THE UNIVERSITY OF CHICAGO

HETEROATOM GUIDED TOTAL SYNTHESIS: APPLICATION TO POLYHALOGENATED AND POLYOXYGENATED NATURAL PRODUCTS

A DISSERTATION SUBMITTED TO

THE FACULTY OF THE DIVISION OF THE PHYSICAL SCIENCES

IN CANDIDACY FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

DEPARTMENT OF CHEMISTRY

BY

COOPER ASHLEY TAYLOR

CHICAGO, ILLINOIS

DECEMBER 2021

"Luck is a dividend of sweat. The more you sweat, the luckier you get."

– Ray Kroc

Table of Contents

List of Schemes vii

List of Figures xii

List of Tables xiii

List of Abbreviations xiv

Acknowledgements xvii

Abstract xxi

Chapter 1. The Enantioselective Total Synthesis of Laurendecumallene B 1

1.1 Introduction 2

1.1.1 Laurencia Family of Natural Products 2

1.1.2 Biosynthetic Proposals of Laurencia Compounds 3

1.1.3 Snyder Group General Strategy 5

1.2 The Enantioselective Total Synthesis of Laurendecumallene B 7

1.2.1 Previous Study Towards Laurendecumallene B 8

1.2.2 Alteration of Previous Desepilaurallene Synthesis 10

1.2.3 Construction of Boc-protected Bicyclic Lactone Precursor 15

1.2.4 Computational Guidance 17

1.2.5 Completion of Laurendecumallene B 18

1.3 Conclusion 28

1.4 References 28

1.5 Experimental Section 31

1.5.1 General Procedures 31

1.5.2 Synthesis of Laurendecumallene B 32

1.6 Computational General Information 62

1.6.1 Minimized Structures 62

1.7 Physical NMR Comparison 68

1.8 NMR Spectra of Selected Intermediates 69

Chapter 2. Studies Toward the Grayanane Diterpenoid Family of Natural Products 126

2.1 Introduction 127

2.1.1 Structures and Bioactivities of Selected Grayanane Diterpenoids 127

2.1.2 Proposed Biogenesis of Grayanane Diterpenoids 128

2.1.3 Previous Synthetic Efforts Toward Grayanane Diterpenoids 129

2.2 Synthetic Study Towards Ten Grayanane Diterpenoids 136

2.2.1 Envisioned Use of Common Intermediate 136

2.2.2 Forward Synthesis of Radical Coupling Fragments 138

2.2.3 Attempted Coupling and Model Studies 143

2.2.4 Intramolecular Approach 146

2.2.5 Route Redesign 149

2.3 Suspension of Project 151

2.4 Conclusion 153

2.5 References 154

2.6 Experimental Section 157

2.6.1 General Procedures 157

2.6.2 Syntheses of Selected Intermediates 158

2.7 NMR Spectra of Selected Intermediates 181

Chapter 3. Studies Toward Cinncassiol F and Related Cinncassiol Diterpenoids 213

3.1 Introduction 214

3.1.1 Structures and Bioactivities of Selected Cinncassiol Diterpenoids 214

3.1.2 Proposed Biogenesis of Cinncassiol Diterpenoids 216

3.1.3 Previous Efforts Toward Related Compounds 217

3.2 Studies Toward Cinncassiol F – Carbon Skeleton First Approach 223

3.2.1 Retrosynthetic Analysis Featuring a Prenyl Michael Addition 224

3.2.2 Forward Synthesis – Probing of Oxidative Dearomatization and its Derivatives 225

3.2.3 Forward Synthesis – Oxidation Model Studies 229

3.2.4 Completion of the Carbon Framework 232

3.2.5 Summary of Initial Oxidative Dearomatization Approach 242

3.2.6 Nazarov Cyclization to Fashion Carbon Skeleton 243

3.2.7 Summary of Nazarov Cyclization Attempts to Fashion Carbon Skeleton 253

3.3 Studies Toward Cinncassiol F – Bridged Bicycle First 254

3.3.1 Initial Bridge-First Approach Featuring Ring-Closing Metathesis 254

3.3.2 Second Generation Bridge-First Approach Featuring a Michael Addition 256

3.3.3 Summary of Initial Bridge-First Efforts 262

3.3.4 Third Generation Bridge-First Approach Featuring a Conia-Ene Cyclization 262

3.3.5 Outlook of the Conia-Ene Cyclization Route 277

3.4 Conclusion 279

3.5 References 281

3.6 Experimental Section 285

3.6.1 General Procedures 285

3.6.2 Syntheses of Selected Intermediates 286

3.7 Computational General Information 378

3.7.1 Minimized Structures 378

3.8 Xray Crystallography Data 381

3.8.1 General Information 381

3.9 NMR Spectra of Selected Intermediates 391

List of Schemes

Scheme 1.1. Biosynthesis of deacetyllaurencin (**8**), laureoxanyne (**9**), and laurefucin (**3**) by Murai and coworkers utilizing partially purified bromoperoxidase……...4

Scheme 1.2. Adjusted biosynthetic proposal by the Snyder group in which an initial 5-*endo*-trig cyclization occurs which is then readily extrapolated to several *Laurencia* targets (**3**, **8**, **9**) through a critical oxonium intermediate (**11**) ……5

Scheme 1.3. Snyder group general strategy for the construction of the various *Laurencia* cores in which the β-bromide can be installed either externally (**14**) or internally (**17**) based on olefin placement.……6

Scheme 1.4. Applying the previously developed BDSB reagent (initially used for the polyene cyclization of **18** to **20**) to the ring-expansion of **21** to deliver desepilaurallene (**23**) directly……7

Scheme 1.5. Previously reported study towards laurendecumallene B (**6**) by the Fujii/Ohno groups in 2013……..9

Scheme 1.6. Proposed dihydroxylation of diastereomer **30** to access oxidized core of laurendecumallene B (**6**) ……10

Scheme 1.7. Forward synthesis of *iso*-desepilaurallene (**30**) and subsequent Upjohn dihydroxylation yielding undesired diol diastereomer (**44**) ……...12

Scheme 1.8. Production of undesired *cis*-diol diastereomer **44** from Upjohn dihydroxylation….14

Scheme 1.9. Adjusted retrosynthetic analysis of laurendecumallene B (**6**) through a similar bicyclic lactone precursor, but utilizing a Boc-protected 2° alcohol (**48**) to promote the ring expansion process……15

Scheme 1.10. Forward synthesis of bicyclic lactone ring-expansion precursor **48** and failed cyclization……..16

Scheme 1.11. Retrosynthetic analysis of laurendecumallene B (**6**) utilizing a fully furnished tetrahydrofuran BDSB-induced ring expansion precursor (**54**) as elucidated through DFT calculations ……19

Scheme 1.12. Forward synthesis of aldehyde **62** featuring a diastereoselective NIS-induced cyclization……..20

Scheme 1.13. Completion of ring expansion precursor **54**……22

Scheme 1.14. Completion of laurendecumallene B (**6**) featuring a second BDSB cyclization…..25

Scheme 2.1. (A) Proposed biogenesis of the grayanane skeleton from the related kaurane scaffold. (B) Recent synthetic and computational evidence for a similar alkyl shift as observed during the total synthesis of justicioside E aglycone (**18**) ……129

Scheme 2.2. (A) Original partial synthesis of **27** by the Matsumoto group starting from a degradation product of grayanotoxin II (**27**). (B) A subsequent study establishing a relay synthesis of **27** to produce precursor **36**, just one step from intermediate **21** of the original work…….131

Scheme 2.3. Total synthesis of grayanotoxin III (**2**) by the Matsuda and Shirahama groups in 1994……..134

Scheme 2.4. Studies toward the total synthesis of pierisformoside C (**57**) by the Williams group in 2011 featuring a Sonogoshira coupling and NaOMe mediated cyclization……..135

Scheme 2.5. Retrosynthetic analysis of **1** - **10** utilizing a common intermediate (**58**) and building block approach…….137

Scheme 2.6. Proposed divergent routes for the syntheses of ten grayanane diterpenoids from common intermediate **58**……..138

Scheme 2.7. A) Retrosynthetic analysis of **60** and B) inability to generate desired enolate…….139

Scheme 2.8. Forward Synthesis of western fragment **60** in partnership with Mr. Evgeny Gulyak……..140

Scheme 2.9. Forward Synthesis of Eastern Fragment **61**…….142

Scheme 2.10. A) Failed radical cascade and B) follow-up model studies highlighting the challenge of this transformation……...144

Scheme 2.11. A) Proposed vinyl Michael addition approach and B) probing of vinyl Michael additions on unsaturated ester **102** and unsaturated aldehyde **104**……145

Scheme 2.12. Forward Push to Michael Addition Cascade……..146

Scheme 2.13. Retrosynthetic Analysis of Tethered Intramolecular Approach……147

Scheme 2.14. Forward Synthesis of Alcohol **112**……148

Scheme 2.15. Forward Synthesis of **111** and Attempted Model Cyclization……149

Scheme 2.16. Retrosynthetic Analysis of Addition Reversal Approach……..150

Scheme 2.17. Initial Results of Adjusted Route……151

Scheme 2.18. The total synthesis of principinol D (**146**) by the Newhouse group (2019) ……153

Scheme 3.1. 6/5/5 ryanodane-type and 5/6/5 isoryanodane-type scaffolds along with representative members of the cinncassiol diterpenoid family drawn in both a planar and a 3D configuration…215

Scheme 3.2. Biogenetic relationship of the nine known classes of cinncassiol diterpenoid cores as proposed by Yao and coworkers in 2019……..216

Scheme 3.3. Ensley's synthetic study towards cinncassiol D_1 (**11**) featuring an intramolecular Diels-Alder……...219

Scheme 3.4. Inoue's synthetic study towards vignaticol (**38**) starting from a known ryanodol intermediate (**30**) …….220

Scheme 3.5. Reisman's convergent total synthesis of perseanol (**55**) utilizing fragments **41** and **47**……..222

Scheme 3.6. Retrosynthetic analysis of cinncassiol F (**2**) featuring an oxidative dearomatization and prenyl-Michael addition to establish the carbon skeleton prior to global oxidation.…….225

Scheme 3.7. Forward Push to Bicyclic Phenol **66** from *p*-Cresol (**61**) ……226

Scheme 3.8. Forward Push to Dienedione **68**……...227

Scheme 3.9. Initial Probe of Core Oxidations……..230

Scheme 3.10. Forward Push to Diepoxide **84**……..232

Scheme 3.11. Initial Efforts Toward Prenyl Installation……..233

Scheme 3.12. Anionic Oxy-Cope Rearrangement Allows for Generation of Carbon Skeleton…235

Scheme 3.13. Exploration of Metathesized Tricyclic Core……..242

Scheme 3.14. Retrosynthetic analysis of cinncassiol F (**2**) featuring a Nazarov cyclization and oxidative dearomatization to establish the carbon skeleton prior to global oxidation…….244

Scheme 3.15. Forward Synthesis through Nazarov Cyclization……..245

Scheme 3.16. Exploration of Tricyclic Phenol Reactivity……246

Scheme 3.17. Attempts to Circumnavigate Unstable Phenol……248

Scheme 3.18. Attempts to Utilize Inherent Symmetry…….252

Scheme 3.19. Retrosynthetic analysis of cinncassiol F (**2**) featuring an oxidative dearomatization and ring closing metathesis sequence to fashion the bridged bicycle system prior to ketal formation and final installation of left-hand ring……..255

Scheme 3.20. Attempted Use of Oxidative Dearomatization toward Early Installation of Bridged System……..256

Scheme 3.21. Retrosynthetic analysis of cinncassiol F (**2**) featuring an initial Michael addition to install central quaternary center and ring closing metathesis to fashion the bridged bicycle system…….. 257

Scheme 3.22. Forward Push to Attempted α-Hydroxylation of **162** and Computational Comparison of its Conformers……. 258

Scheme 3.23. Forward Push through Metathesis Showing Undesired Diastereoselectivity……260

Scheme 3.24. Forward Push through Undesired Umpolung Addition…….261

Scheme 3.25. Retrosynthetic analysis of cinncassiol F (**2**) featuring a late-stage Conia-ene cyclization to install bridged bicycle……263

Scheme 3.26. Attempted Late-Stage Conia-ene Approach……..265

Scheme 3.27. Attempted Early-Stage Oxidation of Conia-ene Product……267

Scheme 3.28. Elongated Reduction/Oxidation Path to Explore Manipulations of Right-Hand Side of Bicycle **193**…….. 269

Scheme 3.29. Confirmation of Undesired Diastereoselectivity with Silyl Enol Ether……270

Scheme 3.30. Diastereoselectivity Reversal Using sp^3 Center and Unexpected Decarboxylative Cyclization…….. 271

Scheme 3.31. Initial Attempts to Furnish Left-Hand Ring……273

Scheme 3.32. Diastereoselective Installation of Handle for Left-Hand Ring……275

Scheme 3.33. Initial Attempts to Homologate Allyl Sidechain……276

Scheme 3.34. Use of Boronic Ester Protection……277

Scheme 3.35. Envisioned Completion of Left-Hand Ring……278

Scheme 3.36. Proposed Completion of **2** through a Slightly Modified Route…….279

List of Figures

Figure 1.1. Selected members of the *Laurencia* family……3

Figure 1.2. *Laurencia* targets completed by the Snyder group with BDSB…….8

Figure 1.3. Geometry optimization of reactive intermediates for both the failed cyclization of **48** and the proposed alternative precursor **54**……..18

Figure 1.4. Sakurai allylation of aldehyde **62** and discussion of observed diastereoselectivity…...21

Figure 1.5. (A) Selected *Laurencia* natural products and their optical rotations. (B) Explanation of Lowe's rule outlining how the screw pattern of polarizability predicts the configuration of the bromoallene moiety……27

Figure 2.1. Selection of grayanane diterpenoid targets……127

Figure 3.1. Selection of various cinncassiol diterpenoids with wide range of bioactivities……214

Figure 3.2. Explanation of diastereoselectivities for the oxidative dearomatization…….229

Figure 3.3. ORTEP representation of **105**……384

Figure 3.4. ORTEP representation of **170**……385

Figure 3.5. ORTEP representation of **191**……386

Figure 3.6. ORTEP representation of **212**……387

Figure 3.7. ORTEP representation of **222**……388

Figure 3.8. ORTEP representation of **228**……389

Figure 3.9. ORTEP representation of **235**……390

List of Tables

Table 1.1. Screening of ring expansion conditions…… 23

Table 1.2. Screening of Cyclization Conditions to Generate **71**……26

Table 1.3. Comparative ^{1}H NMR data for laurendecumallene B (**6**) ……60

Table 1.4. Comparative ^{13}C NMR data for laurendecumallene B (**6**) ……61

Table 2.1. Screening of methyl addition……...143

Table 3.1. Trials in the Oxidation of Enol **95** to Dienedione **97**……..236

Table 3.2. Access to Dienedione **97** through Selenide **96**……238

Table 3.3. Nucleophilic Epoxidation Attempts of Dienedione **97**……240

Table 3.4. Access to Unstable Conjugated Phenol **113**……247

Table 3.5. Oxidative Cleavage of Methyl-Capped Phenol **124**……250

Table 3.6. Attempts to Demethylate Cleaved **130**…… 251

Table 3.7. Nazarov Cyclization Trials……..253

List of Abbreviations

Ac	acetyl
AIBN	2,2'-azobis(2-methylpropionitrile)
BDSB	bromodiethylsulfonium bromopentachloroantimonate(V)
Bn	benzyl
brsm	based on recovered starting material
Boc	*tert*-butyloxycarbonyl
$Br(coll)_2PF_6$	bis-collidine bromonium hexafluorophosphate
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DDQ	2,3-dicyano-5,6-dichlorobenzoquinone
DIBAL-H	diisobutylaluminum hydride
DIPEA	diisopropylethylamine
DMA	*N,N*-dimethylacetamide
DMAP	4-(*N,N*-dimethylamino)pyridine
DME	1,2-dimethoxyethane
DMF	*N,N*-dimethylformamide
DMP	Dess–Martin periodinane
DMSO	dimethylsulfoxide
dr	diastereomeric ratio
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
Et	ethyl
$EtNO_2$	nitroethane

HFIP	1,1,1,3,3,3-hexafluoroisopropanol
HMPA	hexamethylphosphoramide
HRMS	high-resolution mass spectrometry
IBX	2-iodoxybenzoic acid
$ICyBF_4$	1,3-dicyclohexylimidazolium tetrafluoroborate salt
*i*Pr	*iso*-propyl
IR	infrared
KHMDS	potassium bis(trimethylsilyl)amide
LDA	lithium diisopropylamide
*m*CPBA	*meta*-chloroperbenzoic acid
Me	methyl
$MeNO_2$	nitromethane
*n*Bu	butyl
NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser effect spectroscopy
NR	no reaction
Ph	phenyl
pin	pinacolato
PPTS	pyridinium *para*-toluenesulfonate
*p*TSA	*para*-toluenesulfonic acid
*t*Bu	*tert*-butyl
TBDPS	*tert*-butyldiphenylsilyl

TBS	*tert*-butyldimethylsilyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFE	2,2,2-trifluoroethanol
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TMS	trimethylsilyl

Acknowledgements

Compiling this dissertation has been a cathartic process, to say the least, as it has given me a chance to deeply reflect on my journey to the completion of my PhD. Starting from my upbringing in a small, one stoplight town amongst the cornfields in Maryland, to my undergraduate studies at the University of Richmond, and of course ending at the University of Chicago, I have had the honor to be taught and mentored by, work and interact with, and teach and mentor a large array of inspiring and supportive people, all playing a critical role in my own personal success. Throughout all these adventures, I have not only gained a profound appreciation for chemistry and the world around us, but also for the simplicity of meaningful, constructive, and supportive personal relationships. Each step along the way, I have been blessed to have someone telling me the only limits placed on one's potential is their own, to act boldly, and take risks. There is no document long enough for me to share the level of gratitude I have for everyone that has helped me, so to those who may go unnamed below, please know I am forever thankful.

First, I would like to express my gratitude for **Professor Scott A. Snyder**. Your commitment to shaping me as a synthetic organic chemist from the ground up, allowing me the space to simply explore the chemistry, and trusting me to apply my computational training to our experimental work promoted my professional and personal growth beyond what I could have imagined four years ago. Thank you for your patience during the times of struggle and your continued encouragement when things were going well. The opportunities you granted me over the years, be it presenting my work to external speakers, mentoring junior students, being involved in collaborations, or proofreading manuscripts have equipped me with invaluable tools that I know will serve me throughout my career. Having taken a risk by recruiting a student with a theoretical background, you altered the course of my life dramatically, and for that I am eternally grateful.

I would also like to take the time to thank **Professor Guangbin Dong** and **Professor Viresh H. Rawal** for serving as my committee members and taking the time to go through this dissertation. Furthermore, I would also like to thank them for the education I have received from them, in the classroom setting, through interactions at lecture series, super group meetings, and during our collaborative work related to COVID-19.

To obtain a PhD is not a solitary process, as the people you work with shape not only yourself but also the directions of your projects. I cannot begin to express the profound gratitude I have for **Dr. Yu-An Zhang**, the greatest mentor, and friend, I could have asked for. Showing patience beyond the call of duty, you've always allowed me to bombard you with questions about chemistry, politics, music, and beer. Thank you to **Dr. Charles Cole**, **Philipp Gemmell**, and **Russell Kielawa** for being the best quaranteam out there. Our friendship was truly the silver lining of the world altering COVID-19 pandemic, and I cannot express how deeply I appreciate my relationship with each of you. I would like to put additional respect on **Russell Kielawa**'s name for proofreading this entire dissertation, a favor I am whole-heartedly thankful for. I would also like to thank **Sofía Natividad**, **Julia Noel**, **Jonathan Keim**, **Professor Hyung Min Chi**, **Dr. Lilia Fuentes**, **Dr. Vlad Lisnyak**, **Dr. Masato Kono**, **Natalie Yaw**, **Sarah Greta**, **Will Guy**, **Dr. Dipendu Das**, **Evgeny Gulyak**, **Dr. Alison Gao**, and **Dr. Pei Gan**, fellow Snyder Lab members/alumni, for being wonderful friends, coworkers, and collaborators, constantly giving insightful advice on projects, and being consistent points of clarity over the years.

My time in Chicago has also been shaped by many people outside of the Snyder Lab, and I would like to emphasize my gratitude for **Matthew Zajac**, **Linda Zhang**, and **Nanetta Pon**. We've been the core four since First Year, and our weekly breakfasts at Salonica with Angie and the gang will always be one of the warmest highlights of graduate school. Many people behind the

scenes also deserve endless praise, starting with **Laura Luburich** and **Mike Reedy**, who constantly kept Searle running smoothly, and for being consistent points of soulful nourishment with every conversation. I would like to thank **Dr. Antoni Jurkiewicz**, **Dr. Josh Kurutz**, **Dr. Jin Qin**, **Dr. Alex Filatov**, **Dr. Andrew McNeece**, **Dr. Kate Jesse**, and **Sophie Whitmeyer** for maintaining the NMR, Mass Spectrometry, and X-ray crystallography facilities and for your help with structure elucidation. Lastly, I would like to thank **Dr. Vera Dragisich** and **Melinda Moore** for being on-call to help ensure my graduate school experience was as orderly as possible.

Outside of the University, the community at **St. Paul & the Redeemer** provided me a space for spiritual nourishment, and my appreciation for SPR could never be measured. Thanks be to God, and to all those that wholeheartedly embraced me as a member of the community. Lastly, I would like to thank **Dr. Dominique Walker-Barnes** – I am forever grateful for all the guidance, support, and friendship you have provided me, especially in my darkest hours.

As an undergraduate student, I had the honor to work with **Professor Carol A. Parish**, whom I consider one of my greatest mentors and friends. Your ability to teach scientific approaches and thought processes, as well as inspire curiosity, perseverance, and exploration is unmatched. You showed me my potential as a chemist, and I am forever indebted to you. I will never forget the time you had me line the entire hallway in Gottwald with all my results and asked me to defend them as we moved down the hall in rolling chairs for over an hour – I truly believe that was a turning point in my confidence as a scientist, and I fondly hold onto that memory. I would also like to thank Parish Lab members **Professor Billy Miller III**, **Thais Scott**, **Quincy McKoy**, **Arjun Jaini**, **Erica Modeste**, **Lauren McRae**, and **Boyi Abbott** for your support and friendship. Furthermore, **Professor Wade Downey** inspired me to pursue organic synthesis for my graduate studies, and I could not be more appreciative of your ability to make organic

chemistry entertaining and approachable to all. Lastly, I would also like to thank **Professor Mike Leopold** and **Professor Kelling Donald** for everything you have taught me, both about chemistry and life. You both have worked tirelessly to make chemistry an accessible subject for everyone, and your friendship, guidance, and encouragement has served me beyond description. Thank you.

I also want to acknowledge my high school chemistry teachers **Dr. Pierre Tshimanga** and **Lisa Haack** for fostering my love for chemistry. Two of the sincerest people I have ever known, and two of the greatest sources of inspiration for when I wanted to embark on this journey. Special thanks to **Lisa Haack** for playing a large role in the college selection process, for if it wasn't for your guidance, I never would have been on the amazing path I find myself on today. Thank you as well to **Cate Barry** and **Monique Zastrow** for teaching me to fight for what I want in life, and for being unwavering in your support at every turn.

Most importantly, thank you to my family. This is all for y'all. **Mom** and **Dad**, you have given everything for me to pursue a path completely different from yourselves, and I can ever only hope to be half as supportive, loving, and generous as y'all are. **Casey**, **Billy**, **Kirby**, and **Maddy**, thank you for always being there for me, and for being the best siblings I could ever have. I love y'all, and I hope to make you proud. **Guppy** and **Grampy**, I wish you were here to see the end of this journey, as y'all inspired me from the start. **Milan Essex**, my best friend and chosen family, Lord knows none of this would be possible without your support, and I am forever grateful for you. The durability of our long-distance friendship is unmatched, and I am honored you are part of my life. Above all, I must thank **Claudia Partida**. This experience has been filled with ups and downs, and you have been unwavering throughout. All our morning texts, late-night FaceTimes, flights between Chicago and Virginia – I wouldn't trade it for the world. Te quiero con todo mi corazón. Palavras não podem descrever o meu amor por você.

ABSTRACT

Heteroatom Guided Total Synthesis: Application to Polyhalogenated and Polyoxygenated Natural Products

Cooper Ashley Taylor

Natural products and their derivatives account for 62% of all FDA-approved small molecules from 1981 to 2014. However, the use of natural products for pharmaceutical purposes is often limited by both the low natural abundance of such targets and general synthetic inefficiency in making complex molecules on scale. Herein, we hope to explore how we may surmount the latter limitation, as we discuss our efforts in the production of compounds with not only a high proportion of stereochemical information, but also stereochemically dense, heteroatom containing cores. These two attributes can be daunting on their own, however we believe they can be quite synergistic when approached as a cooperative problem, in which the presence of the heteroatoms throughout such scaffolds informs how best to tackle the overall targets. This dissertation will describe such synthetic efforts across three families of natural products: the *Laurencia* ethers, grayanotoxin diterpenoids, and cinncassiol diterpenoids.

Chapter 1 will outline our efforts to complete the inaugural total synthesis of laurendecumallene B, a polyhalogenated and polycyclic *Laurencia* ether. The composition of this target consists of eight stereocenters within its 15-carbon skeleton, two bromines, and four oxygens. In this work, we will describe how we utilized the presence and placement of these heteroatoms, in concert with the various stereocenters throughout the system, to elucidate the first successful synthesis of this target. Furthermore, we also discuss the pivotal application of DFT to

inform a critical route redesign alongside the unique reactivity of BDSB, a highly electrophilic bromonium source which introduces both bromines within laurendecumallene B.

In Chapter 2, we outline initial efforts to potentially access several members of the grayanotoxin diterpenoids, a class of highly oxygenated tetracyclic compounds with a wide range of bioactivities. Herein, a general approach for the total synthesis of ten grayanane diterpenoids is proposed, all potentially stemming from a common intermediate. Of note, an intermolecular radical coupling cascade was planned to construct the common intermediate, the design of which was guided by the conserved placement of several oxygens across nearly the entire family of targets. Ultimately, these studies were ceased due to a recent publication sharing a similar approach to a related target.

Finally, Chapter 3 will discuss current efforts focused on a second class of highly oxygenated natural products: the cinncassiol diterpenoids. These compounds are part of and/or related to the isoryanodane family and have shown a plethora of various biological activities accompanying their wide-ranging levels of oxidation. Our approach is centered on the total synthesis of cinncassiol F, differing from cinnamomol A by a single C-C bond proposed to be biosynthetically fashioned through an intramolecular aldol addition.

CHAPTER 1

THE ENANTIOSELECTIVE TOTAL SYNTHESIS OF LAURENDECUMALLENE B

1.1 Introduction

1.1.1 Laurencia Family of Natural Products

Since the isolation of laurencin (**1**) in 1965, chemists have identified over 150 halogenated ethers from the various red algae of the *Laurencia* genus.[1] Although one characteristic of these targets is their conserved 15-carbon skeleton (aptly named C_{15}-acetogenins), most of the attention they have been given from the synthetic community is arguably due to the fact that over half of these molecules possess an 8-membered cyclic ether, featuring a bromine on the carbon β-to the ethereal linkage either within the ring (as in **1**-**3**, Figure 1.1)[2] or just outside it (as in **5**-**6**).[3] Furthermore, it is common for there to be additional fused ring systems and an additional halogen atom elsewhere in the molecule, typically as part of an exocyclic allene.[4] It is due to these features that these targets have been utilized as a proving ground for various synthetic transformations and methodological developments in the realm of mid-sized cyclic ether formation and halogenation chemistry. There is no better way to highlight how attractive these compounds have been to the synthetic community than to simply note that nearly 20 total and formal syntheses have been reported for laurencin (**1**) alone.[5]

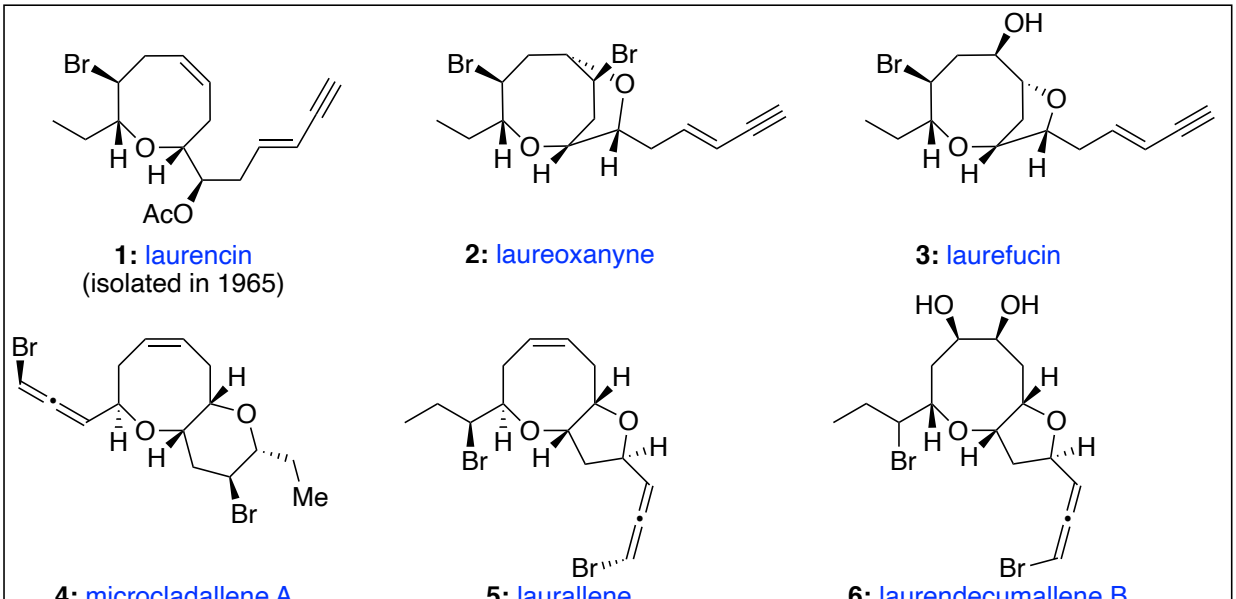
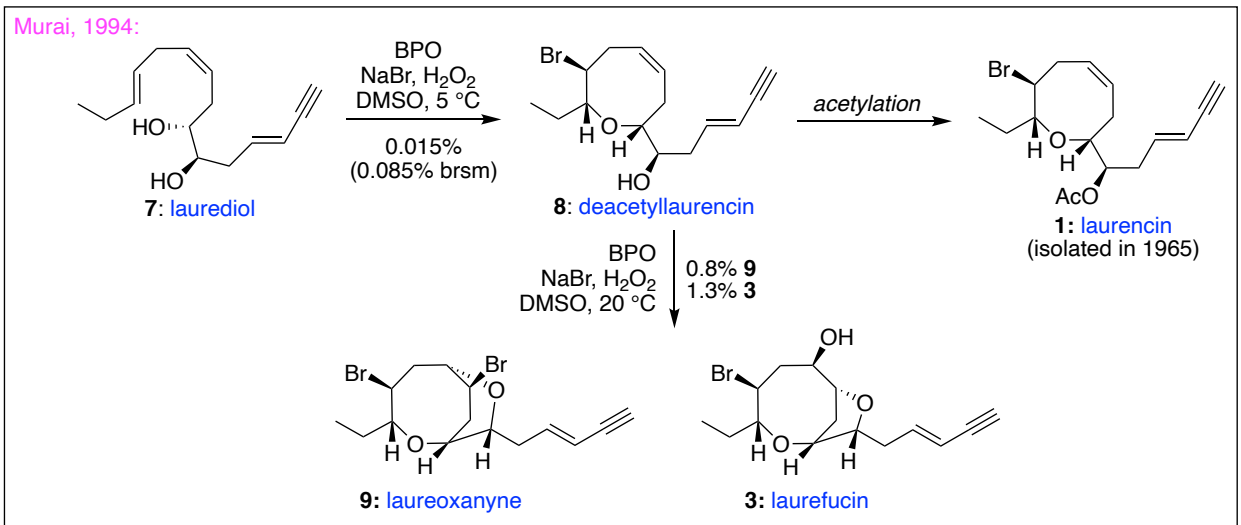


Figure 1.1. Selected members of the *Laurencia* family.

1.1.2 Biosynthetic Proposals of Laurencia Compounds

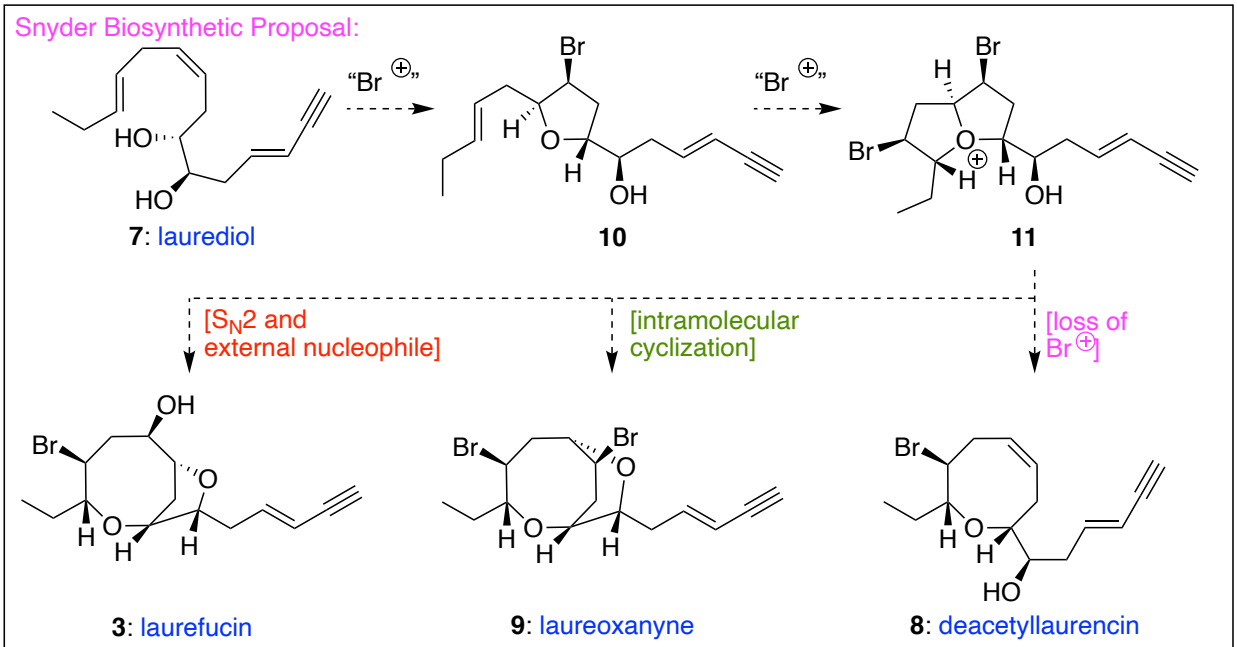
In many cases, total synthesis can reap bountiful inspiration from Nature's own approach to complex targets. It is with this in mind that the pioneering biosynthesis of deacetyllaurencin (**8**), as well as laureoxanyne (**9**) and laurefucin (**3**) by Murai and coworkers in 1994 serves as a critical turning point in how these molecules can be approached from a synthetic standpoint (Scheme 1.1).[6] Having partially purified bromoperoxidase (BPO) from *Laurencia nipponica*, a red algae found off the coast of Hokkaido Island, Japan, they were able to observe the cyclization of linear-chained laurediol **7** into deacetyllaurencin **8**, albeit in 0.015% yield (whilst recovering 82.4% of the starting material). They were able to confirm this result through the acylation of the free alcohol to produce laurencin (**1**), perfectly matching the spectral data of the naturally occurring compound.[1a] This result inspired them to propose a direct 8-*endo*-trig cyclization of the free alcohol onto a bromonium intermediate, formed on the distal olefin as the biogenetic pathway. Furthermore, they could further subject the produced deacetyllaurencin (**8**) to BPO a second time and observe the

production of laureoxanyne (**9**) and laurefucin (**3**) in 0.8% and 1.3%, respectively, recovering 72.2% of the starting **8**. Of note, this second set of reactions was performed at a higher temperature (20 °C) than the initial cyclization to **8** (performed at 5 °C).



Scheme 1.1. Biosynthesis of deacetyllaurencin (**8**), laureoxanyne (**9**), and laurefucin (**3**) by Murai and coworkers utilizing partially purified bromoperoxidase.

Although technically possible, no further mechanistic evidence was provided for the direct 8-*endo*-trig cyclization. However, this proposed mid-sized ring formation event does not seem all too entropically or enthalpically favorable, especially since there exists a competing 5-*endo*-trig cyclization of the secondary alcohol onto the proximal bromonium ion, resulting in a potential, and more commonly encountered, tetrahydrofuran intermediate (Scheme 1.2).[7] The oxygen of the tetrahydrofuran ring can then act as the nucleophile upon a second bromonium coordination event to the distal olefin, producing the critical bicyclic oxonium intermediate **11**.



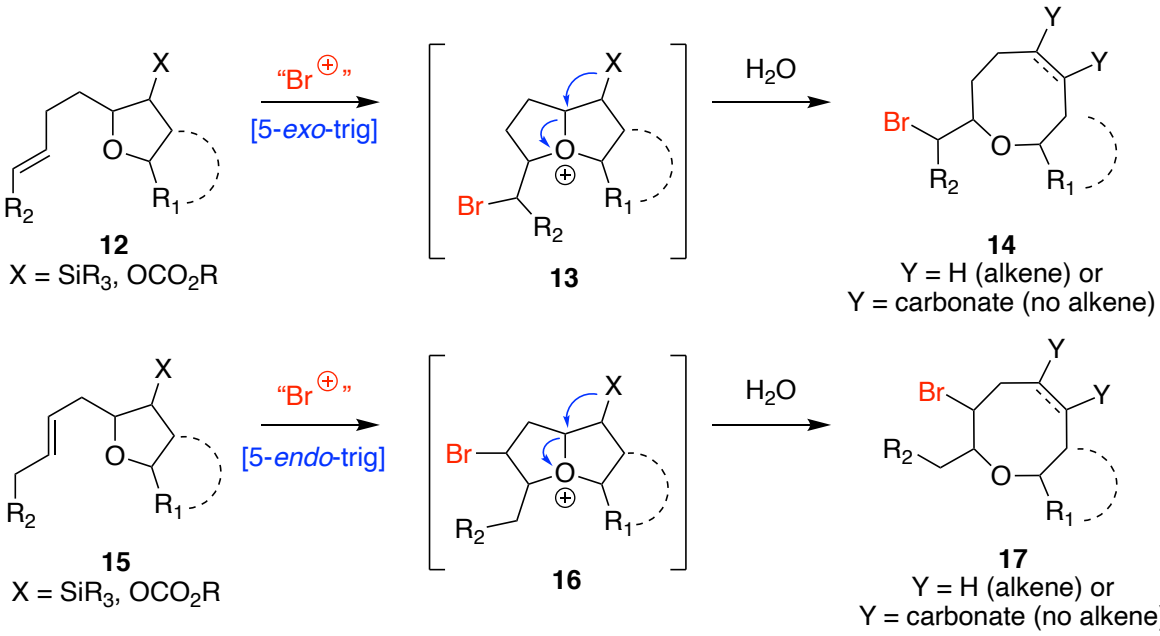
Scheme 1.2. Adjusted biosynthetic proposal by the Snyder group in which an initial 5-*endo*-trig cyclization occurs which is then readily extrapolated to several *Laurencia* targets (**3, 8, 9**) through a critical oxonium intermediate (**11**).

With oxonium intermediate **11** in mind, it is then clear how each of the three products produced by the Murai group could then be produced directly through various ring expansion processes. A simple loss of the Br^+ would allow for the formation of the internal olefin, promoting the opening of the oxonium to produce deacetyllaurencin (**8**), intramolecular attack of the free secondary alcohol onto the oxonium would open to the caged laureoxanyne (**9**), or an even more complex reaction mixture in which water acts as an external nucleophile to promote the opening of the oxonium alongside bromide displacement through an intramolecular S_N2 attack of the free alcohol would produce laurefucin (**3**).

1.1.3 Snyder Group General Strategy

Key to the Murai biosynthesis of deacetyllaurencin is the use of bromine as an electrophile, versus the more traditional nucleophilic form, to introduce the skeletal bromide.[8] Nearly all synthetic efforts to the *Laurencia* ethers thus far have utilized nucleophilic bromide in alcohol displacement chemistry to introduce such a moiety, which begs the question of whether a more

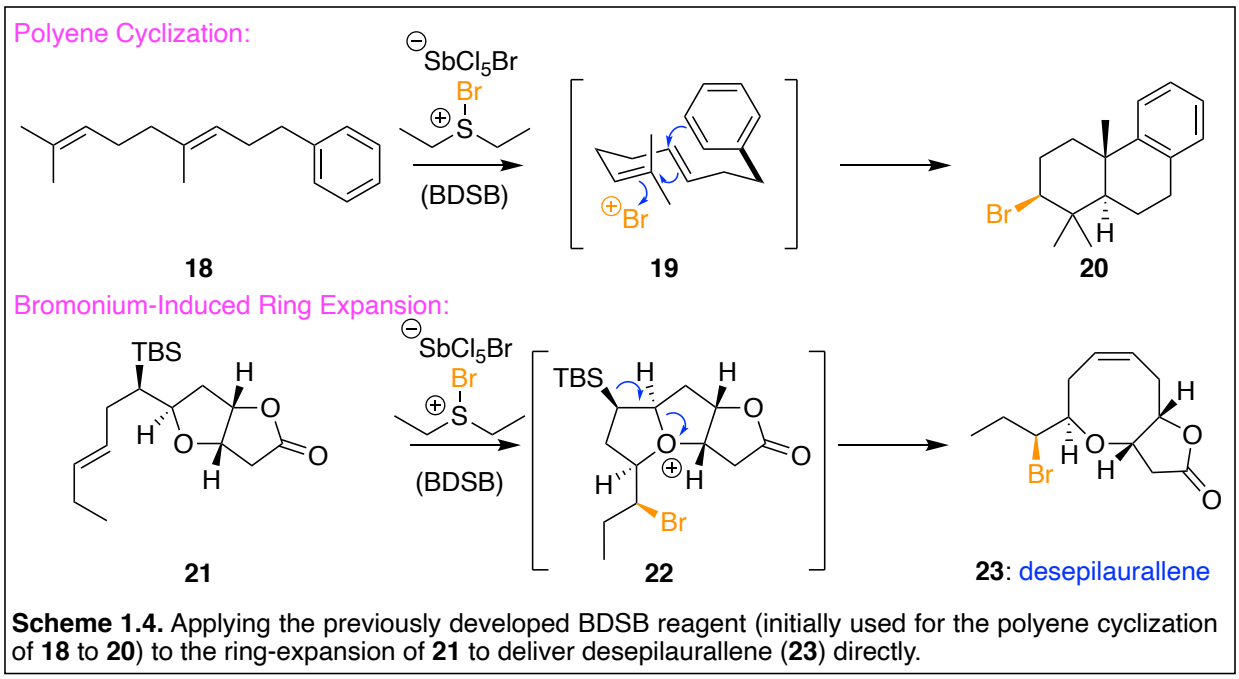
biomimetic approach could be achieved in which a synthetic, electrophilic source of bromine is utilized to streamline the production of these targets. To put this idea into practice, our group designed a general strategy in which we could potentially harness the power of our proposed tetrahydrofuran intermediate to promote various ring-expansion processes, delivering mid-sized cyclic ethers with the characteristic β-bromide located externally (**14**) or internally (**17**) simply controlled by the placement of the distal olefin (Scheme 1.3).[7, 9] We envisioned the need of some promoter group to facilitate the expansion process of the oxonium, be it a neighboring silyl group that could eliminate to deliver an internal olefin (such as that found in laurencin, **1**) or a carbonate protected alcohol that could serve as an intramolecular nucleophile to deliver a *cis*-diol with full stereocontrol (such as that found in laurendecumallene B, **6**).



Scheme 1.3. Snyder group general strategy for the construction of the various *Laurencia* cores in which the β-Br can be installed either externally (**14**) or internally (**17**) based on olefin placement.

Just as it was critical for the Murai biosynthesis, an electrophilic source of bromine is also required to enact this general strategy. Thankfully, our group previously developed one of the most electrophilic brominating reagents, bromodiethylsulfonium bromopentachloroantimonate(V)

($Et_2SBr•SbCl_5Br$, BDSB, Scheme 1.4).[10] Although BDSB was originally utilized for highly diastereoselective polyene cyclizations (**18**→**20**), we were curious as to whether it would allow for the proposed ring expansion processes. Pleasingly, it proved to be quite fruitful. For instance, when bicyclic lactone **21** was subjected to BDSB, the natural product desepilaurallene (**23**) was produced.[11] This general strategy has now been utilized to produce eight members of the *Laurencia* family, including the first total synthesis of laurendecumallene B (**6**), disclosed herein.[9, 11-12]



Scheme 1.4. Applying the previously developed BDSB reagent (initially used for the polyene cyclization of **18** to **20**) to the ring-expansion of **21** to deliver desepilaurallene (**23**) directly.

1.2 The Enantioselective Total Synthesis of Laurendecumallene B

Our group has extensive experience in the synthesis of the *Laurencia* family of natural products, having developed routes to (±)-laurefucin (**3**), (±)-Z- and (±)-E-pinnatifidenyne (**24** and **25**), desepilaurallene (**23**), microcladallenes A and B (**4** and **26**), and laurallene (**5**) using a unique and highly reactive bromonium source we previously developed, BDSB.[7, 9-10, 11] Herein, we present the first total synthesis of another member of the *Laurencia* family, laurendecumallene B (**6**).[12] This unique natural product was originally isolated in 2007 from *Laurencia decumbens* Kützing, a marine red algae found off the coast of Weizhou Island in China.[13] From 500 g of dried *Laurencia*

decumbens, 13.0 mg of pure **6** was obtained. A synthetically alluring molecule, **6** contains a bromoallene moiety, an 8-membered cyclic ether ring, and a total of eight stereocenters in a compact fifteen carbon skeleton. An interesting structural variation of **6** exists in the unique *cis*-oxacycle, as it is the only known fused bicyclic member of the family with this disposition. All other known fused-bicyclic members of the *Laurencia* family present a *trans*-oxacycle, whereas **6** has a *cis*-disposed core as denoted by the starred positions in Figure 1.2, only observed in the bridged and open-chain systems (such as pinnatifidenynes **24**/**25** and laurefucin, **3**).[13] Furthermore, although the partial relative stereochemistry of **6** has been reported, the axial chirality of the bromoallene substituent and the stereochemistry of the C-13 center has yet to be determined (Figure 1.2); its absolute configuration is also unestablished.

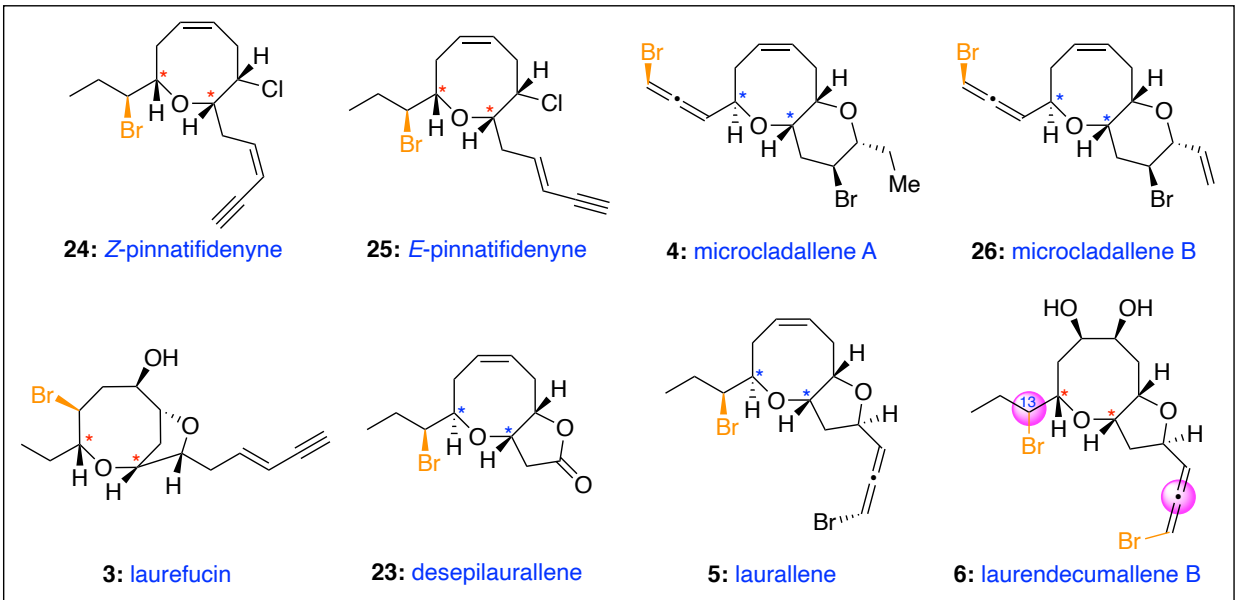
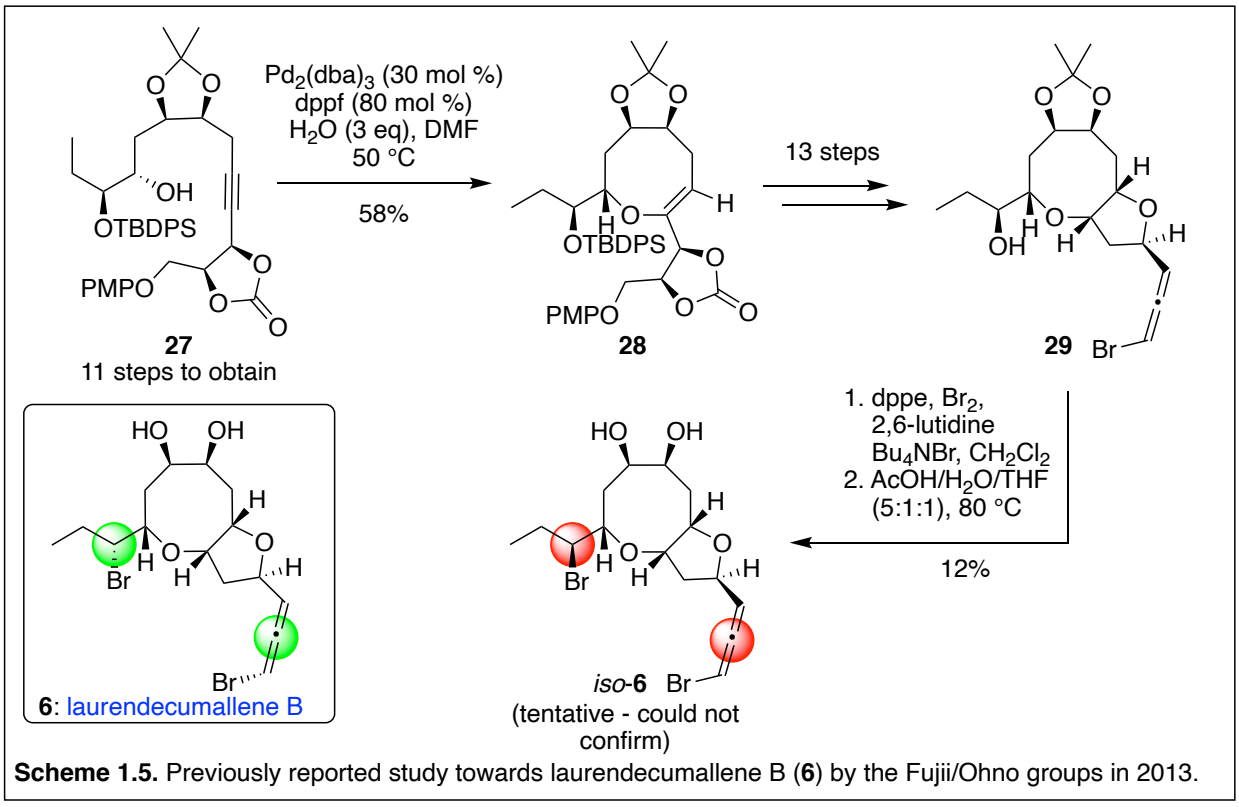


Figure 1.2. *Laurencia* targets completed by the Snyder group with BDSB. All bromine atoms introduced by BDSB are highlighted in orange. Key *cis*-disposed protons of **6** and non-fused bicycles are denoted by red stars, and *trans*-disposed protons are highlighted in blue. Previously undisclosed stereochemistry of **6** is highlighted in pink.

1.2.1 Previous Study Towards Laurendecumallene B

To date, there has been only one reported attempt to achieve a total synthesis of **6**.[14] As shown in Scheme 1.5, Fujii, Ohno, and co-workers were able to obtain the mid-sized cyclic ether

of **6** through a Pd-catalyzed 8-*endo*-dig cyclization of alkyne precursor **27**, achieved in 11 steps.[15] This type of direct 8-membered ring formation can be viewed as a Pd-catalyzed variant of that proposed by Murai;[6] however, the system certainly presents a greater deal of structural rigidity due to the pre-installed acetonide-protected *cis*-diol and the alkyne itself, versus the mostly linear lauredіol **7** (Scheme 1.1). With the oxacycle in hand, they were able to push forward through 15 additional steps to develop most of the final target but were unable to confirm whether they had obtained **6**.



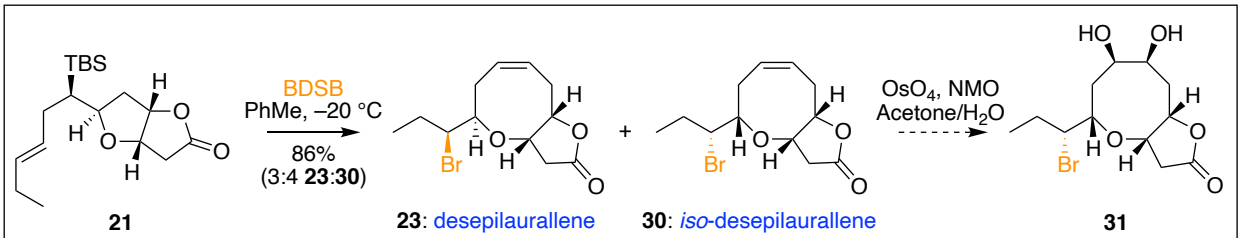
Scheme 1.5. Previously reported study towards laurendecumallene B (**6**) by the Fujii/Ohno groups in 2013.

The final two steps of the Fujii/Ohno approach were to perform a bromination of the C-13 position followed by acetal deprotection of the *cis*-diol.[14] When conducting the bromination through a traditional Appel S_N2 displacement (*i.e.* $Oct_3P–CBr_4$) typically used for the introduction of the bromine atom of *Laurencia* targets,[16] they observed clean conversion based on TLC analysis, but then full decomposition of the resultant material following acetal deprotection

attempts; this outcome was ascribed to be the result of instability of either the initial intermediate or the final product to acid. Their proposed intermediate was not isolated. When utilizing dppe-Br_2 with 2,6-lutidine and *n*Bu_4NBr to form the product of net stereochemical retention through an oxonium intermediate,[5e, 16e, 17] they were able to successfully perform the acetal deprotection of the crude material, albeit in 12% yield over the two steps with the total obtained mass being 0.3 mg with inseparable impurities. Using this material, they were able to obtain a crude ^{1}H NMR spectrum, along with an optical rotation value ($[\alpha]^{25}_D$ +63.1, *c* = 0.03 in $CHCl_3$); the literature optical rotation is $[\alpha]^{25}_D$ +60.6 (*c* = 0.33, $CHCl_3$).[13] However, they were unable to prove whether they truly obtained the stereoretained product in the bromination step, determine the axial chirality of the bromoallene moiety, or confirm the production of laurendecumallene B (**6**). Of note, as shown in Scheme 1.5, we found the stereochemistry of the C-13 position to be opposite of that proposed by Fujii/Ohno.

1.2.2 Alteration of Previous Desepilaurallene Synthesis

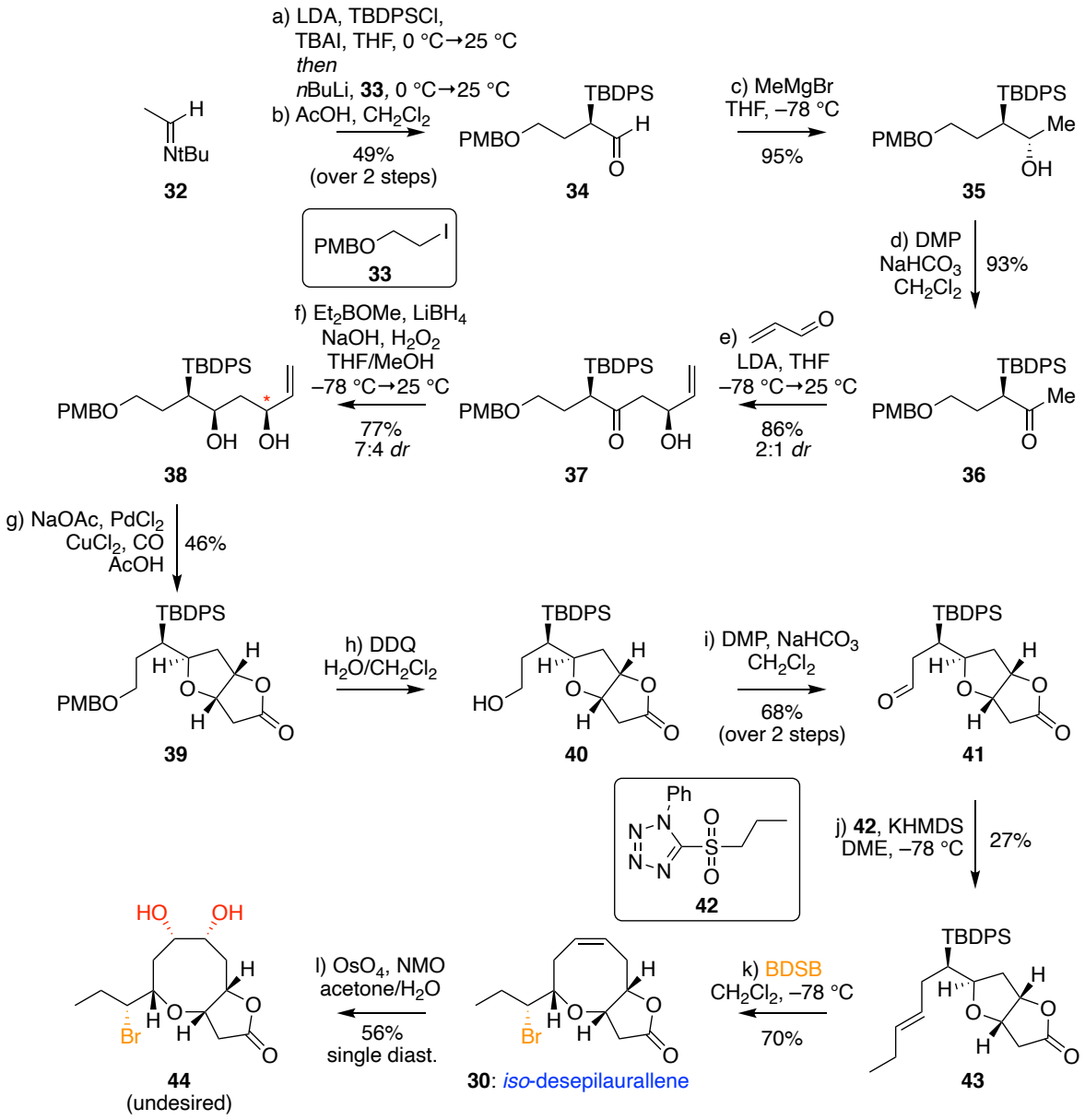
Based on a recent synthesis of laurallene (**5**) achieved in our group,[11] we initially believed that a simple dihydroxylation of alkene **30**, an isomer of the natural product desepilaurallene (**23**), would yield the desired diol. As shown in Scheme 1.6, we were able to produce **23** and **30** as a 3:4 diastereomeric mixture upon subjecting bicyclic lactone **21** to BDSB. Although the desired natural product **23** was observed to be the minor diastereomer, we were hoping to utilize the major diastereomer (**30**) to quickly access laurendecumallene B (**6**).



Scheme 1.6. Proposed dihydroxylation of diastereomer **30** to access oxidized core of laurendecumallene B (**6**).

Given a 3:4 *dr* of **23**:**30** was generated when the eliminating silyl group was TBS, we proposed a bulkier silyl group may lead to higher selectivity for our desired isomer (**30**). With this in mind, we were able to produce the TBDPS-containing ring expansion precursor **43** in a similar 10-step sequence starting with imine **32** (Scheme 1.7). Initial silylation and alkylation of imine **32**, followed by hydrolysis allowed for the efficient production of aldehyde **34**.[18] From here, a simple methyl Grignard addition and subsequent oxidation set the stage for an analogous aldol addition, this time utilizing acrolein as the electrophile to produce **37**, albeit in an inseparable 2:1 diastereomeric mix. Pushing forward, though, we could then take advantage of the secondary alcohol to perform a directed Narasaka-Prasad reduction, furnishing our desired *cis* diol **38**.[19] Pleasingly, the two diastereomers could be separated at this point. With the *cis* diol in hand, all requisite stereocenters were in place to perform our previously developed Pd-mediated cyclocarbonylation to construct the desired bicyclic lactone **39**.[11, 20] Of note, this reaction proved to show a major loss in yield if performed above the 300 mg scale, requiring multiple smaller scale reactions to be performed in serial to ensure high levels of material throughput. Additionally, several mechanisms for this reaction have been proposed. Seminal work by the Semmelhack group in 1983, along with additional studies by the Chen and Yang groups in 2005 suggest an attack of the starred alcohol in **38** onto the $PdCl_2$, before CO insertion, and intramolecular nucleophilic addition, followed by reductive elimination of the Pd to release the bicyclic lactone. However, a Wacker-type mechanism could also reasonably be envisioned. Lastly, the presence of *dr* (not explicitly observed in this exact example, but seen for similar systems) is believed to be attributed to the orientation of the terminal olefin upon attack, as Semmelhack reported, in the case of internal olefins, varying diastereomeric mixtures based on whether the starting alkene was of *E*- or *Z*-geometry.

Scheme 1.7. Forward synthesis of *iso*-desepilaurallene (**30**) and subsequent Upjohn dihydroxylation yielding undesired diol diastereomer (**44**).[a]



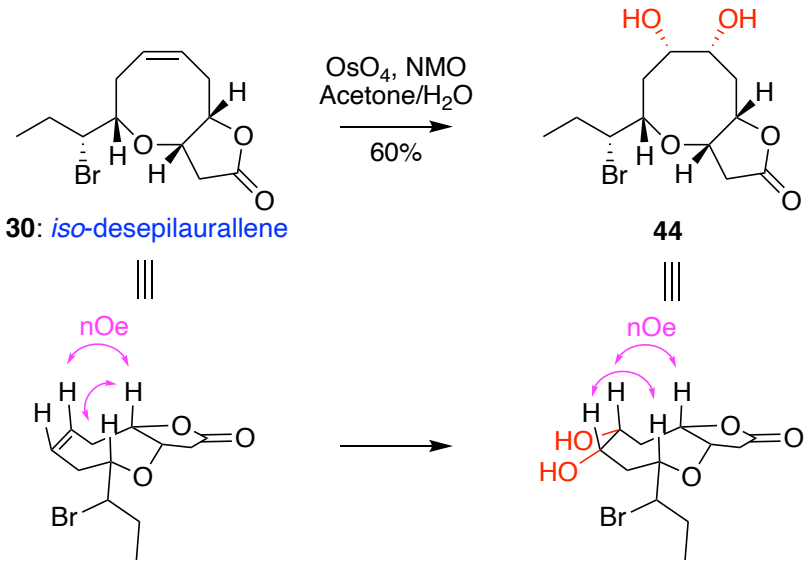
[a] Reagents and conditions: (a) iPr$_2$NH (1.0 equiv), nBuLi (1.0 equiv), THF (1.0 M), 0 °C, 0.5 h, *then* TBDPSCl (1.0 equiv), TBAI (0.05 equiv), 25 °C, 3 h, *then* nBuLi (1.0 equiv), 0 °C, 1 h, *then* **33** (1.2 equiv), 25 °C, 12 h; (b) AcOH (1.0 equiv), CH_2Cl_2 (0.4 M), 25 °C, 0.5 h, 49% (2 steps); (c) MeMgBr (2.2 equiv), THF (0.5 M), –78 °C, 5 min, 95%; (d) $NaHCO_3$ (5.0 equiv), DMP (1.1 equiv), CH_2Cl_2 (0.1 M), 25 °C, 5 min, 93%; (e) iPr$_2$NH (1.6 equiv), nBuLi (1.5 equiv), THF (0.3 M), 0 °C, 0.5 h, *then* **36** (1.0 equiv), –78 °C, 0.5 h, *then* acrolein (1.6 equiv), –78 °C, 5 min, 86% (2:1 *dr*); (f) Et$_2$BOMe (1.2 equiv), THF/MeOH (4:1, 0.5 M), –78 °C, 0.5 h, *then* $LiBH_4$ (20 equiv), –78 °C→25 °C, 4 h, *then* NaOH (2.5 equiv), H_2O_2 (2.7 equiv), 25 °C, 0.5 h, 77% (7:4 *dr*, separable); (g) $PdCl_2$ (0.4 equiv), $CuCl_2$ (3.0 equiv), NaOAc (5.0 equiv), CO (balloon), AcOH (0.1 M), 25 °C, 10 min, 46%; (h) DDQ (1.5 equiv), CH_2Cl_2/H_2O (9:1, 0.1 M), 25 °C, 30 min; (i) $NaHCO_3$ (5.0 equiv), DMP (1.1 equiv), CH_2Cl_2 (0.1 M), 25 °C, 5 min, 68% (2 steps); **42** (4.0 equiv), KHMDS (3.5 equiv), DME (0.1 M), –78 °C, 0.5 h, *then* **41** (1.0 equiv), –78 °C, 0.5 h, 27%; (k) BDSB (0.8 equiv), CH_2Cl_2 (0.1 M), –78 °C, 15 min, 70%; (l) OsO_4 (0.04 equiv), NMO (2.0 equiv), acetone/H_2O (5:1, 0.05 M), 25 °C, 2 h, 56%.

Having obtained bicyclic lactone **39**, the final manipulations required to reach the critical *iso*-desepilaurallene precursor (**30**) were to simply convert the PMB-protected primary alcohol into the complete alkyl sidechain (Scheme 1.7). This was done through a 3-step sequence including a DDQ-mediated deprotection, subsequent Dess-Martin periodinane oxidation of the primary alcohol to the respective aldehyde (**41**), and a final Julia-Kocienski olefination to furnish the final 3-carbon unit and complete the BDSB-promoted cyclization precursor **43**.[21] Of note, due to the low yield of the olefination step, we explored an alternative approach with a simple methylene olefination which could be subsequently metathesized with *trans*-3-hexene, however no appreciable product was observed during the initial olefination. None the less, we could then subject bicyclic lactone **43** to BDSB in CH_2Cl_2 at –78 °C and were pleased to find our initial assumption regarding the bulkier silyl group did in fact yield higher diastereoselectivity (>20:1 *dr* observed).

Having now established a more diastereoselective route to *iso*-desepilaurallene (**30**), it seemed as though we were only a few steps away from our desired target, laurendecumallene B (**6**), as the only missing components were the *cis*-diol and right-hand bromoallene. In an attempt to tackle the former piece, we performed an Upjohn dihydroxylation of the internal disubstituted olefin with the hopes of directly installing the *cis*-diol. However, the undesired diol diastereomer **44** was exclusively observed (Scheme 1.7); nOe correlations between the highlighted hydrogens in Scheme 1.8 were critical in the confirmation of this result. When subjecting the starting alkene to nOe analysis, a strong correlation between the alkene proton and the α-proton of the lactone was detected, suggesting the chair-like conformation of the alkene as drawn in Scheme 1.8. Such a conformation would expose the bottom-face of the oxacycle, providing a possible explanation as

to why the dihydroxylation only occurred from that side, resulting in the single observed diastereomer.

Scheme 1.8. Production of undesired *cis*-diol diastereomer **44** from Upjohn dihydroxylation.[a]



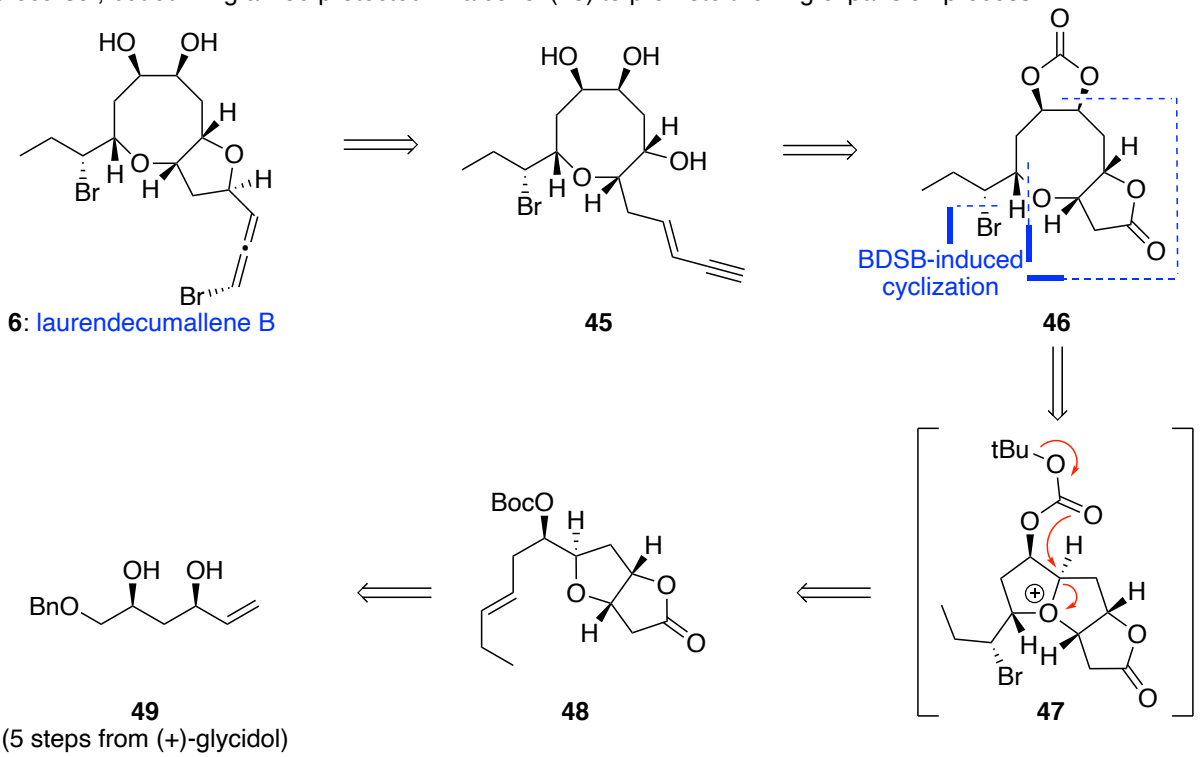
[a] Reagents and conditions: OsO_4 (0.04 equiv), NMO (2.0 equiv), acetone/H_2O (5:1, 0.05 M), 25 °C, 2 h, 60%.

Overall, although we were unable to have a unified approach to laurendecumallene B (**6**), we still learned several valuable lessons from this initial approach. First, the cyclocarbonylation conditions previously developed to construct the bicyclic lactone can be translated well to substrates of varying steric bulk. Second, the diastereoselectivity of the BDSB-induced ring expansion process is heavily influenced by the steric environment of distal positions, as the change from TBS- to TBDPS-silylated material increased the *dr* from 4:3 (**30**:**23**) to >20:1. Lastly, and arguably the most critical lesson, it became apparent that the *cis*-diol would need to be introduced intramolecularly to ensure correct facial selectivity. It is with this in mind that we were able to draft up another related route to laurendecumallene B (**6**), this time utilizing a carbonate-protected secondary alcohol to promote the ring-expansion process as opposed to eliminating a silyl group.

1.2.3 Construction of Boc-protected Bicyclic Lactone Precursor

With the inability to utilize a byproduct from our laurallene (**5**) synthesis, we needed to formulate a new approach. As noted in Scheme 1.3, our group's general strategy for a productive BDSB-induced ring expansion process can involve either the elimination of a silyl group or intramolecular attack from a carbonate-protected alcohol.[7] As we observed a smooth ring-expansion process with the silylated bicyclic lactone (**43**), we believed we could still achieve laurendecumallene B (**6**) through an analogous bicyclic intermediate, differentiated by a neighboring Boc-protected secondary alcohol (**48**, Scheme 1.9).

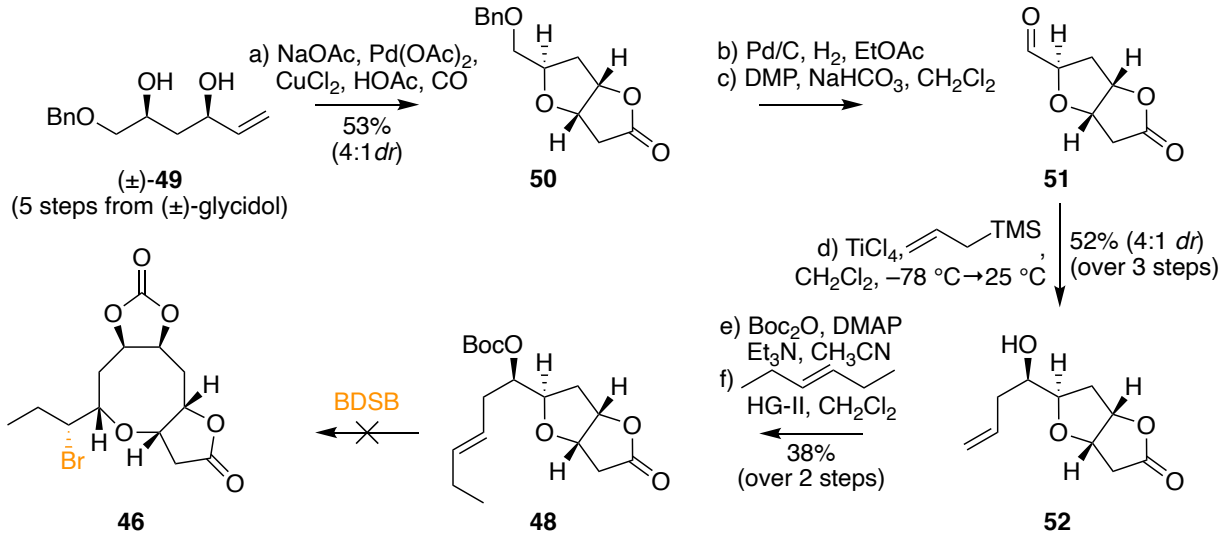
Scheme 1.9. Adjusted retrosynthetic analysis of laurendecumallene B (**6**) through a similar bicyclic lactone precursor, but utilizing a Boc-protected 2° alcohol (**48**) to promote the ring expansion process.



To this end, we were able to achieve the bicyclic lactone in an efficient 11 steps, starting from commercially available glycidol (Scheme 1.10). Pushing forward from known racemic diol (±)-**49** (achieved in 5 steps from glycidol),[22] we were able to perform the palladium-mediated

cyclocarbonylation in commensurate yield (59%, 4:1 *dr*), this time utilizing $Pd(OAc)_2$ instead of $PdCl_2$ as the optimal Pd(II) source. Once again, the yield exhibited a steep decrease when performed above the 300 mg scale. With the bicyclic lactone framework constructed, simple benzyl deprotection followed by subsequent oxidation to aldehyde **51** set the stage for a $TiCl_4$-mediated Sakurai allylation to produce **52**.[23] Although this allylation showed modest diastereoselectivity for the desired intermediate (~4:1 *dr*), the material was subjected to Boc-protection, followed by a metathesis with *trans*-3-hexene to provide the desired BDSB precursor (**48**), albeit in poor yield (38% over 2 steps). To our disappointment, though, we were unable to obtain any desired cyclization product (**46**) when **48** was treated with BDSB in a variety of solvents (CH_2Cl_2, $MeNO_2$, $EtNO_2$, toluene) at varying temperatures (–78 °C → 0 °C).

Scheme 1.10. Forward synthesis of bicyclic lactone ring-expansion precursor **48** and failed cyclization.[a]



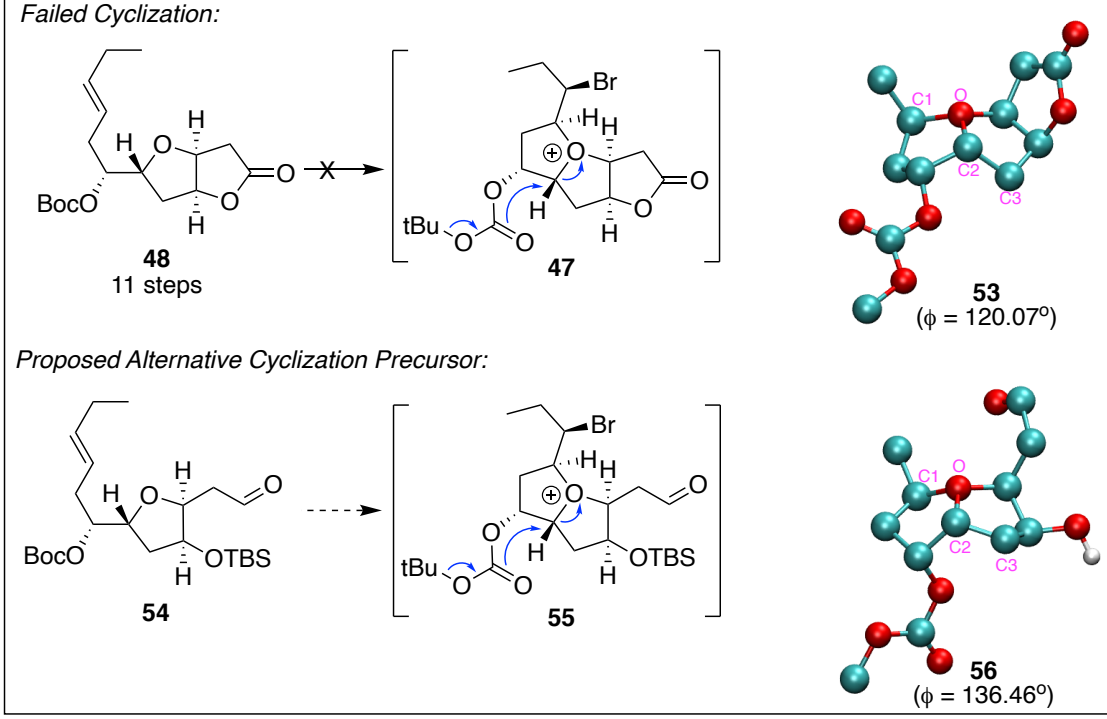
[a] Reagents and conditions: (a) NaOAc (3.0 equiv), $CuCl_2$ (3.0 equiv), $Pd(OAc)_2$ (0.1 equiv), CO (balloon), AcOH (0.2 M), 25 °C, 1 h, 53% (4:1 *dr*, separable); (b) Pd/C (0.06 equiv), H_2 (balloon), EtOAc (0.1 M), 25 °C, 10 h; (c) $NaHCO_3$ (5.0 equiv), DMP (1.1 equiv), CH_2Cl_2 (0.1 M), 25 °C, 20 min, 71%; (d) $TiCl_4$ (1.0 equiv), allylTMS (1.5 equiv), –78 °C→25 °C, 40 min, CH_2Cl_2 (0.1 M), 52% (3 steps, 4:1 *dr*); (e) Boc_2O (1.1 equiv), Et_3N (3.0 equiv), DMAP (0.1 equiv), CH_3CN (0.1 M), 25 °C, 8 h, 42%; (f) *trans*-3-hexene (6.0 equiv), HG-II (0.05 equiv), CH_2Cl_2 (0.1 M), 25 °C, 1 h, 90%.

1.2.4 Computational Guidance

Given that the Boc-protected variant **48** and silylated **43** are nearly identical, except for that single functionality, it was quite intriguing that silylated **43** underwent the ring-expansion process with such efficiency, whereas Boc-protected **48** failed to yield any desired product. This stark contrast could potentially stem from the difference in the mode of ring-expansion promotion – the silyl group simply proceeds through an elimination pathway, whereas the Boc group must perform an intramolecular nucleophilic attack.[7] Thus, we believe the rigidity of the bicyclic lactone system prevents the aforementioned attack, and therefore limits the success of this approach.

To explore this theory further, we utilized DFT calculations to determine the optimal geometry of a model system (**53**) of reactive intermediate **47** (in which the sidechain was truncated in model **53**). When the geometry optimization was performed using B3LYP/cc-PVDZ, it became apparent that the bicyclic lactone precursor led to a highly strained tricyclic oxonium, in which the dihedral angle of the C1-O-C2-C3 junction (as highlighted in Figure 1.3) presented as anti-eclipsed at 120.07°, being the most likely culprit for preventing productive attack of the Boc group at the C2 position. To circumvent this, we set out to computationally explore alternative, related intermediates to find a potential cyclization precursor with a more relaxed dihedral angle which may be more amenable to nucleophilic attack. Fortunately, we found that by simply opening the lactone to its respective aldehyde and secondary alcohol (**54**), we could attain the necessary flexibility. Model substrate **56** (based on reactive intermediate **55**) yielded a C1-O-C2-C3 dihedral angle of 136.46°, nearly 16.5° larger than that of **53**, thus providing us with our next synthetic target (**54**).

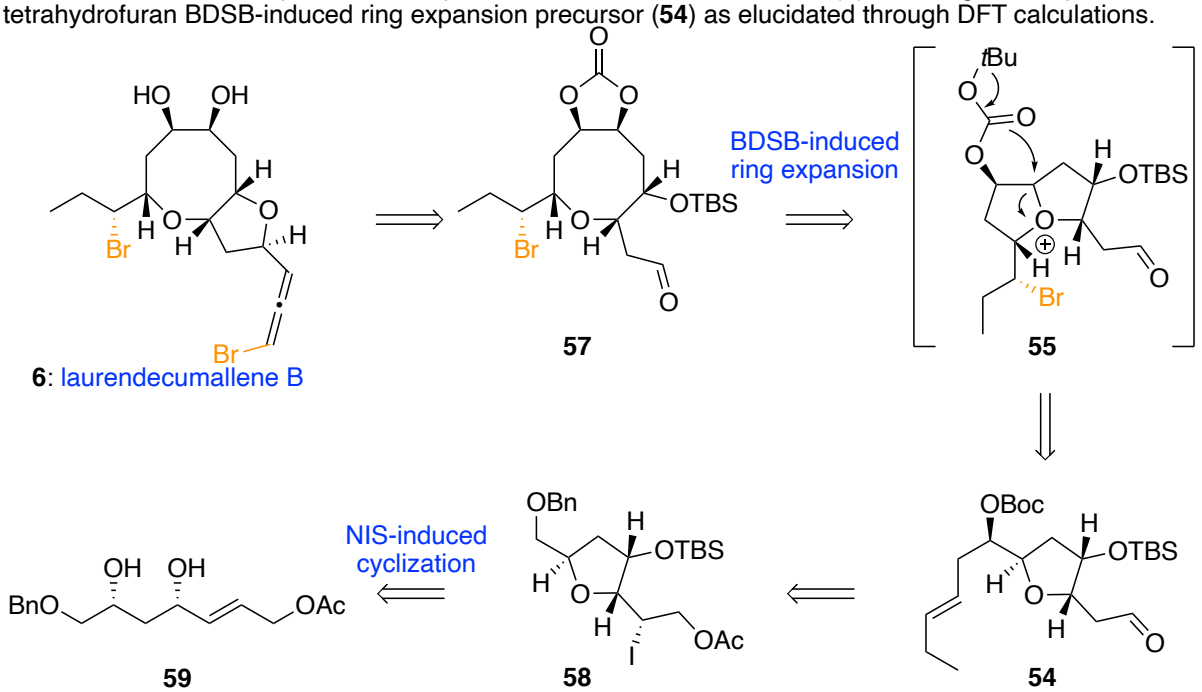
Figure 1.3. Geometry optimization of reactive intermediates for both the failed cyclization of **48** and the proposed alternative precursor **54**. Geometry optimization calculations were performed using B3LYP/cc-PVDZ.



1.2.5 Completion of Laurendecumallene B

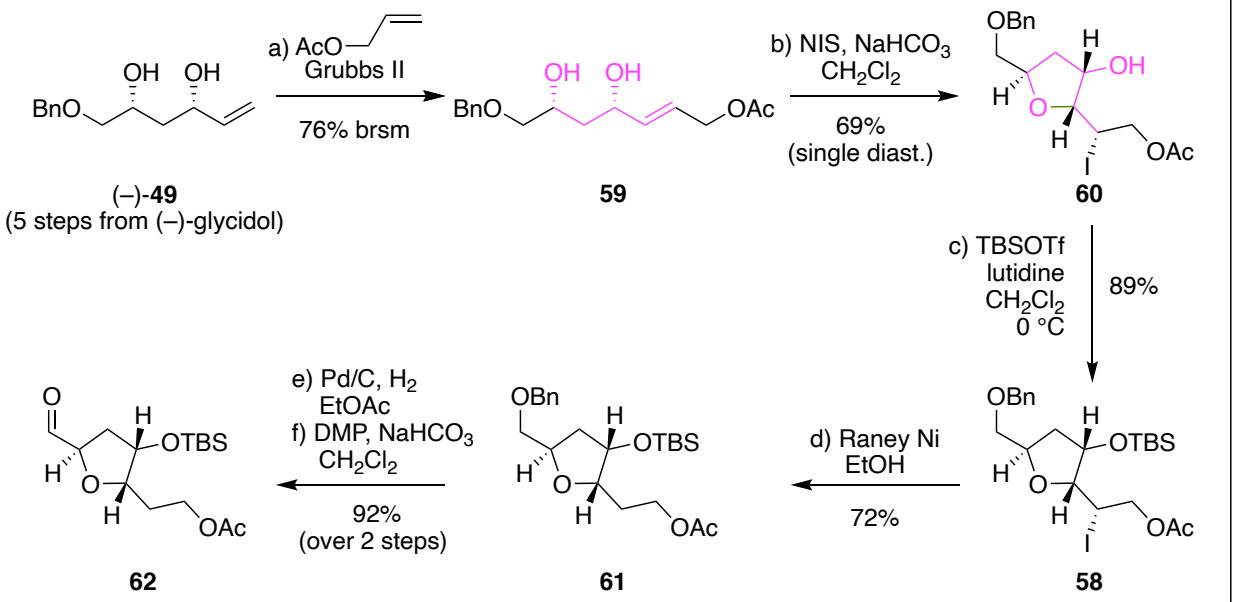
Considering the inability to utilize either *iso*-desepilaurallene (**30**) or the bicyclic lactone intermediate **48** effectively, we turned our attention toward generating our BDSB cyclization precursor **54** through the intermediacy of a THF ring as suggested by the DFT results presented above (Figure 1.3). As indicated in Scheme 1.11, we believed a fully furnished THF ring intermediate (**54**) could undergo a BDSB-induced ring expansion to yield carbonate-protected 8-membered bromoether diol **57** with full stereocontrol. In turn, the *trans*-THF ring (essential for the ring expansion) could likely result via an NIS-induced cyclization from diol **59**, which itself could be the product of a cross metathesis between allyl acetate and diol (–)-**49** (both enantiomers of the originating glycidol are commercially available).[22]

Scheme 1.11. Retrosynthetic analysis of laurendecumallene B (**6**) utilizing a fully furnished tetrahydrofuran BDSB-induced ring expansion precursor (**54**) as elucidated through DFT calculations.



As proposed, our efforts commenced from diol (–)-**49**, performing a cross metathesis with allyl acetate as the solvent to yield diol **59** (Scheme 1.12). This product could then successfully undergo the NIS-induced cyclization (**59**, $NaHCO_3$ and NIS in CH_2Cl_2, 23 °C for 8 h) to yield the *trans*-THF ring intermediate **60** as a single diastereomer.[24] The alkene sidechain was then introduced through a four-step functional group interconversion sequence, including de-iodination, to afford aldehyde **62**.

Scheme 1.12. Forward synthesis of aldehyde **62** featuring a diastereoselective NIS-induced cyclization.[a]

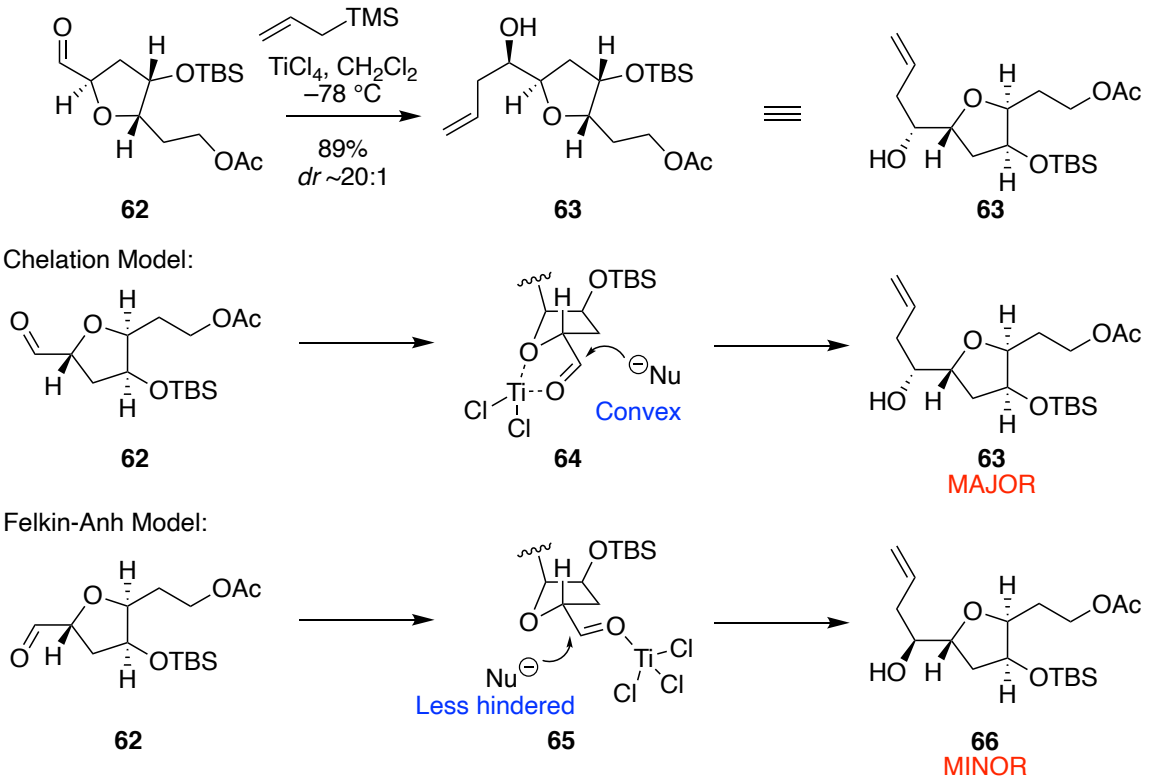


[a] Reagents and conditions: (a) allyl acetate (10.0 equiv), Grubbs 2nd Generation Initiator (0.03 equiv), 25 °C, 4 h, 54%, 76% brsm; (b) $NaHCO_3$ (6.0 equiv), NIS (2.5 equiv), CH_2Cl_2 (0.3 M), 25 °C, 8 h, 69%; (c) lutidine (4.0 equiv), TBSOTf (1.6 equiv), CH_2Cl_2 (0.3 M), 0 °C, 1 h, 89%; (d) Raney Ni (excess), EtOH (0.2 M), 25 °C, 10 min, 72%; (e) Pd/C (0.13 equiv), H_2 (balloon), EtOAc (0.07 M), 25 °C, 2 h; (f) $NaHCO_3$ (5.0 equiv), DMP (1.1 equiv), CH_2Cl_2 (0.1 M), 25 °C, 30 min, 92% (2 steps).

With aldehyde **62** in hand, the stage was set to complete the left-hand sidechain of the ring-expansion precursor (**54**), with the critical secondary alcohol stereochemistry having yet to be established. To this end, we began to probe a 1,2-addition into the existing aldehyde to not only generate the essential stereocenter, but also install the required distal olefin as well. This was performed through a traditional Sakurai allylation (**62**, $TiCl_4$ and allyltrimethylsilane in THF, –78 °C),[25] and we were pleased to find that the use of the bidentate Lewis acid $TiCl_4$ allowed the reaction to proceed in a highly diastereoselective fashion (~20:1 *dr*) favoring our desired product (**63**, Figure 1.4). We attribute this high level of success to the chelation model, in which the Ti(IV) species is able to coordinate to both the aldehyde and the oxygen atom of the tetrahydrofuran ring, rigidifying the convex nature of the face of nucleophilic attack. Intriguingly, we still observed some of the undesired diastereomer (**66**), suggesting that the $TiCl_4$ could still serve partially as a monodentate Lewis acid, promoting nucleophilic addition that follows the Felkin-Anh model.[23]

Furthermore, when utilizing the monodentate Lewis acid BF_3•Et_2O, the selectivity was not reversed (1:1 *dr*), suggesting that the substrate itself also presents additional bias.

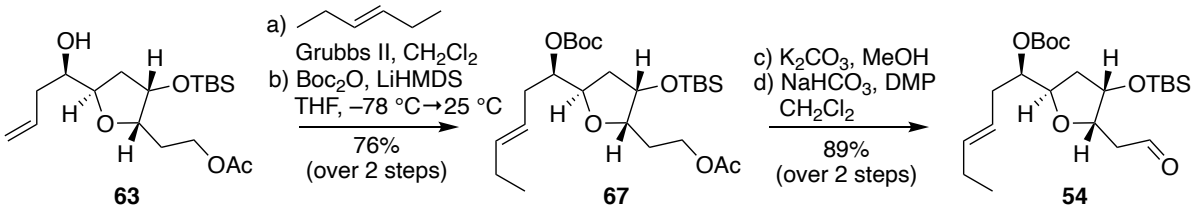
Figure 1.4. Sakurai allylation of aldehyde **62** and discussion of observed diastereoselectivity.[a]



[a] Reagents and conditions: (a) $TiCl_4$ (1.0 equiv), allylTMS (1.5 equiv), –78 °C, 30 min, CH_2Cl_2 (0.1 M), 52%.

To finalize the sidechain, the remaining ethyl group was then introduced through an additional cross metathesis, this time with *trans*-3-hexene (Scheme 1.13). With the left-hand portion complete, the next step was to Boc-protect the secondary alcohol, and we discovered it was necessary to use a stronger base than the typical Et_3N for success, likely due to the presence of intramolecular hydrogen bonding with the oxygen atom of the THF ring.[26] Notably, the yield for these two steps was greatly reduced if the Boc-protection was performed prior to the metathesis. Finally, the acetyl-capped alcohol was hydrolyzed and subsequently oxidized with Dess–Martin periodinane to complete the synthesis of the BDSB-cyclization precursor **54** in 16 steps.

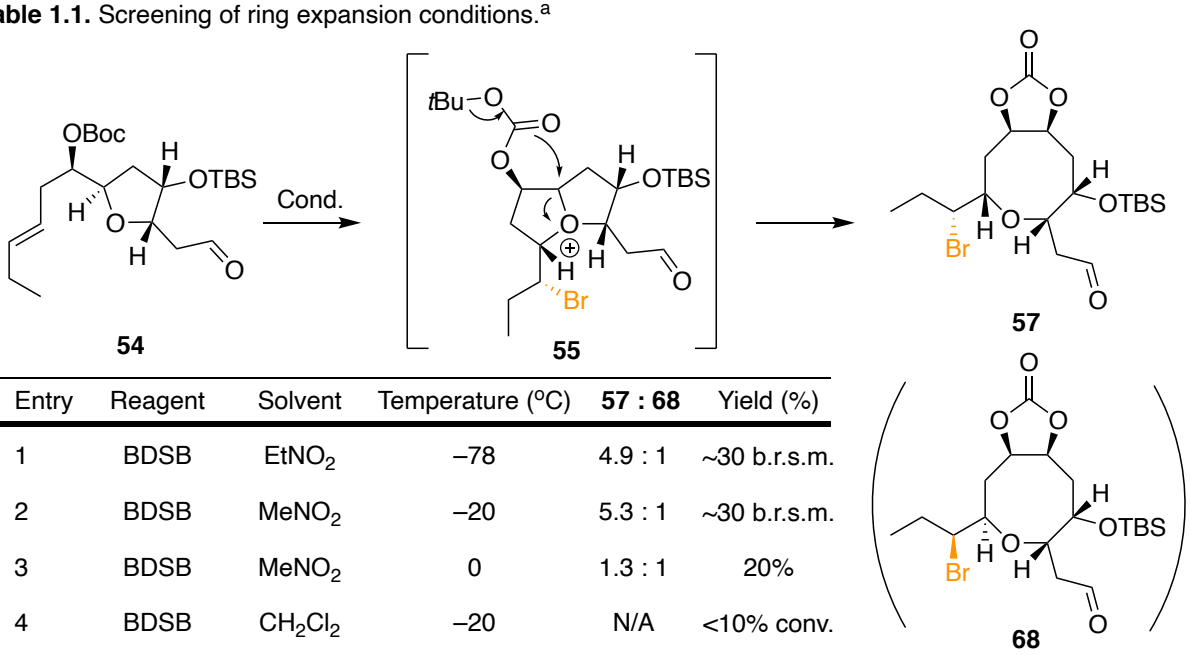
Scheme 1.13. Completion of ring expansion precursor **54**.[a]



[a] Reagents and conditions: (a) *trans*-3-hexene, Grubbs 2nd generation initiator (5 mol%), CH_2Cl_2, 25 °C, 8 h, 69%, 79% brsm; (b) Boc_2O (2.0 equiv), LiHMDS (1.3 equiv), THF, –78 to 25 °C, 8 h, 96%; (c) K_2CO_3 (6.0 equiv), MeOH, 25 °C, 2 h, 96%; (d) $NaHCO_3$ (4.0 equiv), Dess–Martin periodinane (1.1 equiv), CH_2Cl_2, 25 °C, 30 min, 93%.

With the stage set, **54** was initially subjected to the previously developed ring expansion conditions (BDSB in $MeNO_2$, –20 °C, 10 min).[7, 9-10] Pleasingly, we were able to observe the desired product, albeit in yields around 30% based on recovered starting material (Table 1.1). Of note, the diastereomers produced here were inseparable, but previous experience and visual NMR comparisons led us to suspect that the *trans*-oxacycle was produced as the minor product, with a *dr* of ~5:1. Interestingly, although full conversion was achieved at 0 °C in $MeNO_2$, there was complete erosion of the diastereoselectivity (1:1 *dr*). We then decided to test this late-stage cyclization in CH_2Cl_2 as part of standard solvent screening and were disappointed to see that at –20 °C only minimal conversion of starting material was observed. Pleasingly, though, when the temperature was raised to 0 °C, complete conversion was observed after 10 min with an improvement in yield (49%) and, fortunately, a bump in the diastereoselectivity (7:1 *dr*) from the lower yielding $MeNO_2$/$EtNO_2$ cases. Furthermore, recent findings suggested the brominating conditions of NBS and morpholine in HFIP at 0 °C could be comparable to that of BDSB (at least for bromonium-induced polyene cyclizations), so the reported conditions were tested for this system.[27] However, no reaction was observed at 0 °C, as well as through the reflux temperature of HFIP (58 °C). With these results, in combination with those obtained through the various BDSB tests, we pushed forward utilizing BDSB in CH_2Cl_2 at 0 °C as our optimal conditions.

Table 1.1. Screening of ring expansion conditions.[a]



Entry	Reagent	Solvent	Temperature (°C)	**57 : 68**	Yield (%)
1	BDSB	$EtNO_2$	–78	4.9 : 1	~30 b.r.s.m.
2	BDSB	$MeNO_2$	–20	5.3 : 1	~30 b.r.s.m.
3	BDSB	$MeNO_2$	0	1.3 : 1	20%
4	BDSB	CH_2Cl_2	–20	N/A	<10% conv.
5	BDSB	CH_2Cl_2	0	7.0 : 1	49%
6	NBS, morpholine	HFIP	0 to reflux	N/A	N.R.

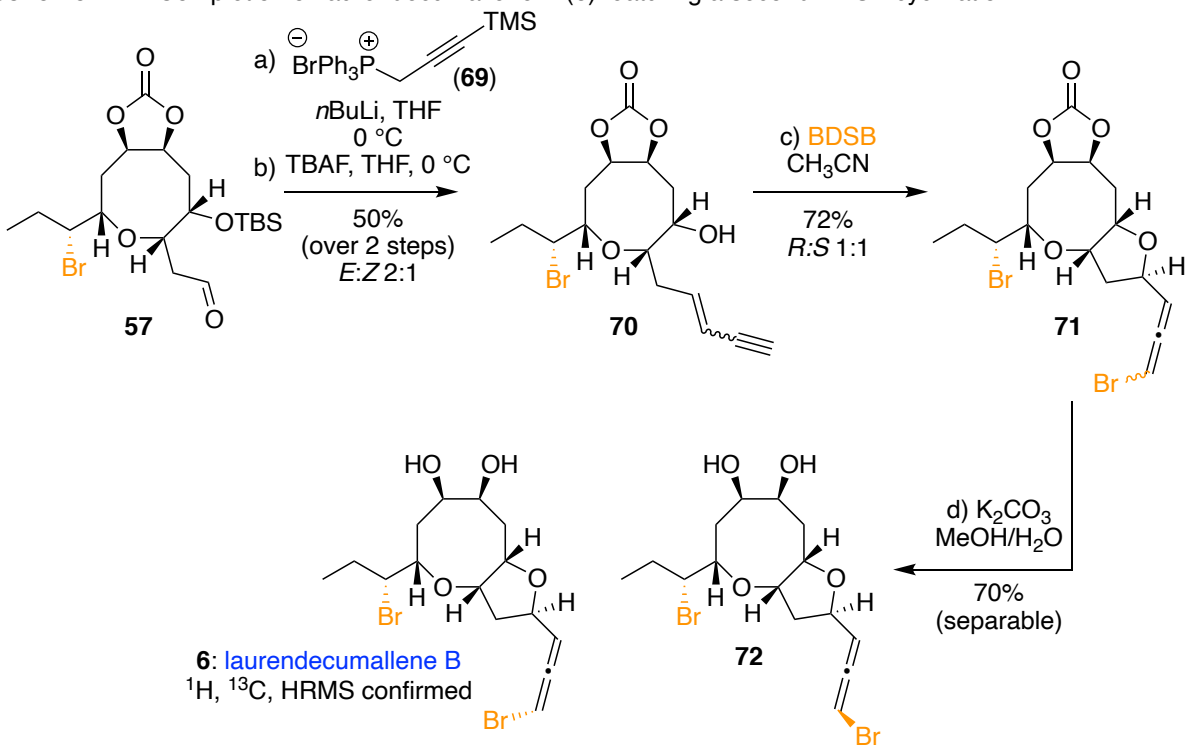
[a] Reactions were performed using 0.06 mmol of **54**; all reactions using BDSB were ran for 10 min total.

It is also important to note that this transformation was attempted on both the acetyl-protected (**67**) and the subsequent free alcohol substrates, and neither intermediate provided the desired product. This is quite intriguing since the same DFT-based conformational analysis described earlier revealed that the dihedral angles of these two intermediates (ϕ = 132.22° and ϕ = 134.32°, respectively – see experimental section for further detail) were closer to that of aldehyde **54** (ϕ = 136.46°) than the previously failed bicyclic lactone **48** (ϕ = 120.07°), but still of lower value. Whether this body of results suggests there is a threshold angle for success is unclear, as there may still be additional factors at play besides conformational flexibility. Nevertheless, given that the successful aldehyde case does have the highest dihedral angle observed, we believe that the low-level DFT conformational analysis presented here could potentially be predictive in assessing the order of potential precursors to test for other variants of the cyclization/ring-

expansion process. Finally, we also observed no α-bromination of the aldehyde in any case despite the relative acidity and potential enal character of such a functionality.[28]

With this key step completed, aldehyde **57** was then subjected to a Wittig olefination with **69** (**69**[29] and *n*BuLi in THF, 30 min at 0 °C, then **57** for additional 30 min at 0 °C) and subsequent silyl-deprotection, yielding an inseparable mixture of 2:1 *E*:*Z* enyne **70** in modest yield. Various screens were performed to determine if initially removing the TBS-protecting group to form the lactol prior to olefination, as well as performing an HWE-olefination instead, would prove more stereoselective; unfortunately, these efforts were fruitless, with the HWE-olefination yielding a 1:1 *E:Z* mixture. Pressing forward, **70** was then converted into laurendecumallene B (**6**) and its allene epimer (**72**) in an isolated 1.3:1 ratio through a second BDSB-induced cyclization and terminating carbonate cleavage.

Scheme 1.14. Completion of laurendecumallene B (**6**) featuring a second BDSB cyclization.[a]

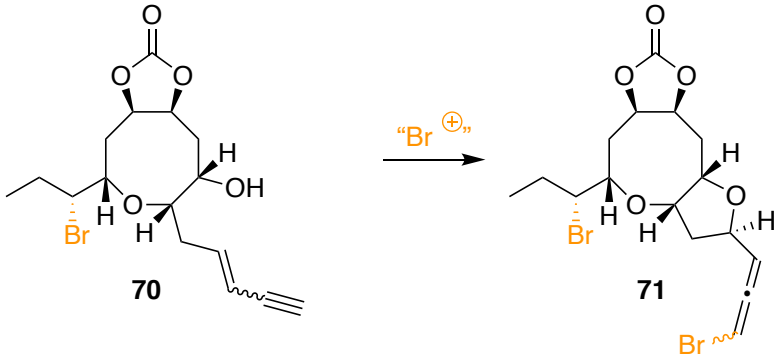


[a] Reagents and conditions: (a) Wittig salt **69** (1.8 equiv), *n*BuLi (1.6 equiv), THF (0.04 M), 0 °C, 30 min, *then* **57** (1.0 equiv), THF (0.04 M), 0 °C, 30 min, 58%, 80% brsm; (b) TBAF (2.0 equiv), THF (0.03 M), 0 °C, 5 min, 81%, 2:1 *E/Z*; (c) BDSB (1.2 equiv), CH_3CN (0.02 M), 25 °C, 2 h, 72%, 81% brsm, 1:1 *R/S*; (d) K_2CO_3 (10 equiv), MeOH/H_2O (0.01 M, 10:1), 25 °C, 2 h, 30% **72**, 40% **6**.

Based on a prior report by Canesi and co-workers, the selectivity of *R* vs. *S* bromoallene formation through such a process is highly dependent on solvent.[30] Given that the absolute stereochemistry of laurendecumallene B (**6**) was unknown, including the axial chirality of the bromoallene moiety, CH_3CN was selected as the solvent of choice, as Canesi and co-workers had observed a 1:1 distribution of *R* and *S* axial chirality when performing this type of transformation with TBCO in CH_3CN. Although BDSB has never been shown to produce bromoallene moieties in CH_3CN, we attempted the cyclization with such conditions (ambient temperature, 2 h), and were pleasantly surprised to find comparable results as those reported by Canesi and co-workers.[30] When screening other solvents, we did not, however, observe any change in the epimeric ratio that was produced, even when using different starting isomeric ratios of enyne precursor **70** (Table

1.2). Of note, BDSB in CH_3CN also proved superior to TBCO, the typical reagent of choice for these transformations.[29, 31] Furthermore, it is the first example in which a bromoallene moiety could be derived from a free alcohol/enyne precursor utilizing BDSB. When BDSB was deployed in such a reaction during the previous laurallene (**5**) synthesis,[11] only decomposition was observed, likely because of the more reactive alkene present on that 8-membered ring precursor.

Table 1.2. Screening of Cyclization Conditions to Generate **71**.[a]



Entry	Reagent	Solvent	Temperature (°C)	*E-/Z-*[a]	Yield (%)
1	TBCO	CH_3CN	23	1 : 1	63%
2	TBCO	benzene	23	1 : 1	decomp.
3	BDSB	HFIP	23	1 : 1	54%
4	BDSB	CH_3CN	23	1 : 1	75%
5	BDSB	CH_3CN	23	2 : 1	72% (81% brsm)
6	BDSB	$EtNO_2$	–78 to 23	2 : 1	52% (78% brsm)
7	BDSB	$MeNO_2$	0 to 23	2 : 1	34%

[a] Starting ratio of enyne isomers; in all cases product **71** was generated as an ~1:1 mixture of *R*-/*S*-bromoallenes based on crude NMR. For the actual case run on scale, the final ratio was 1.3:1 after isolation.

After extensive efforts, we were able to separate the two epimers and to our delight, one epimer directly matched the ^1H and ^{13}C NMR spectra of **6** as reported by Ji et al.[13] It is important to note, though, that the optical rotation obtained for our synthesized product was higher ($[\alpha]_D^{24}$ +117.4, c = 0.33 in $CHCl_3$) but still of the same rotational direction as the natural sample ($[\alpha]_D^{24}$

+60.6, *c* = 0.33 in $CHCl_3$).[13] Again, all other obtained spectra as well as HRMS mass (using ES) all matched those found by Wang and co-workers. Furthermore, extensive efforts were made to crystallize either **6** or a related analogue to gain additional and definitive structural proof, but to no avail. Nevertheless, we are confident in the stereochemical assignment of the bromoallene moiety as presented herein based on Lowe's rule[32] and further analysis recently reported by the Kim group (Figure 1.5).[33] Furthermore, the chirality about the exocyclic, C-13 center is believed to be analogous to the array of tetrahydrofuran-containing alkenes previously accessed through our key 8-membered ring formation process, many of which have been confirmed through X-ray analysis, with that stereochemistry encoded by the alkene geometry of the cyclization precursor.[7, 9, 11]

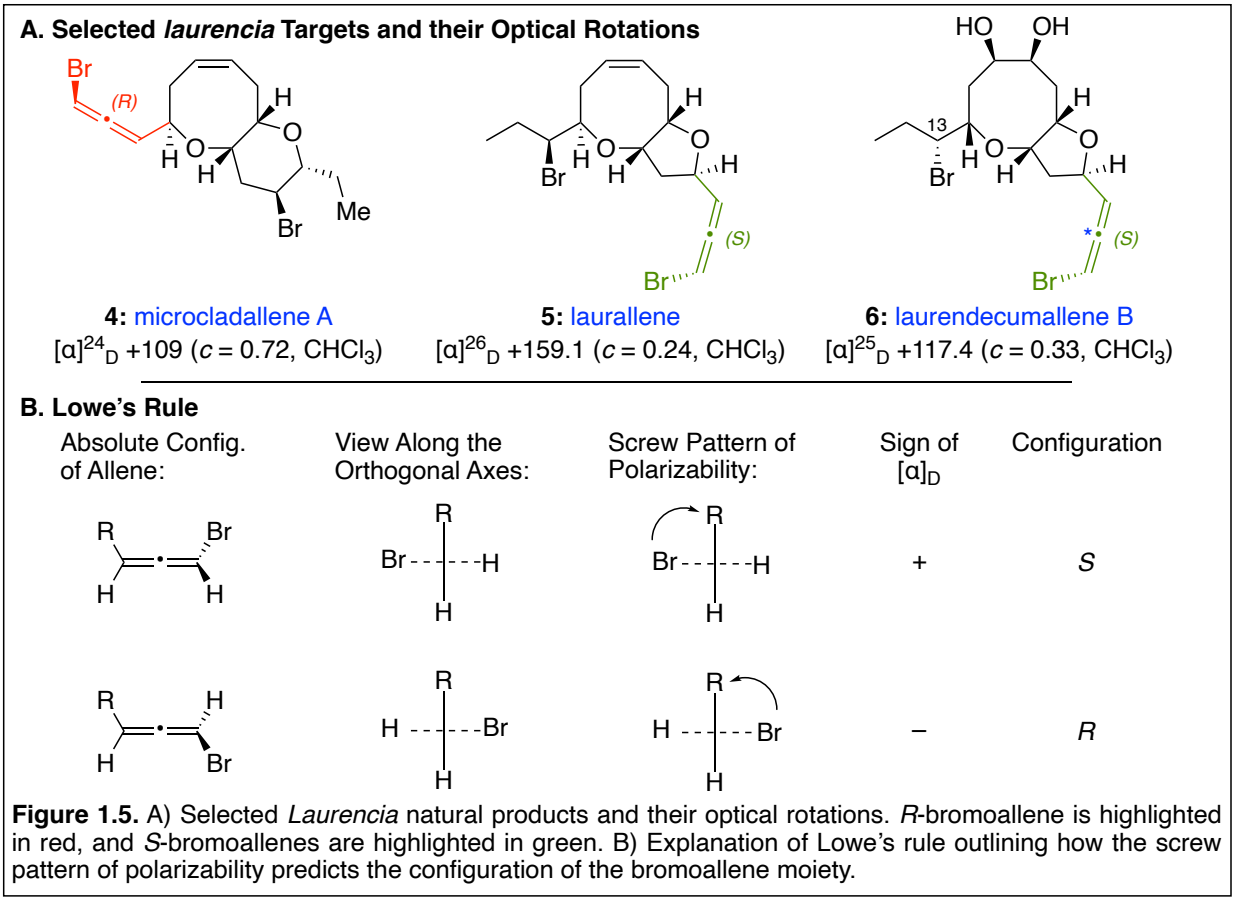


Figure 1.5. A) Selected *Laurencia* natural products and their optical rotations. *R*-bromoallene is highlighted in red, and *S*-bromoallenes are highlighted in green. B) Explanation of Lowe's rule outlining how the screw pattern of polarizability predicts the configuration of the bromoallene moiety.

1.3 Conclusion

Due to its global stereochemical and functional group array, a highly specific variant of our general cyclization/ring-expansion strategy proved necessary to achieve the synthesis of **6** in 21 linear steps from commercially available (–)-glycidol, with BDSB ultimately being essential for the incorporation of both bromine atoms.[12] This synthesis also allowed us to determine the target's absolute stereochemistry as well as its complete relative stereochemical assignments. To the best of our knowledge, the bromine disposition established here, relative to the *cis*-hydrogen of the ether ring fusion is unprecedented within the class. Furthermore, molecular modeling of potential oxonium intermediates was also predictive of the structural unit needed for ultimate success, proving valuable for future applications of this design. Finally, this work produced the eighth member of the *Laurencia* family generated to date within our lab, further affirming the utility of our process in forging 8-membered bromoether rings in a general fashion and the power of electrophilic halonium reagents such as BDSB.

1.4 References

1. (a) Irie, T.; Suzuki, M.; Masamune, T., *Tetrahedron Letters* **1965**, *6*, 1091; (b) Wang, B.-G.; Gloer, J. B.; Ji, N.-Y.; Zhao, J.-C., *Chemical Reviews* **2013**, *113*, 3632; (c) Wanke, T.; Philippus, A. C.; Zatelli, G. A.; Vieira, L. F. O.; Lhullier, C.; Falkenberg, M., *Revista Brasileira de Farmacognosia* **2015**, *25*, 569.
2. Fukuzawa, A.; Kurosawa, E.; Irie, T., *Tetrahedron Letters* **1972**, *13*, 3.
3. (a) González, A. G.; Martín, J. D.; Martín, V. S.; Norte, M.; Pérez, R.; Ruano, J. Z.; Drexler, S. A.; Clardy, J., *Tetrahedron* **1982**, *38*, 1009; (b) Noite, M.; Gonzalez, A. G.; Cataldo, F.; Rodríguez, M. L.; Brito, I., *Tetrahedron* **1991**, *47*, 9411; (c) Li, X.-D.; Miao, F.-P.; Li, K.; Ji, N.-Y., *Fitoterapia* **2012**, *83*, 518; (d) Fukuzawa, A.; Kurosawa, E., *Tetrahedron Letters* **1979**, *20*, 2797.
4. (a) Kennedy, D. J.; Selby, I. A.; Cowe, H. J.; Cox, P. J.; Thomson, R. H., *Journal of the Chemical Society, Chemical Communications* **1984**, 153; (b) Suzuki, M.; Nakano, S.; Takahashi, Y.; Abe, T.; Masuda, M.; Takahashi, H.; Kobayashi, K., *J. Nat. Prod.* **2002**, *65*, 801.
5. (a) Masamune, T.; Matsue, H., *Chemistry Letters* **1975**, *4*, 895; (b) Murai, A.; Murase, H.; Matsue, H.; Masamune, T., *Tetrahedron Letters* **1977**, *18*, 2507; (c) Clark, J. S.; Holmes, A. B., *Tetrahedron Letters* **1988**, *29*, 4333; (d) Tsushima, K.; Murai, A., *Tetrahedron Letters* **1992**, *33*, 4345; (e) Bratz, M.; Bullock, W. H.; Overman, L. E.; Takemoto, T., *J.*

Am. Chem. Soc. **1995**, *117*, 5958; (f) Mujica, M. T.; Afonso, M. M.; Galindo, A.; Palenzuela, J. A., *Synlett* **1996**, *1996*, 983; (g) Burton, J. W.; Clark, J. S.; Derrer, S.; Stork, T. C.; Bendall, J. G.; Holmes, A. B., *J. Am. Chem. Soc.* **1997**, *119*, 7483; (h) Krüger, J.; Hoffmann, R. W., *J. Am. Chem. Soc.* **1997**, *119*, 7499; (i) Crimmins, M. T.; Choy, A. L., *J. Am. Chem. Soc.* **1999**, *121*, 5653; (j) Crimmins, M. T.; Emmitte, K. A., *Org. Lett.* **1999**, *1*, 2029; (k) Baek, S.; Jo, H.; Kim, H.; Kim, H.; Kim, S.; Kim, D., *Org. Lett.* **2005**, *7*, 75; (l) Fujiwara, K.; Yoshimoto, S.; Takizawa, A.; Souma, S.-i.; Mishima, H.; Murai, A.; Kawai, H.; Suzuki, T., *Tetrahedron Letters* **2005**, *46*, 6819; (m) Adsool, V. A.; Pansare, S. V., *Org Biomol Chem* **2008**, *6*, 2011; (n) Li, J.; Suh, J. M.; Chin, E., *Org. Lett.* **2010**, *12*, 4712; (o) Ortega, N.; Martín, V. S.; Martín, T., *J. Org. Chem.* **2010**, *75*, 6660; (p) Lanier, M. L.; Park, H.; Mukherjee, P.; Timmerman, J. C.; Ribeiro, A. A.; Widenhoefer, R. A.; Hong, J., *Chem. Eur. J.* **2017**, *23*, 7180; (q) Lin, R.; Cao, L.; West, F. G., *Org. Lett.* **2017**, *19*, 552.

6. Fukuzawa, A.; Aye, M.; Takasugi, Y.; Nakamura, M.; Tamura, M.; Murai, A., *Chemistry Letters* **1994**, *23*, 2307.
7. Snyder, S. A.; Treitler, D. S.; Brucks, A. P.; Sattler, W., *J. Am. Chem. Soc.* **2011**, *133*, 15898.
8. (a) Fujiwara, K., *Topics in Heterocyclic Chemistry*. 2006; Vol. 5, p 97; (b) Chung, W.-j.; Vanderwal, C. D., *Angew. Chem. Int. Ed.* **2016**, *55*, 4396.
9. Snyder, S. A.; Brucks, A. P.; Treitler, D. S.; Moga, I., *J. Am. Chem. Soc.* **2012**, *134*, 17714.
10. (a) Snyder, S. A.; Treitler, D. S., *Angew. Chem. Int. Ed.* **2009**, *48*, 7899; (b) Taylor, C. A.; Snyder, S. A., *Organic Syntheses* **2020**, *97*, 339.
11. Zhang, Y.-A.; Yaw, N.; Snyder, S. A., *J. Am. Chem. Soc.* **2019**, *141*, 7776.
12. Taylor, C. A.; Zhang, Y.-A.; Snyder, S. A., *Chemical Science* **2020**, *11*, 3036.
13. Ji, N.-Y.; Li, X.-M.; Li, K.; Wang, B.-G., *J. Nat. Prod.* **2007**, *70*, 1499.
14. Yoshimitsu, Y.; Inuki, S.; Oishi, S.; Fujii, N.; Ohno, H., *Org. Lett.* **2013**, *15*, 3046.
15. (a) Yoshida, M.; Fujita, M.; Ishii, T.; Ihara, M., *J. Am. Chem. Soc.* **2003**, *125*, 4874; (b) Yoshida, M.; Ihara, M., *Angew. Chem. Int. Ed.* **2001**, *40*, 616.
16. (a) Jeong, W.; Kim, M. J.; Kim, H.; Kim, S.; Kim, D.; Shin, K. J., *Angew. Chem. Int. Ed.* **2010**, *49*, 752; (b) Sasaki, M.; Oyamada, K.; Takeda, K., *J. Org. Chem.* **2010**, *75*, 3941; (c) Kim, M. J.; Sohn, T.-i.; Kim, D.; Paton, R. S., *J. Am. Chem. Soc.* **2012**, *134*, 20178; (d) Kim, B.; Lee, M.; Kim, M. J.; Lee, H.; Kim, S.; Kim, D.; Koh, M.; Park, S. B.; Shin, K. J., *J. Am. Chem. Soc.* **2008**, *130*, 16807; (e) Fujiwara, K.; Kobayashi, M.; Awakura, D.; Murai, A., *Synlett* **2000**, *2000*, 1187; (f) Kim, H.; Lee, H.; Lee, D.; Kim, S.; Kim, D., *J. Am. Chem. Soc.* **2007**, *129*, 2269.
17. Fujiwara, K.; Tsunashima, M.; Awakura, D.; Murai, A., *Tetrahedron Letters* **1995**, *36*, 8263.
18. Tietze, L. F.; Neumann, T.; Kajino, M.; Pretor, M., *Synthesis* **1995**, *1995*, 1003.
19. Dias, L. C.; Polo, E. C.; Ferreira, M. A. B.; Tormena, C. F., *J. Org. Chem.* **2012**, *77*, 3766.
20. (a) Guérard, K. C.; Sabot, C.; Beaulieu, M.-A.; Giroux, M.-A.; Canesi, S., *Tetrahedron* **2010**, *66*, 5893; (b) Tang, Y.; Zhang, Y.; Dai, M.; Luo, T.; Deng, L.; Chen, J.; Yang, Z., *Org. Lett.* **2005**, *7*, 885; (c) Xu, X.-S.; Li, Z.-W.; Zhang, Y.-J.; Peng, X.-S.; Wong, H. N. C., *Chemical Communications* **2012**, *48*, 8517; (d) Markovič, M.; Ďuranová, M.; Koóš, P.; Szolcsányi, P.; Gracza, T., *Tetrahedron* **2013**, *69*, 4185; (e) Semmelhack, M. F.; Zask, A., *J. Am. Chem. Soc.* **1983**, *105*, 2034.

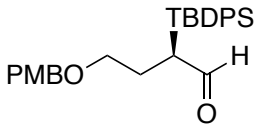
21. (a) Bonini, C.; Chiummiento, L.; Videtta, V., *Synlett* **2006**, *2006*, 2079; (b) Kumar, R.; Zajc, B., *J. Org. Chem.* **2012**, *77*, 8417.
22. (a) Jeon, O.-Y.; Carreira, E. M., *Org. Lett.* **2010**, *12*, 1772; (b) Bonini, C.; Campaniello, M.; Chiummiento, L.; Videtta, V., *Tetrahedron* **2008**, *64*, 8766; (c) Wang, L.; Li, P.; Menche, D., *Angew. Chem. Int. Ed.* **2010**, *49*, 9270; (d) Wang, L.; Menche, D., *Angew. Chem. Int. Ed.* **2012**, *51*, 9425; (e) Stork, G.; Rychnovsky, S. D., *J. Am. Chem. Soc.* **1987**, *109*, 1565.
23. Danishefsky, S. J.; DeNinno, M. P.; Phillips, G. B.; Zelle, R. E.; Lartey, P. A., *Tetrahedron* **1986**, *42*, 2809.
24. Nicolaou, K. C.; Koftis, T. V.; Vyskocil, S.; Petrovic, G.; Tang, W.; Frederick, M. O.; Chen, D. Y. K.; Li, Y.; Ling, T.; Yamada, Y. M. A., *J. Am. Chem. Soc.* **2006**, *128*, 2859.
25. Hosomi, A.; Sakurai, H., *Tetrahedron Letters* **1976**, *17*, 1295.
26. Lee, J. H.; Lee, S.-g., *Chemical Science* **2013**, *4*, 2922.
27. Arnold, A. M.; Pöthig, A.; Drees, M.; Gulder, T., *J. Am. Chem. Soc.* **2018**, *140*, 4344.
28. Shen, M.; Kretschmer, M.; Brill, Z. G.; Snyder, S. A., *Org. Lett.* **2016**, *18*, 5018.
29. Evans, P. A.; Murthy, V. S.; Roseman, J. D.; Rheingold, A. L., *Angew. Chem. Int. Ed.* **1999**, *38*, 3175.
30. Sabot, C.; Bérard, D.; Canesi, S., *Org. Lett.* **2008**, *10*, 4629.
31. (a) Crimmins, M. T.; Tabet, E. A., *J. Am. Chem. Soc.* **2000**, *122*, 5473; (b) Ishihara, J.; Shimada, Y.; Kanoh, N.; Takasugi, Y.; Fukuzawa, A.; Murai, A., *Tetrahedron* **1997**, *53*, 8371.
32. Lowe, G., *Chemical Communications (London)* **1965**, 411.
33. Sohn, T.-i.; Kim, D.; Paton, R. S., *Chem. Eur. J.* **2015**, *21*, 15988.
34. Ghosh, A. K.; Zajc, B., *J. Org. Chem.* **2009**, *74*, 8531.
35. Snyder, S. A.; Treitler, D. S., *Org. Synth.* **2011**, *88*, 54.
36. Zürcher, M.; Hof, F.; Barandun, L.; Schütz, A.; Schweizer, W. B.; Meyer, S.; Bur, D.; Diederich, F., *Eur. J. Org. Chem.* **2009**, *2009*, 1707.

1.5 Experimental Section

1.5.1 General Procedures.

All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dry tetrahydrofuran (THF), toluene, diethyl ether (Et_2O) dichloromethane (CH_2Cl_2), and acetonitrile (CH_3CN) were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Yields refer to chromatographically and spectroscopically (^1H and ^{13}C NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent, and an ethanolic solution of phosphomolybdic acid and cerium sulfate or a solution of $KMnO_4$ in aq. $NaHCO_3$ and heat as developing agents. SiliCycle silica gel (60, academic grade, particle size 0.040–0.063 mm) was used for flash column chromatography. Preparative thin-layer chromatography separations were carried out on 0.50 mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on Bruker 500 MHz instruments and calibrated using residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, br = broad, app = apparent. IR spectra were recorded on a Perkin-Elmer 1000 series FT-IR spectrometer. High-resolution mass spectra (HRMS) were recorded on Agilent 6244 Tof-MS using ESI (Electrospray Ionization) at the University of Chicago Mass Spectroscopy Core Facility.

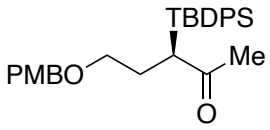
1.5.2 Synthesis of Laurendecumallene B



34

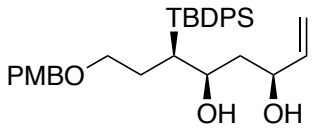
Aldehyde 34. To a solution of *i*-Pr_2NH (1.39 mL, 1.00 g, 10.0 mmol, 1.0 equiv) in THF (10.0 mL) at 0 °C was slowly added *n*BuLi (6.3 mL, 1.6 M in hexanes, 10.0 mmol, 1.0 equiv) and then the reaction mixture was stirred at 0 °C for 15 min. Next, acetaldehyde N-*t*-butylimine **32** (1.00 g, 10.00 mmol, 1.0 equiv) was added to the freshly prepared solution of LDA and the resultant solution was stirred for an additional 30 min at 0 °C before TBDPSCl (2.75 g, 10.0 mmol, 1.0 equiv) and TBAI (0.18 g, 0.50 mmol, 0.05 equiv) were added sequentially. The resultant reaction mixture was then stirred for an additional 1 h at 25 °C. The resultant dark red solution was cooled to 0 °C, and a second aliquot of *n*BuLi (6.3 mL, 1.6 M in hexanes, 10.0 mmol, 1.0 equiv) was added slowly. After stirring at 0 °C for 30 min, the PMB-protected iodide **33**[11] (3.50 g, 12.00 mmol, 1.2 equiv) was added and the resultant mixture was stirred at 25 °C for 12 h. Upon completion, the reaction contents were quenched by the addition of NH_4Cl (50 mL), diluted with CH_2Cl_2 (25 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated to provide the desired intermediate. Pressing forward without any further purification, the crude product was dissolved in CH_2Cl_2 (25.0 mL), AcOH (25.0 mL) was added, and the resultant biphasic mixture was stirred vigorously at 25 °C for 0.5 h. Upon completion, the mixture was poured directly into a separatory funnel. The two phases were separated, and the aqueous layer was washed with CH_2Cl_2 (2 × 50 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 40:1→30:1→20:1) afforded the desired aldehyde **34** (2.20 g, 4.93 mmol, 49% yield) as a yellow oil. **34**: R_f = 0.15 (silica gel,

hexanes:EtOAc, 20:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.82 (d, J = 3.2 Hz, 1H), 7.64 – 7.57 (m, 4H), 7.47 – 7.34 (m, 6H), 7.22 – 7.15 (m, 2H), 6.89 – 6.81 (m, 2H), 4.34 – 4.27 (m, 2H), 3.80 (s, 3H), 3.32 (ddt, J = 9.4, 5.3, 3.0 Hz, 2H), 3.19 (ddd, J = 11.2, 3.3, 1.6 Hz, 1H), 2.30 (ddt, J = 14.5, 11.2, 5.6 Hz, 1H), 1.74 (dt, J = 13.4, 6.1 Hz, 1H), 1.12 (s, 9H).



36

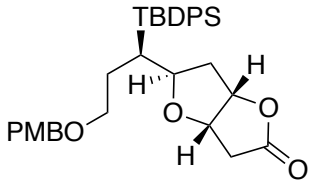
Ketone 36. To a solution of aldehyde **34** (1.94 g, 4.30 mmol, 1.0 equiv) in THF (8.6 mL) at –78 °C was added MeMgBr (3.4 mL, 2.8 M in Et2O, 9.5 mmol, 2.2 equiv). After stirring the resultant mixture at –78 °C for 5 min, the reaction contents were quenched by the slow addition of saturated aqueous NH_4Cl (25 mL), warmed to 25 °C, poured into a separatory funnel, and diluted with CH_2Cl_2 (50 mL). The two phases were then separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 10:1) afforded the desired secondary alcohol **35** (1.92 g, 4.10 mmol, 95% yield) as a colorless liquid. Pushing forward, to a solution of secondary alcohol **35** (1.92 g, 4.10 mmol, 1.0 equiv) in CH_2Cl_2 (8.2 mL) at 25 °C was added solid $NaHCO_3$ (1.72 g, 20.5 mmol, 5.0 equiv) and Dess–Martin periodinane (1.91 g, 4.51 mmol, 1.1 equiv). The resultant mixture was stirred at 25 °C for 5 min. Upon completion, the reaction contents were concentrated directly. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 20:1) afforded the desired ketone **36** (1.76 g, 93% yield) as a colorless oil. **36**: R_f = 0.20 (silica gel, hexanes:EtOAc, 10:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 – 7.59 (m, 4H), 7.47 – 7.33 (m, 6H), 7.22 (d, *J* = 6.7 Hz, 2H), 6.96 – 6.83 (m, 2H), 4.36 (t, *J* = 10.5 Hz, 2H), 3.80 (s, 3H), 3.37 (t, *J* = 5.1 Hz, 2H), 3.22 (d, *J* = 12.1 Hz, 1H), 2.37 – 2.24 (m, 1H), 2.09 – 1.97 (m, 1H), 1.73 (s, 3H), 1.12 (s, 9H).



38

Diol 38. To a solution of *i*-Pr_2NH (0.85 mL, 0.617 g, 6.10 mmol, 1.6 equiv) in THF (7.6 mL) at 0 °C was slowly added *n*BuLi (3.6 mL, 1.6 M in hexanes, 5.70 mmol, 1.5 equiv). The resultant solution was then stirred at 0 °C for 10 min. Next, a solution of ketone **36** (1.76 g, 3.80 mmol, 1.0 equiv) in THF (7.6 mL) was added to the freshly prepared LDA solution at –78 °C and the resultant solution was stirred at –78 °C for an additional 30 min. Acrolein (0.41 mL, 0.342 g, 6.10 mmol, 1.6 equiv) was then added and the resultant mixture was allowed to stir at –78 °C for 30 min. Upon completion, the reaction contents were quenched by the addition of saturated aqueous NH_4Cl (50 mL) and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The resultant residue was purified by flash column chromatography (silica gel, hexanes:EtOAc, 10:1→5:1) to afford desired β-hydroxy ketone **37** (1.69 g, 86% yield) as a colorless liquid and as a mixture of two inseparable diastereomers (*dr* ~2:1). Pushing forward, to a solution of β-hydroxy ketone **37** (1.86 g, 3.60 mmol, 1.0 equiv) in THF/MeOH (4:1, 7.5 mL) at –78 °C was added Et_2BOMe (4.3 mL, 1.0 M in THF, 4.30 mmol, 1.2 equiv). The resultant reaction mixture was then stirred for 30 min at – 78 °C, at which point $LiBH_4$ (1.57 g, 72.0 mmol, 20.0 equiv) was added in a single portion. The resultant heterogeneous mixture was then warmed slowly to 25 °C over the course of 4 h [Caution: large amounts of gas were generated during this period]. Upon completion, the reaction contents were quenched by the slow addition of aqueous 3.8 M NaOH (2.4 mL, 9.00 mmol, 2.5 equiv) and H_2O_2 (1.1 mL, 30% w/w in water, 9.70 mmol, 2.7 equiv). The resultant mixture was stirred for an additional 0.5 h, diluted with H_2O (30 mL) and EtOAc (30 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with EtOAc (3 × 30

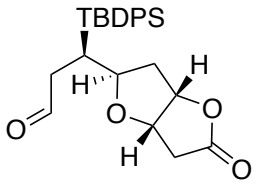
mL). The combined organic layers were washed with 1 M aqueous NaOH (100 mL), dried (Na_2SO_4), filtered, and concentrated. The resultant residue was purified by flash column chromatography (silica gel, hexanes:EtOAc, 30:1→20:1→10:1→5:1) to afford the desired diol **38** (0.809 g, 43% yield) as a viscous, colorless oil along with the undesired diastereomer (0.638 g, 34% yield). **38**: R_f = 0.05 (silica gel, hexanes:EtOAc, 5:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 – 7.59 (m, 2H), 7.51 – 7.43 (m, 2H), 7.42 – 7.29 (m, 7H), 7.24 (s, 1H), 6.89 (d, *J* = 8.4 Hz, 2H), 5.62 – 5.45 (m, 1H), 5.03 – 4.95 (m, 1H), 4.91 – 4.84 (m, 1H), 4.53 – 4.44 (m, 2H), 4.39 – 4.22 (m, 2H), 4.20 – 4.01 (m, 2H), 3.80 (s, 4H), 3.60 (t, *J* = 4.9 Hz, 1H), 3.44 – 3.36 (m, 1H), 1.98 (d, *J* = 9.6 Hz, 2H), 1.26 (t, *J* = 7.1 Hz, 1H), 1.09 (d, *J* = 6.0 Hz, 9H).



39

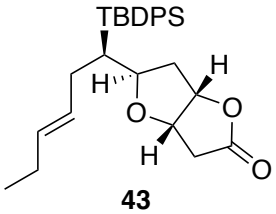
Bicyclic Lactone 39. A flame-dried flask was charged with NaOAc (0.235 g, 2.70 mmol, 5.0 equiv), $CuCl_2$ (0.215 g, 1.62 mmol, 3.0 equiv), and $PdCl_2$ (0.039 g, 0.22 mmol, 0.4 equiv) before being flushed with CO and evacuated three times. The CO balloon was then transferred to the flask, followed by the addition of AcOH (2.7 mL). A solution of diol **38** (0.281 g, 0.54 mmol, 1.0 equiv) in AcOH (2.7 mL) was then added. The resultant suspension was then stirred under a CO atmosphere (balloon pressure) for 10 min at 25 °C. Upon completion, the reaction contents were filtered through a short pad of Celite and washed with EtOAc (150 mL). The filtrate was concentrated directly and the resultant residue was purified by flash column chromatography (silica gel, hexanes:EtOAc, 3:1) to afford the desired bicyclic lactone **39** (0.136 g, 0.25 mmol, 46% yield) as a slightly yellow oil. **39**: R_f = 0.50 (silica gel, hexanes:EtOAc, 2:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 – 7.52 (m, 4H), 7.42 – 7.29 (m, 7H), 7.20 (d, *J* = 8.5 Hz, 1H), 6.87 (t, *J* = 8.0 Hz, 2H), 4.87 (t, *J* = 4.6 Hz, 1H), 4.56 – 4.43 (m, 2H), 4.36 (d, *J* = 3.4 Hz, 2H),

3.81 (d, *J* = 2.4 Hz, 3H), 3.54 (td, *J* = 9.5, 4.9 Hz, 1H), 3.42 – 3.33 (m, 1H), 2.68 – 2.46 (m, 2H), 1.78 (dd, *J* = 14.1, 4.3 Hz, 1H), 1.65 (dt, *J* = 11.1, 6.0 Hz, 1H), 1.45 (ddd, *J* = 14.2, 11.1, 4.6 Hz, 1H), 1.08 (s, 9H).



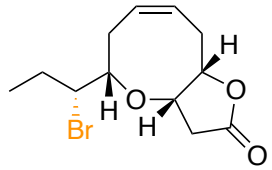
41

Aldehyde 41. To a solution of bicyclic lactone **39** (135.5 mg, 0.25 mmol, 1.0 equiv) in CH_2Cl_2/H_2O (9:1 v/v, 2.5 mL) at 25 °C was added DDQ (86.3 mg, 0.38 mmol, 1.5 equiv). After stirring for 0.5 h at 25 °C, the reaction contents were quenched by the addition of saturated aqueous Na_2CO_3 (10 mL), transferred to a separatory funnel, and diluted with CH_2Cl_2 (10 mL). The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated. Pushing forward, the crude free alcohol **40** (106.2 mg, 0.25 mmol, 1.0 equiv) in CH_2Cl_2 (2.5 mL) at 25 °C was added $NaHCO_3$ (105.0 mg, 1.25 mmol, 5.0 equiv) and Dess–Martin periodinane (118.8 mg, 0.28 mmol, 1.1 equiv) sequentially. The reaction was stirred for 1 h at 25 °C and concentrated directly. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 3:1) afforded aldehyde **41** (70.3 mg, 68% yield over 2 steps) as a colorless oil. **41**: R_f = 0.50 (silica gel, hexanes:EtOAc, 1:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.55 (d, *J* = 5.8 Hz, 1H), 7.64 – 7.61 (m, 2H), 7.52 (dt, *J* = 6.9, 1.5 Hz, 2H), 7.47 – 7.36 (m, 6H), 4.82 (t, *J* = 4.3 Hz, 1H), 4.70 (dt, *J* = 11.3, 4.7 Hz, 1H), 4.35 – 4.28 (m, 1H), 2.97 (dt, *J* = 12.2, 3.3 Hz, 1H), 2.62 – 2.48 (m, 3H), 2.22 (ddd, *J* = 15.8, 12.3, 5.9 Hz, 1H), 1.72 (dd, *J* = 14.4, 5.0 Hz, 1H), 1.30 – 1.26 (m, 1H), 1.14 (s, 9H).



43

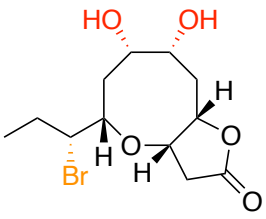
Olefin 43. To a solution of Julia–Kocienski reagent **42** (131.2 mg, 0.52 mmol, 4.0 equiv, prepared according to the literature procedure reported by Zajc and co-workers[34] with all the spectroscopic data matching that reported in Ref. 35) in DME (0.8 mL) at –78 °C was slowly added KHMDS (0.46 mL, 1.0 M in THF, 0.46 mmol, 3.5 equiv). The resultant mixture was stirred at –78 °C for 30 min, and then a solution of aldehyde **41** (0.157 g, 0.527 mmol, 1.0 equiv) in DME (0.5 mL) was added in one portion at –78 °C. The resultant mixture was stirred for another 30 min at –78 °C. Upon completion, the reaction contents were quenched by the addition of saturated aqueous NH_4Cl (10 mL), poured into a separatory funnel, and diluted with CH_2Cl_2 (10 mL). The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The resultant residue was purified by flash column chromatography (silica gel, pure CH_2Cl_2) to afford olefin **43** (15.7 mg, 27% yield) as a yellow oil. **43**: R_f = 0.25 (silica gel, pure CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 – 7.61 (m, 2H), 7.56 (dt, *J* = 6.9, 1.5 Hz, 2H), 7.46 – 7.28 (m, 6H), 5.47 – 5.34 (m, 1H), 5.30 – 5.23 (m, 1H), 4.90 (t, *J* = 4.7 Hz, 1H), 4.56 (t, *J* = 5.4 Hz, 1H), 4.47 – 4.35 (m, 1H), 2.66 – 2.60 (m, 1H), 2.51 – 2.36 (m, 2H), 2.14 – 2.01 (m, 2H), 1.99 – 1.89 (m, 3H), 1.54 – 1.49 (m, 1H), 1.08 (s, 9H), 0.91 (t, *J* = 7.5 Hz, 3H).



30: *iso*-desepilaurallene

***Iso*-desepilaurallene 30.** Olefin **43** (123.0 mg, 0.27 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (2.7 mL), the reaction contents were cooled to –78 °C, and then solid BDSB[35]

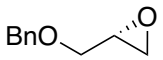
(67.6 mg, 0.123 mmol, 0.8 equiv) was added in a single portion. The reaction contents were then stirred at –78 °C for 15 min. Upon completion, the reaction mixture was quenched by the addition of saturated aqueous NH_4Cl (5 mL), warmed to 25 °C, and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant crude residue flash column chromatography (silica gel, hexanes:EtOAc, 8:1→ 7:1 → 6:1) afforded *iso*-desepilaurallene **30** (54.8 mg, 0.19 mmol, 70% yield) as a white foam. **30**: R_f = 0.05 (silica gel, hexanes:EtOAc, 5:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.04–5.84 (m, 1 H), 5.80–5.67 (m, 1 H), 4.45 (dt, J = 11.9, 4.2 Hz, 1 H), 4.12 (t, J = 4.8 Hz, 1 H), 3.96–3.86 (m, 1 H), 3.48 (dd, J = 10.1, 5.0 Hz, 1 H), 2.90–2.64 (m, 3 H), 2.51 (dt, J = 11.7, 6.3 Hz, 2 H), 2.36 (dd, J = 14.0, 8.5 Hz, 1 H), 1.93–1.82 (m, 2 H), 1.05 (t, J = 7.2 Hz, 3 H).



44
(undesired)

Undesired Diastereomer Diol 44. To a solution of *rac*-alkene **30** (29.5 mg, 0.102 mmol, 1.0 equiv) in acetone (1.0 mL) and H_2O (0.2 mL) at 25 °C was added NMO (24.0 mg, 0.204 mmol, 2.0 equiv) and then the reaction was allowed to stir at 25 °C for 20 min. Next, OsO_4 (0.05 mL, 2.5% by weight in *t*-BuOH, 0.004 mmol, 0.04 equiv) was added and the reaction mixture was stirred at 25 °C for 2 h. Upon completion, the reaction contents were quenched by the addition of saturated aqueous Na_2SO_3 (5 mL), diluted with CH_2Cl_2 (10 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel,

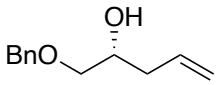
CH_2Cl_2:MeOH, 30:1→25:1→20:1) afforded diol **44** (18.4 mg, 0.057 mmol, 56% yield) as a gray powder. **44**: R_f = 0.25 (silica gel, CH_2Cl_2:MeOH, 20:1); IR (film) ν_{max} 3421, 2971, 2921, 2852, 1825, 1751, 1653, 1507, 1465, 994 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 4.58 (dt, *J* = 10.9, 4.3 Hz, 1 H), 4.38 (dd, *J* = 7.0, 4.3 Hz, 1 H), 4.15 (dt, *J* = 9.8, 3.7 Hz, 1 H), 3.73 (tt, *J* = 8.6, 3.3 Hz, 3 H), 3.34 (br s, 2 H), 3.03 (dd, *J* = 18.1, 7.0 Hz, 1 H), 2.31 (d, *J* = 18.1 Hz, 1 H), 2.17 (ddd, *J* = 14.7, 11.1, 8.5 Hz, 1 H), 2.02–1.91 (m, 2 H), 1.87 (ddd, *J* = 14.7, 7.3, 3.3 Hz, 1 H), 1.69 (ddd, *J* = 14.7, 9.7, 7.3 Hz, 1 H), 1.54 (d, *J* = 14.6 Hz, 1 H), 0.98 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 175.1, 83.6, 80.5, 77.6, 69.7, 68.1, 63.4, 37.9, 35.1, 32.1, 27.0, 12.1; HRMS (CI) calcd for $C_{12}H_{20}BrO_5$ $[M+H]^+$ 323.0496, found 323.0476.



S1

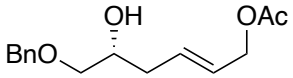
Epoxide S1. To a solution of (*S*)-(–)-glycidol (3.60 mL, 4.00 g, 54.0 mmol, 1.0 equiv) in DMF (21.6 mL) at 25 °C was added BnBr (8.35 mL, 12.0 g, 70.2 mmol, 1.3 equiv) and then the reaction was cooled to 0 °C. Next, NaH (2.81 g, 60% by weight in mineral oil, 70.2 mmol, 1.3 equiv) was added and the reaction mixture was stirred at 0 °C for 5 min before allowing the solution to warm to 25 °C over 10 min. Upon completion, the reaction contents were quenched by the addition of saturated aqueous NH_4Cl (100 mL), diluted with EtOAc (50 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 8:1) afforded the desired epoxide **S1** (8.37 g, 50.97 mmol, 94% yield) as a colorless liquid. **S1**: R_f = 0.60 (silica gel, hexanes:EtOAc, 4:1); IR (film) ν_{max} 3030, 2998, 2861, 1495, 1454, 1254, 1095, 1028, 899, 739 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.39–7.25 (m, 5 H), 4.59 (dd, 2 H), 3.77 (dd, *J* = 11.4, 3.0 Hz, 1 H), 3.45 (q, *J* = 11.5, 5.9 Hz, 1 H), 3.20 (m, 1 H), 2.81 (t, *J* = 4.6 Hz, 1 H), 2.63 (dd, *J* = 5.0, 2.7 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.8, 128.4,

127.7, 73.3, 70.8, 50.9, 44.3; HRMS (ES) calcd for $C_{20}H_{25}O_4$ $[2M+H]^+$ 329.1754, found 329.1751; $[\alpha]_D^{24}$ = +2.4° (*c* = 1.0, $CHCl_3$).



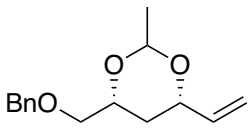
S2

Alcohol S2. To a solution of epoxide **S1** (8.27 g, 50.4 mmol, 1.0 equiv) in THF (50 mL) at –20 °C was added CuI (2.40 g, 12.6 mmol, 0.25 equiv) and then the reaction mixture was stirred at –20 °C for 5 min. Next, vinylmagnesium bromide (60.4 mL, 1.0 M in THF, 60.4 mmol, 1.2 equiv) was added dropwise and the resultant mixture was stirred for an additional 10 min at –20 °C. Upon completion, the reaction contents were quenched by the addition of saturated aqueous NH_4Cl (100 mL), diluted with EtOAc (50 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 10:1) afforded the desired alcohol **S2** (11.0 g, 57.16 mmol, 114% yield) as a colorless liquid containing inseparable impurities (~15%) that were ultimately removed in the next step. [Note: at this point, the impurities were only separable by preparative TLC, CH_2Cl_2:Et_2O, 20:1. Therefore, a sample of the so-obtained fully pure compound was utilized for characterization purposes.] **S2**: R_f = 0.30 (silica gel, hexanes:EtOAc, 8:1); IR (film) ν_{max} 3431, 3066, 3030, 2907, 2861, 1453, 1207, 1101, 996, 915, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.39–7.28 (m, 5 H), 5.88–5.78 (m, 1 H), 5.15–5.07 (m, 2 H), 4.56 (s, 2 H), 3.89 (dq, *J* = 6.9, 3.5 Hz, 1 H), 3.52 (dd, *J* = 9.5, 3.4 Hz, 1 H), 3.38 (dd, *J* = 9.5, 7.4 Hz, 1 H), 2.36 (s, 1 H), 2.27 (t, *J* = 6.8 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.9, 134.2, 128.5, 127.8, 127.7, 117.7, 73.9, 73.4, 69.7, 37.9; HRMS (CI) calcd for $C_{12}H_{17}O_2$ $[M+H]^+$ 193.1230, found 193.1229; $[\alpha]_D^{24}$ = –2.5° (*c* = 1.0, $CHCl_3$).



S3

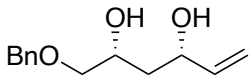
Alkene S3. To neat alcohol **S2** (10.9 g, 56.7 mmol, 1.0 equiv) at 25 °C was added allyl acetate (36.7 mL, 340.14 mmol, 6.00 equiv) and the Grubbs 2nd generation initiator (1.44 g, 1.70 mmol, 0.03 equiv). The resultant brown mixture was stirred at 25 °C for 4 h. Upon completion, the reaction mixture was purified directly by flash column chromatography (silica gel, hexanes:EtOAc, 5:1→1:1) to yield the resultant alkene **S3** (5.18 g, 19.59 mmol, 39% yield over 2 steps as calculated against starting 50.4 mmol of **S1**) as a clear brown liquid. **S3**: R_f = 0.20 (silica gel, hexanes:EtOAc, 4:1); IR (film) ν_{max} 3455, 2905, 2862, 1737, 1454, 1382, 1365, 1236, 1096, 1027, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38–7.28 (m, 5 H), 5.83–5.76 (m, 1 H), 5.71–5.62 (m, 1 H), 4.56 (s, 2 H), 4.52 (d, *J* = 6.3 Hz, 2 H), 3.88 (tt, *J* = 7.0, 3.4 Hz, 1 H), 3.51 (dd, *J* = 9.5, 3.4 Hz, 1 H), 3.37 (dd, *J* = 9.5, 7.4 Hz, 1 H), 2.27 (t, *J* = 6.9 Hz, 2 H), 2.06 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 137.8, 131.3, 128.5, 127.8, 127.7, 126.9, 73.8, 73.4, 69.7, 64.9, 36.3, 21.0; HRMS (ES) calcd for $C_{15}H_{21}O_4$ $[M+H]^+$ 265.1442, found 265.1426; $[\alpha]_D^{26}$ = –1.3° (*c* = 1.0, $CHCl_3$).



S4

Protected diol S4. To a solution of alkene **S3** (5.11 g, 19.3 mmol, 1.0 equiv) in toluene (19.3 mL) at –78 °C was added acetaldehyde (19.3 mL, 34.4 mmol, 1.78 equiv), Ph_3P (1.52 g, 5.80 mmol, 0.3 equiv), $[Pd(allyl)Cl]_2$ (0.706 g, 1.93 mmol, 0.1 equiv), and KHMDS (9.66 mL, 1.0 M in THF, 9.66 mmol, 0.5 equiv). The resultant yellow mixture was allowed to warm to 25 °C and was stirred for an additional 2 h. Upon completion, the reaction contents were quenched by the addition of saturated aqueous NH_4Cl (50 mL), diluted with EtOAc (25 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with

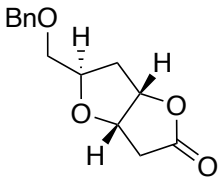
EtOAc (3 × 50 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 15:1) afforded the desired protected diol **S4** (3.54 g, 14.26 mmol, 74% yield) as a pale yellow liquid. **S4**: R_f = 0.60 (silica gel, hexanes:EtOAc, 3:1); IR (film) ν_{max} 3453, 2991, 2939, 2864, 1721, 1453, 1376, 1113, 994, 920, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37–7.27 (m, 5 H), 5.87 (ddd, *J* = 16.7, 10.6, 5.7 Hz, 1 H), 5.28 (dq, *J* = 17.3, 1.3 Hz, 1 H), 5.16 (dq, *J* = 10.6, 1.2 Hz, 1 H), 4.80 (q, *J* = 5.1 Hz, 1 H), 4.63–4.54 (m, 2 H), 4.17–4.12 (m, 1 H), 3.95–3.90 (m, 1 H), 3.56 (dd, *J* = 10.1, 6.3 Hz, 1 H), 3.44 (dd, *J* = 10.2, 4.4 Hz, 1 H), 1.61–1.57 (m, 1 H), 1.48–1.43 (m, 1 H), 1.40–1.38 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.0, 137.7, 128.4, 127.8, 127.7, 115.8, 98.5, 76.6, 75.2, 73.5, 72.8, 33.1, 21.1; HRMS (CI/ES): No molecular ion peak was observed; $[\alpha]_D^{24}$ = –6.9° (*c* = 1.0, $CHCl_3$).



(–)-**49**

Diol (–)-49. Protected diol **S4** (3.50 g, 14.1 mmol, 1.0 equiv) was diluted in a solution of HCl/MeOH (282 mL, 1:3) before warming to 60 °C. The solution was allowed to stir at 60 °C for 72 h. Although full conversion was not observed at this time based on TLC analysis, the reaction contents were diluted with CH_2Cl_2 (100 mL) and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 250 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 3:1→1:1) afforded recovered protected diol **S4** (0.582 g, 2.34 mmol) along with the desired diol **49** (2.44 g, 10.99 mmol,78% yield, 94% yield based on recovered starting material) as a pale yellow oil. **49**: R_f = 0.15 (silica gel, hexanes:EtOAc, 3:1); IR (film) ν_{max} 3382, 2912, 2862, 1453, 1324, 1096, 1027, 992, 924, 737, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38–7.28 (m, 5 H), 5.87 (ddd, *J* = 16.7,

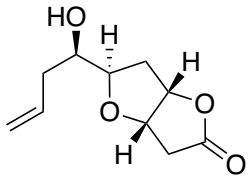
10.4, 5.8 Hz, 1 H), 5.32–5.24 (m, 1 H), 5.10 (dt, *J* = 10.5, 1.4 Hz, 1 H), 4.56 (s, 2 H), 4.39 (d, *J* = 6.4 Hz, 1 H), 4.14–4.04 (m, 1 H), 3.48 (dd, *J* = 9.4, 3.8 Hz, 1 H), 3.40 (dd, *J* = 9.4, 7.1 Hz, 1 H), 3.09 (s, 1 H), 3.00 (d, *J* = 2.8 Hz, 1 H), 1.68–1.64 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.4, 137.8, 128.5, 127.9, 127.8, 114.6, 74.2, 73.4, 72.8, 70.7, 39.5; HRMS (CI/ES): No molecular ion peak was observed; $[\alpha]_D^{24} = -1.3°$ (*c* = 1.0, $CHCl_3$).



50

Bicyclic lactone 50. A flame-dried flask was charged with NaOAc (0.371 g, 4.26 mmol, 3.0 equiv) and $CuCl_2$ (0.565 g, 4.26 mmol, 3.0 equiv) before being flushed with CO and evacuated three times. The CO balloon was then transferred to the flask, followed by the addition of AcOH (7.1 mL). A solution of diol (±)-**49** (0.316 g, 1.42 mmol, 1.0 equiv) in AcOH (7.1 mL) was then added, followed by $Pd(OAc)_2$ (0.031 g, 0.14 mmol, 0.1 equiv). The resultant suspension was then purged by direct bubbling with a balloon of CO gas for 1 h at 25 °C. Upon completion, the reaction contents were filtered through a short pad of Celite and washed with EtOAc (150 mL). This procedure was repeated a total of 4 times with a combined starting mass of diol (±)-**49** of 1.272 g (5.72 mmol). The filtrates were combined and concentrated directly and the resultant residue was purified by flash column chromatography (silica gel, hexanes:EtOAc, 4:1 → 3:2) to afford the desired bicylic lactone **50** (0.750 g, 3.01 mmol, 53% yield over 4 batches) as a slightly yellow oil. **50**: R_f = 0.23 (silica gel, hexanes:EtOAc, 3:2); IR (film) ν_{max} 3064, 3030, 2935, 2863, 1781, 1496, 1453, 1402, 1352, 1257, 1181, 1148, 1077, 1050, 912, 831, 700 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.27 (m, 5H), 5.11 (t, *J* = 4.8 Hz, 1H), 4.86 – 4.83 (m, 1H), 4.57 (s, 2H), 4.37 (m, 1H), 3.62 (dd, *J* = 10.5, 3.1 Hz, 1H), 3.48 (dd, *J* = 10.5, 5.0 Hz, 1H), 2.74 – 2.70 (m, 2H), 2.34 (dd, *J* = 14.0, 5.8 Hz, 1H), 2.09 – 2.01 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ

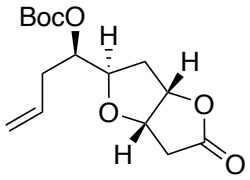
175.6, 137.9, 128.4, 127.7, 127.6, 84.7, 78.5, 77.9, 73.5, 71.5, 36.7, 34.8; HRMS (CI) calcd for $C_{14}H_{17}O_4$ $[M+H]^+$ 249.1127, found 249.1123.



52

Allylic alcohol 52. Pd/C (0.187 g, 10% by weight, 0.18 mmol, 0.06 equiv) was carefully added to a solution of bicyclic lactone **50** (0.749 g, 3.01 mmol, 1.0 equiv) in EtOAc (30.1 mL) at 25 °C. The resultant suspension was then purged by direct bubbling with a balloon of H_2 gas for 0.5 h and then stirred under a H_2 atmosphere for 10 h at 25 °C. Upon completion, the reaction contents were filtered through a short pad of Celite and washed with EtOAc (200 mL). The filtrate was concentrated directly to afford the desired crude alcohol as a colorless oil. Pressing forward without any additional purification, the so-obtained alcohol (3.01 mmol assumed) was dissolved in CH_2Cl_2 (30.1 mL) at 25 °C and solid $NaHCO_3$ (1.26 g, 15.05 mmol, 5.0 equiv) and Dess–Martin periodinane (1.40 g, 3.31 mmol, 1.1 equiv) were added sequentially. The resultant mixture was stirred at 25 °C for 20 min. Upon completion, the reaction contents were concentrated directly and the resultant residue was purified by flash column chromatography twice (silica gel, CH_2Cl_2:MeOH, 30:1, *then* silica gel, pure EtOAc) to afford the desired aldehyde **51** with inseparable impurities as a colorless liquid. Pushing forward, to a solution of aldehyde **51** (0.437 g, 2.80 mmol, 1.0 equiv) in CH_2Cl_2 (28.0 mL) at –78 °C was slowly added $TiCl_4$ (0.31 mL, 2.80 mmol, 1.0 equiv) and the resultant mixture was stirred at –78 °C for 10 min. Next, allyltrimethylsilane (0.67 mL, 4.20 mmol, 1.50 equiv) was added dropwise, and the reaction mixture was allowed to stir at –78 °C for a further 20 min. The reaction was then warmed to 25 °C and stirred for a further 10 min. Upon completion, the reaction contents were quenched by the addition of saturated aqueous Rochelle's Salt (50 mL), diluted with CH_2Cl_2 (25 mL), and poured

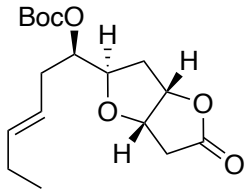
into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, CH_2Cl_2:MeOH, 40:1) afforded the desired allylic alcohol **52** (0.309 g, 1.56 mmol, 52% yield over 3 steps) as a colorless oil. **52**: R_f = 0.17 (silica gel, CH_2Cl_2:MeOH, 20:1); IR (film) ν_{max} 3466, 3076, 2924, 1780, 1641, 1435, 1402, 1356, 1181, 1150, 1064, 919, 838 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.84 (ddt, *J* = 17.5, 10.1, 7.2 Hz, 1H), 5.18 – 5.11 (m, 3H), 4.82 (t, *J* = 5.2 Hz, 1H), 4.11 (dd, *J* = 9.9, 5.0 Hz, 1H), 3.56 (t, *J* = 5.8 Hz, 1H), 2.78 – 2.67 (m, 2H), 2.35 – 2.28 (m, 2H), 2.22 – 2.12 (m, 1H), 2.06 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ175.5, 133.9, 118.3, 84.9, 81.0, 78.5, 72.1, 38.8, 36.8, 34.9; HRMS (CI/ES) calcd for $C_{10}H_{15}O_4$ $[M+H]^+$ 199.0970, found 199.0961.



S5

Protected allylic alcohol S5. To a solution of allylic alcohol **52** (0.182 g, 0.92 mmol, 1.0 equiv) in CH_3CN (9.2 mL) at 25 °C was added Boc_2O (0.220 g, 1.01 mmol, 1.1 equiv), Et_3N (0.39 mL, 2.76 mmol, 3.0 equiv), and DMAP (0.010 g, 0.09 mmol, 0.1 equiv) and the resultant reaction mixture was stirred at 25 °C for 8 h. Upon completion, the reaction contents were quenched by the addition of saturated aqueous NH_4Cl (25 mL), diluted with CH_2Cl_2 (15 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 5:1 → 3:1) afforded the desired protected allylic alcohol **S5** (0.116 g, 0.39 mmol, 42% yield) as a white amorphous solid. **S5**: R_f = 0.15 (silica gel, hexanes:EtOAc, 3:1); IR (film) ν_{max} 2984, 2929, 1786, 1739, 1460, 1395, 1369, 1279, 1255, 1160, 750 cm^{-1}; ^1H NMR

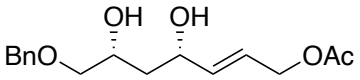
(500 MHz, $CDCl_3$) δ 5.77 (td, *J* = 10.1, 7.1 Hz, 1H), 5.18 – 5.08 (m, 3H), 4.83 (ddd, *J* = 5.7, 4.3, 1.4 Hz, 1H), 4.68 (td, *J* = 6.5, 4.5 Hz, 1H), 4.26 (ddd, *J* = 9.2, 6.0, 4.6 Hz, 1H), 2.77 – 2.65 (m, 2H), 2.45 – 2.34 (m, 3H), 1.94 (m, 1H), 1.48 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.5, 153.3, 132.6, 118.6, 84.4, 82.4, 78.7, 78.3, 76.5, 36.6, 35.7, 34.8, 27.8; HRMS (ES) calcd for $C_{15}H_{23}O_6$ $[M+H]^+$ 299.1495, found 299.1445.



48

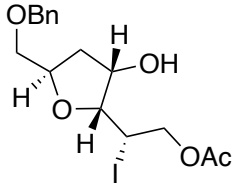
Bicyclic lactone alkene 48. To a solution of protected allylic alcohol **S5** (0.116 g, 0.39 mmol, 1.0 equiv) in CH_2Cl_2 (3.9 mL) at 25 °C was added *trans*-3-hexene (0.29 mL, 2.34 mmol, 6.0 equiv) and the Hoveyda-Grubbs 2nd generation initiator (0.013 g, 0.02 mmol, 0.05 equiv). The resultant mixture was stirred at 25 °C for 1 h. Upon completion, the reaction contents were quenched by the addition of saturated aqueous NH_4Cl (15 mL), diluted with CH_2Cl_2 (10 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 4:1) to afford the desired bicylic lactone **48** (0.115 g, 0.35 mmol, 90% yield) as a slightly purple solid. **48**: R_f = 0.17 (silica gel, hexanes:EtOAc, 3:1); IR (film) ν_{max} 2966, 2935, 1788, 1741, 1460, 1395, 1369, 1279, 1255, 1162, 1074, 968, 846 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.61 – 5.50 (m, 1H), 5.38 – 5.27 (m, 1H), 5.10 (t, *J* = 4.6 Hz, 1H), 4.86 (td, *J* = 6.6, 4.3 Hz, 1H), 4.77 (td, *J* = 4.5, 1.9 Hz, 1H), 4.23 (ddd, *J* = 9.8, 5.8, 4.2 Hz, 1H), 2.77 – 2.63 (m, 2H), 2.35 (dd, *J* = 14.1, 5.8 Hz, 1H), 2.29 – 2.23 (m, 2H), 2.14 (ddd, *J* = 14.3, 9.5, 5.2 Hz, 1H), 2.00 (tdd, *J* = 7.7, 6.2, 1.5 Hz, 2H), 1.47 (s, 9H), 0.96 (td, *J* = 7.5, 5.4 Hz, 3H); ^{13}C NMR

(125 MHz, $CDCl_3$) δ 175.5, 153.1, 136.2, 122.6, 84.6, 82.2, 79.3, 78.5, 76.2, 36.8, 34.6, 33.3, 27.8, 25.5, 13.6; HRMS (CI/ES) calcd for $C_{17}H_{27}O_6$ $[M+H]^+$ 327.1808, found 327.1802.



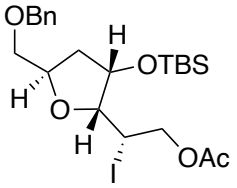
59

Alkene 59. To neat diol (–)-**49** (2.42 g, 10.9 mmol, 1.0 equiv) at 25 °C was added allyl acetate (11.8 mL, 109.0 mmol, 10.00 equiv) and the Grubbs 2nd generation initiator (0.280 g, 0.33 mmol, 0.03 equiv). The resultant brown mixture was stirred at 25 °C for 4 h. Upon completion, the reaction mixture was directly purified by flash column chromatography (silica gel, hexanes:EtOAc, 4:1→1:2) to afford recovered diol (–)-**49** (0.701 g, 3.16 mmol) along with the desired alkene **59** (1.73 g, 5.87 mmol, 54% yield, 76% yield based on recovered starting material) as a colorless oil. The recovered diol (–)-**49** was subjected to the same conditions, yielding an additional batch of the desired alkene **59** (0.561 g, 1.91 mmol, 60% yield, 75% yield based on recovered starting material, 71% combined yield over two iterations of the process). **59**: R_f = 0.40 (silica gel, hexanes:EtOAc, 1:1); IR (film) ν_{max} 3406, 2862, 1736, 1453, 1365, 1241, 1098, 1027, 971, 738 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.43–7.27 (m, 5 H), 5.81 (ddd, *J* = 16.4, 6.9, 4.7 Hz, 2 H), 4.55 (d, *J* = 4.7 Hz, 4 H), 4.42 (d, *J* = 6.1 Hz, 1 H), 4.10–4.03 (m, 1 H), 3.46 (dd, *J* = 9.4, 3.7 Hz, 1 H), 3.42–3.37 (m, 1 H), 3.36 (d, *J* = 3.6 Hz, 1 H), 3.03 (d, *J* = 2.9 Hz, 1 H), 2.06 (s, 3 H), 1.67–1.62 (t, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 137.7, 136.4, 128.5, 127.9, 127.8, 124.3, 74.2, 73.4, 71.6, 70.8, 64.2, 39.4, 20.9; HRMS (ES) calcd for $C_{16}H_{23}O_5$ $[M+H]^+$ 295.1547, found 295.1542; $[\alpha]_D^{24}$ = –0.9° (*c* = 1.0, $CHCl_3$).



60

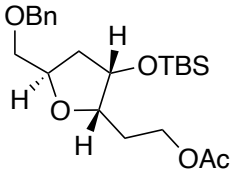
***trans* THF alcohol 60.** To a solution of alkene **59** (2.26 g, 7.68 mmol, 1.0 equiv) in CH_2Cl_2 (25.6 mL) at 25 °C was added $NaHCO_3$ (3.87 g, 46.1 mmol, 6.0 equiv) and *N*-iodosuccinimide (4.32 g, 19.2 mmol, 2.5 equiv). The resultant pink colored reaction mixture was allowed to stir for 8 h. Upon completion, the reaction contents were directly concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 4:1→3:1) afforded the desired *trans* THF alcohol **60** (2.23 g, 5.31 mmol, 69% yield) as a clear pink oil. **60**: R_f = 0.60 (silica gel, hexanes:EtOAc, 1:1); IR (film) ν_{max} 3459, 2926, 2861, 1742, 1453, 1379, 1240, 1054, 1029, 737, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37–7.26 (m, 5 H), 4.60–4.52 (m, 5 H), 4.37 (dd, *J* = 12.2, 6.6 Hz, 1 H), 4.29–4.24 (m, 1 H), 4.20 (dd, *J* = 10.6, 2.8 Hz, 1 H), 3.53 (dd, *J* = 10.5, 3.6 Hz, 1 H), 3.45 (dd, *J* = 10.5, 4.9 Hz, 1 H), 2.10 (s, 3 H), 2.07–2.03 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 138.2, 128.4, 127.6, 127.5, 83.4, 79.0, 74.1, 73.3, 72.3, 67.1, 37.0, 27.1, 20.9; HRMS (ES) calcd for $C_{48}H_{63}I_3O_{15}Na$ $[3M+Na]^+$ 1283.1202, found 1283.1241; $[\alpha]_D^{24}$ = +20.4° (*c* = 1.0, $CHCl_3$).



58

TBS protected alcohol 58. To a solution of *trans* THF alcohol **60** (2.20 g, 5.23 mmol, 1.0 equiv) in CH_2Cl_2 (17.4 mL) at 0 °C was added TBSOTf (1.51 mL, 8.37 mmol, 1.6 equiv) and 2,6-lutidine (2.42 mL, 20.9 mmol, 4.0 equiv). The resultant reaction mixture was then stirred at 0 °C for 1 h. Upon completion, the reaction contents were quenched by the addition of saturated aqueous NH_4Cl (50 mL), diluted with CH_2Cl_2 (25 mL), and poured into a separatory

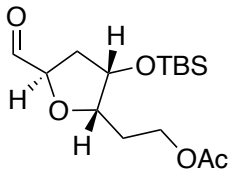
funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 15:1) afforded the desired TBS protected alcohol **58** (2.49 g, 4.65 mmol, 89% yield) as a colorless liquid. **58**: R_f = 0.80 (silica gel, hexanes:EtOAc, 4:1); IR (film) ν_{max} 2953, 2928, 2885, 2856, 1746, 1471, 1454, 1361, 1237, 1055, 937, 837 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37–7.27 (m, 5 H), 4.59–4.56 (m, 3 H), 4.53 (t, *J* = 3.0 Hz, 1 H), 4.48 (q, *J* = 4.5 Hz, 1 H), 4.40 (dd, *J* = 12.1, 6.7 Hz, 1 H), 4.26 (dd, *J* = 6.8, 3.0 Hz, 1 H), 4.18 (dd, *J* = 10.4, 2.6 Hz, 1 H), 3.52 (dd, *J* = 10.5, 3.7 Hz, 1H), 3.45 (dd, *J* = 10.5, 5.0 Hz, 1 H), 2.10 (s, 3 H), 1.99–1.88 (m, 2 H), 0.92 (s, 9 H), 0.20 (s, 3 H), 0.13 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6, 138.3, 128.4, 127.6 (2 C), 84.5, 79.0, 74.1, 73.4, 72.5, 67.3, 37.8, 27.2, 25.9, 21.0, 18.0, –4.1, –4.4; HRMS (CI/ES): No molecular ion peak was observed; $[\alpha]_D^{24}$ = +35.7° (*c* = 1.0, $CHCl_3$).



61

Deiodinated *trans* THF 61. A suspension of Raney Nickel (reagent grade, 30 mL of an aqueous slurry, excess) was added to a round bottom flask under an Ar atmosphere and rinsed with EtOH (3 × 20 mL, removing the solvent each time with a Pasteur pipette). Next, to a solution of TBS protected alcohol **58** (2.46 g, 4.61 mmol, 1.0 equiv) in EtOH (20.0 mL) at 25 °C was slowly added the above prepared Raney Nickel suspension in EtOH. The resultant suspension was then stirred vigorously at 25 °C for 10 min. Upon completion, the reaction mixture was filtered through Celite, rinsed with EtOAc (150 mL), and the filtrate was concentrated. The resultant crude material was purified by flash column chromatography (silica gel, hexanes:EtOAc, 12:1) to afford the deiodinated *trans* THF **61** (1.35 g, 3.31 mmol, 72% yield). **61**: R_f = 0.30 (silica

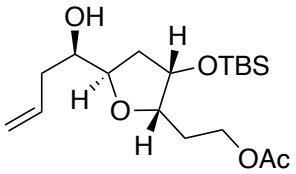
gel, hexanes:EtOAc, 8:1); IR (film) ν_{max} 2955, 2929, 2897, 2857, 1740, 1472, 1363, 1242, 1093, 1058, 836 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37–7.26 (m, 5 H), 4.58 (s, 2 H), 4.40–4.34 (m, 1 H), 4.28 (q, *J* = 3.2 Hz, 1 H), 4.22 (dt, *J* = 11.0, 6.3 Hz, 1 H), 4.15 (ddd, *J* = 11.0, 7.6, 6.2 Hz, 1 H), 3.97 (ddd, *J* = 8.3, 5.0, 3.4 Hz, 1 H), 3.54–3.46 (m, 2 H), 2.03 (s, 3 H), 1.95–1.84 (m, 4 H), 0.89 (s, 9 H), 0.07 (d, *J* = 4.6 Hz, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.1, 138.4, 128.3, 127.6, 127.5, 79.7, 76.3, 73.4, 73.3, 72.6, 62.2, 38.3, 29.0, 25.7, 21.0, 18.0, –4.5, –5.1; HRMS (CI/ES): No molecular ion peak was observed; $[\alpha]_D^{24}$ = +9.6° (*c* = 1.0, $CHCl_3$).



62

***trans* THF aldehyde 62.** Pd/C (0.443 g, 10% by weight, 0.42 mmol, 0.13 equiv) was carefully added to a solution of deiodinated *trans* THF **61** (1.33 g, 3.25 mmol, 1.0 equiv) in EtOAc (46.0 mL) at 25 °C. The resultant suspension was then purged by direct bubbling with a balloon of H_2 gas for 2 h at 25 °C. Upon completion, the reaction contents were filtered through a short pad of Celite and washed with EtOAc (200 mL). The filtrate was concentrated directly to afford the desired crude alcohol as a colorless oil. Pressing forward without any additional purification, the so-obtained alcohol (3.25 mmol assumed) was dissolved in CH_2Cl_2 (32.5 mL) at 25 °C and solid $NaHCO_3$ (1.36 g, 16.3 mmol, 5.0 equiv) and Dess–Martin periodinane (1.52 g, 3.58 mmol, 1.1 equiv) were added sequentially. The resultant mixture was stirred at 25 °C for 30 min. Upon completion, the reaction contents were concentrated directly and the resultant residue was purified by flash column chromatography (silica gel, hexanes:EtOAc, 2:1→1:1) to afford the desired aldehyde **62** (0.942 g, 2.98 mmol, 92% yield over 2 steps) as a colorless liquid. **62**: R_f = 0.60 (silica gel, hexanes:EtOAc, 1:1); IR (film) ν_{max} 2955, 2929, 2899, 2857, 1738, 1472, 1463, 1364, 1252, 1052, 836 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.69 (d, *J* = 2.1 Hz, 1 H), 4.48 (d, *J* =

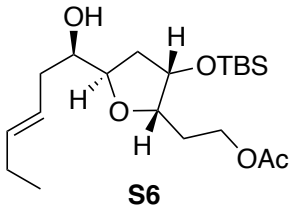
2.2 Hz, 1 H), 4.33–4.30 (m, 1 H), 4.29–4.23 (m, 1 H), 4.21–4.16 (m, 1 H), 4.00 (ddd, J = 8.2, 4.5, 3.2 Hz, 1 H), 2.14–2.08 (m, 2 H), 2.06 (s, 3 H), 1.99 (dd, J = 8.5, 5.9 Hz, 1 H), 1.89 (ddd, J = 7.9, 6.4, 4.5 Hz, 1 H), 0.89 (s, 9 H), 0.09 (d, J = 6.8 Hz, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.7, 171.1, 81.3, 81.2, 72.7, 61.9, 37.3, 28.9, 25.7, 21.0, 18.0, –4.6, –5.1; HRMS (CI/ES): No molecular ion peak was observed; $[\alpha]_D^{24}$ = +19.2° (c = 1.0, $CHCl_3$).



63

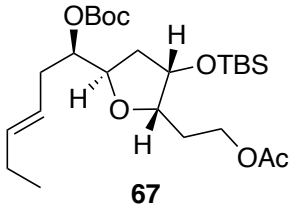
Allylic Alcohol 63. To a solution of *trans* THF aldehyde **62** (0.919 g, 2.90 mmol, 1.0 equiv) in CH_2Cl_2 (29.0 mL) at –78 °C was slowly added $TiCl_4$ (0.320 mL, 2.90 mmol, 1.0 equiv) and the resultant mixture was stirred at –78 °C for 5 min. Next, allyltrimethylsilane (0.69 mL, 4.35 mmol, 1.50 equiv) was added dropwise, and the reaction mixture was allowed to stir at –78 °C for a further 30 min. Upon completion, the reaction contents were quenched by the addition of saturated aqueous NH_4Cl (50 mL), diluted with CH_2Cl_2 (25 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 5:1→4:1) afforded the desired allylic alcohol **63** (0.928 g, 2.59 mmol, 89% yield) as a colorless oil. **63**: R_f = 0.40 (silica gel, hexanes:EtOAc, 2:1); IR (film) ν_{max} 3468, 2929, 2857, 1739, 1643, 1472, 1364, 1256, 1048, 940, 775 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.94–5.84 (m, 1 H), 5.16–5.07 (m, 2 H), 4.28 (q, J = 3.4, 3.0 Hz, 1 H), 4.25–4.14 (m, 2 H), 4.10–4.04 (m, 1 H), 3.93–3.88 (m, 1 H), 3.47 (ddd, J = 7.4, 4.8, 2.1 Hz, 1 H), 2.27–2.22 (m, 2 H), 2.05 (s, 3 H), 1.94 (tt, J = 11.6, 4.2 Hz, 1 H), 1.90–1.87 (m, 2 H), 1.85–1.78 (m, 1 H), 0.89 (s, 9 H), 0.07 (d, J = 5.6 Hz, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 134.7, 117.3, 79.8, 79.8, 73.9, 73.3, 62.2, 38.4,

38.3, 29.1, 25.7, 21.1, 18.0, –4.5, –5.0; HRMS (CI) calcd for $C_{15}H_{35}O_5Si$ $[M+H]^+$ 359.2256, found 359.2248; $[\alpha]_D^{24}$ = +5.3° (*c* = 1.0, $CHCl_3$).



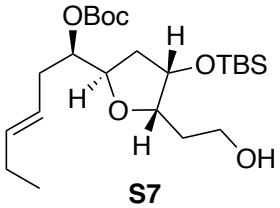
S6

***trans* THF alkene S6.** To a solution of allylic alcohol **63** (0.910 g, 2.54 mmol, 1.0 equiv) in CH_2Cl_2 (5.1 mL) at 25 °C was added *trans*-3-hexene (2.53 mL, 20.3 mmol, 8.0 equiv) and the Grubbs 2nd generation initiator (0.110 g, 0.13 mmol, 0.05 equiv). The resultant mixture was stirred at 25 °C for 8 h. Upon completion, the reaction contents were concentrated directly and the resultant residue was purified by flash column chromatography (silica gel, hexanes:EtOAc, 10:1) to afford recovered allyl alcohol **63** (0.111 g, 0.31 mmol) and the desired alkene **S6** (0.684 g, 1.76 mmol, 69% yield, 79% yield based on recovered starting material) as a colorless oil. **S6**: R_f = 0.50 (silica gel, hexanes:EtOAc, 2:1); IR (film) ν_{max} 3468, 2958, 2929, 2857, 1741, 1463, 1364, 1251, 1048, 971, 941, 836 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.64–5.40 (m, 2 H), 4.30–4.26 (m, 1 H), 4.19 (tdd, *J* = 13.8, 11.0, 6.0 Hz, 2 H), 4.07 (tt, *J* = 7.9, 5.0 Hz, 1 H), 3.91 (dq, *J* = 8.2, 4.0 Hz, 1 H), 3.42 (dq, *J* = 7.2, 5.1 Hz, 1 H), 2.25 (dd, *J* = 5.1, 3.3 Hz, 1 H), 2.18 (q, *J* = 7.2, 6.5 Hz, 2 H), 2.09–2.00 (m, 5 H), 1.98–1.91 (m, 1 H), 1.90–1.85 (m, 2 H), 1.84–1.78 (m, 1 H), 1.60 (s, 1 H), 1.02–0.94 (m, 3 H), 0.90 (d, *J* = 4.8 Hz, 9 H), 0.08 (t, *J* = 5.1 Hz, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 135.2, 124.6, 79.8, 79.7, 73.9, 73.7, 62.2, 38.3, 37.1, 29.1, 25.7, 25.6, 21.1, 18.0, 13.7, –4.5, –5.0; HRMS (CI/ES): No molecular ion peak was observed; $[\alpha]_D^{24}$ = +5.4° (*c* = 1.0, $CHCl_3$).



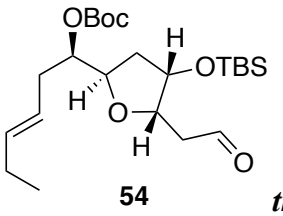
67

***trans* THF protected allylic alcohol 67.** To a solution of alkene **S6** (0.682 g, 1.75 mmol, 1.0 equiv) in THF (11.7 mL) at –78 °C was added Boc_2O (0.7634 g, 3.50 mmol, 2.0 equiv) and LiHMDS (2.28 mL, 1.0 M in THF, 2.28 mmol, 1.3 equiv) and the resultant reaction mixture was allowed to warm to 25 °C over 8 h. Upon completion, the reaction contents were quenched by the addition of saturated aqueous NH_4Cl (25 mL), diluted with CH_2Cl_2 (15 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 15:1→10:1) afforded the desired protected allylic alcohol **67** (0.819 g, 1.68 mmol, 96% yield) as a colorless oil. **67**: R_f = 0.65 (silica gel, hexanes:EtOAc, 6:1); IR (film) ν_{max} 2958, 2931, 2857, 1740, 1472, 1463, 1367, 1279, 1254, 1165, 1052, 836 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.60–5.52 (m, 1 H), 5.38 (dtd, *J* = 16.9, 6.4, 1.6 Hz, 1 H), 4.60 (dt, *J* = 6.9, 5.4 Hz, 1 H), 4.30–4.26 (m, 1 H), 4.24–4.16 (m, 2 H), 4.15–4.08 (m, 1 H), 3.97–3.92 (m, 1 H), 2.40–2.27 (m, 2 H), 2.04 (s, 3 H), 2.02–1.95 (m, 2 H), 1.94–1.86 (m, 2 H), 1.80 (dtt, *J* = 13.6, 9.2, 4.7 Hz, 2 H), 1.47 (s, 9 H), 0.95 (t, *J* = 7.4 Hz, 3 H), 0.88 (s, 9 H), 0.06 (d, *J* = 4.3 Hz, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.1, 153.6, 135.6, 123.4, 81.7, 79.4, 77.9, 77.4, 73.4, 62.3, 38.1, 34.4, 28.9, 27.8, 25.7, 25.6, 21.0, 18.0, 13.6, –4.6, –5.0; HRMS (ES) calcd for $C_{25}H_{47}O_7Si$ $[M+H]^+$ 487.3093, found 487.3089; $[\alpha]_D^{24}$ = +2.3° (*c* = 1.0, $CHCl_3$).



S7

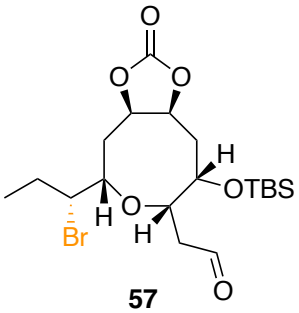
***trans* THF primary alcohol S7.** To a solution of protected allylic alcohol **67** (0.799 g, 1.64 mmol, 1.0 equiv) in MeOH (10.9 mL) at 25 °C was added K_2CO_3 (1.36 g, 9.84 mmol, 6.0 equiv). The resultant white solution was stirred at 25 °C for 2 h. Upon completion, the reaction contents were quenched by the addition of saturated aqueous NH_4Cl (25 mL), diluted with EtOAc (15 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 6:1→4:1) afforded the desired primary alcohol **S7** (0.701 g, 1.58 mmol, 96% yield) as a colorless liquid. **S7**: R_f = 0.40 (silica gel, hexanes:EtOAc, 4:1); IR (film) ν_{max} 3448, 2958, 2930, 2857, 1739, 1472, 1368, 1255, 1166, 1057, 835 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.60–5.52 (m, 1 H), 5.41–5.33 (m, 1 H), 4.61 (q, *J* = 6.2 Hz, 1 H), 4.28–4.20 (m, 2 H), 4.02 (dt, *J* = 10.2, 3.3 Hz, 1 H), 3.76 (q, *J* = 5.9 Hz, 2 H), 2.65 (t, *J* = 6.1 Hz, 1 H), 2.28 (t, *J* = 6.8 Hz, 2 H), 2.03–1.95 (m, 2 H), 1.93–1.87 (m, 2 H), 1.79 (ddd, *J* = 13.1, 8.6, 4.7 Hz, 1 H), 1.67–1.57 (m, 2 H), 1.48 (s, 9 H), 0.95 (q, *J* = 7.3 Hz, 3 H), 0.88 (s, 9 H), 0.06 (d, *J* = 4.5 Hz, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.8, 135.7, 123.2, 81.9, 81.7, 78.0, 77.6, 74.0, 61.1, 38.0, 34.1, 31.9, 27.8, 25.7, 25.6, 18.1, 13.7, –4.7, –5.0; HRMS (CI) calcd for $C_{23}H_{42}O_5SiNa$ $[M+Na–H_2O]^+$ 450.2727, found 450.2716; $[\alpha]_D^{24}$ = +5.2° (*c* = 1.0, $CHCl_3$).



54

***trans* THF aldehyde 54.** To a solution of primary alcohol **S7** (0.680 g, 1.53 mmol, 1.0 equiv) in CH_2Cl_2 (10.2 mL) at 25 °C was sequentially added solid $NaHCO_3$ (0.643 g,

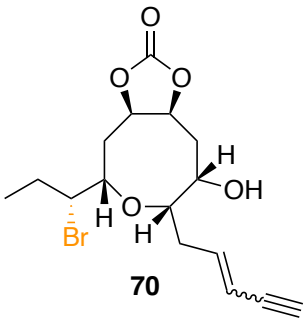
7.65 mmol, 5.00 equiv) and Dess–Martin periodinane (0.713 g, 1.68 mmol, 1.1 equiv). The resultant mixture was stirred at 25 °C for 30 min. Upon completion, the reaction contents were concentrated directly and the resultant residue was purified by flash column chromatography (silica gel, hexanes:EtOAc, 10:1) to afford the desired aldehyde **54** (0.631 g, 1.43 mmol, 93% yield) as a colorless liquid. **54**: R_f = 0.65 (silica gel, hexanes:EtOAc, 4:1); IR (film) ν_{max} 2958, 2931, 2857, 1738, 1472, 1368, 1279, 1255, 1165, 1077, 836 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.79 (t, *J* = 1.8 Hz, 1 H), 5.61–5.51 (m, 1 H), 5.41–5.32 (m, 1 H), 4.61 (dt, *J* = 6.9, 5.2 Hz, 1 H), 4.42–4.39 (m, 1 H), 4.33 (td, *J* = 6.4, 3.5 Hz, 1 H), 4.25 (dt, *J* = 9.4, 6.0 Hz, 1 H), 2.68 (ddd, *J* = 6.6, 3.0, 1.8 Hz, 2 H), 2.35–2.29 (m, 2 H), 2.03–1.96 (m, 2 H), 1.94–1.82 (m, 2 H), 1.47 (s, 9 H), 0.95 (t, *J* = 7.4 Hz, 3 H), 0.86 (s, 9 H), 0.06 (s, 3 H), 0.01 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.5, 153.5, 135.8, 123.2, 81.8, 78.1, 77.7, 77.7, 73.3, 44.1, 37.9, 34.4, 27.8, 25.7, 25.5, 18.0, 13.6, –4.7, –5.1; HRMS (ES) calcd for $C_{23}H_{43}O_6Si$ $[M+H]^+$ 443.2831, found 443.2834; $[\alpha]_D^{24}$ = +14.0° (*c* = 1.0, $CHCl_3$).



57

Bromoether aldehyde 57. To a solution of aldehyde **54** (0.603 g, 1.36 mmol, 1.0 equiv) in CH_2Cl_2 (27.2 mL) at 0 °C was added BDSB[2] (0.895 g, 1.63 mmol, 1.2 equiv). The resultant orange solution was stirred at 0 °C for 10 min. Upon completion, the reaction contents were quenched by the addition of saturated aqueous NH_4Cl (50 mL), diluted with CH_2Cl_2 (25 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column

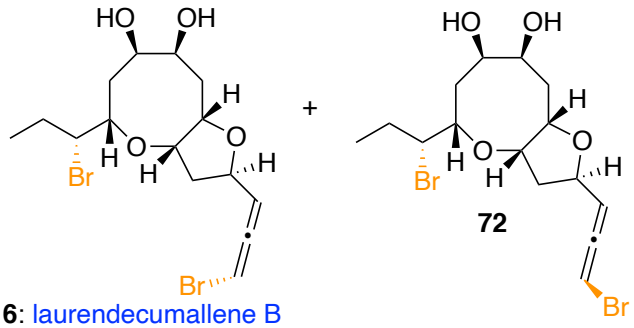
chromatography (silica gel, hexanes:EtOAc, 8:1→5:1) afforded the desired bromoether aldehyde **57** as a mixture of two inseparable diastereomers (0.241 g, 0.52 mmol, *dr* = 7:1, 38% yield) as a pale yellow oil. **57**: R_f = 0.50 (silica gel, hexanes:EtOAc, 2:1); IR (film) ν_{max} 2930, 2856, 1801, 1724, 1463, 1360, 1256, 1179, 1074, 833, 777 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.80 (s, 1 H), 5.24 (dd, *J* = 10.8, 7.1 Hz, 1 H), 4.98–4.92 (m, 1 H), 3.88 (dd, *J* = 8.8, 5.9 Hz, 3 H), 3.81–3.75 (m, 1 H), 2.95–2.84 (m, 2 H), 2.40–2.23 (m, 3 H), 2.05–1.95 (m, 2 H), 1.57 (d, *J* = 3.9 Hz, 1 H), 1.04 (t, *J* = 7.3 Hz, 3 H), 0.93 (s, 9 H), 0.12 (s, 3 H), 0.07 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.8, 154.3, 78.9, 76.6, 76.1, 75.4, 70.5, 56.5, 47.7, 35.1, 29.5, 28.2, 25.8, 18.1, 12.2, –4.4, –5.0; HRMS (CI/ES) calcd for $C_{38}H_{66}BrO_{12}Si_2$ $[2M]^+$ 928.2460, found 928.2415; $[\alpha]_D^{24}$ = –6.5° (*c* = 1.0, $CHCl_3$).



70

***E/Z* Bromoether enyne 70.** To a solution of Wittig salt **69** (0.390 g, 0.86 mmol, 1.80 equiv; prepared according to the literature procedure reported by Diederich and co-workers[36] with all the spectroscopic data matching that reported in Ref. 30) in THF (12.0 mL) was added *n*BuLi (0.48 mL, 1.6 M in hexanes, 0.77 mmol, 1.6 equiv) dropwise at 0 °C. The resultant dark solution was stirred at 0 °C for 30 min before a solution of bromoether aldehyde **57** (0.225 g, 0.48 mmol, 1.0 equiv) in THF (12.0 mL) was added in a single portion at 0 °C. Upon completion, the reaction contents were quenched by the addition of saturated aqueous NH_4Cl (50 mL), diluted with CH_2Cl_2 (25 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were

then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 8:1→5:1) afforded recovered aldehyde **57** (59.6 mg, 0.13 mmol) and the desired protected enyne (0.158 g, 0.28 mmol, *E/Z* = 2:1, 58% yield, 80% yield b.r.s.m.) as a colorless oil and as inseparable *E/Z* isomers. Pressing forward, to a solution of protected enyne (0.145 g, 0.26 mmol, 1.0 equiv) in THF (10.4 mL) at 0 °C was added TBAF (0.52 mL, 1.0 M in THF, 0.52 mmol, 2.0 equiv) and the reaction mixture was stirred at 0 °C for 5 min. Upon completion, the reaction contents were quenched by the addition of saturated aqueous NH_4Cl (25 mL), diluted with EtOAc (15 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 3:1→2:1) afforded the desired bromoether enyne **70** (78.0 mg, 0.21 mmol, *E/Z* = 2:1, 81% yield) as a colorless oil and as a mixture of inseparable *E/Z* isomers. **70**: R_f = 0.20 (silica gel, hexanes:EtOAc, 2:1); IR (film) ν_{max} 3469, 3288, 2925, 2360, 2339, 1797, 1458, 1358, 1192, 1047, 962, 779 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.15 (dt, *J* = 15.5, 7.6 Hz, 0.66 H), 6.00 (d, *J* = 10.8 Hz, 0.33 H), 5.61 (ddt, *J* = 15.9, 14.2, 2.1 Hz, 1 H), 5.26–5.17 (m, 1 H), 4.96 (dtd, *J* = 15.5, 8.3, 7.7, 3.5 Hz, 1 H), 3.94 (t, *J* = 6.5 Hz, 1 H), 3.83 (dtd, *J* = 9.6, 7.0, 3.6 Hz, 1 H), 3.66 (dd, *J* = 9.7, 5.6 Hz, 1 H), 3.46–3.39 (m, 1 H), 2.87 (dd, *J* = 15.4, 3.2 Hz, 1 H), 2.79–2.59 (m, 0.66 H), 2.54–2.41 (m, 1.33 H), 2.35–2.10 (m, 4 H), 1.91 (d, *J* = 6.8 Hz, 1 H), 1.75–1.64 (m, 1 H), 1.08 (td, *J* = 7.2, 1.6 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.1, 140.5, 112.8, 83.3, 80.6, 78.9, 76.1, 75.1, 68.7, 56.1, 36.2, 35.2, 33.1, 29.2, 28.6, 12.1 (only one isomer reported); HRMS (CI/ES): No molecular ion peak was observed; $[\alpha]_D^{24}$ = +4.8° (*c* = 0.8, $CHCl_3$).



Laurendecumallene B (6) and *epi*-laurendecumallene B (72). To a solution of enyne **70** (66.2 mg, 0.18 mmol, 1.0 equiv) in CH_3CN (9.0 mL) at 25 °C was added BDSB[35] (0.121 g, 0.22 mmol, 1.2 equiv) and the reaction mixture was stirred at 25 °C for 2 h. Upon completion, the reaction contents were quenched by the addition of saturated aqueous NH_4Cl (25 mL), diluted with EtOAc (15 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 4:1→2:1) afforded recovered enyne **70** (7.9 mg, 0.021 mmol) and the desired protected diol bromoallene (56.6 mg, 0.13 mmol, *R*/*S* = 1.0:1.3, 72% yield, 81% yield based on recovered starting material) as a colorless oil and as a mixture of inseparable epimers. Pressing forward, to a solution of protected diol bromoallene (44.9 mg, 0.099 mmol, 1.0 equiv) in MeOH (9.9 mL) and H_2O (1.0 mL) at 25 °C was added K_2CO_3 (0.137 g, 0.99 mmol, 10 equiv). The resultant mixture was stirred for 2 h at 25 °C. Upon completion, the reaction contents were quenched by the addition of saturated aqueous NH_4Cl (25 mL), diluted with EtOAc (15 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by preparative thin-layer chromatography (silica gel, CH_2Cl_2:Et_2O, 1:1) over six consecutive full development iterations afforded the undesired *epi*-

laurendecumallene B (**72**, 12.6 mg, 0.030 mmol, 30% yield) and desired laurendecumallene B (**6**, 17.1 mg, 0.040 mmol, 40% yield), both as colorless oils. **72**: R_f = 0.65 (silica gel, hexanes:EtOAc, 2:1); IR (film) ν_{max} 3403, 3055, 2922, 2851, 1958, 1557, 1437, 1334, 1194, 1106, 1064, 869 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.09 (dd, J = 5.7, 1.7 Hz, 1 H), 5.43 (t, *J* = 6.0 Hz, 1 H), 4.77 (m, 1 H), 4.31 (d, *J* = 6.6 Hz, 1 H), 4.20 (m, 1 H), 4.17 (m, 1 H), 4.10 (m, 1 H), 3.87 (m, 1 H), 3.82 (m, 1 H), 2.42 (ddd, *J* = 15.8, 7.4, 2.1 Hz, 1 H), 2.20 (dd, *J* = 12.4, 7.4 Hz, 1 H), 2.07–2.06 (m, 3 H), 2.01 (m, 1 H), 1.96 (m, 1 H), 1.77 (m, 1 H), 1.06 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.6, 101.9, 81.3, 78.6, 78.5, 74.0, 73.9, 70.7, 69.0, 60.8, 40.1, 35.2, 32.4, 27.4, 12.1; HRMS (ES) calcd for $C_{15}H_{22}Br_2O_4Na$ $[M+Na]^+$ 446.9785, found 446.9763; $[\alpha]_D^{24}$ = –82.2° (*c* = 1.0, $CHCl_3$). **6**: R_f = 0.65 (silica gel, hexanes:EtOAc, 2:1); IR (film) ν_{max} 3405, 3056, 2933, 1959, 1438, 1335, 1196, 1065, 868, 659 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.06 (dd, *J* = 5.7, 1.9 Hz, 1 H), 5.45 (t, *J* = 5.7 Hz, 1 H), 4.77 (m, 1 H), 4.31 (d, *J* = 8.3 Hz, 1 H), 4.20 (m, 1 H), 4.18 (m, 1 H), 4.10 (m, 1 H), 3.87 (m, 1 H), 3.82 (m, 1 H), 2.42 (dd, *J* = 15.0, 7.9 Hz, 1 H), 2.19 (m, 1 H), 2.08–2.03 (m, 3 H), 2.01 (m, 1 H), 1.97 (m, 1 H), 1.77 (m, 1 H), 1.06 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.2, 102.2, 81.2, 78.7, 78.5, 74.1, 73.5, 70.6, 69.0, 60.8, 40.1, 35.2, 32.4, 27.4, 12.2; HRMS (ES) calcd for $C_{15}H_{22}Br_2O_4Na$ $[M+Na]^+$ 446.9785, found 446.9761; $[\alpha]_D^{24}$ = +117.4° (*c* = 0.33, $CHCl_3$).

Table 1.3. Comparative ^{1}H NMR data for laurendecumallene B (**6**)

Natural (Wang)[14] (500 MHz, $CDCl_3$)	Synthetic (this work) (500 MHz, $CDCl_3$)
6.06 (dd, *J* = 5.7, 1.7 Hz, 1 H)	6.06 (dd, *J* = 5.7, 1.9 Hz, 1 H)
5.45 (dd, *J* = 5.7, 5.7 Hz, 1 H)	5.45 (t, *J* = 5.7 Hz, 1 H)
4.77 (m, 1 H)	4.77 (m, 1 H)
4.31 (br d, *J* = 7.3 Hz, 1 H)	4.31 (d, *J* = 8.3 Hz, 1 H)
4.20 (m, 1 H)	4.20 (m, 1 H)
4.18 (m, 1 H)	4.18 (m, 1 H)
4.10 (m, 1 H)	4.10 (m, 1 H)
3.87 (m, 1 H)	3.87 (m, 1 H)
3.82 (m, 1 H)	3.82 (m, 1 H)
2.42 (ddd, *J* = 15.8, 7.3, 1.6 Hz, 1 H)	2.42 (dd, *J* = 15.0, 7.9 Hz, 1 H)
2.19 (ddd, *J* = 13.2, 6.6, 1.8 Hz, 1 H)	2.19 (m, 1 H)
2.07–2.03 (m, 3 H)	2.08–2.03 (m, 3 H)
2.01 (m, 1 H)	2.01 (m, 1 H)
1.97 (m, 1 H)	1.97 (m, 1 H)
1.77 (m, 1 H)	1.77 (m, 1 H)
1.06 (t, *J* = 7.2 Hz, 3 H)	1.06 (t, *J* = 7.2 Hz, 3 H)

Table 1.4. Comparative ^{13}C NMR data for laurendecumallene B (**6**)

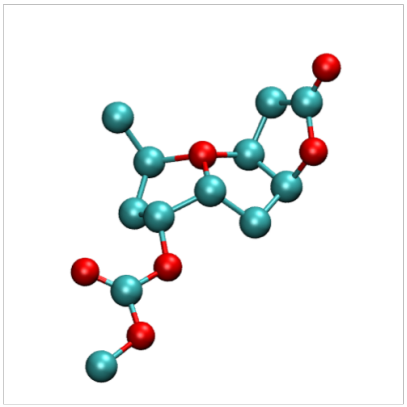
Natural (Wang)[14] (125 MHz, $CDCl_3$)	Synthetic (this work) (125 MHz, $CDCl_3$)
201.3	201.2
102.3	102.2
81.3	81.2
78.8	78.7
78.5	78.5
74.0	74.1
73.4	73.5
70.7	70.6
69.1	69.0
60.8	60.8
40.2	40.1
35.2	35.2
32.5	32.4
27.4	27.4
12.1	12.2

1.6 Computational General Information

DFT optimizations were performed through Gaussian 09 on the Midway2 Cluster at the University of Chicago's Research Computing Center. Ground state geometry optimizations and free energies (kcal/mol) were determined using the B3LYP/cc-pVDZ level of theory in the gas phase at 298K. All ground state structures display no imaginary frequencies.

