SYNTHETIC STUDIES OF IRIOMOTEOLIDE-1A

TOTAL SYNTHESIS OF ALOTAKETAL A AND AN ANTIFUNGAL *O*-HYDROXY-*P*-QUINONE METHIDE DITERPENOID

A Dissertation

by

JINHUA HUANG

Submitted to the Office of Graduate and Professional Studies of
Texas A&M University
in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

Chair of Committee,	Jiong Yang
Committee Members,	Daniel Romo
	Karen L. Wooley
	Yue Kuo
Head of Department,	David H. Russell

December 2013

Major Subject: Chemistry

ABSTRACT

Natural products are a rich source of compounds with interesting structures and biological activities. Three bioactive natural products, iriomoteolide-1a, alotaketal A, and an unnamed quinone methide diterpenoid, attracted our attention during our course of exploring natural products as potential leads for biomedical discovery.

The structure of iriomoteolide-1a had been misassigned, but the potent cytotoxicity reported for this natural product warranted further studies to elucidate its true structure. As part of our effort toward this goal, we finished the total synthesis of a diastereomer of iriomoteolide-1a. Our total synthesis featured a lithium acetylide-chloroformate coupling to assemble the alkyne and chloroformate fragments, the ring closing metathesis to exclusively generate the 15*E*-macrocyclic diolide, and a SmI_2-mediated intramolecular reductive allylation to form the cyclic hemiketal. The bioactivities of this diastereomer were evaluated, but only weak inhibition of cell proliferation was observed at 10 μM toward HeLa and PC3 cell lines.

Alotaketal A was reported to potently (EC_{50} = 18 nM) activate the cAMP (cyclic adenosine monophosphate) signaling pathway in HEK293 cells transformed with the pHTS-CRE plasmid. Our synthetic efforts toward this natural product culminated in the first enantioselective total synthesis of (-)-alotaketal A. Our total synthesis employed both intra- and inter-molecular reductive allylation of esters for assembling the bicyclic lactone and coupling the fragments. A $Hg(OAc)_2$-mediated allylic mercuration was used to introduce the C22-hydroxyl group. The subtle influence of substituents over the

course of the spiroketalization process was revealed. The synthesis confirmed the relative and absolute stereochemistry of (-)-alotaketal A and allowed verification of alotaketal A's effect over cAMP signaling using reporter-based FRET imaging assays with HEK293 cells. Our studies also revealed alotaketal A's unique activity in selectively targeting nuclear PKA signaling in living cells.

Our synthetic efforts toward the unnamed quinone methide diterpenoid 1.67 led to the first total synthesis of this potent antifungal product (MIC = 0.19 μM). Our total synthesis was highlighted by a Stille coupling to introduce the allyl group, a lithium/naphthalene-mediated coupling reaction for fragment assembling, and a BBr_3-mediated one-pot *bis*-demethylation and intramolecular Friedel-Crafts alkylation to build the tricyclic molecular framework. Our preliminary structure-activity relationship study showed that the 2'-hydroxyethyl side chain of the natural product was nonessential to its antifungal activity.

DEDICATION

To my wife Xiaowei Hu

my son Gavin Huang

my coming baby

my parents

ACKNOWLEDGEMENTS

I earnestly thank my advisor, Prof. Jiong Yang, for his guidance, support and friendship that he extended throughout my graduate study at Texas A&M University. It is really wonderful to have him as my advisor in the past four years and wish to have him in my whole life.

I also extend my appreciation to Prof. Romo, Prof. Wooley, and Prof. Kuo, for their time and graciously serving on my committee. I really enjoyed Prof. Romo's class especially his idea of building the reaction database which gave me insight and broader view of organic chemistry. I would like to give many thanks to Prof. Wooley and Prof. Kuo for taking an interest in my research and being a contributing committee member. I appreciate Prof. Bergbreiter for serving on my 681 seminar. Also, I express my gratitude to Dr. Connell for helpful discussions and instructions. Additionally, I would like to thank Prof. Weiping Tang of University of Wisconsin-Madison for his suggestion on the alotaketal A project.

My sincere thanks go to Prof. Jun Liu and Prof. Jin Zhang of Johns Hopkins University for their collaboration in the biological investigation of iriomoteolide-1a and alotaketal A, respectively. I highly appreciate Jessica Yang of Prof. Jin Zhang's group for all her efforts on the alotaketal A project. I thank Prof. Xiaorong Lin and her student, Dylan Foyle, of the Biology Department of Texas A&M University for biological investigation in the *o*-hydroxy-*p*-quinone methide diterpenoid project.

I thank all of the former and current group members, Dr. Lijing Fang, Dr. Guoqiang Tian, Dr. Haoran Xue, Fei Yang, Thomas Kaiser, Tyler Hood, Kellymar Rosa-Perez, Bryan Huehls, Mohamed Hashim, Dr. Aijun Lin, and Dr. Zhiwei Zhang, for their help and friendship. Also, I thank Mr. Gaines Taylor (NSF REU student) of the University of Maryland, Baltimore County, for preparing some of the starting materials. My personal thanks go to my friends and colleagues at Chemistry Department, especially, Hua Zhou and Gang Liu.

Finally, great thanks to my wife, Xiaowei Hu for her love and patience. Without her support, the journey would be more difficult. Also I would like to express my appreciation to my parents, my sister and brother.

NOMENCLATURE

2,6-lutidine	2,6-dimethylpyridine
BBN	borabicyclo[3.3.1]nonane
BMS	borane dimethyl sulfide
Bn	benzyl
Bu	butyl
cAMP	cyclic adenosine monophosphate
c-Hex	cyclohexyl
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DIBAL-H	diisobutylaluminium hydride
DMAP	4-dimethylaminopyridine
DMDO	dimethyldioxirane
DME	dimethoxyethane
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
dppf	1,1'-bis(diphenylphosphino)ferrocene
EC_{50}	half maximal effective concentration
Et	ethyl

HEK	human embryonic kidney
HMPA	hexamethylphosphoramide
IBX	2-iodoxybenzoic acid
IC_{50}	half maximal inhibitory concentration
InI	indium iodide
KHMDS	potassium bis(trimethylsilyl)amide
LiDBB	lithium *di-tert*-butylbiphenyl
Me	methyl
mCPBA	meta-chloroperbenzoic acid
Mes	mesityl
MFC	minimum fungicidal concentration
MIC	minimum inhibitory concentration
MOM	methoxymethyl
Ms	mesylate
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NIS	*N*-iodosuccinimide
NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
PhH	benzene
PMB	*p*-methoxybenzyl
PMBTCA	*p*-methoxybenzyl trichloroacetimidate

PPTS	pyridinium *p*-toluenesulfonate
pTSA	*p*-toluenesulfonic acid
Py	pyridine
RCM	ring closing metathesis
ROESY	rotating-frame nuclear overhauser effect correlation spectroscopy
sp.	species
TBAF	tetra-*n*-butylammonium bromide
TBS	*tert*-butyldimethylsilyl
TBSOTf	trimethylsilyl trifluoromethanesulfonate
TCBC	2,4,6-trichlorobenzoyl chloride
TES	triethylsilyl
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TMS	trimethylsilyl
TMSOTf	trimethylsilyl trifluoromethansulfonate

TABLE OF CONTENTS

Page

CHAPTER Page

CHAPTER Page

LIST OF FIGURES

LIST OF TABLES

CHAPTER I

BACKGROUND OF IRIOMOTEOLIDE-1A, ALOTAKETAL A AND AN ANTIFUNGAL *O*-HYDROXY-*P*-QUINONE METHIDE DITERPENOID

1.1 Background of Iriomoteolide-1a

1.1.1 Isolation and Bioactivities of Iriomoteolide-1a

Amphidinolides are a group of macrolides isolated from marine dinoflagellates *Amphidinium* sp.[1] They are characterized by highly oxygenated macrocyclic lactones of various sizes (12 to 29-membered rings) and side chains of different lengths and substitutions. The potent cytotoxicity and the unique molecular structure of amphidinolides attracted the attention of synthetic chemists and the syntheses of several of these macrolides have been reported.[2] Continued research of *Amphidinium* sp. in the laboratory of Tsuda led to the isolation of three new macrolides named iriomoteolide-1a, -1b and -1c (Figure 1.1) from monoclonal HYA024 strain originated from sea sand collected off Iriomote Island, Japan in 2007.[3]

The relative and absolute stereochemistry of iriomoteolide-1a were assigned by the combination of conformational analyses using NMR data and modified Mosher's method while the structures of iriomoteolide-1b and -1c were elucidated on the basis of analyses of NMR and chemical correlation with iriomoteolide-1a. The absolute configurations at C22 and C23 of the side chain of iriomoteolide-1c have not been determined. Iriomoteolide-1a and -1c share the same 20-membered macrolide core possessing the characteristic exocyclic C11-C26 alkene, six-membered C9/C13-cyclic

hemiketal, C2-C3 trisubstituted *Z*-double bond and two *E*-endocyclic double bonds. Iriomoteolide-1b features an endocyclic C11-C12 alkene, thus a stable enone in iriomoteolide-1b replaces the cyclic hemiketal present in iriomoteolide-1a and -1c.

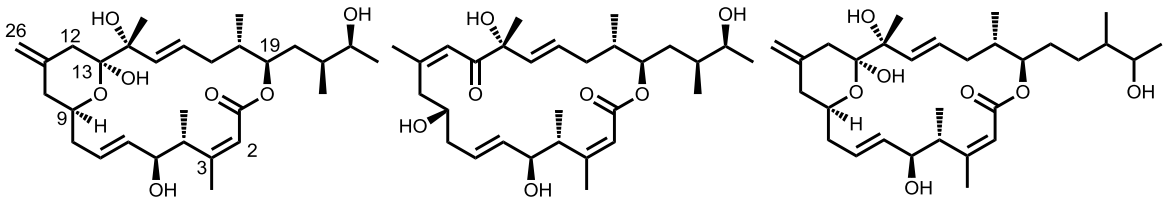


Figure 1.1. Originally proposed structures of iriomoteolides

Preliminary studies showed iriomoteolide-1a and -1c to be potently cytotoxic against human B lymphocyte DG-75 cells (IC_{50} value of 2 ng/mL for both of the macrolides) and Epstein-Barr virus-infected human B lymphocyte Raji cells (IC_{50} values of 3-4 ng/mL). However, the IC_{50} value (900 ng/mL) of iriomoteolide-1b against DG-75 cells is 450 times less potent than those of iriomoteolide-1a and -1c. This result suggested that the C9/C13-cyclic hemiketal and/or the exocyclic C11-C26 alkene are essential for the observed potent cytotoxicity of iriomoteolide-1a and -1c.

1.1.2 Synthetic Efforts Toward Iriomoteolide-1a

The intriguing molecular architecture and potent biological activity of iriomoteolide-1a attracted considerable attention for its total synthesis.[4] In 2010, Horne,[4m] Ghosh[4n] and our groups[4o] independently arrived at the conclusion that the

original structural assignment of iriomoteolide-1a was incorrect. While both Horne and Ghosh synthesized the originally proposed iriomoteolide-1a and reported the inconsistency of its spectra with those of the natural product, our conclusion that the C2-C3 trisubstituted *Z*-double bond of the original structure must have been misassigned prompted us to target the 2*E* diastereomer (i.e., **1.1**, Figure 1.2). This isomer was found to be different from the natural product too. Our group also synthesized two additional 2*E*-diastereomers (i.e., **1.2** and **1.3**). However, they didn't match the natural product either. More recently, Dai and co-workers reported their syntheses of **1.1** and another 2*E*-diastereomer **1.4**,[4q] which were also found to be different from the natural product. These results collectively show that, if the connectivity of the natural product has been correctly assigned, the original structure of iriomoteolide-1a likely has been misassigned at more than one stereocenter.

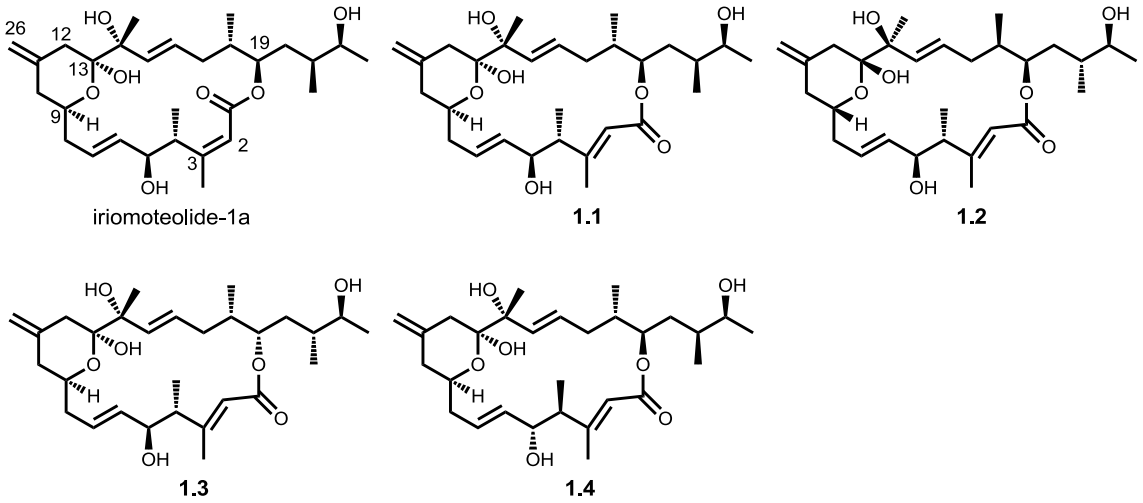


Figure 1.2. The original iriomoteolide-1a and some of the diastereomers

1.1.2.1 Horne's Total Synthesis of the Proposed Iriomoteolide-1a

Horne and co-workers accomplished the first total synthesis of the proposed structure of iriomoteolide-1a.[4m] They disconnected the complex molecule into three key building blocks: C1-C6, C7-C16 and C17-C23 fragments (Figure 1.3 and Scheme 1.1). The stereocenters in C1-C6 fragment **1.6** were obtained from the known compound **1.5**. The key step in the synthesis of C7-C16 fragment **1.12** was a Sakurai reaction between allyltrimethylsilane **1.9** and aldehyde **1.11** mediated by $SnCl_4$. The synthesis of C17-C23 fragment **1.17** featured an *anti*-aldol reaction with chiral auxiliary **1.15** to control the stereocenters at C18 and C19.

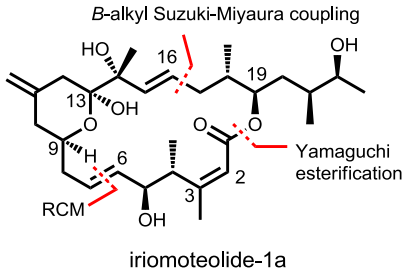
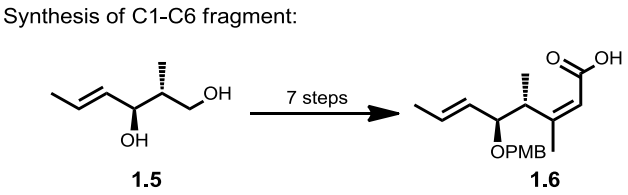
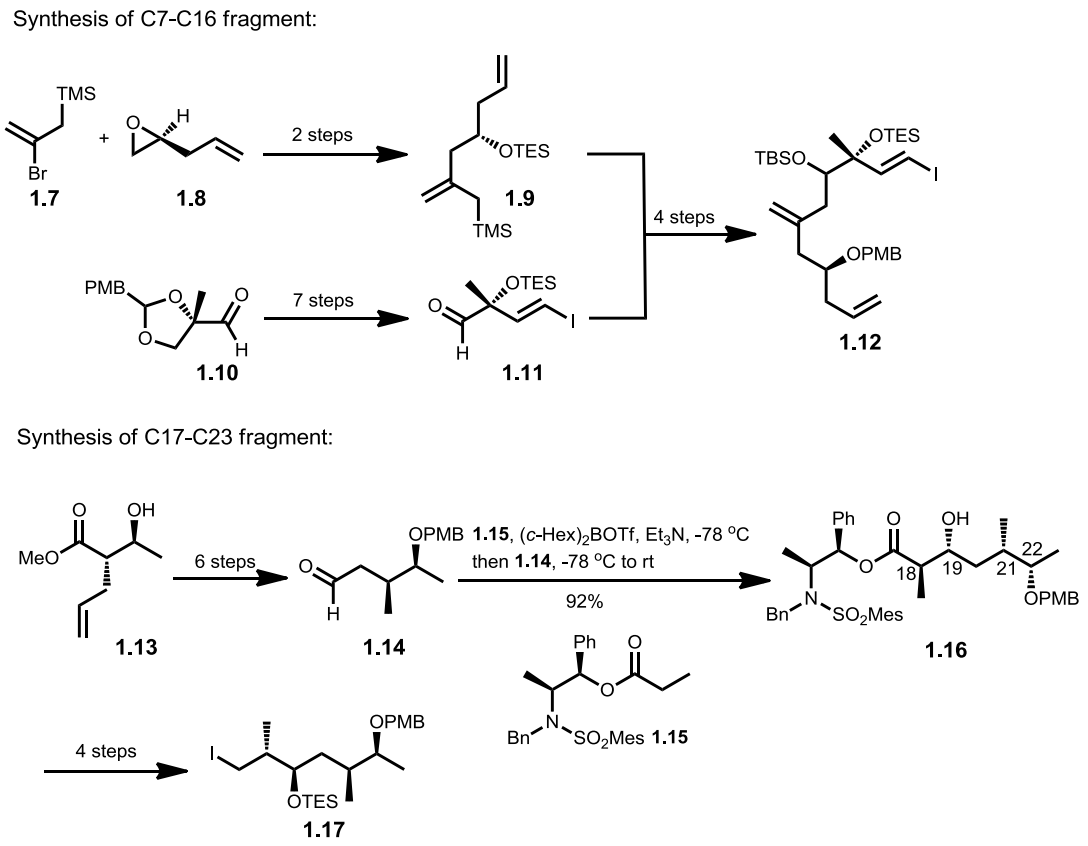


Figure 1.3. Horne's disconnection of iriomoteolide-1a

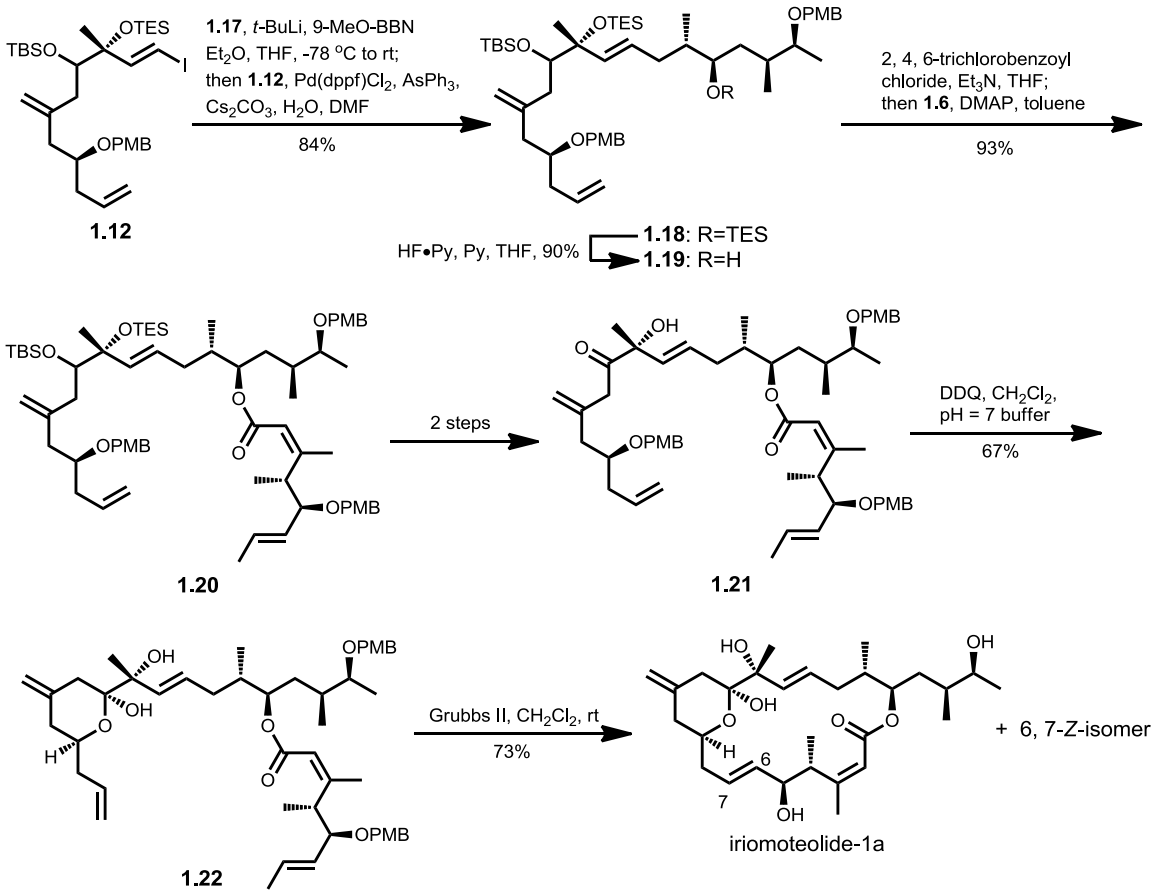


Scheme 1.1. Horne's synthesis of key fragments



Scheme 1.1. (Continued) Horne's synthesis of key fragments

The coupling of these fragments and the completion of the synthesis of the original iriomoteolide-1a were shown in Scheme 1.2. Suzuki-Miyaura coupling between **1.12** and **1.17** produced C7-C23 fragment **1.18**. Selective removal of the TES protecting group afforded alcohol **1.19** for Yamaguchi esterification. Global deprotection along with concomitant hemiketalization occurred upon treatment of **1.21** with DDQ afforded intermediate **1.22**. Treatment of **1.22** with Grubbs II catalyst gave the original iriomoteolide-1a and its 6, 7-*Z*-isomer in 2.5:1 ratio.



Scheme 1.2. Horne's total synthesis of proposed iriomoteolide-1a

1.1.2.2 Ghosh's Total Synthesis of Proposed Iriomoteolide-1a

Ghosh and co-workers also accomplished the synthesis of the proposed structures of iriomoteolide-1a and -1b.[4n] Unlike Horne's synthesis, they employed two stages of Julia-Kocienski olefination to control the two *E*-alkenes (Figure 1.4). Ghosh's strategy also involved disassembling iriomoteolide-1a into three portions (Scheme 1.3), i.e. C1-C6, C7-C15 and C16-C23 fragments. The C7-C15 fragment was derived from a Sakurai

reaction of aldehyde **1.26** and allyl silane **1.28**. The C1-C6 and C16-C23 fragments were prepared from known compounds **1.23** and **1.30**, respectively.

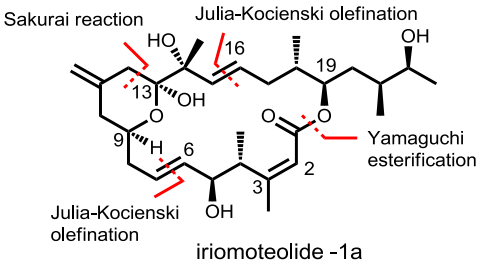
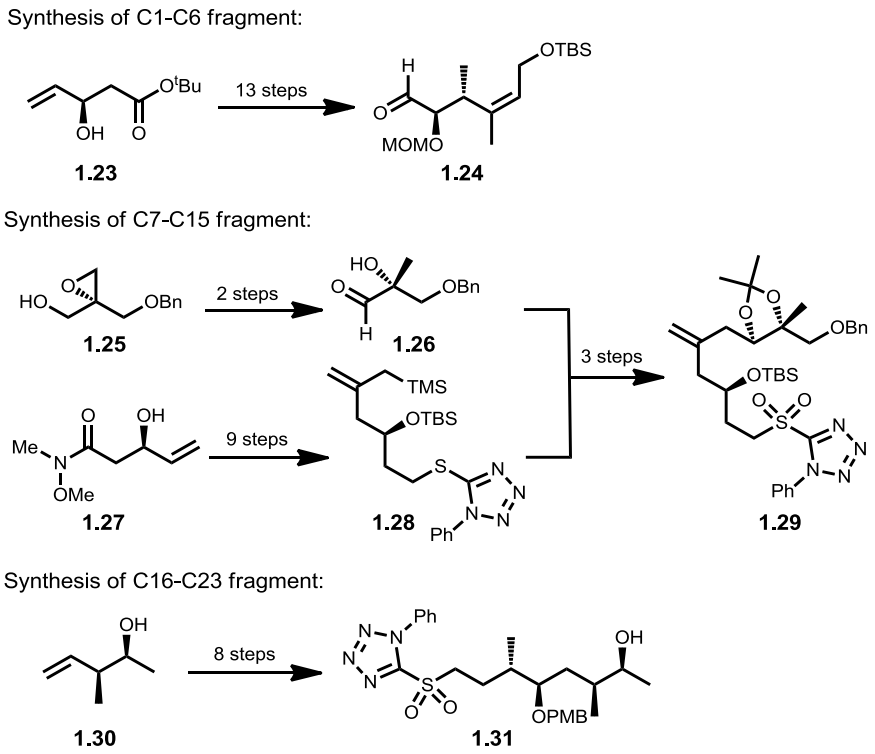
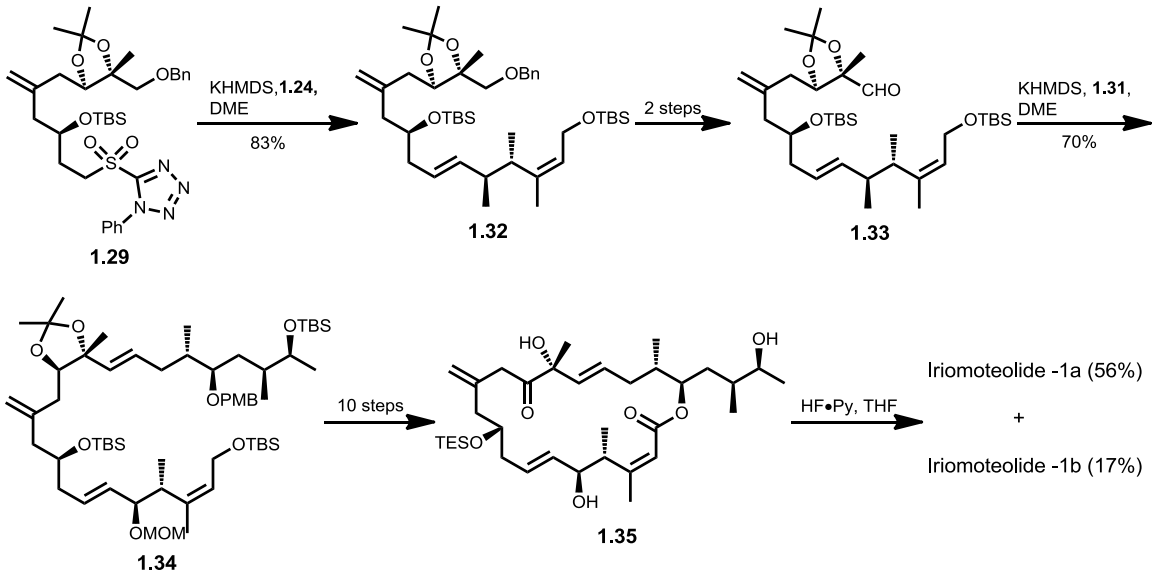


Figure 1.4. Ghosh's disconnection of iriomoteolide-1a



Scheme 1.3. Ghosh's synthesis of key fragments

The above three fragments were coupled by two stages of Julia-Kocienski olefination to give the intermediate **1.34**, which was converted to **1.35** in 10 steps including a Yamaguchi esterification to form the macrocyclic lactone (Scheme 1.4). Removal of the silyl ethers with HF•Py resulted in a mixture (3:1) of the proposed iriomoteolide-1a and -1b. The ^{1}H and ^{13}C NMR spectra of Ghosh's synthetic iriomoteolide-1a were consistent with those of Horne's, but none of them matched the data reported for the natural product. Both of these research groups suggested that the configuration of the C2-C3 double bond of the natural product is *E* rather than *Z*.



Scheme 1.4. Ghosh's total synthesis of iriomoteolide-1a and -1b

1.1.2.3 Yang's Total Synthesis of Iriomoteolide-1a Diastereomers

Our group is the first to report the synthesis of the C1-C12 fragment of the originally proposed iriomoteolide-1a.[4k] However, during our studies, it became clear that the C2-C3 alkene of the natural product should be revised to 2*E*- instead of the originally proposed 2*Z*- configuration. Thus, we adjusted our synthetic plan to target the 2*E*-isomer **1.1** rather than the originally proposed iriomoteolide-1a.[4o] We disconnected the 2*E*-isomer **1.1** into three fragments: alkyne fragment, chloroformate fragment and a known α-hydroxy fragment (Figure 1.5 and Scheme 1.5). Our synthesis of alkyne fragment was highlighted by a catalytic asymmetric vinylogous Mukaiyama aldol reaction to introduce the C9 stereocenter. Another key reaction was the formation of *anti*-homopropargylic alcohol **1.41** from aldehyde **1.39** by addition of the triisopropylsilylallenylindium reagent generated *in situ* from mesylate **1.40**.

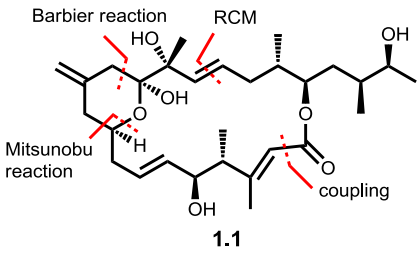
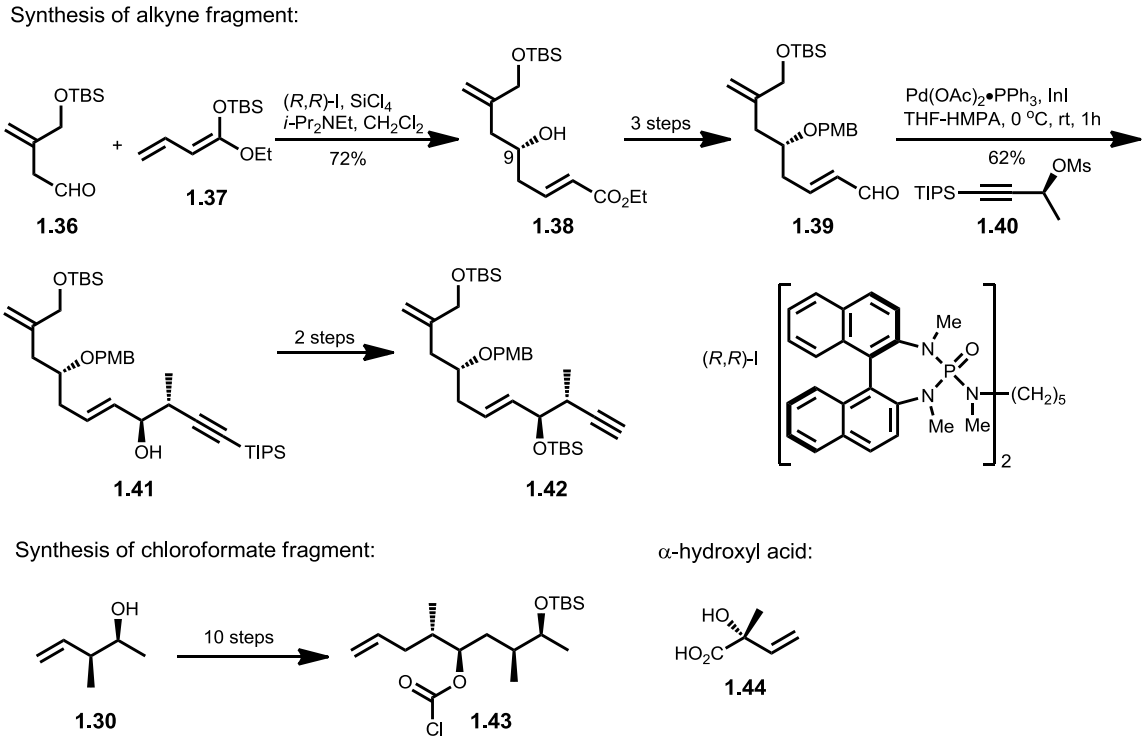


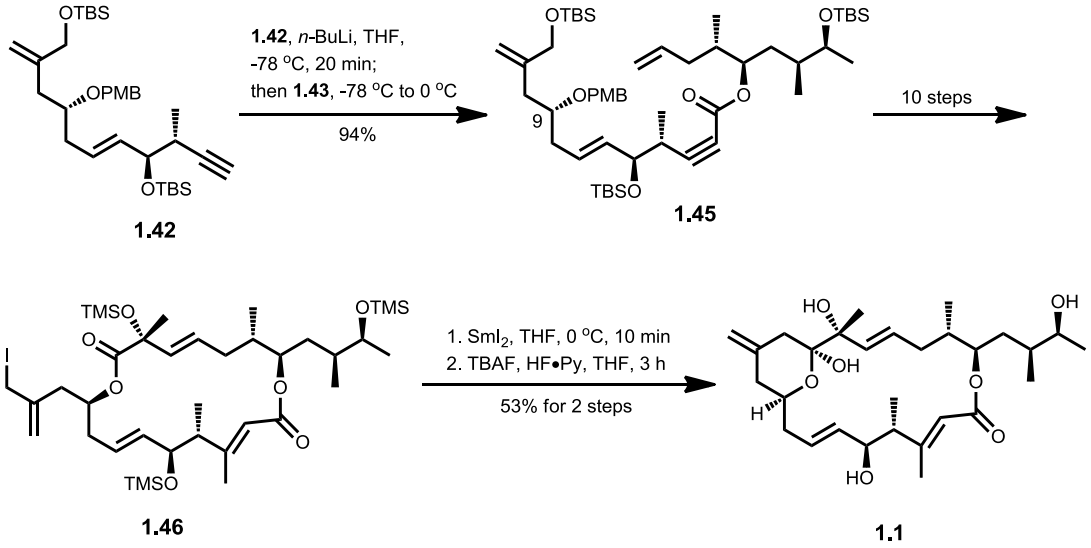
Figure 1.5. Yang's disconnection of iriomoteolide-1a



Scheme 1.5. Yang's synthesis of key fragments

Our enantioselective synthesis of **1.1**, a diastereomer of iriomoteolide-1a, was shown in Scheme 1.6. It featured an acetylide-chloroformate coupling strategy to synthesize the intermediate **1.45**, which could be converted to macrocyclic lactone **1.46** in 10 steps. Among these ten steps, a Mitsunobu reaction was used to invert the stereocenter at C9 with α-hydroxy fragment **1.44** and a ring closing metathesis was employed to build the macrocycle. Also highlighted in our total synthesis was a SmI_2-mediated intramolecular reductive cyclization approach to the complex cyclic hemiketal. Two additional 2*E*-diastereomers **1.2** and **1.3** (Figure 1.2) were also synthesized in order

to determine the correct structure of the natural product. Unfortunately, none of them matched the natural product.



Scheme 1.6. Yang's total synthesis of a diastereomer of iriomoteolide-1a, **1.1**

1.1.2.4 Dai's Total Synthesis of Iriomoteolide-1a Diastereomers

In 2011, employing a strategy similar to that of Horne's, the Dai group accomplished the total syntheses of two 2*E*-isomers of the original iriomoteolide-1a with different stereocenters at C4 and C5 (**1.1** and **1.4**, Figure 1.1).[4q] The key reactions of Dai's approach were shown in Figure 1.6. The C1-C6 fragment **1.49** and its enantiomer were prepared from acrolein **1.48** through *anti*-selective aldol reactions with chiral propionate **1.47** and **1.15**, respectively (Scheme 1.7). Unlike Horne's disconnection of C7-C23 into C7-C16 and C17-C23 fragments, Dai's approach involved preparation of the C13-C23 fragment at first through the *B*-alkyl Suzuki-Miyaura coupling between

primary iodide **1.53** and vinyl iodide **1.55**. The C7-C23 fragment was then achieved through the indium-mediated aldehyde allylation of C13-C23 fragment **1.56** with C7-C12 fragment **1.51**. The final product **1.1** was synthesized using a reaction sequence that is similar to Horne's, i.e. Yamaguchi esterification, hemiketalization and ring closing metathesis.

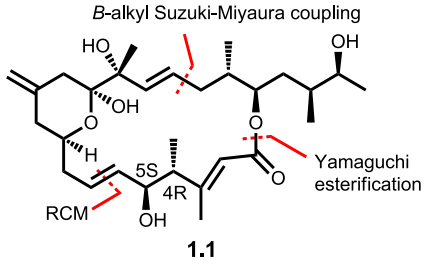
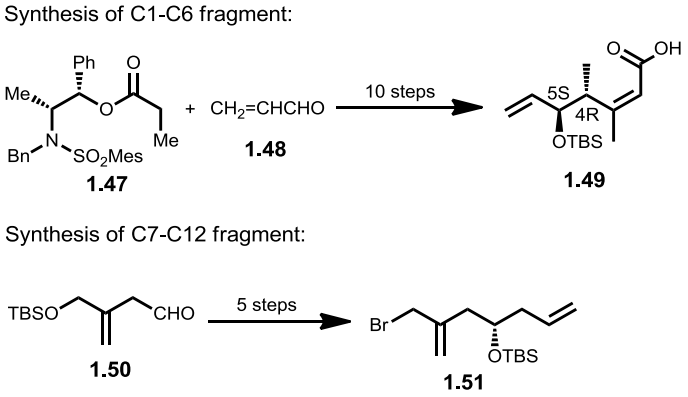
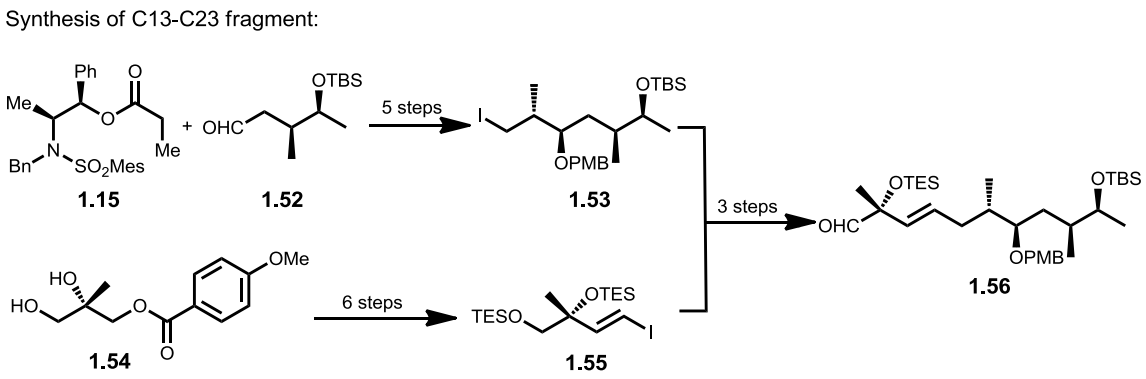


Figure 1.6. Dai's disconnection of iriomoteolide-1a



Scheme 1.7. Dai's synthesis of key fragments



Scheme 1.7. (Continued) Dai's synthesis of key fragments

1.1.2.5 Other Research Groups' Synthetic Studies Toward Iriomoteolide-1a

Except the above total syntheses of proposed iriomoteolide-1a or its diastereomers, other research groups also reported their synthetic efforts toward iriomoteolide-1a. Loh and co-workers developed two different synthetic routes to the C13-C23 fragments.[4f, h] The C13-C23 fragment was also achieved by Zhao and co-workers.[4g] Their synthetic efforts eventually led to the enantioselective total synthesis of the proposed structure of iriomoteolide-1b.[4r] Paterson group accomplished the construction of C1-C9 and C11-C23 segments using lactate aldol chemistry.[4c] Crimmins and co-workers finished the enantioselective syntheses of the C1-C6 and C7-C23 fragments using various aldol reactions of metallo enolates of thiazolidinethiones to set up 7 of the 9 stereocenters of the proposed iriomoteolide-1a.[4a] The advanced macrocyclic core of iriomoteolide-1a was prepared by Ye team utilizing ring-closing metathesis (RCM) to construct the C15-C16 *E*-alkene.[4d]

1.2 Background of Alotaketal A

1.2.1 Isolation and Bioactivity of Alotaketal A

Marine organisms continue to provide an unrivalled array of novel, biologically active natural products as potential lead compounds for the development of new therapeutic agents and tools for biomedical studies.[5] In search of these compounds, recent screening of extracts of the marine sponge *Hamigera* sp., collected in Papua New Guinea by Andersen and co-workers, led to the isolation of new sesterterpenoids alotaketal A and B (Figure 1.7).[6] These natural products feature an "alotane" terpenoid carbon skeleton that cyclizes into a unique tricyclic spiroketal ring system. In particular, simultaneous substitution of the spiroketal center of alotaketal A by both ally and vinyl groups is unprecedented in natural spiroketals. Contemporaneous to the Andersen report, the Rho group described the isolation of the closely related phorbaketal A-C from the sponge *Phorbas* sp.[7]

The structures of these natural products were mostly assigned based on 1D and 2D NMR studies. Rho and co-workers assigned the absolute configuration of the phorbaketals as those drawn in Figure 1.7 using Mosher ester methodology. Andersen and co-workers originally assigned the absolute configuration of alotaketals based on the positive Cotton effect of the enone n to π^* transition observed in the CD spectrum using Snatzke's rules. However, their assignment for C1, C6, C9, C13 were opposite to those assigned by Rho group in phorbaketals. Andersen group subsequently revised their stereochemical assignment to the same as that of the Rho group.[8]

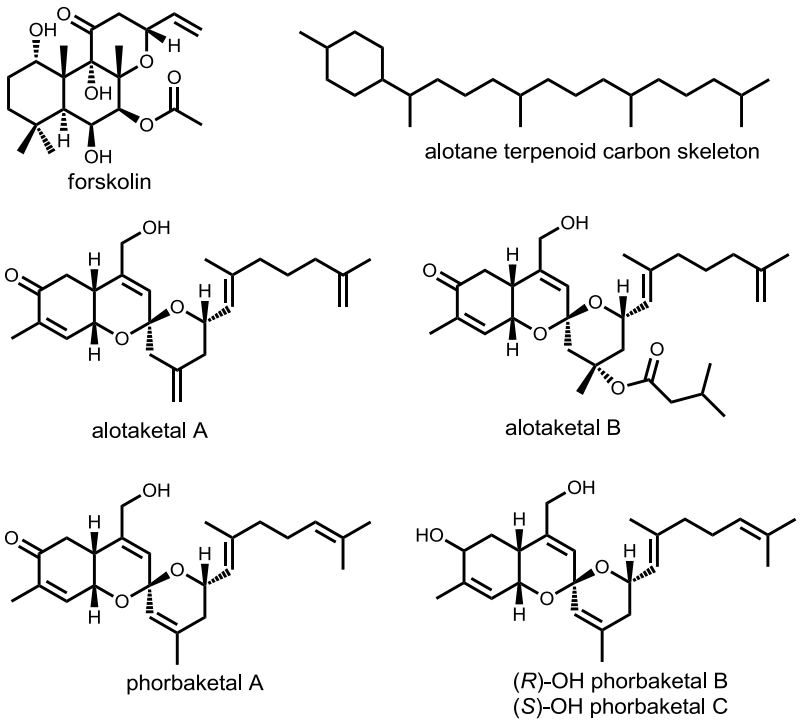


Figure 1.7. Structures of forskolin, alotaketals and phorbaketals

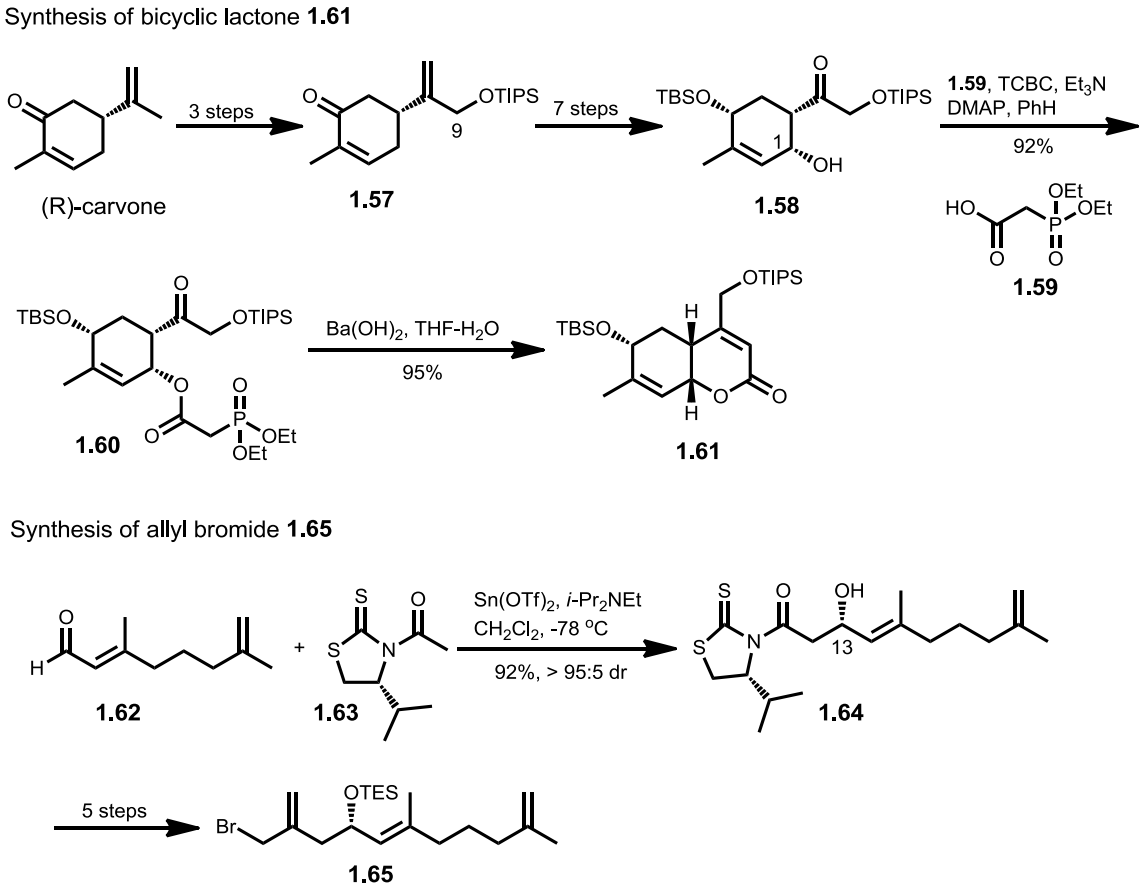
Along with their unique molecular structures, these natural products exhibit interesting biological activities.[6] For example, using HEK293 cells transformed with pHTS-CRE luciferase reporter genes, alotaketal A and B were found to potently activate the cAMP signaling pathway with EC_{50} values of 18 nM and 240 nM in the absence of hormone binding. cAMP is a secondary messenger used for intracellular signal transduction, which is fundamental to cell signaling.[9] Such signaling is typically initiated by the binding of hormones to cell-surface G protein-coupled receptors (GPCRs), which leads to the recruitment of trimeric guanine-nucleotide binding proteins (G proteins) and activation of adenylyl cyclases, the enzyme responsible for converting adenosine triphosphate (ATP) to cAMP. The cAMP thus formed binds to and activates cAMP-

dependent protein kinase (PKA) that regulates a wide array of cellular events including cell growth and differentiation.[10] Small molecules that selectively modulate signaling pathways are important tools for cell biology research and potential lead compounds for drug development.[11] Forskolin, a natural product activator of adenylyl cyclase,[12] has been widely used by biologists to raise intracellular cAMP levels. It also attracted some attention as a drug candidate.[13] However, compared with alotaketal A, forskolin is a relatively inefficient signaling molecule for cAMP pathway activation with an EC_{50} of 3 μM in the same assay using HEK-pHTS-CRE. Alotaketal A shows an EC_{50} that is 167-fold more potent than that of forskolin. Thus, alotaketal A represents a potentially superior small molecule probe for studying cAMP signaling and a potential lead for therapeutic development.

1.2.2 Synthetic Efforts Toward Alotaketal A

Attracted by its unprecedented spiroketal molecular structure and appealing bioactivities in potently activation the cAMP signaling pathway, we accomplished the first total synthesis of alotaketal A and elucidated its structure-activity relationship in 2012. Five months later, the second total synthesis of alotaketal A was achieved by Dalby and co-workers.[14] They developed a convergent synthetic approach to alotaketal A through coupling of bicyclic lactone **1.61** and allyl bromide **1.65**. The two hydroxyl groups in the intermediate **1.58** were introduced using a stepwise sequence from (*R*)-carvone (Scheme 1.8). Yamaguchi esterification of the allyl alcohol with phosphonate **1.59** provided keto-phosphonate **1.60**, which was subjected to Horner-Wadsworth-

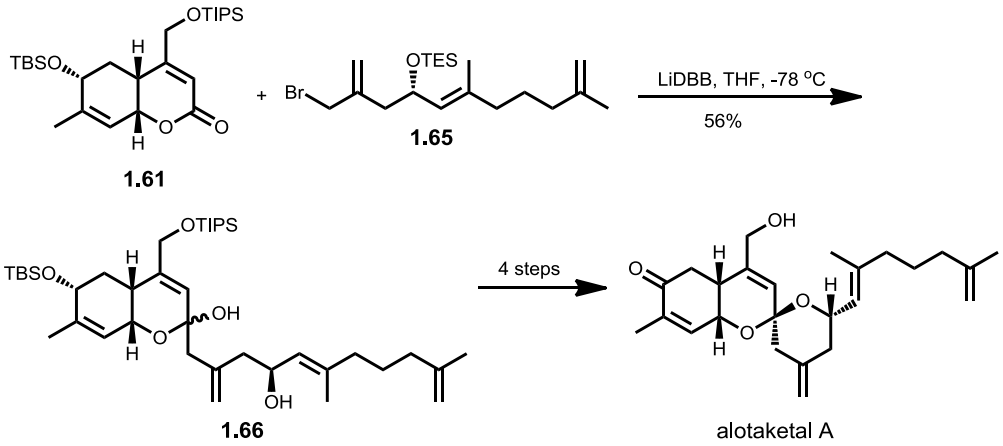
Emmons reaction to finish the bicyclic lactone **1.61**. Nagao-Fujita aldol reaction was featured in the synthesis of allyl bromide **1.65** to install the C13 hydroxyl group with excellent yield and high diastereoselectivity.



Scheme 1.8. Dalby's synthesis of key fragments

With both key fragments in hand, the pivotal coupling of bicyclic lactone **1.61** and allyl bromide **1.65** was achieved through the addition of excess lithium *di-tert*-butylbiphenyl (LiDBB) to a solution of **1.61** and **1.65** in THF (Scheme 1.9). The rather

acid-sensitive hemiketal **1.66** thus obtained was then converted to the alotaketal A in 4 steps through thermodynamically controlled spiroketalization upon desilylation. Dalby and co-workers completed the total synthesis of alotaketal A in 0.5% yield over 17 steps.



Scheme 1.9. Dalby's total synthesis of alotaketal A

1.3 Background of an Antifungal *o*-Hydroxy-*p*-Quinone Methide Diterpenoid

1.3.1 Introduction of *o*-Hydroxy-*p*-Quinone Methide Terpenoids

Quinone methides are typically reactive electrophilic species that are formed as transient intermediates in chemical transformations.[15] However, in the presence of stabilizing structural elements, such as extended conjugation, relatively stable quinone methides may form. Indeed, a number of *o*-hydroxy-*p*-quinone methide diterpenoids and triterpenoids, such as fuerstion, taxodione and its dimer **1.68**, pristimerin, celastrol, tingenone, many of which show interesting biological activities, have been isolated from Nature (Figure 1.8).[16] As part of our efforts in investigating natural products with useful pharmacological properties, we became interested in **1.67**, an unnamed *o*-hydroxy-*p*-quinone methide diterpenoid isolated from *Bobgunnia madagascariensis.*[17]

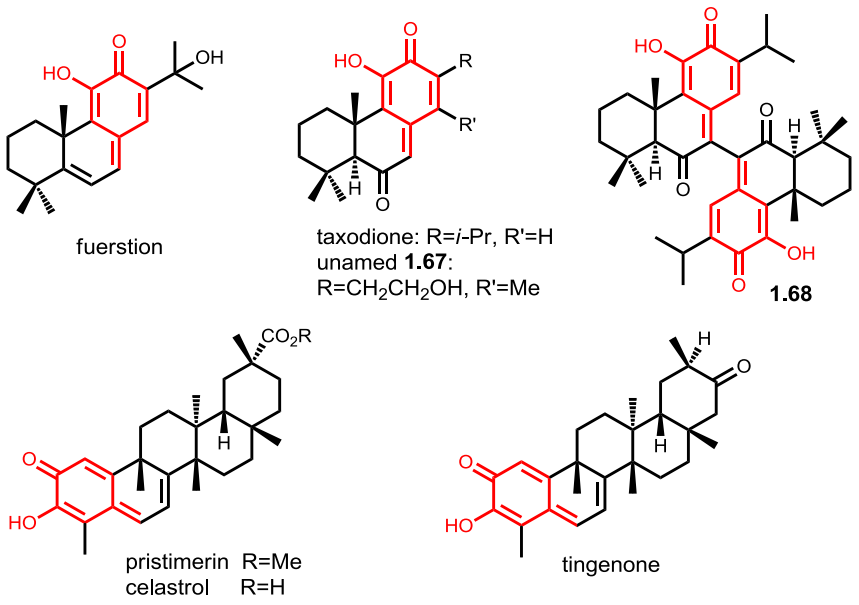


Figure 1.8. Structures of some *o*-hydroxy-*p*-quinone methide terpenoids

1.3.2 Isolation and Bioactivities of Unnamed *o*-Hydroxy-*p*-Quinone Methide Diterpenoid 1.67

Bobgunnia madagascariensis (Desv.) J.H.Kirkbr & Wiersema (formerly known as *Swartzia madagascariensis*) is a tree widely distributed in tropical Africa.[18] Various parts of this plant have been used by traditional healers for medicinal purposes. For example, its roots have been employed as a cure for leprosy and syphilis.[19] Phytochemical investigation of its dried fruits gave triterpenoid saponins, which were shown to be responsible for its high molluscicidal activity against *B.* glabrata.[20] *B. madagascariensis* has attracted much attention in the past decade. The screening efforts aimed at the discovery of new antifungal lead compounds in the laboratory of Hostettmann led to the isolation of a new *o*-hydroxy-*p*-quinone methide diterpenoid **1.67** from the root bark of *B. madagascariensis* (Figure 1.9).[17] The relative and absolute stereochemical structure of **1.67**, which features a cassane skeleton, were assigned by NMR and confirmed by single-crystal X-ray analysis. Whereas unnamed, this quinone methide diterpenoid **1.67** shows potent antifungal activity (MIC = 0.19 μM) that even rivals amphotercin B and fluconazole, two antifungal drugs that are currently in clinical use.

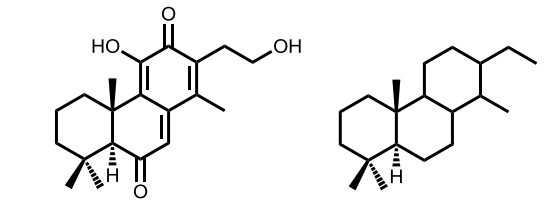
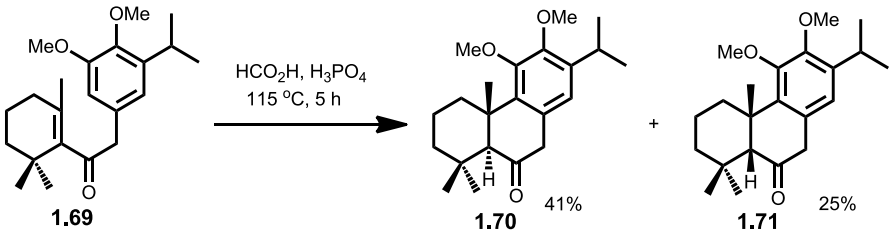


Figure 1.9. Structures of **1.67** and cassane skeleton

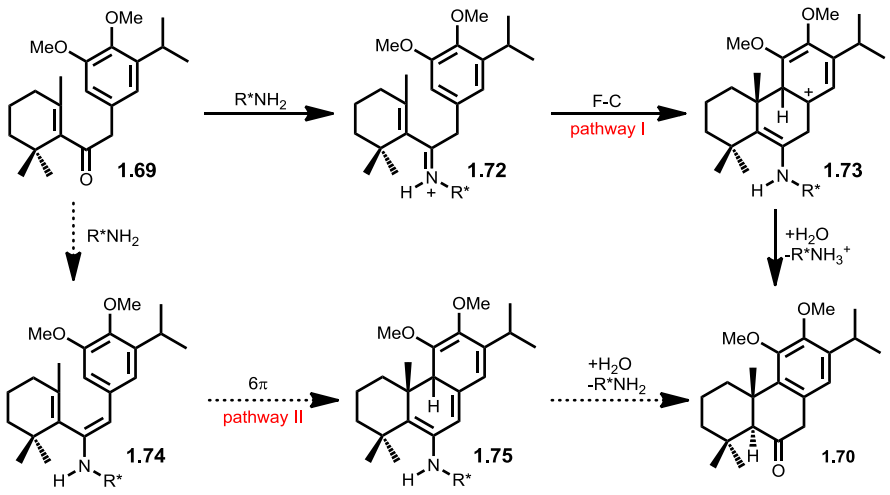
1.3.3 Synthetic Background of *o*-Hydroxy-*p*-Quinone Methide Diterpenoid 1.67

Despite its potent antifungal activity, no synthetic studies have been reported toward **1.67** in the past decade. However, the structurally similar taxodione has been synthesized for several times (Figure 1.8). Most of these syntheses, developed prior to 1995, were racemic and required stepwise construction of the tricyclic quinone methide moiety.[21] Among them, we were attracted by Stevens' approach,[21f] which used the intramolecular Friedel-Crafts alkylation as the key reaction to build the tricyclic core. However, the synthetic route employed rather harsh conditions using formic acid as the solvent at high temperature.



Scheme 1.10. Stevens' approach to taxodione

Recently, a number of asymmetric intermolecular Friedel-Crafts alkylations using Brønsted acid catalysts have been reported.[22] We were also aware of one example of Brønsted acid catalyzed asymmetric intramolecular Friedel-Crafts reaction reported by You and co-workers.[23] Most of these reactions involve electron-rich heteroarenes, but 1- and 2-hydroxynaphthalenes have also been used.[24] Based on these results, a catalytic asymmetric intramolecular Friedel-Crafts alkylation approach was envisioned for synthesis of the tricyclic molecular skeleton of this family of diterpenoids. As an alternative, we would also test chiral amines for iminium-catalyzed asymmetric Friedel-Crafts alkylations. The focus would be on quinidine-derived primary amines since they were more likely to form the electrophilic iminium intermediate **1.72** with the relatively hindered carbonyl of **1.69** for asymmetric catalysis through iminium activation (Scheme 1.11, pathway I).[25] A reaction pathway of 6π-electrocyclization of the enamine intermediate **1.74** is also possible (Scheme 1.11, pathway II).



Scheme 1.11. Cyclization catalyzed by an amine

CHAPTER II

SYNTHETIC STUDIES OF IRIOMOTEOLIDE-1A*

2.1 Retrosynthesis of Iriomoteolide-1a

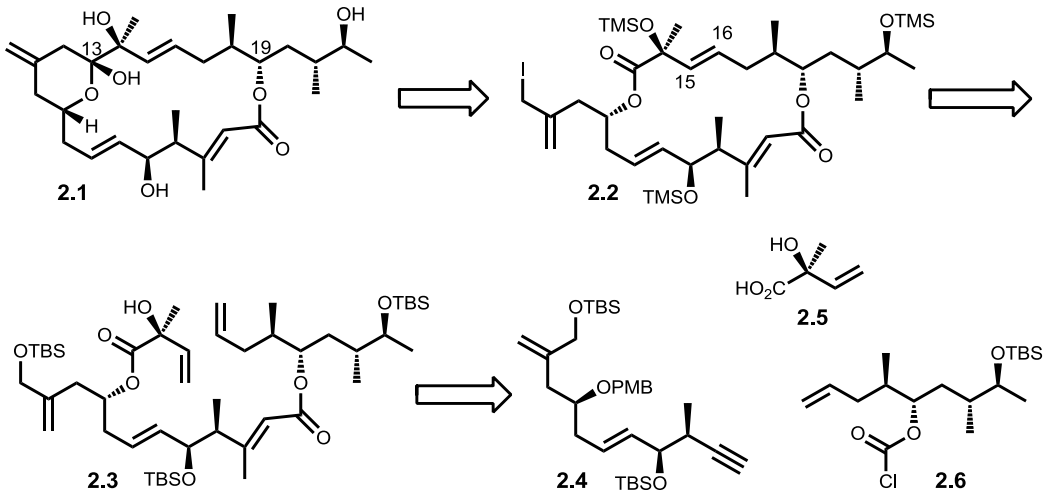
The structure of iriomoteolide-1a had been misassigned, but the potent cytotoxicity reported for iriomoteolide-1a warranted further studies to elucidate the true structure of the natural product and enable mode-of-action studies of this potent cytotoxin. As part of our effort toward this goal, we decided to synthesize macrolide **2.1** (Scheme 2.1) based on our observation of a significant ROESY ($CDCl_3$) correlation between H19 and 13-OH from the original report by Tsuda group.[3] Molecular mechanics simulation at the MM2 level suggests that H19 and 13-OH have to be oriented to the same side of the macrocycle in order for such a correlation to occur. This and results obtained in our previous work prompted us to choose **2.1** as the target.[26] The goal for synthesizing **2.1** was to identify if it matches the real structure of iriomoteolide-1a or (if it does not), in combination with the diasteromers that have been previously synthesized, to provide a 'training set' for computational elucidation of the stereochemical structure of the natural product.

Our retrosynthetic analysis of iriomoteolide-1a was shown in Scheme 2.1. To maximize synthetic convergency, our synthetic plan relied on a late stage intramolecular

---

* Reprinted with permission from "Studies Toward Elucidating the Stereochemical Structure of Iriomoteolide 1a" by Huang, J.; Yang, J. *Synlett* **2012**, *23*, 737-740, Copyright [2012] by Georg Thieme Verlag Stuttgart • New York.

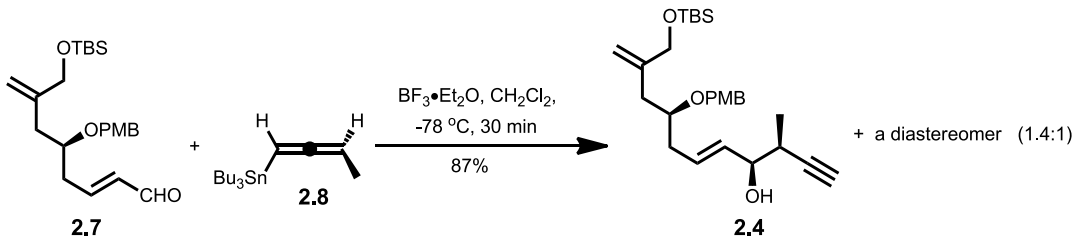
reductive allylation to form the C9/C13 cyclic hemiketal from iodoester **2.2**. The macrocycle **2.2** could be prepared by ring closing metathesis across the C15-C16 double bond of diene **2.3**, which in turn would be assembled from building blocks **2.4**-**2.6**.



Scheme 2.1. Retrosynthetic analysis of **2.1**

2.2 The First Synthetic Approach to Alkyne Fragment 2.4

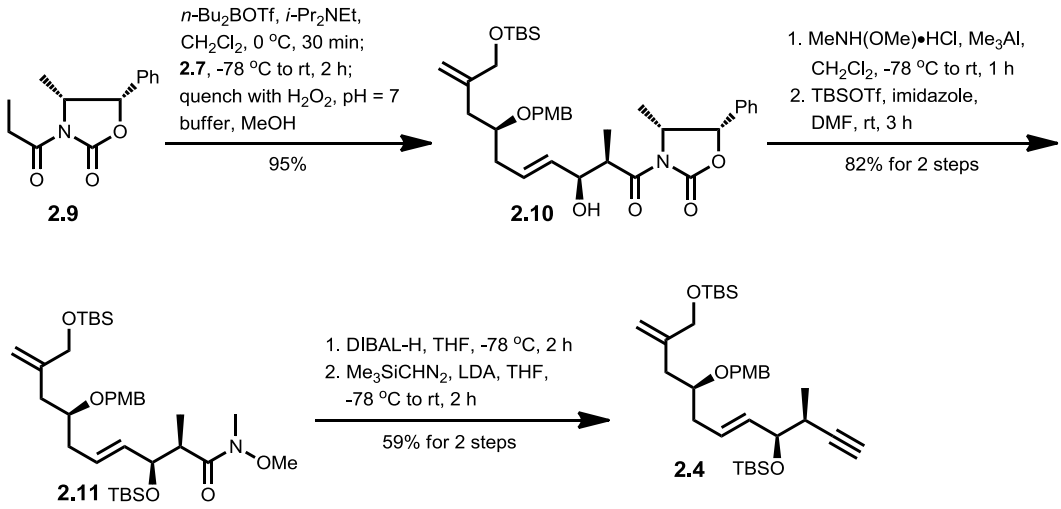
Our synthesis commenced with the preparation of alkyne fragment **2.4**. Stereoselective preparation of alkyne **2.4** by direct coupling of α, β-unsaturated aldehydes and allenic tin reagents developed by Marshall and co-workers was problematic.[27] For example, the reaction of **2.7**[4o] with **2.8** led to a mixture of the desired homopropargylic alcohol **2.4** and an unassigned diastereomer with high yield but little stereochemical control (1.4:1 ratio, Scheme 2.2). Additionally, these two diasteromers couldn't be separated even after silylation of the resulting hydroxyl group.



Scheme 2.2. Homopropargylation of **2.7**

2.3 The Second Synthetic Approach to Alkyne Fragment 2.4

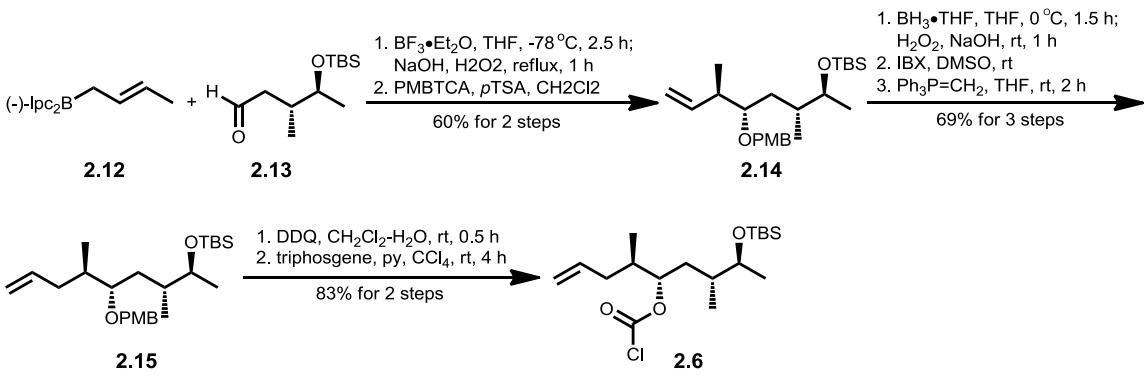
To address this difficulty, we opted to apply the Evans chiral auxiliary approach to synthesize alkyne **2.4** (Scheme 2.3). While being stepwise, this approach was expected to be reliable in delivering the desired homopropargylic alcohol in a diasteroselective manner. To this end, the α, β-unsaturated aldehyde **2.7** was reacted with chiral auxiliary **2.9** under the standard *syn*-aldol reaction conditions to give **2.10**.[28] This was followed by the Weinreb amidation with MeNH(OMe)•HCl/Me_3Al and silylation of the hydroxyl group to give **2.11** in high yield.[29] DIBAL-H reduction of the Weinreb amide gave an aldehyde intermediate, which was converted to **2.4** as a single diasteromer by the Colvin rearrangement under the conditions developed by Aoyama and Shioiri.[30] Although multiple steps were necessary, this procedure provided a reliable approach for preparation of adequate quantities of diastereomerically pure **2.4** to complete the synthesis of the macrolide **2.1**



Scheme 2.3. Synthesis of alkyne **2.4**

2.4 Synthesis of Chloroformate Fragment 2.6

Preparation of chloroformate **2.6** started from the known aldehyde **2.13**[4h] (Scheme 2.4). Brown asymmetric crotylation of **2.13** and protection of the resulting secondary alcohol as PMB ether led to alkene **2.14**,[31] which was subjected to a three-step homologation sequence (hydroboration, IBX oxidation, and Witting olefination) to give homologated alkene **2.15**. The PMB ether **2.15** was oxidatively hydrolyzed with DDQ, and the building block **2.6** was synthesized through the reaction of the resulting secondary alcohol with triphosgene, which was used for next step without any purification.



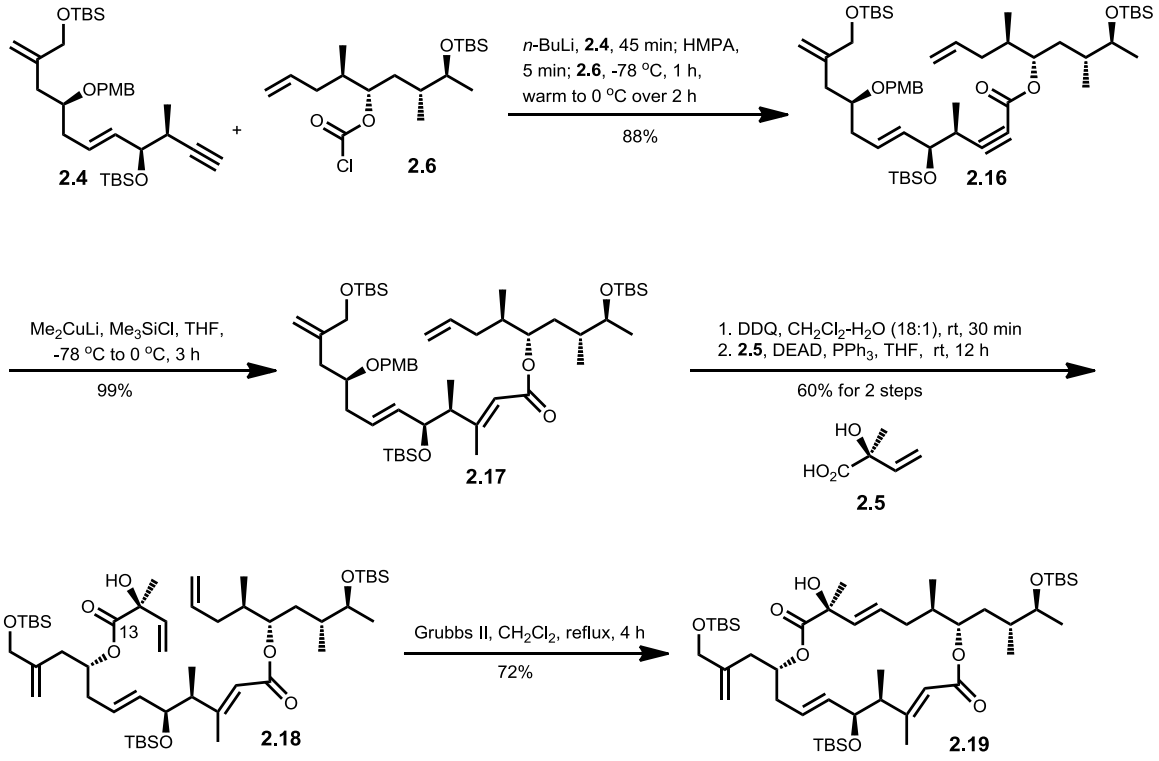
Scheme 2.4. Synthesis of chloroformate **2.6**

2.5 Synthesis of Macrocycle 2.19

With both of the key building blocks in hand, our attention turned to their coupling and conversion to the trisubstituted 2*E*-alkenoic ester **2.17**. For this purpose, it requires deprotonation of the terminal alkyne of **2.4** to form an acetylide prior to addition of chloroformate **2.6**. To our surprise, this coupling reaction couldn't be consistently reproduced when the *syn* diastereomer **2.4** was employed. After extensive experimentation, this coupling was eventually solved through addition of HMPA as a co-solvent. The coupling product **2.16** was subjected to the conjugate addition with the Gilman reagent in the presence of TMSCl, followed by acidic work up to hydrolize the silyl ketene acetal intermediate to stereoselectively give the (*E*)-trisubstituted C2-C3 alkenoic ester **2.17** in 99% yield.

With the C1-trisubtituted alkenoic ester functionality secured, the C13 ester was introduced by oxidative hydrolysis of the C9 PMB ether of **2.16** followed by Mitsunobu reaction with known α-hydroxy acid **2.5**.[32] The strategic decision of assembling the

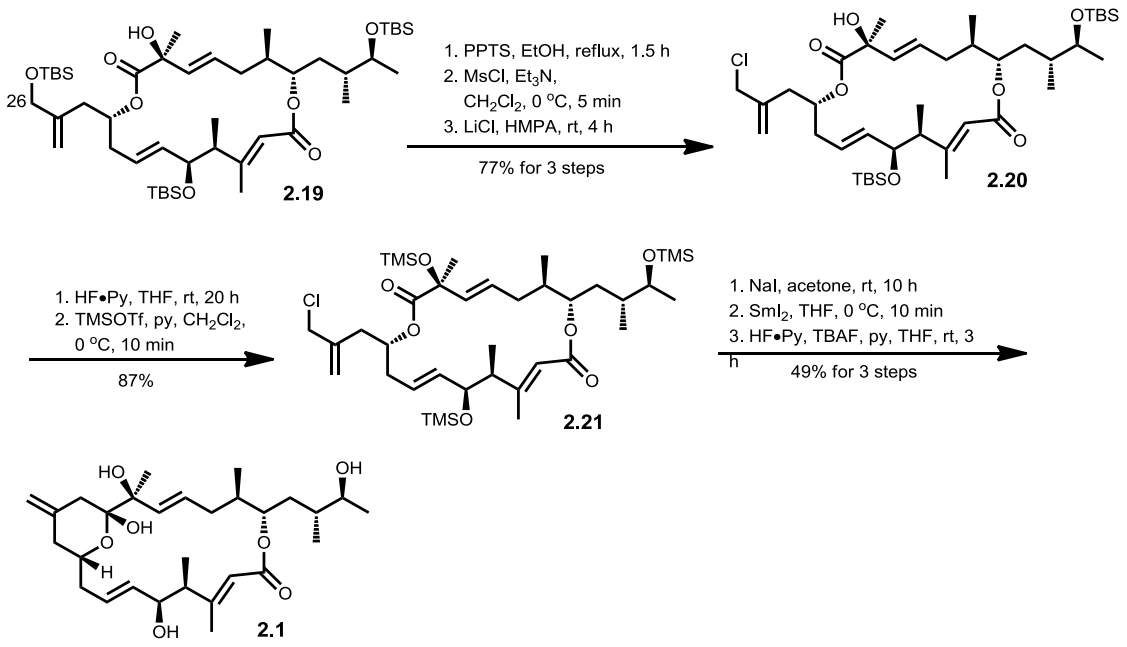
macrocyclic diolide **2.19** by ring-closing metathesis was demanding as it required selective activation of two of the five double bonds of the cyclization precursor **2.18**. Moreover, stereochemical control of the resulting C15-C16 double bond was also necessary. Thus, we were gratified to observe that the desired *E*-isomer of the C15-C16 double bond was formed exclusively with 72% yield when **2.18** was treated with the second-generation Grubbs catalyst.[33]



Scheme 2.5. Synthesis of macrocycle **2.19**

2.6 Completing the Total Synthesis of 2.1

To prepare for the intramolecular reductive cyclization to build the C9/C13 cyclic hemiketal, functional group manipulations of **2.18** was carried out. This involved selective desilylation of the C26 hydroxyl group under acidic conditions (PPTS, EtOH, reflux), chlorination (MsCl, Et_3N, CH_2Cl_2; LiCl, HMPA), and exchange the protection of the hydroxy groups from TBS to the more labile trimethylsilyl group to give **2.20** (Scheme 2.6). This allyl chloride **2.20** was converted to the iodide by the Finkelstein reaction.[34] Employing the intramolecular reductive cyclization conditions recently reported by Keck,[35] formation of the six-membered cyclic hemiketal of **2.1** was successfully implemented despite the presence of a myriad of other functional groups. While this reaction was facile, the crude product had to be immediately desilylated under buffered conditions (pH = 7).[36] The final product was obtained as a mixture of **2.1** and a minor isomer (~ 7:1 ratio) which was tentatively assigned as the ketol form of the C9/C13 cyclic hemiketal. These two isomers could be resolved by preparative thin-layer chromatography. However, mixtures of the same composition were recovered when these resolved component were eluted with ethyl acetate, suggesting relatively rapid equilibration of the two isomers. A similar equilibration was observed for **1.1**, but not for the natural product or the other diasteromers (i.e., **1.2**-**1.4**, Chapter I). The NMR spectra of **2.1** was found to be different from those reported for the natural product.



Scheme 2.6. Synthesis of macrolide **2.1** by the reductive allylation

2.7 Bioactivities of Synthetic Diastereomers 1.1-1.3 and 2.1

With diastereomer **2.1** in hand, we collaborated with Prof. Jun Liu of Johns Hopkins University to evaluate the bioactivities of diastereomer **2.1** and previously synthesized diastereomers **1.1**-**1.3** using cell proliferation assays with HeLa and PC3 cell lines. As shown in the Table 2.1, only diastereomer **2.1** showed weak inhibition of cell proliferation on both cell lines at 10 μM.

2.8 Summary

We accomplished the total synthesis of **2.1** using a synthetic route that featured a lithium acetylide-chloroformate coupling in the presence of HMPA as the co-solvent, the ring-closing metathesis to form the macrocyclic diolide, and a SmI_2-mediated

intramolecular reductive allylation to form the cyclic hemiketal. The bioactivities of **1.1**-**1.3** and **2.1** were evaluated using cell proliferation assays with HeLa and PC3 cell lines. Only **2.1** showed weak cell growth inhibition at 10 μM.

Table 2.1. Bioactivities of synthetic diastereomers

Concentration (μM)	Growth inhibition(%) of HeLa				Growth inhibition(%) of PC3			
	1.1	**1.2**	**1.3**	**2.1**	**1.1**	**1.2**	**1.3**	**2.1**
10.00	2.78	-4.15	-6.42	19.12	11.35	-5.72	8.08	17.94
1.00	-10.56	-10.39	-3.86	6.08	-3.48	-5.89	8.80	-0.75
0.10	-3.53	-7.19	4.90	-1.90	-9.89	-2.97	-0.37	-1.87

CHAPTER III

TOTAL SYNTHESIS OF ALOTAKETAL A*

3.1 Retrosynthesis of Alotaketal A

Alotaketal A, isolated by Andersen and co-workers in 2009, potently activates the cAMP signaling pathway with an EC_{50} value of 18 nM. Along with its potent bioactivity, it also possesses an unprecedented tricyclic spiroketal molecular skeleton in which the spiroketal center is simultaneously substituted by both an allyl and a vinyl group. No synthetic studies of alotaketal A have been reported until we published the first enantioselective total synthesis of this potent cAMP signaling agonist in 2012.

Our convergent synthetic design of alotaketal A relied on a late stage spiroketalization to assemble its tricyclic spiroketal ring system. Two such cyclization processes could be envisioned as shown in Scheme 3.1. One involved spiroketalization through lactol **3.1** (process I) while the other involved a similar process through lactol **3.2** (process II). The former lactol **3.1** could be assembled by intermolecular reductive allylation of bicyclic lactone **3.4** with allyl iodide **3.5** while the latter **3.2** could be accessed by intramolecular reductive allylation of ester **3.3**, which in turn could be

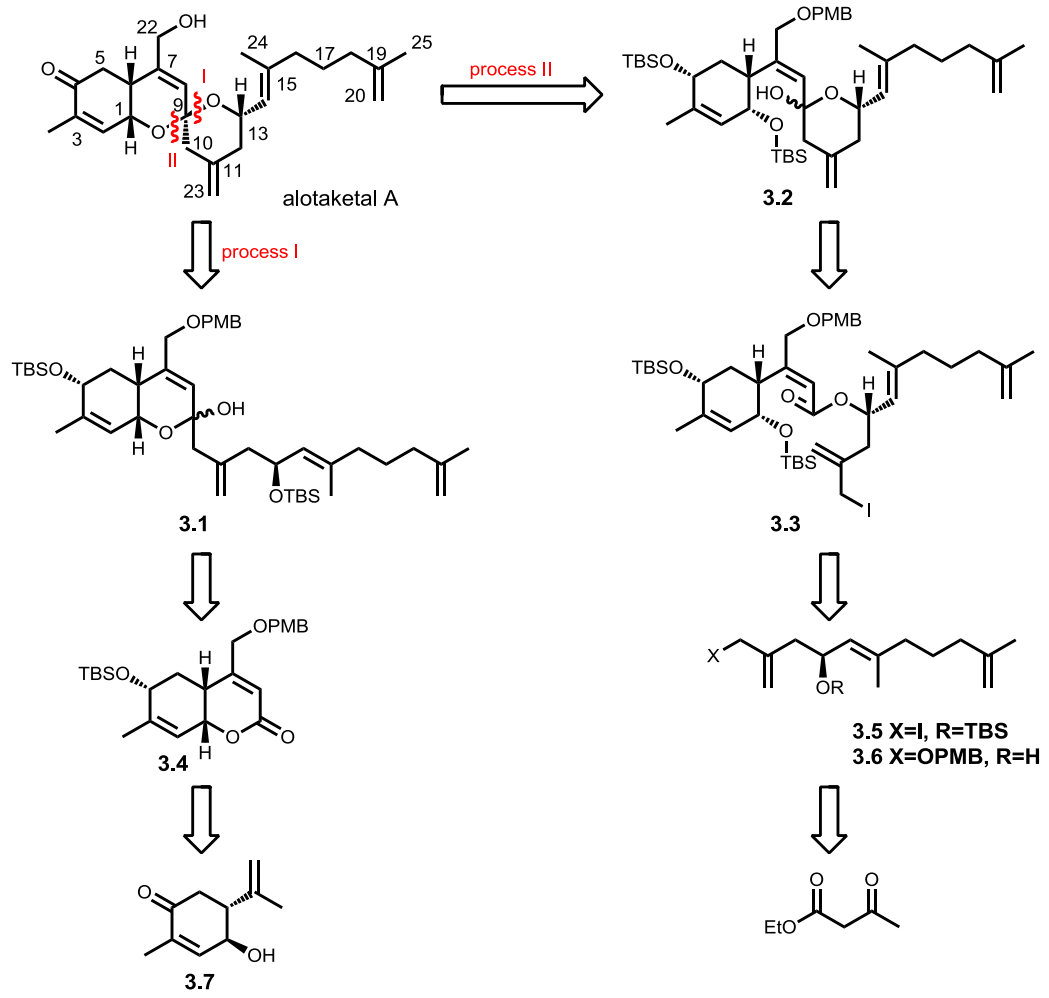
---

* Reprinted with permission from "Total Synthesis of the Potent cAMP Signaling Agonist (-)-Alotaketal A" by Huang, J.; Yang. J. R.; Zhang, J.; Yang, J. *J. Am. Chem. Chem. Soc*. **2012**, *134*, 8806-8809, Copyright [2012] by American Chemical Society; Reprinted with permission from "Total Synthesis and Structure-Activity Relationship Study of the Potent cAMP Signaling Agonist (-)-Alotaketal A" by Huang, J.; Yang. J. R.; Zhang, J.; Yang, J. *Org. Biomol. Chem*. **2013**, *11*, 3212-3222, Copyright [2013] by The Royal Society of Chemistry.

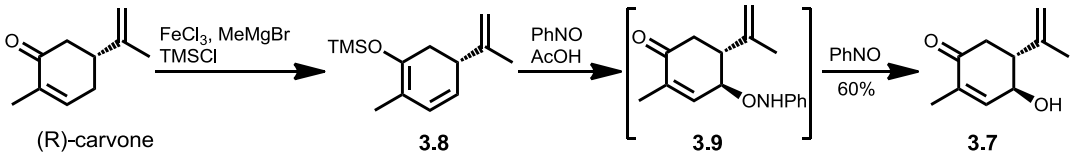
synthesized by coupling of **3.4** and **3.6**. These building blocks (i.e. **3.4**, **3.5**, **3.6**) could be prepared from 5β-hydroxyl carvone **3.7** and ethyl acetoacetate. Unknown at the outset was the compatibility of the $\Delta^{11,23}$ alkene with the acidic conditions that would be necessary to elaborate the unprecedented spiroketal ring system. Specifically, activation of the C10 methylene by both the $\Delta^{11,23}$ alkene and C9 oxocarbenium intermediate formed during spiroketalization would significantly increase the chance of *exo*-to-*endo* migration of the alkene through a process of deprotonation and re-protonation. With the expectation that the alkene isomerization could be suppressed by fine-tuning the reaction conditions and the substrates themselves, we initiated our synthetic studies.

3.2 Efforts Toward a Ring-Closing Metathesis Approach to Bicyclic Lactone 3.4

Our synthesis of alotaketal A required 5β-hydroxyl carvone **3.7** as a starting material. A natural product by itself, 5β-hydroxyl carvone **3.7** was previously synthesized by Yoshikoshi and co-workers in 9 steps from *R*-carvone.[37] Our group designed a γ-oxygenation process based on vinylogous *O*-nitroso Mukaiyama aldol reactions to convert *R*-carvone into 5β-hydroxyl carvone **3.7** in just two steps.[38] It involves regioselective formation of the extended silyl dienol ether **3.8** using the Kharasch reagent followed by treatment with nitrosobenzene in the presence of acetic acid. A *γ*-aminoxylation product **3.9** was initially formed, but heterolysis of its N-O bond by the excess nitrosobenzene led to a one-pot procedure to 5β-hydroxy carvone.

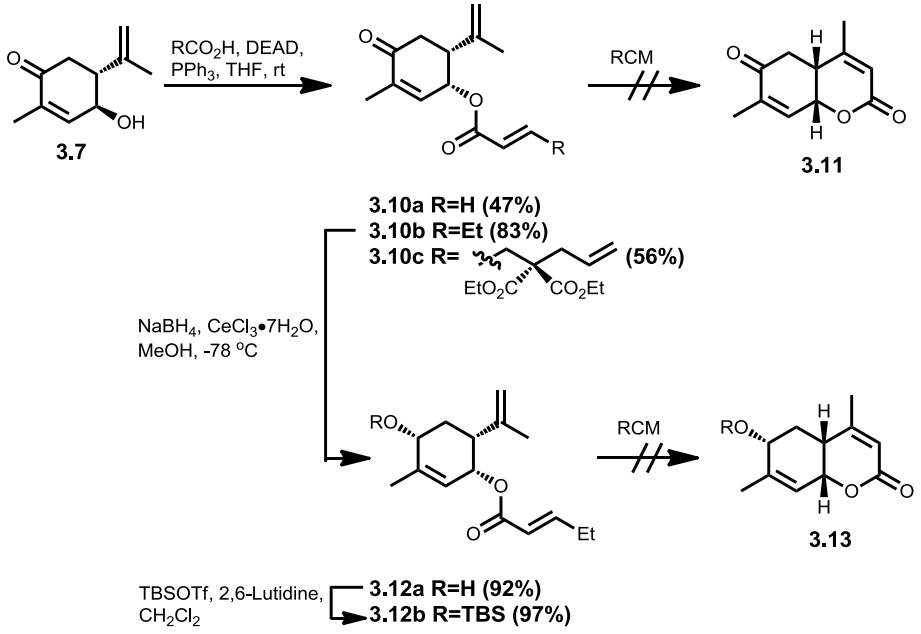


Scheme 3.1. Synthetic design



Scheme 3.2. Synthesis of 5β-hydroxy carvone

With 5β-hydroxy carvone in hand, we initiated our synthetic efforts focusing on developing a ring-closing metathesis approach to bicyclic lactone **3.11** en route to hydrobenzopyranone **3.4** (Scheme 3.3). The metathesis substrates **3.10a**/**3.10b** were synthesized by Mitsunobu reaction of 5β-hydroxy carvone **3.7** and acrylic/*trans*-2-pentenoic acid, which also served to invert the configuration of hydroxyl group to that of the natural product. Unfortunately, only the starting material was recovered when **3.10a**/**3.10b** was subjected to ring closing metathesis conditions with different Grubbs catalysts in various solvents (dichloromethane and toluene) and reaction temperatures (room temperature, 40 ^{o}C and 80 ^{o}C).[39]



Scheme 3.3. Studies of a ring-closing metathesis approach

We then turned to the "relay metathesis" approach, which was expected to facilitate the cyclization by assisted formation of the initiating ruthenium alkylidene species.[40] To this end, ester **3.10**c was prepared and subjected to reaction with the second-generation Grubbs catalyst (Scheme 3.3). To our surprise, **3.10a** was isolated as the sole product. The formation of **3.10a** suggested that the β-carbonyl carbene species **3.14** was indeed generated from **3.10c** and was competent for intermolecular cross metathesis with styrene, but not for the intramolecular ring-closing metathesis to give **3.11** (Figure 3.1).[41] Despite their electronically and sterically deactivated nature, acrylates and 1, 1-disubstituted alkenes have been shown to be effective for ring-closing metathesis to give related benzohydropyranones.[42] Thus, the difficulty for the metathesis cyclization of **3.10** likely was due to unfavorable conformational effects, such as developing 1, 2-interactions during the formation of the metallocyclobutane intermediate **3.15**. Esters **3.12a**/**b**, prepared by diastereoselective Luche reduction of **3.10b** and TBS-protection of the derived allyl alcohol, also remained intact under ring-closing metathesis conditions (Scheme 3.3).

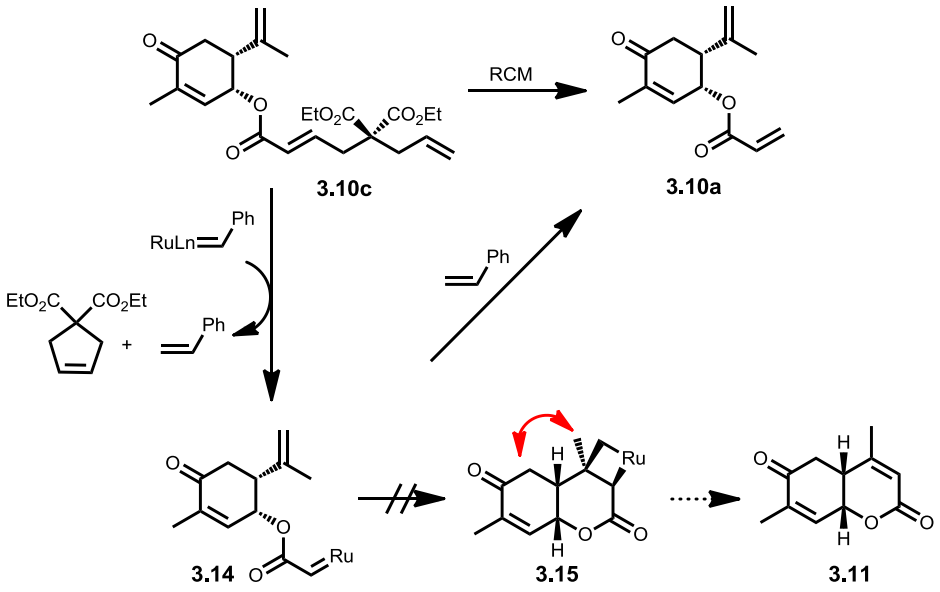


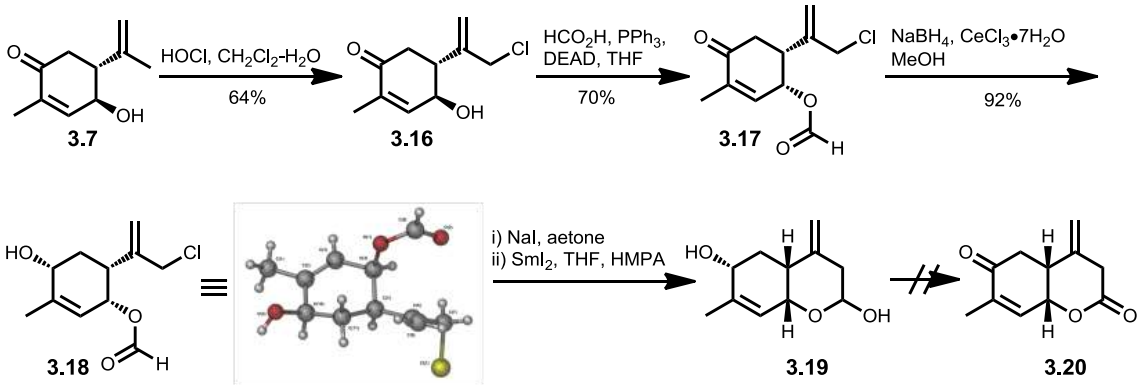
Figure 3.1. Relay ring-closing metathesis approach

3.3 An Intramolecular Reductive Allylation Approach to Bicyclic Lactone 3.4

3.3.1 Synthetic Efforts Toward Bicyclic Lactone 3.20

The difficulty encountered in ring-closing metathesis of **3.10** and **3.12** prompted us to develop a second generation approach to bicyclic lactone **3.20** based on intramolecular reductive allylation of ester (Scheme 3.4). This new route commenced with regioselective allylic chlorination of **3.7** with hypochloric acid, generated *in situ* from calcium hypochlorite and CO_2, to give allyl chloride **3.16**.[43] Formate **3.17** was formed when **3.16** was subjected to Mitsunobu reaction with formic acid, DEAD, and PPh_3. The allylic chloride of **3.16** remain intact in the presence of nucleophilic PPh_3. The α, β-unsaturated cyclic ketone **3.17** was exposed to Luche reduction conditions and only one diastereomer was obtained (based on ^1H NMR analysis) in 92% yield.[44] The structure of **3.18** was further confirmed by X-ray crystallography. With allyl chloride

3.18 in hand, our next step was to construct the bicyclic AB rings of alotaketal A, which was proved to be difficult using the ring-closing metathesis approach. For this purpose, allyl chloride **3.18** was converted to allyl iodide by reaction with NaI under Finkelstein conditions to give the corresponding allyl iodide and set up the stage for intramolecular reductive allylation. Despite some initial concerns, the free hydroxyl group proved to be compatible with SmI_2-mediated intramolecular reductive allylation. The cyclization went smoothly upon treating the allyl iodide with SmI_2 to give epimers of bicyclic lactol **3.19** at 0 ^oC in the presence of HMPA. However, despite our efforts, further functionalization of **3.19** was problematic.

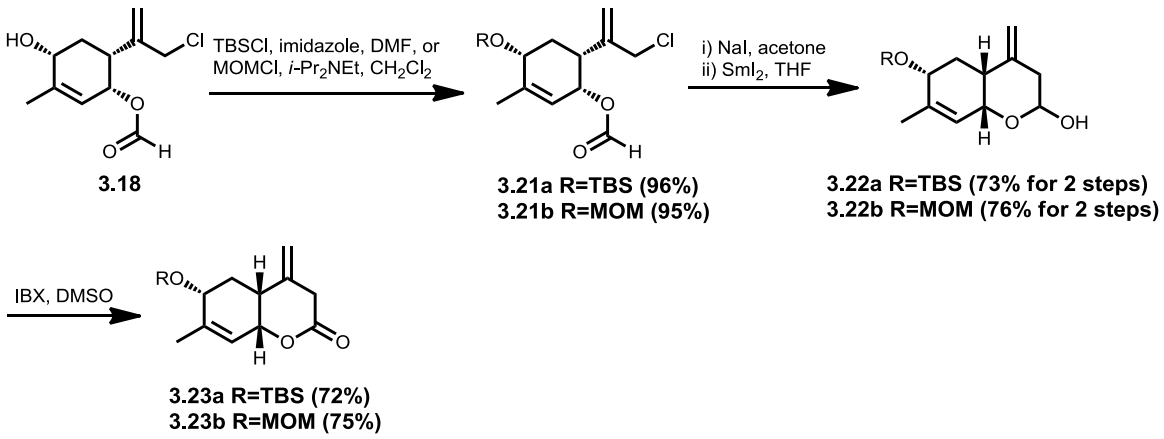


Scheme 3.4. Synthetic efforts toward **3.20**

3.3.2 Synthesis of Bicyclic Lactone 3.23a/b

Since we have been unsuccessful in further functionalization of diol **3.19**, we decided to protect the allyl alcohol first. Thus, allyl alcohol **3.18** was protected as its *tert*-butyldimethylsilyl ether **3.21a**, and converted to allyl iodide by reaction with NaI.

Again, SmI_2-mediated reductive allylation under the conditions developed by Keck and co-workers gave bicyclic lactol **3.22a**. The cyclic hemiacetal was obtained as an inconsequential 1:1 mixture of diastereomers, which were oxidized by IBX at 40 ^oC to give the desired β, γ-unsaturated lactone **3.22a**. During this process, a MOM-protected variant **3.22b** was similarly prepared from **3.18** in three steps. However, it was not further pursued because of the relatively harsh conditions that would be necessary for removal of the MOM-protecting group.



3.18

3.21a R=TBS (96%)
3.21b R=MOM (95%)

3.22a R=TBS (73% for 2 steps)
3.22b R=MOM (76% for 2 steps)

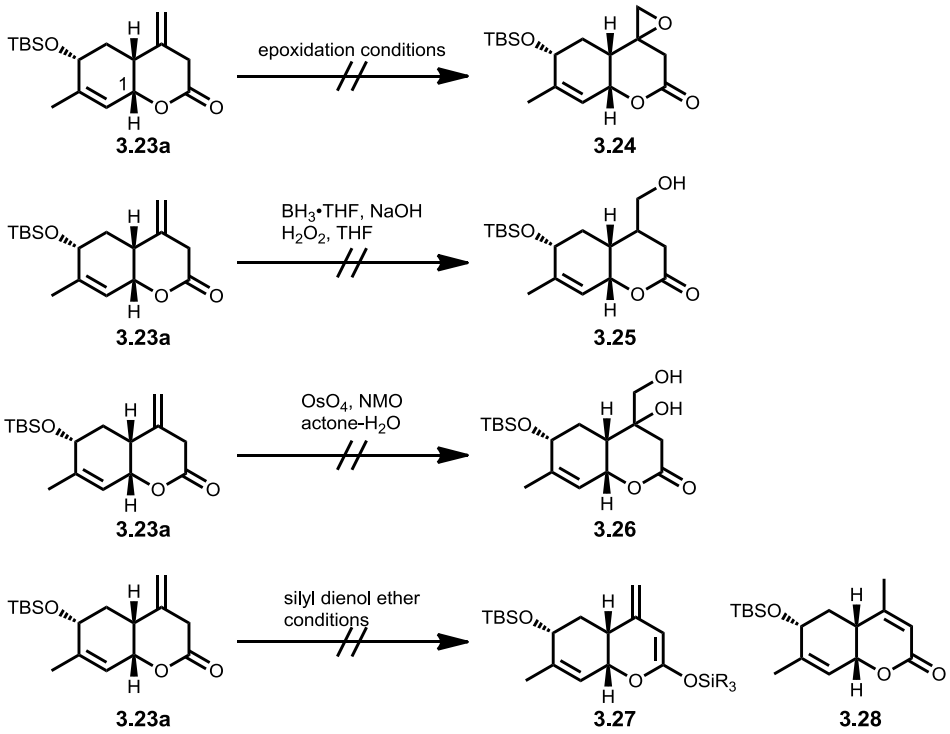
3.23a R=TBS (72%)
3.23b R=MOM (75%)

Scheme 3.5. Synthesis of bicyclic lactone **3.23a/b**

3.3.3 Synthetic Studies Toward γ-Oxygenation of 3.23a

After the bicyclic ring system was secured, our next objective was to functionalize the β, γ-unsaturated lactone **3.23a** to introduce the C22-hydroxyl group of **3.4**. We envisioned that the 1, 1-disubstituted $\Delta^{7,22}$ alkene could be selectively epoxidized in the presence of the sterically hindered and electronically deactivated (by

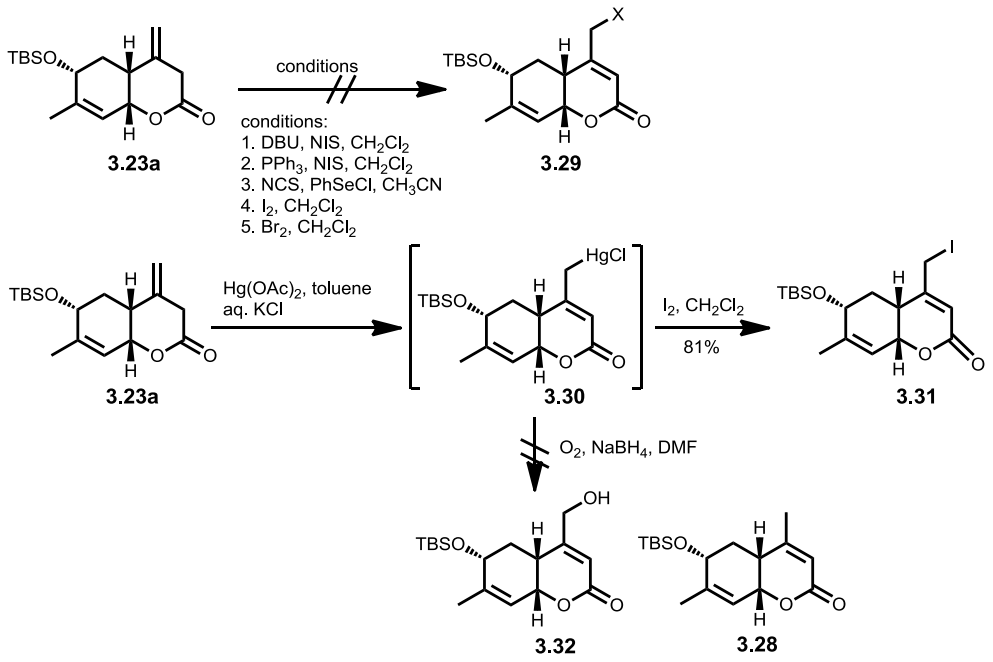
the C1-oxygen, Scheme 3.6) trisubstituted $\Delta^{2,3}$ alkene. However, to our surprise, β, γ-unsaturated lactone **3.23a** was recovered when it was subjected to epoxidation with *m*CPBA at rt to 40 ^{o}C while complex mixtures were obtained with low conversion when **3.23a** was treated with DMDO or CF_3CO_3H. Treatment of β, γ-unsaturated lactone **3.23a** with B_2H_6 also led to full recovery of the starting material while dihydroxylation with OsO_4 gave a complex mixture. Efforts to prepare the silyl dienol ether **3.27** for vinylogous oxidation were also unsuccessful,[38] as only α, β-unsaturated bicyclic lactone **3.28** was isolated upon reaction of **3.23a** with TBSOTf-Et_3N or under other silylation conditions.



Scheme 3.6. Synthetic studies toward γ-oxygenation of **3.23a**

3.3.4 Completing the Synthesis of Bicyclic Allyl Iodide 3.31

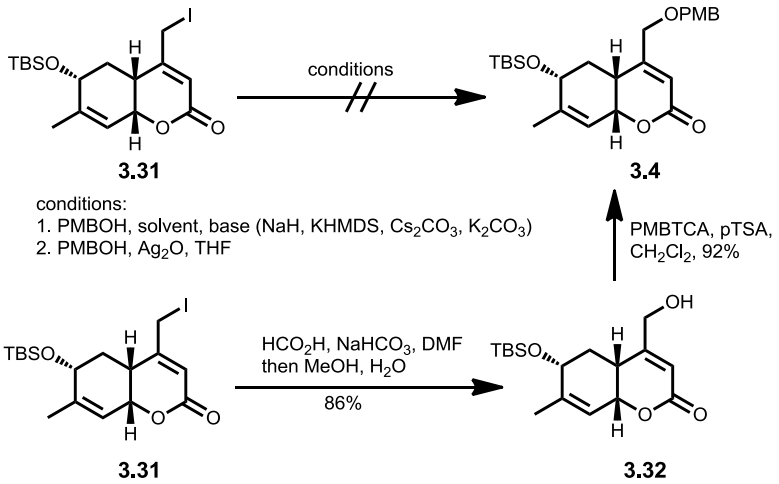
Since γ-oxygenation of **3.23a** was problematic, we turned to γ-halogenation for preparation of the corresponding allyl halide as an intermediate for introducing the hydroxyl group. However, attempts at allylic halogenation of **3.23a** with NIS, NCS, I_2, or Br_2 led to complex reaction mixtures or recovery of **3.23a**. A solution was eventually identified after extensive experimentation. It started from migratory mecuration of **3.23a** with $Hg(OAc)_2$ to give allylmercury intermediate **3.30**, apparently through facile rearrangement of the reversibly formed $\Delta^{7,\ 22}$ mercurinium intermediate under the influence of the lactone. Iodinolysis of **3.30** with I_2 gave allyl iodide **3.31**. Attempts for direct oxidation of allyl mercury intermediate **3.30** to give allyl alcohol **3.32** afforded reductive demercuration product **3.28** only.[45]



Scheme 3.7. Synthesis of allyl iodide **3.31**

3.3.5 Completing the Synthesis of Bicyclic Lactone 3.4

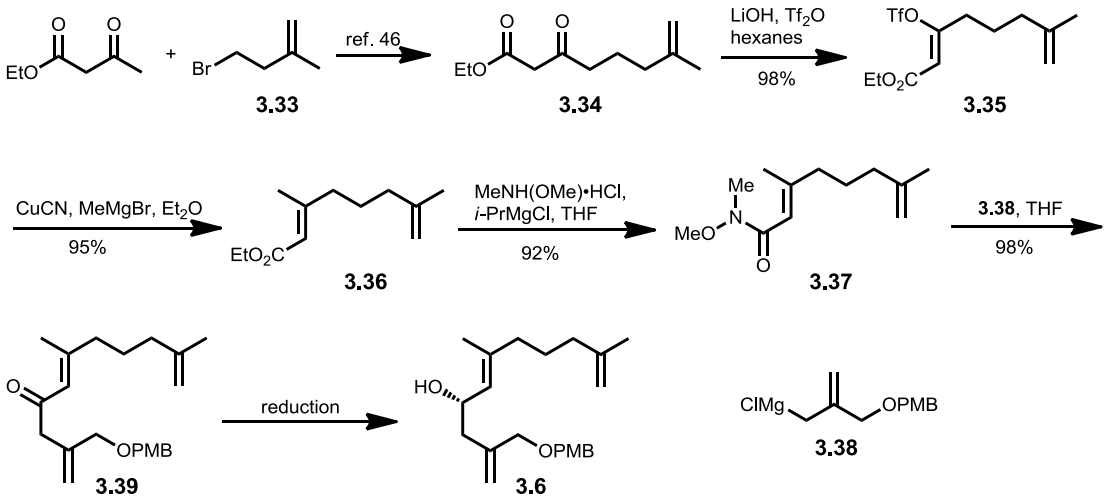
With allyl iodide **3.31** in hand, our next step was to introduce the C22-hydroxyl group. Because it was still necessary to protect the hydroxyl group before the coupling of the two fragments, direct introduction of a PMB protected hydroxyl group would be more straightforward. We tested the possibility of displacing allyl iodide **3.31** with *p*-methoxybenzyl alcohol (Scheme 3.8). However, common substitution reaction conditions, such as with NaH, KHMDS, Cs_2CO_3, K_2CO_3, or Ag_2O, all failed to deliver **3.4** directly. This problem was finally solved using a two-step sequence. Treatment of allyl iodide **3.31** with sodium formate, formed *in situ* from formic acid and sodium bicarbonate, provided allyl alcohol **3.32** after basic workup. The hydroxyl group was protected as its PMB ether to give bicyclic lactone **3.4**.



Scheme 3.8. Synthesis of bicyclic lactone **3.4**

3.4 Synthetic Studies Toward Fragment 3.6

Our efforts toward synthesis of fragment **3.**6 built upon the ease of access of known β-keto ester **3.34** through γ-alkylation of the dienolate of ethyl acetoacetate with 4-bromo-2-methylbut-1-ene **3.33** (Scheme 3.9).[46] β-keto ester **3.34** was stereoselectively (>20:1) converted to *E*-enoate **3.36** by CuCN-mediated methylation of the corresponding *Z*-enol triflate **3.35**,[47] which was prepared from **3.34** under biphasic reaction conditions with aqueous LiOH-Tf_2O.[48] Whereas Fe-catalyzed methylation of enol triflate often proceeds with excellent yield and stereoselectivity,[49] we were surprised that the reaction of **3.35** under such conditions caused significant isomerization of the enoate alkene of **3.36** (*E*:*Z* ~ 3:1 to 1:1). Reaction of **3.36** with *N*, *O*-dimethylhydroxylamine by the Merck procedure gave Weinreb amide **3.37**,[50] which was converted to ketone **3.39** upon alkylation with allylmagnesium chloride **3.38**.[51] To our relief, no isomerization of the β, γ-enone moiety of **3.39** was observed. Preparation of allyl alcohol **3.6** required enantioselective reduction of ketone **3.39**. However, this β, β-disubstituted enone was unreactive under Noyori transfer hydrogenation[52] and $LiAlH_4$/*R*-(+)-BINOL reduction conditions.[53] While allyl alcohol **3.6** could be obtained by the CBS reduction of **3.39**, [54] no enantioselectivity was observed during this process.

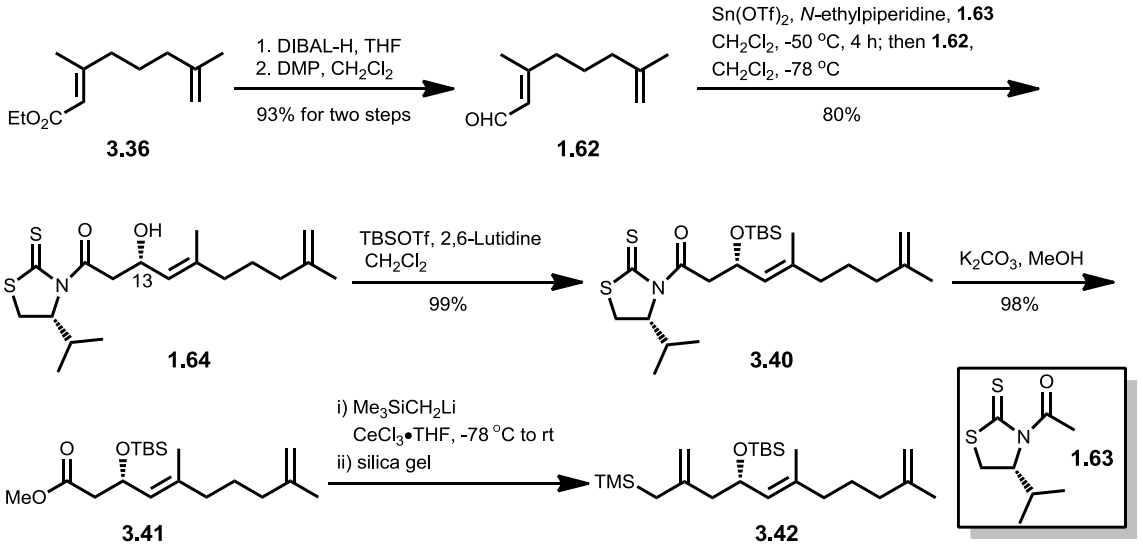


Scheme 3.9. Preparation of fragment **3.6**

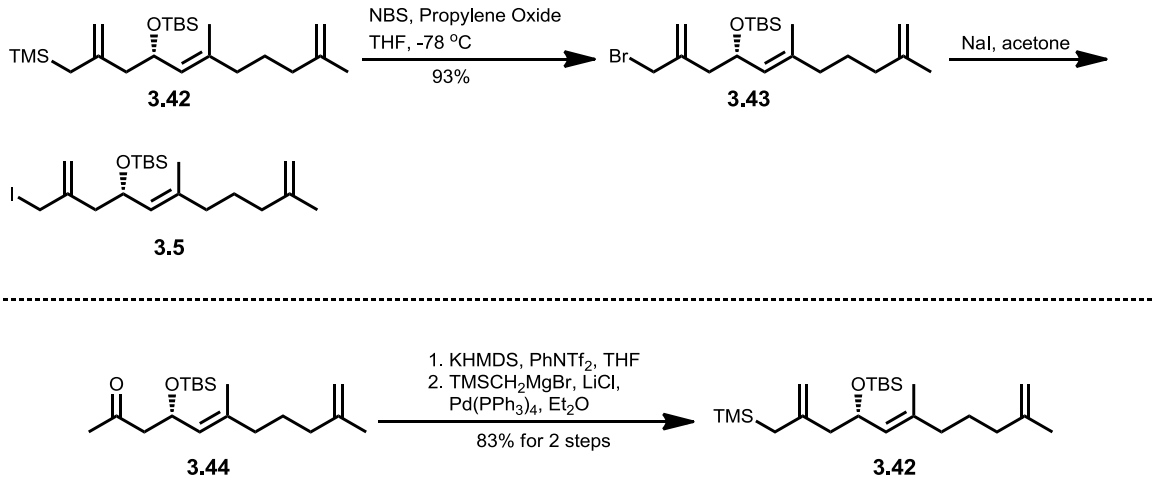
3.5 Synthesis of the Allyl Iodide Fragment 3.5

We then turned to an aldol approach for stereoselective introduction of the C13 hydroxyl group (Scheme 3.10). For this purpose, treatment of ester **3.36** with DIBAL-H followed by oxidation of the resulting allyl alcohol with Dess-Martin periodinane gave aldehyde **1.62**. The tin (II) triflate mediated Nagao-Fujita aldol reaction of **1.62** with thiazolidinethione **1.63** in the presence of *N*-ethylpiperidine proceeded with excellent diastereoselectivity (>20:1, based on ^{1}H NMR analysis) to give aldol product **1.64**.[55] Protection of **1.64** as its *tert*-butyldimethylsilyl ether and methanolysis of the thione chiral auxiliary gave ester **3.41**. Treatment of ester **3.41** with 3 equiv of organocerium reagent generated *in situ* by the reaction of trimethylsilylmethyllithium with anhydrous cerium (III) chloride resulted in double addition to give a bis(silylmethyl)carbinol.[56] Workup and exposure of the crude tertiary alcohol to silica gel facilitated Peterson elimination and delivered the allyl silane **3.42**. Consistent with previous reports,

successful preparation of the allylsilane required the trimethylsilylmethylcerium reagent to be meticulously prepared. Under less stringent conditions, methyl ketone **3.44** was formed as the major product (>95% yield).[57] Fortunately, methyl ketone **3.44** could be converted to allylsilane **3.42** in a two-step sequence that consists of transformation of methyl ketone **3.44** into its enol triflate followed by Pd-catalyzed Kumada coupling with trimethylsilylmethylmagnesium bromide (under the dash line, Scheme 3.10). Various protocols for iodinolyisis of allylsilane **3.42** were tested. The optimal results were obtained when **3.42** was treated with freshly recrystallized NBS followed by Finkelstein reaction with NaI to give allyl iodide **3.5**. It was crucial to maintain the reaction in the dark to suppress radical bromination of the remote terminal 1, 1-disubstituted alkene.



Scheme 3.10. Synthesis of fragment **3.5**

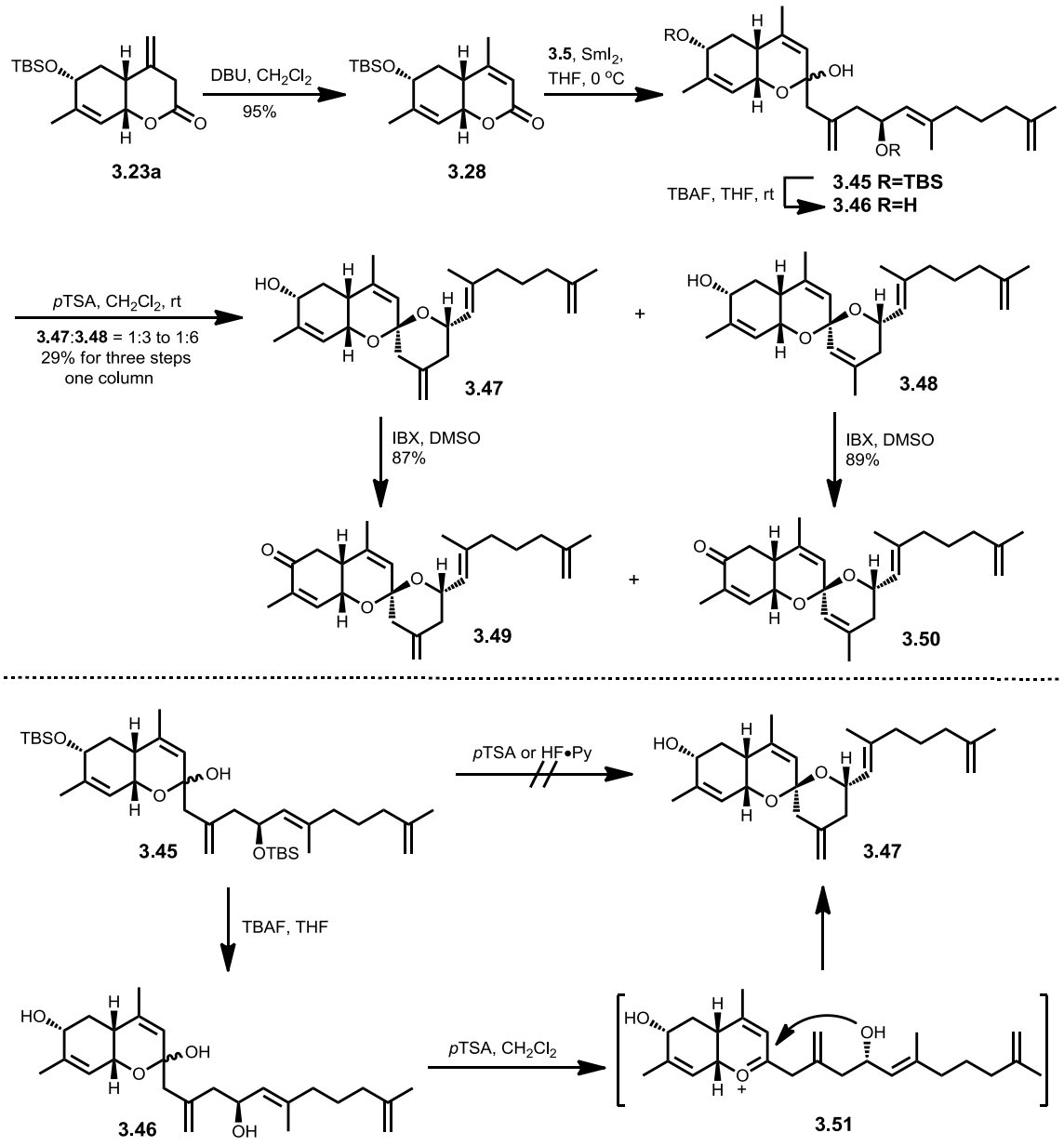


Scheme 3.10. (Continued) Synthesis of fragment **3.5**

3.6 Synthesis of C22-Deoxyalotaketal A

To shed light on potential obstacles that might be encountered in the synthetic route, a pilot study of fragment coupling and subsequent transformations was carried out using **3.5** and **3.28** as model substrates. This study not only would illuminate nuances in assembling the unique spiroketal ring system of alotaketal A, but also would provide access to C22-deoxy and other analogues of alotaketal A for structure-activity relationship (SAR) studies. Process I of our synthetic design (Scheme 3.1) was employed because of the availability of fragment **3.5** and the perceived simplicity of its coupling event. Bicyclic lactone **3.28** was previously isolated as a side product (Scheme 3.6 and Scheme 3.7). It could also be obtained in 95% yield upon treating **3.23a** with DBU (Scheme 3.11). With **3.28** in hand, we explored its coupling with allyl iodide **3.5** and the corresponding bromide **3.43** under a variety of conditions. Whereas all attempts

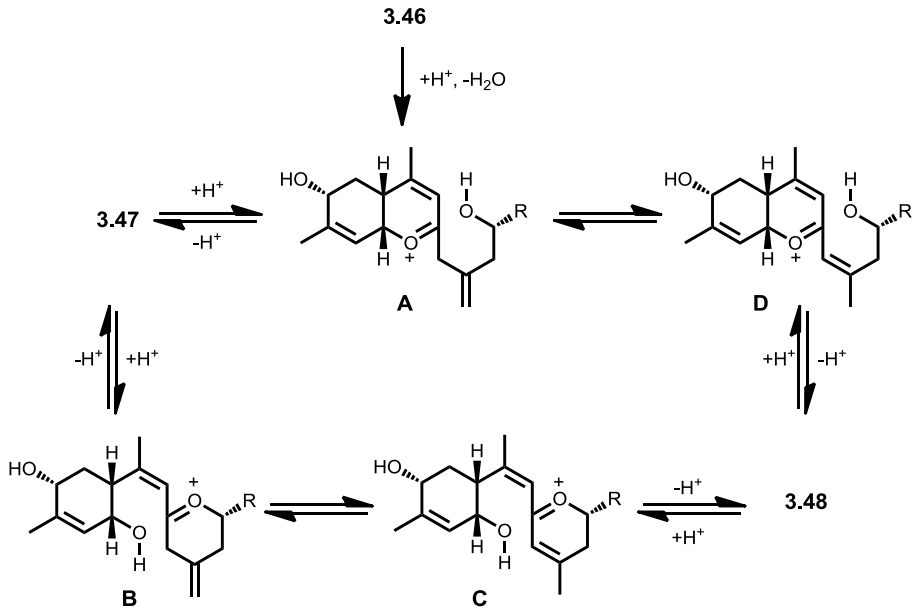
of coupling through the intermediacy of the allyllithium or allyl Grignard reagents prepared *in situ* were hampered by competing dimerization of the allyl halides, the two fragments (i.e. **3.28** and **3.5**) were eventually coupled under Barbier conditions with SmI_2 through an intermolecular reductive allylation to give lactol **3.45**. No over reduction was observed even though excess of SmI_2 was used. Our attempts for global desilylation and spiroketalization of **3.45** with HF•Py or *p*TSA were unsuccessful due to the acid-sensitive nature of **3.45**. Fortunately, the desired transformations could be effected in a stepwise manner. Thus, global desilylation of crude **3.45** with TBAF gave lactol **3.46**, which was subjected to *p*TSA-mediated spiroketalization without purification. This led to the formation of tricyclic spiroketal **3.47** and its $\Delta^{10,11}$ isomer **3.48** due to migration of $\Delta^{11,23}$ alkene under the acidic conditions, with the latter isolated as the major product (1:3 to 1:6). Spiroketals **3.47** and **3.48** were oxidized with IBX to give C22-deoxyalotaketal A **3.49** and its isomer **3.50**, respectively. The stereochemistry of the spiroketal centers was assigned by analogy to that of the natural product.



Scheme 3.11. Synthesis of C22-deoxyalotaketal A

The formation of **3.48** was mechanistically interesting because it could arise either from isomerization of oxocarbenium intermediate **A** by deprotonation/protonation to form **D** followed by cyclization to give **3.48** or from isomerization of the initially

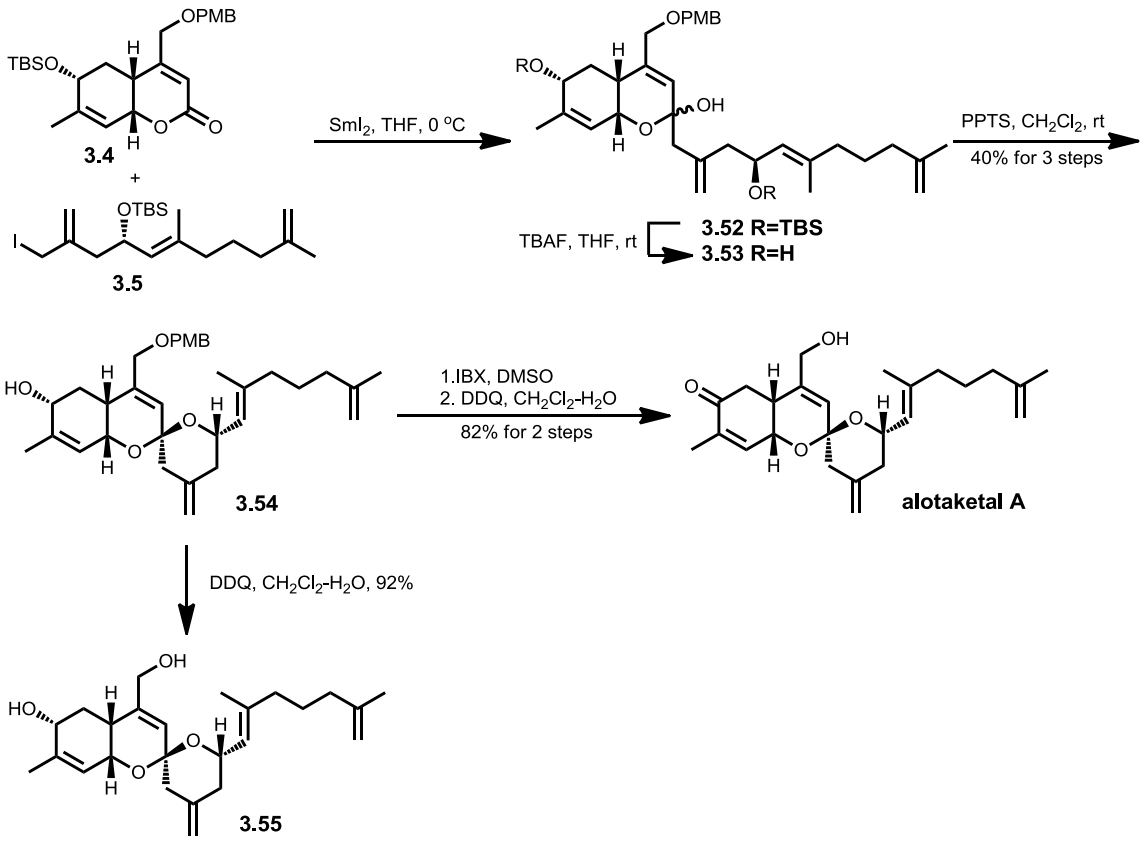
formed product **3.47** through the intermediacy of oxocarbenium **A** and/ or **B** under the acidic conditions (Scheme 3.12). To illuminate the mechanistic subtleties of this process, the spiroketalization of **3.46** was tested with less acidic pyridinium *p*-toluenesulfonate (PPTS). Interestingly, spiroketalization of **3.46** with PPTS led to the formation of spiroketals **3.47** and **3.48** in equal amounts. Further experiments showed that **3.47** could be easily isomerized to **3.48** upon treatment with *p*TSA. However, no isomerization of **3.47** was observed when it was treated with PPTS. These results suggested that part of the exo-to-endo isomerization of the $\Delta^{11,23}$ alkene occurred through the intermediary of oxocarbenium **A** prior to spiroketalization. However, the significant isomerization of the alkene in the *p*TSA-promoted spiroketalization of **3.47** was mostly due to the unchecked equilibration of **3.47** to its thermodynamically more favorable $\Delta^{10,11}$ isomer **3.48**.



Scheme 3.12. Isomerization of the $\Delta^{11,23}$ alkene

3.7 Completing the Total Synthesis of Alotaketal A

Building upon our preliminary studies, the successful synthesis of alotaketal A was shown in Scheme 3.13. The coupling of fragments **3.4** and **3.5** went smoothly by SmI_2 mediated intermolecular reductive allylation under Barbier conditions to give lactol **3.52**. Desilylation of **3.52** with TBAF gave **3.53**. This was followed by spiroketalization of crude **3.53** with PPTS. Interestingly, only the desired spiroketal **3.54** was formed during this process and the *exo*-to-*endo* isomerization of $\Delta^{7,22}$ alkene was not observed. Since **3.46** and **3.53** differ only by the C22 *p*-methoxybenzyloxy group, we speculated that the electron-withdrawing inductive effect of the alkoxy group and/or the cation-π stabilization of the oxocarbenium by the *p*-methoxybenzyloxy group might be responsible for their different reactivity profiles for spiroketalization. Oxidative removal of the PMB group with DDQ gave diol **3.55**, an alotaketal A analogue with the enone moiety reduced to an allyl alcohol. Oxidation of **3.54** with IBX followed by oxidative cleavage of PMB group with DDQ gave synthetic alotaketal A. Its ^{1}H and ^{13}C NMR spectra were consistent with those of the natural product, as was its specific optical rotation. In addition, synthetic (-)-aloketal A was found to be identical to an authentic sample of the natural product on the basis of TLC and HPLC.



Scheme 3.13. Synthesis of (-)-alotaketal A

3.8 Investigating the Bioactivity of Alotaketal A and Analogs

The goal of the next series of experiments was to collaborate with Prof. Jin Zhang from Johns Hopkins University to examine the effects of alotaketal A and its analogs **3.47-3.50** and **3.55** on cAMP/Protein Kinase A (PKA) signaling pathway. These effects were studied in HEK293 cells by fluorescence imaging using an optimized genetically encoded A kinase activity reporter (AKAR4),[58] which is able to directly report the PKA activity by its change in fluorescence. The change in fluorescence is due to the phosphorylation-dependent conformational change of a tandem fusion domain,

composed of a substrate peptide for PKA and a phosphorylation recognition domain (Figure 3.2, a). The conformation change alters the distance or orientation between the two fluorescent proteins at the N and C termini of the reporter, generating a change in Förster resonance energy transfer (FRET) between them. In the context of AKAR4, the phosphorylation of the substrate domain by activated PKA causes a conformational change that brings the fluorescent proteins in close proximity to produce an increase in FRET which is detected as an increase in the ratio of yellow to cyan emission.

First, we tested each of these compounds (alotaketal A and its analogs **3.47**-**3.50** and **3.55**) in HEK293 cells transfected with AKAR4. Among them, **3.47**-**3.50** at 1 μM only induced slight changes in the ratio of yellow to cyan emission from the reporter, increasing the emission ratio by 1.07 ± 0.3% (n = 11; n = number of cells), 1.55 ± 0.8% (n =8), 1.28 ± 0.6% (n = 5), 1.22 ± 0.4% (n = 8), respectively (Figure 3.2, b and c). The relatively small responses from analogs **3.47**-**3.50** were due to the inactivity of the analogs and not from poorly functioning AKAR4 which was confirmed by the control experiment. The probes responded maximally upon addition of a cAMP-elevating cocktail consisting of the AC activator forskolin (Fsk) and the general PDE inhibitor 3-isobutyl-1-methylxanthine (IBMX).[59] In contrast to analogs **3.47**-**3.50**, **3.55** and alotaketal A produced significant responses of 6.7 ± 2.2% (n = 24) and 5.3 ± 2.5% (n = 13) from AKAR4, respectively (Figure 3.2, b and c). Thus, these results show that **3.55** and alotaketal A are active and involved in PKA activation.

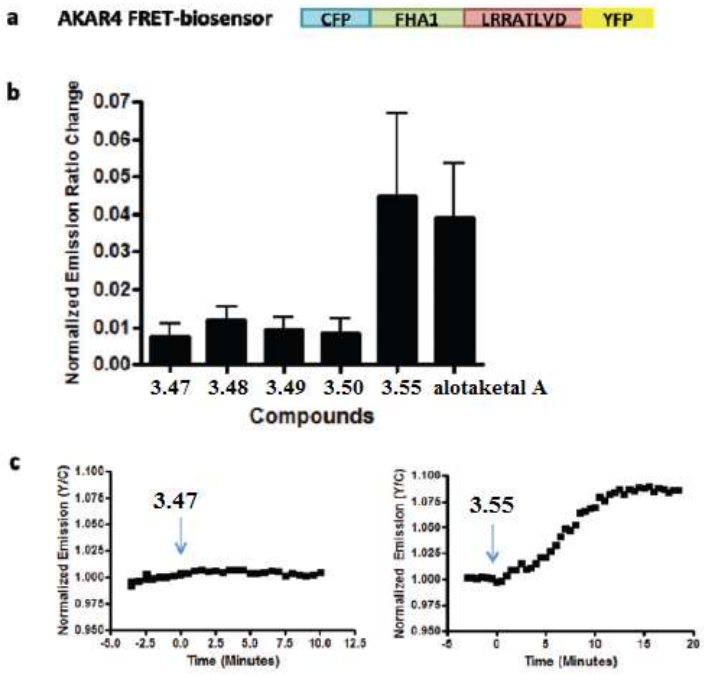


Figure 3.2. Effects of alotaketal A and its analogs on cAMP/PKA signaling. (a) Schematic diagram of the AKAR4 FRET-based biosensor used in this series of experiments. (b) Bar graph showing AKAR4 responses in HEK 293T cells following treatment with **3.47** (1 μM; n = 11), **3.48** (1 μM; n = 8), **3.49** (1 μM; n = 5), **3.50** (1 μM; n = 8), **3.55** (1 μM; n = 24), and alotaketal A (1 μM; n = 13). (c) Representative time course graphs depicting AKAR4 responses to the inactive compound **3.47** (left) and active compound **3.55** (right).

We further evaluated the specificity of the alotaketal-induced AKAR4 responses by utilizing an AKAR4 T/A mutant probe containing a mutated PKA phosphorylation site within the PKA substrate domain. This mutation abolishes PKA phosphorylation and the PKA activity-induced FRET changes. No response was detected when cells

expressing the AKAR4 T/A mutant were treated with alotaketal A and **3.57**, confirming that these compounds induce PKA activity *via* the cAMP/PKA signaling pathway (Figure 3.3).

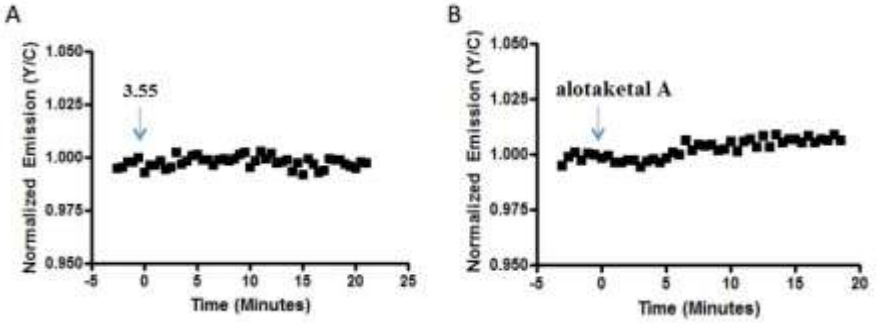


Figure 3.3. HEK293 cell expressing AKAR4 T/A mutant (A) were treated with **3.55** (1 μM, n=6) and (B) alotaketal A (1 μM, n=4)

To examine further the effects of alotaketal A and **3.55** on cAMP accumulation, we used ICUE3, a FRET-based reporter for cAMP.[60] The binding of cAMP to ICUE3 induces a conformational change that results in a decrease in FRET, which is detected as an increase in the cyan/yellow emission ratio. When treated with 1 μM alotaketal A and **3.55**, the cells expressing ICUE3 showed 6.5 ± 0.32% (n = 10) and 4.4 ± 1.1% (n = 6) increases in the cyan/yellow emission ratio, respectively (Figure 3.4). These data suggest that both alotaketal A and **3.55** increase PKA activity by increasing cellular levels of cAMP.

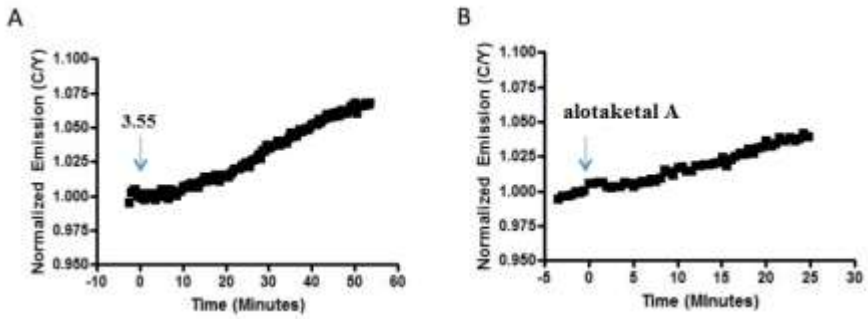


Figure 3.4. HEK293 cells expressing ICUE3 were (A) treated with **3.55** (1 μM, n = 10) and (B) alotaketal A (1 μM, n = 6)

The mechanisms by which these compounds induce cAMP production and PKA activation are unknown. However, the following observation from imaging experiments suggested that they exhibited subcellular specificity when activating the pathway in living cells. As illustrated in the ratiometric images (Figure 3.5), the nuclear region showed a more drastic color change compared to the cytosol upon the addition of **3.55** or alotaketal A (Figure 3.5, a). We then quantitated the responses in these two cellular compartments. Alotaketal A elicited a response of 6.3 ± 2.5% (n = 6) in the nucleus and a mere 2.5 ± 0.21% (n = 6) in the cytosol, while analog **3.55** also had a similar response of 7.2 ± 0.71% (n = 5) in the nucleus and 2.5 ± 0.72% (n = 5) in the cytosol (Figure 3.5, b). These results are quite different from what has been seen when naïve HEK293 cells expressing AKAR4 are treated with forskolin and IBMX. As previously observed, the magnitude of the AKAR4 responses is smaller and kinetically slower in the nucleus than in the cytosol (Figure 3.5, c), 16.1 ± 0.11% (n = 8) and 70.8 ± 0.09% (n = 8) respectively, due to the activation of cytosolic PKA and subsequent translocation of the catalytic

domain of cytosolic PKA to the nucleus.[61] These results show that alotaketals are possibly targeting a different pool of cAMP/PKA signaling components, more specifically those found in the nucleus.

