg, 77%).

$R_f$  = 0.30 (50% ethyl acetate–hexanes; CAM).  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ ):  $\delta$  5.19 (s,  $\text{H}_1$ , 1H), 5.05 (s,  $\text{H}_{22}$ , 1H), 4.88 (d,  $J$  = 6.9 Hz,  $\text{H}_{18a}$ , 1H), 4.83 (d,  $J$  = 4.6 Hz,  $\text{H}_2$ , 1H), 4.77 (d,

$J = 6.9$  Hz,  $H_{18b}$ , 1H), 4.59 (q,  $J = 6.4$  Hz,  $H_{16}$ , 2H), 4.45 (s,  $H_6$ , 1H), 4.25 (d,  $J = 4.6$  Hz,  $H_3$ , 1H), 4.04 (d,  $J = 9.0$  Hz,  $H_{12a}$ , 1H), 3.51 (d,  $J = 9.0$  Hz,  $H_{12b}$ , 1H), 3.44 (s,  $H_{17}$ , 3H), 3.34 (s,  $H_{19}$ , 3H), 2.90 (s,  $H_7$ , 1H), 2.90 – 2.80 (m,  $H_8$ , 2H), 1.63 (s,  $H_{14}$ , 3H), 1.56 (s,  $H_{21}$ , 3H), 1.41 (s,  $H_{20}$ , 3H), 1.31 (s,  $H_{13}$ , 3H).  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ ):  $\delta$  210.1 (C), 171.6 (C), 112.4 (C), 96.9 ( $\text{CH}_2$ ), 96.7 ( $\text{CH}_2$ ), 88.7 (C), 86.1 (C), 84.8 (CH), 81.6 (CH), 81.3 (CH), 80.3 (C), 74.0 (CH), 73.3 ( $\text{CH}_2$ ), 67.5 (C), 56.9 ( $\text{CH}_3$ ), 55.5 ( $\text{CH}_3$ ), 45.1 ( $\text{CH}_2$ ), 40.3 (CH), 26.7 ( $\text{CH}_3$ ), 25.7 ( $\text{CH}_3$ ), 25.6 ( $\text{CH}_3$ ), 23.3 ( $\text{CH}_3$ ). IR (ATR-FTIR),  $\text{cm}^{-1}$ : 3734 (m), 3629 (m), 2955 (s), 1772 (s). HRMS-CI ( $m/z$ ):  $[\text{M} + \text{Na}]^+$  calculated for  $\text{C}_{22}\text{H}_{32}\text{NaO}_{11}$ , 495.1842; found 495.1843.  $[\alpha]_D^{20} = 10.9$  ( $c = 0.07$ ,  $\text{CHCl}_3$ ).

*Synthesis of the silyl ether 200:*



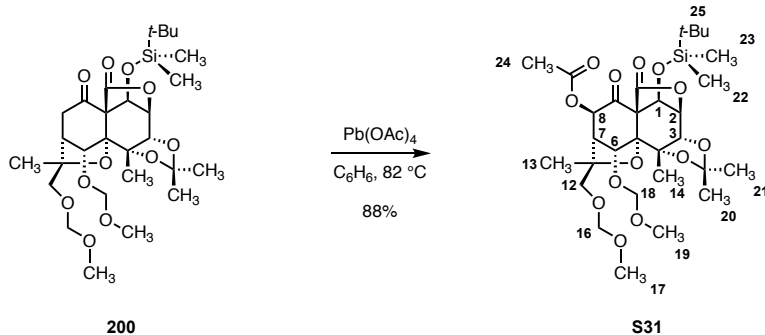
Triethylamine (113  $\mu\text{L}$ , 813  $\mu\text{mol}$ , 6.00 equiv) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (54.0  $\mu\text{L}$ , 230  $\mu\text{mol}$ , 1.70 equiv) were added in sequence to a solution of the ketone **S30** (64.0 mg, 135  $\mu\text{mol}$ , 1 equiv) in dichloromethane (1.4 mL) at 0  $^{\circ}\text{C}$ . The reaction mixture was stirred for 1 h at 0  $^{\circ}\text{C}$ . The cold product mixture was diluted sequentially with dichloromethane (10 mL) and water (20 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with dichloromethane ( $3 \times 50$  mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (50 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 33% ethyl acetate–hexanes) to provide silyl ether **200** as a yellow oil (73.0 mg, 92%).

$R_f = 0.60$  (50% ethyl acetate–hexanes; CAM).  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  5.30 (s,  $\text{H}_1$ , 1H), 4.86 (d,  $J = 6.9$  Hz,  $\text{H}_{16a}$ , 1H), 4.75 (d,  $J = 6.9$  Hz,  $\text{H}_{16b}$ , 1H), 4.64 (d,  $J = 4.5$  Hz,  $\text{H}_2$ , 1H), 4.62 – 4.57 (m,  $\text{H}_{18}$ , 2H), 4.35 (s,  $\text{H}_6$ , 1H), 4.20 (d,  $J = 4.5$  Hz,  $\text{H}_3$ , 1H), 4.03 (d,  $J = 8.9$  Hz,  $\text{H}_{12a}$ , 1H), 3.55 (d,  $J = 8.9$  Hz,  $\text{H}_{12b}$ , 1H), 3.42 (s,  $\text{H}_{17}$ , 3H), 3.34 (s,  $\text{H}_{19}$ , 3H), 2.85

– 2.67 (m, H<sub>7,6</sub>, 3H), 1.60 (s, H<sub>14</sub>, 3H), 1.58 (s, H<sub>20</sub>, 3H), 1.41 (s, H<sub>21</sub>, 3H), 1.34 (s, H<sub>13</sub>, 3H), 0.92 (s, H<sub>24</sub>, 9H), 0.07 (d, J = 3.1 Hz, H<sub>22,23</sub>, 6H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 199.8 (C), 173.1 (C), 112.3 (C), 96.9 (CH<sub>2</sub>), 96.8 (CH<sub>2</sub>), 89.1 (C), 85.6 (C), 85.2 (CH), 82.5 (CH), 82.2 (CH), 80.3 (C), 75.2 (CH), 73.5 (CH<sub>2</sub>), 69.8 (C), 57.0 (CH<sub>3</sub>), 55.6 (CH<sub>3</sub>), 44.3 (CH<sub>2</sub>), 40.2 (CH), 26.9 (CH<sub>3</sub>), 25.9 (CH<sub>3</sub>), 25.8 (3 × CH<sub>3</sub>), 25.44 (CH<sub>3</sub>), 23.7 (CH<sub>3</sub>), 18.1 (C), -4.5 (CH<sub>3</sub>), -4.6 (CH<sub>3</sub>). IR (ATR-FTIR), cm<sup>-1</sup>: 3726 (m), 3627 (m), 2929 (s), 2859 (m), 1784 (s), 1716 (s). HRMS-CI (m/z): [M + Na]<sup>+</sup> calculated for C<sub>28</sub>H<sub>46</sub>NaO<sub>11</sub>Si, 609.2707; found 609.2703.  $[\alpha]_D^{20} = 13.6$  (*c* = 0.32, CHCl<sub>3</sub>).

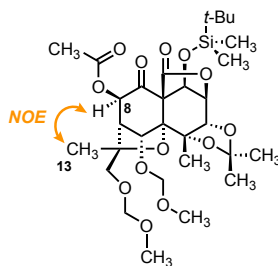


*Synthesis of the acetate S31:*



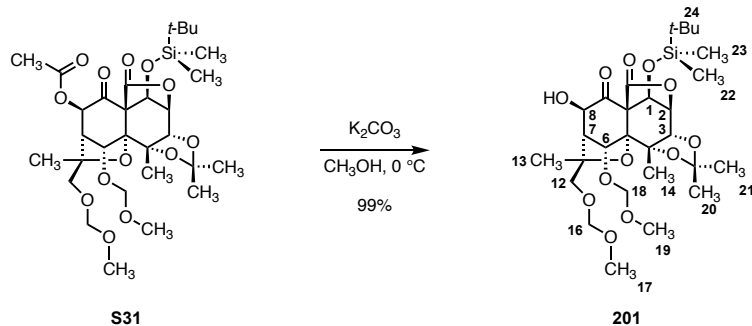
Lead tetraacetate (291 mg, 654  $\mu\text{mol}$ , 3.00 equiv) was added in a single portion to a screw-capped vessel containing a solution of the ketone **200** (128 mg, 218  $\mu\text{mol}$ , 1 equiv) in benzene (4.4 mL) at 23 °C. The reaction vessel sealed and the sealed reaction vessel was placed in an oil bath that had been preheated to 82 °C. The reaction mixture was stirred for 14 h at 82 °C. The product mixture was cooled to 23 °C over 30 min. The cooled product mixture was filtered through a short pad of Celite (1.5  $\times$  2.0 cm). The filter cake was rinsed with ethyl acetate (3  $\times$  10 mL). The filtrates were combined and the combined filtrates were diluted sequentially with water (20 mL) and saturated aqueous sodium bicarbonate solution (20 mL). The diluted product mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3  $\times$  50 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (50 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 33% ethyl acetate–hexanes) to provide the acetate **S31** as a yellow oil (124 mg, 88%).

Within the limits of detection, the acetate **S31** was formed as a single diastereomer ( $^1\text{H}$  NMR analysis, 500 MHz). NOE correlations between the C8 equatorial hydrogen and the C13 methyl substituent support the relative configuration depicted.



$R_f = 0.40$  (50% ethyl acetate–hexanes; CAM).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  5.35 (d,  $J = 2.4$  Hz,  $\text{H}_8$ , 1H), 5.30 (s,  $\text{H}_1$ , 1H), 4.78 (d,  $J = 6.8$  Hz,  $\text{H}_{18a}$ , 1H), 4.74 (d,  $J = 6.8$  Hz,  $\text{H}_{18b}$ , 1H), 4.66 (d,  $J = 4.4$  Hz,  $\text{H}_2$ , 1H), 4.60 (s,  $\text{H}_{16a}$ , 1H), 4.60 (s,  $\text{H}_{16b}$ , 1H), 4.57 (s,  $\text{H}_6$ , 1H), 4.22 (d,  $J = 4.4$  Hz,  $\text{H}_3$ , 1H), 4.00 (d,  $J = 9.0$  Hz,  $\text{H}_{12a}$ , 1H), 3.56 (d,  $J = 9.0$  Hz,  $\text{H}_{12b}$ , 1H), 3.38 (s,  $\text{H}_{17}$ , 3H), 3.34 (s,  $\text{H}_{19}$ , 3H), 2.90 (d,  $J = 2.6$  Hz,  $\text{H}_7$ , 1H), 2.15 (s,  $\text{H}_{24}$ , 3H), 1.61 (s,  $\text{H}_{14}$ , 3H), 1.59 (s,  $\text{H}_{20}$ , 3H), 1.43 (s,  $\text{H}_{21}$ , 3H), 1.41 (s,  $\text{H}_{13}$ , 3H), 0.90 (s,  $\text{H}_{25}$ , 9H), 0.07 (s,  $\text{H}_{22}$ , 3H), 0.04 (s,  $\text{H}_{23}$ , 3H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  196.7 (C), 172.2 (C), 169.8 (C), 112.4 (C), 97.2 ( $\text{CH}_2$ ), 96.8 ( $\text{CH}_2$ ), 89.0 (C), 84.1 (C), 82.2 (CH), 82.1 ( $2 \times \text{CH}$ ), 80.1 (C), 75.2 (CH), 74.1 (CH), 73.8 ( $\text{CH}_2$ ), 70.4 (C), 57.0 ( $\text{CH}_3$ ), 55.6 ( $\text{CH}_3$ ), 46.1 (CH), 26.8 ( $\text{CH}_3$ ), 25.9 ( $\text{CH}_3$ ), 25.7 ( $3 \times \text{CH}_3$ ), 25.1 ( $\text{CH}_3$ ), 23.3 ( $\text{CH}_3$ ), 21.0 ( $\text{CH}_3$ ), -4.52 ( $\text{CH}_3$ ), -4.54 ( $\text{CH}_3$ ). IR (ATR-FTIR),  $\text{cm}^{-1}$ : 3734 (s), 3710 (m), 1717(s). HRMS-CI ( $m/z$ ):  $[\text{M} + \text{Na}]^+$  calculated for  $\text{C}_{30}\text{H}_{48}\text{NaO}_{13}\text{Si}$ , 667.2762; found 667.2766.  $[\alpha]_D^{20} = 40.7$  ( $c = 0.08$ ,  $\text{CHCl}_3$ ).

*Synthesis of the  $\alpha$ -hydroxy ketone 201:*

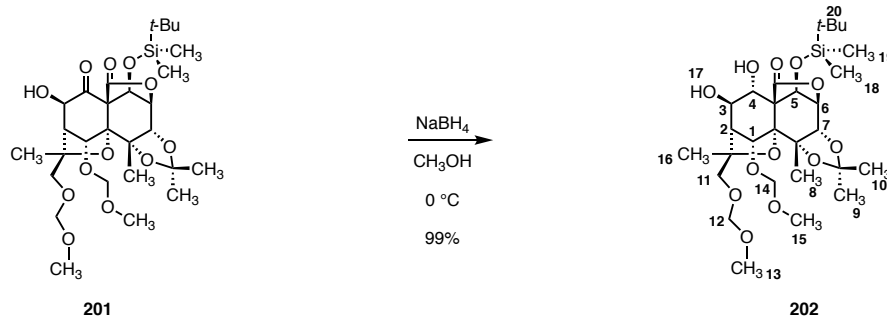


Potassium carbonate (39.9 mg, 288  $\mu\text{mol}$ , 1.50 equiv) was added in a single portion to a solution of the acetate **S31** (124 mg, 192  $\mu\text{mol}$ , 1 equiv) in methanol (3.7 mL) at 0  $^\circ\text{C}$ . The reaction mixture was stirred for 2 h at 0  $^\circ\text{C}$ . The product mixture was diluted sequentially with ethyl acetate (20 mL), water (10 mL), and saturated aqueous ammonium chloride solution (10 mL). The diluted product mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3  $\times$  20 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (15 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 50% ethyl acetate–hexanes) to provide the  $\alpha$ -hydroxy ketone **201** as a colorless oil (115 mg, 99%).

$R_f = 0.55$  (33% ethyl acetate–hexanes; CAM).  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  5.30 (s, H<sub>1</sub>, 1H), 4.84 (d,  $J = 6.7$  Hz, H<sub>18a</sub>, 1H), 4.76 (d, H<sub>18b</sub>,  $J = 6.7$  Hz, 1H), 4.65 – 4.57 (m, H<sub>2,16,6</sub>, 4H), 4.22 (d,  $J = 4.4$  Hz, H<sub>3</sub>, 1H), 4.16 (t,  $J = 2.0$  Hz, H<sub>8</sub>, 1H), 4.06 (d,  $J = 8.9$  Hz, H<sub>12a</sub>, 1H), 3.54 (d,  $J = 8.9$  Hz, H<sub>12b</sub>, 1H), 3.43 (s, H<sub>19</sub>, 3H), 3.35 (s, H<sub>17</sub>, 3H), 2.97 (d,  $J = 2.2$  Hz,

H<sub>7</sub>, 1H), 2.76k (d, J = 1.7 Hz, H<sub>25</sub>, 1H), 1.63 (s, H<sub>14</sub>, 3H), 1.59 (s, H<sub>20</sub>, 3H), 1.41 (s, H<sub>21</sub>, 3H), 1.35 (s, H<sub>13</sub>, 3H), 0.90 (s, H<sub>24</sub>, 9H), 0.08 (s, H<sub>22</sub>, 3H), 0.03 (s, H<sub>23</sub>, 3H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 203.4 (C), 172.4 (C), 112.3 (C), 96.86 (CH<sub>2</sub>), 96.86 (CH<sub>2</sub>), 89.0 (C), 83.9 (C), 82.3 (CH), 82.0 (CH), 81.8 (CH), 80.2 (C), 75.1 (CH), 74.1 (CH), 73.9 (CH<sub>2</sub>), 70.7 (C), 57.3 (CH<sub>3</sub>), 55.6 (CH<sub>3</sub>), 46.6 (CH), 26.8 (CH<sub>3</sub>), 26.0 (CH<sub>3</sub>), 25.7 (3 × CH<sub>3</sub>), 25.1 (CH<sub>3</sub>), 23.6 (CH<sub>3</sub>), 18.0 (C), -4.5 (CH<sub>3</sub>), -4.6 (CH<sub>3</sub>). IR (ATR-FTIR), cm<sup>-1</sup>: 3734 (s), 3628 (m), 2917 (s), 1792 (m). HRMS-Cl (m/z): [M + Na]<sup>+</sup> calculated for C<sub>28</sub>H<sub>46</sub>NaO<sub>12</sub>Si, 625.2656; found 625.2634.  $[\alpha]_D^{20} = 23.8$  (c = 0.02, CHCl<sub>3</sub>).

*Synthesis of the vicinal diol 202:*

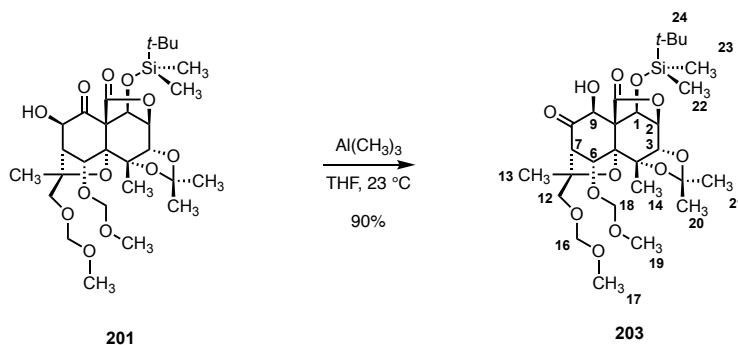


Sodium borohydride (2.0 mg, 50.0  $\mu\text{mol}$ , 10.0 equiv) was added in one portion to a solution of the ketone **201** (3.0 mg, 5.00  $\mu\text{mol}$ , 1 equiv) in methanol (500  $\mu\text{L}$ ) at 0 °C. The resulting mixture was stirred for 20 min at 0 °C. The cold product mixture was subsequently diluted sequentially with ethyl acetate (10 mL), water (5.0 mL), and saturated aqueous sodium chloride solution (5.0 mL). The resulting mixture was allowed to warm to 23 °C over 30 min. The warmed biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3  $\times$  5.0 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (5.0 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by preparative thin-layer chromatography (eluting with 50% ethyl acetate–hexanes) to provide the diol **202** as a colorless oil (3.0 mg, 99%).

Within the limits of detection, the diol **202** was formed as a single diastereomer ( $^1\text{H}$  NMR analysis, 600 MHz). The relative stereochemistry of the C4 hydroxyl substituent was established by the indicative  $J_{\text{H}4-\text{H}3} = 0$  Hz supporting the diequatorial configuration depicted.

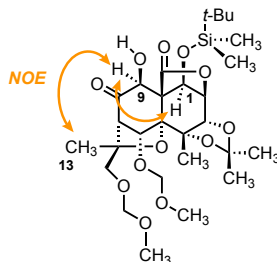
$R_f = 0.30$  (33% ethyl acetate–hexanes; PAA).  $^1\text{H NMR}$  (600 MHz,  $\text{CDCl}_3$ ):  $\delta$  5.22 (s,  $\text{H}_5$ , 1H), 4.77 (d,  $J = 6.8$  Hz,  $\text{H}_{12a}$ , 1H), 4.74 (d,  $J = 4.8$  Hz,  $\text{H}_6$ , 1H), 4.69 (d,  $J = 6.7$  Hz,  $\text{H}_{12b}$ , 1H), 4.61 (d,  $J = 6.3$  Hz,  $\text{H}_{14a}$ , 1H), 4.58 (d,  $J = 6.3$  Hz,  $\text{H}_{14b}$ , 1H), 4.47 (d,  $J = 1.6$  Hz,  $\text{H}_{17}$ , 1H), 4.35 (s,  $\text{H}_4$ , 1H), 4.34 (s,  $\text{H}_1$ , 1H), 4.32 (d,  $J = 2.9$  Hz,  $\text{H}_3$ , 1H), 4.22 (d,  $J = 4.8$  Hz,  $\text{H}_7$ , 1H), 4.08 (d,  $J = 8.8$  Hz,  $\text{H}_{11a}$ , 1H), 3.44 (d,  $J = 8.7$  Hz,  $\text{H}_{11b}$ , 1H), 3.41 (s,  $\text{H}_{13}$ , 3H), 3.35 (s,  $\text{H}_{15}$ , 3H), 2.74 (d,  $J = 2.9$  Hz,  $\text{H}_2$ , 1H), 1.64 (s,  $\text{H}_{16}$ , 3H), 1.59 (s,  $\text{H}_8$ , 3H), 1.58 (s,  $\text{H}_9$ , 3H), 1.40 (s,  $\text{H}_{10}$ , 3H), 0.91 (s,  $\text{H}_{20}$ , 9H), 0.21 (s,  $\text{H}_{18}$ , 3H), 0.20 (s,  $\text{H}_{19}$ , 3H).  $^{13}\text{C NMR}$  (150 MHz,  $\text{CDCl}_3$ ):  $\delta$  176.6 (C), 112.3 (C), 96.7 ( $\text{CH}_2$ ), 96.6 ( $\text{CH}_2$ ), 89.2 (C), 85.2 (C), 81.9 (CH), 80.7 (CH), 80.6 (C), 80.3 (CH), 76.5 (CH), 75.3 (CH), 75.0 (CH), 74.4 ( $\text{CH}_2$ ), 63.1 (C), 57.0 ( $\text{CH}_3$ ), 55.4 ( $\text{CH}_3$ ), 49.1 (CH), 26.8 ( $\text{CH}_3$ ), 25.8 ( $\text{CH}_3$ ), 25.8 ( $3 \times \text{CH}_3$ ), 25.4 ( $\text{CH}_3$ ), 21.9 ( $\text{CH}_3$ ), 17.8 (C),  $-4.1$  ( $\text{CH}_3$ ),  $-5.0$  ( $\text{CH}_3$ ). IR (ATR-FTIR),  $\text{cm}^{-1}$ : 3015 (s), 2975 (s), 2361 (s), 1784 (m), 1412 (s). HRMS-CI ( $m/z$ ):  $[\text{M} + \text{Na}]^+$  calculated for  $\text{C}_{28}\text{H}_{48}\text{NaO}_{12}\text{Si}$ , 627.2813; found, 627.2820.  $[\alpha]_D^{20} = 5.33$  ( $c = 0.03$ ,  $\text{CHCl}_3$ ).

*Synthesis of the transposed  $\alpha$ -hydroxy ketone 203:*



A solution of trimethylaluminum in toluene (2.00 M, 471  $\mu\text{L}$ , 942  $\mu\text{mol}$ , 6.00 equiv) was added dropwise via syringe to a solution of the  $\alpha$ -hydroxy ketone **201** (94.6 mg, 157  $\mu\text{mol}$ , 1 equiv) in tetrahydrofuran (2.2 mL) at 0 °C. Upon completion of the addition, the cooling bath was removed and the reaction mixture was allowed to warm to 23 °C over 20 min. The warmed product mixture was stirred for 6 h at 23 °C. The product mixture was diluted sequentially with saturated aqueous potassium sodium tartrate solution (10 mL), saturated aqueous sodium chloride solution (50 mL), and ethyl acetate (50 mL). The diluted product mixture was vigorously stirred for 45 min at 23 °C. The resulting clear, biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3  $\times$  25 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (30 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 20% ethyl acetate–hexanes) to provide the transposed  $\alpha$ -hydroxy ketone **203** as a white solid (85.0 mg, 90%).

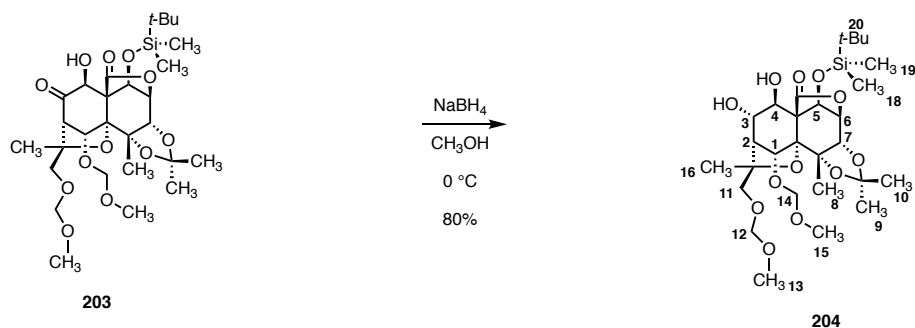
Within the limits of detection, the transposed  $\alpha$ -hydroxyketone **203** was formed as a single diastereomer ( $^1\text{H}$  NMR analysis, 500 MHz). NOE correlations between the C9 hydrogen and the C13 methyl substituent, as well as the C9 and C1 hydrogen atoms support the relative configuration depicted.



$R_f = 0.50$  (33% ethyl acetate–hexanes; CAM).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  5.12 (s, H<sub>1</sub>, 1H), 4.75 (d,  $J = 2.2$  Hz, H<sub>16a</sub>, 1H), 4.74 (s, H<sub>2</sub>, 1H), 4.65 (d,  $J = 6.7$  Hz, H<sub>16b</sub>, 1H), 4.61 (d,  $J = 6.4$  Hz, H<sub>18a</sub>, 1H), 4.57 (d,  $J = 6.4$  Hz, H<sub>18b</sub>, 1H), 4.38 (d,  $J = 5.3$  Hz, H<sub>9</sub>, 1H), 4.32 (s, H<sub>6</sub>, 1H), 4.27 (d,  $J = 4.7$  Hz, H<sub>3</sub>, 1H), 4.10 (d,  $J = 9.1$  Hz, H<sub>12a</sub>, 1H), 3.54 (s, H<sub>7</sub>, 1H), 3.51 (d,  $J = 9.0$  Hz, H<sub>12b</sub>, 1H), 3.39 (s, H<sub>17</sub>, 3H), 3.34 (s, H<sub>19</sub>, 3H), 1.62 (s, H<sub>14</sub>, 3H), 1.58 (s, H<sub>20</sub>, 3H), 1.42 (s, H<sub>21</sub>, 3H), 1.40 (s, H<sub>13</sub>, 3H), 0.93 (s, H<sub>24</sub>, 9H), 0.16 (s, H<sub>22</sub>, 3H), 0.15 (s, H<sub>23</sub>, 3H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  204.0 (C), 172.7 (C), 112.8 (C), 97.3 (CH<sub>2</sub>), 96.8 (CH<sub>2</sub>), 91.0 (C), 85.6 (C), 82.8 (CH), 82.1 (C), 80.8 (C), 80.5 (CH), 74.5 (CH), 73.4 (CH<sub>2</sub>), 72.4 (CH), 62.9 (C), 59.4 (CH), 57.2 (CH<sub>3</sub>), 55.7 (CH<sub>3</sub>), 26.4 (CH<sub>3</sub>), 26.0 (CH<sub>3</sub>), 25.7 (3  $\times$  CH<sub>3</sub>), 22.1 (CH<sub>3</sub>), 18.1 (C), -4.4 (CH<sub>3</sub>), -4.7 (CH<sub>3</sub>). IR (ATR-FTIR),  $\text{cm}^{-1}$ : 3734 (s), 3628 (m), 2930 (s), 1784 (s), 1733 (s). HRMS-CI ( $m/z$ ):  $[\text{M} + \text{Na}]^+$  calculated for  $\text{C}_{28}\text{H}_{46}\text{NaO}_{12}\text{Si}$ , 625.2656; found 625.2634.  $[\alpha]_D^{20} = 27.6$  ( $c = 0.10$ ,  $\text{CHCl}_3$ ).



*Synthesis of the vicinal diol 204:*



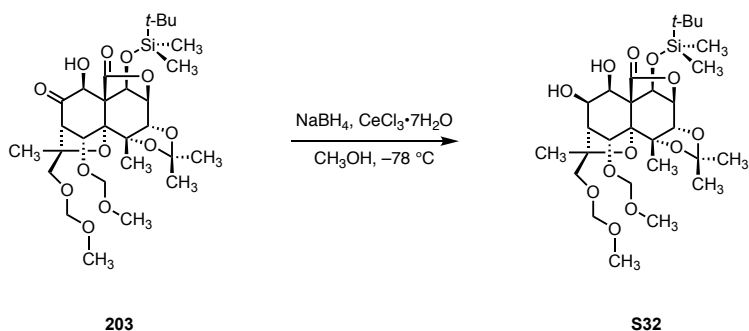
Sodium borohydride (1.5 mg, 40.0  $\mu\text{mol}$ , 6.0 equiv) was added in one portion to a solution of the ketone **203** (4.0 mg, 7.00  $\mu\text{mol}$ , 1 equiv) in methanol (500  $\mu\text{L}$ ) at  $0\text{ }^\circ\text{C}$ . The resulting mixture was stirred for 40 min at  $0\text{ }^\circ\text{C}$ . The cold product mixture was subsequently diluted sequentially with ethyl acetate (10 mL), water (5.0 mL), and saturated aqueous sodium chloride solution (5.0 mL). The resulting mixture was allowed to warm to  $23\text{ }^\circ\text{C}$  over 30 min. The warmed biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate ( $3 \times 5.0$  mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (5.0 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by preparative thin-layer chromatography (eluting with 50% ethyl acetate–hexanes) to provide the diol **204** as a colorless oil (3.2 mg, 80%).

Within the limits of detection, the diol **204** was formed as a 8:1 mixture of diastereomers ( $^1\text{H}$  NMR analysis, 500 MHz). The relative stereochemistry of the C3 hydroxyl substituent was established by the  $J_{\text{H}_4-\text{H}_3} = 9.1\text{ Hz}$  supporting the diaxial configuration depicted.

$R_f = 0.20$  (33% ethyl acetate–hexanes; PAA).  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  5.06 (s,  $\text{H}_5$ , 1H), 4.79 (d,  $J = 6.8$  Hz,  $\text{H}_{14a}$ , 1H), 4.67 (m,  $\text{H}_{6, 14b}$ , 2H), 4.62 – 4.56 (m,  $\text{H}_{12}$ , 2H), 4.31 (d,  $J = 9.1$  Hz,  $\text{H}_4$ , 1H), 4.20 (d,  $J = 4.7$  Hz,  $\text{H}_{3, 7}$ , 2H), 4.15 (s,  $\text{H}_1$ , 1H), 4.09 (d,  $J = 9.0$  Hz,  $\text{H}_{11a}$ , 1H), 3.40 (s,  $\text{H}_{11b, 13}$ , 4H), 3.34 (s,  $\text{H}_{15}$ , 3H), 2.86 (d,  $J = 3.4$  Hz,  $\text{H}_2$ , 1H), 1.62 (s,  $\text{H}_{16}$ , 3H), 1.59 (s,  $\text{H}_8$ , 3H), 1.56 (s,  $\text{H}_{10}$ , 3H), 1.39 (s,  $\text{H}_9$ , 3H), 0.95 (s,  $\text{H}_{20}$ , 9H), 0.21 (s,  $\text{H}_{18}$ , 3H), 0.19 (s,  $\text{H}_{19}$ , 3H).  $^{13}\text{C NMR}$  (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  173.2 (C), 112.5 (C), 96.8 ( $\text{CH}_2$ ), 96.6 ( $\text{CH}_2$ ), 89.9 (C), 86.1 (C), 82.9 (CH), 82.7 (CH), 80.7 (C), 80.0 (CH), 75.9 (CH), 74.3 ( $\text{CH}_2$ ), 74.3 (CH), 71.9 (CH), 61.7 (C), 56.9 ( $\text{CH}_3$ ), 55.4 ( $\text{CH}_3$ ), 46.4 (CH), 26.9 ( $\text{CH}_3$ ), 26.3 ( $\text{CH}_3$ ), 25.8 ( $3 \times \text{CH}_3$ ), 25.7 ( $\text{CH}_3$ ), 22.0 (C), 17.9 (C),  $-4.6$  ( $\text{CH}_3$ ),  $-4.8$  ( $\text{CH}_3$ ). IR (ATR-FTIR),  $\text{cm}^{-1}$ : 3015 (s), 2995 (m), 2975 (s), 2956 (m), 2360 (s), 1785 (m), 1721 (m), 1412 (s). HRMS-Cl ( $m/z$ ):  $[\text{M} + \text{Na}]^+$  calculated for  $\text{C}_{28}\text{H}_{48}\text{NaO}_{12}\text{Si}$ , 627.2813; found, 627.2822.  $[\alpha]_D^{20} = -0.20$  ( $c = 0.10$ ,  $\text{CHCl}_3$ ).

*Synthesis of the bis(acetonide) 206:*

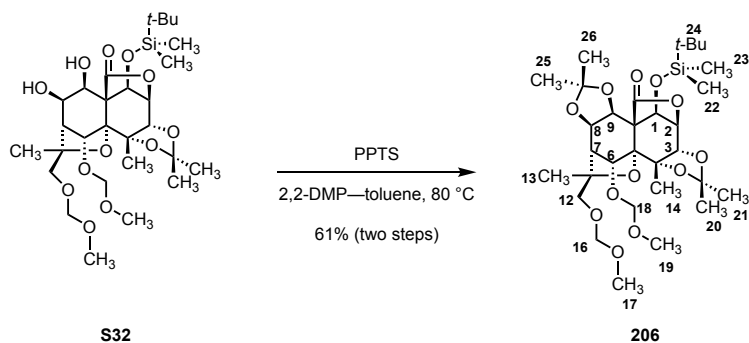
*Part 1: Synthesis of the diol S32:*



Cerium (III) chloride heptahydrate (131 mg, 353  $\mu\text{mol}$ , 2.50 equiv) was added in one portion to a solution of the  $\alpha$ -hydroxy ketone **203** (85.0 mg, 141  $\mu\text{mol}$ , 1 equiv) in methanol (2.8 mL) at 23  $^{\circ}\text{C}$ . The resulting solution was cooled to  $-78$   $^{\circ}\text{C}$ . Sodium borohydride (26.7 mg, 705  $\mu\text{mol}$ , 5.00 equiv) was added in one portion and the resulting mixture was stirred for 35 min at  $-78$   $^{\circ}\text{C}$ . The cold product mixture was diluted sequentially with ethyl acetate (10 mL), water (5.0 mL), and saturated aqueous sodium chloride solution (50 mL). The resulting mixture was allowed to warm to 23  $^{\circ}\text{C}$  over 20 min. The warmed biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate ( $3 \times 10$  mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was used directly in the following step.

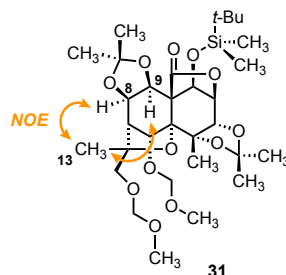
$^1\text{H}$  NMR analysis of the unpurified product mixture indicated the presence of 4.1:1 mixture of diastereomers. The relative stereochemistry of the C8 hydroxyl substituent was established by conversion of diol **S32** to the bis(acetonide) **206**.

Part 2: Synthesis of the bis(acetonide) **206**:



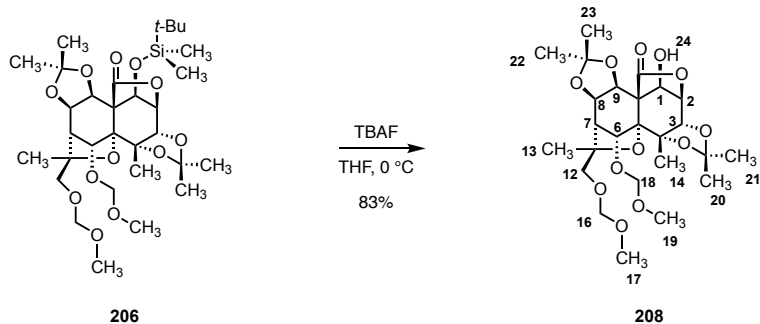
Pyridinium *para*-toluenesulfonate (10.6 mg, 42.3  $\mu\text{mol}$ , 0.30 equiv) was added in one portion to a screw-capped vessel containing a solution of the unpurified diol **S32** obtained in the preceding step (nominally 141  $\mu\text{mol}$ , 1 equiv) in toluene (2.3 mL) and 2,2-dimethoxypropane (2.3 mL) at 23 °C. The reaction vessel was sealed and the sealed vessel was placed in an oil bath that had been preheated to 80 °C. The reaction mixture was stirred and heated for 24 h at 80 °C. The product mixture was cooled to 23 °C over 30 min. The cooled product mixture was diluted sequentially with ethyl acetate (10 mL), water (10 mL), and saturated aqueous sodium bicarbonate solution (10 mL). The diluted product mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3  $\times$  10 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 33% ethyl acetate–hexanes) to provide the bis(acetonide) **206** as a colorless oil (55.1 mg, 61% over two steps).

NOE correlations between the C8 hydrogen atom and the C13 methyl substituent, as well as the C9 hydrogen and the C13 methyl substituent, support the relative configuration depicted.



$R_f = 0.20$  (33% ethyl acetate–hexanes; CAM).  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  4.82 (s,  $\text{H}_1$ , 1H), 4.77 (d,  $J = 6.7$  Hz,  $\text{H}_{16a}$ , 1H), 4.70 (d,  $J = 6.7$  Hz,  $\text{H}_{16b}$ , 1H), 4.63 (s,  $\text{H}_6$ , 1H), 4.62 – 4.55 (m,  $\text{H}_{2,8,18}$ , 4H), 4.37 (d,  $J = 7.1$  Hz,  $\text{H}_9$ , 1H), 4.18 (d,  $J = 4.7$  Hz,  $\text{H}_3$ , 1H), 4.11 (d,  $J = 8.9$  Hz,  $\text{H}_{12a}$ , 1H), 3.47 – 3.41 (m,  $\text{H}_{12a,17}$ , 3H), 3.35 (s,  $\text{H}_{19}$ , 3H), 2.99 (d,  $J = 3.1$  Hz,  $\text{H}_7$ , 1H), 1.69 (s,  $\text{H}_{25}$ , 3H), 1.61 (s,  $\text{H}_{14}$ , 3H), 1.54 (s,  $\text{H}_{20}$ , 3H), 1.41 (s,  $\text{H}_{13}$ , 3H), 1.38 (s,  $\text{H}_{21}$ , 3H), 1.29 (s,  $\text{H}_{26}$ , 3H), 0.92 (s,  $\text{H}_{24}$ , 9H), 0.13. (d,  $J = 5.1$  Hz,  $\text{H}_{22,23}$ , 6H).  $^{13}\text{C NMR}$  (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  171.7 (C), 112.0 (C), 110.7 (C), 97.2 ( $\text{CH}_2$ ), 96.7 ( $\text{CH}_2$ ), 89.6 (C), 84.4 (C), 82.7 (CH), 80.9 (C), 80.2 (CH), 78.8 (CH), 76.1 (CH), 73.7 ( $\text{CH}_2$ ), 73.4 (CH), 71.2 (CH), 62.6 (C), 57.1 ( $\text{CH}_3$ ), 55.4 ( $\text{CH}_3$ ), 45.0 (CH), 26.8 ( $\text{CH}_3$ ), 26.0 ( $\text{CH}_3$ ), 25.9 ( $\text{CH}_3$ ), 25.5 ( $3 \times \text{CH}_3$ ), 25.1 ( $\text{CH}_3$ ), 24.6 ( $\text{CH}_3$ ), 22.0 ( $\text{CH}_3$ ), 18.0 (C),  $-4.3$  ( $\text{CH}_3$ ),  $-5.1$  ( $\text{CH}_3$ ). IR (ATR-FTIR),  $\text{cm}^{-1}$ : 3735 (s), 3649 (m), 2929 (s), 1792 (s). HRMS-CI ( $m/z$ ):  $[\text{M} + \text{Na}]^+$  calculated for  $\text{C}_{31}\text{H}_{52}\text{NaO}_{12}\text{Si}$ , 667.3126; found 667.3105.  $[\alpha]_D^{20} = 2.56$  ( $c = 0.05$ ,  $\text{CHCl}_3$ ).

*Synthesis of the alcohol 208:*

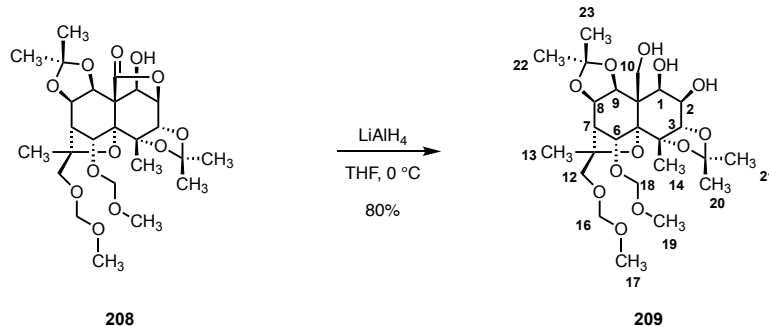


A solution of tetra-*n*-butylammonium fluoride in tetrahydrofuran (1.00 M, 140  $\mu$ L, 140  $\mu$ mol, 2.00 equiv) was added dropwise via syringe to a solution of the bis(acetonide) **206** (45.0 mg, 70.0  $\mu$ mol, 1 equiv) in tetrahydrofuran (690  $\mu$ L) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C. The cold product mixture was diluted sequentially with ethyl acetate (10 mL), saturated aqueous ammonium chloride solution (5.0 mL), and water (5.0 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3  $\times$  5 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 33% ethyl acetate–hexanes) to provide the alcohol **208** as a colorless oil (31.0 mg, 83%).

R<sub>f</sub> = 0.50 (50% ethyl acetate–hexanes; CAM). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  4.82 (s, H<sub>1</sub>, 1H), 4.78 (d, J = 6.7 Hz, H<sub>18a</sub>, 1H), 4.75 (d, J = 4.7 Hz, H<sub>2</sub>, 1H), 4.71 (d, J = 6.7 Hz, H<sub>18b</sub>, 1H), 4.68 (s, H<sub>6</sub>, 1H), 4.64 – 4.56 (m, H<sub>8,9,16</sub>, 4H), 4.21 (d, J = 4.7 Hz, H<sub>3</sub>, 1H), 4.12 (d, J = 8.9 Hz, H<sub>12a</sub>, 1H), 3.44 (d, J = 8.9 Hz, H<sub>12b</sub>, 1H), 3.43 (s, H<sub>19</sub>, 3H), 3.35 (s, H<sub>17</sub>, 3H), 3.03 (d, J = 3.1 Hz, H<sub>7</sub>, 1H), 1.72 (s, H<sub>23</sub>, 3H), 1.63 (s, H<sub>14</sub>, 3H), 1.55 (s, H<sub>20</sub>, 3H), 1.44 (s, H<sub>13</sub>,

3H), 1.39 (s, H<sub>22</sub>, 3H), 1.36 (s, H<sub>21</sub>, 3H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 171.5 (C), 112.4 (C), 111.8 (C), 97.5 (CH<sub>2</sub>), 96.9 (CH<sub>2</sub>), 89.8 (C), 85.1 (C), 82.8 (CH), 81.1 (C), 80.3 (CH), 79.2 (CH), 76.5 (CH), 74.0 (CH<sub>2</sub>), 73.2 (CH), 71.6 (CH), 62.8 (C), 57.3 (CH<sub>3</sub>), 55.7 (CH<sub>3</sub>), 45.1 (CH), 27.1 (CH<sub>3</sub>), 26.2 (CH<sub>3</sub>), 26.1 (CH<sub>3</sub>), 25.4 (CH<sub>3</sub>), 25.3 (CH<sub>3</sub>), 22.3 (CH<sub>3</sub>). IR (ATR-FTIR), cm<sup>-1</sup>: 3452 (m), 2983 (m), 2930 (s), 1787 (s). HRMS-CI (m/z): [M + Na]<sup>+</sup> calculated for C<sub>25</sub>H<sub>38</sub>NaO<sub>12</sub>, 553.2261; found 553.2252.  $[\alpha]_D^{20} = -9.14$  (*c* = 0.27, CHCl<sub>3</sub>).

*Synthesis of the triol 209:*



A solution of lithium aluminum hydride in tetrahydrofuran (1.00 M, 132  $\mu\text{L}$ , 132  $\mu\text{mol}$ , 5.00 equiv) was added dropwise via syringe to a solution of the alcohol **208** (14.0 mg, 26.0  $\mu\text{mol}$ , 1 equiv) in tetrahydrofuran (1.0 mL) at 0  $^\circ\text{C}$ . The reaction mixture was stirred for 1 h at 0  $^\circ\text{C}$ . Five drops of water were then added to the cold product mixture, and the resulting solution was stirred for 30 min at 0  $^\circ\text{C}$ . The product mixture was diluted sequentially with ethyl acetate (10 mL) and saturated aqueous potassium sodium tartrate solution (5.0 mL). The diluted product mixture was warmed to 23  $^\circ\text{C}$  over 30 min. The warmed biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate ( $5 \times 8$  mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 70% ethyl acetate–hexanes) to provide the triol **209** as a colorless oil (11.5 mg, 80%).

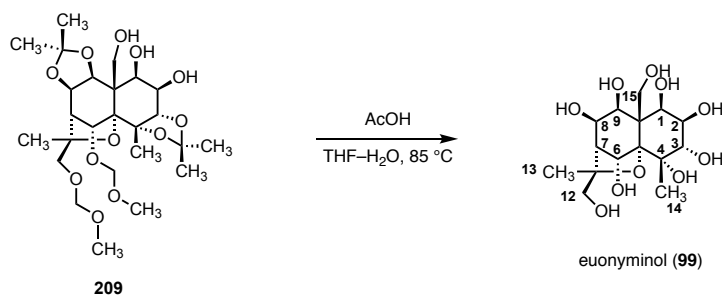
$R_f = 0.30$  (70% ethyl acetate–hexanes; CAM).  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  4.78 (d,  $J = 6.9$  Hz,  $\text{H}_{18a}$ , 1H), 4.68 (d,  $J = 6.9$  Hz,  $\text{H}_{18b}$ , 1H), 4.63 (dd,  $J = 6.6, 3.2$  Hz,  $\text{H}_8$ , 1H), 4.61 – 4.53 (m,  $\text{H}_{9,10a,16}$ , 4H), 4.40 – 4.33 (m,  $\text{H}_{1,2,3}$ , 3H), 3.93 (d,  $J = 11.5$  Hz,  $\text{H}_{10a}$ , 1H), 3.44 (s,



H<sub>17</sub>, 3H), 3.39 (d, J = 8.7 Hz, H<sub>12b</sub>, 1H), 3.34 (s, H<sub>19</sub>, 3H), 3.05 (d, J = 3.2 Hz, H<sub>7</sub>, 1H), 1.67 (s, H<sub>14</sub>, 3H), 1.63 (s, H<sub>22</sub>, 3H), 1.46 (s, H<sub>20</sub>, 3H), 1.43 (s, H<sub>23</sub>, 3H), 1.41 (s, H<sub>13</sub>, 3H), 1.39 (s, H<sub>21</sub>, 3H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 109.4 (C), 108.1 (C), 96.7 (CH<sub>2</sub>), 96.3 (CH<sub>2</sub>), 91.3 (C), 86.1 (CH), 83.3 (C), 80.8 (CH), 79.4 (CH), 78.4 (C), 77.3 (CH), 74.1 (CH<sub>2</sub>), 73.9 (CH), 70.6 (CH), 67.5 (CH<sub>2</sub>), 56.9 (CH), 55.5 (CH), 52.7 (C), 44.9 (CH), 27.6 (CH<sub>3</sub>), 26.4 (CH<sub>3</sub>), 26.2 (CH<sub>3</sub>), 25.9 (CH<sub>3</sub>), 24.7 (CH<sub>3</sub>), 22.4 (CH<sub>3</sub>). IR (ATR-FTIR), cm<sup>-1</sup>: 3734 (CH<sub>3</sub>) (m), 3628 (m), 3446 (m), 2936 (m). HRMS-CI (m/z): [M + Na]<sup>+</sup> calculated for C<sub>25</sub>H<sub>42</sub>NaO<sub>12</sub>, 557.2574; found 557.2574.  $[\alpha]_D^{20} = -25.3$  (c = 0.12, CHCl<sub>3</sub>).

*Synthesis of the euonyminol octaacetate (116):*

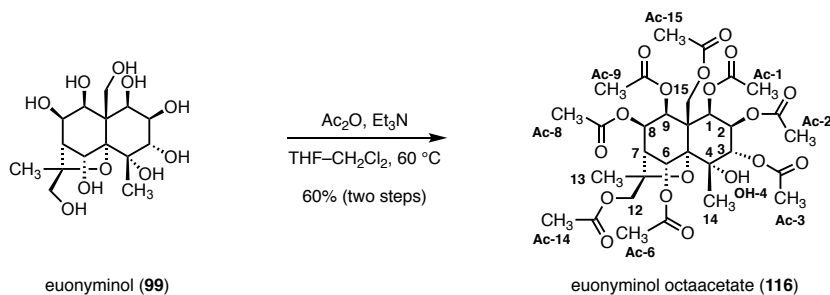
*Part 1: Synthesis of euonyminol (99):*



Glacial acetic acid (900  $\mu\text{L}$ ) was added in one portion to a screw-capped vessel containing a solution of the triol **209** (11.0 mg, 20.6  $\mu\text{mol}$ , 1 equiv) in tetrahydrofuran–water (1:1 v/v, 600  $\mu\text{L}$ ) at 23 °C. The reaction vessel was sealed and the sealed vessel was placed in an oil bath that had been preheated to 85 °C. The reaction mixture was stirred and heated for 42 h at 85 °C. The product mixture was cooled to 23 °C over 30 min. The cooled product mixture was concentrated and the residue obtained was used directly in the following step.

The product **99** was converted to the known euonyminol octaacetate (**116**) to facilitate purification and characterization.

Part 2: Synthesis of the euonyminol octaacetate (**116**):

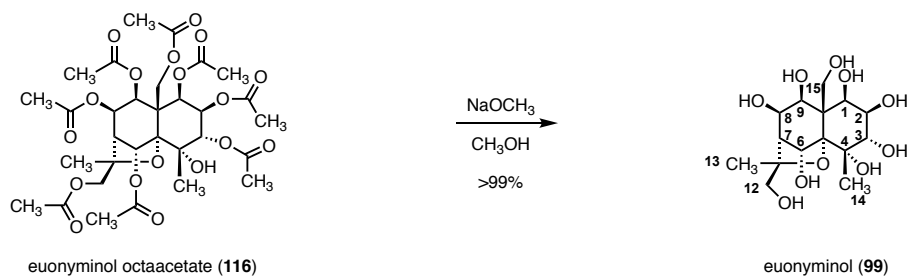


Triethylamine (1.15 mL, 8.24 mmol, 400 equiv) and acetic anhydride (583  $\mu$ L, 6.18 mmol, 300 equiv) were added in sequence to a solution of the residue obtained in the preceding step (nominally 20.6  $\mu$ mol, 1 equiv) in tetrahydrofuran–dichloromethane (1:1 v/v, 440  $\mu$ L) in a screw-capped vial at 23 °C. The reaction vessel was sealed and the sealed reaction vessel was placed in an oil bath that had been preheated to 60 °C. The reaction mixture was stirred for 1 h at 60 °C. The product mixture was cooled to 23 °C over 15 min and the cooled reaction mixture was then sonicated for 5 min at 23 °C. The reaction vessel was then placed in an oil bath that had been preheated to 60 °C and heated for an additional hour. This heating–cooling–sonicating procedure was repeated a total of six times as described above. After the sixth cycle, the product mixture was diluted sequentially with ethyl acetate (10 mL), water (5.0 mL), and saturated aqueous sodium bicarbonate solution (5.0 mL). The diluted product mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3  $\times$  5.0 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (5.0 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 50%

ethyl acetate–hexanes) to provide euonyminol octaacetate (**116**) as a colorless oil (8.7 mg, 60% over two steps).

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.77 (s,  $\text{H}_6$ , 1H), 5.58 (d,  $J = 3.7$  Hz,  $\text{H}_1$ , 1H), 5.48 (dd,  $J = 5.8, 3.9$  Hz,  $\text{H}_8$ , 1H), 5.34 (d,  $J = 6.0$  Hz,  $\text{H}_9$ , 1H), 5.29 – 5.25 (m,  $\text{H}_2$ , 1H), 5.21 (d,  $J = 13.3$  Hz,  $\text{H}_{15a}$ , 1H), 4.89 (d,  $J = 11.6$  Hz,  $\text{H}_{12a}$ , 1H), 4.82 (d,  $J = 2.5$  Hz,  $\text{H}_3$ , 1H), 4.42 (d,  $J = 13.3$  Hz,  $\text{H}_{15b}$ , 1H), 4.16 (s,  $\text{H}_{\text{OH-4}}$ , 1H), 3.95 (d,  $J = 11.6$  Hz,  $\text{H}_{12b}$ , 1H), 2.32 (d,  $J = 3.9$  Hz,  $\text{H}_7$ , 1H), 2.25 (s,  $\text{H}_{\text{Ac-15}}$ , 3H), 2.17 (s,  $\text{H}_{\text{Ac-8}}$ , 3H), 2.16 (s,  $\text{H}_{\text{Ac-3}}$ , 3H), 2.13 (s,  $\text{H}_{\text{Ac-6}}$ , 3H), 2.12 (s,  $\text{H}_{\text{Ac-2}}$ , 3H), 2.11 (s,  $\text{H}_{\text{Ac-12}}$ , 3H), 1.98 (s,  $\text{H}_{\text{Ac-9}}$ , 3H), 1.88 (s,  $\text{H}_{\text{Ac-1}}$ , 3H), 1.57 (s,  $\text{H}_{13}$ , 3H), 1.48 (s,  $\text{H}_{14}$ , 3H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  170.7 (C), 170.13 (C), 170.07 (C), 169.8 (C), 169.5 (C), 169.3 (C), 168.9 (C), 168.7 (C), 93.0 (C), 84.1 (C), 75.8 (CH), 73.9 (CH), 73.2 (CH), 71.0 (CH), 69.5 ( $\text{CH}_2$ ), 69.3 (C), 69.03 (CH), 68.98 (CH), 60.3 ( $\text{CH}_2$ ), 51.9 (C), 50.7 (CH), 23.3 ( $\text{CH}_3$ ), 21.5 ( $\text{CH}_3$ ), 21.3 ( $\text{CH}_3$ ), 21.0 ( $\text{CH}_3$ ), 20.9 ( $\text{CH}_3$ ), 20.8 ( $\text{CH}_3$ ), 20.54 ( $\text{CH}_3$ ), 20.50 ( $\text{CH}_3$ ), 18.3 ( $\text{CH}_3$ ). IR (ATR-FTIR),  $\text{cm}^{-1}$ : 3468 (m), 3456 (m), 2957 (m), 2919 (m), 2850 (m), 1743 (s). HRMS-CI ( $m/z$ ):  $[\text{M} + \text{Na}]^+$  calculated for  $\text{C}_{31}\text{H}_{42}\text{NaO}_{18}$ , 725.2269; found 725.2247.  $[\alpha]_D^{20} = -5.96$  ( $c = 0.20$ ,  $\text{CHCl}_3$ ).

Synthesis of euonyminol (**99**):



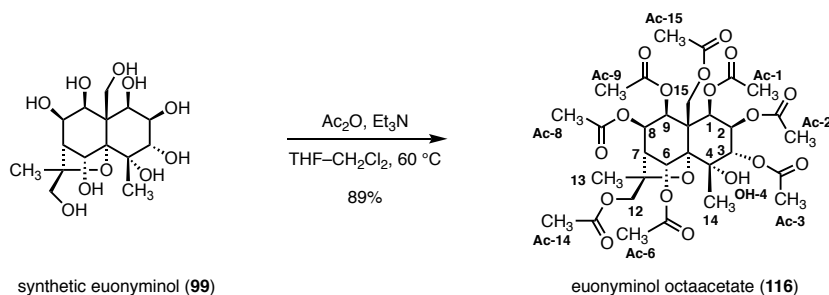
A solution of a freshly prepared sodium methoxide in methanol (0.10 M, 7.0  $\mu$ L, 0.70  $\mu$ mol, 0.20 equiv) was added dropwise via syringe to a solution of euonyminol octaacetate (**116**, 2.50 mg, 3.60  $\mu$ mol, 1 equiv) in methanol (300  $\mu$ L) at 23  $^{\circ}$ C. The reaction mixture was stirred for 36 h at 23  $^{\circ}$ C. The product mixture was concentrated to provide analytically pure euonyminol (**99**) as an off-white solid (1.30 mg, >99%).

$^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  5.37 (s,  $\text{H}_6$ , 1H), 4.44 (d,  $J = 12.9$  Hz,  $\text{H}_{15a}$ , 1H), 4.30 – 4.27 (m,  $\text{H}_{1,9}$ , 2H), 4.16 – 4.05 (m,  $\text{H}_{8,15b}$ , 2H), 3.97 – 3.87 (m,  $\text{H}_{12a,2}$ , 2H), 3.64 (d,  $J = 11.1$  Hz,  $\text{H}_{12b}$ , 1H), 3.57 (d,  $J = 3.0$  Hz,  $\text{H}_3$ , 1H), 2.28 (dd,  $J = 4.2, 1.1$  Hz,  $\text{H}_7$ , 1H), 1.77 (s,  $\text{H}_{14}$ , 3H), 1.43 (s,  $\text{H}_{13}$ , 3H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  94.5 (C), 85.9 (C), 79.3 (CH), 76.9 (CH), 75.8 (CH), 74.97 (CH), 74.97 (CH), 73.4 (C), 71.0 (CH), 68.9 ( $\text{CH}_2$ ), 59.6 ( $\text{CH}_2$ ), 55.0 (C), 53.9 (CH), 25.9 ( $\text{CH}_3$ ), 18.9 ( $\text{CH}_3$ ). IR (ATR-FTIR),  $\text{cm}^{-1}$ : 3354 (s), 2920 (m), 2852 (m), 1653 (m), 1053 (m). HRMS-CI ( $m/z$ ):  $[\text{M} + \text{Na}]^+$  calculated for  $\text{C}_{15}\text{H}_{26}\text{NaO}_{10}$ , 389.1424; found 389.1418.  $[\alpha]_D^{20} = -4.70$  ( $c = 0.08$ ,  $\text{CD}_3\text{OD}$ ).

$^1\text{H}$  NMR (500 MHz,  $\text{D}_2\text{O}$ ):  $\delta$  5.22 (s,  $\text{H}_6$ , 1H), 4.43 (d,  $J = 13.1$  Hz,  $\text{H}_{15a}$ , 1H), 4.37 (d,  $J = 5.4$  Hz,  $\text{H}_9$ , 1H), 4.33 (d,  $J = 3.5$  Hz,  $\text{H}_1$ , 1H), 4.21 (dd,  $J = 5.3, 4.1$  Hz,  $\text{H}_8$ , 1H), 4.09 (d,  $J = 13.1$  Hz,  $\text{H}_{15b}$ , 1H), 4.03 (t,  $J = 3.2$  Hz,  $\text{H}_2$ , 1H), 3.92 (d,  $J = 11.4$  Hz,  $\text{H}_{12a}$ , 1H), 3.73 (d,  $J =$

11.4 Hz, H<sub>12b</sub>, 1H), 3.66 (d, J = 2.9 Hz, H<sub>3</sub>, 1H), 2.39 (d, J = 4.0 Hz, H<sub>7</sub>, 1H), 1.74 (s, H<sub>14</sub>, 3H), 1.44 (s, H<sub>13</sub>, 3H). <sup>13</sup>C NMR (125 MHz, D<sub>2</sub>O): δ 92.7 (C), 84.4 (C), 77.1 (CH), 74.8 (CH), 74.0 (CH), 73.0 (CH), 72.8 (CH), 71.7 (C), 69.4 (CH), 67.2 (CH<sub>2</sub>), 58.2 (CH<sub>2</sub>), 53.5 (C), 61.9 (CH), 24.0 (CH<sub>3</sub>), 17.8 (CH<sub>3</sub>).

Re-acylation of synthetic euonyminol (**99**) to provide euonyminol octaacetate (**116**):

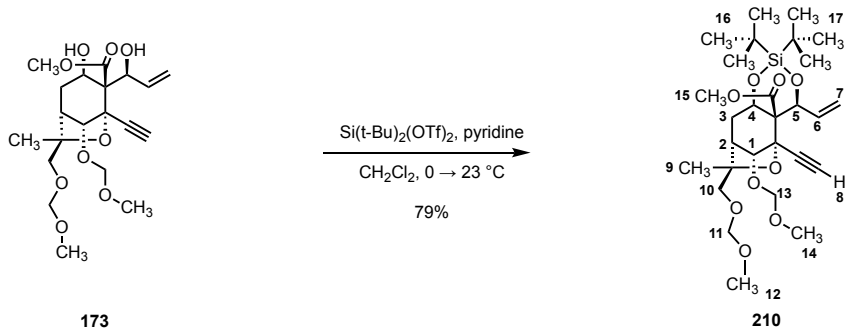


Triethylamine (197  $\mu$ L, 1.42 mmol, 400 equiv) and acetic anhydride (100  $\mu$ L, 1.06 mmol, 300 equiv) were added in sequence to a solution of synthetic euonyminol (**99**) obtained in the preceding experiment (1.30 mg, 3.50  $\mu$ mol, 1 equiv) in tetrahydrofuran–dichloromethane (1:1 v/v, 300  $\mu$ L) in a screw-capped vial at 23 °C. The reaction vessel was sealed and the sealed reaction vessel was placed in an oil bath that had been preheated to 60 °C. The reaction mixture was stirred for 9 h at 60 °C. The product mixture was cooled to 23 °C over 15 min. The cooled product mixture was diluted sequentially with ethyl acetate (8.0 mL), water (3.0 mL), and saturated aqueous sodium bicarbonate solution (3.0 mL). The diluted product mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3  $\times$  5.0 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (5.0 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by preparative thin-column chromatography (eluting with 50% ethyl acetate–hexanes) to provide euonyminol octaacetate (**116**) as a colorless oil (2.2 mg, 89%).

$^1\text{H}$  NMR analysis of the re-acylated euonyminol octaacetate (**116**) was in complete agreement with the  $^1\text{H}$  NMR of synthetic **116**.



*Synthesis of the silylene ether 210:*

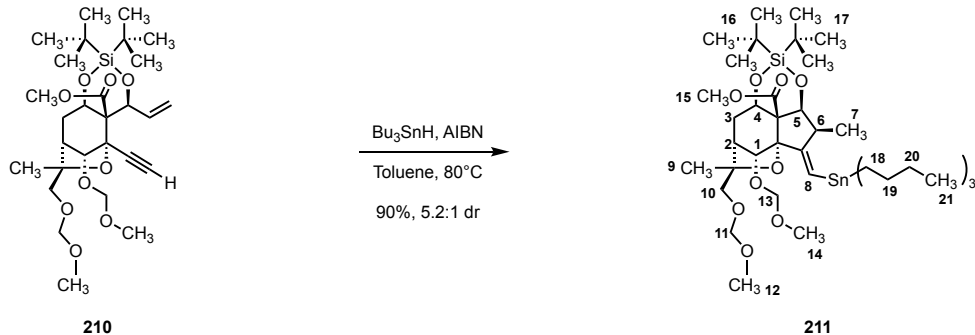


Di-tert-butylsilyl bis(trifluoromethanesulfonate) (118  $\mu\text{L}$ , 362  $\mu\text{mol}$ , 1.50 equiv) was added dropwise via syringe to a solution of the diol **173** (100 mg, 241  $\mu\text{mol}$ , 1 equiv) and pyridine (97.0  $\mu\text{L}$ , 1.21 mmol, 5.00 equiv) in dichloromethane (1.5 mL) at 0  $^\circ\text{C}$ . The reaction mixture was stirred for 30 min at 0  $^\circ\text{C}$  and then the cooling bath was removed. The reaction mixture was allowed to warm to 23  $^\circ\text{C}$  and then stirred for 12 h at 23  $^\circ\text{C}$ . The product mixture was diluted sequentially with saturated aqueous ammonium chloride solution (5.0 mL), water (5.0 mL), and dichloromethane (15 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with dichloromethane ( $3 \times 10.0$  mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (10.0 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 25% ethyl acetate–hexanes) to provide the silylene ether **210** as a yellow oil (106 mg, 79%).

$R_f = 0.30$  (33% ethyl acetate–hexanes; PAA).  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.95 (ddd,  $\text{H}_6$ ,  $J = 16.9, 10.4, 5.1$  Hz, 1H), 5.37 (d,  $\text{H}_{7a}$ ,  $J = 18.6$  Hz, 1H), 5.11 (d,  $\text{H}_{7b}$ ,  $J = 10.4$  Hz, 1H), 5.01 (d,  $\text{H}_5$ ,  $J = 5.1$  Hz, 1H), 4.72 – 4.57 (m,  $\text{H}_{5,11,13}$ , 5H), 4.41 (s,  $\text{H}_1$ , 195H), 3.98 (d,

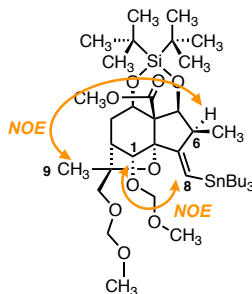
H<sub>10a</sub>, J = 9.2 Hz, 1H), 3.69 (s, H<sub>15</sub>, 3H), 3.57 (d, H<sub>10b</sub>, J = 9.2 Hz, 1H), 3.35 (s, H<sub>12,14</sub>, 6H), 2.67 (s, H<sub>8</sub>, 1H), 2.50 (t, H<sub>2</sub>, J = 2.9 Hz, 1H), 2.37 – 2.26 (m, H<sub>3a</sub>, 1H), 2.19 – 2.08 (m, H<sub>3b</sub>, 1H), 1.47 (s, H<sub>9</sub>, 3H), 1.11 (s, H<sub>16</sub>, 9H), 0.96 (s, H<sub>17</sub>, 9H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 169.7 (C), 138.6 (CH), 114.5 (CH<sub>2</sub>), 96.7 (CH<sub>2</sub>), 95.5 (CH<sub>2</sub>), 87.6 (C), 83.4 (CH), 83.3 (C), 80.6 (CH), 79.9 (C), 79.2 (C), 73.8 (CH<sub>2</sub>), 72.9 (CH), 63.9 (C), 55.5 (CH<sub>3</sub>), 55.2 (CH<sub>3</sub>), 51.4 (CH<sub>3</sub>), 42.8 (CH), 33.3 (CH<sub>2</sub>), 28.7 (3 × CH<sub>3</sub>), 27.2 (3 × CH<sub>3</sub>), 22.7 (C), 19.8 (C), 19.2 (CH<sub>3</sub>). IR (ATR-FTIR), cm<sup>-1</sup>: 3015 (s), 2996 (m), 2975 (s), 2360 (m), 2003 (m), 1400 (s). HRMS-Cl (m/z): [M + Na]<sup>+</sup> calculated for C<sub>28</sub>H<sub>46</sub>NaO<sub>9</sub>Si, 577.2809; found, 577.2819. [α]<sub>D</sub><sup>20</sup> = 2.48 (c = 0.10, CHCl<sub>3</sub>).

*Synthesis of the vinyl stannane 211:*



A solution of azobisisobutyronitrile (1.0 mg, 5.0  $\mu\text{mol}$ , 0.10 equiv) in degassed toluene (1.00 mL) and a solution of tributyltin hydride (29.0  $\mu\text{L}$ , 108  $\mu\text{mol}$ , 2.00 equiv) in degassed toluene (1.00 mL) were added simultaneously via two syringe pumps over 2 h to a solution of the silylene ether **210** (25.0 mg, 54.0  $\mu\text{mol}$ , 1 equiv) in a degassed toluene (2.70 mL) at 80  $^\circ\text{C}$ . Upon completion of the addition, the reaction mixture was stirred for an additional 1 h at 80  $^\circ\text{C}$ . The product mixture was then cooled to 23  $^\circ\text{C}$  over 1 h. The cooled product mixture was concentrated and the residue obtained was directly purified by flash-column chromatography (eluting with 15% ethyl acetate–hexanes) to provide the vinyl stannane **211** as a yellow oil (41.0 mg, 90%).

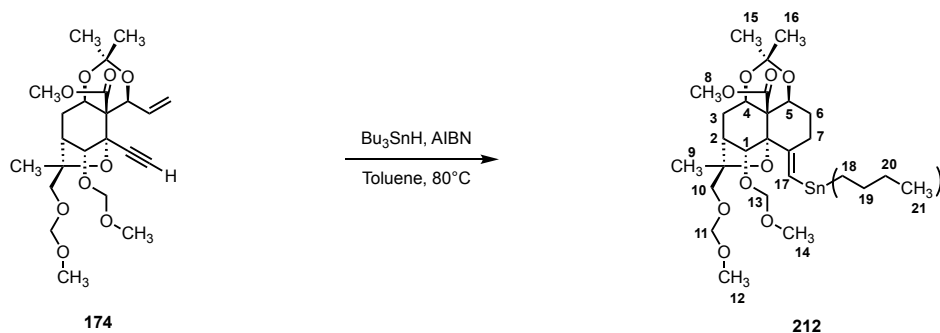
NOE correlations between the C6 hydrogen and the C9 methyl substituent and C8 vinyl hydrogen and the C1 hydrogen substituent support the shown stereochemical configuration.



$R_f = 0.50$  (25% ethyl acetate–hexanes; PAA).  $^1\text{H NMR}$  (500 MHz,  $\text{C}_6\text{D}_6$ ):  $\delta$  7.02 (d,  $\text{H}_8$ ,  $J = 2.4$  Hz, 1H), 5.11 (dd,  $\text{H}_4$ ,  $J = 11.8, 6.0$  Hz, 1H), 4.74 (d,  $\text{H}_5$ ,  $J = 9.2$  Hz, 1H), 4.64 – 4.58 (m,  $\text{H}_{1,13a}$ , 2H), 4.56 (d,  $\text{H}_{13b}$ ,  $J = 6.5$  Hz, 1H), 4.51 – 4.42 (m,  $\text{H}_{11}$ , 2H), 4.27 (d,  $\text{H}_{10a}$ ,  $J = 9.2$  Hz, 1H), 3.78 (ddd,  $\text{H}_6$ ,  $J = 9.3, 6.7, 2.5$  Hz, 1H), 3.62 (d,  $\text{H}_{10b}$ ,  $J = 9.1$  Hz, 1H), 3.50 (s,  $\text{H}_{15}$ , 3H), 3.23 (s,  $\text{H}_{12}$ , 3H), 3.12 (s,  $\text{H}_{14}$ , 3H), 3.00 – 2.90 (m,  $\text{H}_{3a}$ , 1H), 2.54 (t,  $\text{H}_2$ ,  $J = 3.3$  Hz, 1H), 2.15 (ddd,  $\text{H}_{3b}$ ,  $J = 13.1, 5.9, 3.6$  Hz, 1H), 1.62 (dtd,  $\text{H}_{18}$ ,  $J = 14.3, 7.6, 7.2, 3.2$  Hz, 6H), 1.55 (d,  $\text{H}_{9,7}$ ,  $J = 6.3$  Hz, 6H), 1.36 (q,  $\text{H}_{20}$ ,  $J = 7.4$  Hz, 6H), 1.31 (s,  $\text{H}_{16}$ , 9H), 1.15 (s,  $\text{H}_{17}$ , 9H), 1.07 (td,  $\text{H}_{19}$ ,  $J = 7.4, 3.1$  Hz, 6H), 0.93 (t,  $\text{H}_{21}$ ,  $J = 7.3$  Hz, 9H).  $^{13}\text{C NMR}$  (125 MHz,  $\text{C}_6\text{D}_6$ ):  $\delta$  171.2 (C), 162.1 (C), 127.8 (CH), 96.8 ( $\text{CH}_2$ ), 94.9 ( $\text{CH}_2$ ), 88.4 (C), 87.8 (CH), 83.9 (C), 83.5 (CH), 75.9 (CH), 75.1 ( $\text{CH}_2$ ), 66.5 (C), 55.3 ( $\text{CH}_3$ ), 54.9 ( $\text{CH}_3$ ), 51.4 ( $\text{CH}_3$ ), 45.6 (CH), 44.5 (CH), 32.4 ( $\text{CH}_2$ ), 29.6 ( $3 \times \text{CH}_3$ ), 29.5 ( $3 \times \text{CH}_2$ ), 27.7 ( $3 \times \text{CH}_2$ ), 27.5 ( $3 \times \text{CH}_3$ ), 23.4 (C), 21.1 ( $\text{CH}_3$ ), 20.1 (C), 19.8 ( $\text{CH}_3$ ), 13.9 ( $3 \times \text{CH}_3$ ), 10.7 ( $3 \times \text{CH}_2$ ). IR (ATR-FTIR),  $\text{cm}^{-1}$ : 3015 (s), 2996 (m), 2975 (s), 1400 (s). HRMS-Cl ( $m/z$ ):  $[\text{M} + \text{Na}]^+$  calculated for  $\text{C}_{40}\text{H}_{74}\text{NaO}_9\text{SiSn}$ , 864.4022; found, 573.1631.  $[\alpha]_D^{20} = -1.44$  ( $c = 0.13$ ,  $\text{CHCl}_3$ ).

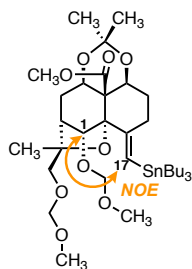
*Synthesis of the olefin 213:*

*Part 1: Synthesis of the vinyl stannane 212:*



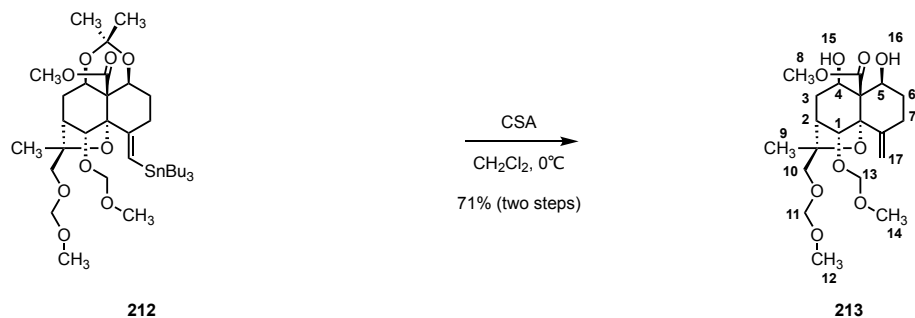
A solution of azobisisobutyronitrile (2.0 mg, 11.0  $\mu\text{mol}$ , 0.10 equiv) in degassed toluene (1.50 mL) and a solution of tributyltin hydride (36.0  $\mu\text{L}$ , 132  $\mu\text{mol}$ , 1.20 equiv) in degassed toluene (1.50 mL) were added simultaneously via two syringe pumps over 2 h to a solution of the acetone **174** (50.0 mg, 110  $\mu\text{mol}$ , 1 equiv) in a degassed toluene (5.50 mL) at  $80^\circ\text{C}$ . Upon completion of the addition, the reaction mixture was stirred for an additional 1 h at  $80^\circ\text{C}$ . The product mixture was then cooled to  $23^\circ\text{C}$  over 1 h. The cooled product mixture was directly concentrated and the residue obtained was used directly in the following step.

An analytically pure sample of the vinyl stannane **212** was obtained by a preparative thin-layered chromatography (eluting with 25% ethyl acetate–hexanes). NOE correlations between the C17 hydrogen and the C1 hydrogen support the configuration depicted.



$R_f = 0.50$  (25% ethyl acetate–hexanes; PAA).  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.11 (s,  $\text{H}_{17}$ , 1H), 4.70 (d,  $\text{H}_{13a}$ ,  $J = 6.7$  Hz, 1H), 4.63 – 4.56 (m,  $\text{H}_{13b,11}$ , 3H), 4.53 (s,  $\text{H}_1$ , 1H), 4.48 (dd,  $\text{H}_4$ ,  $J = 12.3, 6.1$  Hz, 1H), 4.34 (dd,  $\text{H}_5$ ,  $J = 12.0, 5.3$  Hz, 1H), 3.90 (d,  $\text{H}_{10a}$ ,  $J = 9.0$  Hz, 1H), 3.67 (d,  $\text{H}_8$ ,  $J = 1.6$  Hz, 3H), 3.60 (d,  $\text{H}_{10b}$ ,  $J = 9.1$  Hz, 1H), 3.38 (s,  $\text{H}_{12}$ , 3H), 3.34 (s,  $\text{H}_{14}$ , 3H), 2.73 – 2.56 (m,  $\text{H}_{7a,2}$ , 2H), 2.55 – 2.38 (m,  $\text{H}_{3a,6a}$ , 2H), 2.13 – 2.03 (m,  $\text{H}_{7b}$ , 1H), 1.99 (dd,  $\text{H}_{3b}$ ,  $J = 11.6, 6.1$  Hz, 1H), 1.80 – 1.72 (m,  $\text{H}_{6b}$ , 1H), 1.58 – 1.44 (m,  $\text{H}_{18,15,9}$ , 12H), 1.41 – 1.20 (m,  $\text{H}_{16,20}$ , 9H), 0.98 – 0.82 (m,  $\text{H}_{19,21}$ , 15H).  $^{13}\text{C NMR}$  (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  171.1 (C), 149.8 (C), 127.1 (CH), 101.7 (C), 96.7 (CH<sub>2</sub>), 95.9 (CH<sub>2</sub>), 87.3 (C), 84.4 (C), 83.2 (CH), 75.5 (CH), 74.9 (CH<sub>2</sub>), 72.9 (CH), 60.1 (C), 56.5 (CH<sub>3</sub>), 55.3 (CH<sub>3</sub>), 51.1 (CH<sub>3</sub>), 43.4 (CH), 34.5 (CH<sub>2</sub>), 30.1 (CH<sub>2</sub>), 29.8 (CH<sub>2</sub>), 29.7 (CH<sub>3</sub>), 29.2 (3  $\times$  CH<sub>2</sub>), 27.3 (3  $\times$  CH<sub>2</sub>), 20.3 (CH<sub>3</sub>), 19.8 (CH<sub>3</sub>), 13.7 (3  $\times$  CH<sub>3</sub>), 10.2 (3  $\times$  CH<sub>2</sub>). IR (ATR-FTIR),  $\text{cm}^{-1}$ : 3015 (s), 2996 (m), 2975 (s), 1401 (s). HRMS-Cl ( $m/z$ ):  $[\text{M} + \text{Na}]^+$  calculated for  $\text{C}_{35}\text{H}_{62}\text{NaO}_9\text{Sn}$ , 769.3313; found, 769.3335.  $[\alpha]_D^{20} = -63.3$  ( $c = 0.17$ ,  $\text{CHCl}_3$ ).

Part 2: Synthesis of the olefine **213**:



Camphorsulfonic acid (43.4 mg, 187  $\mu\text{mol}$ , 1.70 equiv) was added in a single portion to a solution of the residue obtained in the preceding step (nominally, 110  $\mu\text{mol}$ , 1 equiv) in dichloromethane (1.5 mL) at 0  $^\circ\text{C}$ . The reaction mixture was stirred for 1 h at 0  $^\circ\text{C}$ . The cold product mixture was diluted sequentially with dichloromethane (10 mL), saturated aqueous sodium bicarbonate solution (5.0 mL), and water (5.0 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with dichloromethane ( $3 \times 10$  mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 50% ethyl acetate–hexanes) to provide the olefin **213** as a colorless oil (32.5 mg, 71% two steps).

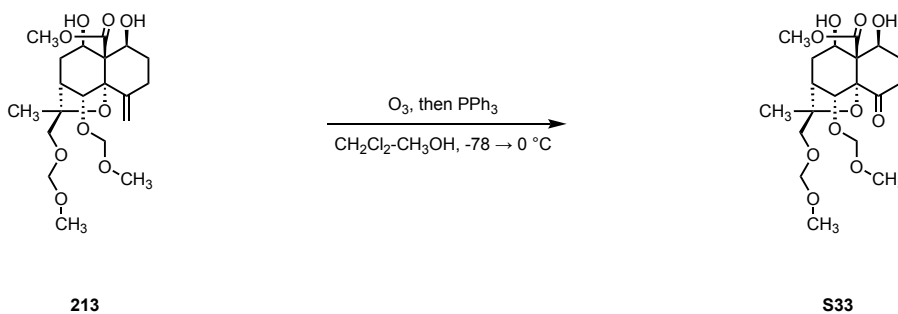
$R_f = 0.50$  (25% ethyl acetate–hexanes; PAA).  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  5.08 (s,  $\text{H}_1$ , 1H), 5.01 (s,  $\text{H}_{17a}$ , 1H), 4.97 (s,  $\text{H}_{17b}$ , 1H), 4.77 (d,  $\text{H}_{13a}$ ,  $J = 6.6$  Hz, 1H), 4.67 (d,  $\text{H}_{13b}$ ,  $J = 6.8$  Hz, 1H), 4.57 (s,  $\text{H}_{11}$ , 2H), 4.48 (dt,  $\text{H}_4$ ,  $J = 12.0, 6.4$  Hz, 1H), 4.36 – 4.24 (m,  $\text{H}_5$ , 1H), 3.89 (d,  $\text{H}_{10a}$ ,  $J = 9.0$  Hz, 1H), 3.74 (s,  $\text{H}_8$ , 3H), 3.48 (d,  $\text{H}_{10b}$ ,  $J = 9.1$  Hz, 1H), 3.43 (s,  $\text{H}_{12}$ , 3H), 3.33 (s,  $\text{H}_{14}$ , 3H), 3.30 (d,  $\text{H}_{16}$ ,  $J = 9.4$  Hz, 1H), 3.04 (d,  $\text{H}_{15}$ ,  $J = 5.7$  Hz, 1H), 2.63 –

2.47 (m, H<sub>2,6a</sub>, 2H), 2.29 (ddd, H<sub>3a</sub>, J = 13.8, 7.0, 4.1 Hz, 1H), 2.13 (ddd, H<sub>6b</sub>, J = 13.1, 5.3, 2.1 Hz, 1H), 2.07 – 1.87 (m, H<sub>3b,7</sub>, 3H), 1.49 (s, H<sub>9</sub>, 3H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 172.2 (C), 143.6 (C), 111.9 (CH<sub>2</sub>), 96.7 (CH<sub>2</sub>), 96.1 (CH<sub>2</sub>), 88.5 (C), 83.7 (C), 82.8 (CH), 77.5 (CH), 74.6 (CH<sub>2</sub>), 73.8 (CH), 65.7 (C), 56.6 (CH<sub>3</sub>), 55.4 (CH<sub>3</sub>), 51.8 (CH<sub>3</sub>), 42.1 (CH), 33.9 (CH<sub>2</sub>), 33.1 (CH<sub>2</sub>), 31.4 (CH<sub>2</sub>), 20.4 (CH<sub>3</sub>). IR (ATR-FTIR), cm<sup>-1</sup>: 3499 (m), 3015 (s), 2996 (m), 2975 (s), 2957 (m), 2691 (m), 2265 (m), 2069 (m), 2003 (m), 1710 (s), 1458 (s). HRMS-Cl (m/z): [M + Na]<sup>+</sup> calculated for C<sub>20</sub>H<sub>32</sub>NaO<sub>9</sub>, 439.1944; found, 439.1946.  $[\alpha]_D^{20} = -48.1$  (*c* = 0.10, CHCl<sub>3</sub>).



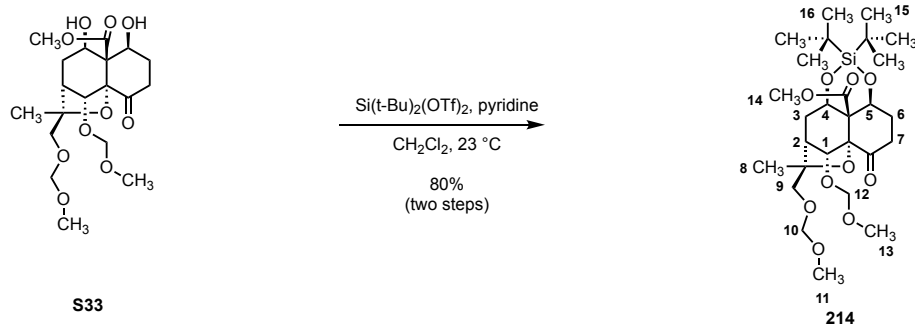
*Synthesis of the silylene ether 214:*

*Part 1: Synthesis of the ketone S33:*



Ozone was passed through a solution of the olefin **213** (30.0 mg, 72.0  $\mu\text{mol}$ , 1 equiv) in dichloromethane (1.30 mL) and methanol (500  $\mu\text{L}$ ) at  $-78\text{ }^{\circ}\text{C}$  until a dark blue color persisted. Dioxygen was then passed through the solution to remove any unreacted ozone, resulting in a colorless solution. Triphenylphosphne (37.8 mg, 141  $\mu\text{mol}$ , 2.00 equiv) was then added in one portion. The cooling bath was removed, and the mixture was allowed to warm to  $23\text{ }^{\circ}\text{C}$  over 1 h. The warmed product mixture was concentrated and the residue obtained was partially purified by elution over a short plug of silica gel (2.0 cm  $\times$  1.0 cm, eluting with 50% ethyl acetate – hexanes). The filtrate was collected and the residue obtained was used directly in the following step.

Part 2: Synthesis of the silylene ether **214**:

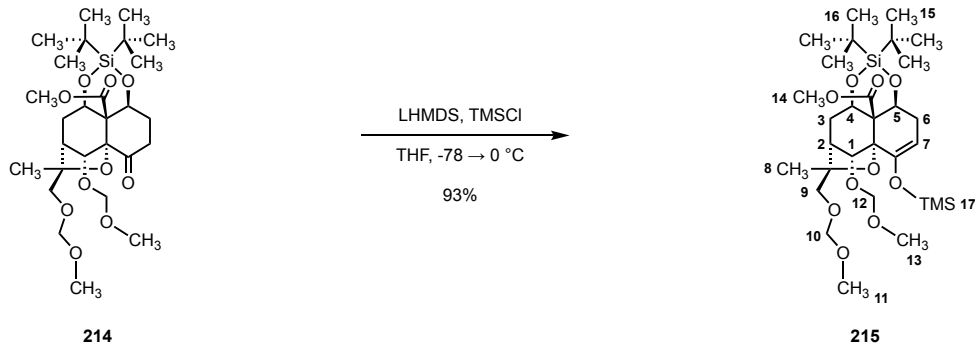


Di-*tert*-butylsilyl bis(trifluoromethanesulfonate) (25.0  $\mu\text{L}$ , 79.2  $\mu\text{mol}$ , 1.10 equiv) was added dropwise via syringe to a solution of the residue obtained in the preceding step (nominally 72.0  $\mu\text{mol}$ , 1 equiv) and pyridine (16.0  $\mu\text{L}$ , 202  $\mu\text{mol}$ , 2.80 equiv) in dichloromethane (500  $\mu\text{L}$ ) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C and then the cooling bath was removed. The reaction mixture was allowed to warm to 23 °C and then stirred for 1 d at 23 °C. The product mixture was diluted sequentially with saturated aqueous ammonium chloride solution (3.0 mL), water (3.0 mL), and dichloromethane (10 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with dichloromethane (3  $\times$  5.0 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (5.0 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 25% ethyl acetate–hexanes) to provide the silylene ether ketone **214** as a colorless oil (32.0 mg, 80% over two steps).