1.6.1 Minimized Structures

53 – lactone



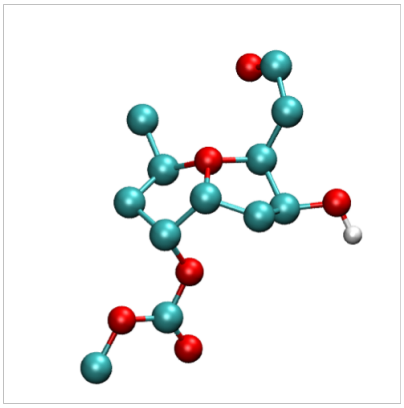
Zero-point correction= 0.288371 (Hartree/Particle)
Thermal correction to Energy= 0.305236
Thermal correction to Enthalpy= 0.306180
Thermal correction to Gibbs Free Energy= 0.242399
Sum of electronic and zero-point Energies= -918.365941
Sum of electronic and thermal Energies= -918.349076
Sum of electronic and thermal Enthalpies= -918.348131
Sum of electronic and thermal Free Energies= -918.411913

1 1

C	-3.64380600	0.39443800	0.36462400
C	-3.79993300	-0.83745800	-0.53160200
C	-2.28415000	0.20763000	0.99436200
H	-4.42549000	0.36628900	1.14216100
H	-3.77202300	1.32325500	-0.20503600
C	-2.01476600	-1.30122200	0.90038800
O	-2.82874600	-1.76080000	-0.18291000
O	-1.21804900	0.79011500	0.08512800
H	-2.12410400	0.64827300	1.98525300
C	-0.25571100	-0.29881700	-0.38859100
C	-0.53415800	-1.44968100	0.56486200
H	-2.29591100	-1.82952100	1.82439900
H	-0.32411100	-2.41944100	0.09543000
H	0.07321500	-1.37168500	1.47811400
C	1.11551200	0.38912600	-0.32610800
H	-0.58663800	-0.51460300	-1.41080500

C	-0.43737700	2.06518500	0.51842300
C	0.96442500	1.51447200	0.71519600
C	-0.62529300	3.10126400	-0.56509500
H	1.73075100	2.28712800	0.57170800
H	1.08387600	1.08879600	1.72341300
H	1.38995500	0.80783300	-1.30388700
O	2.06652500	-0.59888800	0.04630100
O	-4.59140500	-1.03344800	-1.39772200
C	3.36941100	-0.24967500	-0.21847700
H	-0.17621300	2.79220200	-1.52065200
H	-0.12415100	4.02747300	-0.24069800
H	-1.68844300	3.33075300	-0.72369800
O	4.12885700	-1.27619300	0.11312300
C	5.55118800	-1.08210000	-0.09697200
O	3.69994700	0.82056100	-0.66761100
H	5.90876900	-0.23282400	0.50143200
H	5.75298300	-0.89797700	-1.16109600
H	6.01636000	-2.01682500	0.23295200
H	-0.92790400	2.36113000	1.45447600

56 – aldehyde

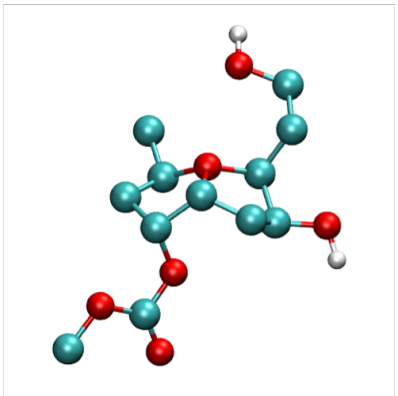


Zero-point correction= 0.308678 (Hartree/Particle)
Thermal correction to Energy= 0.327302
Thermal correction to Enthalpy= 0.328246
Thermal correction to Gibbs Free Energy= 0.261242
Sum of electronic and zero-point Energies= -919.533630
Sum of electronic and thermal Energies= -919.515006
Sum of electronic and thermal Enthalpies= -919.514061
Sum of electronic and thermal Free Energies= -919.581066
1 1

C	-3.29699600	0.62307100	0.26990900
C	-4.26350400	-0.43336500	-0.23014500
C	-1.90081100	0.50792400	-0.31398900
H	-3.29481400	0.62627800	1.37347600
H	-3.70021400	1.61042900	-0.01931300

C	-1.04145100	1.78717000	-0.21707400
O	-1.87758600	2.90656500	-0.37634800
O	-1.09888800	-0.49808000	0.48370600
H	-1.94719000	0.08857200	-1.32617700
C	-0.09833400	0.22998800	1.40819800
C	-0.39369000	1.70014400	1.18354100
H	-0.25582300	1.74682100	-0.98680400
H	-1.10773900	2.07898600	1.92846500
H	0.52732000	2.29535000	1.24114500
C	1.24582700	-0.33854600	0.96848100
H	-0.35398800	-0.13543200	2.41008200
C	-0.37680200	-1.65985000	-0.25933000
C	0.90800100	-1.77041500	0.54800200
C	-1.27372100	-2.86902300	-0.28574400
H	1.71516400	-2.21572800	-0.04831400
H	0.75409800	-2.40025800	1.43859500
H	1.97924400	-0.29676900	1.78438000
O	1.68281400	0.44353100	-0.15168600
O	-3.97451000	-1.26875900	-1.05647900
C	2.99822300	0.44489900	-0.54583500
H	-5.28991400	-0.37685300	0.20377400
H	-1.37355900	3.62952900	-0.77730100
H	-1.51151000	-3.21009700	0.73326700
H	-0.72739600	-3.67817000	-0.79807400
H	-2.20196000	-2.67682100	-0.83788900
H	-0.18705100	-1.24822700	-1.26041400
O	3.73188200	-0.38678400	0.20199500
C	5.14644900	-0.41538500	-0.12940300
H	5.58540200	0.58016900	0.02069500
H	5.27972500	-0.72425500	-1.17483800
H	5.58720000	-1.14606200	0.55729000
O	3.36177000	1.13013700	-1.45640100

S8 – Free Alcohol



Zero-point correction= 0.332858 (Hartree/Particle)

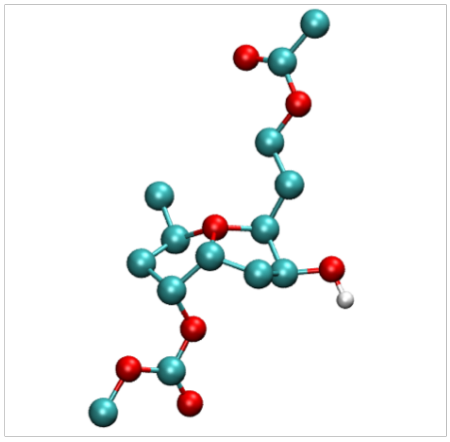
Thermal correction to Energy= 0.352024
Thermal correction to Enthalpy= 0.352968
Thermal correction to Gibbs Free Energy= 0.283881
Sum of electronic and zero-point Energies= -920.718684
Sum of electronic and thermal Energies= -920.699518
Sum of electronic and thermal Enthalpies= -920.698574
Sum of electronic and thermal Free Energies= -920.767661

1 1

C	-3.24328900	0.77164200	0.19824000
C	-4.30677900	-0.21914400	-0.25270600
C	-1.87047600	0.60563200	-0.43828500
H	-3.15241900	0.74263100	1.29645500
H	-3.57341100	1.78841000	-0.06604900
C	-0.94206700	1.83277700	-0.29737200
O	-1.70314000	3.00123600	-0.46872100
O	-1.07696900	-0.46623800	0.28651700
H	-1.93893300	0.24814800	-1.47416700
C	-0.10524600	0.18998200	1.29199400
C	-0.34005600	1.67921500	1.11777900
H	-0.13501800	1.75624100	-1.04369700
H	-1.06052000	2.05710100	1.85613800
H	0.60061400	2.23606500	1.21895400
C	1.24677000	-0.39813500	0.90025900
H	-0.42776800	-0.21012200	2.26047400
C	-0.33155000	-1.53882500	-0.53523600
C	0.89183100	-1.77532600	0.33687100
C	-1.23169100	-2.72299000	-0.77223800
H	1.72186400	-2.20059100	-0.24215900
H	0.65335000	-2.47119800	1.15693500
H	1.91957700	-0.45244900	1.76573900
O	1.79788000	0.45001800	-0.11827700
O	-3.91457300	-1.52522500	0.15128300
C	3.13815500	0.42548400	-0.40942900
H	-1.12287300	3.71815300	-0.76362000
H	-1.54402800	-3.17883500	0.17755000
H	-0.65863700	-3.46418600	-1.35314400
H	-2.13288300	-2.45203100	-1.33417300
H	-0.05706100	-1.02158800	-1.46636000
O	3.78128400	-0.48970500	0.32564900
C	5.21512000	-0.55041600	0.10283500
H	5.67562500	0.41142000	0.36600900
H	5.42121600	-0.78215000	-0.95073100
H	5.57425200	-1.34966100	0.76016300
O	3.59929500	1.15961200	-1.23404800
H	-4.43276200	-0.15704700	-1.35320400
H	-5.26968100	0.07337500	0.20397000

H	-4.65504700	-2.12865200	-0.01059000

S9 – Acetate-protected alcohol



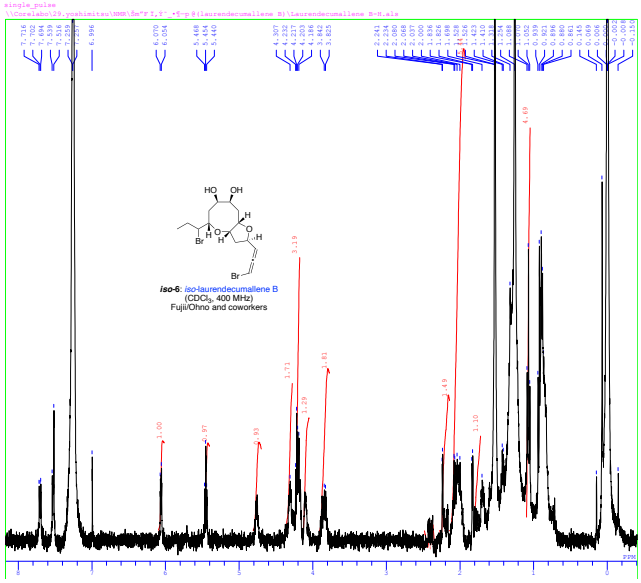
Zero-point correction= 0.369805 (Hartree/Particle)
Thermal correction to Energy= 0.392585
Thermal correction to Enthalpy= 0.393529
Thermal correction to Gibbs Free Energy= 0.314822
Sum of electronic and zero-point Energies= -1073.351401
Sum of electronic and thermal Energies= -1073.328622
Sum of electronic and thermal Enthalpies= -1073.327678
Sum of electronic and thermal Free Energies= -1073.406384

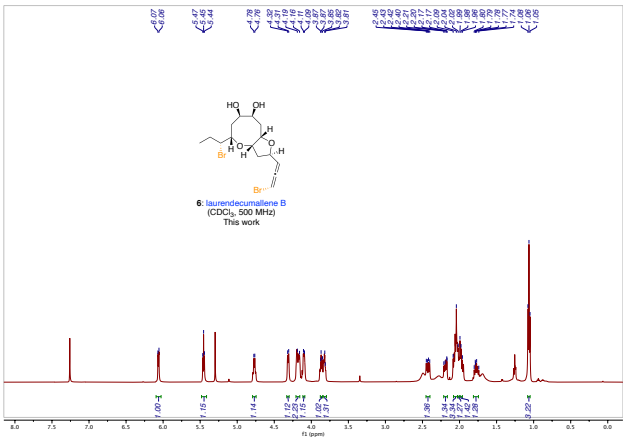
1 1

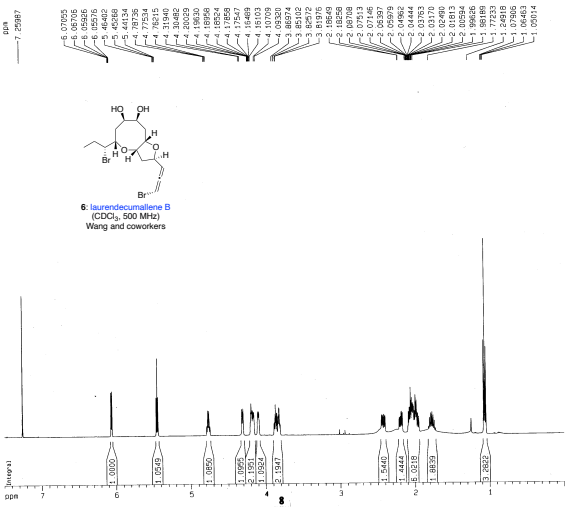
C	-2.16165300	1.10317000	-0.09337600
C	-3.11515300	-0.05470300	-0.34888600
C	-0.75359300	0.85395400	-0.59391900
H	-2.15519500	1.35797100	0.97859300
H	-2.51416900	2.00435600	-0.61926900
C	0.24765300	2.00271900	-0.34779000
O	-0.42831600	3.22299500	-0.50842000
O	-0.13063300	-0.29422300	0.18790800
H	-0.74772600	0.50509400	-1.63535900
C	0.84430000	0.25459900	1.25470800
C	0.75422700	1.76029200	1.09411100
H	1.09013900	1.89946300	-1.04992100
H	0.03152700	2.19064500	1.80100000
H	1.73428500	2.22723200	1.25902200
C	2.14789900	-0.46029700	0.91698700
H	0.43565300	-0.12456600	2.19900400
C	0.53240300	-1.45542300	-0.58141200
C	1.68404800	-1.80477500	0.34963900
C	-0.48965600	-2.53265700	-0.84180100
H	2.49349800	-2.31593500	-0.18765900
H	1.34147600	-2.46381200	1.16319300
H	2.78288400	-0.56935600	1.80568800

O	2.80545000	0.32343000	-0.08828600
O	-4.40884900	0.37080200	0.08435300
C	4.15027600	0.18326000	-0.32917400
H	0.20928500	3.91125500	-0.74779000
H	-0.90969000	-2.92519100	0.09597400
H	0.01645400	-3.36043800	-1.36466500
H	-1.30804800	-2.18726100	-1.48840500
H	0.90207000	-0.98930200	-1.50601600
O	4.68481200	-0.77589900	0.43501800
C	6.11630100	-0.96078400	0.26722600
H	6.64682700	-0.03977000	0.54404300
H	6.34072600	-1.21700000	-0.77681000
H	6.38024800	-1.78291600	0.94113500
O	4.69992500	0.86874800	-1.14075400
H	-3.15079200	-0.31665500	-1.42172600
H	-2.82265700	-0.96289100	0.20018700
C	-5.36380600	-0.61406300	0.08319200
C	-6.69564300	-0.07414000	0.52331800
H	-6.59910800	0.43468600	1.49415900
H	-7.41849600	-0.89488800	0.59193200
H	-7.04940200	0.67427900	-0.20320500
O	-5.11181400	-1.74859200	-0.24357500

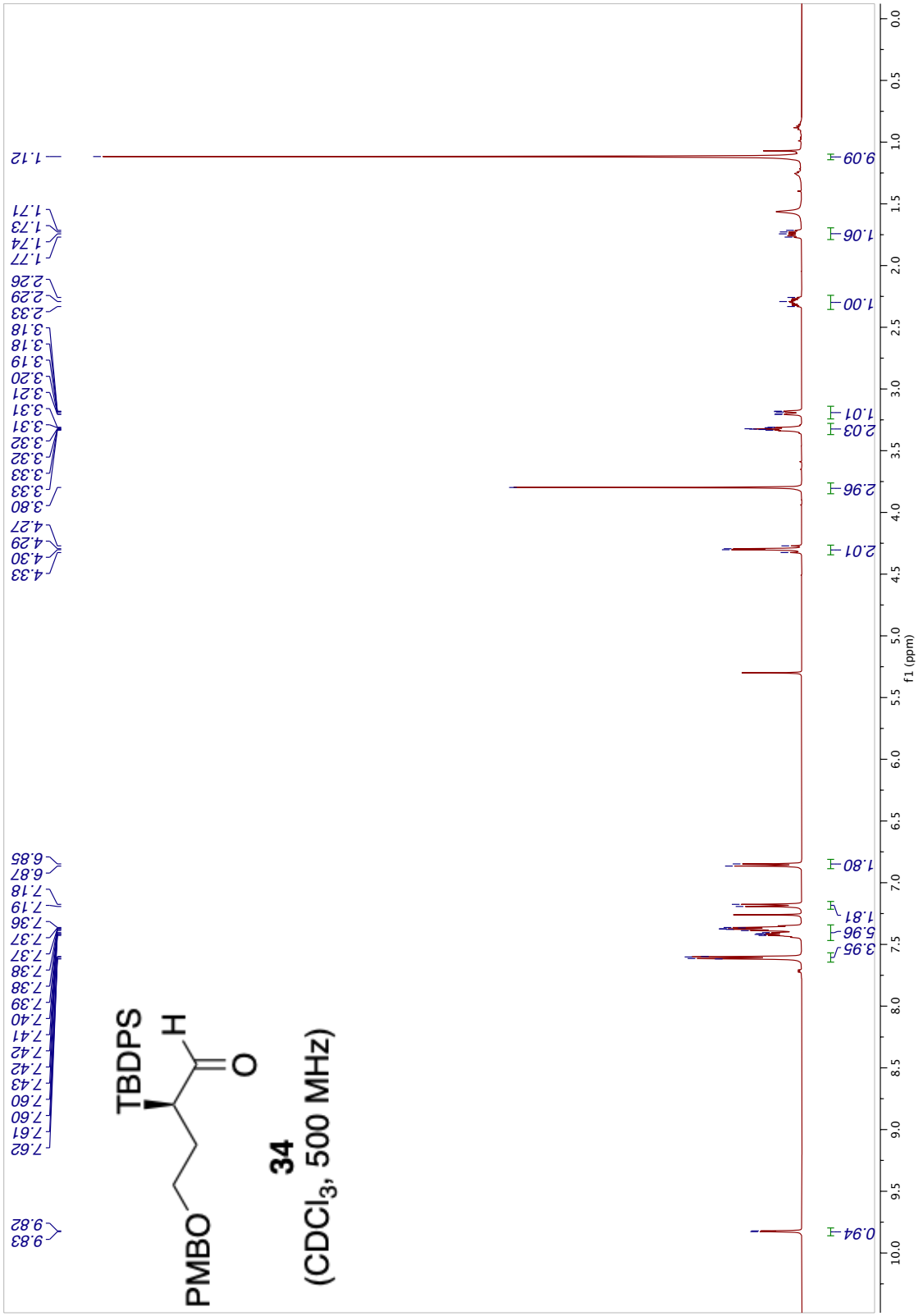
1.7 Physical NMR Comparison

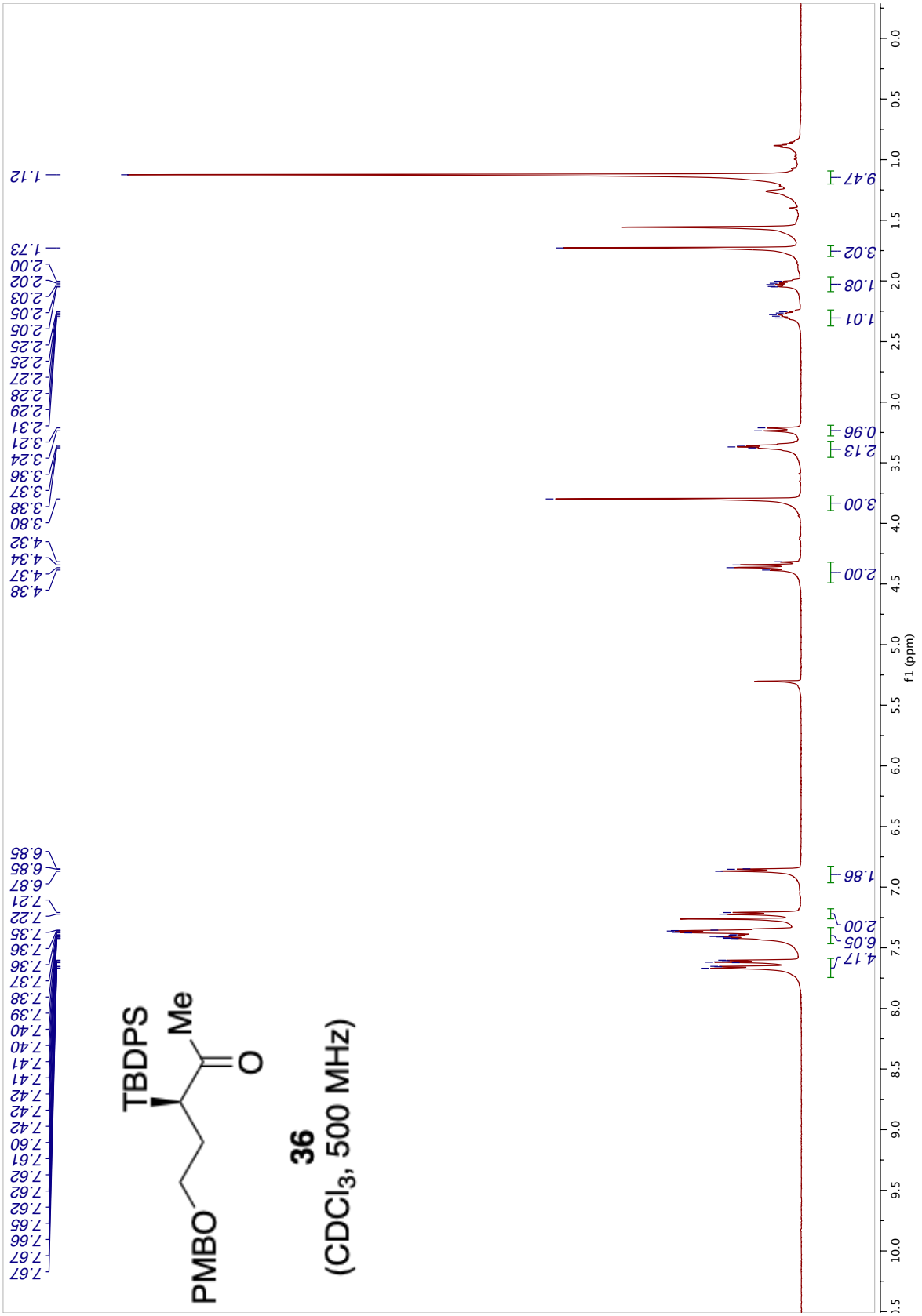


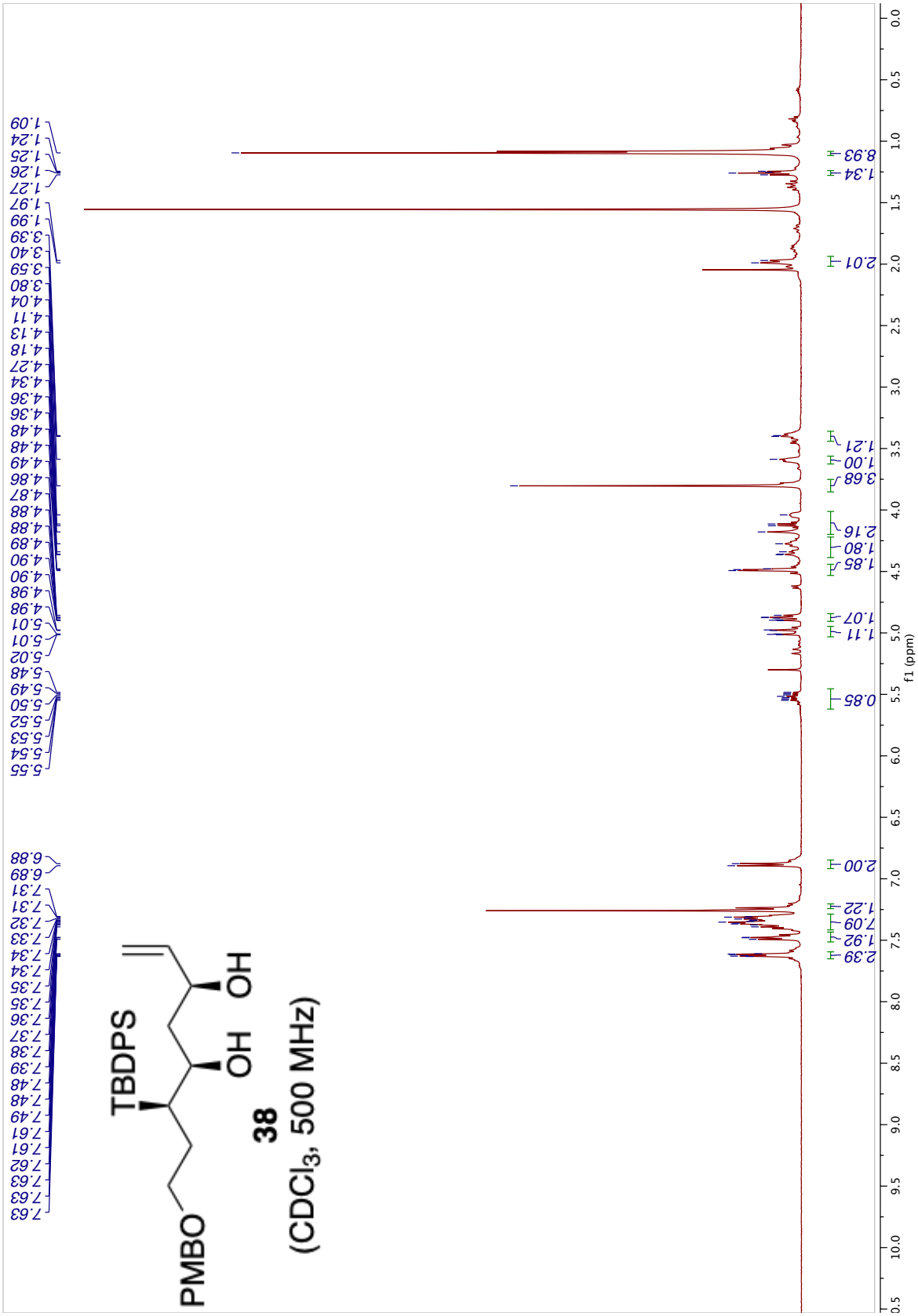


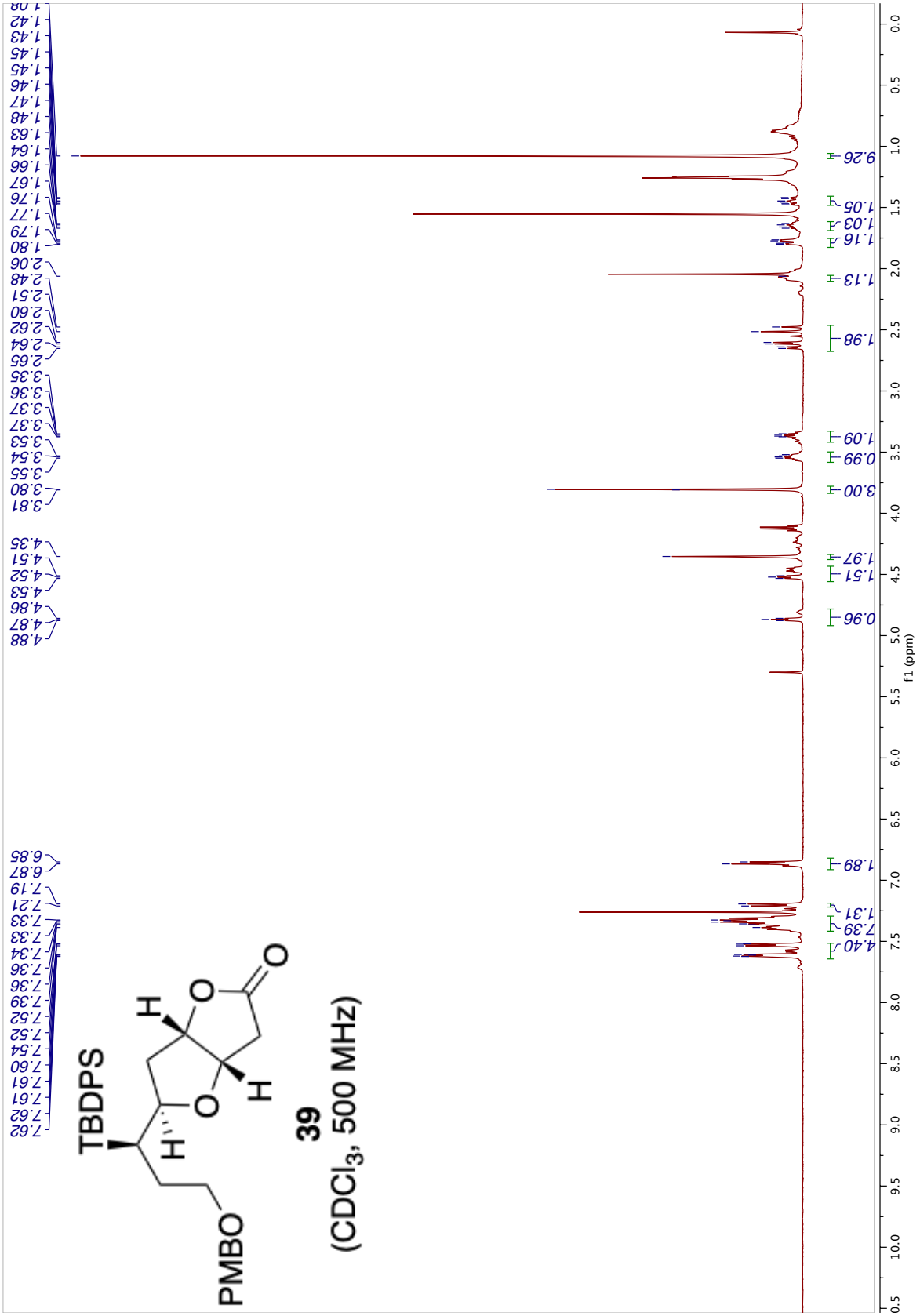


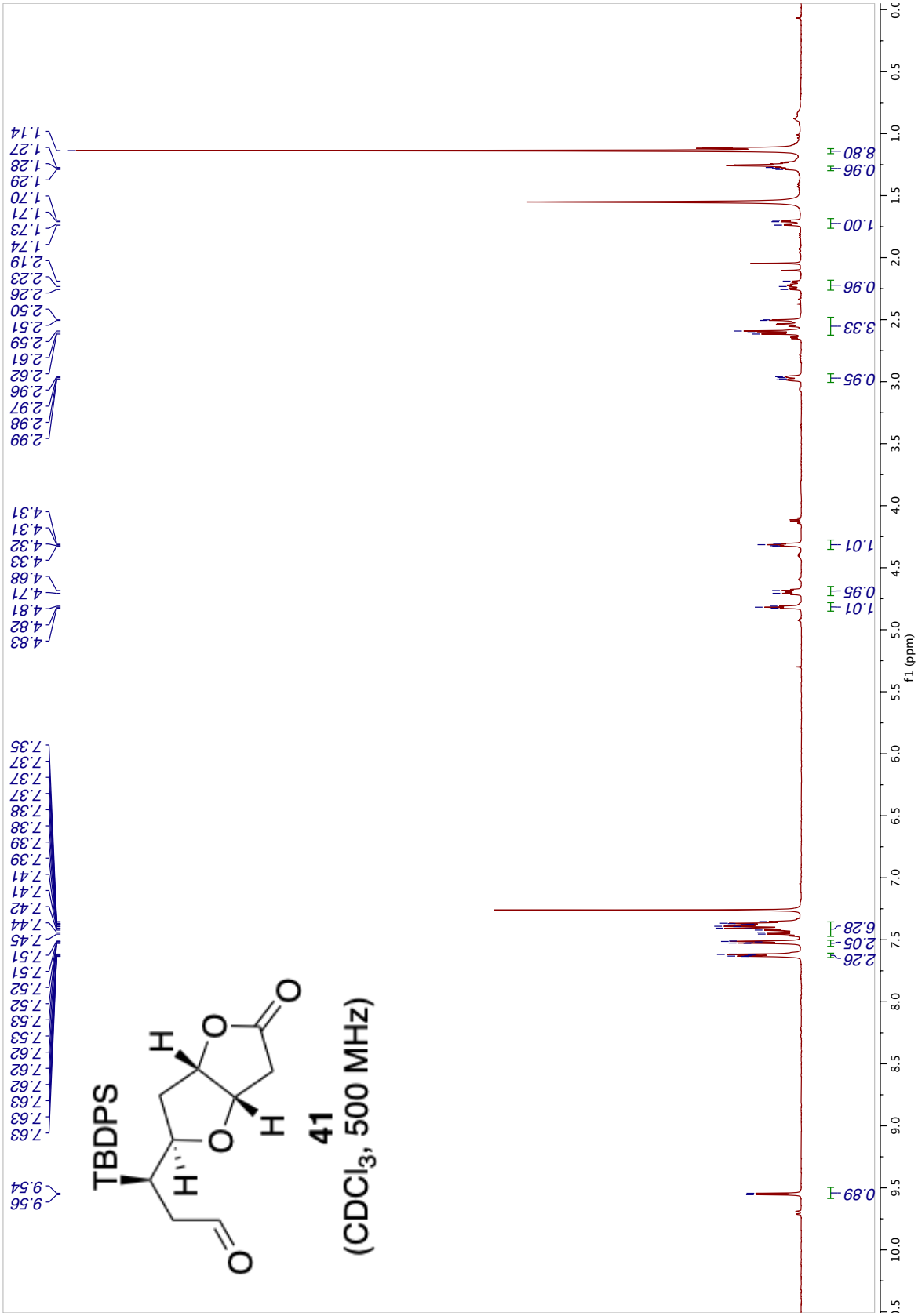
1.8 NMR Spectra of Selected Intermediates

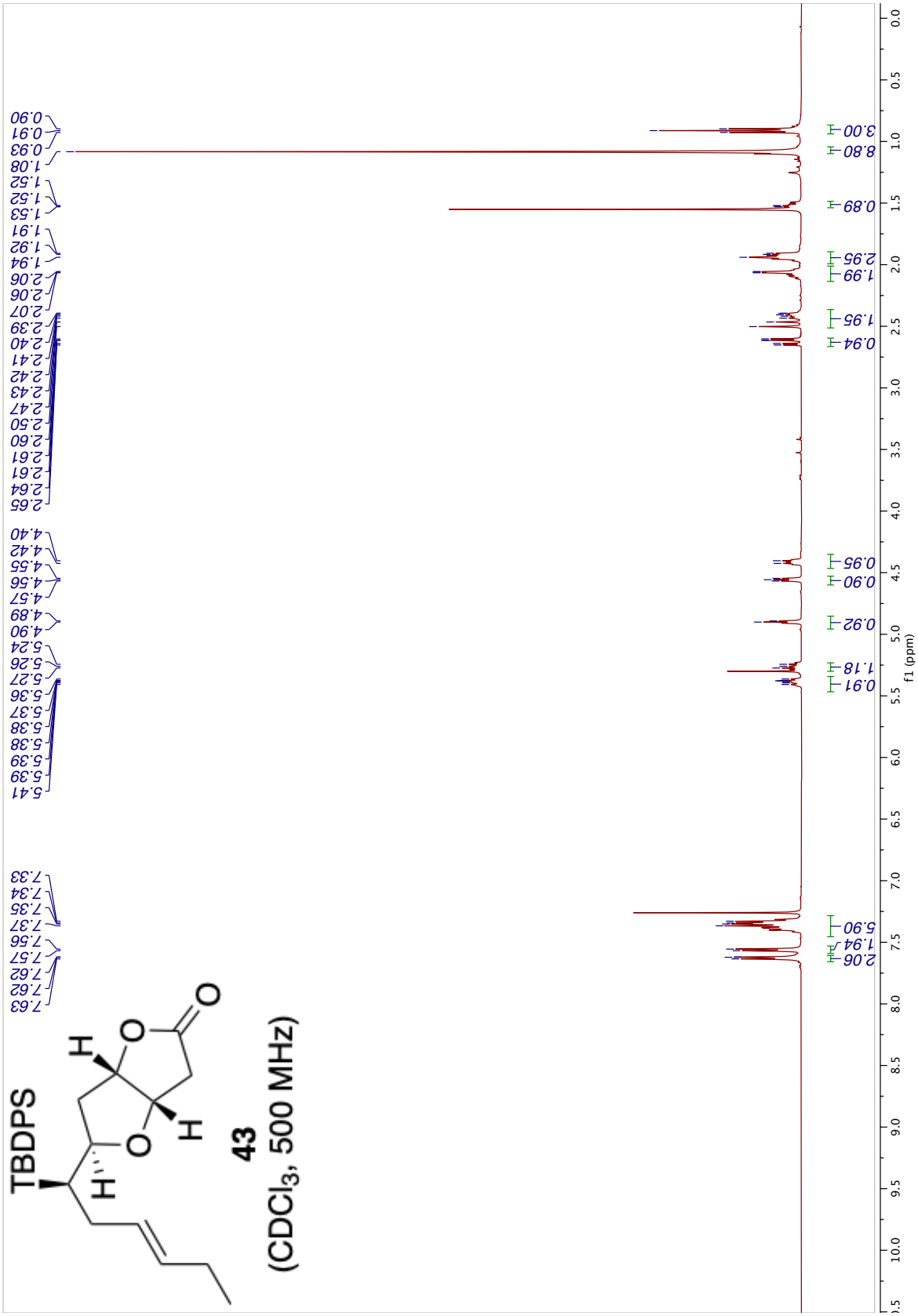


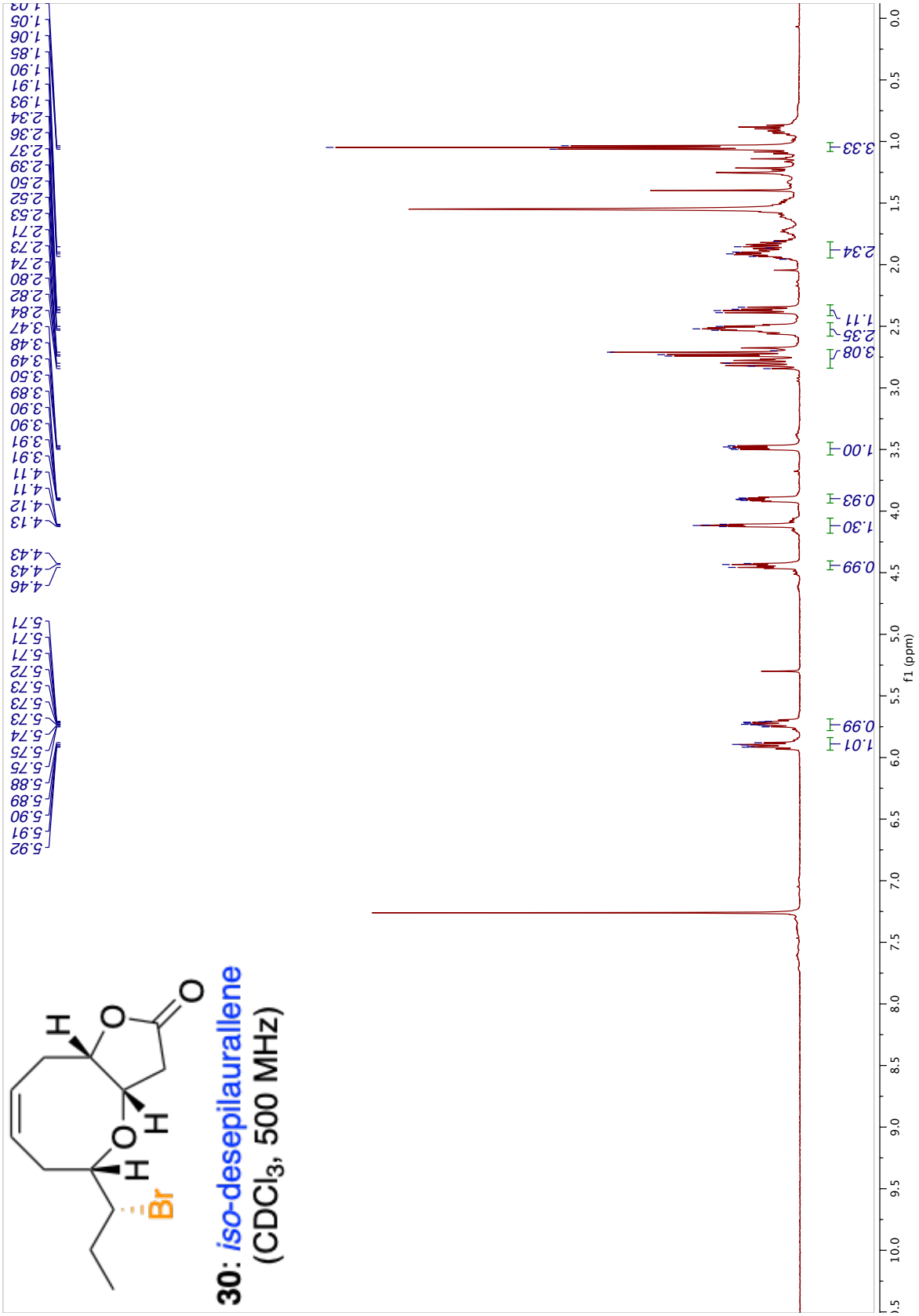

TBDPS
Me
O
PMBO
36
(CDCl3, 500 MHz)
f1 (ppm)

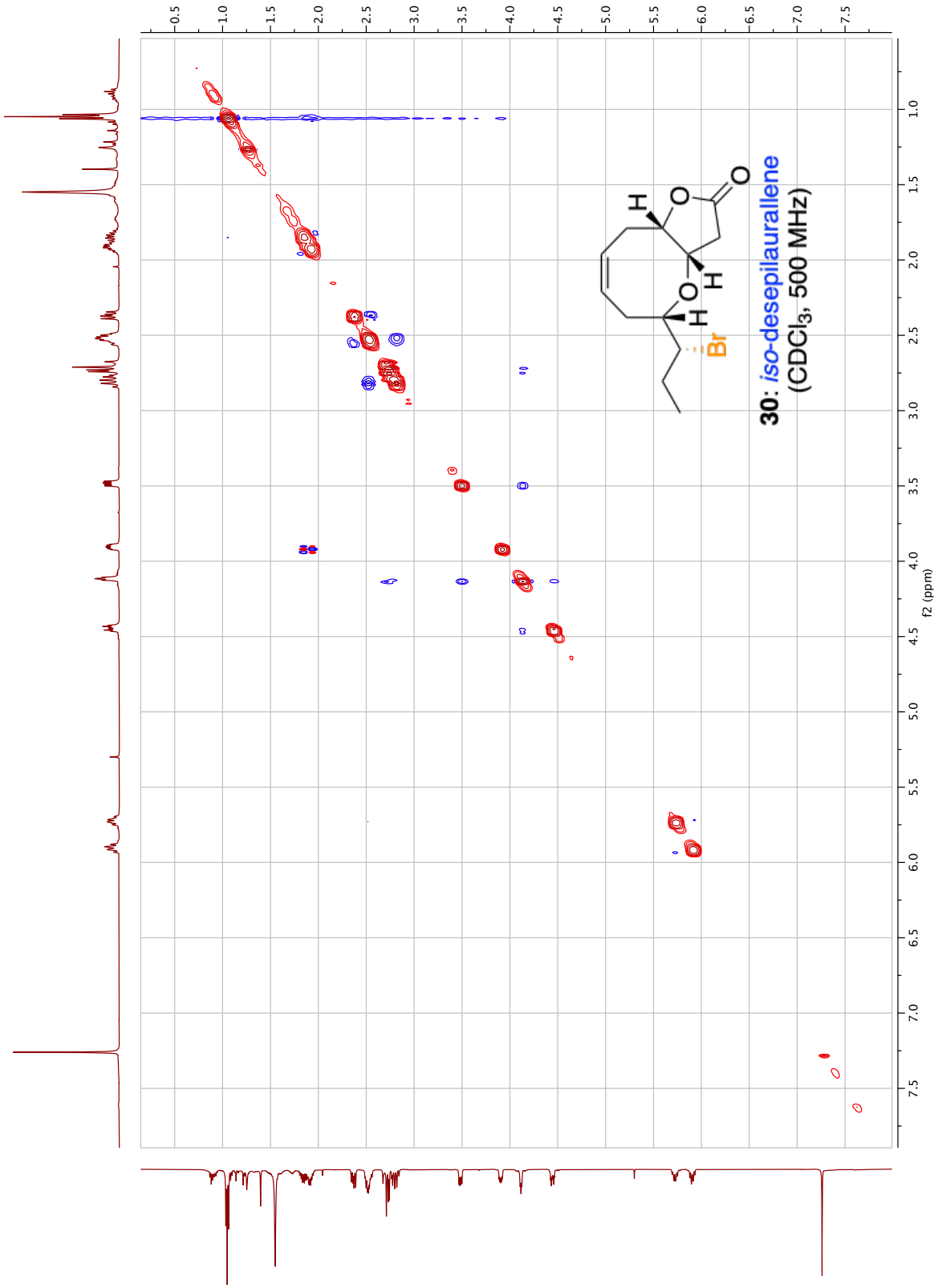

PMBO
TBDPS
OH
OH
38
(CDCl3, 500 MHz)
f1 (ppm)

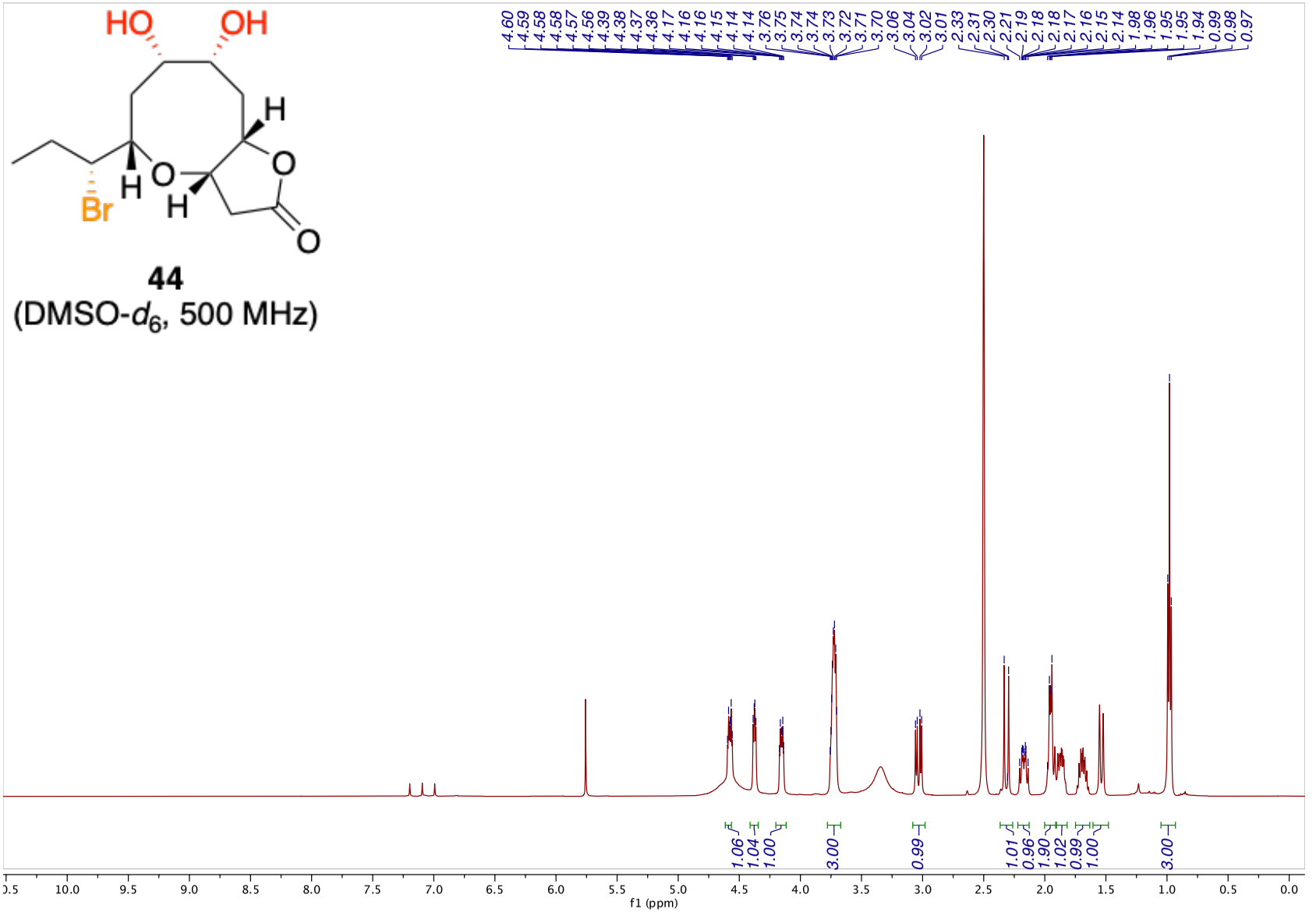

TBDPS
PMBO
H
H
H
O
O
O
39
(CDCl3, 500 MHz)
f1 (ppm)

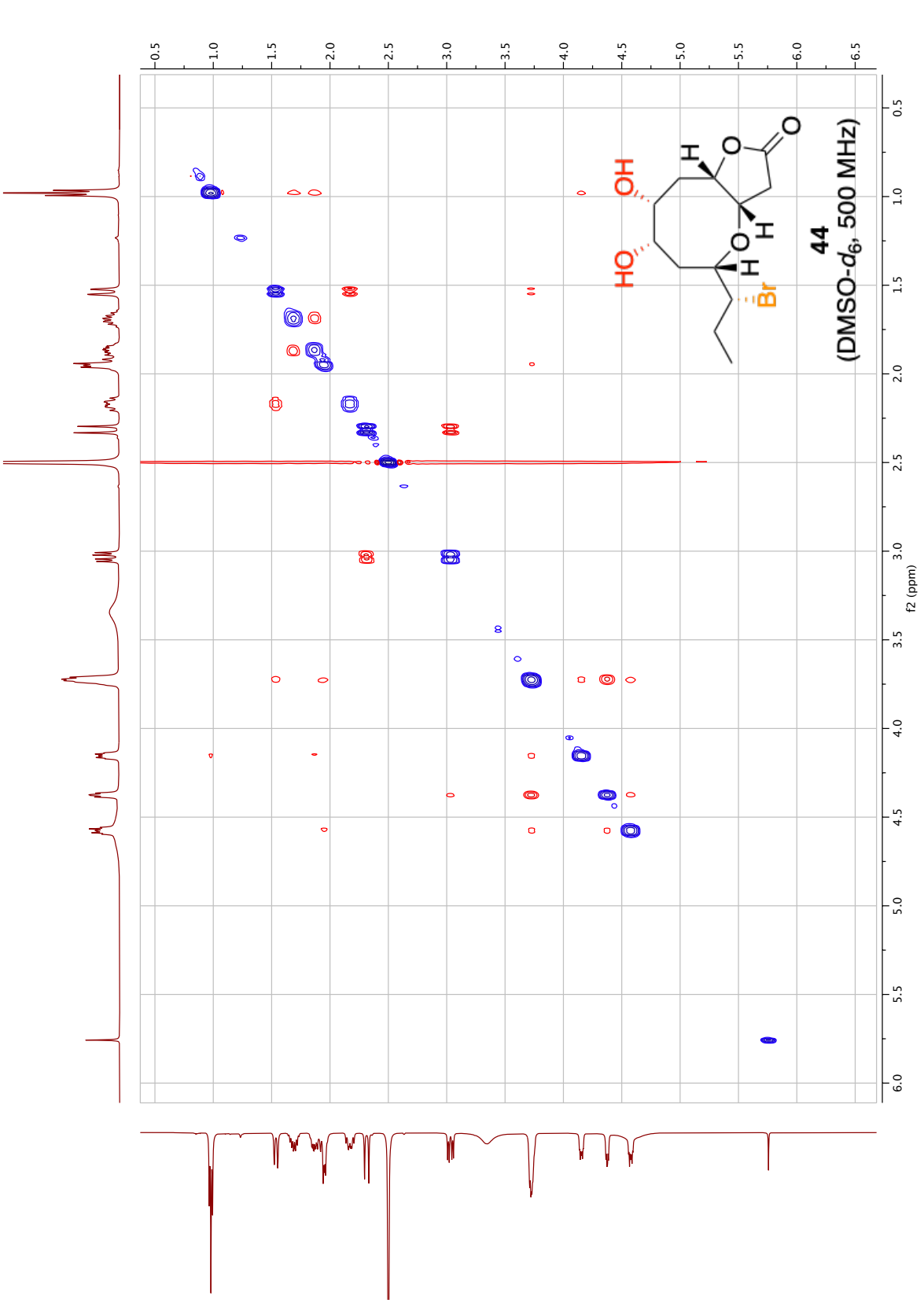

TBDPS
41
(CDCl3, 500 MHz)
f1 (ppm)

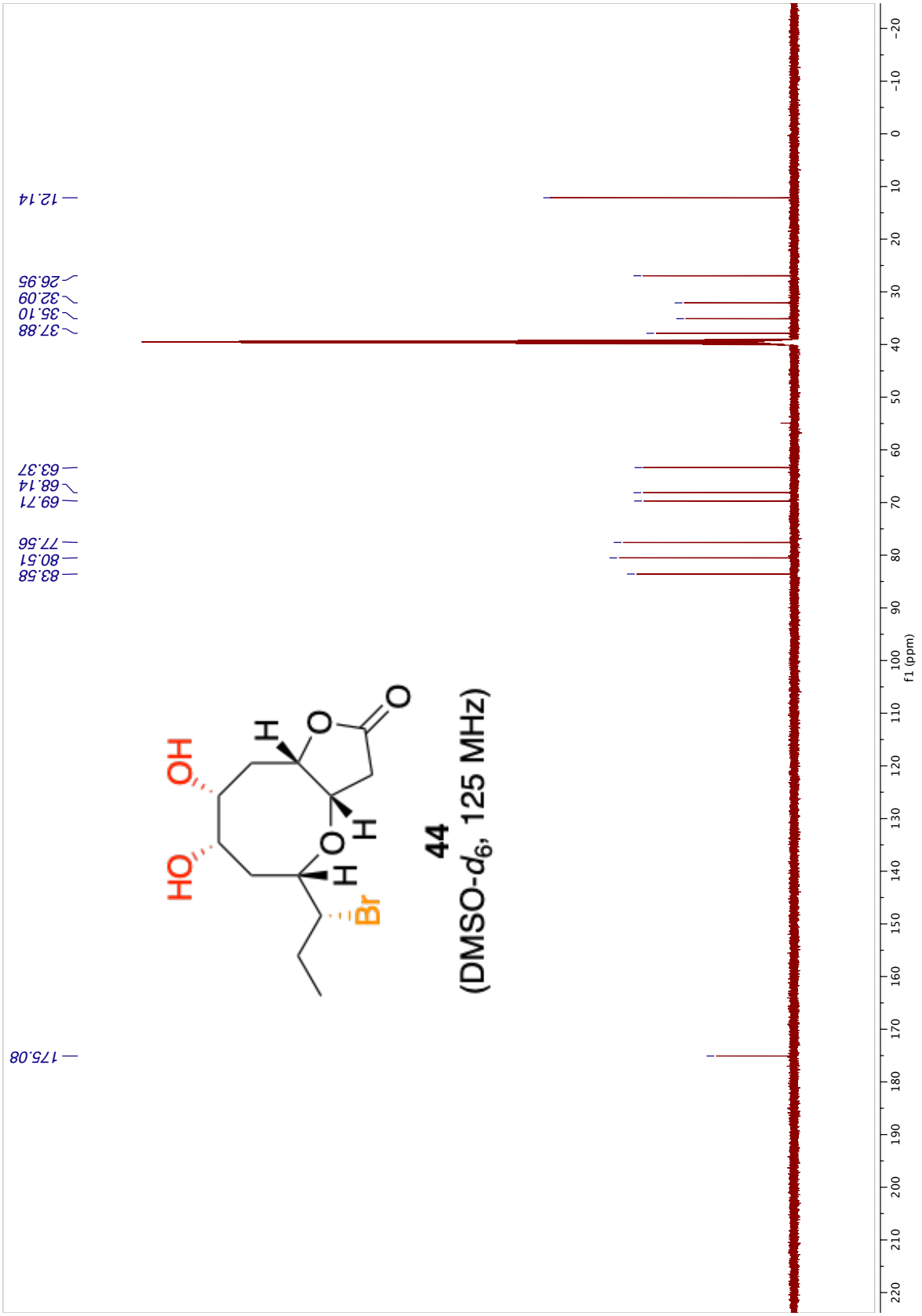

TBDPS
43
(CDCl3, 500 MHz)
f1 (ppm)

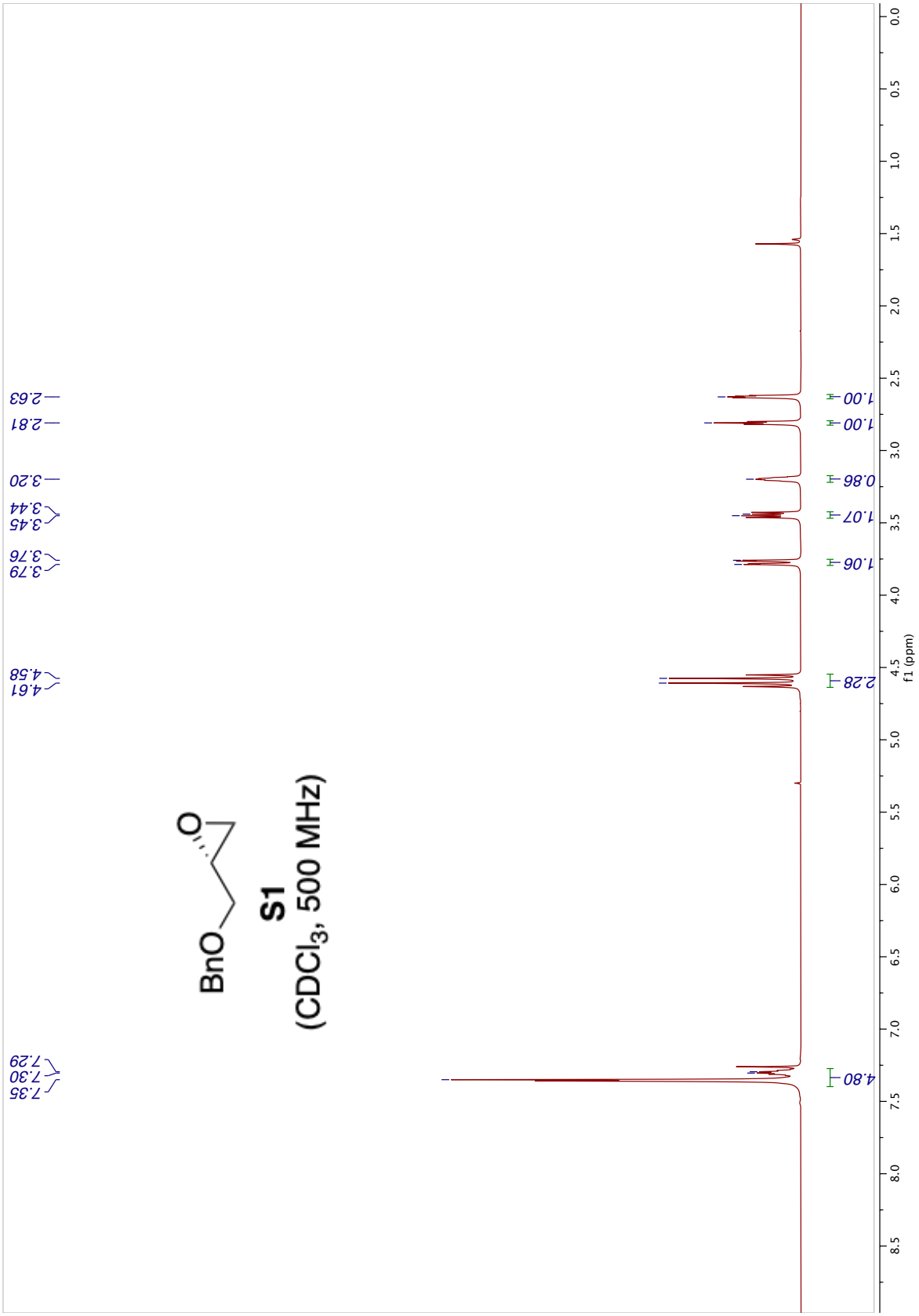

30: iso-desepilaurallene
(CDCl3, 500 MHz)
Br
O
H
f1 (ppm)

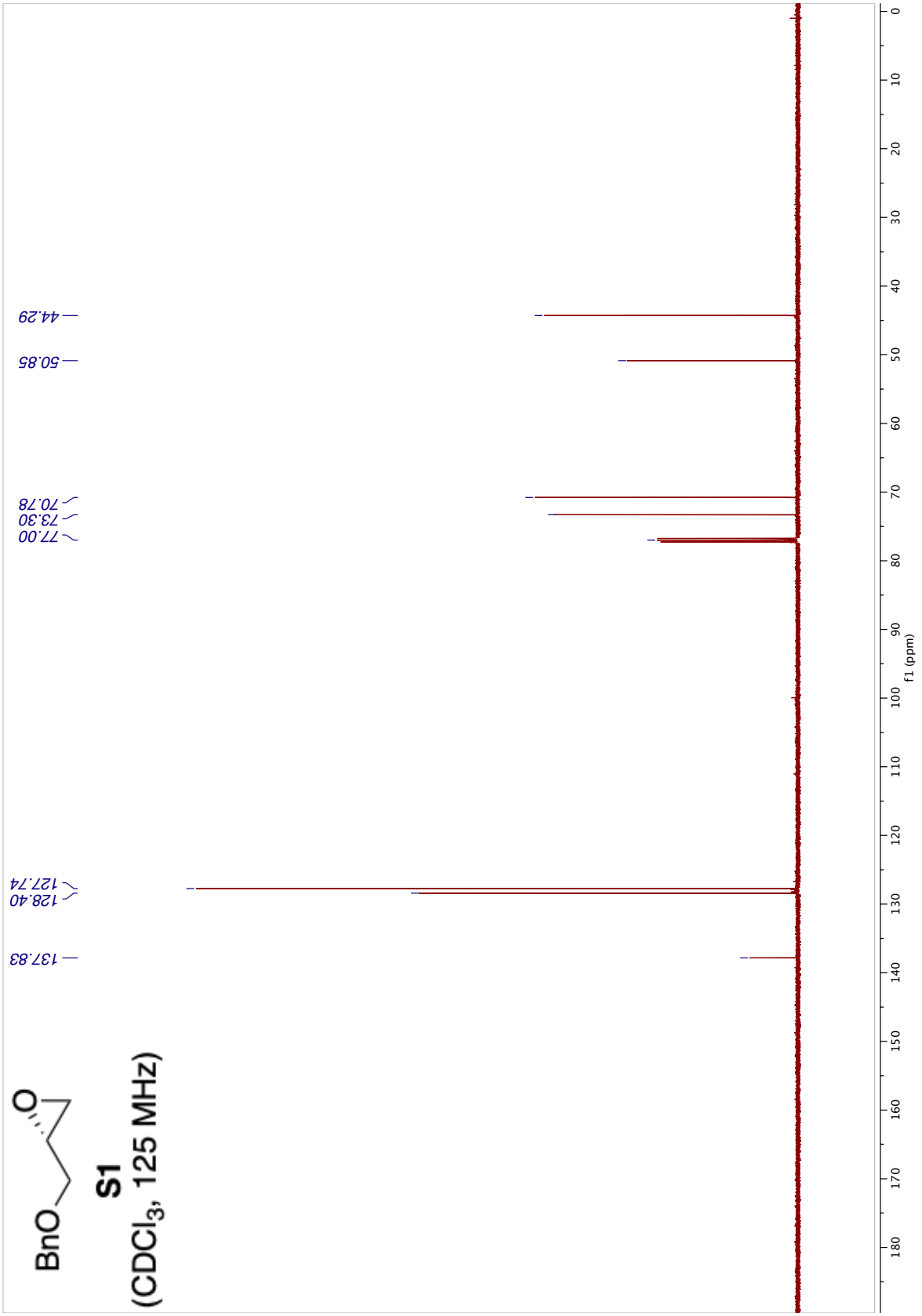

f1 (ppm)
f2 (ppm)
30: iso-desepilaurallene
(CDCl3, 500 MHz)
Br
O
O
H
H
O
H

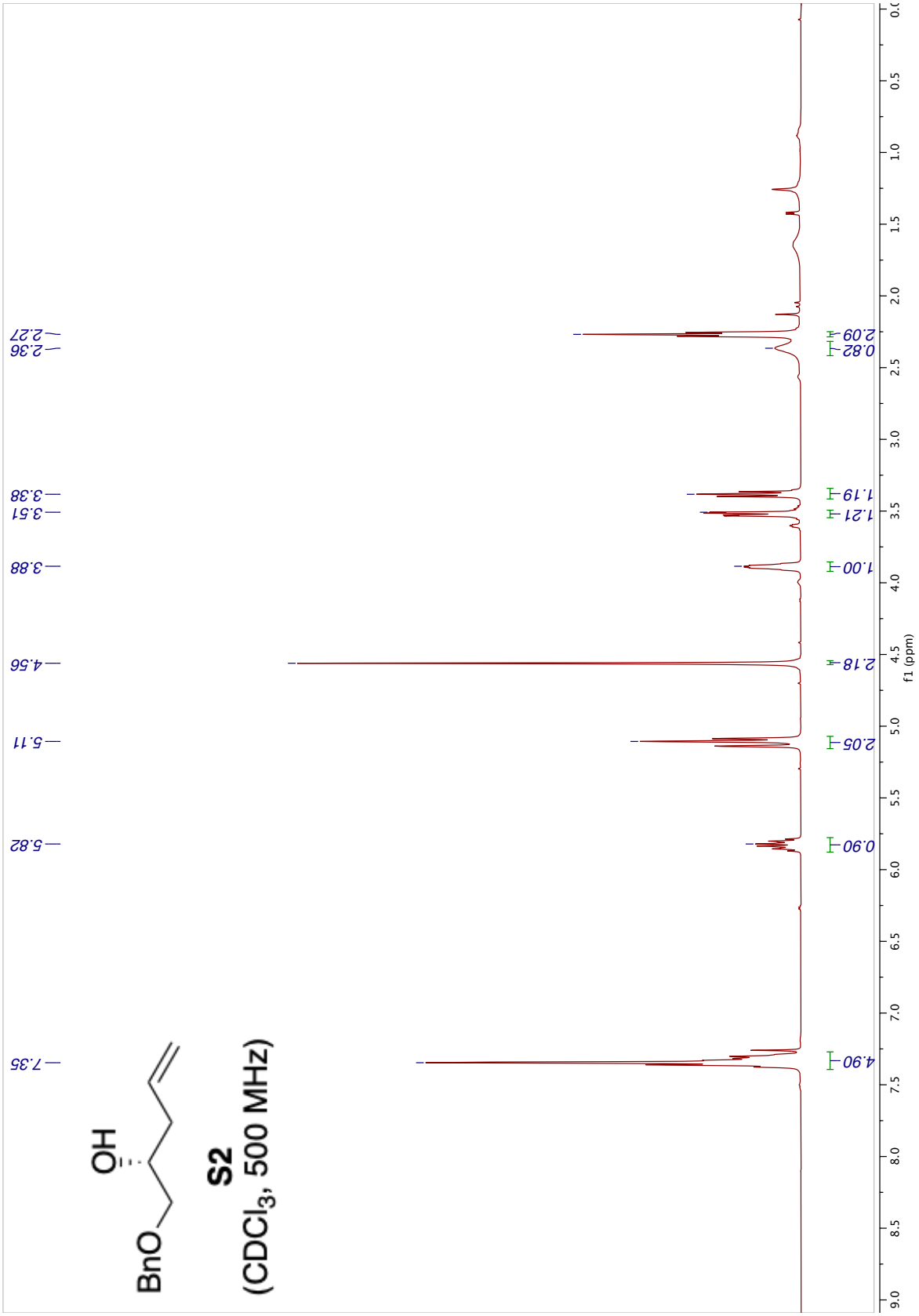

HO
OH
H
O
O
H
O
H
Br
O
44
(DMSO-d_6, 500 MHz)
4.60 4.59 4.58 4.58 4.57 4.56 4.39 4.38 4.37 4.36 4.17 4.16 4.16 4.15 4.14 4.14 3.76 3.75 3.74 3.74 3.73 3.72 3.71 3.70 3.06 3.04 3.02 3.01 2.33 2.31 2.30 2.21 2.19 2.18 2.18 2.17 2.16 2.15 2.14 1.98 1.96 1.95 1.95 1.94 0.99 0.98 0.97
1.06 1.04 1.00 3.00 0.99 1.01 0.96 1.90 1.02 0.99 1.00 3.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

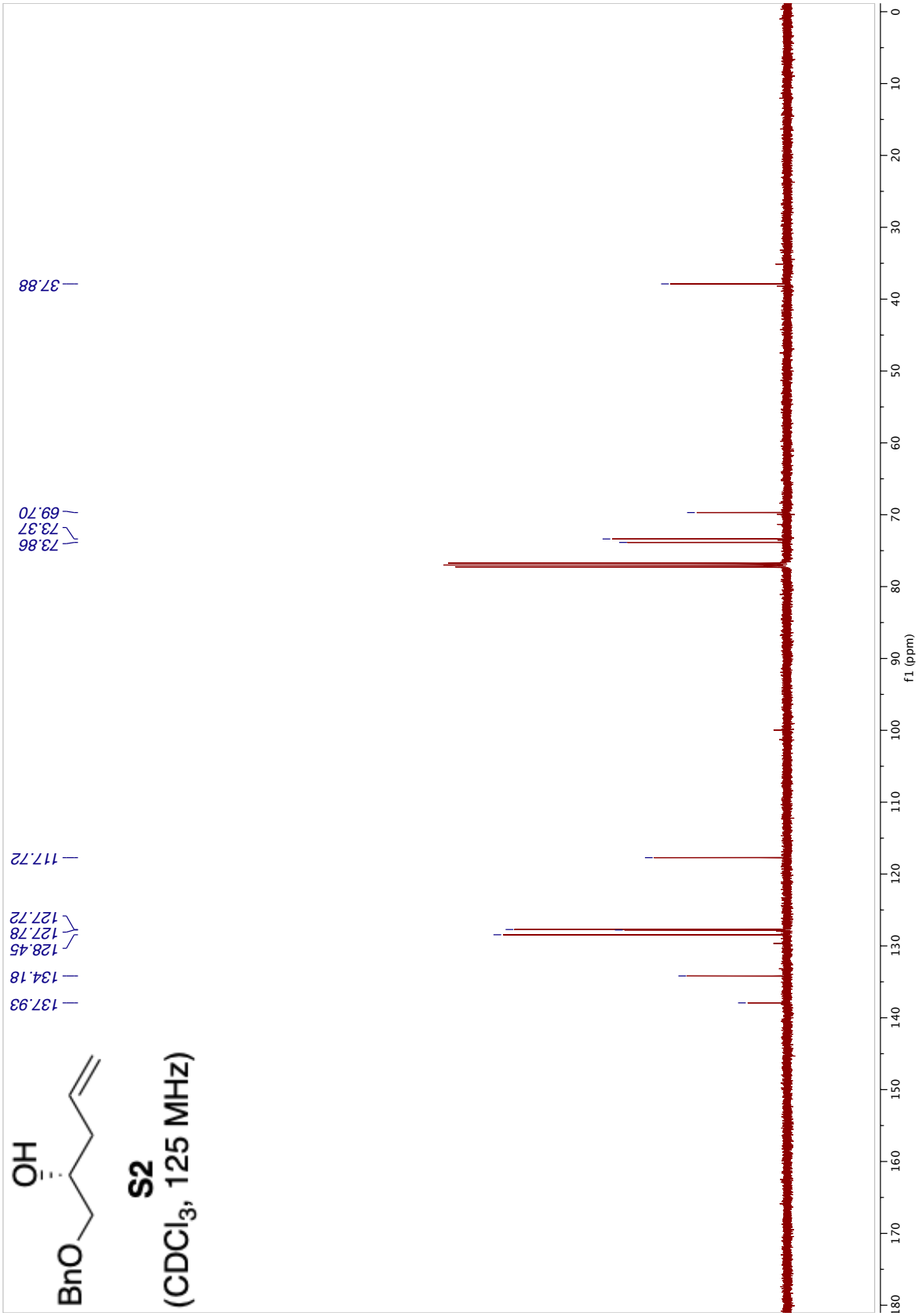

f1 (ppm)
f2 (ppm)
44
(DMSO-d_6, 500 MHz)
OH
HO
Br
O
H

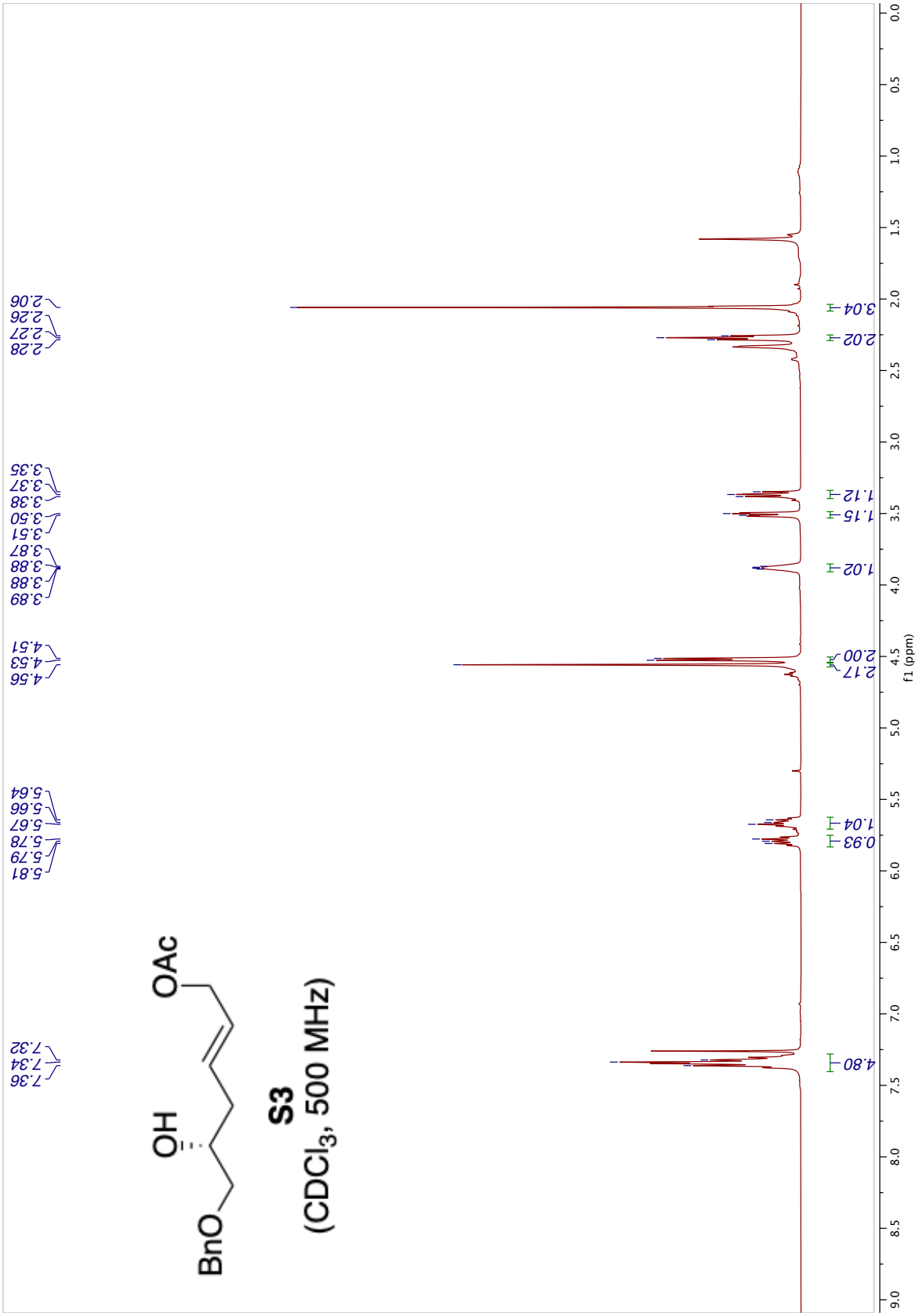

175.08
83.58
80.51
77.56
69.71
68.14
63.37
37.88
36.10
32.09
26.95
12.14
f1 (ppm)
OH
HO
Br
O
H
44
(DMSO-d_6, 125 MHz)

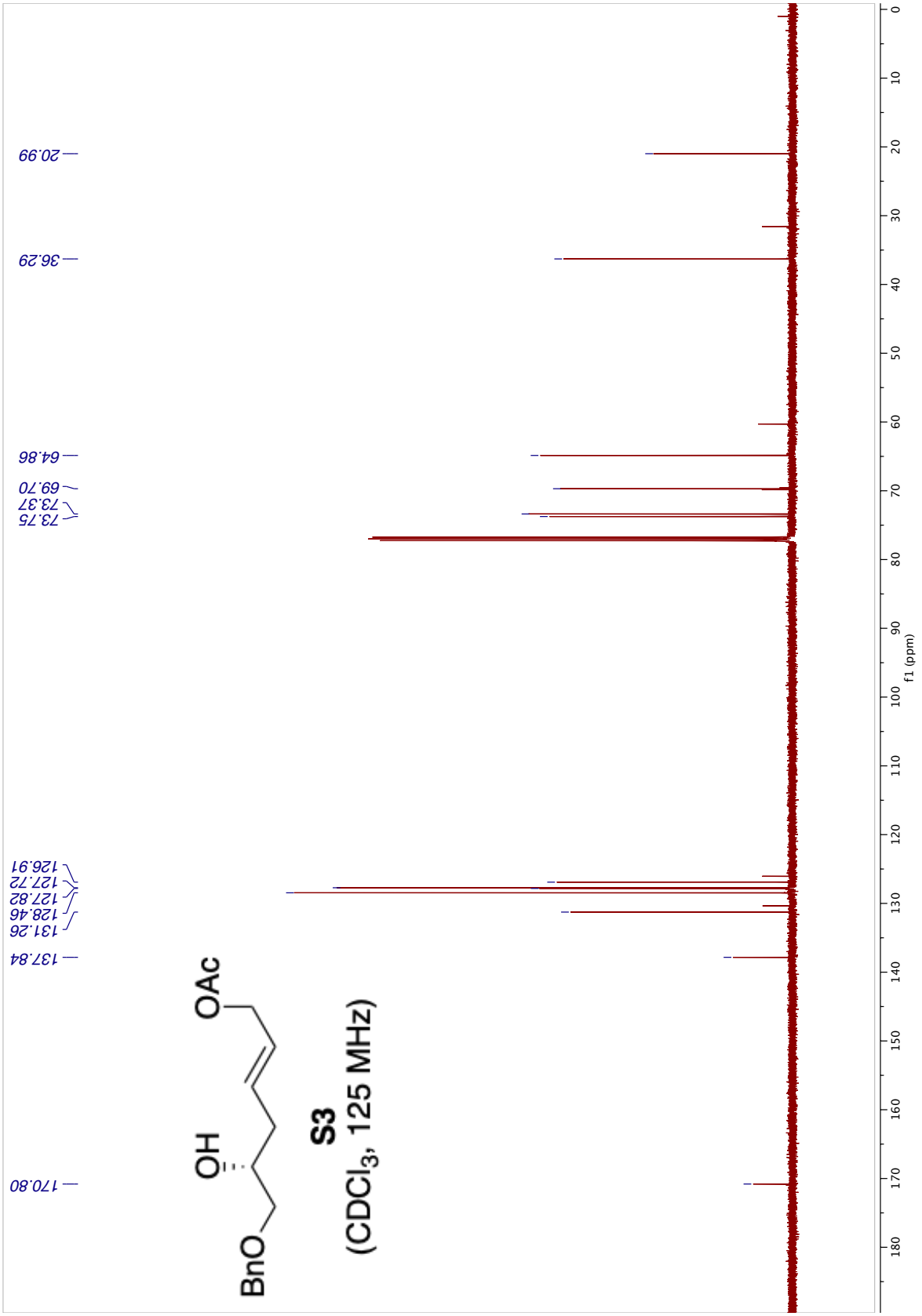

BnO
O
S1
(CDCl3, 500 MHz)
7.35
7.30
7.29
4.61
4.58
3.79
3.76
3.45
3.44
3.20
2.81
2.63
4.80
2.28
1.06
1.07
0.86
1.00
1.00
f1 (ppm)

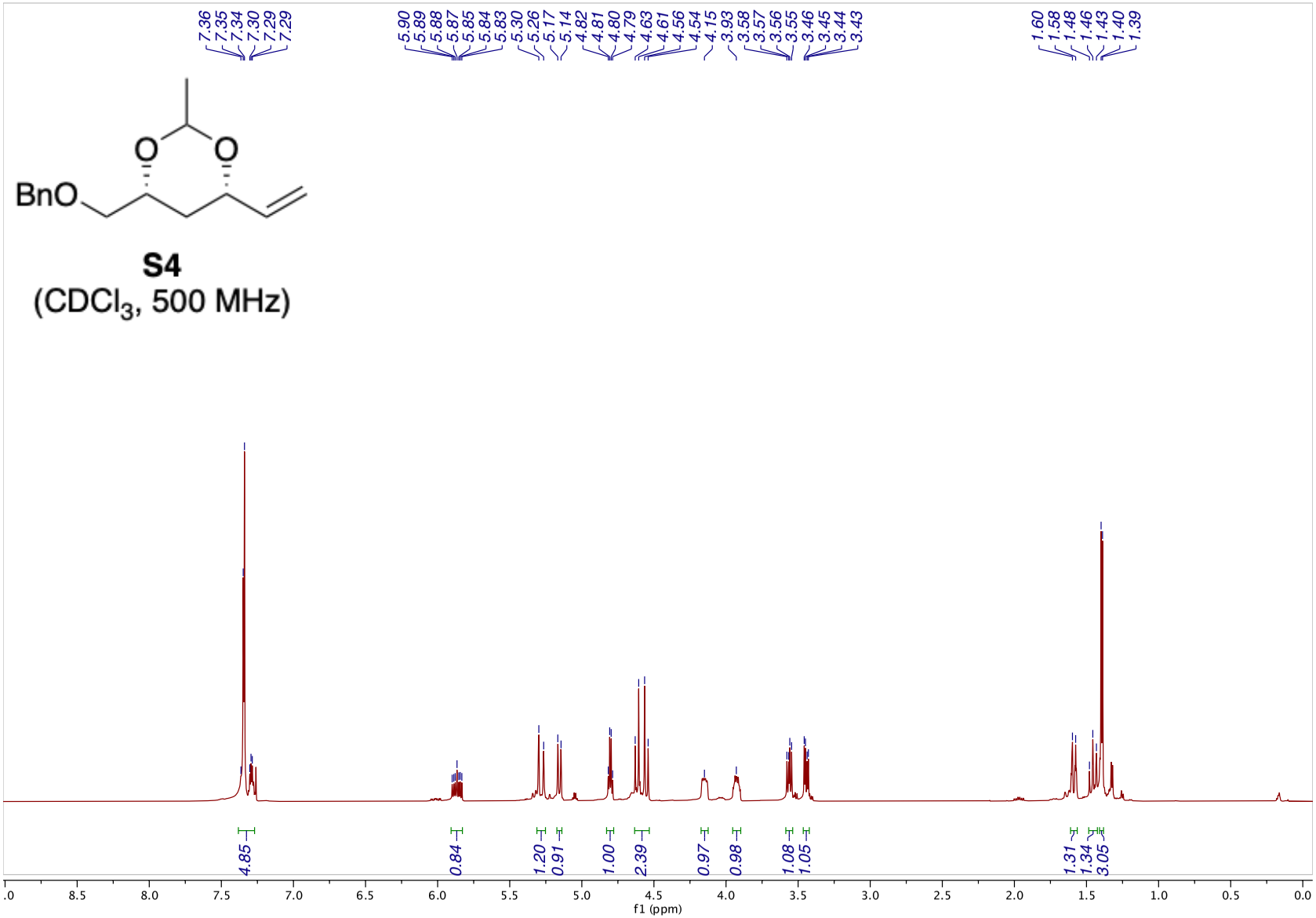

BnO
O
S1
(CDCl3, 125 MHz)
137.83
128.40
127.74
77.00
73.30
70.78
50.85
44.29
f1 (ppm)

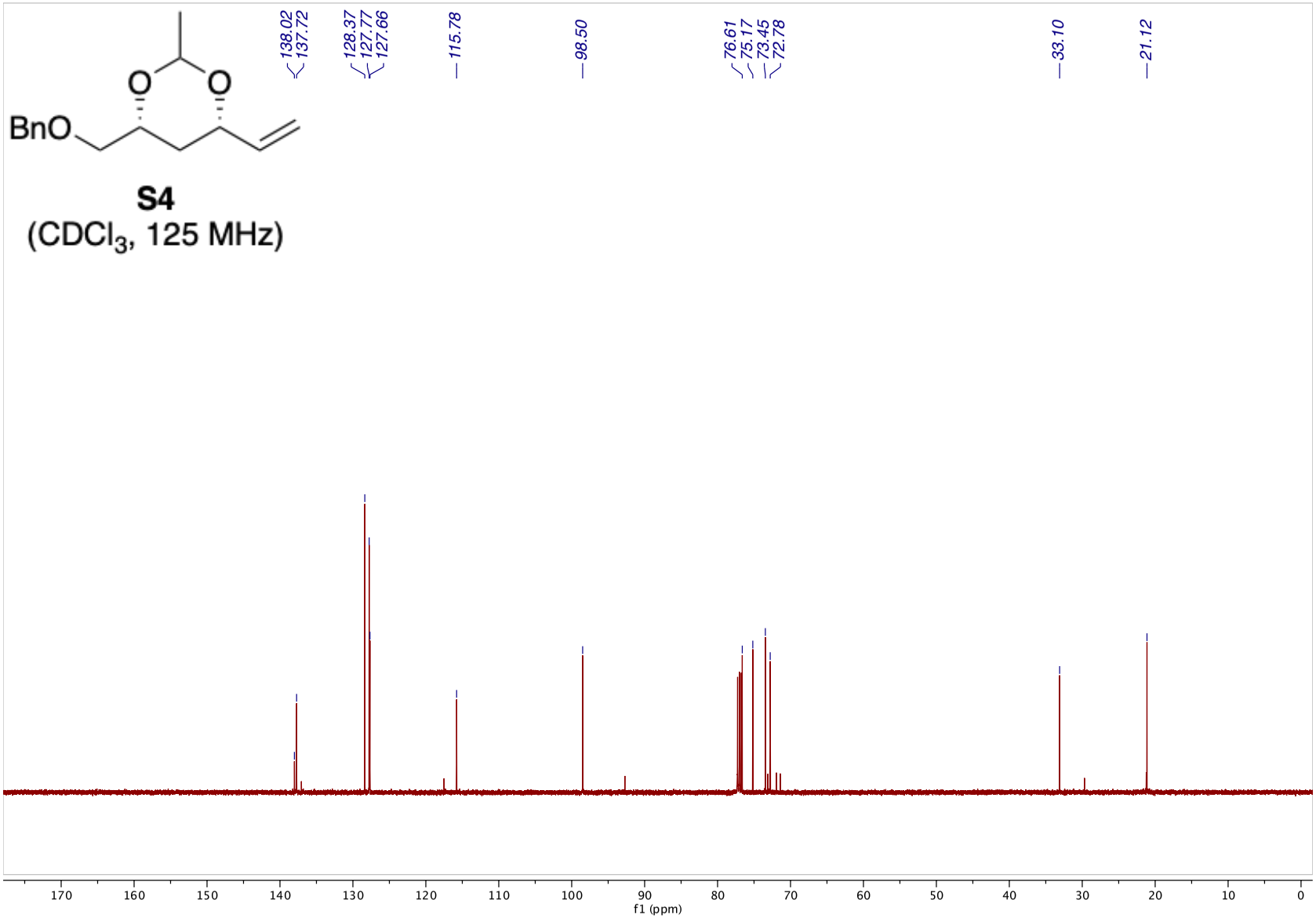

BnO
OH
S2
(CDCl3, 500 MHz)
7.35
5.82
5.11
4.56
3.88
3.51
3.38
2.36
2.27
4.90
0.90
2.05
2.18
1.00
1.21
1.19
0.82
2.09
f1 (ppm)

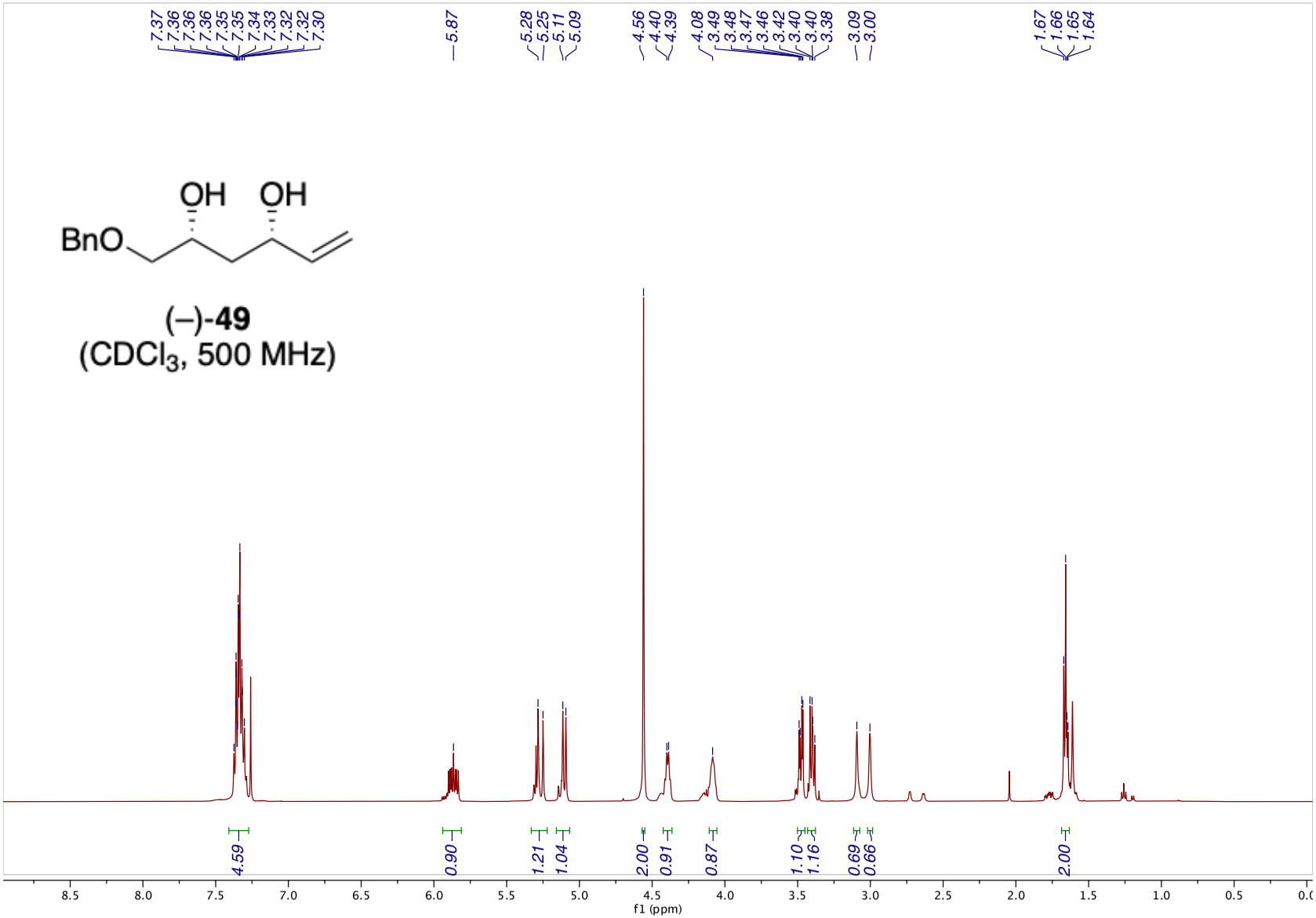

OH
BnO
S2
(CDCl3, 125 MHz)
137.93
134.18
128.45
127.78
127.72
117.72
73.86
73.37
69.70
37.88
f1 (ppm)

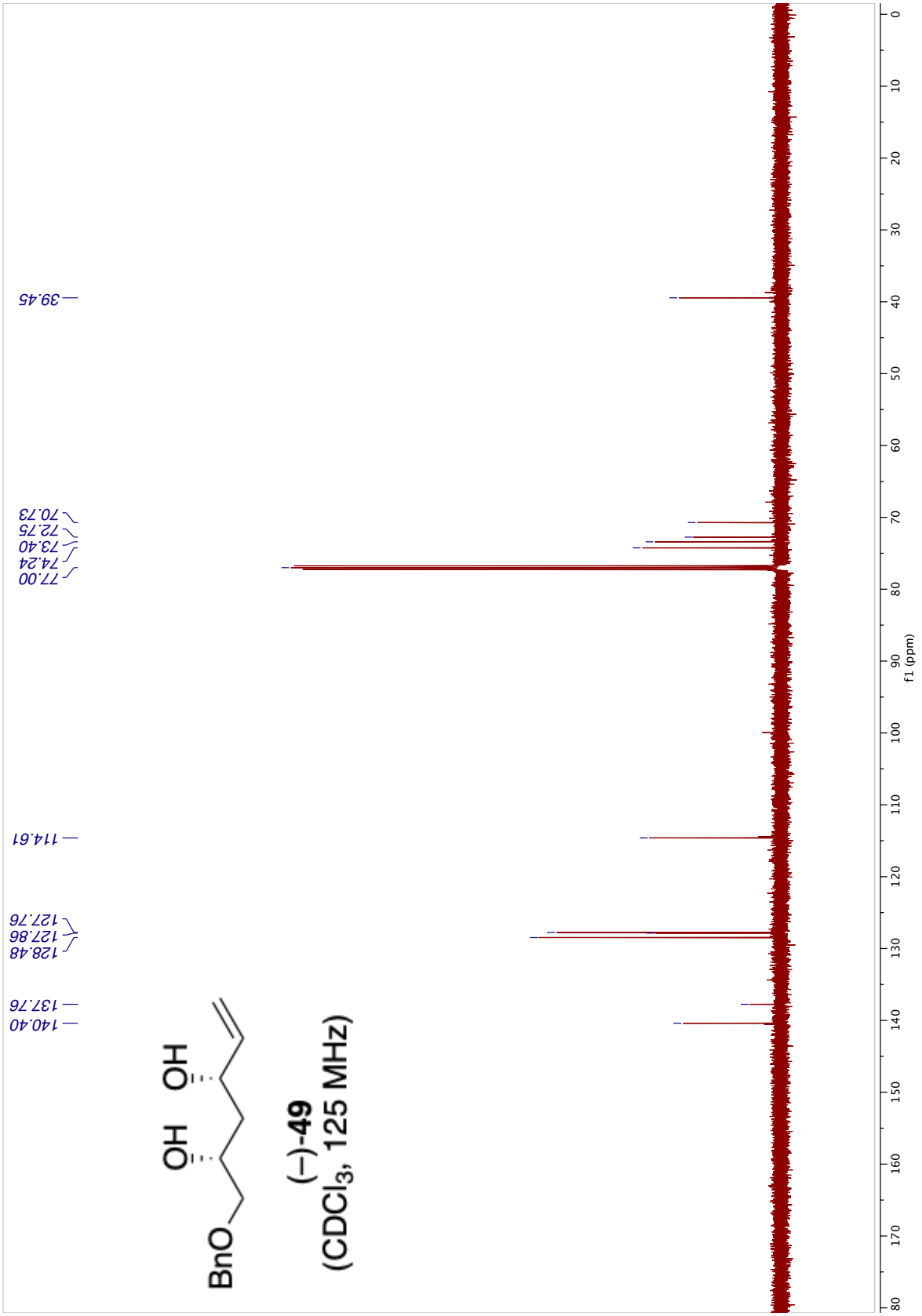

S3
(CDCl3, 500 MHz)
BnO
OH
OAc
7.36
7.34
7.32
5.81
5.79
5.78
5.67
5.66
5.64
4.56
4.53
4.51
3.89
3.88
3.88
3.87
3.51
3.50
3.38
3.37
3.35
2.28
2.27
2.26
2.06
4.80
0.93
1.04
2.17
2.00
1.02
1.15
1.12
3.04
2.02
f1 (ppm)

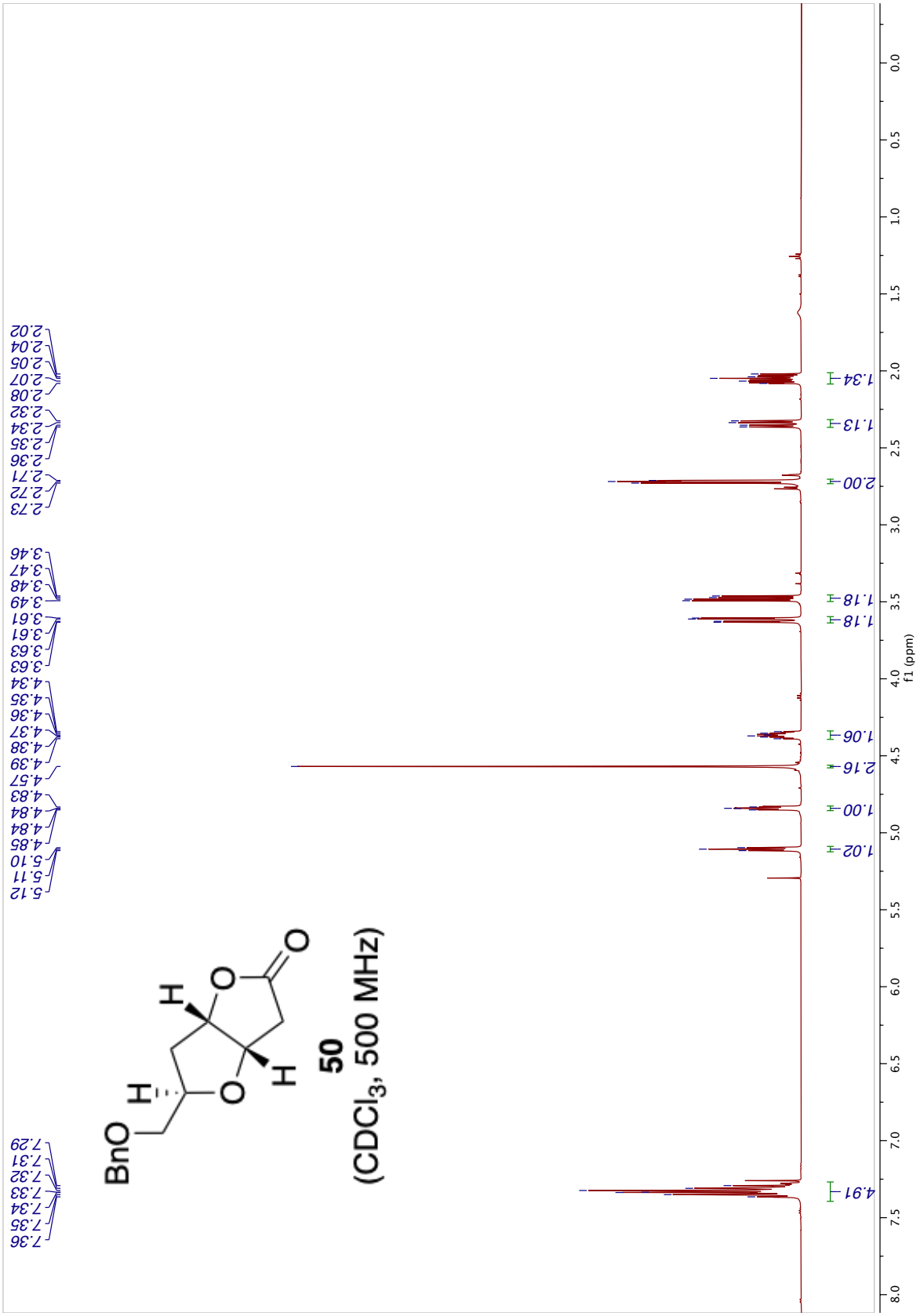

BnO
OH
OAc
S3
(CDCl3, 125 MHz)
170.80
137.84
131.26
128.46
127.82
127.72
126.91
73.75
73.37
69.70
64.86
36.29
20.99
f1 (ppm)

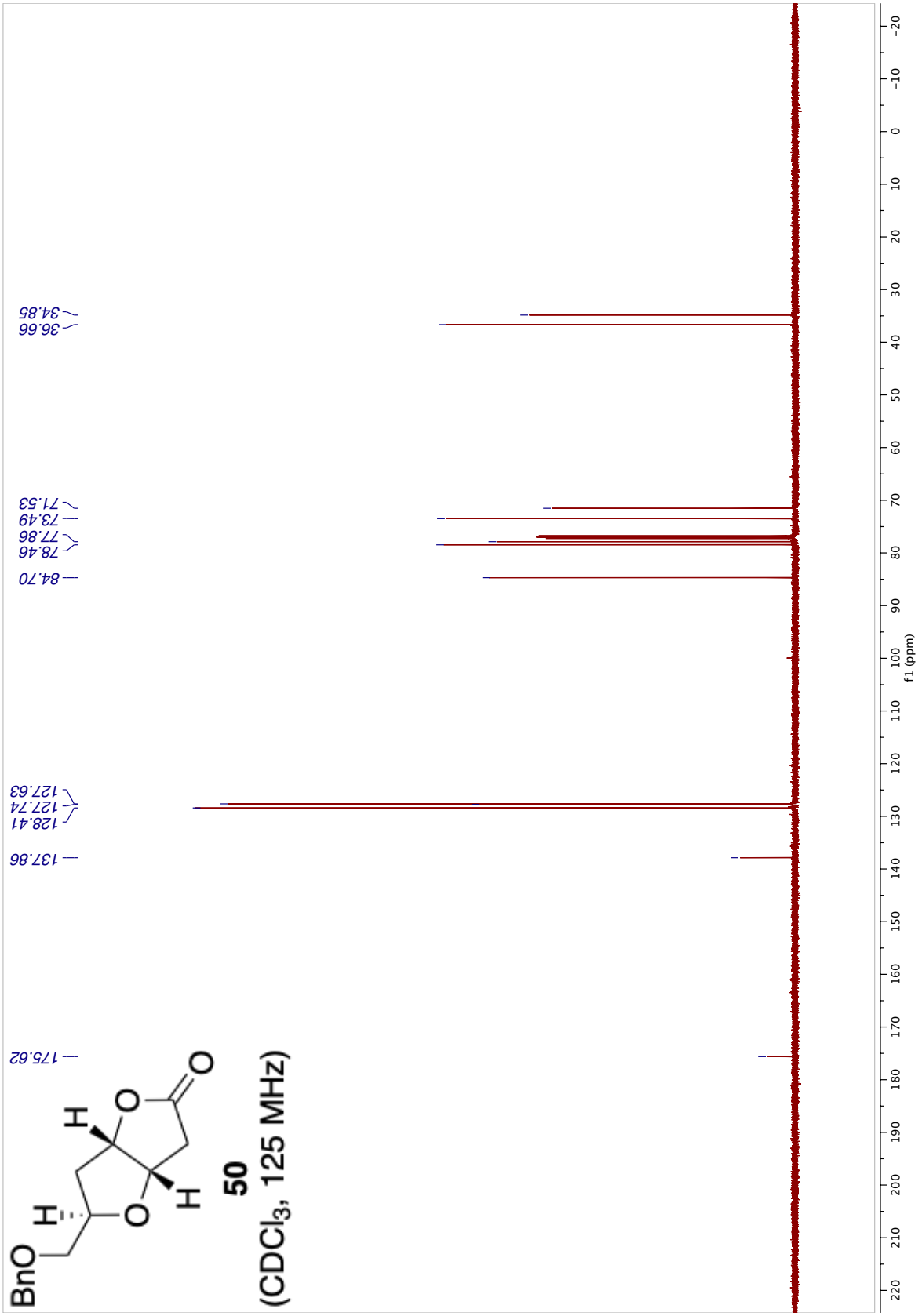

7.36
7.35
7.34
7.30
7.29
7.29
5.90
5.89
5.88
5.87
5.85
5.84
5.83
5.30
5.26
5.17
5.14
4.82
4.81
4.80
4.79
4.63
4.61
4.56
4.54
4.15
3.93
3.58
3.57
3.56
3.55
3.46
3.45
3.44
3.43
1.60
1.58
1.48
1.46
1.43
1.40
1.39
BnO
O
O
S4
(CDCl3, 500 MHz)
4.85
0.84
1.20
0.91
1.00
2.39
0.97
0.98
1.08
1.05
1.31
1.34
3.05
f1 (ppm)

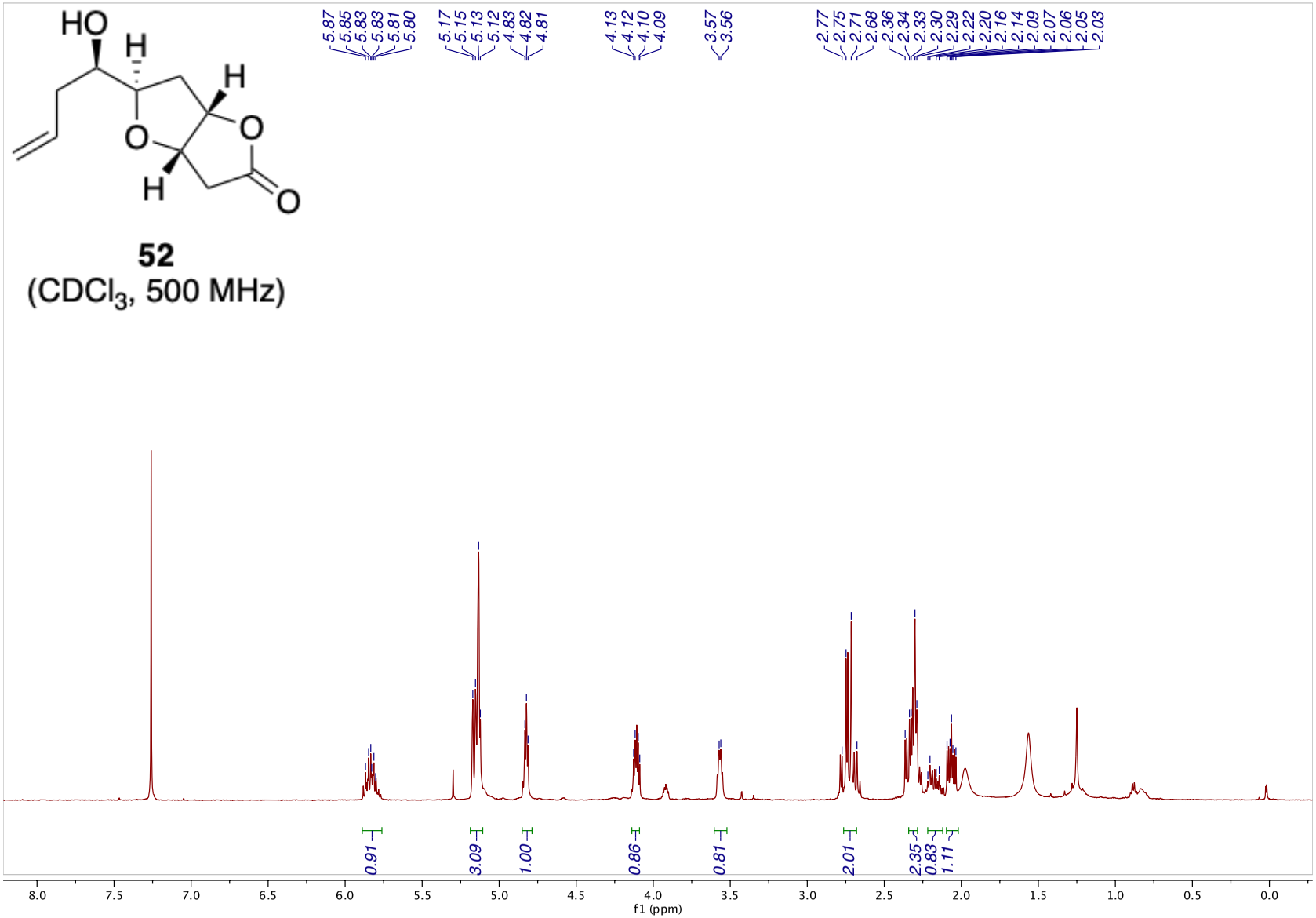

138.02
137.72
128.37
127.77
127.66
115.78
98.50
76.61
75.17
73.45
72.78
33.10
21.12
BnO
O
O
S4
(CDCl3, 125 MHz)
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

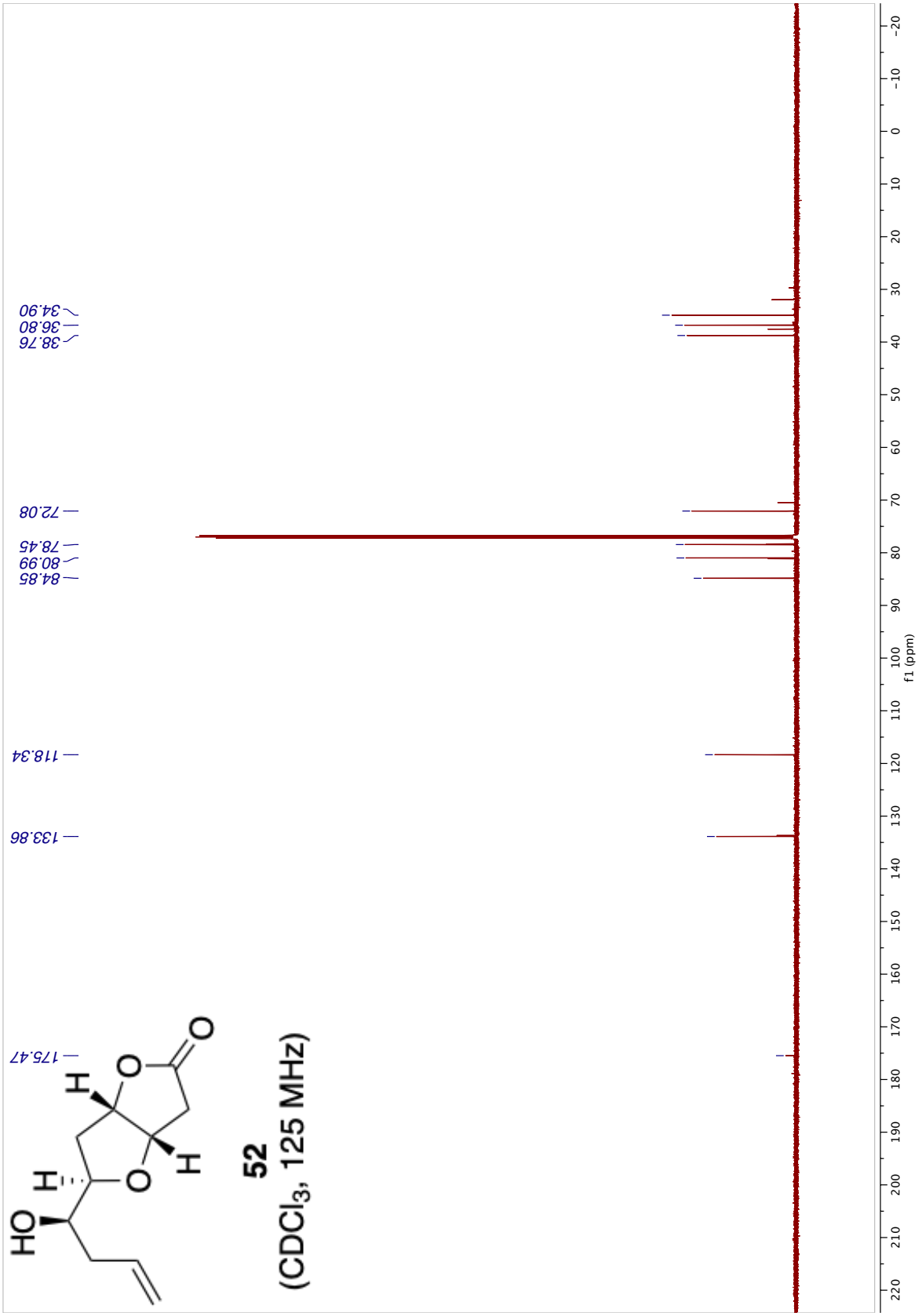

7.37
7.36
7.36
7.36
7.35
7.35
7.34
7.33
7.32
7.32
7.30
5.87
5.28
5.25
5.11
5.09
4.56
4.40
4.39
4.08
3.49
3.48
3.47
3.46
3.42
3.40
3.40
3.38
3.09
3.00
1.67
1.66
1.65
1.64
OH
OH
BnO
(–)-49
(CDCl3, 500 MHz)
4.59
0.90
1.21
1.04
2.00
0.91
0.87
1.10
1.16
0.69
0.66
2.00
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

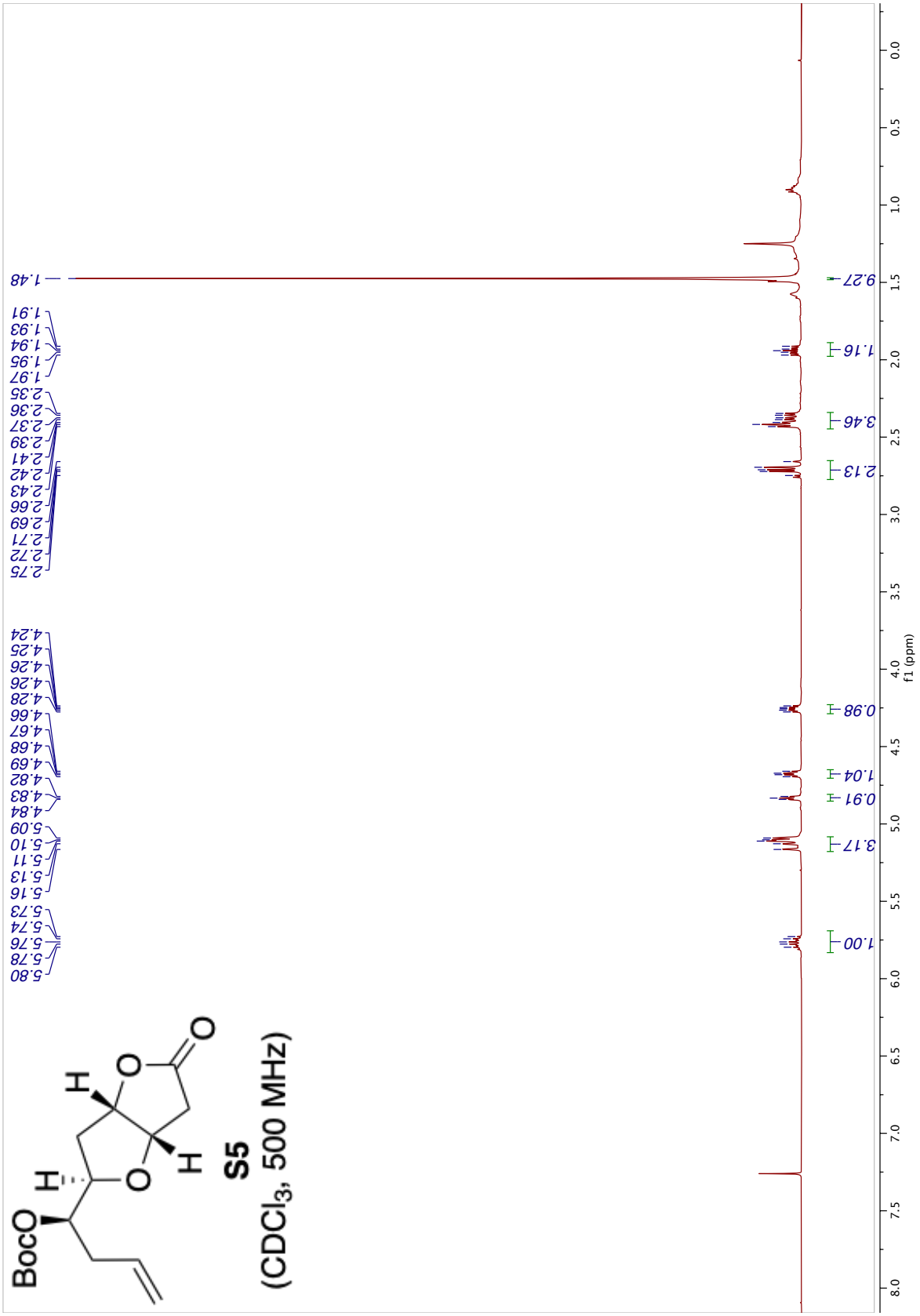

BnO
OH
OH
(–)-49
(CDCl3, 125 MHz)
140.40
137.76
128.48
127.86
127.76
114.61
77.00
74.24
73.40
72.75
70.73
39.45
f1 (ppm)

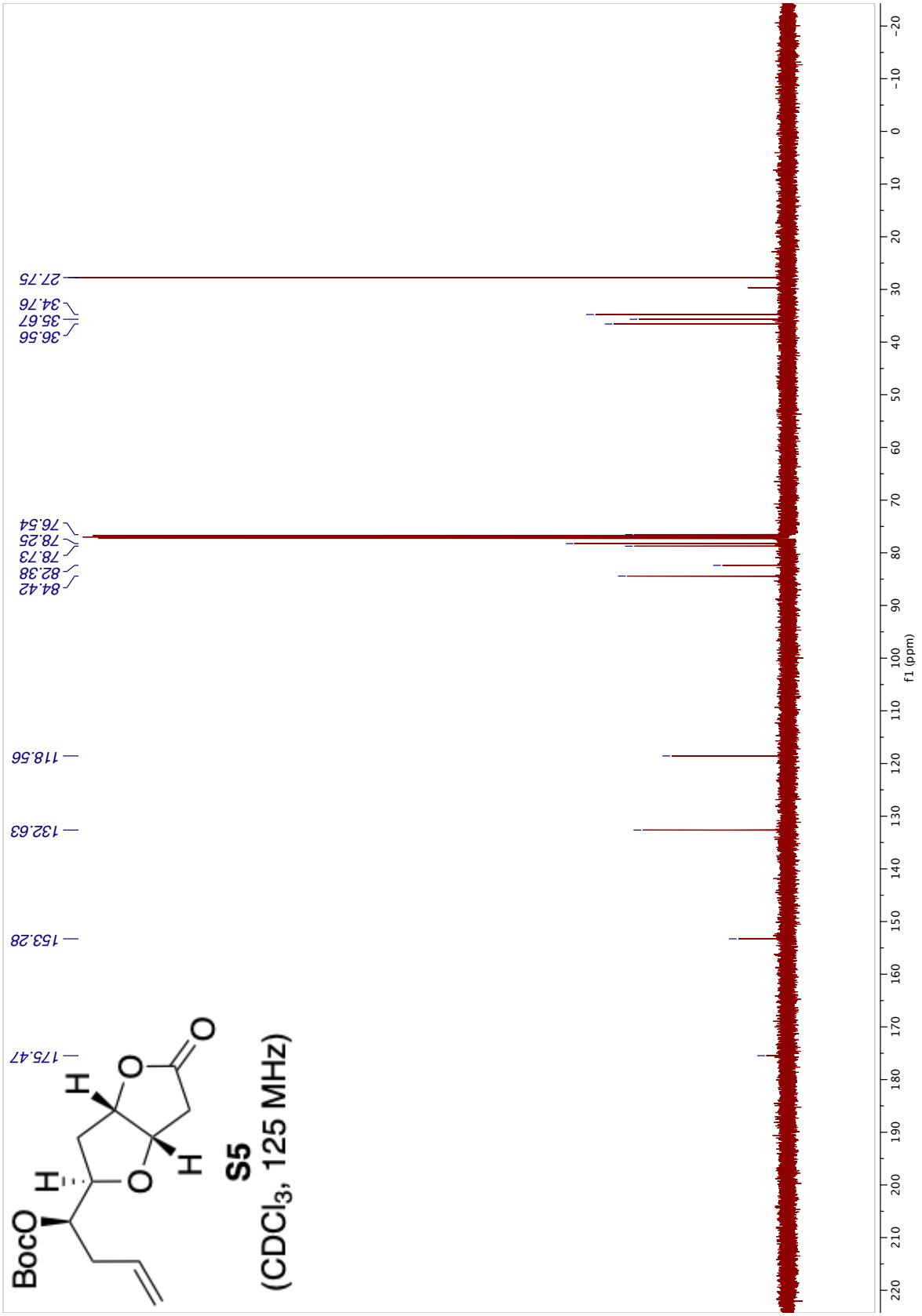

BnO
O
O
O
H
H
H
50
(CDCl3, 500 MHz)
7.36
7.35
7.34
7.33
7.32
7.31
7.29
5.12
5.11
5.10
4.85
4.84
4.84
4.83
4.57
4.39
4.38
4.37
4.36
4.35
4.34
3.63
3.63
3.61
3.61
3.49
3.48
3.47
3.46
2.73
2.72
2.71
2.36
2.35
2.34
2.32
2.08
2.07
2.05
2.04
2.02
4.91
1.34
1.13
2.00
1.18
1.18
1.06
2.16
1.00
1.02
f1 (ppm)

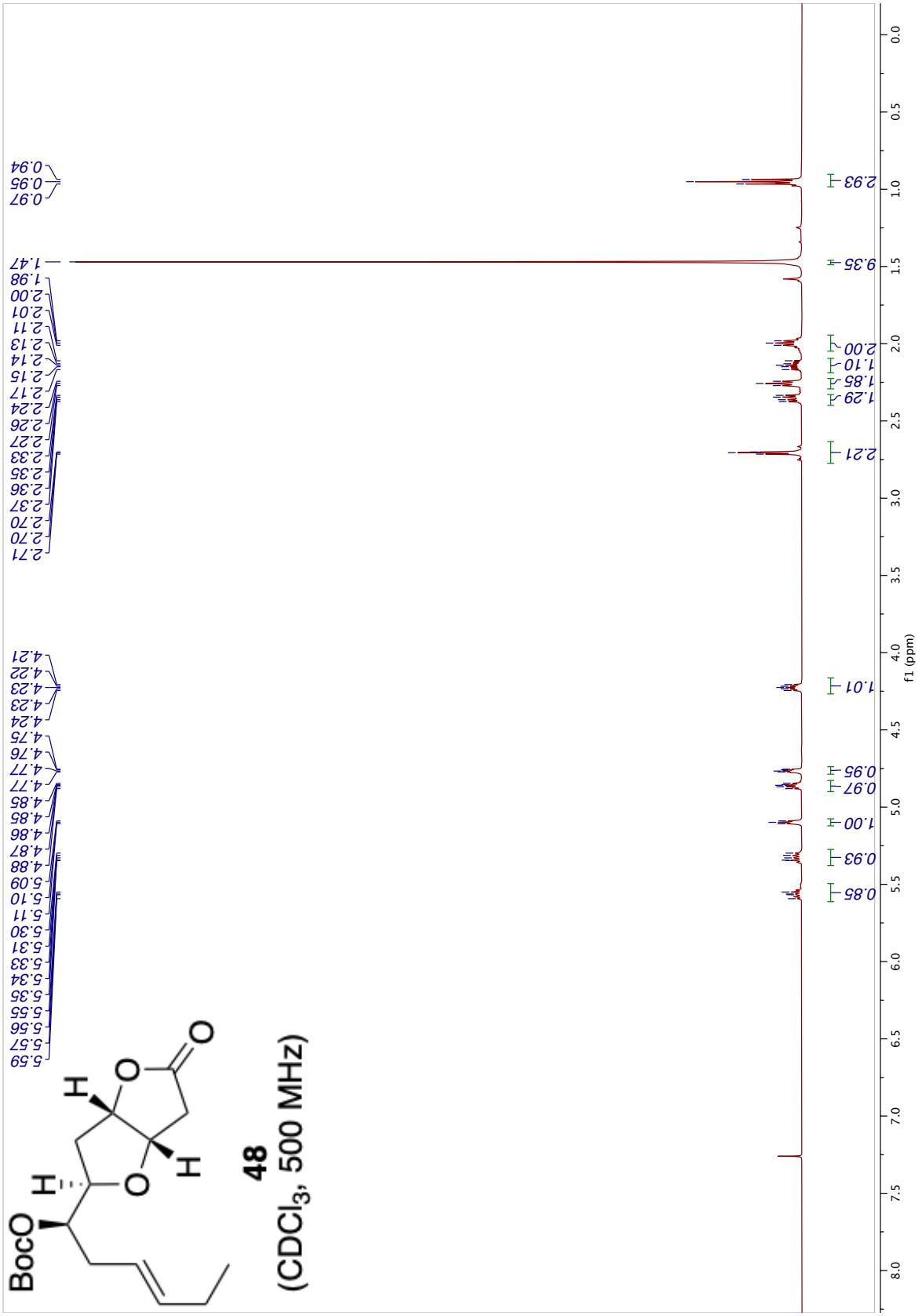

BnO
H
H
O
O
O
H
50
(CDCl3, 125 MHz)
175.62
137.86
128.41
127.74
127.63
84.70
78.46
77.86
73.49
71.53
36.66
34.85
f1 (ppm)

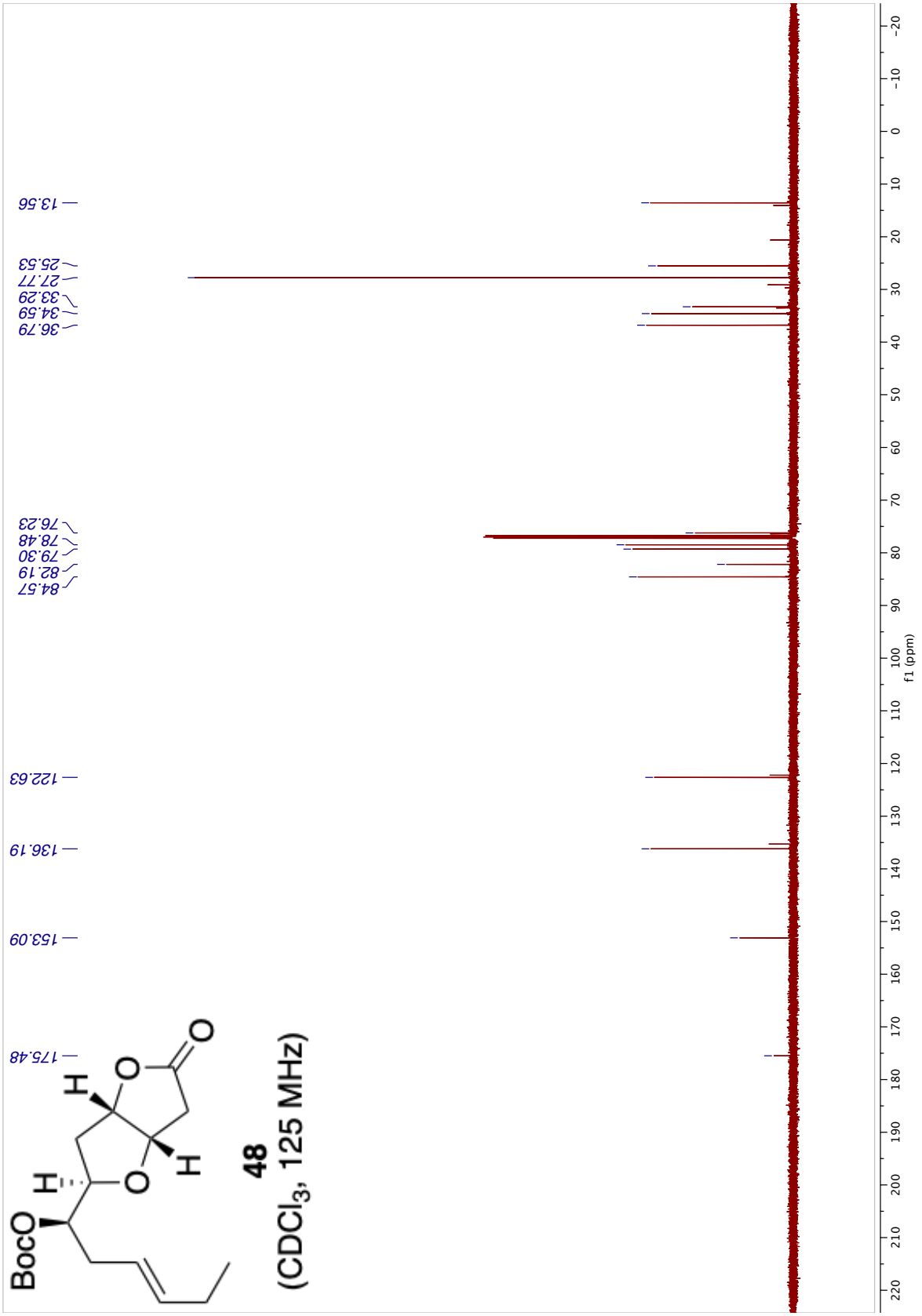

HO
H
H
O
O
H
O
52
(CDCl3, 500 MHz)
5.87
5.85
5.83
5.83
5.81
5.80
5.17
5.15
5.13
5.12
4.83
4.82
4.81
4.13
4.12
4.10
4.09
3.57
3.56
2.77
2.75
2.71
2.68
2.36
2.34
2.33
2.30
2.29
2.22
2.20
2.16
2.14
2.09
2.07
2.06
2.05
2.03
0.91
3.09
1.00
0.86
0.81
2.01
2.35
0.83
1.11
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

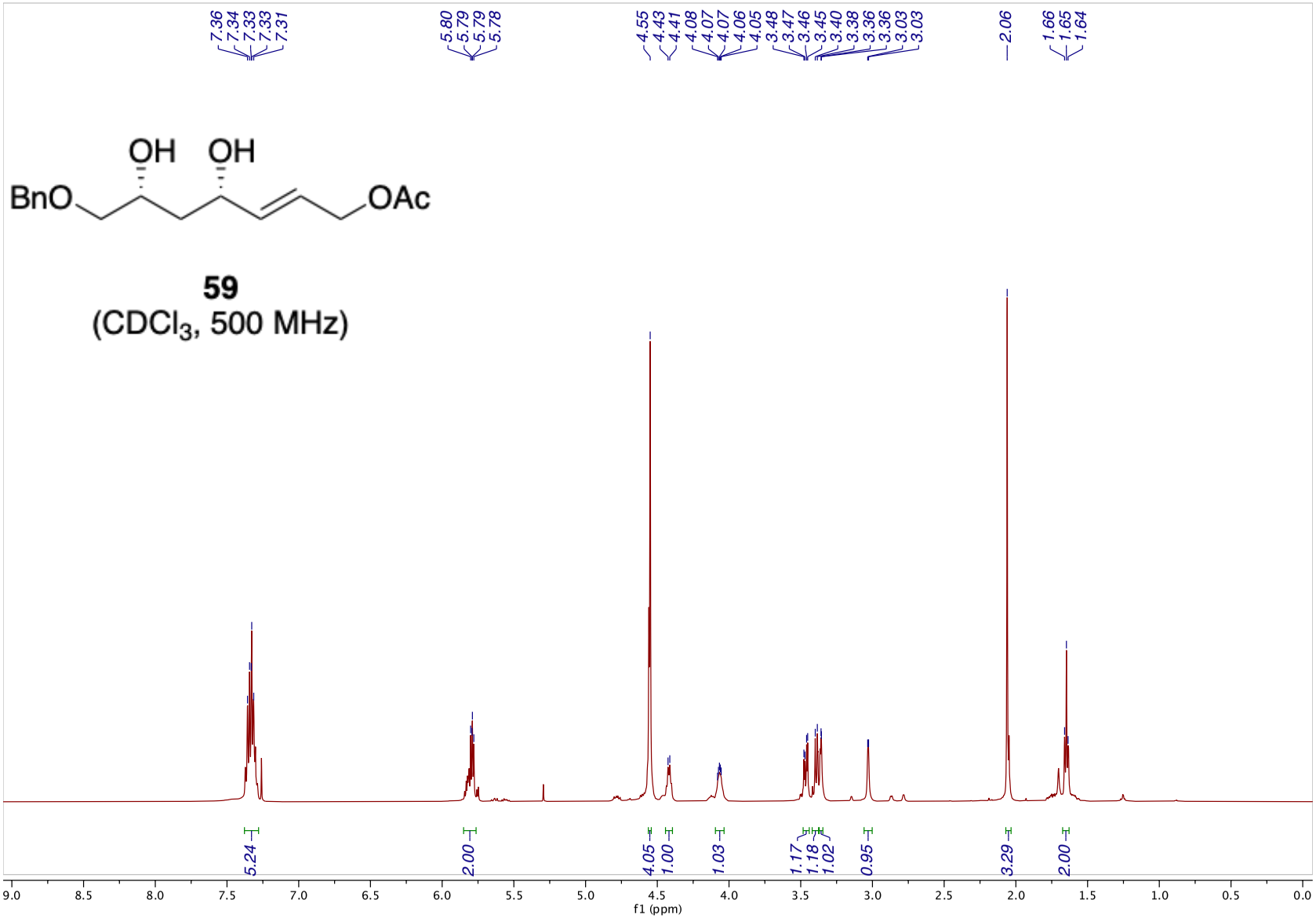

52
(CDCl3, 125 MHz)
175.47
133.86
118.34
84.85
80.99
78.45
72.08
38.76
36.80
34.90
f1 (ppm)

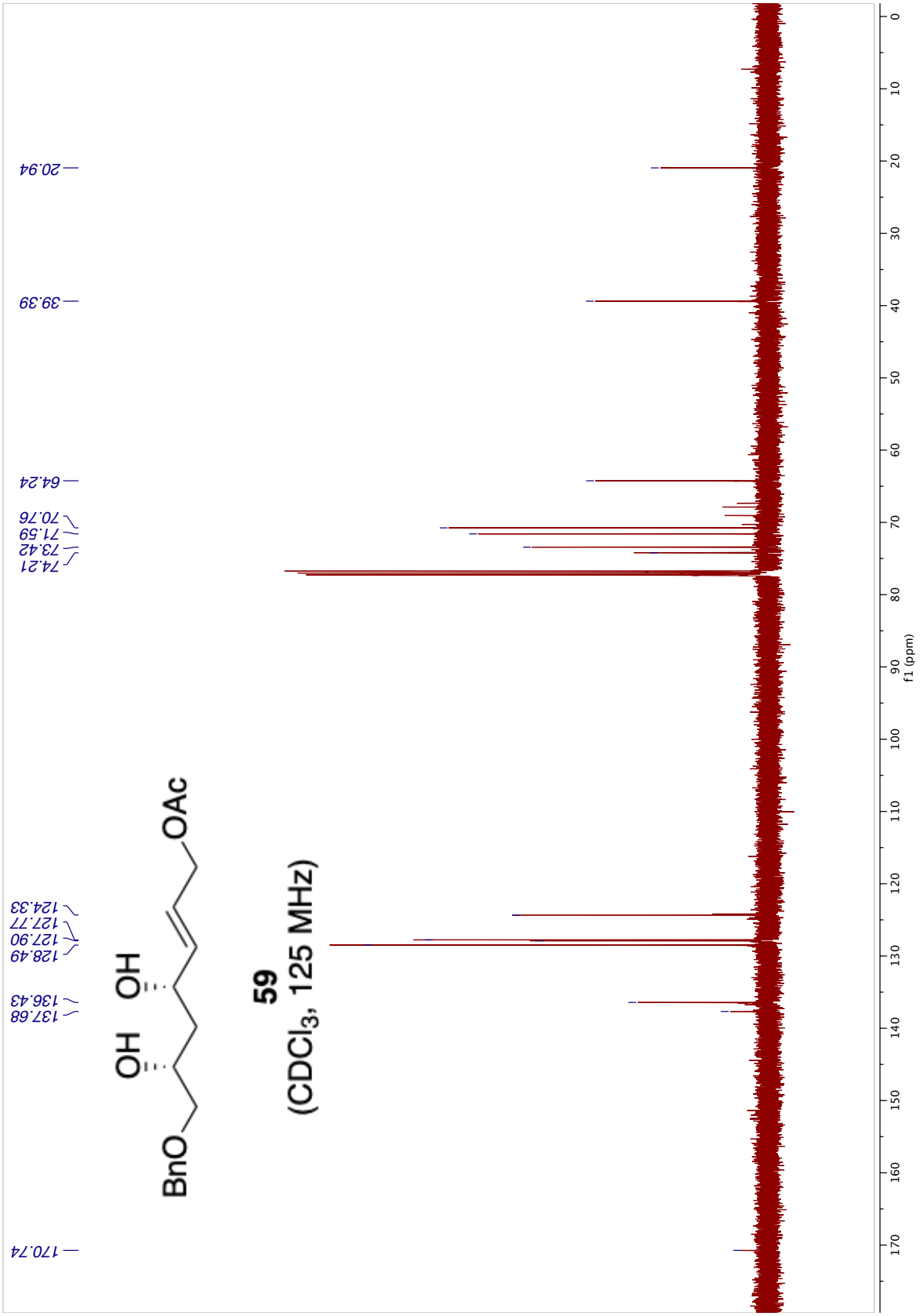

BocO
H
O
O
H
H
O
S5
(CDCl3, 500 MHz)
1.48
1.91
1.93
1.94
1.95
1.97
2.35
2.36
2.37
2.39
2.41
2.42
2.43
2.66
2.69
2.71
2.72
2.75
4.24
4.25
4.26
4.26
4.28
4.66
4.67
4.68
4.69
4.82
4.83
4.84
5.09
5.10
5.11
5.13
5.16
5.73
5.74
5.76
5.78
5.80
9.27
1.16
3.46
2.13
0.98
1.04
0.91
3.17
1.00
f1 (ppm)

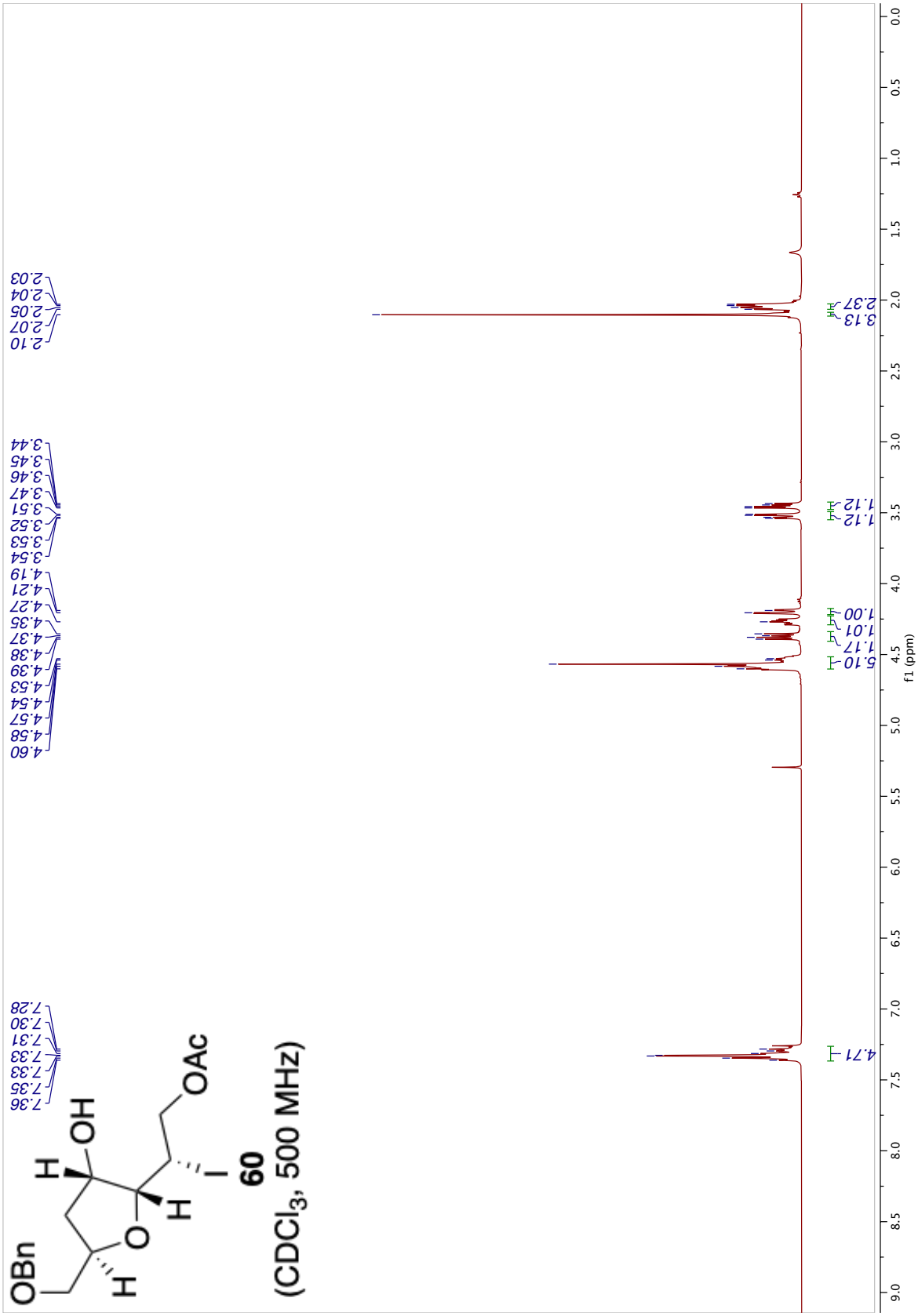

BocO
H
H
O
O
O
H
S5
(CDCl3, 125 MHz)
175.47
153.28
132.63
118.56
84.42
82.38
78.73
78.25
76.54
36.56
35.67
34.76
27.75
f1 (ppm)

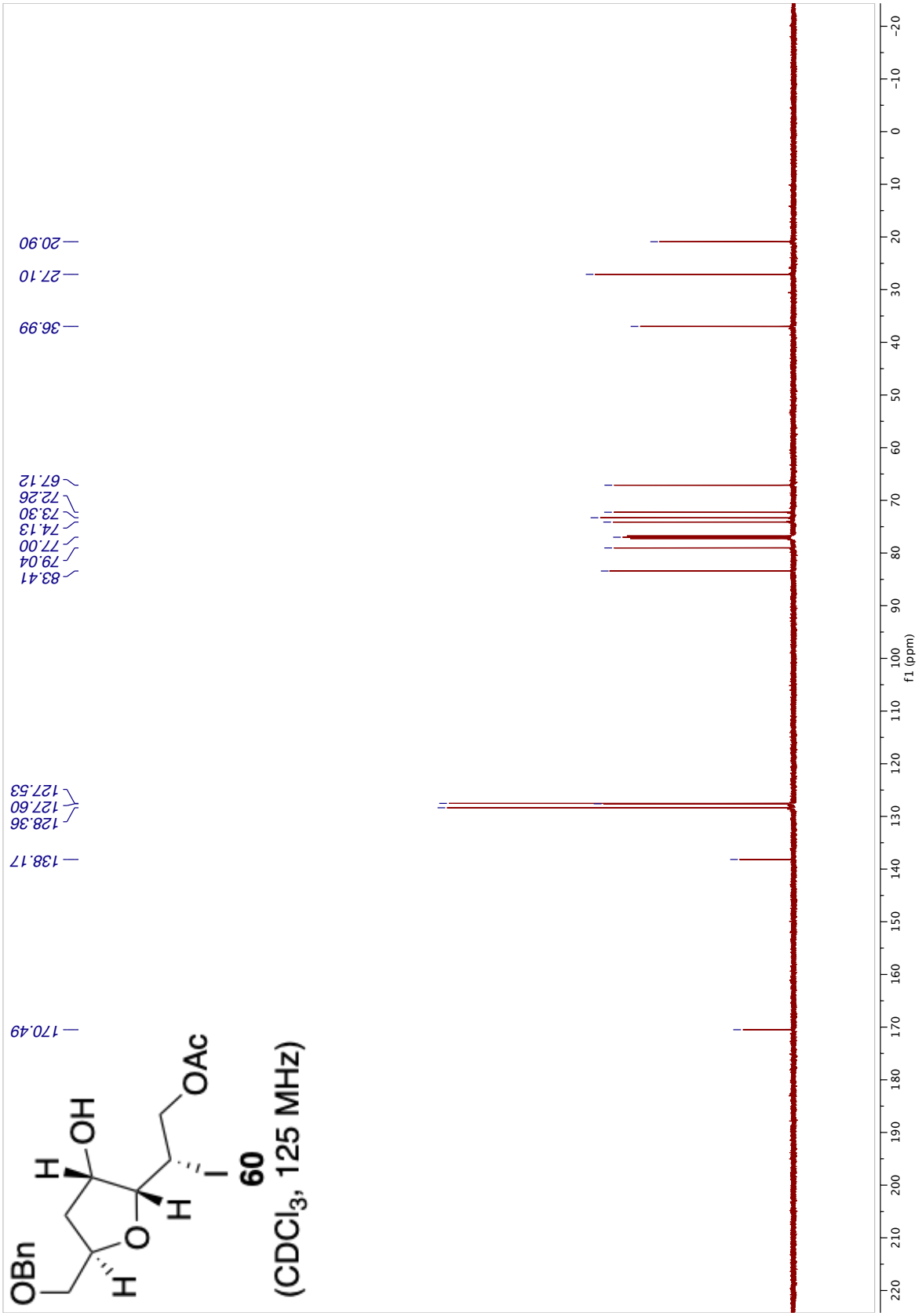

BocO
H
O
O
H
H
O
48
(CDCl3, 500 MHz)
f1 (ppm)

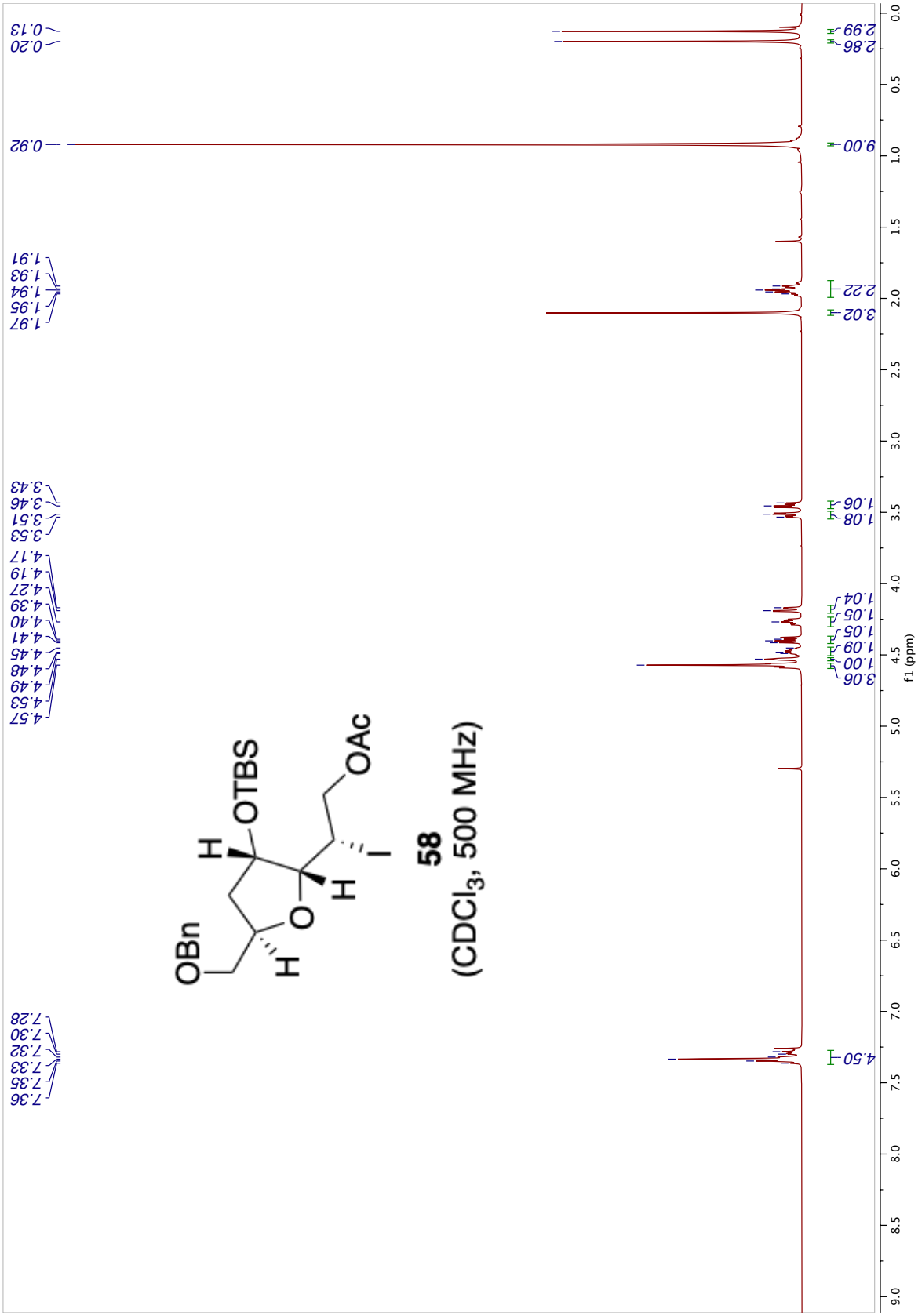

BocO
H
H
O
O
O
H
48
(CDCl3, 125 MHz)
175.48
153.09
136.19
122.63
84.57
82.19
79.30
78.48
76.23
36.79
34.59
33.29
27.77
25.53
13.56
f1 (ppm)

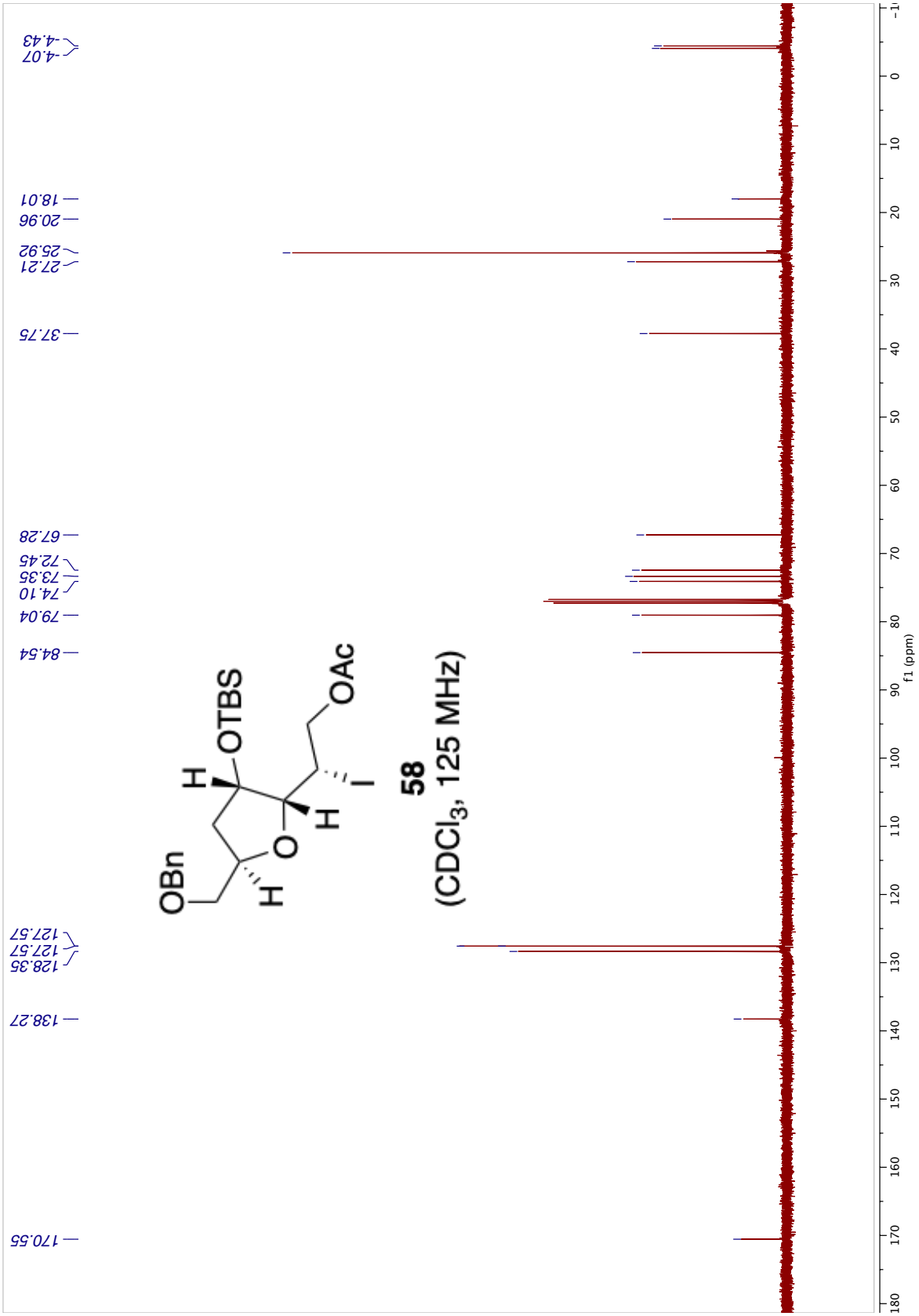

7.36
7.34
7.33
7.33
7.31
5.80
5.79
5.79
5.78
4.55
4.43
4.41
4.08
4.07
4.07
4.06
4.05
3.48
3.47
3.46
3.45
3.40
3.38
3.36
3.36
3.03
3.03
2.06
1.66
1.65
1.64
OH
OH
BnO
OAc
59
(CDCl3, 500 MHz)
5.24
2.00
4.05
1.00
1.03
1.17
1.18
1.02
0.95
3.29
2.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

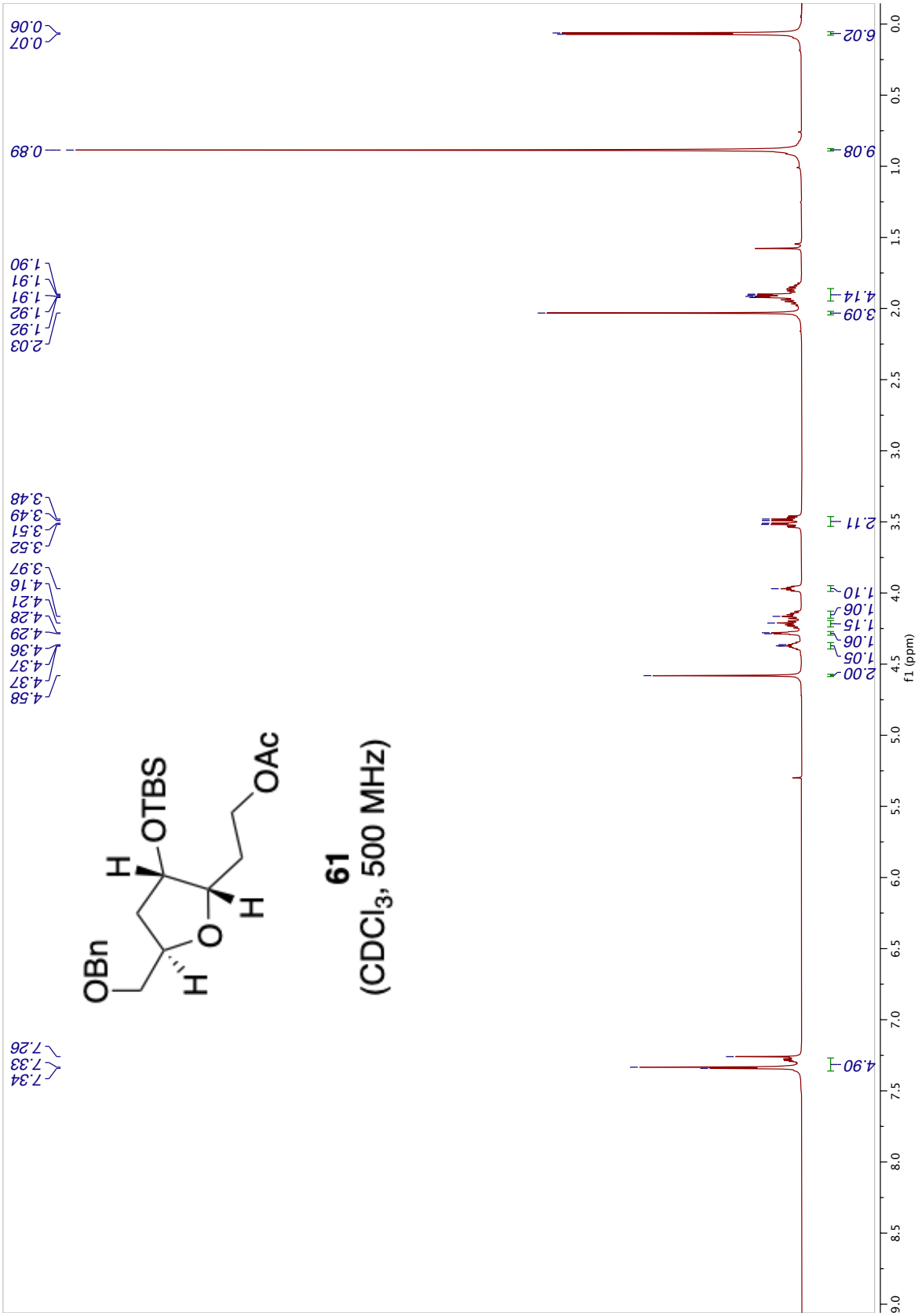

59
(CDCl3, 125 MHz)
BnO
OH
OH
OAc
170.74
137.68
136.43
128.49
127.90
127.77
124.33
74.21
73.42
71.59
70.76
64.24
39.39
20.94
f1 (ppm)

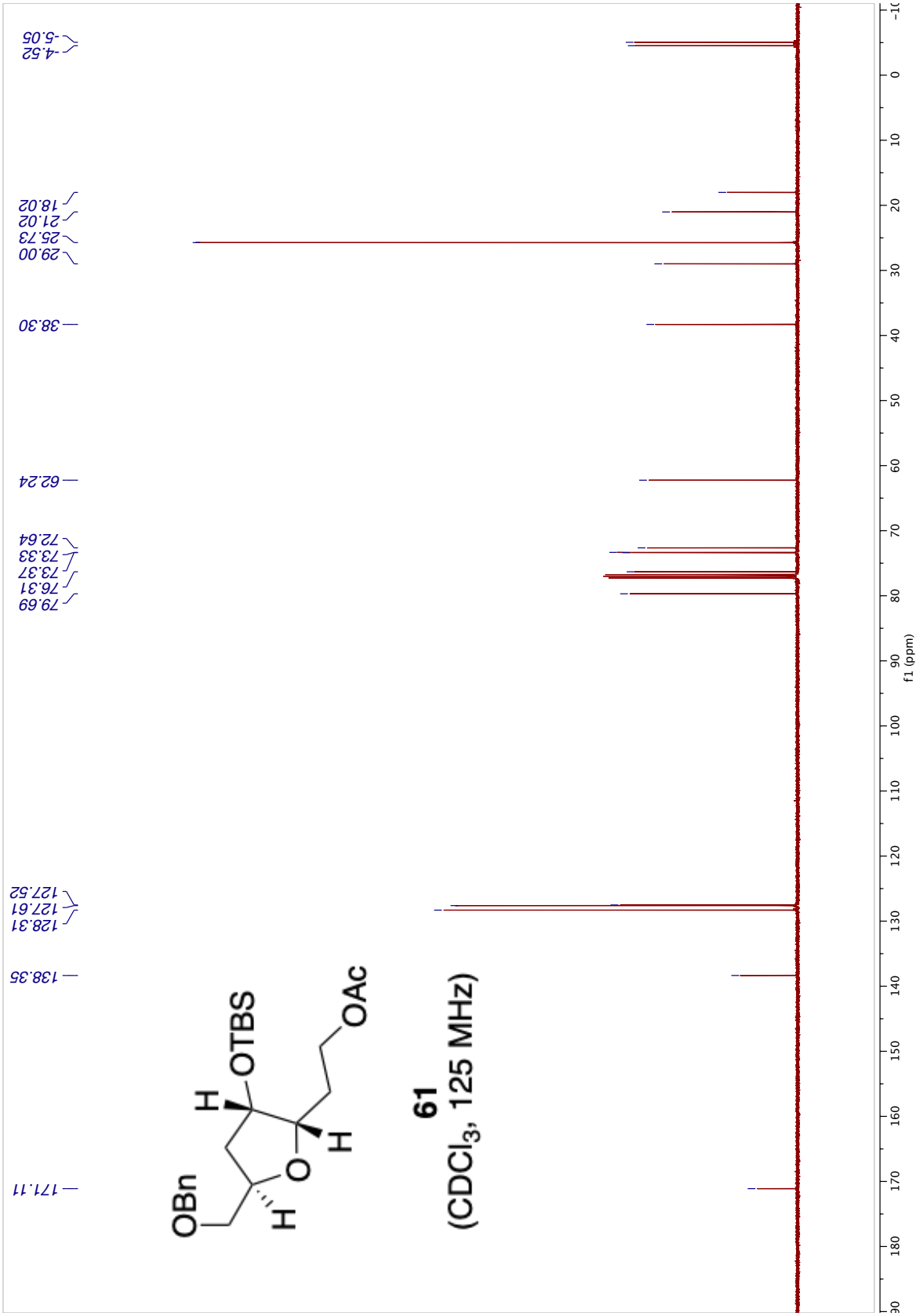

OBn
H
OH
H
O
H
I
OAc
60
(CDCl3, 500 MHz)
7.36
7.35
7.33
7.33
7.31
7.30
7.28
4.60
4.58
4.57
4.54
4.53
4.39
4.38
4.37
4.35
4.27
4.21
4.19
3.54
3.53
3.52
3.51
3.47
3.46
3.45
3.44
2.10
2.07
2.05
2.04
2.03
4.71
5.10
1.17
1.01
1.00
1.12
1.12
3.13
2.37
f1 (ppm)

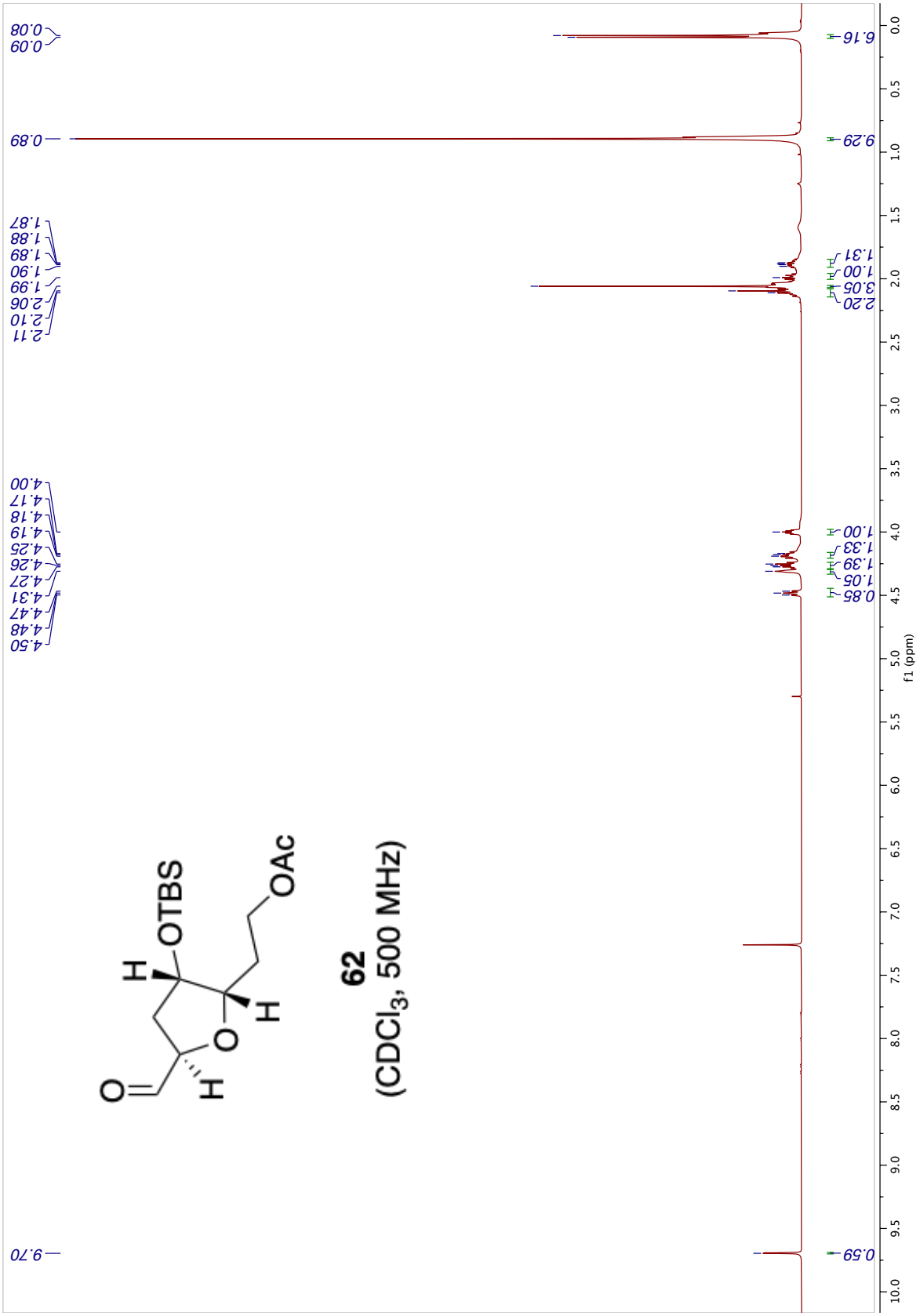

OBn
H
O
H
OH
H
I
OAc
60
(CDCl3, 125 MHz)
170.49
138.17
128.36
127.60
127.53
83.41
79.04
77.00
74.13
73.30
72.26
67.12
36.99
27.10
20.90
f1 (ppm)

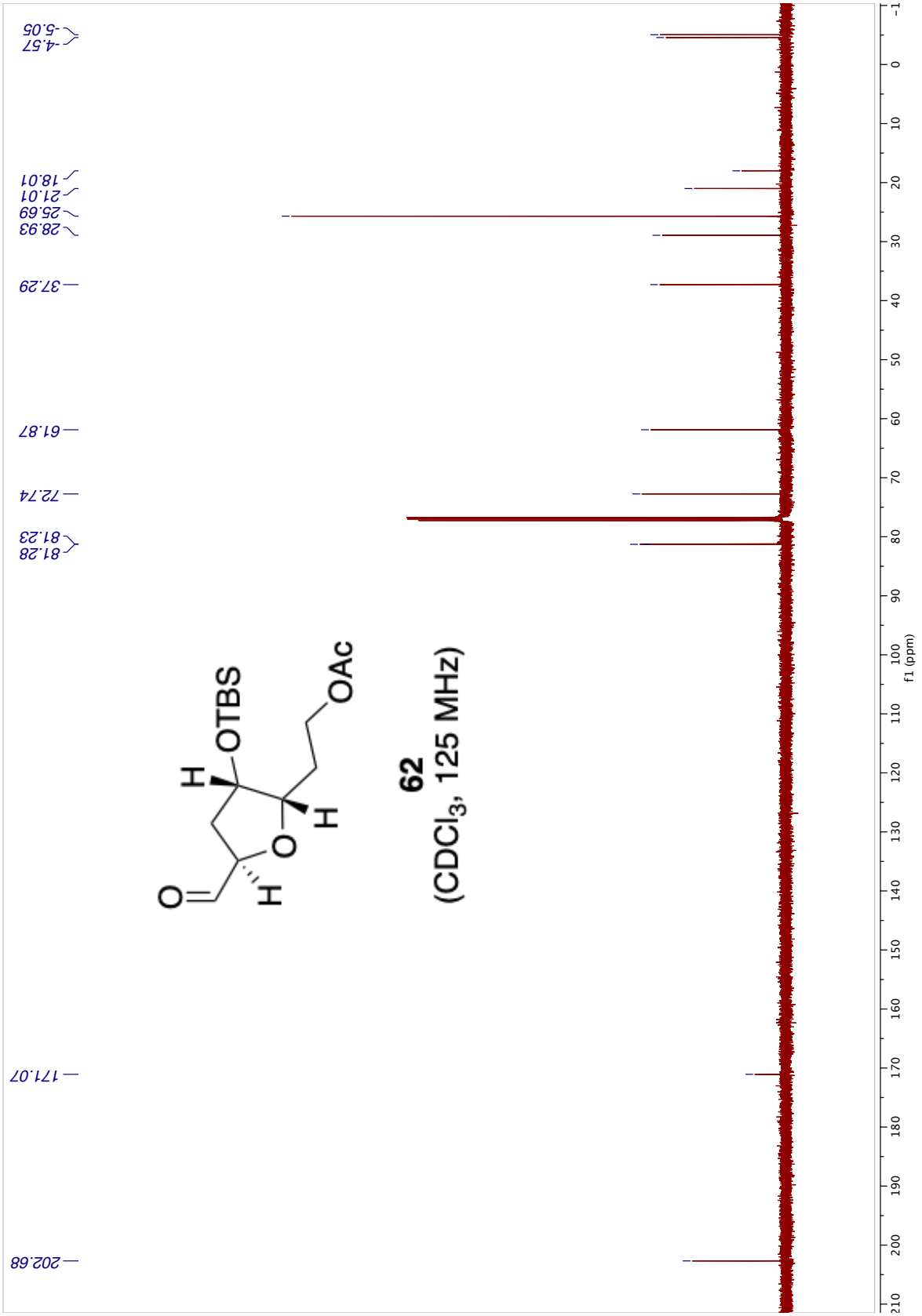

OBn
H
O
H
OTBS
H
I
OAc
58
(CDCl3, 500 MHz)
f1 (ppm)

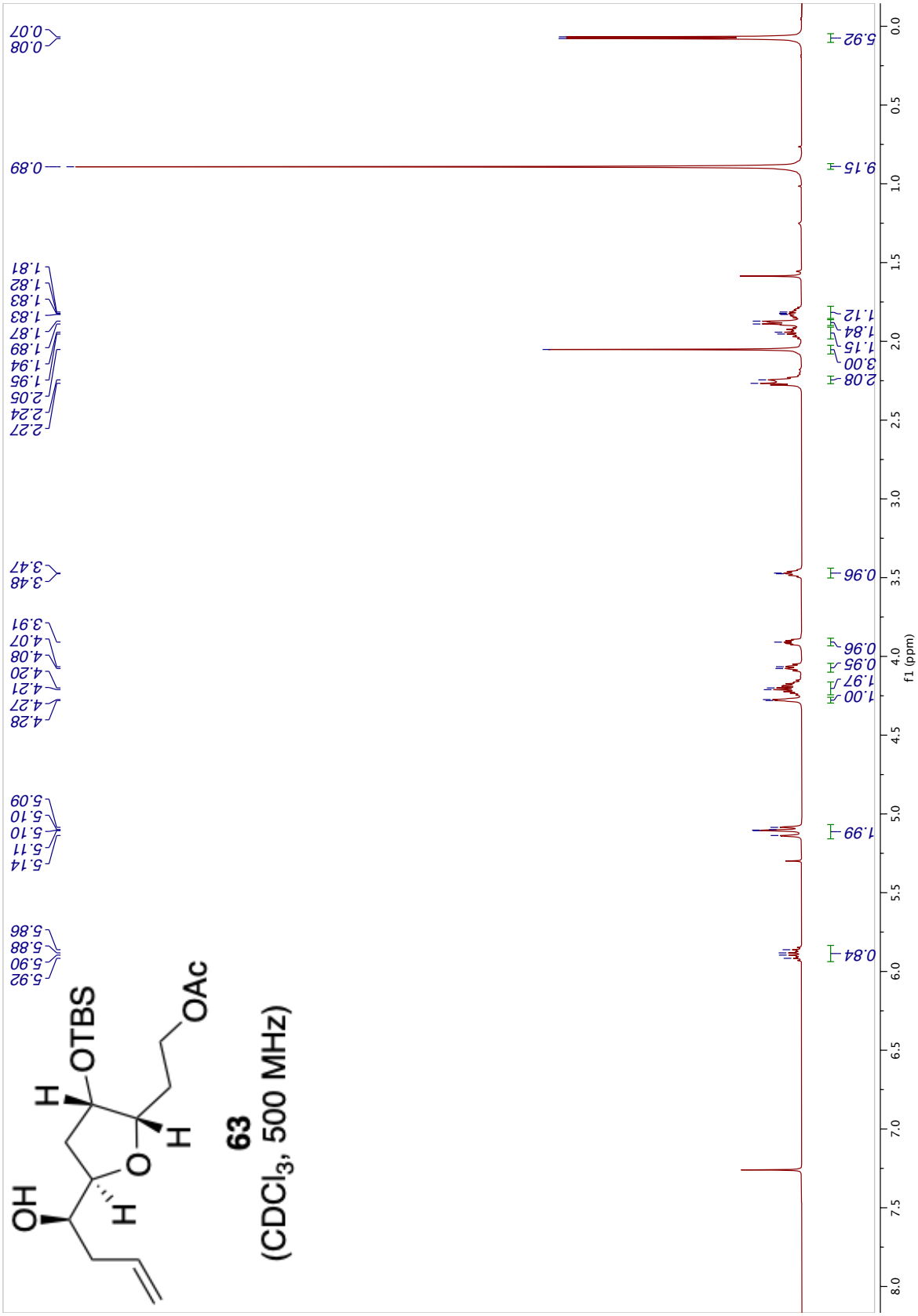

-4.43
-4.07
18.01
20.96
25.92
27.21
37.75
67.28
72.45
73.35
74.10
79.04
84.54
127.57
127.57
128.35
138.27
170.55
f1 (ppm)
OBn
OTBS
OAc
H
O
58
(CDCl3, 125 MHz)

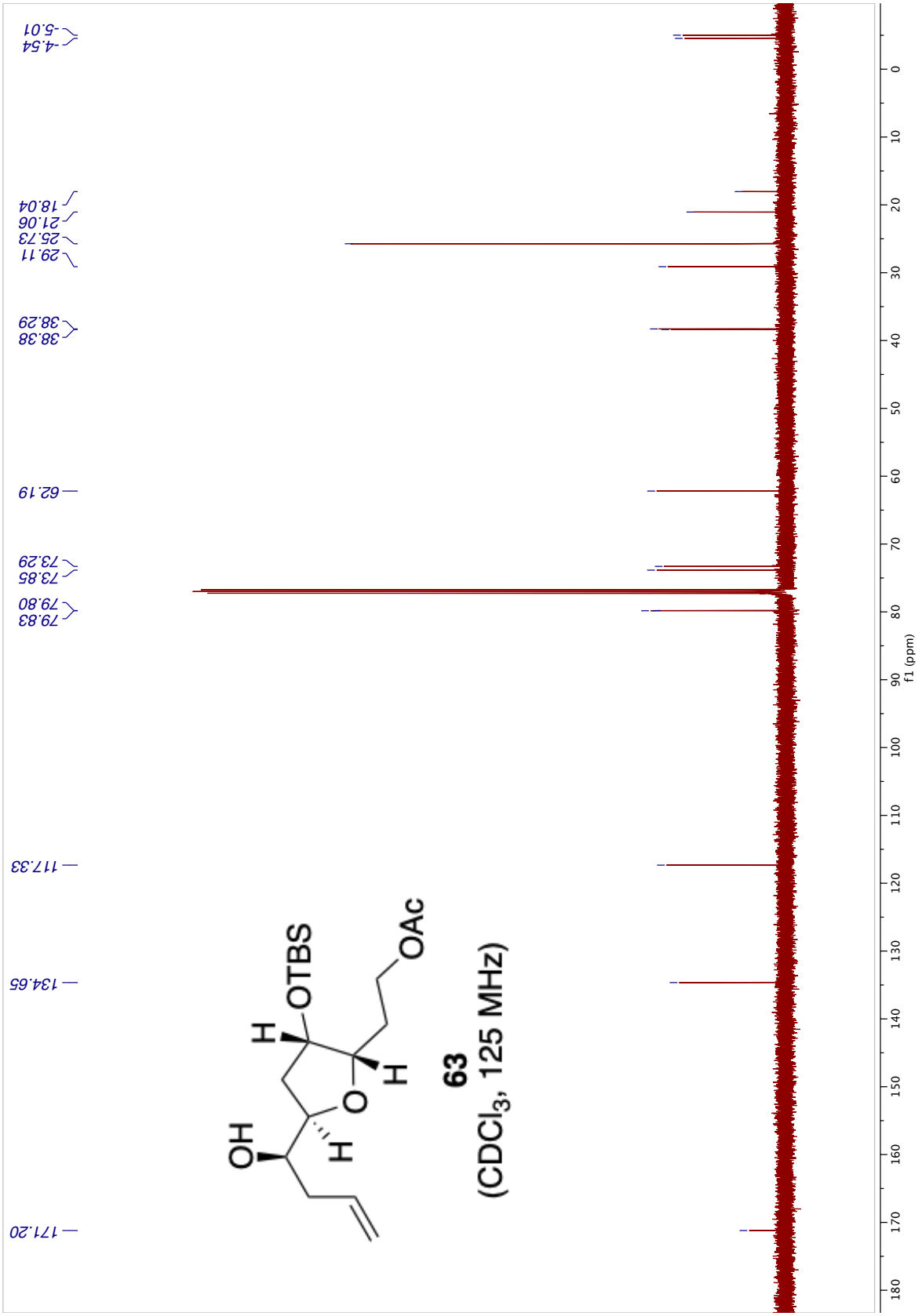

61
(CDCl3, 500 MHz)
OBn
OTBS
OAc
H
O
f1 (ppm)

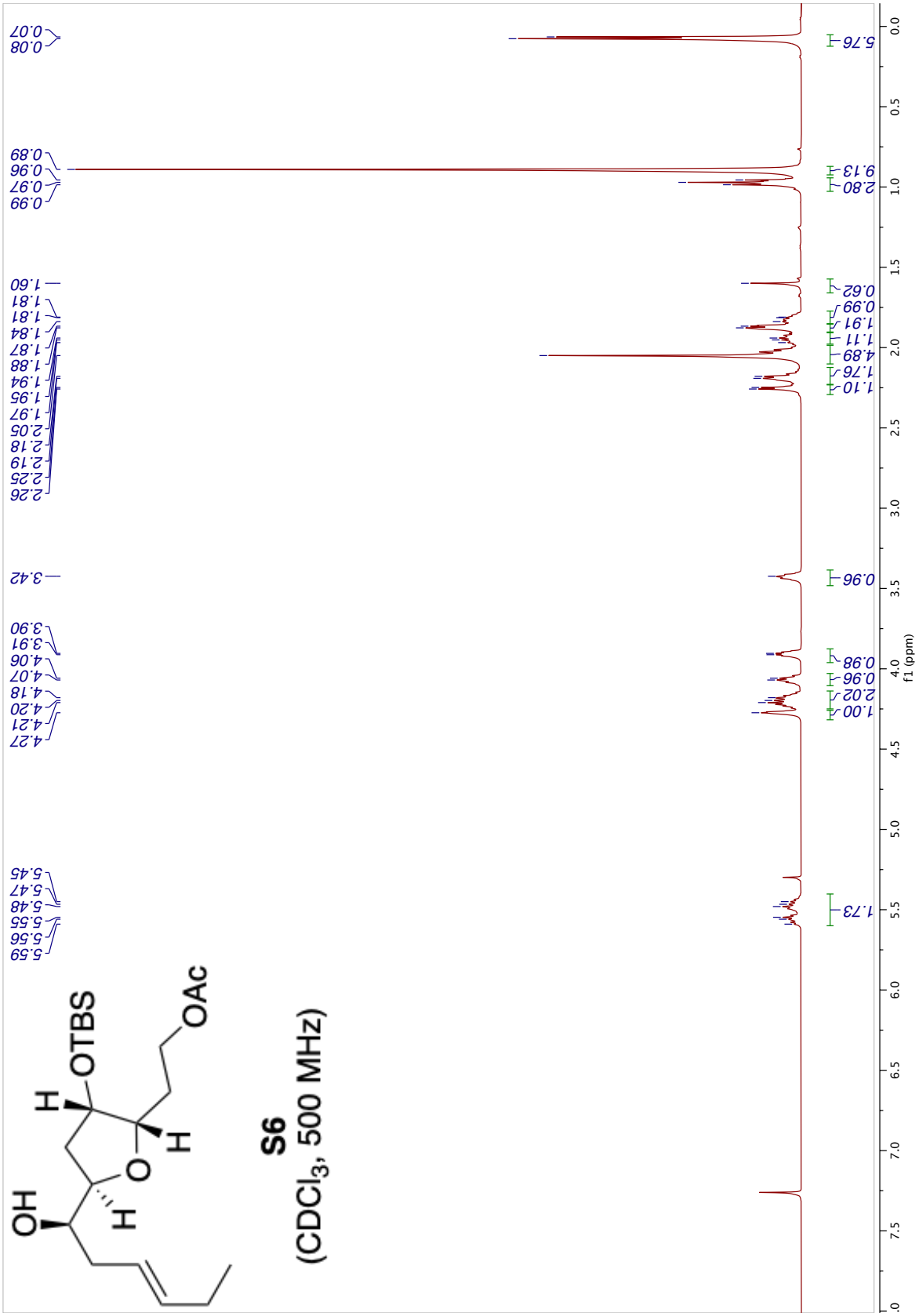

61
(CDCl3, 125 MHz)
OBn
H
OTBS
O
H
H
OAc
-4.52
-5.05
18.02
21.02
25.73
29.00
38.30
62.24
72.64
73.33
73.37
76.31
79.69
127.52
127.61
128.31
138.35
171.11
f1 (ppm)

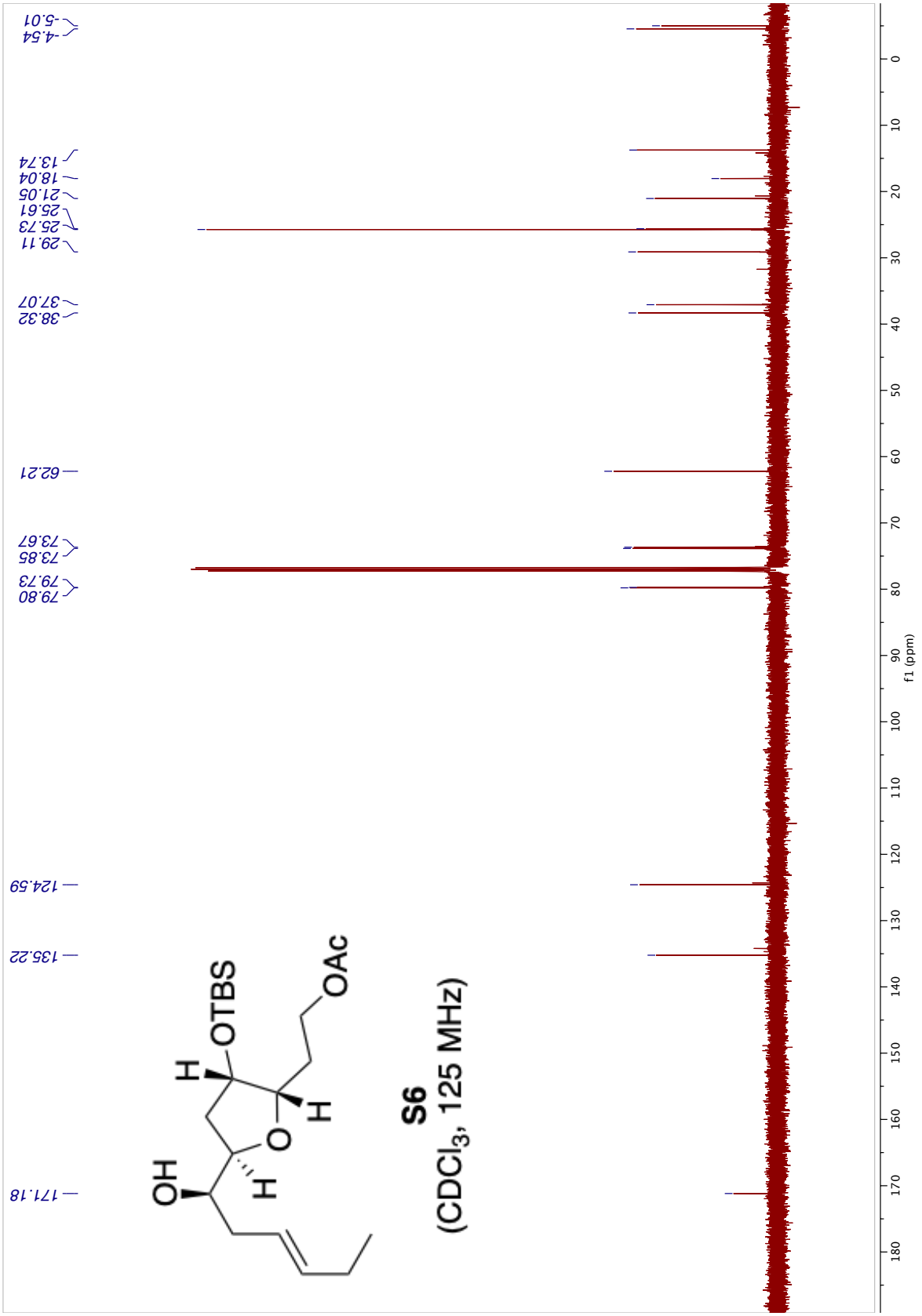

62
(CDCl3, 500 MHz)
OTBS
OAc
H
O
H
O
H
f1 (ppm)

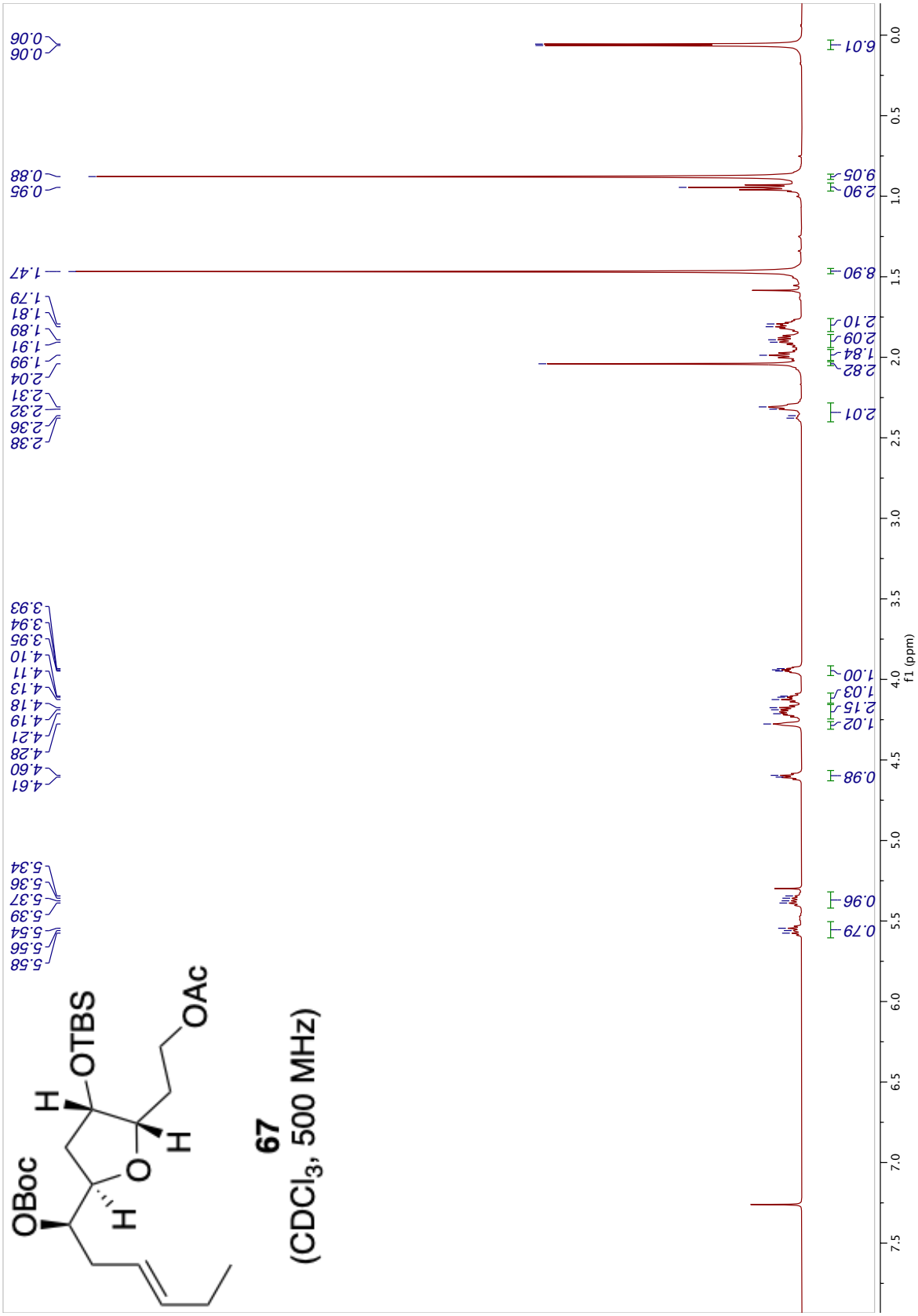

-4.57
-5.05
18.01
21.01
25.69
28.93
37.29
61.87
72.74
81.28
81.23
171.07
202.68
OTBS
OAc
H
O
H
O
H
62
(CDCl3, 125 MHz)
f1 (ppm)

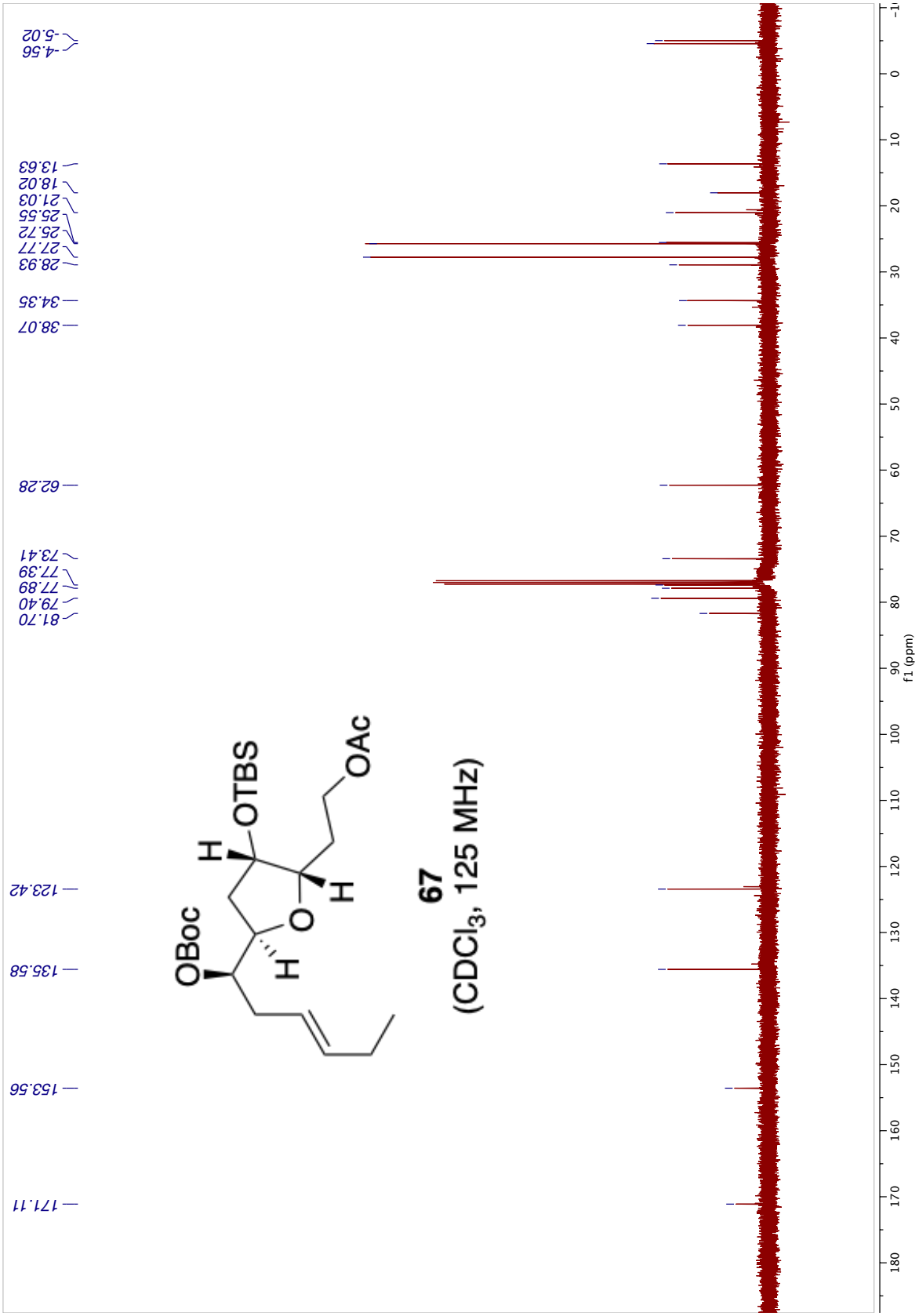

OH
H
O
H
OTBS
H
OAc
63
(CDCl3, 500 MHz)
f1 (ppm)

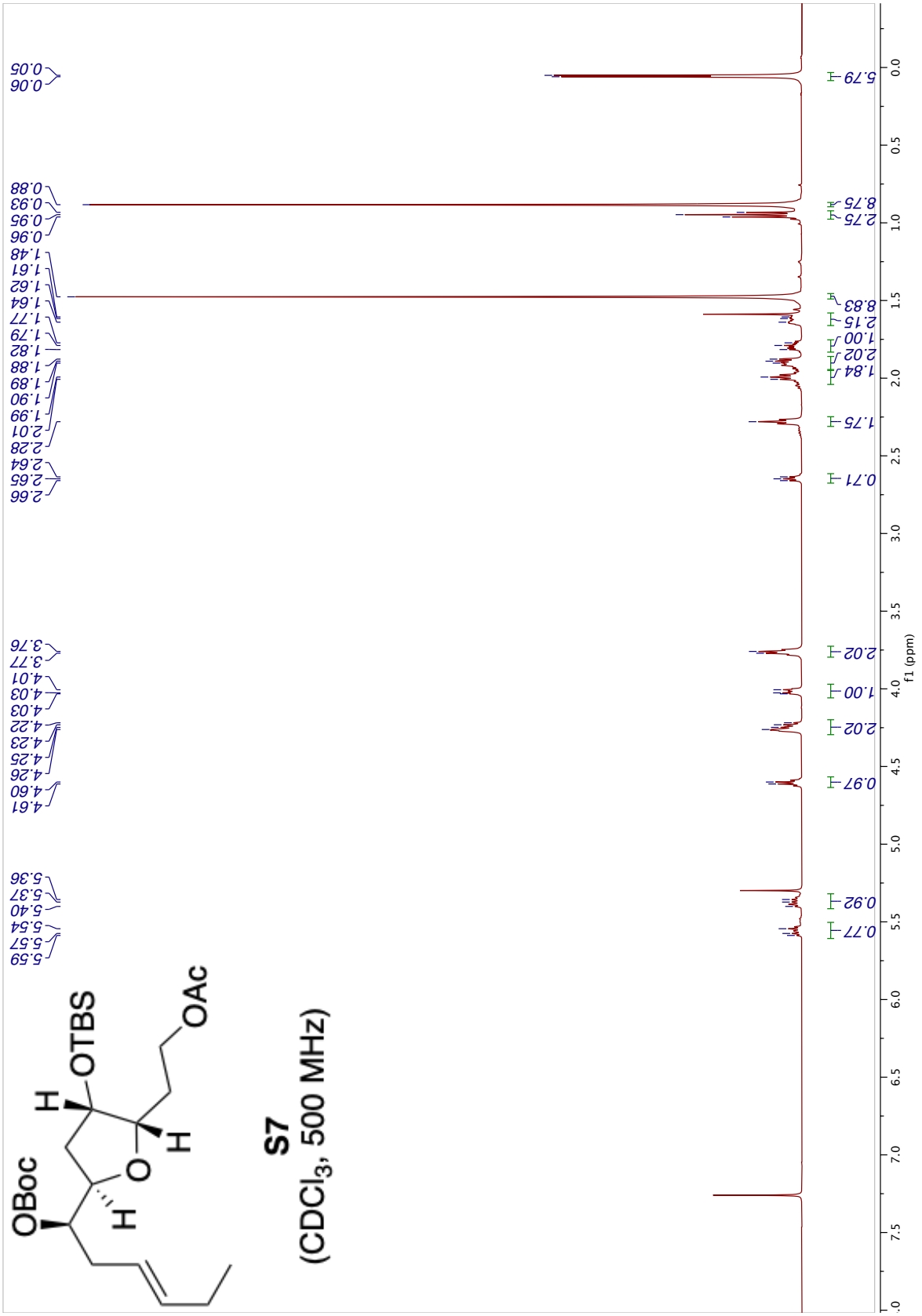

-5.01
-4.54
18.04
21.06
25.73
29.11
38.29
38.38
62.19
73.29
73.85
79.80
79.83
117.33
134.65
171.20
OH
H
O
H
OTBS
H
OAc
63
(CDCl3, 125 MHz)
f1 (ppm)

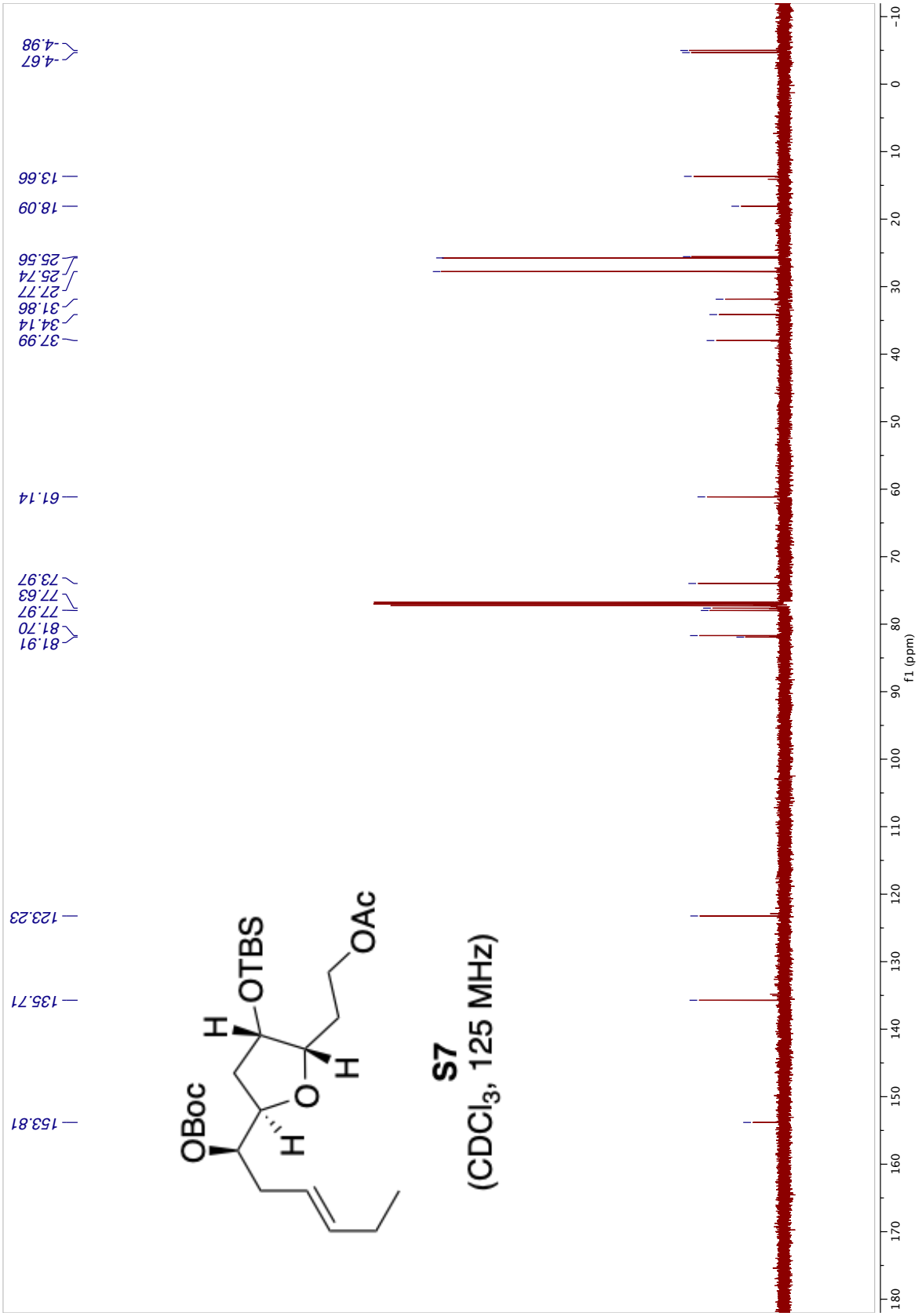

OH
H
O
H
OTBS
H
OAc
S6
(CDCl3, 500 MHz)
f1 (ppm)

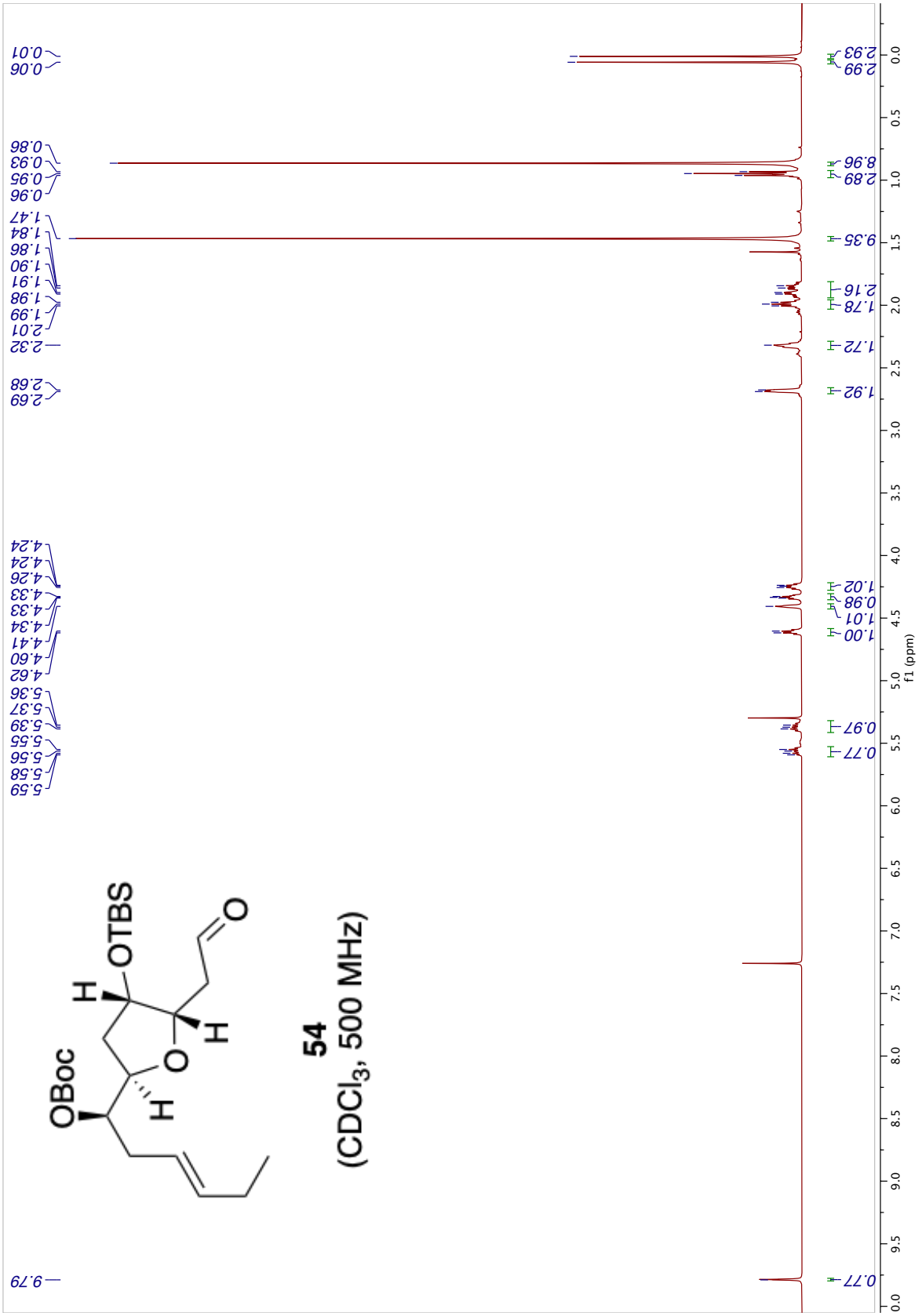

-5.01
-4.54
13.74
18.04
21.05
25.61
25.73
29.11
37.07
38.32
62.21
73.67
73.85
79.73
79.80
124.59
135.22
171.18
OH
H
O
H
OTBS
H
OAc
S6
(CDCl3, 125 MHz)
f1 (ppm)

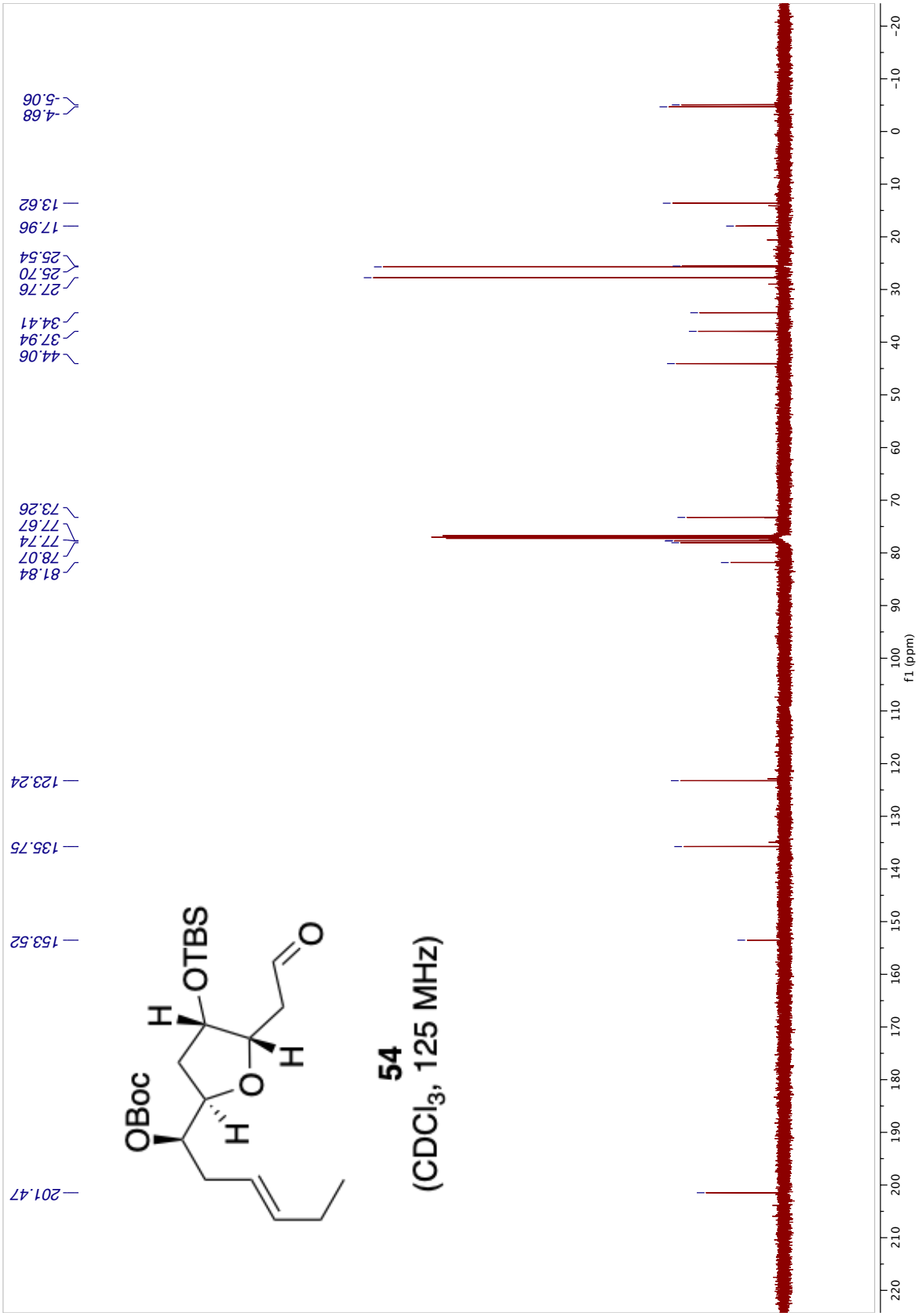

OBoc
H
OTBS
H
O
H
OAc
67
(CDCl3, 500 MHz)
f1 (ppm)

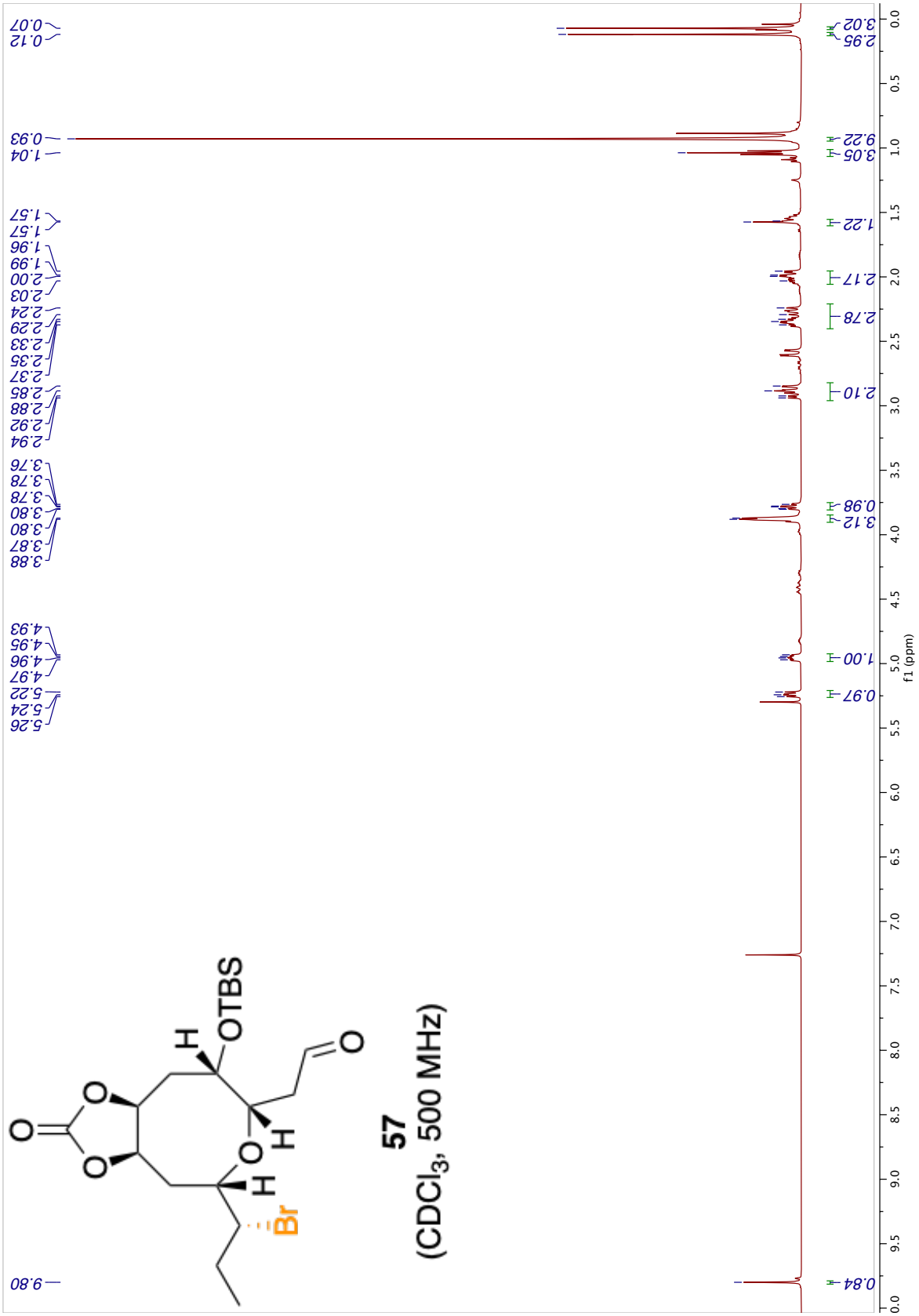

-4.56
-5.02
13.63
18.02
21.03
25.55
25.72
27.77
28.93
34.35
38.07
62.28
73.41
77.39
77.89
79.40
81.70
123.42
135.58
153.56
171.11
OBoc
OTBS
OAc
H
H
H
O
67
(CDCl3, 125 MHz)
f1 (ppm)

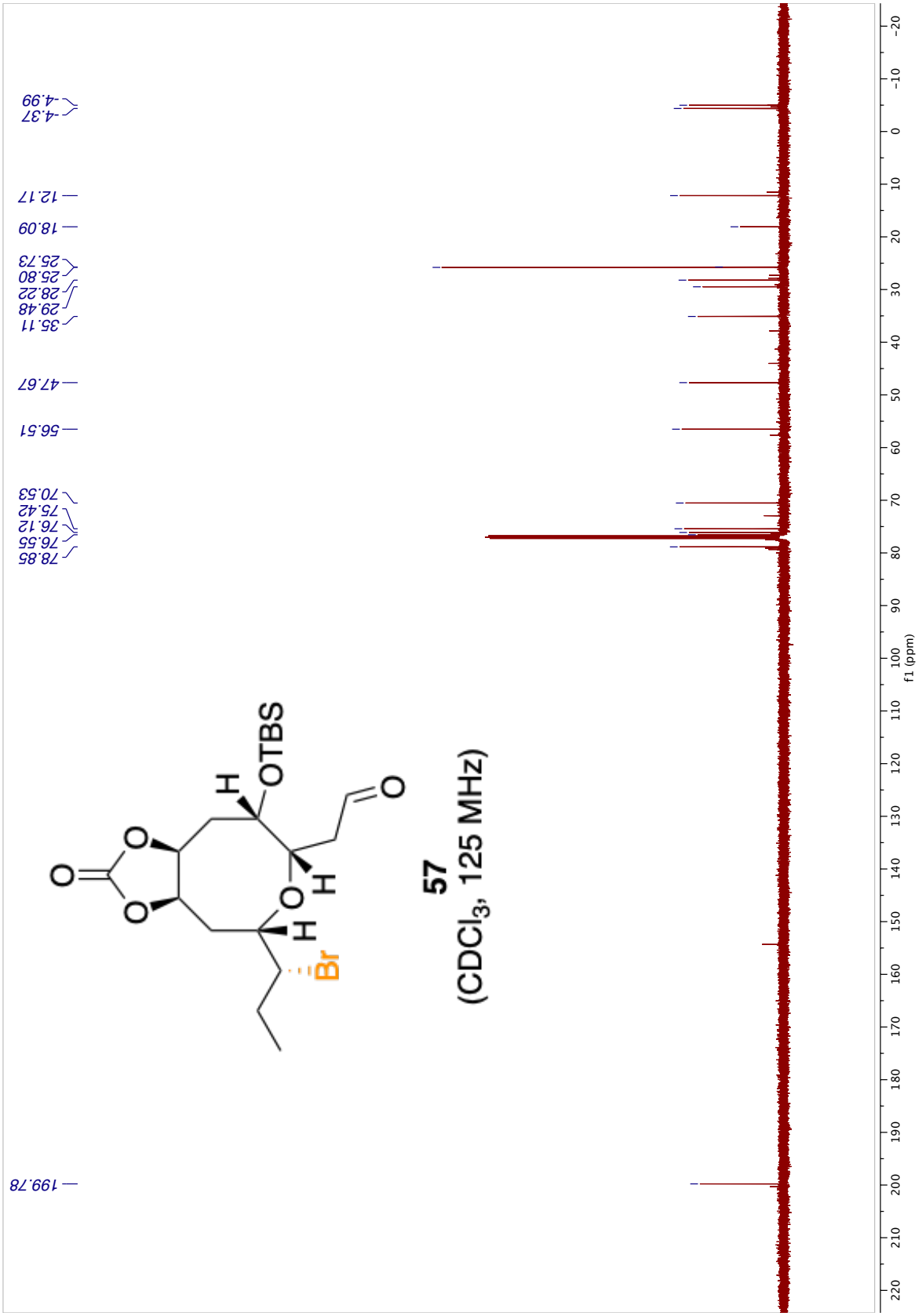

OBoc
H
OTBS
H
O
H
OAc
S7
(CDCl3, 500 MHz)
f1 (ppm)