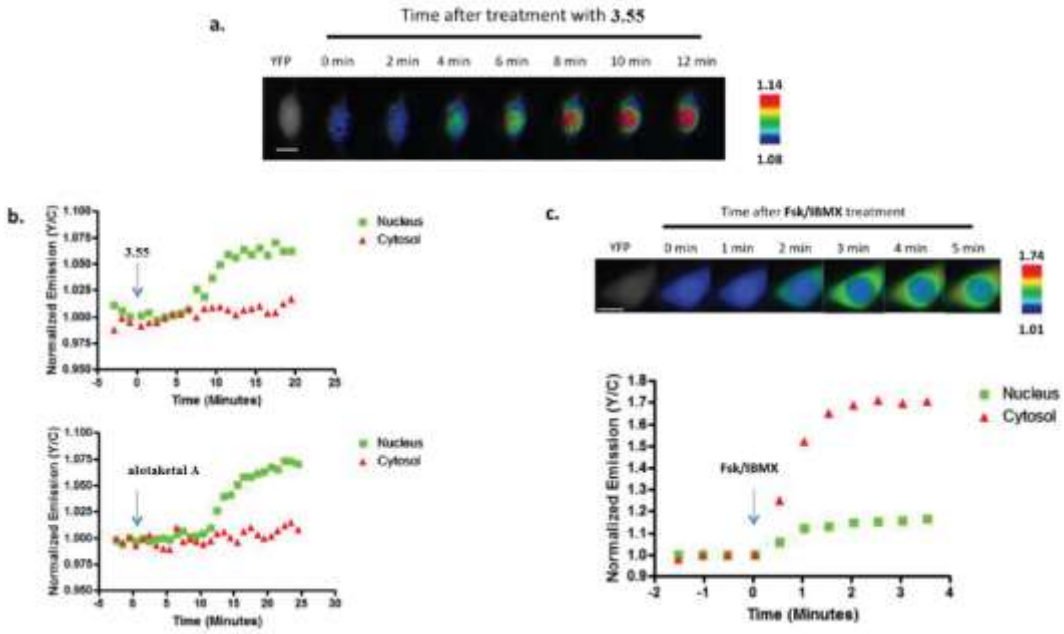


Figure 3.5. Alotaketal A and **3.55** preferentially activate nuclear cAMP/PKA signaling. (a) Representative YFP and ratiometric images of AKAR4-expressing HEK293 cells treated with **3.55**. (b) Time course graph depicting AKAR4 responses in the nucleus and cytoplasm of HEK293 cells after the addition of **3.55** (top panel) and alotaketal A (bottom panel). (c) YFP and ratiometric images of AKAR4 response after Fsk (50 μM) and IBMX (100 μM) treatment (top panel). Corresponding time course graph depicting AKAR4 responses in the nucleus and cytoplasm after the treatment (n = 8) (bottom panel).

3.9 Summary

We accomplished the first enantioselective total synthesis of the tricyclic sesterterpenoid (-)-alotaketal A, a potent cAMP signaling agonist that features an unprecedented spiroketal ring system. Two Barbier-type SmI_2-mediated reductive allylation of esters with allyl iodides were employed in this convergent synthetic route: an intramolecular reductive coupling was crucial for the preparation of the key bicyclic lactone fragment whereas an intermolecular reductive coupling was employed to join the fragments and complete the sesterterpenoid molecular skeleton. During the spiroketalization to form the unique spiroketal ring system, our study revealed the subtle interplay of the structure and functional group stability/reactivity. Also highlighted is the $Hg(OAc)_2$-mediated allylic mercuration of β, γ-unsaturated lactone to introduce the C22-hydroxyl group with high chemo- and regio-selectivity. Using FRET imaging assays with genetically encoded AKAR4 reporter genes, we verified that the cAMP signaling pathway was activated by alotaketal A. Our preliminary SAR studies revealed the C22-hydroxyl group to be important to alotaketal A's bioactivity. On the other hand, reduction of the enone moiety to an allyl alcohol was tolerated, suggesting the enone moiety to be nonessential. Our FRET imaging studies revealed that alotaketal A and analog **3.55** activated the cAMP/PKA pathway in a subcellular specific manner.

CHAPTER IV

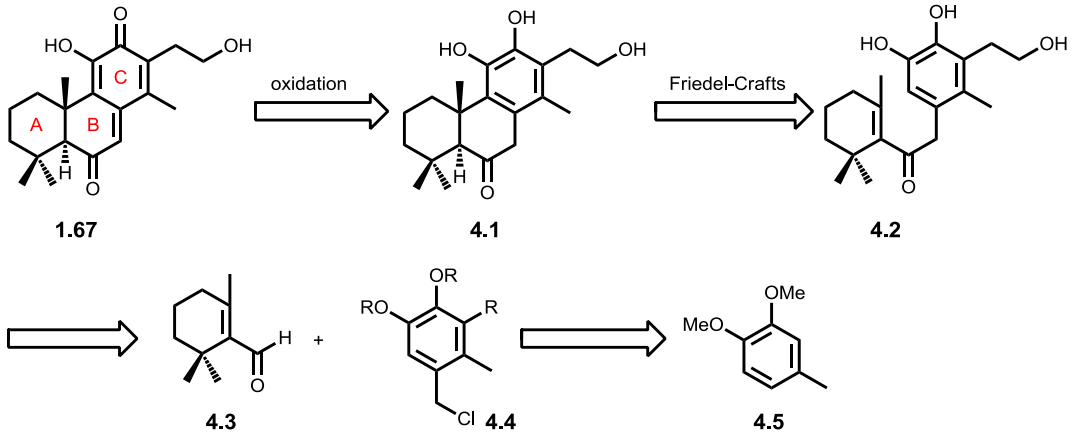
TOTAL SYNTHESIS OF AN ANTIFUNGAL *O*-HYDROXY-*P*-QUINIONE METHIDE DITERPENOID*

4.1 Retrosynthesis of *o*-Hydroxy-*p*-Quinone Methide Diterpenoid 1.67

The unnamed *o*-hydroxy-*p*-quinone methide diterpenoid **1.67** was reported to be potently antifungal (MIC=0.19 μM), even more potent than that of the clinical antifungal drugs amphotercin B and fluconazole. Although a number of approaches had been reported toward the structurally related taxodione prior to 1995,[21] no any synthetic studies have been reported for this diterpenoid **1.67** since its isolation in 2000 by Hostettmann and co-workers from *Bobgunnia madagascariensis*.[20] As part of our efforts toward chemical and biological characterization and potential biomedical application of this compound, we envisioned a convergent approach to **1.67**. This route would serve to not only enable access of the natural product itself, but also allow preparation of analogs for structure-activity relationship and mode-of-action studies. In this regard, we envisioned that the *o*-hydroxyl-*p*-quinone methide moiety of **1.67** be prepared by oxidation of catechol **4.1** (Scheme 4.1). An intramolecular Friedel-Crafts alkylation of **4.2** would be relied upon to build the tricyclic molecular framework. The precursor **4.2** could be assembled by intermolecular coupling of commercially available β-cyclocitral

* Reprinted with permission from "Total Synthesis and Biological Evaluation of an Antifungal Tricyclic *o*-Hydroxy-*p*-Quinone Methide Diterpenoid" by Huang, J.; Foyle. D.; Lin, X.; Yang, J. *J. Org. Chem*. **2013**, *78*, 9166-9173, Copyright [2013] by American Chemical Society

4.3 and benzyl chloride **4.4**, which in turn could be synthesized from 3, 4-dimethoxytoluene **4.5**. With the intention of developing an asymmetric intramolecular Friedel-Crafts alkylation for enantioselective synthesis of **1.67**, we initiated our synthetic studies.



Scheme 4.1. Retrosynthesis of **1.67**

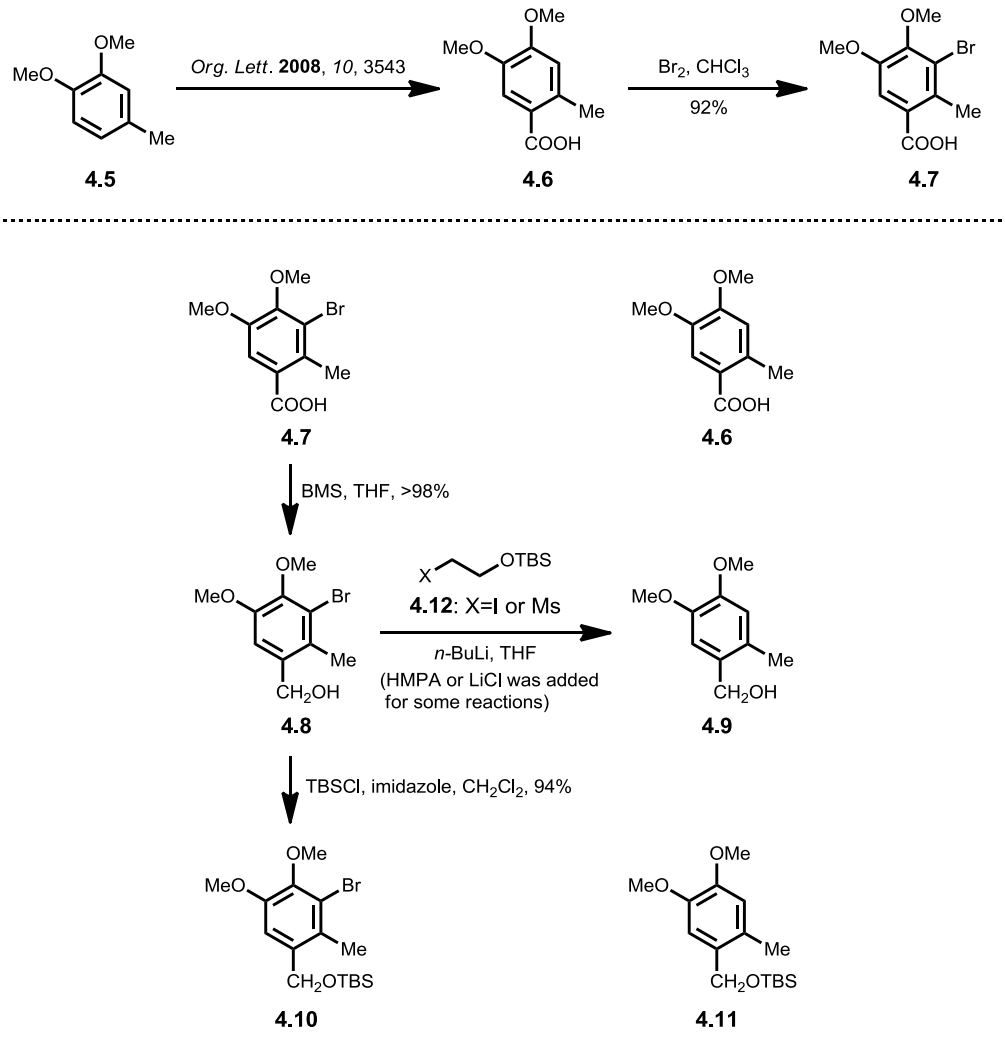
4.2 Synthetic Studies Toward Introducing the 2'-Hydroxyethyl Side Chain

Since compound **4.6** has been previously synthesized,[62] our initial efforts focused on introducing a 2'-hydroxyethyl group to access a fully functionalized C ring of **1.67**. We envisioned that it could be introduced through the coupling of the dianion of **4.7** or **4.8** and known electrophile **4.12**[63,64] (Scheme 4.2). The aryl bromide **4.7** was prepared by bromination of known carboxylic acid **4.6**. Reduction of the carboxyl group of **4.7** with borane dimethyl sulfide provided benzyl alcohol **4.8** in quantitative yield. With **4.7** and **4.8** in hand, we tested their coupling with **4.12** through their corresponding dianions generated by treatment with *n*-BuLi. However, only protonated product **4.6** and **4.9** were

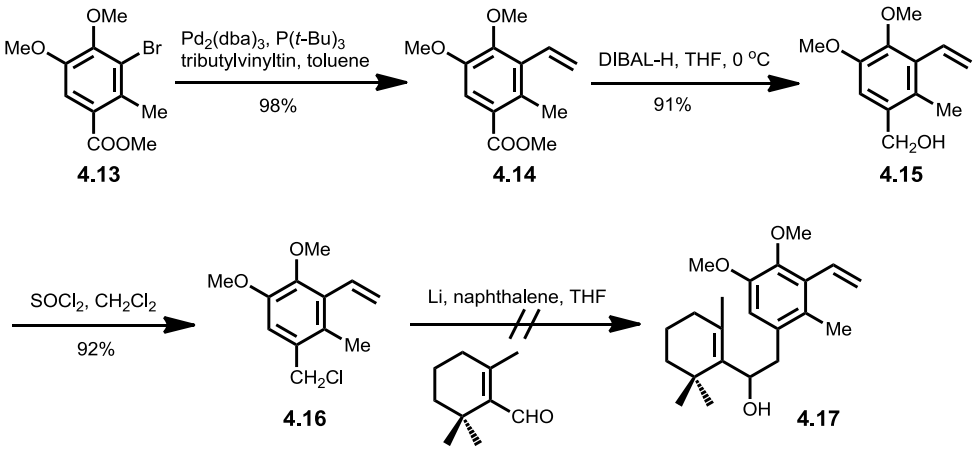
isolated even when LiCl or HMPA was used as the additive to improve the nucleophilicity of the dianions. Since the carbon anion generated through the halogen-metal exchange might be quenched by the carboxylic acid or benzyl hydroxyl group present in the substrate, the benzyl hydroxyl group of **4.7** was protected with TBS to give compound **4.10** and subjected to the coupling reaction. Again, only protonated product was isolated. We speculated that the congested environment of **4.7** and **4.8** might be the reason for their low reactivity in the coupling reactions.

4.3 Synthetic Studies Toward Introducing an Ethylene Side Chain

Because of the difficulties encountered in direct introduction of the 2'-hydroxyethyl group, our attention turned to Stille coupling to introduce an ethylene group as its surrogate (Scheme 4.3). After extensive screening of reaction conditions, the coupling of known **4.13** with tributylvinyltin was achieved using $Pd_2(dba)_3$ and P(*t*-Bu)$_3$ to give **4.14** in 98% yield.[65] DIBAL-H reduction of ester **4.14** yielded benzyl alcohol **4.15**, which was converted to benzyl chloride **4.16** in 92% yield. Whereas complex mixtures were obtained when lithium/naphthalene was used for coupling benzyl chloride **4.16** and β-cyclocitral,[21c] no desired product (i.e. **4.17**) could be isolated from our attempts of coupling through the corresponding Grignard reagents of **4.16**. We speculated that the extended conjugation system, the ethylene side chain, likely was incompatible with the radical reaction conditions.

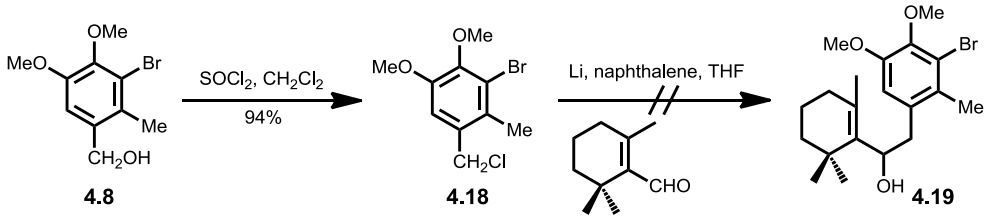


Scheme 4.2. Studies for introducing the 2'-hydroxyethyl group



Scheme 4.3. Studies toward **4.17**

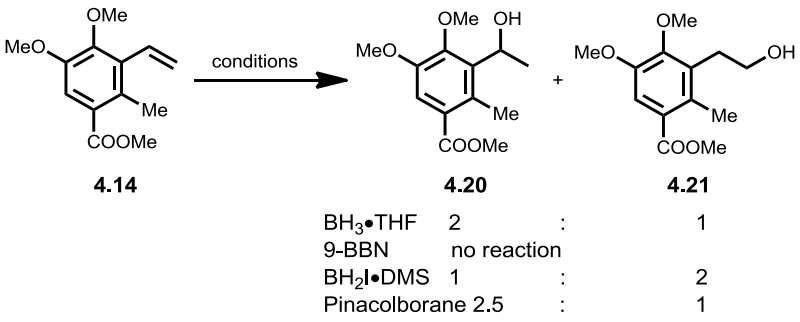
We also tested the coupling of cyclocitral and **4.18**, prepared from **4.8** through chlorination. The desired coupling did not occur either. (Scheme 4.4).



Scheme 4.4. Studies toward **4.19**

Since the ethylene side chain was the likely cause of the difficulty under the radical reaction conditions, we explored the possibility of furnishing the 2'-hydroxyethyl group prior to the coupling (Scheme 4.5). However, attempts to introduce the 2'-hydroxyethyl group through hydroboration/oxidation with **4.14** was only partially successful as the undesired regio-isomer (i.e. **4.20**) was formed as the major product

under all conditions except when BH_2I•DMS was used,[66] which gave the desired regio-isomeric product **4.21** slightly preferentially (2:1).

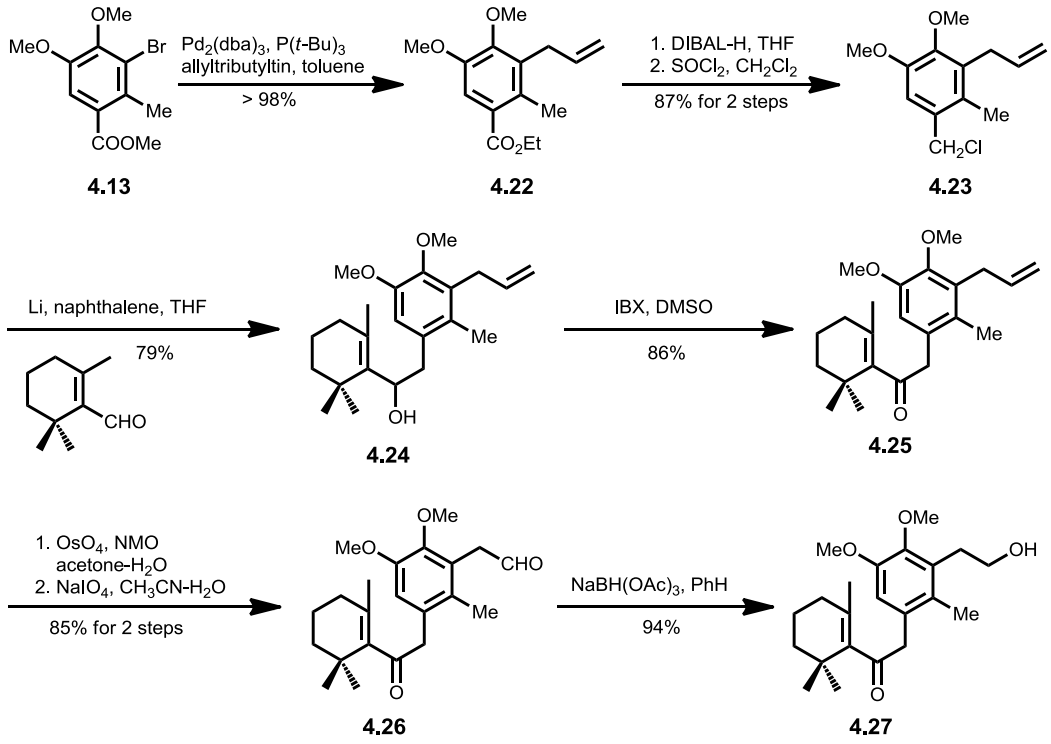


Scheme 4.5. Hydroboration/oxidation

4.4 Synthesis of 4.27

In order to improve the efficiency of the synthesis, we turn to allyl benzene **4.22** (Scheme 4.6). We envisioned that the allyl group to be compatible with the lithium/naphthalene mediated coupling reaction since the extended conjugation is absent. To our glad, Stille coupling conditions proved to be also effective for reaction of **4.13** and allyltributyltin to give **4.22** in quantitative yield. DIBAL-H reduction of ester **4.22** followed by chlorination gave the desired benzyl chloride **4.23**. As we had expected, the coupling of benzyl chloride **4.23** and β-cyclocitral went smoothly to give **4.24** in 79% yield. IBX oxidation of the benzyl alcohol provided the α, β-unsaturated ketone **4.25**. Our next task was to convert the allyl group to the 2'-hydroxyethyl side chain. Following the standard oxidative cleavage of the alkene of **4.25**, aldehyde **4.26** was obtained in 85% yield over two steps. Selective reduction of the aldehyde in the presence of the α, β-

unsaturated ketone functionality was achieved with $NaBH(OAc)_3$ to give the primary alcohol **4.27**. With this key intermediate in hand, our attention turned to the key intramolecular Friedel-Crafts alkylation.

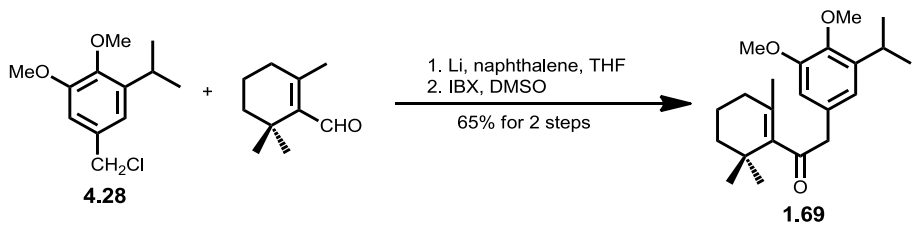


Scheme 4.6. Synthesis of **4.27**

4.5 Model Study of the Intramolecular Friedel-Crafts Alkylation

The intramolecular Friedel-Crafts reaction of **4.27** to form the carbon tricycle is challenging because it requires simultaneous dearomatization and formation of an all-carbon quaternary center. Thus, to evaluate the feasibility and elucidate the nuances of this transformation, we used **1.69** as a model substrate to test various reaction conditions for the cyclization. The aromatic enone **1.69** was synthesized through

lithium/naphthalene mediated coupling of the known benzyl chloride **4.28** and β-cyclocitral followed by oxidation with IBX (Scheme 4.7).



Scheme 4.7. Synthesis of **1.69**

4.5.1 Studies Toward Brønsted and Lewis Acid-Mediated Friedel-Crafts Alkylation

With enone **1.69** in hand, we tested both Brønsted and Lewis Acid acid-mediated intramolecular asymmetric Friedel-Crafts alkylation. A series of chiral phosphoric acids **4.29**[67] and bisoxazoline ligands **4.30** and **4.31**[68] were prepared based on literature procedures or bought from Sigma Adrich. As shown in Figure 4.1, different chiral phosphoric acids **4.29** were evaluated for the Friedel-Crafts alkylation of **1.69** in various solvents at different temperatures. No desired product was favored. We also tested a number of Lewis acids as shown in Figure 4.1 with or without ligands (**4.30**-**4.32**). The desired product was not formed either.

The combination of formic acid and phosphoric acid was reported to be suitable for cyclization of **1.69** to give **1.70** in 41% yield at 115 ^{o}C (Scheme 4.8).[21f] Interestingly, an extended reaction under such conditions led to formation of the undesired *cis*-isomeric **1.71** as the major (38%), suggesting its thermodynamic nature. The BINOL-

based chiral phosphoric acid **4.29c** was also effective for the cyclization. The desired *trans*-isomer **1.70** was obtained in 43% yield, but no enantioselectivity was observed under the harsh conditions necessary for the reaction to proceed.

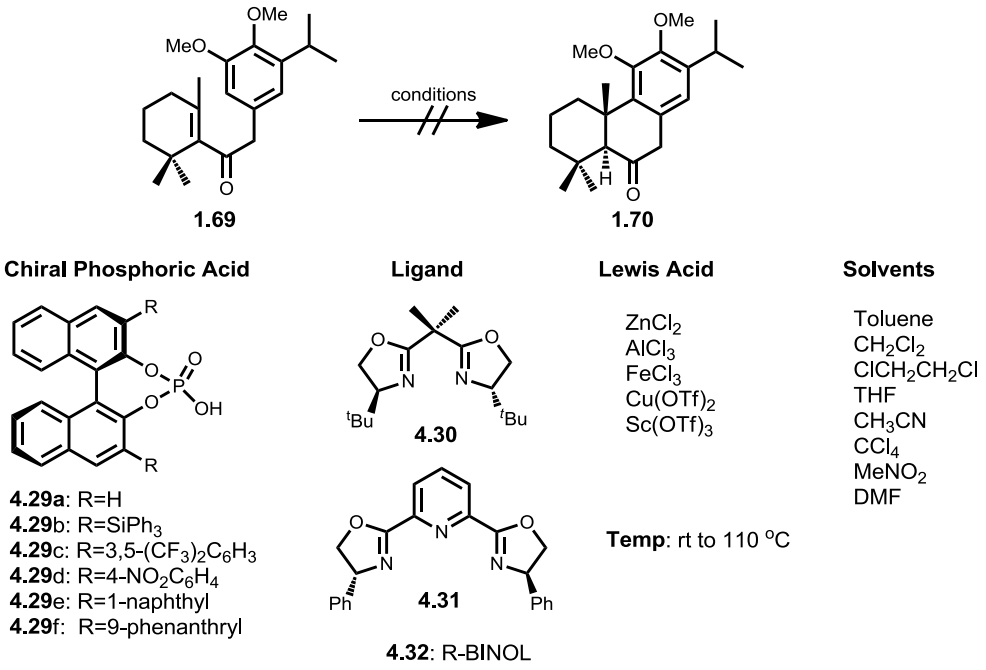
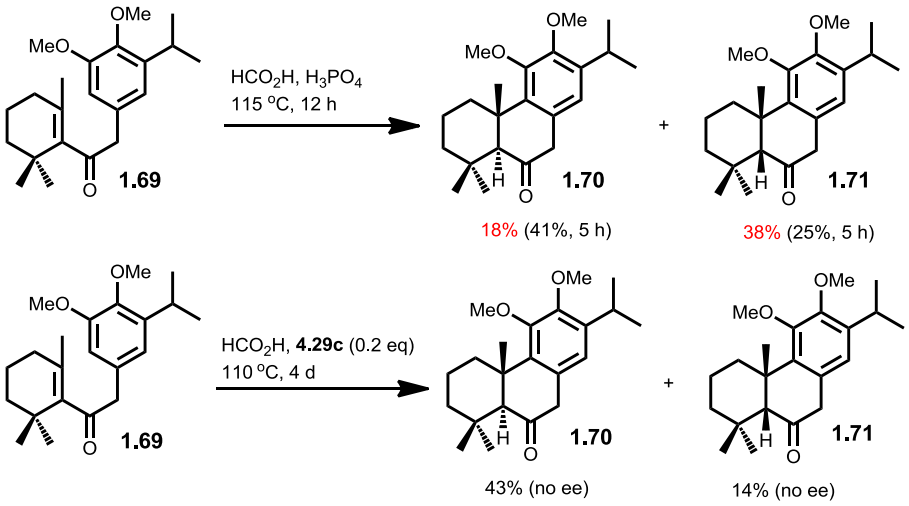


Figure 4.1. Acid approach to Friedel-Crafts alkylation



Scheme 4.8. Acid-mediated Friedel-Crafts alkylation

4.5.2 Studies Toward Chiral Amine-Mediated Friedel-Crafts Alkylation

Aiming to develop a catalytic asymmetric intramolecular Friedel-Crafts reaction through iminium catalysis, we also tested a primary-amine based chiral catalyst for the reaction with **1.69**. Because of the sterically congested nature of the substrate, we focused on quinidine-derived primary amine **4.33** as the catalyst.[69] Unfortunately, as shown in Figure 4.2, no cyclization was observed when enone **1.69** was treated with primary amine **4.33** and trifluroacetic acid in various solvents at different temperatures.

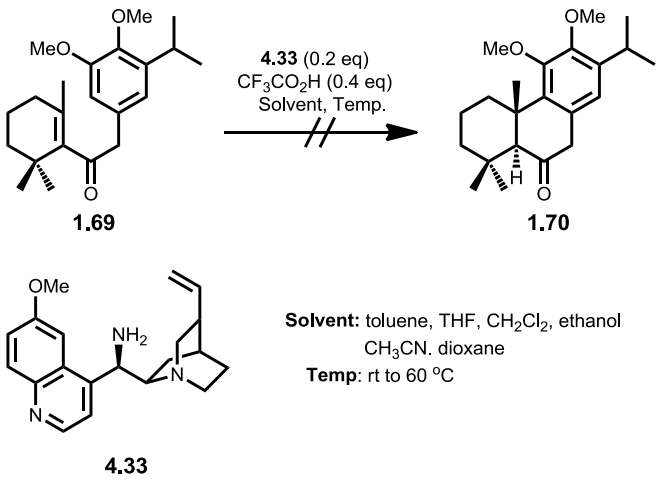
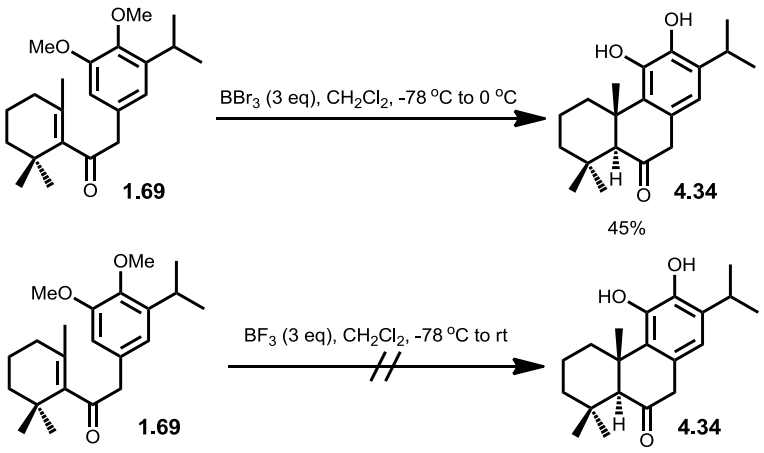


Figure 4.2. Attempts for Friedel-Crafts alkylation through iminium activation

4.5.3 BBr_3-Mediated Friedel-Crafts Alkylation

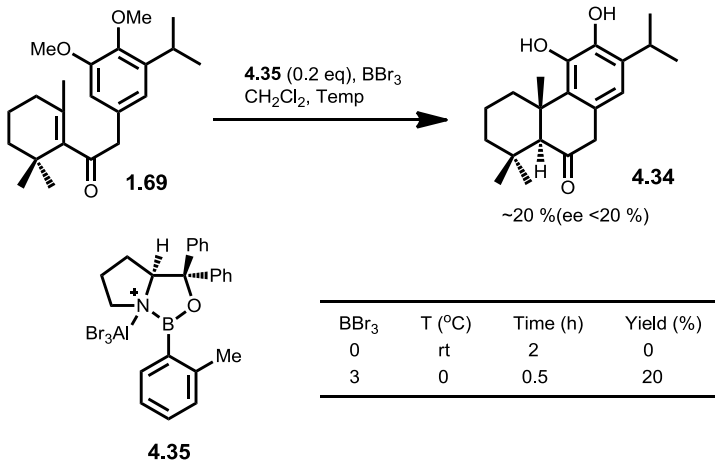
Although the *trans*-isomeric **1.70** could be synthesized by acid-mediated intramolecular Friedel-Crafts alkylation using a combination of formic acid and chiral phosphoric acid at elevated temperature, the harsh conditions of the reaction limited its substrate scope and rendered enantioselection less likely. To address this difficulty, we envisioned that the reaction might be able to proceed under milder conditions upon demethylation of **1.69** to give the corresponding catechol, which was expected to be more nucleophilic. To our surprise, treatment of enone **1.69** with BBr_3 led to **4.34** as the only isomeric product (Scheme 4.9). Thus, BBr_3 not only initiated *bis*-demethylation, it was also involved in the intramolecular Friedel-Crafts reaction in one-pot to give the cyclization product. The cyclization proceeded under much milder conditions than those reported by Stevens which was shown in Scheme 4.6 (Temp: 0 ^oC *vs* 115 ^oC; solvent: CH_2Cl_2 *vs* the mixture of HCO_2H and H_3PO_4). No obvious oxidation of catechol **4.34**

was observed when it was kept at -20 ^{o}C for one month. When **1.69** was treated with $BF_3 \bullet Et_2O$, no cyclization was observed and the starting material was recovered.



Scheme 4.9. BBr_3-mediated Friedel-Crafts alkylation

Encouraged by this result, we tested cationic oxazaborolidine **4.35** developed by Corey for potential asymmetric Friedel-Crafts cyclization of **1.69**.[70] However, no desired product was formed even when the reaction was warmed to room temperature (Figure 4.3). With the addition of BBr_3, the cyclization did proceed at 0 ^{o}C in less than 30 min to give **4.34** in 20% yield, but with less than 20% enantioselectivity.

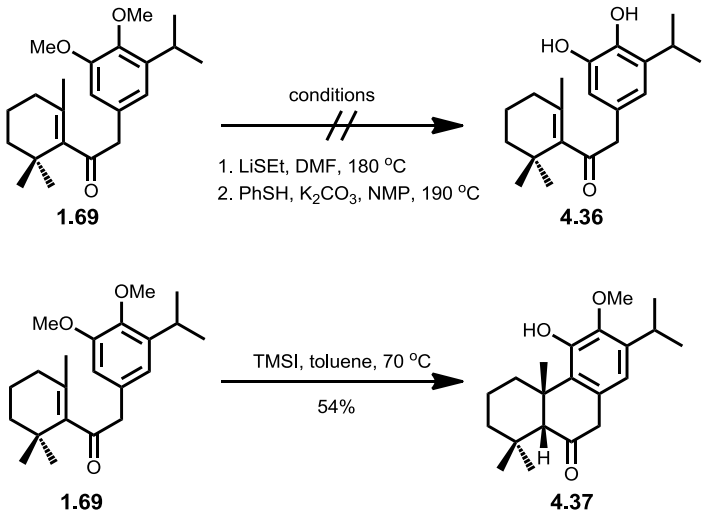


BBr_3	T (^oC)	Time (h)	Yield (%)
0	rt	2	0
3	0	0.5	20

Figure 4.3. Chiral borane-mediated Friedel-Crafts alkylation

4.5.4 TMSI-Mediated Friedel-Crafts Alkylation

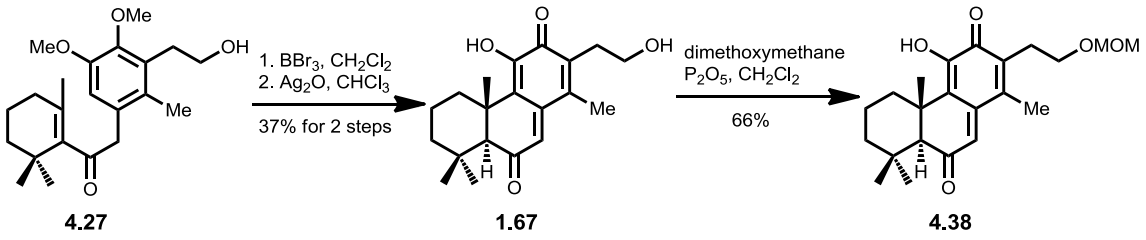
As part of our efforts of developing an enantioselective Friedel-Crafts cyclization of **1.69**, we sought to identify reaction conditions that decouple the demethylation reaction from the subsequent Friedel-Crafts cyclization process, which occurred in one-pot when BBr_3 was used. As shown in the Scheme 4.10, no desired product was isolated when enone **1.69** was treated with thiolate-based demethylating reagents, such as LiSEt and PhSK. Surprisingly, subjecting **1.69** to TMSI in toluene at 70 ^oC gave the *cis*-isomeric **4.37** as the only product, with only one of the methoxyl group hydrolyzed.



Scheme 4.10. Demethylation of **1.69**

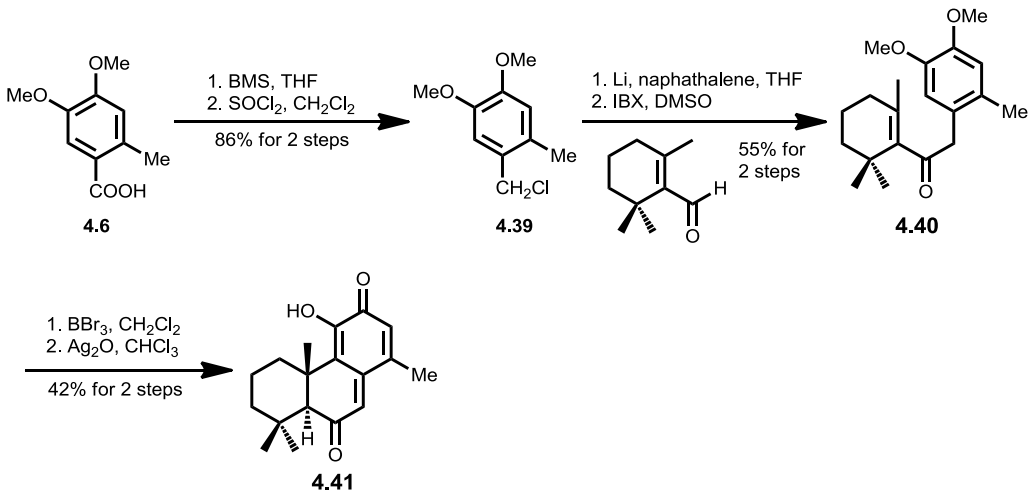
4.6 Total Synthesis of *o*-Hydroxy-*p*-Quinone Methide Diterpenoid 1.67 and Its Analogs

We applied the BBr_3-mediated Friedel-Crafts alkylation for total synthesis of **1.67** and analogs (Scheme 4.11). Thus, treatment of **4.27** with BBr_3 led to one-pot *bis*-demethylation and Friedel-Crafts cyclization to form a tricyclic catechol, which was subjected to oxidation with Ag_2O to finish the total synthesis of **1.67**. Comparison of the spectra of **1.67** with those reported for the natural product confirmed its identify. To elucidate the structure-activity relationship, analog **4.38** was prepared by protecting the 2'-hydroxyethyl side chain with methyl chloromethyl ether.



Scheme 4.11. Total synthesis of **1.67** and its analog **4.38**

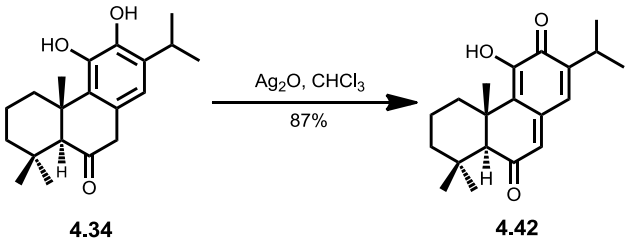
To evaluate the effect of the 2'-hydroxyethyl side chain on the antifungal activity of **1.67**, we also prepared analog **4.41** from known acid **4.6** (Scheme 4.12). Reduction of carboxylic acid **4.6** with borane dimethyl sulfide complex followed by chlorination provided the benzyl chloride **4.39**. The coupling of benzyl chloride **4.39** and β-cyclocitral went smoothly to give an allyl alcohol, which was oxidized by IBX to give enone **4.40**. The analog **4.41** was obtained by BBr_3-mediated one-pot *bis*-demethylation and intramolecular Friedel-Crafts alkylation to give the tricyclic core, followed by Ag_2O mediated oxidation of the resulting catechol.



Scheme 4.12. Synthesis of **4.41**

4.7 Synthesis of Taxodione

For further structure-activity relationship studies, we also applied the BBr_3-mediated one-pot *bis*-demethylation/Friedel-Crafts alkylation to synthesize taxodione (as shown in Scheme 4.9). Treatment of catechol **4.34** with Ag_2O delivered the taxodione in 87% yield (Scheme 4.13).



Scheme 4.13. Synthesis of taxodione

4.8 Investigating the Bioactivity of Taxodione, 1.67 and Its Analogs

With taxodione, **1.67** and analogs in hand, we collaborated with Prof. Xiaorong Lin of Department of Biology at Texas A&M University to evaluate their antifungal activity against strains of pathogenic yeasts (*Candida* spp. and *Cryptococcus* spp.) and the filamentous fungus *Aspergillus fumigatus*. *Candida*, *Cryptococcus*, and *Aspergillus* species are the major fungal pathogens of global significance (Table 4.1).[71] Consistent with the original report, the synthetic *o*-hydroxy-*p*-quinone methide **1.67** was found to be potently cytotoxic toward all the yeast strains tested, with MIC_{100} values ranging from 0.4 to 6.4 mg/L. The MIC_{100} values were found to be similar to those of MFC (minimum fungicidal concentration), indicative of fungicidal rather than fungistatic nature of this compound. Compound **4.41** was also found to be effective against the yeast strains that have been tested, including the *Candida glabrata*, *Candida krusei*, and *Candida parapsilosis* strains that are resistant to the commonly used antifungal fluconazole.[72] These results suggest both **1.67** and **4.41** differ in their mode-of-action against fungi from fluconazole. Taxodione showed potent activity as well. However, the methoxymethyl ether of **1.67** (i.e. **4.38**) showed significantly diminished growth inhibition activity. None of these compounds were effective against the mold *A. fumigatus*. It appears that the cytotoxicity of these compounds is correlated with the fungal growth mode (yeast *vs* mold) rather than their evolutionary relatedness, given that *Candida* and *Aspergillus* spp. are closely related while *Cryptococcus* spp. belongs to a different fungal phylum. The cause of the differential cytotoxicity of these compounds against yeasts and the filamentous fungal stains is currently unknown.

Table 4.1. Taxodione, **1.67** and its analogs exhibiting fungicidal effect (mg/L)

Yeast/fungal strain	**MIC_{100} 1.67**	**MFC* 1.67**	**MIC_{100} 4.41**	**MFC 4.41**	**MIC_{100}** taxodione	**MFC** taxodione	**MIC_{100} 4.38**	**MFC 4.38**
Cryptococcus gattii R265	0.4	0.4	0.8	0.8	0.8	0.8	6.4	12.8
Cryptococcus neoformans H99α	0.4	0.8	0.8	0.8	1.6	1.6	6.4	12.8
Candida albicans SC5314	6.4	12.8	3.2	6.4	6.4	>12.8	>12.8	>100
Candida glabrata PAT2ISO3	1.6	6.4	1.6	3.2	3.2	>6.4	6.4	>12.8
Candida krusei DUMC132.91	1.6	1.6	1.6	3.2	3.2	6.4	12.8	>12.8
Candida parapsilosis MMRL1594	3.2	6.4	1.6	3.2	6.4	12.8	12.8	>100
Aspergillus fumigatus Af293	25.6	25.6	17.1	17.1	>100	>100	100	>100
Aspergillus fumigatus CEA10	25.6	25.6	17.1	17.1	>100	>100	100	>100

*: MFC is defined as the lowest drug concentration at which at least 99% of cells were killed compared to the original inoculums. Suspensions from the microdilution assay after 24 h (*Candida* species and *Aspergillus fumigatus* strains) or 48 h (for *Cryptococcus*) of incubation were plated on drug-free medium for obtaining the values of colony forming units (CFU) to determine the minimal fungicidal concentration (MFC). Successive 2x serial dilutions of the drugs were used.

4.9 Summary

We achieved the first total synthesis of **1.67**, an unnamed tricyclic *o*-hydroxy-*p*-quinone methide diterpenoid with potent antifungal activity. Stille coupling was employed to introduce the allyl group as a masked 2'-hydroxyethyl side chain. The lithium/naphthalene mediated coupling was used to assemble the benzyl chloride **4.23** and β-cyclocitral. We developed a BBr_3-mediated one-pot *bis*-demethylation

/intramolecular Friedel-Crafts alkylation to assemble the tricyclic molecular skeleton of the diterpenoid, and finished the total synthesis of **1.67** and its analogs **4.38** and **4.41**. We also applied our BBr_3-mediated one-pot cyclization process to synthesize taxodione. Cell-proliferation assays in the presence of these compounds showed that **1.67**, **4.41**, and taxodione to be potently cytotoxic against strains of pathogenic yeasts, but etherification of the 2'-hydroxyethyl led to significantly attenuated activity. Surprisingly, these compounds were found to be ineffective against the fungal strain *Aspergillus fumigatus*. The cause of this discrepancy of activity against the yeasts versus filamentous fungi is currently unknown.

CHAPTER V

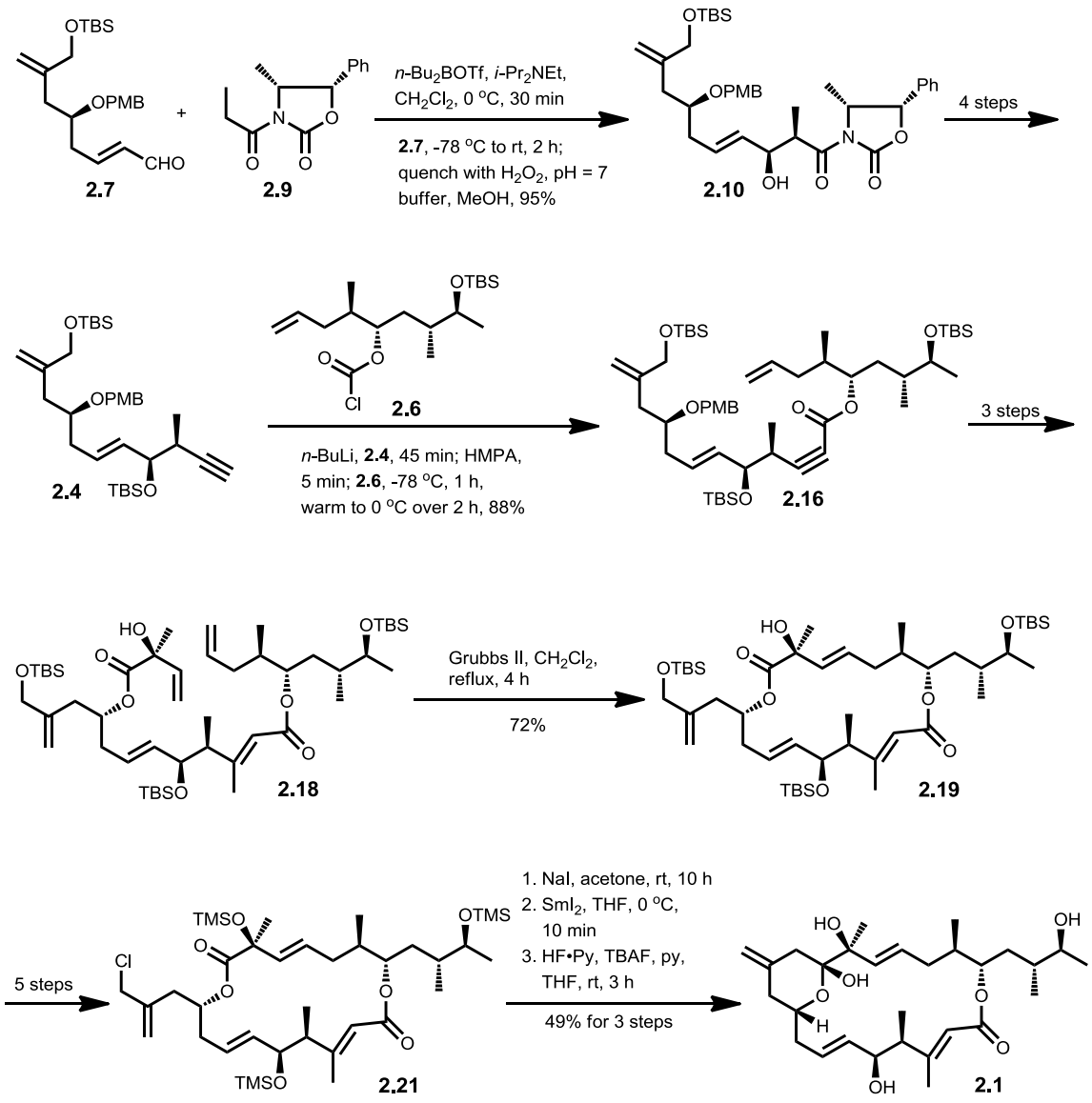
CONCLUSIONS

5.1 Synthetic Studies of Iriomoteolide-1a

Macrolide **2.1** was synthesized as part of our effort to identify the so far unknown stereochemical structure of iriomoteolide- 1a. Key features of the synthesis include using Evans chiral auxiliary-mediated *syn*-aldol reaction to deliver alkyne **2.4**, a lithium acetylide-chloroformate coupling to synthesize **2.16**, the ring closing metathesis to form the macrocycle **2.19** and a SmI_2-mediated intramolecular reductive allylation for formation of the cyclic hemiketal (Scheme 5.1).

We collaborated with Dr. Jun Liu of Johns Hopkins University to investigate the cytotoxicity of **2.1** and previously synthesized diastereomers **1.1**-**1.3** using cell proliferation assays with HeLa and PC3 cell lines. Only diastereomer **2.1** showed a weak inhibiting effect on both cell lines at 10 μM.

Whereas **2.1** is still different from the natural product, it provides a useful reference for our future studies to elucidate the stereochemical structure of iriomoteolide-1a by computational methods, and enable the future mode-of-action study of the nature product.

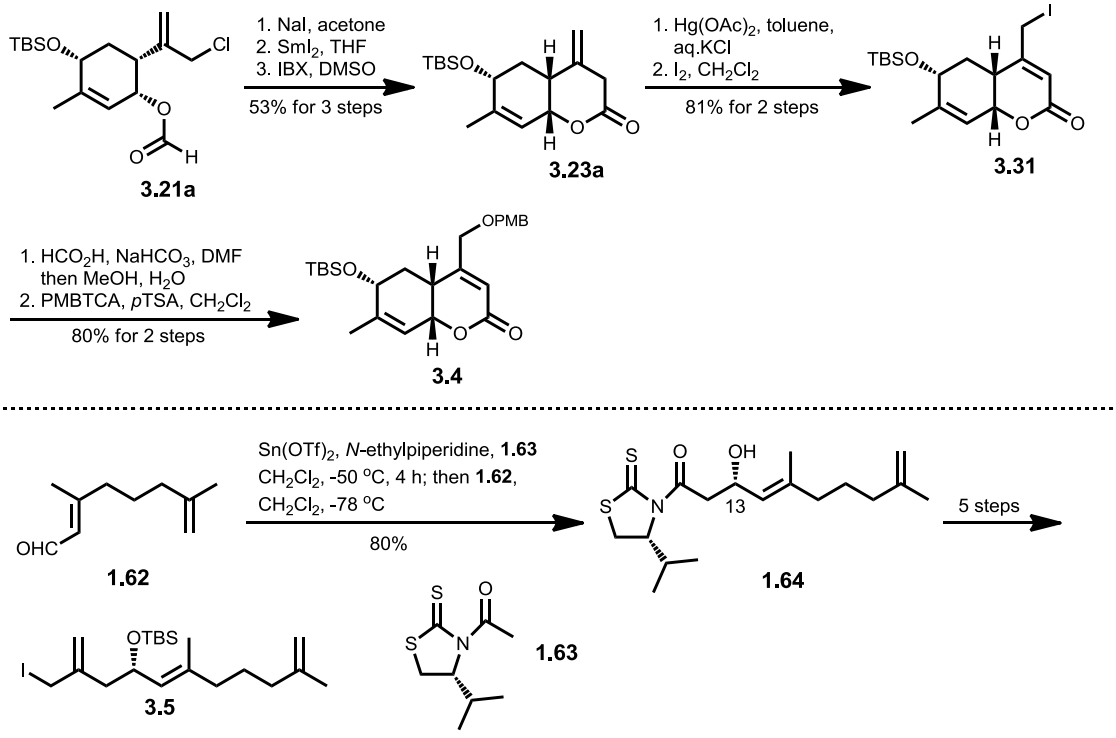


Scheme 5.1. Synthesis of **2.1**

5.2 Total Synthesis of Alotaketal A

We accomplished the first enantioselective total synthesis of the potent cAMP signaling agonist (-)-alotaketal A. Our synthesis of fragment **3.4** featured a SmI_2-

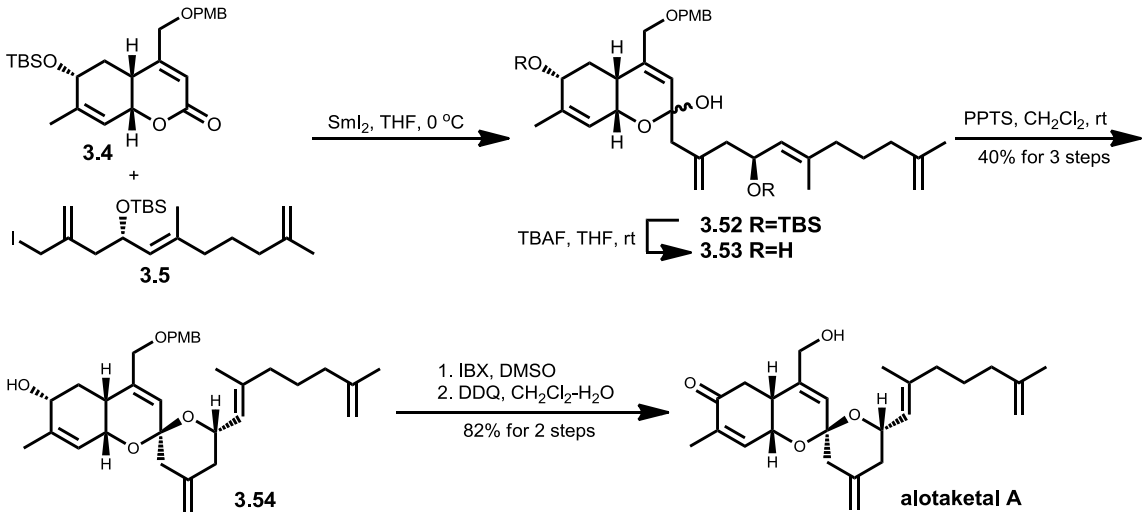
mediated intramolecular reductive allylation to build the key bicyclic lactone **3.23a** and a $Hg(OAc)_2$-mediated allylic mercuration of β, γ-unsaturated lactone **3.23a** to introduce the C22-hydroxyl group of **3.4**. The preparation of fragment **3.5** made use of Nagao-Fujita aldol reaction of aldehyde **1.62** and thiazolidinethione **1.63** to provide excellent diastereocontrol of the newly formed C13 hydroxyl group. The aldol product **1.64** was converted to allyl iodide **3.5** in five steps.



Scheme 5.2. Synthesis of fragment **3.4** and **3.5**

Our total synthesis of alotaketal A also highlighted the Barbier-type SmI_2-mediated intermolecular reductive coupling for joining the fragments **3.4** and **3.5**.

During the acid-mediated spiroketalization to form the unprecedented spiroketal ring system, our study revealed the subtle interplay of the structure and functional group stability/reactivity. With C22-deoxy **3.46** as the substrate, a 1:1 mixture of the desired spiroketal **3.47** and its $\Delta^{10, 11}$ isomer **3.48** was formed when PPTS was employed. To our surprise, no isomerization of $\Delta^{11, 23}$ alkene was observed when **3.53** was treated with PPTS. Since **3.46** and **3.53** differ only by the C22 *p*-methoxybenzyloxy group, we speculated that the electron-withdrawing inductive effect of the alkoxy group or the cation-π stabilization of the oxocarbenium by the phenyl ring might be responsible for their differential reactivity profiles for the spiroketalization.



Scheme 5.3. Total synthesis of alotaketal A

During the total synthesis of alotaketal A, we also synthesized the analogs **3.47**-**3.50** and **3.55** to elucidate the structure activity relationship (Figure 5.1). Using live cell FRET imaging assays with genetically encoded AKAR4 reporter genes, we verified that

the cAMP signaling pathway was activated by alotaketal A. Our preliminary SAR studies revealed that the C22-hydroxyl group was essential to alotaketal A's bioactivity. Without the C22-hydroxyl group, the analogs **3.47**-**3.50** gave no response in the reporter gene assay. On the other hand, reduction of the enone moiety to an allyl alcohol was tolerated, suggesting that the enone functional group is not important to its activity. Thus, this hydroxy group provides a potential site for immobilization for activity-based protein target identification. Our FRET imaging studies also revealed alotaketal A's unique activity in selectively targeting PKA signaling in the nucleus of living cells.

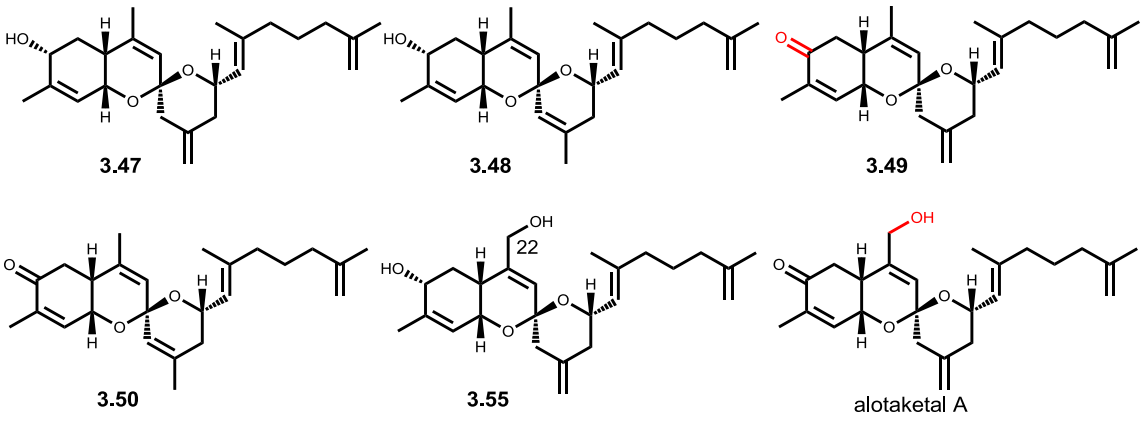


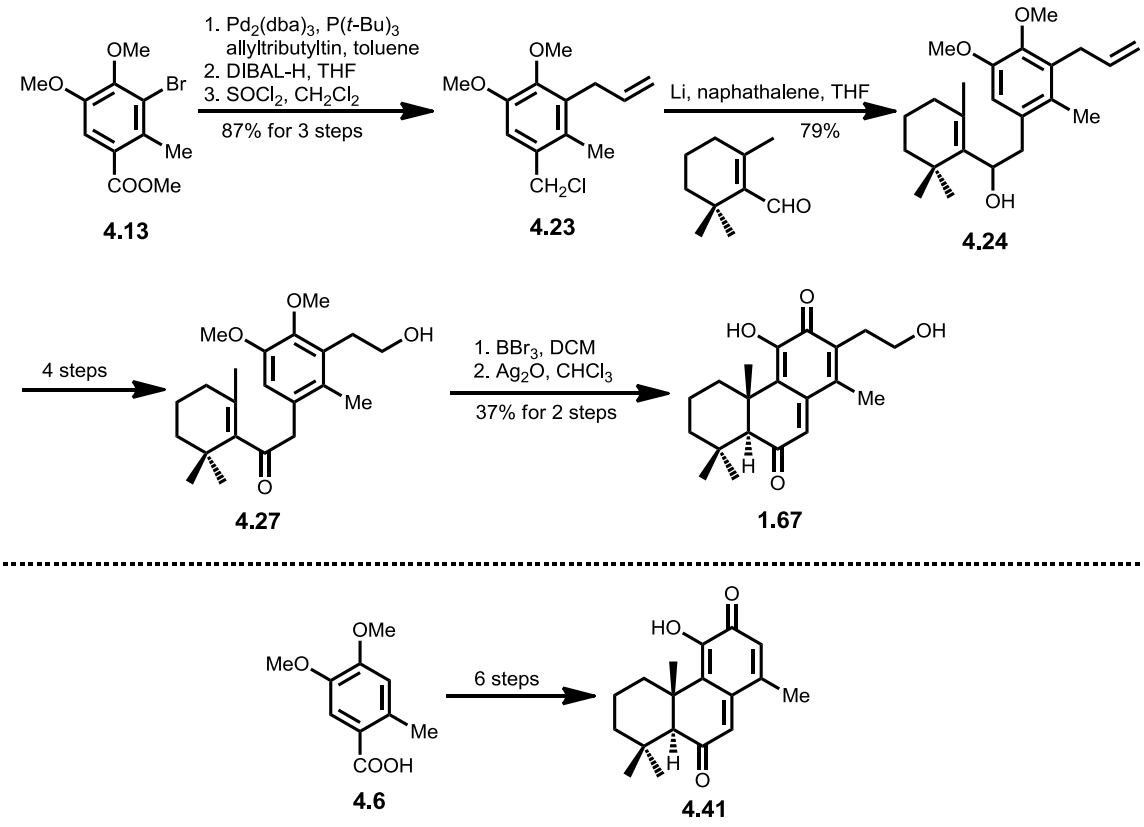
Figure 5.1. Alotaketal A and its analogs

Recent studies had suggested that cAMP elicited highly specific cellular response to external stimuli via highly compartmentalized cAMP signaling.[73] Evidence of subcellular cAMP signaling domains in specific regions such as the nucleus has been presented through the identification of a functional pool of nuclear PKA holoenzyme,

and its regulators, the phosphodiesterase, PDE4, and scaffolding proteins such as A-kinase anchoring proteins (AKAPs).[74] Therefore, future experiments will focus on the identification of cellular targets of alotaketals and elucidation of their functions within the nucleus.

5.3 Total Synthesis of *o*-Hydroxy-*p*-Quinone Methide Diterpenoid 1.67

We achieved the first total synthesis of an unnamed potently antifungal *o*-hydroxy-*p*-quinone methide diterpenoid **1.67** in 10 steps from the known **4.13**. Our total synthesis featured a Stille coupling to introduce the allyl group as the masked 2'-hydroxyethyl side chain, a lithium/naphthalene mediated coupling reaction to assemble the fragments benzyl chloride **4.23** and β-cyclocitral, and BBr_3-mediated one-pot *bis*-demethylation/intramolecular Friedel-Crafts alkylation to build the tricyclic molecular framework of **1.67**. To elucidate the effect of the 2'-hydroxyethyl side chain of **1.67** over its bioactivity, the analog **4.41** was prepared in 6 steps from known **4.6** employing similar strategy. Our preliminary structure-activity relationship study showed that both **1.67** and **4.41** are effective against yeast strains, including *Candida glabrata*, *Candida krusei*, and *Candida parapsilosis*, that are resistant to the commonly used antifungal fluconazole. Thus, the 2'-hydroxyethyl side chain of **1.67** is nonessential to its antifungal activity. Our future experiments will focus on elucidation of its antifungal mechanism and identification of the cellular targets.



Scheme 5.4. Total synthesis of **1.67** and **4.41**

REFERENCES

(1) For some recent reviews: (a) Kobayashi, J. *J. Antibiot*. **2008**, *61*, 271. (b) Kobayashi, J.; Kubota, T. *J. Nat. Prod*. **2007**, *70*, 451. (c) Kobayashi, J.; Tsuda, M. *Nat. Prod. Rep*. **2004**, *21*, 77.

(2) For some examples since 2006, see: (a) Lu, L.; Zhang, W.; Carter, R. *J. Am. Chem. Soc*. **2008**, *130*, 7253. (b) Fürstner, A.; Bouchez, L. C.; Funel, J.-A.; Liepins, V.; Poree, F.-H.; Gilmour, R.; Beaufils, F.; Laurich, D.; Tamiya, M. *Angew. Chem., Int. Ed*. **2007**, *46*, 9265. (c) Fürstner, A.; Larionov, O.; Fluegge, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 5545. (d) Jin, J.; Chen, Y.; Li, Y.; Wu, J.; Dai, W.-M. *Org. Lett*. **2007**, *9*, 2585. (e) Va, P.; Roush, W. R. *Tetrahedron* **2007**, *63*, 5768. (f) Kim, C. H.; An, H. J.; Shin, W. K.; Yu, W.; Woo, S. K.; Jung, S. K.; Lee, E. *Angew. Chem., Int. Ed*. **2006**, *45*, 8019. (g) Va, P.; Roush, W. R. *J. Am. Chem. Soc*. **2006**, *128*, 15960. (h) Fürstner, A.; Kattnig, E.; Lepage, O. *J. Am. Chem. Soc*. **2006**, *128*, 9194. (i) Deng, L.-S.; Huang, X.-P.; Zhao, G. *J. Org. Chem*. **2006**, *71*, 4625. (j) Ghosh, A. K.; Gong, G. *J. Org. Chem*. **2006**, *71*, 1085.

(3) (a) Tsuda, M.; Oguchi, K.; Iwamoto, R.; Okamoto, Y.; Fukushi, E.; Kawabata, J.; Ozawa, T.; Masuda, A. *J. Nat. Prod*. **2007**, *70*, 1661. (b) Tsuda, M.; Oguchi, K.; Iwamoto, R.; Okamoto, Y.; Kobayashi, J.; Fukushi, E.; Kawabata, J.; Ozawa, T.; Masuda, A.; Kitaya, Y.; Omasa, K. *J. Org. Chem*. **2007**, *72*, 4469.

(4) For fragment studies, see: (a) Crimmins, M. T.; Dechert, A. R. *Org. Lett*. **2012**, *14*,

2366. (b) Liu, Y.; Wang, J.; Li, H.; Wu, J.; Feng, G.; Dai, W.-M. *Synlett* **2010**, 2184. (c) Paterson, I.; Rubenbauer, P. *Synlett* **2010**, 571. (d) Li, S.; Chen, Z.; Xu, Z.; Ye, T. *Chem. Commun*. **2010**, *46*, 4773. (e) Xie, J.; Ma, Y.; Horne, D. A. *Org. Lett*. **2009**, *11*, 5082. (f) Wang, S.-Y.; Chen, Y.-J.; Loh, T.-P. *Synthesis* **2009**, 3557. (g) Ye, Z.; Deng, L.; Qian, S.; Zhao, G. *Synlett* **2009**, 2469. (h) Chin, Y.-J.; Wang, S.-Y.; Loh, T.-P. *Org. Lett*. **2009**, *11*, 3674. (i) Xie, J.; Horne, D. A. *Tetrahedron Lett*. **2009**, *50*, 4485. (j) Ghosh, A. K.; Yuan, H. *Tetrahedron Lett*. **2009**, *50*, 1416. (k) Fang, L.; Xue, H.; Yang, J. *Org. Lett*. **2008**, *10*, 4645. For total synthesis of proposed iriomoteolide-1a or its diastereomers, see: (l) Xie, J.; Ma, Y.; Horne, D. A. *Tetrahedron* **2011**, *67*, 7485. (m) Xie, J.; Ma, Y.; Horne, D. A. *Chem. Commun*. **2010**, *46*, 4770. (n) Ghosh, A. L.; Yuan, H. *Org. Lett*. **2010**, *12*, 3120. (o) Fang, L.; Yang, J.; Yang, F. *Org. Lett*. **2010**, *12*, 3124. (p) Huang, J.; Yang, J. *Synlett* **2012**, 737. (q) Liu, Y.; Feng, G.; Wang, J.; Wu, J.; Dai, W.-M. *Synlett* **2011**, 1774. For a recent synthesis of the proposed iriomoteolide 1b: (r) Ye, Z.; Gao, T.; Zhao, G. *Tetrahedron* **2011**, *67*, 5979.

(5) (a) Blunt, J. W.; Copp, B. R.; Keyzers, R. A.; Munro, M. H. G.; Prinsep, M. R. *Nat. Prod. Rep*. **2012**, *29*, 144. (b) Dalby, S. M.; Paterson, I. *Curr. Opin. Drug Discovery Dev.* **2010**, *13*, 777. (c) Paterson, I.; Anderson, E. A. *Science* **2005**, *310*, 451.

(6) Forestieri, R.; Merchant, C. E.; de Voogd, N. J.; Matainaho, T.; Kieffer, T. J.; Andersen, R. J. *Org. Lett*. **2009**, *11*, 5166.

(7) Rho, J.-R.; Hwang, B. S.; Sim, C. J.; Joung, S.; Lee, H.-Y.; Kim, H.-J. *Org. Lett*. **2009**, *11*, 5590.

(8) Daoust, J.; Fontana, A.; Merchant, C. E.; de Voogd, N. J.; Patrick, B. O.; Kieffer, T. J.; Andersen, R. J. *Org. Lett*. **2010**, *12*, 3208.

(9) Beavo, J. A.; Brunton, L. L. *Nat. Rev. Mol. Cell. Biol*. **2002**, *3*, 710.

(10) Krebs, E. G. *Curr. Top. Cell. Regul*. **1972**, *5*, 99-133.

(11) (a) Kawasumi, M.; Nghiem, P. J. *InVest. Dermatol* **2007**, *127*, 1577. (b) Spring, D. R. *Chem. Soc. Rev*. **2005**, *34*, 472. (c) Walsh, D. P.; Chang, Y.-T. *Chem. Rev*. **2006**, *106*, 2476.

(12) (a) Bhat, S. V.; Bajwa, B. S.; Dornauer, H.; de Souza, N. J.; Fehlhaber, H. W. *Tetrahedron Lett*. **1977**, 1669. (b) Seamon, K. B.; Padgett, W.; Daly, J. W. *Proc. Natl. Acad. Sci. U.S.A*. **1981**, *78*, 3363.

(13) Gonzalez-Sanchez, R.; Trujillo-Hernandez, B.; Vasquez, C.; Huerta, M.; Elizalde, A. J. *Intl. Med. Res.* **2006**, *34*, 200.

(14) Xuan, M.; Paterson, I.; Dalby, S. M. *Org. Lett*. **2012**, *14*, 5492.

(15) Van De Water, R. W.; Pettus, T. R. R. *Tetrahedron* **2002**, *58*, 5367.

(16) For a review, see: Zhou, Q. Natural Diterpene and Triterpene Quinone Methides: Structures, Synthesis and Biological Potentials. In *Quinone Methides*; Rokita, S. E., Ed.; Wiley: Hoboken, NJ, **2009**.

(17) (a) Schaller, F.; Rahalison, L.; Islam, N.; Potterat, O.; Hostettmann, K. *Helv. Chim,*

Acta. **2000**, *83*, 407. (b) Schaller, F.; Wolfender, J. -L.; Hostettmann, K. *Helv. Chim, Acta*. **2001**, *84*, 222.

(18) Kirkbride, J. H.; Wiersema, J. H. *Brittonia* **1997**, *49*, 1.

(19) Watt, J.M. and Breyer-Brandwijk, M. *The Medicinal and Poisonous Plants of Southern and Eastern Africa*, E&S Livingstone, Edinburgh, UK, **1962**.

(20) (a) Borel, C. and Hostettmann, K. *Helv. Chim. Acta*, **1987**, *70*, 570. (b) Hostettmann, K.; Marston,A.; Ndjoko, K. and Wolfender, J. *Current Org. Chem*. **2000**, 973.

(21) (a) Mori, K.; Matsui, M. *Tetrahedron* **1970**, *26*, 3467. (b) Mastumoto, T.; Tachibana, Y.; Uchida, J.; Fukui, K. *Bull. Chem. Soc. Jpn*. **1971**, *44*, 2766. (c) Mastumoto, T.; Usui, S.; Morimoto, T. A. *Bull. Chem. Soc. Jpn*. **1977**, *50*, 1575. (d) Snitman, D. L.; Himmelsbach, R. J.; Haltiwanger, R. C.; Watt, D. S. *Tetrahedron Lett*. **1979**, 2477. (e) Johnson, W. S.; Shenvi, A. B.; Boots, S. G. *Tetrahedron* **1982**, *38*, 1397. (f) Stevens, R. V.; Bisacchi, G. S. *J. Org. Chem*. **1982**, *47*, 2396. (g) Burnell, R. H.; Jean, M.; Poirier, D. *Can. J. Chem*. **1987**, *65*, 775. (h) Harring, S. R.; Livinghouse, T. *Tetrahedron Lett*. **1989**, *30*, 1499. (i) Engler, T. A.; Sampath, U.; Naganathan, S.; Velde, D. V.; Takusagawa, F.; Yohames, D. *J. Org. Chem*. **1989**, *54*, 5712. (j) Harring S.; Livinghouse, T. *J. Chem. Soc., Chem. Commun*. **1992**, 502. (k) Sanchez, A. J.; Konopelski, J. P. *J. Org. Chem*. **1994**, *59*, 5445. (l) Harring, S. R.; Livinghouse, T.

Tetrahedron, **1994**, *50*, 9229.

(22) (a) You, S. -L.; Cai, Q.; Zeng, M. *Chem. Sov. Rev*. **2009**, *38*, 2190. (b) Zeng, M.; You, S. -L. *Synlett* **2010**, *9*, 1289.

(23) Cai, Q.; Zhou, Z.-A.; You, S. -L. *Angew. Chem. Int. Ed*. **2009**, *48*, 7428.

(24) Liu, T. -Y.; Cui, H. -L.; Chai, Q.; Long, J.; Li, B. -J. Wu, Y.; Ding, L. -S.; Chen, Y. -C. *Chem. Commun*. **2007**, 2228.

(25) Erkkila, A.; Majander, I.; Pihko, P. M. *Chem. Rev*. **2007**, *107*, 5416.

(26) Fang, L.; Yang, J. *unpublished results*.

(27) Marshall, J. A. *J. Org. Chem*. **2007**, *72*, 8153.

(28) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc*. **1981**, *103*, 2127.

(29) (a) Levin, J. I.; Turos, E.; Weinreb, S. M. *Synth. Commun*. **1982**, *12*, 989. (b) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett*. **1977**, *18*, 4171.

(30) (a) Miwa, K.; Aoyama, T.; Shioiri, T. *Synlett* **1994**, 107. For a recent review, see: (b) Habrant, D.; Rauhala, V.; Koskinen, A. M. P. *Chem. Soc. Rev*. **2010**, *39*, 2007

(31) (a) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc*. **1986**, *108*, 293. (b) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc*. **1986**, *108*, 5919.

(32) For two reviews of the Mitsunobu reaction, see: (a) Mitsunobu, O. *Synthesis* **1981**, 1. (b) Kumara Swamy, K. C.; Bhuvan Kumar, N. N.; Balaraman, E.; Pavan Kumar, K. V. P. *Chem. Rev*. **2009**, *109*, 2551.

(33) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett*. **1999**, *1*, 953.

(34) Finkelstein, H. Ber. *Dtsch. Chem. Ges*. **1910**, *43*, 1528.

(35) Heumann, L. V.; Keck, G. E. *Org. Lett*. **2007**, *9*, 1951.

(36) (a) Gaffney, B. L.; Jones, R. A. *Tetrahedron Lett*. **1982**, *23*, 2257. (b) Coleman, R. S.; Li, J.; Navarro, A. *Angew. Chem. Int. Ed*. **2001**, *40*, 1736.

(37) Miyashita, M.; Suzuki, T.; Yoshikoshi, A.; *J. Org. Chem*. **1985**, *50*, 3377.

(38) Tian, G.-Q.; Yang, J.; Rosa-Perez, K.; *Org. Lett*. **2010**, *12*, 5072.

(39) For some reviews: (a) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res*. **2001**, *34*, 18; (b) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012; (c) Schrock, R. R.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4592; (d) Deiters, A.; Martin,S. F. *Chem. Rev*. **2004**, *104*, 2199; (e) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed*. **2005**, *44*, 4490.

(40) Hoye, T. R.; Jeffrey, C. S.; Tennakoon, M. A.; Wang, J.; Zhao, H. *J. Am. Chem. Soc.* **2004**, *126*, 10210.

(41) The β-carbonyl-carbene species [Ru] = CH(CO)R are less stable than the corresponding alkylidene carbenes [Ru] = CHR. Typically they are not responsible for the majority of the metathesis reactions; Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc*. **2000**, *122*, 3783.

(42) Chatterjee, A. K.; Toste, F. D.; Goldberg, S. D.; Grubbs, R. H. *Pure Appl. Chem*. **2003**, *75*, 421.

(43) (a) Hegde, S. G.; Vogel, M. K.; Saddler, J.; Hrinyo, T.; Rockwell, N.; Haynes, R.;

Oliver, M.; Wolinsky, J. *Tetrahedron Lett*. **1980**, *21*, 441; (b) Hegde, S. G.; Wolinsky, J. *J. Org. Chem*. **1982**, *47*, 3148.

(44) (a) Luche, J. L. *J. Am. Chem. Soc*. **1978**, *100*, 2226; (b) Gemal, A. L.; Luche, J. L. *J. Am. Chem. Soc.*, **1981**, *103*, 5454.

(45) Harding, K. E.; Marman, T. H.; Nam, D.-H. *Tetrahedron Lett*. **1988**, *29*, 1627 and references cited therein.

(46) (a) Ishihara, K.; Mori, A.; Yamamoto, H. *Tetrahedron*, **1990**, *46*, 4595; (b) Lombardo, D. A.; Weedon, A. C. *Tetrahedron Lett*. **1986**, *27*, 5555.

(47) Zahn,T. J.; Weinbaum, C. Gibbs, R. A. *Bioorg. Med. Chem. Lett.*, **2000**, *10*, 1763.

(48) Babinski, D.; Soltani, O.; Frantz, D. E. *Org. Lett.* **2008**, *10*, 2901.

(49) (a) Cahiez, G.; Avedissian, H. *Synthesis*, **1998**, 1199; (b) Scheiper, B.; Bonnekessel, M.; Krause, H.; Fürstner, A. *J. Org. Chem.* **2004**, *69*, 3943; (c) Xue, H.; Yang, J.; Gopal, P. *Org. Lett*., **2011**, *13*, 5696.

(50) Williams, J. M.; Jobson, R. B.; Yasuda, N.; Marchesini, G.; Dolling, U.-H.; Grabowski, E. J. J. *Tetrahedron Lett*. **1995**, *36*, 5461.

(51) Boulet, S. L.; Paquette, L. A. *Synthesis*, **2002**, 895.

(52) (a) Noyori, R.; Yamakawa, M.; Hashiguchi, S. *J. Org. Chem*. **2001**, *66*, 7931; (b) Hashiguchi, S.; Fujii, A.; Takehara, J.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc*. **1995**, *117*, 7562; (c) Matsumura, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 8738; (d) Fujii, A.; Hashiguchi, S.; Uematsu, N.; Ikariya, T.;

Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 2521; (e) Yamakawa, M.; Ito, H.; Noyori, R. *J. Am. Chem. Soc*. **2000**, *122*, 1466.

(53) (a) Noyori, R.; Tomino, I.; Tanimoto, Y.; Nishizawa, M. *J. Am. Chem. Soc*. **1984**, *106*, 6709. (b) Noyori, R.; Tomino, I.; Tanimoto, Y. *J. Am. Chem.Soc*. **197**9, *101*, 3129

(54) (a) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem.Soc.* **198**7, *109*, 5551. (b) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C. P.; Singh, V. L. *J. Am. Chem. Soc*. **1987**, *109*, 7925.

(55) Nagao, Y.; Hagiwara, Y.; Kumagai, T.; Ochiai, M.; Inoue, T.; Hashimoto, K.; *J. Org. Chem*. **1986**, *51*, 2391.

(56) Narayanan, B. A.; Bunnelle, W. H. *Tetrahedron Lett*. **1987**, *28*, 6261.

(57) (a) Nicolaou, K. C.; Li, A.; Edmonds, D. J.; Tria, G. S.; Ellery, S. P. *J. Am. Chem. Soc*. **2009**, *131*, 16905. (b) Gesinski, M. R.; Rychnovsky, S. D. *J. Am. Chem. Soc*. **2011**, *133*, 9727.

(58) Depry, C.; Allen, M. D. Zhang, *J. Mol. BioSyst.* **2011**, *7*, 52

(59) Herbst, K. J.; Coltharp, C.; Amzel, L. M.; Zhang, *J. Chem. Biol*. **2011**, *18*, 243.

(60) DiPilato, L. M.; Zhang, *J. Mol. BioSyst*. **2009**, *5*, 832

(61) Allen, M. D.; Zhang, J. *Biochem. Biophys. Res. Commun*. **2006**, *348*, 716.

(62) Kim, J. K.; Kim, Y. H.; Nam, H. T.; Kim, B. T.; Heo, J. -N. *Org. Lett*. **2008**, *10*, 3543.

(63) Yamashita, S.; Iso, K.; Hirama, M. *Org. Lett*. **2008**, *10*, 3413.

(64) Jensen, M.; Schmidt, S.; Fedosova, N. U.; Mollenhauer, J.; Jensen, H. H. *Bio & Med. Chem*. **2011**, *19*, 2407.

(65) Littke, A. F.; Schwarz, L.; Fu, G. C. *J. Am. Chem. Soc*. **2002**, *124*, 6343.

(66) Ramachandran, P. V.; Madhi, S.; O' Donnell, M. J. *J. Fluorine Chem*. **2006**, *127*, 1252-1255.

(67) Catalyst **4.29a** was purchased from Aldrich and used as supplied. Catalyst **4.29b**, **4.29e** and **4.29f**, see: Storer, R.; Carrera, D. E.; Ni. Y.; MacMillan, D. W. C. *J. Am. Chem. Soc*. **2006**, *128*, 84. Catalyst **4.29c** and **4.29d**, see: Akiyama, T.; Morita, H.; Itoh, J.; Fuchibe, K. *Org. Lett*. **2005**, *7*, 2583.

(68) Davies, I. W.; Gerena, L.; Lu, N.; Larsen, R. D.; Reider, P. J. *J. Org. Chem*. **1996**, *61*, 9629.

(69) Oliva, C. G.; Silva, A. M. S.; Resende, D. I. S. P.; Paz, F. A. A. A.; Cavaleiro, J. A. S. *Eur. J. Org. Chem*. **2010**, 3449.

(70) Corey, E. J. *Angew. Chem. Int. Ed*. **2009**, *48*, 2100.

(71) Brown, G. D.; Denning, D. W.; Gow, N. A.; Levitz, S. M.; Netea, M. G.; White, T. C. *Sci. Transl. Med.* **2012**, *4*, 165rv113.

(72) Zhai, B.; Zhou, H.; Yang, L.; Zhang, J.; Jung, K.; Giam, C. Z.; Xiang, X.; Lin, X. *J. Antimicrob. Chemother.* **2010**, *65*, 931.

(73) (a) Steinberg, S. F.; Brunton, L. L. *Annu. Rev. Pharmacol.Toxicol*. **2001**, *41*, 751;

(b) Houslay, M. D.; *Trends Biochem. Sci.* **2010**, *35*, 91.

(74) Sample, V.; Dipilato, L. M.; Yang, J. H.; Ni, Q.; Saucerman, J. J.; Zhang, J. *Nat. Chem. Biol.* **2012**, *8*, 375

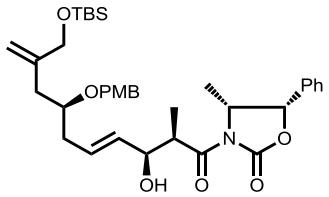
APPENDIX A

EXPERIMENTAL PROCEDURES

A.1 General Information

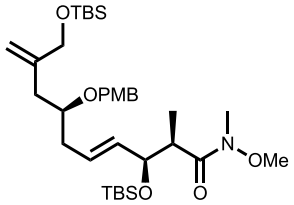
All moisture sensitive reactions were carried out in flame-dried flasks under nitrogen atmosphere. Dichloromethane and diethyl ether were purified by passing through an activated molecular sieve solvent purification system. Tetrahydrofuran was freshly distilled over sodium and benzophenone. All other commercial reagents were used as received. In general, reactions were magnetically stirred and monitored by TLC performed on pre-coated glass-backed TLC plates, Silica Gel 60 F254 (EMD, 250 μm thickness). Spots were visualized with UV or through staining with an ethanolic solution of phosphomolybdic acid. Flash column chromatography was performed using 60Å Silica Gel (Silicycle, 230-400 mesh) as the stationary phase. ^{1}H NMR chemical shifts are reported as δ values in ppm relative to $CDCl_3$ (7.26 ppm) or C_6D_6 (7.16 ppm), coupling constants (*J*) are reported in Hertz (Hz), and multiplicity follows normal convention. $CDCl_3$ (77.0 ppm) or C_6D_6 (128.39 ppm) served as the internal standard for ^{13}C NMR spectra. All ^{13}C NMR spectra were measured with complete proton decoupling. Infrared spectra (IR) were recorded on a Bruker TENSOR 27 FT-IR Spectrophotometer. Resonance frequencies are given as wavenumbers in cm^{-1}. Optical rotation were measured on a Rudolph Autopol II polarimeter and are reported as follows: $[\alpha]^{D}_{T}$ (c[10mg/mL], solvent).

A.2 Experimental Procedures for Total Synthesis of 2.1



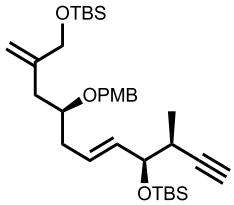
(4R,5S)-3-((2R,3S,7S,E)-9-(((tert-butyldimethylsilyl)oxy)methyl)-3-hydroxy-7-((4-methoxybenzyl)oxy)-2-methyldeca-4,9-dienoyl)-4-methyl-5-phenyloxazolidin-2-one (2.10). To a stirred solution of Evans chiral auxiliary **2.9** (520 mg, 2.23 mmol) in CH_2Cl_2 (10 mL) was added *n*-Bu_2BOTf (2.44 mL, 2.44 mmol) followed by DIPEA (0.46 mL, 2.64 mmol) at 0 ^oC under nitrogen. After being stirred for 30 min, the reaction was cooled to -78 ^oC and a solution of aldehyde **2.7** (820 mg, 2.03 mmol) in CH_2Cl_2 (2 mL) was added. The reaction was stirred at -78 ^oC for 1h, then warmed to 0 ^oC, and stirred for 45 min. The reaction was quenched by the addition of a solution of pH = 7 phosphate buffer and MeOH (10 mL, 3:1, v/v). To the resulting slurry was then slowly added a mixture of MeOH / 30% aqueous H_2O_2 (7 mL, 2:1, v/v) and the mixture was stirred vigorously for 45 min at room temperature. The reaction was then extracted with ether and the combined organic layers were washed with water, saturated aqueous $NaHCO_3$, brine and dried over Na_2SO_4, After concentration *in vacuo*, the residue was purified by flash column chromatography (silica gel, eluted with ethyl acetate/petroleum ether = 1/5) to provide product **2.10** (1.23 g, 95 %) as a colorless oil. $[\alpha]_D^{20}$ 8.55 (*c* 2.27, $CHCl_3$); IR (film) 3020, 2954, 2928, 2851, 1776, 1649, 1607, 1513, 1457, 1247, 1211, 838, 752, 663 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45-7.37 (m, 3H), 7.29-7.25 (m, 4H), 6. 87 (d, *J*=8.7 Hz, 2H), 5.86-5.76 (m, 1H), 5.69-5.53 (m, 2H), 5.13 (d, *J*=1.7 Hz, 1H), 4.90 (s,

1H), 4.79-4.70 (m, 1H), 4.51-4.43 (m, 2H), 4.07 (s, 2H), 3.94-3.86 (m, 1H), 3.79 (s, 3H), 3.67-3.50 (m, 1H), 2.69 (d, *J*=2.8 Hz, 1H), 2.38-2.21 (m, 4H), 1.23 (d, *J*=7.0 Hz, 3H), 0.91 (s, 9H), 0.87 (d, *J*=6.6 Hz, 3 H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.3, 159.1, 152.7, 145.6, 133.1, 131.6, 130.7, 129.4, 128.8, 128.7, 125.6, 116.4, 113.7, 111.2, 78.9, 77.3, 72.8, 70.8, 66.1, 55.3, 54.8, 42.9, 37.8, 36.8, 25.9, 18.37, 14.4, 11.3, -5.4; HRMS (ESI): calculated for $C_{36}H_{52}NO_7Si^+$ [M+H$^+$] 638.3513, found 638.3533.



(2R,3S,7S,E)-3-((tert-butyldimethylsilyl)oxy)-9-(((tert-butyldimethylsilyl)oxy) methyl)-N-methoxy-7-((4-methoxybenzyl)oxy)-N,2-dimethyldeca-4,9-dienamide (2.11). To a suspension of MeNHOMe hydrochloride (564 mg, 5.78 mmol) in THF (10 mL) was cautiously added Me_3Al (2M solution in toluene, 2.89 mL, 5.78 mmol) dropwise at 0 °C under nitrogen. Gas evolution was noted. After being stirred for 30 min, the reaction was cooled to –78 °C and a solution of aldol imide **2.10** (1.23 g, 1.93 mmol) in THF (2 mL) was added *via* cannula. The reaction was then warmed to room temperature, stirred for 1 h before it was quenched with saturated aqueous NH_4Cl (25 mL). The mixture was acidified with 1N HCl (25 mL) and extracted with EtOAc. The combined organic layers were washed with 1N HCl, saturated aqueous $NaHCO_3$, brine then dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified by flash column chromatography (silica gel, eluted with ethyl acetate/petroleum ether = 1/2) to provide product weinreb amide (0.86 g, 85 %) as a colorless oil.

To a solution of the above Weinreb amide (0.86 g, 1.65 mmol) in DMF (1.7 mL) was added imidazole (169 mg, 2.48 mmol) and TBSCl (298 mg, 1.98 mmol). The reaction was stirred at room temperature for 3h before it was diluted with EtOAc. The organic layer was washed with H_2O, brine, and dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified by flash column chromatography (silica gel, eluted with ethyl acetate/petroleum ether, 1/5 gradient to 1/2) to provide silylated product **2.11** (1.01 g, 97 %) as a colorless oil. $[\alpha]_D^{20}$ 5.35 (*c* 2.20, $CHCl_3$); IR (film) 3017, 2952, 2928, 2854, 1658, 1510, 1459, 1252, 1211, 835, 778, 666 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.3 Hz, 2H), 6.85 (d, *J*=7.7 Hz, 2H), 5.73-5.59 (m, 1H), 5.50 (dd, *J* = 16.0, 6.4 Hz, 1H), 5.12 (s, 1H), 4.87 (s, 1H), 4.46 (d, *J* = 11.1 Hz, 1H), 4.40 (d, *J* = 11.1 Hz, 1H), 4.21 (t, *J* = 7.6 Hz, 1H), 4.05 (s, 2H), 3.79 (d, *J* = 1.2 Hz, 3H), 3.61 (d, *J* = 1.2 Hz, 3H), 3.57-3.45 (m, 1H), 3.10 (s, 3H), 3.03-2.86 (m, 1H), 2.30-2.17 (m, 4H), 1.17 (d, *J* = 6.8 Hz, 3H), 0.90 (d, *J* = 1.2 Hz, 9H), 0.89 (d, *J* = 1.2 Hz, 9H), 0.06 (d, *J* = 0.9 Hz, 3H), 0.04 (d, *J* = 1.2 Hz, 3H), 0.01 (d, *J* = 0.8 Hz, 3H), -0.00 (d, *J* = 1.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.0, 145.7, 134.2, 130.8, 129.1, 127.7, 113.7, 113.7, 110.8, 77.6, 75.4, 70.6, 66.0, 61.4, 55.2, 42.8, 37.6, 36.7, 25.9, 25.9, 18.4, 18.2, 14.5, -4.0, -4.7, -5.4; HRMS (ESI): calculated for $C_{34}H_{62}NO_6Si_2^+$ [M+H$^+$] 636. 4116, found 636.4104.

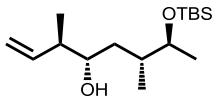


(5S,9S,E)-5-((S)-but-3-yn-2-yl)-9-((4-methoxybenzyl)oxy)-2,2,3,3,14,14,15,15-octamethyl-11-methylene-4,13-dioxa-3,14-disilahexadec-6-ene (2.4). To a well stirred

solution of silylated weinreb amide **2.11** (1.00 g, 1.57 mmol) in THF (15 mL) was added DIBAL-H (1 M in hexanes, 2.36 mL, 2.36 mmol) at -78 ^{o}C under nitrogen. The reaction was stirred at -78 °C for 2h before it was quenched by EtOAc (3 mL) and saturated aqueous Rochelle salt (10 mL). The mixture was stirred at room temperature until it became clear. The mixture was extracted with EtOAc and the combined organic layers were dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified by flash column chromatography (silica gel, eluted with ethyl acetate/petroleum ether = 1/10) to provide aldehyde (0.86 g, 95 %) as a colorless oil.

To a well stirred solution of *i*-Pr_2NH (0.25 mL, 1.79 mmol) in THF (12 mL) was added *n*-BuLi (1.6 M in hexanes, 1.11 mL, 1.79 mmol) at 0 ^{o}C under nitrogen. After being stirred for 30 min, a solution of $TMSCHN_2$ (2.0 M in hexane, 0.89 mL, 1.79 mmol) was added dropwise at -78 ^{o}C, stirred for 20 min. A solution of the above aldehyde (0.86 g, 1.49 mmol) in THF (3 mL) was added. The reaction was slowly warmed to room temperature over 2h. After being quenched with aqueous NH_4Cl, the mixture was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified by column chromatography (silica gel, ethyl acetate/petroleum ether, 1/60 gradient to 1/20) to provide alkyne **2.4** (0.53 g, 62 %) as a pale-yellow oil. $[\alpha]_D^{21}$ 1.48 (*c* 2.13, $CHCl_3$); IR (thin film) 2961, 2931, 2851, 1510, 1460, 1247, 1102, 871, 832, 746 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.3 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 5.79-5.63 (m, 1H), 5.57 (dd, *J*=15.5, 6.5 Hz, 1H), 5.13 (s, 1H), 4.90 (s, 1H), 4.50 (d, *J* = 11.1 Hz, 1H), 4.44 (d, *J* = 11.1 Hz, 1H), 4.08 (s, 2H), 3.98 (t, *J*=6.4 Hz, 1H), 3.80 (s, 3H), 3.62-3.55 (m,

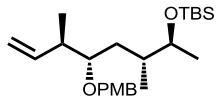
1H), 2.57-2.41 (m, 1H), 2.38-2.17 (m, 4H), 2.03 (dd, *J*=2.4, 0.9 Hz, 1H), 1.17 (d, *J* = 7.0 Hz, 3H), 0.92 (d, *J* = 1.0 Hz, 9H), 0.90 (d, *J* = 1.0 Hz, 9H), 0.08 (s, 3H), 0.06 (d, *J* = 1.0 Hz, 3H), 0.03 (s, 3H), 0.01 (d, *J* = 1.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.0, 145.7, 133.6, 130.8, 129.2, 128.2, 113.7, 111.0, 86.8, 77.6, 76.4, 70.8, 69.7, 66.1, 55.2, 37.6, 36.5, 33.7, 25.9, 25.9, 18.4, 18.2, 16.7, -4.0, -4.7, -5.4; HRMS (ESI): calculated for $C_{33}H_{56}O_4Si_2Li^+$ [M+Li^+] 579.3877, found 579.3858.



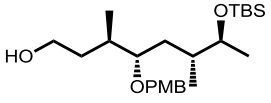
(3R,4S,6R,7S)-7-((tert-butyldimethylsilyl)oxy)-3,6-dimethyloct-1-en-4-ol

(A.1). To a solution of **2.12** (ca. 0.4 M in ether/THF, ~39 mL, 15.66 mmol) was added boron trifluoride etherate (2.22 mL, 18.01 mmol) followed by aldehyde **2.13** (1.80 g, 7.83 mmol) at -78 °C. After being stirred at -78 °C for 2.5 h, the mixture was treated with 3 N NaOH (7.4 mL) and 35% H_2O_2 (4.0 mL). The mixture was refluxed for 1 h before it was cooled to room temperature and extracted with EtOAc. The combined organic extracts were washed with H_2O, brine, and dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified by column chromatography (silica gel, ether/petroleum ether = 1/10) to provide alcohol **A.1** (1.70 g, 76 %) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.86-5.74 (m, 1H), 5.08 (s, 1H), 5.05-5.02 (m,1H), 3.80-3.73 (m, 1H), 3.57-3.50 (m, 1H), 2.79 (d, *J*=3.5Hz, 1H), 2.28-2.17 (m, 1H), 1.76-1.66 (m, 1H), 1.54-1.35 (m, 2H), 1.11 (d, *J* = 6.3 Hz, 3H), 1.04 (d, *J* = 6.9 Hz, 3H), 0.94 (d, *J* =7.0 Hz, 3H), 0.89 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.4, 115.3,

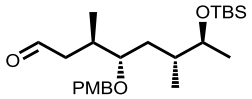
72.0, 71.5, 43.7, 37.3, 36.2, 25.8, 20.3, 18.0, 16.3, 15.9, -4.5, -4.9; HRMS (ESI): calculated for $C_{16}H_{34}O_2SiLi^+$ [M+Li^+] 293.2488, found 293.2480.



tert-butyl(((2S,3R,5S,6R)-5-((4-methoxybenzyl)oxy)-3,6-dimethyloct-7-en-2-yl)oxy)dimethylsilane (2.14). To a solution of alcohol **A.1** (1.70 g, 5.94 mmol) and *p*-methoxybenzyl trichloro-acetimidate (3.36 g, 11.88 mmol) in CH_2Cl_2 (10 mL) was added *p*TSA (114 mg, 0.6 mmol) and PPTS (141 mg, 0.6 mmol) at room temperature. After being stirred for 5 h, the reaction was diluted with ether (100 mL) and washed with water (30 mL). The aqueous layer was extracted with ether and the combined organic layers were dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified by column chromatography (silica gel, ether/petroleum ether = 1/20) to provide product **2.14** (1.43 g, 79 %) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (d, J = 8.7 Hz, 2H), 6.87 (d, J = 8.4 Hz, 2H), 5.88-5.76 (m, 1H), 5.06 (s, 1H), 5.01 (d, J = 7.2 Hz, 1H), 4.46 (s, 2H), 3.80 (s, 3H), 3.72-3.64 (m, 1H), 3.37-3.32 (m, 1H), 2.51-2.46 (m, 1H), 1.66-1.47 (m, 2H), 1.34-1.19 (m, 1H), 1.04 (d, J = 6.9 Hz, 3H), 1.01 (d, J = 6.3 Hz, 3H), 0.89 (d, J = 0.6 Hz, 9H), 0.87 (d, J = 2.2 Hz, 3H), 0.03 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.0, 140.5, 131.1, 129.3, 114.8, 113.6, 81.1, 71.7, 70.9, 55.2, 40.3, 37.2, 33.5, 25.9, 19.1, 18.1, 15.3, 15.1, -4.4, -4.8; HRMS (ESI): calculated for $C_{24}H_{42}O_3SiLi^+$ [M+Li^+] 413.3063, found 413.3064.

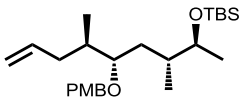


(3R,4S,6R,7S)-7-((tert-butyldimethylsilyl)oxy)-4-((4-methoxybenzyl)oxy)-3,6-dimethyloctan-1-ol (A.2). To an ice cold solution of PMB ether **2.14** (1.40 g, 3.45 mmol) in dry THF (10 mL) was added BH_3·THF (1.0 M in THF, 4.2 mL, 4.14 mmol) under nitrogen. The mixture was stirred at 0 °C for 1.5 h. After successive addition of water (0.8 mL), 3 N NaOH (1.1 mL), and 30% H_2O_2 (1.1 mL), the resulting mixture was stirred for an additional hour. The mixture was extracted with EtOAc (3x30 mL). The combined organic extracts were washed with brine (10 mL) and dried over anhydrous Na_2SO_4. After concentration *in vacuo*, the residue was purified by column chromatography (silica gel, ethyl acetate/petroleum ether = 1/5) to provide the alcohol **A.2** (1.18 g, 81 %) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, J = 8.7 Hz, 2H), 6.86 (d, J = 8.7 Hz, 2H), 4.48 (d, J = 11.0 Hz, 1H), 4.41 (d, J = 11.1 Hz, 1H), 3.79 (s, 3H), 3.73-3.65 (m, 2H), 3.61-3.53 (m, 1H), 3.35-3.30 (m, 1H), 2.41 (brs, 1H), 1.98-1.89 (m, 1H), 1.67-1.52 (m, 4H), 1.36-1.27 (m, 1H), 1.04 (d, J = 6.3 Hz, 3H), 0.96 (d, J = 6.9 Hz, 3H), 0.89-0.87 (m, 12H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.0, 130.6, 129.3, 113.7, 81.6, 71.9, 71.0, 60.1, 55.2, 37.4, 34.3, 33.1, 32.2, 25.8, 19.4, 18.0, 15.6, 15.3, -4.4, -4.8; HRMS (ESI): calculated for $C_{24}H_{44}O_4SiLi^+$ [M+Li^+] 431.3169, found 431.3166.



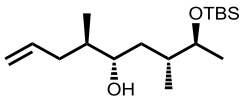
(3R,4S,6R,7S)-7-((tert-butyldimethylsilyl)oxy)-4-((4-methoxybenzyl)oxy)-3,6-dimethyloctanal (A.3). To a solution of alcohol **A.2** (1.50 g, 3.54 mmol) in DMSO (6 mL) was added IBX (1.49 g, 5.31 mmol) at room temperature. After being stirred for

2h, the reaction was quenched with H_2O (6 mL). The mixture was filtered and the aqueous phase was extracted with EtOAc. The combined organic layers were washed with brine, and dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified by column chromatography (silica gel, eluted with ethyl acetate/petroleum ether = 1/4) to provide the aldehyde **A.3** (1.36 g, 90 %) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.74 (s, 1H), 7.24 (d, J = 9.0 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 4.45 (t, J = 9.3 Hz, 1H), 4.36 (d, J = 11.0 Hz, 1H), 3.80 (s, 3H), 3.70-3.63 (m, 1H), 3.28-3.23 (m, 1H), 2.53-2.41 (m, 1H), 2.38-2.26 (m, 2H), 1.64-1.50 (m, 2H), 1.36-1.23 (m, 1H), 1.04 (d, J = 6.2 Hz, 3H), 1.00 (d, J = 6.6 Hz, 3H), 0.91-0.88 (m, 12H), 0.03 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.3, 159.0, 130.6, 129.3, 113.6, 81.3, 71.9, 70.9, 55.2, 46.8, 37.3, 33.6, 31.5, 25.8, 19.6, 18.0, 16.9, 15.7, -4.4, -4.8; HRMS (ESI): calculated for $C_{24}H_{42}O_4SiLi^+$ [M+Li^+] 429.3012, found 429.3018.



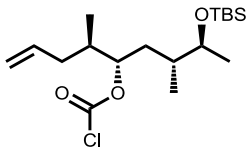
tert-butyl(((2S,3R,5S,6R)-5-((4-methoxybenzyl)oxy)-3,6-dimethylnon-8-en-2-yl)oxy)dimethylsilane (2.15). To a stirred suspension of methyltriphosphonium iodide (2.61 g, 6.4 mmol) in THF (60 mL) was added dropwise *n*-BuLi (1.6 M in THF, 3.80 ml, 6.1 mmol) until it became a clear yellow solution. Aldehyde **A.3** (1.36 g, 3.2 mmol) in dry THF (2 mL) was added slowly. The reaction mixture was stirred at room temperature for 2 h before it was quenched with saturated aqueous NH_4Cl (10 mL). The mixture was extracted with EtOAc (3x50 mL). The combined organic extracts were washed with H_2O (10 mL) and brine (20 mL), and dried over Na_2SO_4. After

concentration *in vacuo*, the residue was purified by column chromatography (silica gel, ethyl acetate/petroleum ether, 1/15) to provide alkene **2.15** (1.26 g, 94%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (d, J = 8.6 Hz, 2H), 6.87 (d, J = 8.6 Hz, 2H), 5.85-5.71 (m, 1H), 5.03 (d, J = 9.8 Hz, 1H), 4.98 (s, 1H), 4.53-4.31 (m, 2H), 3.80 (s, 3H), 3.75-3.67 (m, 1H), 3.33-3.29 (m, 1H), 2.19-2.12 (m, 1H), 1.98-1.83 (m, 2H), 1.69-1.49 (m, 2H), 1.32-1.20 (m, 1H), 1.03 (d, J = 6.2 Hz, 3H), 0.9-0.89 (m, 15H), 0.03 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.9, 137.8, 131.2, 129.2, 115.6, 113.6, 81.3, 71.6, 70.7, 55.2, 37.6, 36.9, 35.2, 33.0, 25.9, 19.0, 18.1, 15.4, 14.8, -4.4, -4.8; HRMS (ESI): calculated for $C_{25}H_{45}O_3Si^+$ [M+H$^+$] 421.3138, found 421.3135.

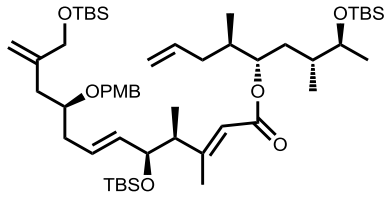


(4R,5S,7R,8S)-8-((tert-butyldimethylsilyl)oxy)-4,7-dimethylnon-1-en-5-ol (A.4). To a mixture of PMB ether **2.15** (1.26 g, 3.0 mmol) in CH_2Cl_2 (18 mL) and H_2O (1 mL) was added DDQ (817 mg, 3.6 mmol). The resulting mixture was stirred at room temperature for 0.5 h before it was quenched by saturated aqueous $NaHCO_3$ (10 mL). After being stirred for a further 15 min, the reaction mixture was extracted with EtOAc. The organic phase was washed with water, saturated aqueous $NaHCO_3$, brine, and dried over anhydrous Na_2SO4. After concentration *in vacuo*, the residue was purified by column chromatography (silica gel, ethyl acetate/petroleum ether, 1/10) to provide alcohol **A.4** (757 mg, 84 %) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.87-5.72 (m, 1H), 5.05-4.95 (m, 2H), 3.83-3.75 (m, 1H), 3.57-3.50 (m, 1H), 3.27 (d, J=3.2 Hz, 1H), 2.30-2.20 (m, 1H), 1.97-1.86 (m, 1H), 1.78-1.70 (m, 1H), 1.67-1.61 (m, 1H), 1.50

(t, J = 5.7 Hz, 2H), 1.16 (d, J = 6.3 Hz, 3H), 0.96 (d, J = 7.1 Hz, 3H), 0.93-0.87 (m, 12H), 0.07 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.8, 115.6, 72.3, 71.1, 38.4, 37.5, 37.0, 34.8, 25.8, 25.8, 20.8, 18.1, 16.7, 15.2 -4.4, -4.9; HRMS (ESI): calculated for $C_{17}H_{37}O_2Si^+$ [M+H$^+$] 301.2563, found 301.2567.



(4R,5S,7R,8S)-8-((tert-butyldimethylsilyl)oxy)-4,7-dimethylnon-1-en-5-yl carbonochloridate (2.6). To a stirred solution of alcohol **A.4** (388 mg, 1.29 mmol) in carbon tetrachloride (5 mL) was added pyridine (120 μL, 1.49 mmol) followed by triphosgene (153 mg, 0.52 mmol). The resulting mixture was stirred at room temperature for 4 h before it was diluted with hexanes (60 mL). The solids were removed by filtration and the filtrate was evaporated to afford chloroformate **2.6** (459 mg, 98%) as a colorless oil. It was used directly for the next step without further purification.

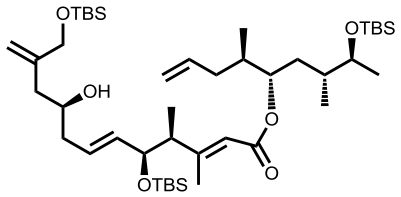


(2E,4S,5S,6E,9S)-(4R,5S,7R,8S)-8-((tert-butyldimethylsilyl)oxy)-4,7-dimethylnon-1-en-5-yl 5-((tert-butyldimethylsilyl)oxy)-11-(((tert-butyldimethylsilyl) oxy)methyl)-9-((4-methoxybenzyl)oxy)-3,4-dimethyldodeca-2,6,11-trienoate (2.17). To a solution of alkyne **2.4** (490 mg, 0.86 mmol) in THF (3.5 mL) was added *n*-BuLi (1.6 M in hexanes, 0.56 mL, 0.90 mmol) dropwise at −78 °C. After being stirred at −78 °C for 45 min, HMPA (0.30 mL, 1.72 mmol) was added, stirred for 5 min, and then a

solution of chloroformate **2.6** (310 mg, 0.86 mmol) in THF (0.8 mL) was added dropwise at −78 °C. After being stirred at −78 °C for 1 h, the reaction mixture was warmed to 0 °C over a period of 2 h and subsequently quenched by addition of saturated aqueous NH_4Cl. The layers were separated and the aqueous phase was extracted with EtOAc (3x30 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, ethyl acetate/petroleum ether, 1/60 gradient to 1/5) to provide alkyne **2.4** (193 mg) and alkynoate **2.16** (411 mg, 88% based on recovering staring material) as a clear oil.

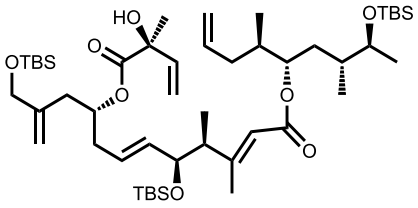
To an ice-cold suspension of CuI (644 mg, 3.38 mmol) in THF (7 mL) was added MeLi (1.5 M in Et_2O, 4.51 mL, 6.76 mmol) dropwise to give a clear solution. After being stirred at 0 °C for 1 h, the solution was cooled to −78 °C, treated with TMSCl (0.43 mL, 3.38 mmol), and stirred at this temperature for 5 min. A solution of alkynoate **2.16** (304 mg, 0.33 mmol) in THF (2 mL) was added. The bright yellow solution was slowly warmed to 0 °C over a period of 3 h and quenched by addition of saturated aqueous NH_4Cl (5 mL) and H_2O (2 mL). The resulting biphasic solution was stirred vigorously for 20 min. The layers were separated and the aqueous phase was extracted with EtOAc (3x30 mL). The combined organic layer was washed with brine (10 mL), dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified by column chromatography (silica gel, ethyl acetate/petroleum ether, 1/60 gradient to 1/20) to afford the alkenoate **2.17** (299 mg, 99%) as a light yellow oil. $[\alpha]_D^{18}$ 4.89 (*c* 2.15, $CHCl_3$); IR (thin film) 2961, 2925, 2860, 1706, 1640, 1513, 1463, 1247, 1075, 832, 770 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.24 (d, J = 8.7 Hz, 2H), 6.86 (d, J = 8.7 Hz, 2H),

5.83-5.57 (m, 3H), 5.45 (dd, J = 15.5, 6.6 Hz, 1H), 5.13 (d, J = 1.8 Hz, 1H), 5.03 (d, J = 6.2 Hz, 1H), 4.98 (s, 1H), 4.96-4.89 (m, 1H), 4.88 (s, 1H), 4.45 (s, 2H), 4.12-4.07 (m, 3H), 3.80 (s, 3H), 3.75-3.67 (m, 1H), 3.60-3.47 (m, 1H), 2.31-2.13 (m, 6H), 2.16 (d, J = 1.1 Hz, 3H), 1.94-1.75 (m, 2H), 1.70-1.50 (m, 1H), 1.39-1.23 (m, 2H), 1.07 (d, J = 6.9 Hz, 3H), 1.01 (d, J = 6.2 Hz, 3H), 0.94-0.84(m, 33H), 0.06-0.03 (m, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 161.5, 159.1, 145.6, 137.2, 134.5, 130.8, 129.2, 127.1, 117.0, 116.0, 113.7, 111.0, 77.6, 75.1, 75.0, 70.9, 70.7, 66.1, 55.2, 50.7, 37.6, 37.2, 36.6, 36.5, 36.2, 33.2, 25.9, 25.9, 25.9, 18.8, 18.4, 18.4, 18.2, 18.0, 15.1, 15.1, 13.6, -4.0, -4.5, -4.8, -4.9, -5.4; HRMS (ESI): calculated for $C_{52}H_{94}O_7Si_3Li^+$ [M+Li^+] 921.6467, found 921.6451.



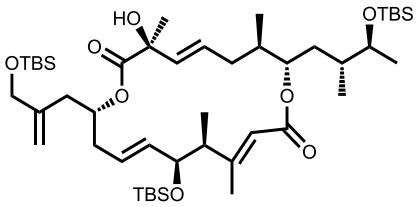
(2E,4S,5S,6E,9S)-(4R,5S,7R,8S)-8-((tert-butyldimethylsilyl)oxy)-4,7-dimethylnon-1-en-5-yl 5-((tert-butyldimethylsilyl)oxy)-11-(((tert-butyldimethylsilyl) oxy)methyl)-9-hydroxy-3,4-dimethyldodeca-2,6,11-trienoate (A.5). To a solution of the **2.17** (300 mg, 0.33 mmol) in CH_2Cl_2 (9.90 mL) and H_2O (0.55 mL) was added DDQ (112 mg, 0.49 mmol). The resulting mixture was stirred at room temperature for 0.5 h before it was quenched by saturated aqueous $NaHCO_3$ (4 mL). After being stirred for a further 15 min, the reaction mixture was extracted with EtOAc. The organic phase was washed with water, saturated aqueous $NaHCO_3$, brine, and dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified by column chromatography (silica gel,

ether/petroleum ether, 1/10 to 1/7) to provide **A.5** (214 mg, 82 %) as colorless oils. $[\alpha]_D^{19}$ 4.76 (*c* 2.04, $CHCl_3$); IR (thin film) 3020, 2958, 2934, 2857, 1709, 1643, 1463, 1247, 1217, 832, 746 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.85-5.67 (m, 1H), 5.65 (s, 1H), 5.63-5.56 (m, 1H), 5.44 (dd, *J* = 15.5, 6.6 Hz, 1H), 5.12 (d, *J*=1.5 Hz, 1H), 5.02 (d, *J* = 6.2 Hz, 1H), 4.98 (s, 1H), 4.93 (s, 2H), 4.15-4.04 (m, 1H), 4.09 (s, 2H), 3.75-3.66 (m, 2H), 2.73 (d, *J*=3.0 Hz, 1H), 2.32-2.04 (m, 7H), 2.14 (s, 3H), 1.91-1.78 (m, 2H), 1.60-1.51 (m, 1H), 1.34-1.24 (m, 1H), 1.07 (d, *J* = 6.9 Hz, 3H), 1.01 (d, *J* = 6.2 Hz, 3H), 0.95-0.78 (m, 33H), 0.08 (s, 6H), 0.02-0.01(m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 161.4, 145.4, 137.2, 134.9, 127.2, 117.0, 115.9, 113.7, 75.2, 75.0, 71.0, 69.8, 66.7, 50.7, 41.5, 39.9, 37.2, 36.5, 36.2, 33.2, 25.9, 18.8, 18.3, 18.2, 18.0, 15.1, 15.1, 13.9, -4.0, -4.5, -4.8, -4.9, -5.4; HRMS (ESI): calculated for $C_{44}H_{86}O_6Si_3Na^+$ [M+Na^+] 817.5624, found 817.5655.



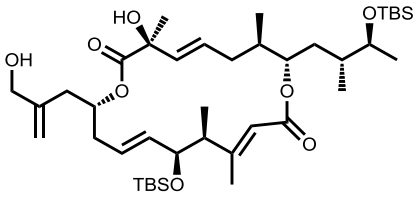
(2E,4S,5S,6E,9R)-(4R,5S,7R,8S)-8-((tert-butyldimethylsilyl)oxy)-4,7-dimethylnon-1-en-5-yl 5-((tert-butyldimethylsilyl)oxy)-11-(((tert-butyldimethylsilyl) oxy)methyl)-9-(((S)-2-hydroxy-2-methylbut-3-enoyl)oxy)-3,4-dimethyldodeca-2,6,11-trienoate (2.18). To a solution of alcohol **A.5** (180 mg, 0.22 mmol), acid **2.5** (79 mg, 0.68 mmol), and PPh_3 (178 mg, 0.68 mmol) in THF (3 mL) was added DEAD (40% in toluene, 0.31 mL, 0.68 mmol) dropwise under nitrogen. After being stirred for overnight at room temperature, the reaction mixture was extracted with EtOAc (3x30

mL). The combined organic layers were washed with water, brine, and dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified by column chromatography (silica gel, ethyl acetate/petroleum ether, 1/15 gradient to 1/12) to provide ester **2.18** (148 mg, 73%) as a clear oil. $[\alpha]_D^{20}$ -6.05 (*c* 2.11, $CHCl_3$); IR (thin film) 3020, 2961, 2931, 2857, 1720, 1706, 1640, 1466, 1250, 1214, 1104,, 838, 770, 669 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.97 (dd, *J* = 17.1, 10.5 Hz, 1H), 5.83-5.69 (m, 1H), 5.65 (s, 1H), 5.54-5.42 (m, 3H), 5.17-5.07 (m, 3H), 5.02 (d, *J*=5.6 Hz, 1H), 4.98 (s, 1H), 4.95-4.88(m, 1H), 4.85 (s, 1H), 4.12-4.05 (m, 1H), 4.07 (s, 2H), 3.78-3.65 (m, 1H), 3.32 (s, 1H), 2.36-2.27 (m, 4H), 2.24-2.11 (m, 3H), 2.14 (d, J=1.1, 3H), 1.92-1.73 (m, 2H), 1.70-1.50 (m, 1H), 1.44 (s, 3H), 1.37-1.22 (m, 1H), 1.04 (d, *J* = 6.9 Hz, 3H), 1.02 (d, *J*=6.2 Hz, 3H), 0.94-0.83 (m, 33H), 0.15--0.15 (m, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.9, 166.4, 161.1, 143.8, 139.5, 137.2, 136.1, 124.5, 117.1, 116.0, 114.5, 112.4, 75.0, 74.6, 74.4, 73.7, 70.9, 65.6, 50.4, 37.2, 37.0, 36.5, 36.4, 36.2, 33.2, 25.9, 18.8, 18.5, 18.3, 18.1, 18.0, 15.1, 15.1, 13.4, –4.1, -4.5, –4.8, –4.9, –5.4; -5.4 HRMS (ESI): calculated for $C_{49}H_{92}O_8Si_3Na^+$ [M+Na^+] 915.5991, found 915.5959.



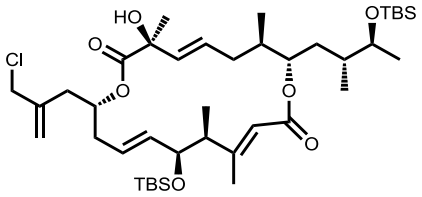
(3S,4E,7R,8S,11E,13S,14S,15E,18R)-14-((tert-butyldimethylsilyl)oxy)-8-((2R,3S)-3-((tert-butyldimethylsilyl)oxy)-2-methylbutyl)-18-(2-(((tert-butyldimethyl silyl) oxy) methyl)allyl)-3-hydroxy-3,7,12,13-tetramethyl-1,9-dioxacyclooctadeca-4, 11,15 -triene-2,10-dione (2.19). To a solution of Grubbs' 2nd generation catalyst (20

mg, 0.024 mmol) in CH_2Cl_2 (50 mL) was added a solution of diene **2.18** (140 mg, 0.16 mmol) in CH_2Cl_2 (7 mL) and the resulting solution was refluxed for 4 h under nitrogen. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (silica gel, ether/petroleum ether, 1/8 to 1/5) to afford compound **2.19** (98 mg, 72%) as a colorless oil. $[\alpha]_D^{20}$ -35.64 (*c* 2.10, $CHCl_3$); IR (thin film) 3023, 2961, 2928, 2857, 1703, 1643, 1466, 1256, 1214, 829, 767 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 5.88-5.79 (m, 1H), δ 5.62 (d, J=1.2 Hz, 1H), 5.53 (d, *J* = 15.2 Hz, 1H), 5.43-5.37 (m, 2H), 5.22-5.15 (m, 1H), 5.08 (s, 1H), 4.99-4.93 (m, 1H), 4.83 (s, 1H), 4.13-4.01 (m, 2H), 3.87-3.82 (m, 1H), 3.75-3.67 (m, 1H), 3.39 (s, 1H), 2.41-1.97 (m, 7H), 2.07 (s, 3H), 1.89-1.80 (m, 1H), 1.77-1.67 (m, 1H), 1.42 (s, 3H), 1.35-1.26 (m, 2H), 1.15 (d, *J* = 6.8 Hz, 3H), 1.02 (d, *J* = 6.2 Hz, 3H), 0.96-0.81 (s, 30H), 0.71 (d, J=6.7 Hz, 3H), 0.18--0.13 (m, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.2, 166.6, 162.0, 143.9, 136.4, 133.7, 128.2, 124.9, 116.6, 112.1, 79.0, 75.3, 74.0, 72.7, 71.2, 65.5, 50.5, 37.1, 36.7, 36.4, 36.1, 35.0, 33.0, 25.9, 25.8, 25.5, 21.1, 19.1, 18.3, 18.2, 18.0, 17.7, 16.7, 15.5, -3.8, -4.5, -4.6, -4.8, -5.4, -5.4; HRMS (ESI): calculated for $C_{47}H_{89}O_8Si_3^+$ $[M+H^+]$ 865.5865, found 865.5846.



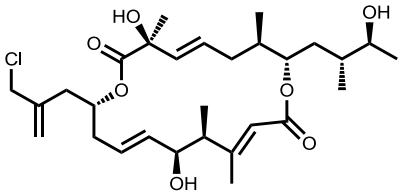
(3S,4E,7R,8S,11E,13S,14S,15E,18R)-14-((tert-butyldimethylsilyl)oxy)-8-((2R,3S)-3-((tert-butyldimethylsilyl)oxy)-2-methylbutyl)-3-hydroxy-18-(2-(hydroxymethyl)allyl)-3,7,12,13-tetramethyl-1,9-dioxacyclooctadeca-4,11,15-triene-2,10-dione (A.6). To a solution of **2.19** (77 mg, 0.093 mmol) in anhydrous EtOH (5 mL) was

added PPTS (2.33 mg, 0.010 mmol) and the reaction mixture was refluxed for 1.5 h under nitrogen. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (silica gel, ethyl acetate/petroleum ether, 1/2) to afford **2.19** (33.7 mg) and the primary alcohol **A.6** (33.7 mg, 90% based on recovered starting material) as a colorless oil: $[\alpha]_D^{20}$ -34.40 (*c* 1.85, $CHCl_3$); IR (thin film) 3449, 2961, 2931, 2851, 1723, 1649, 1460, 1385, 1060, 1253, 838, 776 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.89-5.80 (m, 1H), 5.60 (s, 1H), 5.54 (d, *J* = 15.2 Hz, 1H), 5.47-5.34 (m, 2H), 5.22-5.15 (m, 1H), 5.08 (s, 1H), 4.97-4.87 (m, 1H), 4.86 (s, 1H), 4.08 (s, 2H), 3.87-3.80 (m, 1H), 3.77-3.59 (m, 1H), 3.41 (s, 1H), 2.46-1.95 (m, 7H), 2.07 (s, 3H), 1.87-1.78 (m, 1H), 1.77-1.67 (m, 1H), 1.64-1.52 (m, 1H), 1.42 (s, 3H), 1.35-1.21 (m, 1H), 1.14 (d, *J*=6.8 Hz, 3H), 1.00 (d, *J*=6.1 Hz, 3H), 0.93-0.81 (m, 21H), 0.74 (d, *J*=6.8 Hz, 3H), 0.12 (s, 3H), 0.06 (s, 3H), 0.01 (s, 3H), -0.01 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.6, 166.5, 162.4, 144.2, 136.5, 133.7, 128.1, 124.9, 116.4, 113.5, 79.0, 75.1, 74.1, 73.2, 71.2, 65.9, 50.5, 37.6, 36.9, 36.4, 35.1, 33.3, 25.8, 25.8, 25.7, 21.3, 19.0, 18.2, 18.0, 17.7, 16.7, 15.5, -3.8, -4.5, -4.6, -4.8; HRMS (ESI): calculated for $C_{41}H_{75}O_8Si_2^+[M+H^+]$ 751.5001, found 751.5016.



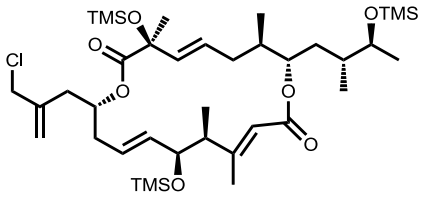
(3S,4E,7R,8S,11E,13S,14S,15E,18R)-14-((tert-butyldimethylsilyl)oxy)-8-((2R,3S)-3-((tert-butyldimethylsilyl)oxy)-2-methylbutyl)-18-(2-(chloromethyl)allyl)-3-hydroxy-3,7,12,13-tetramethyl-1,9-dioxacyclooctadeca-4,11,15-triene-2,10-dione

(2.20). To an ice-cold solution of alcohol **A.6** (60 mg, 0.080 mmol) in anhydrous CH_2Cl_2 (3 mL) was added Et_3N (17 μL, 0.12 mmol) followed by MsCl (7.5 μL, 0.096 mmol). The reaction mixture was stirred for 5 min at 0 °C before it was directly purified by flash chromatography (silica gel, ethyl acetate/petroleum ether, 1/3) to afford the crude mesylate (60.4 mg) as a colorless oil, which was dissolved in HMPA (1 mL) and treated with LiCl (31 mg, 0.73 mmol). The resulting mixture was stirred at room temperature for 4 h and extracted with EtOAc (3x20 mL). The combined organic layers were washed with water, brine, and dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified by column chromatography (silica gel, ethyl acetate/petroleum ether, 1/5) to provide chloride **2.20** (52.5 mg, 85% for two steps) as a clear oil: $[\alpha]_D^{19}$ -36.80 (*c* 1.22, $CHCl_3$); IR (thin film) 2961, 2928, 2857, 1717, 1640, 1457, 1380, 1256, 1217, 1105, 835, 776 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.89-5.79 (m, 1H), 5.62 (d, *J*=1.3 Hz, 1H), 5.54 (d, *J*=15.1 Hz, 1H), 5.46-5.39 (m, 2H), 5.28-5.20 (m, 1H), 5.19 (s, 1H), 4.99-4.93 (m, 2H), 4.09 (d, *J* = 11.2 Hz, 1H), 4.00 (d, *J* = 12.3 Hz, 1H), 3.90-3.83 (m, 1H), 3.75-3.64 (m, 1H), 3.34 (s, 1H), 2.52-2.29 (m, 3H), 2.25-2.13 (m, 3H), 2.08 (d, *J*=1.3, 3H), 2.04-1.96 (m, 1H), 1.87-1.80 (m, 1H), 1.80-1.69 (m, 1H), 1.63-1.51 (m, 1H), 1.42 (s, 3H), 1.35-1.24 (m, 1H), 1.16 (d, *J*=6.8 Hz, 3H), 1.02 (d, *J*=6.2 Hz, 3H), 0.95-0.81 (m, 21H), 0.71 (d, *J*=6.8 Hz, 3H), 0.14 (s, 3H), 0.09 (s, 3H), 0.02 (s, 3H), 0.00 (s,3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.3, 166.6, 162.1, 140.8,. 136.7, 133.6, 128.4, 124.6, 117.5, 116.6, 78.9, 75.3, 74.1, 72.2, 71.2, 50.5, 47.7, 37.1, 36.9, 36.4, 36.3, 35.0, 33.0, 29.7, 25.9, 25.8, 25.5, 21.1, 19.1, 18.2, 18.0, 17.7, 16.7, 15.5, -3.8, -4.5, -4.6, -4.8; HRMS (ESI): calculated for $C_{41}H_{74}ClO_7Si_2^+$ [M+H^+] 769.4662, found 769.4658.



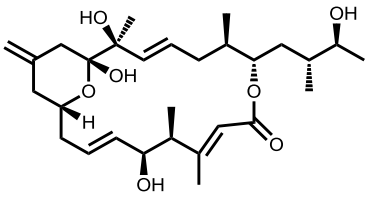
(3S,4E,7R,8S,11E,13S,14S,15E,18R)-18-(2-(chloromethyl)allyl)-3,14-dihydroxy-8-((2R,3S)-3-hydroxy-2-methylbutyl)-3,7,12,13-tetramethyl-1,9-dioxacyclooctadeca-4,11,15-triene-2,10-dione (A.7). To a stirred solution of TBS ether **2.20** (52.5 mg, 0.068 mmol) in THF (2.4 mL) was added a solution of HF·py complex (0.80 mL). The reaction mixture was stirred for 20 h at room temperature and quenched by saturated aqueous $NaHCO_3$ (5 mL). After stirring for a further 15 min, the reaction mixture was extracted with EtOAc. The organic phase was washed with water, saturated aqueous $NaHCO_3$, brine, and dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified by column chromatography (silica gel, ethyl acetate/petroleum ether, 1/2 to 1/1) to provide triol **A.7** (34.5 mg, 94%) as a colorless oil: $[\alpha]_D^{19}$ -74.22 (*c* 0.6, $CHCl_3$); IR (thin film) 3446, 2958, 2928, 2848, 1729, 1709, 1640, 1460, 1377, 1214, 1093, 870, 832, 752 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.89-5.79 (m, 1H), 5.65 (d, *J*=1.4 Hz, 1H), 5.63-5.44 (m, 3H), 5.25-5.18 (m, 2H), 5.05-4.98 (m, 2H), 4.10 (d, *J* = 11.7 Hz, 1H), 4.01 (d, *J* = 11.1 Hz, 1H), 3.97-3.90 (m, 1H), 3.72-3.64 (m, 1H), 3.31 (s, 1H), 2.46-2.31 (m, 3H), 2.26-2.15 (m, 3H), 2.12 (d, *J*=1.3 Hz, 3H), 2.07-1.96 (m, 1H), 1.86-1.70 (m, 2H), 1.63-1.52 (m, 1H), 1.47-1.37 (m, 1H), 1.42 (s, 3H), 1.25 (d, *J* = 7.0 Hz, 3H), 1.12 (d, *J* = 6.3 Hz, 3H), 0.90 (d, *J* = 6.8 Hz, 3H), 0.73 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.3, 166.9, 162.1, 140.7, 135.4, 133.6, 128.3, 126.7, 117.9, 116.5, 78.2, 75.5, 74.1, 72.1, 71.5, 49.5, 47.8, 37.0, 36.7, 36.6, 36.1, 36.0, 33.1, 25.5,

21.2, 19.7, 17.2, 16.6, 16.2; HRMS (ESI): calculated for $C_{29}H_{46}ClO_7^+$ [M+H$^+$] 541.2932, found 541.2958.



(3S,4E,7R,8S,11E,13S,14S,15E,18R)-18-(2-(chloromethyl)allyl)-3,7,12,13-tetramethyl-8-((2R,3S)-2-methyl-3-((trimethylsilyl)oxy)butyl)-3,14-bis((trimethyl silyl)oxy)-1,9-dioxacyclooctadeca-4,11,15-triene-2,10-dione (2.21). To an ice-cold solution of alcohol **A.7** (34.5 mg, 0.06 mmol) in anhydrous CH_2Cl_2 (1 mL) was added pyridine (46 μL, 0.58 mmol) followed by TMSOTf (52 μL, 0.29 mmol). The reaction mixture was stirred at 0 °C for 10 min before it was directly purified by flash chromatography (silica gel, petroleum ether/EtOAc, 20/1) to afford TMS silyl ether **2.21** (45 mg, 93%) as a colorless oil: $[\alpha]_D^{19}$ -45.76 (*c* 0.54, $CHCl_3$); IR (thin film) 2961, 2925, 2857, 1744, 1714, 1649, 1252, 1211, 1105, 835, 752 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.78-5.68 (m, 1H), 5.63 (d, *J*=1.3 Hz, 1H), 5.53 (d, *J*=15.1 Hz, 1H), 5.45-5.40 (m, 2H), 5.29-5.22 (m, 1H), 5.17 (s, 1H), 5.03-4.97 (m, 1H), 4.95 (s, 1H), 4.08 (d, *J* = 10.9 Hz, 1H), 3.99 (d, *J* = 11.8 Hz, 1H), 3.86 (dd, *J* = 9.6, 7.0 Hz, 1H), 3.72-3.64 (m, 1H), 2.49-2.28 (m, 3H), 2.23-2.04 (m, 4H), 2.08 (d, *J*=1.3, 3H), 1.97-1.86 (m, 1H), 1.82-1.73 (m, 2H), 1.45 (s, 3H), 1.36-1.25 (m, 1H), 1.14 (d, *J* = 6.8 Hz, 3H), 1.05 (d, *J* = 6.1 Hz, 3H), 0.89 (d, *J* = 6.8 Hz, 3H), 0.68 (d, *J* = 6.7 Hz, 3H), 0.18 (s, 9H), 0.15 (s, 9H), 0.09 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.3, 166.7, 161.6, 141.2, 136.1, 134.7, 128.4, 124.9, 117.0, 116.7, 78.9, 77.1, 75.7, 71.5, 70.3, 50.2, 47.8, 37.3, 36.8, 36.4, 36.1, 35.1,

32.9, 26.9, 21.0, 19.5, 17.5, 16.7, 15.6, -2.3, -0.6, -0.2; HRMS (ESI): calculated for $C_{38}H_{69}ClO_7SiLi^+$ [M+Li^+] 763.4200, found 763.4241.



(1R,2S,3E,6R,7S,10E,12S,13S,14E,17R)-1,2,13-trihydroxy-7-((2R,3S)-3-hydroxy-2-methylbutyl)-2,6,11,12-tetramethyl-19-methylene-8,21-dioxabicyclo [15.3.1] henicosa-3,10,14-trien-9-one (2.1). To a stirred solution of chloride **2.21** (43 mg, 0.057 mmol) in acetone (2 mL) was added NaI (85 mg, 0.57 mmol). The reaction mixture was stirred at room temperature for 10 h before it was diluted with Et_2O (50 mL) and filtered by a short pad of silica gel. After concentration *in vacuo*, the crude iodide was used directly without further purification.

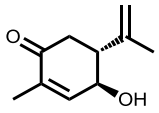
To an ice-cold solution of SmI_2 (3.8 mL, 0.1 M in THF, 0.38 mmol) was added dropwise a solution of the above iodide (15.2 mg, 0.018 mmol) in THF (0.7 mL) under nitrogen. The deep blue mixture was stirred at 0 °C for 10 min before it was quenched by a mixture of saturated aqueous $NaHCO_3$ (2 mL) and sodium potassium phosphate buffer solution (pH = 7). After stirring for a further 15 min, the reaction mixture was extracted with EtOAc. The organic phase was washed with water, saturated aqueous $NaHCO_3$, brine, and dried over anhydrous Na_2SO_4. After concentration *in vacuo*, the residue was dissolved in THF (1.0 mL), to which was added a mixture of HF·py complex (20 μL) and HF/TBAF/Py (20 μL). The reaction mixture was stirred at room temperature for 3 h and quenched by saturated aqueous $NaHCO_3$ (1 mL). After stirring

for a further 15 min, the reaction mixture was extracted with EtOAc. The organic phase was washed with water, saturated aqueous $NaHCO_3$, brine, and dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified by column chromatography (silica gel, petroleum ether/acetone, 2/1) to provide the diastereomeric iriomoteolide 1a **1** (4.6 mg, 49% for three steps) as a colorless oil consisting of an equilibrating mixture of hemiketal **2.1** and its ketol form. $[\alpha]_D^{19}$ -11.07 (*c* 0.6, $CHCl_3$); IR (thin film) 2967, 2928, 2854, 1661 1638, 1427, 1013, 871 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ= 5.72 (s, 1 H), 5.72-5.70 (m, 2 H), 5.62-5.57 (m, 1 H), 5.45 (dd, *J* = 16.2, 9.1 Hz, 1 H), 4.87 (s, 1 H), 4.85-4.80 (m, 1 H), 4.83 (s, 1 H), 3.77 (t, *J* = 9.1 Hz, 1 H), 3.64(dd, *J* = 11.9, 2.4 Hz, 1 H), 3.61-3.53 (m, 1 H), 3.03 (s, 1 H),2.50-2.46 (m, 1 H), 2.44-2.35 (m, 1 H), 2.33 (d, *J* = 8.1 Hz, 1 H), 2.25 (dd, *J* = 13.6, 10.3 Hz, 1 H), 2.17-2.11 (m, 3 H), 2.08 (s, 3 H), 2.06-1.98 (m, 1 H), 1.93-1.88 (m, 1 H), 1.84-1.79 (m, 1 H), 1.51-1.45 (m, 1 H), 1.28 (d, *J* = 6.8 Hz, 3 H), 1.15 (s, 3 H), 1.17-1.11 (m, 1 H), 1.07 (d, *J* = 6.3 Hz, 3 H), 1.02 (d, *J* = 7.1 Hz, 3 H), 0.85 (d, *J* = 6.8 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 162.6, 141.2, 139.0, 135.0, 128.0, 120.7, 115.7, 111.3, 97.0, 79.9, 75.8, 75.6, 73.7, 72.4, 48.4, 45.9, 43.8, 38.0, 37.0, 36.2, 35.4, 33.6, 23.2, 21.5, 20.4, 17.7, 16.9, 15.9; HRMS (ESI): calculated for $C_{29}H_{46}O_7Na^+$ [M+Na^+] 529.3141, found 529.3152.