$R_f = 0.50$  (33% ethyl acetate–hexanes; PAA).  $^1\text{H NMR}$  (600 MHz,  $\text{CDCl}_3$ ):  $\delta$  4.87 (dd,  $\text{H}_4$ ,  $J = 11.8, 6.4$  Hz, 1H), 4.85 – 4.79 (m,  $\text{H}_5$ , 1H), 4.69 (d,  $\text{H}_{12a}$ ,  $J = 6.9$  Hz, 1H), 4.63 (d,  $\text{H}_{12b}$ ,

$J = 7.0$  Hz, 1H), 4.59 (d, H<sub>10a</sub>,  $J = 7.2$  Hz, 1H), 4.56 (d, H<sub>10b</sub>,  $J = 7.1$  Hz, 1H), 4.25 (s, H<sub>1</sub>, 1H), 3.91 (d, H<sub>9a</sub>,  $J = 9.3$  Hz, 1H), 3.67 (s, H<sub>14</sub>, 1H), 3.54 (d, H<sub>9b</sub>,  $J = 9.2$  Hz, 1H), 3.36 (s, H<sub>11</sub>, 3H), 3.33 (s, H<sub>13</sub>, 1H), 2.97 – 2.83 (m, H<sub>7a</sub>, 1H), 2.74 – 2.63 (m, H<sub>6a</sub>, 1H), 2.47 (s, H<sub>2</sub>, 1H), 2.44 – 2.30 (m, H<sub>3a,7b</sub>, 2H), 2.22 – 2.03 (m, H<sub>3b,6b</sub>, 2H), 1.54 (s, H<sub>8</sub>, 3H), 1.14 (s, H<sub>16</sub>, 9H), 0.93 (s, H<sub>15</sub>, 9H). <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>):  $\delta$  202.9 (C), 170.2 (C), 97.1 (CH<sub>2</sub>), 96.6 (CH<sub>2</sub>), 87.5 (C), 86.6 (C), 81.4 (CH), 77.3 (CH), 74.8 (CH), 74.3 (CH<sub>2</sub>), 63.7 (C), 55.5 (CH<sub>3</sub>), 55.2 (CH<sub>3</sub>), 51.7 (CH<sub>3</sub>), 44.5 (CH), 37.7 (CH<sub>2</sub>), 32.4 (CH<sub>2</sub>), 31.6 (CH<sub>2</sub>), 29.0 (3  $\times$  CH<sub>3</sub>), 27.1 (3  $\times$  CH<sub>3</sub>), 23.1 (C), 19.6 (C), 19.5 (CH<sub>3</sub>). IR (ATR-FTIR), cm<sup>-1</sup>: 3014 (s), 2997 (m), 2975 (s), 2958 (m), 2808 (m), 2691 (m), 2262 (s), 2070 (m), 2004 (s), 1458 (s). HRMS-CI (m/z): [M + Na]<sup>+</sup> calculated for C<sub>27</sub>H<sub>46</sub>NaO<sub>10</sub>Si, 581.2758; found, 581.2769.  $[\alpha]_D^{20} = 12.2$  ( $c = 0.07$ , CHCl<sub>3</sub>).

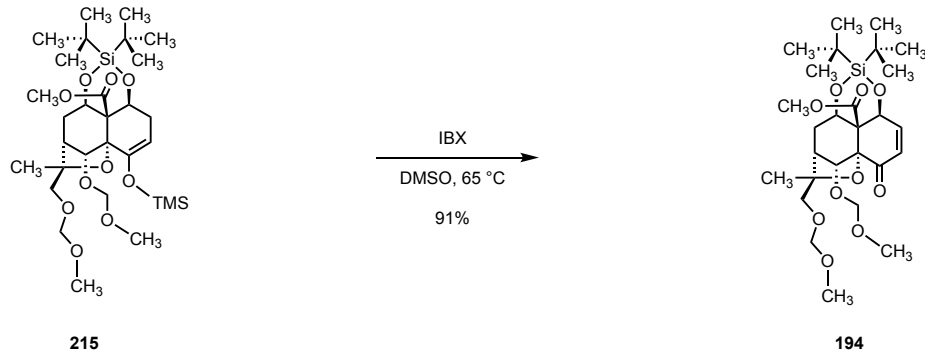
*Synthesis of the enoxysilane ether 215:*



A solution of lithium bis(trimethylsilyl)amide in tetrahydrofuran (1.00 M, 179  $\mu\text{L}$ , 179  $\mu\text{mol}$ , 5.00 equiv) was added dropwise via a syringe to a solution of ketone **214** (20.0 mg, 35.8  $\mu\text{mol}$ , 1 equiv) in tetrahydrofuran (900  $\mu\text{L}$ ) at  $-78 \text{ } ^\circ\text{C}$ . The resulting solution was stirred for 15 min at  $-78 \text{ } ^\circ\text{C}$ . The reaction vessel was then placed in an ice bath. The mixture was stirred for 1 h at  $0 \text{ } ^\circ\text{C}$ . The reaction vessel was then cooled to  $-78 \text{ } ^\circ\text{C}$ . Chlorotrimethylsilane (36.0  $\mu\text{L}$ , 285  $\mu\text{mol}$ , 8.00 equiv) was added dropwise via a syringe to the reaction mixture at  $-78 \text{ } ^\circ\text{C}$ . The resulting solution was stirred for 15 min at  $-78 \text{ } ^\circ\text{C}$ . The reaction vessel was then again placed in an ice bath and stirred at  $0 \text{ } ^\circ\text{C}$  for 30 min. The cold product mixture was diluted sequentially with ethyl acetate (10 mL), water (4.0 mL), and aqueous sodium bicarbonate solution (5.0 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate ( $3 \times 5.0 \text{ mL}$ ). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (10.0 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 5% ethyl acetate–hexanes) to provide the enoxysilane **215** as a colorless oil (21.0 mg, 93%).

$R_f = 0.30$  (15% ethyl acetate–hexanes; PAA).  $^1\text{H NMR}$  (500 MHz,  $\text{C}_6\text{D}_6$ ):  $\delta$  5.13 – 5.00 (m,  $\text{H}_{7,4}$ , 2H), 4.92 – 4.84 (m,  $\text{H}_5$ , 1H), 4.72 (d,  $\text{H}_{12a}$ ,  $J = 6.8$  Hz, 1H), 4.66 (s,  $\text{H}_2$ , 1H), 4.63 (d,  $\text{H}_{10a}$ ,  $J = 6.2$  Hz, 1H), 4.59 (d,  $\text{H}_{10b}$ ,  $J = 6.2$  Hz, 1H), 4.42 (dd,  $\text{H}_{12b,9a}$ ,  $J = 15.3, 8.0$  Hz, 2H), 3.52 (d,  $\text{H}_{9b,14}$ ,  $J = 11.3$  Hz, 4H), 3.22 (s,  $\text{H}_{11}$ , 3H), 3.16 – 3.02 (m,  $\text{H}_{13,6a}$ , 4H), 2.82 – 2.70 (m,  $\text{H}_{3a}$ , 1H), 2.57 – 2.46 (m,  $\text{H}_{2,6b}$ , 2H), 2.28 – 2.14 (m,  $\text{H}_{3b}$ , 1H), 1.57 (s,  $\text{H}_8$ , 3H), 1.19 (s,  $\text{H}_{16}$ , 9H), 1.14 (s,  $\text{H}_{15}$ , 9H), 0.22 (s,  $\text{H}_{17}$ , 9H).  $^{13}\text{C NMR}$  (125 MHz,  $\text{C}_6\text{D}_6$ ):  $\delta$  170.6 (C), 146.9 (C), 107.7 (CH), 96.8 ( $\text{CH}_2$ ), 95.8 ( $\text{CH}_2$ ), 85.5 (C), 85.0 (C), 82.6 (CH), 74.8 (CH), 74.6 ( $\text{CH}_2$ ), 74.6 (CH), 60.7 (C), 55.0 ( $\text{CH}_3$ ), 54.7 ( $\text{CH}_3$ ), 51.2 ( $\text{CH}_3$ ), 45.7 (CH), 33.2 ( $\text{CH}_2$ ), 31.6 ( $\text{CH}_2$ ), 29.2 ( $3 \times \text{CH}_3$ ), 27.6 ( $3 \times \text{CH}_3$ ), 23.2 (C), 19.9 (C), 19.5 ( $\text{CH}_3$ ), 0.35 ( $3 \times \text{CH}_3$ ). IR (ATR-FTIR),  $\text{cm}^{-1}$ : 3015 (s), 2996 (m), 2975 (s), 2808 (m), 2691 (m), 2067 (m), 2005 (m), 1400 (s).  $[\alpha]_D^{20} = -5.92$  ( $c = 0.10$ ,  $\text{CHCl}_3$ ).

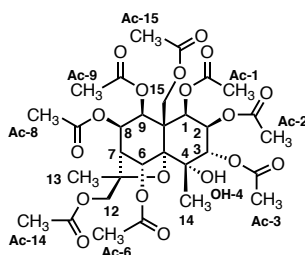
Synthesis of the unsaturated ketone **194** via oxidation of the enoxysilane **215**:



2-Iodoxybenzoic acid (4.30 mg, 15.2  $\mu\text{mol}$ , 1.20 equiv) was vigorously stirred for 30 min in dimethyl sulfoxide (150  $\mu\text{L}$ ) at 23  $^{\circ}\text{C}$ . After 30 min, enoxysilane **215** (8.00 mg, 12.7  $\mu\text{mol}$ , 1 equiv) dissolved in dimethyl sulfoxide (150  $\mu\text{L}$ ) was added via a syringe to the homogeneous 2-iodoxybenzoic acid solution at 23  $^{\circ}\text{C}$ . The reaction vessel was then placed to an oil bath that had been preheated to 65  $^{\circ}\text{C}$ . The reaction mixture was stirred for 5 h at 65  $^{\circ}\text{C}$ . The product mixture was then cooled to 23  $^{\circ}\text{C}$  over 30 min. The cooled product mixture was subsequently diluted sequentially with ethyl acetate (8.0 mL), water (3.0 mL), and saturated aqueous sodium bicarbonate solution (3.0 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3  $\times$  8.0 mL). The organic layers were combined and the combined organic layers were washed with water (8.0 mL), and saturated aqueous sodium chloride solution (10.0 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 15% ethyl acetate–hexanes) to provide the unsaturated ketone **194** as a colorless oil (6.4 mg, 91%).

$^1\text{H}$  and  $^{13}\text{C}$  NMR spectroscopic data for the unsaturated ketone **194** obtained in this way was in agreement with shown from the aldol–dehydration sequence.

**Table S2.** Comparison of  $^1\text{H}$  NMR data of natural and synthetic euonyminol octaacetate (116).

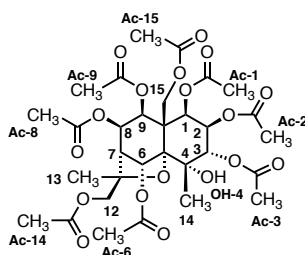


euonyminol octaacetate (116)

position	natural (-)- <b>116</b> <sup>23</sup> [CDCl <sub>3</sub> ]	synthetic (-)- <b>116</b> [500 MHz, CDCl <sub>3</sub> ]
H-1	5.58 (d, 3.6)	5.58 (d, 3.7)
H-2	5.26 (dd, 3.6, 2.8)	5.29 – 5.25 (m)
H-3	4.82 (d, 2.8)	4.82 (d, 2.5)
H-6	6.76 (s)	6.77 (s)
H-7	2.32 (d, 3.6)	2.32 (d, 3.9)
H-8	5.48 (dd, 5.9, 3.6)	5.48 (dd, 5.8, 3.9)
H-9	5.34 (d, 5.9)	5.34 (d, 6.0)
H-12 <sub>a</sub>	4.89 (d, 11.6)	4.89 (d, 11.6)
H-12 <sub>b</sub>	3.94 (d, 11.6)	3.95 (d, 11.6)
H-13	1.56 (s)	1.57 (s)
H-14	1.47 (s)	1.48 (s)
H-15 <sub>a</sub>	5.25 (d, 13.3)	5.21 (d, 13.3)
H-15 <sub>b</sub>	4.42 (d, 13.3)	4.42 (d, 13.3)
Ac-1	1.88 (s)	1.88 (s)
Ac-2	2.12 (s)	2.12 (s)
Ac-3	2.15 (s)	2.16 (s)
Ac-6	2.13 (s)	2.13 (s)
Ac-8	2.16 (s)	2.17 (s)
Ac-9	1.98 (s)	1.98 (s)
Ac-14	2.11 (s)	2.11 (s)
Ac-15	2.25 (s)	2.25 (s)

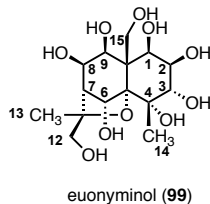


**Table S3.** Comparison of  $^{13}\text{C}$  NMR data of natural and synthetic euonyminol octaacetate (116).



euonyminol octaacetate (116)

position	natural <sup>23</sup> (-)-116 [CDCl <sub>3</sub> ]	synthetic (-)-116 [500 MHz, CDCl <sub>3</sub> ]	position	natural <sup>23</sup> (-)-116 [CDCl <sub>3</sub> ]	synthetic (-)-116 [500 MHz, CDCl <sub>3</sub> ]
C-1	73.1	73.2	Ac-1	20.5	20.5
C-2	69.0	69.0	Ac-2	169.3	169.3
C-3	75.8	75.8	Ac-3	20.8	20.8
C-4	69.3	69.3	Ac-6	168.7	168.7
C-5	92.9	92.9	Ac-8	20.8	20.9
C-6	73.9	73.9	Ac-9	169.5	169.5
C-7	50.7	50.7	Ac-14	21.0	21.0
C-8	68.9	68.9	Ac-15	169.8	169.8
C-9	70.9	70.9		170.0	170.1
C-10	51.9	51.9		20.5	20.5
C-11	84.0	84.1		168.9	169.0
C-12	69.4	69.5		21.4	21.5
C-13	18.3	18.3		170.7	170.7
C-14	23.3	23.3		21.2	21.3
C-15	60.3	60.3		170.1	170.1

**Table S4.** Comparison of  $^1\text{H}$  NMR data of synthetic euonyminol (**99**).

position	synthetic ( $\pm$ )- <b>99</b> <sup>25</sup> (White and co-workers) [D <sub>2</sub> O] <sup>a</sup>	synthetic (-)- <b>99</b> [500 MHz, D <sub>2</sub> O]
H-1	4.30 (m)	4.33 (d, 3.5)
H-2	4.00 (m)	4.03 (t, 3.2)
H-3	3.65 (d, 4)	3.66 (d, 2.9)
H-6	5.10 (s)	5.22 (s)
H-7	2.30 (s)	2.39 (d, 4.0)
H-8	4.30 (m)	4.21 (dd, 5.3, 4.1)
H-9	4.30 (m)	4.37 (d, 5.4)
H-12 <sub>a</sub>	3.95 (m)	3.92 (d, 11.4)
H-12 <sub>b</sub>	3.68 (d, 11)	3.7.3 (d, 11.4)
H-13	1.36 (s)	1.44 (s)
H-14	1.58 (s)	1.74 (s)
H-15 <sub>a</sub>	4.30 (m)	4.43 (d, 13.1)
H-15 <sub>b</sub>	4.09 (d, 11)	4.09 (d, 13.1)

<sup>a</sup> $^{13}\text{C}$  NMR data for ( $\pm$ )-**99** were not reported.

## 2.7 Bibliography.

1. Brüning, R.; Wagner, H., Übersicht über die celastraceen-inhaltsstoffe: Chemie, chemotaxonomie, biosynthese, pharmakologie. *Phytochemistry* **1978**, *17*, 1821-1858.
2. Spivey, A. C.; Weston, M.; Woodhead, S., Celastraceae sesquiterpenoids: biological activity and synthesis. *Chem. Soc. Rev.* **2002**, *31*, 43-59.
3. Gao, J.-M.; Wu, W.-J.; Zhang, J.-W.; Konishi, Y., The dihydro- $\beta$ -agarofuran sesquiterpenoids. *Nat. Prod. Rep.* **2007**, *24*, 1153-1189.
4. Getasetegn, M. Chemical composition of *Catha edulis* (khat): a review. *Phytochem. Rev.* **2016**, *15*, 907-917.
5. Elhag, H. M.; Mossa, J.; El-Olemy, M. M. In *Antimicrobial and Cytotoxic Activity of the Extracts of Khat Callus Cultures*, Alexandria, VA, 1999; Janick, J., Ed. ASHS Press: Alexandria, VA, p. 463–466.
6. Baxter, R. L.; Crombie, L.; Simmonds, D. J.; Whiting, D. A.; Braenden, O. J.; Szendrei, K. Alkaloids of *catha edulis*(khat). Part 1. Isolation and characterisation of eleven new alkaloids with sesquiterpene cores (cathedulins); identification of the quinone–methide root pigments. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2965-2971.
7. Baxter, R. L.; Crombie, L.; Simmonds, D. J.; Whiting, D. A., Alkaloids of *catha edulis*. Part 2. Constitution of cathedulins E2 and E8, polyesters of a new sesquiterpene pentaol. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2972-2975.
8. Crombie, L.; Crombie, W. M. L.; Whiting, D. A.; Szendrei, K., Alkaloids of *Catha edulis*. Part 3. Structures of cathedulins K1, K2, K6, and K15; new Macrolide-bridged polyesters of euonyminol. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2976-2981

9. González, A. G.; Bazzocchi, I. L.; Moujir, L.; Jiménez, I. A., Ethnobotanical uses of Celastraceae. Bioactive metabolites. In *Stud. Nat. Prod. Chem.* **2000**, *23*, 649-738.
10. D. J. Mabberley, *The Plant-book. A portable dictionary of the vascular plants*, Cambridge University Press, Cambridge, 2<sup>nd</sup> ed., 1997.
11. Gonzalez, A. G.; Jimenez, I. A.; Ravelo, A. G.; Coll, J.; Gonzalez, J. A.; Lloria, J., Antifeedant activity of sesquiterpenes from Celastraceae. *Biochem. System. Ecol.* **1997**, *25*, 513-519.
12. Ji-Kai, L.; Zhong-Jian, J.; Da-Gang, W.; Jun, Z.; Qi-Guang, W., Insect antifeeding agents: Sesquiterpene alkaloids from *Celastrus angulatus*. *Phytochemistry* **1990**, *29*, 2503-2506.
13. Wakabayashi, N.; Wu, W. J.; Waters, R. M.; Redfern, R. E.; Mills, G. D.; DeMilo, A. B.; Lusby, W. R.; Andrzejewski, D., Celangulin: A Nonalkaloidal Insect Antifeedant from Chinese Bittersweet, *Celastrus angulatus*. *J. Nat. Prod.* **1988**, *51*, 537-542.
14. Monache, F. D.; Bettolo, G. B. M.; Bernays, E. A., Isolation of insect antifeedant alkaloids from *Maytenus rigida* (Celastraceae). *Zeitschrift für Angewandte Entomologie* **1984**, *97*, 406-414.
15. Ujita, K.; Takaishi, Y.; Tokuda, H.; Nishino, H.; Iwashima, A.; Fujita, T., Inhibitory effects of triptogelin A-1 on 12-O-tetradecanoylphorbol-13-acetate-induced skin tumor promotion. *Cancer Lett.* **1993**, *68*, 129-133.

16. Takaishi, Y.; Ujita, K.; Tokuda, H.; Nishino, H.; Iwashima, A.; Fujita, T., Inhibitory effects of dihydroagarofuran sesquiterpenes on Epstein-Barr virus activation. *Cancer Lett.* **1992**, *65*, 19-26.
17. Modzelewska A, Sur S, Kumar SK, Khan SR. Sesquiterpenes: natural products that decrease cancer growth. *Curr. Med. Chem.-Anticancer Agents.* **2005**, *5*, 477-99.
18. Takaishi, Y.; Ohshima, S.; Nakano, K.; Tomimatsu, T.; Tokuda, H.; Nishino, H.; Iwashima, A., Structures of Sesquiterpene Polyol Esters from *Celastrus stephanotiifolius* with Potential Tumor-Promotion Inhibitory Activity. *J. Nat. Prod.* **1993**, *56*, 815-824.
19. Wolfes, O. Occurrence of d-nor-isoephedrine in *Catha edulis*. *Arch. Pharm. Ber. Dtsch. Pharm. Ges.* **1930**, *268*, 81.
20. Beroza, M., Alkaloids from *Tripterygium wilfordii* Hook. The Structure of Wilforine, Wilfordine, Wilforgine and Wilfortrine. *J. Am. Chem. Soc.* **1953**, *75*, 44-49.
21. Wada, H.; Shizuri, Y.; Sugiura, K.; Yamada, K.; Hirata, Y., Stereochemistry of evonine, neo-evonine, euonymine, and neo-euonymine, alkaloids obtained from *Euonymus Sieboldiana blume*. *Tetrahedron Lett.* **1971**, *12*, 3131-3132.
22. Sasaki, K.; Hirata, Y., Structure of new alkaloids, evonine and neoevonine: X-ray analysis of bromoacetylneoevonine monohydrate. *J. Chem. Soc., Perkin Trans. 2* **1972**, *9*, 1268-1272.
23. Shizuri, Y.; Wada, H.; Sugiura, K.; Yamada, K.; Hirata, Y. The structures of evonine and neoevonine alkaloids obtained from *Euonymus Sieboldiana blume*. *Tetrahedron* **1973**, *29*, 1773.

24. White, J. D.; Cutshall, N. S.; Kim, T.-S.; Shin, H. Total Synthesis of (+-)-Euonyminol, the Sesquiterpenoid Nucleus of Cathedulin K-19, via an Epoxide Cascade Cyclization. *J. Am. Chem. Soc.* **1995**, *117*, 9780-9780.
25. White, J. D.; Shin, H.; Kim, T.-S.; Cutshall, N. S. Total Synthesis of the Sesquiterpenoid Polyols (±)-Euonyminol and (±)-3,4-Dideoxymaytol, Core Constituents of Esters of the Celastraceae. *J. Am. Chem. Soc.* **1997**, *119*, 2404-2419.
26. Webber, M. J.; Warren, S. A.; Grainger, D. M.; Weston, M.; Clark, S.; Woodhead, S. J.; Powell, L.; Stokes, S.; Alanine, A.; Stonehouse, J. P.; Frampton, C. S.; White, A. J. P.; Spivey, A. C. Towards the enantioselective synthesis of (-)-euonyminol - preparation of a fully functionalised lower-rim model. *Org. Biomol. Chem.* **2013**, *11*, 2514-2533.
27. Todoroki, H.; Iwatsu, M.; Urabe, D.; Inoue, M., Total Synthesis of (-)-4-Hydroxyzinowol. *J. Org. Chem.* **2014**, *79*, 8835-8849.
28. Isayama, S.; Mukaiyama, T., A New Method for Preparation of Alcohols from Olefins with Molecular Oxygen and Phenylsilane by the Use of Bis(acetylacetonato)cobalt(II). *Chem. Lett.* **1989**, *18*, 1071-1074.
29. Montgomery, J. Nickel-catalyzed reductive cyclizations and couplings. *Angew. Chem., Int. Ed.* **2004**, *43*, 3890-3908.
30. Lee, C. A.; Floreancig, P. E. Studies in multidrug resistance reversal: a rapid and stereoselective synthesis of the dihydroagarofuran ring system. *Tetrahedron Lett.* **2004**, *45*, 7193-7196.

31. Song, Z.-L.; Fan, C.-A.; Tu, Y.-Q., Semipinacol Rearrangement in Natural Product Synthesis. *Chem. Rev.* **2011**, *111*, 7523-7556.
32. Davies, H. M. L.; Calvo, R. L. Effect of tether position on the intramolecular reaction between rhodium stabilized carbenoids and furans. *Tetrahedron Lett.* **1997**, *38*, 5623-5626.
- 32a. Pirrung, M. C.; Zhang, J.; Lackey, K.; Sternbach, D. D.; Brown, F. Reactions of a cyclic rhodium carbenoid with aromatic compounds and vinyl ethers. *J. Org. Chem.* **1995**, *60*, 2112-2124.
33. Williams, C. M.; Whittaker, D. Rearrangements of pinane derivatives. Part ii. Products of acid-catalysed rearrangement of  $\alpha$ -pinene and  $\beta$ -pinene in acetic acid. *J. Chem. Soc. B.* **1971**, 672-677.
34. Krasovskiy, A.; Kopp, F.; Knochel, P. Soluble lanthanide salts ( $\text{LnCl}_3 \cdot 2\text{LiCl}$ ) for the improved addition of organomagnesium reagents to carbonyl compounds. *Angew. Chem., Int. Ed. Engl.* **2006**, *45*, 497-500.
35. Moriyama, K.; Takemura, M.; Togo, H., Selective Oxidation of Alcohols with Alkali Metal Bromides as Bromide Catalysts: Experimental Study of the Reaction Mechanism. *J. Org. Chem.* **2014**, *79*, 6094-6104.
36. Wang, H.; Negretti, S.; Knauff, A. R.; Montgomery, J., Exo-Selective Reductive Macrocyclization of Ynals. *Org. Lett.* **2015**, *17*, 1493-1496.
- 36a. Dorel, R.; Echavarren, A. M., Gold(I)-Catalyzed Activation of Alkynes for the Construction of Molecular Complexity. *Chem. Rev.* **2015**, *115*, 9028-9072.

37. Nishizawa, M.; Skwarczynski, M.; Imagawa, H.; Sugihara, T. Mercuric Triflate-TMU Catalyzed Hydration of Terminal Alkyne to give Methyl Ketone under Mild Conditions. *Chem. Lett.* **2002**, *31*, 12-14.
38. Mello, R.; Fiorentino, M.; Fusco, C.; Curci, R. Oxidations by methyl(trifluoromethyl)dioxirane. 2. Oxyfunctionalization of saturated hydrocarbons. *J. Am. Chem. Soc.* **1989**, *111*, 6749-6757.
39. Bovicelli, P.; Lupattelli, P.; Mincione, E.; Prencipe, T.; Curci, R. Oxidation of natural targets by dioxiranes. 2. Direct hydroxylation at the side chain C-25 of cholestane derivatives and of vitamin D3 Windaus-Grundmann ketone. *J. Org. Chem.* **1992**, *57*, 5052-5054.
40. Chen, M. S.; White, M. C. Combined effects on selectivity in Fe-catalyzed methylene oxidation. *Science* **2010**, *327*, 566-571.
41. White, M. C.; Zhao, J. Aliphatic C–H Oxidations for Late-Stage Functionalization. *J. Am. Chem. Soc.* **2018**, *140*, 13988-14009.
42. Schmidt, V. A.; Quinn, R. K.; Brusoe, A. T.; Alexanian, E. J. Site-Selective Aliphatic C–H Bromination Using N-Bromoamides and Visible Light. *J. Am. Chem. Soc.* **2014**, *136*, 14389-14392.
43. Czaplyski, W. L.; Na, C. G.; Alexanian, E. J. C–H Xanthylation: A Synthetic Platform for Alkane Functionalization. *J. Am. Chem. Soc.* **2016**, *138*, 13854-13857.
44. Dorta, R. L.; Francisco, C. G.; Freire, R.; Suárez, E., Intramolecular hydrogen abstraction. The use of organoselenium reagents for the generation of alkoxy radicals. *Tetrahedron Lett.* **1988**, *29*, 5429-5432.

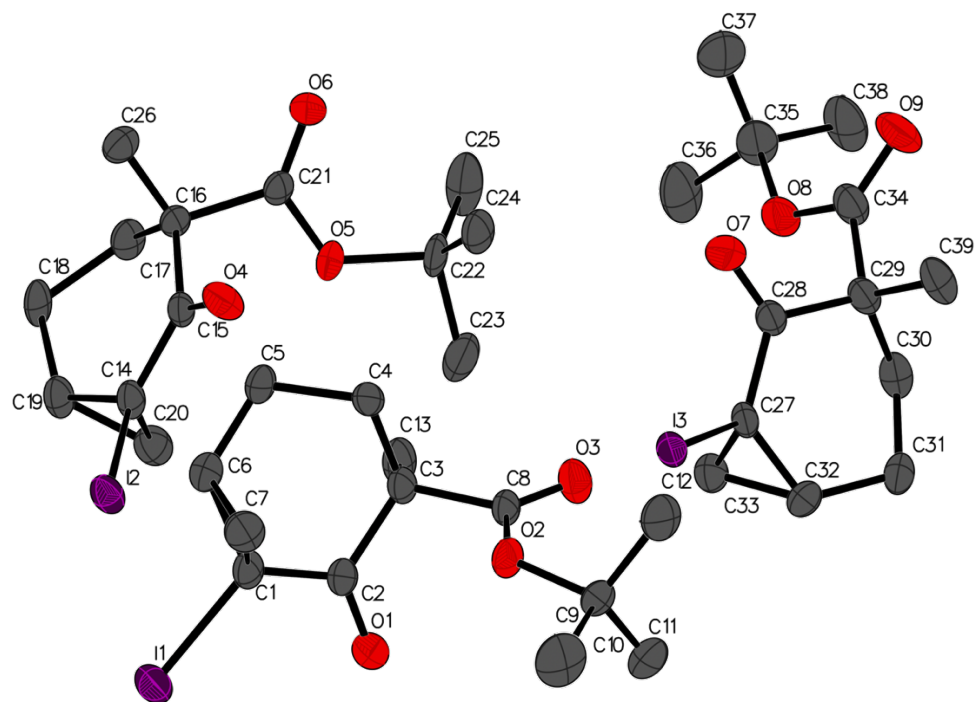


45. Luche, J. L., Lanthanides in organic chemistry. 1. Selective 1,2 reductions of conjugated ketones. *J. Am. Chem. Soc.* **1978**, *100*, 2226-2227.
46. Tomanik, M.; Xu, Z.; Herzon, S. B., Enantioselective Synthesis of Euonyminol. *J. Am. Chem. Soc.* **2021**, *143*, 699-704.
47. Nicolaou, K. C.; Gray, D. L. F.; Montagnon, T.; Harrison, S. T., Oxidation of Silyl Enol Ethers by Using IBX and IBX·N-Oxide Complexes: A Mild and Selective Reaction for the Synthesis of Enones. *Angew. Chem. Int. Ed.* **2002**, *41*, 996-1000.
48. Still, W. C.; Kahn, M.; Mitra, A. Rapid chromatographic technique for preparative separations with moderate resolution. *J. Org. Chem.* **1978**, *43*, 2923-2925.
49. Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. Safe and Convenient Procedure for Solvent Purification. *Organometallics* **1996**, *15*, 1518-1520.
50. Lin, H.-S.; Paquette, L. A. A Convenient Method for Determining the Concentration of Grignard Reagents. *Synth. Commun.* **1994**, *24*, 2503-2506.
51. Beenakker, T. J. M.; Wander, D. P. A.; Codée, J. D. C.; Aerts, J. M. F. G.; van der Marel, G. A.; Overkleeft, H. S. Synthesis of Carba - Cyclophellitols: a New Class of Carbohydrate Mimetics. *Eur. J. Org. Chem.* **2018**, 2504-2517.
52. Arndt, F. Diazomethane. *Org. Synth.* **1935**, *15*, 3.
53. Taber, D. F.; DeMatteo, P. W.; Hassan, R. A. Simplified Preparation of Dimethyldioxirane. *Org. Synth.* **2013**, *90*, 350-357.
54. Wang, Z.X.; Tu, Y.; Frohn, M.; Zhang, J.R.; Shi, Y. An Efficient Catalytic Asymmetric Epoxidation Method. *J. Am. Chem. Soc.* **1997**, *119*, 11224-11225.

**Appendix A: Catalogue of Crystallographic Data.**

### Crystallographic data for the cyclopropyl iodide **37**.

Single crystals of compound **37** suitable for the X-ray crystal structure analysis were obtained by the slow evaporation of a solution of compound **37** in *n*-pentane/diethyl ether (v/v = 10:1) at room temperature. Low-temperature diffraction data ( $\omega$ -scans) were collected on a Rigaku MicroMax- 007HF diffractometer coupled to a Saturn994+ CCD detector with Cu K $\alpha$  ( $\lambda = 1.54178 \text{ \AA}$ ) for the structure of 007-15166. The diffraction images were processed and scaled using the Rigaku CrystalClear software (CrystalClear and CrystalStructure; Rigaku/MSK: The Woodlands, TX, 2005). The structure was solved with SHELXT and was refined against  $F^2$  on all data by full-matrix least squares with SHELXL (Sheldrick, G. M. Acta Cryst. 2008, A64, 112–122). All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included in the model at geometrically calculated positions and refined using a riding model. The isotropic displacement parameters of all hydrogen atoms were fixed to 1.2 times the U value of the atoms to which they are linked (1.5 times for methyl groups). The full numbering scheme of compound 007-15166 can be found in the Supporting Information. Full details of the X-ray structure determination are in the CIF included as Supporting Information. CCDC number 1992798 (007-15166) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).



**Figure S1.** The complete numbering scheme of cyclopropane **37** with 50% thermal ellipsoid probability levels. The hydrogen atoms have been omitted for clarity.

**Table S5.** X-ray crystal data and structure refinement for compound **37**.

Identification code	007-15166
Empirical formula	C <sub>13</sub> H <sub>19</sub> IO <sub>3</sub>
Formula weight	350.18
Temperature	93(2) K
Wavelength	1.54178 Å
Crystal system	Monoclinic
Space group	P2 <sub>1</sub> /n

Unit cell dimensions	a = 24.9006(17) Å	$\alpha = 90^\circ$ .
	b = 6.3095(4) Å	$\beta = 110.855(2)^\circ$ .
	c = 28.910(2) Å	$\gamma = 90^\circ$ .
Volume	4244.5(5) Å <sup>3</sup>	
Z	12	
Density (calculated)	1.644 Mg/m <sup>3</sup>	
Absorption coefficient	17.753 mm <sup>-1</sup>	
F(000)	2088	
Crystal size	0.200 x 0.080 x 0.020 mm <sup>3</sup>	
Crystal color and habit	Colorless Needel	
Diffractometer	Rigaku Saturn 944+ CCD	
Theta range for data collection	3.272 to 66.592°.	
Index ranges	-29 ≤ h ≤ 28, -7 ≤ k ≤ 7, -34 ≤ l ≤ 34	
Reflections collected	131210	
Independent reflections	7415 [R(int) = 0.1267]	
Observed reflections (I > 2σ(I))	6646	
Completeness to theta = 66.592°	98.5 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.718 and 0.384	
Solution method	SHELXT-2014/5 (Sheldrick, 2014)	
Refinement method	SHELXL-2014/7 (Sheldrick, 2014)	
Data / restraints / parameters	7415 / 0 / 472	
Goodness-of-fit on F <sup>2</sup>	1.019	

Final R indices [ $I > 2\sigma(I)$ ]

R1 = 0.0474, wR2 = 0.1220

R indices (all data)

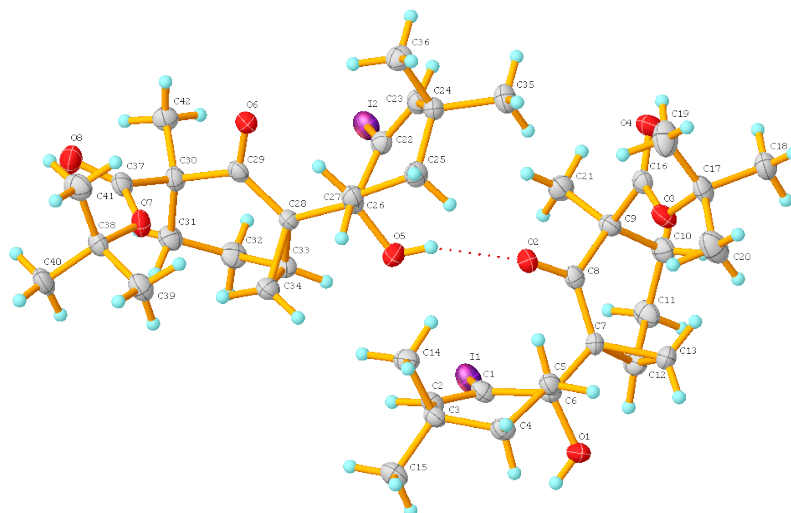
R1 = 0.0519, wR2 = 0.1262

Largest diff. peak and hole

1.079 and -1.984 e.Å<sup>-3</sup>

### **Crystallographic data for the vinyl iodide 41.**

Single crystals of compound **41** suitable for the X-ray crystal structure analysis were obtained by the slow evaporation of a solution of compound **41** in *n*-pentane/diethyl ether (v/v = 20:1) at room temperature. Low-temperature diffraction data ( $\omega$ -scans) were collected on a Rigaku MicroMax-007HF diffractometer coupled to a Saturn994+ CCD detector with Cu K $\alpha$  ( $\lambda = 1.54178 \text{ \AA}$ ) for the structure of 007-17082. The diffraction images were processed and scaled using Rigaku Oxford Diffraction software (CrysAlisPro; Rigaku OD: The Woodlands, TX, 2015). The structure was solved with SHELXT and was refined against  $F^2$  on all data by full-matrix least squares with SHELXL (Sheldrick, G. M. Acta Cryst. 2008, A64, 112–122). All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included in the model at geometrically calculated positions and refined using a riding model. The isotropic displacement parameters of all hydrogen atoms were fixed to 1.2 times the U value of the atoms to which they are linked (1.5 times for methyl groups). The only exceptions are H1 and H5, which were found and semi-freely refined with distance restraints of 0.83(2), as suggested by the difference map. The full numbering scheme of compound 007-17082 can be found in the full details of the X-ray structure determination (CIF), which is included as Supporting Information. CCDC number 1992803 (007-17082) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).



**Figure S2.** The complete numbering scheme of the vinyl iodine **41** with 50% thermal ellipsoid probability levels. The hydrogen atoms are shown as circles for clarity. Dashed lines highlight hydrogen bond interactions.

**Table S6.** X-ray crystal data and structure refinement for compound **41**.

Identification code	007-17082	
Empirical formula	C <sub>21</sub> H <sub>31</sub> I O <sub>4</sub>	
Formula weight	474.36	
Temperature	93(2) K	
Wavelength	1.54184 Å	
Crystal system	Monoclinic	
Space group	P2 <sub>1</sub> /c	
Unit cell dimensions	a = 17.2644(4) Å	α = 90°.



	$b = 11.1326(3) \text{ \AA}$	$\beta = 110.142(2)^\circ$ .
	$c = 23.6238(5) \text{ \AA}$	$\gamma = 90^\circ$ .
Volume	4262.75(18) $\text{\AA}^3$	
Z	8	
Density (calculated)	1.478 $\text{Mg/m}^3$	
Absorption coefficient	11.978 $\text{mm}^{-1}$	
F(000)	1936	
Crystal size	0.100 x 0.100 x 0.020 $\text{mm}^3$	
Crystal color and habit	Colorless Plate	
Diffractometer	Rigaku Saturn 944+ CCD	
Theta range for data collection	2.726 to 66.598°.	
Index ranges	$-20 \leq h \leq 20$ , $-13 \leq k \leq 12$ , $-28 \leq l \leq 28$	
Reflections collected	151643	
Independent reflections	7514 [R(int) = 0.0881]	
Observed reflections ( $I > 2\sigma(I)$ )	6222	
Completeness to $\theta = 66.598^\circ$	99.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00000 and 0.59010	
Solution method	SHELXT-2014/5 (Sheldrick, 2014)	
Refinement method	SHELXL-2014/7 (Sheldrick, 2014)	
Data / restraints / parameters	7514 / 2 / 489	
Goodness-of-fit on $F^2$	1.057	
Final R indices [ $I > 2\sigma(I)$ ]	R1 = 0.0381, wR2 = 0.0832	

R indices (all data)

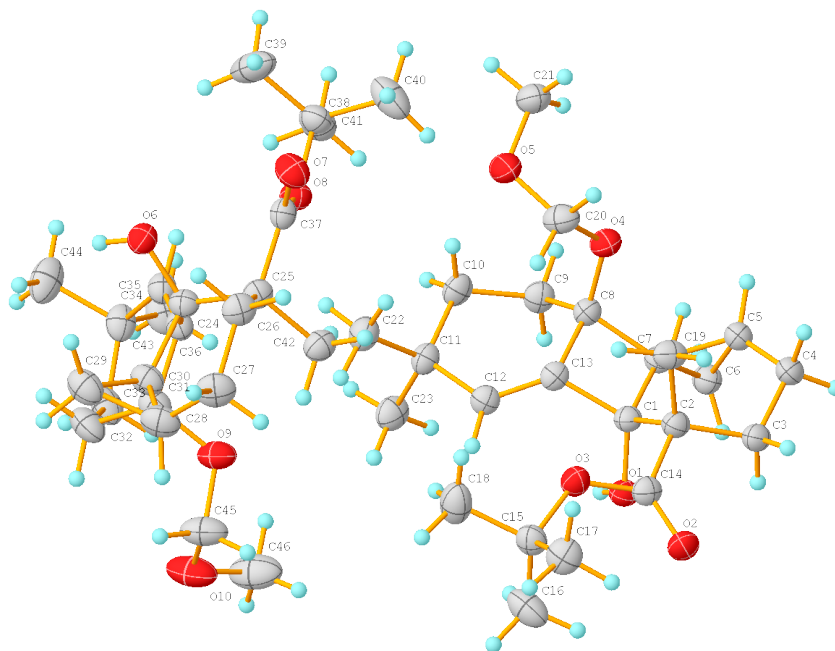
$R_1 = 0.0514$ ,  $wR_2 = 0.0892$

Largest diff. peak and hole

0.831 and  $-1.078 \text{ e.}\text{\AA}^{-3}$

### Crystallographic data for the cyclobutanol **51**.

Single crystals of compound **51** suitable for the X-ray crystal structure analysis were obtained by the slow evaporation of a solution of compound **51** in *n*-hexanes/diethyl ether (v/v = 4:1) at room temperature. Low-temperature diffraction data ( $\omega$ -scans) were collected on a Rigaku MicroMax-007HF diffractometer coupled to a Saturn994+ CCD detector with Cu K $\alpha$  ( $\lambda = 1.54178 \text{ \AA}$ ) for the structure of 007a-18078. The diffraction images were processed and scaled using Rigaku Oxford Diffraction software (CrysAlisPro; Rigaku OD: The Woodlands, TX, 2015). The structure was solved with SHELXT and was refined against  $F^2$  on all data by full-matrix least squares with SHELXL (Sheldrick, G. M. Acta Cryst. 2008, A64, 112–122). All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included in the model at geometrically calculated positions and refined using a riding model. The isotropic displacement parameters of all hydrogen atoms were fixed to 1.2 times the U value of the atoms to which they are linked (1.5 times for methyl groups). The only exception are the hydrogen atoms associated with oxygen atoms. These sites were found in the difference map and freely refined (see Table 7). The full numbering scheme of compound 007a-18078 can be found in the full details of the X-ray structure determination (CIF), which is included as Supporting Information. CCDC number 1992800 (007a-18078) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).



**Figure S3.** The complete numbering scheme of compound **51** with 50% thermal ellipsoid probability levels. The hydrogen atoms are shown as circles for clarity.

**Table S7.** X-ray crystal data and structure refinement for compound **51**.

Identification code	007a-18078
Empirical formula	C <sub>23</sub> H <sub>36</sub> O <sub>5</sub>
Formula weight	392.52
Temperature	93(2) K
Wavelength	1.54184 Å
Crystal system	Orthorhombic
Space group	Pca <sub>21</sub>

Unit cell dimensions	a = 19.7853(3) Å	α = 90°.
	b = 22.1644(4) Å	β = 90°.
	c = 10.4000(2) Å	γ = 90°.
Volume	4560.70(14) Å <sup>3</sup>	
Z	8	
Density (calculated)	1.143 Mg/m <sup>3</sup>	
Absorption coefficient	0.633 mm <sup>-1</sup>	
F(000)	1712	
Crystal size	0.100 x 0.100 x 0.070 mm <sup>3</sup>	
Crystal color and habit	Colorless Block	
Diffractometer	Rigaku Saturn 944+ CCD	
Theta range for data collection	1.993 to 66.599°.	
Index ranges	-23 ≤ h ≤ 23, -26 ≤ k ≤ 26, -12 ≤ l ≤ 12	
Reflections collected	164334	
Independent reflections	8074 [R(int) = 0.0727]	
Observed reflections (I > 2σ(I))	7400	
Completeness to theta = 66.599°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00000 and 0.65736	
Solution method	SHELXT-2014/5 (Sheldrick, 2014)	
Refinement method	SHELXL-2014/7 (Sheldrick, 2014)	
Data / restraints / parameters	8074 / 1 / 527	
Goodness-of-fit on F <sup>2</sup>	1.035	

Final R indices [ $I > 2\sigma(I)$ ]	$R_1 = 0.0318, wR_2 = 0.0736$
R indices (all data)	$R_1 = 0.0368, wR_2 = 0.0761$
Absolute structure parameter	0.07(6)
Largest diff. peak and hole	0.218 and -0.120 e.Å <sup>-3</sup>

### **Crystallographic data for the geminal dimethyl analog (–)-65.**

Crystals of compound (–)-65 for the X-ray crystal structure analysis were obtained by the slow evaporation of a solution of compound (–)-65 in ethyl acetate/methanol (v/v = 5:1) at room temperature. Low-temperature diffraction data ( $\omega$ -scans) were collected on a Rigaku MicroMax-007HF diffractometer coupled to a Saturn994+ CCD detector with Cu K $\alpha$  ( $\lambda$  = 1.54178 Å) for the structure of 007b-20019. The diffraction images were processed and scaled using Rigaku Oxford Diffraction software (CrysAlisPro; Rigaku OD: The Woodlands, TX, 2015). The structure was solved with SHELXT and was refined against  $F^2$  on all data by full-matrix least squares with SHELXL (Sheldrick, G. M. Acta Cryst. 2008, A64, 112–122). All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included in the model at geometrically calculated positions and refined using a riding model. The isotropic displacement parameters of all hydrogen atoms were fixed to 1.2 times the U value of the atoms to which they are linked (1.5 times for methyl groups). The only exceptions are H1, H3, and H5 which were found in the difference map and freely refined. The full numbering scheme of compound 007b-20019 can be found in the full details of the X-ray structure determination (CIF), which is included as Supporting Information. CCDC number 1992801 (007b-20019) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).

The crystal used for the diffraction experiment was small and only had light atoms present which made measuring any differences from anomalous dispersion in Bijvoet pairs difficult. The output from the analysis performed by SHELXL is copied below.

Flack x = -0.476(533) by classical fit to all intensities

-0.876(401) from 791 selected quotients (Parsons' method)

However, A Bayesian statistical analysis of the Bijvoet pairs suggest the model reported here, (-)-**65** with stereocenters *S,S,S,S*, is the most likely model, with only an exceedingly small probability of a model with the opposite chirality or a racemic twin. This analysis was calculated with the PLATON software package (A.L.Spek, Acta Cryst. 2009, D65, 148-155.).

***S,S,S,S model***

<i>Space Group</i>	<i>P2<sub>1</sub></i>
Wavelength	1.54184
Flack x ....	-0.9(4)
Parsons z ..	-0.5(2)

<i>Bijvoet Pairs</i>	<i>1310</i>
Coverage ...	98



DiffCalcMax. 9.24

Outlier Crit 18.48

*Student-T Prob. Plot*

Sample Size. 1300

Corr. Coeff. 0.999

Intercept .. 0.291

Slope ..... 1.222

*Bayesian Statistics*

Student\_T Nu 39

Select Pairs 1310

Theta\_Min .. 7.94

Theta\_Max .. 66.55

P2(true).... 1.000

P3(true).... 0.990

P3(racemic-twin) 0.010

P3(false) .. 0.6E-05

G ..... 2.1385

G (su) ..... 0.5973

Hooft y .... -0.6(3)

**R,R,R,R model**

*Space Group*             $P2_1$

Wavelength    1.54184

Flack x ....    1.9(4)

Parsons z ..    1.5(2)

Bijvoet Pairs            1310

Coverage ...            98

DiffCalcMax.            9.25

Outlier Crit    18.50

*Student-T Prob. Plot*

Sample Size.            1300

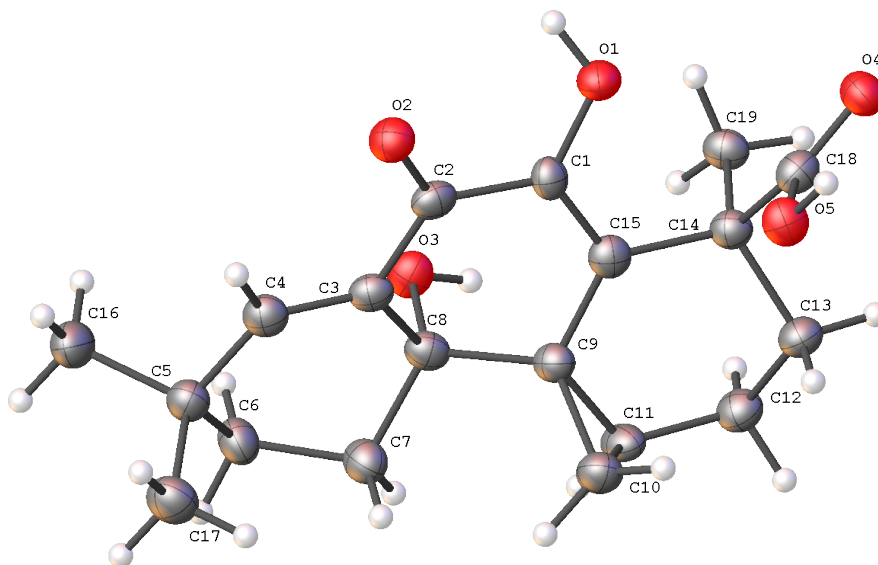
Corr. Coeff.    0.999

Intercept ..    0.291

Slope .....    1.222

*Bayesian Statistics*

Student_T Nu	39
Select Pairs	1310
Theta_Min ..	7.94
Theta_Max ..	66.55
P2(true)....	0.7E-05
P3(true)....	0.7E-05
P3(racemic -twin)	0.010
P3(false) ..	0.990
G .....	-2.1426
G (su) .....	0.5989
Hooft y ....	1.6(3)



**Figure S4.** The complete numbering scheme of the geminal dimethyl analog (–)-**65** with 50% thermal ellipsoid probability levels. The hydrogen atoms are shown as circles for clarity.

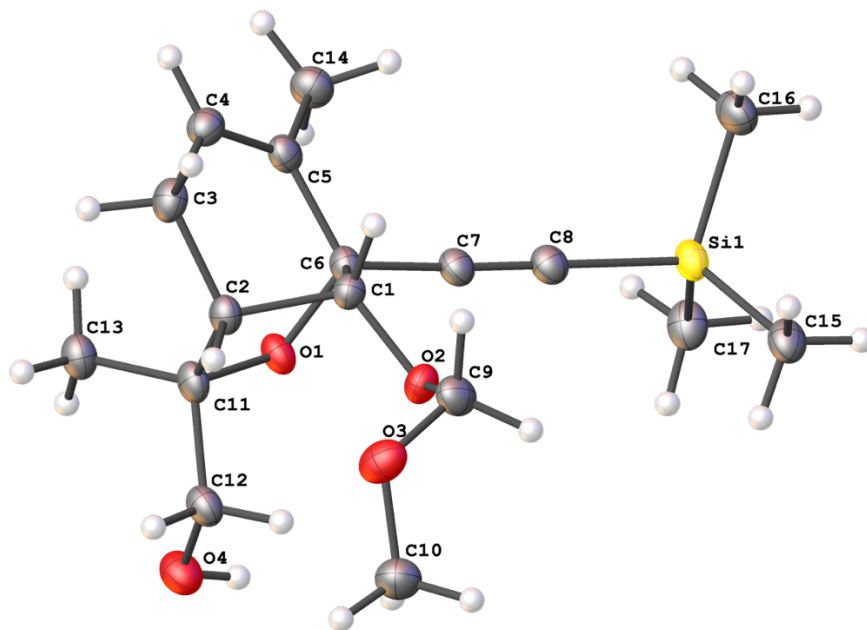
**Table S8.** X-ray crystal data and structure refinement for compound (–)-**65**.

Identification code	007b-20019
Empirical formula	C <sub>19</sub> H <sub>24</sub> O <sub>5</sub>
Formula weight	332.38
Temperature	93(2) K
Wavelength	1.54184 Å
Crystal system	Monoclinic
Space group	P2 <sub>1</sub>
Unit cell dimensions	a = 11.2611(6) Å      α = 90°. b = 6.3708(2) Å      β = 105.942(5)°. c = 12.0672(4) Å      γ = 90°.
Volume	832.43(6) Å <sup>3</sup>
Z	2
Density (calculated)	1.326 Mg/m <sup>3</sup>
Absorption coefficient	0.779 mm <sup>-1</sup>
F(000)	356
Crystal size	0.050 x 0.040 x 0.010 mm <sup>3</sup>
Crystal color and habit	Colorless Needle
Diffractometer	Rigaku Saturn 944+ CCD
Theta range for data collection	3.810 to 66.548°.
Index ranges	-13 ≤ h ≤ 13, -7 ≤ k ≤ 7, -14 ≤ l ≤ 14
Reflections collected	28622

Independent reflections	2906 [R(int) = 0.1509]
Observed reflections (I > 2sigma(I))	2243
Completeness to theta = 66.548°	98.3 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.32765
Solution method	SHELXT-2014/5 (Sheldrick, 2014)
Refinement method	SHELXL-2014/7 (Sheldrick, 2014)
Data / restraints / parameters	2906 / 1 / 232
Goodness-of-fit on F <sup>2</sup>	1.030
Final R indices [I>2sigma(I)]	R1 = 0.0575, wR2 = 0.1260
R indices (all data)	R1 = 0.0824, wR2 = 0.1414
Absolute structure parameter	-0.9(4)
Largest diff. peak and hole	0.168 and -0.216 e.Å <sup>-3</sup>

### Crystallographic data for the cyclic ether **141**.

Single crystals of the cyclic ether **141** suitable for X-ray crystal analysis were obtained by the slow evaporation of a solution of **141** in *n*-pentane–ethyl acetate (6:1 v/v) at 23 °C. Low-temperature diffraction data ( $\omega$ -scans) were collected on a Rigaku MicroMax-007HF diffractometer coupled to a Saturn994+ CCD detector with Cu K $\alpha$  ( $\lambda = 1.54178 \text{ \AA}$ ) for the structure of 007c-20068. The diffraction images were processed and scaled using Rigaku Oxford Diffraction software (CrysAlisPro; Rigaku OD: The Woodlands, TX, 2015). The structure was solved with SHELXT and was refined against  $F^2$  on all data by full-matrix least squares with SHELXL (Sheldrick, G. M. Acta Cryst. 2008, A64, 112–122). All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included in the model at geometrically calculated positions and refined using a riding model. The isotropic displacement parameters of all hydrogen atoms were fixed to 1.2 times the U value of the atoms to which they are linked (1.5 times for methyl and alcohol groups). The full numbering scheme of compound 007c-20068 can be found in the full details of the X-ray structure determination (CIF), which is included as Supporting Information. CCDC number 2047849 (007b-20068) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).



**Figure S5.** The complete numbering scheme of cyclic ether **141** with 50% thermal ellipsoid probability levels. The hydrogen atoms are shown as circles for clarity.

**Table S9.** Crystal data and structure refinement for the cyclic ether **141**:

Identification code	007b-20068
Empirical formula	C <sub>68</sub> H <sub>112</sub> O <sub>16</sub> Si <sub>4</sub>
Formula weight	1297.93
Temperature	93(2) K
Wavelength	1.54184 Å
Crystal system	Orthorhombic
Space group	P <sub>2</sub> <sub>1</sub> <sub>2</sub> <sub>1</sub> <sub>2</sub> <sub>1</sub>
Unit cell dimensions	a = 6.05410(10) Å      α = 90°.

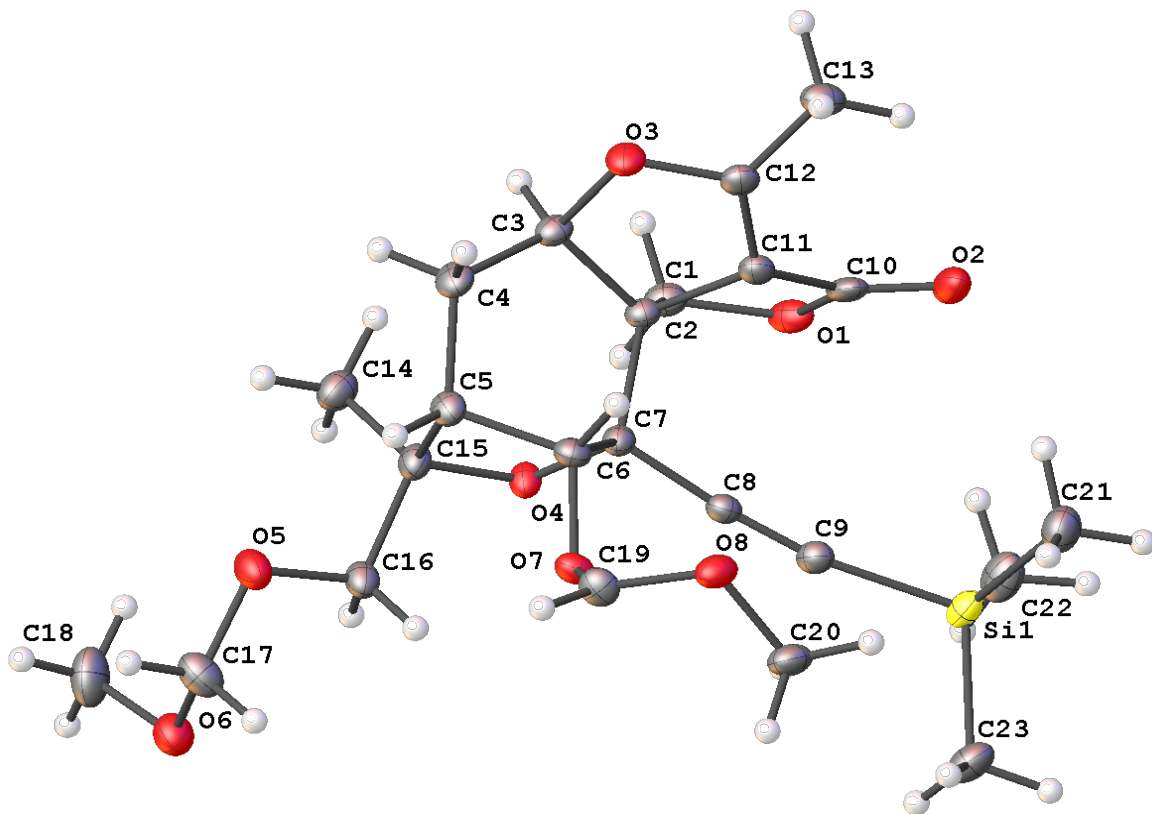
	$b = 14.1336(3) \text{ \AA}$	$\beta = 90^\circ$ .
	$c = 21.0131(3) \text{ \AA}$	$\gamma = 90^\circ$ .
Volume	1798.01(5) $\text{\AA}^3$	
Z	1	
Density (calculated)	1.199 $\text{Mg/m}^3$	
Absorption coefficient	1.275 $\text{mm}^{-1}$	
F(000)	704	
Crystal size	0.100 x 0.080 x 0.060 $\text{mm}^3$	
Crystal color and habit	Colorless Block	
Diffractometer	Rigaku Saturn 944+ CCD	
Theta range for data collection	3.769 to 66.590°.	
Index ranges	$-7 \leq h \leq 7$ , $-16 \leq k \leq 16$ , $-25 \leq l \leq 25$	
Reflections collected	62296	
Independent reflections	3166 [R(int) = 0.0686]	
Observed reflections ( $I > 2\sigma(I)$ )	2963	
Completeness to $\theta = 66.590^\circ$	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00000 and 0.51229	
Solution method	SHELXT-2014/5 (Sheldrick, 2014)	
Refinement method	SHELXL-2014/7 (Sheldrick, 2014)	
Data / restraints / parameters	3166 / 0 / 206	
Goodness-of-fit on $F^2$	1.040	
Final R indices [ $I > 2\sigma(I)$ ]	R1 = 0.0298, wR2 = 0.0694	



R indices (all data)	$R1 = 0.0336, wR2 = 0.0711$
Absolute structure parameter	$-0.023(12)$
Largest diff. peak and hole	$0.154$ and $-0.250 \text{ e.}\text{\AA}^{-3}$

### Crystallographic data for the vinylogous carbonate **147**.

Single crystals of the vinylogous carbonate compound **147** suitable for X-ray analysis were obtained by the slow evaporation of a solution of compound **147** in *n*-pentane–ethyl acetate (10:1 v/v) at 23 °C. Low-temperature diffraction data ( $\omega$ -scans) were collected on a Rigaku MicroMax-007HF diffractometer coupled to a Saturn994+ CCD detector with Cu K $\alpha$  ( $\lambda = 1.54178 \text{ \AA}$ ) for the structure of 007b-20073. The diffraction images were processed and scaled using Rigaku Oxford Diffraction software (CrysAlisPro; Rigaku OD: The Woodlands, TX, 2015). The structure was solved with SHELXT and was refined against  $F^2$  on all data by full-matrix least squares with SHELXL (Sheldrick, G. M. Acta Cryst. 2008, A64, 112–122). All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included in the model at geometrically calculated positions and refined using a riding model. The isotropic displacement parameters of all hydrogen atoms were fixed to 1.2 times the U value of the atoms to which they are linked (1.5 times for methyl groups). The full numbering scheme of compound 007b-20073 can be found in the full details of the X-ray structure determination (CIF), which is included as Supporting Information. CCDC number 2047844 (007b-20073) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).



**Figure S6.** The complete numbering the vinyllogous carbonate **147** with 50% thermal ellipsoid probability levels. The hydrogen atoms are shown as circles for clarity.

**Table S10.** Crystal data and structure refinement for the vinyllogous carbonate **147**:

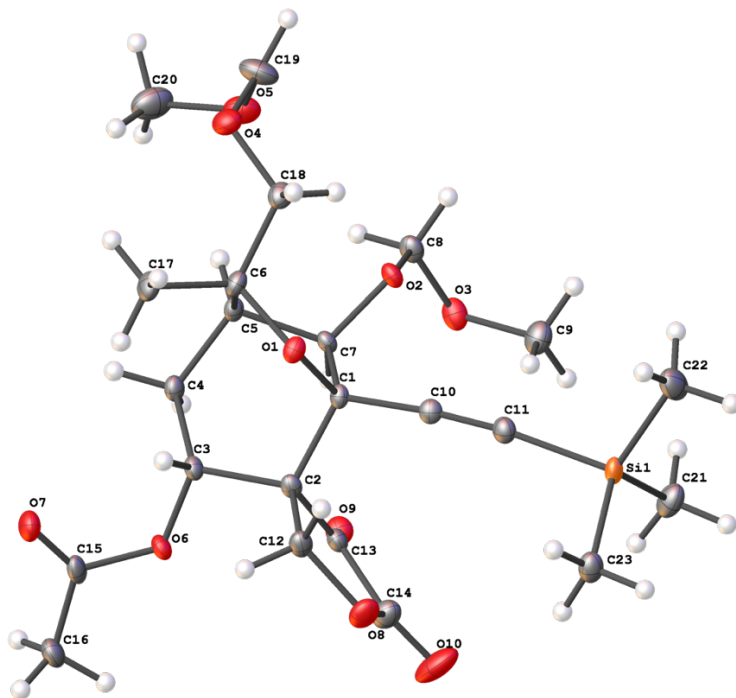
Identification code	007b-20073
Empirical formula	C <sub>23</sub> H <sub>33</sub> O <sub>8</sub> Si
Formula weight	465.58
Temperature	93(2) K
Wavelength	1.54184 Å

Crystal system	Monoclinic
Space group	P2 <sub>1</sub>
Unit cell dimensions	a = 9.19220(10) Å      α = 90°. b = 11.22070(10) Å      β = 100.280(10)°. c = 11.73690(10) Å      γ = 90°.
Volume	1191.15(2) Å <sup>3</sup>
Z	2
Density (calculated)	1.298 Mg/m <sup>3</sup>
Absorption coefficient	1.258 mm <sup>-1</sup>
F(000)	498
Crystal size	0.200 x 0.200 x 0.200 mm <sup>3</sup>
Crystal color and habit	Colorless Block
Diffractometer	Rigaku Saturn 944+ CCD
Theta range for data collection	3.828 to 66.543°.
Index ranges	-10 ≤ h ≤ 10, -13 ≤ k ≤ 12, -13 ≤ l ≤ 13
Reflections collected	41790
Independent reflections	4112 [R(int) = 0.0318]
Observed reflections (I > 2σ(I))	4009
Completeness to theta = 66.543°	100.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.80843
Solution method	SHELXT-2014/5 (Sheldrick, 2014)
Refinement method	SHELXL-2014/7 (Sheldrick, 2014)

Data / restraints / parameters	4112 / 1 / 296
Goodness-of-fit on $F^2$	1.084
Final R indices [ $I > 2\sigma(I)$ ]	R1 = 0.0294, wR2 = 0.0810
R indices (all data)	R1 = 0.0304, wR2 = 0.0818
Absolute structure parameter	0.000(7)
Largest diff. peak and hole	0.502 and -0.458 e.Å <sup>-3</sup>

### Crystallographic data for the $\alpha$ -ketolactone **169**.

Single crystals of the  $\alpha$ -ketolactone **169** suitable for X-ray analysis were obtained by the slow evaporation of a solution of compound **169** in *n*-pentane–ethyl acetate (4:1 v/v) at 23 °C. Low-temperature diffraction data ( $\omega$ -scans) were collected on a Rigaku MicroMax-007HF diffractometer coupled to a Saturn994+ CCD detector with Cu K $\alpha$  ( $\lambda = 1.54178 \text{ \AA}$ ) for the structure of 007b-19082. The diffraction images were processed and scaled using Rigaku Oxford Diffraction software (CrysAlisPro; Rigaku OD: The Woodlands, TX, 2015). The structure was solved with SHELXT and was refined against  $F^2$  on all data by full-matrix least squares with SHELXL (Sheldrick, G. M. Acta Cryst. 2008, A64, 112–122). All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included in the model at geometrically calculated positions and refined using a riding model. The isotropic displacement parameters of all hydrogen atoms were fixed to 1.2 times the U value of the atoms to which they are linked (1.5 times for methyl groups). The full numbering scheme of compound 007b-19082 can be found in the full details of the X-ray structure determination (CIF), which is included as Supporting Information. CCDC number 2047847 (007b-19082) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).



**Figure S7.** The complete numbering scheme of  $\alpha$ -ketolactone **169** with 50% thermal ellipsoid probability levels. The hydrogen atoms are shown as circles for clarity.

**Table S11.** Crystal data and structure refinement for the  $\alpha$ -ketolactone **169**:

Identification code	007b-19082
Empirical formula	C <sub>23</sub> H <sub>33</sub> O <sub>10</sub> Si
Formula weight	497.58
Temperature	93(2) K
Wavelength	1.54184 Å
Crystal system	Orthorhombic
Space group	P2 <sub>1</sub> 2 <sub>1</sub> 2 <sub>1</sub>

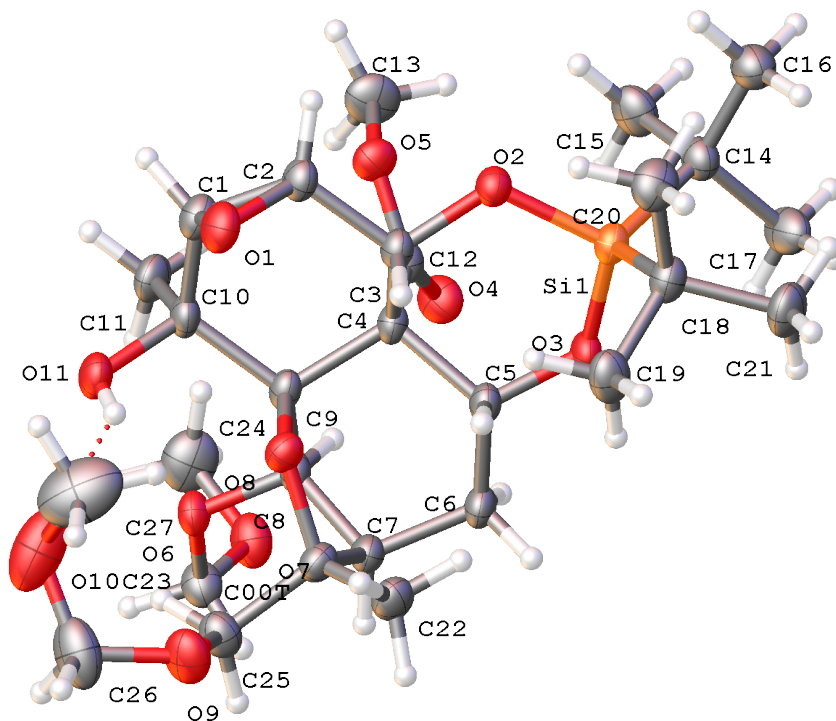
Unit cell dimensions	a = 10.13664(18) Å	$\alpha = 90^\circ$ .
	b = 12.97562(19) Å	$\beta = 90^\circ$ .
	c = 19.3014(3) Å	$\gamma = 90^\circ$ .
Volume	2538.69(7) Å <sup>3</sup>	
Z	4	
Density (calculated)	1.302 Mg/m <sup>3</sup>	
Absorption coefficient	1.276 mm <sup>-1</sup>	
F(000)	1060	
Crystal size	0.200 x 0.200 x 0.020 mm <sup>3</sup>	
Crystal color and habit	colorless plate	
Diffractometer	Rigaku Saturn 944+ CCD	
Theta range for data collection	4.105 to 66.753°.	
Index ranges	-12 ≤ h ≤ 12, -15 ≤ k ≤ 15, -22 ≤ l ≤ 22	
Reflections collected	89551	
Independent reflections	4500 [R(int) = 0.0886]	
Observed reflections (I > 2σ(I))	4410	
Completeness to theta = 66.753°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00000 and 0.41076	
Solution method	SHELXT-2014/5 (Sheldrick, 2014)	
Refinement method	SHELXL-2014/7 (Sheldrick, 2014)	
Data / restraints / parameters	4500 / 0 / 314	
Goodness-of-fit on F <sup>2</sup>	1.037	



Final R indices [I>2sigma(I)]	R1 = 0.0278, wR2 = 0.0745
R indices (all data)	R1 = 0.0285, wR2 = 0.0751
Absolute structure parameter	0.000(9)
Largest diff. peak and hole	0.469 and -0.356 e.Å <sup>-3</sup>

### Crystallographic data for the epoxide **196**.

Single crystals of the epoxide **196** suitable for the X-ray analysis were obtained by the slow evaporation of a solution of compound **196** in *n*-pentane–ethyl acetate (4:1 v/v) at 23 °C. Low-temperature diffraction data ( $\omega$ -scans) were collected on a Rigaku MicroMax-007HF diffractometer coupled to a Saturn994+ CCD detector with Cu K $\alpha$  ( $\lambda = 1.54178 \text{ \AA}$ ) for the structure of 007a-20027. The diffraction images were processed and scaled using Rigaku Oxford Diffraction software (CrysAlisPro; Rigaku OD: The Woodlands, TX, 2015). The structure was solved with SHELXT and was refined against  $F^2$  on all data by full-matrix least squares with SHELXL (Sheldrick, G. M. Acta Cryst. 2008, A64, 112–122). All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included in the model at geometrically calculated positions and refined using a riding model. The isotropic displacement parameters of all hydrogen atoms were fixed to 1.2 times the U value of the atoms to which they are linked (1.5 times for methyl groups). The full numbering scheme of compound 007a-20027 can be found in the full details of the X-ray structure determination (CIF), which is included as Supporting Information. CCDC number 2047848 (007a-20027) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).



**Figure S8.** The complete numbering scheme of the epoxide **196** with 50% thermal ellipsoid probability levels. The hydrogen atoms are shown as circles for clarity.

**Table S12.** Crystal data and structure refinement for the epoxide **196**:

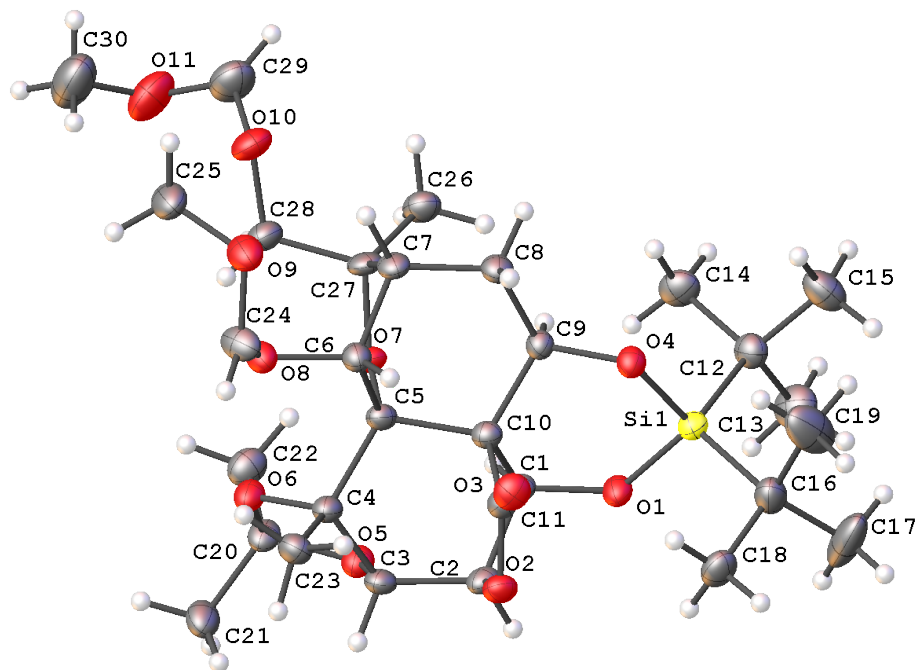
Identification code	007a-20027
Empirical formula	C <sub>28</sub> H <sub>48</sub> O <sub>11</sub> Si
Formula weight	588.75
Temperature	93(2) K
Wavelength	1.54184 Å
Crystal system	Monoclinic
Space group	P2 <sub>1</sub>

Unit cell dimensions	a = 10.7097(3) Å	$\alpha = 90^\circ$ .
	b = 9.3455(3) Å	$\beta = 90.187(2)^\circ$ .
	c = 14.9090(4) Å	$\gamma = 90^\circ$ .
Volume	1492.20(8) Å <sup>3</sup>	
Z	2	
Density (calculated)	1.310 Mg/m <sup>3</sup>	
Absorption coefficient	1.188 mm <sup>-1</sup>	
F(000)	636	
Crystal size	0.200 x 0.020 x 0.020 mm <sup>3</sup>	
Crystal color and habit	Colorless Needle	
Diffractometer	Rigaku Saturn 944+ CCD	
Theta range for data collection	2.964 to 66.595°.	
Index ranges	-12 ≤ h ≤ 12, -11 ≤ k ≤ 10, -17 ≤ l ≤ 17	
Reflections collected	53607	
Independent reflections	5217 [R(int) = 0.1009]	
Observed reflections (I > 2σ(I))	4686	
Completeness to theta = 66.595°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00000 and 0.75758	
Solution method	SHELXT-2014/5 (Sheldrick, 2014)	
Refinement method	SHELXL-2014/7 (Sheldrick, 2014)	
Data / restraints / parameters	5217 / 1 / 373	
Goodness-of-fit on F <sup>2</sup>	1.062	

Final R indices [ $I > 2\sigma(I)$ ]	R1 = 0.0429, wR2 = 0.1067
R indices (all data)	R1 = 0.0493, wR2 = 0.1108
Absolute structure parameter	-0.03(2)
Largest diff. peak and hole	0.165 and -0.356 e.Å <sup>-3</sup>

### Crystallographic data for the lactone **197**.

Single crystals of the lactone **197** suitable for X-ray analysis were obtained by the slow evaporation of a solution of compound **197** in *n*-pentane–ethyl acetate (3:1 v/v) at 23 °C. Low-temperature diffraction data ( $\omega$ -scans) were collected on a Rigaku MicroMax-007HF diffractometer coupled to a Saturn994+ CCD detector with Cu K $\alpha$  ( $\lambda = 1.54178 \text{ \AA}$ ) for the structure of 007a-20025. The diffraction images were processed and scaled using Rigaku Oxford Diffraction software (CrysAlisPro; Rigaku OD: The Woodlands, TX, 2015). The structure was solved with SHELXT and was refined against  $F^2$  on all data by full-matrix least squares with SHELXL (Sheldrick, G. M. Acta Cryst. 2008, A64, 112–122). All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included in the model at geometrically calculated positions and refined using a riding model. The isotropic displacement parameters of all hydrogen atoms were fixed to 1.2 times the U value of the atoms to which they are linked (1.5 times for methyl groups). The full numbering scheme of compound 007a-20025 can be found in the full details of the X-ray structure determination (CIF), which is included as Supporting Information. CCDC number 2047845 (007a-20025) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).



**Figure S9.** The complete numbering of one of the lactone **197** with 50% thermal ellipsoid probability levels. The hydrogen atoms are shown as circles for clarity.

**Table S13.** Crystal data and structure refinement for the lactone **197**:

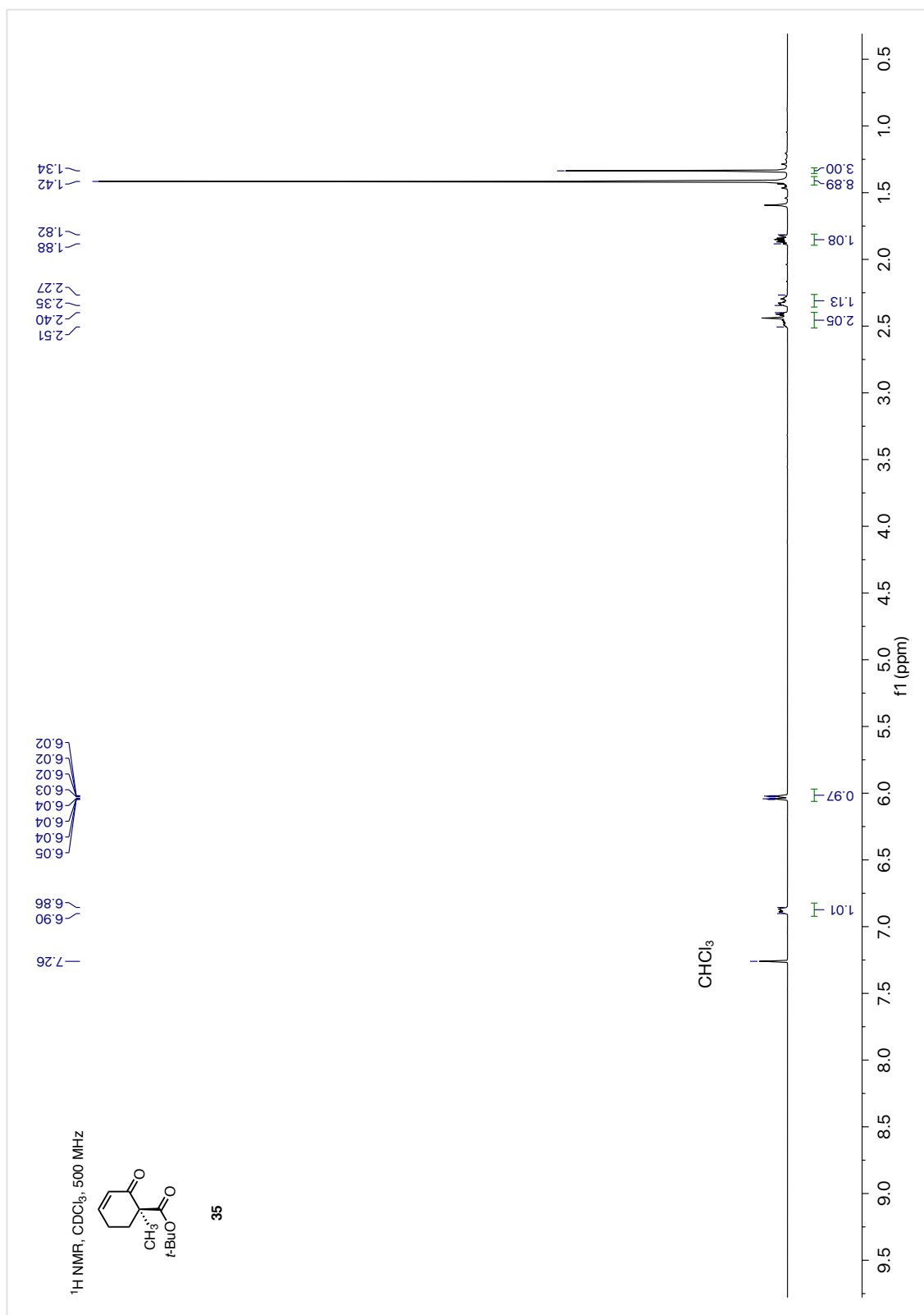
Identification code	007a-20025	
Empirical formula	C <sub>30</sub> H <sub>50</sub> O <sub>11</sub> Si	
Formula weight	614.79	
Temperature	93(2) K	
Wavelength	1.54184 Å	
Crystal system	Orthorhombic	
Space group	P2 <sub>1</sub> 2 <sub>1</sub> 2 <sub>1</sub>	
Unit cell dimensions	a = 11.95000(10) Å	α = 90°.