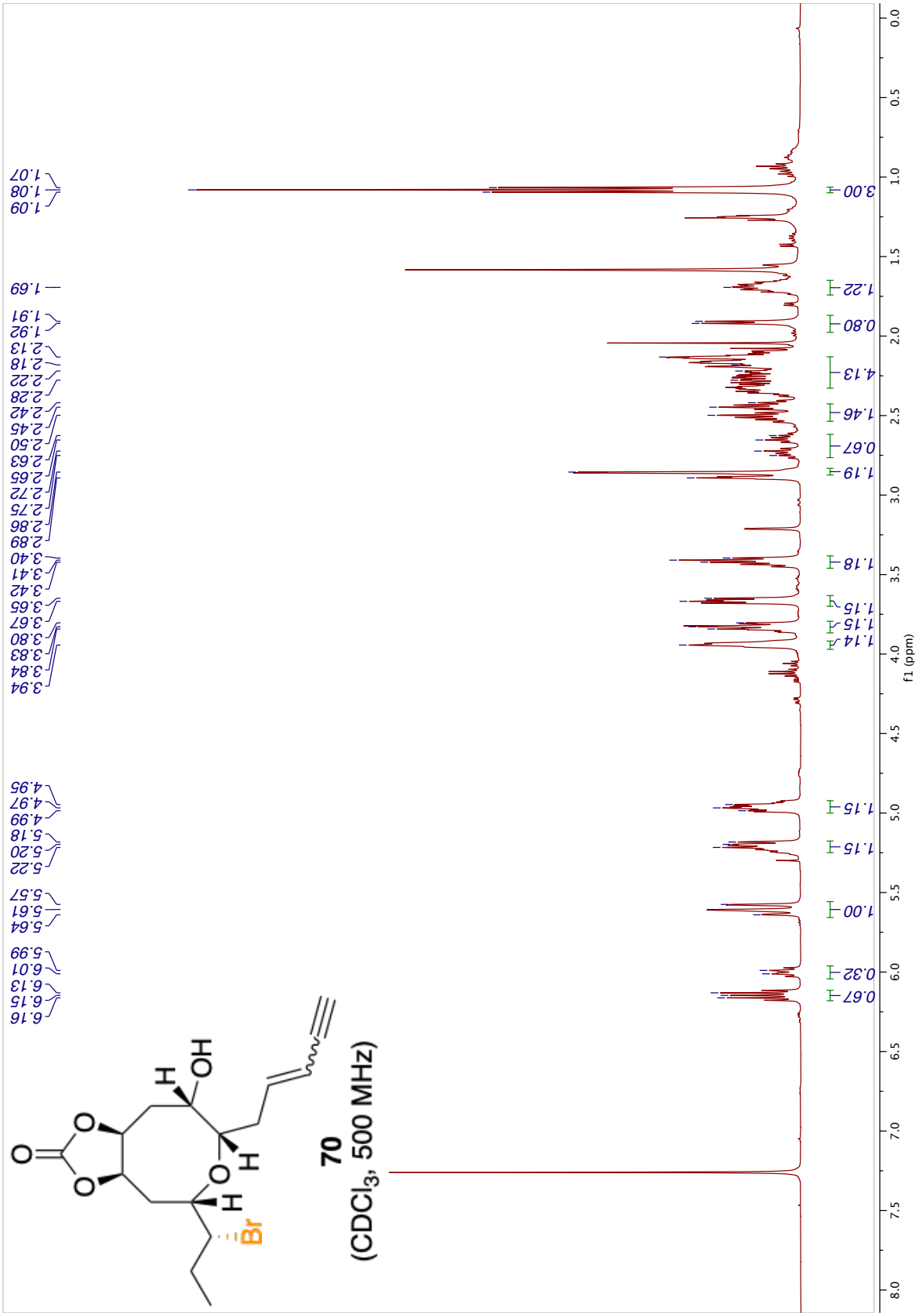

-4.67
-4.98
13.66
18.09
25.56
25.74
27.77
31.86
34.14
37.99
61.14
73.97
77.63
77.97
81.70
81.91
123.23
135.71
153.81
OBoc
H
OTBS
O
H
H
OAc
S7
(CDCl3, 125 MHz)
f1 (ppm)

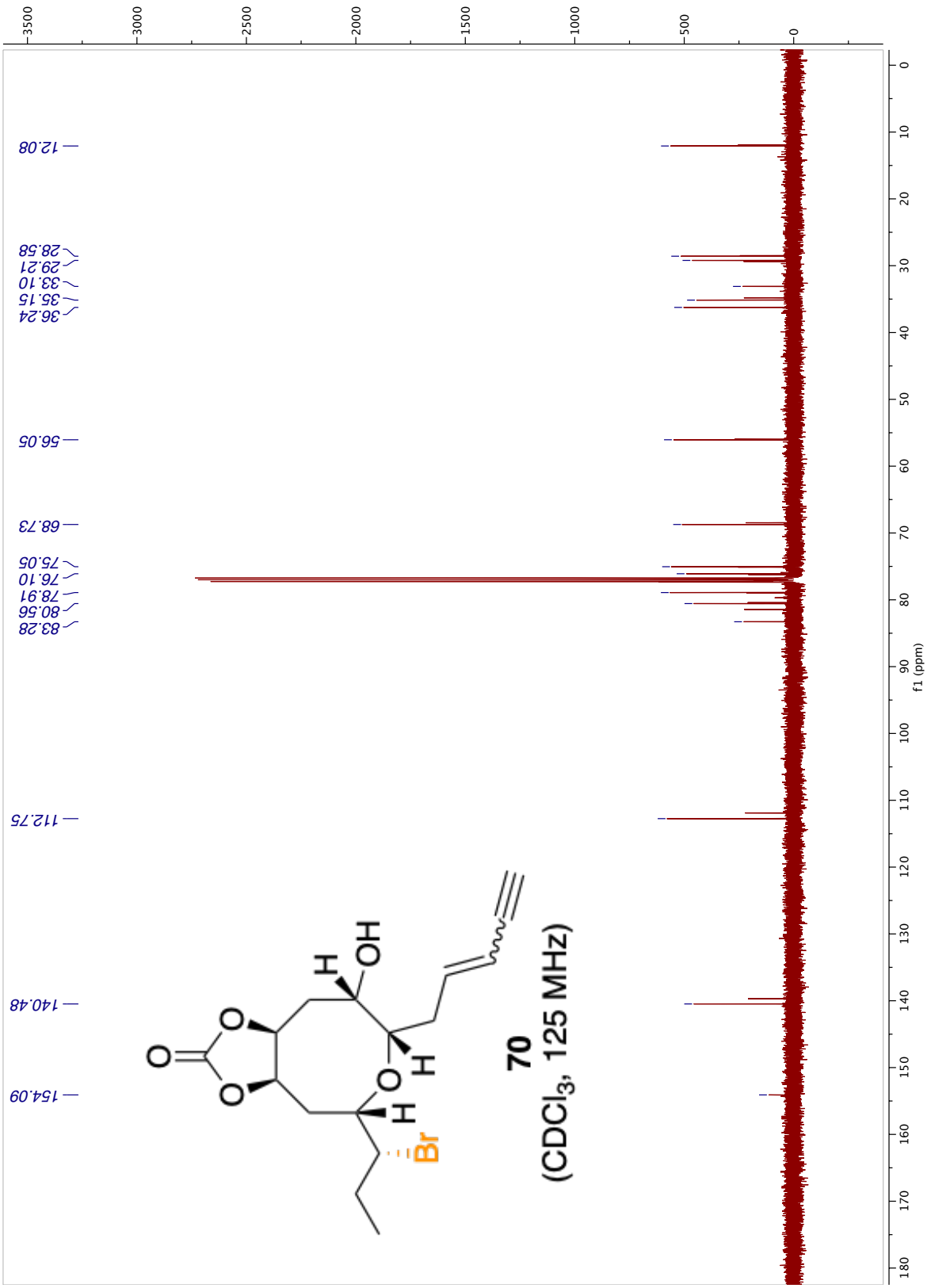

54
(CDCl3, 500 MHz)
OBoc
H
OTBS
O
H
O
H
f1 (ppm)

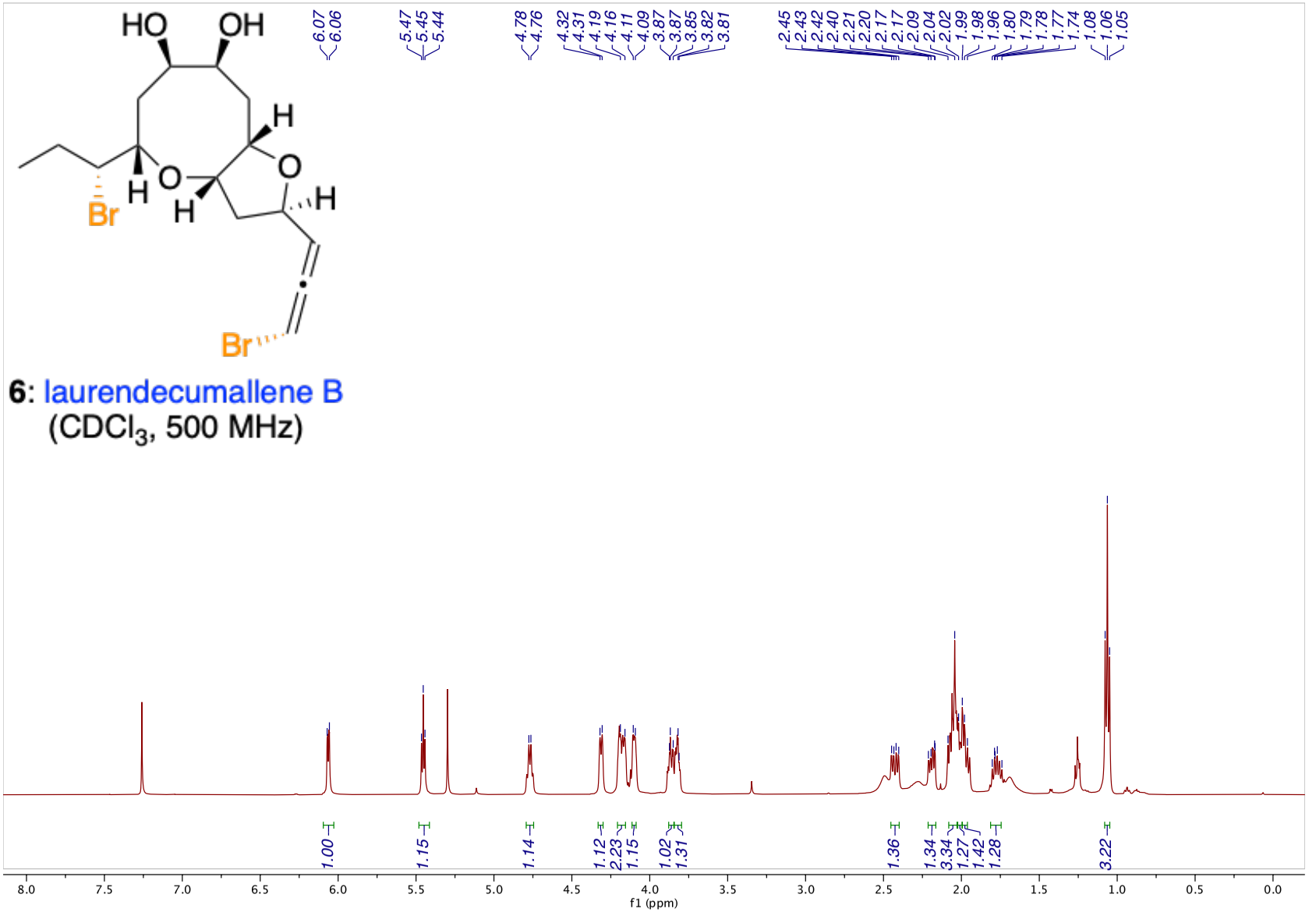

-4.68
-5.06
13.62
17.96
25.54
25.70
27.76
34.41
37.94
44.06
73.26
77.67
77.74
78.07
81.84
123.24
135.75
153.52
201.47
OBoc
H
OTBS
O
H
O
H
54
(CDCl3, 125 MHz)
f1 (ppm)

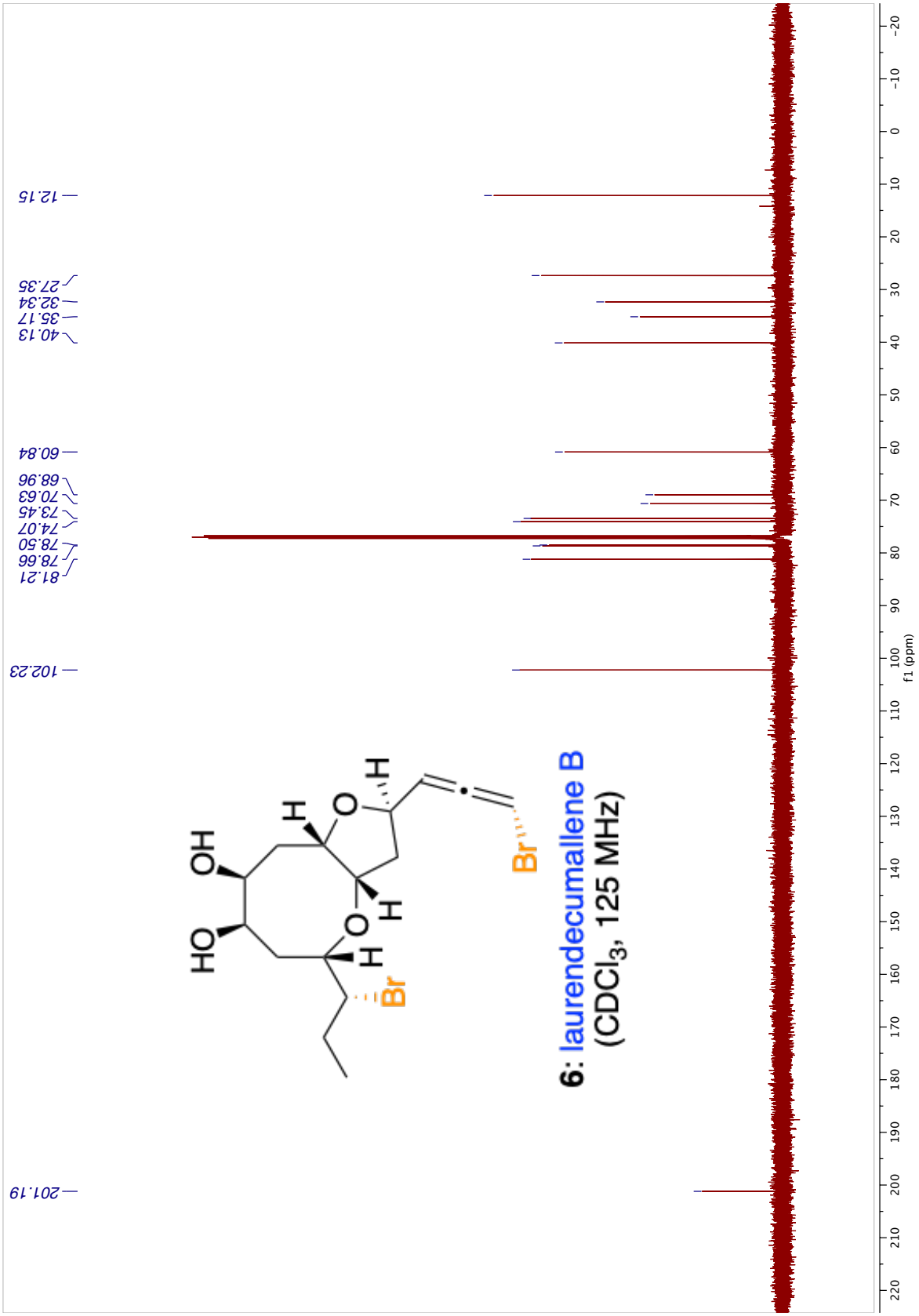

57
(CDCl3, 500 MHz)
OTBS
Br
f1 (ppm)

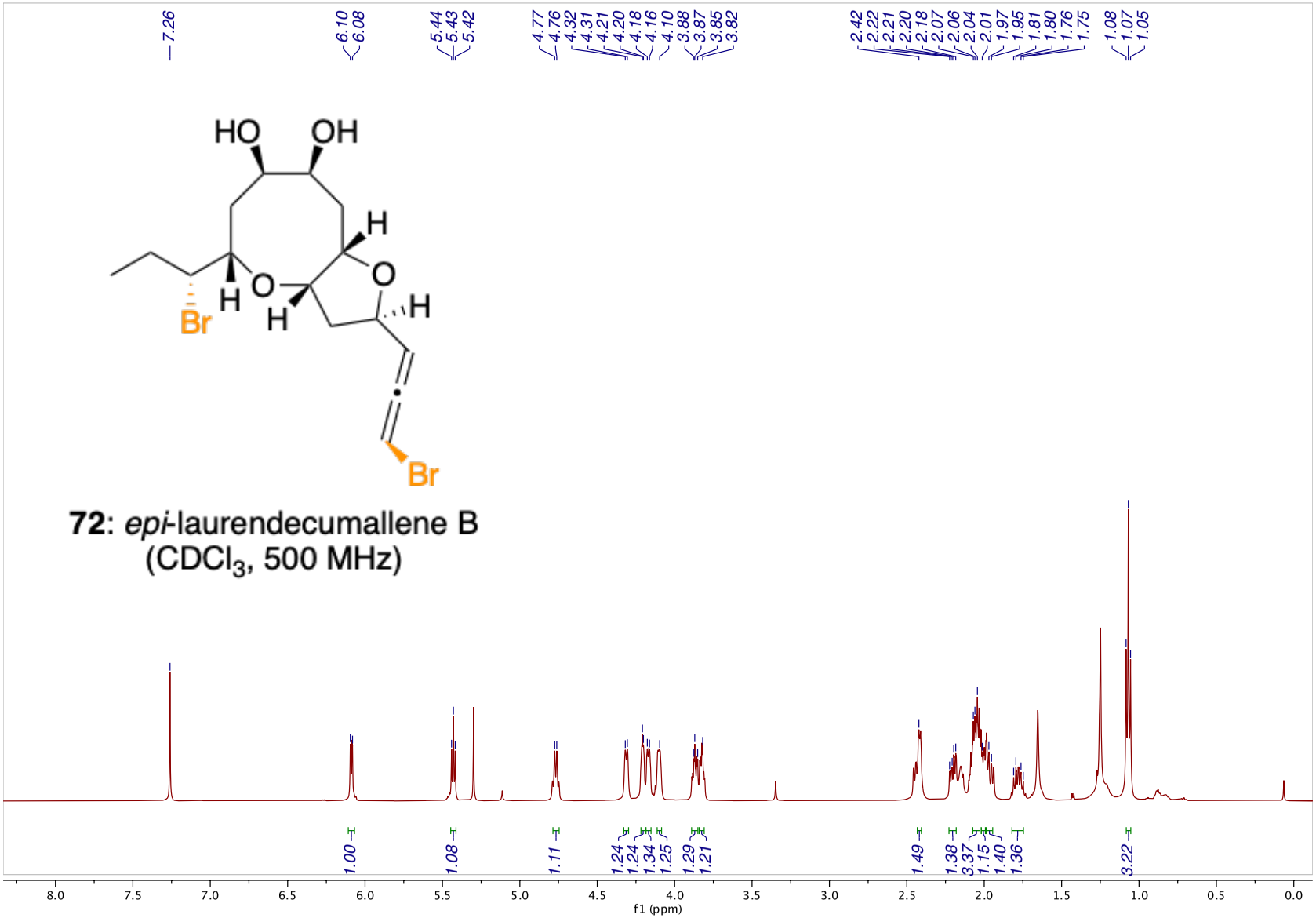

57
(CDCl3, 125 MHz)
OTBS
Br
O
H
f1 (ppm)
-4.99
-4.37
12.17
18.09
25.73
25.80
28.22
29.48
35.11
47.67
56.51
70.53
75.42
76.12
76.55
78.85
199.78

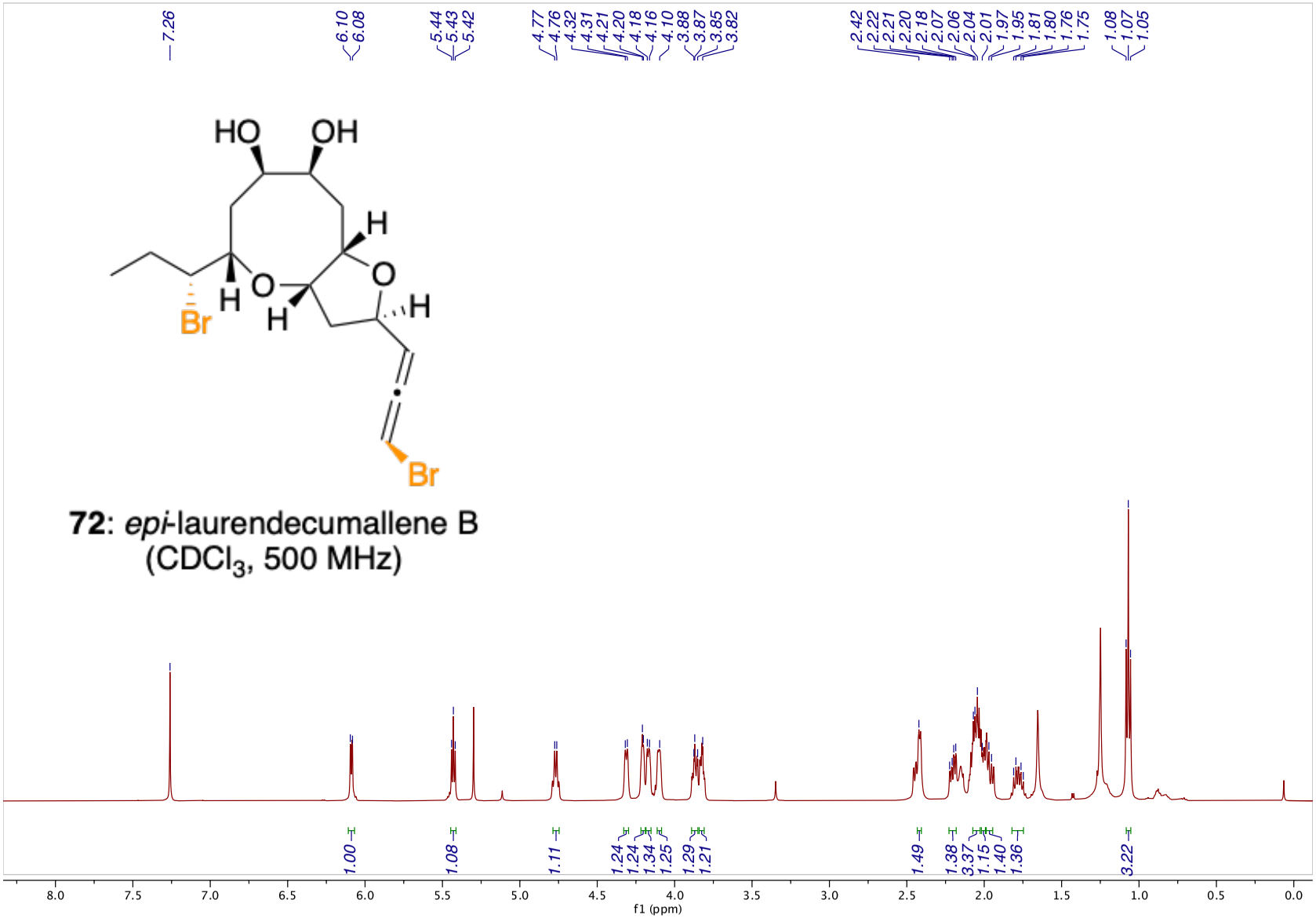

70
(CDCl3, 500 MHz)
f1 (ppm)


12.08
28.58
29.21
33.10
35.15
36.24
56.05
68.73
75.05
76.10
78.91
80.56
83.28
112.75
140.48
154.09
f1 (ppm)
70
(CDCl3, 125 MHz)
OH
H
O
Br


HO
OH
H
O
O
H
H
O
H
Br
Br
6.07
6.06
5.47
5.45
5.44
4.78
4.76
4.32
4.31
4.19
4.16
4.11
4.09
3.87
3.87
3.85
3.82
3.81
2.45
2.43
2.42
2.40
2.21
2.20
2.17
2.17
2.09
2.04
2.02
1.99
1.98
1.96
1.80
1.79
1.78
1.77
1.74
1.08
1.06
1.05
6: laurendecumallene B
(CDCl3, 500 MHz)
1.00
1.15
1.14
1.12
2.23
1.15
1.02
1.31
1.36
1.34
3.34
1.27
1.42
1.28
3.22
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


6: laurendecumallene B
(CDCl3, 125 MHz)
201.19
102.23
81.21
78.66
78.50
74.07
73.45
70.63
68.96
60.84
40.13
35.17
32.34
27.35
12.15
f1 (ppm)


7.26
6.10
6.08
5.44
5.43
5.42
4.77
4.76
4.32
4.31
4.21
4.20
4.18
4.16
4.10
3.88
3.87
3.85
3.82
2.42
2.22
2.21
2.20
2.18
2.07
2.06
2.04
2.01
1.97
1.95
1.81
1.80
1.76
1.75
1.08
1.07
1.05
HO
OH
H
O
H
O
H
H
Br
Br
72: epi-laurendecumallene B
(CDCl3, 500 MHz)
1.00
1.08
1.11
1.24
1.24
1.34
1.25
1.29
1.21
1.49
1.38
3.37
1.15
1.40
1.36
3.22
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


7.26
6.10
6.08
5.44
5.43
5.42
4.77
4.76
4.32
4.31
4.21
4.20
4.18
4.16
4.10
3.88
3.87
3.85
3.82
2.42
2.22
2.21
2.20
2.18
2.07
2.06
2.04
2.01
1.97
1.95
1.81
1.80
1.76
1.75
1.08
1.07
1.05
HO
OH
H
O
H
O
H
H
Br
Br
72: epi-laurendecumallene B
(CDCl3, 500 MHz)
1.00
1.08
1.11
1.24
1.24
1.34
1.25
1.29
1.21
1.49
1.38
3.37
1.15
1.40
1.36
3.22
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

CHAPTER 2

STUDIES TOWARD THE GRAYANANE DITERPENOID FAMILY OF NATURAL PRODUCTS

2.1 Introduction

2.1.1 Structures and Bioactivities of Selected Grayanane Diterpenoids

Another significant class of bioactive molecules suffering from the dual issues of general laboratory synthetic inefficiency and low natural abundance is the grayanane diterpenoids. From the original isolation of grayanotoxin I (**1**, Figure 2.1) in 1956[1] through the end of 2018, there had been nearly 300 grayanane diterpenoids isolated, with two extensive reviews by Yu[2] and Li/Gao[3] detailing their structures and biological activities. Since Li and Gao's review in January of 2019, there have been an additional 40 novel grayanane diterpenoids isolated.[4] Although this family consists of many closely related molecules, typically sharing a *trans/cis/cis*-fused 5/7/6/5 skeleton, it exhibits a diverse range of bioactivity. For example, the flagship members of this family, grayanotoxins I and III (**1** and **2**), along with rhodojaponin III (**5**), exhibit strong sodium channel antagonism whereas rhodojaponin I (**3**) exhibits strong anti-nociceptive properties.[5]

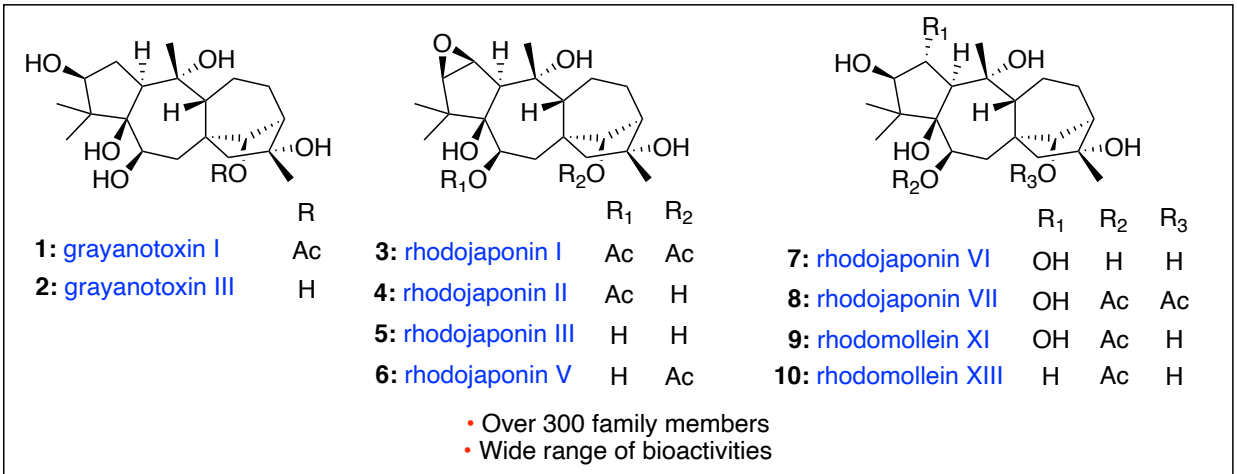


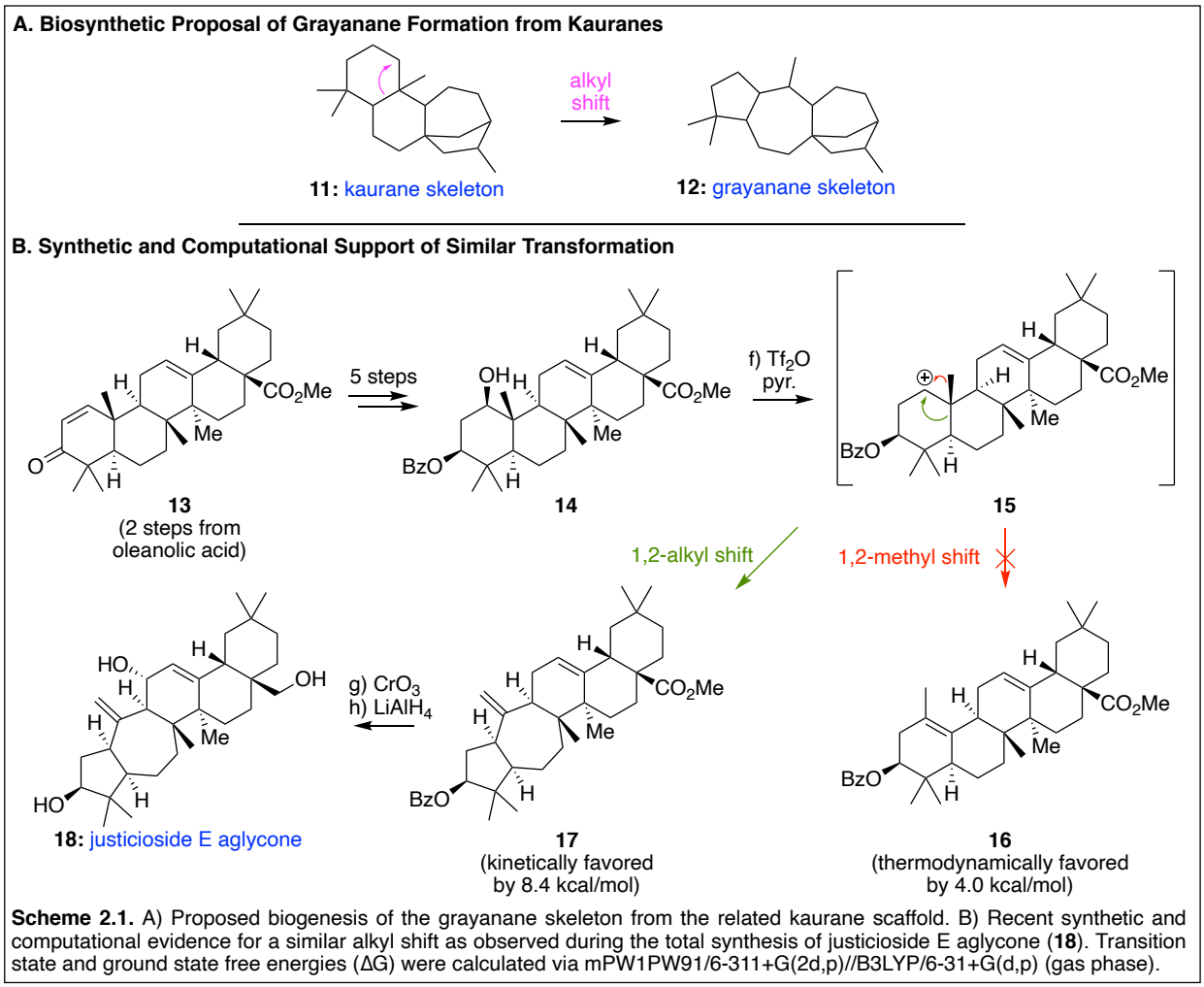
Figure 2.1. Selection of grayane diterpenoid targets.

In a recent report by the Yao group, twenty-nine members of this family were isolated from the leaves of *Rhododendron mole* (fourteen of which were previously unknown), and each was evaluated for anti-inflammatory properties; ten demonstrated IC_{50} values between 2.8 and 35.4 μM when tested for their ability to inhibit nitric oxide production in mouse microphages.[6] However,

the natural abundance of these molecules is also quite low: from 25.0 kg of air-dried *R. molle* leaves, the largest amount of pure **7** extracted by Yao and co-workers was 35.7 mg.[6] For 21 of the 29 isolated compounds, quantities of less than 10.0 mg were obtained. As such, accomplishing an efficient pathway to this bioactive and scarce class of molecules would allow for the exploration of another area of untouched chemical space within the pharmaceutical sector.

2.1.2 Proposed Biogenesis of Grayanane Diterpenoids

Biosynthetically, the Newhouse group has proposed that the grayanane skeleton is derived through a single C-C bond migration of the kaurane scaffold, rearranging the tetracyclic system from 6/6/6/5 to 5/7/6/5 (Scheme 2.1, panel A).[7] Although this exact rearrangement has not been reported, the Newhouse group has recently elucidated a similar 1,2-alkyl shift within the justicane class of natural products (Scheme 2.1, panel B). Upon generating the secondary carbocation (**15**) by subjecting precursor **14** to triflic anhydride in pyridine, they observed immediate and complete conversion to the rearranged **17**.[7] Initially, they were unsure of the efficiency of this potential alkyl-migration as a competing 1,2-methyl shift is easily envisioned as well. However, upon computational analysis of the two pathways, they observed a very clear kinetic bias for the desired 1,2-alkyl shift ($\Delta\Delta G^{\ddagger}$ = 8.4 kcal/mol) with a nearly barrierless transition state ($\Delta G^{\ddagger}$ = 0.2 kcal/mol), even though the 1,2-methyl shift yielded a more thermodynamically stable product ($\Delta\Delta G$ = 4.0 kcal/mol). This stark difference in transition state barriers is attributed to the subtle geometrical change between **14** and **17** since the starting A-ring of **14** sits in a chair-like conformation, allowing for antiperiplanar overlap between the p_{C1} orbital and the migrating bond.[8] The transformation of **14→16**, on the other hand, requires the A-ring to convert to a half-chair conformation in order for successful methyl migration.



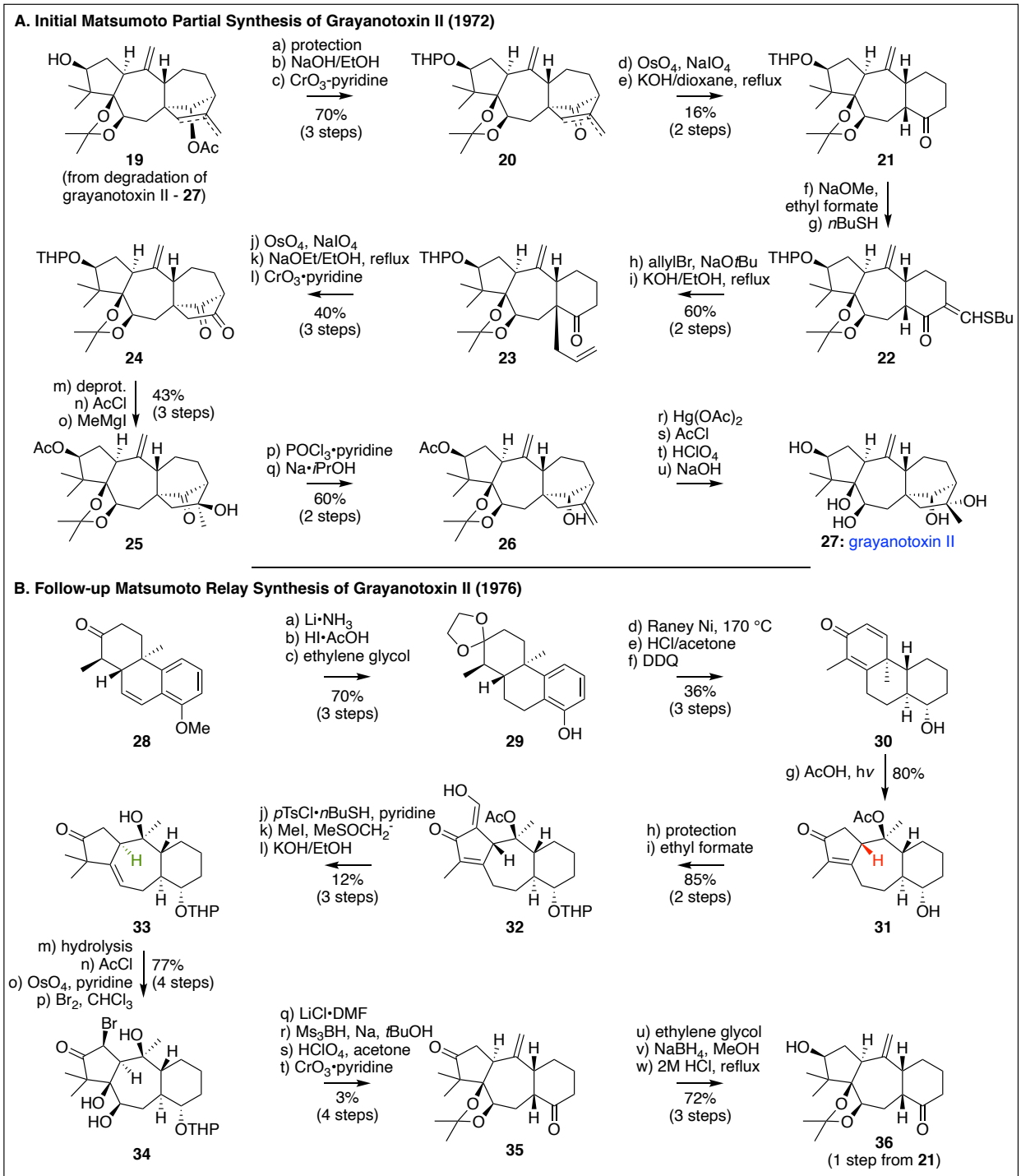
Scheme 2.1. A) Proposed biogenesis of the grayanane skeleton from the related kaurane scaffold. B) Recent synthetic and computational evidence for a similar alkyl shift as observed during the total synthesis of justicioside E aglycone (**18**). Transition state and ground state free energies (ΔG) were calculated via mPW1PW91/6-311+G(2d,p)//B3LYP/6-31+G(d,p) (gas phase).

2.1.3 Previous Synthetic Efforts Toward Grayanane Diterpenoids

Although these molecules have consistently been reported to have strong bioactivities, there had been just a handful of synthetic studies toward grayanotoxin II (**27**)[9] and pierisformaside C (**57**),[10] and just a single published total synthesis of one member of the family (grayanotoxin III, **2**)[11] at the outset of this project. Although work in this area has been sparce, each report offers valuable insight into the challenges presented by these oxidized and stereochemically intricate compounds.

The first report of any synthetic efforts regarding the grayanane diterpenoids was the partial synthesis of grayanotoxin II (**27**) by the Matsumoto group in 1972, which highlighted the difficulty

of regio- and chemoselective design when it comes to these highly functionalized targets (Scheme 2.2).[9a] Initially starting from tetracyclic **19** (a degradation product of naturally occurring **27**), Matsumoto performed a 3 step sequence involving the THP protection of the free secondary alcohol and subsequent deprotection and oxidation of the acetyl-protected secondary alcohol, resulting in a 1:1 mixture of *endo*/*exo* olefin isomers **20**. From here, a Lemieux-Johnson oxidation, followed by deformylation and deacetylation in the presence of potassium hydroxide under refluxing conditions delivered what they state as their key intermediate, tricyclic **21**. Of note, the Lemieux-Johnson oxidation showed poor selectivity in the presence of the central olefin, yielding 27% of the desired enol intermediate (in relation to the preexisting ketone), 24% of the central ketone product resulting from cleavage of the central 1,1-disubstituted olefin, and 4% of a doubly cleaved byproduct as well. However, with **21** in hand, they were able to advance to the allylated **23** over 4 steps, in which the use of a target superfluous vinylogous thioester allowed for regioselective allylation.[12] From here, a second (and more selective) Lemieux-Johnson oxidation of the mono-substituted olefin followed by aldol addition and further oxidation then reintroduced the tetracyclic core of grayanotoxin II in intermediate **24**. After converting the THP-protecting group to acetyl, a non-selective methyl Grignard addition was performed, yielding 43% of the desired **25**, along with 34% of the undesired ketone addition. However, they were able to push forth through dehydration of the tertiary alcohol, and a Na•*i*PrOH mediated reduction of the sole ketone fashioned **26**. A final four step sequence including a non-selective oxymercuration (24% yield), acetate protection of each free alcohol, acetonide deprotection, and subsequent global hydrolysis yielded the target compound, grayanatoxin II (**27**), in a total of 21 steps from degradation product **19**.



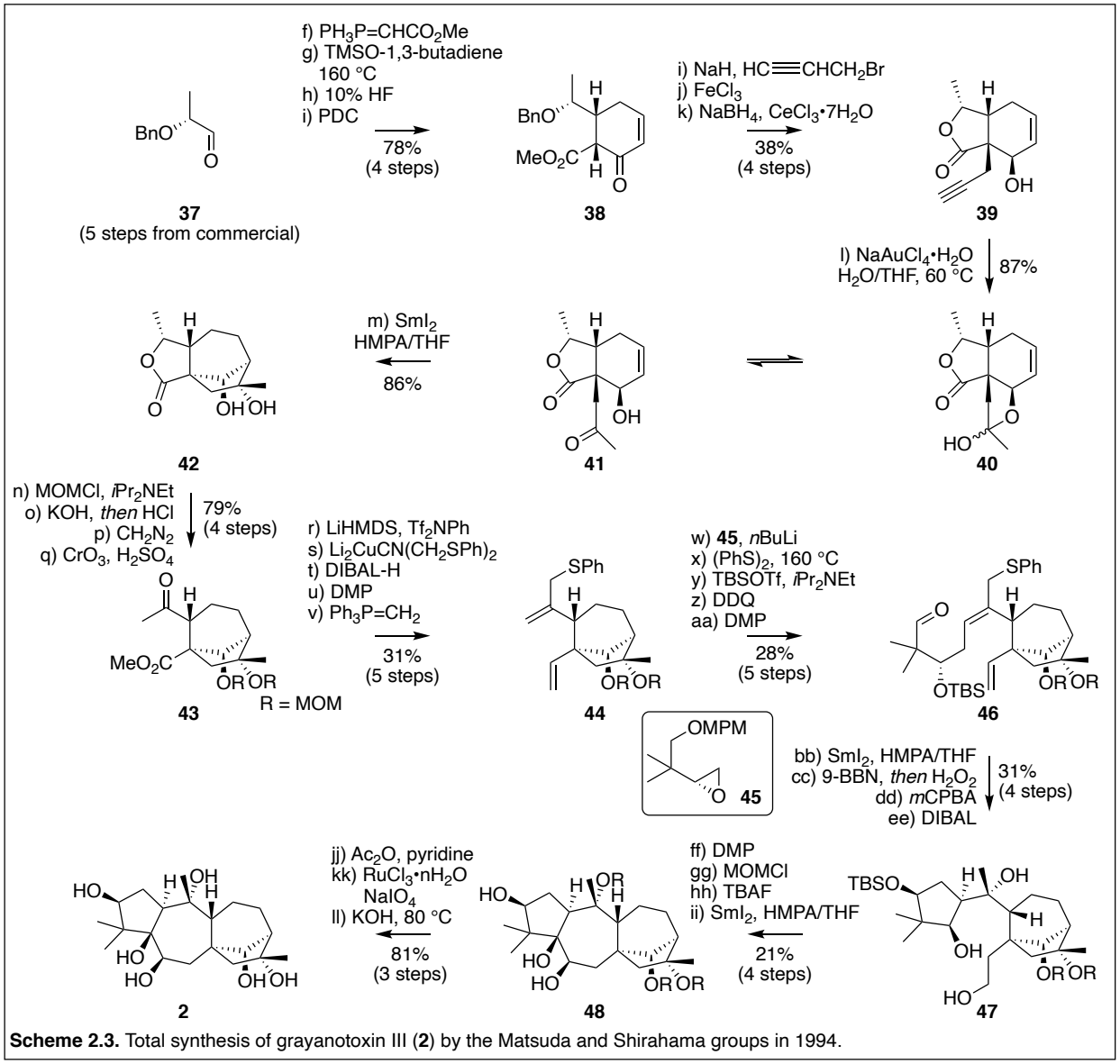
Scheme 2.2. A) Original partial synthesis of **27** by the Matsumoto group starting from a degradation product of grayanotoxin II (**27**) and B) a subsequent study establishing a relay synthesis of **27** to produce precursor **36**, just one step from intermediate **21** of the original work.

In a follow-up study four years later in 1976, the Matsumoto group reported a relay synthesis of **27**, in which they focused on achieving the key tricyclic intermediate **36**.[9b] Starting from known tricyclic **28**,[13] a three-step reduction, demethylation, and ketal protection yielded

phenol **29** in 70% yield. From here, full hydrogenation of the phenol followed by deprotection of the ketal and subsequent dienone formation produced ring-expansion precursor **30**, which upon exposure to UV-irradiation in acetic acid smoothly delivered **31**, constructing the 5/7/6 framework in good yield (80%). Even though the tricyclic skeleton of their target intermediate was achieved at this point, it still took another 16 steps to complete the construction of alcohol **36**, one step away from intermediate **21** in their original partial synthesis. The high step-count necessary to accomplish the installation of the 1,2-diol moiety and inversion of the red-highlighted proton in **31** emphasizes the challenge these highly functionalized compounds pose. In total, if the extra THP-protection step were performed, this would result in a combined 40-step synthesis of grayanotoxin II (**27**) from known tricycle **28**.

Another impressive feat towards this class of compounds was not seen again until 1994, when Matsuda, Shirahama, and co-workers accomplished an enantiospecific total synthesis of grayanotoxin III (**2**) in 39 linear steps, utilizing three SmI_2-induced reactions as critical steps (Scheme 2.3).[11] Starting from known chiral aldehyde **37**,[14] a four-step sequence involving Wittig olefination of the aldehyde, subsequent facial and diastereoselective Diels-Alder with 1-((trimethylsilyl)oxy)-1,3-butadiene, desilylation and oxidation delivered enone **38**. This 1,3-dicarbonyl could then be converted into the first SmI_2-mediated cyclization precursor **40** after introduction of the propargyl sidechain (establishing the first quaternary center of the target), debenzylation,[15] Luche reduction, and final lactol formation as promoted by $NaAuCl_4$ in the presence of water.[16] This lactol was reported to exist in an equilibrium between the closed **40** and open **41**, allowing for the critical reductive coupling between the carbonyl and the olefin in a 5-*exo*-trig fashion, with the coordination of the Sm(III) to the free hydroxyl of the starting material allowing for full diastereoselectivity.[17] With tricycle **42** in hand, further functional group and

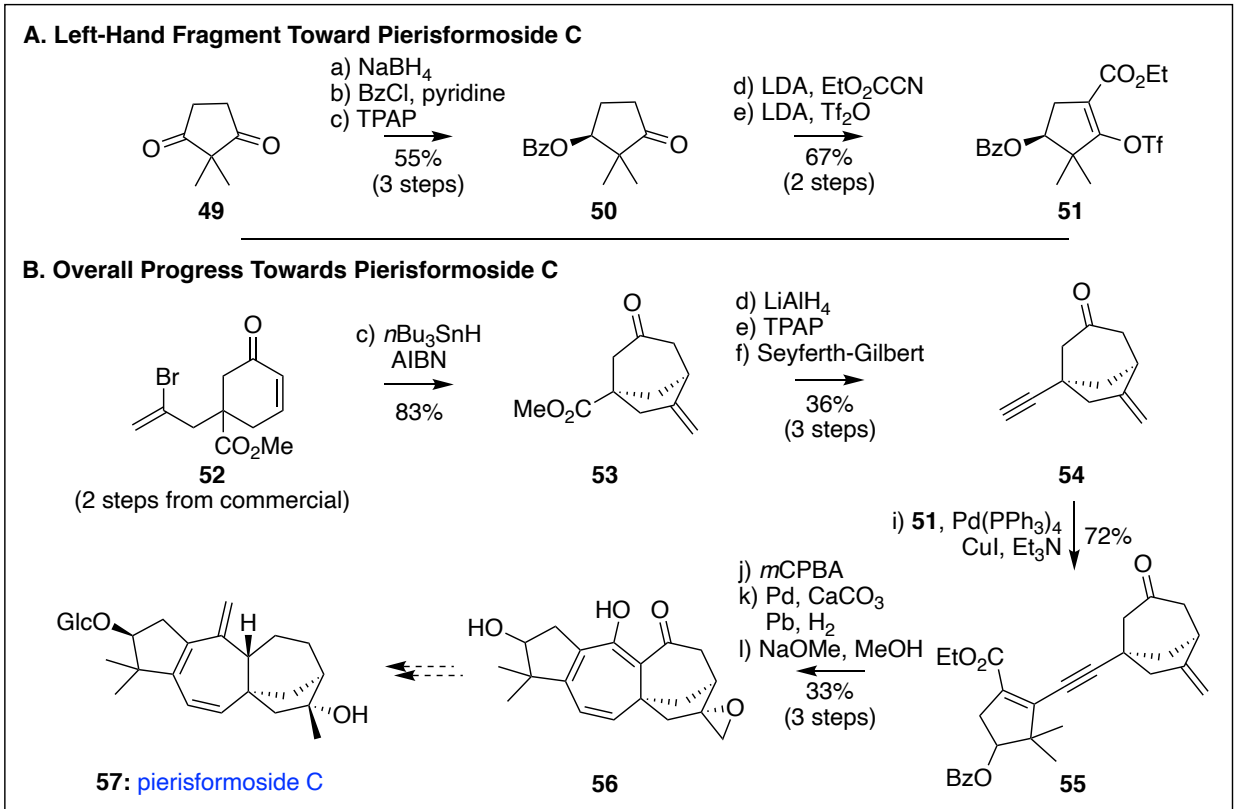
oxidation state manipulations over the course of 14 additional steps (with an overall yield of 7%) set the stage for the second radical cyclization of **46**, in which the allyl sulfide serves as the ketyl radical acceptor furnishing an exocyclic olefin which could be further extrapolated to the tertiary alcohol in **47** through a simple hydroboration-process.[17f] After oxidizing the free alcohols of **47** to their respective aldehyde and ketone with DMP, MOM-protection of the tertiary alcohol, silyl-deprotection, and a final pinacol coupling could be effected once again through the use of SmI_2 with the diastereoselectivity being reinforced by the hydroxyl coordination.[18] Intriguingly, although the system was only three MOM-ethers away from grayanotoxin III (**2**), simple acid-promoted deprotection was ineffective. This forced Matsuda/Shirahama to protect the remaining free alcohols as acetates, oxidize the methylene units of the MOM groups to their respective carbonates,[19] and then perform the final global deprotection through basic hydrolysis to deliver **2**. All said and done, although artful, this construction of the *trans/cis/cis*-fused 5/7/6/5 skeleton is likely not translatable to an industrial setting, in neither native or derivatized form, due principally to its overall length and linear nature. However, it is important to reiterate that this 39-step synthesis from 1994 had been the only completed synthesis of any member of this elaborate family upon the outset of our own work, exemplifying the difficulty associated with, and aversion to, such complex targets.



Scheme 2.3. Total synthesis of grayanotoxin III (**2**) by the Matsuda and Shirahama groups in 1994.

The next synthetic study for a related compound (pierisformaside C, **57**), had not been published until 2011 by the Williams group, a full 17 years after the Matsuda/Shirahama synthesis.[10] Therein, they sought to address some of the critical pitfalls of the seminal synthesis of the grayanane diterpenoids by developing a convergent synthesis through the employment of two key fragments (**51** and **54**, Scheme 2.4). Starting from commercially available diketone **49**, triflate **51** was quickly established through well-developed chemistry over the course of 5 steps.[20] Alkyne **54** was constructed over six steps, featuring an intramolecular radical cyclization of vinyl bromide

52,[21] fashioning the same C-C bond that was built through the SmI_2 coupling outlined by Matsuda/Shirahama.[11] With both fragments quickly obtained, a simple Sonogoshira coupling of **51** and **54** delivered **55** in 72% yield,[22] which could be further extrapolated into what is claimed to be a probable advanced synthetic intermediate of pierisformoside C, **56**, in 3 additional steps,[23] with construction of the central seven-membered ring taking place through a Claisen cyclization between the ethyl ester and ketone. Although the skeleton of the grayanane diterpenoids was developed in an efficient 10 steps (longest linear sequence), there are various paths that can be envisioned to obtain the desired final target **57**. The difficulty of affecting a concise chemo- and regioselective transformation of **56** to **57**, presents a similar downfall as the grayanotoxin III synthesis. However, this body of work does signal that a convergent approach to this family can build the central framework in a swift manner, opening the door for further inquiry.



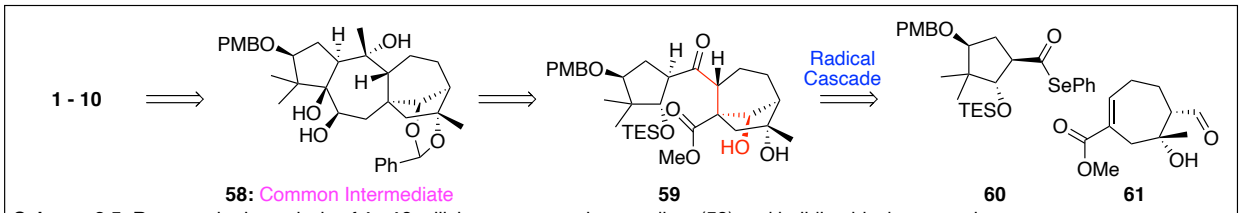
Scheme 2.4. Studies toward the total synthesis of pierisformoside C (**57**) by the Williams group in 2011 featuring a Sonogoshira coupling and NaOMe mediated cyclization.

2.2 Synthetic Study Towards Ten Grayanane Diterpenoids

Herein, we outline our synthetic efforts toward developing a highly divergent approach to the grayanane diterpenoid family. Two main approaches are presented, with the first featuring what we hoped to be an intermolecular radical coupling cascade to construct the righthand bridged bicycle as well as introduce the left-hand portion of the common scaffold, and the second featuring a key lithiation of a vinyl halide to bring the two fragments together. Both approaches allowed us to envision the construction of each family member from a common intermediate in a longest linear sequence ranging from 14 to 20 steps.

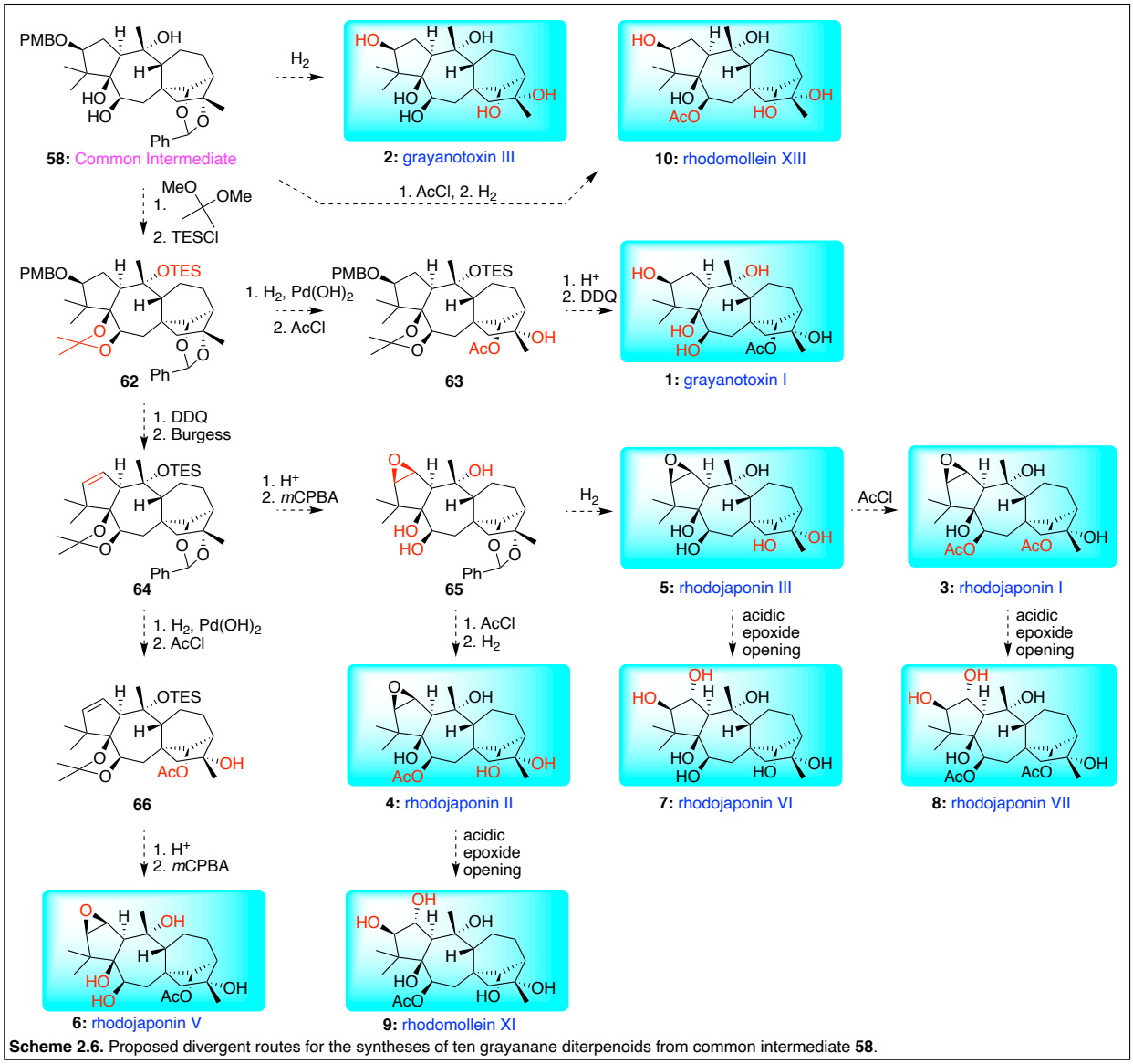
2.2.1 Envisioned Use of Common Intermediate

The use of a common intermediate to achieve several natural products, also known as a divergent synthesis,[24] has become a powerful approach to economically access a large swath of targets that could potentially be derivatized further and biologically tested.[25] Given the wide range of bioactivities and highly conserved skeleton of the grayanane diterpenoids, we hoped to utilize a divergent synthesis approach to access a total of ten closely related targets (**1**–**10**, Figure 2.1), all potentially through the use of a common intermediate (**58,** Scheme 2.5). **58** is hopefully accessible through various functional group interconversions and a previously reported C–C coupling starting from **59**.[11] Of note, an intermolecular radical coupling cascade was initially planned to construct **59** from building blocks **60** and **61**. The most formidable challenge we anticipated in regard to this transformation was preventing the terminating radical attack on the aldehyde from reverting back to the stabilized tertiary radical. The initial Michael addition utilizing an acyl selenide, on the other hand, was viewed as well precedented as a large body of work has been reported in this area by Crich,[26] Boger,[27] and Bennasar,[28] in both intramolecular and intermolecular cases, in which the electron-deficient olefin could be either acyclic or cyclic.



Scheme 2.5. Retrosynthetic analysis of **1 - 10** utilizing a common intermediate (**58**) and building block approach.

If common intermediate **58** was achieved then **1** – **10** could each reasonably be envisioned to be accessible in an additional one to nine steps, with several targets being derived from one another (Scheme 2.6). For instance, grayanotoxin III (**2**) would be a simple hydrogenation from **58**, delivering the final target in a single step. However, an acylation of the secondary alcohol followed by simultaneous deprotection of the PMB-alcohol and benzylidene acetal through hydrogenation could potentially deliver rhodomollein XIII (**10**) in two steps from **58**.[29] A second common intermediate, **65**, could also possibly be achieved in six steps from **58**, taking advantage of the orthogonality of the PMB group and the benzylidene acetal, reasonably allowing access to six additional targets of interest (Scheme 2.6).[30]



Scheme 2.6. Proposed divergent routes for the syntheses of ten grayanane diterpenoids from common intermediate **58**.

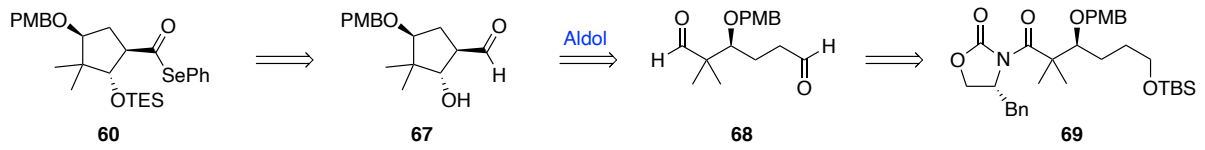
2.2.2 Forward Synthesis of Radical Coupling Fragments

As illustrated previously in Scheme 2.5, our initial approach to the grayanane diterpenoids focused on the convergent synthesis of key intermediate **58** by bringing together two fragments: **60** and **61**. To this end, we set out to accomplish each of these pieces in either an enantio- or diastereoselective fashion.

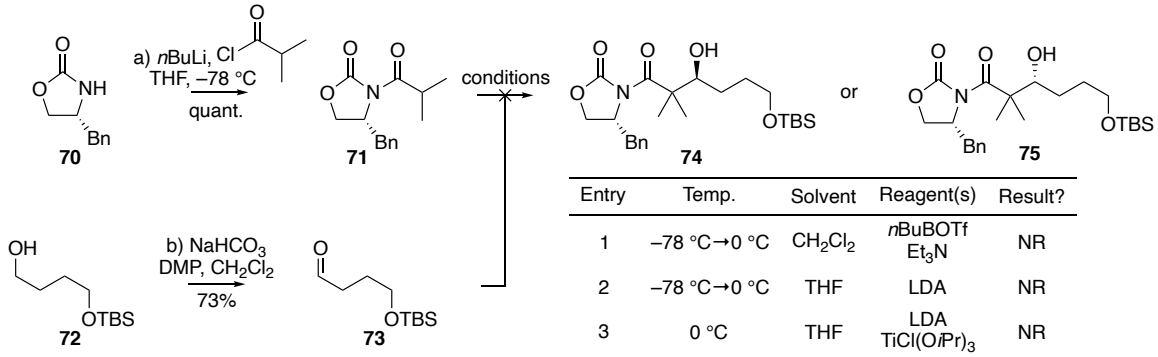
Given the oxidative patterning of western fragment **60**, we believed the cyclopropane ring could be fashioned through an asymmetric, proline-catalyzed aldol cyclization of starting

dialdehyde (**68**, Scheme 2.7).[31] This could be further traced back to diol **69**, containing a single stereocenter, which we envisioned could be set through another asymmetric aldol addition, this time using Evans' chiral auxiliary to dictate the stereochemical outcome.[32] In a forward sense, generation of the desired chiral auxiliary **71** proceeded in quantitative yield with isobutyryl chloride and (*R*)-4-benzyl-2-oxazolidinone (**70**).[33] The requisite aldehyde for the following aldol addition was also easily produced by oxidation of commercially available 4-(*tert*-butyldimethylsiloxy)butanol (**72**) with Dess–Martin periodinane, providing **73** in 73% yield. However, any attempts to join these two pieces together failed to provide any desired product, even in the presence of TiCl(O*i*Pr)$_3$ (which would have delivered the undesired alcohol diastereomer **75** with the chiral auxiliary used here).[34] Intriguingly, by quenching the reactions with D_2O, no enolate generation was observed.

A. Western Fragment Retrosynthetic Analysis



B. Failed Forward Approach to Western Fragment[a]



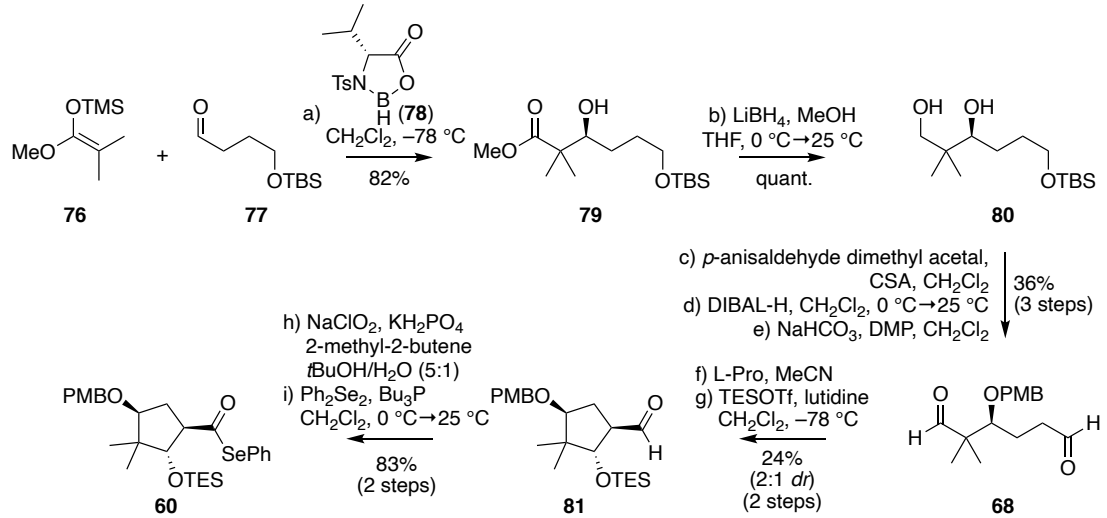
Entry	Temp.	Solvent	Reagent(s)	Result?
1	–78 °C→0 °C	CH_2Cl_2	*n*BuBOTf Et_3N	NR
2	–78 °C→0 °C	THF	LDA	NR
3	0 °C	THF	LDA TiCl(O*i*Pr)$_3$	NR

Scheme 2.7. A) Retrosynthetic analysis of **60** and B) inability to generate desired enolate.
[a] Reagents and conditions: (a) *n*BuLi (1.0 equiv), THF (0.2 M), –78 °C, 1 h, *then* iosbutyryl chloride (2.5 equiv), –78 °C, 20 min, quant.; (b) $NaHCO_3$ (5.0 equiv), DMP (1.1 equiv), CH_2Cl_2 (0.1 M), 25 °C, 20 min, 73%.

Given the unexpected difficulty of forming the desired enolate with the Evans auxiliary, we turned to a Mukaiyama aldol instead, as the silyl enol ether **76** all but guarantees the desired

nucleophile would be in play for the given reaction (Scheme 2.8). Pleasingly, in the presence of chiral borane **78** (generated in situ), the reaction provided **79** in 82% yield at –78 °C, without the need to remove any auxiliary.[35] However, the next challenge was the efficient PMB-protection of the secondary alcohol. Any attempts to directly perform this protection under basic or acidic conditions with PMBCl, PMB-trichloroacetimidate, or 2-PMBO-lepidine failed to show any reactivity. Instead, a three-step procedure was instead performed to first reduce the methyl ester to a primary alcohol with $LiBH_4$ before being subjected to 1,3-diol protection conditions with *p*-anisaldehyde dimethyl acetal.[36] By utilizing strongly acidic conditions, the TBS group could be removed concomitantly while performing the diol protection. Of note, the initial ester reduction required $LiBH_4$, as both $LiAlH_4$ and DIBAL-H in various solvents led to full reduction along with TBS deprotection. Finally, the diol could be regioselectively deprotected to produce the primary alcohol along with the PMB-protected secondary alcohol when subjected to DIBAL-H.

Scheme 2.8. Forward Synthesis of western fragment **60** in partnership with Mr. Evgeny Gulyak.[a]

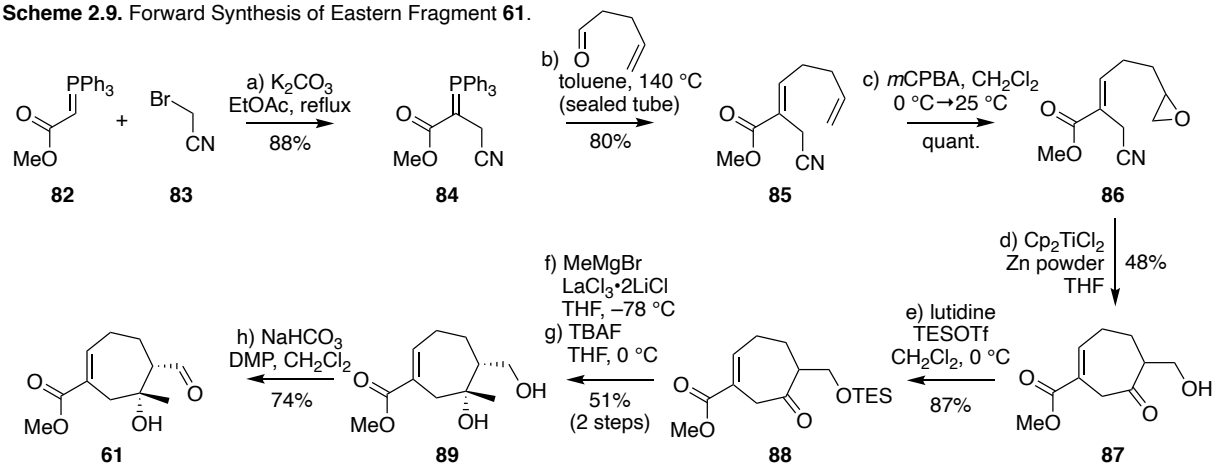


[a] Reagents and conditions: (a) **78** (1.1 equiv), **76** (1.2 equiv), CH_2Cl_2 (0.04 M), –78 °C, 2 h, 82%; (b) MeOH (48.0 equiv), $LiBH_4$ (12.0 equiv), THF (0.05 M), 0 °C→25 °C, 2 h, quant.; (c) *p*-anisaldehyde dimethyl acetal (3.0 equiv), CSA (0.4 equiv), CH_2Cl_2 (0.07 M), 25 °C, 24 h, 61%; (d) DIBAL-H (3.0 equiv), CH_2Cl_2 (0.03 M), 0 °C→25 °C, 1.5 h, 91%; (e) $NaHCO_3$ (6.0 equiv), DMP (2.2 equiv), CH_2Cl_2 (0.1 M), 25 °C, 30 min, 65%; (f) L-proline (1.0 equiv), MeCN (0.02 M), 25 °C, 45 min, 54%; (g) lutidine (2.0 equiv), TESOTf (2.0 equiv), CH_2Cl_2 (0.03 M), –78 °C, 30 min, 44% (2:1 *dr*); (h) KH_2PO_4 (2.0 equiv), 2-methyl-2-butene (8.0 equiv), $NaClO_2$ (4.0 equiv), *t*BuOH/H_2O (5:1, 0.1 M), 25 °C, 12 h, 91%; (i) Ph_2Se_2 (1.5 equiv), Bu_3P (1.5 equiv), CH_2Cl_2 (0.03 M), 0 °C→25 °C, 5 min, 91%.

Subsequent oxidation of the two primary alcohols yielded dialdehyde **68** (Scheme 2.8), which was then subjected to aldol cyclization conditions (work done in part by Mr. Evgeny Gulyak).[31] Thankfully, we found that for our particular system the use of MeCN as solvent favored the aldol addition product over the condensation adduct, even at ambient temperature. Efforts to probe the effect of lower temperatures in this process along with solvent screening failed to improve the overall yield of this transformation, however each step through this point was operationally simple, still allowing for modest material throughput. Finally, TES-protection of the secondary alcohol further prevents the condensation product from forming in subsequent reactions, allowing phenyl selenide **60** to be achieved in two more steps.[37]

As for the righthand fragment, we took inspiration from the recent total syntheses of labdane diterpenes galanal A and B by the Chein group, in which we hoped to form **61** through a titanocene-mediated radical cyclization (Scheme 2.9).[38] To obtain precursor **86**, we began with commercially available 4-pentenal and subjected it to Wittig conditions in a sealed tube; the intermediate product (**85**) was then subsequently exposed to *m*CPBA. With epoxide **86** synthesized, the following radical cyclization (Cp_2TiCl_2, Zn powder) proceeded in modest yield (48%) to produce the desired 7-membered ring intermediate **87**. Thankfully, when performing the TES-protection of the resulting primary alcohol, no double bond isomerization into a conjugated variant was observed.

Scheme 2.9. Forward Synthesis of Eastern Fragment **61**.

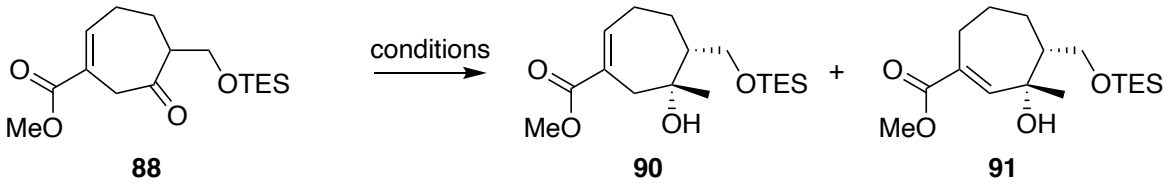


[a] Reagents and conditions: (a) **83** (1.2 equiv), K_2CO_3 (2.0 equiv), EtOAc (0.1 M), reflux, 8 h, 88%; (b) **84** (3.0 equiv), 4-pentenal (1.0 equiv), toluene (0.1 M), 140 °C (sealed tube), 48 h, 80%; (c) *m*CPBA (2.0 equiv), CH_2Cl_2 (0.2 M), 0 °C, 1 h, *then* 25 °C, 5 h, quant.; (d) Cp_2TiCl_2 (2.2 equiv), Zn (6.6 equiv), THF (0.07 M), 25 °C, 2 h, 48%; (e) lutidine (2.0 equiv), TESOTf (2.0 equiv), CH_2Cl_2 (0.1 M), –78 °C, 20 min, 87%; (f) $LaCl_3$•2LiCl (3.0 equiv), MeMgBr (1.1 equiv), THF (0.03 M), –78 °C, 30 min, 57% (95% brsm); (g) TBAF (1.1 equiv), THF (0.02 M), 0 °C, 5 min, 89%; (h) $NaHCO_3$ (5.0 equiv), DMP (1.4 equiv), CH_2Cl_2 (0.03 M), 25 °C, 2 h, 74%.

However, while these reactions proceeded smoothly, the next step, a chemoselective 1,2-Grignard addition to the ketone, proved challenging. It was not until a Lewis acid additive developed by the Knochel group was implemented, namely $LaCl_3$•2LiCl, that we observed the desired product in any measurable yield (**88** and $LaCl_3$•2LiCl in THF, –78 °C for 1 h, then MeMgBr dropwise, –78 °C for 2 h).[39] The optimized conditions afford up to 57% of the desired product, in which the Grignard reagent used in this process is a solution in Et_2O, whereas the precedent by Knochel utilizes THF.[39] Screening temperature, nucleophile, and equivalencies showed the sensitivity of this particular transformation, with the major by-product observed in this reaction proving to be the isomerization of the olefin (Table 2.1). Isomerization was observed when the reaction was performed at 0 °C in the presence of MeMgBr (entries 1 and 2) or when using MeLi as the nucleophile (entries 3 and 4). Furthermore, it was found that higher product yield was observed when the Lewis acid was in excess relative to the Grignard reagent itself. In any event, with the desired methyl group installed, the primary alcohol was then desilylated and oxidized into its corresponding aldehyde to yield the fully functionalized **61**. Of note, if the methyl

1,2-addition was performed on the desilylated ketoester, only 1,2-addition into the ester was observed.

Table 2.1. Screening of methyl addition.[a]



88 **90** **91**

Entry	Temp.	Reagents	Yield	**90**:**91**
1	0 °C	$LaCl_3$•2LiCl (1.1 eq) MeMgBr (2.2 eq)	21% 25% bsmr	5:1
2	0 °C	$LaCl_3$•2LiCl (3 eq) MeMgBr (2 eq)	25% 36% bsmr	4:1
3	0 °C	$LaCl_3$•2LiCl (3 eq) MeLi (1.5 eq)	47%	only **91**
4	–78 °C	$LaCl_3$•2LiCl (3 eq) MeLi (1 eq)	16% 20% bsmr	6:1
5	–78 °C	$LaCl_3$•2LiCl (3 eq) MeMgBr (3 eq)	24% 28% bsmr	only **90**
6	–78 °C	$LaCl_3$•2LiCl (3 eq) MeMgBr (1.1 eq)	57% 95% bsmr	only **90**
7	–78 °C	$LaCl_3$•2LiCl (3 eq) MeMgBr (1.6 eq)	52%	only **90**

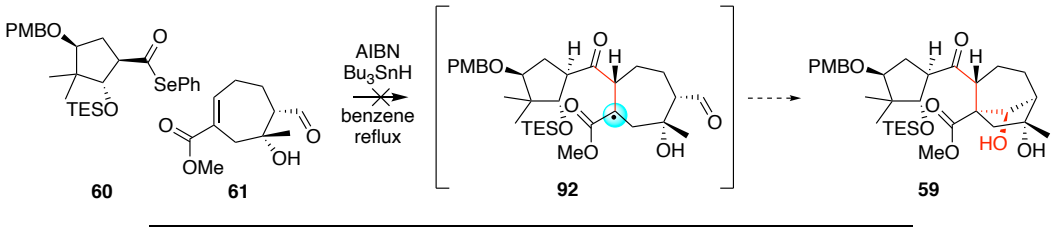
[a] All reactions performed on 20 mg scale in THF (0.1 M).

2.2.3 Attempted Coupling and Model Studies

With both fragments in hand, the stage was set to perform the desired radical cascade to couple **60** and **61** as well as fashion the bridged system. Although the initial radical-Michael addition was thought to be the easier step within the cascade based on the literature precedent,[26-28] we sadly observed no desired product when subjecting our acyl selenide radical precursor **60** and unsaturated ester **61** to AIBN and nBu$_3$SnH in refluxing benzene (Scheme 2.10, panel A). Although the reaction profile was quite messy, full consumption of the acyl selenide was observed, suggesting the radical was generated, but failed to undergo the anticipated conjugate addition.

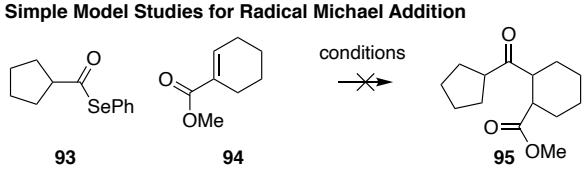
Given the initial Michael addition was unsuccessful, we decided to turn to simpler model studies to potentially elucidate a more reasonable approach to the desired coupling.

A. Failed Radical Cascade

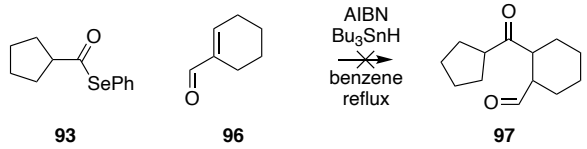


60 61 92 59

B. Simple Model Studies for Radical Michael Addition



93 94 95



93 96 97

Entry	Temp.	Solvent	Reagent(s)	Result?
1	reflux	benzene	nBu$_3$SnH AIBN	reduction
2	–78 °C→25 °C	CH_2Cl_2/THF (4:1)	nBu$_3$SnH Et_3B, O_2	N.R.
3	0 °C	benzene	nBu$_3$SnH Et_3B, O_2	low conv.
4	25 °C	benzene	nBu$_3$SnH Et_3B, O_2	reduction

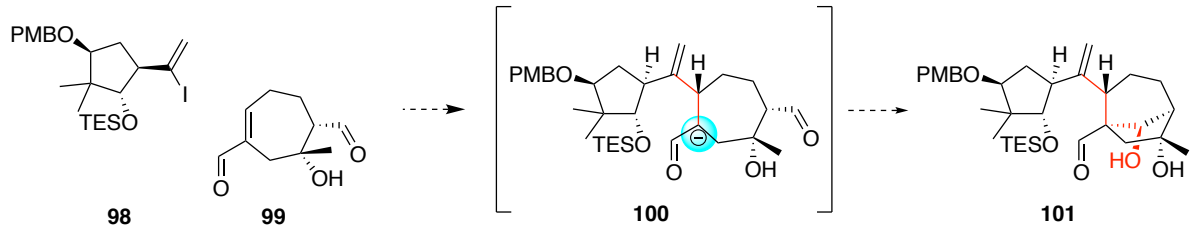
Scheme 2.10. A) Failed radical cascade and B) follow-up model studies highlighting the challenge of this transformation.

Utilizing cyclopentanecarboxylic acid, we could easily fashion a stripped-down version of the acyl selenide in 80% yield (**93**, Scheme 2.10, panel B).[37c] Utilizing **93** along with methyl 1-cyclohexene-1-carboxylate **94**, we screened various radical coupling conditions, applying both AIBN and Et_3B/O_2 as the radical initiators under various conditions. Sadly, the only observed reactivity was reduction of the acyl selenide, with no successful Michael addition. Furthermore, we also tried altering the electronic properties of the Michael acceptor and attempted this model coupling with 1-cyclohexene-1-carboxaldehyde **96**, but once again failed to yield any desired product.

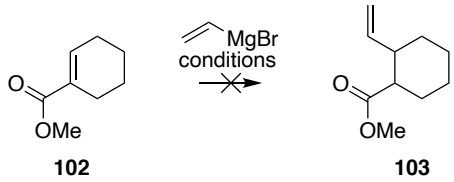
With these simple model systems proving this desired Giese reaction to be quite challenging, we decided to shift to an anionic approach instead (Scheme 2.11, panel A). Learning from our previous efforts, we opted to screen an arguably simpler vinyl Michael addition before completing the left-hand fragment, **98**. When attempting to use CuI in either a catalytic or

stoichiometric amount, we were unable to induce the desired addition onto methyl 1-cyclohexene-1-carboxylate **102**, with only trace 1,2-addition being observed in both cases.[40] When switching the Michael acceptor once again to the corresponding unsaturated aldehyde, CuI once again only resulted in trace 1,2-addition; however, we began to see production of the desired Michael addition (**103**), albeit in small amounts, when utilizing CuBr•Me_2S, HMPA, and TMSCl.[41] Of note, TMSCl proved to be critical to promoting this transformation, as no reaction was observed in its absence. Furthermore, although low yields were observed for these reactions, the mass balance was also quite low likely due to the volatility of the product, and loss of material during handling and concentration.

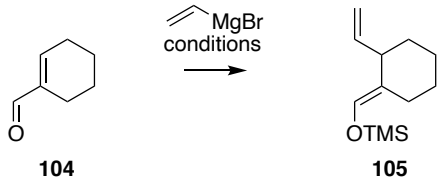
A. Proposed Anionic Cascade Alternative



B. Simple Model Studies for Vinyl Michael Addition



Entry	Temp.	Additive(s)	Result?
1	–15 °C	CuI (0.25 equiv)	trace 1,2
2	–78 °C → –15 °C	CuI (1 equiv)	trace 1,2



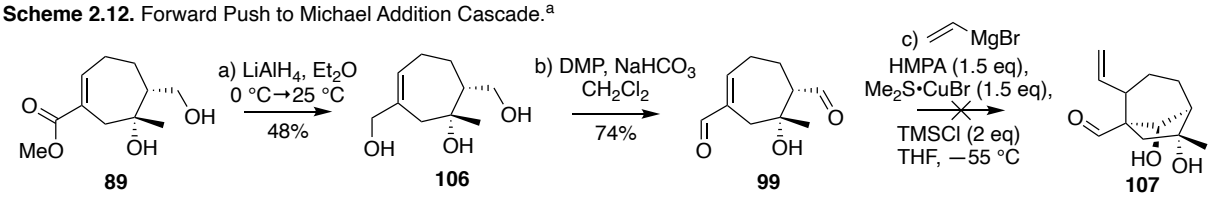
Entry	Temp.	Additive(s)	Result?
1	–15 °C	CuI	trace 1,2
2	–55 °C	HMPA (3 eq) CuBr•Me_2S (0.3 eq) TMSCl (2 eq)	1,4*
3	–55 °C	HMPA (1.5 eq), CuBr•Me_2S (1.5 eq)	N.R.
4	–55 °C	HMPA (1.5 eq), CuBr•Me_2S (1.5 eq), TMSCl (2 eq)	1,4*

*low yield, but low mass recovery - volatile

Scheme 2.11. A) Proposed vinyl Michael addition approach and B) probing of vinyl Michael additions on unsaturated ester **102** and unsaturated aldehyde **104**.

With reasonable Michael addition conditions developed, we wanted to attempt this model transformation on the real dialdehyde system **99**, just two steps from the previously obtained **89** (Scheme 2.12). Reduction of the methyl ester **89** with $LiAlH_4$ yielded triol **106**, which could subsequently be subjected to a global oxidation with Dess-Martin periodinane to provide dialdehyde **99**. Sadly, when the CuBr•Me_2S mediated vinyl Michael addition conditions were attempted on a 5 mg scale, we observed full consumption of the starting material, with potential trace product **107**, however this result could not be confirmed.[41] Furthermore, we were unable to reproduce this result. Additional attempts to optimize the conditions for this system, including varying the temperature between –78 °C and –40 °C, proved fruitless, forcing us to rethink our approach again, this time opting for an intramolecular cascade which would exploit an ester tether.

Scheme 2.12. Forward Push to Michael Addition Cascade.[a]



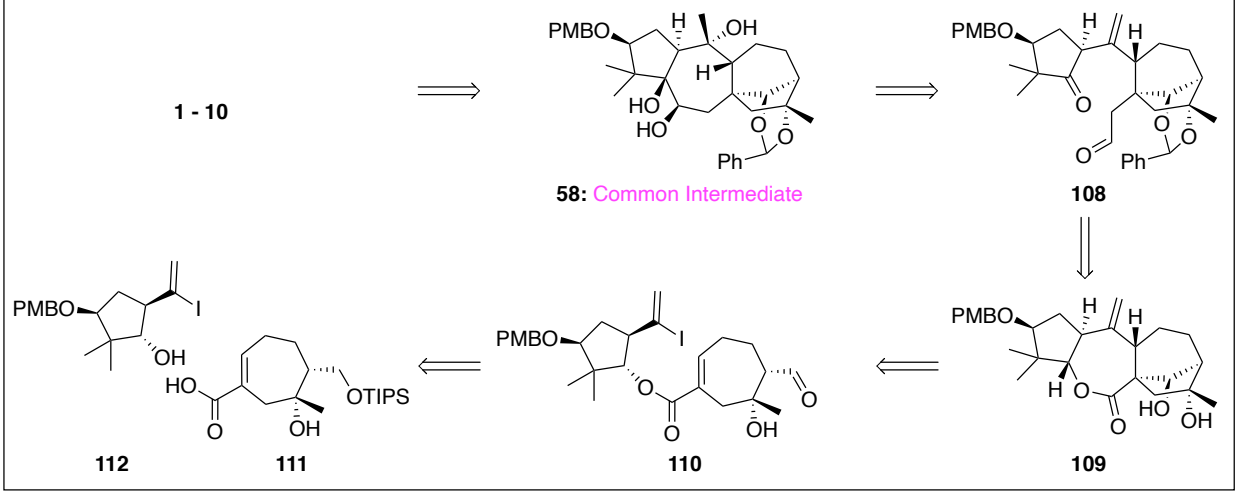
[a] Reagents and conditions: (a) $LiAlH_4$ (4.0 equiv), Et_2O (0.1 M), 0 °C→25 °C, 1 h, 48%; (b) $NaHCO_3$ (6.1 equiv), DMP (3.1 equiv), CH_2Cl_2 (0.05 M), 25 °C, 2 h, 74%.

2.2.4 Intramolecular Approach

Given the challenges we faced when attempting an intermolecular cascade, we hoped to achieve our desired transformation using a tethered system, allowing for an intramolecular Michael addition (Scheme 2.13). Since we had observed tentative, trace success with dialdehyde **99**, we believed that if the initial Michael addition were to occur, the proposed terminating aldol addition was possible as well. To this end, we envisioned a similar endgame intermediate **108**, which could still undergo pinacol coupling, but now required a Mukaiyama hydration instead of a methyl Grignard addition to deliver common intermediate **58**.[11, 42] Dicarbonyl **108** would be built up through the opening and one-carbon homologation of lactone **109**, which was envisioned to be the

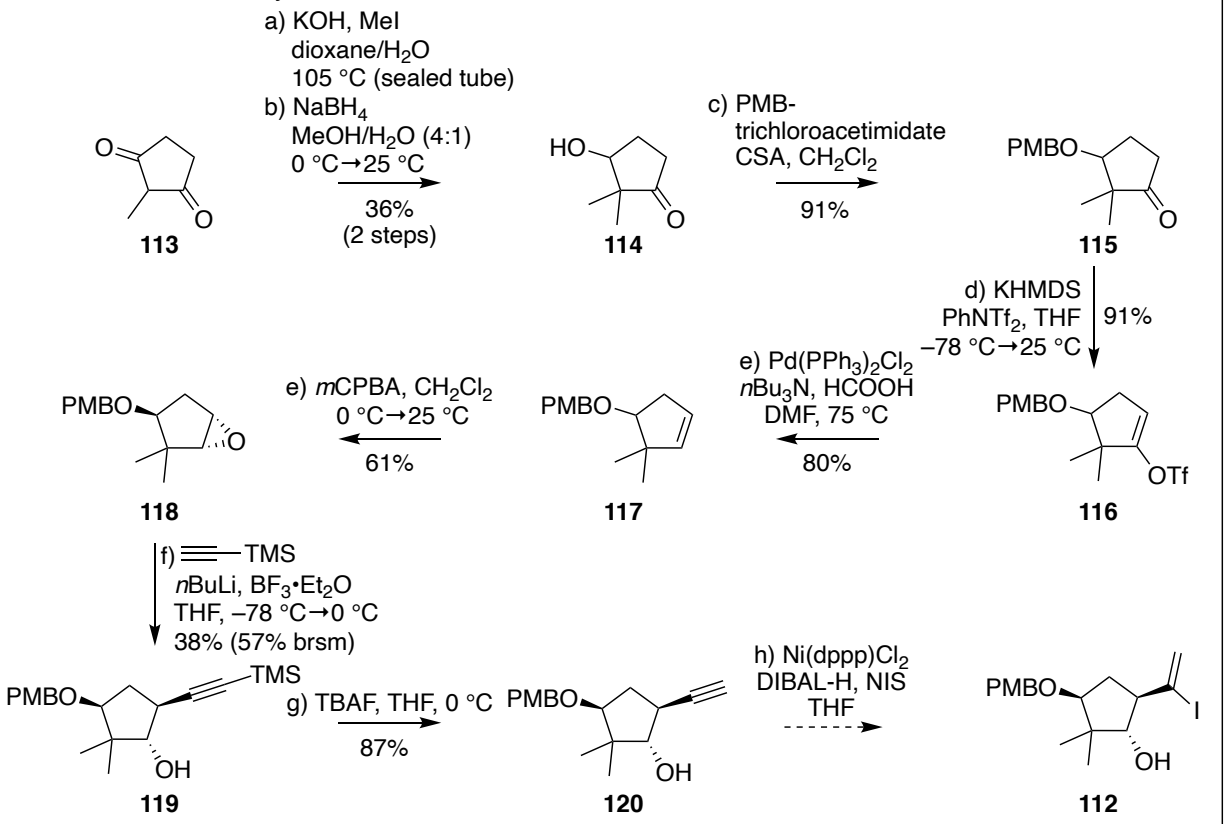
product of the intramolecular cascade starting from aldehyde **110**.[41, 43] Tethered **110** was proposed to be derived from the simple DCC coupling of vinyl iodide **112** and carboxylic acid **111**.[44]

Scheme 2.13. Retrosynthetic Analysis of Tethered Intramolecular Approach.



To this end, we set out to build vinyl iodide **112**, starting from commercially available 2-methyl-1,3-cyclopentanedione (**113**, Scheme 2.14). Simple α-methylation followed by monoreduction with $NaBH_4$ yielded alcohol **114** in 76% yield, which could be facilely protected as its respective PMB ether.[45] Protected alcohol **115** could then be converted into vinyl triflate utilizing bis(trifluoromethanesulfonyl)aniline and KHMDS, before the triflate was burned off in the presence of $Pd(PPh_3)_2Cl_2$, delivering alkene **117**.[46] Electrophilic epoxidation with *m*CPBA provided a single diastereomer of **118**, most likely controlled by the steric bulk of the PMB-ether, albeit in modest yield (50%). Taking advantage of the location of the quaternary center of **118**, we could then regioselectively open the epoxide with lithiated trimethylsilylacetylene which was then desilylated to provide terminal alkyne **120**.[47] Based on previous success with the α-iodination as outlined by the Hoveyda group on 3-butyn-1-ol, we were hopeful the same conditions would then allow for us to access desired iodinated **112** in one further step.[48]

Scheme 2.14. Forward Synthesis of Alcohol **112**.[a]

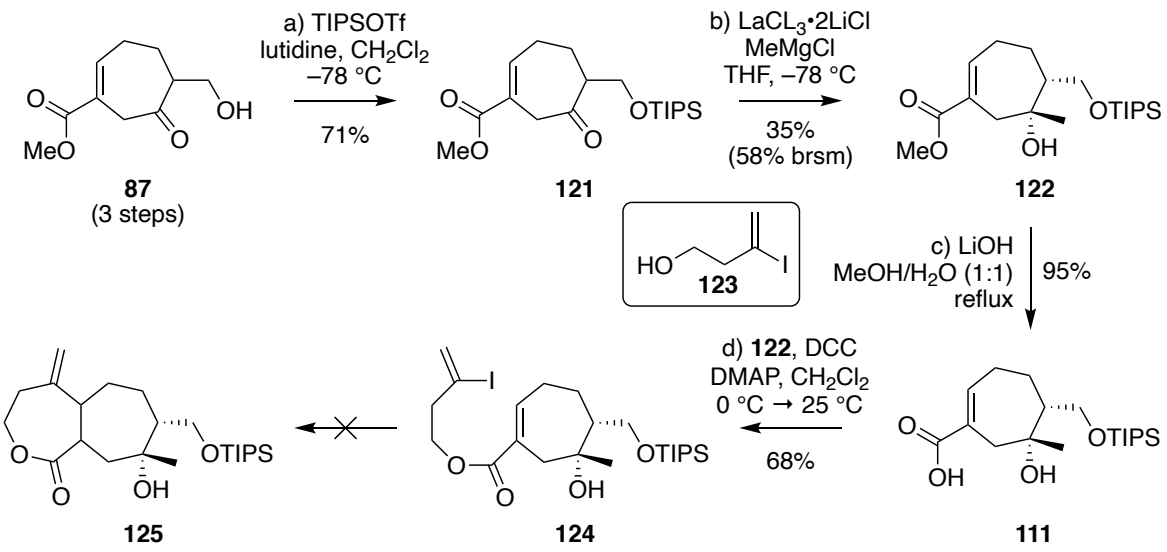


[a] Reagents and conditions: (a) KOH (1.1 equiv), MeI (1.1 equiv), dioxane/H_2O (3:1, 0.45 M), 105 °C (sealed tube), 6 h, *then* 10% HCl (0.36 M), reflux, 10 min, 40%; (b) $NaBH_4$ (0.27 equiv), MeOH/H_2O (4:1, 0.1 M), 0 °C→25 °C, 4 h, 89%; (c) PMB-trichloroacetimidate (2.0 equiv), CSA (0.2 equiv), CH_2Cl_2 (0.35 M), 25 °C, 8 h, 92%; (d) KHMDS (2.0 equiv), THF (0.1 M), –78 °C, 30 min, *then* $PhNTf_2$ (2.0 equiv), –78 °C→25 °C, 8 h, 91%; (e) $Pd(PPh_3)_2Cl_2$ (0.05 equiv), nBu_3N (3.0 equiv), HCOOH (2.5 equiv), DMF (0.1 M), 75 °C, 1 h, 80%; (e) *m*CPBA (2.2 equiv), CH_2Cl_2 (0.05 M), 0 °C→25 °C, 3 h, 61%; (f) trimethylsilylacetylene (3.0 equiv), *n*BuLi (3.0 equiv), THF (0.23 M), –78 °C, *then* **118** (1.0 equiv), $BF_3•Et_2O$ (3.0 equiv), THF (0.1 M), –78 °C, 3.5 h, 38% (57% brsm); (g) TBAF (2.7 equiv), THF (0.02 M), 0 °C, 5 min, 87%.

While developing our route to vinyl iodide **112**, we also needed to convert methyl ester **87** into carboxylic acid **111** (Scheme 2.15). This was done in a slightly modified approach in which the primary alcohol of **87** was first TIPS-protected before being subjected to the previously optimized Knochel Grignard addition conditions and LiOH-mediated hydrolysis, the latter step prompting the protecting group switch due to decomposition of the analogous TES substrate.[39] Given we were still working on completing fragment **112**, we decided to begin probing the intramolecular cyclization, utilizing vinyl iodide **123** as our model sidechain. **123** was easily produced through α-iodination of 3-butyn-1-ol and was easily coupled to carboxylic acid **111** using

DCC.[44, 49] Before attempting the full cascade, we first wanted to test the initial Michael addition. Unfortunately, all attempts to cyclize this tethered sidechain into the unsaturated system failed to proceed productively.[40-41] Utilizing radical conditions such as *n*Bu_3SnH and AIBN or Et_3B, as well as anionic conditions such as *t*BuLi and *t*BuLi with HMPA all failed to deliver the cyclization product **125**, with only deiodination being observed.[27a, 28] Although we had successfully achieved fragment **111** and were one step from **112** at this point, we believed approaching these targets in this manner was no longer promising, prompting us to reconsider our overall strategy.

Scheme 2.15. Forward Synthesis of **111** and Attempted Model Cyclization.[a]

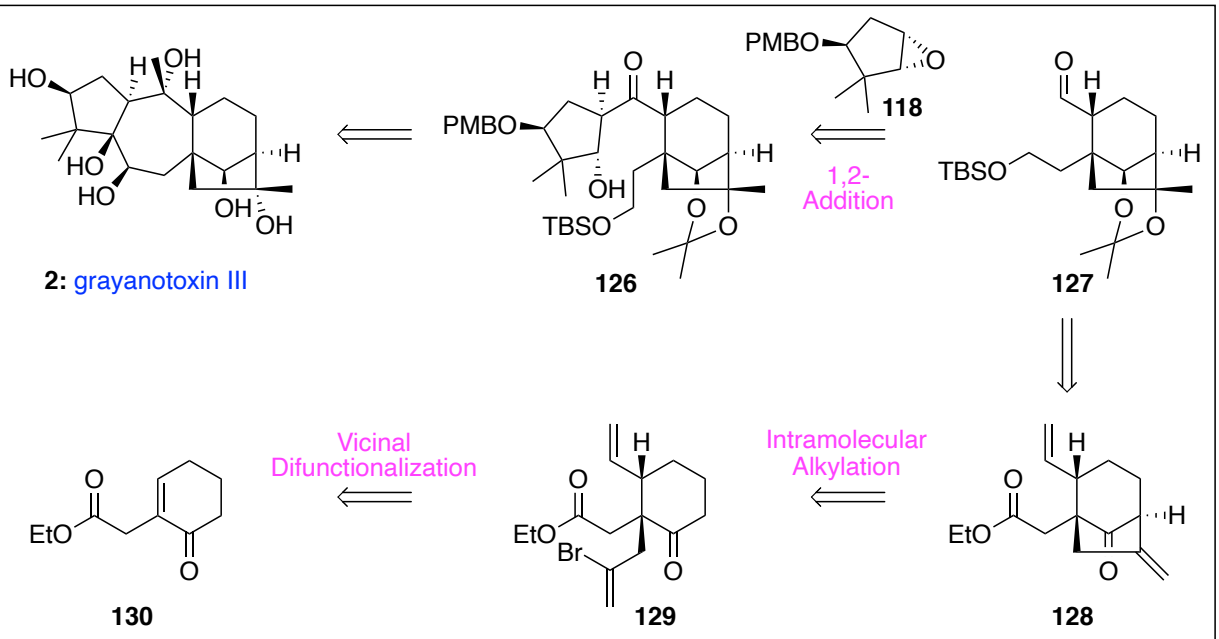


[a] Reagents and conditions: (a) lutidine (1.5 equiv), TIPSOTf (1.5 equiv), CH_2Cl_2 (0.2 M), –78 °C, 30 min, 71%; (b) $LaCl_3$•2LiCl (3.0 equiv), MeMgCl (1.1 equiv), THF (0.05 M), –78 °C, 30 min, 35% (58% brsm); (c) LiOH (1.0 equiv), MeOH/H_2O (1:1, 0.02 M), reflux, 5 h, 95%; (d) **123** (1.5 equiv), DMAP (0.2 equiv), DCC (1.4 equiv), CH_2Cl_2 (0.1 M), 0 °C→25 °C, 8 h, 68%.

2.2.5 Route Redesign

Given the difficulty in constructing the bridged system through a cascade coupling reaction, initiated by a Michael addition of the left-hand fragment onto the right-hand side, we believed switching the direction of attack could potentially serve us better in our quest towards the total syntheses of grayanotoxin III (**2**) and its related grayanane diterpenoids (Scheme 2.16). Having previously demonstrated that we could regioselectively add into epoxide **118** (**118→119**,

Scheme 2.14), we believed we could utilize the developed route for the left-hand portion of the molecule and add into it either through a radical promoted event, or an umpolung addition of aldehyde **127**, which in turn could be traced back to bicycle **128**.[47] This bridged system was envisioned to be built through a simple intramolecular alkylation of vinyl bromide **129**, constructed through a vicinal difunctionalization of enone **130**.

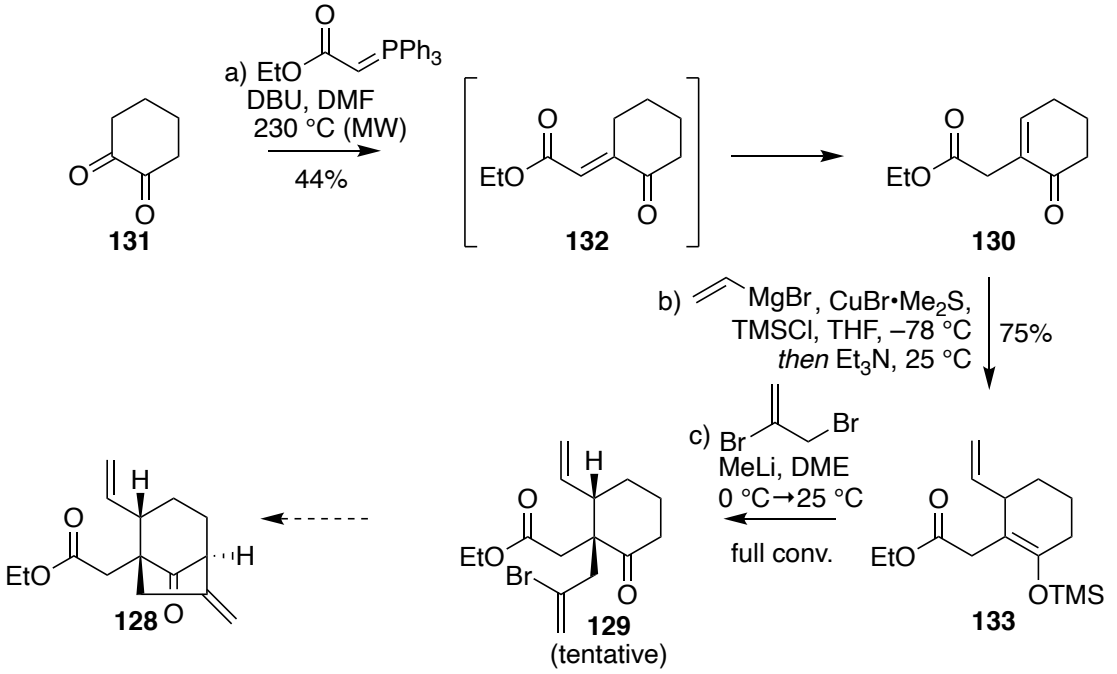


Scheme 2.16. Retrosynthetic Analysis of Addition Reversal Approach.

Having already completed the left-hand fragment **118**, we set out to build bridged bicycle **127**, starting from 1,2-cyclohexanedione **131** (Scheme 2.17). When exposing dione **131** to (carbethoxymethylene)triphenylphosphorane and DBU under microwave irradiation, the desired olefination proceeded smoothly and was accompanied with *in situ* isomerization to the internal olefin, delivering enone **130** directly.[50] A large range of concentrations, equivalencies, temperatures, and reaction times were screened, and our optimized conditions provided enone **130** in a modest 44% yield. However, the subsequent vinyl Michael addition (utilizing the same conditions as previously developed for our α,β-unsaturated aldehyde) proceeded in 75% yield,

with the enolate being trapped as the stable, tetrasubstituted silyl enol ether **133**.[41] Subjecting this material to 2,3-dibromopropene in the presence of MeLi showed full conversion to what is assumed to have been desired **129**,[51] but unfortunately further spectroscopic data was not obtained, as it was at this moment that tragedy had struck: the project had been scooped[52] and was immediately terminated.

Scheme 2.17. Initial Results of Adjusted Route.[a]

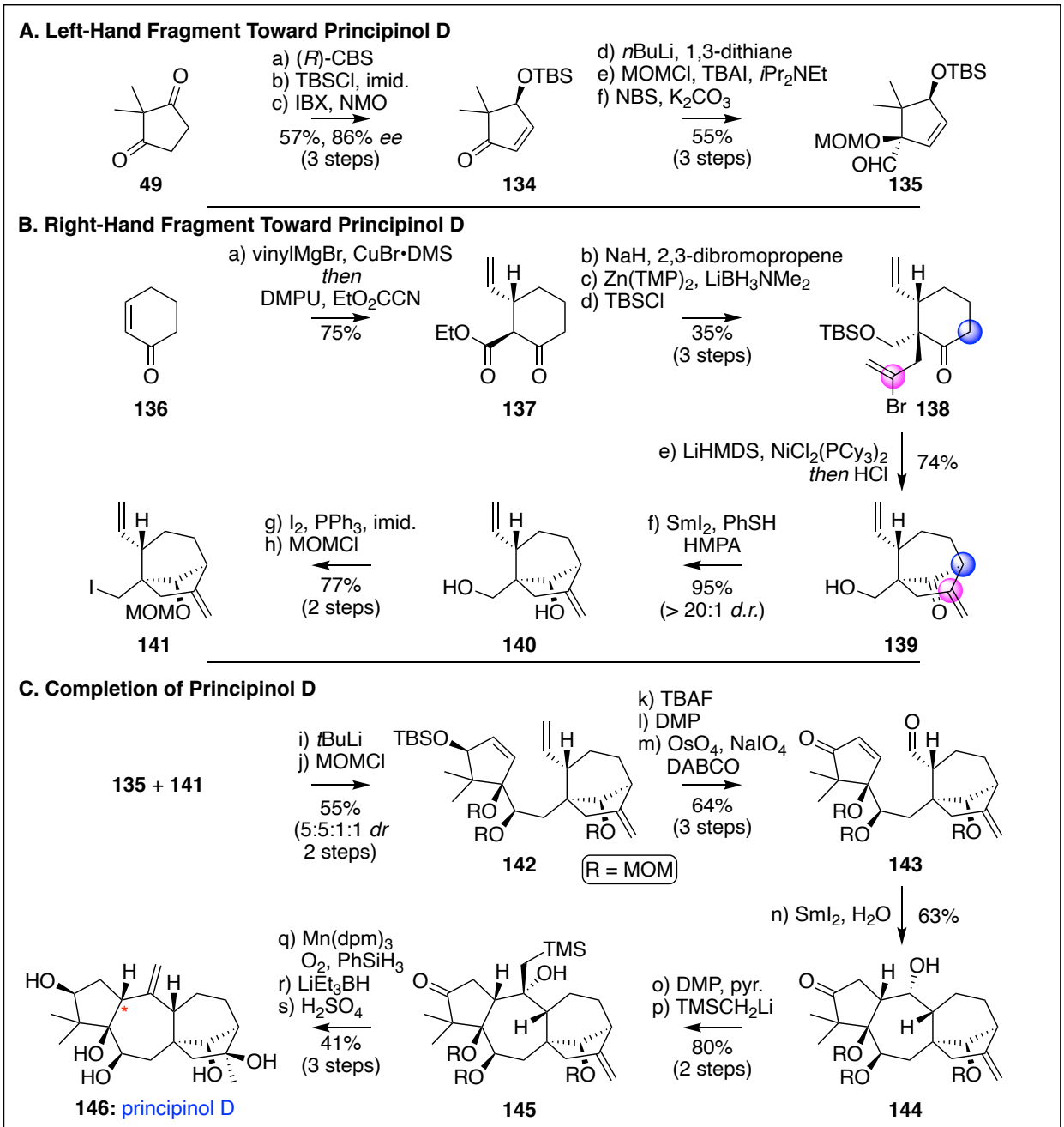


[a] Reagents and conditions: (a) (carbethoxymethylene)triphenylphosphorane (1.0 equiv), **131** (3.0 equiv), DBU (0.2 equiv), DMF (0.15 M), 230 °C (microwave), 20 min, 44%; (b) CuBr•Me_2S (0.3 equiv), vinylmagnesium bromide (3.0 equiv), THF (0.05 M), –78 °C, 15 min, *then* TMSCl (5.0 equiv), **130** (1.0 equiv), –78 °C→25 °C, 8 h, *then* Et_3N (3.0 equiv), 5 min, 75%; (c) MeLi (1.5 equiv), DME (0.05 M), 0 °C, 5 min, *then* 2,3-dibromopropene, 0 °C→25 °C, 2 h, full conversion.

2.3 Suspension of Project

As initial results were obtained regarding the route redesign, we became aware of a new publication on the preprint server ChemRxiv by the Newhouse group in which they reported the total synthesis of principinol D (**148**), a related member of the grayanane diterpenoid family (Scheme 2.18).[52] Although not one of our targets, given the alternate stereochemistry as highlighted by the red star in **148**, we observed their approach was very similar to our own. They

too utilized a convergent strategy, in which they initially constructed two fragments, the five-membered **135** and the caged **141**. The cyclopentene ring featured a Corey-Bakshi-Shibata asymmetric reduction to produce the desired fragment in 86% *ee* over the course of 6 steps. For their right-hand fragment, they featured a vinyl Michael addition akin to our own, along with an α-alkylation like that which we had been in the process of performing. From here, they did a further Appel reaction to install a primary alkyl-iodide, yielding **141** in a total of 8 steps. To bring the fragments together, a simple lithium-halogen exchange was enough to couple the two fragments together, adding the methylene of **141** directly into the aldehyde of **135** in 62% overall yield and 5:5:1:1 *dr* (26% yield of the desired diastereomer). Following global MOM-protection, silyl deprotection, oxidation to the enone and Lemieux-Johnson oxidation to the requisite aldehyde **143** set the stage for a SmI_2-mediated radical Michael addition to provide **144** in 63% yield as a single diastereomer, a similar disconnection to our proposed epoxide opening and subsequent pinacol coupling. With tetracyclic **144** in hand, oxidation and 1,2-addition of trimethylsilylmethyllithium provided silylated **145** as a single, inconsequential diastereomer in 80% yield. From here, principinol D (**146**) was completed after Mukaiyama hydration, reduction, and global MOM-deprotection, accompanied by dehydration, accomplishing the synthesis in a longest linear sequence of 19 steps.



Scheme 2.18. The total synthesis of principinol D (**146**) by the Newhouse group (2019).

2.4 Conclusion

We initially set out to achieve the total syntheses of ten grayanane diterpenoids, all potentially accessible through a common intermediate (**58**). As opposed to the fully linear campaign utilized by Matsuda, Shirahama, and coworkers, we envisioned the use of an

intermolecular radical coupling cascade to connect the two roughly equally complex fragments that in turn leads to the closing of the eastern *cis*-fused 5/6-bicyclic moiety. The construction of the western fragment featured an enantioselective Mukaiyama-aldol to introduce the chirality of the PMB-protected alcohol stereocenter, and an intramolecular aldol of a 1,6-dialdehyde to form the 5-membered ring (**60**). Inspired by the total syntheses of labdane diterpenes galanal A, B by the Chein group, the 7-membered ring was formed through a titanocene-mediated radical cyclization, allowing us to complete **61** in 7 steps.

With both fragments in hand, testing of coupling conditions that also close the *cis*-fused 6/5-bicycle was performed. After extensive screening, it was clear that the desired intermolecular radical coupling would not be fruitful. Alternative attempts were then probed, beginning with the use of a vinyl halide as the initial radical source in place of the acyl selenide. Through these efforts, it was found that the α,β-unsaturated methyl ester was not reactive enough, but an α,β-unsaturated aldehyde (**99**) resulted in enhanced reactivity, utilizing vinyl magnesium bromide as a model system. Unfortunately, though, this result was irreproducible. We next probed a tethered system in hopes of the intramolecular cyclization proceeding with greater ease, but this too proved futile. Lastly, we began probing a reversal in the direction of the coupling, but it was at this time that the total synthesis of principinol D (**146**), a related natural product, was reported by the Newhouse group in 19 longest linear steps, prompting the termination of our efforts given the homology of their approach.

2.5 References

1. Kohanawa, M., *The Japanese Journal of Pharmacology* **1956**, *6*, 46.
2. Li, Y.; Liu, Y.-B.; Yu, S.-S., *Phytochemistry Reviews* **2013**, *12*, 305.
3. Li, C.-H.; Zhang, J.-Y.; Zhang, X.-Y.; Li, S.-H.; Gao, J.-M., *European Journal of Medicinal Chemistry* **2019**, *166*, 400.
4. (a) Sun, N.; Zheng, G.; He, M.; Feng, Y.; Liu, J.; Wang, M.; Zhang, H.; Zhou, J.; Yao, G., *J. Nat. Prod.* **2019**, *82*, 1849; (b) Li, Y.; Zhu, Y.; Zhang, Z.; Li, L.; Liu, Y.; Qu, J.; Ma, S.;

Yu, S., *Acta Pharmaceutica Sinica B* **2020**, *10*, 1073; (c) Zheng, G.; Zhou, J.; Huang, L.; Zhang, H.; Sun, N.; Zhang, H.; Jin, P.; Yue, M.; Meng, L.; Yao, G., *J. Nat. Prod.* **2019**, *82*, 3330; (d) Zhou, J.; Zuo, Z.; Liu, J.; Zhang, H.; Zheng, G.; Yao, G., *Organic Chemistry Frontiers* **2020**, *7*, 820.

5. (a) Chanjun, L.; Hui, L.; Liquan, W.; Manwen, J.; Shaonong, C.; Guanhu, B.; Guowei, Q., *Acta Chim. Sinica* **2003**, *61*, 1153; (b) Jansen, S. A.; Kleerekooper, I.; Hofman, Z. L. M.; Kappen, I. F. P. M.; Stary-Weinzinger, A.; van der Heyden, M. A. G., *Cardiovascular Toxicology* **2012**, *12*, 208; (c) Li, Y.; Liu, Y.-B.; Zhang, J.-J.; Liu, Y.; Ma, S.-G.; Qu, J.; Lv, H.-N.; Yu, S.-S., *J. Nat. Prod.* **2015**, *78*, 2887.
6. Zhou, J.; Liu, T.; Zhang, H.; Zheng, G.; Qiu, Y.; Deng, M.; Zhang, C.; Yao, G., *J. Nat. Prod.* **2018**, *81*, 151.
7. Elkin, M.; Scruse, A. C.; Turlik, A.; Newhouse, T. R., *Angew. Chem. Int. Ed.* **2019**, *58*, 1025.
8. (a) Rauk, A.; Sorensen, T. S.; Maerker, C.; Carneiro, J. W. d. M.; Sieber, S.; Schleyer, P. v. R., *J. Am. Chem. Soc.* **1996**, *118*, 3761; (b) Rauk, A.; Sorensen, T. S.; von Ragué Schleyer, P., *Journal of the Chemical Society, Perkin Transactions 2* **2001**, 869.
9. (a) Hamanaka, N.; Matsumoto, T., *Tetrahedron Letters* **1972**, *13*, 3087; (b) Gasa, S.; Hamanaka, N.; Matsunaga, S.; Okuno, T.; Takeda, N.; Matsumoto, T., *Tetrahedron Letters* **1976**, *17*, 553.
10. Chow, S.; Kreß, C.; Albæk, N.; Jessen, C.; Williams, C. M., *Org. Lett.* **2011**, *13*, 5286.
11. Kan, T.; Hosokawa, S.; Nara, S.; Oikawa, M.; Ito, S.; Matsuda, F.; Shirahama, H., *J. Org. Chem.* **1994**, *59*, 5532.
12. (a) Church, R. F.; Ireland, R. E.; Marshall, J. A., *J. Org. Chem.* **1966**, *31*, 2526; (b) Stork, G.; Meisels, A.; Davies, J. E., *J. Am. Chem. Soc.* **1963**, *85*, 3419.
13. Shiozaki, M.; Mori, K.; Matsui, M., *Agricultural and Biological Chemistry* **1972**, *36*, 2539.
14. (a) Baker, D. C.; Hawkins, L. D., *J. Org. Chem.* **1982**, *47*, 2179; (b) Hoppe, D.; Tarara, G.; Wilckens, M., *Synthesis* **1989**, *1989*, 83; (c) Bianchi, O.; Cesti, P.; Golini, P., *Tetrahedron* **1989**, *45*, 869.
15. Ganem, B.; Small, V. R., *J. Org. Chem.* **1974**, *39*, 3728.
16. Fukuda, Y.; Utimoto, K., *J. Org. Chem.* **1991**, *56*, 3729.
17. (a) Corey, E. J.; Carney, R. L., *J. Am. Chem. Soc.* **1971**, *93*, 7318; (b) Corey, E. J.; Danheiser, R. L.; Chandrasekaran, S., *J. Org. Chem.* **1976**, *41*, 260; (c) Corey, E. J.; Danheiser, R. L.; Chandrasekaran, S.; Siret, P.; Keck, G. E.; Gras, J. L., *J. Am. Chem. Soc.* **1978**, *100*, 8031; (d) Stork, G.; Malhotra, S.; Thompson, H.; Uchibayashi, M., *J. Am. Chem. Soc.* **1965**, *87*, 1148; (e) Stork, G.; Boeckmann, R. K.; Taber, D. F.; Still, W. C.; Singh, J., *J. Am. Chem. Soc.* **1979**, *101*, 7107; (f) Matsuda, F., *Journal of Synthetic Organic Chemistry, Japan* **1995**, *53*, 987.
18. Kan, T.; Matsuda, F.; Yanagiya, M.; Shirahama, H., *Synlett* **1991**, *1991*, 391.
19. (a) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B., *J. Org. Chem.* **1981**, *46*, 3936; (b) Schuda, P. F.; Cichowicz, M. B.; Heimann, M. R., *Tetrahedron Letters* **1983**, *24*, 3829.
20. (a) Molander, G. A.; Huérou, Y. L.; Brown, G. A., *J. Org. Chem.* **2001**, *66*, 4511; (b) Mander, L. N.; Sethi, S. P., *Tetrahedron Letters* **1983**, *24*, 5425.
21. (a) Marinovic, N. N.; Ramanathan, H., *Tetrahedron Letters* **1983**, *24*, 1871; (b) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P., *Synthesis* **1994**, *1994*, 639; (c) Roth, G. J.; Liepold, B.; Müller, S. G.; Bestmann, H. J., *Synthesis* **2004**, *2004*, 59.

22. Negishi, E.-i.; Anastasia, L., *Chemical Reviews* **2003**, *103*, 1979.
23. Wei, L.-L.; Wei, L.-M.; Pan, W.-B.; Leou, S.-P.; Wu, M.-J., *Tetrahedron Letters* **2003**, *44*, 1979.
24. Boger, D. L.; Brotherton, C. E., *J. Org. Chem.* **1984**, *49*, 4050.
25. (a) Snyder, S. A.; Gollner, A.; Chiriac, M. I., *Nature* **2011**, *474*, 461; (b) Kuroda, Y.; Nicacio, K. J.; da Silva-Jr, I. A.; Leger, P. R.; Chang, S.; Gubiani, J. R.; Deflon, V. M.; Nagashima, N.; Rode, A.; Blackford, K.; Ferreira, A. G.; Sette, L. D.; Williams, D. E.; Andersen, R. J.; Jancar, S.; Berlinck, R. G. S.; Sarpong, R., *Nature Chemistry* **2018**, *10*, 938; (c) Jones, S. B.; Simmons, B.; Mastracchio, A.; MacMillan, D. W. C., *Nature* **2011**, *475*, 183.
26. (a) Crich, D.; Fortt, S. M., *Tetrahedron Letters* **1988**, *29*, 2585; (b) Crich, D.; Fortt, S. M., *Tetrahedron Letters* **1987**, *28*, 2895.
27. (a) Boger, D. L.; Mathvink, R. J., *J. Org. Chem.* **1989**, *54*, 1777; (b) Boger, D. L.; Mathvink, R. J., *J. Org. Chem.* **1988**, *53*, 3377; (c) Boger, D. L.; Mathvink, R. J., *J. Org. Chem.* **1992**, *57*, 1429; (d) Boger, D. L.; Mathvink, R. J., *J. Am. Chem. Soc.* **1990**, *112*, 4003.
28. Bennasar, M. L.; Roca, T.; Griera, R.; Bassa, M.; Bosch, J., *J. Org. Chem.* **2002**, *67*, 6268.
29. Morihira, K.; Hara, R.; Kawahara, S.; Nishimori, T.; Nakamura, N.; Kusama, H.; Kuwajima, I., *J. Am. Chem. Soc.* **1998**, *120*, 12980.
30. (a) Zhang, Z.; Magnusson, G., *J. Org. Chem.* **1996**, *61*, 2394; (b) Shokri, A.; Wang, Y.; O'Doherty, G. A.; Wang, X.-B.; Kass, S. R., *J. Am. Chem. Soc.* **2013**, *135*, 17919.
31. (a) Pidathala, C.; Hoang, L.; Vignola, N.; List, B., *Angew. Chem. Int. Ed.* **2003**, *42*, 2785; (b) Rahimi, M.; Geertsema, E. M.; Miao, Y.; van der Meer, J.-Y.; van den Bosch, T.; de Haan, P.; Zandvoort, E.; Poelarends, G. J., *Org Biomol Chem* **2017**, *15*, 2809; (c) Biktagirov, I. M.; Faizullina, L. K.; Salikhov, S. M.; Safarov, M. G.; Valeev, F. A., *Russ. J. Org. Chem.* **2015**, *51*, 1457.
32. Evans, D. A.; Bartroli, J.; Shih, T. L., *J. Am. Chem. Soc.* **1981**, *103*, 2127.
33. Nunnery, J. K.; Suyama, T. L.; Linington, R. G.; Gerwick, W. H., *Tetrahedron Letters* **2011**, *52*, 2929.
34. (a) Nerz-Stonies, M.; Thornton, E. R., *Tetrahedron Letters* **1986**, *27*, 897; (b) Nerz-Stormes, M.; Thornton, E. R., *J. Org. Chem.* **1991**, *56*, 2489.
35. Yu, S.; Pan, X.; Lin, X.; Ma, D., *Angew. Chem. Int. Ed.* **2004**, *44*, 135.
36. Shiina, I.; Kikuchi, T.; Sasaki, A., *Org. Lett.* **2006**, *8*, 4955.
37. (a) Allin, S. M.; Thomas, C. I.; Allard, J. E.; Doyle, K.; Elsegood, M. R. J., *Eur. J. Org. Chem.* **2005**, *2005*, 4179; (b) Zhao, G.-L.; Ibrahem, I.; Dziedzic, P.; Sun, J.; Bonneau, C.; Córdova, A., *Chem. Eur. J.* **2008**, *14*, 10007; (c) Toyofuku, M.; Murase, E.; Fujiwara, S.-i.; Shin-ike, T.; Kuniyasu, H.; Kambe, N., *Org. Lett.* **2008**, *10*, 3957.
38. Lin, S.-C.; Chein, R.-J., *J. Org. Chem.* **2017**, *82*, 1575.
39. Krasovskiy, A.; Kopp, F.; Knochel, P., *Angew. Chem. Int. Ed.* **2006**, *45*, 497.
40. Quirante, J.; Vila, X.; Bonjoch, J.; Kozikowski, A. P.; Johnson, K. M., *Bioorganic & Medicinal Chemistry* **2004**, *12*, 1383.
41. Zou, Y.; Melvin, J. E.; Gonzales, S. S.; Spafford, M. J.; Smith, A. B., *J. Am. Chem. Soc.* **2015**, *137*, 7095.
42. Isayama, S.; Mukaiyama, T., *Chemistry Letters* **1989**, *18*, 1071.
43. Evans, P. A.; Inglesby, P. A.; Kilbride, K., *Org. Lett.* **2013**, *15*, 1798.
44. Back, T. G.; Bey, M. A.; Parvez, M.; Pharis, R. P., *Tetrahedron: Asymmetry* **2004**, *15*, 873.

45. (a) Duan, J. J. W.; Lu, Z.; Jiang, B.; Yang, B. V.; Doweyko, L. M.; Nirschl, D. S.; Haque, L. E.; Lin, S.; Brown, G.; Hynes, J.; Tokarski, J. S.; Sack, J. S.; Khan, J.; Lippy, J. S.; Zhang, R. F.; Pitt, S.; Shen, G.; Pitts, W. J.; Carter, P. H.; Barrish, J. C.; Nadler, S. G.; Salter-Cid, L. M.; McKinnon, M.; Fura, A.; Schieven, G. L.; Wrobleski, S. T., *Bioorganic & Medicinal Chemistry Letters* **2014**, *24*, 5721; (b) Budny, M.; Włodarczyk, J.; Muzioł, T.; Bosiak, M. J.; Wolan, A., *Tetrahedron Letters* **2017**, *58*, 4285.
46. (a) Huang, J.-Z.; Jie, X.-K.; Wei, K.; Zhang, H.; Wang, M.-C.; Yang, Y.-R., *Synlett* **2013**, *24*, 1303; (b) Hog, D. T.; Huber, F. M. E.; Jiménez-Osés, G.; Mayer, P.; Houk, K. N.; Trauner, D., *Chem. Eur. J.* **2015**, *21*, 13646.
47. Jing, W.; De Clercq, P. J., *Tetrahedron Letters* **1996**, *37*, 3395.
48. Gao, F.; Hoveyda, A. H., *J. Am. Chem. Soc.* **2010**, *132*, 10961.
49. (a) Brooks, J. L.; Frontier, A. J., *J. Am. Chem. Soc.* **2012**, *134*, 16551; (b) Ando, K.; Kobayashi, T.; Uchida, N., *Org. Lett.* **2015**, *17*, 2554.
50. Wu, J.; Li, D.; Wu, H.; Sun, L.; Dai, W.-M., *Tetrahedron* **2006**, *62*, 4643.
51. Hagiwara, H.; Fukushima, M.; Kinugawa, K.; Matsui, T.; Hoshi, T.; Suzuki, T., *Tetrahedron* **2011**, *67*, 4061.
52. Turlik, A.; Chen, Y.; Scruse, A. C.; Newhouse, T. R., *J. Am. Chem. Soc.* **2019**, *141*, 8088.

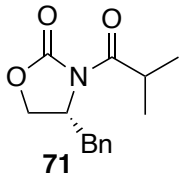
2.6 Experimental Section

2.6.1 General Procedures.

All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dry tetrahydrofuran (THF), toluene, diethyl ether (Et_2O) dichloromethane (CH_2Cl_2), and acetonitrile (CH_3CN) were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Yields refer to chromatographically and spectroscopically (^1H and ^{13}C NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent, and an ethanolic solution of phosphomolybdic acid and cerium sulfate or a solution of $KMnO_4$ in aq. $NaHCO_3$ and heat as developing agents. SiliCycle silica gel (60, academic grade, particle size 0.040–0.063 mm) was used for flash column chromatography. Preparative thin-layer chromatography separations were carried out on 0.50 mm

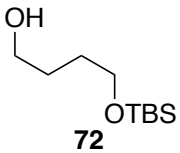
E. Merck silica gel plates (60F-254). NMR spectra were recorded on Bruker 500 MHz instruments and calibrated using residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, br = broad, app = apparent. IR spectra were recorded on a Perkin-Elmer 1000 series FT-IR spectrometer. High-resolution mass spectra (HRMS) were recorded on Agilent 6244 Tof-MS using ESI (Electrospray Ionization) at the University of Chicago Mass Spectroscopy Core Facility.

2.6.2 Syntheses of Selected Intermediates



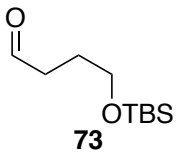
71

Ketone 71. To a solution of (R)-(+)-4-benzyl-oxazolidin-2-one (500.0 mg, 2.82 mmol, 1.0 equiv) in THF (14.1 mL) at –78 °C was slowly added *n*-BuLi (1.76 mL, 1.6 M in hexanes, 2.82 mmol, 1.0 equiv) and then the reaction mixture was stirred at –78 °C for 1 h. Next, a solution of isobutyryl chloride (0.74 mL, 7.05 mmol, 2.5 equiv) in THF (4.6 mL) was added dropwise. The resultant reaction mixture was then stirred for an additional 20 min at –78 °C. Upon completion, the reaction contents were quenched by the addition of NH_4Cl (50 mL), diluted with CH_2Cl_2 (25 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 12:1→10:1) afforded the desired ketone **71** (697.1 mg, 2.82 mmol, quant.) as a white crystal. **71**: R_f = 0.30 (silica gel, hexanes:EtOAc, 6:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.26 (m, 3H), 7.21 (d, J = 6.9 Hz, 2H), 4.74 – 4.63 (m, 1H), 4.24 – 4.14 (m, 2H), 3.83 – 3.70 (m, 1H), 3.27 (dd, J = 13.4, 3.4 Hz, 1H), 2.77 (dd, J = 13.4, 9.6 Hz, 1H), 1.24 (d, J = 6.8 Hz, 3H), 1.20 (d, J = 6.8 Hz, 3H).



72

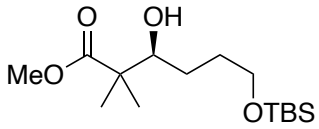
Alcohol 72. To a solution of 1,4-butanediol (0.89 mL, 10.00 mmol, 1.0 equiv) in THF (10.0 mL) at 0 °C was added NaH (280.0 mg, 60% by weight in mineral oil, 7.00 mmol, 0.7 equiv) and then the reaction mixture was stirred at 0 °C for 30 min. Next, TBSCl (1.06 g, 7.00 mmol, 0.7 equiv) was added in a single portion. The resultant reaction mixture was then stirred for an additional 1 h at 0 °C. Upon completion, the reaction contents were quenched by the addition of NH_4Cl (50 mL), diluted with EtOAc (25 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 8:1) afforded the desired alcohol **72** (812.9 mg, 3.98 mmol, 57% yield) as a clear and colorless oil. **72**: R_f = 0.60 (silica gel, hexanes:EtOAc, 3:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.66 (dt, J = 9.5, 5.6 Hz, 4H), 1.70 – 1.60 (m, 4H), 0.90 (s, 9H), 0.07 (s, 6H).



73

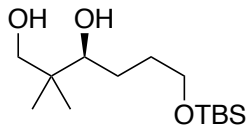
Aldehyde 73. To a solution of alcohol **72** (53.6 mg, 0.26 mmol, 1.0 equiv) in CH_2Cl_2 (2.6 mL) at 25 °C was added solid $NaHCO_3$ (109.2 mg, 1.30 mmol, 5.0 equiv) and Dess–Martin periodinane (123.0 mg, 0.29 mmol, 1.1 equiv) sequentially. The resultant mixture was stirred at 25 °C for 30 min. Upon completion, the reaction contents were concentrated directly and the resultant residue was purified by flash column chromatography (silica gel, hexanes:EtOAc, 15:1→10:1) to afford the desired aldehyde **73** (39.4 mg, 0.19 mmol, 73% yield) as a colorless oil. **73**: R_f = 0.80 (silica gel, hexanes:EtOAc, 4:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.79 (s, 1H), 3.65

(t, J = 6.0 Hz, 2H), 2.50 (td, J = 7.1, 1.7 Hz, 2H), 1.86 (ddd, J = 7.1, 6.0, 1.1 Hz, 2H), 0.88 (s, 9H), 0.04 (s, 6H).



79

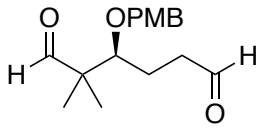
Ester 79. To a solution of *N*-Ts-L-valine (65.1 mg, 0.24 mmol, 1.1 equiv) in CH_2Cl_2 (4.8 mL) at 25 °C was added BH_3•THF (0.24 mL, 1.0 M in THF, 0.24 mmol, 1.1 equiv) dropwise and the resultant mixture was stirred for 30 min to generate chiral borane **78**. Next, the solution was cooled to –78 °C before a solution of aldehyde **77** (45.2 mg, 0.22 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL) and a solution of methyl-trimethylsilyl-dimethylketene acetal (0.05 mL, 0.26 mmol, 1.2 equiv) in CH_2Cl_2 (0.5 mL) were added sequentially. The resultant mixture was stirred at –78 °C for 2 h. Upon completion, the reaction contents were quenched by the addition of phosphate buffer pH 7.0 (25 mL), diluted with CH_2Cl_2 (10 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 20:1→15:1) afforded the desired ester **79** (53.6 mg, 0.18 mmol, 82% yield) as a clear and colorless oil. **79**: R_f = 0.60 (silica gel, hexanes:EtOAc, 4:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.69 (s, 3H), 3.67 (t, J = 5.8 Hz, 3H), 1.79 – 1.69 (m, 1H), 1.68 – 1.60 (m, 2H), 1.38 – 1.23 (m, 2H), 1.18 (d, J = 1.3 Hz, 6H), 0.89 (s, 9H), 0.06 (d, J = 1.6 Hz, 6H).



80

Diol 80. To a solution of ester **79** (31.2 mg, 0.10 mmol, 1.0 equiv) in THF (2.0 mL) at 0 °C was added MeOH (0.20 mL, 4.90 mmol, 48.0 equiv) and $LiBH_4$ (26.7 mg, 1.22 mmol, 12.0 equiv) sequentially. The resultant mixture was warmed to 25 °C and stirred for an additional

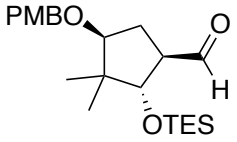
2 h. Upon completion, the reaction contents were quenched by the addition of NH_4Cl (15 mL), diluted with EtOAc (10 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 3:1→2:1) afforded the desired diol **80** (26.3 mg, 0.10 mmol, quant.) as a clear and colorless oil. **80**: R_f = 0.20 (silica gel, hexanes:EtOAc, 2:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.78 – 3.47 (m, 5H), 1.89 – 1.73 (m, 1H), 1.68 – 1.50 (m, 2H), 1.43 – 1.24 (m, 1H), 0.95 – 0.85 (m, 15H), 0.10 – 0.02 (m, 6H).



68

Dialdehyde 68. To a solution of diol **80** (896.5 mg, 3.24 mmol, 1.0 equiv) in CH_2Cl_2 (46.0 mL) at 25 °C was added anisaldehyde dimethyl acetal (1.66 mL, 9.72 mmol, 3.0 equiv) and CSA (301.1 mg, 1.30 mmol, 0.4 equiv) sequentially. The resultant mixture was stirred at 25 °C for 24 h. Upon completion, the reaction contents were quenched by the addition of $NaHCO_3$ (125 mL), diluted with EtOAc (50 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 6:1→3:1→2:1) afforded the desired diol (554.0 mg, 1.98 mmol, 61% yield) as a clear and colorless oil. Pushing forward, the so-obtained diol (554.0 mg, 1.98 mmol, 1.0 equiv) was redissolved in CH_2Cl_2 (61.0 mL) and was cooled to 0 °C before the dropwise addition of DIBAL-H (5.92 mL, 1.0 M in CH_2Cl_2, 5.92 mmol, 3.0 equiv). The resultant mixture was stirred at 0 °C for 1 h, before being allowed to slowly warm to 25 °C over 30 min. Upon completion, the reaction contents were quenched by the

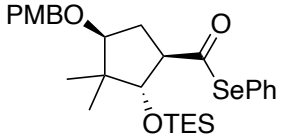
addition of Rochelle's Salt (125 mL – stirred 12 h), diluted with EtOAc (50 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 3:1→2:1→pure EA) afforded the desired monoprotected intermediate (508.1 mg, 1.80 mmol, 91% yield) as a clear and colorless oil. Carrying on, the monoprotected material forward (72.9 mg, 0.26 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (2.6 mL) at 25 °C before $NaHCO_3$ (130.0 mg, 1.55 mmol, 6.0 equiv) and Dess–Martin periodinane (240.7 mg, 0.57 mmol, 2.2 equiv) were added sequentially. The resultant mixture was stirred at 25 °C for 30 min. Upon completion, the reaction contents were concentrated directly and the resultant residue was purified by flash column chromatography (silica gel, hexanes:EtOAc, 20:1→10:1→5:1) to afford the desired dialdehyde **68** (47.1 mg, 0.17 mmol, 65% yield) as a colorless oil. **68**: R_f = 0.70 (silica gel, hexanes:EtOAc, 1:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.74 (d, J = 1.4 Hz, 1H), 9.66 (s, 1H), 7.24 (d, J = 8.6 Hz, 2H), 6.90 (d, J = 8.7 Hz, 2H), 4.54 – 4.39 (m, 2H), 3.83 (s, 3H), 3.60 (dd, J = 9.4, 3.1 Hz, 1H), 2.63 – 2.48 (m, 2H), 1.96 – 1.90 (m, 1H), 1.80 (dddd, J = 14.3, 9.3, 7.7, 6.3 Hz, 1H), 1.17 (s, 3H), 1.12 (s, 3H).



81

TES-protected aldehyde 81. To a solution of dialdehyde **68** (97.9 mg, 0.35 mmol, 1.0 equiv) in MeCN (18.0 mL) at 25 °C was added L-proline (40.4 mg, 0.351 mmol, 1.0 equiv). The resultant mixture was stirred for 45 min. Upon completion, the reaction contents were quenched by the addition of H_2O (50 mL), diluted with EtOAc (25 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with EtOAc

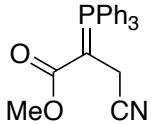
(3 × 25 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 10:1→5:1→2:1) to afford the desired β-hydroxy aldehyde (53.0 mg, 0.19 mmol, 54% yield) along with its diastereomer (11.1 mg, 0.04 mmol, 11% yield) and its respective enal (27.4 mg, 0.11 mmol, 31% yield). Pushing forward, to a solution of the major diastereomer (53.0 mg, 0.19 mmol, 1.0 equiv) in was dissolved in CH_2Cl_2 (6.3 mL) at –78 °C was added lutidine (0.04 mL, 0.38 mmol, 2.0 equiv) and TESOTf (0.09 mL, 0.38 mmol, 2.0 equiv) sequentially. The reaction was stirred for 30 min at –78 °C. Upon completion, the reaction contents were quenched by the addition of NH_4Cl (30 mL), diluted with CH_2Cl_2 (10 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 40:1→35:1) to afford the desired TES-protected aldehyde **81** (33.1 mg, 0.084 mmol, 44% yield, 2:1 *d.r.*) as a clear and colorless oil. **81**: R_f = 0.90 (silica gel, hexanes:EtOAc, 2:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.72 (dd, J = 16.1, 2.3 Hz, 1H), 7.22 (d, J = 9.1 Hz, 2H), 6.87 (d, J = 8.6 Hz, 2H), 4.56 – 4.30 (m, 2H), 3.81 (s, 3H), 3.53 – 3.32 (m, 1H), 2.91 – 2.64 (m, 1H), 2.23 – 2.08 (m, 1H), 1.95 – 1.75 (m, 1H), 1.53 – 1.50 (m, 1H), 1.02 – 0.90 (m, 15H), 0.63 – 0.56 (m, 6H).



60

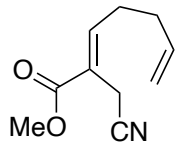
Acyl Selenide 60. To a solution of TES-protected aldehyde **81** (13.9 mg, 0.035 mmol, 1.0 equiv) in *t*BuOH/H_2O (0.40 mL, 5:1) at 25 °C was added KH_2PO_4 (0.7 mg, 0.071 mmol, 2.0 equiv), 2-methyl-2-butene (0.03 mL, 0.283 mmol, 8.0 equiv), and $NaClO_2$ (12.8 mg, 0.142 mmol, 4.0 equiv) sequentially. The reaction mixture was then allowed to stir at 25 °C for 12

h. Upon completion, the reaction contents were quenched by the addition of H_2O (15 mL), diluted with CH_2Cl_2 (10 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 20:1→10:1→5:1) to afford the desired carboxylic acid (12.9 mg, 0.032 mmol, 91% yield) as a white foam. Pushing forward, to a solution of the so-obtained carboxylic acid (12.6 mg, 0.031 mmol, 1.0 equiv) in CH_2Cl_2 (0.10 mL) at 0 °C was added a solution of Ph_2Se_2 (14.4 mg, 0.046 mmol, 1.5 equiv) in CH_2Cl_2 (0.30 mL) and a solution of Bu_3P (0.01 mL, 0.046 mmol, 1.5 equiv) in CH_2Cl_2 (0.50 mL) sequentially. The reaction mixture was then allowed to warm to 25 °C over 5 min. Upon completion, the reaction contents were quenched by the addition of H_2O (15 mL), diluted with CH_2Cl_2 (10 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, pure CH_2Cl_2) to afford the desired acyl selenide **60** (16.9 mg, 0.032 mmol, 91% yield) as a white foam. **60**: R_f = 0.90 (silica gel, hexanes:EtOAc, 2:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 – 7.45 (m, 2H), 7.38 (ddd, J = 5.0, 3.7, 1.9 Hz, 3H), 7.26 – 7.21 (m, 2H), 6.87 (d, J = 8.7 Hz, 2H), 4.58 – 4.47 (m, 1H), 4.39 – 4.30 (m, 1H), 3.80 (s, 3H), 3.50 – 3.42 (m, 1H), 3.25 – 3.06 (m, 1H), 2.37 (ddd, J = 14.0, 10.6, 5.9 Hz, 1H), 2.10 – 1.91 (m, 2H), 1.03 – 0.92 (m, 15H), 0.65 – 0.58 (m, 6H).



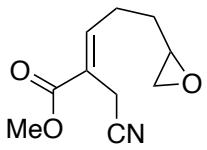
84 **Ylide 84.** To a solution of methyl(triphenylphosphoranylidene)acetate (1.00 g, 2.99 mmol, 1.0 equiv) in EtOAc (30 mL) at 25 °C was added bromoacetonitrile (0.25 mL, 3.59 mmol,

1.2 equiv) and K_2CO_3 (826.5 mg, 5.98 mmol, 2.0 equiv) sequentially. The resulting mixture was then placed in a preheated oil bath (90 °C) and was allowed to reflux for 8 h. Upon completion, the reaction contents were then dried (Na_2SO_4), filtered through a short pad of Celite, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 1:1→1:2→1:3) to afford the desired ylide **84** (980.1 mg, 2.62 mmol, 88% yield) as a yellow solid. **84**: R_f = 0.10 (silica gel, hexanes:EtOAc, 1:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 – 7.45 (m, 15H), 3.64 (s, 1H), 3.20 (s, 1H), 3.09 – 2.89 (m, 2H).



85

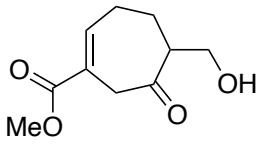
Olefin 85. A solution of ylide **84** (4.48 g, 12.00 mmol, 3.0 equiv) in toluene (40.0 mL) was transferred to a sealed tube before the subsequent addition of 4-pentenal (0.39 mL, 4.00 mmol, 1.0 equiv). The reaction vessel was then sealed and placed in a preheated oil bath (140 °C). The reaction mixture was allowed to stir undisturbed for 48 h. Upon completion, the reaction was cooled to 25 °C, and the reaction contents were directly concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 10:1) to afford the desired olefin **85** (573.9 mg, 3.20 mmol, 80% yield) as a yellow oil. **85**: R_f = 0.20 (silica gel, hexanes:EtOAc, 8:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.09 – 7.01 (m, 1H), 5.89 – 5.71 (m, 1H), 5.16 – 4.99 (m, 2H), 3.81 (s, 3H), 3.40 – 3.35 (m, 2H), 2.39 (q, J = 7.4 Hz, 2H), 2.32 – 2.22 (m, 2H).



86

Epoxide 86. To a solution of olefin **85** (133.0 mg, 0.74 mmol, 1.0 equiv) in CH_2Cl_2 (3.7 mL) at 0 °C was added *m*CPBA (364.9 mg, 70% by weight, 1.48 mmol, 2.0 equiv) in one

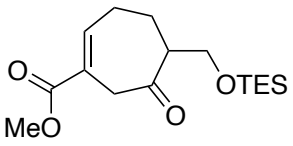
portion. The resultant mixture was stirred for 1 h at 0 °C. The cooling bath was then removed, and the reaction was allowed to stir at 25 °C for an additional 5 h. Upon completion, the reaction contents were quenched by the addition of $NaHCO_3$ (15 mL), diluted with CH_2Cl_2 (10 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc 8:1→1:1) to afford the desired epoxide **86** (145.4 mg, 0.74 mmol, quantitative yield) as a yellow oil. **86**: R_f = 0.25 (silica gel, hexanes:EtOAc, 1:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.08 (t, J = 7.7 Hz, 1H), 3.81 (s, 3H), 3.42 (s, 2H), 3.01 – 2.93 (m, 1H), 2.80 (dd, J = 4.8, 3.9 Hz, 1H), 2.55 – 2.42 (m, 3H), 1.89 (dtd, J = 14.1, 7.6, 4.2 Hz, 1H), 1.65 (dq, J = 14.3, 7.2 Hz, 1H).



87

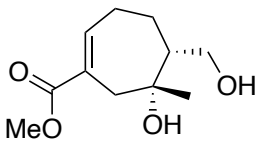
Alcohol 87. To a solution of Cp_2TiCl_2 (114.5 mg, 0.46 mmol, 2.2 equiv) in deoxygenated THF (3.0 mL) was added Zn powder (90.9 mg, 1.39 mmol, 6.6 equiv). The reaction mixture was stirred until green (~15 min). In a separate flask, epoxide **86** (41.9 mg, 0.21 mmol, 1.0 equiv) was flushed three times with N_2 before the Ti(III) mixture was transferred to it via canula. The resulting mixture was stirred vigorously at 25 °C for 2 h. Upon completion, the reaction contents were quenched by the addition of NH_4Cl (15 mL), stirred for 15 min, diluted with EtOAc (10 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 1:1) to afford the desired alcohol **87** (19.6 mg, 0.10

mmol, 48% yield) as a clear, colorless oil. **87:** R_f = 0.10 (silica gel, hexanes:EtOAc, 1:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 (t, J = 6.1 Hz, 1H), 3.75 (s, 3H), 3.72 – 3.67 (m, 1H), 3.63 (d, J = 15.6 Hz, 1H), 3.51 (d, J = 16.6 Hz, 1H), 2.89 – 2.80 (m, 1H), 2.53 – 2.42 (m, 3H), 2.05 – 1.96 (m, 1H), 1.92 – 1.83 (m, 1H), 1.79 – 1.70 (m, 1H).



88

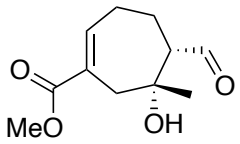
TES-protected alcohol 88. To a solution of alcohol **87** (166.8 mg, 0.84 mmol, 1.0 equiv) in CH_2Cl_2 (8.4 mL) at –78 °C was added lutidine (0.19 mL, 1.68 mmol, 2.0 equiv) and TESOTf (0.38 mL, 1.68 mmol, 2.0 equiv) sequentially. The reaction mixture was stirred for 20 min further at –78 °C. Upon completion, the reaction contents were quenched by the addition of NH_4Cl (15 mL), diluted with CH_2Cl_2 (10 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 12:1) to afford the desired TES-protected alcohol **88** (228.3 mg, 0.73 mmol, 87% yield) as a clear and colorless oil. **88**: R_f = 0.50 (silica gel, hexanes:EtOAc, 8:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14 – 7.09 (m, 1H), 3.85 (dd, J = 9.9, 4.7 Hz, 1H), 3.74 (s, 4H), 3.62 – 3.53 (m, 2H), 2.73 – 2.65 (m, 1H), 2.63 – 2.53 (m, 1H), 2.41 – 2.31 (m, 1H), 2.01 (tdd, J = 9.9, 5.8, 3.8 Hz, 2H), 0.97 – 0.92 (m, 9H), 0.58 (dd, J = 8.5, 7.3 Hz, 6H).



89

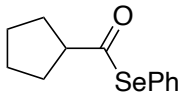
Diol 89. To a flame-dried and N_2 flushed flask was added THF (1.0 mL), $LaCl_3$•2LiCl (0.31 mL, 0.6 M in THF, 0.183 mmol, 3.0 equiv), and a solution of TES-protected

alcohol **88** (19.0 mg, 0.061 mmol, 1.0 equiv) in THF (1.0 mL) sequentially at 25 °C. The reaction mixture was allowed to stir for 1 h before being cooled to –78 °C. Then, MeMgBr (0.02 mL, 3.0 M in Et_2O, 0.067 mmol, 1.1 equiv) was added and the result mixture was stirred for an additional 30 min. At that time, the reaction contents were quenched by the addition of NH_4Cl (15 mL), diluted with CH_2Cl_2 (10 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 8:1) to afford recovered TES-protected alcohol **88** (7.4 mg, 0.024 mmol, 39% recovered) and the desired 1,2-addition product (11.4 mg, 0.035 mmol, 57% yield, 95% yield brsm). Pushing forward, the 1,2-addition product (9.3 mg, 0.028 mmol, 1.0 equiv) was dissolved in THF (1.4 mL) at 0 °C. Then, TBAF (0.03 mL, 1.0 M in THF, 0.031 mmol, 1.1 equiv) was added to the reaction mixture, which was stirred for a further 5 min. Upon completion, the reaction contents were quenched by the addition of NH_4Cl (15 mL), diluted with EtOAc (10 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 1:1) to afford desired diol **89** (5.3 mg, 0.025 mmol, 89% yield) as a clear and colorless oil. **89**: R_f = 0.0.15 (silica gel, hexanes:EtOAc, 1:1); ^1H NMR (500 MHz, $CDCl_3$) δ 7.20 (t, J = 6.4 Hz, 1H), 4.02 (dd, J = 11.3, 3.1 Hz, 1H), 3.74 (s, 4H), 2.93 (d, J = 14.8 Hz, 1H), 2.88 – 2.77 (m, 1H), 2.60 (d, J = 14.8 Hz, 1H), 2.46 (dtd, J = 16.9, 7.1, 2.8 Hz, 1H), 2.32 – 2.22 (m, 2H), 1.95 – 1.86 (m, 1H), 1.69 (ddd, J = 10.9, 5.4, 3.2 Hz, 2H), 1.41 (s, 3H).



61

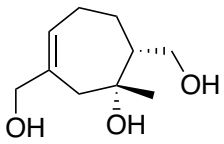
Aldehyde 61. To a solution of diol **89** (19.8 mg, 0.092 mmol, 1.0 equiv) in CH_2Cl_2 (3.0 mL) was added $NaHCO_3$ (38.6 mg, 0.460 mmol, 5.0 equiv), and Dess-Martin periodinane (54.7 mg, 0.129 mmol, 1.4 equiv) sequentially. The resultant mixture was stirred for 2 h at 25 °C. Upon completion, the reaction contents were concentrated directly and the resultant residue was purified by flash column chromatography (silica gel, hexanes:EtOAc, 4:1→3:1) to afford the desired aldehyde **61** (14.5 mg, 0.068 mmol, 74% yield) as a colorless oil. **61**: R_f = 0.20 (silica gel, hexanes:EtOAc, 3:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.83 (d, J = 1.9 Hz, 1H), 7.19 (t, J = 6.5 Hz, 1H), 3.75 (s, 3H), 2.93 (d, J = 14.9 Hz, 1H), 2.68 (d, J = 14.9 Hz, 1H), 2.55 – 2.42 (m, 3H), 2.32 (dddd, J = 16.2, 9.8, 6.7, 3.0 Hz, 1H), 1.97 (dddd, J = 14.5, 9.8, 8.7, 2.8 Hz, 1H), 1.80 (ddt, J = 14.6, 8.1, 3.3 Hz, 1H), 1.39 (s, 3H).



93

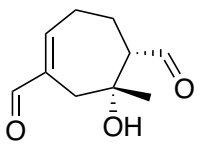
Acyl selenide 93. To a solution of cyclopentanecarboxylic acid (0.12 mL, 1.00 mmol, 1.0 equiv) in CH_2Cl_2 (3.0 mL) was added a solution of Ph_2Se_2 (468.2 mg, 1.50 mmol, 1.5 equiv) in CH_2Cl_2 (10.0 mL). The resultant reaction mixture was cooled to 0 °C before the dropwise addition of a solution of PBu_3 (0.37 mL, 1.50 mmol, 1.5 equiv) in CH_2Cl_2 (2.0 mL). Once the addition was complete, the reaction was warmed to 25 °C and was allowed to stir for an additional 2 h. Upon completion, the reaction contents were quenched by the addition of H_2O (15 mL), diluted with CH_2Cl_2 (10 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:CH_2Cl_2, 12:1→hexanes:EtOAc, 20:1) to afford the

desired acyl selenide **93** (202.0 mg, 0.80 mmol, 80% yield) as a white foam. **93**: R_f = 0.15 (silica gel, hexanes:CH_2Cl_2, 10:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 – 7.47 (m, 2H), 7.37 (qd, J = 3.9, 1.8 Hz, 3H), 3.15 (p, J = 7.8 Hz, 1H), 1.99 – 1.88 (m, 4H), 1.77 – 1.67 (m, 2H), 1.67 – 1.57 (m, 2H).



106

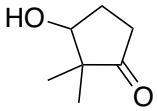
Triol 106. To a solution of diol **89** (35.0 mg, 0.16 mmol, 1.0 equiv) in Et_2O (1.6 mL) at 0 °C was added solid $LiAlH_4$ (24.3 mg, 0.64 mmol, 4.0 equiv). The reaction mixture was allowed to warm to 25 °C and was stirred for an additional 1 h. Upon completion, the reaction contents were quenched by the addition of Rochelle's Salt (15 mL – stirred 2 h), diluted with EtOAc (10 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, pure EtOAc) afforded the desired triol **106** (14.1 mg, 0.076 mmol, 48% yield) as a colorless oil. **106**: R_f = 0.10 (silica gel, pure EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.95 (t, J = 6.6 Hz, 1H), 4.11 (dt, J = 11.3, 2.6 Hz, 1H), 3.93 (s, 2H), 3.65 (dd, J = 11.0, 3.3 Hz, 1H), 2.49 (d, J = 14.7 Hz, 1H), 2.35 (d, J = 14.6 Hz, 1H), 2.24 (dtd, J = 15.1, 7.4, 2.1 Hz, 1H), 2.14 – 2.06 (m, 1H), 1.83 (dtd, J = 13.7, 11.4, 2.0 Hz, 1H), 1.60 (ddd, J = 11.5, 8.2, 3.0 Hz, 2H), 1.41 (s, 3H), 1.38 – 1.23 (m, 2H).



99

Dialdehyde 99. To a solution of triol **106** (13.1 mg, 0.070 mmol, 1.0 equiv) in CH_2Cl_2 (1.4 mL) at 25 °C was added solid $NaHCO_3$ (36.3 mg, 0.43 mmol, 6.1 equiv) and Dess–

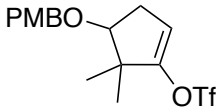
Martin periodinane (91.6 mg, 0.22 mmol, 3.1 equiv) sequentially. The resultant mixture was stirred at 25 °C for 30 min. Upon completion, the reaction contents were concentrated directly and the resultant residue was purified by flash column chromatography (silica gel, hexanes:EtOAc, 2:1) to afford the desired aldehyde **99** (9.4 mg, 0.052 mmol, 74% yield) as a colorless oil. **99**: R_f = 0.20 (silica gel, hexanes:EtOAc, 1:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.87 (d, J = 1.7 Hz, 1H), 9.40 (s, 1H), 6.90 (t, J = 6.1 Hz, 1H), 2.84 (d, J = 15.0 Hz, 1H), 2.66 (dddd, J = 14.1, 8.6, 5.9, 2.7 Hz, 1H), 2.59 (d, J = 15.0 Hz, 1H), 2.56 – 2.44 (m, 2H), 2.37 (s, 1H), 2.13 – 2.03 (m, 1H), 1.87 (ddt, J = 14.7, 8.3, 3.3 Hz, 1H), 1.38 (s, 3H).



114

Ketone 114. To a sealed tube was added solid 2-methylcyclopentane-1,3-dione (2.00 g, 17.82 mmol, 1.0 equiv), dioxane (30 mL), and H_2O (10 mL) at 25 °C. Then, solid KOH (1.10 g, 19.60 mmol, 1.1 equiv) and MeI (1.22 mL, 19.60 mmol, 1.1 equiv) were added sequentially. The reaction vessel was then sealed and placed in a preheated oil bath at 105 °C. The resultant mixture was stirred vigorously for 6 h. Upon completion, the reaction contents were diluted with CH_2Cl_2 (30 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. The resulting residue was then redissolved in 10% HCl (50 mL) and was subsequently boiled for 5 min before being quenched by the addition of $NaHCO_3$ (125 mL), diluted with CH_2Cl_2 (60 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 60 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated to yield the desired diketone (909.2 mg, 7.21 mmol, 40% yield) directly as a white solid. Pushing forward, the diketone (255.0 mg, 2.02 mmol, 1.0 equiv) was dissolved in MeOH (16 mL) and H_2O (4 mL) before being cooled to 0

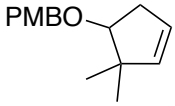
°C. To the reaction mixture was added $NaBH_4$ (20.6 mg, 0.55 mmol, 0.27 equiv) in a single portion and the reaction mixture was allowed to warm to 25 °C over 4 h. Upon completion, the reaction contents were quenched by the addition of NH_4Cl (30 mL), diluted with CH_2Cl_2 (25 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 2:1) yielded the desired ketone **114** (230.4 mg, 1.80 mmol, 89% yield) as a colorless oil. **114**: R_f = 0.20 (silica gel, hexanes:EtOAc, 2:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.05 (t, J = 5.2 Hz, 1H), 2.52 – 2.42 (m, 1H), 2.32 – 2.21 (m, 2H), 1.90 (ddt, J = 12.8, 10.5, 4.8 Hz, 1H), 1.03 (s, 6H).



116

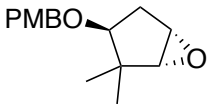
Triflate 116. To a solution of ketone **114** (447.0 mg, 3.49 mmol, 1.0 equiv) in CH_2Cl_2 (10.0 mL) at 25 °C was sequentially added PMB-trichloroacetimidate (1.97 g, 6.98 mmol, 2.0 equiv) and CSA (162.6 mg, 0.70 mmol, 0.2 equiv). The reaction mixture was allowed to stir at 25 °C for 8 h. Upon completion, the reaction contents were quenched by the addition of $NaHCO_3$ (15 mL), diluted with CH_2Cl_2 (10 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 18:1→15:1) yielded the desired PMB-protected alcohol **115** (793.8 mg, 3.20 mmol, 92% yield) as a colorless oil. Pushing forward, to a solution of the so-obtained PMB-protected alcohol **115** (56.5 mg, 0.23 mmol, 1.0 equiv) in THF (2.3 mL) at –78 °C was added KHMDS (0.46 mL, 1.0 M in THF, 0.46 mmol, 2.0 equiv) dropwise. The resultant mixture was stirred for an additional 30 min before the subsequent addition

of solid $PhNTf_2$ (164.3 mg, 0.46 mmol, 2.0 equiv). The reaction mixture was then allowed to slowly warm to 25 °C over 8 h. Upon completion, the reaction contents were quenched by the addition of NH_4Cl (15 mL), diluted with CH_2Cl_2 (10 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 50:1) yielded the desired triflate **116** (78.1 mg, 0.21 mmol, 91% yield) as a colorless oil. **116**: R_f = 0.40 (silica gel, hexanes:EtOAc, 50:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (d, J = 8.6 Hz, 2H), 6.92 – 6.85 (m, 2H), 5.45 (t, J = 2.6 Hz, 1H), 4.56 – 4.46 (m, 2H), 3.81 (s, 4H), 2.60 (ddd, J = 15.7, 7.3, 3.2 Hz, 1H), 2.30 (ddd, J = 15.7, 6.6, 2.3 Hz, 1H), 1.14 (d, J = 5.1 Hz, 6H).



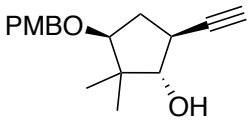
117 **Olefin 117.** To a solution of triflate **116** (74.7 mg, 0.20 mmol, 1.0 equiv) in DMF (2.0 mL) at 25 °C was sequentially added $Pd(PPh_3)_2Cl_2$ (7.0 mg, 0.01 mmol, 0.05 equiv), nBu$_3$N (0.14 mL, 0.60 mmol, 3.0 equiv), and formic acid (0.02 mL, 0.50 mmol, 2.5 equiv). The reaction mixture was then placed in a preheated oil bath (75 °C) and was allowed to stir for 1 h. Upon completion, the reaction contents were quenched by the addition of brine (15 mL), diluted with CH_2Cl_2 (10 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 50:1) yielded the desired triflate **117** (37.5 mg, 0.16 mmol, 80% yield) as a colorless oil. **117**: R_f = 0.35 (silica gel, hexanes:EtOAc, 50:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (d, J = 8.3 Hz, 2H), 6.88 (d, J = 8.5 Hz, 2H), 5.62 – 5.42 (m, 2H), 4.57 – 4.45 (m, 2H), 3.81 (s, 3H), 3.74 (t, J = 6.7 Hz, 1H), 2.62 – 2.51 (m, 1H), 2.36 – 2.28 (m, 1H),

1.08 (d, J = 14.9 Hz, 6H)); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.12, 141.14, 131.37, 129.01, 125.11, 113.81, 86.87, 71.70, 55.40, 46.90, 37.29, 27.63, 21.21.



118

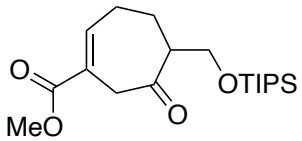
Epoxide 118. To a solution of olefin **117** (36.2 mg, 0.16 mmol, 1.0 equiv) in CH_2Cl_2 (3.2 mL) at 0 °C was added *m*CPBA (86.3 mg, 70% by weight, 0.35 mmol, 2.2 equiv) in one portion. The cooling bath was then removed, and the reaction was allowed to stir at 25 °C for an additional 3 h. Upon completion, the reaction contents were quenched by the addition of $NaHCO_3$ (15 mL), diluted with CH_2Cl_2 (10 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and then washed twice with a mix of $Na_2S_2O_3$ (5 mL) and $NaHCO_3$ (5 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc 20:1) to afford the desired epoxide **118** (24.1 mg, 0.097 mmol, 61%) as a yellow oil. **118**: R_f = 0.20 (silica gel, hexanes:EtOAc, 20:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (d, J = 8.5 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 4.46 – 4.37 (m, 2H), 3.80 (s, 3H), 3.40 (dd, J = 2.7, 1.3 Hz, 1H), 3.36 – 3.30 (m, 1H), 3.09 (d, J = 3.0 Hz, 1H), 2.40 (dd, J = 13.9, 7.1 Hz, 1H), 1.59 (dd, J = 13.9, 8.1 Hz, 1H), 1.19 (s, 3H), 0.93 (s, 3H).



120

Alkyne 120. To a solution of trimethylsilylacetylene (0.03 mL, 0.234 mmol, 3.0 equiv) in THF (1.0 mL) at –78 °C was added *n*BuLi (0.15 mL, 1.6 M in hexanes, 0.234 mmol, 3.0 equiv) dropwise. The reaction mixture was stirred for 15 min at –78 °C before the sequential dropwise addition of a solution of epoxide **118** (19.3 mg, 0.078 mmol, 1.0 equiv) in THF (0.6 mL) and BF_3•Et_2O (0.03 mL, 0.234 mmol, 3.0 equiv). The reaction was allowed to stir for an additional

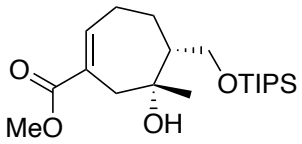
3.5 h before the reaction contents were quenched by the addition of NH_4Cl (15 mL), diluted with CH_2Cl_2 (10 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 20:1→15:1) yielded recovered starting epoxide **118** (6.1 mg, 0.025 mmol, 32% recovered) and the desired TMS-capped alkyne **119** (10.4 mg, 0.030 mmol, 38% yield, 57% yield brsm) as a colorless oil. Pushing forward, to a solution of the so-obtained **119** (10.4 mg, 0.030 mmol, 1.0 equiv) in THF (2.0 mL) at 0 °C was added TBAF (0.08 mL, 1.0 M in THF, 0.08 mmol, 2.7 equiv). The reaction mixture was then allowed to stir at 0 °C for 5 min. Upon completion, the reaction contents were quenched by the addition of NH_4Cl (15 mL), diluted with CH_2Cl_2 (10 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 8:1) yielded the desired alkyne **120** (7.1 mg, 0.026 mmol, 87% yield) as a colorless oil. **120**: R_f = 0.10 (silica gel, hexanes:EtOAc, 5:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, J = 8.3 Hz, 2H), 6.87 (d, J = 8.6 Hz, 2H), 4.50 (d, J = 11.7 Hz, 1H), 4.34 (d, J = 11.6 Hz, 1H), 3.94 (dd, J = 7.9, 3.5 Hz, 1H), 3.81 (s, 3H), 3.43 (dd, J = 6.3, 4.4 Hz, 1H), 2.61 (ddd, J = 10.4, 6.2, 2.4 Hz, 1H), 2.41 (ddd, J = 13.9, 10.0, 6.3 Hz, 1H), 1.85 (d, J = 4.2 Hz, 1H), 1.77 (ddd, J = 13.9, 8.3, 4.3 Hz, 1H), 1.09 (s, 3H), 0.88 (s, 3H).



121

TIPS-protected Alcohol 121. To a solution of alcohol **87** (185.8 mg, 0.94 mmol, 1.0 equiv) in CH_2Cl_2 (4.7 mL) at –78 °C was added lutidine (0.16 mL, 1.41 mmol, 1.5

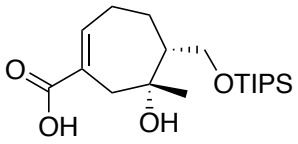
equiv) and TIPSOTf (0.38 mL, 1.41 mmol, 1.5 equiv) sequentially. The reaction mixture was stirred for 30 min further at –78 °C. Upon completion, the reaction contents were quenched by the addition of NH_4Cl (15 mL), diluted with CH_2Cl_2 (10 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:CH_2Cl_2, 2:1 → hexanes:EtOAc, 10:1) to afford the desired TIPS-protected alcohol **121** (239.0 mg, 0.67 mmol, 71% yield) as a clear and colorless oil. **121**: R_f = 0.60 (silica gel, hexanes:EtOAc, 8:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 – 7.08 (m, 1H), 3.92 (qd, J = 9.7, 5.2 Hz, 2H), 3.75 (s, 3H), 3.65 – 3.57 (m, 2H), 2.72 – 2.58 (m, 2H), 2.44 – 2.31 (m, 1H), 2.19 – 2.11 (m, 1H), 2.01 (ddt, J = 14.2, 8.1, 4.3 Hz, 1H), 1.04 (d, J = 5.8 Hz, 21H).



122

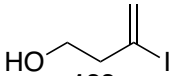
Tertiary Alcohol 122. To a solution of TIPS-protected alcohol **121** (234.5 mg, 0.66 mmol, 1.0 equiv) in THF (13.2 mL) was added $LaCl_3$•2LiCl (3.3 mL, 0.6 M in THF, 1.98 mmol, 3.0 equiv) at 25 °C. The reaction mixture was allowed to stir for 1 h before being cooled to –78 °C. Then, MeMgCl (0.24 mL, 3.0 M in THF, 0.73 mmol, 1.1 equiv) was added and the result mixture was stirred for an additional 30 min. At that time, the reaction contents were quenched by the addition of NH_4Cl (30 mL), diluted with CH_2Cl_2 (25 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 15:1→12:1) to afford recovered TIPS-protected alcohol **121** (92.5 mg, 0.26 mmol, 39% recovered) and the

desired tertiary alcohol **122** (86.7 mg, 0.23 mmol, 35% yield, 58% yield brsm) as a colorless oil. **122**: R_f = 0.10 (silica gel, hexanes:EtOAc, 12:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 (t, J = 6.4 Hz, 1H), 4.10 (dd, J = 10.1, 4.1 Hz, 1H), 3.89 (dd, J = 10.1, 4.4 Hz, 1H), 3.79 – 3.68 (m, 4H), 2.95 (d, J = 15.0 Hz, 1H), 2.53 (d, J = 14.9 Hz, 1H), 2.45 (dd, J = 12.2, 5.4 Hz, 1H), 2.26 – 2.18 (m, 1H), 1.99 – 1.90 (m, 1H), 1.73 – 1.59 (m, 2H), 1.39 (s, 3H), 1.06 (d, J = 6.1 Hz, 21H).



111

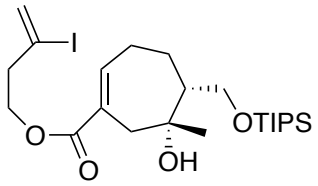
Carboxylic Acid 111. To a solution of tertiary alcohol **121** (14.4 mg, 0.039 mmol, 1.0 equiv) in MeOH (1.0 mL) and H_2O (1.0 mL) was added solid LiOH (0.9 mg, 0.039 mmol, 1.0 equiv) at 25 °C. The reaction mixture was then placed in a preheated oil bath (115 °C) and was allowed to reflux for 5 h. Upon completion, the reaction contents were quenched by the addition of NH_4Cl (15 mL), diluted with EtOAc (10 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated to afford the desired carboxylic acid **111** (13.2 mg, 0.037 mmol, 95% yield) as a clear and colorless oil without further purification. **111**: R_f = 0.20 (silica gel, CH_2Cl_2:MeOH, 10:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (t, 1H), 4.12 (dd, J = 10.1, 4.0 Hz, 1H), 3.87 (dd, J = 10.1, 4.2 Hz, 1H), 2.90 (d, J = 15.0 Hz, 1H), 2.56 – 2.43 (m, 2H), 2.25 (ddd, J = 17.5, 8.3, 5.3 Hz, 1H), 1.96 (dtd, J = 13.5, 10.5, 2.8 Hz, 1H), 1.72 – 1.58 (m, 2H), 1.40 (d, J = 11.3 Hz, 3H), 1.06 (q, J = 4.8 Hz, 21H).



123

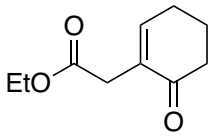
Vinyl Iodide 123. To a solution of NaI (2.14 g, 14.26 mmol, 2.0 equiv) in MeCN (15 mL) at 25 °C was sequentially added TMSCl (1.81 mL, 14.26 mmol, 2.0 equiv) and H_2O (0.13 mL, 7.13 mmol, 1.0 equiv). After stirring at 25 °C for 10 min, neat but-3-yn-1-ol (0.54 mL, 7.13

mmol, 1.0 equiv) was added dropwise. The reaction mixture was then allowed to stir for an additional 2 h. Upon completion, the reaction contents were quenched by the addition of 15% NaOH (30 mL), diluted with CH_2Cl_2 (25 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 6:1) afforded desired vinyl iodide **123** (810.1 mg, 4.01 mmol, 56% yield) as a yellow oil. **123**: R_f = 0.20 (silica gel, hexanes:EtOAc, 6:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.18 (d, J = 1.6 Hz, 1H), 5.86 (d, J = 1.5 Hz, 1H), 3.76 (q, J = 5.9 Hz, 3H), 2.63 (t, J = 5.8 Hz, 2H), 1.48 (t, J = 6.0 Hz, 1H).



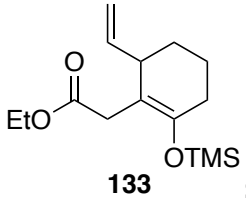
124

Tethered Iodide 124. To a solution of carboxylic acid **111** (46.8 mg, 0.13 mmol, 1.0 equiv) and vinyl iodide **123** (39.6 mg, 0.20 mmol, 1.5 equiv) in CH_2Cl_2 (1.3 mL) at 25 °C was added DMAP (6.2 mg, 0.03 mmol, 0.2 equiv) in one portion. The reaction mixture was then cooled to 0 °C before the addition of DCC (20.2 mg, 0.18 mmol, 1.4 equiv). The resultant solution was then allowed to warm to 25 °C over 8 h. Upon completion, the reaction contents were directly concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 12:1) afforded desired tethered iodide **124** (48.0 mg, 0.089 mmol, 68% yield) as a yellow oil. **124**: R_f = 0.20 (silica gel, hexanes:EtOAc, 12:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 (t, J = 6.3 Hz, 1H), 6.13 (s, 1H), 5.80 (s, 1H), 4.25 (t, J = 6.3 Hz, 2H), 4.08 (dd, J = 10.2, 4.1 Hz, 1H), 3.89 (dd, J = 10.1, 4.6 Hz, 1H), 3.68 (s, 1H), 2.92 (d, J = 15.0 Hz, 1H), 2.76 (t, J = 6.3 Hz, 2H), 2.53 (d, J = 15.0 Hz, 1H), 2.49 – 2.41 (m, 1H), 2.27 – 2.18 (m, 1H), 1.99 – 1.89 (m, 1H), 1.72 – 1.66 (m, 1H), 1.65 – 1.60 (m, 1H), 1.37 (s, 3H), 1.06 (d, J = 6.2 Hz, 21H).



130

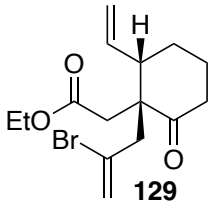
Enone 130. To a microwave vial was sequentially added (carbethoxymethylene)triphenylphosphorane (156.8 mg, 0.45 mmol, 1.0 equiv), 1,2-cyclohexanedione (150.0 mg, 1.34 mmol, 3.0 equiv), DBU (0.01 mL, 0.09 mmol, 0.2 equiv), and DMF (3.0 mL). The microwave vial was then sealed and irradiated under microwave conditions at 230 °C for 20 min. Upon completion, the reaction contents were quenched by the addition of NH_4Cl (10 mL), diluted with EtOAc (15 mL), and poured into a separatory funnel. The two phases were separated, and the organic layer was washed with NH_4Cl (3 × 10 mL). The organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 8:1) afforded desired enone **130** (36.0 mg, 0.20 mmol, 44% yield) as a colorless oil. **130**: R_f = 0.30 (silica gel, hexanes:EtOAc, 6:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.87 (t, J = 5.0 Hz, 1H), 4.18 – 4.04 (m, 2H), 3.19 (s, 2H), 2.47 (t, J = 6.8 Hz, 2H), 2.41 (d, J = 5.8 Hz, 2H), 2.03 (t, J = 6.6 Hz, 2H), 1.25 (t, J = 7.2 Hz, 3H).



133

Silyl Enol Ether 133. To a solution of CuBr•DMS (8.2 mg, 0.04 mmol, 0.3 equiv) in THF (2.0 mL) at –78 °C was added vinylmagnesium bromide (0.36 mL, 1.0 M in THF, 0.36 mmol, 3.0 equiv) dropwise. The resulting solution was then stirred for 15 min at –78 °C. Then, a premixed solution of TMSCl (0.08 mL, 0.60 mmol, 5.0 equiv) and enone **130** (22.0 mg, 0.12 mmol, 1.0 equiv) in THF (0.5 mL) was added dropwise and the resultant reaction mixture was allowed to warm to 25 °C over 8 h. Upon completion, the reaction contents were quenched by the addition of Et_3N (0.08 mL, 0.60 mmol, 3.0 equiv) followed by H_2O (15 mL), diluted with

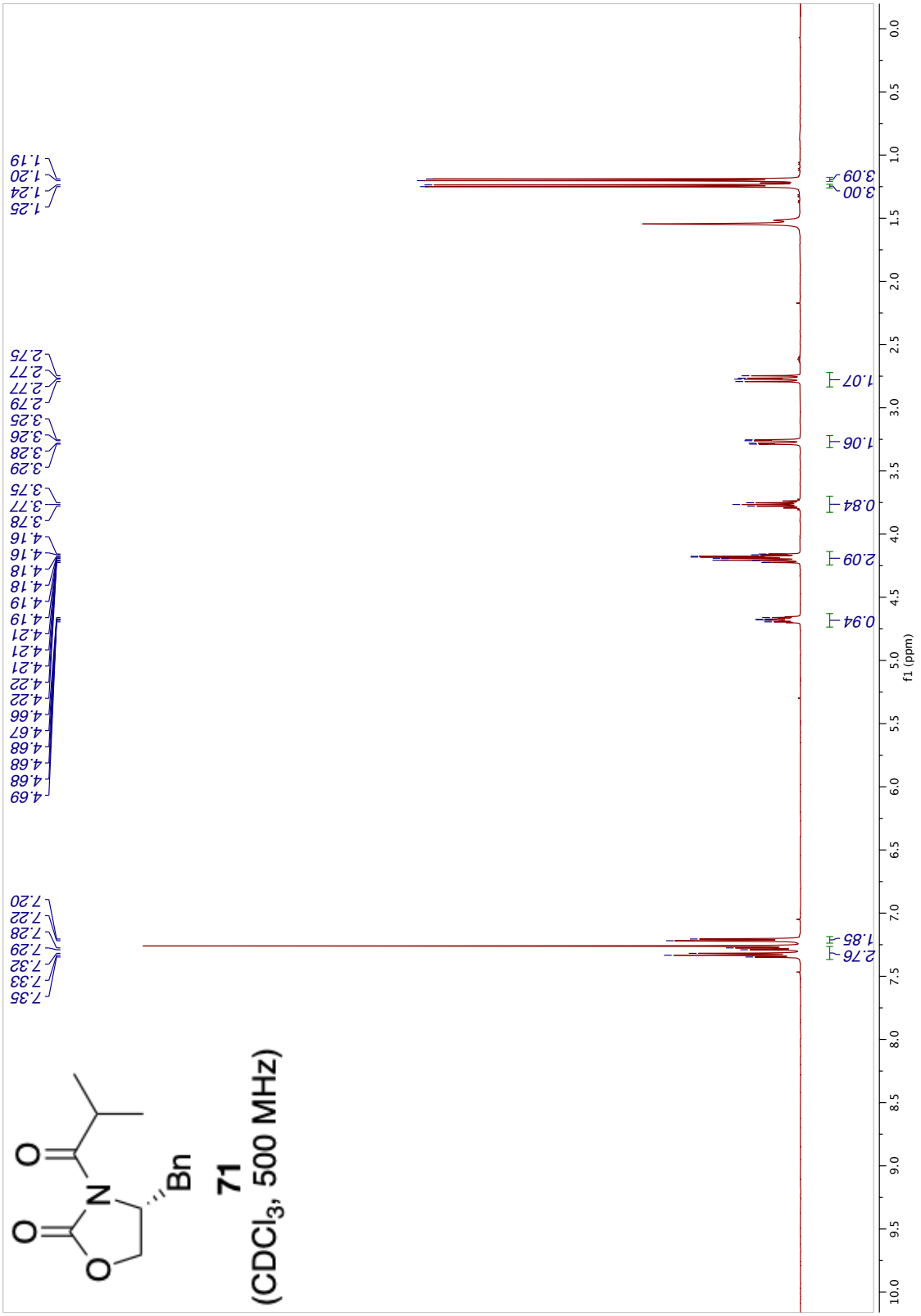
CH_2Cl_2 (10 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 20:1) afforded desired silyl enol ether **133** (25.0 mg, 0.09 mmol, 75% yield) as a yellow oil. **133**: R_f = 0.40 (silica gel, hexanes:EtOAc, 20:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.68 (ddd, J = 16.9, 10.2, 8.2 Hz, 1H), 5.04 – 4.94 (m, 2H), 3.25 (d, J = 16.0 Hz, 1H), 2.89 (d, J = 8.0 Hz, 1H), 2.79 (d, J = 16.0 Hz, 1H), 2.15 – 2.01 (m, 2H), 1.75 – 1.66 (m, 2H), 1.67 – 1.58 (m, 1H), 1.49 (ddd, J = 9.9, 7.0, 4.8 Hz, 1H), 0.18 (s, 9H).

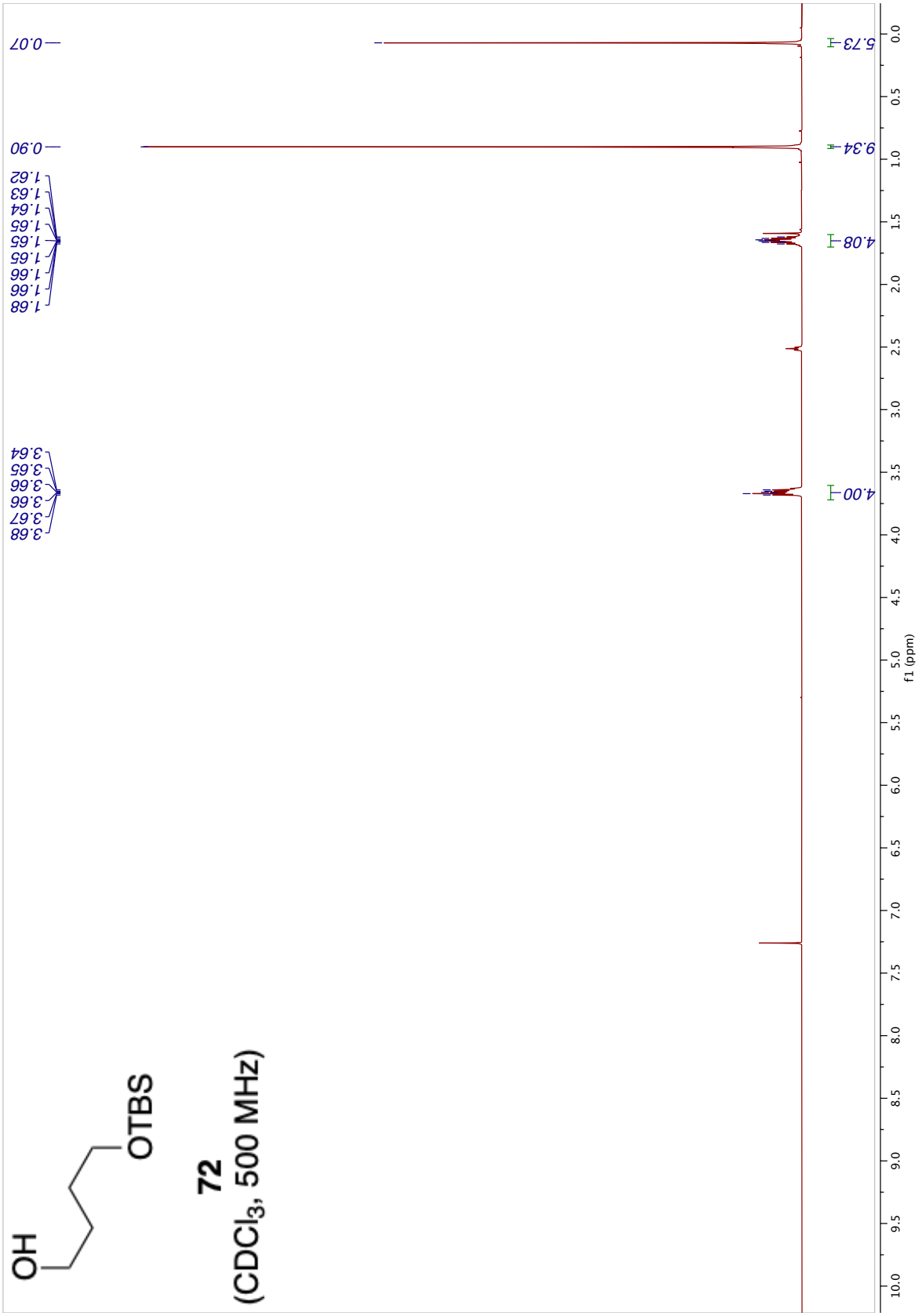


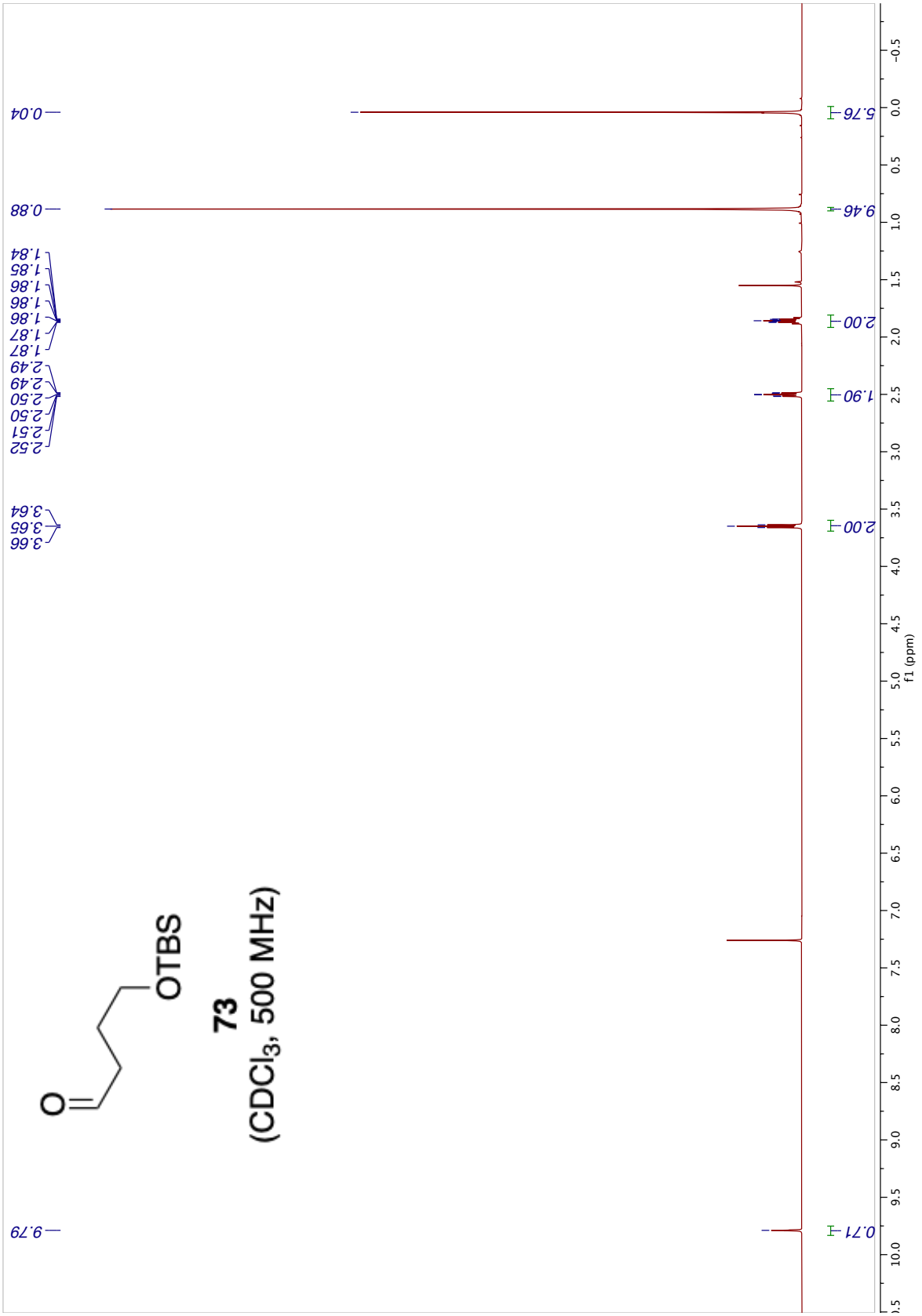
129
(tentative)

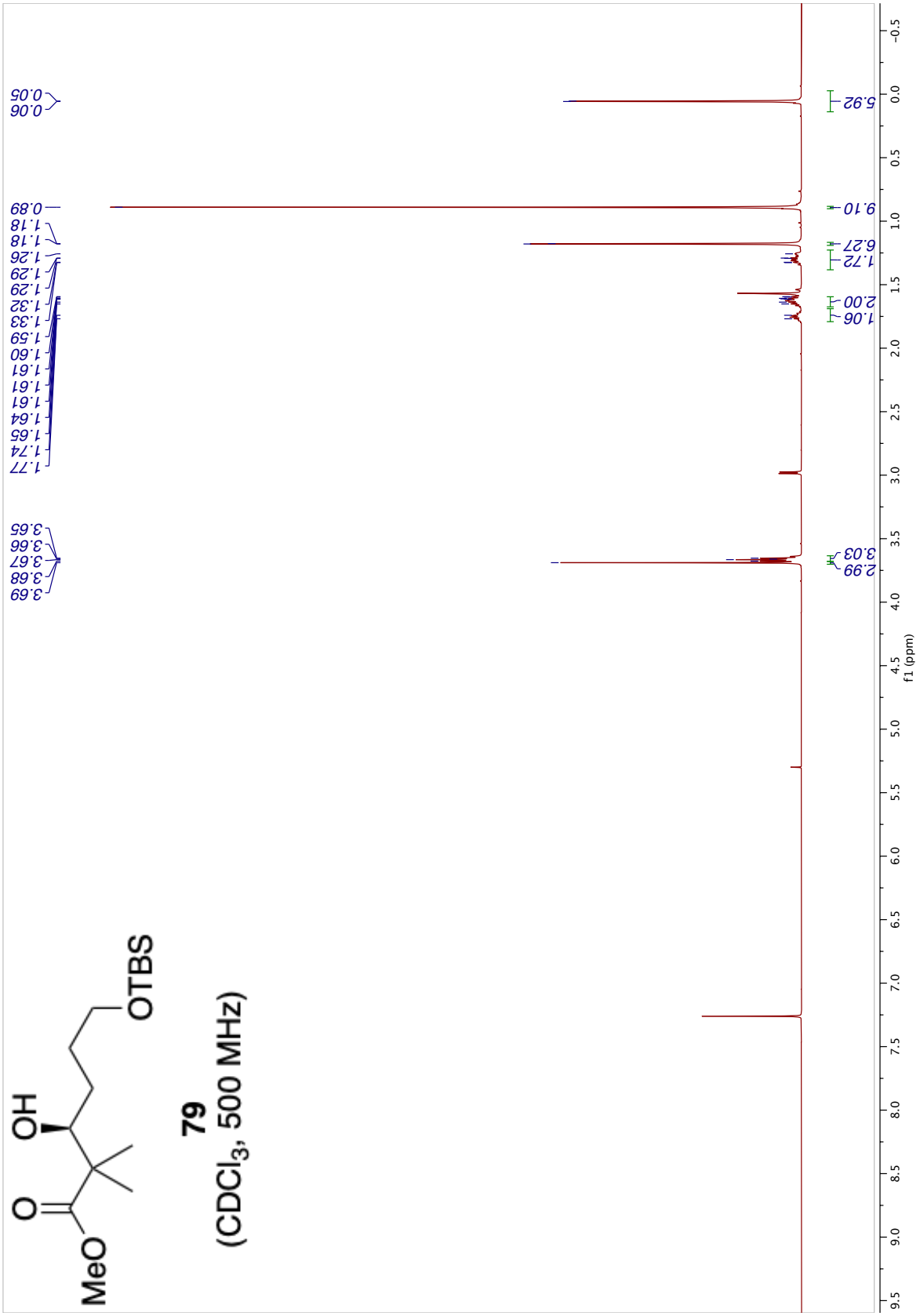
Vinyl Bromide 129. To a solution of silyl enol ether **133** (20.7 mg, 0.073 mmol, 1.0 equiv) in DME (1.4 mL) at 0 °C was added MeLi (0.04 M, 3.1 M in Et_2O, 0.110 mmol, 1.5 equiv). The resultant solution was stirred for 5 min before the subsequent addition of 2,3-dibromopropene. The reaction mixture was then allowed to warm to 25 °C over 2 h. At this time, full conversion of the starting material was observed, with a clear, more polar spot having formed on TLC (R_f = 0.10, silica gel, hexanes:EtOAc, 20:1).