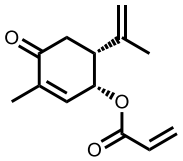
Table A.1. Comparison of NMR data for natural iriomoteolide-1a and synthetic **2.1**

Position	^{1}H natural	^{1}H synthetic	^{13}C natural	^{13}C synthetic	*J* natural	*J* synthetic
1			167.4	168.1		
2	5.72	5.72	115.8	115.7	brs	s
3			162.0	162.6		
4	2.46	2.17-2.11	47.9	48.4	dq, 2.9, 7.3	m
5	4.28	3.77	72.3	79.9	m	t, 9.1
6	5.57	5.45	132.0	135.0	dd, 4.1, 15.7	dd, 9.1, 16.2
7	5.68	5.62-5.57	126.8	128.0	m	m
8a	2.18	2.44-2.35	39.5	45.9	m	m
8b		2.17-2.11				m
9	3.81	3.64	71.8	75.7	brt, 11.5	dd, 2.4, 11.9
10a	2.21	2.06-1.98	40.7	38.0	brd, 12.7	m
10b	1.90				brt, 12.3	
11			141.7	141.2		
12a	2.40	2.50-2.46	36.9	43.8	d, 13.6	m
12b	2.26	2.33			brd, 13.6	d, 8.1
13	3.52	3.03	99.7	97.0	brd, 1.9	s
14			77.2	73.7		
15	5.68	5.72-5.70	134.9	139.0	brd, 15.5	m
16	5.76	5.72-5.70	128.8	120.7	ddd, 3.1, 10.8, 15.5	m
17a	2.15	2.25	38.2	37.0	m	dd, 10.3, 13.6
17b	1.96	2.17-2.11			dt, 11.6, 14.1	m
18	1.82	1.93-1.88	36.9	36.2	m	m
19	5.11	4.85-4.80	70.8	75.8	m	m
20a	1.80	1.84-1.79	36.5	35.4	ddd, 4.4, 8.7, 13.8	m
20b	1.15	1.17-1.11			ddd, 4.4, 8.8, 13.8	m
21	1.40	1.51-1.45	36.5	33.6	m	m
22	3.58	3.61-3.53	72.2	72.4	quint, 6.3	m
23	1.11	1.07	19.8	20.4	d, 6.3	d, 6.3
24	2.12	2.08	23.8	23.2	s	s
25	1.24	1.28	15.6	17.7	d, 7.3	d, 6.8
26a	4.82	4.87	110.6	111.3	brs	s
26b		4.83				s
27	1.25	1.15	23.1	21.5	s	s
28	0.99	1.02	14.2	15.9	d, 6.8	d, 7.1
29	0.91	0.85	15.5	16.9	d, 6.7	d, 6.8

A.3 Experimental Procedures for Total Synthesis of Alotaketal A



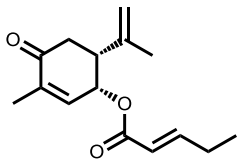
(4S,5R)-4-Hydroxy-2-methyl-5-(prop-1-en-2-yl)cyclohex-2-enone (3.7). To a solution of nitrosobenzene (10.80 g, 100.7 mmol) in CH_2Cl_2 (210 mL) were added acetic acid (5.76 mL, 100 mmol) and (5-isopropenyl-2-methyl-cyclohexa-1,3-dienyloxy)-trimethyl silane **3.8**[1] (9.33 g, 42.0 mmol) at −78 °C. The solution was stirred at this temperature for 12 h before being warmed to room temperature and further stirred for 4 h. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (silica gel, ethyl acetate/petroleum ether, 1/2) to provide **3.7** (4.12 g, 59%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.71-6.70 (m, 1H), 4.98-4.97 (m, 1H), 4.95-4.94 (m, 1H), 4.46-4.42 (m, 1H), 2.72-2.67 (m, 1H), 2.50 (dd, *J* = 16.3, 3.9 Hz, 1H), 2.38 (dd, *J* = 16.4, 13.8 Hz, 1H), 1.79-1.78 (m, 3H), 1.76-1.75 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.5, 147.4, 143.0, 135.1, 114.8, 68.4, 52.7, 40.8, 19.0, 15.4.



(1R,6R)-3-Methyl-4-oxo-6-(prop-1-en-2-yl)cyclohex-2-en-1-ylacrylate (3.10a). To a solution of 5β-hydroxycarvone **3.7** (83 mg, 0.5 mmol), acrylic acid (103 μL, 1.5 mmol) and triphenylphosphine (394 mg, 1.5 mmol) in THF (2.5 mL) was added diethyl

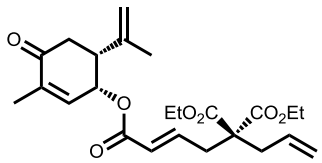
(1) Sarabèr,F. C. E.; Baranovsky, A.; Jansen, B. J. M.; Posthumus, M. A.; Groot, A. d. *Tetrahedron* **2006**, *62*, 1726.

azodicarboxylate (0.68 mL, 40% in toluene, 1.5 mmol) dropwise at 0 °C under nitrogen. The resulting mixture was stirred at room temperature for 3 h, diluted with EtOAc (30 mL), and washed with H_2O and brine. The organic layer was dried over Na_2SO_4, concentrated and purified by flash column chromatography (silica gel, ethyl acetate/petroleum ether, 1/5) to provide **3.10**a (52 mg, 47%) as a light yellow oil. $[\alpha]_D^{21}$ -98.3 (c 1.96, $CHCl_3$); IR (film, cm^{-1}) 2976, 2919, 1729, 1685, 1407, 1262, 1182, 1042, 900, 809; ^1H NMR (500 MHz, $CDCl_3$) δ 6.79 (dd, *J* = 5.6, 1.5 Hz, 1H), 6.38 (dd, *J* = 17.3, 1.4 Hz, 1H), 6.07 (dd, *J* = 17.3, 10.4 Hz, 1H), 5.84 (dd, *J* = 10.4, 1.4 Hz, 1H), 5.63-5.61 (m, 1H), 4.94 (s, 1H), 4.75 (s, 1H), 2.86 (d, *J* = 12.6 Hz, 2H), 2.55 (dd, *J* = 12.5, 0.9 Hz, 1H), 1.83 (dd, *J* = 1.4, 0.8 Hz, 3H), 1.78 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 199.2, 165.4, 142.8, 138.9, 138.6, 131.4, 128.0, 113.0, 66.4, 44.3, 37.9, 21.9, 15.6; HRMS (ESI): calculated for $C_{13}H_{16}O_3$ $[M+Li^+]$ 227.1259, found 227.1249.



(*E*)-(1R,6R)-3-methyl-4-oxo-6-(prop-1-en-2-yl)cyclohex-2-en-1-ylpent-2-enoate (3.10b). To a solution of 5β-hydroxycarvone **3.7** (50 mg, 0.3 mmol), 2-pentenoic acid (0.09 mL, 0.9 mmol) and triphenylphosphine (237 mg, 0.9 mmol) in THF (2 mL) was added diethyl azodicarboxylate (0.42 mL, 40% in toluene, 0.9 mmol) dropwise at 0 °C under nitrogen. The resulting mixture was stirred at room temperature for 3 h, diluted with EtOAc (30 mL) and washed with H_2O and brine. The organic layer was dried over Na_2SO_4, concentrated and purified by flash column chromatography (silica gel, ethyl acetate/petroleum ether, 1/5) to provide product **3.10b** (61.8 mg, 83%) as a light yellow

oil. $[\alpha]_D^{21}$ -287.77 (c 2.14, $CHCl_3$); IR (film, cm^{-1}) 2970, 2919, 1720, 1679, 1649, 1244, 1176, 1116, 1025, 971; ^1H NMR (300 MHz, $CDCl_3$) δ 7.05-6.96 (m, 1H), 6.79 (dd, *J* = 5.6, 1.5 Hz, 1H), 5.76 (dt, *J* =15.7, 1.7 Hz, 1H), 5.61-5.58 (m, 1H), 4.94 (s, 1H), 4.75 (s, 1H), 2.88-2.80 (m, 2H), 2.60-2.47 (m, 1H), 2.27-2.17 (m, 2H), 1.83 (dd, *J* = 1.5, 0.8 Hz, 3H), 1.78 (s, 3H), 1.06 (t, *J* = 7.4 Hz, 3H);^{13}C NMR (75 MHz, $CDCl_3$) δ 199.3, 166.0, 151.8, 142.9, 139.0, 138.7, 119.7, 112.9, 66.1, 44.3, 37.9, 25.4, 21.9, 15.6, 12.0; HRMS (ESI): molecular ion was not observed.

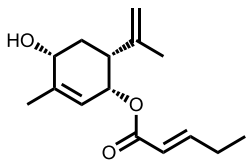


(*E*)-4,4-diethyl 1-((1R,6R)-3-methyl-4-oxo-6-(prop-1-en-2-yl)cyclohex-2-en-1-yl) hepta-1,6-diene-1,4,4-tricarboxylate (3.10c). To a solution of triethyl pent-4-ene-1,2,2-tricarboxylate[2] (5.0 g, 16 mmol) in EtOH (20 mL) was added 1 N NaOH (19.2 mL, 19.2 mmol) at room temperature. The resulting mixture was stirred for 4 h before it was acidified with 2 N HCl. The aqueous layer was extracted with EtOAc. The combined organic layer was dried over Na_2SO_4, concentrated and purified by flash column chromatography (silica gel, ethyl acetate/petroleum ether, 1/2) to provide 3,3-bis(ethoxycarbonyl)hex-5-enoic acid **A.8** (3.51 g, 77%) as a colorless oil. IR (film, cm^{-1}) 2985, 1735, 1700, 1652, 1282, 1208, 1096, 927, 856; ^1H NMR (500 MHz, $CDCl_3$) δ 6.92 (dt, *J* = 15.5, 7.7 Hz, 1H), 5.87 (dd, *J* = 15.5, 0.8 Hz, 1H), 5.66-5.58 (m, 1H), 5.15 (dd, *J* = 2.8, 0.9 Hz, 1H), 5.12 (d, *J* = 0.9 Hz, 1H), 4.20 (q, *J* = 7.1 Hz, 4H), 2.78 (d, *J* =

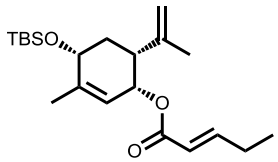
(2) De Riggi, I.; Gastaldi, S.; Surzur, J.-M.; Bertrand, M. P. *J. Org. Chem.* **1992**, *57*, 6118.

7.7 Hz, 2H), 2.65 (d, J = 7.4 Hz, 2H), 1.25 (t, J = 7.1 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.1, 170.1, 145.8, 131.7, 124.2, 119.8, 61.6, 56.9, 37.4, 35.3, 14.1; HRMS (ESI): calculated for $C_{14}H_{20}O_6$ [M+Li$^+$] 291.1420, found 291.1433.

To a solution of 5β-hydroxycarvone **3.7** (83 mg, 0.5 mmol), 3,3-bis(ethoxy carbonyl)hex-5-enoic acid **A.8** (426 mg, 1.5 mmol) and triphenylphosphine (394 mg, 1.5 mmol) in THF (2.5 mL) was added diethyl azodicarboxylate (0.68 mL, 40% in toluene, 1.5 mmol) dropwise at 0 °C under nitrogen. The resulting mixture was stirred at room temperature for 3 h, diluted with EtOAc (30 mL), washed with H_2O and brine. The organic layer was dried over Na_2SO_4, concentrated and purified by flash column chromatography (silica gel, ethyl acetate/petroleum ether, 1/5) to provide **3.10c** (121 mg, 56%) as light yellow oil. $[\alpha]_D^{19}$ -174.17 (*c* 1.81, $CHCl_3$); IR (film, cm^{-1}) 2985, 1726, 1685, 1649, 1448, 1173, 1045, 915; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.82-6.76 (m, 2H), 5.81 (d, J = 15.6 Hz, 1H), 5.65-5.56 (m, 2H), 5.13 (d, J =1.2, 1H), 5.10 (dd, J = 9.3, 1.9 Hz, 1H), 4.92 (s, 1H), 4.73 (s, 1H), 4.19-4.16 (m, 4H), 2.88-2.77 (m, 2H), 2.74 (dd, J = 7.7, 1.3 Hz, 2H), 2.62 (d, J = 7.5 Hz, 2H), 2.53 (dd, J = 15.2, 2.6 Hz, 1H), 1.83 (s, 3H), 1.76 (s, 3H), 1.29-1.18 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.2, 170.1, 170.1, 165.0, 143.9, 142.9, 138.8, 138.7, 131.7, 124.3, 119.7, 112.9, 66.3, 61.6, 56.9, 44.3, 37.9, 37.3, 35.3, 21.9, 15.6, 14.1; HRMS (ESI): calculated for $C_{24}H_{32}O_7$ [M+Li$^+$] 439.2308, found 439.2288.

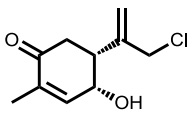


(*E*)-(1*R*,4*R*,6*R*)-4-Hydroxy-3-methyl-6-(prop-1-en-2-yl)cyclohex-2-en-1-yl pent-2-enoate (3.12a). To a solution of enone **3.10b** (19 mg, 0.076 mmol) in MeOH (1.5 mL) was added $CeCl_3 \cdot 7H_2O$ (43 mg, 0.12 mmol) at room temperature under nitrogen. The resulting suspension was stirred for 10 min, and cooled to -78 °C, then $NaBH_4$ (3.5 mg, 0.092 mmol) was added in one portion. Once the reaction was complete (typically <10 min), it was immediately quenched with saturated aqueous $NaHCO_3$. The aqueous phase was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, concentrated and purified by flash column chromatography (silica gel, ethyl acetate/petroleum ether, 1/4) to provide **3.12a** (17.5 mg, 92 %) as yellow oil. $[\alpha]_D^{19}$ -261.6 (*c* 2.02, $CHCl_3$); IR (film) 2967, 2875, 2854, 1714, 1694, 1653, 1448, 1285, 1178, 1119, 1093, 1045, 974, 918, 885; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.95 (dt, *J* = 15.6, 6.3 Hz, 1H), 5.80-5.65 (m, 2H), 5.44-5.32 (m, 1H), 4.85 (s, 1H), 4.74 (s, 1H), 4.14 (brs, 1H), 2.31 (d, *J* = 13.1 Hz, 1H), 2.25-2.03 (m, 3H), 1.95-1.84 (m, 1H), 1.83 (s, 3H), 1.75 (s, 3H), 1.04 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 166.3, 150.7, 144.6, 143.5, 121.9, 120.4, 111.6, 70.8, 66.8, 43.3, 32.2, 25.3, 22.0, 18.8, 12.1; HRMS (ESI): calculated for $C_{15}H_{22}O_3$ [M+Li$^+$] 257.1729, found 257.1724.



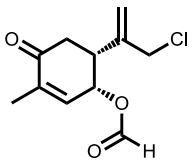
(*E*)-(1*R*,4*R*,6*R*)-4-((*tert*-Butyldimethylsilyl)oxy)-3-methyl-6-(prop-1-en-2-yl)cyclohex-2-en-1-yl pent-2-enoate (3.12b): To a solution of allyl alcohol **3.12a** (12 mg, 0.048 mmol) in CH_2Cl_2 (1 mL) was added 2,6-lutidine (14 µL, 0.12 mmol) and TBSOTf

(22 μL, 0.096 mmol) at 0 °C. After 15 min, the reaction was quenched with a sodium potassium phosphate buffer solution (pH = 7, 1 mL) and extracted with CH_2Cl_2 (3x10 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and dried over Na_2SO_4. After concentration in *vacuo*, the residue was purified by flash column chromatography (silica gel, ethyl acetate/petroleum ether, 1/15) to provide **3.12b** (16.7 mg, 97 %) as yellow oil. $[\alpha]_D^{19}$ -188.8 (*c* 1.58, $CHCl_3$); IR (film, cm^{-1}) 2958, 2928, 2854, 1717, 1646, 1253, 1179, 1105, 891, 832; ^1H NMR (300 MHz, $CDCl_3$) δ 6.96 (dt, *J* = 15.7, 6.3 Hz, 1H), 5.74 (dt, *J* = 15.6, 1.6 Hz, 1H), 5.65-5.63 (m, 1H), 5.36-5.33 (m, 1H), 4.85 (s, 1H), 4.73 (s, 1H), 4.14 (t, *J* = 8.0 Hz, 1H), 2.34-2.23 (m, 1H), 2.22-2.14 (m, 2H), 1.94-1.82 (m, 2H), 1.75 (s, 6H), 1.04 (t, *J* = 7.4 Hz, 3H), 0.92 (s, 9H), 0.11 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 166.4, 150.5, 144.9, 144.8, 121.0, 120.5, 111.5, 71.4, 66.8, 43.3, 32.5, 25.9, 25.6, 25.3, 22.1, 19.6, 12.1, -4.1, -4.9; HRMS (ESI): calculated for $C_{21}H_{36}O_3Si$ $[M+Li^+]$ 371.2594, found 371.2606.



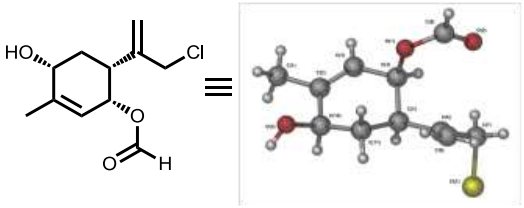
(4*S*,5*R*)-5-(3-Chloroprop-1-en-2-yl)-4-hydroxy-2-methylcyclohex-2-enone (3.16). To a suspension of calcium hypochlorite (1.50 g, 70% purity, 7.4 mmol) in water (3.4 mL) was added a solution of 5β-hydroxycarvone **3.7** (1.88 g, 11.3 mmol) in dichloromethane (34 mL). Approximately 10 g of dry ice was added in small portions to this mixture with stirring over a period of 2 h. At the end of this period, the reaction mixture was filtered to remove insoluble salts. The organic layer was separated, dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash column

chromatography (silica gel, eluted with ethyl acetate/petroleum ether = 1/2) provided product **3.16** (1.45 g, 64 %) as a yellow oil. $[\alpha]_D^{21}$ 106 (*c* 1.98, $CHCl_3$); IR (film) 2964, 2919, 1673, 1448, 1368, 1262, 1116, 1028, 891; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.70 (t, *J* = 1.8, 1H), 5.42 (s, 1H), 5.23 (s, 1H), 4.59 (d, *J* = 9.7 Hz, 1H), 4.16 (d, *J* = 11.8 Hz, 1H), 4.11 (d, *J* = 11.8 Hz, 1H), 2.91-2.82 (m, 1H), 2.60 (dd, *J* = 16.3, 4.0 Hz, 1H), 2.48-2.38 (m, 2H), 1.79 (t, *J* = 1.8, 3H);); ^{13}C NMR (75 MHz, $CDCl_3$) 197.9, 147.6, 144.1, 135.3, 118.2, 70.4, 48.4, 47.1, 41.7, 15.3; HRMS (ESI): calculated for $C_{10}H_{13}ClO_2$ [M+Cl^+] 235.0293, found 235.0288.

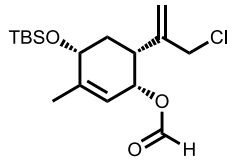


(1*R*,6*R*)-6-(3-Chloroprop-1-en-2-yl)-3-methyl-4-oxocyclohex-2-en-1-yl formate (3.17). To a solution of hydroxycarvone **3.16** (1.27 g, 6.3 mmol), formic acid (0.48 mL, 12.7 mmol) and triphenylphosphine (3.33 g, 12.7 mmol) in THF (63 mL) was added diethyl azodicarboxylate (5.78 mL, 40% in toluene, 12.7 mmol) dropwise at 0 °C under nitrogen. The resulting mixture was stirred at room temperature for 3h and then diluted with EtOAc (100 mL), washed with H_2O and brine. The organic lay was dried over Na_2SO_4, concentrated and purified by flash column chromatography (silica gel, eluted with ethyl acetate/petroleum ether = 1/5) to provide product **3.17** (1.01 g, 70 %) as a light yellow oil. $[\alpha]_D^{21}$ -245 (2.05, $CHCl_3$); IR (film) 2961, 2928, 1720, 1679, 1451, 1359, 1261, 1158, 912; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (d, *J* = 0.9 Hz, 1H), 6.76 (d, *J* = 5.8 Hz, 1H), 5.68 (brs, 1H), 5.38 (s, 1H), 5.06 (s, 1H), 4.18 (d, *J* = 12.0 Hz, 1H), 4.07 (d, *J* = 12.0 Hz, 1H), 3.28 (d, *J* = 12.9 Hz, 1H), 2.90-2.80 (m, 1H), 2.55(dd, *J* =

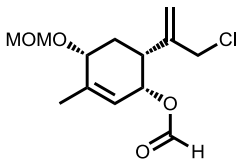
16.4, 3.9 Hz, 1H), 1.85 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 198.1, 160.1, 142.4, 139.6, 137.3, 118.1, 65.4, 47.2, 39.7, 37.4, 15.6; HRMS (ESI, MALDI): molecular ion was not observed.



(1*R*,4*R*,6*R*)-6-(3-chloroprop-1-en-2-yl)-4-hydroxy-3-methylcyclohex-2-en-1-yl formate (3.18). To a solution of ester **3.17** (920 mg, 4.0 mmol) in MeOH (80 mL) was added $CeCl_3 \cdot 7H_2O$ (2.26 g, 6.1 mmol) at room temperature under nitrogen. The resulting suspension was stirred for 10 min and cooled to -78 °C, then $NaBH_4$ (185 mg, 4.8 mmol) was added in one portion. Once the reaction was complete (typically <10 min), it was immediately quenched with saturated aqueous $NaHCO_3$. The aqueous phase was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, concentrated and purified by flash column chromatography (silica gel, eluted with ethyl acetate/petroleum ether = 1/2) to provide product **3.18** (857 mg, 92 %) as a yellow oil. $[\alpha]_D^{19}$-117 (*c* 2.35, $CHCl_3$); IR (film) 2952, 2925, 2872, 1712, 1451, 1170, 1042, 924, 888; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (s, 1H), 5.69-5.65 (m, 1H), 5.44 (brs, 1H), 5.30 (s, 1H), 5.05 (s, 1H), 4.25-4.02 (m, 3H), 2.76 (d, *J* = 13.2 Hz, 1H), 2.14-2.07 (m, 1H), 1.94-1.79 (m, 1H), 1.86 (s, 3H), 1.74 (d, *J* = 7.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$); 160.5, 144.8, 144.0, 120.6, 117.1, 70.4, 66.2, 47.5, 38.6, 31.8, 18.8; HRMS (MALDI): calculated for $C_{11}H_{15}ClO_3$ [M+Cl$^+$] 266.0471, found 266.0482.

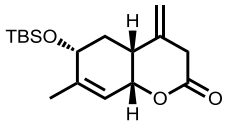


(1*R*,4*R*,6*R*)-4-((tert-Butyldimethylsilyl)oxy)-6-(3-chloroprop-1-en-2-yl)-3-methylcyclohex-2-en-1-yl formate (3.21a). To a solution of allyl alcohol **3.18** (857 mg, 3.7 mmol) in DMF (3.7 mL) was added imidazole (507 mg, 7.5 mmol) and TBSCl (841 mg, 5.6 mmol). The reaction was stirred at room temperature for 3h before it was diluted with EtOAc. The organic layer was washed with H_2O, brine, and dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified by flash column chromatography (silica gel, eluted with ethyl acetate/petroleum ether = 1/20) to provide **3.21a** (1.23 g, 96 %) as a yellow oil. $[\alpha]_D^{19}$ -152 (*c* 2.19, $CHCl_3$); IR (film) 2958, 2934, 2860, 1717, 1256, 1173, 1096, 1060, 903, 838; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (s, 1H), 5.62 (d, *J* = 5.4 Hz, 1H), 5.43-5.40 (m, 1H), 5.29 (s, 1H), 5.04 (s, 1H), 4.22-4.02 (m, 3H), 2.73 (t, *J* = 9.5 Hz, 1H), 1.95-1.88 (m, 2H), 1.78 (s, 3H), 0.92 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$); 160.5, 146.0, 144.3, 119.7, 116.9, 70.9, 66.2, 47.5, 38.6, 32.1, 25.8, 19.6, 18.1, -4.1, -4.9; HRMS (ESI): calculated for $C_{17}H_{29}ClO_3Si$ [M+Li$^+$] 351.1735, found 351.1739.



(1*R*,4*R*,6*R*)-6-(3-Chloroprop-1-en-2-yl)-4-(methoxymethoxy)-3-methylcyclo hex-2-en-1-yl formate (3.21b): To a solution of allyl alcohol **3.18** (400 mg, 1.73 mmol) in dichloromethane (11 mL) was added *N*, *N*-diisopropylethylamine (0.58 mL, 3.46

mmol). The reaction mixture was cooled to 0 °C before methyl chloromethyl ether (2.1 mL, 2.1 M in toluene, 4.35 mmol) was introduced. The solution was stirred at room temperature for 12 h before it was poured into water (20 mL) and extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4. After concentration in *vacuo*, the residue was purified by flash column chromatography (silica gel, ethyl acetate/petroleum ether, 1/5) to provide **3.21b** (450 mg, 95 %) as yellow oil. $[\alpha]_D^{21}$ -209.4 (*c* 0.71, $CHCl_3$); IR (film, cm^{-1}) 2949, 2931, 2890, 1720, 1173, 1143, 1101, 1034, 927; ^1H NMR (500 MHz, $CDCl_3$) δ 7.97 (s, 1H), 5.70 (d, *J* = 5.5Hz, 1H), 5.43 (brs, 1H), 5.30 (s, 1H), 5.06 (s, 1H), 4.82 (d, *J* = 6.9 Hz, 1H), 4.70 (d, *J* = 6.9 Hz, 1H), 4.16 (d, *J* = 11.9, 1H), 4.14-4.10 (m, 1H), 4.04 (d, *J* = 11.9, 1H), 3.44 (s, 3H), 2.73 (d, *J* = 13.5 Hz, 1H), 2.17-2.12 (m, 1H), 1.96-1.88 (m, , 1H), 1.83 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 160.5, 144.2, 143.8, 121.2, 117.1, 95.8, 75.5, 65.9, 55.7, 47.5, 38.4, 28.9, 19.3; HRMS (ESI): molecular ion not observed.

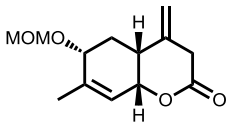


(4a*R*,6*R*,8a*R*)-6-((tert-Butyldimethylsilyl)oxy)-7-methyl-4-methylene-3,4,4a,5,6,8a-hexahydro-2*H*-chromen-2-one (3.23a). To a solution of allyl chloride **3.21a** (0.98 g, 2.8 mmol) in acetone (28 mL) was added anhydrous NaI (4.29 g, 28 mmol) at room temperature. The resulting mixture was stirred overnight before it was concentrated. The mixture was suspended in ether (20 mL) and filtered through a short pad of silica gel. After concentration *in vacuo*, the crude allyl iodide was used without further purification.

To an ice-cold solution of SmI_2 (200 mL, 0.1 M in THF, 18.9 mmol) was added a solution of the above allyl iodide (1.19 g, 2.7 mmol) in dry THF (10 mL) via cannula under nitrogen. The deep blue mixture was stirred at 0 °C for 10 min before it was quenched by a mixture of saturated aqueous $NaHCO_3$ (40 mL) and sodium potassium phosphate buffer solution (pH = 7, 40 mL). After 15 min, the reaction mixture was extracted with EtOAc. The combined organic layers were washed with water, saturated aqueous $NaHCO_3$, brine, and dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified by flash column chromatography (silica gel, eluted with ethyl acetate/petroleum ether = 1/2) to provide lactols **3.22a** (1:1 mixture of epimers, 643 mg, 73%) as a colorless oil.

To a solution of lactols **3.22a** (100 mg, 0.32 mmol) in DMSO (3 mL) was added IBX (180 mg, 0.64 mmol) at room temperature. The resulting mixture was stirred at 40 °C. The reaction was quenched with H_2O (3 mL) when it was complete (monitored by ^1H NMR due to similar R_f of **3.22a** and **3.23a** on TLC). The mixture was filtered and the aqueous phase was extracted with EtOAc. The combined organic layers were washed with brine, and dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified by column chromatography (silica gel, eluted with ethyl acetate/petroleum ether = 1/2) to provide the product **3.23a** (72 mg, 72%) as a light yellow oil. $[\alpha]_D^{21}$ -0.23 (*c* 1.5, $CHCl_3$); IR (film) 2955, 2925, 2851, 1750, 1643, 1250, 1096, 832; ^1H NMR (300 MHz, $CDCl_3$) δ 5.59 (d, *J* = 5.0 Hz, 1H), 5.05 (s, 1H), 5.03 (s, 1H), 4.66 (t, *J* = 4.5 Hz, 1H), 4.20-4.15 (m, 1H), 3.26 (s, 2H), 2.71 (d, *J* = 13.0 Hz, 1H), 1.92-1.70 (m, 2H), 1.79 (s, 3H), 0.89 (s, 9H), 0.10 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 170.3,

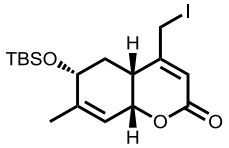
146.7, 140.1, 118.9, 112.9, 73.4, 69.9, 37.9, 37.3, 34.5, 25.8, 19.8, 18.0, -4.1, -4.9; HRMS (ESI): calculated for $C_{17}H_{28}O_3Si$ [M+H$^+$] 309.1886, found 309.1874.



(4a*R*,6*R*,8a*R*)-6-(Methoxymethoxy)-7-methyl-4-methylene-3,4,4a,5,6,8a-hexahydro-2*H*-chromen-2-one (3.23b): To a solution of allyl chloride **3.21b** (450 mg, 1.64 mmol) in acetone (16 mL) was added anhydrous NaI (2.46 g, 16.4 mmol) at room temperature. The resulting mixture was stirred overnight before it was concentrated. The mixture was suspended in ether (20 mL) and filtered through a short pad of silica gel. After concentration in vacuo, the crude allyl iodide was used without further purification.

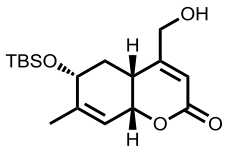
To an ice-cold solution of SmI_2 (93 mL, 0.1 M in THF, 9.28 mmol) was added a solution of the above allyl iodide (485 mg, 1.32 mmol) in dry THF (5 mL) via cannula under nitrogen. The deep blue mixture was stirred at 0 °C for 10 min before it was quenched by a mixture of saturated aqueous $NaHCO_3$ (30 mL) and a sodium potassium phosphate buffer solution (pH = 7, 30 mL). After 15 min, the reaction mixture was extracted with EtOAc. The combined organic layers were washed with water, saturated aqueous $NaHCO_3$, brine, and dried over Na_2SO_4. After concentration in vacuo, the residue was purified by flash column chromatography (silica gel, eluted with ethyl acetate/petroleum ether = 1/2) to provide lactols **3.22b** (1:1 mixture of epimers, 258 mg, 76%) as colorless oil.

To a solution of lactols **3.22b** (113 mg, 0.47 mmol) in DMSO (4 mL) was added 2-iodoxybenzoic acid (266 mg, 0.95 mmol) at room temperature. The resulting mixture was stirred at 45 °C. The reaction was quenched with H_2O (3 mL) when it was complete. The mixture was filtered and the aqueous phase was extracted with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4. After concentration in vacuo, the residue was purified by column chromatography (silica gel, eluted with ethyl acetate/petroleum ether = 1/2) to provide **3.23b** (84 mg, 75%) as light yellow oil. $[\alpha]_D^{21}$ -27.12 (*c* 2.12, $CHCl_3$); IR (film, cm^{-1}) 2949, 2925, 2889, 1741, 1448, 1241, 1152, 1102, 1028, 968, 906; ^1H NMR (500 MHz, $CDCl_3$) δ 5.69-5.66 (m, 1H), 5.08-5.06 (m, 2H), 4.79 (d, *J* = 7.0 Hz, 1H), 4.69-4.67 (m, 1H), 4.67 (d, *J* = 7.0 Hz, 1H), 4.12-4.09 (m, 1H), 3.41 (s, 3H), 3.31 (d, *J* = 17.6 Hz, 1H), 3.25 (d, *J* = 17.6 Hz, 1H), 2.72 (d, *J* = 13.2 Hz, 1H), 2.23-2.09 (m, 1H), 1.85 (s, 3H), 1.80-1.73 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.2, 144.5, 139.8, 120.2, 113.1, 95.8, 74.6, 73.0, 55.7, 37.9, 36.9, 31.2, 19.4; HRMS (ESI): calculated for $C_{13}H_{18}O_4$ $[M+H^+]$ 239.1284, found 239.1288.



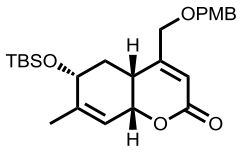
(4a*R*,6*R*,8a*R*)-6-((tert-Butyldimethylsilyl)oxy)-4-(iodomethyl)-7-methyl-4a,5,6,8a-tetrahydro-2*H*-chromen-2-one (3.31). To a solution of β, γ-unsaturated lactone **3.23a** (320 mg, 1.0 mmol) in toluene (20 mL) was added $Hg(OAc)_2$ (364 mg, 1.1 mmol) under nitrogen. The mixture was stirred at 80 °C for 2 h. The reaction was cooled to room temperature and treated with aqueous KCl (619 mg, 8.3 mmol) in 5 mL of H_2O. The mixture was stirred for 30 min, diluted with EtOAc, washed with brine, and dried

over Na_2SO_4. After concentration *in vacuo*, the residue was dissolved in CH_2Cl_2 (10 mL). To this mixture was added a solution of I_2 (527 mg, 2.1 mmol) in CH_2Cl_2 (10 mL) under nitrogen. The resulting mixture was stirred for 30 min, quenched with saturated aqueous $Na_2S_2O_3$ (10 mL), diluted with EtOAc, washed with water, and dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified by column chromatography (silica gel, eluted with ethyl acetate/petroleum ether = 1/5) to provide allyl iodide **3.31** (367 mg, 81%) as a white solid. $[\alpha]_D^{21}$ -3.24 (*c* 1.03, $CHCl_3$); IR (film) 2955, 2922, 2854, 1709, 1250, 1090, 974, 832; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.07 (s, 1H), 5.65 (d, *J* = 5.0 Hz, 1H), 4.70 (t, *J* = 4.3 Hz, 1H), 4.17 (dd, *J* = 9.9, 5.8 Hz, 1H), 4.05 (d, *J* = 9.8 Hz, 1H), 4.00 (d, *J* = 9.8 Hz, 1H), 2.67 (dt, *J* = 13.3, 3.3 Hz, 1H), 2.02-1.94 (m, 1H), 1.82 (s, 3H), 1.80-1.67 (m, 1H), 0.90 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 163.7, 158.2, 146.3, 119.1, 117.3, 72.9, 69.8, 34.8, 32.2, 25.7, 19.8, 18.0, 2.9, -4.1, -4.9; HRMS (ESI): calculated for $C_{17}H_{27}IO_3Si$ [M+H$^+$] 435.0853, found 435.0861.



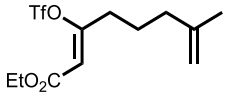
(4a*R*,6*R*,8a*R*)-6-((tert-Butyldimethylsilyl)oxy)-4-(hydroxymethyl)-7-methyl-4a,5,6,8a-tetrahydro-2H-chromen-2-one (3.32). To a solution of allyl iodide **3.31** (367 mg, 0.80 mmol) in DMF (10 mL) was added $NaHCO_3$ (852 mg, 10.1 mmol) and formic acid (64 μl, 1.7 mmol) at room temperature under nitrogen. The mixture was stirred for 3 h before MeOH (12 mL) and H_2O (8 mL) were added. After additional 1 h, the mixture was concentrated. The residue was taken into EtOAc, washed with H_2O, brine, and dried

over Na_2SO_4. After concentration *in vacuo*, the residue was purified by column chromatography (silica gel, eluted with acetate/petroleum ether = 2/1) to provide the product **3.32** (237 mg, 86%) as a white solid. $[\alpha]_D^{18}$ -113 (*c* 2.02, $CHCl_3$); IR (film) 2958, 2925, 2854, 1682, 1253, 1105, 980, 888, 935; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.05 (s, 1H), 5.63 (d, *J* = 5.0 Hz, 1H), 4.67 (t, *J* = 4.3 Hz, 1H), 4.41-4.26 (m, 2H), 4.14 (dd, *J* = 9.4, 5.8 Hz, 1H), 2.34 (dt, *J* = 13.4, 3.3 Hz, 1H), 1.97-1.90 (m, 1H), 1.80 (s, 3H), 1.76-1.64 (m, 1H), 0.88 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 164.6, 162.1, 146.4, 119.1, 113.9, 72.7, 69.9, 62.6, 33.2, 32.2, 25.7, 19.8, 18.0, -4.2, -4.9; HRMS (ESI): calculated for $C_{17}H_{28}O_4Si$ [M+H$^+$] 325.1835, found 325.1823.



(4a*R*,6*R*,8a*R*)-6-((tert-Butyldimethylsilyl)oxy)-4-(((4-methoxybenzyl) oxy)methyl)-7-methyl-4a,5,6,8a-tetrahydro-2*H*-chromen-2-one (3.4). To a solution of allyl alcohol **3.32** (160 mg, 0.49 mmol) in CH_2Cl_2 (10 mL) was added freshly prepared *p*-(methoxybenzyl)-trichloroacetimidate (PMBTCA) (180 mg, 0.64 mmol) and *p*TSA (28 mg, 0.15 mmol). The mixture was stirred at room temperature for 5 h before it was diluted with EtOAc. The organic layer was washed with saturated aqueous $NaHCO_3$, H_2O, brine, and dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified by column chromatography (silica gel, eluted with ethyl acetate/petroleum ether = 1/2) to give **3.4** (200 mg, 93%) as a white solid. $[\alpha]_D^{18}$ -65.6 (*c* 0.26, $CHCl_3$); IR (film) 2958, 2928, 2857, 1703, 1516, 1247, 1108, 977, 835; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.6 Hz, 2H), 6.90 (d, *J* = 8.1 Hz, 2H), 6.03 (s, 1H), 5.63 (d, *J* = 5.1 Hz,

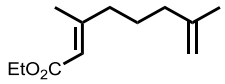
1H), 4.65 (t, J = 4.3, 1H), 4.54 (d, J = 11.6 Hz, 1H), 4.45 (d, J = 11.5 Hz, 1H), 4.21-4.08 (m, 3H), 3.82 (s, 3H), 2.37 (dt, J = 13.3, 3.1 Hz, 1H), 2.00-1.85 (m, 1H), 1.80 (s, 3H), 1.77-1.61 (m, 1H), 0.89 (s, 9H), 0.09 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.2, 159.5, 159.1, 146.4, 129.5, 129.2, 119.2, 115.7, 114.0, 72.6, 72.6, 70.0, 69.1, 55.3, 33.3, 32.0, 25.7, 19.7, 18.0, -4.2, -4.9; HRMS (ESI): calculated for $C_{25}H_{36}O_5Si$ [M+H$^+$] 445.2410, found 445.2397



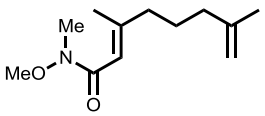
(*Z*)-Ethyl 7-methyl-3-(((trifluoromethyl)sulfonyl)oxy)octa-2,7-dienoate (3.35)

A well-stirred solution of **3.34**[46a] (7.93 g, 40 mmol) in hexanes (200 mL, 0.2 M) was cooled with an ice bath to 5-10 °C (internal temperature) and treated with a saturated aqueous solution of LiOH (60 mL, ~300 mmol) slowly. The resulting biphasic mixture was vigorously stirred at 5-10°C for ~ 5 minutes before dropwise addition of triflic anhydride (16.82 mL, 100 mmol) at a rate that maintained the internal temperature between 5-15 ºC. Upon completion of the reaction (as judged by TLC, typically <10 min), triethylamine (20 mL) was added slowly followed by H_2O (50 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2x100 mL). The combined organic layers were washed with H_2O, brine, and dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified by flash column chromatography (silica gel, eluted with EtOAc/petroleum ether = 1/10) to provide product **3.35** (12.99 g, 98 %) as a light yellow liquid. IR (film) 3079, 2987, 2946, 1732, 1673, 1427, 1211, 1137, 1027, 921 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.76 (s, 1H), 4.77 (s, 1H), 4.68 (s, 1H),

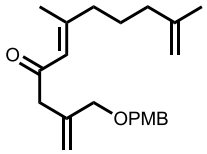
4.24 (q, J = 7.1 Hz, 2H), 2.37(t, J = 7.6 Hz, 2H), 2.07 (t, J = 7.4 Hz, 2H), 1.77-1.69 (m, 5H), 1.30 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.4, 158.6, 143.8, 118.3 (q, J = 319 Hz), 112.0, 111.3, 61.2, 35.4, 33.8, 23.5, 22.0, 14.0; HRMS (ESI): calculated for $C_{12}H_{17}F_3O_5S^+$ [M+H$^+$] 331.0827, found 331.0824.



(*E*)-Ethyl 3,7-dimethylocta-2,7-dienoate (3.36). To a stirred suspension of CuCN (3.46 g, 38.6 mmol) in dry ether (80 mL), methylmagnesium bromide (3M in ether, 7.8 mL, 23.2 mmol) was added dropwise at –78 °C under nitrogen and the resulting suspension was stirred at 0 °C for 5 min. The suspension was re-cooled to –78 °C and a solution of enol triflate **3.35** (5.10 g, 15.5 mmol) in ether (10 mL) was added dropwise. After 15 min at –78 °C, the reaction mixture was quenched with saturated aqueous NH_4Cl. The aqueous layer was extracted with ethyl acetate and the combined organic layers were dried with Na_2SO_4 and concentrated. The residue was purified by flash column chromatography (silica gel, eluted with EtOAc/petroleum ether = 1/20) to provide product **3.36** (2.88 g, 95 %) as a light yellow liquid. IR (film) 3076, 2981, 2934, 1712, 1643, 1371, 1226, 1143, 1030, 885 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.65 (s, 1H), 4.70 (s, 1H), 4.65 (s, 1H),, 4.12 (q, J = 6.9 Hz, 2H), 2.13-2.08 (m, 5H), 1.98 (t, J = 7.7 Hz, 2H), 1.68 (s, 3H), 1.64-1.54 (m, 2H), 1.25 (t, J = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8, 159.8, 145.1, 115.6, 110.3, 59.4, 40.3, 37.1, 25.2, 22.2, 18.7, 14.3; HRMS (ESI): calculated for $C_{12}H_{20}O_2$ [M+H$^+$] 197.1542, found 197.1550.

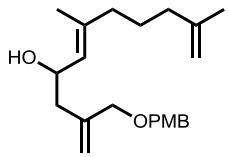


(*E*)-*N*-Methoxy-*N*,3,7-trimethylocta-2,7-dienamide (3.37). To a solution of *E*-alkenoic ester **3.36** (904 mg, 4.61 mmol) and *N*,*O*-dimethylhydroxyamine hydrochloride (899 mg, 9.22 mmol) in THF (12 mL) was added *i*-PrMgCl (10.4 mL, 2 M in THF, 20.75 mmol) dropwise at -5 °C. The mixture was stirred for 30 min and quenched with sat. aq. NH_4Cl (30 mL). The mixture was extracted with ethyl acetate. The combined organic layers were washed with brine and dried over Na_2SO_4. After concentration in *vacuo*, the residue was purified by flash column chromatography (silica gel, ethyl acetate/petroleum ether = 1/5) to give Weinreb amide **3.37** (896 mg, 92% yield) as colorless oil. IR (film, cm^{-1}) 2970, 2940, 1658, 1635, 1436, 1362, 1173, 1099, 980, 883; ^1H NMR (300 MHz, $CDCl_3$) δ 6.10 (s, 1H), 4.71 (s, 1H), 4.67 (s, 1H), 3.65 (s, 3H), 3.20 (s, 3H), 2.15-2.10 (m, 5H), 2.01 (t, *J* = 7.5, 2H), 1.70 (s, 3H), 1.66-1.56 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) 145.3, 114.0, 110.2, 61.3, 40.6, 37.2, 25.4, 22.3, 18.6; HRMS (ESI): calculated for $C_{12}H_{21}NO_2$ [$M+H^+$] 212.1651, found 212.1653.



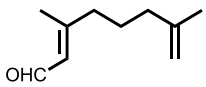
(*E*)-2-(((4-Methoxybenzyl)oxy)methyl)-6,10-dimethylundeca-1,5,10-trien-4-one (3.39). To a well-stirred suspension of magnesium turnings (1.38 g, 57.0 mmol) in anhydrous THF (12 mL) was added 1,2-dibromoethane (0.17 mL, 1.97 mmol) under nitrogen. The reaction mixture was stirred at room temperature for 30 min and a solution of the corresponding allyl chloride (1.77 g, 7.86 mmol) in anhydrous THF (4 mL) was introduced dropwise in 30 min. After an additional 1.5 h, the freshly prepared Grignard

reagent was transferred to Weinreb amide **3.37** (565 mg, 2.68 mmol) in THF (10 mL) at -78 °C via cannula. The reaction mixture was stirred at -78 °C for 30 min and quenched with aqueous NH_4Cl. After warming to room temperature, the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with H_2O, brine and dried over Na_2SO_4. After concentration in *vacuo*, the residue was purified by flash column chromatography (silica gel, ethyl acetate/petroleum ether, 1/10) to give **3.39** (910 mg, 98% yield) as colorless oil. IR (film, cm^{-1}) 2937, 2854, 1679, 1611, 1513, 1244, 1173, 1099, 1028, 883, 814; ^1H NMR (300 MHz, $CDCl_3$) δ 7.28 (d, J = 8.1 Hz, 2H), 6.90 (d, J = 8.7 Hz, 2H), 6.14 (s, 1H), 5.27 (s, 1H), 5.07 (s, 1H), 4.76 (s, 1H), 4.71 (s, 1H), 4.44 (s, 2H), 4.01 (s, 2H), 3.83 (s, 3H), 3.24 (s, 2H), 2.16-2.11 (m, 5H), 2.03 (t, J = 7.6 Hz, 2H), 1.74 (s, 3H), 1.68-1.58 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) 198.2, 159.6, 159.1, 145.2, 140.4, 130.3, 129.3, 122.7, 115.9, 113.7, 110.4, 72.7, 71.8, 55.3, 48.8, 40.7, 37.2, 25.3, 22.3, 18.4; HRMS (ESI): calculated for $C_{22}H_{30}O_3$ [$M+H^+$] 343.2273, found 343.2278.



(*E*)-2-(((4-Methoxybenzyl)oxy)methyl)-6,10-dimethylundeca-1,5,10-trien-4-ol (3.6): A solution of (*R*)-(+)-2-methyl-CBS-oxazaborolidine (60 μL, 0.06 mmol) in THF (0.3 mL) was treated with BH_3·DMS (30 μL, 2 M in THF, 0.06 mmol) at room temperature. After stirring for 15 min, the mixture was cooled to -78 °C and a solution of enone **3.39** (17 mg, 0.05 mmol) in THF (0.3 mL) was added through cannula. The

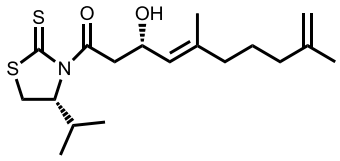
reaction was stirred at -78 °C for 3 h before it was slowly warmed to room temperature. The reaction was quenched by the addition of MeOH followed by H_2O. The aqueous phase was extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4. After concentration in *vacuo*, the residue was purified by flash column chromatography (silica gel, ethyl acetate/petroleum ether, 1/2) to give racemic **3.6** (14.6 mg, 85% yield) as colorless oil.. IR (film, cm^{-1}) 2935, 2854, 1649, 1617, 1513, 1442, 1247, 1170, 1037, 891, 820; ^1H NMR (500 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 5.20 (d, *J* = 8.4 Hz, 1H), 5.16 (s, 1H), 5.05 (s, 1H), 4.70 (s, 1H), 4.67 (s, 1H), 4.52-4.48 (m, 1H), 4.47 (d, *J* = 11.7 Hz, 1H), 4.45 (d, *J* = 11.5 Hz, 1H), 3.99 (d, *J* = 11.3 Hz, 1H), 3.95 (d, *J* = 11.9 Hz, 1H), 3.80 (s, 3H), 2.35-2.26 (m, 2H), 1.98 (t, *J* = 7.7 Hz, 4H), 1.71 (s, 3H), 1.66 (d, *J* = 1.3 Hz, 3H), 1.58-1.51 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) 159.2, 145.8, 142.8, 138.2, 129.9, 129.5, 127.3, 116.3, 113.8, 109.9, 73.2, 72.0, 67.2, 55.3, 42.7, 39.0, 37.3, 25.6, 22.4, 16.6; HRMS (ESI): calculated for $C_{22}H_{32}O_3$ $[M+Li^+]$ 351.2511, found 351.2503.



(*E*)-3,7-Dimethylocta-2,7-dienal (1.62). To a well-stirred solution of *E*-alkenoic ester **3.36** (3.29 g, 16.7 mmol) in THF (110 mL) was added DIBAL-H (1 M in Hexane, 50.1 mL, 50.1 mmol) at -78 °C under N_2. The reaction was stirred at -78 °C for 2h before it was quenched by EtOAc (5 mL) and saturated aqueous Rochelle salt (50 mL). The mixture was stirred at room temperature until it became clear. The mixture was extracted with CH_2Cl_2 and the combined organic layers were dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified by flash column chromatography (silica

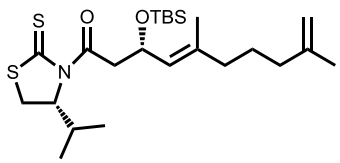
gel, eluted with EtOAc/petroleum ether = 1/2) to provide allyl alcohol (2.51 g, 97 %) as a light yellow liquid. IR (film) 3073, 2966, 2931, 1649, 1442, 1371, 1001, 886; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.42 (t, *J* = 6.3 Hz, 1H), 4.71 (s, 1H), 4.67 (s, 1H), 4.15 (d, *J* = 6.9 Hz, 2H), 2.11-1.91 (m, 4H), 1.71 (s, 3H), 1.67 (s, 3H), 1.63-1.49 (m, 2H), 1.39-1.21 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 145.8, 139.6, 123.4, 109.9, 59.3, 39.1, 37.4, 25.6, 22.4, 16.2; HRMS (ESI): molecular ion was not observed.

To a well stirred solution of allyl alcohol (2.30 g, 14.9 mmol) in CH_2Cl_2 (75 mL) was added Dess-Martin periodinane (7.59 g, 17.9 mmol) at 0 °C. The mixture was stirred at this temperature for 2 h and quenched with saturated aqueous $NaHCO_3$ (30 mL). It was extracted with CH_2Cl_2, dried over Na_2SO_4, filtered and concentration *in vacuo*. The residue was purified by flash column chromatography (silica gel, eluted with ether/petroleum ether = 1/2) to provide product **1.62** (2.18 g, 96 %) as a light yellow liquid. IR (film) 3073, 2937, 2860, 1676, 1442, 1374, 1193, 1116, 883 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.98 (d, *J* = 8.1 Hz, 1H), 5.88 (d, *J* = 8.1 Hz, 1H), 4.73 (s, 1H), 4.67 (s, 1H), 2.22-2.15 (m, 5H), 2.02 (t, *J* = 7.5 Hz, 2H), 1.70 (d, *J* = 0.7 Hz, 3H), 1.70-1.57 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 191.3, 164.0, 144.8, 127.4, 110.5, 40.0, 37.1, 24.9, 22.2, 17.5; HRMS (ESI): calculated for $C_{10}H_{16}O$ [M+H$^+$] 153.1279, found 153.1283.

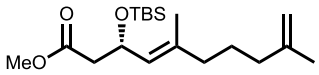


(*S*,*E*)-3-Hydroxy-1-((*R*)-4-isopropyl-2-thioxothiazolidin-3-yl)-5,9-dimethyl deca-4,9-dien-1-one (1.64). To a suspension of tin (II) triflate (5.84 g, 14.0 mmol) in

CH_2Cl_2 (29 mL) was added *N*-ethylpiperidine (1.93 mL, 14.0 mmol) at -78 °C under nitrogen. From a separate flask, thione **1.63** (2.44 g, 12.0 mmol) in CH_2Cl_2 (12 mL) was added to the cold tin triflate mixture via a cannula. The reaction was allowed to warm to –50 ºC and was stirred for 4 h before cooling back to –78 ºC. In a separate flask, aldehyde **1.62** (1.52 g, 10 mmol) was dissolved in CH_2Cl_2 (9 mL) and cooled to –78 ºC before it was added to the enolate solution over 15 minutes. After being stirred for an additional hour, the reaction mixture was quenched with pH = 7 phosphate buffer (30 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified by flash column chromatography (silica gel, eluted with ethyl acetate/petroleum ether = 1/5) to provide product **1.64** (2.86 g, 80 %) as a yellow oil. $[\alpha]_D^{22}$ -319 (*c* 2.00, $CHCl_3$); IR (film) 2964, 2934, 1691, 1368, 1252, 1155, 1039, 880; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.25 (d, *J* = 8.6, 1H), 5.18-5.13 (m, 1H), 4.91 (td, *J* = 8.7, 3.0 Hz, 1H), 4.69 (s, 1H), 4.66 (s, 1H), 3.57-3.49 (m, 2H), 3.32 (dd, *J* = 17.7, 8.8 Hz, 1H), 3.03 (d, *J* = 11.5, 1H), 2.65 (brs, 1H), 2.43-2.31 (m, 6.8 Hz, 1H), 2.01-1.95 (m, 4H), 1.71 (s, 6H), 1.60-1.50 (m, 2H), 1.06 (d, *J* = 6.8 Hz, 3H), 0.98 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 202.9, 172.8, 145.7, 139.4, 125.3, 110.0, 71.4, 65.1, 45.7, 39.0, 37.3, 30.8, 30.6, 25.5, 22.4, 19.1, 17.8, 16.7; HRMS (ESI): calculated for $C_{18}H_{29}NO_2S_2$ [M+H$^+$] 356.1718, found 356.1731.

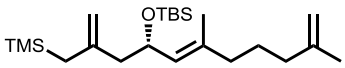


(*S*,*E*)-3-((tert-Butyldimethylsilyl)oxy)-1-((*R*)-4-isopropyl-2-thioxothiazolidin-3-yl)-5,9-dimethyldeca-4,9-dien-1-one (3.40). To a solution of aldol product **1.64** (2.80 g, 7.9 mmol) in CH_2Cl_2 (74 mL) at 0 °C was added 2,6-lutidine (2.29 mL, 19.7 mmol) and TBSOTf (3.62 mL, 15.8 mmol). After being stirred for 15 min, the reaction was quenched with a pH = 7 sodium potassium phosphate buffer solution (50 mL) and extracted with CH_2Cl_2. The combined organic extracts were washed with saturated aqueous $NaHCO_3$ and dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified by flash column chromatography (silica gel, eluted with ethyl acetate/petroleum ether = 1/20) to provide product **3.40** (3.66 g, 99 %) as a yellow oil. $[\alpha]_D^{22}$ -238 (*c* 2.21, $CHCl_3$); IR (film) 2961, 2934, 2860, 1670, 1466, 1362, 1250, 1155, 1078, 826; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.17 (d, *J* = 8.9 Hz, 1H), 5.02-4.95 (m, 2H), 4.70 (s, 1H), 4.66 (s, 1H), 3.72 (dd, *J* = 16.1, 8.7 Hz, 1H), 3.45 (dd, *J* = 11.4, 7.8 Hz, 1H), 3.04-2.93 (m, 2H), 2.44-2.33 (m, 1H), 2.00-1.92 (m, 4H), 1.70 (s, 3H), 1.66 (s, 3H), 1.58-1.47 (m, 2H), 1.05 (d, *J* = 6.8 Hz, 3H), 0.97 (d, *J* = 6.9 Hz, 3H), 0.83 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 202.8, 171.4, 145.8, 135.9, 127.8, 109.9, 71.8, 67.0, 46.1, 38.9, 37.3, 31.0, 30.8, 25.8, 25.5, 22.4, 19.1, 18.0, 17.8, 16.6, -4.2, -4.9; HRMS (ESI): calculated for $C_{24}H_{43}NO_2S_2Si_2$ [M+Li^+] 476.2650, found 476.2628.



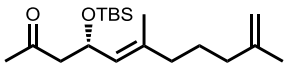
(*S*,*E*)-Methyl 3-((tert-butyldimethylsilyl)oxy)-5,9-dimethyldeca-4,9-dienoate (3.41). To a solution of thione **3.40** (3.38 g, 7.21 mmol) in MeOH (36 mL) at 0 °C was added K_2CO_3 (300 mg, 2.16 mmol). After 3 h, the solution was allowed to warm to room temperature and stirred for an additional 3 h during which the yellow color disappeared.

The reaction mixture was diluted with saturated aqueous NH_4Cl (50 mL) and extracted with Et_2O (3x50 mL). The combined organic extracts were washed with brine and dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified by flash column chromatography (silica gel, eluted with ethyl acetate/petroleum ether = 1/20) to provide product **3.41** (2.40 g, 98 %) as a clear oil. $[\alpha]_D^{22}$ -6.79 (*c* 1.99, $CHCl_3$); IR (film) 2958, 2937, 2863, 1738, 1439, 1250, 1149, 1075, 835; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.14 (d, *J* = 8.8 Hz, 1H), 4.87-4.79 (m, 1H), 4.70 (s, 1H), 4.66 (s, 1H), 3.64 (s, 3H), 2.53 (dd, *J* = 14.2, 8.6 Hz, 1H), 2.34 (dd, *J* = 14.2, 4.9 Hz, 1H), 1.99-1.92 (m, 4H), 1.70 (s, 3H), 1.65 (d, *J* = 1.1 Hz, 3H), 1.57-1.47 (m, 2H), 0.84 (s, 9H), 0.02 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 171.6, 145.7, 136.0, 127.7, 109.9, 66.9, 51.4, 43.7, 38.9, 37.2, 25.7, 25.5, 22.4, 18.0, 16.4, -4.3, -5.1; HRMS (ESI): calculated for $C_{19}H_{36}O_3Si$ [M+Li^+] 347.2594, found 347.2587.



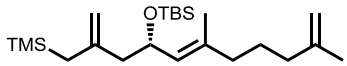
(*S*,*E*)-tert-Butyl((6,10-dimethyl-2-((trimethylsilyl)methyl)undeca-1,5,10-trien -4-yl)oxy) dimethylsilane (3.42). Powdered $CeCl_3 \cdot 7H_2O$ (2.80 g, 7.5 mmol) was dried in a flask at 130-140 °C overnight before it was cooled to room temperature, and maintained in a dry-nitrogen atmosphere. Dry THF (6 mL) was added, and the mixture was stirred at room temperature for 2 h before the slurry was cooled to -78 °C and treated with trimethylsilylmethyllithium (1 M in pentane, 7.5 mL, 7.5 mmol). The suspension was stirred at -78 °C for 1 h, at which time the ester **3.41** (0.51 g, 1.5 mmol) was added over 2-3 minutes. Stirring was continued for 2 h at -78 °C. Then the reaction was allowed to warm to room temperature overnight. After quenching with 1 M HCl (30

mL), the crude *bis*(trimethylsilylmethy1)carbinol was isolated by extraction with CH_2Cl_2, drying over Na_2SO_4, and concentrated *in vacuo*. The subsequent Petersen elimination was accomplished by stirring the crude with 1.5 g of silica gel (column chromatography grade) and 15 mL of CH_2C1_2 for 2-3 h. After concentration *in vacuo*, the residue was purified by flash chromatography to provide the allylsilane **3.42** (0.51 g, 86%) as a light yellow oil. $[\alpha]_D^{22}$ -0.51 (*c* 2.3, $CHCl_3$); IR (film) 2955, 2928, 2857, 1250, 1066, 832; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.14 (d, *J* = 7.4 Hz, 1H), 4.70 (s, 1H), 4.67 (s, 1H), 4.60 (s, 1H), 4.54 (s, 1H), 4.52-4.44 (m, 1H), 2.18 (dd, *J* = 13.4, 7.2 Hz, 1H), 2.04-1.93 (m, 5H), 1.71 (s, 3H), 1.61 (s, 3H), 1.56-1.49 (m, 4H), 0.87 (s, 9H), 0.03 (s, 3H), 0.02-0.01 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) 145.9, 144.0, 134.3, 129.5, 109.8, 109.7, 69.2, 47.3, 39.0, 37.3, 27.3, 25.9, 25.6, 22.4, 18.2, 16.5, -1.4, -4.3, -4.8; HRMS (ESI): molecular ion was not observed.



(*S*,*E*)-4-((*tert*-Butyldimethylsilyl)oxy)-6,10-dimethylundeca-5,10-dien-2-one (3.44) was formed as the major product during synthesis of **3.42** when less stringently prepared $TMSCH_2Li$-$CeC1_3$ reagent was used. Isolate by flash column chromatography (silica gel, ethyl acetate/petroleum ether = 1/20) as light yellow oil. $[\alpha]_D^{21}$ -24.28 (*c* 2.72, $CHCl_3$); IR (film) 2955, 2931, 2860, 1362, 1256, 1075, 838; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.13 (dd, *J* = 8.8, 1.2 Hz, 1H), 4.87-4.80 (m, 1H), 4.70 (s, 1H), 4.66 (s, 1H), 2.69 (dd, *J* = 14.3, 8.4 Hz, 1H), 2.34 (dd, *J* = 14.3, 4.6 Hz, 1H), 2.15 (s, 3H), 1.96 (dd, *J* = 15.1, 7.4 Hz, 4H), 1.70 (s, 3H), 1.64 (d, *J* = 1.3 Hz, 3H), 1.57-1.47 (m, 2H), 0.84 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.7, 145.7, 135.7, 127.9,

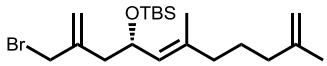
109.9, 67.0, 51.8, 38.9, 37.3, 31.9, 25.8, 25.5, 22.4, 18.0, 16.5, -4.3, -5.0; HRMS (ESI): calculated for $C_{19}H_{36}O_2Si$ [M+Li^+] 331.2645, found 331.2637.



(S,E)-tert-Butyl((6,10-dimethyl-2-((trimethylsilyl)methyl)undeca-1,5,10-trien-4-yl)oxy) dimethylsilane (3.42). A solution of methyl ketone **3.44** (1.50 g, 4.62 mmol) in THF (10 mL) was cooled to –78 °C and treated with a solution of potassium bis(trimethylsilyl)amide (5.55 mL, 1.0 M in THF, 5.55 mmol) dropwise. After stirring for 1 h, a solution of *N*-phenyltrifluoromethanesulfonimide (1.98 g, 5.55 mmol) in 4 mL of THF was added dropwise. After 2 h, the solution was poured over 20 mL of saturated aqueous $NaHCO_3$ and extracted with ethyl acetate (2x50 mL). The combined organic layers were dried with Na_2SO_4 and concentrated in vacuo. Purification of the residue by flash column chromatography (silica gel, ethyl acetate/petroleum ether = 1/20) provided **3.44**-enol triflate (2.06 g, 98 %) as clear oil. $[\alpha]_D^{21}$ -9.56 (c 2.38, $CHCl_3$); IR (film, cm^{-1}) 2955, 2937, 2863, 1673, 1649, 1418, 1247, 1208, 1146, 1069, 954, 891, 838; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.14-5.11 (m, 2H), 4.97 (d, *J* = 3.2 Hz, 1H), 4.71 (s, 1H), 4.67 (s, 1H), 4.64-4.58 (m, 1H), 2.50 (dd, *J* = 14.8, 8.0 Hz, 1H), 2.39 (dd, *J* = 14.9, 4.9 Hz, 1H), 2.00-1.94 (m, 4H), 1.71 (s, 3H), 1.63 (d, *J* = 1.3 Hz, 3H), 1.61-1.48 (m, 2H), 0.85 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.8, 145.7, 136.7, 127.4, 109.9, 106.8, 66.3, 43.3, 38.9, 37.3, 25.7, 25.5, 22.4, 18.1, 16.4, -4.4, -5.1; HRMS (ESI): molecular ion not observed.

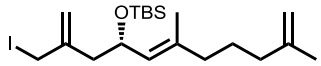
A round-bottom flask was charged with LiCl (783 mg, 18.48 mmol), flame-dried under reduced pressure, and purged with argon. The anhydrous LiCl thus prepared was

taken into diethyl ether (20 mL) followed by a solution of **3.44**-enol triflate (2.06 g, 4.52 mmol) in 10 mL of diethyl ether. The suspension was cooled to 0 °C and tetrakis(triphenylphosphine)palladium(0) (267 mg, 0.23 mmol) was added. This was followed by a solution of (trimethylsilyl)methylmagnesium chloride (1.0 M in Et_2O, 9.24 mL, 9.24 mmol). After 2 h, the yellow suspension was filtered through a pad of celite and eluted with diethyl ether (50 mL). The ether solution was washed with 50 mL of saturated aqueous $NaHCO_3$, which was back-extracted with Et_2O (3x50 mL). The combined organic fractions were dried with Na_2SO_4 and concentrated in vacuo. Purification of the residue by flash column chromatography (silica gel, ethyl acetate/petroleum ether, 1/20) gave **3.42** (1.51 g, 85 %) as clear oil.

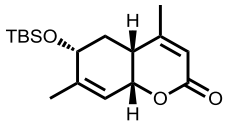


(*S*,*E*)-((2-(Bromomethyl)-6,10-dimethylundeca-1,5,10-trien-4-yl)oxy)(tert-butyl)dimethylsilane (3.43). To a solution of allylsilane **3.42** (417 mg, 1.05 mmol) in THF (10.5 mL) was added propylene oxide (0.19 mL, 2.6 mmol) and NBS (207 mg, 1.2 mmol) at -78 °C under nitrogen. The resulting mixture was stirred in the dark for 1 h. After the reaction was complete (TLC), the mixture was diluted with EtOAc, washed with H_2O and brine. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash column chromatography (silica gel, eluted with ethyl acetate/petroleum ether = 1/20) to provide product **3.43** (389 mg, 93 %) as a clear oil. $[\alpha]_D^{21}$ -3.02 (*c* 1.33, $CHCl_3$); IR (film) 2961, 2934, 2857, 1253, 1208, 1069, 832; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.21 (s, 1H), 5.14 (d, *J* = 9.2 Hz, 1H), 4.98 (s, 1H), 4.71 (s, 1H); 4.67 (s, 1H), 4.56-4.49 (m, 1H), 4.03 (q, *J* = 9.9 Hz, 2H), 2.35 (d, *J* = 6.6 Hz, 2H),

2.00-1.93 (m, 4H), 1.71 (s, 3H), 1.63 (s, 3H), 1.58-1.48 (m, 2H), 0.86 (s, 9H), 0.02 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.8, 142.6, 135.1, 128.7, 117.7, 109.8, 69.0, 42.1, 39.0, 37.7, 37.3, 25.8, 25.6, 22.4, 18.1, 16.5, -4.2, -4.8; HRMS (ESI): molecular ion was not observed.

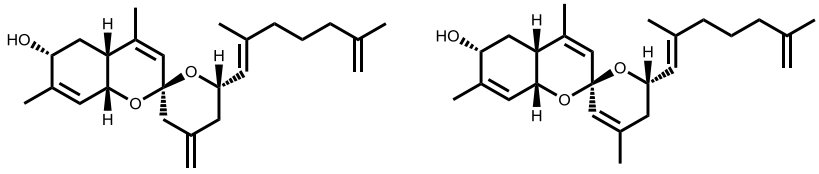


(*S*,*E*)-tert-Butyl((2-(iodomethyl)-6,10-dimethylundeca-1,5,10-trien-4-yl)oxy) dimethylsilane (3.5). To a solution of allyl bromide **3.43** (160 mg, 0.4 mmol) in acetone (4 mL) was added anhydrous NaI (600 mg, 4 mmol) at room temperature. The resulting mixture was stirred overnight before it was concentrated. The residue was suspended in ether (20 mL) and filtered through a short pad of silica gel. After concentration *in vacuo*, the crude allyl iodide **3.5** (171 mg, 95%) was used without further purification. $[\alpha]_D^{21}$ -2.95 (*c* 1.27, $CHCl_3$); IR (film) 2952, 2934, 2857, 1247, 1152, 1072, 936, 883, 835; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.27 (s, 1H), 5.14 (d, *J* =8.5 Hz, 1H), 4.92 (s, 1H), 4.70 (s, 1H), 4.67 (s, 1H), 4.55-4.48 (m, 1H), 4.00 (q, *J* = 9.0 Hz, 2H), 2.36 (d, *J* = 6.3 Hz, 2H), 2.01-1.93 (m, 4H), 1.71 (s, 3H), 1.64 (s, 3H), 1.59-1.48 (m, 2H), 0.86 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.8, 143.8, 135.1, 128.7, 116.4, 109.8, 69.1, 42.8, 39.0, 37.3, 25.8, 25.6, 22.4, 18.1, 16.6, 12.1, -4.2, -4.8; HRMS (ESI): calculated for $C_{20}H_{37}IOSi$ [M+Li^+] 455.1805, found 455.1816.



(4a*R*,6*R*,8a*R*)-6-((tert-Butyldimethylsilyl)oxy)-4,7-dimethyl-4a,5,6,8a-tetrahydro-2H-chromen-2-one (3.28). To a solution of β, γ-unsaturated lactone **3.23a**

(154 mg, 0.5 mmol) in CH_2Cl_2 (5 mL) was added 1,8-diazabicycloundec-7-ene (0.12 mL, 0.75 mmol) at room temperature under nitrogen. After 10 min, the mixture was concentrated and the residue was purified by column chromatography (silica gel, eluted with ethyl acetate/petroleum ether = 1/2) to provide product **3.28** (146 mg, 95%) as a light yellow oil. $[\alpha]_D^{21}$ -100 (*c* 2.33, $CHCl_3$); IR (film) 2958, 2931, 2857, 1720, 1244, 1099, 968, 835; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.81 (s, 1H), 5.62 (d, *J* = 3.9 Hz, 1H), 4.65 (t, *J* = 4.3 Hz, 1H), 4.17-4.11 (m, 1H), 2.17 (dt, *J* = 13.4, 3.2 Hz, 1H), 2.00 (s, 3H), 1.97-1.90 (m, 1H), 1.80 (s, 3H), 1.72-1.58 (m, 1H), 0.89 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 164.3, 159.4, 146.1, 119.3, 116.4, 72.2, 70.2, 37.6, 31.6, 25.7, 21.3, 19.7, 18.0, -4.2, -4.9; HRMS (ESI): calculated for $C_{17}H_{28}O_3Si$ [M+H$^+$] 309.1886, found 309.1896.

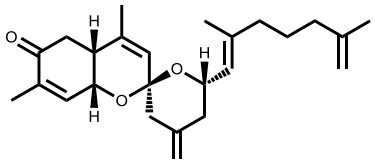


(2*S*,4a*R*,6*R*,6'*S*,8a*R*)-6'-((*E*)-2,6-Dimethylhepta-1,6-dien-1-yl)-4,7-dimethyl-4'-methylene-3',4a,4',5,5',6,6',8a-octahydrospiro[chromene-2,2'-pyran]-6-ol (3.47) and **(2*S*,4a*R*,6*R*,6'*S*,8a*R*)-6'-((*E*)-2,6-Dimethylhepta-1,6-dien-1-yl)-4,4',7-trimethyl-4a,5,5',6,6',8a-hexahydrospiro[chromene-2,2'-pyran]-6-ol (3.48)**. To an ice-cold solution of SmI_2 (8.6 mL, 0.1 M in THF, 0.86 mmol) was added a mixture of the allyl iodide **3.5** (93 mg, 0.21 mmol) and α, β-unsaturated lactone **3.28** (53 mg, 0.17 mmol) in dry THF (2 mL) under nitrogen. The deep blue mixture was stirred at 0 °C for 15 min before it was quenched with saturated aqueous $NaHCO_3$ (10 mL). The mixture was

extracted with EtOAc (modified with 1% Et_3N). The combined organic layers were dried over Na_2SO_4. After concentration *in vacuo*, the residue was dissolved in THF (10 mL), treated with TBAF (0.86 mL, 1M in THF, 0.86 mmol), and stirred at room temperature under nitrogen. After 4h, the mixture was diluted with EtOAc (modified with 1% Et_3N). The organic layer was washed with saturated aqueous NH_4Cl, and dried over Na_2SO_4. After concentration *in vacuo*, the residue was dissolved in CH_2Cl_2 (10 mL). To this mixture was added *p*TSA (36 mg, 0.19 mmol) at room temperature. The mixture was stirred for 30 min before it was diluted with CH_2Cl_2. The organic layer was washed with water, brine, and dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified by column chromatography (silica gel, eluted with ethyl acetate/petroleum ether = 1/5) to provide the spiroketal **3.47** and the isomeric spiroketal **3.48** (18.9 mg, 29% for three steps, ratio varies from 1:3 to 1:6) as colorless oils.

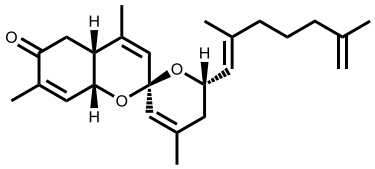
Spiroketal **3.47**. $[\alpha]_D^{19}$ -69.7 (*c* 0.50, MeOH); IR (film) 3073, 2937, 2854, 1679, 1649, 1442, 1377, 1250, 1232, 1037, 1016, 980, 965, 886; ^{1}H NMR (500 MHz, C_6D_6) δ 5.61 (d, *J* = 5.1 Hz, 1H), 5.48 (d, *J* = 8.4 Hz, 1H), 5.45 (s, 1H), 4.94-4.88 (m, 1H), 4.90-4.88 (m, 2H), 4.78 (s, 1H), 4.77 (s, 1H), 4.38 (s, 1H), 3.66 (brs, 1H), 2.47-2.19 (m, 4H), 1.95-1.89 (m, 4H), 1.80-1.76 (m, 1H), 1.71 (d, *J* = 1.2 Hz, 3H), 1.68 (d, *J* = 1.3 Hz, 3H), 1.59 (s, 3H), 1.58-1.43 (m, 4H), 1.48 (d, *J* = 1.4 Hz, 3H); ^{13}C NMR (75 MHz, C_6D_6) *δ* 146.0, 143.7, 142.3, 139.1, 139.0, 127.2, 126.2, 123.6, 111.0, 110.8, 96.7, 70.7, 68.2, 64.2, 44.9, 41.0, 39.7, 38.1, 38.0, 32.9, 26.3, 22.8, 21.2, 19.5, 17.1; HRMS (ESI): calculated for $C_{25}H_{36}O_3$ [M+Li^+] 391.2824, found 391.2809.

Migrated spiroketal **3.48**. $[\alpha]_D^{19}$ -146 (*c* 0.50, MeOH); IR (film) 2967, 2937, 2854, 1679, 1649, 1445, 1377, 1164, 1119, 968, 886; ^{1}H NMR (500 MHz, C_6D_6) δ 5.71 (d, *J* = 5.2 Hz, 1H), 5.56 (s, 1H), 5.52 (s, 2H), 5.09-5.04 (m, 1H), 4.80 (s, 1H), 4.79 (s, 1H), 4.55 (s, 1H), 3.72 (brs. 1H), 2.09-2.02 (m, 2H), 1.98-1.91 (m, 4H), 1.84-1.80 (m, 1H), 1.80 (s, 3H), 1.72 (s, 3H), 1.62 (s, 3H), 1.59 (s, 3H), 1.57-1.47 (m, 4H), 1.54 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6) *δ* 146.0, 143.5, 139.6, 138.6, 136.0, 126.9, 125.5, 125.0, 124.0, 110.8, 94.9, 70.7, 65.9, 64.6, 39.7, 38.1, 38.0, 36.3, 32.9, 26.4, 23.2, 22.8, 21.3, 19.5, 17.0; HRMS (ESI): calculated for $C_{25}H_{36}O_3$ [M+Li$^+$] 391.2824, found 391.2809.



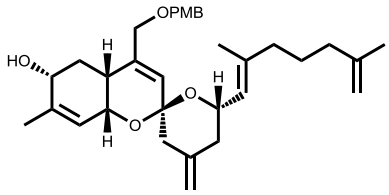
(2*S*,4a*R*,6'*S*,8a*R*)-6'-((*E*)-2,6-Dimethylhepta-1,6-dien-1-yl)-4,7-dimethyl-4'-methylene-3',4a,4',5,5',6'-hexahydrospiro[chromene-2,2'-pyran]-6(8a*H*)-one (3.49). To a solution of allyl alcohol **3.47** (2.9 mg, 0.0075 mmol) in DMSO (0.6 mL) was added IBX (4.3 mg, 0.015 mmol) at room temperature. The resulting mixture was stirred for 1h before H_2O (1 mL) was added. The resulting mixture was filtered. The aqueous layer was extracted with EtOAc. The combined organic phase was washed with brine, and dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified by column chromatography (silica gel, eluted with ethyl acetate/petroleum ether = 1/10) to provide the product **3.49** (2.5 mg, 87%) as a light yellow oil. $[\alpha]_D^{18}$ -61.6 (*c* 0.24, MeOH); IR (film) 2925, 2851, 1685, 1445, 1377, 1250, 1122, 983, 880; ^{1}H NMR (500 MHz, C_6D_6) δ 6.32 (dd, *J* = 5.7, 1.5 Hz, 1H), 5.49 (d, *J* = 8.3 Hz, 1H), 5.32 (s, 1H), 4.89 (d, *J* = 1.9 Hz, 1H), 4.87 (d, *J* = 1.8 Hz, 1H), 4.85-4.83 (m, 1H), 4.81 (s, 1H), 4.80 (s, 1H), 4.38-4.37

(m, 1H), 2.48-2.18 (m, 6H), 1.99-1.92 (m, 4H), 1.77-1.70 (m, 1H), 1.72 (s, 3H), 1.68 (d, *J* = 1.3 Hz, 3H), 1.62 (s, 3H), 1.58-1.51 (m, 2H), 1.31 (d, *J* = 1.4 Hz, 3H); ^{13}C NMR (75 MHz, C_6D_6) δ 197.8, 145.9, 141.8, 139.7, 139.0, 138.9, 138.6, 127.0, 125.8, 111.2, 110.9, 97.2, 68.5, 63.5, 44.3, 40.8, 39.7, 38.2, 38.0, 30.6, 26.3, 22.8, 20.7, 17.1, 16.4; HRMS (ESI): calculated for $C_{25}H_{34}O_3$ [M+H$^+$] 383.2586, found 383.2599.



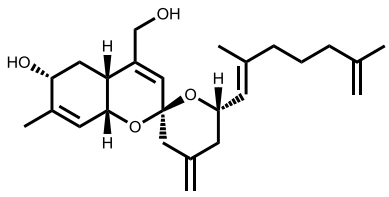
(2*S*,4a*R*,6'*S*,8a*R*)-6'-((*E*)-2,6-dimethylhepta-1,6-dien-1-yl)-4,4',7-trimethyl-4a,5,5',6'-tetrahydrospiro[chromene-2,2'-pyran]-6(8a*H*)-one (3.50). To a solution of allyl alcohol **3.48** (6.2 mg, 0.018 mmol) in DMSO (0.8 mL) was added IBX (10.2 mg, 0.036 mmol) at room temperature. The resulting mixture was stirred for 1 h before H_2O (1 mL) was added. The resulting mixture was filtered. The aqueous layer was extracted with EtOAc. The combined organic phase was washed with brine, and dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified by column chromatography (silica gel, eluted with ethyl acetate/petroleum ether = 1/10) to provide the product **3.50** (6.2 mg, 89%) as a light yellow oil. $[\alpha]_D^{18}$ -111 (*c* 0.60, MeOH); IR (film) 2967, 2931, 2857, 1679, 1445, 1377, 1170, 1128, 1004, 977, 927, 877; ^{1}H NMR (500 MHz, C_6D_6) δ 6.40 (dd, *J* = 5.7, 1.5 Hz, 1H), 5.50 (d, *J* = 8.0, 1H), 5.41 (s, 1H), 5.37 (s, 1H), 4.97 (ddd, *J* = 11.2, 8.0, 3.4 Hz, 1H), 4.81 (s, 1H), 4.80 (s, 1H), 4.53-4.51 (m, 1H), 2.50-2.44 (m, 2H), 2.05-1.93 (m, 5H), 1.81 (s, 3H), 1.79-1.71 (m, 2H), 1.68 (d, *J* = 1.3 Hz, 3H), 1.63 (s, 3H), 1.59-1.52 (m, 2H), 1.56 (s, 3H), 1.35 (d, *J* = 1.4 Hz, 3H);

^{13}C NMR (75 MHz, C_6D_6) δ 198.1, 145.9, 140.3, 139.6, 138.7, 138.3, 136.4, 126.7, 125.2, 124.1, 110.9, 95.3, 66.1, 63.8, 39.7, 38.3, 38.0, 38.0, 36.2, 26.4, 23.1, 22.8, 20.8, 17.0, 16.4; HRMS (ESI): calculated for $C_{25}H_{34}O_3$ [M+H$^+$] 383.2586, found 383.2599.



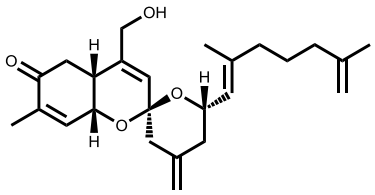
(2*S*,4a*R*,6*R*,6'*S*,8a*R*)-6'-((*E*)-2,6-Dimethylhepta-1,6-dien-1-yl)-4-(((4-methoxy benzyl)oxy)methyl)-7-methyl-4'-methylene-3',4a,4',5,5',6,6',8a-octahydrospiro [chromene-2,2'-pyran]-6-ol (3.54). To an ice-cold solution of SmI_2 (2.5 mL, 0.1 M in THF, 0.25 mmol) was added a mixture of the allyl iodide **3.5** (25 mg, 0.055 mmol) and lactone **3.4** (23 mg, 0.05 mmol) in dry THF (1 mL) under nitrogen. The deep blue mixture was stirred at 0 °C for 15 min before it was treated with saturated aqueous $NaHCO_3$ (1 mL). The mixture was extracted with EtOAc (modified with1% Et_3N). The combined organic layers were dried over Na_2SO_4. After concentration *in vacuo*, the residue was dissolved in THF (2 mL) and treated with TBAF (0.25 mL, 1M in THF, 0.25 mmol) at room temperature under nitrogen. After 4 h, the mixture was diluted with EtOAc (modified with 1% Et_3N), washed with saturated aqueous NH_4Cl, and dried over Na_2SO_4. After concentration *in vacuo*, the residue was dissolved in CH_2Cl_2 (2 mL) and treated with PPTS (12 mg, 0.05 mmol) at room temperature under nitrogen. The mixture was stirred for 30 min before it was diluted with CH_2Cl_2. The organic layer was washed with water, brine, and dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified by column chromatography (silica gel, eluted with ethyl acetate/petroleum ether

= 1/1) to provide the product **3.54** (10.4 mg, 40%) as a colorless oil. $[\alpha]_D^{18}$ -42.5 (*c* 0.21, MeOH); IR (film) 2931, 2854, 1614, 1510, 1445, 1250, 1039, 974; ^{1}H NMR (500 MHz, C_6D_6) δ 7.20 (d, *J* = 8.7 Hz, 2H), 6.78 (d, *J* = 8.7 Hz, 2H), 5.83 (s, 1H), 5.63 (d, *J* = 5.2, 1H), 5.49 (d, *J* = 8.4, 1H), 4.94 (ddd, *J* = 11.2, 8.4, 2.8 Hz, 1H), 4.89-4.88 (m, 2H), 4.78 (s, 1H), 4.77 (s, 1H), 4.43 (s,1H), 4.34 (d, *J* = 11.6 Hz, 1H), 4.25 (d, *J* = 11.6 Hz, 1H), 3.88 (d, *J* = 12.8 Hz, 1H), 3.73 (d, *J* = 12.7 Hz, 1H), 3.69 (brs, 1H), 3.28 (s, 3H), 2.46-2.20 (m, 4H), 1.95-1.84 (m, 5H), 1.69 (d, *J* = 1.1 Hz, 3H), 1.67 (d, *J* = 1.3 Hz, 3H), 1.65-1.55 (m, 2H), 1.59 (s, 3H), 1.53-1.48 (m, 2H); ^{13}C NMR (125 MHz, C_6D_6) *δ* 160.2, 145.9, 143.9, 142.1, 140.5, 139.1, 131.2, 129.9, 127.5, 127.0, 123.4, 114.5, 111.1, 110.8, 96.7, 72.4, 71.2, 70.6, 68.3, 64.4, 55.1, 44.6, 40.9, 39.7, 38.0, 34.2, 33.1, 26.3, 22.8, 19.5, 17.1; HRMS (ESI): calculated for $C_{33}H_{44}O_5$ [M+H$^+$] 521.3267, found 521.3273.



(2*S*,4a*R*,6*R*,6'*S*,8a*R*)-6'-((*E*)-2,6-Dimethylhepta-1,6-dien-1-yl)-4-(hydroxymethyl)-7-methyl-4'-methylene-3',4a,4',5,5',6,6',8a-octahydrospiro [chromene-2,2'-pyran]-6-ol (3.55). To a mixture of PMB ether **3.57** (4.1 mg, 0.008 mmol) in CH_2Cl_2 (1.8 mL) and H_2O (0.1 mL) was added DDQ (2.8 mg, 0.012 mmol). The resulting mixture was stirred at room temperature for 2 h before it was quenched by saturated aqueous $NaHCO_3$ (1 mL). After being stirred for 15 min, the reaction mixture was extracted with EtOAc. The organic phase was washed with water, saturated aqueous $NaHCO_3$, brine, and dried over anhydrous Na_2SO_4. After concentration *in vacuo*, the

residue was purified by column chromatography (silica gel, eluted with ethyl acetate/petroleum ether = 2/1) to provide the product **3.55** (2.9 mg, 92%) as a colorless oil. $[\alpha]_D^{20}$ -104 (*c* 0.18, MeOH); IR (film) 3076, 2931, 2857, 1454, 1371, 1259, 1034, 963, 883; ^{1}H NMR (500 MHz, C_6D_6) δ 5.64 (s, 1H), 5.63-5.61 (m, 1H), 5.48 (d, *J* = 8.4 Hz, 1H), 4.94-4.91 (m, 1H), 4.90-4.88 (m, 2H), 4.78 (s, 1H), 4.76 (s, 1H), 4.36 (s, 1H), 3.72 (s, 2H), 3.67 (dd, *J* = 11.1, 6.1 Hz, 1H), 2.45-2.20 (m, 4H), 1.95-1.89 (m, 4H), 1.80-1.77 (m, 1H), 1.70 (s, 3H), 1.68 (d, *J* = 1.3 Hz, 3H), 1.59 (s, 3H), 1.55-1.46 (m, 4H); ^{13}C NMR (125 MHz, C_6D_6) *δ* 145.2, 143.2, 142.4, 141.3, 138.6, 126.3, 125.0, 122.7, 110.5, 110.1, 95.9, 69.8, 67.5, 63.7, 63.6, 43.9, 40.2, 39.0, 37.3, 33.1, 32.5, 25.6, 22.1, 18.8, 16.3; HRMS (ESI): calculated for $C_{25}H_{36}O_4$ [M+H$^+$] 401.2692, found 401.2708.



Alotaketal A. To a solution of alcohol **3.54** (8.3 mg, 0.016 mmol) in DMSO (1.5 mL) was added IBX (9 mg, 0.032 mmol) at room temperature. The resulting mixture was stirred for 1h before H_2O (1.5 mL) was added. The resulting mixture was filtered. The aqueous phase was extracted with EtOAc. The combined organic phase was washed with brine, and dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified by column chromatography (silica gel, eluted with ethyl acetate/petroleum ether = 1/5) to provide the enone **A.9** (7.4 mg, 89%) as a light yellow oil. $[\alpha]_D^{16}$ -35.7 (*c* 0.15, MeOH); IR (film) 2925, 2851, 1679, 1608, 1510, 1448, 1247, 1122, 1039, 980, 880; ^{1}H NMR (500 MHz, C_6D_6) δ 7.17 (d, *J* = 8.5 Hz, 2H), 6.78 (d, *J* = 8.3 Hz, 2H), 6.30 (d, *J* =

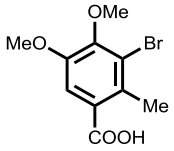
5.7 Hz, 1H), 5.71 (s, 1H), 5.47 (d, *J* = 8.3 Hz, 1H), 4.90-4.71 (m, 5H), 4.40 (s, 1H), 4.26 (d, *J* = 11.7 Hz, 1H), 4.19 (d, *J* = 11.6 Hz, 1H), 3.66 (d, *J* = 13.1 Hz, 1H), 3.58 (d, *J* = 12.8 Hz, 1H), 3.28 (s, 3H), 2.59 (dd, *J* = 15.6, 4.2 Hz, 1H), 2.45 (dd, *J* = 15.6, 13.3 Hz, 1H), 2.34-2.16 (m, 4H), 2.03 (dd, *J* = 14.7, 7.3 Hz, 1H), 1.97-1.90 (m, 4H), 1.68 (s, 3H), 1.65 (s, 3H), 1.61 (s, 3H), 1.56-1.50 (m, 2H); ^{13}C NMR (125 MHz, C_6D_6) δ 197.7, 166.2, 160.2, 145.9, 141.5, 140.1, 139.6, 139.1, 139.0, 130.9, 129.9, 126.9, 126.8, 114.5, 111.4, 110.9, 97.2, 72.7, 70.8, 68.6, 63.7, 55.2, 44.1, 40.8, 39.7, 38.6, 38.0, 34.5, 26.3, 22.8, 17.1, 16.4; HRMS (ESI): calculated for $C_{33}H_{42}O_5$ [M+H$^+$] 519.3110, found 519.3126.

To a mixture of the above enone **A.9** (7.4 mg, 0.014 mmol) in CH_2Cl_2 (2.7 mL) and H_2O (0.15 mL) was added DDQ (5 mg, 0.022 mmol). The resulting mixture was stirred at room temperature for 2 h before it was quenched with saturated aqueous $NaHCO_3$ (1 mL). After being stirred for 15 min, the reaction mixture was extracted with EtOAc. The organic phase was washed with water, saturated aqueous $NaHCO_3$, brine, and dried over anhydrous Na_2SO_4. After concentration *in vacuo*, the residue was purified by column chromatography (silica gel, eluted with ethyl acetate/petroleum ether = 1/1) to provide the natural product alotaketal A (5.1 mg, 92%) as a colorless oil. $[\alpha]_D^{20}$ -40.2 (*c* 0.15, MeOH); IR (film) 2925, 2857, 1684, 1445, 1252, 1122, 974, 882; ^{1}H NMR (500 MHz, C_6D_6) δ 6.32 (dd, *J* = 6.0, 1.5 Hz, 1H), 5.56 (s, 1H), 5.48 (d, *J* = 8.5 Hz, 1H), 4.89 (brs, 1H), 4.87 (brs, 1H), 4.86-4.83 (m, 1H), 4.81 (brs, 1H), 4.80 (brs, 1H), 4.36 (dd, *J* = 5.5, 4.5 Hz, 1H), 3.55-3.49 (m, 2H), 2.47 (dd, *J* = 15.5, 5.0 Hz, 1H), 2.39 (dd, *J* = 15.5, 13.0 Hz, 1H), 2.35-2.27 (m, 3H), 2.20 (t, *J* = 13.0, 1H), 2.06 (dt, *J* = 12.0, 4.5, 1H), 1.98

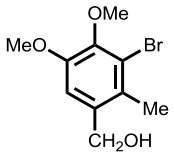
(t, J = 7.5 Hz, 2H), 1.94 (t, J = 7.5 Hz, 2H), 1.71 (s, 3H), 1.68 (s, 3H), 1.62 (s, 3H), 1.57-1.52 (m, 2H); ^{13}C NMR (125 MHz, C_6D_6) δ 197.7, 145.9, 142.5, 141.5, 139.7, 139.2, 139.0, 126.8, 125.1, 111.4, 110.9, 97.2, 68.5, 63.8, 63.6, 44.1, 40.7, 39.7, 38.6, 38.0, 34.0, 26.3, 22.8, 17.1, 16.4; HRMS (ESI): calculated for $C_{25}H_{34}O_4$ [M+Li^+] 405, 2417, found 405.2630.

Cell Culture and Imaging. HEK293 cells were plated in 35 mm glass-bottom dishes and grown to ~60% confluency in DMEM with 10% FBS at 37 °C with 5% CO_2. The cells were transfected with AKAR4, ICUE3, or AKAR4 T/A mutant using Lipofectamine 2000 (Invitrogen) for 24 hours. The next day, the cells were washed with and maintained in Hanks' balanced salt solution (HBSS) in the dark. The cells were imaged on a Zeiss Aioxvert 200M microscope with a 40x/1.3NA oil-immersion objective lens and cooled charged-coupled device (CCD) camera controlled by METAFLUOR software (Molecular Devices, Sunnyvale, CA). Dual emission ratio imaging was used with 420DF20 excitation filter, a 450DRLP dichroic mirror and two emission filters (475DF40 for cyan and 535DF25 for yellow). First baseline emission ratios were acquired and then the compounds were added to the cells as indicated. The ratios of yellow-to-cyan were calculated at different time points and normalized by dividing all ratios by the baseline emission ratio, setting basal emission ratio as 1.

A.4 Experimental Procedures for Total Synthesis of 1.67

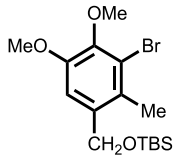


3-bromo-4,5-dimethoxy-2-methylbenzoic acid (4.7). To a solution of carboxylic acid **4.6** (3.77 g, 19.22 mmol) in $CHCl_3$ (50 mL) was added Br_2 (1.19 mL, 23.07 mmol) dropwise at 0 ^oC. The mixture was slowly warmed to room temperature and stirred overnight. The reaction was quenched with saturated aqueous $Na_2S_2O_3$ solution (50 mL). The resulting two phases were separated and the aqueous layer was extracted with EtOAc (2x50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4. After concentration, the residue was purified by flash column chromatography (silica gel, eluted with ethyl acetate/petroleum ether = 1/1) to provide product **4.7** (210 mg, 92 %) as a light yellow solid. ^1H NMR (500 MHz, $CDCl_3$) δ 7.56 (s, 1H), 3.92 (s, 3H), 3.91 (s, 3H), 2.70 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 172.6, 150.6, 150.2, 134.2, 125.1, 123.1, 114.1, 60.5, 56.1, 20.6.

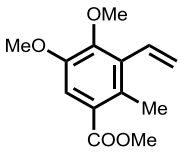


(3-bromo-4,5-dimethoxy-2-methylphenyl)methanol (4.8). To a solution of carboxylic acid **4.7** (240 mg, 0.88 mmol) in THF (2 mL) was added borane dimethyl sulfide (0.70 mL, 1.40 mmol, 2M in THF) at 0 °C. The resulting solution was allowed to warm to room temperature overnight. The reaction was carefully quenched with H_2O and the resulting solution was diluted with EtOAc. Organic Phase was separated, washed

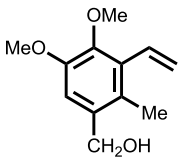
with H_2O, dried over Na_2SO_4. After concentration, the residue was purified by flash column chromatography (silica gel, eluted with ethyl acetate/petroleum ether = 1/1) to provide product **4.8** (210 mg, 92 %) as a white solid. IR (film, cm^{-1}) 2940, 1596, 1557, 1484, 1430, 1309, 1108, 1045, 1010, 971; ^1H NMR (500 MHz, $CDCl_3$) δ 6.91 (s, 1H), 4.63 (s, 2H), 3.83 (s, 3H), 3.80 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 151.0, 145.4, 135.4, 128.2, 121.6, 111.1, 63.8, 60.4, 56.0, 17.9; HRMS (ESI): molecular ion was not observed.



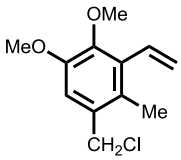
((3-bromo-4,5-dimethoxy-2-methylbenzyl)oxy)(tert-butyl)dimethylsilane (4.10). To a solution of benzyl alcohol **4.8** (173 mg, 0.66 mmol) in DMF (0.7 mL) was added imidazole (90 mg, 1.32 mmol) and TBSCl (149 mg, 0.99 mmol). The reaction was stirred at room temperature for 3h before it was diluted with EtOAc. The organic layer was washed with H_2O, brine, and dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified by flash column chromatography (silica gel, eluted with ethyl acetate/petroleum ether = 1/20) to provide **4.10** (233 mg, 94 %) as a colorless oil. IR (film, cm^{-1}) 2958, 2931, 2848, 1602, 1487, 1312, 1253, 1205, 1122, 1048, 835; ^1H NMR (500 MHz, $CDCl_3$) δ 7.07 (s, 1H), 4.67 (s, 2H), 3.87 (s, 3H), 3.83 (s, 3H), 2.26 (s, 3H), 0.96 (s, 9H), 0.12 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) 151.1, 144.9, 135.9, 126.7, 121.2, 109.9, 63.4, 60.4, 56.0, 25.9, 18.3, 17.5, 5.3; HRMS (ESI): molecular ion was not observed.



methyl 4,5-dimethoxy-2-methyl-3-vinylbenzoate (4.14). To a suspension of ester **4.13** (1.57 g, 5.45 mmol), Pd_2dba_3 (113 mg, 0.11mmol), tributylvinyltin (1.75 mL, 6.0 mmol) in toluene (11 mL) was added P(*t*-Bu)$_3$ (0.22 mL, 0.22 mmol, 1M in toluene) under nitrogen. The reaction was stirred at 60 °C for overnight. Pd_2dba_3 (56 mg, 0.055mmol) was added to the reaction. When the reaction was complete (monitored by TLC, ethyl acetate/petroleum ether = 1:10 for 2~3 times), KF (4 g) was added followed by Et_2O (30 mL) and activated carbon (4 g). The mixture was stirred for 5 min, and then it was filtered through a short pad of silica (washed with ethyl acetate). After concentration, the residue was purified by flash column chromatography (silica gel, eluted with ethyl acetate/petroleum ether = 1/5) to provide product **4.14** (1.26 g, 98 %) as a yellow oil. IR (film, cm^{-1}) 2999, 2955, 2842, 1723, 1590, 1478, 1427, 1324, 1199, 1167, 1110, 983; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (s, 1H), 6.71 (dd, *J* = 17.9, 11.6 Hz, 1H), 5.61 (dd, *J* = 11.6, 2.0 Hz, 1H), 5.52 (dd, *J* = 17.9, 2.0 Hz, 1H), 3.90 (s, 3H), 3.89 (s, 3H), 3.79 (s, 3H), 2.47 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 168.4, 150.0, 149.7, 133.8, 131.2, 131.1, 126.3, 121.1, 112.9, 60.1, 55.9, 52.0, 17.6; GCMS (EI): retention time, 15.60 min; calculated for $C_{13}H_{16}O_4$ $[M]^+$ 236.1, found 236.1.

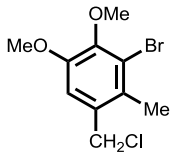


(4,5-dimethoxy-2-methyl-3-vinylphenyl)methanol (4.15). To a well stirred solution of ester **4.14** (1.24 g, 5.25 mmol) in THF (30 mL) was added DIBAL-H (15.75 mL, 1 M in hexanes, 15.75 mmol) at 0 °C under N_2. The reaction was stirred at 0 ^oC for 2h, then quenched by ethyl acetate (3 mL) followed by saturated aqueous Rochelle salt (30 mL). The reaction was stirred for another 1h at room temperature. The organic layer was separated and aqueous phase was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4. After concentration, the residue was purified by flash column chromatography (silica gel, eluted with ethyl acetate/petroleum ether = 1/1) to provide product **4.15** (992 mg, 91 %) as a colorless oil. IR (film, cm^{-1}) 2934, 1587, 1475, 1318, 1235, 1116, 974, 921, 944; ^1H NMR (500 MHz, $CDCl_3$) δ 6.92 (s, 1H), 6.74 (dd, *J* = 17.9, 11.7 Hz, 1H), 5.58 (dd, *J* = 11.7, 2.1 Hz, 1H), 5.54 (dd, *J* = 17.9, 2.1 Hz, 1H), 4.67 (s, 2H), 3.86 (s, 3H), 3.75 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 150.4, 146.3, 134.6, 132.9, 131.5, 126.6, 120.5, 111.2, 63.9, 60.2, 55.9, 15.1; HRMS (ESI): calculated for $C_{12}H_{16}O_3$ $[M+Li^+]$ 215.1259, found 215.1266.



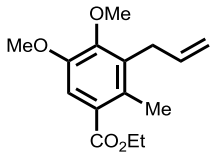
1-(chloromethyl)-4,5-dimethoxy-2-methyl-3-vinylbenzene (4.16). To a solution of alcohol **4.15** (832 mg, 4.0 mmol) in CH_2Cl_2 (20 mL) was added $SOCl_2$ (0.35 mL, 4.8 mmol) dropwise at 0 °C under nitrogen. The reaction was stirred at room temperature for 30 min before it was carefully quenched by the addition of saturated aqueous $NaHCO_3$. The mixture was diluted with CH_2Cl_2. The organic layer was

separated and washed with water, brine, dried over Na_2SO_4. After concentration, the residue was purified by flash column chromatography (silica gel, eluted with ethyl acetate/petroleum ether = 1/20) to provide product **4.16** (832 mg, 92 %) as a yellow oil. IR (film, cm^{-1}) 3005, 2970, 2934, 2837, 1590, 1478, 1318, 1238, 1116, 1045, 980, 927, 853; ^1H NMR (500 MHz, $CDCl_3$) δ 6.84 (s, 1H), 6.73 (dd, *J* = 17.9, 11.7 Hz, 1H), 5.60 (dd, *J* = 11.7, 2.0 Hz, 1H), 5.54 (dd, *J* = 17.9, 2.1 Hz, 1H), 4.62 (s, 2H), 3.88 (s, 3H), 3.76 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 150.5, 147.4, 133.4, 131.3, 131.2, 128.2, 120.7, 113.0, 60.2, 55.9, 45.8, 15.4; GCMS (EI): retention time, 15.34 min; calculated for $C_{12}H_{15}ClO_2$ $[M]^+$ 226.1, found 226.1.

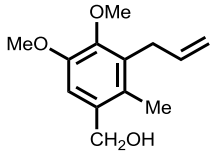


3-bromo-1-(chloromethyl)-4,5-dimethoxy-2-methylbenzene (4.18). To a solution of alcohol **4.9** (52 mg, 0.2 mmol) in CH_2Cl_2 (1 mL) was added $SOCl_2$ (0.018 mL, 0.24 mmol) dropwise at 0 °C under nitrogen. The reaction was stirred at room temperature for 30 min before it was carefully quenched by the addition of saturated aqueous $NaHCO_3$. The mixture was diluted with EtOAc. The organic layer was separated and washed with water, brine, dried over Na_2SO_4. After concentration, the residue was purified by flash column chromatography (silica gel, eluted with ethyl acetate/petroleum ether = 1/20) to provide product **4.18** (52.2 mg, 94 %) as a colorless oil. IR (film, cm^{-1}) 2934, 1599, 1487, 1395, 1318, 1270, 1108, 1045, 1013, 980, 812; ^1H NMR (300 MHz, $CDCl_3$) δ 6.85 (s, 1H), 4.60 (s, 2H), 3.87 (s, 3H), 3.85 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 151.2, 146.8, 131.8, 130.0, 122.1, 113.2, 60.4, 56.2,

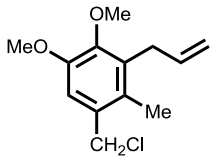
45.6, 18.5; GCMS (EI): retention time, 15.96 min; calculated for $C_{10}H_{12}BrClO_2$ $[M]^+$ 280.0, found 280.0.



ethyl 3-allyl-4,5-dimethoxy-2-methylbenzoate (4.22). To a suspension of ester **4.13** (2.88 g, 10 mmol), Pd_2dba_3 (275 mg, 0.30 mmol), allyltributyltin (3.72 mL, 12 mmol) in toluene (15 mL) was added P(*t*-Bu)$_3$ (0.60 mL, 0.60 mmol, 1M in toluene) under nitrogen. The reaction was stirred at 60 °C for overnight. When the reaction was complete (monitored by TLC, ethyl acetate/petroleum ether = 1:10 for 2~3 times), KF (5 g) was added followed by Et_2O (30 mL) and activated carbon (5 g). The mixture was stirred for 5 min, and then it was filtered through a short pad of silica (washed with ethyl acetate). After concentration, the residue was purified by flash column chromatography (silica gel, eluted with ethyl acetate/petroleum ether = 1/5) to provide product **4.22** in quantitative yield as a yellow oil. IR (film, cm^{-1}) 2949, 2842, 1717, 1596, 1484, 1330, 1211, 1099, 1045, 989, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (s, 1H), 5.95-5.89 (m, 1H), 5.00 (dd, *J* = 10.2, 1.8 Hz, 1H), 4.86 (dd, *J* = 17.1, 1.8 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.83 (s, 3H), 3.49 (dt, *J* = 5.6, 1.8 Hz, 2H), 2.41 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 168.6, 150.2, 150.0, 136.0, 133.3, 132.1, 126.1, 115.1, 112.2, 60.9, 55.7, 51.9, 30.8, 16.1; HRMS (ESI): calculated for $C_{14}H_{18}O_4$ $[M+H^+]$ 251.1283, found 251.1274.

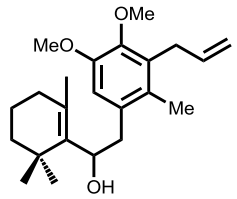


(3-allyl-4,5-dimethoxy-2-methylphenyl)methanol (A.10). To a well stirred solution of ester **4.22** (2.50 g, 10 mmol) in THF (50 mL) was added DIBAL-H (30 mL, 1 M in hexanes, 30 mmol) at 0 °C under N_2. The reaction was stirred at 0 ^oC for 4h, then quenched by ethyl acetate (5 mL) followed by saturated aqueous Rochelle salt (50 mL). The reaction was stirred for another 1h at room temperature. The organic layer was separated and aqueous phase was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4. After concentration, the residue was purified by flash column chromatography (silica gel, eluted with ethyl acetate/petroleum ether = 1/1) to provide corresponding allyl alcohol **A.10** (2.01 g, 90 %) as a colorless liquid. IR (film, cm^{-1}) 3414, 2937, 1640, 1599, 1487, 1309, 1232, 1111, 1042, 906, 850; ^1H NMR (500 MHz, $CDCl_3$) δ 6.87 (s, 1H), 5.92 (ddt, *J* = 17.1, 10.1, 5.8 Hz, 1H)., 4.99 (dd, *J* = 10.2, 1.8 Hz, 1H), 4.90 (dd, *J* = 17.1, 1.9 Hz, 1H), 4.64 (d, *J* = 4.5 Hz, 2H), 3.84 (s, 3H), 3.78 (s, 3H), 3.47 (dt, *J* = 5.8, 1.8 Hz, 2H), 2.18 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 150.4 146.7, 136.5, 134.4, 132.6, 127.5, 115.0, 110.5, 63.9, 60.9, 55.7, 30.9, 13.9; HRMS (ESI): calculated for $C_{13}H_{18}O_3$ $[M+Li^+]$ 229.1416, found 229.1406.



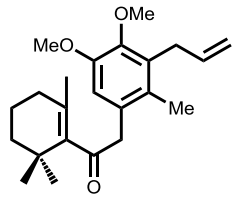
3-allyl-1-(chloromethyl)-4,5-dimethoxy-2-methylbenzene (4.23). To a solution of the above allyl alcohol (1.85 g, 8.32 mmol) in CH_2Cl_2 (40 mL) was added $SOCl_2$ (0.73 mL, 9.99 mmol) dropwise at 0 °C under nitrogen. The reaction was stirred at room temperature for 30 min before it was carefully quenched by the addition of saturated aqueous $NaHCO_3$. The mixture was diluted with CH_2Cl_2. The organic layer was

separated and washed with water, brine, dried over Na_2SO_4. After concentration, the residue was purified by flash column chromatography (silica gel, eluted with ethyl acetate/petroleum ether = 1/10) to provide product **4.23** (1.93 g, 97 %) as a white solid. IR (film, cm^{-1}) 2940, 1602, 1484, 1330, 1226, 1108, 1045, 986, 912; ^1H NMR (500 MHz, $CDCl_3$) δ 6.79 (s, 1H), 5.92 (ddt, *J* = 17.1, 10.2, 5.8 Hz, 1H), 5.01 (dd, *J* = 10.2, 1.8 Hz, 1H), 4.89 (dd, *J* = 17.1, 1.8 Hz, 1H), 4.60 (s, 2H), 3.86 (s, 3H), 3.80 (s, 3H), 3.48 (dt, *J* = 5.8, 1.8 Hz, 2H), 2.26 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 150.5, 147.7, 136.2, 133.1, 131.0, 129.1, 115.1, 112.2, 60.9, 55.7, 45.9, 31.0, 14.3; HRMS (ESI): calculated for $C_{13}H_{17}ClO_2$ $[M+H^+]$ 241.0995, found 241.1003.



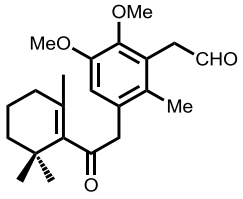
2-(3-allyl-4,5-dimethoxy-2-methylphenyl)-1-(2,6,6-trimethylcyclohex-1-en-1-yl) ethanol (4.24). A mixture of naphthalene (3.61 g, 28.13 mmol) and lithium (196 mg, 28.13 mmol) in THF (30 mL) was stirred at room temperature under nitrogen for 1.5h. To which, a solution of β-cyclocitral (1.26 g, 8.25 mmol) and benzyl chloride **4.23** (1.80 g, 7.50 mmol) in THF (10 mL) was added dropwise via syringe at 0 °C. The mixture was then stirred at room temperature for 2h, diluted with ether and then quenched with saturated aqueous NH_4Cl. The organic phase was separated. The aqueous phase was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4. After concentration, the residue was purified by flash column chromatography (silica gel, eluted with ethyl acetate/petroleum ether = 1/4) to provide product **4.24** (2.13

g, 79%) as a colorless liquid. IR (film, cm^{-1}) 3500, 2931, 1593, 1484, 1291, 1229, 1111, 1048, 989, 906; ^1H NMR (500 MHz, $CDCl_3$) δ 6.70 (s, 1H), 5.94 (dd, *J* = 17.1, 10.1 Hz, 1H), 5.01 (dq, *J* = 10.1, 1.7 Hz, 1H), 4.93 (dq, *J* = 17.1, 1.8 Hz, 1H), 4.45 (dd, *J* = 10.0, 4.3 Hz, 1H), 3.87 (s, 3H), 3.80 (s, 3H), 3.49 (ddd, *J* = 5.8, 3.9, 1.9 Hz, 2H), 3.19 (dd, *J* = 14.2, 10.0 Hz, 1H), 2.88 (dd, *J* = 14.2, 4.3 Hz, 1H), 2.24 (s, 3H), 2.03-1.99 (m, 2H); 2.02 (s, 3H), 1.65-1.54 (m, 2H), 1.46-1.44 (m, 2H), 1.11 (s, 3H), 0.93 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 150.3, 146.0, 139.3, 136.7, 133.3, 132.4, 132.0, 128.3, 114.9, 113.0, 71.2, 60.9, 55.8, 40.5, 40.0, 34.8, 34.2, 31.2, 28.5, 28.3, 21.4, 19.3, 15.2; HRMS (ESI): calculated for $C_{23}H_{34}O_3$ [M+Na^+] 381.2406, found 381.2388.



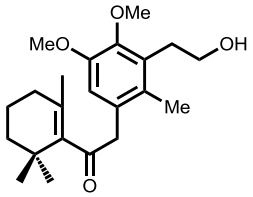
2-(3-allyl-4,5-dimethoxy-2-methylphenyl)-1-(2,6,6-trimethylcyclohex-1-en-1-yl)ethanone (4.25). To a solution of alcohol **4.24** (910 mg, 2.54 mmol) in DMSO (5 mL) was added IBX (1.07 g, 3.81 mmol) at room temperature. The resulting mixture was stirred at room temperature for 3h. The reaction was quenched with H_2O (5 mL) at 0 °C. The mixture was filtered and the aqueous phase was extracted with EtOAc. The combined organic layers were washed with brine, and dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified by column chromatography (silica gel, eluted with ethyl acetate/petroleum ether = 1/1) to provide the product **4.25** (780 mg, 86%) as a yellow liquid. IR (film, cm^{-1}) 2937, 1691, 1596, 1487, 1285, 1226, 1113, 1048, 995; ^1H NMR (500 MHz, $CDCl_3$) δ 6.56 (s, 1H), 5.93 (ddt, *J* = 17.1, 10.2, 5.7 Hz,

1H), 4.99 (dq, J = 10.1, 1.7 Hz, 1H), 4.91 (dq, J = 17.1, 1.9 Hz, 1H), 3.87 (s, 2H), 3.82 (s, 3H), 3.78 (s, 3H), 3.48 (dt, J = 5.7, 1.8 Hz, 2H), 2.11 (s, 3H), 1.99 (t, J = 6.5 Hz, 2H), 1.72-1.67 (m, 2H), 1.63 (s, 3H), 1.48-1.46 (m, 2H), 1.11 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) 207.8, 150.3, 146.4, 143.1, 136.6, 132.4, 129.5, 129.1, 128.4, 114.9, 112.9, 60.8, 55.8, 50.8, 39.0, 33.4, 31.3, 31.2, 28.8, 21.2, 18.9, 15.4; HRMS (ESI): calculated for $C_{23}H_{32}O_3$ [M+H$^+$] 357.2430, found 357.2423.



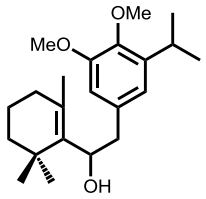
2-(2,3-dimethoxy-6-methyl-5-(2-oxo-2-(2,6,6-trimethylcyclohex-1-en-1-yl)ethyl)phenyl)acetaldehyde (4.26). To a solution of alkene **4.25** (530 mg, 1.49 mmol) in acetone/H_2O (4/1, 15 mL) was added NMO (262 mg, 2.23 mmol) and 5% OsO_4 solution in *t*-BuOH (758 mg, 7.45% mmol, 2.5 wt%). After being stirred at room temperature for overnight, the reaction mixture was concentrated in vacuo. The residue was dissolved in EtOAc, washed with H_2O, brine, and dried over Na_2SO_4. After concentration in *vacuo*, the crude diol was dissolved in CH_3CN/H_2O (1/1, 16 mL). To which, $NaIO_4$ (478 mg, 2.24 mmol) was added at 0 °C. The reaction mixture was allowed to reach room temperature and was stirred for 1h before it was filtered through a short pad of silica gel (eluted with EtOAc) to allow the removal of insoluble salts. The filtrate was then washed with H_2O, brine, dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified by column chromatography (silica gel, eluted with ethyl acetate/petroleum ether = 1/5) to provide the product **4.26** (446 mg, 84% for 2 steps) as a

white solid. IR (film, cm^{-1}) 2937, 1720, 1697, 1484, 1279, 1229, 1108, 1066; ^1H NMR (500 MHz, $CDCl_3$) δ 9.68 (s, 1H), 6.62 (s, 1H), 3.89 (s, 2H), 3.84 (s, 3H), 3.81 (d, *J* = 2.0 Hz, 2H), 3.78 (s, 3H), 2.07 (s, 3H), 2.00 (t, *J* = 6.5 Hz, 2H), 1.72-1.66 (m, 2H), 1.64 (s, 3H), 1.49-1.46 (m, 2H), 1.12 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) 207.6, 199.7, 150.2, 146.6, 143.0, 129.7, 129.2, 128.8, 125.7, 114.2, 60.5, 55.8, 50.8, 42.7, 38.9, 33.5, 31.3, 28.8, 21.2, 18.8, 16.1; HRMS (ESI): calculated for $C_{22}H_{30}O_4$ [M+Li^+] 365.2304, found 365.2312.



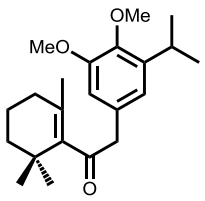
2-(3-(2-hydroxyethyl)-4,5-dimethoxy-2-methylphenyl)-1-(2,6,6-trimethyl cyclohex-1-en-1-yl)ethanone (4.27). To a solution of aldehyde **4.26** (423 mg, 1.18 mmol) in PhH (10 mL) was added $NaBH(OAc)_3$ (376 mg, 1.77 mmol) and acetic acid (0.70 mL). After being stirred at room temperature under nitrogen for 6h, the reaction was quenched with saturated aqueous $NaHCO_3$ at °C. The aqueous phase was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified by column chromatography (silica gel, eluted with ethyl acetate/petroleum ether = 1/1) to provide the product **4.27** (370 mg, 87%) as a white solid. IR (film, cm^{-1}) 3446, 2934, 1694, 1596, 1492, 1300, 1229, 1116, 1048; ^1H NMR (500 MHz, $CDCl_3$) δ 6.55 (s, 1H), 3.88 (s, 2H), 3.83 (s, 3H), 3.82 (s, 3H), 3.77 (t, *J* = 6.7 Hz, 2H), 3.00 (t, *J* = 6.8 Hz, 2H), 2.16 (s, 3H), 2.00 (t, *J* = 6.4 Hz, 2H), 1.72-1.67 (m, 2H), 1.64 (s, 3H), 1.49-1.46 (m, 2H), 1.12 (s, 6H); ^{13}C NMR (125

MHz, $CDCl_3$) 207.8, 150.1, 146.5, 143.0, 131.1, 129.6, 128.8, 128.8, 113.1, 62.7, 60.5, 55.7, 50.9, 38.9, 33.5, 31.3, 30.7, 28.8, 21.2, 18.8, 15.7; HRMS (ESI): calculated for $C_{22}H_{32}O_4$ [M+Li^+] 367.2461, found 367.2469.

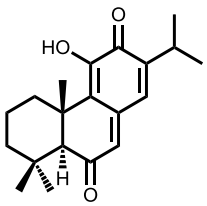


2-(3-isopropyl-4,5-dimethoxyphenyl)-1-(2,6,6-trimethylcyclohex-1-en-1-yl)ethanol (A.11). A mixture of naphthalene (4.92 g, 38.35 mmol) and lithium (266 mg, 38.35 mmol) in THF (40 mL) was stirred at room temperature under nitrogen for 1.5h. To which, a solution of β-cyclocitral (1.28 g, 8.44 mmol) and benzyl chloride **4.28** (1.75 g, 7.67 mmol) in THF (10 mL) was added dropwise via syringe at 0 °C. The mixture was then stirred at room temperature for 2h, diluted with ether and then quenched with saturated aqueous NH_4Cl. The organic phase was separated. The aqueous phase was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4. After concentration, the residue was purified by flash column chromatography (silica gel, eluted with ethyl acetate/petroleum ether = 1/5) to provide allyl alcohol **A.11** (2.26 g, 85%) as a light yellow liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.70 (d, *J* = 1.9 Hz, 1H), 6.66 (d, *J* = 1.9 Hz, 1H), 4.42 (dd, *J* = 10.1, 3.6 Hz, 1H), 3.87 (s, 3H), 3.80 (s, 3H), 3.34 (dt, *J* = 13.9, 6.9 Hz, 1H), 3.06 (dd, *J* = 13.9, 10.1 Hz, 1H), 2.82 (dd, *J* = 13.9, 3.5 Hz, 1H), 2.05-1.94 (m, 2H), 1.96 (s, 3H), 1.62-1.53 (m, 2H), 1.46-1.42 (m, 2H), 1.23 (s, 3H), 1.22 (s, 3H), 1.10 (s, 3H), 0.97 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 152.5, 144.9,

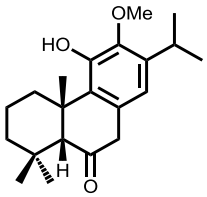
142.4, 139.0, 135.5, 131.8, 118.9, 110.7, 72.4, 60.9, 55.7, 43.4, 39.9, 34.8, 34.1, 28.6, 28.1, 26.8, 23.6, 23.5, 21.4, 19.3.



2-(3-isopropyl-4,5-dimethoxyphenyl)-1-(2,6,6-trimethylcyclohex-1-en-1-yl)ethanone (1.69). To a solution of **A.11** (370 mg, 1.07 mmol) in DMSO (4 mL) was added IBX (449 mg, 1.60 mmol) at room temperature. The resulting mixture was stirred at room temperature for 3h. The reaction was quenched with H_2O (5 mL) at 0 °C. The mixture was filtered and the aqueous phase was extracted with EtOAc. The combined organic layers were washed with brine, and dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified by column chromatography (silica gel, eluted with ethyl acetate/petroleum ether = 1/5) to provide the product **1.69** (285 mg, 77%) as a yellow liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.66 (d, J = 2.0 Hz, 1H), 6.64 (d, J = 2.0 Hz, 1H), 3.85 (s, 3H), 3.80 (s, 3H), 3.79 (s, 2H), 3.33 (dt, J = 13.9, 6.9 Hz, 1H), 1.99-1.96 (m, 2H), 1.69-1.67 (m, 2H), 1.56 (s, 3H), 1.47-1.44 (m, 2H), 1.20 (s, 3H), 1.19 (s, 3H), 1.08 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) 152.3, 145.1, 143.1, 142.0, 129.7, 129.6, 119.7, 111.3, 60.9, 55.7, 52.2, 38.9, 33.4, 31.2, 28.8, 26.7, 23.5, 21.2, 18.8.

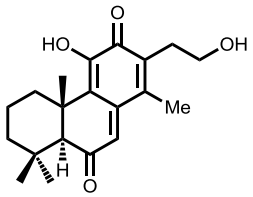


(4bS,8aS)-4-hydroxy-2-isopropyl-1,4b,8,8-tetramethyl-4b,5,6,7,8,8a-hexahydrophenanthrene-3,9-dione (4.42). To a solution of ketone **1.69** (103 mg, 0.30 mmol) in DCM (3 mL) was added freshly prepared BBr_3 solution dropwise (1.80 mL, 1.80 mmol, 1M in DCM) at -78 °C under nitrogen. The reaction was stirred for 30 min then warmed up to 0 °C and stirred for 3h. The reaction was carefully quenched with saturated aqueous $NaHCO_3$. The aqueous phase was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4. After concentration *in vacuo*, the residue was dissolved in $CHCl_3$ (10 mL). To which, Ag_2O was added (104 mg, 0.45 mmol). The mixture was stirred at 50 °C for 30 min and filtered through cotton to allow the removal of insoluble solids. The filtrate was concentrated and purified by column chromatography (silica gel, eluted with ethyl acetate/petroleum ether = 1/4) to provide the product **4.42** (36.8 mg, 39% for 2 steps) as an orange solid.. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (s, 1H), 6.88 (s, 1H), 6.21 (s, 1H), 3.10-3.04 (m, 1H), 2.95-2.92 (m, 1H), 2.60 (s, 1H), 1.78-1.14 (m, 5H), 1.27 (s, 6H), 1.18 (d, J = 6.9 Hz, 3H), 1.16 (d, J = 6.9 Hz, 3H), 1.12 (s, 3H).



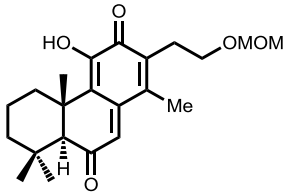
(4bS,8aR)-4-hydroxy-2-isopropyl-3-methoxy-4b,8,8-trimethyl-4b,5,6,7,8,8a-hexahydro phenanthren-9(10H)-one (4.37). A mixture of hexamethyldisilane (0.25 mL, 1.2 mmol) and iodine (305 mg, 1.2 mmol) was heated at 65 °C for 20 min under nitrogen. After cooling down to room temperature, a solution of ketone **1.69** (69 mg, 0.2

mmol) in toluene (1 mL) was added. The reaction mixture was stirred at 70 °C for 4h. After concentration in *vacuo*, the residue was purified by flash column chromatography (silica gel, ethyl acetate/petroleum ether, 1/5) to provide **4.37** (35.9 mg, 54 %) as a yellow solid. IR (film, cm^{-1}) 3414, 2955, 2931, 1694, 1448, 1418, 1300, 1229, 1057, 1033, 998; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.67 (s, 1H), 5.77 (s, 1H), 3.80 (s, 3H), 3.65 (dd, *J* = 22.9, 1.1 Hz, 1H), 3.47 (d, *J* = 22.9 Hz, 1H), 3.27 (dt, *J* = 13.9, 6.9 Hz, 1H), 3.03-2.99 (m, 1H), 1.98 (s, 1H), 1.61-1.15 (m, 5H), 1.26 (d, *J* = 6.9 Hz, 3H), 1.24 (d, *J* = 6.9 Hz, 3H), 1.24 (s, 3H), 0.94 (s, 3H), 0.30 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 213.1, 145.8, 144.9, 133.7, 130.4, 126.4, 122.3, 68.5, 61.9, 44.0, 42.2, 40.1, 37.4, 34.4, 32.4, 31.9, 27.2, 22.8, 22.5, 22.4, 20.2; HRMS (ESI): calculated for $C_{21}H_{30}O_3$ $[M+H^+]$ 331.2268, found 331.2264.



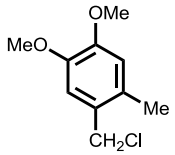
(4bS,8aS)-4-hydroxy-2-(2-hydroxyethyl)-1,4b,8,8-tetramethyl-4b,5,6,7,8,8a-hexahydrophenanthrene-3,9-dione (1.67). To a solution of alcohol **4.27** (301 mg, 0.84 mmol) in DCM (8 mL) was added freshly prepared BBr_3 solution dropwise (5.04 mL, 5.04 mmol, 1M in DCM) at -78 °C under nitrogen. The reaction was stirred for 30 min then warmed up to 0 °C and stirred for 2h. The reaction was carefully quenched with saturated aqueous $NaHCO_3$. The aqueous phase was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4. After concentration *in vacuo*, the residue was dissolved in $CHCl_3$ (10 mL). To which, Ag_2O

was added (223 mg, 0.90 mmol). The mixture was stirred at 50 °C for 30 min and filtered through cotton to allow the removal of insoluble solids. The filtrate was concentrated and purified by column chromatography (silica gel, eluted with ethyl acetate/petroleum ether = 1/1) to provide the natural product **1.67** (103 mg, 37% for 2 steps) as an orange solid. IR (film, cm^{-1}) 3325, 2925, 1670, 1610, 1377, 1223, 1185, 1146, 1045; ^1H NMR (500 MHz, acetone-d_6) δ 8.32 (s, 1H), 6.50 (s, 1H), 3.75 (t, *J* = 5.7 Hz, 1H), 3.63-3.59 (m, 2H), 3.05-3.02 (m, 1H), 2.85-2.81 (m, 2H), 2.65 (s, 1H), 2.34 (s, 3H), 1.76-1.70 (m, 2H), 1.59-1.54 (m, 1H), 1.40-1.36 (m, 1H), 1.29-1.26 (m, 1H), 1.27 (s, 3H), 1.24 (s, 3H), 1.10 (s, 3H); ^1H NMR (500 MHz, acetone-d_6+D_2O) δ 6.52 (s, 1H), 3.59 (t, *J* = 7.1 Hz, 2H), 3.03 (d, *J* = 11.8 Hz, 1H), 2.83 (t, *J* = 7.2 Hz, 2H), 2.66 (s, 1H), 2.33 (s, 3H), 1.73-1.66 (m, 2H), 1.56-1.53 (m, 1H), 1.37 (d, *J* = 11.7 Hz, 1H), 1.26 (s, 3H), 1.23 (s, 3H), 1.10 (s, 3H). ^{13}C NMR (125 MHz, acetone-d_6) δ 201.1, 182.3, 146.4, 145.1, 142.0, 134.8, 131.3, 127.0, 62.3, 61.2, 43.0, 42.9, 37.7, 33.4, 33.3, 31.0, 22.2, 21.6, 19.3, 15.9; HRMS (ESI): calculated for $C_{20}H_{26}O_4$ [M-H^+] 329.1753, found 329.1738.



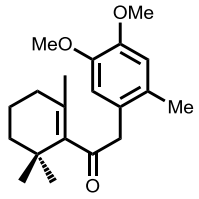
(4bS,8aS)-4-hydroxy-2-(2-(methoxymethoxy)ethyl)-1,4b,8,8-tetramethyl-4b,5,6,7,8,8a-hexahydrophenanthrene-3,9-dione (4.38). To a solution of alcohol **1.67** (9.9 mg, 0.03 mmol) in DCM (2 mL) was added dimethoxymethane (0.027 mL, 0.3 mmol) and P_2O_5 (43 mg, 0.15 mmol). The mixture was stirred at room temperature for

2h before it was diluted with DCM. The organic phase was washed with saturated aqueous $NaHCO_3$ and dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified by column chromatography (silica gel, eluted with ethyl acetate/petroleum ether = 1/5) to provide the product **4.38** (7.4 mg, 66%) as a yellow liquid. IR (film, cm^{-1}) 3322, 2934, 1670, 1611, 1380, 1152, 1116, 1025; ^1H NMR (500 MHz, $CDCl_3$) δ 7.53 (s, 1H), 6.51 (s, 1H), 4.60 (s, 2H), 3.62 (t, J = 6.9 Hz, 2H), 3.33 (s, 3H), 2.98-2.95 (m, 1H), 2.93-2.88 (m, 2H), 2.59 (s, 1H), 2.29 (s, 3H), 1.74-1.70 (m, 2H), 1.62-1.59 (m, 2H), 1.44-1.40 (m, 1H), 1.28 (s, 3H), 1.26 (s, 3H), 1.13 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 201.2, 181.5, 146.1, 143.7, 141.1, 133.5, 131.1, 126.6, 96.3, 65.9, 62.2, 55.2, 42.6, 42.4, 37.1, 33.2, 32.7, 27.2, 21.9, 21.7, 18.6, 15.8; HRMS (ESI): calculated for $C_{22}H_{30}O_5$ $[M+Li^+]$ 381.2248, found 381.2262.



1-(chloromethyl)-4,5-dimethoxy-2-methylbenzene (4.39). To a solution of carboxylic acid **4.6** (3.92 g, 20 mmol) in THF (40 mL) was added borane dimethyl sulfide (16 mL, 32 mmol, 2M in THF) at 0 °C. The resulting solution was allowed to warm to room temperature overnight. The reaction was carefully quenched with H_2O and the resulting solution was diluted with EtOAc. Organic Phase was separated, washed with H_2O, dried over Na_2SO_4. After concentration, the residue was purified by flash column chromatography (silica gel, eluted with ethyl acetate/petroleum ether = 1/1) to provide benzyl alcohol (3.28 g, 90 %) as a white solid.

To a solution of the above benzyl alcohol (1.82 g, 10 mmol) in CH_2Cl_2 (20 mL) was added $SOCl_2$ (0.87 mL, 12 mmol) dropwise at 0 °C under nitrogen. The reaction was stirred at room temperature for 30 min before it was carefully quenched by the addition of saturated aqueous $NaHCO_3$. The organic phase was separated. Aqueous phase was extracted with DCM. The combined organic layers were dried over Na_2SO_4. After concentration, the residue was purified by flash column chromatography (silica gel, eluted with ethyl acetate/petroleum ether = 1/5) to provide product **4.39** (1.90 g, 95 %) as a yellow oil. IR (film, cm^{-1}) 2963, 2934, 1611, 1519, 1466, 1338, 12821226, 1105, 998; ^1H NMR (500 MHz, $CDCl_3$) δ 6.84 (s, 1H), 6.71 (s, 1H), 4.60 (s, 2H), 3.89 (s, 6H), 2.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 149.1, 147.0, 129.8, 127.3, 113.7, 113.0, 56.0, 55.9, 45.2, 18.4; HRMS (ESI): calculated for $C_{10}H_{13}O_2Cl$ [M+H^+] 201.0682, found 201.0692.

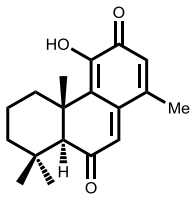


2-(4,5-dimethoxy-2-methylphenyl)-1-(2,6,6-trimethylcyclohex-1-en-1-yl)ethanone (4.40). A mixture of naphthalene (5.77 g, 45 mmol) and lithium (313 mg, 45 mmol) in THF (50 mL) was stirred at room temperature under nitrogen for 1.5h. To which, a solution of β-cyclocitral (1.51 g, 9.9 mmol) and benzyl chloride **4.39** (1.80 g, 9 mmol) in THF (10 mL) was added via syringe at 0 °C. The mixture was then stirred at room temperature for 2h, diluted with ether and then quenched with saturated aqueous NH_4Cl. The organic phase was separated. The aqueous phase was extracted with EtOAc.

The combined organic layers were washed with brine, dried over Na_2SO_4. After concentration, the residue was purified by flash column chromatography (silica gel, eluted with ethyl acetate/petroleum ether = 1/5) to provide allyl alcohol **A.12** (2.17g, 76%) as a light yellow solid. IR (film, cm^{-1}) 3538, 2934, 1608, 1513, 1466, 1270, 1226, 1102, 998; ^1H NMR (500 MHz, $CDCl_3$) δ 6.74 (s, 1H), 6.69 (s, 1H), 4.44 (dd, *J* = 10.2, 4.1 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.14 (dd, *J* = 14.2, 10.2 Hz, 1H), 2.79 (dd, *J* = 14.2, 4.1 Hz, 1H), 2.33 (s, 3H), 2.03-1.94 (m, 3H), 2.00 (s,3H), 1.62- 1.53 (m, 2H), 1.45-1.42 (m, 2H), 1.10 (s, 3H), 0.94 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 147.3, 147.0, 139.3, 131.9, 129.6, 128.8, 113.8, 113.7, 71.4, 56.1, 55.9, 40.0, 39.5, 34.8, 34.2, 28.5, 28.3, 21.4, 19.6, 19.3; HRMS (ESI): calculated for $C_{20}H_{30}O_3$ [M+Li^+] 325.2355, found 325.2339.

To a solution of the above allyl alcohol **A.12** (960 mg, 3.03 mmol) in DMSO (6 mL) was added IBX (1.27 g, 4.55 mmol) at room temperature. The resulting mixture was stirred at room temperature for 2h. The reaction was quenched with H_2O (6 mL) at 0 °C. The mixture was filtered and the aqueous phase was extracted with EtOAc. The combined organic layers were washed with brine, and dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified by column chromatography (silica gel, eluted with ethyl acetate/petroleum ether = 1/3) to provide the product **4.40** (701 mg, 73%) as a light solid. IR (film, cm^{-1}) 2931, 1700, 1516, 1460, 1270, 1229, 1108, 1039, 998; ^1H NMR (500 MHz, $CDCl_3$) δ 6.71 (s, 1H), 6.61 (s, 1H), 3.86 (s, 3H), 3.83 (s, 3H), 3.82 (s, 2H), 2.23 (s, 3H), 1.99 (t, *J* = 6.4 Hz, 2H), 1.71-1.66 (m, 2H), 1.62 (s, 3H), 1.48-1.46 (m, 2H), 1.11 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) 147.8, 146.8, 143.0, 129.5,

129.4, 124.5, 113.7, 113.6, 56.0, 55.8, 49.7, 38.9, 33.4, 31.2, 28.8, 21.1, 19.6, 18.8; HRMS (ESI): calculated for $C_{20}H_{28}O_3$ [M+H$^+$] 317.2117, found 317.2126.



(4bS,8aS)-4-hydroxy-1,4b,8,8-tetramethyl-4b,5,6,7,8,8a-hexahydrophenanthrene-3,9-dione (4.41). To a solution of ketone **4.40** (95 mg, 0.30 mmol) in DCM (3 mL) was added freshly prepared BBr_3 solution dropwise (1.80 mL, 1.80 mmol, 1M in DCM) at -78 °C under nitrogen. The reaction was stirred for 30 min then warmed up to 0 °C and stirred for 3h. The reaction was carefully quenched with saturated aqueous $NaHCO_3$. The aqueous phase was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4. After concentration *in vacuo*, the residue was dissolved in $CHCl_3$ (10 mL). To which, Ag_2O was added (104 mg, 0.45 mmol). The mixture was stirred at 50 °C for 30 min and filtered through cotton to allow the removal of insoluble solids. The filtrate was concentrated and purified by column chromatography (silica gel, eluted with ethyl acetate/petroleum ether = 1/4) to provide the product **4.41** (35.9 mg, 42% for 2 steps) as an orange solid. IR (film, cm^{-1}); 3432, 2925, 1673, 1626, 1413, 1380, 1356, 1223, 1146, 773; ^{1}H NMR (500 MHz, $CDCl_3$); δ 7.42 (s, 1H), 6.43 (s, 1H), 6.42 (d, *J* = 1.2 Hz 1H), 2.97-2.94 (m, 1H), 2.59 (s, 1H), 2.26 (d, *J* = 1.3 Hz, 3H), 1.77-1.66 (m, 2H), 1.62-1.57 (m, 1H), 1.43-1.39 (m, 1H), 1.27 (s, 3H), 1.26 (s, 3H), 1.24-1.16 (m, 1H), 1.12 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 201.1, 181.6, 150.3, 144.5, 140.9, 131.3, 126.9, 126.4, 62.4, 42.9, 42.4, 37.1, 33.2, 32.8, 21.9,

21.7, 19.8, 18.6; HRMS (ESI): calculated for $C_{18}H_{22}O_3$ [M-H^+] 285.1496, found 285.1501.