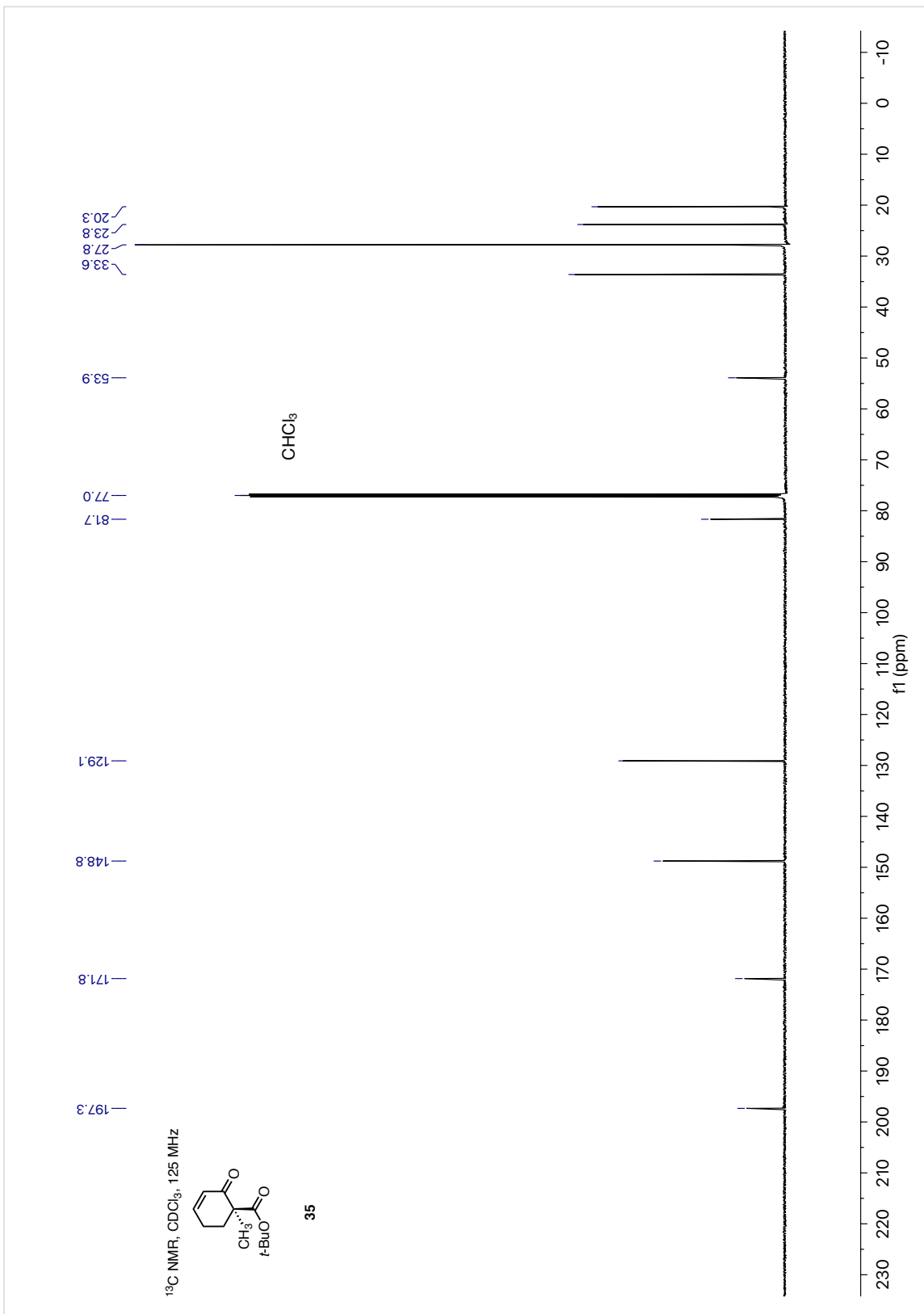
	$b = 16.74580(10) \text{ \AA}$	$\beta = 90^\circ$ .
	$c = 31.7086(2) \text{ \AA}$	$\gamma = 90^\circ$ .
Volume	6345.28(8) $\text{\AA}^3$	
Z	8	
Density (calculated)	1.287 $\text{Mg/m}^3$	
Absorption coefficient	1.140 $\text{mm}^{-1}$	
F(000)	2656	
Crystal size	0.120 x 0.080 x 0.050 $\text{mm}^3$	
Crystal color and habit	Colorless Plate	
Diffractometer	Rigaku Saturn 944+ CCD	
Theta range for data collection	2.787 to 66.593°.	
Index ranges	$-14 \leq h \leq 14$ , $-19 \leq k \leq 19$ , $-37 \leq l \leq 37$	
Reflections collected	179290	
Independent reflections	11215 [R(int) = 0.0886]	
Observed reflections ( $I > 2\sigma(I)$ )	10633	
Completeness to $\theta = 66.593^\circ$	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00000 and 0.60386	
Solution method	SHELXT-2014/5 (Sheldrick, 2014)	
Refinement method	SHELXL-2014/7 (Sheldrick, 2014)	
Data / restraints / parameters	11215 / 0 / 781	
Goodness-of-fit on $F^2$	1.014	
Final R indices [ $I > 2\sigma(I)$ ]	R1 = 0.0329, wR2 = 0.0859	

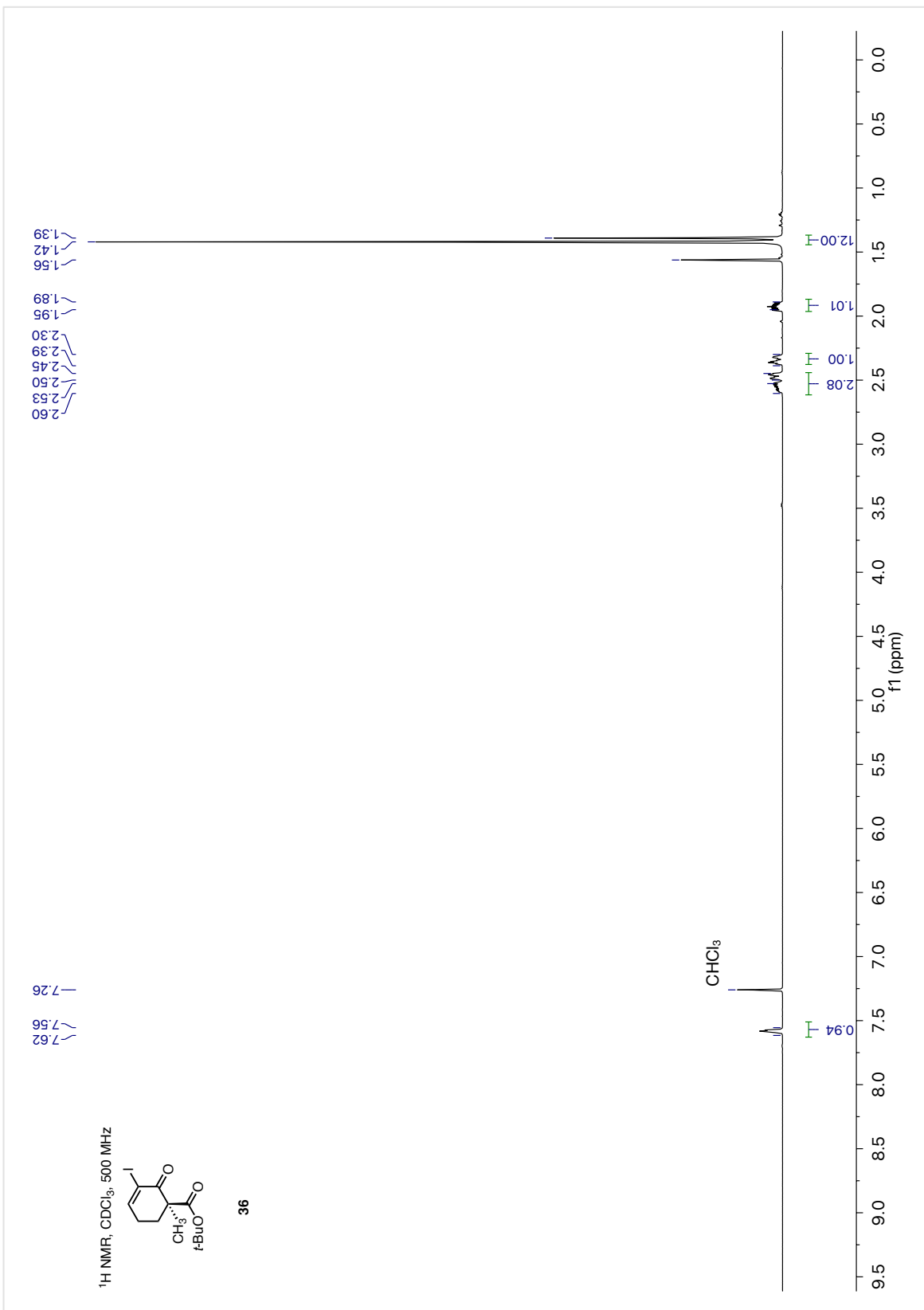


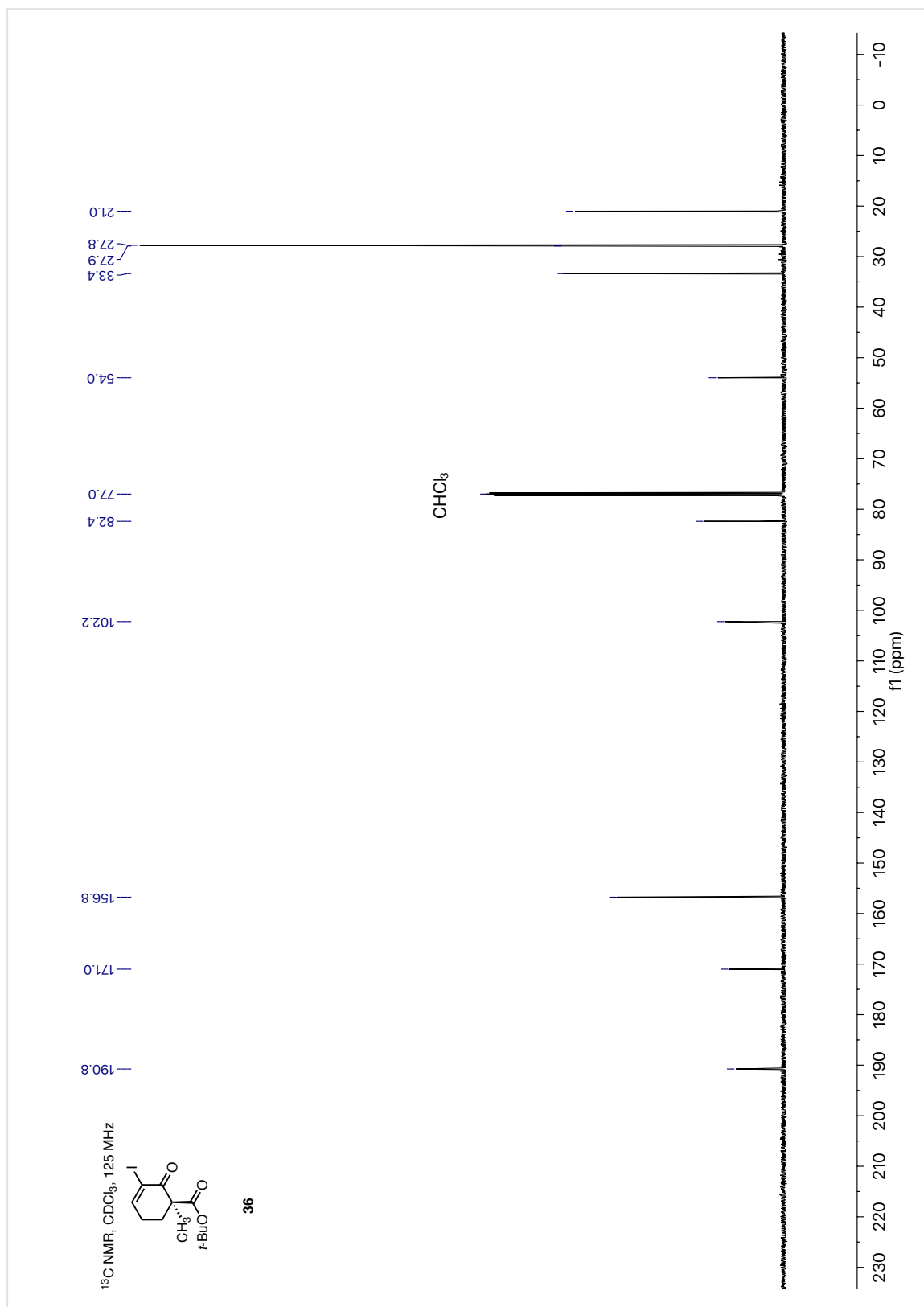
R indices (all data)	$R1 = 0.0355, wR2 = 0.0878$
Absolute structure parameter	$-0.002(8)$
Largest diff. peak and hole	$0.302$ and $-0.184 \text{ e.}\text{\AA}^{-3}$

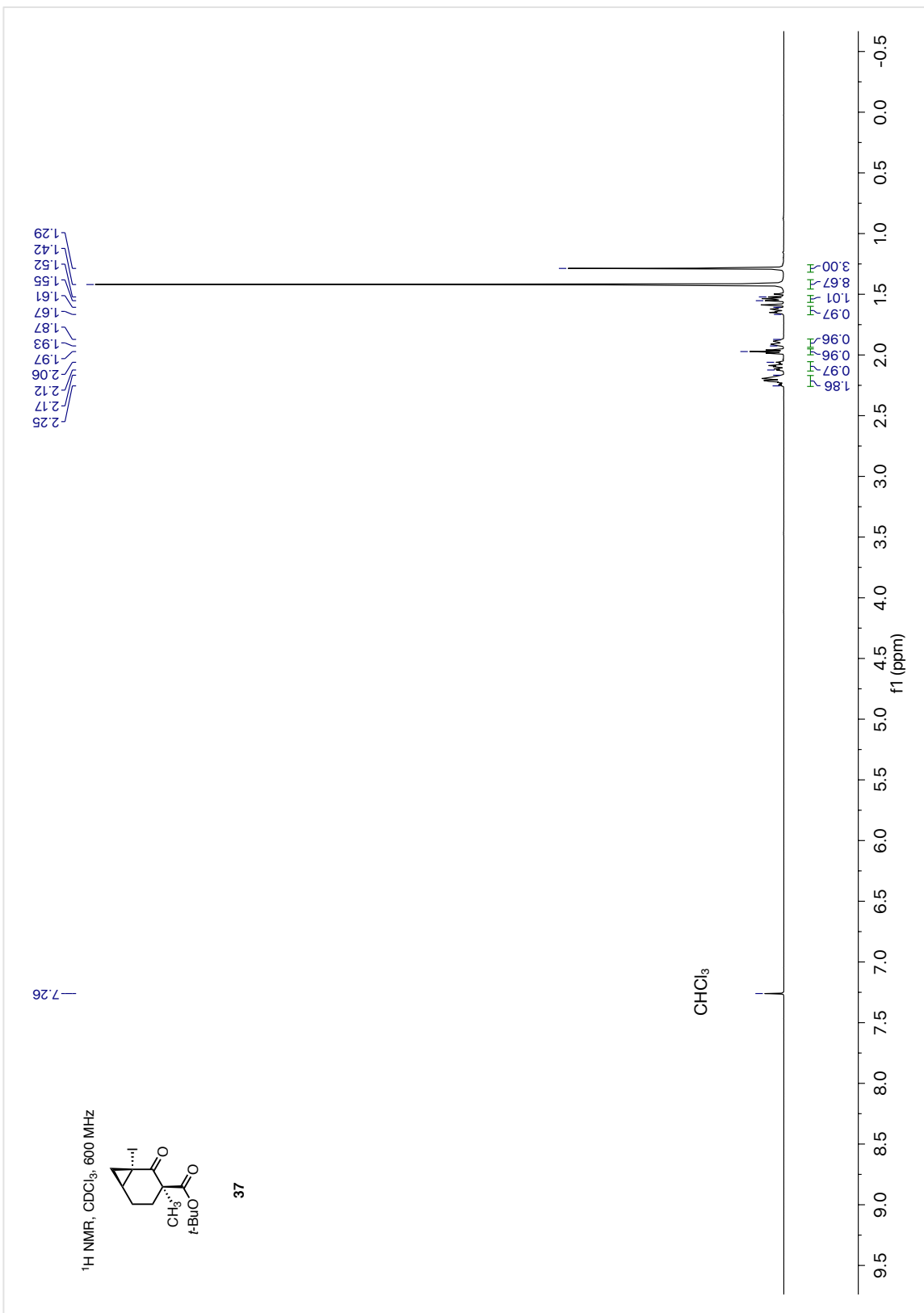
**Appendix B: Catalogue of Spectroscopic Data.**