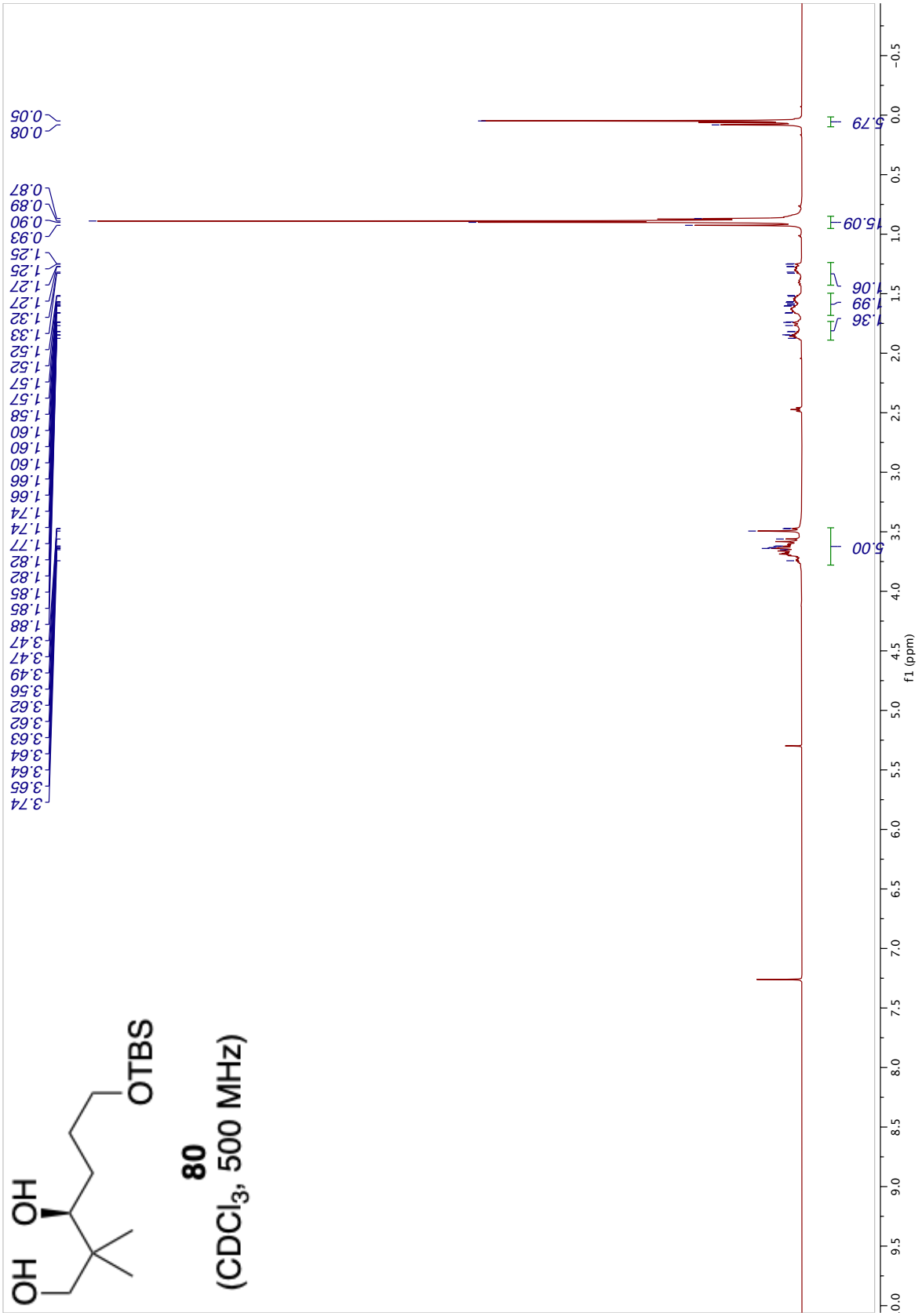
2.7 *NMR Spectra of Selected Intermediates*

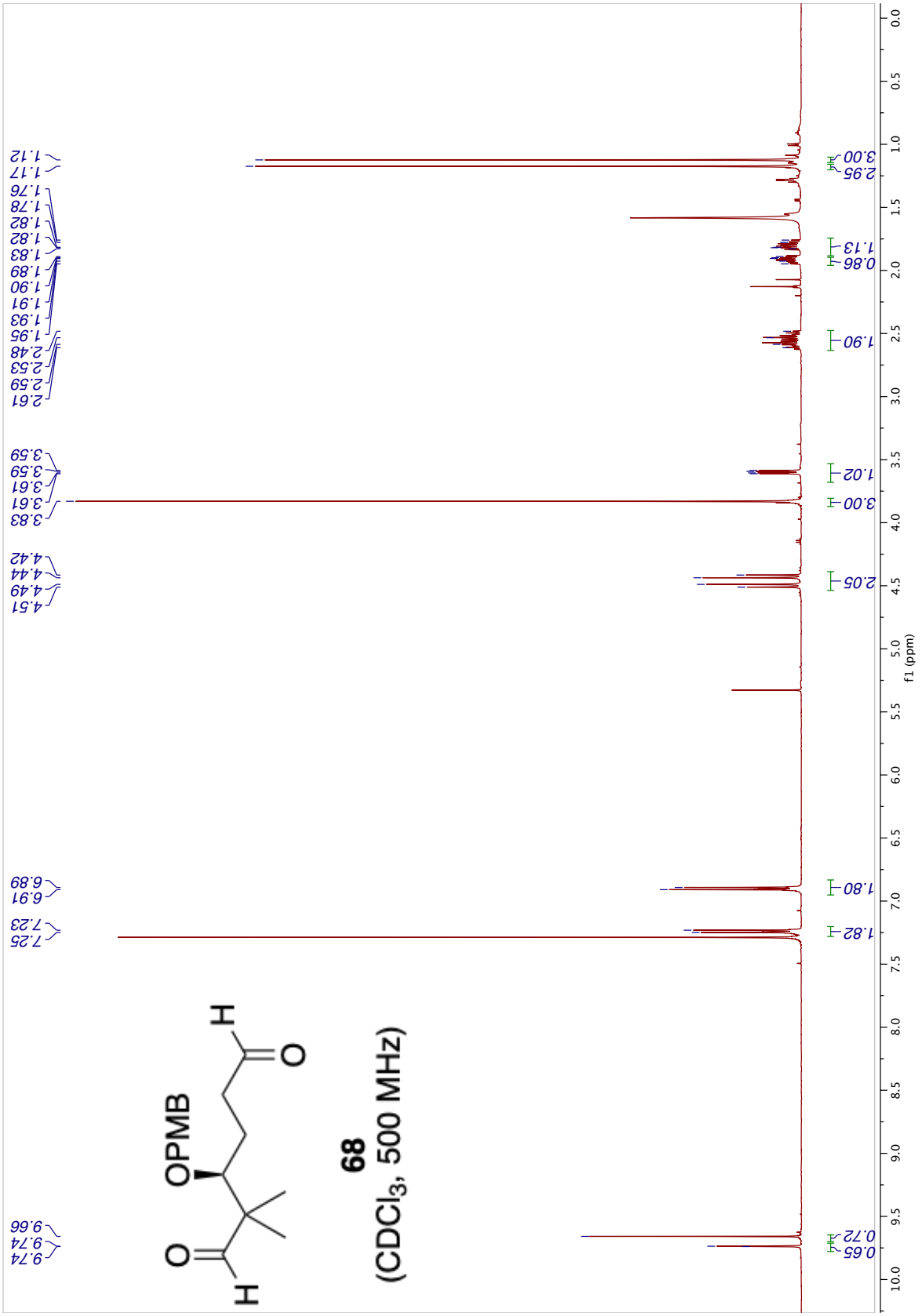


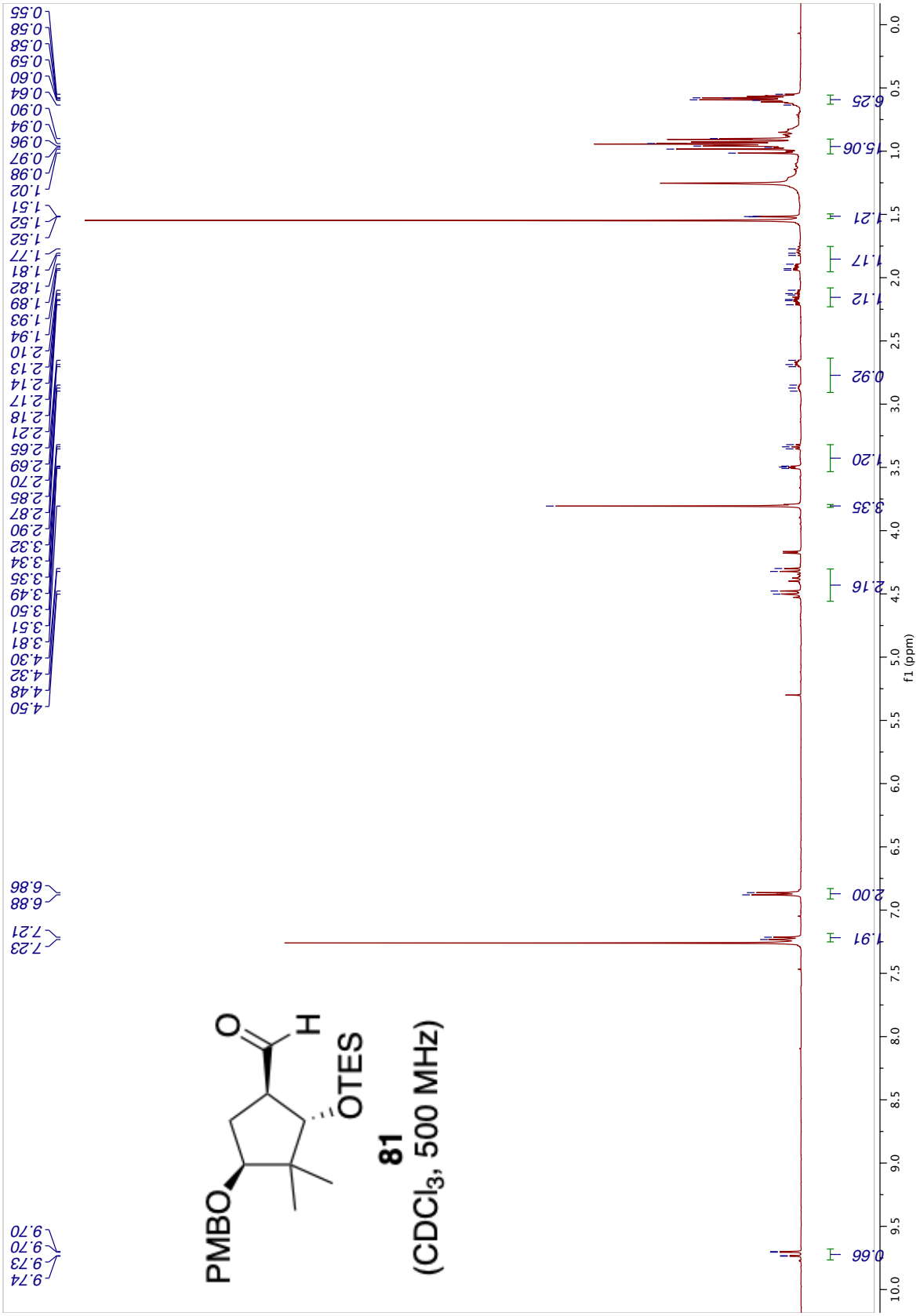

OH
OTBS
72
(CDCl3, 500 MHz)
0.07
0.90
1.62
1.63
1.64
1.65
1.65
1.65
1.66
1.66
1.68
3.64
3.65
3.66
3.66
3.67
3.68
5.73
9.34
4.08
4.00
f1 (ppm)

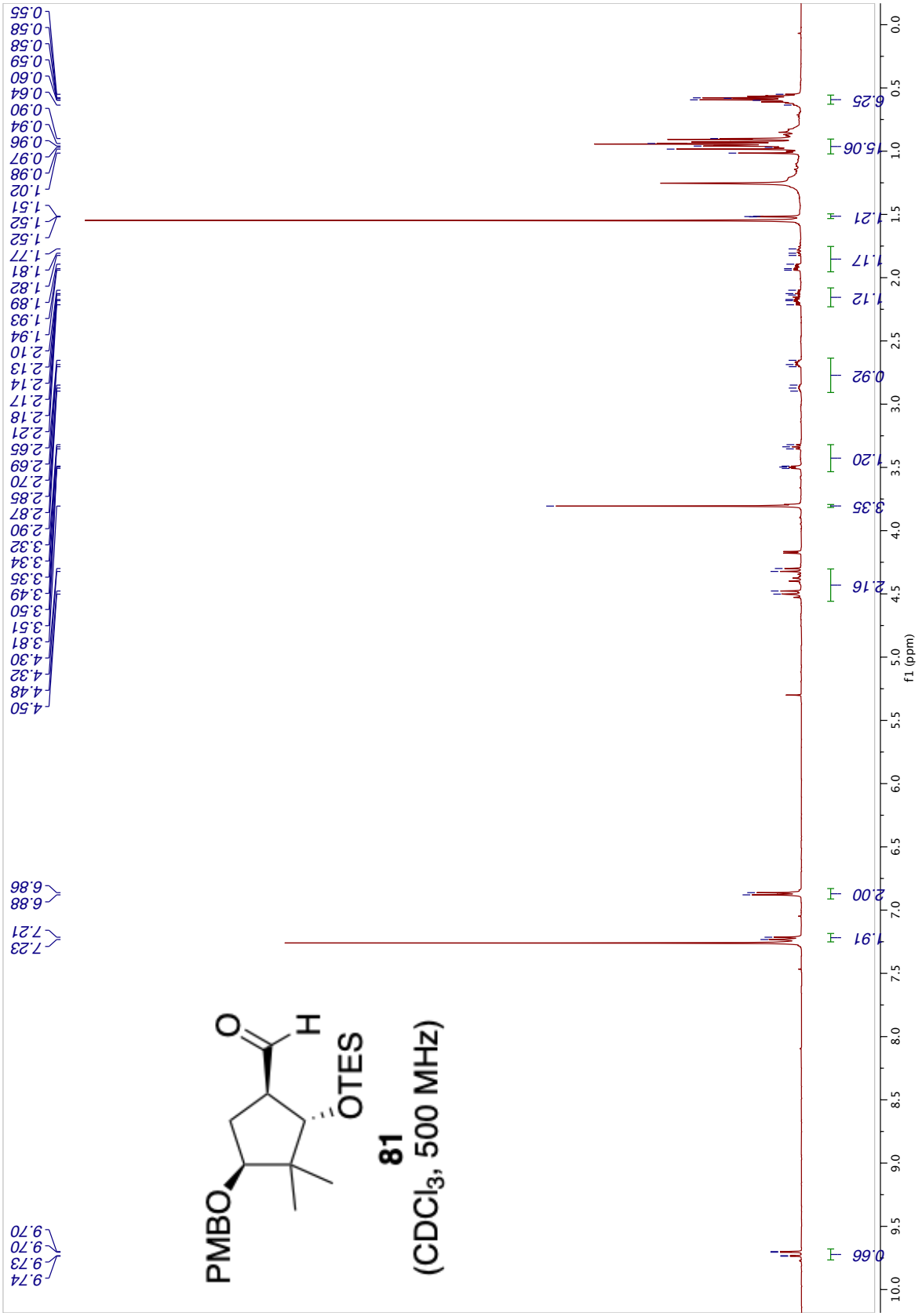

OTBS
O
73
(CDCl3, 500 MHz)
0.04
0.88
1.84
1.85
1.86
1.86
1.86
1.87
1.87
2.49
2.49
2.50
2.50
2.51
2.52
3.64
3.65
3.66
9.79
5.76
9.46
2.00
1.90
2.00
0.71
f1 (ppm)

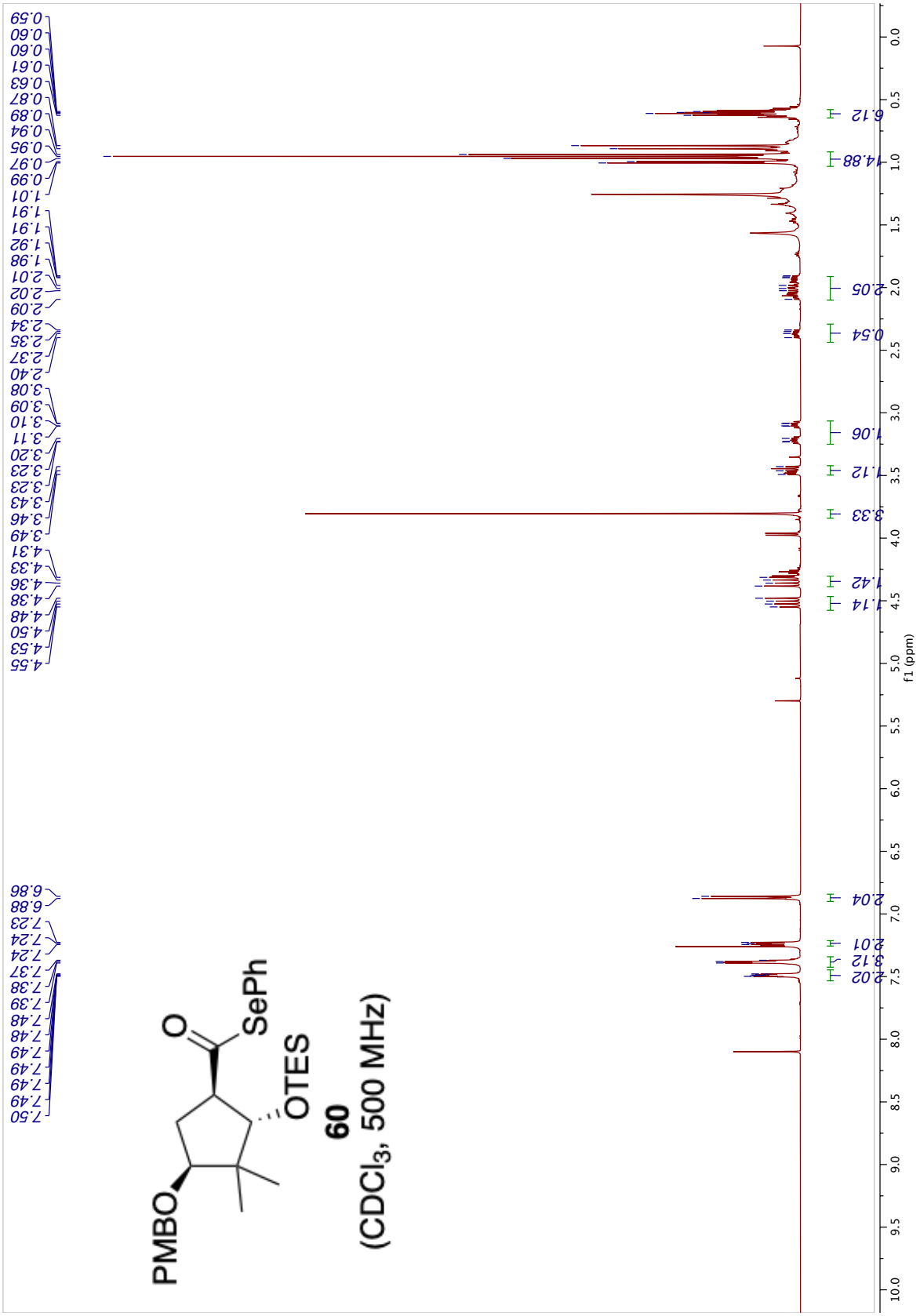

OTBS
OH
O
MeO
79
(CDCl3, 500 MHz)
0.06
0.05
0.89
1.18
1.18
1.26
1.29
1.29
1.32
1.33
1.59
1.60
1.61
1.61
1.61
1.64
1.65
1.74
1.77
3.65
3.66
3.67
3.68
3.69
5.92
9.10
6.27
1.72
2.00
1.06
3.03
2.99
f1 (ppm)

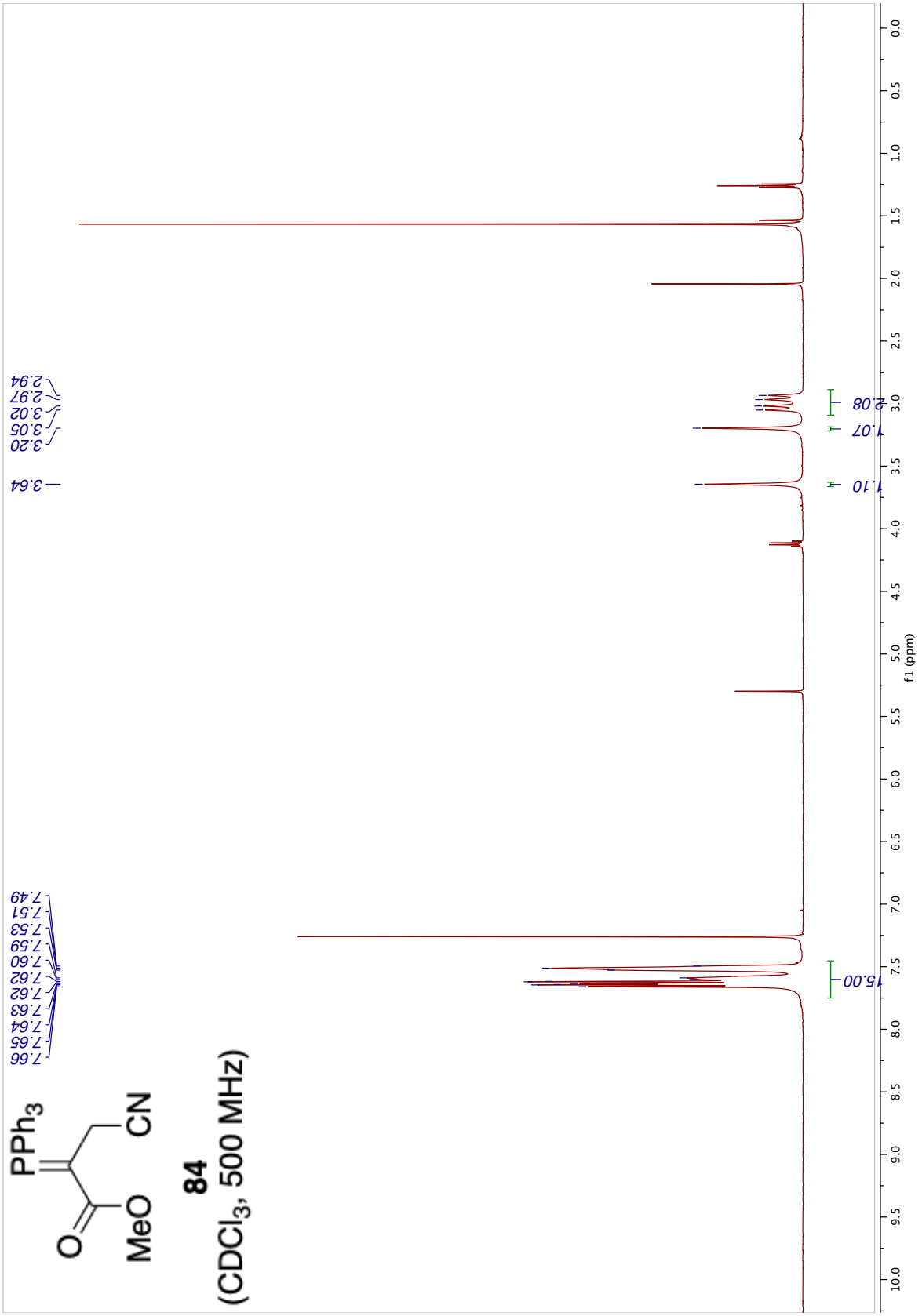

OH
OH
OTBS
80
(CDCl3, 500 MHz)
0.05
0.08
0.87
0.89
0.90
0.93
1.25
1.25
1.27
1.27
1.32
1.33
1.52
1.52
1.57
1.57
1.58
1.60
1.60
1.60
1.66
1.66
1.74
1.74
1.77
1.82
1.82
1.85
1.85
1.88
3.47
3.47
3.49
3.56
3.62
3.62
3.63
3.64
3.64
3.65
3.74
5.79
15.09
1.06
1.99
1.36
5.00
f1 (ppm)

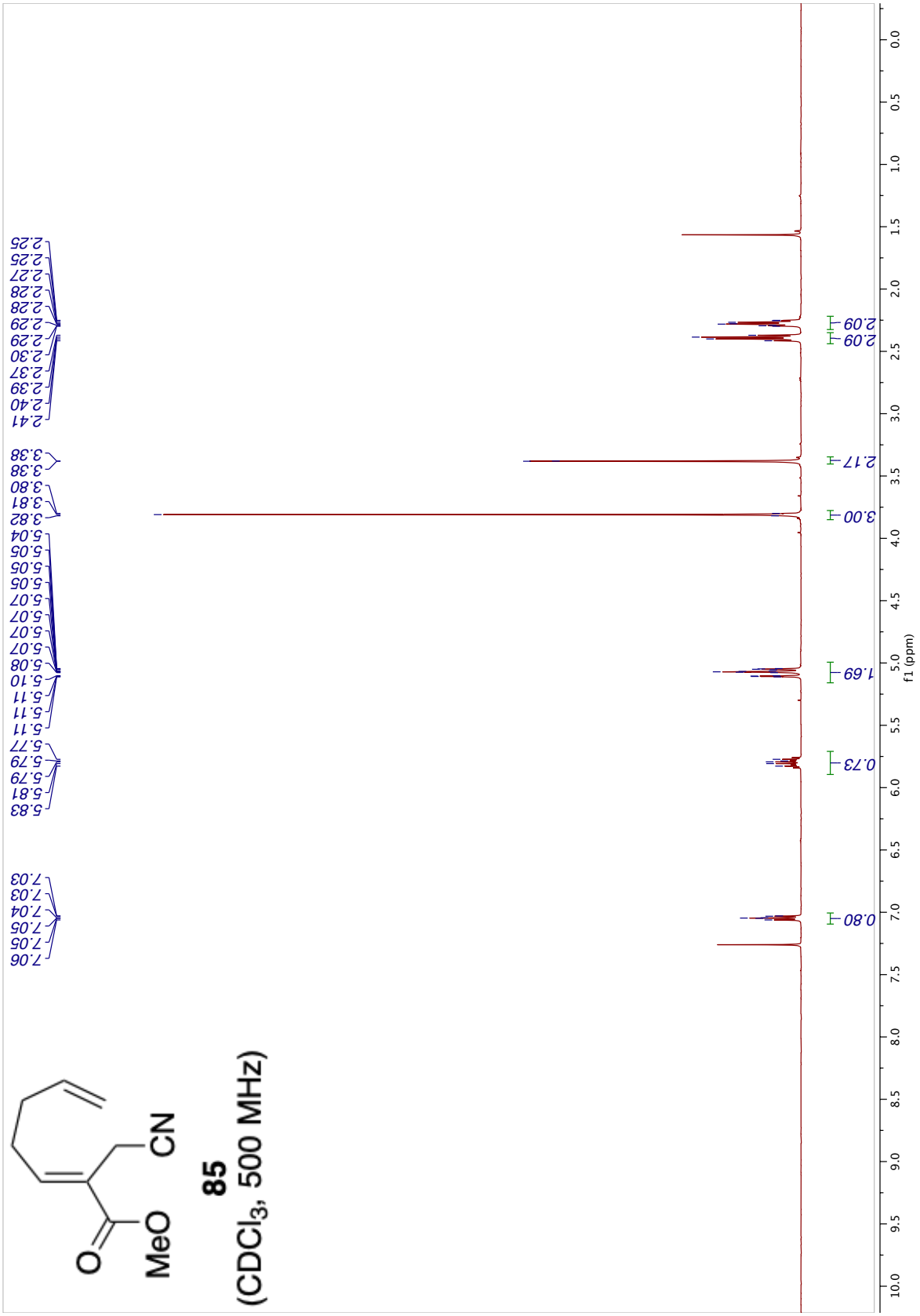

OPMB
O
H
O
H
68
(CDCl3, 500 MHz)
f1 (ppm)

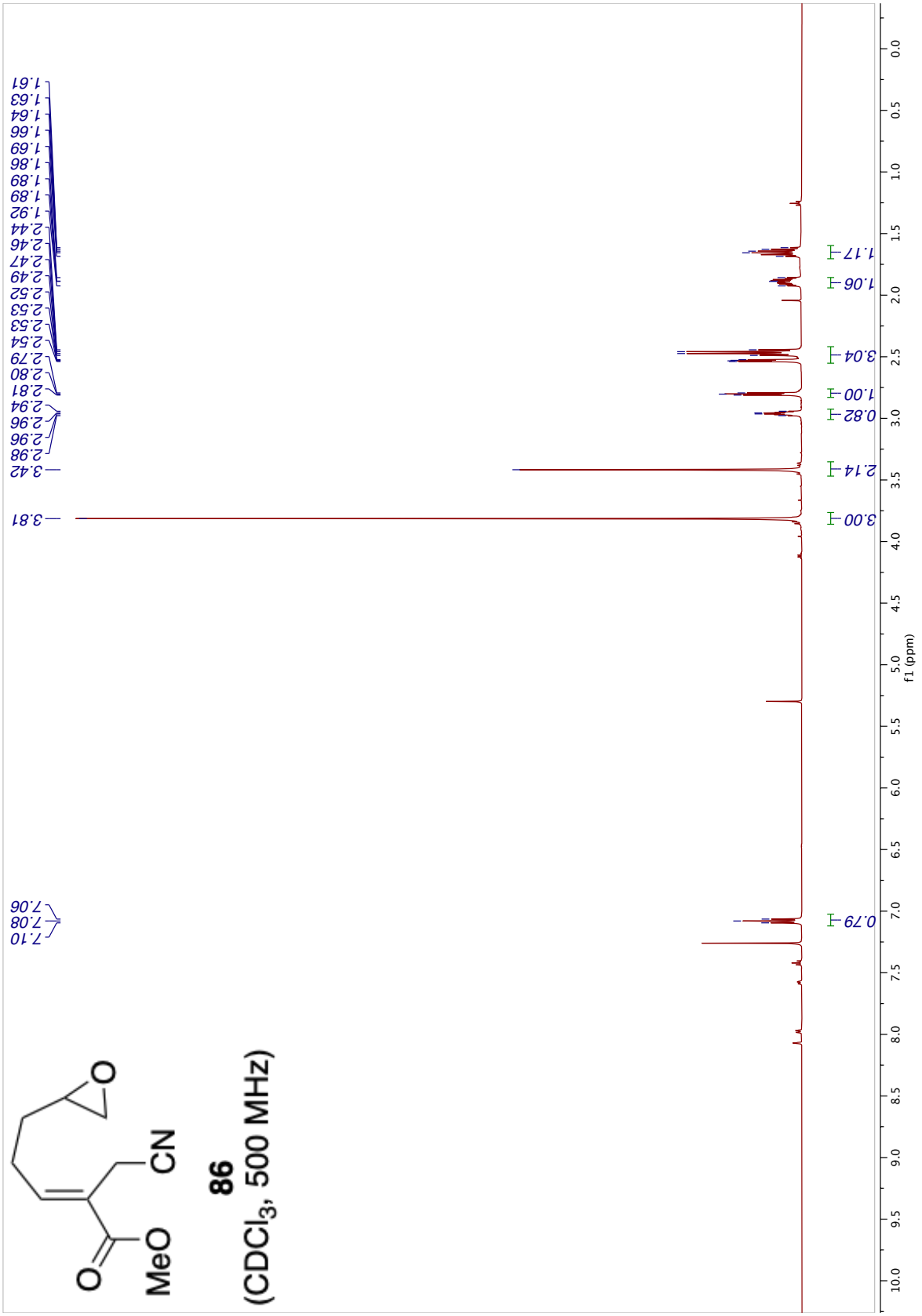

PMBO
OTES
O
H
81
(CDCl3, 500 MHz)
f1 (ppm)

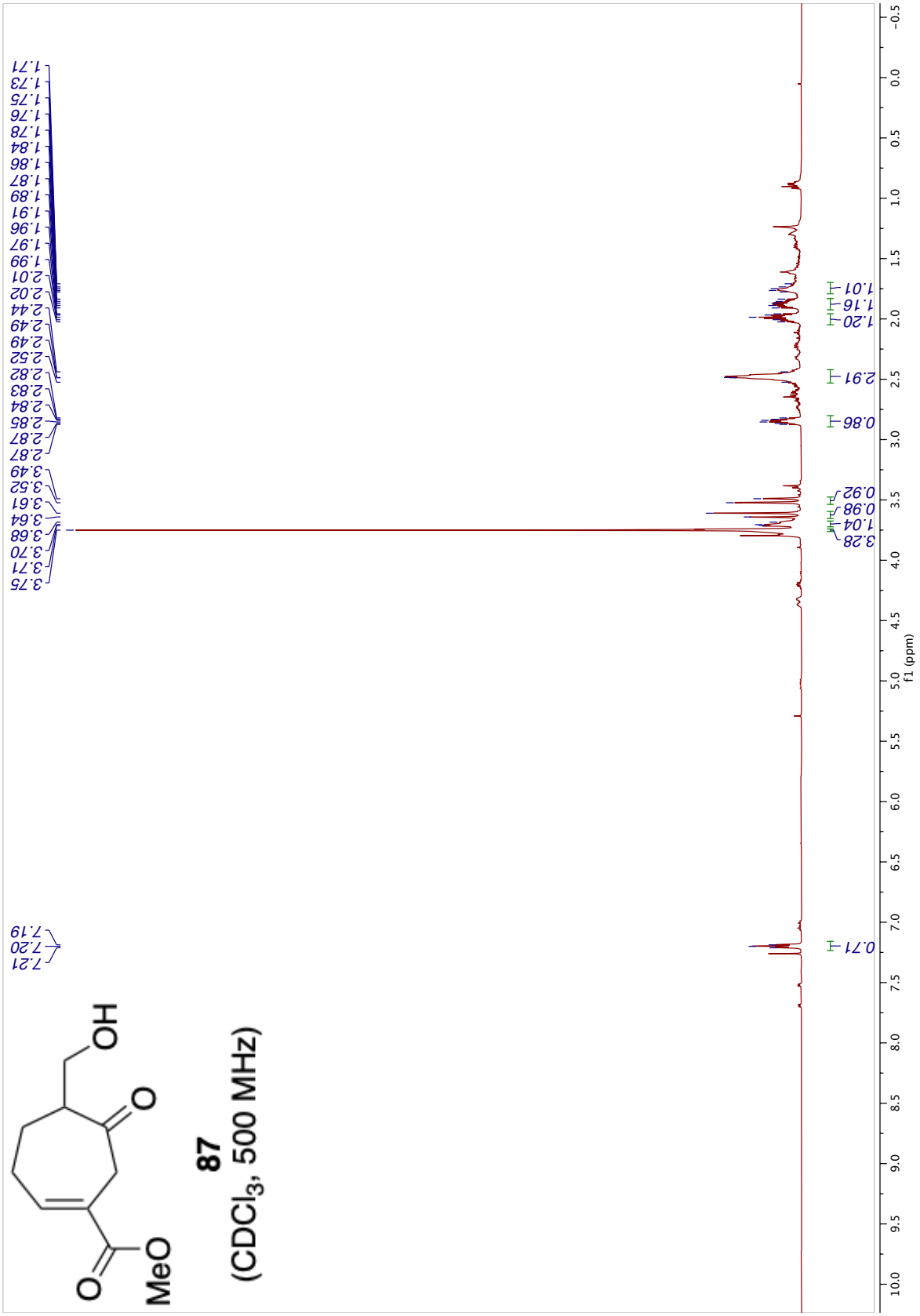

PMBO
OTES
O
H
81
(CDCl3, 500 MHz)
f1 (ppm)

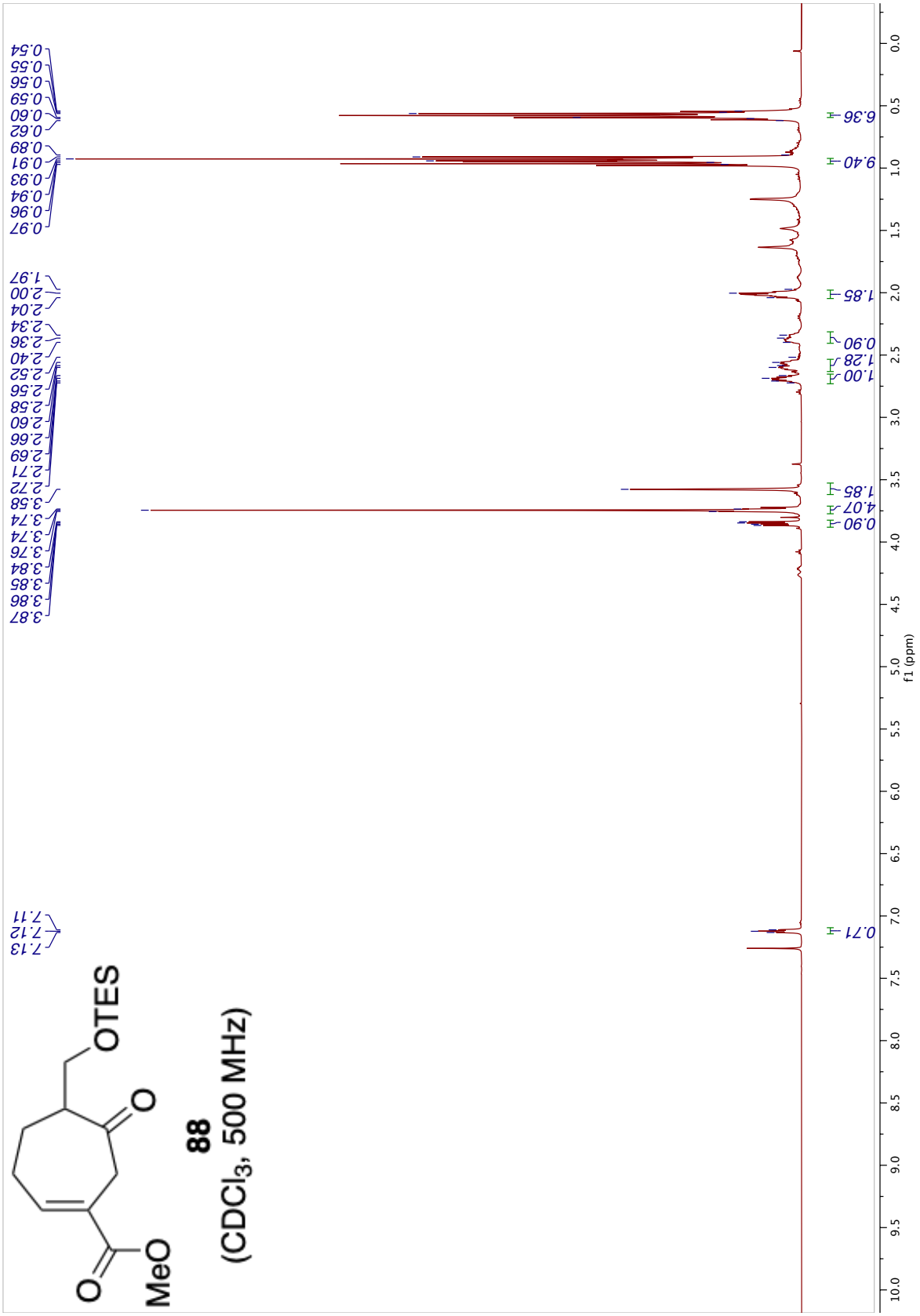

PMBO
O
SePh
OTES
60
(CDCl3, 500 MHz)
f1 (ppm)

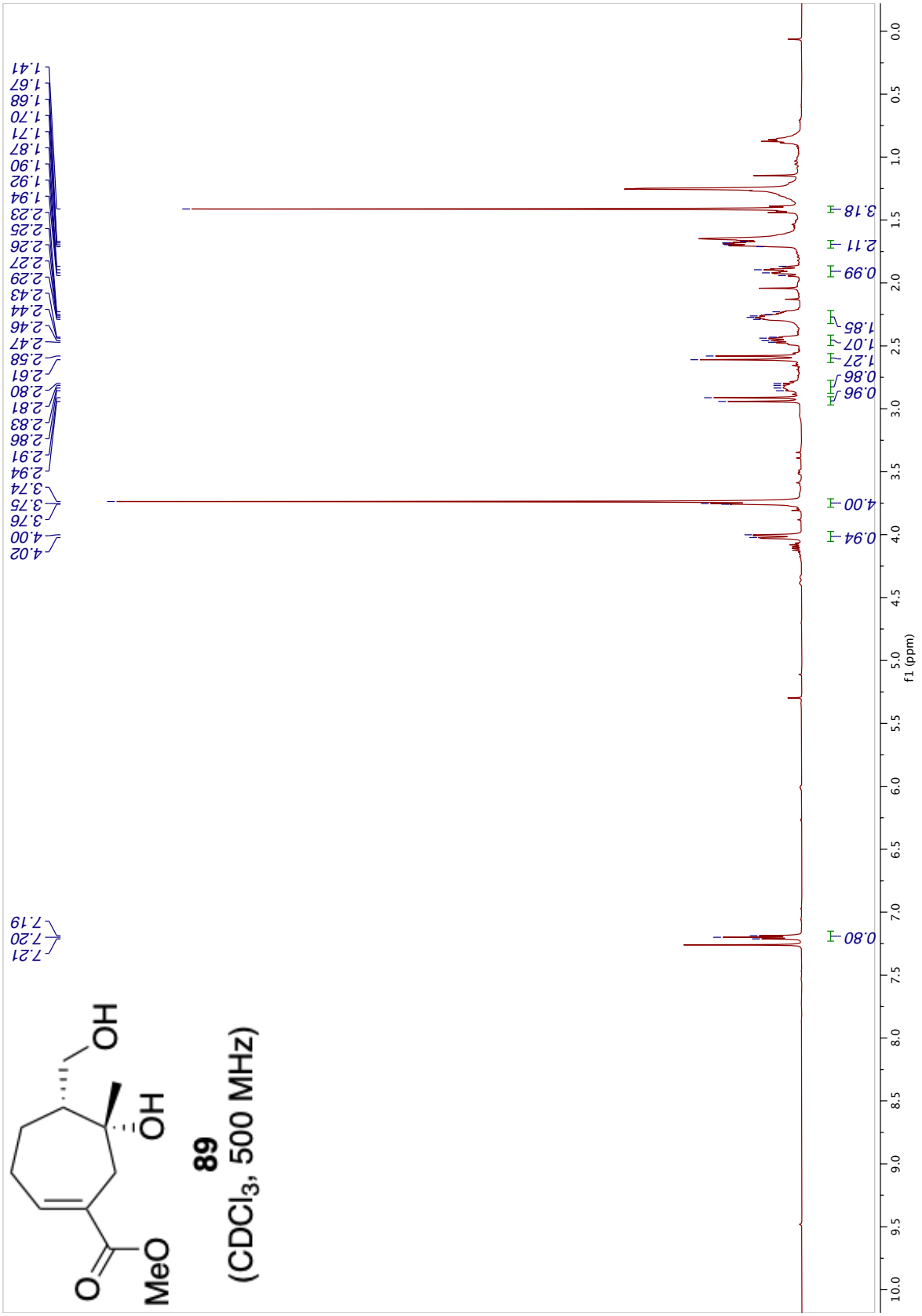

PPh3
CN
MeO
O
84
(CDCl3, 500 MHz)
7.66
7.65
7.64
7.63
7.62
7.62
7.60
7.59
7.53
7.51
7.49
3.64
3.20
3.05
3.02
2.97
2.94
15.00
2.08
1.07
1.10
f1 (ppm)

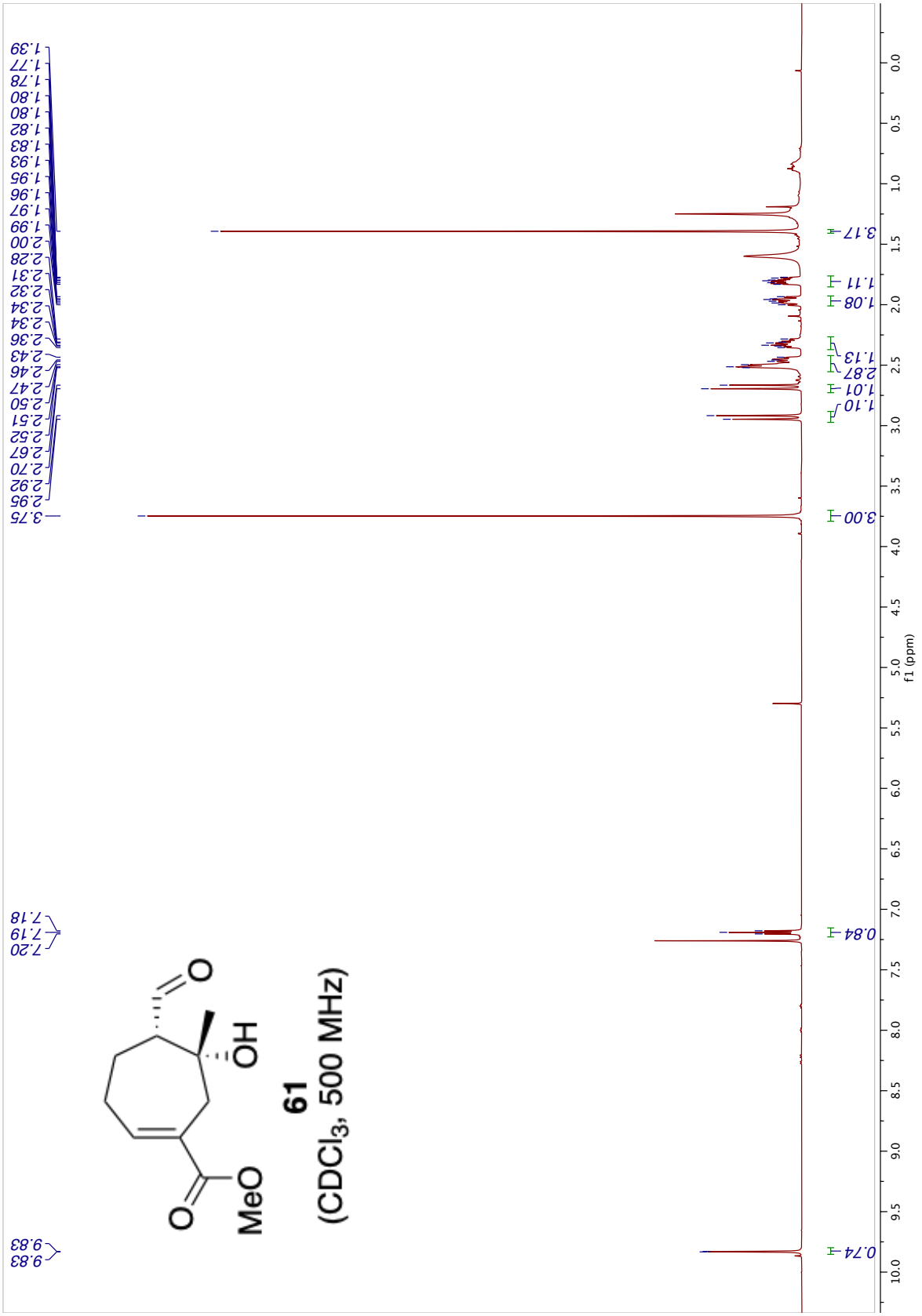

MeO
O
CN
85
(CDCl3, 500 MHz)
7.06
7.05
7.05
7.04
7.03
7.03
5.83
5.81
5.79
5.79
5.77
5.11
5.11
5.11
5.10
5.08
5.07
5.07
5.07
5.07
5.05
5.05
5.05
5.04
3.82
3.81
3.80
3.38
3.38
2.41
2.40
2.39
2.37
2.30
2.29
2.29
2.28
2.28
2.27
2.25
2.25
0.80
2.09
2.09
0.73
1.69
2.17
3.00
f1 (ppm)

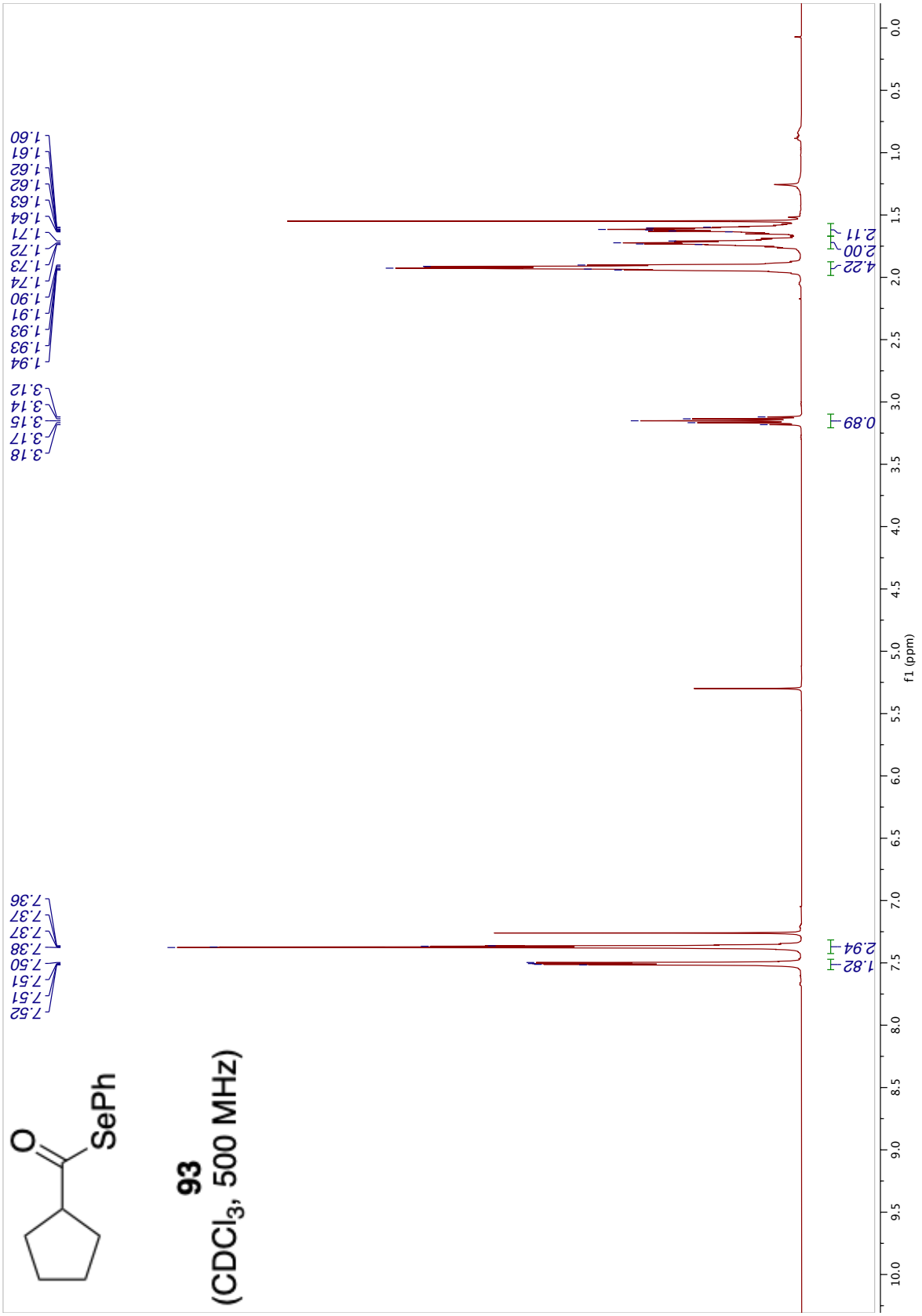

MeO
CN
O
O
86
(CDCl3, 500 MHz)
7.10
7.08
7.06
3.81
3.42
2.98
2.96
2.96
2.94
2.81
2.80
2.79
2.54
2.53
2.53
2.52
2.49
2.47
2.46
2.44
1.92
1.89
1.89
1.86
1.69
1.66
1.64
1.63
1.61
0.79
3.00
2.14
0.82
1.00
3.04
1.06
1.17
f1 (ppm)

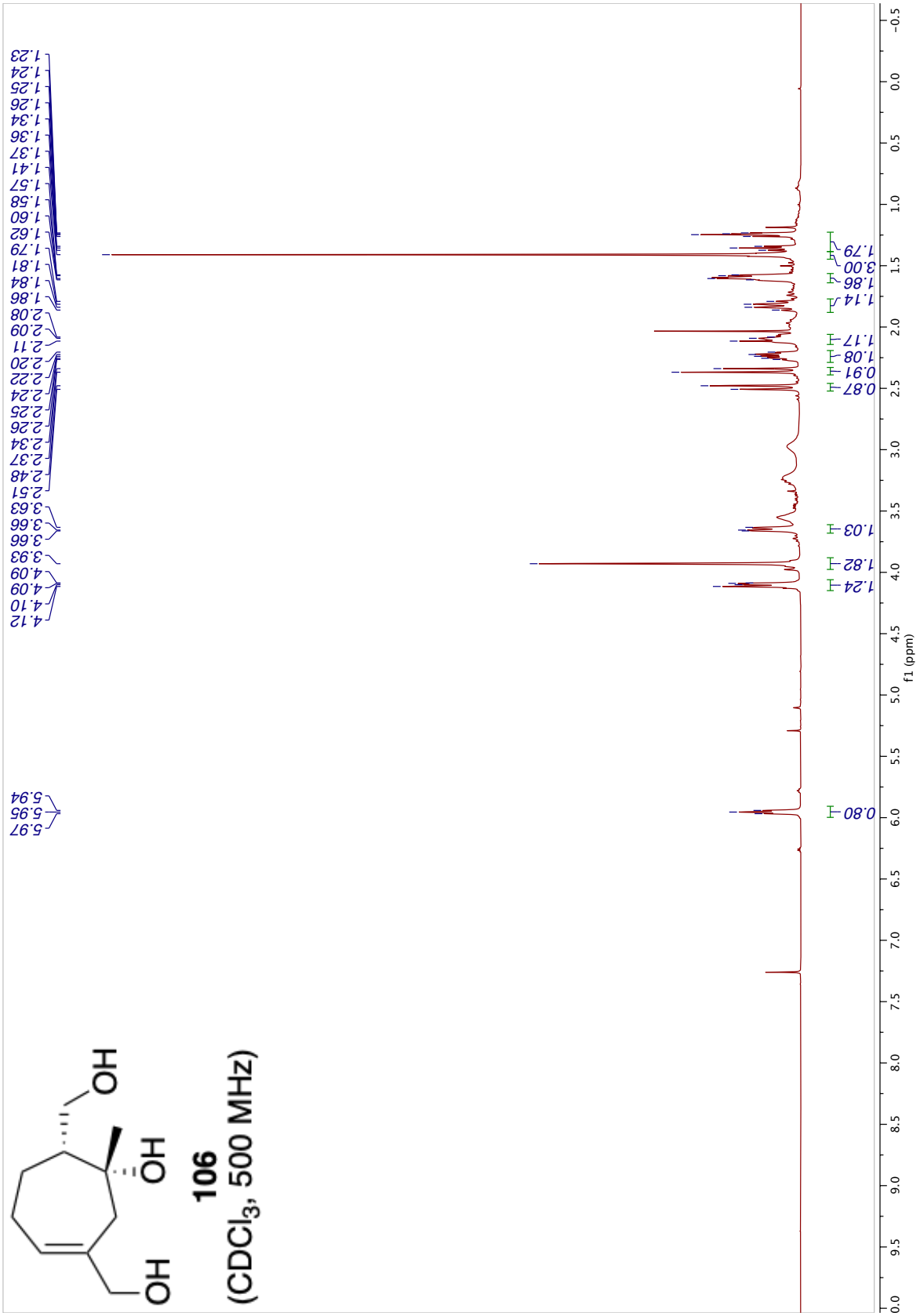

87
(CDCl3, 500 MHz)
OH
O
O
MeO
7.21
7.20
7.19
3.75
3.71
3.70
3.68
3.64
3.61
3.52
3.49
2.87
2.85
2.84
2.83
2.82
2.52
2.49
2.49
2.44
2.02
2.01
1.99
1.97
1.96
1.91
1.89
1.87
1.86
1.84
1.78
1.76
1.75
1.73
1.71
0.71
3.28
1.04
0.98
0.92
0.86
2.91
1.20
1.16
1.01
f1 (ppm)

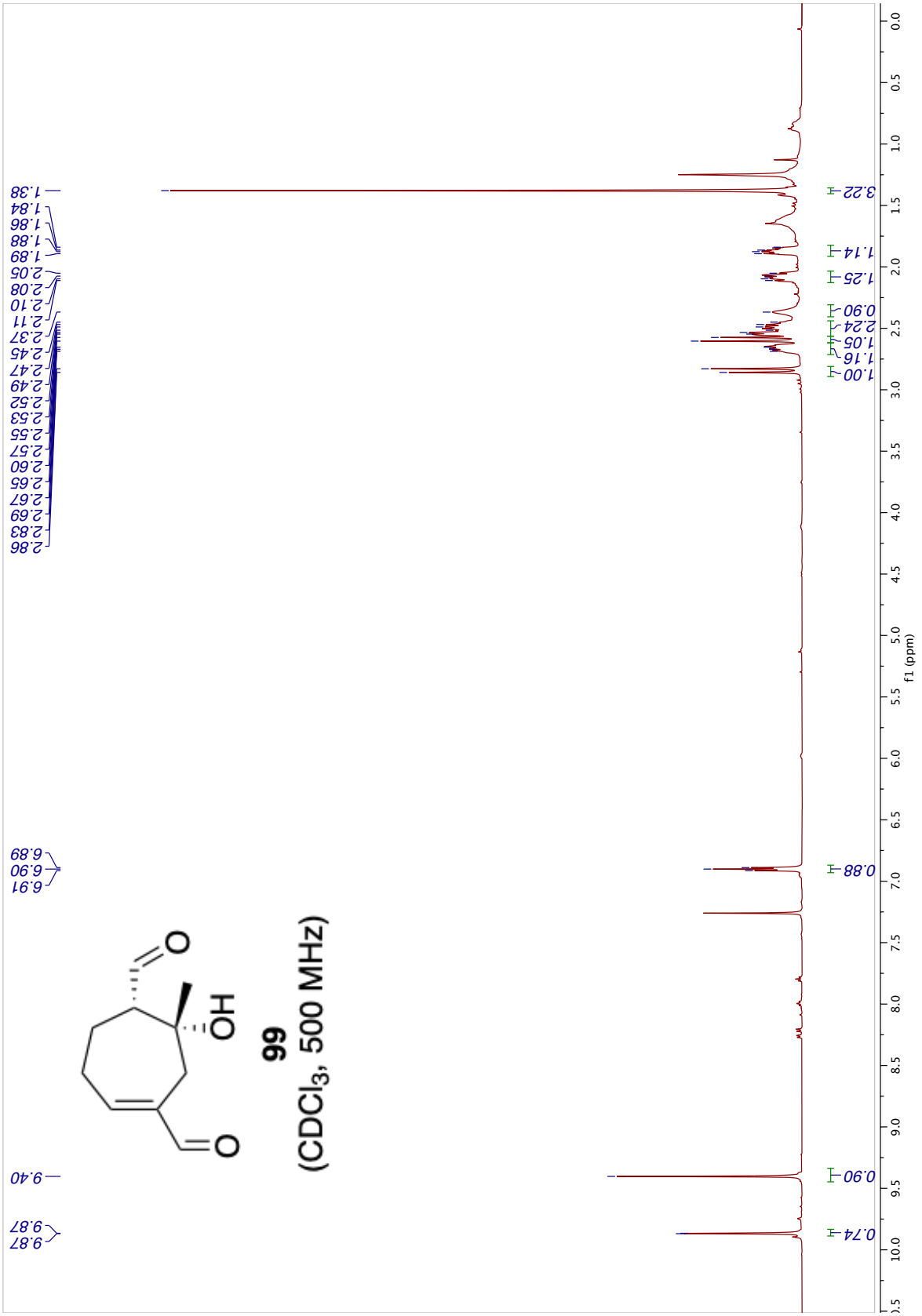

OTES
O
O
MeO
88
(CDCl3, 500 MHz)
7.13
7.12
7.11
3.87
3.86
3.85
3.84
3.76
3.74
3.74
3.58
2.72
2.71
2.69
2.66
2.60
2.58
2.56
2.52
2.40
2.36
2.34
2.04
2.00
1.97
0.97
0.96
0.94
0.93
0.91
0.89
0.62
0.60
0.59
0.56
0.55
0.54
0.71
6.36
9.40
1.85
0.90
1.28
1.00
1.85
4.07
0.90
f1 (ppm)

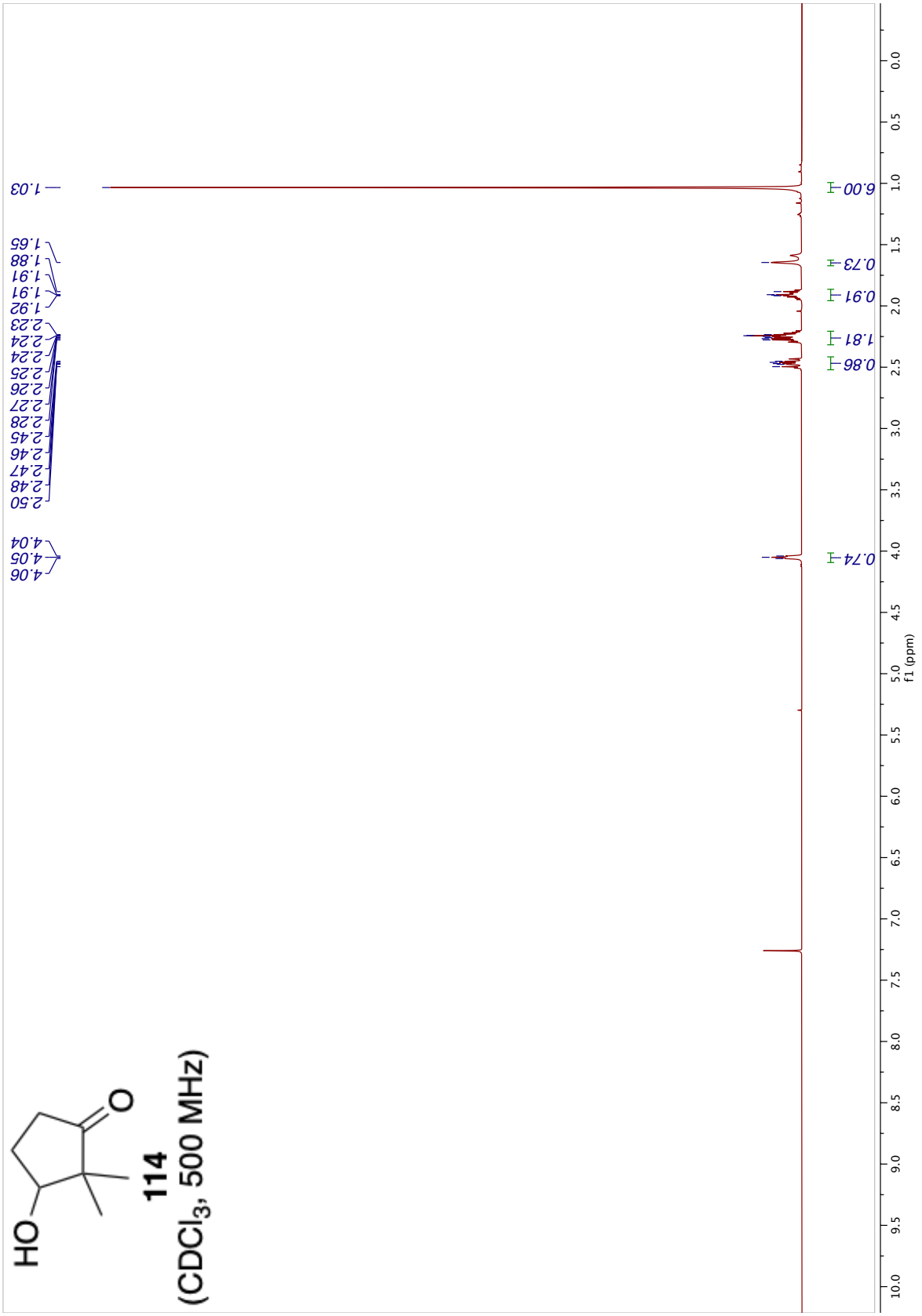

OH
OH
MeO
O
89
(CDCl3, 500 MHz)
7.21
7.20
7.19
4.02
4.00
3.76
3.75
3.74
2.94
2.91
2.86
2.83
2.81
2.80
2.61
2.58
2.47
2.46
2.44
2.43
2.29
2.27
2.26
2.25
2.23
1.94
1.92
1.90
1.87
1.71
1.70
1.68
1.67
1.41
0.80
4.00
0.94
3.18
2.11
0.99
1.85
1.07
1.27
0.96
0.86
f1 (ppm)

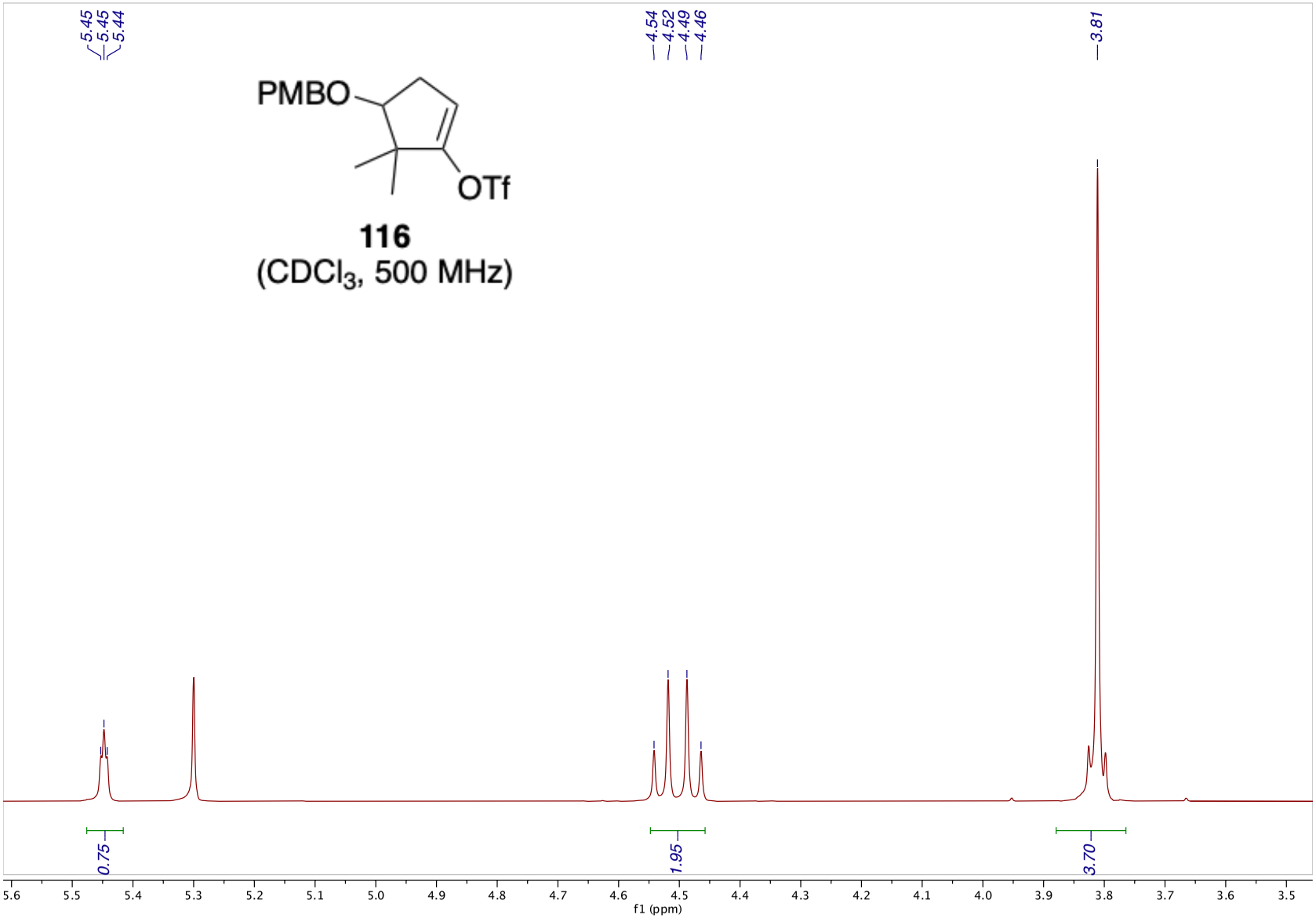

61
(CDCl3, 500 MHz)
MeO
OH
O
O
f1 (ppm)

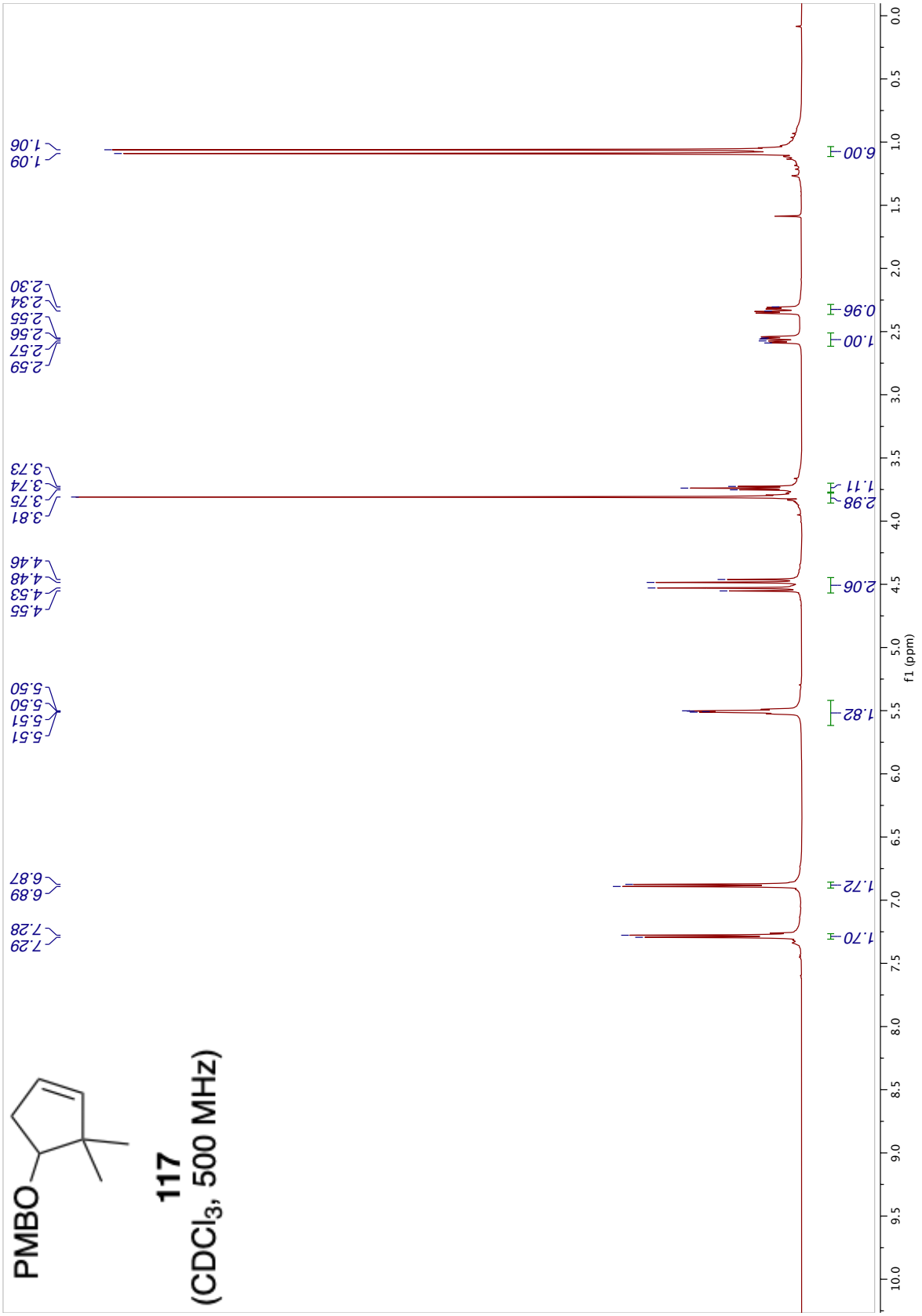

93
(CDCl3, 500 MHz)
O
SePh
7.52
7.51
7.51
7.50
7.38
7.37
7.37
7.36
3.18
3.17
3.15
3.14
3.12
1.94
1.93
1.93
1.91
1.90
1.74
1.73
1.72
1.71
1.64
1.63
1.62
1.62
1.61
1.60
1.82
2.94
0.89
4.22
2.00
2.11
f1 (ppm)

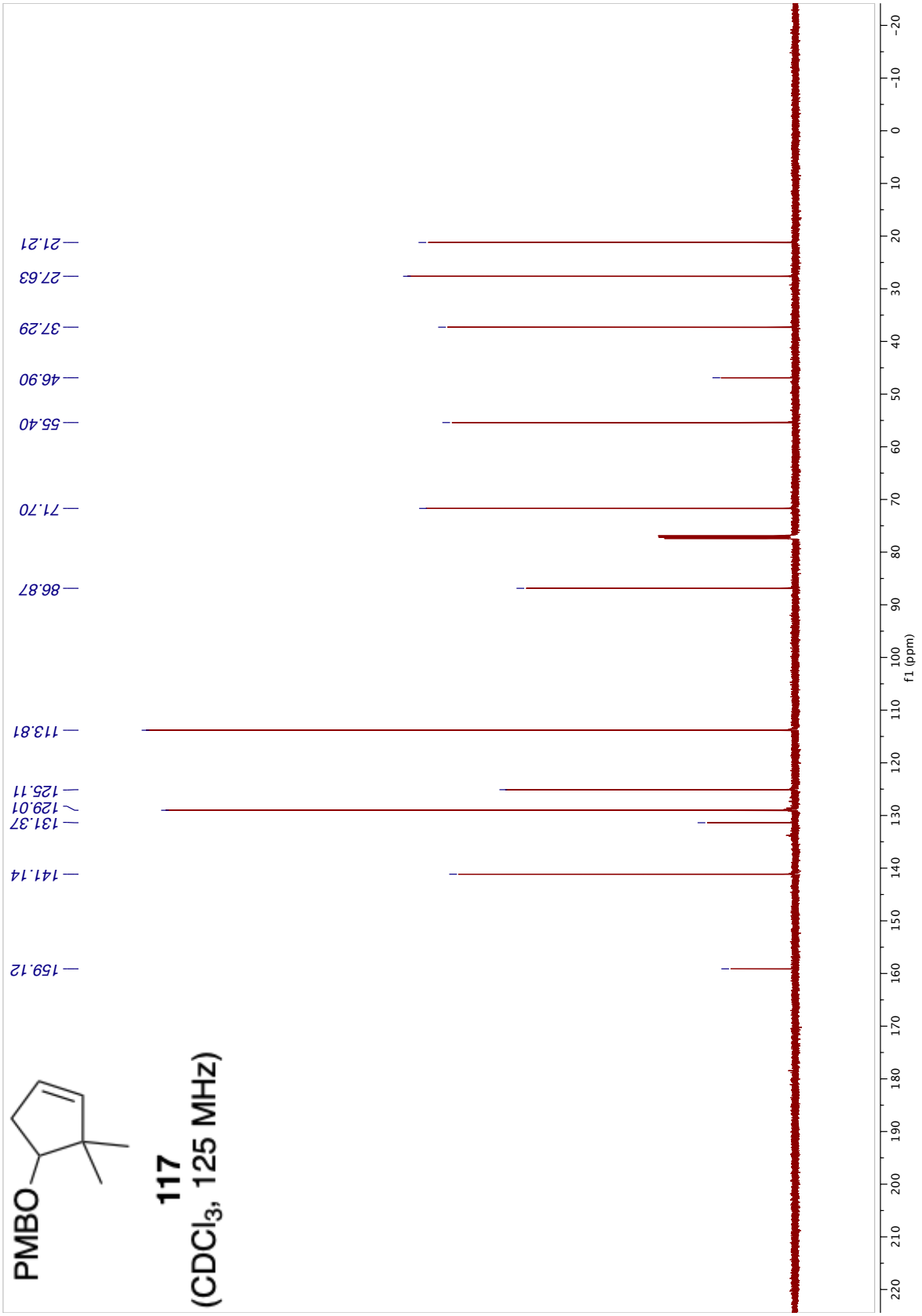

OH
OH
OH
106
(CDCl3, 500 MHz)
f1 (ppm)

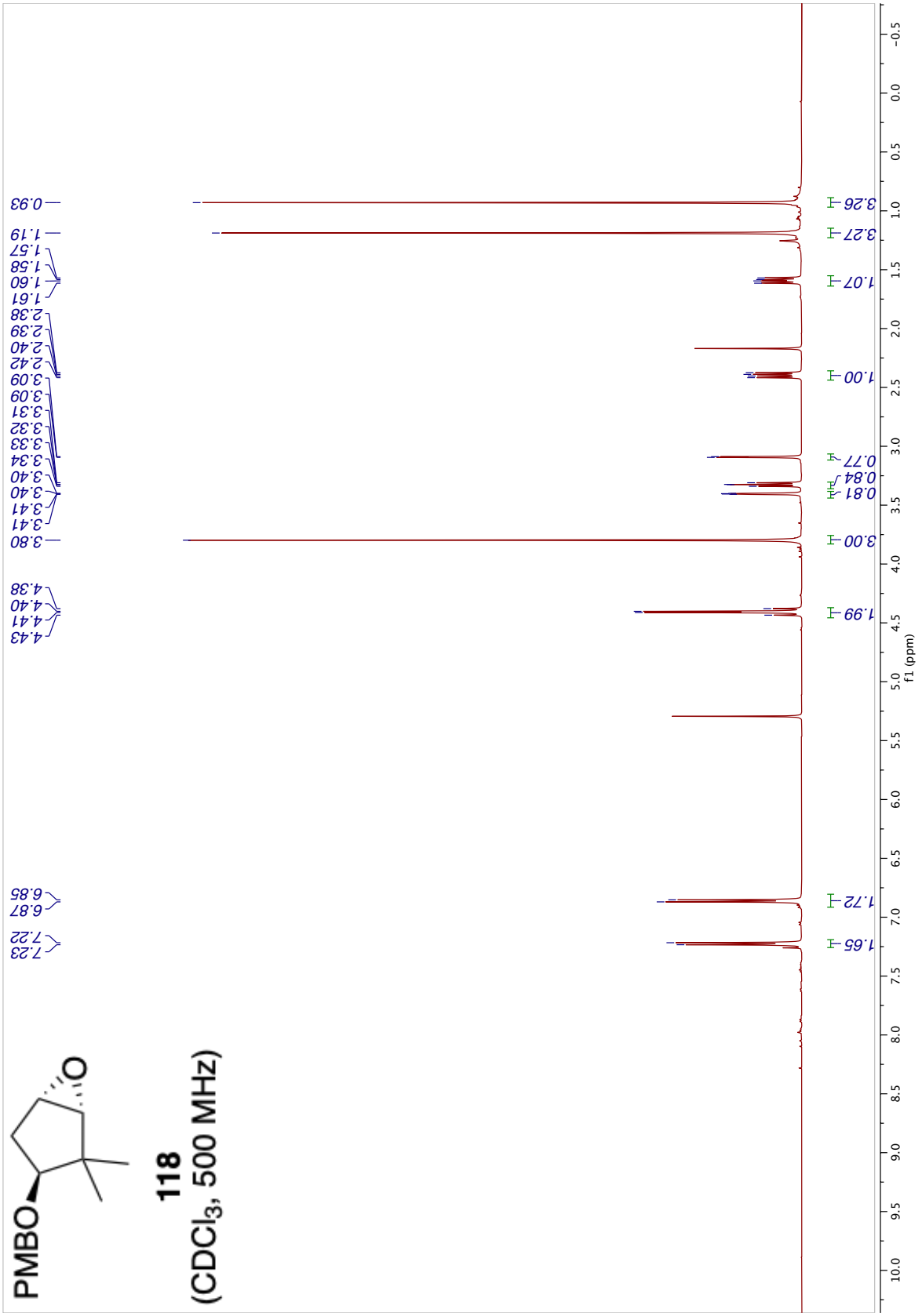

99
(CDCl3, 500 MHz)
OH
O
O
9.87
9.87
9.40
6.91
6.90
6.89
2.86
2.83
2.69
2.67
2.65
2.60
2.57
2.55
2.53
2.52
2.49
2.47
2.45
2.37
2.11
2.10
2.08
2.05
1.89
1.88
1.86
1.84
1.38
0.74
0.90
0.88
1.00
1.16
1.05
2.24
0.90
1.25
1.14
3.22
f1 (ppm)

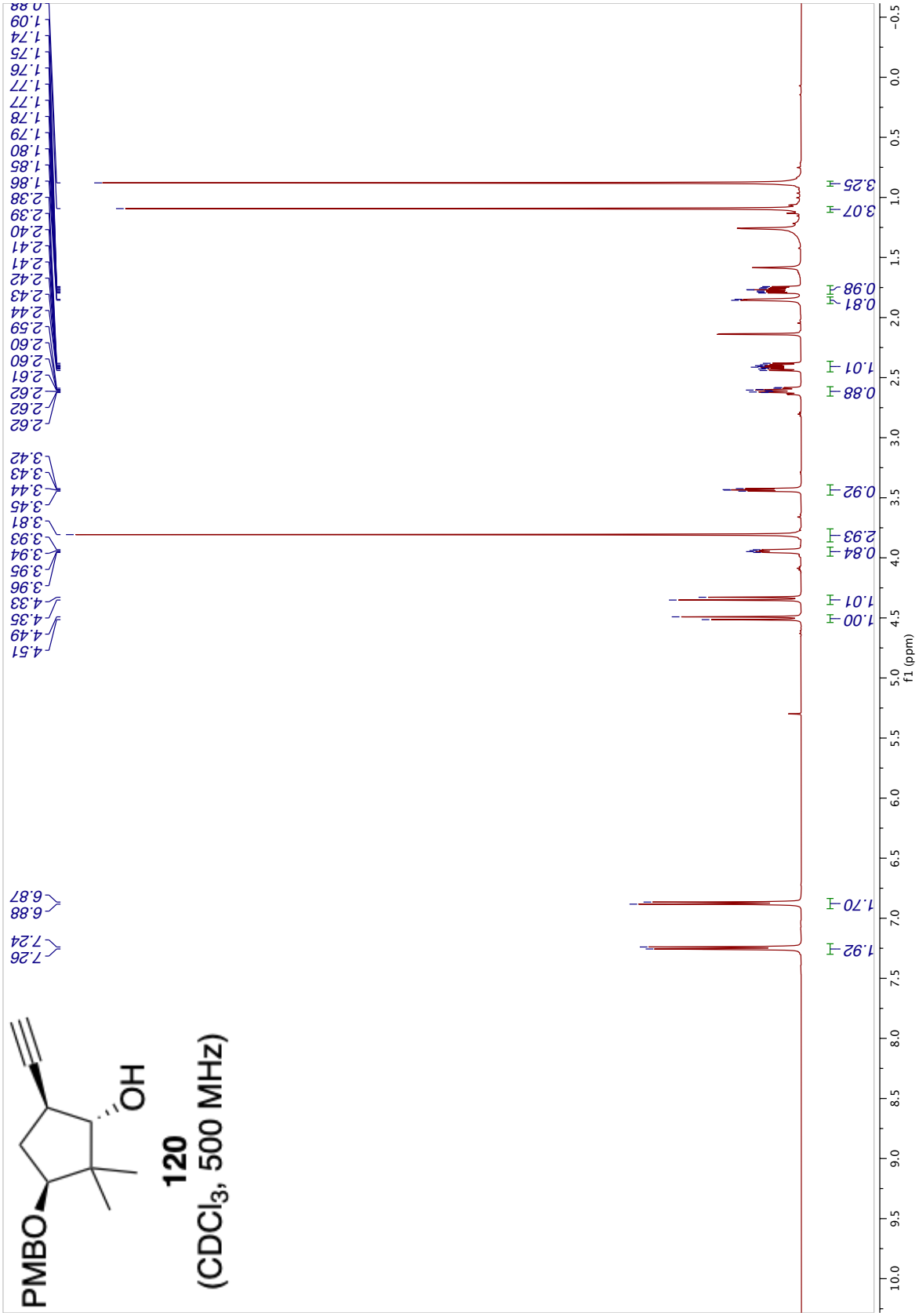

HO
O
114
(CDCl3, 500 MHz)
1.03
1.65
1.88
1.91
1.91
1.92
2.23
2.24
2.24
2.25
2.26
2.27
2.28
2.45
2.46
2.47
2.48
2.50
4.04
4.05
4.06
6.00
0.73
0.91
1.81
0.86
0.74
f1 (ppm)

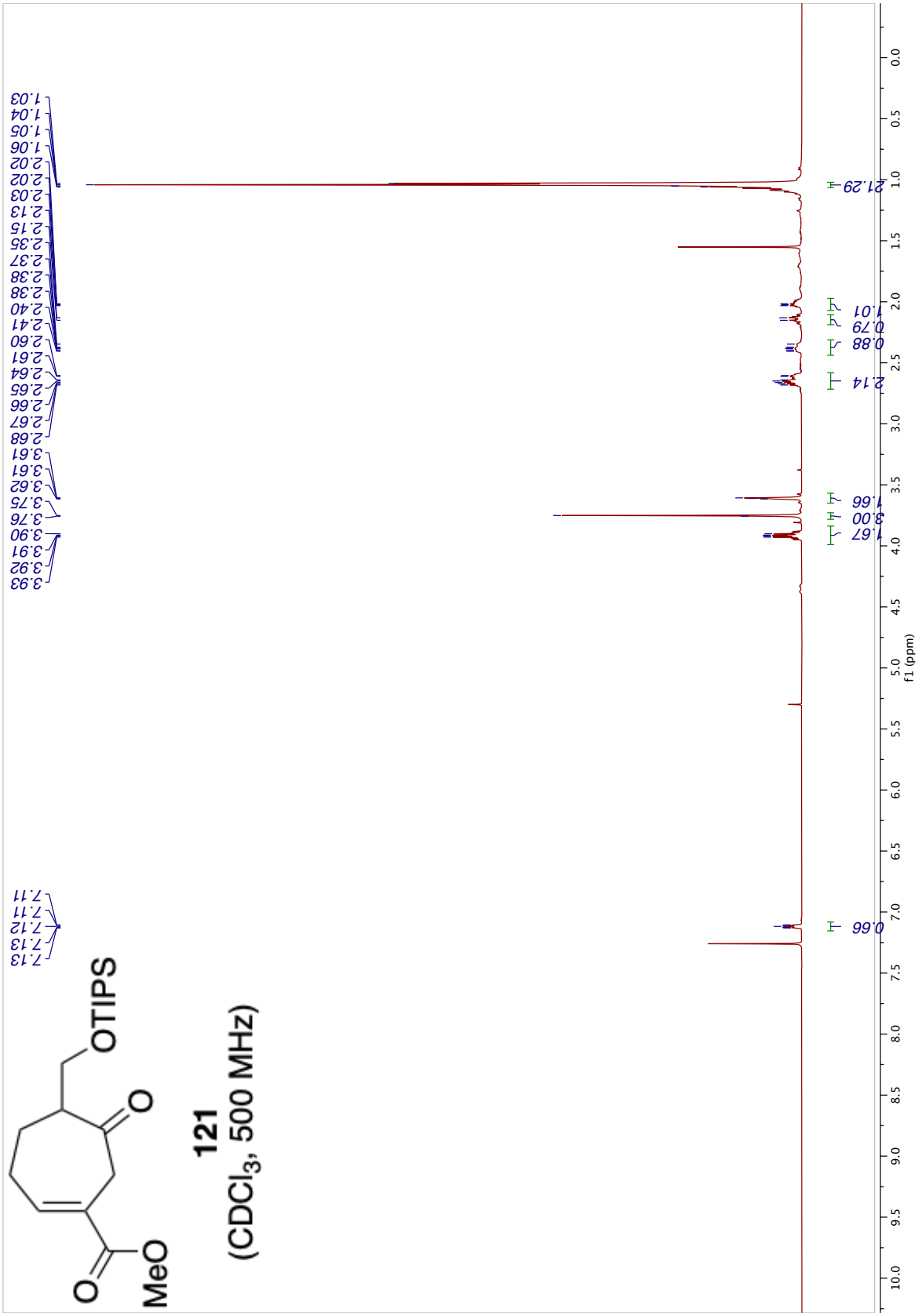

5.45
5.45
5.44
4.54
4.52
4.49
4.46
3.81
PMBO
OTf
116
(CDCl3, 500 MHz)
0.75
1.95
3.70
5.6 5.5 5.4 5.3 5.2 5.1 5.0 4.9 4.8 4.7 4.6 4.5 4.4 4.3 4.2 4.1 4.0 3.9 3.8 3.7 3.6 3.5
f1 (ppm)

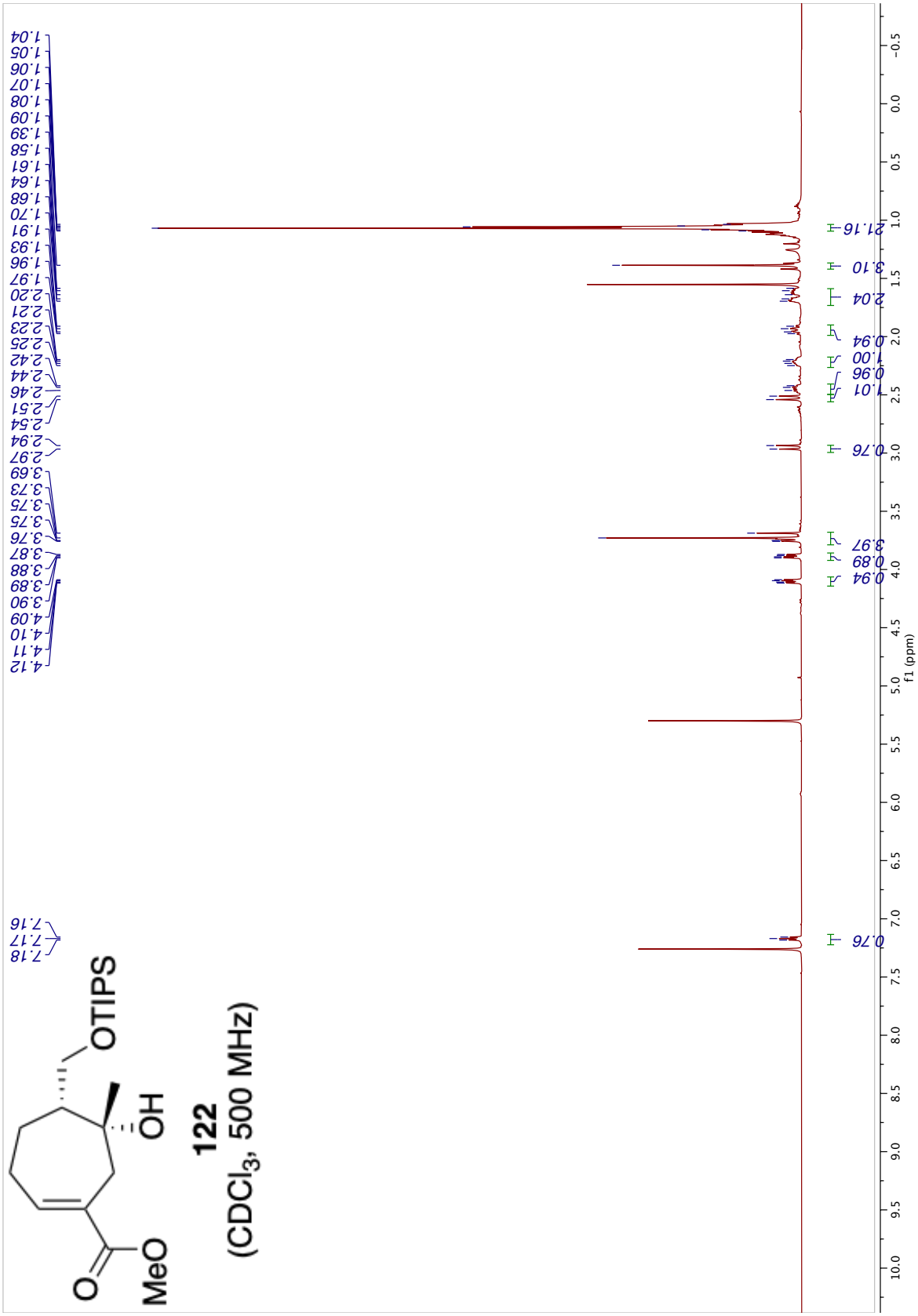

PMBO
117
(CDCl3, 500 MHz)
7.29
7.28
6.89
6.87
5.51
5.50
5.51
5.50
4.55
4.53
4.48
4.46
3.81
3.75
3.74
3.73
2.59
2.57
2.56
2.55
2.34
2.30
1.09
1.06
1.70
1.72
1.82
2.06
2.98
1.11
1.00
0.96
6.00
f1 (ppm)

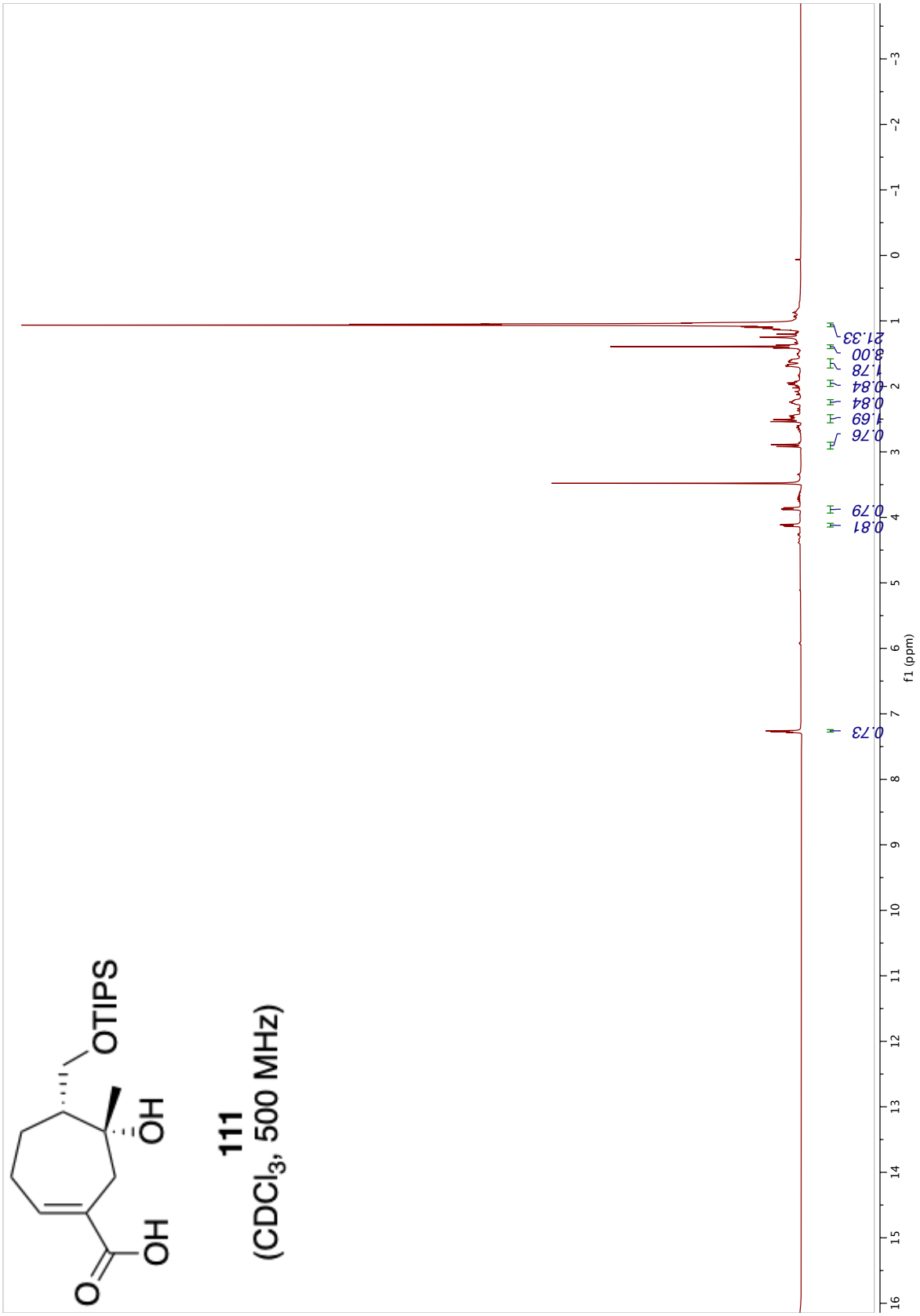

PMBO
117
(CDCl3, 125 MHz)
159.12
141.14
131.37
129.01
125.11
113.81
86.87
71.70
55.40
46.90
37.29
27.63
21.21
f1 (ppm)

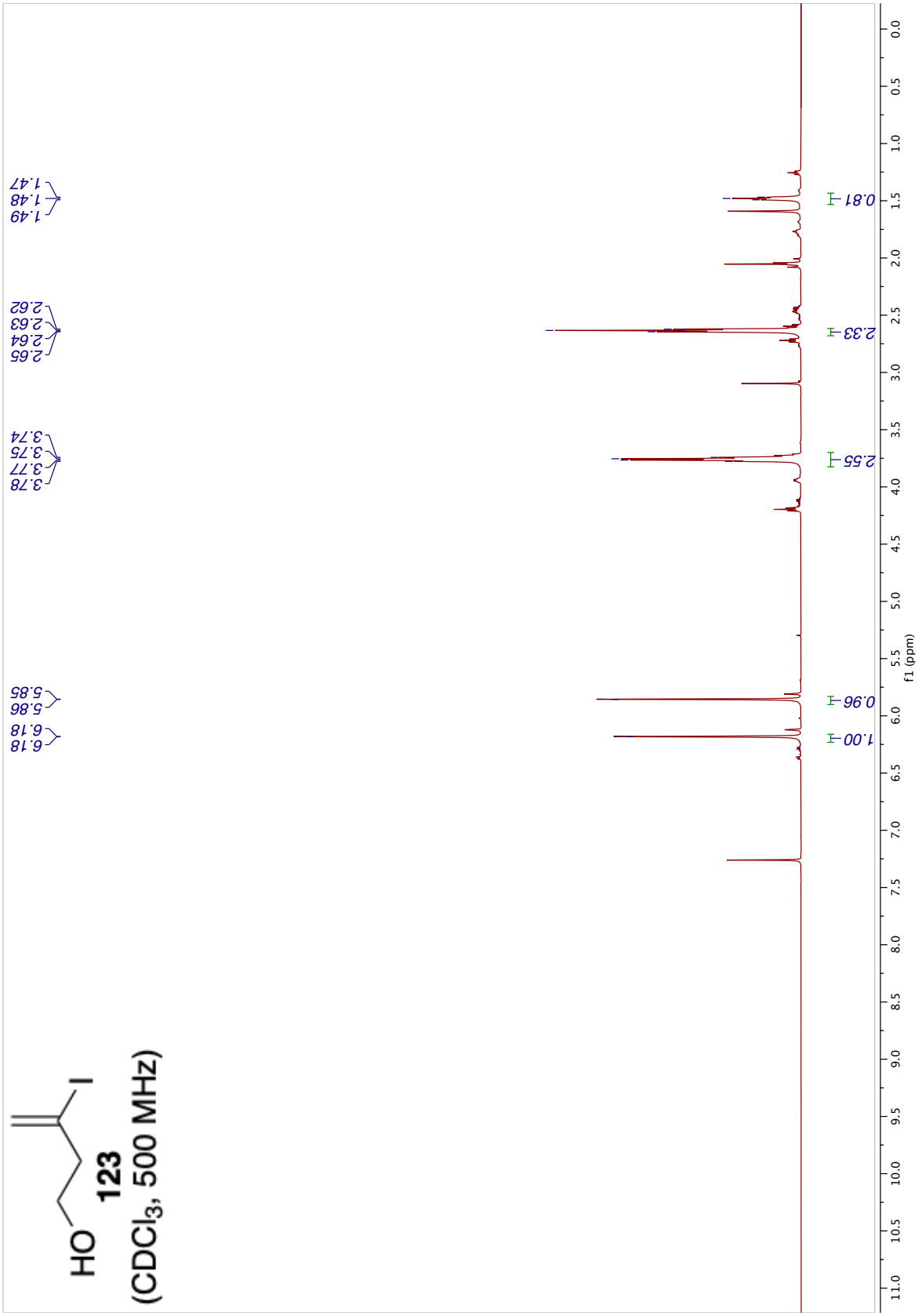

PMBO
O
118
(CDCl3, 500 MHz)
0.93
1.19
1.57
1.58
1.60
1.61
2.38
2.39
2.40
2.42
3.09
3.09
3.31
3.32
3.33
3.34
3.40
3.40
3.41
3.41
3.80
4.38
4.40
4.41
4.43
6.85
6.87
7.22
7.23
3.26
3.27
1.07
1.00
0.77
0.84
0.81
3.00
1.99
1.72
1.65
f1 (ppm)

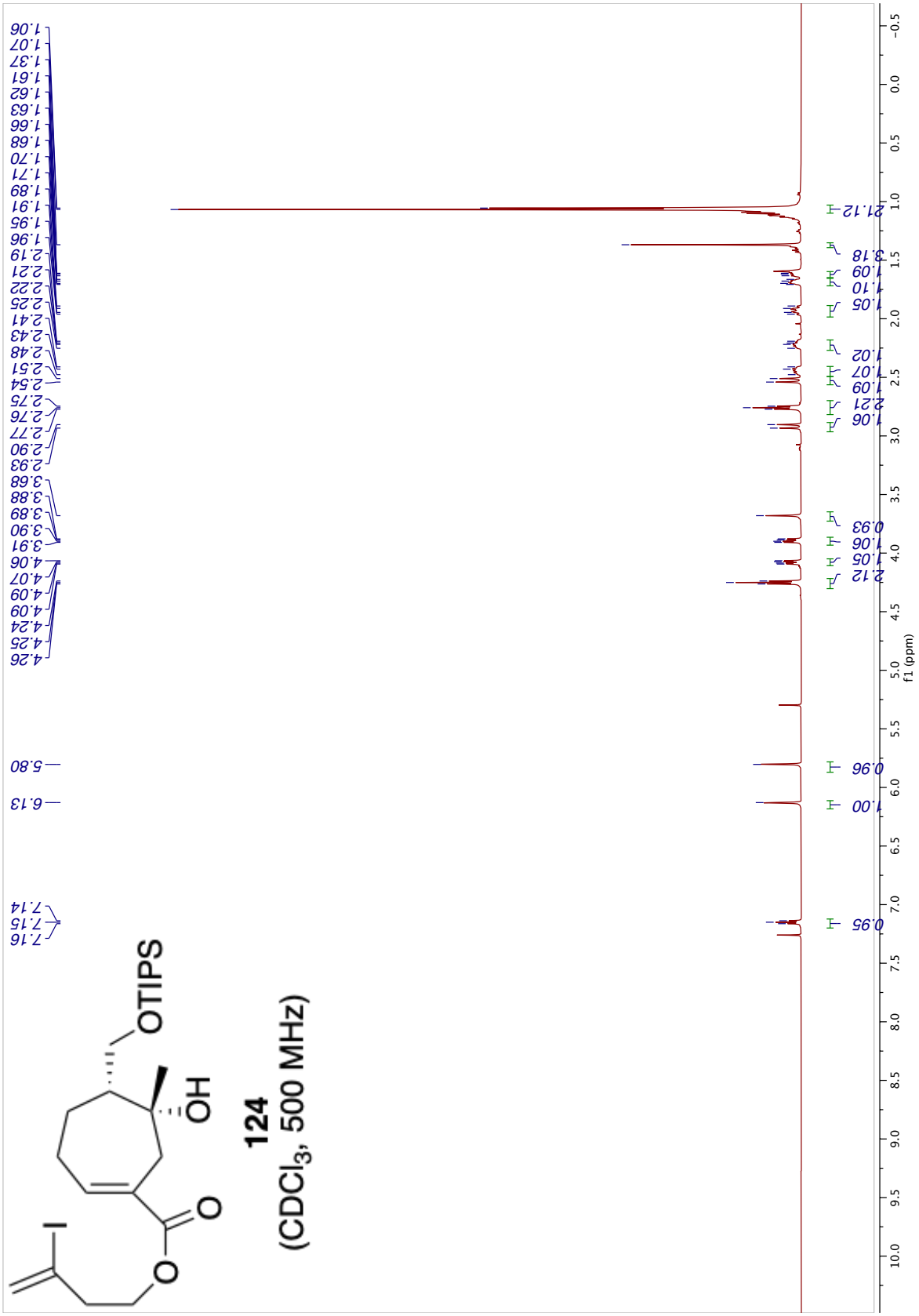

PMBO
OH
120
(CDCl3, 500 MHz)
f1 (ppm)

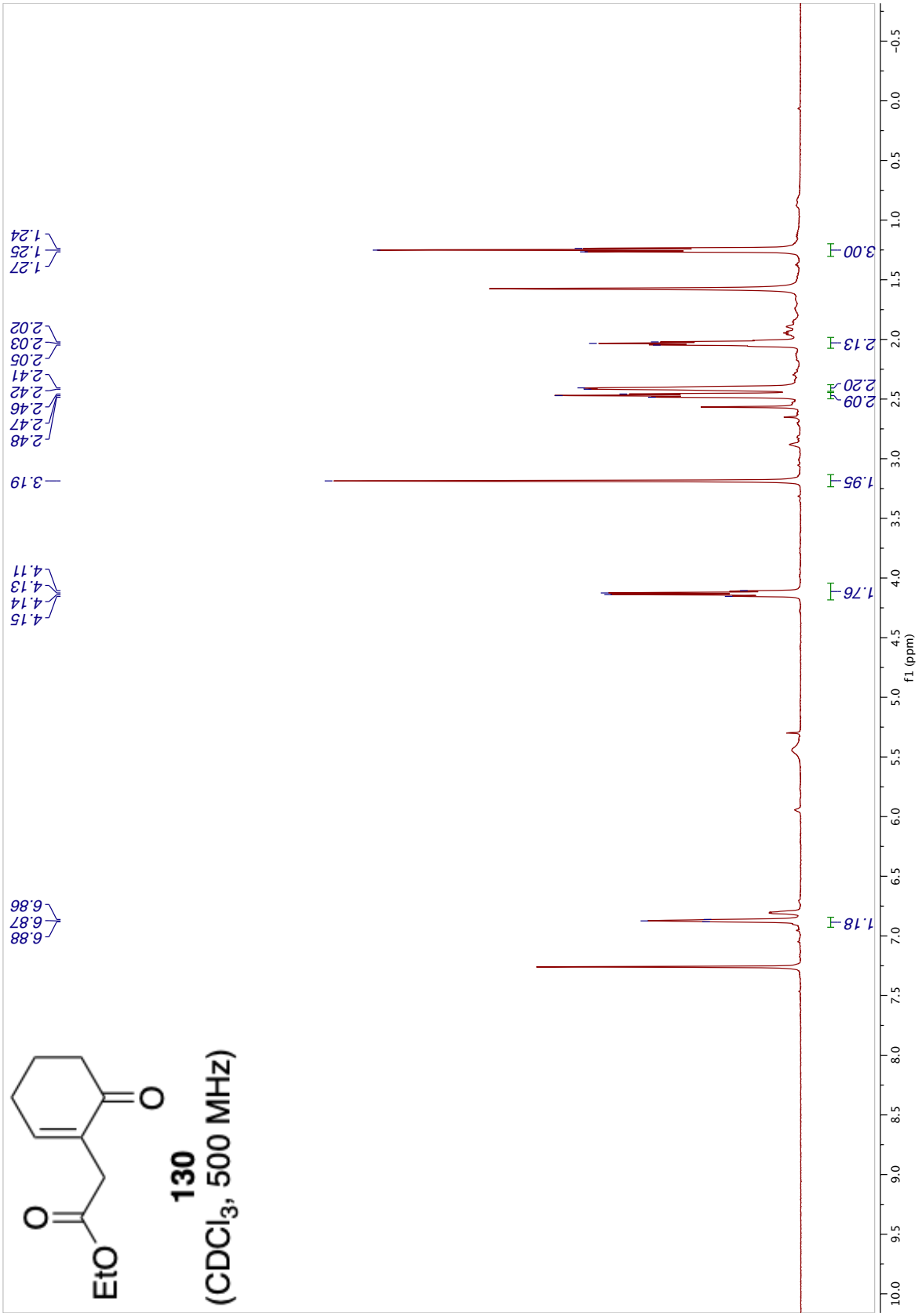

121
(CDCl3, 500 MHz)
OTIPS
O
O
MeO
f1 (ppm)

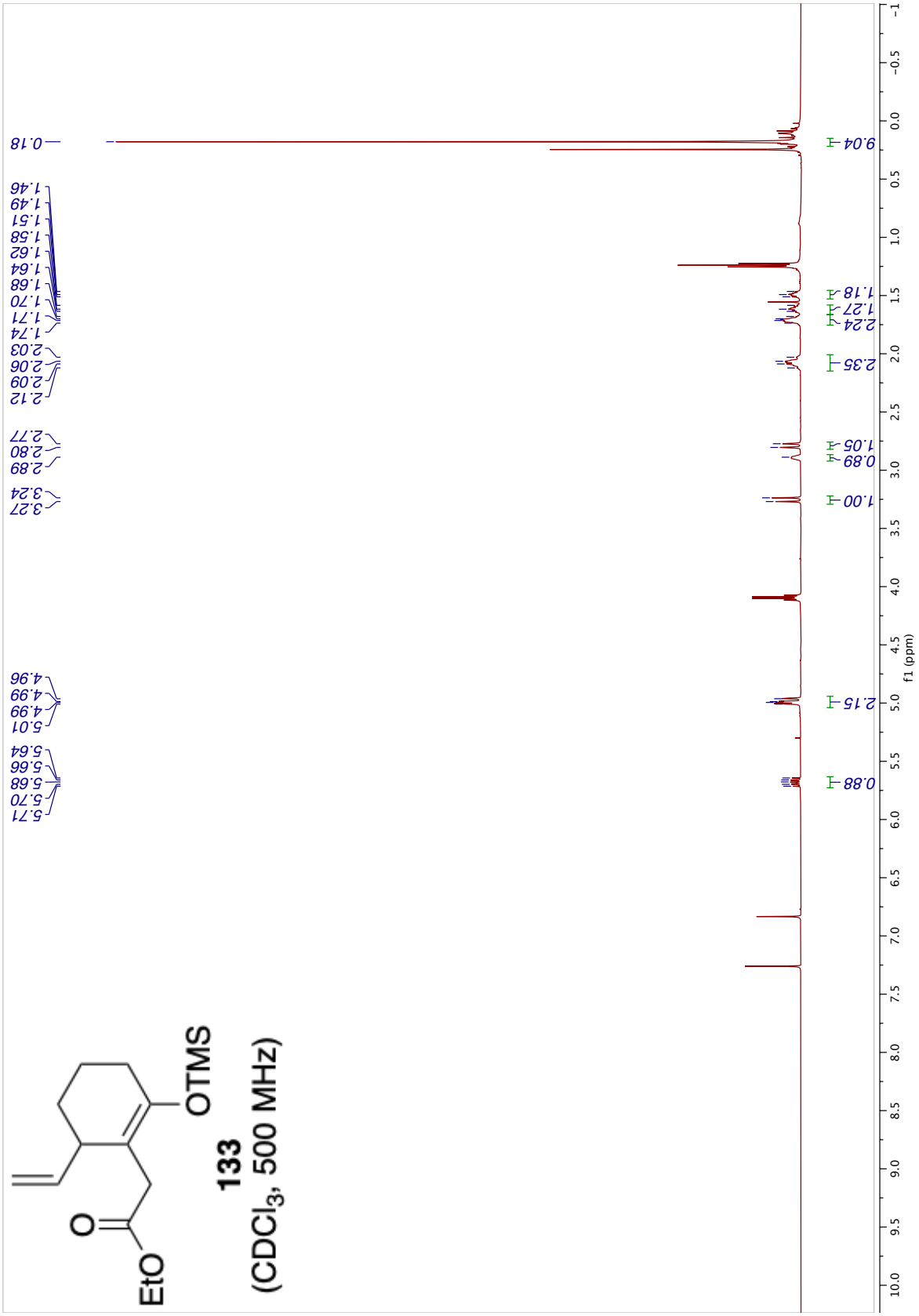

122
(CDCl3, 500 MHz)
OTIPS
OH
MeO
O
f1 (ppm)


OTIPS
OH
OH
O
111
(CDCl3, 500 MHz)
0.73
0.81
0.79
0.76
1.69
0.84
0.84
1.78
8.00
21.33
f1 (ppm)


HO
I
123
(CDCl3, 500 MHz)
6.18
6.18
5.86
5.86
3.78
3.77
3.75
3.74
2.65
2.64
2.63
2.62
1.49
1.48
1.47
1.00
0.96
2.55
2.33
0.81
f1 (ppm)


OTIPS
OH
O
O
124
(CDCl3, 500 MHz)
f1 (ppm)


EtO
O
O
130
(CDCl3, 500 MHz)
6.88
6.87
6.86
4.15
4.14
4.13
4.11
3.19
2.48
2.47
2.46
2.42
2.41
2.05
2.03
2.02
1.27
1.25
1.24
1.18
1.76
1.95
2.09
2.20
2.13
3.00
f1 (ppm)


EtO
O
OTMS
133
(CDCl3, 500 MHz)
0.18
1.46
1.49
1.51
1.58
1.62
1.64
1.68
1.70
1.71
1.74
2.03
2.06
2.09
2.12
2.77
2.80
2.89
3.24
3.27
4.96
4.99
4.99
5.01
5.64
5.66
5.68
5.70
5.71
9.04
1.18
1.27
2.24
2.35
1.05
0.89
1.00
2.15
0.88
f1 (ppm)

CHAPTER 3

STUDIES TOWARD CINNCASSIOL F AND RELATED CINNCASSIOL DITERPENOIDS

3.1 Introduction

3.1.1 Structures and Bioactivities of Selected Cinncassiol Diterpenoids

The third class of molecules explored herein are the cinncassiol diterpenoids, highly oxygenated compounds having been isolated from the *Cinnamomum* genus of plants.[1] To date, over 50 unique isolates have been characterized, with most being derived from *Cinnamomum cassia* Presl (Lauracae), also known as Chinese cinnamon. Traditional Chinese medicine has long utilized cinnamon bark to treat various ailments including gastrointestinal neurosis, irregular menstrual cycles, inconsistent bowel movements, heart palpitations, and rheumatoid arthritis.[2] Since the initial isolation of cinncassiol D_1 glucoside (**1**, Figure 3.1) from the water extracts of the dried bark of *C. cassia* in 1980 by the Nohara group, it has become evident that these medicinal properties can be heavily attributed to the various diterpenoids within this species.

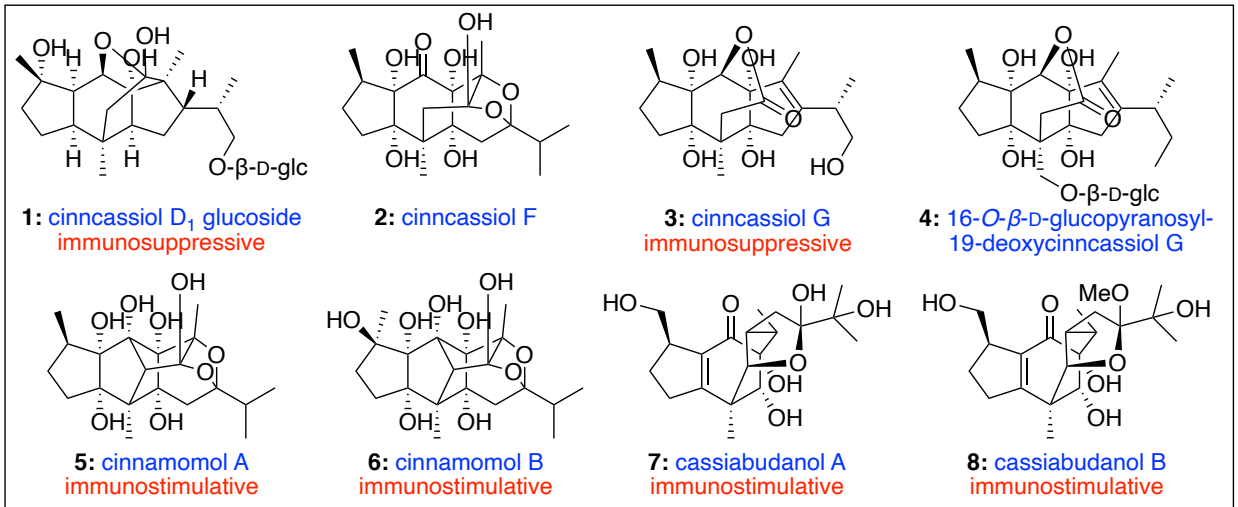
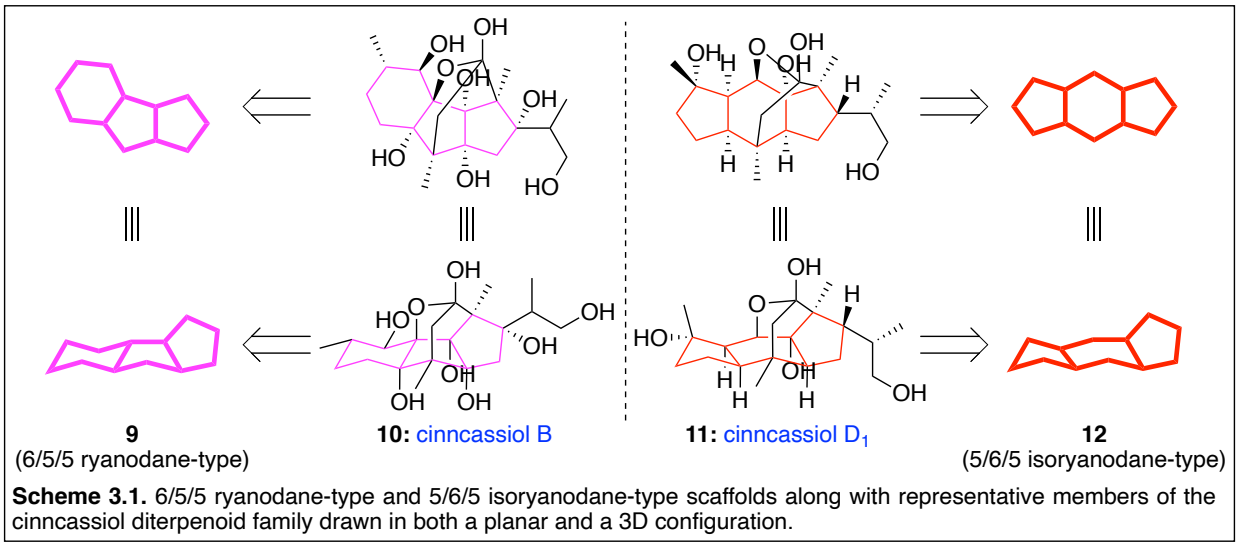


Figure 3.1. Selection of various cinncassiol diterpenoids with wide range of bioactivities.

Just in the past few years, seven novel cinncassiol diterpenoids have been isolated and have shown a variety of bioactivities (Figure 3.1). In 2014, Yao, Zhang, and coworkers isolated cinncassiol F (**2**), cinncassiol G (**3**), and 16-*O*-*β*-D-glucopyranosyl-19-deoxycinncassiol G (**4**) along with several other known cinncassiol diterpenoids and found **3** exhibited strong

immunosuppressive activity by inhibiting ConA-induced T cell proliferation.[3] In 2017, the same team characterized cinnamomols A (**5**) and B (**6**), and found these two compounds were immunostimulative, both showing increased proliferation of ConA-induced T cells, with rates increased up to 64%.[4] Most recently in 2019, the Yao group discovered cassiabudanols A (**7**) and B (**8**), and found they were also highly immunostimulative, enhancing the ConA-induced T cell proliferation by up to 39.99%. Furthermore, **7** and **8** additionally increased LPS-induced B cell proliferation by 92.36% and downregulated Treg production.[5] With such a wide range of potent bioactivities, an efficient route to this complex and highly oxidized class of molecules could potentially allow for further exploration and derivatization of this nearly untapped chemical space.

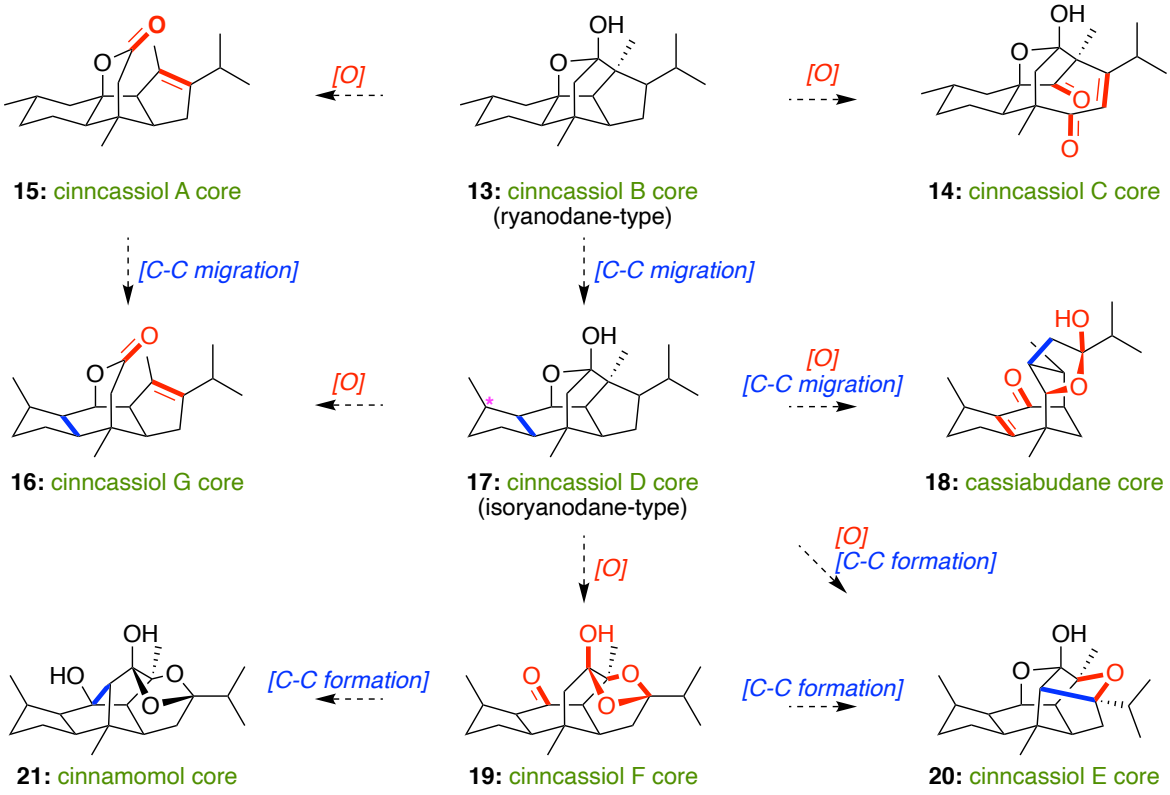
Structurally, there have been nine unique skeletal frameworks established to date with the two most prolific being the ryanodane-type 6/5/5 tricyclic core (**9**) of cinncassiol B (**10**)[6] and the isoryanodane-type 5/6/5 tricyclic core (**12**) of cinncassiol D_1 (**11**) (two different orientations of these compounds will be utilized throughout this text for purposes of clarity, both of which are presented in Scheme 3.1).[7] Interestingly, compounds of both types have been isolated not only from plants of the *Cinnamomum* genus,[3-8] but also those of *Ryania*,[9] *Spigelia*,[10] and *Persea*.[11]



Scheme 3.1. 6/5/5 ryanodane-type and 5/6/5 isoryanodane-type scaffolds along with representative members of the cinncassiol diterpenoid family drawn in both a planar and a 3D configuration.

3.1.2 Proposed Biogenesis of Cinncassiol Diterpenoids

In 2019, the Yao group proposed a potential biogenetic relationship between each of the nine known cinncassiol diterpenoid frameworks, suggesting they could all be derived from the cinncassiol B core (**13**, Scheme 3.2). Both the cinncassiol C core (**14**) and cinncassiol A core (**15**) could reasonably be obtained through enzymatic oxidative cleavage, with **15** just a single carbon-carbon bond migration away from the cinncassiol G core (**16**), delivering the 5/6/5 isoryanodane-type skeleton. **19** could also be achieved by those two transformations in an inverse order, first utilizing a carbon-carbon bond migration from the initial cinncassiol B core (**13**) to obtain the cinncassiol D core (**17**), which could then deliver **19** through oxidation of the hemiketal moiety.



Scheme 3.2. Biogenetic relationship of the nine known classes of cinncassiol diterpenoid cores as proposed by Yao and coworkers in 2019.

Although each of the nine known cinncassiol diterpenoid skeletons can be traced back to cinncassiol B, the Yao group's biogenetic proposal suggests the cinncassiol D core (**17**) is the key

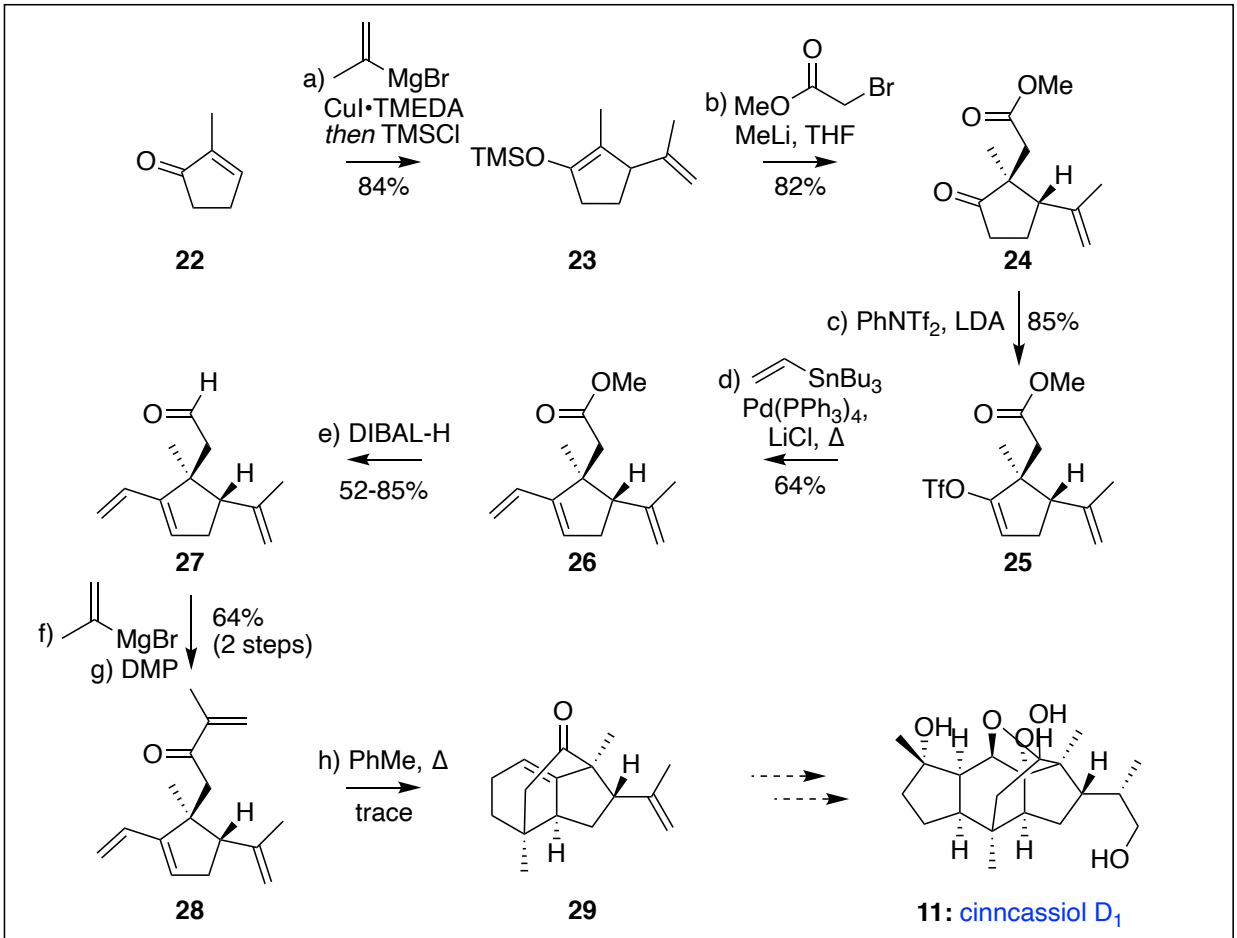
intermediate in the biosynthesis of the remaining isoryanodane-type frameworks. For instance, further oxidation of **17** coupled with a carbon-carbon bond migration can yield the cassiabudane core (**18**), while an oxidation paired with a carbon-carbon bond formation would result in the cinncassiol E core (**20**). As with the generation of **16**, an oxidation of **17** without any alteration of the carbon skeleton could also produce the cinncassiol F core (**19**) through the formation of a novel ketal/hemi-ketal functionality. From **19**, two different carbon-carbon bond formation events could then lead to either the cinncassiol E core (**20**) or the cinnamomol core (**21**). Interestingly, although the Yao group proposed this set of biosynthetic transformations in an exclusively forward path, a recent total synthesis by the Reisman group (to be discussed) suggests a reversible relationship.[12] Starting from a cinncassiol G-type (**16**) intermediate, they were able to obtain a natural product of the cinncassiol D core (**17**), contradicting the Yao proposal.

3.1.3 Previous Efforts Toward Related Compounds

Although there is a wide range of potent bioactivities, there have only been two synthetic studies and a single total synthesis of cinncassiol diterpenoids of the isoryanodane-type (**12**) .[12-13] On the other hand, those of the ryanodane-type skeleton (**9**) have received much greater attention, with a total of 24 reported efforts including a handful of completed total syntheses.[14] This stark contrast highlights the synthetic appeal, as well as challenge of this 5/6/5 framework, with each study marking unique access to the various functionalities of these densely oxygenated targets.

The first reported foray toward a cinncassiol diterpenoid of the isoryanodane-type skeleton was from the Ensley group in 2005, in which the PhD thesis of Patrick G. Sheridan outlines their attempts to access cinncassiol D_1 (**11**).[13a] Given that **11** exhibits a comparatively less oxidized core, the Ensley group wanted to take advantage of the central 6-membered ring to develop the carbon framework through a critical intramolecular Diels-Alder. Starting from 2-methyl

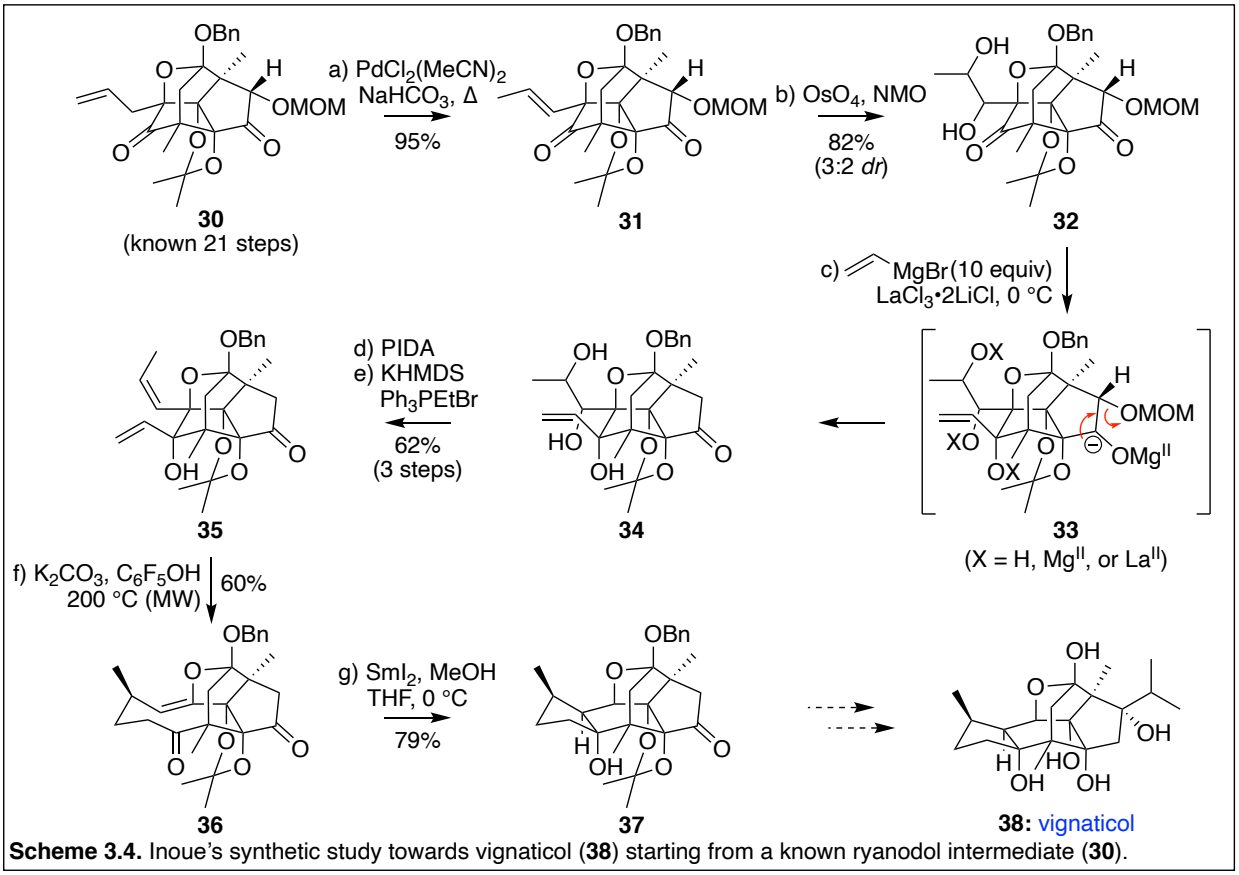
cyclopentenone (**22**), an isopropenyl Michael addition and subsequent α-alkylation yielded quaternary-center containing **24** in modest yield (69% over 2 steps). Triflation of the ketone followed by Stille coupling with vinyl tributyltin produced the desired diene moiety in **26** for the eventual Diels-Alder cyclization. To furnish the dienophile, the methyl ester of **26** was first reduced with DIBAL-H to the respective aldehyde **27**. An isopropenyl Grignard addition and final oxidation of the resultant secondary alcohol provided quick access to Diels-Alder precursor **28**. Although various initial model systems (none of which contained the isopropenyl sidechain) showed varying levels of success (highest yield being 35%), they were unable to fully characterize any desired product when subjecting enone **28** to thermal conditions, reporting that only trace amounts of cyclized **29** was potentially generated due to the presence of a minor peak at 6 ppm in the crude NMR.



Scheme 3.3. Ensley's synthetic study towards cinncassiol D_1 (**11**) featuring an intramolecular Diels-Alder.

In 2018, the Inoue group attempted to leverage their immense total synthesis experience in ryanodane-type targets[14l-s] to elucidate a path toward vignaticol (**38**), another isoryanodane-type cinncassiol diterpenoid.[13b] Starting from a known ryanodol precursor (**30**, constructed in 21 steps),[14p, 14q] the Inoue group began their divergent approach to vignaticol (**38**) with a dihydroxylation of intermediate **31** to yield diol **32** (with an inconsequential 3:2 *dr*). From here, an intriguing diastereo- and regio-selective vinyl Grignard addition to the left-hand ketone proceeded quite smoothly when utilizing a large excess of vinyl magnesium bromide (10 equiv) in the presence of $LaCl_3$•2LiCl (5 equiv).[15] However, although the desired 1,2-addition was successful, there was an unforeseen elimination of the MOM-oxy group, α to the right-hand ketone.

This was attributed to an SET process in which the excess Grignard produces a ketyl radical which is further reduced to ketyl anion **33**. Deoxygenation then occurs in an E1cB fashion, and the resulting enolate then isomerized back to the ketone upon work-up, delivering **34**.

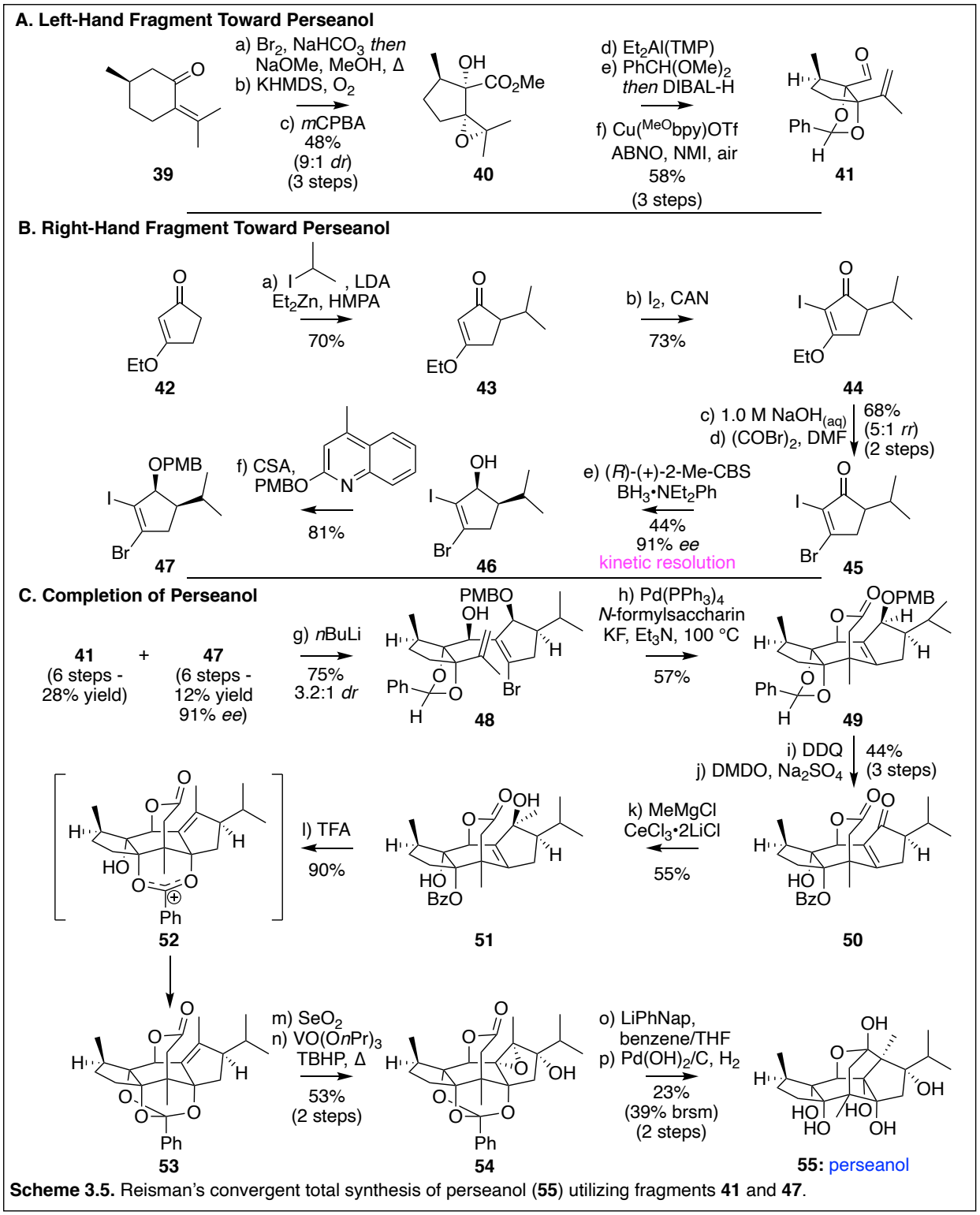


Scheme 3.4. Inoue's synthetic study towards vignaticol (**38**) starting from a known ryanodol intermediate (**30**).

With allyl alcohol **34** in hand, the diol was cleaved in the presence of hypervalent iodine (PIDA) before a subsequent Wittig olefination produced the desired *Z*-olefin **35**. Having both alkenes in place, an anionic-oxy Cope rearrangement promoted by microwave irradiation delivered macrocycle **36**, cleaving the carbon-carbon bond of the central 5-membered ring and setting the left-hand methyl stereocenter. The structure of **36** was unambiguously determined through X-ray crystallographic analysis. Pushing forward, the Inoue group envisioned a radical cyclization to fashion the 5/6/5 tricyclic core of vignaticol (**38**) through a ketyl radical addition onto the olefin of the enol. However, when subjecting **36** to *n*Bu_3SnH and AIBN, the only transannular cyclization

observed was ketyl radical addition into the enol olefin to instead form the 6/5/5 ryanodane-type core. Interestingly, though, when treated with SmI_2 in the presence of MeOH as a protic additive, the desired 5/6/5 tricyclic product **37** was formed in decent yield (79%). Given *n*Bu_3SnH/AIBN and SmI_2 produced different results, the Inoue group turned to DFT calculations to elucidate the two pathways this reaction could take and found that the SmI_2 served a dual-purpose, first as a Lewis acid and then as a reductant to produce **37** through a transannular carbonyl-ene reaction. At this stage, the Inoue group successfully produced the 5/6/5 isoryanodane-type core for the first time in 28 linear steps, but no further plans to reach target compound vignaticol (**38**) were disclosed.

Most recently, the Reisman group in 2019 reported the first total synthesis of any isoryanodane-type cinncassiol diterpenoid, perseanol (**55**, Scheme 3.5), in 16 steps (longest linear sequence).[12] Taking a convergent approach, the Reisman group built the 5/6/5 tricyclic core of **55** by coupling two fragments, **41** and **47** (each completed in 6 steps), through a two-step annulation featuring a palladium-catalyzed carbopalladation-carbonylation cascade. To develop fragment **41**, they began from (*R*)-(+)-pulegone (**39**), to which an oxidative ring contraction, α-hydroxylation of the resultant ester, and epoxidation of the olefin provided **40** in 48% yield with a 9:1 *dr* as related to the epoxide and tertiary alcohol.[16] From here, epoxide isomerization was induced by Et_2Al(TMP), furnishing the requisite *syn*-diol and isopropenyl sidechain.[17] The diol was then protected as a benzylidene acetal before an *in situ* reduction to the primary alcohol. Finally, aerobic oxidation as outlined by the Stahl group yielded fully functionalized fragment **41** in an overall 28% yield.[18]



Scheme 3.5. Reisman's convergent total synthesis of perseanol (**55**) utilizing fragments **41** and **47**.

To obtain the right-hand fragment, the Reisman group began with vinylogous ester **42**, to which an α-alkylation and α-iodination provided **44** (Scheme 3.5).[12] Subjecting **44** to aqueous

NaOH hydrolyzed the ethyl-capped vinylogous ester, producing the intermittent dicarbonyl, which could then be converted to bromoiodocyclopentenone **45** upon exposure to oxalyl bromide and DMF.[19] A subsequent Corey-Bakshi-Shibata reduction of **45** with a methylated variant of the traditional catalyst allowed for a kinetic resolution to yield allylic alcohol **46** in 44% yield and 91% *ee*, which upon PMB-protection led to desired fragment **47** in a combined 12% yield.

With both fragments in hand, the Reisman group set out to complete the 5/6/5 framework of perseanol (**55**, Scheme 3.5).[12] To that end, a simple lithiation of **47** with *n*BuLi allowed for its attack on the aldehyde of **41**, leading to **48** in 75% yield, albeit as a 3.2:1 diastereomeric mixture. Pushing forward, they developed a palladium-catalyzed carbopalladation-carbonylation cascade, in which the optimized conditions of $Pd(Ph_3P)_4$ and *N*-formylsaccharin (serving as an *in situ* CO source) completed the two-step annulation process to provide **49** in 57% yield. Subjection of the free allylic alcohol (after PMB-deprotection) to DMDO resulted in its oxidation to the respective enone. Interestingly, a concomitant benzylic oxidation of the benzylidene acetal was observed, producing **50**. Methyl 1,2-addition into the enone followed by exposure to TFA allowed for the benzoyl group to attack the internal olefin, thus eliminating the allylic alcohol, and concomitantly trapping the free tertiary alcohol to protect the triol successfully and efficiently while introducing the third oxygen of the central ring in **55**. A final four-step sequence including allylic oxidation, directed epoxidation, and subsequent reductive cyclization to yield the Baldwin disfavored 5-*endo*-tet epoxide ring opening and global deprotection produced perseanol (**55**). To date, **55** is the only isoryanodane-type cinncassiol diterpenoid member to have a completed total synthesis.

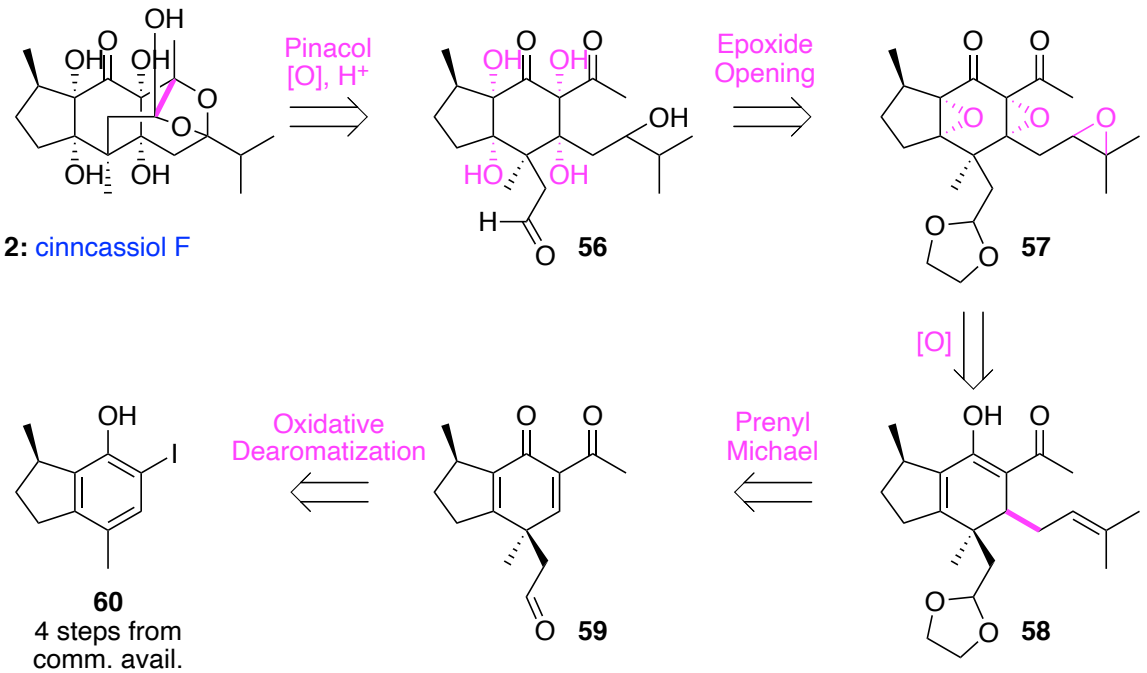
3.2 Studies Toward Cinncassiol F – Carbon Skeleton First Approach

Herein, we outline our initial efforts geared towards the total synthesis of cinncassiol F (**2**), an isoryanodane-type cinncassiol diterpenoid with an alluring ketal/hemiketal moiety.[3] Of note, **2**

only differs from the more recently isolated cinnamomol A (**5**) by a single C-C bond proposed to be biosynthetically fashioned through an intramolecular aldol addition.[4] At the outset of the project, we sought to develop a divergent approach to this class of compounds by first establishing the carbon skeleton then globally oxidizing. To this end, we intended to take advantage of the central 6-membered ring to employ an oxidative dearomatization approach, in which the all-carbon quaternary center would also be fashioned.

3.2.1 Retrosynthetic Analysis Featuring a Prenyl Michael Addition

Retrosynthetically, we initially envisioned the bridged-bicycle of **2** could be forged through a late-stage pinacol coupling of the exocyclic ketone and aldehyde sidechains (Scheme 3.6). A final oxidation of this pinacol product would then hopefully result in the hemiketal/ketal moiety akin to its biogenetic proposal. Tetraol **56** would be derived from bis-epoxide **57** through a dual epoxide opening and double α-hydroxylation of the two carbonyls, with bis-epoxide **57** itself being built up through oxidations of prenylated **58**. A prenyl Michael addition was intended to convert dienone **59** to **58**. Critical to the whole route was the initial oxidative dearomatization event proposed to obtain **59** from phenol **60**, allowing for early installation of the central quaternary center.[20]



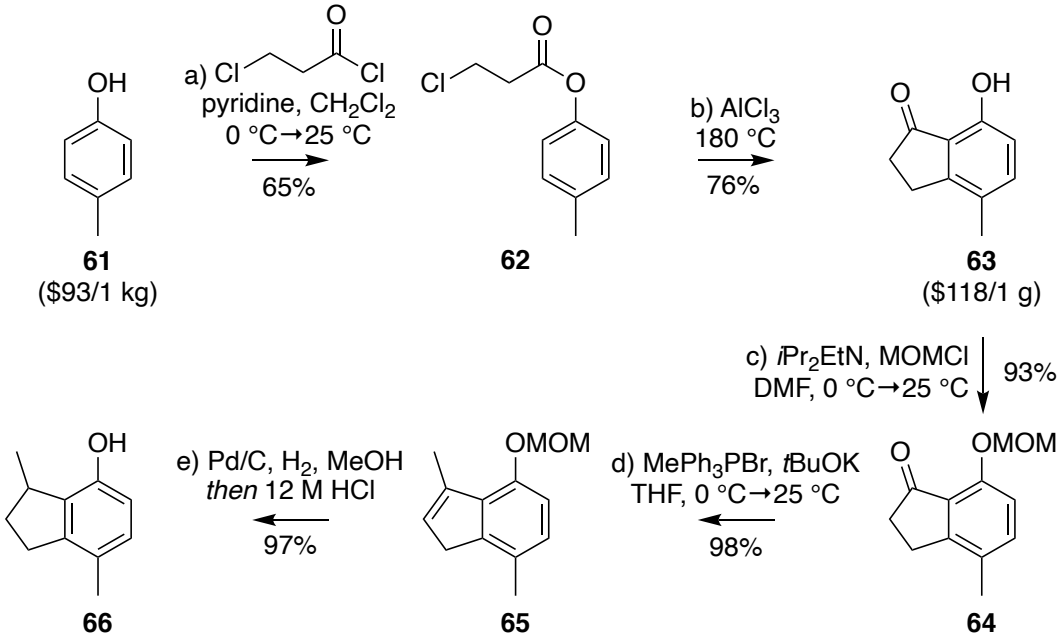
Scheme 3.6. Retrosynthetic analysis of cinncassiol F (**2**) featuring an oxidative dearomatization and prenyl-Michael addition to establish the carbon skeleton prior to global oxidation.

3.2.2 Forward Synthesis – Probing of Oxidative Dearomatization and its Derivatives

In the forward sense, we began with a three-step, two-pot acylation/Fries rearrangement/Friedel-Crafts alkylation sequence starting from *p*-cresol (**61**, Scheme 3.7) to quickly construct 7-hydroxy-4-methyl-1-indanone (**63**).[21] Although **63** is also commercially available, we elected to start from *p*-cresol (**61**) as it was more economically efficient, given that **63** costs $118 for 1 g, whereas **61** costs $93 for 1 kg (prices obtained from Sigma-Aldrich). With indanone **63** in hand, MOM-protection of the phenol allowed for facile olefination of the ketone utilizing *t*BuOK as a reversible base.[22] Unsurprisingly, a concomitant isomerization of the external olefin to the tetrasubstituted **65** was observed. Use of non-reversible bases such as *n*BuLi or other olefination reagents like Julia-Kocienski sulfones resulted in appreciably lower yields (~30-40%). Furthermore, any attempts to perform this olefination without protection of the phenol led to no

reaction. Finally, hydrogenation of **65** followed by an acidic work-up yielded phenol **66** in quantitative yield without the need for any further purification.

Scheme 3.7. Forward Push to Bicyclic Phenol **66** from *p*-Cresol (**61**).[a]

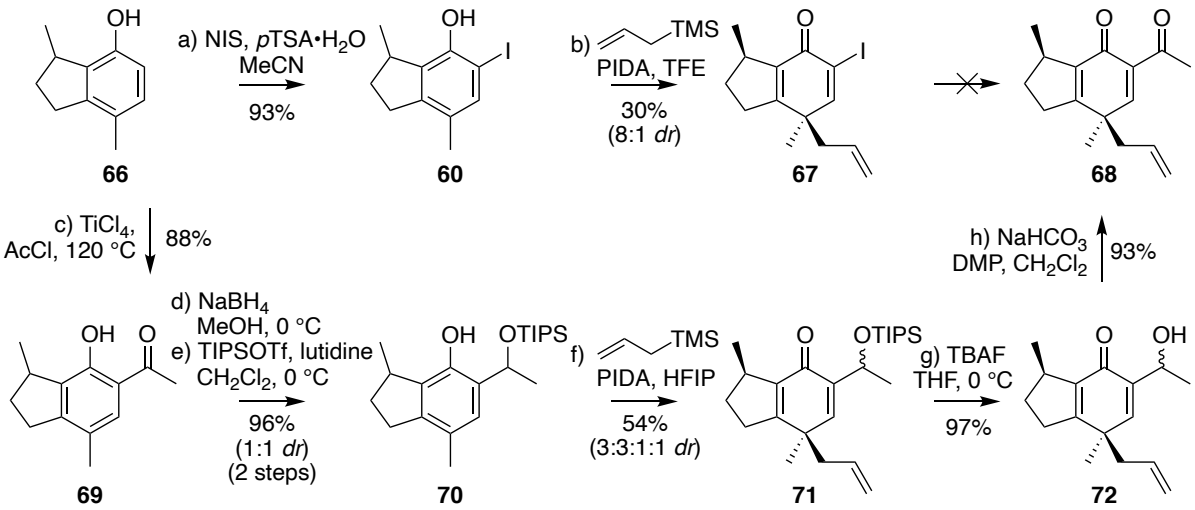


[a] Reagents and conditions: (a) pyridine (1.5 equiv), 3-chloropropionyl chloride (1.3 equiv), CH_2Cl_2 (0.92 M), 0 °C→25 °C, 8 h, 65%; (b) $AlCl_3$ (4.0 equiv), 180 °C, 6 h, 76%; (c) *i*PrEtN (10.0 equiv), MOMCl (4.0 equiv), THF (0.4 M), 0 °C→25 °C, 6 h, 93%; (d) $MePh_3PBr$ (3.0 equiv), *t*BuOK (2.9 equiv), THF (1.7 M), 0 °C, 30 min, *then* **64** (1.0 equiv), THF (0.23 M), 0 °C→25 °C, 1 h, 98%; (e) Pd/C (0.08 equiv), H_2, MeOH (0.56 M), 25 °C, 2 h, *then* 12 M HCl, 25 °C, 8 h, 97%.

With phenol **66** in hand, we set out to explore the key oxidative dearomatization. Inspired by reports from the Canesi group, we hoped to utilize their developed condition set for an oxidative Hosomi-Sakurai allylation of phenols to install our central quaternary center.[20] Due to the demonstrated efficacy of their approach on halogenated phenols, we believed having an iodide installed would then allow for further coupling to the desired acyl sidechain, so we set out by performing an ortho-iodination with NIS promoted by *p*TSA•H_2O to obtain **60** in 93% yield (Scheme 3.8).[23] Pleasingly, when subjecting **60** to the optimized Canesi conditions of 6 equivalents of allyl-TMS followed by 3 equivalents of PIDA (delivered in 2 portions) in 2,2,2-trifluoroethanol (TFE) we observed our desired dearomatization product **67** in a modest 37% yield with an

intriguing 8:1 diastereomeric ratio. Furthermore, we found the major byproduct of this reaction to be the addition of the TFE, prompting our switch to the less nucleophilic 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) for future substrates. Unfortunately, any attempts to then lithiate the vinyl iodide or perform a cross-coupling failed to deliver the desired acylated **68**, with no deiodination observed.[24]

Scheme 3.8. Forward Push to Dienedione **68**.[a]



[a] Reagents and conditions: (a) *p*TSA•H_2O (1.1 equiv), MeCN (0.2 M), 25 °C, 10 min, *then* NIS (1.1 equiv), 25 °C, 1 h, 88%; (b) allyl-TMS (6.0 equiv), PIDA (3.0 equiv), TFE (0.2 M), 25 °C, 10 min, 30%, 8:1 *dr*; (c) $TiCl_4$ (1.1 equiv), AcCl (1.5 equiv), 120 °C, 2 h, 88%; (d) $NaBH_4$ (2.0 equiv), MeOH (0.2 M), 0 °C→25 °C, 45 min, 98%, 1:1 *dr*; (e) lutidine (3.0 equiv), TIPSOTf (1.1 equiv), CH_2Cl_2 (0.1 M), 0 °C, 10 min, 98%; (f) allyl-TMS (6.0 equiv), PIDA (3.0 equiv), HFIP (0.2 M), 25 °C, 10 min, 54%, 3:3:1:1 *dr*; (g) TBAF (3.0 equiv), THF (0.2 M), 0 °C, 2 h, *then* 25 °C, 30 min, 97%; (h) $NaHCO_3$ (5.0 equiv), DMP (2.0 equiv), CH_2Cl_2, 25 °C, 15 min, 93%.

As the acyl group was unable to be installed after dearomatization, we turned to introducing this moiety prior to the oxidation event. $TiCl_4$-mediated direct ortho-acylation proceeded smoothly, delivering **69** in 88% yield (Scheme 3.9).[25] From here, any attempts to perform the subsequent dearomatization proved fruitless, most likely due to the strong electron-withdrawing capability of the carbonyl, rendering the phenol unreactive. However, a two-step reduction and TIPS-protection sequence afforded **70,** which readily underwent the desired allylation providing **71** in a higher yield (54%) than the original iodinated phenol, albeit with a diminished *dr*.[20] With **71** in hand, silyl deprotection and Dess–Martin oxidation then quickly produced the dienedione of

interest (**68**) in excellent yield, thus providing easy access to most of the cinncassiol core (only lacking the prenyl sidechain).

As alluded to, a range of diastereoselectivities was observed during the oxidative dearomatization process (Figure 3.2). Iodinated **67** was constructed with an 8:1 *dr*, TIPS-protected **71** yielded a 3:1 *dr*, and a 1:1 *dr* was observed with a TBDPS-protected analogue (**73**). Computational results by the Harned group alongside analysis of molecular models sheds some light on the rationale for this assortment of selectivities.[26] In 2018, the Harned group performed DFT calculations to map the proposed mechanisms of PIDA-mediated dearomatizations, and found that the phenyl ring of the hypervalent iodide has a strong π-stacking interaction with the phenol to stabilize the reactive intermediate. Pairing this with the non-symmetric nature of the phenols presented here, it can be reasonably presumed the phenyl ring of PIDA would prefer to sit in the least sterically encumbered environment. For iodinated phenol **60**, that means the phenyl would simply sit on the opposite face of the locked left-hand methyl group, resulting in the high diastereoselectivity. However, once an increase in steric bulk and free rotation of a C-C bond is introduced on the right-hand side, the tight π-stacking interaction could be more easily disturbed, resulting in lower selectivity, especially in the presence of additional phenyl rings such as in the TBDPS variant where additional π-π interactions are possible.

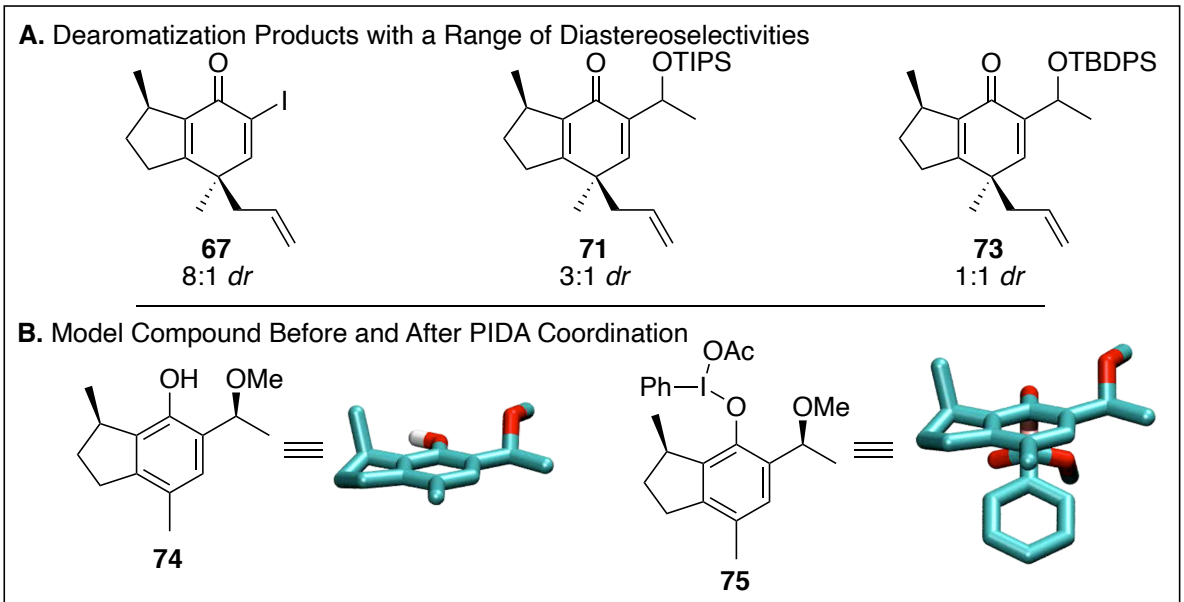


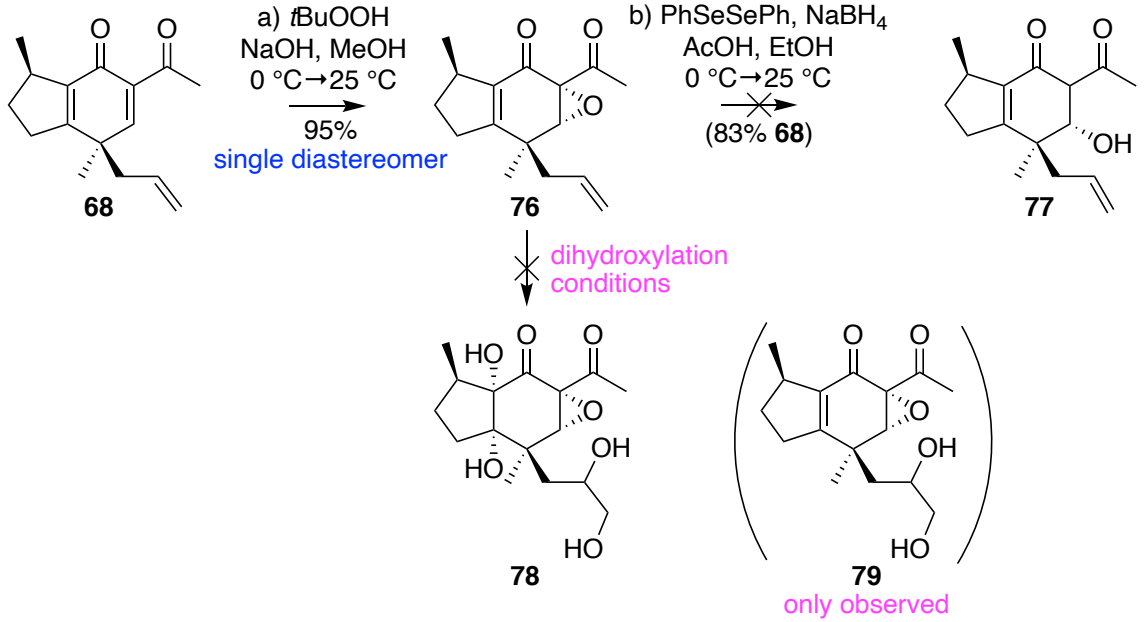
Figure 3.2. Explanation of diastereoselectivites for the oxidative dearomatization.

3.2.3 Forward Synthesis – Oxidation Model Studies

Before tackling the full carbon framework, we wanted to ensure the central ring could accommodate a bis-epoxide moiety, which could be converted into the iconic *cis*-tetraol of the cinncassiol diterpenoid family. Thus, we hoped to directly obtain the bisepoxide moiety through a dual nucleophilic epoxidation of dienedione **68**, but all efforts simply resulted in monoepoxidation to **76** (Scheme 3.9). Of the conditions tried *t*BuOOH in alkaline MeOH proved optimal, proceeding with full facial selectivity and in excellent yield (95%).[27] While unsuccessful in installing the bis-epoxide, we hoped to test the regioselective epoxide opening with diphenyl diselenide and sodium borohydride. Although the reductive epoxide opening is presumed to have proceeded as desired, concomittant dehydration was observed, yielding back dienedione **68** in 83% yield.[28] This adverse reactivity has only been reported a handful of times, and is believed to be attributed to a borane- or selenide-adduct of the resulting alcohol.[29] Despite this reactivity we hoped that additional oxidation of the left hand ring would open more potential avenues by circumventing the stability of the conjugated dienone. We also wanted to probe further oxidation of the left-hand olefin, and

attempted several dihydroxylation conditions.[30] Utilizing stoichiometric osmium tetroxide, as well as known accelerants such as pyridine as the solvent or additives like citric acid failed to oxidize the tetrasubstituted olefin, with only dihydroxylation of the terminal allyl group observed (**79**).

Scheme 3.9. Initial Probe of Core Oxidations.

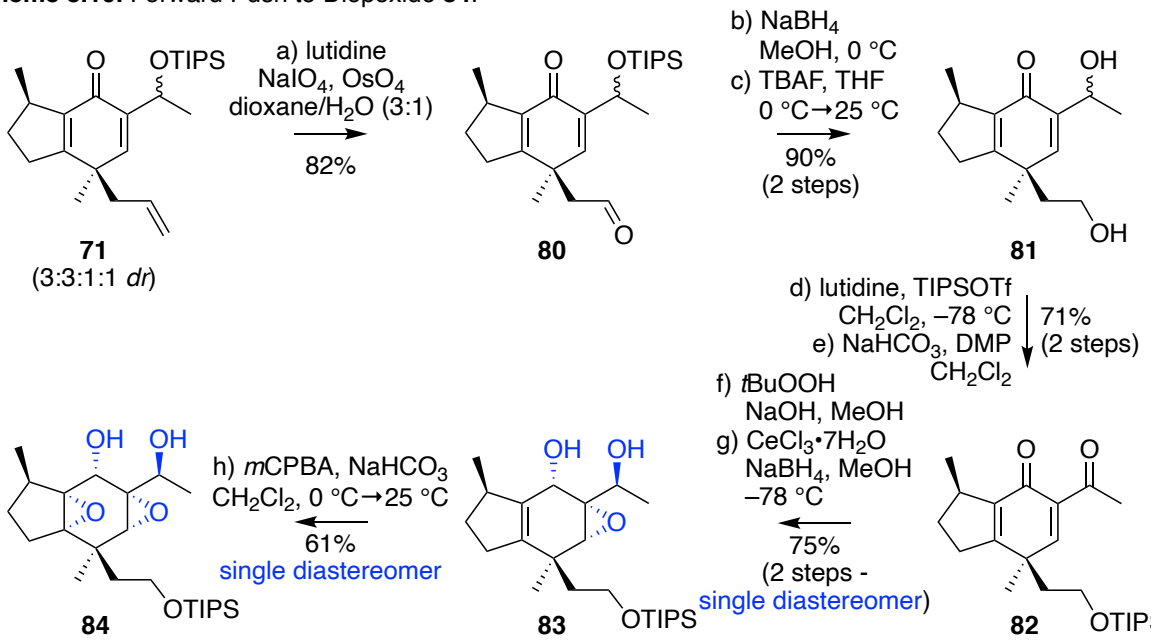


[a] Reagents and conditions: (a) *t*BuOOH (6.0 equiv), NaOH (0.5 equiv), MeOH (0.1 M), 0 °C→25 °C, 1 h, 95%; (b) PhSeSePh (1.5 equiv), $NaBH_4$ (3.0 equiv), AcOH (0.5 equiv), EtOH (0.05 M), 0 °C→25 °C, 5 min, 83% **68**.

To remove the potential for additional undesired reactivity, we converted the allyl group to a primary alcohol (**81**) through a Lemieux-Johnson oxidation followed by reduction (Scheme 3.10).[31] From here, simple redox reactions interconvert the protected secondary alcohol to the primary alcohol of **81**, allowing us to obtain dienedione (**82**) once again after Dess–Martin oxidation. Thankfully, the previously developed nucleophilic epoxidation conditions provided the right-hand epoxide once more in a facially selective fashion.[27] Unfortunately, neither screening of dihydroxylation conditions nor further attempts at nucleophilic epoxidation were effective in functionalizing the now sole olefin. Given the low reactivity of this electron-deficient olefin, we then wanted to probe electrophilic transformations, prompting us to perform a Luche reduction of

dicarbonyl **82**.[32] Gratifyingly, this reduction event proceeded with full facial selectivity, not only with the exocyclic ketone, but for the enone as well. Using a 3D model, we can rationalize this selectivity through the bidentate chelation of the cerium to both carbonyls, forcing the exocyclic carbonyl to have well defined concave and convex faces. The first hydride then attacks from the convex face, forcing the alcohol to sit above the central ring which then directs the borohydride to deliver the second hydride from that same face, rendering the central allylic alcohol *cis* to the epoxide. Unfortunately, all attempts to then dihydroxylate the tetrasubstituted olefin did not proceed as desired. However, we were pleased to find that electrophilic epoxidation with *m*CPBA proceeded smoothly to provide **84** as a single diastereomer, presumably due to the allylic alcohol guiding the diastereoselectivity. With this result in hand, we had established the desired bis-epoxide moiety in a highly diastereoselective fashion and were hopeful that these transformations were translatable to the full carbon skeleton.

Scheme 3.10. Forward Push to Diepoxide **84**.[a]



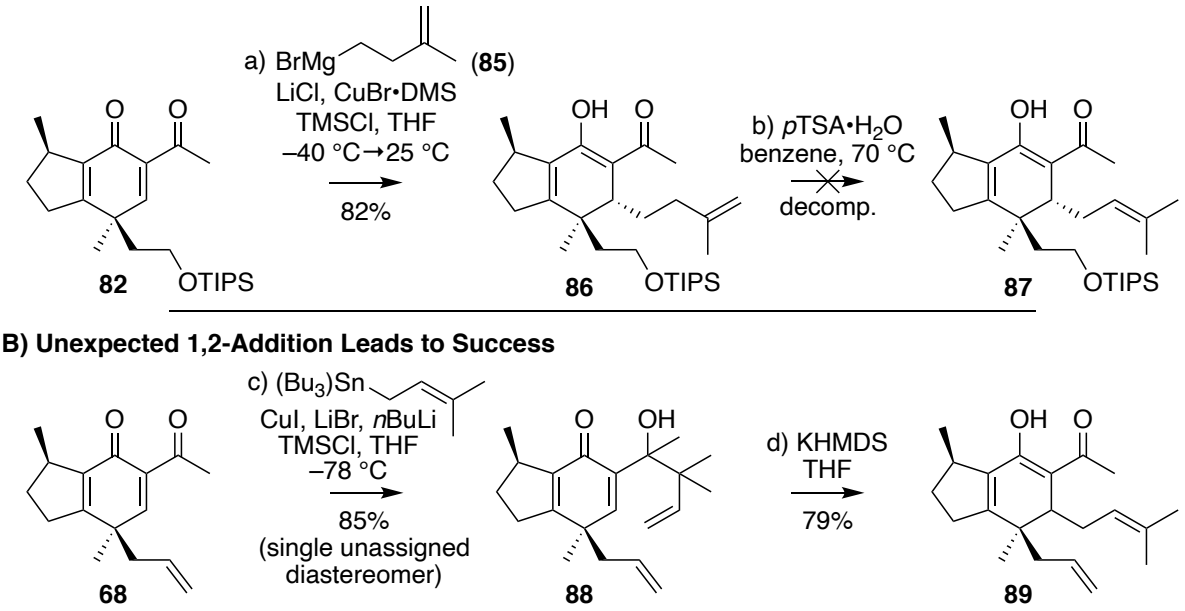
[a] Reagents and conditions: (a) lutidine (2.0 equiv), $NaIO_4$ (4.0 equiv), OsO_4 (0.05 equiv), dioxane/H_2O (3:1, 0.1 M), 25 °C, 1.5 h, 82%; (b) $NaBH_4$ (1.0 equiv), MeOH (0.1 M), 0 °C, 5 min, quant.; (c) TBAF (4.0 equiv), THF (0.1 M), 0 °C, 90%; (d) lutidine (3.0 equiv), TIPSOTf (1.1 equiv), CH_2Cl_2 (0.1 M), 0 °C, 10 min, 73%; (e) $NaHCO_3$ (5.0 equiv), DMP (2.0 equiv), CH_2Cl_2 (0.06 M), 25 °C, 15 min, 97%; (f) *t*BuOOH (5.0 equiv), NaOH (0.5 equiv), MeOH (0.05 M), 0 °C→25 °C, 1 h, 92%; (g) $CeCl_3$•$7H_2O$ (2.5 equiv), MeOH (0.04 M), 25 °C, 10 min, *then* $NaBH_4$ (2.5 equiv), –78 °C, 2 h, 92%; (h) $NaHCO_3$ (3.0 equiv), *m*CPBA (2.0 equiv), CH_2Cl_2 (0.03 M), 0 °C→25 °C, 3 h, 61%.

3.2.4 Completion of the Carbon Framework

Given our successful model substrate campaign, we next set out to complete the carbon framework through the installation of the prenyl sidechain before once again fashioning the bisepoxide. As initially planned, we first attempted a prenyl Michael addition starting from prenyl bromide (Scheme 3.11).[33] However, we found the prenyl Grignard reagent to be unstable and decompose rapidly once generated. This instability is well documented, and two approaches to circumnavigate this problem have been developed. The first workaround we tried was akin to the Maimone group's 2015 synthesis of hyperforin in which an isoprenyl group is used for the 1,4-addition, followed by isomerization of the external olefin to the internal trisubstituted position (**82**→**87**, Scheme 3.11 Panel A).[34] Pleasingly, the initial Michael addition proceeded in 82% yield,

but we were disappointed to find that the alkene isomerization was unsuccessful in this case, only leading to decomposition.

Scheme 3.11. Initial Efforts Toward Prenyl Installation.[a]



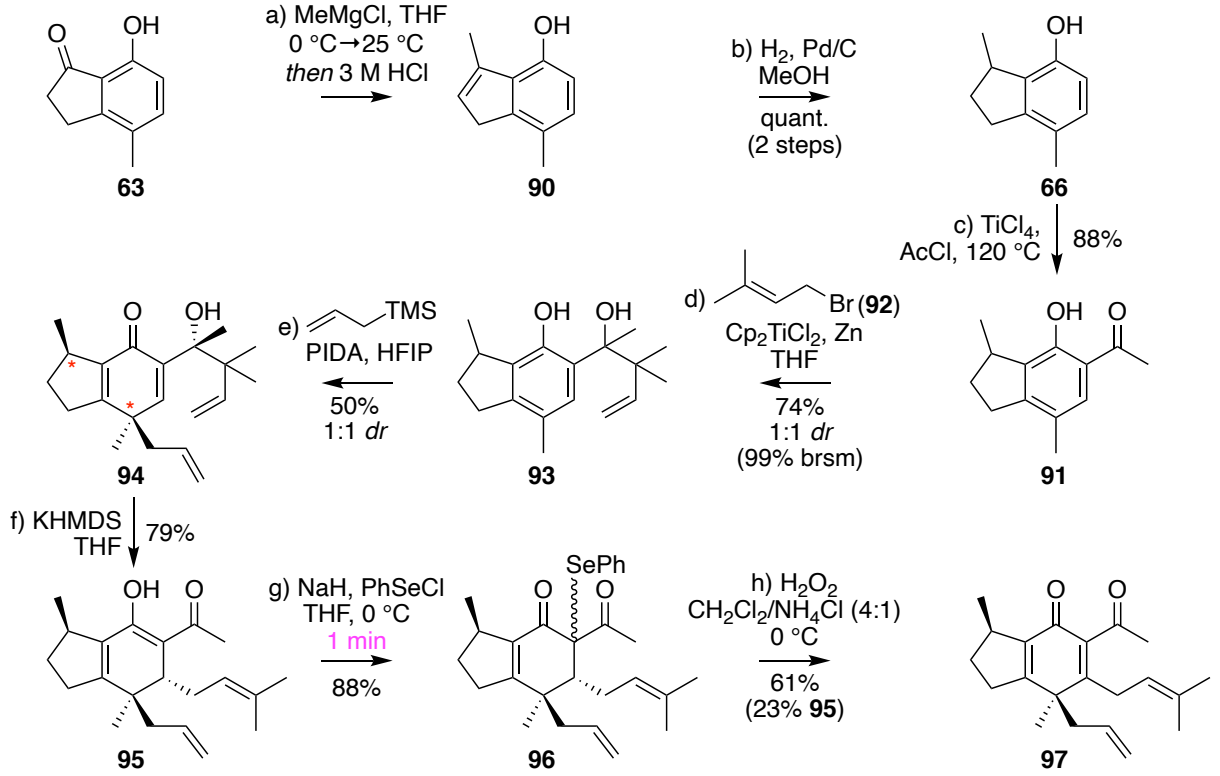
[a] Reagents and conditions: (a) LiCl (5.0 equiv), CuBr•DMS (2.0 equiv), THF (0.06 M), **85** (2.1 equiv), –40 °C, 15 min, *then* TMSCl (2.1 equiv), **82** (1.0 equiv), –40 °C→25 °C, 8 h, 82%; (b) *p*TSA•H_2O (0.2 equiv), benzene (0.05 M), 70 °C, 1 h, 0%; (c) *n*Bu_3(prenyl)Sn (3.0 equiv), *n*BuLi (2.9 equiv), CuI (3.1 equiv), LiBr (3.7 equiv), TMSCl (5.1 equiv), THF (0.1 M), –78 °C, 1 h, 85% (single diastereomer); (d) KHMDS (3.0 equiv), THF (0.2 M), 25 °C, 5 min, 79%.

The second method that is used to perform a prenyl Michael addition directly was developed by Lipshutz in 1990 (Scheme 3.11, Scheme 3.11 Panel B).[35] The Lipshutz group found the formation of prenylcopper•TMSCl derived from tri-*n*-butylprenylstannane, CuI, *n*BuLi, and TMSCl allowed for highly regioselective 1,4-addition onto cyclohexenones. In the case of less-substituted allyl groups, they observed competitive 1,2-addition, but the prenyl reagent presented itself as a much less reactive species. Therefore, when we applied this stannane system to dienedione **68**, we were a little disappointed to find solely 1,2-addition product, producing **88** in 85% yield. Although undesired, we realized the resultant tertiary alcohol of **88** sat in a perfect conformation to potentially undergo an anionic oxy-Cope rearrangement. To our delight, upon

treatment with KHMDS in THF at 25 °C, the desired sigmatropic isomerization was instantaneous, providing prenylated **89** in 74% yield.[36]

Inspired by the unintended isoprenyl 1,2-addition and anionic oxy-Cope rearrangement to prenylated **89**, we sought to install this reactive handle earlier on. Starting from indanone **63**, we were able to obtain phenol **66** in a more efficient two-step sequence in which a Grignard addition followed by acidic work-up produced olefin **90**, which was in turn readily hydrogenated with Pd/C, eliminating the prior need for phenol protection as well as chromatographic purification for either step (Scheme 3.12).[37] Pushing through the same acylation as described before, a Barbier-type 1,2-addition of prenyl bromide efficiently delivered tertiary alcohol **93** albeit in a 1:1 diastereomeric ratio.[38] Although initial efforts involved the protection of this tertiary alcohol prior to dearomatization were successful, the subsequent deprotection of the alcohol presented quite the challenge. Pleasingly, we found that no protection was required in this case as the oxidative dearomatization of **93** proceeded in 50% yield and an intriguing 1:1 diastereomeric mix of **94**. From here, the anionic oxy-Cope rearrangement set the stage to perform the subsequent oxidation to the desired dienedione **97**.[36] After extensive screening, we identified a two-step process involving initial α-selenide formation followed by oxidative cleavage that would deliver **97** in modest yield.[39]

Scheme 3.12. Anionic Oxy-Cope Rearrangement Allows for Generation of Carbon Skeleton.[a]

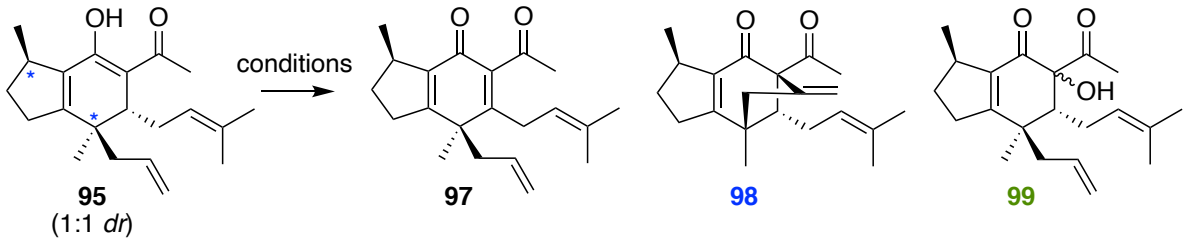


[a] Reagents and conditions: (a) MeMgCl (2.5 equiv), THF (0.3 M), 0 °C→25 °C, 10 min, *then* 3 M HCl, 10 min, quant.; (b) Pd/C (0.08 equiv), H_2, MeOH (0.5 M), 25 °C, 2 h, quant.; (c) $TiCl_4$ (1.1 equiv), AcCl (1.5 equiv), 120 °C, 2 h, 88%; (d) Cp_2TiCl_2 (0.1 equiv), Zn (3.0 equiv), THF (0.2 M), 15 min, *then* **92** (3.0 equiv), **91** (1.0 equiv), 25 °C, 1.5 h, 74%, 99% brsm; (e) allyl-TMS (6.0 equiv), PIDA (3.0 equiv), HFIP (0.2 M), 25 °C, 10 min, 50%, 1:1 *dr*; (f) KHMDS (3.0 equiv), THF (0.2 M), 25 °C, 5 min, 79%; (g) NaH (5.0 equiv), THF (0.1 M), 25 °C, 1 h, *then* PhSeCl (1.3 equiv), 0 °C, 1 min, 88%; (h) H_2O_2 (4.0 equiv), CH_2Cl_2/NH_4Cl (4:1, 0.1 M), 0 °C, 23% **95**, 61% **97**.

Before achieving dienedione **97** through the selenide pathway, several one-step protocols were initially attempted (Table 3.1). Typical enedione synthesis is performed using DDQ, as the enolate can add into the DDQ in a reversible Michael fashion, before the neighboring carbonyl of the DDQ can deprotonate the β-proton, allowing for a syn-elimination.[40] However, any attempts to utilize DDQ to oxidize enol **95** to **97** failed to show any reactivity, even with acidic or basic promoters and higher temperature. When turning to transition metal catalysis, use of the Stahl group's palladium-catalyzed aerobic oxidation fully consumed the starting material, but failed to deliver dienedione **97**.[41] Instead, we received a very intriguing bridged system (**98**) with an external 1,1-disubstituted olefin, which we believe is simply derived from the enolate attacking an

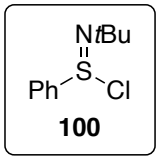
allyl-palladium species, before being quenched through β-hydride elimination. Use of Mukaiyama's dehydrogenative reagent (**100**) with LDA showed no reaction, whereas warming to 25 °C in the presence of LiHMDS resulted in full decomposition of the material.[42] Lastly, attempts to perform IBX-mediated oxidation also did not produce the desired **97**, but instead showed a 1:1:1:1 diastereomeric mix of α-hydroxylated **99**.[43] All efforts to then dehydrate **99** unfortunately proved fruitless as well.

Table 3.1. Trials in the Oxidation of Enol **95** to Dienedione **97**.



95 (1:1 *dr*) **97** **98** **99**

Entry	Solvent	Temp.	Reagent(s)	Result
1	dioxane	25 °C	DDQ	NR
2	dioxane	25 °C	DDQ, AcOH	NR
3	dioxane	75 °C (MW)	DDQ, AcOH	NR
4	THF	25 °C	DDQ, K_2CO_3	NR
5	THF	60 °C	DDQ, K_2CO_3	NR
6	AcOH	80 °C	DMSO, $Pd(TFA)_2$	50% **98**
7	THF	–78 °C→0 °C	LDA, **100**	NR
8	THF	0 °C→25 °C	LiHMDS, **100**	decomp.
9	PhMe/DMSO (2:1)	85 °C	IBX	40% **99**
10	DMSO	25 °C	IBX•MPO	NR
11	DMSO	40 °C	IBX•MPO	65% **99**

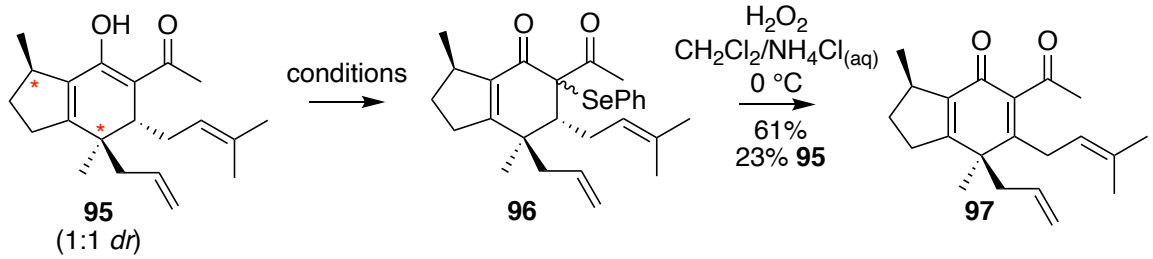


100

Turning away from one-step methods for the oxidation of enol **95** to **97**, we initially tested the traditional reaction conditions for α-selenide formation: stirring the enol with NaH at 0 °C for 1 h before the slow addition of a solution of PhSeCl in THF, followed by warming to 25 °C and

stirring until completion (Table 3.2).[39a] However, after 1 h at 25 °C, we observed only starting material by TLC. Believing this may have been due to poor enolate formation, we then screened several different bases (pyridine, LiHMDS, LDA) and once again saw no α-selenide **96** forming.[39b-d] Given the lack of reactivity, we next screened the selenide source, switching to the more reactive (and less bench stable) PhSeBr. After the initial stirring of the enol with NaH followed by slow addition of the PhSeBr, we observed product formation after 1 h at 25 °C, albeit in modest yield (37% yield, 94% brsm). Given the low conversion, our initial thought was to extend the reaction time past the 1 h at 25 °C, but found that after 16 h, only starting enol **95** was recovered. To test if the opposite is beneficial, we then kept the reaction at 0 °C and quenched it 1 minute after the addition of the PhSeBr solution and observed a boost in the yield of **96** (49% yield). Employing the more stable PhSeCl in this operation (quenching just 1 minute after the addition of selenide) we were able to consistently isolate over 90% yield of the desired **96**. Next, when we attempted to then oxidize **96** to **97** with hydrogen peroxide, we once again were only observing complete reversion back to enol **95**. However, we were pleased to find that by buffering the oxidative cleavage with aqueous NH_4Cl, we could deliver the desired **97** in 61% yield (still with 23% reversion back to enol **95**).[44]

Table 3.2. Access to Dienedione **97** through Selenide **96**.



95 (1:1 *dr*) **96** **97**

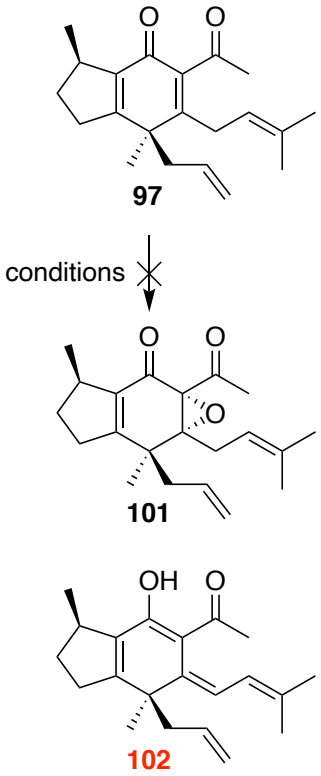
Entry	Solvent	Temp.	Time	Reagent(s)	Result
1	THF	0 °C→25 °C	1 h	PhSeCl, NaH	NR
2	CH_2Cl_2	0 °C	1 h	PhSeCl, pyridine	decomp
3	THF	0 °C→25 °C	1 h	PhSeCl, LiHMDS	NR
4	THF	–78 °C→0 °C	1 h	PhSeCl, LDA	NR
5	THF	0 °C→25 °C	1 h	PhSeBr, NaH	37% 94% brsm
6	THF	0 °C→25 °C	16 h	PhSeBr, NaH	"NR"
7	THF	0 °C	1 min	PhSeBr, NaH	49% 80% brsm
8	THF	0 °C	1 min	PhSeCl, NaH	92%

To the best of our knowledge, this type of retro-α-selenation has not been reported. Mechanistically, we are not certain as to the cause, but believe it is one of two possibilities. First, enolization of the exocyclic ketone could allow for the oxygen to intramolecularly attack the selenide, breaking the C-Se bond, and releasing the substrate back to the starting enol. Second, an external nucleophile, be it potential hydroxide from trace NaOH (a common byproduct when utilizing NaH) or the halide released from the selenium reagent could be attacking the unstable selenide intermolecularly, which may help to explain the difference in yields for the PhSeCl and PhSeBr and suggest why it is critical to buffer the oxidative quench step as well with NH_4Cl.

Having established the full carbon skeleton variant (**97**) of the model dienedione (**82**), the stage was set to undergo the same nucleophilic epoxidation, Luche reduction, electrophilic

epoxidation sequence as used previously to obtain epoxide **101** (Table 3.3).[27, 32] Unfortunately, though, when subjecting **97** to the optimized conditions of *t*BuOOH in alkaline MeOH at 0 °C, we observed no reaction, even upon warming to 25 °C. Assuming this may be due to the increased steric bulk at the β-position, we opted to switch to the smaller hydrogen peroxide, however we once again saw no reaction occur. Warming to 50 °C in the presence of either peroxide source resulted in decomposition of the starting material. On the other hand, when utilizing a nucleophilic peracid (*m*CPBA in the presence of KOH), no reaction was observed, prompting us to return to the more reactive peroxide reagents.[45] Interestingly, the addition of a phase transfer catalyst, namely Triton B, simplified the reaction profile, allowing us to isolate a 53% yield of highly conjugated **102** arising from the facile deprotonation of one of the highly acidic, bis-allylic protons in **97**, elucidating one potential decomposition pathway responsible for the failure of these trials.[46]

Table 3.3. Nucleophilic Epoxidation Attempts of Dienedione **97**.

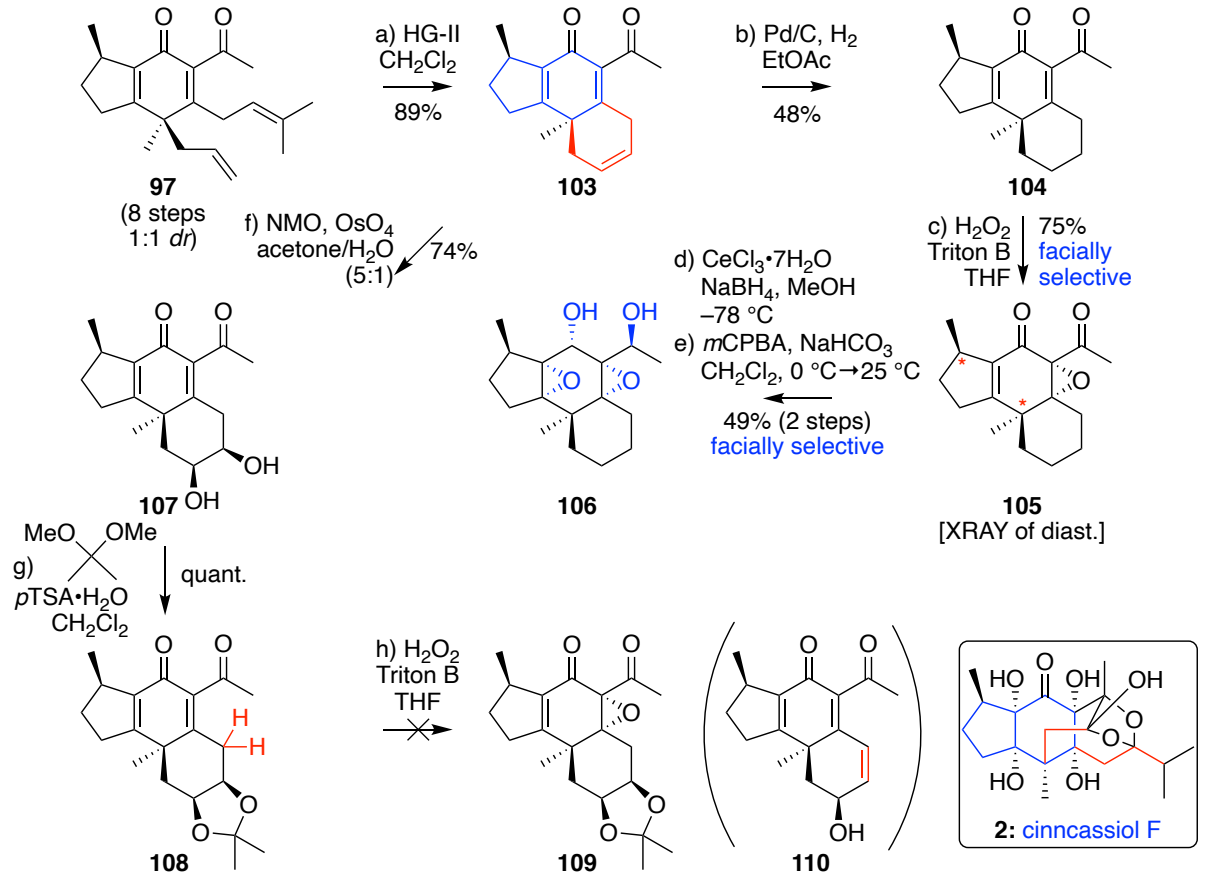


Entry	Solvent	Temp	Reagents	Result
1	MeOH	0 °C→25 °C	*t*BuOOH 0.5 M NaOH	NR
2	MeOH	0 °C→25 °C	H_2O_2 0.5 M NaOH	NR
3	MeOH	25 °C→50 °C	H_2O_2 0.5 M NaOH	decomp
4	MeOH	25 °C→50 °C	*t*BuOOH 0.5 M NaOH	decomp
5	CH_2Cl_2	25 °C	*m*CPBA, KOH	NR
6	THF	25 °C→50 °C	H_2O_2, Triton B	decomp
7	THF	25 °C	*t*BuOOH, Triton B	54% **102**
8	bmim[PF_6]	25 °C→50 °C	H_2O_2, NaOH	NR
9	CH_2Cl_2	25 °C	PhIO	NR

Given the high acidity of the bis-allylic protons of **97**, we hoped to circumvent this problem by fashioning tricycle **103** through a cross metathesis of the allyl and prenyl sidechains (Scheme 3.13). This proceeded quite smoothly with Grubbs 2nd Generation initiator, producing **103** in 82% yield.[47] Before probing the oxidation of the central core, we opted to hydrogenate the disubstituted olefin to simplify the exploratory reaction profiles. From here, we were pleased to find that the 3-step sequence previously developed to install the bis-epoxide proceeded smoothly, once again in a facially selective fashion.[27, 32] Further structural confirmation was also provided through X-ray crystallographic analysis of the monoepoxide **105**, albeit of the undesired diastereomer as denoted by the red starred positions (starting dienedione **104** was a 1:1 mixture of diastereomers). The critical detail here is that the epoxide is installed on the same face as the methyl group, confirming

our previous assumption. Pushing forward in a productive format from tricyclic olefin **103**, we were able to smoothly dihydroxylate the disubstituted olefin under standard Upjohn conditions. By having a diol at this position, we envisioned a later oxidative cleavage would allow us to reinstall the necessary isopropyl unit on the righthand side, as well as provide a pinacol coupling handle. Protection of the newly installed diol as an acetonide then provided the desired dienedione **108**, upon which we could reexplore the epoxidation sequence; however, all conditions once again led to no reaction, decomposition, or undesired reaction with the allylic protons. For example, treatment with H_2O_2 and Triton B produced allylic alcohol **110**, revealing the allylic protons marked in red were still too acidic.[46] Unfortunately, any protecting group, be it acetonide, carbonate, silyl, and even the free diol **107** all resulted in the same reactivity, thus forcing us to rethink our global strategy.

Scheme 3.13. Exploration of Metathesized Tricyclic Core.[a]



[a] Reagents and conditions: (a) HG-II (0.1 equiv), CH_2Cl_2 (0.1 M), 25 °C, 2.5 h, 89%; (b) Pd/C (0.08 equiv), H_2, EtOAc (0.1 M), 0.5 h, 48%; (c) H_2O_2 (10.0 equiv), Triton B (1.5 equiv), THF (0.06 M), 25 °C, 1 h, 72%; (d) $CeCl_3•7H_2O$ (2.5 equiv), MeOH (0.02 M), 25 °C, 10 min, *then* $NaBH_4$ (2.5 equiv), –78 °C, 6 h, 68%; (e) $NaHCO_3$ (3.0 equiv), *m*CPBA (2.0 equiv), CH_2Cl_2 (0.02 M), 0 °C→25 °C, 3 h, 72%; (f) NMO (2.0 equiv), OsO_4 (0.05 equiv), acetone/H_2O (5:1, 0.1 M), 25 °C, 8 h, 74%; (g) 2,2-dimethoxypropane (5.0 equiv), *p*TSA•H_2O (0.1 equiv), CH_2Cl_2 (0.07 M), 25 °C, 2 h, quant.; (h) H_2O_2 (10.0 equiv), Triton B (1.5 equiv), THF (0.06 M), 25 °C, 1 min, quant. **110**.

3.2.5 Summary of Initial Oxidative Dearomatization Approach

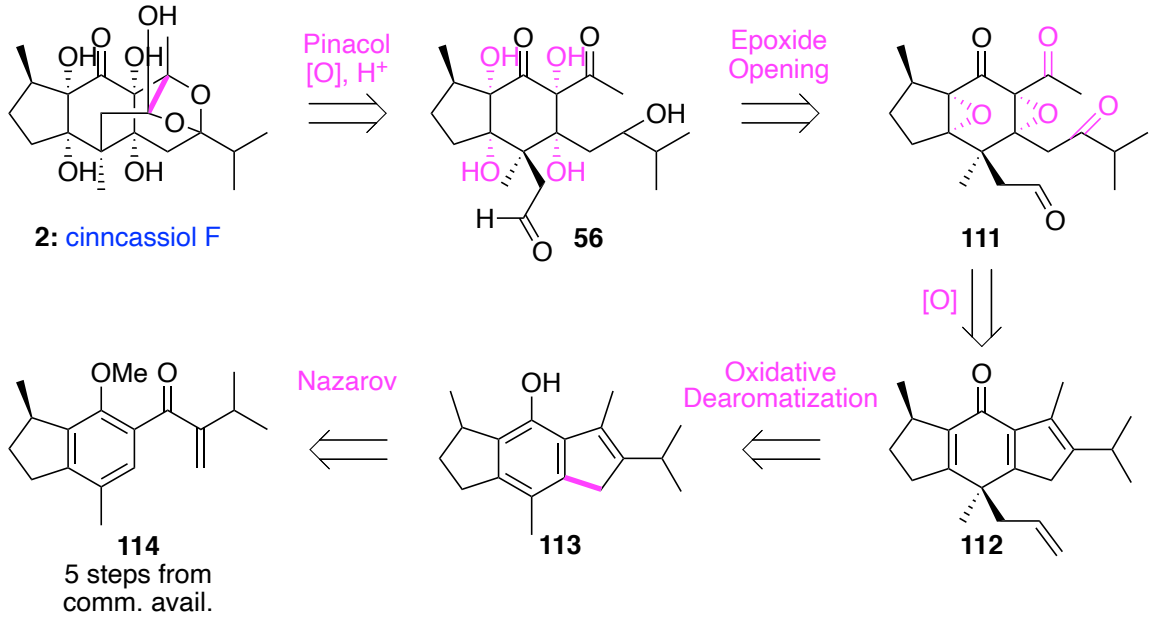
When exploring the carbon-skeleton first approach, we first envisioned the skeleton being built through a key oxidative dearomatization of phenol **70**, which would also efficiently install the critical quaternary center (Scheme 3.8).[20a] Before tackling the full carbon framework, we wanted to ensure the central ring could accommodate a bis-epoxide moiety, which could be converted into the iconic *cis*-tetraol of the cinncassiol diterpenoid family. To this end, we were able to obtain bis-epoxide **84** as a single diastereomer through a three-step sequence from dienedione **82** including a nucleophilic epoxidation, Luche reduction, and electrophilic

epoxidation, with each step being diastereoselective (Scheme 3.10).[27, 32] When trying to apply this strategy to the full carbon skeleton (with the prenyl sidechain installed through an anionic oxy-Cope rearrangement), we were faced with several challenges.[20a, 36, 38] For instance, the oxidation to dienedione **97** was quite fickle, but we found that subjecting the conjugated enol **95** to NaH for 1 h followed by PhSeCl for 1 minute at 0 °C allowed for the full conversion to the α-selenide, with longer reaction times leading to full reversion to **95** (Table 3.2).[39a] Additionally, buffering of the subsequent oxidative H_2O_2 work-up with $NH_4Cl_{(aq)}$ was also required to avoid full reversion.[44] Unfortunately, the resulting bisallylic protons prevented any success with the bis-epoxidation sequence, as they were easily deprotonated, leading to the fully conjugated byproduct **102** (Table 3.3). To circumvent this and to introduce conformational rigidity, the prenyl and allyl groups were metathesized to form tricycle **103**, and although the hydrogenated model led to the desired bis-epoxide (**106**), attempts to perform the same sequence on a system with handles for subsequent manipulation led to elimination product **110**, again due to the ability to generate these extended conjugated systems (Scheme 3.13).

3.2.6 Nazarov Cyclization to Fashion Carbon Skeleton

While investigations were ongoing for the installation of the carbon skeleton of cinncassiol F (**2**) through the anionic oxy-Cope rearrangement approach, we also explored the potential for a Nazarov cyclization to fashion the 5/6/5-isoryanodane-type core (**12**). Although the endgame was similar in both scenarios, the oxidative cleavage required to access **111** from **112** could potentially avoid the acidity problems experienced in the rearrangement approach if the sidechain ketone was reduced prior to the epoxidation of the central ring (Scheme 3.14). **112** itself was envisioned to be constructed from tricyclic phenol **113** through the same oxidative dearomatization previously used,

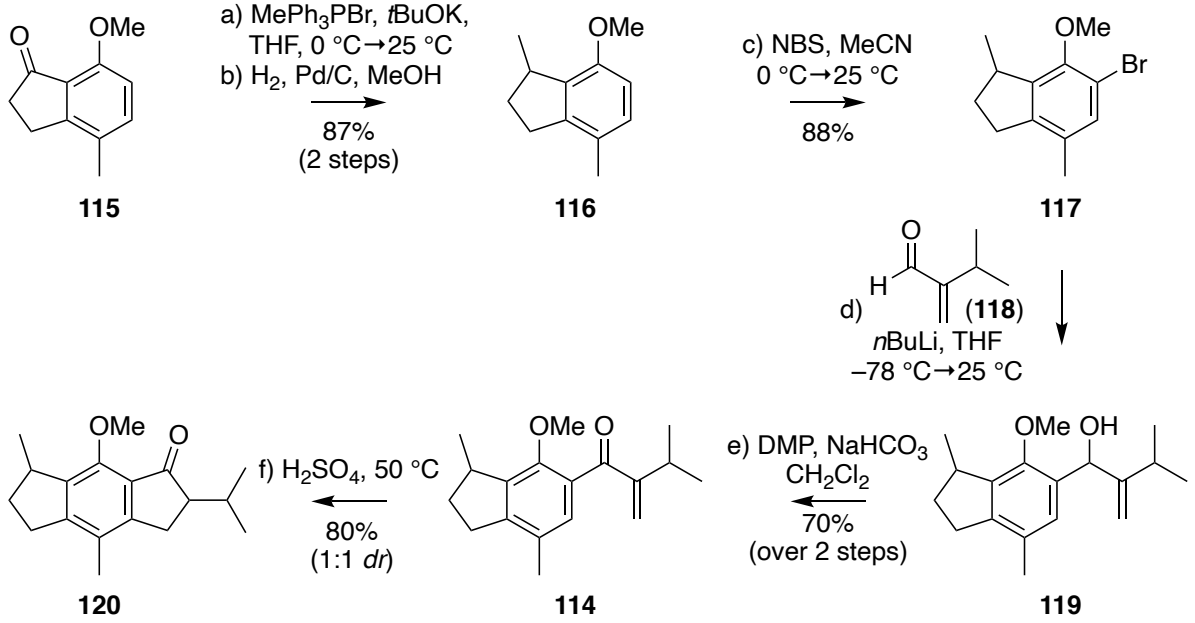
while **113** was thought to be accessible through a Nazarov cyclization of 1,1-disubstituted enone **114**, which in turn is only 5 steps from commercially available material.



Scheme 3.14. Retrosynthetic analysis of cinncassiol F (**2**) featuring a Nazarov cyclization and oxidative dearomatization to establish the carbon skeleton prior to global oxidation.

In a forward sense, methylated phenol **115** was easily obtained in quantitative yield from commercially available indanone **116** through a two-step Wittig olefination and hydrogenation sequence (Scheme 3.15).[48] Subsequent bromination in the presence of NBS followed by lithiation and attack on aldehyde **118** provided allylic alcohol **119**, which was smoothly oxidized to the desired Nazarov precursor, enone **114**.[48] Pleasingly, when subjected to concentrated H_2SO_4 at 50 °C, the desired Nazarov cyclization proceeded as hoped, delivering the 5/6/5-isoryanodane-type tricycle **120** in 80% yield, 6 steps from the commercially available starting material.[49] Of note, no isomerization of the enone to the tetrasubstituted olefin or demethylation of the phenol was observed under these strongly acidic conditions.

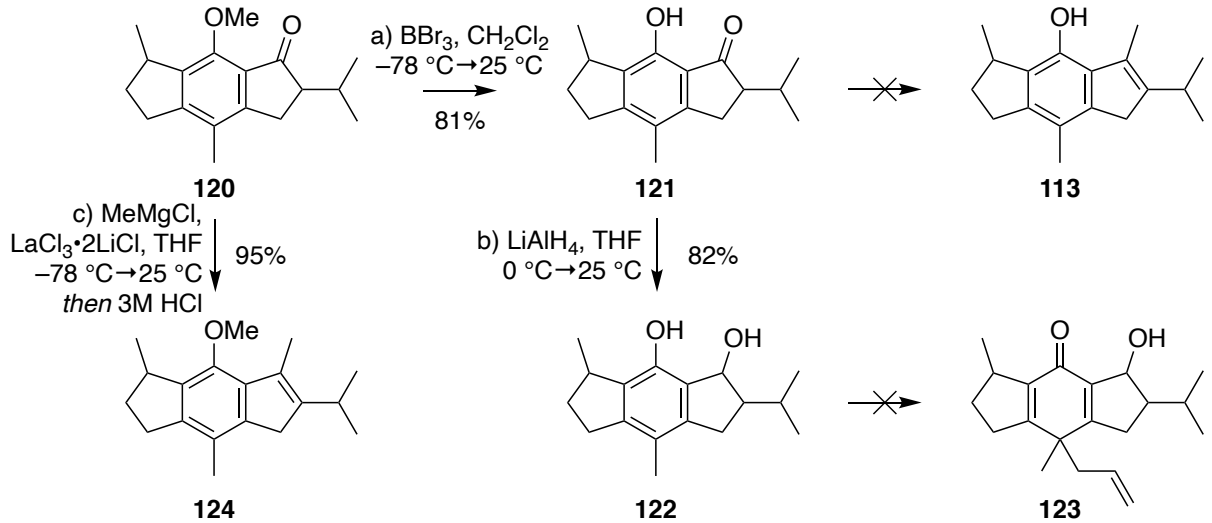
Scheme 3.15. Forward Synthesis through Nazarov Cyclization.[a]



a Reagents and conditions: (a) $MePh_3PBr$ (3.0 equiv), *t*BuOK (2.9 equiv), THF (0.3 M), 0 °C→25 °C, 1 h, 89%; (b) Pd/C (0.08 equiv), MeOH (0.25 M), H_2 (balloon), 1 h, 98%; (c) NBS (1.2 equiv), MeCN (0.1 M), 0 °C→25 °C, 8 h, 88%; (d) *n*BuLi (2.2 equiv), **118** (2.2 equiv), THF (0.3 M), –78 °C, 30 min, 86%; (e) $NaHCO_3$ (5.0 equiv), DMP (1.5 equiv), CH_2Cl_2 (0.20 M), 25 °C, 30 min, 81%; (f) H_2SO_4 (0.25 M), 50 °C, 1.5 h, 80%.

With tricycle **120** in hand, we then set out to install the critical, central quaternary center of cinncassiol F (**2**), as we believed we could utilize a similar sequence as established in our previous work while constructing original phenol **66** (Scheme 3.12), in which a methyl Grignard addition into the carbonyl followed by acidic work-up delivered the internal olefin (Scheme 3.16).[15, 37] Although demethylation of **120** proceeded in 90% yield with BBr_3 to deliver phenol **121**, any attempts to nucleophilically add into the ketone failed, most likely due to the increased steric bulk introduced by the isopropyl group. Interestingly, we were able to reduce the carbonyl to a secondary alcohol **122**, but unfortunately all dearomatization trials were fruitless. Given these challenges, we decided to turn to an alternate order of steps and found that we could install the desired tetrasubstituted olefin when the phenol was still methylated, delivering **124** in 95% yield.

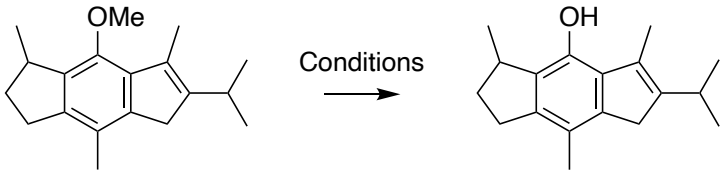
Scheme 3.16. Exploration of Tricyclic Phenol Reactivity.[a]



[a] Reagents and conditions: (a) BBr_3 (1.2 equiv), CH_2Cl_2 (0.05 M), –78 °C→25 °C, 15 min, 81%; (b) $LiAlH_4$ (2.0 equiv), THF (0.1 M), 0 °C→25 °C, 15 min, 82%; (c) $LaCl_3$•2LiCl (1.5 equiv), MeMgCl (1.5 equiv), THF (0.16 M), –78 °C→25 °C, 15 min, *then* 3 M HCl, 25 °C, 30 min, 95%.

Having access to the tetrasubstituted olefin, we simply needed to demethylate the phenol to grant us access to our desired dearomatization precursor **113**, though this task proved to be much trickier than expected, as we discovered the desired styrene-like phenol **113** was quite unstable.[50] Although several conditions allowed us access to phenol **113** (Table 3.4), its instability prevented any sizable quantities to be isolated, with decomposition being observed within minutes of purification, most likely due to air oxidation and potential aromatization. Attempts to utilize crude material from these reactions for the subsequent oxidative dearomatization also failed.

Table 3.4. Access to Unstable Conjugated Phenol **113**.



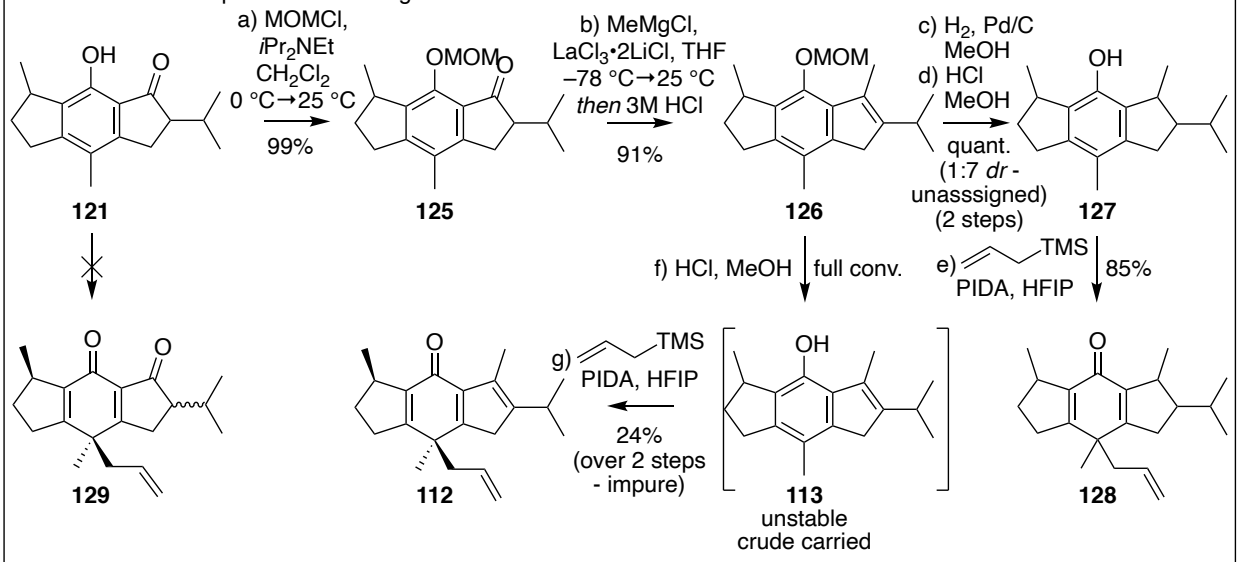
124 **113** UNSTABLE

Entry	Solvent	Temp.	Time	Reagent(s)	Result
1	CH_2Cl_2	0 °C→25 °C	2 h	BBr_3	< 30% - impure
2	$CHCl_3$	50 °C	10 h	TMSI 2-imidazolidone	low conv. (messy)
3	DMF	110 °C	24 h	NaSEt	low conv. (messy)
4	DMF	120 °C (MW)	30 min	LiSEt	30%
5*	DMF	120 °C (MW)	40 min	LiSEt	46%

*Clean NMR, but material decomposed within 15 min of isolation.

Given the inherent instability of conjugated phenol **113**, as well as the inability to utilize crude material from the harsh demethylation conditions, we attempted a stepwise approach (Scheme 3.17). Starting from phenol **121**, we were able to re-protect the phenol as a MOM ether, before performing the subsequent 1,2-methyl addition and tertiary alcohol elimination to yield MOM-protected **126**. To simply test the dearomatization on the tricyclic system, we first hydrogenated the tetrasubstituted olefin, and deprotected the phenol, yielding **127** in quantitative yield with an intriguing 7:1 *dr*. Pleasingly, the oxidative dearomatization produced dienone **128** in 85% yield, the highest yield observed for this transformation across all substrates tested.[20]

Scheme 3.17. Attempts to Circumnavigate Unstable Phenol.[a]



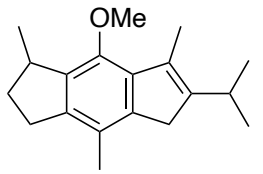
[a] Reagents and conditions: (a) *i*Pr$_2$NEt (10.0 equiv), MOMCl (4.0 equiv), CH_2Cl_2 (0.2 M), 0 °C→25 °C, 16 h, 99%; (b) $LaCl_3$•2LiCl (1.5 equiv), MeMgCl (1.5 equiv), THF (0.16 M), –78 °C→25 °C, 15 min, *then* 3 M HCl, 25 °C, 30 min, 91%; (c) Pd/C (0.12 equiv), MeOH (0.07 M), H_2 (balloon), 1 h, quant.; (d) HCl/MeOH (1:10, 0.1 M), 25 °C, 2 h, quant.; (e) allyl-TMS (6.0 equiv), PIDA (3.0 equiv), HFIP (0.1 M), 25 °C, 10 min, 85%; (f) HCl/MeOH (1:10, 0.15 M), 25 °C, 4 h, quant.; (g) allyl-TMS (6.0 equiv), PIDA (3.0 equiv), HFIP (0.2 M), 25 °C, 10 min, 24%.

With the success of the oxidative dearomatization of the fully substituted phenol, we were hopeful for a similar result if phenol **113** could be obtained in a clean fashion. Starting with MOM-protected **126**, more facile deprotection conditions of HCl in MeOH allowed for full conversion to the unstable **113**, which could then be quickly quenched, extracted, and concentrated, taking care to backfill the rotavap with N_2 to keep air exposure minimal (Scheme 3.17). The crude residue was relatively clean and could then be directly subjected to the oxidative dearomatization conditions to yield dearomatized **112**, albeit in poor yield alongside inseparable impurities.[20] Unfortunately, this body of results began to suggest this may not be a feasible approach to install this quaternary center. With that in mind, we also thought to attempt the dearomatization directly on tricyclic phenol **121**, but failed to yield any desired product **129** under a variety of conditions, even with stronger hypervalent iodide sources such as PIFA and μ-oxo-bridged PIFA.[51]

Attributing the instability of phenol **113** to its indene-like structure and knowing oxidative dearomatization was possible on a fully substituted system (**127**→**128**, Scheme 3.17), we pivoted

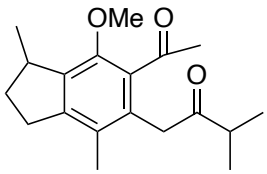
to performing an oxidative cleavage of the tetrasubstituted olefin of **124** first, which we hoped would grant us access to a more stable dearomatization precursor. Once again, this typically straightforward transformation proved fickler than assumed (Table 3.5). Traditional ozonolysis resulted in complex reaction profiles, regardless of solvent and quench. Ruthenium oxide mediated cleavage also led to complete decomposition of the starting material. It was not until we turned to another ruthenium-based catalyst that we began to see the desired reactivity.[52] In 2020, the Albrecht group developed a ruthenium *N,N'*-bis(pyridylidene)oxalamide catalyst (**131**) which showed remarkable activity in the oxidation of styrenyl olefins, inspiring us to test their optimized conditions on **124**. When utilizing 1 mol% catalyst loading at 35 °C (optimized conditions for tetrasubstituted olefins), we were pleased to find 10% yield of cleaved **130**. After a few alterations, we were able to obtain a 43% yield of **130** when utilizing 5 mol% of **131** at 45 °C.

Table 3.5. Oxidative Cleavage of Methyl-Capped Phenol **124**.

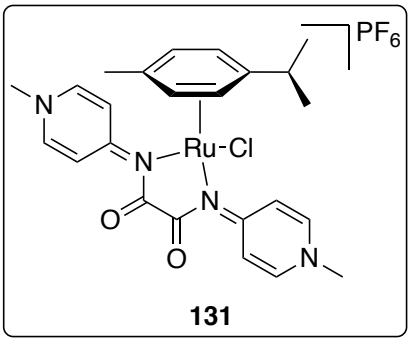


124

Conditions



130

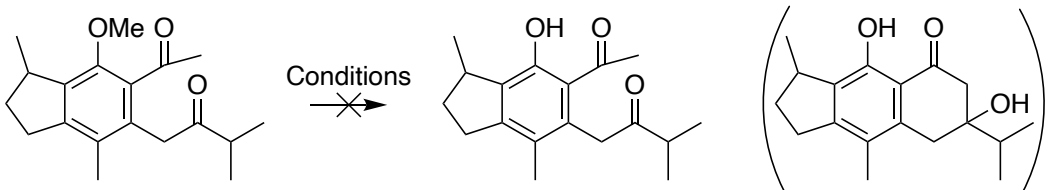


131

Entry	Temp.	Time	Solvent	Reagent(s)	Result
1	–78 °C	5 min	MeOH	O_3, DMS	decomp
2	–78 °C	5 min	CH_2Cl_2	O_3, DMS	decomp
3	–78 °C	5 min	CH_2Cl_2	O_3, PPh_3	decomp
4	25 °C	1 h	EtOAc/H_2O (1:1)	RuO_2•H_2O, $NaIO_4$, TFA	decomp
5	35 °C	30 min	MeCN/CH_2Cl_2/H_2O (1:1:3)	$NaIO_4$, **131** (1%)	10%
6	45 °C	18 h	MeCN/CH_2Cl_2/H_2O (1:1:3)	$NaIO_4$, **131** (1%)	18%
7	45 °C	18 h	MeCN/CH_2Cl_2/H_2O (1:1:3)	$NaIO_4$, **131** (5%)	43%
8	50 °C	18 h	MeCN/CH_2Cl_2/H_2O (1:1:3)	$NaIO_4$, **131** (5%)	40%

Once cleaved, we again needed to demethylate the central phenol. The most traditional condition of BBr_3 unfortunately only led to decomposition of the material (Table 3.6). Upon application of a relatively milder Lewis acid, $AlCl_3$, no reaction was observed, even in refluxing CH_2Cl_2.[53] Once subjected to $AlCl_3$ in CH_2Cl_2 and superheated under microwave radiation, full decomposition was observed. Thiol additives as well as nucleophilic thiolates also led to decomposition.[50a] Finally, when using MgI_2, a potential decomposition pathway was elucidated, as aldol addition product **133** was isolated after heating at 50 °C for 36 h.[54] However, this addition product did not provide a path forward towards cinncassiol F (**2**).

Table 3.6. Attempts to Demethylate Cleaved **130**.



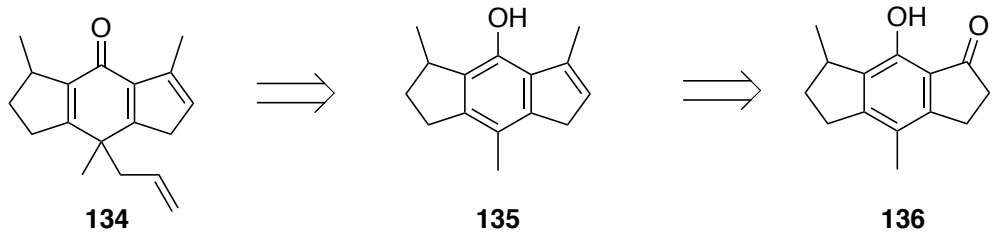
130 **132** **133**

Entry	Temp.	Time	Solvent	Reagent(s)	Result
1	–78 °C→25 °C	1 h	CH_2Cl_2	BBr_3	decomp
2	0°C→25 °C	30 min	CH_2Cl_2	$AlCl_3$	N.R.
3	40 °C	1.5 h	CH_2Cl_2	$AlCl_3$	N.R.
4	70 °C (MW)	30 min	CH_2Cl_2	$AlCl_3$	decomp.
5	0°C→25 °C	2 h	EtSH/CH_2Cl_2 (1:1)	$AlCl_3$	decomp
6	120 °C (MW)	40 min	DMF	LiSEt	decomp
7	50 °C	36 h	Et_2O/THF	MgI_2	41% **133**

Before turning away from the Nazarov cyclization approach, we wanted to examine whether we could take advantage of the inherent symmetry of the 5/6/5-tricyclic core (Scheme 3.18). Since we previously obtained trisubstituted olefin **90** when constructing starting phenol **66** (Scheme 3.12), we hoped to utilize a similar moiety on the right-hand side of the molecule to ultimately deliver dearomatized **134**. By performing an initial Friedel-Crafts acylation on methylated phenol **116** followed by elimination of the primary bromide, enone **138** was furnished in 64% yield over two steps.[55]

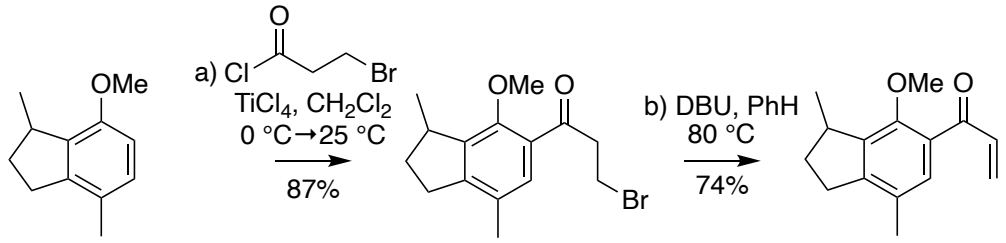
Scheme 3.18. Attempts to Utilize Inherent Symmetry.[a]

A. Retrosynthetic Analysis



134 **135** **136**

B. Forward Synthesis of Nazarov Cyclization Precursor **138**.

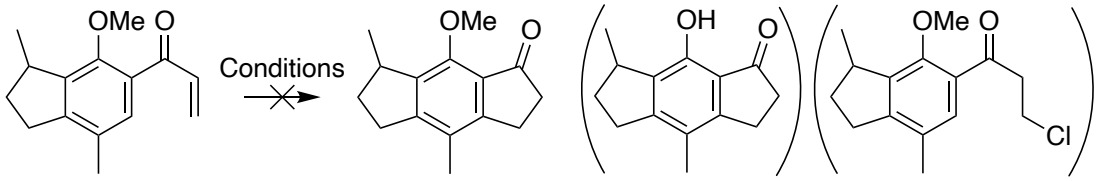


116 **137** **138**

[a] Reagents and conditions: (a) $TiCl_4$ (2.4 equiv), 3-bromopropionyl chloride (2.6 equiv), 0 °C→25 °C, 20 min, 79%; (b) DBU (3.0 equiv), benzene (0.2 M), 80 °C, 1 h, 74%.