A.5 Crystal and Molecular Structure Determination for 3.18

X-ray Diffraction Laboratory
Department of Chemistry
Texas A&M University

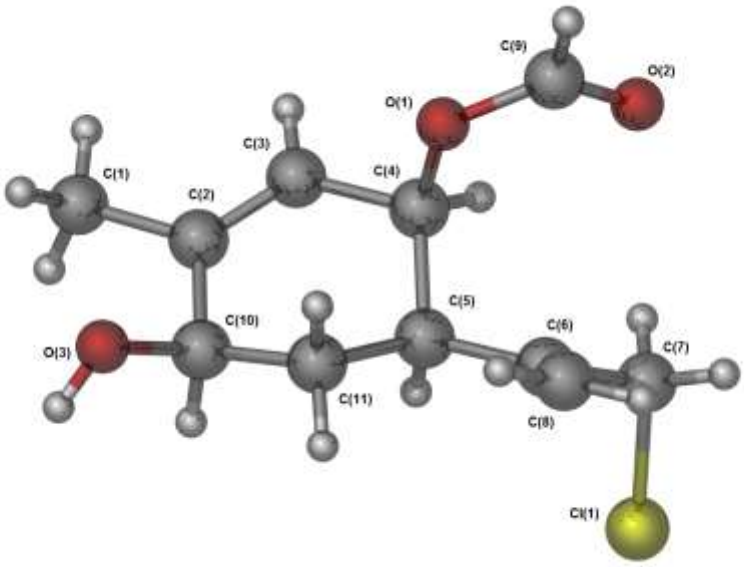


Figure A.1. X-ray structure of **3.18**

Table A.2. Crystal data and structure refinement for **3.18**

Empirical formula	$C_{11}H_{15}ClO_3$	
Formula weight	230.68	
Temperature	110(2) K	
Wavelength	1.54178 Å	
Crystal system	Tetragonal	
Space group	I4(1)	
Unit cell dimensions	a = 18.2294(4) Å	α= 90°.
	b = 18.2294(4) Å	β= 90°.
	c = 7.0465(3) Å	γ = 90°.
Volume	2341.63(12) $Å^3$	
Z	8	
Density (calculated)	1.309 Mg/m^3	
Absorption coefficient	2.785 mm^{-1}	
F(000)	976	
Crystal size	0.10 x 0.05 x 0.02 mm^3	
Theta range for data collection	6.74 to 59.95°.	
Index ranges	-20<=h<=20, -20<=k<=20, -7<=l<=7	
Reflections collected	21338	
Independent reflections	1655 [R(int) = 0.0441]	
Completeness to theta = 59.95°	96.1 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9464 and 0.7681	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1655 / 1 / 138	
Goodness-of-fit on F^2	1.077	
Final R indices [I>2sigma(I)]	R1 = 0.0390, wR2 = 0.0962	
R indices (all data)	R1 = 0.0414, wR2 = 0.0974	
Absolute structure parameter	0.03(2)	
Largest diff. peak and hole	0.840 and -0.186 $e.Å^{-3}$	

Table A.3. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3). U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Cl(1)	9838(1)	11059(1)	11191(1)	30(1)
O(1)	8185(1)	10405(1)	5265(3)	24(1)
O(2)	8657(2)	11546(1)	5138(4)	36(1)
O(3)	7894(1)	8191(1)	8158(3)	27(1)
C(1)	8927(3)	8003(2)	5123(7)	44(1)
C(2)	8796(2)	8734(2)	6084(6)	27(1)
C(3)	8957(2)	9358(2)	5233(6)	29(1)
C(4)	8858(2)	10102(2)	6116(5)	22(1)
C(5)	8766(2)	10048(2)	8280(5)	19(1)
C(6)	8605(2)	10787(2)	9165(4)	22(1)
C(7)	9237(2)	11309(2)	9252(5)	28(1)
C(8)	7958(2)	10978(2)	9850(5)	29(1)
C(9)	8175(2)	11122(2)	4839(5)	27(1)
C(10)	8488(2)	8708(2)	8070(5)	24(1)
C(11)	8223(2)	9445(2)	8760(5)	22(1)

Table A.4. Bond lengths [Å] and angles [°] for **3.18**

Cl(1)-C(7)	1.809(3)
O(1)-C(9)	1.342(4)
O(1)-C(4)	1.473(4)
O(2)-C(9)	1.188(4)
O(3)-C(10)	1.438(4)
O(3)-H(3)	0.8400
C(1)-C(2)	1.513(5)
C(1)-H(1A)	0.9800
C(1)-H(1B)	0.9800
C(1)-H(1C)	0.9800
C(2)-C(3)	1.319(5)
C(2)-C(10)	1.509(5)
C(3)-C(4)	1.504(5)
C(3)-H(3A)	0.9500
C(4)-C(5)	1.537(5)
C(4)-H(4)	1.0000
C(5)-C(6)	1.513(5)
C(5)-C(11)	1.519(4)
C(5)-H(5)	1.0000
C(6)-C(8)	1.321(5)
C(6)-C(7)	1.496(5)
C(7)-H(7A)	0.9900
C(7)-H(7B)	0.9900
C(8)-H(8A)	0.9500
C(8)-H(8B)	0.9500
C(9)-H(9)	0.9500
C(10)-C(11)	1.508(4)
C(10)-H(10)	1.0000
C(11)-H(11A)	0.9900
C(11)-H(11B)	0.9900

Table A.4. (Continued) Bond lengths [Å] and angles [°] for **3.18**

C(9)-O(1)-C(4)	117.8(3)
C(10)-O(3)-H(3)	109.5
C(2)-C(1)-H(1A)	109.5
C(2)-C(1)-H(1B)	109.5
H(1A)-C(1)-H(1B)	109.5
C(2)-C(1)-H(1C)	109.5
H(1A)-C(1)-H(1C)	109.5
H(1B)-C(1)-H(1C)	109.5
C(3)-C(2)-C(10)	122.1(3)
C(3)-C(2)-C(1)	121.4(4)
C(10)-C(2)-C(1)	116.5(3)
C(2)-C(3)-C(4)	124.3(4)
C(2)-C(3)-H(3A)	117.8
C(4)-C(3)-H(3A)	117.8
O(1)-C(4)-C(3)	105.6(3)
O(1)-C(4)-C(5)	109.7(2)
C(3)-C(4)-C(5)	111.4(3)
O(1)-C(4)-H(4)	110.0
C(3)-C(4)-H(4)	110.0
C(5)-C(4)-H(4)	110.0
C(6)-C(5)-C(11)	115.2(3)
C(6)-C(5)-C(4)	111.9(3)
C(11)-C(5)-C(4)	109.8(3)
C(6)-C(5)-H(5)	106.5
C(11)-C(5)-H(5)	106.5
C(4)-C(5)-H(5)	106.5
C(8)-C(6)-C(7)	120.3(3)
C(8)-C(6)-C(5)	124.0(3)
C(7)-C(6)-C(5)	115.7(3)
C(6)-C(7)-Cl(1)	109.7(2)
C(6)-C(7)-H(7A)	109.7

Table A.4. (Continued) Bond lengths [Å] and angles [°] for **3.18**

Cl(1)-C(7)-H(7A)	109.7
C(6)-C(7)-H(7B)	109.7
Cl(1)-C(7)-H(7B)	109.7
H(7A)-C(7)-H(7B)	108.2
C(6)-C(8)-H(8A)	120.0
C(6)-C(8)-H(8B)	120.0
H(8A)-C(8)-H(8B)	120.0
O(2)-C(9)-O(1)	125.7(3)
O(2)-C(9)-H(9)	117.1
O(1)-C(9)-H(9)	117.1
O(3)-C(10)-C(11)	109.2(3)
O(3)-C(10)-C(2)	110.0(3)
C(11)-C(10)-C(2)	113.0(3)
O(3)-C(10)-H(10)	108.2
C(11)-C(10)-H(10)	108.2
C(2)-C(10)-H(10)	108.2
C(10)-C(11)-C(5)	111.4(3)
C(10)-C(11)-H(11A)	109.4
C(5)-C(11)-H(11A)	109.4
C(10)-C(11)-H(11B)	109.4
C(5)-C(11)-H(11B)	109.4
H(11A)-C(11)-H(11B)	108.0

Symmetry transformations used to generate equivalent atoms:

Table A.5. Anisotropic displacement parameters ($Å^2$ x 10^3) for **3.18**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2}U^{11} + ... + 2 hk a^* b^* U^{12}]$

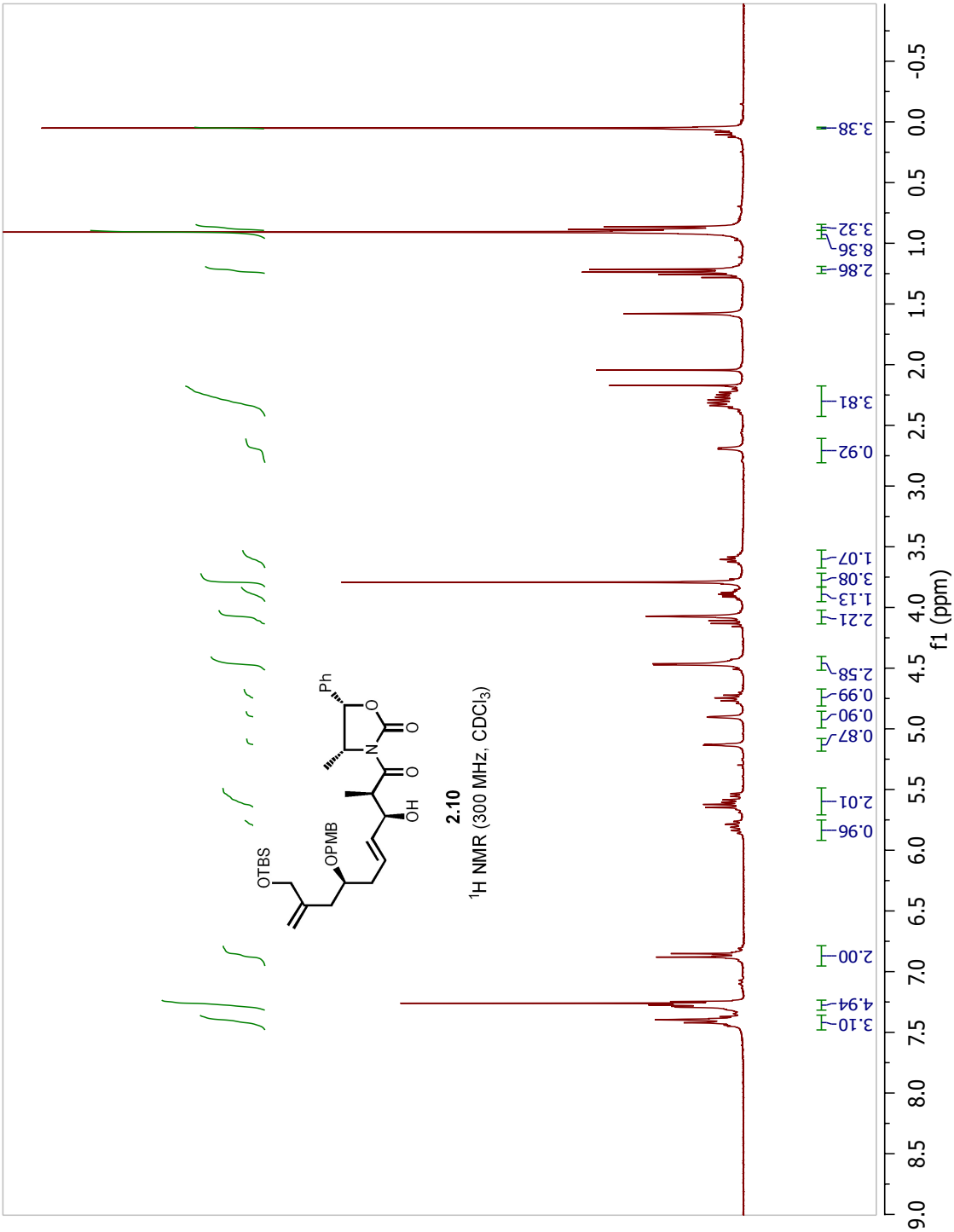
	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Cl(1)	24(1)	31(1)	33(1)	-4(1)	-5(1)	-1(1)
O(1)	25(1)	26(1)	22(1)	1(1)	-1(1)	-2(1)
O(2)	50(2)	26(1)	31(1)	3(1)	1(1)	-4(1)
O(3)	22(1)	22(1)	38(2)	5(1)	-9(1)	-8(1)
C(1)	60(3)	24(2)	49(2)	-11(2)	12(2)	0(2)
C(2)	25(2)	24(2)	33(2)	-8(2)	1(2)	1(1)
C(3)	30(2)	24(2)	33(2)	-3(2)	9(2)	0(2)
C(4)	19(2)	25(2)	23(2)	0(2)	5(1)	1(1)
C(5)	15(2)	22(2)	21(2)	0(1)	4(1)	1(1)
C(6)	27(2)	26(2)	15(2)	4(1)	-9(1)	0(2)
C(7)	32(2)	25(2)	25(2)	-3(1)	-3(2)	-5(2)
C(8)	26(2)	35(2)	26(2)	-5(2)	-1(2)	5(2)
C(9)	40(2)	22(2)	20(2)	0(2)	4(2)	4(2)
C(10)	17(2)	24(2)	30(2)	4(1)	-4(1)	-5(2)
C(11)	19(2)	25(2)	21(2)	0(2)	0(1)	-3(1)

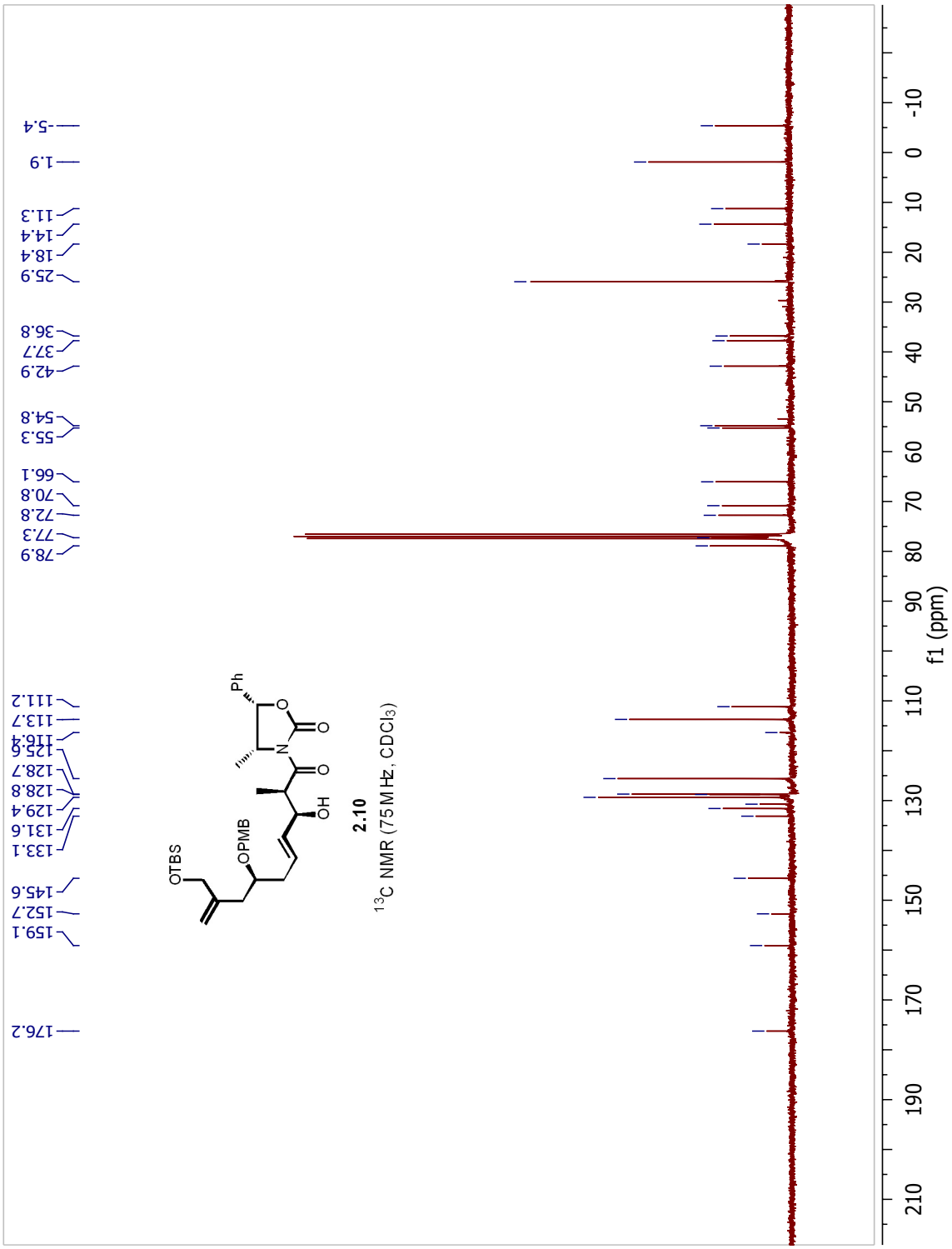
Table A.6. Hydrogen coordinates ($x10^4$) and isotropic displacement parameters ($Å^2$ x 10^3) for **3.18**

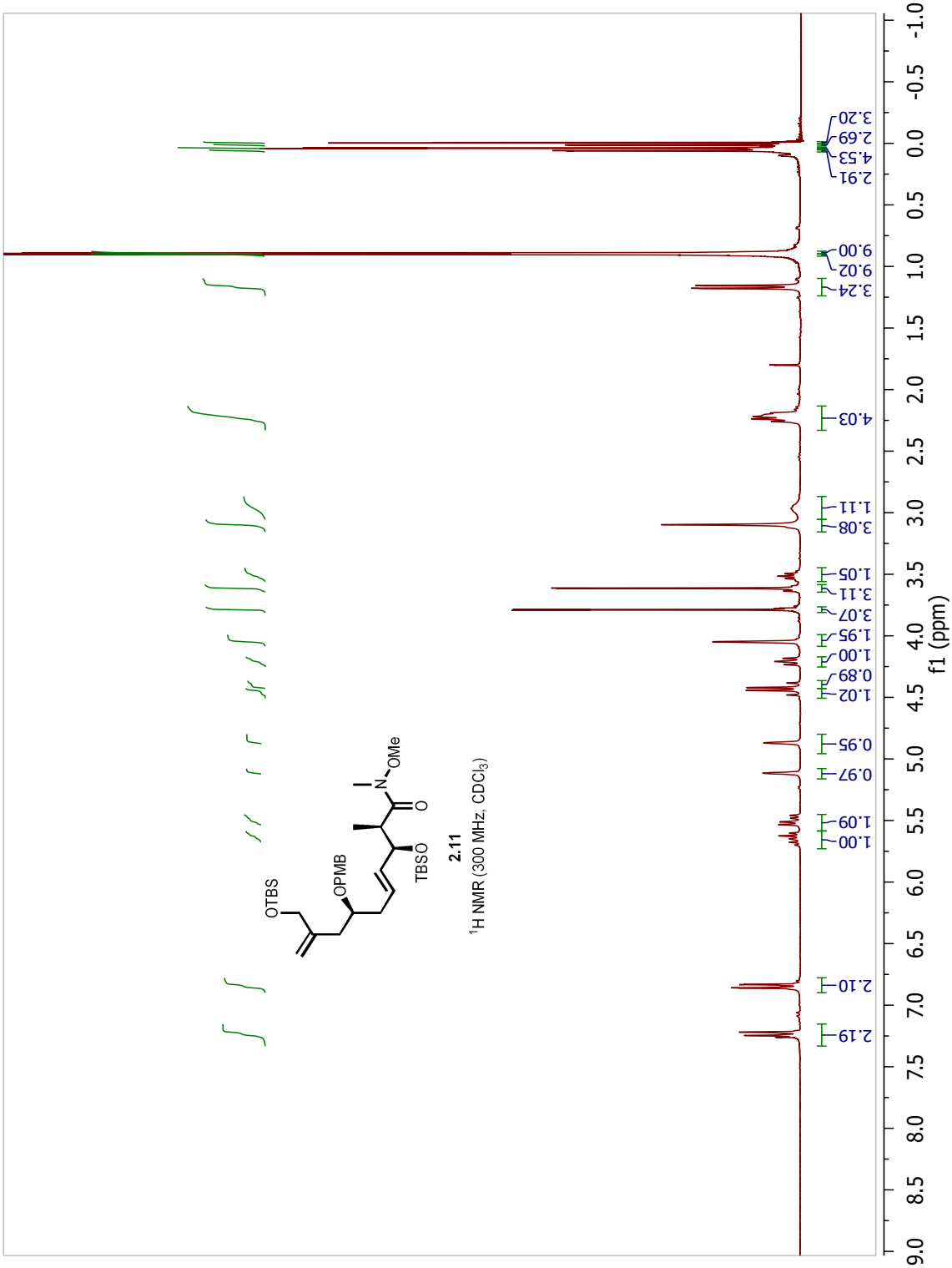
	x	y	z	U(eq)
H(3)	7994	7861	8951	41
H(1A)	9106	8086	3829	66
H(1B)	8467	7726	5077	66
H(1C)	9294	7724	5840	66
H(3A)	9148	9336	3980	35
H(4)	9286	10423	5802	27
H(5)	9251	9887	8796	23
H(7A)	9053	11815	9442	33
H(7B)	9512	11295	8041	33
H(8A)	7893	11450	10401	35
H(8B)	7559	10645	9791	35
H(9)	7746	11308	4247	33
H(10)	8884	8536	8945	28
H(11A)	8151	9426	10152	26
H(11B)	7744	9558	8168	26

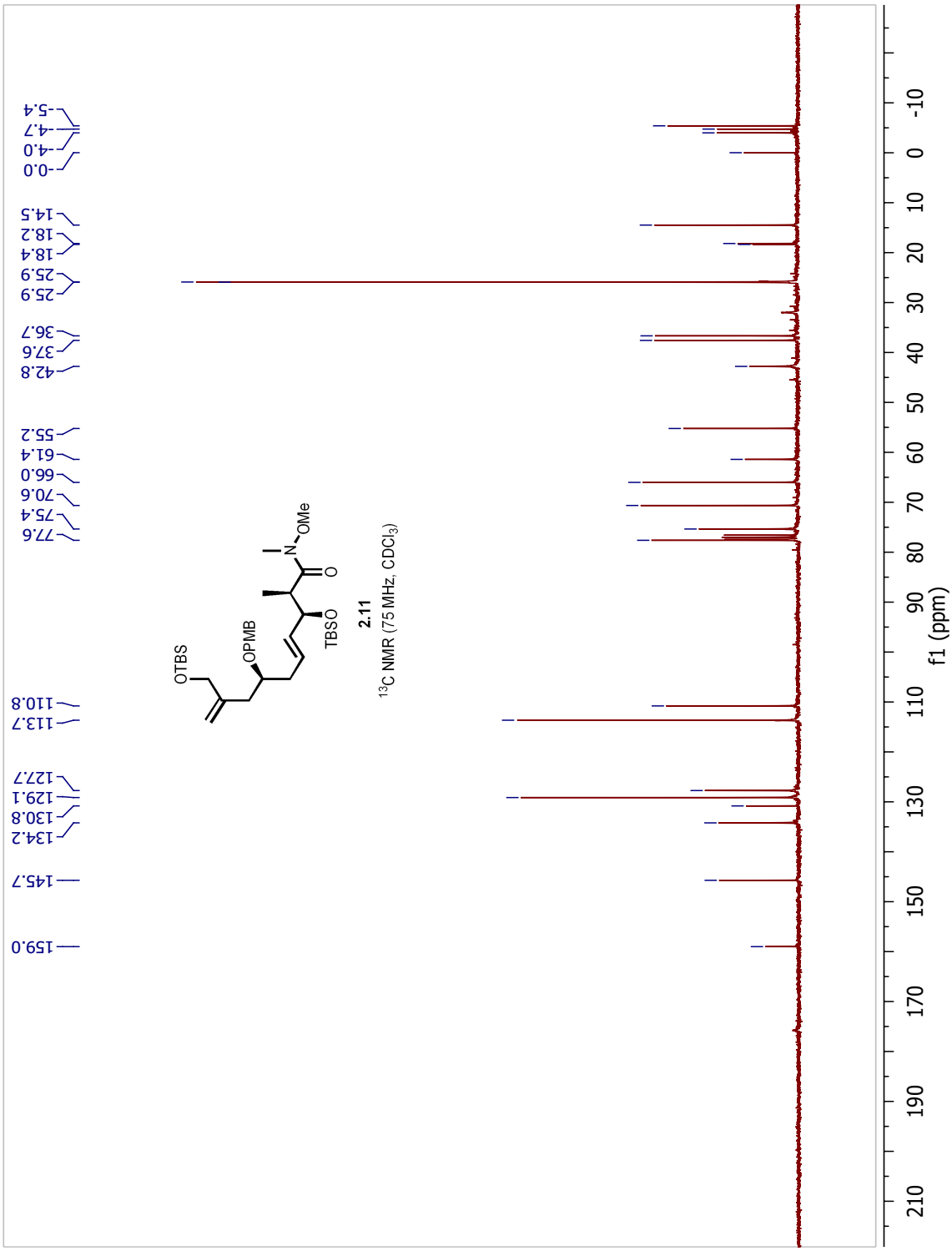
APPENDIX B

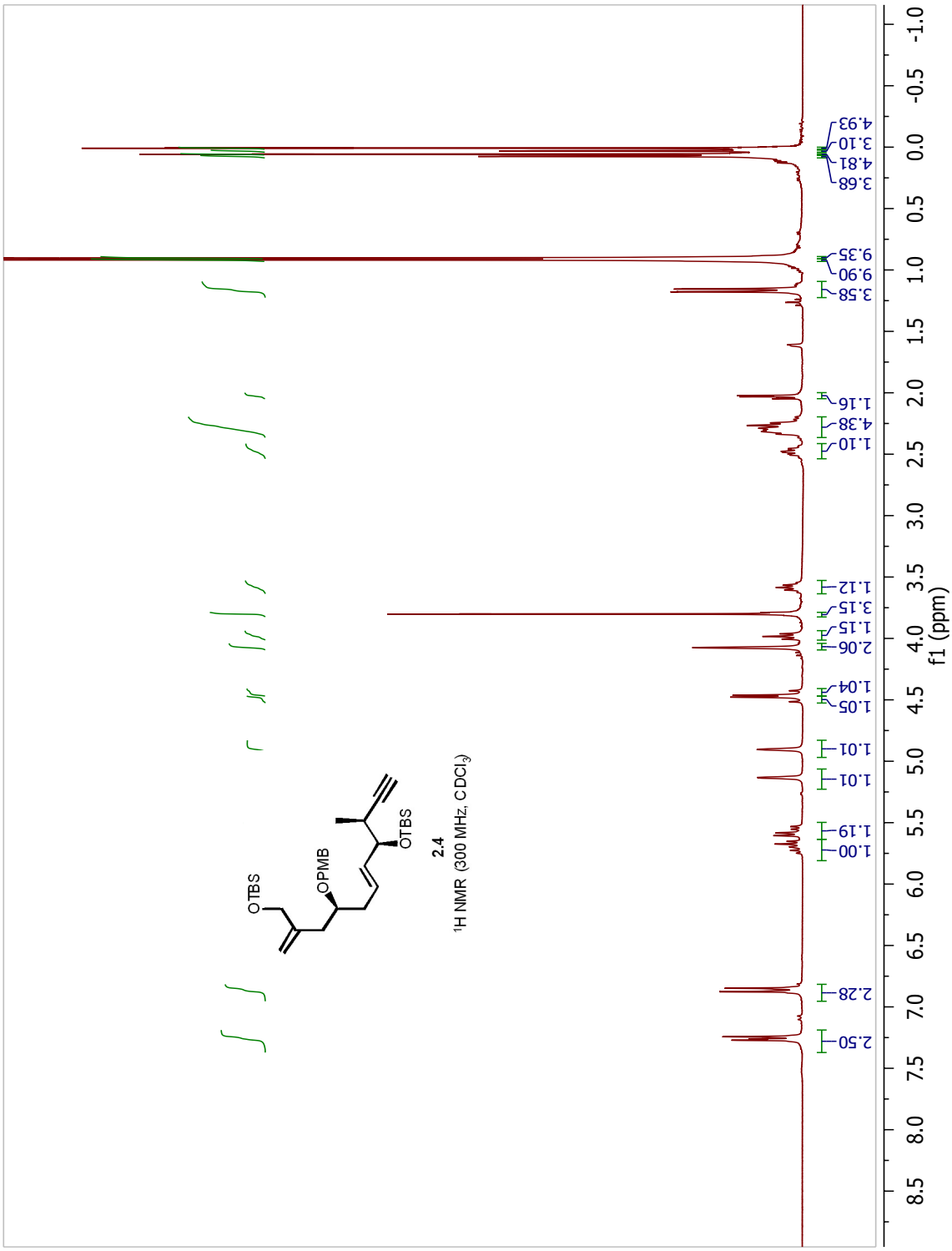
SPECTRA OF IRIOMOTEOLIDE-1A, ALOTAKETAL A and 1.67

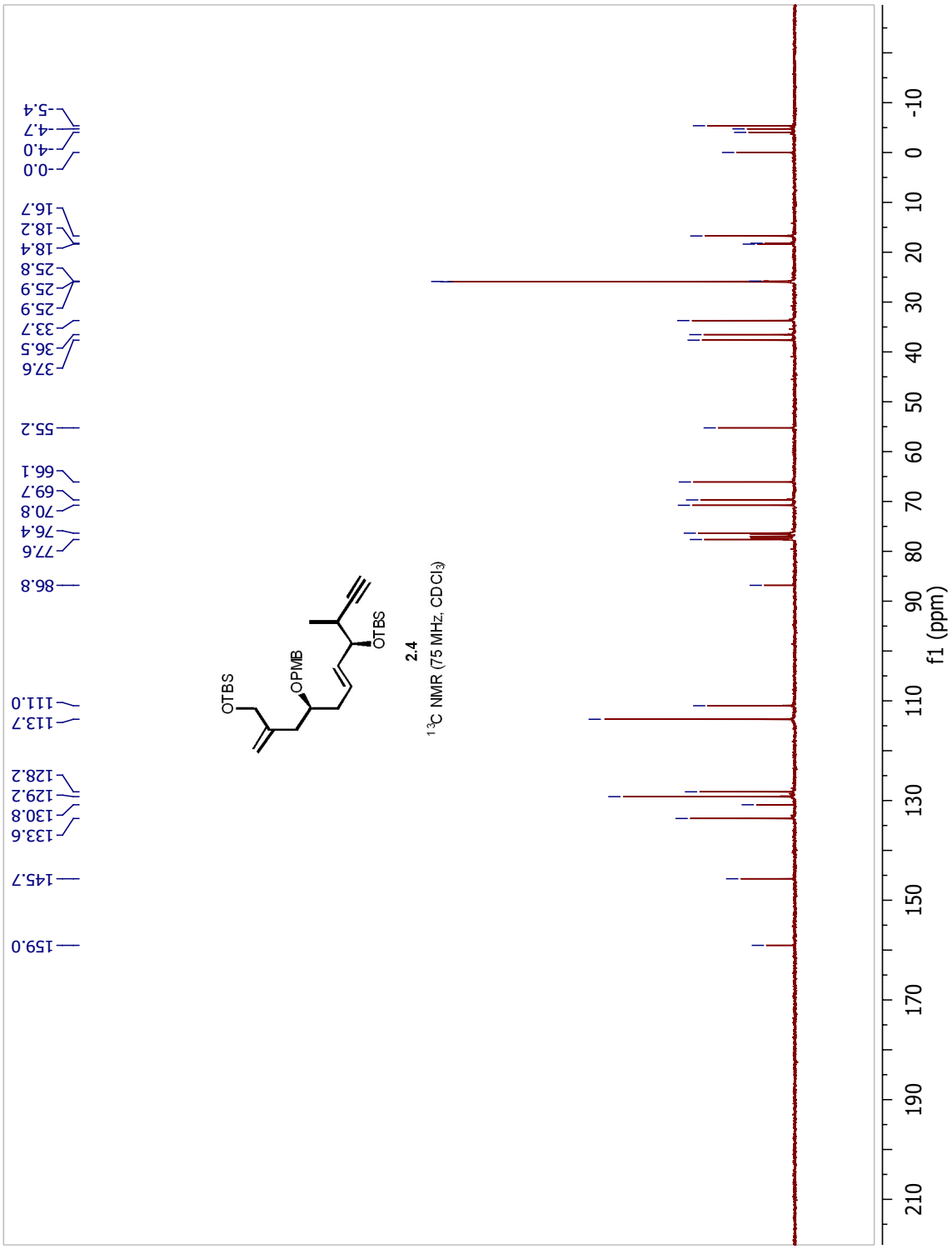

OTBS
OPMB
OH
Ph
2.10
^{1}H NMR (300 MHz, $CDCl_3$)
3.38
3.32
8.36
2.86
3.81
0.92
1.07
3.08
1.13
2.21
2.58
0.99
0.90
0.87
2.01
0.96
2.00
4.94
3.10
f1 (ppm)

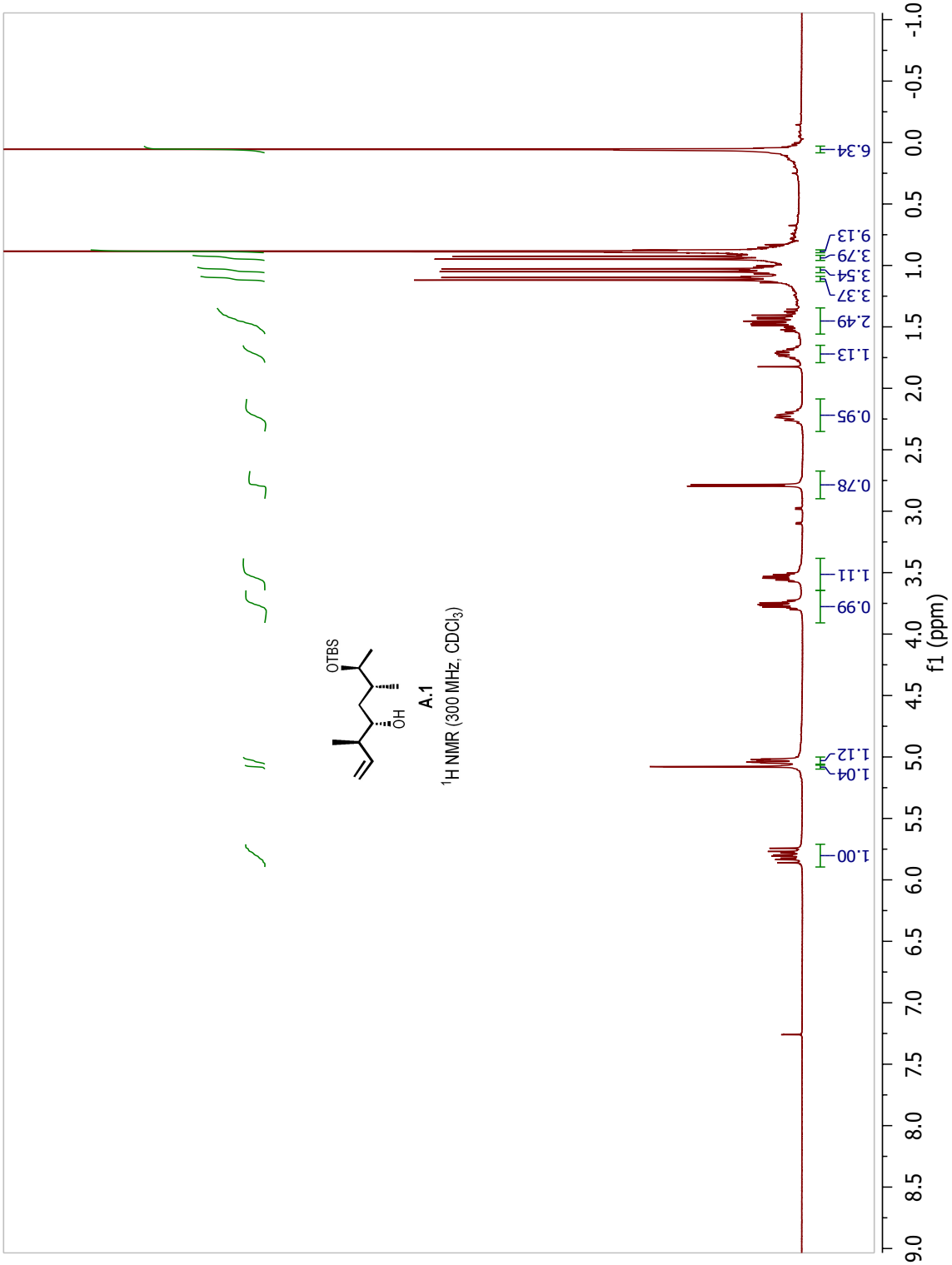

-5.4
1.9
11.3
14.4
18.4
25.9
36.8
37.7
42.9
54.8
55.3
66.1
70.8
72.8
77.3
78.9
111.2
113.7
116.4
125.6
128.7
128.8
129.4
131.6
133.1
145.6
152.7
159.1
176.2
OTBS
OPMB
OH
Ph
O
N
O
O
2.10
^{13}C NMR (75 MHz, CDCl$_3$)
f1 (ppm)
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10

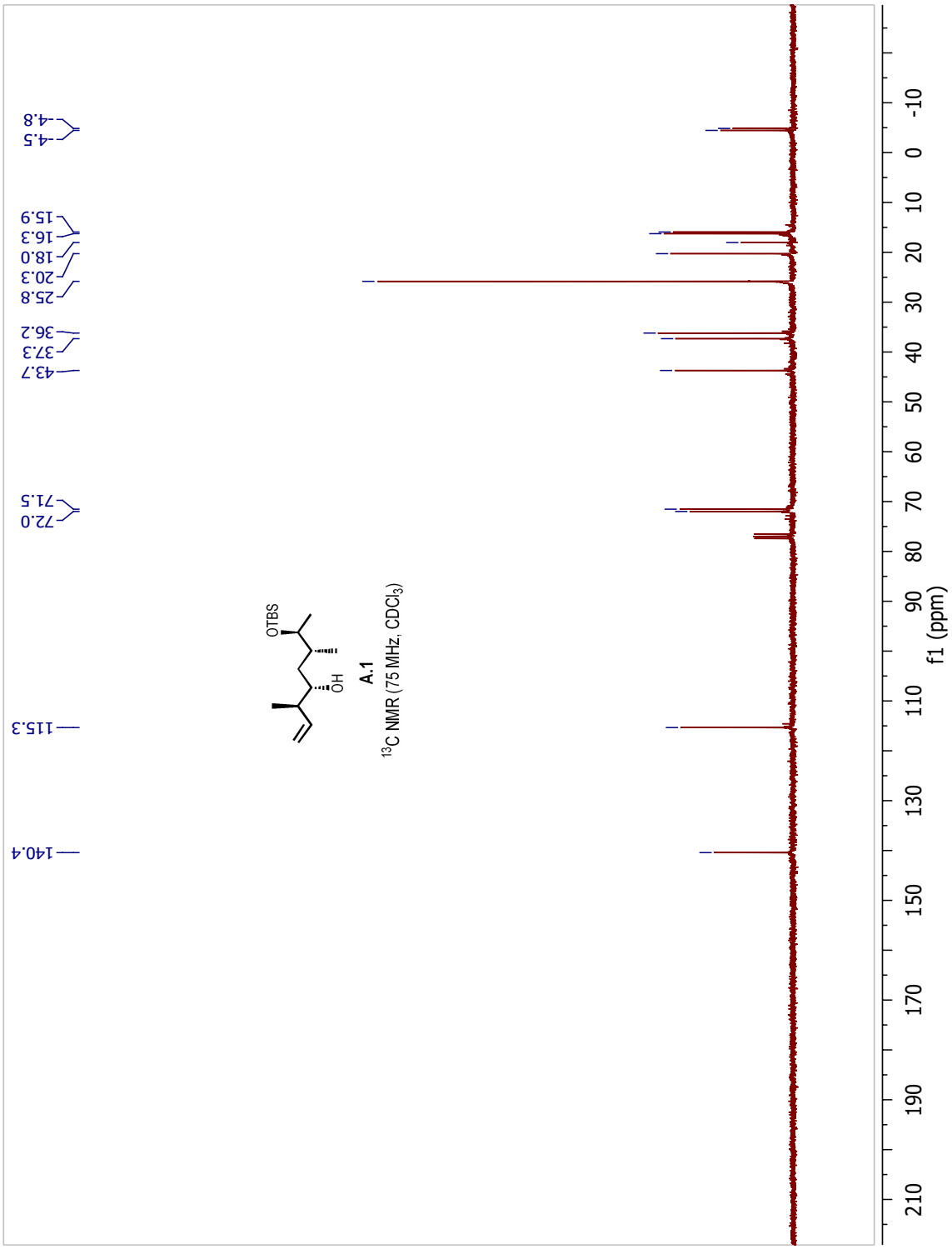

OTBS
OPMB
TBSO
OMe
2.11
^{1}H NMR (300 MHz, $CDCl_3$)
f1 (ppm)

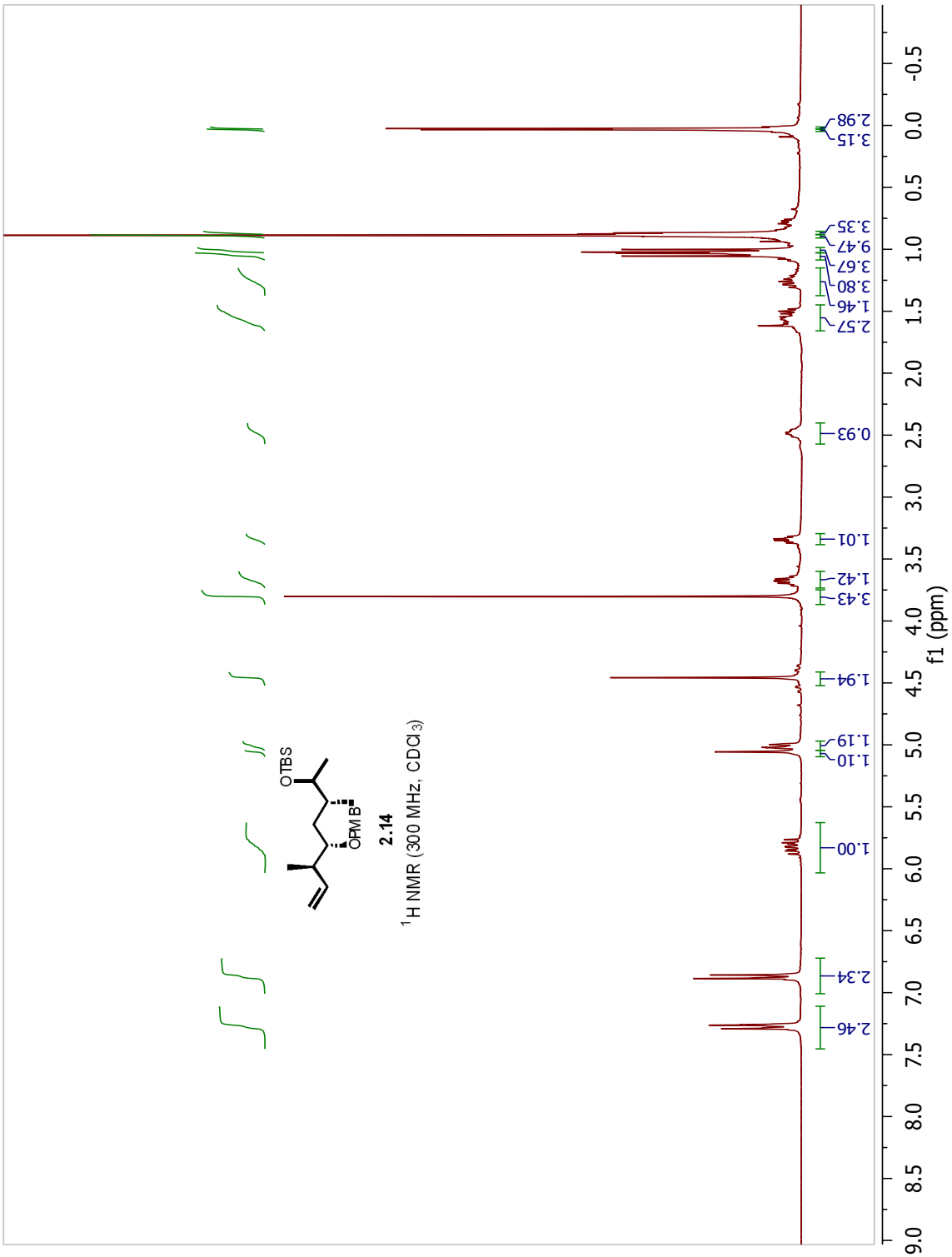

OTBS
OPMB
TBSO
N
OMe
O
2.11
^{13}C NMR (75 MHz, $CDCl_3$)
159.0
145.7
134.2
130.8
129.1
127.7
113.7
110.8
77.6
75.4
70.6
66.0
61.4
55.2
42.8
37.6
36.7
25.9
25.9
18.4
18.2
14.5
-0.0
-4.0
-4.7
-5.4
f1 (ppm)

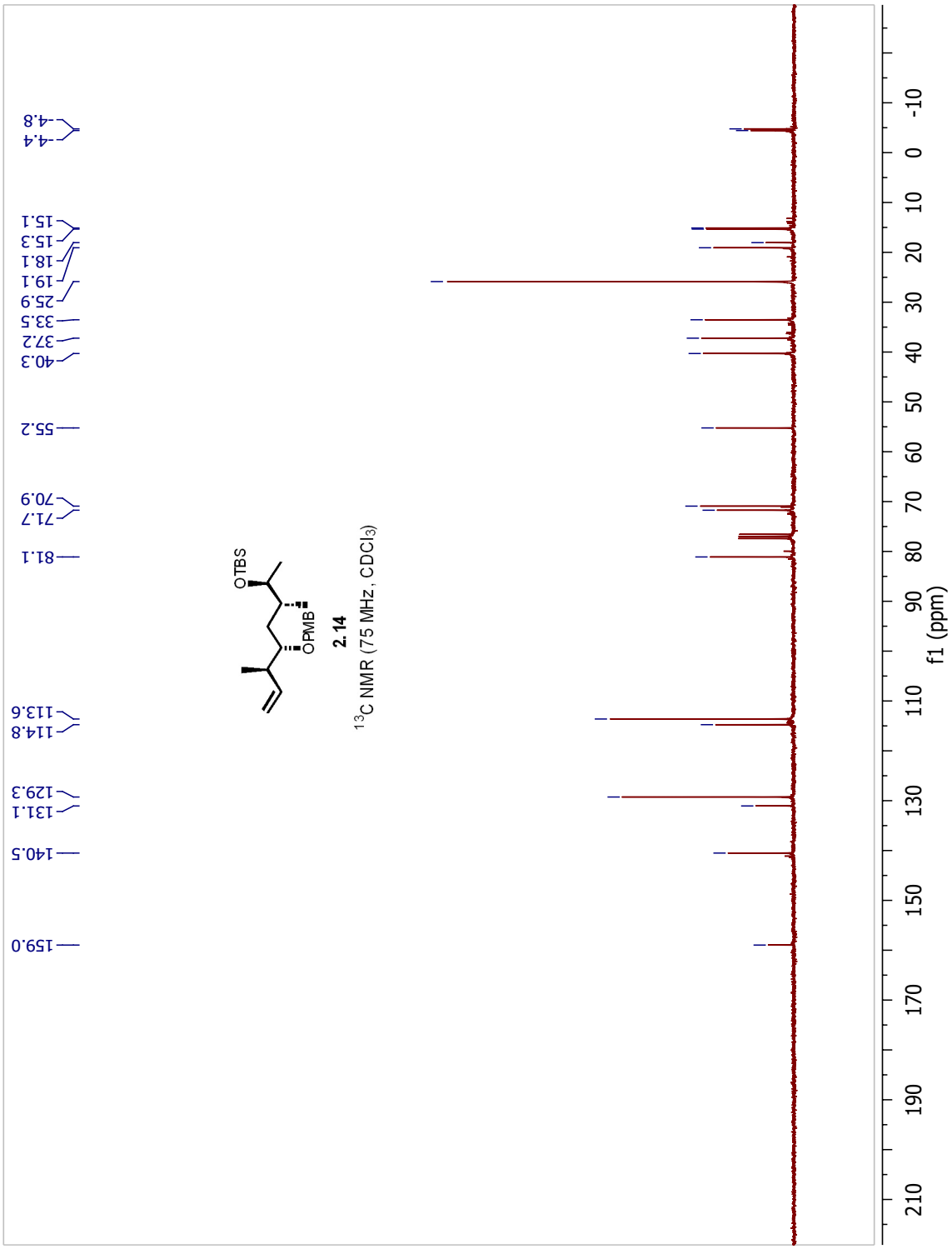

OTBS
OPMB
OTBS
2.4
^{1}H NMR (300 MHz, $CDCl_3$)
f1 (ppm)
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
2.50
2.28
1.00
1.19
1.01
1.01
1.05
1.04
2.06
1.15
3.15
1.12
1.10
4.38
1.16
3.58
9.90
9.35
3.68
4.81
3.10
4.93

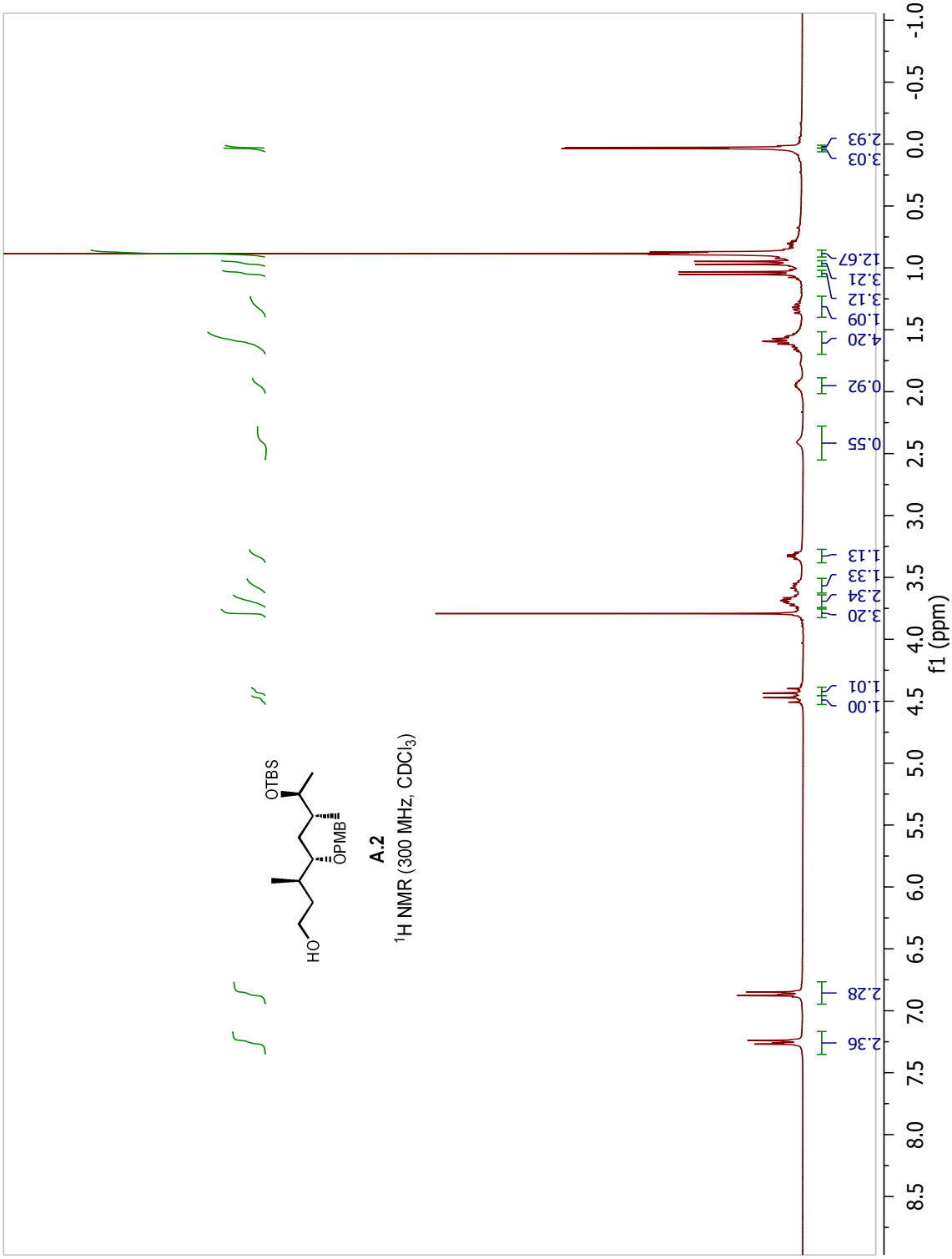

OTBS
OPMB
OTBS
2.4
^{13}C NMR (75 MHz, $CDCl_3$)
-5.4
-4.7
-4.0
-0.0
16.7
18.2
18.4
25.8
25.9
25.9
33.7
36.5
37.6
55.2
66.1
69.7
70.8
76.4
77.6
86.8
111.0
113.7
128.2
129.2
130.8
133.6
145.7
159.0
f1 (ppm)

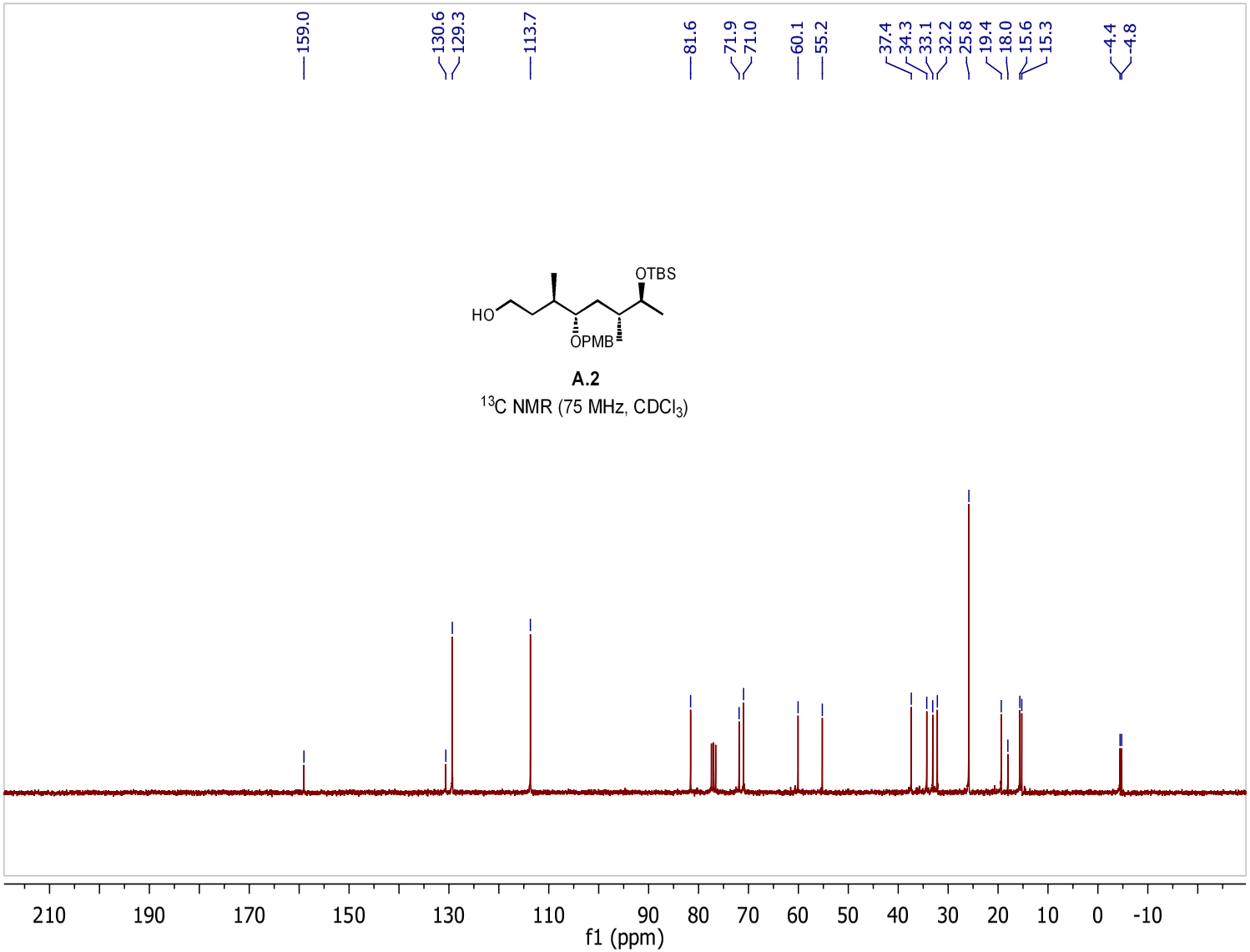

OTBS
OH
A.1
^{1}H NMR (300 MHz, $CDCl_3$)
6.34
9.13
3.79
3.54
3.37
2.49
1.13
0.95
0.78
1.11
0.99
1.04
1.12
1.00
f1 (ppm)


-4.5
-4.8
15.9
16.3
18.0
20.3
25.8
36.2
37.3
43.7
72.0
71.5
115.3
140.4
OTBS
OH
A.1
^{13}C NMR (75 MHz, $CDCl_3$)
f1 (ppm)


OTBS
OPMB
2.14
^{1}H NMR (300 MHz, $CDCl_3$)
2.98
3.15
3.35
9.47
3.67
3.80
1.46
2.57
0.93
1.01
1.42
3.43
1.94
1.10
1.19
1.00
2.34
2.46
f1 (ppm)

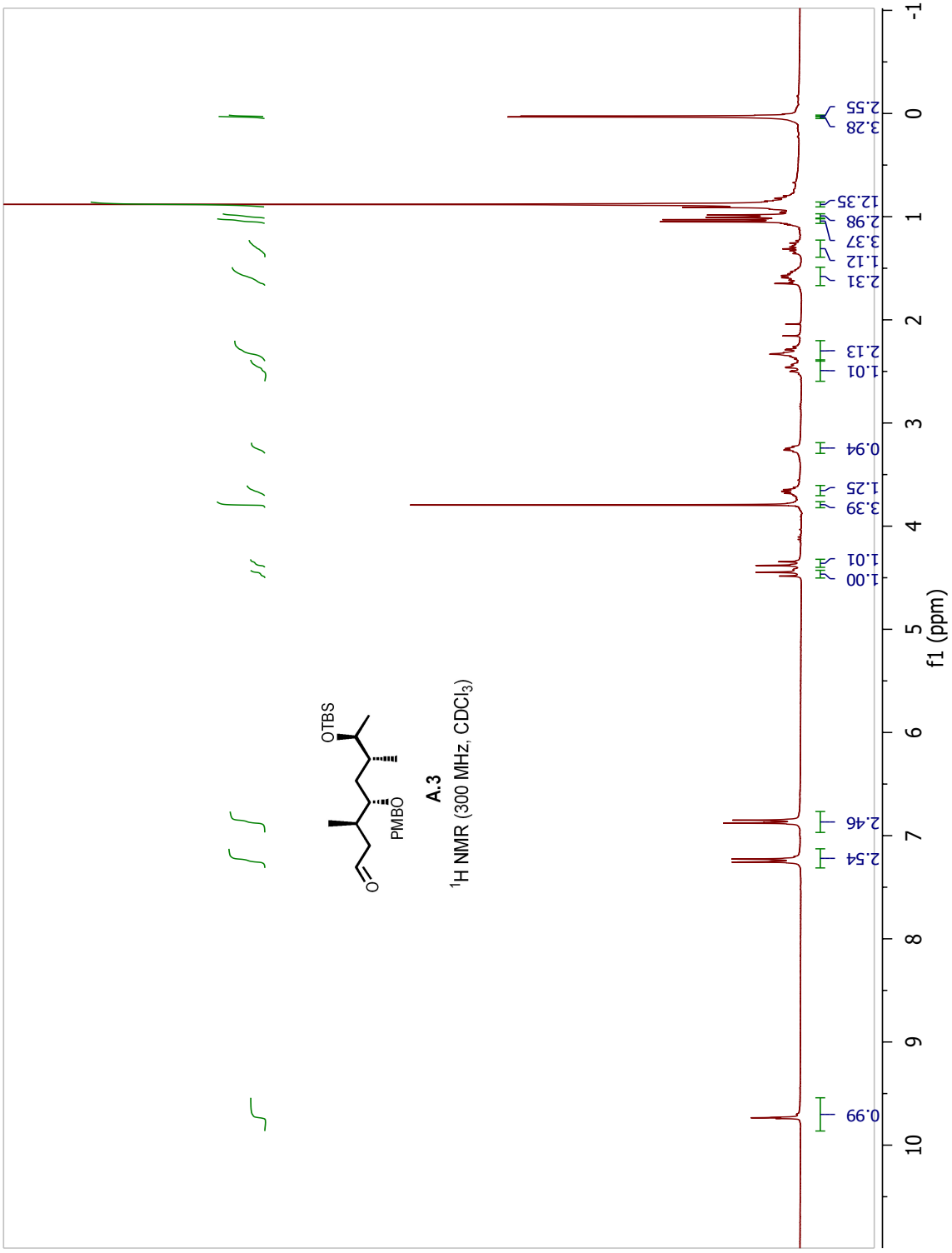

OTBS
OPMB
2.14
^{13}C NMR (75 MHz, $CDCl_3$)
-4.8
-4.4
15.1
15.3
18.1
19.1
25.9
33.5
37.2
40.3
55.2
70.9
71.7
81.1
113.6
114.8
129.3
131.1
140.5
159.0
f1 (ppm)

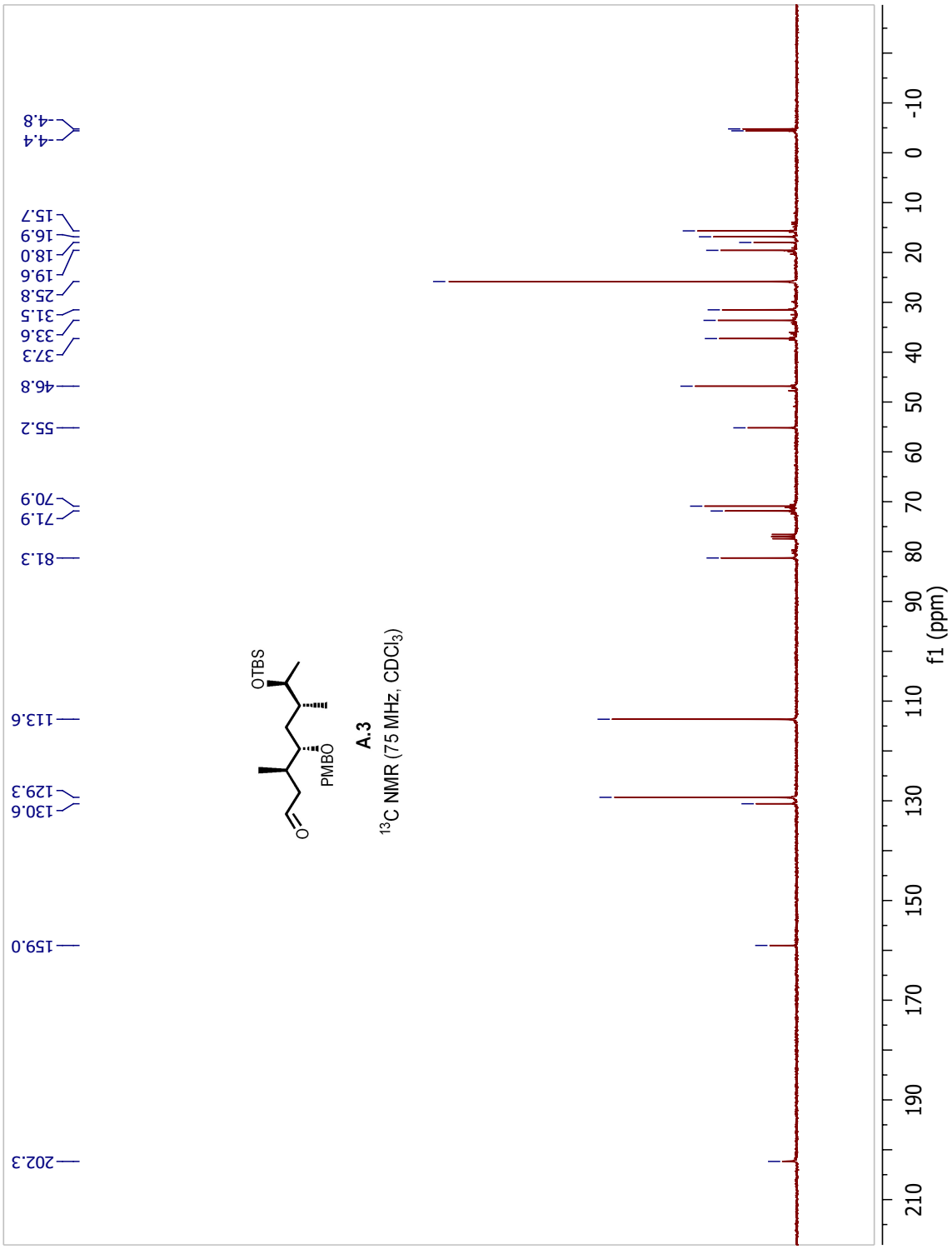

OTBS
OPMB
HO
A.2
^{1}H NMR (300 MHz, $CDCl_3$)
2.93
3.03
12.67
3.21
3.12
1.09
4.20
0.92
0.55
1.13
1.33
2.34
3.20
1.00
1.01
2.28
2.36
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)

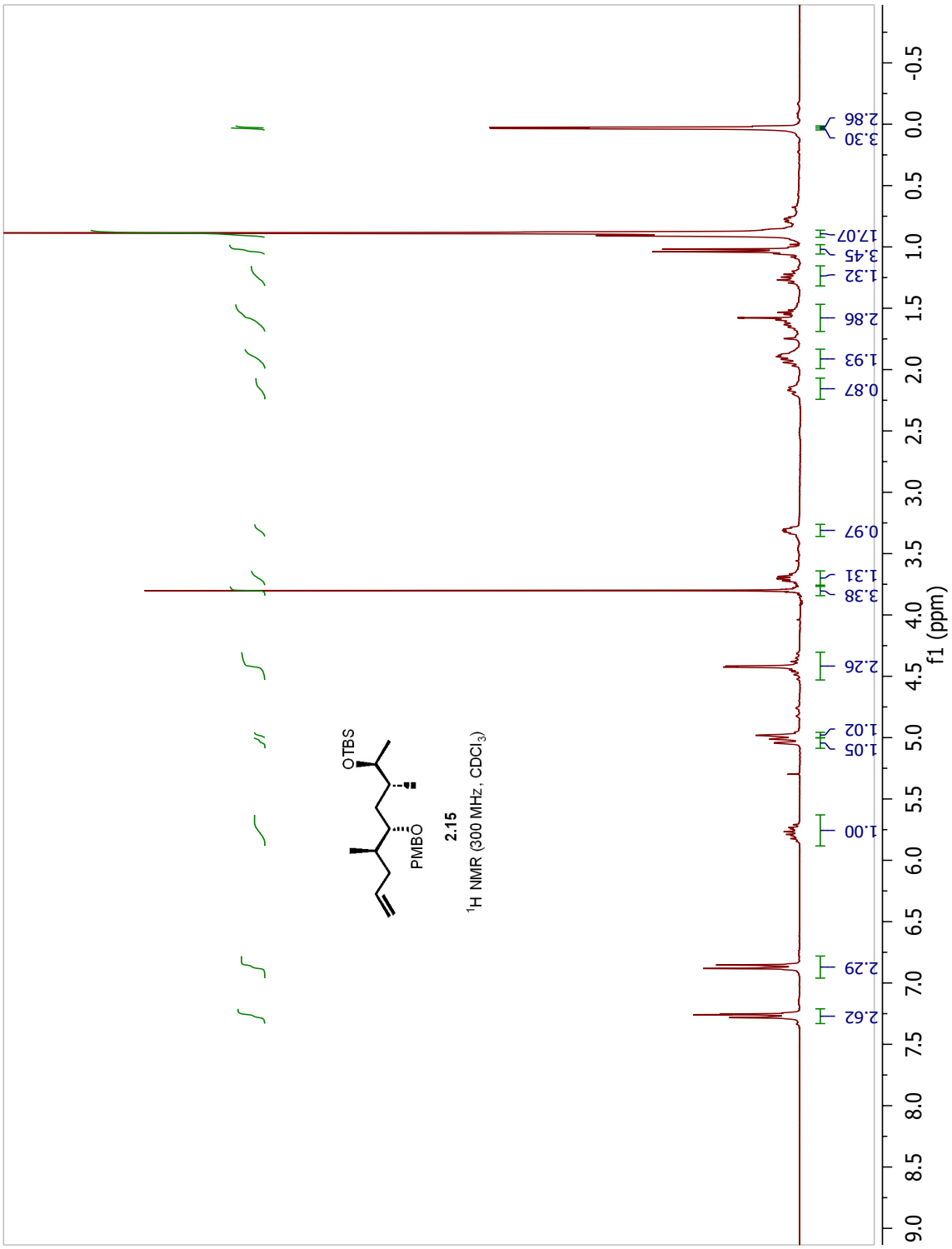


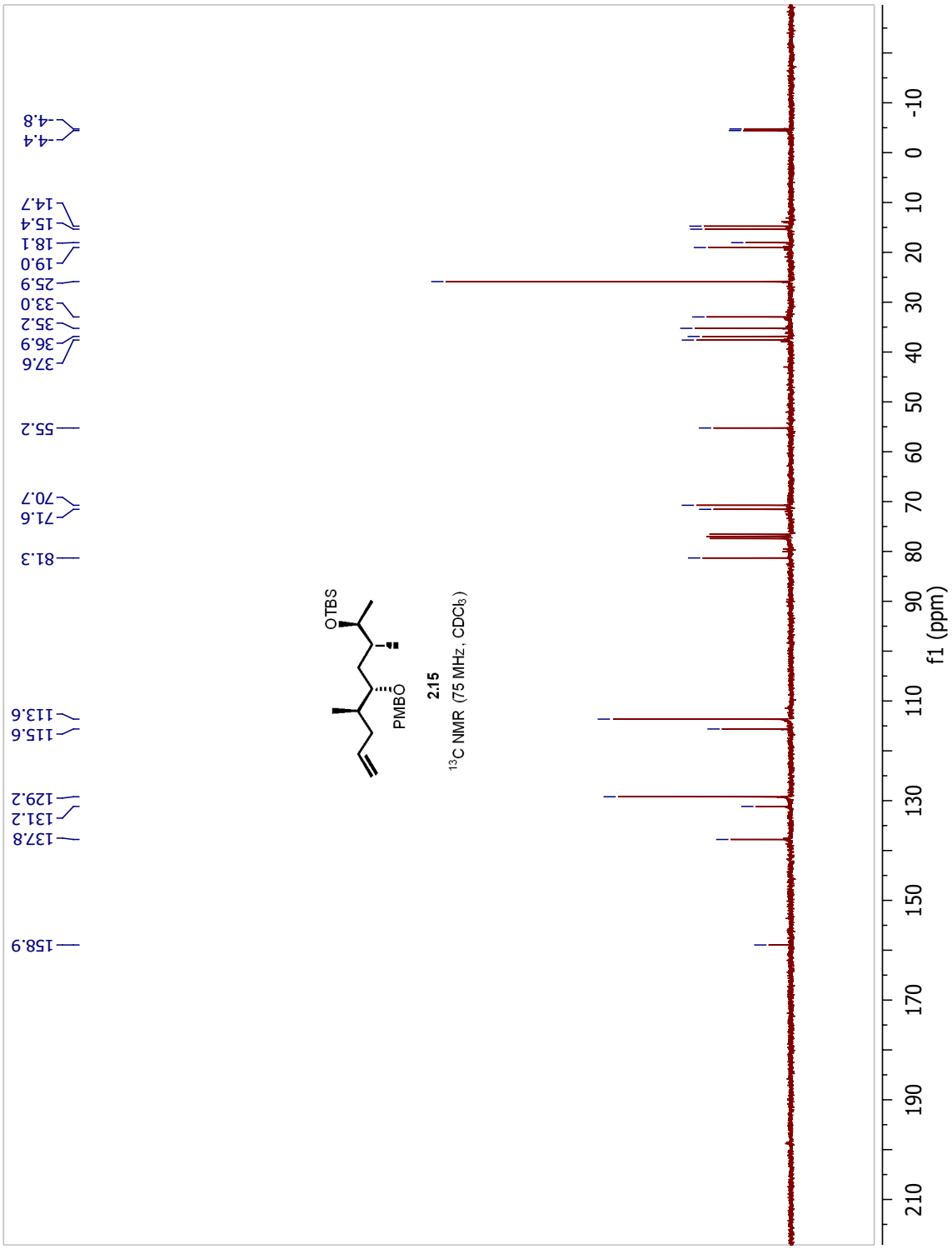
A.2

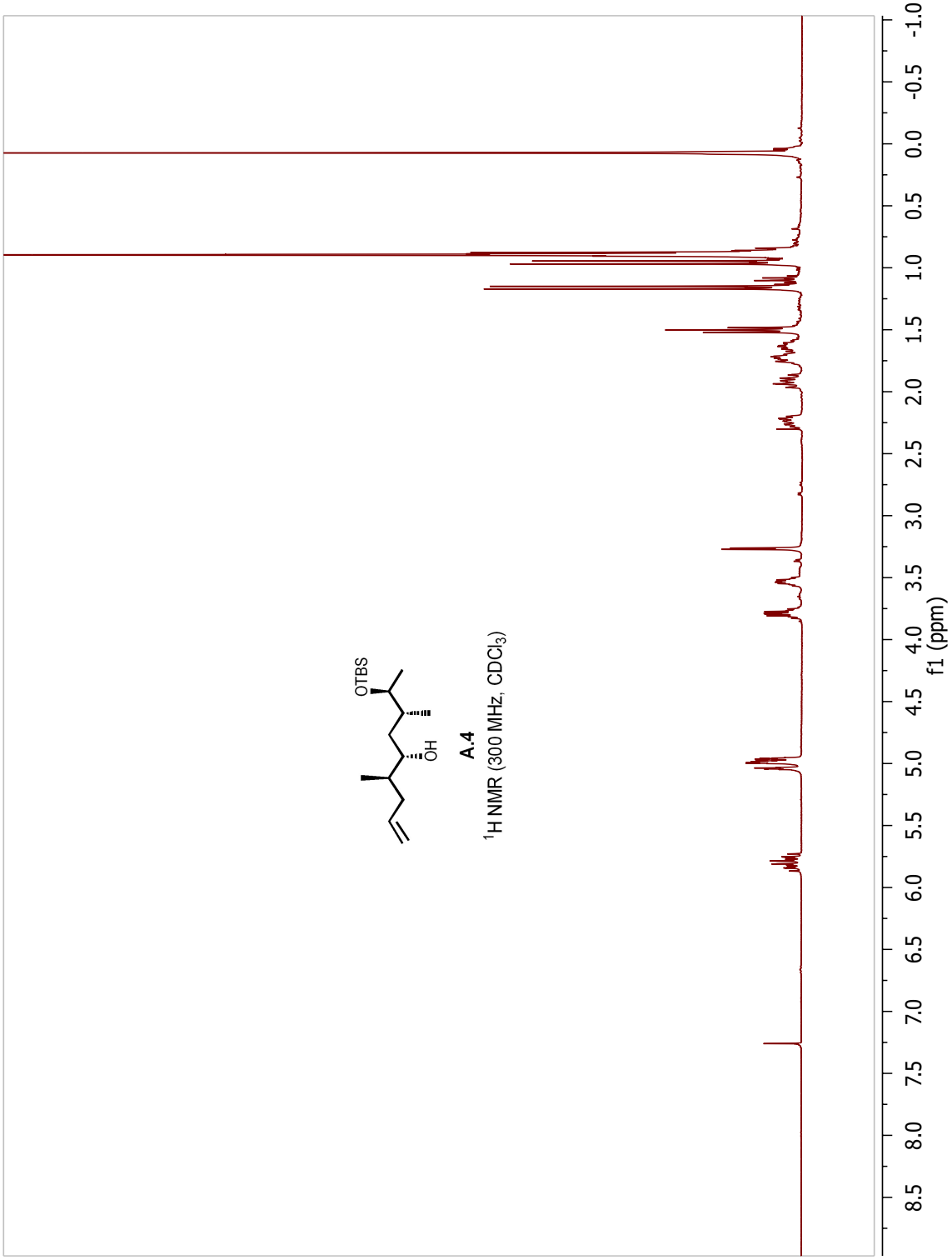
^{13}C NMR (75 MHz, $CDCl_3$)

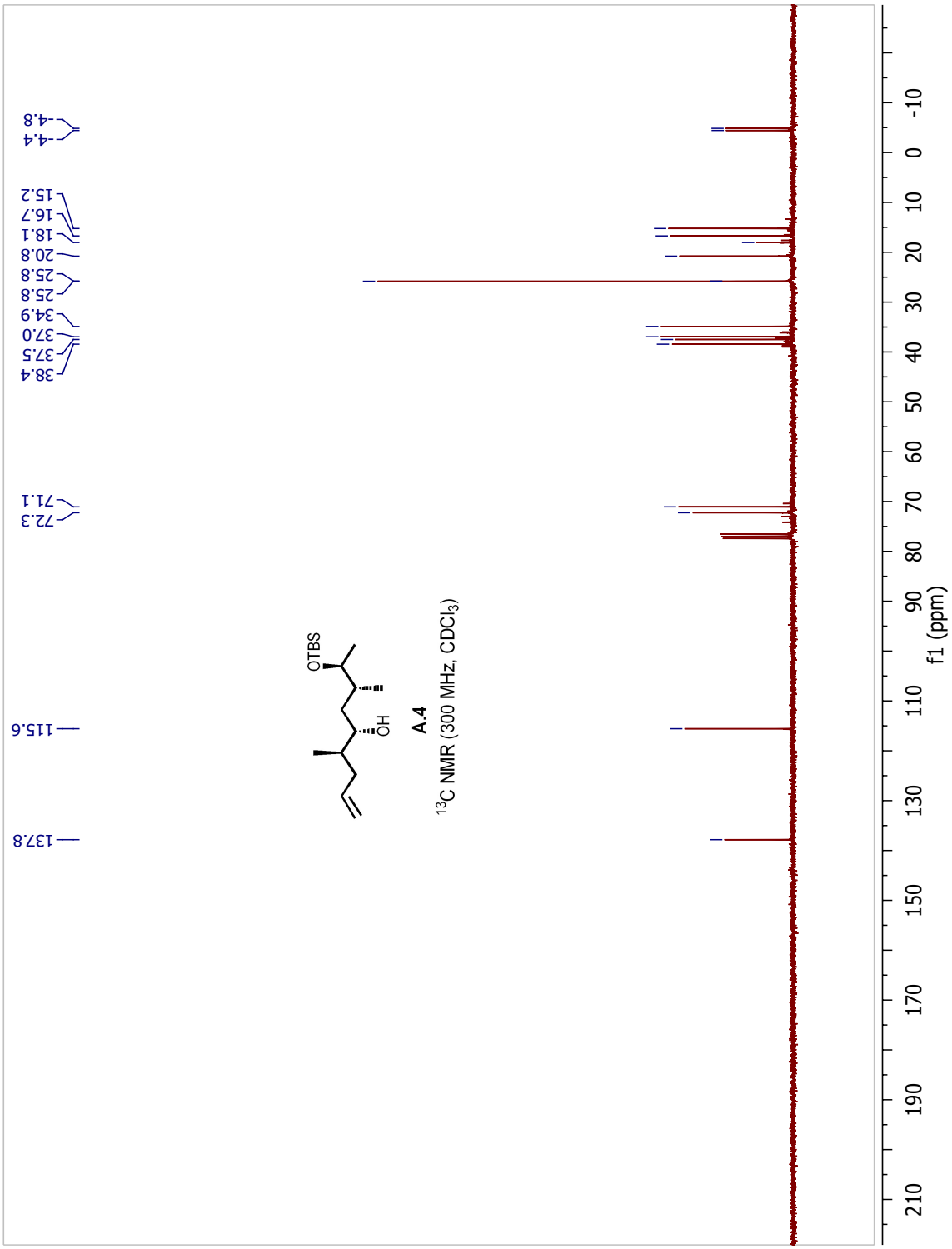

OTBS
PMBO
O
A.3
^{1}H NMR (300 MHz, $CDCl_3$)
f1 (ppm)
10
9
8
7
6
5
4
3
2
1
0
-1
0.99
2.46
2.54
1.00
1.01
3.39
1.25
0.94
1.01
2.13
2.31
1.12
3.37
2.98
12.35
3.28
2.55

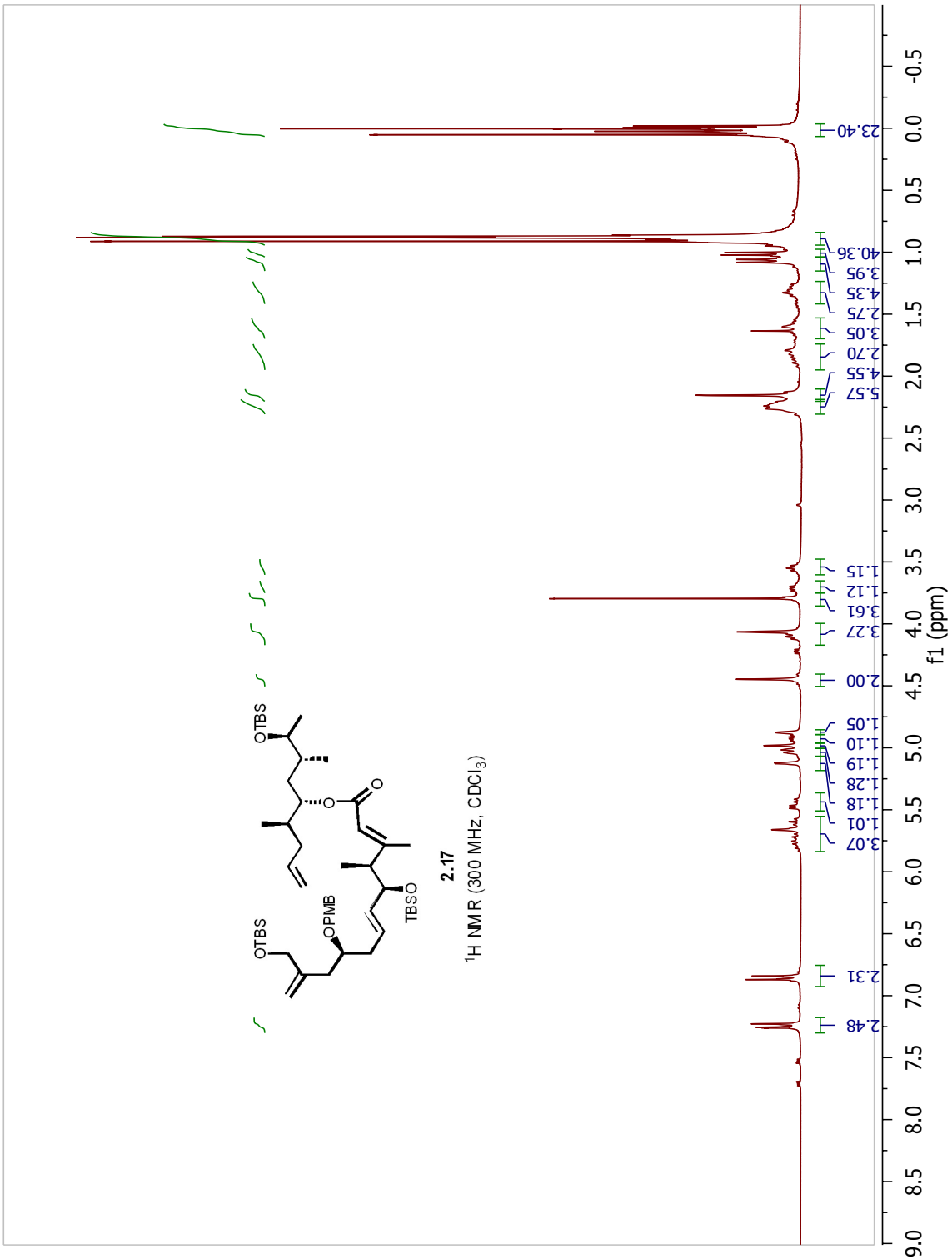

-4.4
-4.8
15.7
16.9
18.0
19.6
25.8
31.5
33.6
37.3
46.8
55.2
70.9
71.9
81.3
113.6
129.3
130.6
159.0
202.3
OTBS
PMBO
O
A.3
^{13}C NMR (75 MHz, $CDCl_3$)
f1 (ppm)

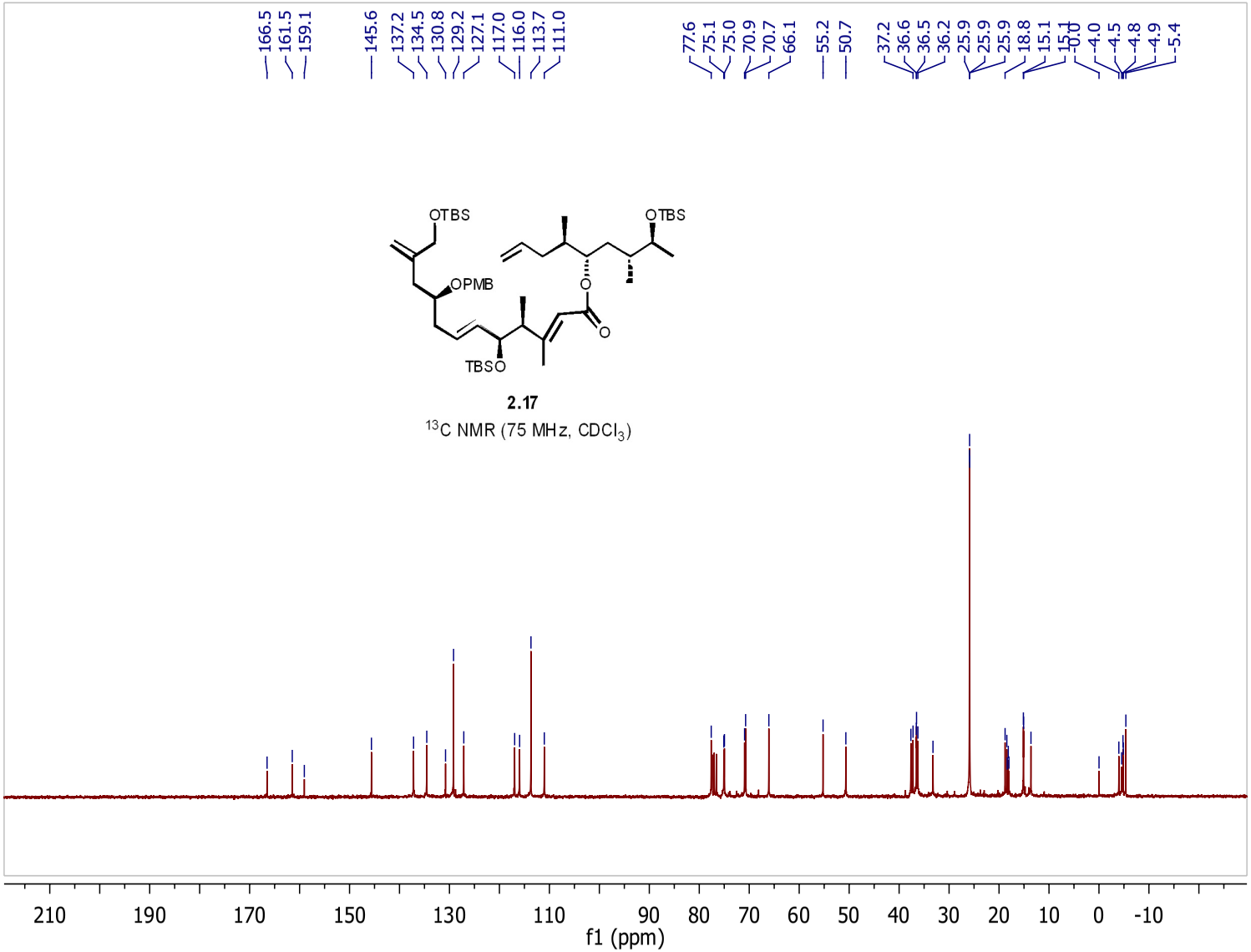

OTBS
PMBO
2.15
^{1}H NMR (300 MHz, $CDCl_3$)
f1 (ppm)
2.62
2.29
1.00
1.05
1.02
2.26
3.38
1.31
0.97
3.30
2.86
17.07
3.45
1.32
2.86
1.93
0.87

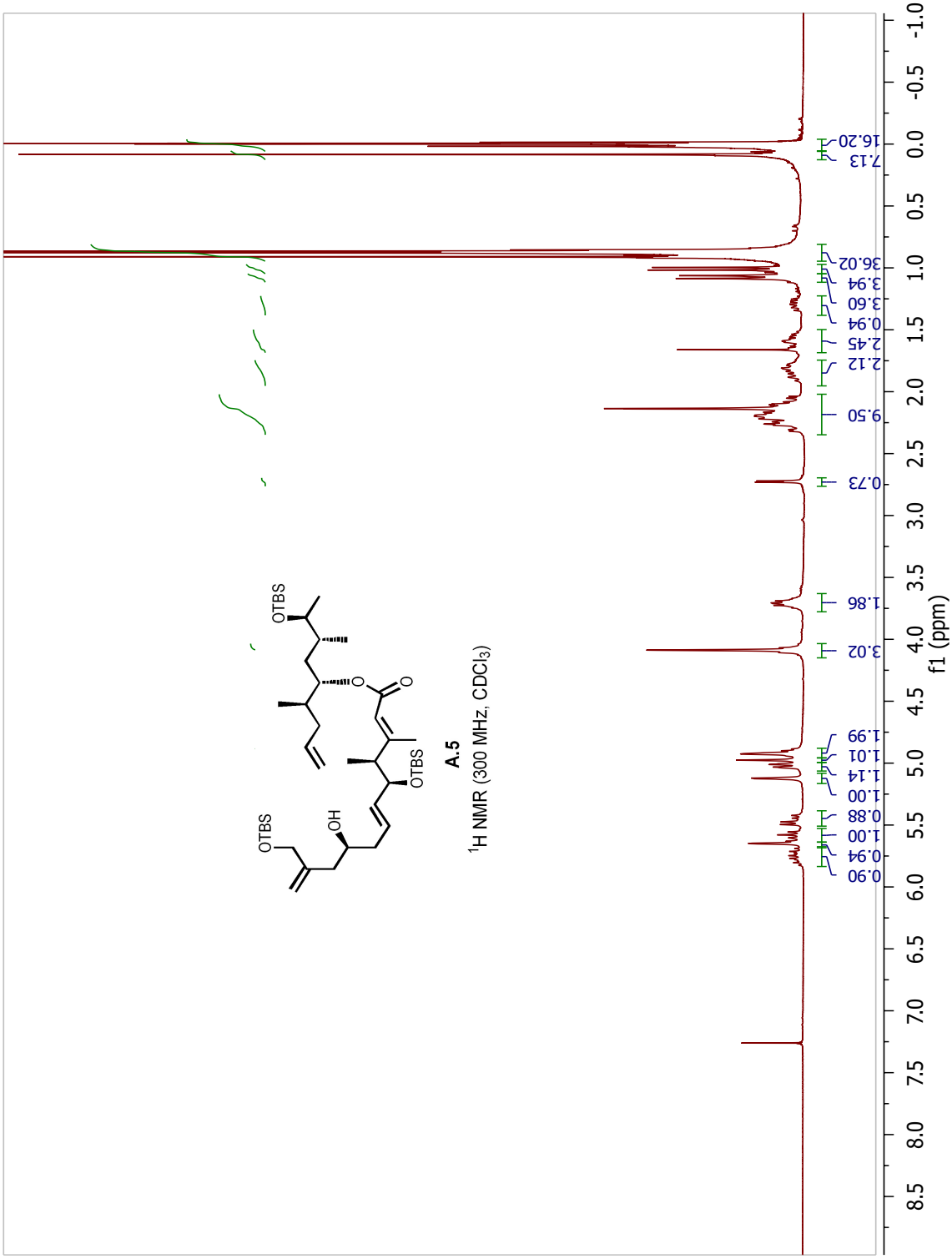

OTBS
PMBO
2.15
^{13}C NMR (75 MHz, $CDCl_3$)
f1 (ppm)
-4.8
-4.4
14.7
15.4
18.1
19.0
25.9
33.0
35.2
36.9
37.6
55.2
70.7
71.6
81.3
113.6
115.6
129.2
131.2
137.8
158.9

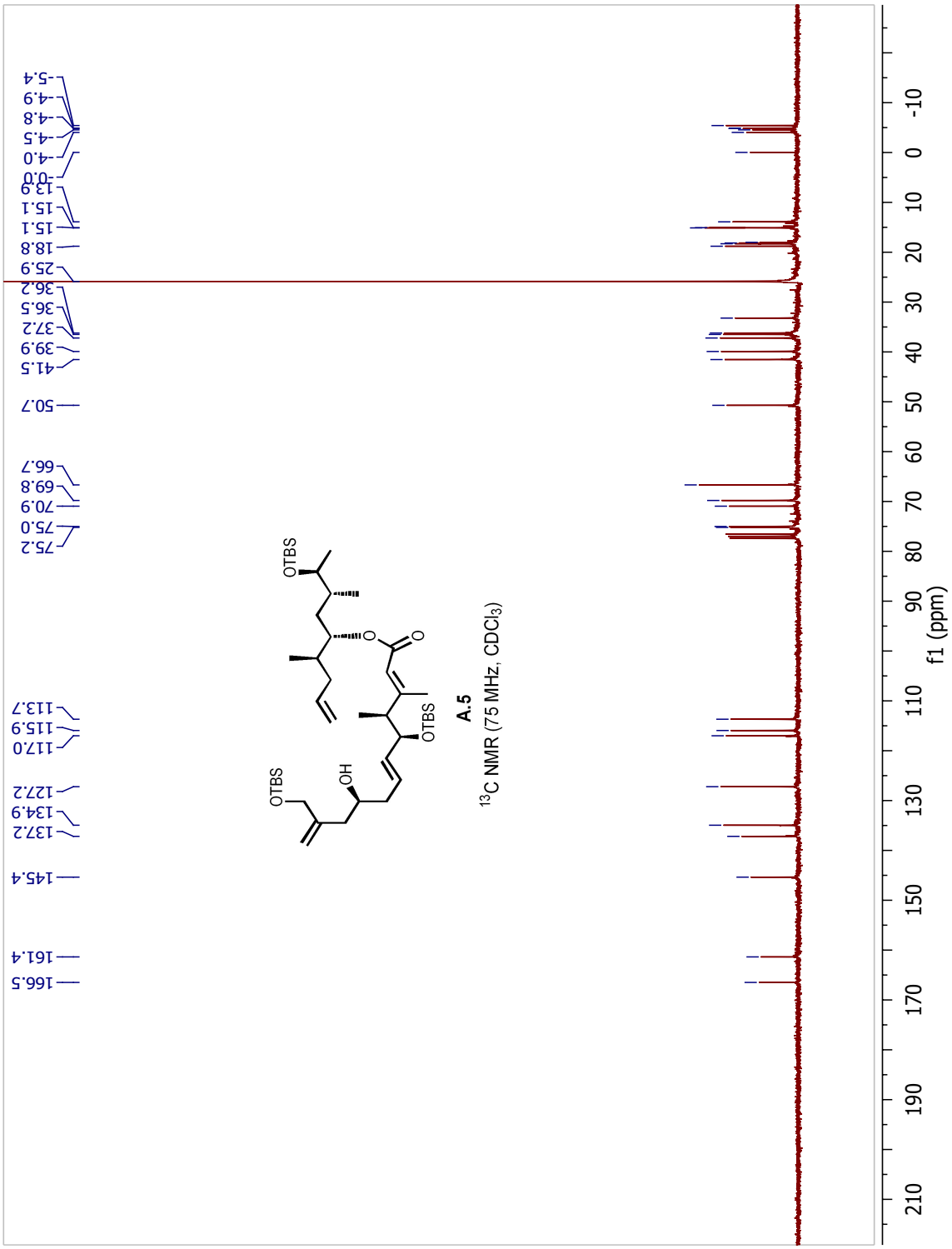

OTBS
OH
A.4
^{1}H NMR (300 MHz, $CDCl_3$)
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)

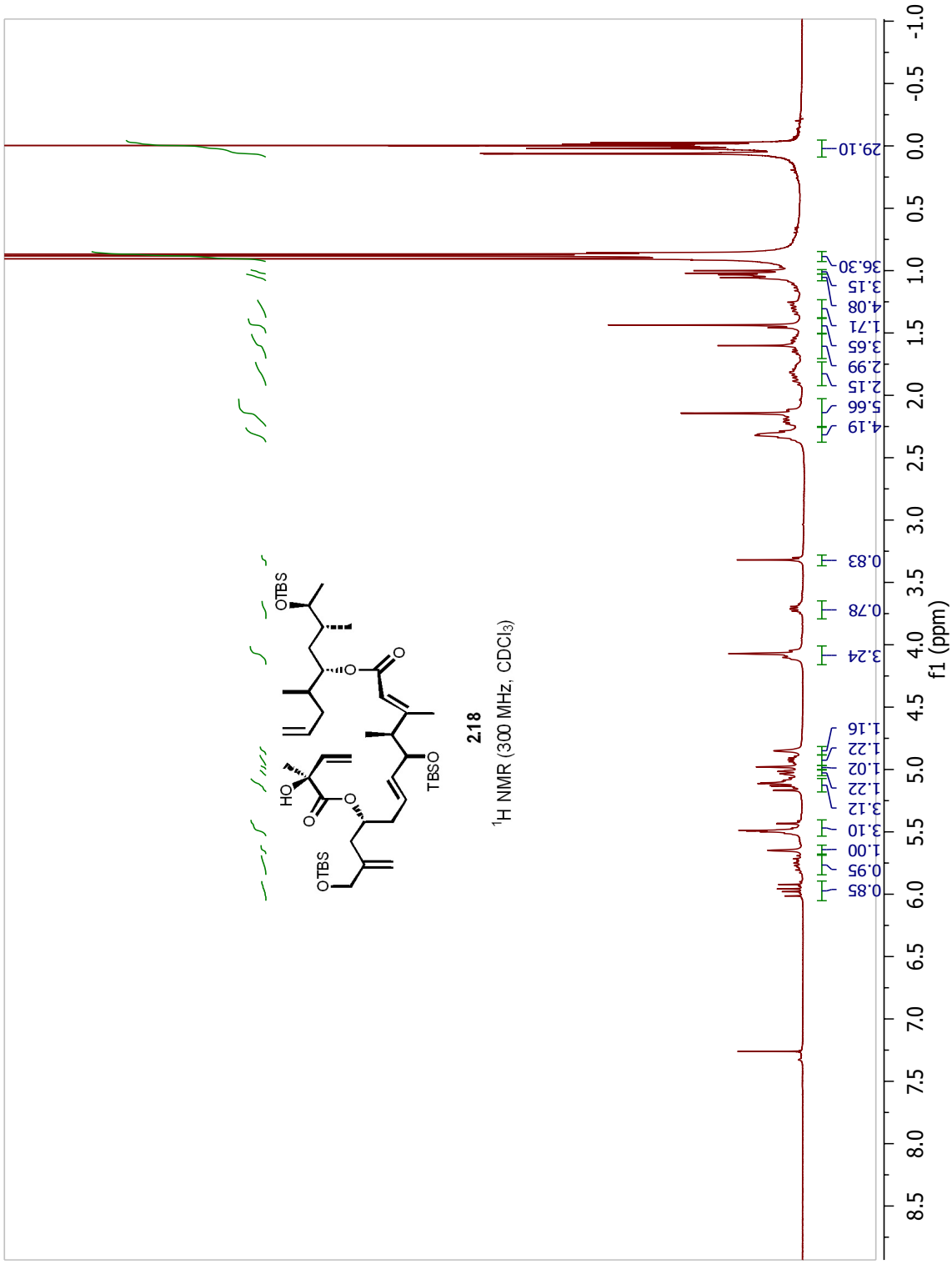

OTBS
OH
A.4
^{13}C NMR (300 MHz, $CDCl_3$)
137.8
115.6
72.3
71.1
38.4
37.5
37.0
34.9
25.8
25.8
20.8
18.1
16.7
15.2
-4.4
-4.8
f1 (ppm)

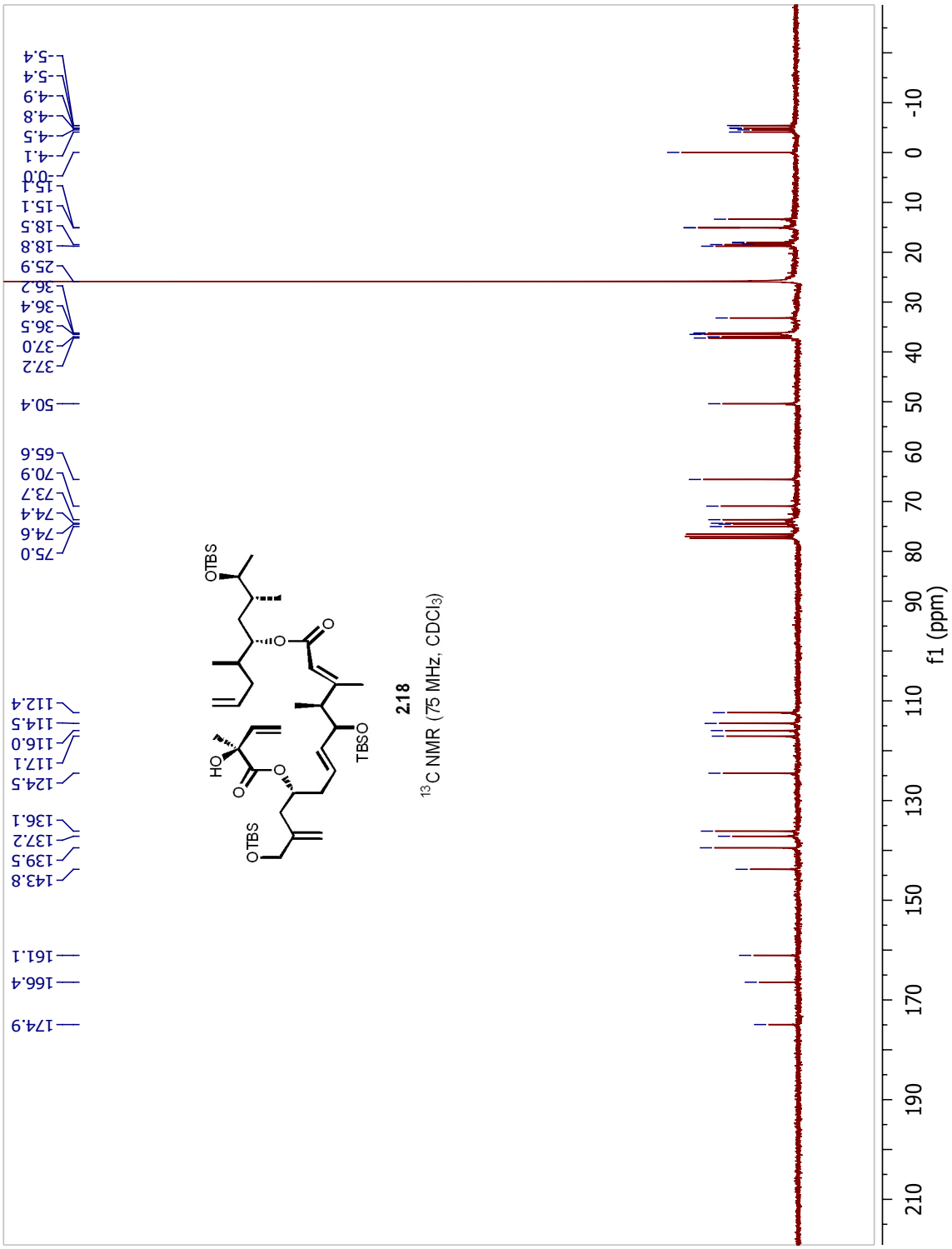

OTBS
OPMB
TBSO
OTBS
O
O
2.17
^{1}H NMR (300 MHz, $CDCl_3$)
23.40
40.36
3.95
4.35
2.75
3.05
2.70
4.55
5.57
1.15
1.12
3.61
3.27
2.00
1.05
1.10
1.19
1.28
1.18
1.01
3.07
2.31
2.48
f1 (ppm)


166.5
161.5
159.1
145.6
137.2
134.5
130.8
129.2
127.1
117.0
116.0
113.7
111.0
77.6
75.1
75.0
70.9
70.7
66.1
55.2
50.7
37.2
36.6
36.5
36.2
25.9
25.9
25.9
18.8
15.1
15.1
-0.0
-4.0
-4.5
-4.8
-4.9
-5.4
OTBS
OTBS
OPMB
O
O
TBSO
2.17
13C NMR (75 MHz, CDCl3)
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


OTBS
OH
OTBS
O
O
OTBS
A.5
^{1}H NMR (300 MHz, $CDCl_3$)
16.20
7.13
36.02
3.94
3.60
0.94
2.45
2.12
9.50
0.73
1.86
3.02
1.99
1.01
1.14
1.00
0.88
1.00
0.94
0.90
f1 (ppm)

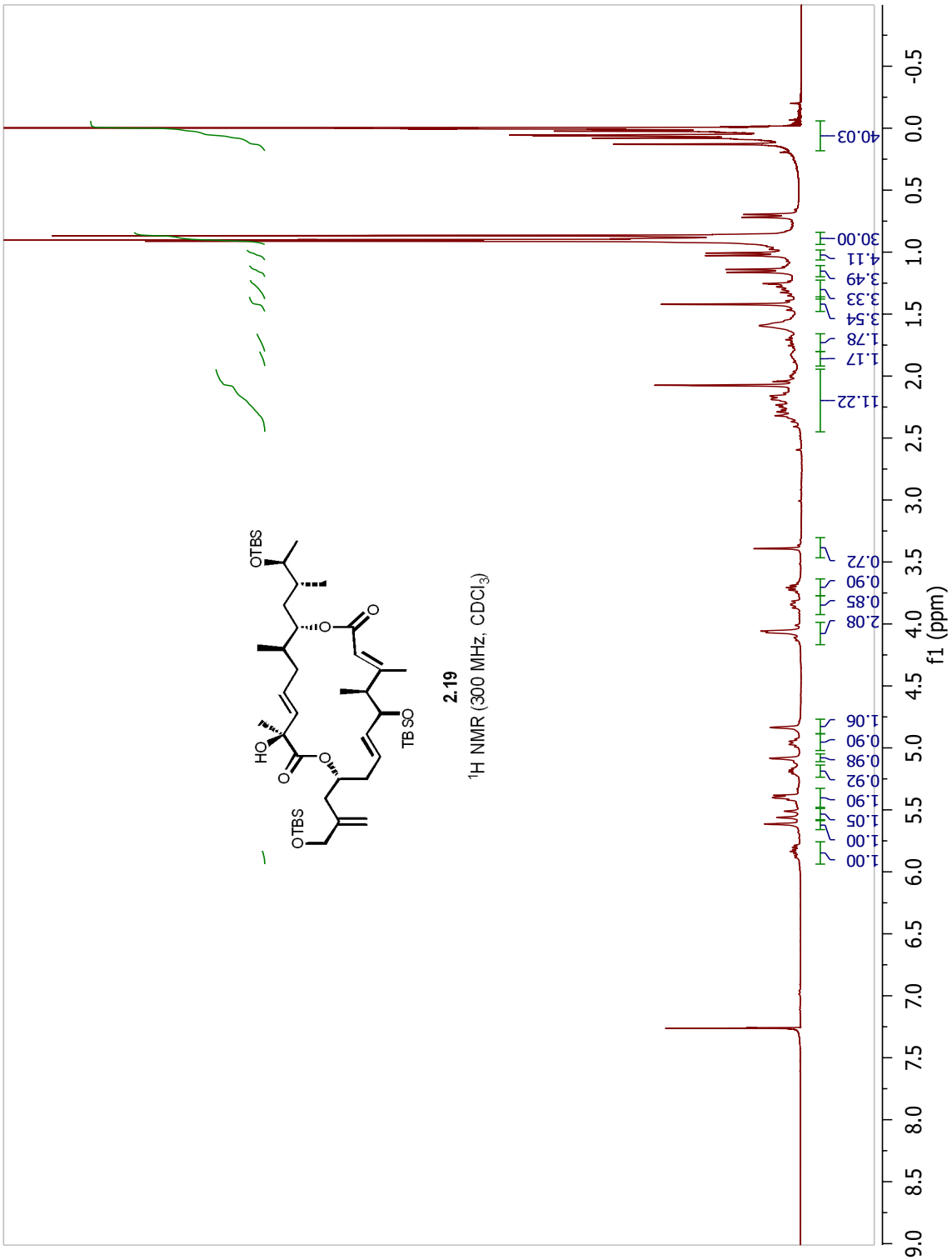

-5.4
-4.9
-4.8
-4.5
-4.0
-0.0
13.9
15.1
15.1
18.8
25.9
36.2
36.5
37.2
39.9
41.5
50.7
66.7
69.8
70.9
75.0
75.2
113.7
115.9
117.0
127.2
134.9
137.2
145.4
161.4
166.5
OTBS
OH
OTBS
OTBS
O
O
A.5
^{13}C NMR (75 MHz, $CDCl_3$)
f1 (ppm)

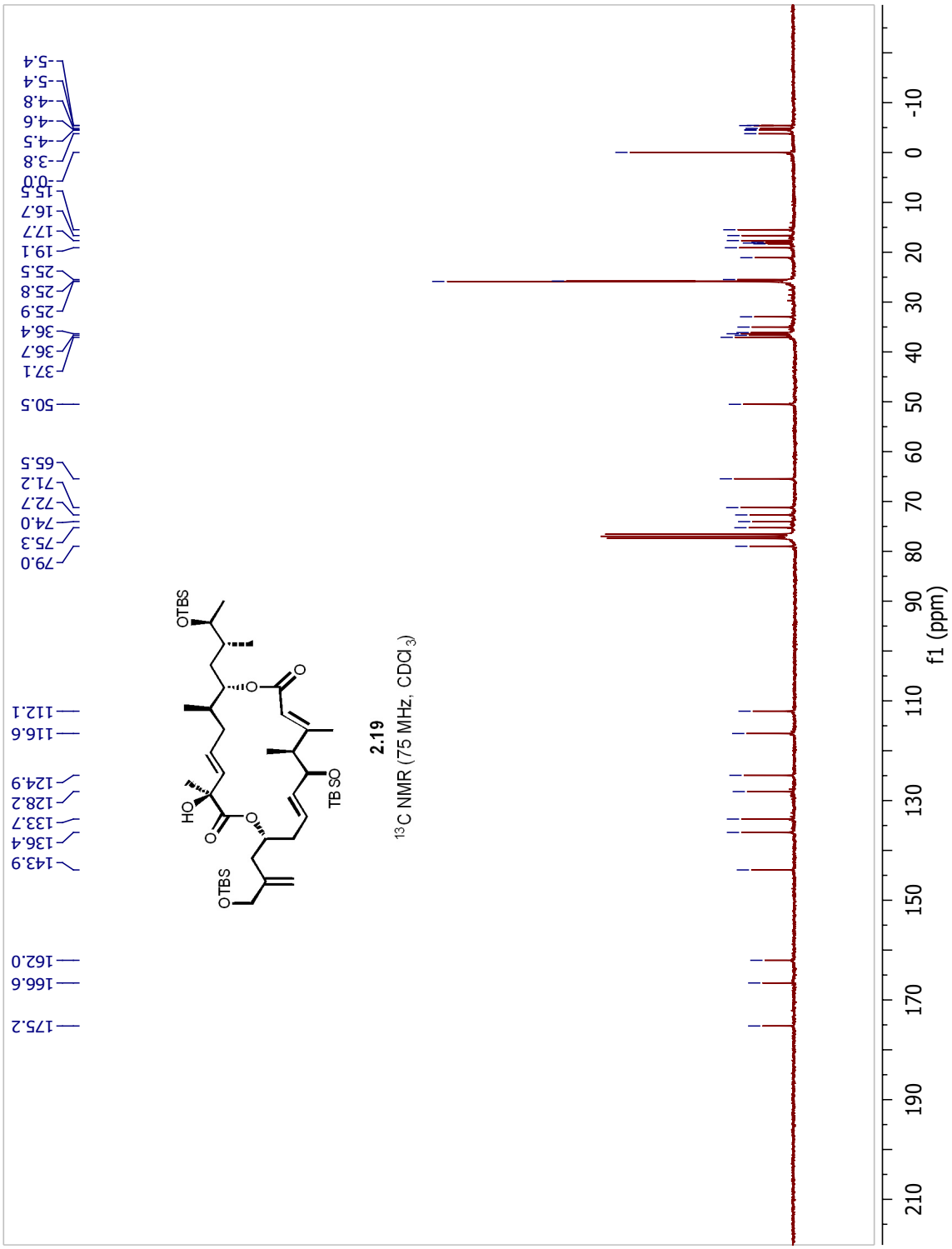

OTBS
HO
O
O
O
O
TBSO
OTBS
218
^{1}H NMR (300 MHz, CDCl$_3$)
29.10
36.30
3.15
4.08
1.71
3.65
2.99
2.15
5.66
4.19
0.83
0.78
3.24
1.16
1.22
1.02
1.22
3.12
3.10
1.00
0.95
0.85
f1 (ppm)

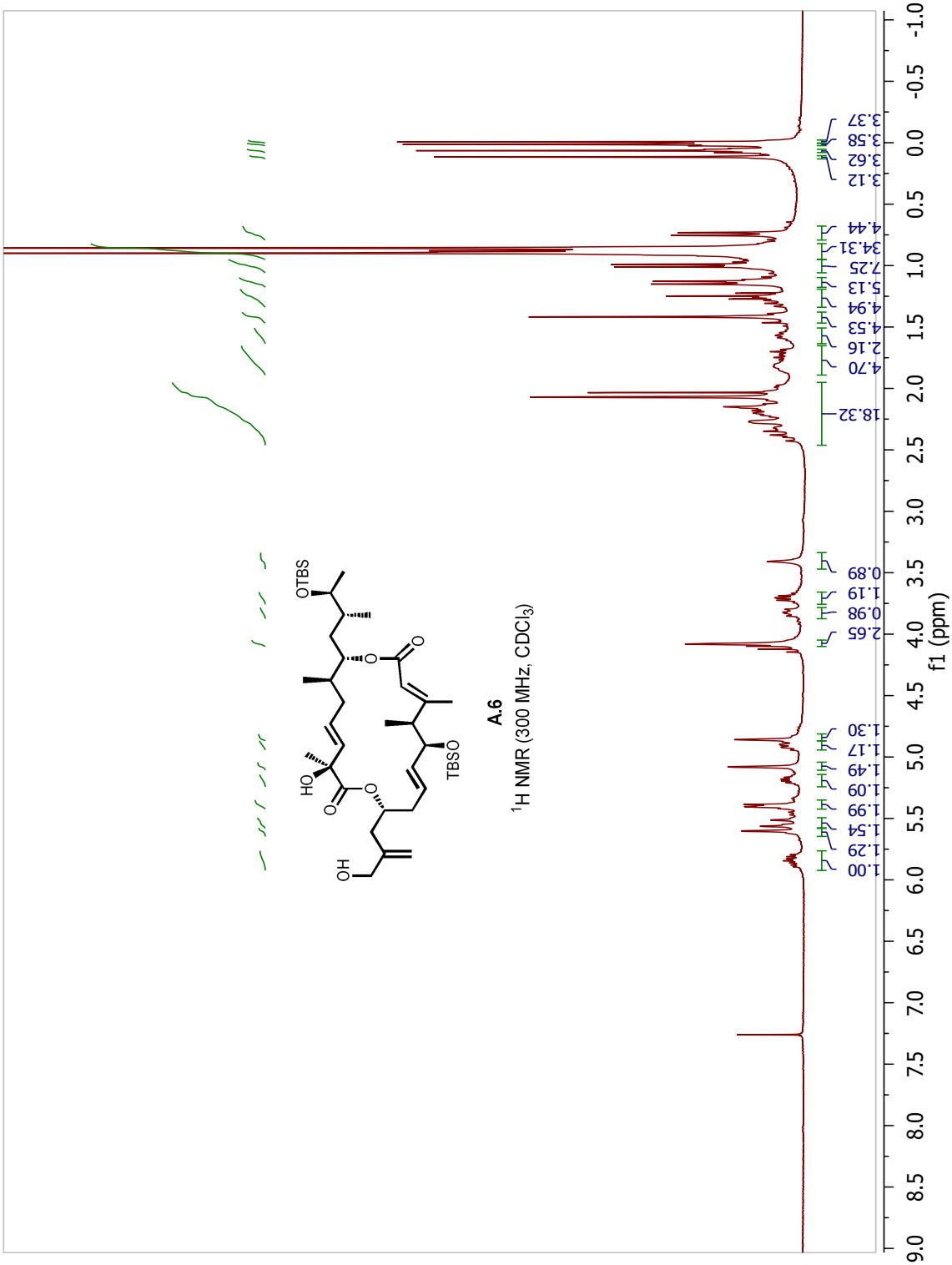


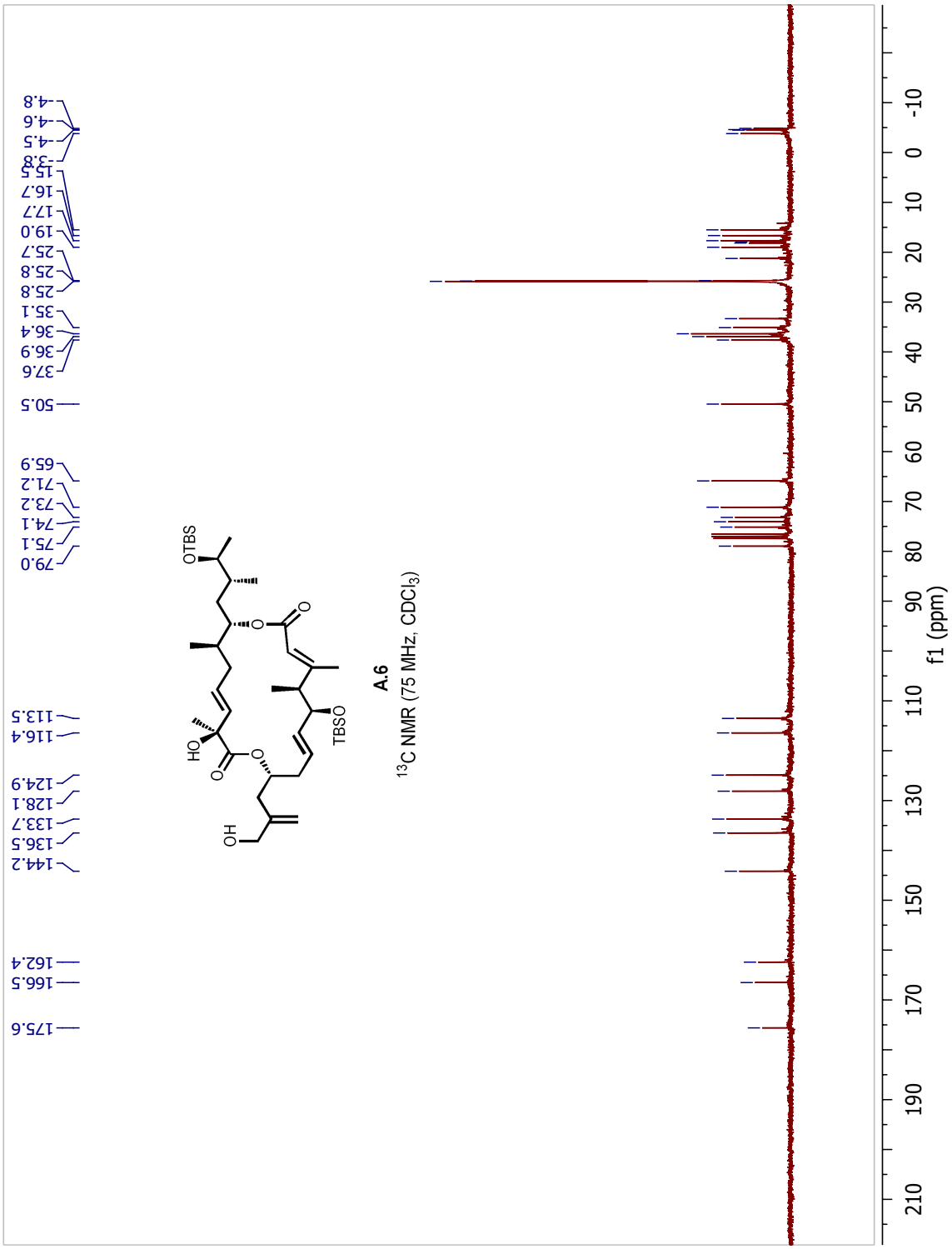
218

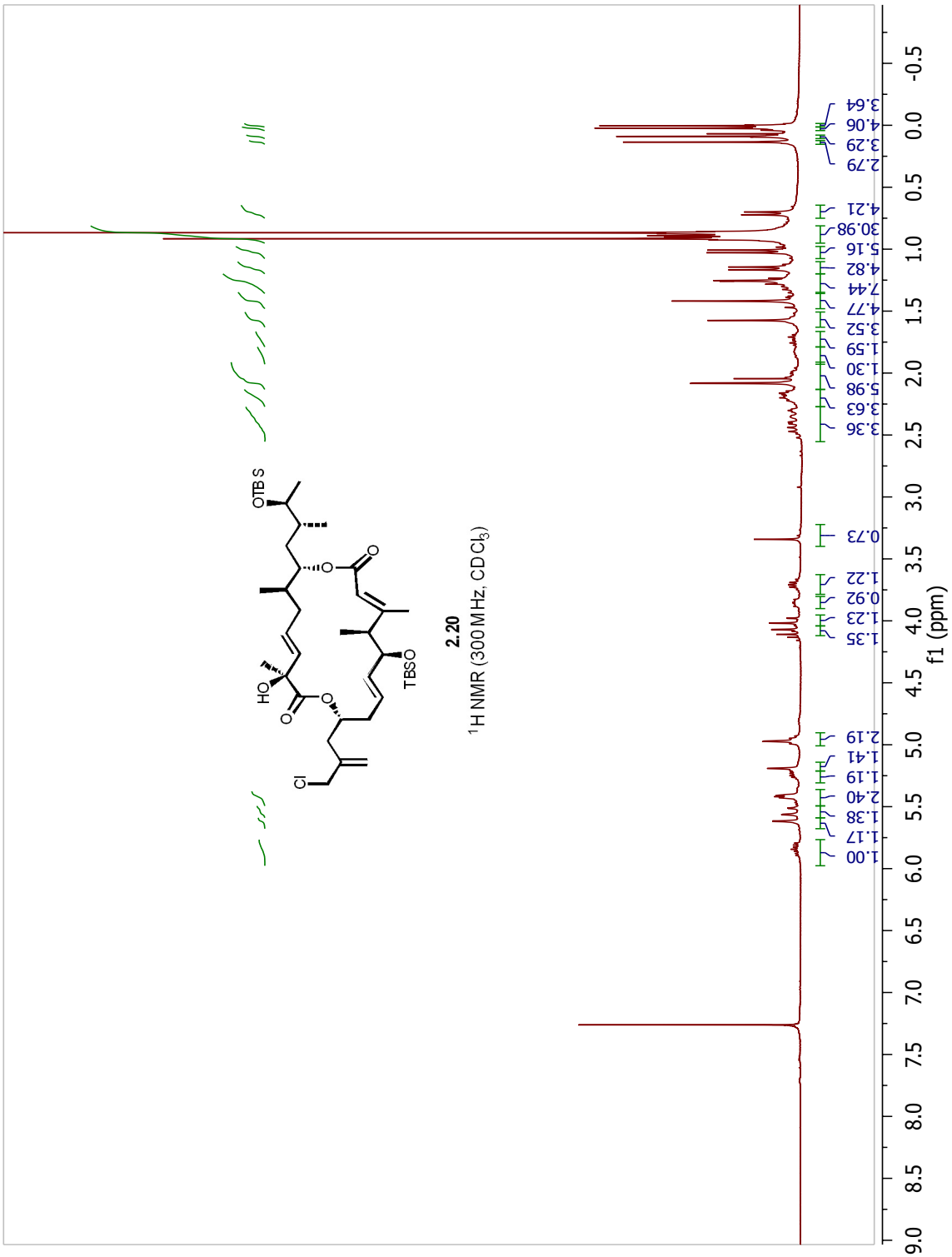
^{13}C NMR (75 MHz, $CDCl_3$)

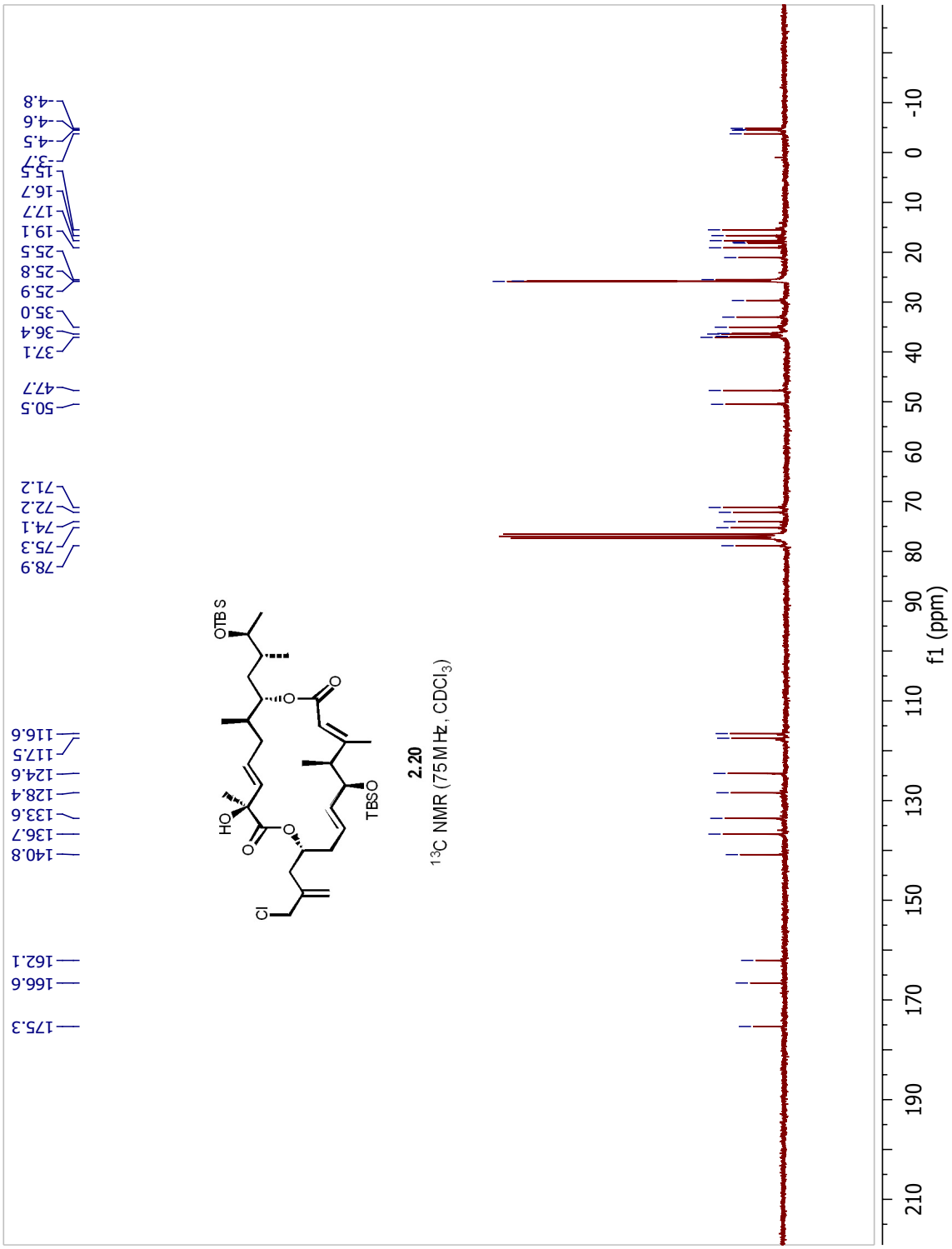

OTBS
HO
TBSO
OTBS
2.19
^{1}H NMR (300 MHz, $CDCl_3$)
40.03
30.00
4.11
3.49
3.33
3.54
1.78
1.17
11.22
0.72
0.90
0.85
2.08
1.06
0.90
0.98
0.92
1.90
1.05
1.00
1.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

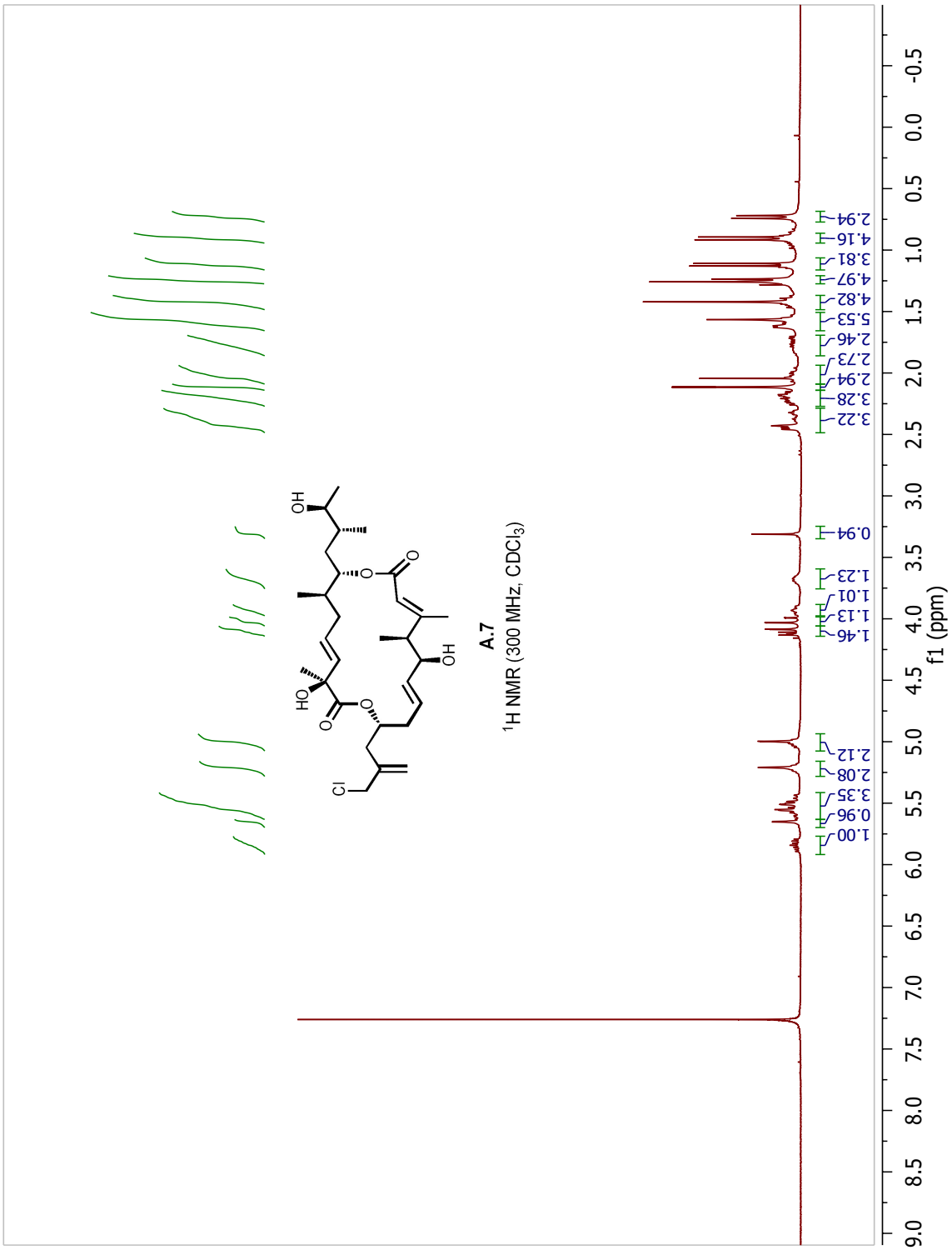

-5.4
-5.4
-4.8
-4.6
-4.5
-3.8
0.0
15.5
16.7
17.7
19.1
25.5
25.8
25.9
36.4
36.7
37.1
50.5
65.5
71.2
72.7
74.0
75.3
79.0
112.1
116.6
124.9
128.2
133.7
136.4
143.9
162.0
166.6
175.2
OTBS
HO
O
O
O
O
O
TBSO
OTBS
2.19
^{13}C NMR (75 MHz, $CDCl_3$)
f1 (ppm)

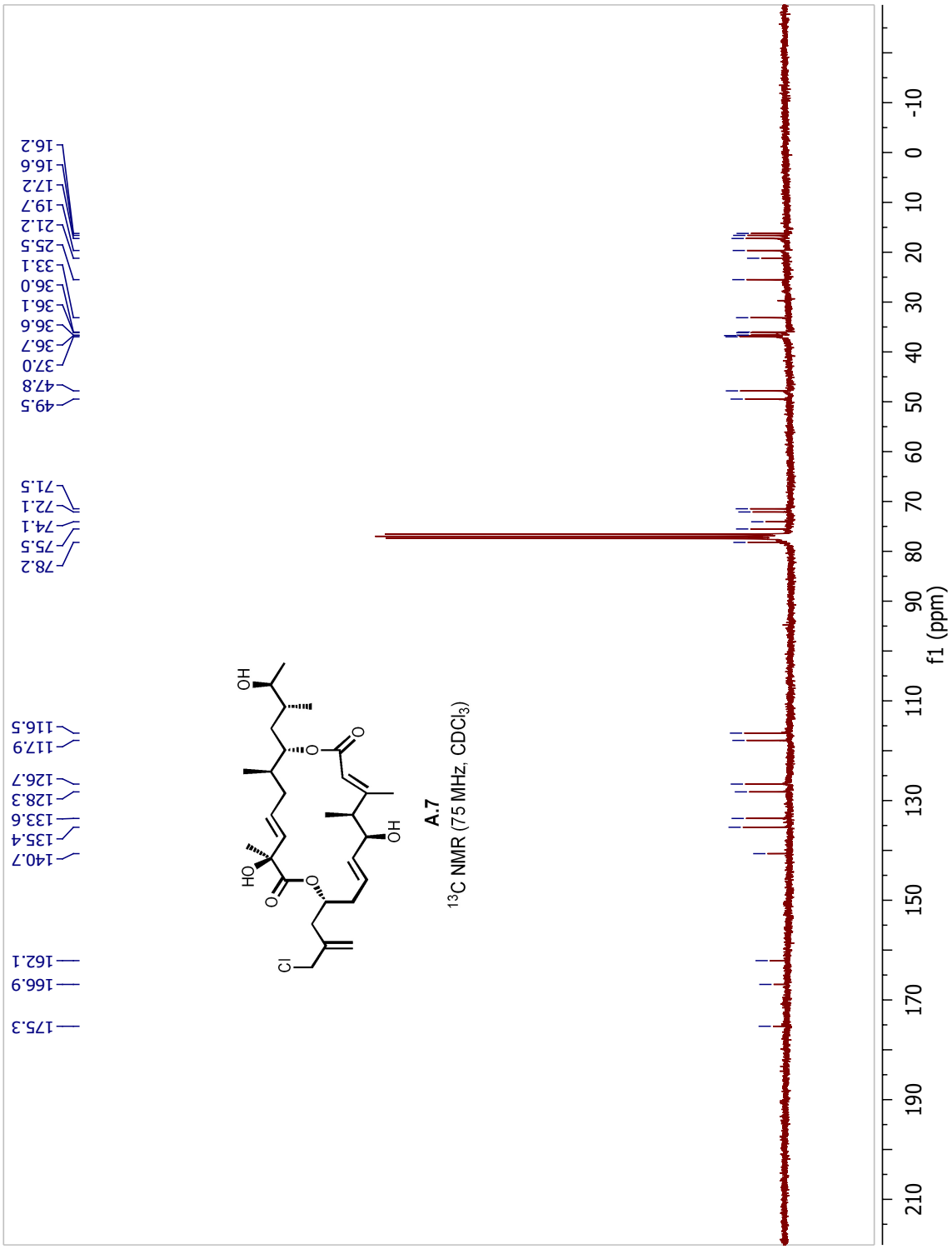

OTBS
HO
O
O
O
O
TBSO
OH
A.6
^{1}H NMR (300 MHz, $CDCl_3$)
f1 (ppm)
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
1.00
1.29
1.54
1.99
1.09
1.49
1.17
1.30
2.65
0.98
1.19
0.89
18.32
4.70
2.16
4.53
4.94
5.13
7.25
34.31
4.44
3.12
3.62
3.58
3.37