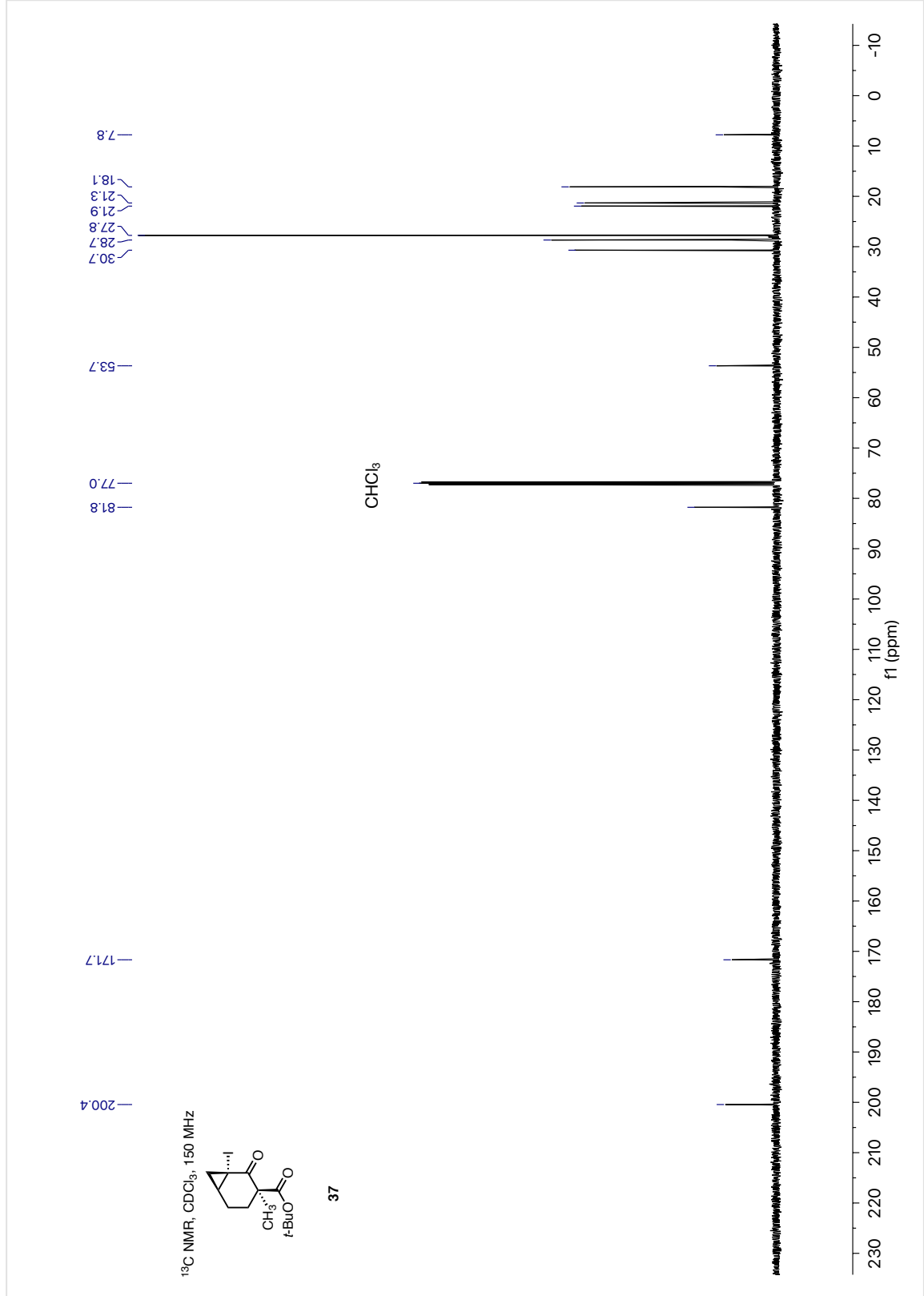




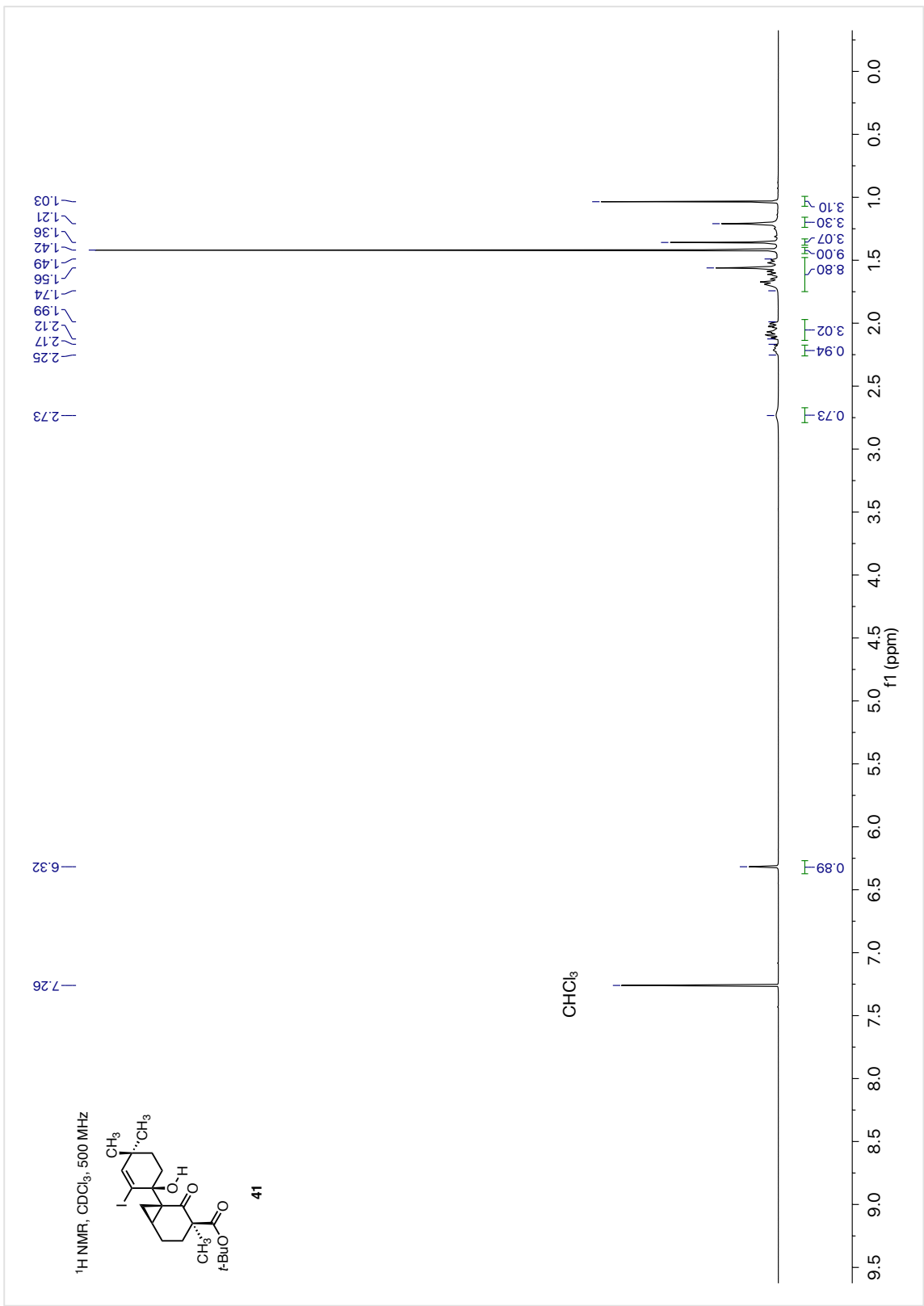


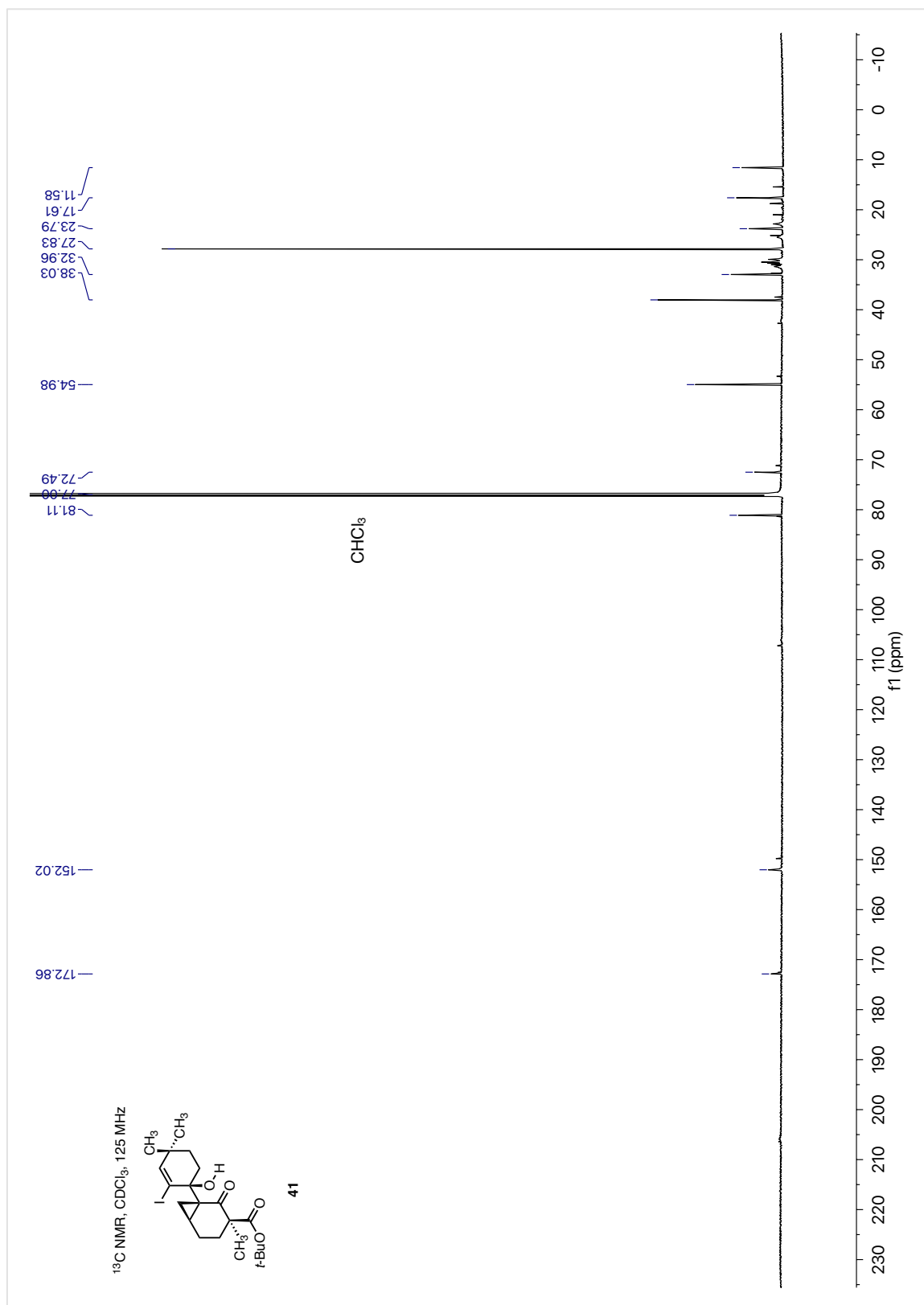


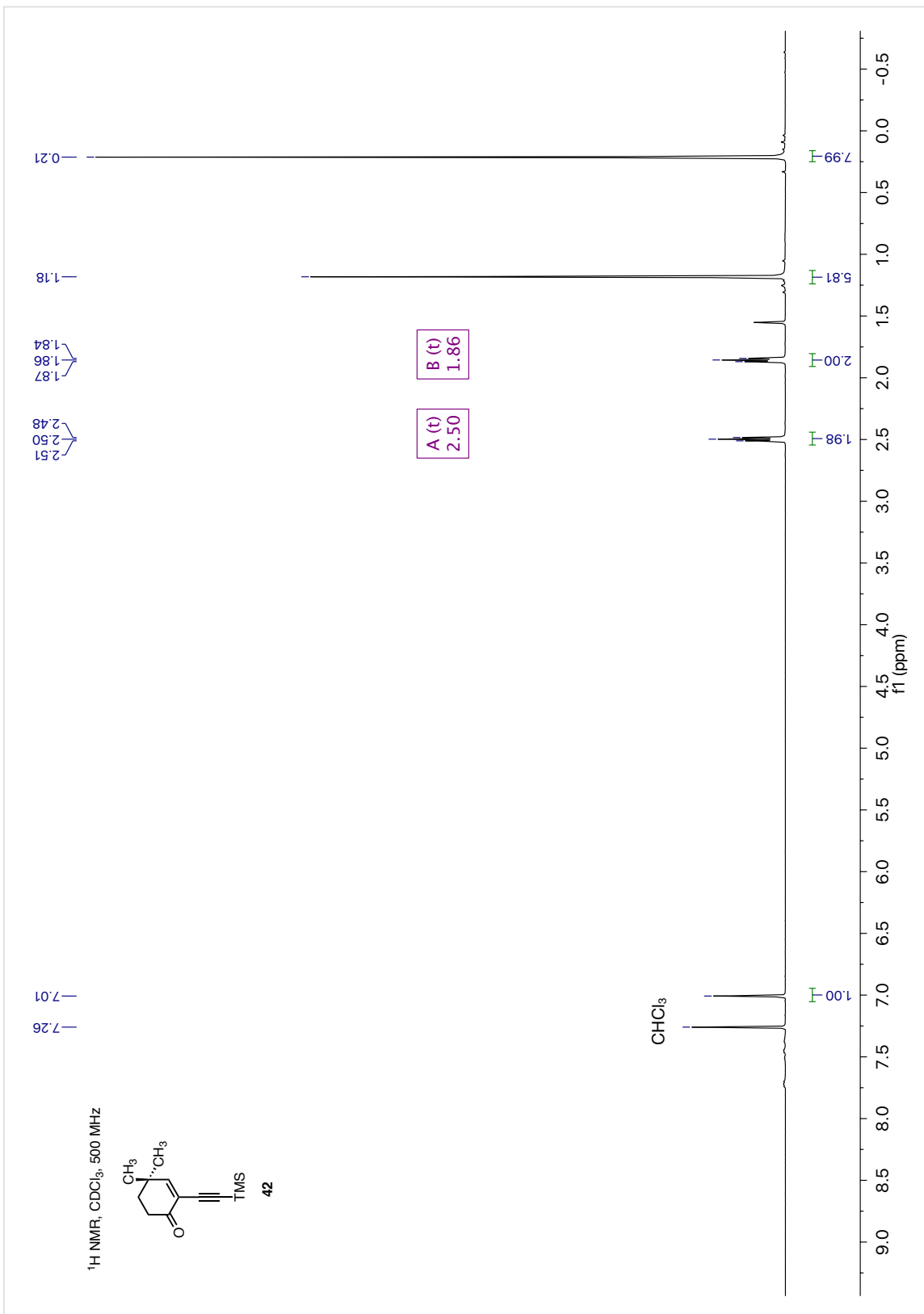


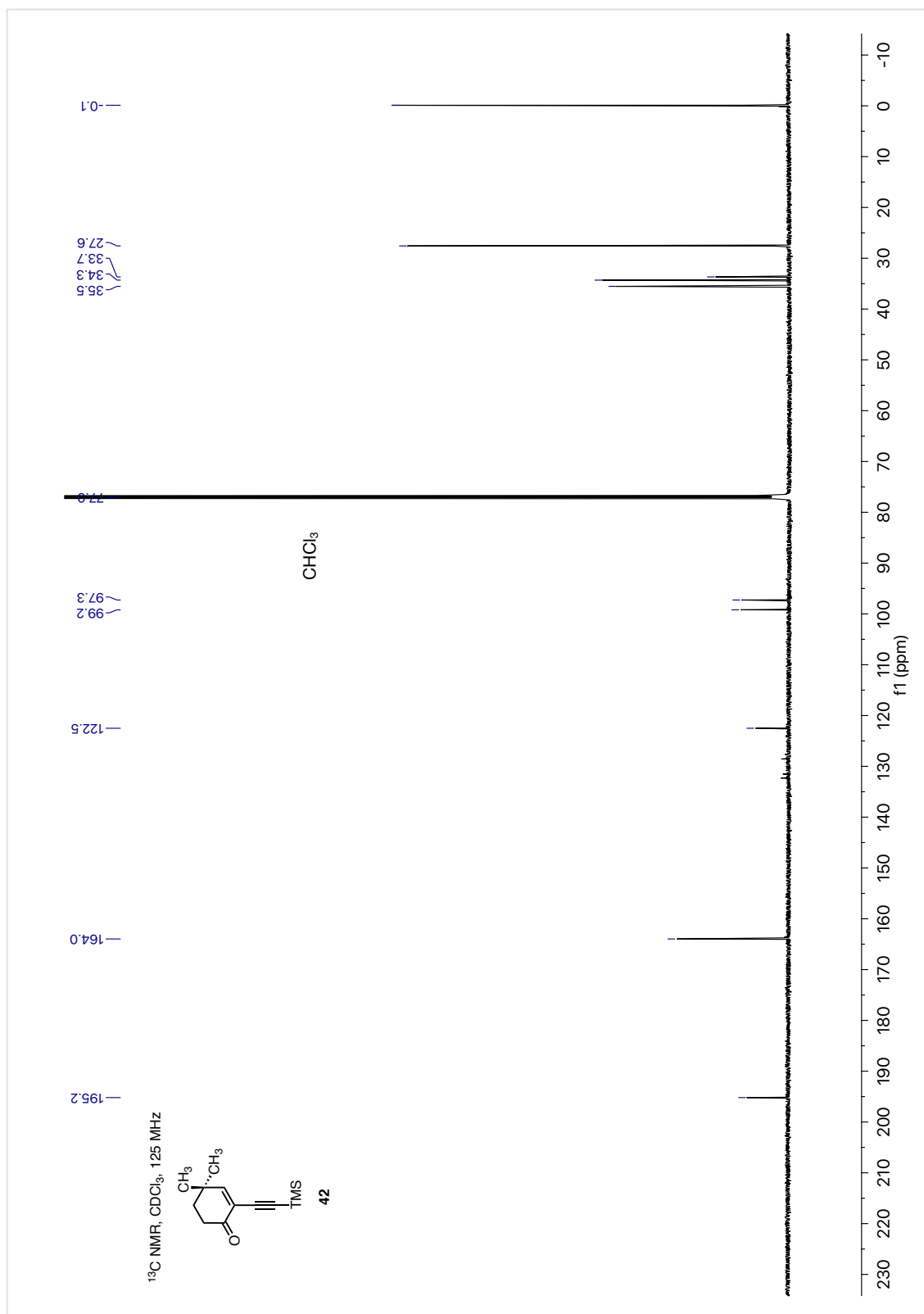


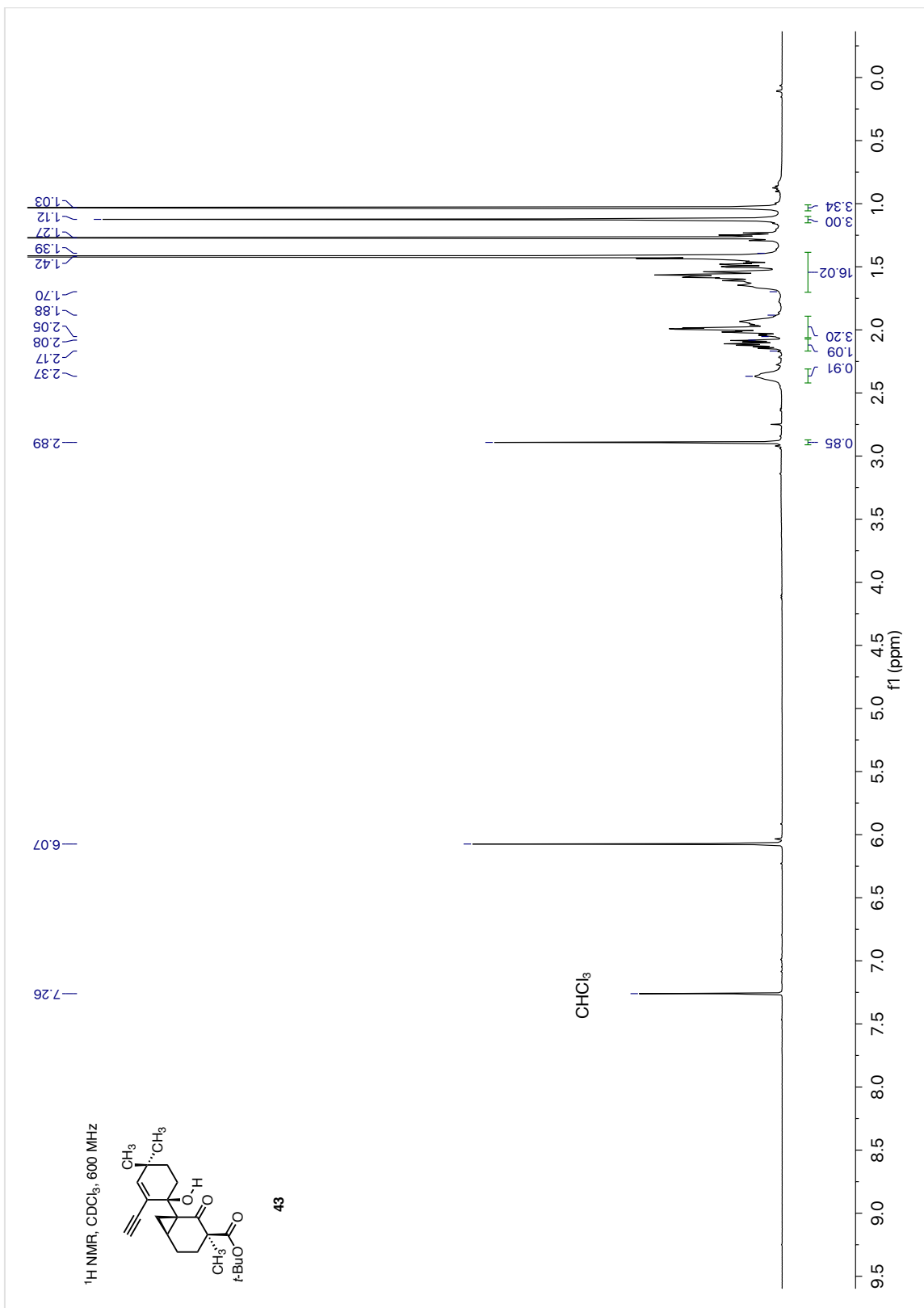


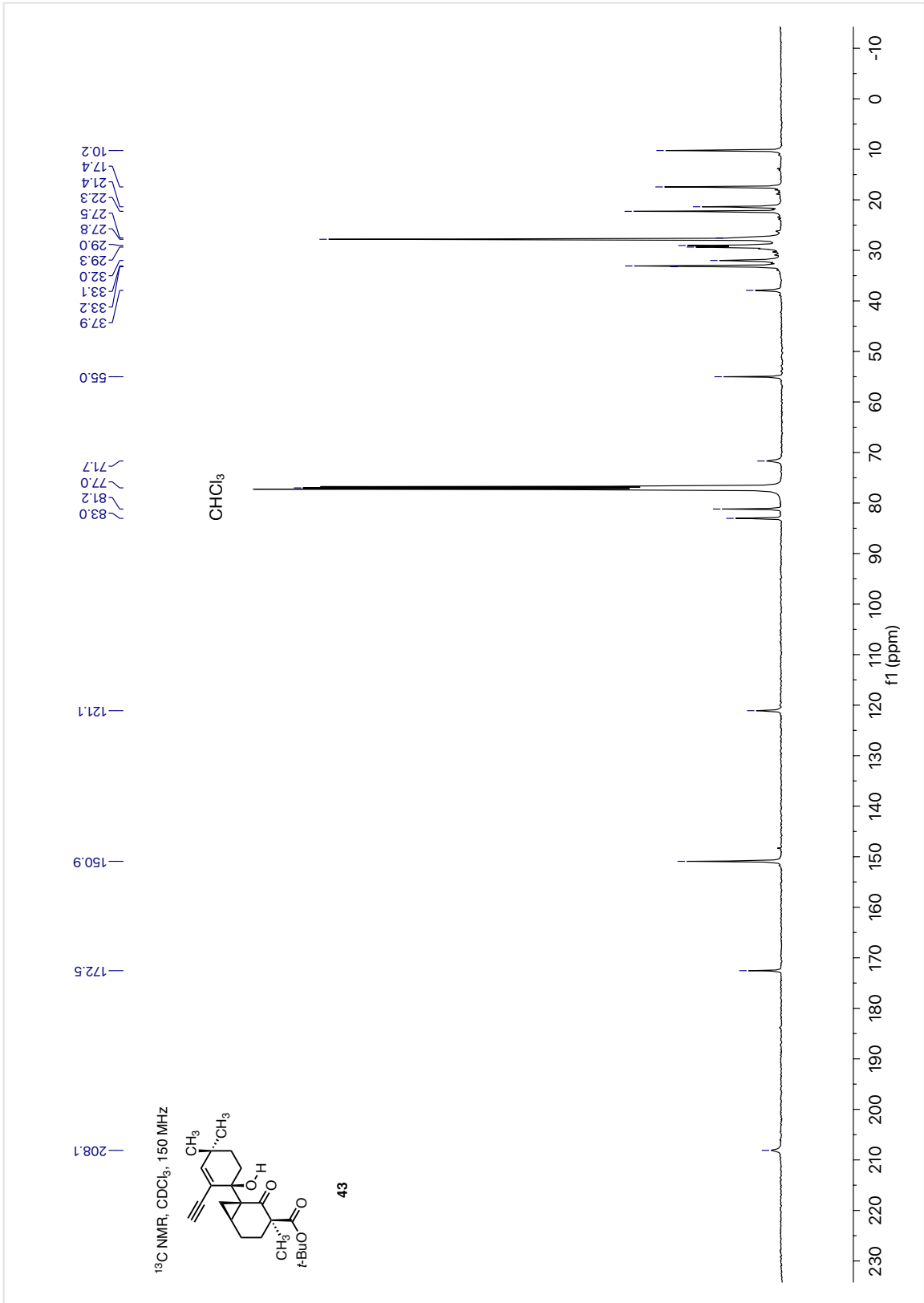


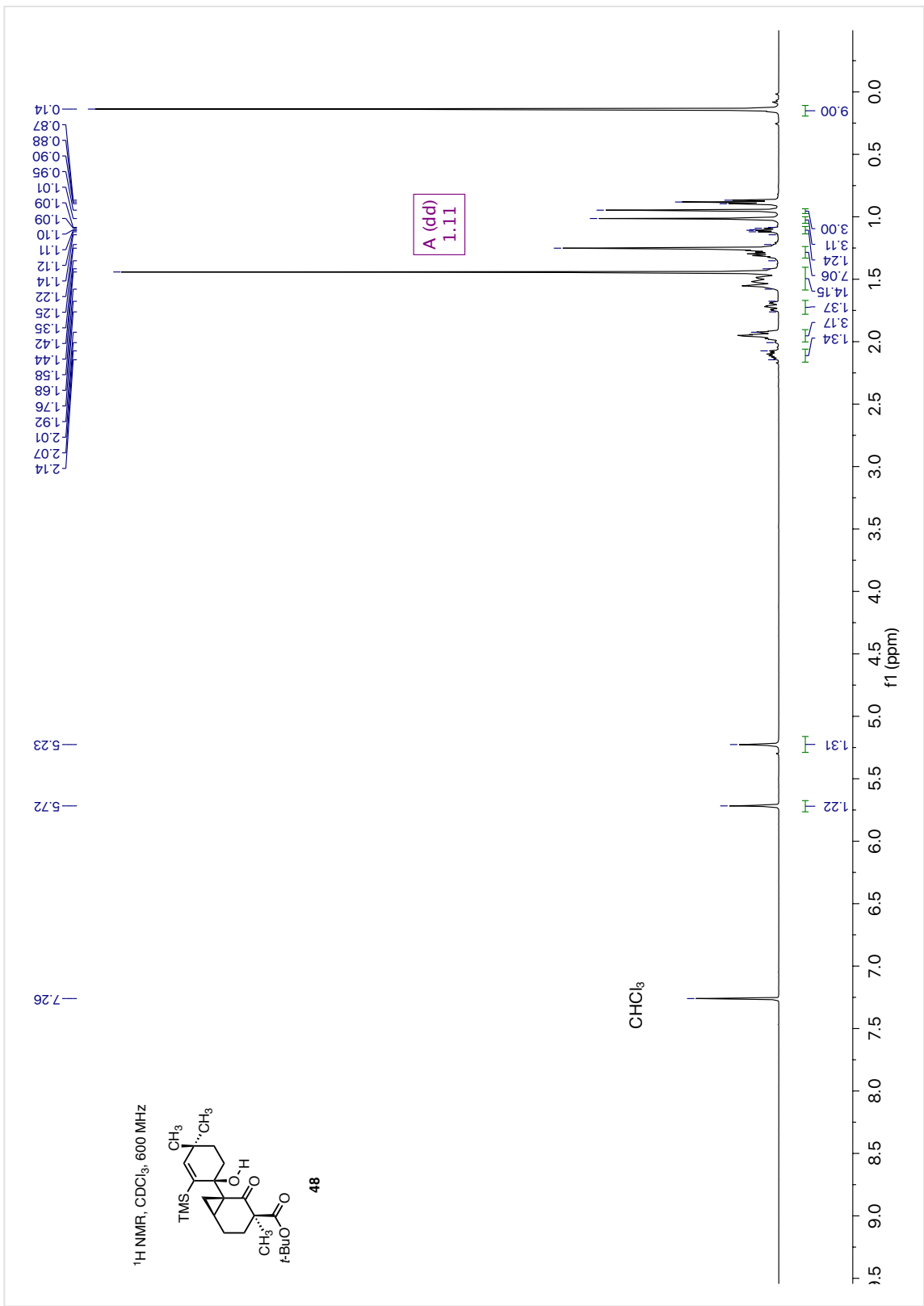


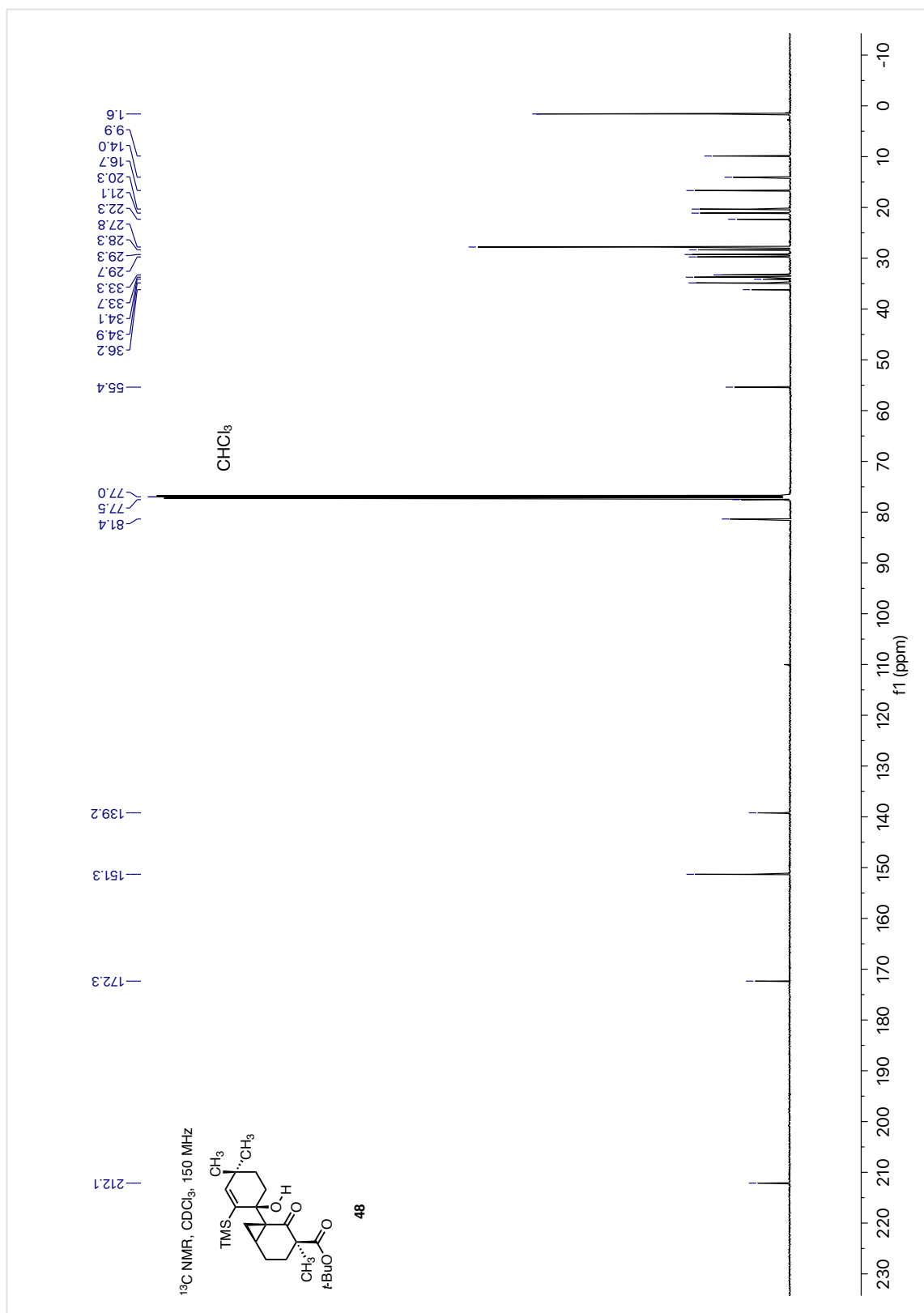




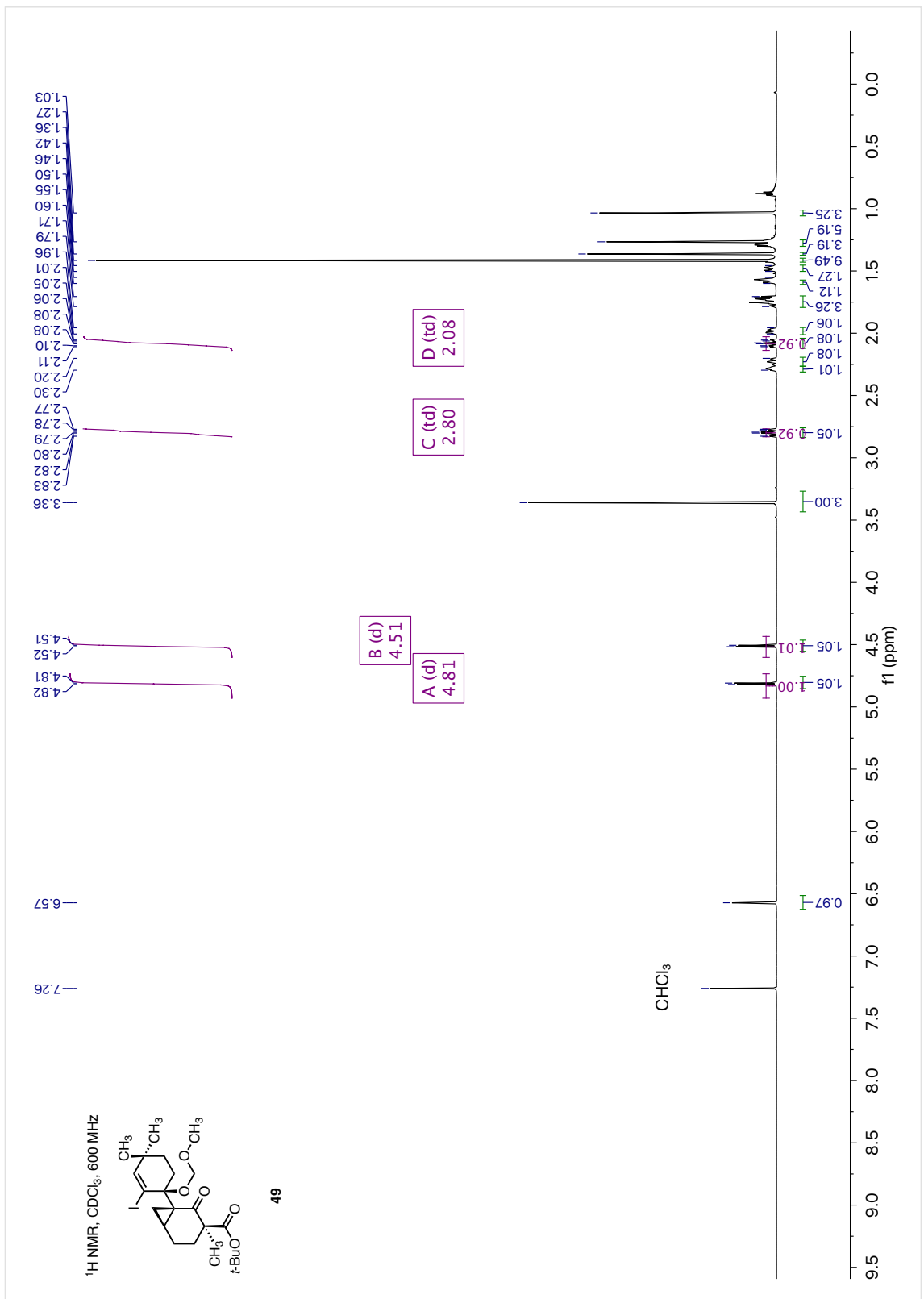




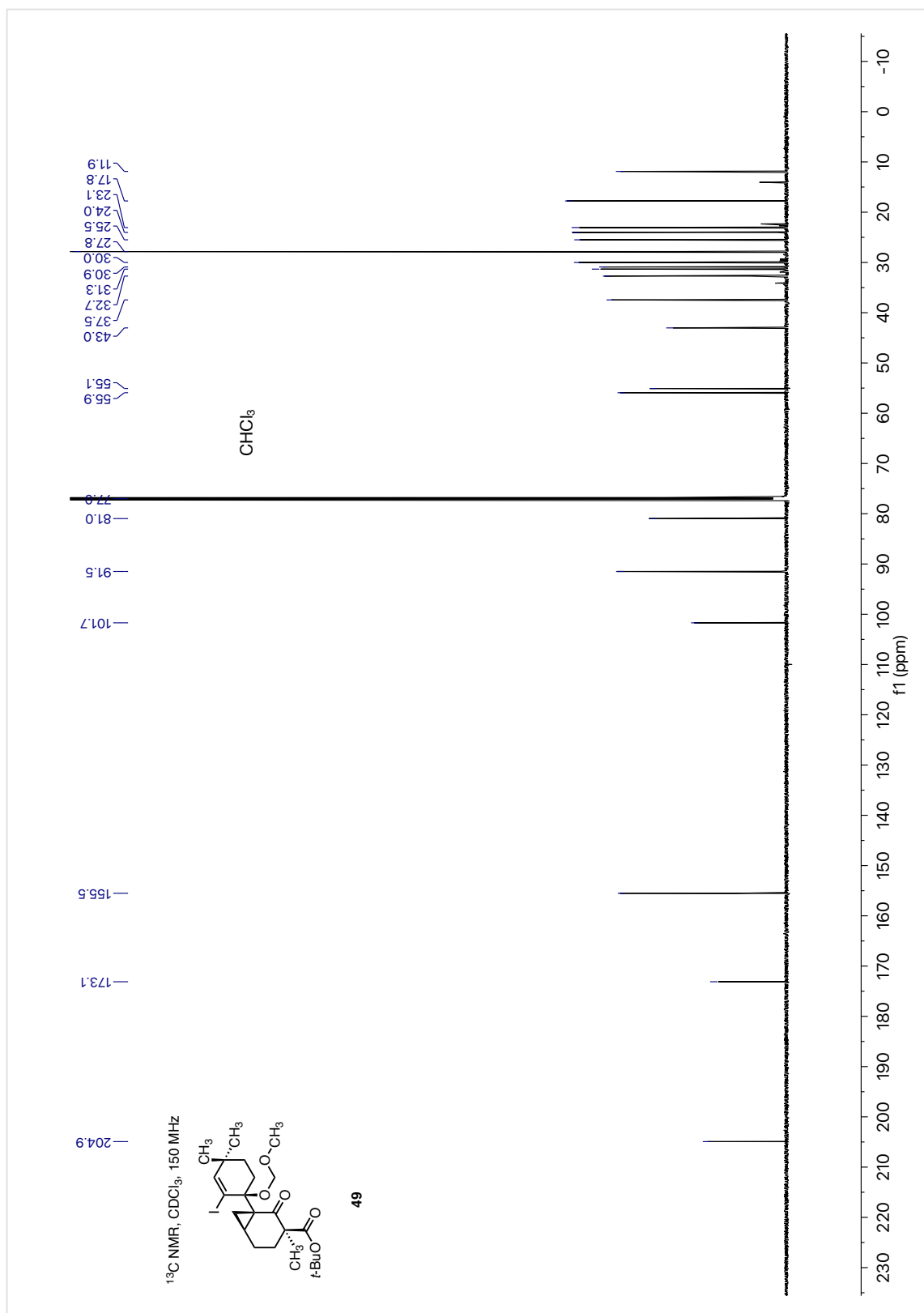




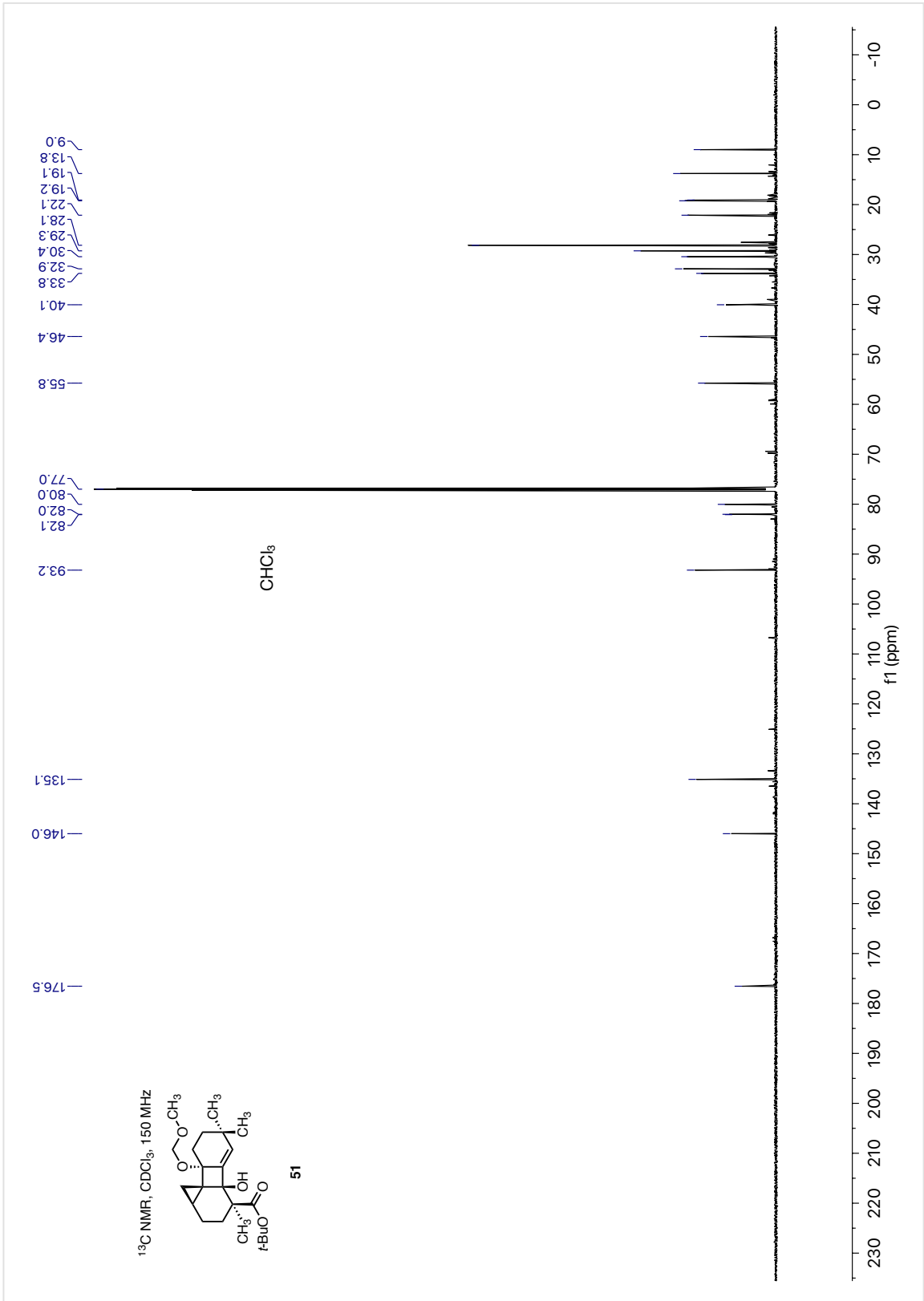


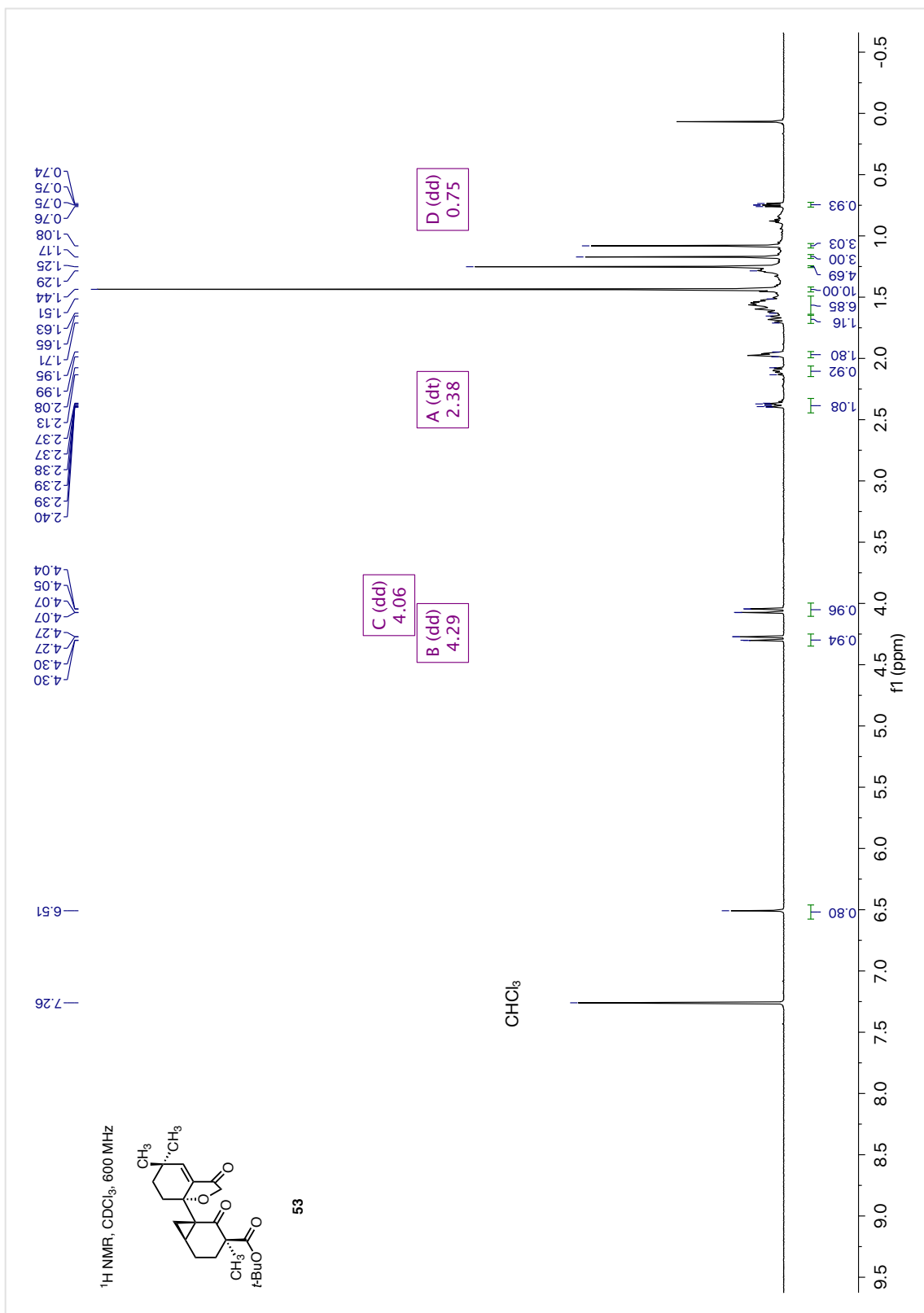


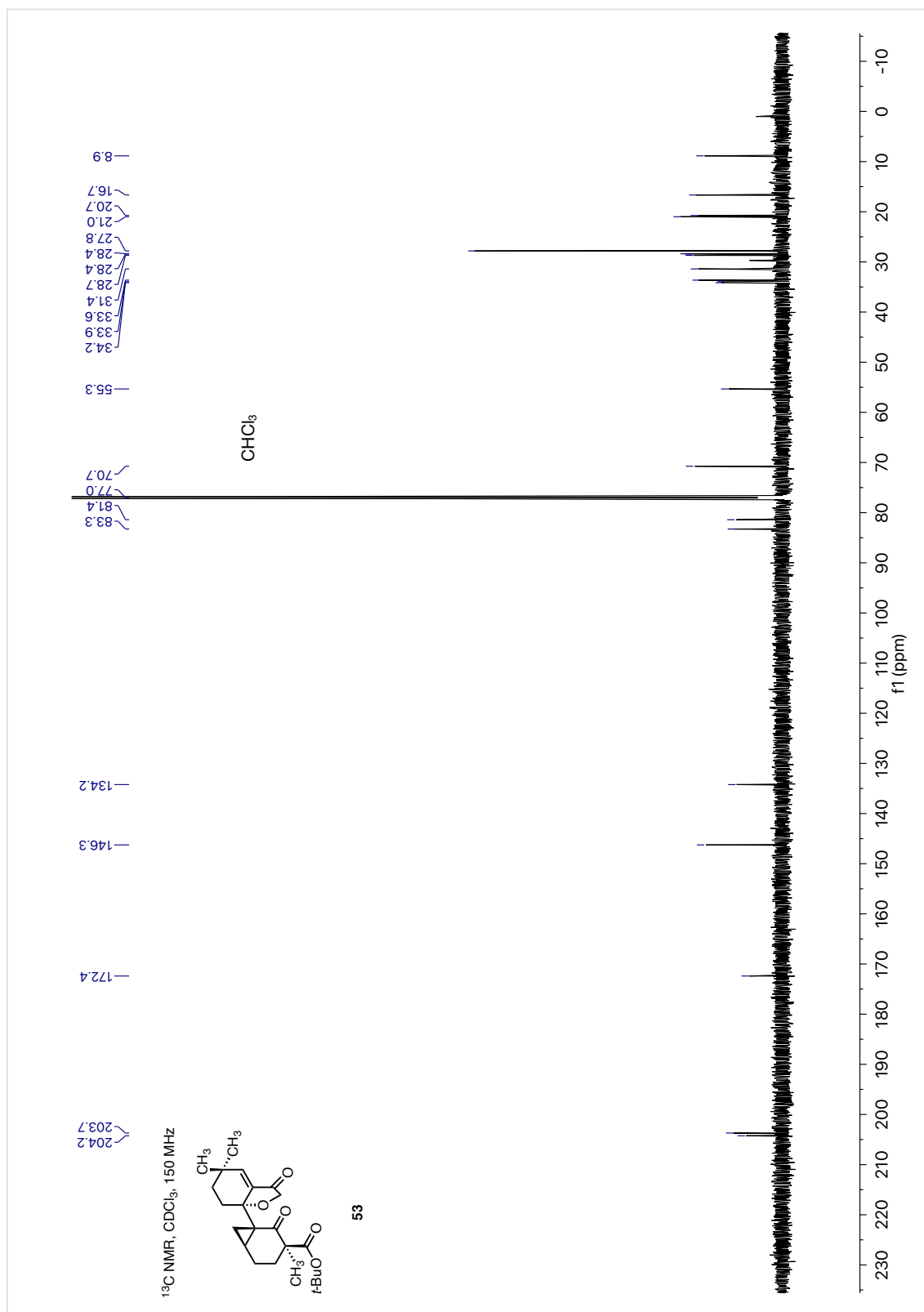
49



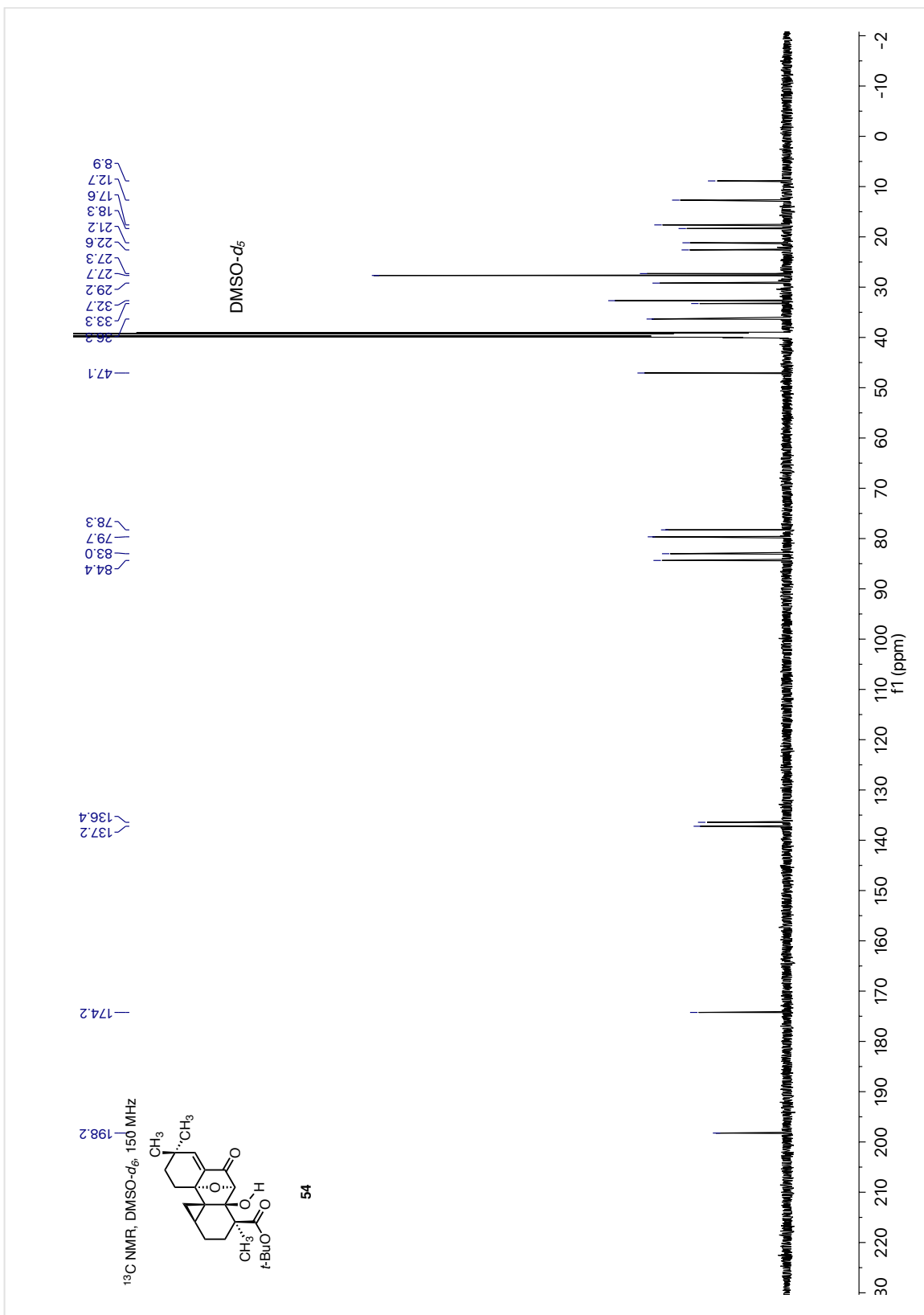




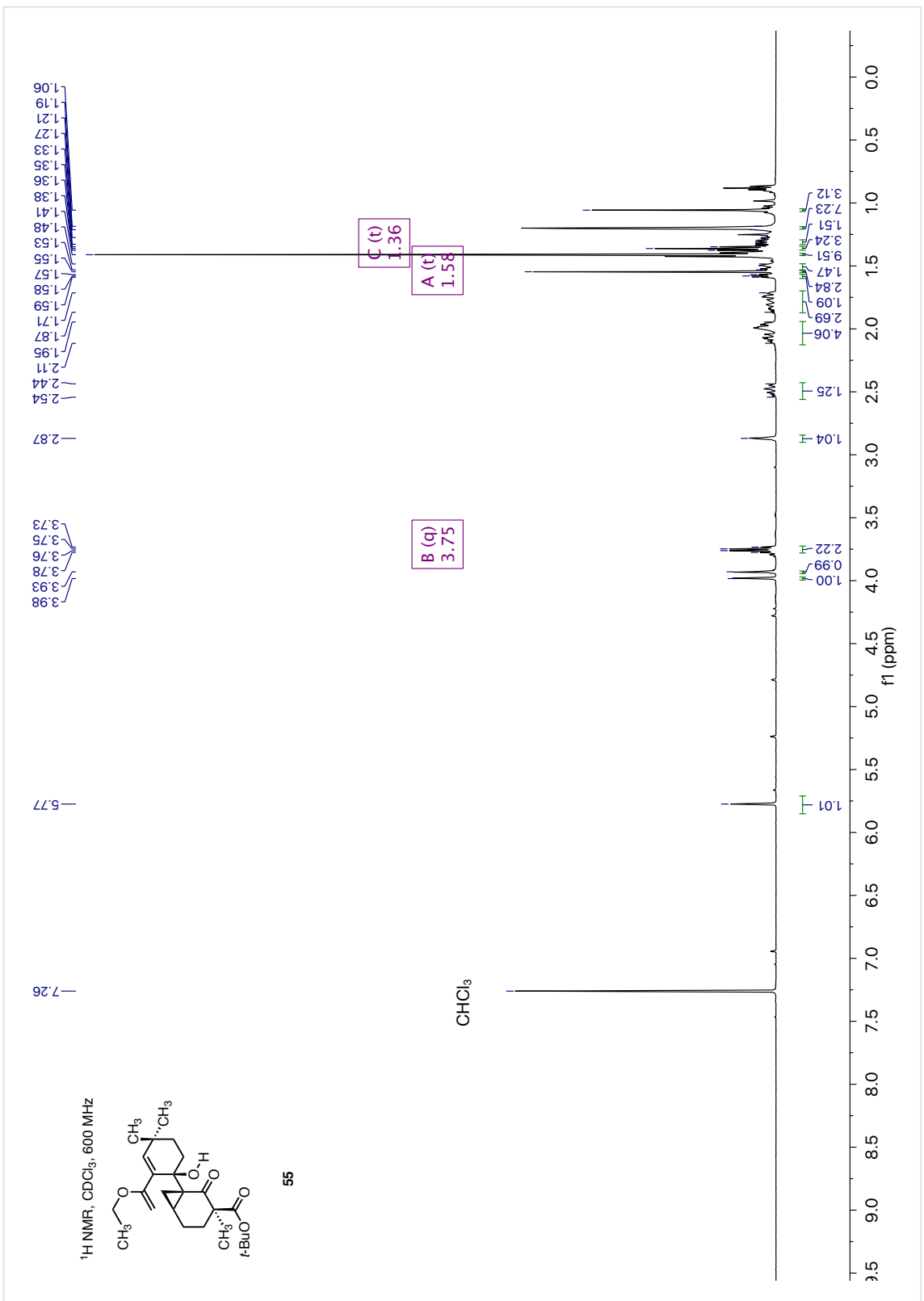




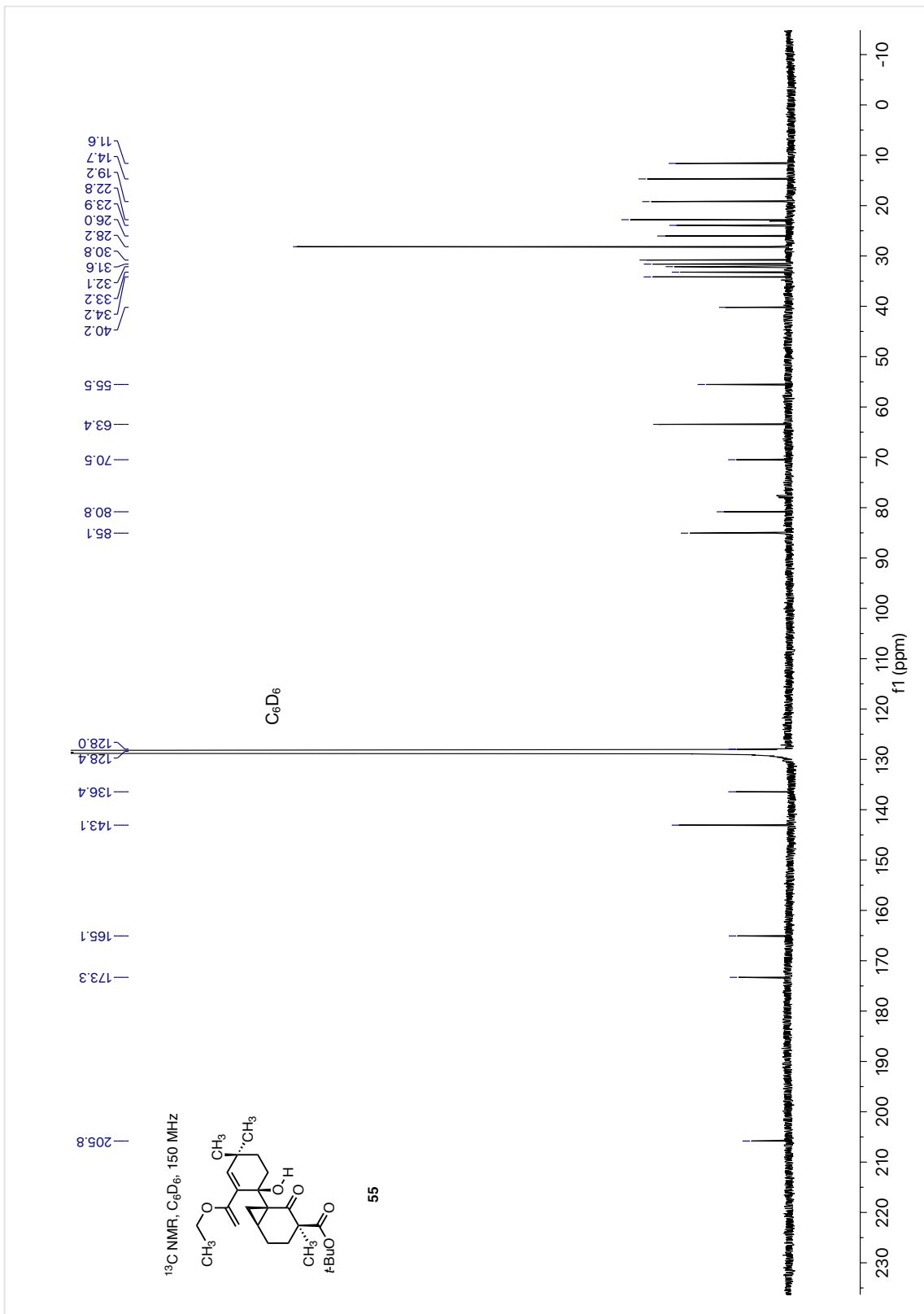


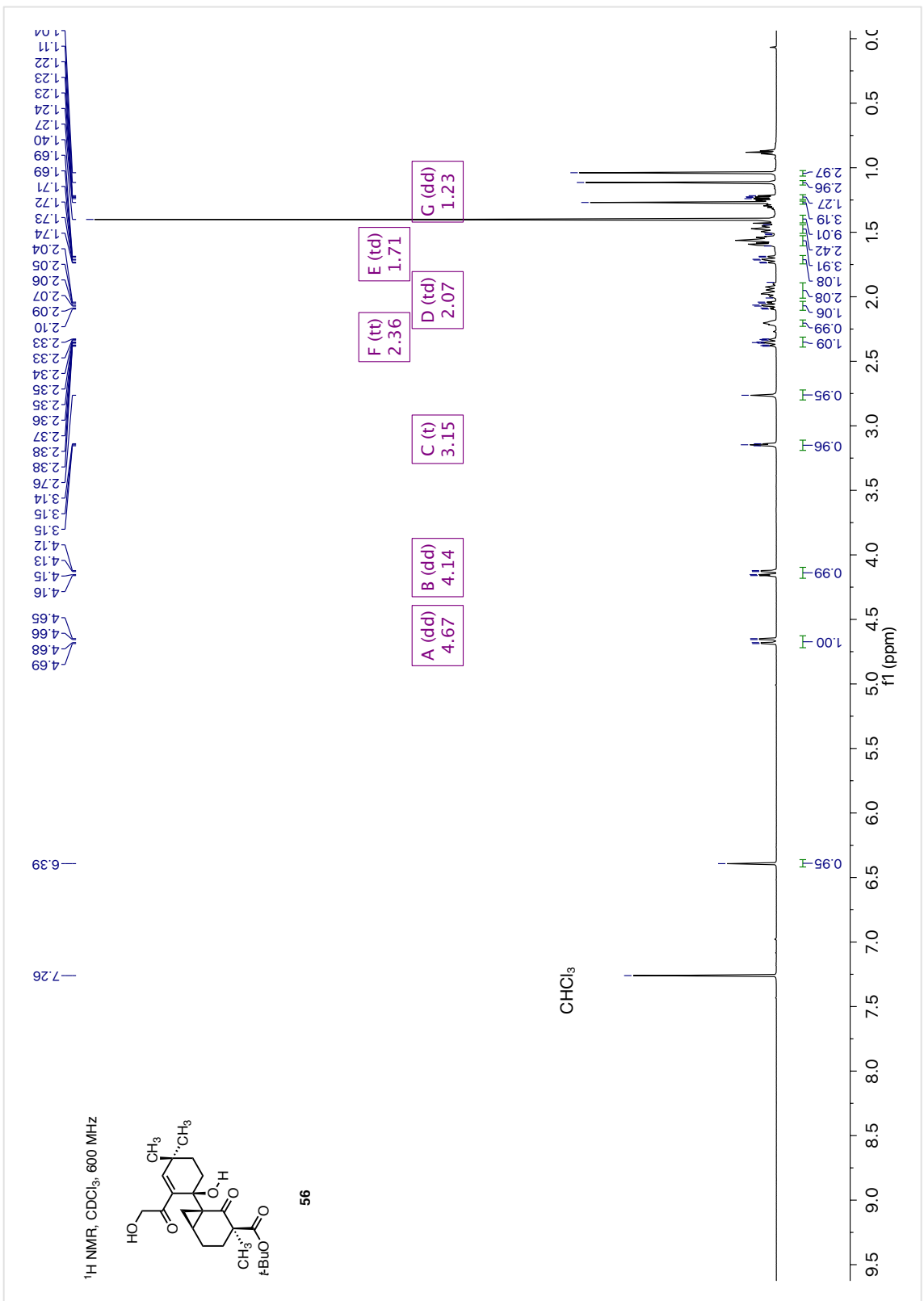




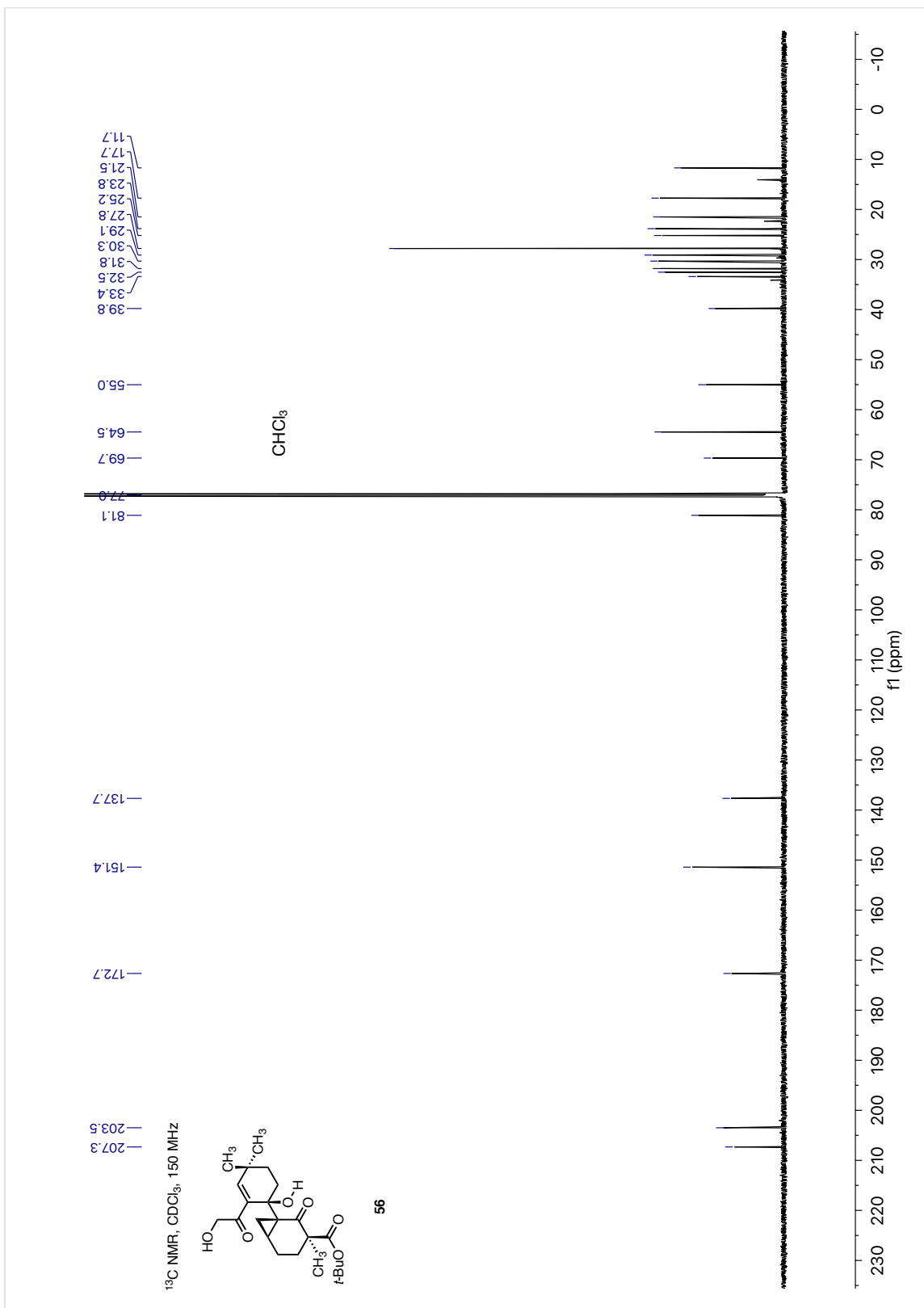


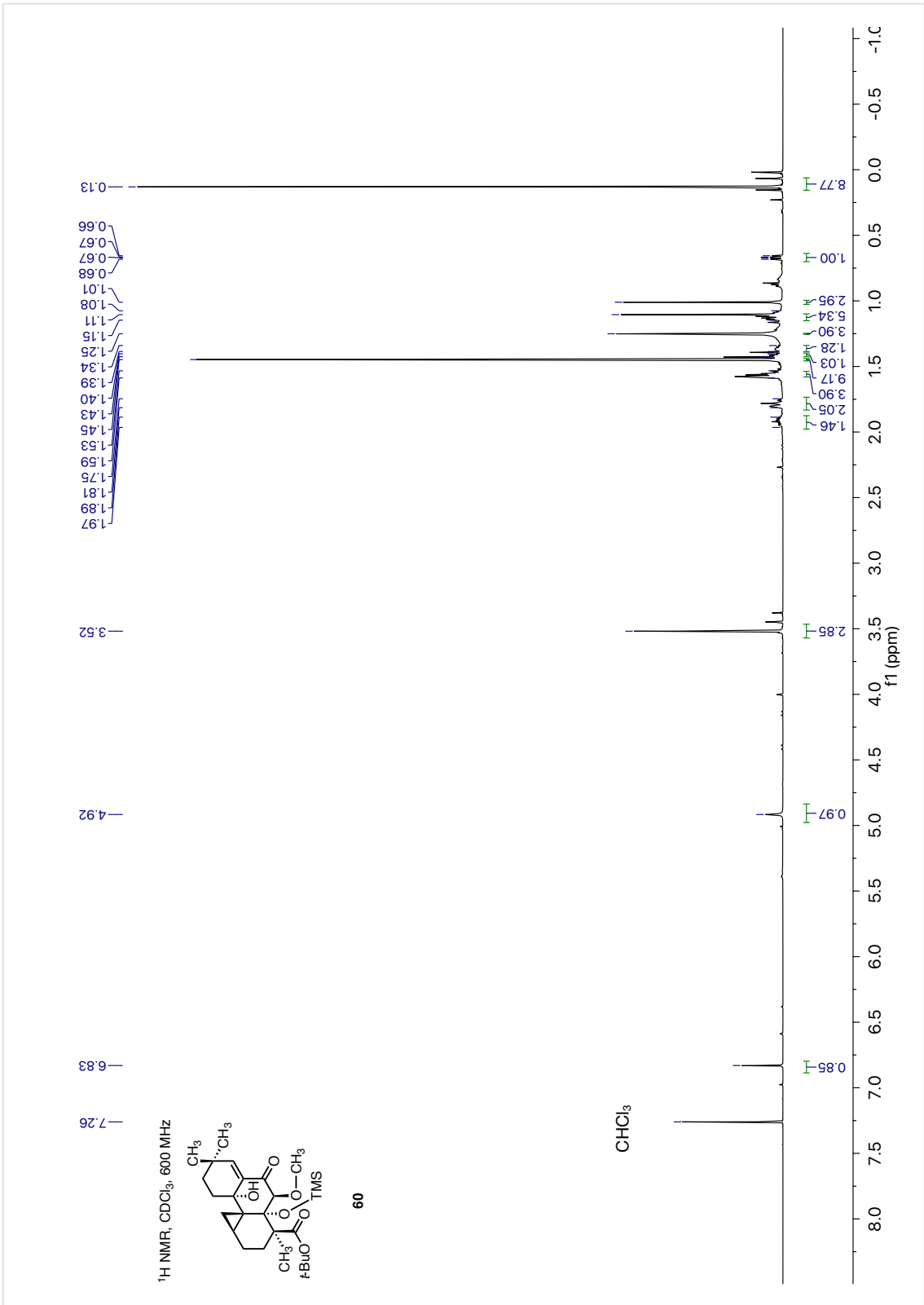
55

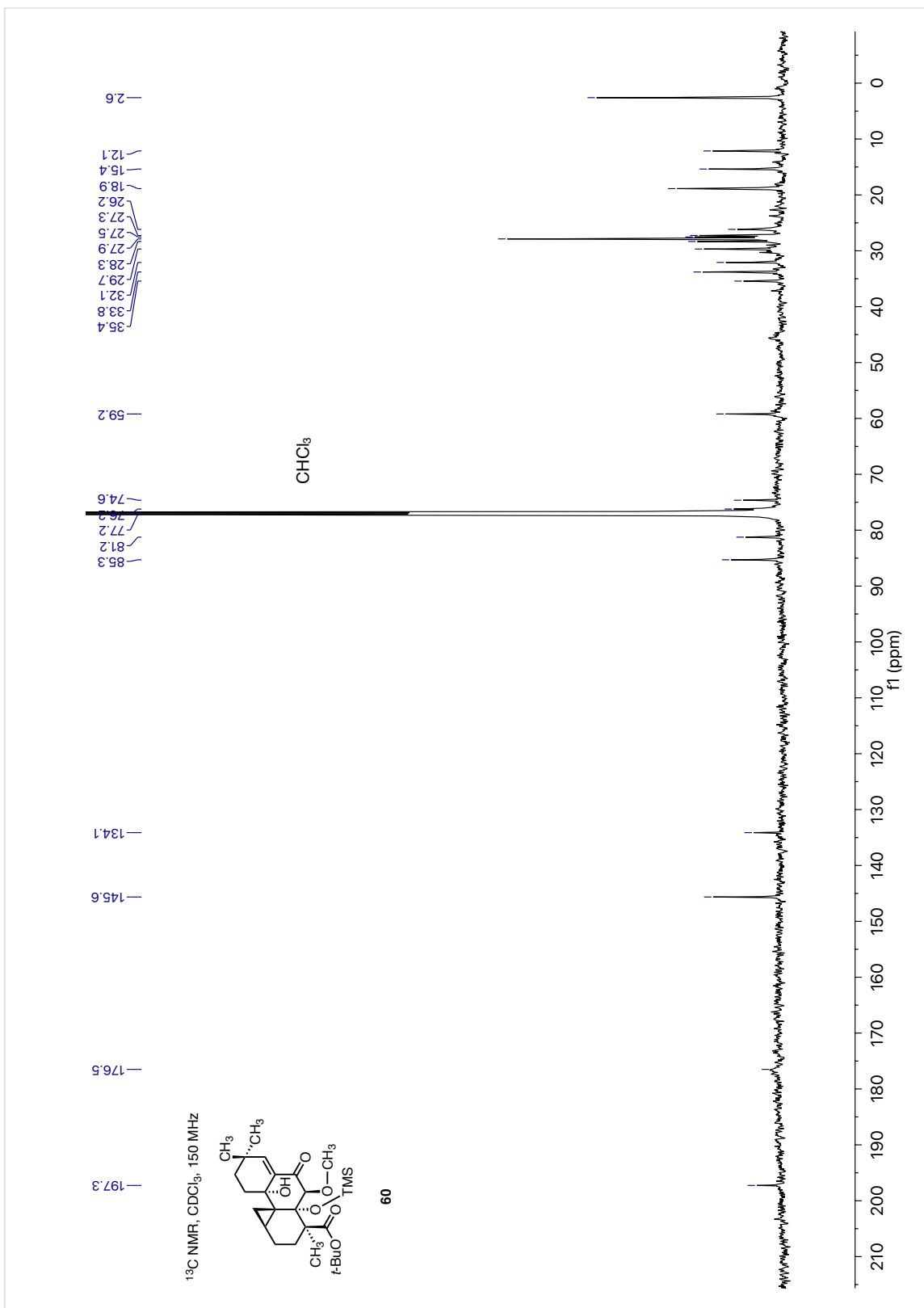




56



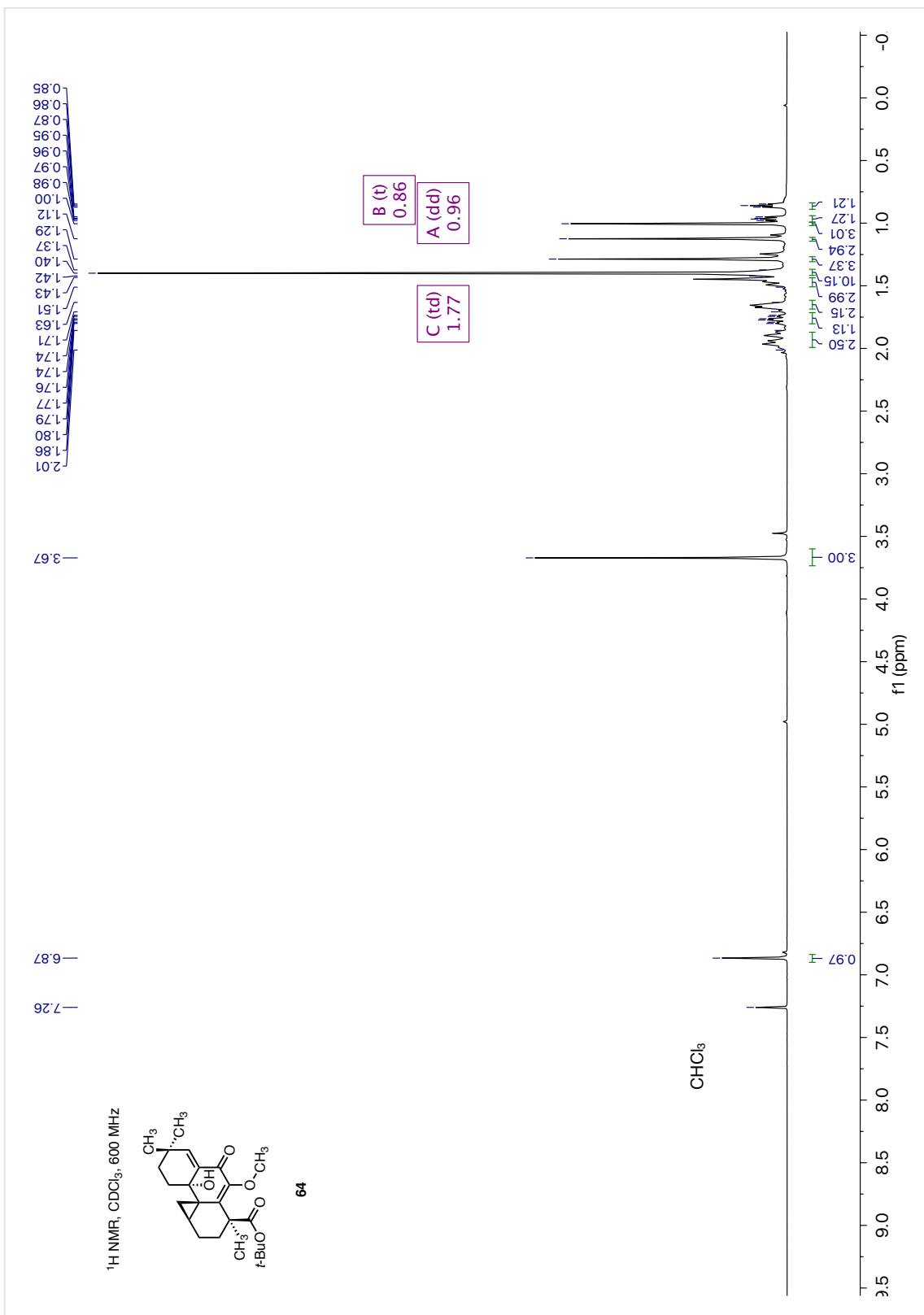


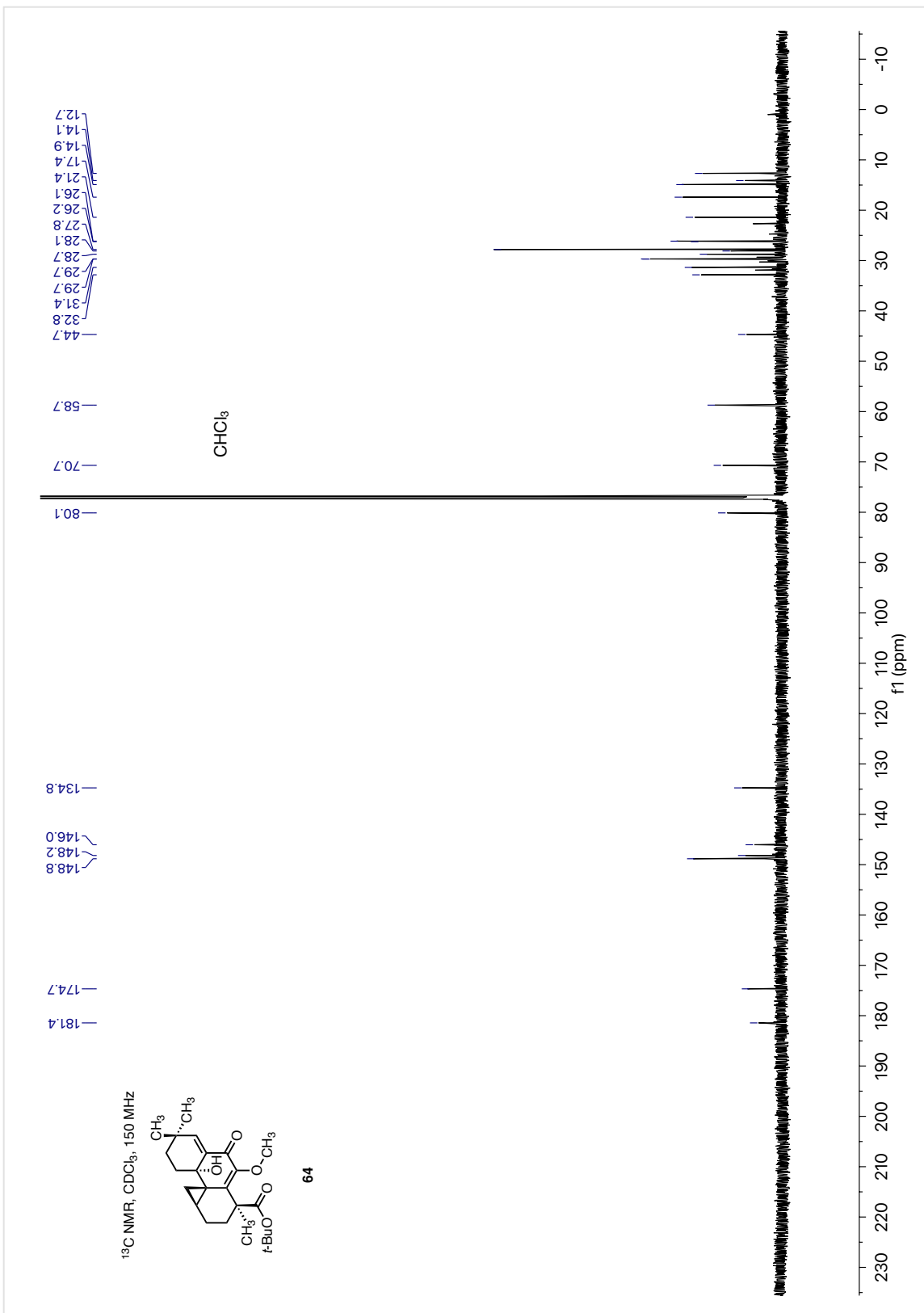


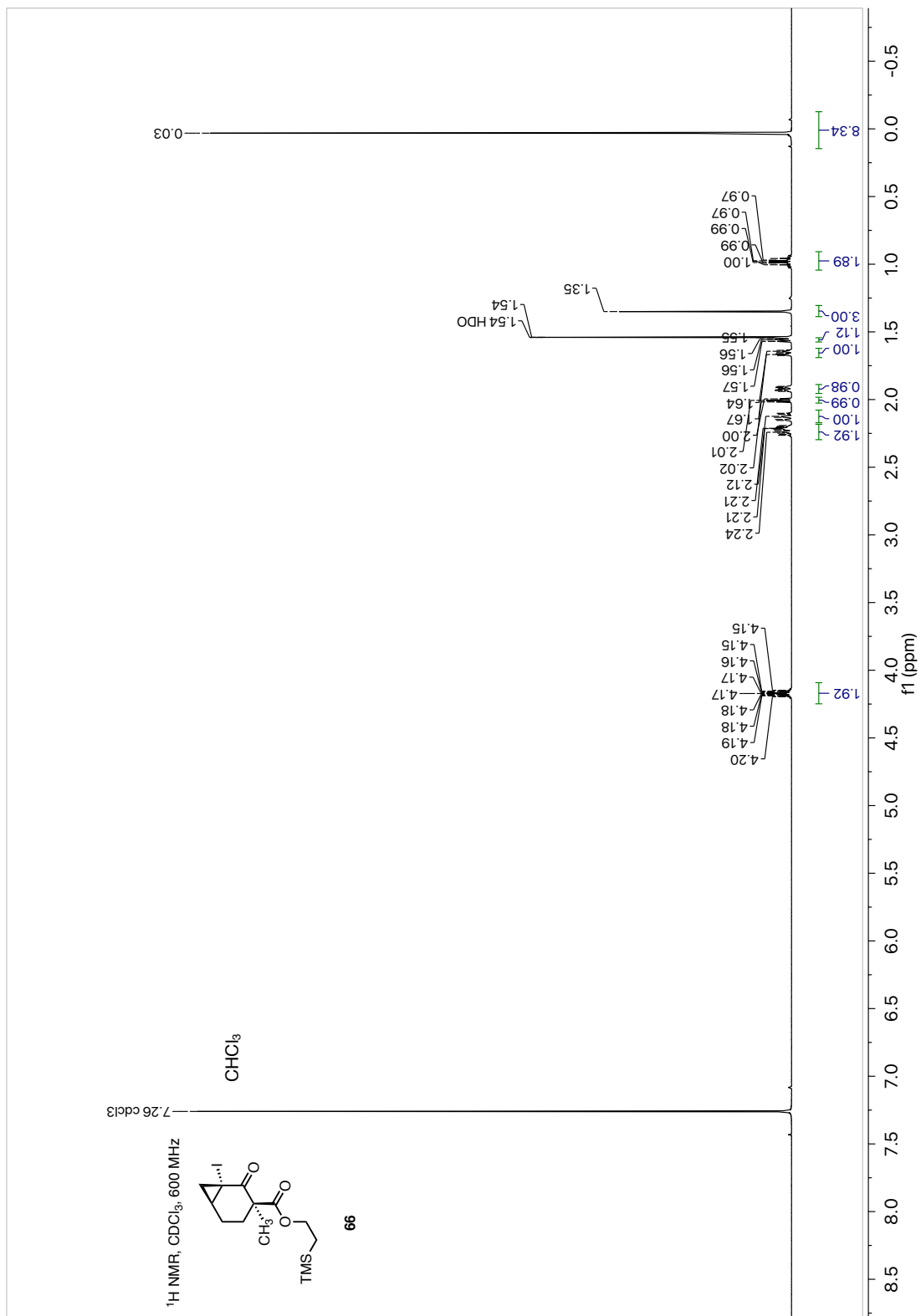


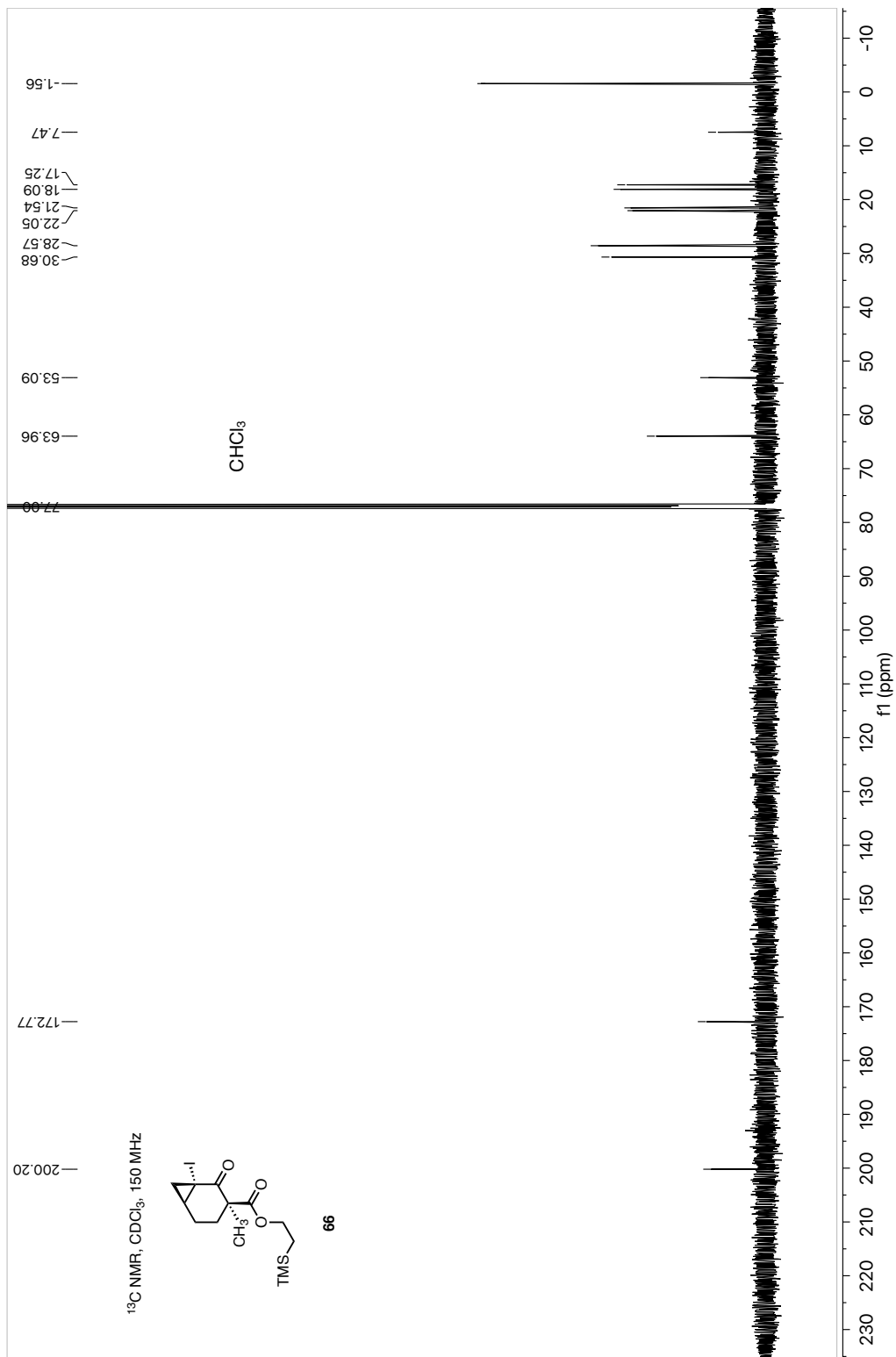


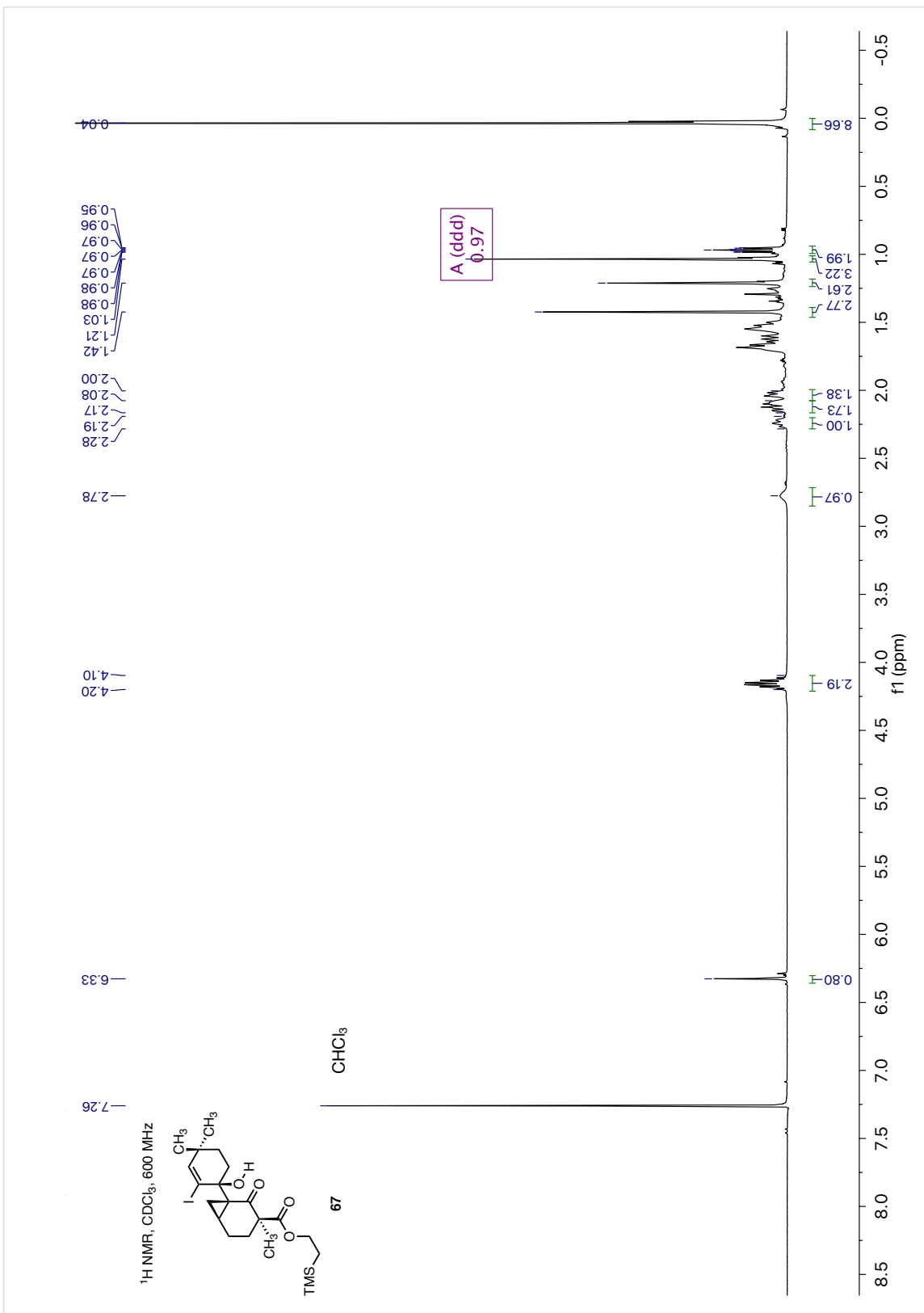