With monosubstituted enone **138** in hand, we then set out to screen various Brønsted acid and Lewis acid promoters for the desired Nazarov cyclization (Table 3.7).[56] When utilizing the previously successful H_2SO_4 at 50 °C, we observed some cyclized product (**136**), albeit in low yield, along with concomitant demethylation.[49] Attempting to use lower temperature proved fruitless, with simply a much-reduced yield of **136** obtained. The only other condition tested that resulted in any identifiable reactivity was subjecting **138** to $AlCl_3$ at 25 °C for 18 h, after which trace amounts of the olefin was simply chlorinated (**140**).

Table 3.7. Nazarov Cyclization Trials.



138 **139** **136** **140**

Entry	Temp	Time	Solvent	Reagent	Result
1	50 °C	1 h	—	H_2SO_4	16% **136**
2	0°C→25 °C	2.5 h	—	H_2SO_4	7% **136**
3	85 °C	1 h	—	H_3PO_4	decomp
4	25 °C	18 h	toluene	$AlCl_3$	trace **140**
5	90 °C	30 min	$MeNO_2$	TMSOTf	decomp
6	0°C→25 °C	3 h	CH_2Cl_2	$Sc(OTf)_3$	NR
7	60 °C	18 h	DCE	$Cu(OTf)_2$	NR
8	0°C→25 °C	18 h	CH_2Cl_2	TfOH	decomp

3.2.7 Summary of Nazarov Cyclization Attempts to Fashion Carbon Skeleton

Our hope for the Nazarov cyclization approach was that the required oxidative cleavage of cyclized **124** to access **130** (Table 3.5) would allow for us to circumnavigate the acidity problems we experienced with the anionic oxy-Cope strategy, as the sidechain ketone could be reduced or protected before going through the bis-epoxidation sequence. Pleasingly, the desired Nazarov cyclization proceeded as hoped, delivering the 5/6/5-isoryanodane-type tricycle **120** in just 6 steps (Scheme 3.15), which in turn could be extrapolated to the tetrasubstituted olefin **124** through a simple methyl Grignard addition with subsequent elimination upon acidic work-up (Scheme 3.16). However, further attempts to then demethylate this material proved challenging, as the styrene-type free phenol proved highly sensitive, and decomposition was quite rapid under most conditions. Of note, when the tetrasubstituted olefin was hydrogenated, demethylation was

straightforward, and the oxidative dearomatization process also proceeded in high yield (Scheme 3.17). Attempts to oxidatively cleave the olefin prior to demethylation also presented a roadblock, but we found a recently developed catalyst by the Albrecht group allowed for such a transformation (Table 3.5).[52] Unfortunately, the following demethylation of the phenol led to decomposition, most likely through an aldol pathway (aldol addition product **133** was isolated when subjecting **130** to the mild demethylation conditions of MgI_2, Table 3.6).

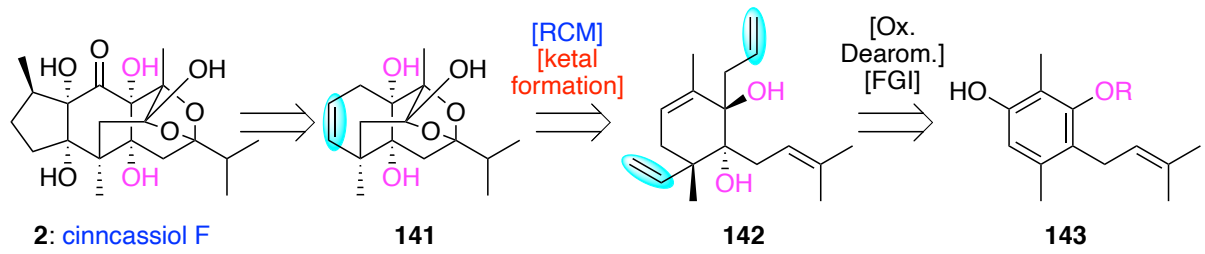
3.3 Studies Toward Cinncassiol F – Bridged Bicycle First Approach

Given the inability to perform late-stage chemoselective oxidative manipulations of the full carbon skeleton to install the central oxygens, as well as the final bridged system of cinncassiol F (**2**), we decided to reorient our approach to the cinncassiol diterpenoid core. Instead of first completing the carbon skeleton, we believed the installation of the bridged bicycle as well as several central oxygens may help prevent some of the chemoselectivity problems we had previously faced. To that end, we propose two approaches featuring a critical ring-closing metathesis to fashion the bridged bicycle as well as two related Conia-ene routes, through which we have been able to rapidly establish the bicyclic system alongside several key oxygens.

3.3.1 Initial Bridge-First Approach Featuring Ring-Closing Metathesis

Taking several lessons from our initial oxidative dearomatization work, we initially hoped to utilize a phenol-type starting material to introduce several points of molecular complexity through an oxidative dearomatization event (Scheme 3.19). However, the difference here is the 6-membered ring being taken advantage of was no longer the central ring of the 5/6/5-tricycle, but instead was the bridging cyclohexane of the bicyclo[3,3,1]nonane. The rigidity required for the biomimetic formation of the hemiketal moiety is envisioned to be introduced through a ring closing metathesis of **142**, where the requisite vinyl and allyl groups are introduced by a Michael-addition

and 1,2-addition, respectively, to establish the bicyclo[3,3,1]nonane.[57] As for the central alcohols, the two highlighted in pink in Scheme 3.19 would be introduced initially, one from the starting material itself and the second through the intramolecular oxidative dearomatization of **143**.

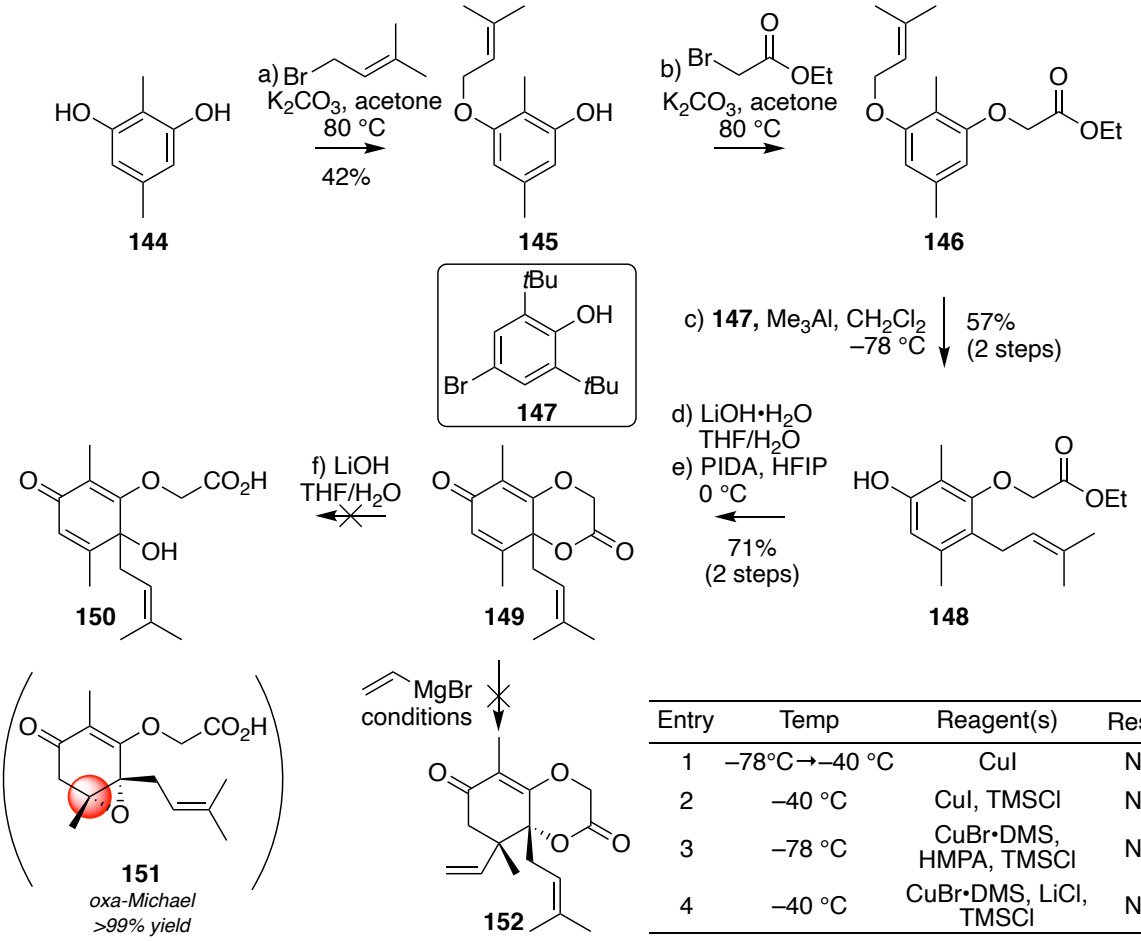


2: cinncassiol F **141** **142** **143**

Scheme 3.19. Retrosynthetic analysis of cinncassiol F (**2**) featuring an oxidative dearomatization and ring closing metathesis sequence to fashion the bridged bicycle system prior to ketal formation and final installation of left-hand ring.

In a forward sense, we have built the dearomatized intermediate **149** from commercially available 2,5-dimethyl resorcinol (**144**, Scheme 3.20), utilizing a known aluminum-promoted Claisen rearrangement of the prenyl group to **148**.[58] Subsequent hydrolysis of the ethyl ester to its carboxylic acid variant allowed for hypervalent iodine-promoted dearomatization, leading to product **149** in 71% yield. From here, we hoped to initially deprotect the tertiary alcohol to unveil **150** and subsequently introduce the α-hydroxyl group required for the hemiketal, however such attempts led to quantitative conversion to epoxide **151**.[59] Although undesired, this suggests dienone **149** could serve as a suitable Michael acceptor, potentially allowing for the introduction of the vinyl sidechain whilst still in the protected form. However, when attempting to utilize this Michael acceptor for a vinyl cuprate addition we observed no reaction, even with various copper sources and additives like HMPA, TMSCl, and LiCl. This low reactivity could potentially stem from both the electronics of the enone, as it is less electron deficient than a cyclohexenone due to its conjugation with the enol ether, as well as the steric congestion arising from the neighboring fully substituted center.

Scheme 3.20. Attempted Use of Oxidative Dearomatization toward Early Installation of Bridged System.[a]

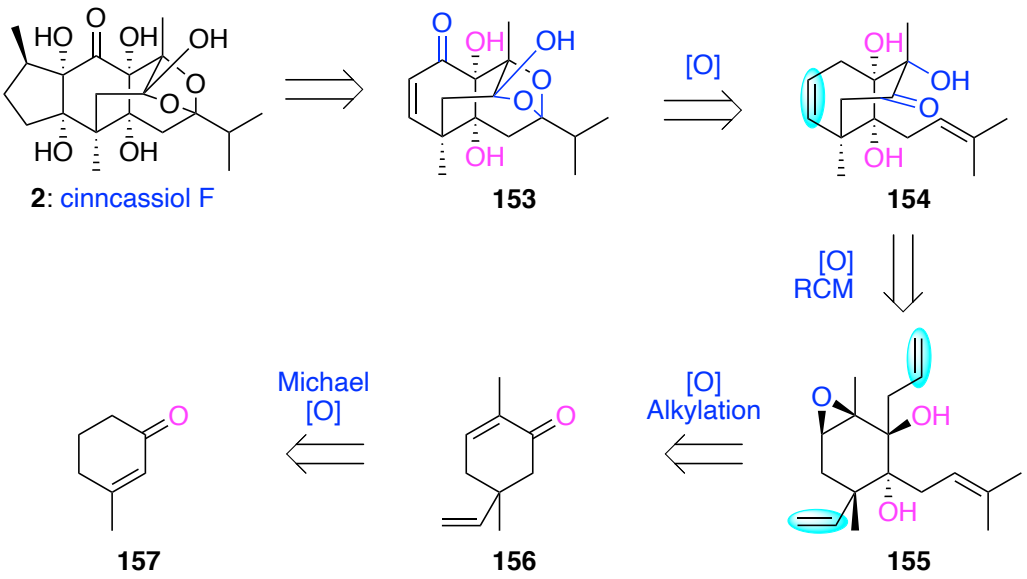


Entry	Temp	Reagent(s)	Result
1	–78°C→–40 °C	CuI	NR
2	–40 °C	CuI, TMSCl	NR
3	–78 °C	CuBr•DMS, HMPA, TMSCl	NR
4	–40 °C	CuBr•DMS, LiCl, TMSCl	NR

[a] Reagents and conditions: (a) prenyl bromide (1.0 equiv), **144** (2.0 equiv), K_2CO_3 (5.0 equiv), acetone (0.1 M), 80 °C, 8 h, 42%; (b) ethyl bromoacetate (1.2 equiv), K_2CO_3 (5.0 equiv), acetone (0.1 M), 80 °C, 8 h, quant.; (c) **147** (4.0 equiv), Me_3Al (2.0 equiv), CH_2Cl_2, –78 °C, 2 h, 57%; (d) LiOH•H_2O (4.0 equiv), THF/H_2O (1:1, 0.05 M), 25 °C, 20 min, quant.; (e) PIDA (1.1 equiv), HFIP (0.07 M), 0 °C, 15 min, 71%; (f) LiOH•H_2O (4.0 equiv), THF/H_2O (1:1, 0.05 M), 25 °C, 10 min, quant.

3.3.2 Second Generation Bridge-First Approach Featuring a Michael Addition

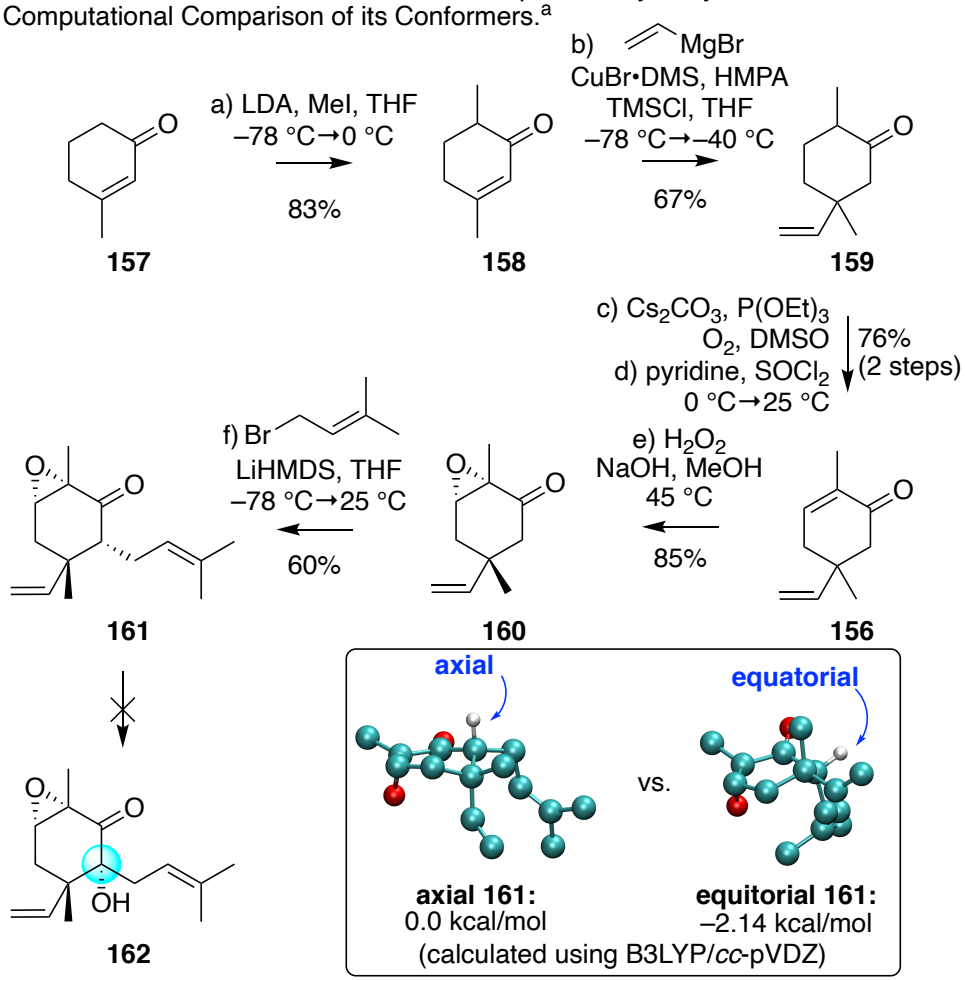
Although we were unable to utilize a Michael addition to fashion the desired quaternary center post oxidative dearomatization, we believed we could perform this transformation in a more efficient manner on a simpler system (Scheme 3.21). Still envisioning a ring-closing cross metathesis to obtain ketal formation precursor **154** from allylated **155**, we could trace this fully functionalized cyclohexane core back to 3-methyl-2-cyclohexenone (**157**).



Scheme 3.21. Retrosynthetic analysis of cinncassiol F (**2**) featuring an initial Michael addition to install central quaternary center and ring closing metathesis to fashion the bridged bicycle system.

As proposed, starting from 3-methyl-2-cyclohexenone (**157**), we were able to quickly construct cyclohexenone **156** in four steps (Scheme 3.22). After a regioselective α-methylation of **157**, the quaternary center was efficiently fashioned through the desired vinyl Michael addition, requiring HMPA as an additive along with TMSCl, obtaining **159** in 67% yield.[60] From here, the subsequent enone of **156** was introduced through a two-step procedure in which an initial regioselective α-hydroxylation promoted by Cs_2CO_3 allowed for a subsequent elimination using $SOCl_2$ in pyridine, providing the internal enone **156** as the sole product.[61] Of note, other oxidation methods all resulted in low yield and low regioselectivity. For instance, IBX and Saegusa oxidation of the analogous silyl-enol ether of **159** resulted in yields < 20% with mixtures of *endo*/*exo*-olefin products.[43, 62]

Scheme 3.22. Forward Push to Attempted α-Hydroxylation of **162** and Computational Comparison of its Conformers.[a]



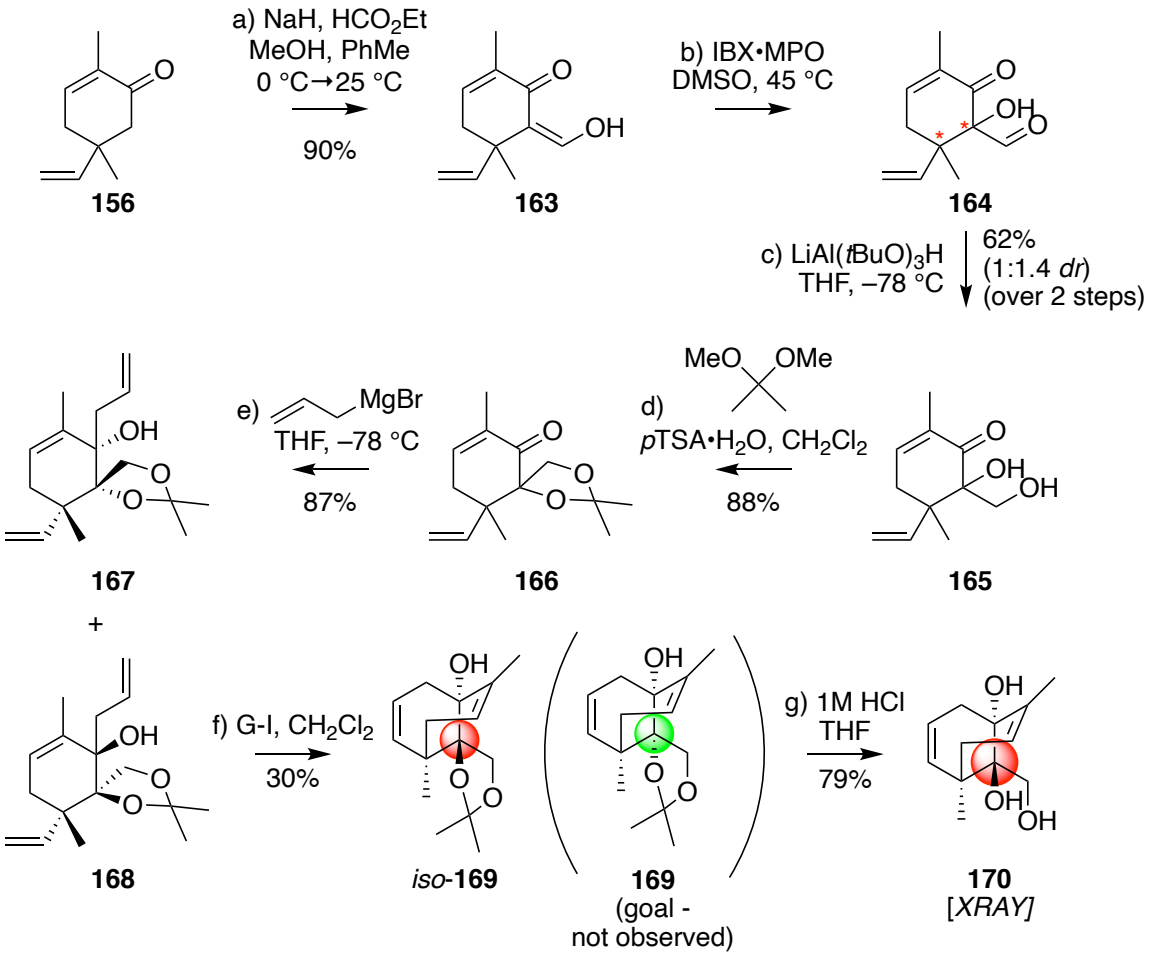
[a] Reagents and conditions: (a) *i*Pr_2NH (1.2 equiv), *n*BuLi (1.1 equiv), MeI (2.0 equiv), THF (0.5 M), –78 °C→0 °C, 1 h, 83%; (b) CuBr•DMS (0.15 equiv), vinylmagnesium bromide (2.1 equiv), HMPA (6.0 equiv), TMSCl (5.0 equiv), –78°C→–40 °C, 3 h, 67%; (c) Cs_2CO_3 (0.5 equiv), $P(OEt)_3$ (2.0 equiv), DMSO (0.28 M), 25 °C, 20 h, 83%; (d) $SOCl_2$ (2.0 equiv), pyridine (0.1 M), 0 °C→25 °C, 3 h, 92%; (e) H_2O_2 (10.0 equiv), NaOH (3.0 equiv), MeOH (0.1 M), 45 °C, 1 h, 85%; (f) LiHMDS (1.2 equiv), prenyl bromide (1.2 equiv), –78 °C→25 °C, 20 h, 34%, 46% brsm.

With **156** in hand, only a few steps were left to obtain metathesis precursor **155** (Scheme 3.22). The subsequent nucleophilic epoxidation proceeded smoothly with alkaline hydrogen peroxide at 45 °C, albeit in a 1:1 diastereomeric mixture. Nonetheless, we could push forward and install the necessary prenyl sidechain through another α-alkylation utilizing LiHMDS and prenyl bromide.[63] Of note, this transformation was diastereoselective, and was believed to result from

approach of the prenyl group from the same face as the vinyl substituent, as this would allow for the smaller methyl group to sit axially, effectively blocking the top face. Disappointingly, any attempts to then perform the following α-hydroxylation failed. When observing **161** from a computational standpoint, we were surprised to find a preference of about 2.1 kcal/mol for the α-proton to sit equatorially, which would prevent the necessary deprotonation of that position. This then prompted us to consider how we may install that tertiary alcohol earlier on in the sequence to lock in the necessary stereochemistry and circumvent the observed deprotonation dilemma.

Recalling a previous byproduct from the initial oxidative dearomatization approach in which we observed α-hydroxylation of our 1,3-dicarbonyl **95** when trying to oxidize to the dienedione **97** with IBX (Table 3.1), we wondered if we could utilize that same reactivity in this scenario. To test this, we performed an α-formylation of **156** and were pleased to find that subjecting it to IBX•MPO in DMSO at 45 °C, we observed clean conversion to the α-hydroxylated product (**164**) as an inseparable 1:1.4 diastereomeric mixture (Scheme 3.23).[43, 64] From here, we were able to then reduce the resultant aldehyde with $LiAl(tBuO)_3H$ before acetonide-protecting the 1,2-diol, producing **166** in 88% yield. With protected enone **166** in hand, we could then install the final allyl sidechain to furnish metathesis precursor **167**/**168** in 87% yield. Interestingly, this 1,2-addition proceeded in a diastereoselective fashion. Nonetheless, we were able to push forward and perform the metathesis of the vinyl and allyl sidechains with Grubbs I initiator, yielding bridged bicycle *iso*-**169**.[65] Unfortunately, X-ray crystallographic analysis of the hydrolyzed **170** revealed we had obtained the undesired diastereomer from the 1,2-addition in a mismatch manner with the allyl group attacking from the same face as the methylene of the fully substituted carbon center.

Scheme 3.23. Forward Push through Metathesis Showing Undesired Diastereoselectivity.[a]

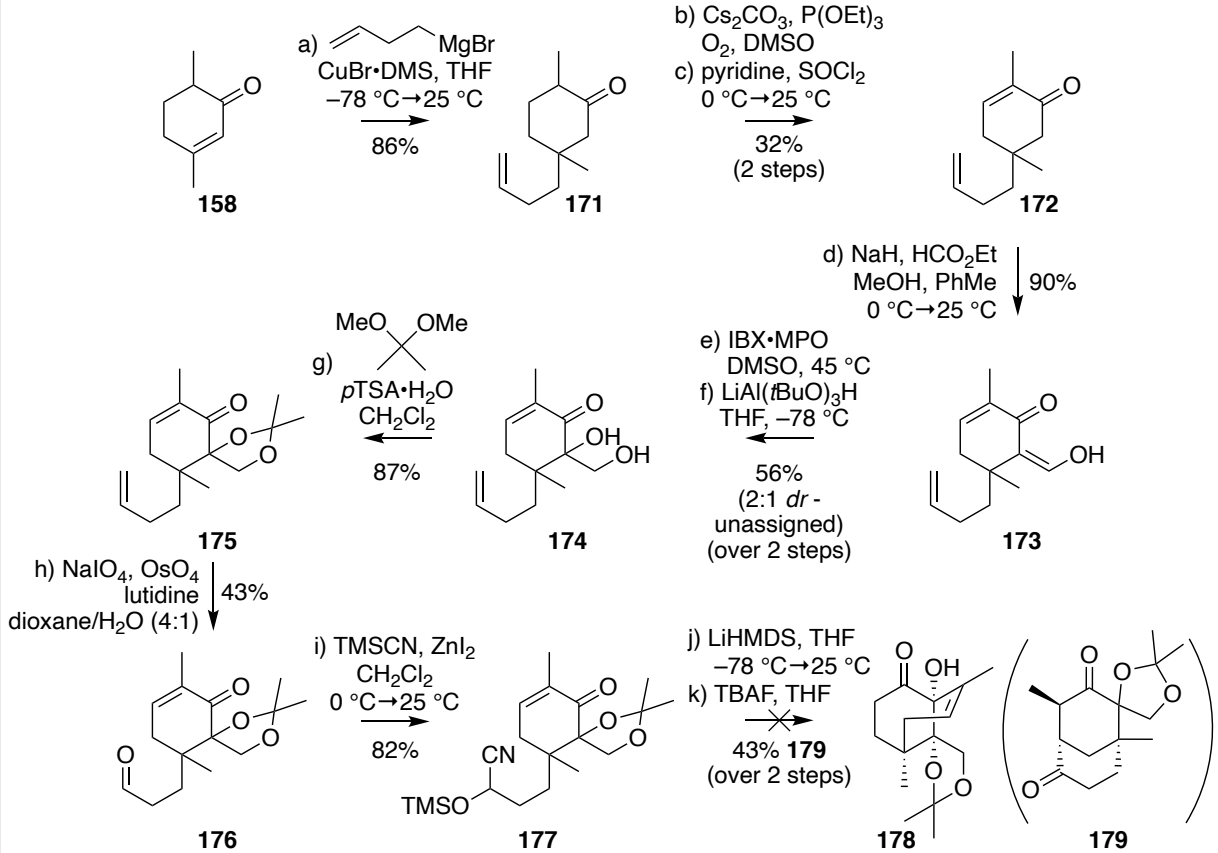


[a] Reagents and conditions: (a) ethyl formate (7.0 equiv), NaH (3.0 equiv), MeOH (1.0 equiv), toluene (0.5 M), 0 °C→25 °C, 8 h, 90%; (b) IBX•MPO (3.0 equiv), DMSO (0.2 M), 45 °C, 30 min, 82% yield (1:1.4 *dr*); (c) LiAl(*t*BuO)$_3$H (3.0 equiv), THF (0.15 M), –78 °C, 30 min, 76% (62% over 2 steps); (d) 2,2-dimethoxypropane (5.0 equiv), *p*TSA•H$_2$O (0.1 equiv), CH_2Cl_2 (0.1 M), 25 °C, 8 h, 88%; (e) allylmagnesium bromide (2.0 equiv), THF (0.1 M), –78 °C, 5 min, 87%; (f) Grubbs 1st generation initiator (0.1 equiv), CH_2Cl_2 (0.1 M), 25 °C, 3 h, 30%; (g) 1M HCl/THF (1:1, 0.05 M), 25 °C, 12 h, 79%.

To hopefully force the desired selectivity, we altered the mode of attack from an intermolecular Grignard addition to an intramolecular umpolung addition to the enone. Utilizing a homoallylic Michael-addition in place of the original vinyl Michael-adduct, we were able to push through the same sequence as before to produce protected diol **175** in 7 steps from methylated enone **158** (Scheme 3.24).[66] From protected diol **175**, we were pleased to find a Lemieux-Johnson oxidation allowed for us to access the desired aldehyde **176** in 43% yield, which could then be

further converted into TMS-protected cyanohydrin **177** in 82% yield using TMSCN and ZnI_2.[31, 67] With the umpolung precursor in hand, a subsequent lithiation resulted in the desired deprotonation, but sadly, although unsurprisingly, we only observed 1,4-addition into the enone (**179**), instead of the desired 1,2-addition. Given that the desired stereochemistry of the bridged system was unable to be fashioned through an intermolecular Grignard addition or an intramolecular umpolung addition, we realized we may find more success in fashioning the bridged system in a more direct manner, namely through a Conia-ene cyclization.

Scheme 3.24. Forward Push through Undesired Umpolung Addition.[a]



[a] Reagents and conditions: (a) CuBr•DMS (0.2 equiv), homoallylmagnesium bromide (1.0 equiv), THF (0.35 M), –40 °C, 30 min, *then* **158** (1.0 equiv), THF (2.0 M), –78 °C→25 °C, 1 h, 86%; (b) Cs_2CO_3 (0.5 equiv), $P(OEt)_3$ (2.0 equiv), O_2 (balloon), DMSO (0.5 M), 25 °C, 20 h, 92%; (c) $SOCl_2$ (2.0 equiv), pyridine (0.15 M), 0 °C→25 °C, 8 h, 35% (32% over 2 steps); (d) ethyl formate (7.0 equiv), NaH (3.0 equiv), MeOH (1.0 equiv), toluene (0.5 M), 0 °C→25 °C, 8 h, 90%; (e) IBX•MPO (3.0 equiv), DMSO (0.2 M), 45 °C, 30 min, 83% yield (2:1 *dr*); (f) LiAl(*t*BuO)$_3$H (3.0 equiv), THF (0.15 M), –78 °C, 30 min, 68% (diastereomers separated - 56% over 2 steps); (g) 2,2-dimethoxypropane (5.0 equiv), *p*TSA•H_2O (0.1 equiv), CH_2Cl_2 (0.1 M), 25 °C, 8 h, 87%; (h) $NaIO_4$ (2.0 equiv), lutidine (4.0 equiv), OsO_4 (0.05 equiv), dioxane/H_2O (4:1, 0.1 M), 25 °C, 1.5 h, 43%; (i) TMSCN (1.2 equiv), ZnI_2 (0.2 equiv), 0 °C→25 °C, 1 h, 82%; (j) LiHMDS (1.2 equiv), THF (0.08 M), –78 °C→25 °C, 30 min; (k) TBAF (3.0 equiv), THF (0.1 M), 25 °C, 5 min, 43% **179** (over 2 steps).

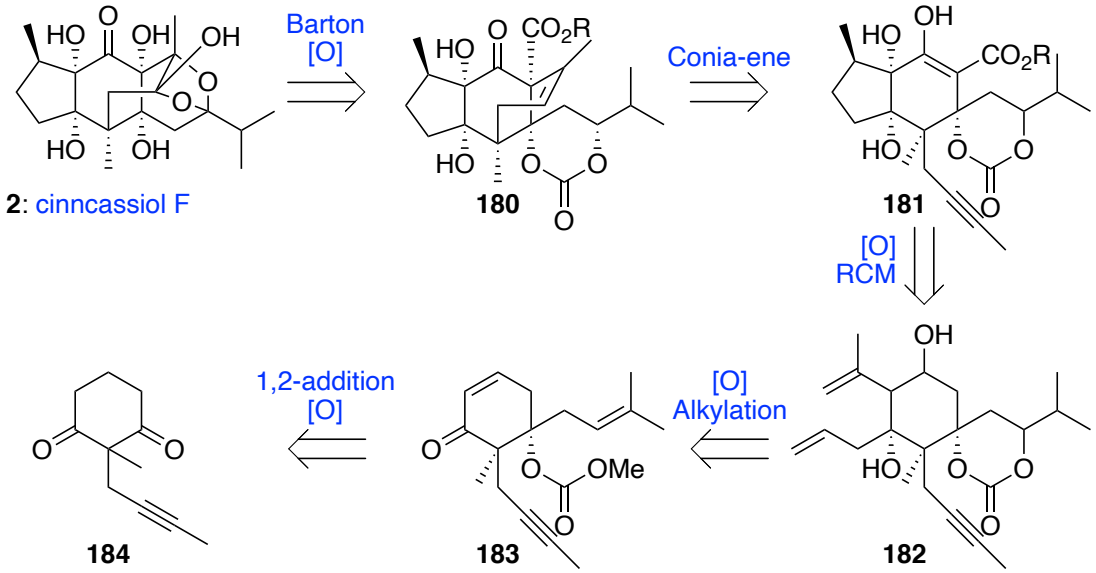
3.3.3 Summary of Initial Bridge-First Efforts

Having switched to the bridge-first approach, we began our investigations with our sights set on fashioning the bridged system through an intramolecular cross metathesis between a vinyl and allyl sidechain. The critical difference here being the starting 6-membered ring on which the rest of the target was to be constructed was actually that of the bridging cyclohexane of the bicyclo[3,3,1]nonane, not the central ring of the 5/6/5 tricyclic isoryanodane-type core. Pleasingly, we were able to achieve prenylated **161** in just 6 steps from commercially available material, but any attempts to perform the requisite α-hydroxylation failed to produce **162**, which we were able to rationalize through ground state energy calculations (Scheme 3.22). Intriguingly, there was a 2.1 kcal/mol preference for the α-proton to sit equatorially, effectively preventing its deprotonation, forcing us to consider how we may install that tertiary alcohol at an earlier stage. Thankfully, we previously found an efficient α-hydroxylation of a 1,3-dicarbonyl during our initial oxidative dearomatization studies (**95→99**, Table 3.1) when utilizing IBX, and although undesired for that route, we postulated whether we could utilize that reactivity to our advantage here. Pleasingly, we observed clean conversion to the α-hydroxylated product (**164**) after forming the 1,3-dicarbonyl through a formylation process, allowing us to extrapolate this material further to allylated **167/168**, setting the stage for the bridge-forming cross-metathesis (Scheme 3.23). To our disappointment, subsequent X-ray crystallographic analysis showed the 1,2-addition of the allyl group was selective for the undesired diastereomer, once again leading us to rethink our approach.

3.3.4 Third Generation Bridge-First Approach Featuring a Conia-Ene Cyclization

When considering efficient ways to construct bridged bicycles, one of the most powerful methods available is a Conia-ene cyclization, as it allows for highly regioselective functionalization as well as provides further reactive handles within the resulting product (i.e.

ketone, ester, and olefin). As cinncassiol F (**2**) and its related compounds exhibit a high level of oxidation, this patterning of functionality maps nicely to our target molecules. Thus, we set out to build **2** with a late-stage Conia-ene cyclization to provide **180** from **181**, requiring a few final oxidative manipulations to install the hemiketal moiety (Scheme 3.25). Ester **181** was envisioned to be developed through the ring closing metathesis of the allyl and isopropenyl sidechains of **182** followed by α-hydroxylation, hydrogenation of the internal olefin, and introduction of the methyl ester utilizing Mander's reagent. The secondary alcohol and alkenyl sidechains of **182** could in turn be established through a nucleophilic epoxidation of **183** followed by a directed epoxide opening sequence recently developed by Coltart and coworkers, with a subsequent allyl 1,2-addition into the resulting ketone.[68] Finally, enone **183** could reasonably be traced back to dicarbonyl **184**.

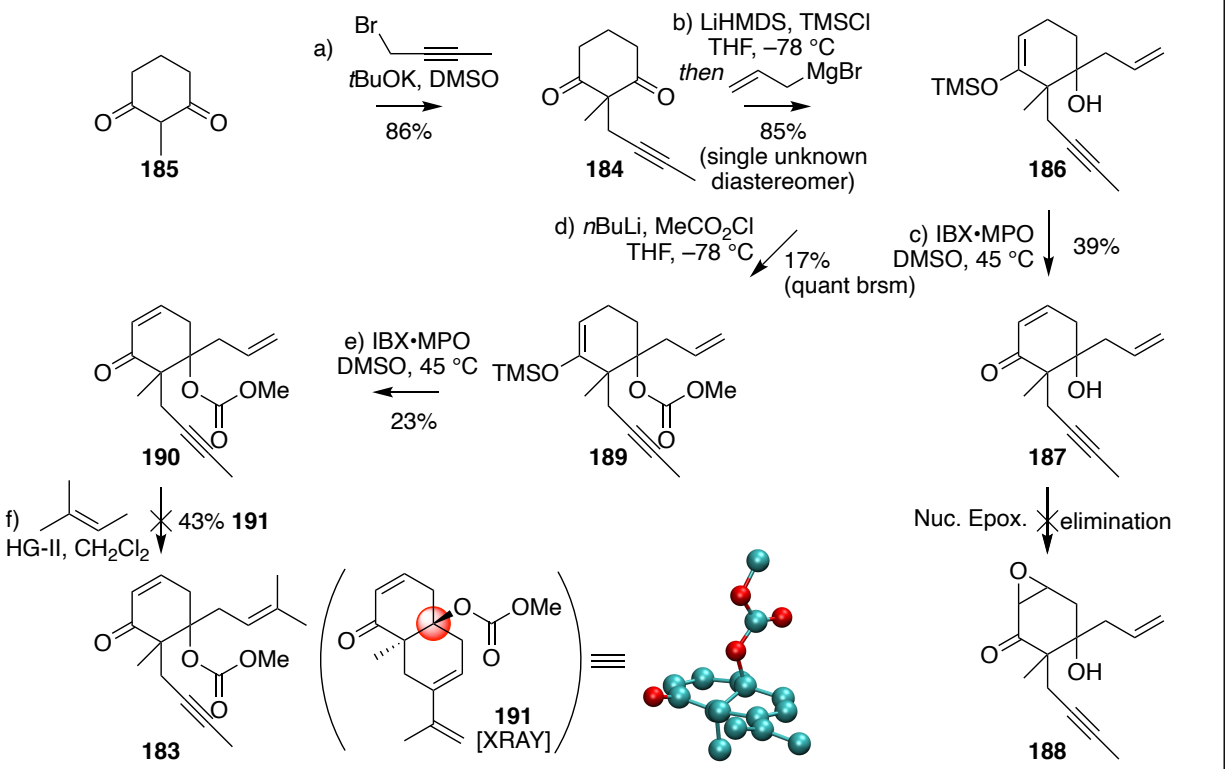


Scheme 3.25. Retrosynthetic analysis of cinncassiol F (**2**) featuring a late-stage Conia-ene cyclization to install bridged bicycle.

In a forward sense, 2-methyl-1,3-cyclohexanedione (**185**) was alkylated with 4-bromo-2-butyne to yield the desired dicarbonyl **184**, immediately establishing the central quaternary center of cinncassiol F (**2**, Scheme 3.26).[69] Initially, we hoped to install the epoxide at an early stage to

facilitate the chemoselective etherification of **183** to **182**. To this end, a monoallylation of **184** could be effected by initially trapping one of the carbonyls as a silyl enol ether upon enolization with LiHMDS before the introduction of allylmagnesium bromide, producing **186** in 85% yield. Interestingly, a single diastereomer was observed, suggesting the quaternary center provides strong control over the facial selectivity of the nucleophilic addition. Unfortunately, the flexibility of **186** did not allow for any diagnostic nOe interactions to help elucidate the diastereomer being produced. Nonetheless, we were pleased to find we could push forward through IBX oxidation to the respective enone (**187**) albeit in modest yield (39%), setting the stage for the nucleophilic epoxidation.[43] Unfortunately, upon exposure to base, we once again observed problems with elimination, suggesting the tertiary alcohol may need to be protected prior to enone formation.

Scheme 3.26. Attempted Late-Stage Conia-ene Approach.[a]



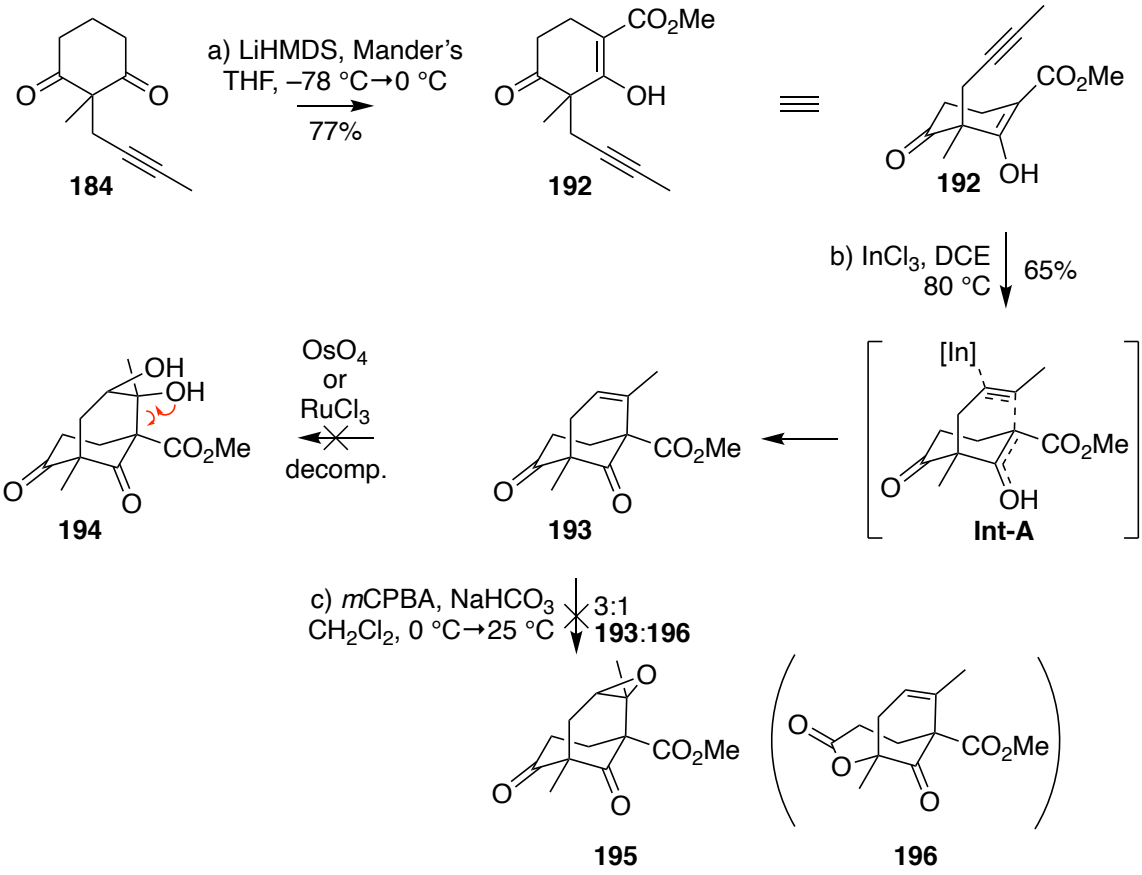
[a] Reagents and conditions: (a) *t*BuOK (1.0 equiv), 1-bromo-2-butyne (1.1 equiv), DMSO (0.5 M), 25 °C, 16 h, 86%; (b) LiHMDS (1.2 equiv), THF (0.1 M), –78 °C, 1 h, *then* TMSCl (1.1 equiv), –78 °C, 5 min, *then* allylmagnesium bromide (3.0 equiv), –78 °C, 5 min, 85% (single diastereomer); (c) IBX (2.0 equiv), MPO (2.0 equiv), DMSO (0.2 M), 45 °C, 1.5 h, 38%; (d) *n*BuLi (2.5 equiv), THF (0.1 M), –78 °C, 1 h, *then* methyl chloroformate (4.0 equiv), –78 °C, 2 h, 17%, quant. brsm; (e) IBX (2.0 equiv), MPO (2.0 equiv), DMSO (0.2 M), 45 °C, 1.5 h, 23%; (f) Hoveyda-Grubbs 2nd Generation initiator (0.2 equiv), CH_2Cl_2/2-methyl-2-butene (1:1, 0.02 M), 25 °C, 12 h, 40% **191**, 80% brsm.

Although low conversion was consistently observed, we were able to protect the tertiary alcohol of **186** with methyl chloroformate (Scheme 3.26). Of note, the only base allowing for successful deprotonation of this buried alcohol was *n*BuLi, producing **189** in 17% yield (quantitative based on the recovered starting material). The subsequent IBX-mediated oxidation to enone **190** also proceeded in lower yield (23%) but allowed for enough material throughput to attempt the desired cross metathesis with 2-methyl-2-butene.[43] Intriguingly, although 2-methyl-2-butene was used as a cosolvent, only the intramolecular enyne metathesis product, bicyclic **191**, was observed in 43% yield. Although undesired, **191** was obtained as a while crystalline solid, allowing for X-ray crystallographic analysis, revealing that the initial 1,2-addition of the allyl

group was unfortunately selective for the undesired diastereomer. Although both the reaction did not proceed as planned and the diastereomer was incorrect, we were able to adjust our approach to hopefully correct for both shortcomings by fashioning the bridged bicycle first before introducing the sidechain.

Instead of delaying the construction of the bridged system, we pivoted to establishing the central bicyclic core at a much earlier stage. To do this, in lieu of the original mono-allylation of **184**, we did a mono-acylation utilizing Mander's reagent to deliver **192** (Scheme 3.27).[70] From here, the stage was set to perform the critical Conia-ene cyclization, which proceeded smoothly in the presence of stoichiometric $InCl_3$ at 80 °C in DCE.[71] Of note, a low concentration (0.06 M) is critical for the success of this reaction, as higher concentrations proved to yield complex reaction mixtures. With **193** in hand, we hoped to then oxidize the trisubstituted olefin through a dihydroxylation event, however we consistently found full decomposition of the starting material regardless of the conditions screened, be it osmium or ruthenium catalyzed. When monitoring such attempts, a clean reaction profile was observed by TLC when utilizing mostly neutral conditions (i.e. OsO_4 and NMO in acetone/H_2O), but we were disappointed to once again find full decomposition upon work-up. It is believed that the dihydroxylation proceeded as desired, but simple deprotonation of the resulting tertiary alcohol could then lead to a retro-aldol, releasing the malonate-type 1,3-dicarbonyl of the central bicyclic core. To circumvent this undesired reactivity, we tried to epoxidize the olefin instead, but unfortunately observed a 3:1 mixture of the starting **193** and Baeyer-Villiger product **196**. Thus, we knew we needed to remove the functionality of the various carbonyls before tackling the oxidation of the trisubstituted olefin.

Scheme 3.27. Attempted Early-Stage Oxidation of Conia-ene Product.[a]

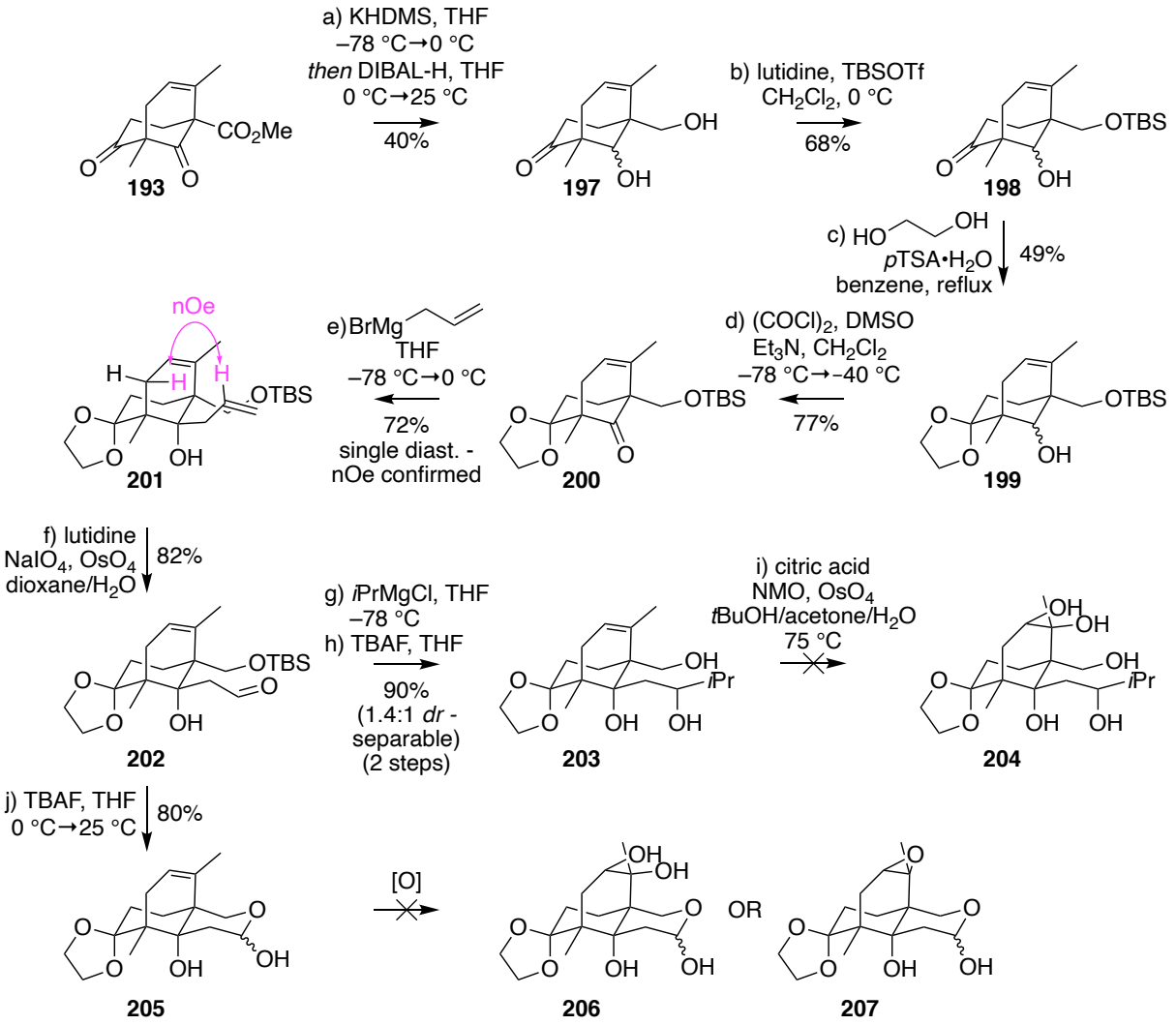


[a] Reagents and conditions: (a) LiHMDS (1.2 equiv), THF (0.28 M), –78 °C, 1 h, *then* Mander's (1.1 equiv), –78 °C→0 °C, 20 min, 77%; (b) $InCl_3$ (1.0 equiv), DCE (0.06 M), 80 °C, 12 h, 65%; (c) $NaHCO_3$ (3.0 equiv), *m*CPBA (2.0 equiv), CH_2Cl_2 (0.04 M), 0 °C→25 °C, 4 h, 3:1 **193**:**196**.

Initially, we performed a full reduction of the methyl ester and bridgehead ketone of **193** by first enolizing the less-hindered ketone with KHMDS before the introduction of DIBAL-H at 0 °C (Scheme 3.28).[71] Upon warming to 25 °C, we were happy to find a 40% yield of diol **197** with an inconsequential 2:1 mix of diastereomers about the secondary alcohol. After protection of the primary alcohol and ketone along with oxidation of the bridgehead alcohol, we were pleased that our subsequent allyl addition into the resulting ketone yielded **201** in a diastereoselective fashion. Furthermore, 1D NOE analysis of this intermediate showed a correlation between one allylic proton of the bridged system and the monosubstituted olefin proton of the allyl group,

suggesting we had successfully obtained our desired diastereomer (**201**, nOe correlations highlighted in pink). Lemieux-Johnson oxidation of **201** then allowed for exploration of various oxidative chemistry.[31] First, an initial isopropyl Grignard addition followed by TBS deprotection provided diol **203** (with a 1.4:1 *dr* from the 1,2-addition process). Unfortunately, subsequent attempts to dihydroxylate the trisubstituted olefin proved challenging, with traditional conditions of NMO and OsO_4 providing no reaction. When utilizing a citric acid buffer, though, we observed full decomposition of the starting material.[30b] Alternatively, if the primary alcohol was desilylated first, the instantaneous formation of lactol **205** was observed. Unfortunately, all attempts to either epoxidize or dihydroxylate the trisubstituted olefin once again failed, showing no reaction in each case. This body of results, in conjunction with those observed with the Conia-ene product (**193**), suggest the oxidation of this position is quite sensitive to the steric environment. To potentially solve this problem of steric encumbrance, as well as remove a source of potential retro-Aldol complications, we then turned our sights to exploring a decarboxylation/oxygenation sequence of the methyl ester.

Scheme 3.28. Elongated Reduction/Oxidation Path to Explore Manipulations of Right-Hand Side of Bicycle **193**.[a]

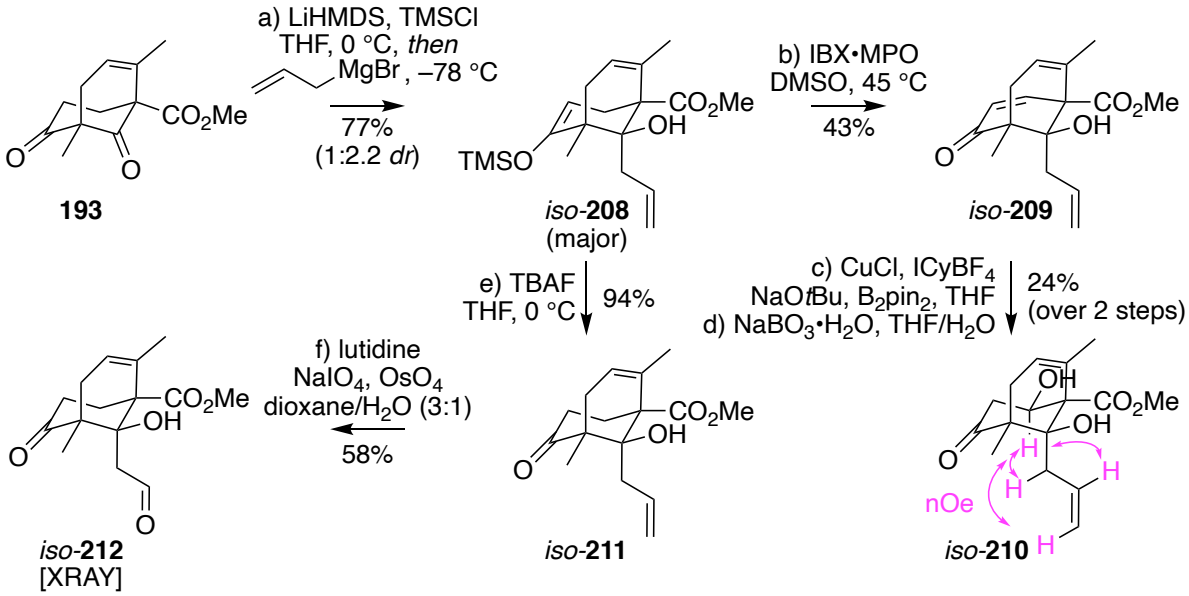


[a] Reagents and conditions: (a) KHMDS (2.0 equiv), THF (0.1 M), –78 °C→0 °C, 45 min, *then* DIBAL-H (4.2 equiv), 0 °C→25 °C, 8 h, 40%; (b) lutidine (3.0 equiv), TBSOTf (1.05 equiv), CH_2Cl_2 (0.1 M), 0 °C, 5 min, 68%; (c) ethylene glycol (15.0 equiv), *p*TSA•H_2O (0.1 equiv), benzene (0.06 M), reflux (Dean-Stark), 2 h, 49%; (d) $(COCl)_2$ (5.0 equiv), DMSO (10.0 equiv), CH_2Cl_2 (0.1 M), –78 °C, 15 min, *then* **199** (1.0 equiv), –78 °C, 1 h, *then* Et_3N (20.0 equv), –78 °C→–40 °C, 1 h, 77%; (e) allylmagnesium bromide (2.0 equiv), THF (0.1 M), –78°C→0 °C, 35 min, 72%; (f) lutidine (2.0 equiv), $NaIO_4$ (4.0 equiv), OsO_4 (0.05 equiv), dioxane/H_2O (3:1, 0.05 M), 1 h, 82%; (g) isopropylmagnesium chloride (2.2 equiv), THF (0.1 M), –78 °C→0 °C, 5 min, 90% combined (1.4:1 *dr*, separable); (h) TBAF (4.0 equiv), THF (0.1 M), 25 °C, 5 min, quant.; (j) TBAF (2.2 equiv), THF (0.06 M), 0 °C→25 °C, 20 min, 80%.

Once again utilizing the enolizable ketone to our advantage, we were able to introduce the allyl sidechain directly on Conia-ene product **193** in a chemoselective fashion, yielding *iso*-**208** in a separable 1:2.2 *dr*, in which the enolate was captured as the TMS-enol ether (Scheme 3.29). Unfortunately, we found through two different means that the major diastereomer was the undesired *iso*-**208**. By oxidizing the silyl enol ether to the respective enone with IBX•MPO,

followed by a borylation/oxidation sequence, 1D NOE analysis showed strong correlations between the allylic and olefinic protons of the allyl sidechain with the α-proton of the secondary alcohol of *iso*-**210**.[43, 72] Furthermore, X-ray crystallographic analysis of aldehyde *iso*-**212** (arising from desilylation of *iso*-**208** followed by Lemieux-Johnson oxidation of the allyl group) gave unambiguous proof that the major diastereomer unfortunately had the allyl group sitting axially.[31]

Scheme 3.29. Confirmation of Undesired Diastereoselectivity with Silyl Enol Ether.[a]

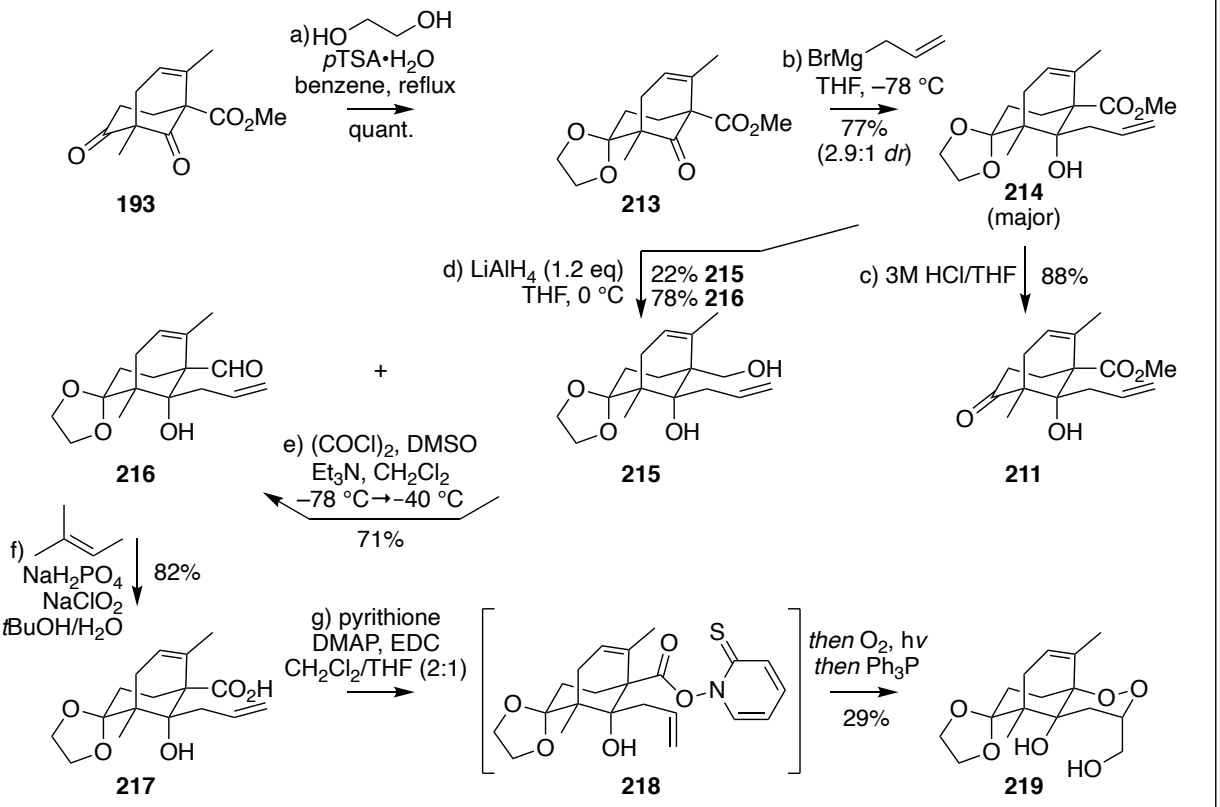


[a] Reagents and conditions: (a) LiHMDS (2.0 equiv), TMSCl (1.5 equiv), THF (0.1 M), 0 °C, 30 min, *then* allylmagnesium bromide (5.0 equiv), –78 °C, 1.5 h, 77% (1:2.2 *dr* - separable); (b) IBX (2.0 equiv), MPO (2.0 equiv), DMSO (0.2 M), 45 °C, 2 h, 43%; (c) CuCl (1.0 equiv), $ICyBF_4$ (0.5 equiv), NaO*t*Bu (2.0 equiv), THF (0.05 M), 25 °C, 1 h, *then iso*-**209** (1.0 equiv), B_2pin_2 (1.5 equiv), 12 h, 34%; (d) $NaBO_3•H_2O$ (10.0 equiv), THF/H_2O (1:1, 0.07 M), 25 °C, 72%; (e) TBAF (2.0 equiv), THF (0.1 M), 0 °C, 5 min, 94%; (f) lutidine (2.0 equiv), $NaIO_4$ (4.0 equiv), OsO_4 (0.05 equiv), dioxane/H_2O (3:1, 0.1 M), 1 h, 58%

Given our previous diastereoselective allyl addition into ketal protected **200** (Scheme 3.28), we were curious to see whether the introduction of an sp^3 center would assist in this case as well. To that end, we were able to quantitatively ketalize the less hindered ketone to yield **213**. Pleasingly, our hypothesis was correct, and we were able to obtain our desired allylated diastereomer **214** in a 2.9:1 *dr* (determined by deprotection of the ketal to produce **211**, Scheme 3.30). With efficient access to the desired diastereomer, we then pushed forward toward carboxylic

acid **217**. Intriguingly, when subjecting ester **214** to $LiAlH_4$ at 0 °C, the reaction would stall, allowing direct formation of aldehyde **216**, which could then be oxidized to **217** under traditional Pinnick conditions.

Scheme 3.30. Diastereoselectivity Reversal Using sp^3 Center and Unexpected Decarboxylative Cyclization.[a]



[a] Reagents and conditions: (a) ethylene glycol (15.0 equiv), *p*TSA•H_2O (0.1 equiv), benzene (0.06 M), reflux (Dean-Stark), 4 h, quant.; (b) allylmagnesium bromide (3.0 equiv), THF (0.1 M), –78°C, 30 min, 77% (2.9:1 *dr* - separable); (c) 3M HCl/THF (1:1, 0.1 M), 25 °C, 1 h, 88%; (d) $LiAlH_4$ (1.2 equiv), THF (0.1 M), 0 °C, 30 min, 22% **215**, 78% **216**; (e) $(COCl)_2$ (5.0 equiv), DMSO (10.0 equiv), CH_2Cl_2 (0.1 M), –78 °C, 15 min, *then* **215** (1.0 equiv), –78 °C, 1 h, *then* Et_3N (20.0 equv), –78 °C→–40 °C, 1 h, 71%; (f) NaH_2PO_4 (10.0 equiv), $NaClO_2$ (15.0 equiv), 2-methyl-2-butene/ *t*BuOH/H_2O (1:1:1, 0.03 M), 25 °C, 12 h, 82%; (g) DMAP (1.5 equiv), EDC (1.5 equiv), pyrithione (1.5 equiv), CH_2Cl_2/ THF (2:1, 0.05 M), 25 °C (dark), 12 h, *then* O_2, h*ν*, 25 °C, 30 min, *then* Ph_3P (3.0 equiv), 25 °C, 10 min, 29%.

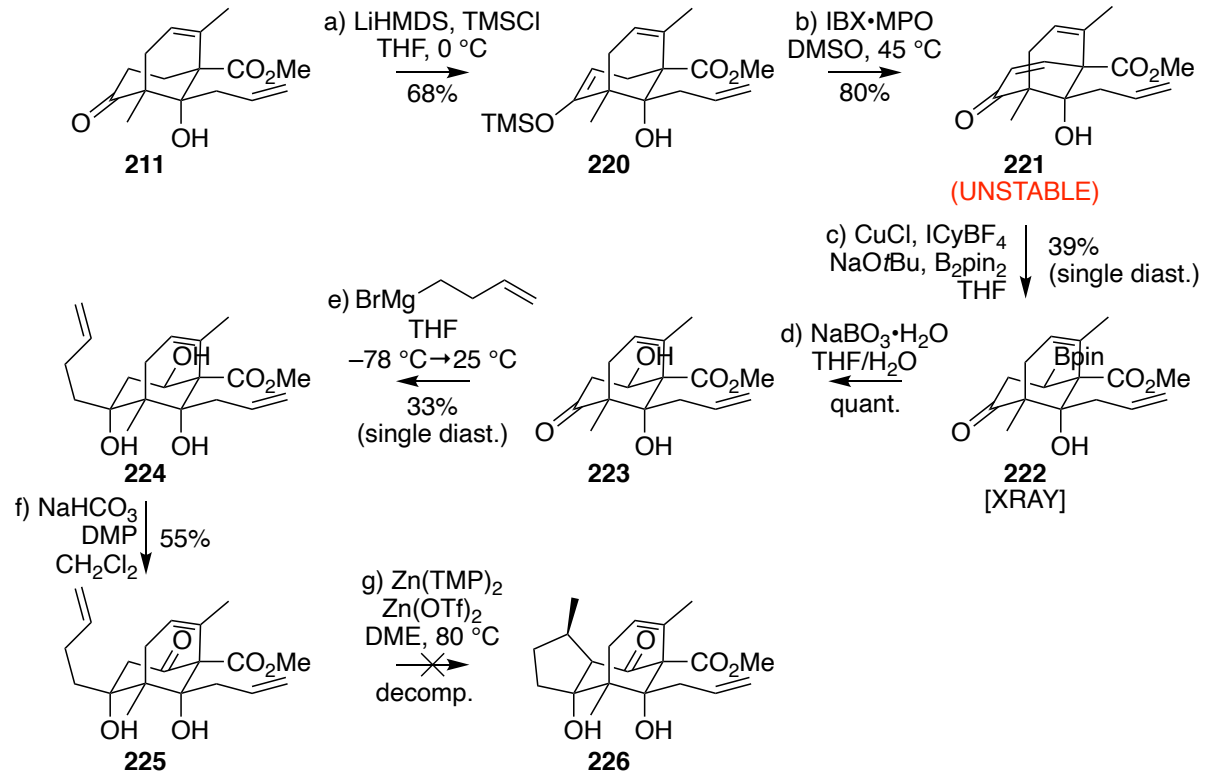
With the stage set for the decarboxylation/oxygenation sequence, we were able to observe full conversion to the Barton ester **218** utilizing EDC and DMAP in a mixed solvent system of CH_2Cl_2/THF (2:1), as shown in Scheme 3.30.[73] Once fully consumed, direct bubbling of O_2 and irradiation of **218** with a 500 W floodlamp allowed for the desired decarboxylation. However, the resulting NMR revealed no allyl group was present. After extensive NMR studies including ^1H,

COSY, and DEPT 135, we were able to elucidate that after the bridgehead radical attacked molecular oxygen, the resulting peroxy radical could then cyclize directly into the allyl group, producing the unstable primary alkyl radical, which in turn quickly captured a second molecule of O_2. Upon quenching with Ph_3P or Me_2S, the 6-membered endoperoxide was not cleaved, but the terminal peroxide was reduced, providing primary alcohol **219**. Furthermore, **219** was produced as a single diastereomer. This type of radical-mediated endoperoxide-forming transformation has been shown to be quite facile, with a seminal example being presented by Corey in 1994.[74] Although a fascinating transformation, we were unfortunately unable to successfully extrapolate this material further, as the endoperoxide proved resistant to reduction. Attempts to directly perform an oxidative cleavage to the aldehyde with $NaIO_4$ also led to full decomposition, most likely due to the presence of the second diol that would then be present on the central core, allowing for subsequent cleavage. Knowing this problem would be present until the initial tertiary alcohol could be effectively protected, we turned to focus on the installation of the left-hand ring, as we believed that would allow us to perform a diol protection.

Thus, we returned to ketone **211** hoping to retain the allyl group so it could be subjected to the decarboxylation/oxygenation cascade in the late stage (Scheme 3.31). By extrapolating ketal-deprotected **211** to enone **221** through the IBX-mediated oxidation of silyl enol ether **220**, we could once again follow the same borylation/oxidation sequence as before to yield **223** as a single diastereomer (confirmed through X-ray crystallographic analysis of borylated **222**).[43, 72] Of note, enone **221** proved highly unstable, with any bases leading to rapid decomposition, once again resulting from the probable retro-aldol, post deprotonation of the tertiary alcohol. Surprisingly, though, the Bpin conjugate addition proved to outcompete this pathway, allowing for **222** to be obtained in a consistent 30-40% yield. With **223** in hand, we were pleased to find the

homoallylmagnesium bromide addition proceeded in 33% yield at 25 °C, providing **224** as a single diastereomer. Subsequent oxidation to ketone **225** then allowed us to attempt a zinc-enolate mediated cyclization onto the terminal olefin as outlined by the Newhouse group; however, full decomposition was observed within moments, likely arising again from the retro-aldol pathway, given the presence of the 1,3-dicarbonyl post DMP oxidation.[75]

Scheme 3.31. Initial Attempts to Furnish Left-Hand Ring.[a]

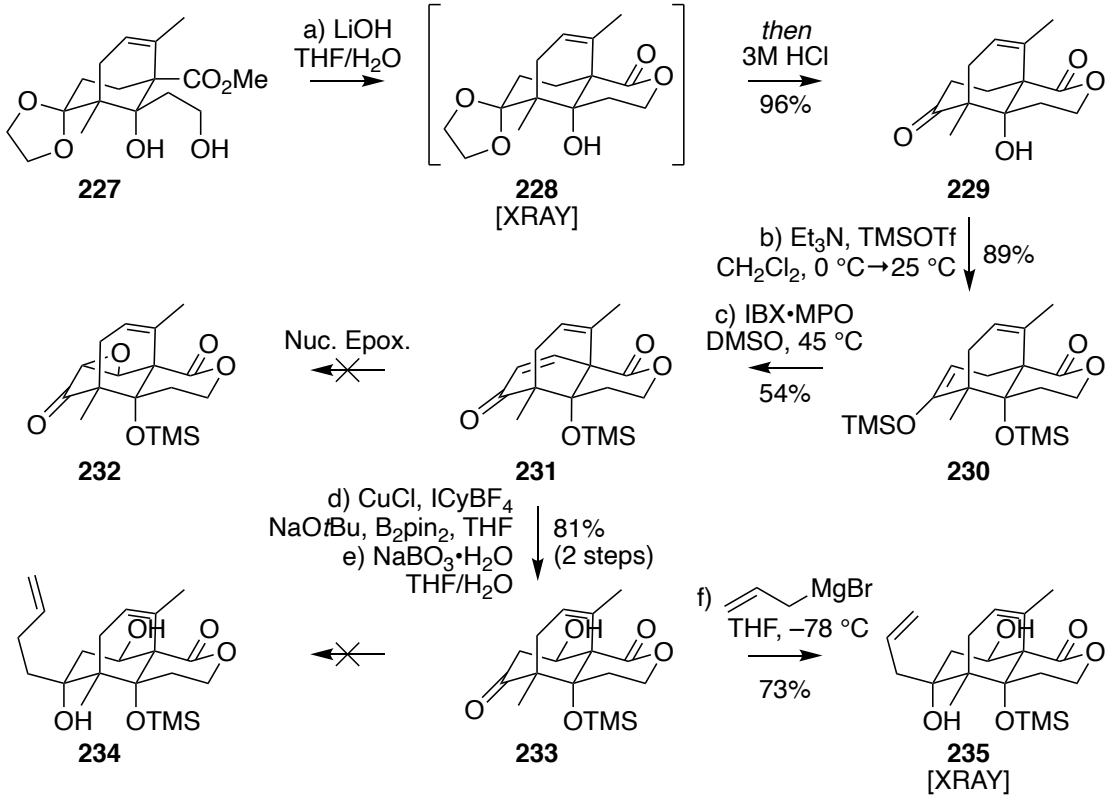


[a] Reagents and conditions: (a) LiHMDS (3.0 equiv), TMSCl (1.5 equiv), THF (0.1 M), 0 °C, 1 h, 68%; (b) IBX (2.0 equiv), MPO (2.0 equiv), DMSO (0.2 M), 45 °C, 2 h, 80%; (c) CuCl (1.0 equiv), $ICyBF_4$ (0.5 equiv), NaO*t*Bu (2.0 equiv), THF (0.05 M), 25 °C, 1 h, *then* **221** (1.0 equiv), B_2pin_2 (1.5 equiv), 25 °C, 15 min, 39% (single diastereomer); (d) $NaBO_3•H_2O$ (10.0 equiv), THF/H_2O (1:1, 0.05 M), 25 °C, 2 h, quant.; (e) homoallylmagnesium bromide (5.0 equiv), THF (0.1 M), –78 °C→25 °C, 12 h, 33% (single diastereomer); (f) $NaHCO_3$ (5.0 equiv), DMP (3.0 equiv), CH_2Cl_2 (0.05 M), 25 °C, 1 h, 55%.

Altogether, the consistent struggle against the retro-aldol reactivity suggests the need for an earlier protection of the troublesome tertiary alcohol. Unfortunately, any attempts to perform such a protection in the presence of the methyl ester proved fruitless. This poor reactivity can be explained when examining any of the several crystal structures we have obtained, as in each there

is a prominent H-bond between the tertiary alcohol and the ester moiety, inducing a very stable 6-membered configuration. By removing the ester functionality, we hoped to remove this stabilization, allowing for more facile protection. To that end, we could easily obtain **227** by performing a Lemieux-Johnson oxidation followed by $NaBH_4$-mediated reduction of allylated **211** (Scheme 3.32).[31] Subjecting **227** to LiOH, we were pleased to find rapid formation of lactone **228**, the structure of which was unambiguously assigned by X-ray crystallographic analysis, before inducing a one-pot ketal deprotection with 3M HCl. With the crystal structure of the intermittent **228**, it was clear that there was no H-bonding potential with the lactone moiety and the tertiary alcohol, giving us hope the desired protection may proceed as postulated. With lactone **229** in hand, an excess of TMSOTf (6 equiv) and Et_3N (8 equiv) in THF pleasingly provided disilylated **230** in 88% yield upon warming from 0 °C→25°C. With the promiscuous tertiary alcohol finally protected, we could confidently go through the same pathway as before to obtain alcohol **233** in sufficient yield. However, we were disappointed that the subsequent homoallylic Grignard addition failed to provide any reactivity in this case. Thankfully, a simple allyl sidechain could be introduced in a diastereoselective fashion, providing **235**, confirmed once again through X-ray crystallographic analysis.

Scheme 3.32. Diastereoselective Installation of Handle for Left-Hand Ring.[a]

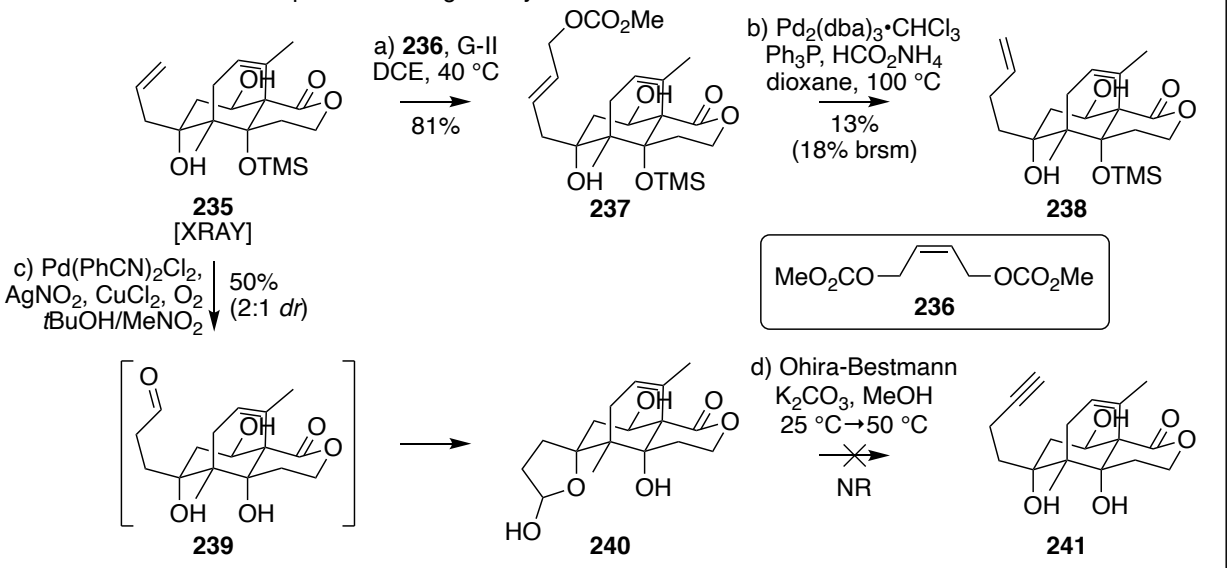


[a] Reagents and conditions: (a) LiOH (5.0 equiv), THF/H_2O (3:1, 0.1 M), 25 °C, 10 min, *then* 3M HCl (0.05 M), 25 °C, 1 h, 96%; (b) Et_3N (8.0 equiv), TMSOTf (6.0 equiv), CH_2Cl_2 (0.05 M), 0 °C→25 °C, 15 min, 89%; (c) IBX (2.0 equiv), MPO (2.0 equiv), DMSO (0.2 M), 45 °C, 2 h, 54%; (d) CuCl (1.0 equiv), $ICyBF_4$ (0.5 equiv), NaO*t*Bu (2.0 equiv), THF (0.05 M), 25 °C, 1 h, *then* **231** (1.0 equiv), B_2pin_2 (1.5 equiv), 25 °C, 15 min, 85% (single diastereomer); (e) $NaBO_3•H_2O$ (15.0 equiv), THF/H_2O (1:1, 0.05 M), 25 °C, 8 h, quant.; (f) allylmagnesium bromide (4.0 equiv), THF (0.1 M), –78 °C, 15 min, 73% (single diastereomer).

With allyl **235** in hand, we then needed to homologate the sidechain to allow for the proposed cyclization to complete the left-hand ring (Scheme 3.33). Initially, we hoped to perform a reductive elimination of allylic carbonate **237** as outlined by the Tsuji group but were disappointed to find very poor yields of **238**.[76] Instead, we then turned to trying aldehyde-selective Wacker oxidations, as recently reported by Grubbs and Stoltz.[77] Intriguingly, the desired reactivity was observed, however concomitant lactol formation and silyl deprotection of the tertiary alcohol also occurred, providing **240** in 50% yield. Having assumed the lactol formation was possible, we still believed the subsequent desired Ohira-Bestmann modification of the Seyforth-Gilbert

homologation could still proceed as planned, undeterred by this unforeseen deprotection.[78] However, no reaction took place, even at 50 °C, suggesting the lactol isomer is heavily stabilized, potentially by the H-bond with the tertiary alcohol.

Scheme 3.33. Initial Attempts to Homologate Allyl Sidechain.[a]

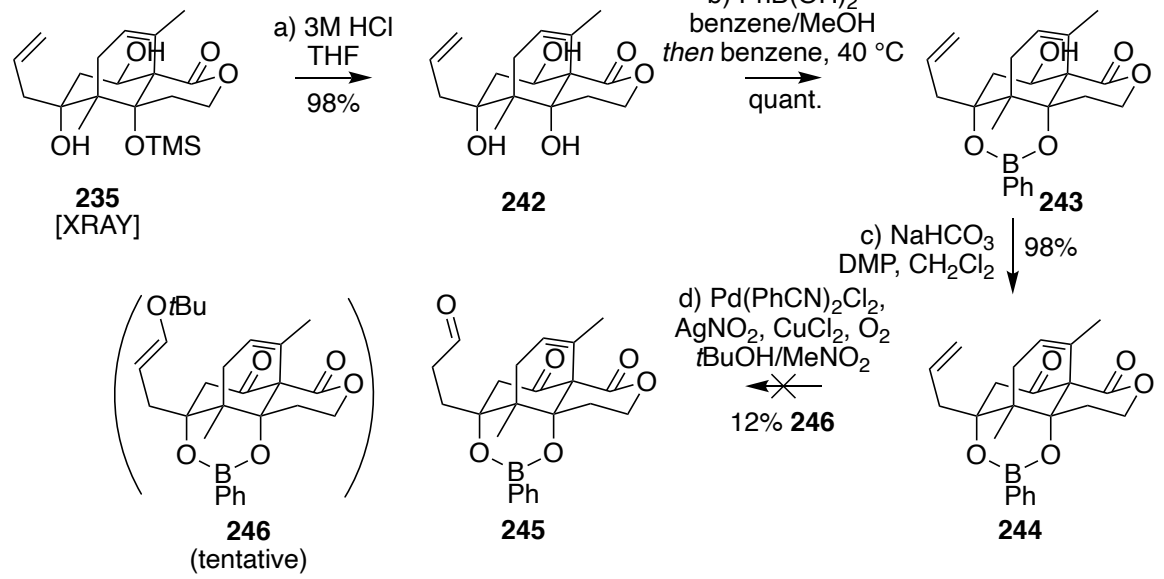


[a] Reagents and conditions: (a) **236** (4.0 equiv), Grubbs 2nd Generation initiator (0.1 equiv), DCE (0.05 M), 40 °C, 16 h, 81%; (b) $Pd_2(dba)_3$•$CHCl_3$ (0.05 equiv), Ph_3P (0.2 equiv), HCO_2NH_4 (2.0 equiv), 1,4-dioxane (0.03 M), 100 °C, 8 h, 13%, 18% brsm; (c) $Pd(PhCN)_2Cl_2$ (0.12 equiv), $CuCl_2$ (0.12 equiv), $AgNO_2$ (0.06 equiv), O_2 (balloon), *t*BuOH/$MeNO_2$ (15:1, 0.05 M), 25 °C, 8 h, 50% (2:1 *dr*).

Inspired by the success of the Wacker oxidation, albeit with its unexpected side reactivity, we hoped instead to employ a diol protection to avoid the lactol formation, as well as accomplish simultaneous tertiary alcohol protection (Scheme 3.34). Inoue has previously shown during a synthesis of related ryanodane-type natural products that similar 1,3-diols comprised of hindered tertiary alcohols could be efficiently protected as a phenyl boronic ester.[14q] Pleasingly, when applying their conditions to triol **242**, we were able to obtain boronic ester **243** in high yield, which was then easily oxidized to ketone **244**, setting the stage for the critical Wacker oxidation. When utilizing the same conditions as before, we unfortunately did not observe any desired aldehyde, but instead isolated the enol ether intermediate **246**, albeit in low yield.[77] Although the products obtained in both attempts of the Wacker oxidation are not ideal, in combination these results do

suggest the Wacker oxidation is a viable path to install the desired aldehyde functionality, which, if not trapped as the lactol, can reasonably be envisioned to undergo Ohira-Bestmann homologation. Key to success, though, would be the stability of the diol protection.

Scheme 3.34. Use of Boronic Ester Protection.[a]

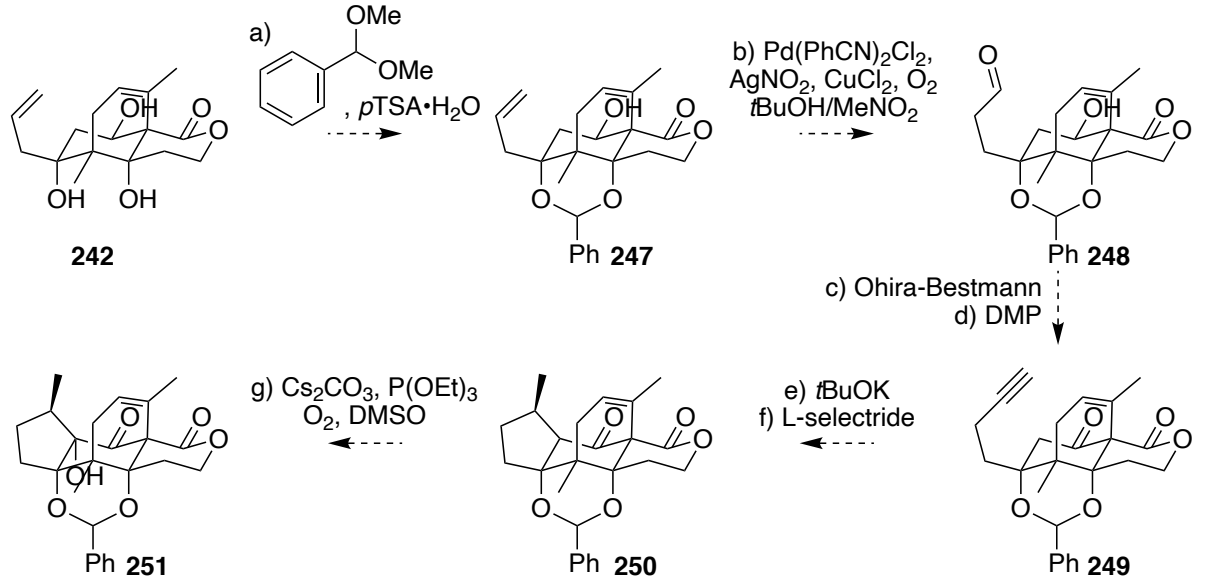


[a] Reagents and conditions: (a) 3M HCl/THF (1:1, 0.03 M), 25 °C, 5 min, 98%; (b) $PhB(OH)_2$ (10.0 equiv), benzene/MeOH (3:1, 0.05 M), 25 °C, 20 min, *then* benzene (0.05 M), 40 °C, 1.5 h, quant.; (c) $NaHCO_3$ (5.0 equiv), DMP (2.0 equiv), CH_2Cl_2 (0.05 M), 25 °C, 1 h, 98%; (d) $Pd(PhCN)_2Cl_2$ (0.12 equiv), $CuCl_2$ (0.12 equiv), $AgNO_2$ (0.06 equiv), O_2 (balloon), *t*BuOH/$MeNO_2$ (15:1, 0.05 M), 25 °C, 8 h, 12% **246**.

3.3.5 Outlook of the Conia-Ene Cyclization Route

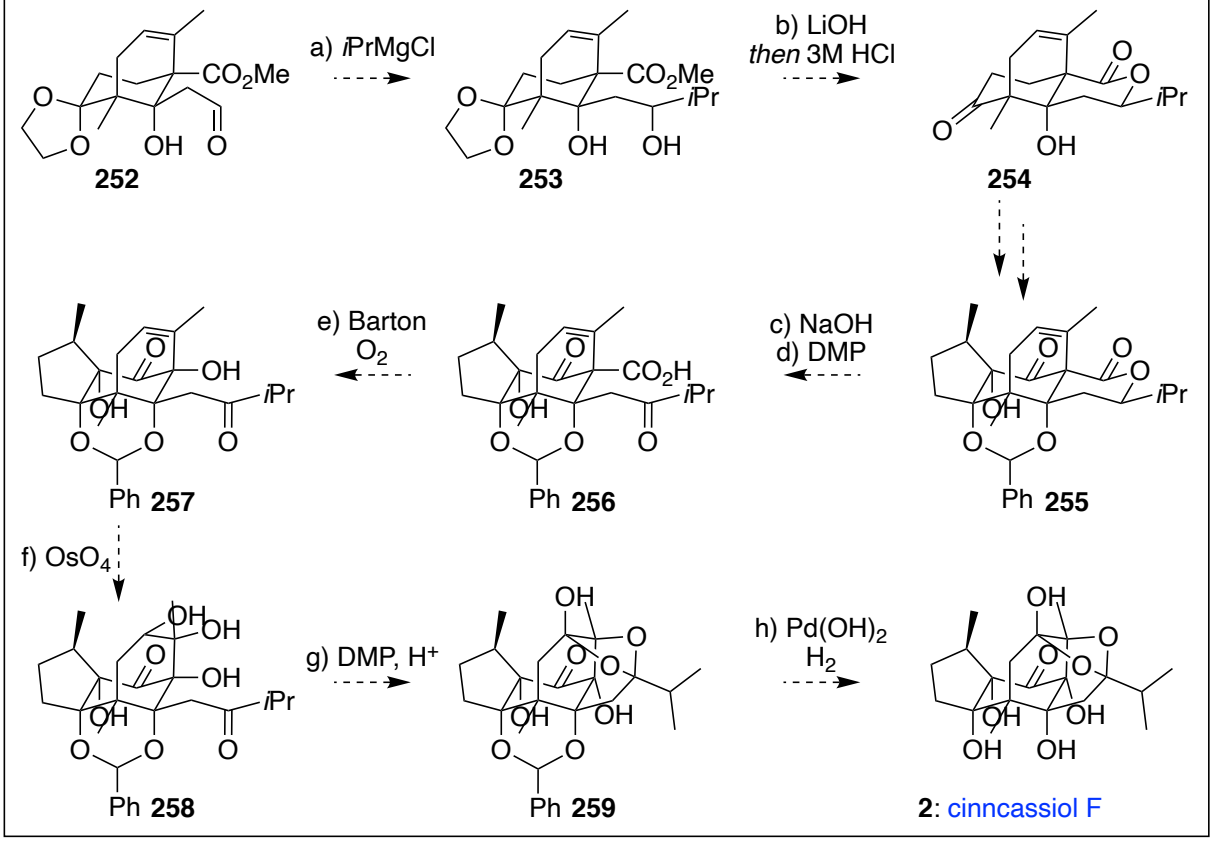
Looking ahead, we hope to protect the 1,3-diol moiety as a benzylidene acetal instead of a boronic ester, hopefully providing greater stability under the Wacker oxidation conditions (Scheme 3.35).[77] Aldehyde **248** would then be subjected to Ohira-Bestmann homologation and subsequent oxidation, before a base-mediated Conia-ene-type cyclization as developed by the Trauner group would hopefully deliver cyclopentenone the intermittent. [78-79] Reduction of the resulting enone followed by an α-hydroxylation as previously shown would then potentially finalize the left-hand side of cinncassiol F (**2**).[61a]

Scheme 3.35. Envisioned Completion of Left-Hand Ring.



In a more global sense, once we accomplish the left-hand ring, we hope to make a slight modification at the earlier stage of the synthesis, facilitating the synthesis of the right-hand portion of **2**, allowing for a more streamlined endgame. The one change would be instead of reducing aldehyde **252** with $NaBH_4$, we would instead want to introduce the isopropyl group, forming the secondary alcohol which could then engage the methyl ester to form the lactone moiety when subjected to LiOH. This material would then be carried through the same sequence as before, fashioning the left-hand portion of the molecule, before being saponified and oxidized to carboxylic acid **256**, which in turn could be decarboxylated/oxygenated to provide **257**. With the bridgehead position now sterically less encumbered, a dihydroxylation would hopefully proceed as desired, allowing for the biomimetic hemiacetal formation upon oxidation to the respective ketone, leaving just the benzylidene acetal deprotection to optimistically deliver cinncassiol F (**2**).

Scheme 3.36. Proposed Completion of **2** through a Slightly Modified Route.



3.4 Conclusion

For this body of work, our overarching goal is to develop a divergent approach to the cinncassiol diterpenoid family. To date, we have attempted two main strategies: the carbon-skeleton first approach and the bridged-bicycle first approach. Most recently, we have been focused on utilizing a Conia-ene cyclization to install the bicyclic bridged system. Although attempts to install various components of the carbon framework prior to the Conia-ene cyclization proved fruitless, as they were selective for the undesired diastereomer (Scheme 3.26), we were pleased to find that an early stage Conia-ene efficiently allowed access to the bridged core of cinncassiol F (**2**, Scheme 3.27). Attempts to directly oxidize the resulting trisubstituted olefin of the bridged system showed some promise when monitoring by TLC, but ultimately led to decomposition upon work-up, most likely due to retro-aldol fracturing. Furthermore, we found the

diastereoselectivity of the allyl 1,2-addition into the more hindered ketone was heavily influenced by distal steric encumbrance, with a reversal in selectivity being observed when the less-hindered ketone was trapped as a silyl enol ether versus protected as a ketal (Scheme 3.30). When attempting to perform a decarboxylation/oxygenation sequence with the methyl ester at an early stage, in the presence of the allyl sidechain, an intriguing radical cascade took place instead. The oxygen radical cyclized onto the allyl group, before the capture of a second oxygen molecule, leading to the *endo*-peroxide and primary alcohol upon reductive quenching. Unfortunately, attempts to cleave this peroxide to the desired aldehyde from here led to decomposition, which was attributed to the presence of the additional 1,2-diol on the central core of the molecule, prompting us to focus on building the left-hand ring prior to tackling the decarboxylation sequence.

Although we were able to obtain homoallylic **225**, we observed full instantaneous decomposition when attempting to perform a zinc-enolate mediated cyclization onto the terminal olefin, again most likely arising from a retro-aldol process involving the free tertiary alcohol β to both carbonyls (Scheme 3.31). To remedy this, we were pleased to find that by transforming the allyl sidechain into a primary alcohol through a Lemieux-Johnson and $NaBH_4$ reduction, we could form a lactone with the methyl ester, breaking up the strong H-bond between the tertiary alcohol and the ester group (Scheme 3.32). This then allowed for the disilylation of **229**, which not only protected the promiscuous tertiary alcohol, but also set the stage for our desired enone formation. Finally, we have now established an efficient and reliable route to allylated **235**. In collaboration with fellow graduate student Julia Noel, current efforts are focused on the homologation to terminal alkyne **249**, which we envision could undergo a second Conia-ene with the central ketone to fashion our desired left-hand ring (Scheme 3.35). Furthermore, if we introduce the isopropyl group in place of the $NaBH_4$ reduction prior to lactonization, we could potentially streamline the

endgame to hopefully deliver cinncassiol F (**2**) in about 6 steps from the completed left-hand ring intermediate (Scheme 3.36).

3.5 References

1. Wu, M.; Ni, L.; Lu, H.; Xu, H.; Zou, S.; Zou, X., *Journal of Chemistry* **2020**, *2020*, 5097542.
2. Hu, X. M.; Zhang, W. K.; Zhu, Q. S., *Chinese Materia Medica (Zhonghua Bencao)*. 1998; Vol. 7, p 1625.
3. Zeng, J.; Xue, Y.; Shu, P.; Qian, H.; Sa, R.; Xiang, M.; Li, X.-N.; Luo, Z.; Yao, G.; Zhang, Y., *J. Nat. Prod.* **2014**, *77*, 1948.
4. Zhou, L.; Tuo, Y.; Hao, Y.; Guo, X.; Tang, W.; Xue, Y.; Zeng, J.; Zhou, Y.; Xiang, M.; Zuo, J.; Yao, G.; Zhang, Y., *Org. Lett.* **2017**, *19*, 3029.
5. Zhou, H.; Guoruoluo, Y.; Tuo, Y.; Zhou, J.; Zhang, H.; Wang, W.; Xiang, M.; Aisa, H. A.; Yao, G., *Org. Lett.* **2019**, *21*, 549.
6. Nohara, T.; Tokubuchi, N.; Kuroiwa, M.; Nishioka, I., *Chemical and Pharmaceutical Bulletin* **1980**, *28*, 2682.
7. Nohara, T.; Kashiwada, Y.; Tomimatsu, T.; Kido, M.; Tokubuchi, N.; Nishioka, I., *Tetrahedron Letters* **1980**, *21*, 2647.
8. (a) Yagi, A.; Tokubuchi, N.; Nohara, T.; Nonaka, G.; Nishioka, I.; Koda, A., *Chemical & Pharmaceutical Bulletin* **1980**, *28*, 1432; (b) Kashiwada, Y.; Nohara, T.; Tomimatsu, T.; Nishioka, I., *Chemical & Pharmaceutical Bulletin* **1981**, *29*, 2686; (c) Nohara, T.; Kashiwada, Y.; Tomimatsu, T.; Nishioka, I., *Phytochemistry* **1982**, *21*, 2130; (d) Nohara, T.; Kashiwada, Y.; Nishioka, I., *Phytochemistry* **1985**, *24*, 1849; (e) Chen, F.-C.; Peng, C.-F.; Tsai, I.-L.; Chen, I.-S., *J. Nat. Prod.* **2005**, *68*, 1318; (f) Ngoc, T. M.; Ha, D. T.; Lee, I.-S.; Min, B.-S.; Na, M.-K.; Jung, H.-J.; Lee, S.-M.; Bae, K.-H., *Helvetica Chimica Acta* **2009**, *92*, 2058; (g) Chen, C. Y.; Wang, Y. D.; Wang, C. J., *Chemistry of Natural Compounds* **2011**, *46*, 941; (h) Zhou, L. Studies on the Chemical Constituents and Immunomodulatory Activities of the Leaves of Cinnamomum cassia. 2016; (i) He, S.; Jiang, Y.; Tu, P.-F., *Journal of Asian Natural Products Research* **2016**, *18*, 134; (j) Hu, Q. L. The Discovery of Components and Research on Bioactivities of Cinnamomum Cassia and Carpesium Abrotanoides. Lanzhou University, Lanzhou, China, 2018; (k) Zhang, C.; Fan, L.; Fan, S.; Wang, J.; Luo, T.; Tang, Y.; Chen, Z.; Yu, L., *Molecules* **2019**, *24*; (l) Pham, V. C.; Nguyen, T. T. A.; Vu, T. O.; Cao, T. Q.; Min, B. S.; Kim, J. A., *Phytochemistry Letters* **2019**, *32*, 23.
9. (a) Waterhouse, A. L.; Holden, I.; Casida, J. E., *Journal of the Chemical Society, Chemical Communications* **1984**, 1265; (b) Jefferies, P. R.; Toia, R. F.; Casida, J. E., *J. Nat. Prod.* **1991**, *54*, 1147; (c) Jefferies, P. R.; Toia, R. F.; Brannigan, B.; Pessah, I.; Casida, J. E., *Journal of Agricultural and Food Chemistry* **1992**, *40*, 142; (d) Ruest, L.; Dodier, M., *Canadian Journal of Chemistry* **1996**, *74*, 2424; (e) Ruest, L.; Berthelette, C.; Dodier, M.; Dubé, L.; St-Martin, D., *Canadian Journal of Chemistry* **1999**, *77*, 12; (f) Ruest, L.; Dodier, M.; De Sève, H.; Lessard, C.; Mongrain, P., *Canadian Journal of Chemistry* **2002**, *80*, 483.
10. (a) Achenbach, H.; Hübner, H.; Vierling, W.; Brandt, W.; Reiter, M., *J. Nat. Prod.* **1995**, *58*, 1092; (b) Hübner, H.; Vierling, W.; Brandt, W.; Reiter, M.; Achenbach, H., *Phytochemistry* **2001**, *57*, 285.

11. (a) González-Coloma, A.; Hernandez, M. G.; Perales, A.; Fraga, B. M., *Journal of Chemical Ecology* **1990**, *16*, 2723; (b) González-Coloma, A.; Terrero, D.; Perales, A.; Escoubas, P.; Fraga, B. M., *Journal of Agricultural and Food Chemistry* **1996**, *44*, 296; (c) Fraga, B. M.; González-Coloma, A.; Gutiérrez, C.; Terrero, D., *J. Nat. Prod.* **1997**, *60*, 880; (d) Fraga, B. M.; Terrero, D.; Gutiérrez, C.; González-Coloma, A., *Phytochemistry* **2001**, *56*, 315.
12. Han, A.; Tao, Y.; Reisman, S. E., *Nature* **2019**, *573*, 563.
13. (a) Sheridan, P. G. Toward the total synthesis of Cinncassiol D1: A novel biologically active diterpene. Ph.D. Thesis, Tulane University, 2005; (b) Koshimizu, M.; Nagatomo, M.; Inoue, M., *Tetrahedron* **2018**, *74*, 3384.
14. (a) Brownlee, B. G.; Ho, P.-T.; Wiesner, K., *Canadian Journal of Chemistry* **1972**, *50*, 4013; (b) Bélanger, A.; Berney, D. J. F.; Borschberg, H. J.; Brousseau, R.; Doutheau, A.; Durand, R.; Katayama, H.; Lapalme, R.; Leturc, D. M.; Liao, C.-C.; MacLachlan, F. N.; Maffrand, J.-P.; Marazza, F.; Martino, R.; Moreau, C.; Saint-Laurent, L.; Saintonge, R.; Soucy, P.; Ruest, L.; Deslongchamps, P., *Canadian Journal of Chemistry* **1979**, *57*, 3348; (c) Deslongchamps, P.; Bélanger, A.; Berney, D. J. F.; Borschberg, H.-J.; Brousseau, R.; Doutheau, A.; Durand, R.; Katayama, H.; Lapalme, R.; Leturc, D. M.; Liao, C.-C.; MacLachlan, F. N.; Maffrand, J.-P.; Marazza, F.; Martino, R.; Moreau, C.; Ruest, L.; Saint-Laurent, L.; Saintonge, R.; Soucy, P., *Canadian Journal of Chemistry* **1990**, *68*, 115; (d) Deslongchamps, P.; Bélanger, A.; Berney, D. J. F.; Borschberg, H.-J.; Brousseau, R.; Doutheau, A.; Durand, R.; Katayama, H.; Lapalme, R.; Leturc, D. M.; Liao, C.-C.; MacLachlan, F. N.; Maffrand, J.-P.; Marazza, F.; Martino, R.; Moreau, C.; Ruest, L.; Saint-Laurent, L.; Saintonge, R.; Soucy, P., *Canadian Journal of Chemistry* **1990**, *68*, 127; (e) Deslongchamps, P.; Bélanger, A.; Berney, D. J. F.; Borschberg, H.-J.; Brousseau, R.; Doutheau, A.; Durand, R.; Katayama, H.; Lapalme, R.; Leturc, D. M.; Liao, C.-C.; MacLachlan, F. N.; Maffrand, J.-P.; Marazza, F.; Martino, R.; Moreau, C.; Ruest, L.; Saint-Laurent, L.; Saintonge, R.; Soucy, P., *Canadian Journal of Chemistry* **1990**, *68*, 153; (f) Deslongchamps, P.; Bélanger, A.; Berney, D. J. F.; Borschberg, H.-J.; Brousseau, R.; Doutheau, A.; Durand, R.; Katayama, H.; Lapalme, R.; Leturc, D. M.; Liao, C.-C.; MacLachlan, F. N.; Maffrand, J.-P.; Marazza, F.; Martino, R.; Moreau, C.; Ruest, L.; Saint-Laurent, L.; Saintonge, R.; Soucy, P., *Canadian Journal of Chemistry* **1990**, *68*, 186; (g) Wang, B. Photochemistry of 6-alkenyl-2-cyclohexenones: synthetic studies towards precursors of ryanodol. Masters Thesis, Oregon State University, 1998; (h) Graeber, J. K. Studies Toward the Total Synthesis of Ryanodine. Ph.D. Thesis, Yale University, 2003; (i) Morales, C. A. Biomimetic synthesis of (−)-longithorone A and synthesis of the ryanodine core. Ph.D. Thesis, Harvard University, 2004; (j) Sieburth, S. M.; Elena Doval, S., *Tetrahedron Letters* **1994**, *35*, 8127; (k) Wood, J. L.; Graeber, J. K.; Njardarson, J. T., *Tetrahedron* **2003**, *59*, 8855; (l) Hagiwara, K.; Himuro, M.; Hirama, M.; Inoue, M., *Tetrahedron Letters* **2009**, *50*, 1035; (m) Urabe, D.; Nagatomo, M.; Hagiwara, K.; Masuda, K.; Inoue, M., *Chemical Science* **2013**, *4*, 1615; (n) Nagatomo, M.; Koshimizu, M.; Masuda, K.; Tabuchi, T.; Urabe, D.; Inoue, M., *J. Am. Chem. Soc.* **2014**, *136*, 5916; (o) Hagiwara, K.; Urabe, D.; Inoue, M., *Tetrahedron Letters* **2014**, *55*, 3817; (p) Nagatomo, M.; Hagiwara, K.; Masuda, K.; Koshimizu, M.; Kawamata, T.; Matsui, Y.; Urabe, D.; Inoue, M., *Chem. Eur. J.* **2016**, *22*, 222; (q) Masuda, K.; Koshimizu, M.; Nagatomo, M.; Inoue, M., *Chem. Eur. J.* **2016**, *22*, 230; (r) Masuda, K.; Nagatomo, M.; Inoue, M., *Chemical and Pharmaceutical Bulletin* **2016**, *64*, 874; (s) Koshimizu, M.; Nagatomo, M.;

Inoue, M., *Angew. Chem. Int. Ed.* **2016**, *55*, 2493; (t) Chuang, K. V.; Xu, C.; Reisman, S. E., *Science* **2016**, *353*, 912; (u) Xu, C.; Han, A.; Virgil, S. C.; Reisman, S. E., *ACS Central Science* **2017**, *3*, 278; (v) Xu, C.; Han, A.; Reisman, S. E., *Org. Lett.* **2018**, *20*, 3793; (w) Du, K.; Kier, M. J.; Rheingold, A. L.; Micalizio, G. C., *Org. Lett.* **2018**, *20*, 6457; (x) Du, K.; Kier, M. J.; Stempel, Z. D.; Jeso, V.; Rheingold, A. L.; Micalizio, G. C., *J. Am. Chem. Soc.* **2020**, *142*, 12937.

15. Krasovskiy, A.; Kopp, F.; Knochel, P., *Angew. Chem. Int. Ed.* **2006**, *45*, 497.
16. Shen, Y.; Li, L.; Pan, Z.; Wang, Y.; Li, J.; Wang, K.; Wang, X.; Zhang, Y.; Hu, T.; Zhang, Y., *Org. Lett.* **2015**, *17*, 5480.
17. Yasuda, A.; Yamamoto, H.; Nozaki, H., *Bulletin of the Chemical Society of Japan* **1979**, *52*, 1705.
18. Steves, J. E.; Stahl, S. S., *J. Am. Chem. Soc.* **2013**, *135*, 15742.
19. Mewshaw, R. E., *Tetrahedron Letters* **1989**, *30*, 3753.
20. (a) Sabot, C.; Commare, B.; Duceppe, M.-A.; Nahi, S.; Guérard, K. C.; Canesi, S., *Synlett* **2008**, *2008*, 3226; (b) Sabot, C.; Guérard, K. C.; Canesi, S., *Chemical Communications* **2009**, 2941.
21. Tsukada, T.; Kanno, O.; Yamane, T.; Tanaka, J.; Yoshida, T.; Okuno, A.; Shiiki, T.; Takahashi, M.; Nishi, T., *Bioorganic & Medicinal Chemistry* **2010**, *18*, 5346.
22. Hu, J.; Hirao, H.; Li, Y.; Zhou, J., *Angew. Chem. Int. Ed.* **2013**, *52*, 8676.
23. Zhou, Q.-Q.; Lu, F.-D.; Liu, D.; Lu, L.-Q.; Xiao, W.-J., *Organic Chemistry Frontiers* **2018**, *5*, 3098.
24. (a) Economou, C.; Tomanik, M.; Herzon, S. B., *J. Am. Chem. Soc.* **2018**, *140*, 16058; (b) Baron, O.; Knochel, P., *Angew. Chem. Int. Ed.* **2005**, *44*, 3133.
25. Bensari, A.; Zaveri, N. T., *Synthesis* **2003**, *2003*, 0267.
26. Harned, A. M., *Org Biomol Chem* **2018**, *16*, 2324.
27. Vlad, P. F.; Edu, K. G.; Koltsa, M. N.; Chokyrlan, A. G.; Nikolescu, A.; Delyanu, K., *Chemistry of Natural Compounds* **2011**, *47*, 574.
28. Lifchits, O.; Mahlau, M.; Reisinger, C. M.; Lee, A.; Farès, C.; Polyak, I.; Gopakumar, G.; Thiel, W.; List, B., *J. Am. Chem. Soc.* **2013**, *135*, 6677.
29. (a) Miyashita, M.; Suzuki, T.; Yoshikoshi, A., *Chemistry Letters* **1987**, *16*, 2387; (b) Engman, L.; Stern, D., *J. Org. Chem.* **1994**, *59*, 5179; (c) Renata, H.; Zhou, Q.; Dünstl, G.; Felding, J.; Merchant, R. R.; Yeh, C.-H.; Baran, P. S., *J. Am. Chem. Soc.* **2015**, *137*, 1330; (d) Khatri, H. R.; Bhattarai, B.; Kaplan, W.; Li, Z.; Curtis Long, M. J.; Aye, Y.; Nagorny, P., *J. Am. Chem. Soc.* **2019**, *141*, 4849.
30. (a) Hashimoto, S.; Sakata, S.; Sonegawa, M.; Ikegami, S., *J. Am. Chem. Soc.* **1988**, *110*, 3670; (b) Dupau, P.; Epple, R.; Thomas, A. A.; Fokin, V. V.; Sharpless, K. B., *Advanced Synthesis & Catalysis* **2002**, *344*, 421.
31. Schneider, L. M.; Schmiedel, V. M.; Pecchioli, T.; Lentz, D.; Merten, C.; Christmann, M., *Org. Lett.* **2017**, *19*, 2310.
32. Luche, J. L., *J. Am. Chem. Soc.* **1978**, *100*, 2226.
33. Lipshutz, B. H.; Hackmann, C., *J. Org. Chem.* **1994**, *59*, 7437.
34. Ting, C. P.; Maimone, T. J., *J. Am. Chem. Soc.* **2015**, *137*, 10516.
35. Lipshutz, B. H.; Ellsworth, E. L.; Dimock, S. H.; Smith, R. A. J., *J. Am. Chem. Soc.* **1990**, *112*, 4404.
36. Paquette, L. A.; Pegg, N. A.; Toops, D.; Maynard, G. D.; Rogers, R. D., *J. Am. Chem. Soc.* **1990**, *112*, 277.

37. Davis, B. R.; Johnson, S. J.; Woodgate, P. D., *Journal of the Chemical Society, Perkin Transactions 1* **1985**, 2545.
38. Fleury, L. M.; Kosal, A. D.; Masters, J. T.; Ashfeld, B. L., *J. Org. Chem.* **2013**, *78*, 253.
39. (a) Renga, J. M.; Reich, H. J., *Organic Syntheses* **1979**, *59*, 58; (b) Ramachandran, S. A.; Kharul, R. K.; Marque, S.; Soucy, P.; Jacques, F.; Chênevert, R.; Deslongchamps, P., *J. Org. Chem.* **2006**, *71*, 6149; (c) Deny, L. J.; Traboulsi, H.; Cantin, A. M.; Marsault, É.; Richter, M. V.; Bélanger, G., *Journal of medicinal chemistry* **2016**, *59*, 9431; (d) Boger, D. L.; Mullican, M. D., *J. Org. Chem.* **1985**, *50*, 1904.
40. (a) Chen, K.; Liu, C.; Deng, L.; Xu, G., *Steroids* **2010**, *75*, 513; (b) Chou, H.-H.; Wu, H.-M.; Wu, J.-D.; Ly, T. W.; Jan, N.-W.; Shia, K.-S.; Liu, H.-J., *Org. Lett.* **2008**, *10*, 121.
41. Diao, T.; Stahl, S. S., *J. Am. Chem. Soc.* **2011**, *133*, 14566.
42. Mukaiyama, T.; Matsuo, J.-i.; Kitagawa, H., *Chemistry Letters* **2000**, *29*, 1250.
43. Nicolaou, K. C.; Zhong, Y. L.; Baran, P. S., *J. Am. Chem. Soc.* **2000**, *122*, 7596.
44. Kögl, M.; Brecker, L.; Warrass, R.; Mulzer, J., *Angew. Chem. Int. Ed.* **2007**, *46*, 9320.
45. García Ruano, J. L.; Fajardo, C.; Fraile, A.; Martín, M. R., *J. Org. Chem.* **2005**, *70*, 4300.
46. Wang, L.-F.; Shi, Z.-F.; Cao, X.-P.; Li, B.-S.; An, P., *Chemical Communications* **2014**, *50*, 8061.
47. Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H., *Org. Lett.* **1999**, *1*, 953.
48. Ma, W.; Fang, J.; Ren, J.; Wang, Z., *Org. Lett.* **2015**, *17*, 4180.
49. Woltersdorf, O. W.; DeSolms, S. J.; Schultz, E. M.; Cragoe, E. J., *Journal of medicinal chemistry* **1977**, *20*, 1400.
50. (a) Cvengroš, J.; Neufeind, S.; Becker, A.; Schmalz, H.-G., *Synlett* **2008**, *2008*, 1993; (b) Danjou, P.-E.; De Leener, G.; Cornut, D.; Moerkerke, S.; Mameri, S.; Lascaux, A.; Wouters, J.; Brugnara, A.; Colasson, B.; Reinaud, O.; Jabin, I., *J. Org. Chem.* **2015**, *80*, 5084.
51. Dohi, T.; Uchiyama, T.; Yamashita, D.; Washimi, N.; Kita, Y., *Tetrahedron Letters* **2011**, *52*, 2212.
52. Salzmann, K.; Segarra, C.; Albrecht, M., *Angew. Chem. Int. Ed.* **2020**, *59*, 8932.
53. Asakawa, T.; Sagara, H.; Kanakogi, M.; Hiza, A.; Tsukaguchi, Y.; Ogawa, T.; Nakayama, M.; Ouchi, H.; Inai, M.; Kan, T., *Organic Process Research & Development* **2019**, *23*, 595.
54. Snyder, S. A.; Tang, Z.-Y.; Gupta, R., *J. Am. Chem. Soc.* **2009**, *131*, 5744.
55. Bianco, A.; Cavarischia, C.; Farina, A.; Guiso, M.; Marra, C., *Tetrahedron Letters* **2003**, *44*, 9107.
56. Frontier, A. J.; Collison, C., *Tetrahedron* **2005**, *61*, 7577.
57. (a) Ramesh, S.; Mehta, G., *Tetrahedron Letters* **2015**, *56*, 5545; (b) Dixon, D. J.; Horan, R. A. J.; Monck, N. J. T., *Org. Lett.* **2004**, *6*, 4423.
58. (a) Maruoka, K.; Sato, J.; Banno, H.; Yamamoto, H., *Tetrahedron Letters* **1990**, *31*, 377; (b) Lee, K.; Goo, J.-I.; Jung, H. Y.; Kim, M.; Boovanahalli, S. K.; Park, H. R.; Kim, M.-O.; Kim, D.-H.; Lee, H. S.; Choi, Y., *Bioorganic & Medicinal Chemistry Letters* **2012**, *22*, 7456.
59. Mejorado, L. H.; Pettus, T. R. R., *J. Am. Chem. Soc.* **2006**, *128*, 15625.
60. de Miguel, I.; Herradón, B.; Mann, E., *Advanced Synthesis & Catalysis* **2012**, *354*, 1731.
61. (a) Liang, Y.-F.; Jiao, N., *Angew. Chem. Int. Ed.* **2014**, *53*, 548; (b) Shen, M.; Kretschmer, M.; Brill, Z. G.; Snyder, S. A., *Org. Lett.* **2016**, *18*, 5018.
62. Ito, Y.; Hirao, T.; Saegusa, T., *J. Org. Chem.* **1978**, *43*, 1011.

63. Li, Z.; Jung, H.; Park, M.; Lah, M. S.; Koo, S., *Advanced Synthesis & Catalysis* **2011**, *353*, 1913.
64. Hayakawa, K.; Ohsuki, S.; Kanematsu, K., *Tetrahedron Letters* **1986**, *27*, 4205.
65. (a) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H., *Angewandte Chemie International Edition in English* **1995**, *34*, 2039; (b) Schwab, P.; Grubbs, R. H.; Ziller, J. W., *J. Am. Chem. Soc.* **1996**, *118*, 100.
66. Schevenels, F.; Markó, I. E., *Chemical Communications* **2011**, *47*, 3287.
67. Mai, K.; Patil, G., *Tetrahedron Letters* **1984**, *25*, 4583.
68. Uteuliyev, M. M.; Nguyen, T. T.; Coltart, D. M., *Nature Chemistry* **2015**, *7*, 1024.
69. Selmani, A.; Darses, S., *Org. Lett.* **2020**, *22*, 2681.
70. Crabtree, S. R.; Chu, W. L. A.; Mander, L. N., *Synlett* **1990**, *1990*, 169.
71. Ye, Q.; Qu, P.; Snyder, S. A., *J. Am. Chem. Soc.* **2017**, *139*, 18428.
72. Li, H.; Chen, Q.; Lu, Z.; Li, A., *J. Am. Chem. Soc.* **2016**, *138*, 15555.
73. Barton, D. H. R.; Crich, D.; Motherwell, W. B., *Tetrahedron* **1985**, *41*, 3901.
74. (a) Corey, E. J.; Wang, Z., *Tetrahedron Letters* **1994**, *35*, 539; (b) Korshin, E. E.; Hoos, R.; Szpilman, A. M.; Konstantinovski, L.; Posner, G. H.; Bachi, M. D., *Tetrahedron* **2002**, *58*, 2449; (c) Boukouvalas, J.; Pouliot, R.; Fréchette, Y., *Tetrahedron Letters* **1995**, *36*, 4167; (d) Hu, X.; Musacchio, A. J.; Shen, X.; Tao, Y.; Maimone, T. J., *J. Am. Chem. Soc.* **2019**, *141*, 14904.
75. (a) Huang, D.; Olivieri, D.; Sun, Y.; Zhang, P.; Newhouse, T. R., *J. Am. Chem. Soc.* **2019**, *141*, 16249; (b) Olivieri, D.; Huang, D.; Bodnar, A. K.; Yu, S.; Newhouse, T. R., *Tetrahedron* **2020**, *76*, 131417.
76. (a) Tsuji, J.; Yamakawa, T., *Tetrahedron Letters* **1979**, *20*, 613; (b) Ikeda, S.; Shibuya, M.; Kanoh, N.; Iwabuchi, Y., *Org. Lett.* **2009**, *11*, 1833.
77. Kim, K. E.; Li, J.; Grubbs, R. H.; Stoltz, B. M., *J. Am. Chem. Soc.* **2016**, *138*, 13179.
78. Roth, G. J.; Liepold, B.; Müller, S. G.; Bestmann, H. J., *Synthesis* **2004**, *2004*, 59.
79. Hartrampf, F. W. W.; Furukawa, T.; Trauner, D., *Angew. Chem. Int. Ed.* **2017**, *56*, 893.

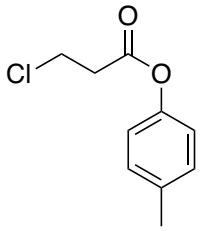
3.6 Experimental Section

3.6.1 General Procedures

All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dry tetrahydrofuran (THF), toluene, diethyl ether (Et_2O) dichloromethane (CH_2Cl_2), and acetonitrile (CH_3CN) were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Yields refer to chromatographically and spectroscopically (^1H and ^{13}C NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were magnetically stirred and

monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent, and an ethanolic solution of phosphomolybdic acid and cerium sulfate or a solution of $KMnO_4$ in aq. $NaHCO_3$ and heat as developing agents. SiliCycle silica gel (60, academic grade, particle size 0.040–0.063 mm) was used for flash column chromatography. Preparative thin-layer chromatography separations were carried out on 0.50 mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on Bruker 500 MHz instruments and calibrated using residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, br = broad, app = apparent. IR spectra were recorded on a Perkin-Elmer 1000 series FT-IR spectrometer. High-resolution mass spectra (HRMS) were recorded on Agilent 6244 Tof-MS using ESI (Electrospray Ionization) at the University of Chicago Mass Spectroscopy Core Facility.

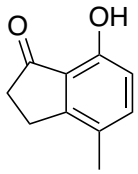
3.6.2 Syntheses of Selected Intermediates



62

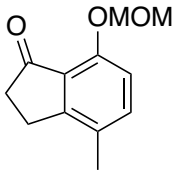
Acylated Phenol 62. To a solution of *p*-cresol (10.00 g, 92.48 mmol, 1.0 equiv) in CH_2Cl_2 (100 mL) at 0 °C was sequentially added pyridine (11.2 mL, 138.72 mmol, 1.5 equiv) and 3-chloropropionyl chloride (11.6 mL, 120.22 mmol, 1.3 equiv). The reaction mixture was then warmed to 25 °C and was then stirred for 8 h. Upon completion, the reaction contents were quenched by the addition of NH_4Cl (150 mL), diluted with CH_2Cl_2 (50 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 150 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel,

hexanes:EtOAc, 20:1) afforded the desired acylated phenol **62** (11.86 g, 59.71 mmol, 65% yield) as a yellow oil. **62**: R_f = 0.60 (silica gel, hexanes:EtOAc, 3:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 (d, *J* = 8.5 Hz, 2H), 6.98 (d, *J* = 8.5 Hz, 2H), 3.87 (t, *J* = 6.7 Hz, 2H), 3.04 (t, *J* = 6.7 Hz, 2H), 2.35 (s, 3H).



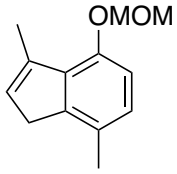
63

Indanone 63. To neat acylated phenol **62** (11.86 g, 59.71 mmol, 1.0 equiv) was added solid $AlCl_3$ (31.85 g, 238.84 mmol, 4.0 equiv). The reaction flask was then equipped with a reflux condenser before being placed in a preheated oil bath (180 °C). The reaction mixture was then stirred at this temperature for 6 h [CAUTION: large amounts of gas were generated during this period]. Upon completion, the reaction contents were cooled to 25 °C and quenched by the slow addition of ice until gas evolution ended. The reaction was quenched further by the addition of concentrated HCl until the aluminum amalgam was fully dissolved (~100 mL). The reaction contents were then diluted with CH_2Cl_2 (250 mL) and H_2O (100 mL) and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 150 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 20:1→15:1) afforded the desired indanone **63** (7.38 g, 45.50 mmol, 76% yield) as a light yellow solid. **63**: R_f = 0.40 (silica gel, hexanes:EtOAc, 3:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.93 (s, 1H), 7.28 (d, J = 7.8 Hz, 1H), 6.69 (d, J = 8.1 Hz, 1H), 3.03 – 2.97 (m, 2H), 2.75 – 2.69 (m, 2H), 2.24 (s, 3H).



64

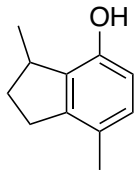
MOM-protected Phenol 64. To a solution of indanone **63** (2.00 g, 12.33 mmol, 1.0 equiv) in CH_2Cl_2 (31 mL) at 0 °C was sequentially added *i*Pr_2EtN (21.0 mL, 123.30 mmol, 10.0 equiv) and MOMCl (3.7 mL, 49.32 mmol, 4.0 equiv). The resulting solution was allowed to slowly warm to 25 °C over 6 h. Upon completion, the reaction contents were quenched by the addition of NH_4Cl (50 mL), diluted with CH_2Cl_2 (50 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 3:1) afforded the desired MOM-protected phenol **64** (2.361 g, 11.45 mmol, 93% yield) as a light yellow oil. **64**: R_f = 0.20 (silica gel, hexanes:EtOAc, 3:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.2 Hz, 1H), 6.97 (d, *J* = 8.2 Hz, 1H), 5.31 (s, 2H), 3.51 (s, 3H), 2.95 (t, *J* = 6.0 Hz, 2H), 2.71 – 2.67 (m, 2H), 2.27 (s, 3H).



65

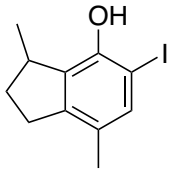
MOM-protected Olefin 65. To a solution of $MePh_3P^+Br^-$ (12.271 g, 34.35 mmol, 3.0 equiv) in THF (20 mL) at 0 °C was added *t*BuOK (13.6 mL, 1.0 M in THF, 13.60 mmol, 2.9 equiv) dropwise. The resulting solution was allowed to stir for 30 min at 0 °C before the addition of MOM-protected phenol **64** (2.361 g, 11.45 mmol, 1.0 equiv) in THF (30 mL). The reaction mixture was stirred at 0 °C for an additional 5 min before the ice bath was removed. The solution was then stirred at 25 °C for 1 h. Upon completion, the reaction contents were quenched by the

addition of NH_4Cl (50 mL), diluted with CH_2Cl_2 (50 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 40:1) afforded the desired MOM-protected olefin **65** (2.2888 g, 11.20 mmol, 98% yield) as a yellow oil. **65**: R_f = 0.80 (silica gel, hexanes:EtOAc, 4:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.92 (s, 2H), 6.07 (d, *J* = 1.7 Hz, 1H), 5.21 (s, 2H), 3.51 (s, 3H), 3.16 (s, 2H), 2.35 (q, *J* = 2.0 Hz, 3H), 2.28 (s, 3H).



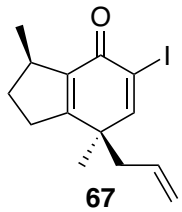
66

Phenol 66. Pd/C (1.0 g, 10% by weight, 0.94 mmol, 0.08 equiv) was carefully added to a solution of MOM-protected olefin **65** (2.2753 g, 11.14 mmol, 1.0 equiv) in MeOH (20 mL) at 25 °C. The resultant suspension was then purged by direct bubbling with a balloon of H_2 gas for 2 h. Upon completion, concentrated HCl (2 mL) was added to the reaction mixture, and the resultant solution was allowed to stir at 25 °C for an additional 8 h. The reaction contents were then filtered through a short pad of Celite and washed with EtOAc (100 mL) before being poured into a separatory funnel and diluted with H_2O (100 mL). The two phases were separated, and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated to yield phenol **66** (1.76 g, 10.85 mmol, 97%) directly with no further purification required. **66**: R_f = 0.60 (silica gel, hexanes:EtOAc, 8:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.84 (d, J = 7.9 Hz, 1H), 6.52 (d, J = 8.0 Hz, 1H), 3.38 (td, J = 7.4, 3.7 Hz, 1H), 2.89 (dt, J = 16.3, 8.2 Hz, 1H), 2.74 (ddd, J = 16.1, 9.1, 4.2 Hz, 1H), 2.28 (ddt, J = 12.7, 9.1, 8.1 Hz, 1H), 2.18 (s, 3H), 1.74 (ddt, J = 12.5, 8.2, 3.9 Hz, 1H), 1.27 (d, J = 7.0 Hz, 3H).



60

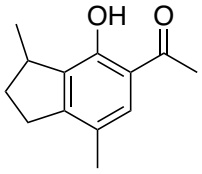
Aryl Iodide 60. To a solution of phenol **66** (253.8 mg, 1.56 mmol, 1.0 equiv) in MeCN (7.8 mL) was added PTSA•H_2O (327.2 mg, 1.72 mmol, 1.1 equiv). The reaction contents were then stirred at 25 °C for 10 min before the addition of solid NIS (387.0 mg, 1.72 mmol, 1.1 equiv). The pink solution was then allowed to stir for an additional 1 h at this temperature. Upon completion, the reaction contents were quenched by the addition of $Na_2S_2O_3$ (25 mL), diluted with CH_2Cl_2 (25 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:CH_2Cl_2, 10:1) afforded the desired aryl iodide **60** (395.5 mg, 1.37 mmol, 88% yield) as a yellow oil. **60**: R_f = 0.20 (silica gel, hexanes:CH_2Cl_2, 8:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (s, 1H), 5.06 (s, 1H), 3.41 (ddt, J = 10.9, 7.1, 3.4 Hz, 1H), 2.85 (dt, J = 16.4, 8.2 Hz, 1H), 2.71 (ddd, J = 16.2, 9.1, 4.2 Hz, 1H), 2.27 (ddt, J = 12.7, 9.2, 8.1 Hz, 1H), 2.14 (s, 3H), 1.72 (ddt, J = 12.6, 8.3, 4.0 Hz, 1H), 1.25 (d, J = 7.0 Hz, 3H).



67

Dearomatized Iodide 67. To a solution of aryl iodide **60** (386.0 mg, 1.34 mmol, 1.0 equiv) in TFE (6.7 mL) at 25 °C was added allyl-TMS (1.3 mL, 8.04 mmol, 6.0 equiv) and a solution of PIDA (647.4 mg, 2.01 mmol, 1.5 equiv) in TFE (3.0 mL). The reaction contents were allowed to stir for 5 min before the addition of a second portion PIDA (647.4 mg, 2.01 mmol, 1.5 equiv) in TFE (3.0 mL). The resultant solution was then stirred for a further 5 min. Upon

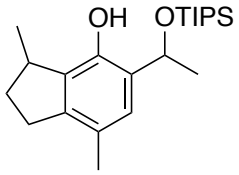
completion, the reaction contents were quenched by the addition of $NaHCO_3$ (25 mL), diluted with CH_2Cl_2 (20 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:CH_2Cl_2, 2:1→1:1) afforded the desired dearomatized iodide **67** (130.0 mg, 0.40 mmol, 30% yield) as a bright yellow oil. **67**: R_f = 0.10 (silica gel, hexanes:CH_2Cl_2, 2:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 – 7.46 (d, 1H), 5.60 – 5.30 (m, 1H), 5.07 – 4.95 (m, 2H), 3.17 (s, 1H), 2.67 – 2.28 (m, 5H), 2.19 – 2.11 (m, 1H), 1.55 – 1.49 (m, 1H), 1.25 (d, J = 1.2 Hz, 3H), 1.15 (dd, J = 11.1, 6.9 Hz, 3H).



69

Ketone 69. To neat phenol **66** (302.2 mg, 1.86 mmol, 1.0 equiv) was added neat $TiCl_4$ (0.22 mL, 2.05 mmol, 1.1 equiv) dropwise. After gas evolution ceased (~ 5 min), acetyl chloride (0.20 mL, 2.79 mmol, 1.5 equiv) was added to the reaction mixture dropwise. The viscous mixture was allowed to stir at 25 °C for 5 min before being placed in a preheated oil bath (120 °C) in which it was stirred for a further 2 h. Upon completion, the reaction contents were quenched by the addition of H_2O (25 mL), diluted with CH_2Cl_2 (20 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:CH_2Cl_2, 2:1) afforded the desired ketone **69** (334.2 mg, 1.64 mmol, 88% yield) as a yellow oil. **69**: R_f = 0.30 (silica gel, hexanes:CH_2Cl_2, 1:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.26 (s, 1H), 7.34 (s, 1H), 3.45 (pd, J = 7.0, 3.7 Hz, 1H), 2.91 (dt, J = 16.7, 8.2 Hz, 1H), 2.76 (ddd, J = 17.1, 9.2, 4.2 Hz, 1H), 2.59 (s, 3H),

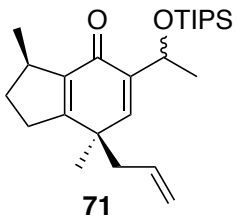
2.30 (ddt, J = 12.8, 9.1, 8.1 Hz, 1H), 2.21 (s, 3H), 1.75 (ddt, J = 12.7, 8.4, 4.0 Hz, 1H), 1.28 (d, J = 7.0 Hz, 3H).



70

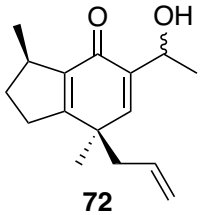
TIPS-protected Phenol 70. To a solution of ketone **69** (319.2 mg, 1.56 mmol, 1.0 equiv) in MeOH (8.0 mL) at 0 °C was added solid $NaBH_4$ (118.0 mg, 3.12 mmol, 2.0 equiv) in one portion. The reaction solution was allowed to stir at this temperature for 5 min before the cooling bath was removed. The reaction was then stirred for an additional 45 min at 25 °C. Upon completion, the reaction contents were quenched by the addition of NH_4Cl (50 mL), diluted with EtOAc (50 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 7:1) afforded the desired secondary alcohol (315.1 mg, 1.53 mmol, 98% yield). Pushing forward, to a solution of the resultant alcohol (113.4 mg, 0.55 mmol, 1.0 equiv) in CH_2Cl_2 (5.5 mL) at 0 °C was added lutidine (0.19 mL, 1.65 mmol, 3.0 equiv) and TIPSOTf (0.16 mL, 0.61 mmol, 1.1 equiv). The reaction mixture was then allowed to stir for an additional 10 min at 0 °C. Upon completion, the reaction contents were quenched by the addition of NH_4Cl (150 mL), diluted with CH_2Cl_2 (50 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 150 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 40:1) afforded the desired TIPS-protected phenol **70** (196.8 mg, 0.54 mmol, 98% yield) as a yellow oil. **70**: R_f = 0.60 (silica gel, hexanes:EtOAc, 8:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 – 8.15 (m, 1H),

6.48 (s, 1H), 4.98 (qd, J = 6.5, 1.5 Hz, 1H), 3.47 – 3.34 (m, 1H), 2.89 – 2.79 (m, 1H), 2.74 – 2.64 (m, 1H), 2.26 (dtd, J = 12.7, 7.9, 1.3 Hz, 1H), 2.13 (s, 3H), 1.70 (dddd, J = 11.2, 9.9, 5.0, 3.2 Hz, 1H), 1.56 – 1.53 (m, 3H), 1.30 – 1.20 (m, 3H), 1.18 – 1.09 (m, 3H), 1.04 (ddd, J = 13.1, 7.3, 4.1 Hz, 18H).



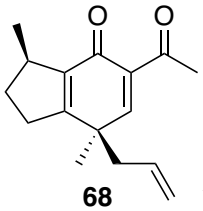
71

TIPS-Protected Dearomatized 71. To a solution of TIPS-protected phenol **70** (196.8 mg, 0.54 mmol, 1.0 equiv) in HFIP (2.7 mL) at 25 °C was added allyl-TMS (0.51 mL, 3.24 mmol, 6.0 equiv) and a solution of PIDA (260.9 mg, 0.81 mmol, 1.5 equiv) in HFIP (0.6 mL). The reaction contents were allowed to stir for 5 min before the addition of a second portion of PIDA (260.9 mg, 0.81 mmol, 1.5 equiv) in HFIP (0.6 mL). The resultant solution was then stirred for a further 5 min. Upon completion, the reaction contents were quenched by the addition of $NaHCO_3$ (15 mL), diluted with CH_2Cl_2 (10 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:CH_2Cl_2, 2:1) afforded the desired TIPS-protected dearomatized **71** (117.3 mg, 0.29 mmol, 54% yield, 3:3:1:1 *dr*) as a yellow oil. **71**: R_f = 0.20 (silica gel, hexanes:CH_2Cl_2, 3:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.88 (d, J = 5.7 Hz, 1H), 5.37 – 5.30 (m, 1H), 5.03 – 4.93 (m, 2H), 4.92 – 4.86 (m, 1H), 3.13 (s, 1H), 2.60 (dddd, J = 15.5, 8.8, 6.8, 2.0 Hz, 1H), 2.44 (ddq, J = 17.3, 8.9, 4.8 Hz, 1H), 2.37 (t, J = 5.9 Hz, 2H), 2.16 – 2.05 (m, 1H), 1.54 – 1.49 (m, 1H), 1.32 – 1.26 (m, 3H), 1.21 (d, J = 3.0 Hz, 3H), 1.14 (ddd, J = 11.1, 6.8, 2.0 Hz, 3H), 1.09 – 1.01 (m, 21H).



72

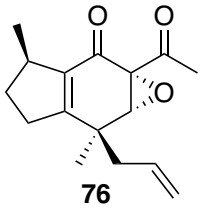
Alcohol 72. To a solution of TIPS-protected dearomatized **71** (283.1 mg, 0.70 mmol, 1.0 equiv) in THF (3.5 mL) at 0 °C was added TBAF (2.1 mL, 1.0 M in THF, 2.10 mmol, 3.0 equiv). The resultant solution was allowed to stir at this temperature for 2 h before being warmed to 25 °C. After stirring for an additional 30 min at 25 °C, the reaction contents were quenched by the addition of $NaHCO_3$ (25 mL), diluted with EtOAc (20 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 5:1) afforded the desired alcohol **72** (139.3 mg, 0.68 mmol, 97% yield) as a clear and colorless oil. **72**: R_f = 0.30 (silica gel, hexanes:EtOAc, 4:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.67 – 6.51 (m, 1H), 5.42 – 5.24 (m, 1H), 5.03 – 4.89 (m, 2H), 4.77 – 4.58 (m, 1H), 3.15 (s, 1H), 2.62 (dddd, J = 17.9, 8.9, 7.1, 2.0 Hz, 1H), 2.51 – 2.34 (m, 3H), 2.19 – 2.10 (m, 1H), 1.56 (tt, J = 8.6, 4.3 Hz, 1H), 1.44 – 1.38 (m, 3H), 1.24 (d, J = 1.2 Hz, 3H), 1.14 (dd, J = 8.4, 6.9 Hz, 3H).



68

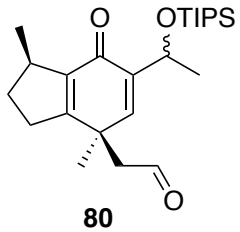
Dienedione 68. To a solution of alcohol **72** (20.9 mg, 0.085 mmol, 1.0 equiv) in CH_2Cl_2 (1.0 mL) was added sequentially $NaHCO_3$ (35.7 mg, 0.425 mmol, 5.0 equiv) and Dess–Martin periodinane (72.1 mg, 0.170 mmol, 2.0 equiv). The reaction mixture was then allowed to stir at 25 °C for 15 min. Upon completion, the reaction contents were concentrated directly and the resultant residue was purified by flash column chromatography (silica gel, hexanes:EtOAc,

10:1) to afford the desired dienedione **68** (19.2 mg, 0.079 mmol, 93% yield) as a clear and colorless oil. **68**: R_f = 0.40 (silica gel, hexanes:EtOAc, 4:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (d, J = 6.1 Hz, 1H), 5.39 – 5.26 (m, 1H), 5.04 – 4.94 (m, 2H), 3.24 – 3.13 (m, 1H), 2.69 – 2.59 (m, 1H), 2.56 (s, 3H), 2.50 – 2.44 (m, 2H), 2.20 – 2.11 (m, 1H), 1.59 – 1.56 (m, 1H), 1.29 (s, 3H), 1.17 (d, J = 6.9 Hz, 3H).



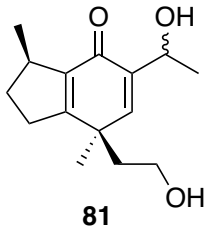
76

Epoxide 76. To a solution of dienedione **68** (47.9 mg, 0.20 mmol, 1.0 equiv) in MeOH (2.0 mL) at 0 °C was added *t*BuOOH (0.22 mL, 5.5 M in decanes, 1.20 mmol, 6.0 equiv) and NaOH (0.20 mL, 0.5 M in MeOH, 0.10 mmol, 0.5 equiv). After stirring for an additional 5 min at 0 °C, the cooling bath was removed and the resultant reaction mixture was allowed to stir at 25 °C for an additional 1 h. Upon completion, the reaction contents were quenched by the addition of $Na_2S_2O_3$ (15 mL), diluted with EtOAc (10 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 9:1) afforded the desired epoxide **76** (49.7 mg, 0.19 mmol, 95% yield) as a colorless oil. **76**: R_f = 0.80 (silica gel, hexanes:EtOAc, 2:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.59 – 5.45 (m, 1H), 5.14 – 5.01 (m, 2H), 3.28 (d, J = 3.1 Hz, 1H), 3.19 – 3.00 (m, 1H), 2.61 – 2.49 (m, 1H), 2.47 – 2.40 (m, 2H), 2.32 (d, J = 8.8 Hz, 4H), 2.15 – 2.04 (m, 1H), 1.54 – 1.47 (m, 1H), 1.36 (d, J = 6.4 Hz, 3H), 1.17 – 1.05 (m, 3H).



80

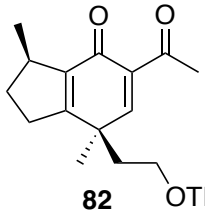
Aldehyde 80. To a solution of TIPS-protected dearomatized **71** (113.0 mg, 0.28 mmol, 1.0 equiv) in 1,4-dioxane (2.1 mL) and H_2O (0.7 mL) was sequentially added lutidine (0.06 mL, 0.56 mmol, 2.0 equiv), $NaIO_4$ (239.6 mg, 1.12 mmol, 4.0 equiv), and OsO_4 (0.09 mL, 4% in H_2O, 0.014 mmol, 0.05 equiv). The reaction mixture was then stirred vigorously for 1.5 h. Upon completion, the reaction contents were quenched by the addition of H_2O (15 mL), diluted with EtOAc (10 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 8:1) afforded the desired aldehyde **80** (91.7 mg, 0.23 mmol, 82% yield) as a yellow oil. **80**: R_f = 0.20 (silica gel, hexanes:EtOAc, 8:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.28 – 9.16 (m, 1H), 7.08 – 6.98 (m, 1H), 5.06 – 4.95 (m, 1H), 3.16 (s, 1H), 2.70 – 2.58 (m, 3H), 2.46 (dddd, J = 17.5, 13.8, 9.6, 4.6 Hz, 1H), 2.21 – 2.12 (m, 1H), 1.59 (dd, J = 8.3, 3.9 Hz, 1H), 1.31 (tt, J = 6.4, 3.0 Hz, 6H), 1.19 – 1.13 (m, 3H), 1.05 (ddt, J = 9.8, 6.8, 3.8 Hz, 21H).



81

Diol 81. To a solution of aldehyde **80** (89.2 mg, 0.22 mmol, 1.0 equiv) in MeOH (2.5 mL) at 0 °C was added $NaBH_4$ (8.3 mg, 0.22 mmol, 1.0 equiv) in a single portion. The reaction mixture was then allowed to stir for 5 min at that temperature. Upon completion, the reaction contents were quenched by the addition of NH_4Cl (15 mL), diluted with EtOAc (10 mL), and

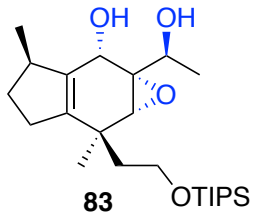
poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated to directly obtain the intermediate primary alcohol (87.6 mg, 0.22 mmol, quant.). Pushing forward, a solution of the resultant crude alcohol (20.3 mg, 0.050 mmol, 1.0 equiv) in THF (0.5 mL) at 0 °C was added TBAF (0.20 mL, 1.0 M in THF, 0.20 mmol, 4.0 equiv). The resultant solution was then stirred for 5 min at this temperature. Upon completion, the reaction contents were quenched by the addition of NH_4Cl (15 mL), diluted with EtOAc (10 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, pure EtOAc) afforded the desired diol **81** (11.3 mg, 0.045 mmol, 90% yield) as a colorless oil. **81**: R_f = 0.15 (silica gel, pure EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.71 – 6.61 (m, 1H), 4.70 (dt, J = 13.0, 6.4 Hz, 1H), 3.32 (dt, J = 17.5, 6.8 Hz, 2H), 3.17 (s, 1H), 2.65 (dtt, J = 16.3, 8.2, 1.9 Hz, 1H), 2.50 (ddd, J = 17.8, 9.2, 4.3 Hz, 1H), 2.15 (ddt, J = 12.5, 10.1, 6.2 Hz, 1H), 2.07 – 2.03 (m, 1H), 1.92 (dtd, J = 13.7, 6.8, 2.8 Hz, 1H), 1.60 (dd, J = 8.6, 4.1 Hz, 1H), 1.42 (dd, J = 6.5, 2.3 Hz, 4H), 1.25 (d, J = 2.3 Hz, 3H), 1.16 (dd, J = 11.3, 6.9 Hz, 3H).



82

TIPS-protected Dienedione 82. To a solution of diol **81** (11.2 mg, 0.045 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL) at 0 °C was added lutidine (0.02 mL, 0.135 mmol, 3.0 equiv) and TIPSOTf (0.05 mL, 0.050 mmol, 1.1 equiv). The reaction mixture was then allowed to stir for an additional 10 min at 0 °C. Upon completion, the reaction contents were quenched by the addition of NH_4Cl (15 mL), diluted with CH_2Cl_2 (10 mL), and poured into a separatory funnel.

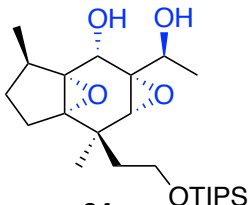
The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 8:1) afforded the desired mono-protected diol (13.4 mg, 0.033 mmol, 73% yield). Pushing forward to a solution of the mono-protected diol (11.8 mg, 0.029 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL) was added sequentially $NaHCO_3$ (12.2 mg, 0.145 mmol, 5.0 equiv) and Dess–Martin periodinane (24.6 mg, 0.058 mmol, 2.0 equiv). The reaction mixture was then allowed to stir at 25 °C for 15 min. Upon completion, the reaction contents were concentrated directly and the resultant residue was purified by flash column chromatography (silica gel, hexanes:EtOAc, 12:1) to afford the desired TIPS-protected dienedione **82** (11.3 mg, 0.028 mmol, 97% yield) as a clear and colorless oil. **82**: R_f = 0.30 (silica gel, hexanes:EtOAc, 10:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (d, J = 16.0 Hz, 1H), 3.36 (t, J = 6.7 Hz, 2H), 3.24 – 3.14 (m, 1H), 2.69 – 2.60 (m, 1H), 2.56 – 2.49 (m, 4H), 2.15 (dtd, J = 12.9, 9.0, 7.5 Hz, 1H), 2.10 – 1.95 (m, 2H), 1.59 (td, J = 8.7, 4.2 Hz, 1H), 1.28 (d, J = 2.5 Hz, 3H), 1.18 (dd, J = 9.2, 6.9 Hz, 3H), 0.98 (q, J = 2.8 Hz, 21H).



83

Epoxy-diol 83. To a solution of TIPS-protected dienedione **82** (10.0 mg, 0.025 mmol, 1.0 equiv) in MeOH (0.5 mL) at 0 °C was added *t*BuOOH (0.02 mL, 5.5 M in decanes, 0.125 mmol, 5.0 equiv) and NaOH (0.03 mL, 0.5 M in MeOH, 0.013 mmol, 0.5 equiv). After stirring for an additional 5 min at 0 °C, the cooling bath was removed and the resultant reaction mixture was allowed to stir at 25 °C for an additional 1 h. Upon completion, the reaction contents were quenched by the addition of $Na_2S_2O_3$ (15 mL), diluted with EtOAc (10 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with

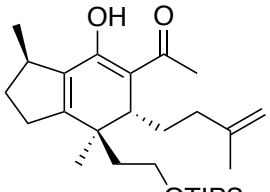
EtOAc (3 × 10 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 15:1) afforded the desired epoxide (9.7 mg, 0.023 mmol, 92% yield) as a colorless oil. Pushing forward, to a solution of the resultant epoxide (8.7 mg, 0.021 mmol, 1.0 equiv) in MeOH (0.5 mL) at 25 °C was added $CeCl_3$•$7H_2O$ (19.7 mg, 0.053 mmol, 2.5 equiv) in a single portion. The reaction mixture was then allowed to stir for 10 min at that temperature before being cooled to –78 °C. Once cooled, $NaBH_4$ (2.0 mg, 0.053 mmol, 2.5 equiv) was added in one portion, and the resultant reaction solution was allowed to stir for 2 h at –78 °C. Upon completion, the reaction contents were quenched by the addition of NH_4Cl (15 mL), diluted with EtOAc (10 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 3:1) afforded the desired epoxide **83** (8.2 mg, 0.019 mmol, 92% yield) as a colorless oil. **83**: R_f = 0.05 (silica gel, hexanes:EtOAc, 8:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.38 (d, J = 8.4 Hz, 1H), 4.25 (p, J = 6.3 Hz, 1H), 3.54 – 3.45 (m, 1H), 3.43 – 3.22 (m, 2H), 2.74 (d, J = 5.7 Hz, 1H), 2.35 – 2.24 (m, 1H), 2.16 – 1.96 (m, 2H), 1.86 (ddd, J = 14.4, 9.4, 5.5 Hz, 1H), 1.69 (ddd, J = 13.9, 9.3, 6.0 Hz, 1H), 1.48 – 1.40 (m, 1H), 1.36 – 1.22 (m, 6H), 1.17 (d, J = 3.0 Hz, 3H), 1.03 (q, J = 3.0 Hz, 21H).



84

Diepoxide 84. To a solution of epoxy-diol **83** (6.2 mg, 0.015 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL) at 0 °C was sequentially added $NaHCO_3$ (3.8 mg, 0.045 mmol, 3.0 equiv) and *m*CPBA (7.4 mg, 70% by weight, 0.030 mmol, 2.0 equiv) in one portion. The resultant mixture

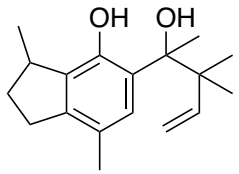
was then stirred for 1 h at 0 °C. The cooling bath was then removed, and the reaction was allowed to stir at 25 °C for an additional 2 h. Upon completion, the reaction contents were quenched by the addition of $NaHCO_3$ (15 mL), diluted with EtOAc (10 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc 3:1) to afford the desired diepoxide **84** (4.0 mg, 0.009 mmol, 61% yield) as a colorless oil. **84**: R_f = 0.40 (silica gel, hexanes:EtOAc, 1:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.33 (s, 1H), 4.11 (q, J = 6.6 Hz, 1H), 3.72 – 3.62 (m, 1H), 3.51 (tt, J = 9.8, 5.4 Hz, 1H), 3.12 (d, J = 4.1 Hz, 1H), 2.01 (qd, J = 6.7, 3.4 Hz, 1H), 1.94 – 1.71 (m, 4H), 1.70 – 1.60 (m, 2H), 1.32 – 1.29 (m, 6H), 1.18 (dd, J = 6.7, 3.4 Hz, 3H), 1.06 (q, J = 4.3 Hz, 21H).



86

Isoprenyl 86. To a solution of LiCl (10.0 mg, 0.310 mmol, 5.0 equiv), CuBr•DMS (25.5 mg, 0.124 mmol, 2.0 equiv) in THF (0.5 mL) at –40 °C was added isoprenylmagnesium bromide (0.20 mL, 0.66 M in THF, 0.13 mmol, 2.1 equiv) dropwise. The resulting solution was then stirred for 15 min at –40 °C. Then, a premixed solution of TMSCl (0.02 mL, 0.13 mmol, 2.1 equiv) and dienedione **82** (25.0 mg, 0.062 mmol, 1.0 equiv) in THF (0.5 mL) was added dropwise and the resultant reaction mixture was allowed to warm to 25 °C over 8 h. Upon completion, the reaction contents were quenched by the addition of Et_3N (0.03 mL, 0.186 mmol, 3.0 equiv) followed by H_2O (15 mL), diluted with CH_2Cl_2 (10 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and

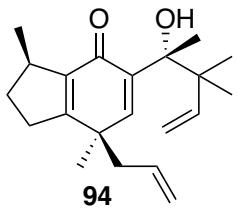
concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:CH_2Cl_2, 1:1) afforded desired isoprenyl **86** (24.1 mg, 0.051 mmol, 82% yield) as a yellow oil. **86**: R_f = 0.20 (silica gel, hexanes:CH_2Cl_2, 1:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 15.99 (d, J = 4.1 Hz, 1H), 4.71 – 4.59 (m, 2H), 3.69 (qdt, J = 7.5, 5.5, 2.5 Hz, 2H), 3.18 – 3.00 (m, 1H), 2.61 – 2.47 (m, 2H), 2.47 – 2.37 (m, 1H), 2.20 – 2.09 (m, 1H), 2.06 (s, 3H), 1.94 – 1.72 (m, 3H), 1.69 – 1.59 (m, 5H), 1.49 (dddd, J = 13.5, 11.3, 6.1, 2.4 Hz, 2H), 1.21 (d, J = 7.5 Hz, 3H), 1.17 – 1.10 (m, 3H), 1.04 (q, J = 3.6 Hz, 21H).



93

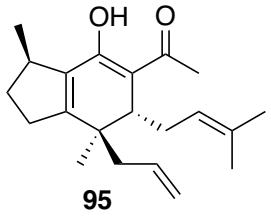
Tertiary Alcohol 93. To a flame-dried flask was added Cp_2TiCl_2 (194.2 mg, 0.78 mmol, 0.1 equiv) and Zn powder (1.54 g, 23.49 mmol, 3.0 equiv) before being flushed three times with N_2. Degassed THF (19 mL) was then added and the resultant mixture was allowed to stir at 25 °C for 15 min at which point the color turned green. Then, a premixed solution of ketone **69** (1.60 g, 7.83 mmol, 1.0 equiv) and prenyl bromide (2.7 mL, 23.49 mmol, 3.0 equiv) in degassed THF (20 mL) was added to the Ti(III) mixture in a dropwise fashion. The reaction solution was then stirred for an additional 1.5 h at 25 °C. Upon completion, the reaction contents were quenched by the addition of NH_4Cl (150 mL), diluted with CH_2Cl_2 (100 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 30:1→25:1→15:1) afforded recovered ketone **69** (401.3 mg, 1.96 mmol, 25% recovered) and the desired tertiary alcohol **93** (1.60 g, 5.81 mmol, 74% yield, 99% brsm) as a light yellow oil. **93**: R_f = 0.15 (silica gel, hexanes: EtOAc, 15:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.33 (d, J = 15.8 Hz, 1H),

6.57 (d, J = 2.6 Hz, 1H), 6.03 (ddd, J = 17.5, 10.8, 4.8 Hz, 1H), 5.23 – 5.12 (m, 2H), 3.40 (ddq, J = 17.5, 10.4, 3.5 Hz, 1H), 2.86 (ddt, J = 16.6, 12.4, 8.4 Hz, 1H), 2.70 (tdd, J = 15.7, 9.2, 3.6 Hz, 1H), 2.42 (d, J = 1.0 Hz, 1H), 2.32 – 2.21 (m, 1H), 2.15 (s, 3H), 1.76 – 1.69 (m, 1H), 1.61 (s, 3H), 1.24 (dd, J = 7.0, 4.1 Hz, 3H), 1.07 (dd, J = 6.4, 2.7 Hz, 6H).



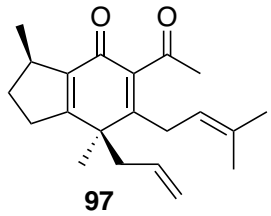
94

Dearomatized Tertiary Alcohol 94. To a solution of tertiary alcohol **93** (1.59 g, 5.79 mmol, 1.0 equiv) in HFIP (29 mL) at 25 °C was added allyl-TMS (5.5 mL, 34.74 mmol, 6.0 equiv) and a solution of PIDA (2.80 g, 8.69 mmol, 1.5 equiv) in HFIP (7.0 mL). The reaction contents were allowed to stir for 5 min before the addition of a second portion of PIDA (2.80 g, 8.69 mmol, 1.5 equiv) in HFIP (7.0 mL). The resultant solution was then stirred for a further 5 min. Upon completion, the reaction contents were quenched by the addition of $NaHCO_3$ (150 mL), diluted with Et_2O (100 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with Et_2O (3 × 100 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 30:1→15:1) afforded the desired dearomatized tertiary alcohol **94** (912.0 mg, 2.90 mmol, 50% yield, 1:1 *dr*) as a yellow oil. **94**: R_f = 0.10 (silica gel, hexanes: EtOAc, 15:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.49 (d, J = 9.5 Hz, 1H), 5.97 (ddd, J = 17.8, 10.9, 7.2 Hz, 1H), 5.40 – 5.31 (m, 1H), 5.03 – 4.84 (m, 4H), 3.14 (d, J = 7.7 Hz, 1H), 2.67 – 2.57 (m, 1H), 2.47 (dtd, J = 18.0, 8.9, 4.1 Hz, 1H), 2.38 (dp, J = 7.1, 1.1 Hz, 2H), 2.14 (dqd, J = 9.9, 8.9, 4.3 Hz, 1H), 1.63 – 1.51 (m, 2H), 1.36 (t, J = 1.4 Hz, 3H), 1.24 (s, 3H), 1.11 (dd, J = 6.9, 5.5 Hz, 3H), 1.03 (d, J = 8.5 Hz, 3H), 0.97 (s, 3H).



95

Prenyl 95. To a solution of dearomatized tertiary alcohol **94** (983.0 mg, 3.13 mmol, 1.0 equiv) in THF (16 mL) at 25 °C was added KHMDS (9.4 mL, 1.0 M in THF, 9.39 mmol, 3.0 equiv). The resulting solution was then stirred at 25 °C for 5 min. Upon completion, the reaction contents were quenched by the addition of NH_4Cl (75 mL), diluted with CH_2Cl_2 (50 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 30:1) afforded the desired prenyl **95** (775.9 mg, 2.47 mmol, 79% yield) as a light yellow oil. **95**: R_f = 0.40 (silica gel, hexanes: EtOAc, 15:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.75 (ddtd, J = 16.8, 10.1, 8.5, 6.5 Hz, 1H), 5.08 (dd, J = 10.2, 2.2 Hz, 1H), 5.06 – 4.95 (m, 2H), 3.18 – 3.02 (m, 1H), 2.53 (dddt, J = 16.9, 10.4, 6.1, 2.2 Hz, 1H), 2.48 – 2.35 (m, 2H), 2.27 – 2.02 (m, 5H), 1.96 (d, J = 3.6 Hz, 3H), 1.64 (dd, J = 5.7, 1.3 Hz, 3H), 1.54 – 1.47 (m, 1H), 1.44 (dd, J = 5.8, 1.4 Hz, 3H), 1.18 – 1.12 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ185.50, 181.12, 165.88, 139.14, 134.32, 133.41, 122.58, 118.29, 108.24, 44.67, 44.43, 40.60, 37.39, 32.48, 31.17, 29.27, 25.98, 20.66, 20.24, 20.06, 17.51. [NOTE: only the major diastereomer ^{13}C NMR peaks are reported here].

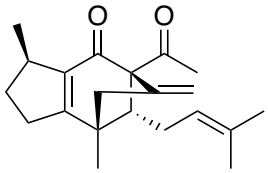


97

Prenylated Dienedione 97. NaH (32.0 mg, 60% dispersion in mineral oil, 0.80 mmol, 5.0 equiv) was washed three times with pentanes before being suspended in THF (1.0

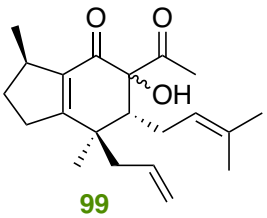
mL). To this suspension was added a solution of prenyl **95** (51.8 mg, 0.16 mmol, 1.0 equiv) in THF (1.0 mL) at 25 °C. The resultant mixture was stirred at this temperature for 1 h. Then, the reaction mixture was cooled to 0 °C before the rapid addition of a solution of PhSeCl (40.2 mg, 0.21 mmol, 1.3 equiv) in THF (0.4 mL). The reaction was stirred at 0 °C for 1 minute before it was quenched by the addition of NH_4Cl (15 mL), diluted with CH_2Cl_2 (10 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 20:1) afforded the desired selenide **96** (63.6 mg, 0.14 mmol, 88% yield). Pushing forward, to a solution of selenide **96** (58.8 mg, 0.125 mmol, 1.0 equiv) in CH_2Cl_2 (1.0 mL) and $NH_4Cl_{(aq)}$ (0.25 mL) at 0 °C was added H_2O_2 (0.05 mL, 30% v/v, 0.500 mmol, 4.0 equiv). The solution was then vigorously stirred for 20 min. Upon completion, the reaction contents were quenched by the addition of H_2O (15 mL), diluted with CH_2Cl_2 (10 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 20:1→10:1) afforded prenyl **95** (9.1 mg, 0.029 mmol, 23%) and the desired dienedione **97** (23.9 mg, 0.076 mmol, 61% yield) as a light yellow oil. **97**: R_f = 0.20 (silica gel, hexanes: EtOAc, 9:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.29 – 5.19 (m, 1H), 5.02 – 4.90 (m, 3H), 3.16 (s, 1H), 3.07 – 2.96 (m, 2H), 2.71 – 2.56 (m, 2H), 2.55 – 2.37 (m, 2H), 2.31 (d, J = 1.6 Hz, 3H), 2.13 (dddd, J = 10.9, 8.1, 6.9, 4.5 Hz, 1H), 1.68 (q, J = 1.5 Hz, 3H), 1.61 (d, J = 1.5 Hz, 3H), 1.52 (dd, J = 8.4, 4.3 Hz, 1H), 1.29 (d, J = 3.4 Hz, 3H), 1.14 (t, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.75, 182.66, 166.30, 161.03, 143.09, 142.13, 134.35, 132.71, 120.92, 117.77,

45.63, 41.77, 37.95, 32.25, 31.56, 31.20, 28.07, 25.66, 23.55, 19.45, 17.99. [NOTE: only the major diastereomer ^{13}C NMR peaks are reported here].



98

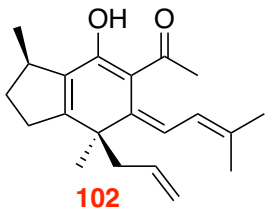
Terminal Olefin 98. To neat prenyl **97** (39.8 mg, 0.13 mmol, 1.0 equiv) was added $Pd(TFA)_2$ (4.3 mg, 0.013 mmol, 0.1 equiv) and the flask was then equipped with a condenser before being purged three times with O_2. DMSO (0.002 mL, 0.026 mmol, 0.2 equiv) was then added, followed by AcOH (0.65 mL). The reaction mixture was then placed in a preheated oil bath (65 °C) and was allowed to stir for 1 h. Upon completion, the reaction contents were concentrated directly and the resultant residue was purified by flash column chromatography (silica gel, hexanes:EtOAc, 15:1) to afford terminal olefin **98** (20.0 mg, 0.064 mmol, 49% yield) as a colorless oil. **98**: R_f = 0.20 (silica gel, hexanes: EtOAc, 15:1); ^1H NMR (500 MHz, $CDCl_3$) δ 5.12 – 5.00 (m, 2H), 4.97 (tdq, J = 7.2, 2.8, 1.4 Hz, 1H), 3.13 – 2.96 (m, 1H), 2.66 – 2.52 (m, 3H), 2.49 (d, J = 4.4 Hz, 3H), 2.46 – 2.37 (m, 1H), 2.36 – 2.30 (m, 1H), 2.19 – 2.09 (m, 1H), 2.08 – 1.97 (m, 2H), 1.62 (q, J = 1.4 Hz, 3H), 1.56 – 1.45 (m, 4H), 1.24 (d, J = 2.6 Hz, 3H), 1.19 (d, J = 6.9 Hz, 2H), 1.03 (d, J = 6.9 Hz, 1H).



99

Hydroxylated 99. To a solution of prenyl **97** (28.0 mg, 0.089 mmol, 1.0 equiv) in DMSO (0.15 mL) at 25 °C was added a homogenous, premixed solution of IBX (37.5 mg, 0.134 mmol, 1.5 equiv) and MPO (16.8 mg, 0.134 mmol, 1.5 equiv) in DMSO (0.35 mL). The reaction mixture was then placed in a preheated oil bath (40 °C) and was allowed to stir at this

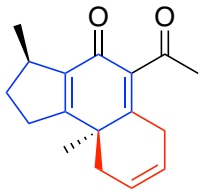
temperature for 2 h. Upon completion, the reaction contents were quenched by the addition of H_2O (10 mL), diluted with Et_2O (15 mL), and poured into a separatory funnel. The two phases were separated, and the organic layer was washed with $NaHCO_3$ (2 × 10 mL), H_2O (1 x 10 mL), and brine (1 x 10 mL). The organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by preparative thin layer chromatography (silica gel, hexanes:EtOAc, 15:1) afforded two independent sets of diastereomers of hydroxylated **99** (combined 18.0 mg, 0.054 mmol, 61% yield). **99**: [NOTE: one set of diastereomers is characterized here for clarity] R_f = 0.10 (silica gel, hexanes: EtOAc, 15:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.42 – 5.27 (m, 1H), 5.27 – 5.20 (m, 1H), 5.09 – 4.91 (m, 2H), 4.71 – 4.62 (m, 1H), 3.15 – 2.96 (m, 1H), 2.72 – 2.44 (m, 3H), 2.35 (ddd, J = 14.6, 7.6, 4.5 Hz, 1H), 2.28 – 2.19 (m, 6H), 2.14 (dtd, J = 12.7, 8.7, 5.8 Hz, 1H), 1.70 (d, J = 1.6 Hz, 3H), 1.65 (d, J = 1.4 Hz, 3H), 1.56 – 1.49 (m, 1H), 1.25 (d, J = 2.1 Hz, 3H), 1.16 (d, J = 6.9 Hz, 1H), 1.03 (d, J = 6.9 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.69, 194.29, 173.40, 139.56, 133.92, 131.82, 124.36, 119.29, 86.70, 49.77, 44.99, 41.91, 37.73, 32.32, 31.23, 28.79, 25.96, 25.92, 21.75, 20.53, 18.00. [NOTE: only the major diastereomer ^{13}C NMR peaks are reported here].



102

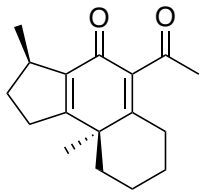
Conjugated 102. To a solution of prenylated dienedione **97** (15.3 mg, 0.049 mmol, 1.0 equiv) in THF (0.5 mL) at 25 °C was added *t*BuOOH (0.11 mL, 5.5 M in decanes, 0.588 mmol, 12.0 equiv) and Triton B (0.07 mL, 40% v/v in MeOH, 0.147 mmol, 3.0 equiv). The reaction mixture was then allowed to stir for 30 min. Upon completion, the reaction contents were quenched by the addition of $Na_2S_2O_3$ (15 mL), diluted with CH_2Cl_2 (10 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10

mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 20:1) afforded conjugated **102** (8.2 mg, 0.026 mmol, 54% yield) as a bright yellow oil. **102**: R_f = 0.30 (silica gel, hexanes: EtOAc, 20:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.07 (dd, J = 10.9, 2.8 Hz, 1H), 5.70 – 5.55 (m, 2H), 5.04 – 4.93 (m, 2H), 3.16 – 3.01 (m, 1H), 2.65 – 2.56 (m, 1H), 2.50 – 2.37 (m, 1H), 2.27 – 2.12 (m, 3H), 1.91 (d, J = 3.0 Hz, 3H), 1.80 (dd, J = 8.5, 1.4 Hz, 6H), 1.49 – 1.40 (m, 1H), 1.30 (d, J = 9.3 Hz, 3H), 1.18 – 1.11 (m, 3H).



103

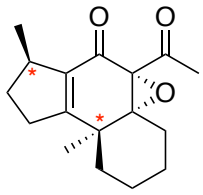
Tricyclic Olefin 103. To a solution of prenylated dienedione **97** (85.6 mg, 0.27 mmol, 1.0 equiv) in CH_2Cl_2 (2.7 mL) at 25 °C was added HG-II (16.9 mg, 0.027 mmol, 0.1 equiv). The resulting solution was then allowed to stir at this temperature for 2.5 h. Upon completion, the reaction contents were concentrated directly and the resultant residue was purified by flash column chromatography (silica gel, hexanes:EtOAc, 11:1→9:1) to afford tricyclic olefin **97** (62.5 mg, 0.24 mmol, 89% yield) as a yellow oil. **97**: R_f = 0.20 (silica gel, hexanes: EtOAc, 8:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.70 (dq, J = 2.6, 1.3 Hz, 2H), 3.24 – 3.13 (m, 1H), 3.10 – 2.94 (m, 2H), 2.78 – 2.51 (m, 2H), 2.40 (d, J = 1.0 Hz, 4H), 2.25 – 2.08 (m, 2H), 1.63 – 1.56 (m, 1H), 1.31 (d, J = 2.9 Hz, 3H), 1.18 (dd, J = 6.9, 3.4 Hz, 3H).



104

Tricycle 104. Pd/C (0.100 g, 10% by weight, 0.09 mmol, 0.08 equiv) was carefully added to a solution of tricyclic olefin **193** (306.9 mg, 1.20 mmol, 1.0 equiv) in EtOAc (12 mL) at

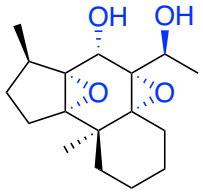
25 °C. The resultant suspension was then purged by direct bubbling with a balloon of H_2 gas for 0.5 h. Upon completion, the reaction contents were filtered through a short pad of Celite and washed with EtOAc (60 mL). The filtrate was concentrated directly and the resultant residue was purified by flash column chromatography (silica gel, hexanes:EtOAc, 7:1) to afford the desired tricycle **104** (151.0 mg, 0.58 mmol, 48% yield) as a colorless oil. **104**: R_f = 0.20 (silica gel, hexanes: EtOAc, 7:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.16 (d, J = 6.6 Hz, 1H), 2.66 (dddt, J = 17.8, 9.0, 6.8, 2.1 Hz, 1H), 2.58 – 2.41 (m, 2H), 2.38 (s, 3H), 2.36 – 2.26 (m, 1H), 2.23 – 2.10 (m, 1H), 2.06 – 1.96 (m, 2H), 1.79 – 1.66 (m, 2H), 1.52 (ddd, J = 8.4, 5.4, 4.2 Hz, 1H), 1.42 – 1.33 (m, 2H), 1.31 (d, J = 1.9 Hz, 3H), 1.17 (dd, J = 6.9, 0.8 Hz, 3H).



105
[XRAY of diast.]

Epoxide 105. To a solution of tricycle **104** (8.3 mg, 0.032 mmol, 1.0 equiv) in THF (0.5 mL) was added H_2O_2 (0.03 mL, 30% v/v, 0.320 mmol, 10.0 equiv) and Triton B (0.02 mL, 40% v/v in MeOH, 0.048 mmol, 1.5 equiv). The reaction mixture was then allowed to stir at 25 °C for 1 h. Upon completion, the reaction contents were quenched by the addition of H_2O (10 mL), diluted with Et_2O (10 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 4:1) afforded epoxide **105** (6.3 mg, 0.022 mmol, 72% yield) as a white crystal. **105**: R_f = 0.20 (silica gel, hexanes: EtOAc, 4:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.13 – 3.00 (m, 1H), 2.62 – 2.40 (m, 2H), 2.33 (d, J = 2.7 Hz, 3H),

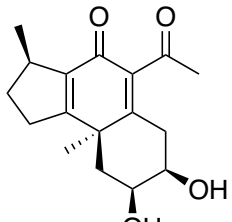
2.19 – 1.97 (m, 3H), 1.84 (dq, J = 13.3, 4.9 Hz, 1H), 1.69 – 1.62 (m, 1H), 1.59 (dd, J = 13.4, 3.6 Hz, 1H), 1.54 – 1.36 (m, 3H), 1.34 (s, 3H), 1.15 (d, J = 6.9 Hz, 1H), 1.10 – 1.05 (m, 3H).



106

Tricyclic Bisepoxide 106. To a solution of epoxide **105** (3.2 mg, 0.012 mmol, 1.0 equiv) in MeOH (0.5 mL) at 25 °C was added $CeCl_3 \bullet 7H_2O$ (11.2 mg, 0.030 mmol, 2.5 equiv) in a single portion. The reaction mixture was then allowed to stir for 10 min at that temperature before being cooled to –78 °C. Once cooled, $NaBH_4$ (1.1 mg, 0.030 mmol, 2.5 equiv) was added in one portion, and the resultant reaction solution was allowed to stir for 6 h at –78 °C. Upon completion, the reaction contents were quenched by the addition of NH_4Cl (15 mL), diluted with EtOAc (10 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 2:1) afforded the desired diol (2.2 mg, 0.0079 mmol, 68% yield) as a colorless oil. Pushing forward, to a solution of the so-obtained diol (2.1 mg, 0.0075 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL) at 0 °C was sequentially added $NaHCO_3$ (1.9 mg, 0.0225 mmol, 3.0 equiv) and *m*CPBA (3.4 mg, 70% by weight, 0.0150 mmol, 2.0 equiv) in one portion. The resultant mixture was then stirred for 1 h at 0 °C. The cooling bath was then removed, and the reaction was allowed to stir at 25 °C for an additional 2 h. Upon completion, the reaction contents were quenched by the addition of $NaHCO_3$ (15 mL), diluted with EtOAc (10 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated.

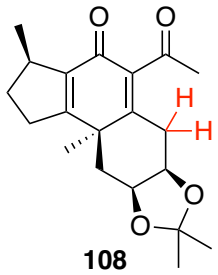
Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc 2:1) to afford the desired diepoxide **106** (1.6 mg, 0.0054 mmol, 72% yield) as a colorless oil. **106**: R_f = 0.15 (silica gel, hexanes:EtOAc, 2:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.37 (d, J = 11.7 Hz, 1H), 4.31 – 4.24 (m, 1H), 2.33 (d, J = 11.9 Hz, 1H), 2.14 (d, J = 6.5 Hz, 1H), 2.04 – 1.97 (m, 1H), 1.84 – 1.75 (m, 6H), 1.70 (ddd, J = 13.5, 10.3, 8.1 Hz, 2H), 1.55 (dt, J = 12.8, 3.8 Hz, 2H), 1.38 (dd, J = 6.7, 2.1 Hz, 3H), 1.31 (d, J = 7.2 Hz, 3H), 1.16 (d, J = 6.7 Hz, 3H).



107

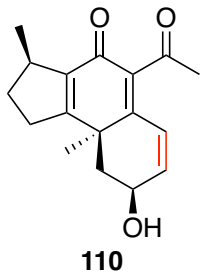
Tricyclic Diol 107. To a solution of tricyclic olefin **103** (14.6 mg, 0.057 mmol, 1.0 equiv) in acetone (0.50 mL) and H_2O (0.10 mL) at 25 °C was added NMO (13.4 mg, 0.114 mmol, 2.0 equiv). The resultant solution was stirred at this temperature for 15 min before the addition of OsO_4 (0.02 mL, 4% in H_2O, 0.003 mmol, 0.05 equiv). The reaction was then allowed to stir for 8 h. Upon completion, the reaction contents were quenched by the addition of $Na_2S_2O_3$ (15 mL), diluted with EtOAc (10 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, CH_2Cl_2:MeOH, 20:1) afforded the desired tricyclic diol **107** (12.1 mg, 0.042 mmol, 74% yield) as a colorless oil. **107**: R_f = 0.20 (silica gel, CH_2Cl_2:MeOH, 20:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.19 (s, 1H), 4.02 (s, 1H), 3.18 (s, 1H), 2.82 (d, J = 2.6 Hz, 1H), 2.72 (tdd, J = 16.9, 7.8, 2.9 Hz, 2H), 2.61 (dd, J = 14.7, 2.6 Hz, 1H), 2.58 –

2.53 (m, 1H), 2.49 (d, J = 1.5 Hz, 3H), 2.20 – 2.15 (m, 1H), 2.11 – 2.02 (m, 2H), 1.60 (d, J = 4.6 Hz, 1H), 1.36 (d, J = 1.7 Hz, 3H), 1.18 (d, J = 6.9 Hz, 3H).



108

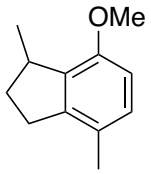
Acetonide 108. To a solution of diol **107** (10.7 mg, 0.037 mmol, 1.0 equiv) in CH_2Cl_2 (0.50 mL) at 0 °C was added 2,2-dimethoxypropane (0.02 mL, 0.185 mmol, 5.0 equiv) and PTSA•H_2O (0.8 mg, 0.004 mmol, 0.1 equiv). The cooling bath was the removed and the solution was allowed to stir at 25 °C for 2 h. Upon completion, the reaction contents were quenched by the addition of $NaHCO_3$ (15 mL), diluted with CH_2Cl_2 (10 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc 2:1) to afford the desired acetonide **108** (12.1 mg, 0.037 mmol, quant.) as a colorless oil. **108**: R_f = 0.10 (silica gel, CH_2Cl_2:MeOH, 20:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.50 – 4.39 (m, 2H), 3.19 (s, 1H), 2.88 (dd, J = 16.2, 1.5 Hz, 1H), 2.78 – 2.55 (m, 3H), 2.43 (d, J = 6.6 Hz, 3H), 2.21 – 2.09 (m, 2H), 2.00 – 1.87 (m, 1H), 1.65 (dd, J = 13.7, 7.9 Hz, 1H), 1.35 (d, J = 11.3 Hz, 3H), 1.29 (d, J = 8.7 Hz, 3H), 1.27 (d, J = 1.6 Hz, 3H), 1.17 (dd, J = 13.2, 6.9 Hz, 3H).



110

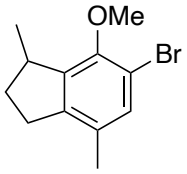
Allylic Alcohol 110. To a solution of acetonide **108** (2.5 mg, 0.008 mmol, 1.0 equiv) in THF (0.30 mL) was added Triton B (0.01 mL, 40% v/v in MeOH, 0.012 mmol, 1.5

equiv). The reaction mixture was then allowed to stir at 25 °C for 1 min. Upon completion, the reaction contents were quenched by the addition of H_2O (10 mL), diluted with Et_2O (10 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, CH_2Cl_2:MeOH, 15:1) afforded alcohol **110** (2.2 mg, 0.008 mmol, quant.) as a white crystal. **110**: R_f = 0.15 (silica gel, CH_2Cl_2:MeOH, 20:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.44 (ddd, J = 10.3, 4.6, 2.3 Hz, 1H), 6.24 – 6.14 (m, 1H), 4.59 (s, 1H), 3.20 (s, 1H), 2.78 – 2.67 (m, 1H), 2.65 – 2.54 (m, 1H), 2.50 – 2.40 (m, 4H), 2.25 – 2.13 (m, 1H), 1.67 – 1.58 (m, 2H), 1.54 – 1.47 (m, 1H), 1.29 (d, J = 6.2 Hz, 3H), 1.18 (t, J = 7.0 Hz, 3H).



116 **Methyl-Capped Phenol 116.** To a solution of indanone **63** (900.0 mg, 5.55 mmol, 1.0 equiv) in acetone (19 mL) at 0 °C was sequentially added K_2CO_3 (5.37 g, 38.85 mmol, 7.0 equiv) and MeI (6.9 mL, 111.00 mmol, 20.0 equiv). The cooling bath was then removed, and the reaction mixture was allowed to stir for an additional 8 h at 25 °C. Upon completion, the reaction contents were quenched by the addition of NH_4Cl (75 mL), diluted with CH_2Cl_2 (50 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 40:1) afforded the intermittent methylated indanone **115** (978.0 mg, 5.55 mmol, quant.) as an off-white solid. Pushing forward, to a solution of $MePh_3P^+Br^-$ (5.95 g, 16.65 mmol, 3.0 equiv) in THF (12 mL) at 0 °C was added *t*BuOK (16.1 mL, 1.0 M in THF, 16.10 mmol, 2.9

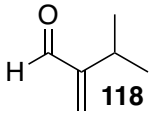
equiv) dropwise. The resulting solution was allowed to stir for 30 min at 0 °C before the addition of methylated indanone **115** (978.0 mg, 5.55 mmol, quant.) in THF (5 mL). The reaction mixture was stirred at 0 °C for an additional 5 min before the ice bath was removed. The solution was then stirred at 25 °C for 1 h. Upon completion, the reaction contents were quenched by the addition of NH_4Cl (50 mL), diluted with CH_2Cl_2 (50 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 40:1) afforded the desired intermediary methyl-protected olefin (861.3 mg, 4.94 mmol, 89% yield). Next, Pd/C (400.0 mg, 10% by weight, 0.38 mmol, 0.08 equiv) was carefully added to a solution of the so-obtained methyl-protected olefin (861.3 mg, 4.94 mmol, 1.0 equiv) in MeOH (20 mL) at 25 °C. The resultant suspension was then purged by direct bubbling with a balloon of H_2 gas for 1 h. Upon completion, the reaction contents were filtered through a short pad of Celite and washed with EtOAc (200 mL). The filtrate was concentrated directly to afford the desired crude methylated phenol **116** (848.7 mg, 4.92 mmol, 98% yield) as a colorless oil, without any additional purification required. **116**: R_f = 0.80 (silica gel, hexanes:EtOAc, 20:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.93 (d, J = 8.1 Hz, 1H), 6.60 (d, J = 8.1 Hz, 1H), 3.80 (s, 3H), 3.44 – 3.35 (m, 1H), 2.88 (dt, J = 16.3, 8.2 Hz, 1H), 2.73 (ddd, J = 16.1, 9.2, 4.1 Hz, 1H), 2.26 (dt, J = 12.6, 8.5 Hz, 1H), 2.19 (s, 3H), 1.71 (ddt, J = 12.4, 8.2, 3.9 Hz, 1H), 1.23 (d, J = 6.9 Hz, 3H).



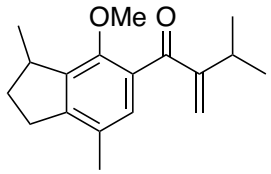
117

Bromophenol 117. To a solution of methylated phenol **116** (105.3 mg, 0.60 mmol, 1.0 equiv) in MeCN (6.0 mL) at 0 °C was added NBS (128.1 mg, 0.72 mmol, 1.2 equiv) in a single

portion. The reaction mixture was then allowed to slowly warm to 25 °C over 8 h. Upon completion, the reaction contents were quenched by the addition of $NaHCO_3$ (25 mL), diluted with CH_2Cl_2 (20 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:CH_2Cl_2, 8:1) afforded the desired bromophenol **117** (134.8 mg, 0.53 mmol, 88% yield) as a yellow oil. **117**: R_f = 0.20 (silica gel, hexanes: CH_2Cl_2, 8:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16 (s, 1H), 3.82 (s, 3H), 3.48 – 3.38 (m, 1H), 2.82 (dt, J = 15.9, 7.8 Hz, 1H), 2.68 (ddd, J = 16.2, 9.0, 5.0 Hz, 1H), 2.33 – 2.23 (m, 1H), 2.17 (s, 3H), 1.71 (ddt, J = 13.1, 8.5, 4.9 Hz, 1H), 1.28 (d, J = 7.0 Hz, 3H).

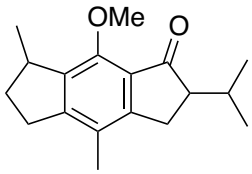


118 **Aldehyde 118.** To a solution of isovaleraldehyde (5.5 mL, 50.00 mmol, 1.0 equiv) in *i*PrOH (5.0 mL) at 25 °C was sequentially added formaldehyde (3.7 mL, 37% by volume, 50.00 mmol, 1.0 equiv), pyrrolidine (0.41 mL, 5.00 mmol, 0.1 equiv), and propionic acid (0.37 mL, 5.00 mmol, 0.1 equiv). The reaction mixture was then placed in a preheated oil bath (45 °C) and was allowed to stir for an additional 8 h. Upon completion, the reaction contents were quenched by the addition of $NaHCO_3$ (25 mL), diluted with CH_2Cl_2 (20 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and **carefully** concentrated. Purification of the resultant residue by flash column chromatography (silica gel, pentane:Et_2O, 9:1) afforded the desired aldehyde **118** (2.84 g, 28.93 mmol, 58% yield) as a clear and colorless oil. **118**: R_f = 0.60 (silica gel, pentane:Et_2O, 4:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.53 (s, 1H), 6.24 (d, J = 1.3 Hz, 1H), 5.95 (s, 1H), 2.80 (pd, J = 6.9, 1.2 Hz, 1H), 1.08 (d, J = 6.9 Hz, 6H).



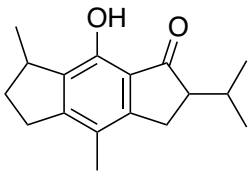
114

Nazarov Precursor 114. To a solution of bromophenol **117** (1.0140 g, 3.97 mmol, 1.0 equiv) in THF (24.0 mL) at –78 °C was slowly added *n*-BuLi (5.5 mL, 1.6 M in hexanes, 8.73 mmol, 2.2 equiv) and then the reaction mixture was stirred at –78 °C for 20 min. Then, aldehyde **118** (0.93 mL, 7.94 mmol, 2.0 equiv) was added in a dropwise manner. The resulting solution was then allowed to stir for a further 10 min. Upon completion, the reaction contents were quenched by the addition of NH_4Cl (50 mL), diluted with CH_2Cl_2 (50 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 20:1) afforded the desired allylic alcohol **119** (936.6 mg, 3.41 mmol, 86% yield) as a colorless oil. Pushing forward, to a solution of allylic alcohol **119** (927.2 mg, 3.38 mmol, 1.0 equiv) in CH_2Cl_2 (17.0 mL) at 25 °C was added solid $NaHCO_3$ (1.42 g, 16.90 mmol, 5.0 equiv) and Dess–Martin periodinane (2.15 g, 5.07 mmol, 1.5 equiv) sequentially. The resultant mixture was stirred at 25 °C for 30 min. Upon completion, the reaction contents were concentrated directly and the resultant residue was purified by flash column chromatography (silica gel, hexanes:EtOAc, 8:1) to afford the desired Nazarov precursor **114** (742.6 mg, 2.73 mmol, 81% yield) as a colorless oil. **114**: R_f = 0.50 (silica gel, hexanes:EtOAc, 8:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.87 (s, 1H), 5.82 (s, 1H), 5.66 (s, 1H), 3.69 (s, 3H), 3.49 – 3.38 (m, 1H), 3.08 (p, J = 6.8 Hz, 1H), 2.88 (dt, J = 16.1, 7.9 Hz, 1H), 2.74 (ddd, J = 16.5, 9.1, 5.1 Hz, 1H), 2.30 (dq, J = 12.7, 8.3 Hz, 1H), 2.20 (s, 3H), 1.73 (ddt, J = 13.2, 9.1, 4.8 Hz, 1H), 1.27 (d, J = 7.0 Hz, 3H), 1.14 (dd, J = 6.9, 3.8 Hz, 6H).



120

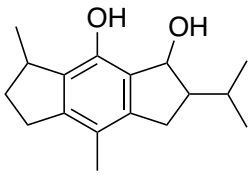
Tricycle 120. To neat enone **114** (69.3 mg, 0.25 mmol, 1.0 equiv) at 25 °C was added concentrated H_2SO_4 (1.0 mL). The resultant solution was then placed in a preheated oil bath (50 °C) and was allowed to stir for a further 1.5 h. were quenched by the addition of ice (10.0 g), diluted with EtOAc (10 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic extracts were then washed with $NaHCO_3$ (15 mL), dried (Na_2SO_4), filtered, and concentrated to yield tricycle **120** (54.0 mg, 0.20 mmol, 80% yield) directly without further purification required. **120**: R_f = 0.30 (silica gel, hexanes:EtOAc, 8:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.96 (d, J = 3.2 Hz, 3H), 3.43 (tt, J = 7.6, 4.3 Hz, 1H), 2.94 (dt, J = 13.3, 7.7 Hz, 2H), 2.79 (ddt, J = 17.0, 8.5, 4.2 Hz, 1H), 2.67 (dtt, J = 16.1, 8.1, 4.5 Hz, 2H), 2.42 (ddt, J = 10.9, 6.8, 4.1 Hz, 1H), 2.29 (dqd, J = 12.2, 8.4, 3.7 Hz, 1H), 2.23 – 2.14 (m, 3H), 1.75 (ddt, J = 12.7, 8.5, 4.3 Hz, 1H), 1.31 – 1.24 (m, 3H), 1.05 (dd, J = 7.0, 2.1 Hz, 3H), 0.78 (dd, J = 14.6, 6.8 Hz, 3H).



121

Phenol 121. To a solution of tricycle **120** (10.0 mg, 0.037 mmol, 1.0 equiv) in CH_2Cl_2 (0.74 mL) at –78 °C was added BBr_3 (0.05 mL, 1.0 M in CH_2Cl_2, 0.044 mmol, 1.2 equiv) dropwise. The reaction solution was then stirred at this temperature for a further 10 min. The cooling bath was then removed, and the reaction mixture was allowed to stir at 25 °C for an additional 5 min. Upon completion, the reaction contents were quenched by the addition of $NaHCO_3$ (15 mL), diluted with CH_2Cl_2 (10 mL), and poured into a separatory funnel. The two

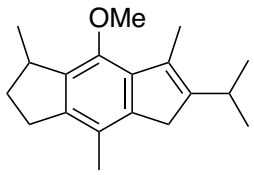
phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 50:1) afforded the desired phenol **121** (7.8 mg, 0.030 mmol, 81% yield) as a colorless oil. **121**: R_f = 0.50 (silica gel, hexanes:EtOAc, 8:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.10 (d, J = 1.7 Hz, 1H), 3.40 (p, J = 6.5 Hz, 1H), 2.99 – 2.87 (m, 2H), 2.82 – 2.66 (m, 3H), 2.41 – 2.26 (m, 2H), 2.14 (d, J = 1.7 Hz, 3H), 1.74 (ddt, J = 13.3, 9.2, 5.0 Hz, 1H), 1.29 (dd, J = 8.3, 6.9 Hz, 3H), 1.06 (dd, J = 6.9, 4.6 Hz, 3H), 0.82 (dd, J = 12.2, 6.8 Hz, 3H).



122

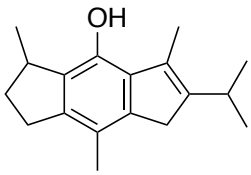
Alcohol 122. To a solution of phenol **121** (315.8 mg, 1.22 mmol, 1.0 equiv) in THF (12.0 mL) at 0 °C was added $LiAlH_4$ (92.6 mg, 2.44 mmol, 2.0 equiv) in a single portion. The reaction mixture was stirred at this temperature for 10 min before the cooling bath was removed. Then, the reaction was allowed to stir at 25 °C for an additional 5 min. Upon completion, the reaction contents were quenched by the addition of NH_4Cl (50 mL), diluted with EtOAc (50 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 10:1→4:1) afforded the desired alcohol **122** (261.3 mg, 1.00 mmol, 82% yield) as a white solid. [NOTE: one set of diastereomers is characterized here for clarity] **122**: R_f = 0.20 (silica gel, hexanes:EtOAc, 10:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.59 – 6.50 (m, 1H), 5.19 (q, J = 8.4 Hz, 1H), 3.39 (dd, J = 13.1, 7.3 Hz, 1H), 3.00 – 2.80 (m, 2H), 2.77 – 2.65 (m, 1H), 2.39 (dt, J = 15.8, 7.7 Hz, 1H), 2.33 – 2.22 (m, 1H), 2.07 (s, 3H), 2.03 – 1.94 (m, 1H), 1.92 –

1.80 (m, 2H), 1.77 – 1.66 (m, 1H), 1.28 (dd, J = 8.1, 6.9 Hz, 3H), 1.12 (d, J = 6.6 Hz, 3H), 1.01 (d, J = 6.6 Hz, 3H).



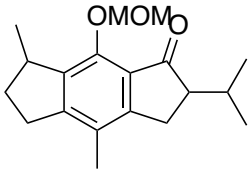
124

Olefin 124. To a solution of tricycle **120** (21.3 mg, 0.078 mmol, 1.0 equiv) in THF (0.50 mL) at 25 °C was added $LaCl_3$•2LiCl (0.20 mL, 0.6 M in THF, 0.117 mmol, 1.5 equiv). The resultant solution was stirred for 15 min before being cooled to –78 °C. Upon cooling, MeMgCl (0.04 mL, 3.0 M in Et_2O, 0.117 mmol, 1.5 equiv) was added dropwise and the cooling bath was removed. The reaction was then allowed to stir for 5 min at 25 °C. 3 M HCl (1.0 mL) was then added and was subsequently stirred for a further 30 min. Upon completion, the reaction contents were quenched by the addition of H_2O (15 mL), diluted with CH_2Cl_2 (10 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:CH_2Cl_2, 4:1) afforded the desired olefin **124** (20.1 mg, 0.074 mmol, 95%) as a colorless oil. **124**: R_f = 0.30 (silica gel, hexanes:CH_2Cl_2, 4:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.79 (s, 3H), 3.46 (td, J = 7.3, 4.8 Hz, 1H), 3.11 (d, J = 2.4 Hz, 2H), 3.03 (hept, J = 6.8 Hz, 1H), 2.91 (dt, J = 15.5, 7.7 Hz, 1H), 2.75 (ddd, J = 15.8, 8.8, 5.2 Hz, 1H), 2.31 (dq, J = 12.4, 7.9 Hz, 1H), 2.24 (d, J = 2.2 Hz, 3H), 2.20 (s, 3H), 1.73 (ddt, J = 13.0, 8.3, 4.9 Hz, 1H), 1.31 (d, J = 6.9 Hz, 3H), 1.13 (t, J = 7.2 Hz, 6H).



113
UNSTABLE

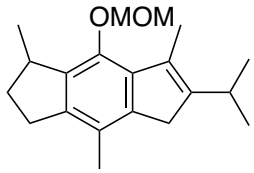
Unstable Phenol 113. To a flame-dried microwave vial was added LiSEt (10.2mg, 0.150 mmol, 3.0 equiv) and was subsequently flushed with N_2 three times before being sealed. To the vial was then added a solution of olefin **124** (13.5 mg, 0.050 mmol, 1.0 equiv) in DMF (0.60 mL). The reaction vessel was then subjected to microwave irradiation at 120 °C for 40 min. Upon completion, the reaction contents were quenched by the addition of 3 M HCl (1.0 mL), diluted with Et_2O (5 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:CH_2Cl_2, 6:1→5:1) afforded the desired olefin **113** (5.8 mg, 0.023 mmol, 46% yield) as a light-yellow oil. **113**: R_f = 0.40 (silica gel, hexanes:EtOAc, 8:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.55 (s, 1H), 3.37 (ddq, J = 14.0, 9.2, 4.5 Hz, 1H), 3.12 (t, J = 2.8 Hz, 2H), 3.04 – 2.90 (m, 2H), 2.78 (ddd, J = 15.9, 9.0, 3.3 Hz, 1H), 2.35 – 2.30 (m, 1H), 2.28 (t, J = 2.2 Hz, 3H), 2.16 (s, 3H), 1.83 – 1.73 (m, 1H), 1.26 (d, J = 6.9 Hz, 3H), 1.13 (dd, J = 6.9, 2.9 Hz, 6H).



125

MOM-protected Tricycle 125. To a solution of phenol **121** (334.7 mg, 1.30 mmol, 1.0 equiv) in CH_2Cl_2 (6.5 mL) at 0 °C was sequentially added *i*Pr_2NEt (2.3 mL, 13.00 mmol, 10.0 equiv) and MOMCl (0.39 mL, 5.20 mmol, 4.0 equiv). The cooling bath was then removed, and the reaction mixture was allowed to stir for 16 h at 25 °C. Upon completion, the reaction

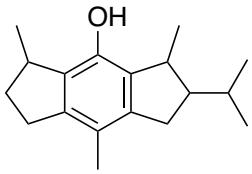
contents were quenched by the addition of NH_4Cl (25 mL), diluted with CH_2Cl_2 (30 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 20:1) afforded the desired MOM-protected tricycle **125** (391.0 mg, 1.29 mmol, 99% yield) as a clear oil. **125**: R_f = 0.30 (silica gel, hexanes:EtOAc, 8:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.31 – 5.17 (m, 2H), 3.63 – 3.54 (m, 3H), 3.47 (tt, J = 7.4, 3.7 Hz, 1H), 3.02 – 2.89 (m, 2H), 2.81 (ddt, J = 16.7, 8.5, 3.7 Hz, 1H), 2.74 – 2.62 (m, 2H), 2.45 – 2.26 (m, 2H), 2.19 (t, J = 3.4 Hz, 3H), 1.76 (ddt, J = 12.5, 8.1, 3.9 Hz, 1H), 1.29 (dd, J = 7.0, 4.1 Hz, 3H), 1.05 (dp, J = 5.1, 2.5 Hz, 3H), 0.77 (t, J = 6.8 Hz, 3H).



126

Olefin 125. To a solution of MOM-protected phenol **125** (385.0 mg, 1.27 mmol, 1.0 equiv) in THF (6.4 mL) at 25 °C was added $LaCl_3$•2LiCl (3.2 mL, 0.6 M in THF, 1.91 mmol, 1.5 equiv). The resultant solution was stirred for 15 min before being cooled to –78 °C. Upon cooling, MeMgCl (0.64 mL, 3.0 M in Et_2O, 1.91 mmol, 1.5 equiv) was added dropwise and the cooling bath was removed. The reaction was then allowed to stir for 5 min at 25 °C. 3 M HCl (15 mL) was then added and was subsequently stirred for a further 30 min. Upon completion, the reaction contents were quenched by the addition of H_2O (30 mL), diluted with CH_2Cl_2 (45 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 45 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 40:1) afforded the desired olefin **126** (345.6 mg, 1.15 mmol, 91%) as

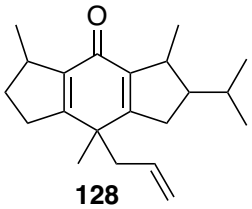
a colorless oil. **126**: R_f = 0.40 (silica gel, hexanes:EtOAc, 20:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.08 – 4.98 (m, 2H), 3.60 (d, J = 2.2 Hz, 3H), 3.50 (td, J = 7.6, 3.1 Hz, 1H), 3.14 – 3.08 (m, 2H), 3.02 (p, J = 7.0 Hz, 1H), 2.92 (dt, J = 16.2, 8.3 Hz, 1H), 2.79 (ddd, J = 11.8, 8.9, 4.5 Hz, 1H), 2.30 (dq, J = 12.2, 8.5 Hz, 1H), 2.25 – 2.17 (m, 6H), 1.73 (ddt, J = 12.2, 8.0, 3.6 Hz, 1H), 1.29 (dd, J = 6.9, 2.2 Hz, 3H), 1.13 (dd, J = 11.2, 6.8 Hz, 6H).



127

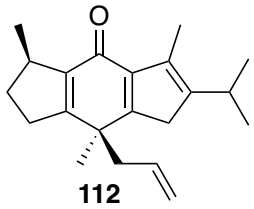
Phenol 127. Pd/C (10.0 mg, 10% by weight, 0.009 mmol, 0.12 equiv) was carefully added to a solution of MOM-protected phenol **126** (21.4 mg, 0.071 mmol, 1.0 equiv) in MeOH (1.0 mL) at 25 °C. The resultant suspension was then purged by direct bubbling with a balloon of H_2 gas for 1 h. Upon completion, the reaction contents were filtered through a short pad of Celite and washed with EtOAc (50 mL). The filtrate was then concentrated to afford the intermediary tricycle (21.4 mg, 0.071 mmol, quant.). Pushing forward, the so-obtained tricycle (19.6 mg, 0.065 mmol, 1.0 equiv) was then dissolved in MeOH (0.60 mL) and concentrated HCl (0.06 mL), and the reaction mixture was allowed to stir at 25 °C for 2 h. Upon completion, the reaction contents were quenched by the addition of $NaHCO_3$ (15 mL), diluted with EtOAc (10 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated to yield phenol **127** (16.9 mg, 0.065 mmol, quant.) as a white solid without further purification necessary. **127**: R_f = 0.20 (silica gel, hexanes:EtOAc, 8:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.27 (s, 1H), 3.33 (dt, J = 11.2, 4.8 Hz, 1H), 3.30 – 3.21 (m, 1H), 2.89 (dt, J = 16.4, 8.2 Hz, 1H), 2.85 – 2.76 (m, 1H), 2.70 (ddd, J = 15.8, 9.0, 4.2 Hz, 1H), 2.48 (dd, J = 15.2,

11.5 Hz, 1H), 2.34 – 2.25 (m, 1H), 2.09 (s, 3H), 1.95 (tt, J = 11.2, 7.2 Hz, 1H), 1.80 – 1.69 (m, 2H), 1.28 (d, J = 7.0 Hz, 3H), 1.04 (d, J = 7.0 Hz, 3H), 1.00 (dd, J = 6.5, 3.8 Hz, 6H).



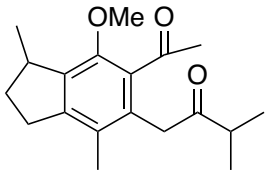
128

Dearomatized 128. To a solution of phenol **127** (15.7 mg, 0.061 mmol, 1.0 equiv) in HFIP (0.6 mL) at 25 °C was added allyl-TMS (0.06 mL, 0.366 mmol, 6.0 equiv) and a solution of PIDA (29.5 mg, 0.09 mmol, 1.5 equiv) in HFIP (0.10 mL). The reaction contents were allowed to stir for 5 min before the addition of a second portion of PIDA (29.5 mg, 0.09 mmol, 1.5 equiv) in HFIP (0.10 mL). The resultant solution was then stirred for a further 5 min. Upon completion, the reaction contents were quenched by the addition of $NaHCO_3$ (10 mL), diluted with EtOAc (10 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 30:1) afforded the desired TIPS-protected dearomatized **128** (15.4 mg, 0.052 mmol, 85% yield) as a colorless oil. **128**: R_f = 0.20 (silica gel, hexanes:EtOAc, 8:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.21 – 5.12 (m, 1H), 4.91 – 4.82 (m, 2H), 3.18 – 3.06 (m, 2H), 2.63 – 2.55 (m, 1H), 2.48 – 2.43 (m, 2H), 2.40 – 2.34 (m, 1H), 2.25 (ddd, J = 16.5, 11.1, 1.7 Hz, 1H), 2.13 (ddd, J = 13.0, 6.4, 3.3 Hz, 1H), 1.84 – 1.76 (m, 2H), 1.72 – 1.64 (m, 1H), 1.53 – 1.47 (m, 1H), 1.20 – 1.10 (m, 6H), 0.99 – 0.90 (m, 12H).



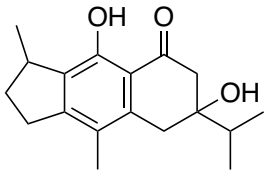
112

Dearomatized Olefin 112. To a solution of MOM-protected olefin **125** (50.2 mg, 0.17 mmol, 1.0 equiv) in MeOH (1.0 mL) at 25 °C was added concentrated HCl (0.10 mL). The resultant reaction mixture was then stirred at 25 °C for 4 h. Upon completion, the reaction contents were quenched by the addition of $NaHCO_3$ (15 mL), diluted with EtOAc (10 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated, taking care to evacuate with N_2. The resultant crude residue was directly dissolved in HFIP (0.85 mL) at 25 °C. To the reaction mixture was added allyl-TMS (0.16 mL, 1.02 mmol, 6.0 equiv) and a solution of PIDA (82.1 mg, 0.25 mmol, 1.5 equiv) in HFIP (0.20 mL). The reaction contents were allowed to stir for 5 min before the addition of a second portion of PIDA (82.1 mg, 0.25 mmol, 1.5 equiv) in HFIP (0.20 mL). The resultant solution was then stirred for a further 5 min. Upon completion, the reaction contents were quenched by the addition of $NaHCO_3$ (10 mL), diluted with EtOAc (10 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by two rounds of flash column chromatography (silica gel, hexanes:EtOAc, 40:1 *then* silica gel, hexanes:CH_2Cl_2, 2:1→1:1) afforded the desired dearomatized olefin **112** (12.0 mg, 0.040 mmol, 24% yield – with inseparable impurities) as a colorless oil. **112**: R_f = 0.20 (silica gel, hexanes:CH_2Cl_2, 1:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.22 – 4.76 (m, 3H), 3.17 (s, 1H), 3.04 – 2.92 (m, 1H), 2.67 – 2.43 (m, 3H), 2.34 – 2.21 (m, 1H), 2.13 (p, J = 7.6 Hz, 1H), 1.36 – 1.07 (m, 15H), 0.92 – 0.82 (m, 2H), 0.72 (dd, J = 12.5, 7.0 Hz, 1H).



130

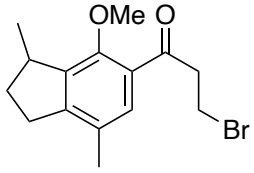
Dicarbonyl 130. To a solution of olefin **124** (100.0 mg, 0.37 mmol, 1.0 equiv) in MeCN (0.40 mL), CH_2Cl_2 (0.40 mL), H_2O (1.2 mL) at 25 °C was added $NaIO_4$ (257.4 mg, 1.11 mmol, 3.0 equiv) before being deoxygenated by direct bubbling of N_2 for 15 min. To the reaction mixture was then added catalyst **131** (12.7 mg, 0.019 mmol, 0.05 equiv), and was then placed into a preheated oil bath (45 °C). The reaction was then allowed to stir for 12 h at this temperature. Upon completion, the reaction contents were quenched by the addition of H_2O (10 mL), diluted with EtOAc (10 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 40:1→30:1→20:1) afforded the desired dicarbonyl **130** (47.6 mg, 0.16 mmol, 43% yield). **130**: R_f = 0.25 (silica gel, hexanes:EtOAc, 8:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.80 (s, 2H), 3.72 (s, 3H), 3.44 (dq, J = 13.9, 6.9 Hz, 1H), 2.91 (dt, J = 15.7, 7.6 Hz, 1H), 2.82 – 2.68 (m, 2H), 2.48 (s, 3H), 2.35 – 2.25 (m, 1H), 2.04 (s, 3H), 1.70 (ddt, J = 13.6, 8.7, 5.3 Hz, 1H), 1.29 (d, J = 6.9 Hz, 3H), 1.14 (dd, J = 6.9, 1.2 Hz, 6H).



133

Aldol Product 133. To a solution of dicarbonyl **130** (5.0 mg, 0.017 mmol, 1.0 equiv) in THF (0.34 mL) at 25 °C was added freshly prepared MgI_2 (0.85 mL, 0.2 M in Et_2O, 0.170 mmol, 10.0 equiv – prepared by dissolving I_2 (253.8 mg, 1.00 mmol, 1.0 equiv) in Et_2O (5.0 mL), adding Mg turnings (48.6 mg, 2.00 mmol, 2.0 equiv), and then stirring until colorless). The

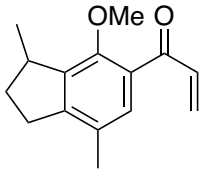
resultant reaction mixture was then placed in a preheated oil bath (50 °C) and was allowed to stir at this temperature for 36 h. Upon completion, the reaction contents were quenched by the addition of NH_4Cl (10 mL), diluted with EtOAc (10 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic extracts were then washed with Na_2SO_3 (30.0 mL), H_2O (30.0 mL), brine (30.0 mL), and then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 10:1) afforded the aldol product **133** (2.0 mg, 0.007 mmol, 41% yield) as a clear oil. **133**: R_f = 0.15 (silica gel, hexanes:EtOAc, 8:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.44 (d, J = 2.7 Hz, 1H), 3.44 (s, 1H), 3.00 – 2.88 (m, 3H), 2.87 – 2.77 (m, 1H), 2.76 – 2.71 (m, 2H), 2.33 – 2.21 (m, 1H), 2.12 (s, 3H), 1.89 – 1.82 (m, 1H), 1.72 (ddt, J = 12.6, 8.2, 4.1 Hz, 1H), 1.45 (d, J = 11.5 Hz, 1H), 1.31 – 1.23 (m, 6H), 1.07 – 1.01 (m, 6H).



137

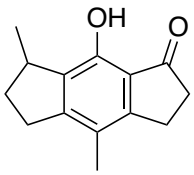
Acylated Aryl 137. To a solution of methylated phenol **116** (220.0 mg, 1.25 mmol, 1.0 equiv) in CH_2Cl_2 (6.3 mL) at 0 °C was added $TiCl_4$ (0.33 mL, 3.00 mmol, 2.4 equiv). The reaction mixture was allowed to stir for 2 min before the addition of 3-bromopropionyl chloride (0.33 mL, 3.25 mmol, 2.6 equiv). The resulting solution was allowed to stir for 10 min at 0 °C before the cooling bath was removed and the mixture stirred for an additional 10 min at 25 °C. Upon completion, the reaction contents were quenched by the addition of H_2O (50 mL), diluted with CH_2Cl_2 (50 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash

column chromatography (silica gel, hexanes:EtOAc, 30:1) afforded the desired acylated aryl **137** (308.5 mg, 0.99 mmol, 79% yield) as a yellow oil. **137**: R_f = 0.35 (silica gel, hexanes:EtOAc, 30:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (s, 1H), 3.91 – 3.84 (m, 1H), 3.80 (d, J = 0.9 Hz, 3H), 3.71 (ddd, J = 7.2, 6.2, 0.9 Hz, 1H), 3.62 – 3.53 (m, 1H), 3.50 – 3.43 (m, 2H), 2.89 (dt, J = 16.0, 7.7 Hz, 1H), 2.75 (ddd, J = 16.7, 9.0, 5.2 Hz, 1H), 2.39 – 2.28 (m, 1H), 2.22 (s, 3H), 1.75 (ddt, J = 13.2, 8.5, 5.0 Hz, 1H), 1.29 (d, J = 6.9 Hz, 3H).