-4.8
-4.6
-4.5
-3.8
15.5
16.7
17.7
19.0
25.7
25.8
25.8
35.1
36.4
36.9
37.6
50.5
65.9
71.2
73.2
74.1
75.1
79.0
113.5
116.4
124.9
128.1
133.7
136.5
144.2
162.4
166.5
175.6
OTBS
TBSO
HO
OH
A.6
^{13}C NMR (75 MHz, $CDCl_3$)
f1 (ppm)


OTBS
HO
TBSO
Cl
2.20
^{1}H NMR (300 MHz, $CDCl_3$)
f1 (ppm)

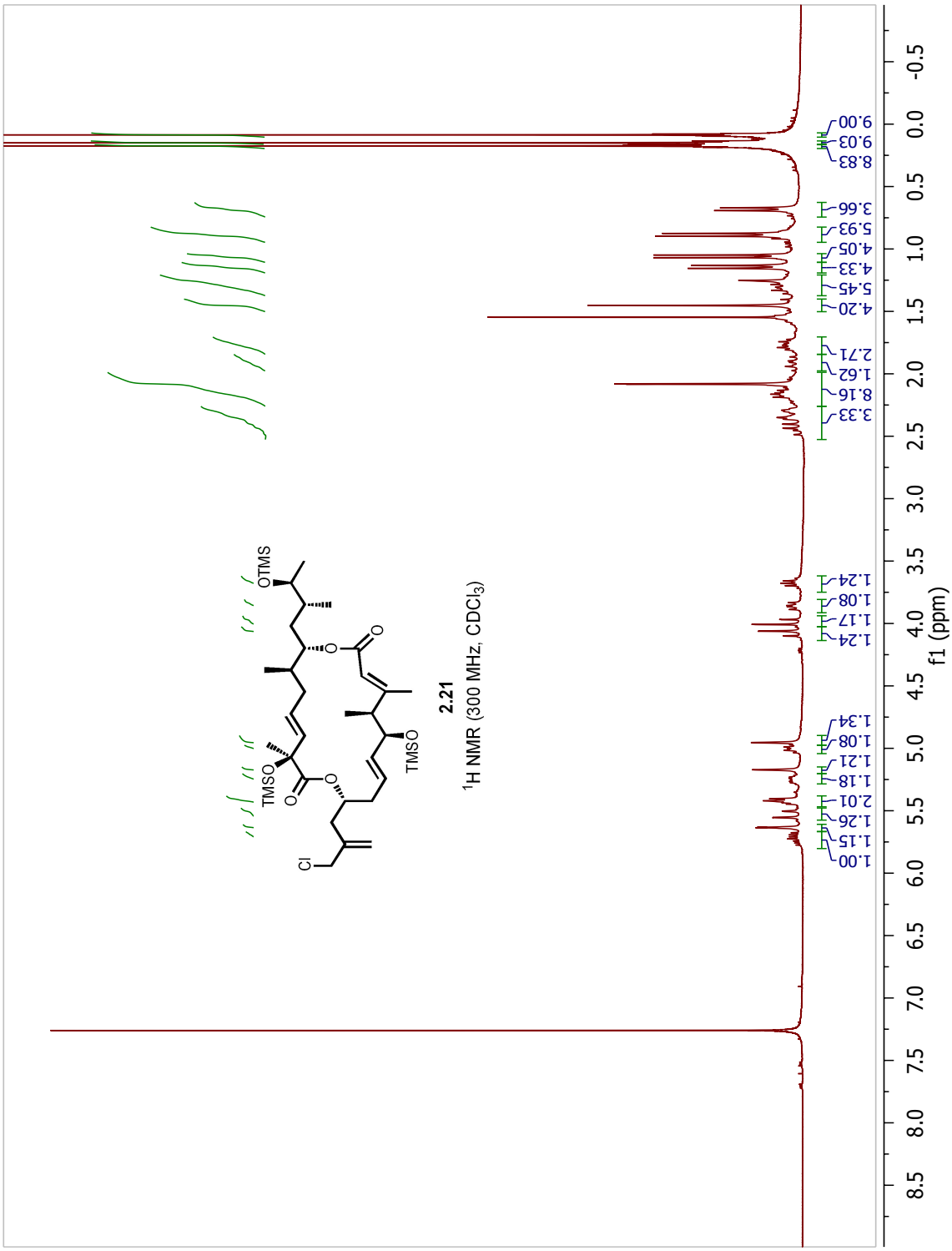

OTBS
TBSO
HO
Cl
2.20
^{13}C NMR (75 MHz, $CDCl_3$)
-4.8
-4.6
-4.5
-3.7
15.5
16.7
17.7
19.1
25.5
25.8
25.9
35.0
36.4
37.1
47.7
50.5
71.2
72.2
74.1
75.3
78.9
116.6
117.5
124.6
128.4
133.6
136.7
140.8
162.1
166.6
175.3
f1 (ppm)

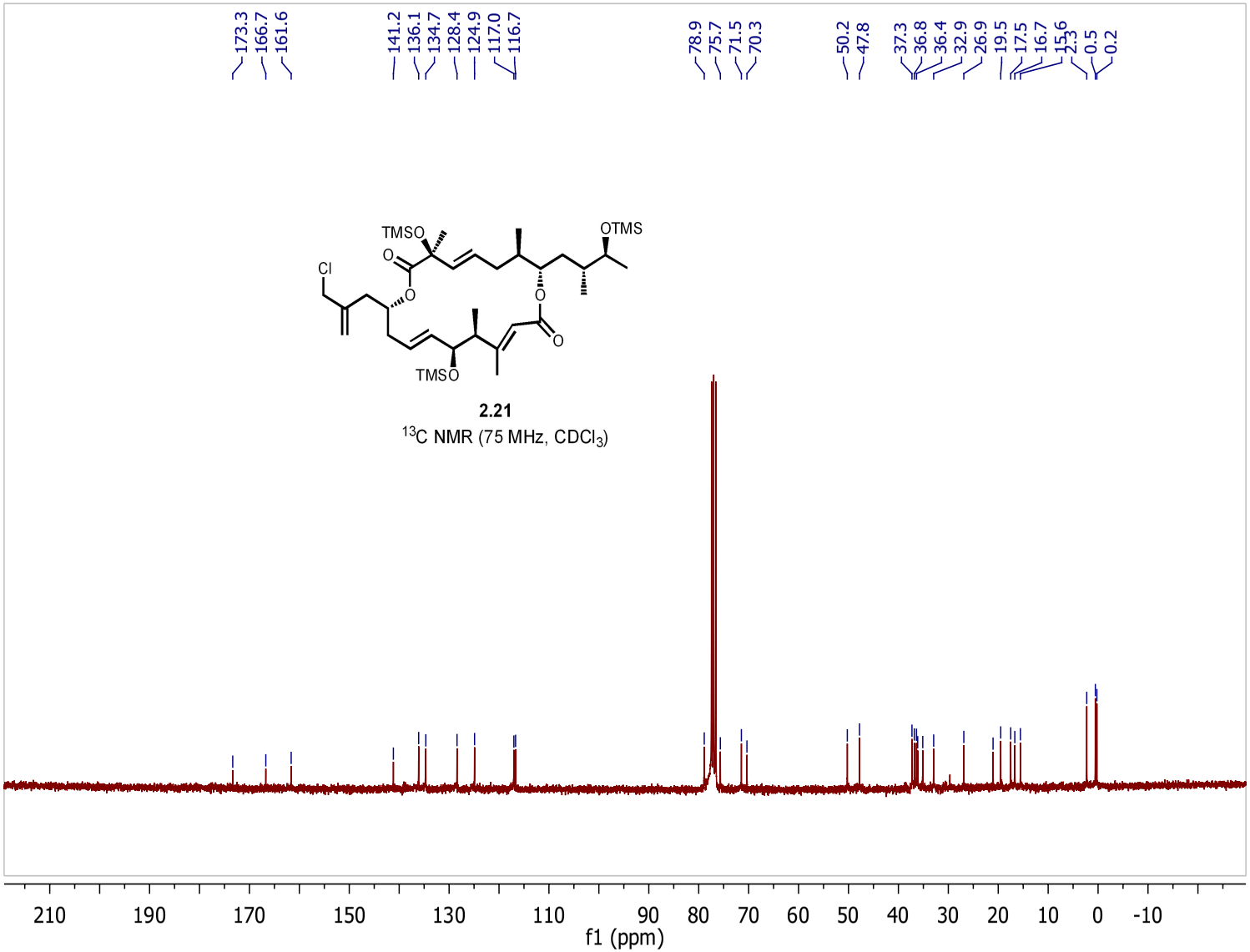

A.7
^{1}H NMR (300 MHz, $CDCl_3$)
f1 (ppm)
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
1.00
0.96
3.35
2.08
2.12
0.94
1.46
1.13
1.01
1.23
3.22
3.28
2.94
2.73
2.46
5.53
4.82
4.97
3.81
4.16
2.94



A.7

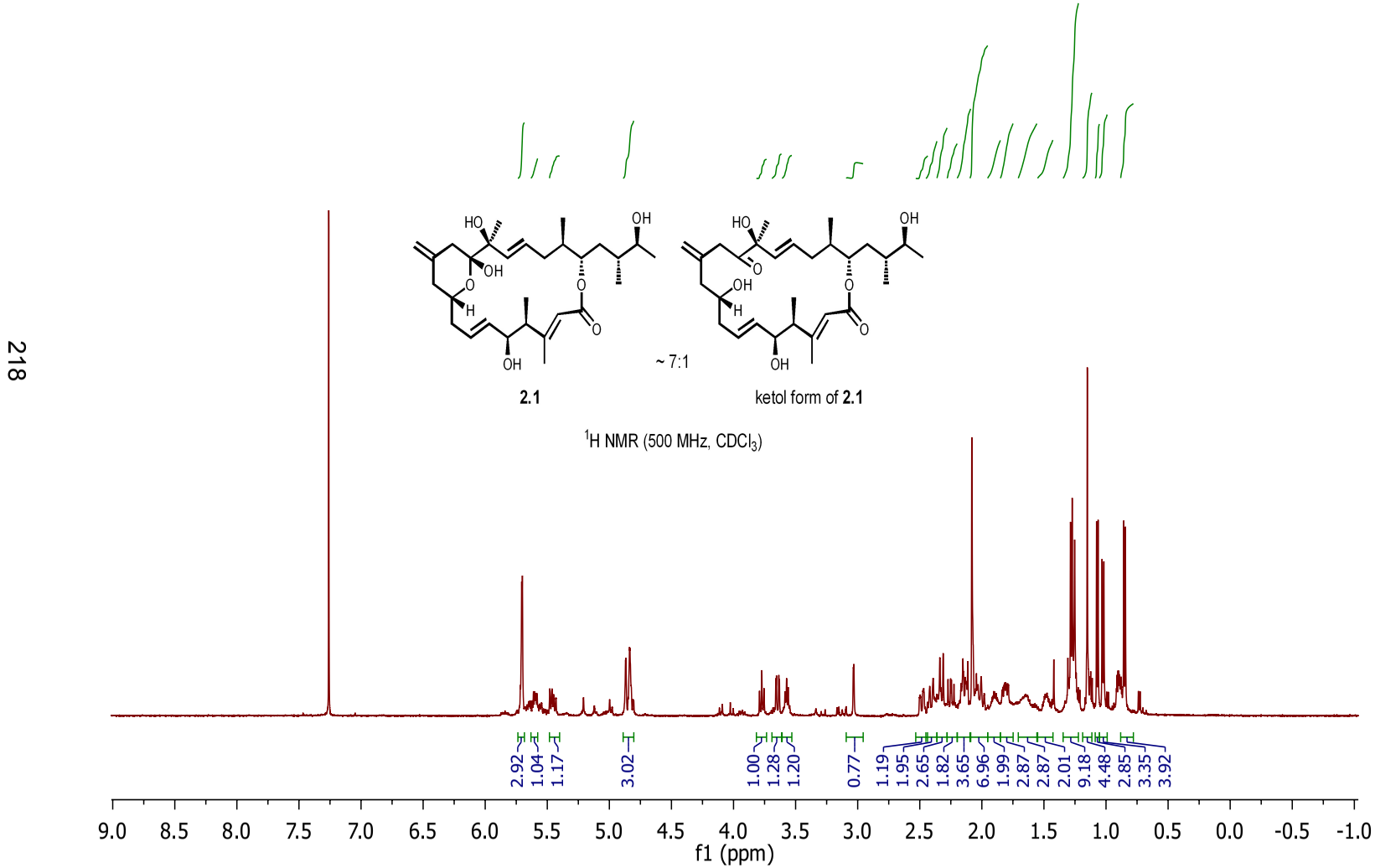
^{13}C NMR (75 MHz, $CDCl_3$)

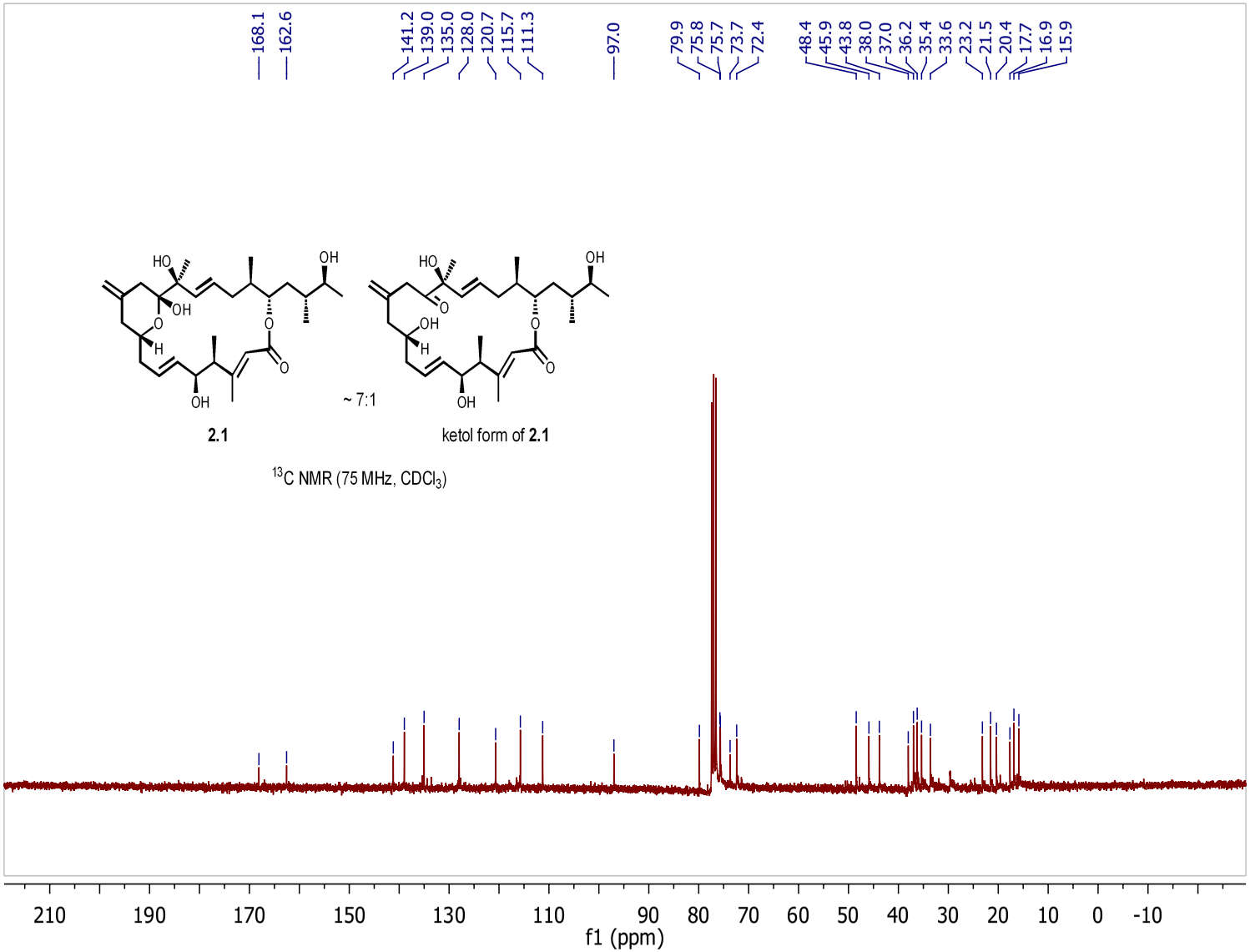

OTMS
TMSO
TMSO
Cl
O
O
O
O
O
2.21
^{1}H NMR (300 MHz, $CDCl_3$)
9.00
9.03
8.83
3.66
5.93
4.05
4.33
5.45
4.20
2.71
1.62
8.16
3.33
1.24
1.17
1.08
1.24
1.34
1.08
1.21
1.18
2.01
1.26
1.15
1.00
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

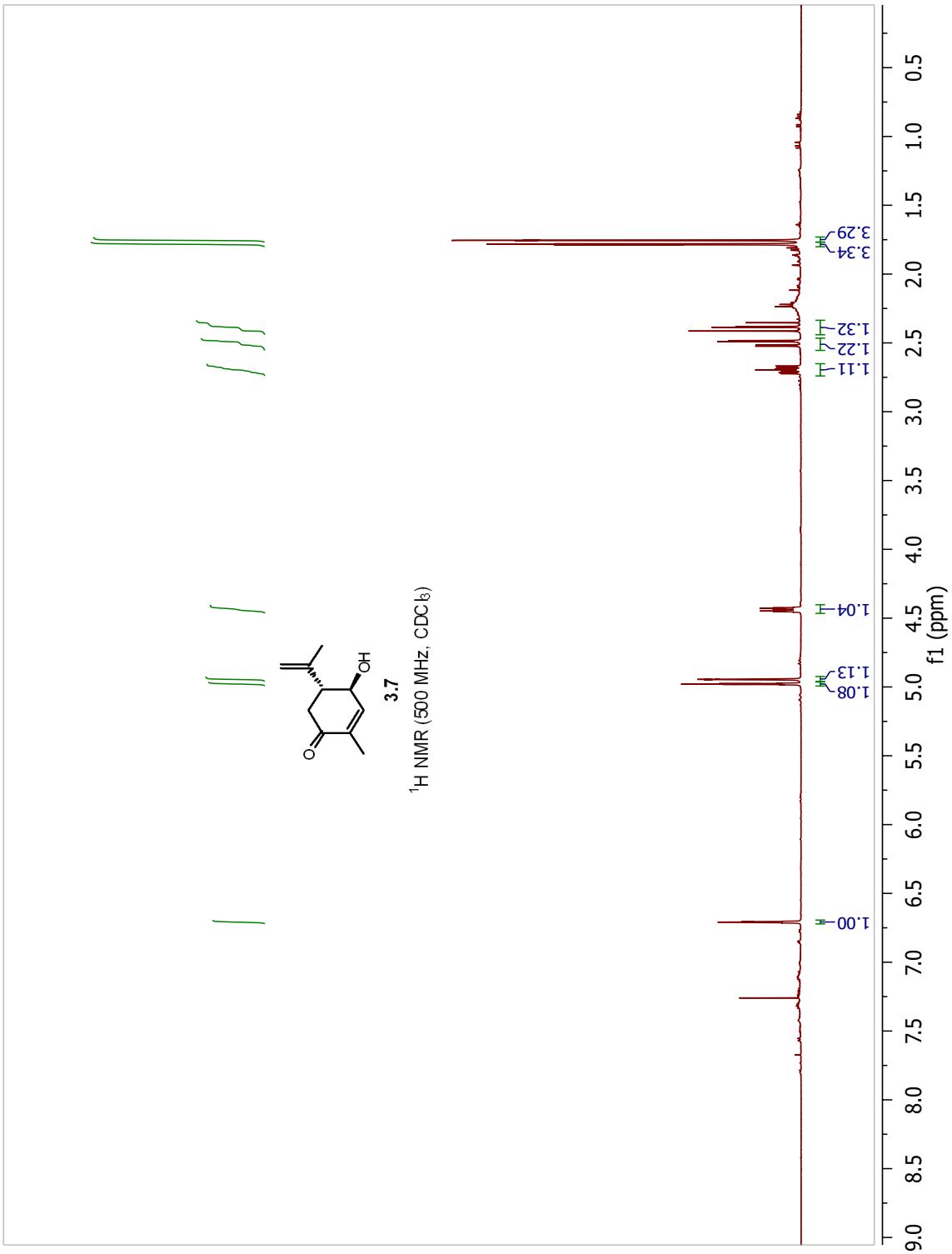


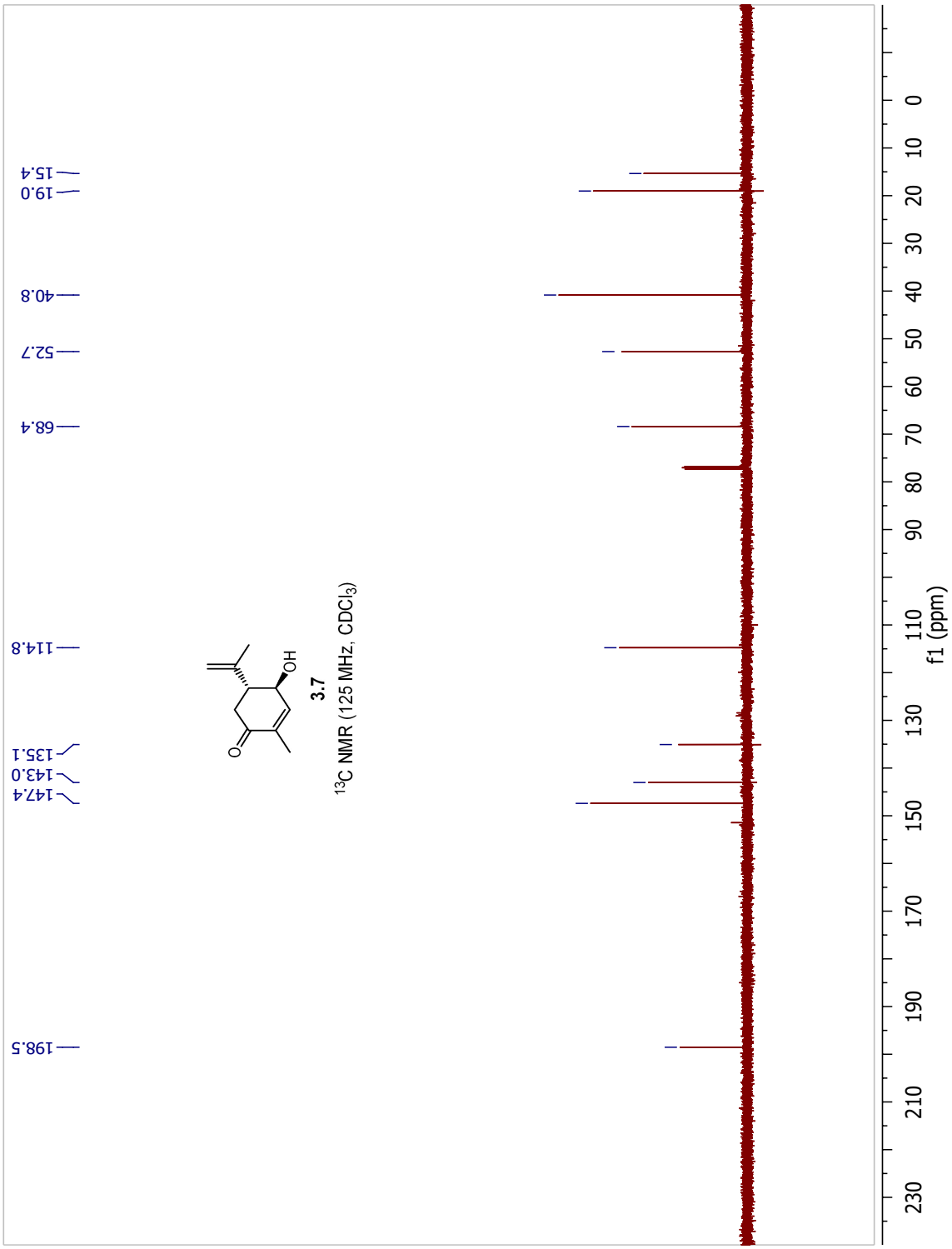
2.21

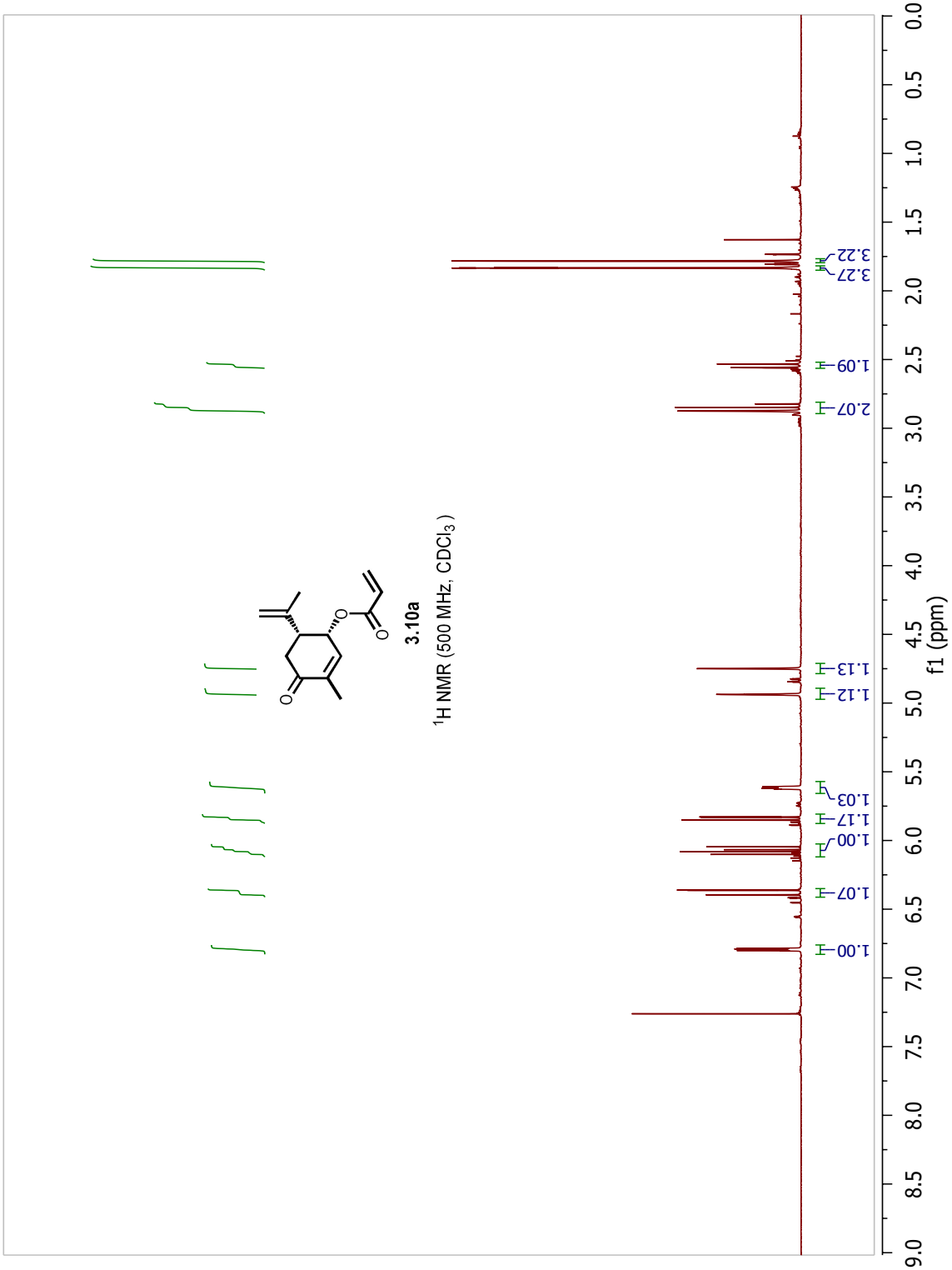
^{13}C NMR (75 MHz, $CDCl_3$)

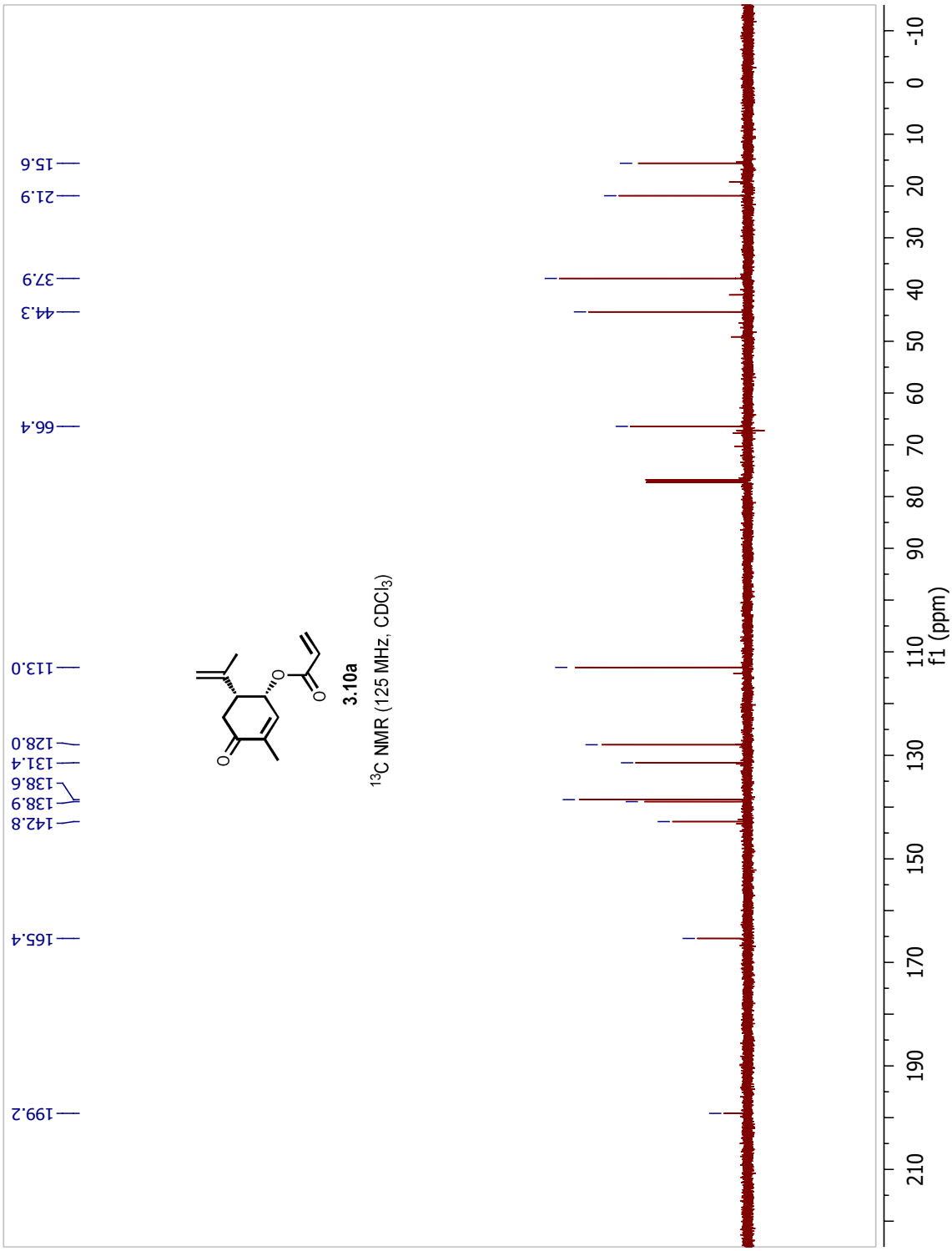

HO
OH
O
H
OH
O
O
OH
~ 7:1
2.1
ketol form of 2.1
^{1}H NMR (500 MHz, $CDCl_3$)
2.92
1.04
1.17
3.02
1.00
1.28
1.20
0.77
1.19
1.95
2.65
1.82
3.65
6.96
1.99
2.87
2.87
2.01
9.18
4.48
2.85
3.35
3.92
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

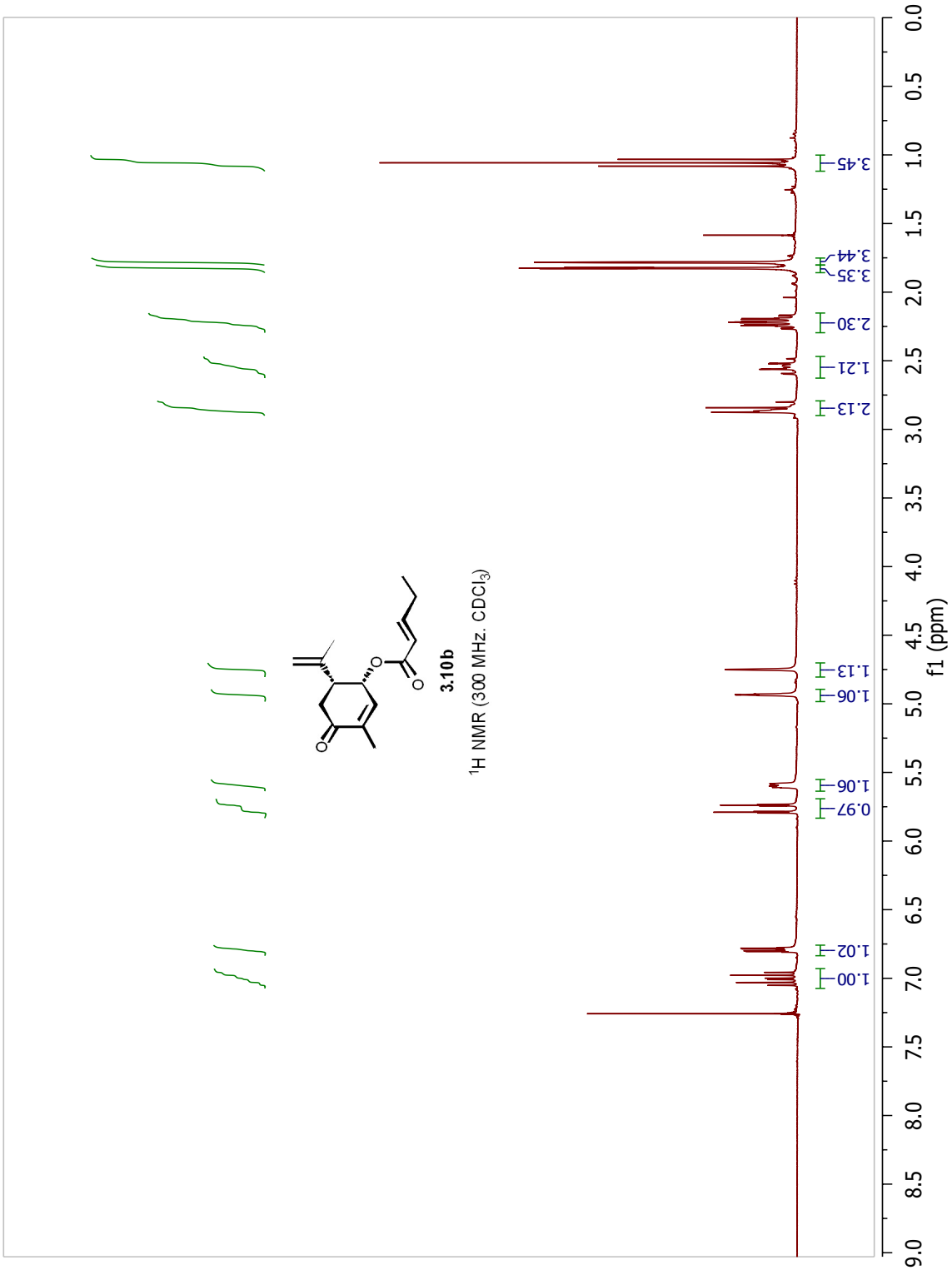

168.1
162.6
141.2
139.0
135.0
128.0
120.7
115.7
111.3
97.0
79.9
75.8
75.7
73.7
72.4
48.4
45.9
43.8
38.0
37.0
36.2
35.4
33.6
23.2
21.5
20.4
17.7
16.9
15.9
HO
OH
OH
O
O
H
O
OH
~ 7:1
2.1
ketol form of 2.1
13C NMR (75 MHz, CDCl3)
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

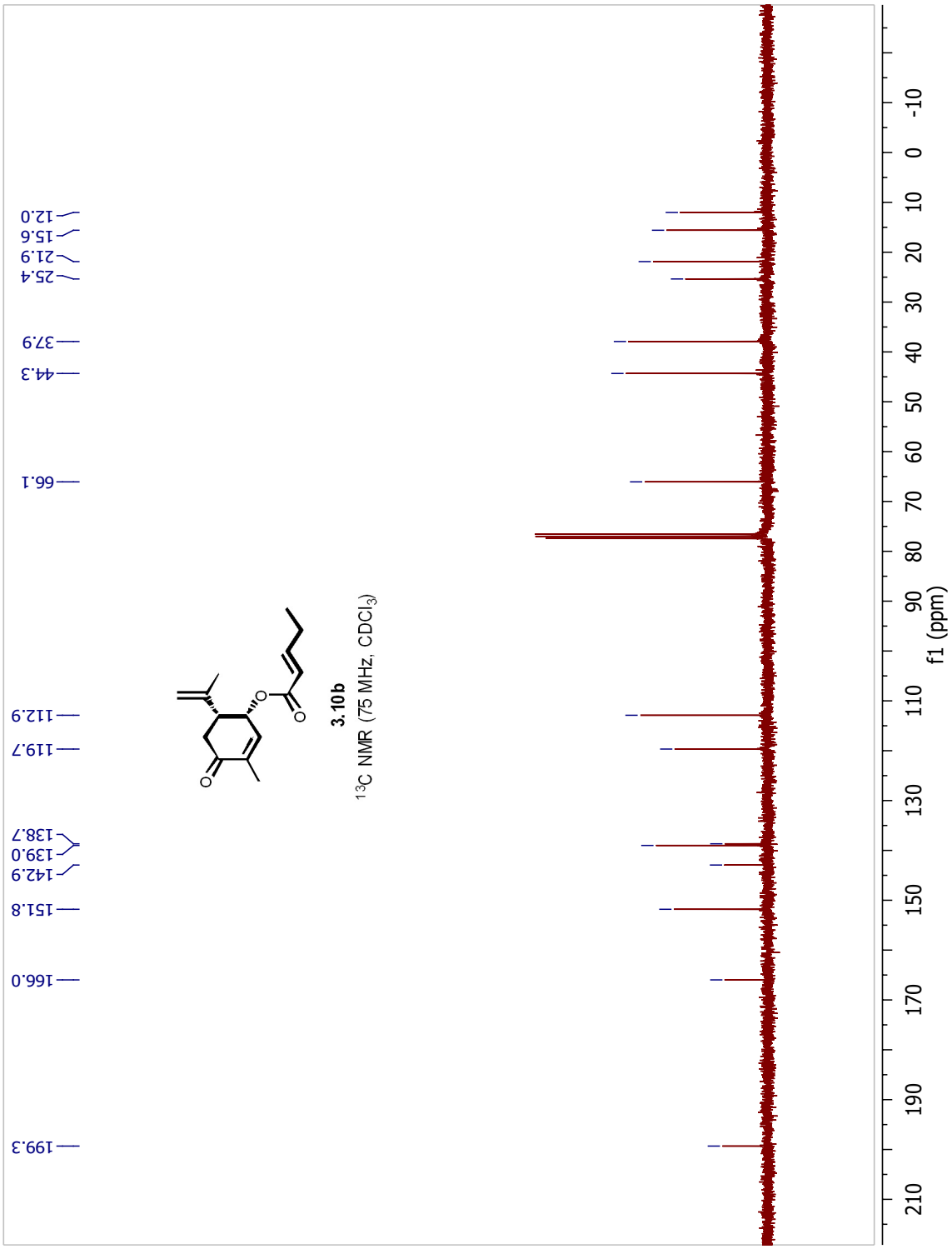

OH
O
3.7
^{1}H NMR (500 MHz, CDCl$_3$)
1.00
1.08
1.13
1.04
1.11
1.22
1.32
3.29
3.34
f1 (ppm)

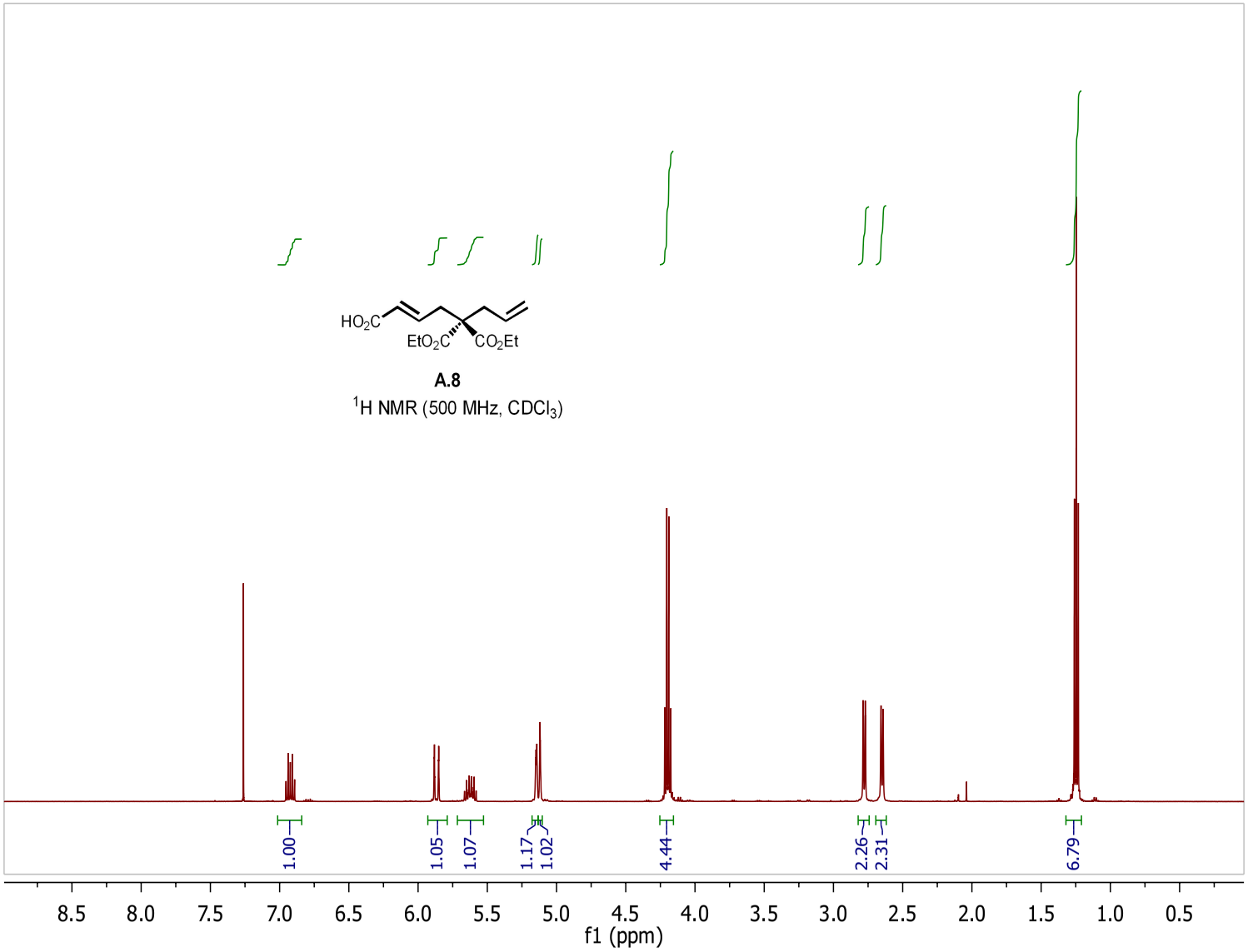

198.5
147.4
143.0
135.1
114.8
68.4
52.7
40.8
19.0
15.4
OH
O
3.7
^{13}C NMR (125 MHz, $CDCl_3$)
f1 (ppm)

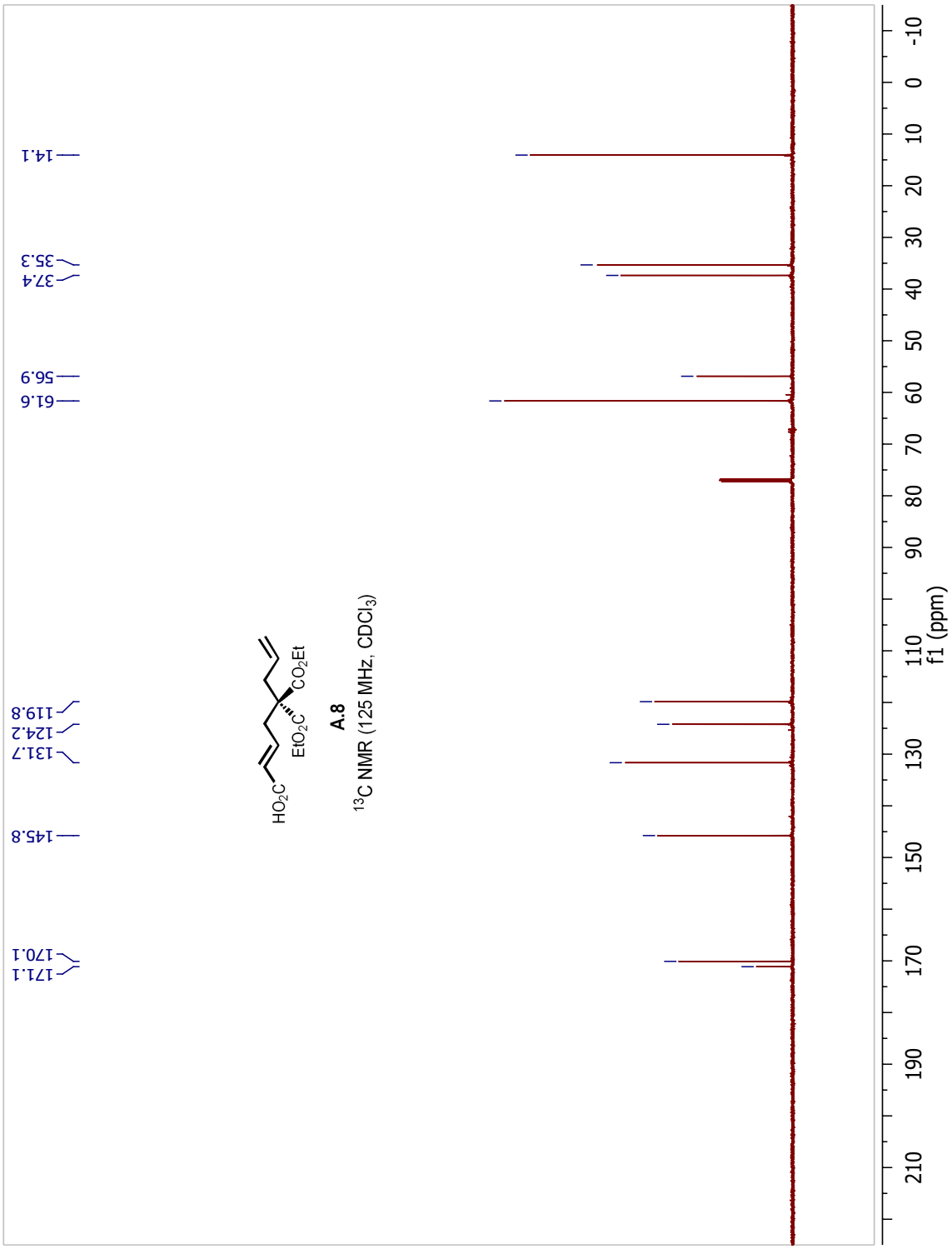

3.10a
^{1}H NMR (500 MHz, CDCl$_3$)
3.27
3.22
1.09
2.07
1.13
1.12
1.03
1.17
1.00
1.07
1.00
f1 (ppm)

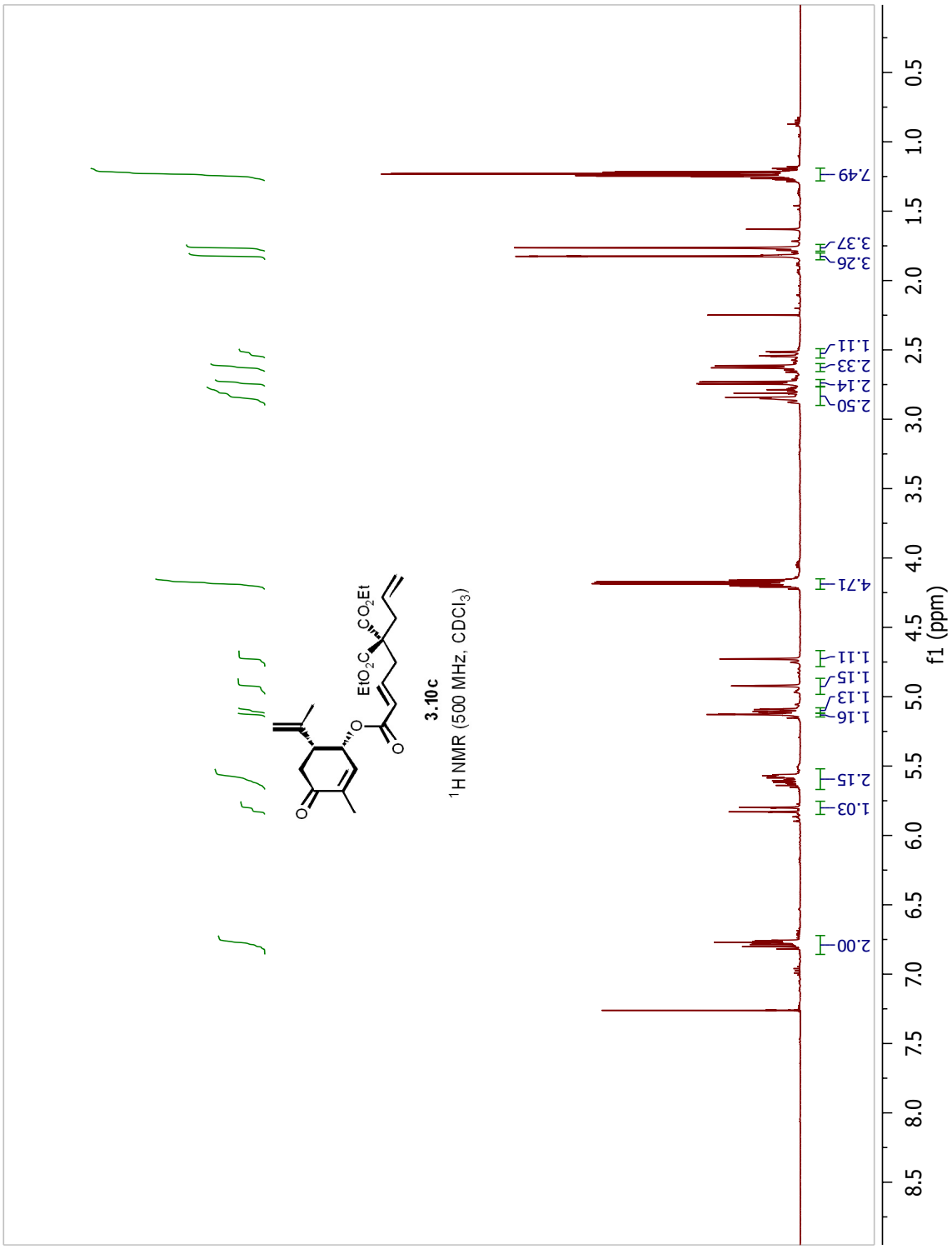

199.2
165.4
142.8
138.9
138.6
131.4
128.0
113.0
66.4
44.3
37.9
21.9
15.6
O
O
O
3.10a
^{13}C NMR (125 MHz, $CDCl_3$)
-10
0
10
20
30
40
50
60
70
80
90
110
130
150
170
190
210
f1 (ppm)

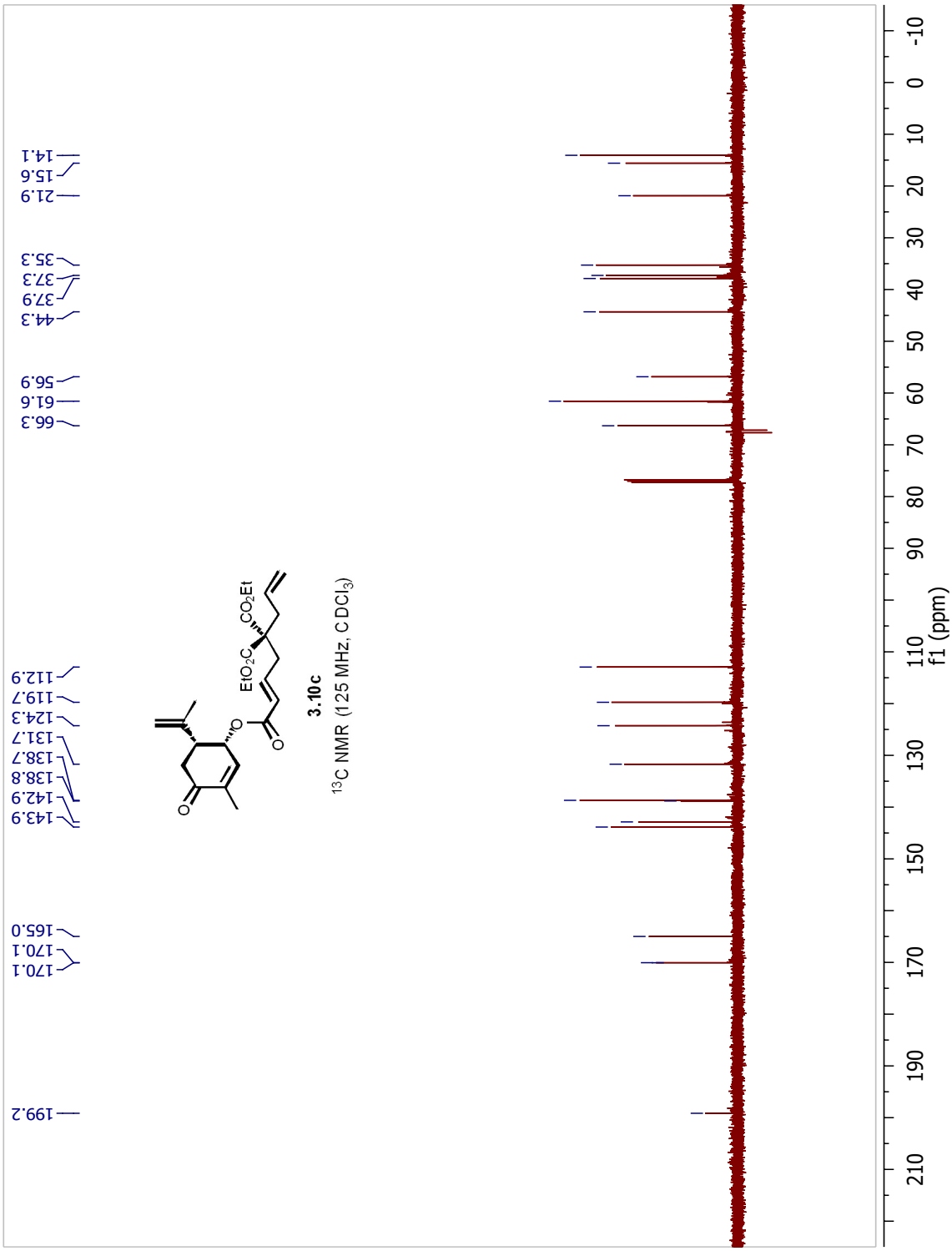

3.10b
^{1}H NMR (300 MHz. $CDCl_3$)
3.45
3.44
3.35
2.30
1.21
2.13
1.13
1.06
1.06
0.97
1.02
1.00
f1 (ppm)

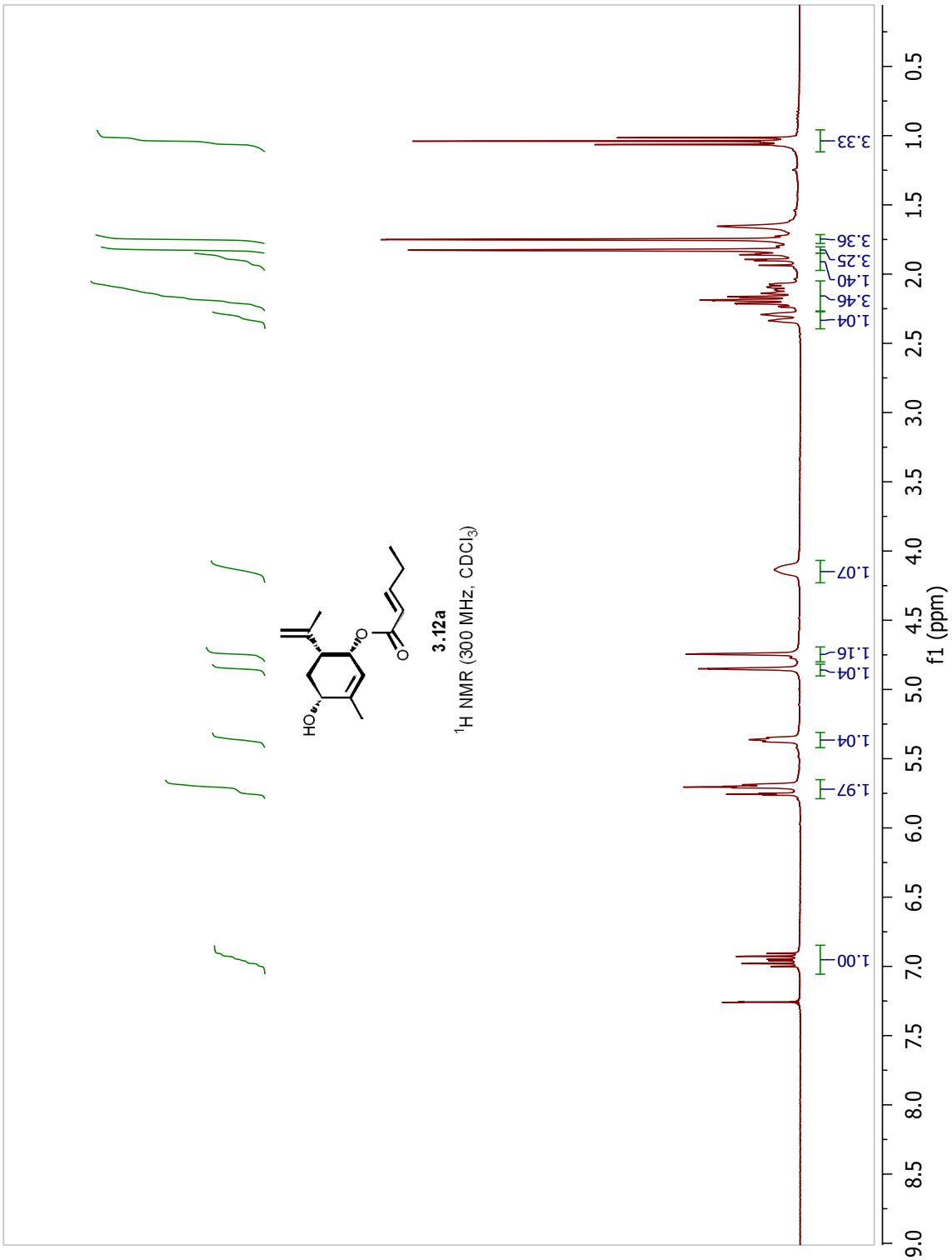

199.3
166.0
151.8
142.9
139.0
138.7
119.7
112.9
66.1
44.3
37.9
25.4
21.9
15.6
12.0
3.10b
^{13}C NMR (75 MHz, $CDCl_3$)
f1 (ppm)

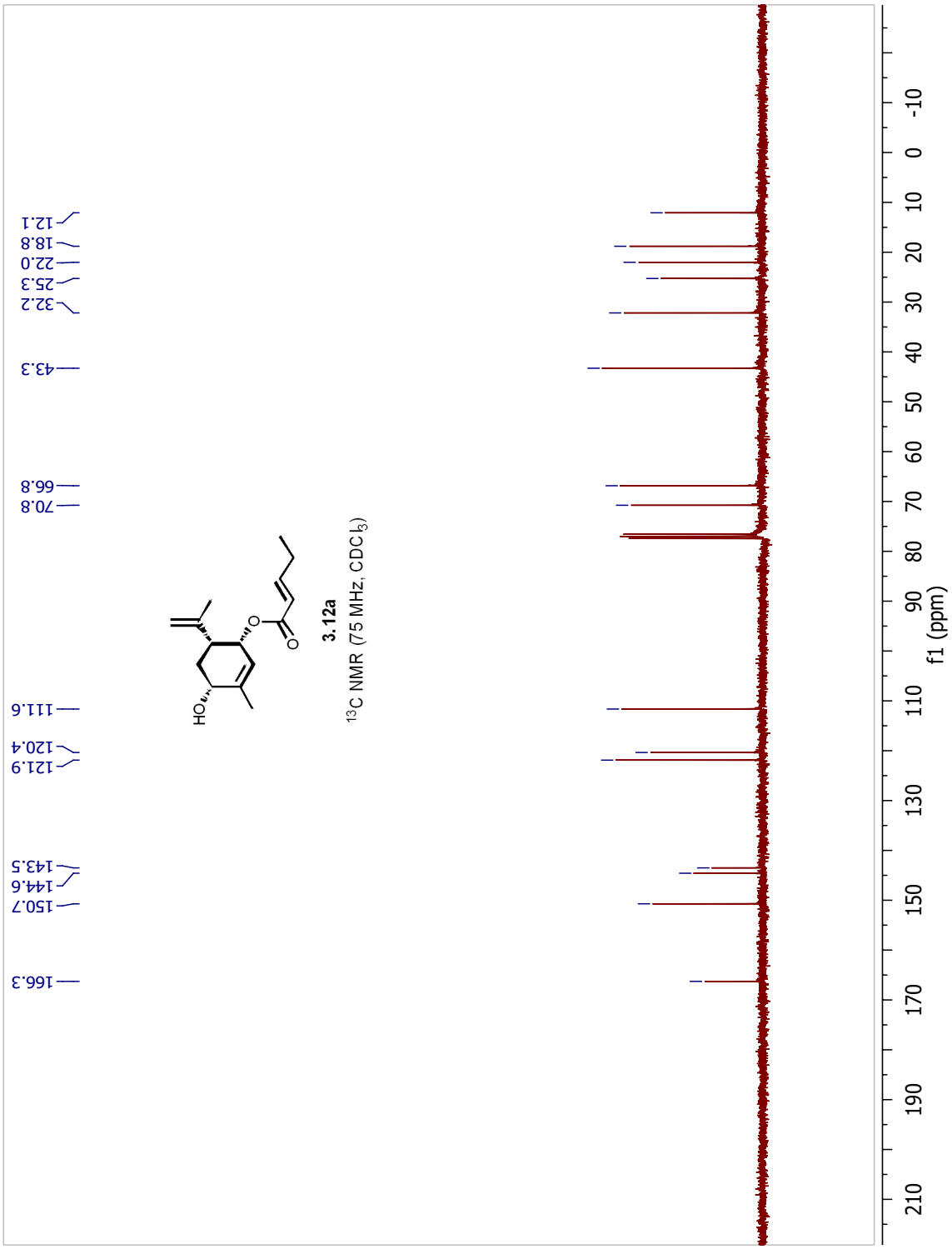

HO2C
EtO2C
CO2Et
A.8
1H NMR (500 MHz, CDCl3)
1.00
1.05
1.07
1.17
1.02
4.44
2.26
2.31
6.79
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

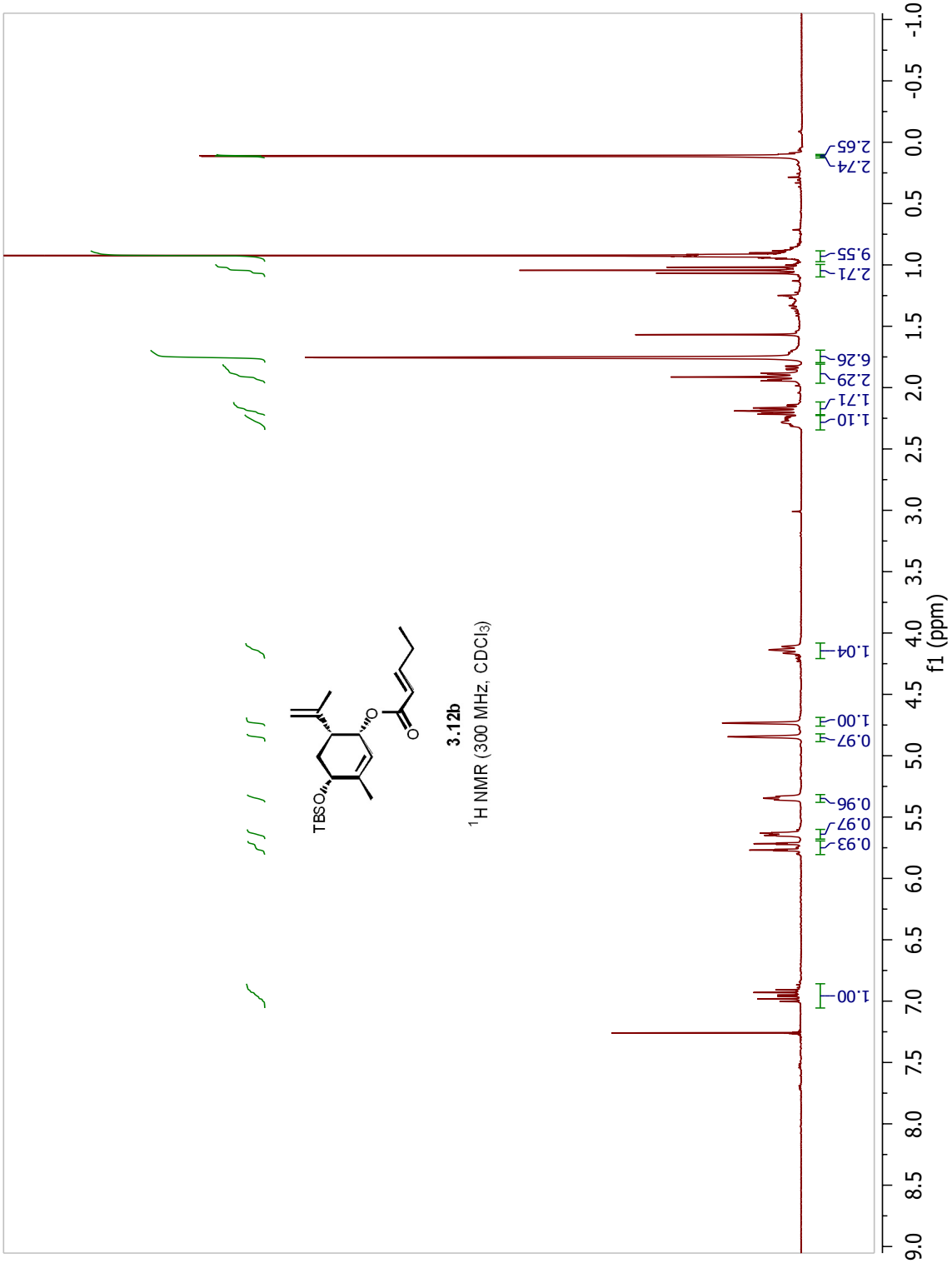

A.8
^{13}C NMR (125 MHz, $CDCl_3$)
HO_2C
EtO_2C
CO_2Et
14.1
35.3
37.4
56.9
61.6
119.8
124.2
131.7
145.8
170.1
171.1
f1 (ppm)

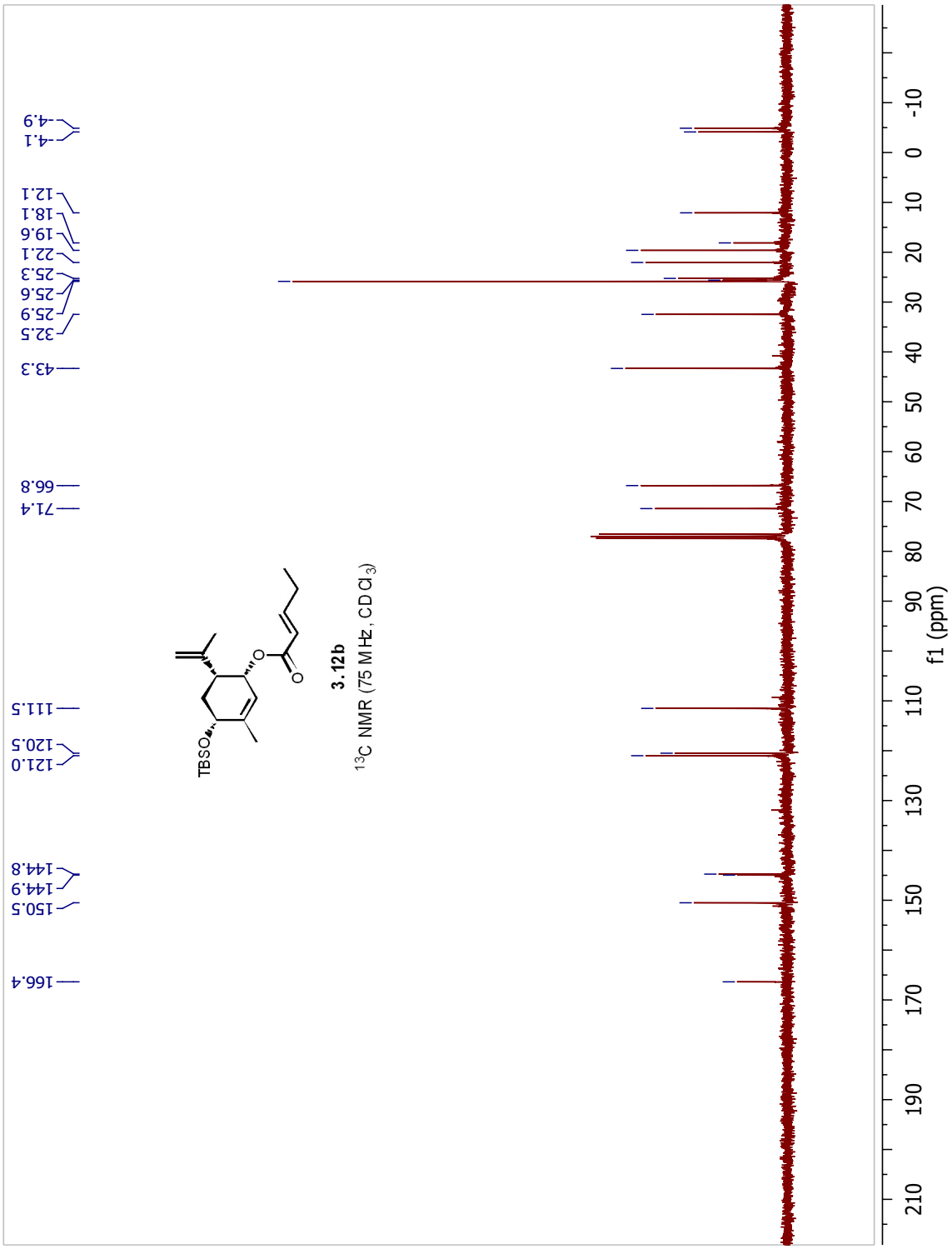

3.10c
^{1}H NMR (500 MHz, $CDCl_3$)
7.49
3.26
3.37
1.11
2.33
2.14
2.50
4.71
1.11
1.15
1.13
1.16
2.15
1.03
2.00
f1 (ppm)

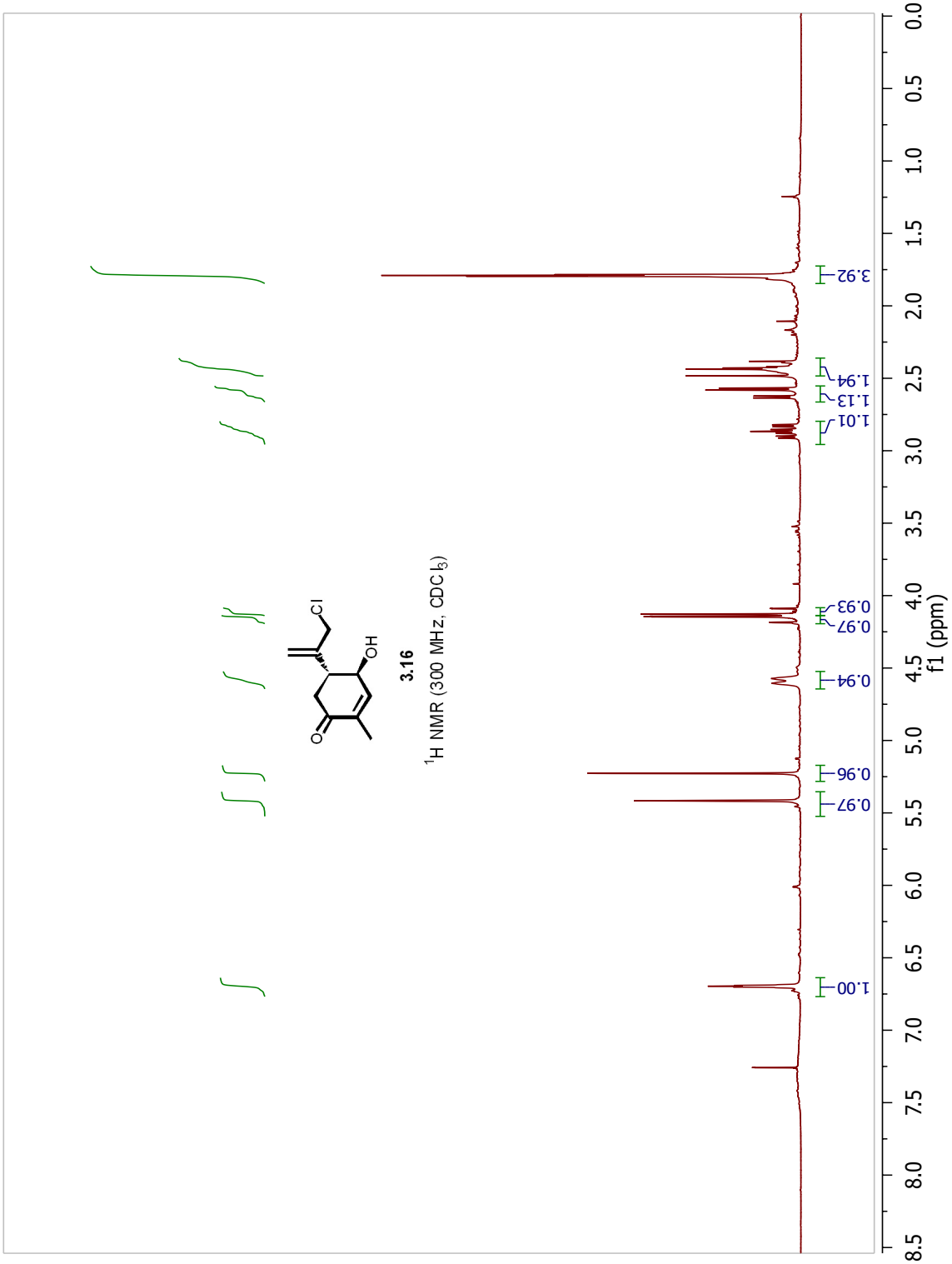

199.2
170.1
170.1
165.0
143.9
142.9
138.8
138.7
131.7
124.3
119.7
112.9
66.3
61.6
56.9
44.3
37.9
37.3
35.3
21.9
15.6
14.1
EtO2C
CO2Et
O
O
O
3.10c
13C NMR (125 MHz, CDCl3)
f1 (ppm)
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10

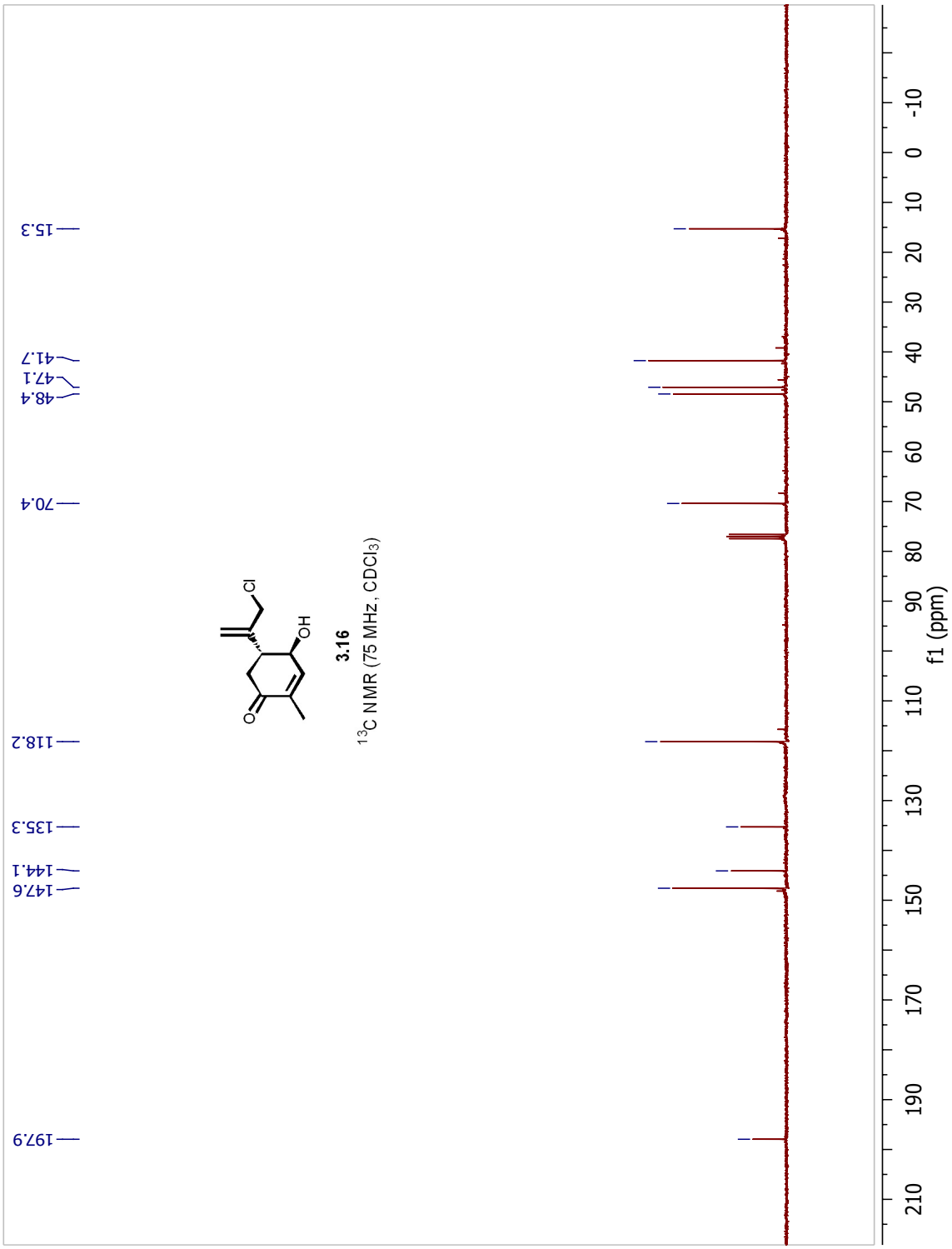

3.12a
^{1}H NMR (300 MHz, $CDCl_3$)
HO
O
O
3.33
3.36
3.25
1.40
3.46
1.04
1.07
1.16
1.04
1.04
1.97
1.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

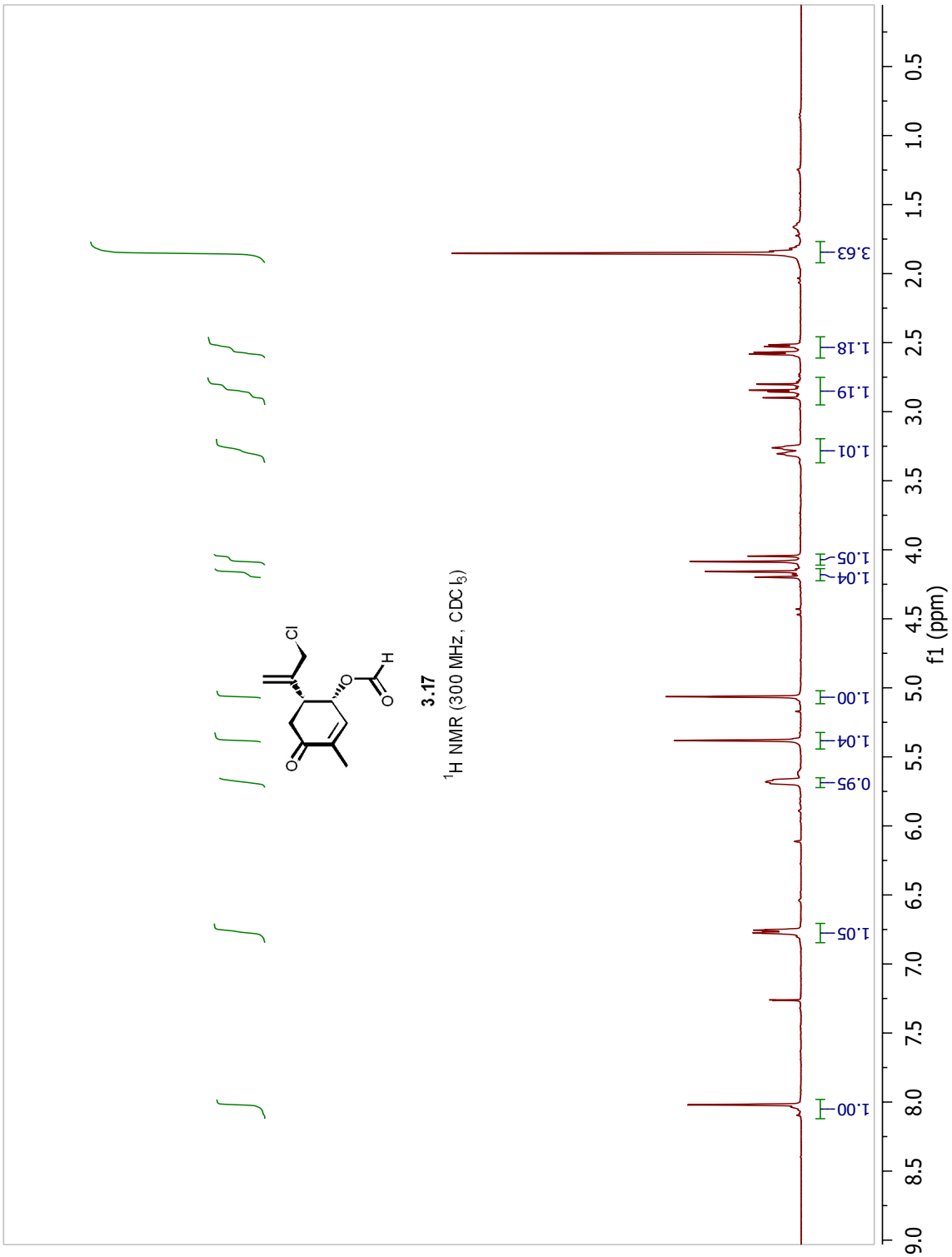

166.3
150.7
144.6
143.5
121.9
120.4
111.6
70.8
66.8
43.3
32.2
25.3
22.0
18.8
12.1
HO
O
O
3. 12a
^{13}C NMR (75 MHz, $CDCl_3$)
f1 (ppm)

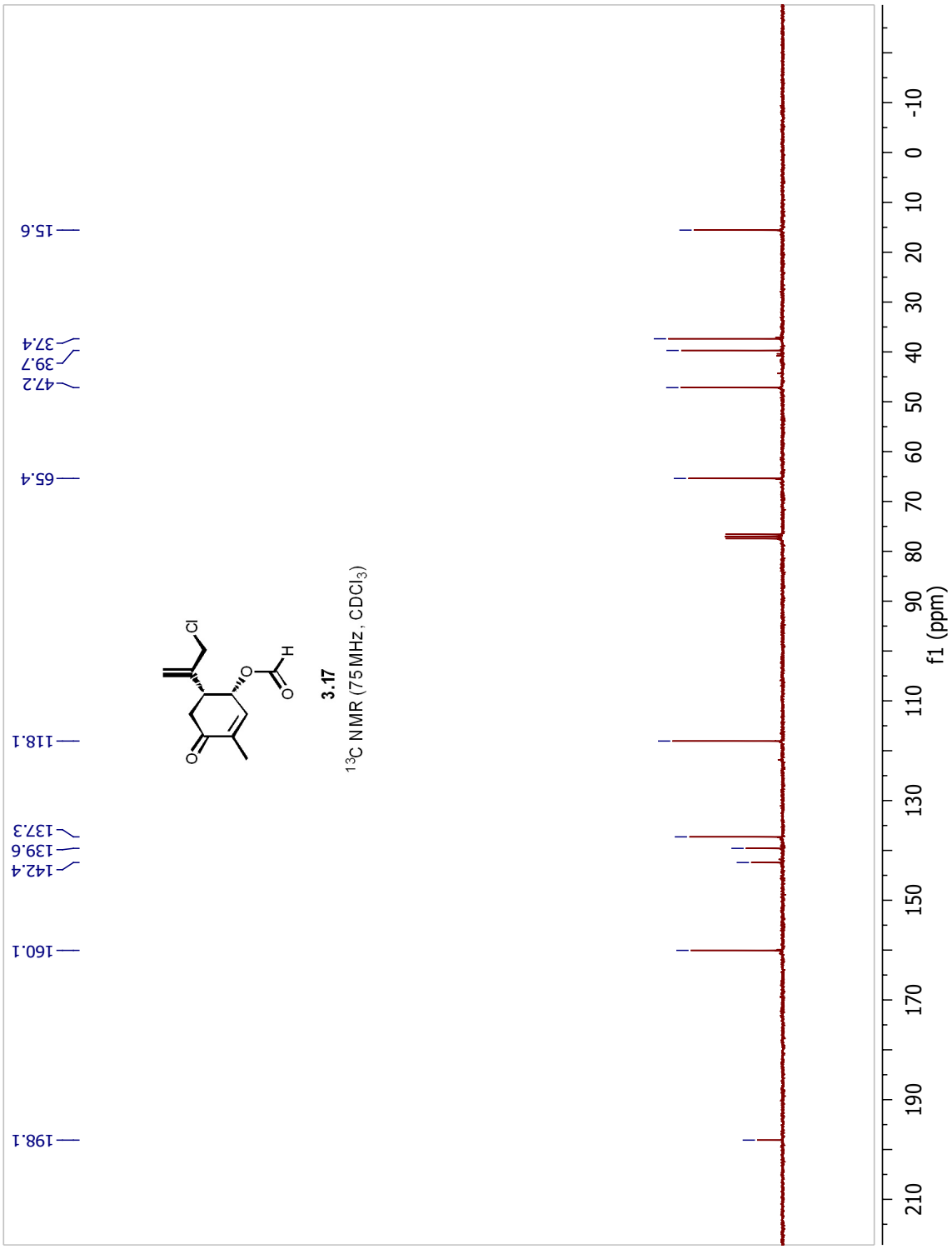

TBSO
O
O
3.12b
^{1}H NMR (300 MHz, $CDCl_3$)
2.74
2.65
9.55
2.71
6.26
2.29
1.71
1.10
1.04
1.00
0.97
0.96
0.93
0.97
1.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)

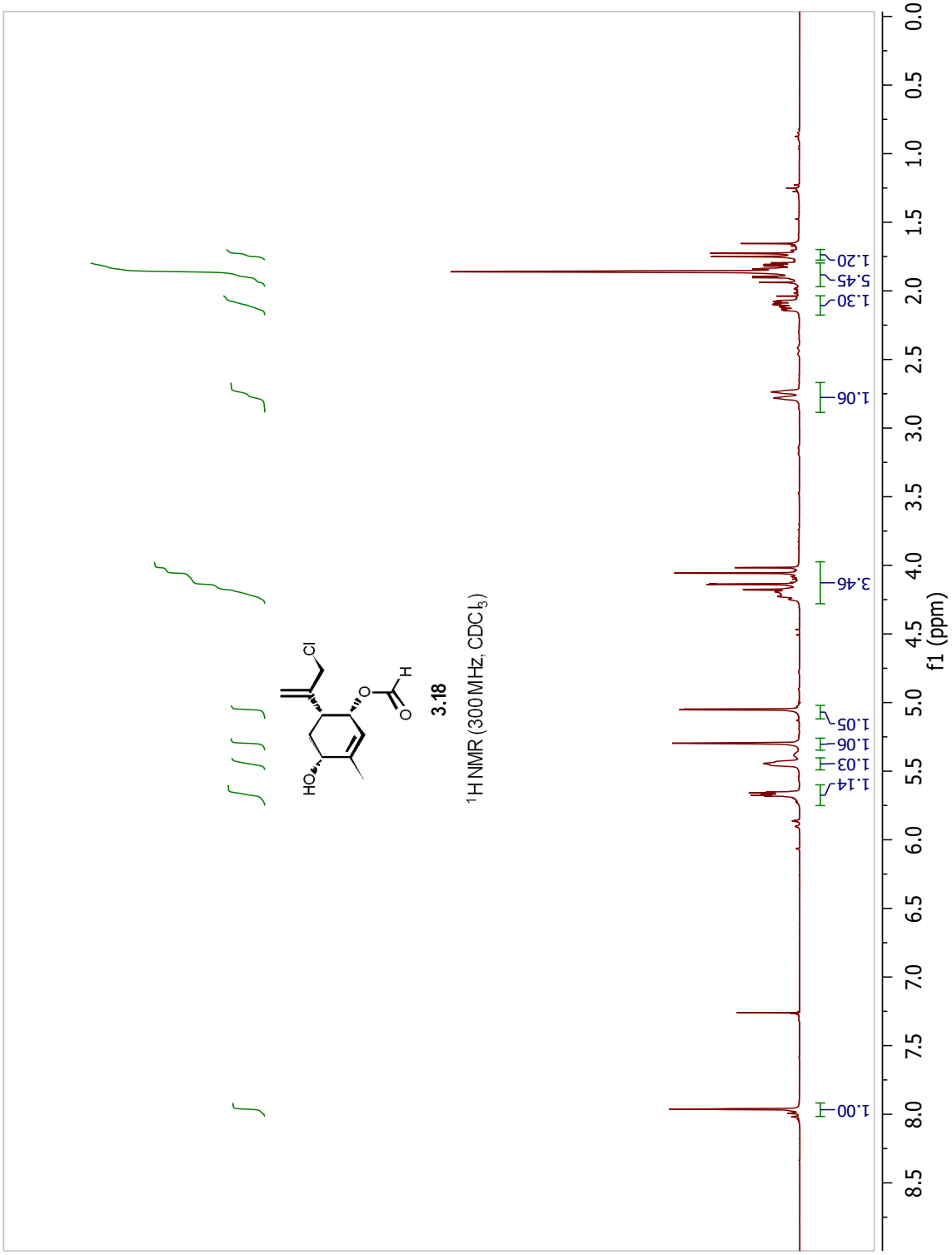

-4.9
-4.1
12.1
18.1
19.6
22.1
25.3
25.6
25.9
32.5
43.3
66.8
71.4
111.5
120.5
121.0
144.8
144.9
150.5
166.4
TBSO
O
O
3.12b
^{13}C NMR (75 MHz, $CDCl_3$)
f1 (ppm)

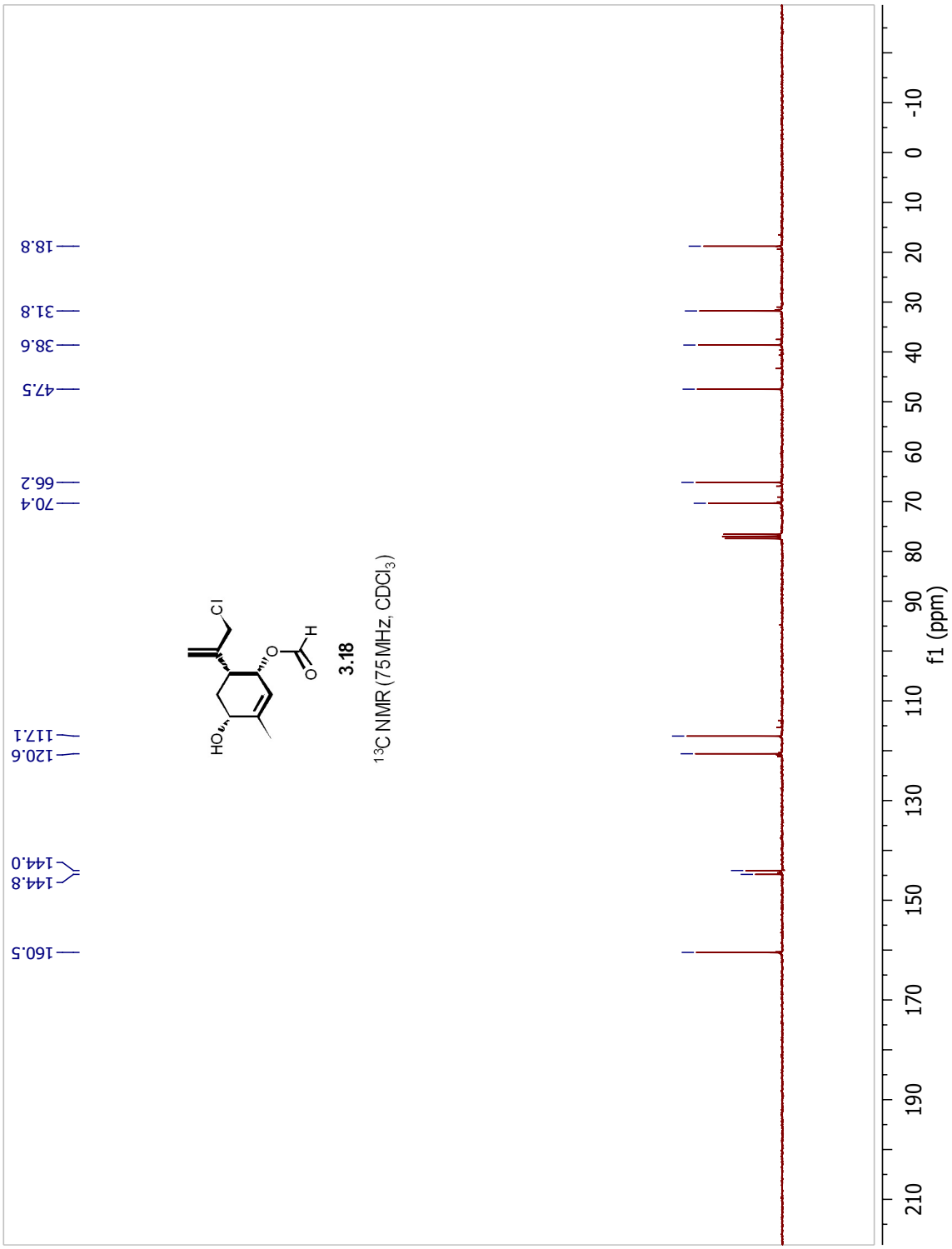

Cl
OH
O
3.16
^{1}H NMR (300 MHz, $CDCl_3$)
3.92
1.94
1.13
1.01
0.97
0.93
0.94
0.96
0.97
1.00
f1 (ppm)

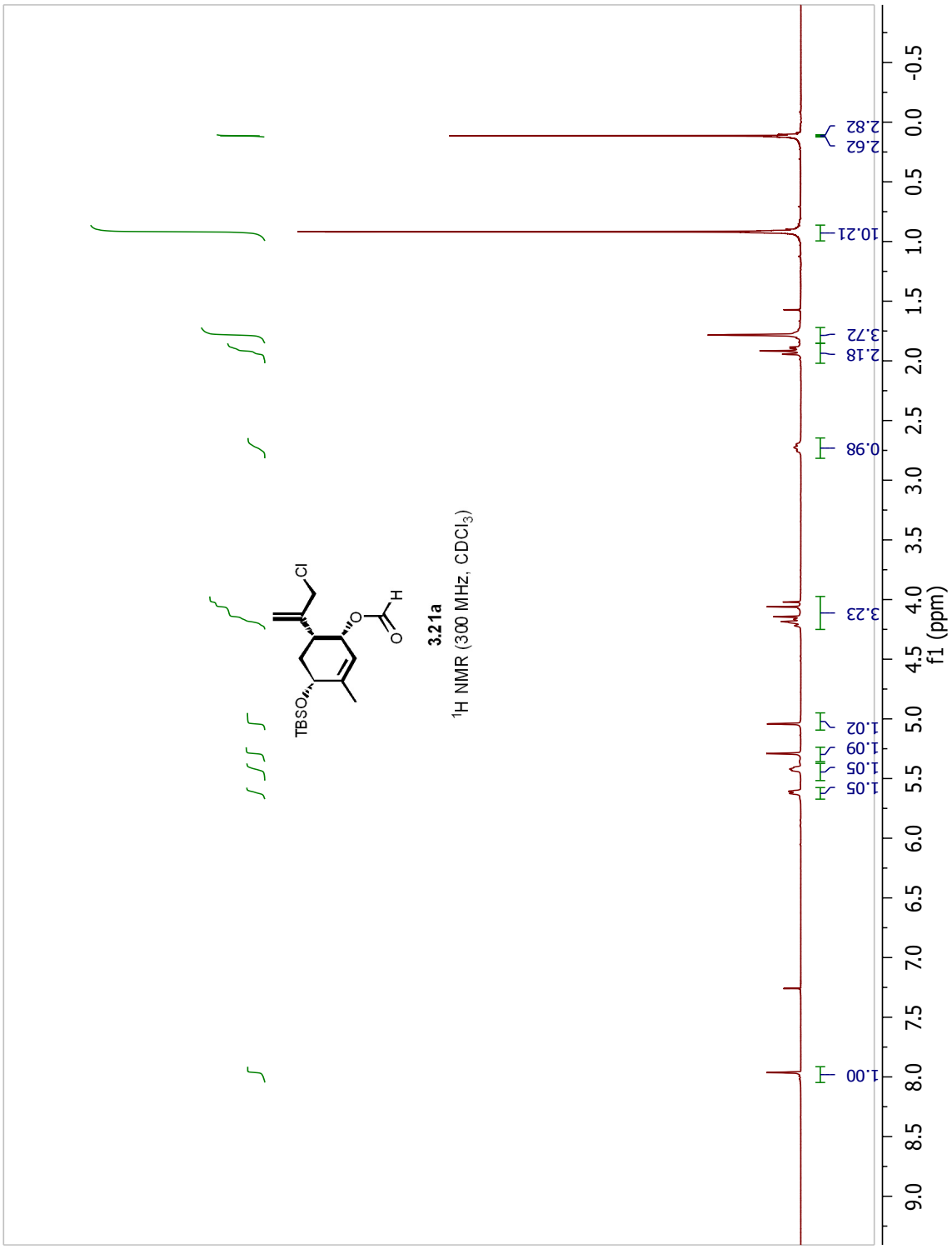

197.9
147.6
144.1
135.3
118.2
70.4
48.4
47.1
41.7
15.3
Cl
OH
O
3.16
^{13}C NMR (75 MHz, $CDCl_3$)
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

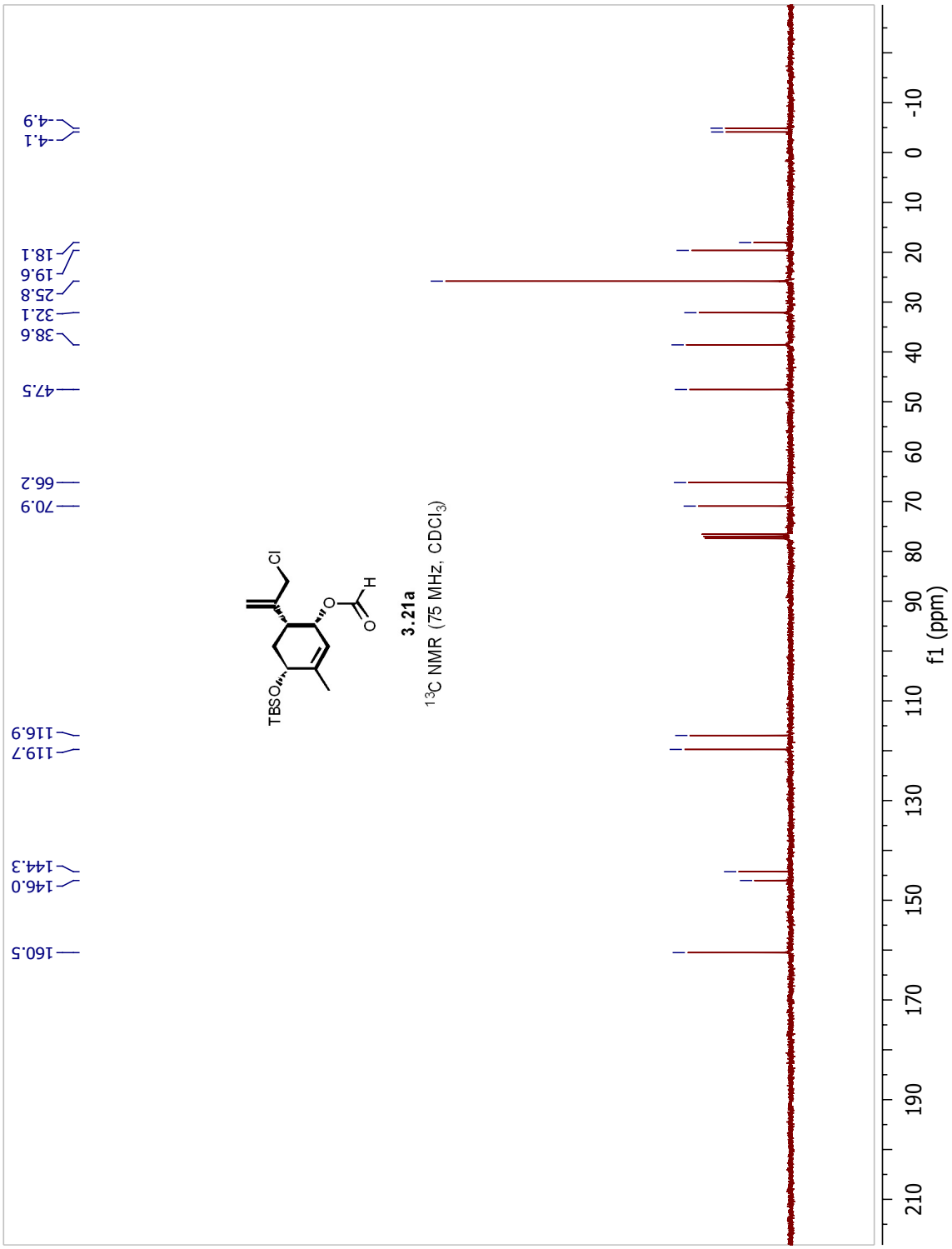

3.63
1.18
1.19
1.01
1.05
1.04
1.00
1.04
0.95
1.05
1.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)
Cl
O
O
H
O
3.17
^{1}H NMR (300 MHz, $CDCl_3$)

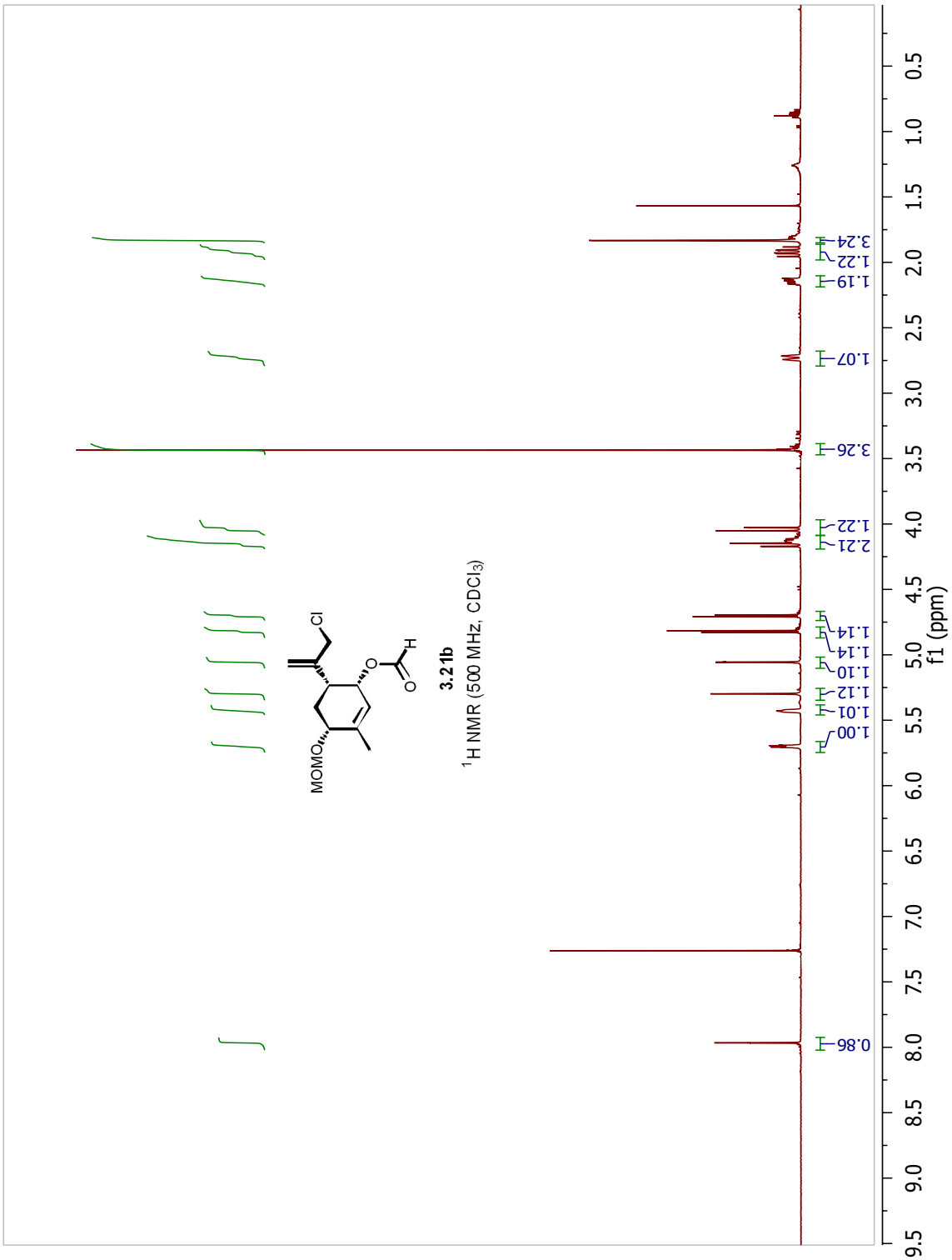

198.1
160.1
142.4
139.6
137.3
118.1
65.4
47.2
39.7
37.4
15.6
Cl
O
O
H
O
3.17
^{13}C NMR (75 MHz, $CDCl_3$)
f1 (ppm)

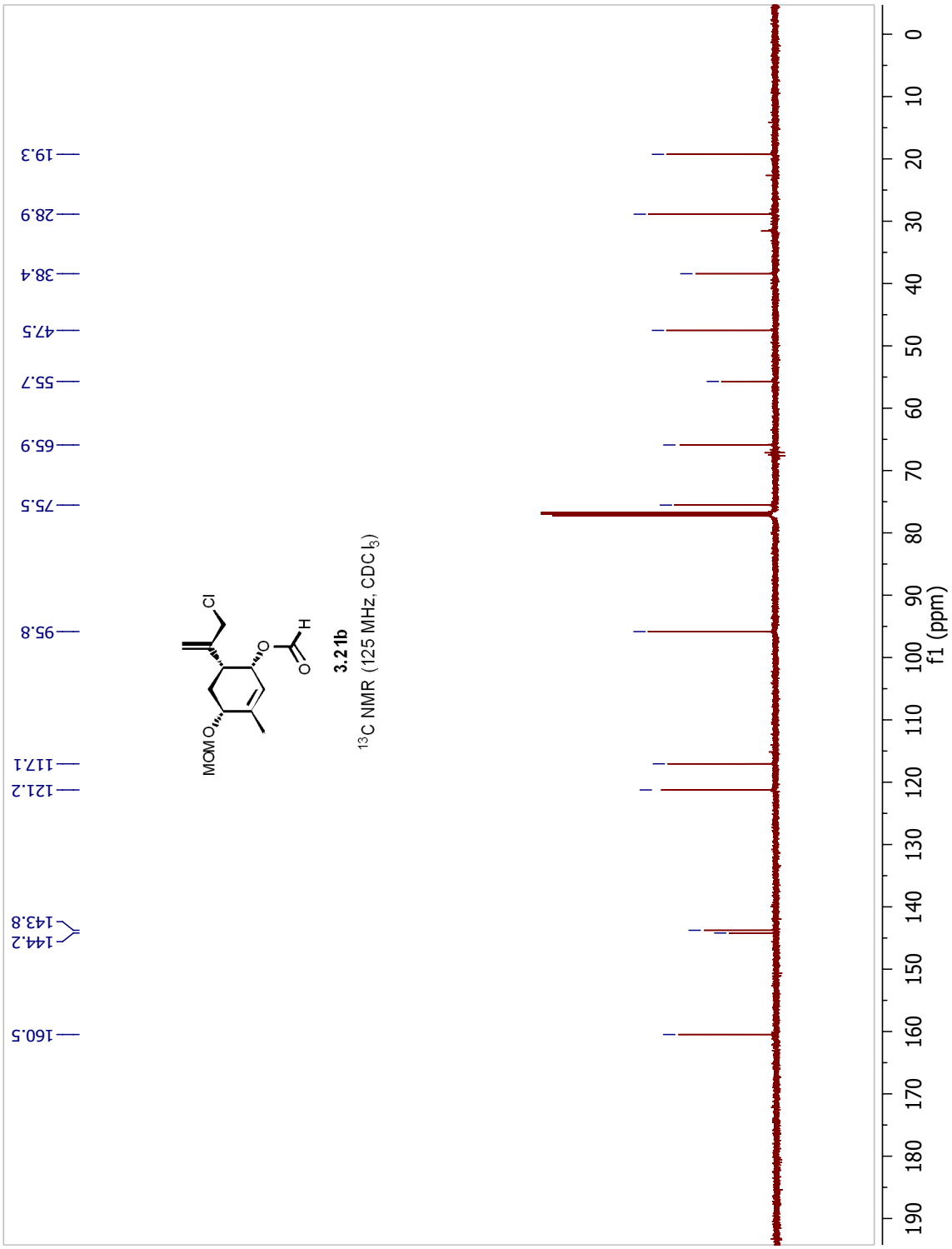

3.18
^{1}H NMR (300 MHz, $CDCl_3$)
f1 (ppm)
1.00
3.46
1.06
1.30
5.45
1.20
1.14
1.03
1.06
1.05

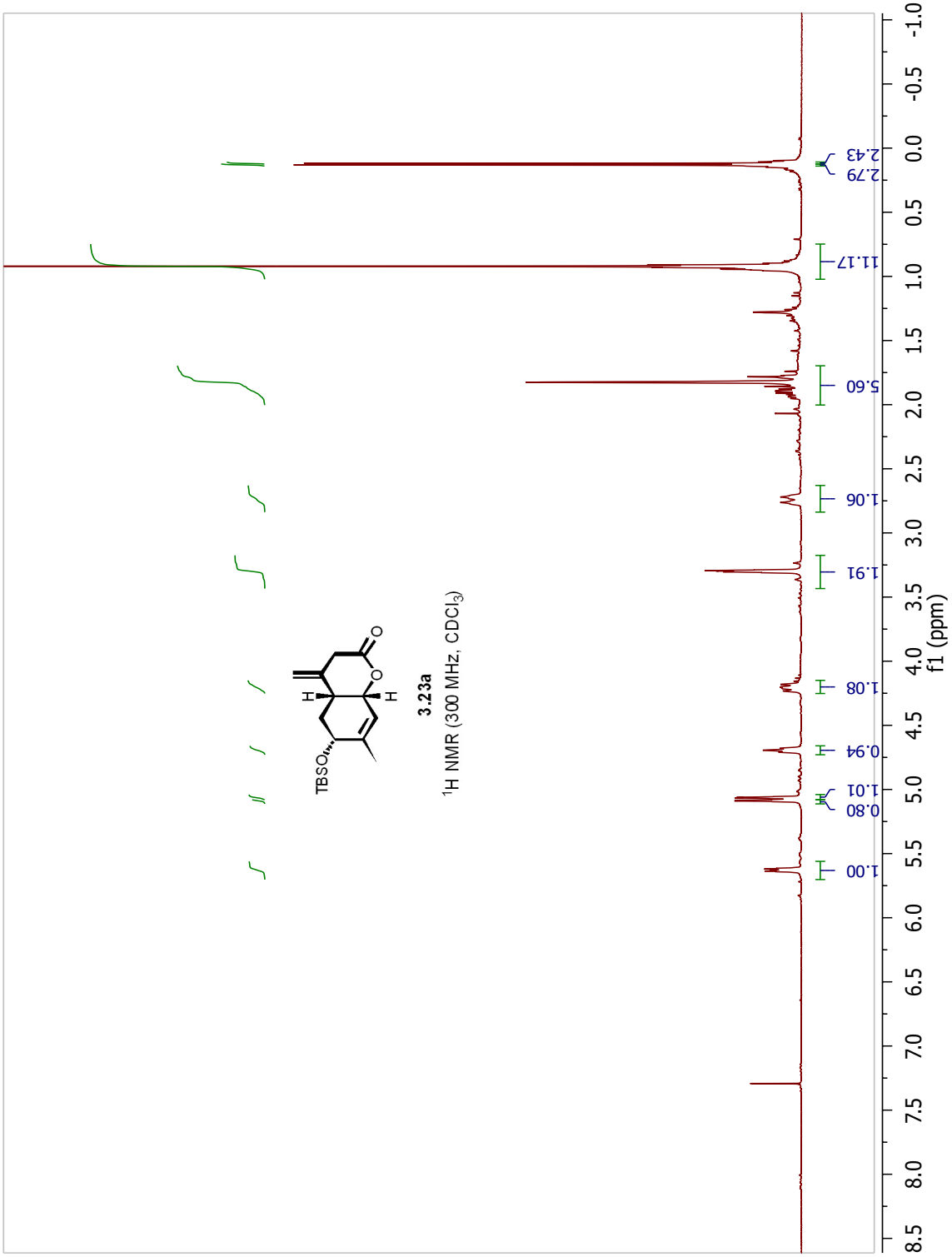

18.8
31.8
38.6
47.5
66.2
70.4
117.1
120.6
144.8
144.0
160.5
Cl
HO
O
O
H
3.18
^{13}C NMR (75 MHz, $CDCl_3$)
f1 (ppm)

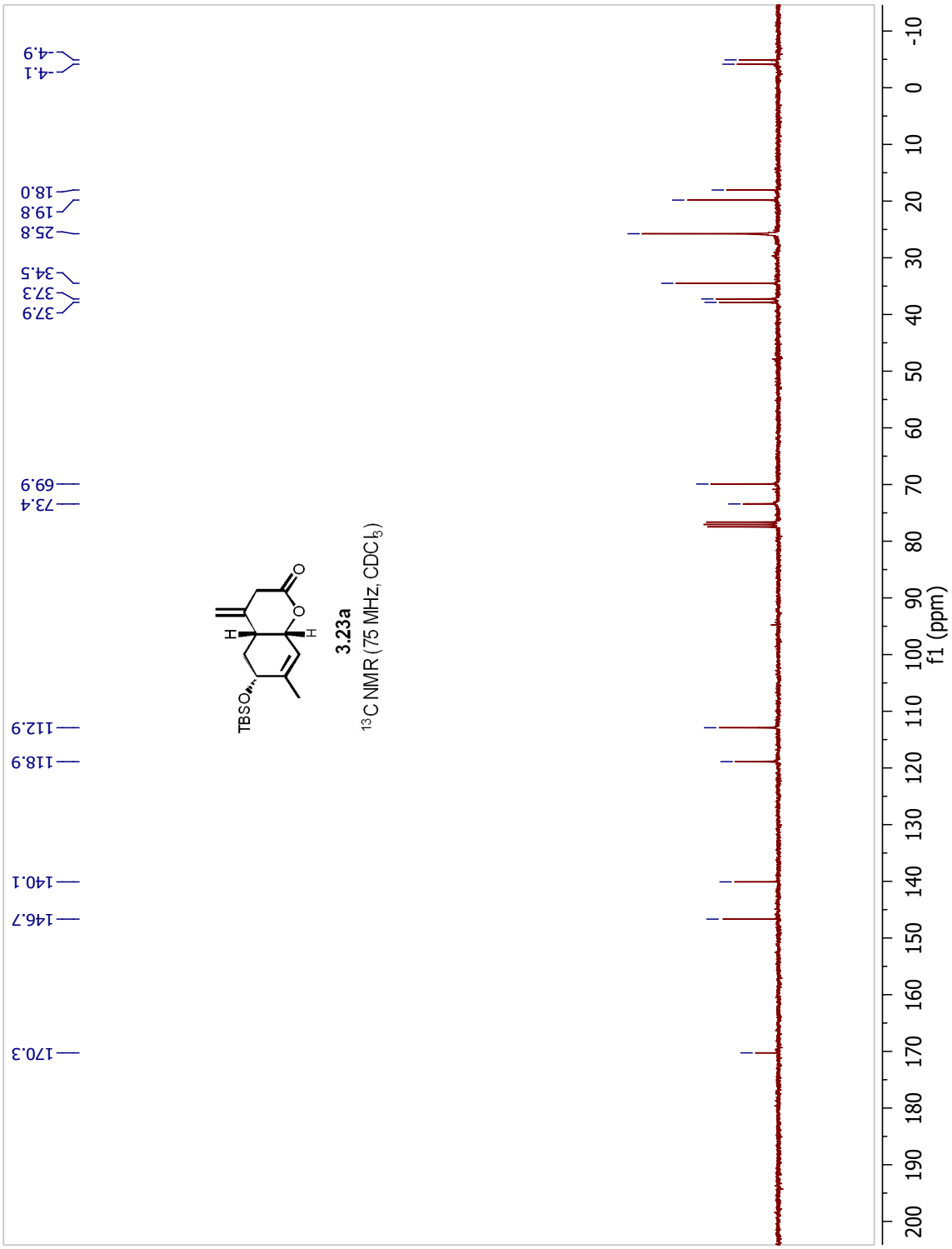

TBSO
Cl
O
O
H
3.21a
^{1}H NMR (300 MHz, $CDCl_3$)
2.82
2.62
10.21
3.72
2.18
0.98
3.23
1.02
1.09
1.05
1.05
1.00
f1 (ppm)

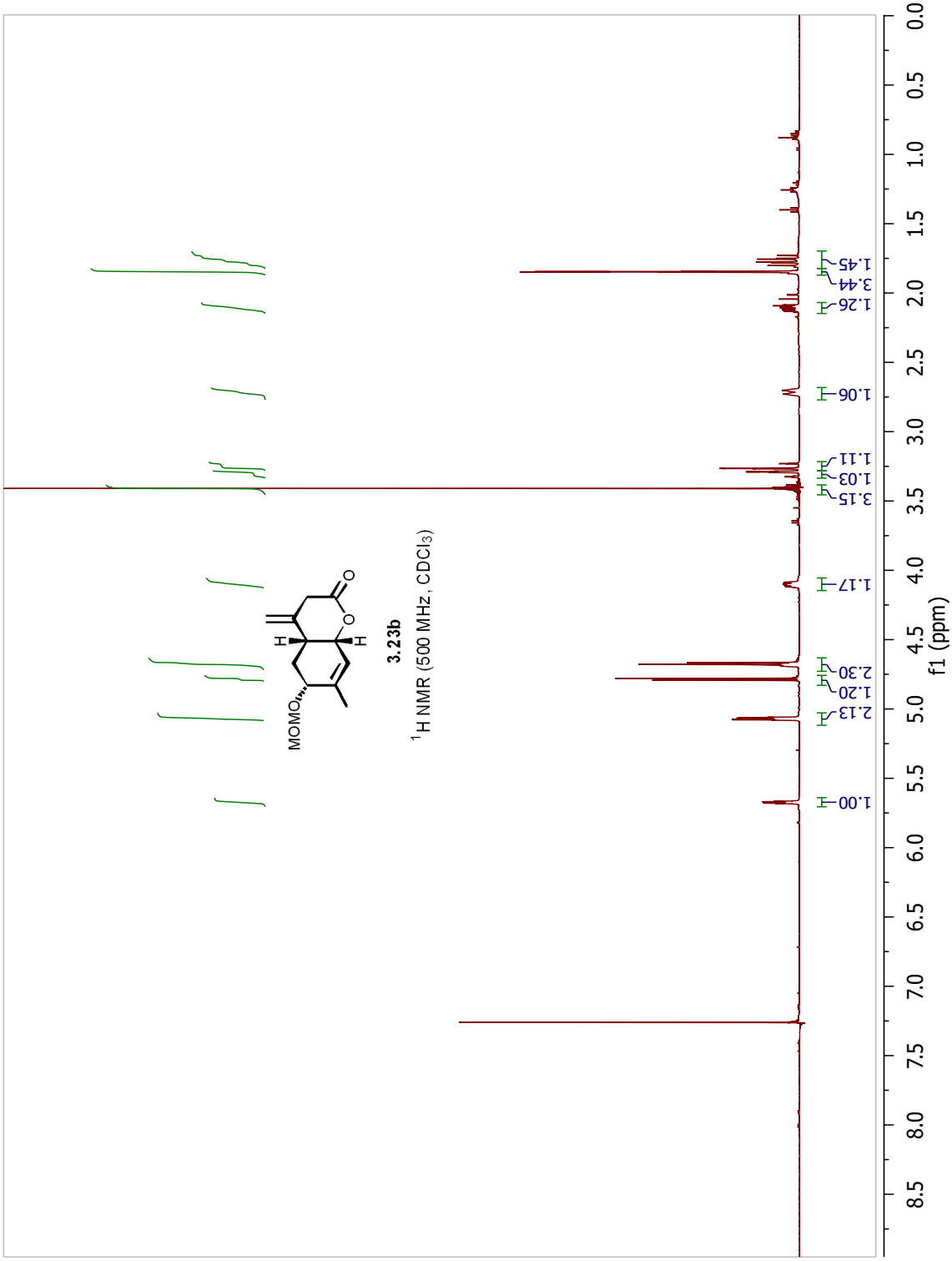

-4.9
-4.1
18.1
19.6
25.8
32.1
38.6
47.5
66.2
70.9
116.9
119.7
144.3
146.0
160.5
TBSO
Cl
O
O
H
3.21a
^{13}C NMR (75 MHz, $CDCl_3$)
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

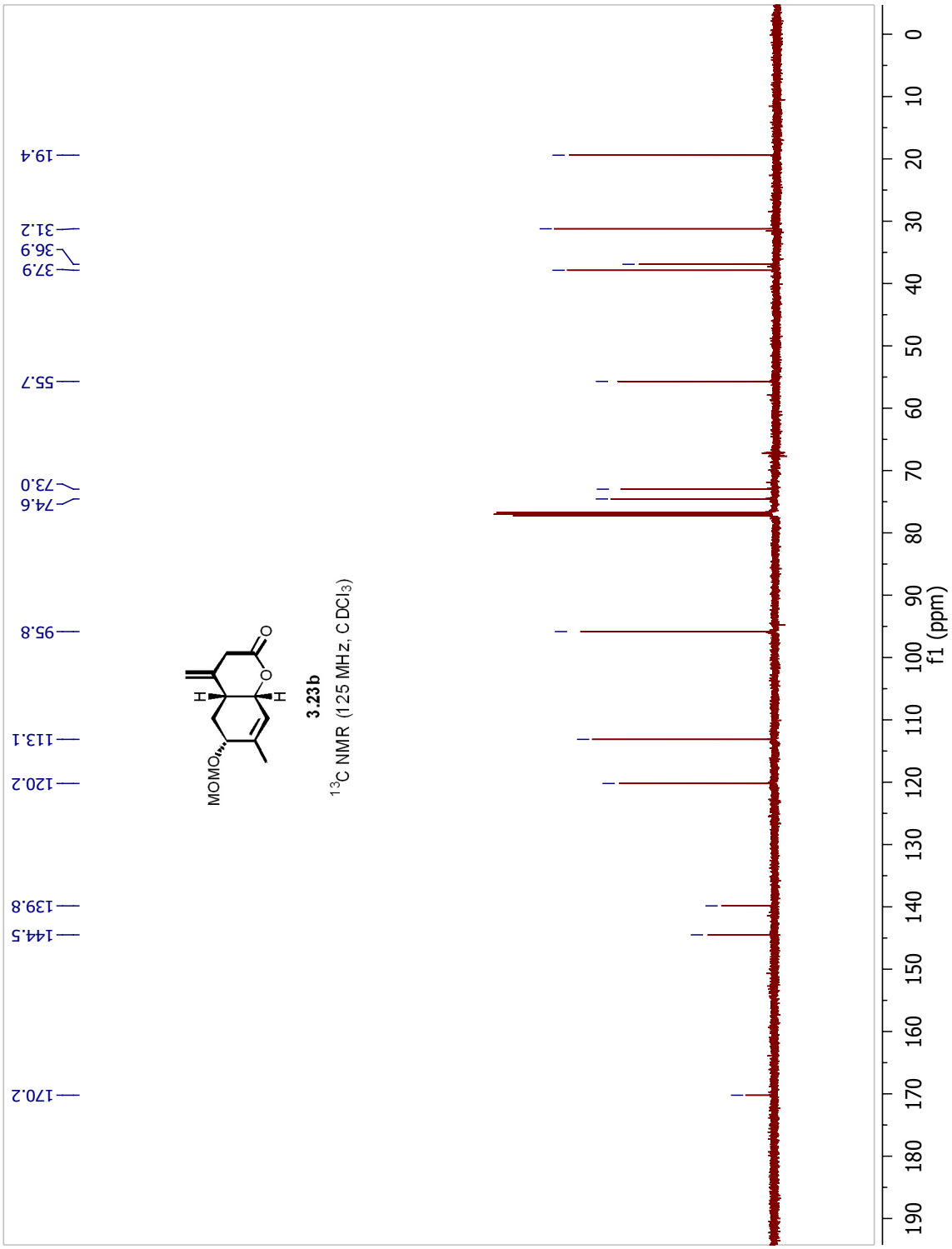

MOMO
Cl
O
O
H
3.21b
^{1}H NMR (500 MHz, $CDCl_3$)
0.86
1.00
1.01
1.12
1.10
1.14
1.14
2.21
1.22
3.26
1.07
1.19
1.22
3.24
f1 (ppm)

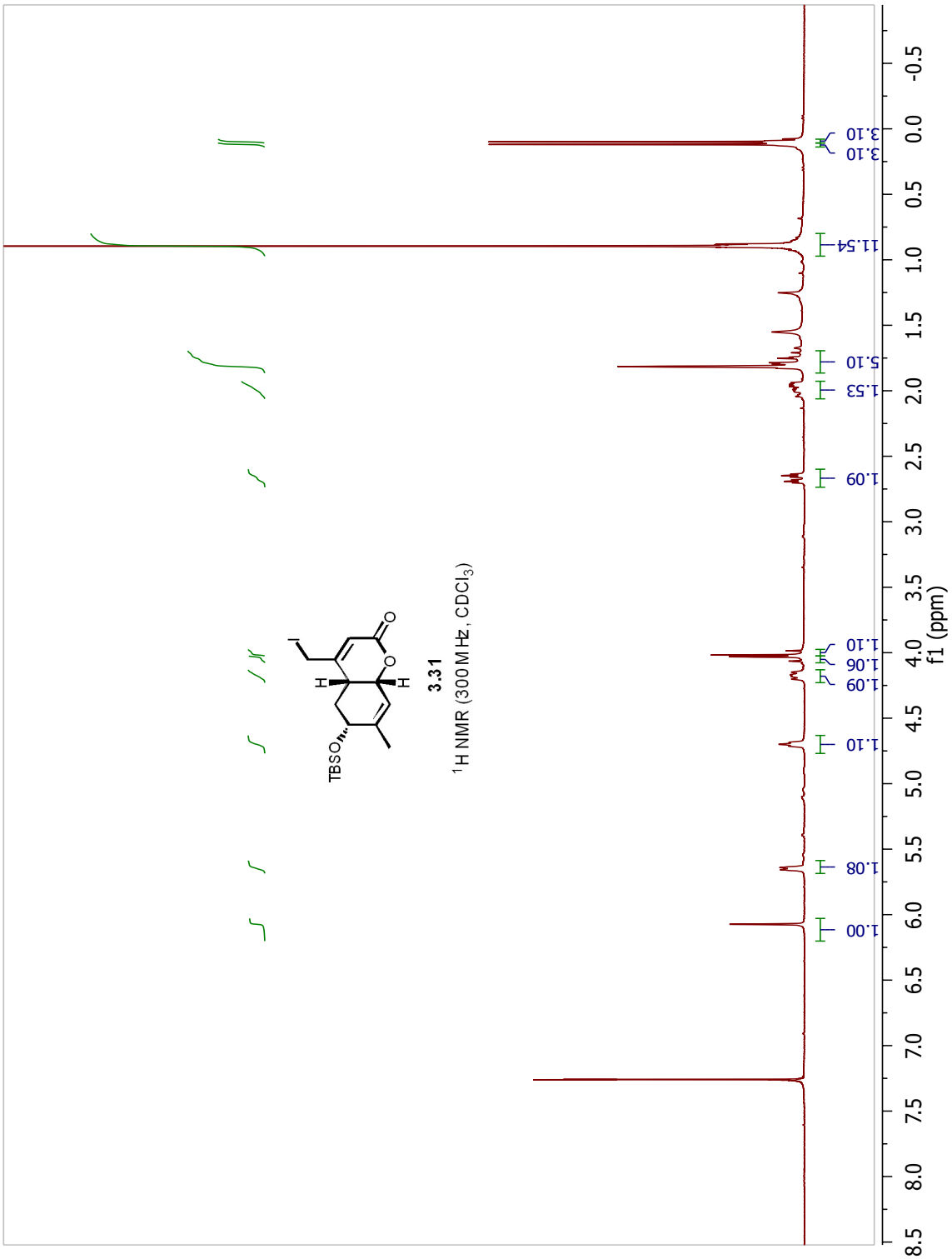

160.5
144.2
143.8
121.2
117.1
95.8
75.5
65.9
55.7
47.5
38.4
28.9
19.3
MOMO
Cl
O
O
H
3.21b
^{13}C NMR (125 MHz, CDCl$_3$)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
f1 (ppm)

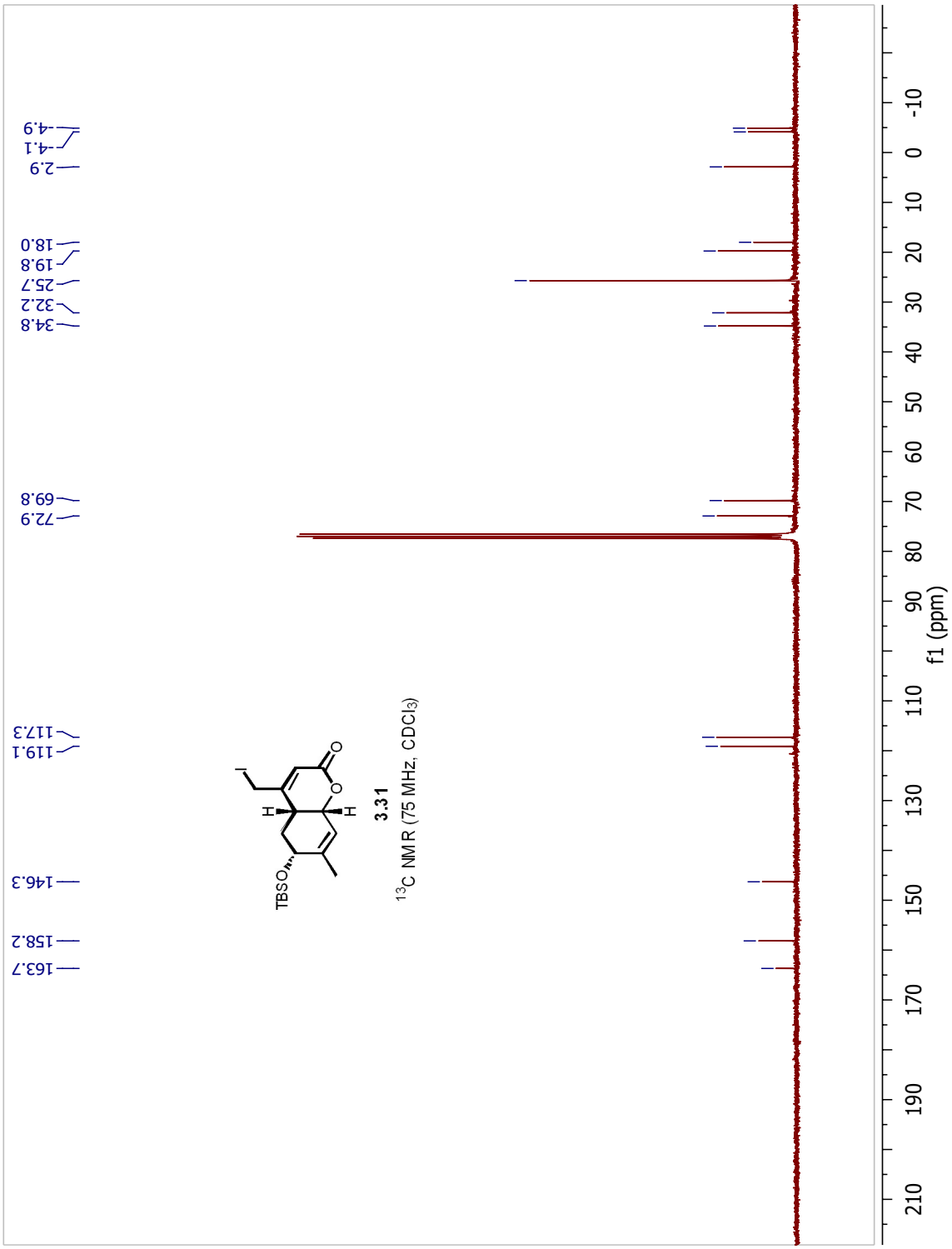

3.23a
^{1}H NMR (300 MHz, $CDCl_3$)
TBSO
O
H
H
2.43
2.79
11.17
5.60
1.06
1.91
1.08
0.94
1.01
0.80
1.00
f1 (ppm)

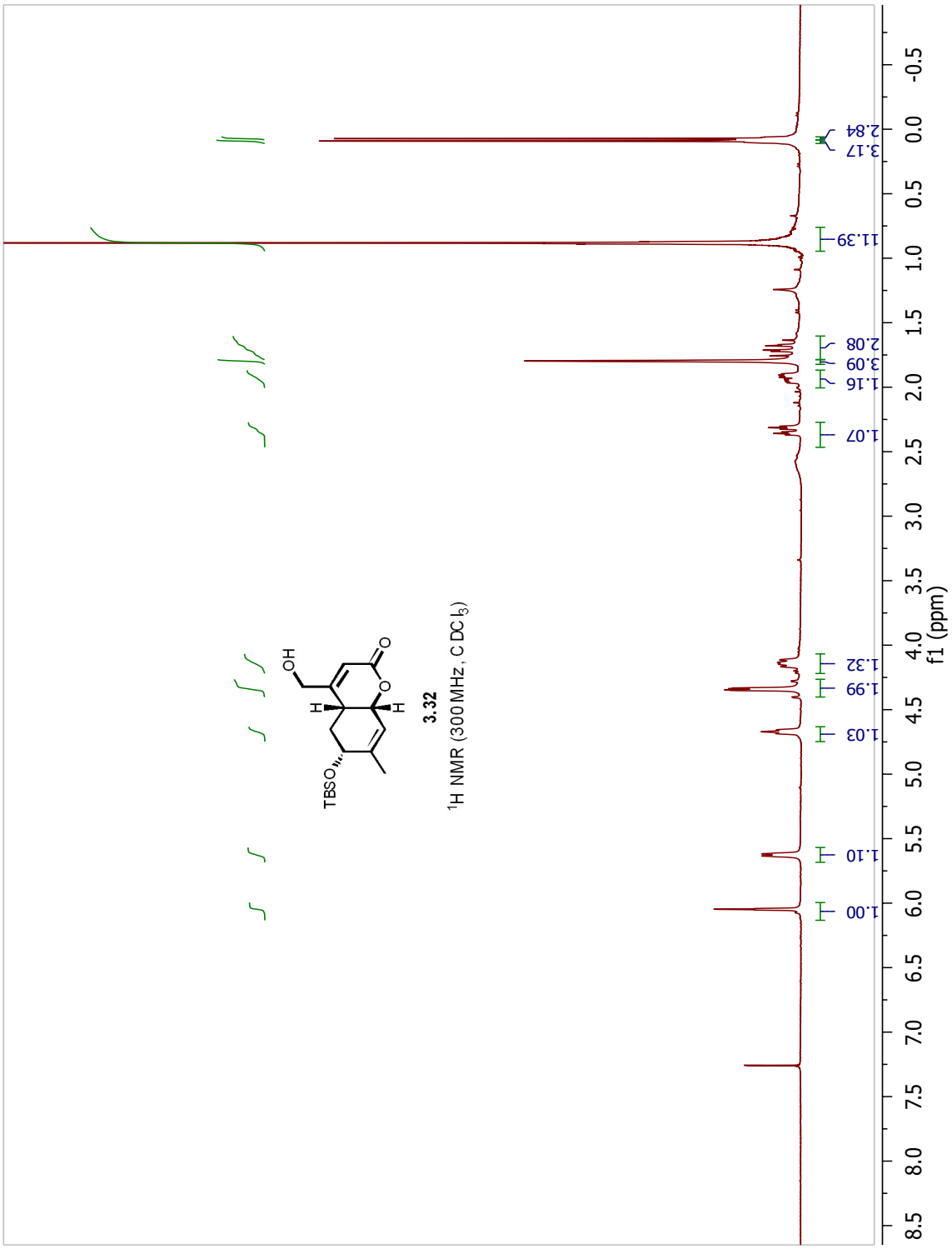

-4.9
-4.1
18.0
19.8
25.8
34.5
37.3
37.9
69.9
73.4
112.9
118.9
140.1
146.7
170.3
TBSO
H
H
O
O
3.23a
^{13}C NMR (75 MHz, CDCl$_3$)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