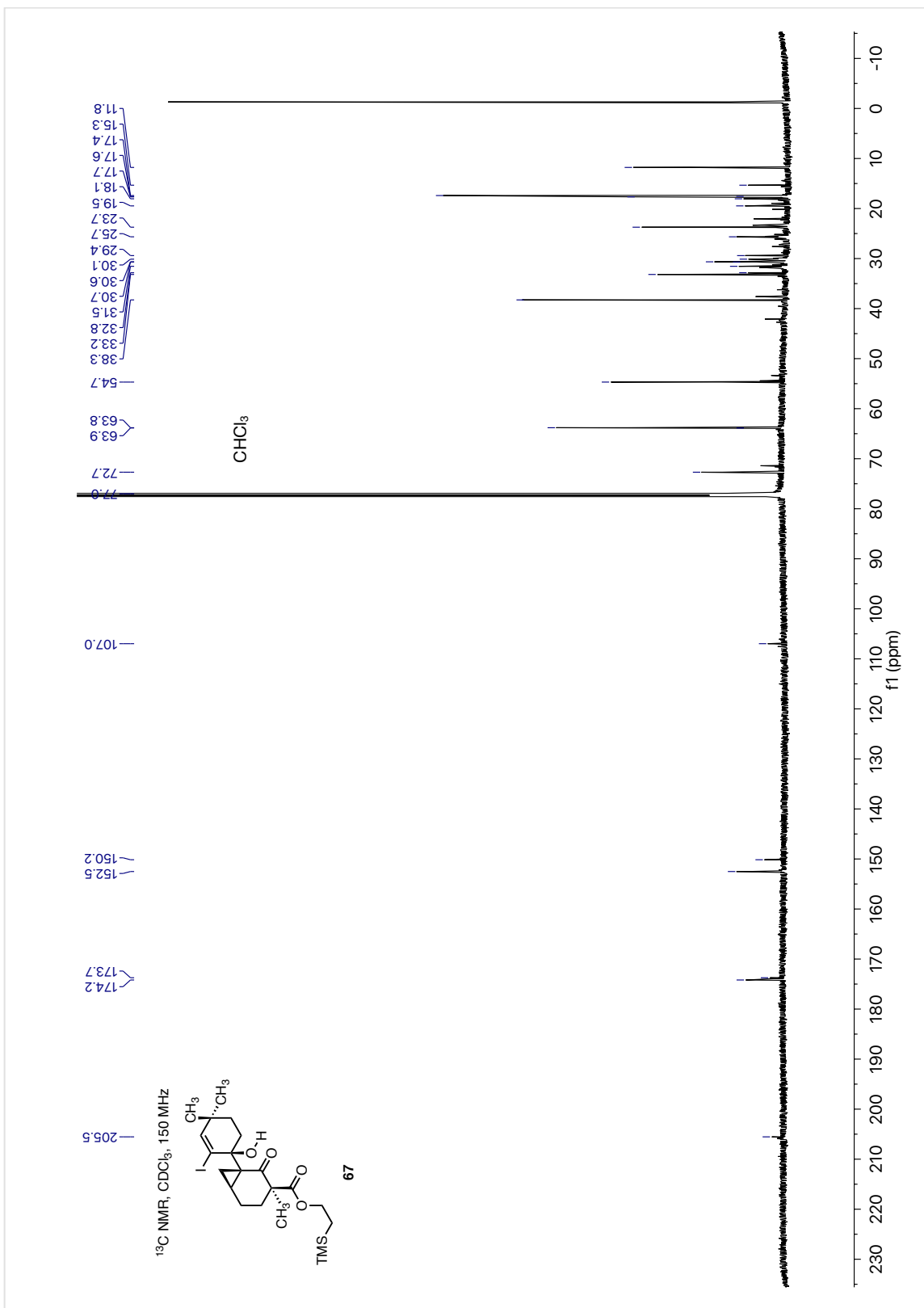


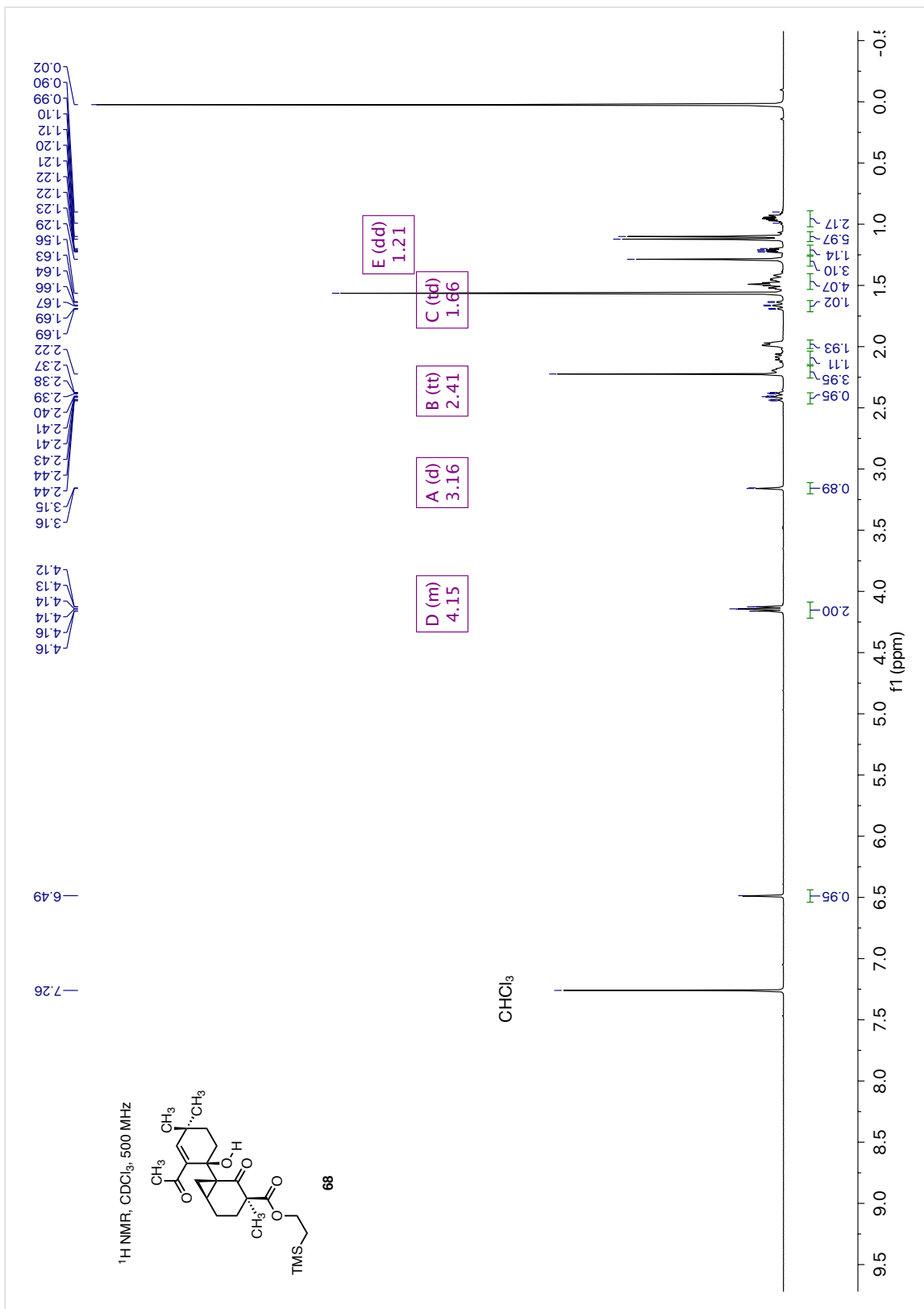


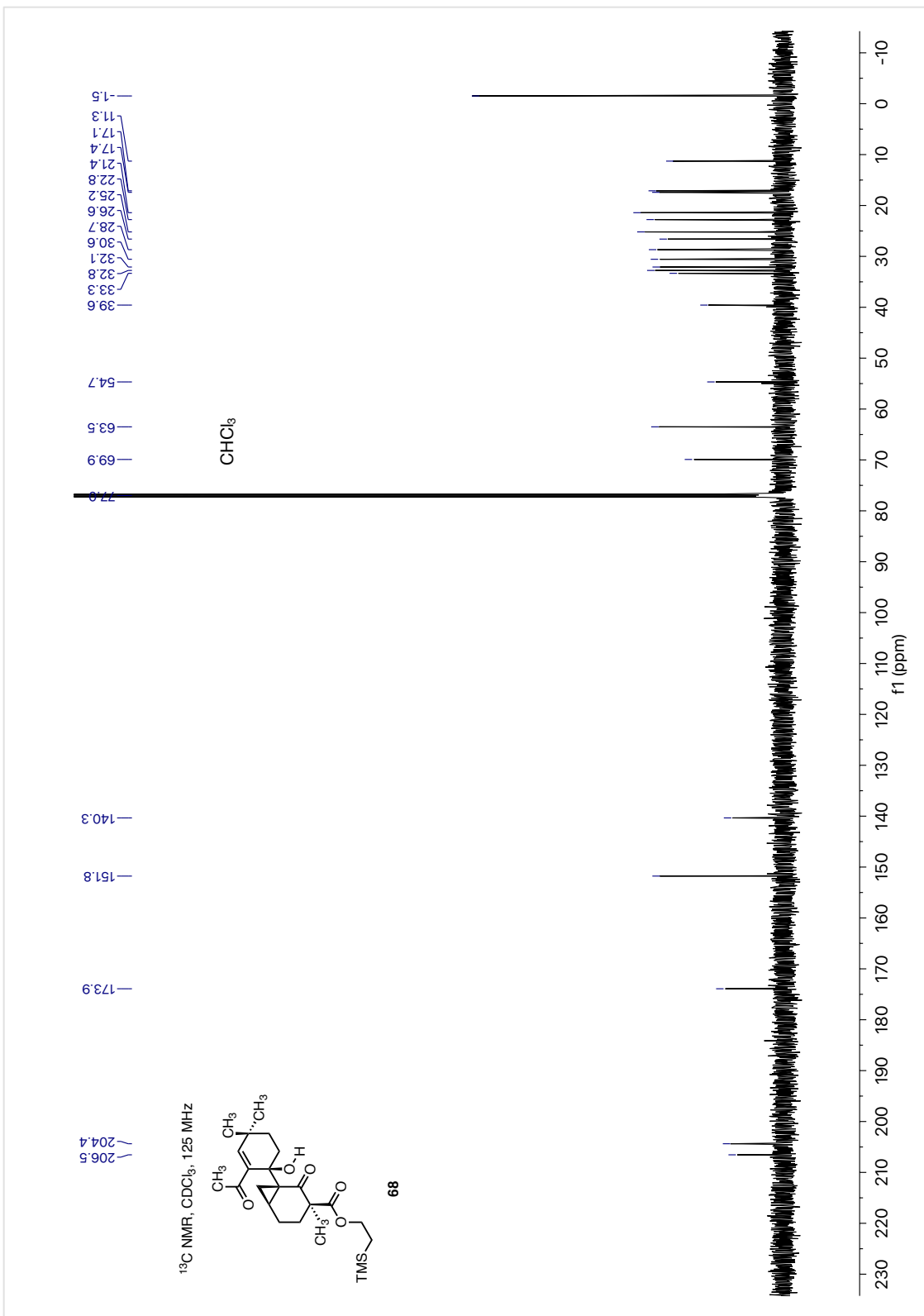




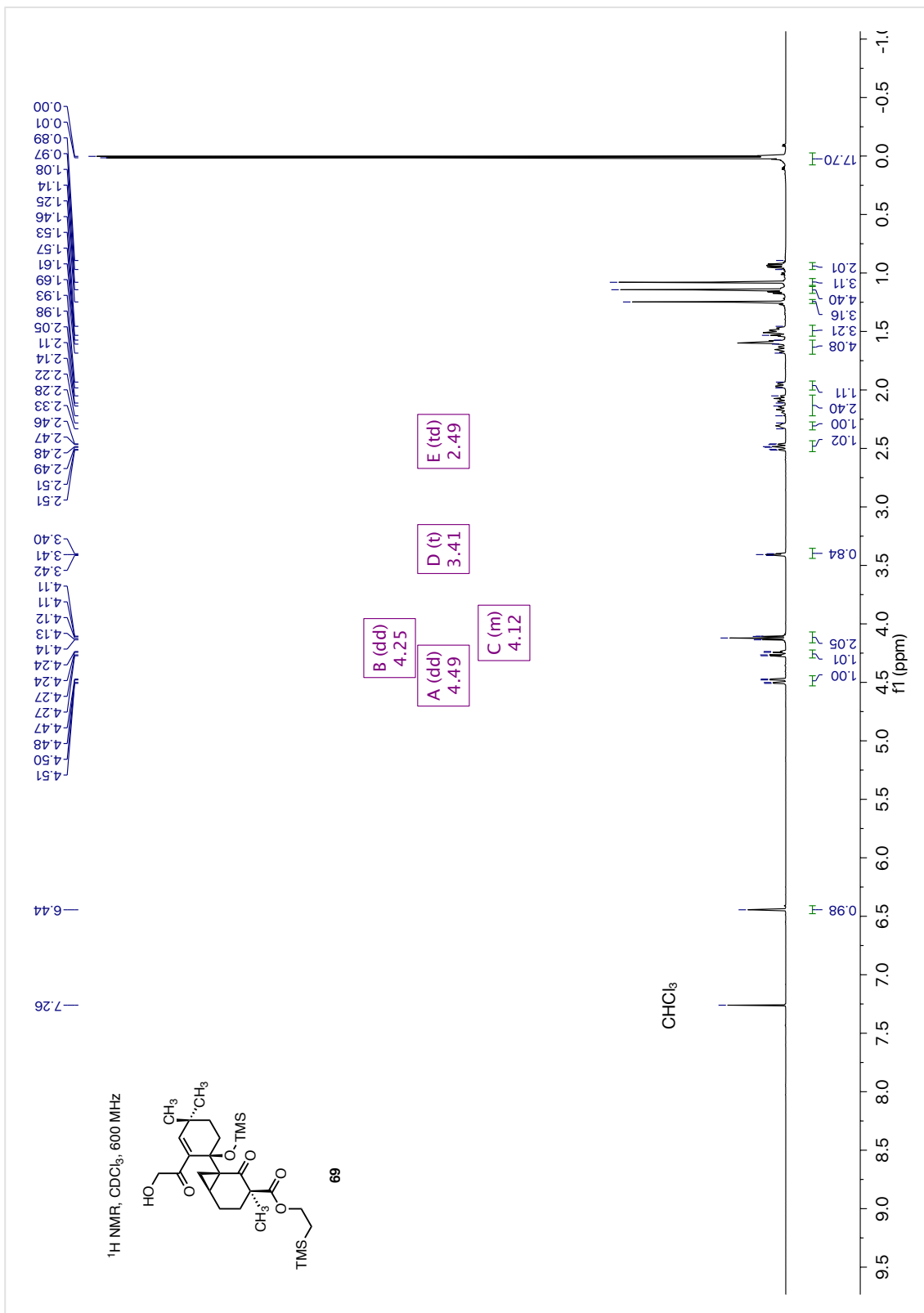


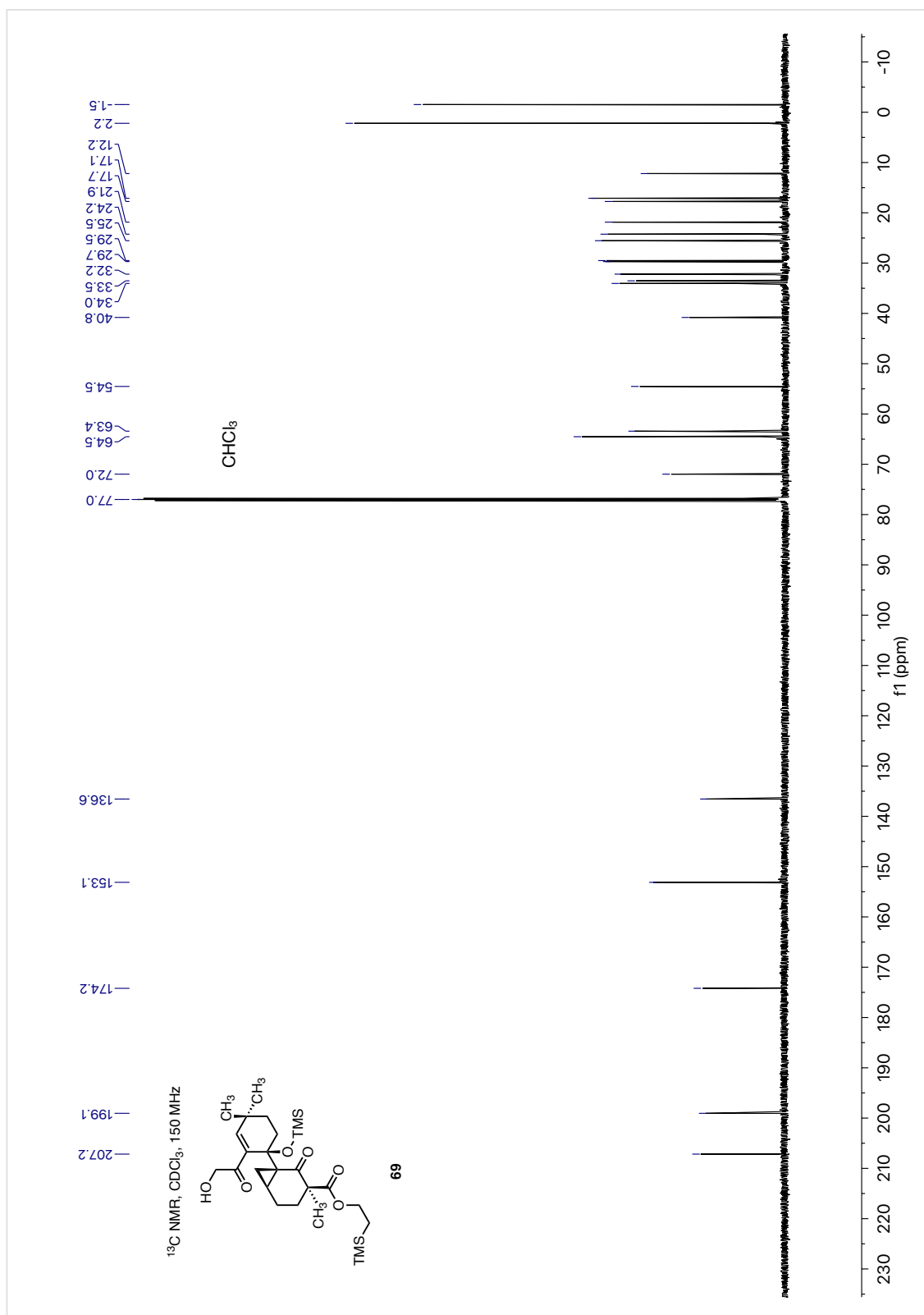


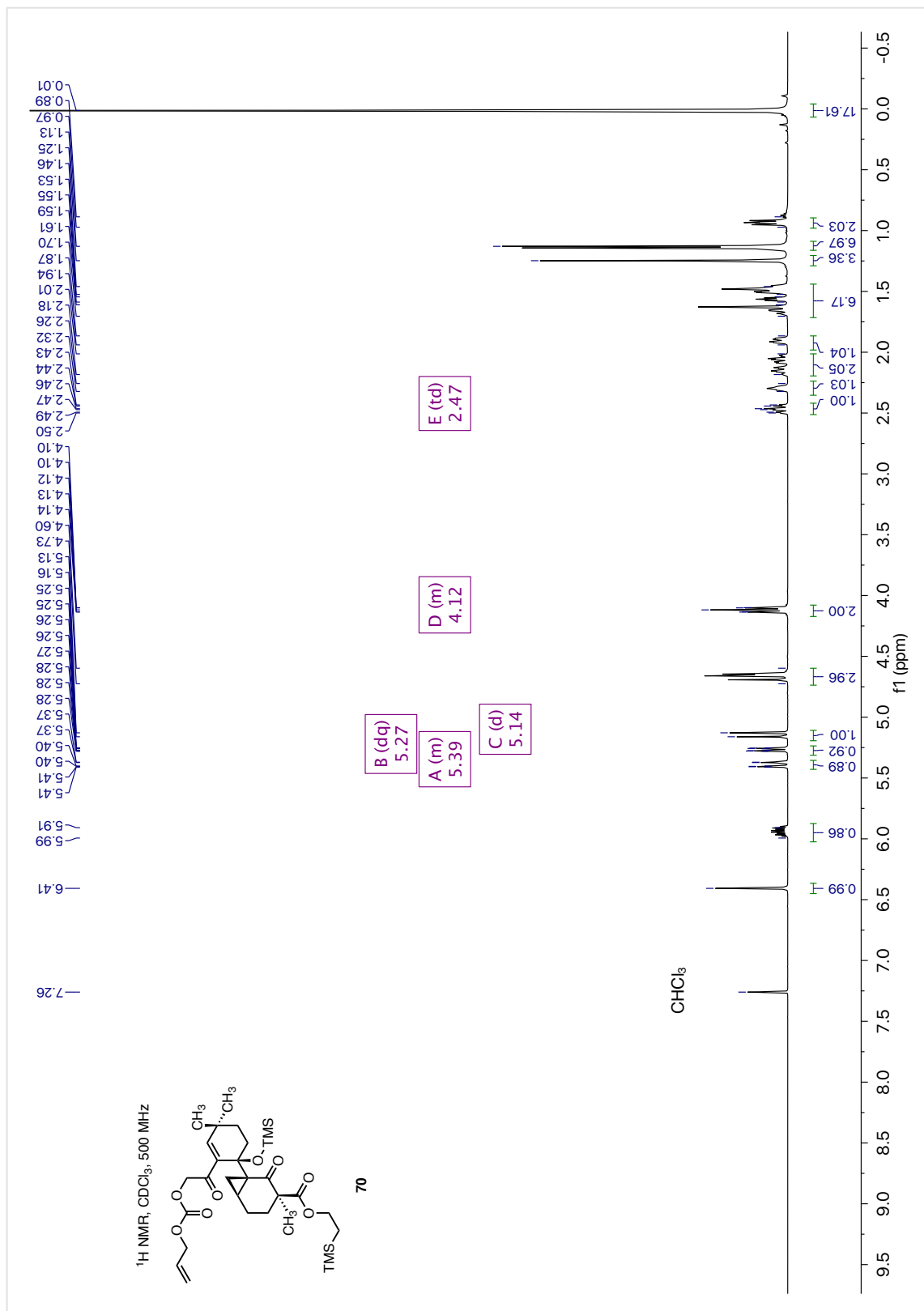


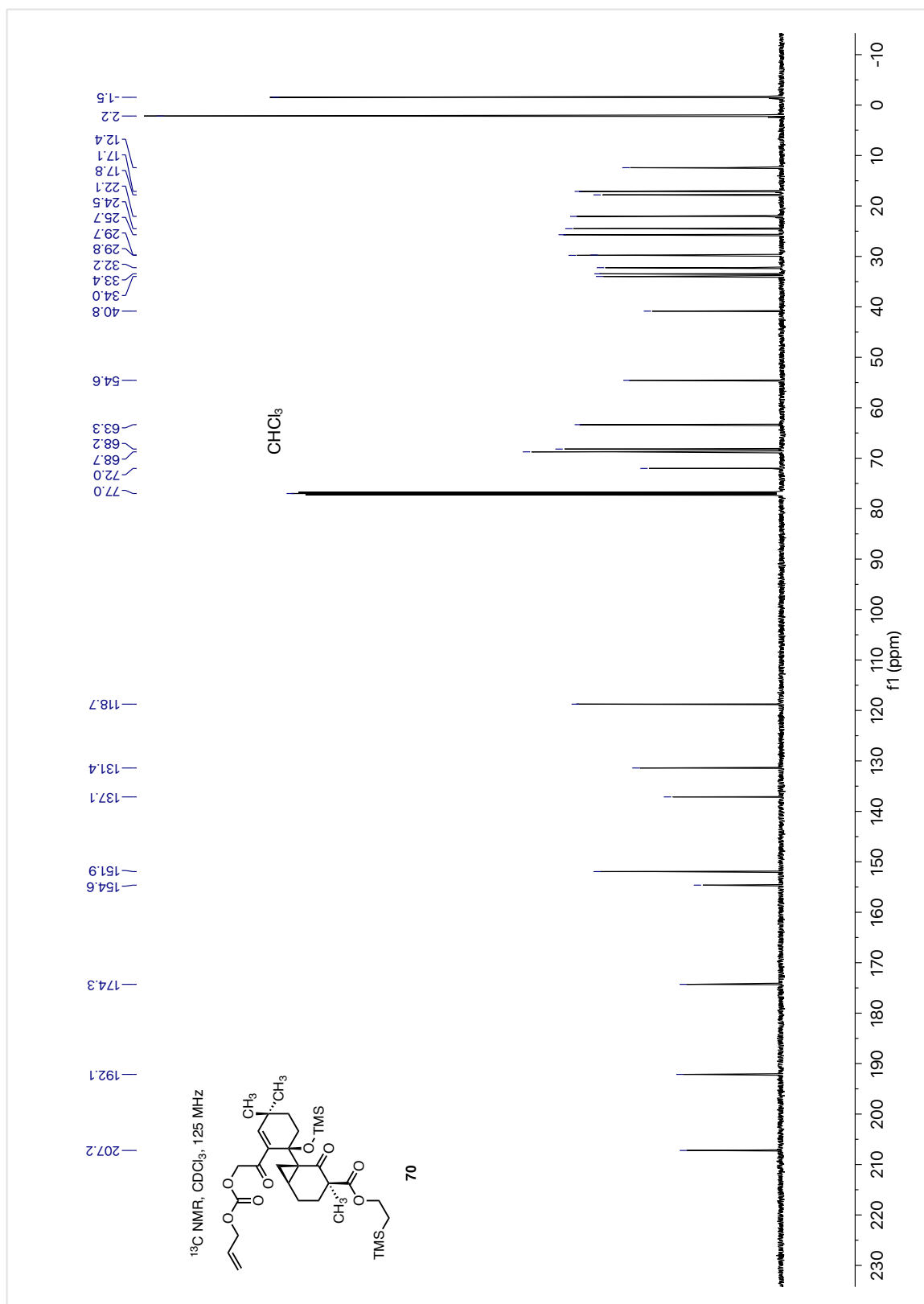


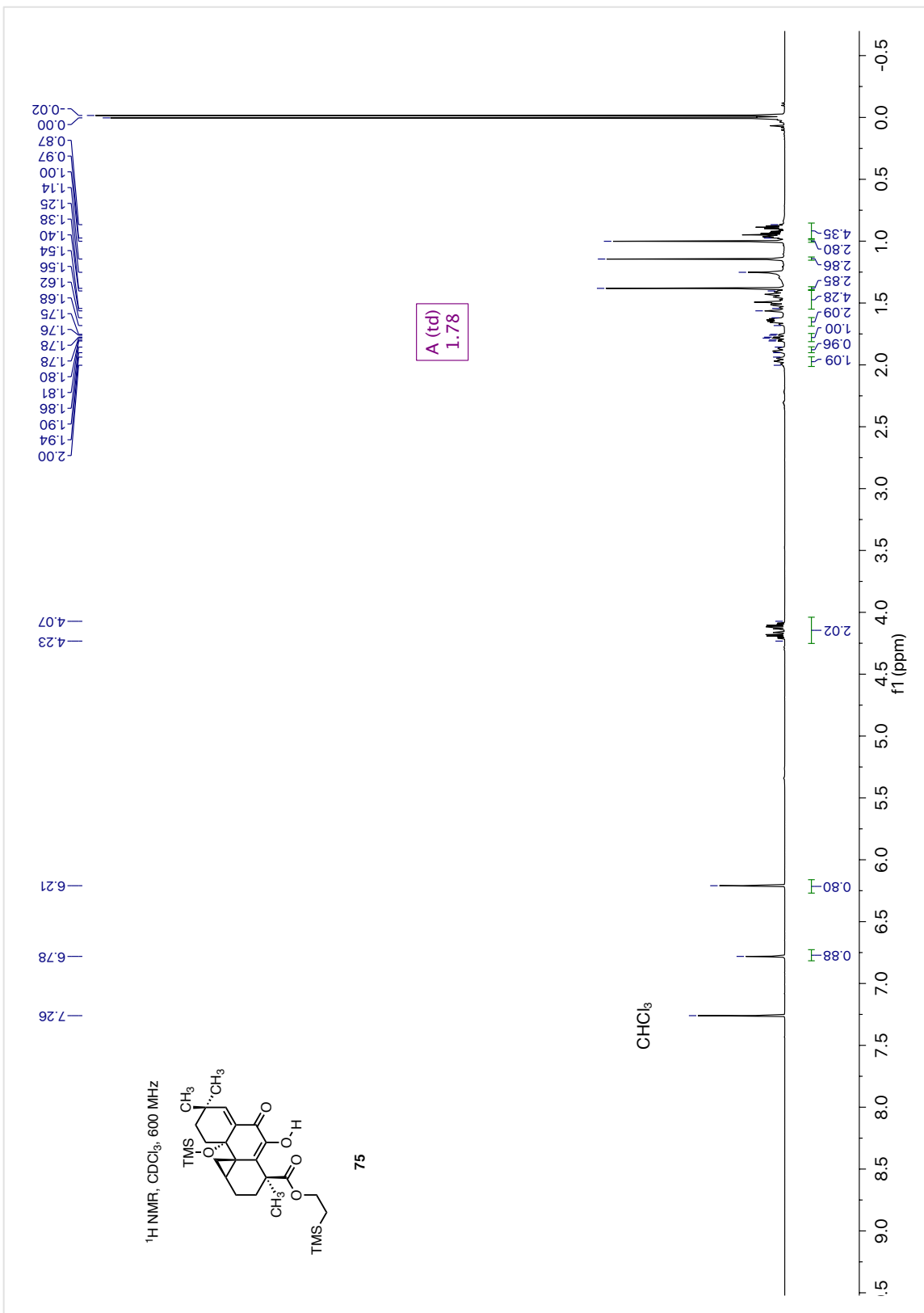


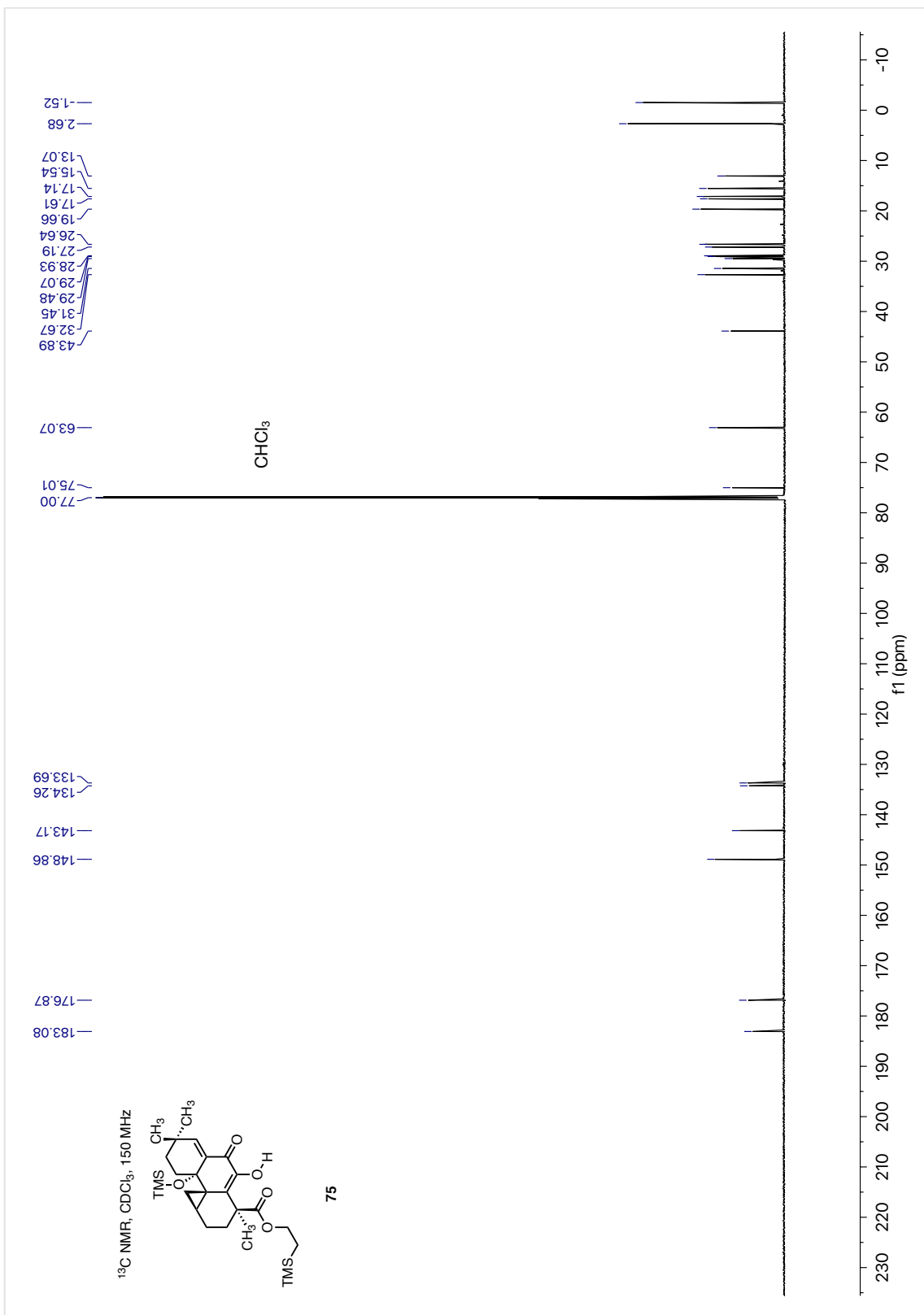


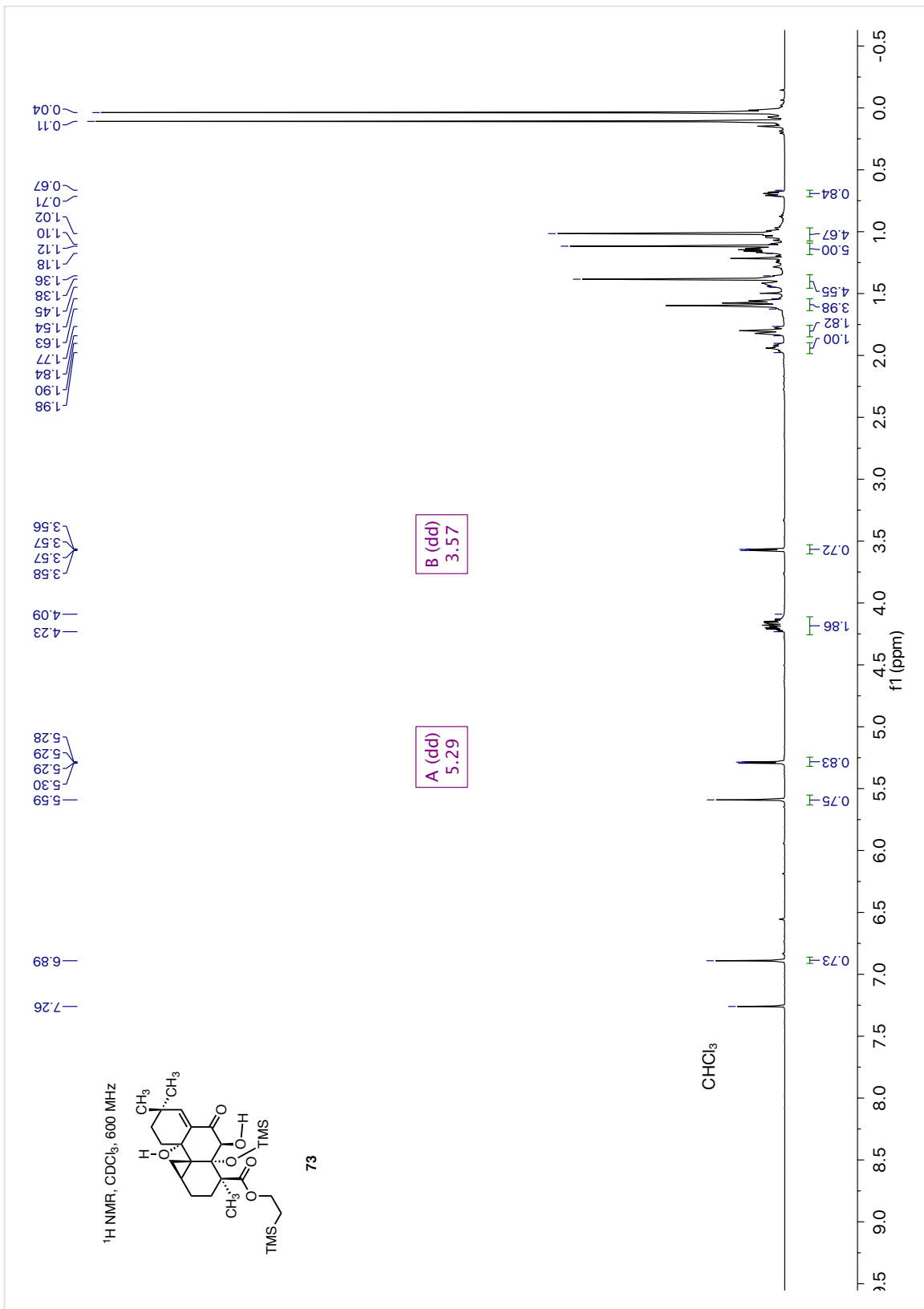


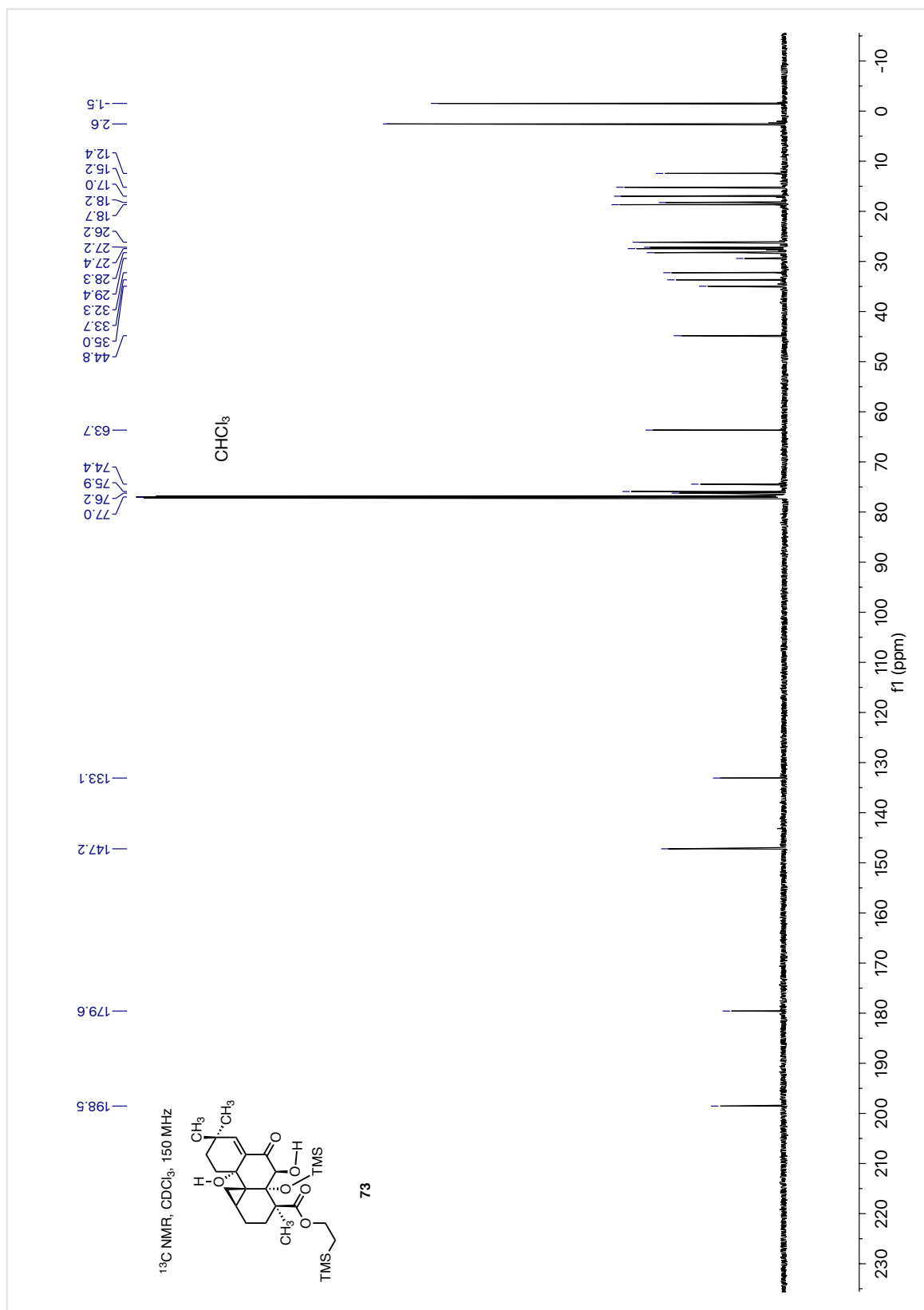




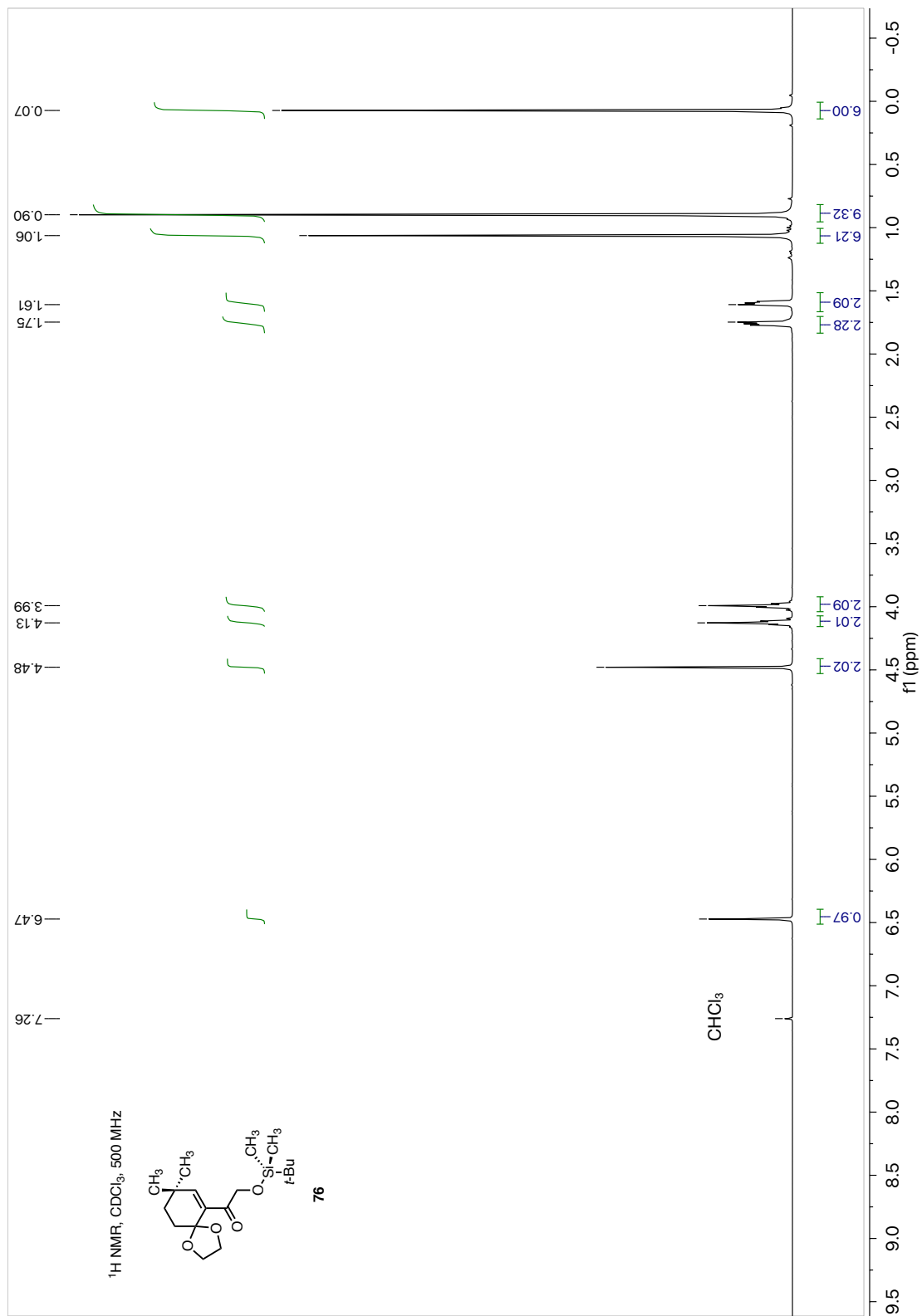


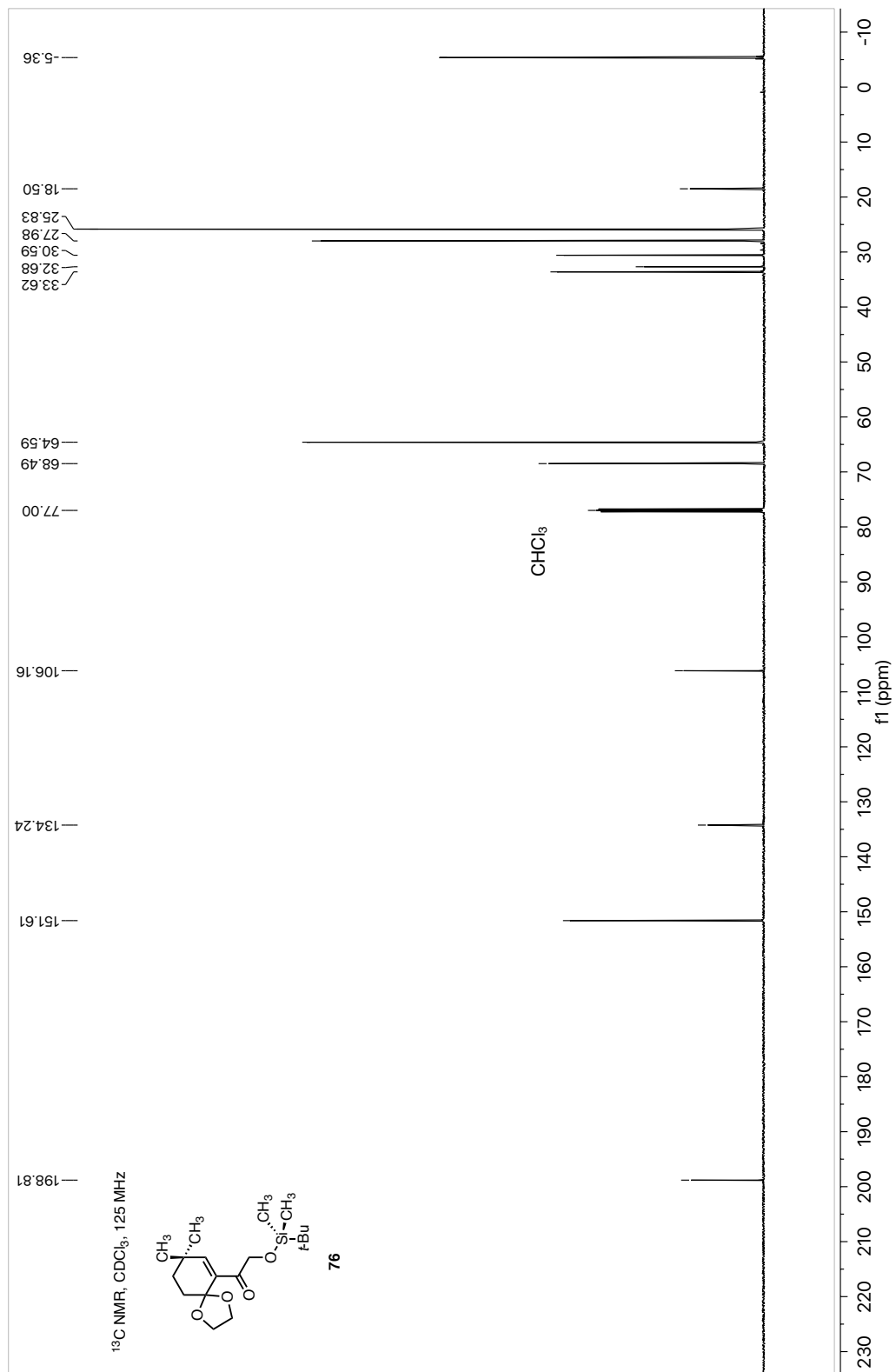


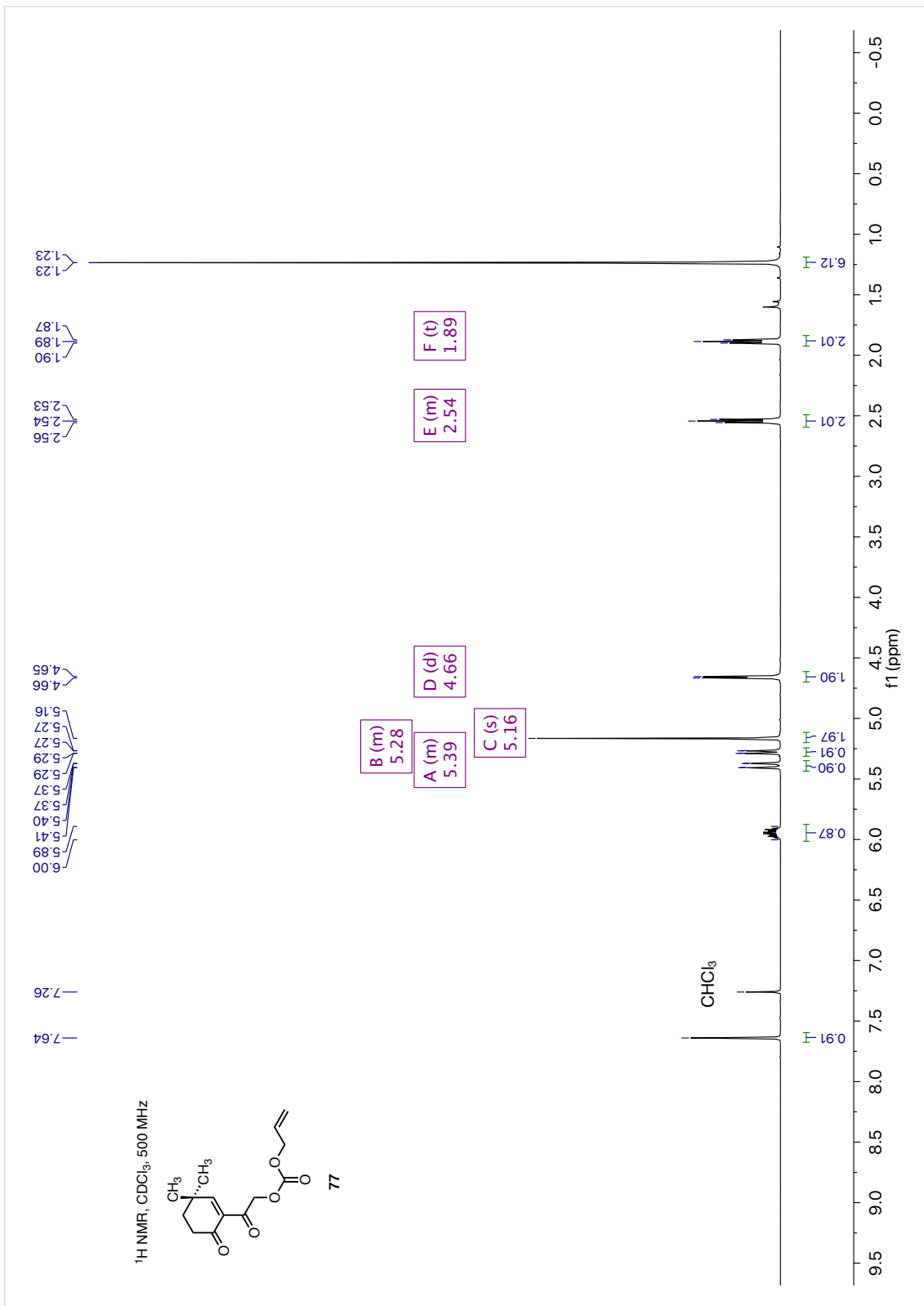


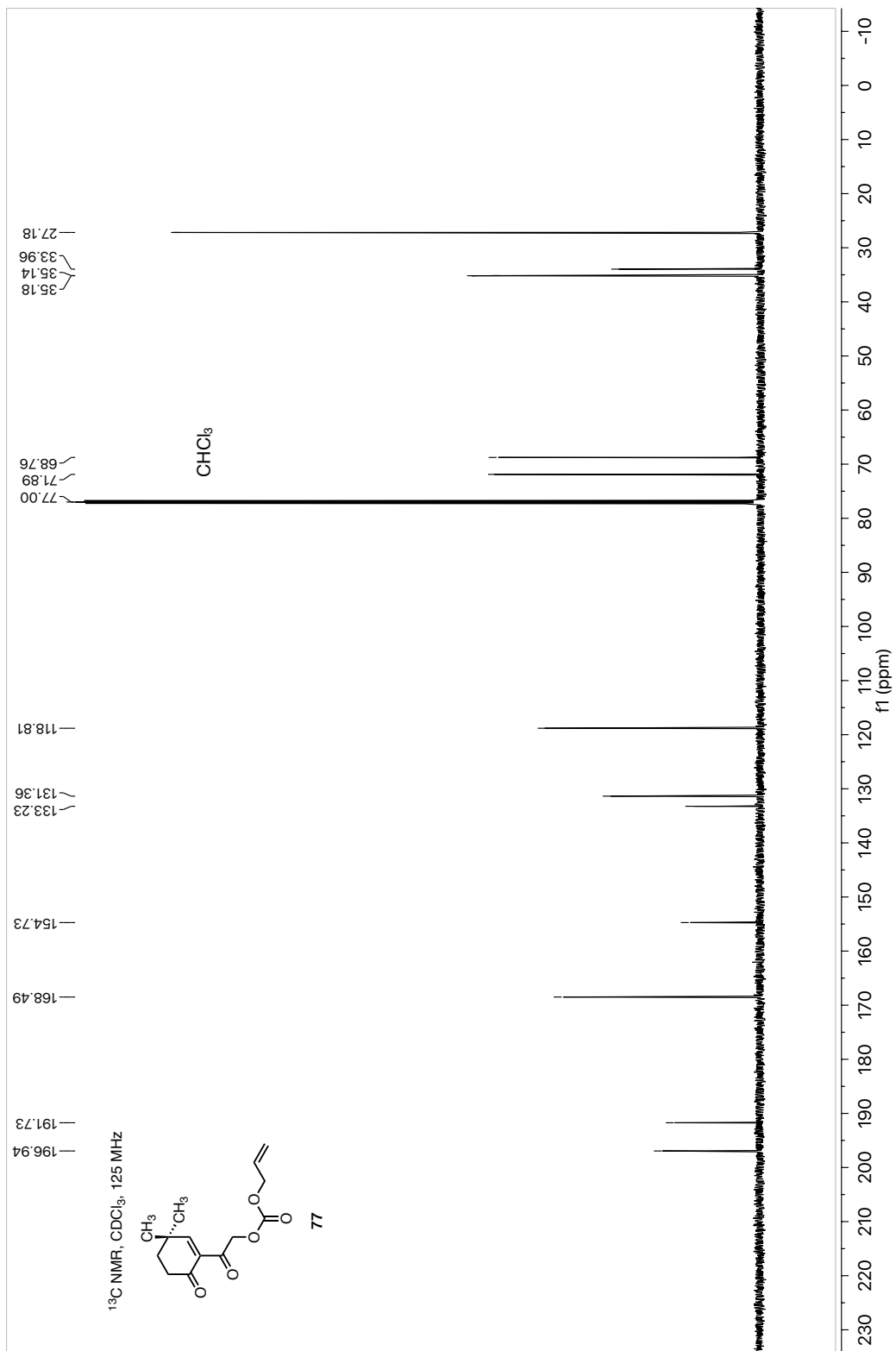


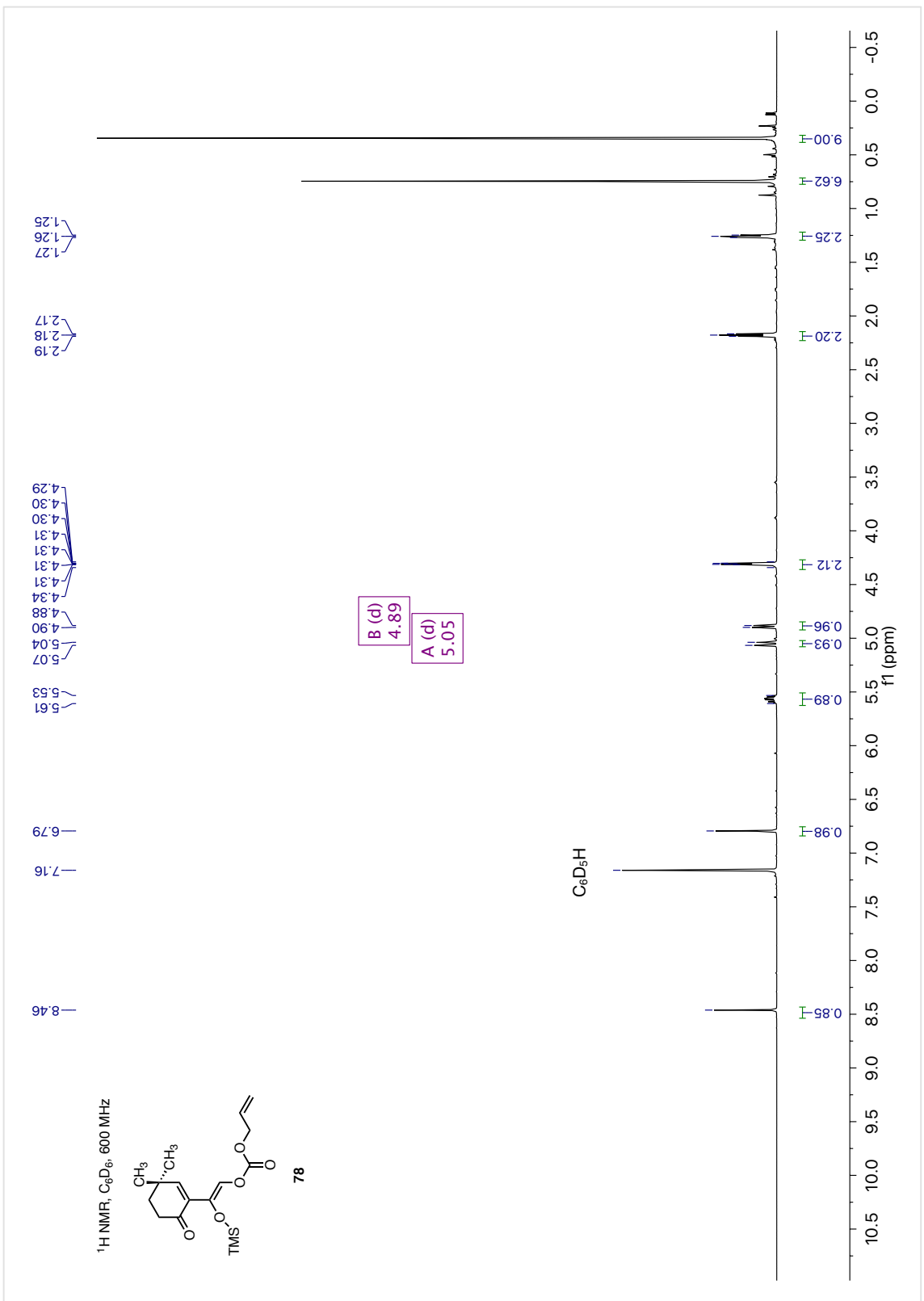


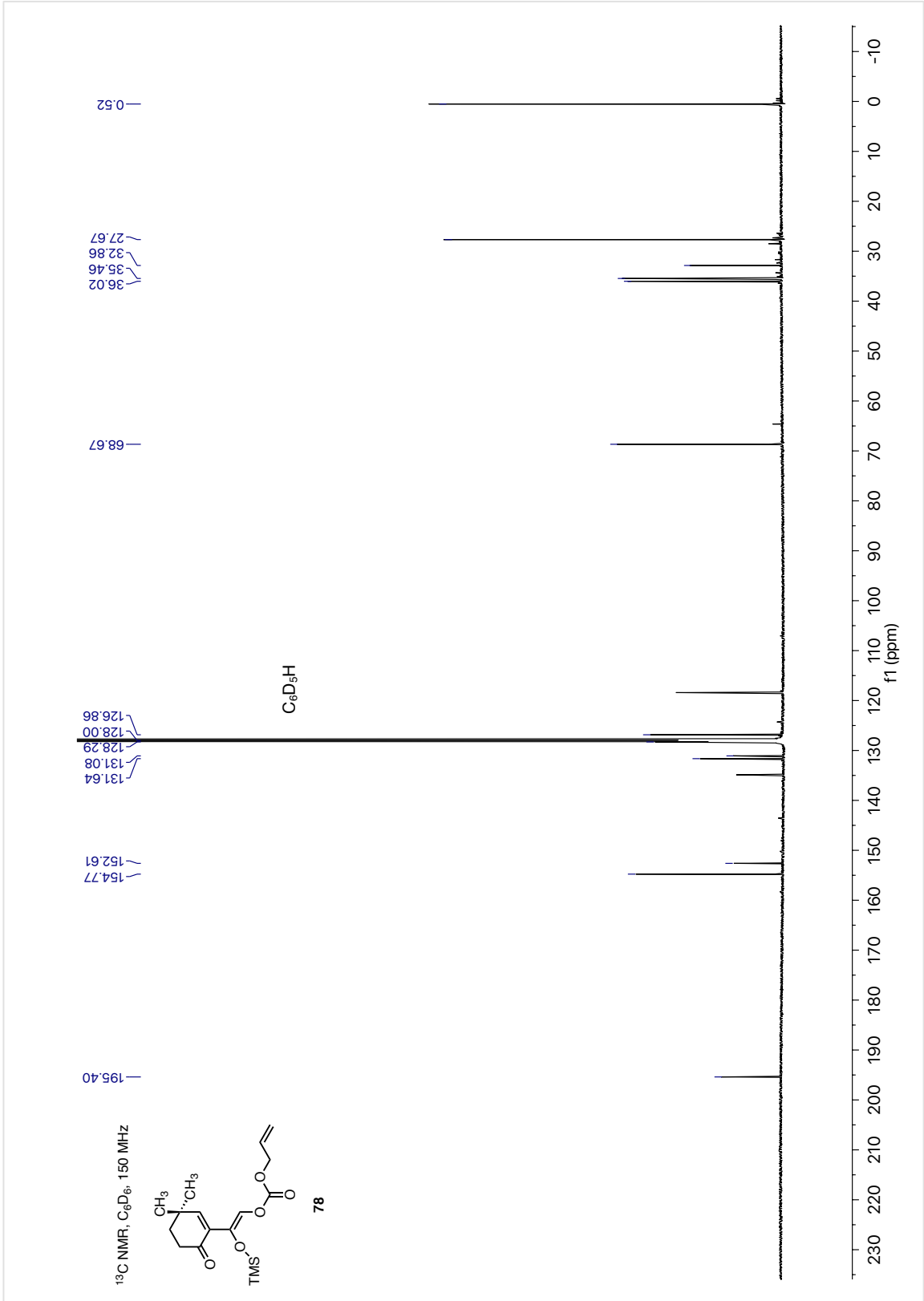


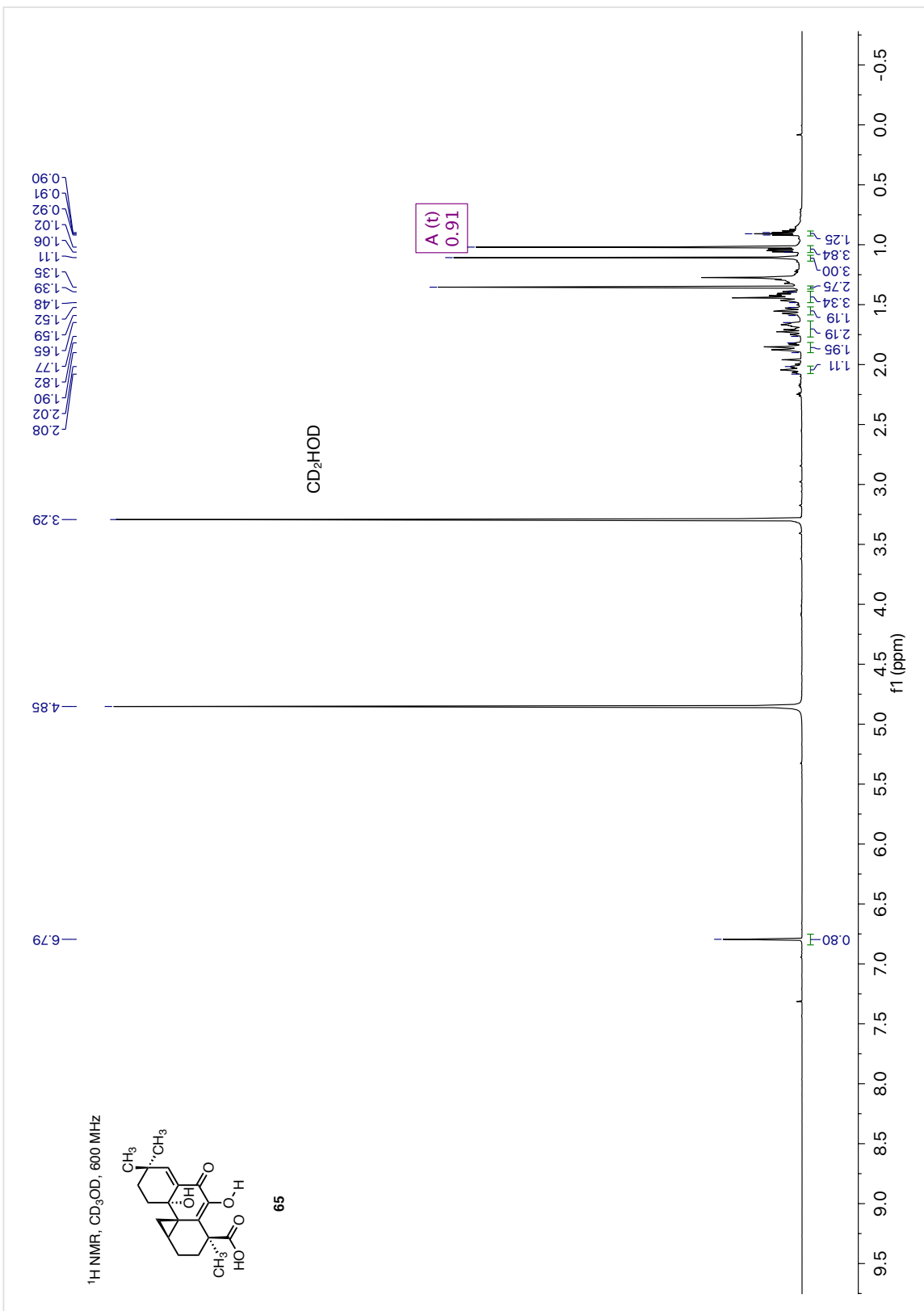


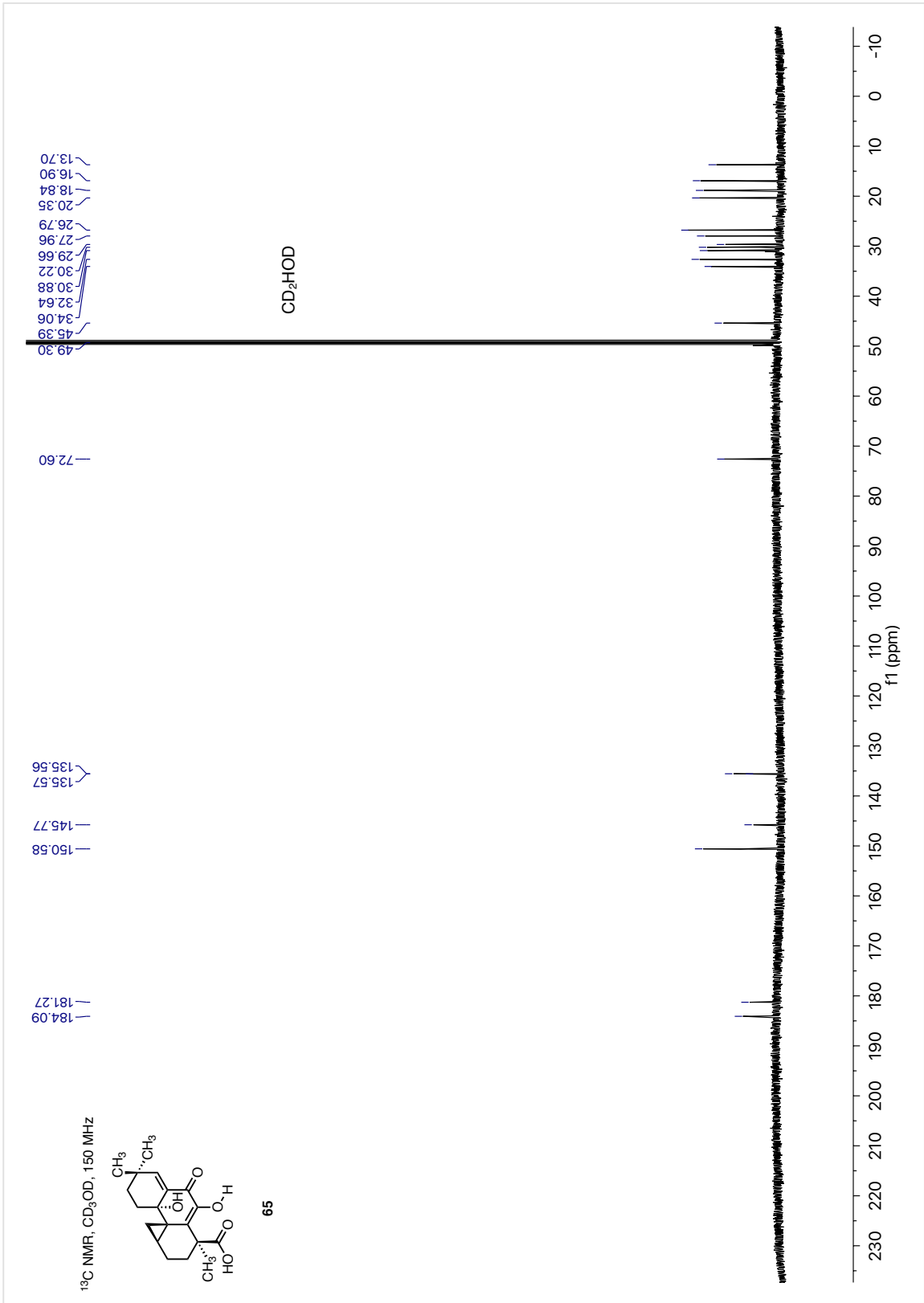




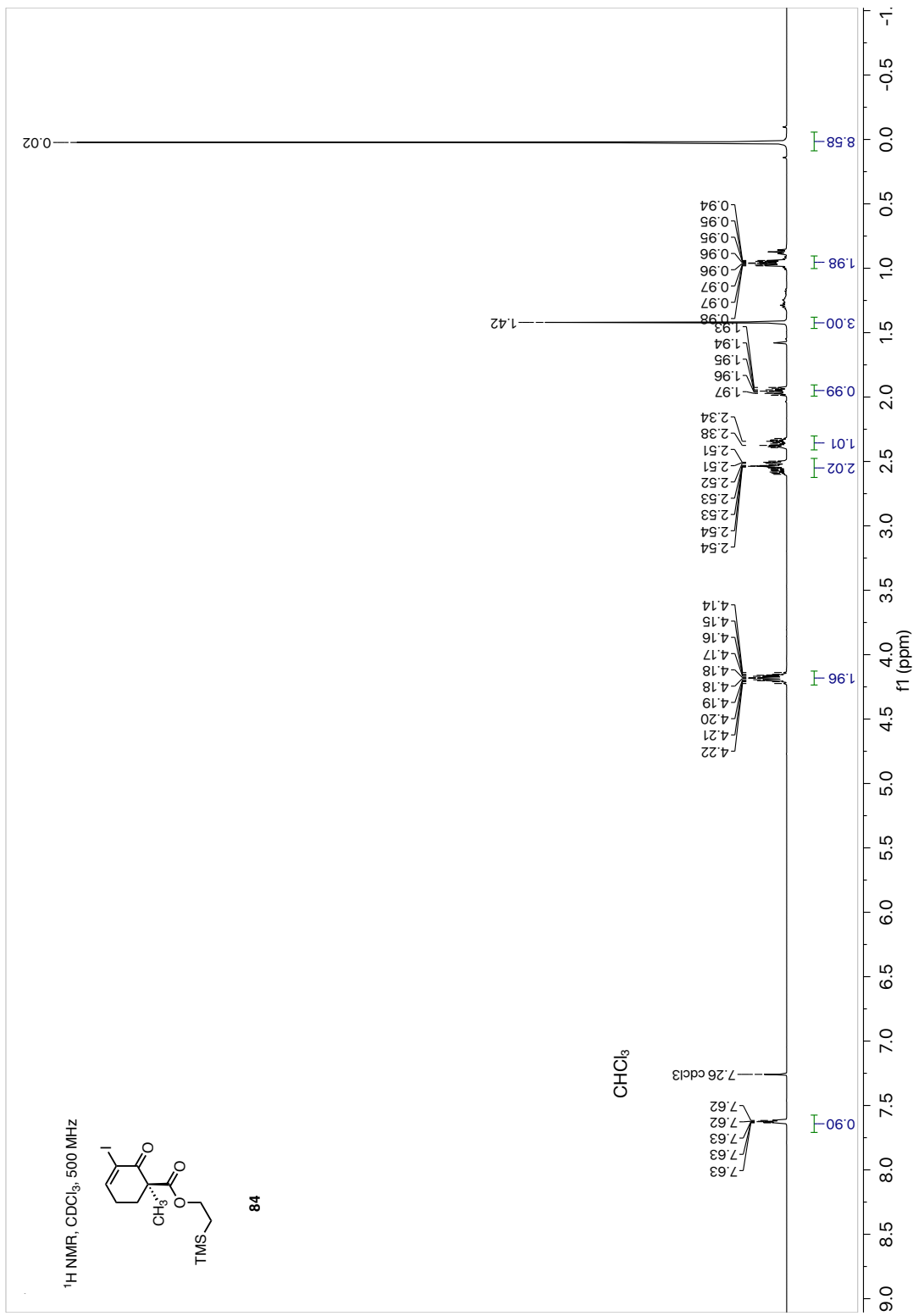


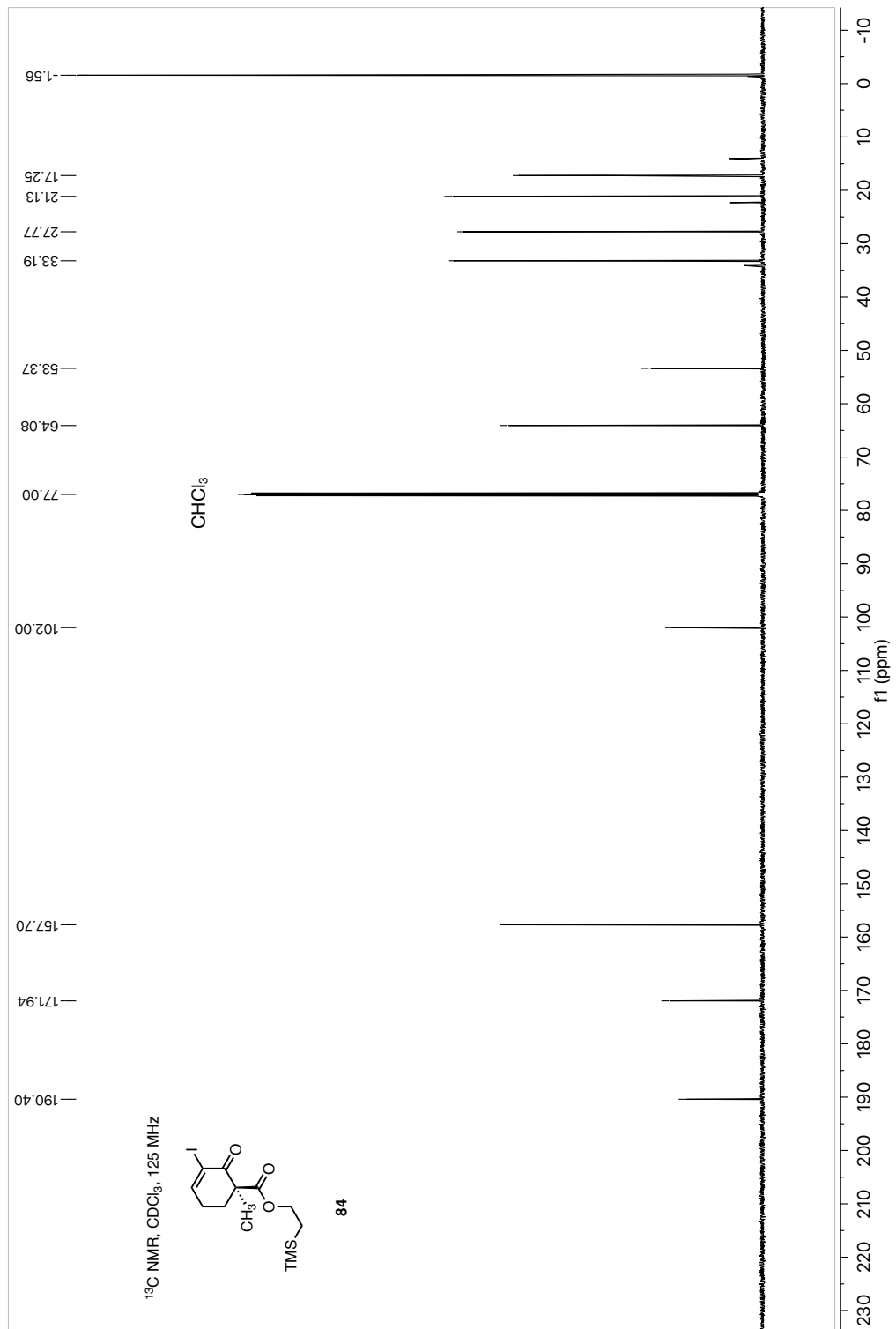




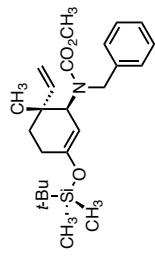




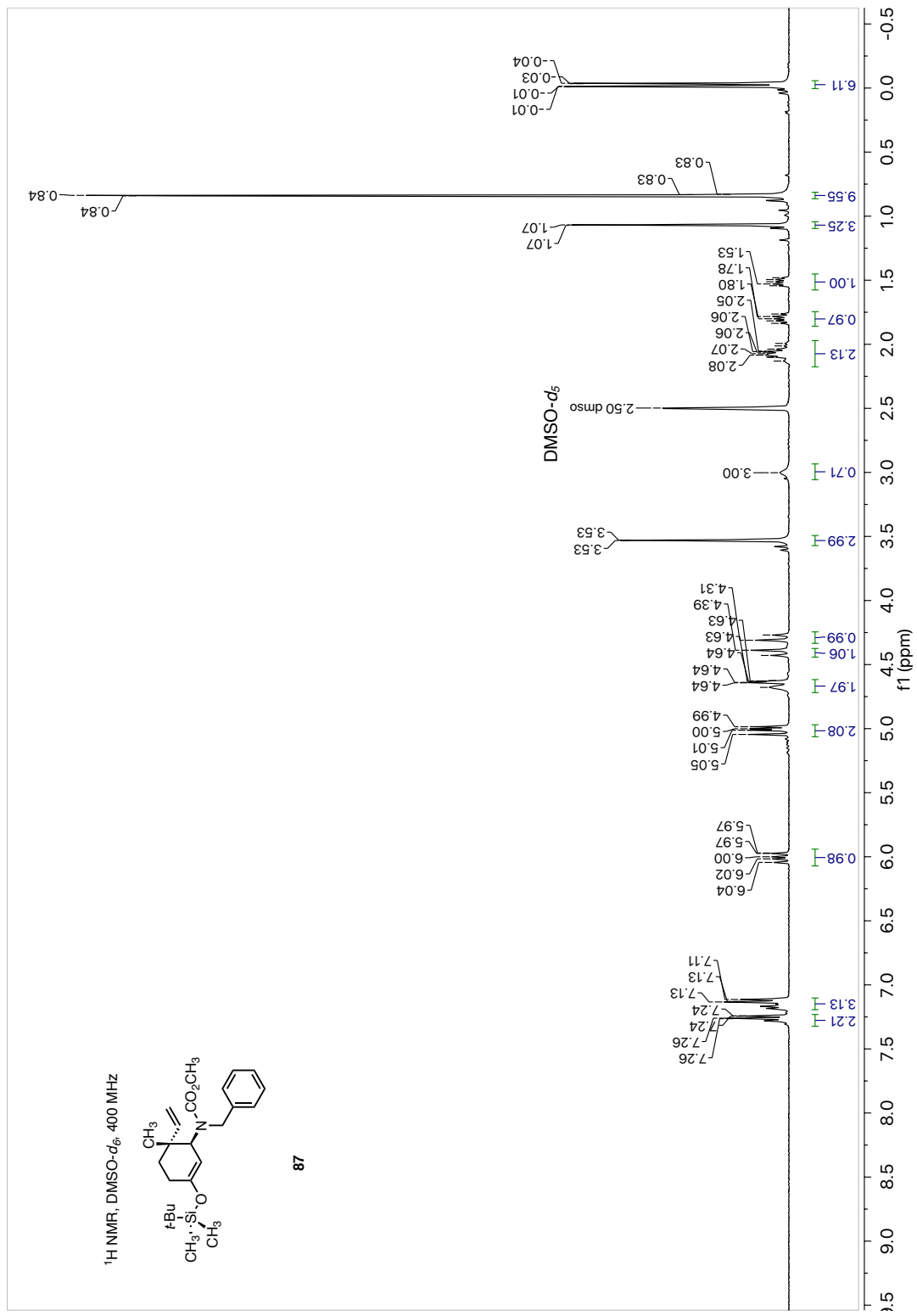


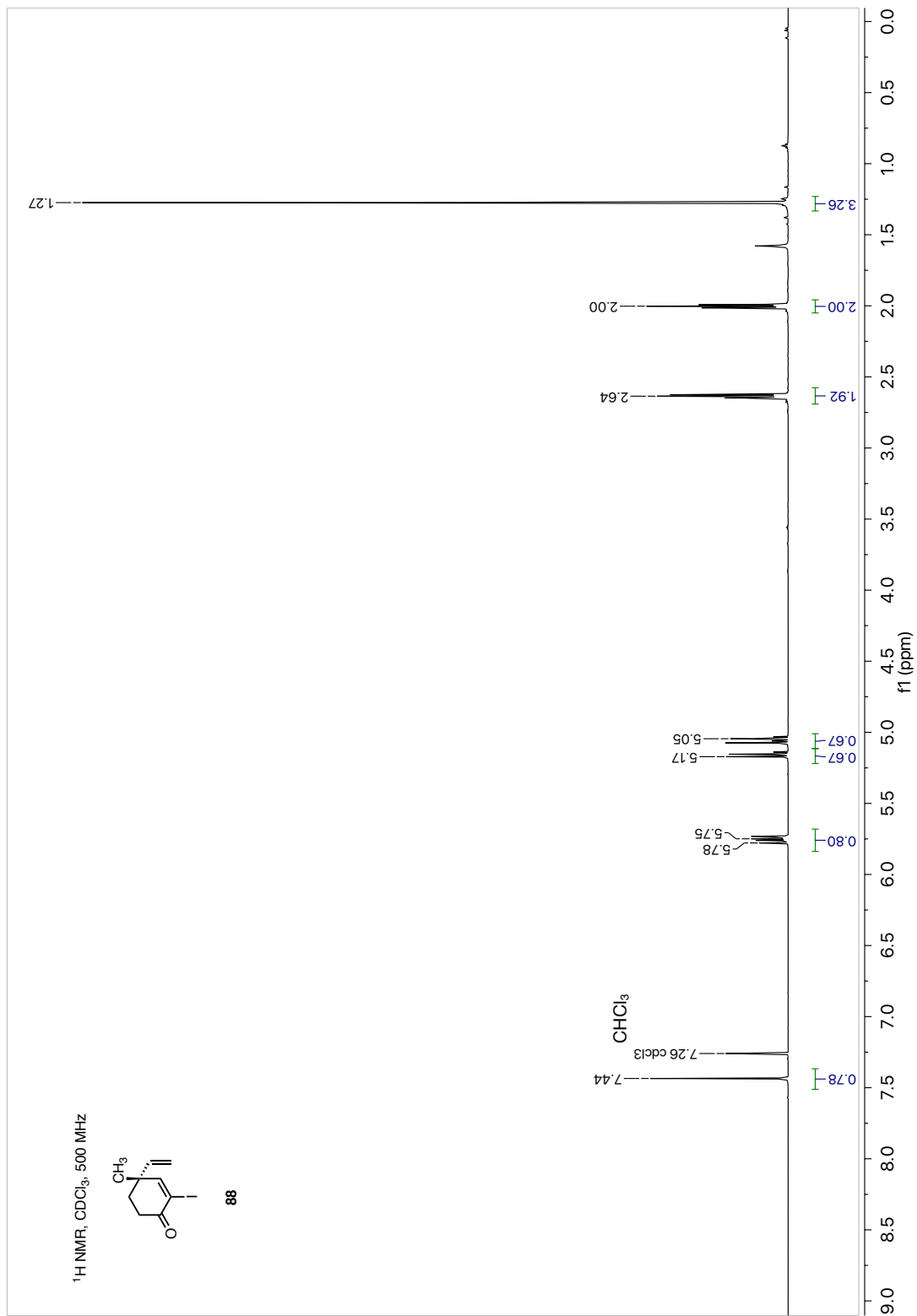


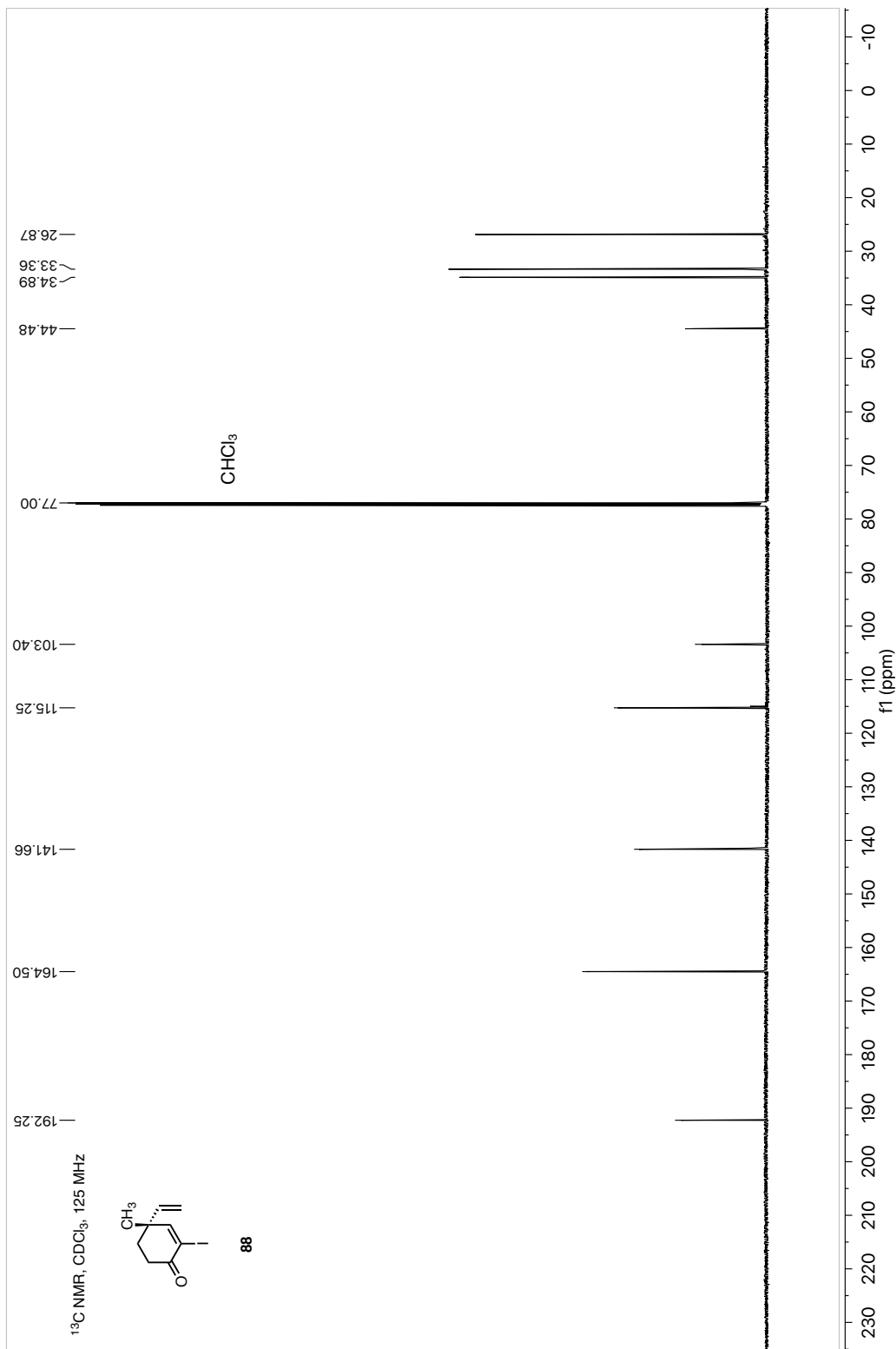
<sup>1</sup>H NMR, DMSO-d<sub>6</sub>, 400 MHz