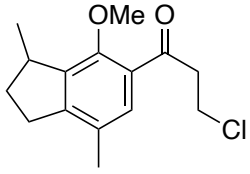
138

Enone 138. To a solution of acylated aryl **137** (306.4 mg, 0.98 mmol, 1.0 equiv) in benzene (4.9 mL) at 25 °C was added DBU (0.44 mL, 2.94 mmol, 3.0 equiv) dropwise. The reaction mixture was then placed in a preheated oil bath (80 °C) and was allowed to stir for 1 h. Upon completion, the reaction contents were quenched by the addition of NH_4Cl (15 mL), diluted with EtOAc (15 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic extracts were then then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 30:1) afforded the desired enone **138** (165.0 mg, 0.72 mmol, 74% yield) as a clear oil. **138**: R_f = 0.35 (silica gel, hexanes:CH_2Cl_2, 2:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 (s, 1H), 7.04 (dd, J = 17.2, 10.4 Hz, 1H), 6.31 (dd, J = 17.2, 1.7 Hz, 1H), 5.83 (dd, J = 10.4, 1.7 Hz, 1H), 3.71 (s, 3H), 3.50 – 3.41 (m, 1H), 2.90 (dt, J = 16.1, 7.9 Hz, 1H), 2.80 – 2.72 (m, 1H), 2.39 – 2.26 (m, 1H), 2.22 (s, 3H), 1.75 (ddt, J = 13.0, 8.5, 4.8 Hz, 1H), 1.29 (d, J = 6.9 Hz, 3H).



136

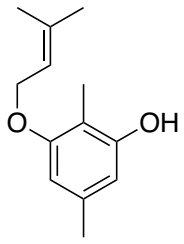
Demethylated Tricycle 136. To neat enone **138** (13.1 mg, 0.057 mmol, 1.0 equiv) at 25 °C was added concentrated H_2SO_4 (0.3 mL). The resulting solution was then placed in a preheated oil bath (50 °C) and was allowed to stir for 1 h. Upon completion, the reaction contents were quenched by the addition of ice (10.0 g), diluted with EtOAc (10 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic extracts were then washed with $NaHCO_3$ (15 mL), dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by preparative thin layer chromatography (silica gel, hexanes:EtOAc, 8:1) afforded demethylated tricycle **136** (2.0 mg, 0.009 mmol, 16% yield) as a colorless oil. **136**: R_f = 0.20 (silica gel, hexanes:EtOAc, 8:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (s, 1H), 4.57 – 4.43 (m, 2H), 3.38 (tt, J = 10.9, 5.5 Hz, 1H), 2.90 (dt, J = 16.6, 8.2 Hz, 1H), 2.81 – 2.68 (m, 3H), 2.37 – 2.27 (m, 1H), 2.19 (s, 3H), 1.75 (ddt, J = 12.8, 8.5, 4.2 Hz, 1H), 1.25 (d, J = 6.9 Hz, 3H).



140

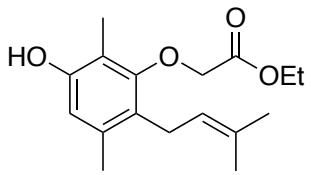
Chlorinated 140. To a solution of $AlCl_3$ (7.5 mg, 0.056 mmol, 1.1 equiv) in toluene (0.30 mL) at 25 °C was added a solution of enone **138** (11.8 mg, 0.051 mmol, 1.0 equiv) in toluene (0.20 mL). The resultant solution was allowed to stir for 12 h at this temperature. Upon completion, the reaction contents were quenched by the addition of 3 M HCl (1.0 mL), diluted with Et_2O (5 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column

chromatography (silica gel, hexanes:EtOAc, 8:1) afforded chlorinated **140** (1.0 mg, 0.004 mmol, 7% yield) as a light-yellow oil. **140**: R_f = 0.35 (silica gel, hexanes:EtOAc, 8:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (s, 1H), 3.92 – 3.84 (m, 2H), 3.80 (s, 3H), 3.51 – 3.34 (m, 3H), 2.89 (dt, J = 16.1, 7.8 Hz, 1H), 2.80 – 2.70 (m, 1H), 2.38 – 2.29 (m, 1H), 2.22 (s, 3H), 1.75 (ddt, J = 13.2, 8.5, 5.0 Hz, 1H), 1.29 (d, J = 6.9 Hz, 3H).



145

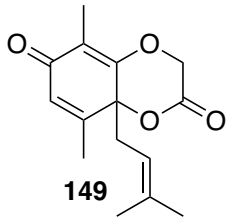
Prenylated Bisphenol 145. To a solution of prenyl bromide (0.25 mL, 2.16 mmol, 1.0 equiv) in acetone (22 mL) was added 2,5-dimethylresorcinol (596.9 mg, 4.32 mmol, 2.0 equiv) and K_2CO_3 (1.49 g, 10.80 mmol, 5.0 equiv) at 25 °C. The reaction mixture was then placed in a preheated oil bath (80 °C) and was allowed to stir at reflux for 8 h. Upon completion, the reaction contents were quenched by the addition of H_2O (30 mL), diluted with EtOAc (30 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 15:1→12:1→8:1→4:1) afforded recovered 2,5-dimethylresorcinol **144** (324.0 mg, 2.35 mmol, 54% recovered) and prenylated phenol **145** (186.3 mg, 0.90 mmol, 42% yield) as a yellow solid. **145**: R_f = 0.10 (silica gel, hexanes:EtOAc, 10:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.30 (d, J = 13.5 Hz, 2H), 5.50 (dddd, J = 6.5, 5.1, 2.8, 1.4 Hz, 1H), 4.55 (s, 1H), 4.48 (d, J = 6.5 Hz, 2H), 2.27 (s, 3H), 2.08 (s, 3H), 1.79 (s, 3H), 1.74 (s, 3H).



148

***para*-Prenylated phenol**. To a solution of prenylated phenol **145** (29.8 mg, 0.14 mmol, 1.0 equiv) in acetone (1.4 mL) at 25 °C in a sealed tube was added ethyl bromoacetate (0.02 mL, 0.17 mmol, 1.2 equiv) and K_2CO_3 (96.7 mg, 0.70 mmol, 5.0 equiv). The reaction vessel was then sealed and placed in a preheated oil bath (80 °C) before being allowed to stir for 8 h. Upon completion, the reaction contents were quenched by the addition of H_2O (15 mL), diluted with CH_2Cl_2 (15 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 15:1) afforded the desired alkylated phenol **146** (39.7 mg, 0.14 mmol, quant.). Pushing forward, to a flame dried flask was added CH_2Cl_2 (1.4 mL) before being degassed by bubbling N_2 for 15 min. To the degassed CH_2Cl_2 was then added 4-bromo-2,6-di-*tert*-butylphenol **147** (159.7 mg, 0.56 mmol, 4.0 equiv) followed by the dropwise addition of Me_3Al (0.14 mL, 2.0 M in hexanes, 0.28 mmol, 2.0 equiv). The resulting solution was then allowed to stir at 25 °C for 1 h before being cooled to –78 °C. Then, a solution of the so-obtained alkylated phenol **146** (39.7 mg, 0.14 mmol, 1.0 equiv) in CH_2Cl_2 (1.0 mL), and the reaction mixture was allowed to stir at –78 °C for an additional 2 h. Upon completion, the reaction contents were quenched by the addition of $NaHCO_3$ (10 mL), diluted with EtOAc (10 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 8:1) afforded desired phenol **148** (22.9 mg, 0.078 mmol, 57% yield)

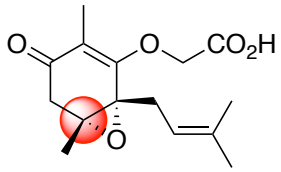
as a yellow oil. **148**: R_f = 0.10 (silica gel, hexanes:EtOAc, 8:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.46 (s, 1H), 5.02 (ddt, J = 6.5, 5.0, 1.4 Hz, 1H), 4.49 (s, 1H), 4.33 (s, 2H), 4.30 (q, J = 7.1 Hz, 2H), 3.32 (d, J = 6.5 Hz, 2H), 2.20 (s, 3H), 2.16 (s, 3H), 1.73 (d, J = 1.3 Hz, 3H), 1.67 (d, J = 1.5 Hz, 3H), 1.33 (t, J = 7.2 Hz, 3H).



149

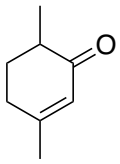
Lactone Dienone 149. To a solution of phenol **148** (21.0 mg, 0.072 mmol, 1.0 equiv) in THF (0.7 mL) and H_2O (0.7 mL) at 25 °C was added LiOH•H_2O (12.1 mg, 0.288 mmol, 4.0 equiv) in a single portion. The resulting mixture was then allowed to stir at 25 °C for an additional 20 min. Upon completion, the reaction contents were acidified by the addition of 1 M HCl (0.5 mL), further diluted with H_2O (10 mL), diluted with EtOAc (10 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated to provide the desired carboxylic acid (19.0 mg, 0.072 mmol, quant.) with no further purification necessary. Pushing forward, to a solution of the so-obtained carboxylic acid (18.3 mg, 0.069 mmol, 1.0 equiv) in HFIP (1.0 mL) at 0 °C was added PIDA (24.5 mg, 0.076 mmol, 1.1 equiv). The solution was then stirred at this temperature for a further 15 min. Upon completion, the reaction contents were quenched by the addition of $NaHCO_3$ (10 mL), diluted with EtOAc (10 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 10:1) afforded desired dienone **149** (12.8 mg, 0.049 mmol, 71% yield) as a yellow oil. **149**: R_f = 0.80 (silica gel, hexanes:EtOAc, 2:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.08

(d, J = 1.5 Hz, 1H), 4.93 (d, J = 17.8 Hz, 1H), 4.78 (d, J = 17.8 Hz, 2H), 2.84 (dd, J = 13.7, 8.2 Hz, 1H), 2.65 (dd, J = 13.7, 7.2 Hz, 1H), 2.09 (d, J = 1.5 Hz, 3H), 1.81 (s, 3H), 1.64 (s, 3H), 1.56 (s, 3H).



151

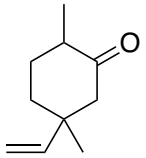
Epoxide 151. To a solution of dienone **149** (28.0 mg, 0.107 mmol, 1.0 equiv) in THF (1.1 mL) and H_2O (1.1 mL) at 25 °C was added LiOH•H_2O (18.0 mg, 0.428 mmol, 4.0 equiv) in a single portion. The resulting mixture was then allowed to stir at 25 °C for an additional 10 min. Upon completion, the reaction contents were acidified by the addition of 3 M HCl (1.4 mL), further diluted with H_2O (10 mL), diluted with EtOAc (10 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated to provide epoxide **151** (30.0 mg, 0.107 mmol, quant.) directly without further purification required. **151**: R_f = 0.05 (silica gel, hexanes:EtOAc, 8:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.02 – 4.94 (m, 1H), 4.90 – 4.75 (m, 2H), 2.79 (d, J = 16.4 Hz, 1H), 2.58 (d, J = 16.4 Hz, 1H), 2.33 (dd, J = 14.3, 7.0 Hz, 1H), 2.18 (dd, J = 14.3, 8.3 Hz, 1H), 1.94 (s, 3H), 1.67 (s, 3H), 1.54 (s, 3H), 1.19 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.46, 197.39, 173.72, 156.66, 136.46, 133.50, 118.47, 67.93, 48.90, 48.88, 37.74, 26.06, 24.09, 18.02, 9.58.



158

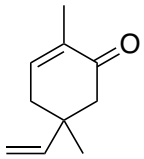
Methylated Enone 158. To a solution of *i*-Pr_2NH (3.7 mL, 26.45 mmol, 1.2 equiv) in THF (44 mL) at 0 °C was slowly added *n*-BuLi (15.2 mL, 1.6 M in hexanes, 24.24 mmol, 1.1 equiv) and then the reaction mixture was stirred at 0 °C for 15 min before being cooled to –78 °C.

Next, enone **157** (2.5 mL, 22.04 mmol, 1.0 equiv) was added to the freshly prepared solution of LDA and the resultant solution was stirred for an additional 30 min at –78 °C before the addition of MeI (2.7 mL, 44.08 mmol, 2.0 equiv). The resultant mixture was then stirred for an additional 30 min at –78 °C before being warmed to 0 °C, at which it was stirred for another 30 min. Upon completion, the reaction contents were quenched by the addition of NH_4Cl (50 mL), diluted with CH_2Cl_2 (50 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 8:1) afforded the desired enone **158** (2.2689 g, 18.27 mmol, 83% yield) as a yellow oil. **158**: R_f = 0.30 (silica gel, hexanes:EtOAc, 8:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.84 (dq, J = 2.3, 1.2 Hz, 1H), 2.41 – 2.23 (m, 3H), 2.05 (dq, J = 13.6, 4.7 Hz, 1H), 1.93 (d, J = 1.3 Hz, 3H), 1.70 (dddd, J = 13.3, 11.7, 10.1, 5.1 Hz, 1H), 1.13 (d, J = 6.8 Hz, 3H).



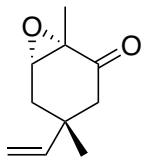
159 **Vinyl 159**. To a suspension of CuBr•DMS (65.8 mg, 0.32 mmol, 0.15 equiv) in THF (7 mL) in a flame-dried flask at –78 °C was sequentially added vinylmagnesium bromide (4.5 mL, 1.0 M in THF, 4.45 mmol, 2.1 equiv) and HMPA (2.2 mL, 12.72 mmol, 6.0 equiv). The resulting mixture was allowed to stir for an additional 15 min before the subsequent addition of a premixed solution of enone **158** (262.7 mg, 2.12 mmol, 1.0 equiv) and TMSCl (1.4 mL, 10.60 mmol, 5.0 equiv) in THF (7 mL). The reaction was then allowed to stir at –78 °C for a further 2 h before being warmed to –40 °C at which it was stirred for an additional 1 h. Upon completion, the reaction contents were quenched by the addition of 1 M HCl (25 mL), diluted with CH_2Cl_2 (25 mL), and

poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were then washed with H_2O (50 mL), $NaHCO_3$ (50 mL), and NH_4Cl/NH_4OH (9:1, 50 mL), before being dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 20:1) afforded the desired vinyl **159** (215.2 mg, 1.41 mmol, 67% yield) as a colorless oil. **159**: R_f = 0.60 (silica gel, hexanes:EtOAc, 7:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.88 – 5.57 (m, 1H), 5.06 – 4.92 (m, 2H), 2.56 – 2.31 (m, 1H), 2.31 – 2.15 (m, 2H), 2.07 – 1.86 (m, 1H), 1.81 – 1.59 (m, 2H), 1.54 – 1.42 (m, 1H), 1.10 (s, 2H), 1.06 – 0.99 (m, 3H), 0.97 (s, 1H).

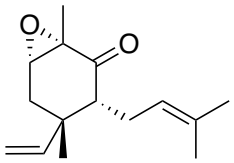


156 **Vinyl enone 156**. Vinyl **159** (213.1 mg, 1.40 mmol, 1.0 equiv) was flushed three times with O_2 before the subsequent addition of DMSO (5 mL), Cs_2CO_3 (228.1 mg, 0.70 mmol, 0.5 equiv), and $P(OEt)_3$ (0.48 mL, 2.80 mmol, 2.0 equiv). The resulting solution was then allowed to stir under an O_2 atmosphere at 25 °C for 20 h. Upon completion, the reaction contents were diluted by the addition of EtOAc (15 mL) and brine (15 mL), before being poured into a separatory funnel. The two phases were separated, and the organic layer was washed with brine (2 × 15 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 7:1) afforded the desired tertiary alcohol (194.6 mg, 1.16 mmol, 83% yield). Pushing forward, to a solution of the so-obtained tertiary alcohol (194.6 mg, 1.16 mmol, 1.0 equiv) in pyridine (12 mL) at 0 °C was added $SOCl_2$ (0.17 mL, 2.32 mmol, 2.0 equiv). The cooling bath was then removed, and the reaction mixture was allowed to stir at 25 °C for 3 h. Upon completion, the reaction contents were quenched by the addition of 3 M HCl (30 mL), diluted with CH_2Cl_2 (30 mL), and poured into a

separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated to directly afford enone **156** (160.2 mg, 1.07 mmol, 92% yield) as a yellow oil with no further purification required. **156**: R_f = 0.30 (silica gel, hexanes:EtOAc, 7:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.63 – 6.57 (m, 1H), 5.77 (dd, J = 17.4, 10.9 Hz, 1H), 5.03 – 4.91 (m, 2H), 2.51 (d, J = 14.6 Hz, 1H), 2.44 – 2.24 (m, 3H), 1.77 (q, J = 2.0 Hz, 3H), 1.11 (s, 3H).

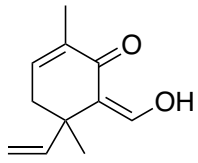


160 **Vinyl epoxide 160**. To a solution of enone **156** (30.5 mg, 0.20 mmol, 1.0 equiv) in MeOH (2.0 mL) at 25 °C was added H_2O_2 (0.21 mL, 30% v/v, 2.00 mmol, 10.0 equiv) and NaOH (0.20 mL, 3.0 M in H_2O, 0.60 mmol, 3.0 equiv). The reaction vessel was then sealed and placed in a preheated oil bath (45 °C) and was allowed to stir for 1 h. Upon completion, the reaction contents were quenched by the addition of NH_4Cl (15 mL), diluted with CH_2Cl_2 (15 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated to directly afford epoxide **160** (28.0 mg, 0.17 mmol, 85% yield) as a colorless oil without further purification required. **160**: R_f = 0.50 (silica gel, hexanes:EtOAc, 9:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.80 – 5.61 (m, 1H), 5.03 – 4.91 (m, 2H), 3.40 (t, J = 4.3 Hz, 1H), 2.85 – 2.70 (m, 1H), 2.22 – 2.02 (m, 2H), 1.95 – 1.76 (m, 1H), 1.44 – 1.32 (m, 3H), 1.09 – 0.99 (m, 3H).



161

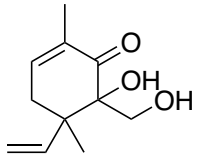
Prenyl 161. To a solution of epoxide **160** (25.2 mg, 0.15 mmol, 1.0 equiv) in THF (1.5 mL) at –78 °C was added LiHMDS (0.18 mL, 1.0 M in THF, 0.18 mmol, 1.2 equiv). The reaction mixture was then allowed to stir for 30 min at –78 °C before the addition of prenyl bromide (0.02 mL, 0.18 mmol, 1.2 equiv). After a further 15 min at –78 °C, the cooling bath was removed, and the solution was then stirred at 25 °C for 20 h. Upon completion, the reaction contents were quenched by the addition of NH_4Cl (15 mL), diluted with CH_2Cl_2 (15 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 40:1) afforded recovered epoxide **160** (6.4 mg, 0.039 mmol, 26% recovered) and the desired prenylated **161** (12.1 mg, 0.052 mmol, 34% yield, 46% yield brsm) as a colorless oil. **161**: R_f = 0.55 (silica gel, hexanes:EtOAc, 9:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.81 – 5.59 (m, 1H), 5.10 – 4.91 (m, 3H), 3.41 – 3.34 (m, 1H), 2.85 – 2.79 (m, 1H), 2.26 (d, J = 15.5 Hz, 1H), 2.15 – 2.11 (m, 1H), 1.87 – 1.70 (m, 2H), 1.65 – 1.55 (m, 6H), 1.45 – 1.37 (m, 3H), 1.13 – 0.85 (m, 3H).



163

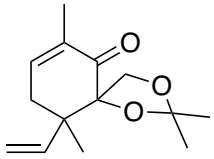
Conjugated Enol 163. To a solution of enone **156** (536.7 mg, 3.57 mmol, 1.0 equiv) in toluene (7.1 mL) at 0 °C was sequentially added ethyl formate (2.0 mL, 24.99 mmol, 7.0 equiv), NaH (428.4 mg, 60% by weight in mineral oil, 3.57 mmol, 3.0 equiv), and MeOH (0.14 mL, 3.57 mmol, 1.0 equiv). The cooling bath was then removed, and the reaction mixture was

allowed to stir at 25 °C for 8 h. Upon completion, the reaction contents were quenched by the addition of 3 M HCl (10 mL), diluted with CH_2Cl_2 (15 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 30:1) afforded conjugated enol **163** (576.4 mg, 3.23 mmol, 90% yield) as a yellow oil. **163**: R_f = 0.60 (silica gel, hexanes:EtOAc, 8:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 14.80 (d, J = 9.7 Hz, 1H), 7.50 (d, J = 9.7 Hz, 1H), 6.46 (ddt, J = 4.5, 3.1, 1.6 Hz, 1H), 5.83 (dd, J = 17.2, 10.5 Hz, 1H), 5.07 – 5.00 (m, 2H), 2.42 – 2.35 (m, 1H), 2.27 – 2.20 (m, 1H), 1.86 (q, J = 1.8 Hz, 3H), 1.27 (s, 3H).



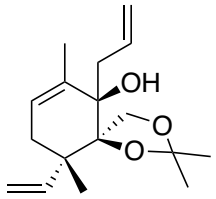
165 **Diol 165**. To a solution of conjugated enol **163** (216.1 mg, 1.21 mmol, 1.0 equiv) in DMSO (0.5 mL) was added a pre-dissolved solution of IBX (1.02 g, 3.63 mmol, 3.0 equiv) and MPO (454.1 mg, 3.63 mmol, 3.0 equiv) in DMSO (5.5 mL) at 25 °C. The reaction mixture was then placed into a preheated oil bath (45 °C) and was allowed to stir for 30 min. Upon completion, the reaction contents were quenched by the addition of $NaHCO_3$ (10 mL), diluted with Et_2O (15 mL), and poured into a separatory funnel. The two phases were separated, and the organic layer was washed with $NaHCO_3$ (15 mL), H_2O (15 mL), and brine (15 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated to afford crude α-hydroxylated aldehyde **164** (170.3 mg, 0.88 mmol, 82% yield, 1:1.4 *dr*) as a white foam. Pushing forward, to a solution of crude α-hydroxylated aldehyde **164** (169.8 mg, 0.87 mmol, 1.0 equiv) in THF (6.0 mL) at –78 °C was added LiAl(*t*BuO)$_3$H (2.6 mL, 1.0 M in THF, 2.61 mmol, 3.0 equiv) dropwise. The resultant mixture was then stirred for a further 30 min at this temperature. Upon completion, the

reaction contents were quenched by the addition of Rochelle's Salt (20 mL), stirred for 1 h, diluted with EtOAc (15 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 2:1) afforded diol **165** (130.0 mg, 0.66 mmol, 62% yield over 2 steps) as a white foam. **165**: R_f = 0.20 (silica gel, hexanes:EtOAc, 2:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.68 – 6.55 (m, 1H), 6.13 – 5.84 (m, 1H), 5.18 – 4.98 (m, 2H), 4.17 – 4.07 (m, 1H), 3.92 – 3.82 (m, 1H), 3.80 – 3.68 (m, 1H), 2.71 – 2.25 (m, 2H), 1.90 – 1.81 (m, 3H), 1.20 – 0.98 (m, 3H).



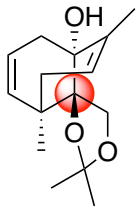
166

Acetonide 166. To a solution of diol **165** (125.5 mg, 0.64 mmol, 1.0 equiv) in CH_2Cl_2 (6.4 mL) at 25 °C was added 2,2-dimethoxypropane (0.39 mL, 3.20 mmol, 5.0 equiv) and *p*TSA•H_2O (11.4 mg, 0.06 mmol, 0.1 equiv). The reaction mixture was then allowed to stir for 8 h at this temperature. Upon completion, the reaction contents were quenched by the addition of $NaHCO_3$ (10 mL), diluted with CH_2Cl_2 (15 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 8:1) afforded acetonide **166** (132.3 mg, 0.56 mmol, 88% yield) as a colorless oil. **166**: R_f = 0.60 (silica gel, hexanes:EtOAc, 2:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.56 (d, J = 11.2 Hz, 1H), 6.12 – 5.86 (m, 1H), 5.20 – 5.03 (m, 2H), 4.22 (s, 1H), 3.97 – 3.79 (m, 1H), 2.74 – 2.27 (m, 2H), 1.87 – 1.78 (m, 3H), 1.46 – 1.32 (m, 6H), 1.18 – 1.02 (m, 3H).



168

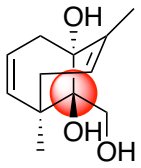
Allyl 168. To a solution of acetonide **166** (129.3 mg, 0.55 mmol, 1.0 equiv) in THF (5.5 mL) at –78 °C was added allylmagnesium bromide (1.1 mL, 1.0 M in THF, 1.10 mmol, 2.0 equiv) in a dropwise fashion. The resultant reaction mixture was then stirred for an additional 5 min at this temperature. Upon completion, the reaction contents were quenched by the addition of NH_4Cl (10 mL), diluted with CH_2Cl_2 (15 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 20:1) afforded allyl **167/168** (134.2 mg, 0.48 mmol, 87% yield) as a colorless oil. **168**: R_f = 0.40 (silica gel, hexanes:EtOAc, 8:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.23 – 5.90 (m, 2H), 5.50 – 5.41 (m, 1H), 5.14 – 4.94 (m, 4H), 4.16 – 3.95 (m, 2H), 2.64 – 2.17 (m, 4H), 1.85 – 1.74 (m, 3H), 1.60 – 1.55 (m, 2H), 1.50 – 1.41 (m, 4H), 1.17 – 1.07 (m, 3H).



iso-**169**

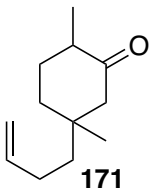
Undesired Bridged Bicycle *iso*-169. To a solution of allyl **167/168** (129.8 mg, 0.47 mmol, 1.0 equiv) in CH_2Cl_2 (4.7 mL) at 25 °C was added Grubbs 1st generation initiator (38.7 mg, 0.047 mmol, 0.1 equiv) in a single portion. The resulting solution was then allowed to stir at 25 °C for a further 3 h. Upon completion, the reaction mixture was concentrated directly. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 12:1) afforded undesired bridged bicycle *iso*-**169** (34.7 mg, 0.14 mmol, 30% yield) as a white crystalline solid

(unreacted material was not recovered). *iso*-**169**: R_f = 0.20 (silica gel, hexanes:EtOAc, 8:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.53 – 5.44 (m, 2H), 5.29 (d, J = 12.7 Hz, 1H), 4.19 (d, J = 8.8 Hz, 1H), 3.94 (d, J = 8.8 Hz, 1H), 2.40 – 2.31 (m, 1H), 2.31 – 2.20 (m, 1H), 2.08 (s, 1H), 2.04 (d, J = 17.9 Hz, 1H), 1.73 (s, 3H), 1.56 (s, 3H), 1.46 (s, 3H), 1.09 (s, 3H).



170
[*XRAY*]

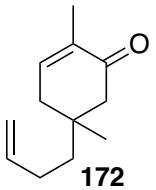
Triol 170. To *iso*-**169** (34.7 mg, 0.14 mmol, 1.0 equiv) was added THF (1.4 mL) and 1M HCl (1.4 mL) at 25 °C. The resulting solution was then allowed to stir at 25 °C for 12 h. Upon completion, the reaction contents were quenched by the addition of H_2O (10 mL), diluted with EtOAc (15 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 1:1) afforded triol **170** (24.1 mg, 0.11 mmol, 79% yield) as a colorless crystalline solid. **170**: R_f = 0.15 (silica gel, hexanes:EtOAc, 1:1); 5.47 (dd, J = 9.8, 5.1 Hz, 1H), 5.42 (s, 1H), 5.29 (d, J = 9.5 Hz, 1H), 4.07 (dd, J = 11.7, 5.2 Hz, 1H), 3.85 (dd, J = 11.7, 5.8 Hz, 1H), 3.42 (s, 1H), 2.83 (s, 1H), 2.54 – 2.43 (m, 2H), 2.29 (s, 2H), 1.74 – 1.65 (m, 4H), 1.01 (d, J = 1.7 Hz, 3H).



171

Homoallyl 171. To a flame-dried flask was added CuBr•DMS (921.0 mg, 4.48 mmol, 0.2 equiv). The flask was the flushed three times with N_2 before the addition of THF (34 mL). The solution was then cooled to –40 °C before the dropwise addition of freshly prepared

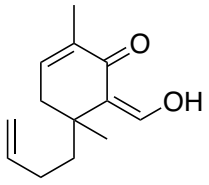
homoallylmagnesium bromide (34 mL, 0.66 M in THF, 22.44 mmol, 1.0 equiv – prepared by flushing a mixture of Mg turnings (1.09 g, 44.78 mmol, 2.0 equiv) and I_2 (1 chip) with N_2, adding THF (34 mL), heating at 70 °C for 10 min, then removing from heat and adding homoallyl bromide (3.4 mL, 33.59 mmol, 1.5 mmol) dropwise, maintaining a gentle reflux, and then heating at 70 °C for a further 30 min). The reaction mixture was then allowed to stir for 30 min before being cooled to –78 °C. Next, a solution of enone **158** (2.78 g, 22.39 mmol, 1.0 equiv) in THF (10 mL) was added dropwise. The resulting solution was then slowly warmed to 25 °C over 1 h. Upon completion, the reaction contents were quenched by the addition of 3 M HCl (60 mL), diluted with CH_2Cl_2 (60 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 60 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 20:1) afforded homoallyl **171** (3.4888 g, 19.35 mmol, 86% yield) as a colorless oil. **171**: R_f = 0.60 (silica gel, hexanes:EtOAc, 8:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.78 (tdt, J = 16.8, 10.3, 6.4 Hz, 1H), 5.05 – 4.88 (m, 2H), 2.32 (dt, J = 11.2, 6.5 Hz, 1H), 2.24 – 2.11 (m, 2H), 1.98 (tdt, J = 16.5, 12.6, 7.8 Hz, 3H), 1.74 – 1.56 (m, 2H), 1.53 – 1.40 (m, 1H), 1.25 (dd, J = 9.4, 7.6 Hz, 2H), 1.06 – 0.84 (m, 6H).



172

Enone 172. Homoallyl **171** (3.4859 g, 19.33 mmol, 1.0 equiv) was flushed three times with O_2 before the subsequent addition of DMSO (40 mL), Cs_2CO_3 (3.15 g, 9.67 mmol, 0.5 equiv), and $P(OEt)_3$ (6.6 mL, 38.66 mmol, 2.0 equiv). The resulting solution was then allowed to stir under an O_2 atmosphere at 25 °C for 20 h. Upon completion, the reaction contents were diluted by the addition of EtOAc (60 mL) and brine (60 mL), before being poured into a separatory funnel. The

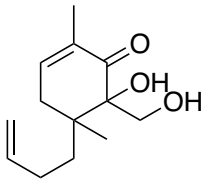
two phases were separated, and the organic layer was washed with brine (2 × 60 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 7:1) afforded the desired tertiary alcohol (3.48 g, 17.73 mmol, 92% yield). Pushing forward, to a solution of the so-obtained tertiary alcohol (3.48 g, 17.73 mmol,1.0 equiv) in pyridine (118 mL) at 0 °C was added $SOCl_2$ (2.6 mL, 35.46 mmol, 2.0 equiv). The cooling bath was then removed, and the reaction mixture was allowed to stir at 25 °C for 8 h. Upon completion, the reaction contents were quenched by the addition of 3 M HCl (120 mL), diluted with CH_2Cl_2 (120 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 120 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 20:1→15:1→8:1) afforded desired enone **172** (1.1063 g, 6.21 mmol, 35% yield) as a yellow oil. **172**: R_f = 0.40 (silica gel, hexanes:EtOAc, 8:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.58 (d, J = 4.9 Hz, 1H), 5.84 – 5.73 (m, 1H), 5.07 – 4.91 (m, 2H), 2.30 (q, J = 15.8 Hz, 3H), 2.20 – 2.12 (m, 1H), 2.02 (hept, J = 6.7 Hz, 2H), 1.78 (q, J = 1.9 Hz, 3H), 1.42 (dd, J = 9.7, 7.8 Hz, 2H), 1.00 (d, J = 1.6 Hz, 3H).



173

Conjugated Enol 173. To a solution of enone **172** (1.1050 mg, 6.20 mmol, 1.0 equiv) in toluene (12.4 mL) at 0 °C was sequentially added ethyl formate (3.5 mL, 43.40 mmol, 7.0 equiv), NaH (744.0 mg, 60% by weight in mineral oil, 18.60 mmol, 3.0 equiv), and MeOH (0.25 mL, 6.20 mmol, 1.0 equiv). The cooling bath was then removed, and the reaction mixture was allowed to stir at 25 °C for 8 h. Upon completion, the reaction contents were quenched by the

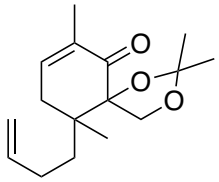
addition of 3 M HCl (15 mL), diluted with CH_2Cl_2 (15 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:CH_2Cl_2, 1:1→1:2) afforded conjugated enol **173** (576.4 mg, 3.23 mmol, 90% yield) as a yellow oil. **173**: R_f = 0.60 (silica gel, hexanes:EtOAc, 9:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 14.95 (d, J = 9.4 Hz, 1H), 7.52 (d, J = 9.4 Hz, 1H), 6.49 (s, 1H), 5.84 – 5.68 (m, 1H), 5.05 – 4.89 (m, 2H), 2.25 (s, 2H), 1.95 (d, J = 6.4 Hz, 2H), 1.86 (s, 3H), 1.67 – 1.57 (m, 1H), 1.51 – 1.43 (m, 1H), 1.17 (s, 3H).



174

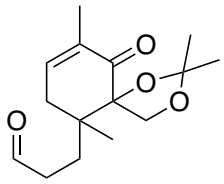
Diol 174. To a solution of conjugated enol **173** (853.3 mg, 4.14 mmol, 1.0 equiv) in DMSO (4 mL) was added a pre-dissolved solution of IBX (3.48 g, 12.42 mmol, 3.0 equiv) and MPO (1.55 g, 12.42 mmol, 3.0 equiv) in DMSO (16 mL) at 25 °C. The reaction mixture was then placed into a preheated oil bath (45 °C) and was allowed to stir for 30 min. Upon completion, the reaction contents were quenched by the addition of $NaHCO_3$ (20 mL), diluted with Et_2O (30 mL), and poured into a separatory funnel. The two phases were separated, and the organic layer was washed with $NaHCO_3$ (20 mL), H_2O (20 mL), and brine (20 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated to afford the crude α-hydroxylated aldehyde (766.6 mg, 3.45 mmol, 83% yield, ~2:1 *dr*) as a white foam. Pushing forward, to a solution of the so-obtained crude α-hydroxylated aldehyde (762.4 mg, 3.43 mmol, 1.0 equiv) in THF (17 mL) at –78 °C was added LiAl(*t*BuO)$_3$H (10.0 mL, 1.0 M in THF, 10.00 mmol, 2.9 equiv) dropwise. The resultant mixture was then stirred for a further 30 min at this temperature. Upon completion, the reaction contents were quenched by the addition of Rochelle's Salt (40 mL), stirred for 1 h, diluted

with EtOAc (30 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 6:1→4:1) afforded diol **174** (526.3 mg, 2.34 mmol, 68% yield – diastereomers were separable and were provided in 357.7 mg, 1.59 mmol, 46% yield and 168.6 mg, 0.75 mmol, 22% yield) as a white foam. [NOTE: one set of diastereomers is characterized here for clarity] **174**: R_f = 0.20 (silica gel, hexanes:EtOAc, 2:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.56 (s, 1H), 5.88 – 5.74 (m, 1H), 5.07 – 4.90 (m, 2H), 4.08 (s, 1H), 3.91 – 3.74 (m, 2H), 2.34 (s, 2H), 2.23 – 2.11 (m, 1H), 2.06 – 1.97 (m, 1H), 1.86 (s, 3H), 1.78 – 1.72 (m, 1H), 1.43 (td, J = 12.7, 4.7 Hz, 1H), 0.90 (s, 3H).



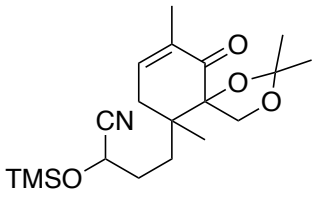
175

Acetonide 175. To a solution of diol **174** (351.5 mg, 1.57 mmol, 1.0 equiv) in CH_2Cl_2 (16 mL) at 25 °C was added 2,2-dimethoxypropane (0.97 mL, 7.85 mmol, 5.0 equiv) and *p*TSA•H_2O (30.4 mg, 0.16 mmol, 0.1 equiv). The reaction mixture was then allowed to stir for 8 h at this temperature. Upon completion, the reaction contents were directly concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 8:1) afforded acetonide **175** (361.1 mg, 1.37 mmol, 87% yield) as a colorless oil. **175**: R_f = 0.60 (silica gel, hexanes:EtOAc, 2:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.50 (s, 1H), 5.77 (d, J = 6.6 Hz, 1H), 5.06 – 4.91 (m, 2H), 3.99 (s, 2H), 2.42 – 2.30 (m, 1H), 2.25 – 2.13 (m, 1H), 2.10 – 2.00 (m, 1H), 1.96 (d, J = 11.4 Hz, 1H), 1.82 (s, 3H), 1.46 (s, 3H), 1.44 – 1.30 (m, 5H), 1.04 (s, 3H).



176

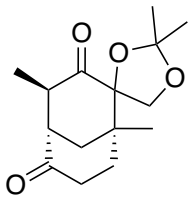
Aldehyde 176. To a solution of acetonide **175** (35.3 mg, 0.13 mmol, 1.0 equiv) in 1,4-dioxane (1.2 mL) and H_2O (0.3 mL) was sequentially added lutidine (0.03 mL, 0.26 mmol, 2.0 equiv), $NaIO_4$ (111.2 mg, 0.52 mmol, 4.0 equiv), and OsO_4 (0.04 mL, 4% in H_2O, 0.007 mmol, 0.05 equiv). The reaction mixture was then stirred vigorously for 1.5 h. Upon completion, the reaction contents were quenched by the addition of H_2O (15 mL), diluted with Et_2O (10 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 4:1) afforded the desired aldehyde **176** (15.0 mg, 0.056 mmol, 43% yield) as a yellow oil. **176**: R_f = 0.40 (silica gel, hexanes:EtOAc, 2:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.78 (s, 1H), 6.48 (s, 1H), 4.04 (s, 2H), 2.52 (s, 2H), 2.49 – 2.29 (m, 3H), 2.16 (s, 1H), 1.83 (s, 3H), 1.48 (s, 3H), 1.38 (s, 3H), 1.02 (s, 3H).



177

Cyanohydrin 177. To a solution of aldehyde **176** (15.0 mg, 0.056 mmol, 1.0 equiv) in CH_2Cl_2 (1.0 mL) at 0 °C was added TMSCN (0.01 mL, 0.067 mmol, 1.2 equiv) and ZnI_2 (3.5 mg, 0.011 mmol, 0.2 equiv). The cooling bath was then removed, and the resulting solution was allowed to stir at 25 °C for 1 h. Upon completion, the reaction contents were quenched by the addition of H_2O (5 mL) and $Na_2S_2O_3$ (5 mL), diluted with Et_2O (10 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with Et_2O

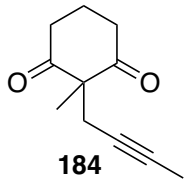
(3 × 10 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 8:1) afforded the desired cyanohydrin **177** (16.9 mg, 0.046 mmol, 82% yield) as a yellow oil. **177**: R_f = 0.15 (silica gel, hexanes:EtOAc, 8:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.49 (s, 1H), 4.35 (d, J = 5.6 Hz, 1H), 4.02 (s, 2H), 2.33 (s, 1H), 2.20 (s, 1H), 1.83 (s, 3H), 1.81 – 1.65 (m, 2H), 1.53 – 1.31 (m, 8H), 1.03 (s, 3H), 0.20 (s, 9H).



179

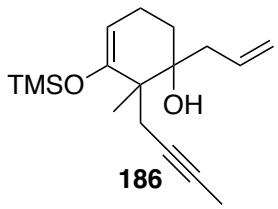
Undesired Bicycle 179. To a solution of cyanohydrin **177** (14.7 mg, 0.040 mmol, 1.0 equiv) in THF (0.5 mL) at –78 °C was added LiHMDS (0.05 mL, 1.0 M in THF, 0.048 mmol, 1.2 equiv). The cooling bath was then removed and the reaction was allowed to stir at 25 °C for 30 min. Upon completion, the reaction contents were quenched by the addition of NH_4Cl (10 mL), diluted with CH_2Cl_2 (10 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. The resulting crude residue (14.1 mg) was redissolved in THF (0.4 mL) before the addition of TBAF (0.12 mL, 0.120 mmol, 3.0 equiv) at 25 °C. The reaction contents were quenched by the addition of NH_4Cl (10 mL), diluted with CH_2Cl_2 (10 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 2:1) afforded the undesired bicycle **179** (4.5 mg, 0.017 mmol, 43% yield over 2 steps) as a colorless oil. **179**: R_f = 0.15 (silica gel, hexanes:EtOAc,

3:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.37 (d, J = 8.7 Hz, 1H), 3.90 (d, J = 8.7 Hz, 1H), 2.87 (q, J = 7.4 Hz, 1H), 2.28 (d, J = 2.9 Hz, 1H), 2.25 – 2.18 (m, 2H), 2.09 – 2.02 (m, 1H), 1.90 (ddd, J = 12.2, 7.9, 4.2 Hz, 1H), 1.68 – 1.59 (m, 2H), 1.51 (s, 3H), 1.43 (s, 3H), 0.99 (s, 3H), 0.88 (d, J = 7.3 Hz, 3H).



184

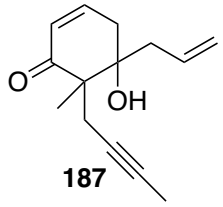
Alkyne 184. To a solution of 2-methyl-1,3-cyclohexanedione **185** (5.00 g, 39.64 mmol, 1.0 equiv) in DMSO (80 mL) at 25 °C was added solid *t*BuOK (4.45 g, 39.64 mmol, 1.0 equiv). The reaction mixture was then allowed to stir for 15 min before the addition of 1-bromo-2-butyne (3.9 mL, 43.60 mmol, 1.1 equiv) before being stirred for a further 16 h at 25 °C. Upon completion, the reaction contents were quenched by the addition of H_2O (40 mL), diluted with EtOAc (80 mL), and poured into a separatory funnel. The two phases were separated, and the organic layer was washed with brine (3 × 60 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 5:1) afforded the desired alkyne **184** (6.10 g, 34.23 mmol, 86% yield) as a faint yellow solid. **184**: R_f = 0.30 (silica gel, hexanes:EtOAc, 4:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.69 (t, J = 6.8 Hz, 4H), 2.58 (d, J = 2.6 Hz, 2H), 2.05 – 1.92 (m, 2H), 1.72 (s, 3H), 1.26 (s, 3H).



186

Silyl Enol Ether 186. To a solution of alkyne **184** (31.4 mg, 0.18 mmol, 1.0 equiv) in THF (1.6 mL) at –78 °C was added LiHMDS (0.22 mL, 1.0 M in THF, 0.22 mmol, 1.2 equiv). The reaction mixture was then allowed to stir for 1 h at –78 °C before the addition of

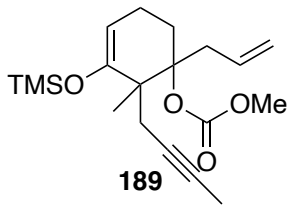
TMSCl (0.03 mL, 0.20 mmol, 1.1 equiv). After a stirring for a further 5 min at –78 °C, allylmagnesium bromide (0.54 mL, 1.0 M in Et_2O, 0.54 mmol, 3.0 equiv) was introduced in a dropwise fashion and stirring continued for 5 minutes at that temperature. Upon completion, the reaction contents were quenched by the addition of $NaHCO_3$ (15 mL), diluted with CH_2Cl_2 (10 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated to directly afford crude silyl enol ether **186** (43.8 mg, 0.15 mmol, 85% yield) as a clear and colorless oil without further purification required. **186**: R_f = 0.80 (silica gel, hexanes:EtOAc, 4:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.00 (m, 1H), 5.18 – 5.06 (m, 2H), 4.73 (t, J = 3.9 Hz, 1H), 2.61 (s, 1H), 2.54 – 2.49 (m, 1H), 2.47 (p, J = 2.6 Hz, 2H), 2.17 (dd, J = 13.9, 8.2 Hz, 1H), 2.06 (dtd, J = 16.3, 6.2, 3.9 Hz, 1H), 1.94 (dtd, J = 17.4, 6.8, 4.0 Hz, 1H), 1.83 – 1.79 (m, 1H), 1.77 (t, J = 2.6 Hz, 3H), 1.63 – 1.57 (m, 1H), 1.10 (s, 3H), 0.21 (d, J = 10.8 Hz, 9H).



187

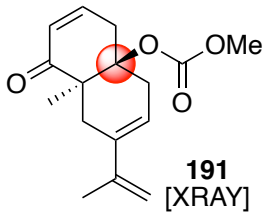
Enone 187. To a solution of silyl enol ether **186** (40.8 mg, 0.14 mmol, 1.0 equiv) in DMSO (0.20 mL) was added a pre-dissolved solution of IBX (78.4 g, 0.28 mmol, 2.0 equiv) and MPO (35.0 mg, 0.28 mmol, 2.0 equiv) in DMSO (0.70 mL) at 25 °C. The reaction mixture was then placed into a preheated oil bath (45 °C) and was allowed to stir for 1.5 h. Upon completion, the reaction contents were quenched by the addition of $NaHCO_3$ (10 mL), diluted with EtOAc (15 mL), and poured into a separatory funnel. The two phases were separated, and the organic layer was washed with $NaHCO_3$ (15 mL), H_2O (15 mL), and brine (15 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 4:1) afforded the desired

enone **187** (11.7 mg, 0.054 mmol, 39% yield) as a light yellow oil. **187**: R_f = 0.20 (silica gel, hexanes:EtOAc, 4:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.72 (dt, J = 10.0, 3.9 Hz, 1H), 6.03 (dt, J = 10.0, 2.0 Hz, 1H), 6.01 – 5.86 (m, 1H), 5.20 – 5.10 (m, 2H), 3.31 (s, 1H), 2.79 (dd, J = 17.1, 2.6 Hz, 1H), 2.62 – 2.52 (m, 1H), 2.51 – 2.45 (m, 2H), 2.43 – 2.33 (m, 1H), 2.29 (dd, J = 13.9, 8.4 Hz, 1H), 1.77 (t, J = 2.6 Hz, 3H), 1.17 (s, 3H).



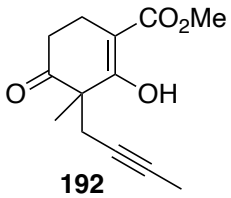
189

Methyl Carbonate 189. To a solution of silyl enol ether **186** (225.4 mg, 0.77 mmol, 1.0 equiv) in THF (7.7 mL) at –78 °C was added *n*BuLi (1.2 mL, 1.6 M in hexanes, 1.93 mmol, 2.5 equiv) in a dropwise fashion. The resultant solution was then allowed to stir for 1 h at this temperature before the introduction of methyl chloroformate (0.24 mL, 3.08 mmol, 4.0 equiv). After stirring for an additional 2 h at –78 °C, the reaction contents were quenched by the addition of NH_4Cl (10 mL), diluted with CH_2Cl_2 (10 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:CH_2Cl_2, 1:1) afforded recovered starting silyl enol ether **186** (187.2 mg, 0.64 mmol, 83% recovered) and the desired methyl carbonate **189** (45.4 mg, 0.13 mmol, 17% yield, quant. brsm) as a light yellow oil. **189**: R_f = 0.15 (silica gel, hexanes:CH_2Cl_2, 2:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.93 – 5.84 (m, 1H), 5.17 – 5.05 (m, 2H), 4.71 (t, J = 3.9 Hz, 1H), 3.70 (s, 3H), 3.05 (dd, J = 14.8, 6.1 Hz, 1H), 2.61 – 2.55 (m, 1H), 2.55 – 2.49 (m, 2H), 2.40 (dt, J = 12.0, 5.8 Hz, 1H), 2.04 – 1.96 (m, 3H), 1.77 (t, J = 2.6 Hz, 3H), 1.25 (s, 3H), 0.19 (s, 9H).



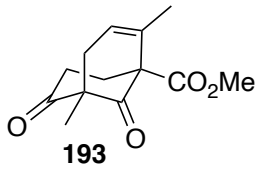
191
[XRAY]

Diene 191. To a solution of methyl carbonate **189** (45.4 mg, 0.13 mmol, 1.0 equiv) in DMSO (0.20 mL) was added a pre-dissolved solution of IBX (109.2 mg, 0.39 mmol, 3.0 equiv) and MPO (48.8 mg, 0.39 mmol, 3.0 equiv) in DMSO (1.0 mL) at 25 °C. The reaction mixture was then placed into a preheated oil bath (45 °C) and was allowed to stir for 1.5 h. Upon completion, the reaction contents were quenched by the addition of $NaHCO_3$ (10 mL), diluted with EtOAc (15 mL), and poured into a separatory funnel. The two phases were separated, and the organic layer was washed with $NaHCO_3$ (15 mL), H_2O (15 mL), and brine (15 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 4:1) afforded the desired enone **190** (8.2 mg, 0.030 mmol, 23% yield) as a light yellow oil. Pushing forward, to a solution of enone **190** (2.6 mg, 0.009 mmol, 1.0 equiv) in CH_2Cl_2 (0.25 mL) and 2-methyl-2-butene (0.25 mL) was added Hoveyda-Grubbs 2nd Generation initiator (1.1 mg, 0.002 mmol, 0.2 eq) at 25 °C. The resulting solution was then allowed to stir for an additional 12 h, at which point it was directly concentrated. Purification of the resultant residue by preparative thin layer chromatography (silica gel, hexanes:EtOAc, 3:1) afforded recovered starting enone **190** (1.2 mg, 0.0045 mmol, 50% recovered) and undesired diene **191** (1.0 mg, 0.0036 mmol, 40% yield) as a white crystalline solid. **191**: R_f = 0.40 (silica gel, hexanes:EtOAc, 3:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.67 (ddd, J = 10.3, 5.7, 2.2 Hz, 1H), 6.07 (dd, J = 10.2, 2.5 Hz, 1H), 5.62 (s, 1H), 5.16 (s, 1H), 4.94 (s, 1H), 3.69 – 3.64 (m, 1H), 3.63 (s, 3H), 3.50 – 3.44 (m, 1H), 2.73 – 2.66 (m, 1H), 2.53 – 2.47 (m, 1H), 2.44 (d, J = 17.9 Hz, 1H), 2.39 – 2.33 (m, 1H), 1.91 (s, 3H), 1.13 (s, 3H).



192

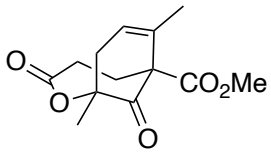
Enol 192. To a flame dried flask was added alkyne **184** (10.19 g, 57.17 mmol, 1.0 equiv) and THF (204 mL) at 25 °C. The solution was then cooled to –78 °C before the dropwise introduction of LiHMDS (68.6 mL, 1.0 M in THF, 68.60 mmol, 1.2 equiv). The reaction mixture was then stirred for a further 1 h at this temperature before the addition of Mander's reagent (5.0 mL, 62.89 mmol, 1.1 equiv). After stirring for 15 min at –78 °C, the reaction vessel was warmed to 0 °C, at which it was stirred for an additional 5 min. Upon completion, the reaction contents were quenched by the addition of NH_4Cl (100 mL), diluted with CH_2Cl_2 (60 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 60 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 15:1) afforded desired enol **192** (10.37 g, 43.89 mmol, 77% yield) as a light yellow oil. **192**: R_f = 0.60 (silica gel, hexanes:EtOAc, 4:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.44 (s, 1H), 3.83 (s, 3H), 2.66 – 2.46 (m, 6H), 1.69 (d, J = 5.1 Hz, 3H), 1.29 (s, 3H).



193

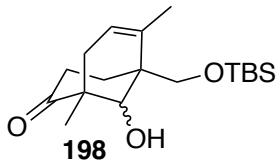
Bridged Bicycle 193. To a flame dried flask was added $InCl_3$ (4.18 g, 18.88 mmol, 1.0 equiv) and DCE (270 mL). To this suspension was added in a dropwise fashion a solution of enol **192** (4.46 g, 18.88 mmol, 1.0 equiv) in DCE (45 mL). The reaction mixture was then placed into a preheated oil bath (80 °C) and was allowed to stir for 12 h. Upon completion, the reaction contents were quenched by the addition of $NaHCO_3$ (250 mL), stirred for 15 min, then filtered through a short pad of Celite and washed with CH_2Cl_2 (100 mL) before being poured into

a separatory funnel and diluted with H_2O (100 mL). The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 6:1) afforded desired bridged bicycle **193** (2.90 g, 12.27 mmol, 65% yield) as a yellow solid. **193**: R_f = 0.20 (silica gel, hexanes:EtOAc, 4:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.73 (s, 1H), 3.83 (s, 3H), 2.65 – 2.59 (m, 2H), 2.58 – 2.49 (m, 2H), 2.23 (ddd, J = 14.2, 6.2, 3.7 Hz, 1H), 2.14 (ddd, J = 14.3, 11.2, 7.7 Hz, 1H), 1.72 (dt, J = 3.1, 1.6 Hz, 3H), 1.22 (s, 3H).



196

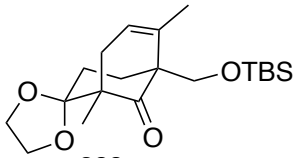
Lactone 196. To a solution of bridged bicycle **193** (8.3 mg, 0.035 mmol, 1.0 equiv) in CH_2Cl_2 (1.0 mL) at 0 °C was sequentially added $NaHCO_3$ (8.8 mg, 0.105 mmol, 3.0 equiv) and *m*CPBA (7.4 mg, 70% by weight, 0.030 mmol, 2.0 equiv). The cooling bath was then removed, and the mixture was allowed to stir at 25 °C for 4 h, at which point the reaction contents were quenched by the addition of $NaHCO_3$ (10 mL), diluted with CH_2Cl_2 (10 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated to directly afford a crude 3:1 mixture of starting bridged bicycle **193** and lactone **196** (8.5 mg). **196**: R_f = 0.30 (silica gel, hexanes:EtOAc, 4:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.62 (d, J = 5.0 Hz, 1H), 3.77 (s, 3H), 2.88 – 2.82 (m, 2H), 2.51 – 2.45 (m, 2H), 2.25 (d, J = 5.4 Hz, 1H), 2.11 (d, J = 7.1 Hz, 1H), 1.67 (s, 3H).



198

TBS-Protected Alcohol 198. To a solution of bridged bicycle **193** (1.41 g, 5.97 mmol, 1.0 equiv) in THF (60 mL) at –78 °C was added KHMDS (24 mL, 0.5 M in THF, 11.94 mmol, 2.0 equiv). The reaction mixture was allowed to stir at this temperature for 15 min before being warmed to 0 °C, at which it was stirred for an additional 30 min. Next, DIBAL-H (25 mL, 1.0 M in THF, 25.07 mmol, 4.2 equiv) was introduced in a dropwise fashion. The resulting solution was then allowed to stir for 8 h, slowly warming to 25 °C. Upon completion, the reaction contents were quenched by the addition of Rochelle's Salt (100 mL), stirred for 1 h, diluted with EtOAc (45 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with EtOAc (3 × 45 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:acetone, 3:1) afforded diol **197** (503.3 mg, 2.39 mmol, 40% yield) as a colorless oil. Pushing forward, to a solution of diol **197** (403.1 mg, 1.92 mmol, 1.0 equiv) in CH_2Cl_2 (19 mL) at 0 °C was sequentially added lutidine (0.67 mL, 5.76 mmol, 3.0 equiv) and TBSOTf (0.46 mL, 2.02 mmol, 1.05 equiv). The reaction mixture was then allowed to stir for an additional 5 min at this temperature. Upon completion, the reaction contents were quenched by the addition of NH_4Cl (20 mL), diluted with CH_2Cl_2 (15 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 10:1) afforded desired TBS-protected alcohol **198** (426.6 mg, 1.31 mmol, 68% yield) as a light yellow oil. **198**: R_f = 0.60 (silica gel, hexanes:EtOAc, 2:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.74 – 5.51 (m, 1H), 4.02 – 3.62 (m, 4H), 2.46 – 2.33 (m, 2H), 2.32 – 2.22 (m, 1H), 2.14 – 1.96 (m, 1H), 1.79

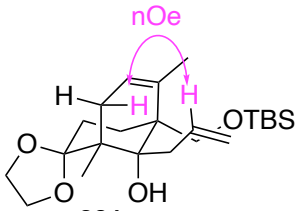
– 1.65 (m, 3H), 1.55 – 1.34 (m, 2H), 1.16 (d, J = 8.4 Hz, 3H), 0.91 (d, J = 1.8 Hz, 9H), 0.11 (dd, J = 9.4, 3.8 Hz, 6H).



200

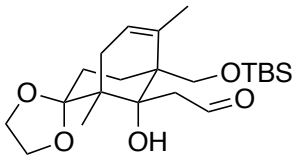
Ketal 200. To a solution of TBS-protected alcohol **198** (296.0 mg, 0.91 mmol, 1.0 equiv) in benzene (15 mL) was added ethylene glycol (0.76 mL, 13.65 mmol, 15.0 equiv) and *p*TSA•H_2O (17.3 mg, 0.091 mmol, 0.1 equiv). The reaction mixture was then placed in a preheated oil bath (125 °C) and was allowed to reflux with a Dean-Stark apparatus for 2 h. Upon completion, the reaction contents were quenched by the addition of $NaHCO_3$ (10 mL), diluted with CH_2Cl_2 (10 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 8:1) afforded the intermittent TBS-protected ketal **199** (165.0 mg, 0.45 mmol, 49% yield) as a light yellow oil. Pushing forward, to a solution of oxalyl chloride (0.18 mL, 2.15 mmol, 5.0 equiv) in CH_2Cl_2 (3.2 mL) at –78 °C was added in a dropwise fashion DMSO (0.31 mL, 4.30 mmol, 10.0 equiv). The reaction mixture was allowed to stir for 15 min at this temperature before the dropwise introduction of a solution of TBS-protected ketal **199** (160.0 mg, 0.43 mmol, 1.0 equiv) in CH_2Cl_2 (1.1 mL). After stirring for an additional 1 h, Et_3N (1.2 mL, 8.60 mmol, 20.0 equiv) was introduced, and the resulting solution was then warmed to –40 °C, at which it was left stirring for 1 h. Upon completion, the reaction contents were quenched by the addition of H_2O (20 mL), diluted with CH_2Cl_2 (15 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and

concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 25:1) afforded desired ketal **200** (120.3 mg, 0.33 mmol, 77% yield) as a light yellow oil. **200**: R_f = 0.40 (silica gel, hexanes:EtOAc, 8:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.51 (s, 1H), 4.02 – 3.87 (m, 5H), 3.68 (d, J = 10.4 Hz, 1H), 2.83 – 2.75 (m, 1H), 2.17 – 2.03 (m, 2H), 1.76 (q, J = 2.3 Hz, 3H), 1.74 – 1.64 (m, 2H), 1.37 (td, J = 13.4, 4.2 Hz, 1H), 1.01 (s, 3H), 0.87 (s, 9H), 0.06 (t, J = 4.6 Hz, 6H).



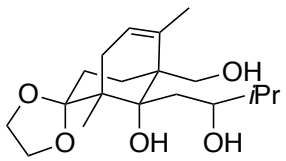
201

Allyl 201. To a solution of TBS-protected ketone **200** (117.1 mg, 0.32 mmol, 1.0 equiv) in THF (3.2 mL) at –78 °C was added allylmagnesium bromide (0.64 mL, 1.0 M in Et_2O, 0.64 mmol, 2.0 equiv). After stirring for 30 min at –78 °C, the reaction mixture was warmed to 0 °C, at which it was stirred for an additional 5 min. Upon completion, the reaction contents were quenched by the addition of NH_4Cl (10 mL), diluted with CH_2Cl_2 (10 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 40:1) afforded desired allyl **201** (94.4 mg, 0.23 mmol, 72% yield) as a single diastereomer as a light yellow oil. **201**: R_f = 0.60 (silica gel, hexanes:EtOAc, 8:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.10 (ddt, J = 17.2, 10.1, 7.2 Hz, 1H), 5.36 (tt, J = 2.8, 1.5 Hz, 1H), 4.97 – 4.83 (m, 2H), 4.17 (s, 1H), 4.03 – 3.97 (m, 2H), 3.92 – 3.88 (m, 2H), 3.84 (dt, J = 7.7, 6.4 Hz, 1H), 3.76 (d, J = 10.0 Hz, 1H), 2.55 (ddt, J = 15.5, 7.2, 1.6 Hz, 1H), 2.41 (ddt, J = 15.4, 7.0, 1.9 Hz, 1H), 2.37 – 2.30 (m, 1H), 1.97 – 1.89 (m, 1H), 1.71 (dq, J = 3.5, 1.8 Hz, 3H), 1.69 – 1.58 (m, 2H), 1.54 – 1.49 (m, 1H), 1.41 (ddd, J = 13.4, 4.5, 2.4 Hz, 1H), 0.95 (s, 3H), 0.88 (s, 9H), 0.06 (s, 6H).



202

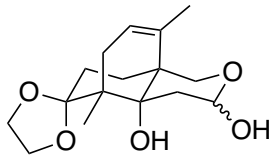
Aldehyde 202. To a solution of allyl **201** (91.7 mg, 0.22 mmol, 1.0 equiv) in 1,4-dioxane (3.3 mL) and H_2O (1.1 mL) was sequentially added lutidine (0.05 mL, 0.44 mmol, 2.0 equiv), $NaIO_4$ (188.2 mg, 0.88 mmol, 4.0 equiv), and OsO_4 (0.07 mL, 4% in H_2O, 0.007 mmol, 0.05 equiv). The reaction mixture was then stirred vigorously for 1 h. Upon completion, the reaction contents were quenched by the addition of H_2O (15 mL), diluted with EtOAc (10 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 10:1) afforded the desired aldehyde **202** (72.0 mg, 0.18 mmol, 82% yield) as a yellow oil. **202**: R_f = 0.20 (silica gel, hexanes:EtOAc, 8:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.90 (dd, J = 3.8, 2.4 Hz, 1H), 5.39 (t, J = 1.5 Hz, 1H), 4.38 (d, J = 1.1 Hz, 1H), 4.07 (d, J = 10.3 Hz, 1H), 4.05 – 3.98 (m, 2H), 3.96 – 3.85 (m, 2H), 3.61 (d, J = 10.3 Hz, 1H), 3.01 (dd, J = 15.9, 2.4 Hz, 1H), 2.55 (ddd, J = 16.0, 3.8, 1.1 Hz, 1H), 2.42 – 2.33 (m, 1H), 1.88 – 1.80 (m, 1H), 1.77 – 1.69 (m, 4H), 1.59 (dd, J = 13.4, 3.9 Hz, 1H), 1.54 – 1.49 (m, 1H), 1.26 – 1.20 (m, 1H), 0.95 (s, 3H), 0.87 (s, 9H), 0.07 (s, 6H).



203

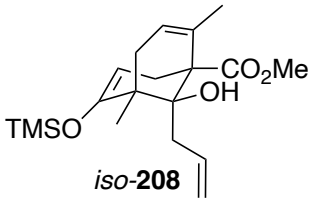
Primary Alcohol 203. To a solution of aldehyde **202** (69.0 mg, 0.17 mmol, 1.0 equiv) in THF (1.7 mL) at –78 °C was added isopropylmagnesium chloride (0.19 mL, 2.0 M in THF, 0.37 mmol, 2.2 equiv). The reaction mixture was then warmed to 0 °C and was allowed to stir for 5 min. Upon completion, the reaction contents were quenched by the addition of NH_4Cl

(10 mL), diluted with CH_2Cl_2 (10 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 9:1) afforded two diastereomers of the intermittent protected isopropyl product **S1** (29.6 mg, 0.065 mmol, 38% yield; 40.1 mg, 0.088 mmol, 52% yield; 90% combined yield). Pushing forward, to a solution of the so-obtained major diastereomer (15.4 mg, 0.034 mmol, 1.0 equiv) in THF (0.34 mL) was added TBAF (0.14 mL, 1.0 M in THF, 0.136 mmol, 4.0 equiv). The reaction mixture was allowed to then stir for 5 min. Upon completion, the reaction contents were quenched by the addition of NH_4Cl (10 mL), diluted with EtOAc (10 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 2:1) afforded desired primary alcohol **203** (11.6 mg, 0.034 mmol, quant.) as a colorless oil. **S1**: R_f = 0.80 (silica gel, hexanes:EtOAc, 2:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.43 – 5.37 (m, 1H), 4.62 (s, 1H), 4.10 – 3.99 (m, 3H), 3.96 – 3.83 (m, 2H), 3.75 (d, J = 9.6 Hz, 1H), 3.61 (dd, J = 10.3, 5.7 Hz, 1H), 2.34 (d, J = 4.2 Hz, 1H), 1.89 – 1.77 (m, 2H), 1.74 – 1.56 (m, 8H), 0.97 – 0.86 (m, 16H), 0.06 (d, J = 4.0 Hz, 6H). **203**: R_f = 0.10 (silica gel, hexanes:EtOAc, 2:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.45 (tt, J = 2.9, 1.5 Hz, 1H), 5.21 (s, 1H), 4.30 (d, J = 9.8 Hz, 1H), 4.07 – 4.00 (m, 2H), 3.98 – 3.90 (m, 2H), 3.81 (dd, J = 10.3, 5.7 Hz, 1H), 3.69 – 3.60 (m, 2H), 2.43 – 2.27 (m, 2H), 1.93 – 1.85 (m, 2H), 1.83 – 1.74 (m, 2H), 1.71 – 1.57 (m, 3H), 1.53 (d, J = 4.3 Hz, 3H), 1.34 (ddd, J = 14.3, 5.0, 2.4 Hz, 1H), 1.00 – 0.92 (m, 9H).



205

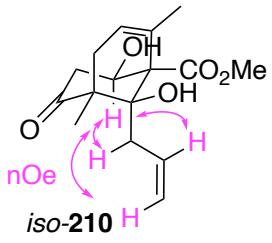
Lactol 205. To a solution of aldehyde **202** (25.4 mg, 0.062 mmol, 1.0 equiv) in THF (1.0 mL) at 0 °C was added TBAF (0.14 mL, 1.0 M in THF, 0.136 mmol, 2.2 equiv). The resulting solution was then stirred at this temperature for 15 min before removing the cooling bath and stirring for an additional 5 min at 25 °C. Upon completion, the reaction contents were quenched by the addition of NH_4Cl (10 mL), diluted with EtOAc (10 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 2:1→1:1) afforded desired lactol **205** (14.6 mg, 0.049 mmol, 80% yield – diastereomers interconvert upon concentration) as a colorless oil. **205**: R_f = 0.15 (silica gel, hexanes:EtOAc, 2:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.86 (d, J = 10.6 Hz, 1H), 5.48 (s, 1H), 5.19 – 5.11 (m, 1H), 4.79 (dd, J = 2.6, 0.9 Hz, 1H), 4.06 – 3.89 (m, 5H), 3.79 – 3.68 (m, 1H), 3.53 (d, J = 12.0 Hz, 1H), 2.45 – 2.36 (m, 1H), 1.97 – 1.71 (m, 7H), 1.54 – 1.42 (m, 2H), 1.13 – 1.02 (m, 1H), 0.91 (d, J = 3.2 Hz, 3H).



iso-**208**

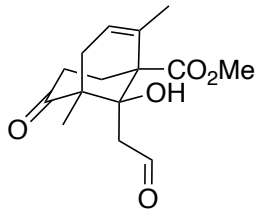
Undesired Allyl *iso*-208. To a solution of bridged bicycle **193** (250.0 mg, 1.06 mmol, 1.0 equiv) in THF (10 mL) at 0 °C was sequentially added LiHMDS (2.1 mL, 1.0 M in THF, 2.12 mmol, 2.0 equiv) and TMSCl (0.20 mL, 1.59 mmol, 1.5 equiv). The resulting solution was then stirred at this temperature for 30 min before being cooled to –78 °C. Then, allylmagnesium bromide (5.3 mL, 1.0 M in Et_2O, 5.30 mmol, 5.0 equiv) was added and the

reaction mixture was allowed to stir at this temperature for an additional 1.5 h. Upon completion, the reaction contents were quenched by the addition of $NaHCO_3$ (10 mL), diluted with CH_2Cl_2 (15 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 30:1→20:1) afforded undesired allyl *iso*-**208** (195.0 mg, 0.56 mmol, 53% yield) and desired allyl **208** (89.1 mg, 0.25 mmol, 24% yield) as separable colorless oils. *iso*-**208**: R_f = 0.40 (silica gel, hexanes:EtOAc, 8:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.85 (dtd, J = 17.2, 9.6, 5.7 Hz, 1H), 5.52 (dt, J = 5.3, 1.8 Hz, 1H), 5.10 – 5.01 (m, 2H), 4.67 (s, 1H), 4.62 (dd, J = 5.7, 2.1 Hz, 1H), 3.67 (s, 3H), 2.57 – 2.48 (m, 2H), 2.36 – 2.17 (m, 3H), 1.95 – 1.87 (m, 1H), 1.51 (dt, J = 2.9, 1.5 Hz, 3H), 1.03 (s, 3H), 0.17 (s, 9H).



Undesired Diol *iso*-210. To a solution of undesired allyl *iso*-**208** (195.0 mg, 0.56 mmol, 1.0 equiv) in DMSO (0.50 mL) was added a pre-dissolved solution of IBX (313.6 mg, 1.12 mmol, 2.0 equiv) and MPO (140.1 mg, 1.12 mmol, 2.0 equiv) in DMSO (2.8 mL) at 25 °C. The reaction mixture was then placed into a preheated oil bath (45 °C) and was allowed to stir for 2 h. Upon completion, the reaction contents were quenched by the addition of $NaHCO_3$ (10 mL), diluted with EtOAc (15 mL), and poured into a separatory funnel. The two phases were separated, and the organic layer was washed with $NaHCO_3$ (15 mL), H_2O (15 mL), and brine (15 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 8:1) afforded enone *iso*-**209** (65.4 mg, 0.24 mmol, 43% yield) as a light yellow oil. Pushing forward, to a suspension

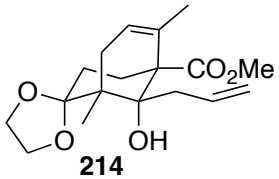
of CuCl (23.8 mg, 0.24 mmol, 1.0 equiv) in THF (1.6 mL) in a flame-dried flask was added $ICyBF_4$ (38.4 mg, 0.12 mmol, 0.5 equiv) and NaO*t*Bu (46.1 mg, 0.48 mmol, 2.0 equiv). The reaction mixture was allowed to stir at 25 °C for 1 h before the introduction of a premixed solution of enone *iso*-**209** (65.0 mg, 0.24 mmol, 1.0 equiv) and B_2pin_2 (91.4 mg, 0.36 mmol, 1.5 equiv) in THF (0.8 mL). The resulting mixture was then stirred for 12 h at this temperature. Upon completion, the reaction contents were quenched by the addition of NH_4Cl/NH_4OH (9:1, 10 mL), diluted with CH_2Cl_2 (15 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 9:1→5:1) afforded the desired borylated intermediate (32.6 mg, 0.081 mmol, 34% yield) as an amorphous solid. Next, the so-obtained borylated intermediate (27.1 mg, 0.067 mmol, 1.0 equiv) was redissolved in THF (0.5 mL) and H_2O (0.5 mL) before the introduction of $NaBO_3•H_2O$ (6.9 mg, 0.670 mmol, 10.0 equiv). The resulting mixture was then stirred vigorously for 16 h. Upon completion, the reaction contents were quenched by the addition of H_2O (10 mL), diluted with Et_2O (15 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with Et_2O (3 × 15 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 2:1) afforded undesired diol *iso*-**210** (14.0 mg, 0.048 mmol, 72% yield) as a colorless oil. *iso*-**210**: R_f = 0.20 (silica gel, hexanes:EtOAc, 2:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.85 (s, 1H), 5.72 (dddd, J = 16.8, 10.1, 8.3, 6.2 Hz, 1H), 5.12 – 5.03 (m, 2H), 4.59 (ddd, J = 11.5, 5.6, 2.9 Hz, 1H), 4.07 – 3.95 (m, 1H), 3.82 (s, 3H), 3.28 (s, 1H), 2.73 (dd, J = 15.5, 5.6 Hz, 1H), 2.63 (dd, J = 15.4, 11.5 Hz, 1H), 2.49 – 2.33 (m, 2H), 1.96 – 1.84 (m, 2H), 1.80 (q, J = 1.7 Hz, 3H), 1.12 (s, 3H).



iso-**212**
[XRAY]

Aldehyde *iso*-212. To a solution of undesired allyl *iso*-**208** (118.8 mg, 0.34 mmol, 1.0 equiv) in THF (3.4 mL) at 0 °C was added TBAF (0.68 mL, 1.0 M in THF, 0.68 mmol, 2.0 equiv). The resulting solution was then stirred for 5 min at this temperature. Upon completion, the reaction contents were quenched by the addition of NH_4Cl (10 mL), diluted with EtOAc (15 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 6:1) afforded the intermittent ketone *iso*-**211** (89.4 mg, 0.32 mmol, 94% yield) as a colorless oil. Pushing forward, to a solution of ketone *iso*-**211** (85.0 mg, 0.31 mmol, 1.0 equiv) in 1,4-dioxane (2.25 mL) and H_2O (0.75 mL) was sequentially added lutidine (0.07 mL, 0.62 mmol, 2.0 equiv), $NaIO_4$ (265.2 mg, 1.24 mmol, 4.0 equiv), and OsO_4 (0.13 mL, 4% in H_2O, 0.02 mmol, 0.05 equiv). The reaction mixture was then stirred vigorously for 1 h. Upon completion, the reaction contents were quenched by the addition of H_2O (15 mL), diluted with EtOAc (10 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:acetone, 8:1→4:1) afforded the undesired aldehyde *iso*-**212** (50.8 mg, 0.18 mmol, 58% yield) as a colorless crystalline solid. *iso*-**212**: R_f = 0.20 (silica gel, hexanes:acetone, 4:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.80 (dd, J = 3.2, 2.3 Hz, 1H), 5.79 (ddd, J = 4.4, 2.7, 1.4 Hz, 1H), 4.76 (s, 1H), 3.82 (s, 3H), 2.54 (dd, J = 15.6, 2.3 Hz, 1H), 2.49 – 2.33 (m,

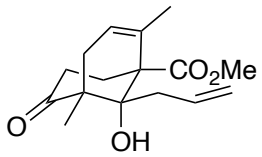
3H), 2.27 (dd, J = 15.5, 3.2 Hz, 1H), 2.14 – 1.98 (m, 2H), 1.89 – 1.82 (m, 1H), 1.67 (dt, J = 3.1, 1.7 Hz, 3H), 1.16 (s, 3H).



214

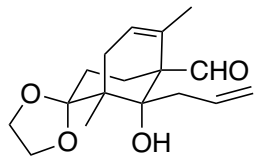
Allyl 214. To a solution of bridged bicycle **193** (1.20 g, 5.08 mmol, 1.0 equiv) in benzene (100 mL) was added ethylene glycol (4.3 mL, 76.20 mmol, 15.0 equiv) and *p*TSA•H_2O (97.0 mg, 0.51 mmol, 0.1 equiv). The reaction mixture was then placed in a preheated oil bath (125 °C) and was allowed to reflux with a Dean-Stark apparatus for 4 h. Upon completion, the reaction contents were quenched by the addition of $NaHCO_3$ (100 mL), diluted with CH_2Cl_2 (60 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 60 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated to directly afford the ketal protected intermediate **213** (1.42 g, 5.08 mmol, quant.). Pushing forward, to a solution of the so-obtained ketal-protected intermediate **213** (1.42 g, 5.08 mmol, 1.0 equiv) in THF (51 mL) at –78 °C was added allylmagnesium bromide (15 mL, 1.0 M in Et_2O, 15.24 mmol, 3.0 equiv) in a dropwise fashion. The resulting solution was then allowed to stir at this temperature for 30 min. Upon completion, the reaction contents were quenched by the addition of NH_4Cl (60 mL), diluted with CH_2Cl_2 (40 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:acetone, 10:1→8:1) afforded the undesired allylated material *iso*-**214** (328.8 mg, 1.71 mmol, 20% yield) as a colorless oil and the desired allyl **214** (942.8 mg, 2.92 mmol, 57% yield) as a colorless crystalline solid. **214**: R_f = 0.25 (silica gel, hexanes:acetone, 4:1); ^{1}H NMR

(500 MHz, $CDCl_3$) δ 6.00 (ddt, J = 17.2, 10.3, 7.0 Hz, 1H), 5.50 (ddq, J = 4.3, 2.9, 1.5 Hz, 1H), 4.99 – 4.87 (m, 2H), 4.34 (s, 1H), 4.02 (td, J = 6.2, 1.7 Hz, 2H), 3.97 – 3.84 (m, 2H), 3.70 (s, 3H), 2.86 (ddt, J = 15.8, 6.8, 1.7 Hz, 1H), 2.51 – 2.32 (m, 3H), 2.08 – 2.00 (m, 1H), 1.69 – 1.61 (m, 4H), 1.59 – 1.56 (m, 1H), 1.55 – 1.48 (m, 1H), 0.99 (s, 3H).



211

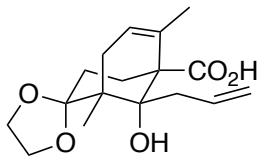
Ketone 211. To a solution of desired allyl **214** (11.1 mg, 0.034 mmol, 1.0 equiv) in THF (0.25 mL) at 25 °C was added 3M HCl (0.25 mL). The reaction mixture was then allowed to stir for 1 h. Upon completion, the reaction contents were quenched by the addition of brine (10 mL), diluted with CH_2Cl_2 (10 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated to directly afford ketone **211** (8.3 mg, 0.030 mmol, 88% yield) as a colorless oil without further purification required. **211**: R_f = 0.20 (silica gel, hexanes:acetone, 4:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.82 – 5.73 (m, 1H), 5.67 – 5.61 (m, 1H), 5.13 – 5.04 (m, 2H), 3.73 (s, 3H), 2.72 (td, J = 13.0, 5.7 Hz, 1H), 2.66 (s, 1H), 2.60 (dd, J = 14.9, 8.1 Hz, 1H), 2.46 – 2.36 (m, 2H), 2.30 (ddd, J = 16.3, 12.6, 7.5 Hz, 1H), 2.20 – 2.13 (m, 1H), 1.98 – 1.93 (m, 1H), 1.85 (dt, J = 2.9, 1.6 Hz, 3H), 1.79 (ddd, J = 13.4, 7.5, 1.8 Hz, 1H), 1.19 (s, 3H).



216

Aldehyde 216. To a solution of allyl **214** (38.4 mg, 0.12 mmol, 1.0 equiv) in THF (1.2 mL) at 0 °C was added $LiAlH_4$ (0.14 mL, 1.0 M in THF, 0.14 mmol, 1.2 equiv). The resulting solution was then stirred for 30 min at this temperature. Upon completion, the reaction

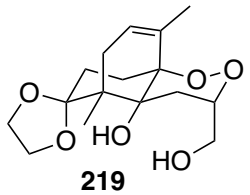
contents were quenched by the addition of NH_4Cl/Rochelle's Salt (1:1, 15 mL), stirred for 10 min, diluted with EtOAc (10 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc 6:1→2:1) afforded fully reduced **215** (7.7 mg, 0.026 mmol, 22% yield) and desired aldehyde **216** (27.1 mg, 0.093 mmol, 78% yield) as colorless oils. **216**: R_f = 0.30 (silica gel, hexanes:acetone, 4:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.06 (s, 1H), 6.03 (dddd, J = 17.1, 10.3, 8.0, 6.1 Hz, 1H), 5.59 (tt, J = 2.8, 1.5 Hz, 1H), 5.07 – 4.99 (m, 2H), 4.42 (s, 1H), 4.06 – 4.00 (m, 2H), 3.99 – 3.86 (m, 2H), 2.74 – 2.58 (m, 2H), 2.49 – 2.39 (m, 1H), 2.17 (td, J = 13.8, 4.6 Hz, 1H), 2.05 – 1.96 (m, 1H), 1.72 – 1.63 (m, 4H), 1.59 (ddd, J = 13.6, 4.7, 2.5 Hz, 1H), 1.41 (ddd, J = 14.2, 4.8, 2.5 Hz, 1H), 0.99 (s, 3H).



217

Carboxylic Acid 217. To a solution of aldehyde **216** (150.3 mg, 0.51 mmol, 1.0 equiv) in *t*BuOH (5.0 mL) and 2-methyl-2-butene (5.0 mL) at 25 °C was added a pre-mixed solution of NaH_2PO_4•$2H_2O$ (795.7 mg, 5.10 mmol, 10.0 equiv) and $NaClO_2$ (507.4 mg, 5.61 mmol, 11.0 equiv) in H_2O (5.0 mL). The reaction mixture was then allowed to stir at this temperature for 12 h. Upon completion, the reaction contents were quenched by the addition of brine (30 mL), diluted with EtOAc (20 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:acetone 4:1) afforded carboxylic acid **217** (128.5 mg, 0.42 mmol, 82% yield) as a white foam. **217**: R_f = 0.40 (silica gel, hexanes:acetone, 2:1); ^{1}H NMR

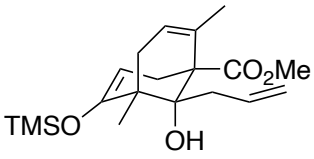
(500 MHz, $CDCl_3$) δ 10.94 (s, 1H), 6.01 (ddt, J = 17.3, 10.2, 7.3 Hz, 1H), 5.66 (s, 1H), 5.52 (dd, J = 4.0, 2.1 Hz, 1H), 5.07 – 4.97 (m, 2H), 4.11 – 4.01 (m, 2H), 3.96 (dd, J = 6.5, 5.3 Hz, 2H), 2.62 – 2.48 (m, 2H), 2.44 – 2.35 (m, 1H), 2.20 – 2.11 (m, 1H), 2.07 – 1.94 (m, 4H), 1.83 – 1.72 (m, 2H), 1.36 – 1.29 (m, 1H), 1.02 (s, 3H).



219

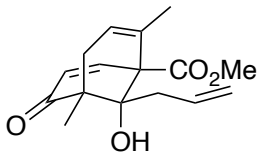
***Endo*-Peroxide 219**. Protected from light, to a solution of carboxylic acid **217** (128.5 mg, 0.42 mmol, 1.0 equiv) in CH_2Cl_2 (6.0 mL) and THF (3.0 mL) was sequentially added DMAP (77.0 mg, 0.63 mmol, 1.5 equiv), EDC (97.8 mg, 0.63 mmol, 1.5 equiv), and a solution of pyrithione (80.1 mg, 0.63 mmol, 1.5 equiv) in CH_2Cl_2 (2.0 mL). The reaction mixture was then allowed to stir in the dark for 12 h, upon which full conversion to Barton ester **218** was observed. Then, the solution was saturated with O_2 by direct bubbling for 5 minutes, before subsequent irradiation with a 500 W floodlamp for 30 min. Upon completion, the reaction contents were quenched by the addition Ph_3P (330.5 mg, 1.26 mmol, 3.0 equiv), stirred for 10 min, diluted with NH_4Cl (10 mL) and EtOAc (10 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:acetone 3:1) afforded *endo*-peroxide **219** (38.6 mg, 0.12 mmol, 29% yield) as a colorless oil. **219**: R_f = 0.20 (silica gel, hexanes:acetone, 2:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.52 – 5.47 (m, 1H), 4.78 (ddt, J = 11.6, 6.8, 2.4 Hz, 1H), 4.48 (d, J = 2.2 Hz, 1H), 4.07 (q, J = 6.4 Hz, 2H), 3.94 (q, J = 6.3 Hz, 2H), 3.66 (d, J = 11.2 Hz, 1H), 3.52 (dd, J = 13.0, 6.7 Hz, 1H), 2.51 – 2.44 (m, 1H), 1.96 – 1.88 (m, 1H), 1.81 – 1.71 (m, 7H), 1.50 (dd, J = 12.5, 2.4 Hz, 1H), 1.39 – 1.35 (m, 1H), 0.96 (s, 3H); DEPT-135 NMR (125 MHz,

$CDCl_3$) δ 123.50 (–), 78.40 (–), 65.72 (+), 64.46 (+), 64.39 (+), 35.16 (+), 30.83 (+), 20.93 (+), 23.87 (+), 17.09 (–), 14.29 (–).



220

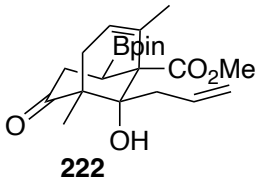
Silyl Enol Ether 220. To a solution of allyl **211** (269.9 mg, 0.97 mmol, 1.0 equiv) in THF (10 mL) at 0 °C was sequentially added LiHMDS (2.9 mL, 1.0 M in THF, 2.91 mmol, 3.0 equiv) and TMSCl (0.19 mL, 1.46 mmol, 1.5 equiv). The reaction mixture was then allowed to stir for 1 h at this temperature. Upon completion, the reaction contents were quenched by the addition of $NaHCO_3$ (25 mL), diluted with CH_2Cl_2 (25 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc 20:1) afforded silyl enol ether **220** (231.7 mg, 0.66 mmol, 68% yield) as a colorless oil. **220**: R_f = 0.80 (silica gel, hexanes:acetone, 4:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.80 (ddt, J = 17.3, 10.4, 7.0 Hz, 1H), 5.46 – 5.41 (m, 1H), 5.09 – 5.00 (m, 2H), 4.71 (dd, J = 5.9, 2.1 Hz, 1H), 3.68 (s, 3H), 2.97 (dt, J = 17.3, 1.9 Hz, 1H), 2.53 (dt, J = 7.0, 1.5 Hz, 2H), 2.37 (s, 1H), 2.08 – 1.96 (m, 3H), 1.71 (dt, J = 2.7, 1.4 Hz, 3H), 1.11 (s, 3H), 0.17 (s, 9H).



221
(UNSTABLE)

Enone 221. To a solution of silyl enol ether **220** (228.4 mg, 0.65 mmol, 1.0 equiv) in DMSO (0.50 mL) was added a pre-dissolved solution of IBX (364.0 g, 1.30 mmol, 2.0 equiv) and MPO (162.6 mg, 1.30 mmol, 2.0 equiv) in DMSO (3.3 mL) at 25 °C. The reaction mixture was then placed into a preheated oil bath (45 °C) and was allowed to stir for 2 h. Upon

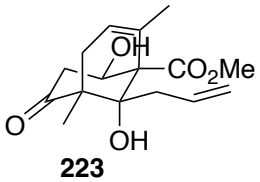
completion, the reaction contents were quenched by the addition of $NaHCO_3$ (10 mL), diluted with EtOAc (15 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 6:1→4:1) afforded the desired enone **221** (144.3 mg, 0.52 mmol, 80% yield) as a light yellow oil. **221**: R_f = 0.20 (silica gel, hexanes:EtOAc, 4:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (d, J = 9.9 Hz, 1H), 6.10 (d, J = 9.9 Hz, 1H), 5.83 (ddt, J = 17.5, 10.3, 7.4 Hz, 1H), 5.34 (tt, J = 2.9, 1.5 Hz, 1H), 5.20 – 5.11 (m, 2H), 3.81 (s, 3H), 3.78 (s, 1H), 2.90 – 2.81 (m, 1H), 2.53 (ddt, J = 15.0, 7.2, 1.5 Hz, 1H), 2.25 – 2.10 (m, 2H), 1.81 (dt, J = 2.7, 1.7 Hz, 3H), 1.33 (s, 3H).



222
[XRAY]

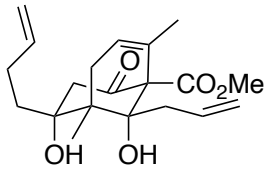
Borane 222. To a suspension of CuCl (56.4 mg, 0.57 mmol, 1.0 equiv) in THF (4.0 mL) in a flame-dried flask was added $ICyBF_4$ (92.9 mg, 0.29 mmol, 0.5 equiv) and NaO*t*Bu (109.6 mg, 1.14 mmol, 2.0 equiv). The reaction mixture was allowed to stir at 25 °C for 1 h before the introduction of a premixed solution of enone **221** (156.4 mg, 0.57 mmol, 1.0 equiv) and B_2pin_2 (218.4 mg, 0.86 mmol, 1.5 equiv) in THF (1.7 mL). The resulting mixture was then stirred for 15 min at this temperature. Upon completion, the reaction contents were quenched by the addition of NH_4Cl/NH_4OH (9:1, 15 mL), diluted with CH_2Cl_2 (15 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 10:1) afforded the desired borane **222** (87.0 mg, 0.22 mmol, 39% yield) as a

colorless crystalline solid. **222**: R_f = 0.50 (silica gel, hexanes:EtOAc, 3:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.81 – 5.74 (m, 1H), 5.65 (s, 1H), 5.09 – 5.00 (m, 2H), 3.69 (s, 3H), 3.10 (s, 1H), 2.60 (dd, J = 13.9, 4.4 Hz, 1H), 2.45 (dd, J = 10.9, 3.8 Hz, 2H), 2.40 (d, J = 4.2 Hz, 1H), 2.37 – 2.32 (m, 1H), 2.14 – 2.08 (m, 1H), 1.99 (dt, J = 2.7, 1.5 Hz, 3H), 1.94 – 1.87 (m, 1H), 1.19 (d, J = 1.3 Hz, 12H), 1.18 (s, 3H).



223

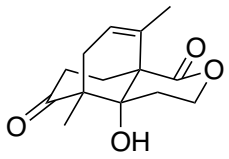
Diol 223. To a solution of borane **222** (87.0 mg, 0.22 mmol, 1.0 equiv) in THF (2.5 mL) and H_2O (2.5 mL) was added $NaBO_3$•H_2O (219.6 mg, 2.20 mmol, 10.0 equiv). The resulting mixture was then stirred vigorously for 2 h. Upon completion, the reaction contents were quenched by the addition of H_2O (10 mL), diluted with EtOAc (15 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 2:1) afforded diol **223** (65.2 mg, 0.22 mmol, quant.) as a colorless oil. **223**: R_f = 0.40 (silica gel, hexanes:EtOAc, 1:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.77 – 5.67 (m, 2H), 5.19 – 5.00 (m, 3H), 3.83 (s, 3H), 2.78 – 2.67 (m, 2H), 2.56 (dd, J = 15.0, 11.6 Hz, 1H), 2.44 – 2.41 (m, 1H), 2.19 – 2.11 (m, 2H), 2.02 (dd, J = 3.2, 1.7 Hz, 4H), 1.16 (s, 3H).



225

Homoallyl 225. To a solution of diol **223** (20.7 mg, 0.070 mmol, 1.0 equiv) in THF (0.70 mL) at –78 °C was added homoallylmagnesium bromide (0.53 mL, 0.66 M in THF, 0.35 mmol, 5.0 equiv – prepared by flushing a mixture of Mg turnings (1.09 g, 44.78 mmol, 2.0

equiv) and I_2 (1 chip) with N_2, adding THF (34 mL), heating at 70 °C for 10 min, then removing from heat and adding homoallyl bromide (3.4 mL, 33.59 mmol, 1.5 mmol) dropwise, maintaining a gentle reflux, and then heating at 70 °C for a further 30 min). The reaction mixture was then stirred for 12 h, slowly warming to 25 °C. Upon completion, the reaction contents were quenched by the addition of NH_4Cl (10 mL), diluted with EtOAc (15 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 2:1) afforded homoallyl **224** (8.0 mg, 0.023 mmol, 33% yield) as a colorless oil. Pushing forward, to a solution of homoallyl **224** (7.0 mg, 0.020 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL) was added sequentially $NaHCO_3$ (8.4 mg, 0.100 mmol, 5.0 equiv) and Dess–Martin periodinane (25.4 mg, 0.060 mmol, 3.0 equiv). The reaction mixture was then allowed to stir at 25 °C for 1 h. Upon completion, the reaction contents were concentrated directly and the resultant residue was purified by flash column chromatography (silica gel, hexanes:EtOAc, 6:1) to afford the desired ketone **225** (3.9 mg, 0.011 mmol, 55% yield) as a clear and colorless oil. **225**: R_f = 0.40 (silica gel, hexanes:EtOAc, 2:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.89 – 5.74 (m, 2H), 5.70 (d, J = 3.5 Hz, 1H), 5.11 – 4.93 (m, 6H), 3.79 (s, 3H), 2.92 (d, J = 16.1 Hz, 1H), 2.70 – 2.63 (m, 2H), 2.54 – 2.47 (m, 1H), 2.38 – 2.33 (m, 1H), 2.30 (s, 1H), 2.26 – 2.20 (m, 1H), 2.03 – 1.94 (m, 1H), 1.84 – 1.80 (m, 3H), 1.80 – 1.76 (m, 1H), 1.46 (dd, J = 17.5, 11.9 Hz, 1H), 1.29 (s, 3H).

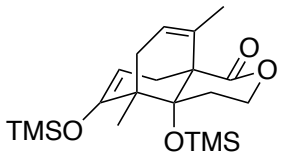


229

Lactone 229. To a solution of allyl **214** (250.0 mg, 0.78 mmol, 1.0 equiv) in 1,4-dioxane (8.0 mL) and H_2O (2.0 mL) was sequentially added lutidine (0.18 mL, 1.56 mmol, 2.0

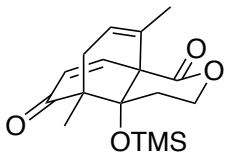
equiv), $NaIO_4$ (667.3 mg, 3.12 mmol, 4.0 equiv), and OsO_4 (0.25 mL, 4% in H_2O, 0.039 mmol, 0.05 equiv). The reaction mixture was then stirred vigorously for 1 h. Upon completion, the reaction contents were quenched by the addition of H_2O (15 mL), diluted with EtOAc (25 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with EtOAc (3 × 25 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:acetone, 6:1) afforded the desired aldehyde (179.4 mg, 0.55 mmol, 71% yield) as a yellow oil. Pushing forward, to a solution of the so-obtained aldehyde (160.3 mg, 0.49 mmol, 1.0 equiv) in MeOH (5.0 mL) at 0 °C was added $NaBH_4$ (55.6 mg, 1.47 mmol, 3.0 equiv) in one portion. The resulting mixture was then stirred at this temperature for 5 min. Upon completion, the reaction contents were quenched by the addition of NH_4Cl (10 mL), diluted with EtOAc (15 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated to directly afford crude diol **227** (157.4 mg, 0.48 mmol, 98% yield) without further purification required. Next, to a solution of crude diol **227** (157.4 mg, 0.48 mmol, 1.0 equiv) in THF (3.6 mL) and H_2O (1.2 mL) at 25 °C was added LiOH (57.5 mg, 2.40 mmol, 5.0 equiv) in a single portion. The reaction mixture was then allowed to stir for 10 min. Upon completion, the reaction contents were quenched by the addition of 3M HCl (5.0 mL), stirred for 1 h, diluted with EtOAc (10 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated to directly afford desired lactone **229** (114.7 mg, 0.46 mmol, 96% yield) without further purification required. **229**: R_f = 0.15 (silica gel, hexanes:EtOAc, 2:1); ^1H NMR (500 MHz, $CDCl_3$) δ 5.72 (td, J = 3.5, 1.5 Hz, 1H), 4.48 (dt, J =

11.6, 6.5 Hz, 1H), 4.36 (dt, J = 11.6, 6.6 Hz, 1H), 2.52 – 2.36 (m, 3H), 2.30 – 2.19 (m, 2H), 2.16 (dq, J = 6.2, 2.4 Hz, 2H), 1.90 – 1.81 (m, 2H), 1.79 (q, J = 2.1 Hz, 3H), 1.13 (s, 3H).



230

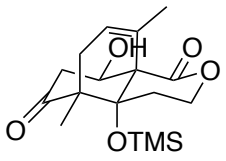
Disilyl 230. To a solution of lactone **229** (13.4 mg, 0.054 mmol, 1.0 equiv) in CH_2Cl_2 (1.1 mL) at 25 °C was added Et_3N (0.06 mL, 0.432 mmol, 8.0 equiv). The reaction mixture was then cooled to 0 °C before the dropwise introduction of TMSOTf (0.06 mL, 0.324 mmol, 6.0 equiv). The cooling bath was then removed and the reaction was allowed to stir for 15 min at 25 °C. Upon completion, the reaction contents were quenched by the addition of $NaHCO_3$ (10 mL), diluted with CH_2Cl_2 (10 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc 10:1) afforded disilyl **230** (18.8 mg, 0.048 mmol, 89% yield) as a colorless oil. **230**: R_f = 0.60 (silica gel, hexanes:EtOAc, 4:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.47 – 5.42 (m, 1H), 4.61 (dd, J = 5.6, 2.2 Hz, 1H), 4.37 – 4.30 (m, 2H), 2.65 (dt, J = 17.1, 2.0 Hz, 1H), 2.31 – 2.24 (m, 1H), 2.21 – 2.15 (m, 2H), 2.07 – 2.01 (m, 1H), 1.99 – 1.93 (m, 1H), 1.66 (dt, J = 2.4, 1.6 Hz, 3H), 1.01 (s, 3H), 0.18 (s, 9H), 0.13 (s, 9H).



231

Enone 231. To a solution of disilyl **230** (197.0 mg, 0.50 mmol, 1.0 equiv) in DMSO (0.40 mL) was added a pre-dissolved solution of IBX (280.0 g, 1.00 mmol, 2.0 equiv) and MPO (125.1 mg, 1.00 mmol, 2.0 equiv) in DMSO (2.5 mL) at 25 °C. The reaction mixture was then placed into a preheated oil bath (45 °C) and was allowed to stir for 2 h. Upon completion, the

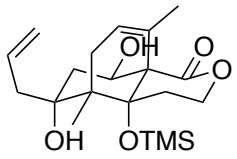
reaction contents were quenched by the addition of $NaHCO_3$ (10 mL), diluted with EtOAc (15 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 4:1) afforded the desired enone **231** (85.7 mg, 0.27 mmol, 54% yield) as a light yellow oil. **231**: R_f = 0.20 (silica gel, hexanes:EtOAc, 4:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (dd, J = 10.0, 0.6 Hz, 1H), 6.03 (d, J = 10.0 Hz, 1H), 5.43 – 5.39 (m, 1H), 4.46 (ddd, J = 11.7, 7.7, 4.8 Hz, 1H), 4.40 – 4.33 (m, 1H), 2.24 – 2.21 (m, 2H), 2.12 (dt, J = 14.8, 7.8 Hz, 2H), 1.76 (dt, J = 3.8, 1.9 Hz, 3H), 1.26 (s, 3H), 0.07 (s, 9H).



233

Alcohol 233. To a suspension of CuCl (25.7 mg, 0.26 mmol, 1.0 equiv) in THF (4.0 mL) in a flame-dried flask was added $ICyBF_4$ (41.6 mg, 0.13 mmol, 0.5 equiv) and NaO*t*Bu (50.0 mg, 0.52 mmol, 2.0 equiv). The reaction mixture was allowed to stir at 25 °C for 1 h before the introduction of a premixed solution of enone **231** (83.6 mg, 0.26 mmol, 1.0 equiv) and B_2pin_2 (99.0 mg, 0.39 mmol, 1.5 equiv) in THF (1.2 mL). The resulting mixture was then stirred for 15 min at this temperature. Upon completion, the reaction contents were quenched by the addition of NH_4Cl/NH_4OH (9:1, 15 mL), diluted with CH_2Cl_2 (15 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 6:1) afforded the desired borane (97.0 mg, 0.22 mmol, 85% yield) as a colorless crystalline solid. Pushing forward, to a solution of the so-obtained borane (97.0 mg, 0.22 mmol, 1.0 equiv) in THF (2.2 mL)

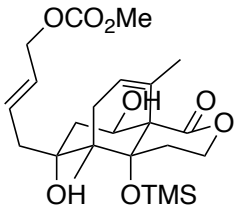
and H_2O (2.2 mL) was added $NaBO_3$•H_2O (329.4 mg, 3.30 mmol, 15.0 equiv). The resulting mixture was then stirred vigorously for 8 h. Upon completion, the reaction contents were quenched by the addition of NH_4Cl (10 mL), diluted with EtOAc (15 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 2:1) afforded alcohol **233** (75.3 mg, 0.22 mmol, quant.) as a colorless crystalline solid. **233**: R_f = 0.20 (silica gel, hexanes:EtOAc, 2:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.85 – 5.81 (m, 1H), 4.75 (ddd, J = 11.4, 5.4, 2.6 Hz, 1H), 4.45 (ddd, J = 12.0, 7.9, 3.1 Hz, 1H), 4.34 (ddd, J = 12.1, 9.7, 7.1 Hz, 1H), 3.64 (d, J = 2.7 Hz, 1H), 2.74 (dd, J = 14.8, 5.5 Hz, 1H), 2.56 (dd, J = 14.9, 11.5 Hz, 1H), 2.21 – 2.08 (m, 4H), 1.95 (td, J = 2.3, 1.5 Hz, 3H), 1.11 (s, 3H), 0.15 (s, 9H).



235
[XRAY]

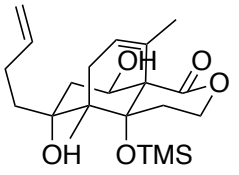
Allyl 235. To a solution of alcohol **233** (73.6 mg, 0.22 mmol, 1.0 equiv) in THF (2.2 mL) at –78 °C was added allylmagnesium bromide (0.88 mL, 1.0 M in THF, 0.88 mmol, 4.0 equiv) in a dropwise fashion. The resultant reaction mixture was then stirred for 15 min at this temperature. Upon completion, the reaction contents were quenched by the addition of NH_4Cl (10 mL), diluted with EtOAc (15 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 4:1) afforded allyl **235** (59.1 mg, 0.16 mmol, 73% yield) as a colorless crystalline solid. **235**: R_f = 0.40 (silica gel, hexanes:EtOAc, 2:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.96 (d, J = 7.0 Hz, 1H), 5.69 (s, 1H), 5.13 – 5.02 (m, 2H),

4.66 – 4.61 (m, 1H), 4.59 (d, J = 2.4 Hz, 1H), 4.41 – 4.30 (m, 2H), 3.60 (d, J = 2.8 Hz, 1H), 2.42 (dt, J = 13.1, 6.5 Hz, 2H), 2.21 – 2.10 (m, 4H), 2.04 – 1.99 (m, 1H), 1.84 – 1.81 (m, 3H), 1.09 (s, 3H), 0.25 (s, 9H).



237

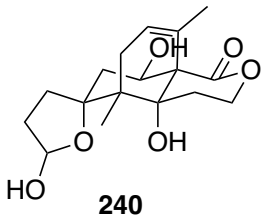
Allylic Carbonate 237. To a solution of allyl **235** (20.6 mg, 0.054 mmol, 1.0 equiv) in DCE (1.1 mL) was added allylic carbonate dimer **236** (44.1 mg, 0.216 mmol, 4.0 equiv) and Grubbs 2nd Generation initiator (4.2 mg, 0.005 mmol, 0.1 eq) at 25 °C. The resulting solution was then placed in a preheated oil bath (40 °C) and was allowed to stir for 16 h at this temperature. Upon completion, the reaction contents were directly concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 2:1) afforded allylic carbonate **237** (20.5 mg, 0.044 mmol, 81% yield) as a colorless oil. **237**: R_f = 0.15 (silica gel, hexanes:EtOAc, 2:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.97 (s, 1H), 5.68 (s, 1H), 5.64 (s, 1H), 4.60 (d, J = 7.8 Hz, 3H), 4.37 (q, J = 12.2 Hz, 2H), 4.21 – 4.10 (m, 1H), 3.77 (s, 3H), 3.59 (s, 1H), 2.53 – 1.92 (m, 8H), 1.82 (s, 3H), 1.07 (s, 3H), 0.25 (s, 9H).



238

Homoallyl 238. To a solution of allylic carbonate **237** (7.5 mg, 0.016 mmol, 1.0 equiv) in 1,4-dioxane (0.50 mL) was sequentially added $Pd_2(dba)_3$•$CHCl_3$ (0.8 mg, 0.0008 mmol, 0.05 equiv), Ph_3P (0.8 mg, 0.003 mmol, 0.2 equiv), and $HCOONH_4$ (2.0 mg, 0.032 mmol, 2.0 equiv). The reaction mixture was then placed in a preheated oil bath (100 °C) and was allowed to stir for 8 h, at which point the reaction contents were quenched by the addition of $NaHCO_3$ (5

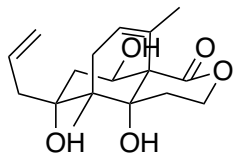
mL), diluted with CH_2Cl_2 (5 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 2:1) afforded recovered starting allylic carbonate **237** (2.2 mg, 0.005 mmol, 31% recovered) and the desired homoallyl **238** (0.8 mg, 0.002 mmol, 13% yield, 18% brsm) as a colorless oil. **238**: R_f = 0.10 (silica gel, hexanes:EtOAc, 2:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.83 (ddt, J = 17.0, 10.0, 6.6 Hz, 1H), 5.68 (s, 1H), 5.08 – 4.90 (m, 1H), 4.65 (dd, J = 13.0, 5.6 Hz, 1H), 4.56 (d, J = 2.3 Hz, 1H), 4.42 – 4.30 (m, 2H), 3.61 (dd, J = 9.3, 2.7 Hz, 1H), 2.47 – 2.37 (m, 1H), 2.37 – 2.23 (m, 1H), 2.22 – 2.08 (m, 4H), 2.03 – 1.96 (m, 1H), 1.82 (q, J = 1.9 Hz, 3H), 1.68 (d, J = 6.2 Hz, 1H), 1.63 (dd, J = 15.0, 4.9 Hz, 1H), 1.54 – 1.45 (m, 1H), 1.07 (d, J = 6.6 Hz, 3H), 0.25 (d, J = 1.6 Hz, 9H).



240

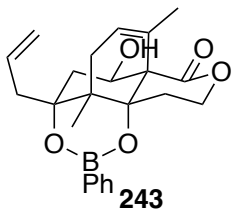
Lactol 240. To a solution of allyl **235** (9.0 mg, 0.024 mmol, 1.0 equiv) in *t*BuOH (0.45 mL) and $MeNO_2$ (0.03 mL) at 25 °C was sequentially added $Pd(PhCN)_2Cl_2$ (1.2 mg, 0.003 mmol, 0.12 equiv), $CuCl_2$ (0.4 mg, 0.003 mmol, 0.12 equiv), and $AgNO_2$ (0.3 mg, 0.002 mmol, 0.06 equiv). The reaction mixture was then purged with O_2 by direct bubbling for 5 min before being stirred under an O_2 atmosphere (balloon) for 8 h. Upon completion, the reaction contents were quenched by the addition of $NaHCO_3$ (5 mL), diluted with Et_2O (5 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 3:1) afforded deprotected lactol **240** (4.0 mg, 0.012 mmol, 50% yield, inseparable

2:1 *dr*) as a colorless oil. **240**: R_f = 0.30 (silica gel, hexanes:EtOAc, 3:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.65 – 5.60 (m, 1H), 5.49 – 5.31 (m, 2H), 4.69 – 4.58 (m, 1H), 4.56 – 4.49 (m, 1H), 4.33 – 4.27 (m, 1H), 4.06 – 3.97 (m, 1H), 2.32 – 2.06 (m, 5H), 1.98 – 1.85 (m, 3H), 1.81 (p, J = 2.0 Hz, 3H), 1.79 – 1.59 (m, 2H), 1.10 (s, 2H), 0.93 (s, 1H).



242

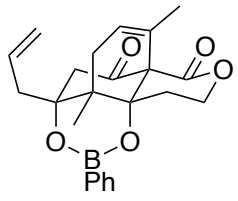
Triol 242. To a solution of allyl **235** (24.2 mg, 0.064 mmol, 1.0 equiv) in THF (1.0 mL) at 25 °C was added 3M HCl (1.0 mL). The reaction mixture was then allowed to stir for 5 min. Upon completion, the reaction contents were quenched by the addition of H_2O (10 mL), diluted with EtOAc (10 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated to directly afford triol **242** (19.5 mg, 0.063 mmol, 98% yield) as a colorless oil without further purification required. **242**: R_f = 0.10 (silica gel, hexanes:acetone, 2:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.91 – 5.81 (m, 1H), 5.65 (d, J = 2.1 Hz, 2H), 5.38 – 5.18 (m, 2H), 4.65 (ddd, J = 11.6, 4.5, 2.0 Hz, 1H), 4.55 (dt, J = 11.3, 6.9 Hz, 1H), 4.32 (dt, J = 11.2, 6.7 Hz, 1H), 4.12 (d, J = 2.1 Hz, 1H), 2.45 – 2.32 (m, 2H), 2.18 – 1.87 (m, 5H), 1.82 (dt, J = 3.1, 1.7 Hz, 3H), 1.75 (dd, J = 14.0, 11.5 Hz, 1H), 1.09 (s, 3H).



243

Boronic Ester 243. To a solution of triol **242** (19.4 mg, 0.063 mmol, 1.0 equiv) in benzene (1.0 mL) and MeOH (0.3 mL) at 25 °C was added $PhB(OH)_2$ (76.8 mg, 0.630 mmol, 10.0 equiv) in a single portion. The resulting reaction mixture was allowed to stir at 25 °C for 20

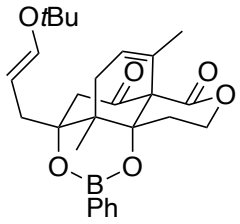
min before being directly concentrated. The resulting residue was redissolved in benzene (1.3 mL) before being placed in a preheated oil bath (40 °C) at which it was stirred for an additional 1.5 h. Upon completion, the reaction contents were quenched by the addition of H_2O (10 mL), diluted with CH_2Cl_2 (10 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes:EtOAc, 5:1) afforded boronic ester **243** (24.8 mg, 0.063 mmol, quant.) as a white foam. **243**: R_f = 0.20 (silica gel, hexanes:EtOAc, 5:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 – 7.76 (m, 2H), 7.52 (t, J = 7.2 Hz, 1H), 7.37 – 7.33 (m, 2H), 6.16 – 6.05 (m, 1H), 5.74 (s, 1H), 5.25 – 5.11 (m, 2H), 4.73 (dt, J = 11.5, 6.9 Hz, 1H), 4.46 – 4.32 (m, 2H), 3.70 (d, J = 2.6 Hz, 1H), 2.58 – 2.43 (m, 2H), 2.28 – 2.15 (m, 3H), 2.13 – 2.02 (m, 2H), 1.84 (q, J = 2.2 Hz, 3H), 1.61 (dd, J = 13.9, 11.4 Hz, 1H), 1.03 (s, 3H).



244

Dicarbonyl 244. To a solution of boronic ester **243** (24.8 mg, 0.063 mmol, 1.0 equiv) in CH_2Cl_2 (1.0 mL) was added sequentially $NaHCO_3$ (20.6 mg, 0.245 mmol, 5.0 equiv) and Dess–Martin periodinane (41.6 mg, 0.098 mmol, 2.0 equiv). The reaction mixture was then allowed to stir at 25 °C for 1 h. Upon completion, the reaction contents were concentrated directly and the resultant residue was purified by flash column chromatography (silica gel, hexanes:EtOAc, 3:2) to afford the desired dicarbonyl **244** (24.2 mg, 0.062 mmol, 98% yield) as a white foam. **244**: R_f = 0.20 (silica gel, hexanes:EtOAc, 1:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 – 7.71 (m, 2H), 7.45 – 7.41 (m, 1H), 7.35 – 7.30 (m, 2H), 6.10 – 5.99 (m, 1H), 5.82 (s, 1H), 5.25 – 5.12 (m, 2H), 4.84 (td, J = 11.1, 4.7 Hz, 1H), 4.38 (ddd, J = 11.2, 6.3, 2.8 Hz, 1H), 3.11 (d, J = 14.9 Hz, 1H),

2.78 – 2.63 (m, 3H), 2.44 – 2.37 (m, 1H), 2.37 – 2.27 (m, 2H), 2.12 – 2.06 (m, 1H), 1.73 (p, J = 1.7 Hz, 3H), 1.18 (s, 3H).



246
(tentative)

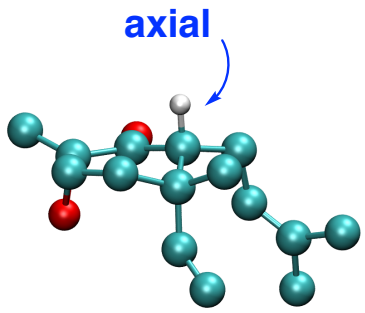
Enol Ether 246. To a solution of dicarbonyl **244** (7.5 mg, 0.019 mmol, 1.0 equiv) in *t*BuOH (0.30 mL) and $MeNO_2$ (0.02 mL) at 25 °C was sequentially added $Pd(PhCN)_2Cl_2$ (0.9 mg, 0.0023 mmol, 0.12 equiv), $CuCl_2$ (0.3 mg, 0.0023 mmol, 0.12 equiv), and $AgNO_2$ (0.2 mg, 0.0011 mmol, 0.06 equiv). The reaction mixture was then purged with O_2 by direct bubbling for 5 min before being stirred under an O_2 atmosphere (balloon) for 8 h. Upon completion, the reaction contents were quenched by the addition of $NaHCO_3$ (5 mL), diluted with Et_2O (5 mL), and poured into a separatory funnel. The two phases were separated, and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by preparative thin layer chromatography (silica gel, hexanes:EtOAc, 1:1) afforded enol ether **246** (1.0 mg, 0.002 mmol, 11% yield) as a colorless oil. **246**: R_f = 0.60 (silica gel, hexanes:EtOAc, 1:1); ^1H NMR (500 MHz, $CDCl_3$) δ 7.81 – 7.77 (m, 2H), 7.38 – 7.34 (m, 1H), 7.28 (t, J = 6.4 Hz, 2H), 6.38 (s, 1H), 5.69 (s, 1H), 5.08 (d, J = 5.4 Hz, 1H), 4.68 (td, J = 11.3, 4.7 Hz, 1H), 4.45 – 4.39 (m, 1H), 2.31 – 2.26 (m, 1H), 2.20 – 2.14 (m, 2H), 2.11 (d, J = 2.1 Hz, 2H), 1.96 (dt, J = 13.3, 6.4 Hz, 1H), 1.87 (dt, J = 3.3, 1.7 Hz, 3H), 1.63 – 1.59 (m, 1H), 1.50 (dd, J = 11.9, 7.3 Hz, 1H), 1.21 (s, 3H), 0.76 (s, 9H).

3.7 Computational General Information

DFT optimizations were performed through Gaussian 16 on the Midway2 Cluster at the University of Chicago's Research Computing Center. Ground state geometry optimizations were determined using the B3LYP/cc-pVDZ level of theory in the gas phase at 298K. In some instances, final free energies (kcal/mol) were determined through a single point calculation using the B3LYP/cc-pVTZ level of theory in the gas phase at 298K and are denoted as such. All ground state structures display no imaginary frequencies, and the free energies are zero-point energy corrected.

3.7.1 Minimized Structures

161 – axial

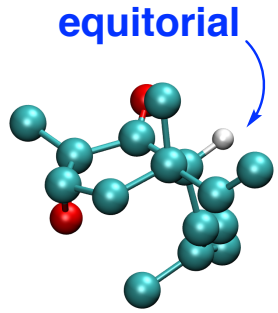


Zero-point correction= 0.335873 (Hartree/Particle)
Thermal correction to Energy= 0.354348
Thermal correction to Enthalpy= 0.355292
Thermal correction to Gibbs Free Energy= 0.289466
Sum of electronic and zero-point Energies= -734.913179
Sum of electronic and thermal Energies= -734.894704
Sum of electronic and thermal Enthalpies= -734.893760
Sum of electronic and thermal Free Energies= -734.959586
0 1

C	0.37815481	2.31435714	-1.30030599
C	-0.34120837	1.30987018	-0.37957277
C	-0.34083179	-0.10666167	-1.05075935
H	-0.83629654	0.06142725	-2.03215924
C	1.03799619	-0.73379985	-1.38109617
C	1.84724160	-1.20880299	-0.20266459
C	3.10016112	-0.86227810	0.14117892

C	3.75895613	-1.47065769	1.35499472
C	3.94968069	0.15024234	-0.58337175
C	0.28517582	1.28502125	1.01036443
C	1.12428391	2.19275535	1.51978081
C	-1.82192327	1.79157950	-0.26789788
C	-2.79566941	0.79549530	0.31219378
H	-3.83642446	1.14129733	0.37979898
C	-2.59042027	-0.66248381	0.19081968
C	-3.72819126	-1.65036657	0.19061932
O	-2.37010538	0.03313233	1.44973898
C	-1.28696313	-1.14213201	-0.42854593
O	-1.06691554	-2.33696427	-0.50082324
H	-0.01980409	2.25571064	-2.32629103
H	1.46132456	2.13506189	-1.34044272
H	0.22538141	3.34600395	-0.94723773
H	0.82808847	-1.60830928	-2.02032833
H	1.60670166	-0.02628800	-1.99868478
H	1.34538111	-1.95832443	0.41803615
H	3.10371108	-2.19727156	1.85778892
H	4.03159854	-0.68861682	2.08772426
H	4.69972237	-1.98414631	1.08460996
H	4.15100792	1.01886302	0.07069585
H	3.49264382	0.52607168	-1.50863209
H	4.93373840	-0.27835503	-0.84424816
H	-0.04598182	0.46561652	1.65194236
H	1.48252897	2.09800641	2.54791224
H	1.49135624	3.05273712	0.95473624
H	-2.19003442	2.05603924	-1.27685545
H	-1.84962730	2.71806366	0.32891633
H	-4.58381435	-1.24244426	0.74730335
H	-3.40698360	-2.59207365	0.65841799
H	-4.04670712	-1.88124430	-0.83875220

161 – equatorial



Zero-point correction= 0.336142 (Hartree/Particle)
Thermal correction to Energy= 0.354692
Thermal correction to Enthalpy= 0.355636
Thermal correction to Gibbs Free Energy= 0.290027
Sum of electronic and zero-point Energies= -734.916594
Sum of electronic and thermal Energies= -734.898044
Sum of electronic and thermal Enthalpies= -734.897100
Sum of electronic and thermal Free Energies= -734.962709
0 1

C	-2.87395030	-0.04126927	-1.06404719
C	-1.96102163	0.51038420	0.04849143
C	-0.49987563	0.62509362	-0.52935738
H	-0.56405309	1.21194626	-1.45979817
C	0.53855299	1.33152649	0.38881786
C	1.88186487	1.49904810	-0.27190934
C	3.06983611	1.01174689	0.12827060
C	3.27811424	0.14765904	1.34837924
C	4.32799478	1.32138993	-0.64604133
C	-2.43583007	1.87075918	0.52843493
C	-3.36108349	2.65435617	-0.03426081
C	-1.99432742	-0.46809667	1.25759903
C	-1.17717054	-1.73519301	1.08283700
H	-1.61458962	-2.65587490	1.49104667
C	-0.18647216	-1.91366713	-0.01615717
C	0.19647298	-3.27528358	-0.53490027
O	0.22588540	-1.61540239	1.34167793
C	-0.02014791	-0.75506513	-0.97970892
O	0.43863360	-0.95159432	-2.08929481
H	-2.57840524	-1.06086047	-1.35633048
H	-2.82672570	0.58069368	-1.97104942
H	-3.92143255	-0.08107997	-0.72734937
H	0.62987163	0.80041138	1.34342275
H	0.14126827	2.33720123	0.61057827
H	1.87022879	2.10468493	-1.18702338
H	3.81288362	0.70730085	2.13801392
H	2.34430262	-0.24546750	1.77009274

H	3.91858868	-0.71620745	1.09717990
H	4.79987680	0.39455289	-1.01953127
H	4.13331293	1.97811702	-1.50693134
H	5.07853319	1.81314879	-0.00027002
H	-1.95428080	2.22662768	1.44657036
H	-3.61607597	3.62066367	0.40796406
H	-3.89632385	2.37866545	-0.94563616
H	-3.04344246	-0.73780690	1.46166037
H	-1.62376915	0.03355231	2.16718715
H	0.06573030	-4.03290627	0.25088184
H	1.24725647	-3.27503454	-0.86072261
H	-0.41664779	-3.54668748	-1.40770679

3.8 X-Ray Crystallography Data

3.8.1 General Information

The diffraction data were measured at 100 K on a Bruker D8 VENTURE diffractometer equipped with a microfocus Mo-target X-ray tube (λ = 0.71073 Å) and PHOTON 100 CMOS detector. Data were collected using ω scans to survey a sphere of reciprocal space. Data reduction and integration were performed with the Bruker APEX3 software package (Bruker AXS, version 2017.3-0, 2018). Data were scaled and corrected for absorption effects using the multi-scan procedure as implemented in SADABS (Bruker AXS, version 2014/5, Krause, Herbst-Irmer, Sheldrick & Stalke, *J. Appl. Cryst.* **2015**, *48*, 3-10). The structure was solved by SHELXT (Version 2018/2: Sheldrick, G. M. *Acta Crystallogr*. **2015**, *A71*, 3-8) and refined by a full-matrix least-squares procedure using OLEX2 (O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard and H. Puschmann. J. Appl. Crystallogr. **2009**, *42*, 339-341) (XL refinement program version 2018/3, Sheldrick, G. M. Acta Crystallogr. **2015**, *C71*, 3-8).

Crystal Structure of 105

Specific details for structure refinement: All atoms were refined with anisotropic thermal parameters. All hydrogen atoms were included in idealized positions for structure factor calculations. All structures are drawn with thermal ellipsoids at 50% probability.

Crystal Structure of 170

Specific details for structure refinement: All atoms were refined with anisotropic thermal parameters. All hydrogen atoms were included in idealized positions for structure factor calculations except all OH groups. The H atoms were observed in the difference Fourier map and refined independently. All structures are drawn with thermal ellipsoids at 50% probability.

Crystal Structure of 191

Specific details for structure refinement: All atoms were refined with anisotropic thermal parameters. All hydrogen atoms were included in idealized positions for structure factor calculations. All structures are drawn with thermal ellipsoids at 50% probability.

Crystal Structure of 212

Specific details for structure refinement: All atoms were refined with anisotropic thermal parameters. All hydrogen atoms were included in idealized positions for structure factor calculations except all OH groups. The H atoms were observed in the difference Fourier map and refined independently. All structures are drawn with thermal ellipsoids at 50% probability.

Crystal Structure of 222

Specific details for structure refinement: All atoms were refined with anisotropic thermal parameters. All hydrogen atoms were included in idealized positions for structure factor calculations except for the OH group. For this, the H atom was observed in the difference Fourier

map and refined independently. All structures are drawn with thermal ellipsoids at 50% probability.

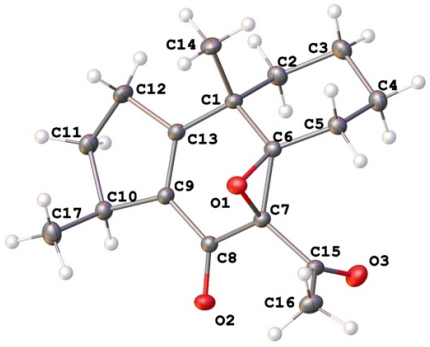
Crystal Structure of 228

Specific details for structure refinement: All atoms were refined with anisotropic thermal parameters. All hydrogen atoms were included in idealized positions for structure factor calculations except for the OH group. For this, the H atom was observed in the difference Fourier map and refined independently. All structures are drawn with thermal ellipsoids at 50% probability.

Crystal Structure of 235

Specific details for structure refinement: All atoms were refined with anisotropic thermal parameters. All hydrogen atoms were included in idealized positions for structure factor calculations except for the OH groups. For those, the H atoms were observed in the difference Fourier map and refined independently. Two -CH_3 substituents on TMS group were found to be disordered in approximately 1:1 ratio. All structures are drawn with thermal ellipsoids at 50% probability. Only one disordered part is shown for clarity.

Figure 3.3. ORTEP representation of **105**.

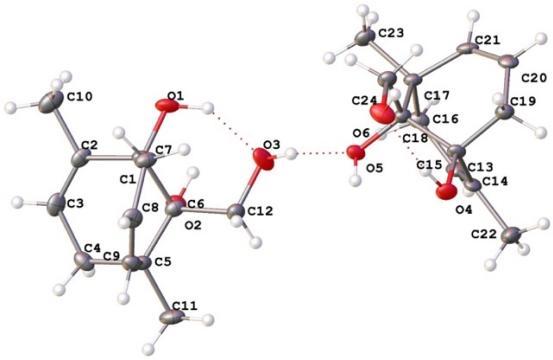


Crystal data and structure refinement for 0955_CT_Snyder_1.

Identification code	0955_CT_Snyder_1
Empirical formula	$C_{17}H_{22}O_3$
Formula weight	274.34
Temperature/K	100(2)
Crystal system	triclinic
Space group	P-1
a/Å	8.525(5)
b/Å	9.537(6)
c/Å	10.295(6)
α/°	104.198(12)
β/°	108.552(12)
γ/°	105.632(12)
Volume/Å^3	712.2(7)
Z	2
ρ_{calc}g/cm^3	1.279
μ/mm^{-1}	0.086
F(000)	296.0
Crystal size/mm^3	0.23 × 0.21 × 0.11
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	4.478 to 61.476
Index ranges	-12 ≤ h ≤ 12, -13 ≤ k ≤ 13, -14 ≤ l ≤ 14
Reflections collected	26381
Independent reflections	4369 [R_{int} = 0.0236, R_{sigma} = 0.0148]
Data/restraints/parameters	4369/0/184
Goodness-of-fit on F^2	1.056
Final R indexes [I>=2σ (I)]	R_1 = 0.0415, wR_2 = 0.1097
Final R indexes [all data]	R_1 = 0.0471, wR_2 = 0.1152
Largest diff. peak/hole / e Å^{-3}	0.54/-0.16

$R_{int} = \Sigma \mid F_o^2 - \langle F_o^2 \rangle \mid / \Sigma \mid F_o^2 \mid$
$R1 = \Sigma \mid \mid F_o \mid - \mid F_c \mid \mid / \Sigma \mid F_o \mid$
$wR2 = [\Sigma [w (F_o^2 - F_c^2)^2] / \Sigma [w (F_o^2)^2]]^{1/2}$
$\text{Goodness-of-fit} = [\Sigma [w (F_o^2 - F_c^2)^2] / (n-p)]^{1/2}$
n: number of independent reflections; p: number of refined parameters

Figure 3.4. ORTEP representation of **170** (Independent Unit Consists of 2 Molecules).

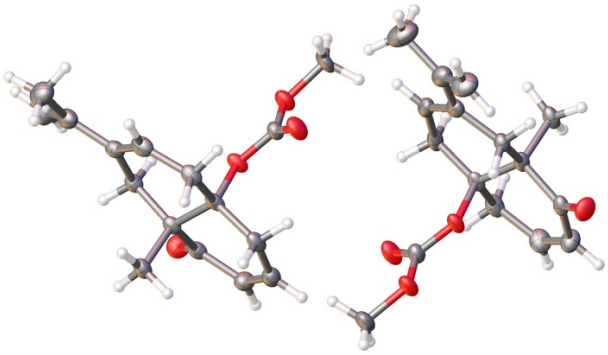


Crystal data and structure refinement for 1006_CT_Snyder_2.

Identification code	1006_CT_Snyder_2
Empirical formula	$C_{12}H_{18}O_3$
Formula weight	210.26
Temperature/K	100(2)
Crystal system	triclinic
Space group	P-1
a/Å	9.7486(16)
b/Å	10.6624(18)
c/Å	11.3405(19)
α/°	105.438(4)
β/°	106.888(4)
γ/°	92.158(4)
Volume/Å^3	1078.8(3)
Z	4
ρ_{calc}g/cm^3	1.295
μ/mm^{-1}	0.091
F(000)	456.0
Crystal size/mm^3	0.324 × 0.156 × 0.03
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	4.4 to 50.094
Index ranges	-11 ≤ h ≤ 11, -12 ≤ k ≤ 12, -13 ≤ l ≤ 13
Reflections collected	8055
Independent reflections	3745 [R_{int} = 0.0663, R_{sigma} = 0.1280]
Data/restraints/parameters	3745/0/299
Goodness-of-fit on F^2	1.000
Final R indexes [I>=2σ (I)]	R_1 = 0.0643, wR_2 = 0.1229
Final R indexes [all data]	R_1 = 0.1468, wR_2 = 0.1484
Largest diff. peak/hole / e Å^{-3}	0.27/-0.27

$R_{int} = \Sigma \mid F_o^2 - \langle F_o^2 \rangle \mid / \Sigma \mid F_o^2 \mid$
$R1 = \Sigma \mid \mid F_o \mid - \mid F_c \mid \mid / \Sigma \mid F_o \mid$
$wR2 = [\Sigma [w (F_o^2 - F_c^2)^2] / \Sigma [w (F_o^2)^2]]^{1/2}$
$\text{Goodness-of-fit} = [\Sigma [w (F_o^2 - F_c^2)^2] / (n-p)^{1/2}$
n: number of independent reflections; p: number of refined parameters

Figure 3.5. ORTEP representation of **191** (Independent Unit Consists of 2 Molecules).

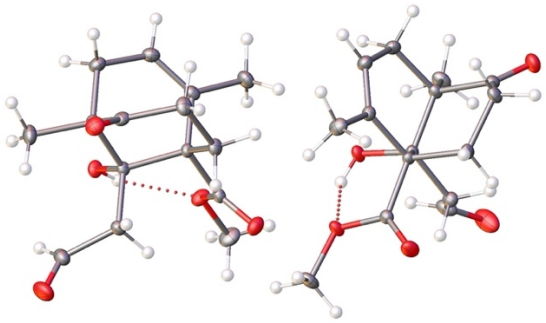


Crystal data and structure refinement for 1075_CT.

Identification code	1075_CT
Empirical formula	$C_{16}H_{20}O_4$
Formula weight	276.32
Temperature/K	100(2)
Crystal system	triclinic
Space group	P-1
a/Å	5.9788(6)
b/Å	14.1916(13)
c/Å	18.7382(17)
α/°	111.123(3)
β/°	90.847(3)
γ/°	100.167(3)
Volume/Å^3	1454.5(2)
Z	4
ρ_{calc}g/cm^3	1.262
μ/mm^{-1}	0.090
F(000)	592.0
Crystal size/mm^3	0.274 × 0.133 × 0.044
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	4.678 to 51.462
Index ranges	$-7 \leq h \leq 7$, $-17 \leq k \leq 17$, $-22 \leq l \leq 21$
Reflections collected	20233
Independent reflections	5546 [R_{int} = 0.1046, R_{sigma} = 0.1105]
Data/restraints/parameters	5546/0/367
Goodness-of-fit on F^2	1.007
Final R indexes [I>=2σ (I)]	R_1 = 0.0575, wR_2 = 0.0964
Final R indexes [all data]	R_1 = 0.1492, wR_2 = 0.1195
Largest diff. peak/hole / e Å^{-3}	0.23/-0.21

$R_{int} = \Sigma \mid F_o^2 - \langle F_o^2 \rangle \mid / \Sigma \mid F_o^2 \mid$
$R1 = \Sigma \mid \mid F_o \mid - \mid F_c \mid \mid / \Sigma \mid F_o \mid$
$wR2 = [\Sigma [w (F_o^2 - F_c^2)^2] / \Sigma [w (F_o^2)^2]]^{1/2}$
$\text{Goodness-of-fit} = [\Sigma [w (F_o^2 - F_c^2)^2] / (n-p)^{1/2}$
n: number of independent reflections; p: number of refined parameters

Figure 3.6. ORTEP representation of **212** (Independent Unit Consists of 2 Molecules).

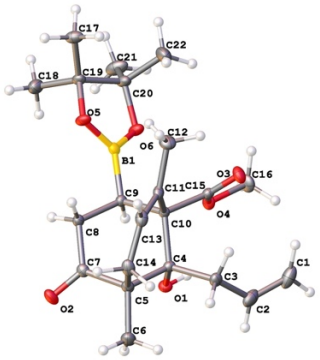


Crystal data and structure refinement for 1037_ct_Snyder2.

Identification code	1037_ct_Snyder2
Empirical formula	$C_{15}H_{20}O_5$
Formula weight	280.31
Temperature/K	100(2)
Crystal system	triclinic
Space group	P-1
a/Å	9.7729(10)
b/Å	10.5060(10)
c/Å	14.1581(14)
α/°	97.886(3)
β/°	99.556(2)
γ/°	104.546(2)
Volume/Å^3	1363.0(2)
Z	4
ρ_{calc}g/cm^3	1.366
μ/mm^{-1}	0.102
F(000)	600.0
Crystal size/mm^3	0.345 × 0.222 × 0.123
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	4.078 to 60.256
Index ranges	-13 ≤ h ≤ 13, -14 ≤ k ≤ 14, -19 ≤ l ≤ 19
Reflections collected	63234
Independent reflections	8012 [R_{int} = 0.0402, R_{sigma} = 0.0185]
Data/restraints/parameters	8012/0/375
Goodness-of-fit on F^2	1.036
Final R indexes [I>=2σ (I)]	R_1 = 0.0365, wR_2 = 0.0997
Final R indexes [all data]	R_1 = 0.0400, wR_2 = 0.1025
Largest diff. peak/hole / e Å^{-3}	0.42/-0.24

$R_{int} = \Sigma \mid F_o^2 - \langle F_o^2 \rangle \mid / \Sigma \mid F_o^2 \mid$
$R1 = \Sigma \mid \mid F_o \mid - \mid F_c \mid \mid / \Sigma \mid F_o \mid$
$wR2 = [\Sigma [w (F_o^2 - F_c^2)^2] / \Sigma [w (F_o^2)^2]]^{1/2}$
$\text{Goodness-of-fit} = [\Sigma [w (F_o^2 - F_c^2)^2] / (n-p)^{1/2}$
n: number of independent reflections; p: number of refined parameters

Figure 3.7. ORTEP representation of **222**.

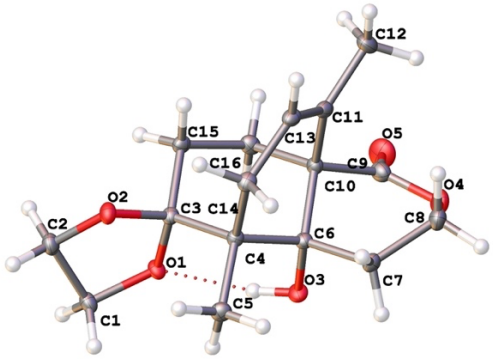


Crystal data and structure refinement for 1046_ct_Snyder1.

Identification code	1046_ct_Snyder1
Empirical formula	$C_{22}H_{33}BO_6$
Formula weight	404.29
Temperature/K	100(2)
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	10.8289(7)
b/Å	9.7660(7)
c/Å	20.5037(14)
α/°	90
β/°	97.504(2)
γ/°	90
Volume/Å^3	2149.8(3)
Z	4
ρ_{calc}g/cm^3	1.249
μ/mm^{-1}	0.088
F(000)	872.0
Crystal size/mm^3	0.238 × 0.094 × 0.079
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	4.628 to 54.59
Index ranges	$-13 \le h \le 13$, $-12 \le k \le 12$, $-26 \le l \le 26$
Reflections collected	34852
Independent reflections	4813 [R_{int} = 0.0448, R_{sigma} = 0.0295]
Data/restraints/parameters	4813/0/281
Goodness-of-fit on F^2	1.017
Final R indexes [I>=2σ (I)]	R_1 = 0.0442, wR_2 = 0.1035
Final R indexes [all data]	R_1 = 0.0620, wR_2 = 0.1130
Largest diff. peak/hole / e Å^{-3}	0.43/-0.24

$R_{int} = \Sigma \mid F_o^2 - \langle F_o^2 \rangle \mid / \Sigma \mid F_o^2 \mid$
$R1 = \Sigma \mid \mid F_o \mid - \mid F_c \mid \mid / \Sigma \mid F_o \mid$
$wR2 = [\Sigma [w (F_o^2 - F_c^2)^2] / \Sigma [w (F_o^2)^2]]^{1/2}$
$\text{Goodness-of-fit} = [\Sigma [w (F_o^2 - F_c^2)^2] / (n-p)^{1/2}$
n: number of independent reflections; p: number of refined parameters

Figure 3.8. ORTEP representation of **228**.

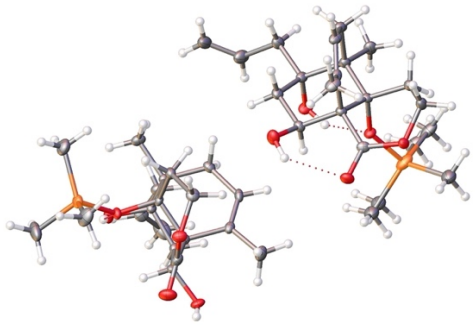


Crystal data and structure refinement for 1069_cooper.

Identification code	1069_cooper
Empirical formula	$C_{16}H_{22}O_5$
Formula weight	294.33
Temperature/K	100(2)
Crystal system	monoclinic
Space group	$P2_1/n$
a/Å	13.7108(7)
b/Å	6.7339(3)
c/Å	15.8430(8)
α/°	90
β/°	105.3740(10)
γ/°	90
Volume/Å^3	1410.40(12)
Z	4
ρ_{calc}g/cm^3	1.386
μ/mm^{-1}	0.102
F(000)	632.0
Crystal size/mm^3	0.321 × 0.154 × 0.076
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	4.578 to 57.498
Index ranges	-18 ≤ h ≤ 18, -9 ≤ k ≤ 9, -21 ≤ l ≤ 21
Reflections collected	28241
Independent reflections	3646 [R_{int} = 0.0286, R_{sigma} = 0.0175]
Data/restraints/parameters	3646/1/196
Goodness-of-fit on F^2	1.053
Final R indexes [I>=2σ (I)]	R_1 = 0.0435, wR_2 = 0.1136
Final R indexes [all data]	R_1 = 0.0521, wR_2 = 0.1196
Largest diff. peak/hole / e Å^{-3}	0.50/-0.20

$R_{int} = \Sigma \mid F_o^2 - \langle F_o^2 \rangle \mid / \Sigma \mid F_o^2 \mid$
$R1 = \Sigma \mid \mid F_o \mid - \mid F_c \mid \mid / \Sigma \mid F_o \mid$
$wR2 = [\Sigma [w (F_o^2 - F_c^2)^2] / \Sigma [w (F_o^2)^2]]^{1/2}$
Goodness-of-fit = $[\Sigma [w (F_o^2 - F_c^2)^2] / (n-p)^{1/2}$
n: number of independent reflections; p: number of refined parameters

Figure 3.9. ORTEP representation of **235** (Independent Unit Consists of 2 Molecules).

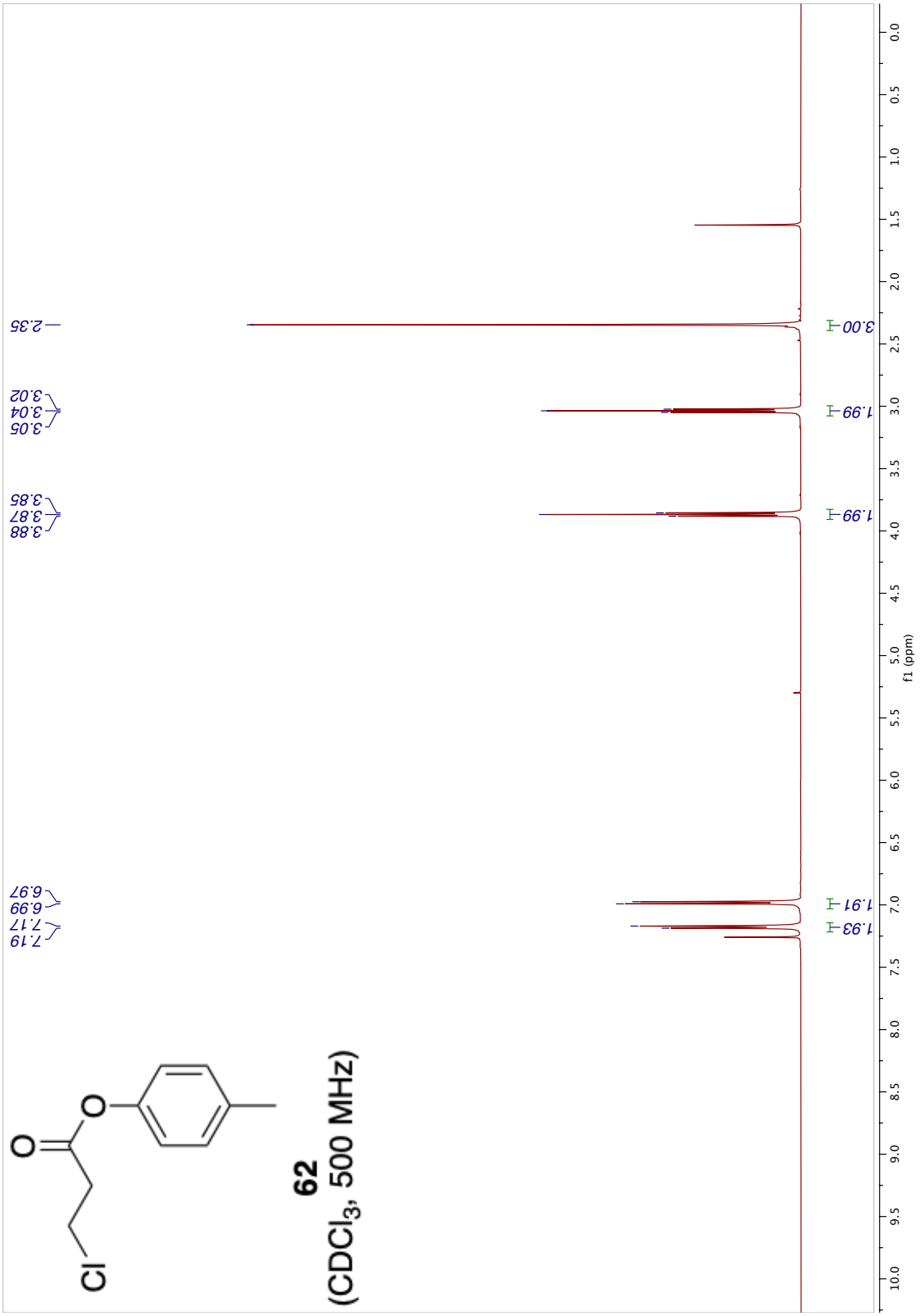


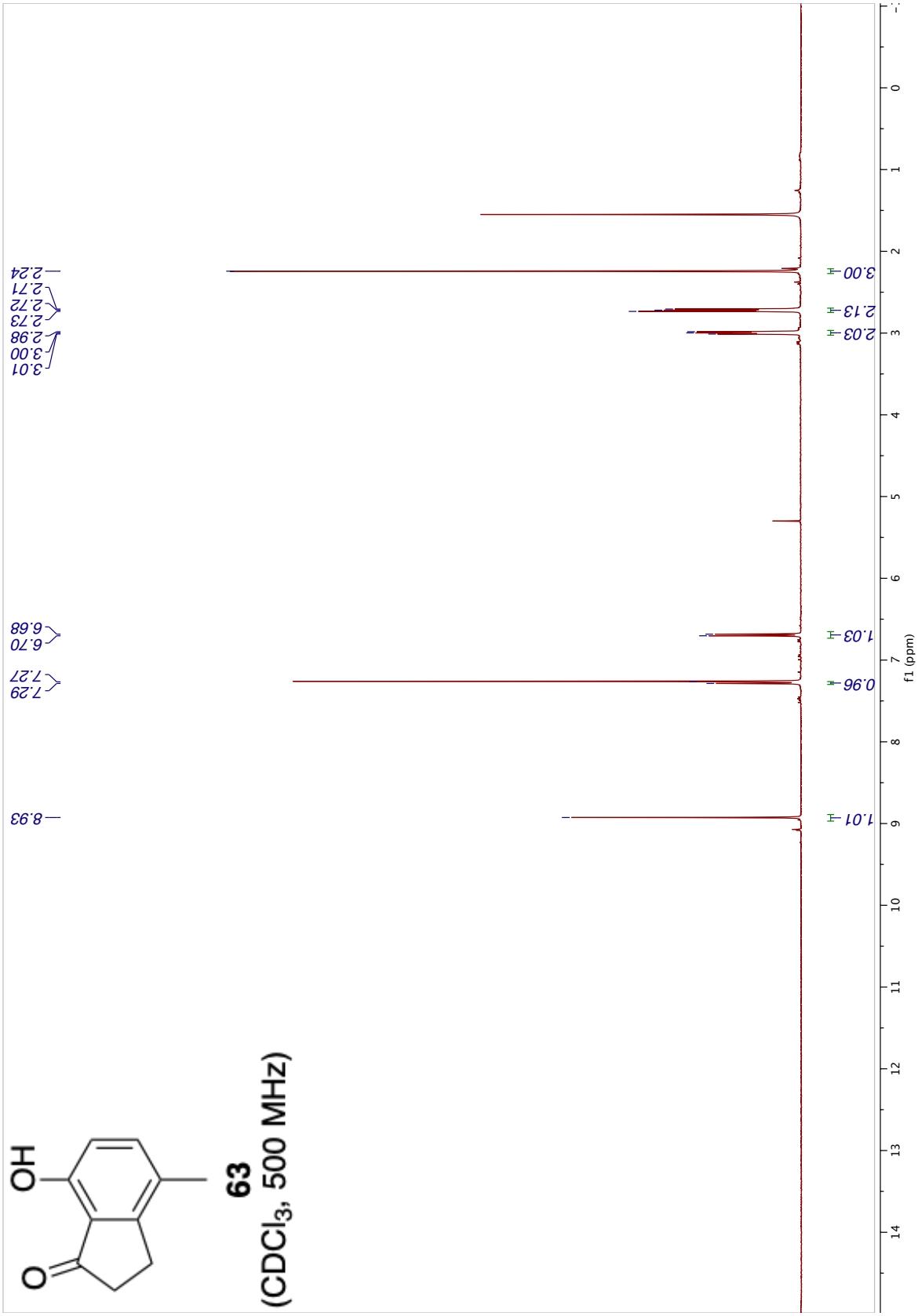
Crystal data and structure refinement for 1081_CT_Snyder1.

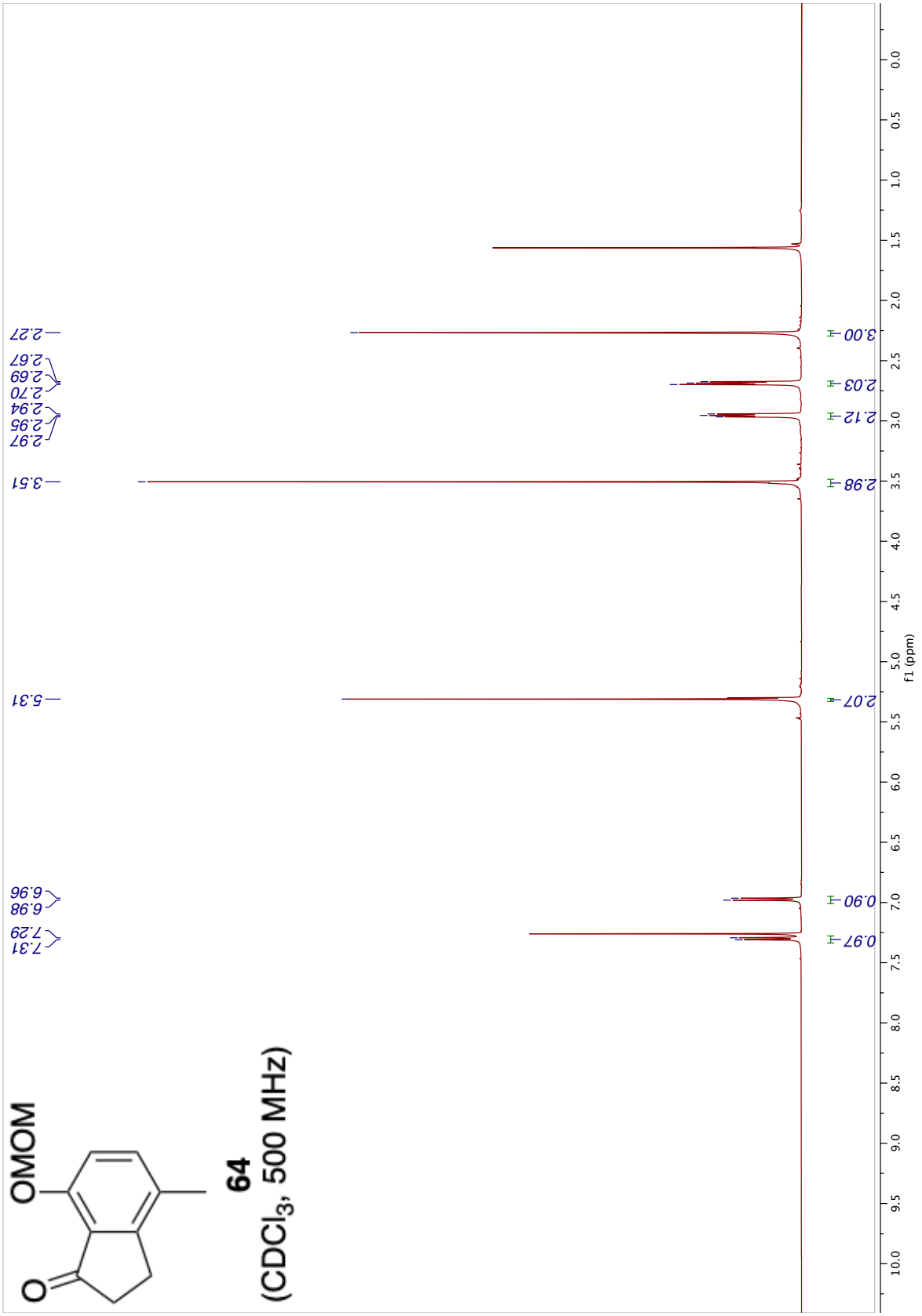
Identification code	1081_CT_Snyder1
Empirical formula	$C_{20}H_{32}O_5Si$
Formula weight	380.54
Temperature/K	100(2)
Crystal system	triclinic
Space group	P-1
a/Å	9.5581(6)
b/Å	13.6935(9)
c/Å	15.9451(10)
α/°	104.026(2)
β/°	92.956(2)
γ/°	92.335(2)
Volume/Å^3	2019.0(2)
Z	4
ρ_{calc}g/cm^3	1.252
μ/mm^{-1}	0.143
F(000)	824.0
Crystal size/mm^3	0.195 × 0.098 × 0.062
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	4.512 to 52.902
Index ranges	-11 ≤ h ≤ 11, -17 ≤ k ≤ 16, -19 ≤ l ≤ 19
Reflections collected	31334
Independent reflections	8287 [R_{int} = 0.0862, R_{sigma} = 0.0925]
Data/restraints/parameters	8287/0/492
Goodness-of-fit on F^2	1.015
Final R indexes [I>=2σ (I)]	R_1 = 0.0604, wR_2 = 0.1089
Final R indexes [all data]	R_1 = 0.1208, wR_2 = 0.1286
Largest diff. peak/hole / e Å^{-3}	0.45/-0.45

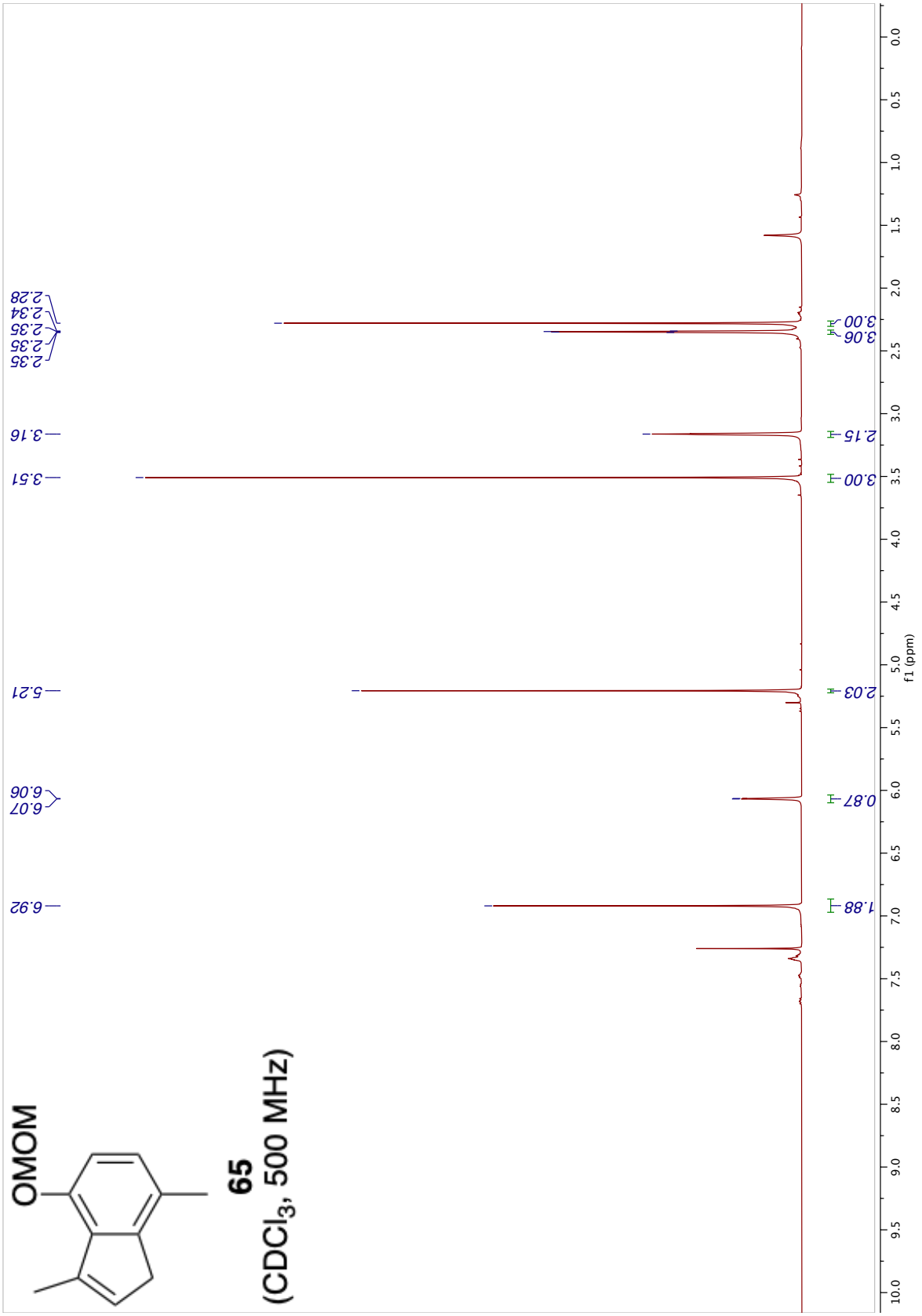
$R_{int} = \Sigma \mid F_o^2 - \langle F_o^2 \rangle \mid / \Sigma \mid F_o^2 \mid$
$R1 = \Sigma \mid \mid F_o \mid - \mid F_c \mid \mid / \Sigma \mid F_o \mid$
$wR2 = [\Sigma [w (F_o^2 - F_c^2)^2] / \Sigma [w (F_o^2)^2]]^{1/2}$
$Goodness\text{-}of\text{-}fit = [\Sigma [w (F_o^2 - F_c^2)^2] / (n-p)^{1/2}$
n: number of independent reflections; p: number of refined parameters

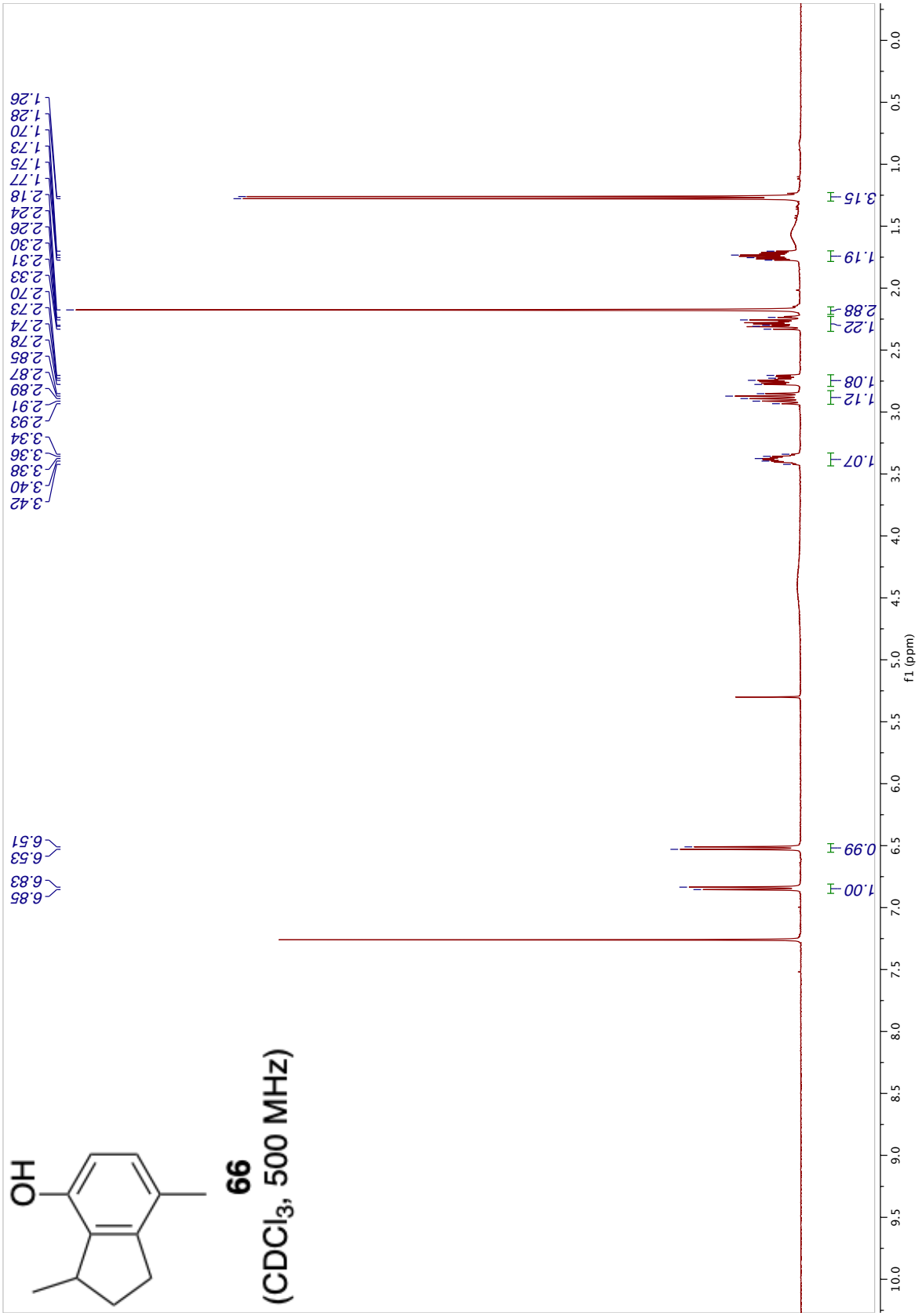
3.9 NMR Spectra of Selected Intermediates

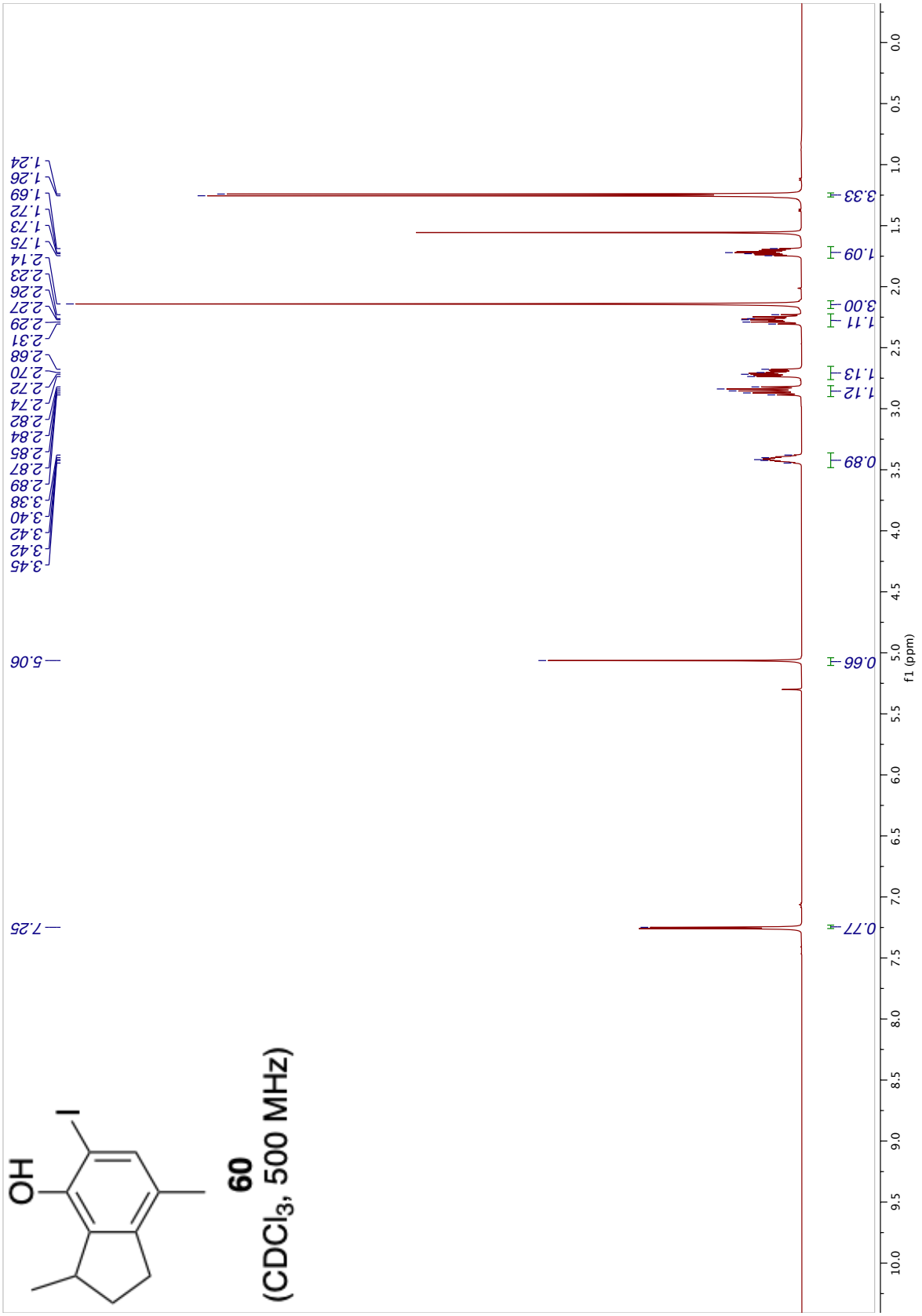


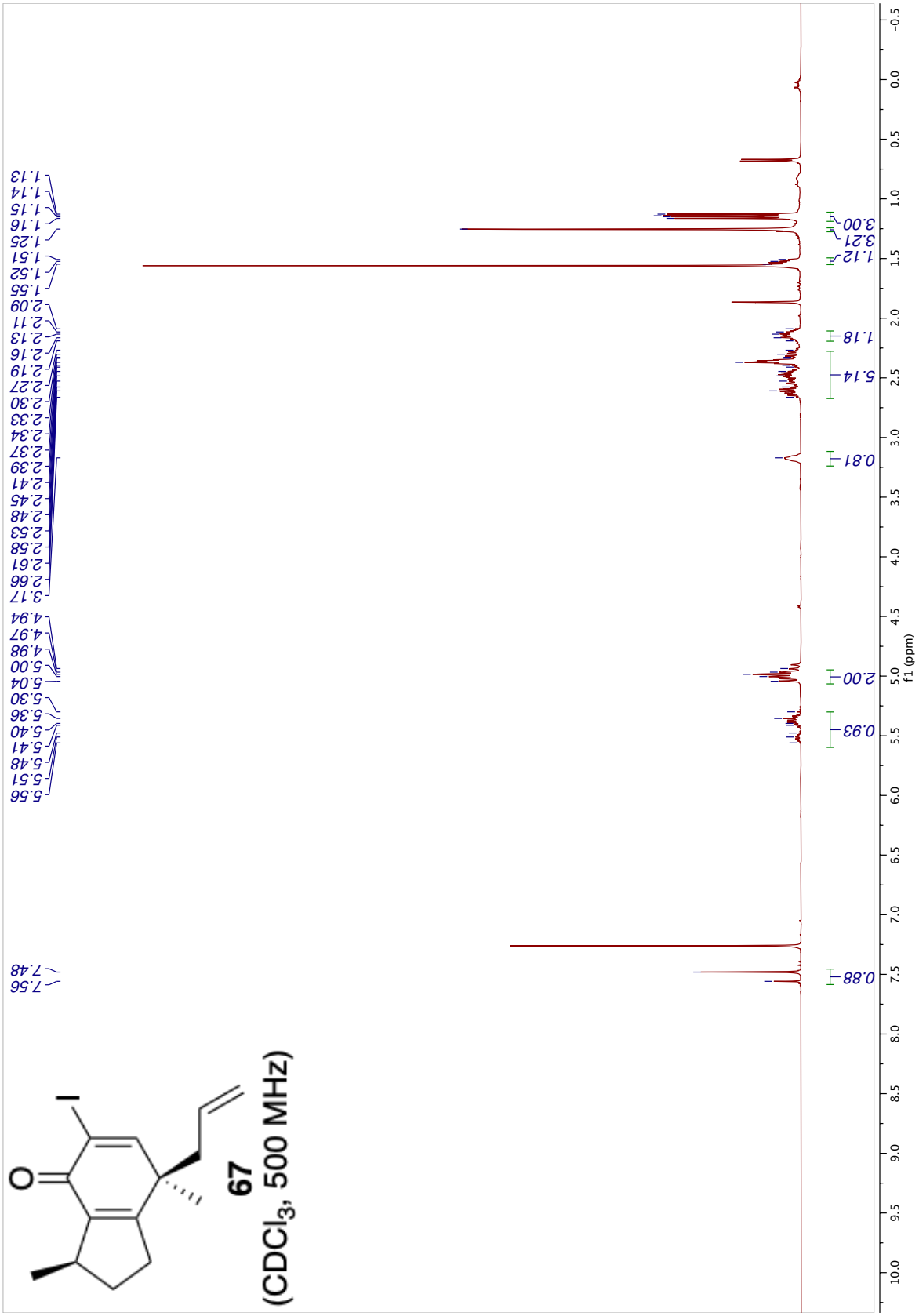

OH
O
63
(CDCl3, 500 MHz)
8.93
7.29
7.27
6.70
6.68
3.01
3.00
2.98
2.73
2.72
2.71
2.24
1.01
0.96
1.03
2.03
2.13
3.00
f1 (ppm)

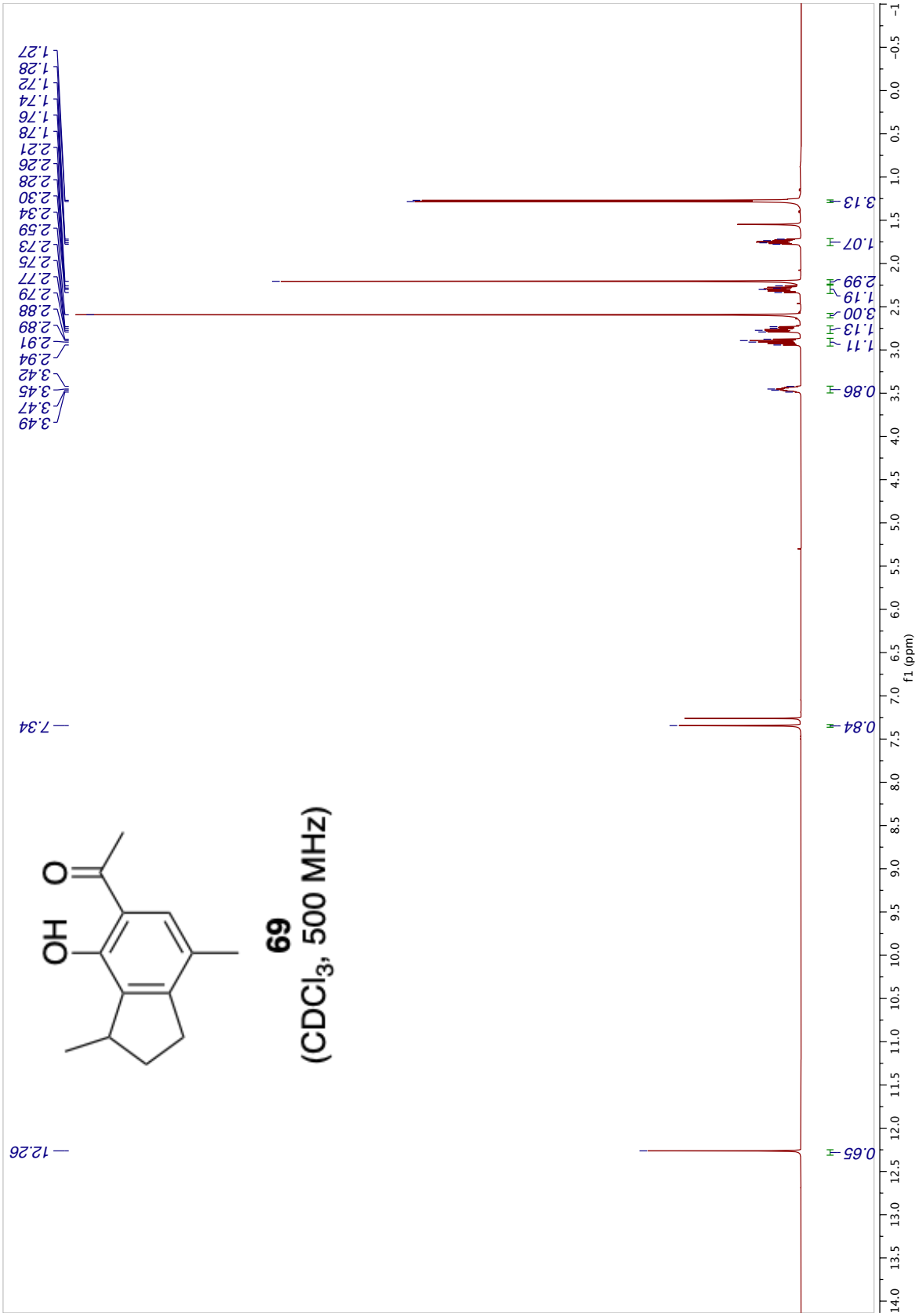

OMOM
O
64
(CDCl3, 500 MHz)
7.31
7.29
6.98
6.96
5.31
3.51
2.97
2.95
2.94
2.70
2.69
2.67
2.27
0.97
0.90
2.07
2.98
2.12
2.03
3.00
f1 (ppm)

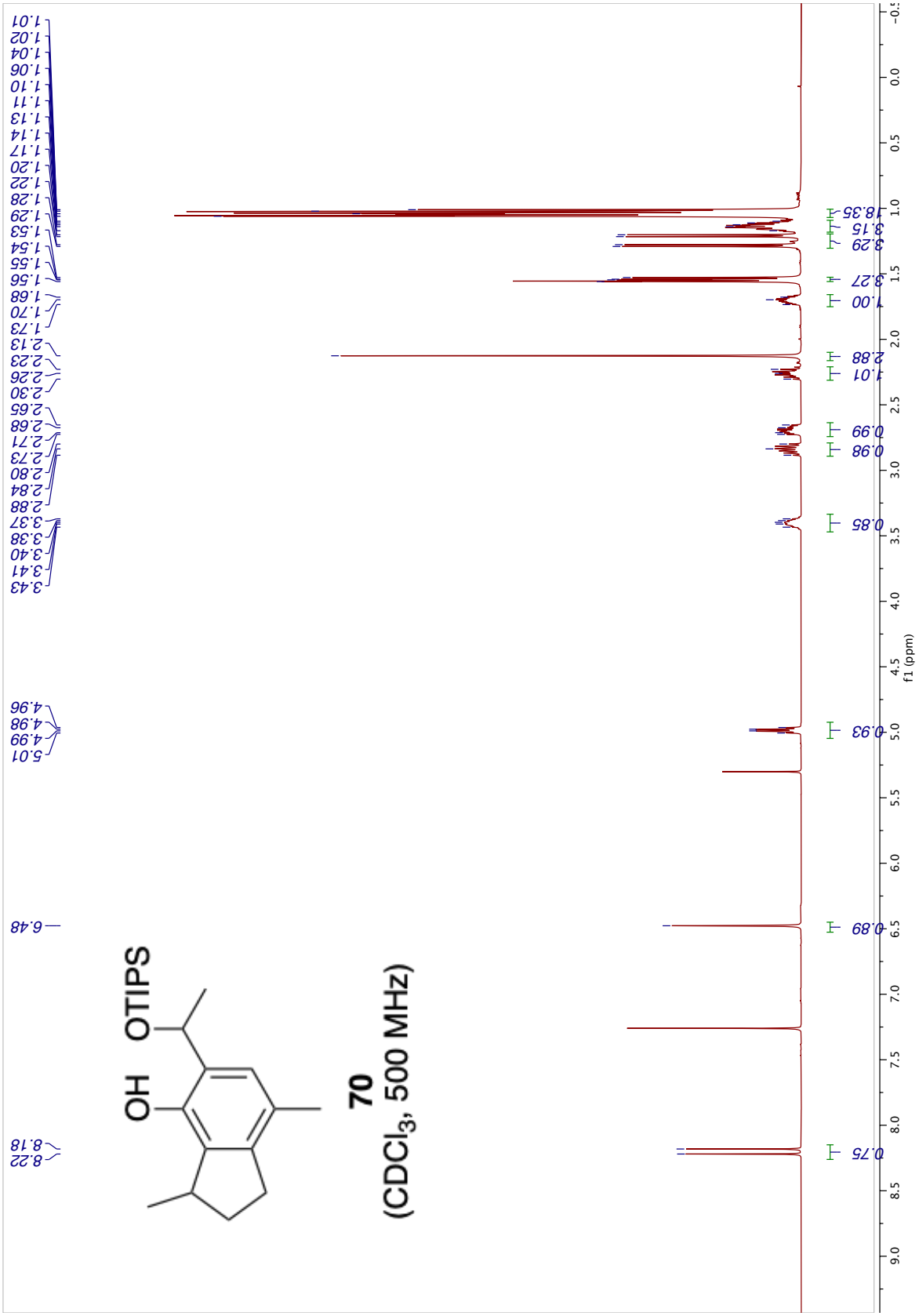

OMOM
65
(CDCl3, 500 MHz)
6.92
6.07
6.06
5.21
3.51
3.16
2.35
2.35
2.35
2.34
2.28
1.88
0.87
2.03
3.00
2.15
3.00
3.06
f1 (ppm)

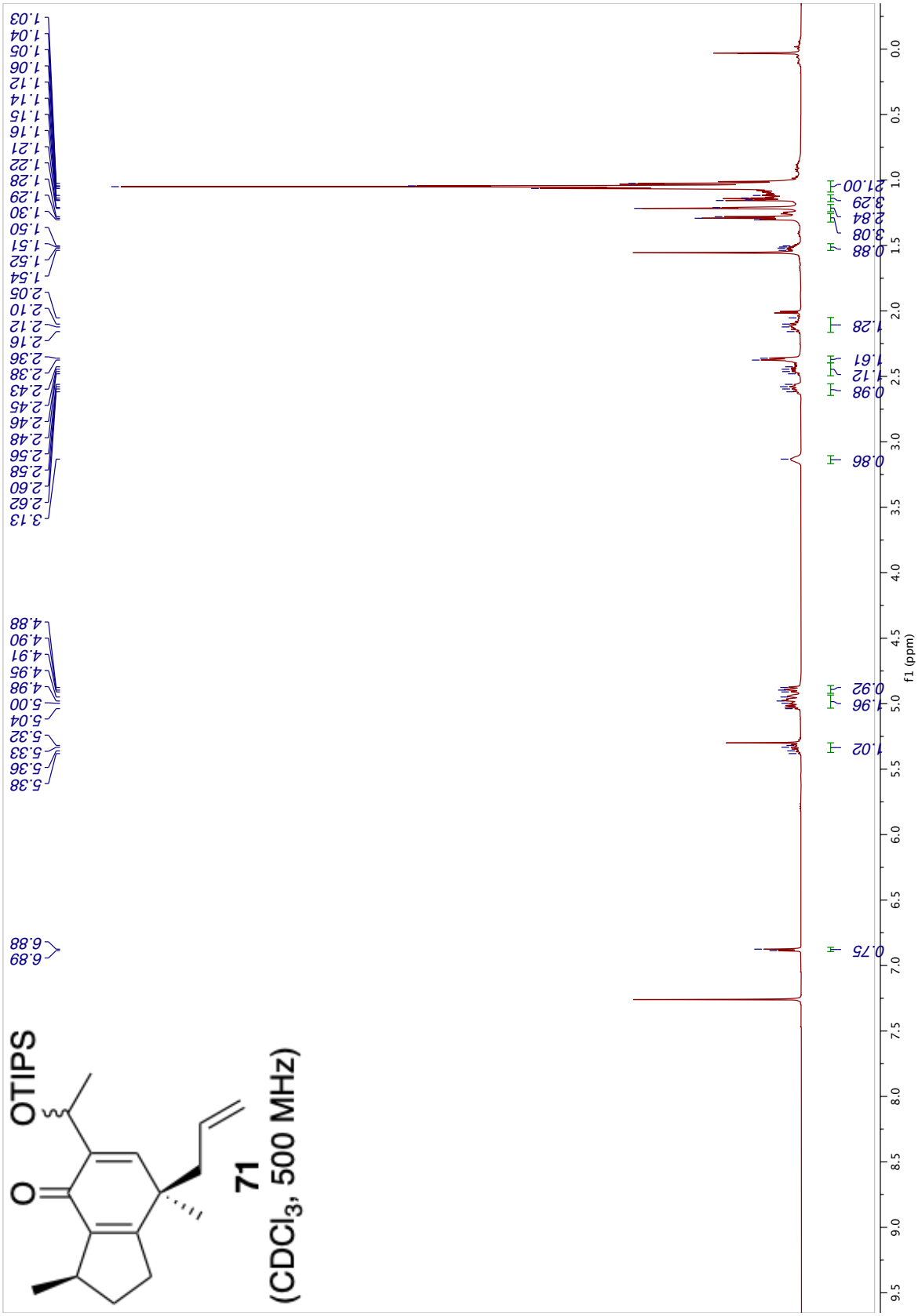

OH
66
(CDCl3, 500 MHz)
6.85
6.83
6.53
6.51
3.42
3.40
3.38
3.36
3.34
2.93
2.91
2.89
2.87
2.85
2.78
2.74
2.73
2.70
2.33
2.31
2.30
2.26
2.24
2.18
1.77
1.75
1.73
1.70
1.28
1.26
3.15
1.19
2.88
1.22
1.08
1.12
1.07
0.99
1.00
f1 (ppm)

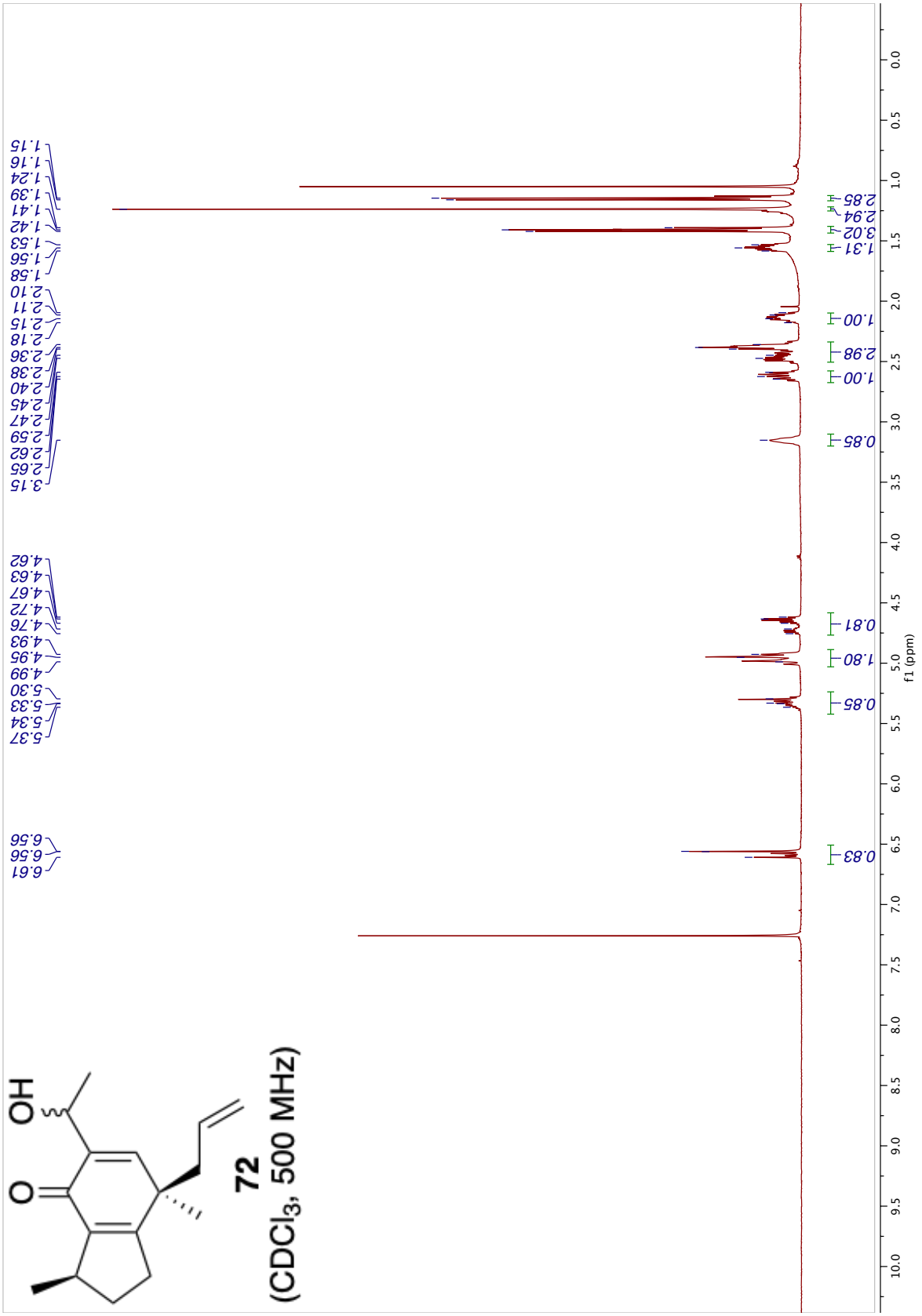

OH
I
60
(CDCl3, 500 MHz)
7.25
5.06
3.45
3.42
3.42
3.40
3.38
2.89
2.87
2.85
2.84
2.82
2.74
2.72
2.70
2.68
2.31
2.29
2.27
2.26
2.23
2.14
1.75
1.73
1.72
1.69
1.26
1.24
0.77
0.66
0.89
1.12
1.13
1.11
3.00
1.09
3.33
f1 (ppm)

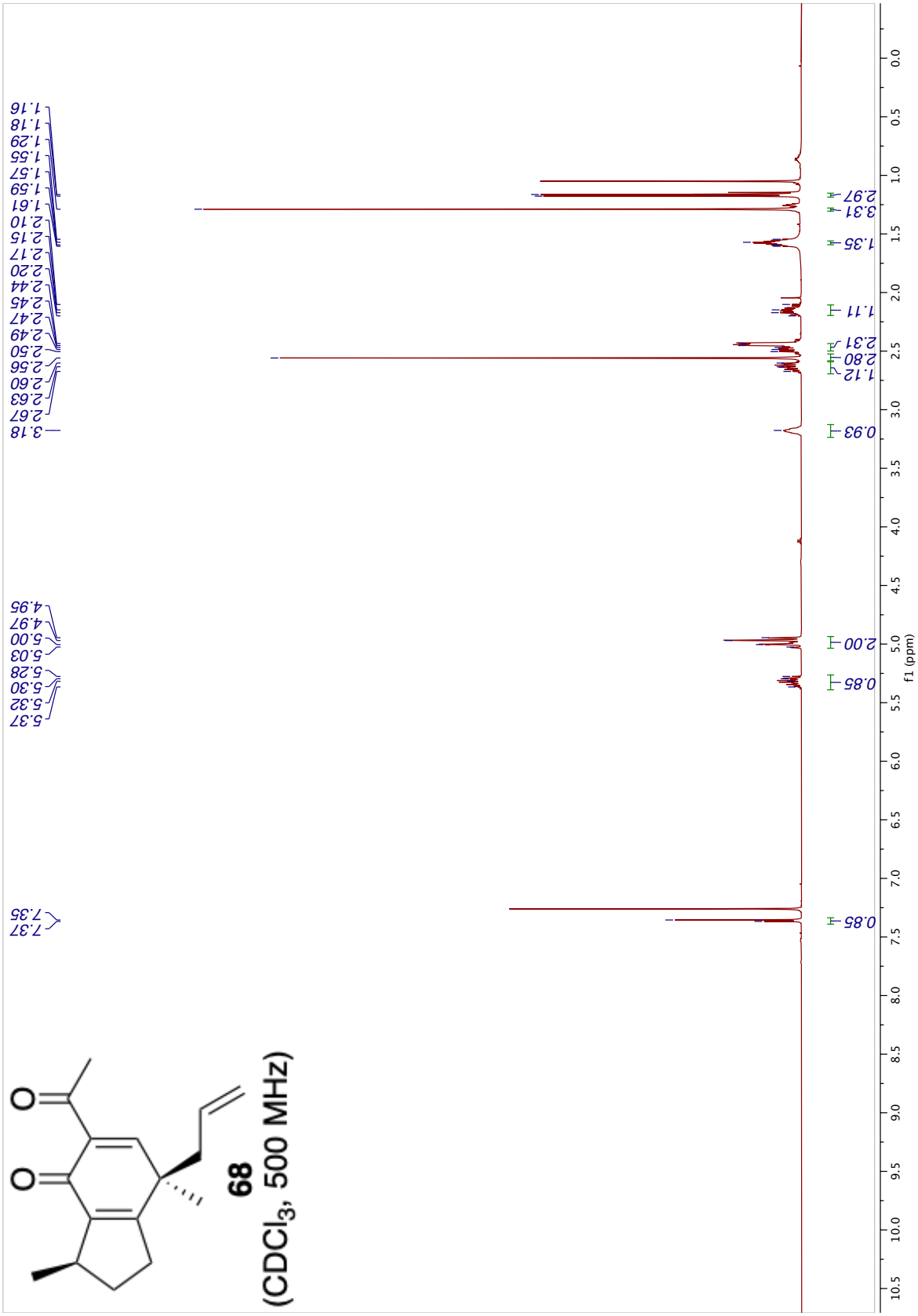

67
(CDCl3, 500 MHz)
O
I
7.56
7.48
5.56
5.51
5.48
5.41
5.40
5.36
5.30
5.04
5.00
4.98
4.97
4.94
3.17
2.66
2.61
2.58
2.53
2.48
2.45
2.41
2.39
2.37
2.34
2.33
2.30
2.27
2.19
2.16
2.13
2.11
2.09
1.55
1.52
1.51
1.25
1.16
1.15
1.14
1.13
0.88
2.00
0.93
0.81
5.14
1.18
1.12
3.21
3.00
f1 (ppm)

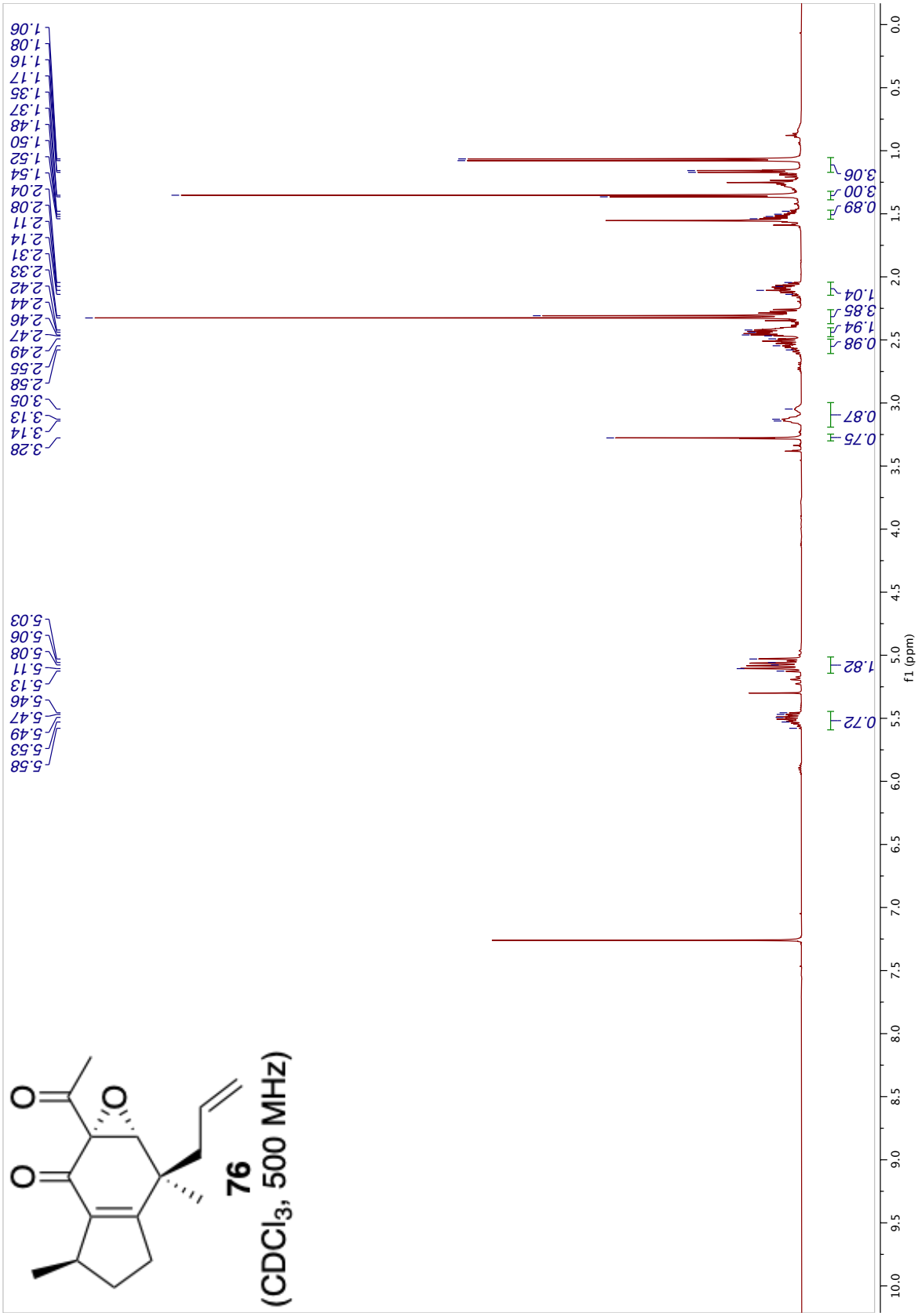

12.26
7.34
3.49
3.47
3.45
3.42
2.94
2.91
2.89
2.88
2.79
2.77
2.75
2.73
2.59
2.34
2.30
2.28
2.26
2.21
1.78
1.76
1.74
1.72
1.28
1.27
0.65
0.84
0.86
3.13
1.07
2.99
1.19
3.00
1.13
1.11
f1 (ppm)
OH
O
69
(CDCl3, 500 MHz)

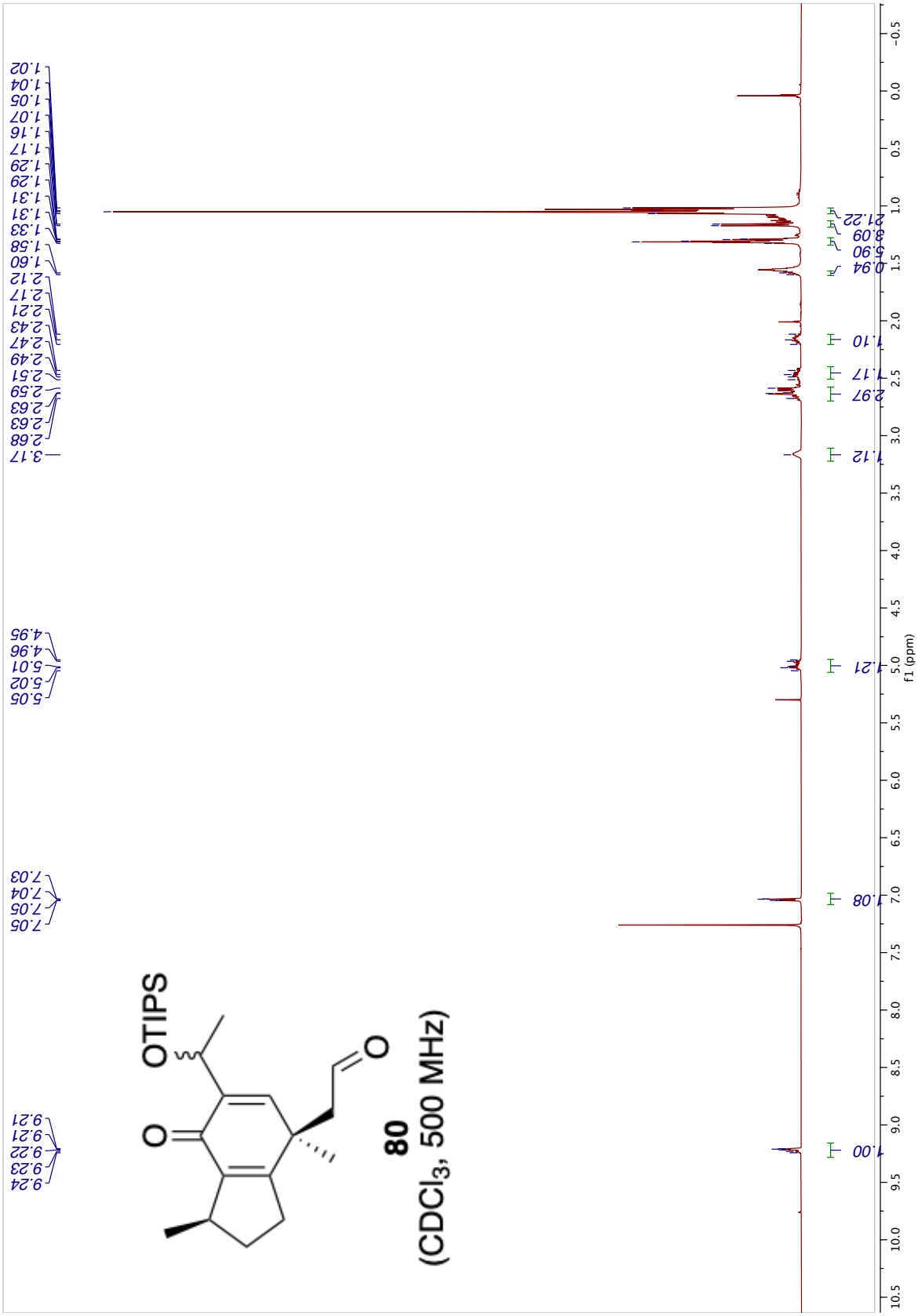

OH OTIPS
70
(CDCl3, 500 MHz)
f1 (ppm)

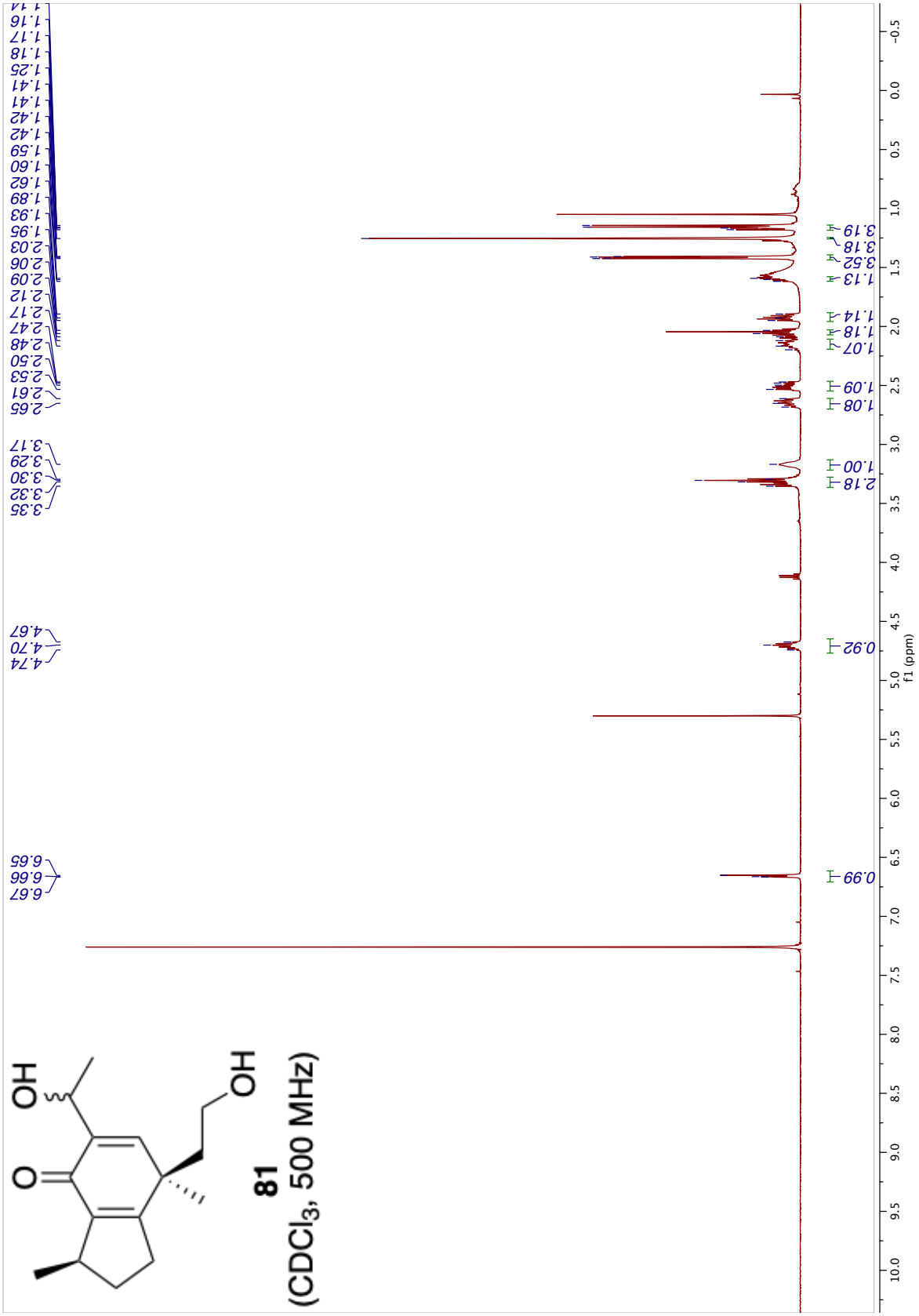

OTIPS
O
71
(CDCl3, 500 MHz)
f1 (ppm)

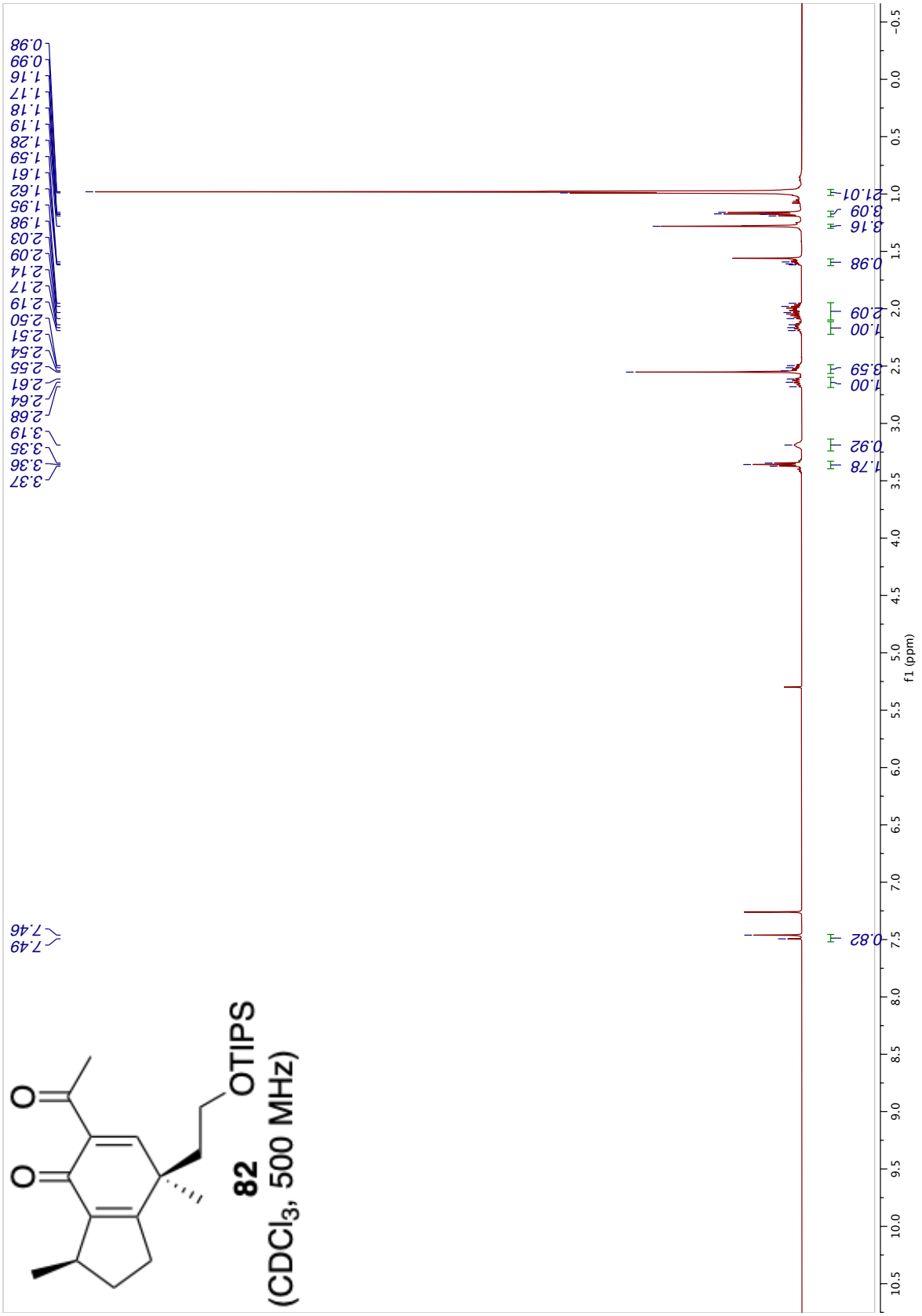

OH
O
72
(CDCl3, 500 MHz)
f1 (ppm)

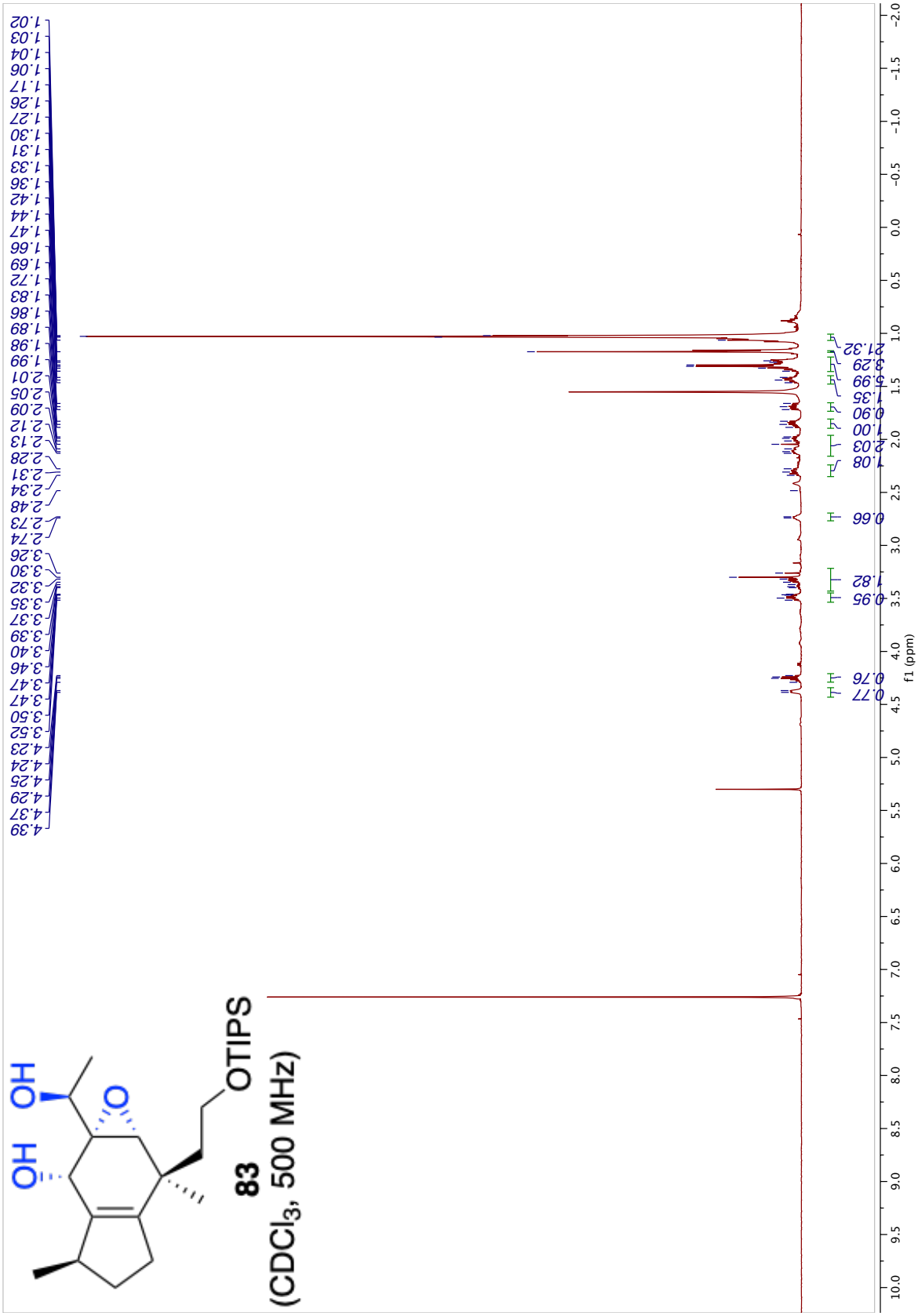

68
(CDCl3, 500 MHz)
f1 (ppm)

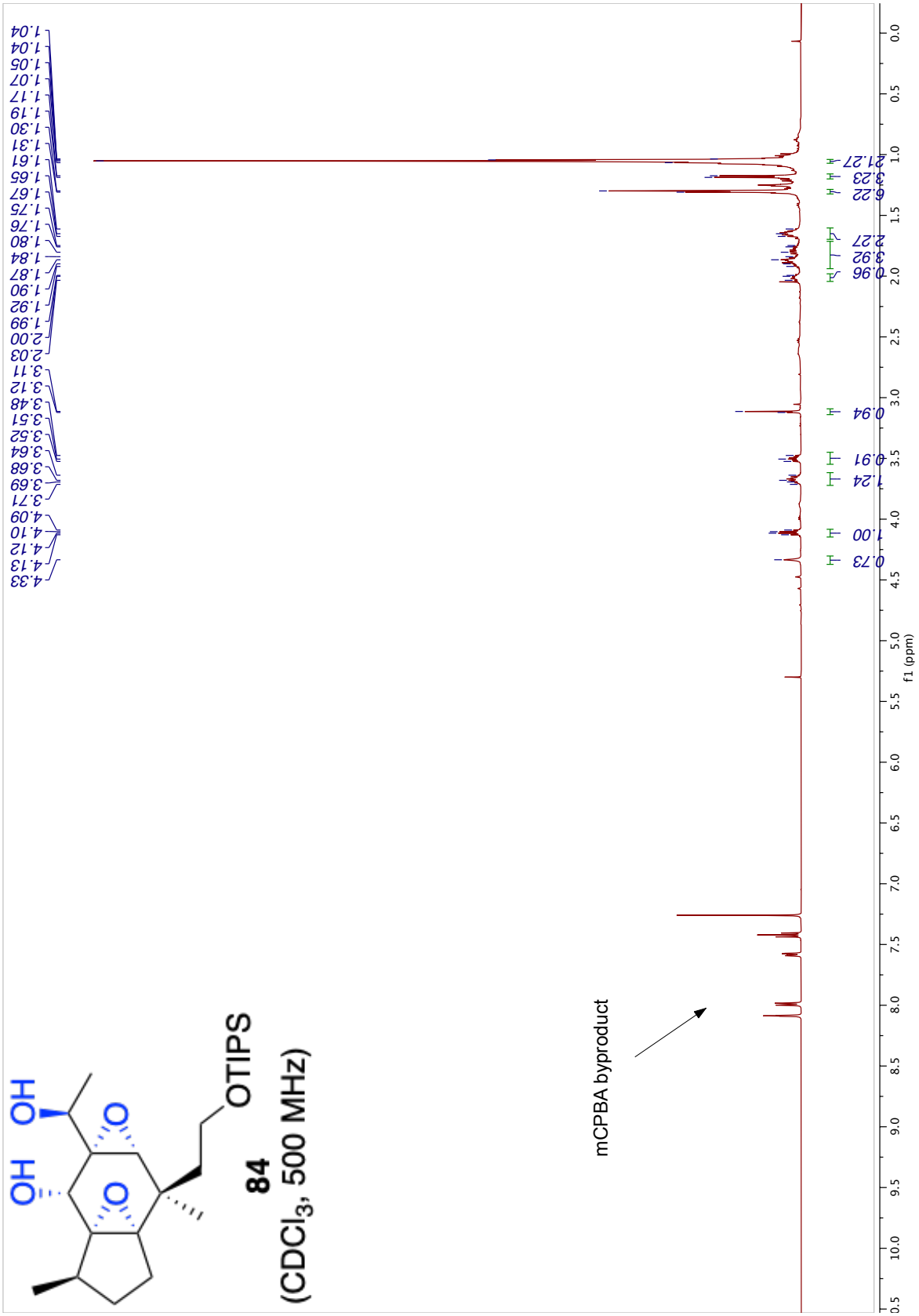

76
(CDCl3, 500 MHz)
f1 (ppm)