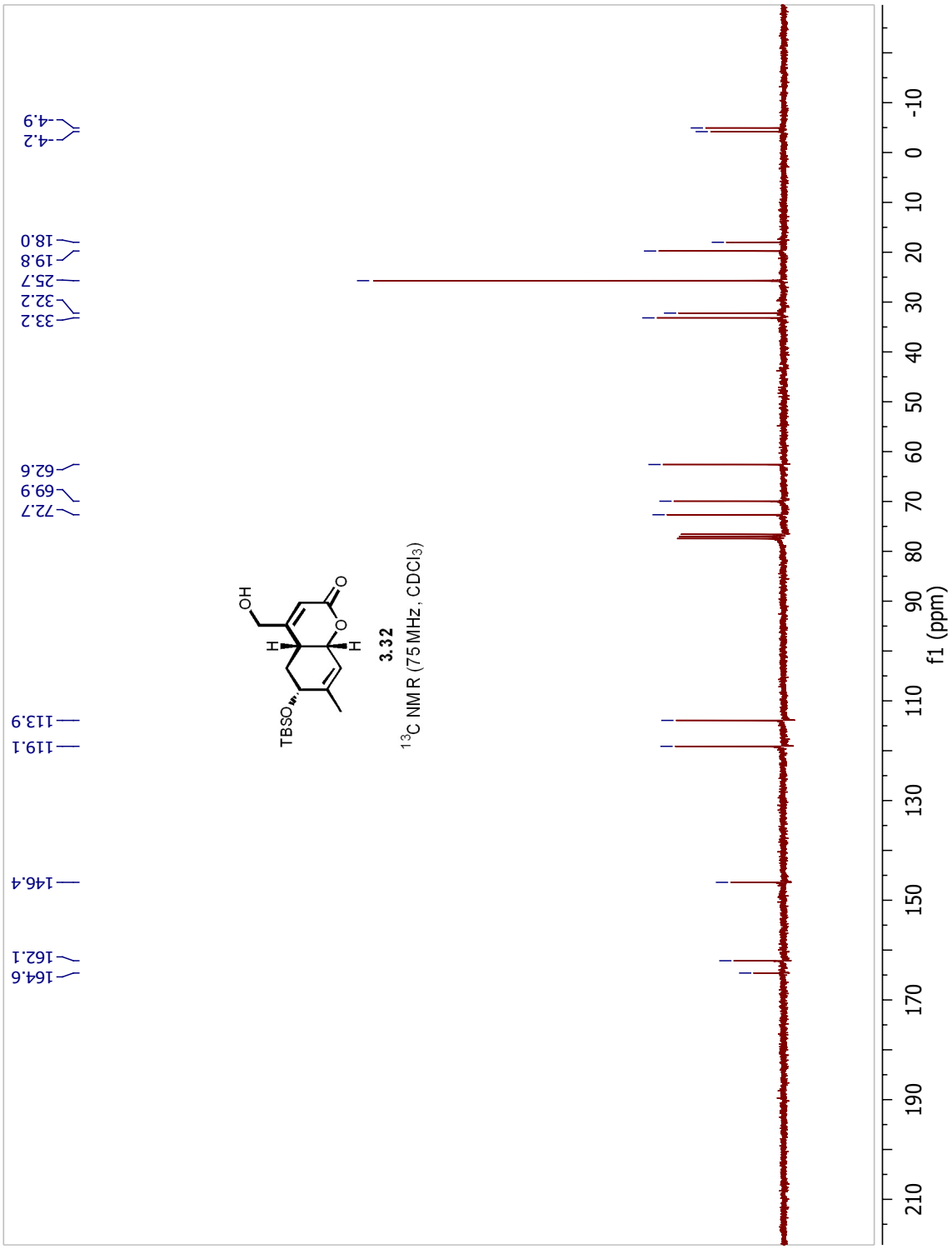

3.23b
^{1}H NMR (500 MHz, $CDCl_3$)
MOMO
1.45
3.44
1.26
1.06
1.11
1.03
3.15
1.17
2.30
1.20
2.13
1.00
f1 (ppm)

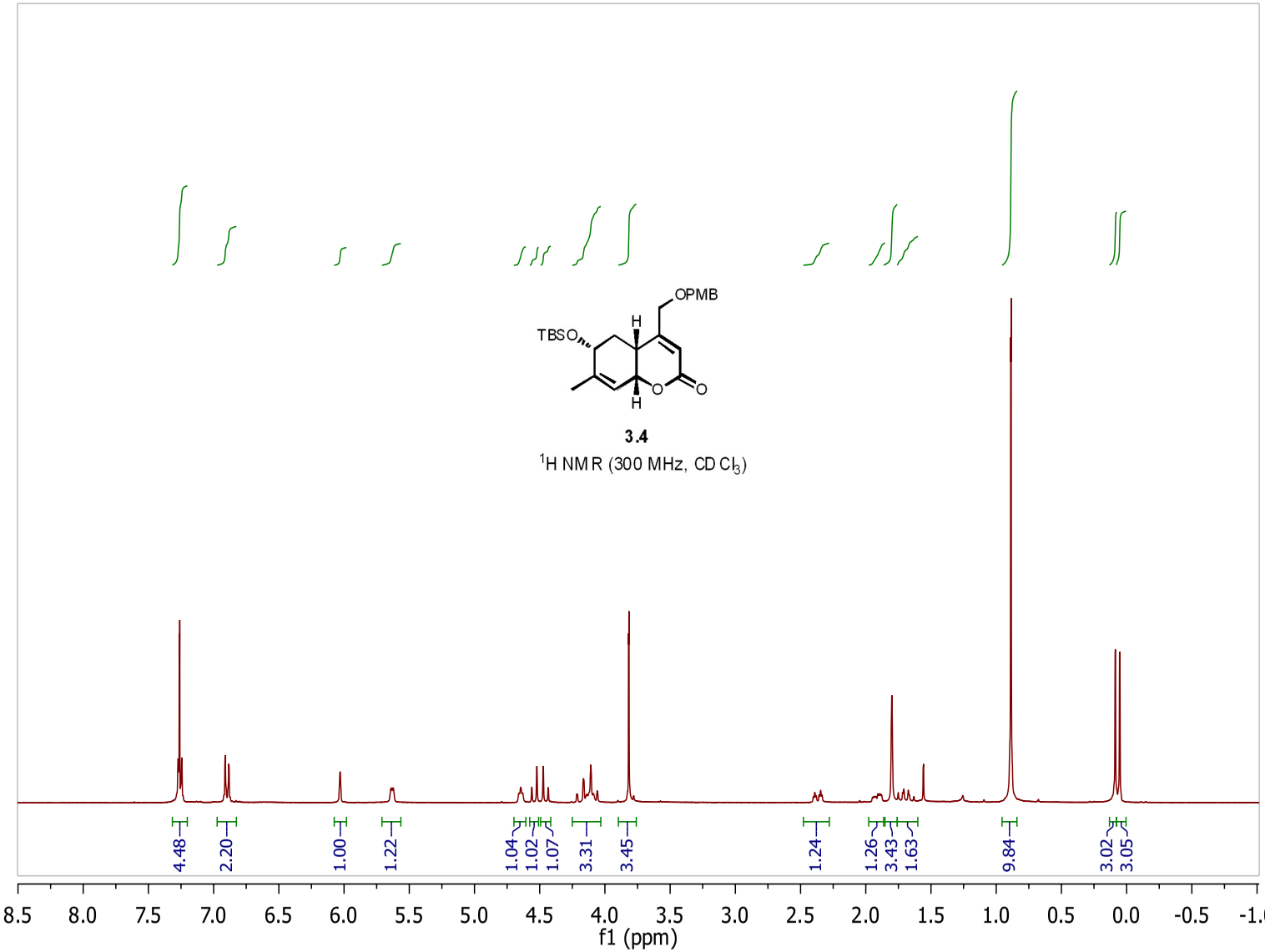

170.2
144.5
139.8
120.2
113.1
95.8
74.6
73.0
55.7
37.9
36.9
31.2
19.4
MOMO
O
O
H
H
3.23b
^{13}C NMR (125 MHz, C DCl$_3$)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
f1 (ppm)

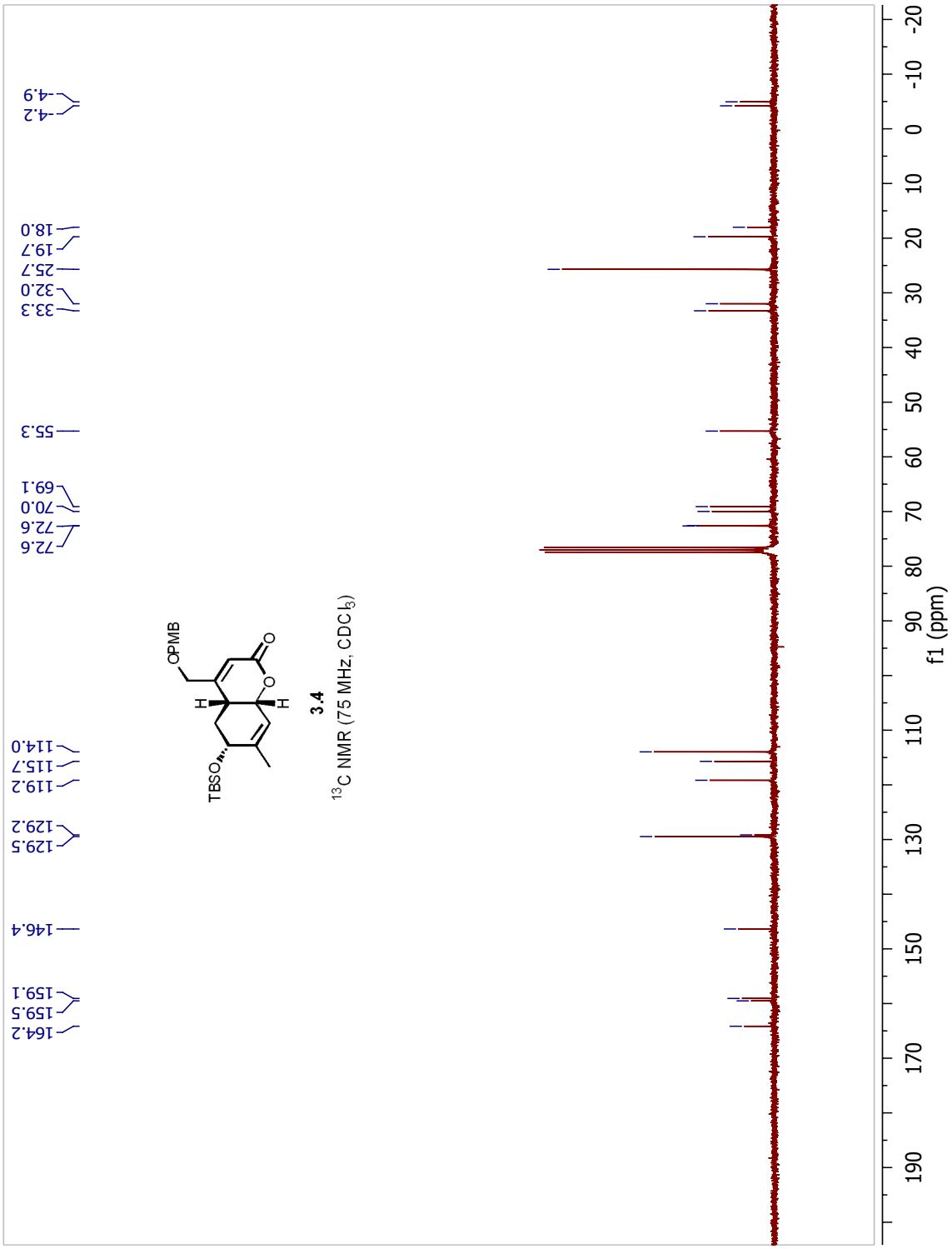

3.31
^{1}H NMR (300 MHz, $CDCl_3$)
TBSO
O
H
H
3.10
3.10
11.54
5.10
1.53
1.09
1.10
1.06
1.09
1.10
1.08
1.00
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

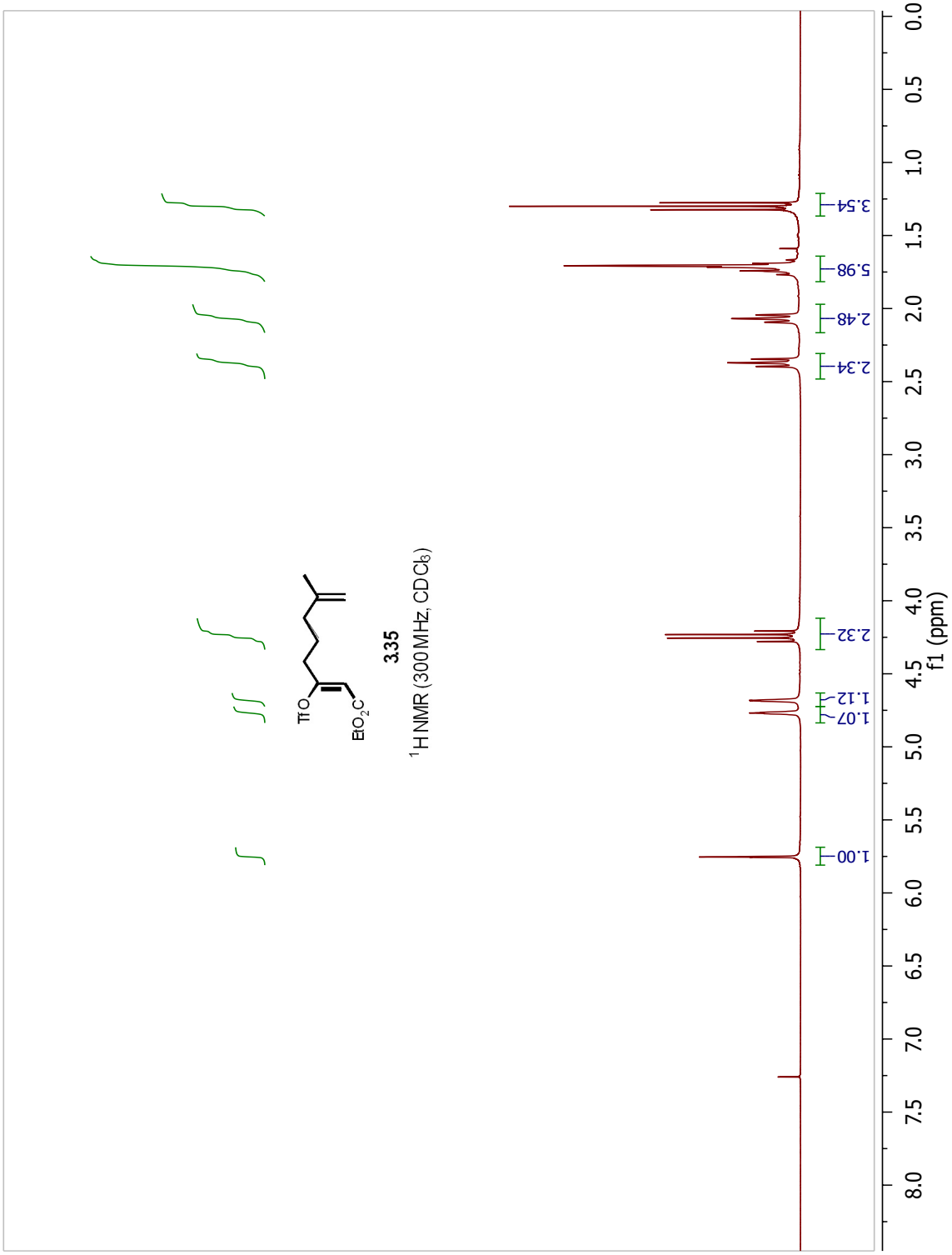

-4.9
-4.1
2.9
18.0
19.8
25.7
32.2
34.8
69.8
72.9
117.3
119.1
146.3
158.2
163.7
TBSO
H
H
O
O
3.31
^{13}C NMR (75 MHz, CDCl$_3$)
f1 (ppm)
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10

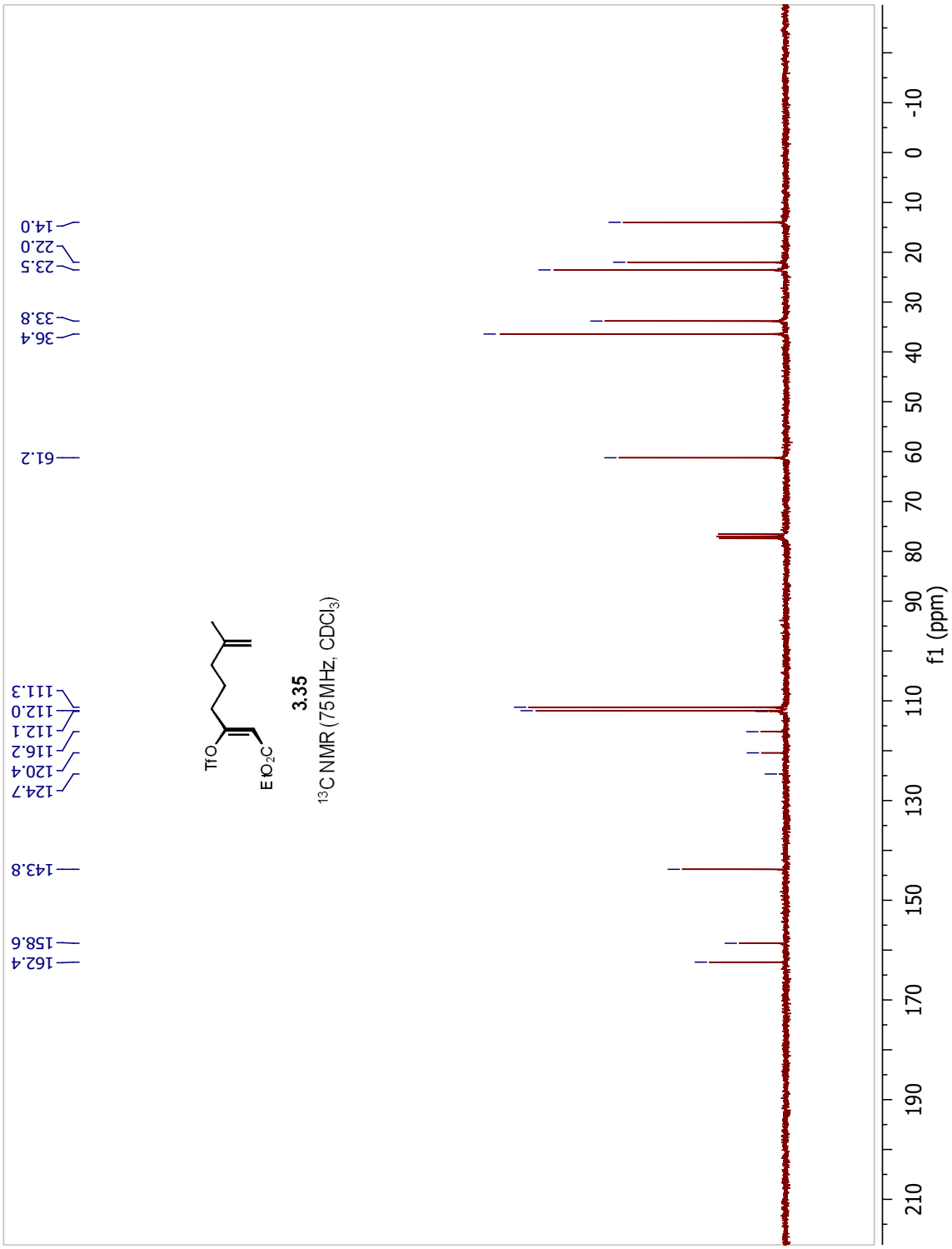

3.32
^{1}H NMR (300 MHz, C_6D_6)
TBSO
OH
O
H
H
1.00
1.10
1.03
1.99
1.32
1.07
1.16
3.09
2.08
11.39
3.17
2.84
f1 (ppm)

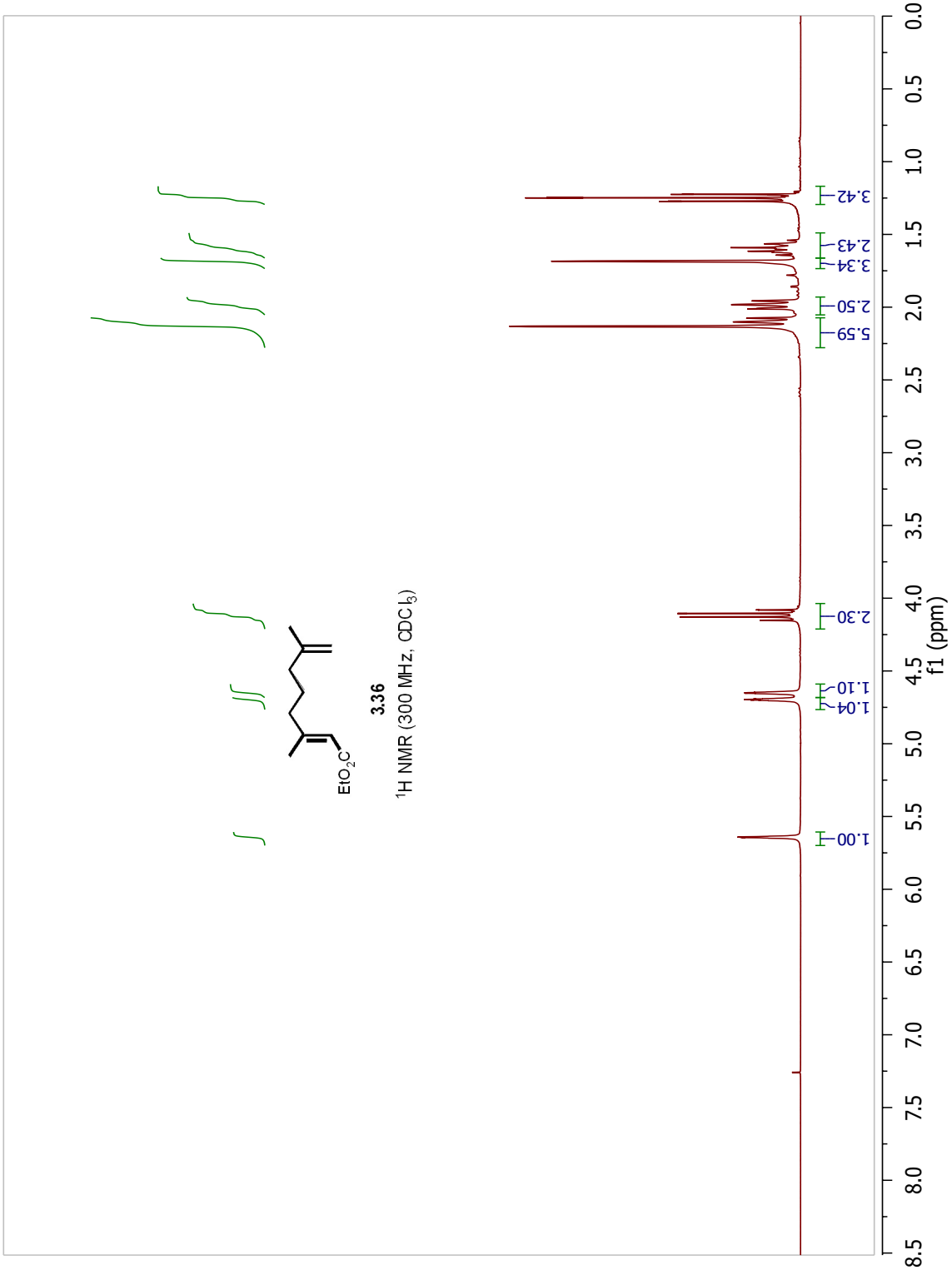

-4.9
-4.2
18.0
19.8
25.7
32.2
33.2
62.6
69.9
72.7
113.9
119.1
146.4
162.1
164.6
TBSO
OH
O
O
H
H
3.32
^{13}C NMR (75 MHz, $CDCl_3$)
f1 (ppm)
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10

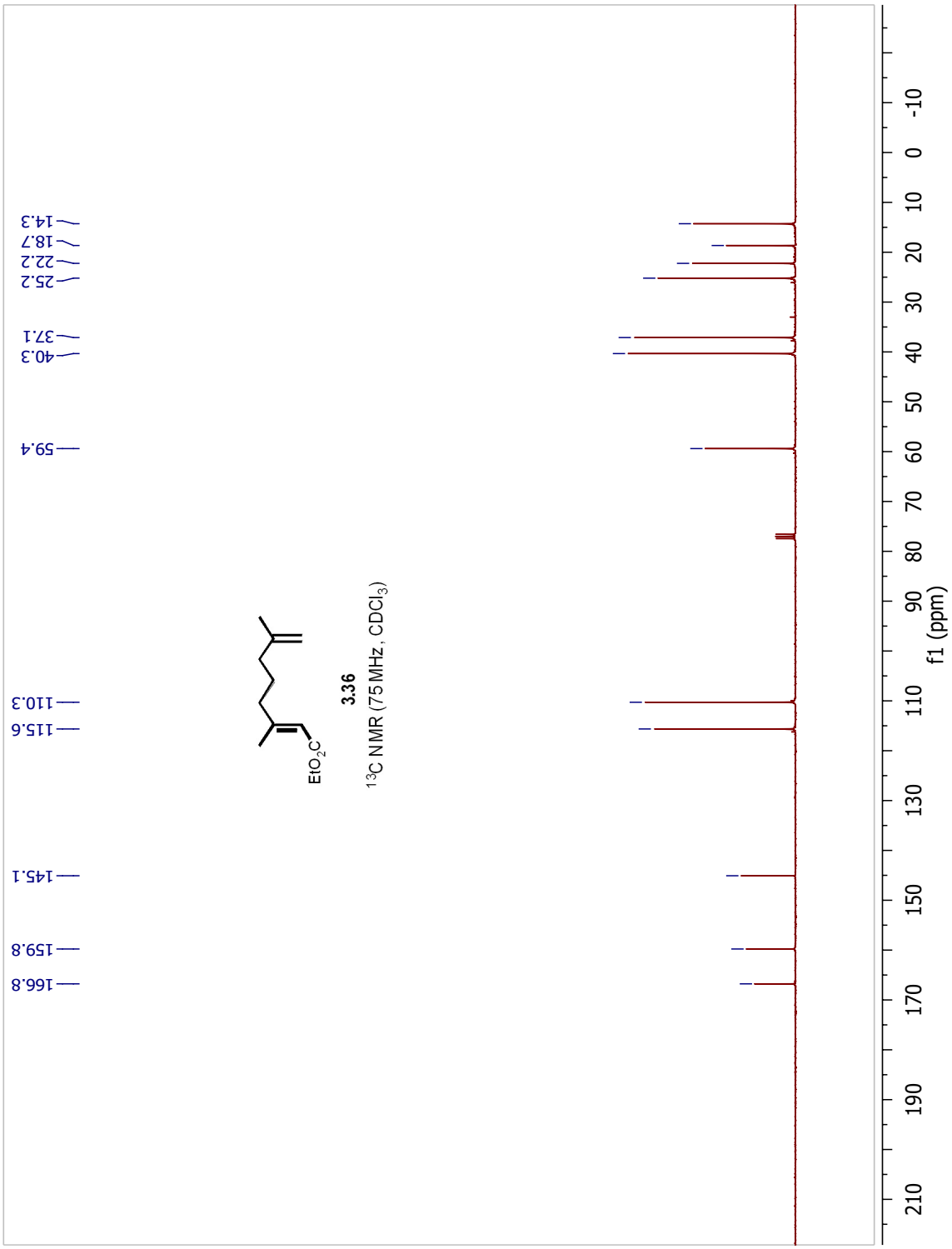

OPMB
TBSO
H
H
O
O
3.4
1H NMR (300 MHz, CDCl3)
4.48
2.20
1.00
1.22
1.04
1.02
1.07
3.31
3.45
1.24
1.26
3.43
1.63
9.84
3.02
3.05
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

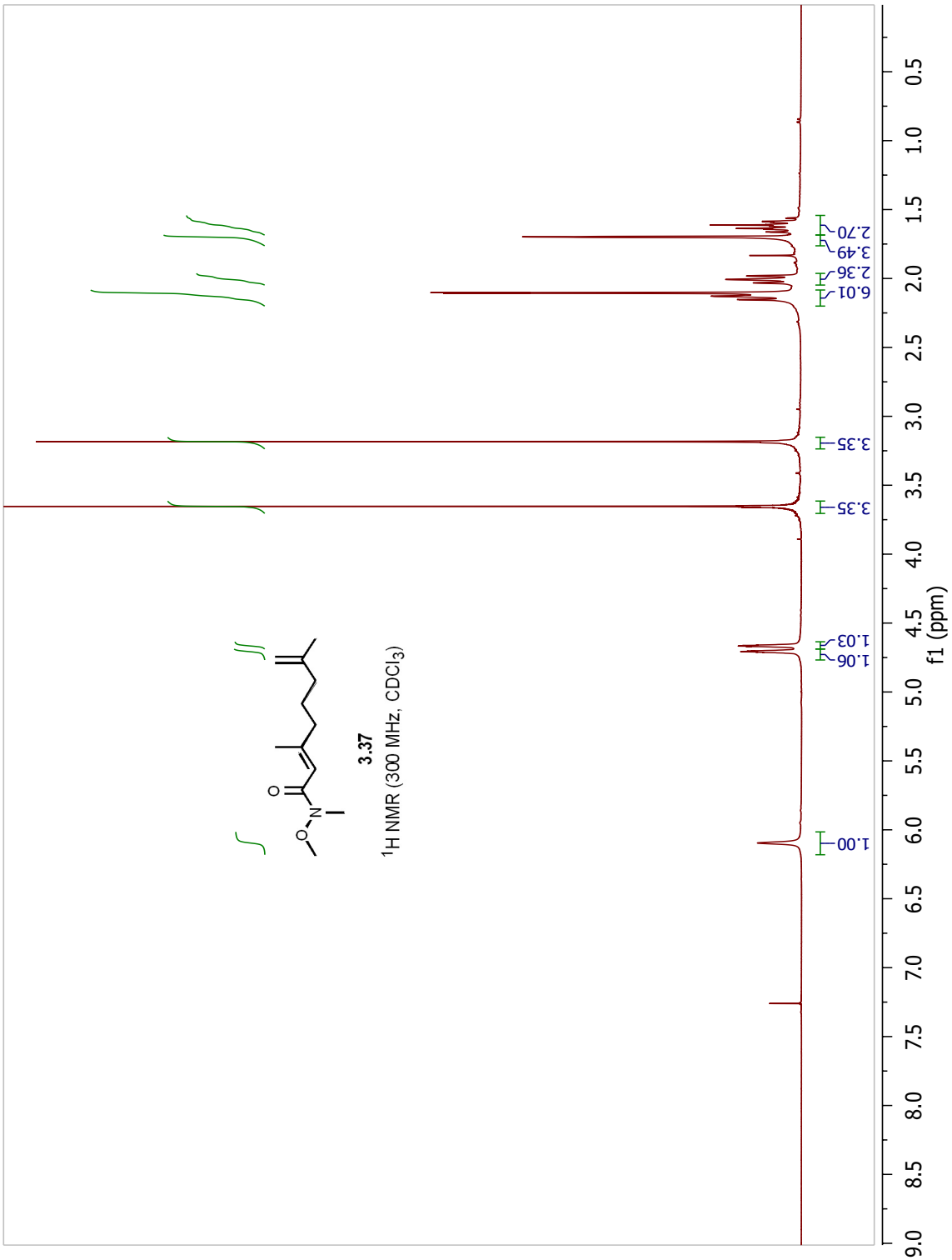

-4.9
-4.2
18.0
19.7
25.7
32.0
33.3
55.3
69.1
70.0
72.6
72.6
114.0
115.7
119.2
129.2
129.5
146.4
159.1
159.5
164.2
OPMB
TBSO
H
H
O
O
3.4
^{13}C NMR (75 MHz, $CDCl_3$)
f1 (ppm)

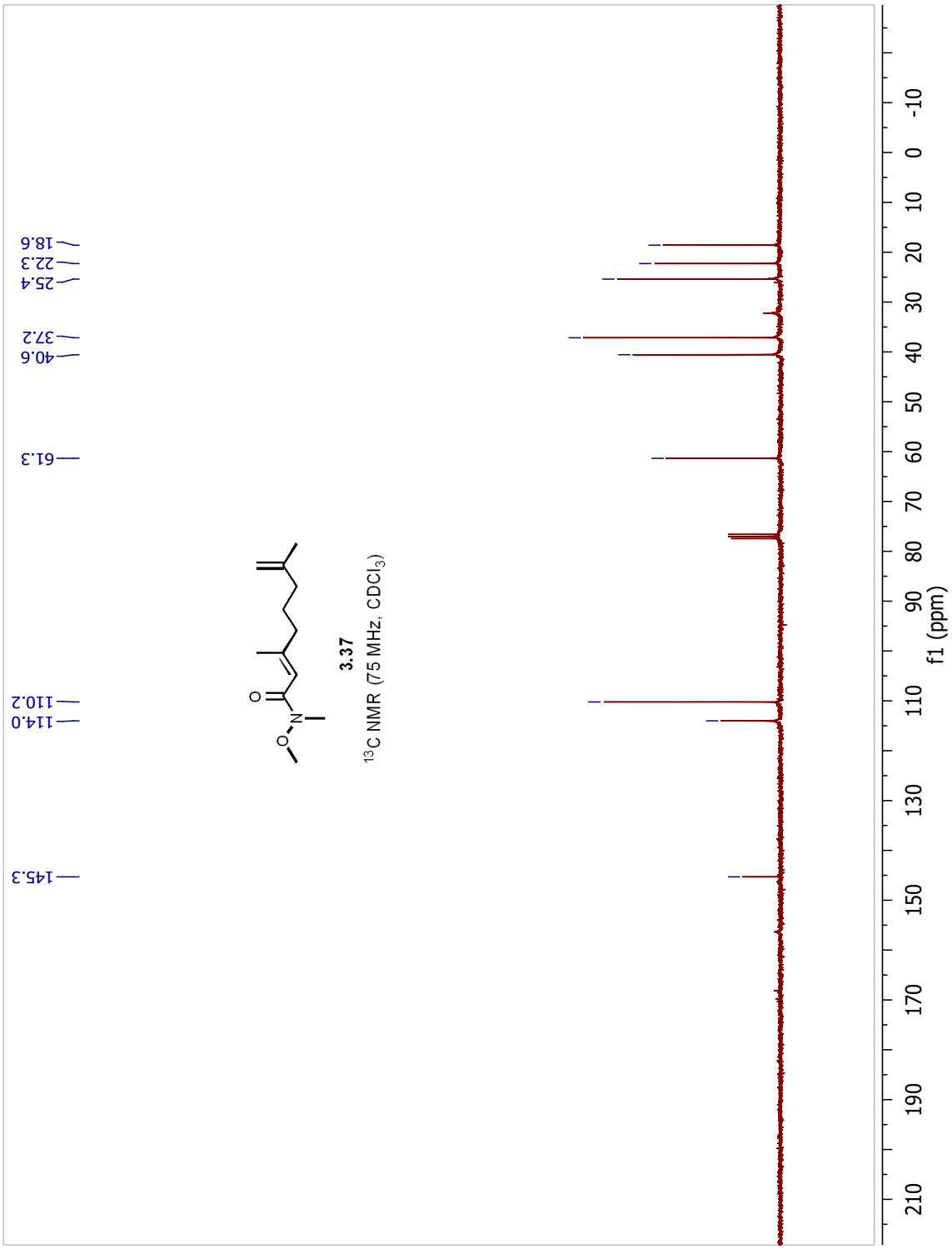

TfO
EtO2C
3.35
1H NMR (300 MHz, CDCl3)
3.54
5.98
2.48
2.34
2.32
1.12
1.07
1.00
f1 (ppm)

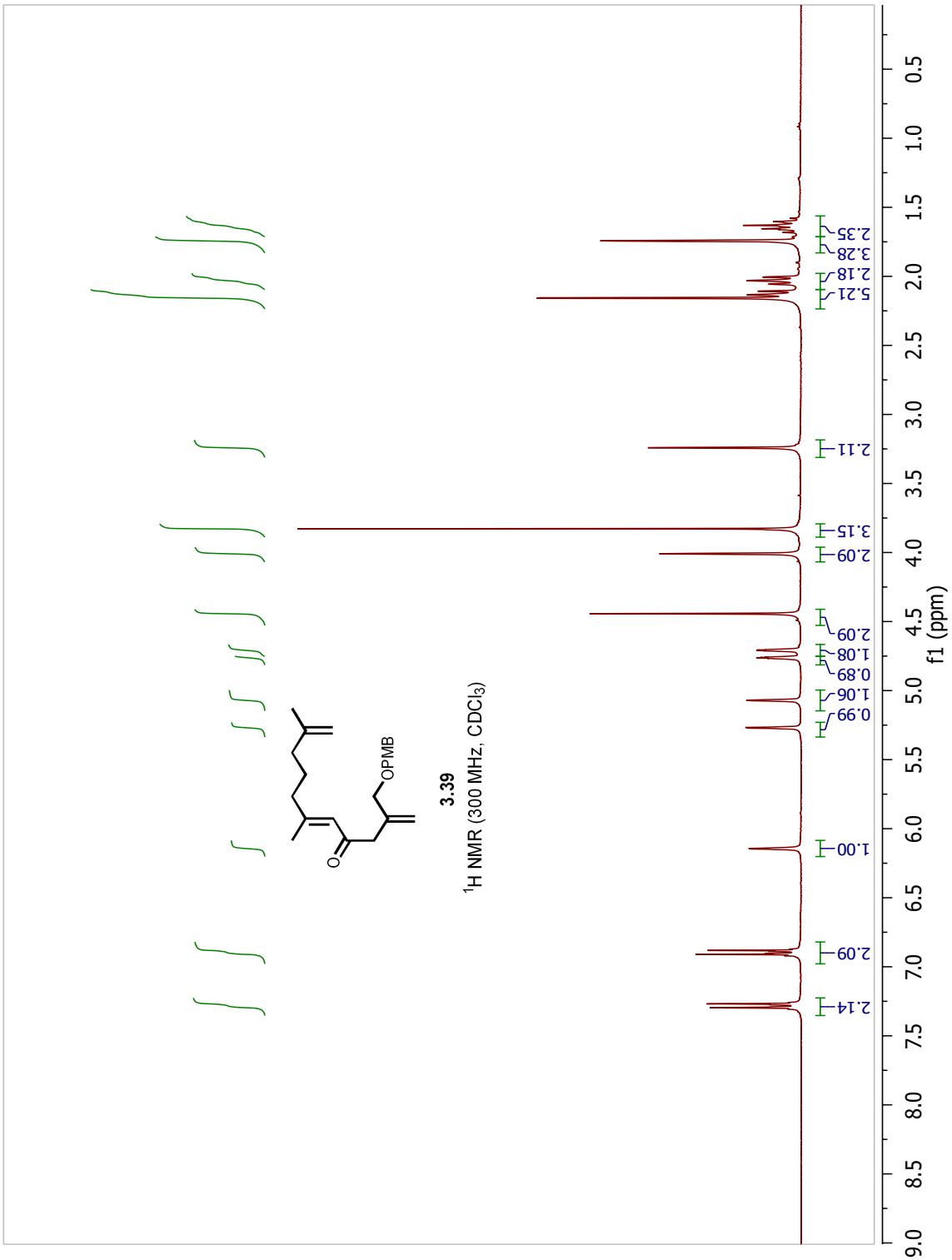

14.0
22.0
23.5
33.8
36.4
61.2
111.3
112.0
112.1
116.2
120.4
124.7
143.8
158.6
162.4
TfO
EtO2C
3.35
13C NMR (75 MHz, CDCl3)
f1 (ppm)

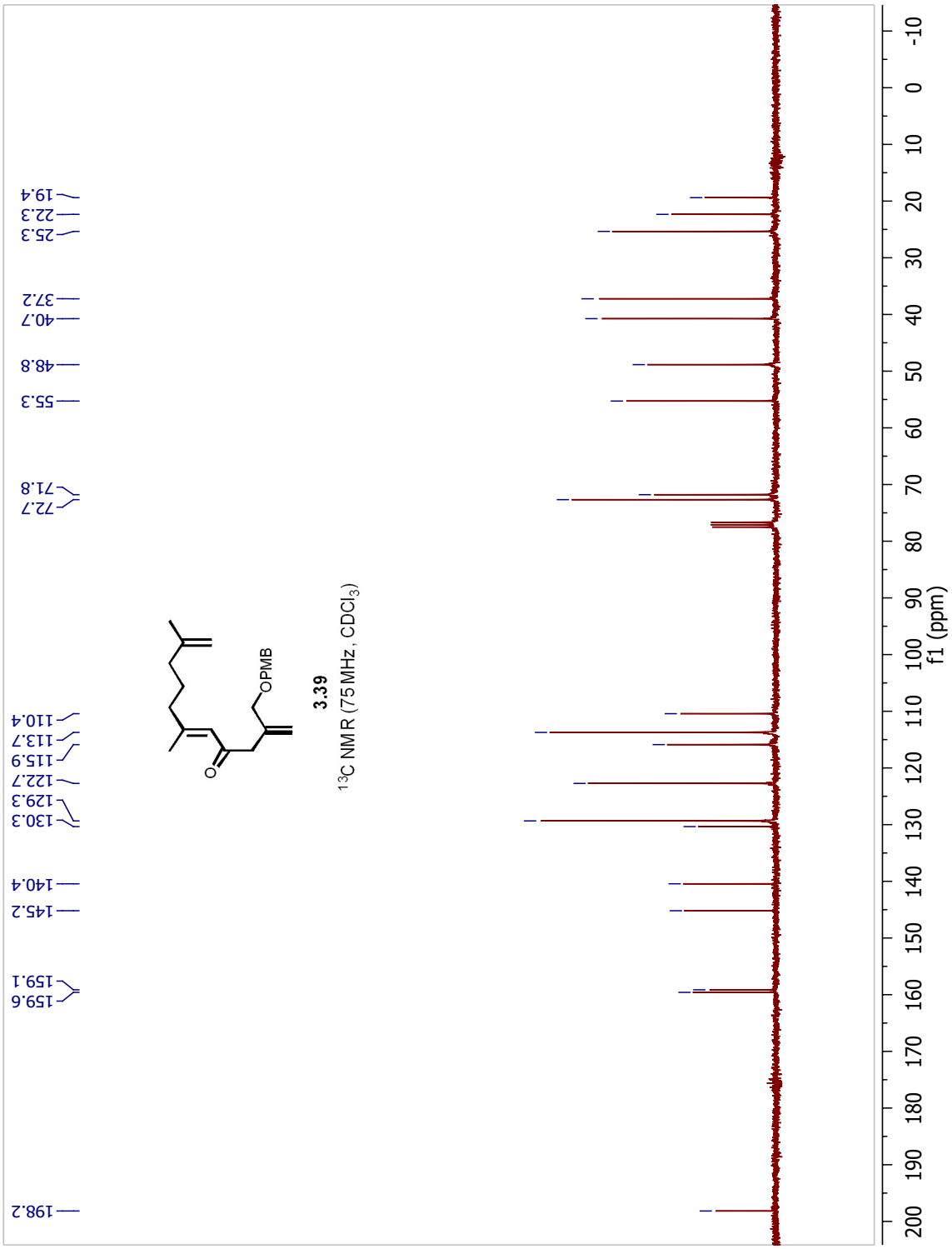

3.36
^{1}H NMR (300 MHz, $CDCl_3$)
EtO_2C
1.00
2.30
1.04
1.10
5.59
2.50
3.34
2.43
3.42
f1 (ppm)

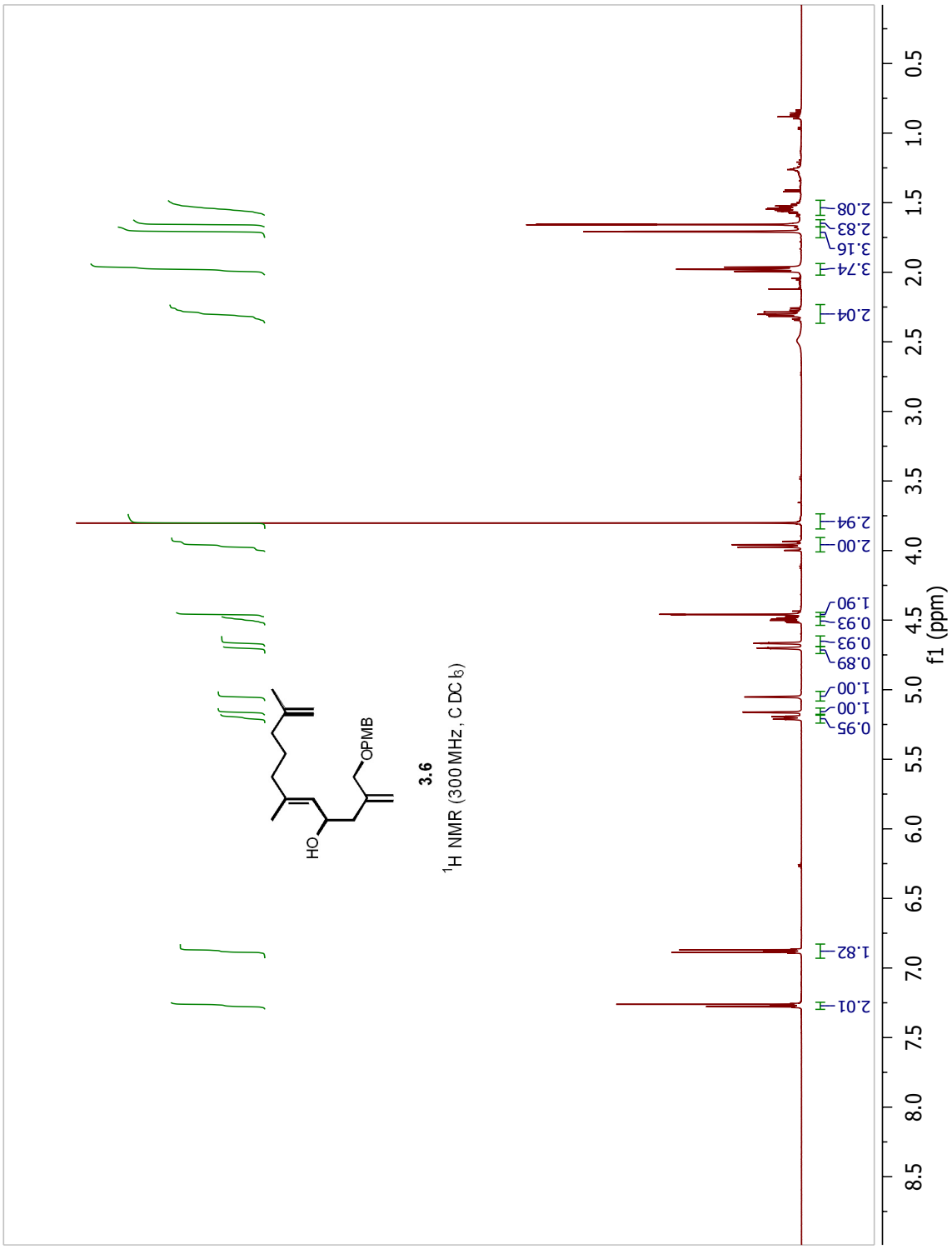

166.8
159.8
145.1
115.6
110.3
59.4
40.3
37.1
25.2
22.2
18.7
14.3
EtO2C
3.36
13C NMR (75 MHz, CDCl3)
f1 (ppm)

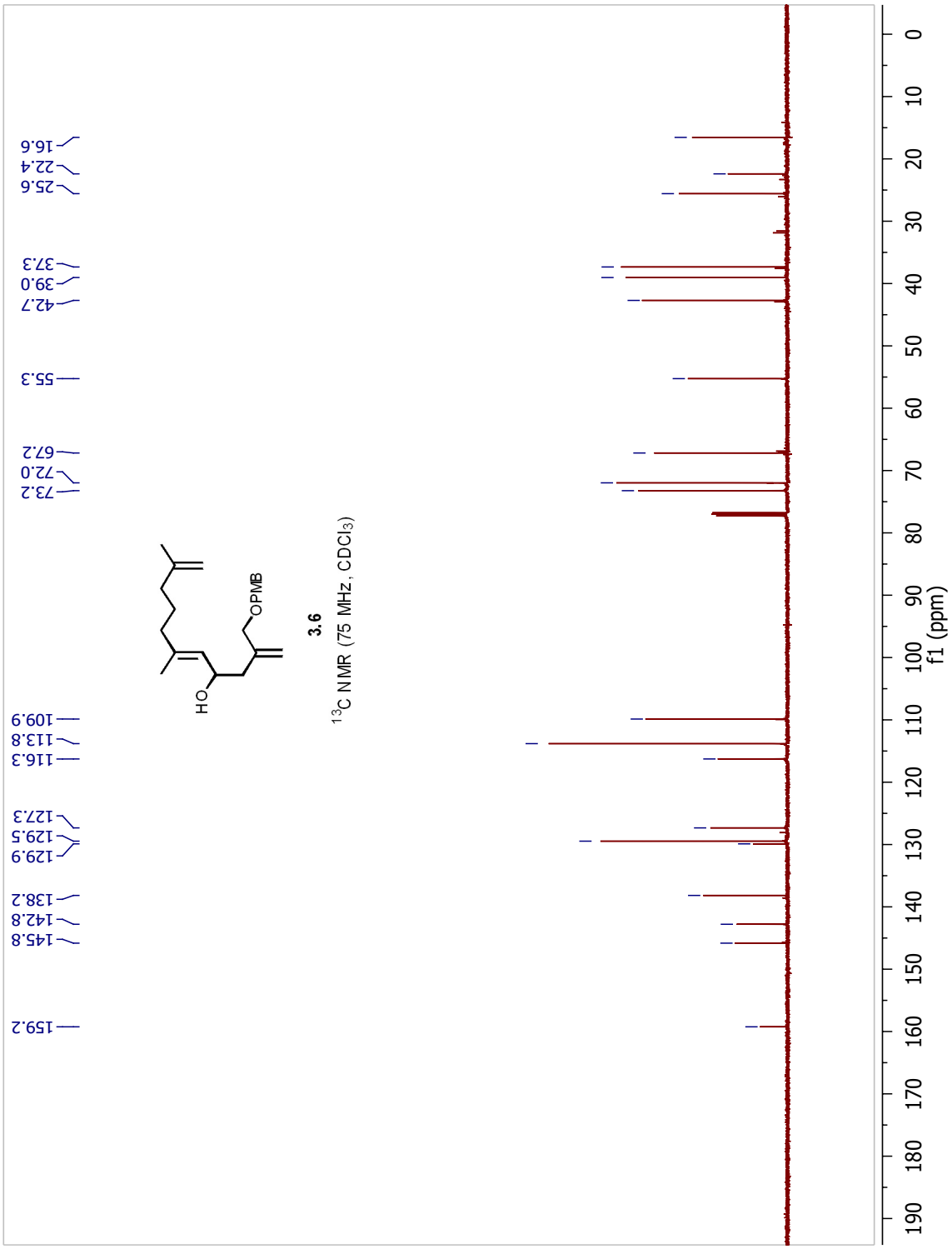

3.37
^{1}H NMR (300 MHz, $CDCl_3$)
1.00
1.06
1.03
3.35
3.35
6.01
2.36
3.49
2.70
f1 (ppm)

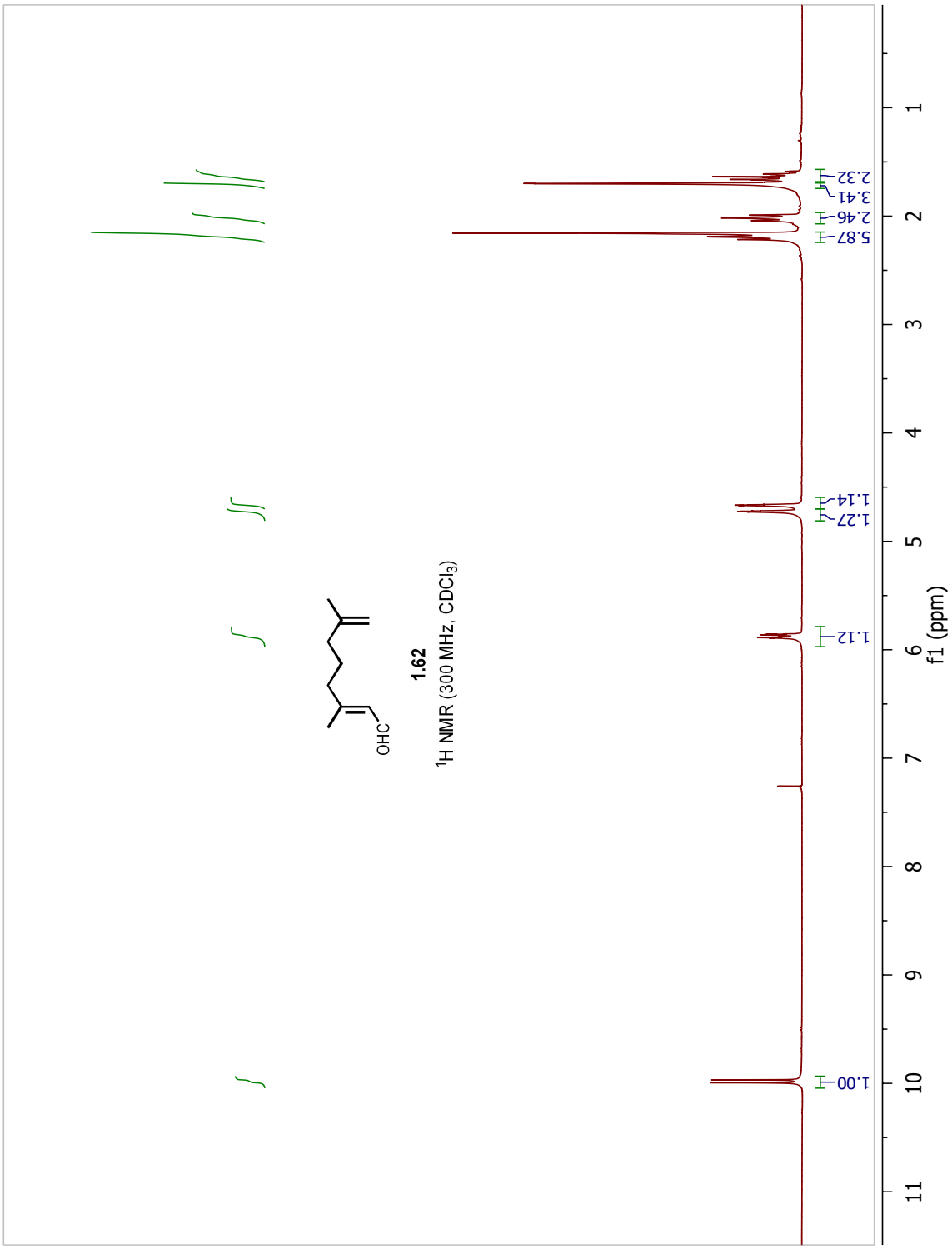

145.3
114.0
110.2
61.3
40.6
37.2
25.4
22.3
18.6
O
N
O
3.37
^{13}C NMR (75 MHz, $CDCl_3$)
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

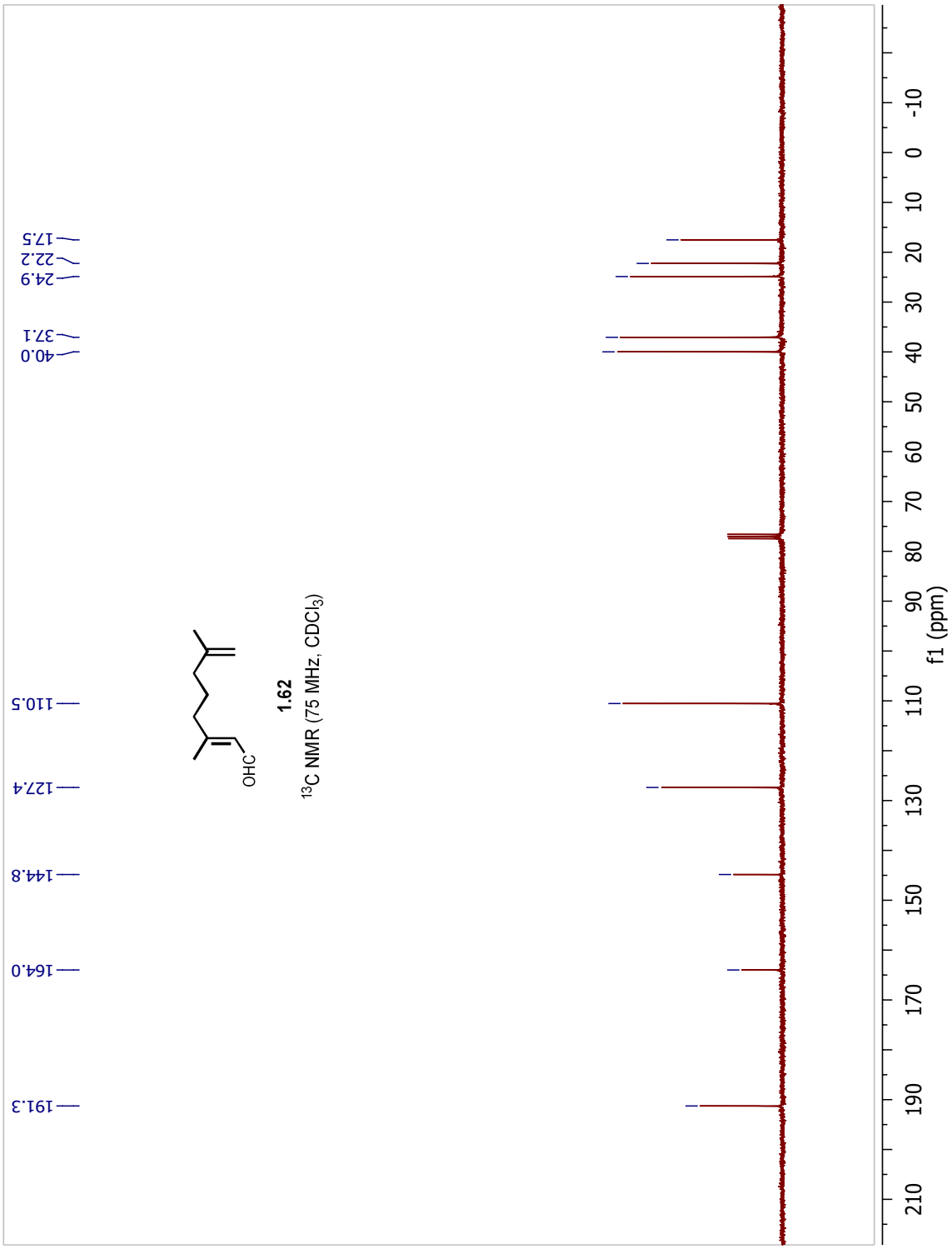

OPMB
O
3.39
^{1}H NMR (300 MHz, $CDCl_3$)
2.35
3.28
2.18
5.21
2.11
3.15
2.09
2.09
1.08
0.89
1.06
0.99
1.00
2.09
2.14
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

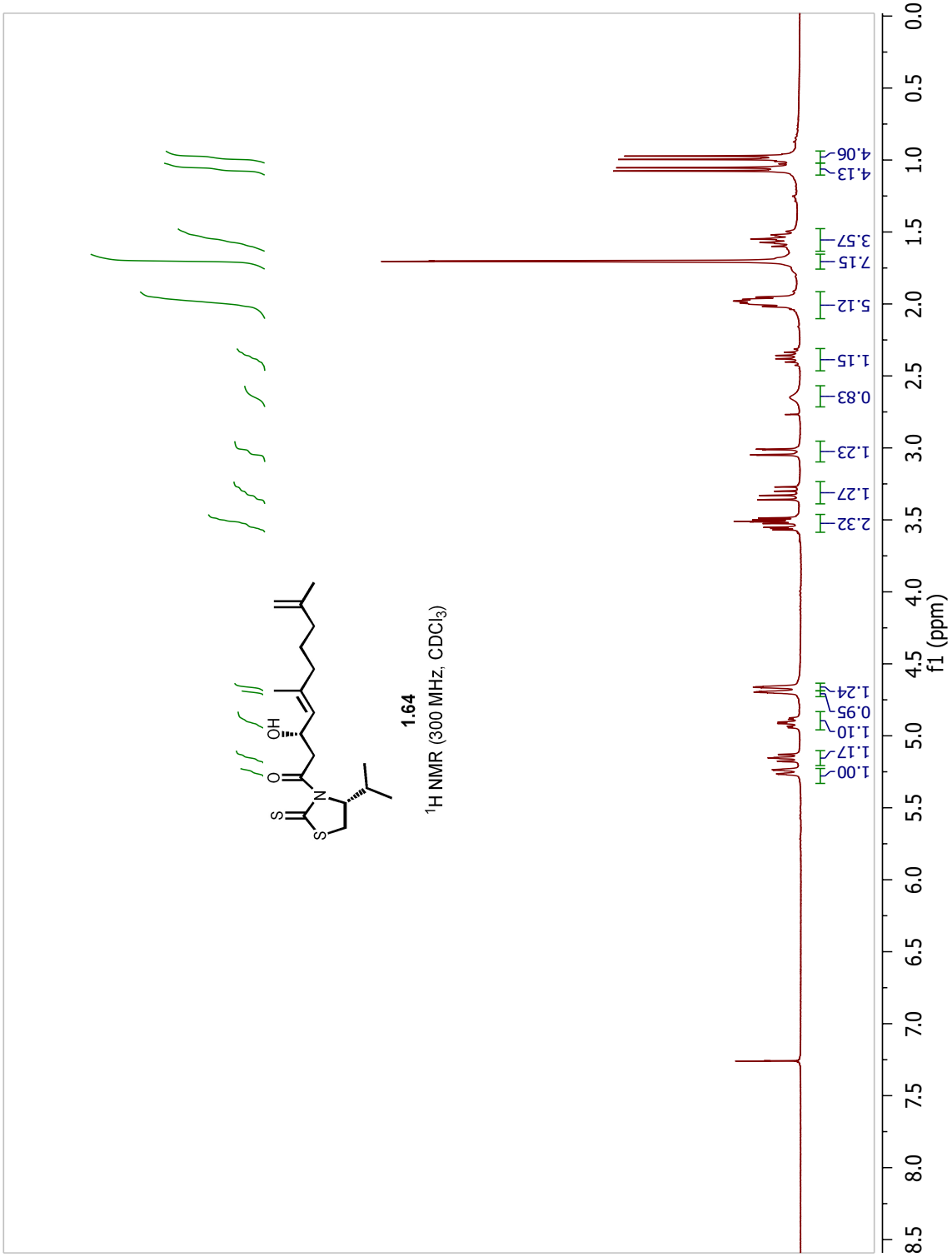

198.2
159.6
159.1
145.2
140.4
130.3
129.3
122.7
115.9
113.7
110.4
72.7
71.8
55.3
48.8
40.7
37.2
25.3
22.3
19.4
OPMB
O
3.39
^{13}C NMR (75 MHz, $CDCl_3$)
f1 (ppm)

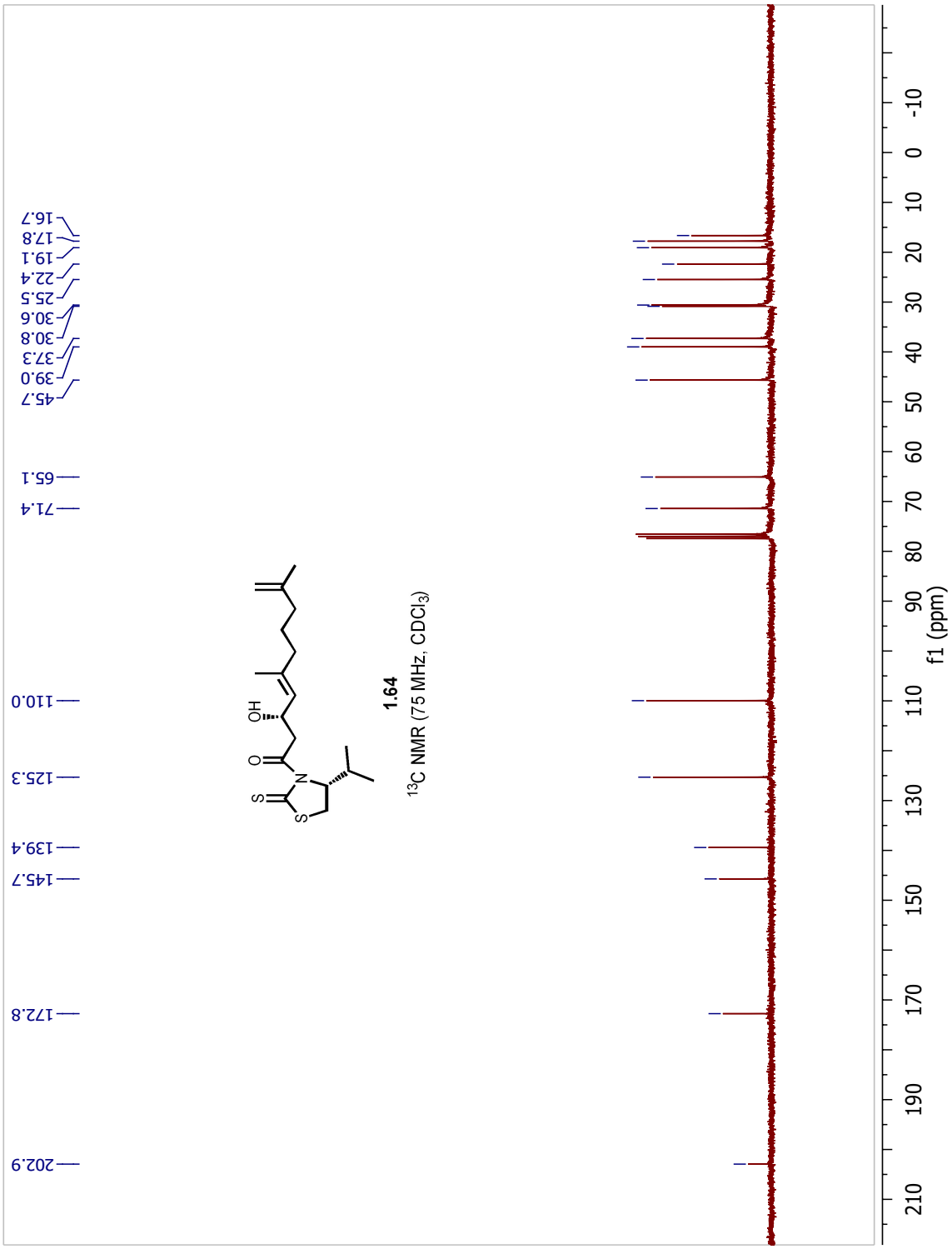

OPMB
HO
3.6
^{1}H NMR (300 MHz, C DC l$_3$)
2.08
2.83
3.16
3.74
2.04
2.94
2.00
1.90
0.93
0.93
0.89
1.00
1.00
0.95
1.82
2.01
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

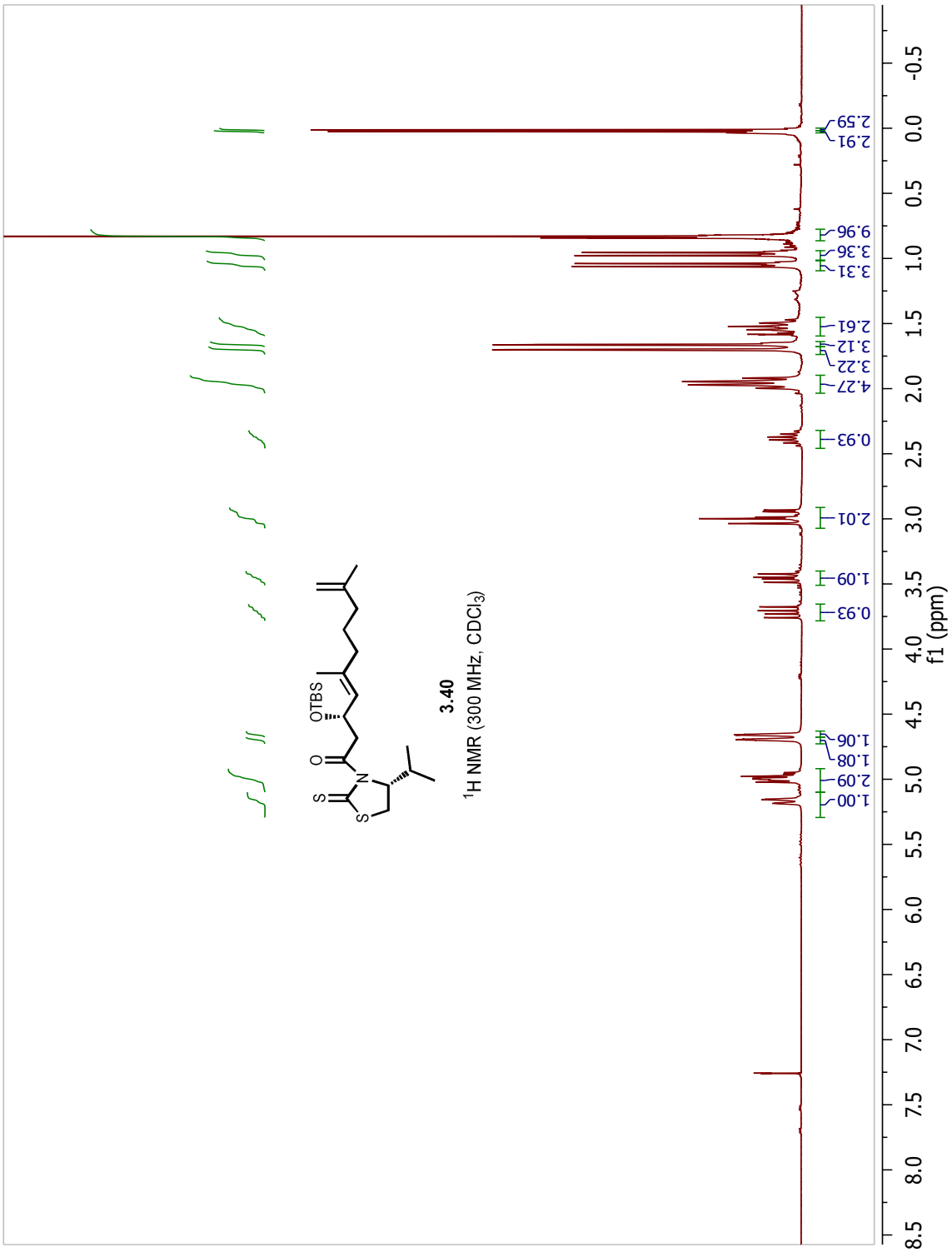

159.2
145.8
142.8
138.2
129.9
129.5
127.3
116.3
113.8
109.9
73.2
72.0
67.2
55.3
42.7
39.0
37.3
25.6
22.4
16.6
HO
OPMB
3.6
^{13}C NMR (75 MHz, $CDCl_3$)
f1 (ppm)

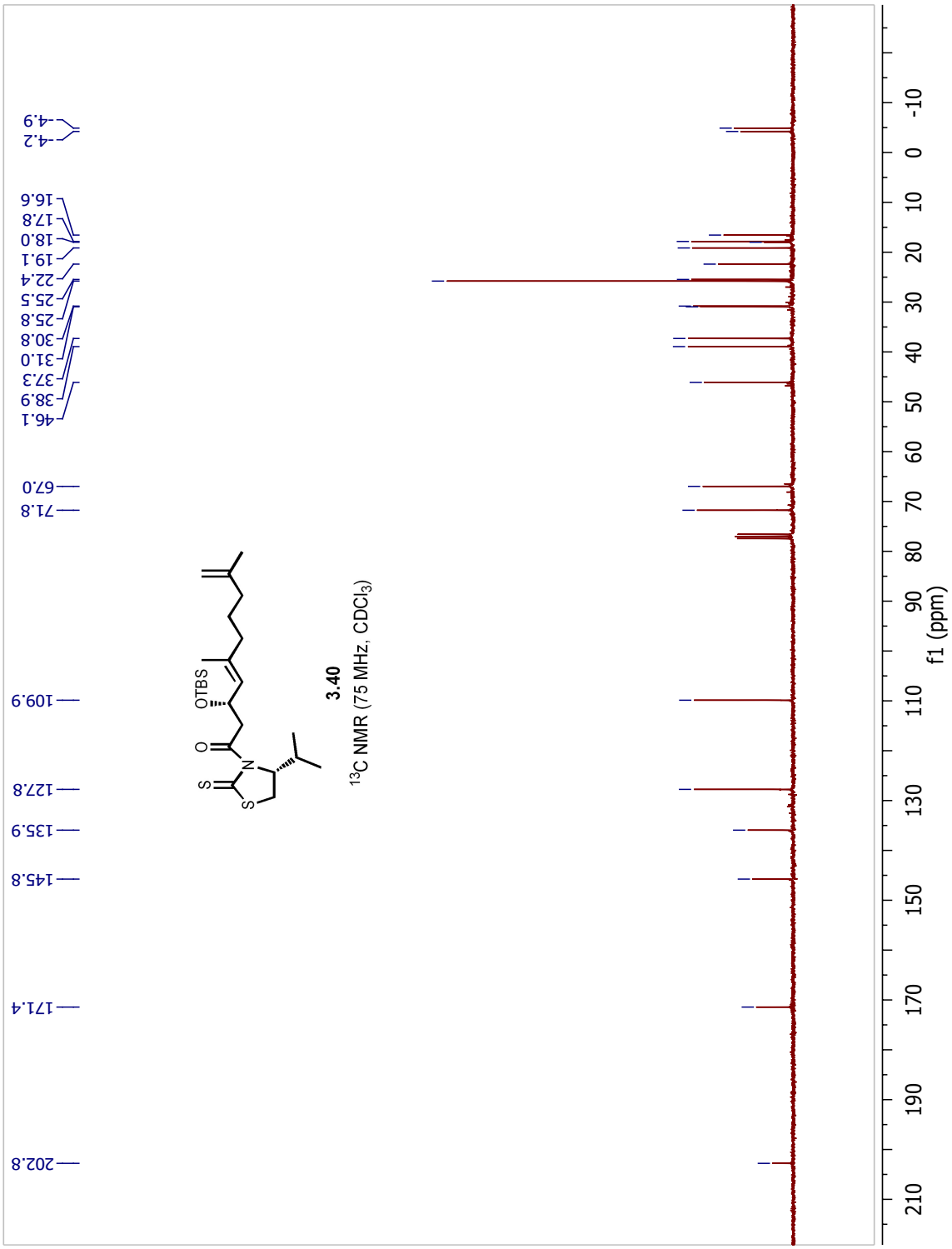

1.62
^{1}H NMR (300 MHz, $CDCl_3$)
OHC
1.00
1.12
1.14
1.27
2.32
3.41
2.46
5.87
f1 (ppm)

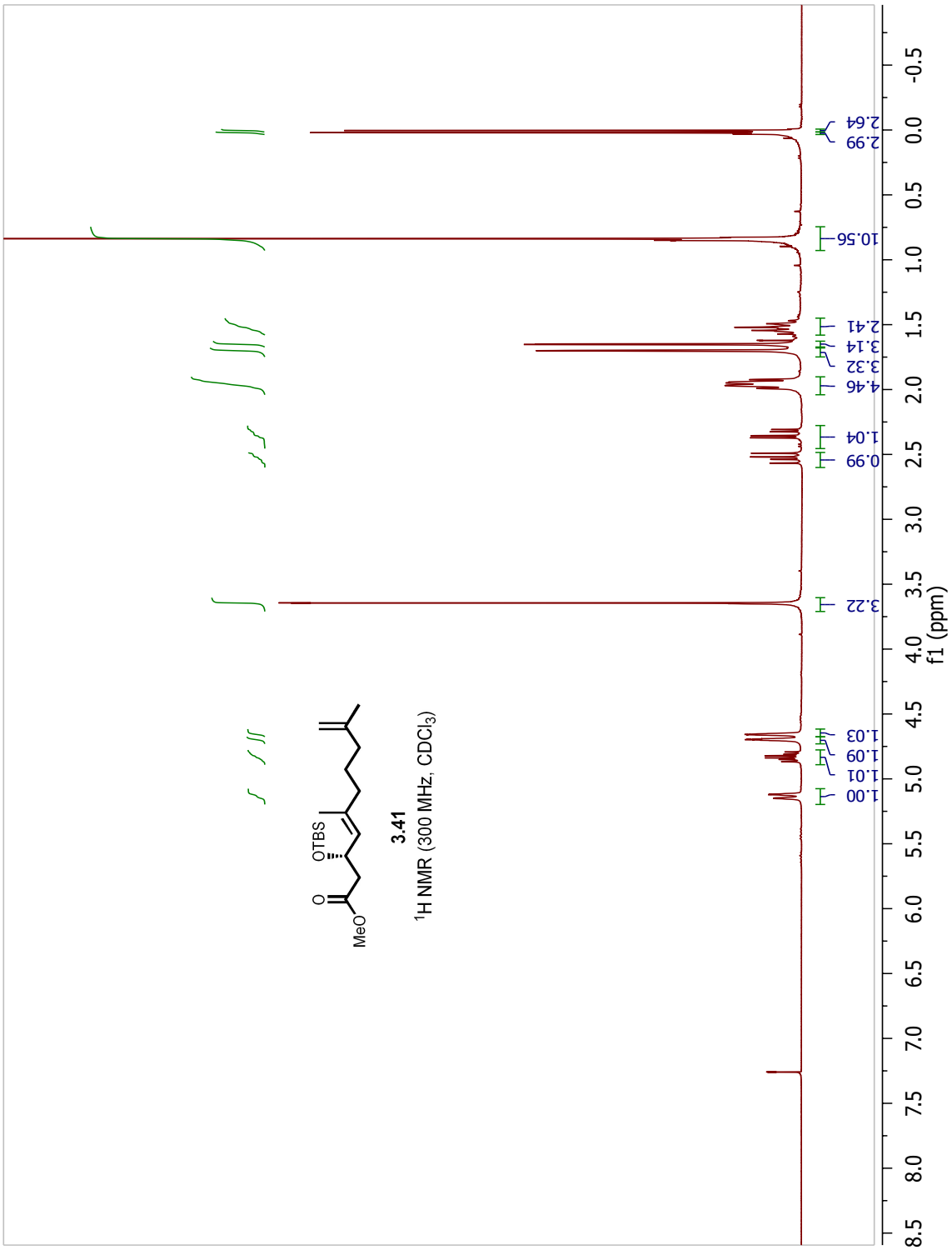

191.3
164.0
144.8
127.4
110.5
40.0
37.1
24.9
22.2
17.5
OHC
1.62
^{13}C NMR (75 MHz, $CDCl_3$)
f1 (ppm)

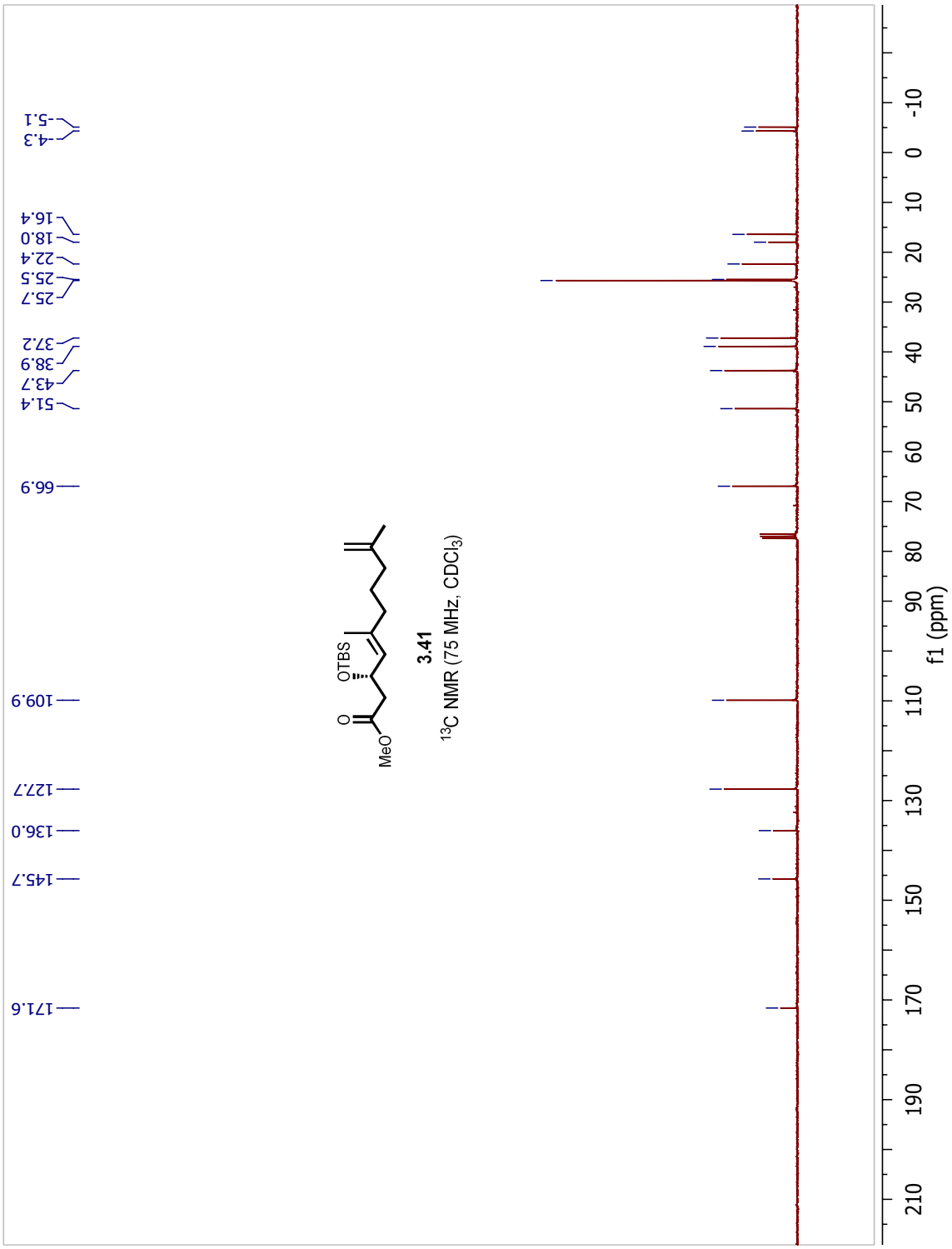

1.64
^{1}H NMR (300 MHz, $CDCl_3$)
OH
O
N
S
S
4.06
4.13
3.57
7.15
5.12
1.15
0.83
1.23
1.27
2.32
1.24
0.95
1.10
1.17
1.00
f1 (ppm)

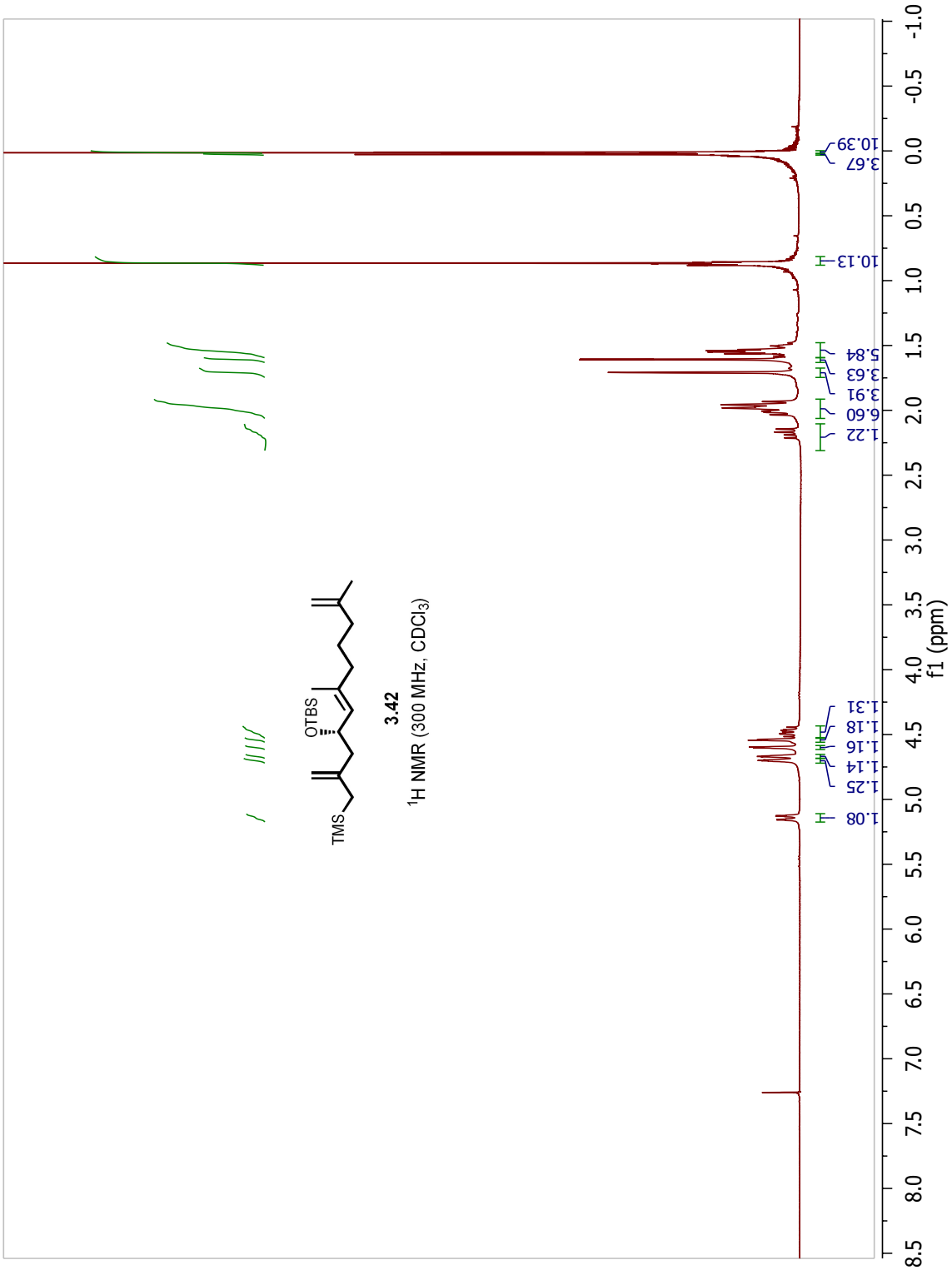

202.9
172.8
145.7
139.4
125.3
110.0
71.4
65.1
45.7
39.0
37.3
30.8
30.6
25.5
22.4
19.1
17.8
16.7
1.64
^{13}C NMR (75 MHz, CDCl$_3$)
f1 (ppm)

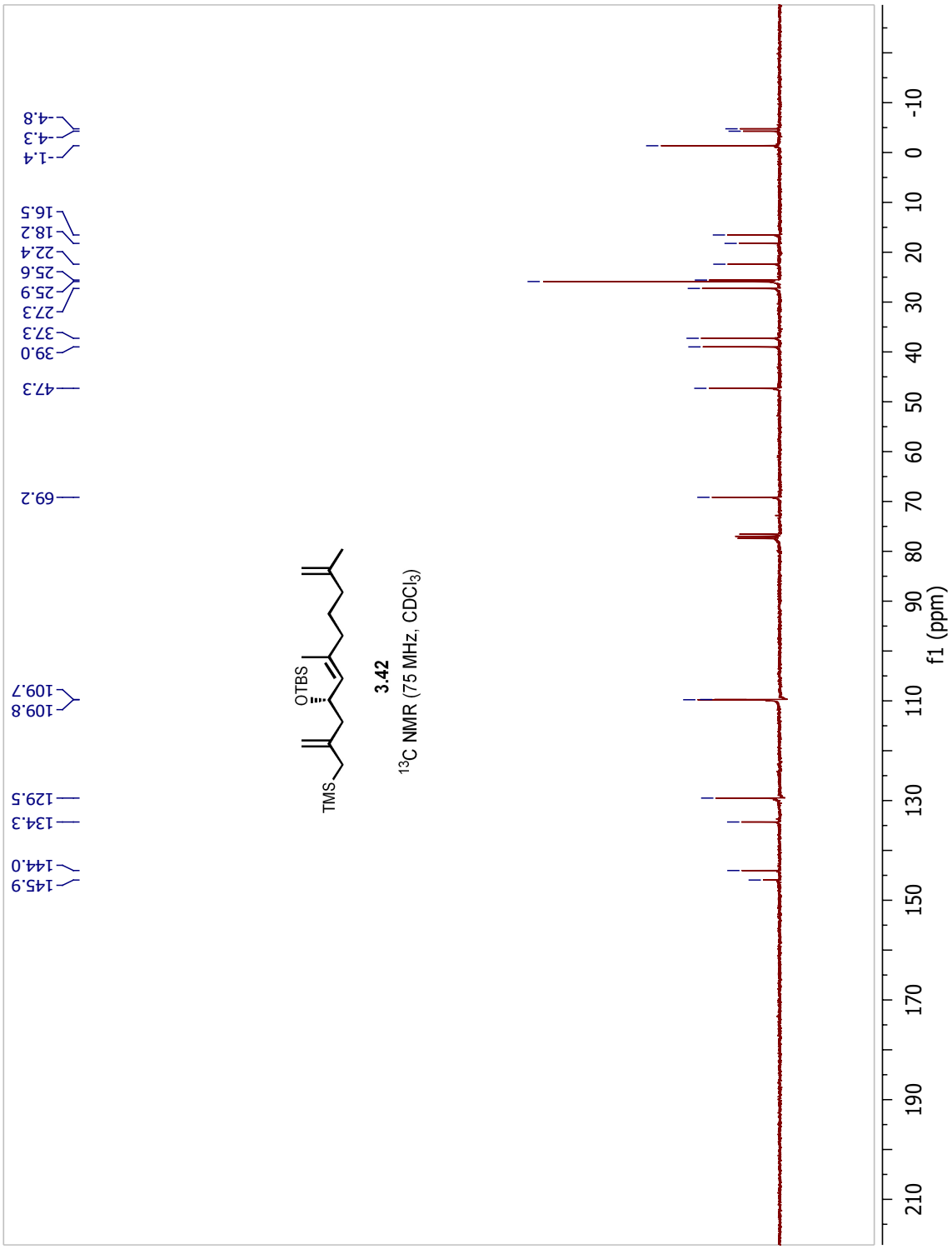

3.40
^{1}H NMR (300 MHz, $CDCl_3$)
OTBS
O
N
S
S
2.91
2.59
9.96
3.36
3.31
2.61
3.12
3.22
4.27
0.93
2.01
1.09
0.93
1.06
1.08
2.09
1.00
f1 (ppm)

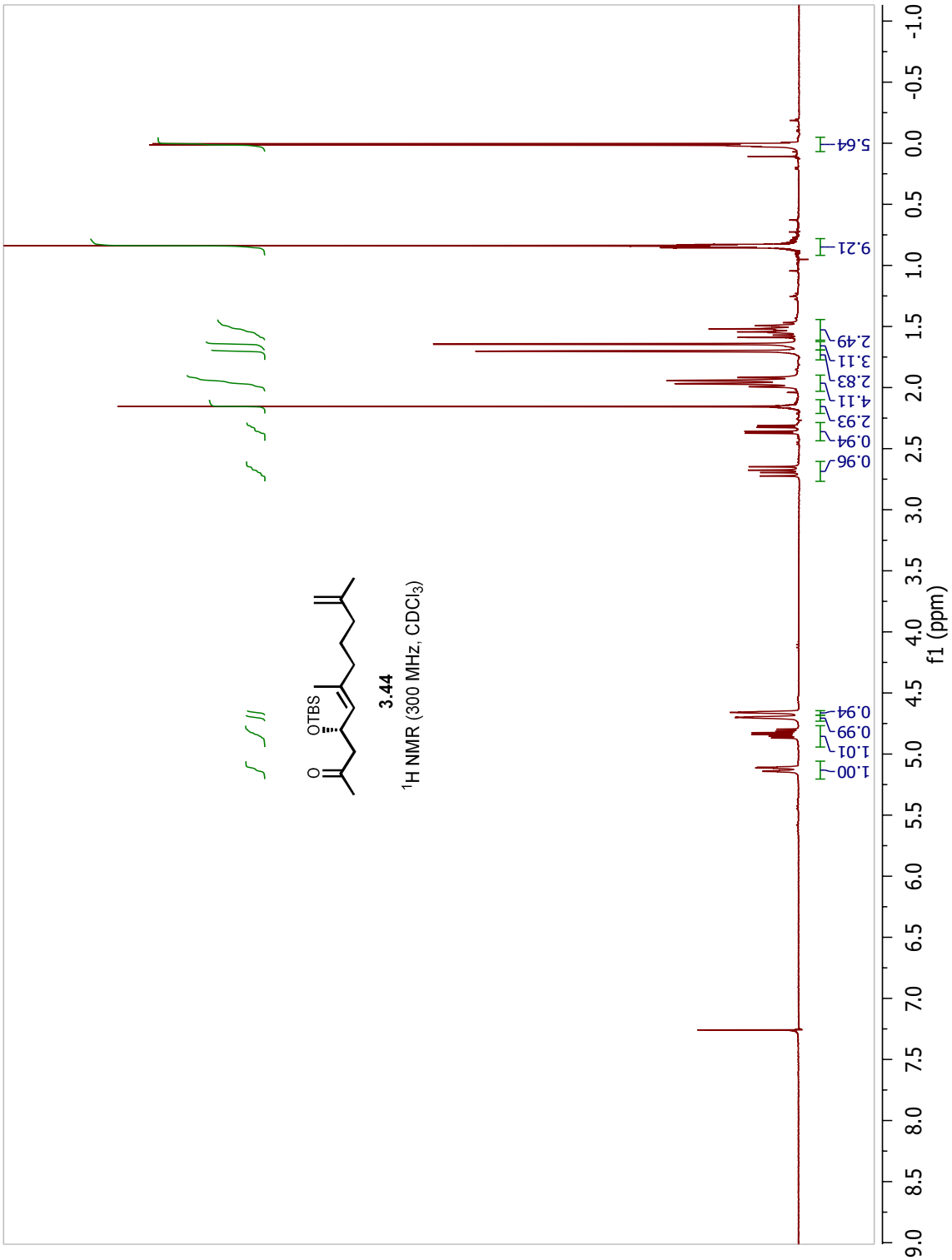

-4.9
-4.2
16.6
17.8
18.0
19.1
22.4
25.5
25.8
30.8
31.0
37.3
38.9
46.1
67.0
71.8
109.9
127.8
135.9
145.8
171.4
202.8
OTBS
O
N
S
S
3.40
^{13}C NMR (75 MHz, $CDCl_3$)
f1 (ppm)

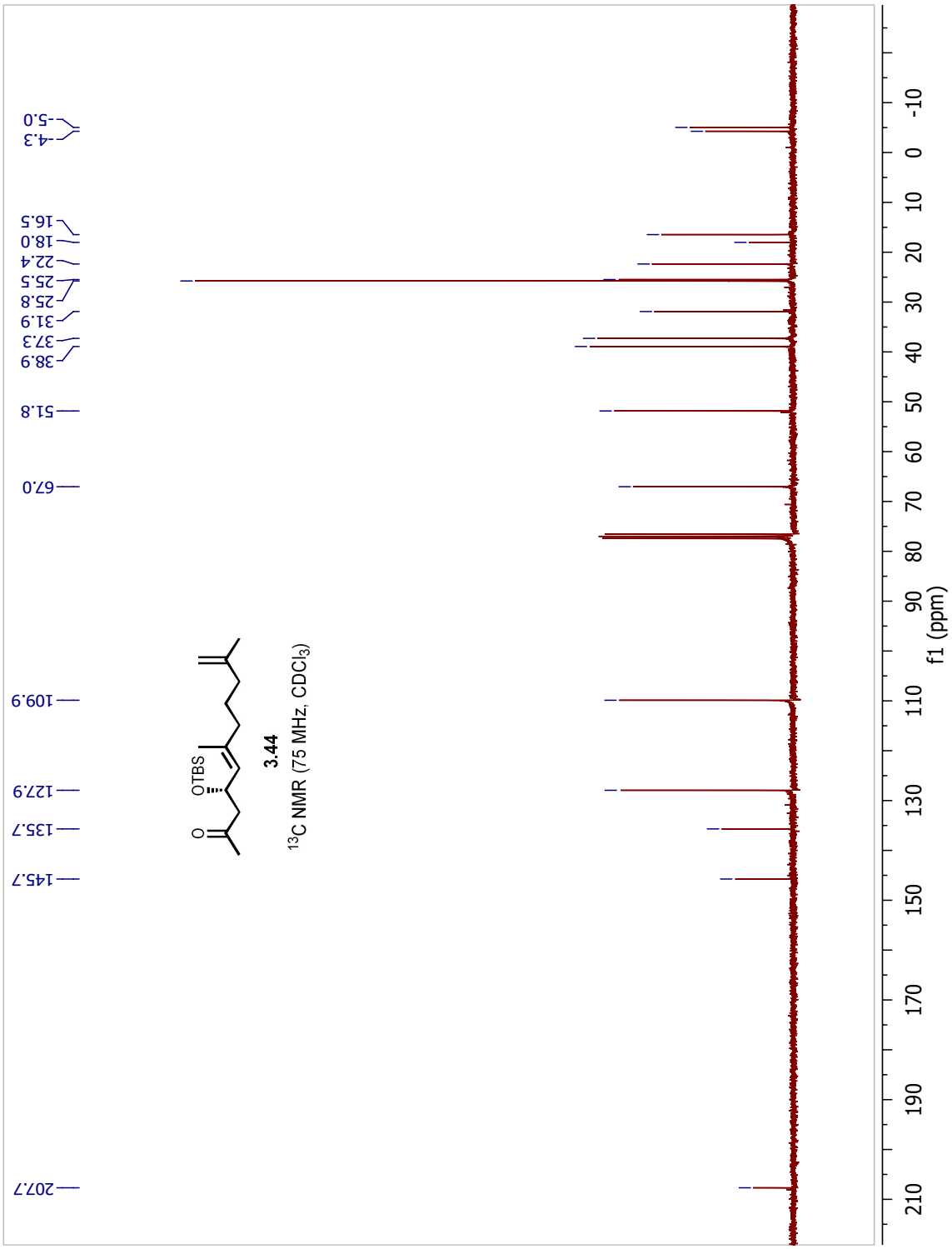

3.41
^{1}H NMR (300 MHz, $CDCl_3$)
OTBS
O
MeO
1.00
1.01
1.09
1.03
3.22
0.99
1.04
4.46
3.32
3.14
2.41
10.56
2.99
2.64
f1 (ppm)

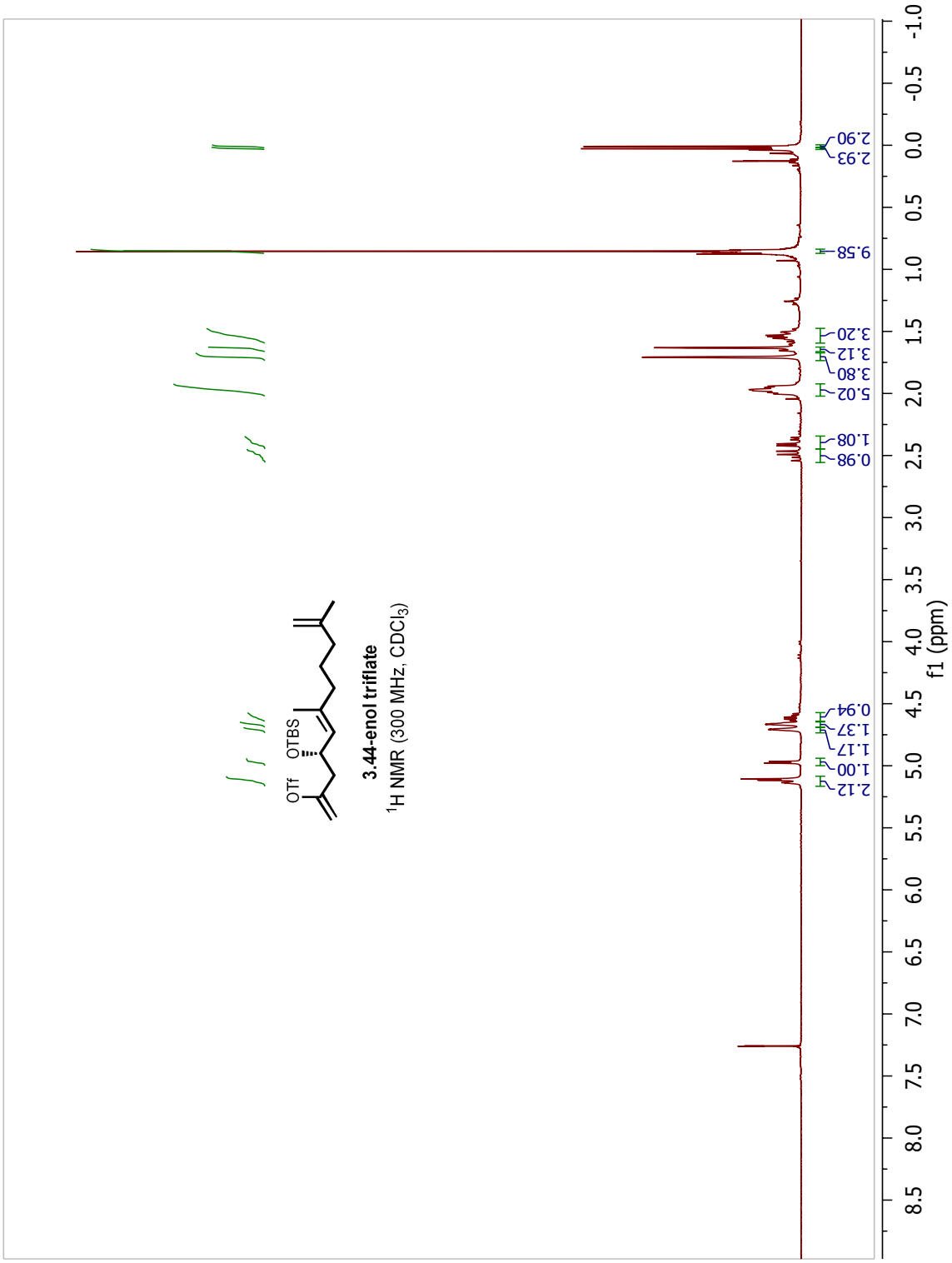

-4.3
-5.1
16.4
18.0
22.4
25.5
25.7
37.2
38.9
43.7
51.4
66.9
109.9
127.7
136.0
145.7
171.6
OTBS
O
MeO
3.41
^{13}C NMR (75 MHz, $CDCl_3$)
f1 (ppm)

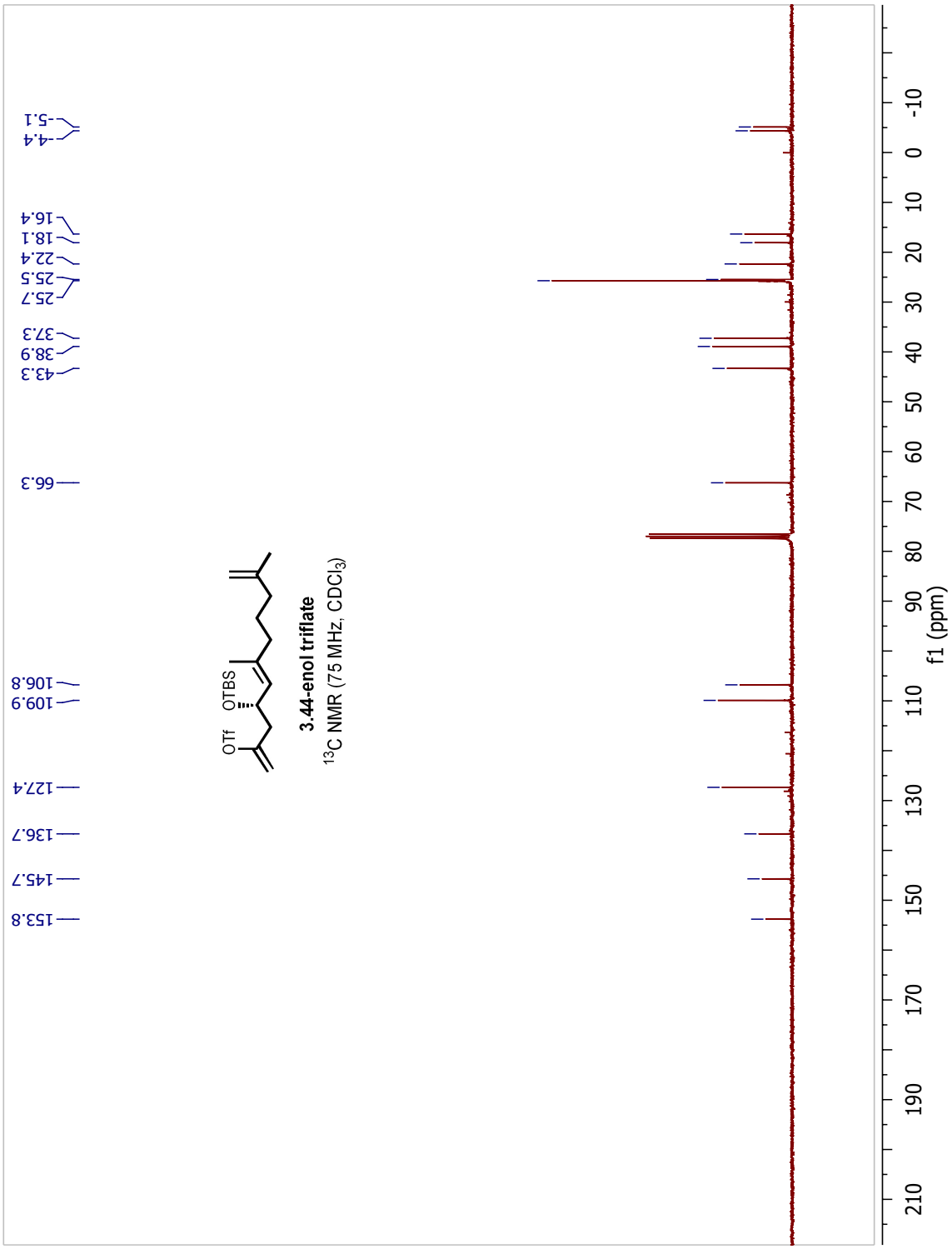

OTBS
TMS
3.42
^{1}H NMR (300 MHz, $CDCl_3$)
10.39
3.67
10.13
5.84
3.63
3.91
6.60
1.22
1.08
1.25
1.14
1.16
1.18
1.31
f1 (ppm)

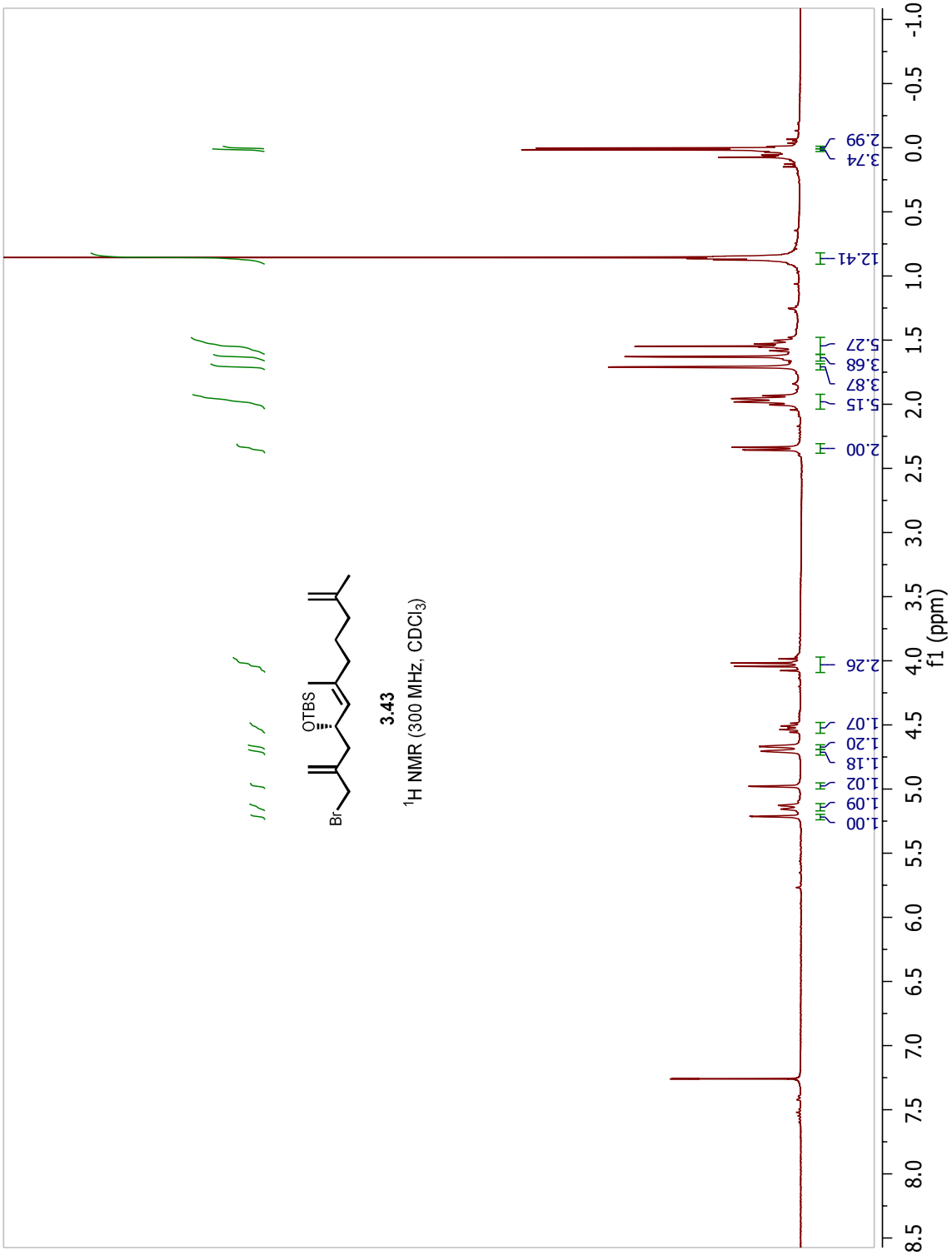

-4.8
-4.3
-1.4
16.5
18.2
22.4
25.6
25.9
27.3
37.3
39.0
47.3
69.2
109.7
109.8
129.5
134.3
144.0
145.9
OTBS
TMS
3.42
^{13}C NMR (75 MHz, $CDCl_3$)
f1 (ppm)

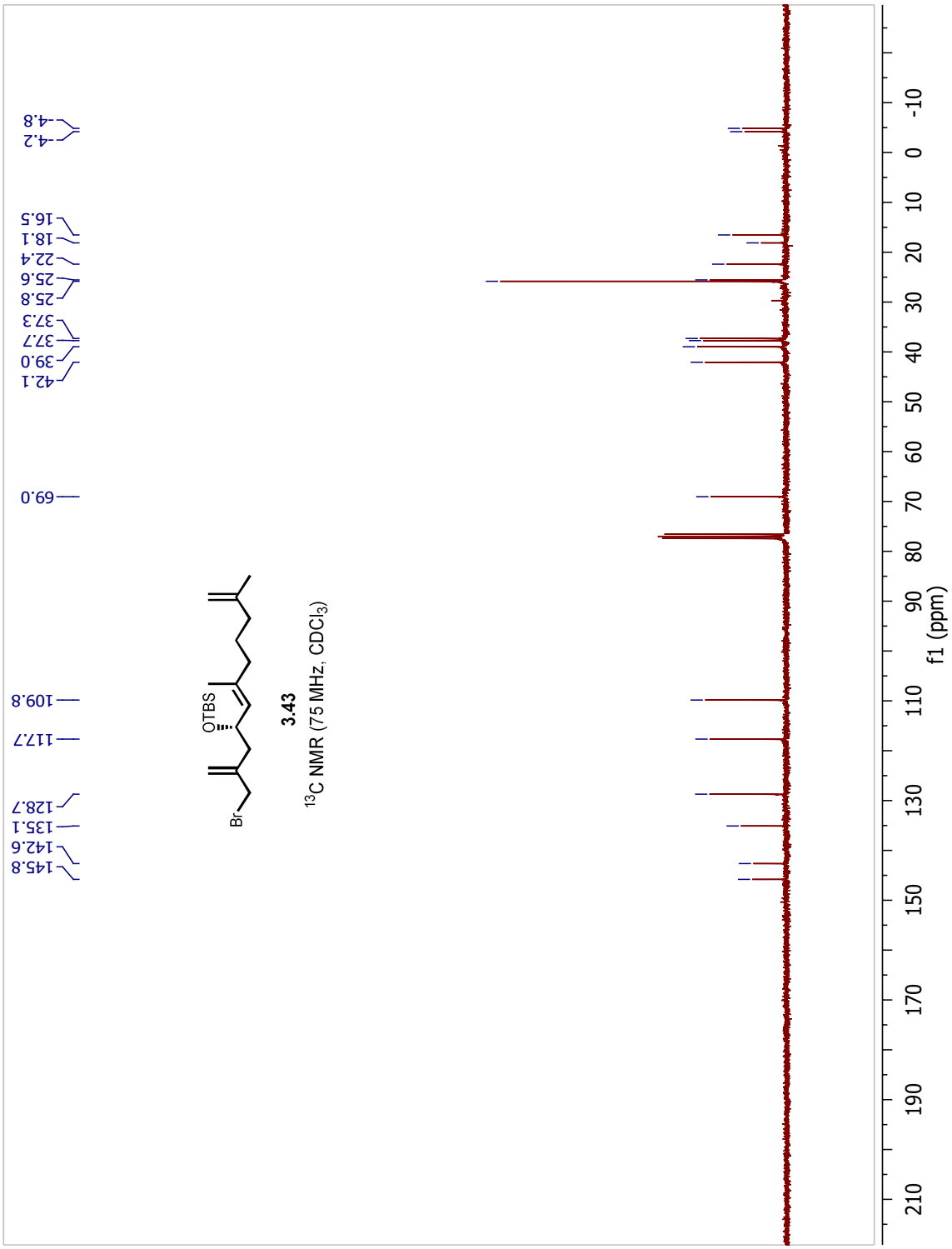

OTBS
O
3.44
^{1}H NMR (300 MHz, CDCl$_3$)
5.64
9.21
2.49
3.11
2.83
4.11
2.93
0.94
0.96
1.00
1.01
0.99
0.94
f1 (ppm)

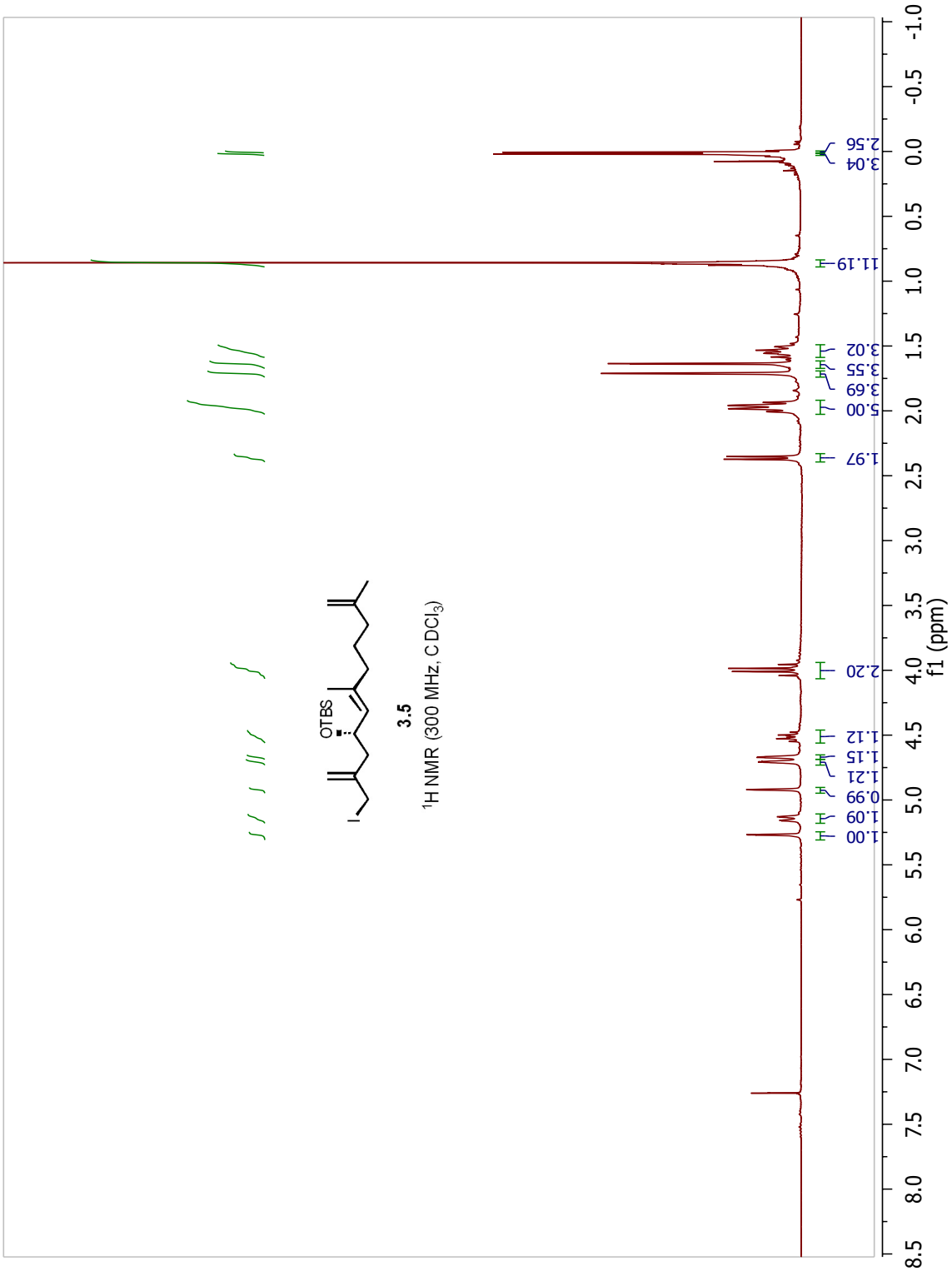

-5.0
-4.3
16.5
18.0
22.4
25.5
25.8
31.9
37.3
38.9
51.8
67.0
109.9
127.9
135.7
145.7
207.7
OTBS
O
3.44
^{13}C NMR (75 MHz, $CDCl_3$)
f1 (ppm)

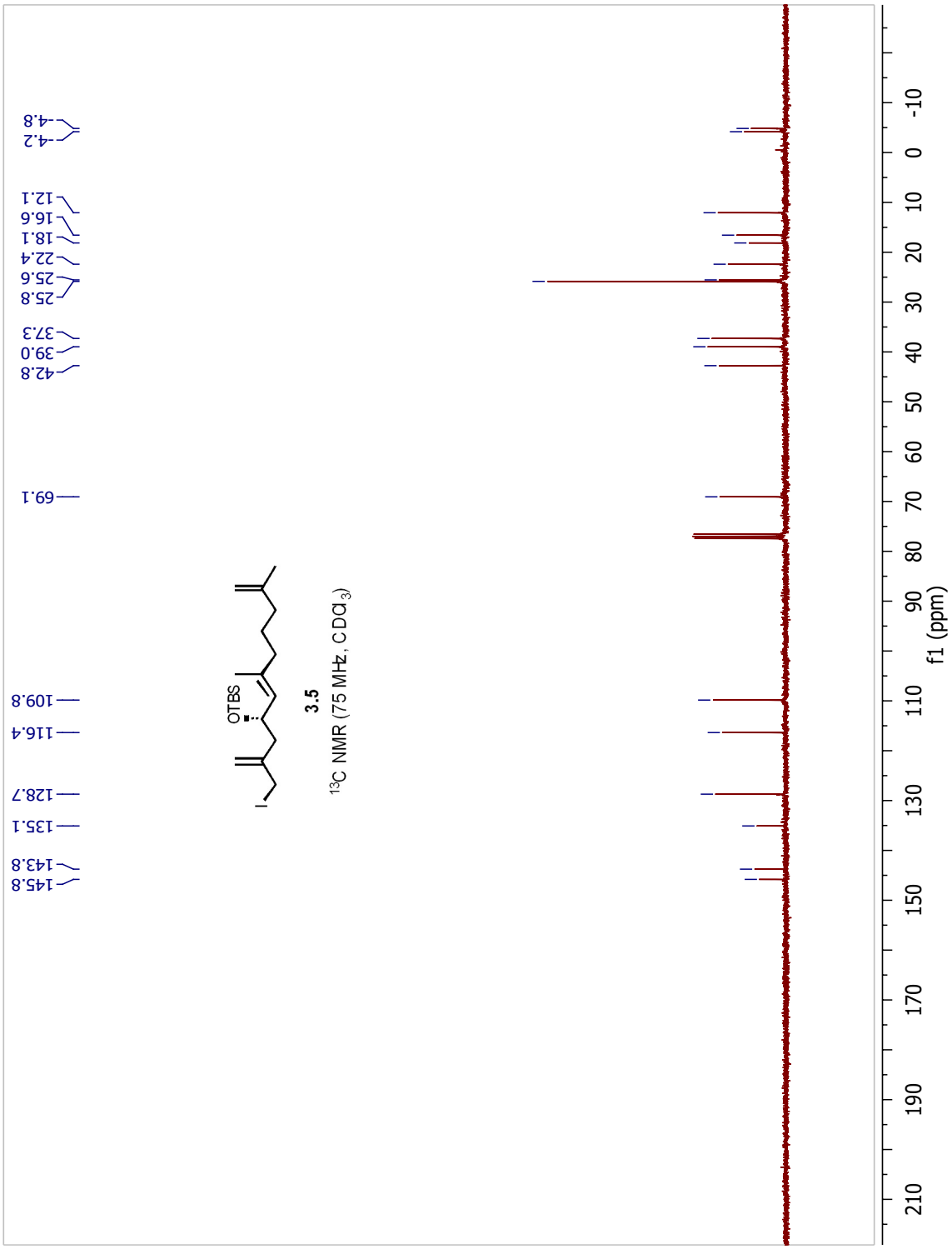

OTf
OTBS
3.44-enol triflate
^{1}H NMR (300 MHz, $CDCl_3$)
2.90
2.93
9.58
3.20
3.12
3.80
5.02
1.08
0.98
0.94
1.37
1.17
1.00
2.12
f1 (ppm)

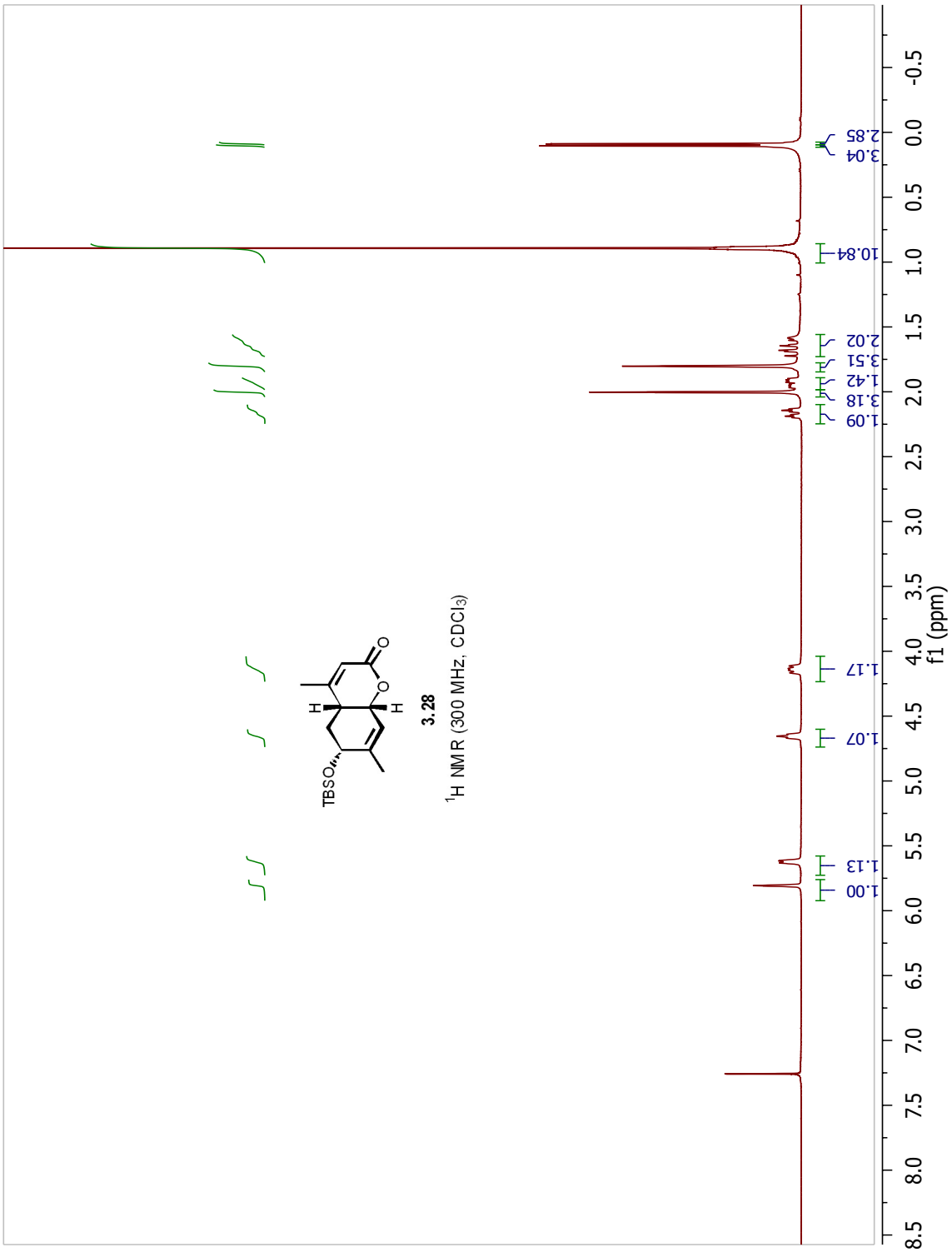

-5.1
-4.4
16.4
18.1
22.4
25.5
25.7
37.3
38.9
43.3
66.3
106.8
109.9
127.4
136.7
145.7
153.8
OTf
OTBS
3.44-enol triflate
^{13}C NMR (75 MHz, $CDCl_3$)
f1 (ppm)

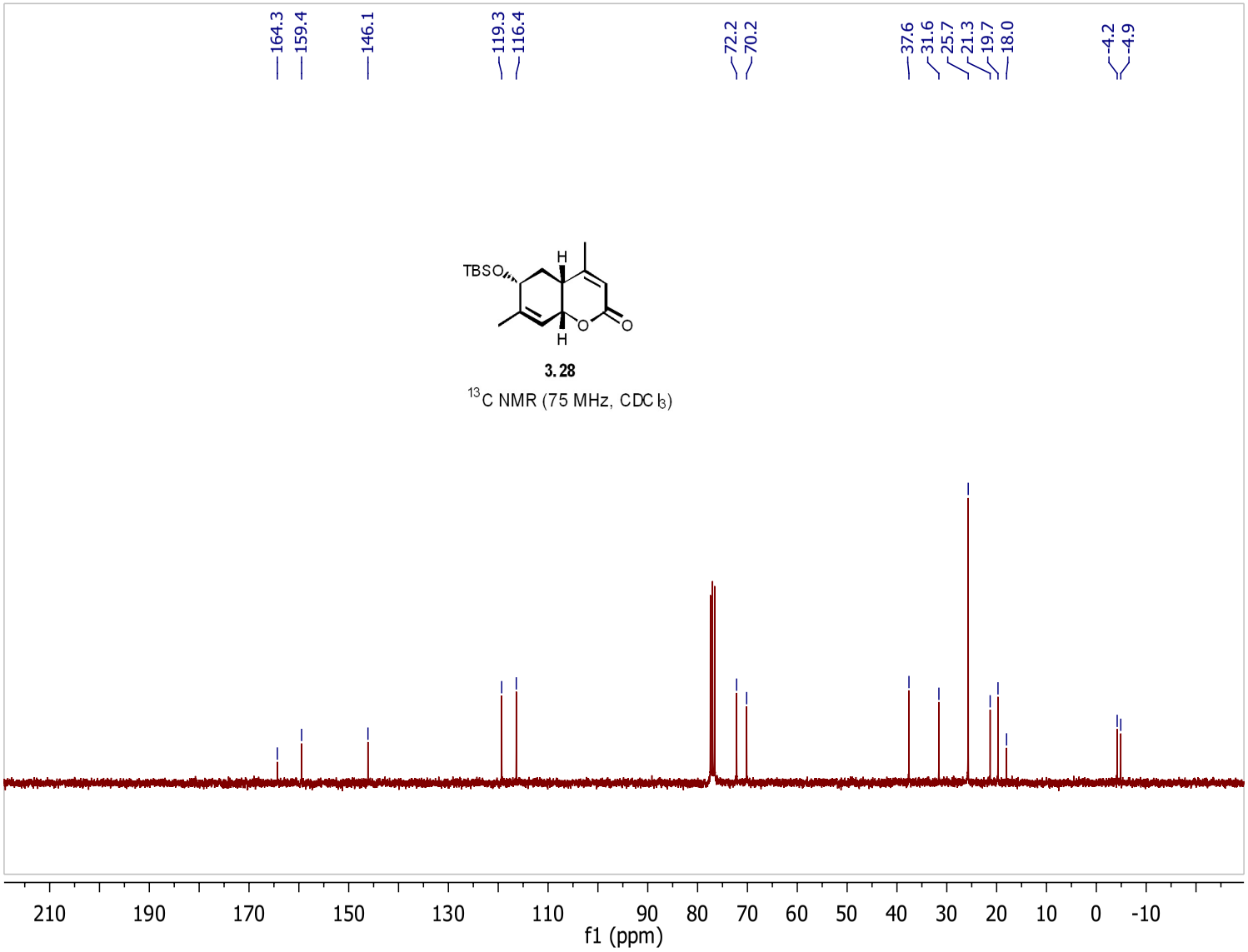

OTBS
Br
3.43
^{1}H NMR (300 MHz, $CDCl_3$)
1.00
1.09
1.02
1.18
1.20
1.07
2.26
2.00
5.15
3.87
3.68
5.27
12.41
3.74
2.99
f1 (ppm)

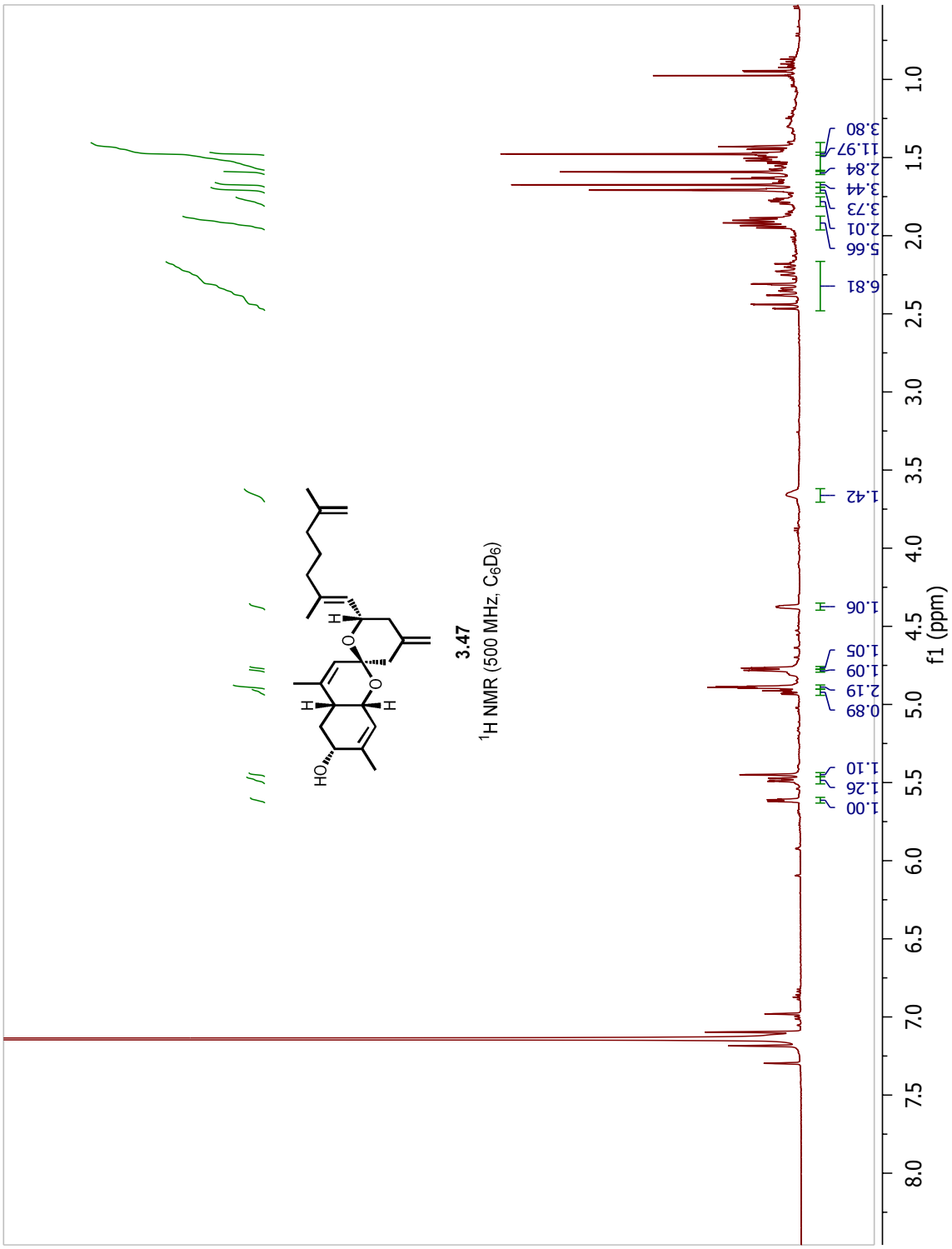

-4.8
-4.2
16.5
18.1
22.4
25.6
25.8
37.3
37.7
39.0
42.1
69.0
109.8
117.7
128.7
135.1
142.6
145.8
OTBS
Br
3.43
^{13}C NMR (75 MHz, $CDCl_3$)
f1 (ppm)