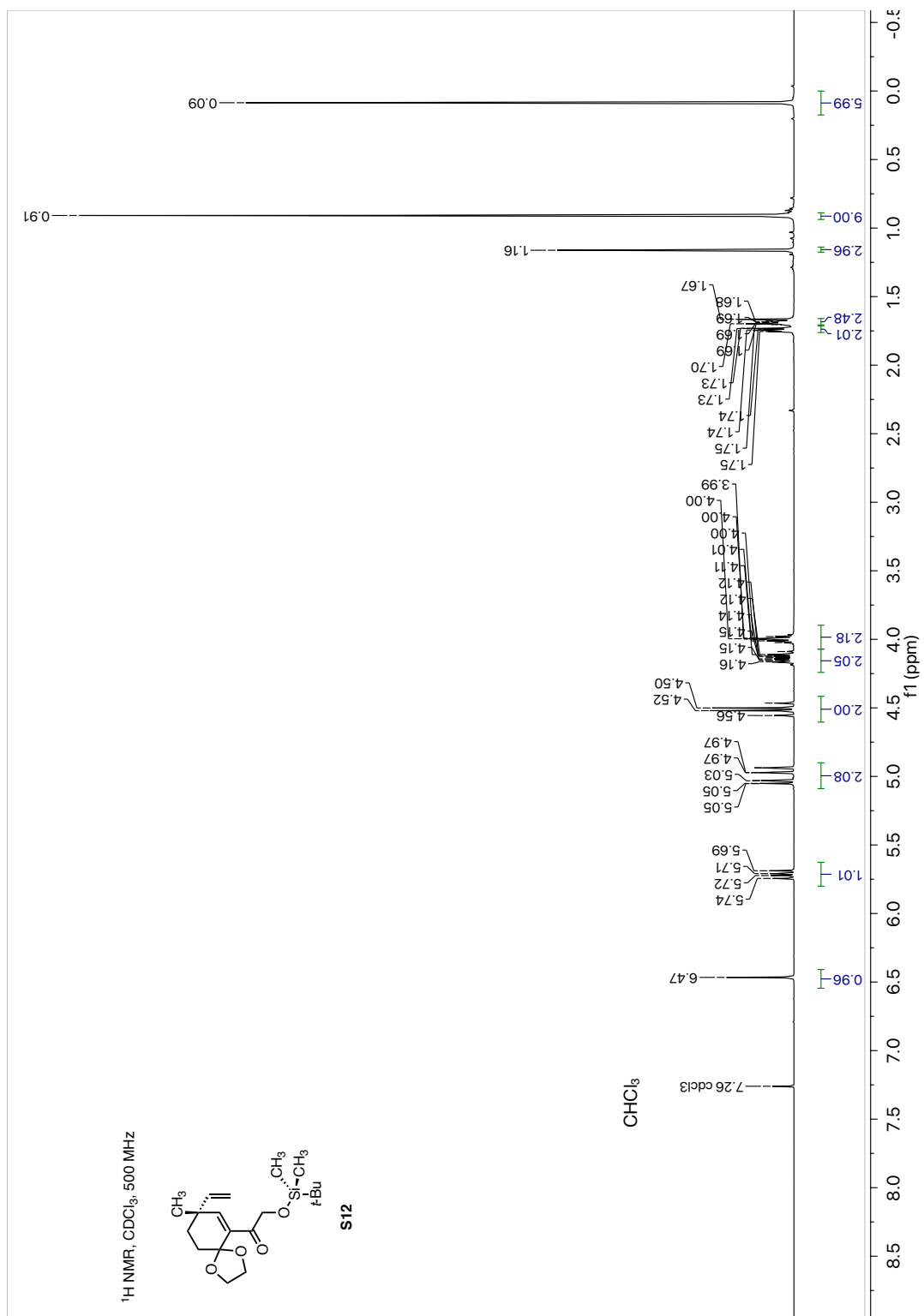


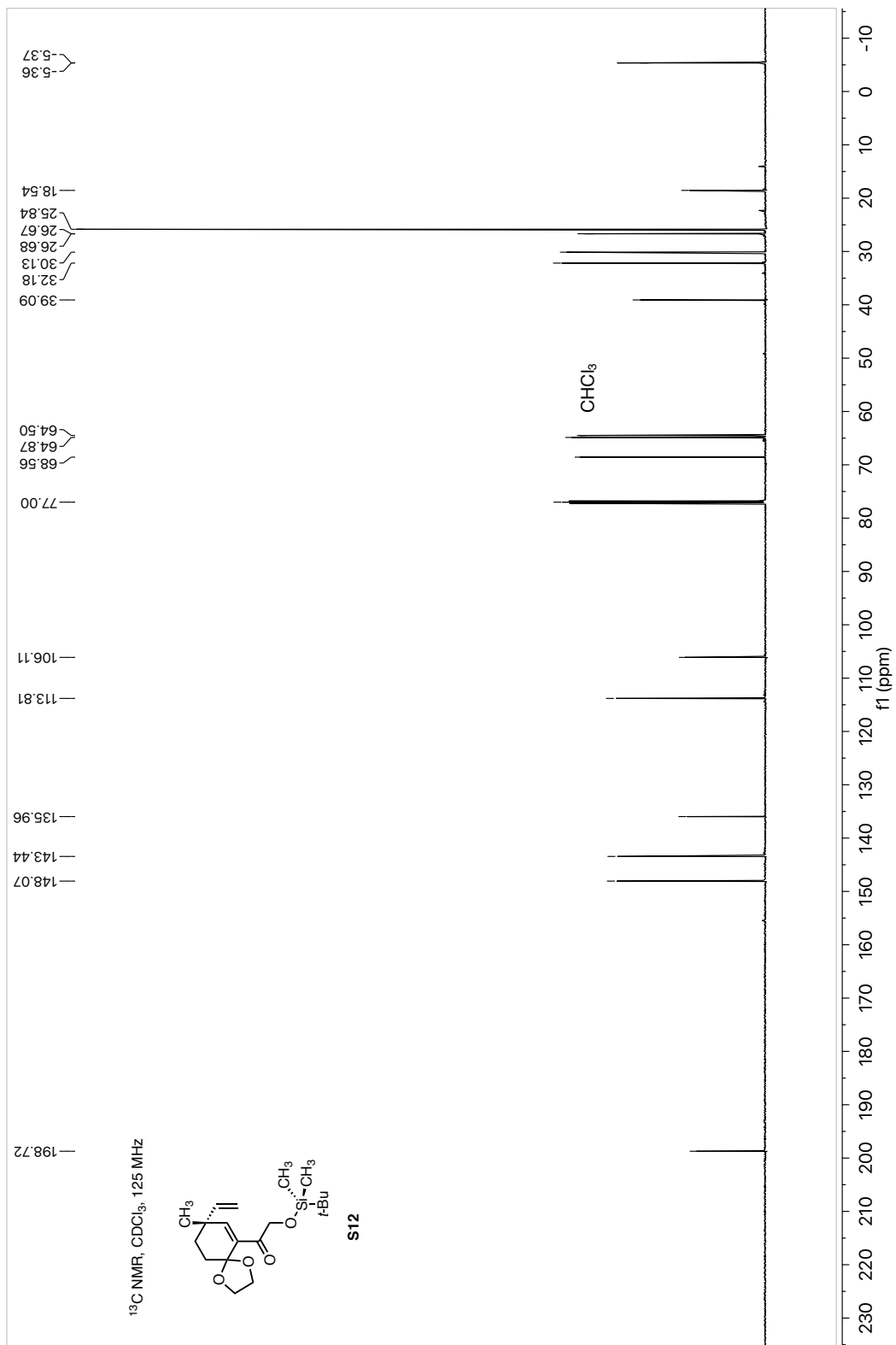
87

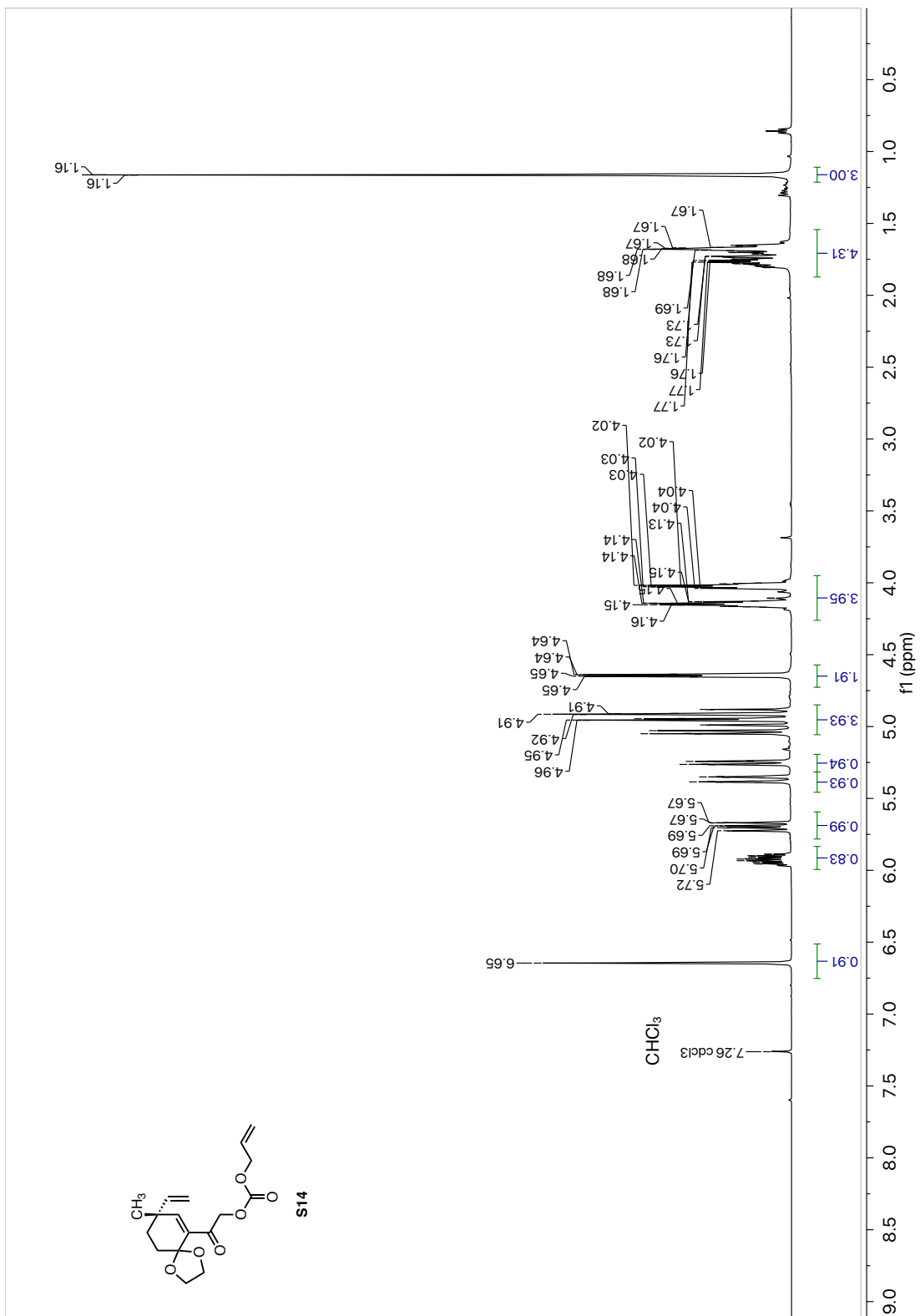




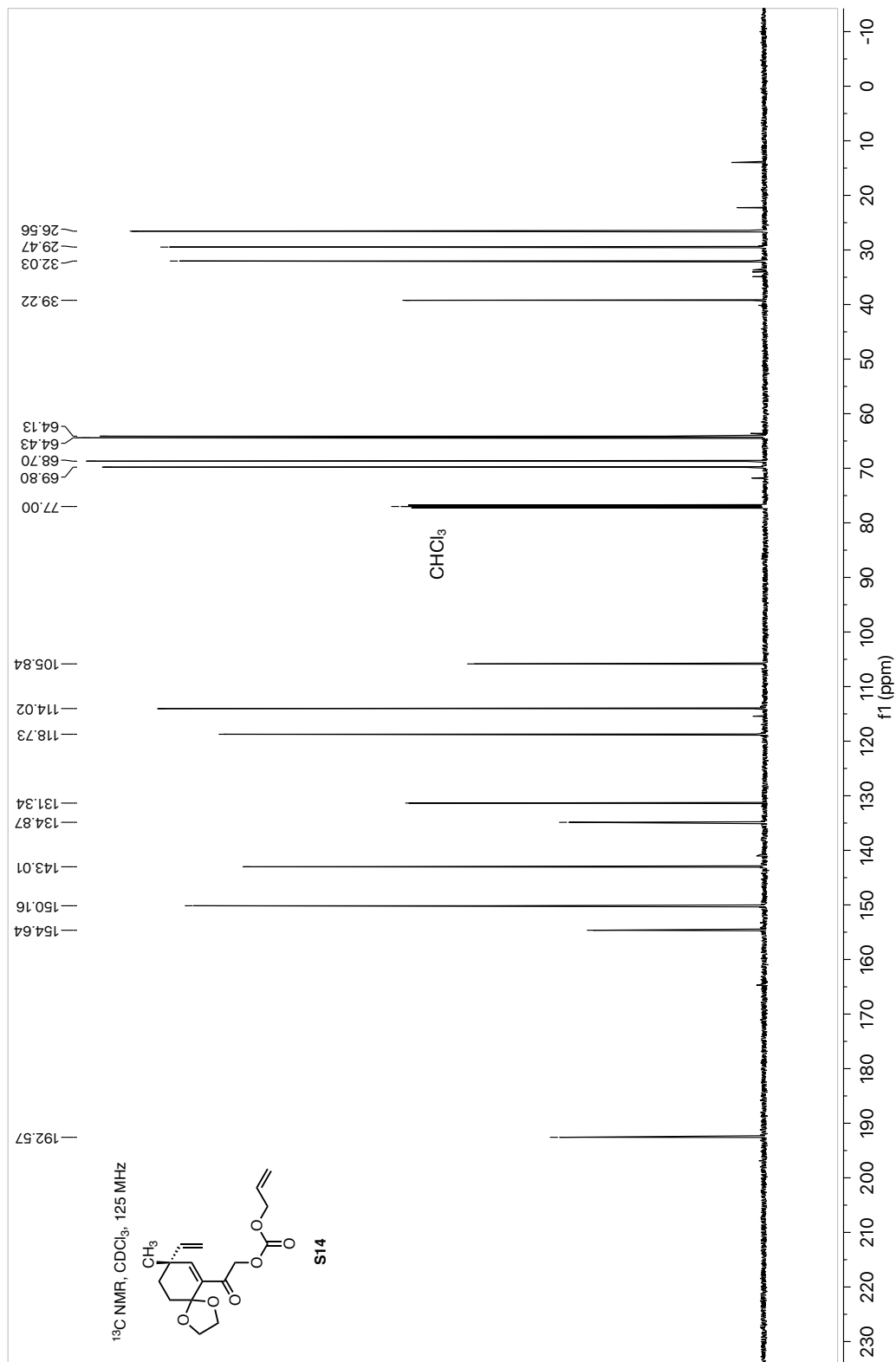


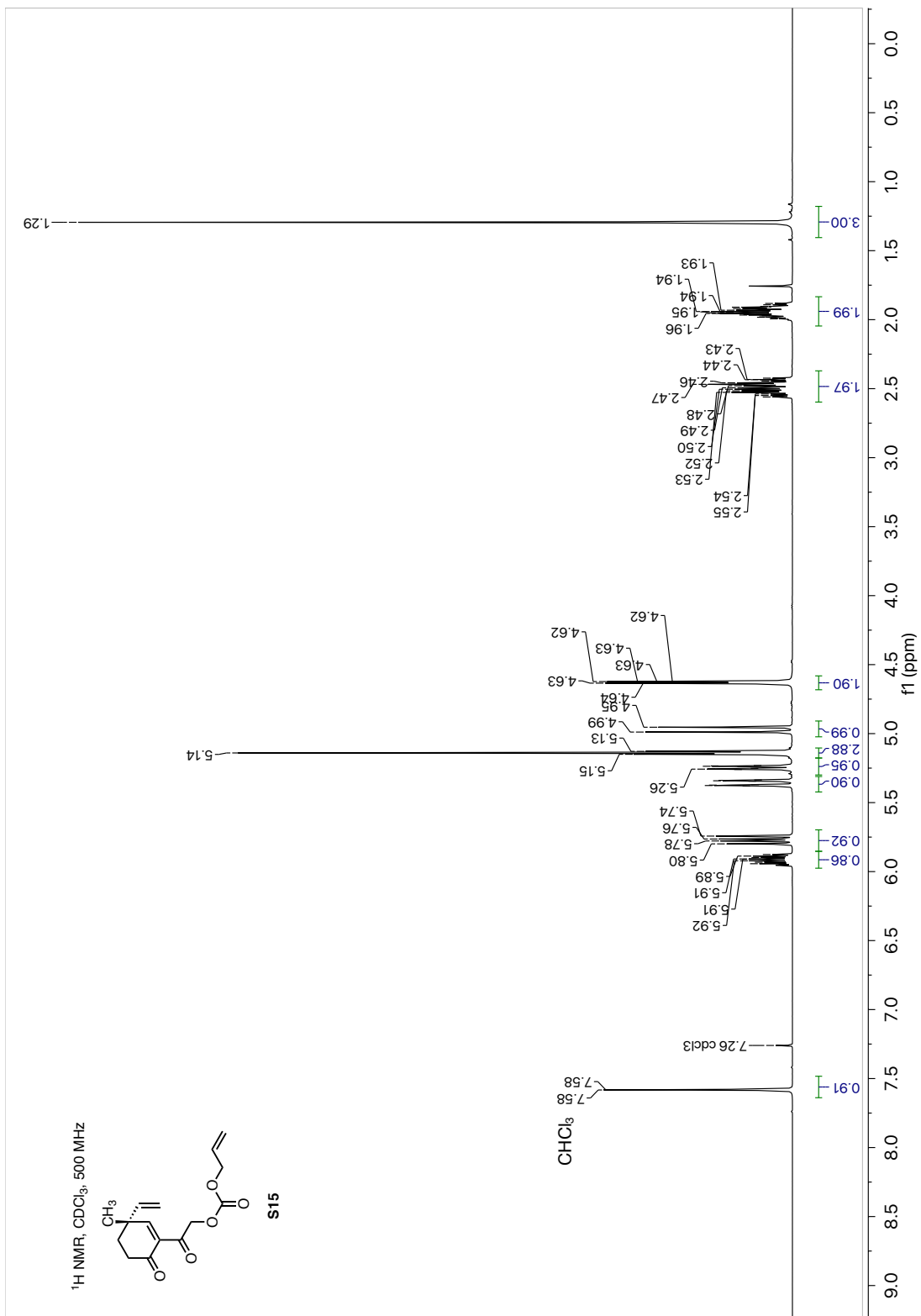


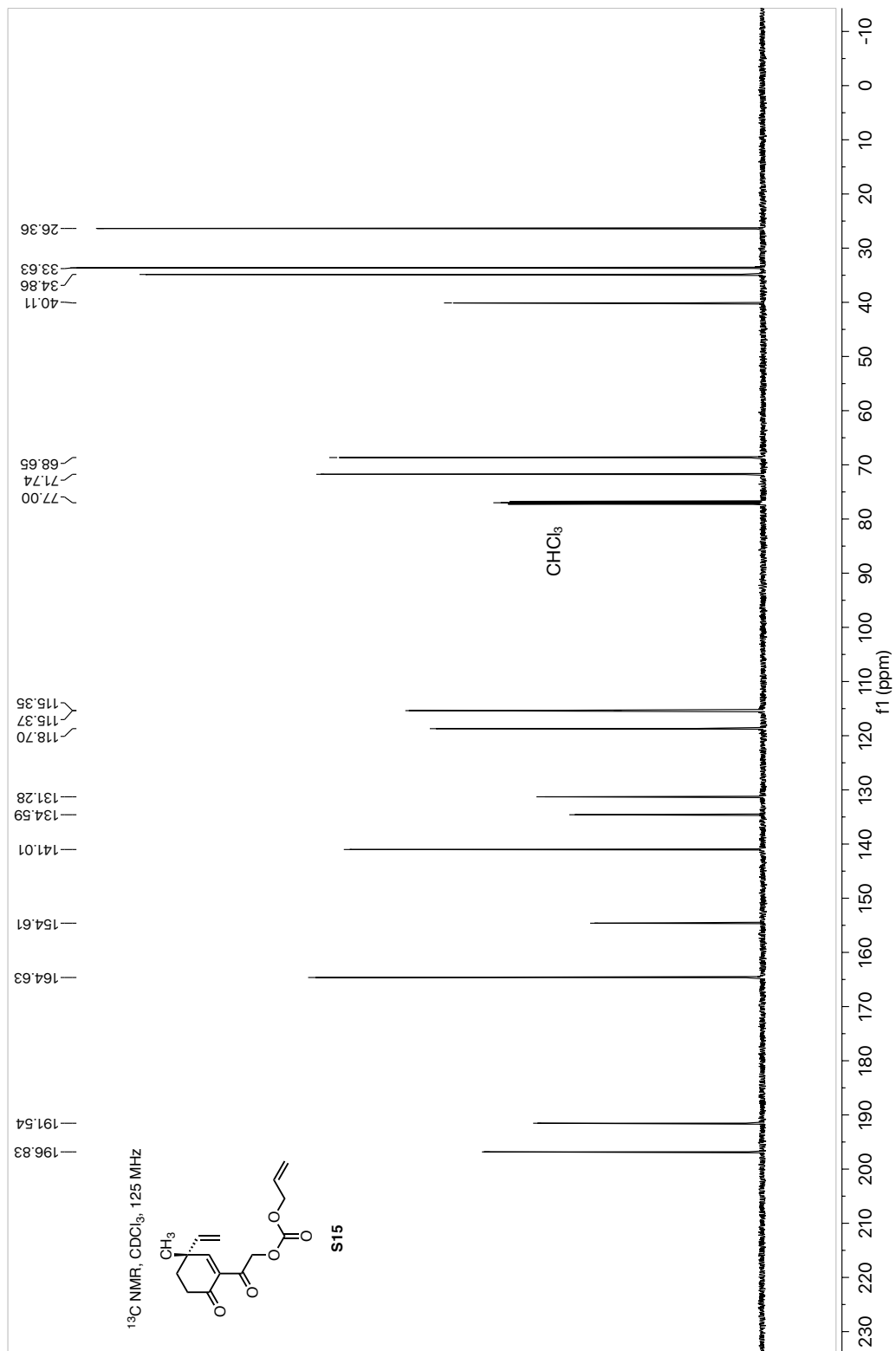


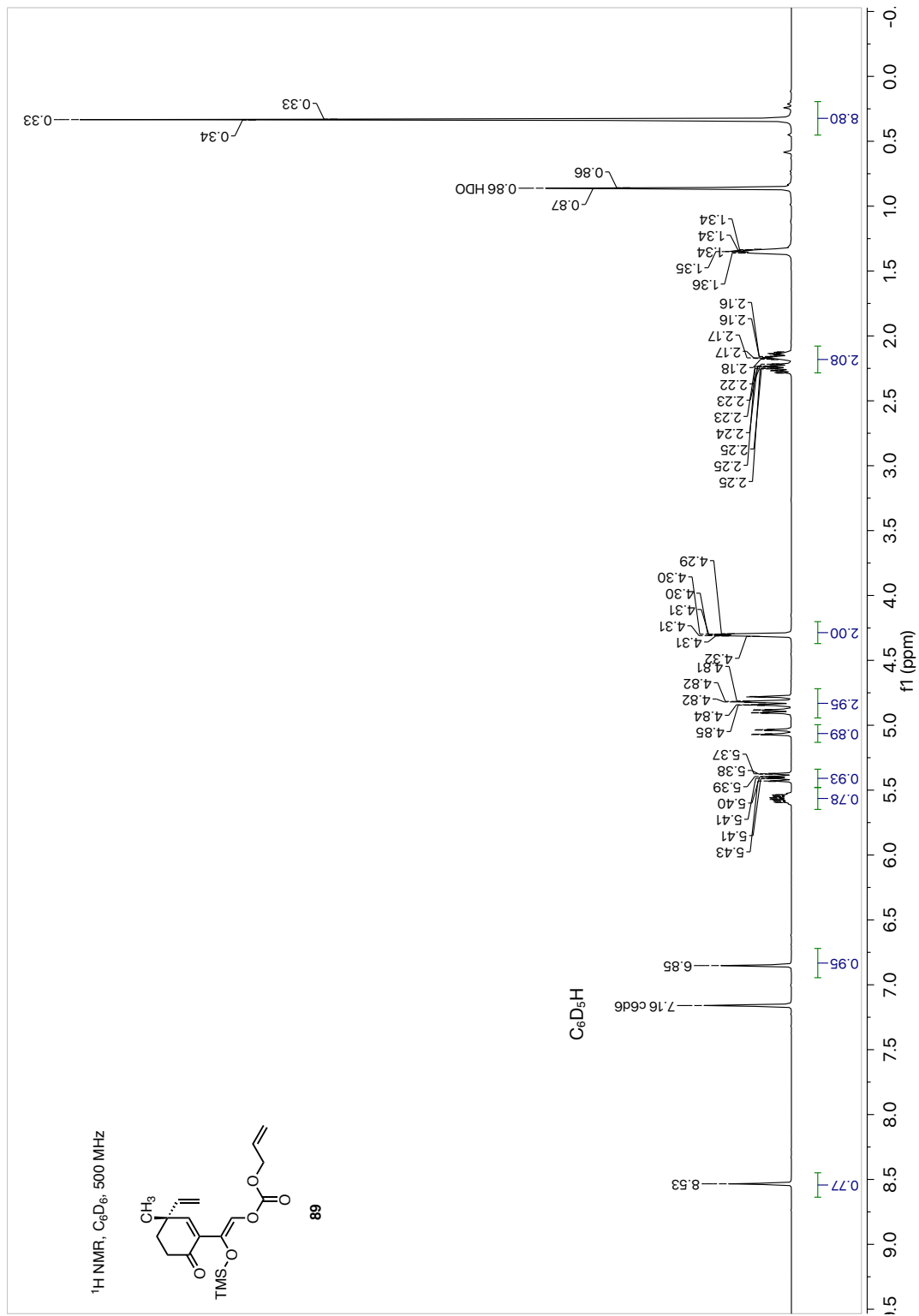


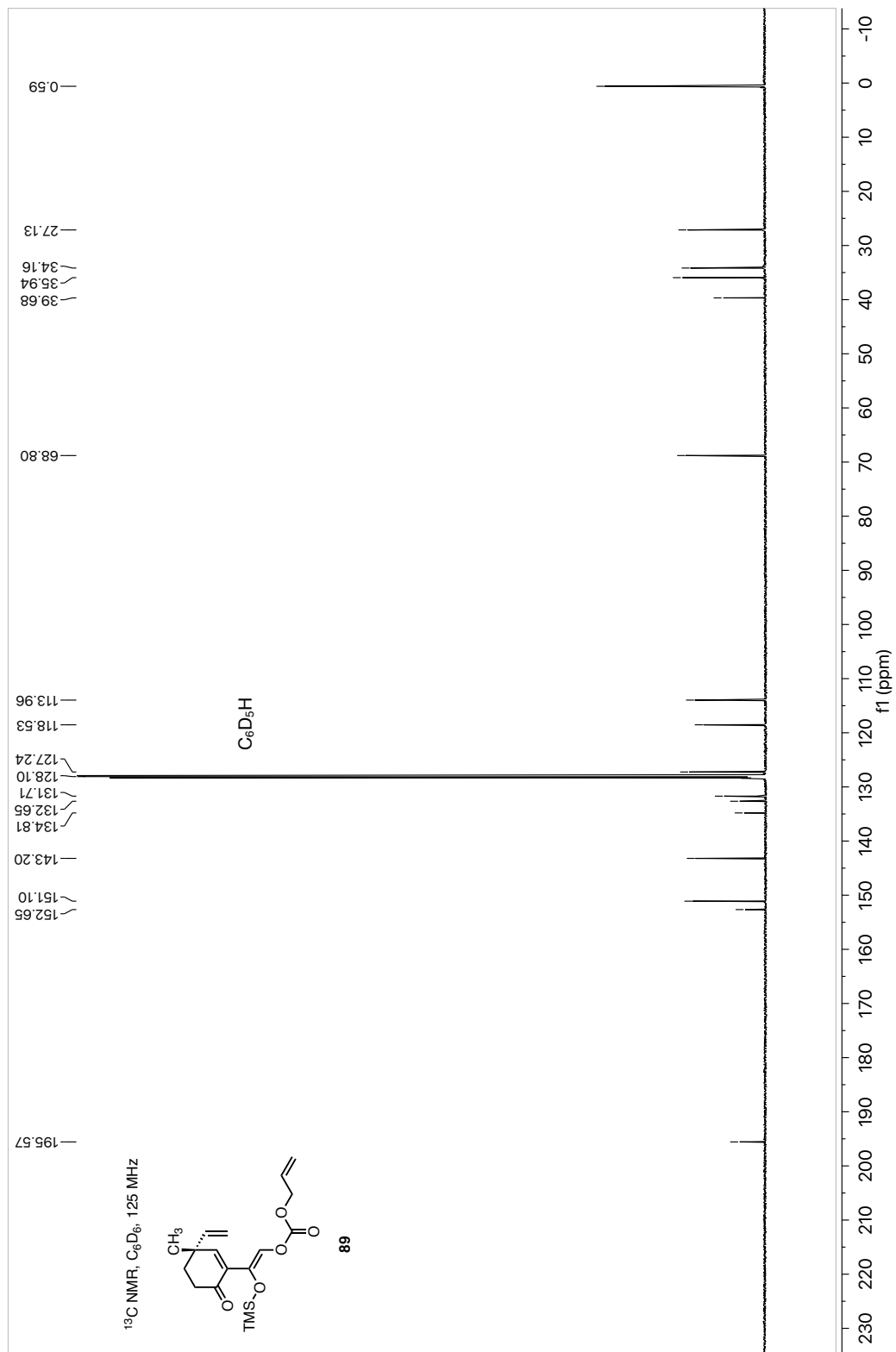


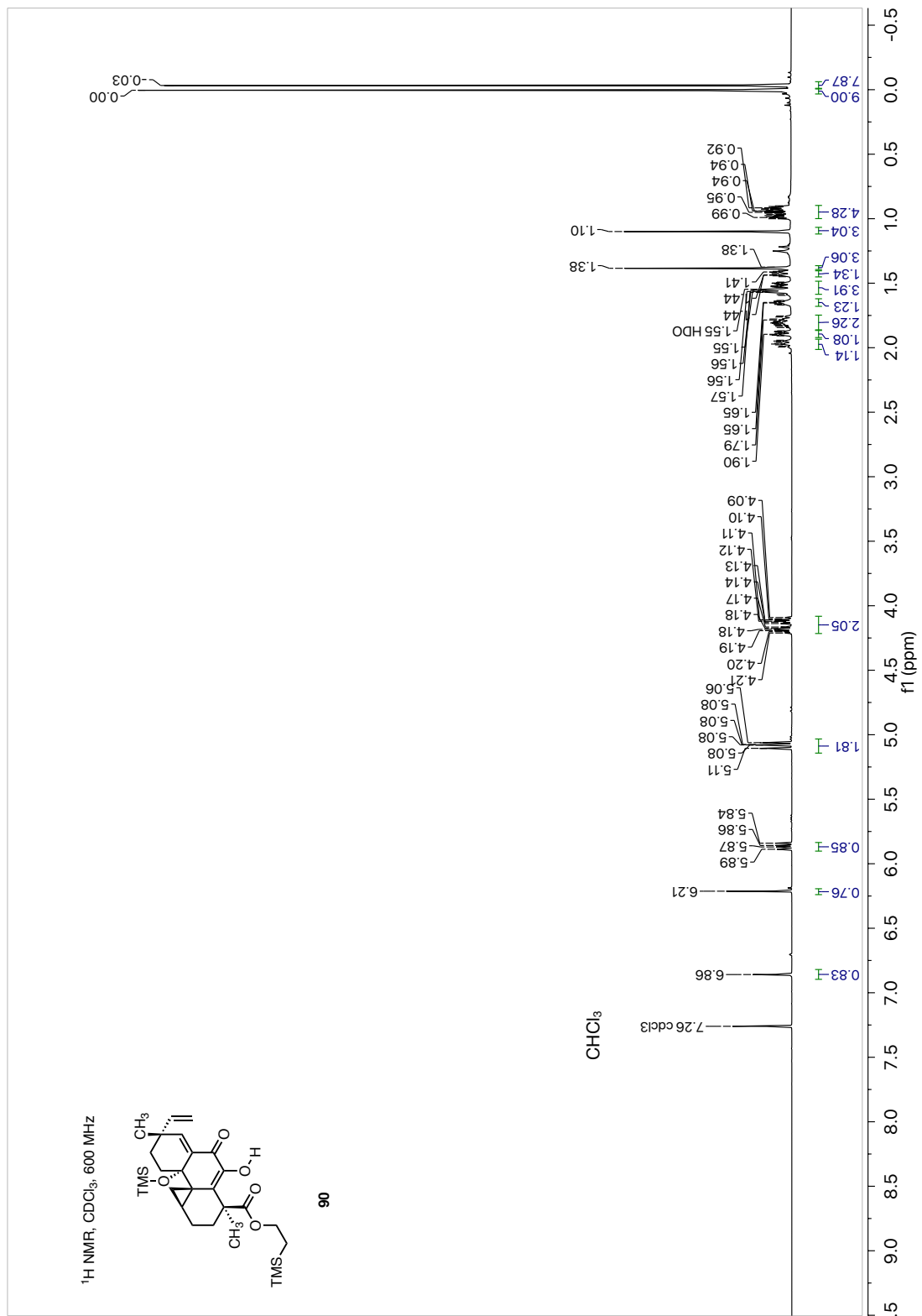


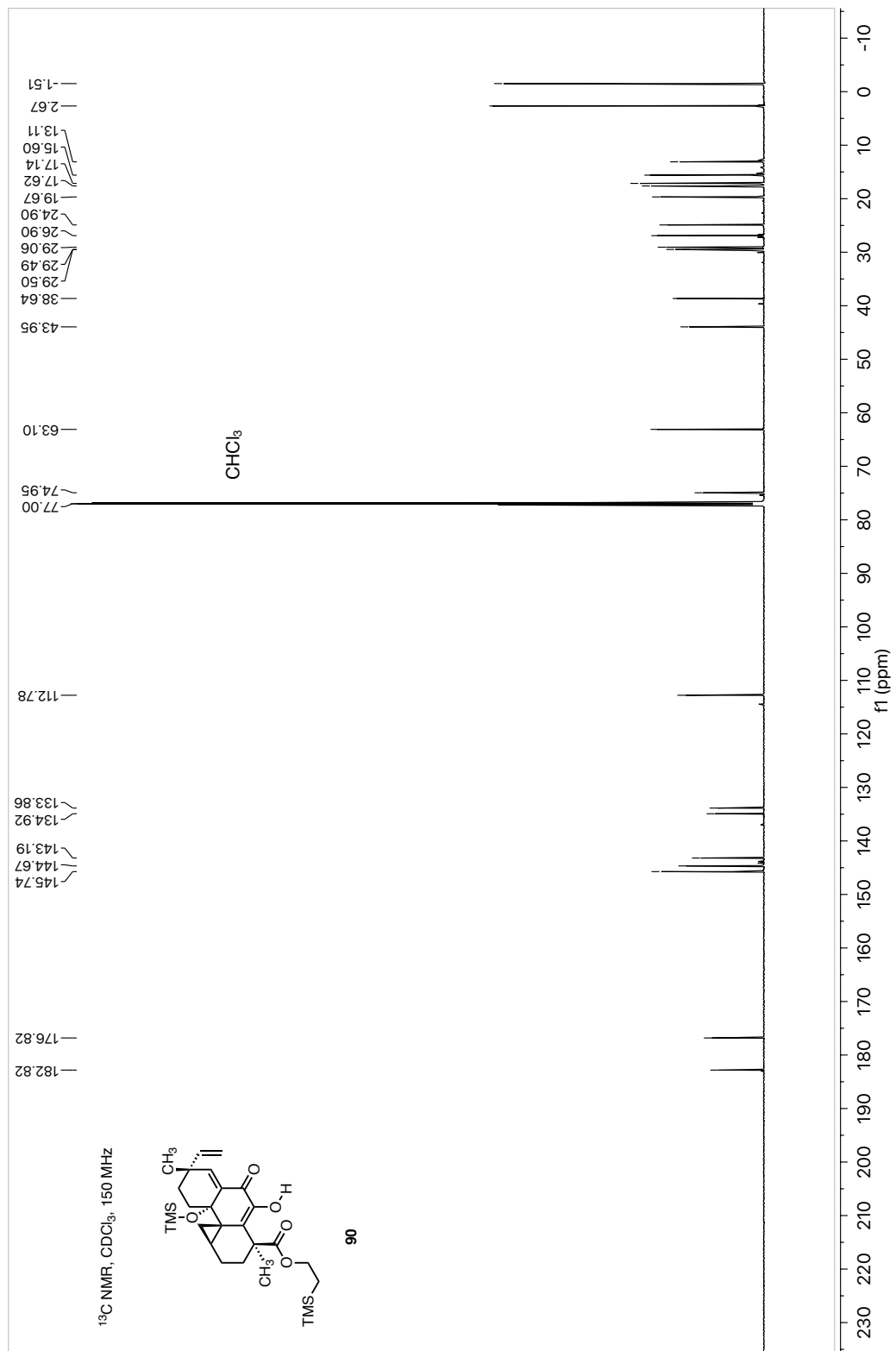


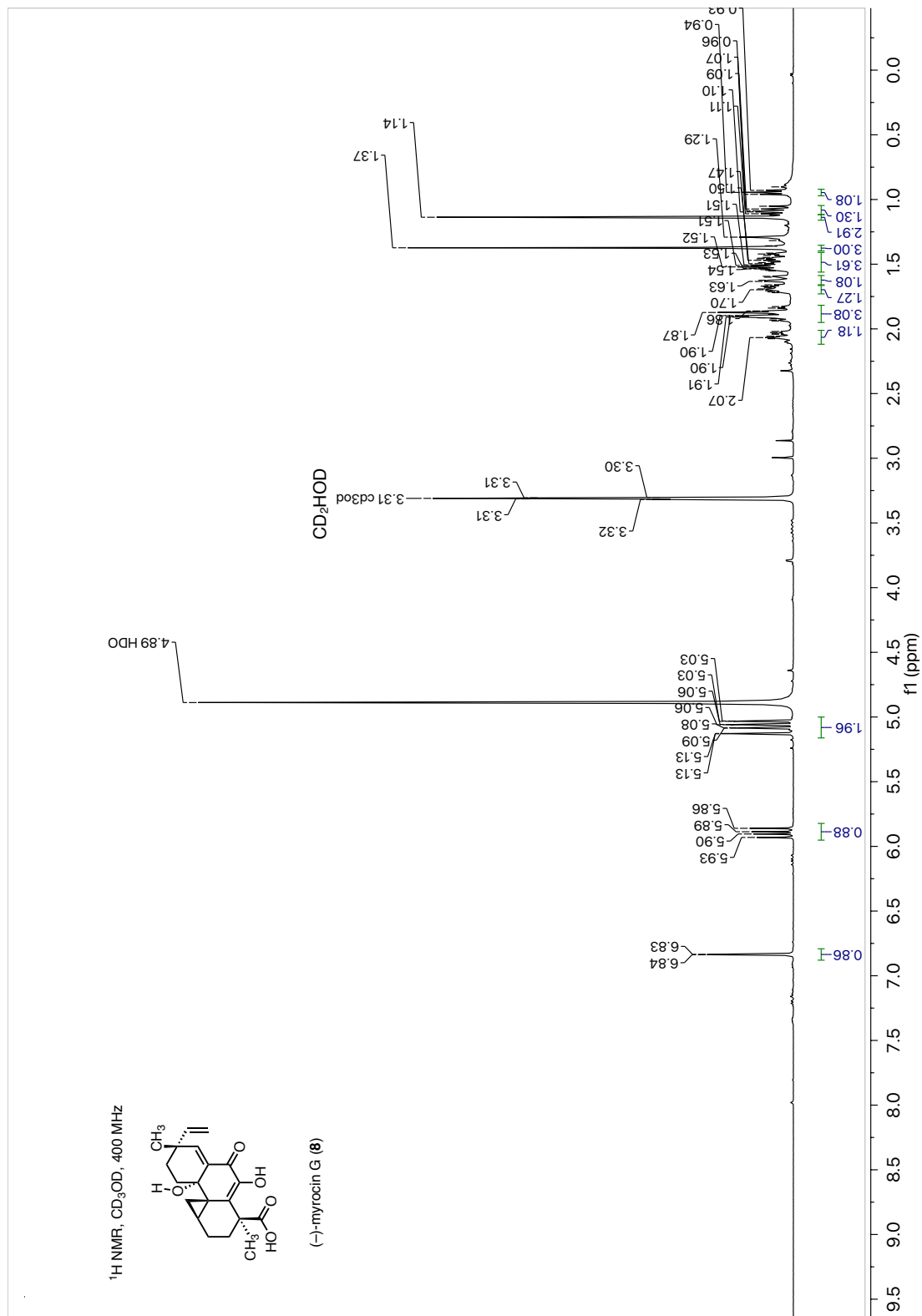




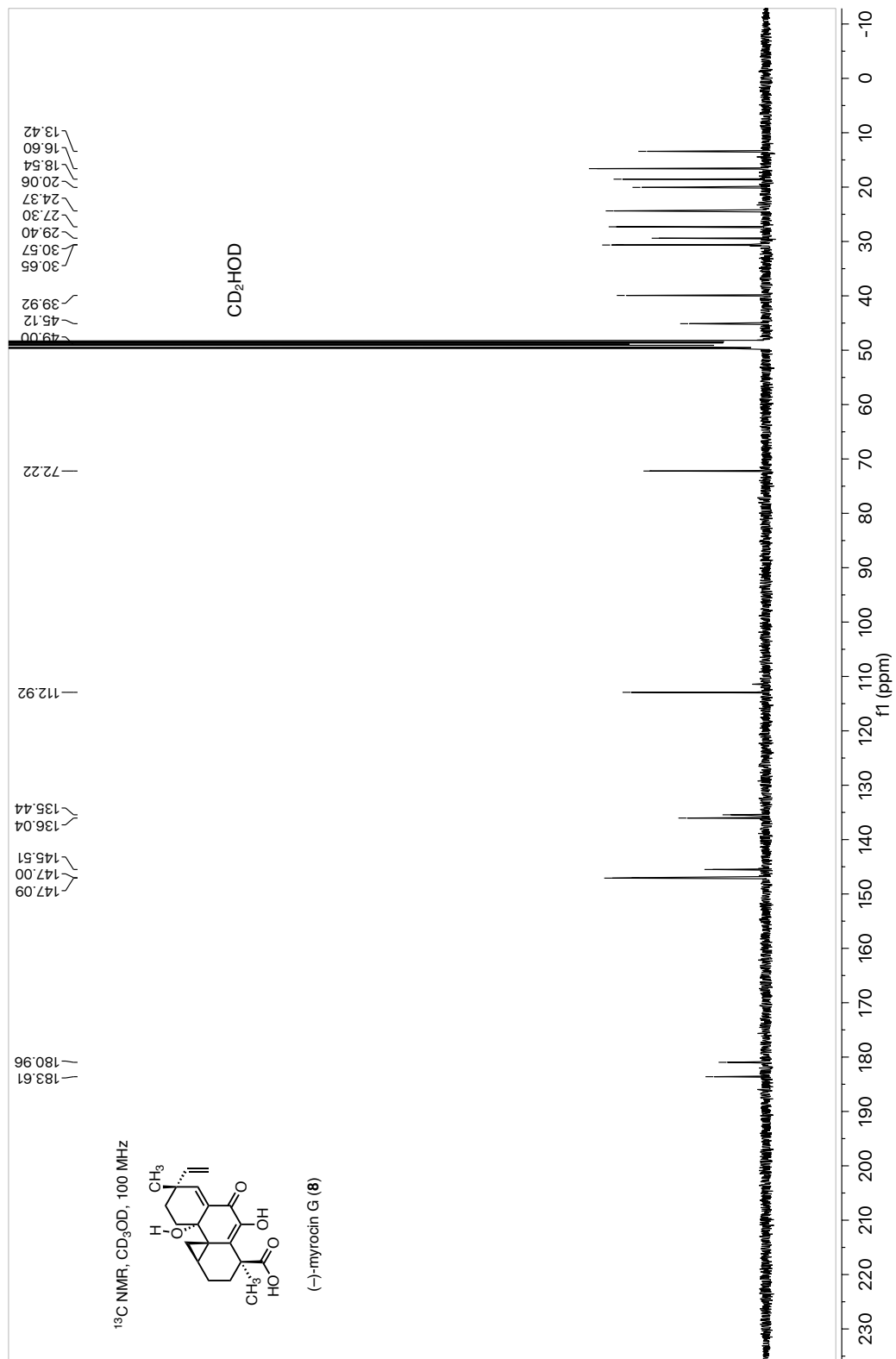


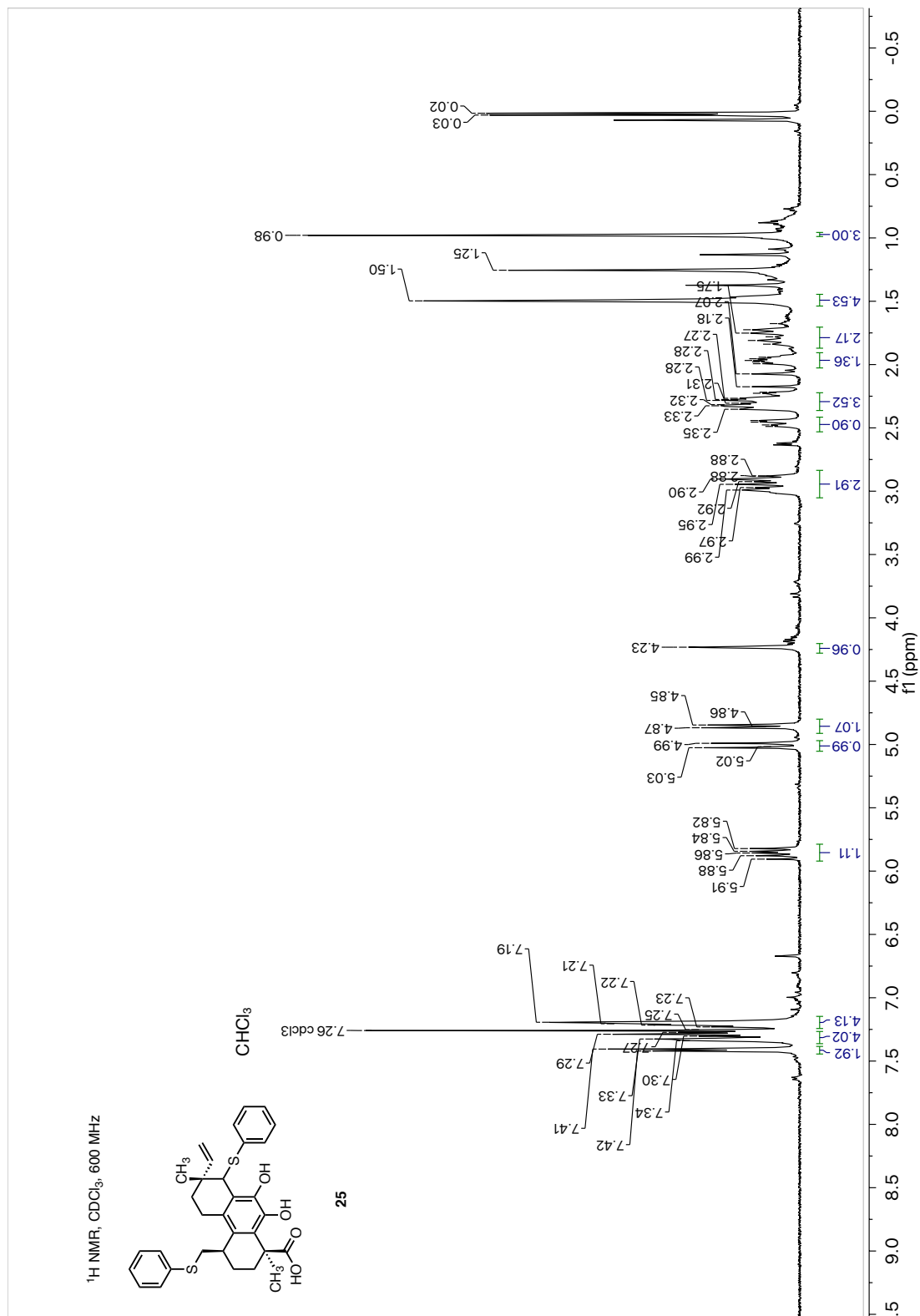


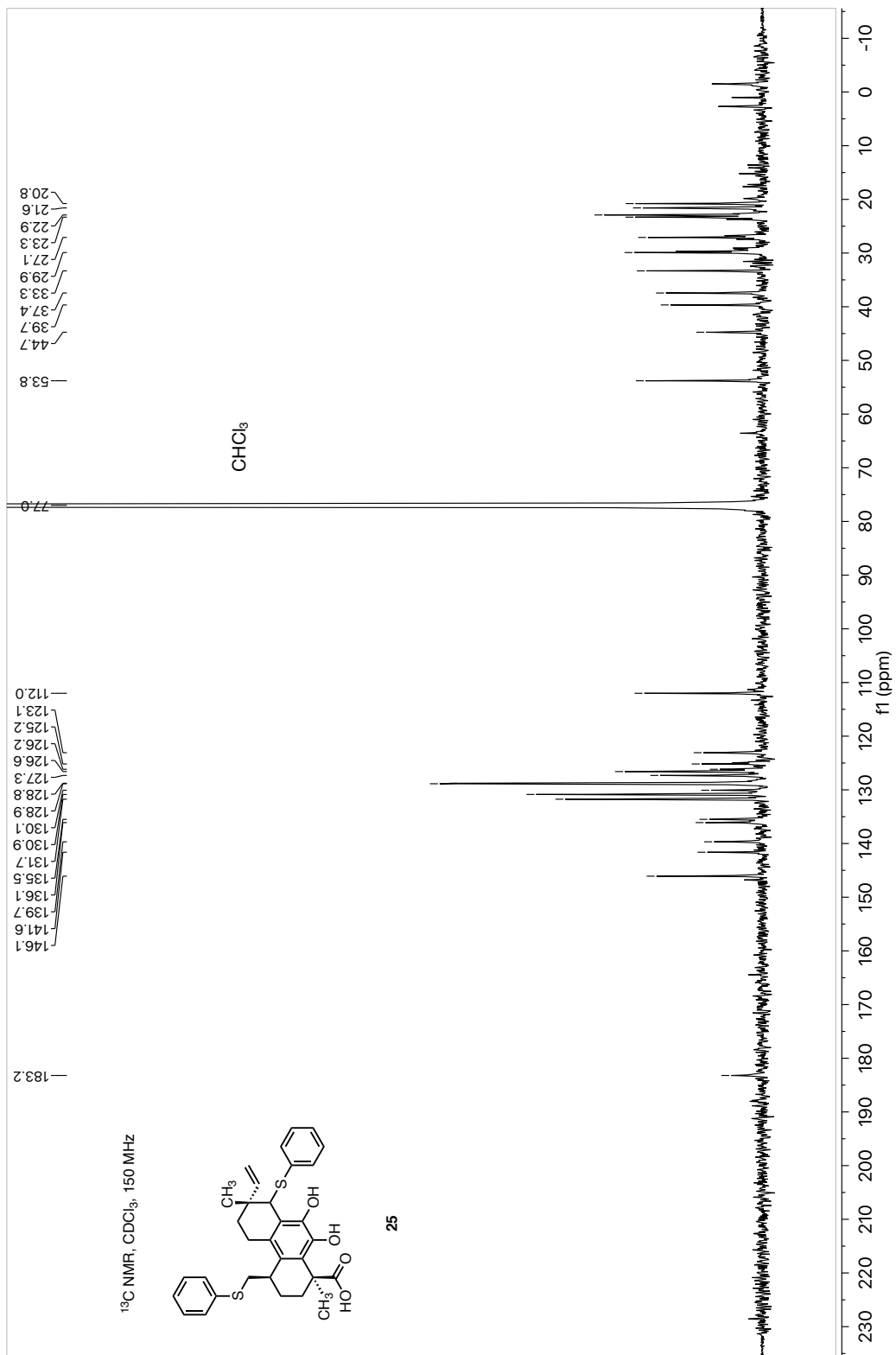


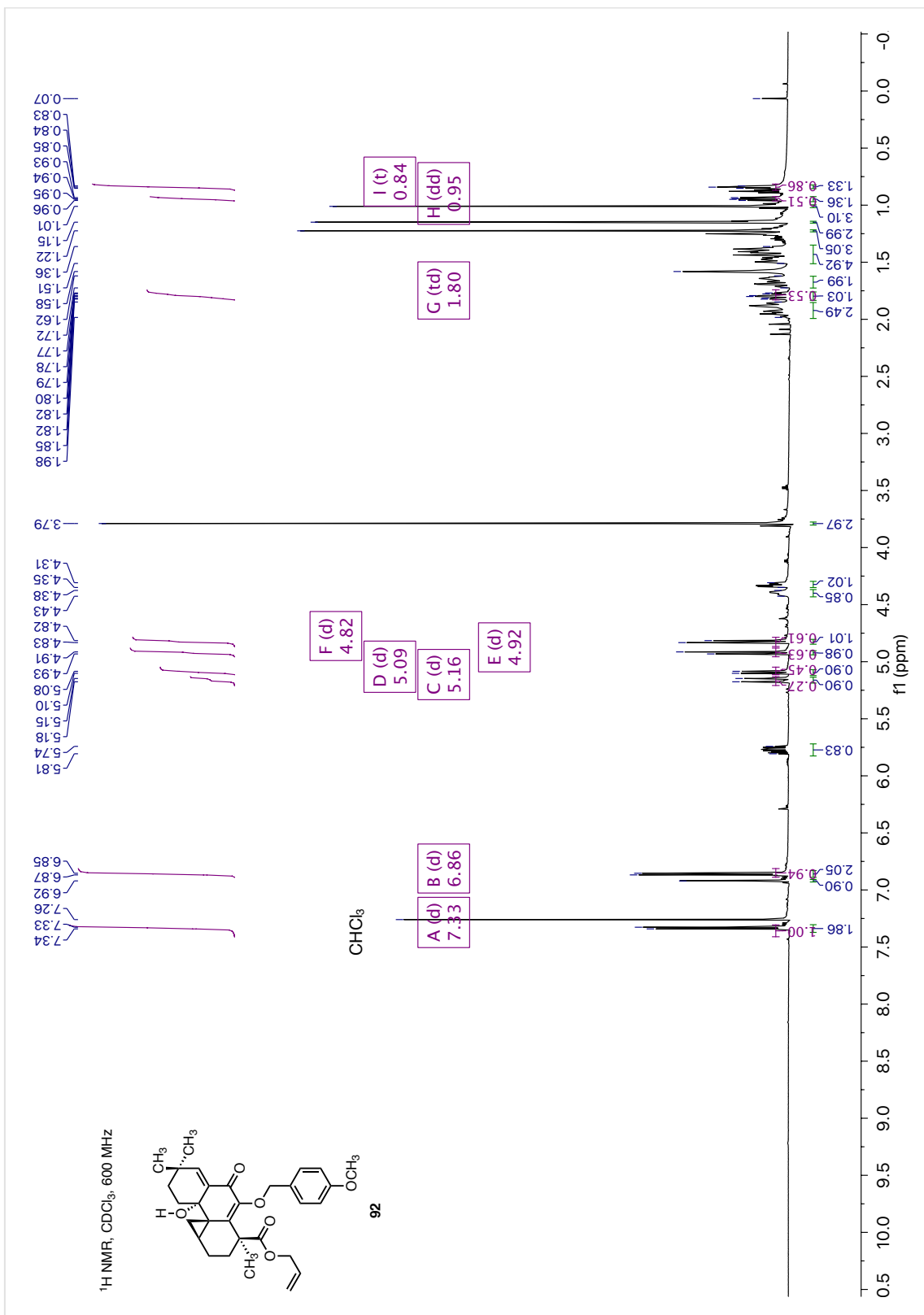


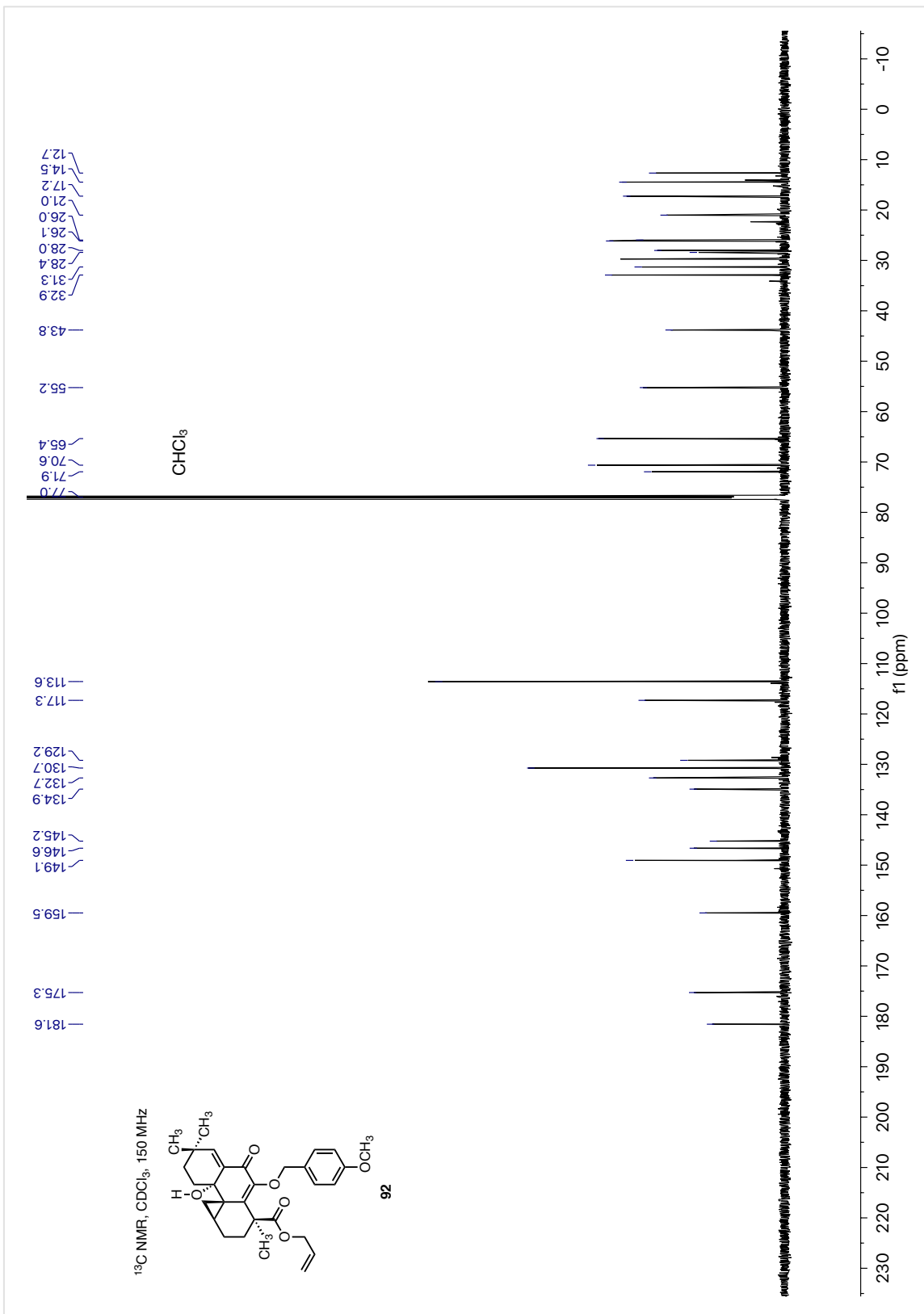


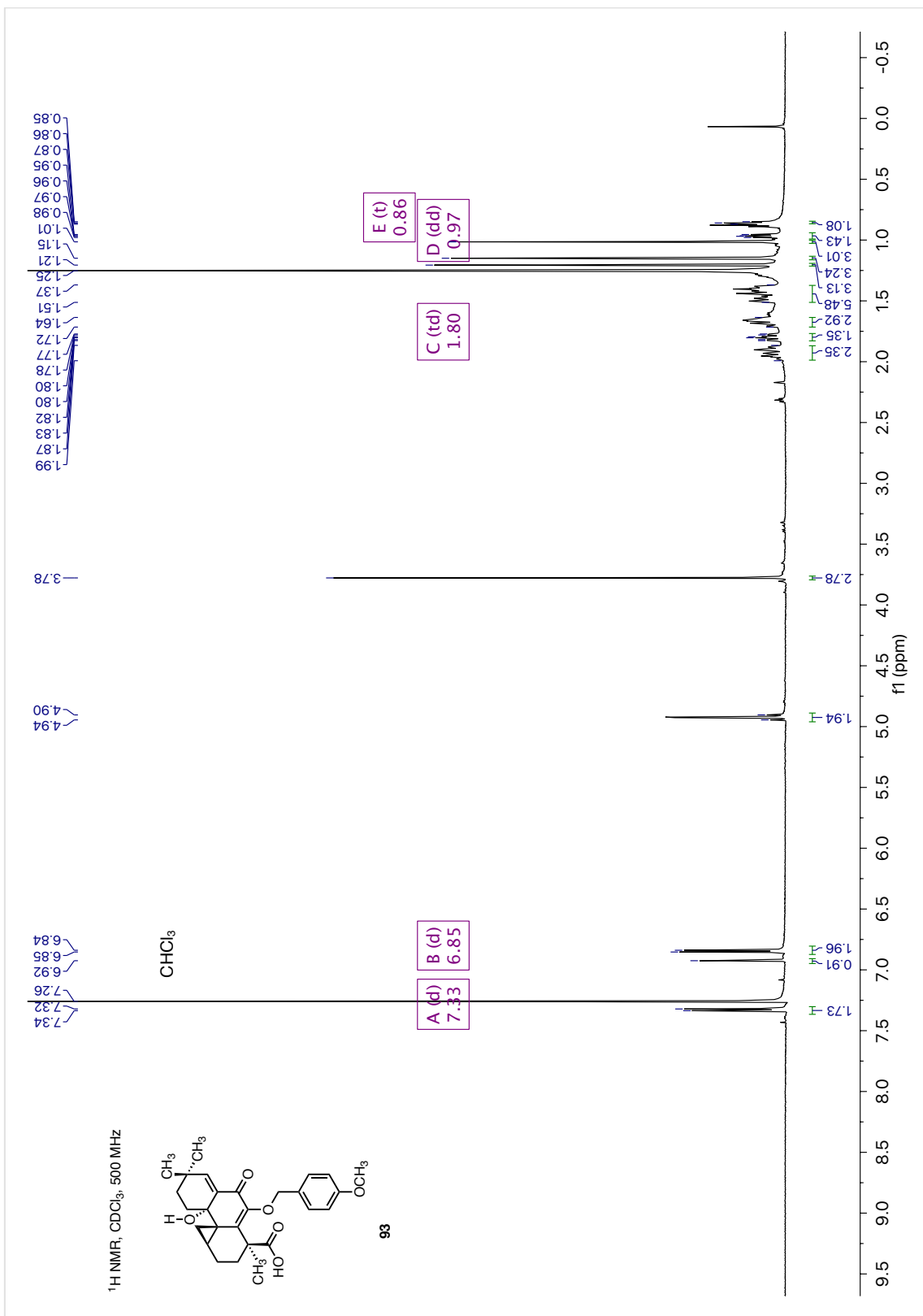


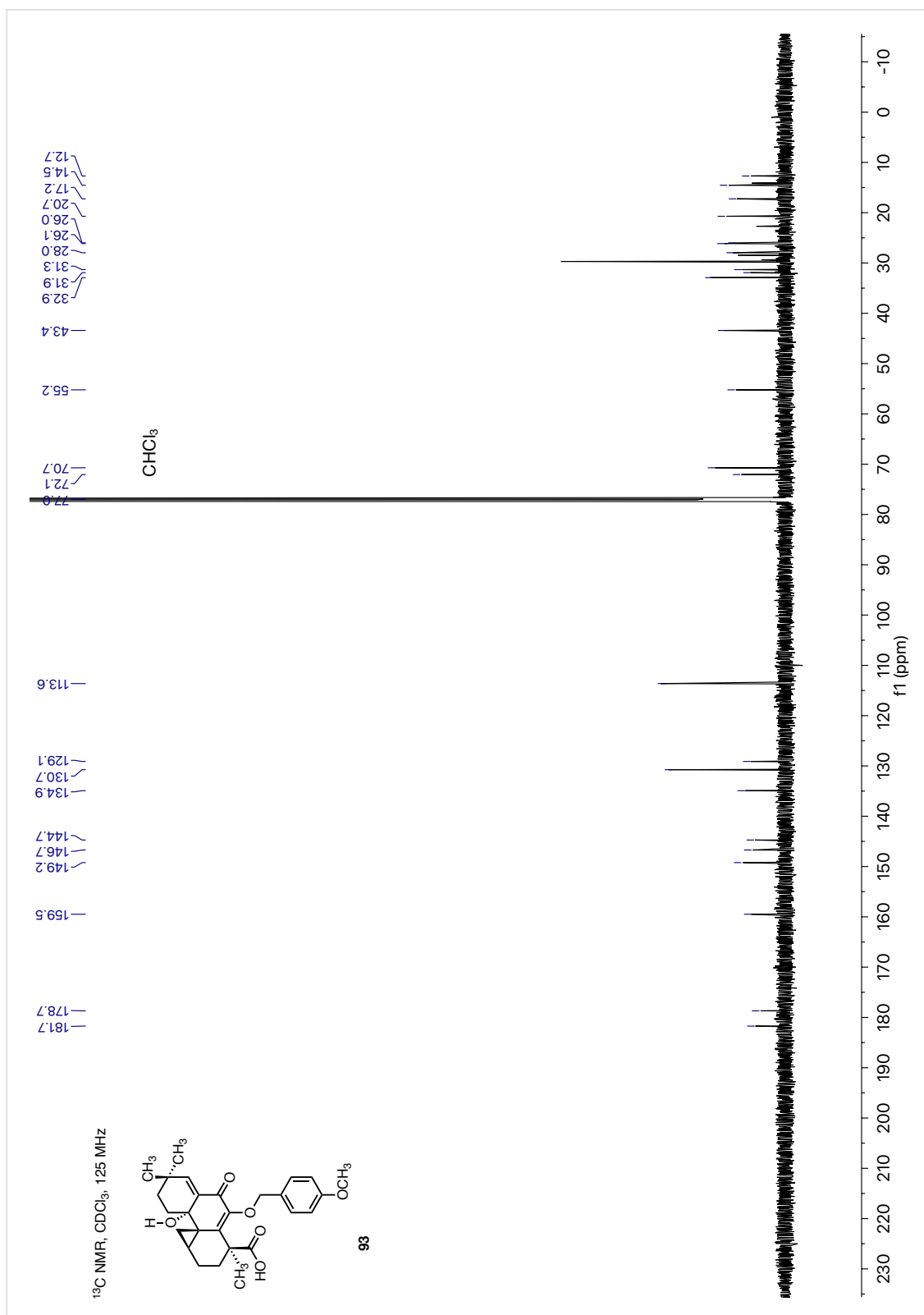


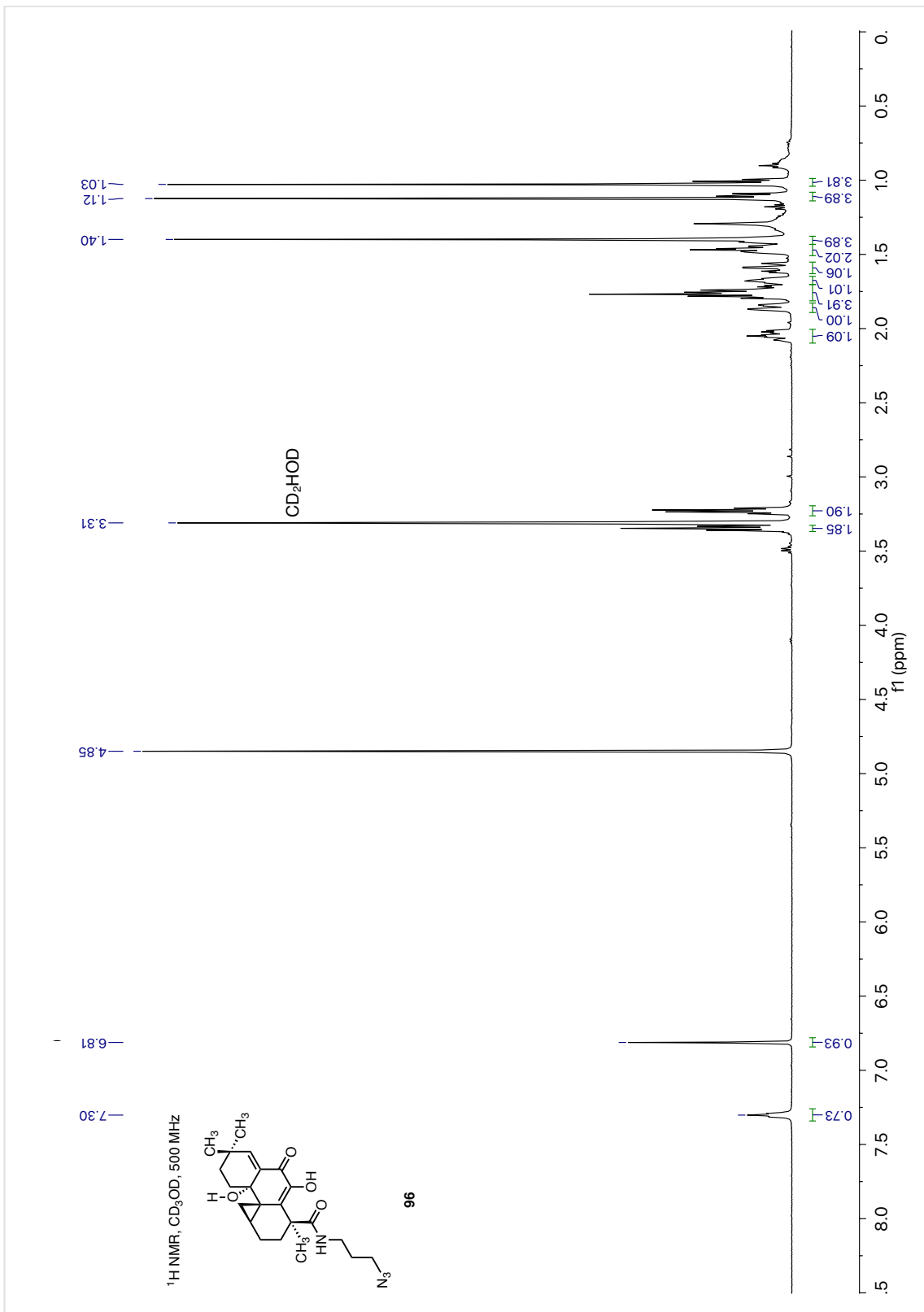




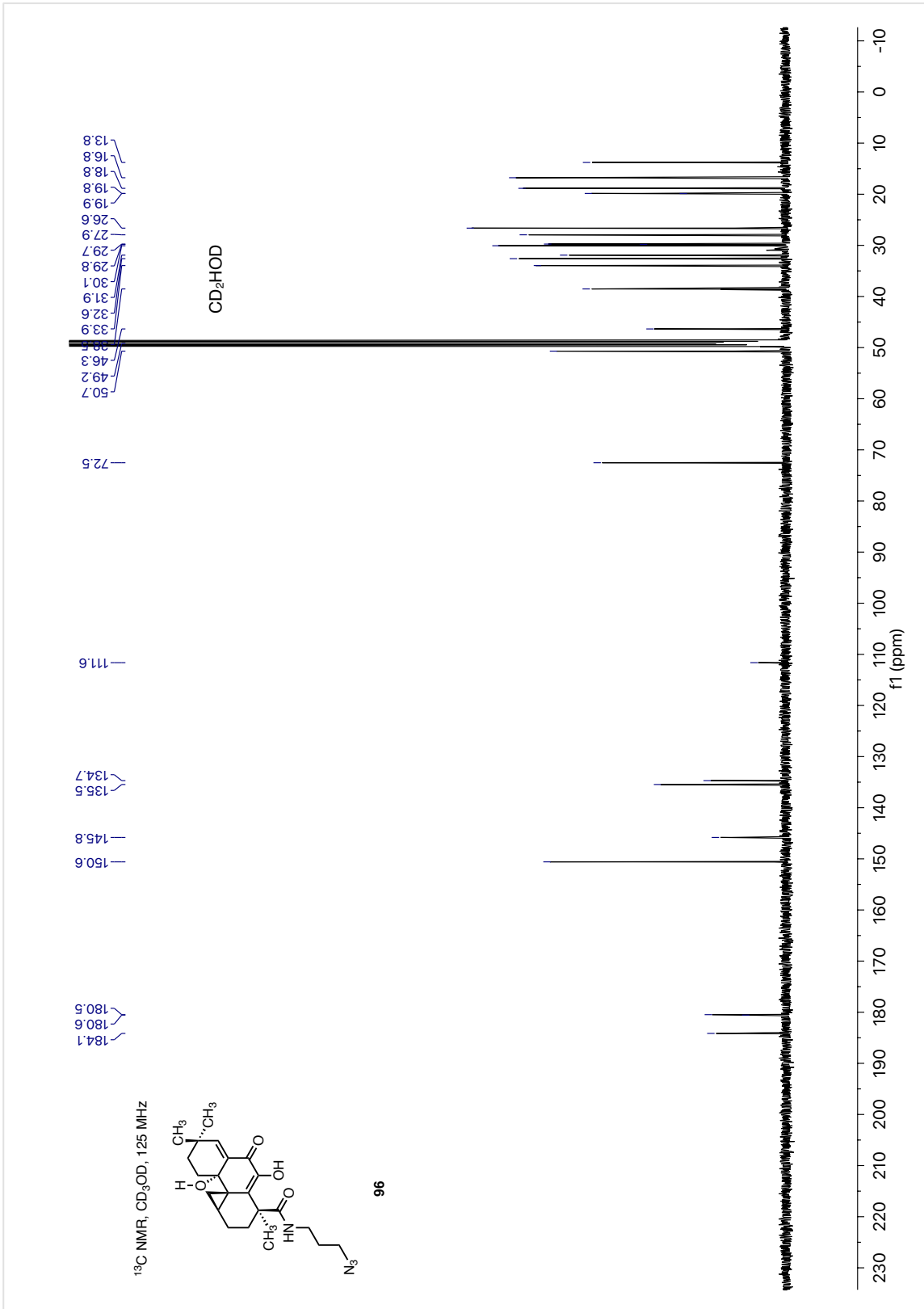


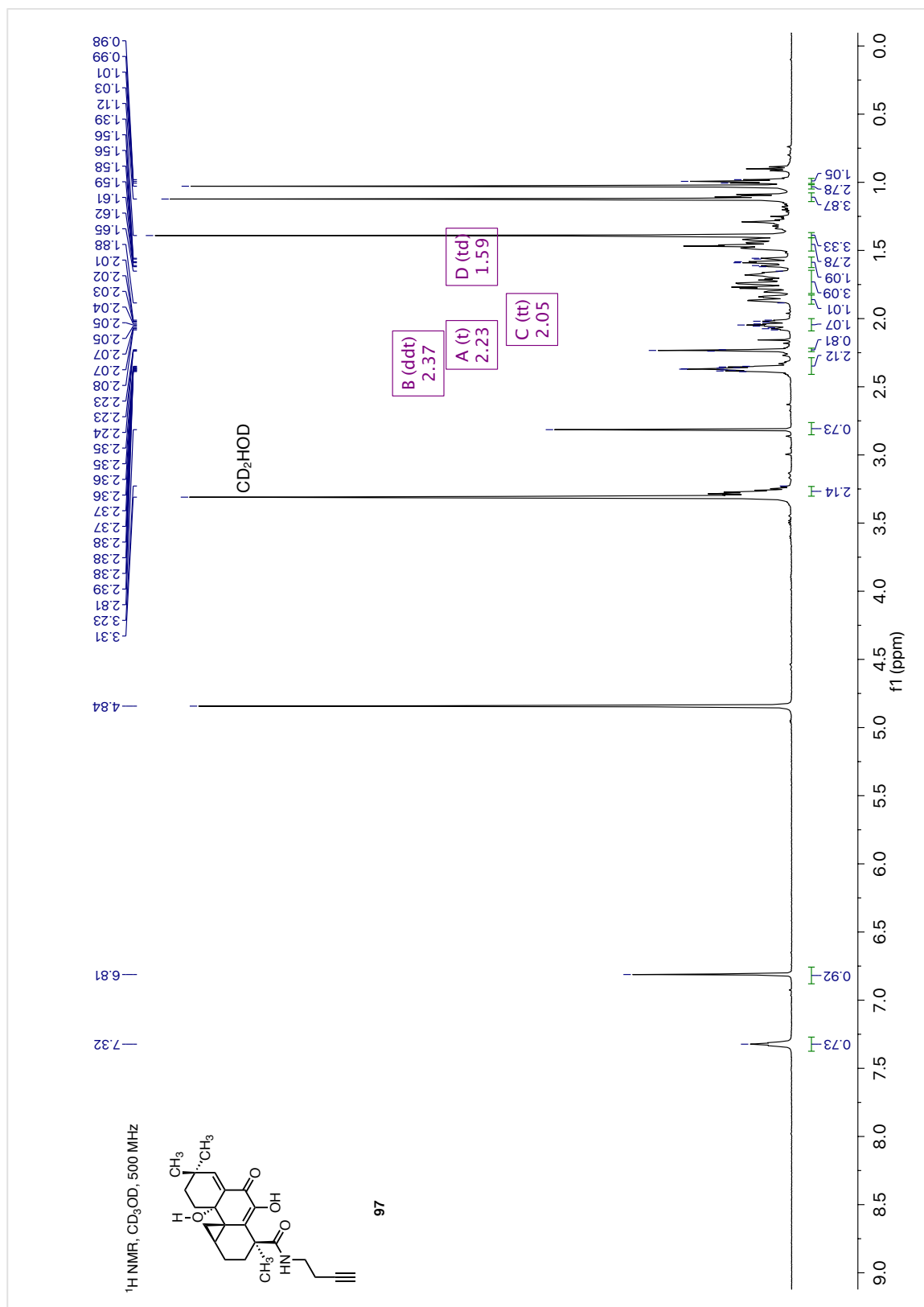


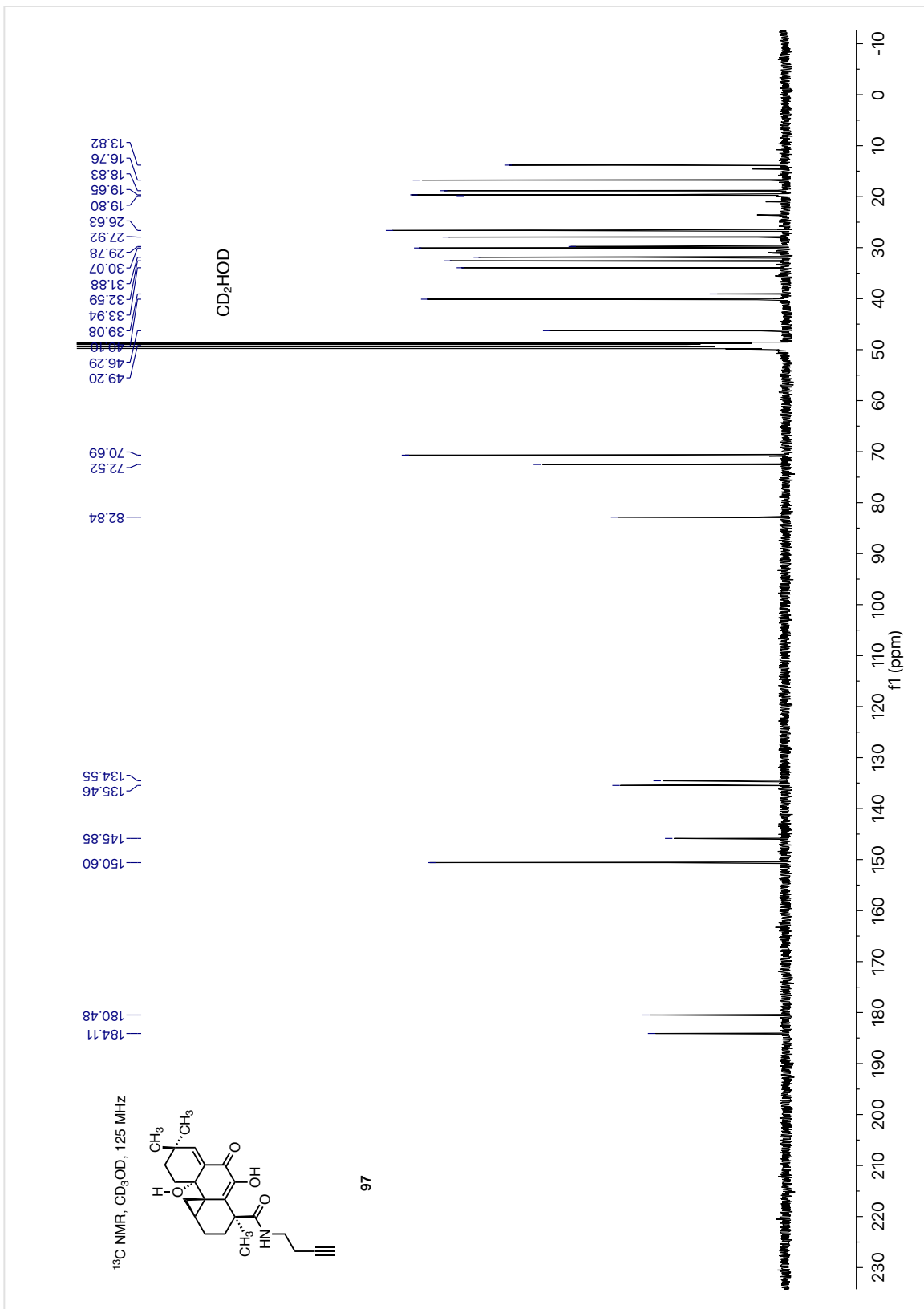


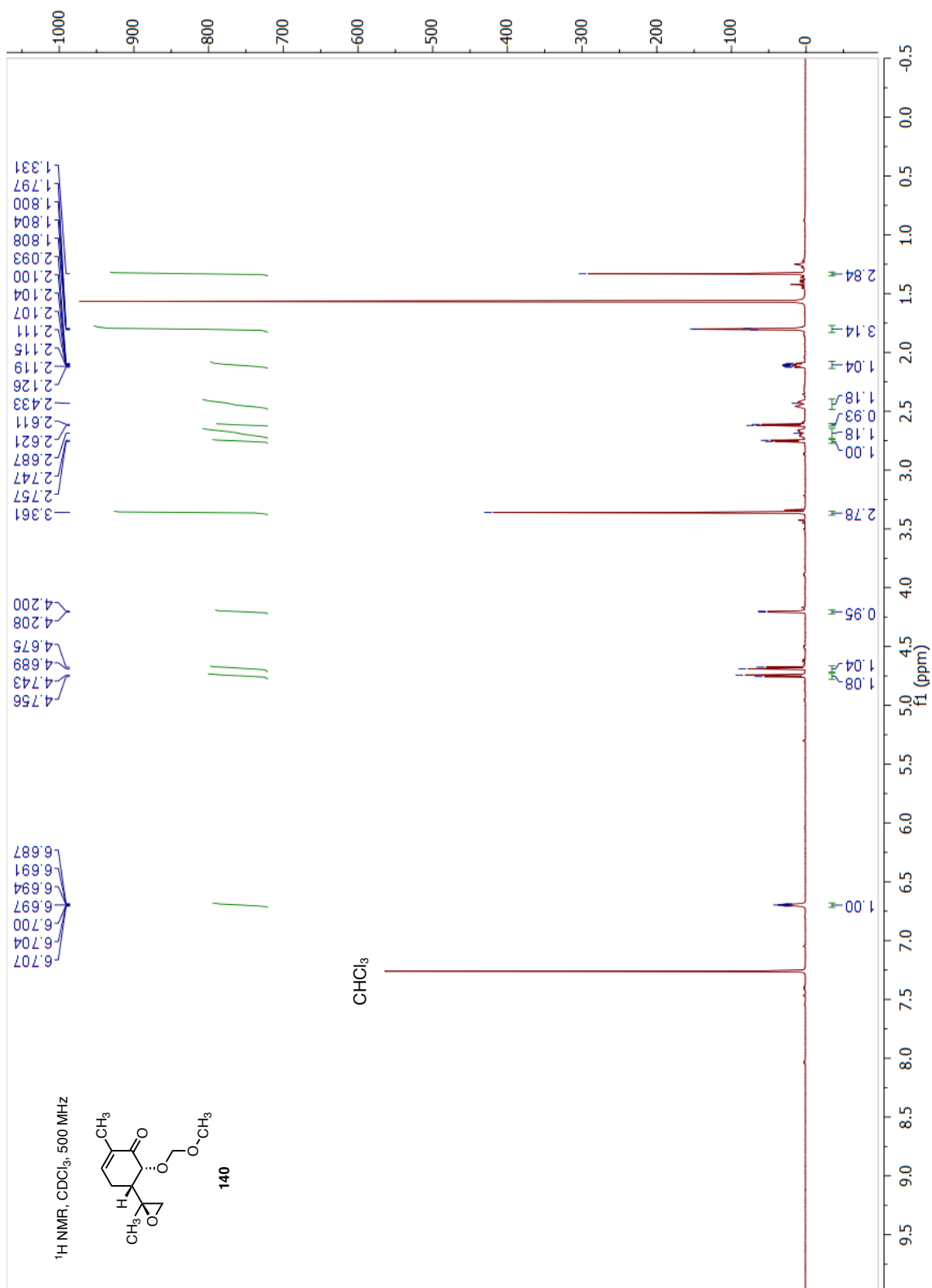


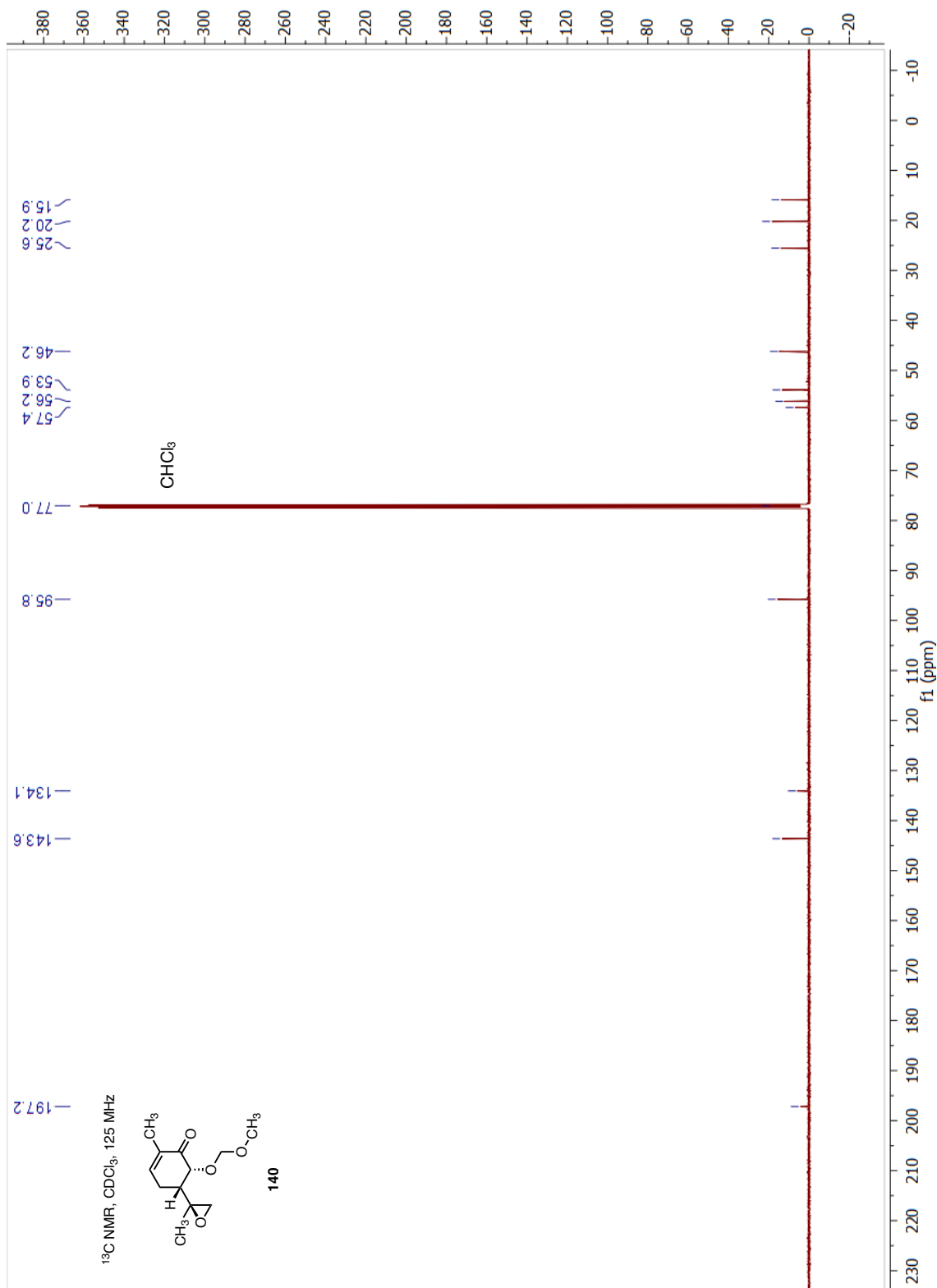


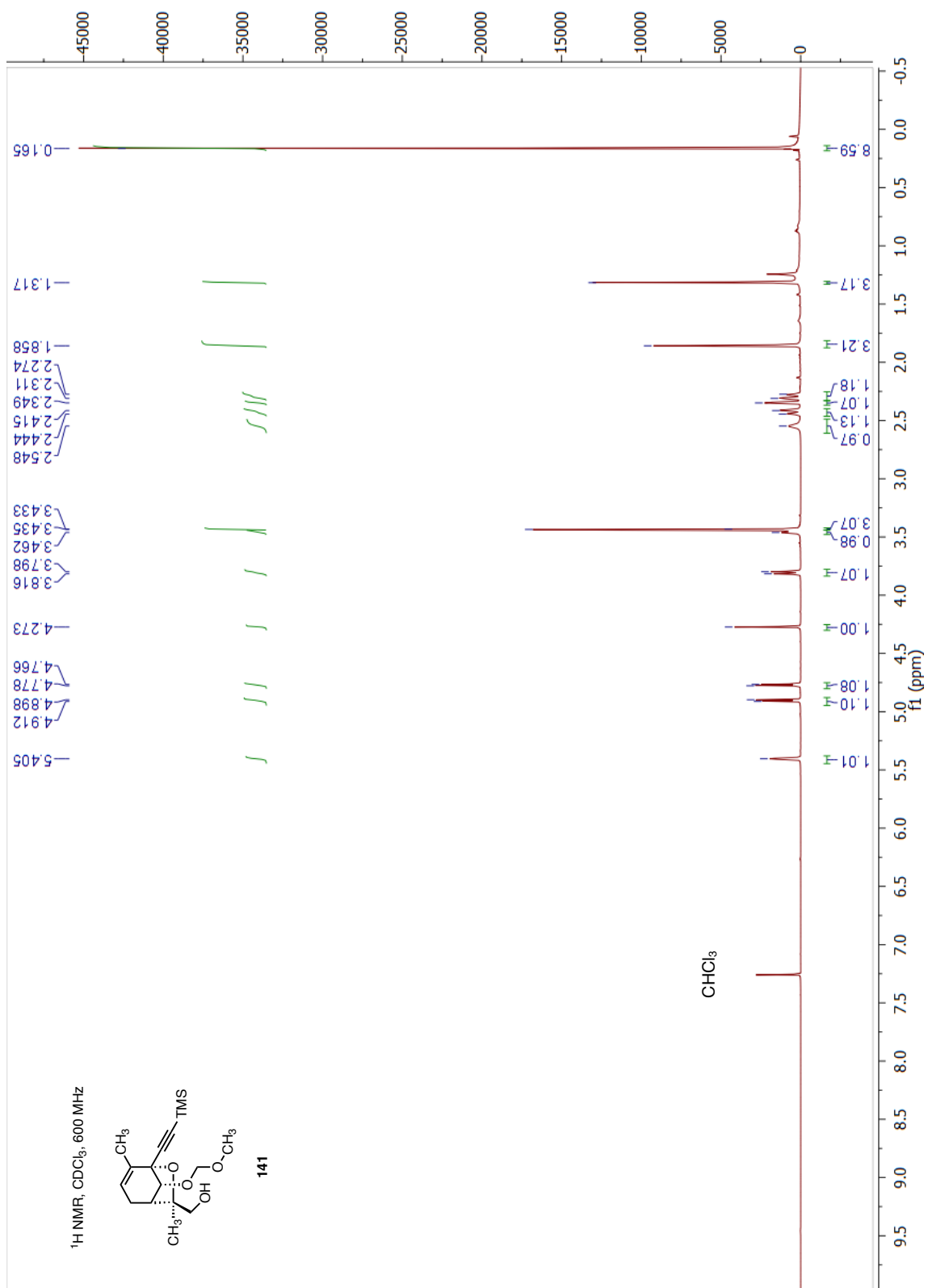


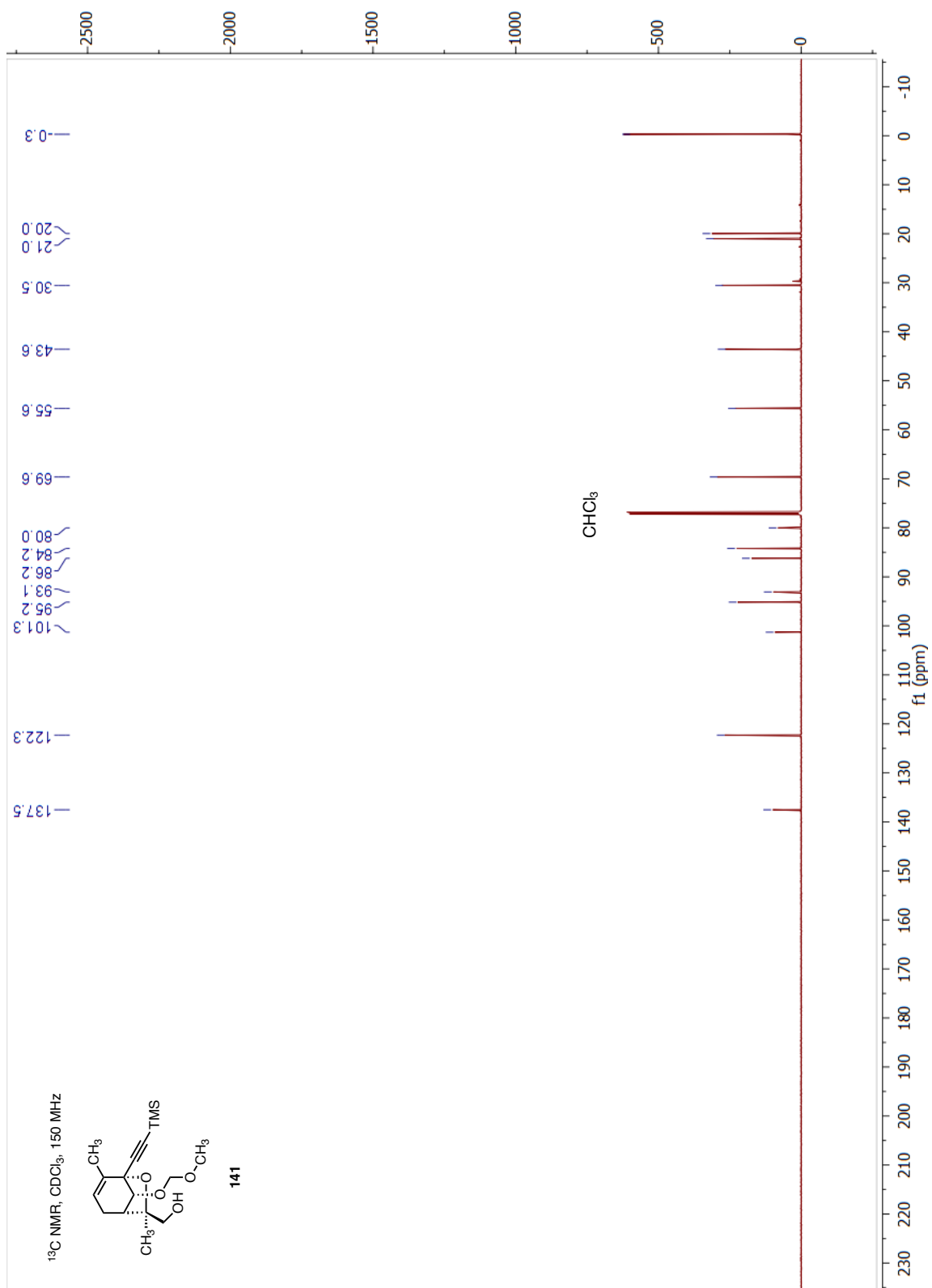


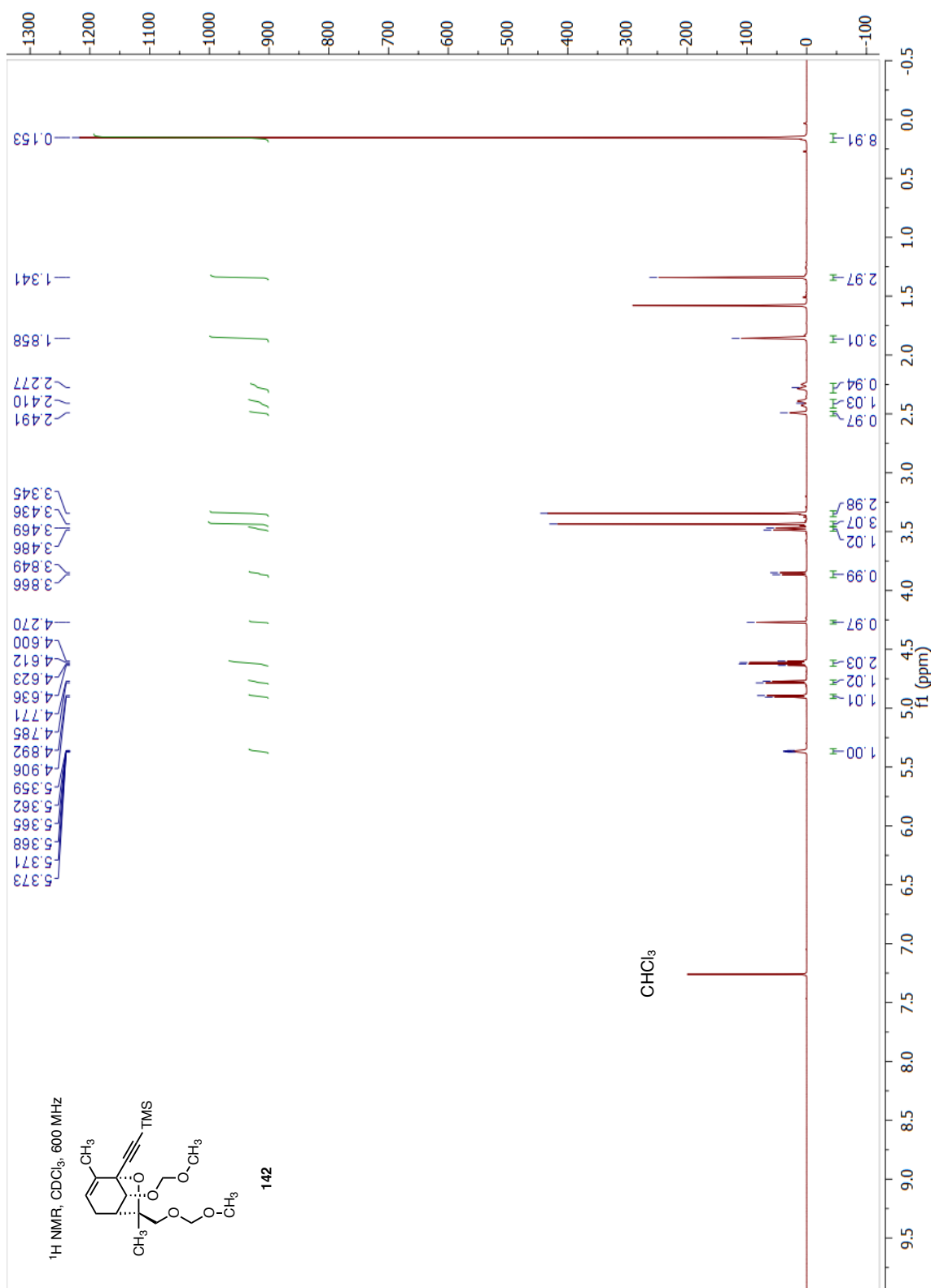




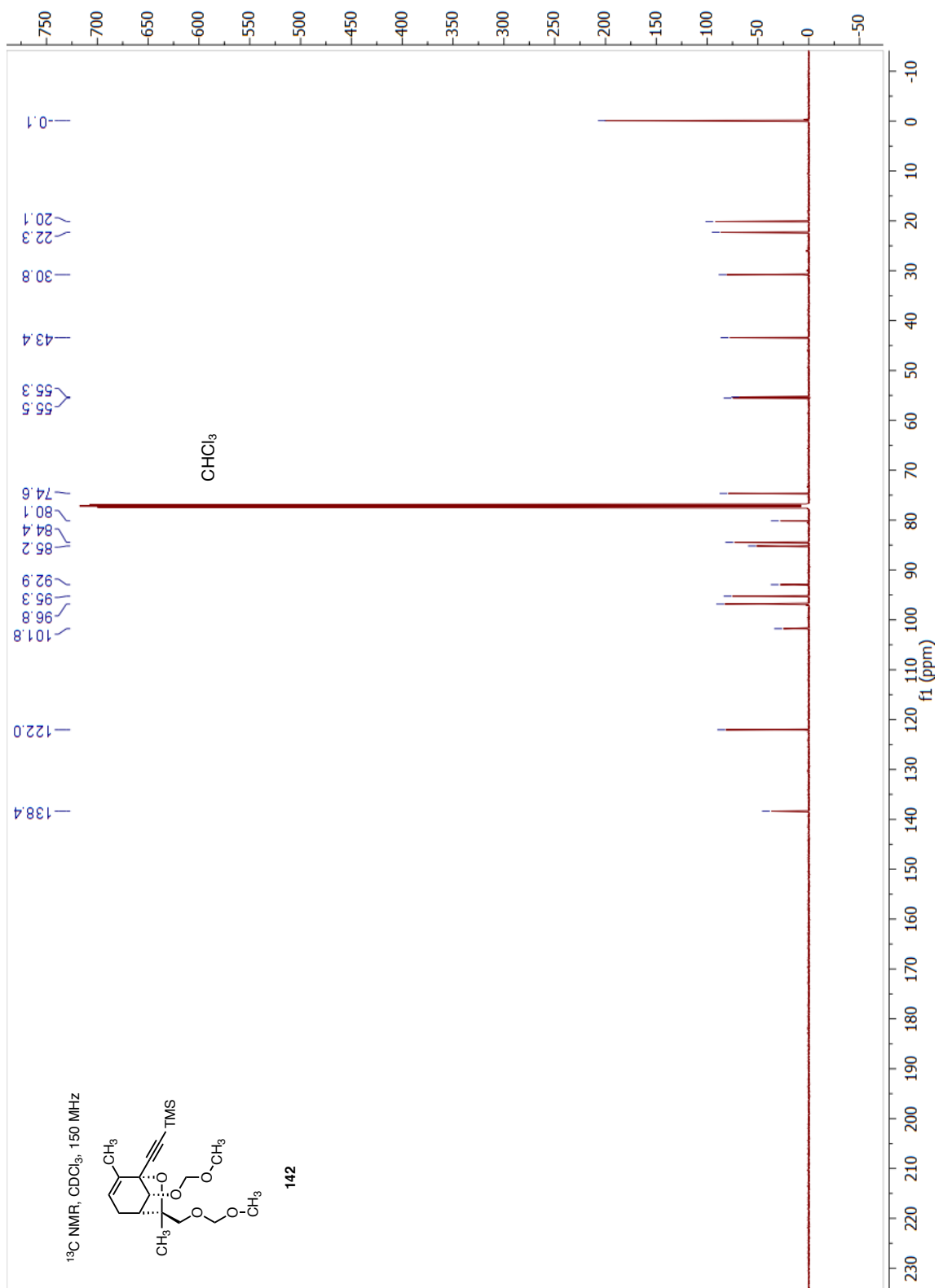


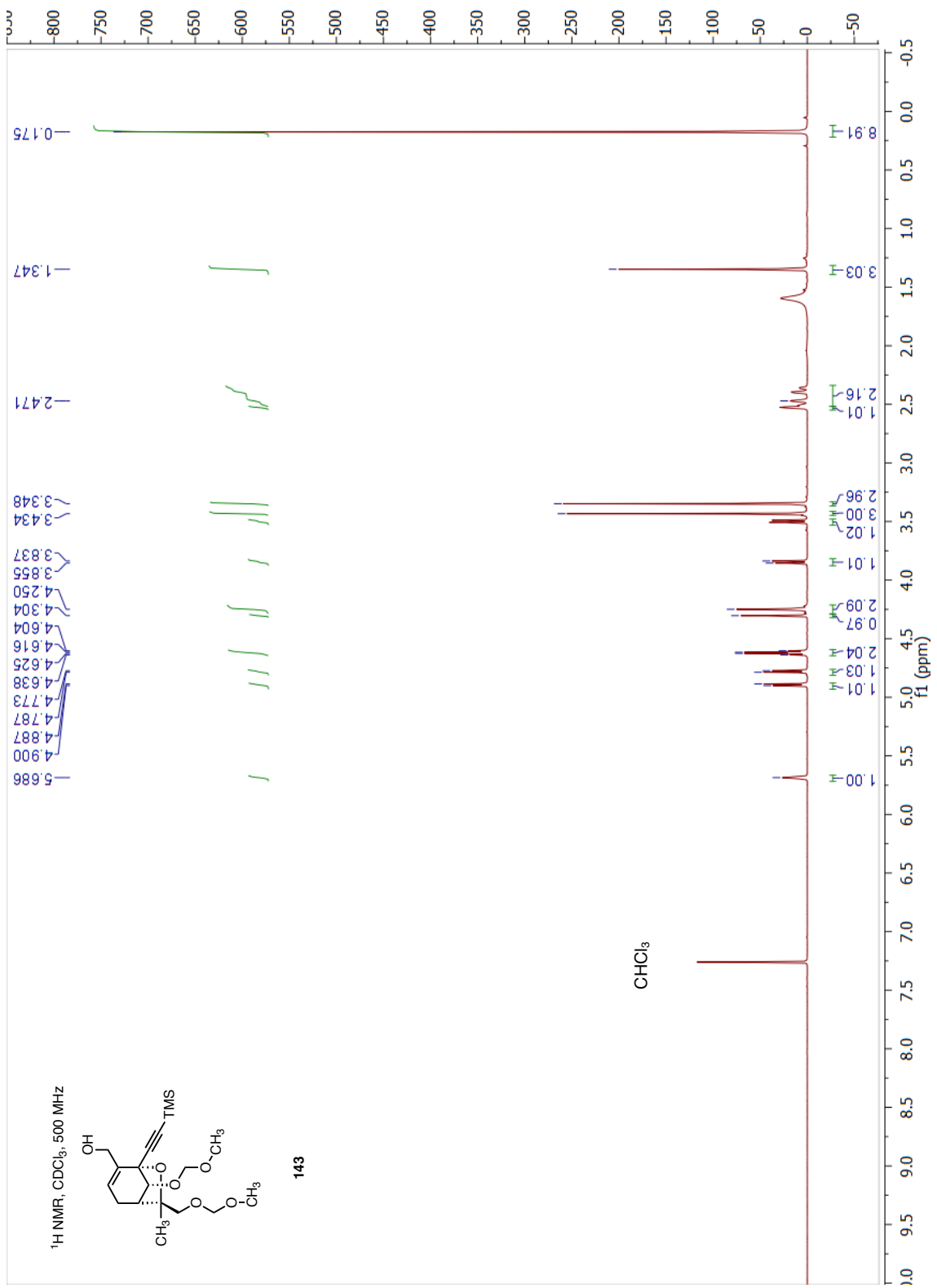


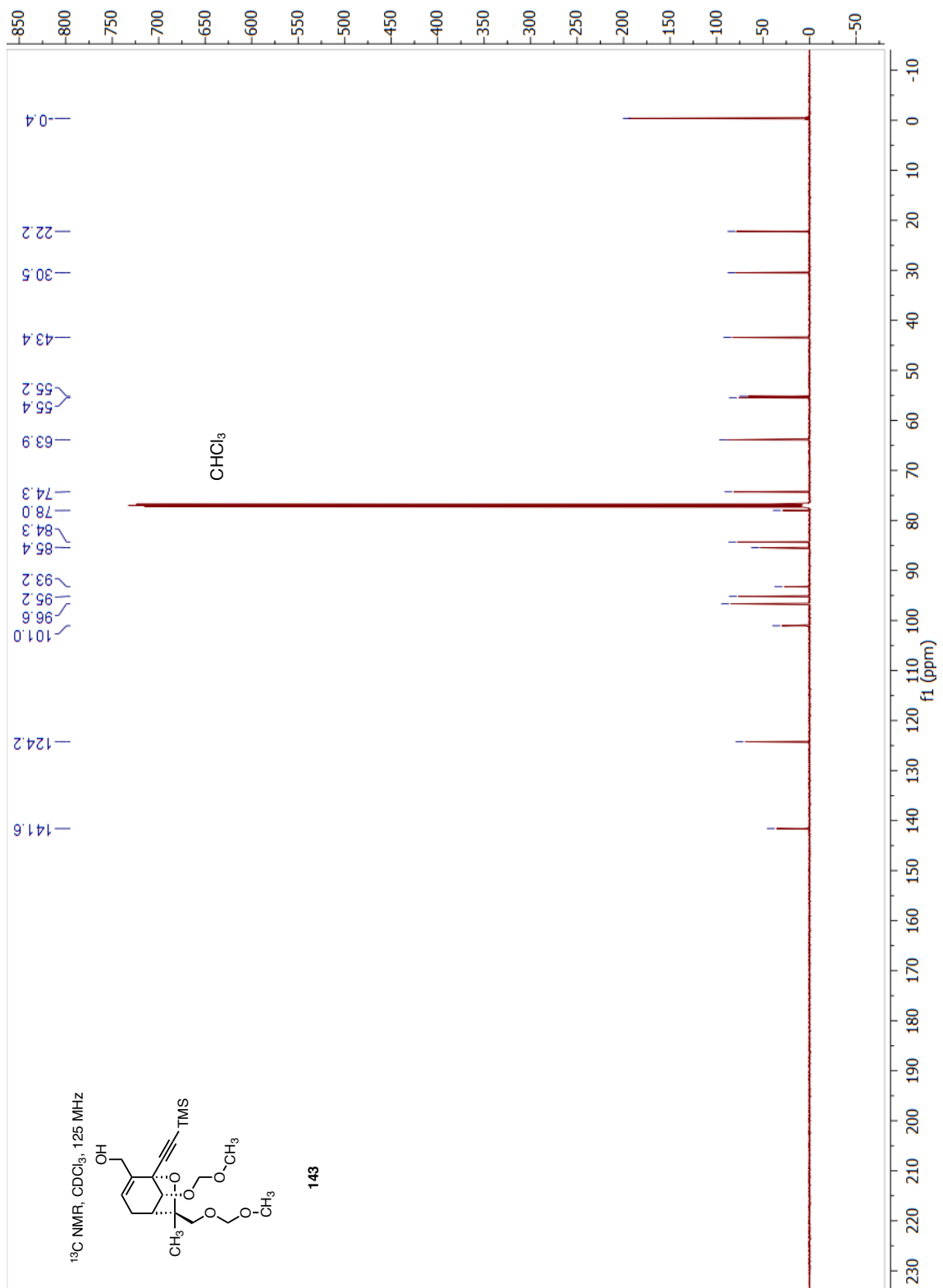


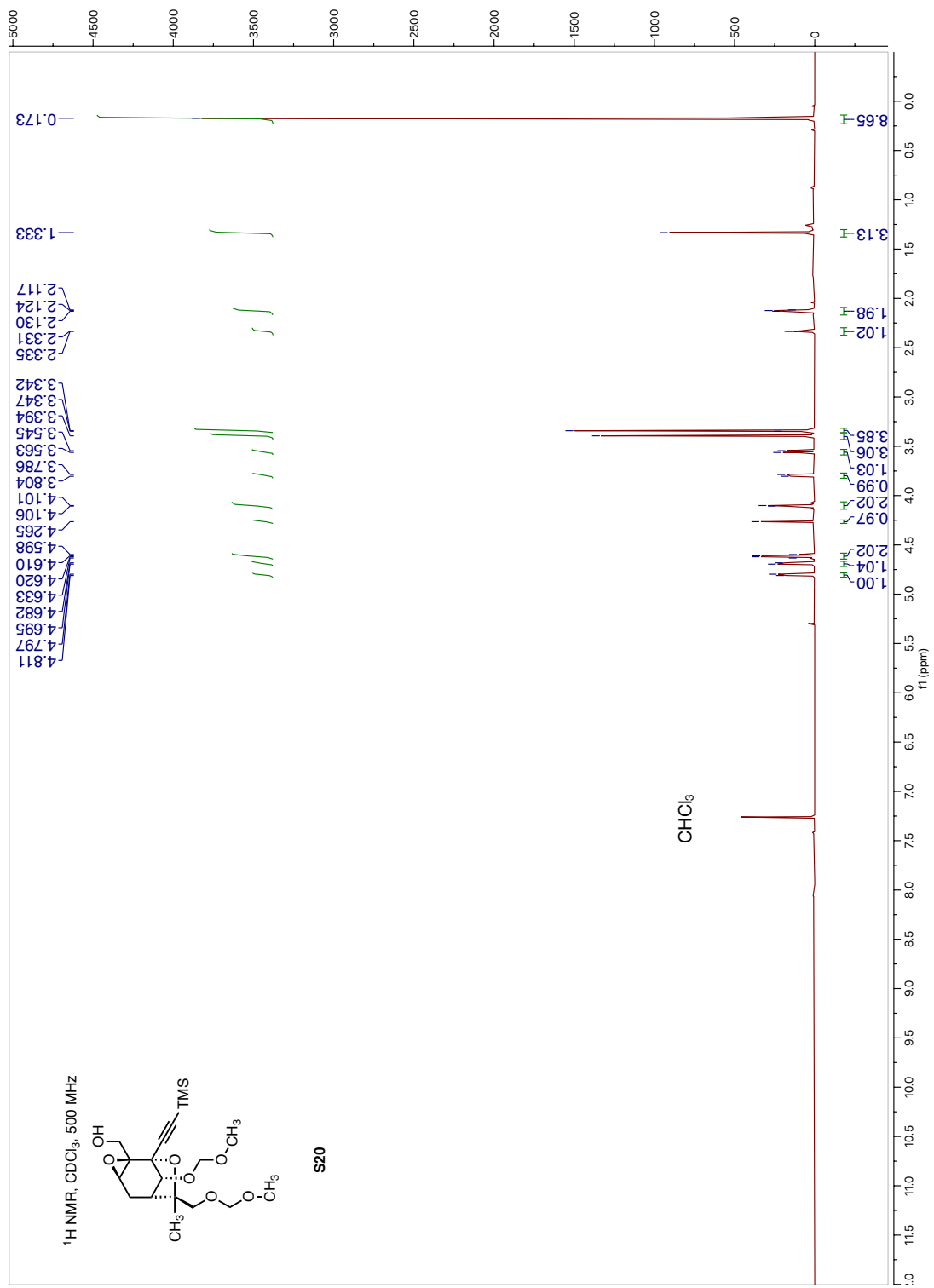


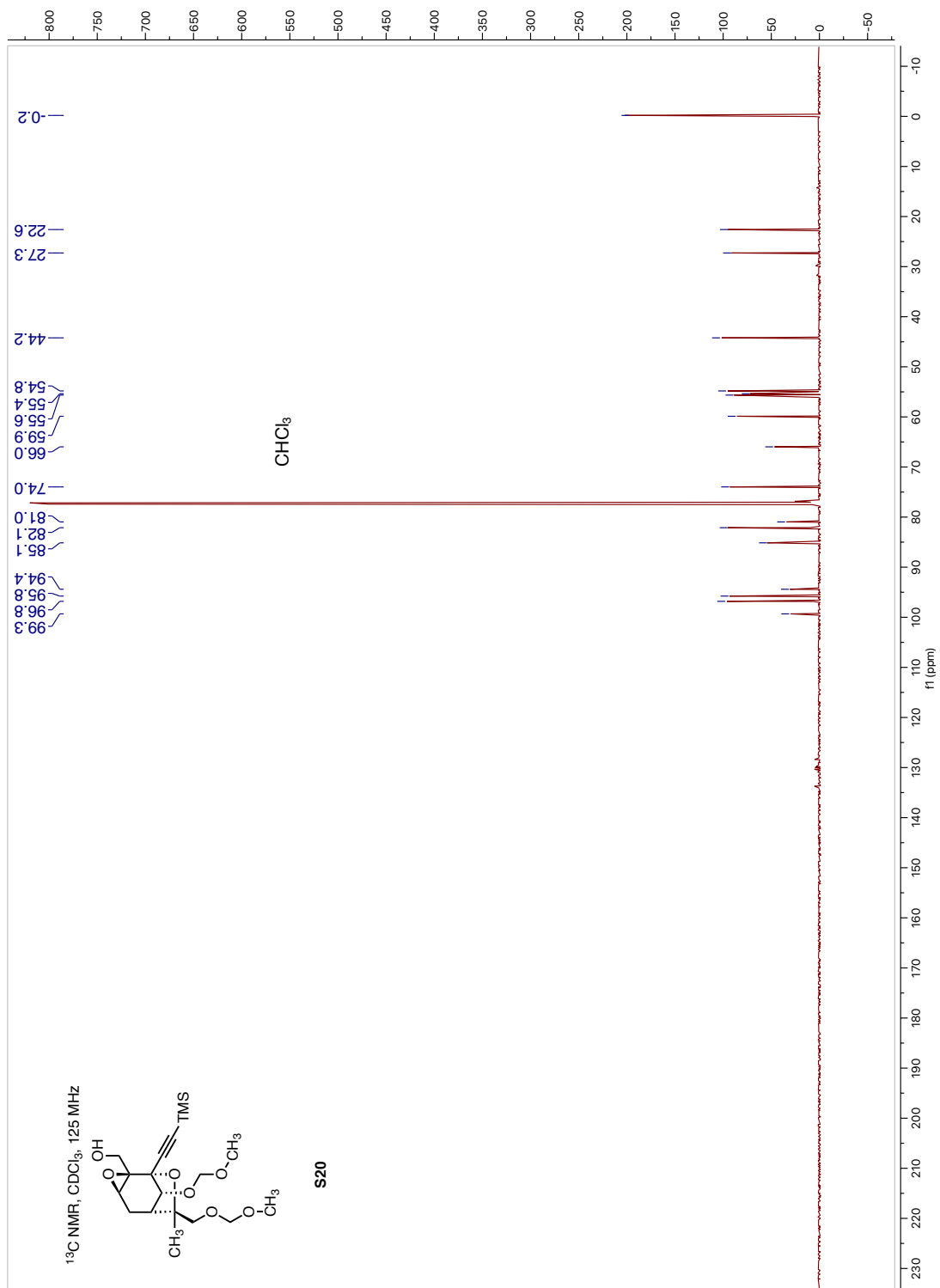


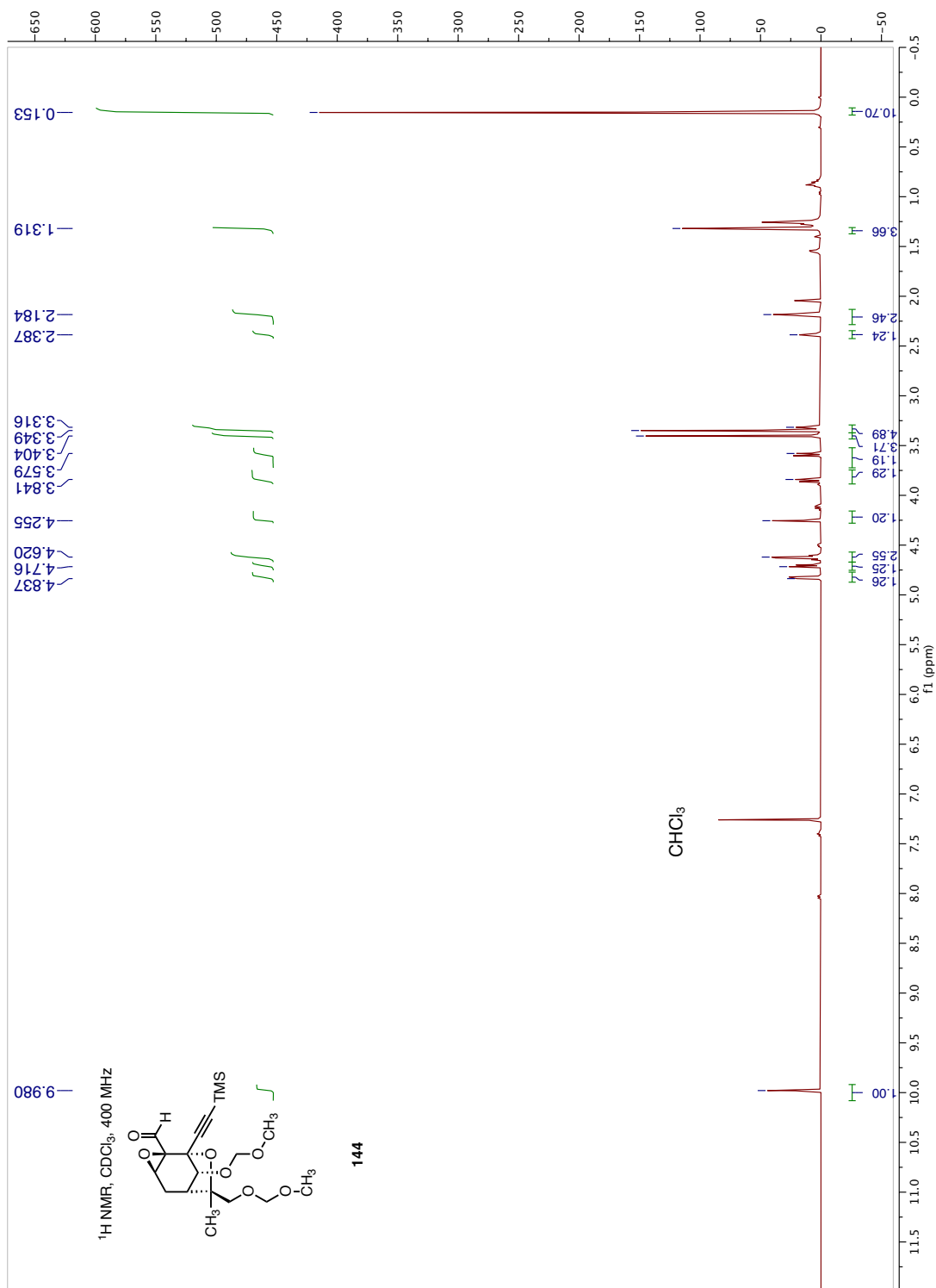


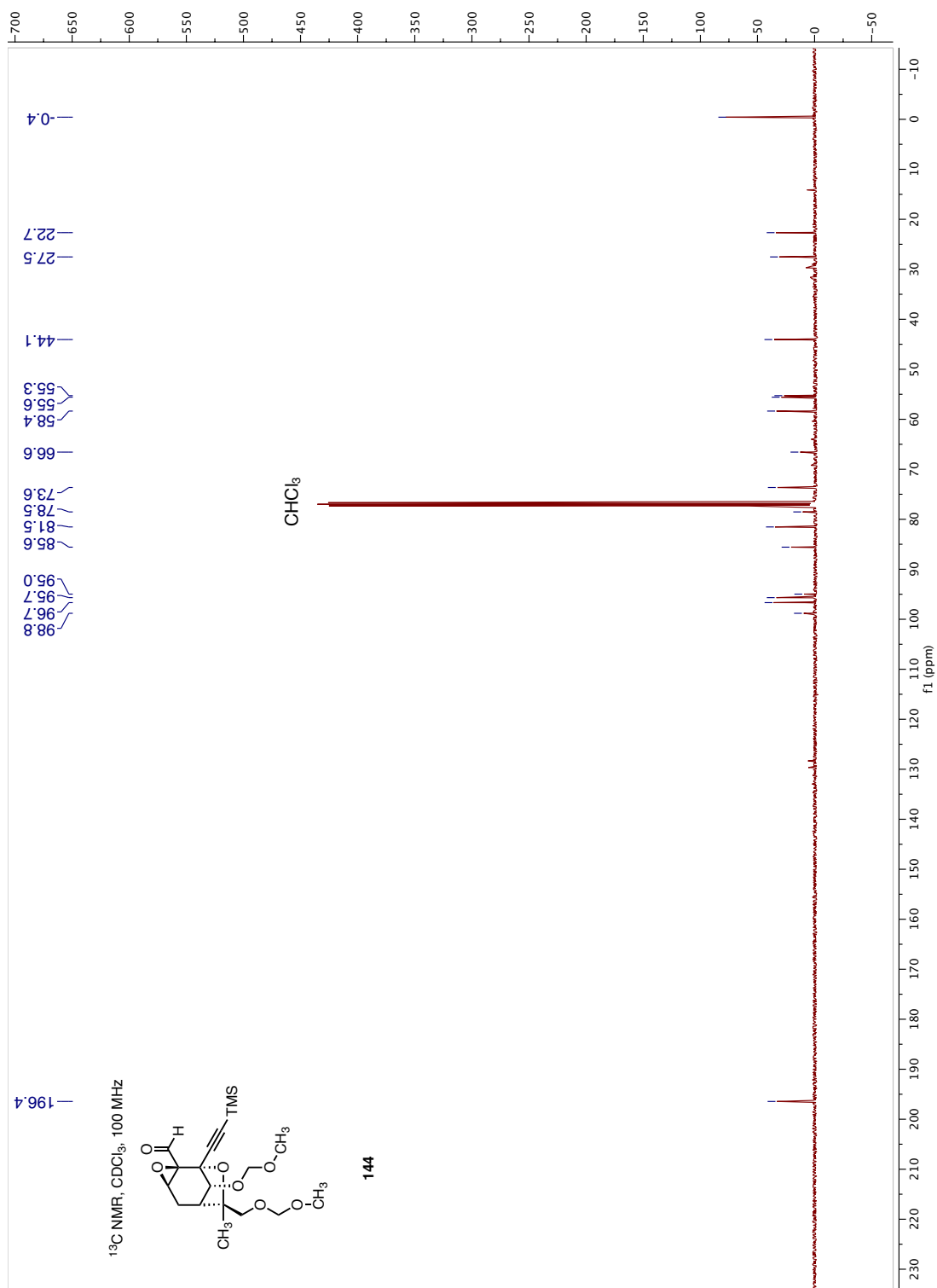






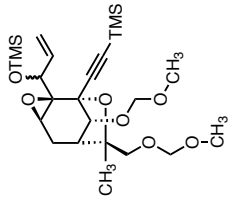




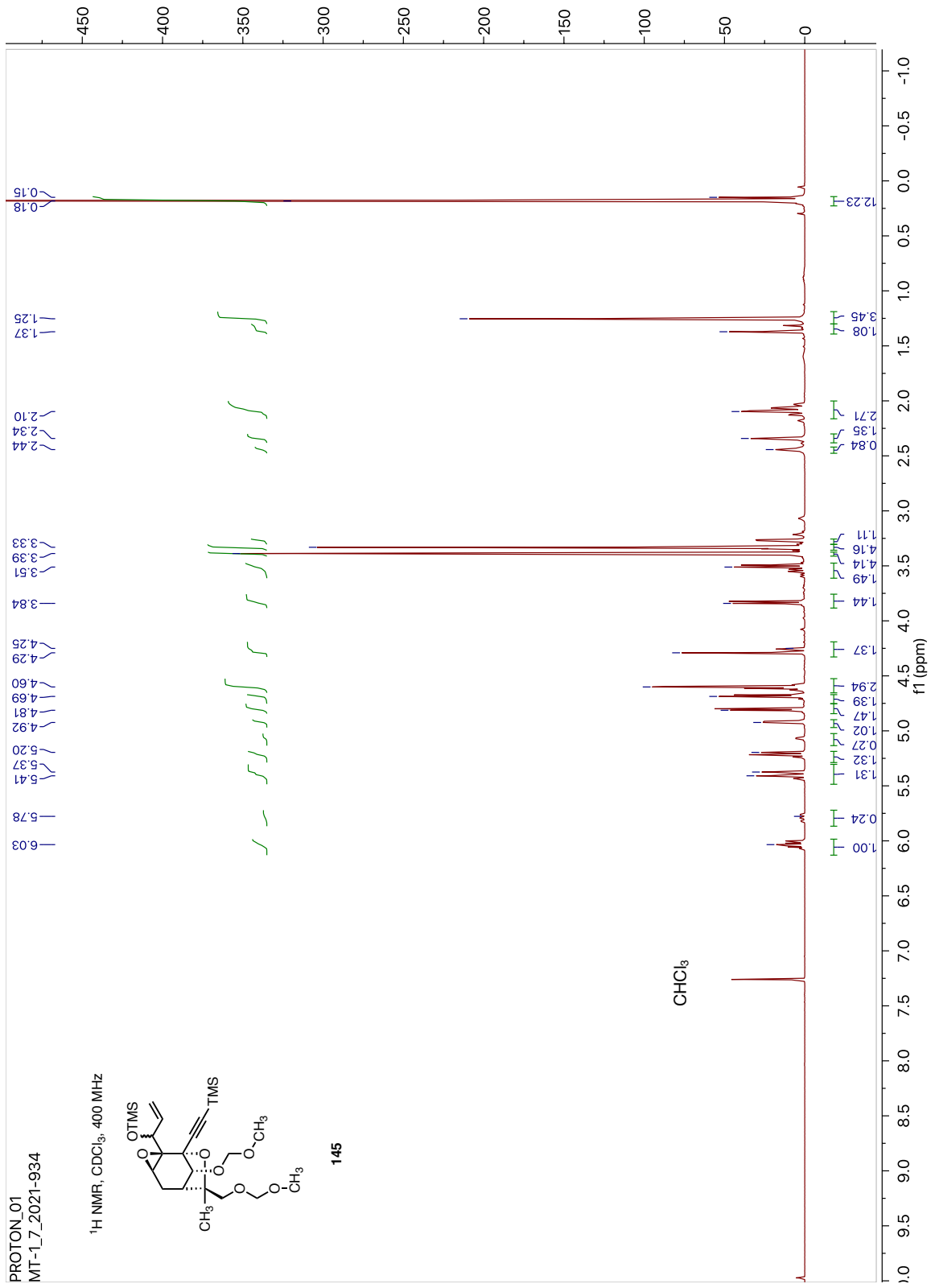


PROTON\_01  
MT-1\_7\_2021-934

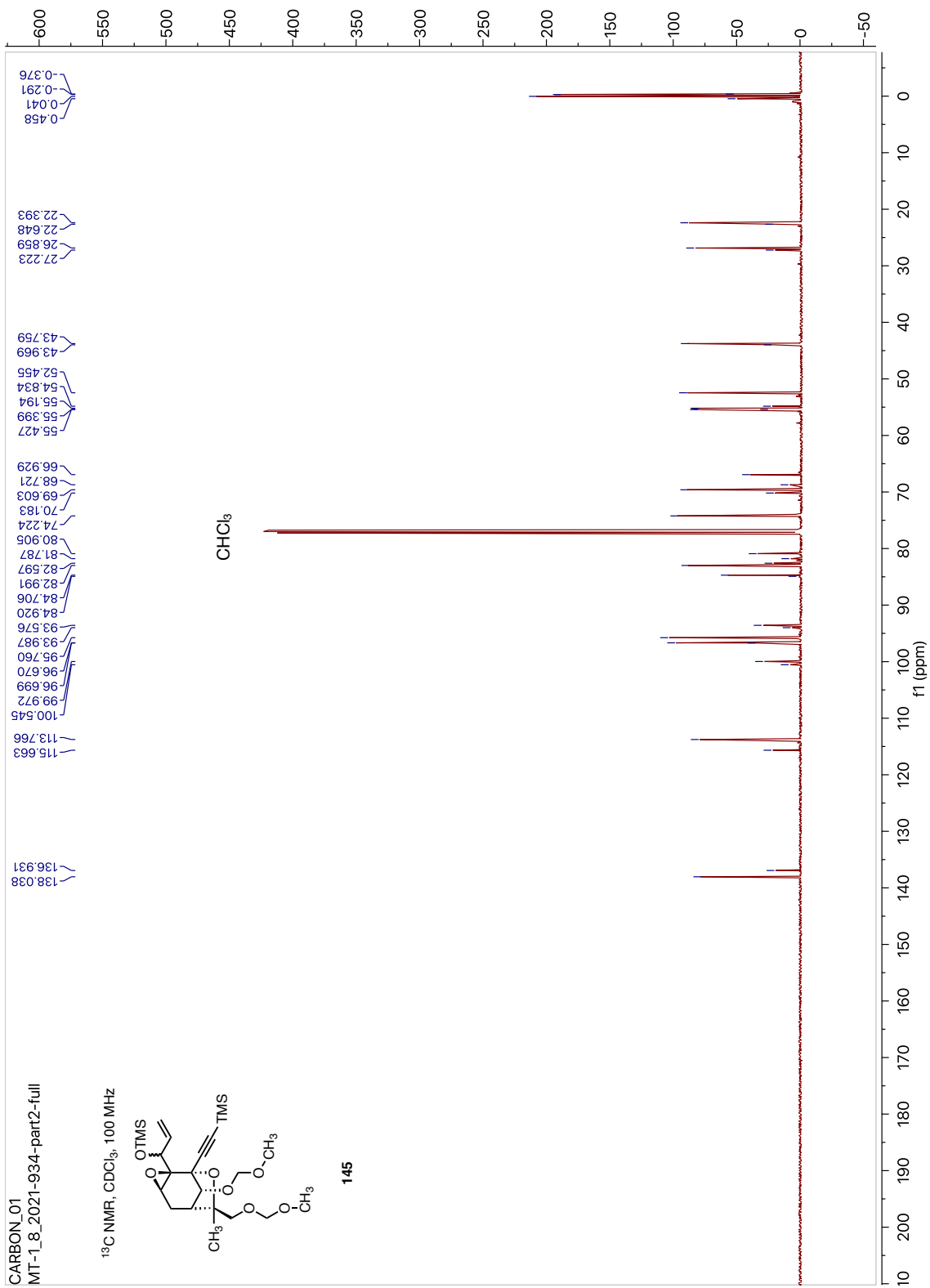
$^1\text{H}$  NMR,  $\text{CDCl}_3$ , 400 MHz