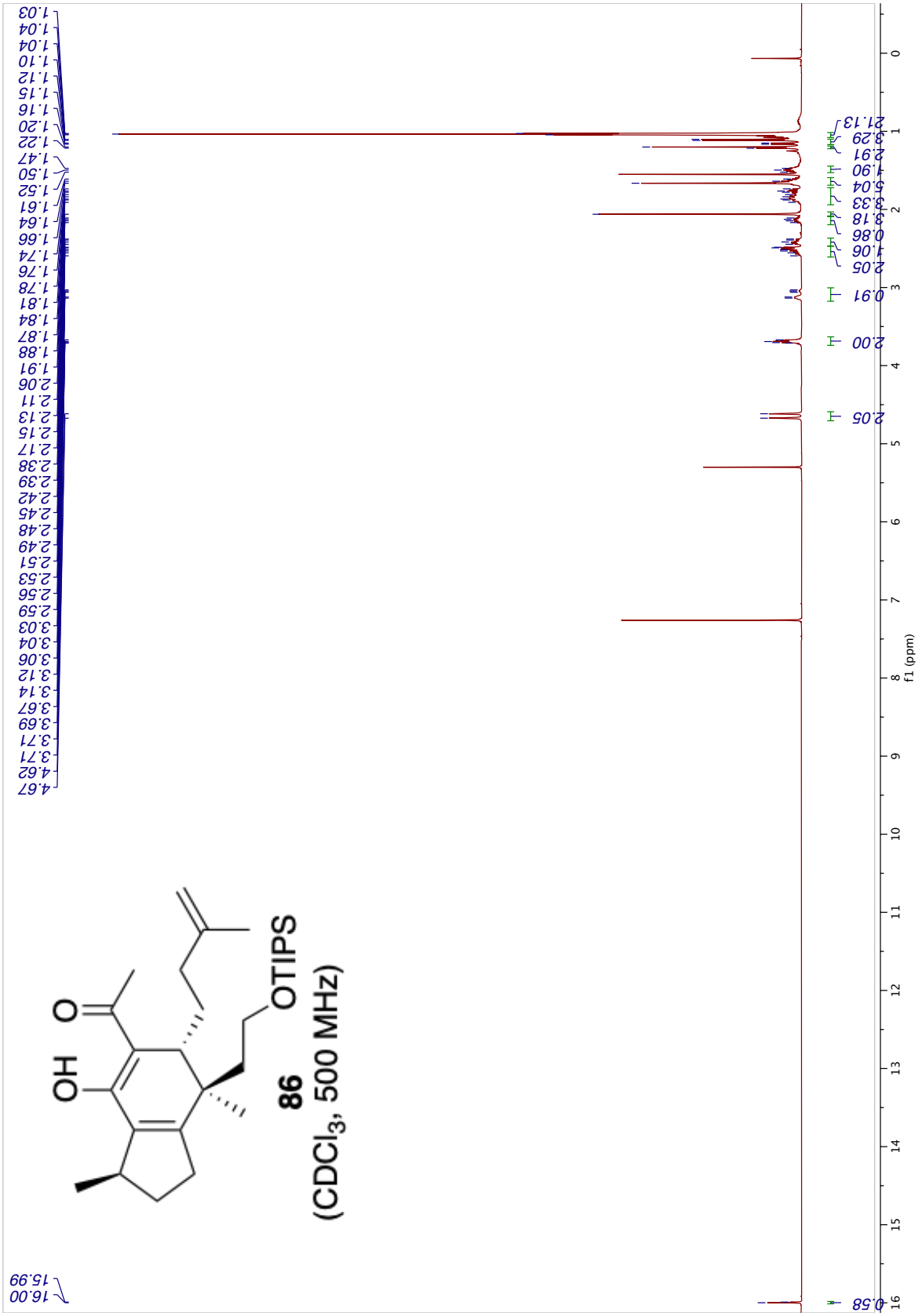

OTIPS
O
O
80
(CDCl3, 500 MHz)
f1 (ppm)

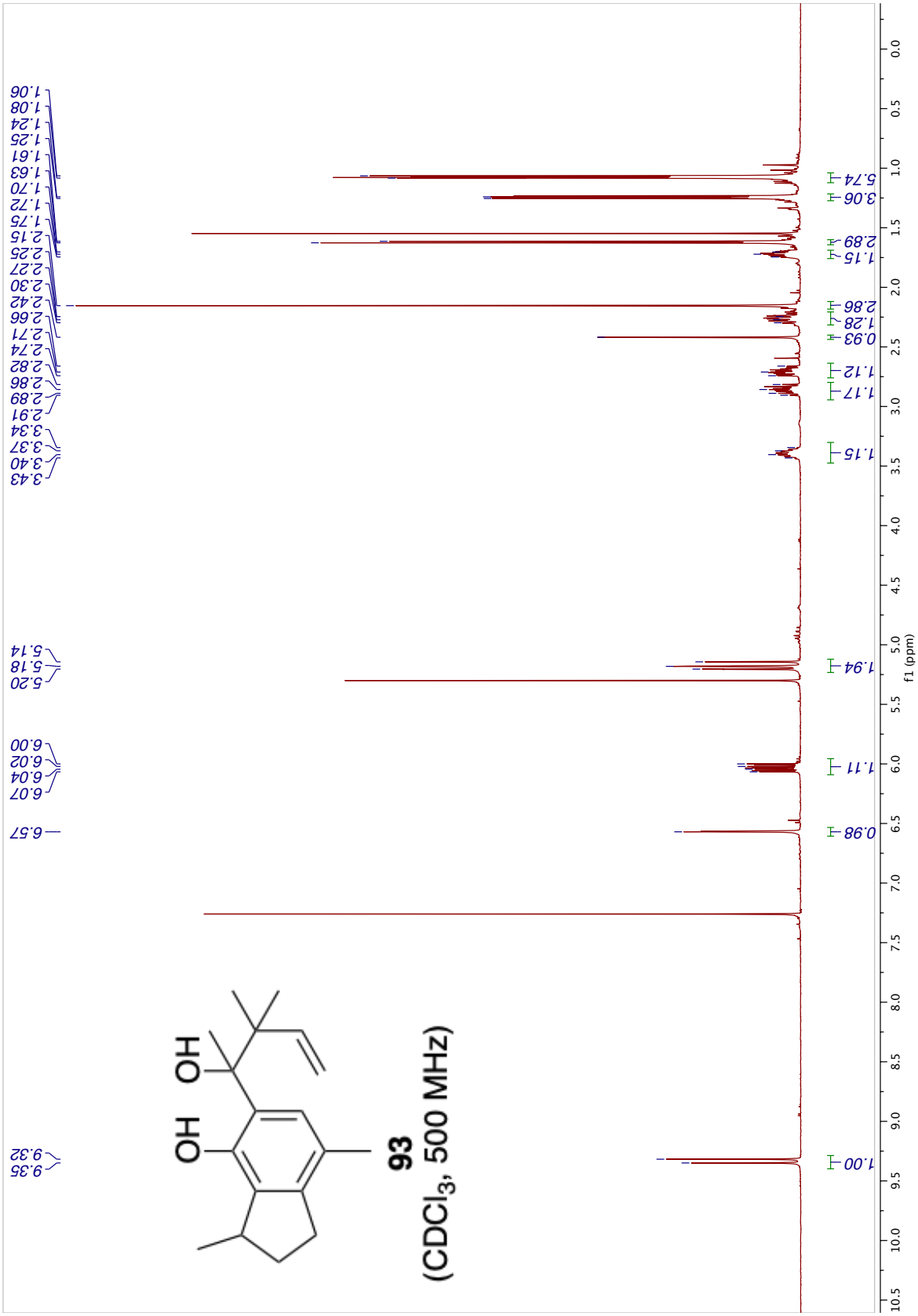

OH
O
OH
81
(CDCl3, 500 MHz)
f1 (ppm)

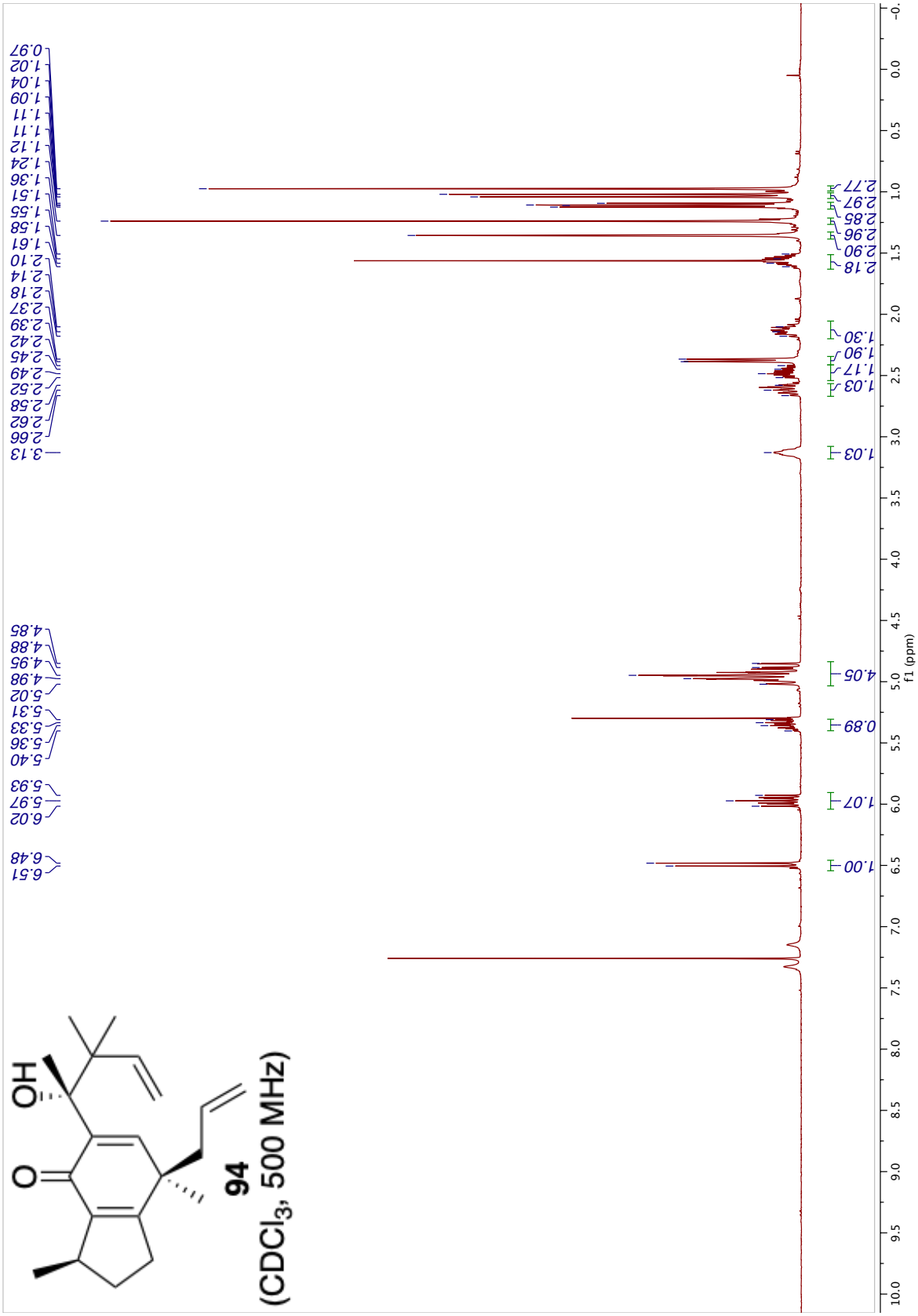

O
O
OTIPS
82
(CDCl3, 500 MHz)
f1 (ppm)

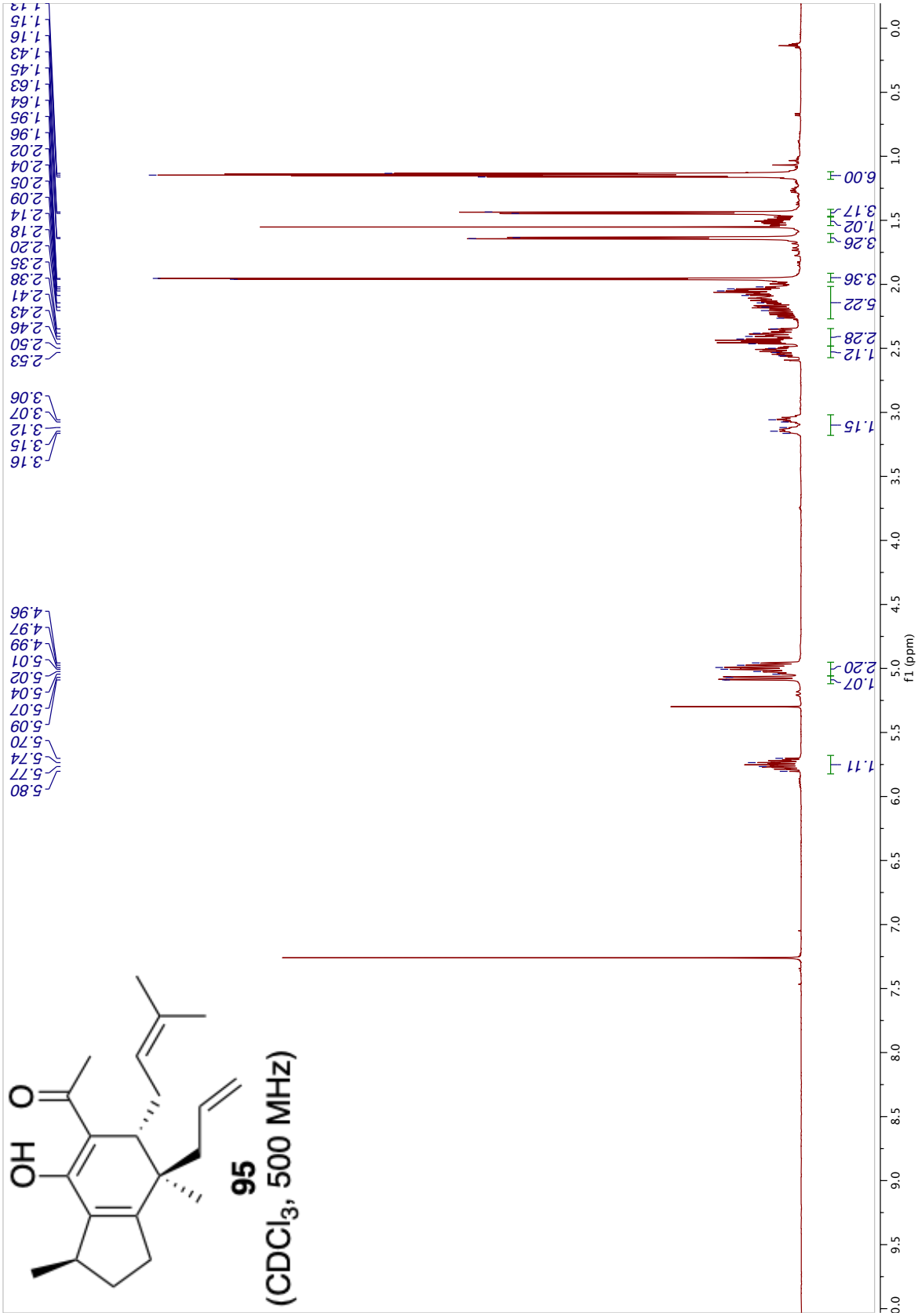

OH
OH
O
OTIPS
83
(CDCl3, 500 MHz)
f1 (ppm)

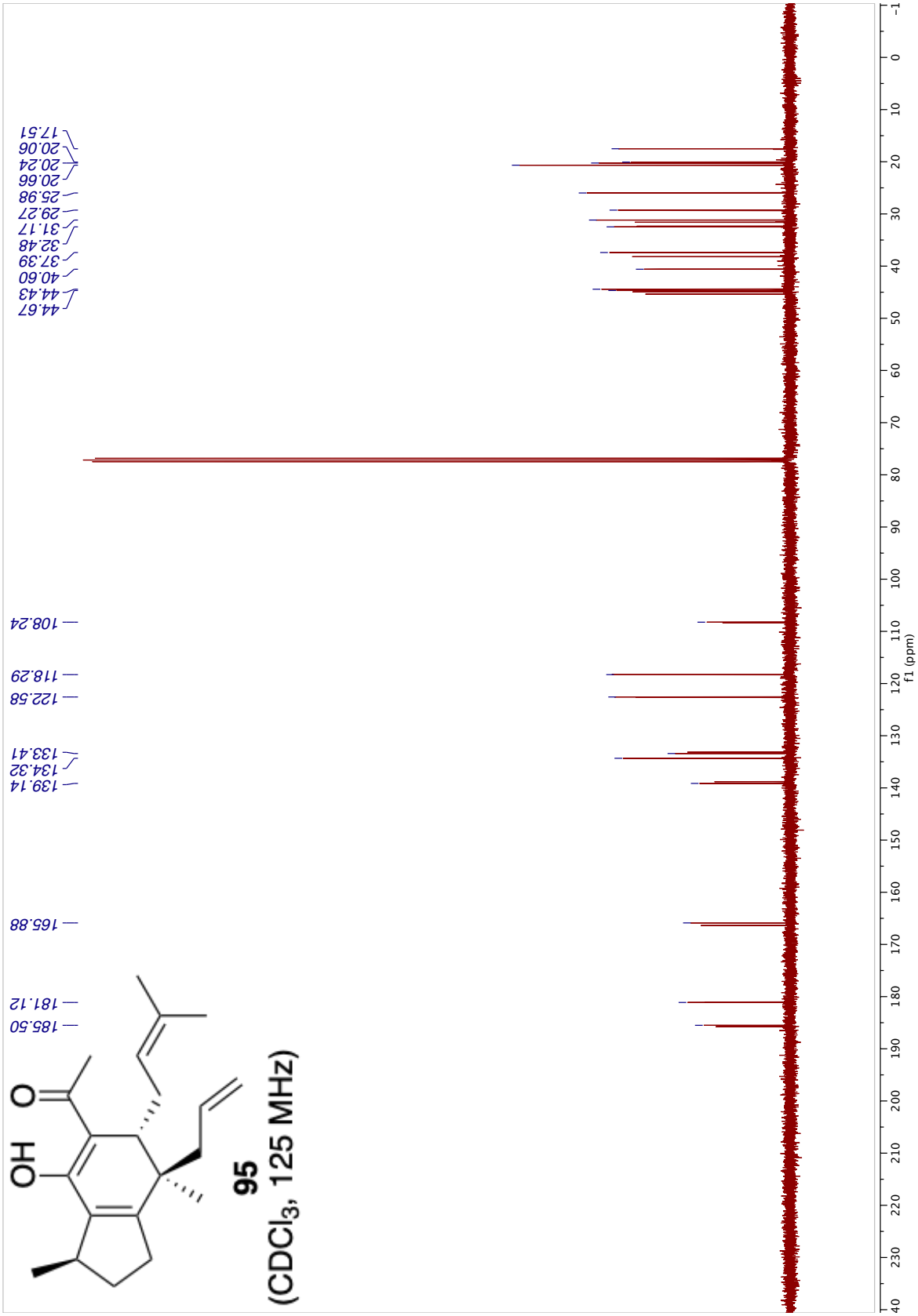

OH
OH
O
O
OTIPS
84
(CDCl3, 500 MHz)
mCPBA byproduct
f1 (ppm)

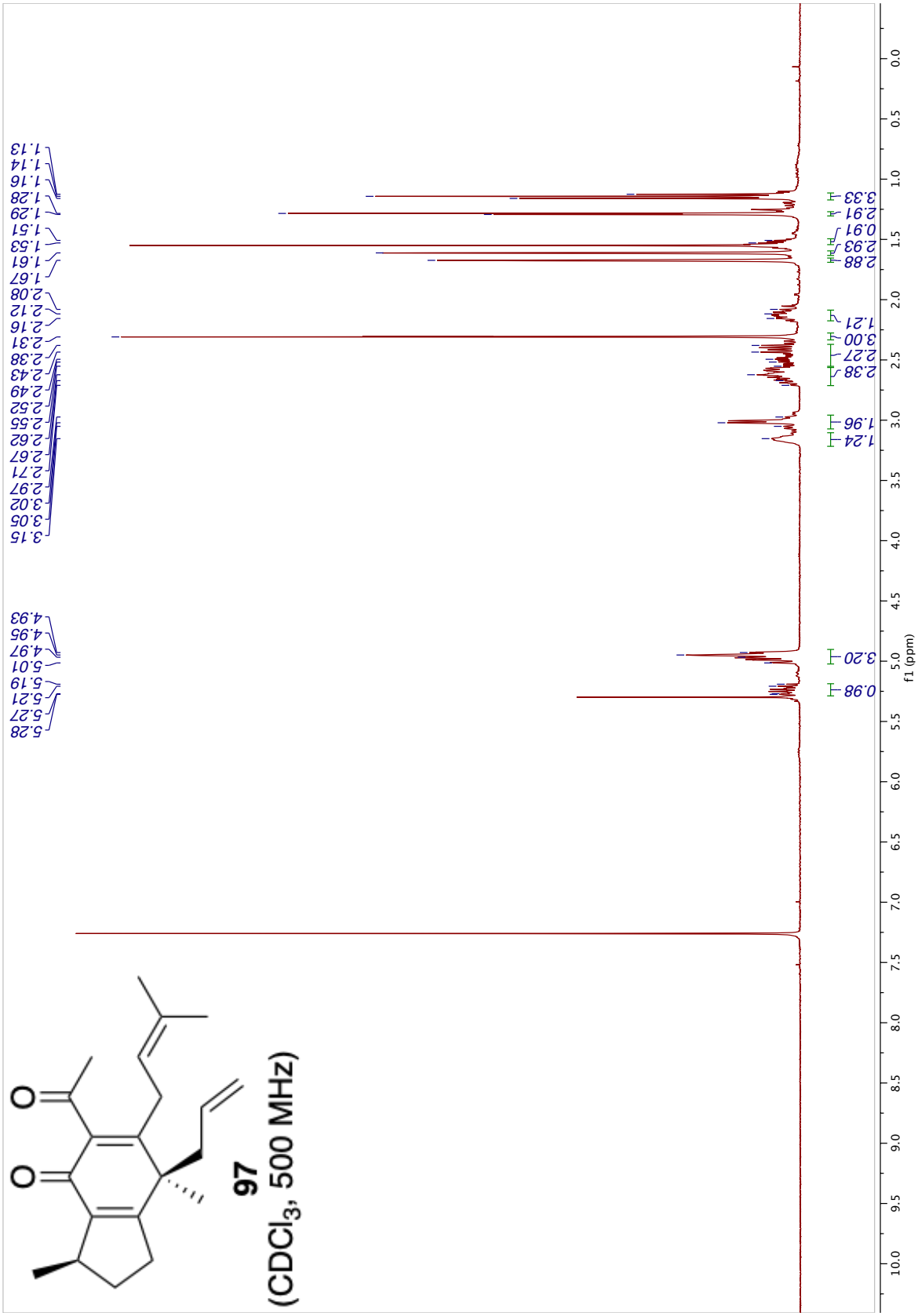

OH O
OTIPS
86
(CDCl3, 500 MHz)
f1 (ppm)

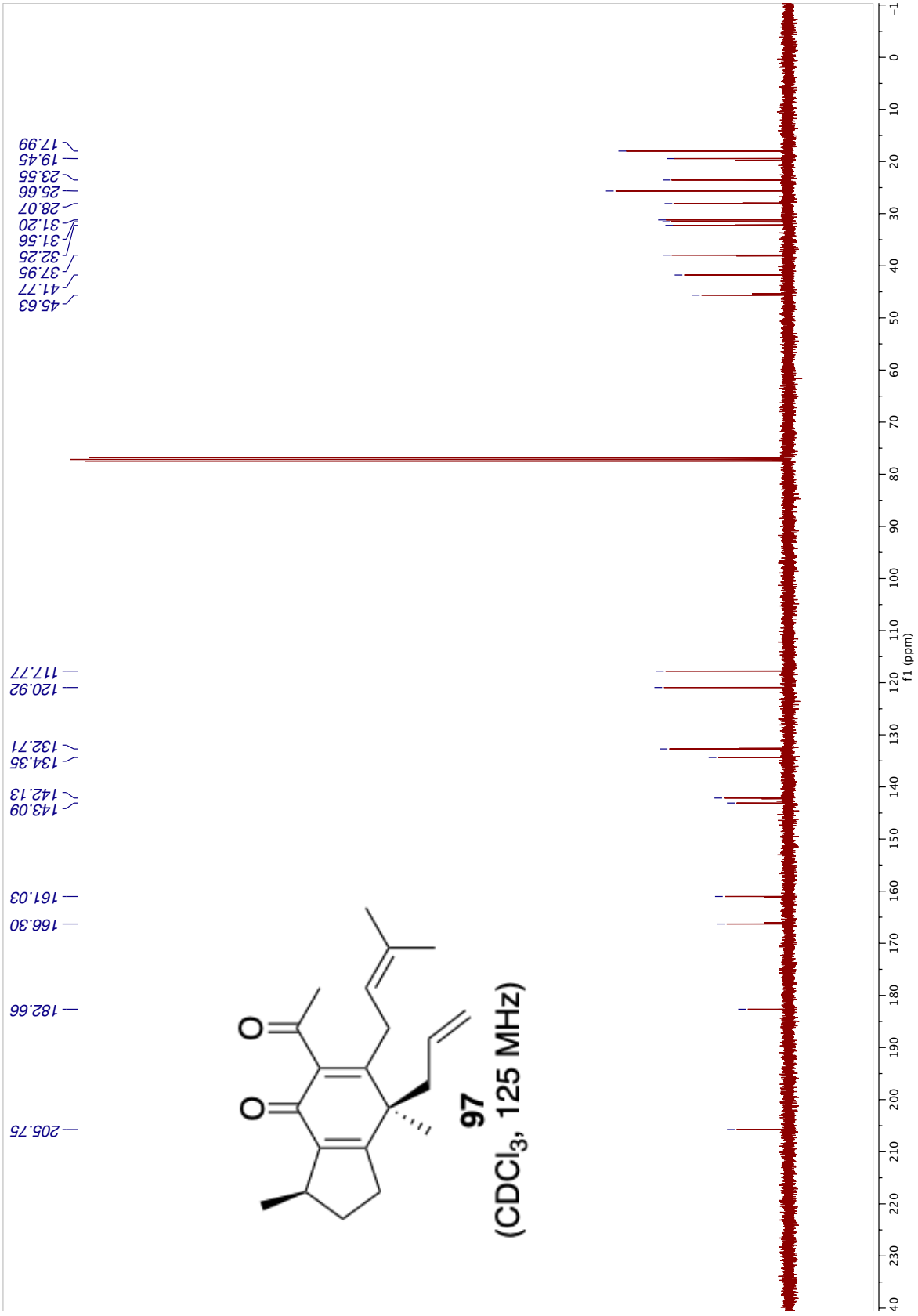

OH
OH
93
(CDCl3, 500 MHz)
f1 (ppm)

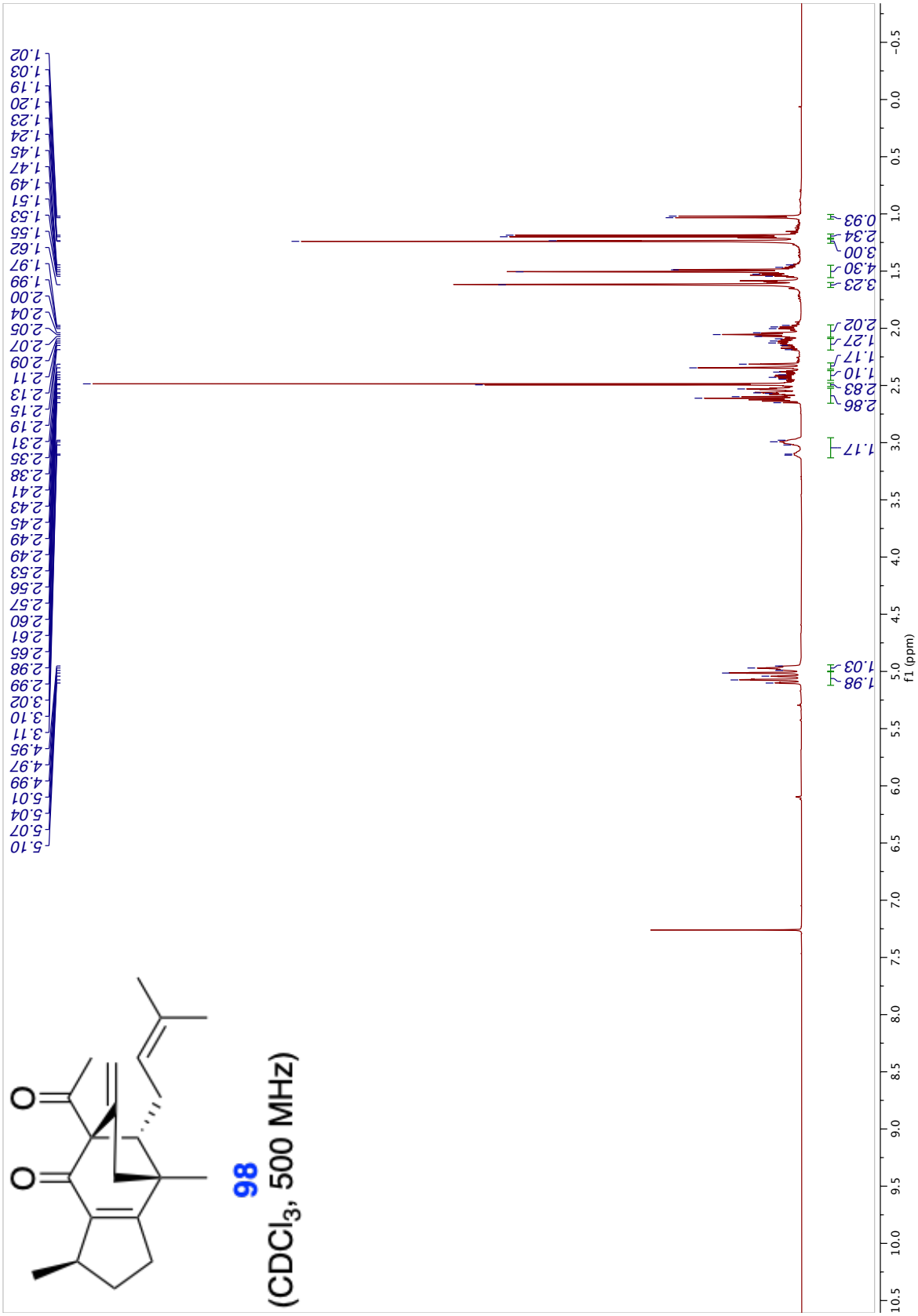

94
(CDCl3, 500 MHz)
f1 (ppm)

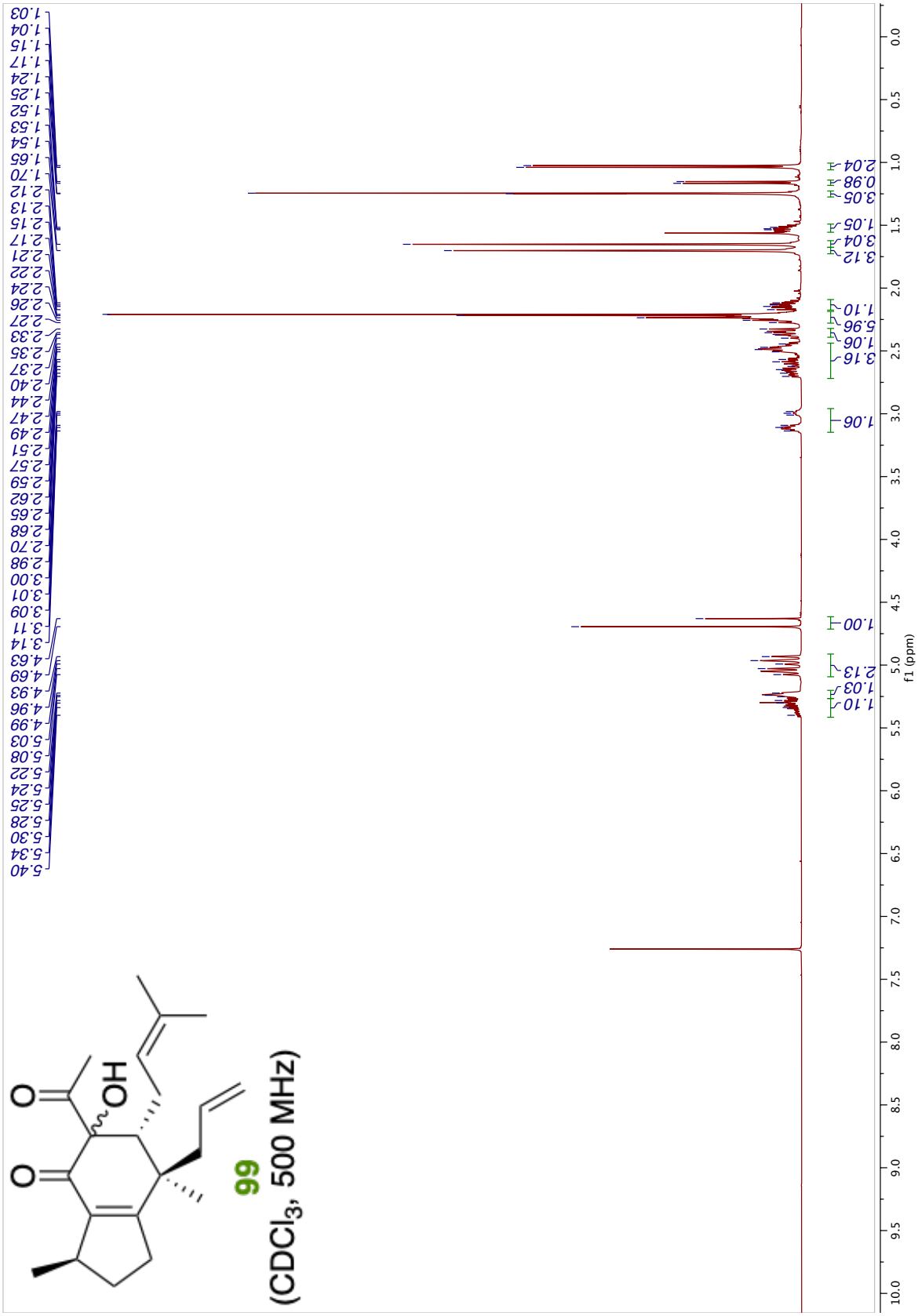

OH
O
95
(CDCl3, 500 MHz)
f1 (ppm)

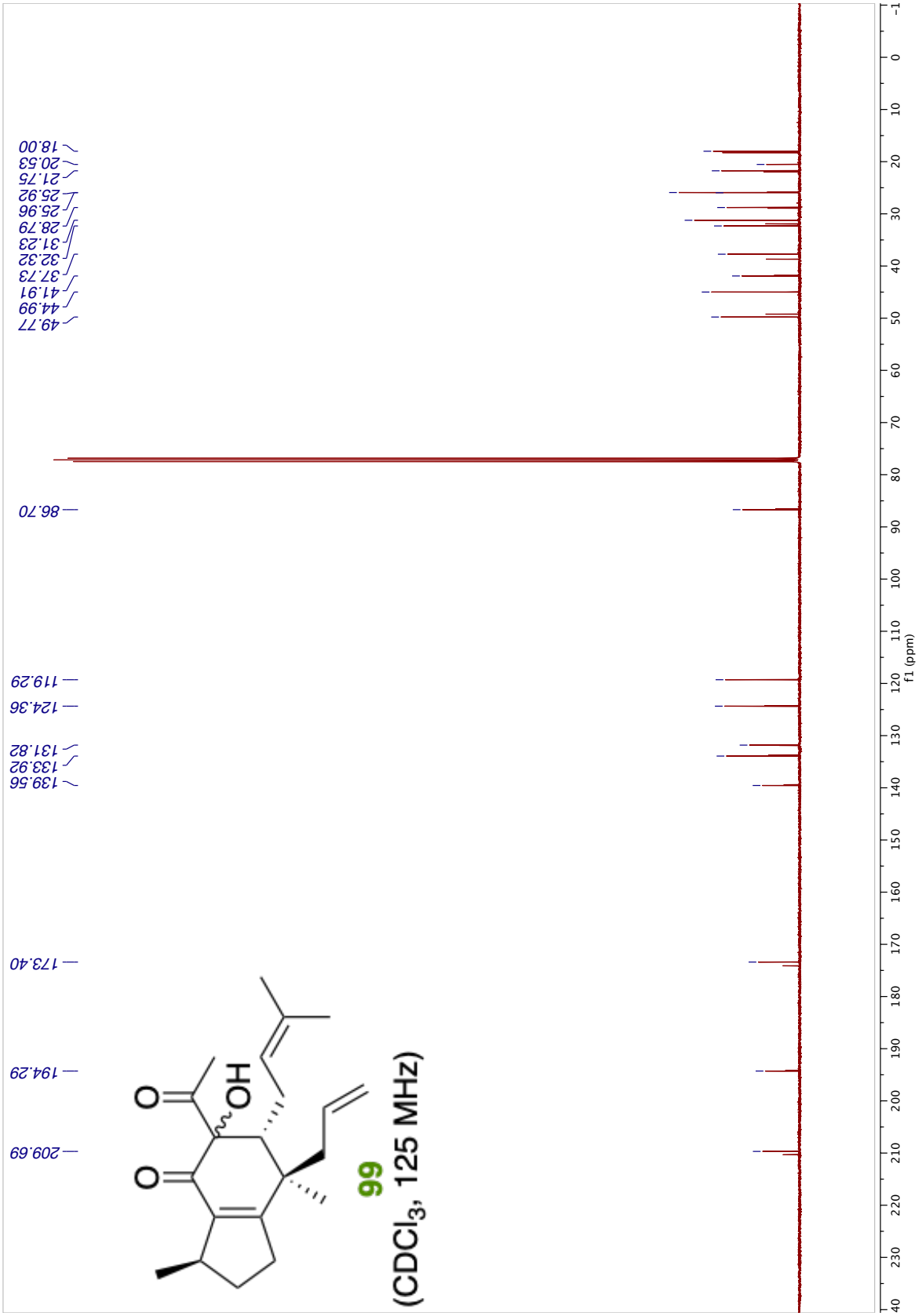

95
(CDCl3, 125 MHz)
OH
O
185.50
181.12
165.88
139.14
134.32
133.41
122.58
118.29
108.24
44.67
44.43
40.60
37.39
32.48
31.17
29.27
25.98
20.66
20.24
20.06
17.51
f1 (ppm)

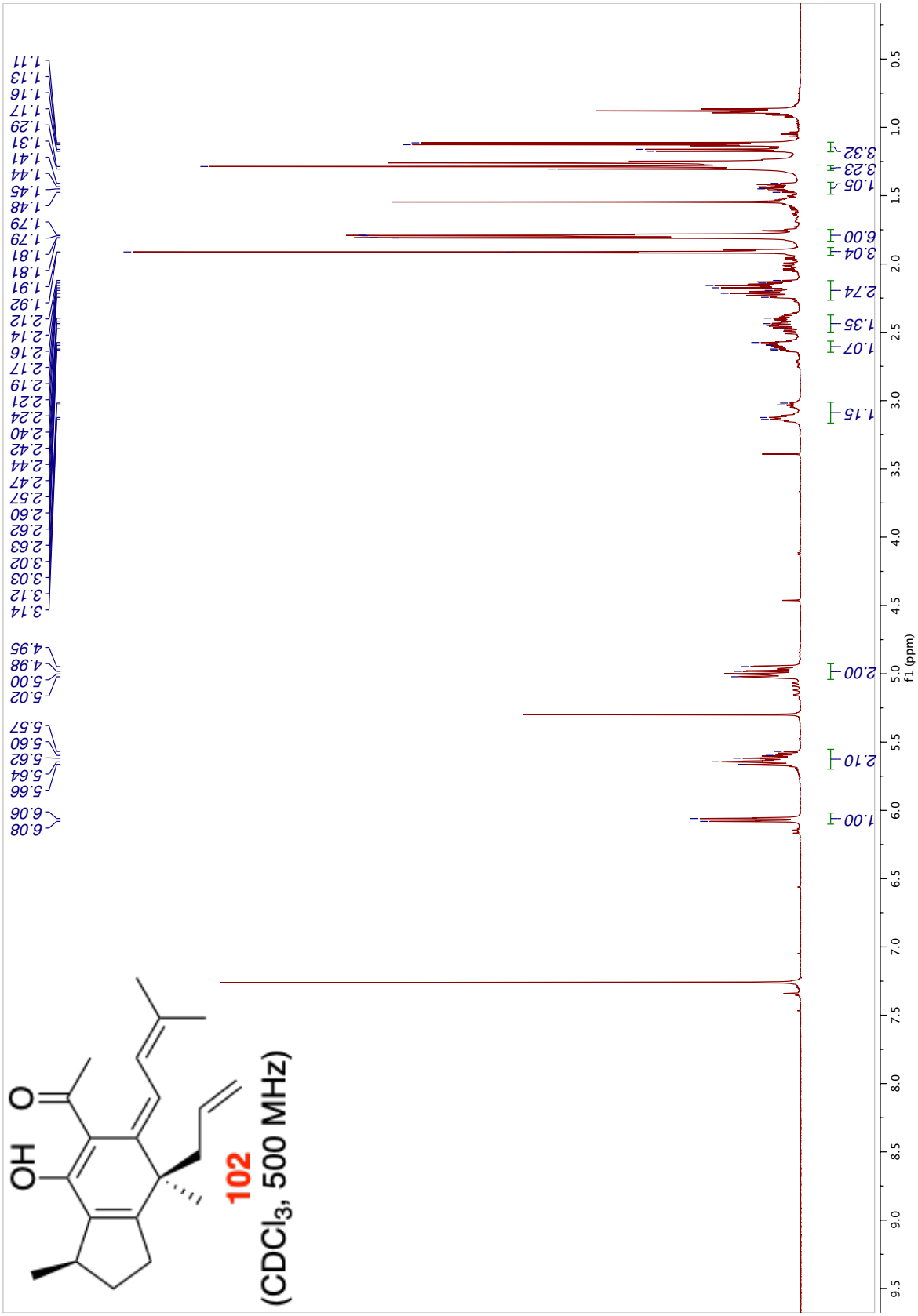

97
(CDCl3, 500 MHz)
f1 (ppm)

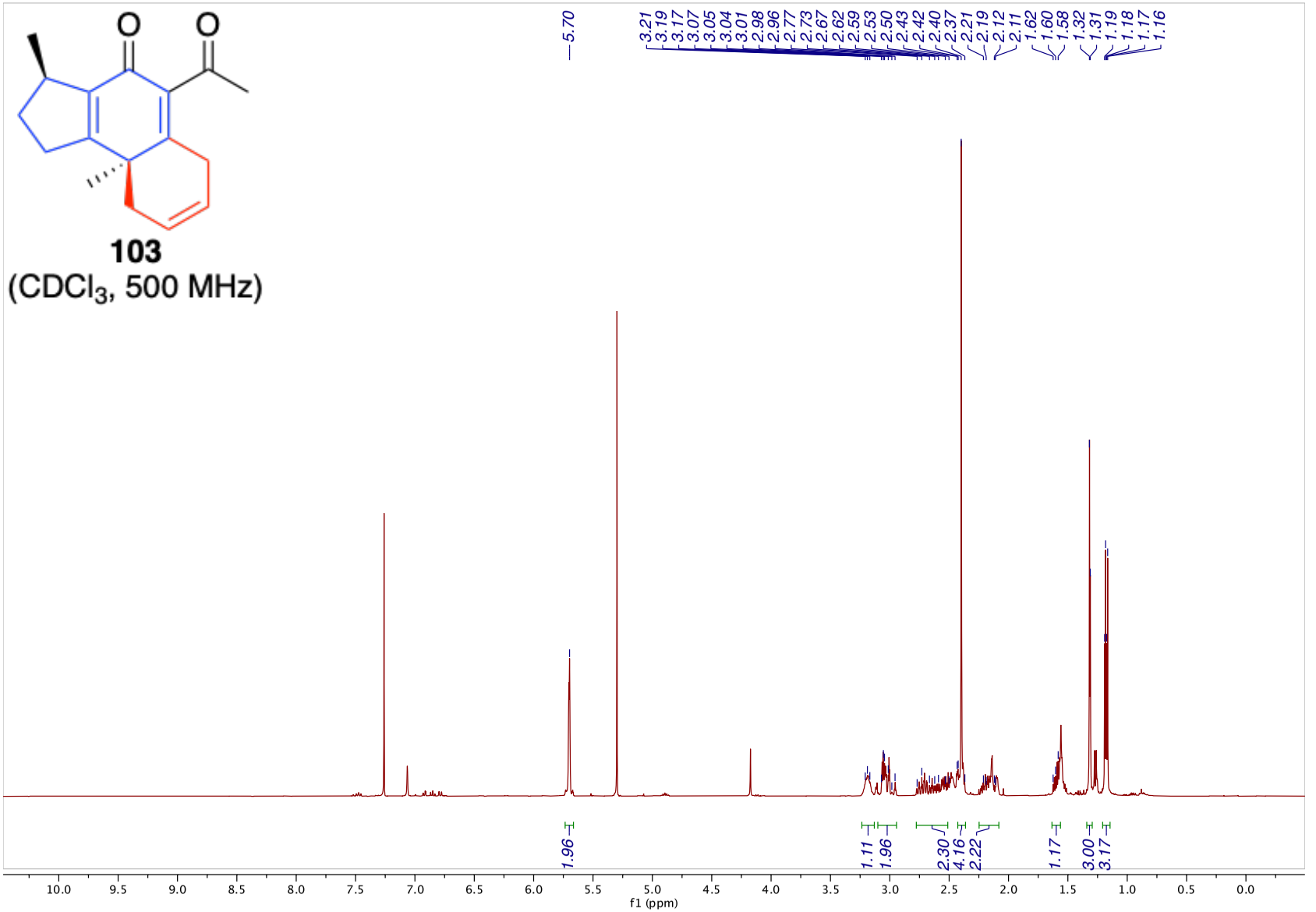

205.75
182.66
166.30
161.03
143.09
142.13
134.35
132.71
120.92
117.77
45.63
41.77
37.95
32.25
31.56
31.20
28.07
25.66
23.55
19.45
17.99
O
O
97
(CDCl3, 125 MHz)
f1 (ppm)

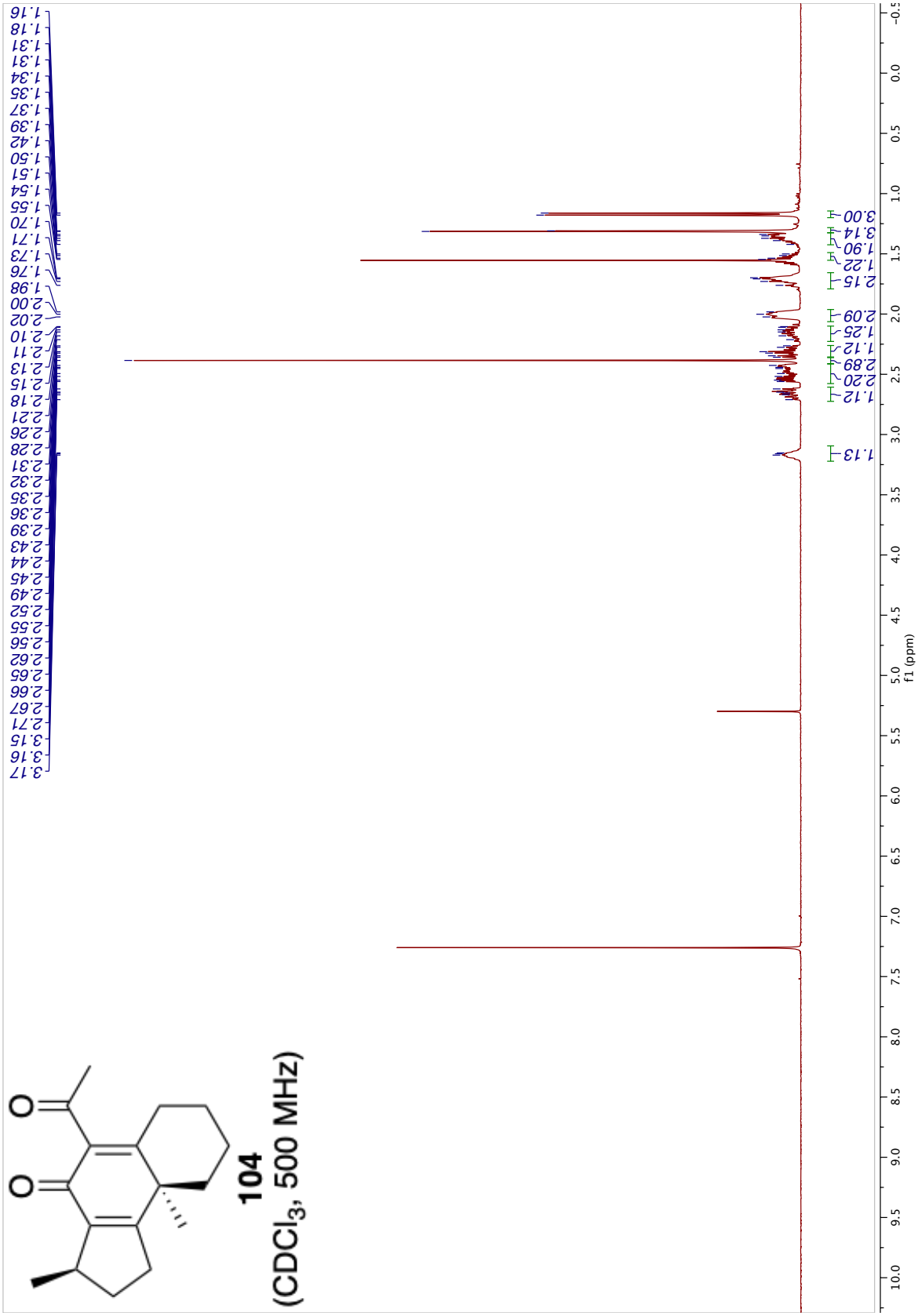

98
(CDCl3, 500 MHz)
f1 (ppm)

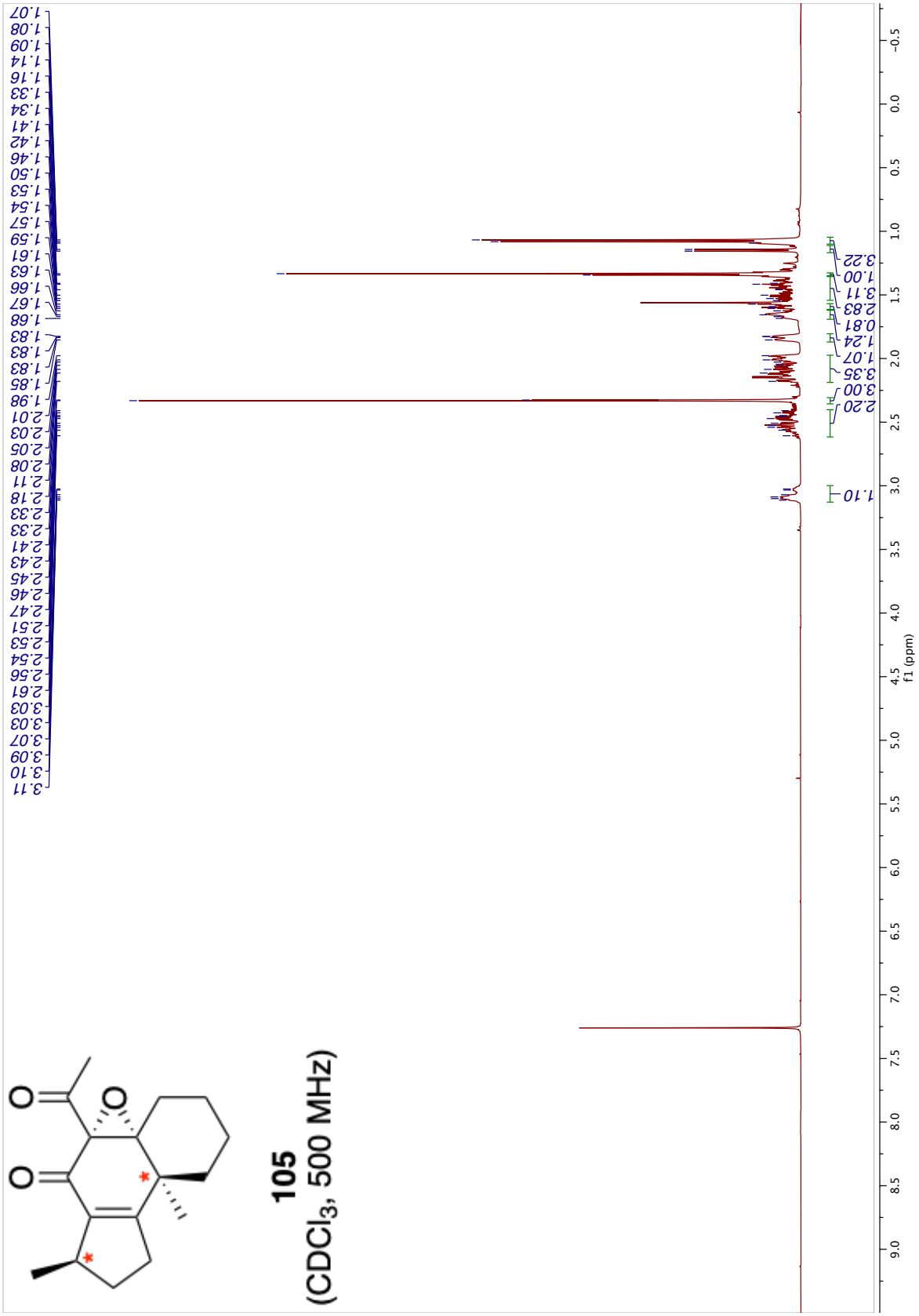

99
(CDCl3, 500 MHz)
OH
O
O
f1 (ppm)

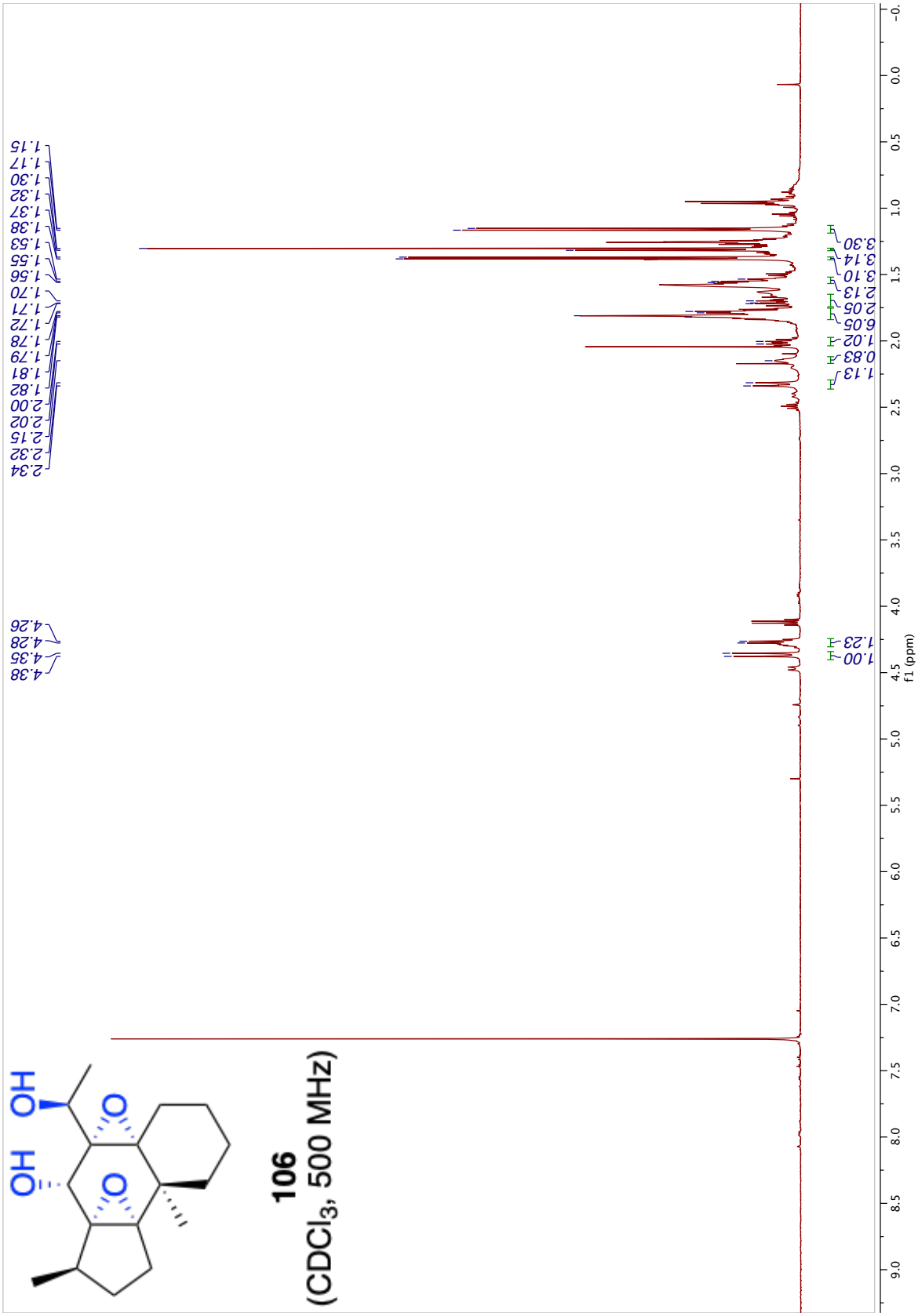

99
(CDCl3, 125 MHz)
209.69
194.29
173.40
139.56
133.92
131.82
124.36
119.29
86.70
49.77
44.99
41.91
37.73
32.32
31.23
28.79
25.96
25.92
21.75
20.53
18.00
f1 (ppm)

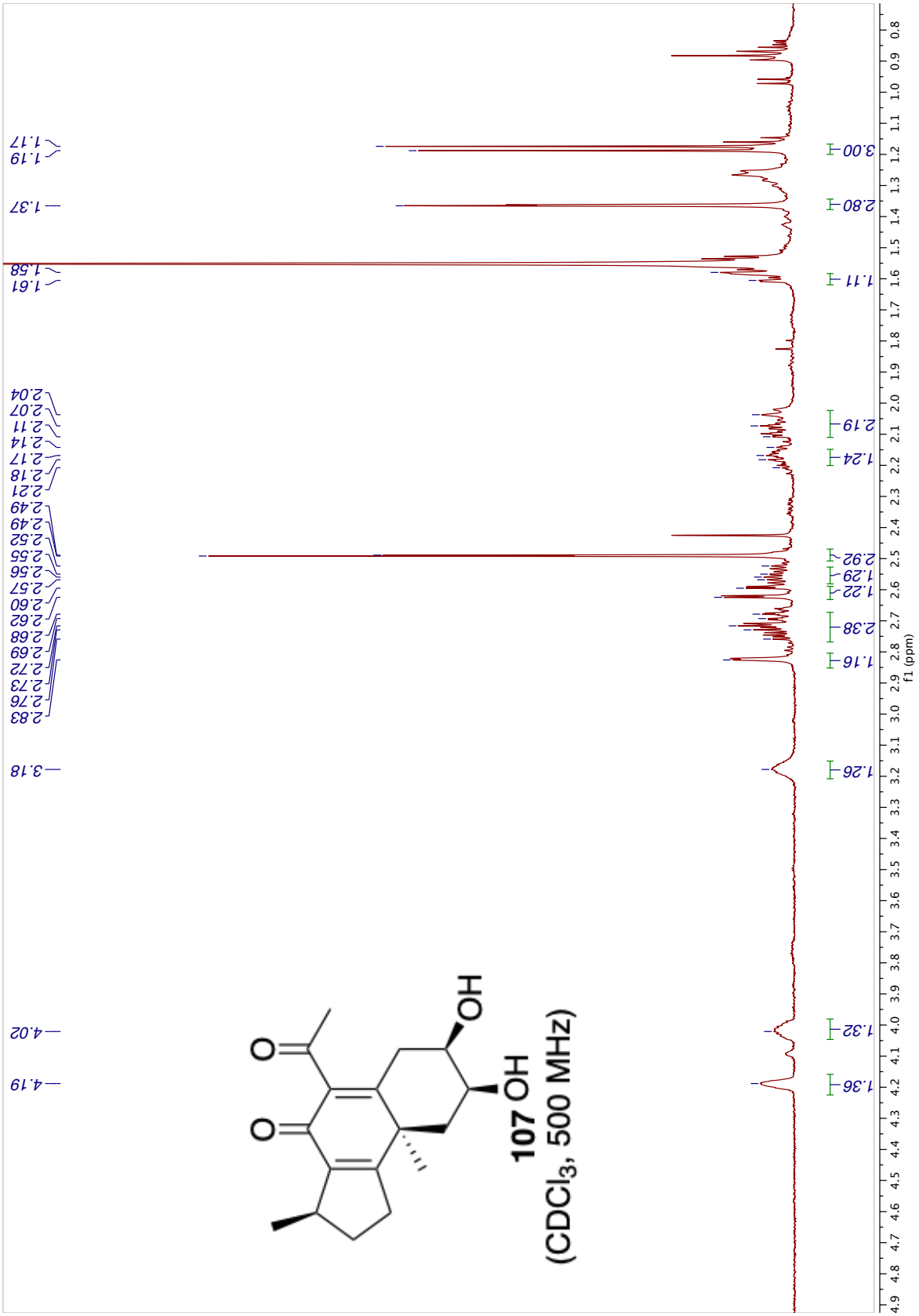

OH
O
102
(CDCl3, 500 MHz)
f1 (ppm)

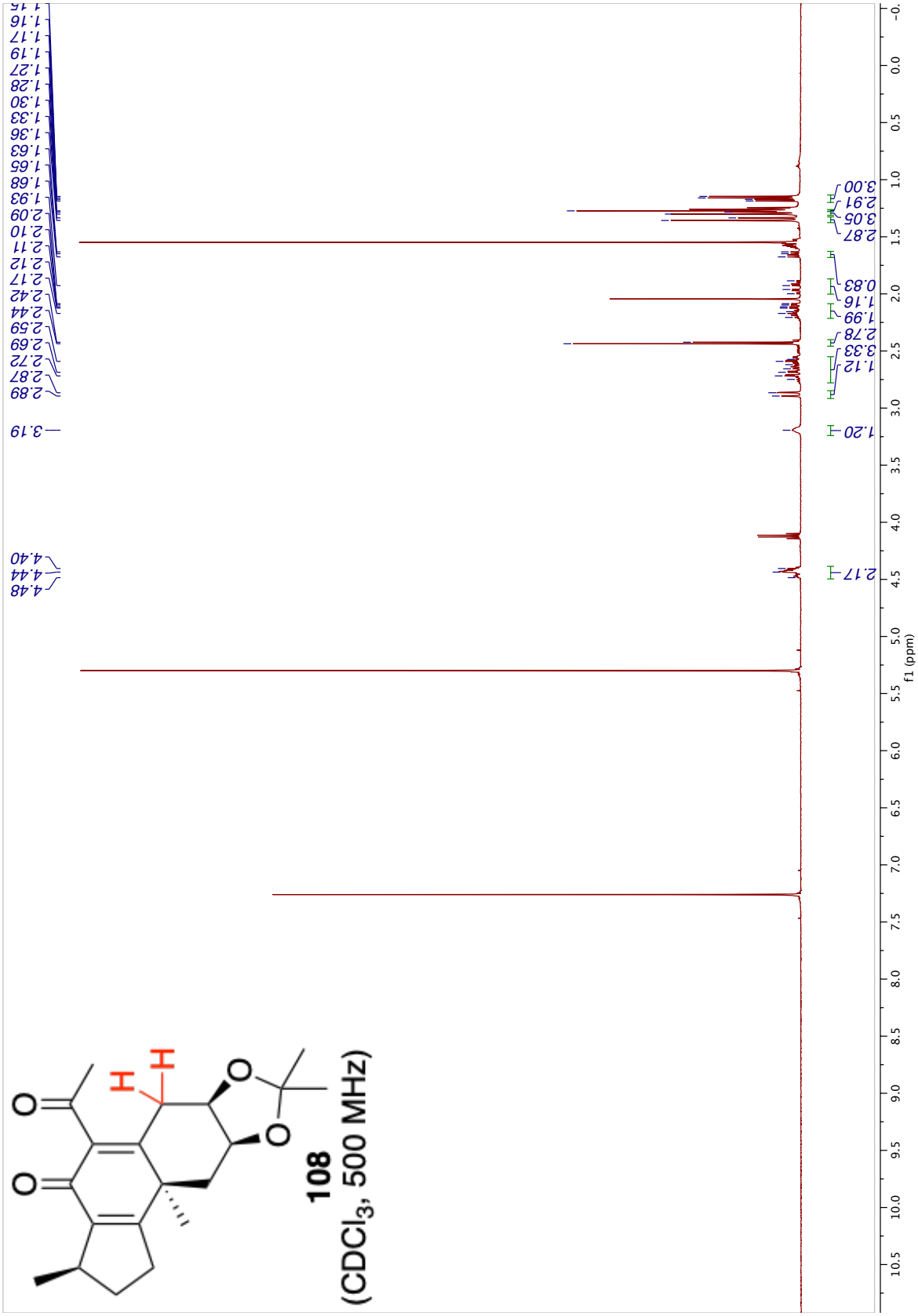

103
(CDCl3, 500 MHz)
5.70
3.21
3.19
3.17
3.07
3.05
3.04
3.01
2.98
2.96
2.77
2.73
2.67
2.62
2.59
2.53
2.50
2.43
2.42
2.40
2.37
2.21
2.19
2.12
2.11
1.62
1.60
1.58
1.32
1.31
1.19
1.18
1.17
1.16
1.96
1.11
1.96
2.30
4.16
2.22
1.17
3.00
3.17
f1 (ppm)

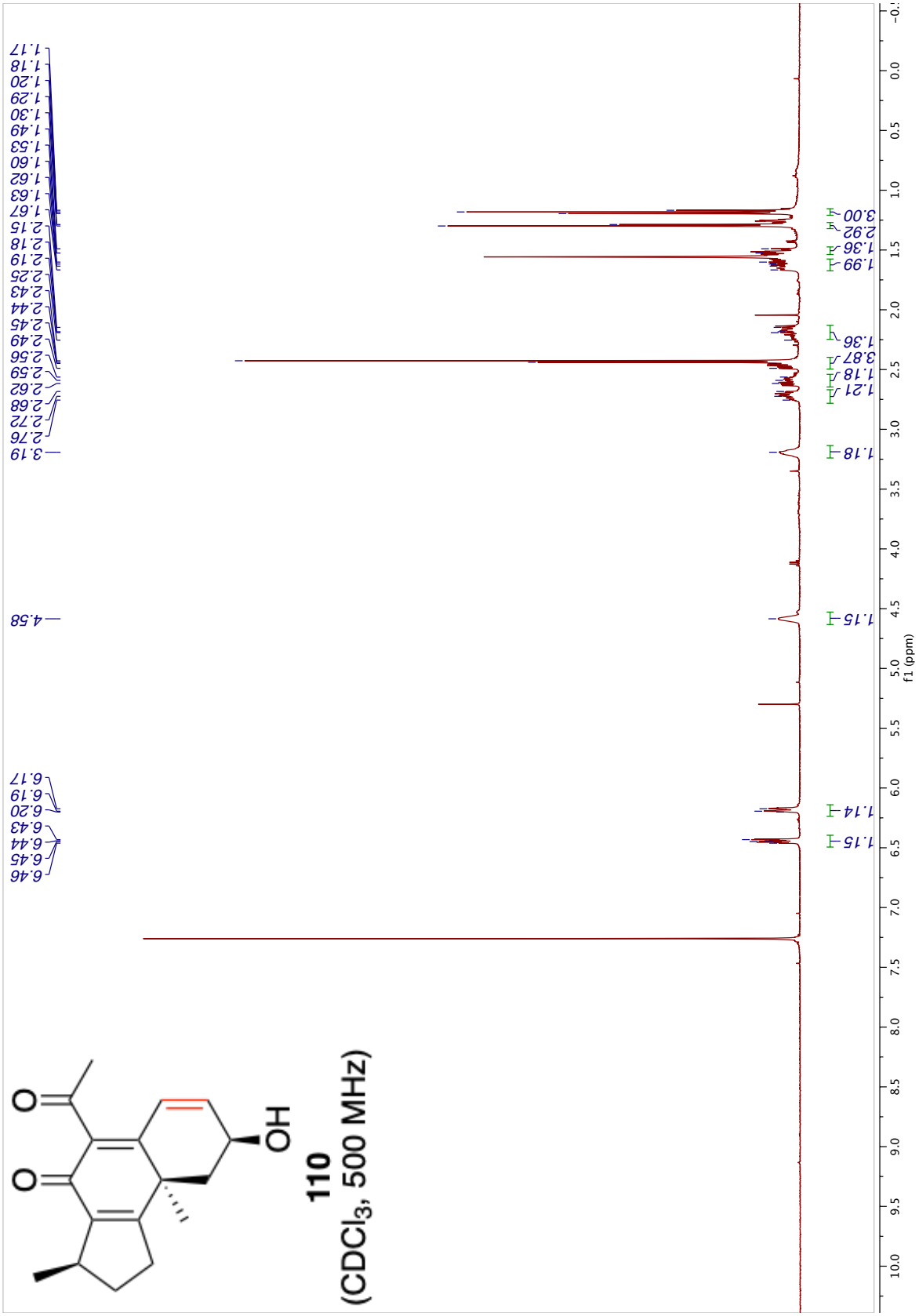

104
(CDCl3, 500 MHz)
f1 (ppm)

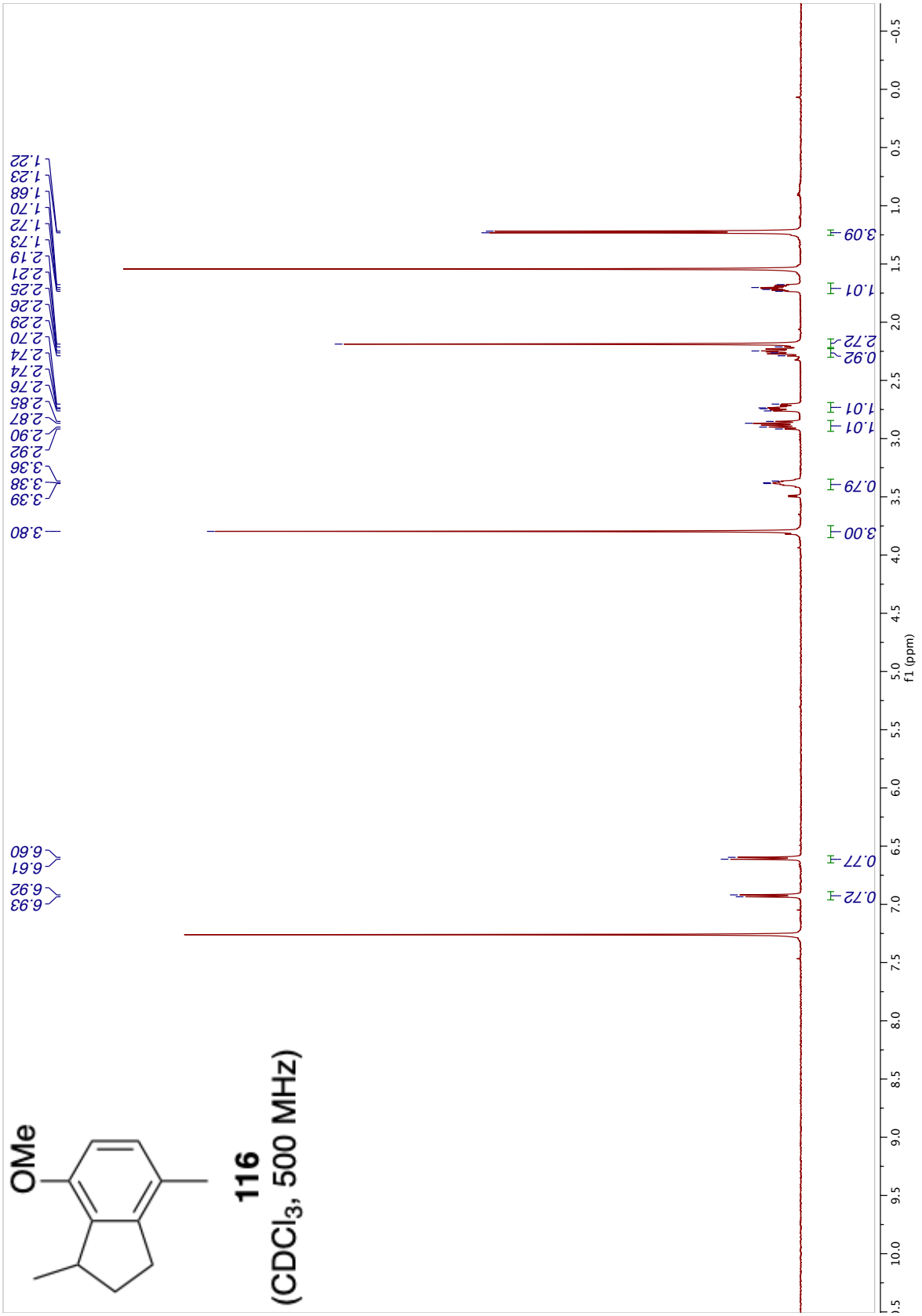

105
(CDCl3, 500 MHz)
f1 (ppm)

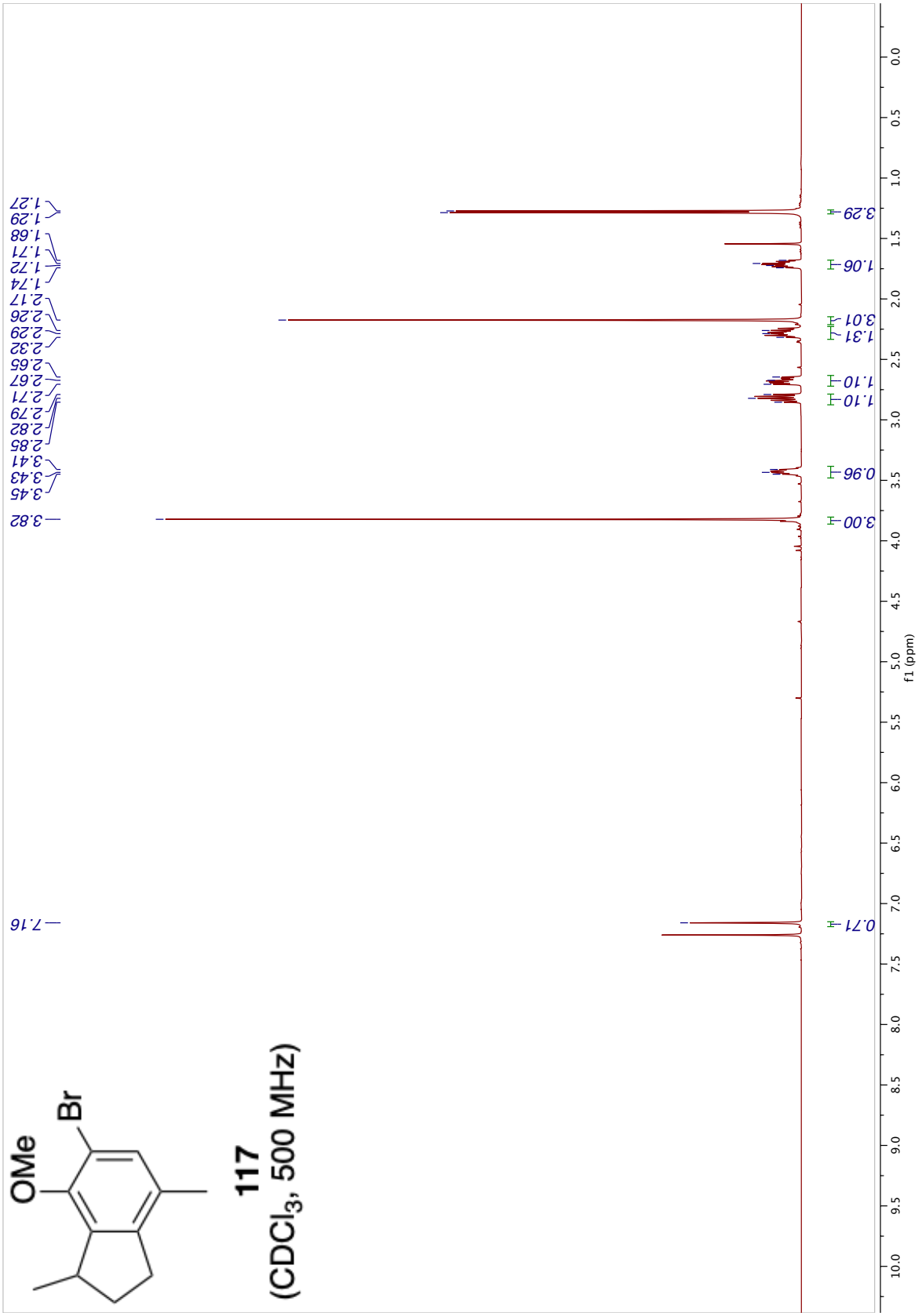

106
(CDCl3, 500 MHz)
OH
OH
O
O
4.38
4.35
4.28
4.26
2.34
2.32
2.15
2.02
2.00
1.82
1.81
1.79
1.78
1.72
1.71
1.70
1.56
1.55
1.53
1.38
1.37
1.32
1.30
1.17
1.15
3.30
3.14
3.10
2.13
2.05
6.05
1.02
0.83
1.13
1.00
1.23
f1 (ppm)

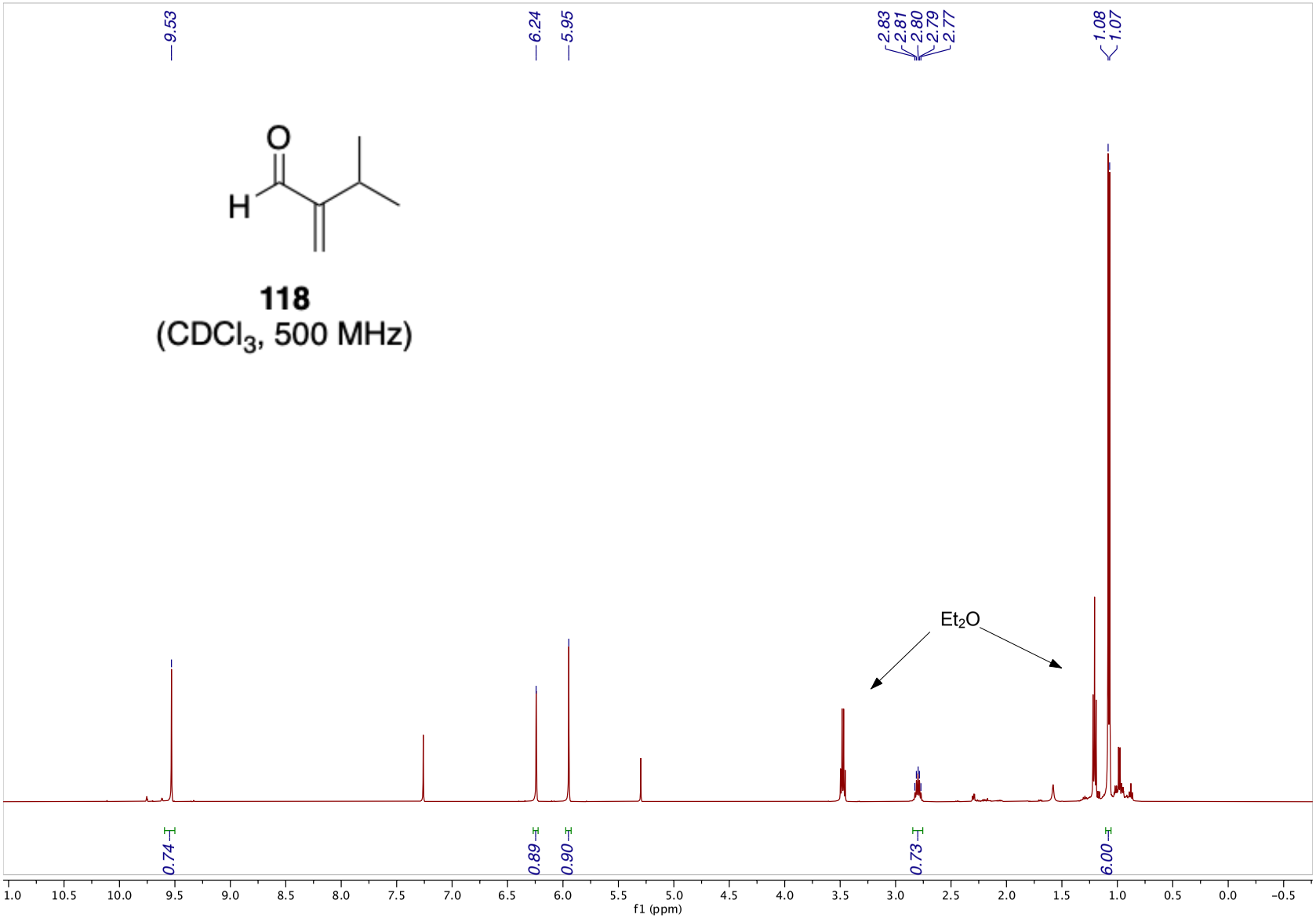

107
(CDCl3, 500 MHz)
OH
O
O
f1 (ppm)

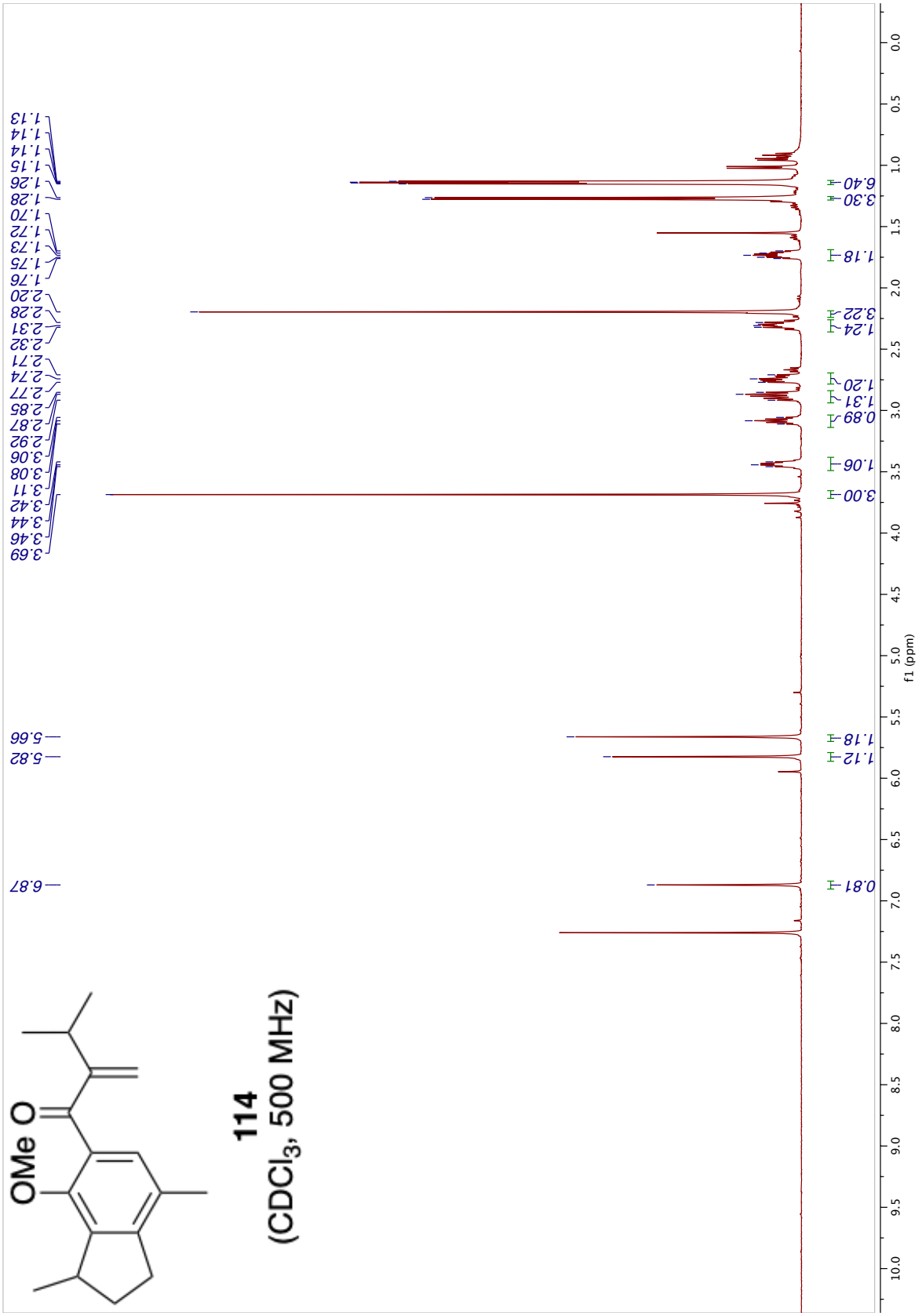

108
(CDCl3, 500 MHz)
f1 (ppm)

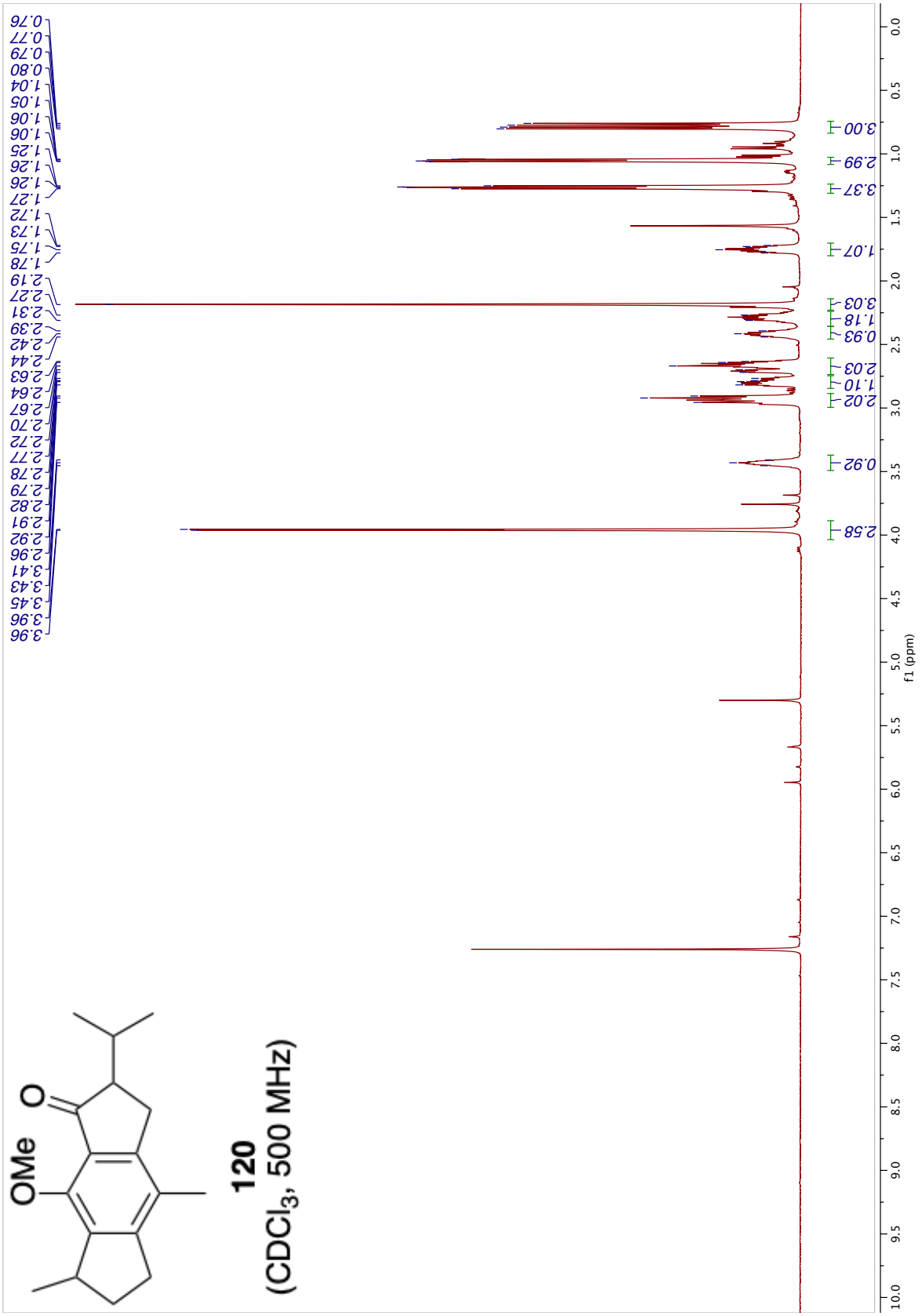

110
(CDCl3, 500 MHz)
O
O
OH
f1 (ppm)

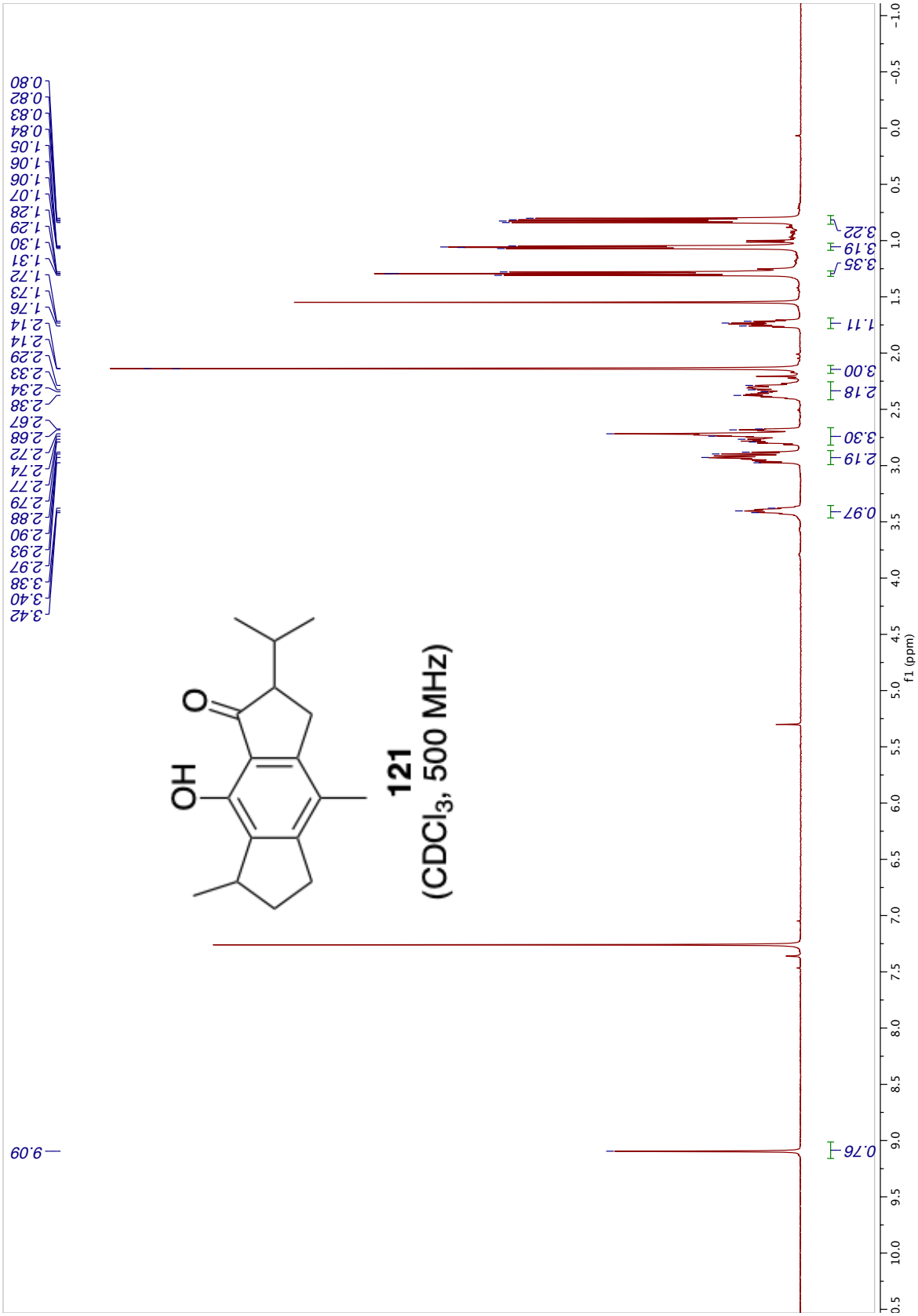

OMe
116
(CDCl3, 500 MHz)
1.22
1.23
1.68
1.70
1.72
1.73
2.19
2.21
2.25
2.26
2.29
2.70
2.74
2.74
2.76
2.85
2.87
2.90
2.92
3.36
3.38
3.39
3.80
6.60
6.61
6.92
6.93
3.09
1.01
2.72
0.92
1.01
1.01
0.79
3.00
0.77
0.72
f1 (ppm)

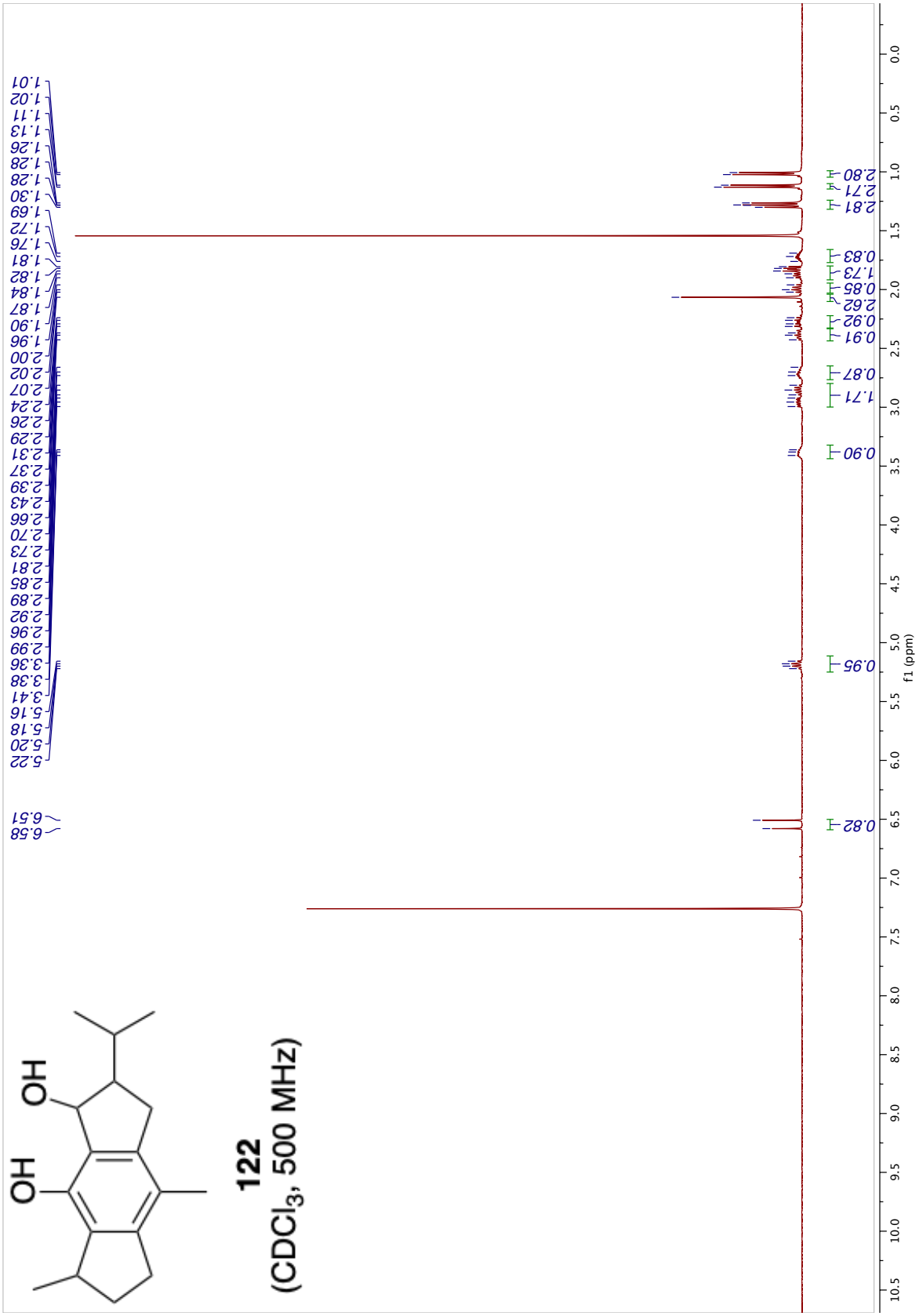

OMe
Br
117
(CDCl3, 500 MHz)
7.16
3.82
3.45
3.43
3.41
2.85
2.82
2.79
2.71
2.67
2.65
2.32
2.29
2.26
2.17
1.74
1.72
1.71
1.68
1.29
1.27
0.71
3.00
0.96
1.10
1.10
3.01
1.31
1.06
3.29
f1 (ppm)

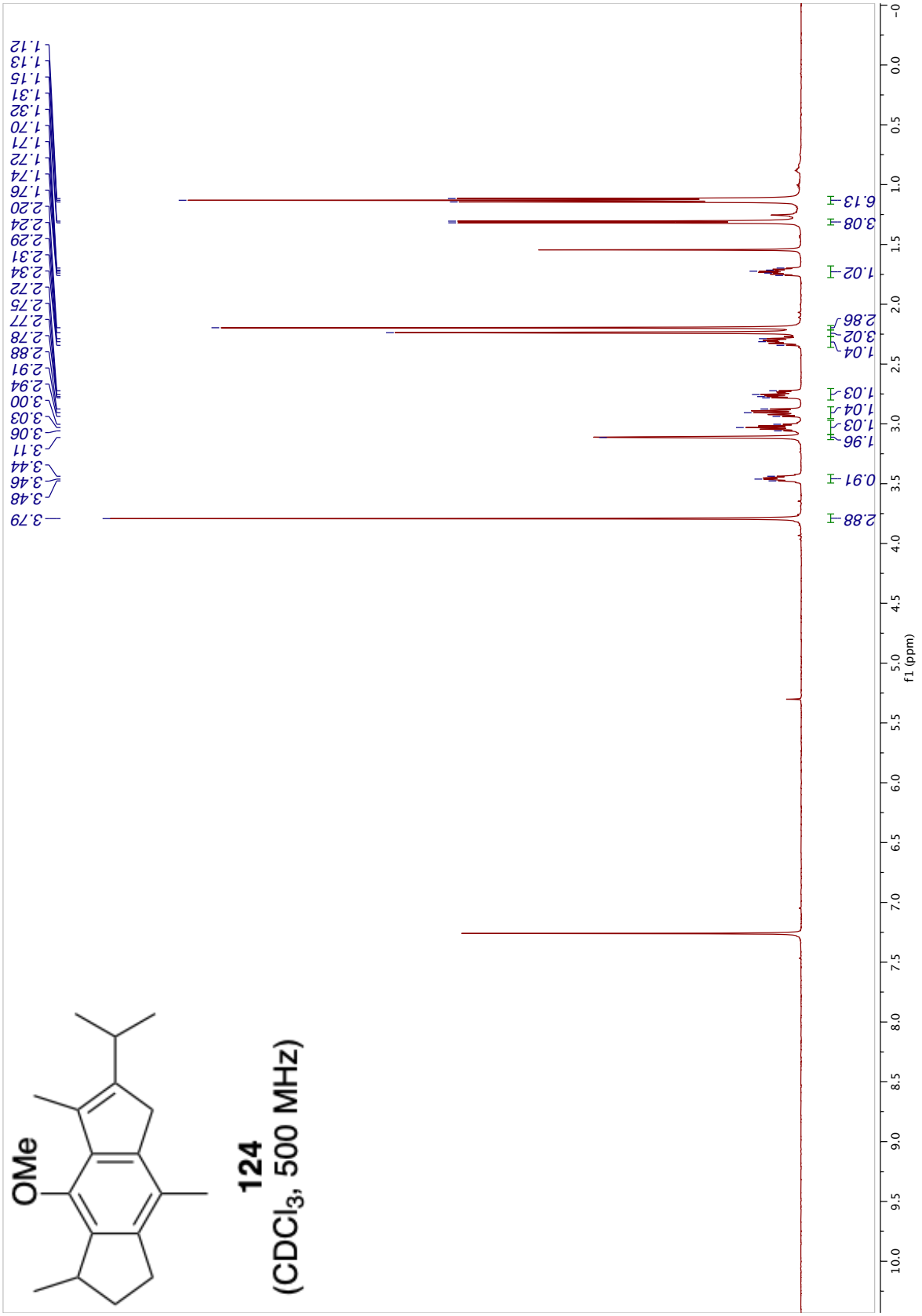

9.53
6.24
5.95
2.83
2.81
2.80
2.79
2.77
1.08
1.07
O
H
118
(CDCl3, 500 MHz)
Et2O
0.74
0.89
0.90
0.73
6.00
f1 (ppm)

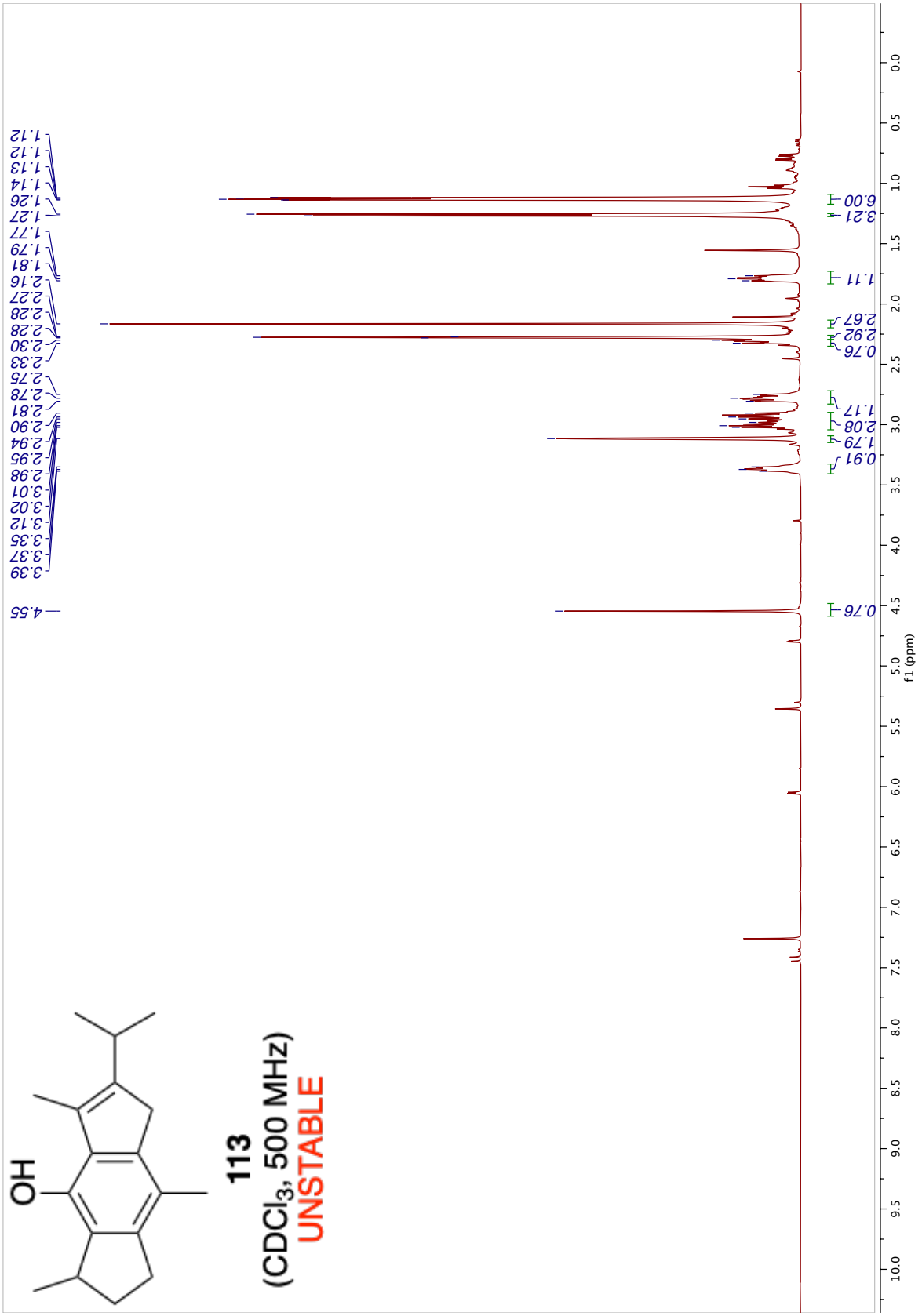

114
(CDCl3, 500 MHz)
OMe O
f1 (ppm)

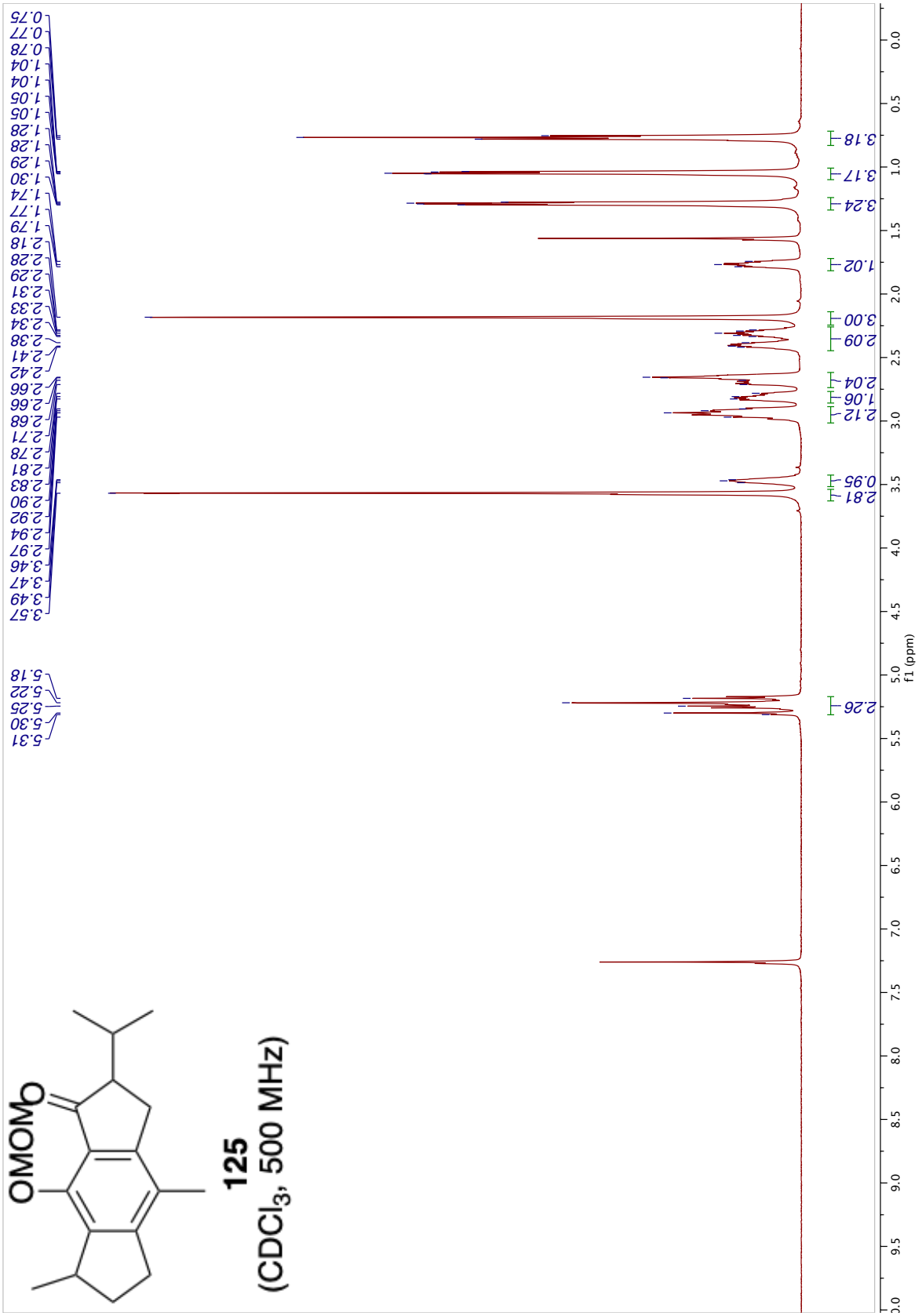

OMe
O
120
(CDCl3, 500 MHz)
f1 (ppm)

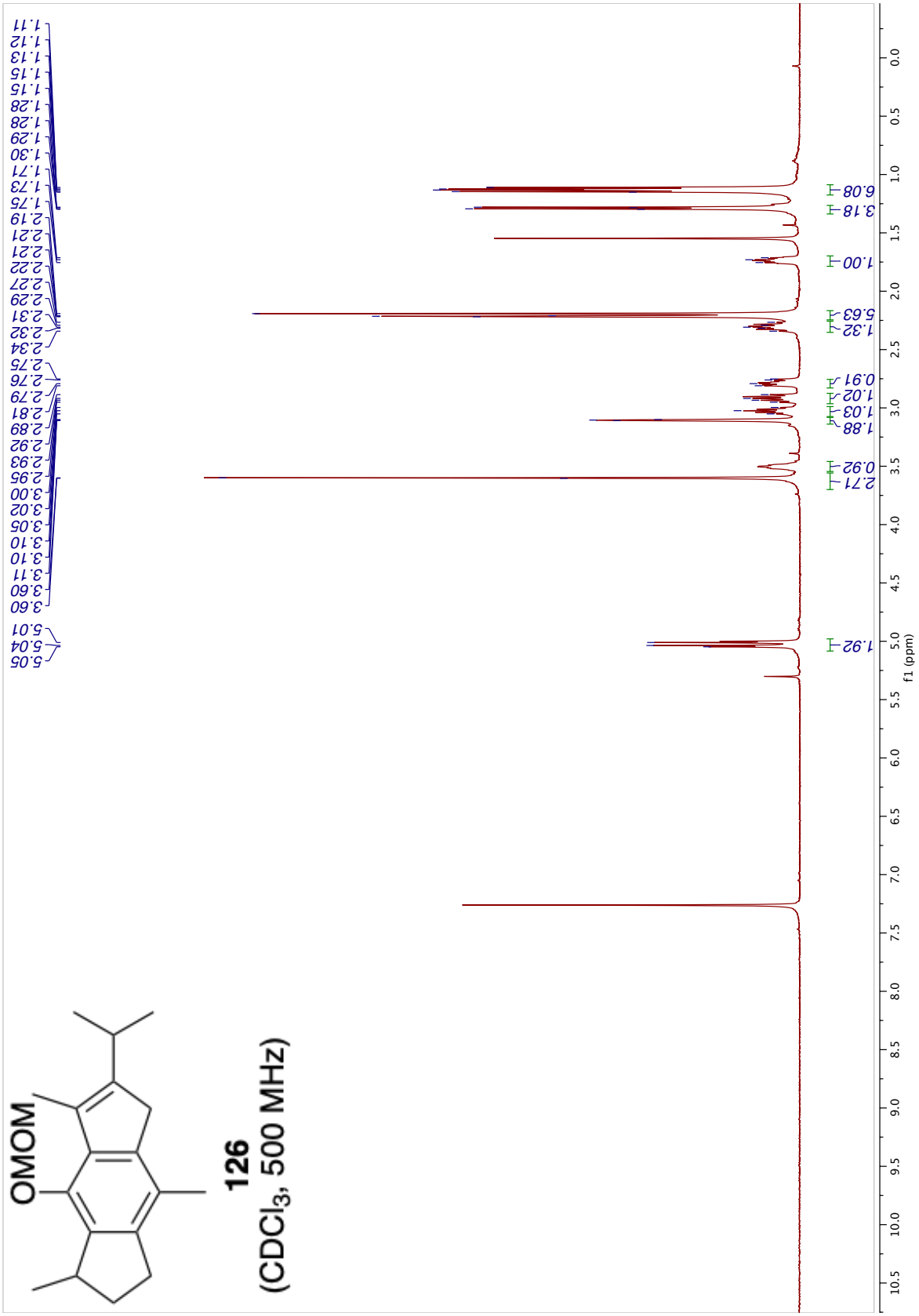

121
(CDCl3, 500 MHz)
OH
O
f1 (ppm)

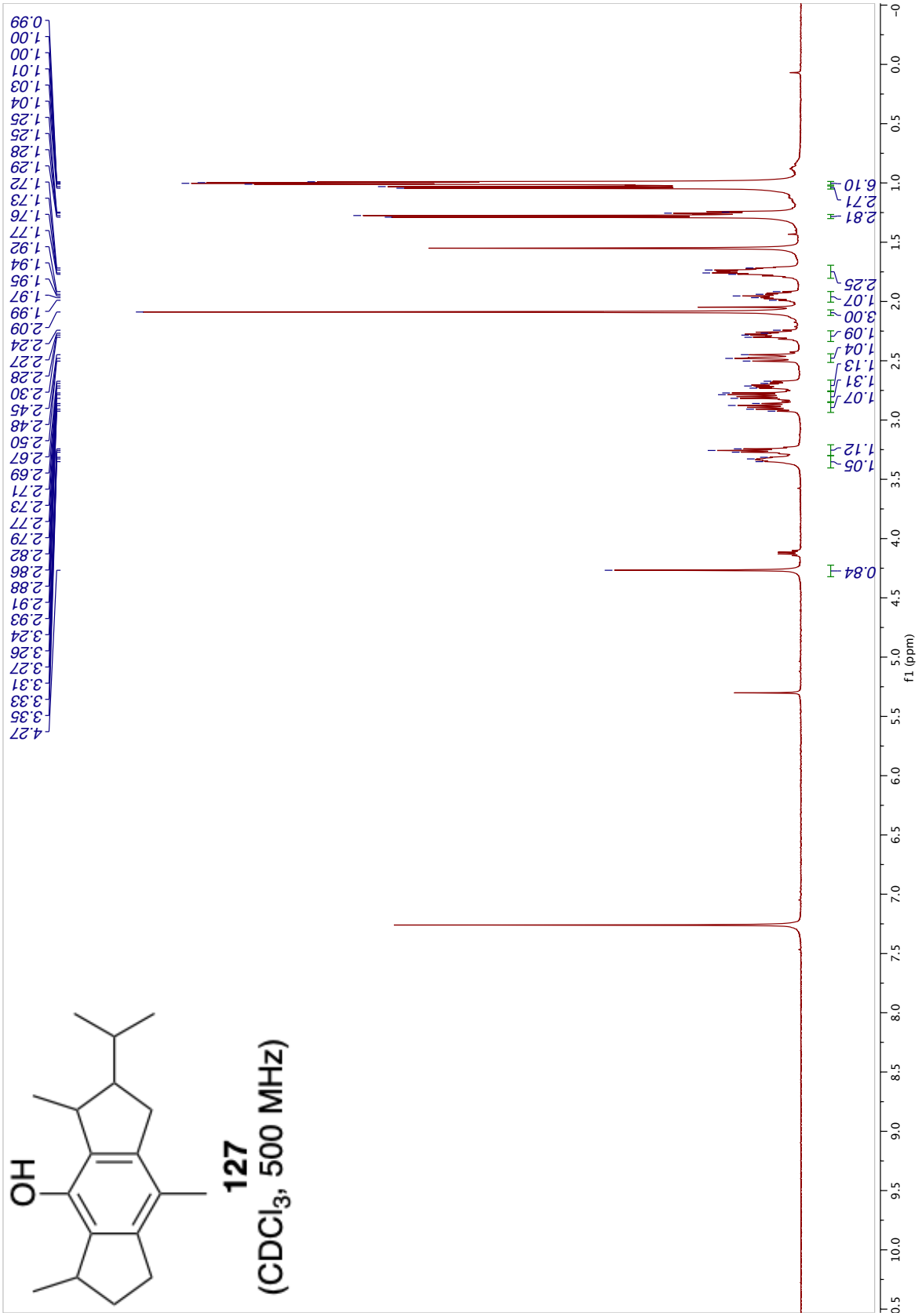

OH
OH
122
(CDCl3, 500 MHz)
f1 (ppm)

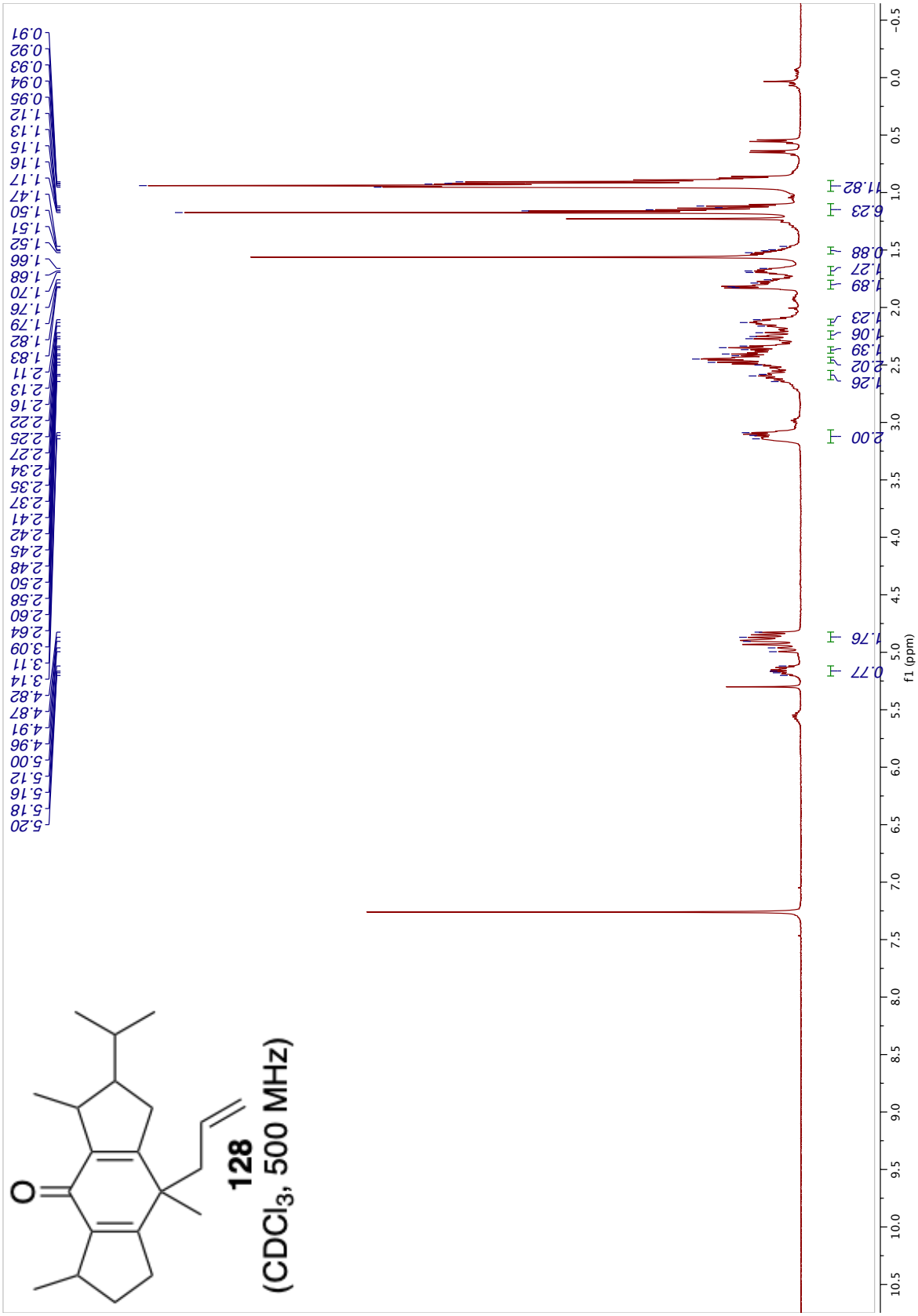

OMe
124
(CDCl3, 500 MHz)
f1 (ppm)

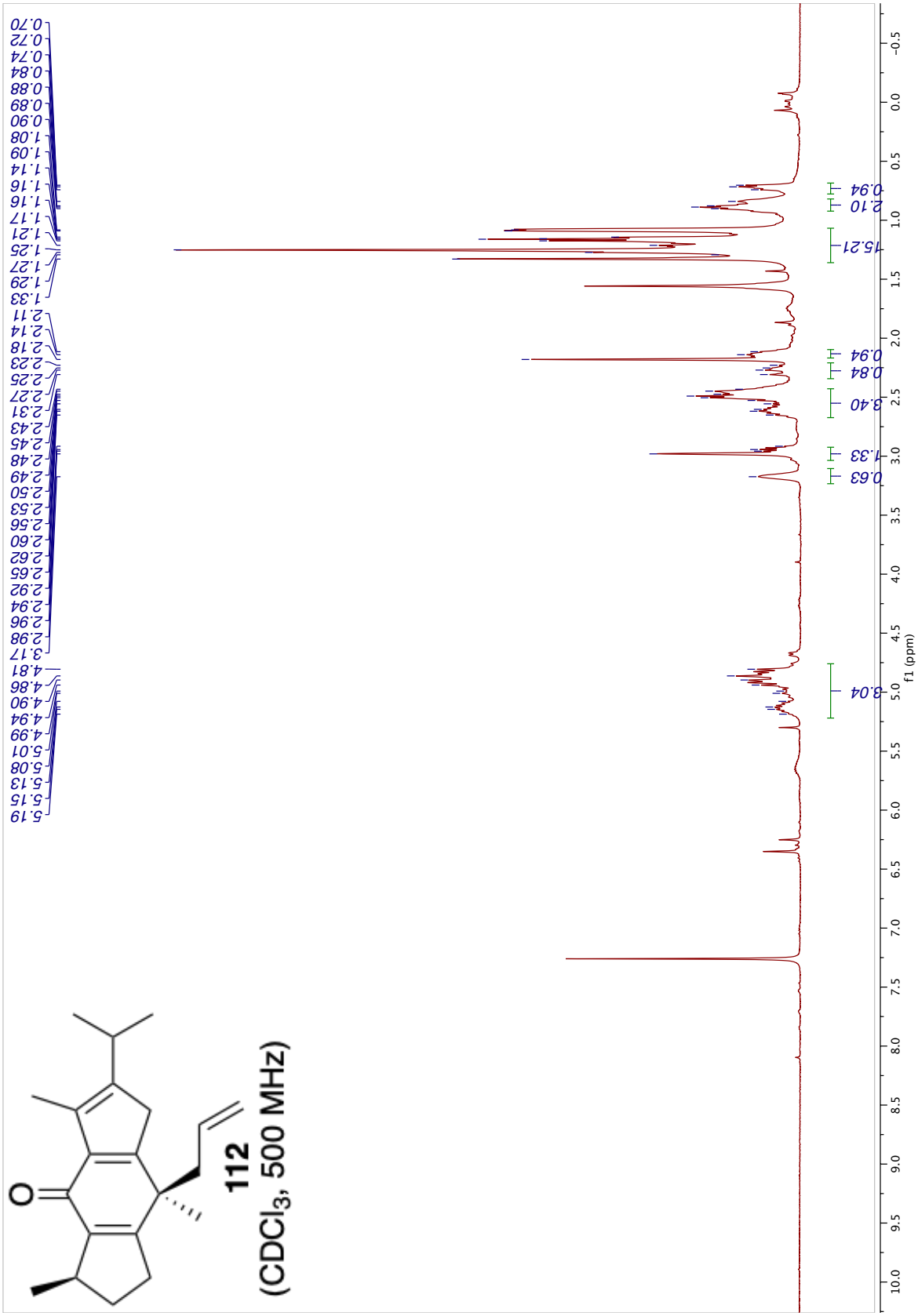

OH
113
(CDCl3, 500 MHz)
UNSTABLE
f1 (ppm)

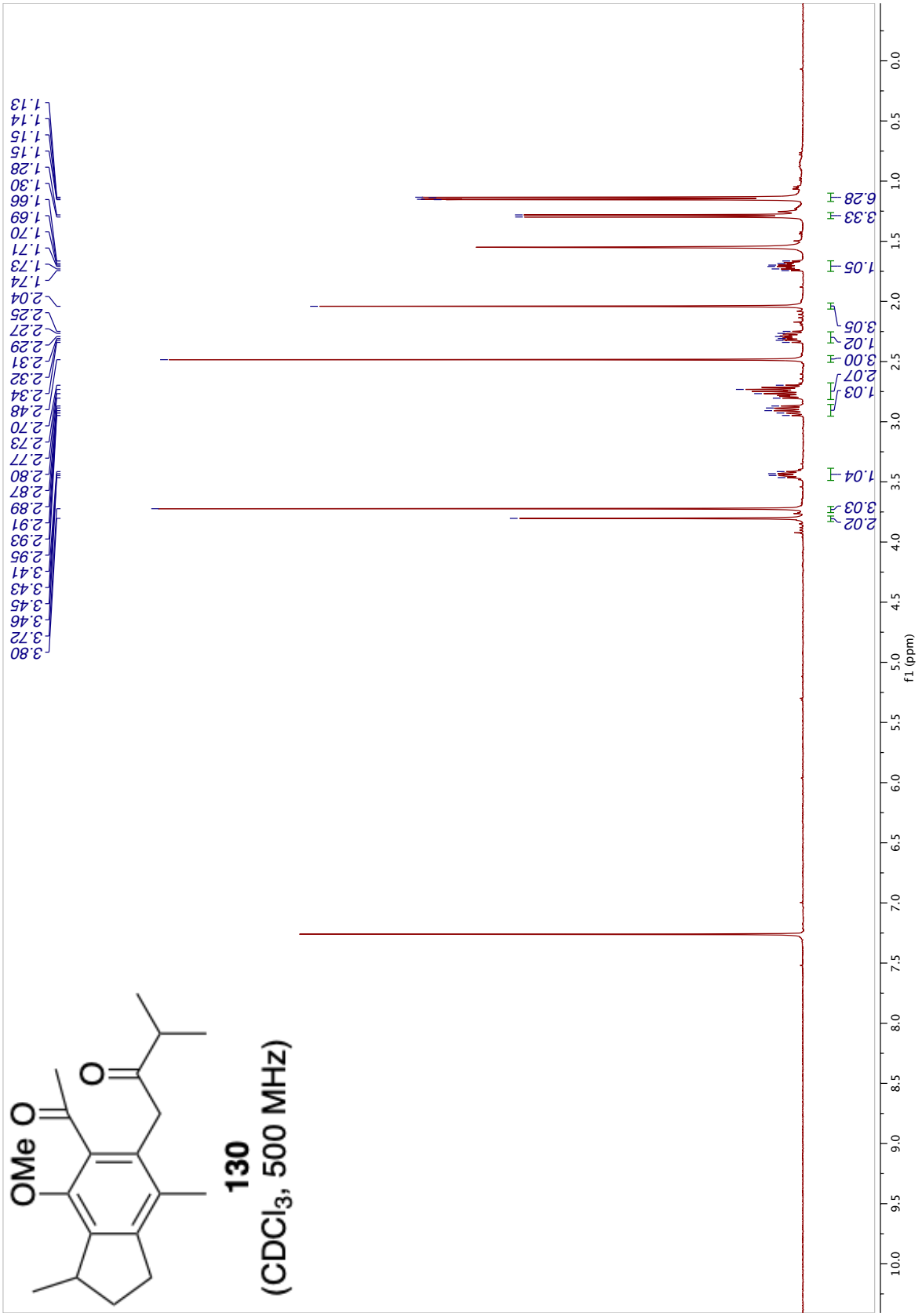

OMOM
O
125
(CDCl3, 500 MHz)
f1 (ppm)

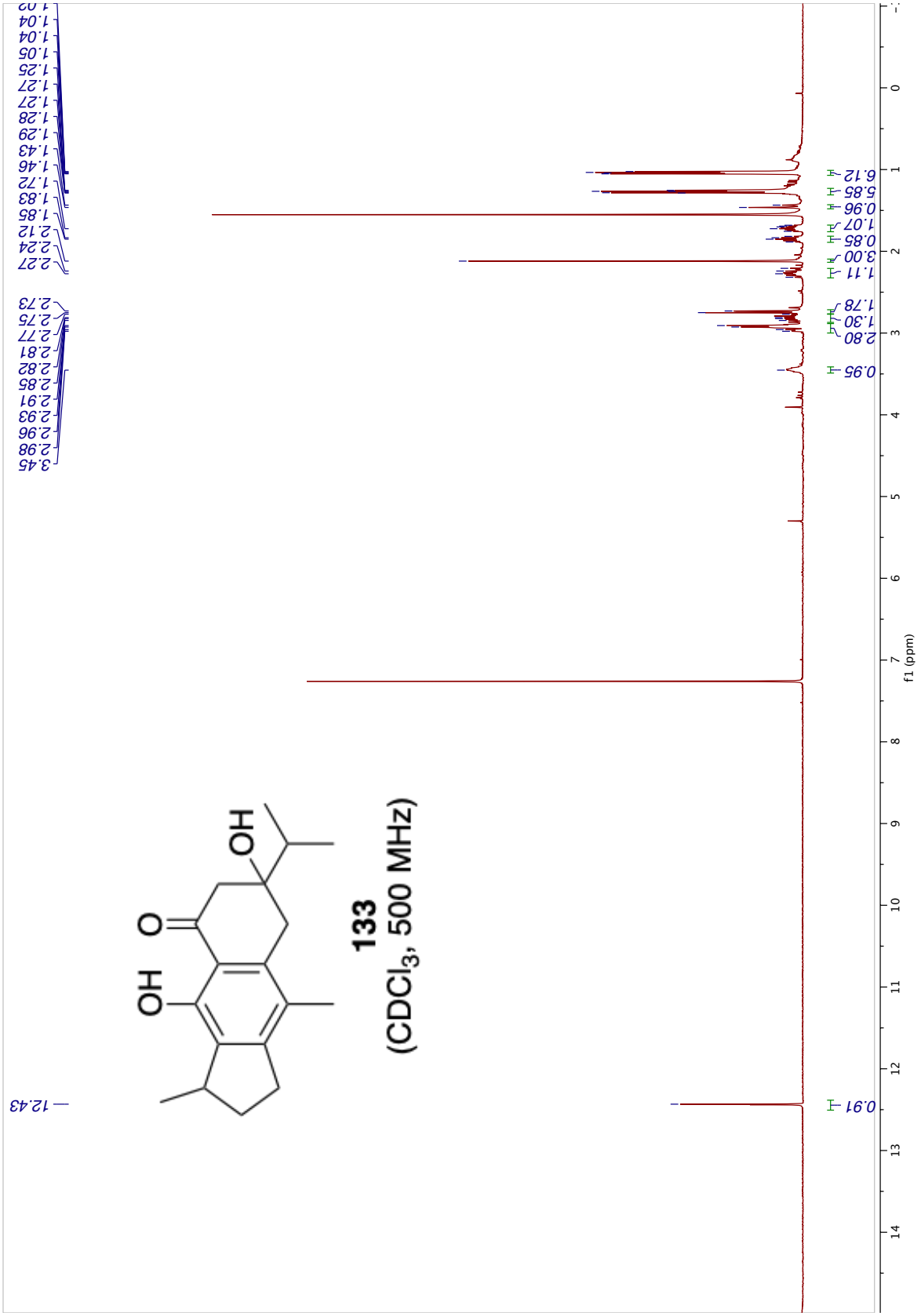

OMOM
126
(CDCl3, 500 MHz)
6.08
3.18
1.00
5.63
1.32
0.91
1.02
1.03
1.88
0.92
2.71
1.92
f1 (ppm)

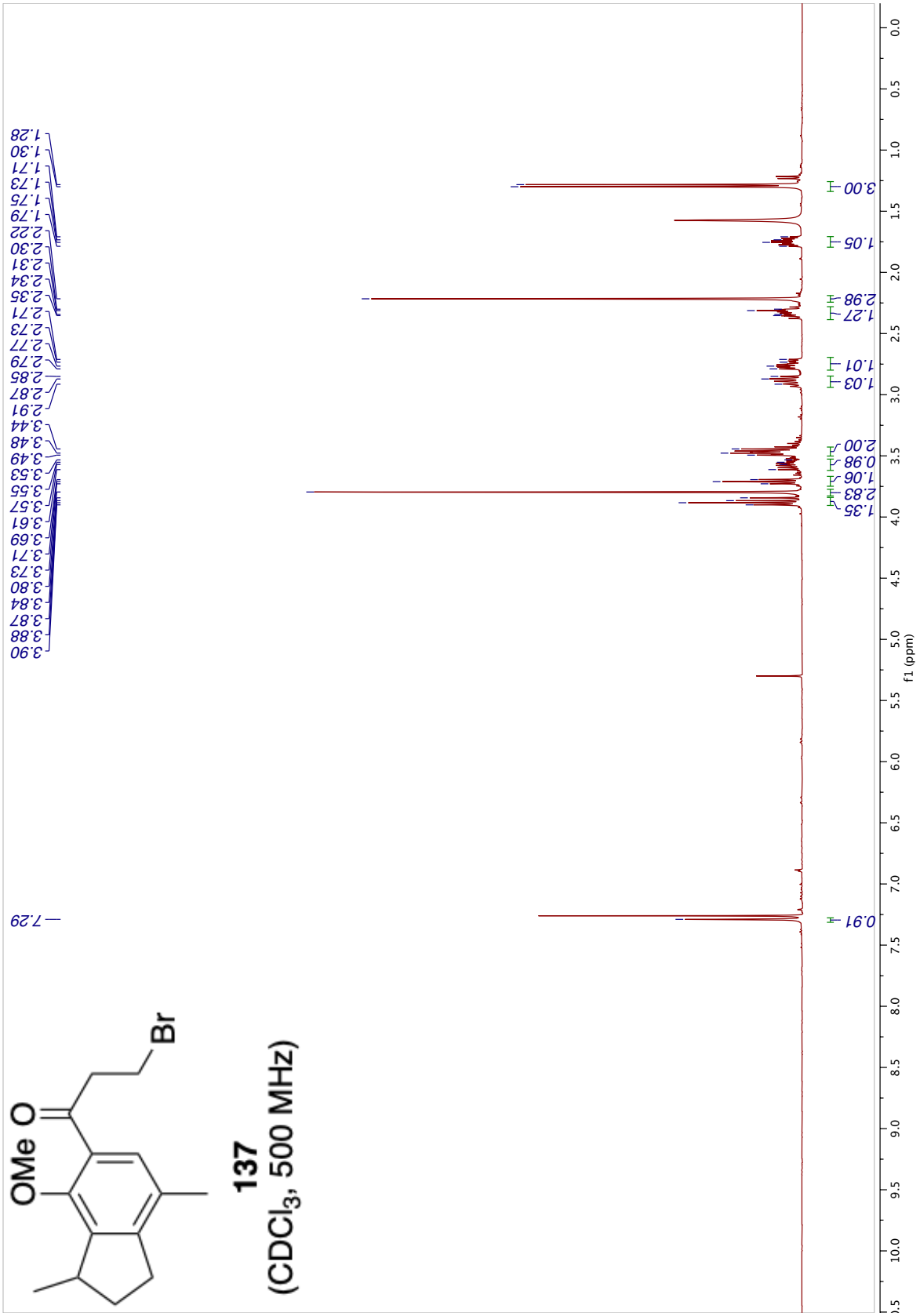

OH
127
(CDCl3, 500 MHz)
f1 (ppm)

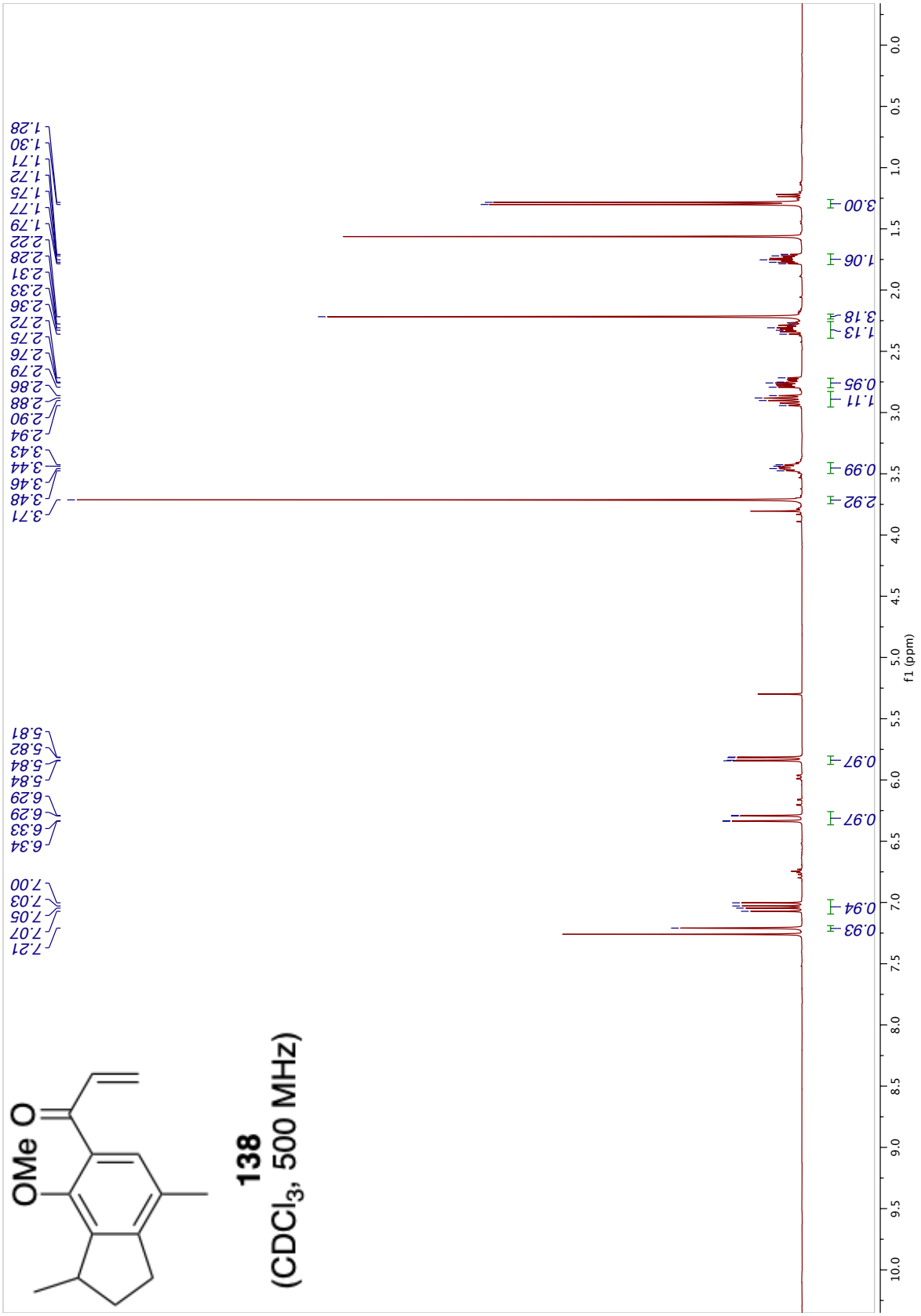

O
128
(CDCl3, 500 MHz)
11.82
6.23
0.88
1.27
1.89
1.23
1.06
1.39
2.02
1.26
2.00
1.76
0.77
f1 (ppm)

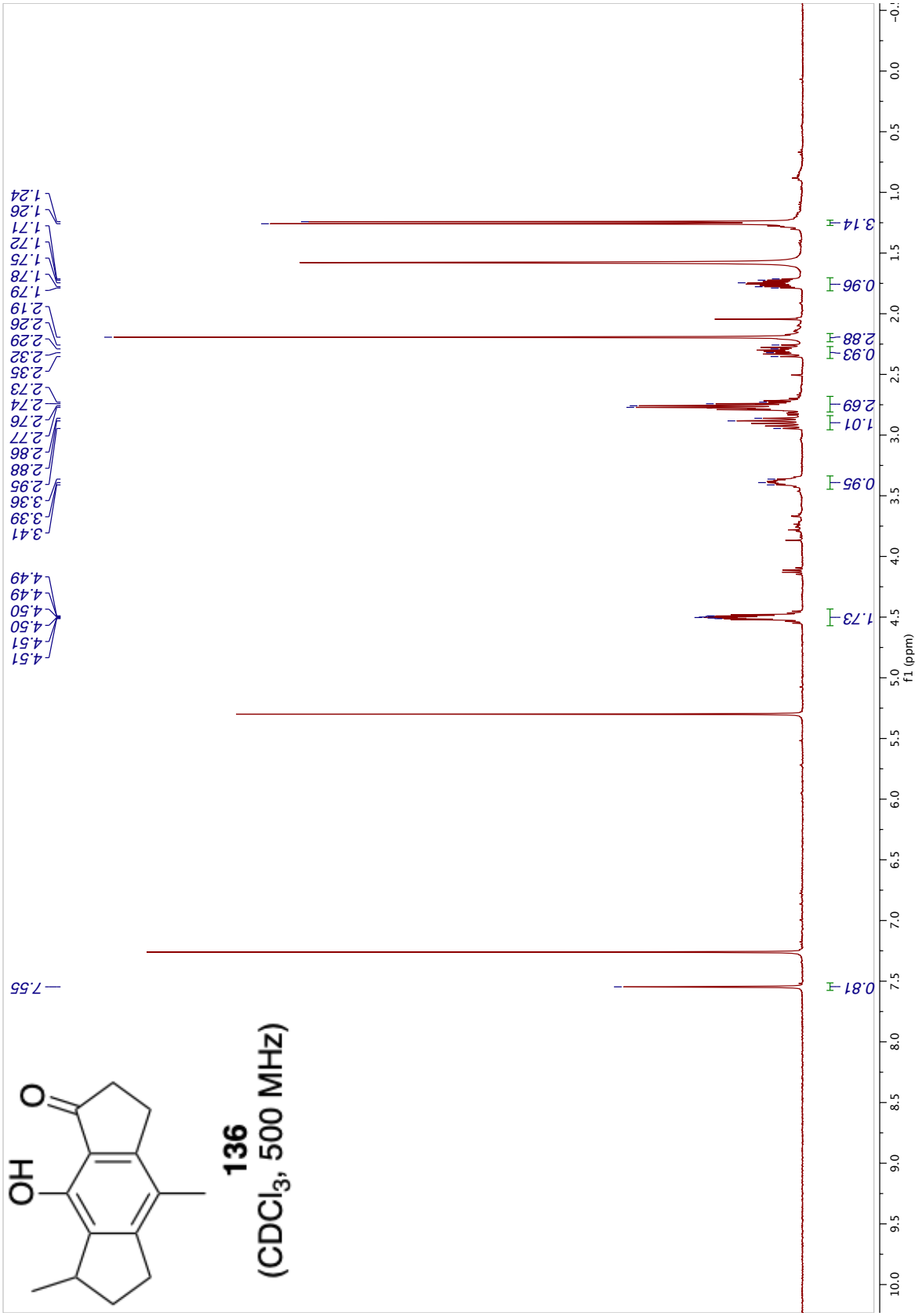

O
112
(CDCl3, 500 MHz)
0.70
0.72
0.74
0.84
0.88
0.89
0.90
1.08
1.09
1.14
1.16
1.16
1.17
1.21
1.25
1.27
1.29
1.33
2.11
2.14
2.18
2.23
2.25
2.27
2.31
2.43
2.45
2.48
2.49
2.50
2.53
2.56
2.60
2.62
2.65
2.92
2.94
2.96
2.98
3.17
4.81
4.86
4.90
4.94
4.99
5.01
5.08
5.13
5.15
5.19
0.94
2.10
15.21
0.84
0.94
3.40
1.33
0.63
8.04
f1 (ppm)

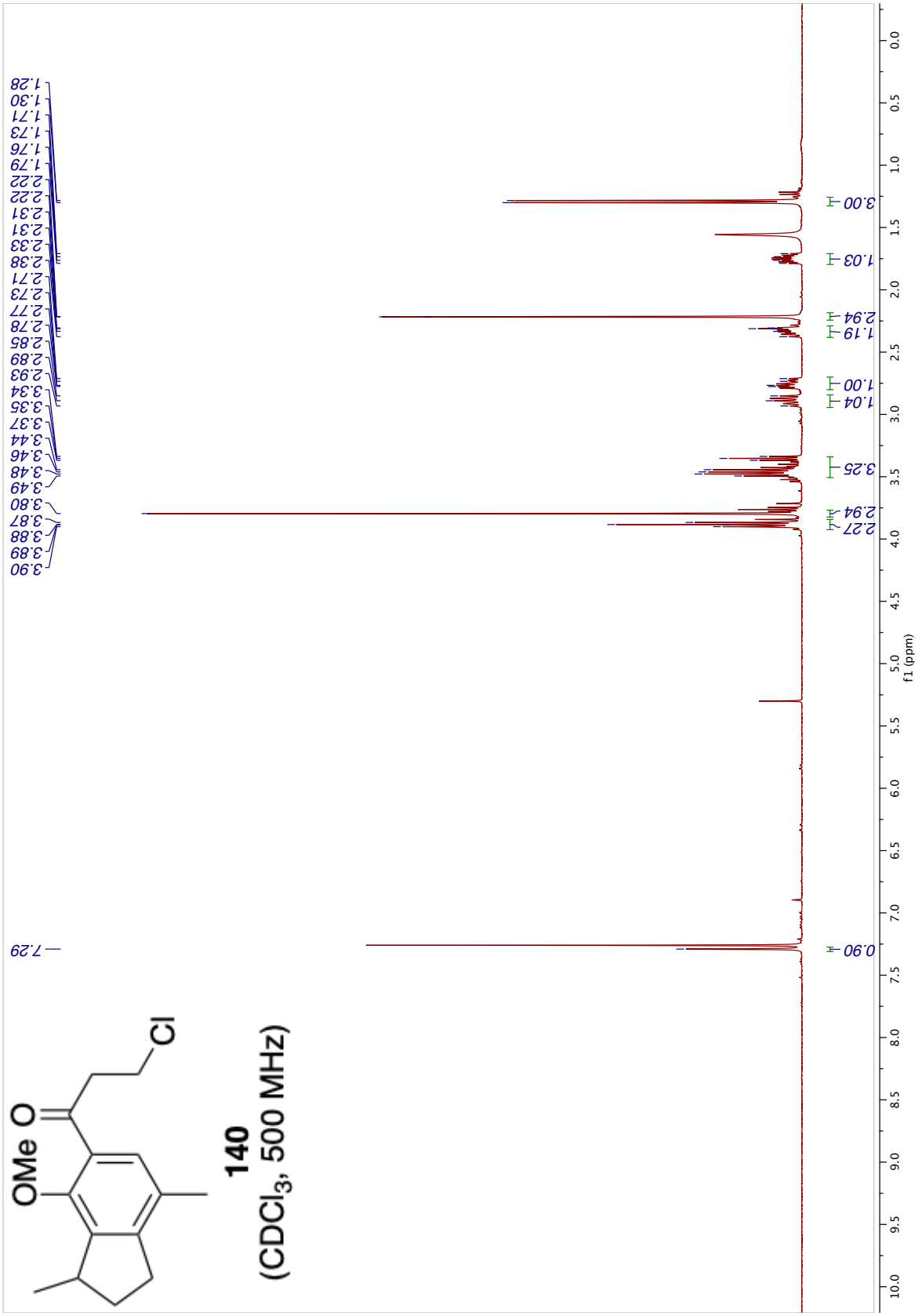

OMe O
O
130
(CDCl3, 500 MHz)
f1 (ppm)

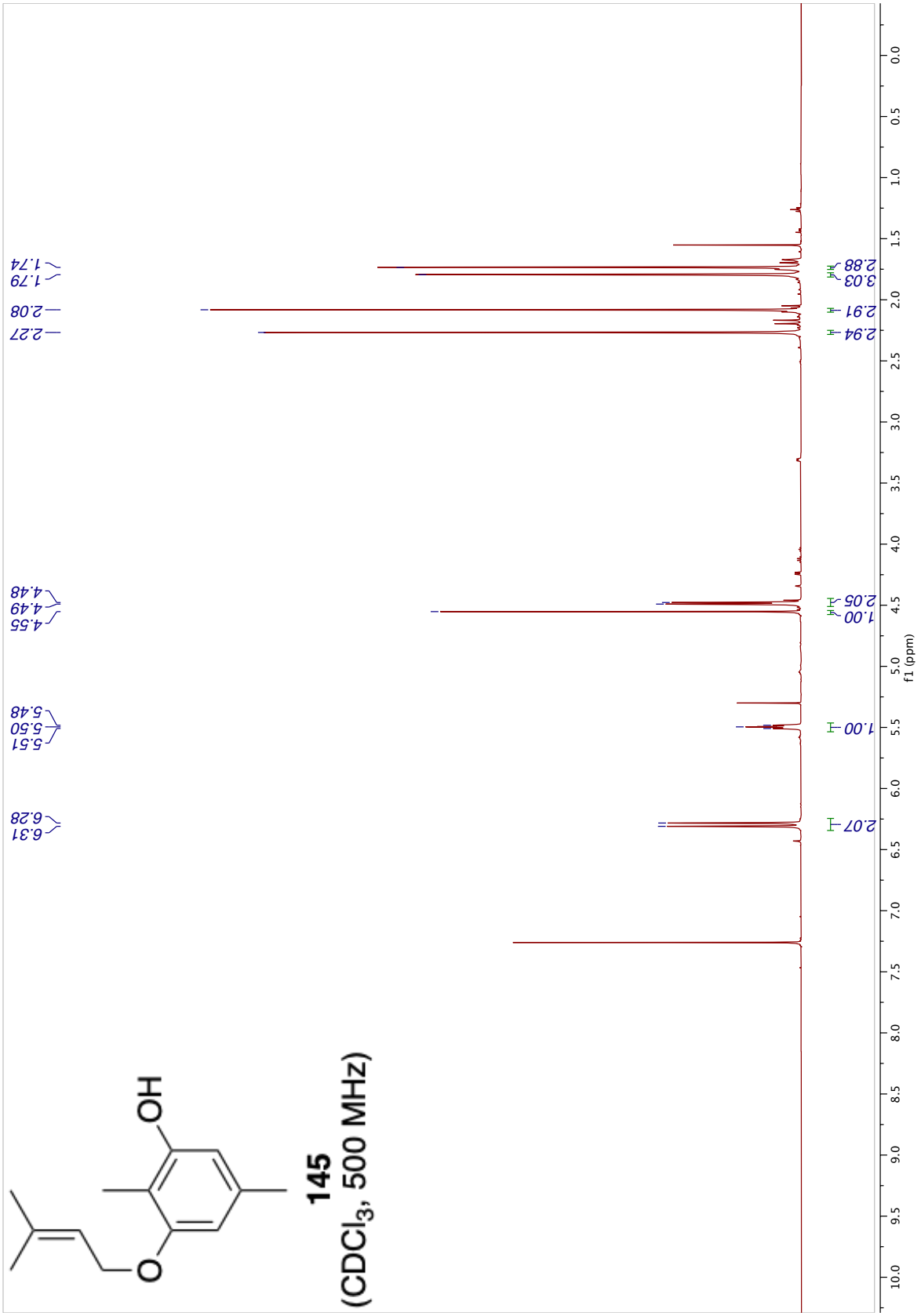

OH
O
OH
133
(CDCl3, 500 MHz)
f1 (ppm)

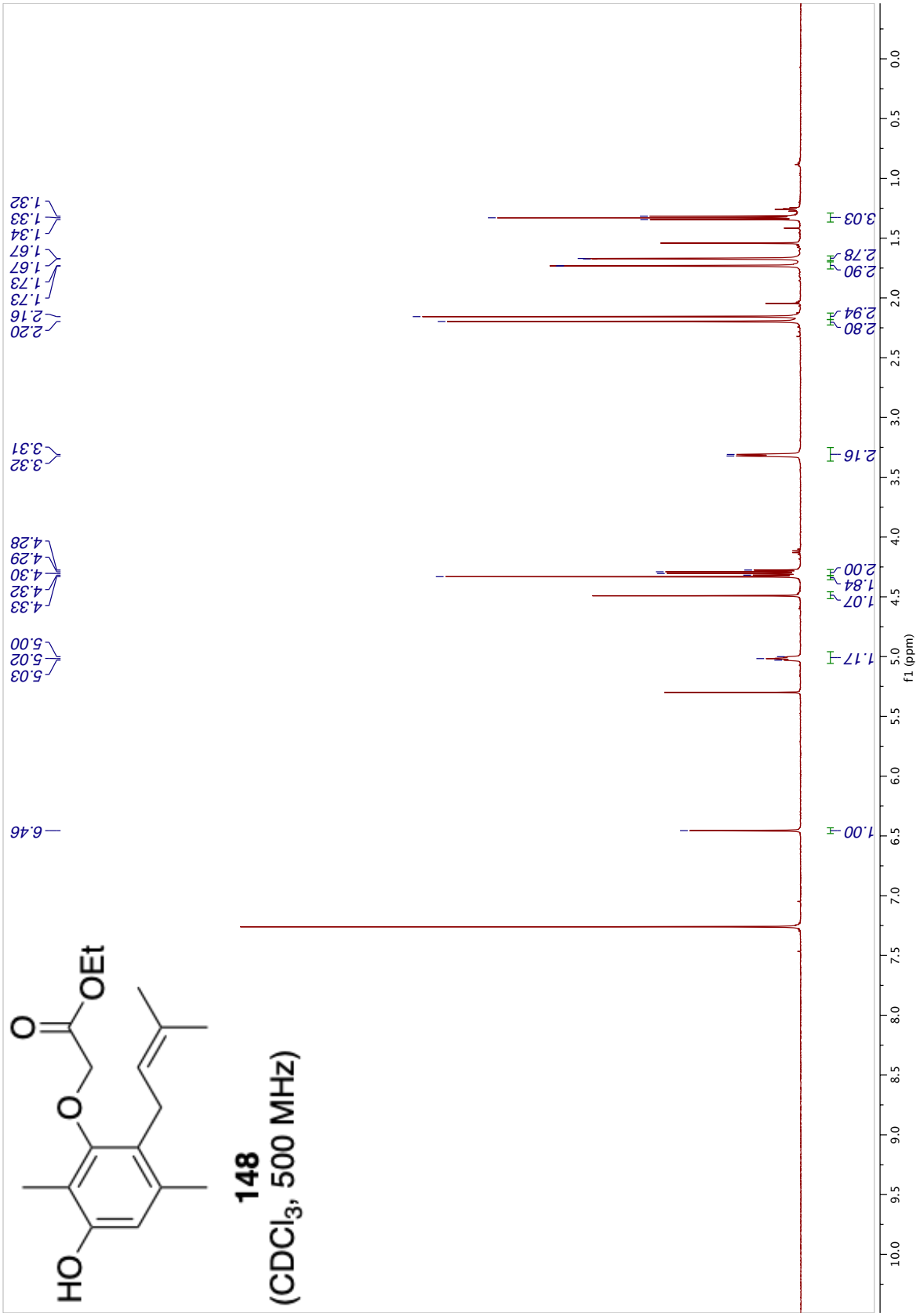

OMe O
Br
137
(CDCl3, 500 MHz)
7.29
3.90
3.88
3.87
3.84
3.80
3.73
3.71
3.69
3.61
3.57
3.55
3.53
3.49
3.48
3.44
2.91
2.87
2.85
2.79
2.77
2.73
2.71
2.35
2.34
2.31
2.30
2.22
1.79
1.75
1.73
1.71
1.30
1.28
0.91
3.00
1.05
2.98
1.27
1.03
1.01
2.00
0.98
1.06
2.83
1.35
f1 (ppm)

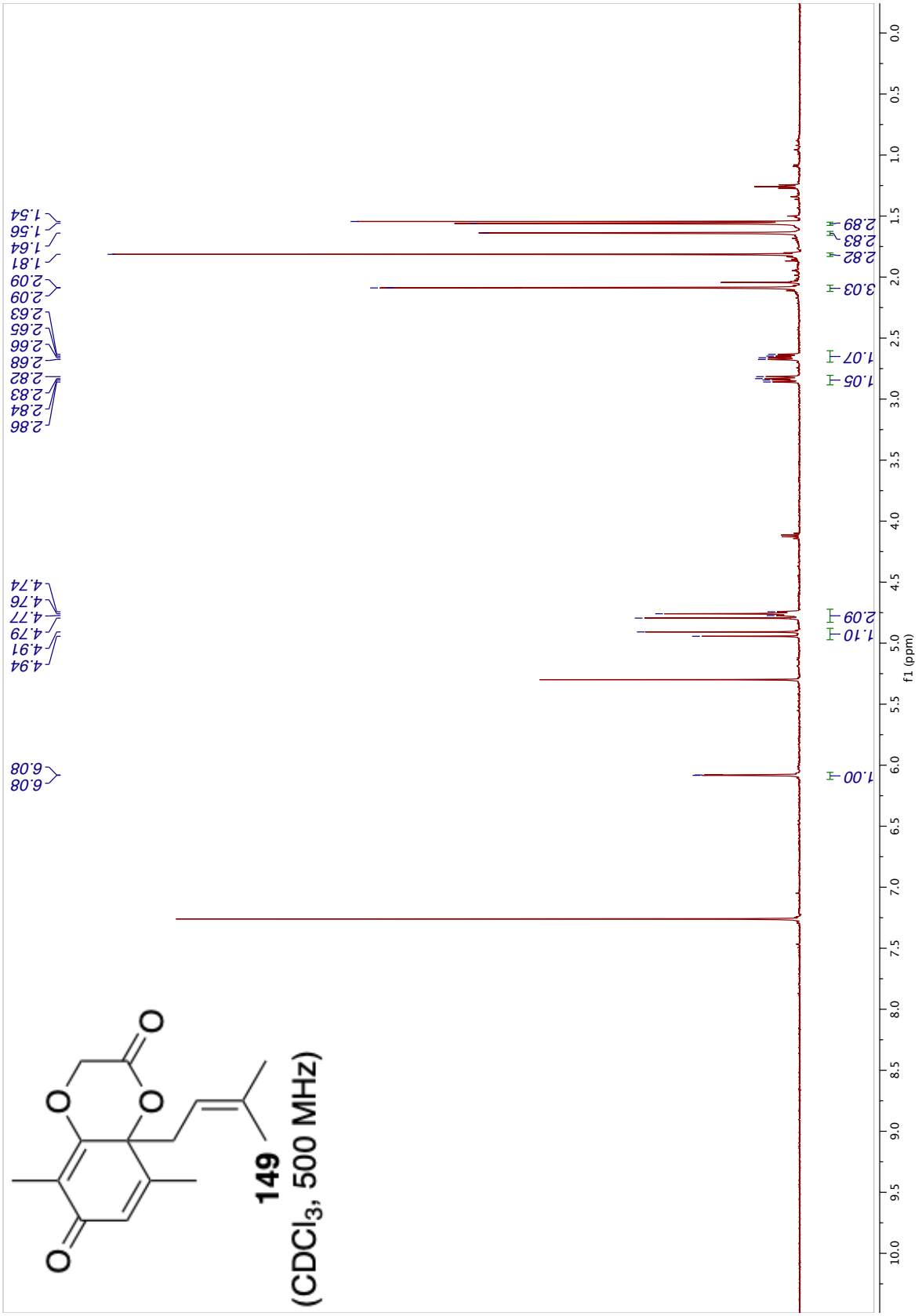

OMe O
138
(CDCl3, 500 MHz)
f1 (ppm)

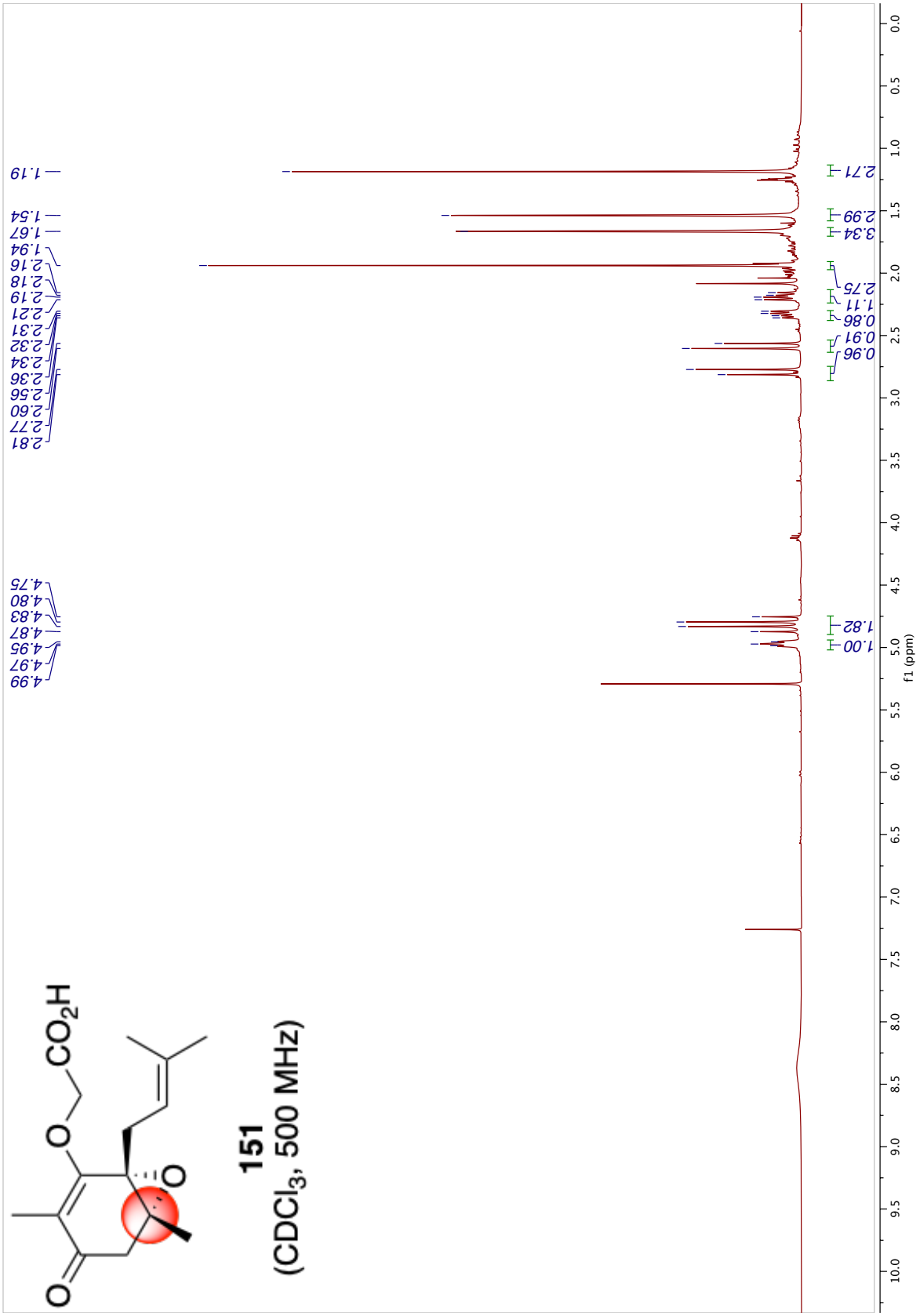

136
(CDCl3, 500 MHz)
OH
O
7.55
4.51
4.51
4.50
4.50
4.49
4.49
3.41
3.39
3.36
2.95
2.88
2.88
2.77
2.76
2.74
2.73
2.35
2.32
2.29
2.26
2.19
1.79
1.78
1.75
1.72
1.71
1.26
1.24
3.14
0.96
2.88
0.93
2.69
1.01
0.95
1.73
0.81
f1 (ppm)

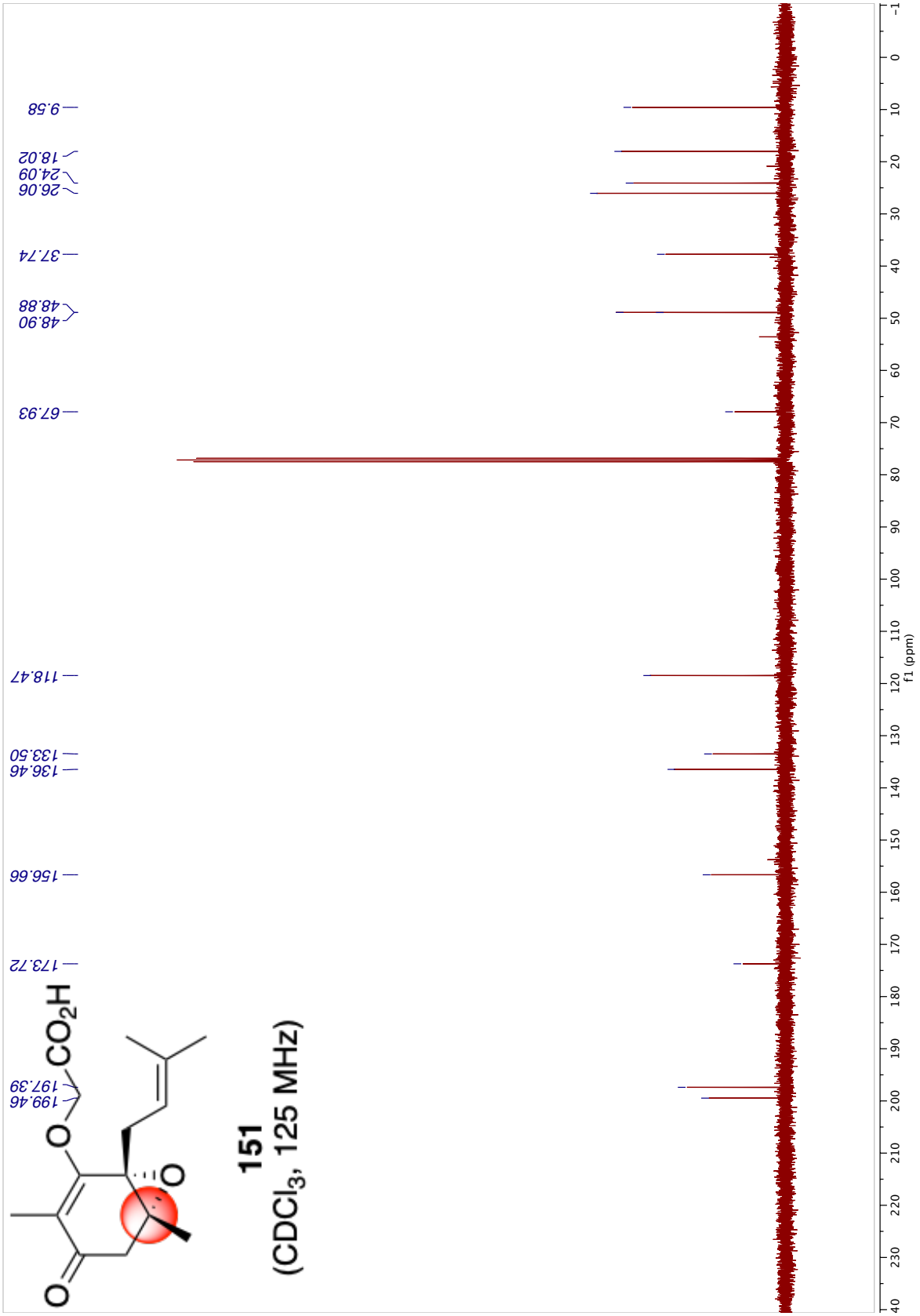

OMe O
Cl
140
(CDCl3, 500 MHz)
7.29
0.90
3.00
1.03
2.94
1.19
1.00
1.04
3.25
2.27
2.94
f1 (ppm)

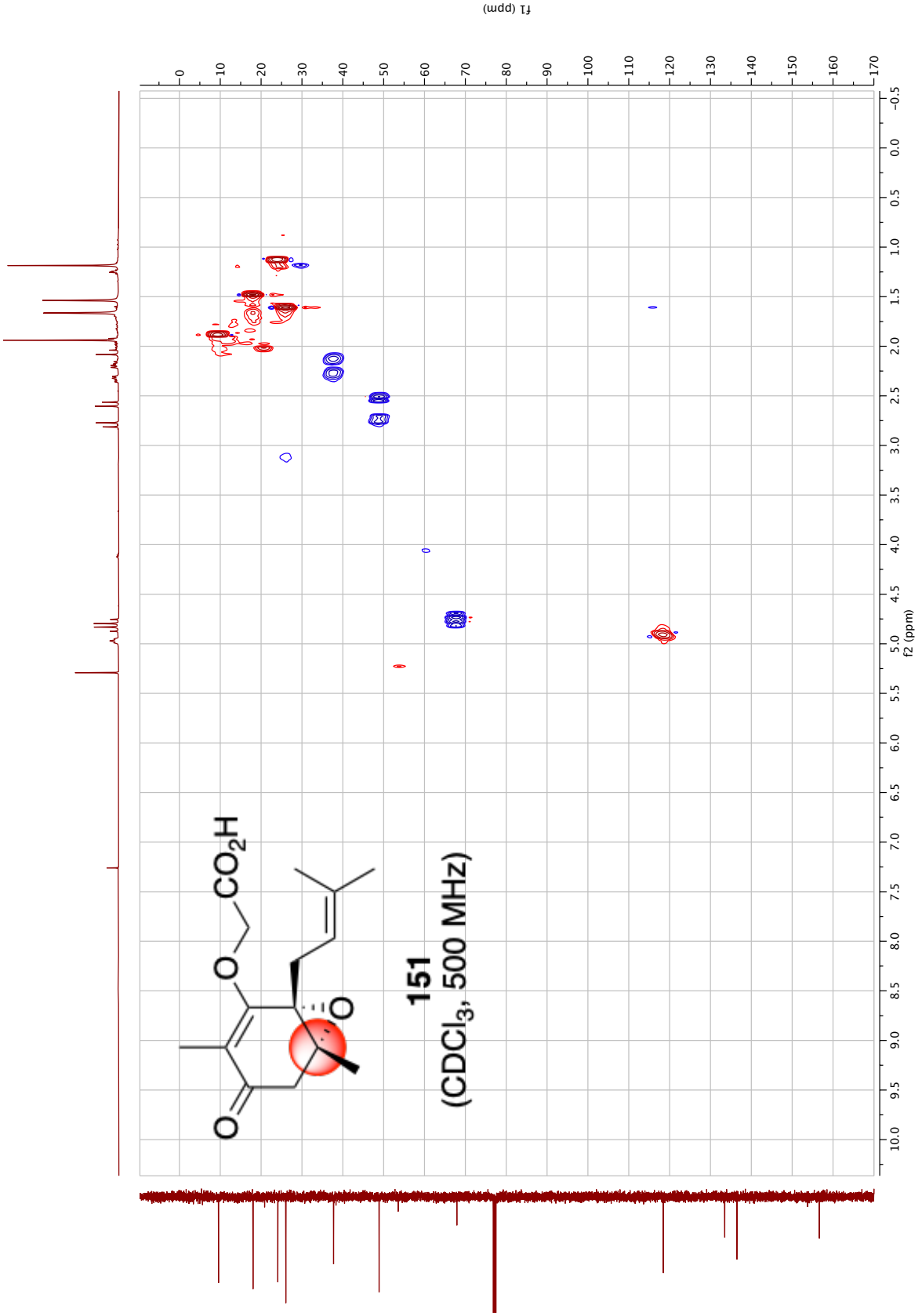

OH
O
145
(CDCl3, 500 MHz)
6.31
6.28
5.51
5.50
5.48
4.55
4.49
4.48
2.08
2.27
1.79
1.74
2.07
1.00
1.00
2.05
2.88
3.03
2.91
2.94
f1 (ppm)

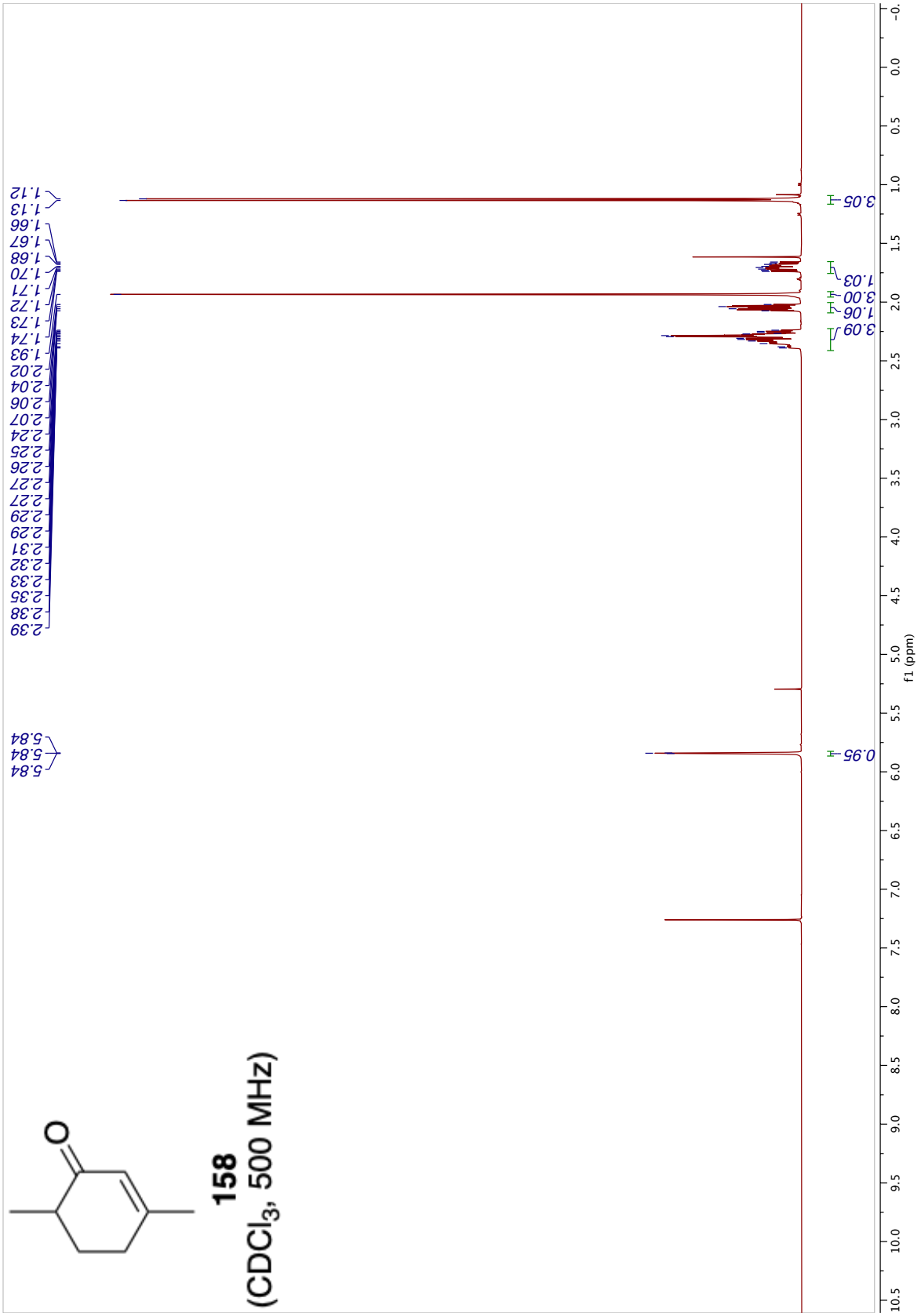

148
(CDCl3, 500 MHz)
HO
O
O
OEt
6.46
5.03
5.02
5.00
4.33
4.32
4.30
4.29
4.28
3.32
3.31
2.20
2.16
1.73
1.73
1.67
1.67
1.34
1.33
1.32
1.00
1.17
2.16
2.00
1.84
1.07
2.80
2.94
2.78
2.90
3.03
f1 (ppm)

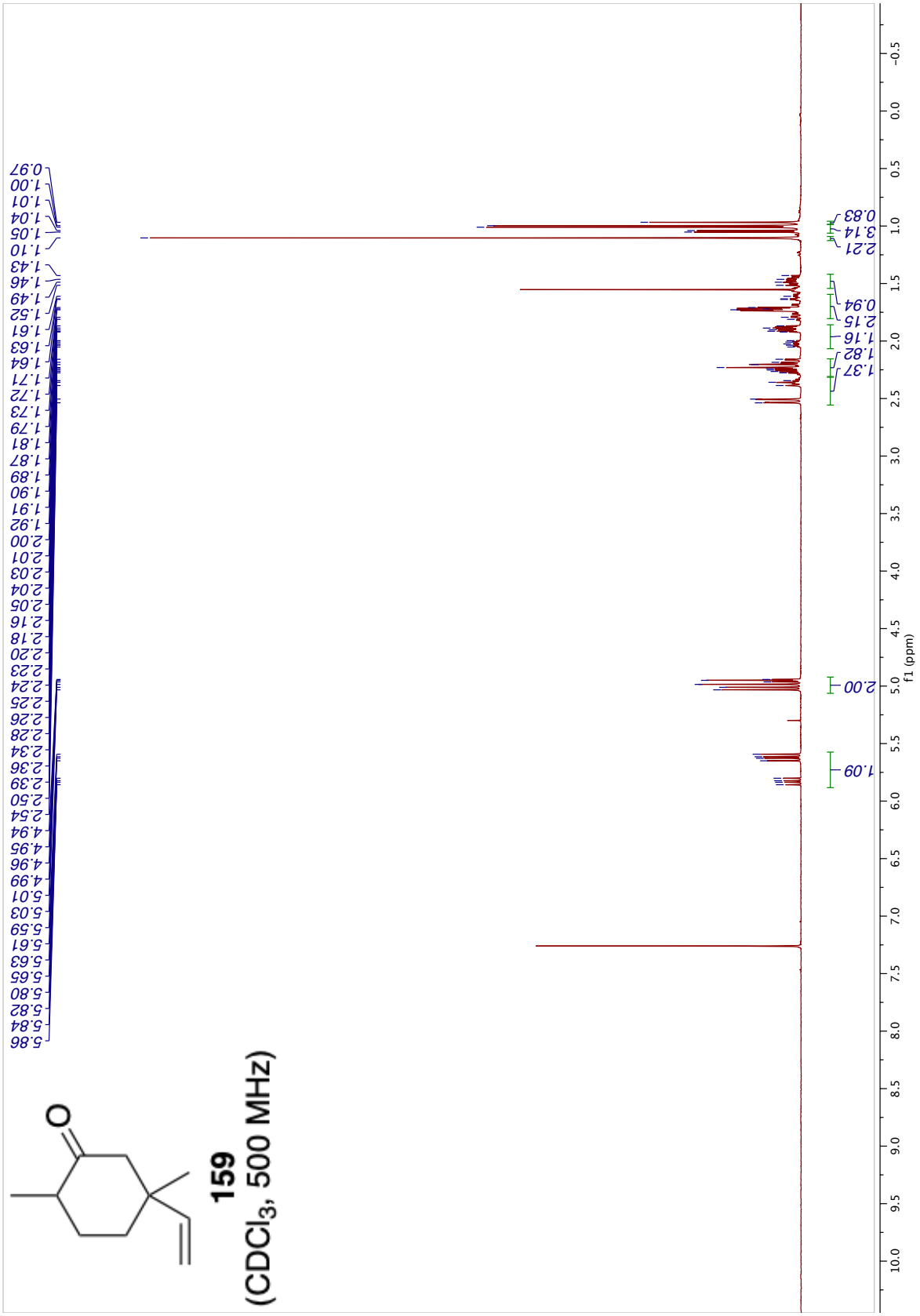

149
(CDCl3, 500 MHz)
O
O
O
O
6.08
6.08
4.94
4.91
4.79
4.77
4.76
4.74
2.86
2.84
2.83
2.82
2.68
2.66
2.65
2.63
2.09
1.81
1.64
1.56
1.54
1.00
1.10
2.09
1.05
1.07
3.03
2.82
2.83
2.89
f1 (ppm)

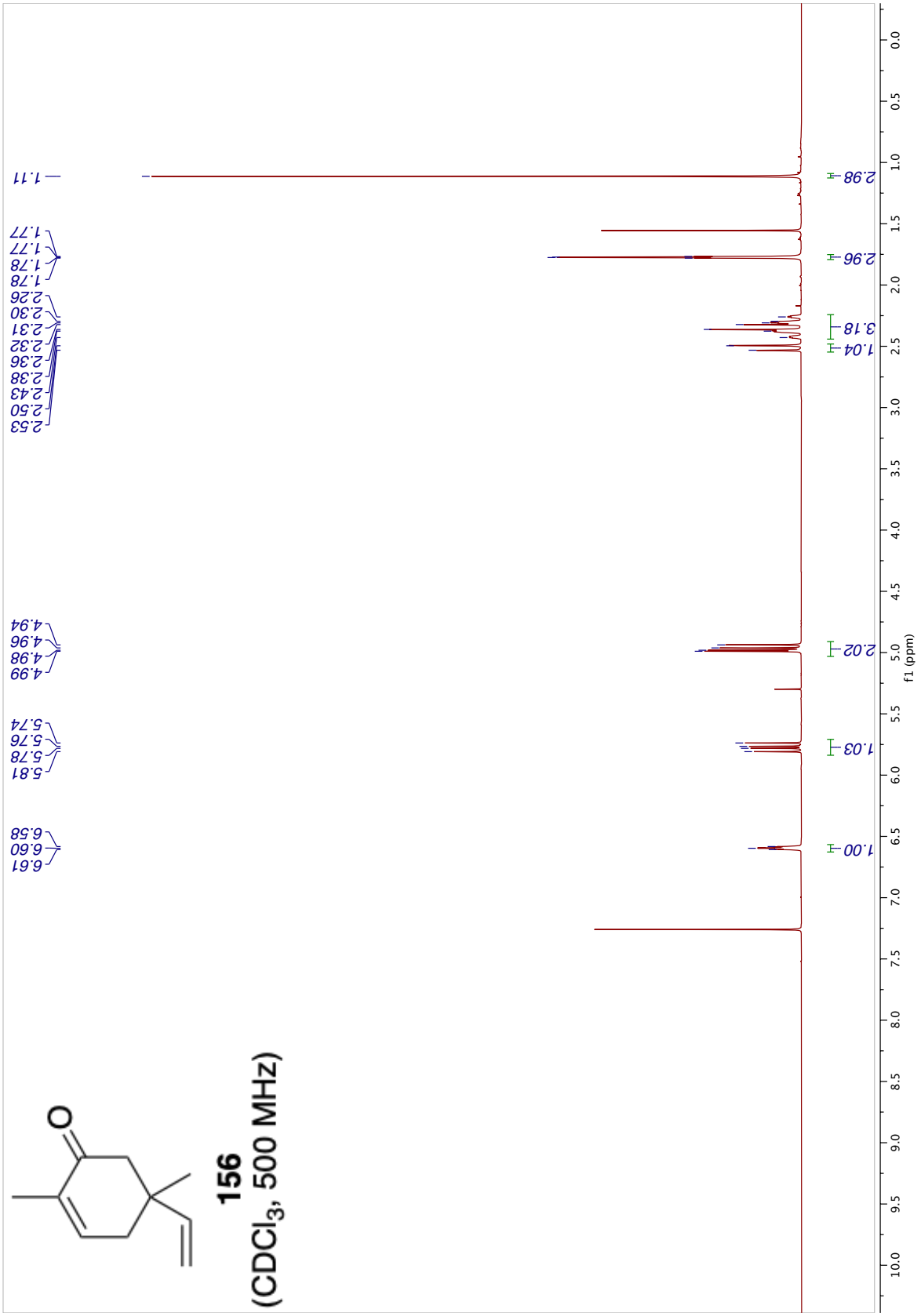

151
(CDCl3, 500 MHz)
CO2H
O
O
O
1.19
1.54
1.67
1.94
2.16
2.18
2.19
2.21
2.31
2.32
2.34
2.36
2.56
2.60
2.77
2.81
4.75
4.80
4.83
4.87
4.95
4.97
4.99
2.71
2.99
3.34
2.75
1.11
0.86
0.91
0.96
1.82
1.00
f1 (ppm)

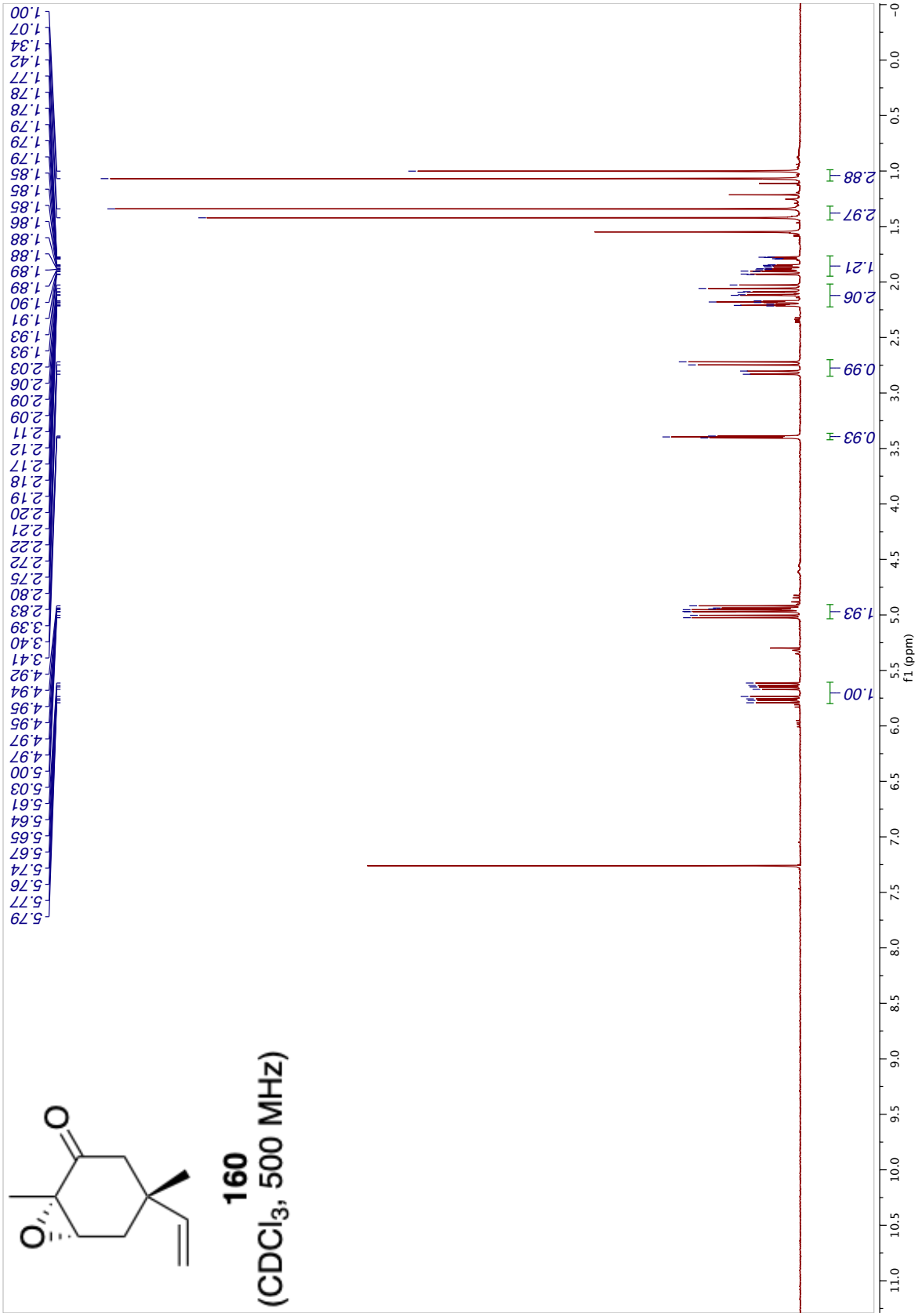

9.58
18.02
24.09
26.06
37.74
48.88
48.90
67.93
118.47
133.50
136.46
156.66
173.72
197.39
199.46
CO2H
O
O
O
151
(CDCl3, 125 MHz)
f1 (ppm)

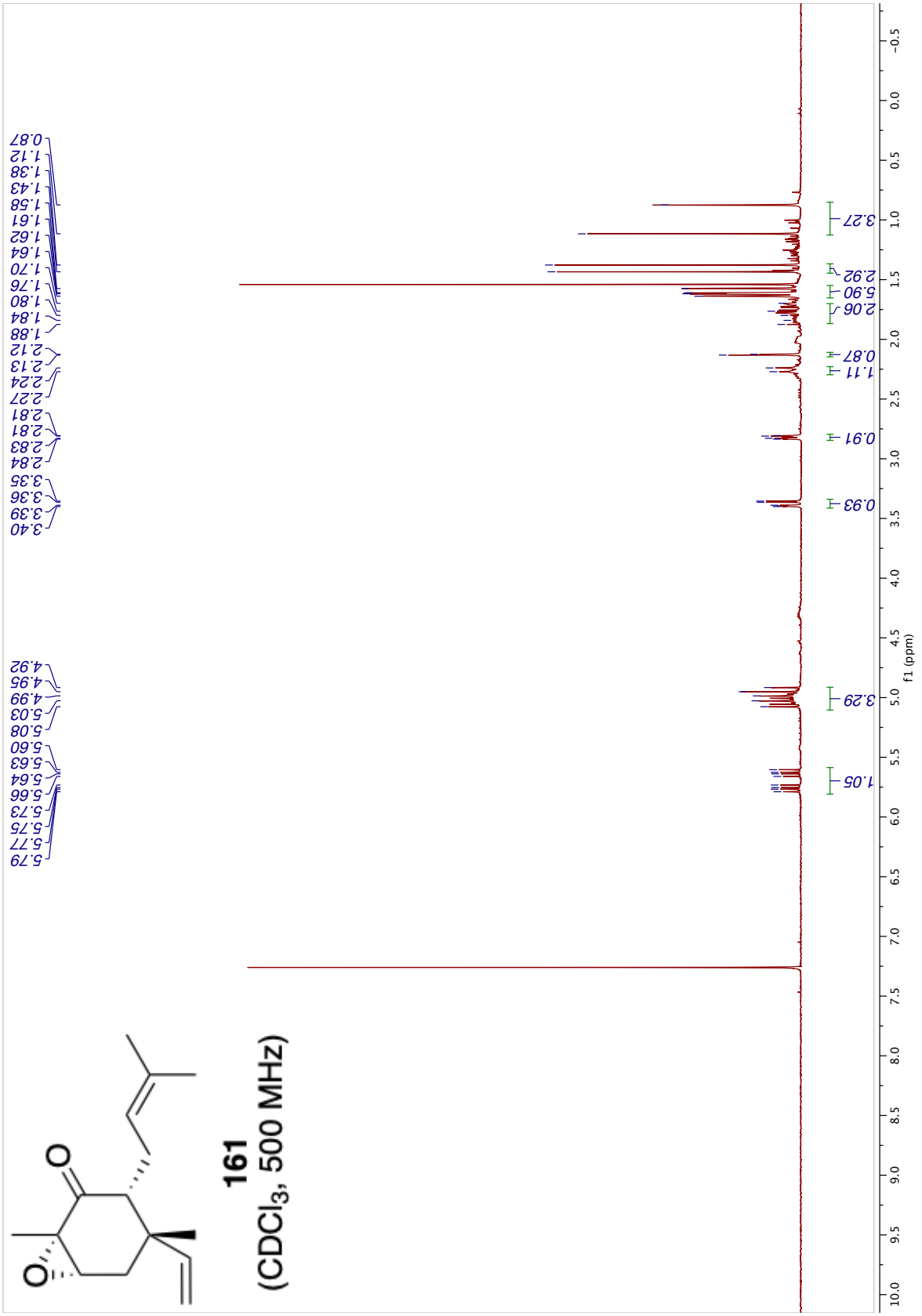

f1 (ppm)
f2 (ppm)
CO2H
O
O
O
151
(CDCl3, 500 MHz)

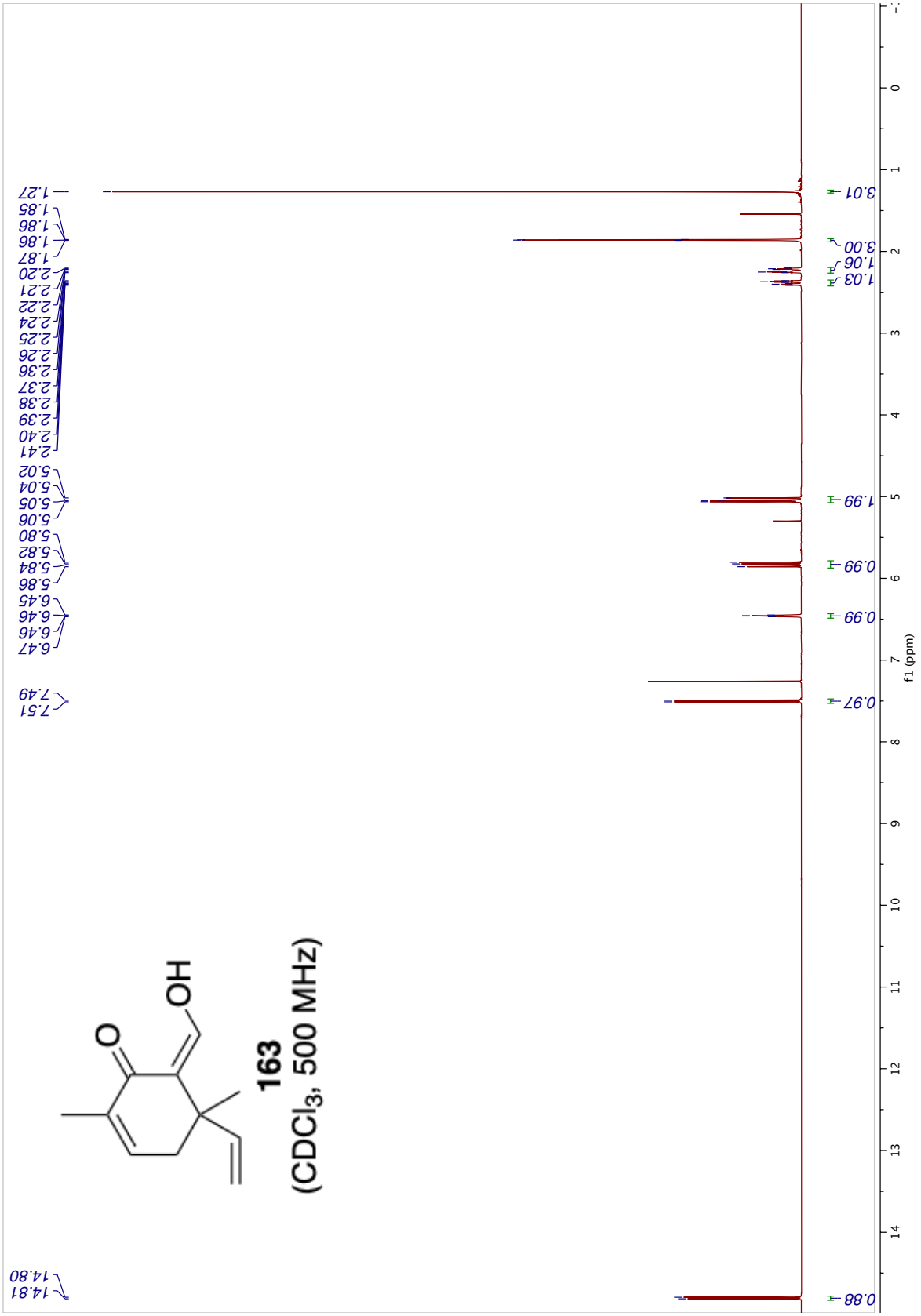

158
(CDCl3, 500 MHz)
O
1.12
1.13
1.66
1.67
1.68
1.70
1.71
1.72
1.73
1.74
1.93
2.02
2.04
2.06
2.07
2.24
2.25
2.26
2.27
2.27
2.29
2.29
2.31
2.32
2.33
2.35
2.38
2.39
5.84
5.84
5.84
3.05
1.03
3.00
1.06
3.09
0.95
f1 (ppm)

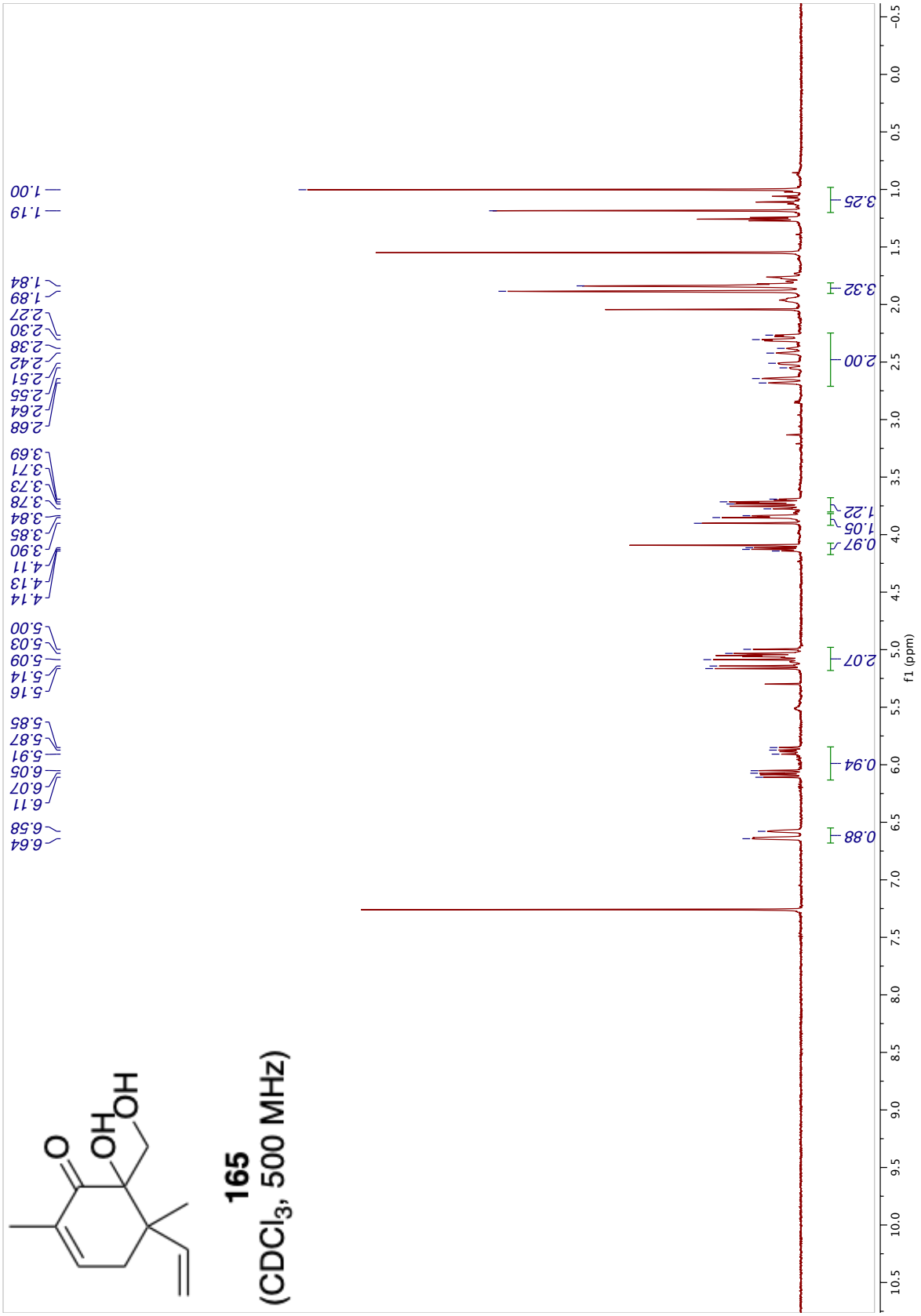

159
(CDCl3, 500 MHz)
O
f1 (ppm)

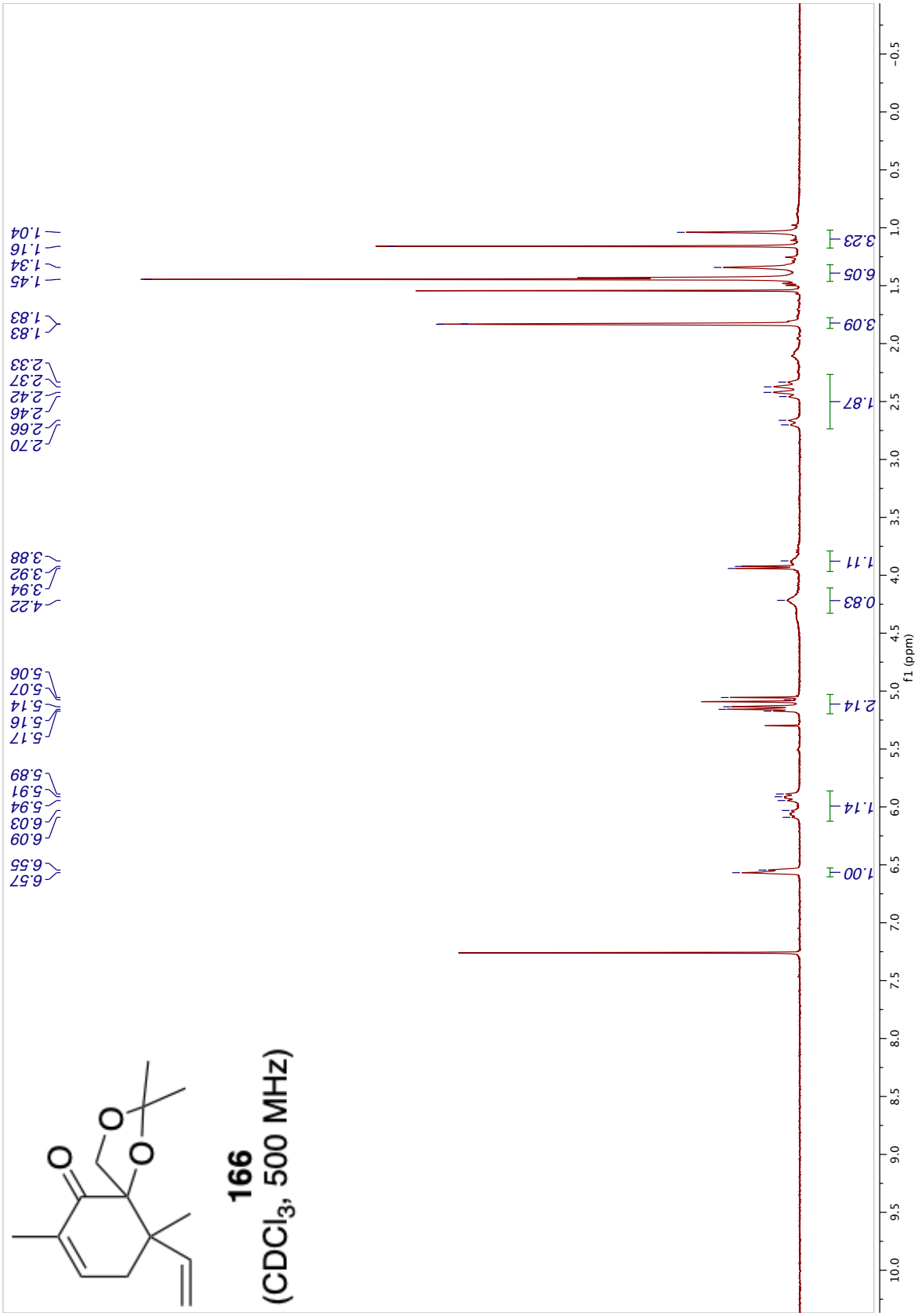

156
(CDCl3, 500 MHz)
O
1.11
1.77
1.77
1.78
1.78
2.26
2.30
2.31
2.32
2.36
2.38
2.43
2.50
2.53
4.94
4.96
4.98
4.99
5.74
5.76
5.78
5.81
6.58
6.60
6.61
1.00
1.03
2.02
1.04
3.18
2.96
2.98
f1 (ppm)

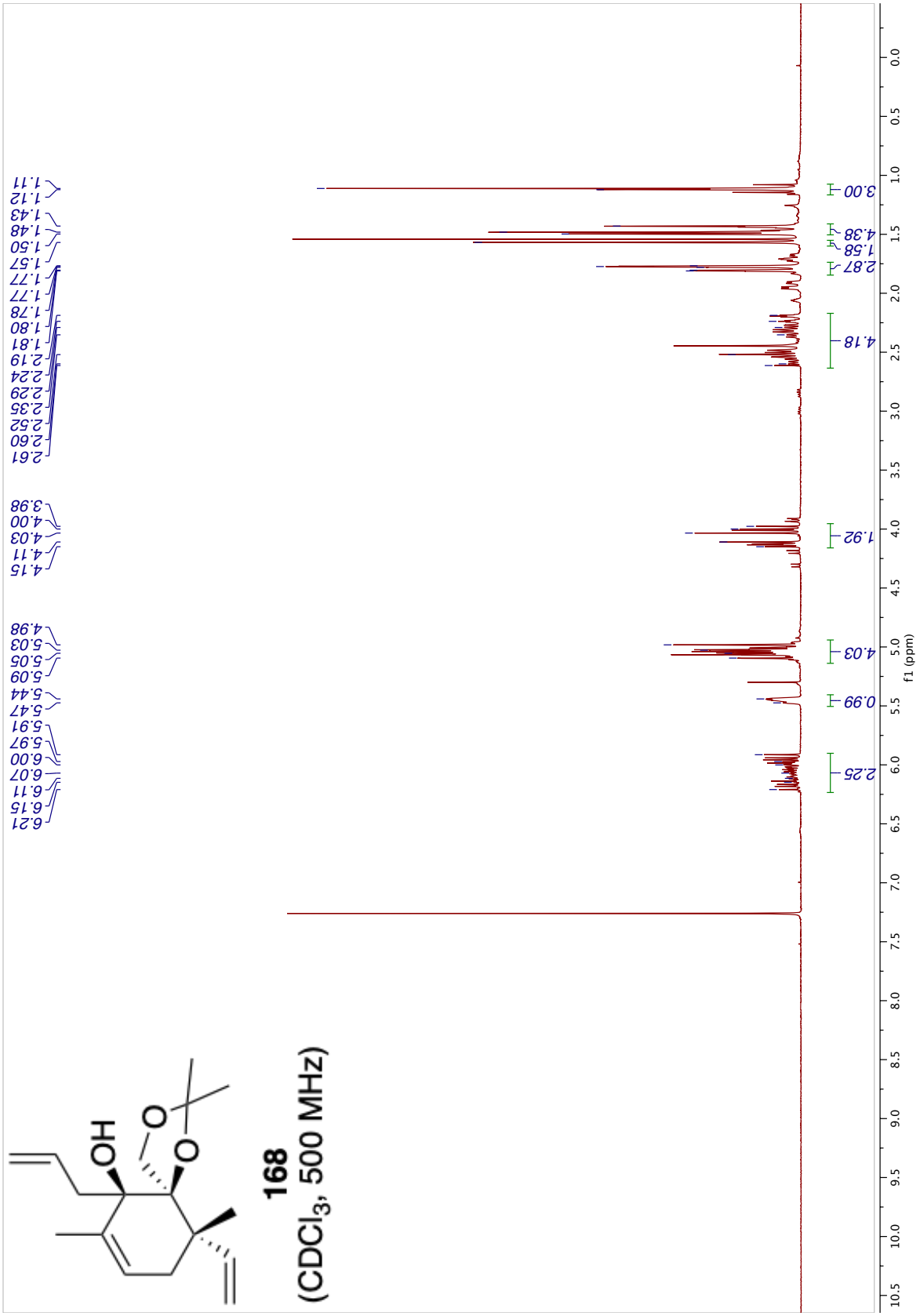

160
(CDCl3, 500 MHz)
2.88
2.97
1.21
2.06
0.99
0.93
1.93
1.00
f1 (ppm)