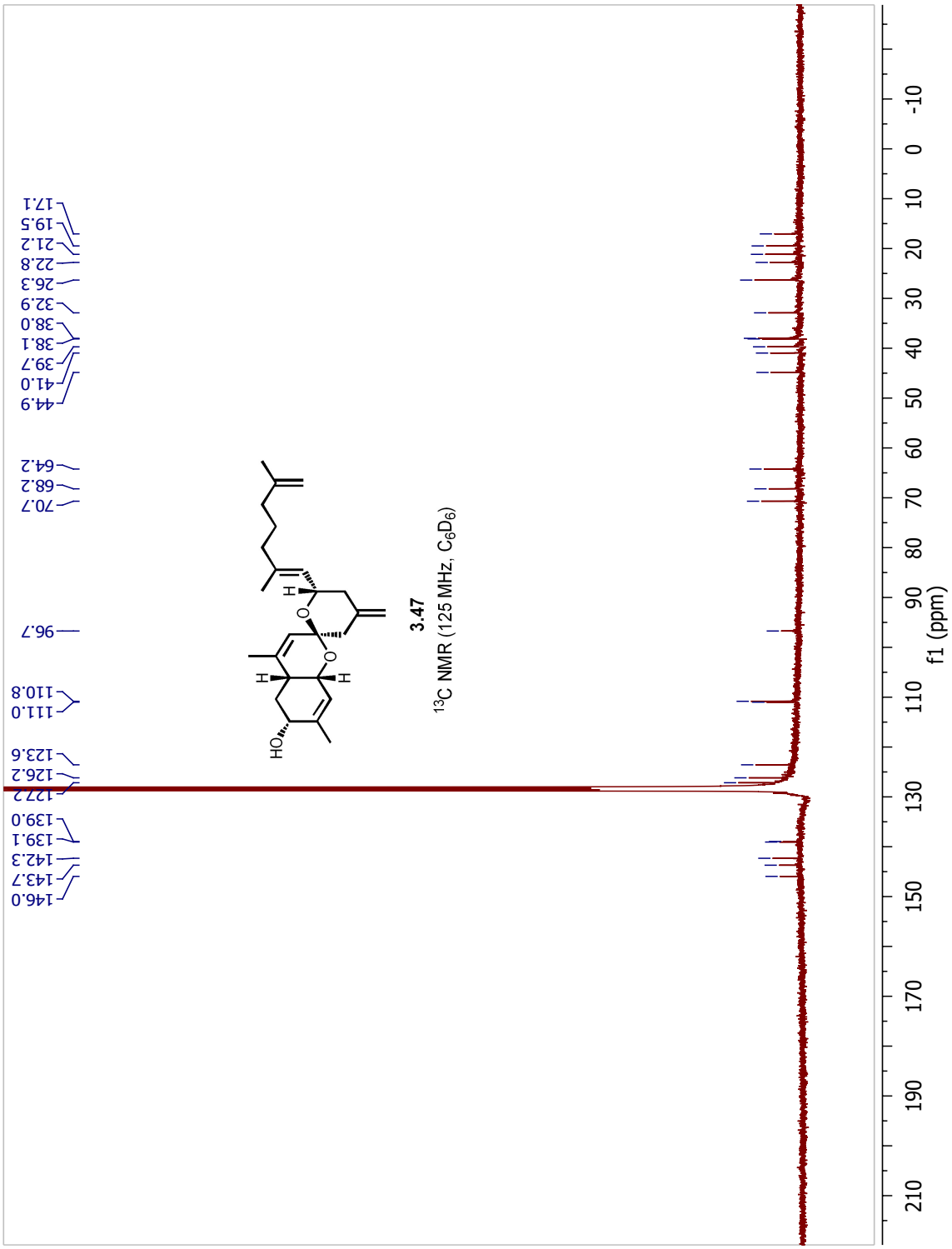

OTBS
3.5
^{1}H NMR (300 MHz, C DCl$_3$)
2.56
3.04
11.19
3.02
3.55
3.69
5.00
1.97
2.20
1.12
1.15
1.21
0.99
1.09
1.00
f1 (ppm)

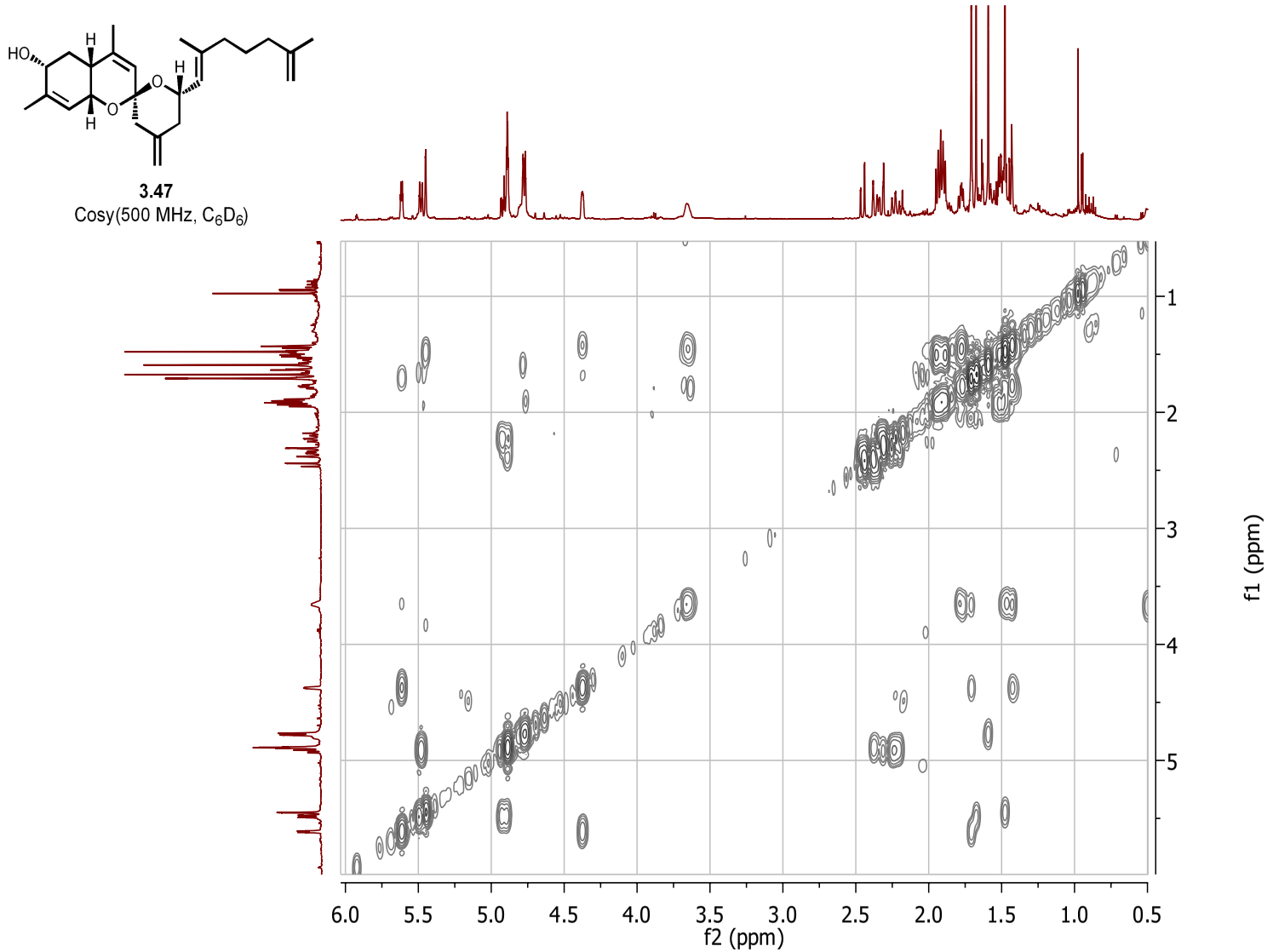

OTBS
I
3.5
^{13}C NMR (75 MHz, $CDCl_3$)
145.8
143.8
135.1
128.7
116.4
109.8
69.1
42.8
39.0
37.3
25.8
25.6
22.4
18.1
16.6
12.1
-4.2
-4.8
f1 (ppm)

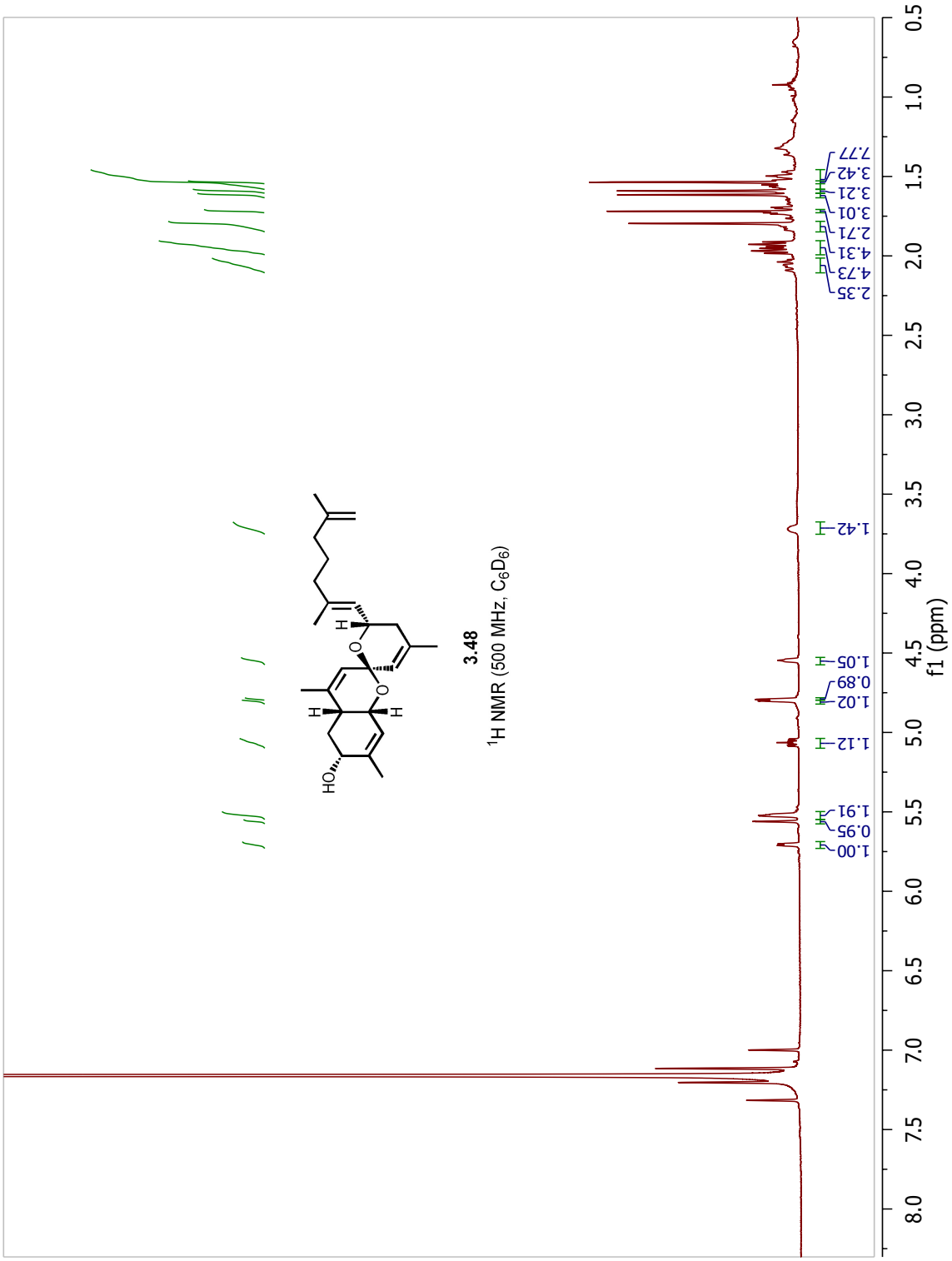

TBSO
H
H
O
O
3.28
^{1}H NMR (300 MHz, CDCl$_3$)
1.00
1.13
1.07
1.17
10.84
2.85
3.04
1.09
3.18
1.42
3.51
2.02
f1 (ppm)

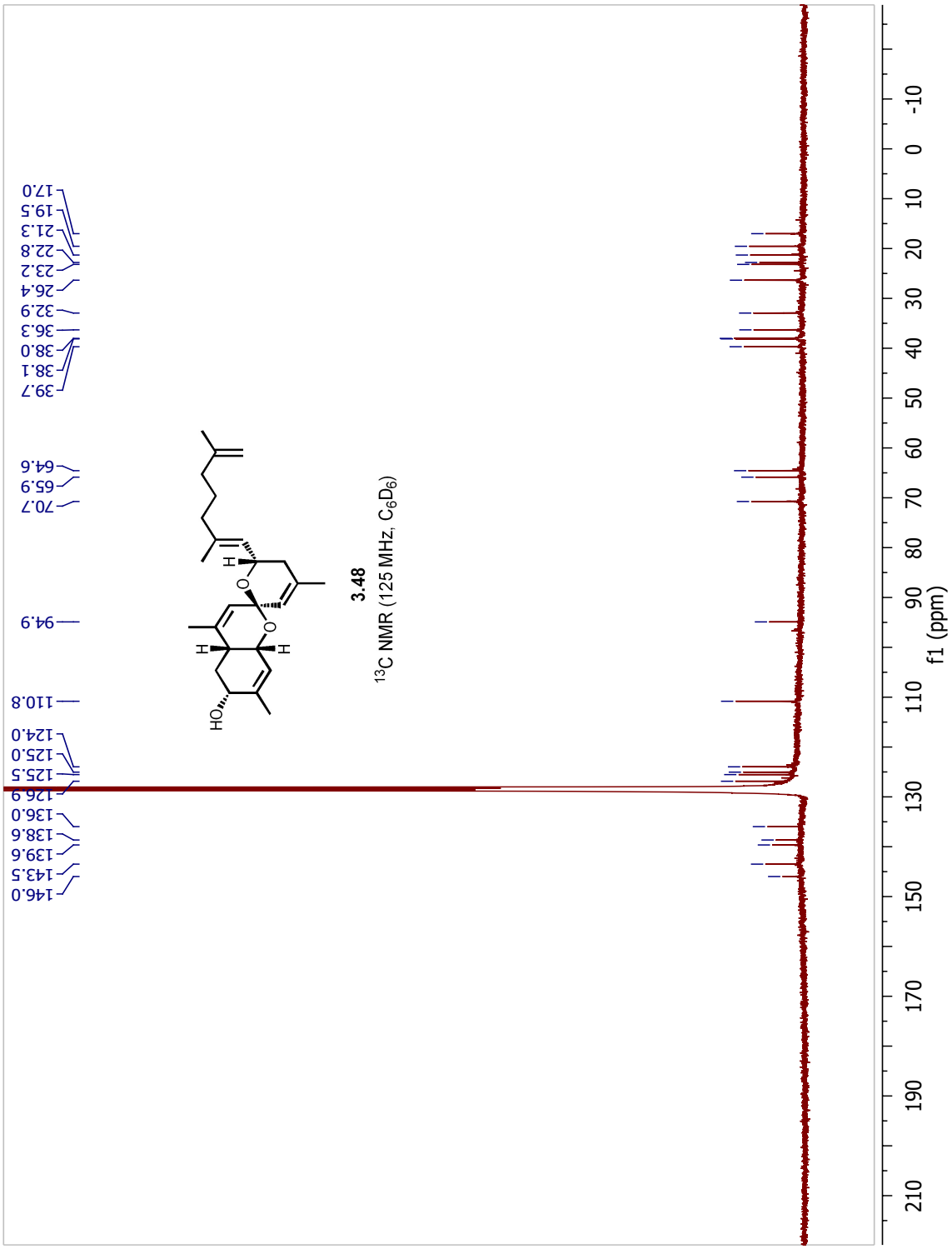

164.3
159.4
146.1
119.3
116.4
72.2
70.2
37.6
31.6
25.7
21.3
19.7
18.0
-4.2
-4.9
TBSO
H
H
O
O
3.28
13C NMR (75 MHz, CDCl3)
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

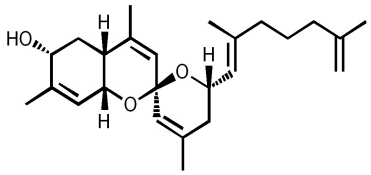

3.47
^{1}H NMR (500 MHz, C_6D_6)
HO
H
O
O
H
H
1.00
1.26
1.10
0.89
2.19
1.09
1.05
1.06
1.42
6.81
5.66
2.01
3.73
3.44
2.84
11.97
3.80
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)


17.1
19.5
21.2
22.8
26.3
32.9
38.0
38.1
39.7
41.0
44.9
64.2
68.2
70.7
96.7
110.8
111.0
123.6
126.2
127.2
139.0
139.1
142.3
143.7
146.0
HO
H
O
O
H
H
3.47
^{13}C NMR (125 MHz, C_6D_6)
f1 (ppm)

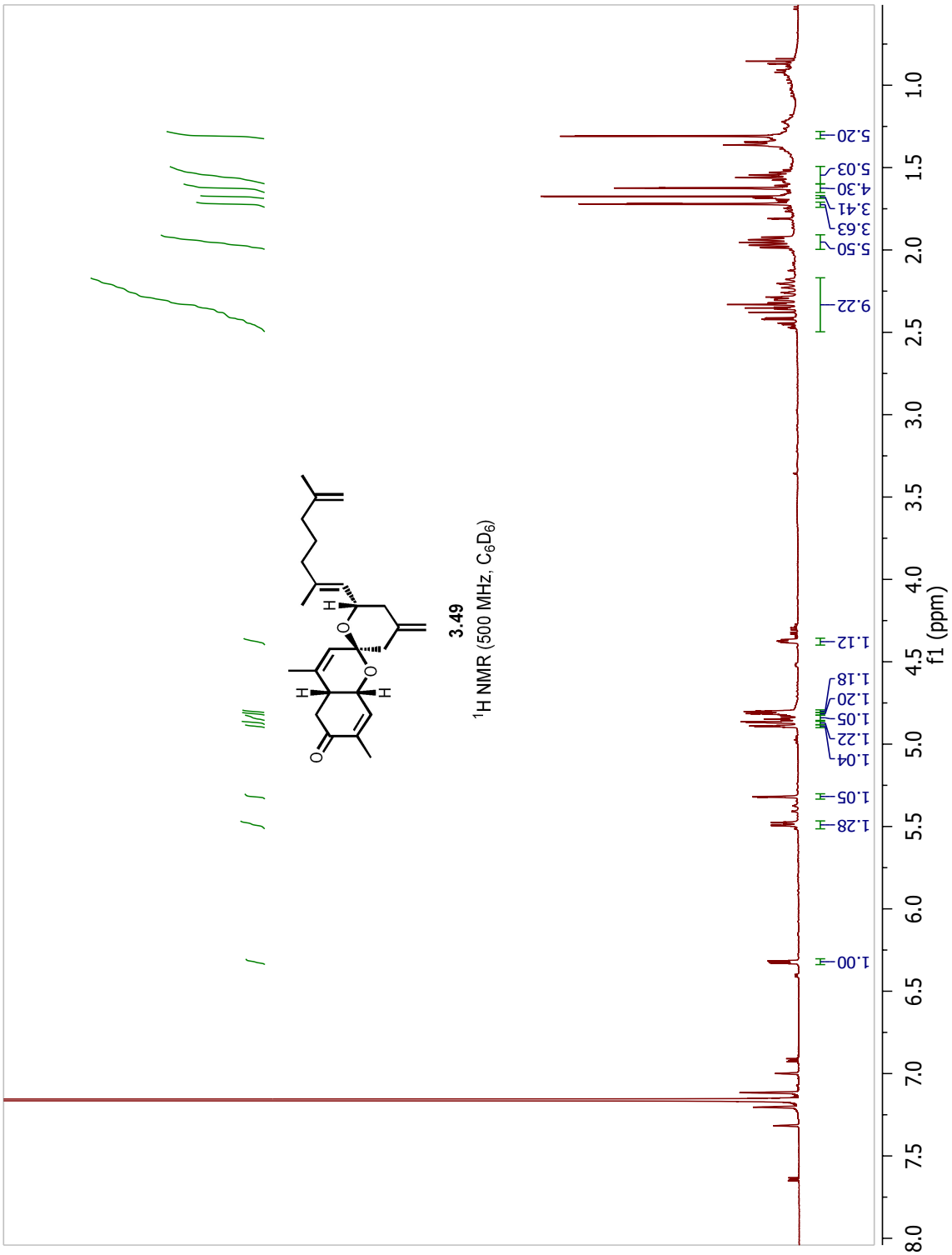

HO
H
O
H
O
H
3.47
Cosy(500 MHz, C_6D_6)
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f2 (ppm)
1
2
3
4
5
f1 (ppm)

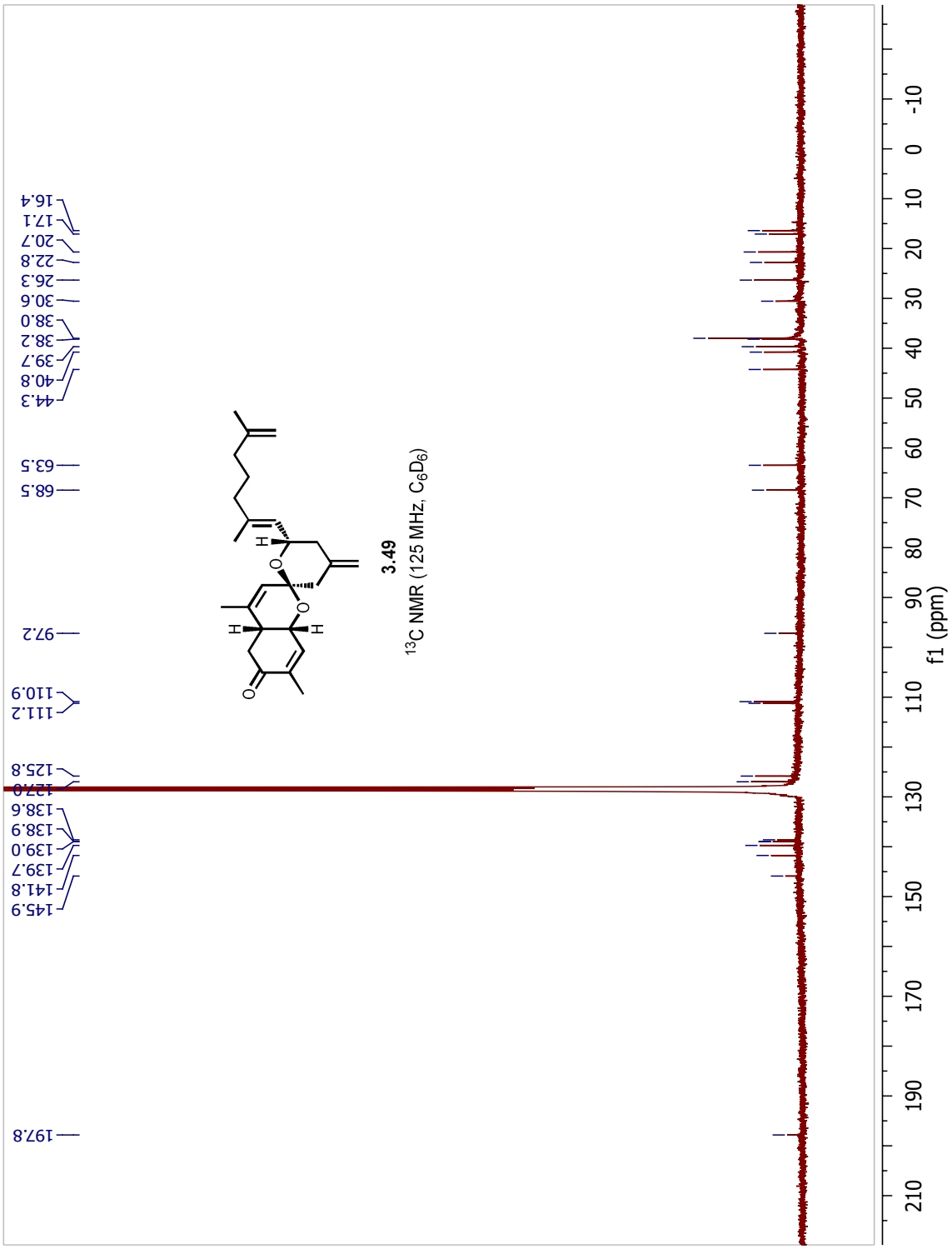

3.48
^{1}H NMR (500 MHz, C_6D_6)
HO
H
O
O
H
H
2.35
4.73
4.31
2.71
3.01
3.21
3.42
7.77
1.42
1.05
0.89
1.02
1.12
1.00
0.95
1.91
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

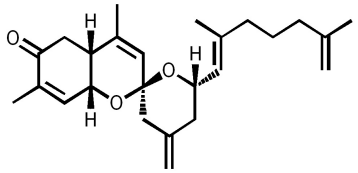

146.0
143.5
139.6
138.6
136.0
126.9
125.5
125.0
124.0
110.8
94.9
70.7
65.9
64.6
39.7
38.1
38.0
36.3
32.9
26.4
23.2
22.8
21.3
19.5
17.0
HO
O
O
H
H
H
3.48
^{13}C NMR (125 MHz, C_6D_6)
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)



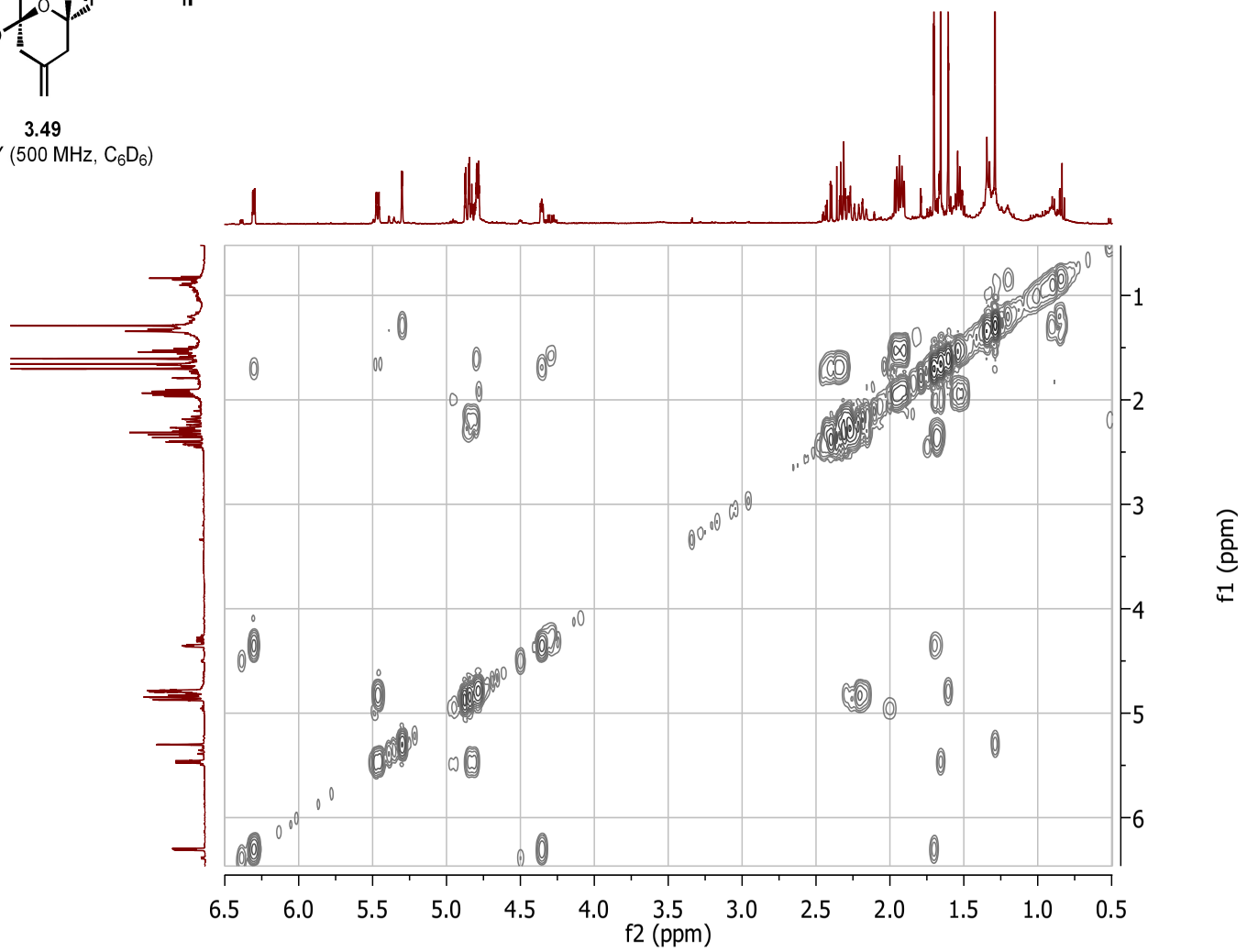
3.48
Cosy (500 MHz, C_6D_6)

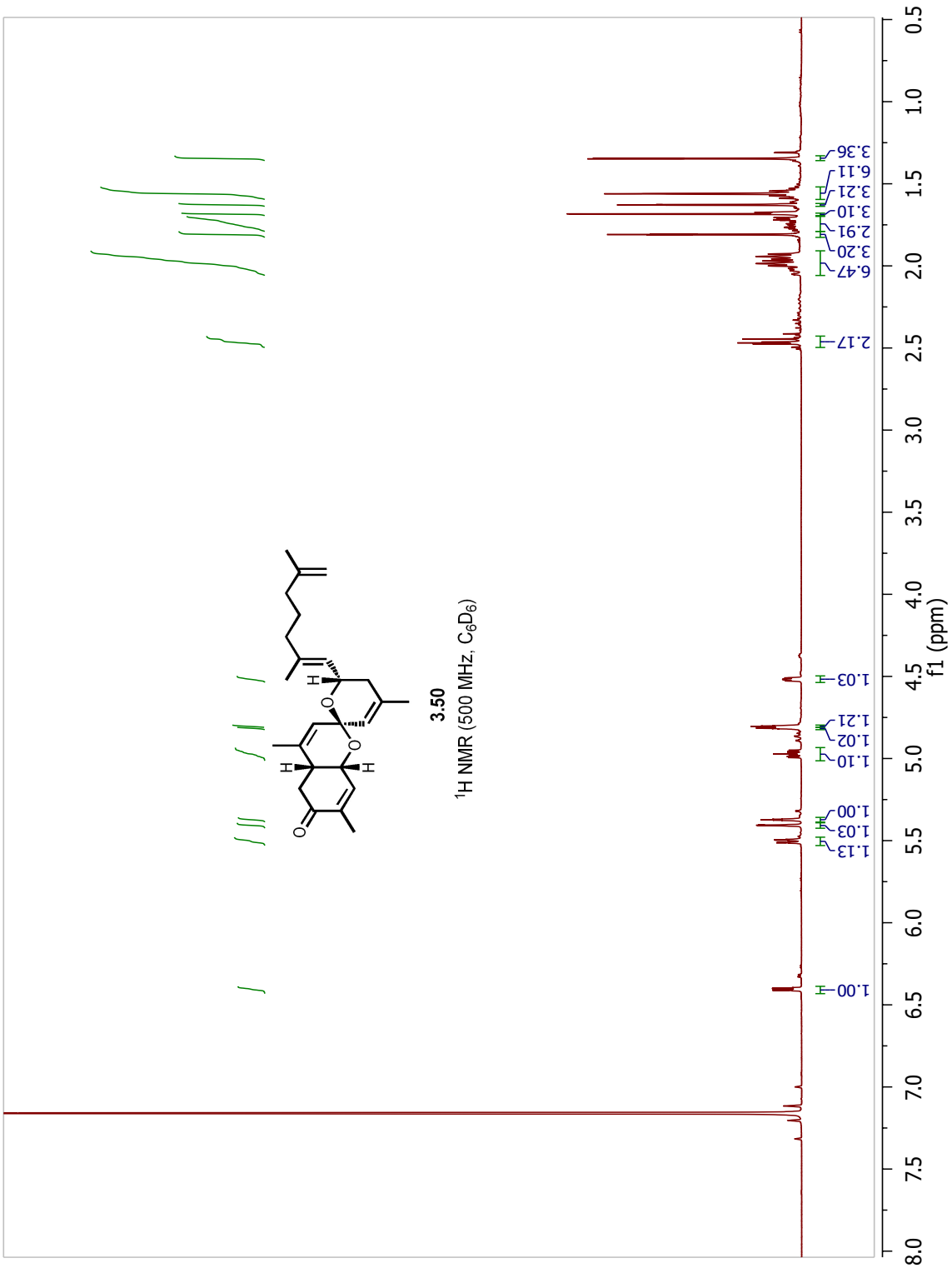

3.49
^{1}H NMR (500 MHz, C_6D_6)
f1 (ppm)
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
1.00
1.28
1.05
1.04
1.22
1.05
1.20
1.18
1.12
9.22
5.50
3.63
4.41
4.30
5.03
5.20

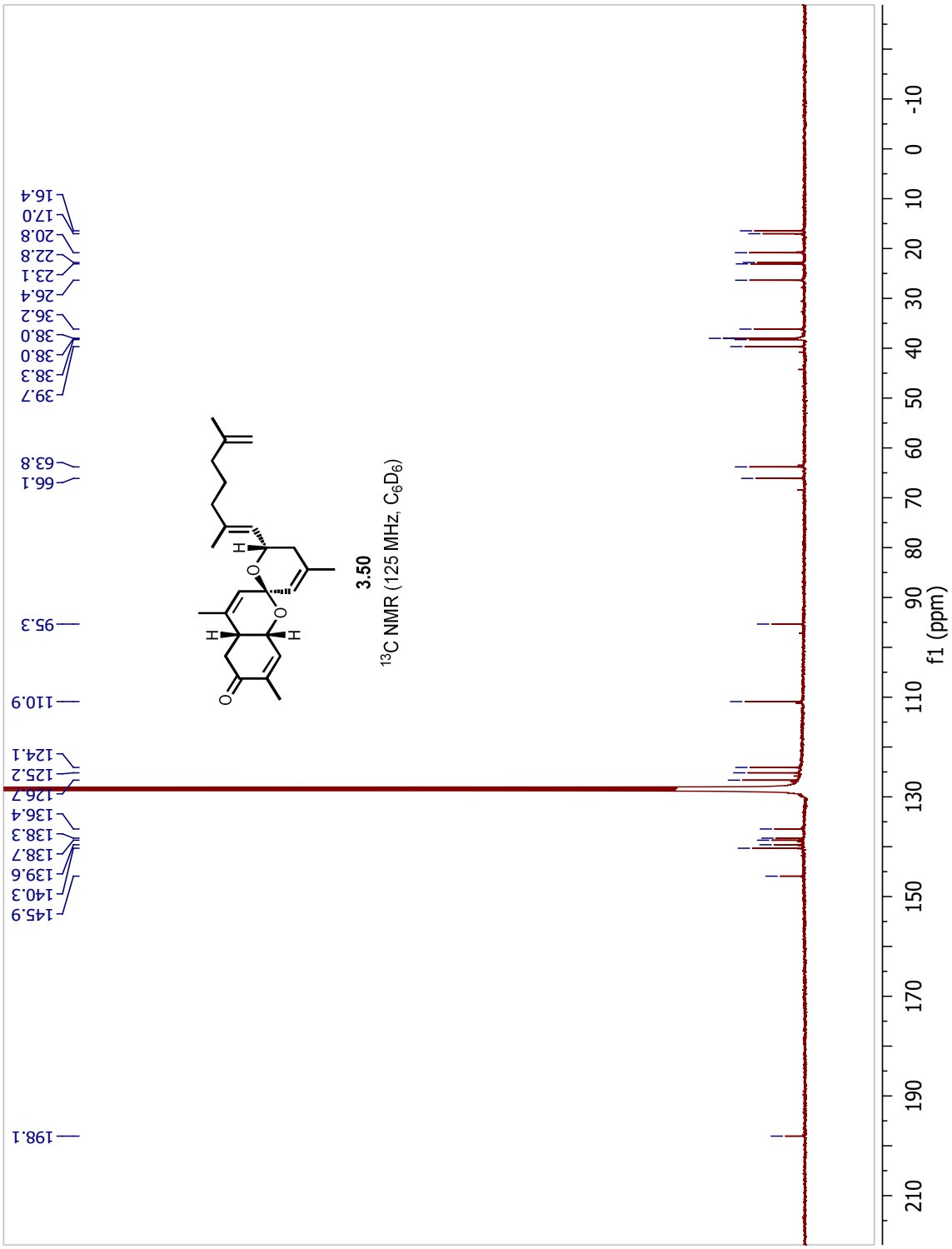

3.49
^{13}C NMR (125 MHz, C_6D_6)
16.4
17.1
20.7
22.8
26.3
30.6
38.0
38.2
39.7
40.8
44.3
63.5
68.5
97.2
110.9
111.2
125.8
127.0
138.6
138.9
139.0
139.7
141.8
145.9
197.8
f1 (ppm)

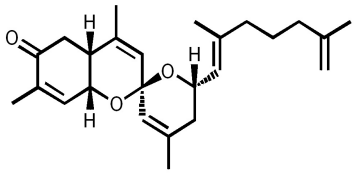


3.49
COSY (500 MHz, C_6D_6)

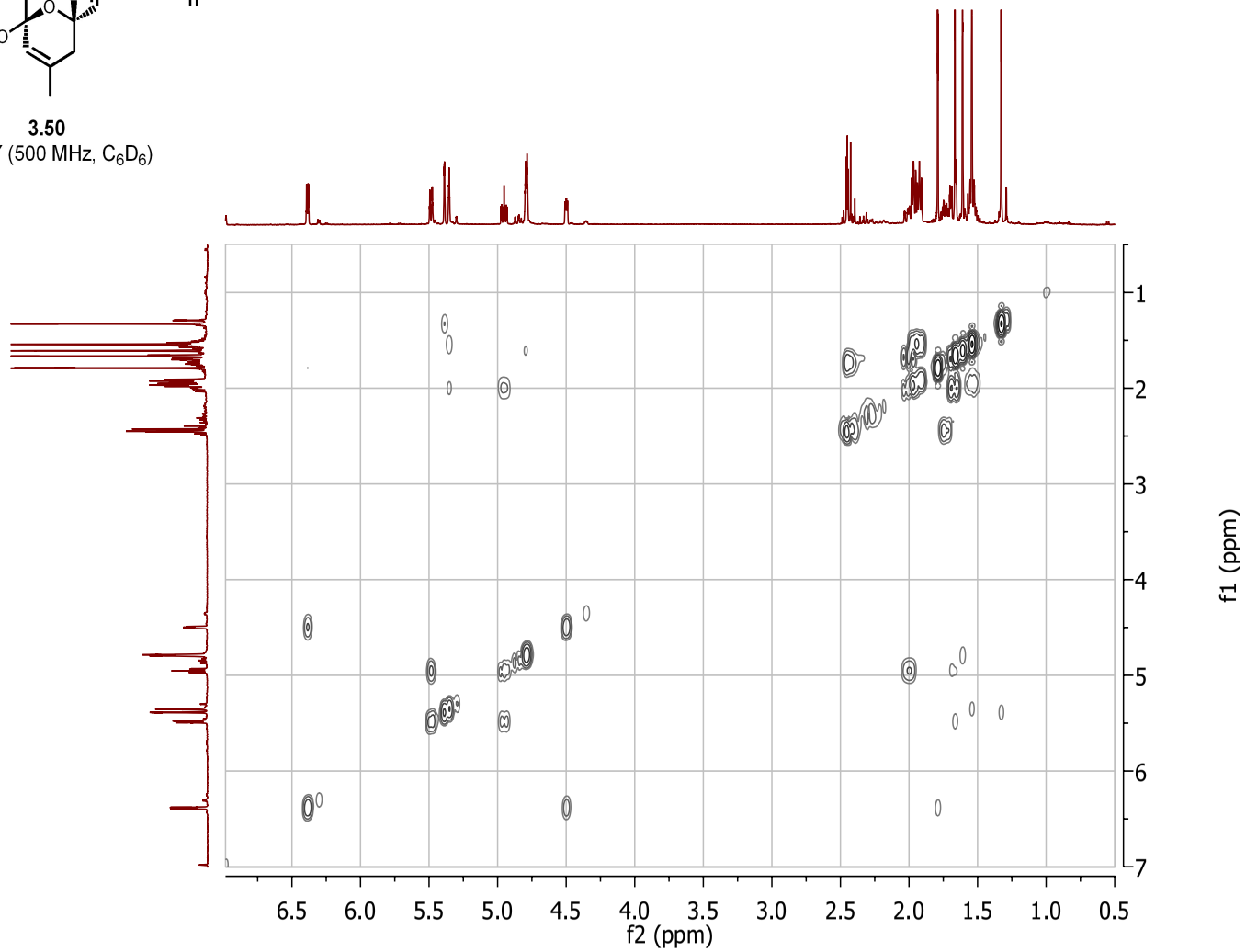


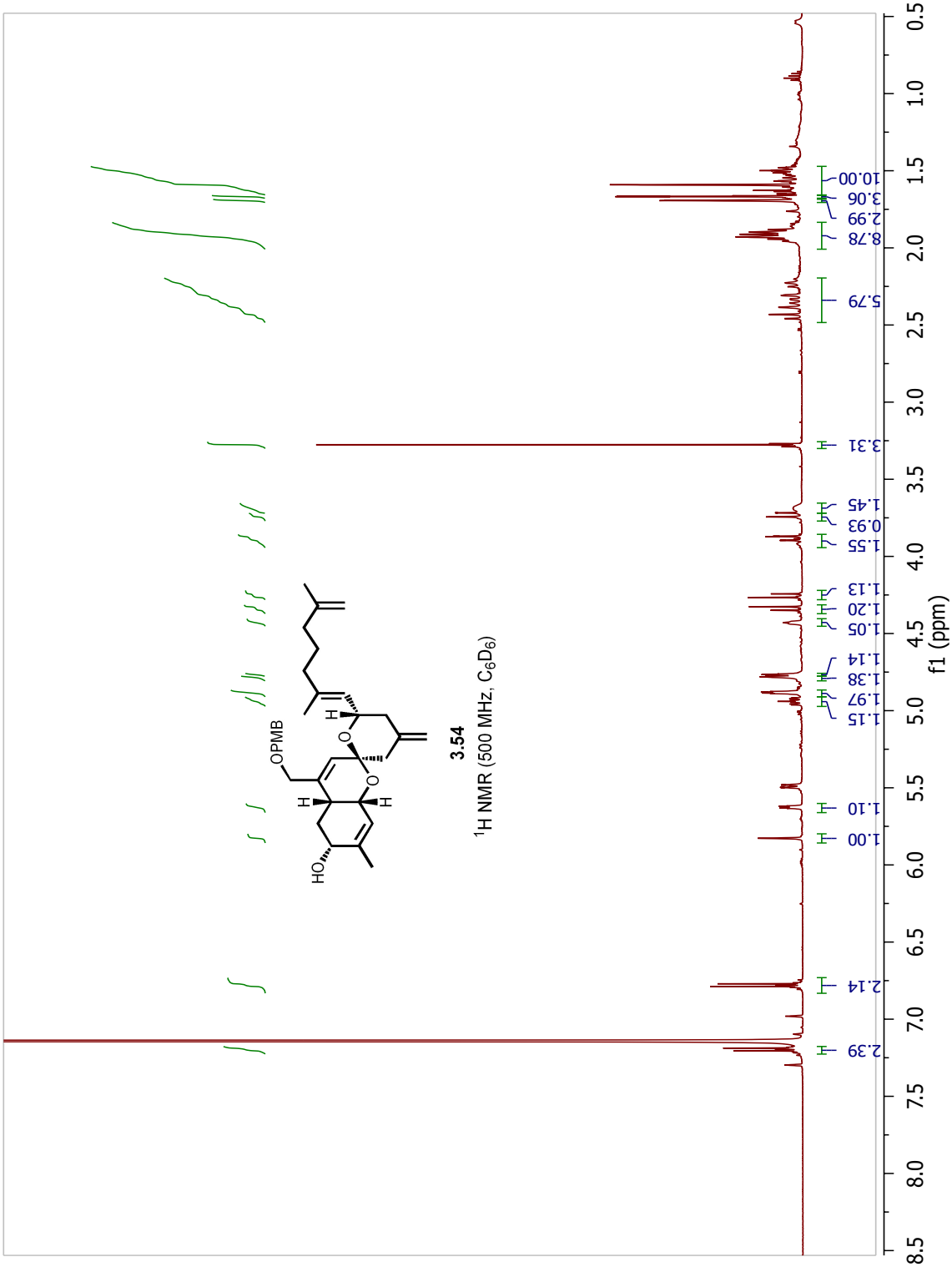

3.50
^{1}H NMR (500 MHz, C_6D_6)
f1 (ppm)
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
1.00
1.13
1.03
1.00
1.10
1.02
1.21
1.03
2.17
6.47
3.20
2.91
3.10
3.21
6.11
3.36

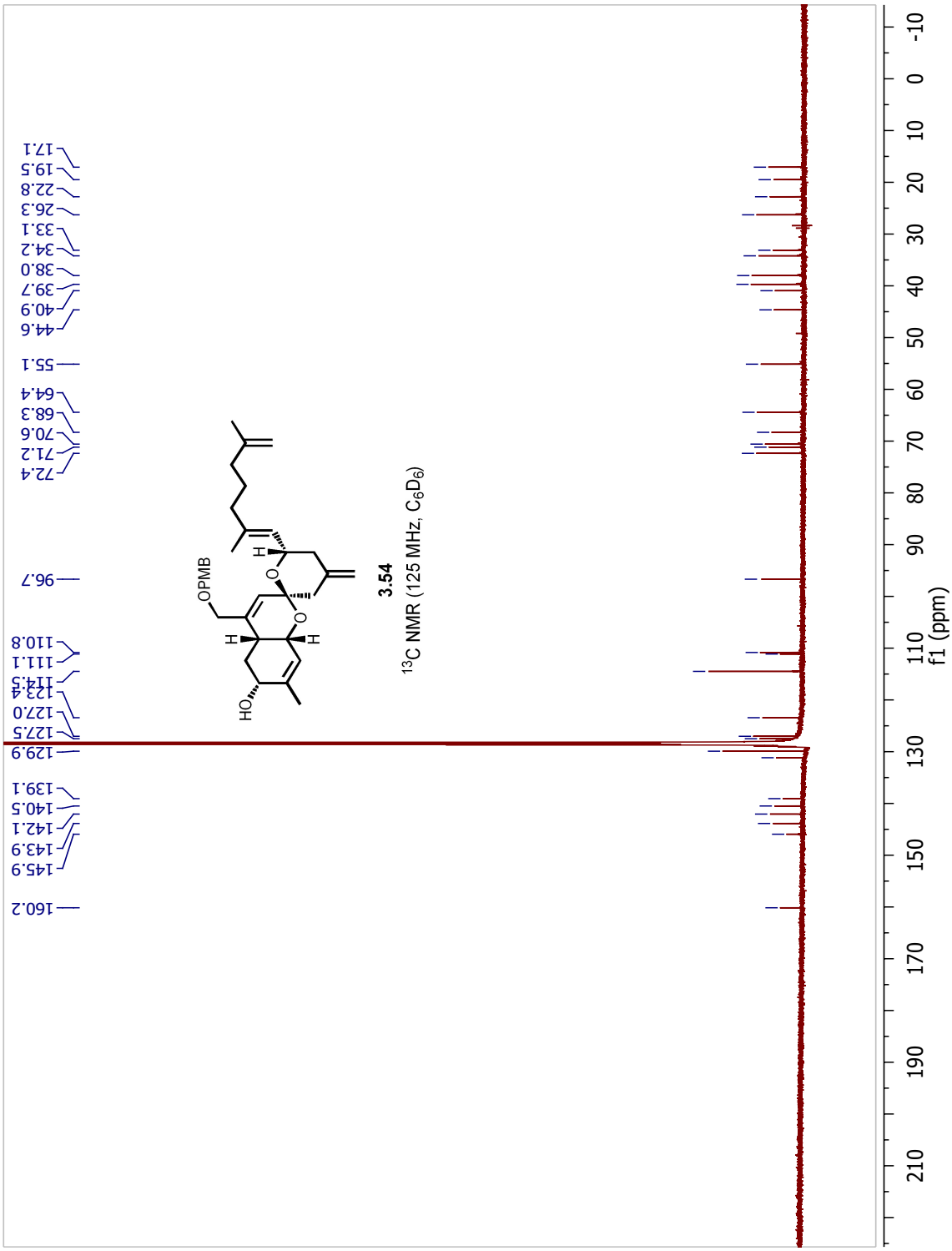

3.50
^{13}C NMR (125 MHz, C_6D_6)
198.1
145.9
140.3
139.6
138.7
138.3
136.4
126.7
125.2
124.1
110.9
95.3
66.1
63.8
39.7
38.3
38.0
38.0
36.2
26.4
23.1
22.8
20.8
17.0
16.4
f1 (ppm)

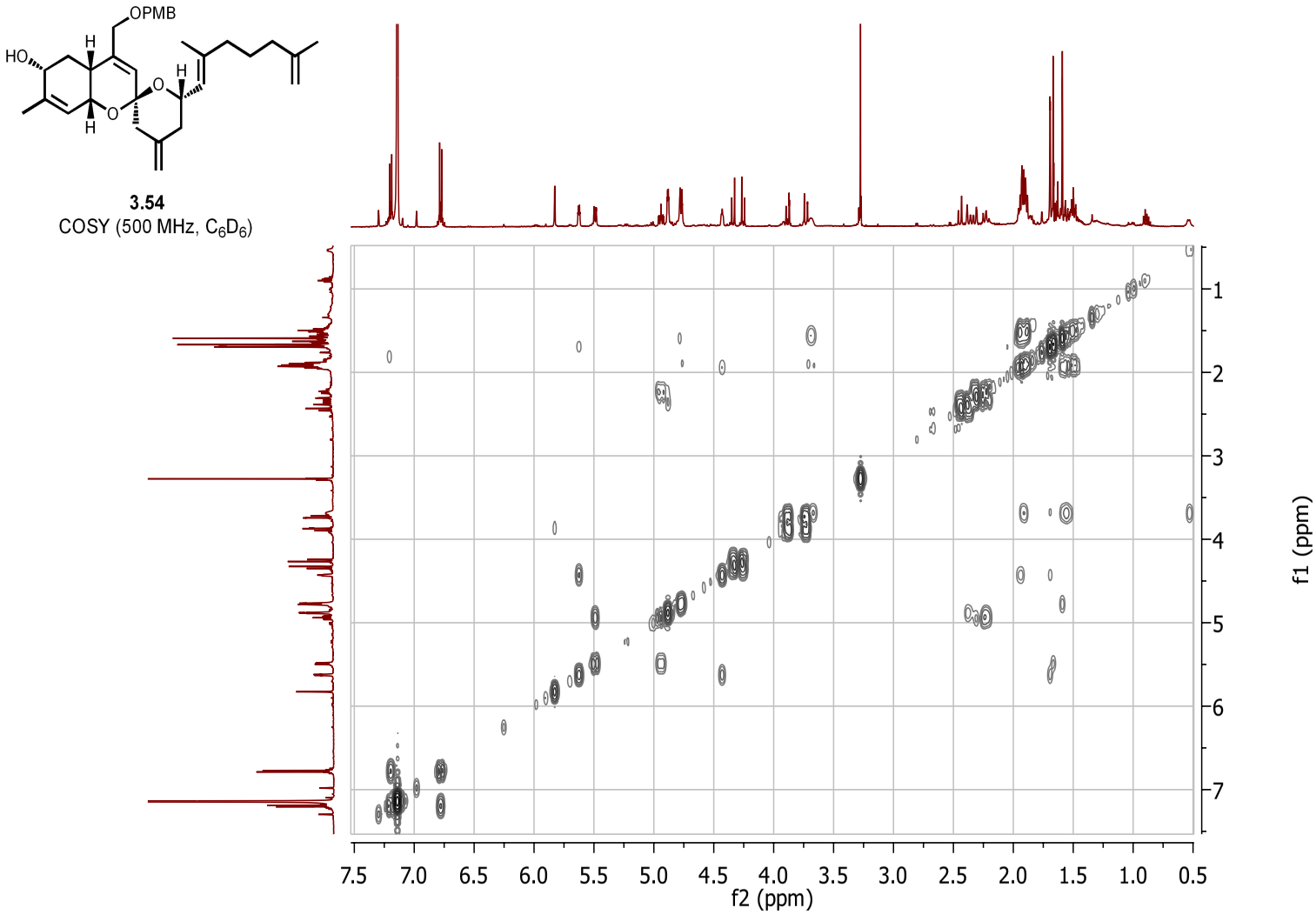


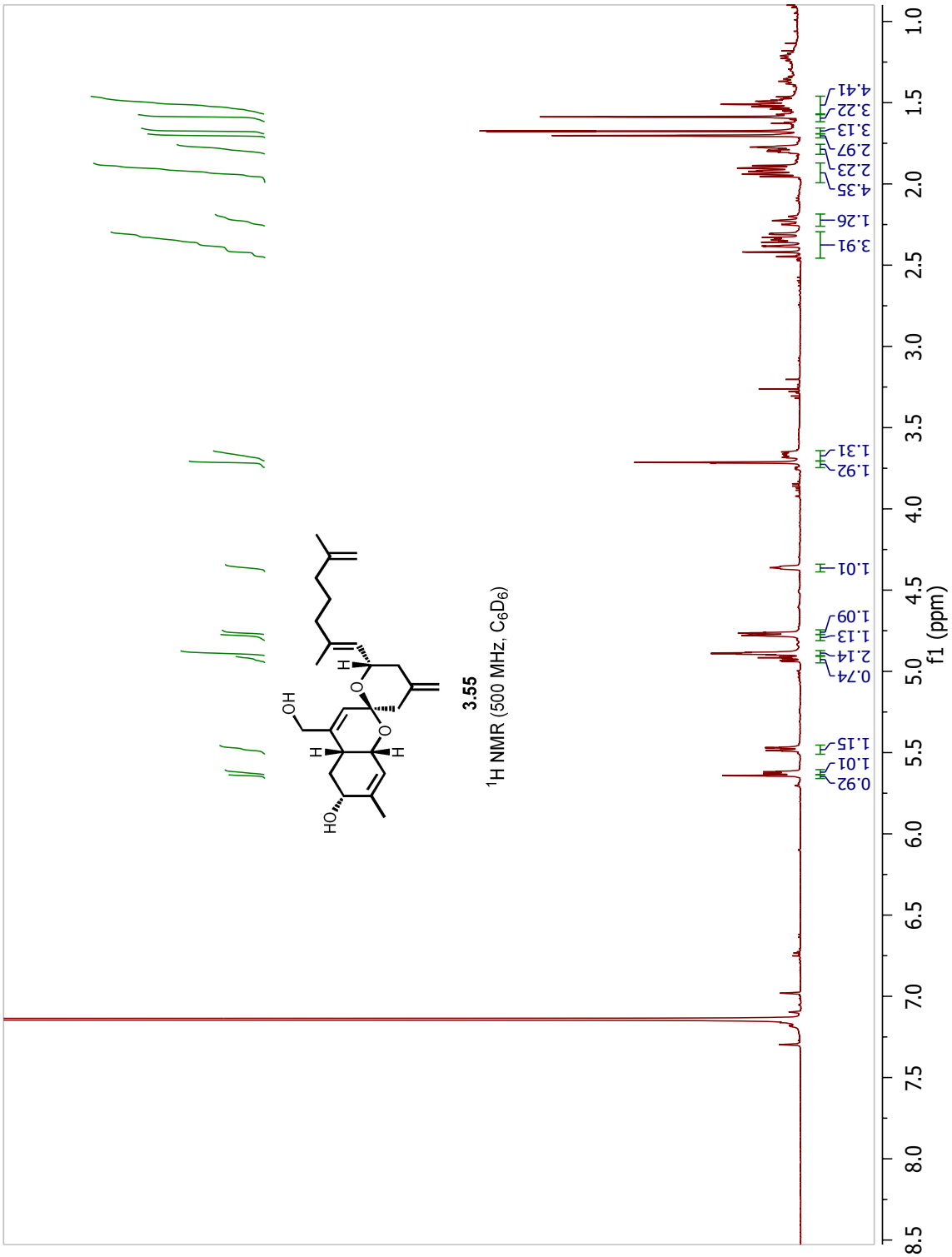
3.50
COSY (500 MHz, C_6D_6)

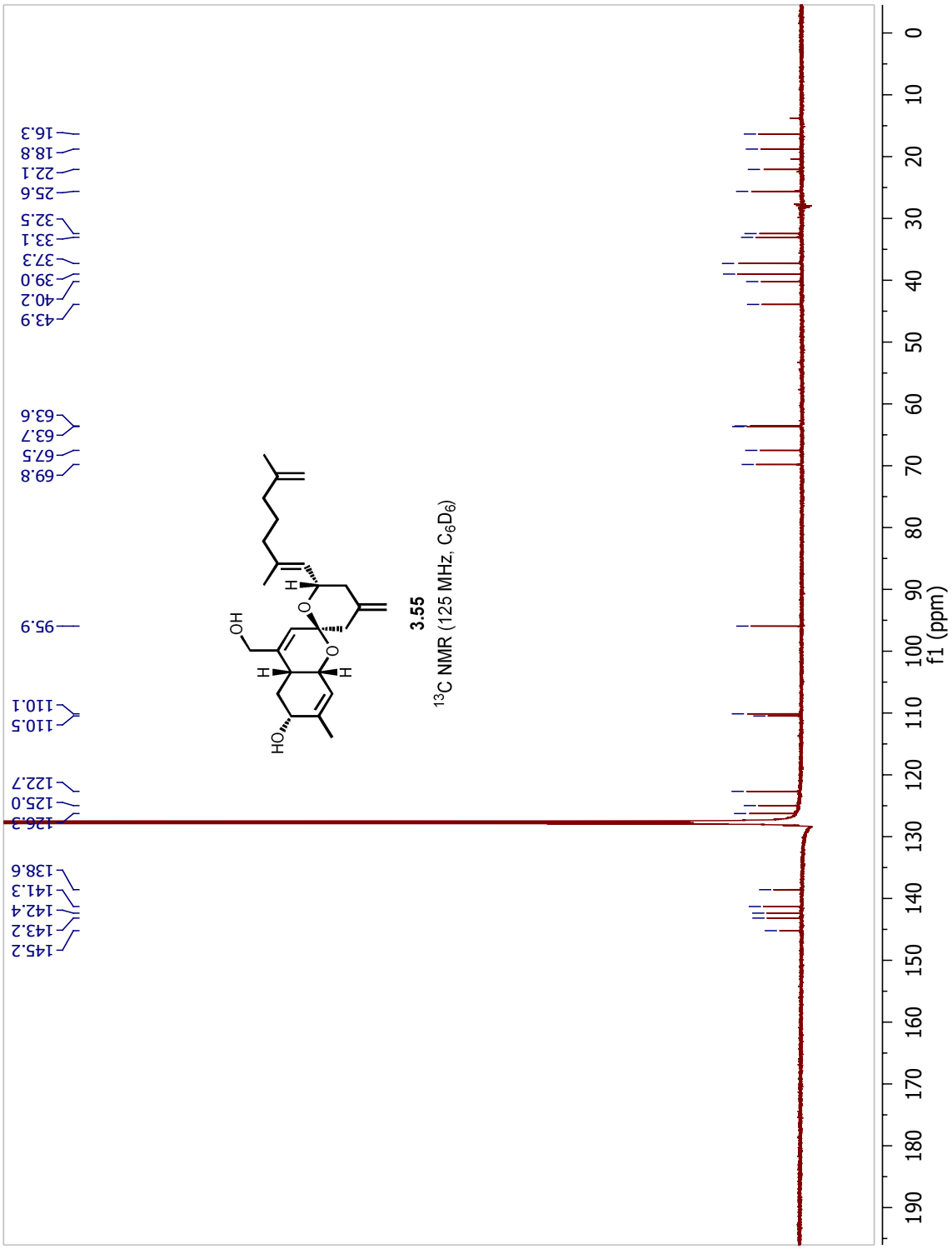


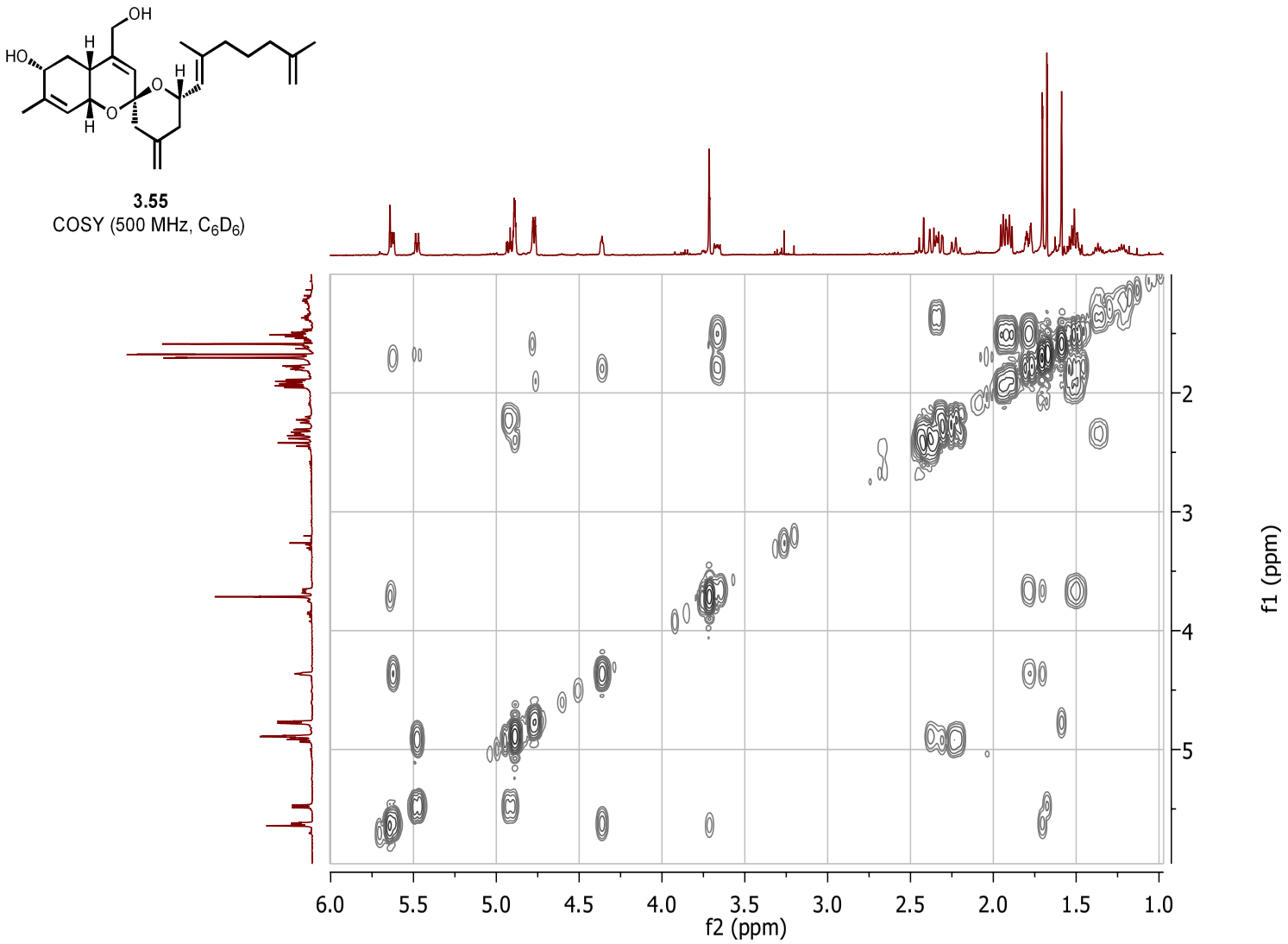

OPMB
HO
H
O
O
H
H
3.54
^{1}H NMR (500 MHz, C_6D_6)
f1 (ppm)
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
2.39
2.14
1.00
1.10
1.15
1.97
1.38
1.14
1.05
1.20
1.13
1.55
0.93
1.45
3.31
5.79
8.78
2.99
3.06
10.00

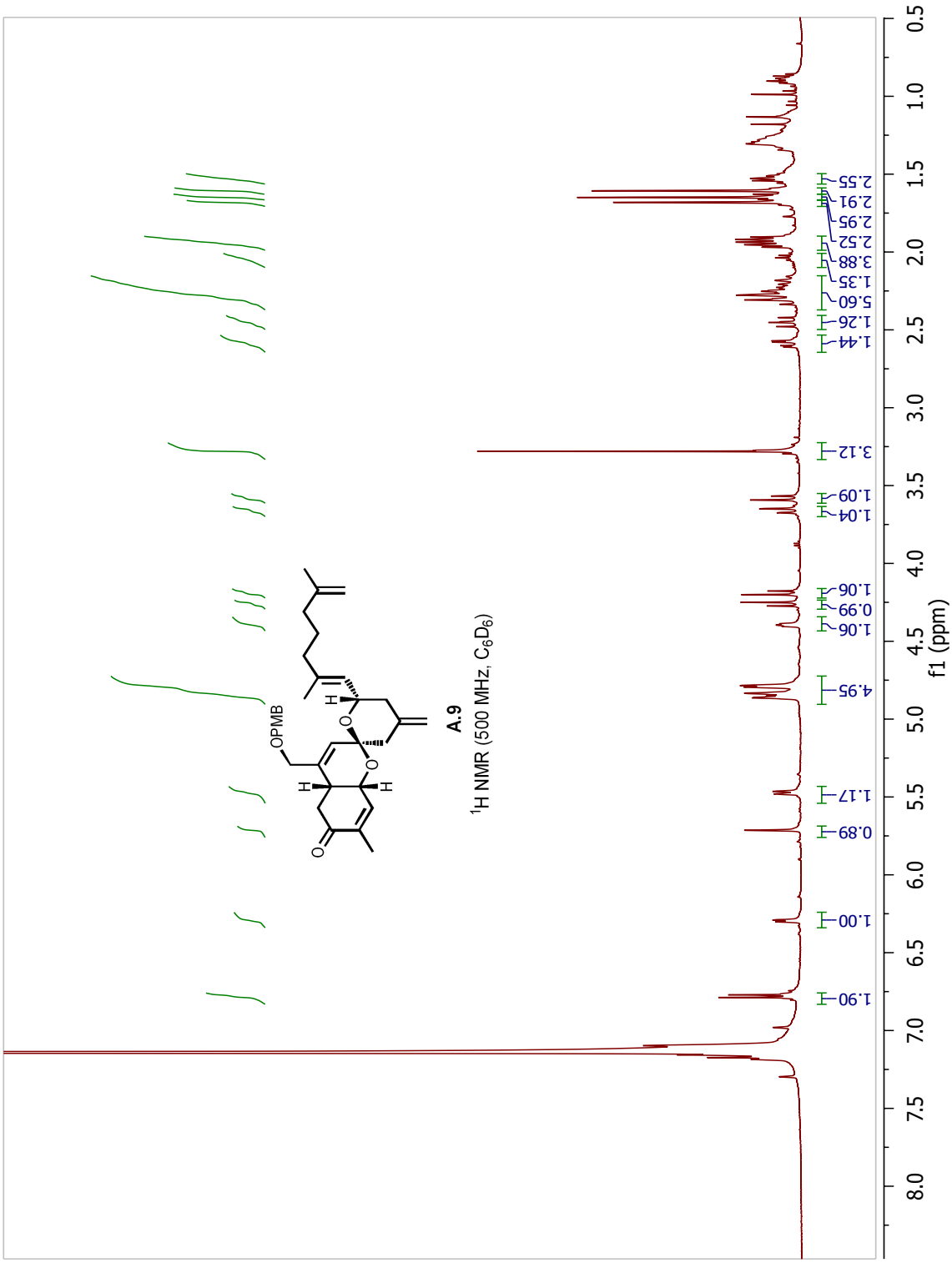

17.1
19.5
22.8
26.3
33.1
34.2
38.0
39.7
40.9
44.6
55.1
64.4
68.3
70.6
71.2
72.4
96.7
110.8
111.1
114.5
123.4
127.0
127.5
129.9
139.1
140.5
142.1
143.9
145.9
160.2
OPMB
HO
H
O
O
H
H
3.54
13C NMR (125 MHz, C6D6)
-10
0
10
20
30
40
50
60
70
80
90
110
130
150
170
190
210
f1 (ppm)

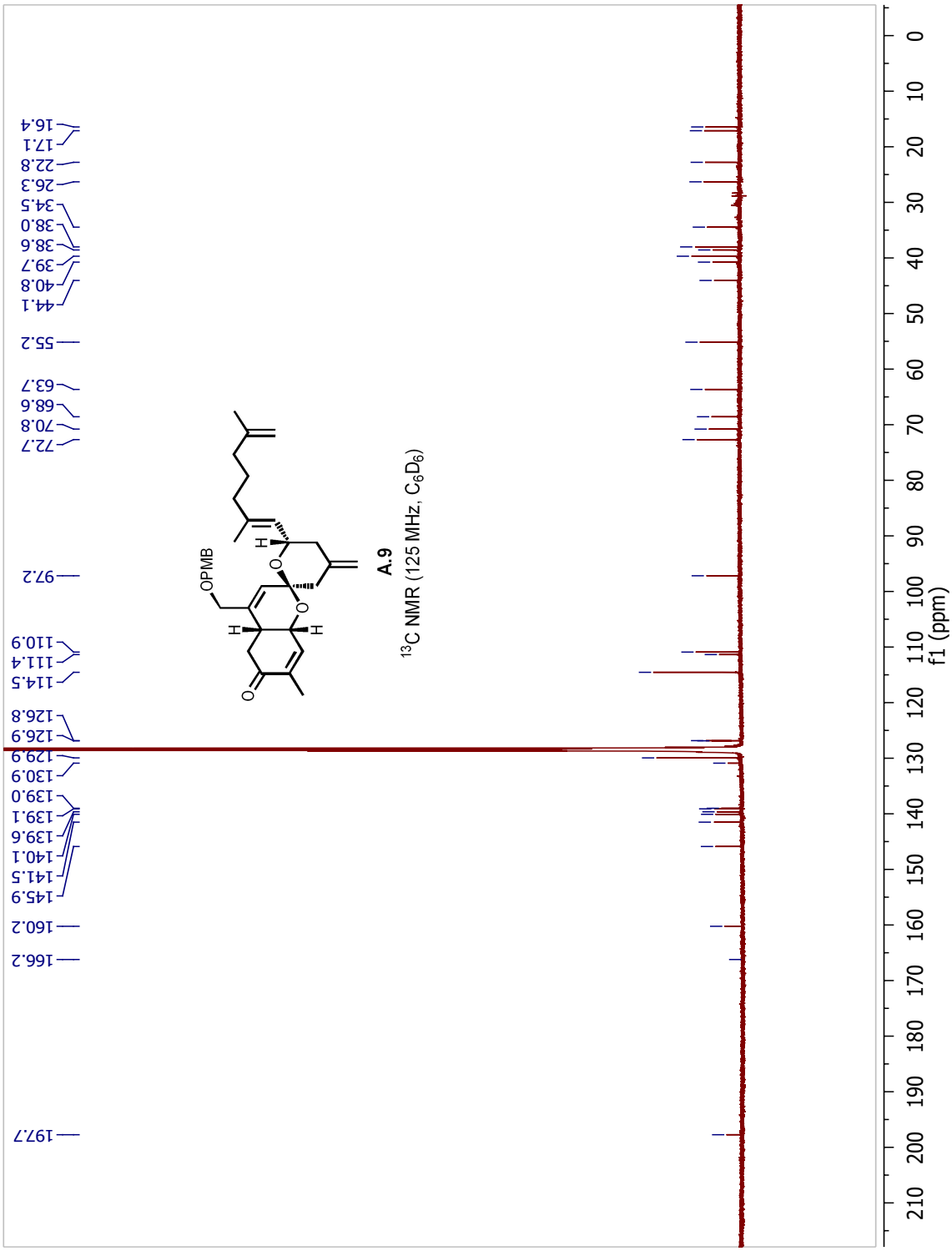

OPMB
HO
H
H
H
O
O
3.54
COSY (500 MHz, C6D6)
f2 (ppm)
f1 (ppm)

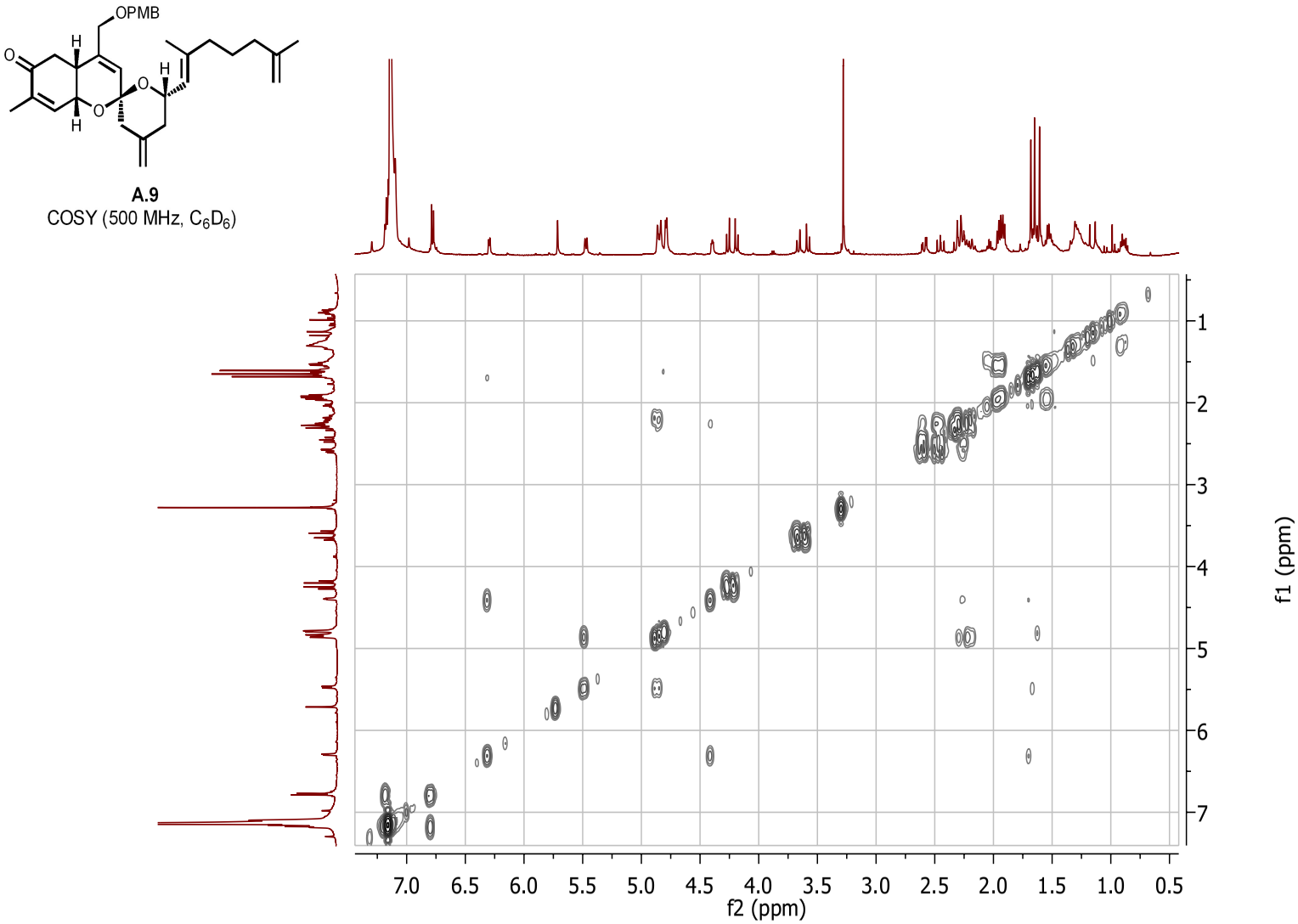

3.55
^{1}H NMR (500 MHz, C_6D_6)
HO
OH
H
O
O
H
H
0.92
1.01
1.15
0.74
2.14
1.13
1.09
1.01
1.92
1.31
3.91
1.26
4.35
2.23
2.97
3.13
3.22
4.41
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)

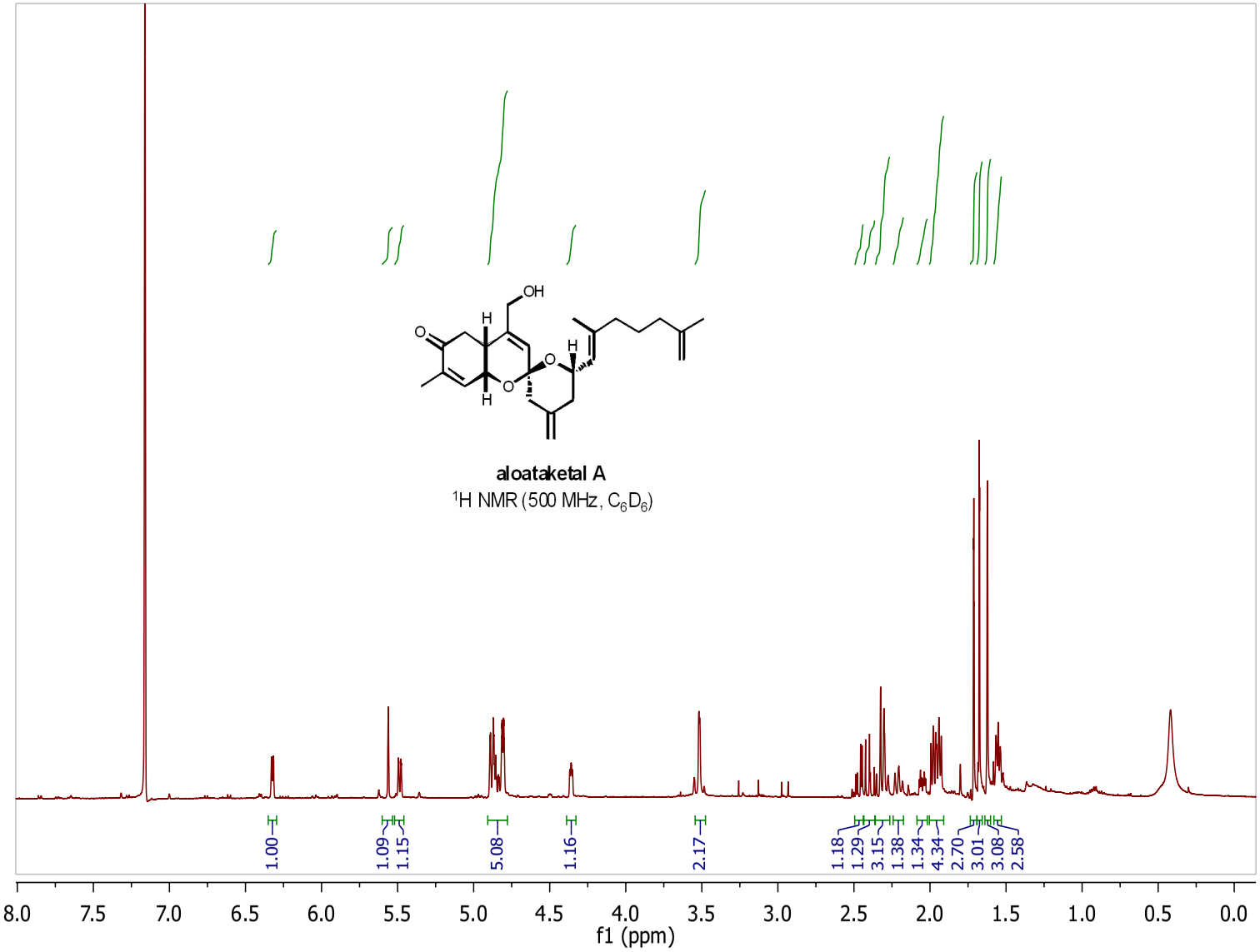

145.2
143.2
142.4
141.3
138.6
126.3
125.0
122.7
110.5
110.1
95.9
69.8
67.5
63.7
63.6
43.9
40.2
39.0
37.3
33.1
32.5
25.6
22.1
18.8
16.3
OH
HO
H
O
O
H
H
O
3.55
^{13}C NMR (125 MHz, C_6D_6)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
f1 (ppm)

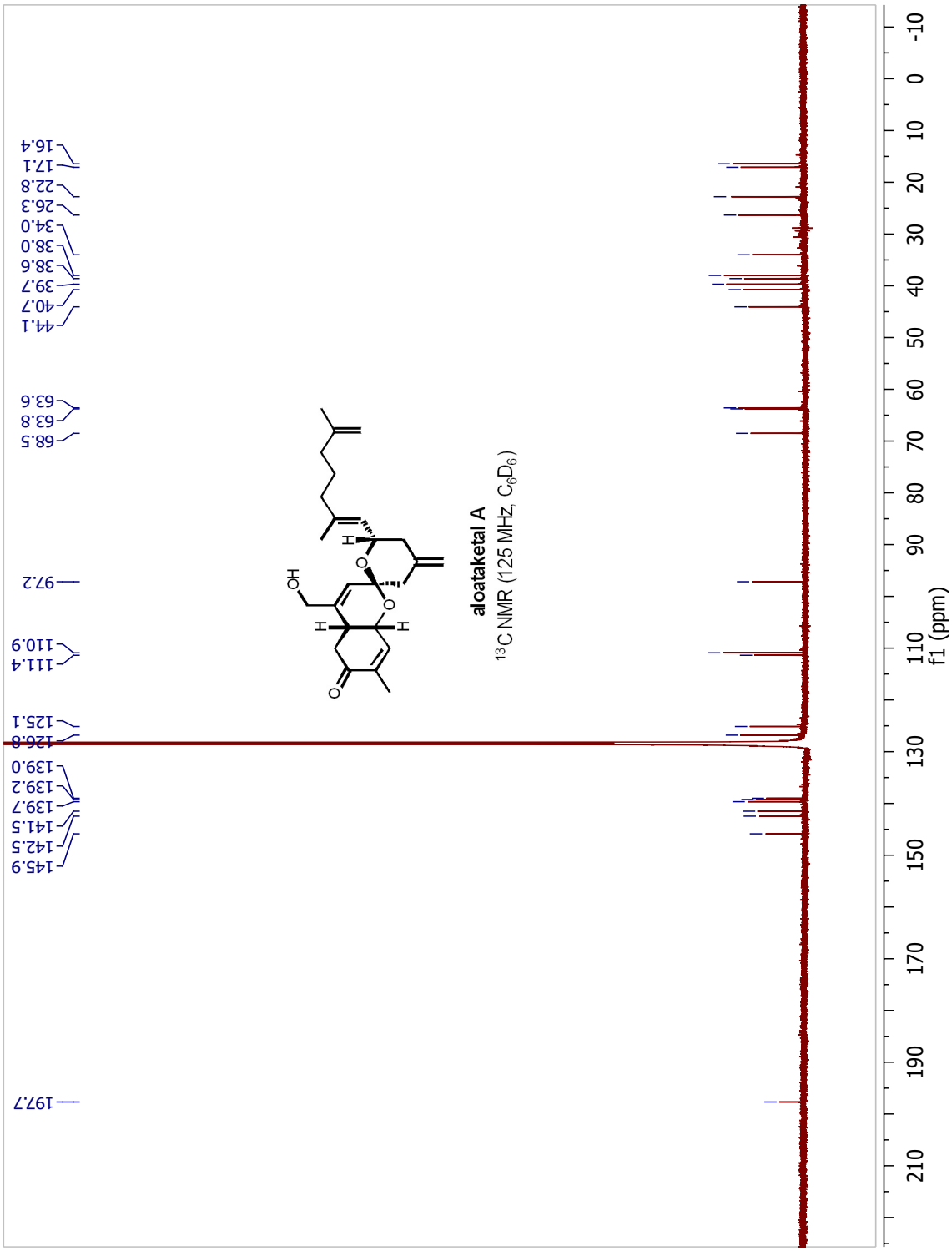

OH
HO
H
H
O
O
H
3.55
COSY (500 MHz, C6D6)
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f2 (ppm)
2
3
4
5
f1 (ppm)

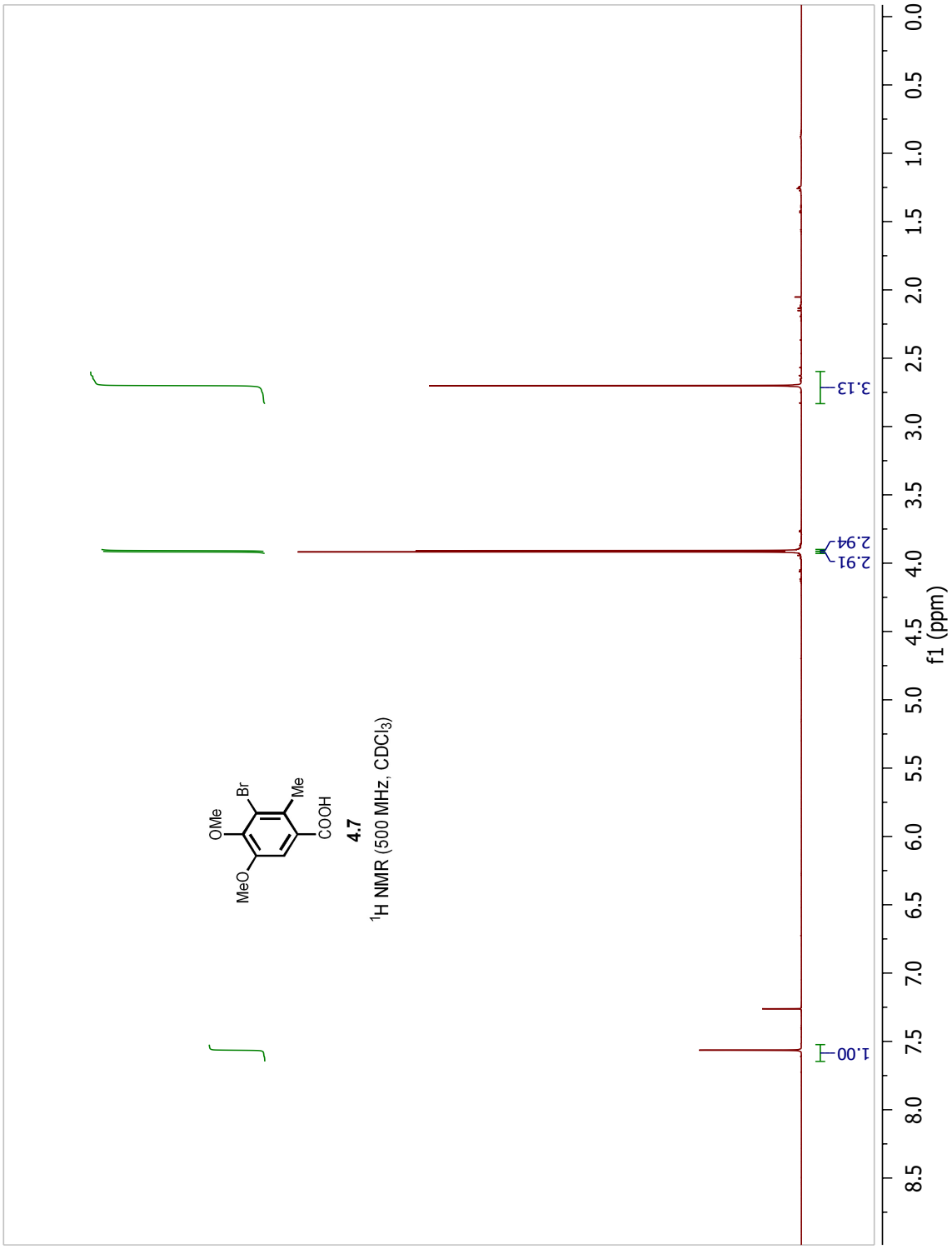

OPMB
O
H
O
O
H
H
O
A.9
^{1}H NMR (500 MHz, C_6D_6)
1.90
1.00
0.89
1.17
4.95
1.06
0.99
1.06
1.04
1.09
3.12
1.44
1.26
5.60
1.35
3.88
2.52
2.95
2.91
2.55
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

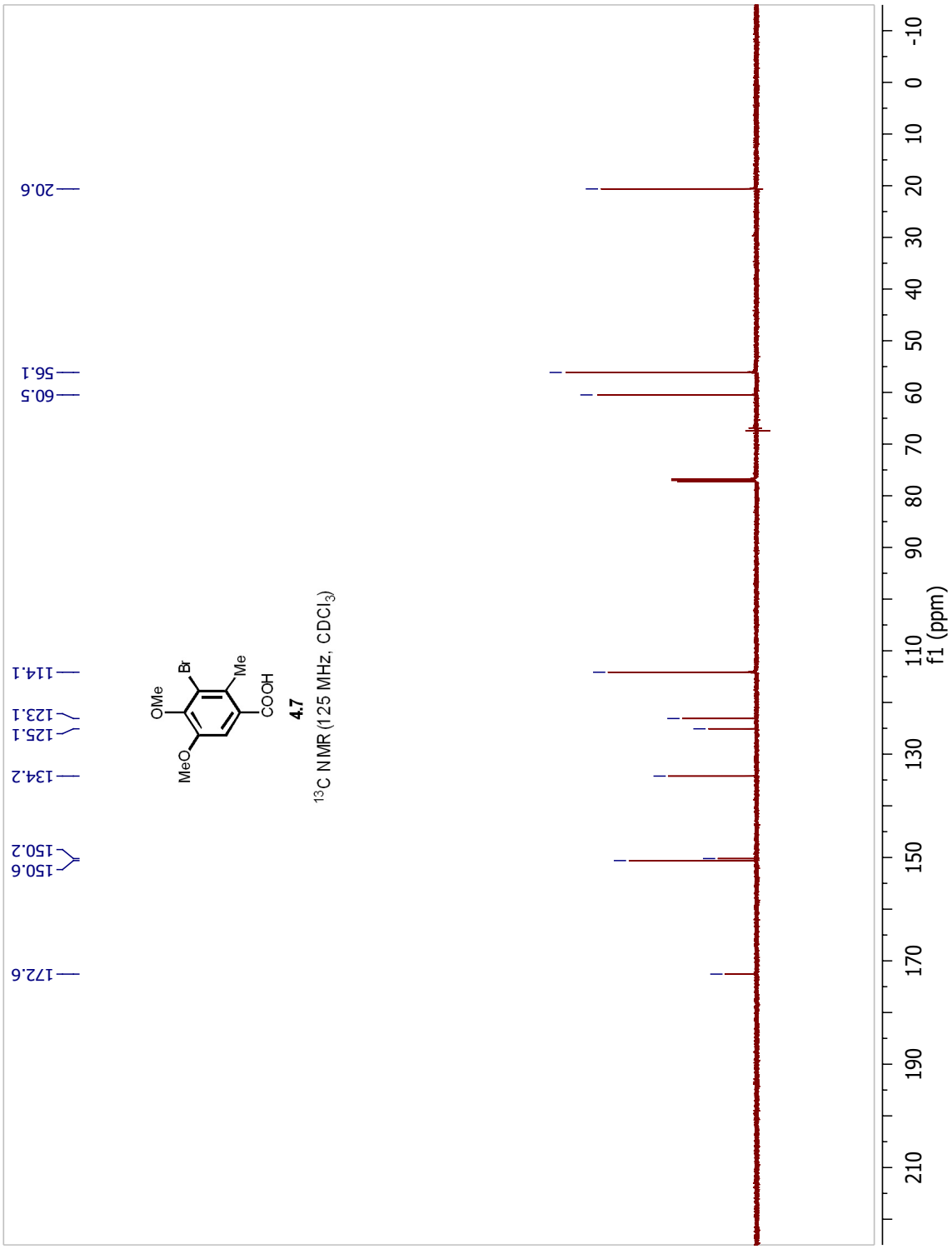

OPMB
O
O
O
H
H
H
A.9
^{13}C NMR (125 MHz, C_6D_6)
197.7
166.2
160.2
145.9
141.5
140.1
139.6
139.1
139.0
130.9
129.9
126.9
126.8
114.5
111.4
110.9
97.2
72.7
70.8
68.6
63.7
55.2
44.1
40.8
39.7
38.6
38.0
34.5
26.3
22.8
17.1
16.4
f1 (ppm)

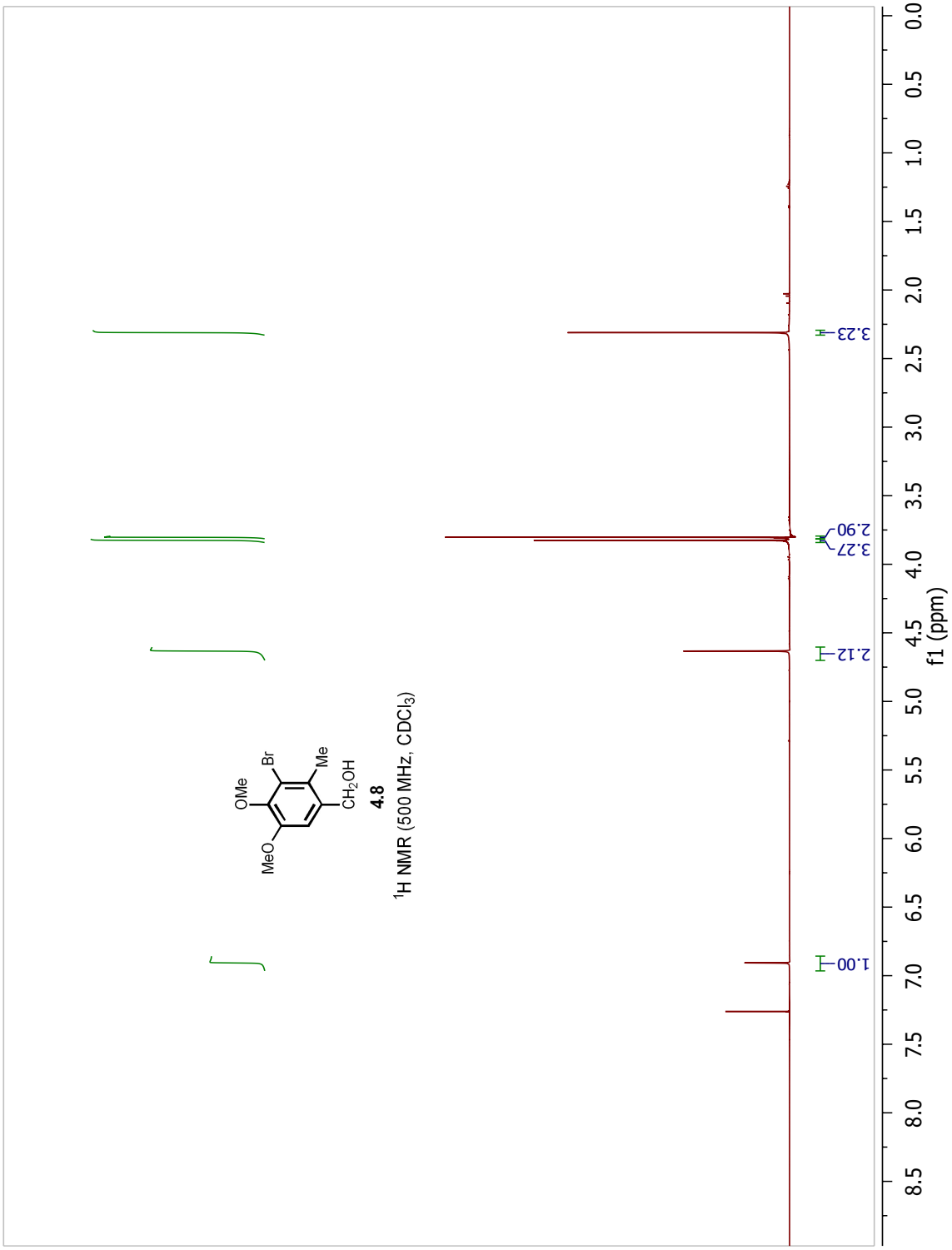

OPMB
H
O
H
O
O
H
A.9
COSY (500 MHz, C6D6)
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f2 (ppm)
1
2
3
4
5
6
7
f1 (ppm)

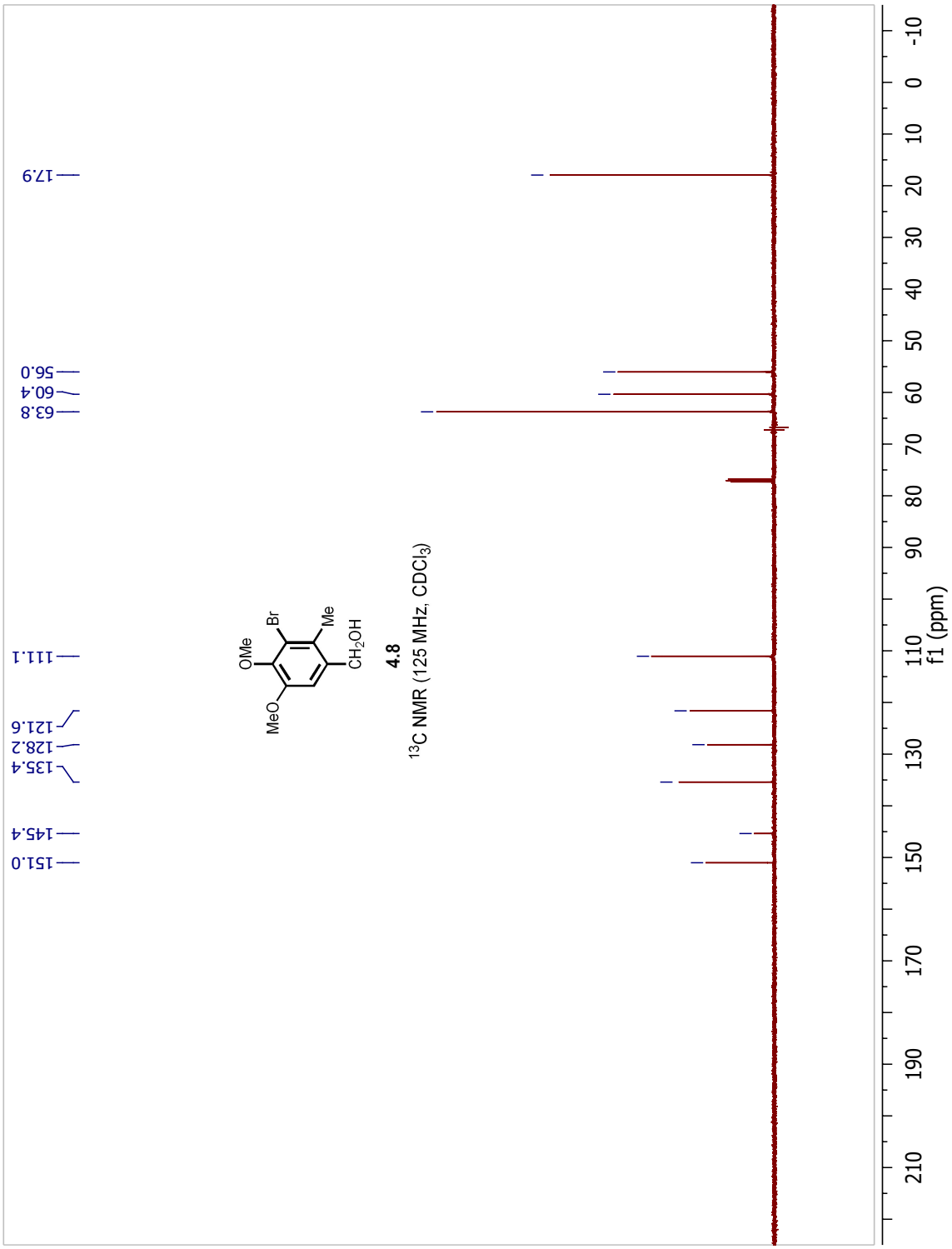

OH
H
O
H
O
O
H
aloataketal A
1H NMR (500 MHz, C6D6)
1.00
1.09
1.15
5.08
1.16
2.17
1.18
1.29
3.15
1.38
1.34
4.34
2.70
3.01
3.08
2.58
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

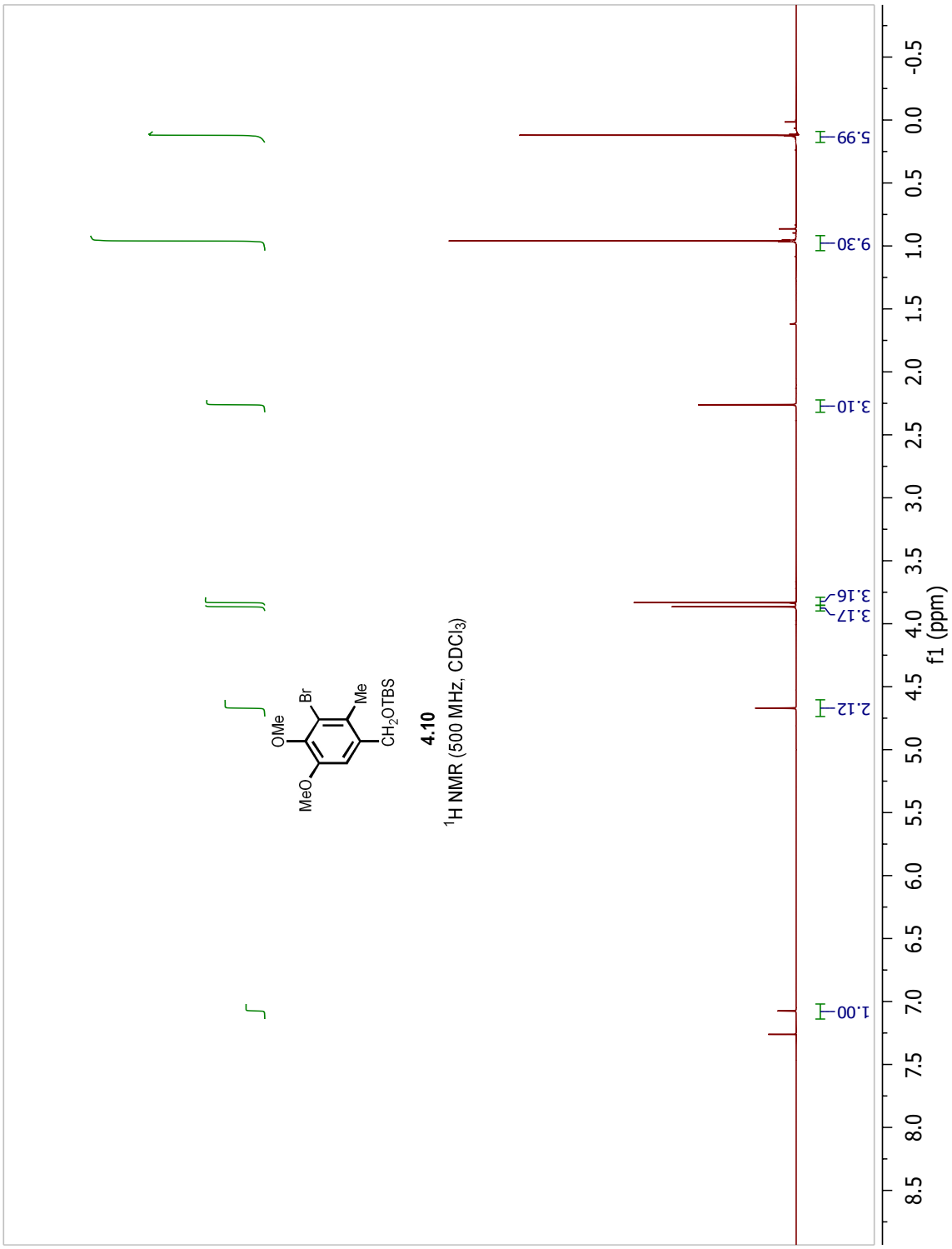

aloataketal A
^{13}C NMR (125 MHz, C_6D_6)
f1 (ppm)
-10
0
10
20
30
40
50
60
70
80
90
110
130
150
170
190
210
16.4
17.1
22.8
26.3
34.0
38.0
38.6
39.7
40.7
44.1
63.6
63.8
68.5
97.2
110.9
111.4
125.1
126.8
139.0
139.2
139.7
141.5
142.5
145.9
197.7

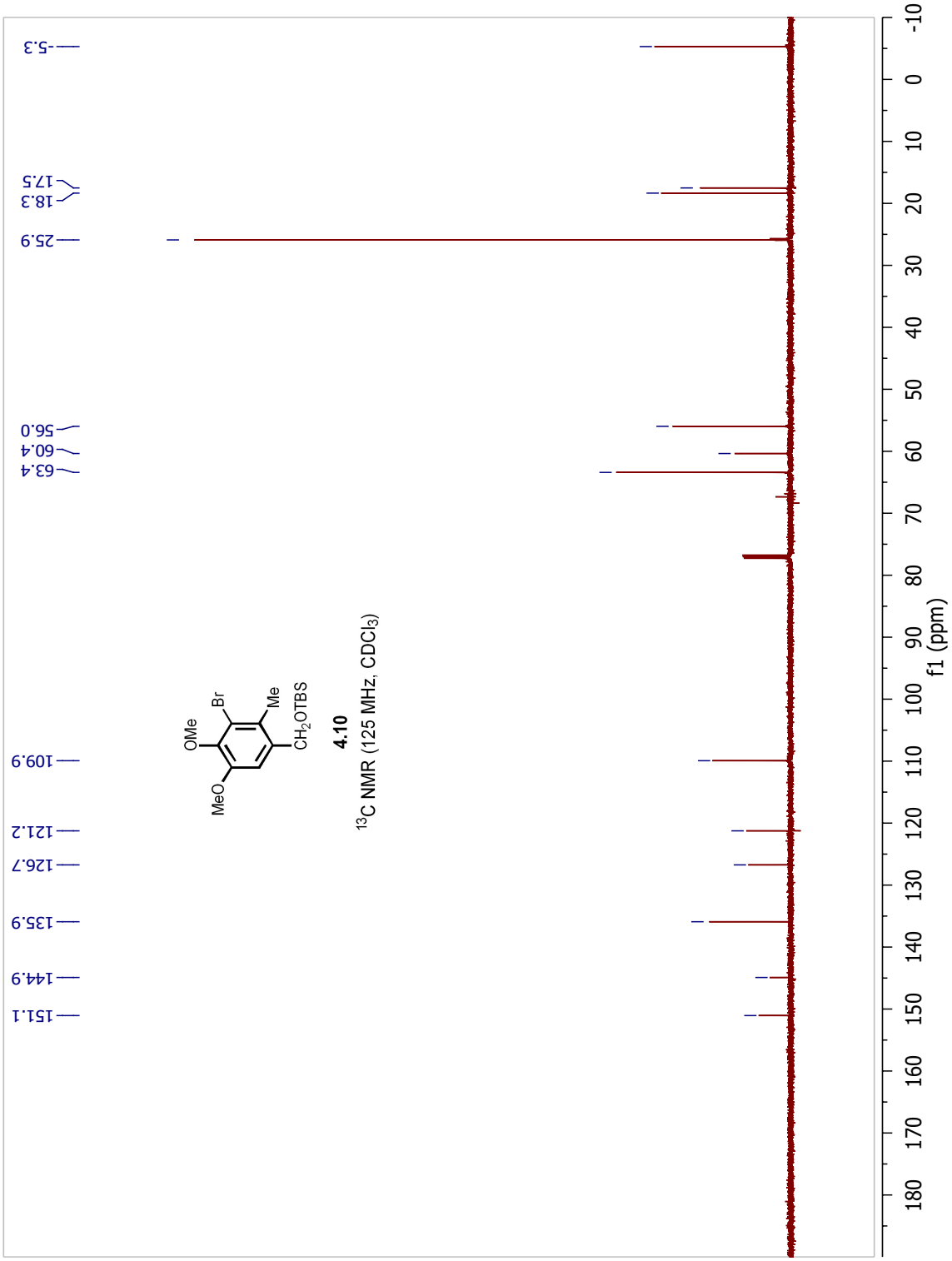

OMe
Br
Me
COOH
MeO
4.7
^{1}H NMR (500 MHz, $CDCl_3$)
3.13
2.91
2.94
1.00
f1 (ppm)

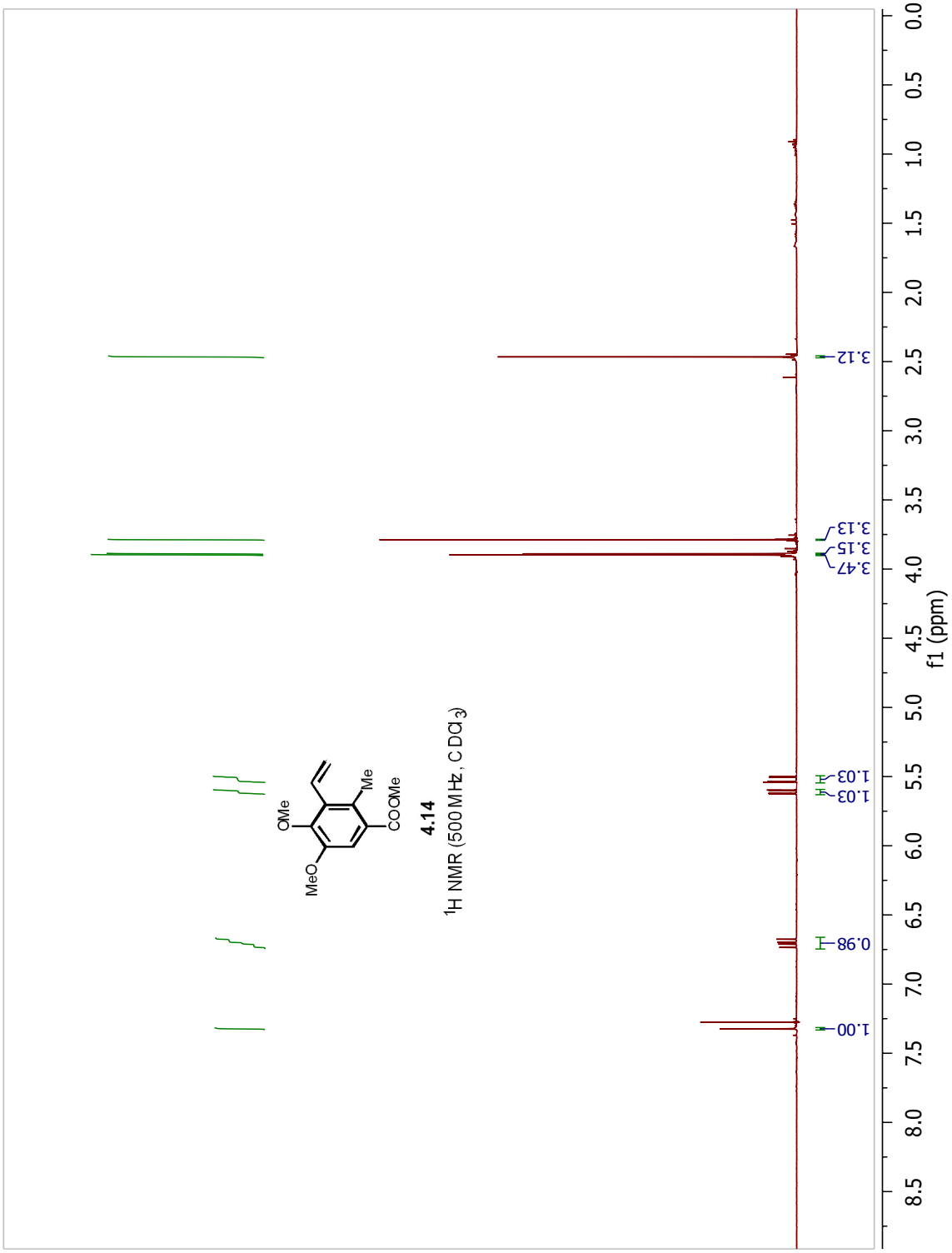

20.6
56.1
60.5
114.1
123.1
125.1
134.2
150.2
150.6
172.6
OMe
Br
Me
COOH
MeO
4.7
^{13}C NMR (125 MHz, $CDCl_3$)
f1 (ppm)

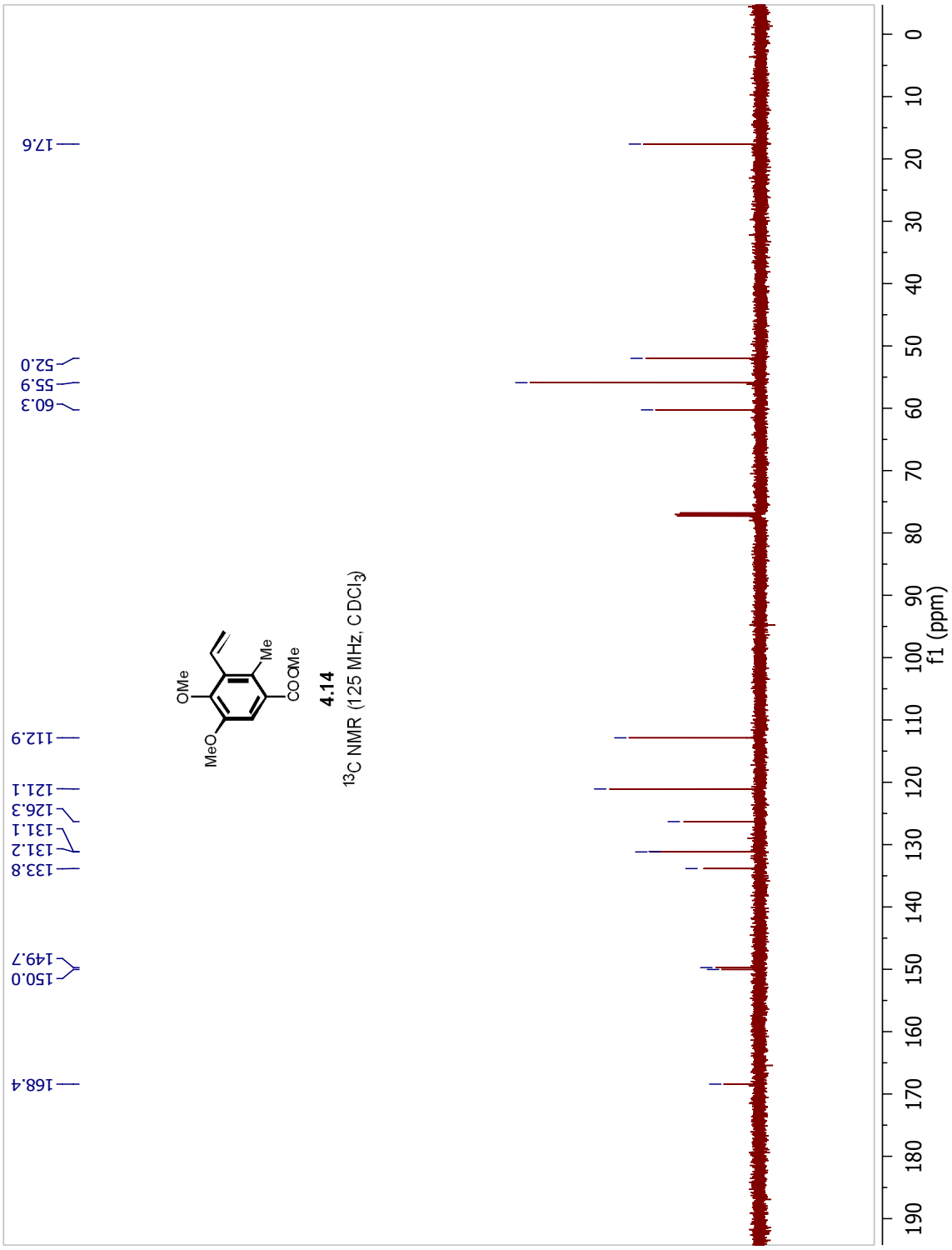

OMe
Br
Me
MeO
CH2OH
4.8
1H NMR (500 MHz, CDCl3)
3.23
3.27
2.90
2.12
1.00
f1 (ppm)

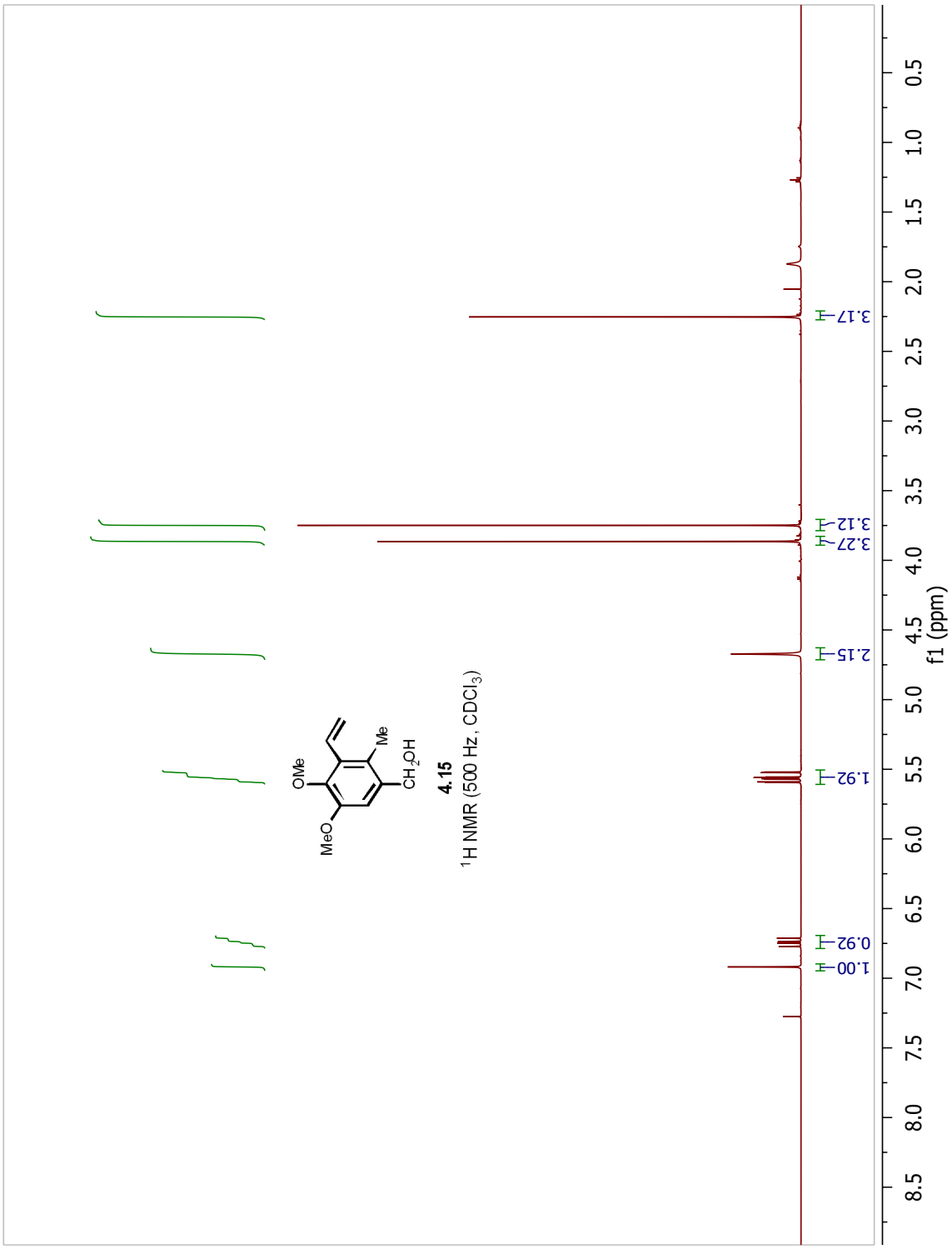

17.9
56.0
60.4
63.8
111.1
121.6
128.2
135.4
145.4
151.0
OMe
Br
Me
MeO
CH2OH
4.8
13C NMR (125 MHz, CDCl3)
f1 (ppm)

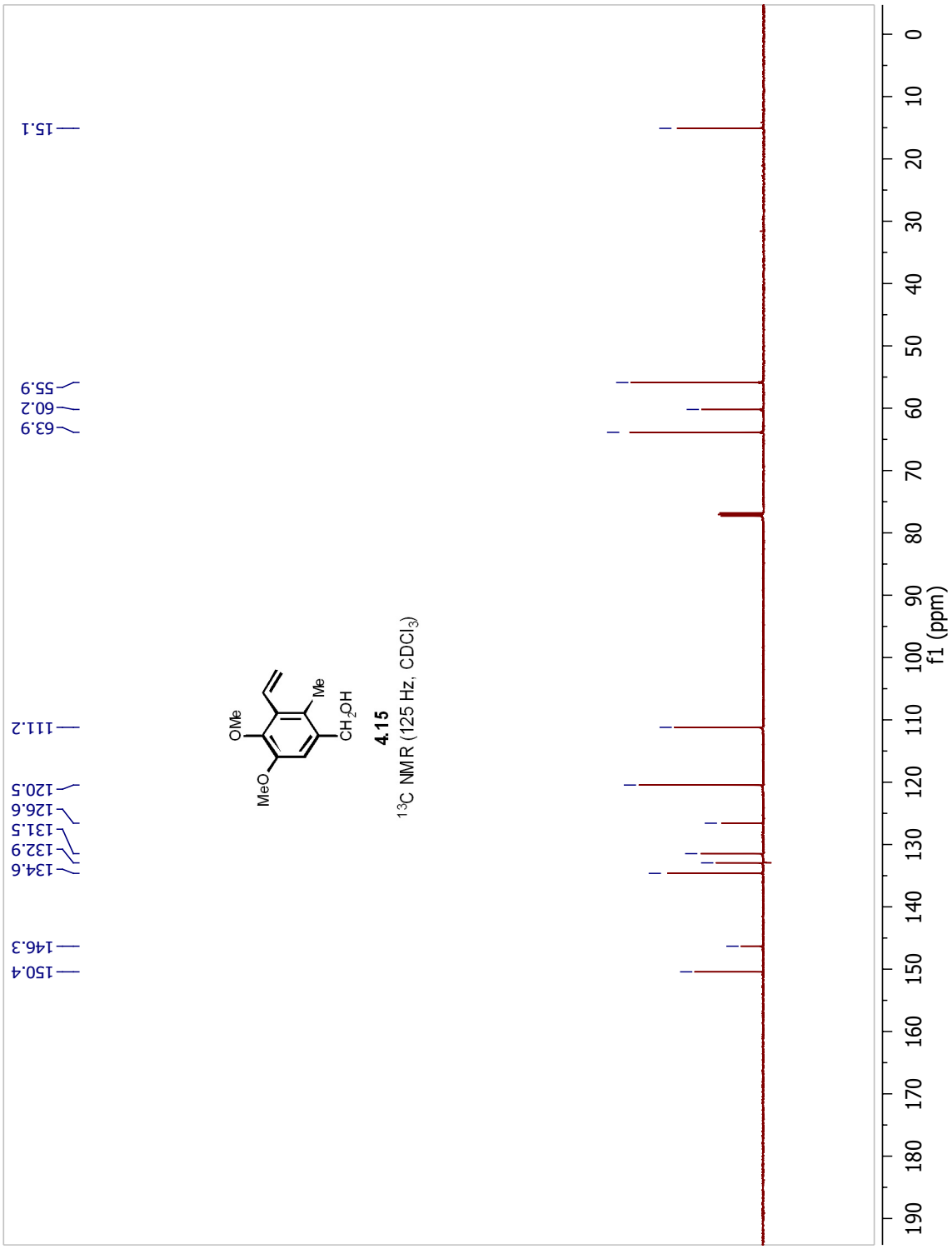

OMe
Br
Me
MeO
CH2OTBS
4.10
1H NMR (500 MHz, CDCl3)
5.99
9.30
3.10
3.17
3.16
2.12
1.00
f1 (ppm)

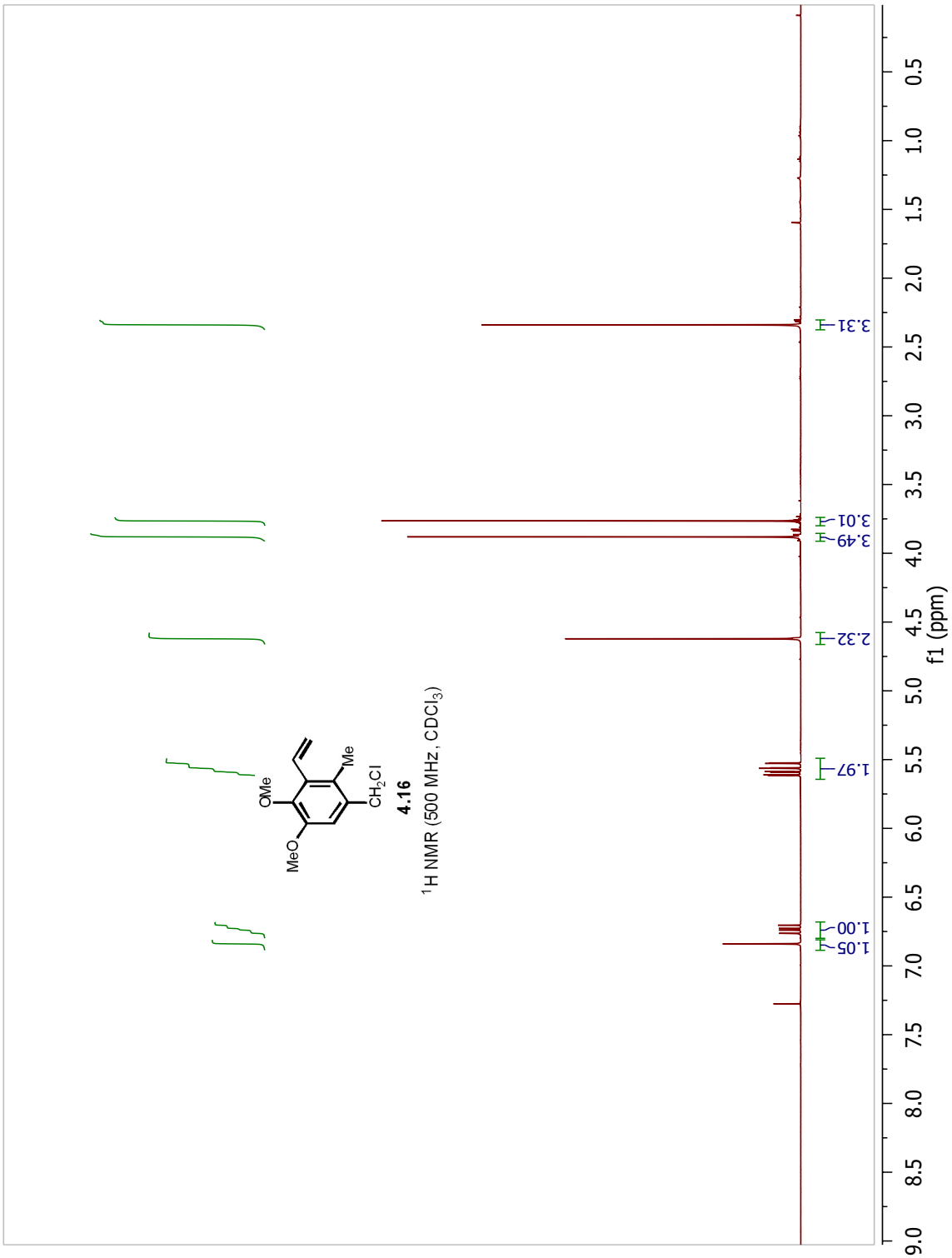

-5.3
17.5
18.3
25.9
56.0
60.4
63.4
109.9
121.2
126.7
135.9
144.9
151.1
OMe
Br
Me
CH2OTBS
MeO
4.10
13C NMR (125 MHz, CDCl3)
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
f1 (ppm)

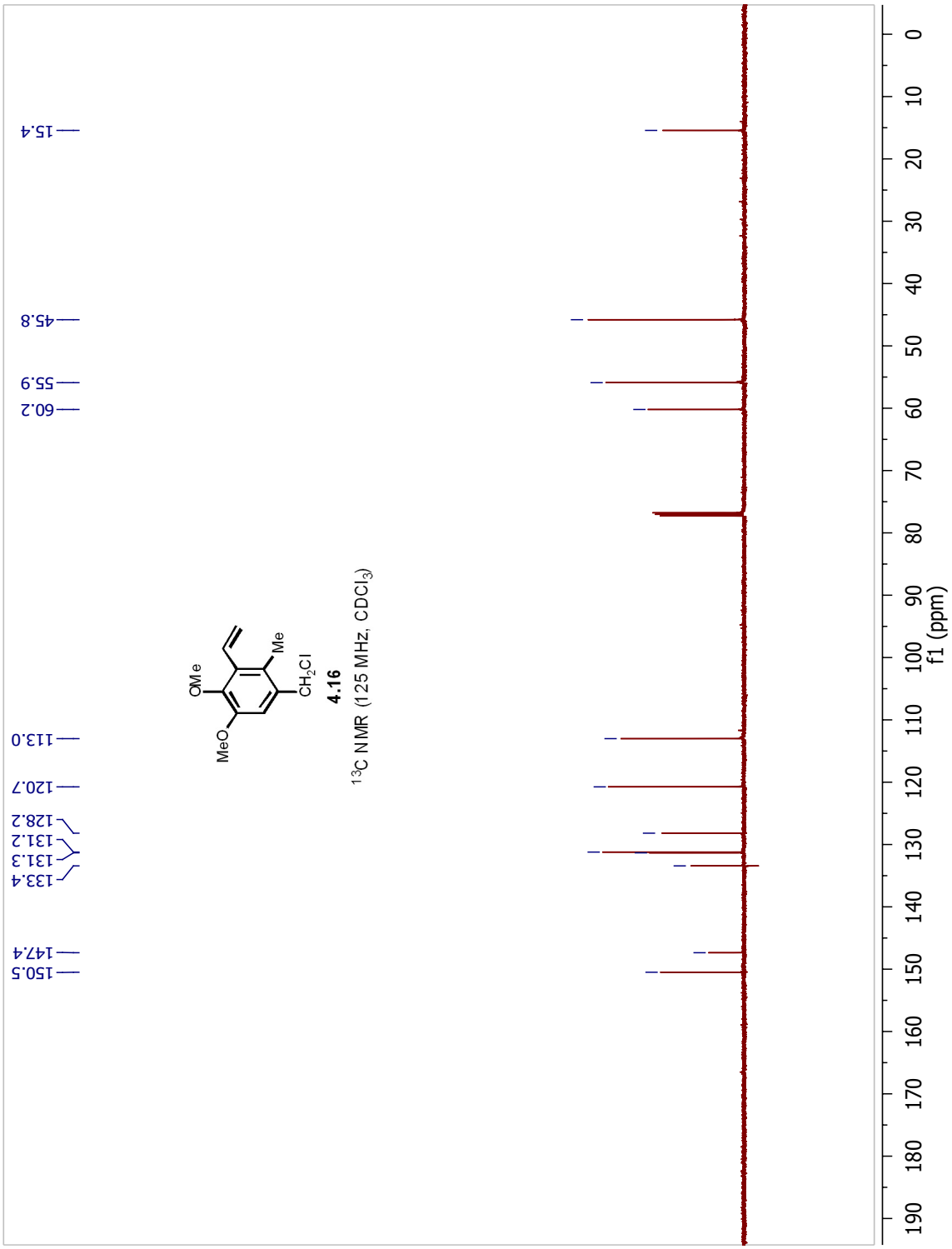

4.14
^{1}H NMR (500 MHz, CDCl$_3$)
OMe
MeO
Me
COOMe
3.12
3.13
3.15
3.47
1.03
1.03
0.98
1.00
f1 (ppm)

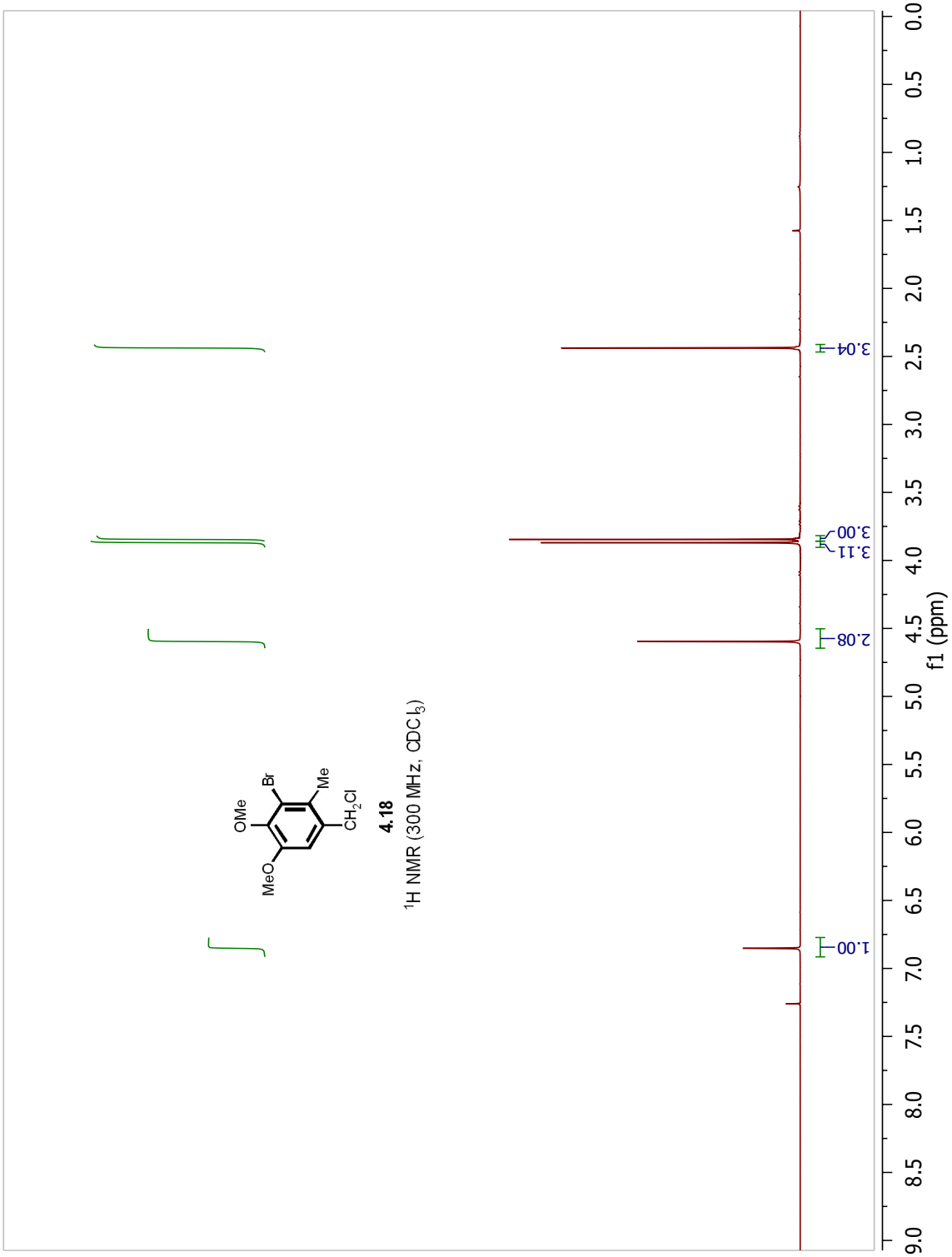

17.6
52.0
55.9
60.3
112.9
121.1
126.3
131.1
131.2
133.8
149.7
150.0
168.4
OMe
MeO
Me
CO2Me
4.14
13C NMR (125 MHz, CDCl3)
f1 (ppm)

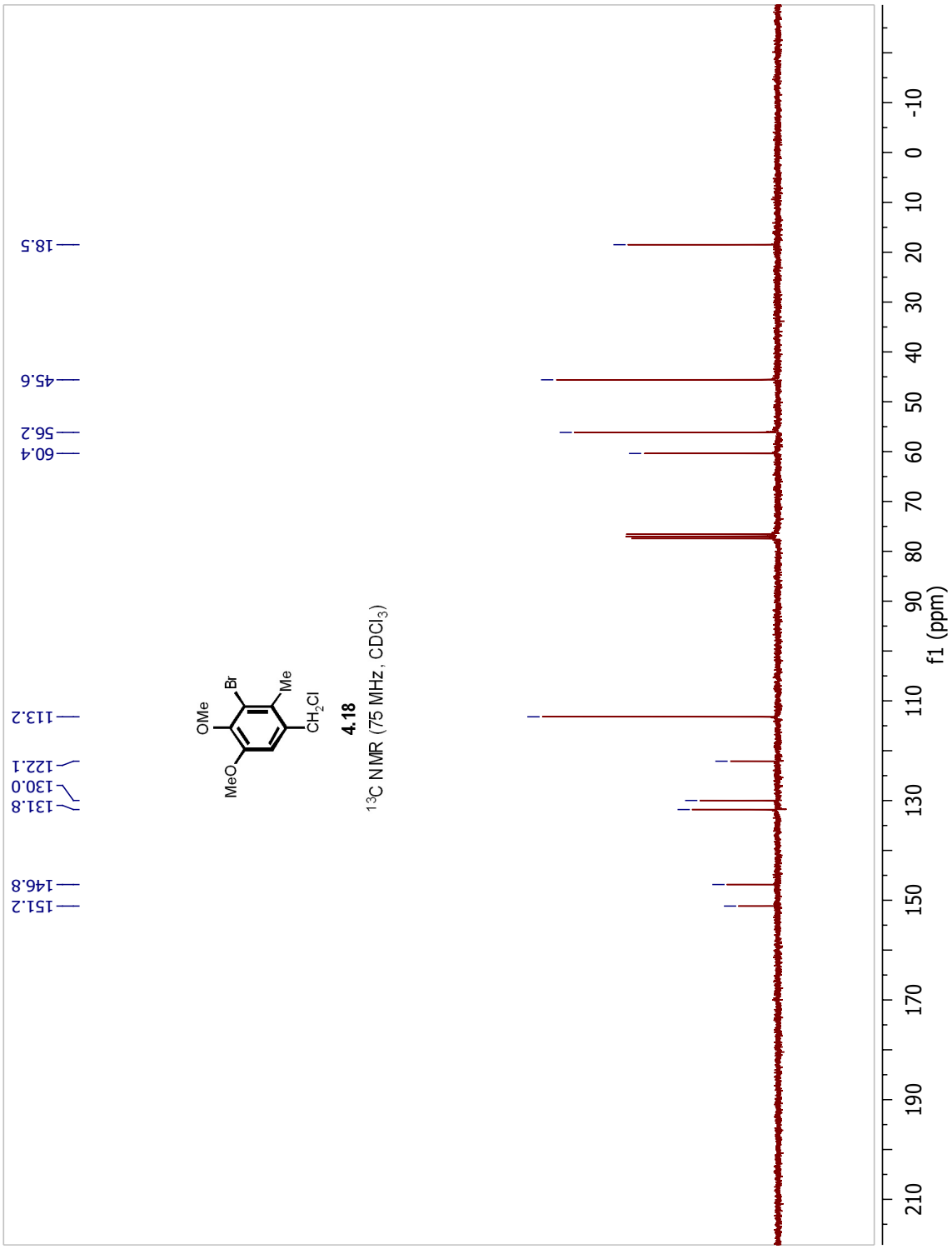

OMe
MeO
Me
CH2OH
4.15
1H NMR (500 Hz, CDCl3)
3.17
3.12
3.27
2.15
1.92
0.92
1.00
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