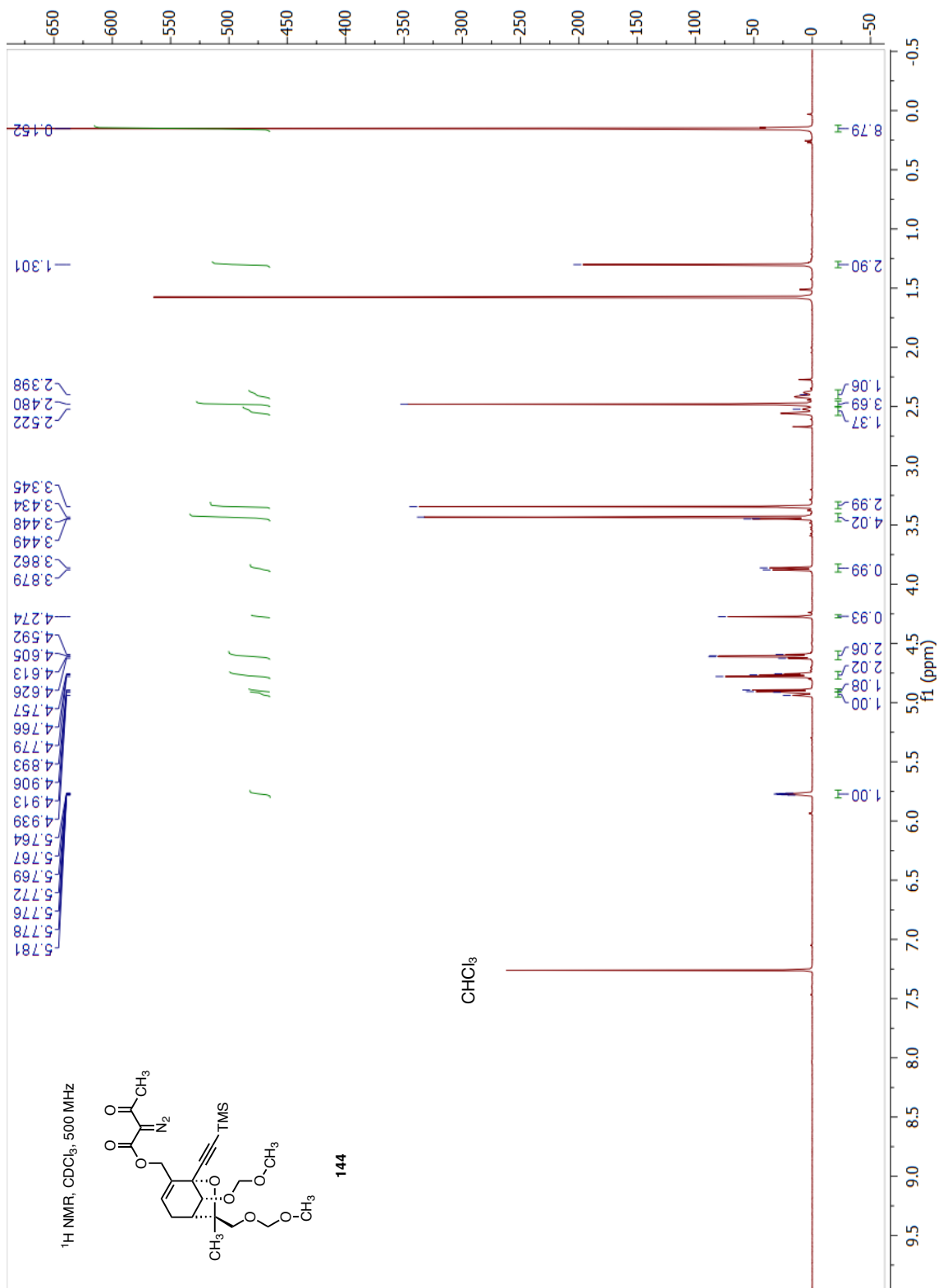


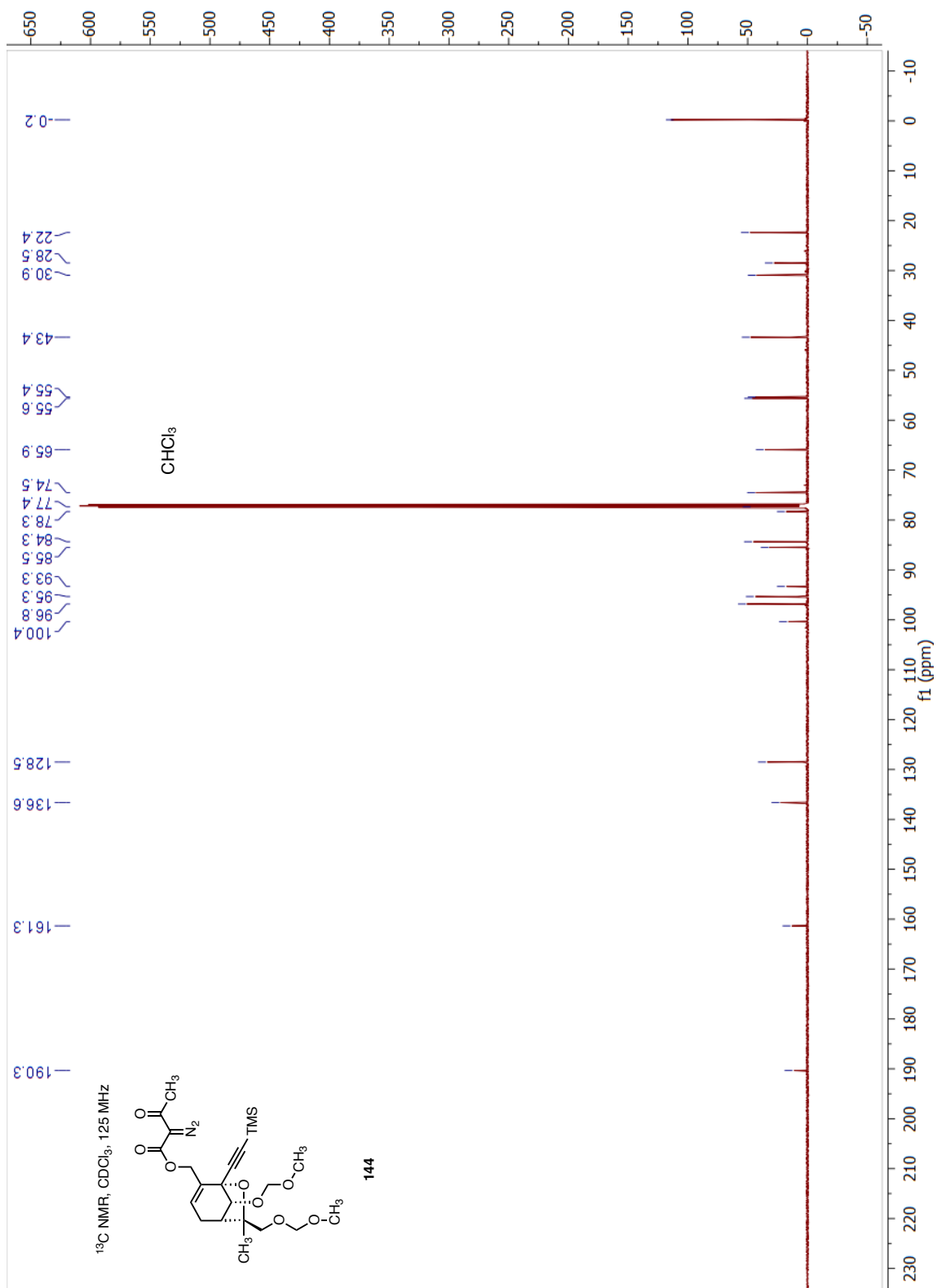
145

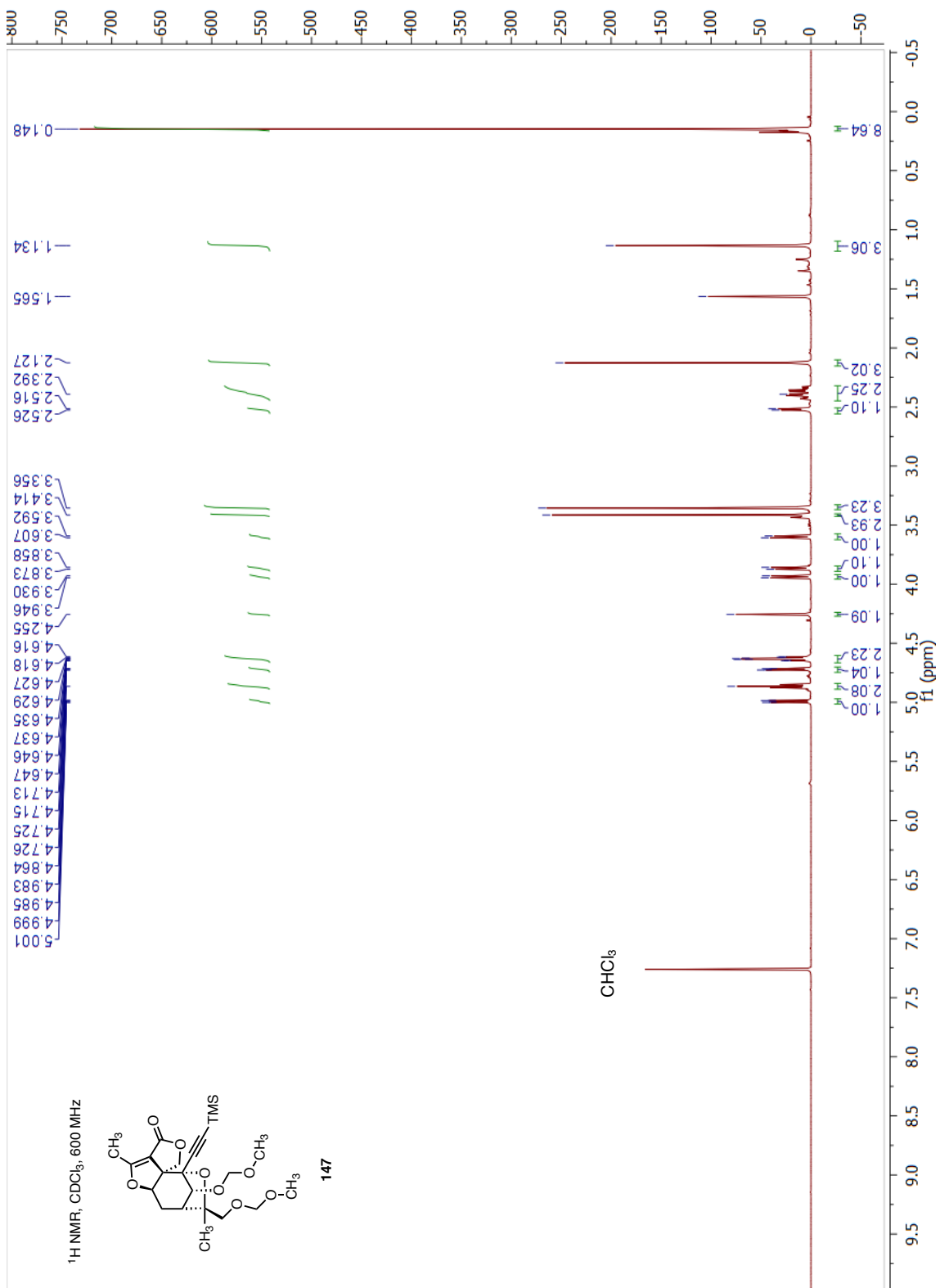


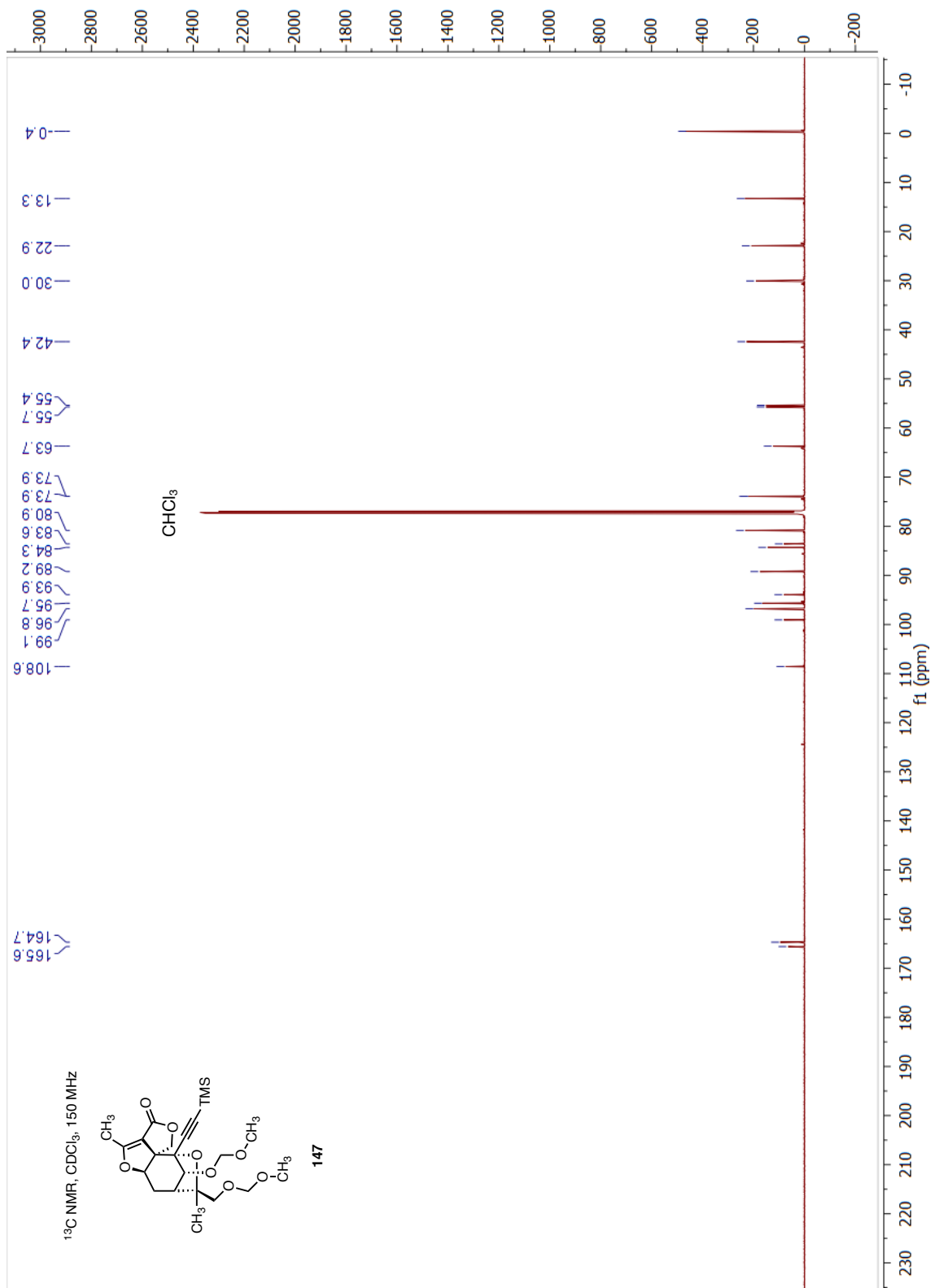




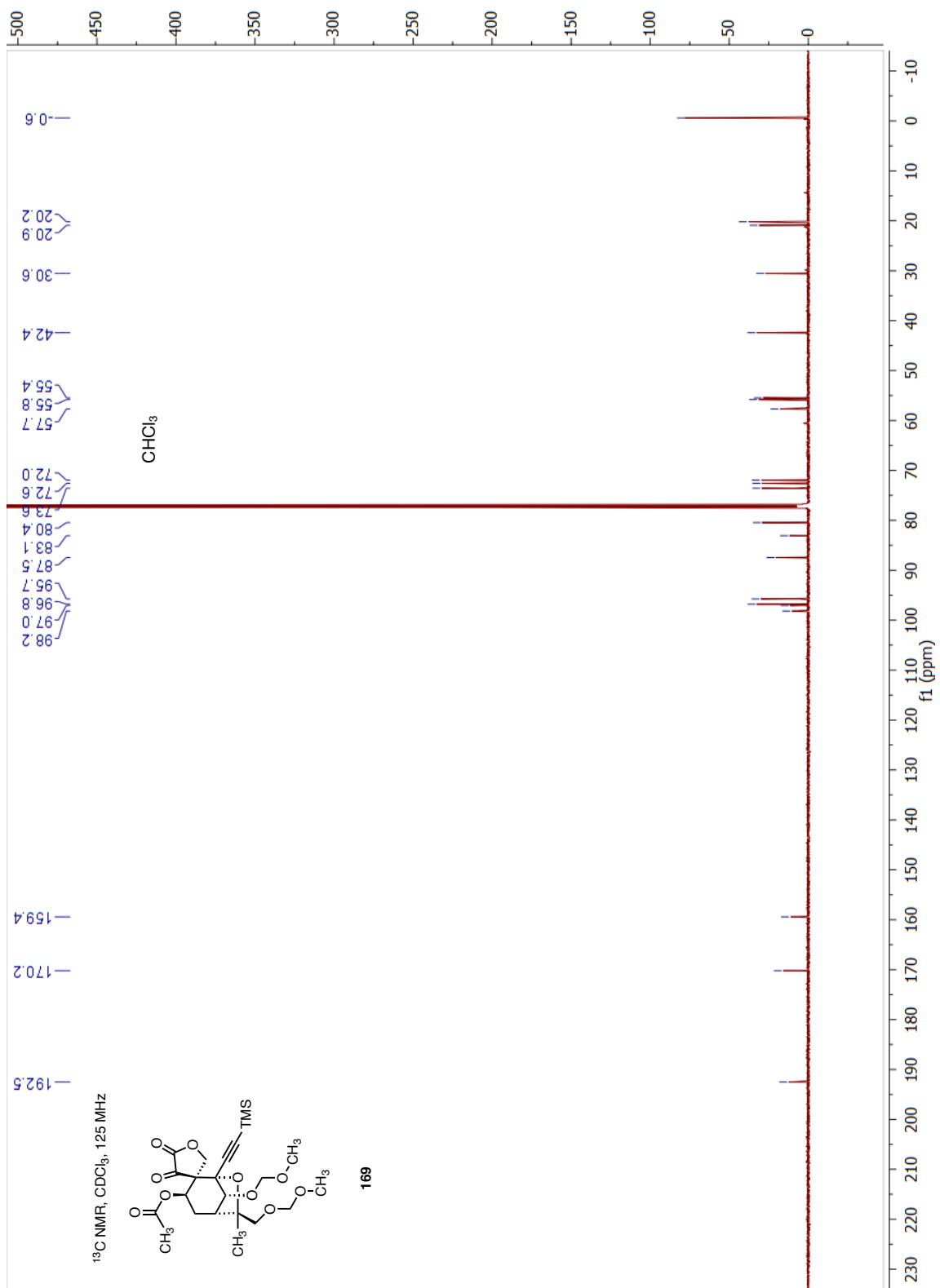






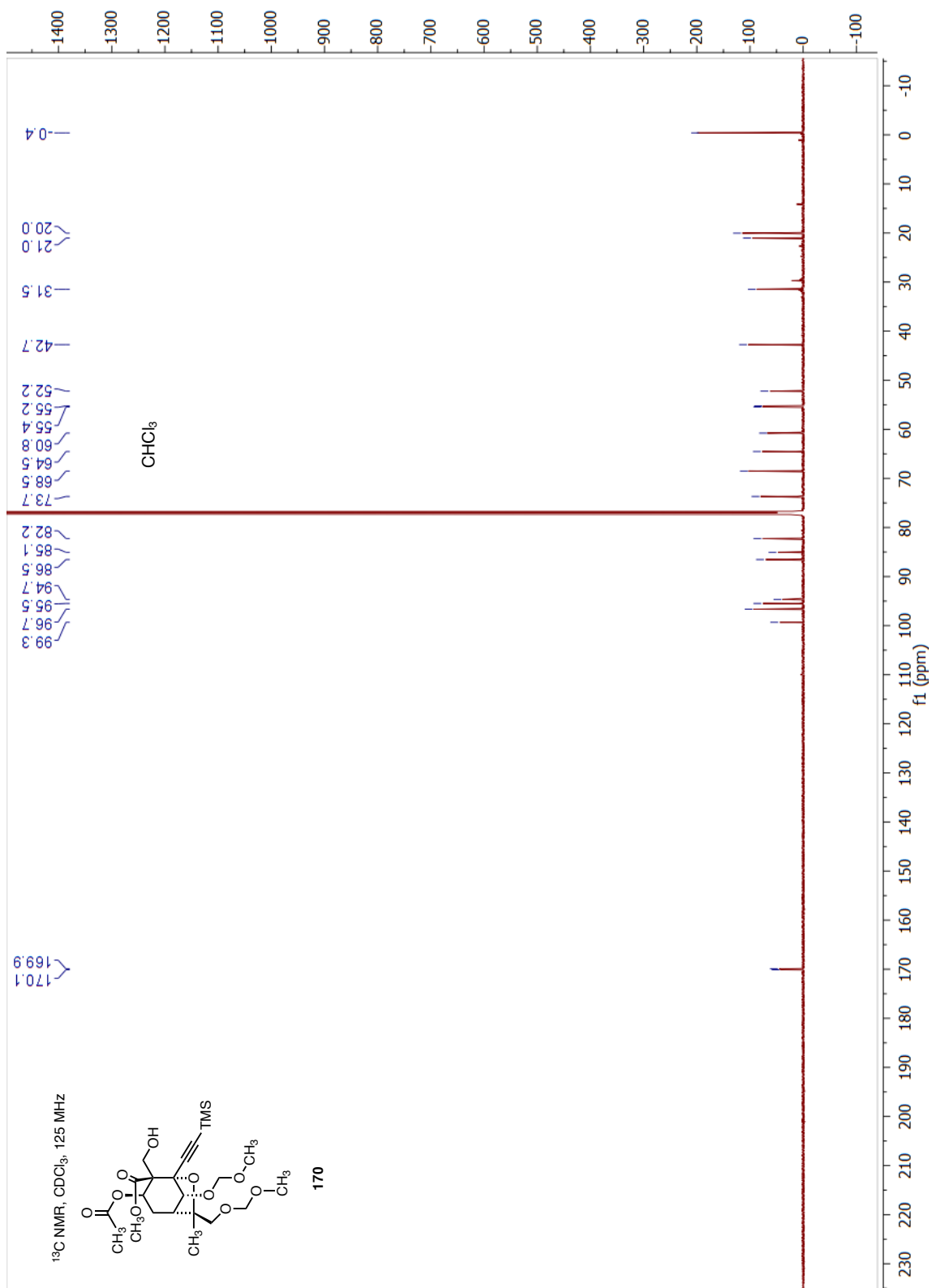


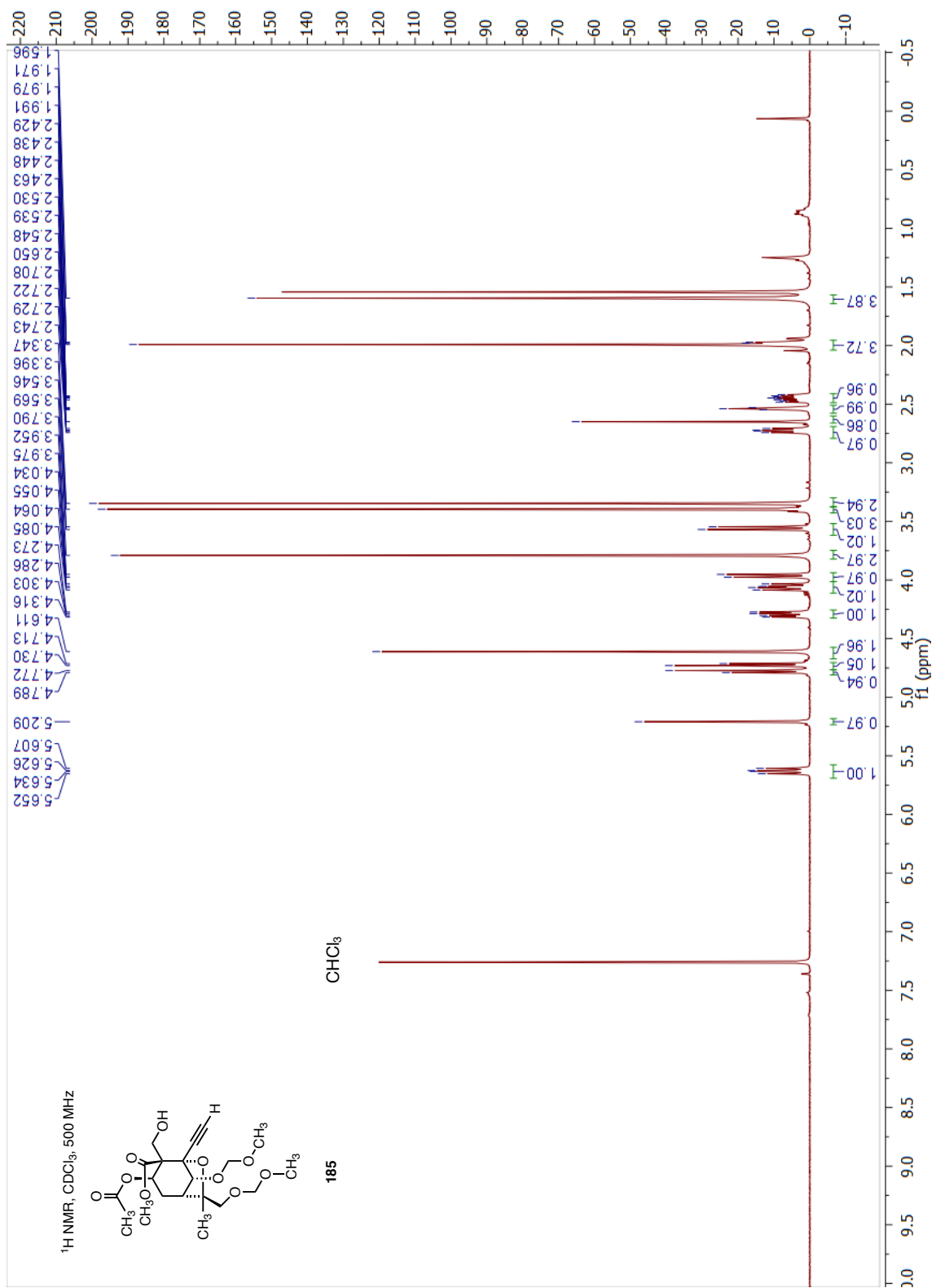


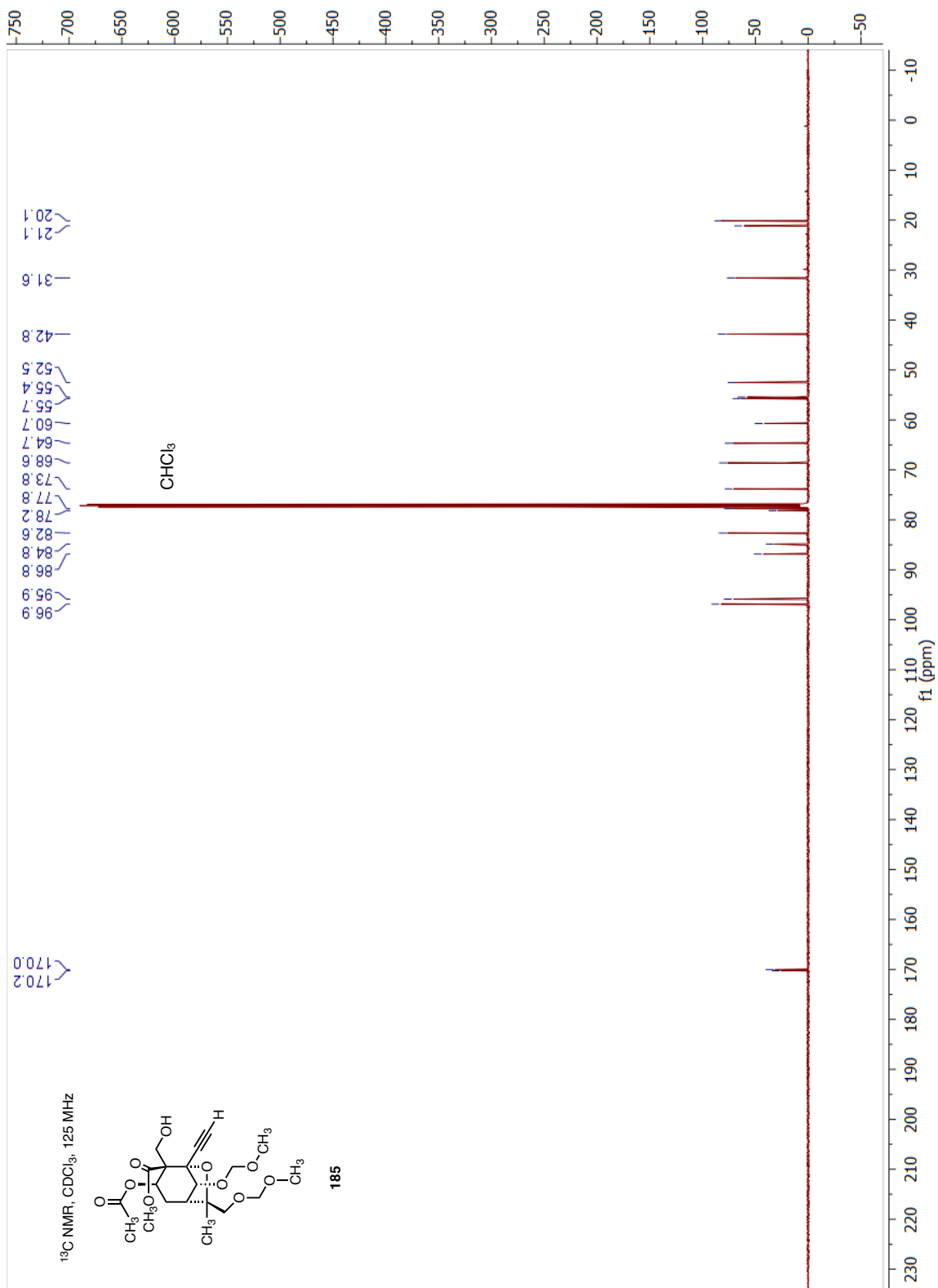


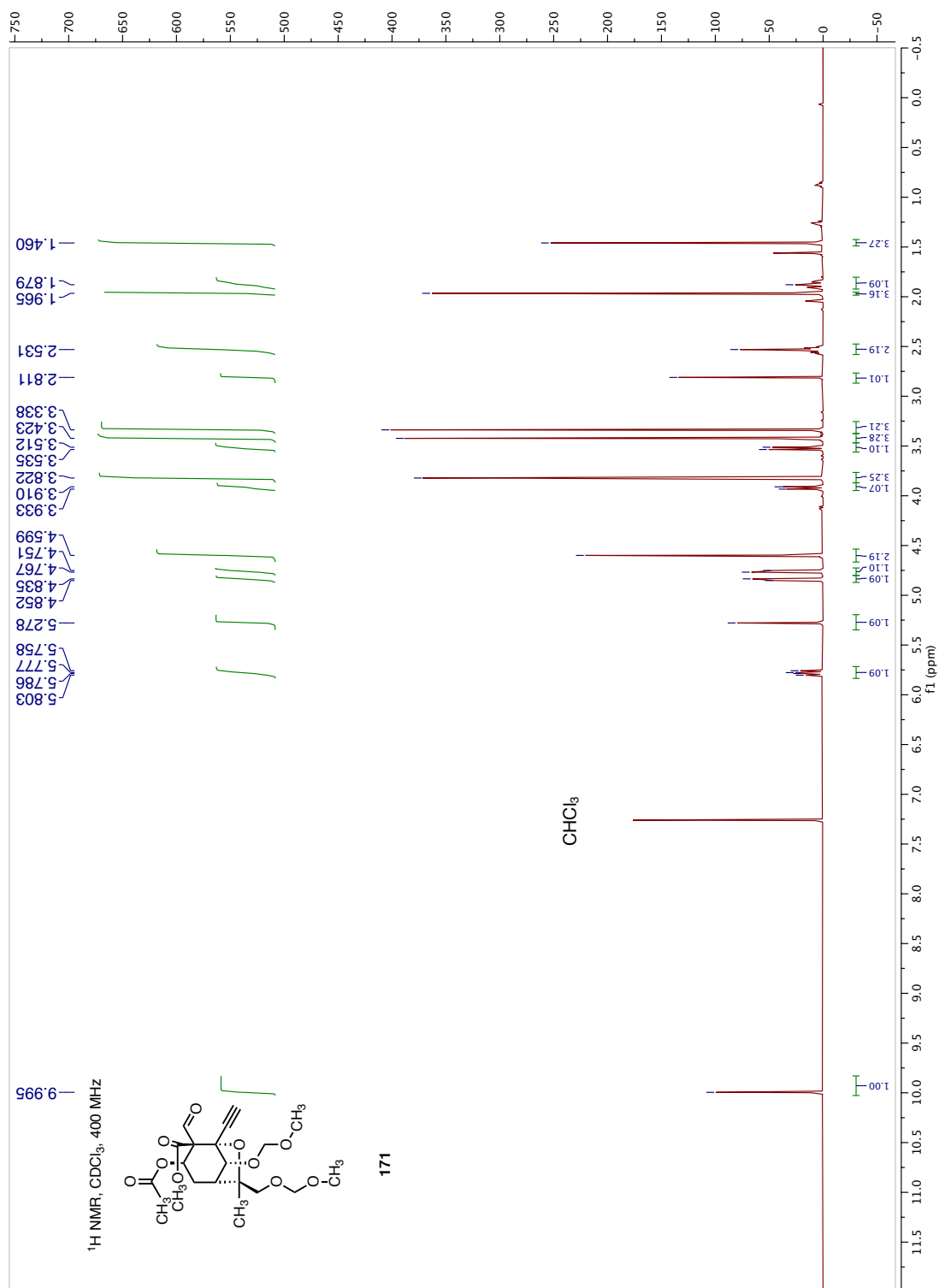


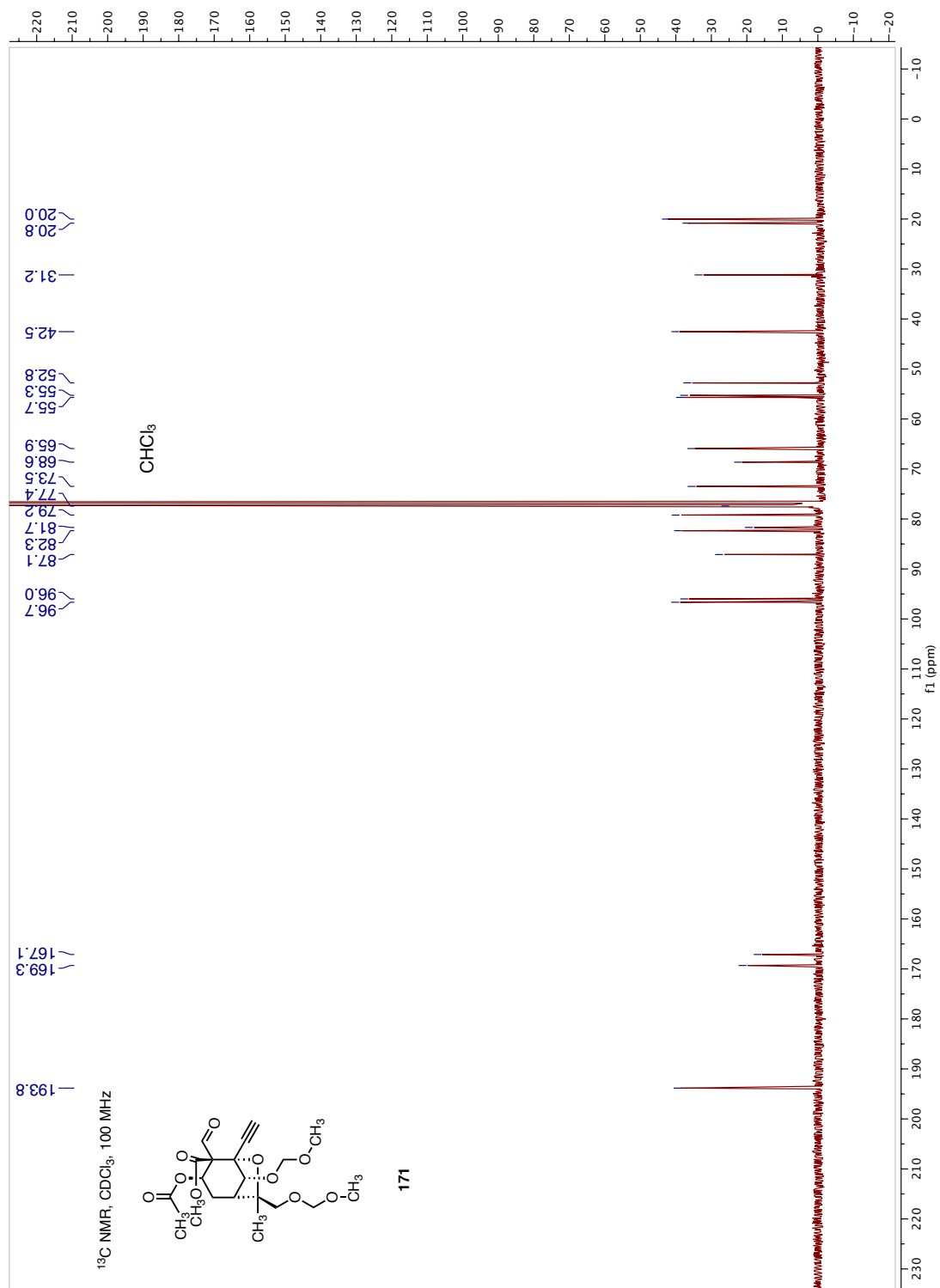


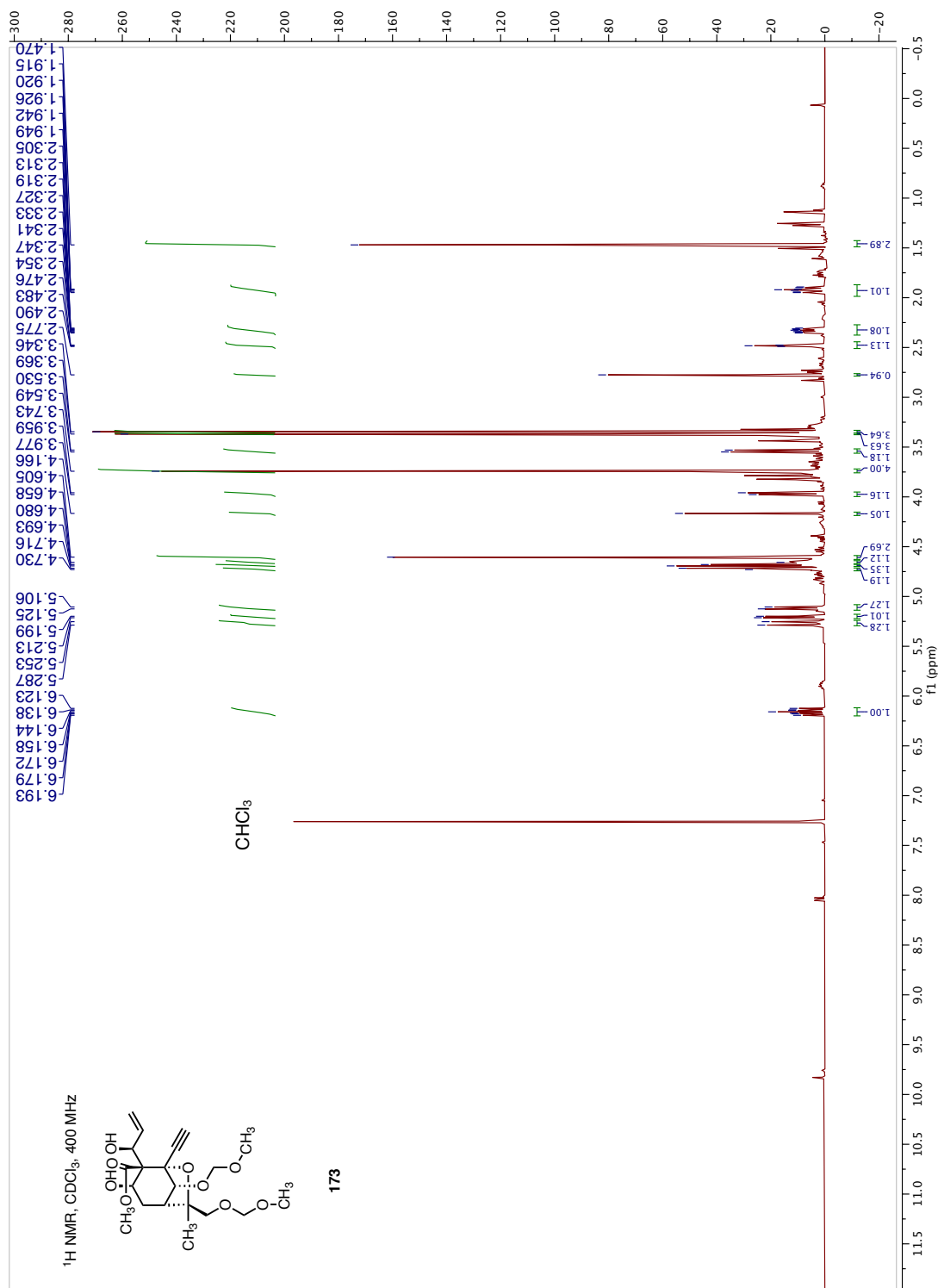


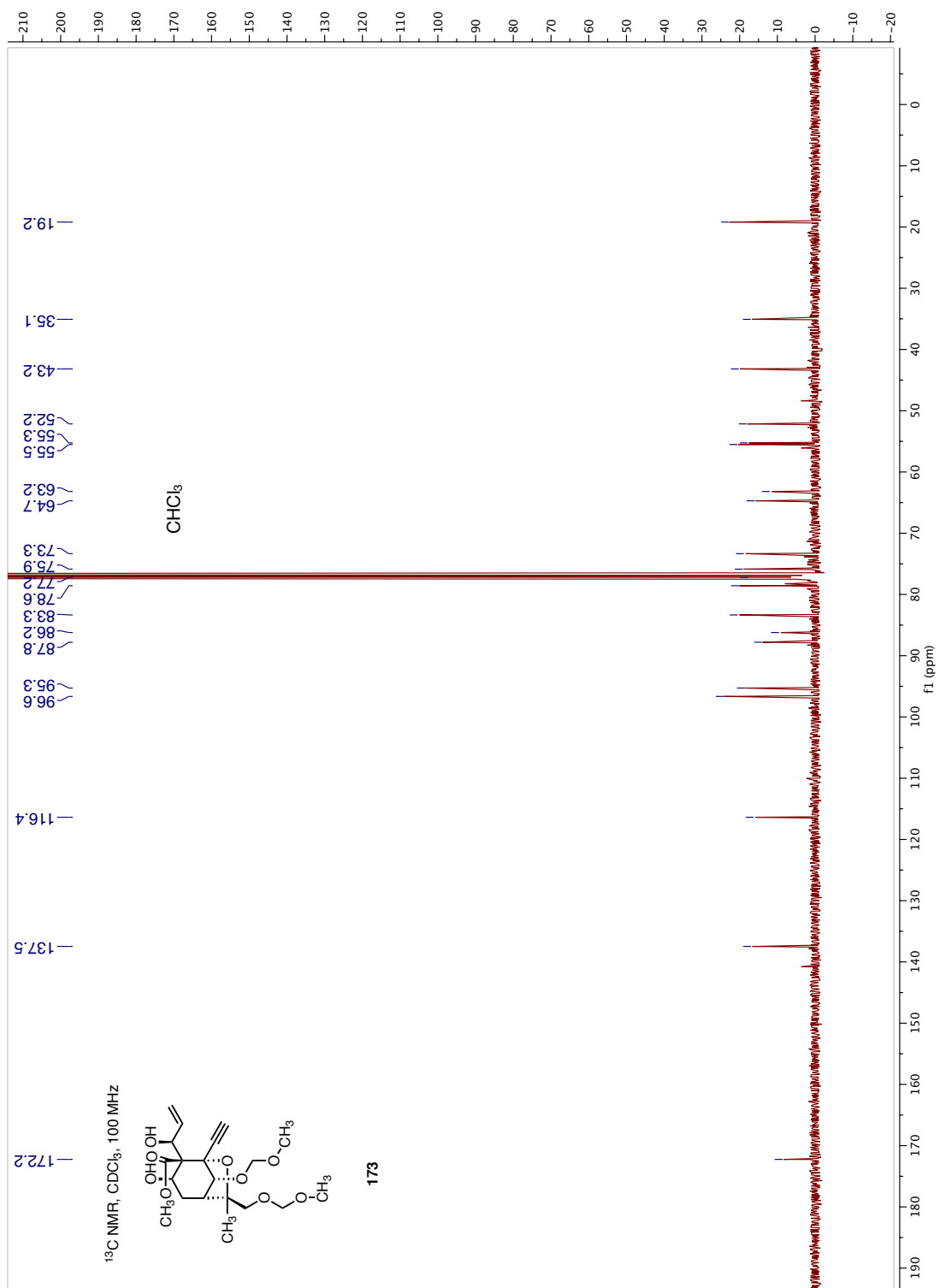


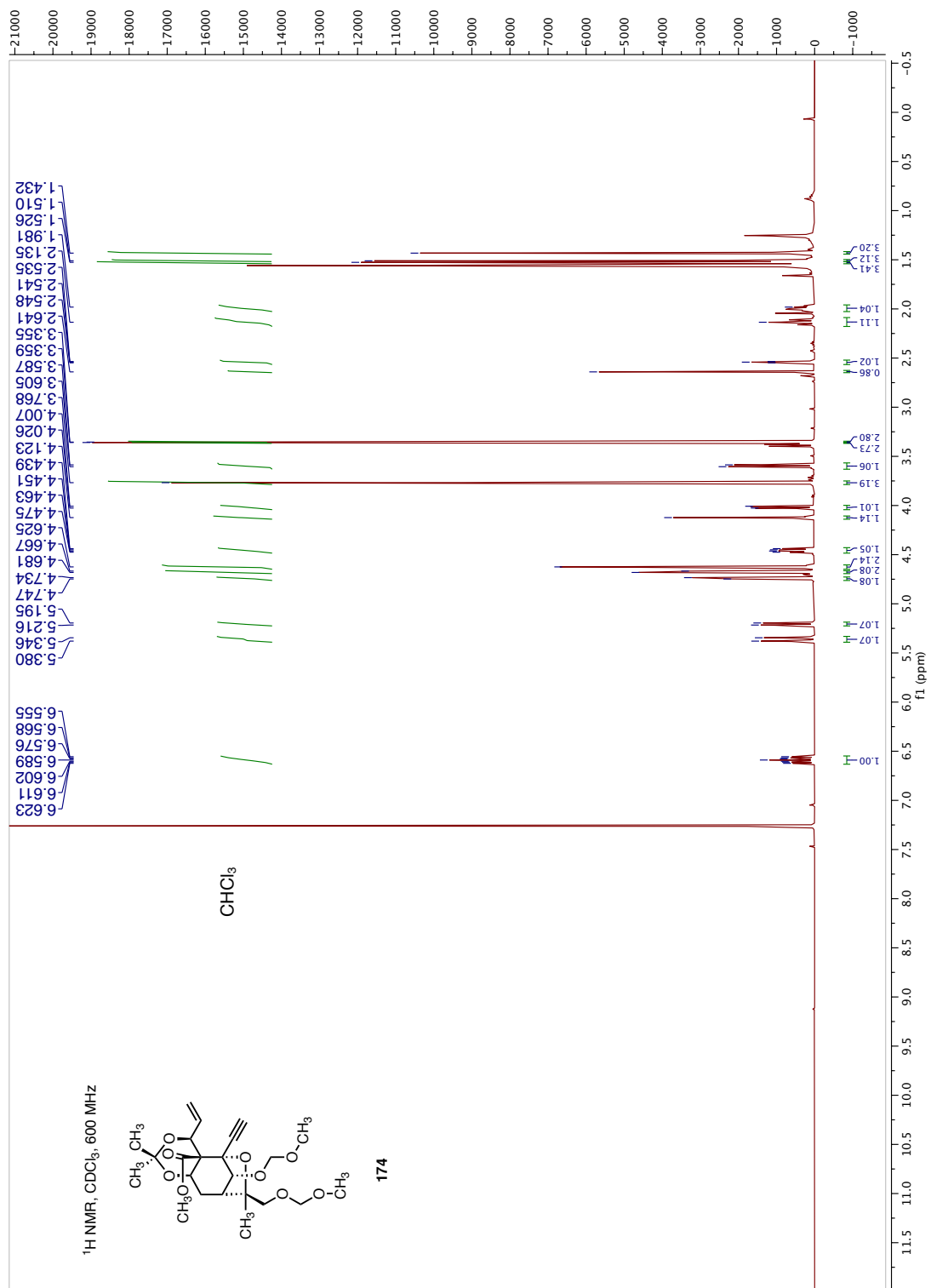




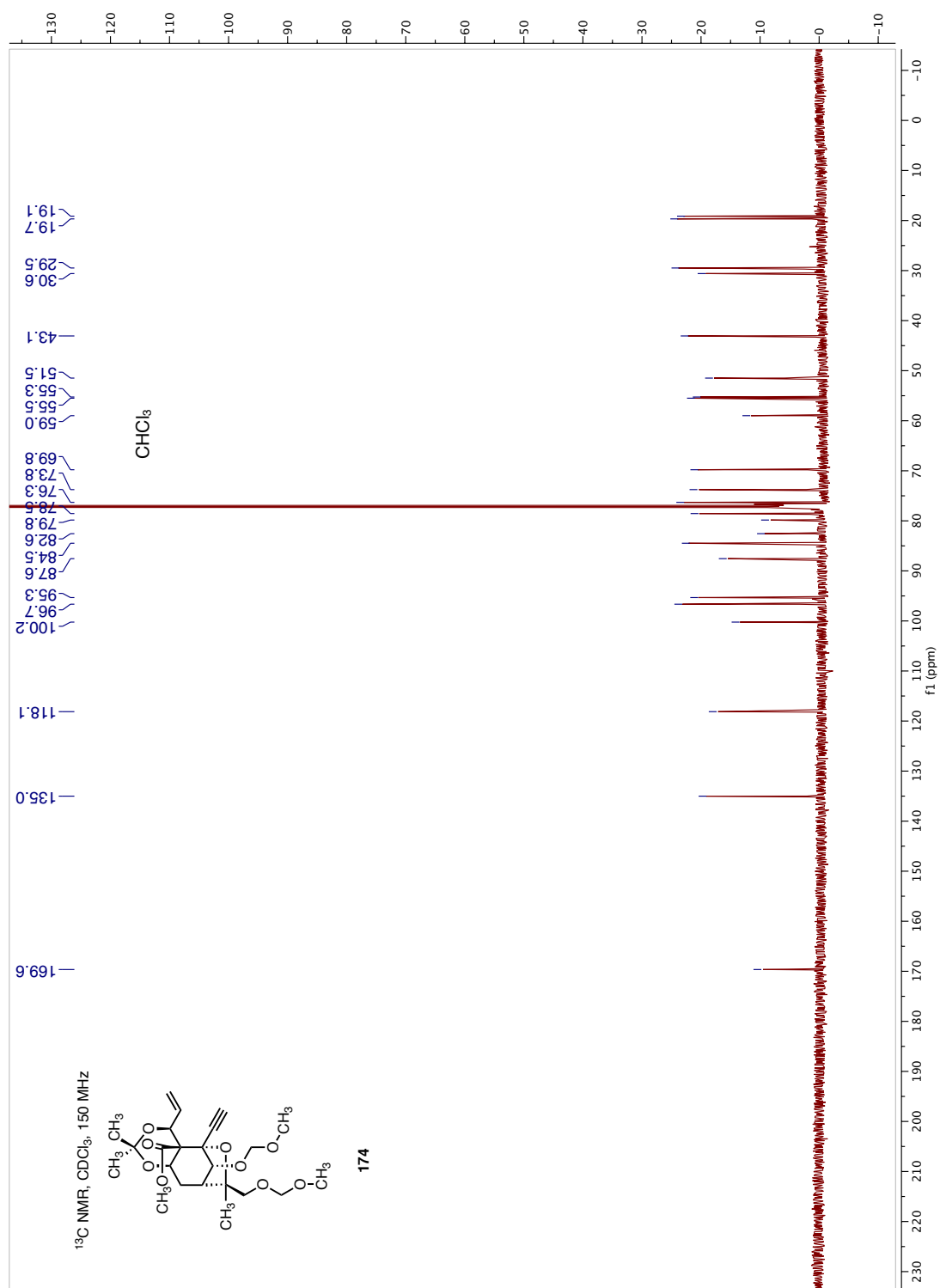


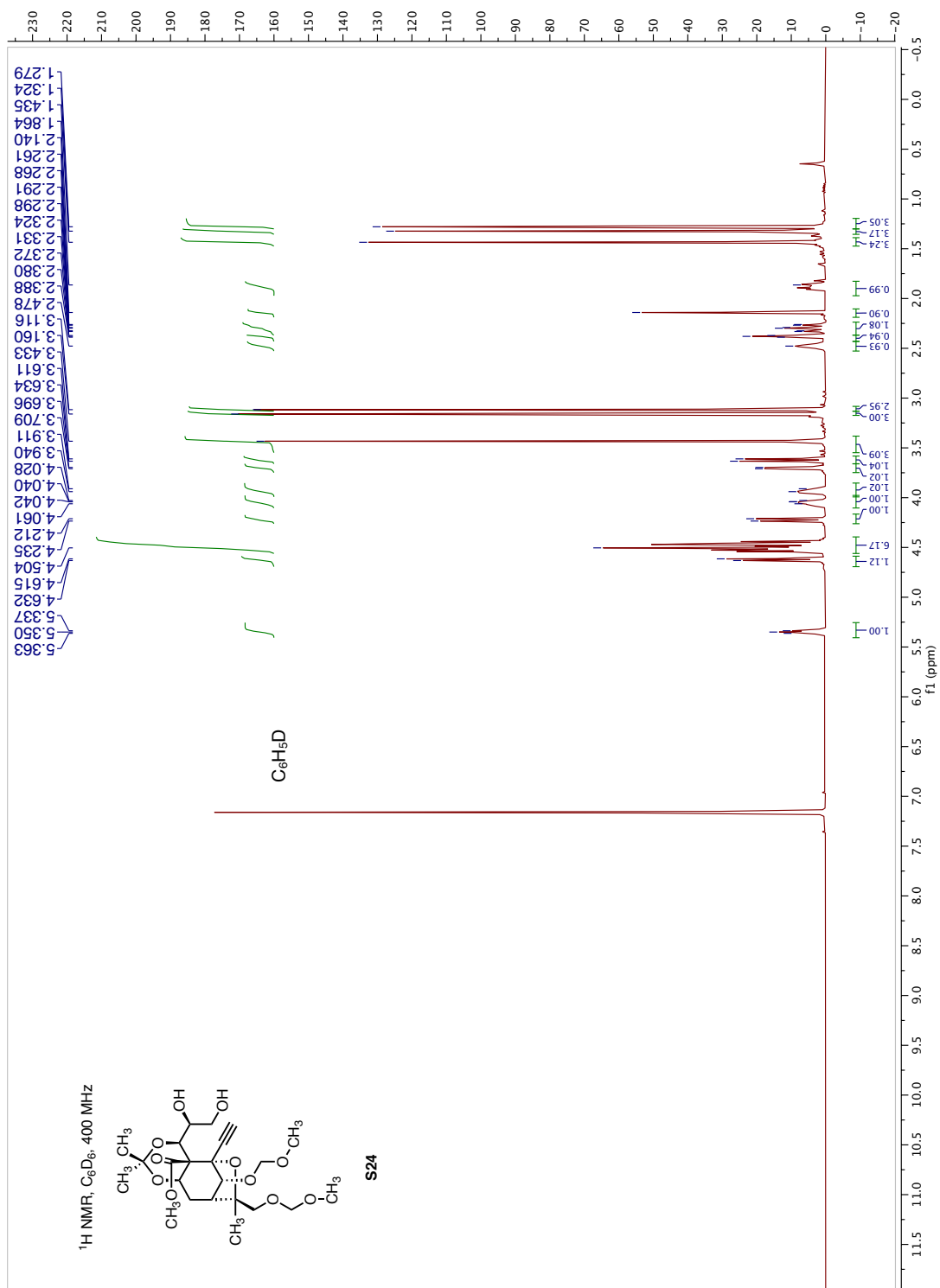


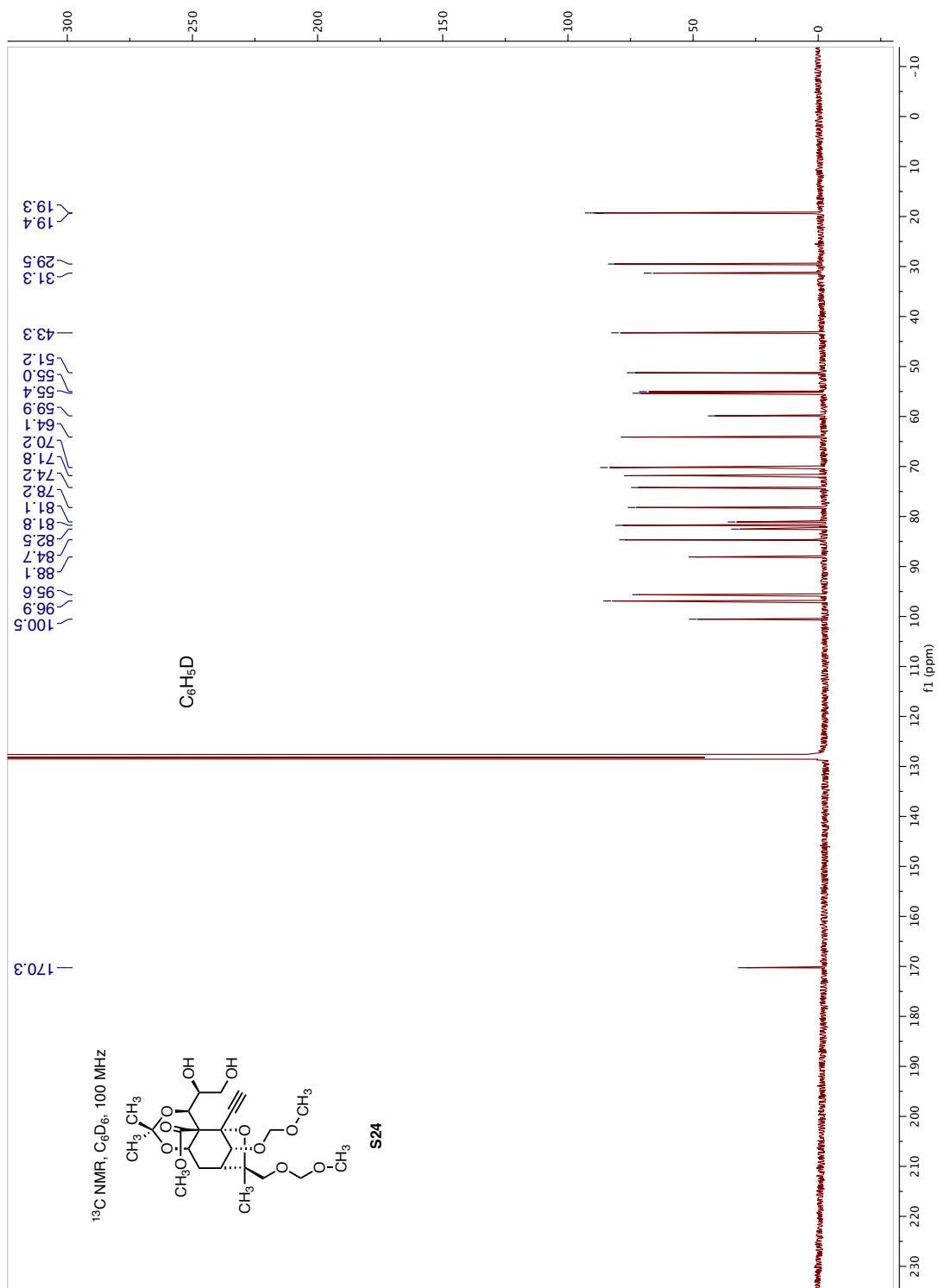


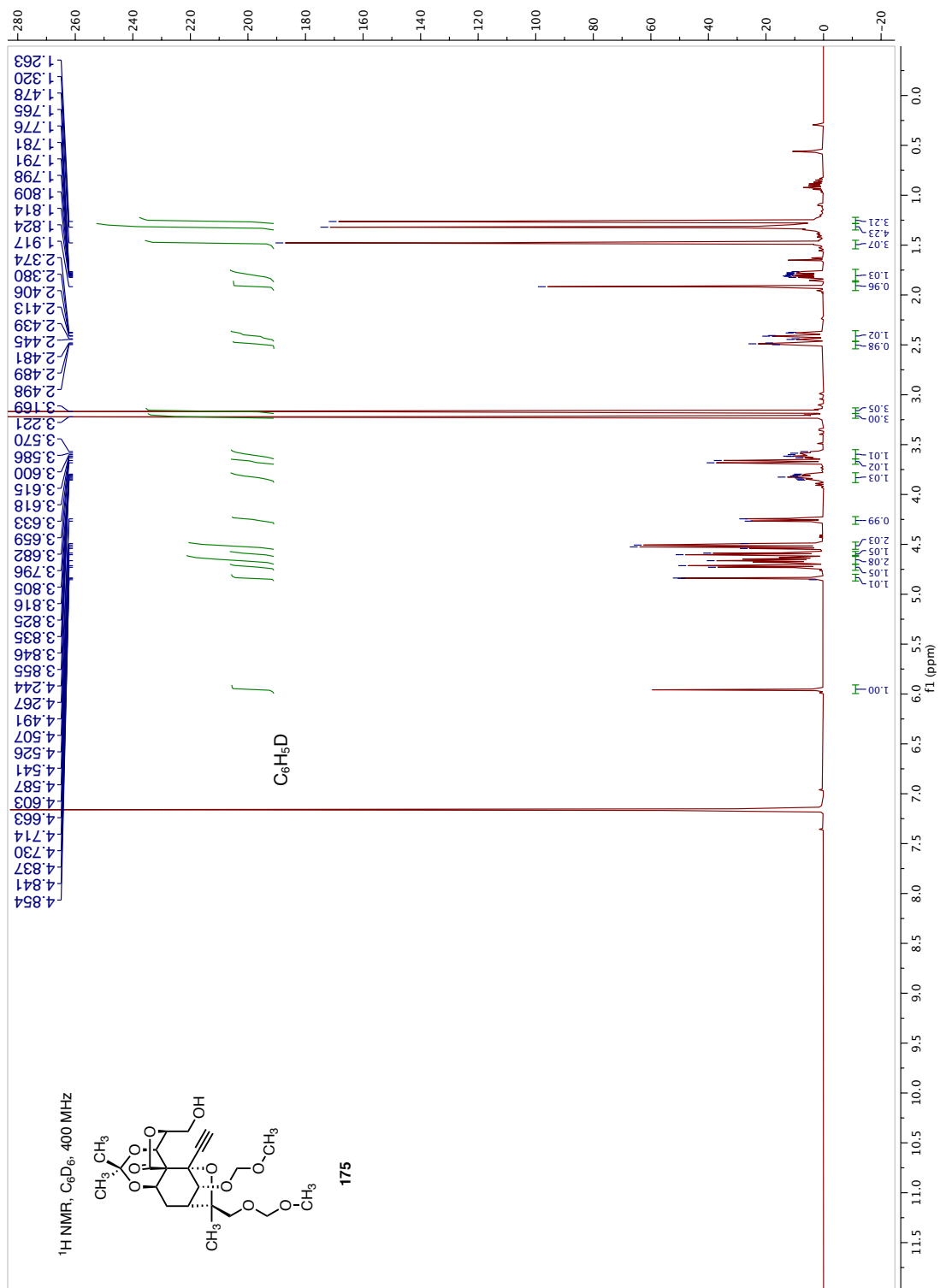


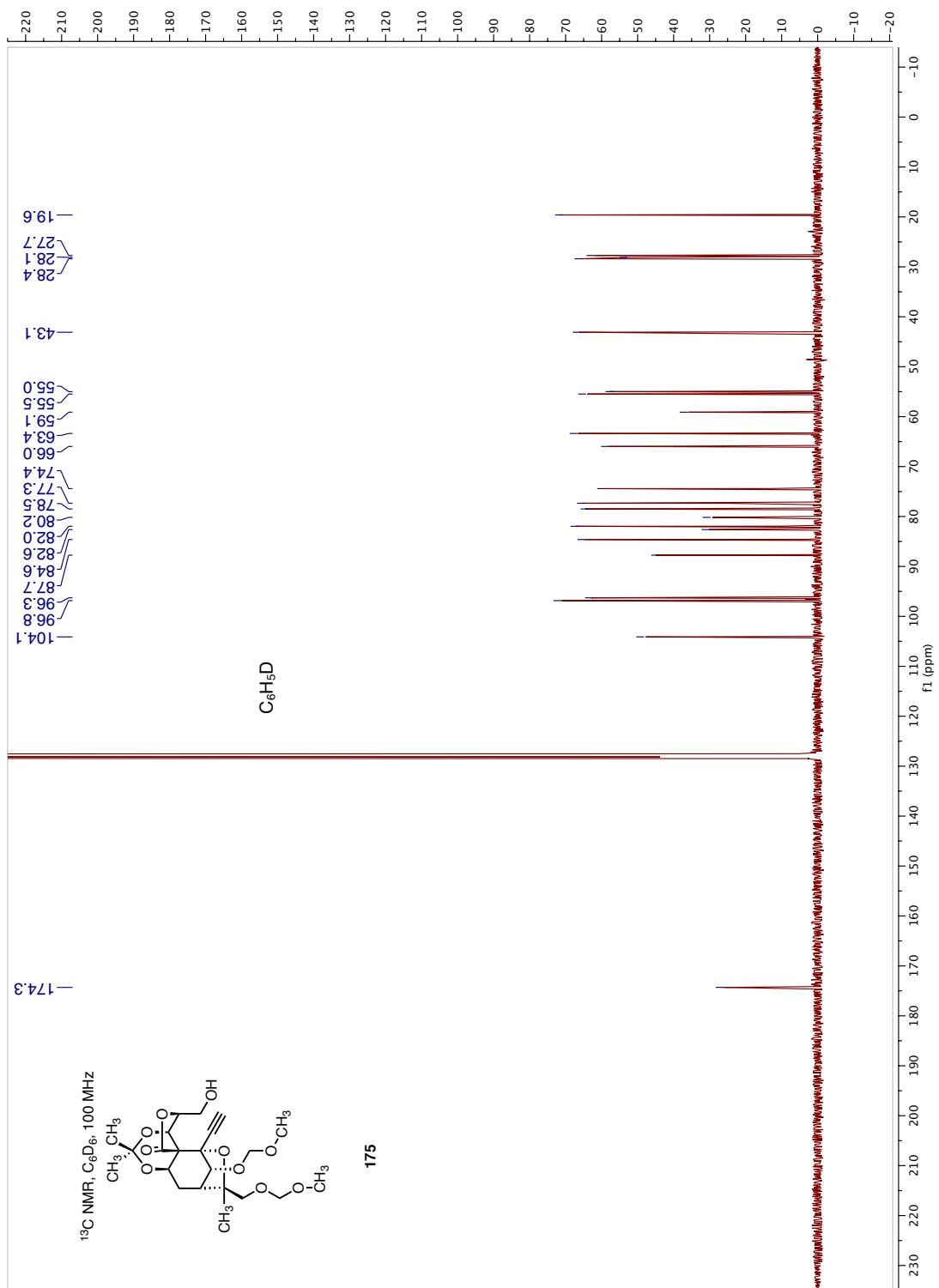




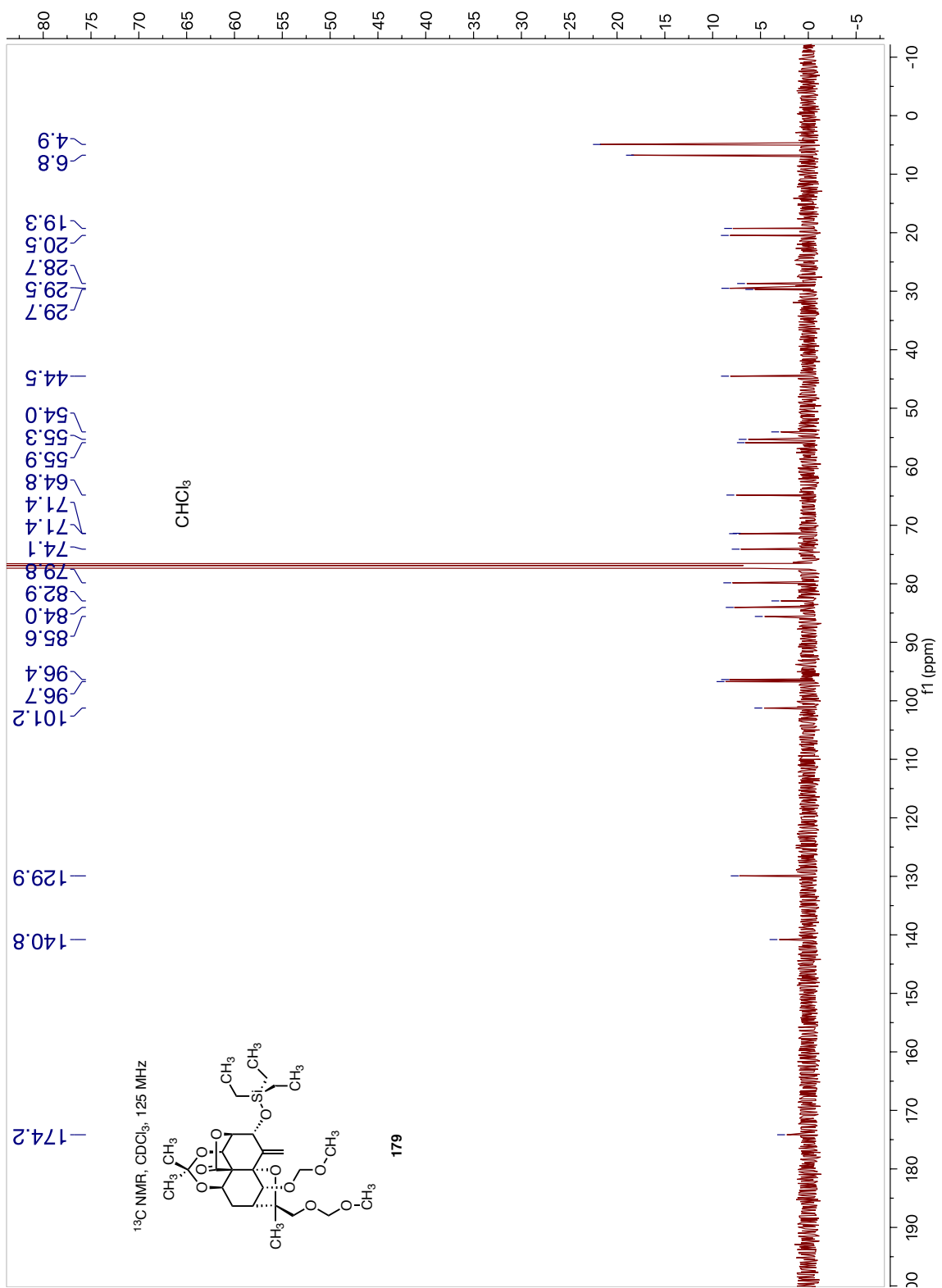


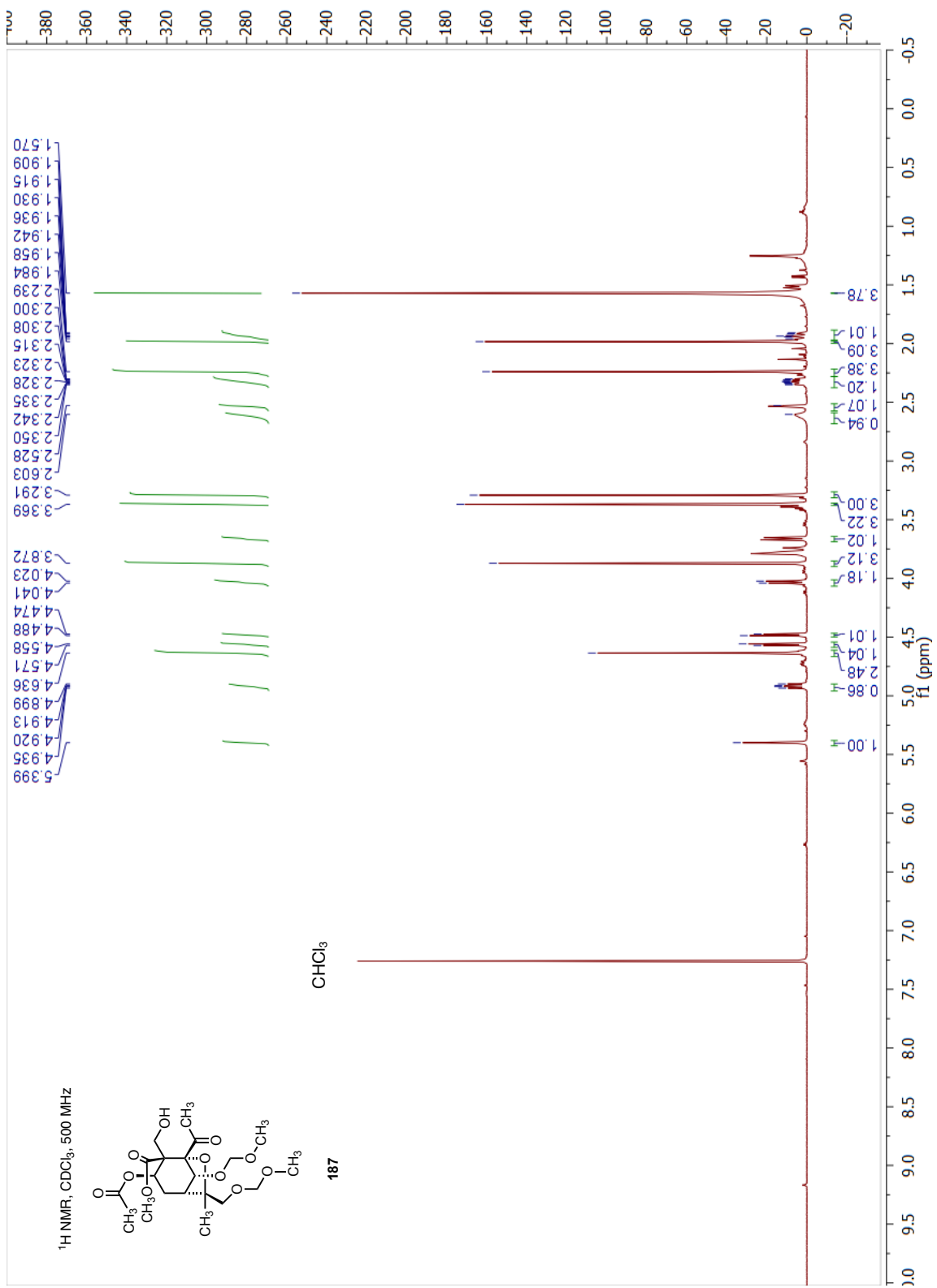






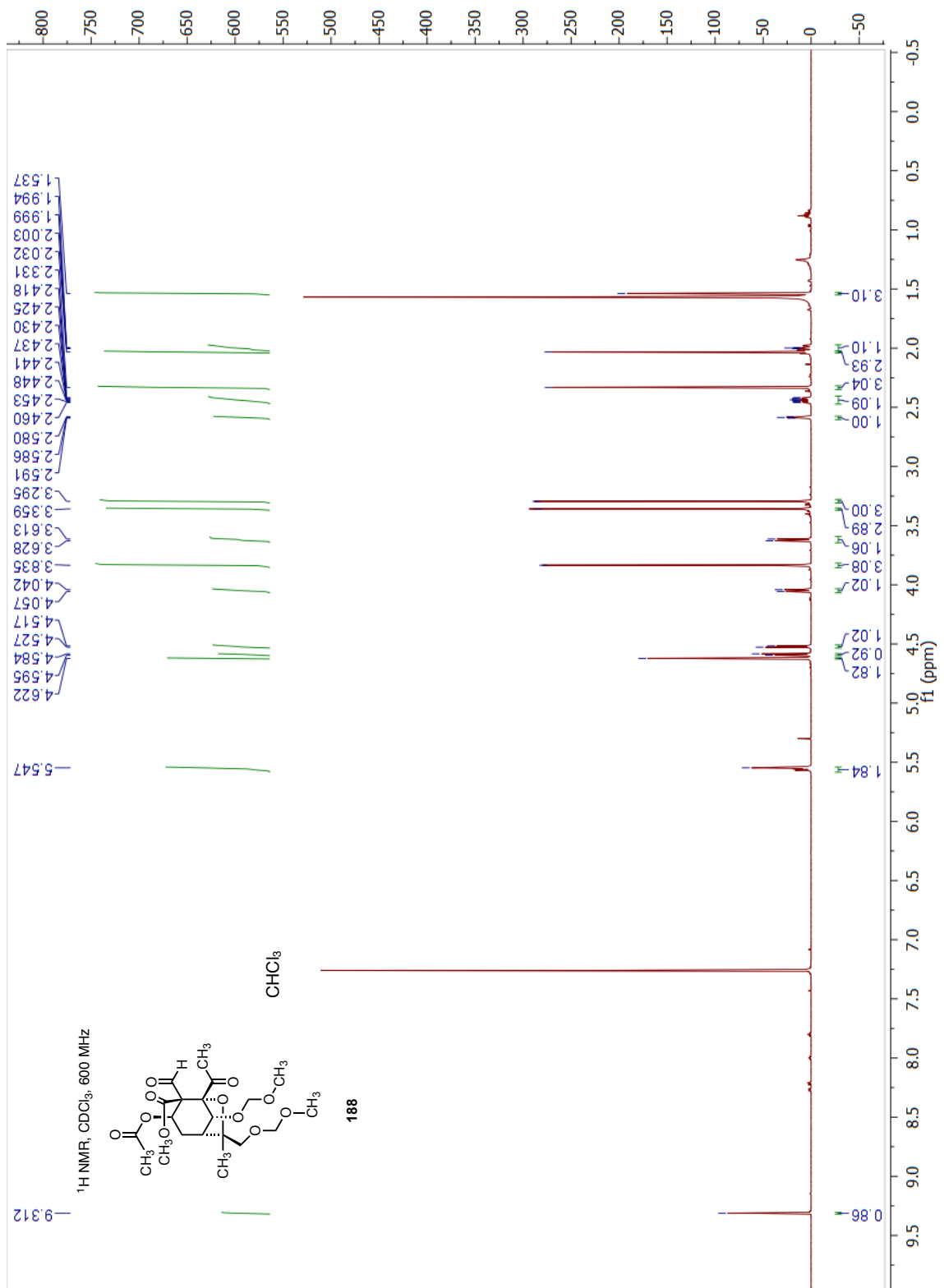




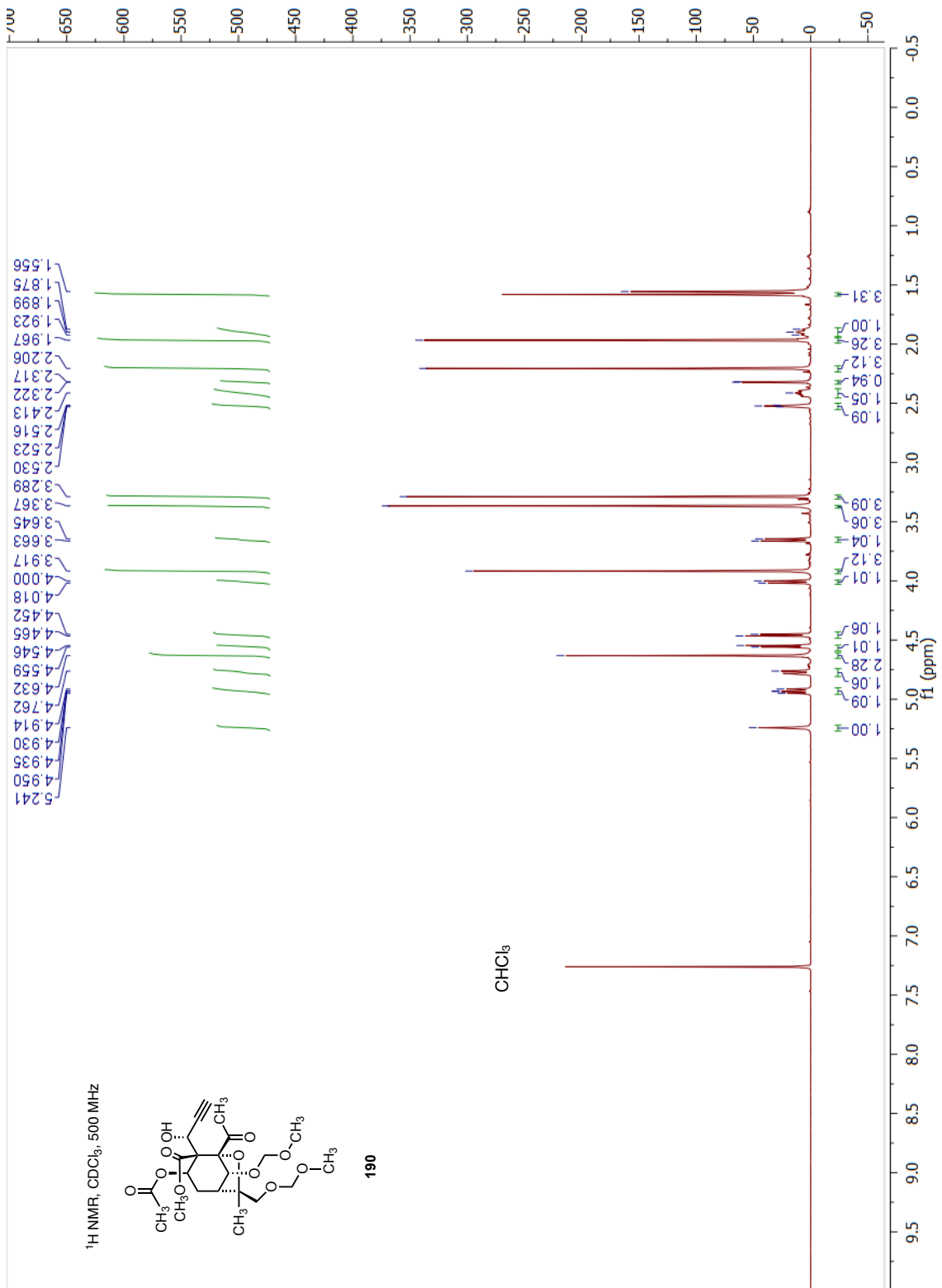


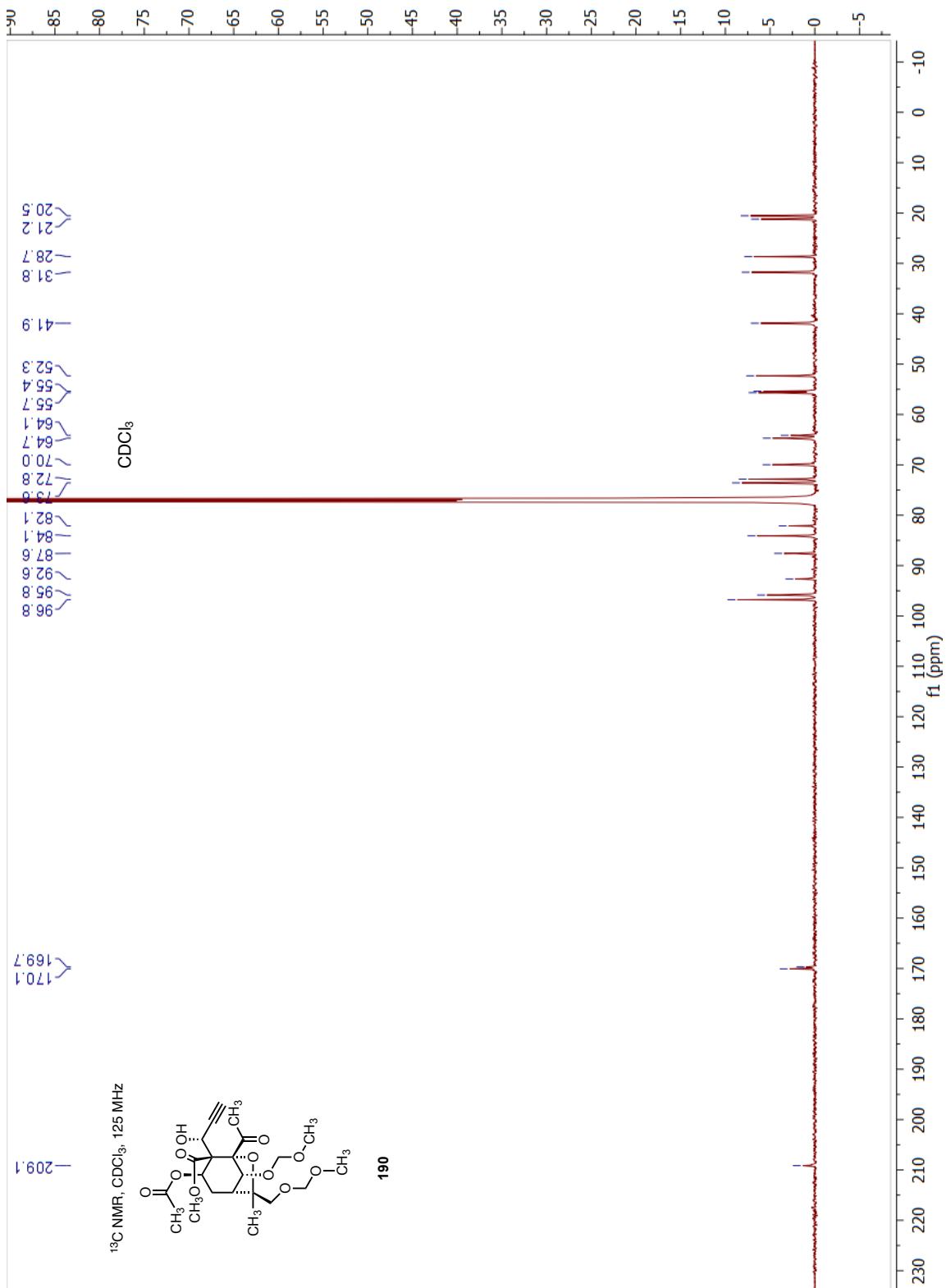


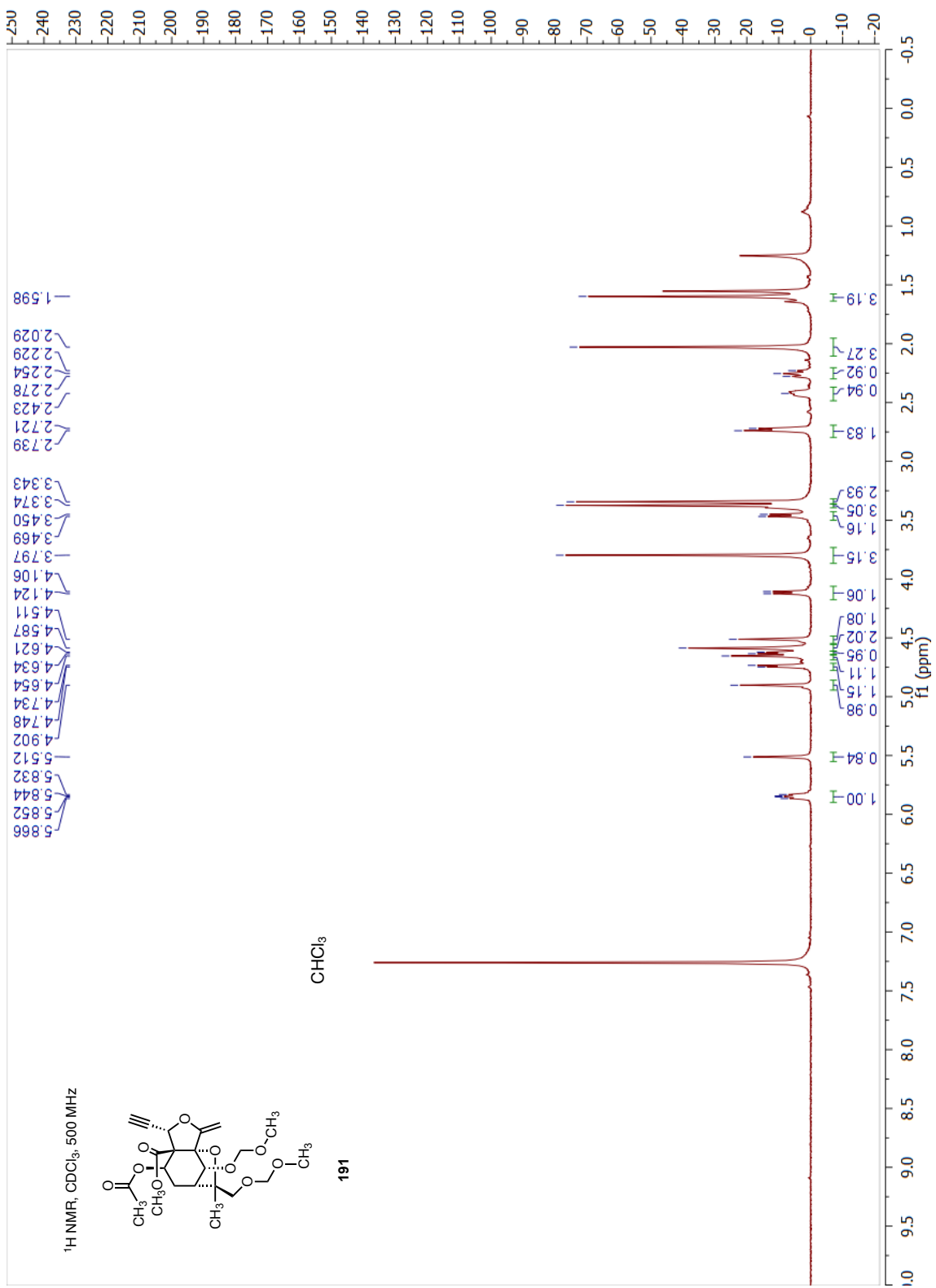


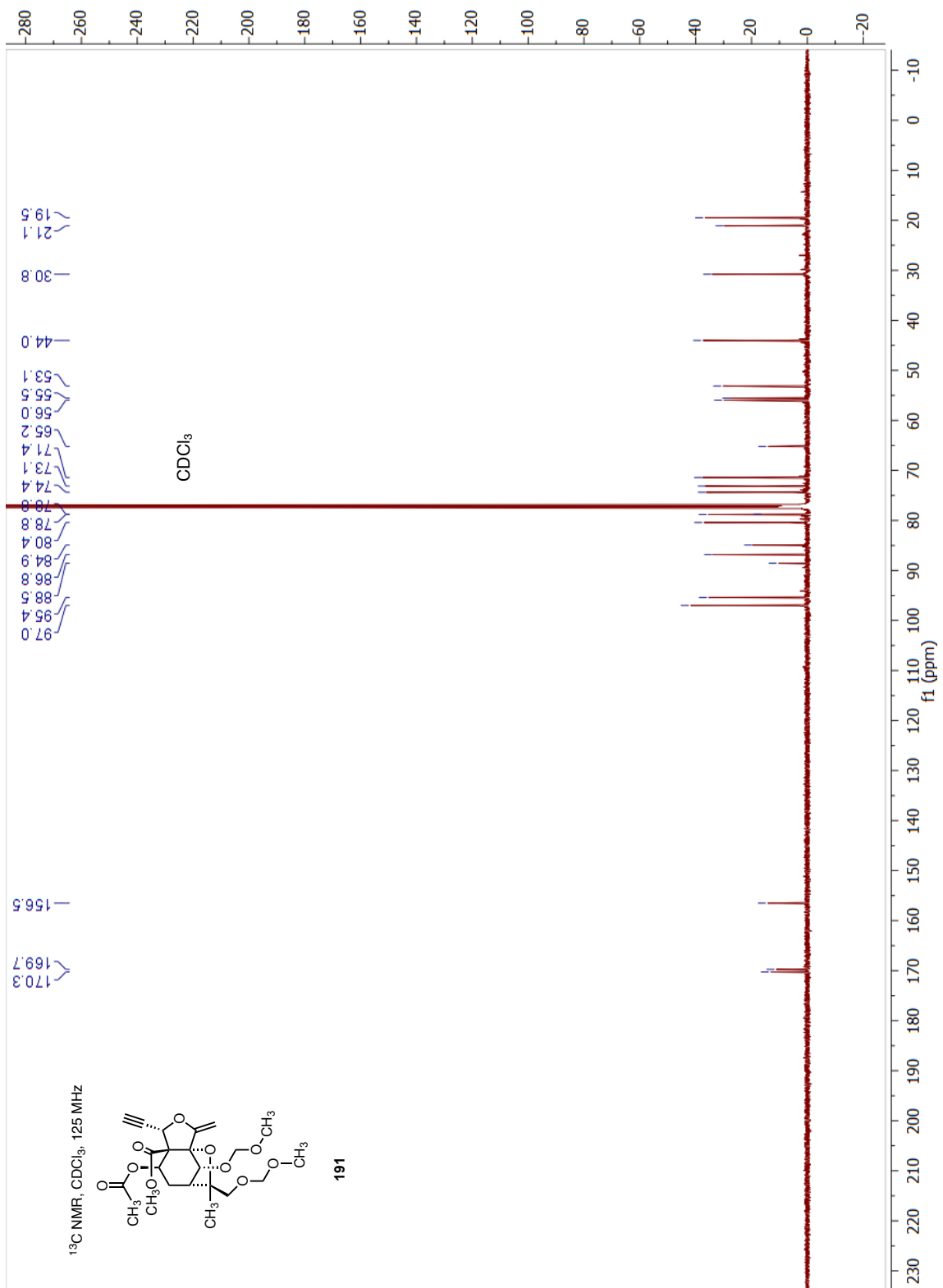