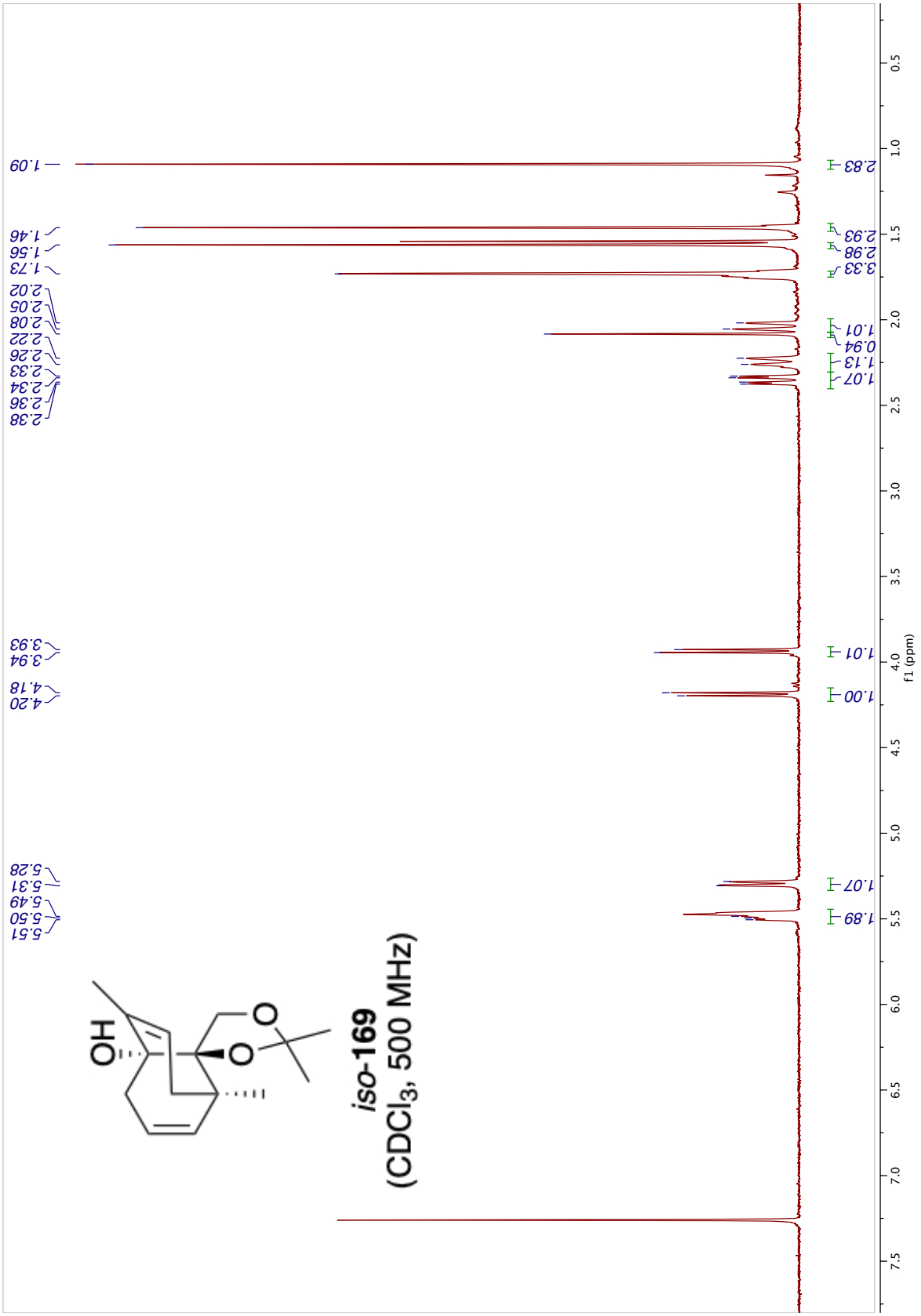

161
(CDCl3, 500 MHz)
O
O
0.87
1.12
1.38
1.43
1.58
1.61
1.62
1.64
1.70
1.76
1.80
1.84
1.88
2.12
2.13
2.24
2.27
2.81
2.81
2.83
2.84
3.35
3.36
3.39
3.40
4.92
4.95
4.99
5.03
5.08
5.60
5.63
5.64
5.66
5.73
5.75
5.77
5.79
3.27
2.92
5.90
2.06
0.87
1.11
0.91
0.93
3.29
1.05
f1 (ppm)

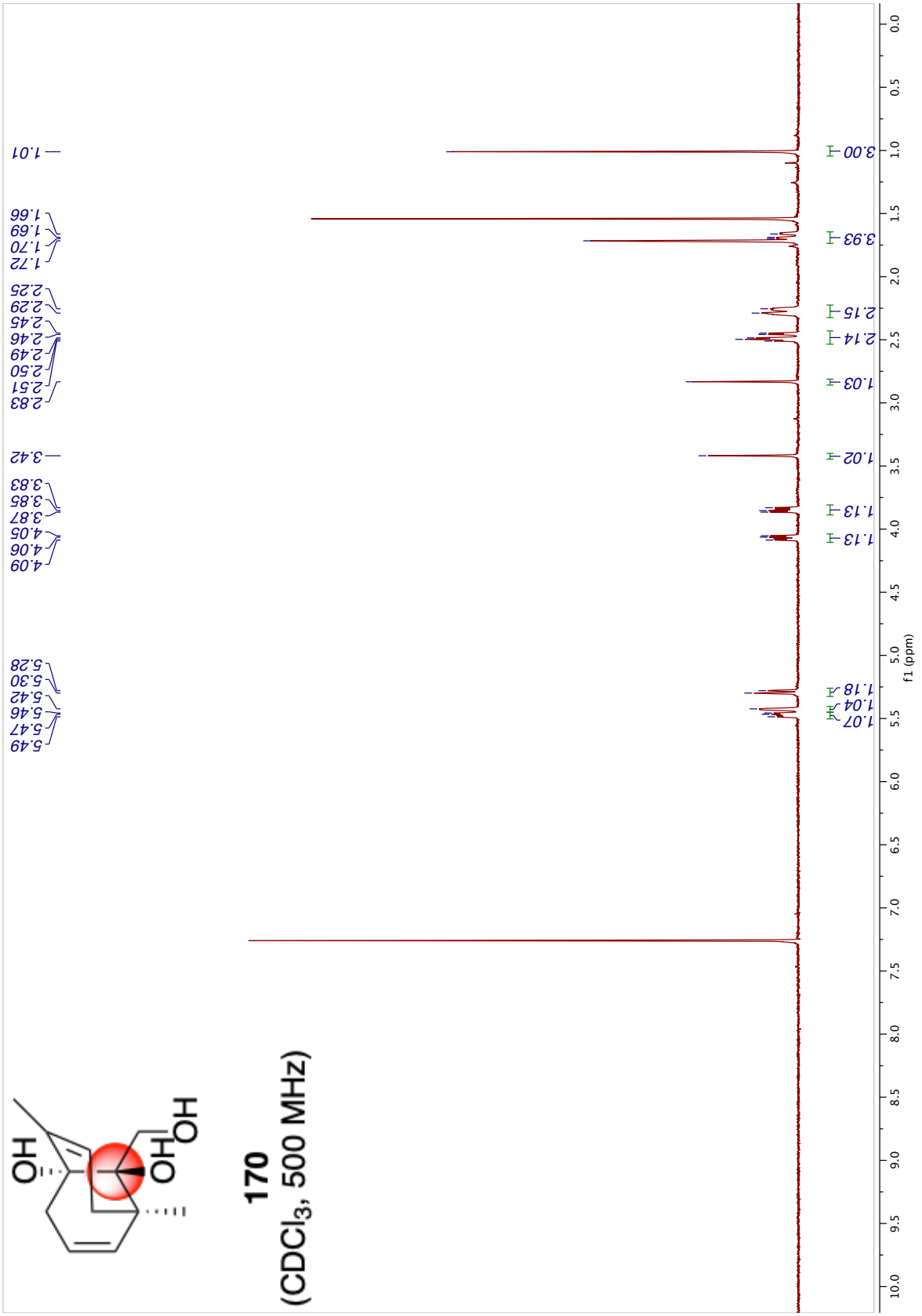

OH
O
163
(CDCl3, 500 MHz)
f1 (ppm)

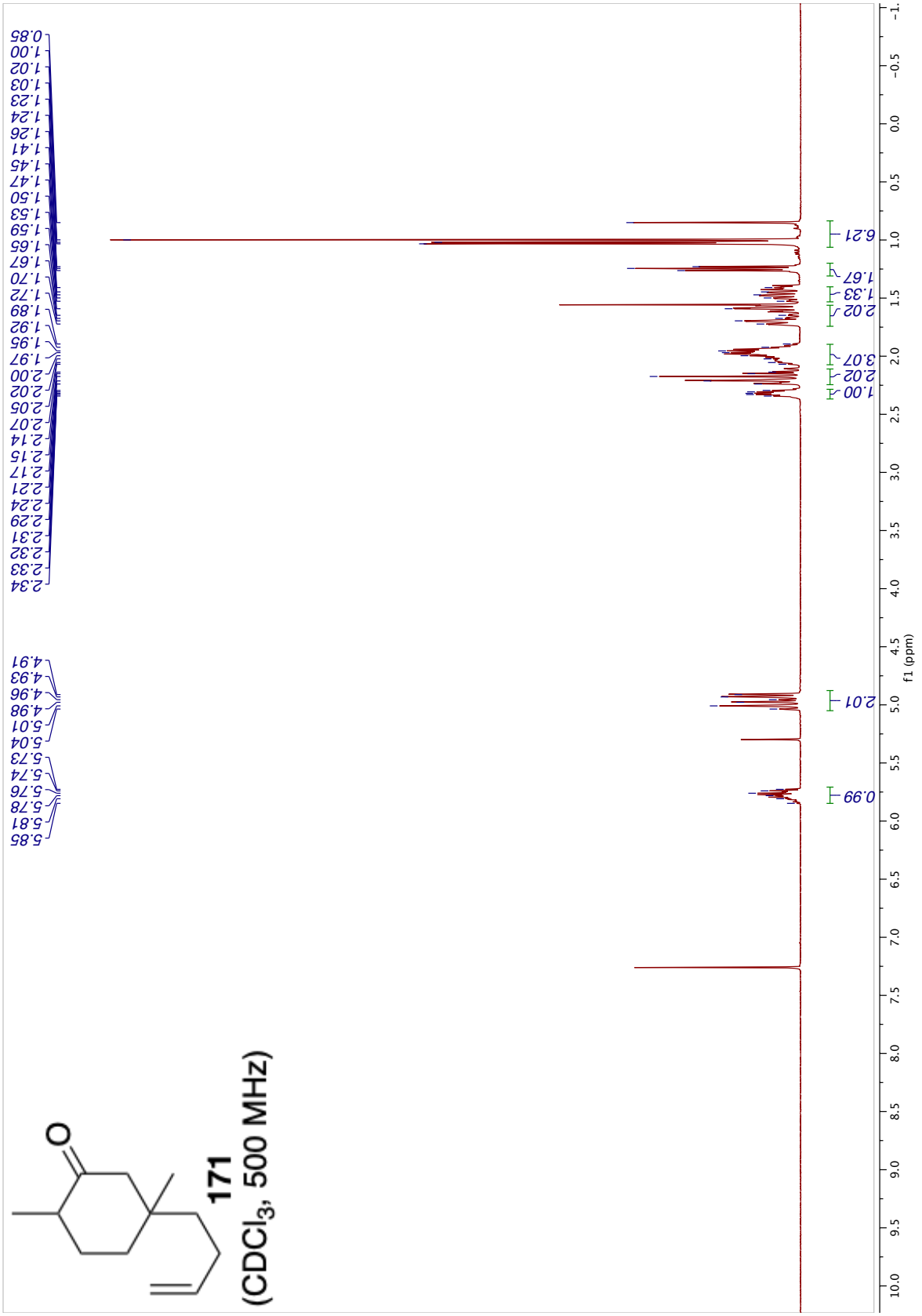

165
(CDCl3, 500 MHz)
O
OH
OH
f1 (ppm)

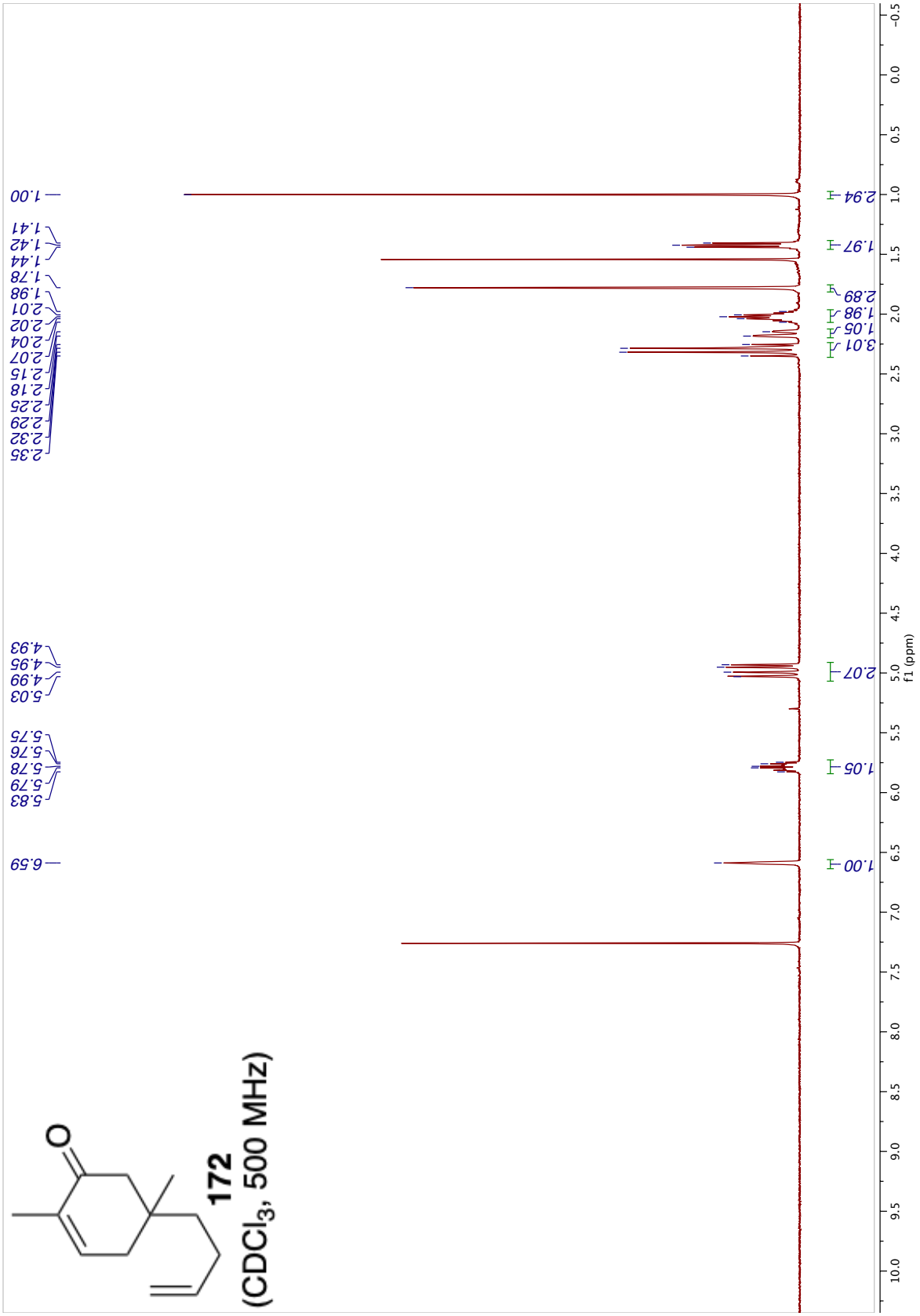

166
(CDCl3, 500 MHz)
f1 (ppm)
1.00
1.14
2.14
0.83
1.11
1.87
3.09
6.05
3.23
6.57
6.55
6.09
6.03
5.94
5.91
5.89
5.17
5.16
5.14
5.07
5.06
4.22
3.94
3.92
3.88
2.70
2.66
2.46
2.42
2.37
2.33
1.83
1.83
1.45
1.34
1.16
1.04

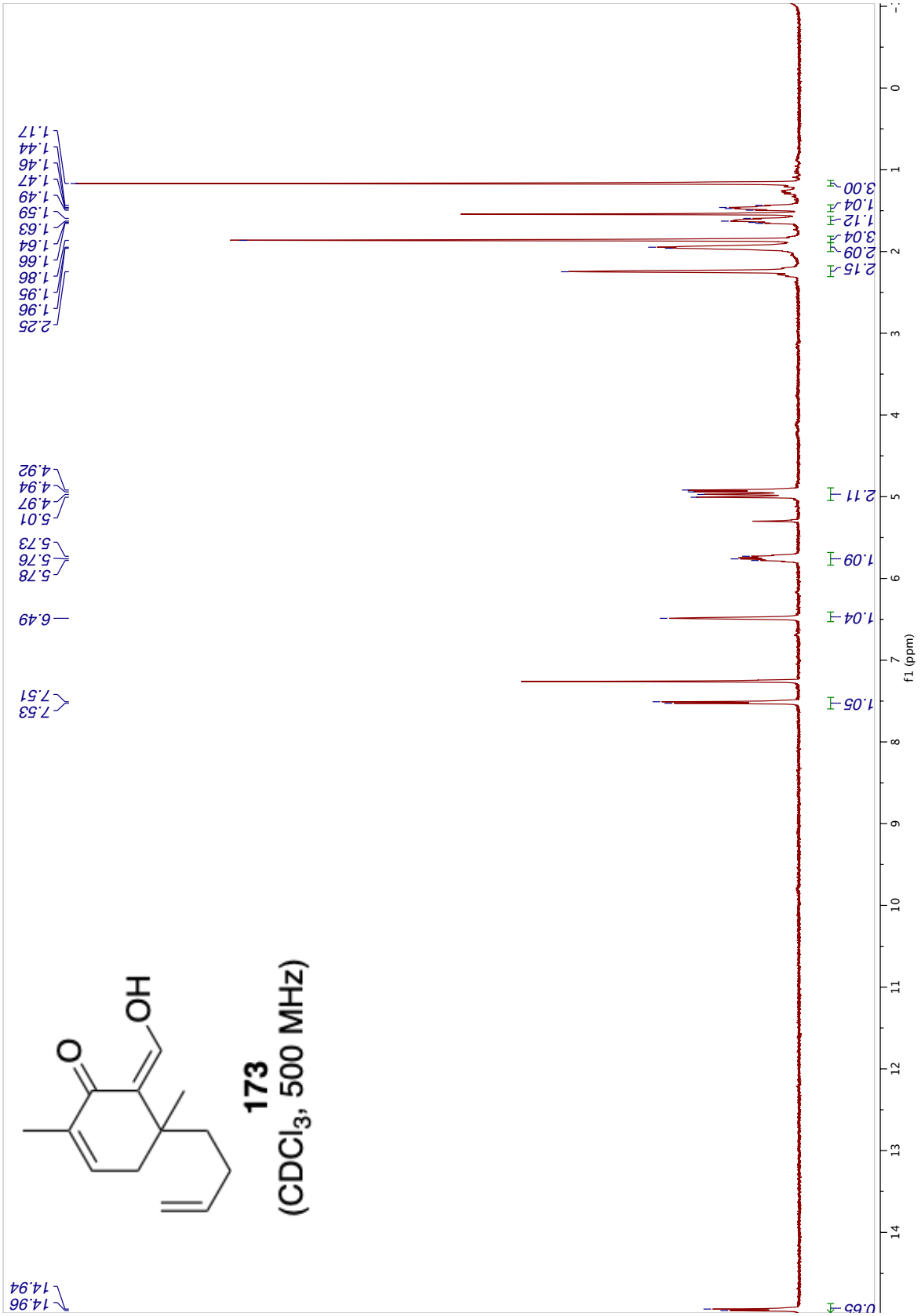

OH
O
O
168
(CDCl3, 500 MHz)
1.11
1.12
1.43
1.48
1.50
1.57
1.77
1.77
1.78
1.80
1.81
2.19
2.24
2.29
2.35
2.52
2.60
2.61
3.98
4.00
4.03
4.11
4.15
4.98
5.03
5.05
5.09
5.44
5.47
5.91
5.97
6.00
6.07
6.11
6.15
6.21
3.00
4.38
1.58
2.87
4.18
1.92
4.03
0.99
2.25
f1 (ppm)

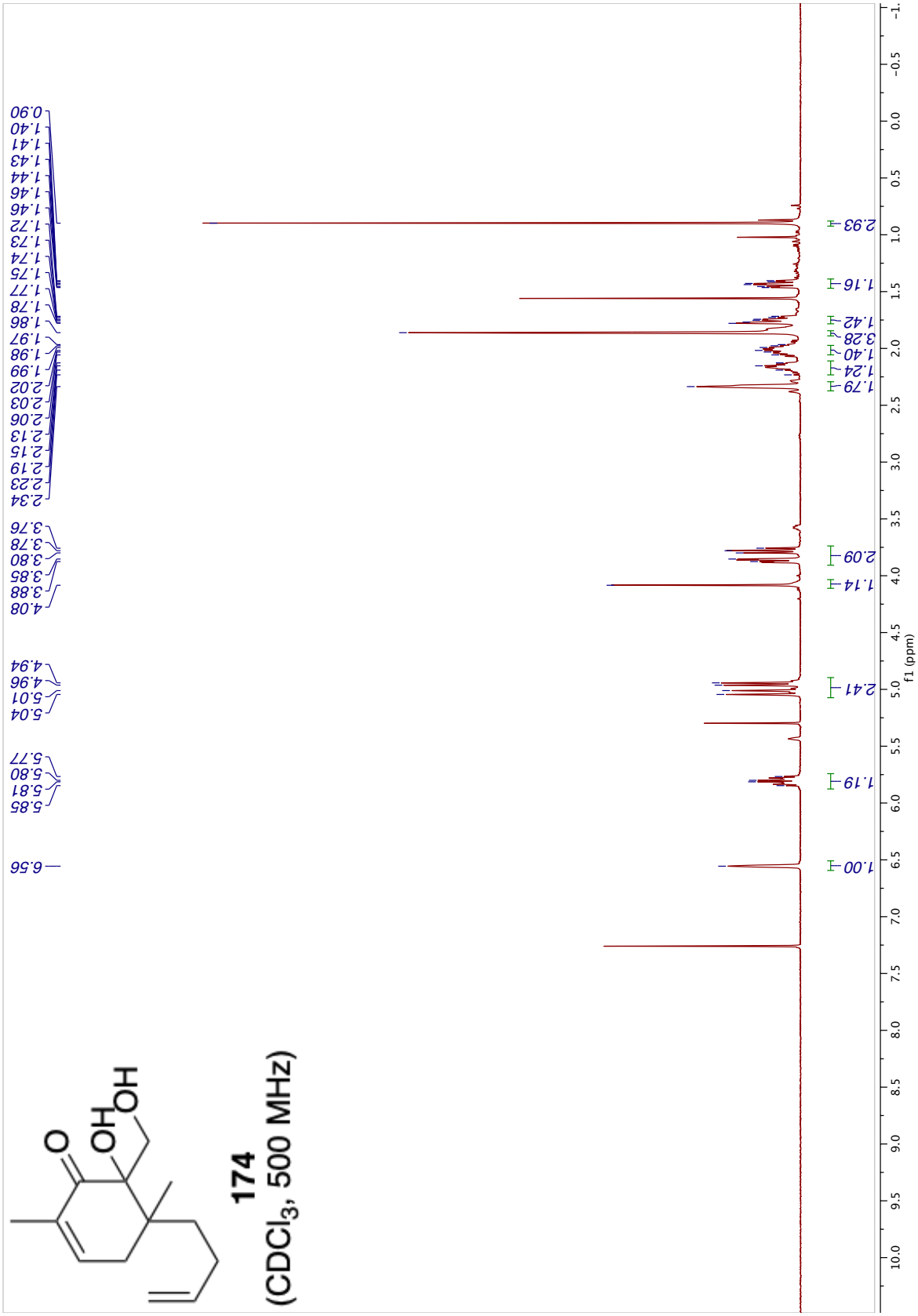

iso-169
(CDCl3, 500 MHz)
OH
O
O
1.09
1.46
1.56
1.73
2.02
2.05
2.08
2.22
2.26
2.33
2.34
2.36
2.38
3.94
3.93
4.20
4.18
5.28
5.31
5.49
5.50
5.51
2.83
2.93
2.98
3.33
1.01
0.94
1.13
1.07
1.01
1.00
1.07
1.89
f1 (ppm)

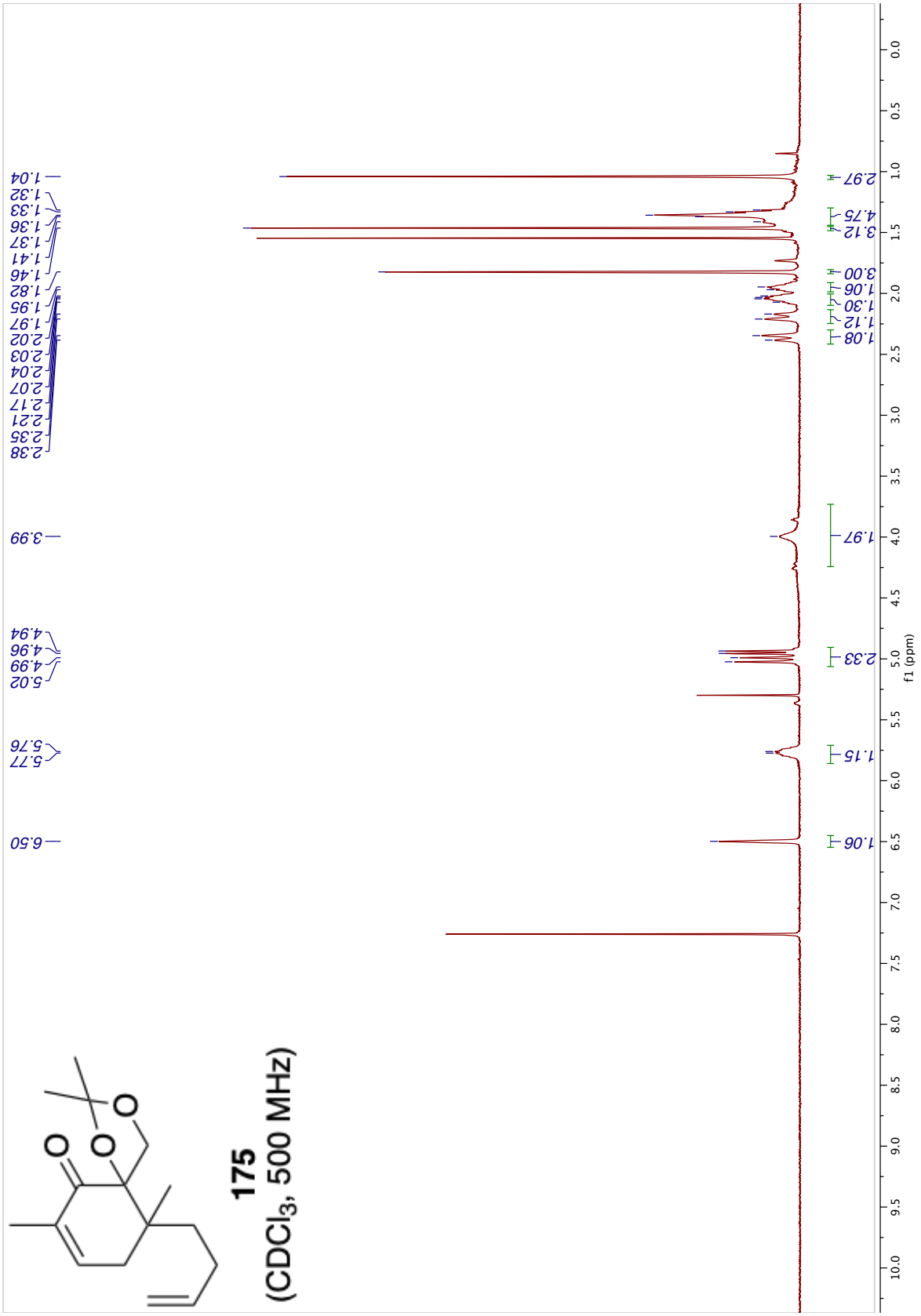

OH
OH
OH
170
(CDCl3, 500 MHz)
1.01
1.66
1.69
1.70
1.72
2.25
2.29
2.45
2.46
2.49
2.50
2.51
2.83
3.42
3.83
3.85
3.87
4.05
4.06
4.09
5.28
5.30
5.42
5.46
5.47
5.49
3.00
3.93
2.15
2.14
1.03
1.02
1.13
1.13
1.18
1.04
1.07
f1 (ppm)

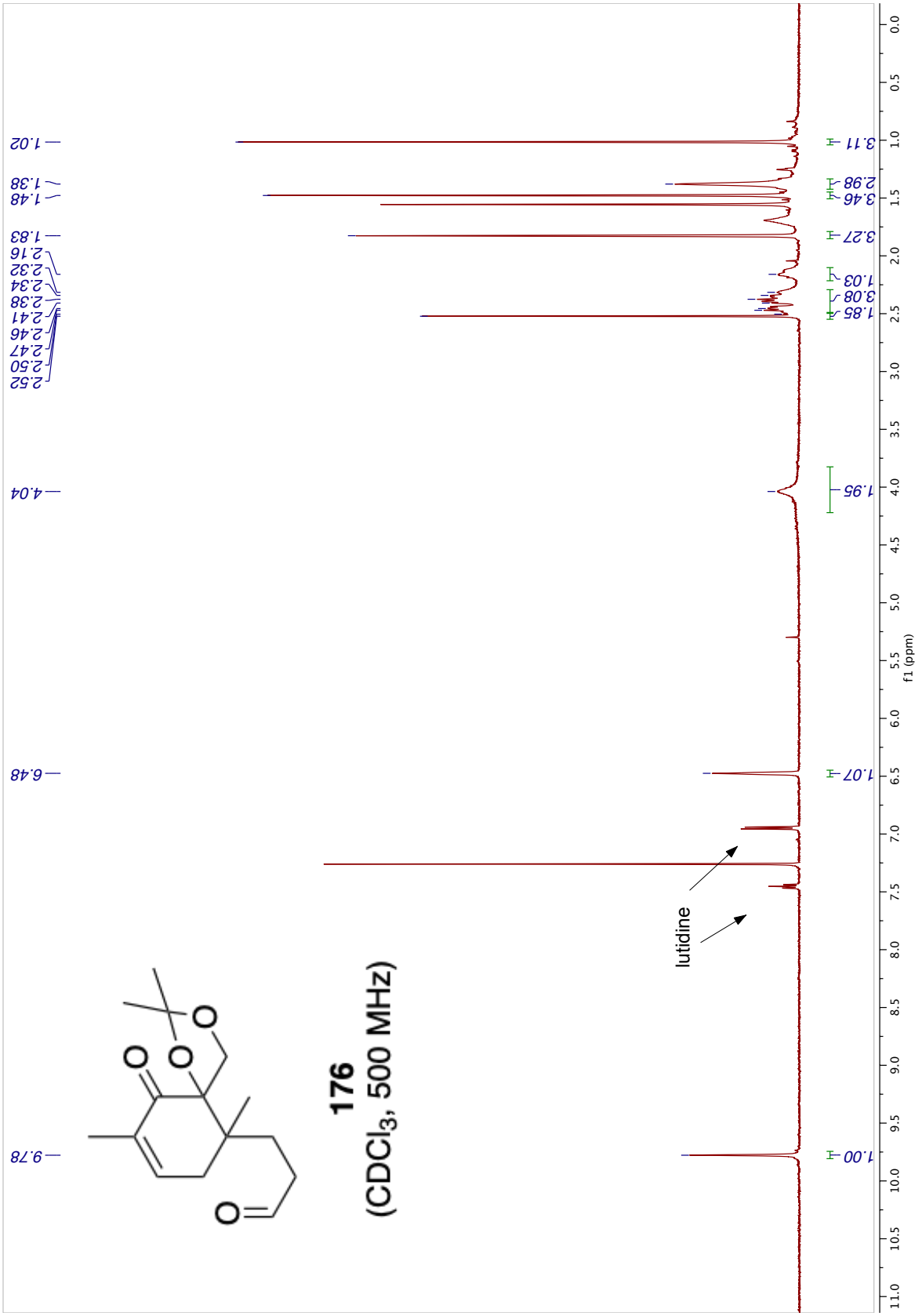

171
(CDCl3, 500 MHz)
O
f1 (ppm)
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.
6.21
1.67
1.33
2.02
3.07
2.02
1.00
2.01
0.99
0.85
1.00
1.02
1.03
1.23
1.24
1.26
1.41
1.45
1.47
1.50
1.53
1.59
1.65
1.67
1.70
1.72
1.89
1.92
1.95
1.97
2.00
2.02
2.05
2.07
2.14
2.15
2.17
2.21
2.24
2.29
2.31
2.32
2.33
2.34
4.91
4.93
4.96
4.98
5.01
5.04
5.73
5.74
5.76
5.78
5.81
5.85

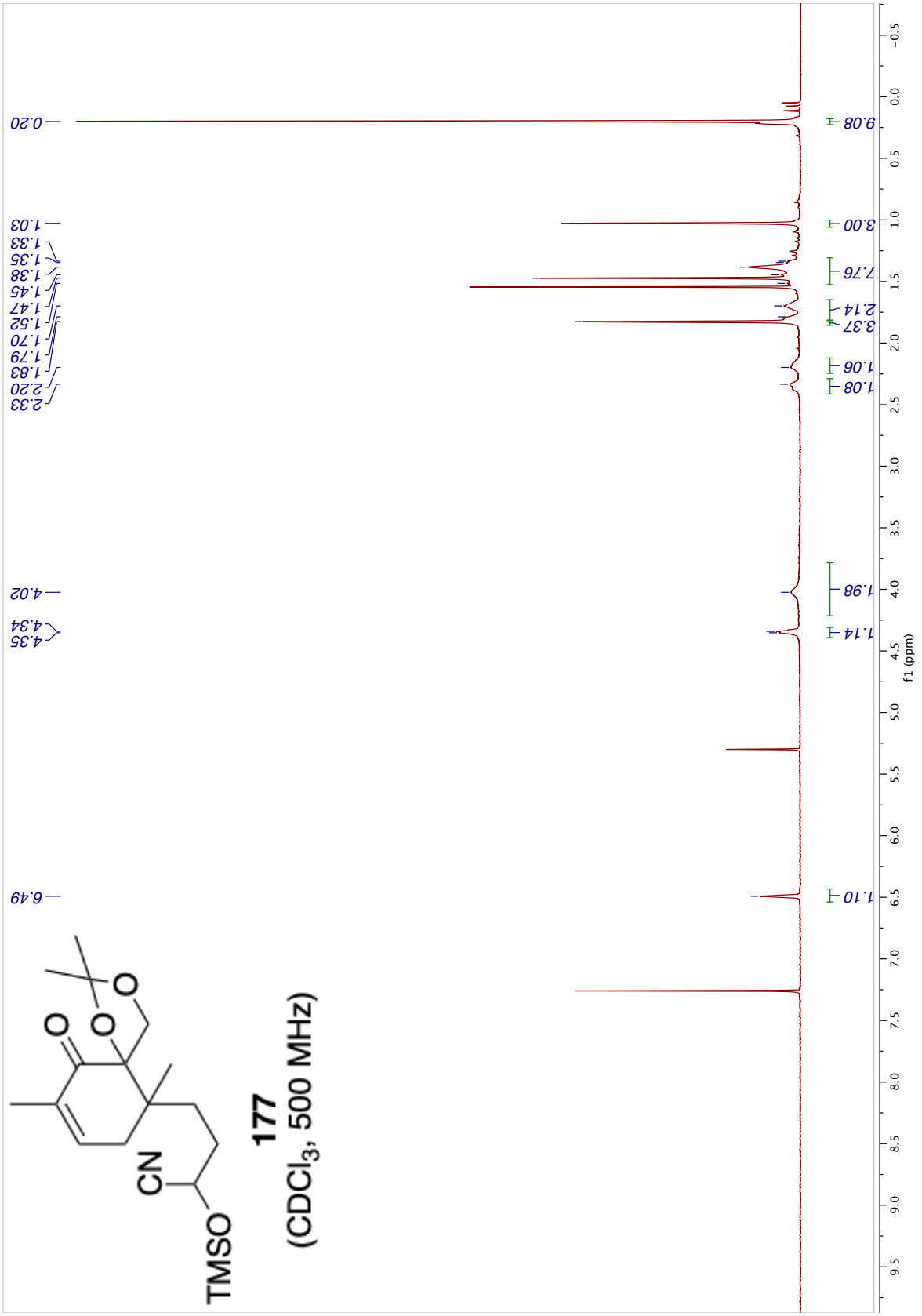

172
(CDCl3, 500 MHz)
O
1.00
1.41
1.42
1.44
1.78
1.98
2.01
2.02
2.04
2.07
2.15
2.18
2.25
2.29
2.32
2.35
4.93
4.95
4.99
5.03
5.75
5.76
5.78
5.79
5.83
6.59
2.94
1.97
2.89
1.98
1.05
3.01
2.07
1.05
1.00
f1 (ppm)

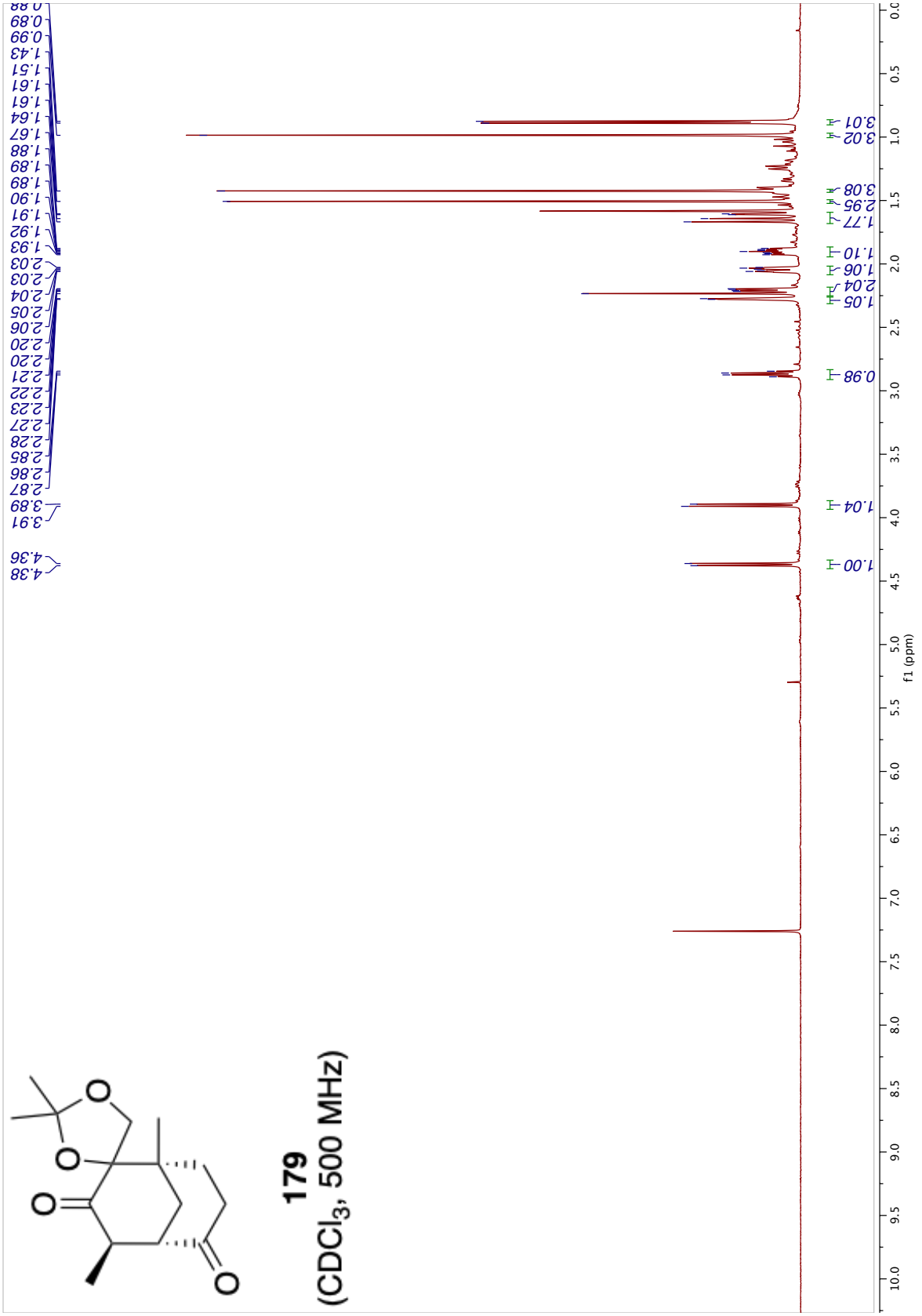

OH
O
173
(CDCl3, 500 MHz)
14.96
14.94
7.53
7.51
6.49
5.78
5.76
5.73
5.01
4.97
4.94
4.92
2.25
1.96
1.95
1.86
1.66
1.64
1.63
1.59
1.49
1.47
1.46
1.44
1.17
0.65
1.05
1.04
1.09
2.11
2.15
2.09
3.04
1.12
1.04
3.00
f1 (ppm)

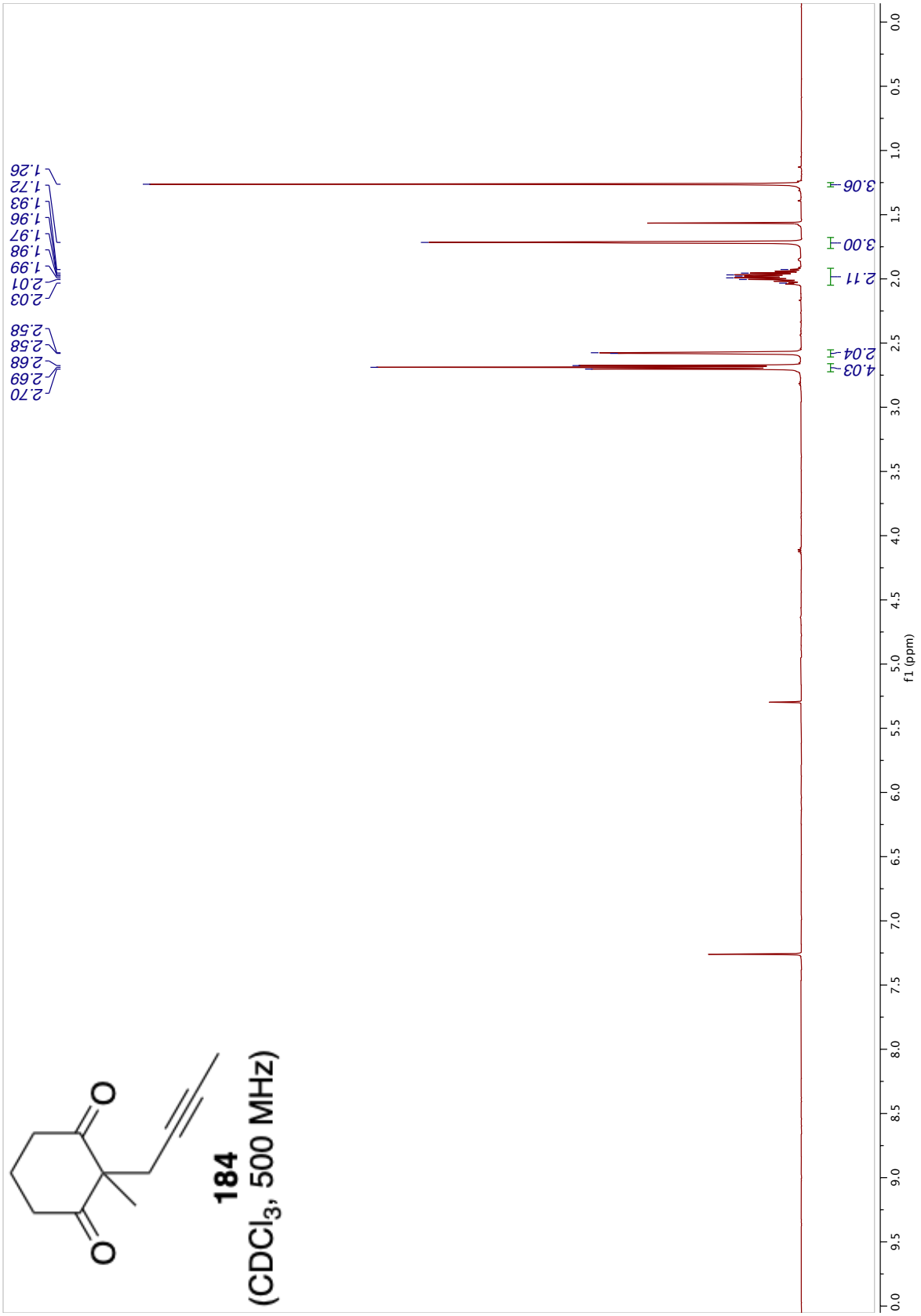

174
(CDCl3, 500 MHz)
OH
OH
O
f1 (ppm)

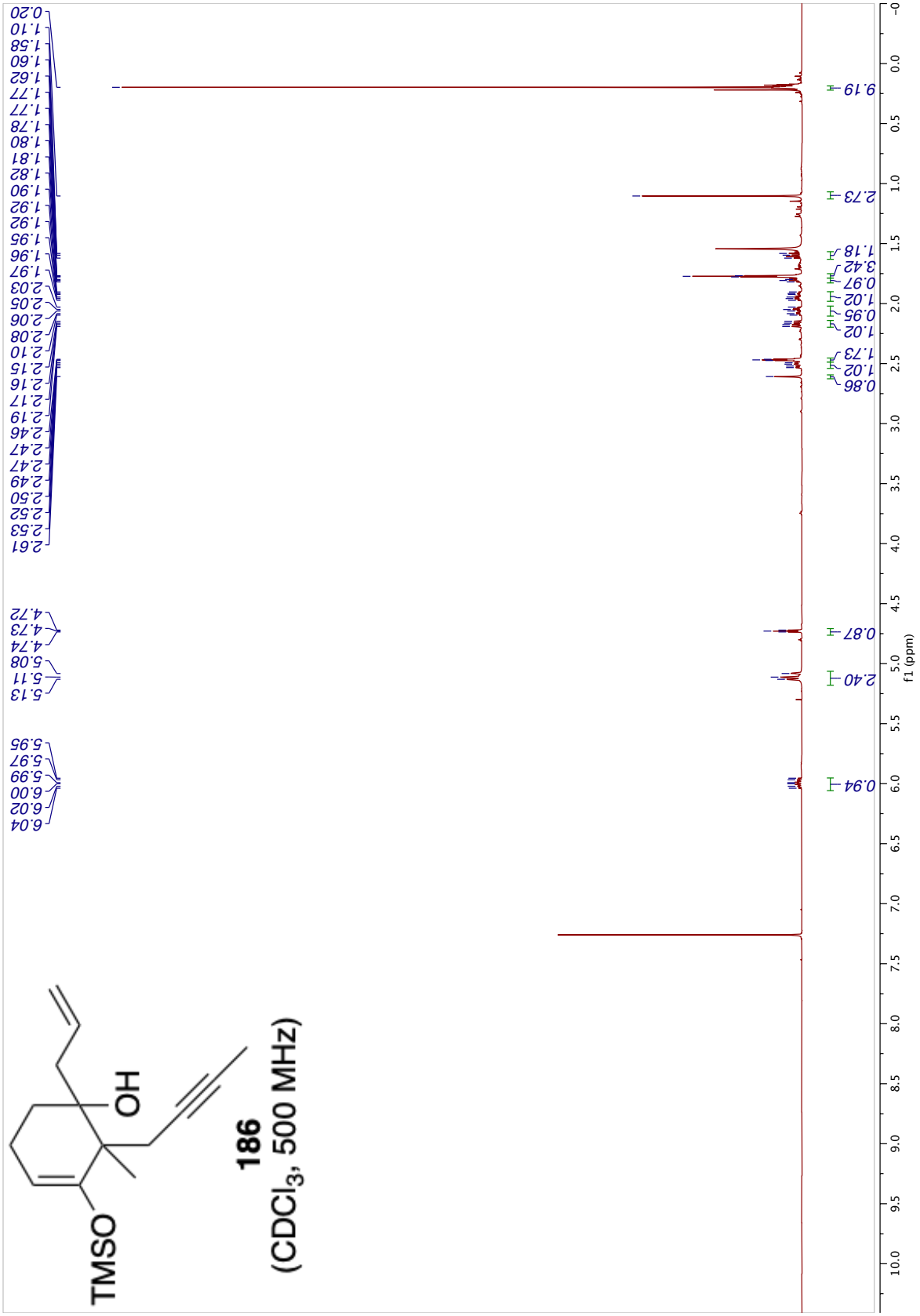

175
(CDCl3, 500 MHz)
O
O
O
6.50
5.77
5.76
5.02
4.99
4.96
4.94
3.99
2.38
2.35
2.21
2.17
2.07
2.04
2.03
2.02
1.97
1.95
1.82
1.46
1.41
1.37
1.36
1.33
1.32
1.04
1.06
1.15
2.33
1.97
1.08
1.12
1.30
1.06
3.00
4.75
3.12
2.97
f1 (ppm)

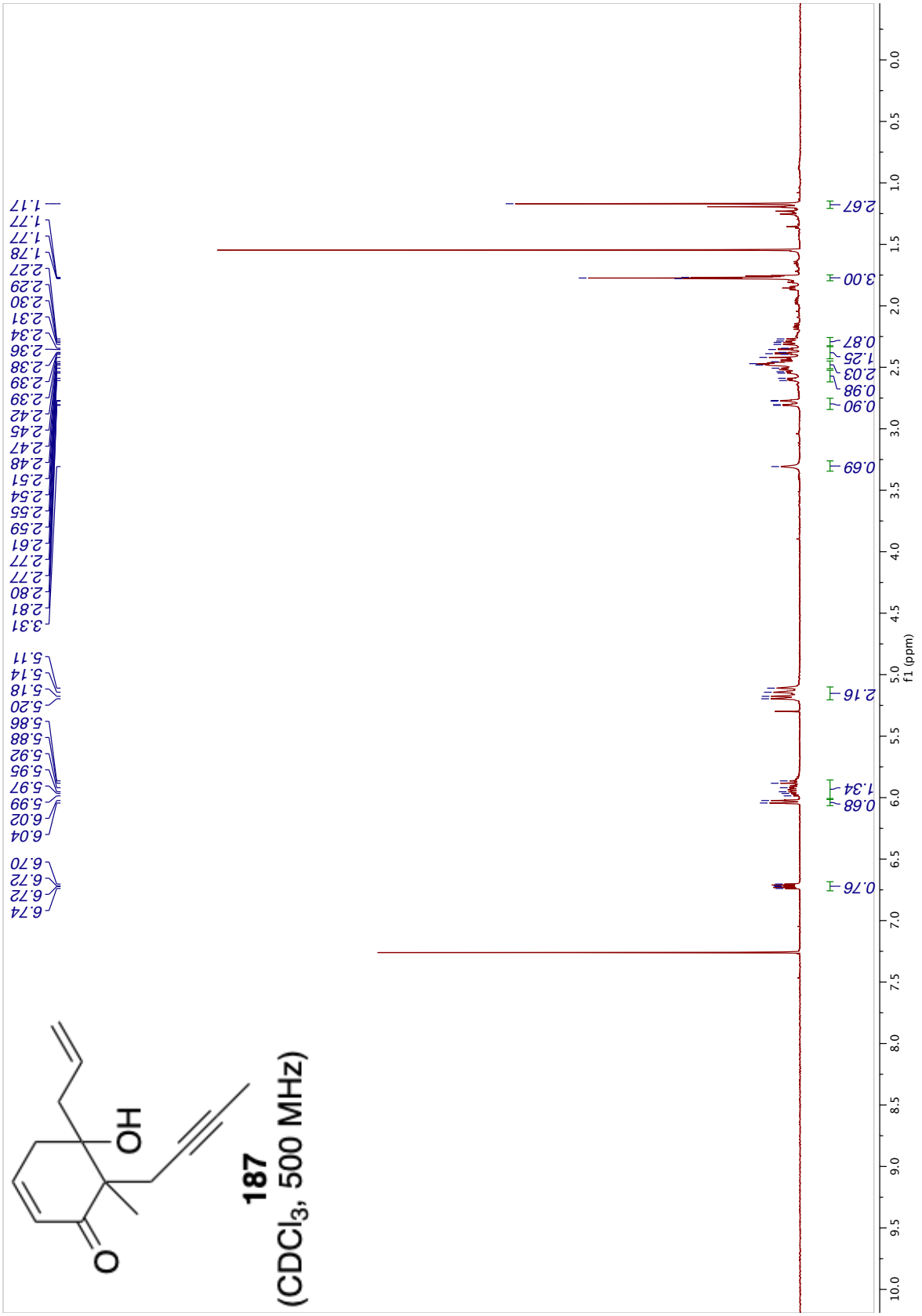

176
(CDCl3, 500 MHz)
lutidine
f1 (ppm)

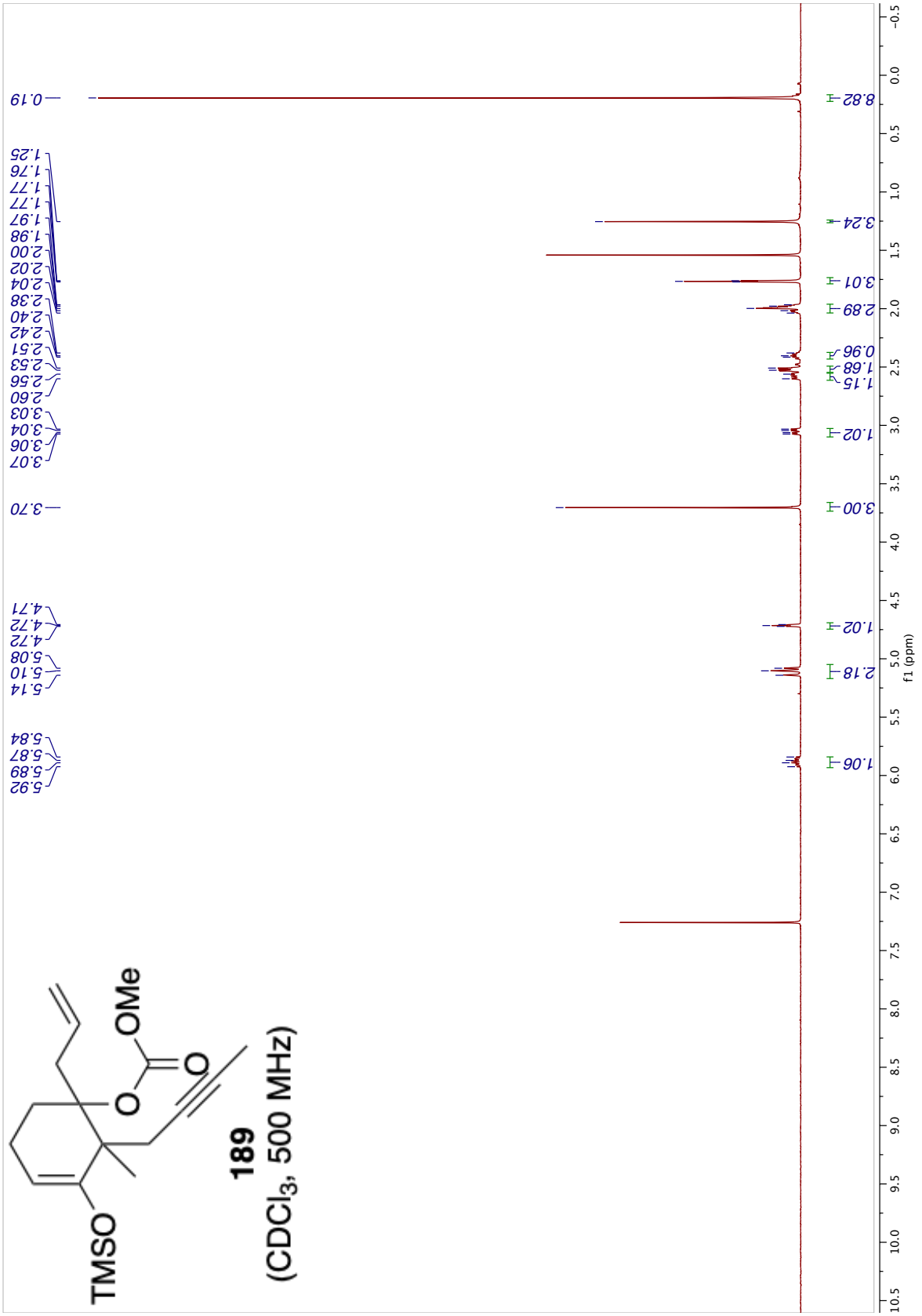

0.20
1.03
1.33
1.35
1.38
1.45
1.47
1.52
1.70
1.79
1.83
2.20
2.33
4.02
4.34
4.35
6.49
9.08
3.00
7.76
2.14
3.37
1.06
1.08
1.98
1.14
1.10
f1 (ppm)
TMSO
CN
O
O
O
177
(CDCl3, 500 MHz)

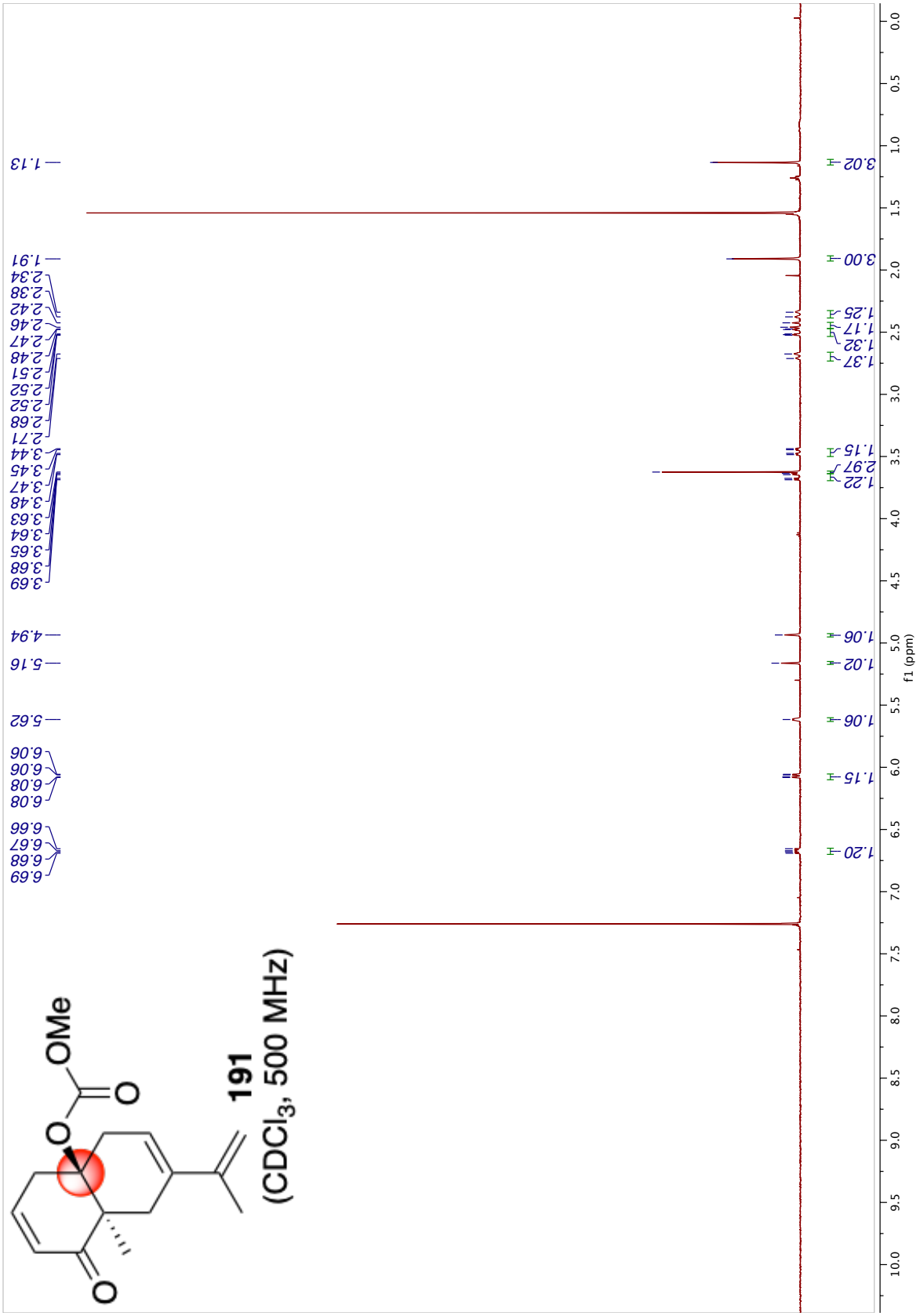

179
(CDCl3, 500 MHz)
f1 (ppm)

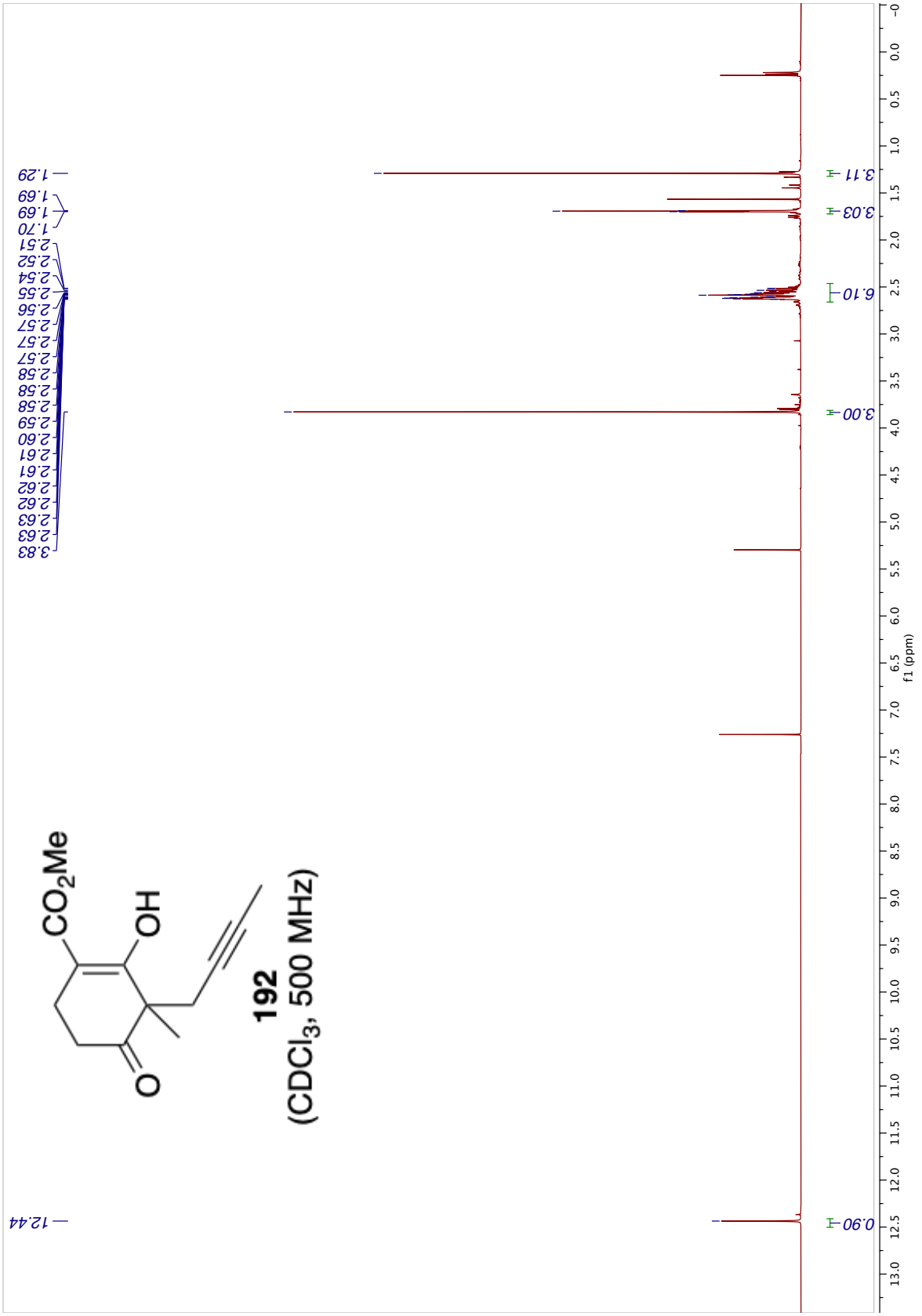

184
(CDCl3, 500 MHz)
O
O
1.26
1.72
1.93
1.96
1.97
1.98
1.99
2.01
2.03
2.58
2.58
2.68
2.69
2.70
3.06
3.00
2.11
2.04
4.03
f1 (ppm)

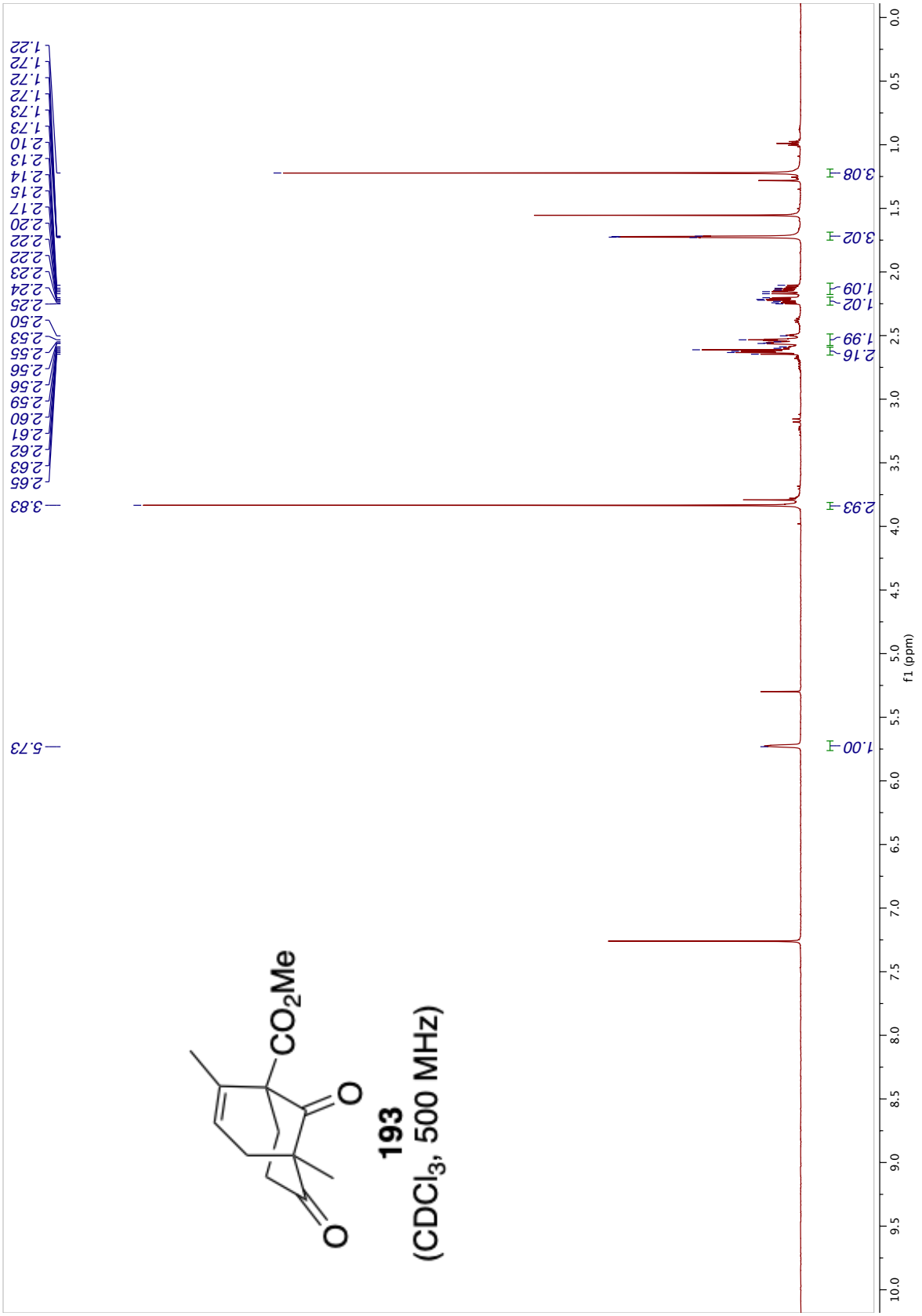

TMSO
OH
186
(CDCl3, 500 MHz)
f1 (ppm)

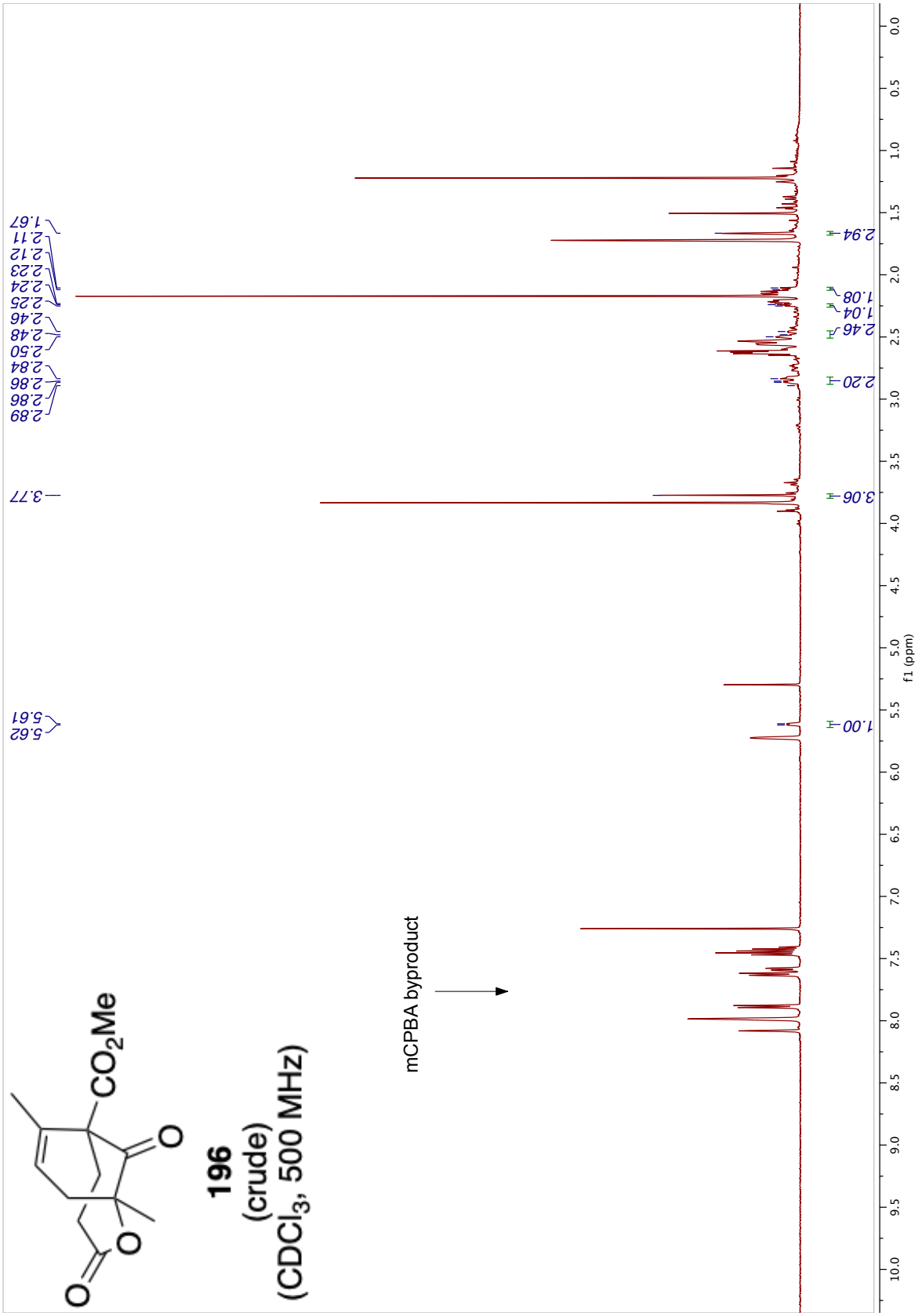

OH
O
187
(CDCl3, 500 MHz)
f1 (ppm)

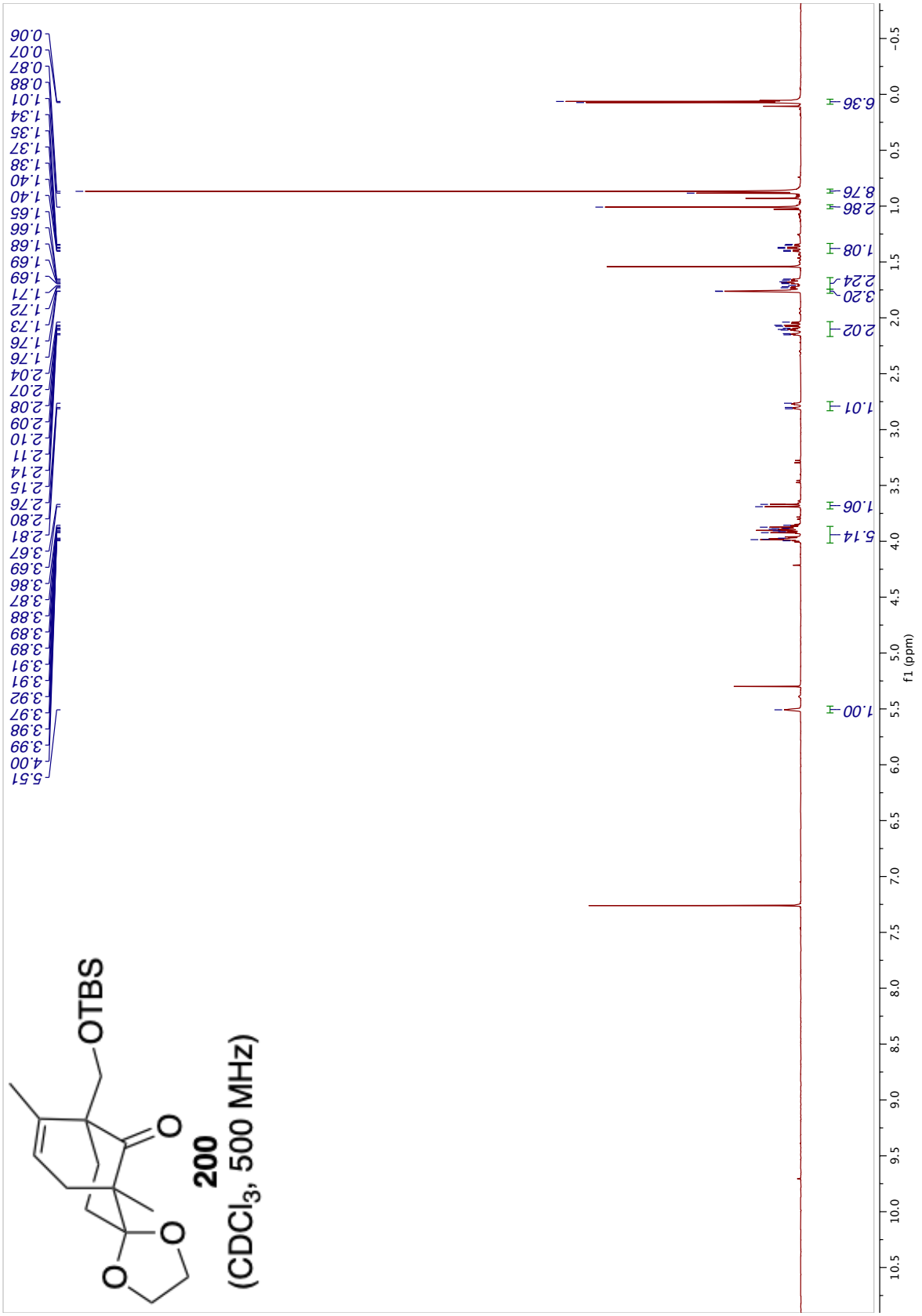

TMSO
OMe
O
O
189
(CDCl3, 500 MHz)
f1 (ppm)

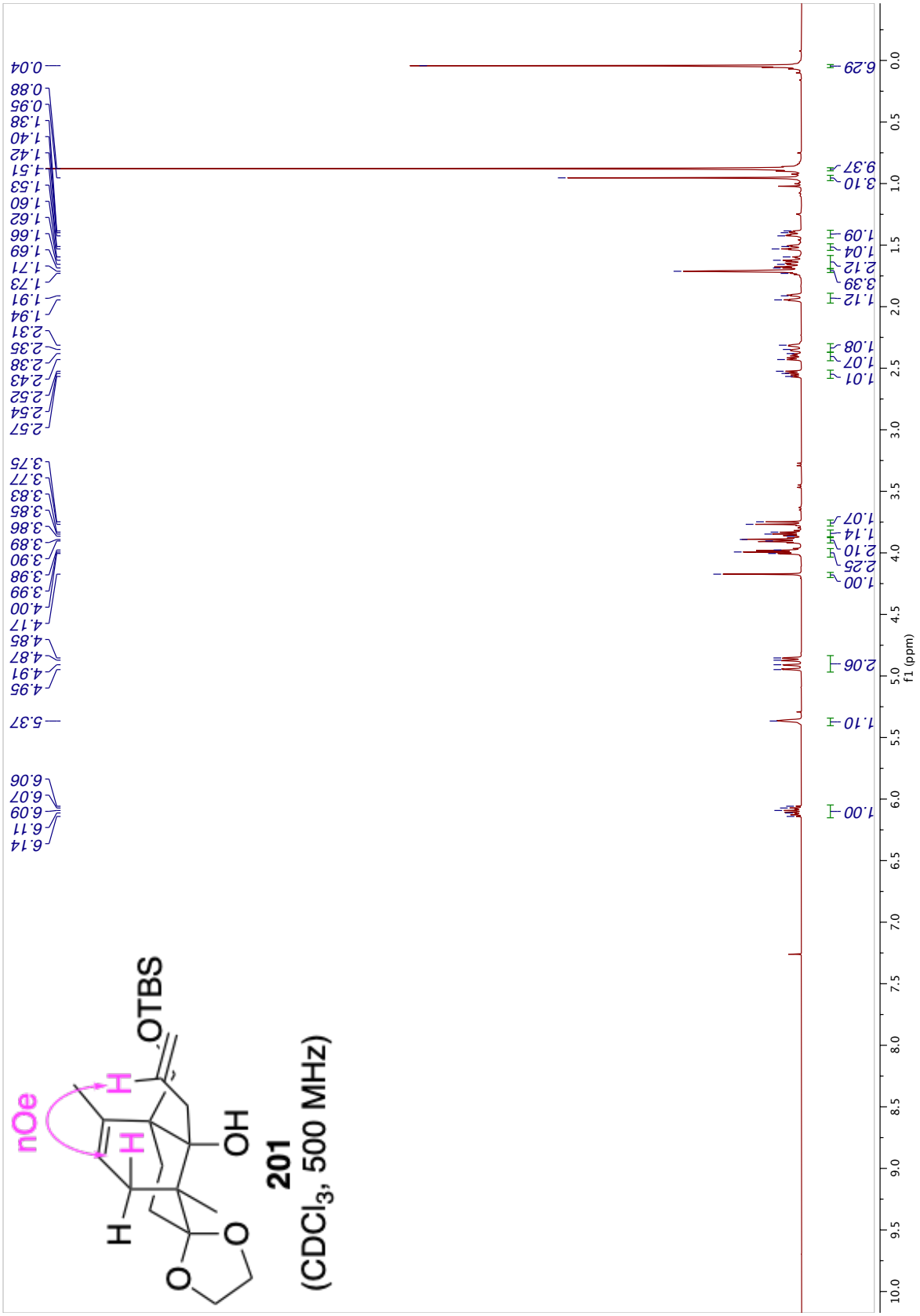

191
(CDCl3, 500 MHz)
OMe
O
O
O
1.13
1.91
2.34
2.38
2.42
2.46
2.47
2.48
2.51
2.52
2.52
2.68
2.71
3.44
3.45
3.47
3.48
3.63
3.64
3.65
3.68
3.69
4.94
5.16
5.62
6.06
6.06
6.08
6.08
6.66
6.67
6.68
6.69
3.02
3.00
1.25
1.17
1.32
1.37
1.15
2.97
1.22
1.06
1.02
1.06
1.15
1.20
f1 (ppm)

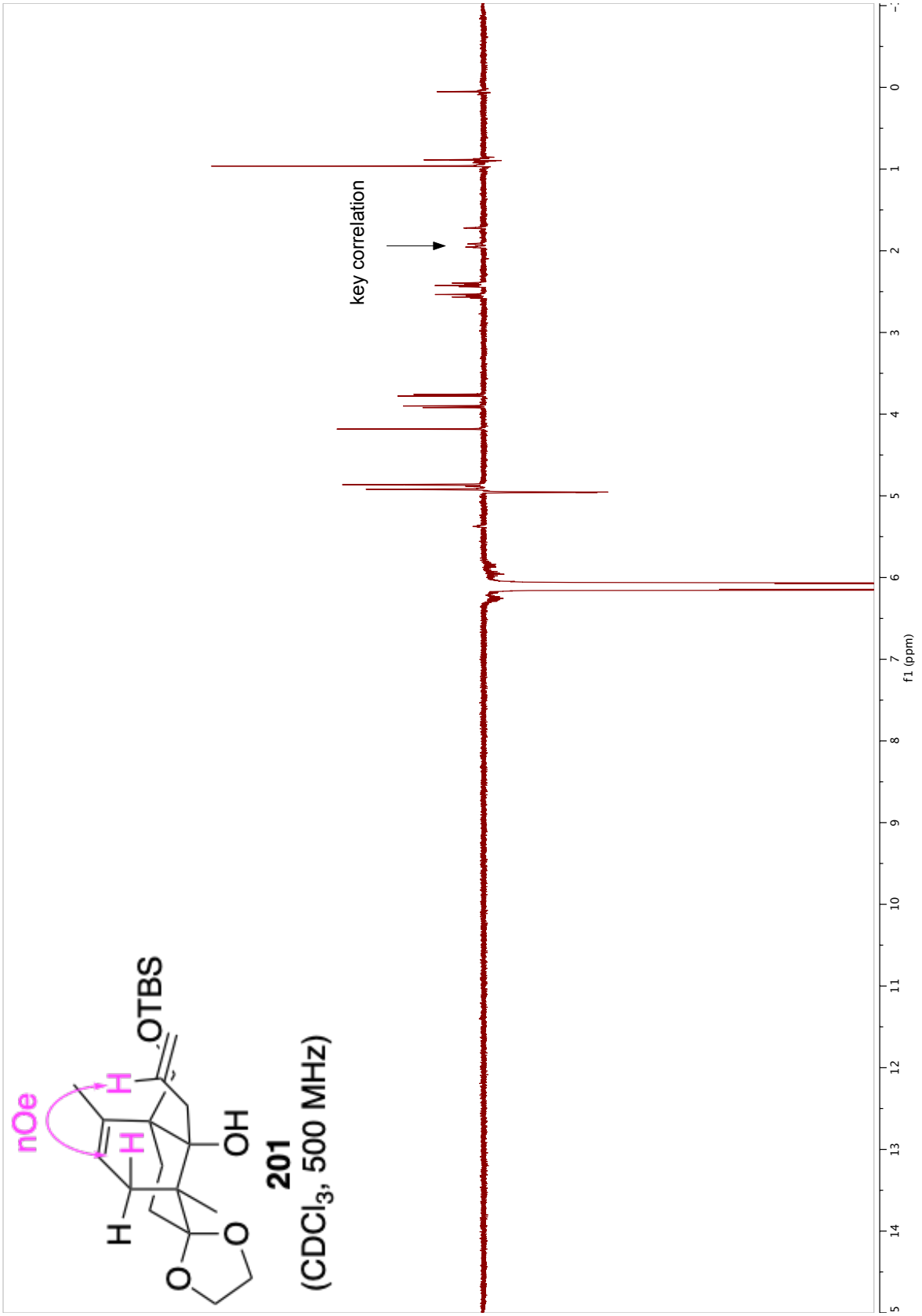

CO2Me
OH
O
192
(CDCl3, 500 MHz)
12.44
3.83
2.63
2.63
2.62
2.62
2.61
2.61
2.60
2.59
2.58
2.58
2.58
2.57
2.57
2.57
2.56
2.55
2.54
2.52
2.51
1.70
1.69
1.69
1.29
0.90
3.00
6.10
3.03
3.11
f1 (ppm)

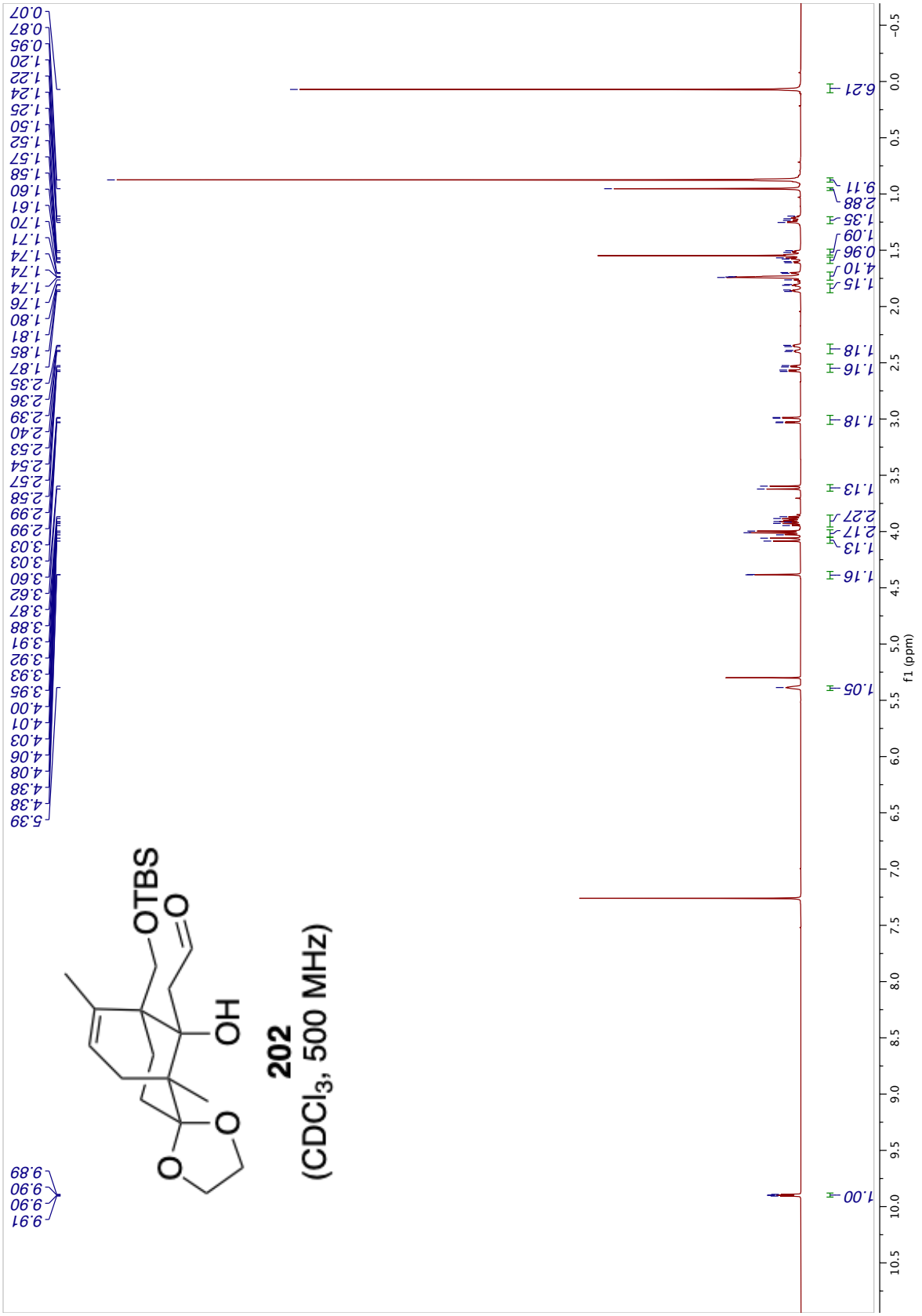

CO2Me
O
O
193
(CDCl3, 500 MHz)
f1 (ppm)

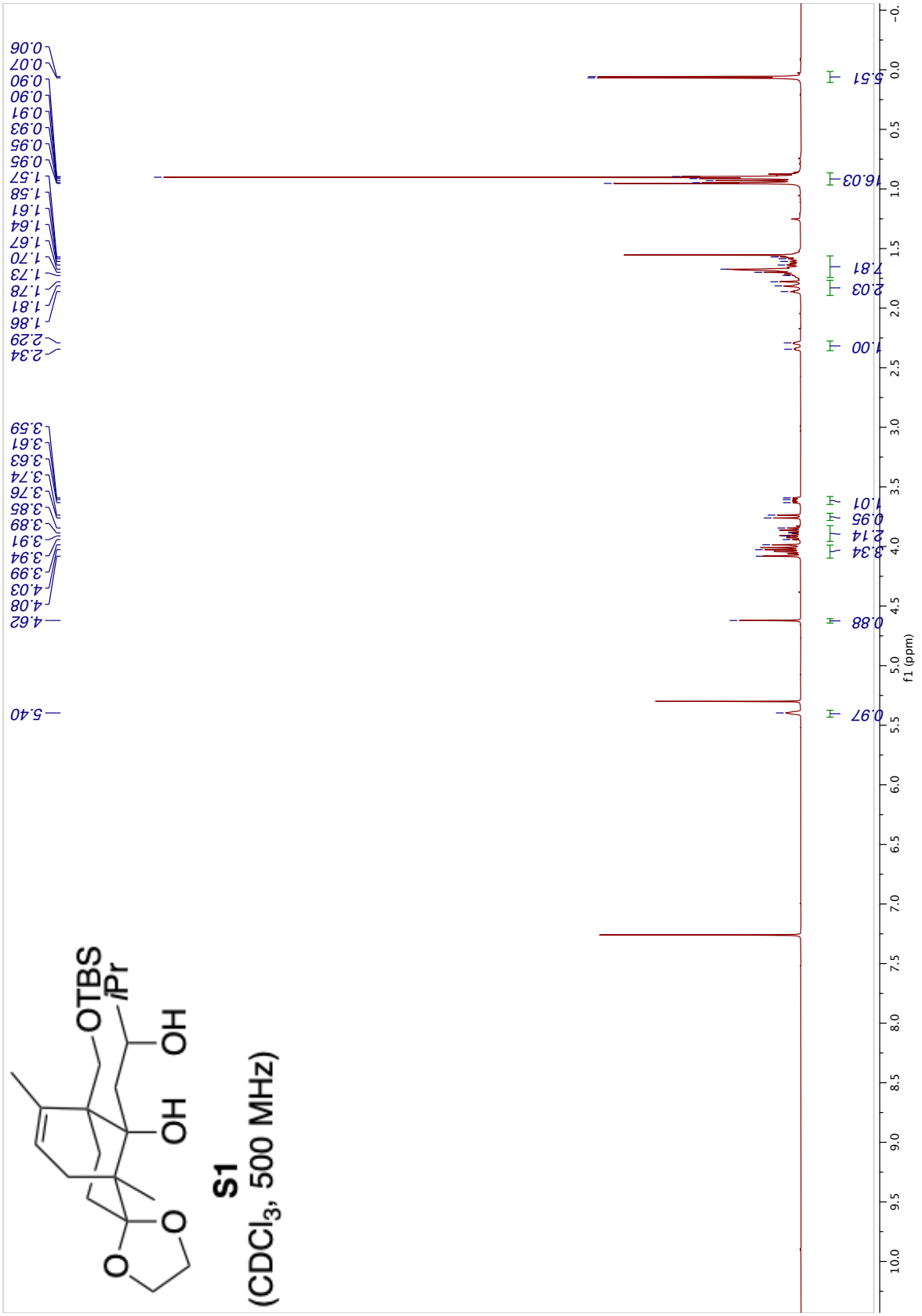

196
(crude)
(CDCl3, 500 MHz)
mCPBA byproduct
f1 (ppm)

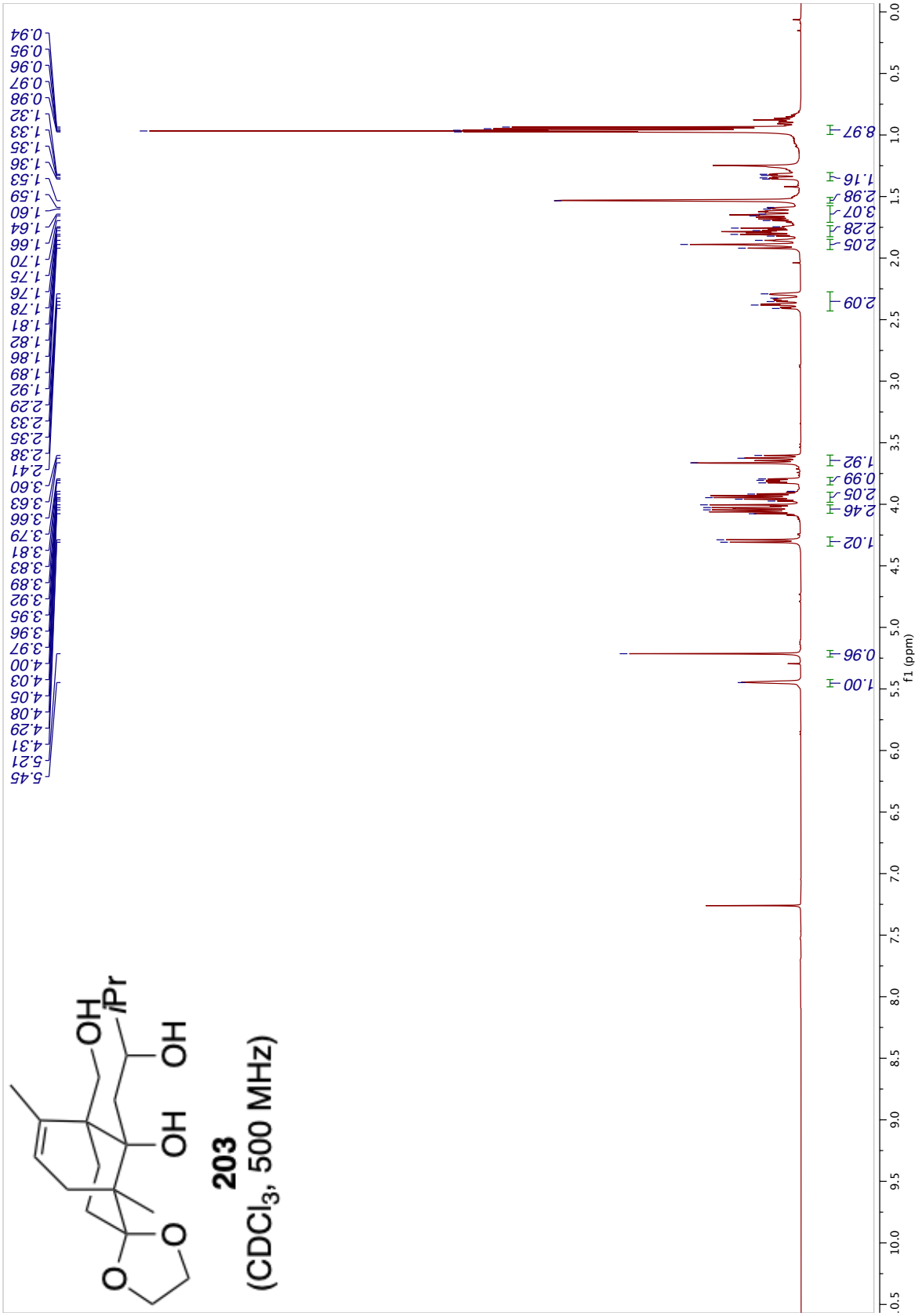

OTBS
O
O
O
200
(CDCl3, 500 MHz)
f1 (ppm)

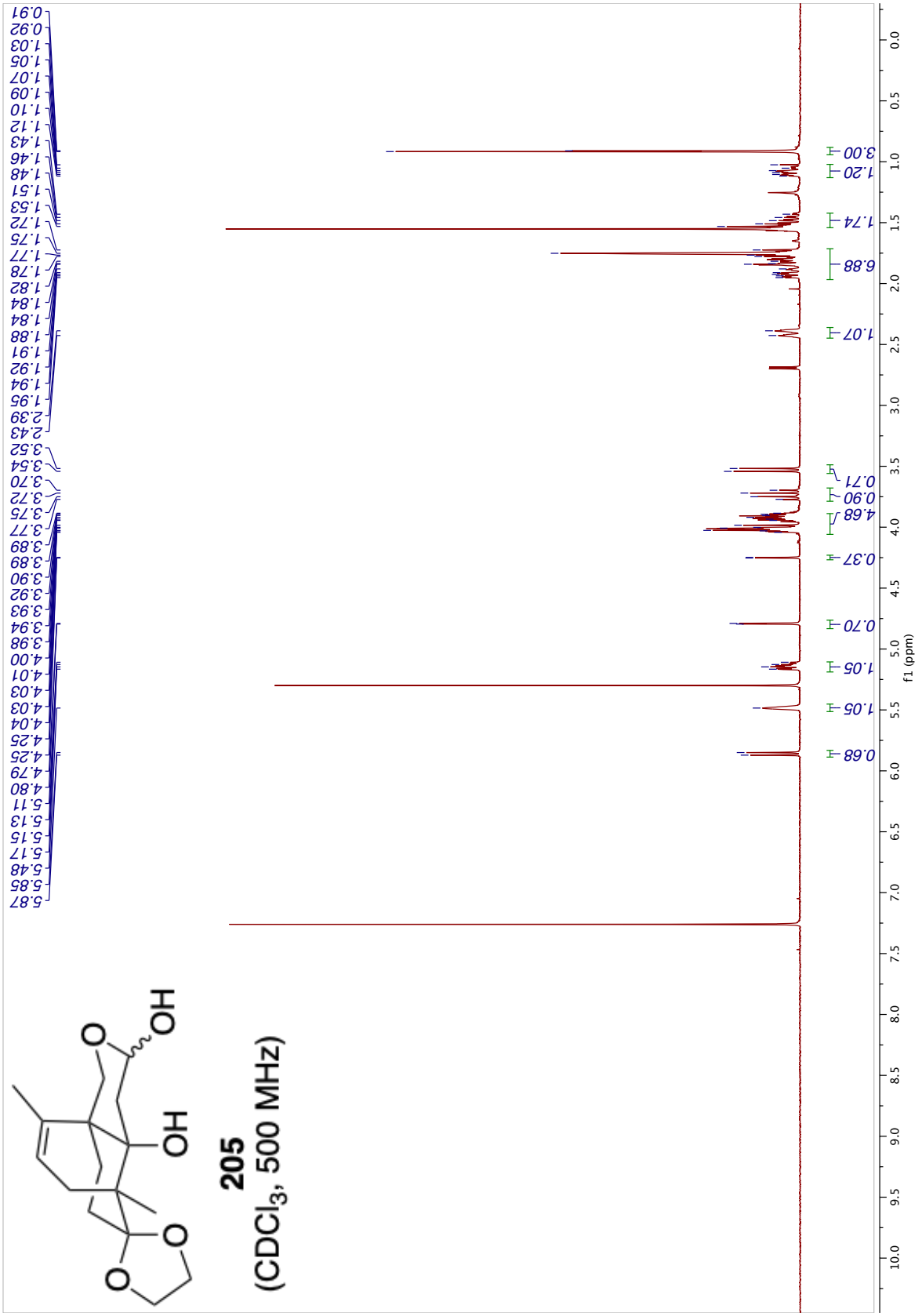

nOe
H
H
H
OTBS
OH
O
O
201
(CDCl3, 500 MHz)
f1 (ppm)

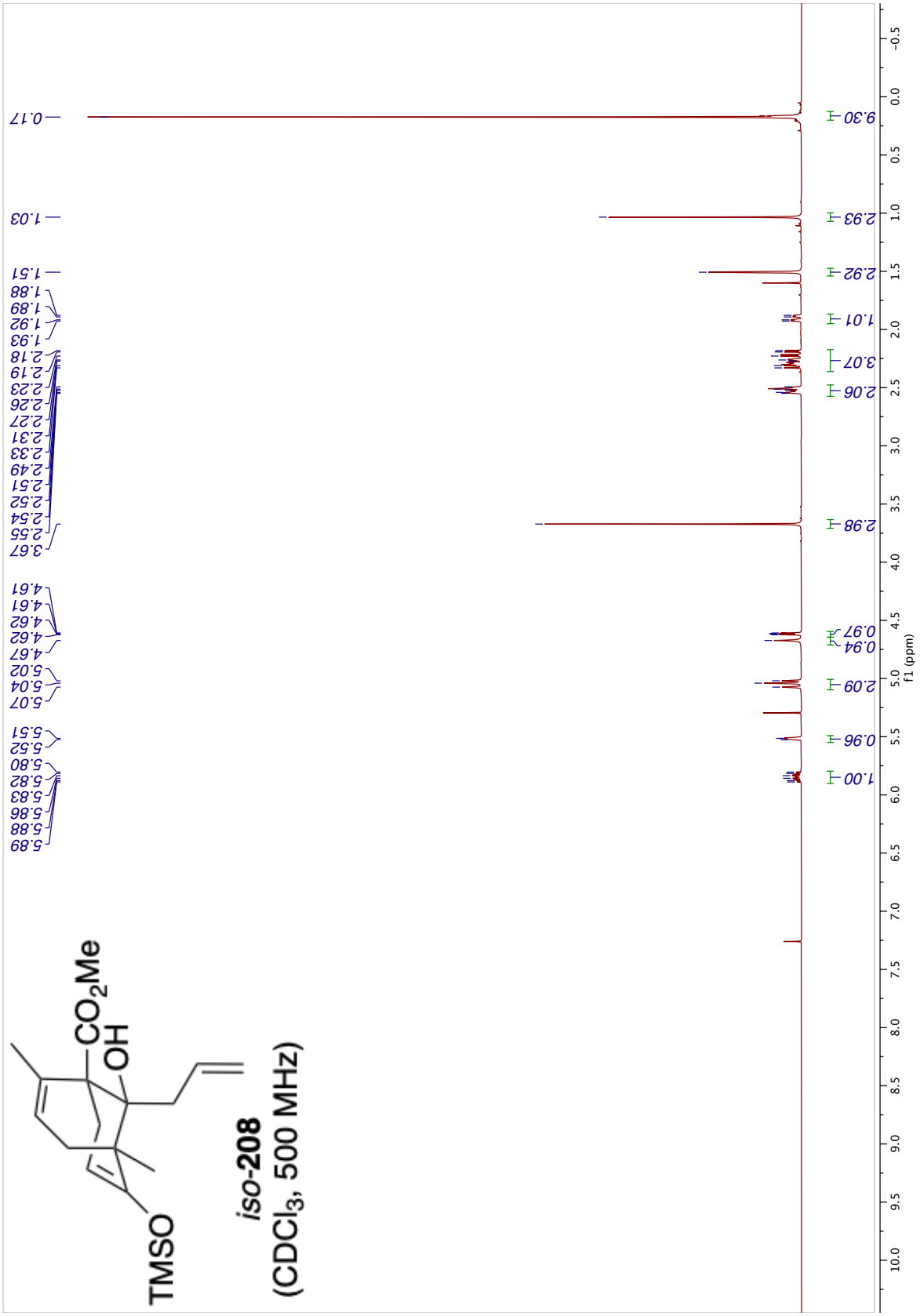

nOe
H
H
H
OTBS
OH
O
O
201
(CDCl3, 500 MHz)
key correlation
f1 (ppm)

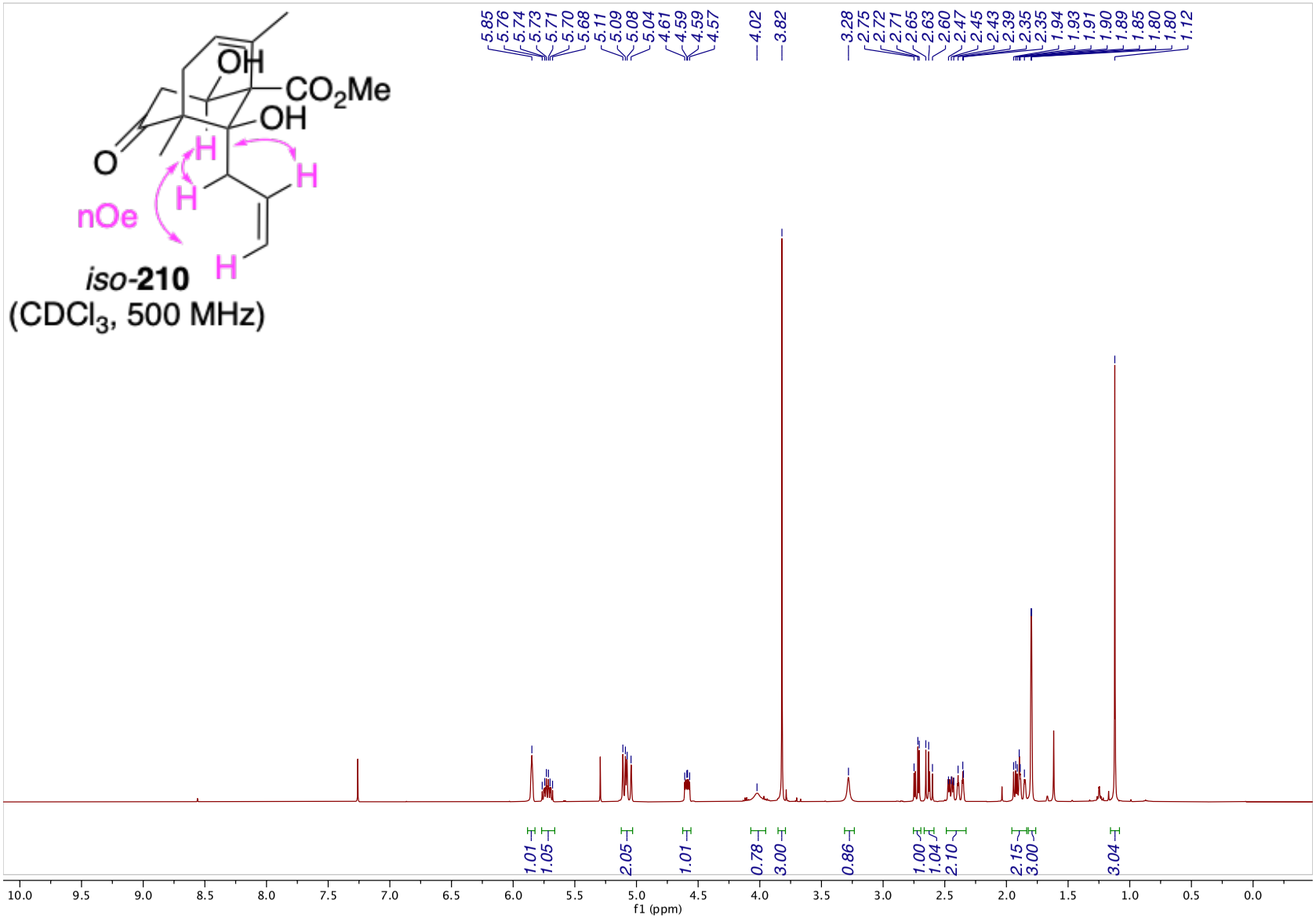

OTBS
O
OH
O
O
202
(CDCl3, 500 MHz)
f1 (ppm)

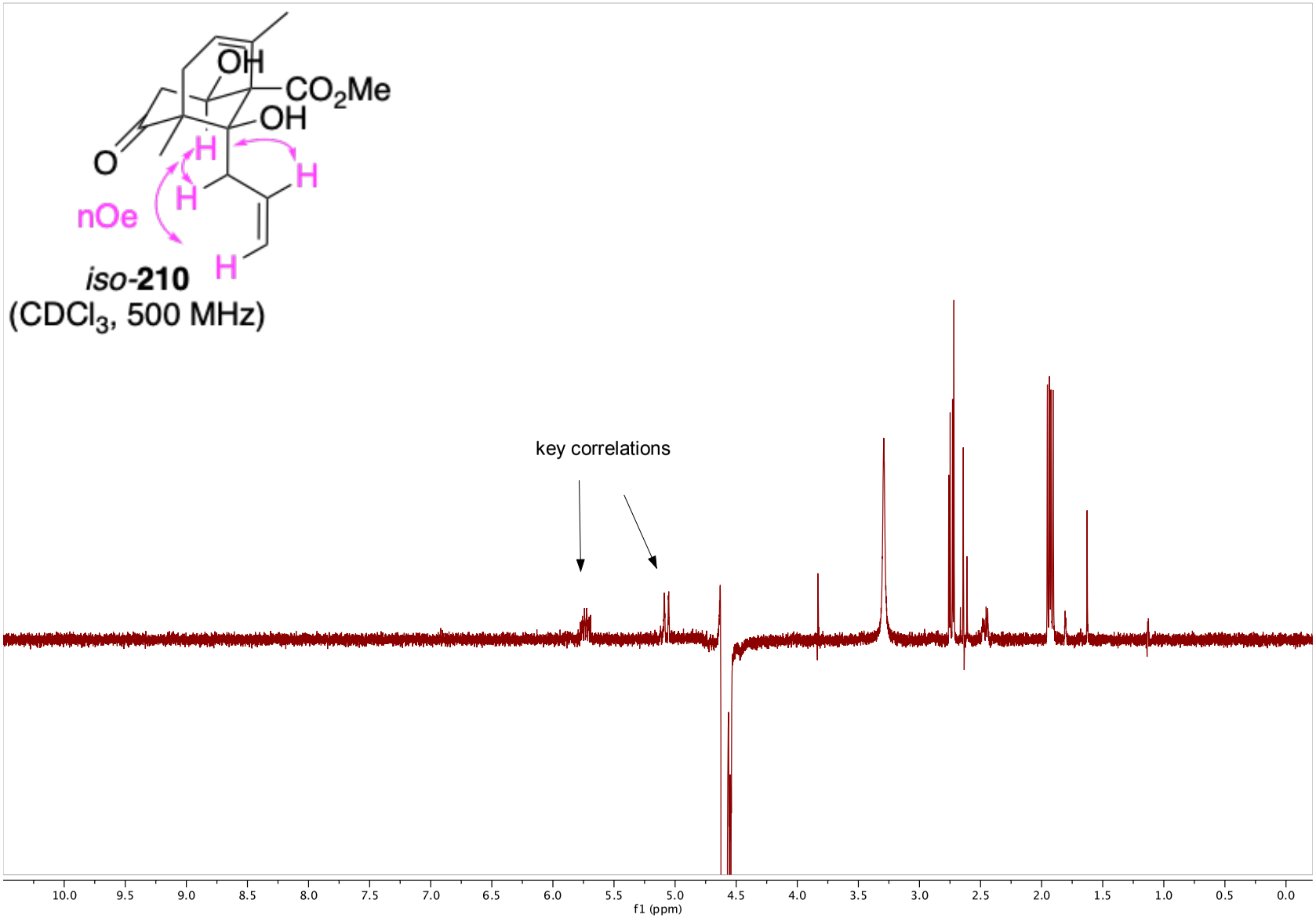

OTBS
iPr
OH
OH
O
O
O
S1
(CDCl3, 500 MHz)
0.06
0.07
0.90
0.90
0.91
0.93
0.95
0.95
1.57
1.58
1.61
1.64
1.67
1.70
1.73
1.78
1.81
1.86
2.29
2.34
3.59
3.61
3.63
3.74
3.76
3.85
3.89
3.91
3.94
3.99
4.03
4.08
4.62
5.40
5.51
16.03
7.81
2.03
1.00
1.01
0.95
2.14
3.34
0.88
0.97
f1 (ppm)

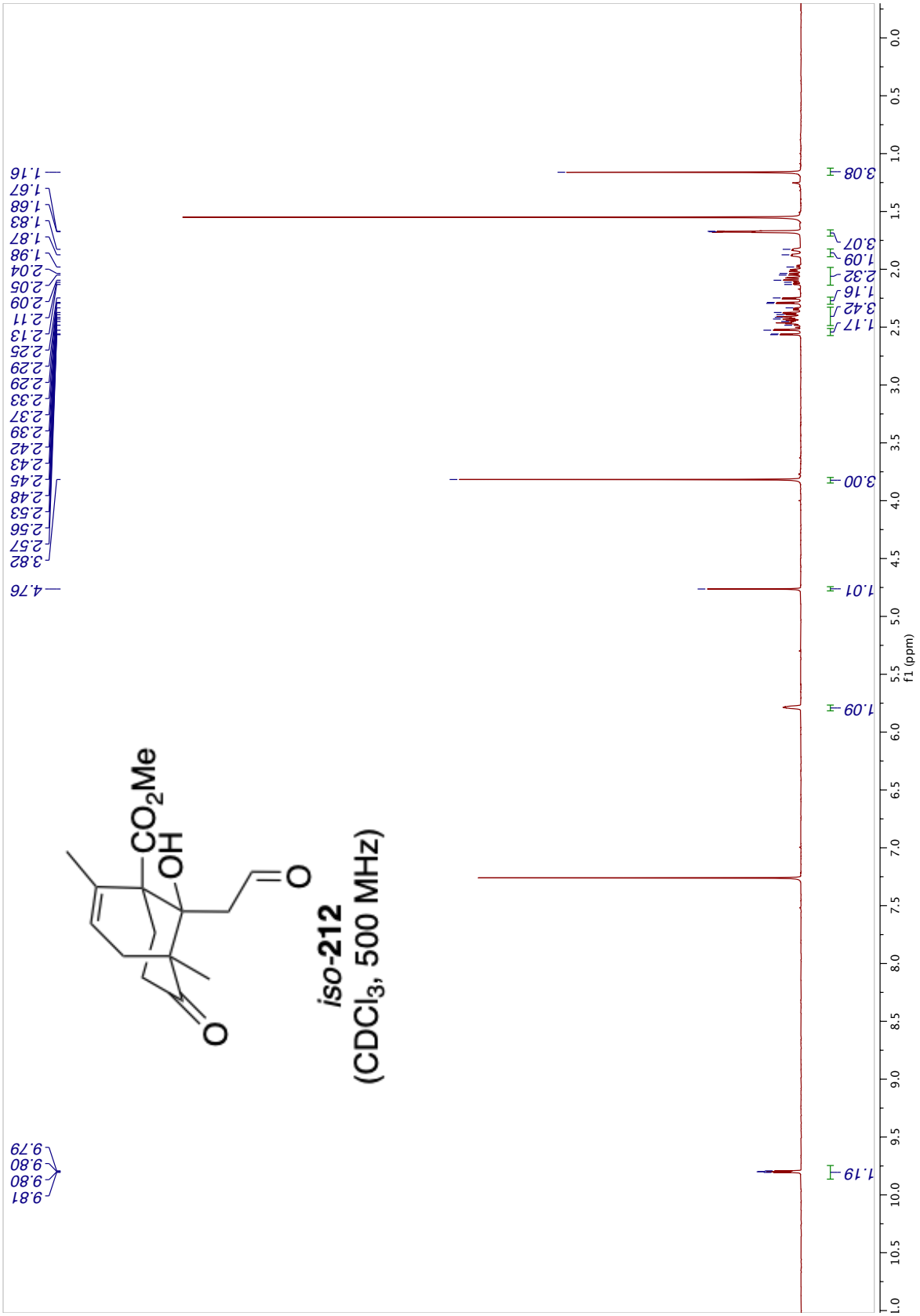

OH
iPr
OH
OH
O
O
O
203
(CDCl3, 500 MHz)
f1 (ppm)

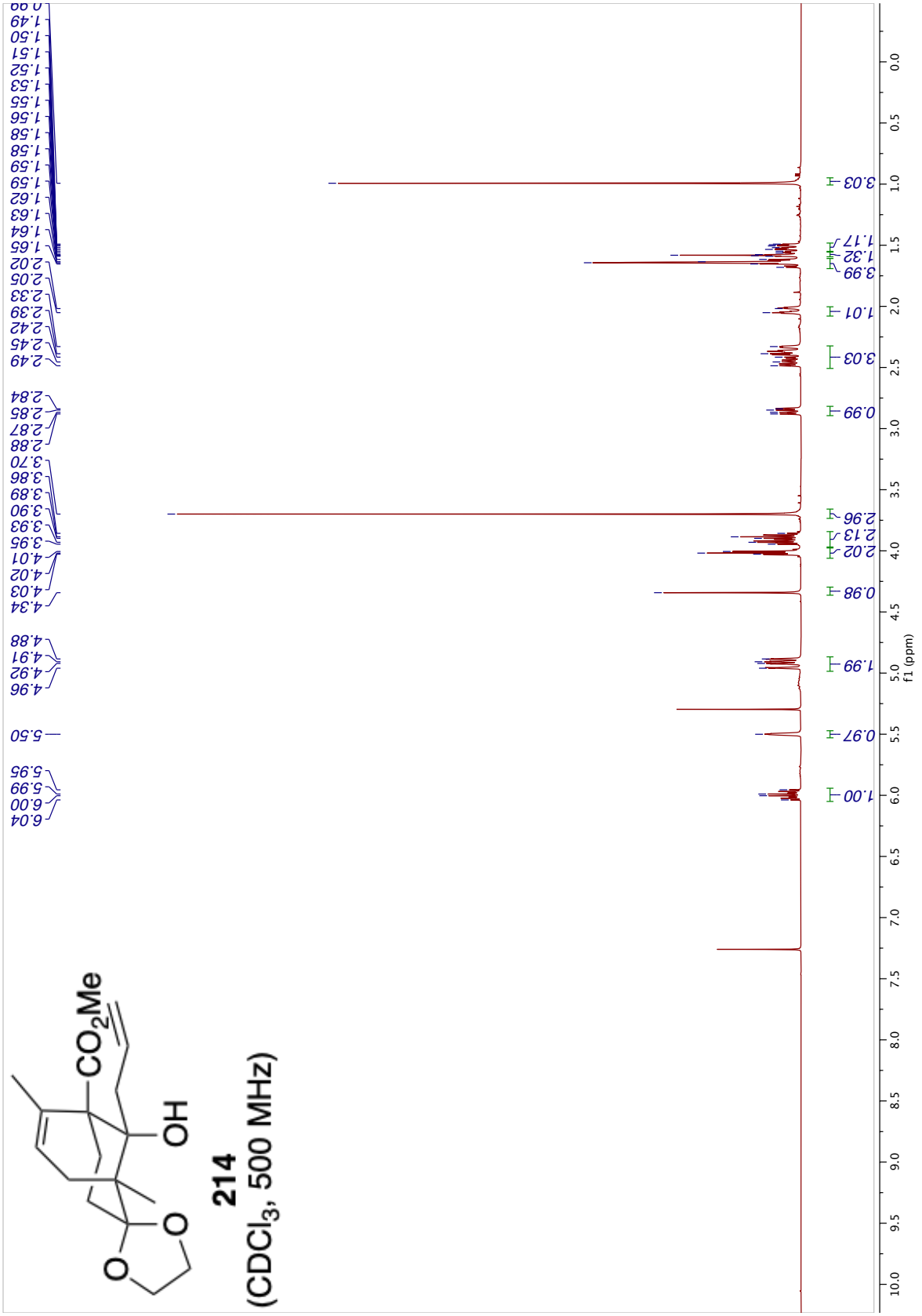

205
(CDCl3, 500 MHz)
OH
OH
O
O
O
f1 (ppm)

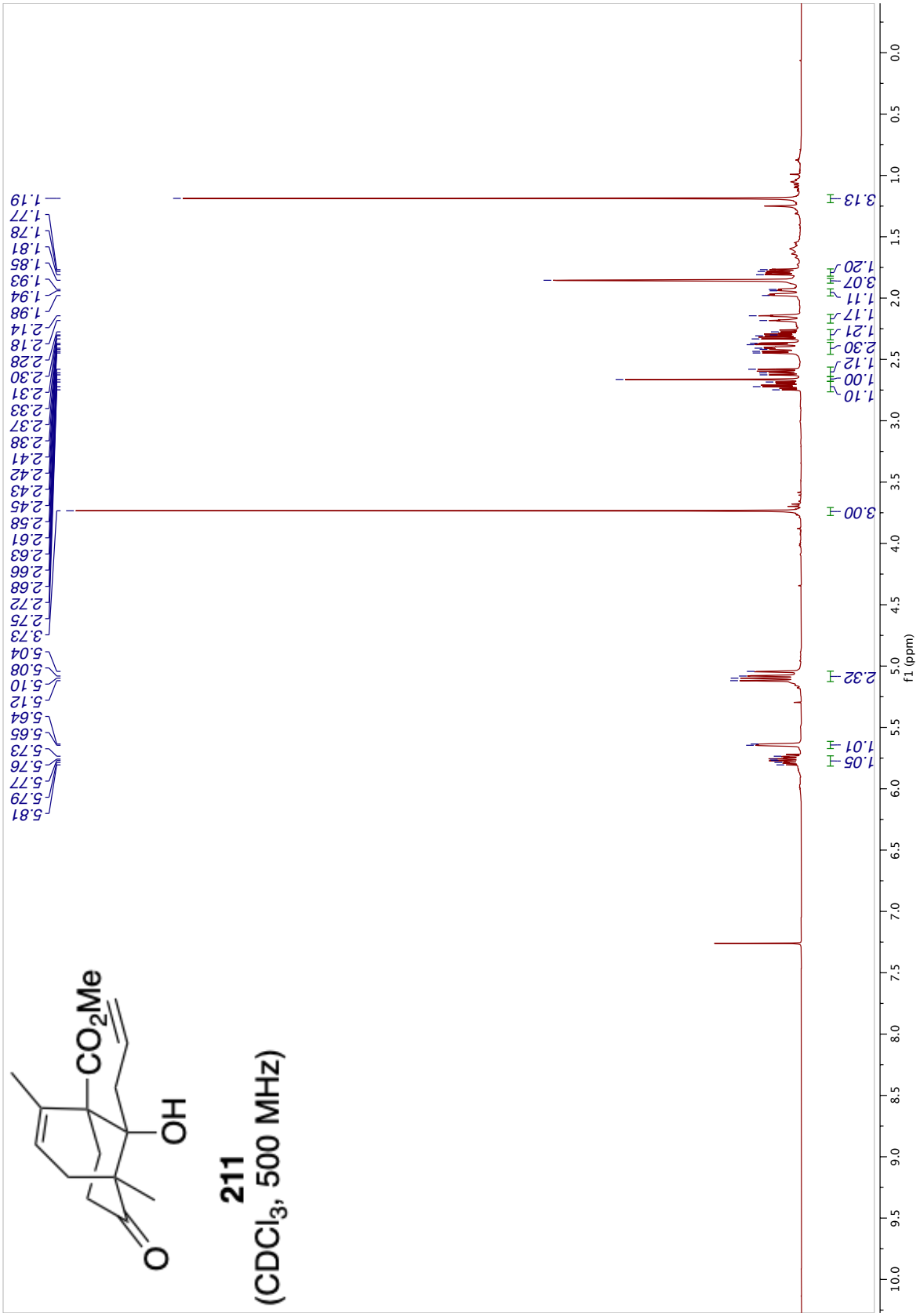

TMSO
OH
CO2Me
iso-208
(CDCl3, 500 MHz)
f1 (ppm)

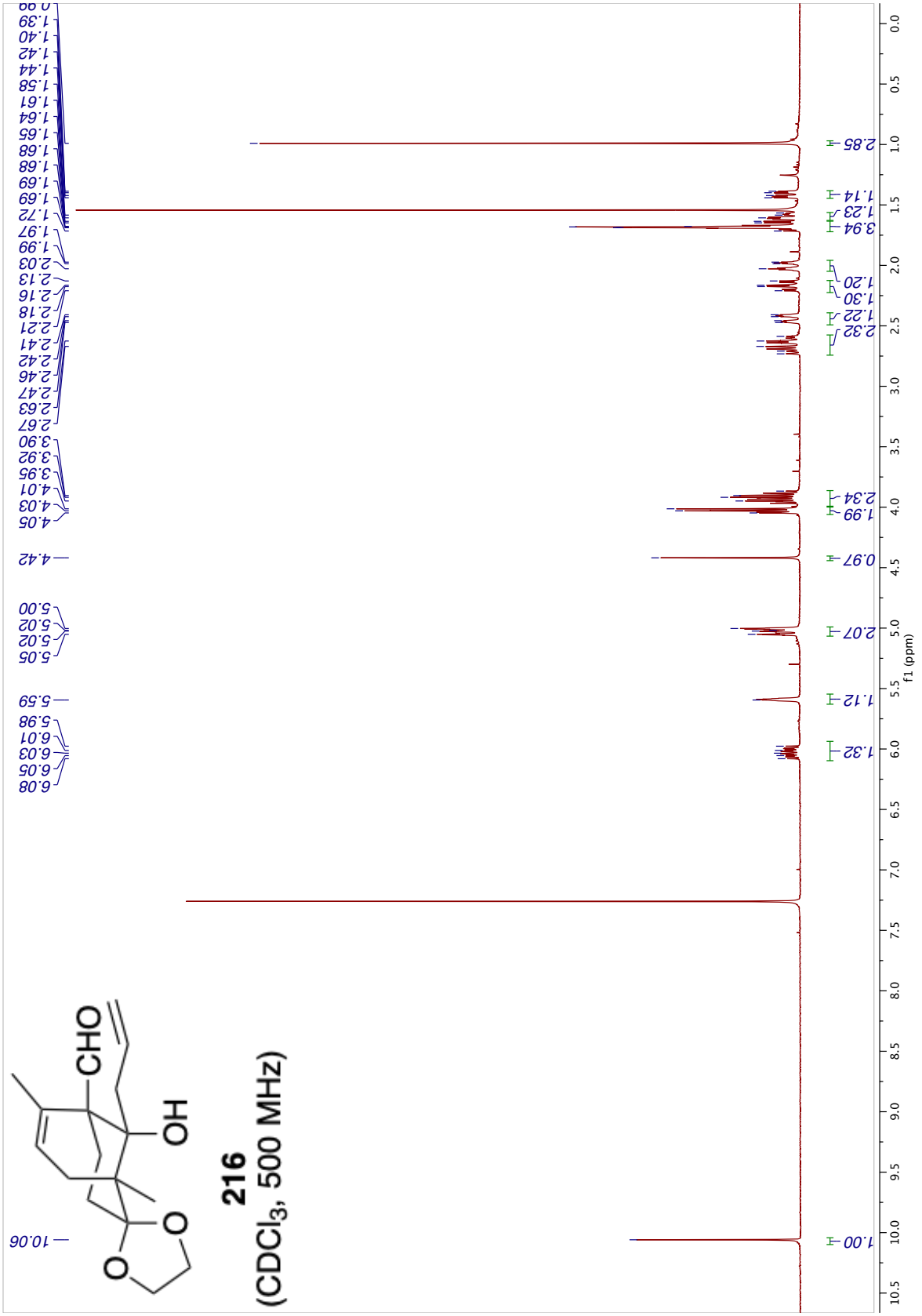

OH
CO2Me
OH
O
H
H
H
nOe
H
iso-210
(CDCl3, 500 MHz)
5.85
5.76
5.74
5.73
5.71
5.70
5.68
5.11
5.09
5.08
5.04
4.61
4.59
4.59
4.57
4.02
3.82
3.28
2.75
2.72
2.71
2.65
2.63
2.60
2.47
2.45
2.43
2.39
2.35
2.35
1.94
1.93
1.91
1.90
1.89
1.85
1.80
1.80
1.12
1.01
1.05
2.05
1.01
0.78
3.00
0.86
1.00
1.04
2.10
2.15
3.00
3.04
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

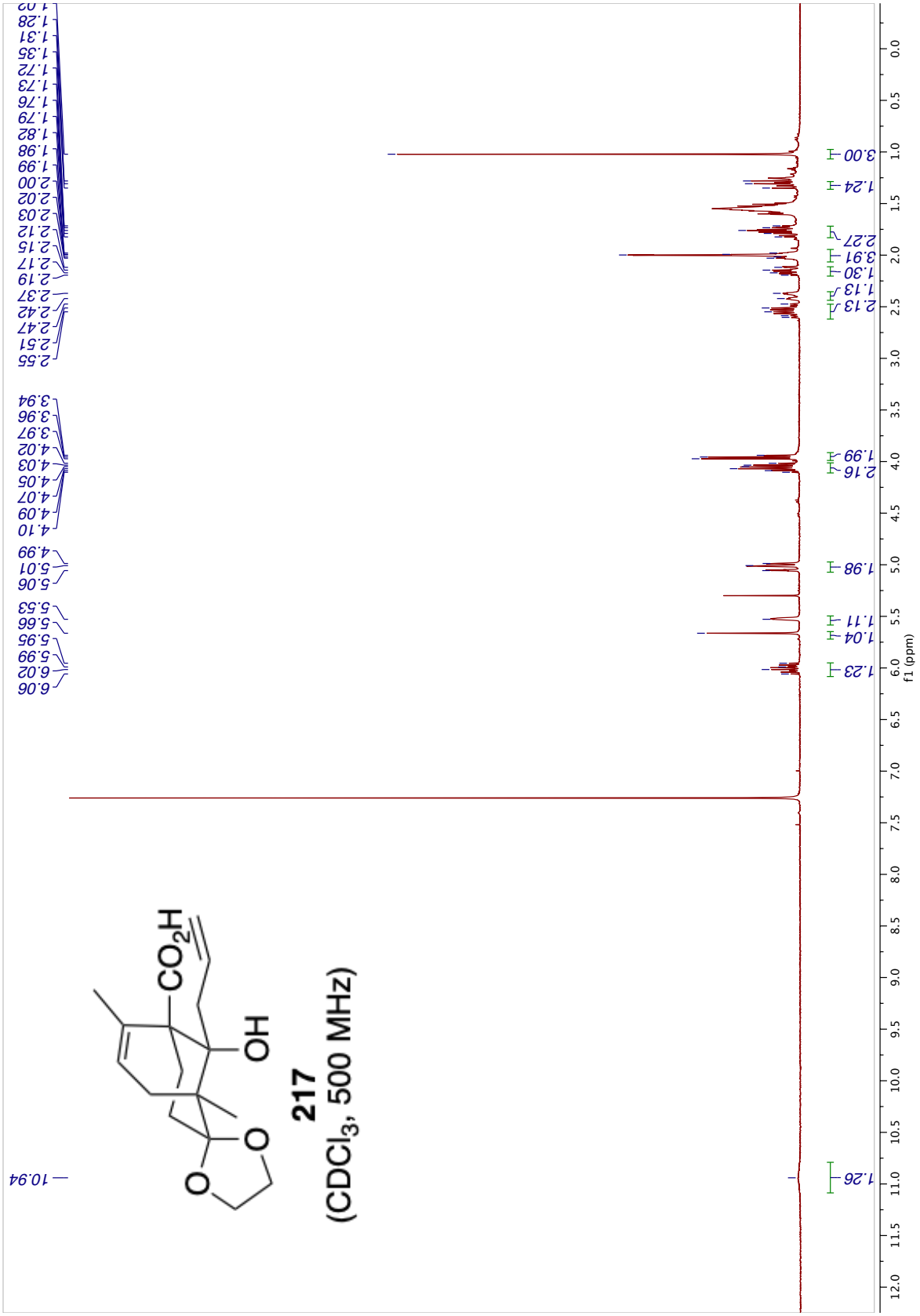

OH
CO2Me
OH
O
H
H
H
nOe
H
iso-210
(CDCl3, 500 MHz)
key correlations
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

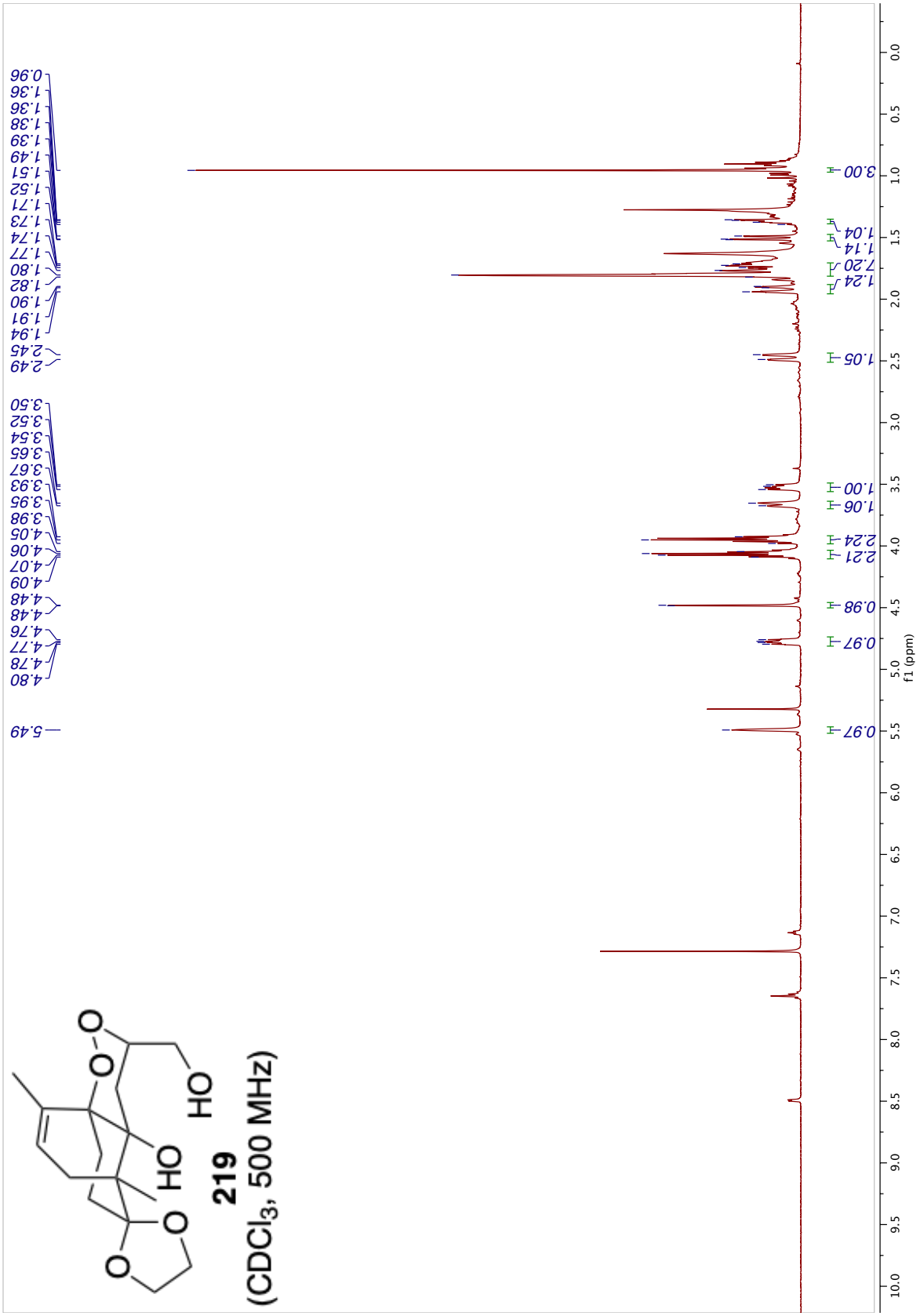

CO2Me
OH
O
O
iso-212
(CDCl3, 500 MHz)
f1 (ppm)

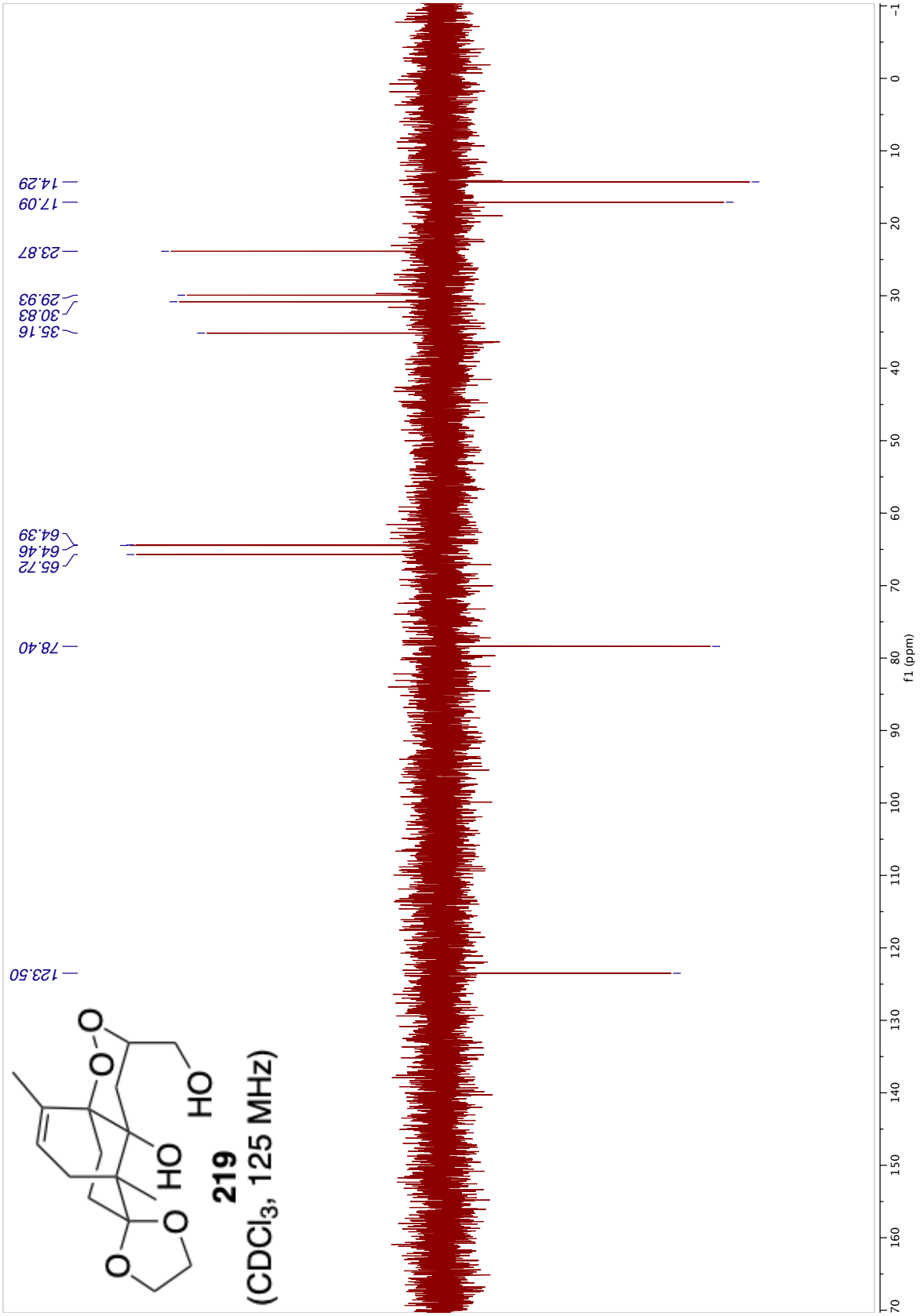

CO2Me
OH
O
O
O
214
(CDCl3, 500 MHz)
f1 (ppm)

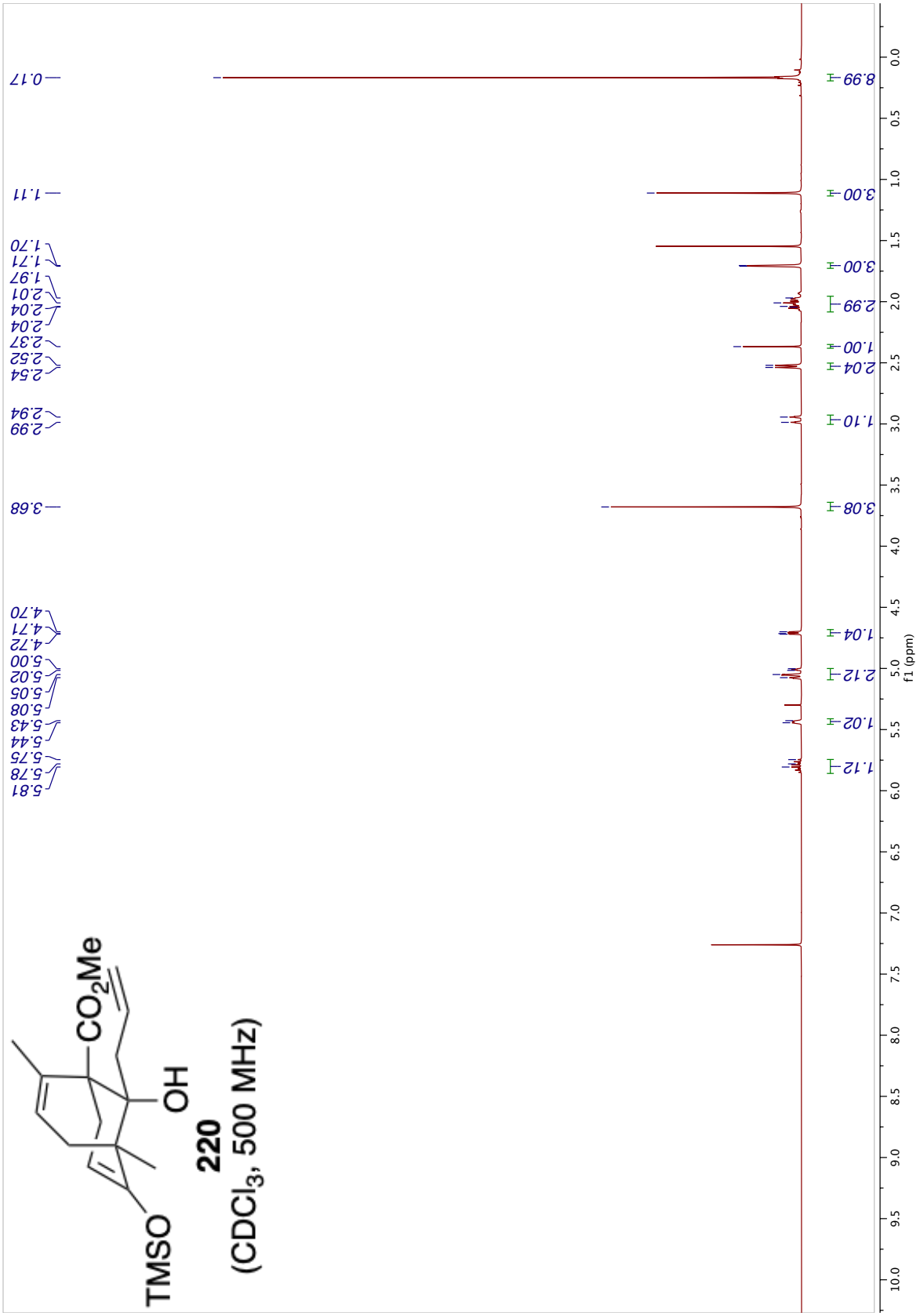

211
(CDCl3, 500 MHz)
CO2Me
OH
O
f1 (ppm)

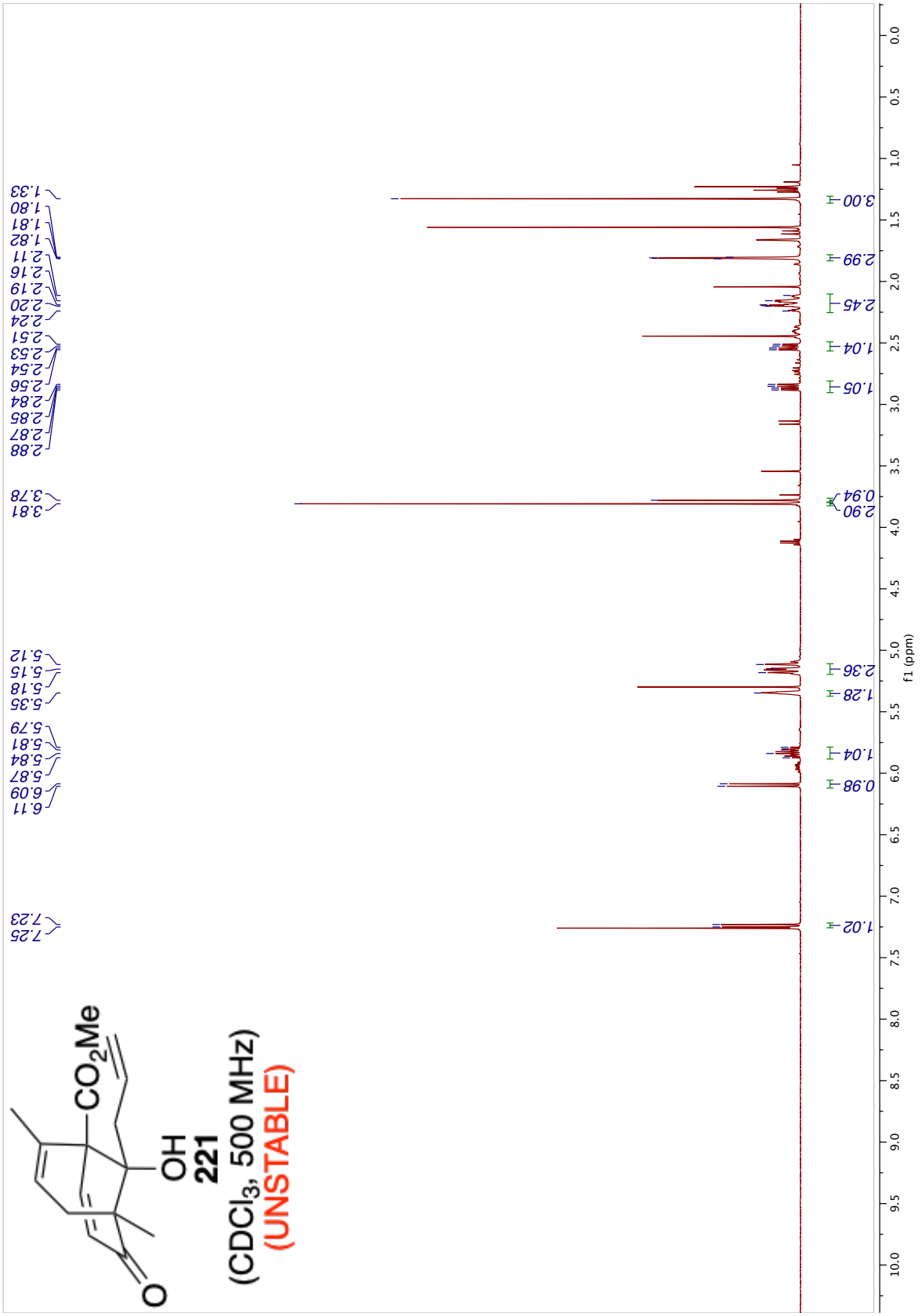

CHO
OH
O
O
O
216
(CDCl3, 500 MHz)
10.06
6.08
6.05
6.03
6.01
5.98
5.59
5.05
5.02
5.02
5.00
4.42
4.05
4.03
4.01
3.95
3.92
3.90
2.67
2.63
2.47
2.46
2.42
2.41
2.21
2.18
2.16
2.13
2.03
1.99
1.97
1.72
1.69
1.69
1.68
1.68
1.65
1.64
1.61
1.58
1.44
1.42
1.40
1.39
0.99
1.00
1.32
1.12
2.07
0.97
2.34
1.99
2.32
1.22
1.30
1.20
3.94
1.23
1.14
2.85
f1 (ppm)

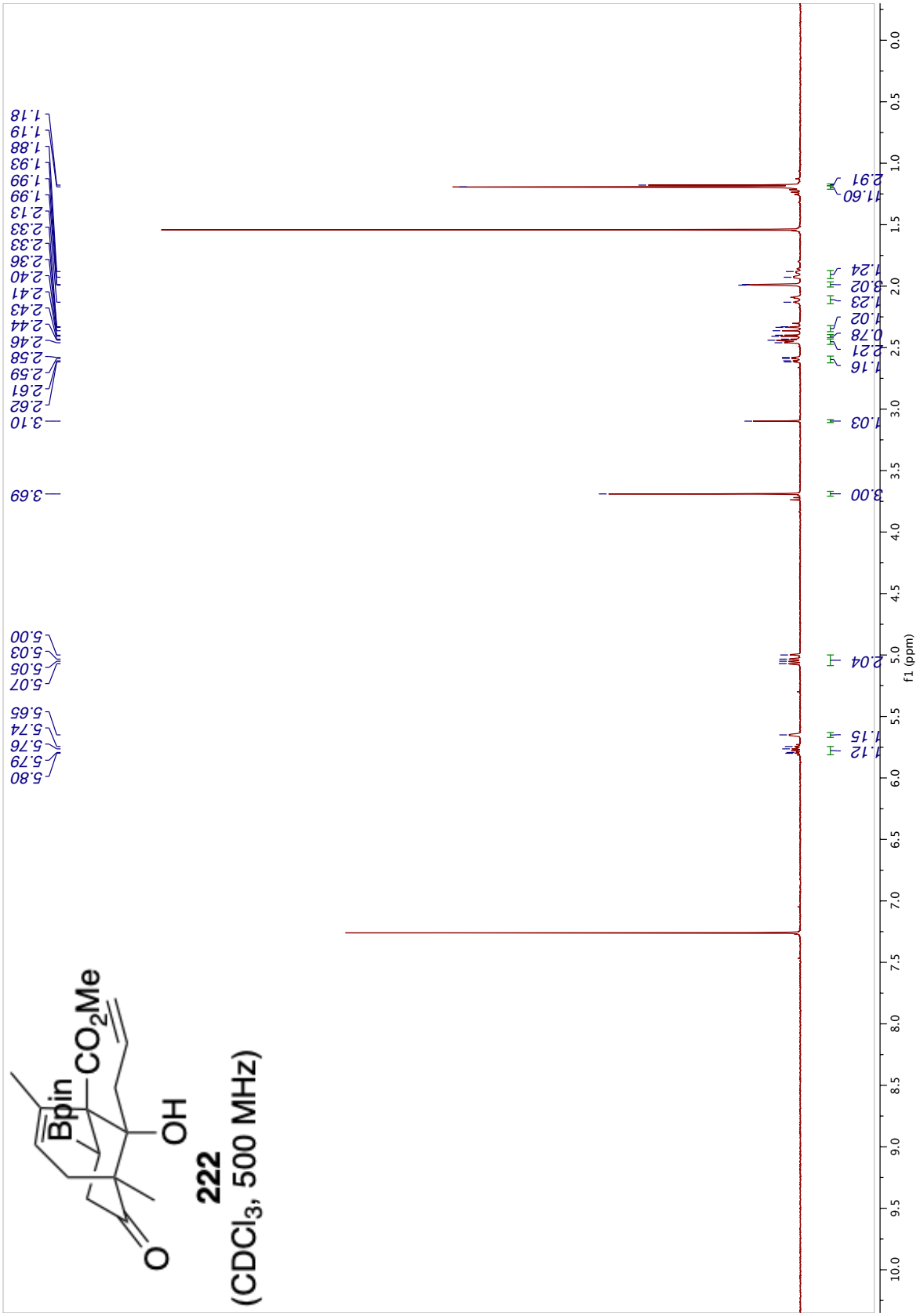

CO2H
OH
O
O
217
(CDCl3, 500 MHz)
f1 (ppm)

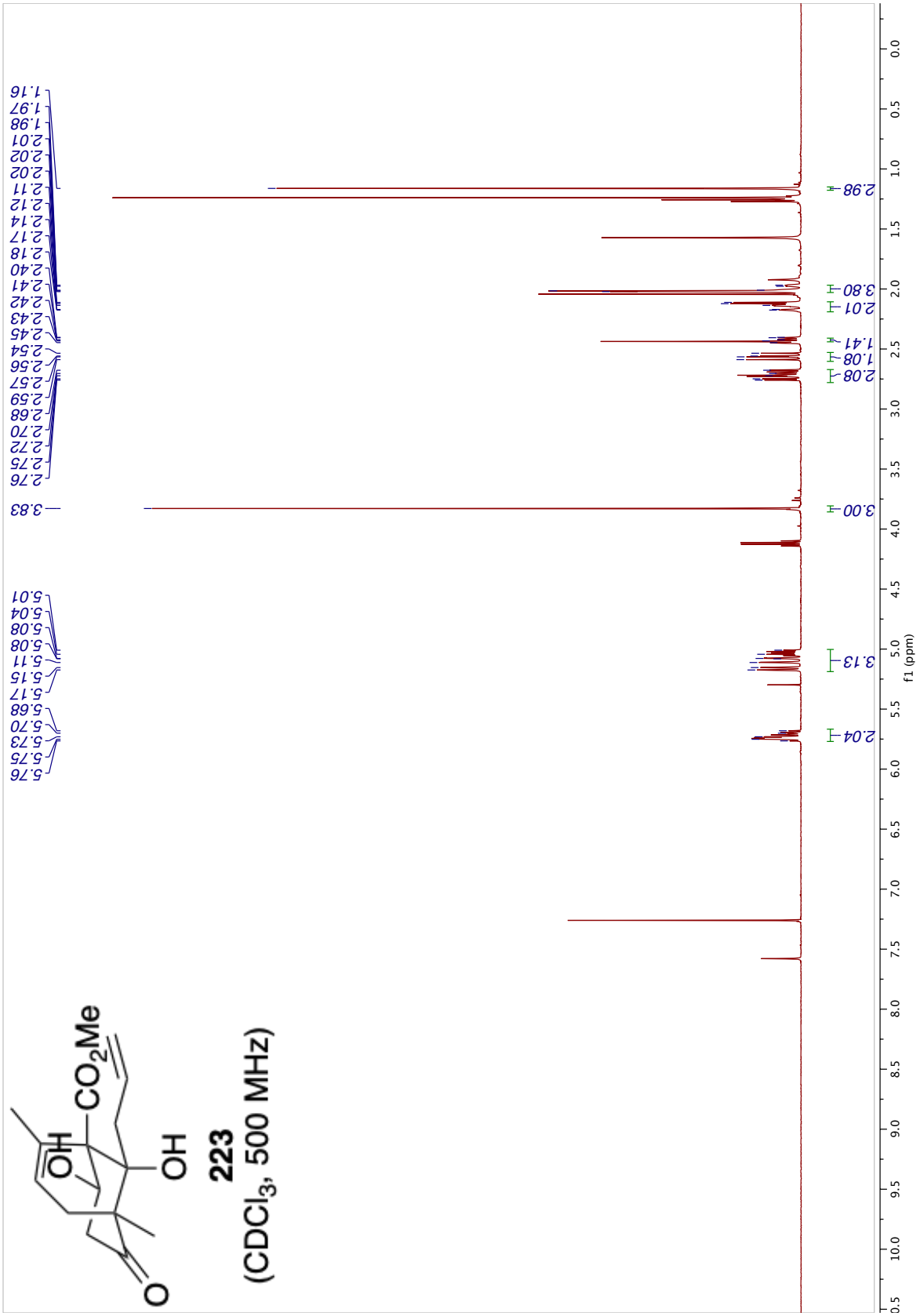

HO
HO
O
O
O
O
219
(CDCl3, 500 MHz)
0.96
1.36
1.36
1.38
1.39
1.49
1.51
1.52
1.71
1.73
1.74
1.77
1.80
1.82
1.90
1.91
1.94
2.45
2.49
3.50
3.52
3.54
3.65
3.67
3.93
3.95
3.98
4.05
4.06
4.07
4.09
4.48
4.48
4.76
4.77
4.78
4.80
5.49
0.97
0.98
2.21
2.24
1.06
1.00
1.05
3.00
1.04
1.14
7.20
1.24
f1 (ppm)

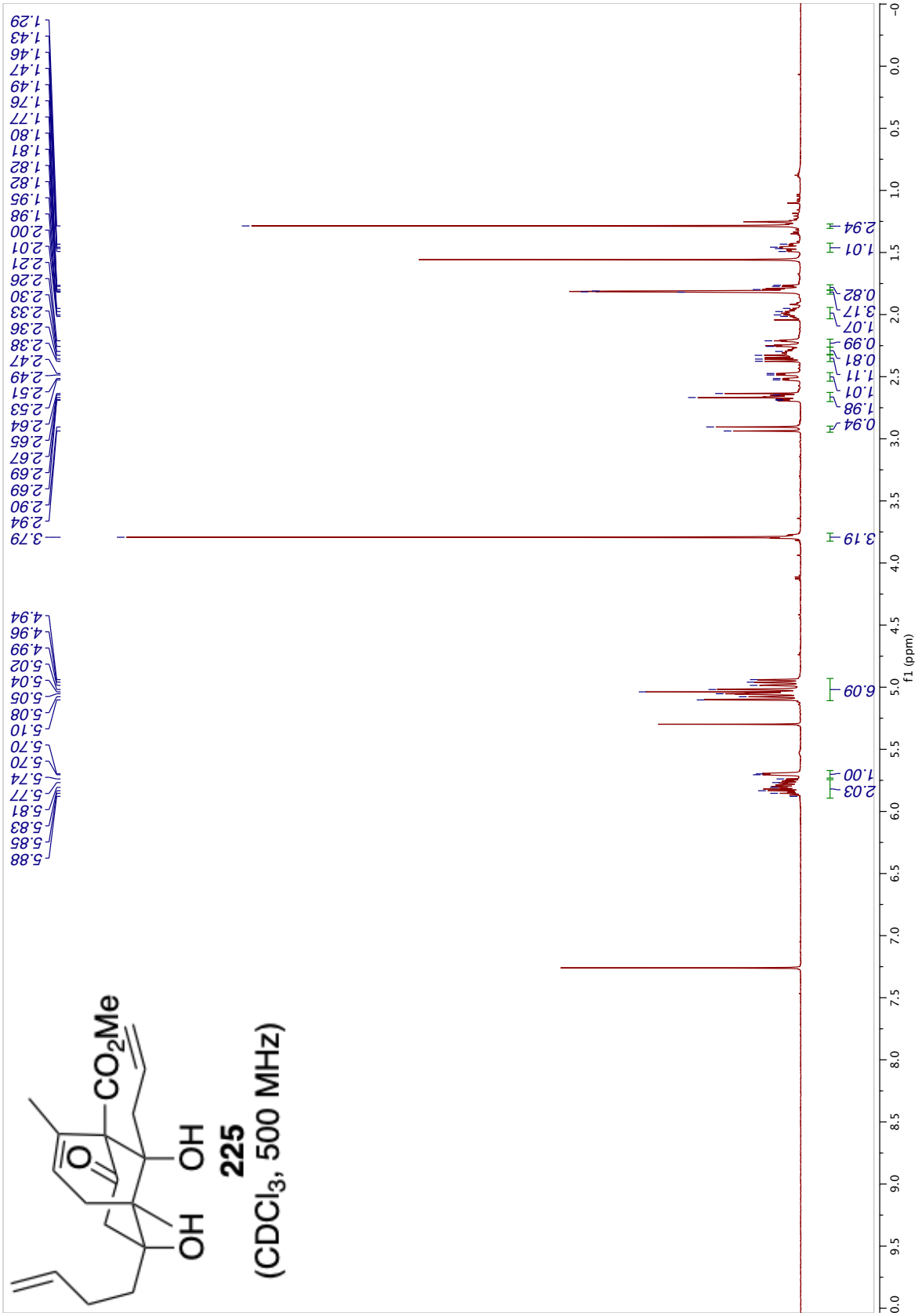

14.29
17.09
23.87
29.93
30.83
35.16
64.39
64.46
65.72
78.40
123.50
HO
HO
O
O
O
O
219
(CDCl3, 125 MHz)
f1 (ppm)

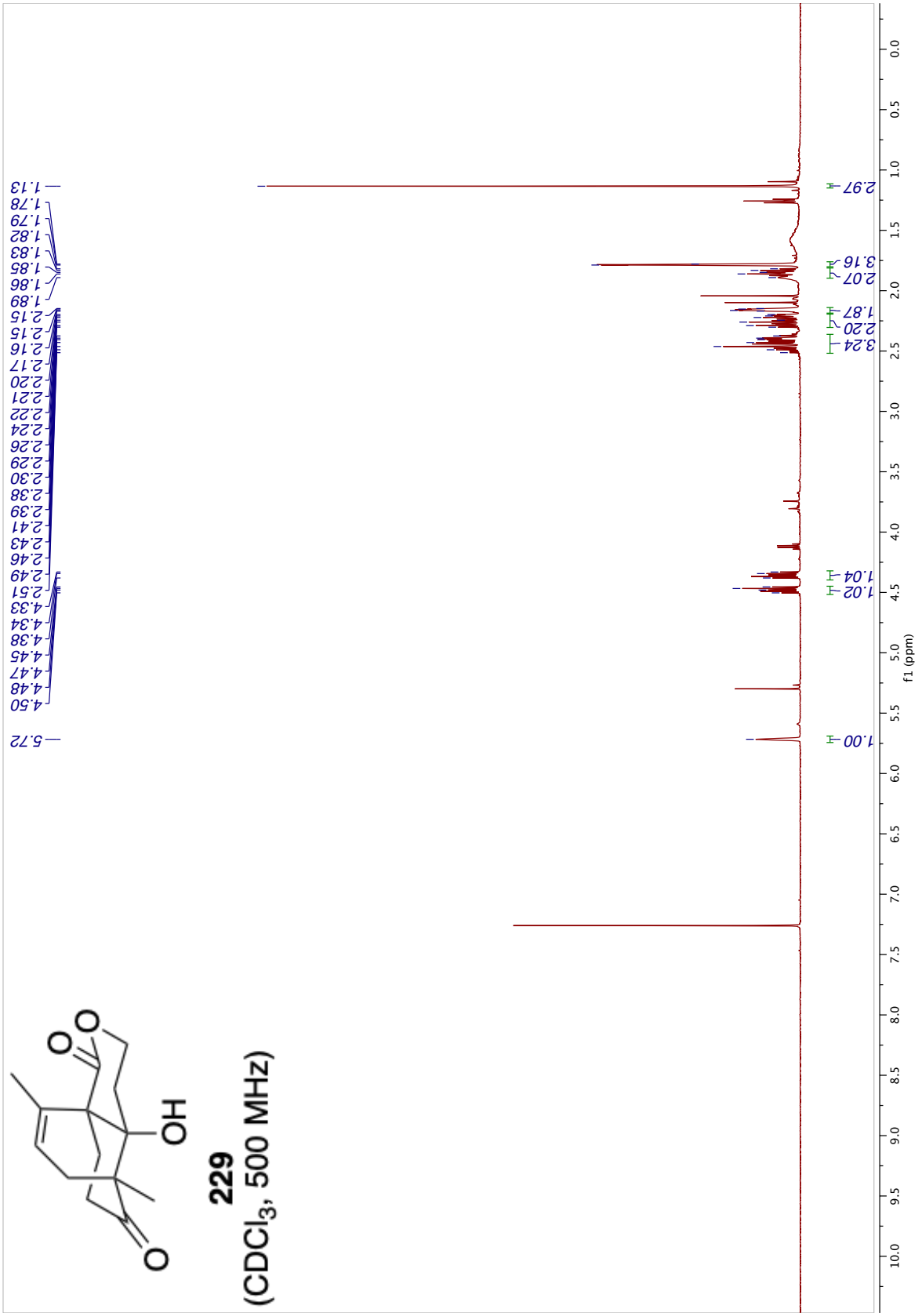

TMSO
OH
CO2Me
220
(CDCl3, 500 MHz)
0.17
1.11
1.70
1.71
1.97
2.01
2.04
2.04
2.37
2.52
2.54
2.94
2.99
3.68
4.70
4.71
4.72
5.00
5.02
5.05
5.08
5.43
5.44
5.75
5.78
5.81
8.99
3.00
3.00
2.99
1.00
2.04
1.10
3.08
1.04
2.12
1.02
1.12
f1 (ppm)

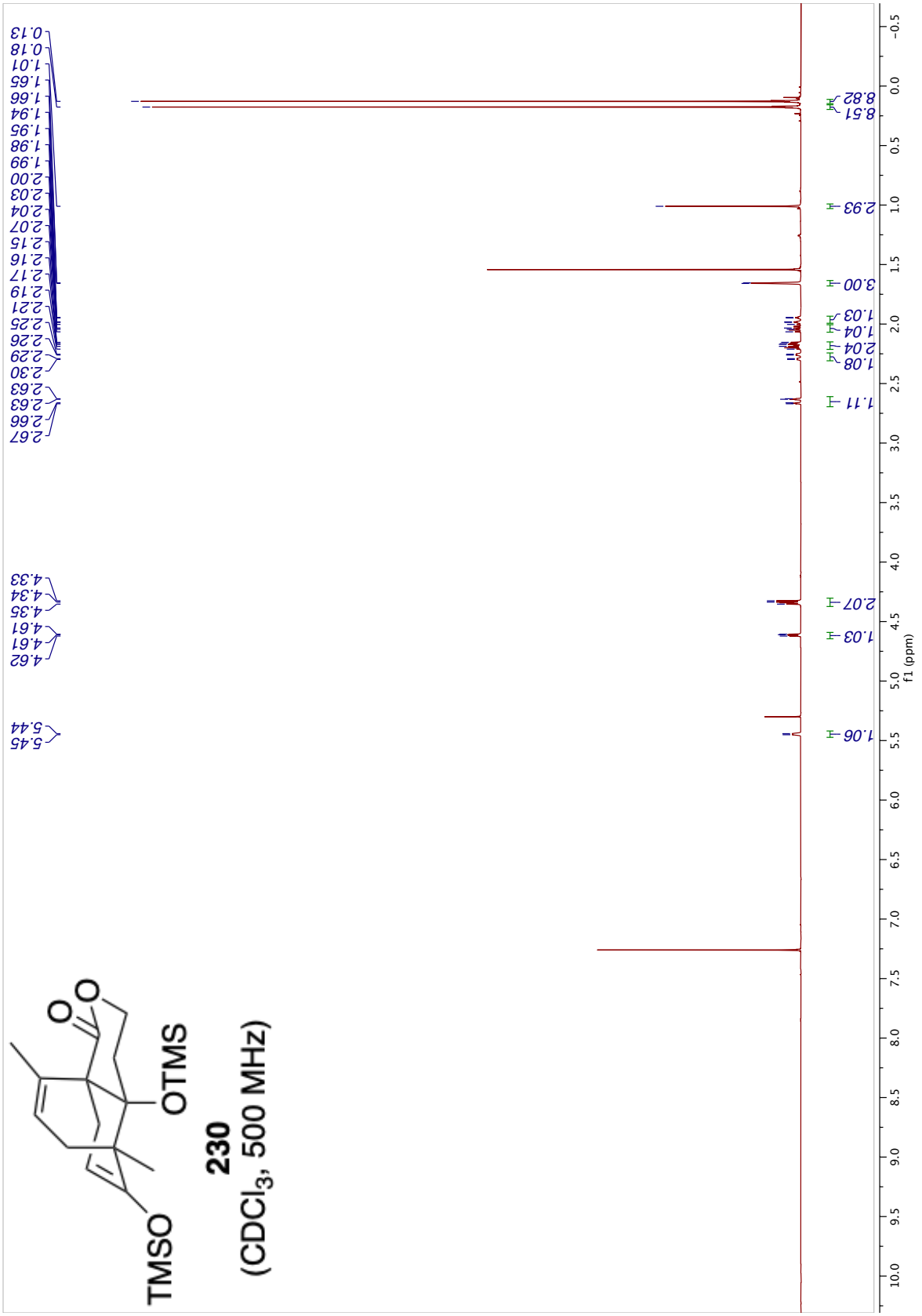

CO2Me
OH
O
221
(CDCl3, 500 MHz)
(UNSTABLE)
f1 (ppm)

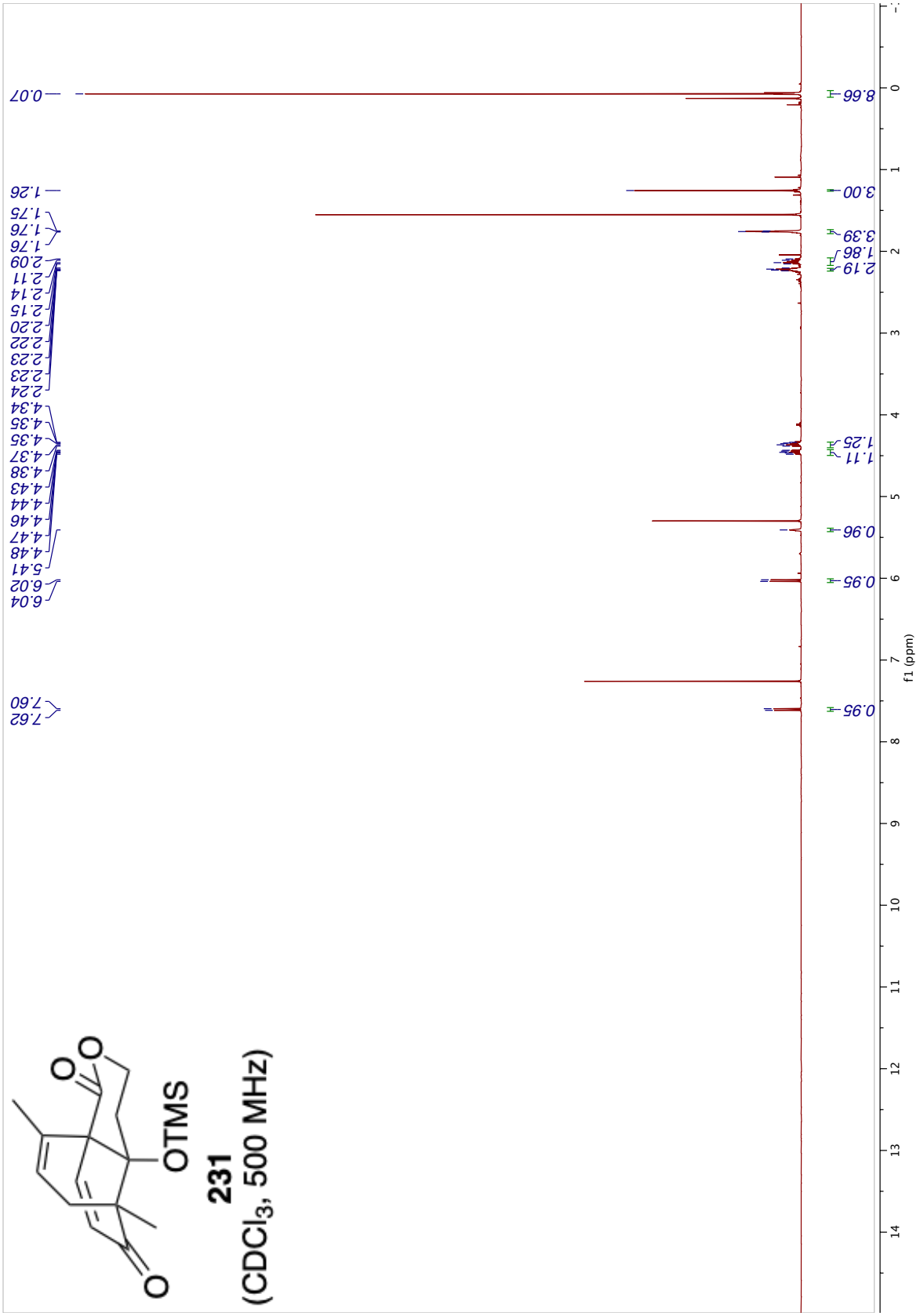

Bpin
CO2Me
OH
O
222
(CDCl3, 500 MHz)
f1 (ppm)

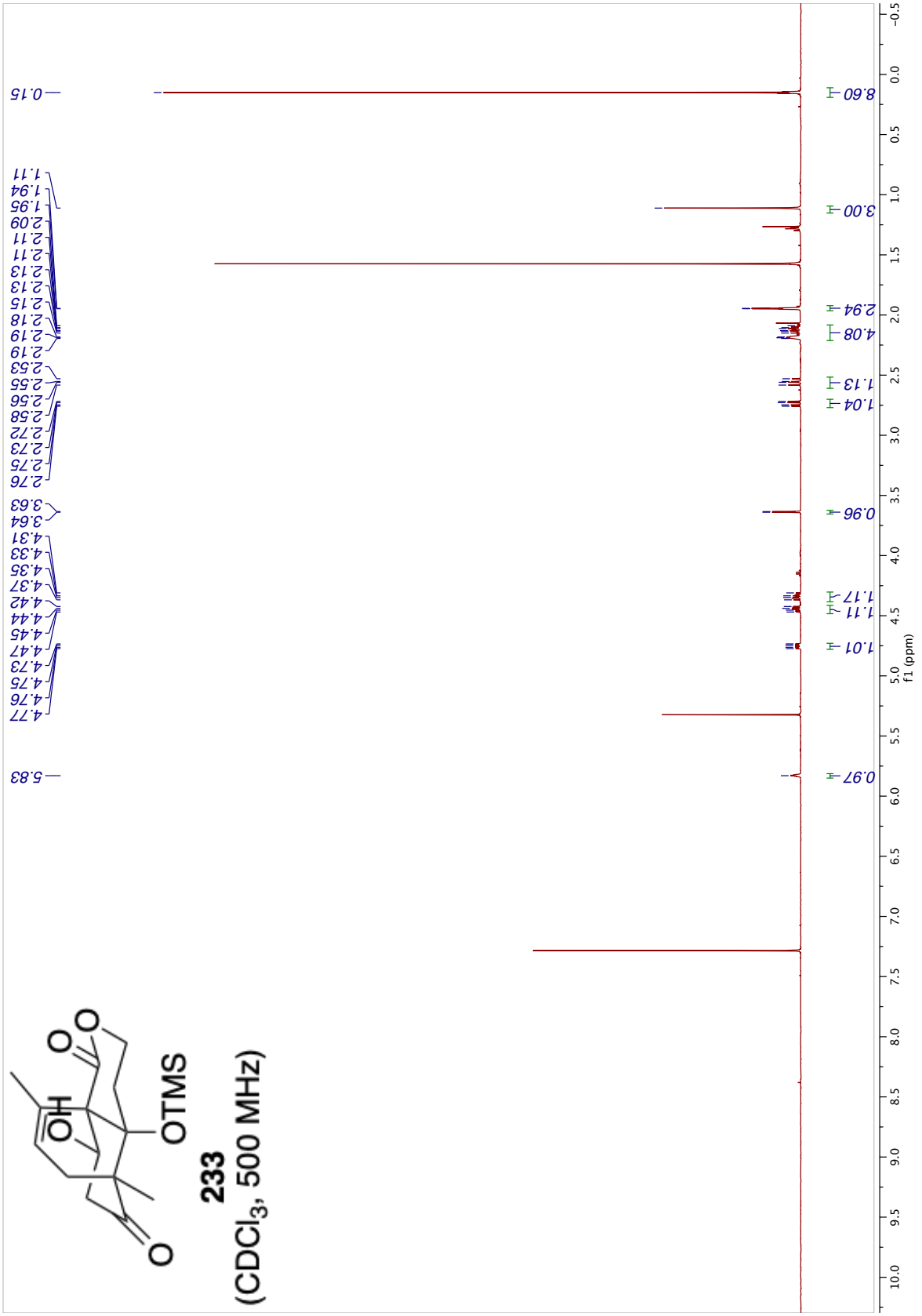

223
(CDCl3, 500 MHz)
OH
CO2Me
OH
O
1.16
1.97
1.98
2.01
2.02
2.02
2.11
2.12
2.14
2.17
2.18
2.40
2.41
2.42
2.43
2.45
2.54
2.56
2.57
2.59
2.68
2.70
2.72
2.75
2.76
3.83
5.01
5.04
5.08
5.08
5.11
5.15
5.17
5.68
5.70
5.73
5.75
5.76
2.98
3.80
2.01
1.41
1.08
2.08
3.00
3.13
2.04
f1 (ppm)

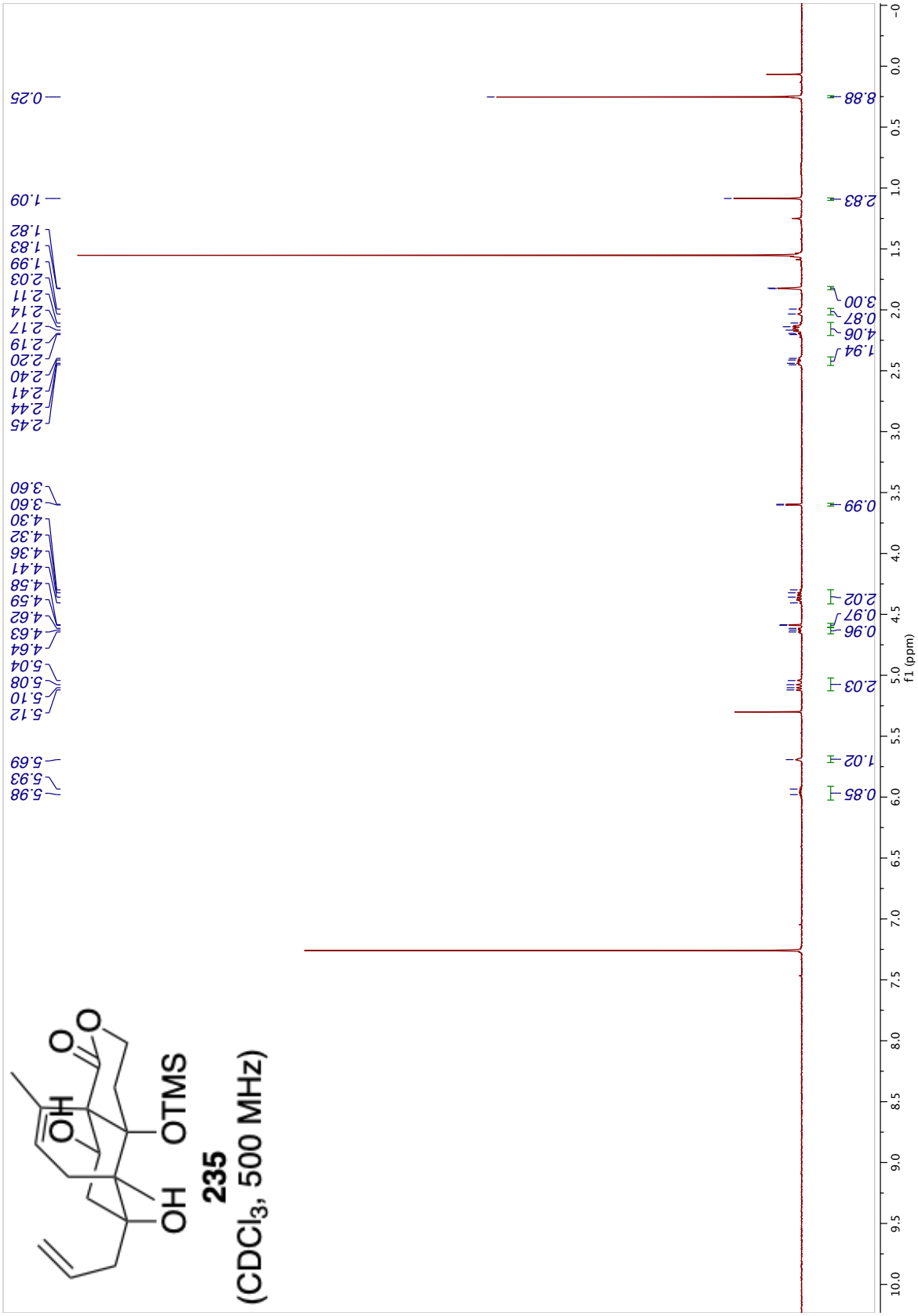

CO2Me
O
OH
OH
225
(CDCl3, 500 MHz)
f1 (ppm)

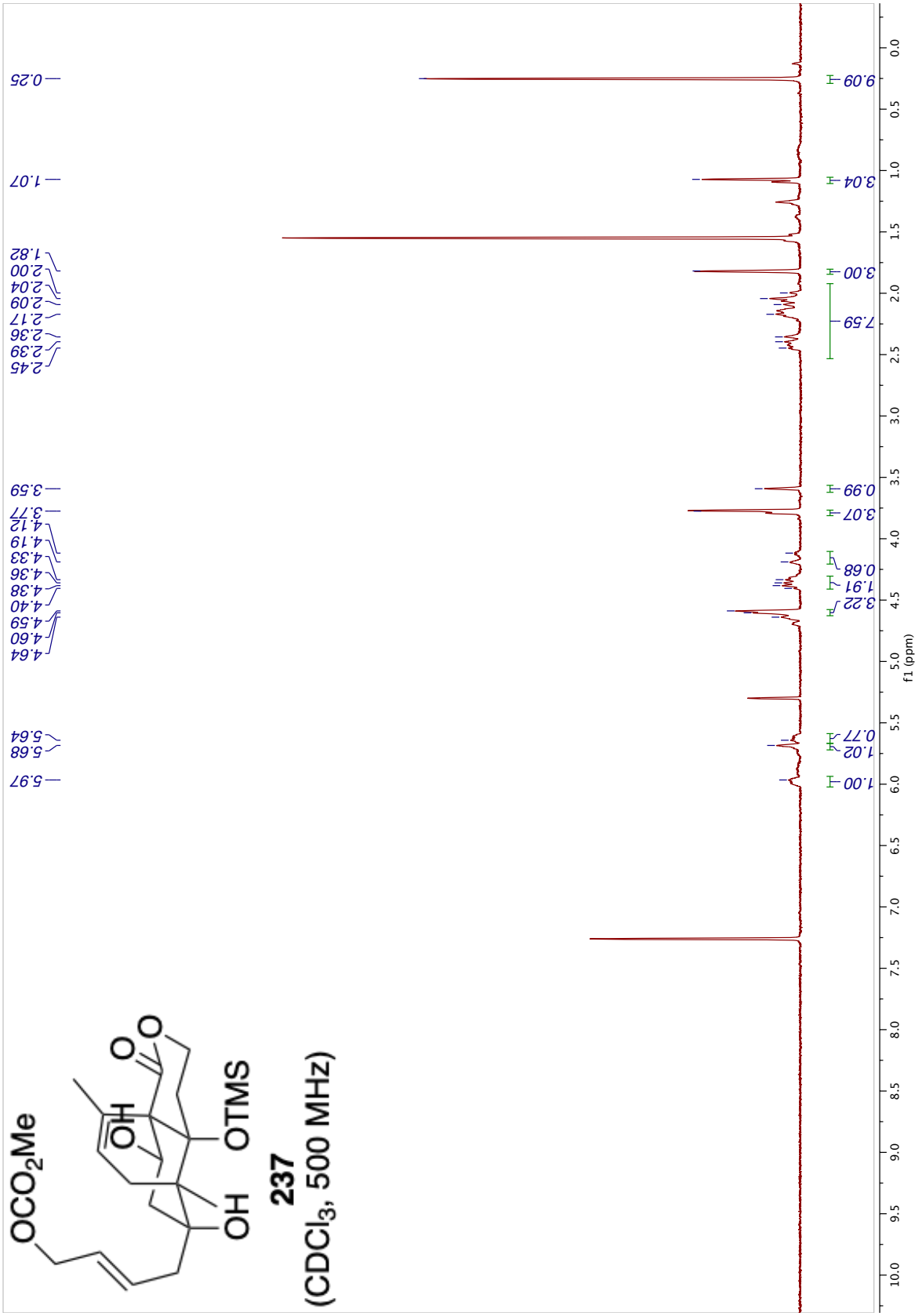

O
O
OH
O
229
(CDCl3, 500 MHz)
1.13
1.78
1.79
1.82
1.83
1.85
1.86
1.89
2.15
2.15
2.16
2.17
2.20
2.21
2.22
2.24
2.26
2.29
2.30
2.38
2.39
2.41
2.43
2.46
2.49
2.51
4.33
4.34
4.38
4.45
4.47
4.48
4.50
5.72
2.97
3.16
2.07
1.87
2.20
3.24
1.02
1.04
1.00
f1 (ppm)

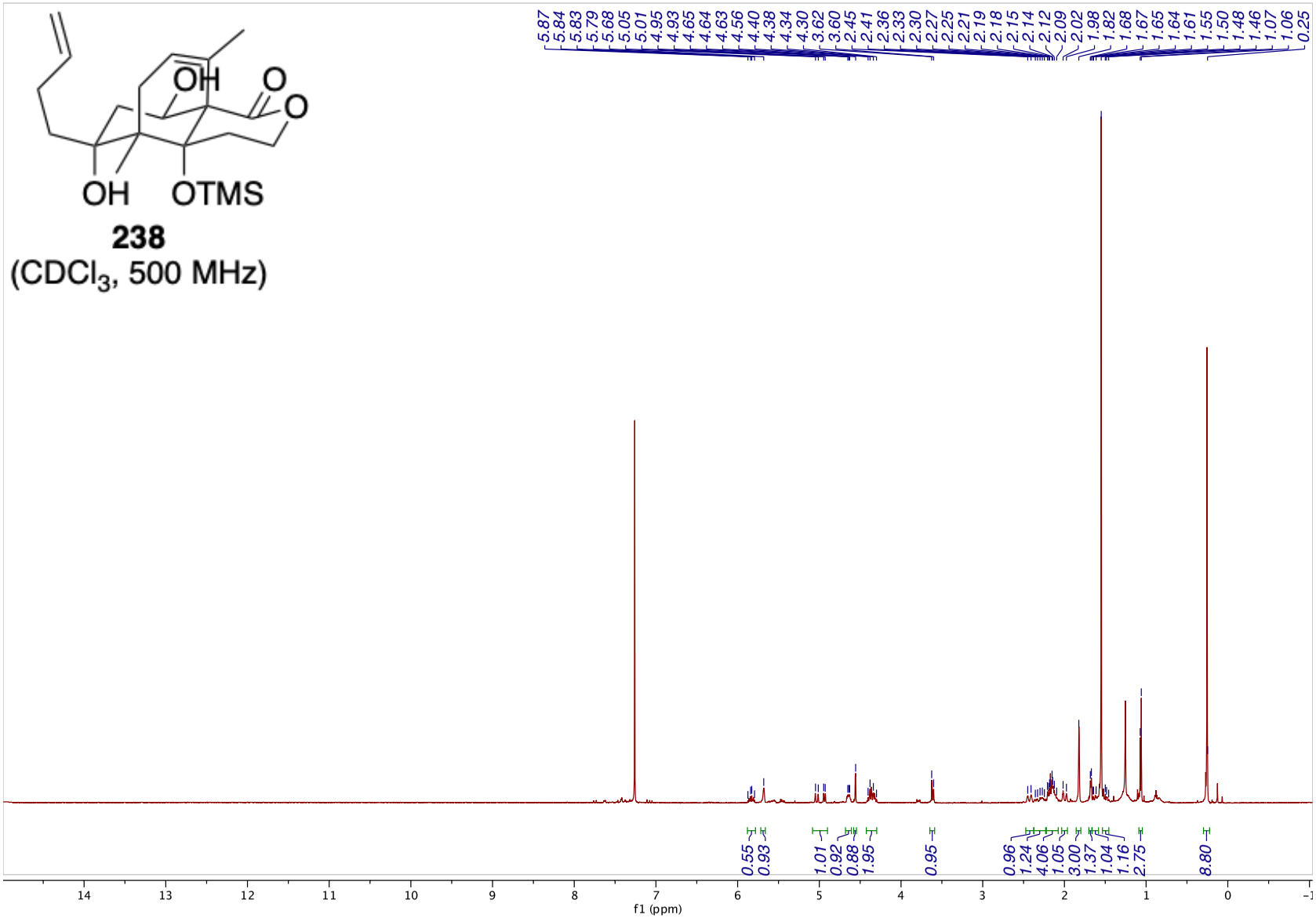

TMSO
OTMS
O
O
230
(CDCl3, 500 MHz)
f1 (ppm)

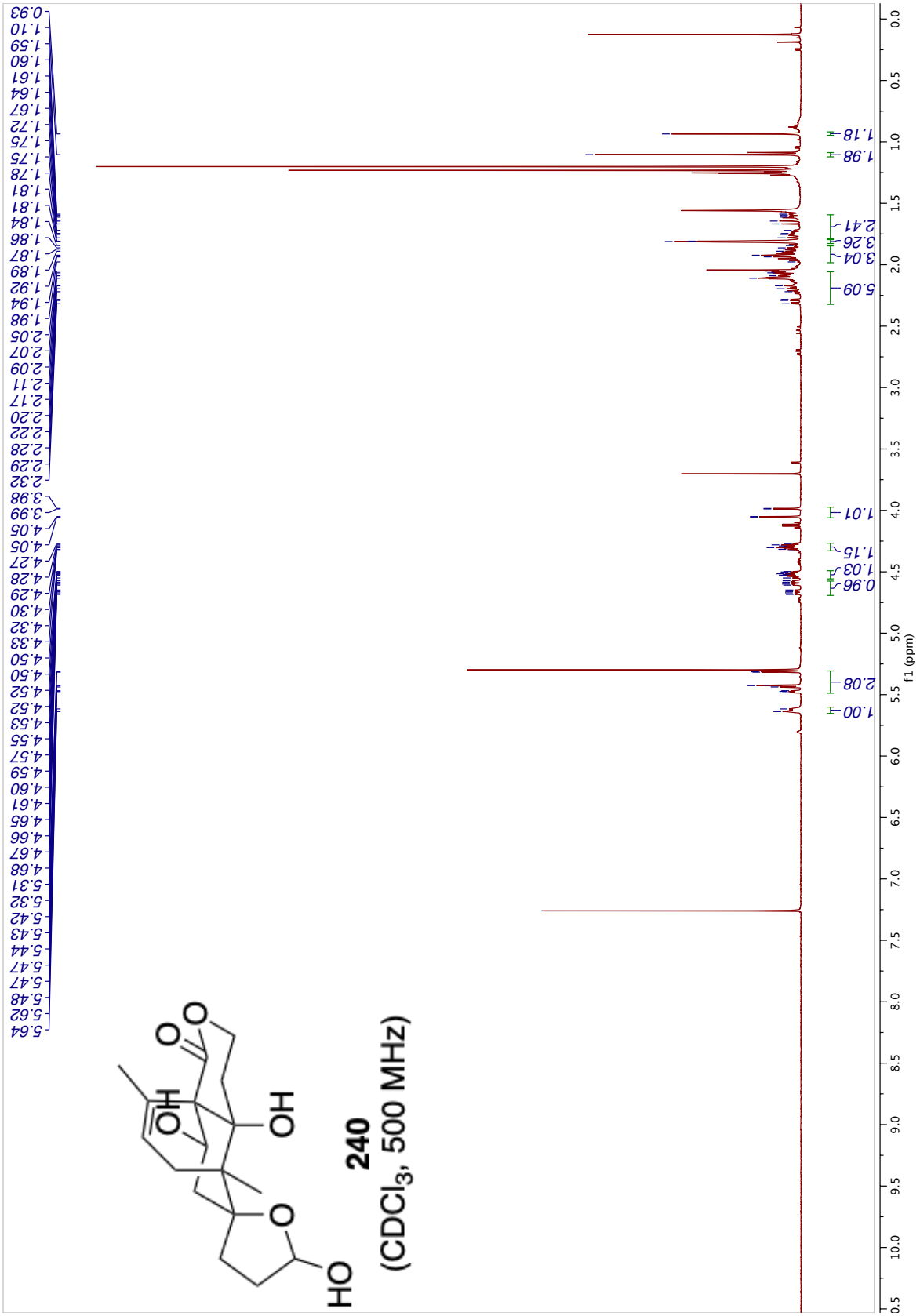

OTMS
231
(CDCl3, 500 MHz)
f1 (ppm)

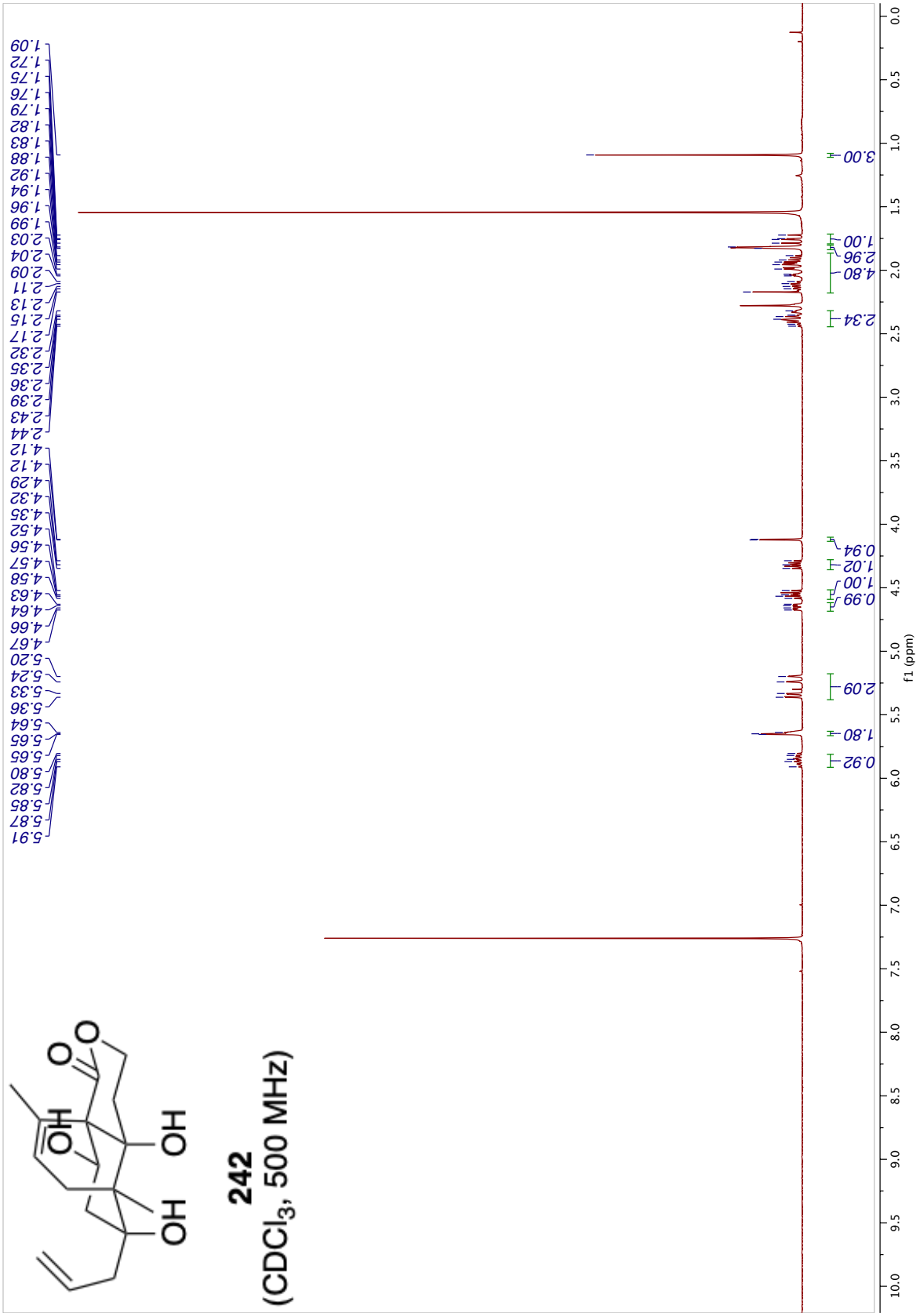

OTMS
233
(CDCl3, 500 MHz)
f1 (ppm)

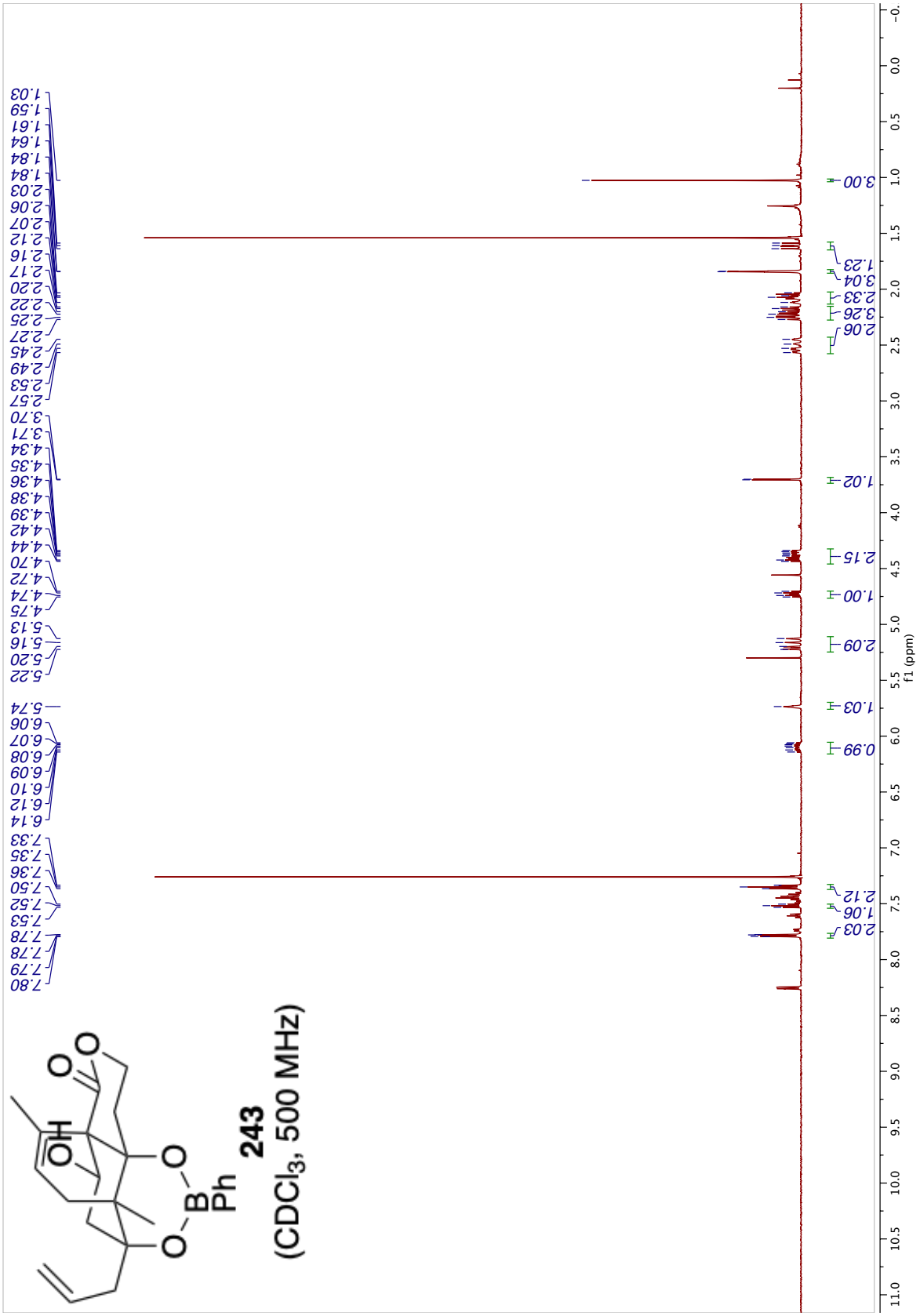

OH
O
O
OH
OTMS
235
(CDCl3, 500 MHz)
f1 (ppm)

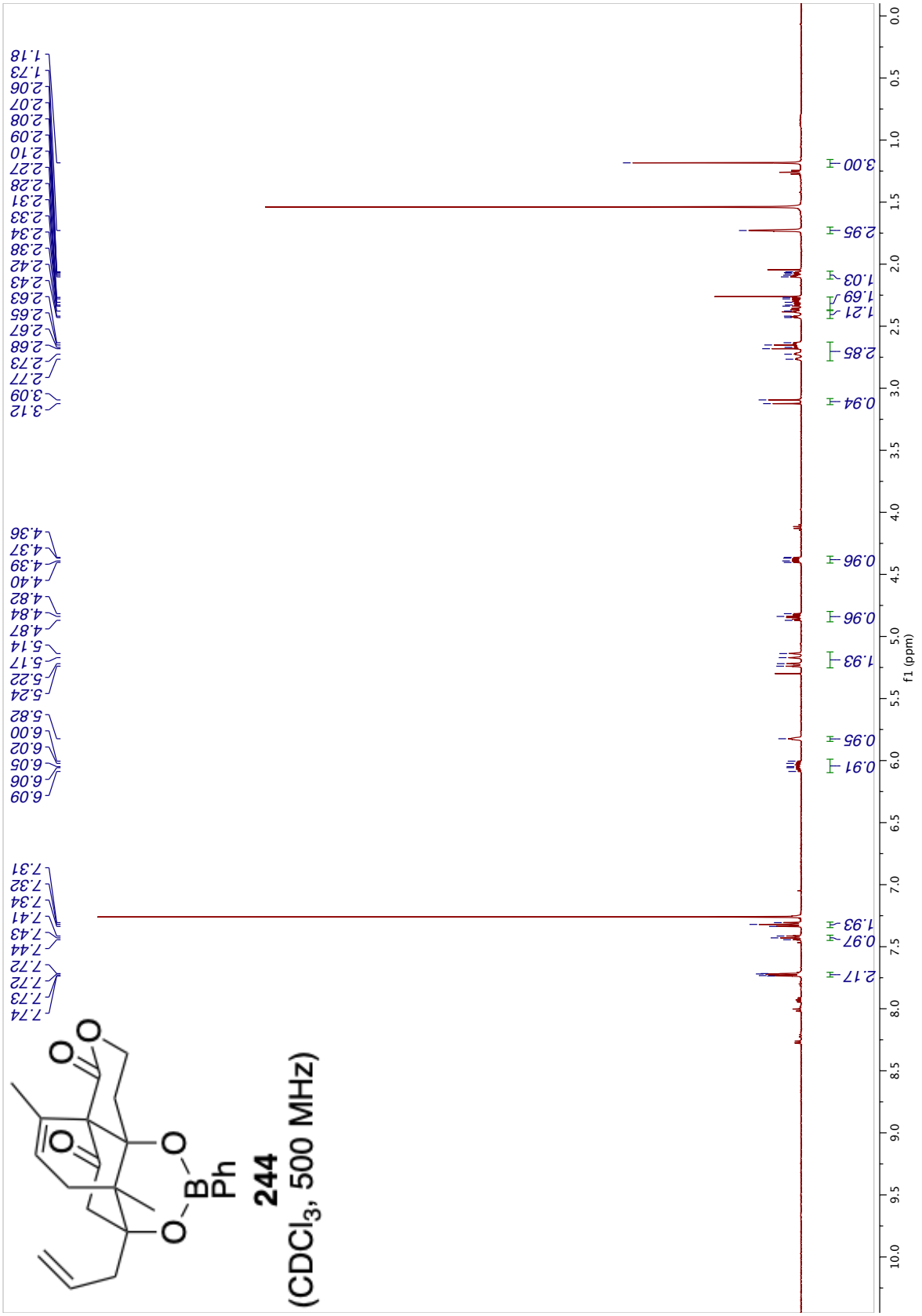

OCO2Me
OH
O
O
OH
OTMS
237
(CDCl3, 500 MHz)
0.25
1.07
1.82
2.00
2.04
2.09
2.17
2.36
2.39
2.45
3.59
3.77
4.12
4.19
4.33
4.36
4.38
4.40
4.59
4.60
4.64
5.64
5.68
5.97
9.09
3.04
3.00
7.59
0.99
3.07
0.68
1.91
3.22
0.77
1.02
1.00
f1 (ppm)

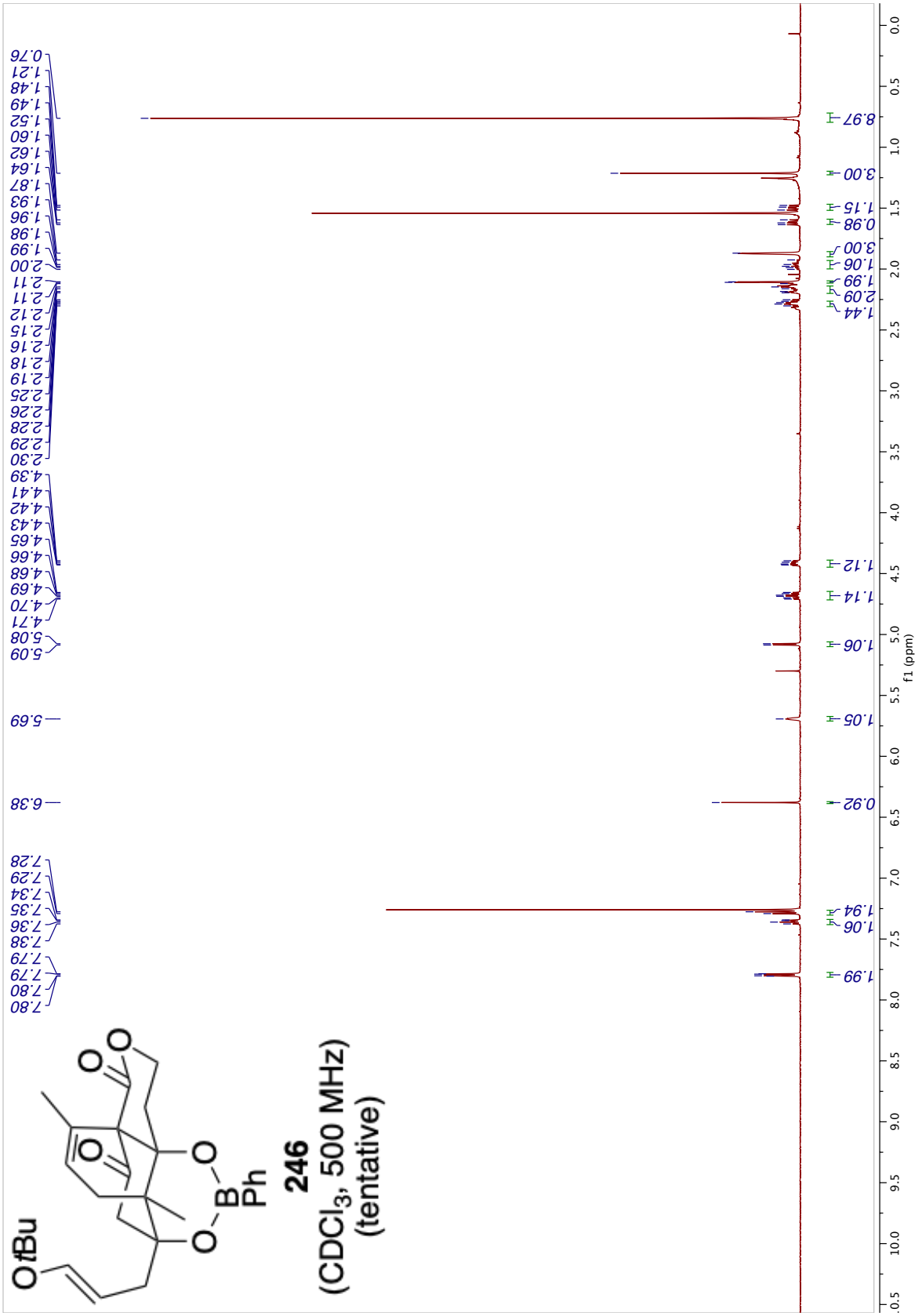

OH
O
O
OH
OTMS
238
(CDCl3, 500 MHz)
5.87
5.84
5.83
5.79
5.68
5.05
5.01
4.95
4.93
4.65
4.64
4.63
4.56
4.40
4.38
4.34
4.30
3.62
3.60
2.45
2.41
2.36
2.33
2.30
2.27
2.25
2.21
2.19
2.18
2.15
2.14
2.12
2.09
2.02
1.98
1.82
1.68
1.67
1.65
1.64
1.61
1.55
1.50
1.48
1.46
1.07
1.06
0.25
0.55
0.93
1.01
0.92
0.88
1.95
0.95
0.96
1.24
4.06
1.05
3.00
1.37
1.04
1.16
2.75
8.80
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)


240
(CDCl3, 500 MHz)
HO
O
O
OH
OH
f1 (ppm)


OH
O
O
OH
OH
242
(CDCl3, 500 MHz)
f1 (ppm)


243
(CDCl3, 500 MHz)
Ph
B
O
OH
f1 (ppm)


244
(CDCl3, 500 MHz)
O
O
O
O
B
Ph
7.74
7.73
7.72
7.72
7.44
7.43
7.41
7.34
7.32
7.31
6.09
6.06
6.05
6.02
6.00
5.82
5.24
5.22
5.17
5.14
4.87
4.84
4.82
4.40
4.39
4.37
4.36
3.12
3.09
2.77
2.73
2.68
2.67
2.65
2.63
2.43
2.42
2.38
2.34
2.33
2.31
2.28
2.27
2.10
2.09
2.08
2.07
2.06
1.73
1.18
2.17
0.97
1.93
0.91
0.95
1.93
0.96
0.96
1.93
2.85
1.21
1.69
1.03
2.95
3.00
0.94
f1 (ppm)


246
(CDCl3, 500 MHz)
(tentative)
OtBu
O
O
O
O
B
Ph
f1 (ppm)