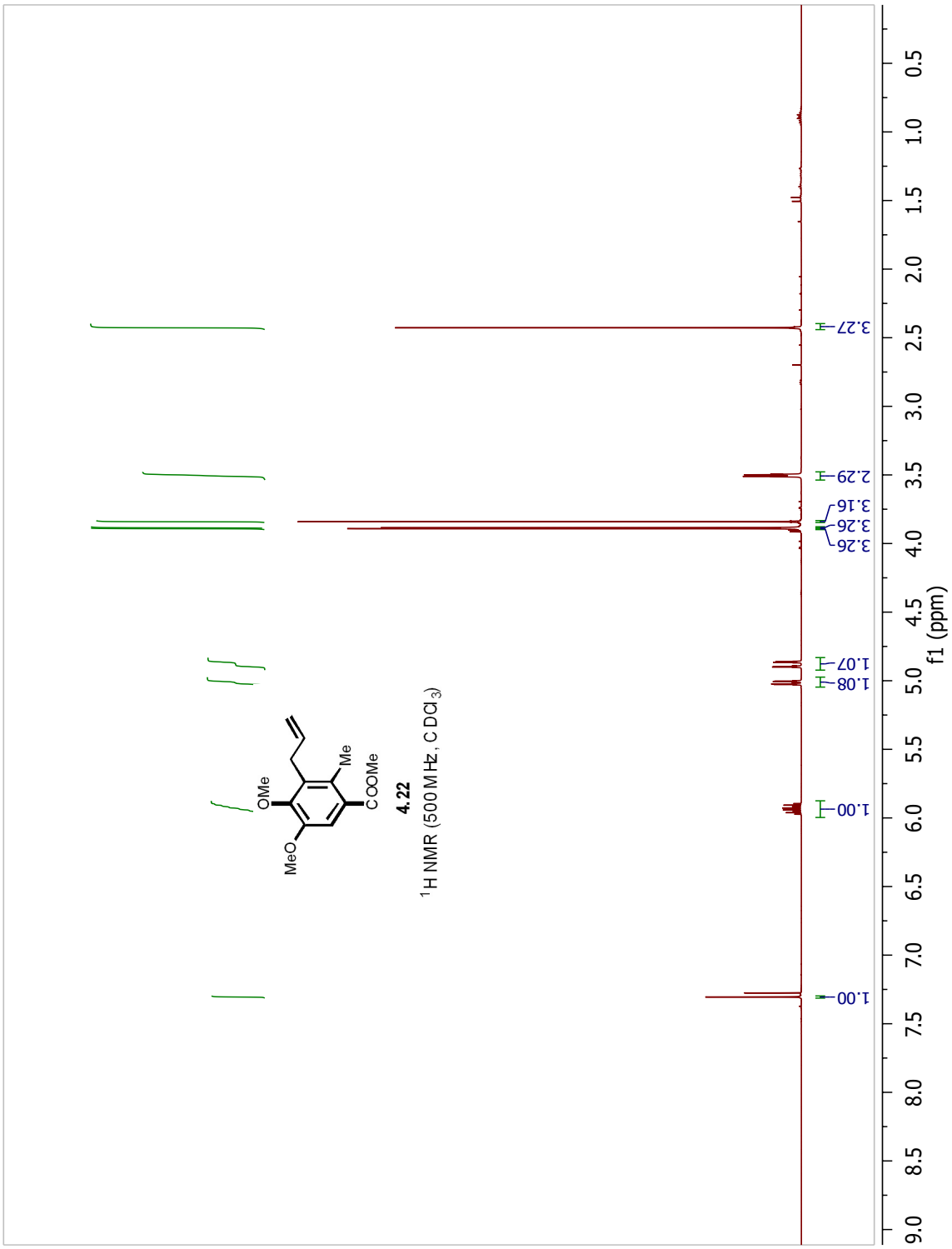

15.1
55.9
60.2
63.9
111.2
120.5
126.6
131.5
132.9
134.6
146.3
150.4
OMe
MeO
Me
CH2OH
4.15
13C NMR (125 Hz, CDCl3)
f1 (ppm)

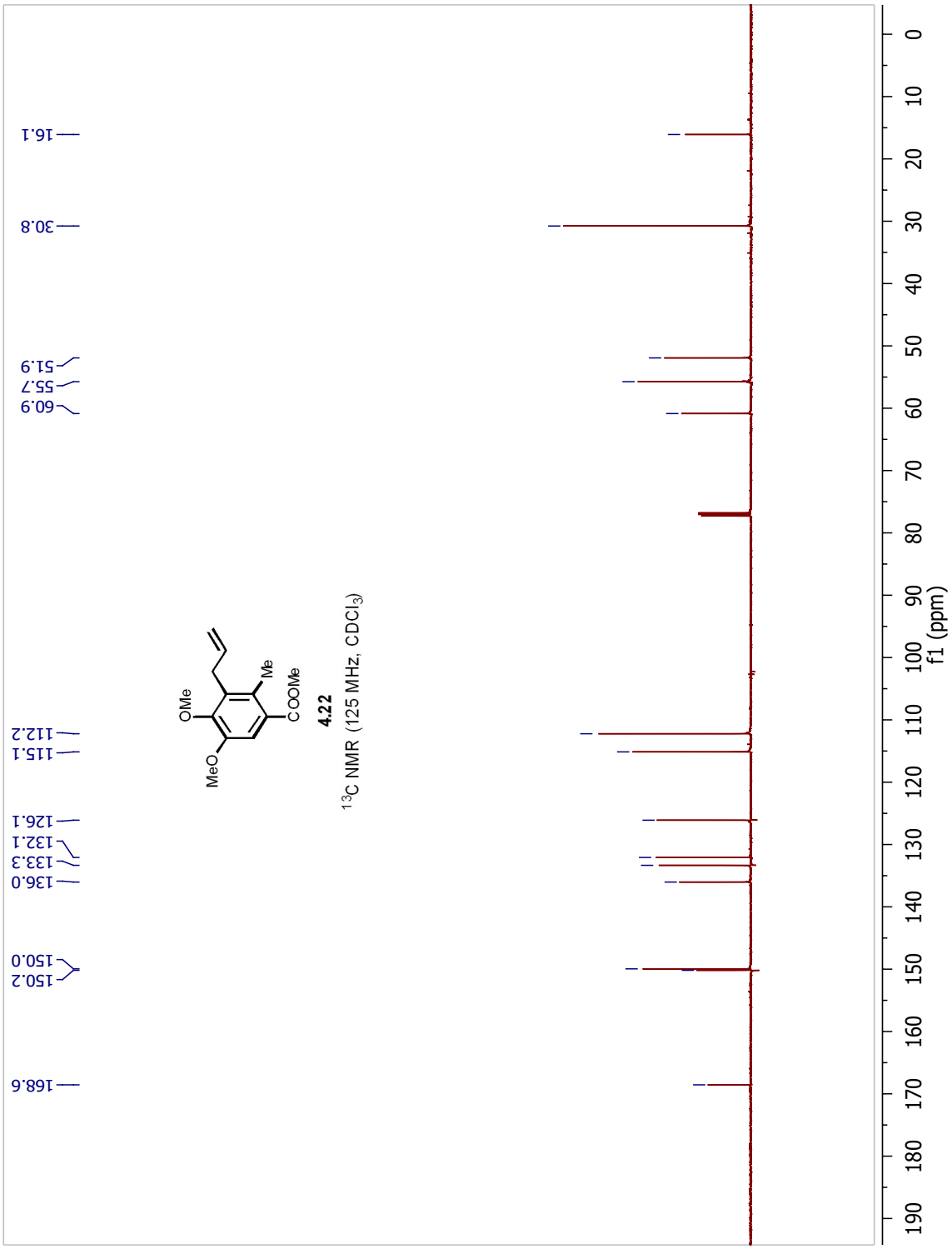

MeO
OMe
Me
CH2Cl
4.16
1H NMR (500 MHz, CDCl3)
3.31
3.01
3.49
2.32
1.97
1.00
1.05
f1 (ppm)

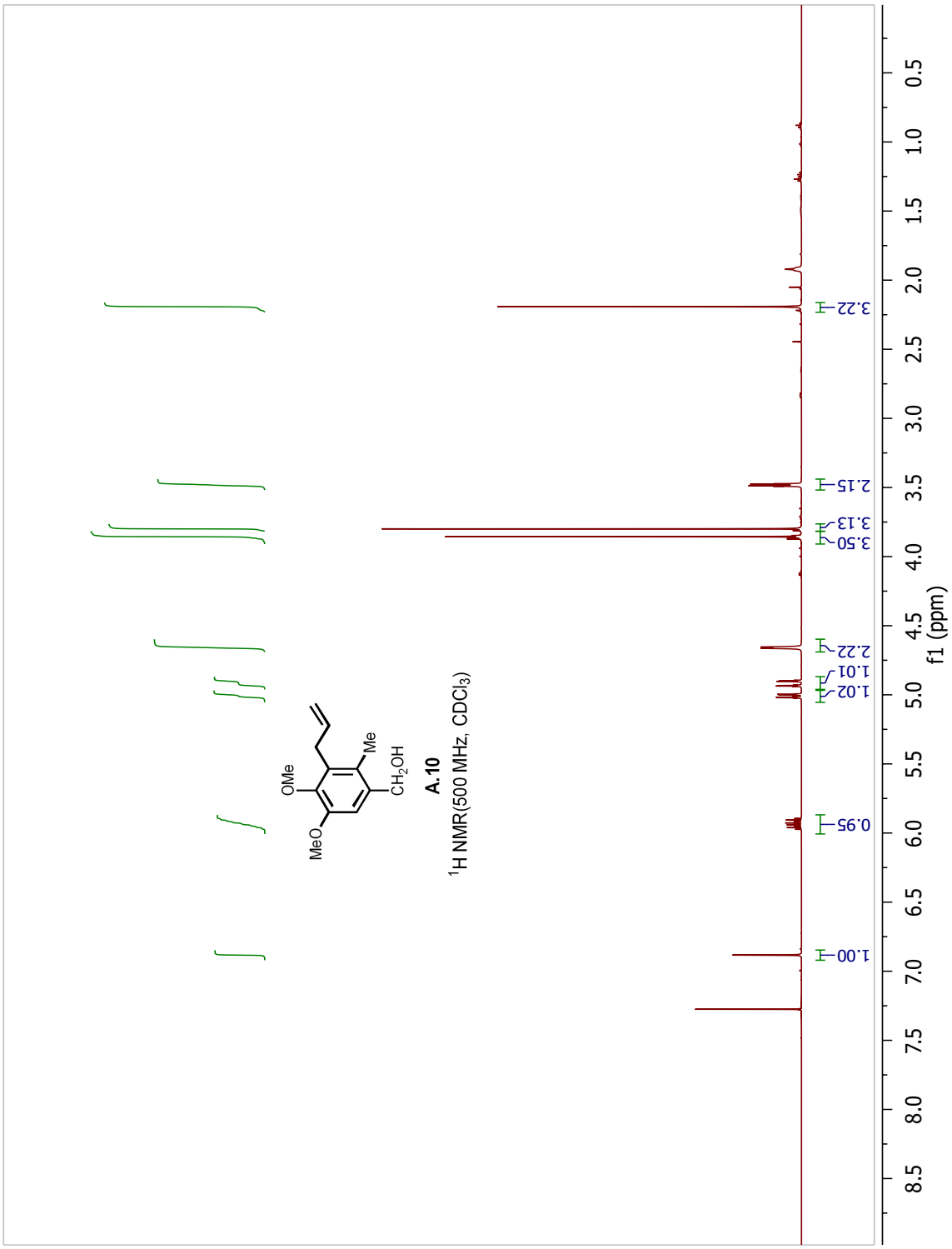

OMe
Me
MeO
CH2Cl
4.16
13C NMR (125 MHz, CDCl3)
15.4
45.8
55.9
60.2
113.0
120.7
128.2
131.2
131.3
133.4
147.4
150.5
f1 (ppm)

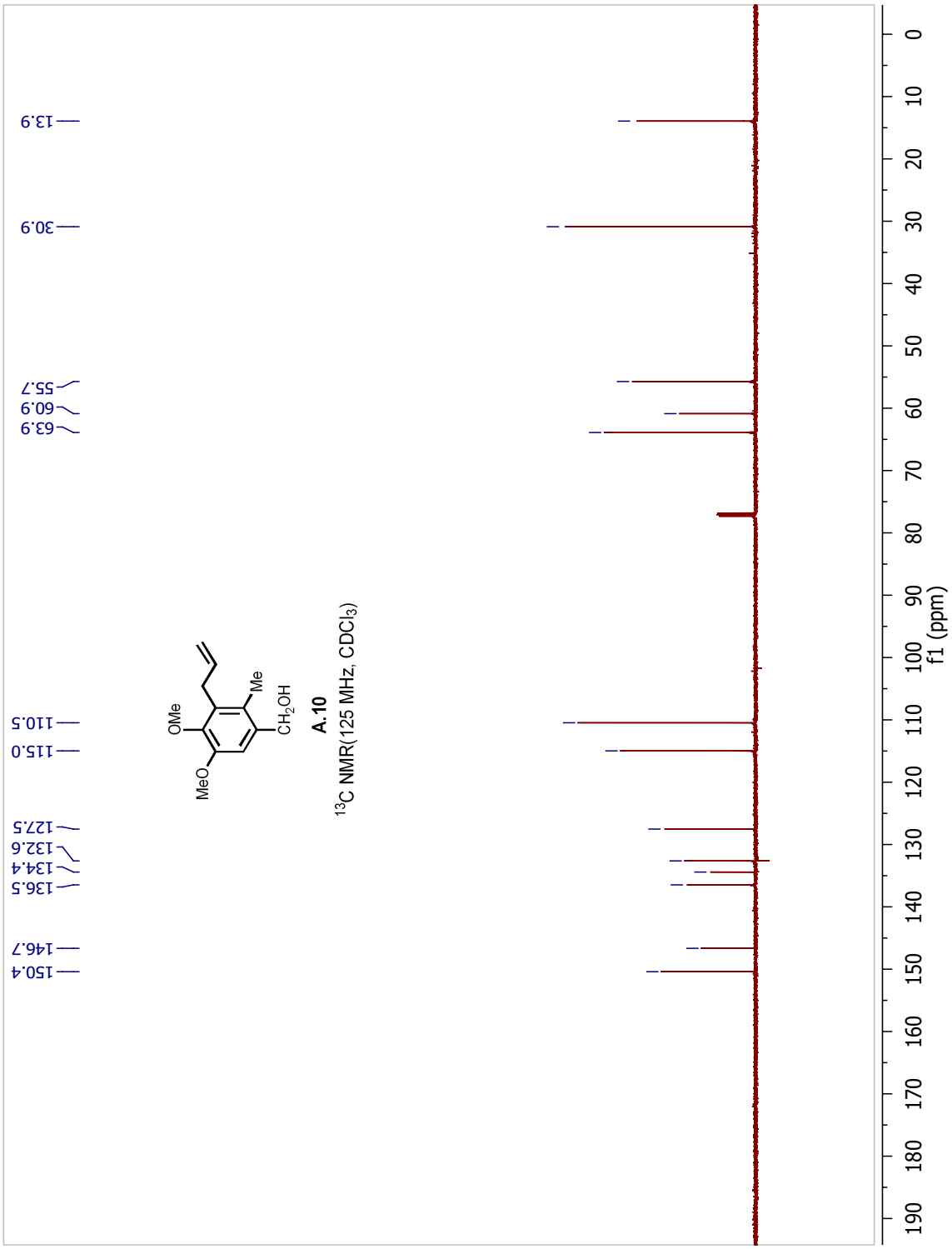

OMe
Br
Me
MeO
CH2Cl
4.18
1H NMR (300 MHz, CDCl3)
3.04
3.11
3.00
2.08
1.00
f1 (ppm)

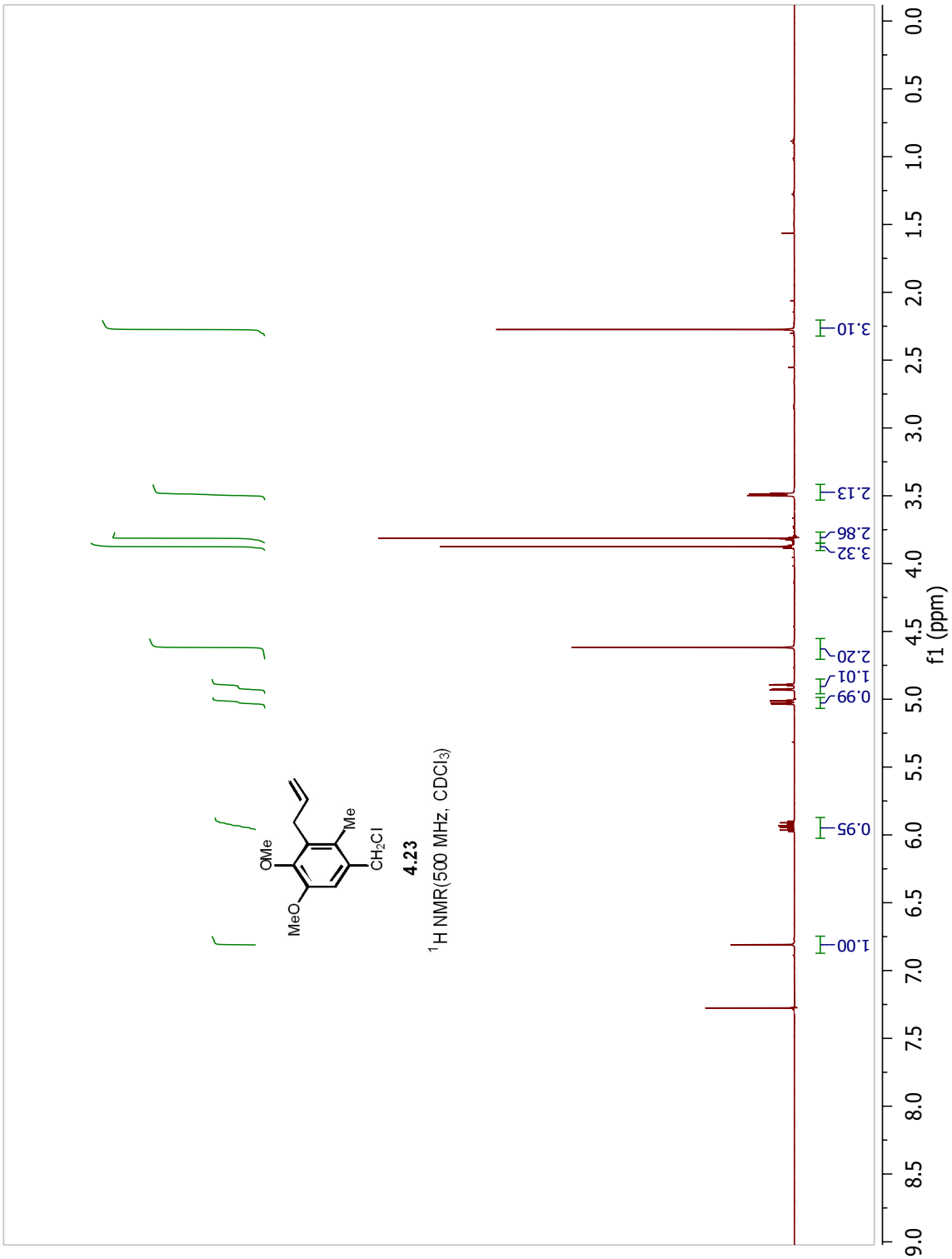

18.5
45.6
56.2
60.4
113.2
122.1
130.0
131.8
146.8
151.2
OMe
Br
Me
MeO
CH2Cl
4.18
13C NMR (75 MHz, CDCl3)
f1 (ppm)

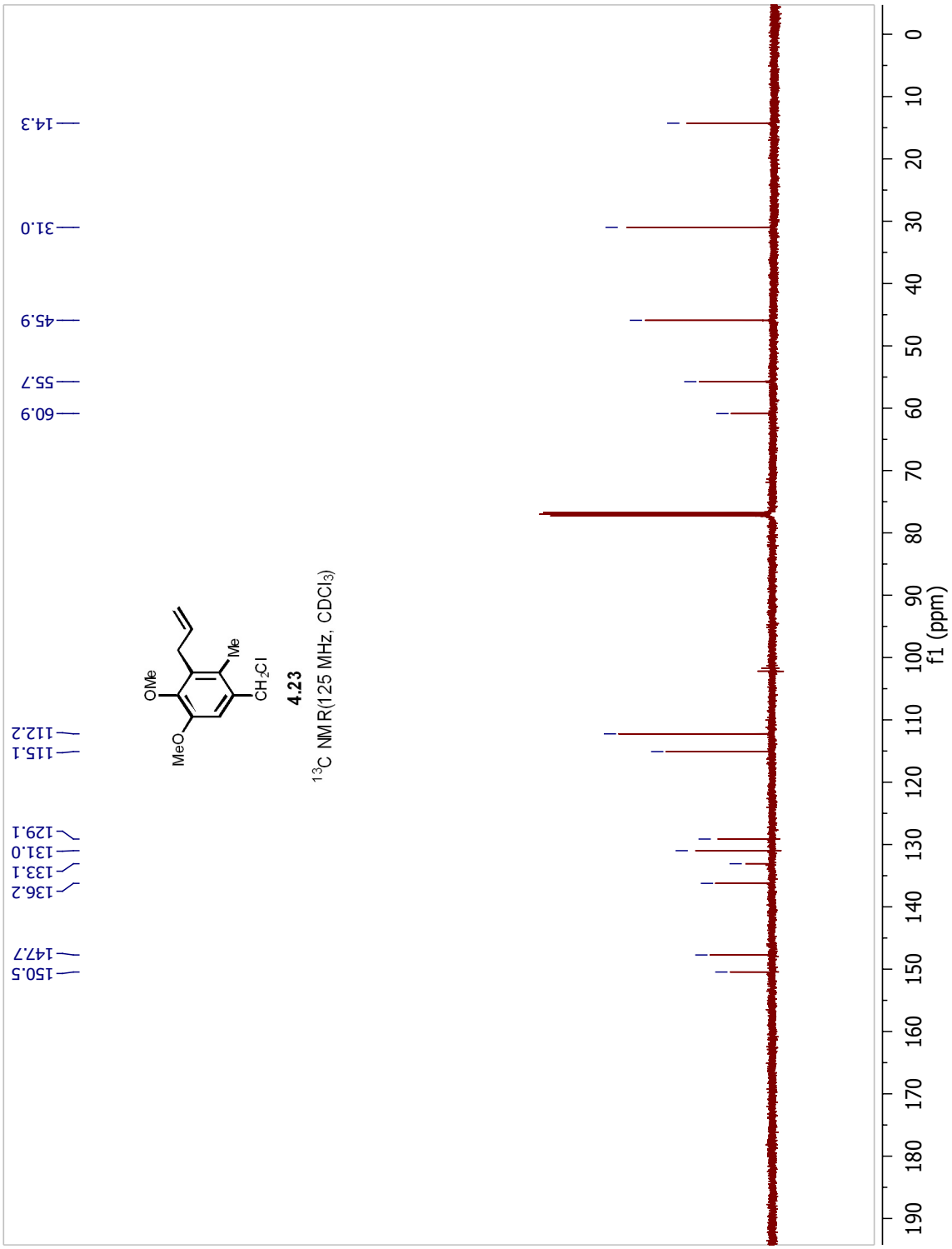

OMe
MeO
Me
COOMe
4.22
^{1}H NMR (500 MHz, $CDCl_3$)
3.27
2.29
3.16
3.26
3.26
1.07
1.08
1.00
1.00
f1 (ppm)

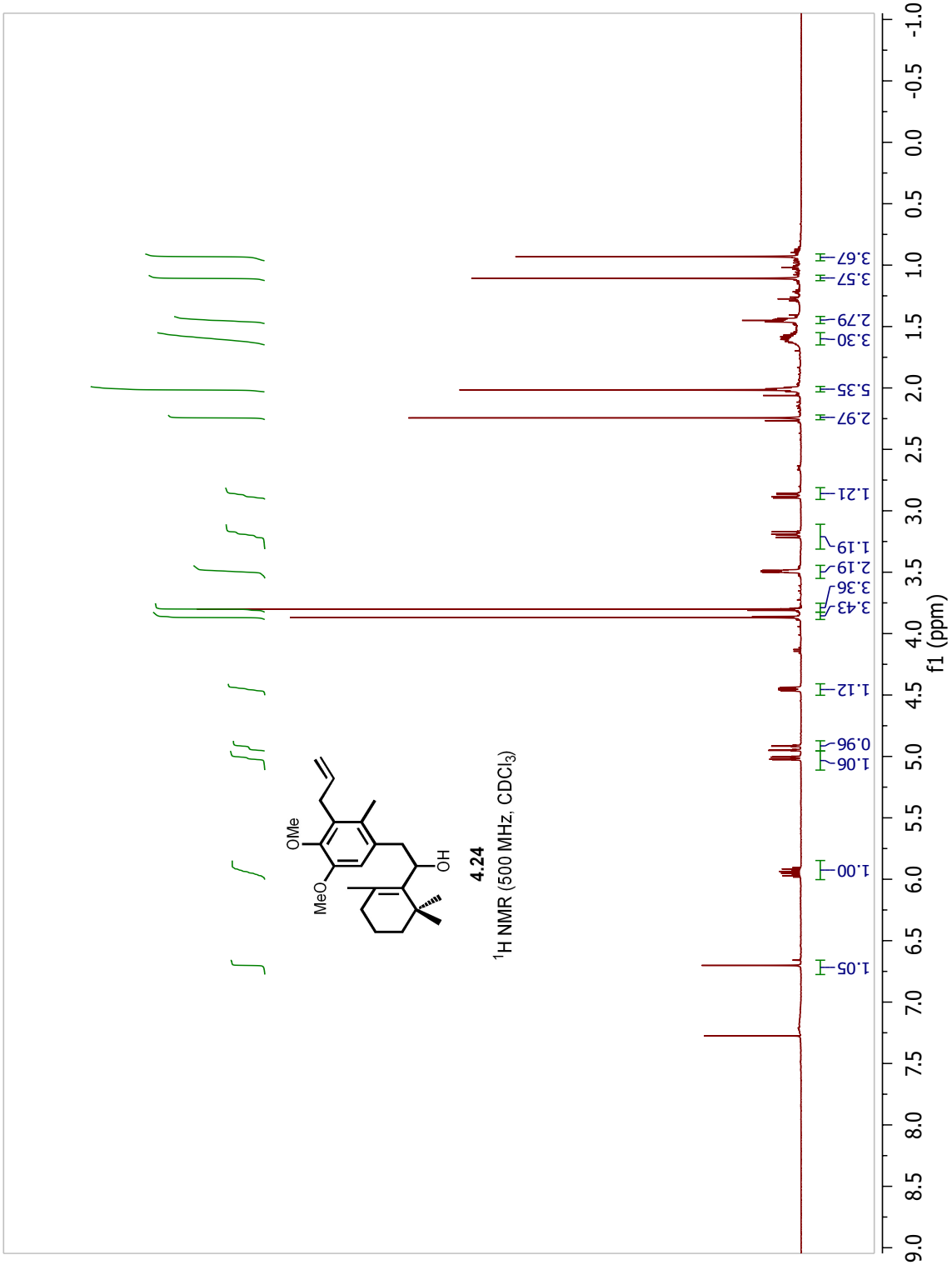

16.1
30.8
51.9
55.7
60.9
112.2
115.1
126.1
132.1
133.3
136.0
150.0
150.2
168.6
OMe
MeO
Me
COOMe
4.22
^{13}C NMR (125 MHz, $CDCl_3$)
f1 (ppm)

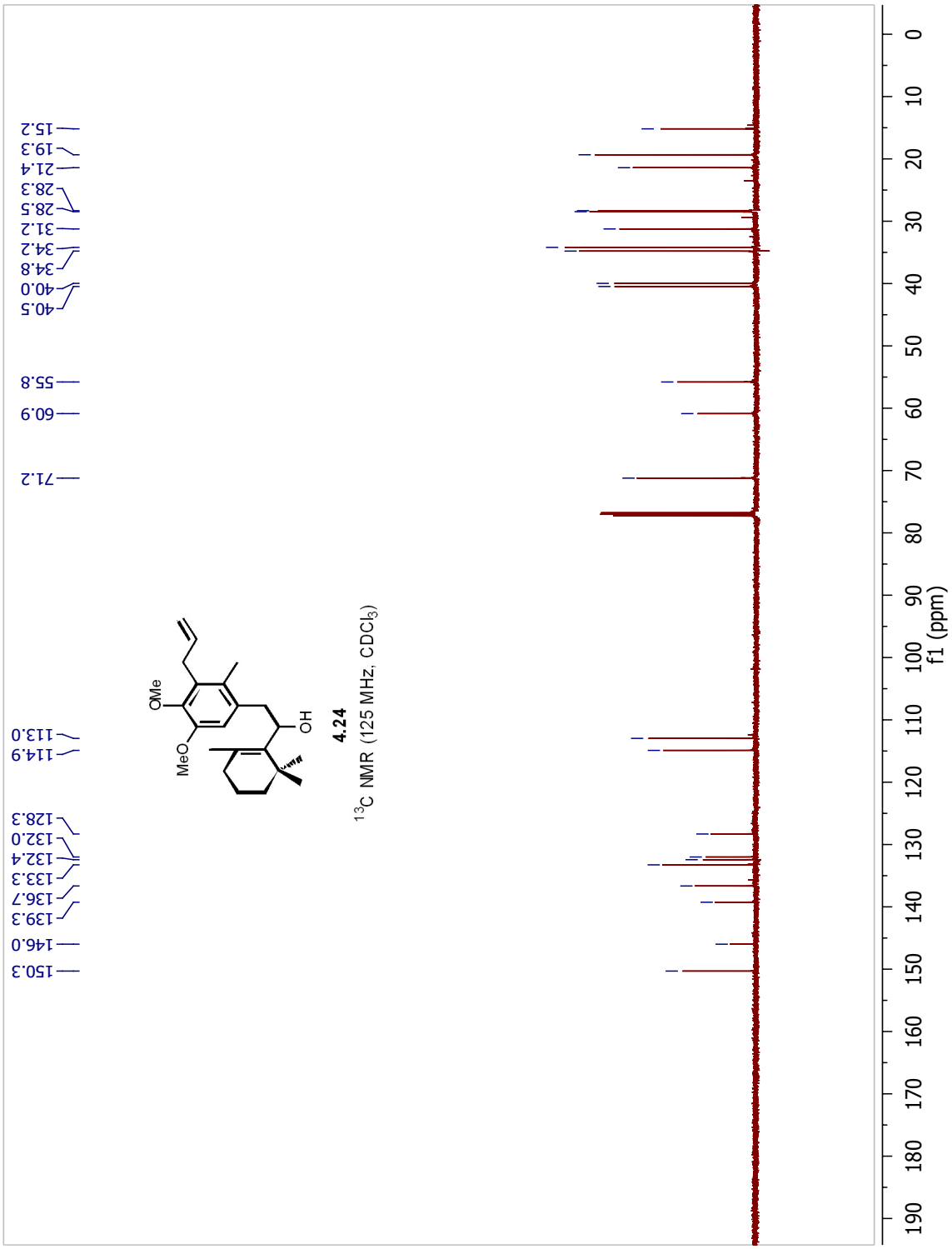

OMe
MeO
Me
CH2OH
A.10
1H NMR(500 MHz, CDCl3)
3.22
2.15
3.13
3.50
2.22
1.01
1.02
0.95
1.00
f1 (ppm)

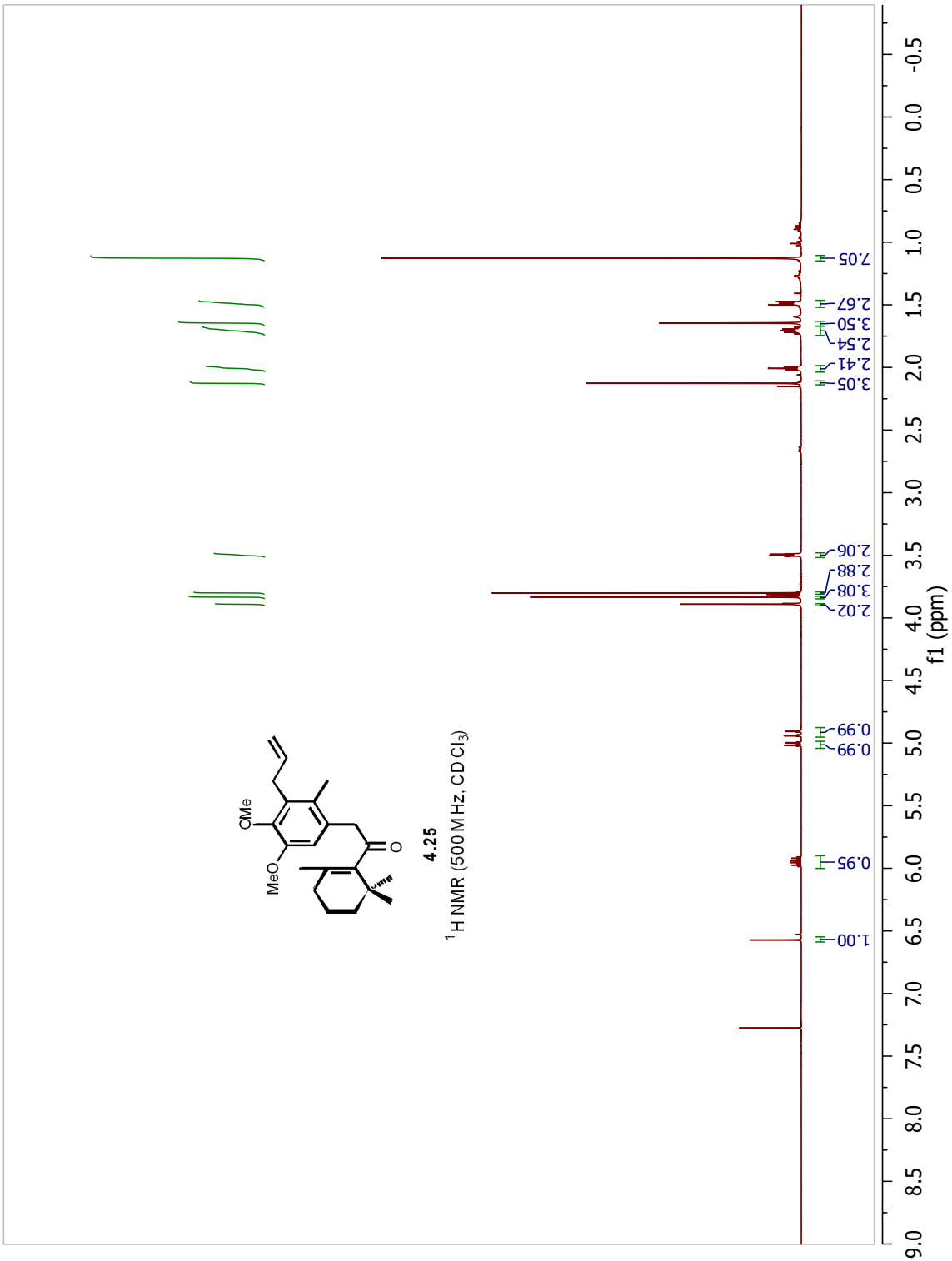

13.9
30.9
55.7
60.9
63.9
110.5
115.0
127.5
132.6
134.4
136.5
146.7
150.4
OMe
MeO
Me
CH2OH
A.10
13C NMR(125 MHz, CDCl3)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
f1 (ppm)

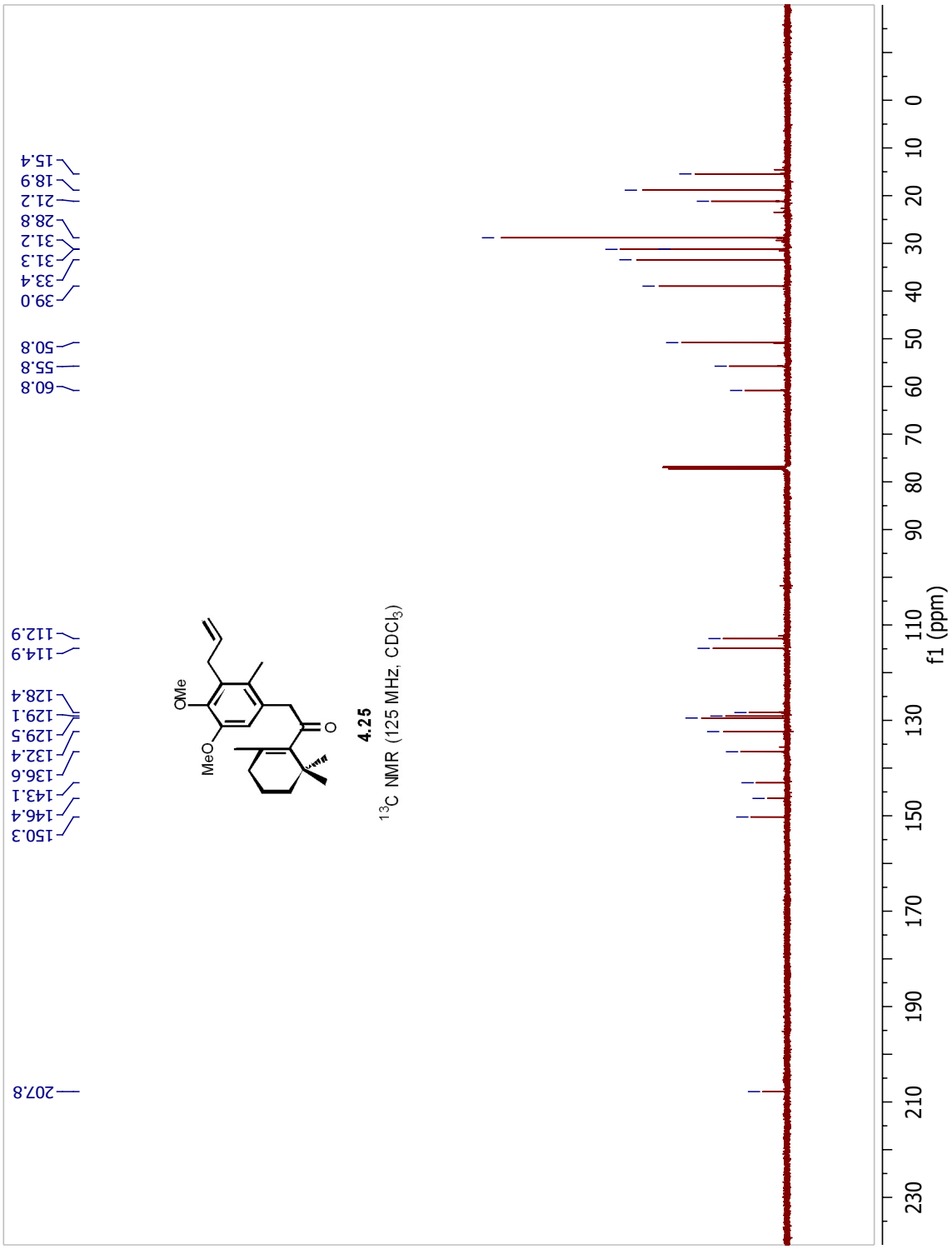

OMe
MeO
Me
CH2Cl
4.23
1H NMR(500 MHz, CDCl3)
3.10
2.13
2.86
3.32
2.20
1.01
0.99
0.95
1.00
f1 (ppm)

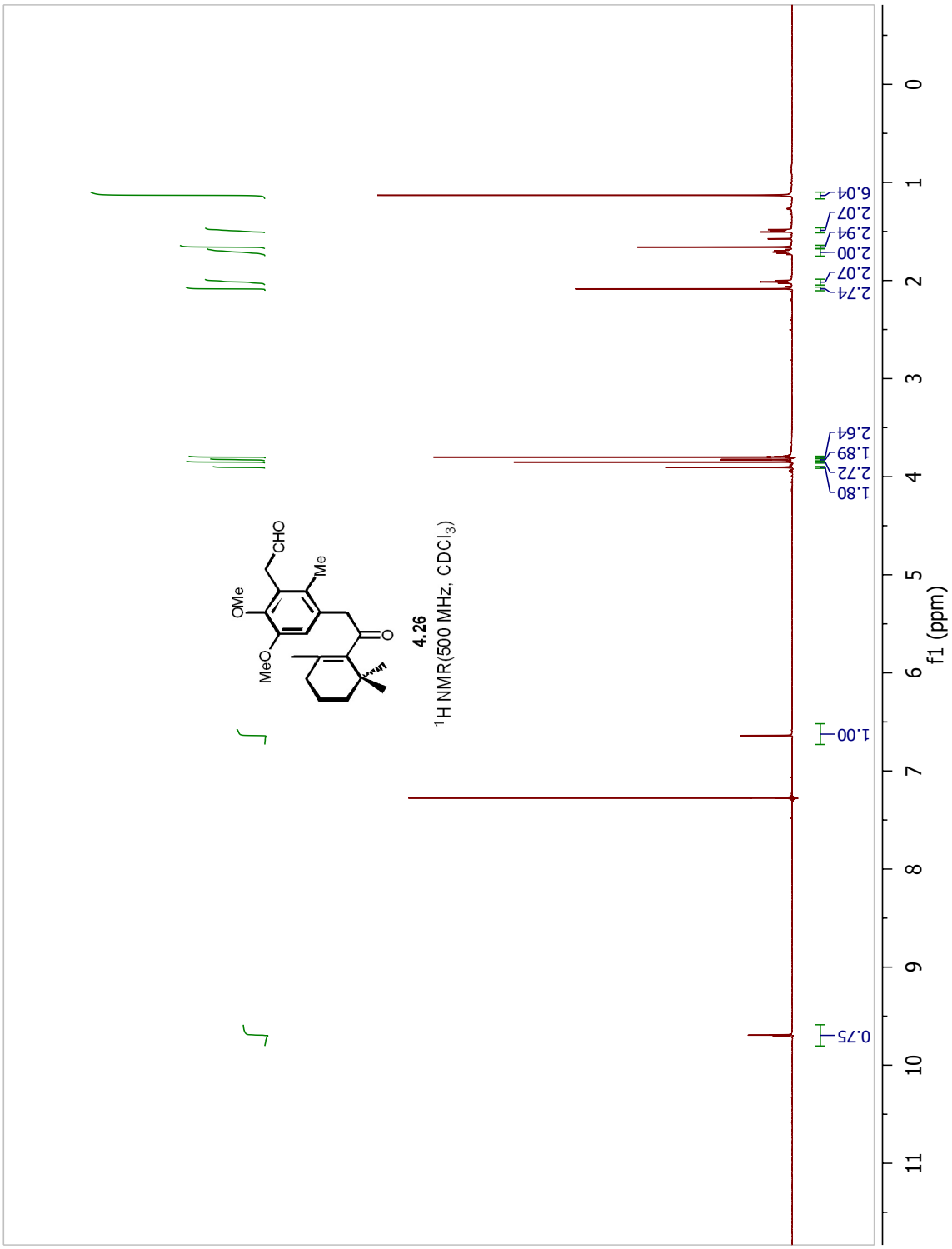

14.3
31.0
45.9
55.7
60.9
112.2
115.1
129.1
131.0
133.1
136.2
147.7
150.5
OMe
MeO
Me
CH2Cl
4.23
13C NMR(125 MHz, CDCl3)
f1 (ppm)

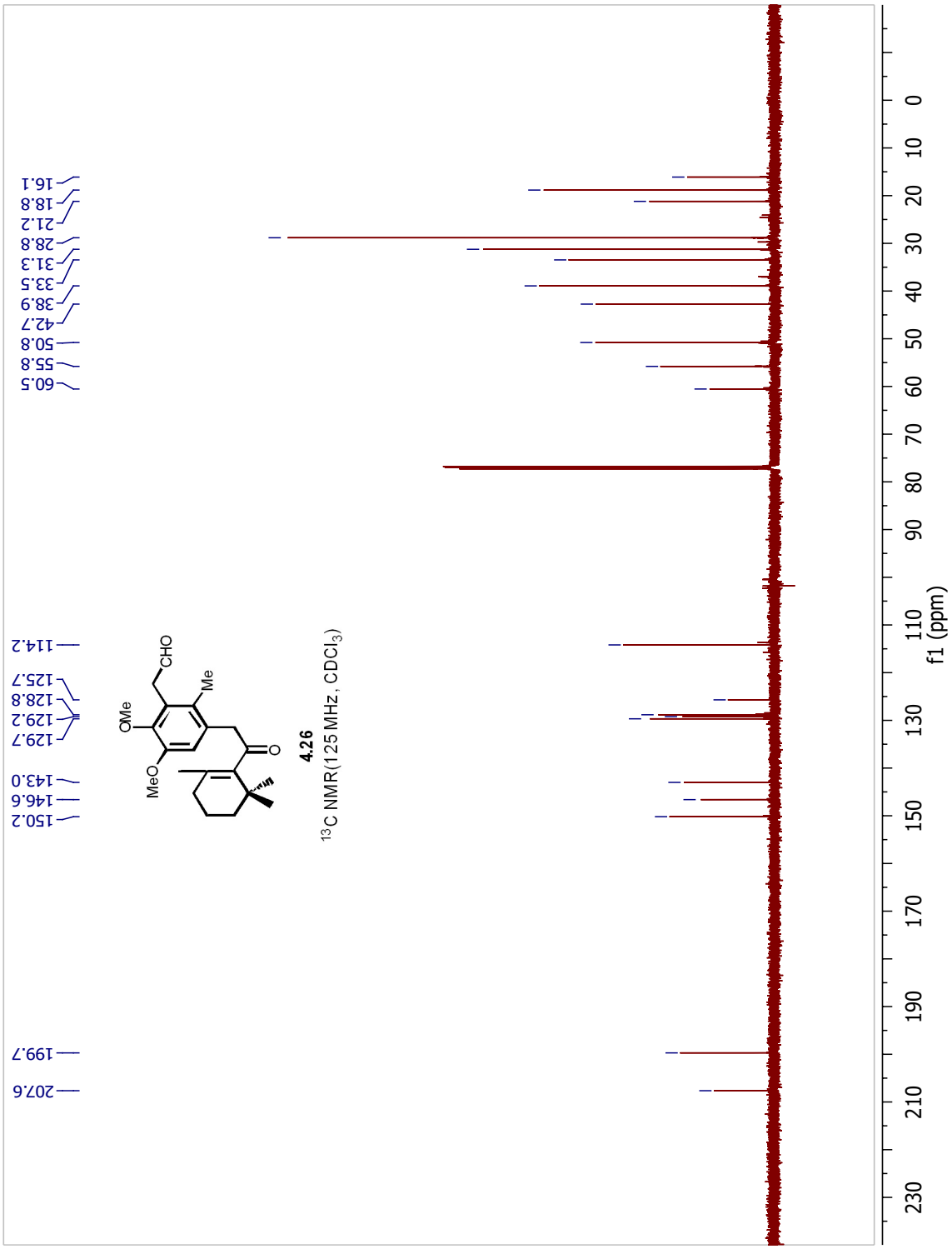

OMe
MeO
OH
4.24
^{1}H NMR (500 MHz, CDCl$_3$)
3.67
3.57
2.79
3.30
5.35
2.97
1.21
1.19
2.19
3.36
3.43
1.12
0.96
1.06
1.00
1.05
f1 (ppm)

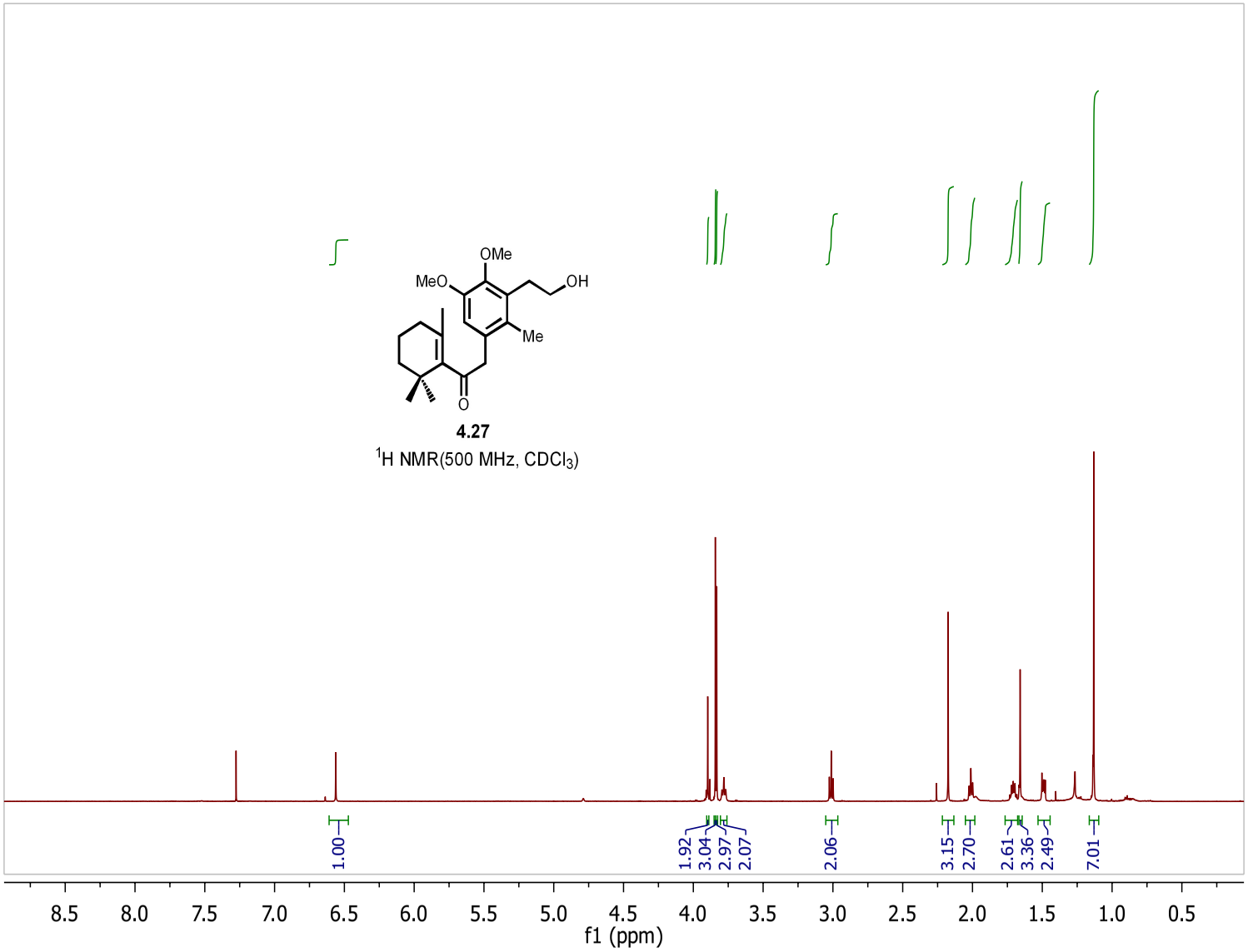

150.3
146.0
139.3
136.7
133.3
132.4
132.0
128.3
114.9
113.0
71.2
60.9
55.8
40.5
40.0
34.8
34.2
31.2
28.5
28.3
21.4
19.3
15.2
OMe
MeO
OH
4.24
^{13}C NMR (125 MHz, $CDCl_3$)
f1 (ppm)

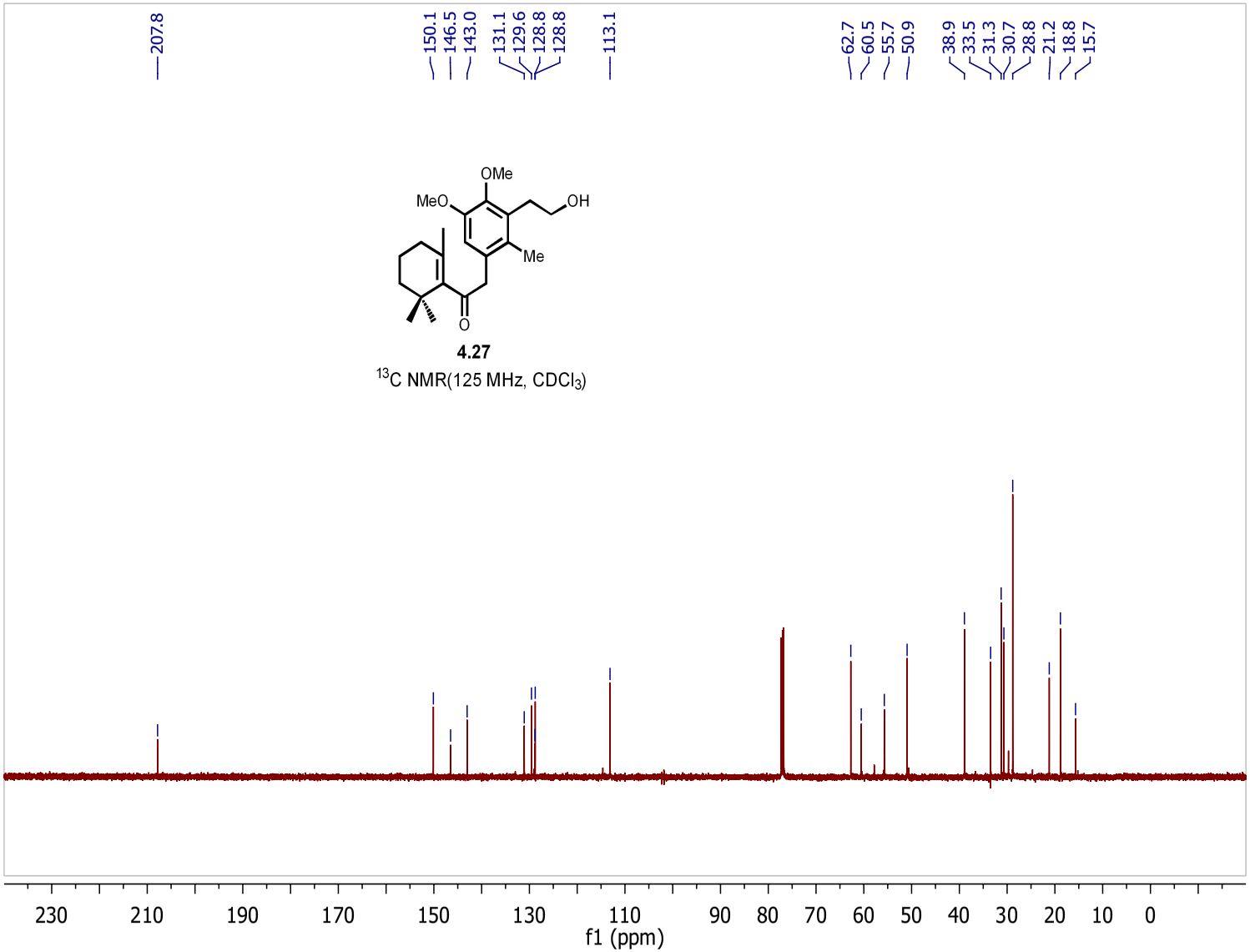

4.25
^{1}H NMR (500 MHz, CD Cl$_3$)
OMe
MeO
O
1.00
0.95
0.99
0.99
2.06
2.88
3.08
2.02
3.05
2.41
2.54
3.50
2.67
7.05
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

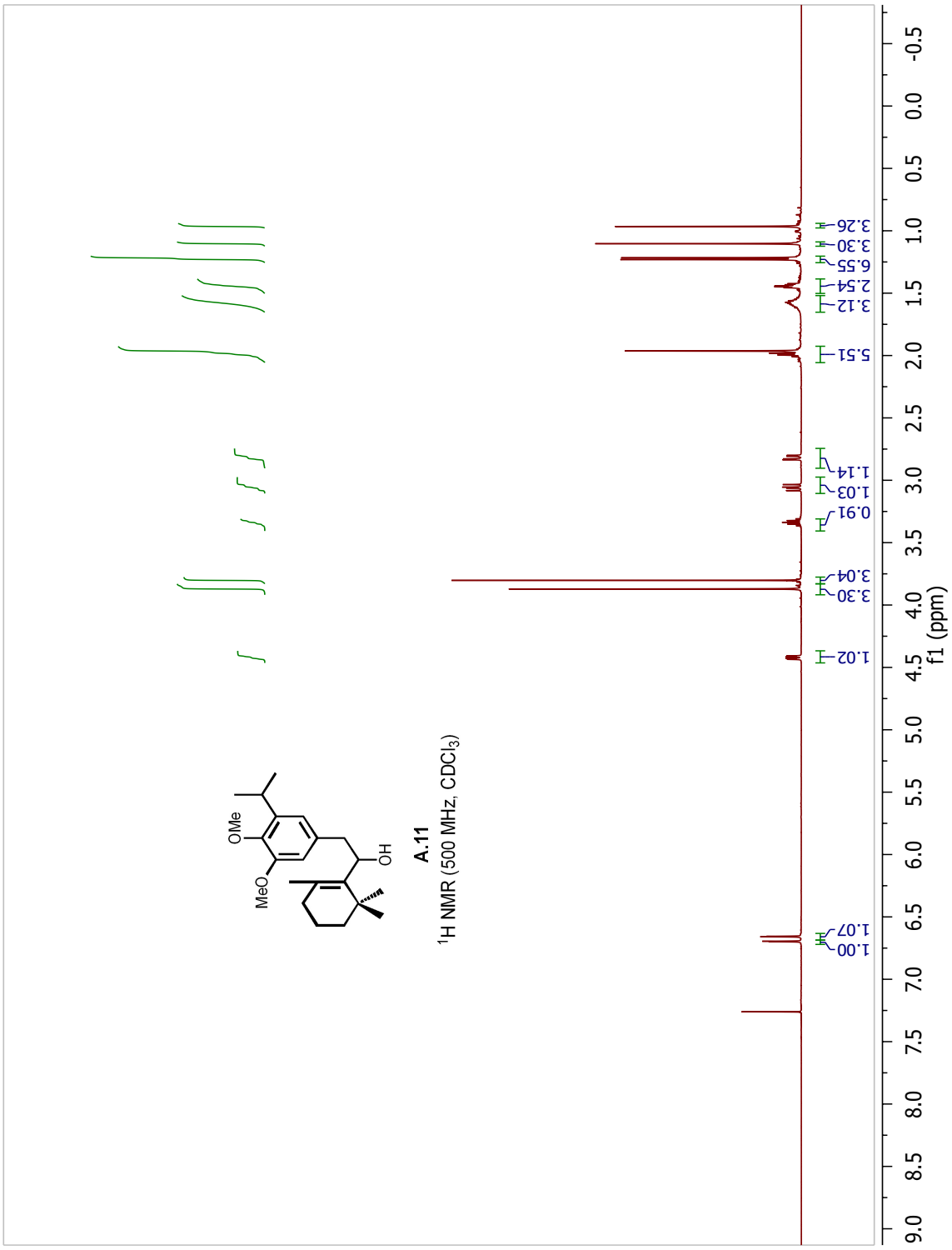

OMe
MeO
O
4.25
^{13}C NMR (125 MHz, $CDCl_3$)
207.8
150.3
146.4
143.1
136.6
132.4
129.5
129.1
128.4
114.9
112.9
60.8
55.8
50.8
39.0
33.4
31.3
31.2
28.8
21.2
18.9
15.4
f1 (ppm)

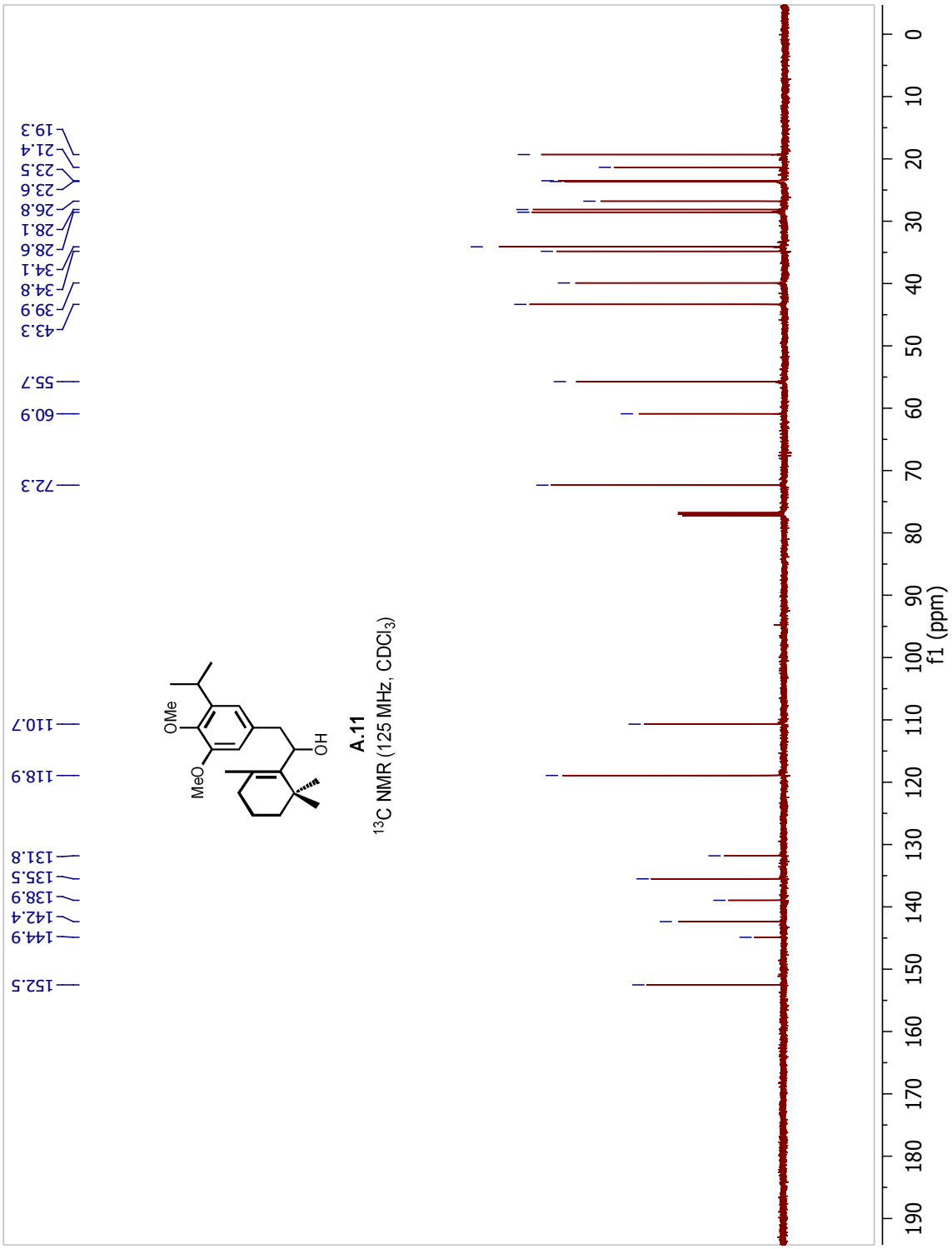

4.26
^{1}H NMR(500 MHz, CDCl$_3$)
CHO
Me
OMe
MeO
O
6.04
2.07
2.94
2.00
2.07
2.74
1.80
2.72
1.89
2.64
1.00
0.75
f1 (ppm)

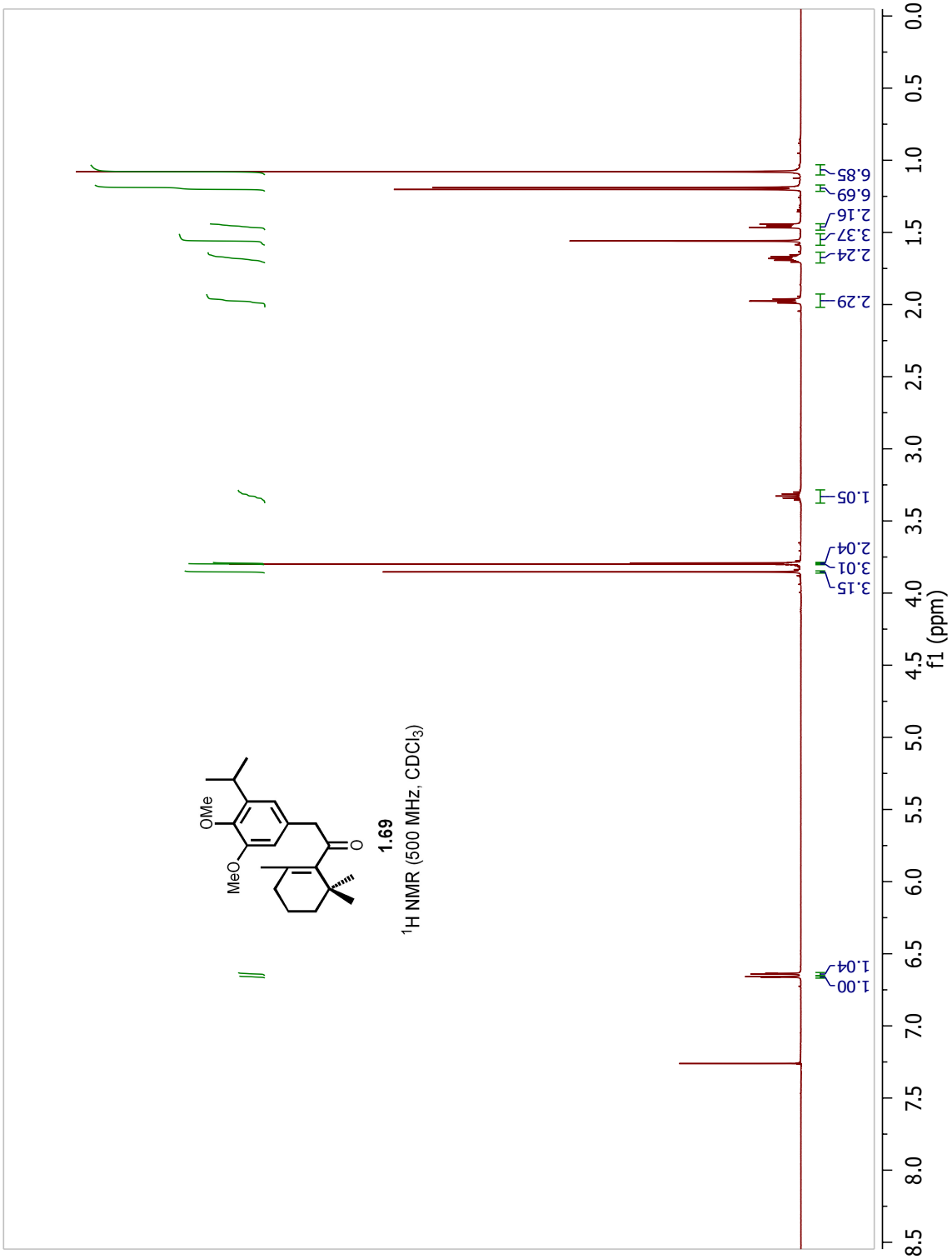

16.1
18.8
21.2
28.8
31.3
33.5
38.9
42.7
50.8
55.8
60.5
114.2
125.7
128.8
129.2
129.7
143.0
146.6
150.2
199.7
207.6
CHO
Me
OMe
MeO
O
4.26
^{13}C NMR(125 MHz, $CDCl_3$)
0
10
20
30
40
50
60
70
80
90
110
130
150
170
190
210
230
f1 (ppm)

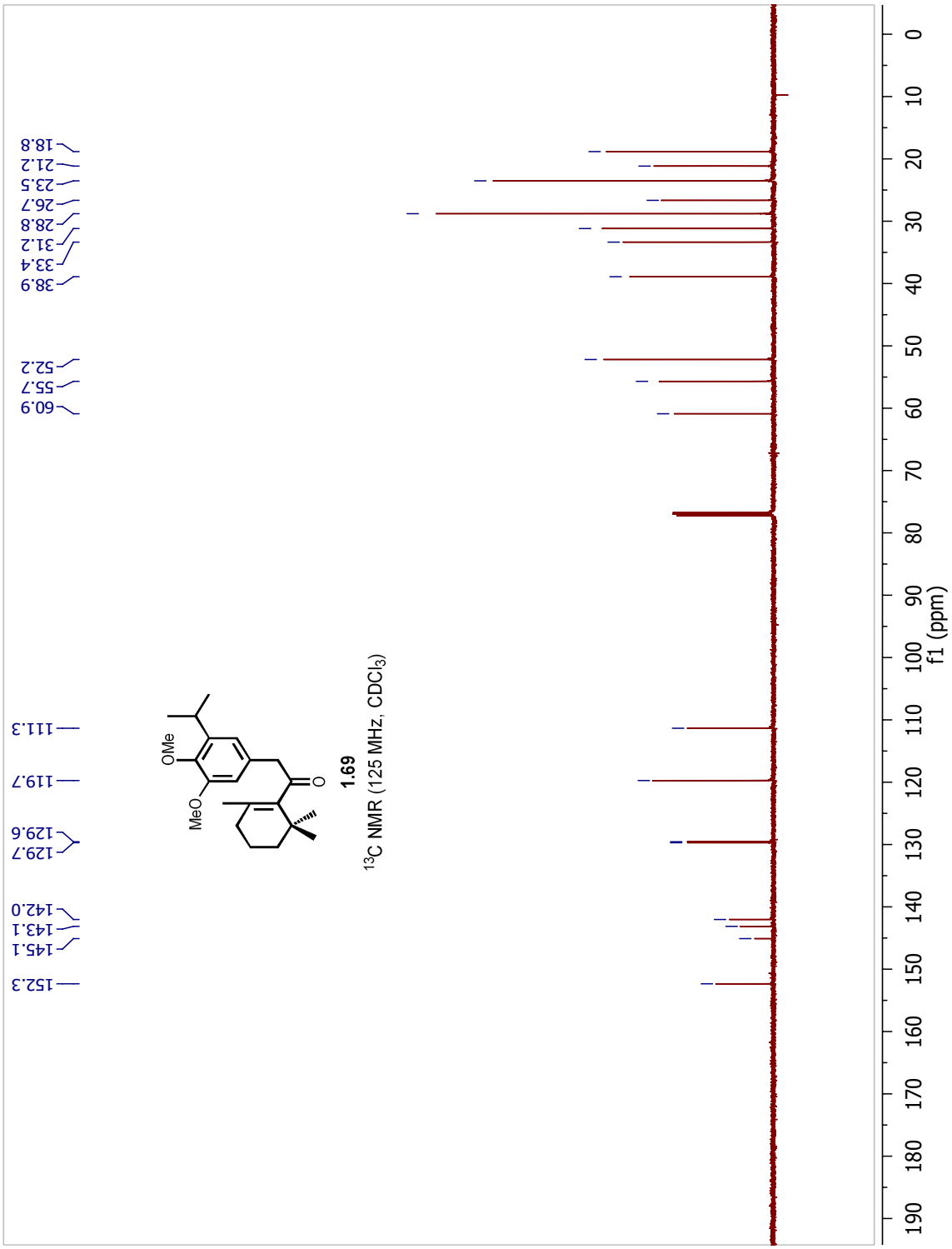

OMe
MeO
OH
Me
O
4.27
^{1}H NMR(500 MHz, $CDCl_3$)
1.00
1.92
3.04
2.97
2.07
2.06
3.15
2.70
2.61
3.36
2.49
7.01
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

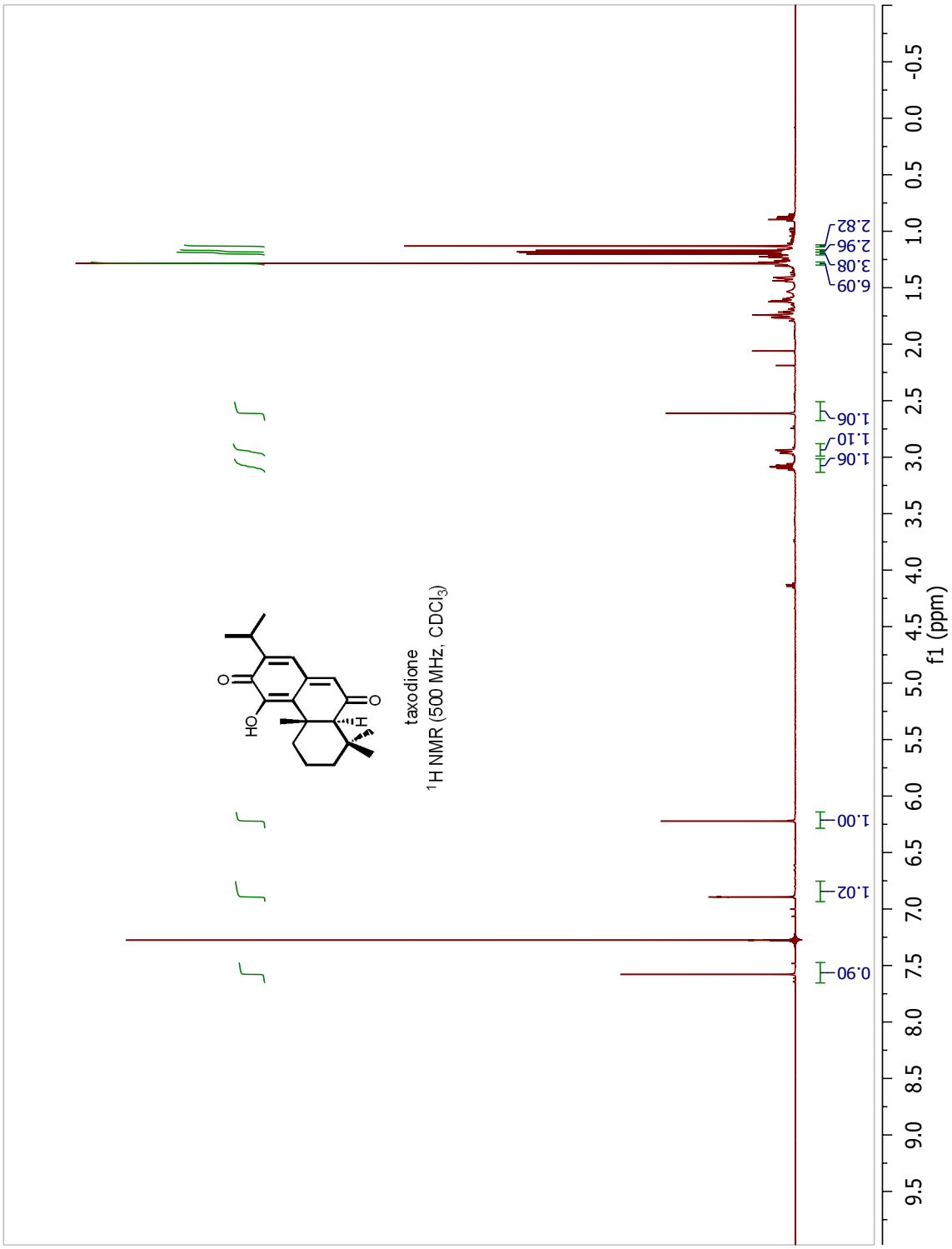

207.8
150.1
146.5
143.0
131.1
129.6
128.8
128.8
113.1
62.7
60.5
55.7
50.9
38.9
33.5
31.3
30.7
28.8
21.2
18.8
15.7
OMe
MeO
OH
Me
O
4.27
13C NMR(125 MHz, CDCl3)
230
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

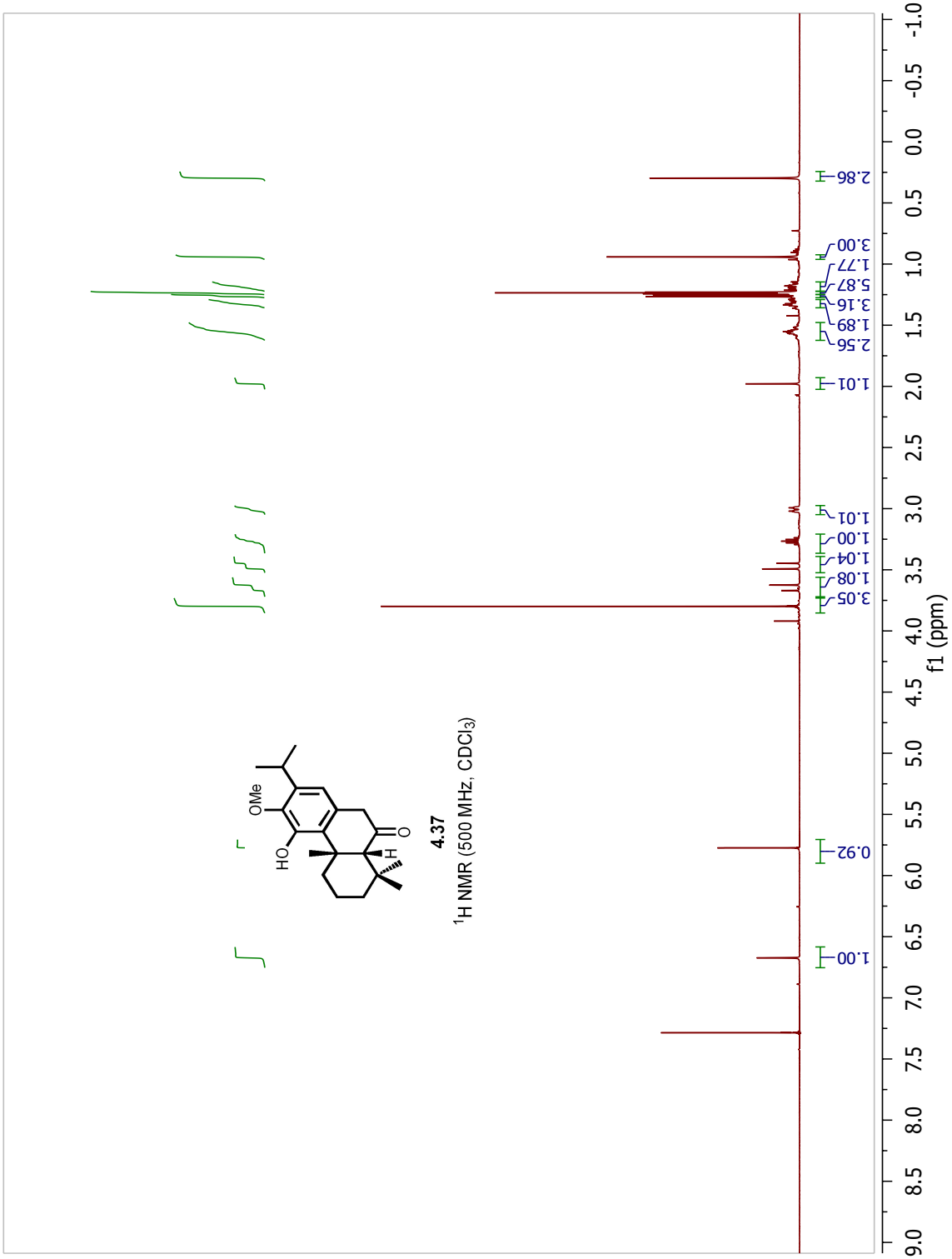

OMe
MeO
OH
A.11
^{1}H NMR (500 MHz, $CDCl_3$)
1.00
1.07
1.02
3.30
3.04
0.91
1.03
1.14
5.51
3.12
2.54
6.55
3.30
3.26
f1 (ppm)

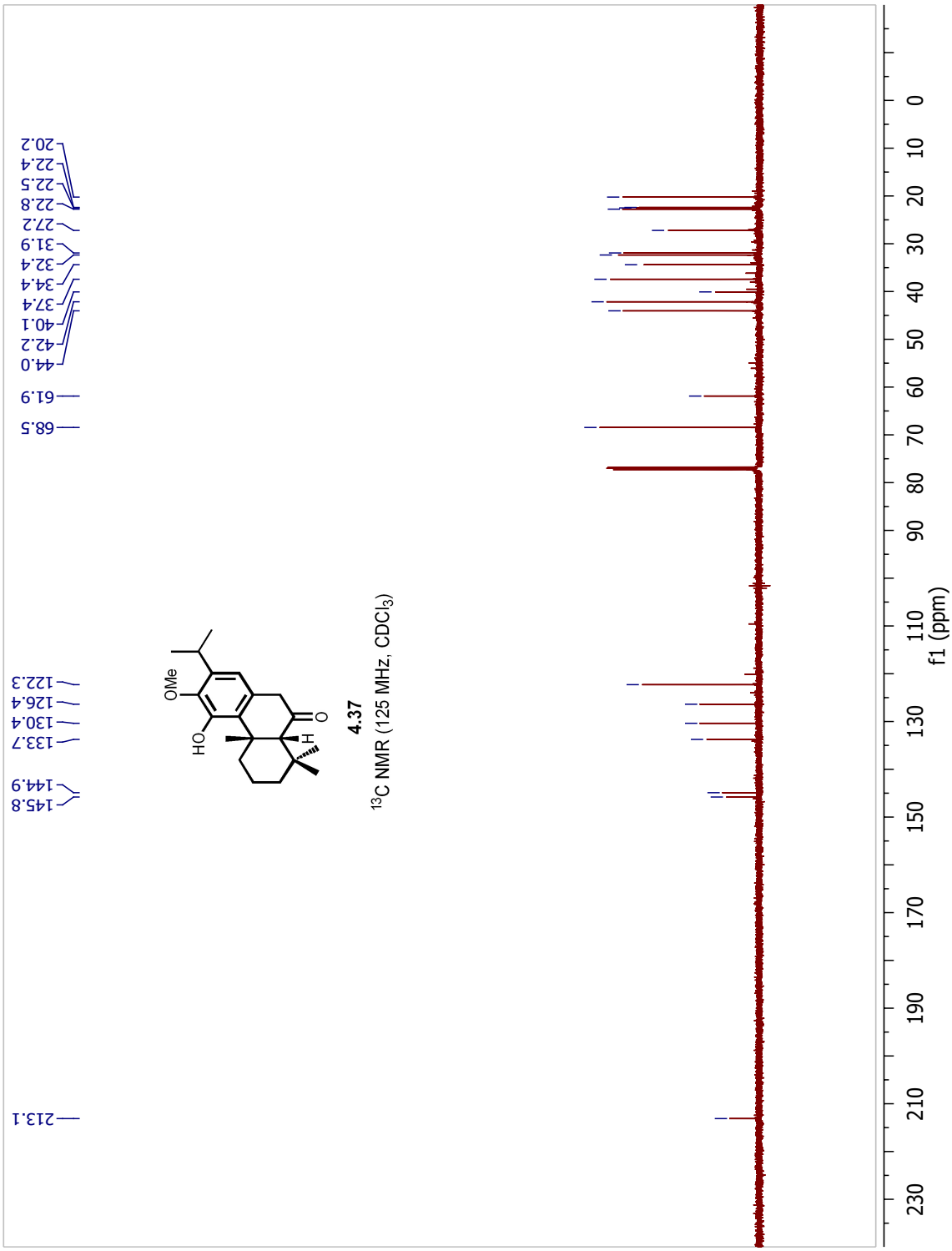

A.11
^{13}C NMR (125 MHz, $CDCl_3$)
OMe
MeO
OH
19.3
21.4
23.5
23.6
26.8
28.1
28.6
34.1
34.8
39.9
43.3
55.7
60.9
72.3
110.7
118.9
131.8
135.5
138.9
142.4
144.9
152.5
f1 (ppm)

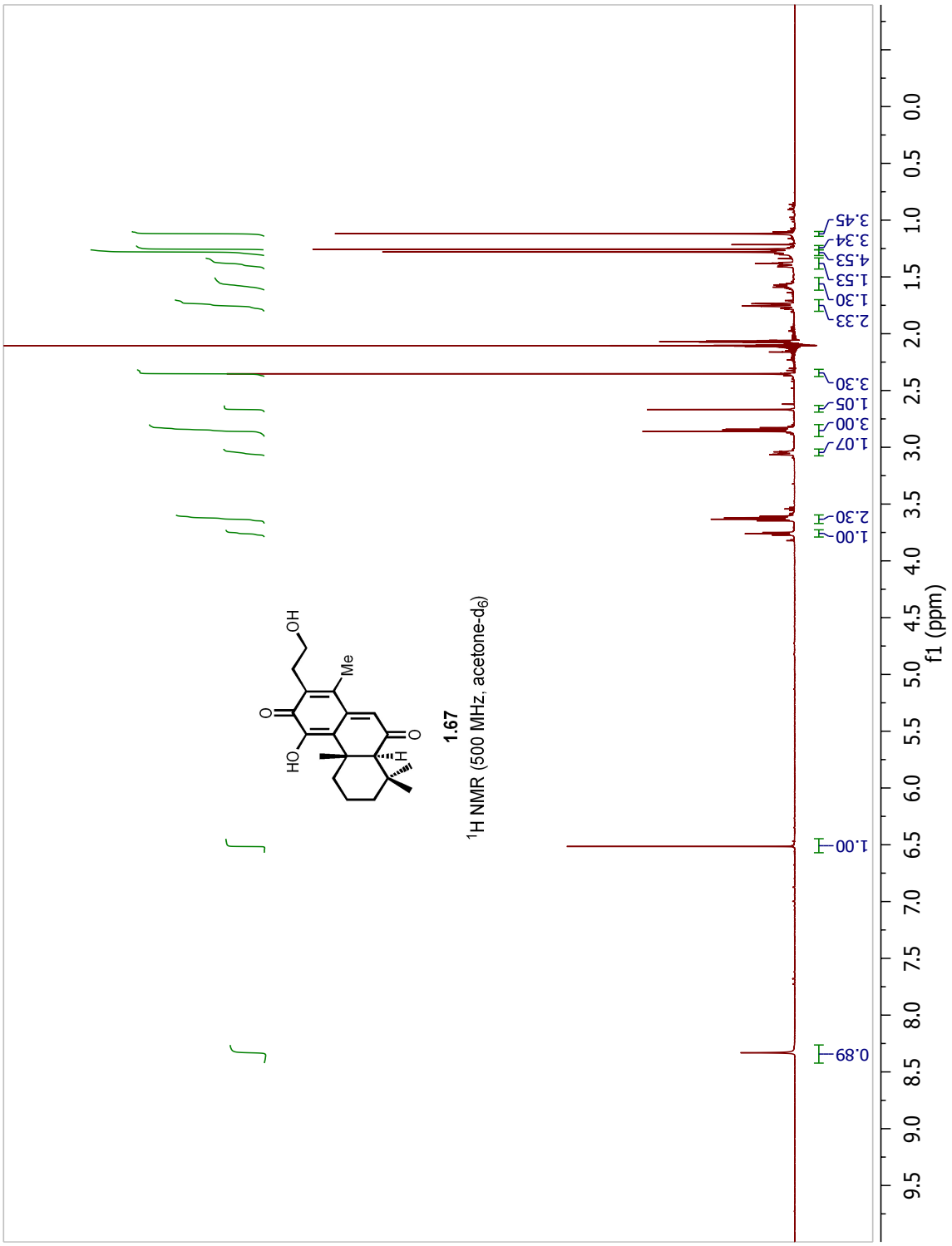

OMe
MeO
O
1.69
^{1}H NMR (500 MHz, CDCl$_3$)
6.85
6.69
2.16
3.37
2.24
2.29
1.05
3.15
3.01
2.04
1.00
1.04
f1 (ppm)

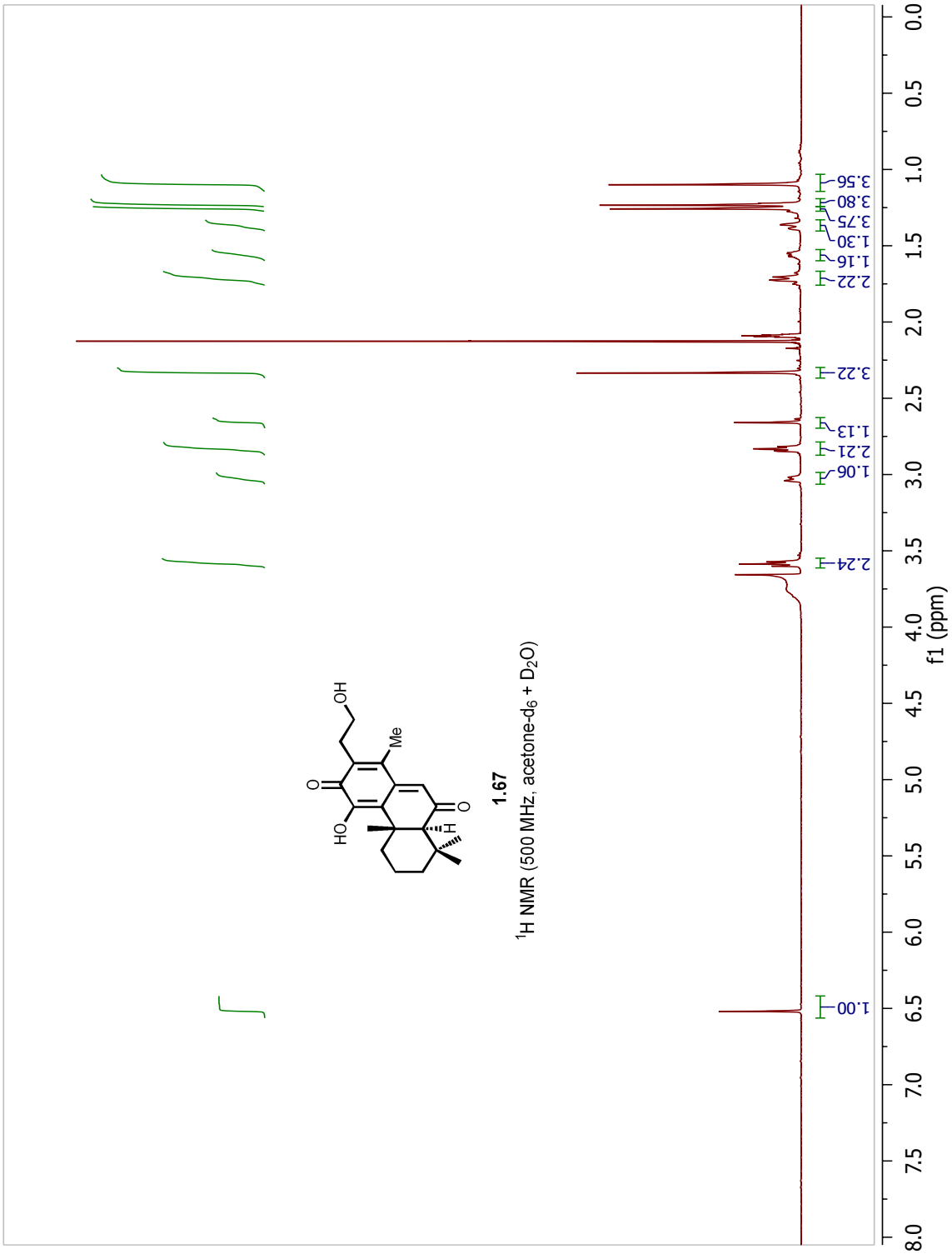

18.8
21.2
23.5
26.7
28.8
31.2
33.4
38.9
52.2
55.7
60.9
111.3
119.7
129.6
129.7
142.0
143.1
145.1
152.3
OMe
MeO
O
1.69
^{13}C NMR (125 MHz, $CDCl_3$)
f1 (ppm)

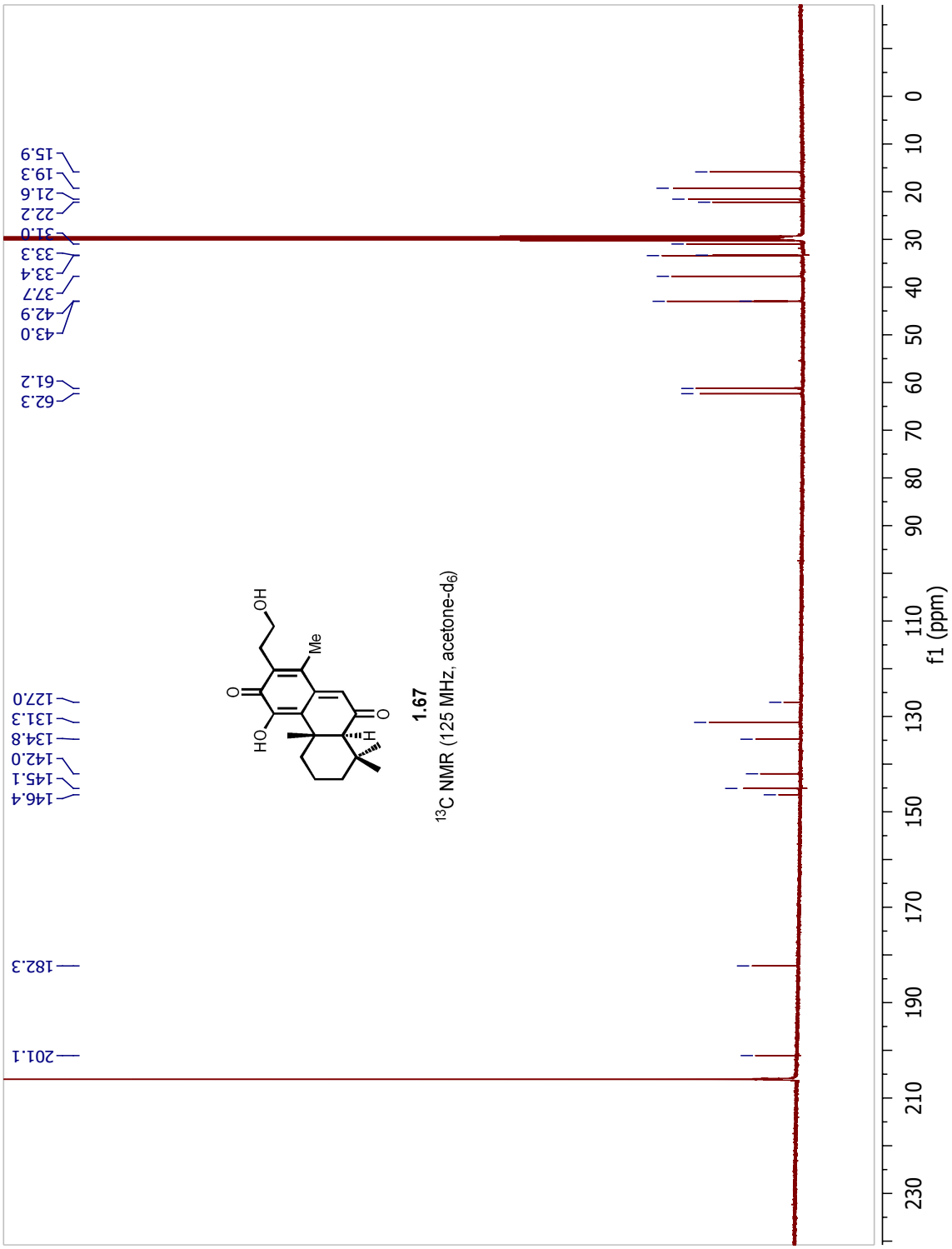

taxodione
^{1}H NMR (500 MHz, CDCl$_3$)
f1 (ppm)
6.09
3.08
2.96
2.82
1.06
1.10
1.06
1.00
1.02
0.90

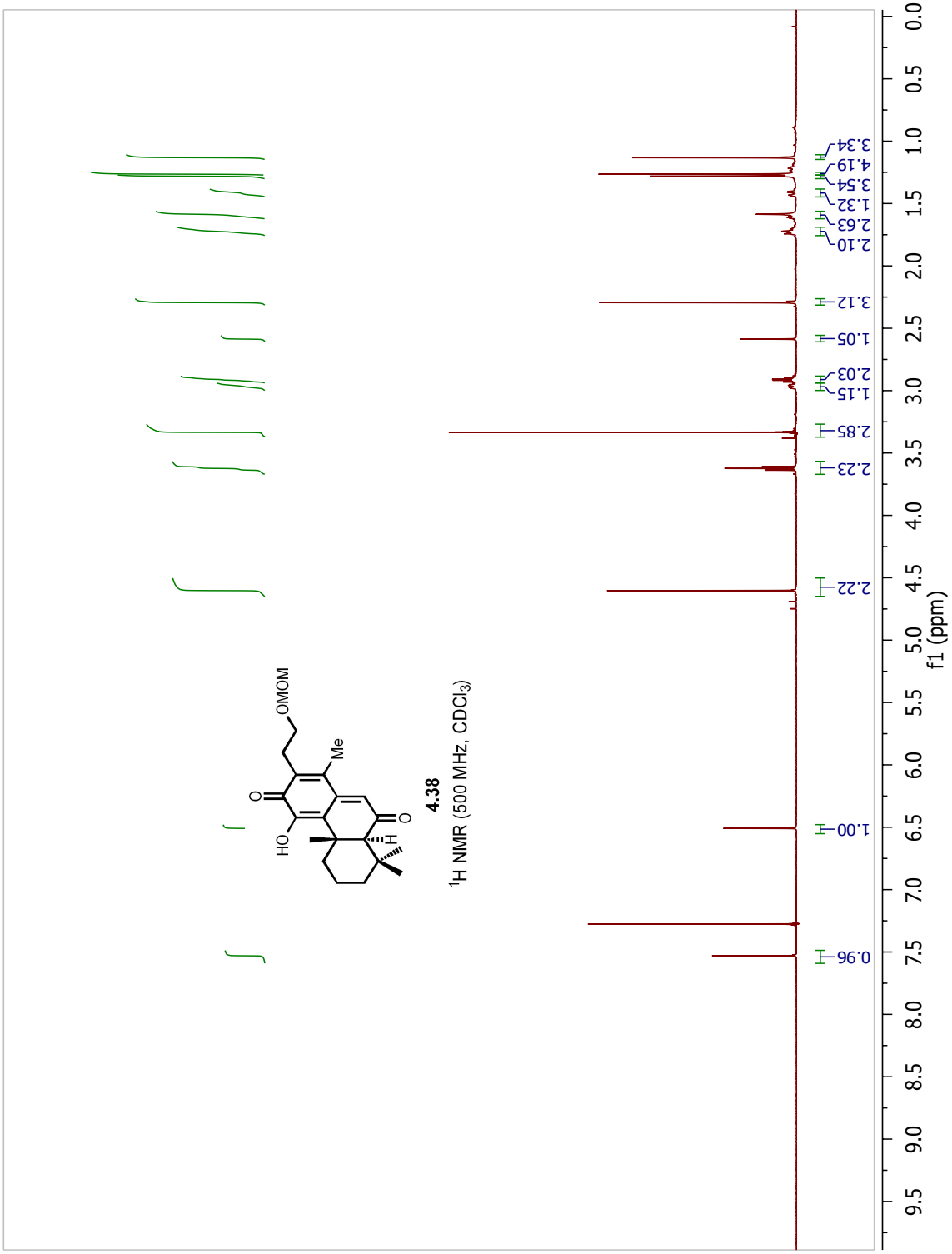

4.37
^{1}H NMR (500 MHz, CDCl$_3$)
OMe
HO
O
H
f1 (ppm)
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
2.86
3.00
1.77
5.87
3.16
1.89
2.56
1.01
1.01
1.00
1.04
1.08
3.05
0.92
1.00

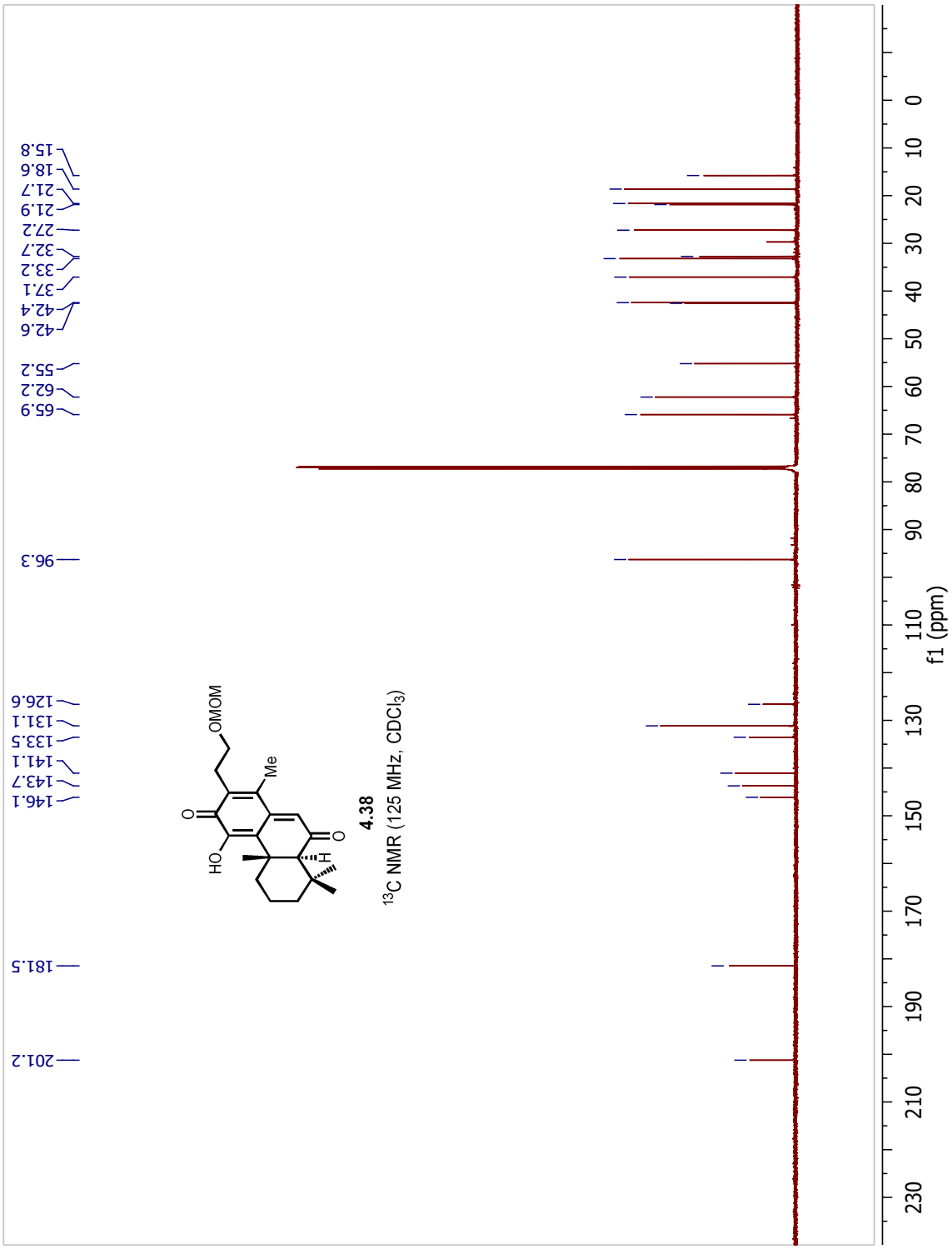

213.1
145.8
144.9
133.7
130.4
126.4
122.3
68.5
61.9
44.0
42.2
40.1
37.4
34.4
32.4
31.9
27.2
22.8
22.5
22.4
20.2
OMe
HO
H
O
4.37
^{13}C NMR (125 MHz, $CDCl_3$)
f1 (ppm)

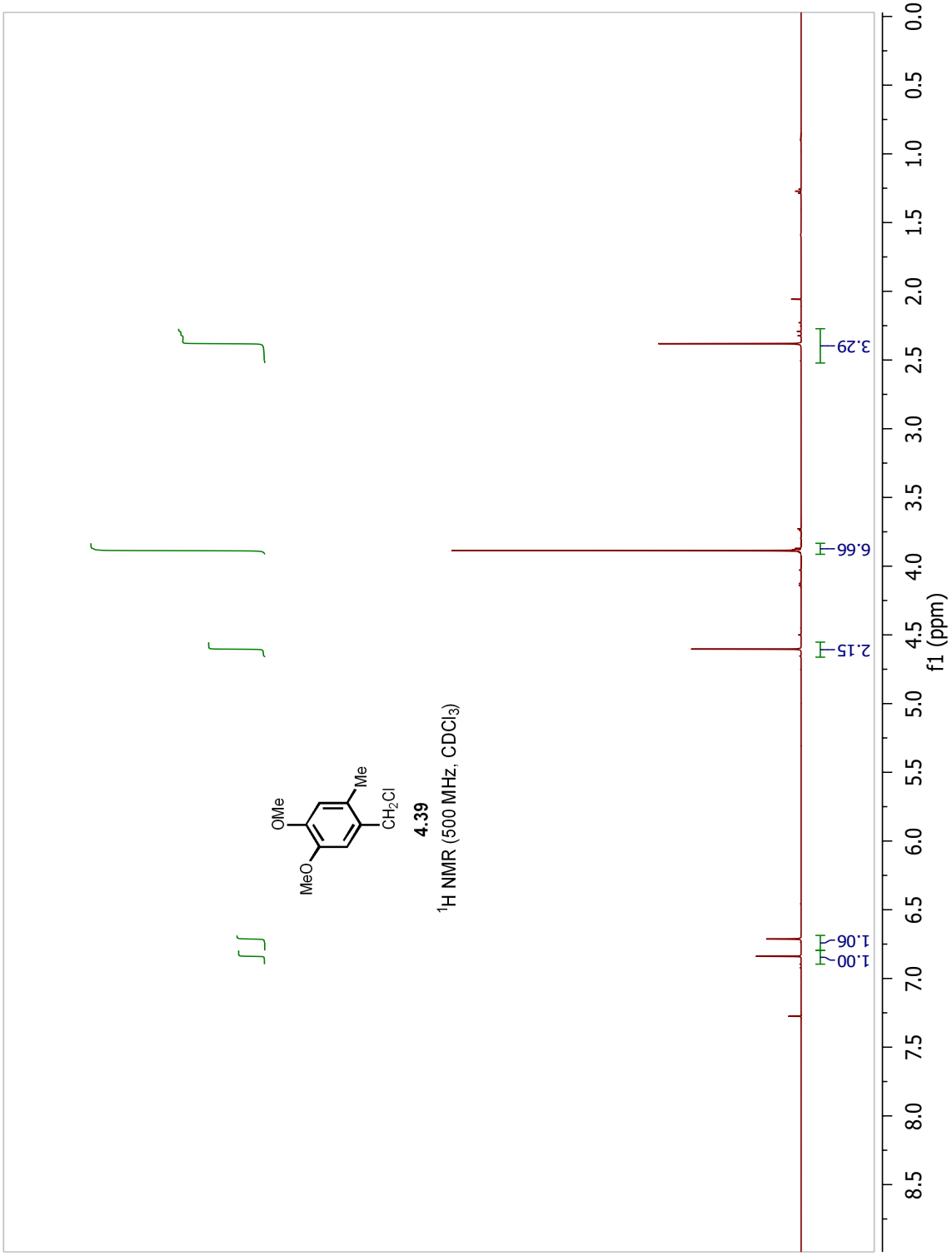

1.67
^{1}H NMR (500 MHz, acetone-d$_6$)
OH
Me
O
HO
O
H
f1 (ppm)
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
0.89
1.00
2.30
1.00
1.07
3.00
1.05
3.30
2.33
1.30
1.53
4.53
3.34
3.45

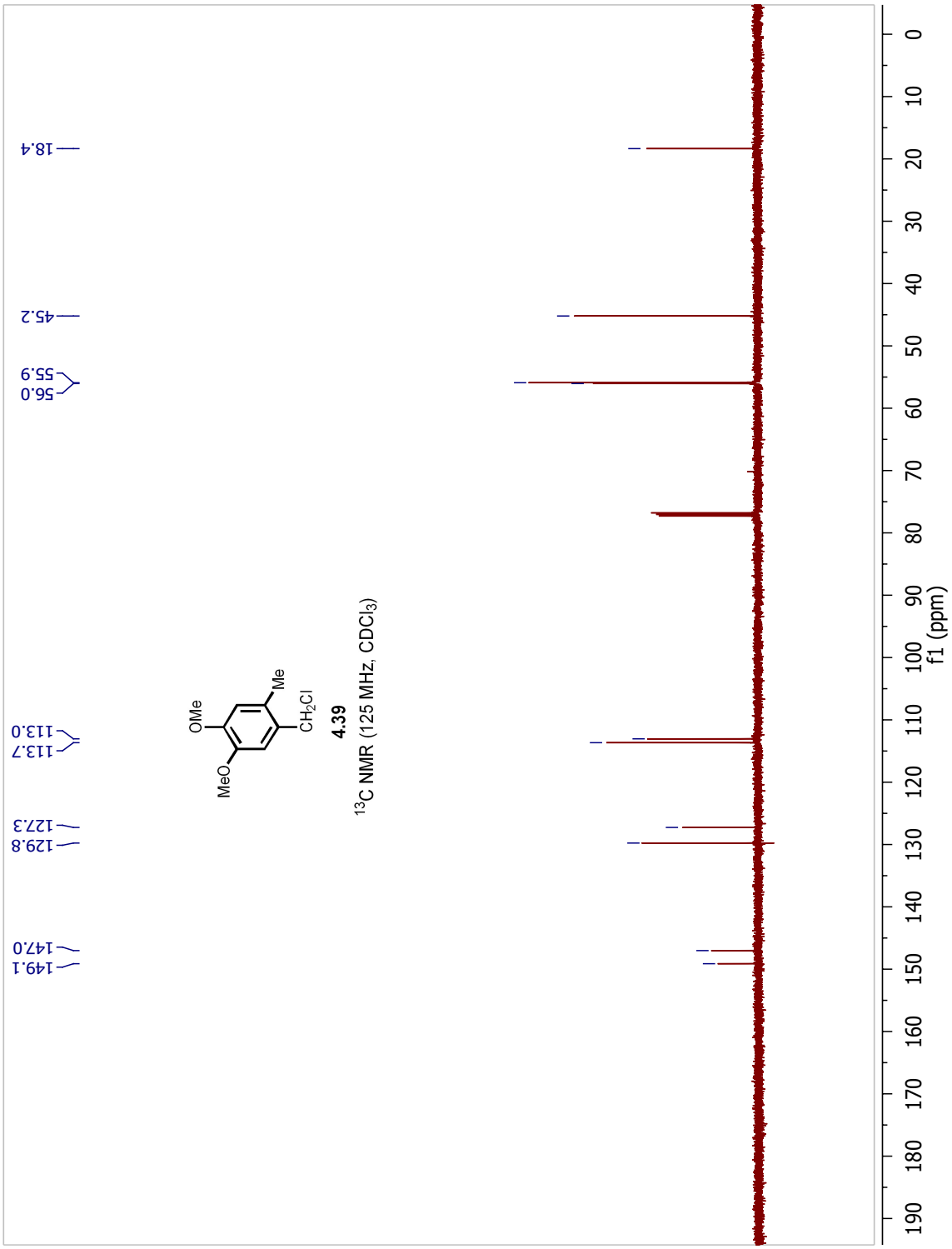

OH
Me
O
HO
O
H
1.67
^{1}H NMR (500 MHz, acetone-d_6 + D_2O)
1.00
2.24
1.06
2.21
1.13
3.22
2.22
1.16
1.30
3.75
3.80
3.56
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

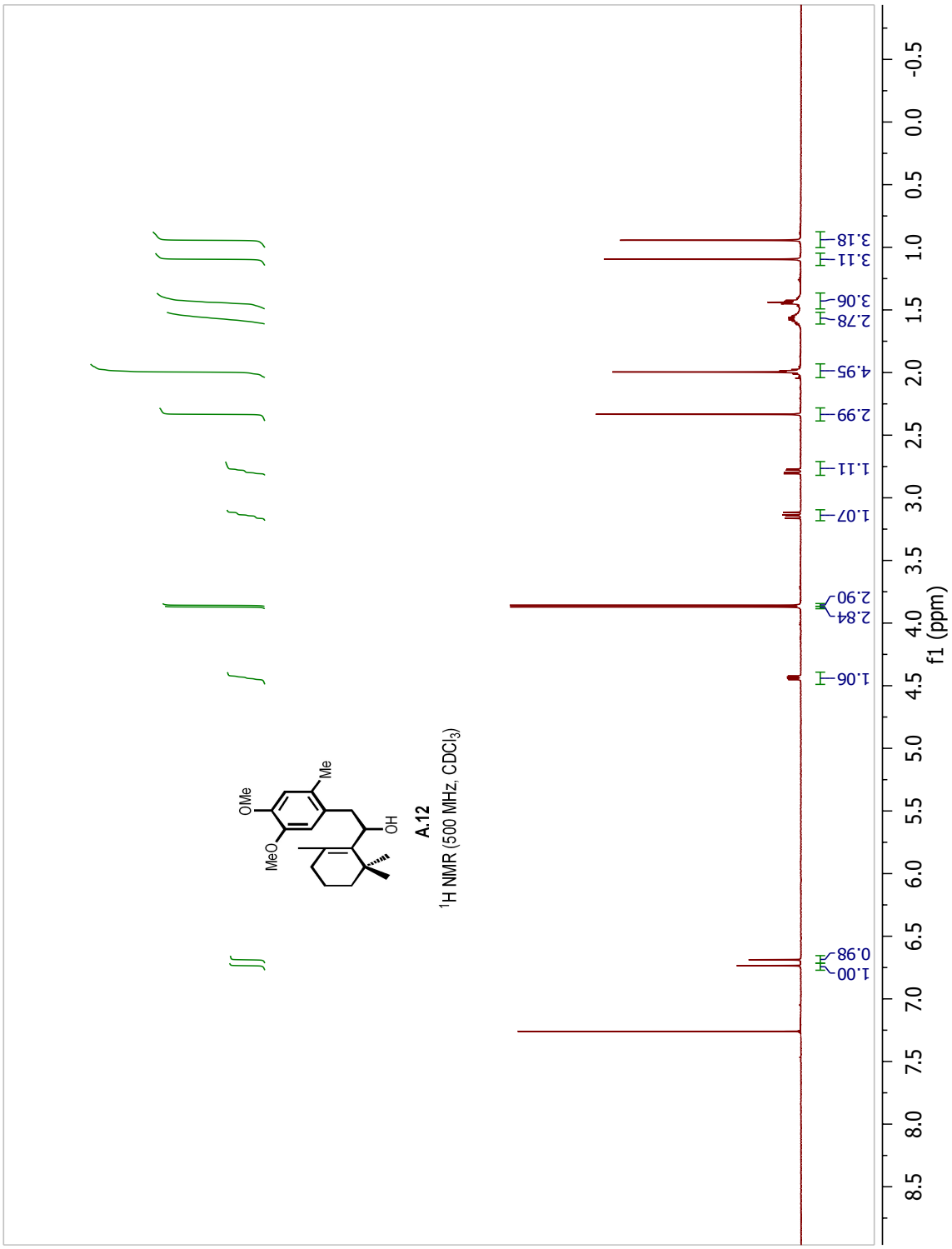

201.1
182.3
146.4
145.1
142.0
134.8
131.3
127.0
62.3
61.2
43.0
42.9
37.7
33.4
33.3
31.0
22.2
21.6
19.3
15.9
OH
Me
O
HO
O
H
1.67
13C NMR (125 MHz, acetone-d6)
0
10
20
30
40
50
60
70
80
90
110
130
150
170
190
210
230
f1 (ppm)

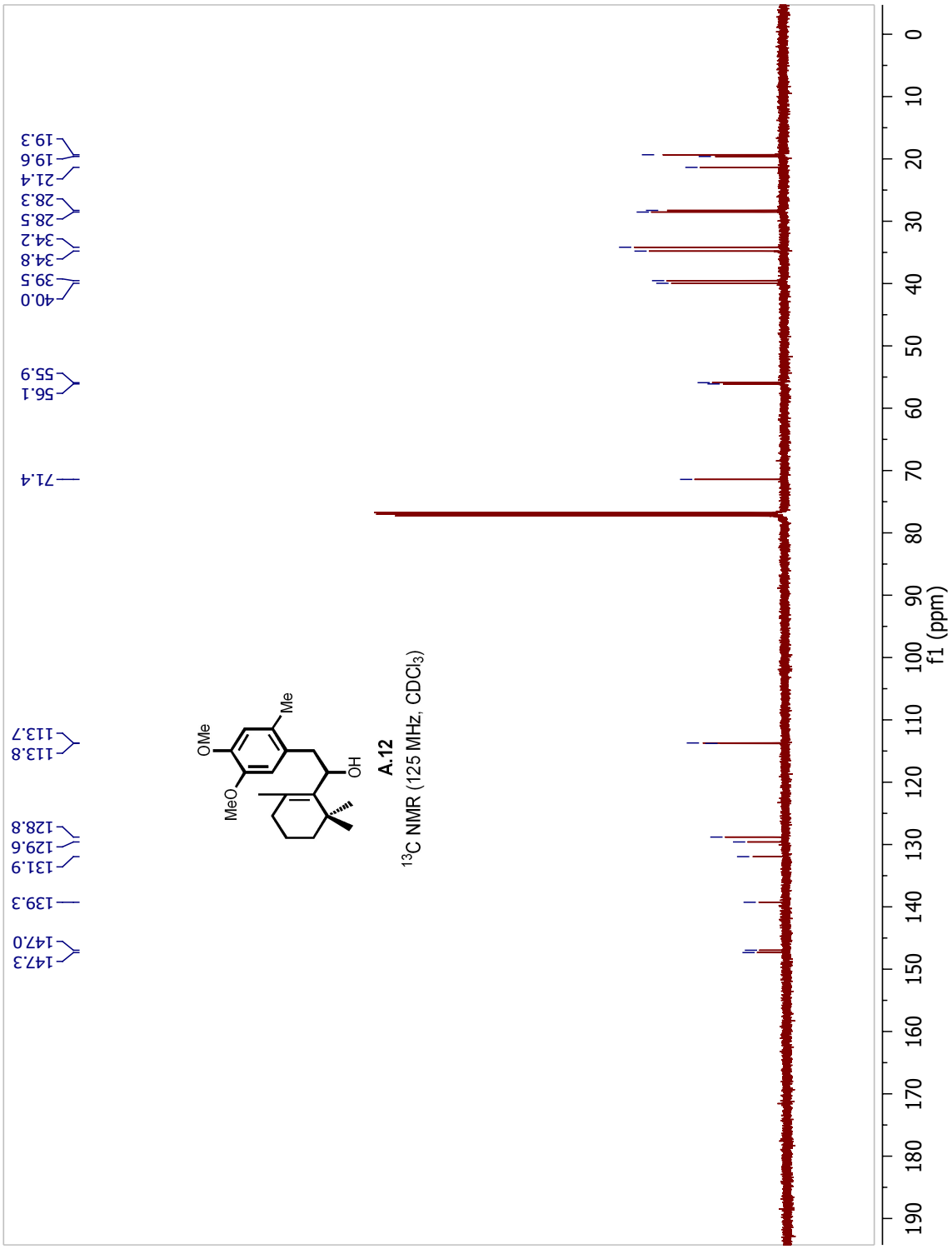

OMOM
Me
HO
O
O
H
4.38
^{1}H NMR (500 MHz, CDCl$_3$)
0.96
1.00
2.22
2.23
2.85
1.15
2.03
1.05
3.12
2.10
2.63
1.32
3.54
4.19
3.34
f1 (ppm)

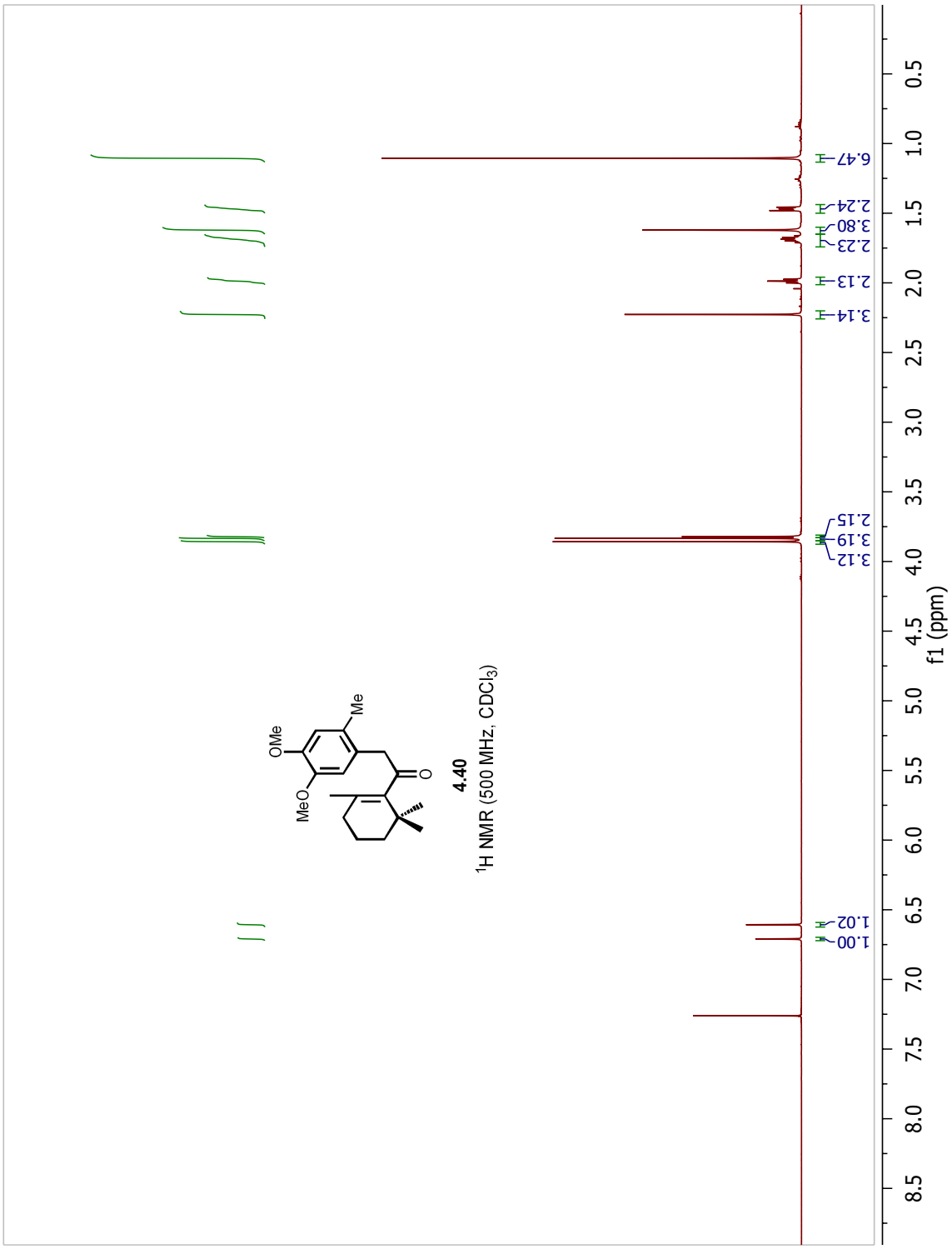

15.8
18.6
21.7
21.9
27.2
32.7
33.2
37.1
42.4
42.6
55.2
62.2
65.9
96.3
126.6
131.1
133.5
141.1
143.7
146.1
181.5
201.2
OMOM
Me
HO
O
O
H
4.38
^{13}C NMR (125 MHz, $CDCl_3$)
0
10
20
30
40
50
60
70
80
90
110
130
150
170
190
210
230
f1 (ppm)

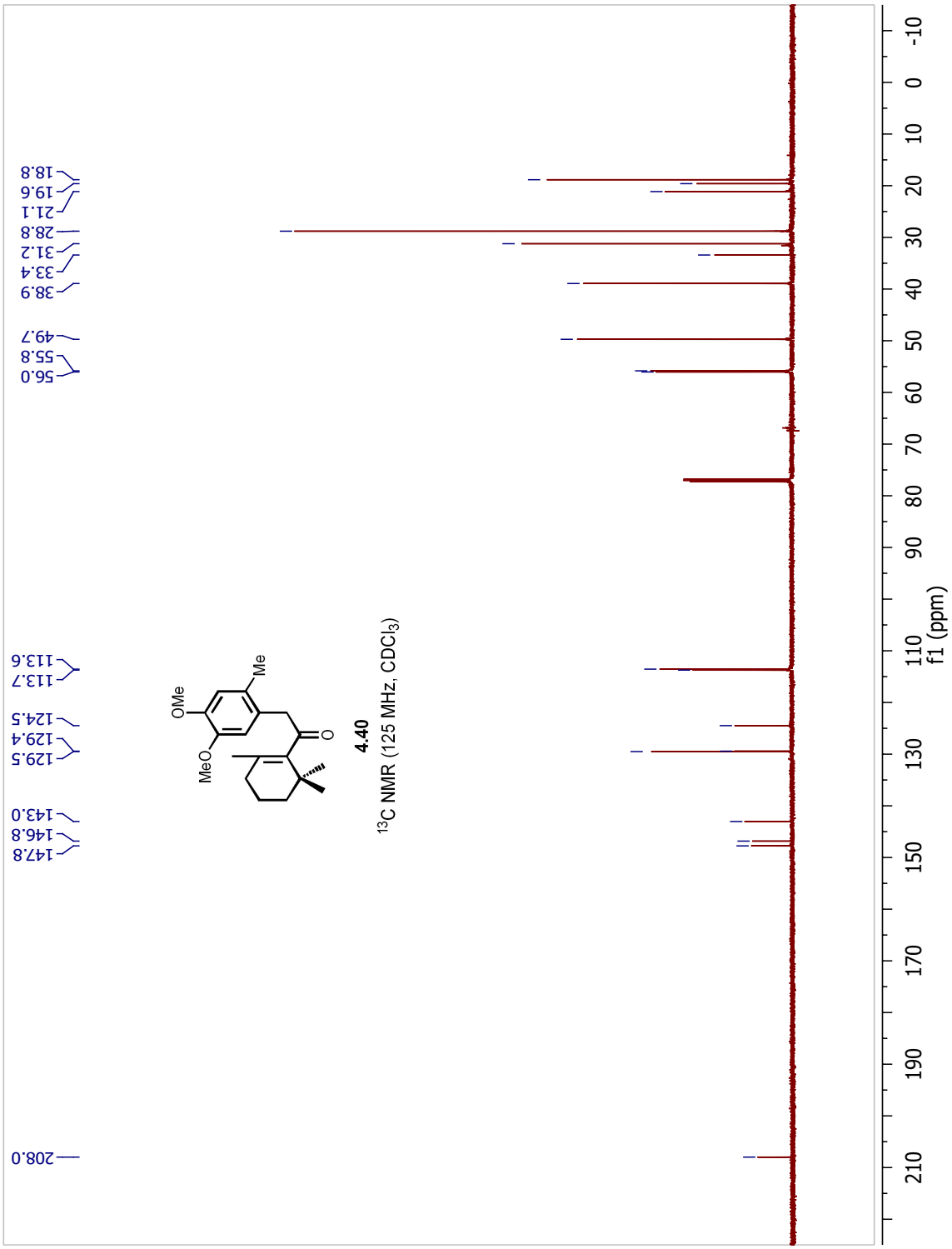

4.39
^{1}H NMR (500 MHz, $CDCl_3$)
OMe
MeO
Me
CH_2Cl
3.29
6.66
2.15
1.06
1.00
f1 (ppm)

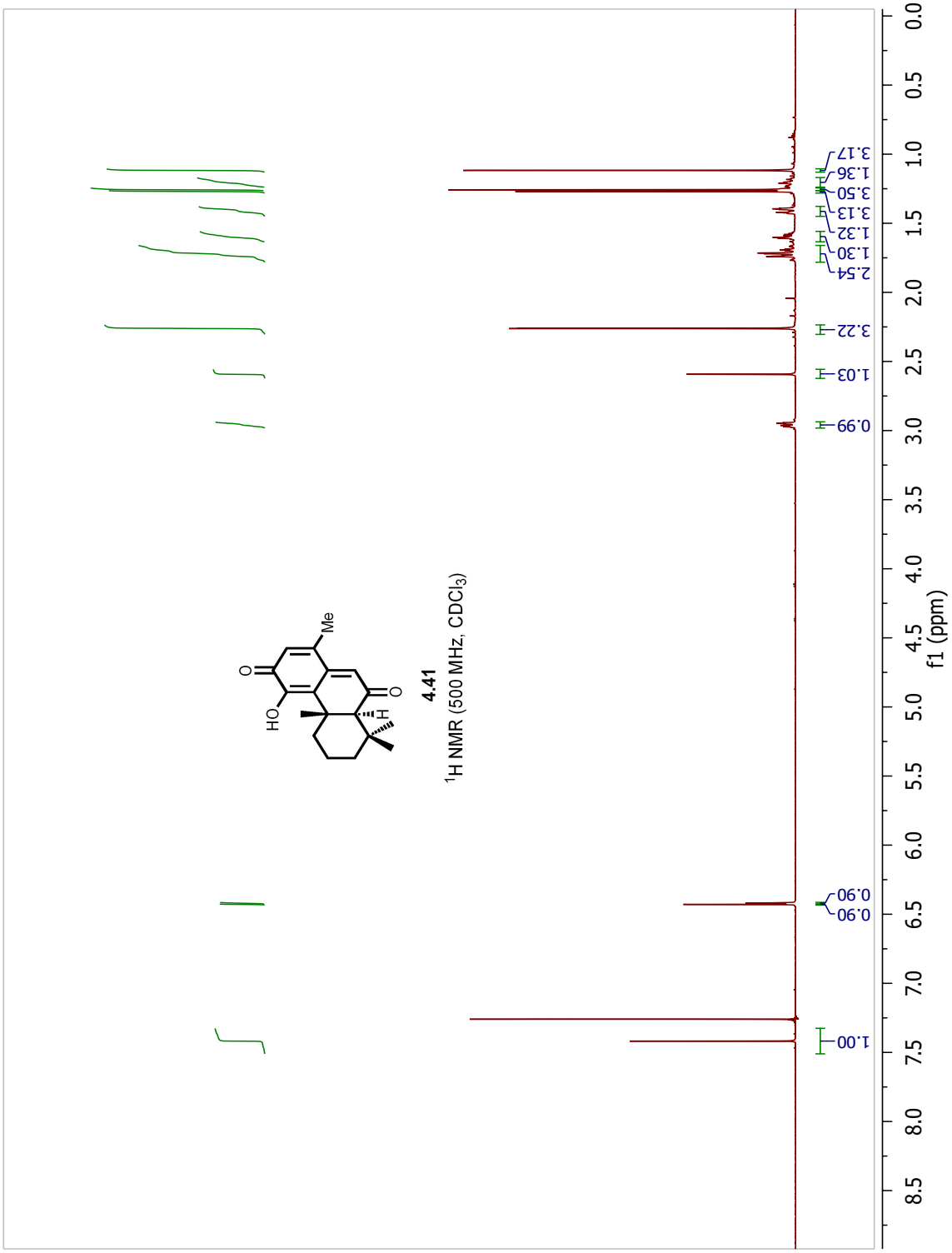

18.4
45.2
56.0
55.9
113.0
113.7
127.3
129.8
147.0
149.1
OMe
MeO
Me
CH2Cl
4.39
13C NMR (125 MHz, CDCl3)
f1 (ppm)

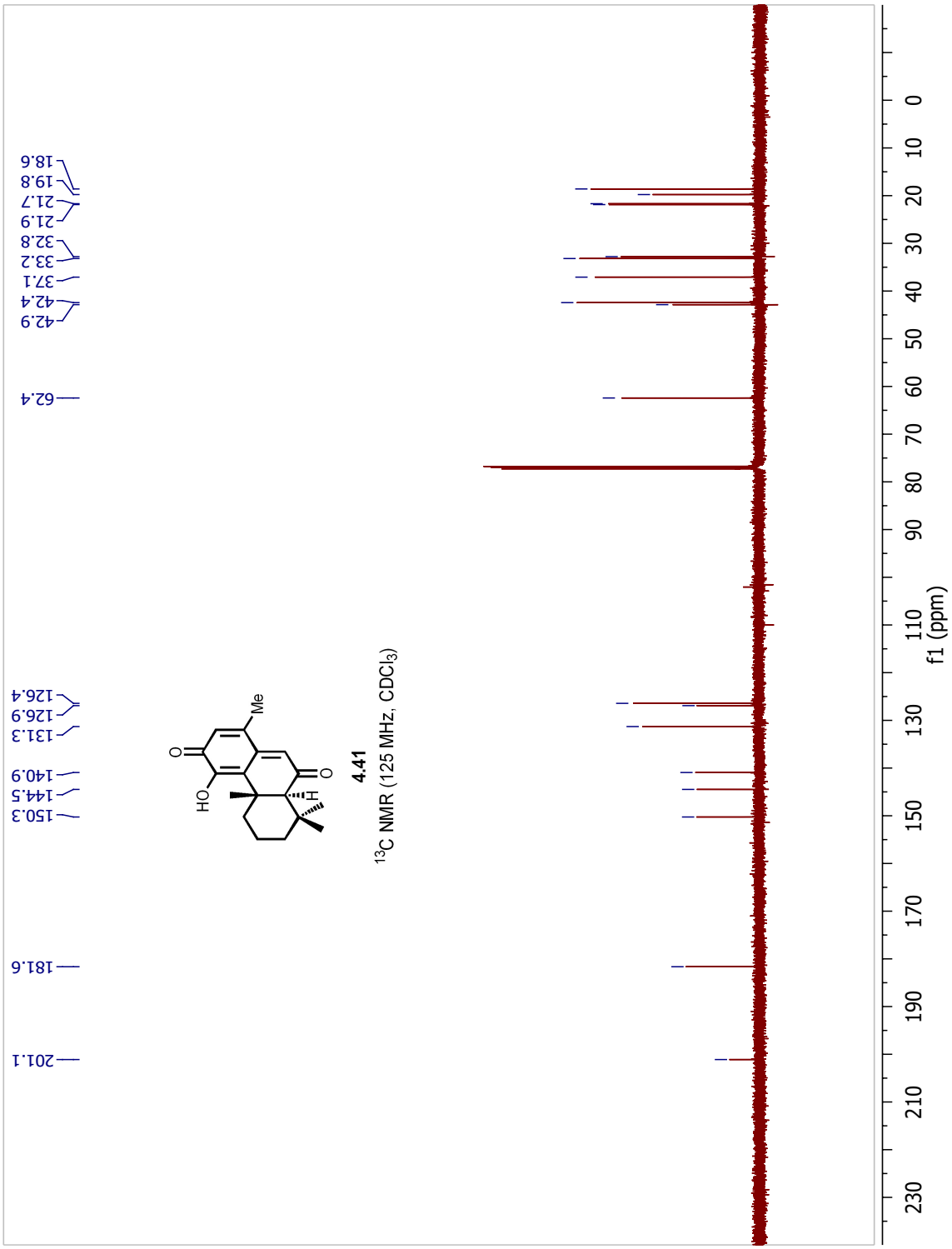

OMe
Me
MeO
OH
A.12
^{1}H NMR (500 MHz, $CDCl_3$)
3.18
3.11
3.06
2.78
4.95
2.99
1.11
1.07
2.84
2.90
1.06
1.00
0.98
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


147.3
147.0
139.3
131.9
129.6
128.8
113.8
113.7
71.4
56.1
55.9
40.0
39.5
34.8
34.2
28.5
28.3
21.4
19.6
19.3
OMe
MeO
Me
OH
A.12
^{13}C NMR (125 MHz, CDCl$_3$)
f1 (ppm)


OMe
Me
MeO
O
4.40
^{1}H NMR (500 MHz, $CDCl_3$)
6.47
2.24
3.80
2.23
2.13
3.14
2.15
3.19
3.12
1.00
1.02
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)


208.0
147.8
146.8
143.0
129.5
129.4
124.5
113.7
113.6
56.0
55.8
49.7
38.9
33.4
31.2
28.8
21.1
19.6
18.8
OMe
MeO
Me
O
4.40
^{13}C NMR (125 MHz, $CDCl_3$)
f1 (ppm)


4.41
^{1}H NMR (500 MHz, CDCl$_3$)
f1 (ppm)
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
3.17
1.36
3.50
3.13
1.32
1.30
2.54
3.22
1.03
0.99
0.90
0.90
1.00


201.1
181.6
150.3
144.5
140.9
131.3
126.9
126.4
62.4
42.9
42.4
37.1
33.2
32.8
21.9
21.7
19.8
18.6
Me
O
HO
O
H
4.41
^{13}C NMR (125 MHz, CDCl$_3$)
f1 (ppm)

APPENDIX C

LETTERS OF PERMISSION

Total synthesis and structure–activity relationship study of the potent cAMP signaling agonist (−)-alotaketal A

J. Huang, J. R. Yang, J. Zhang and J. Yang, *Org. Biomol. Chem.*, 2013, **11**, 3212
DOI: 10.1039/C3OB40120K

- For reproduction of material from PCCP:
  [Original citation] - Reproduced by permission of the PCCP Owner Societies
- For reproduction of material from PPS:
  [Original citation] - Reproduced by permission of The Royal Society of Chemistry (RSC) on behalf of the European Society for Photobiology, the European Photochemistry Association, and RSC
- For reproduction of material from all other RSC journals:
  [Original citation] - Reproduced by permission of The Royal Society of Chemistry

If you are the author of this article you still need to obtain permission to reproduce the whole article in a third party publication with the exception of reproduction of the whole article in a thesis or dissertation.

Information about reproducing material from RSC articles with different licences is available on our Permission Requests page.