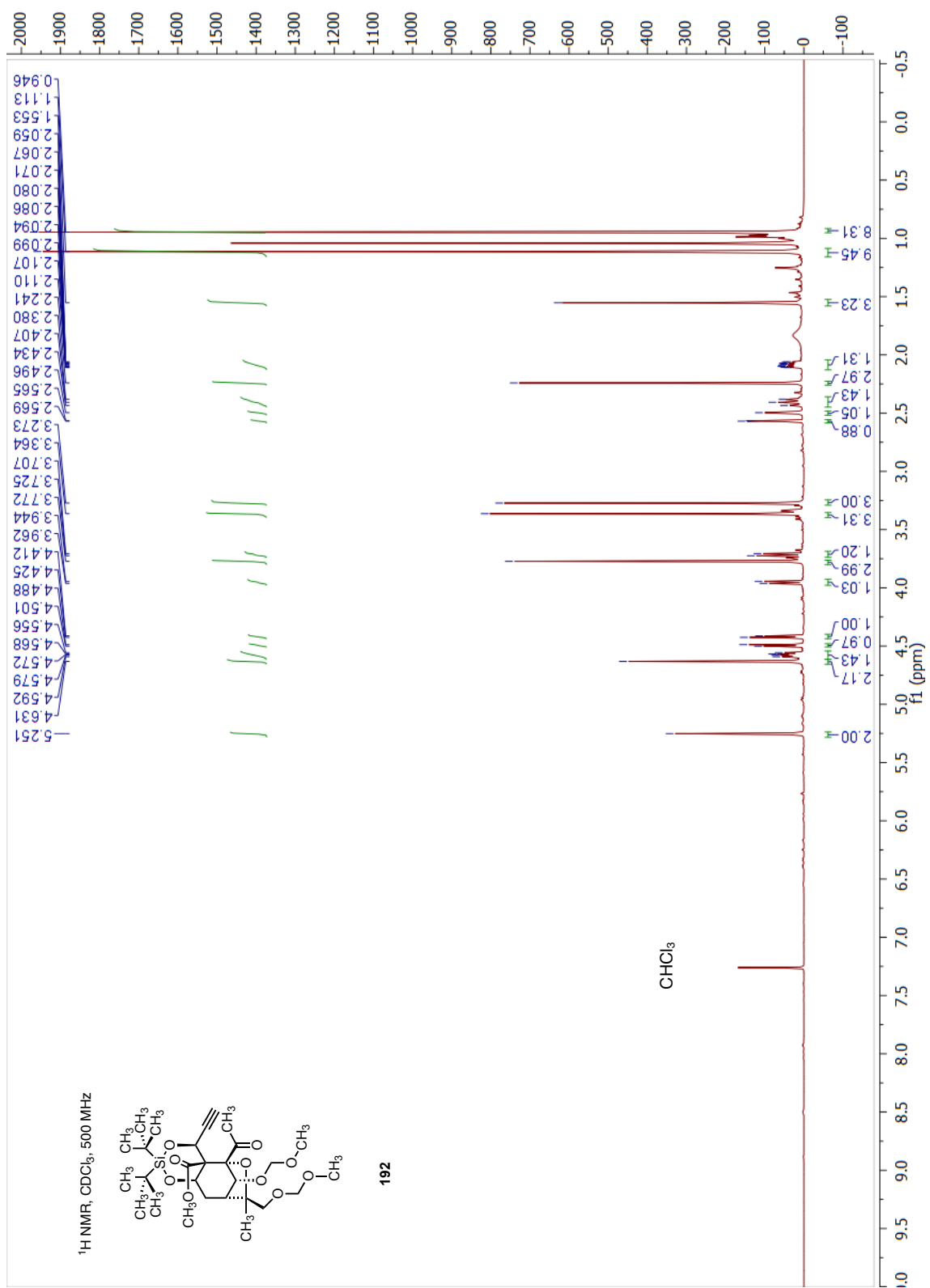




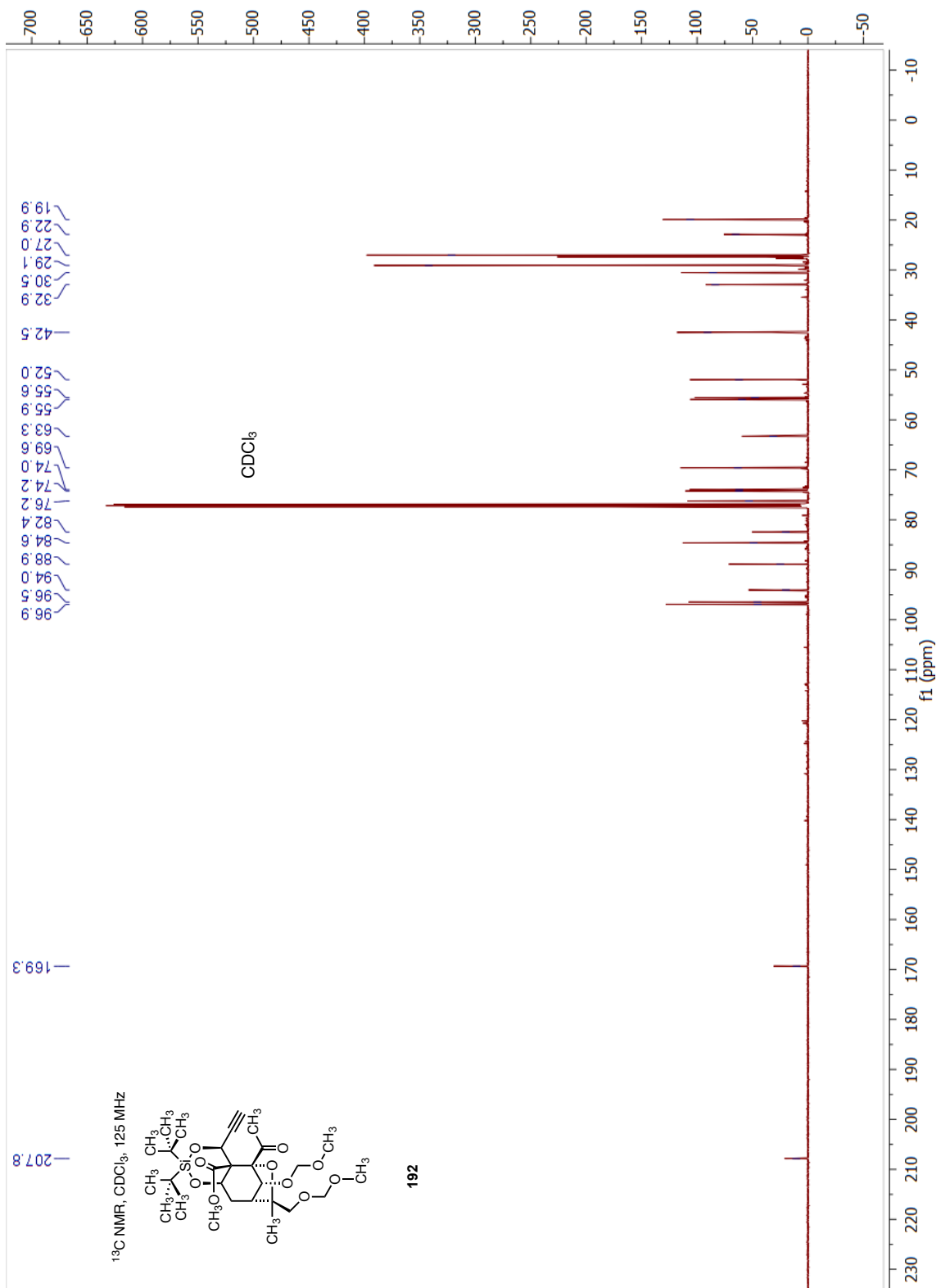




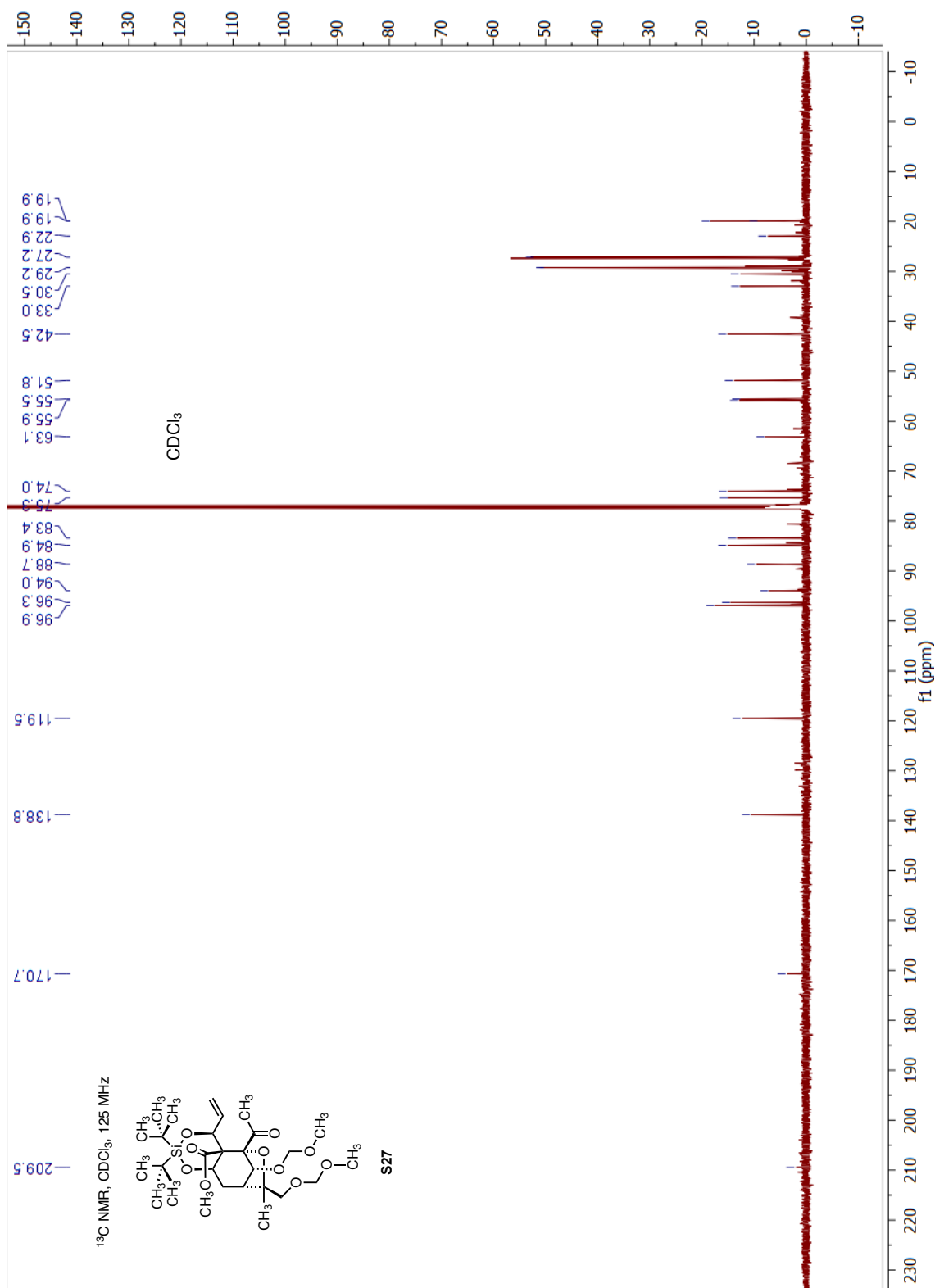


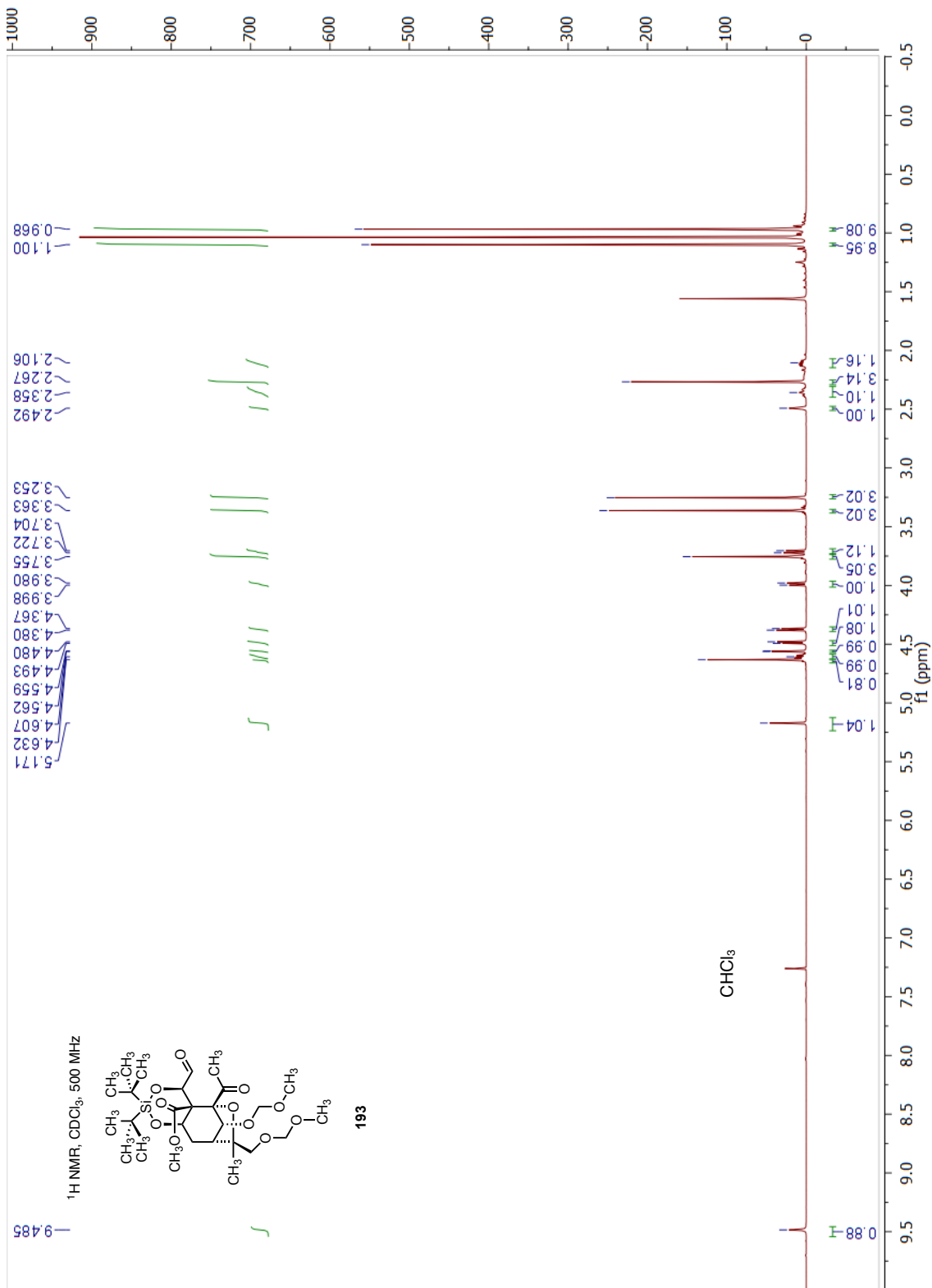






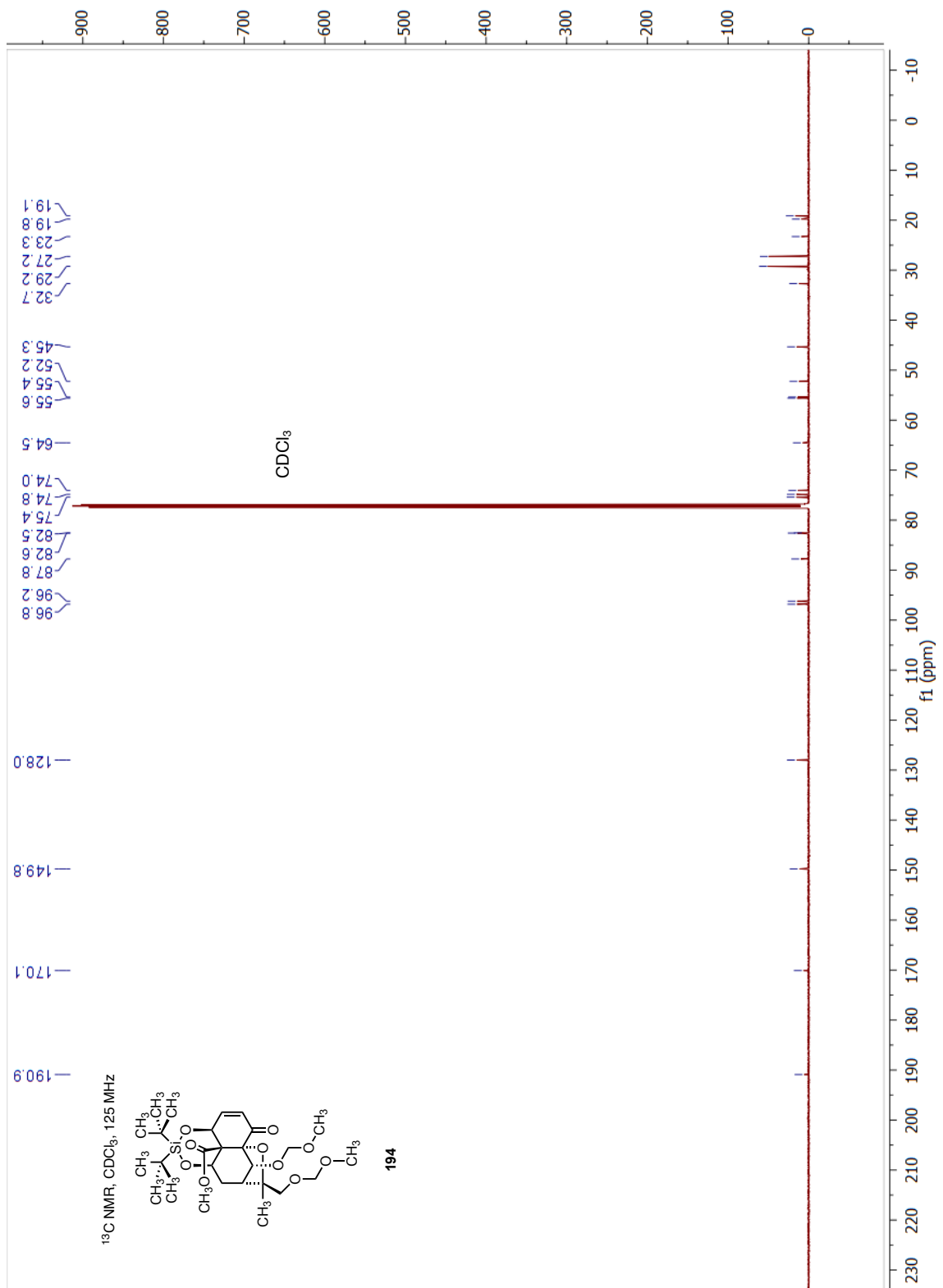


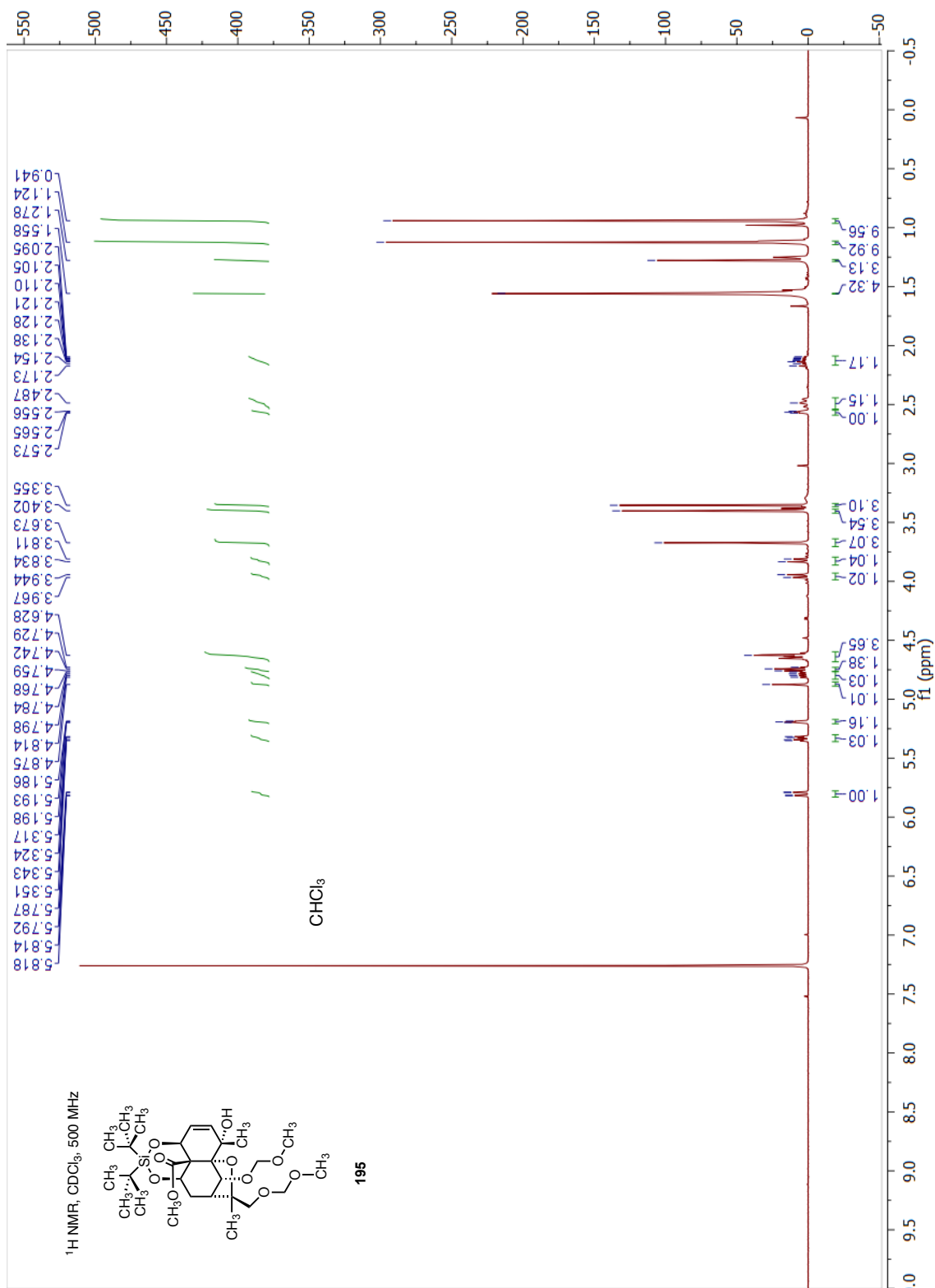




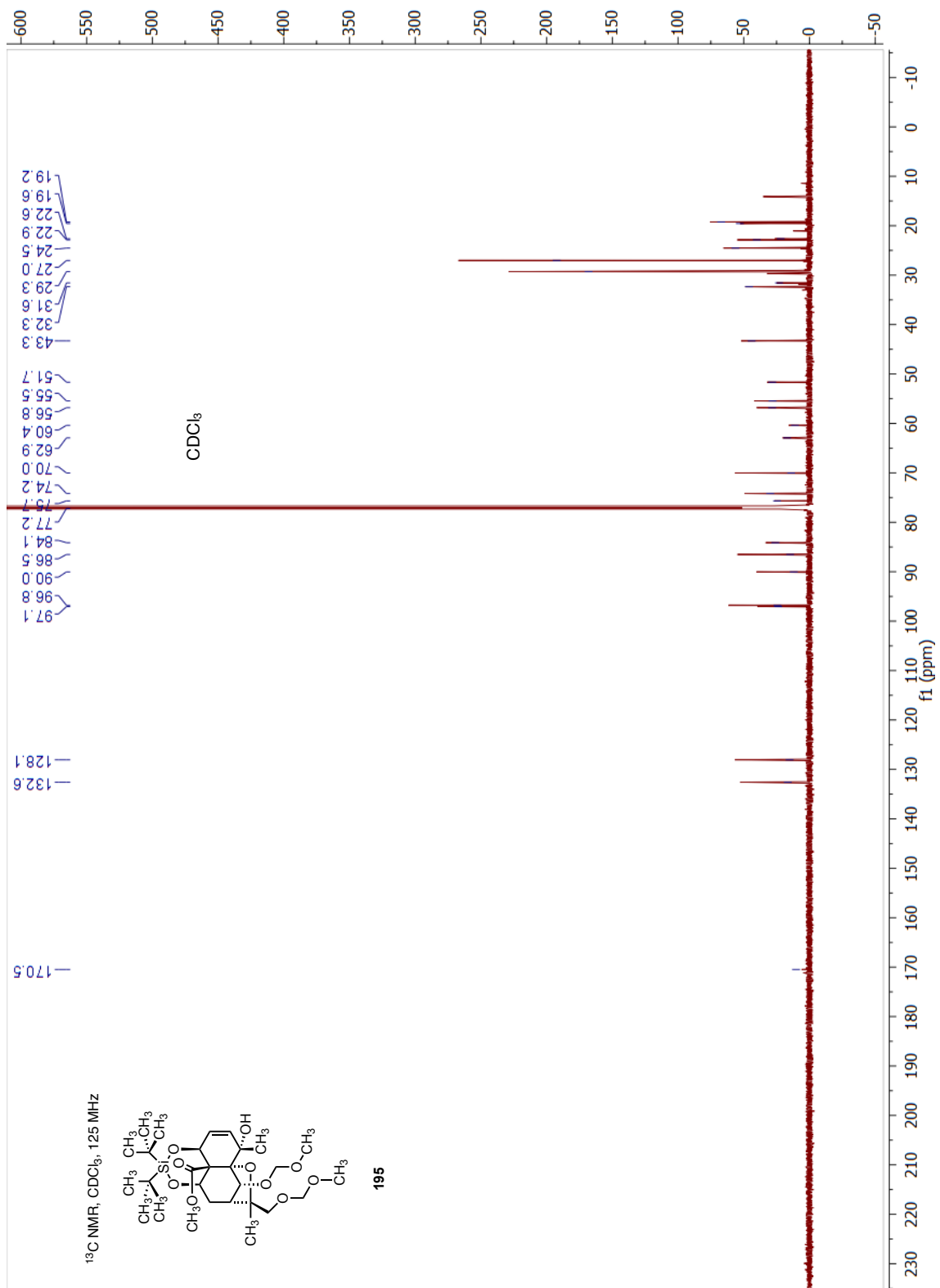


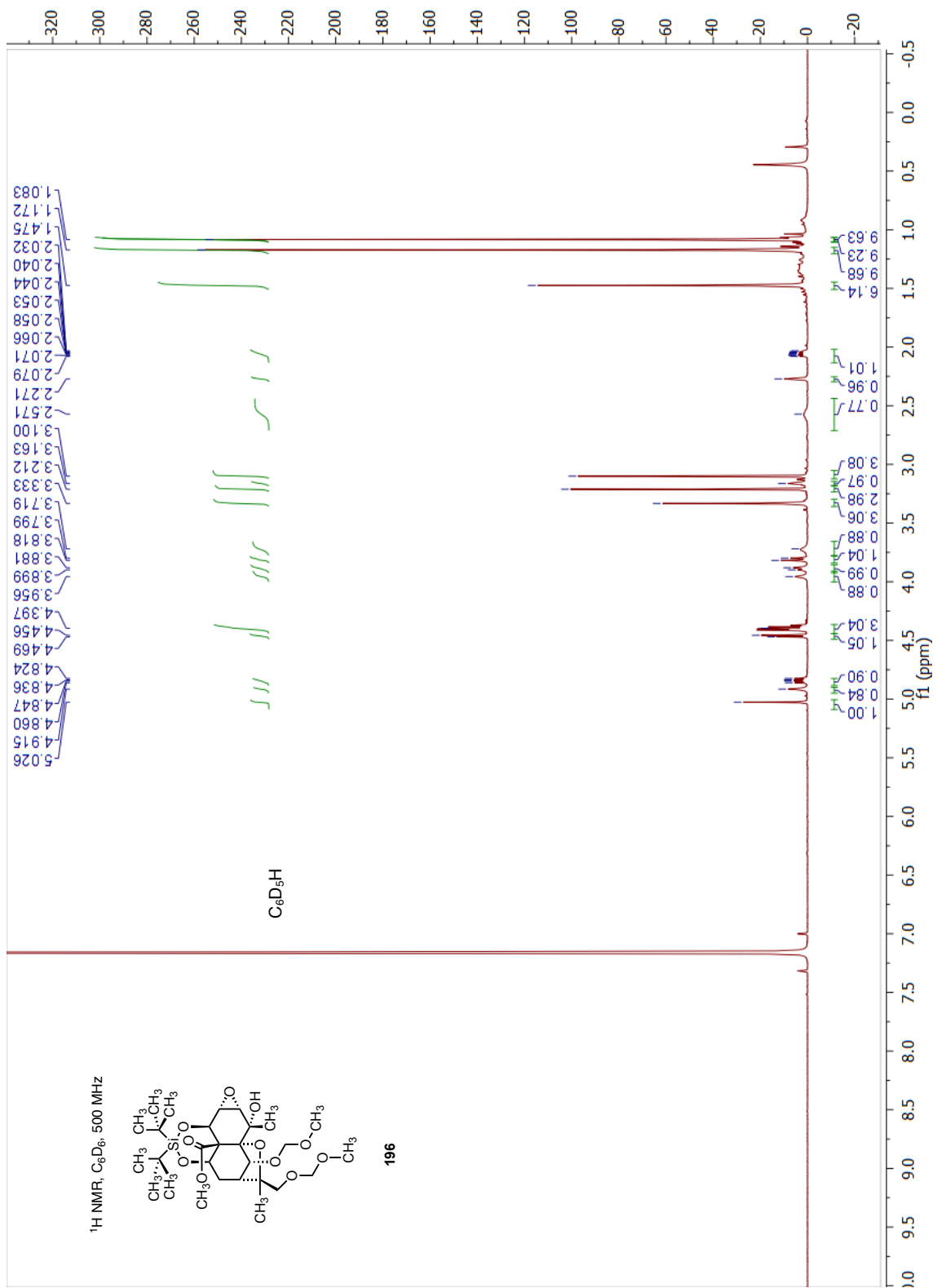


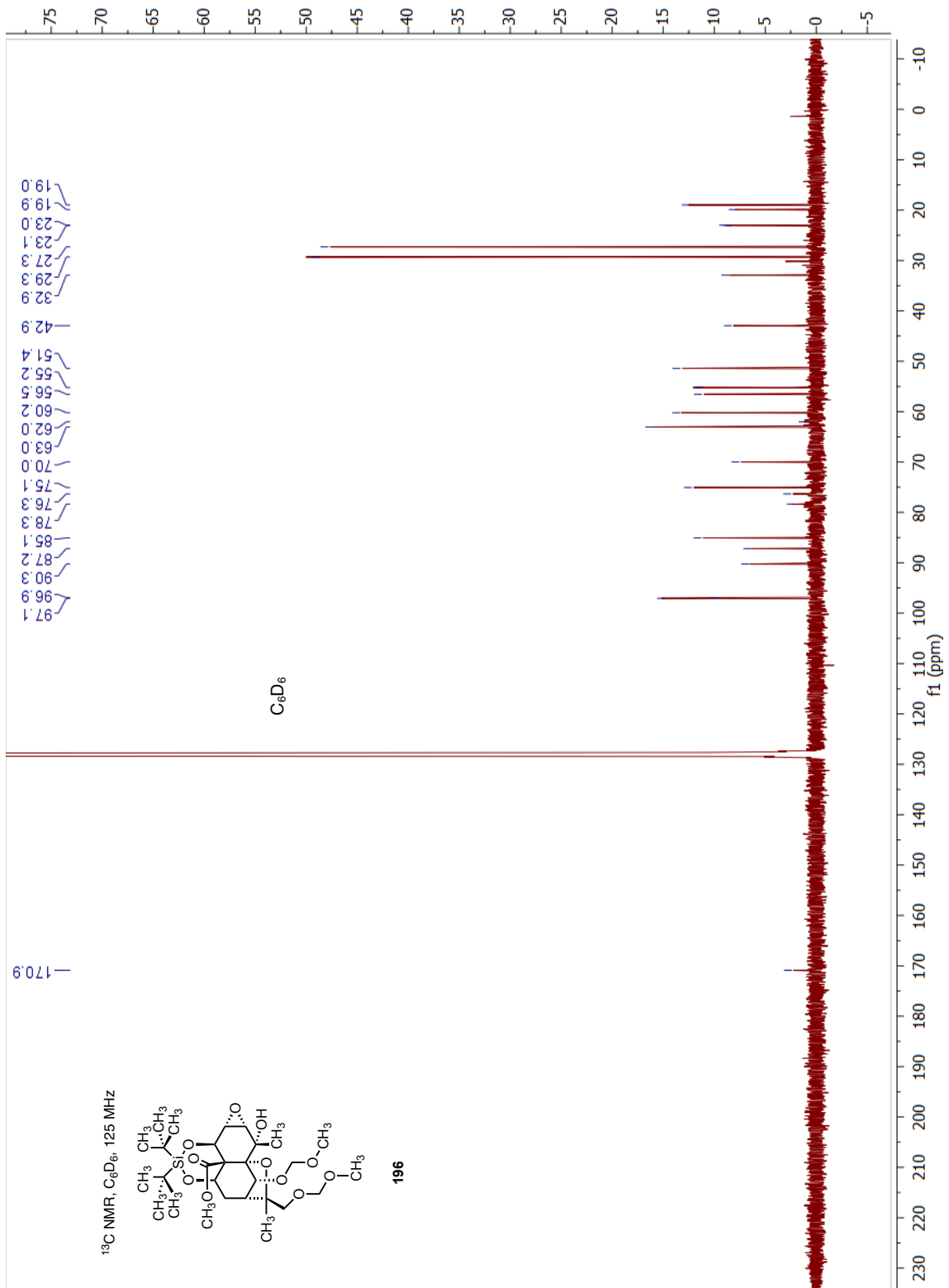


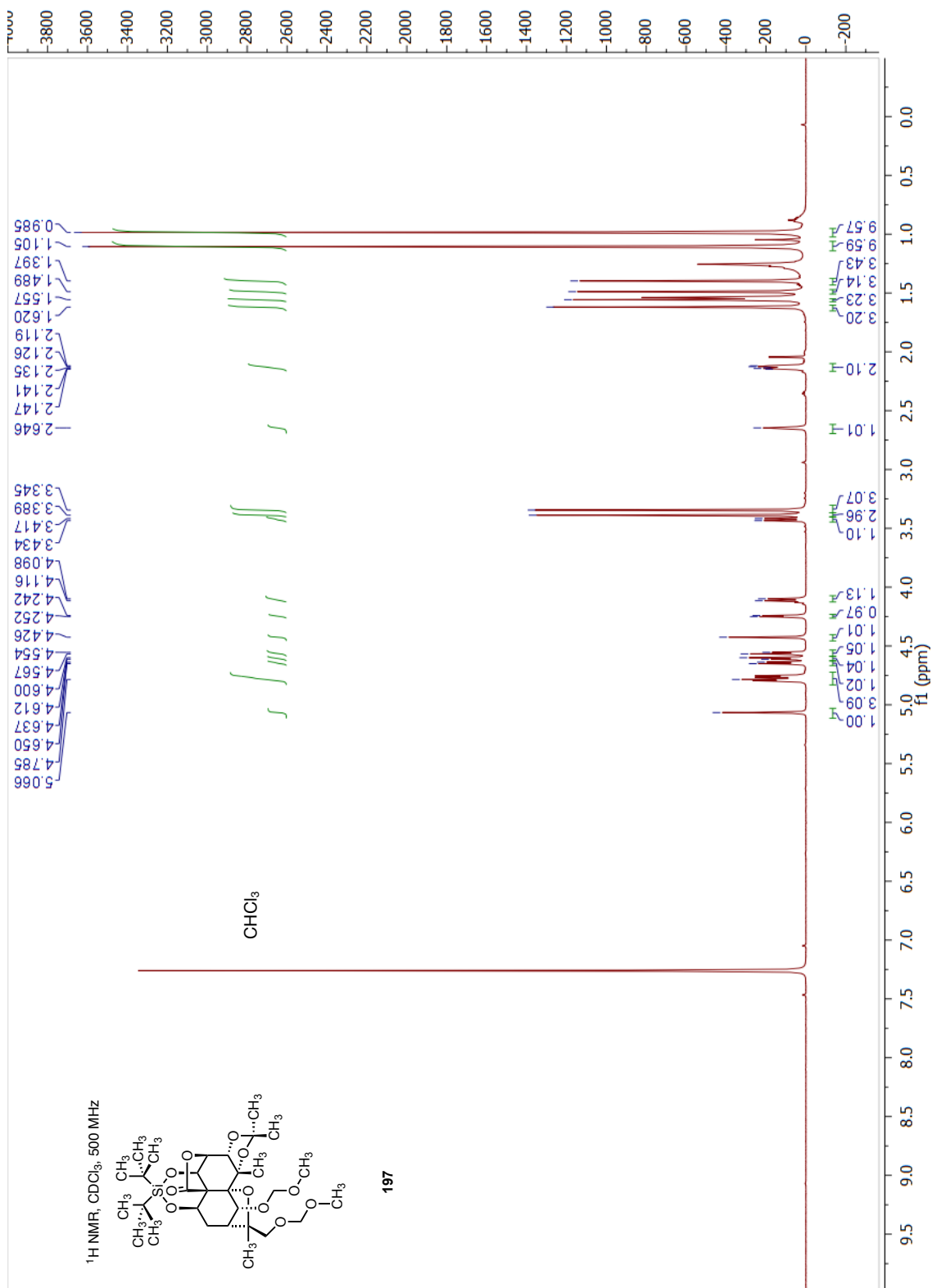


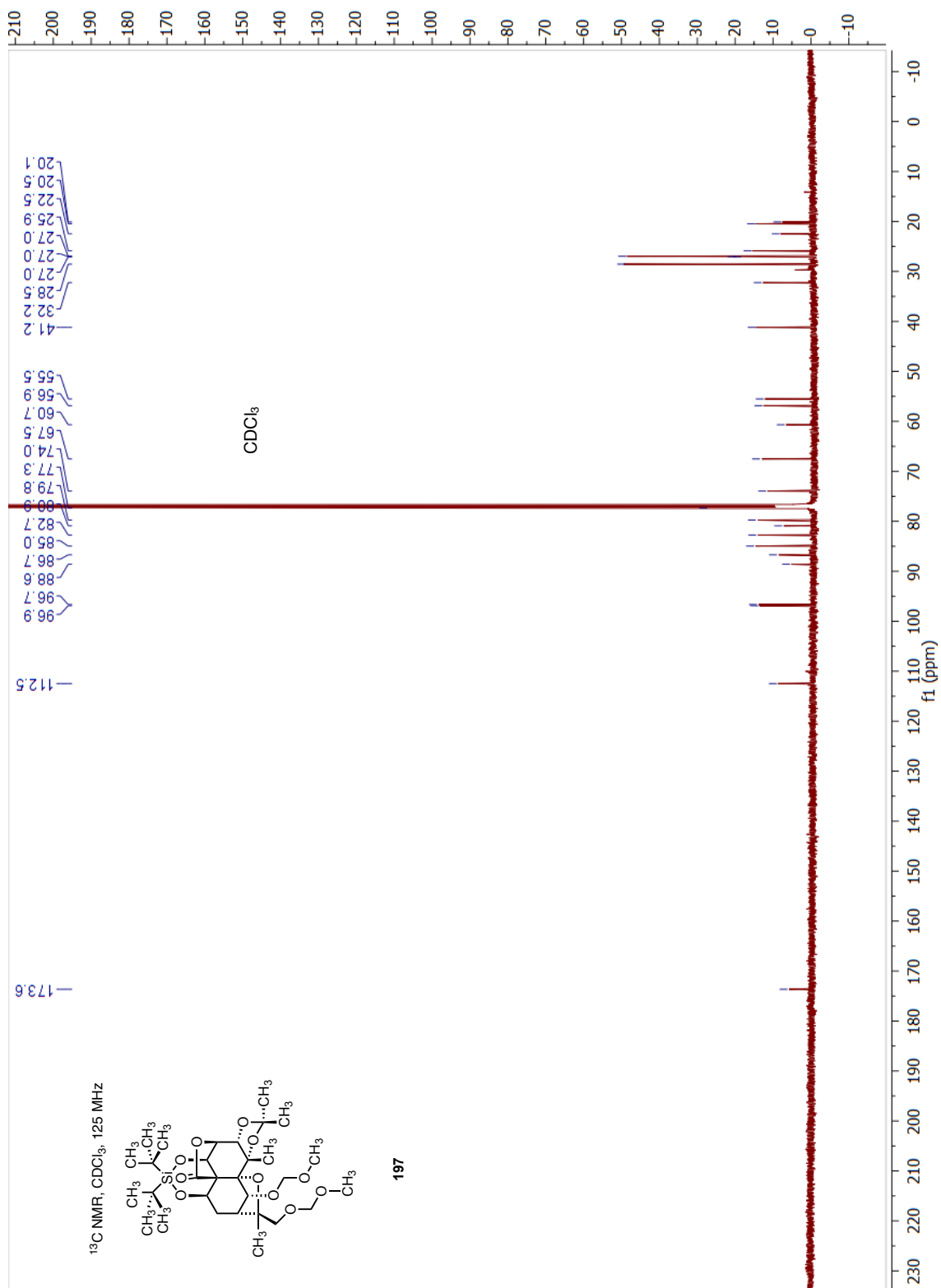


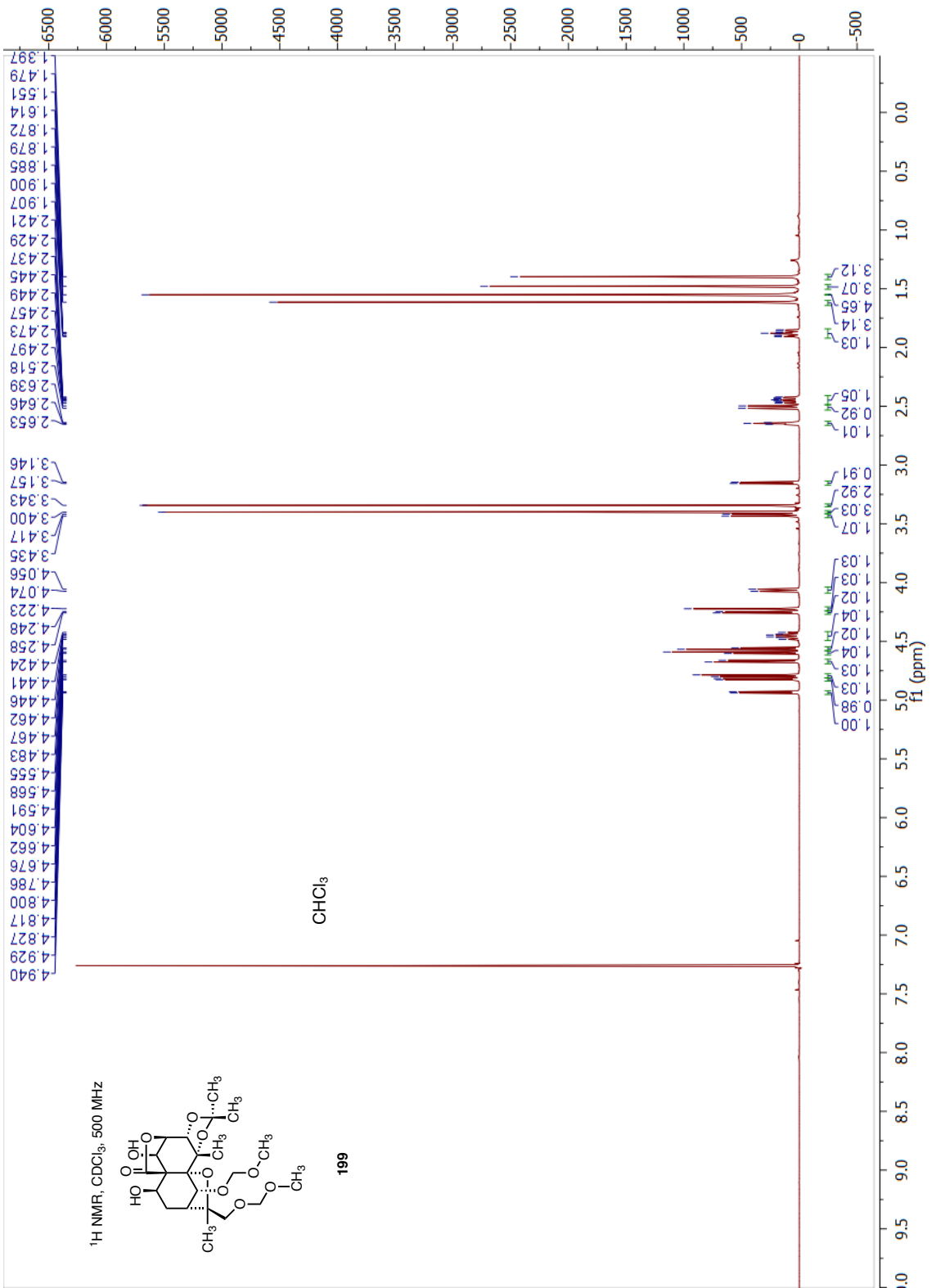


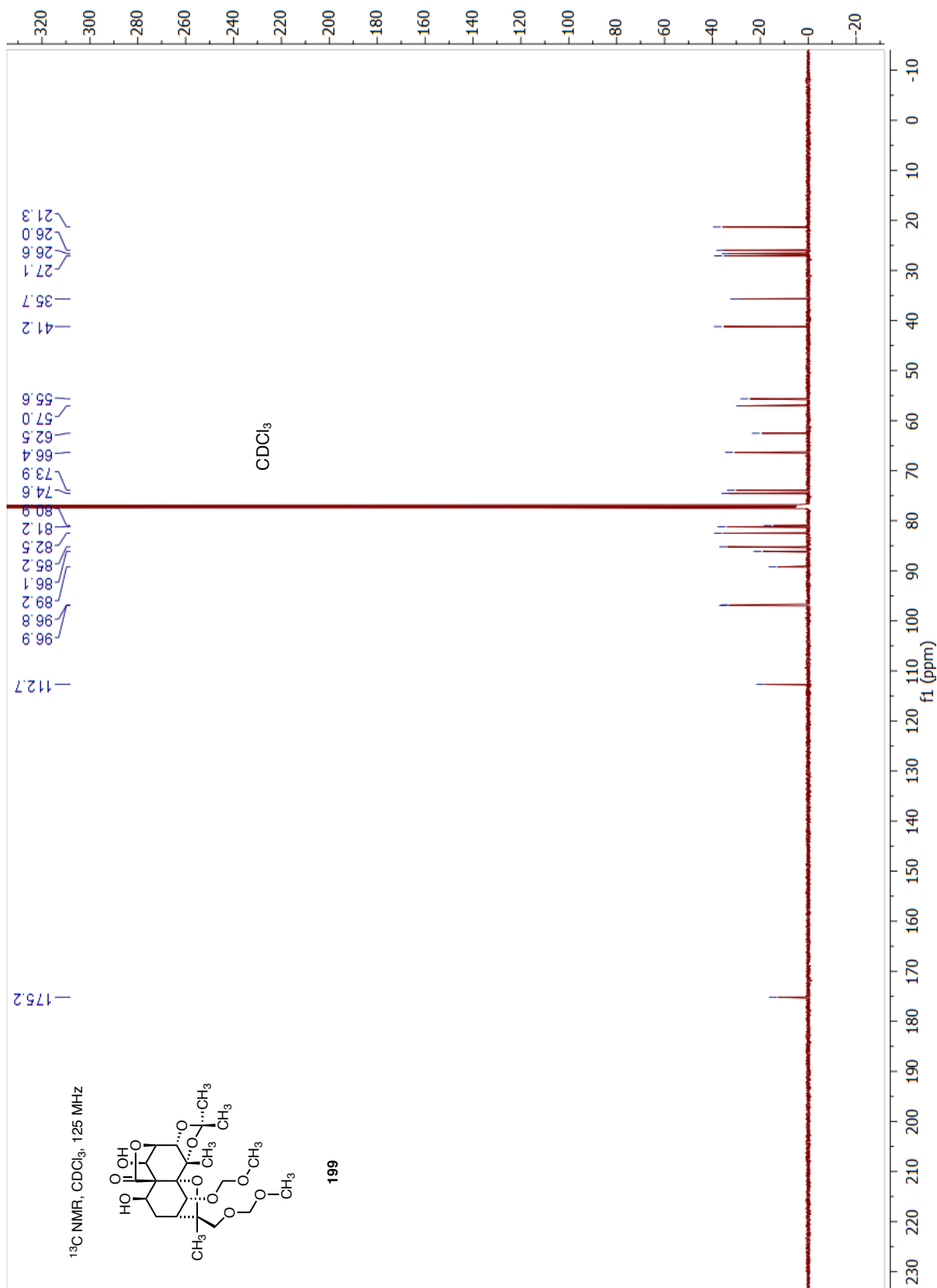


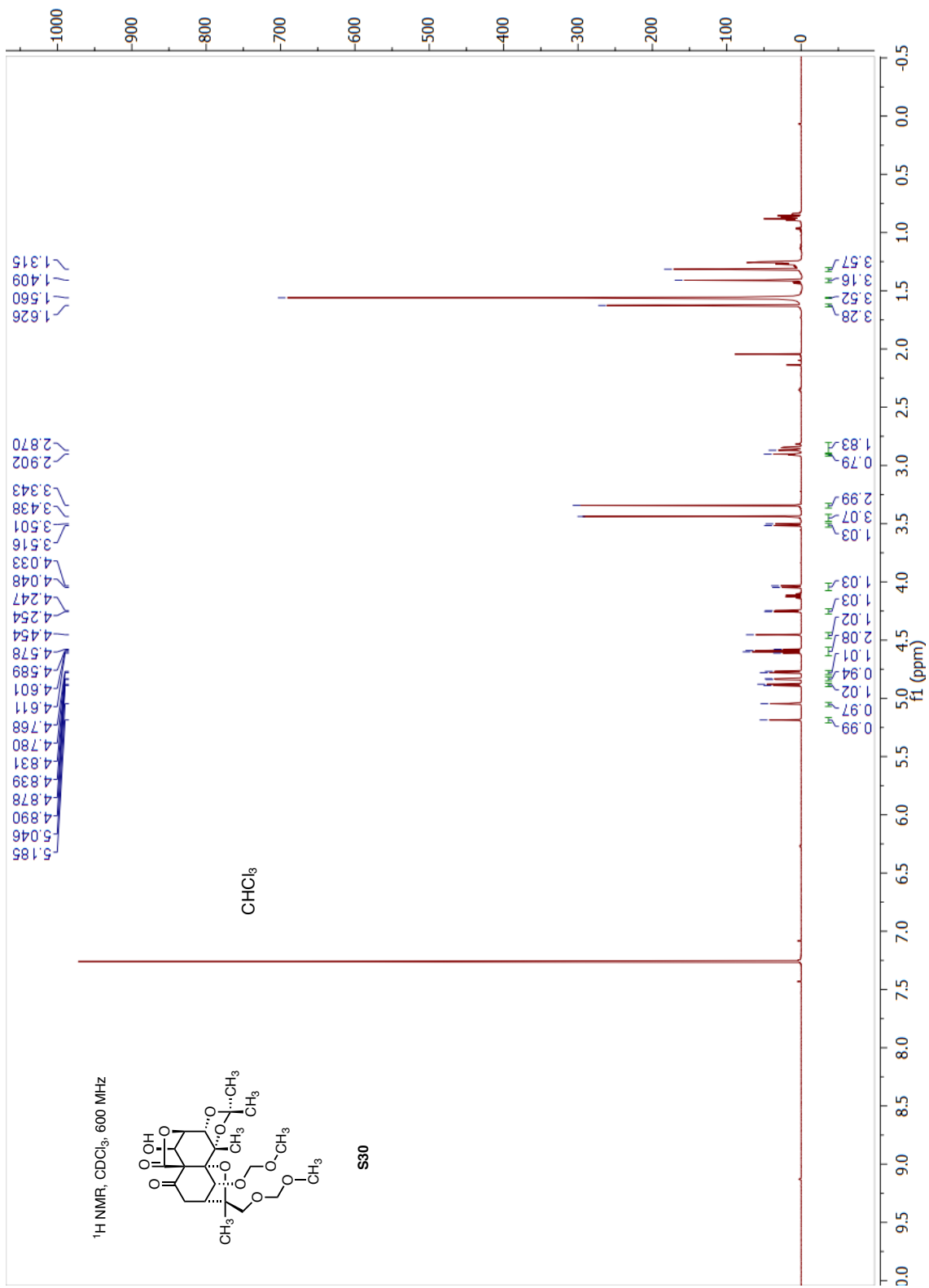




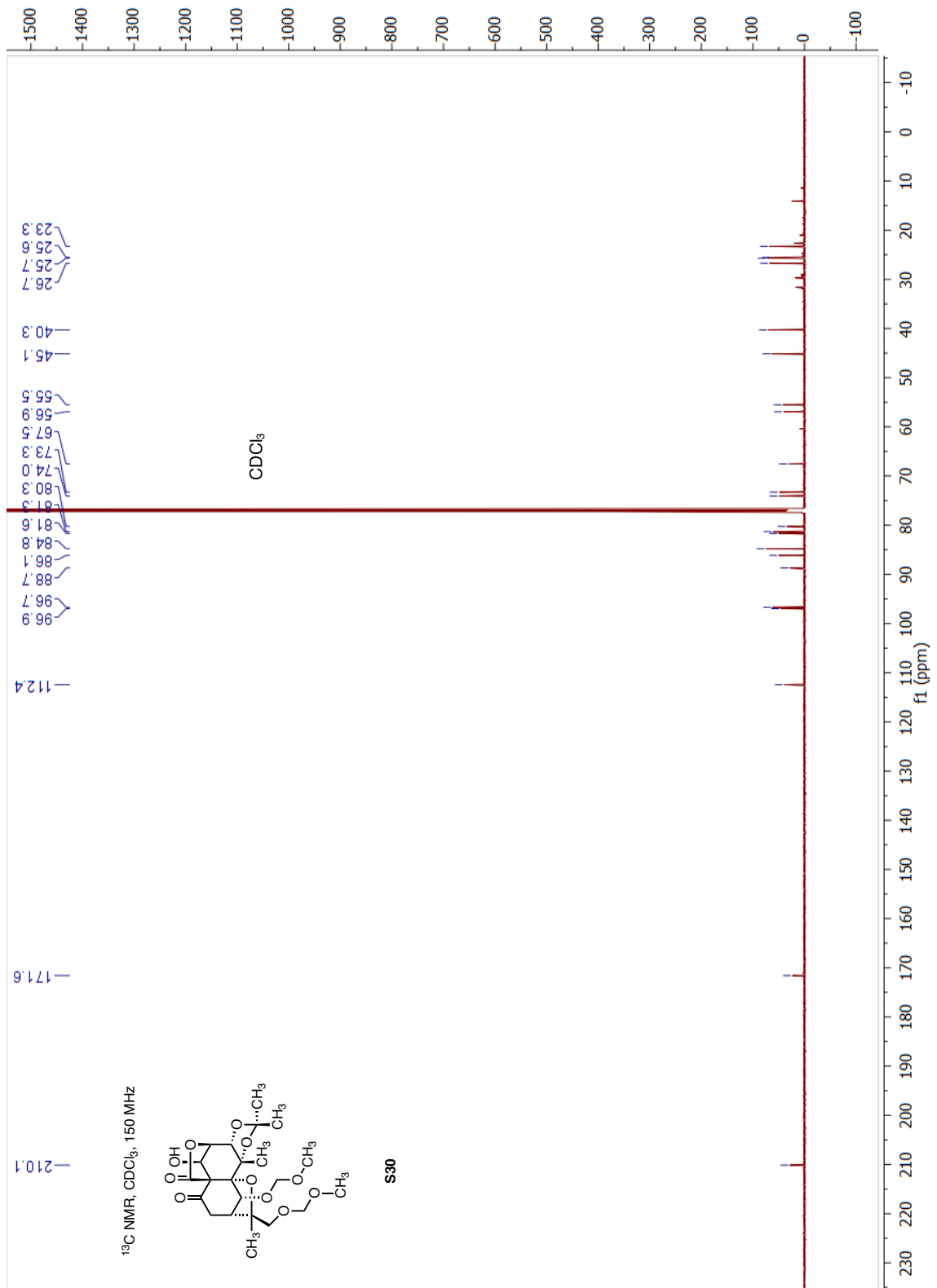


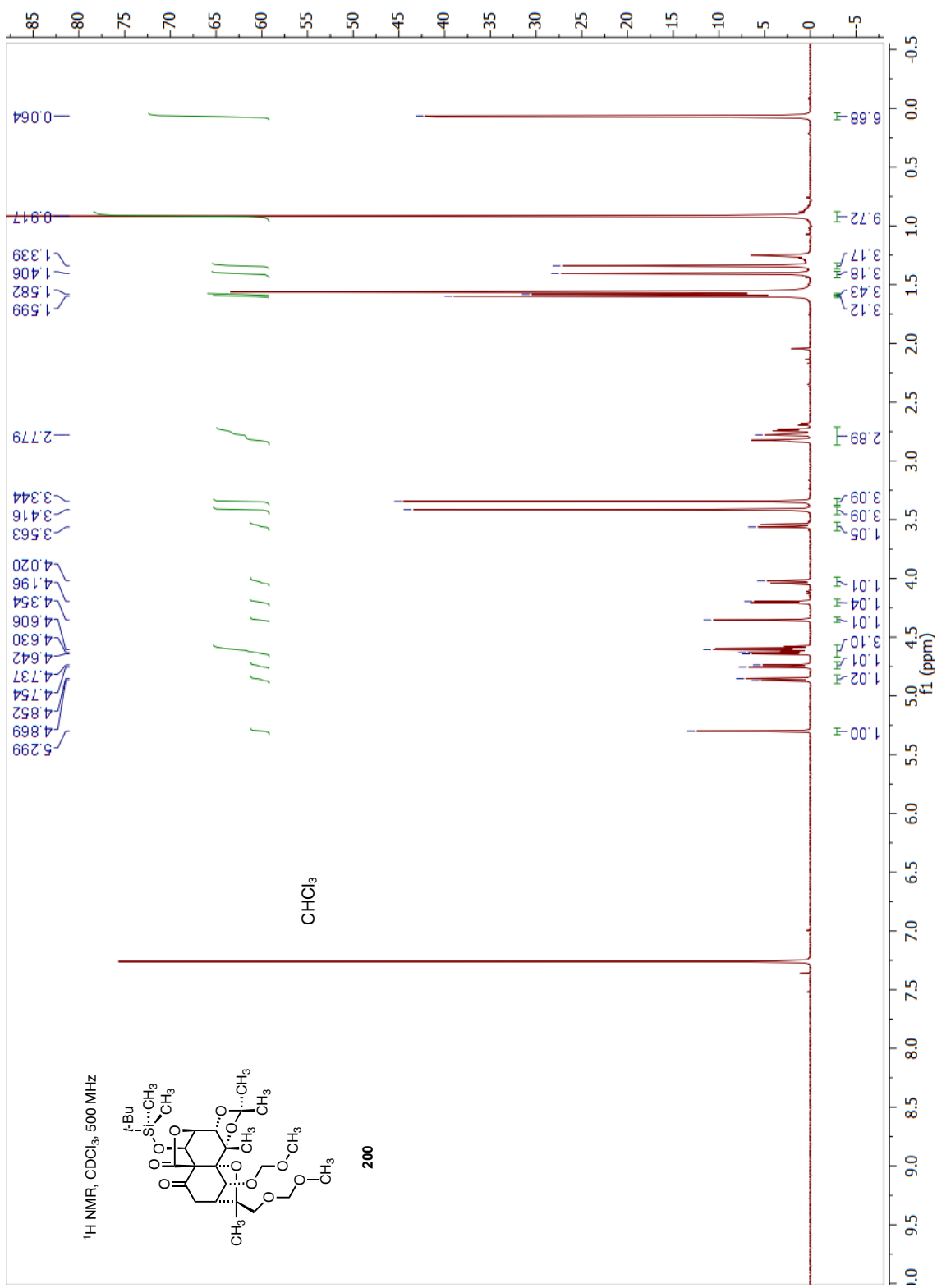




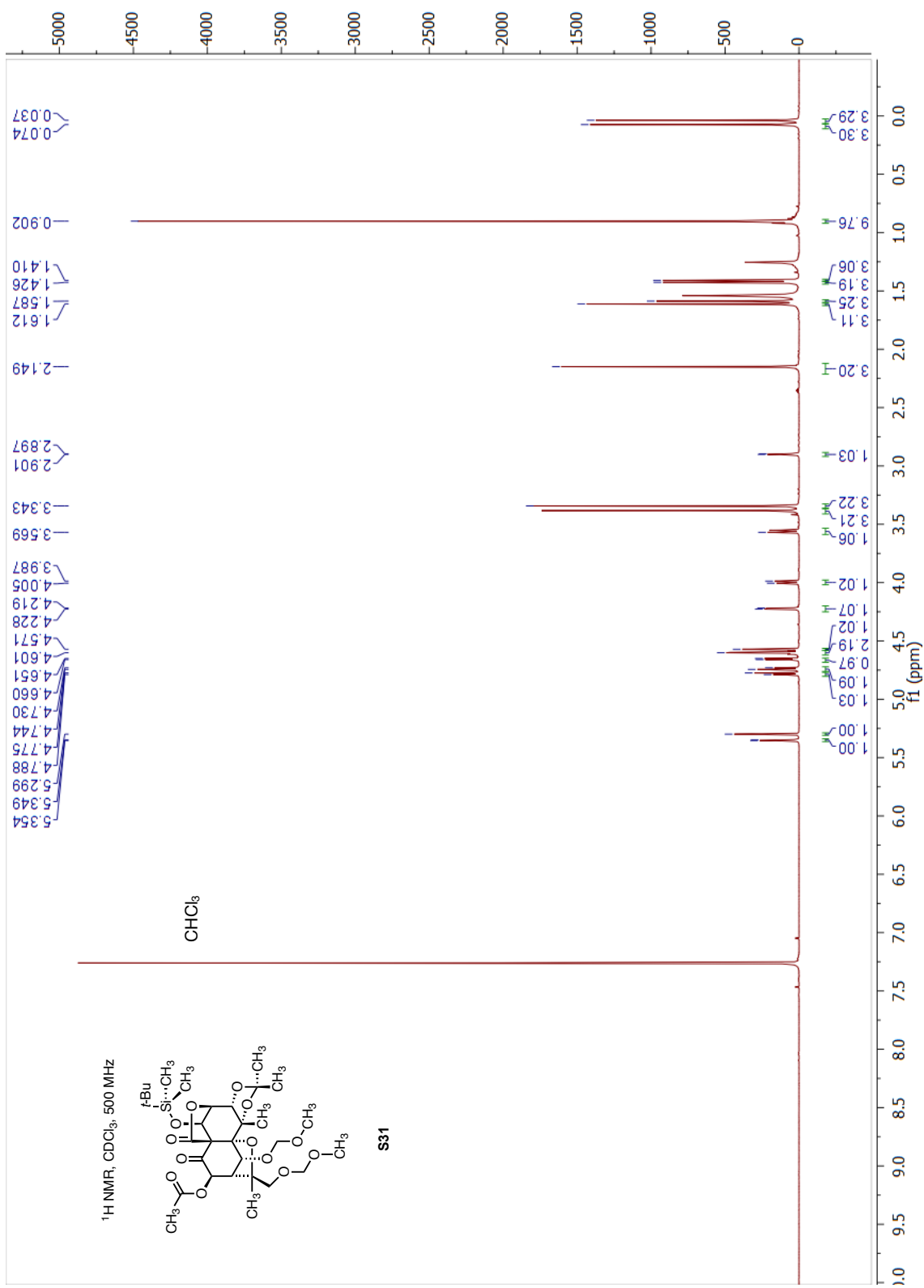




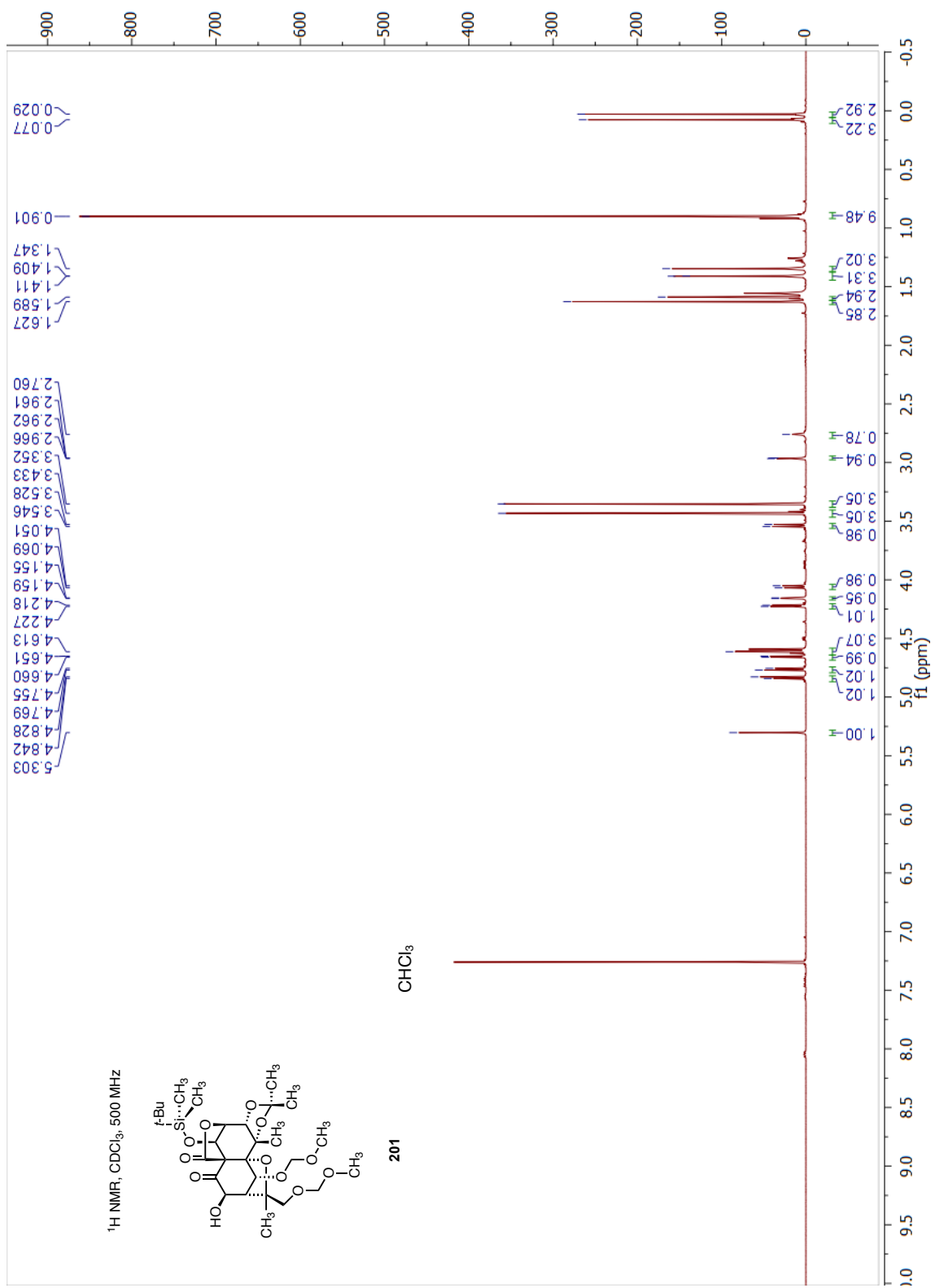


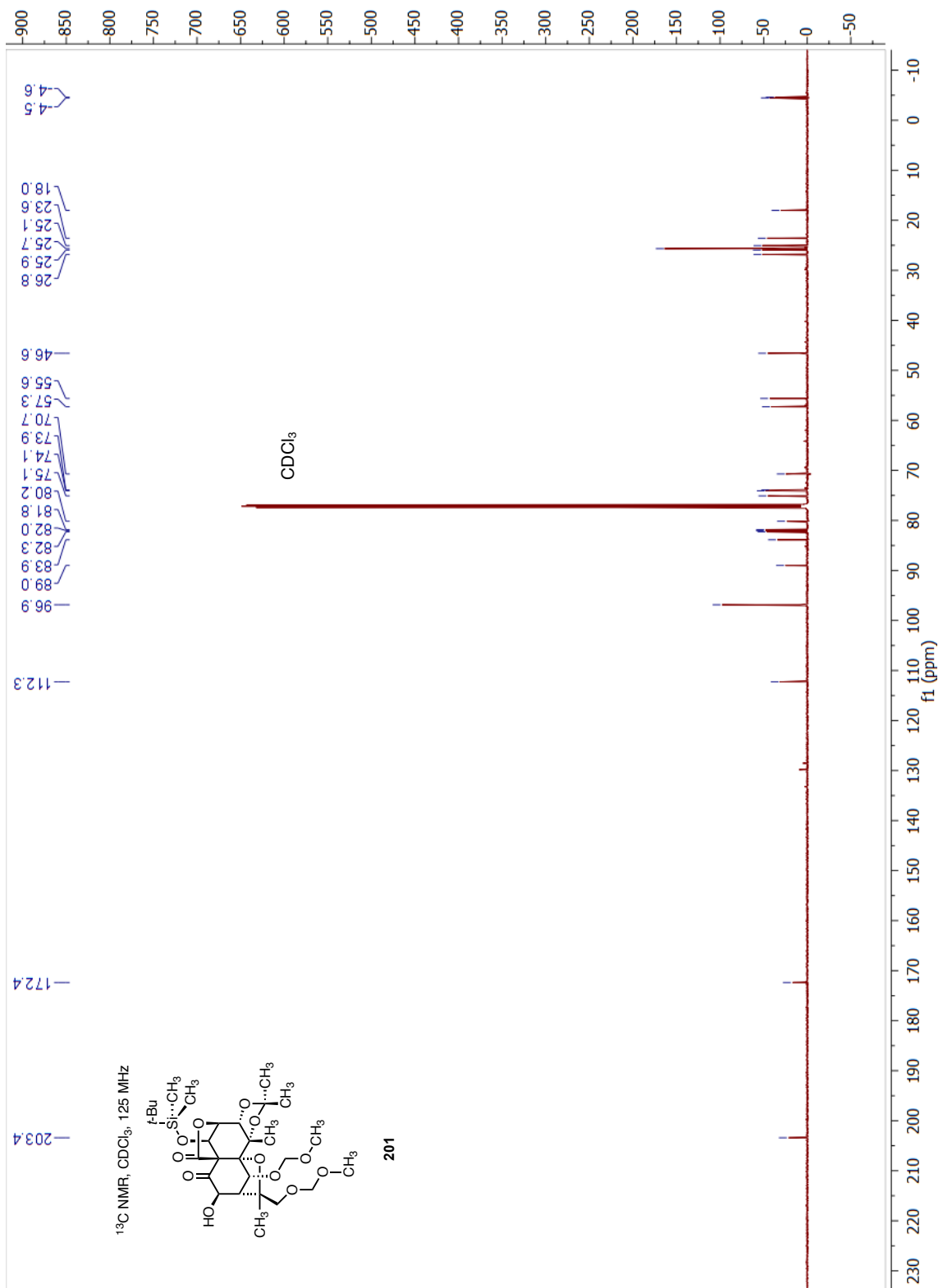


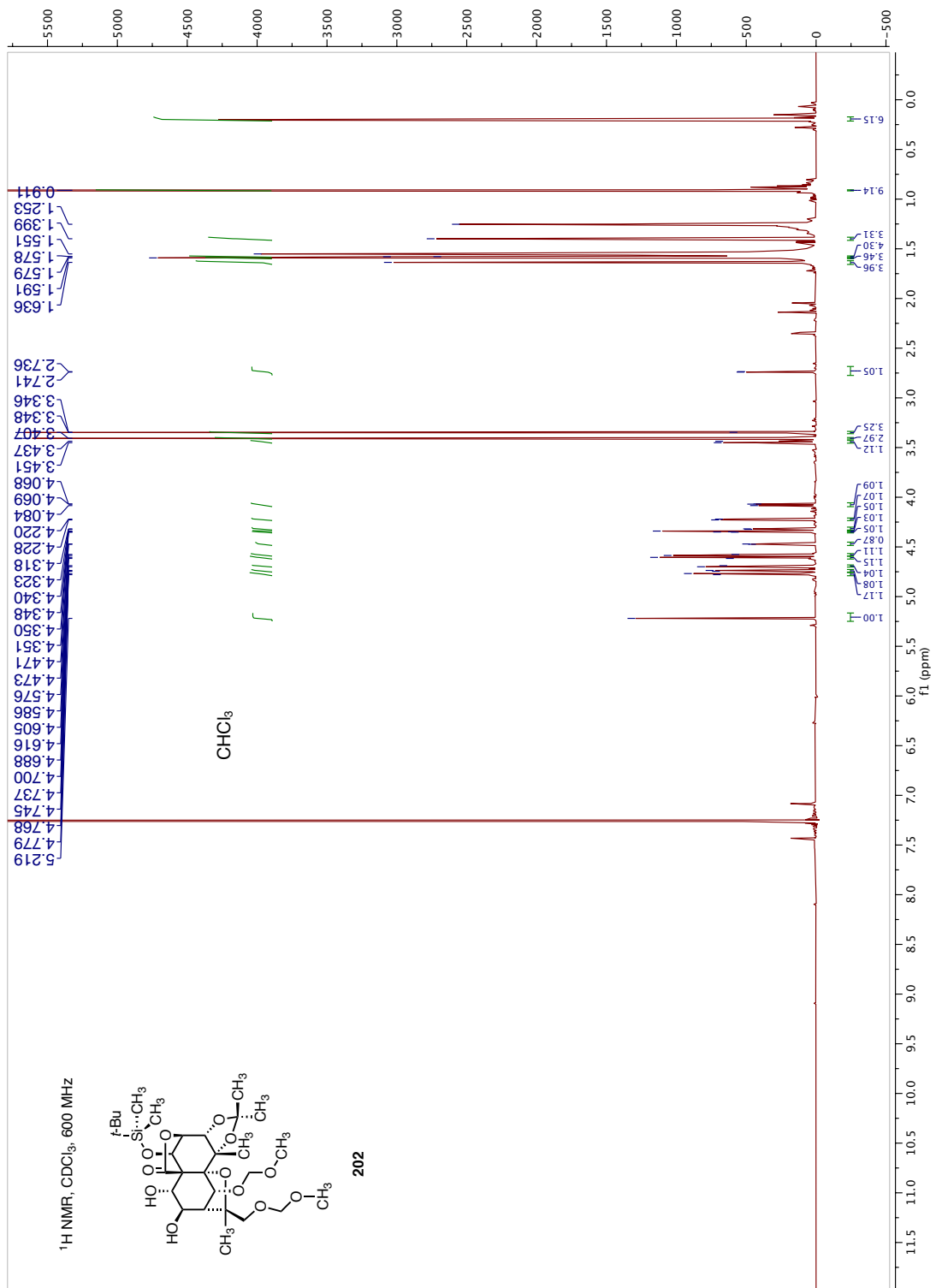




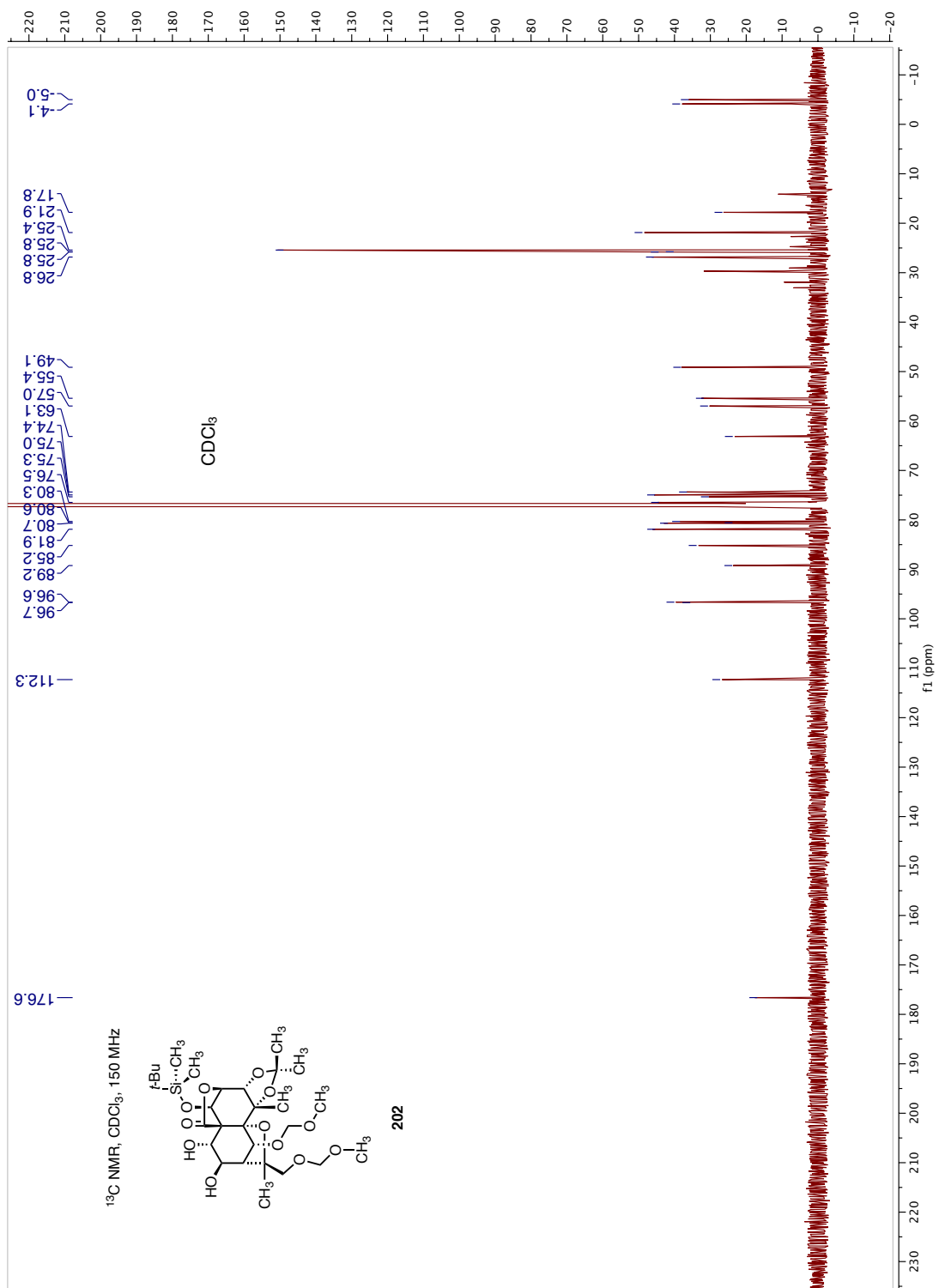


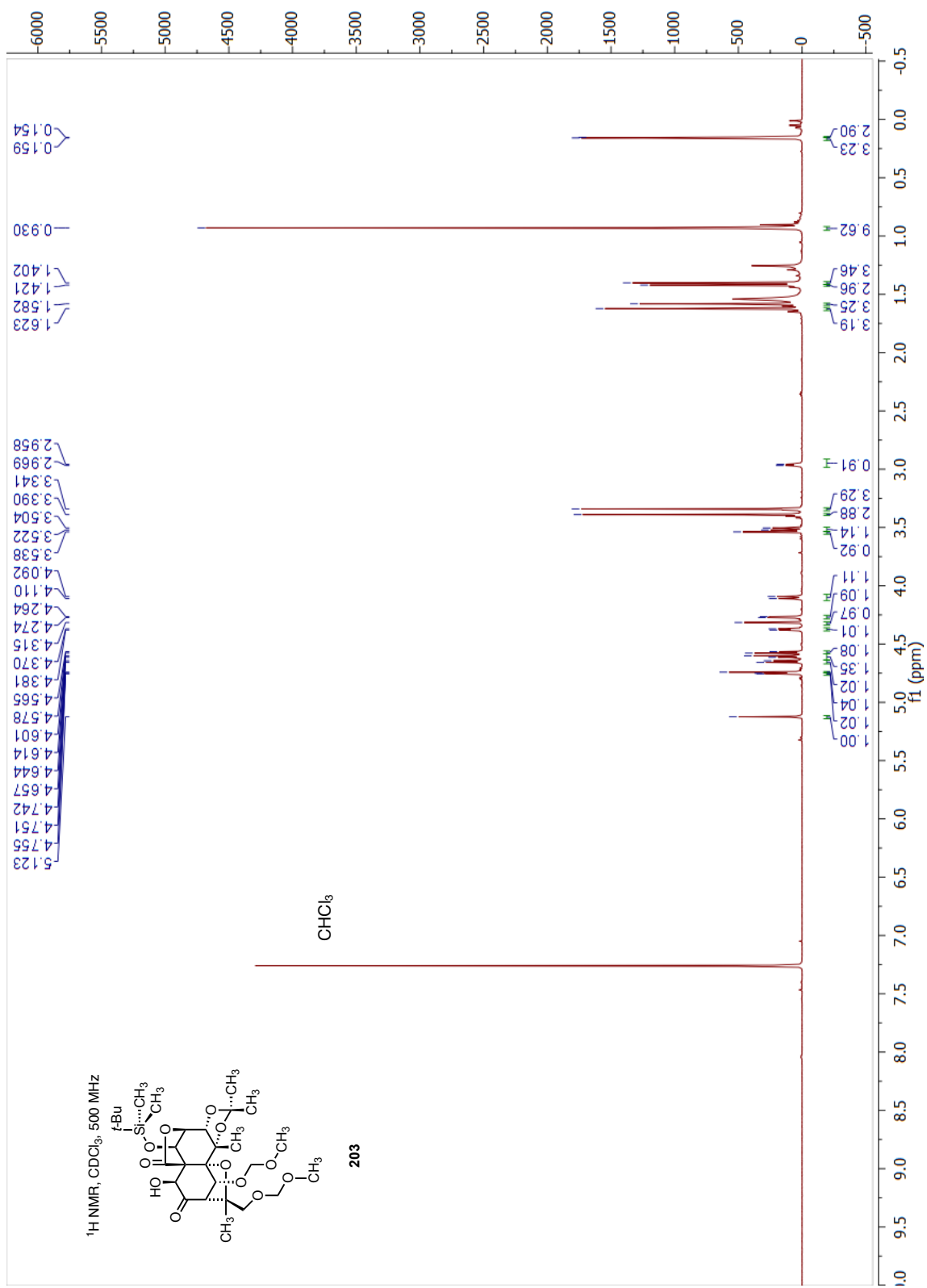




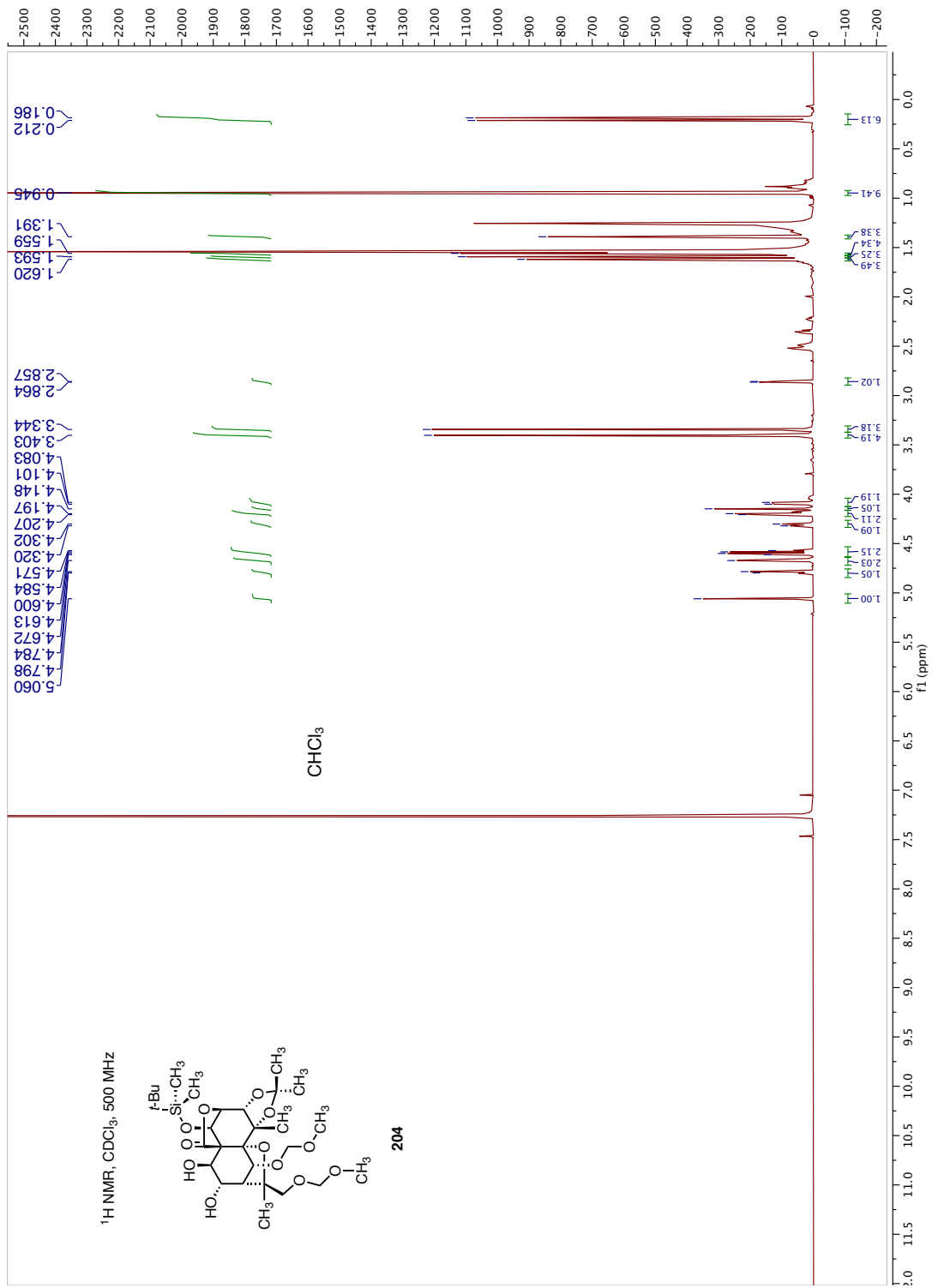


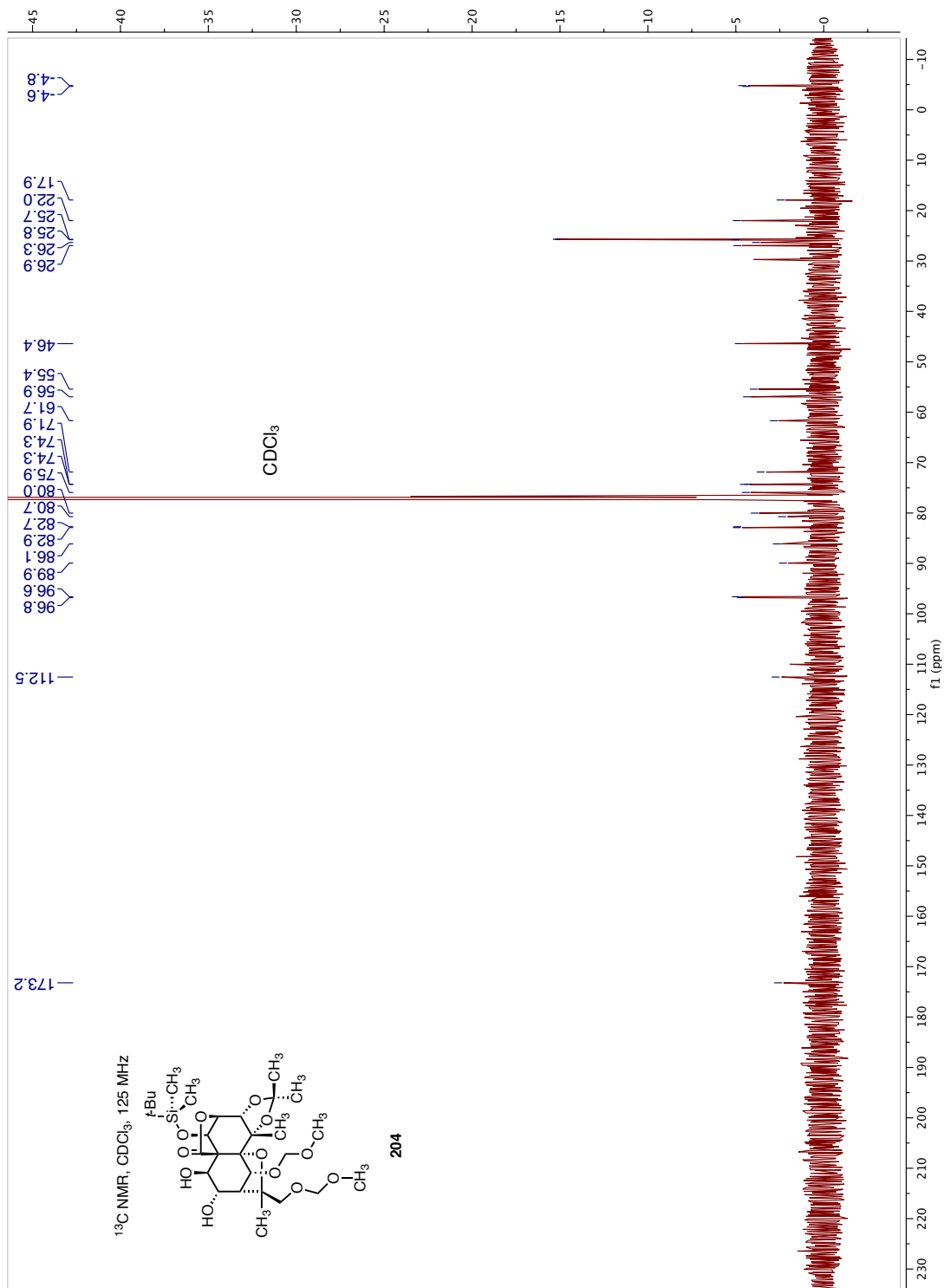


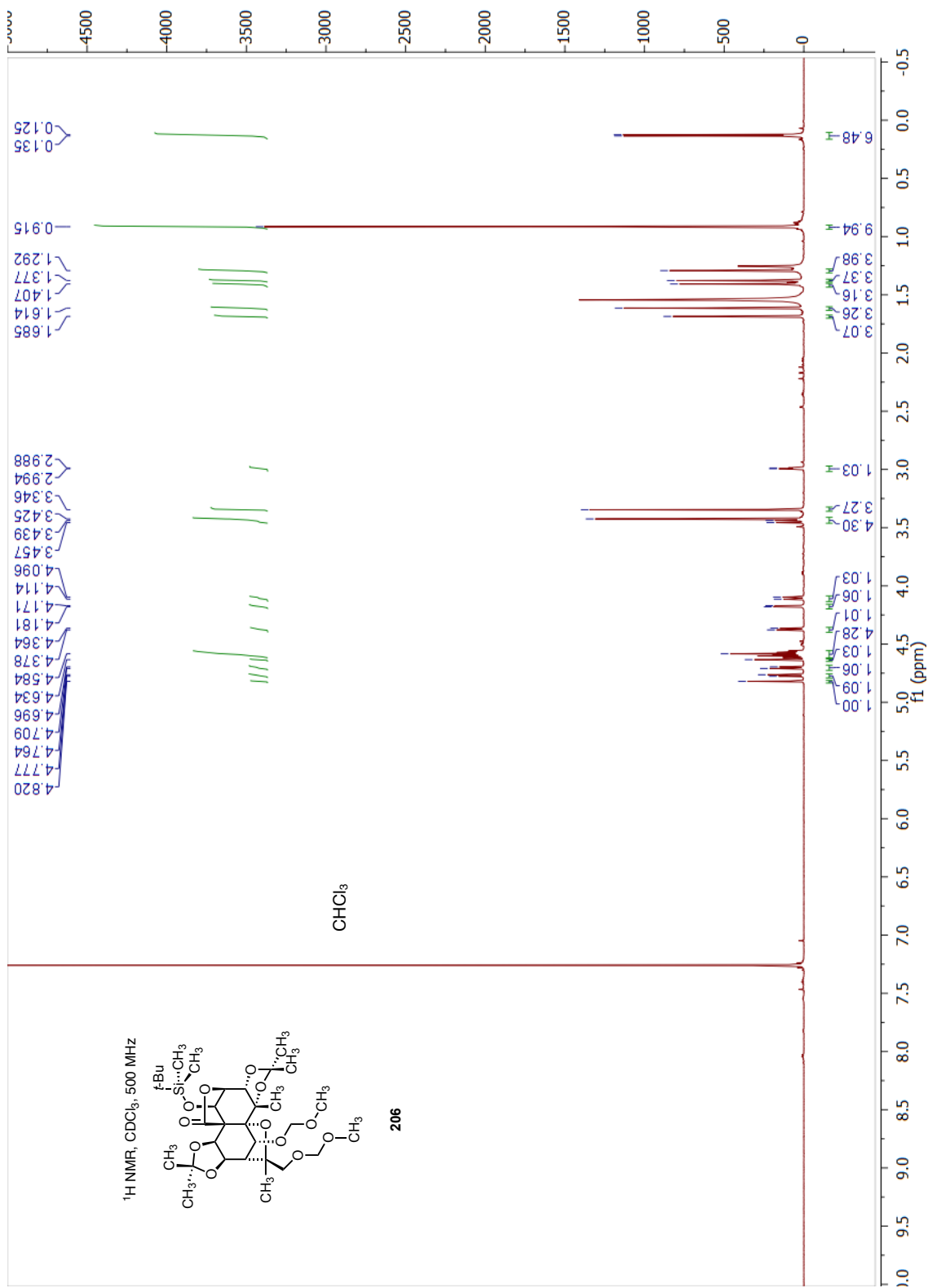












206



